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Palladium approaches to beta- and gamma-carbolines

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Palladium approaches to beta- and gamma-carbolines

by

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has met the dissertation requirement of Iowa State University

Signature was redacted for privacy.

Major Professor

Signature was redacted for privacy.

For the Major Program

To my wife, Ye Gu

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LIST OF ABBREVIATIONS

Ac	acetyl
aq	aqueous
Bn	benzyl
br s	broad singlet
n-Bu	butyl
t-Bu	*tert*-butyl
cat.	catalytic
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublets
dt	doublet of triplets
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
eq	equation
equiv	equivalent
Et	ethyl
h	hour(s)
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
m	multiplet

Me	methyl
mL	milliliter(s)
mol	mole(s)
MOM	methoxymethyl
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
NMR	nuclear magnetic resonance
o	ortho
p	para
Ph	phenyl
n-Pr	propyl
q	quartet
s	singlet
satd	saturated
t	triplet
TBAC	tetra-*n*-butylammonium chloride
tert	tertiary
THF	tetrahydrofuran
TLC	thin-layer chromatrography
TMS	trimethylsilyl
Ts	*p*-toluenesulfonyl

ABSTRACT

A variety of substituted β- and γ-carbolines containing aryl, alkyl, hydroxymethyl, ester and silyl functionality at the 3- and 4-positions have been prepared by the palladium-catalyzed iminoannulation of internal and terminal alkynes. This methodology has been successfully employed to the synthesis of two biologically active β-carboline alkaloids, ZK93423 and abecarnil.

A variety of 3-substituted β- and γ-carbolines have been synthesized from *N*-substituted 3-iodo-1*H*-indole-2-carboxaldehydes and 2-bromo-1*H*-indole-3-carboxaldehydes, respectively. The coupling of these aldehydes with various terminal acetylenes using cat. $PdCl_2(PPh_3)_2$/CuI readily affords the corresponding alkynylindole carboxaldehydes, which have subsequently been converted to the corresponding *tert*-butylimines and cyclized to β- and γ-carbolines by either copper-catalyzed or thermal processes.

A variety of *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehydes incorporating an alkyne-containing tether on the indole nitrogen have been converted to the corresponding *tert*-butylimines, which have been subjected to palladium-catalyzed intramolecular iminoannulation, affording various γ-carboline derivatives with an additional ring fused across the 4- and 5-positions in good to excellent yields. This "intramolecular" concept has been extended to other palladium-catalyzed annulations to synthesize various complex heteropolycycles.

A novel 1,4-palladium migration has been observed by trapping the palladium intermediate generated from *o*-iodobiaryls by way of a Suzuki coupling reaction. The choice of reaction conditions is important in turning "on" and "off" the migration. There are important electronic effects controlling the distribution of the palladium intermediates, which is reflected in the isomer distribution of the Suzuki products.

GENERAL INTRODUCTION

Pyrido[3,4-*b*]indoles and pyrido[4,3-*b*]indoles, commonly known as β- and γ-carbolines, respectively, are the key structural units for a variety of biologically important alkaloids. Numerous β-carbolines possess potent and varied CNS and anticancer activity, and γ-carbolines have been studied extensively as antitumor agents. The latter are condensed analogues of the ellipticine/olivacine anticancer agents, and some do indeed display potent activity. The isolation and synthesis of naturally occurring carbolines and the synthesis of β- and γ-carboline derivatives have received considerable attention in the literature due to their biological and pharmaceutical importance.

Palladium-catalyzed annulation processes have recently proven to be a powerful method for the construction of a wide variety of hetero- and carbocycles in the Larock group. In addition, a variety of hetero- and carbocycles have been successfully synthesized by the copper-catalyzed, the palladium-catalyzed and the electrophile-induced cyclization of alkynes having a *tert*-butylimino group in close proximity to the carbon-carbon triple bond. In this dissertation, palladium-catalyzed intermolecular and intramolecular annulation, and palladium/copper-catalyzed coupling and cyclization of alkynes have been investigated and developed into efficient synthetic methods for the construction of β- and γ-carbolines.

Palladium has been shown to catalyze an extraordinary number of incredibly diverse reactions, making it one of the most useful of all metals for organic synthesis. With the exception of alkene, alkyne and carbon monoxide insertion reactions, the palladium moiety typically stays directly attached to the carbon to which it is originally introduced. However, one of the unique features of palladium is its ability to migrate from one carbon to another. The Larock group has recently observed a number of novel palladium migration reactions. In this dissertation, a novel 1,4-palladium migration in the Suzuki coupling of *o*-iodobiaryls with arylboronic acids has been investigated.

Dissertation Organization

This dissertation is divided into four chapters. Each chapter is a journal paper presented with its own introduction, results and discussion, experimental section, conclusions, acknowledgment and references.

Chapter 1 describes the synthesis of 3,4-disubstituted and 3-subsituted β- and γ-carbolines by the palladium-catalyzed iminoannulation of internal and terminal alkynes, respectively, and its application to the synthesis of two biologically active β-carboline alkaloids, ZK93423 and abecarnil. The regioselectivity issues are discussed and the scope and limitations of this methodology are explored.

Chapter 2 describes the synthesis of 3-substituted β- and γ-carbolines by the palladium/copper-catalyzed coupling and cyclization of terminal alkynes. The scope and limitations of this methodology are explored and mechanisms for these transformations are proposed.

Chapter 3 extends the palladium-catalyzed iminoannulation chemistry to intramolecular iminoannulation to synthesize a variety of annulated γ-carbolines. This intramolecular iminoannulation is mechanistically related to the process examined in Chapter 1, but results in the formation of γ-carbolines with an additional ring fused across the 4- and 5-positions. The extension of this "intramolecular" concept to other palladium-catalyzed annulations to synthesize various complex heteroatom-containing polycycles is also examined.

Chapter 4 describes a novel 1,4-palladium migration in the Suzuki coupling of *o*-iodobiaryls with arylboronic acids. Important electronic effects controlling the distribution of the palladium intermediates, which is reflected in the isomer distribution of the Suzuki products, are discussed.

Finally, a general conclusion to this dissertation and acknowledgments are presented, and the ^{1}H and ^{13}C NMR spectra of all previously unknown starting materials and palladium-catalyzed reaction products are provided in Appendices A-D.

CHAPTER 1. SYNTHESIS OF β- AND γ-CARBOLINES BY THE PALLADIUM-CATALYZED IMINOANNULATION OF ALKYNES

A paper published in the *Journal of Organic Chemistry*

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Abstract

A variety of substituted β- and γ-carbolines have been prepared in moderate to excellent yields by the palladium-catalyzed annulation of internal and terminal acetylenes by the *tert*-butylimines of *N*-substituted 3-iodoindole-2-carboxaldehydes and 2-haloindole-3-carboxaldehydes, respectively. This annulation chemistry is effective for a wide range of alkynes, including aryl-, alkyl-, hydroxymethyl-, ethoxycarbonyl-, and trimethylsilyl-substituted alkynes. When an unsymmetrical internal alkyne is employed, this method generally gives two regioisomers. When a terminal alkyne is employed, only one regioisomer has been isolated. This palladium-catalyzed annulation chemistry has also been successfully applied to the synthesis of two biologically interesting β-carboline alkaloids, ZK93423 and abecarnil (ZK112119).

Introduction

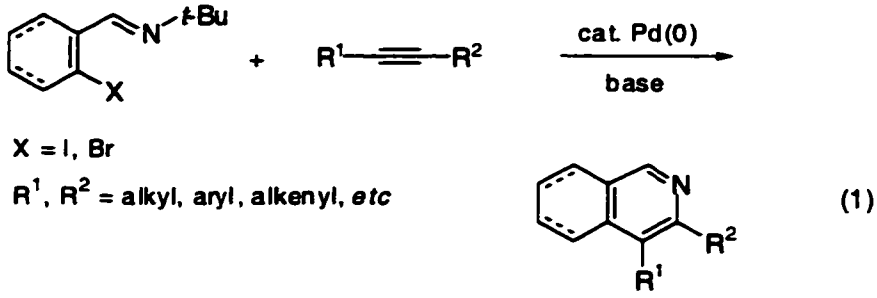
Pyrido[3,4-*b*]indoles[1] and pyrido[4,3-*b*]indoles,[2] commonly known as β- and γ-carbolines, respectively, are the key structural units for a variety of biologically important alkaloids. For example, numerous β-carbolines possess potent and varied CNS and anticancer activity,[1] and γ-carbolines have been studied extensively as antitumor agents.[3] The latter are condensed analogues of the ellipticine/olivacine anticancer agents, and some do indeed display potent activity.[3] The isolation and synthesis of naturally occurring carbolines and the synthesis of β- and γ-carboline

derivatives have received considerable attention in the literature[1,2,4] due to their biological and pharmaceutical importance.

Carboline heterocycles have been synthesized by employing palladium methodology. For instance, a combination of palladium-catalyzed cross-coupling and base-promoted intramolecular nucleophilic aromatic substitution generates the α-, β-, γ-, and δ-carboline parent systems.[5] This strategy has been successfully applied to the synthesis of eudistomin T, a β-carboline alkaloid.[6] A combination of palladium-catalyzed amination and arylation reactions has also been developed to synthesize the carboline parent systems.[4a] A palladium-mediated intramolecular amination, which produces substituted β-carbolines as important intermediates for the total synthesis of lavendamycin methyl ester, has been reported by Boger.[7] This synthesis has the disadvantage of using more than one equivalent of the palladium reagent. Recently, β- and γ-carbolines have also been synthesized by a combination of palladium-catalyzed coupling, imine/oxime formation and cyclization.[4c,f-k] Employing this chemistry, Hibino has synthesized several naturally occurring β-carbolines.[4f,h]

Annulation processes have proven very useful in organic synthesis due to the ease with which a wide variety of complicated hetero- and carbocycles can be rapidly constructed. In our own laboratories, it has been demonstrated that palladium-catalyzed annulation methodology[8] can be effectively employed for the synthesis of indoles,[9] isoindolo[2,1-*a*]indoles,[10] benzofurans,[11] benzopyrans,[11] isocoumarins,[11,12] α-pyrones,[12,13] indenones,[14] and polycyclic aromatic hydrocarbons.[15]

Recently, we have developed a general synthesis of isoquinolines and pyridines by the palladium-catalyzed iminoannulation of internal alkynes (eq 1).[16] Our own interest in extending this type of iminoannulation reaction prompted us

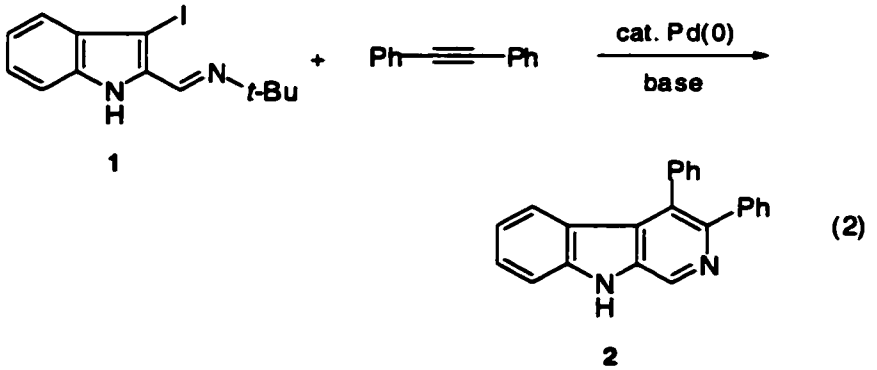


(1)

to examine potential applications to the synthesis of a wide variety of β- and γ-carbolines. A brief communication on this work has been previously reported.[17] Herein, we wish to report the full details of this palladium-catalyzed annulation of internal alkynes for the synthesis of various β- and γ-carbolines, extension of this methodology to terminal alkynes, and applications to the synthesis of two biologically active β-carboline alkaloids ZK93423[18] and abecarnil (ZK112119).[19]

Results and Discussion

Our initial studies focused on the palladium-catalyzed iminoannulation of internal alkynes employing the *tert*-butylimine of 3-iodo-1*H*-indole-2-carboxaldehyde (**1**). The reaction of diphenylacetylene and imine **1** was chosen as the model system for optimization (eq 2). In the early stages of this work, the reaction conditions



1 **2**

(2)

examined were similar to the conditions employed in our earlier isoquinoline synthesis.[16] For example, the reactions were run with 0.25 mmol of the *tert*-butylimine, 2 equiv of diphenylacetylene, 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3 and 1 equiv of Na_2CO_3 as a base in 5 mL of DMF at 100 °C (Table 1, entry 1).

Table 1. Optimization of the Palladium-Catalyzed Formation of 3,4-Diphenyl-β-carboline (eq 2)

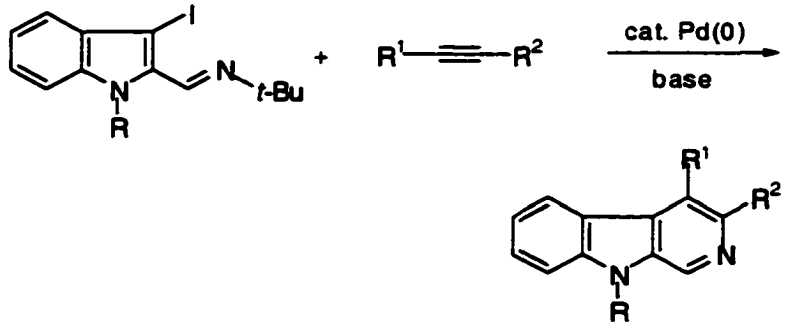
entry	catalyst	% catalyst	% PPh_3	base (equiv)	temp (°C), time (h)	% isolated yield of **2**
1	$Pd(OAc)_2$	5	10	Na_2CO_3 (1)	100, 48	0
2	$Pd(OAc)_2$	5	10	Na_2CO_3 (1)	130, 48	0
3	$Pd(OAc)_2$	5	10	K_2CO_3 (1)	100, 48	0
4	$Pd(OAc)_2$	5	10	Cs_2CO_3 (1)	100, 48	0
5	$Pd(OAc)_2$	5	10	NaOAc (1)	100, 48	0
6	$Pd(OAc)_2$	5	10	KOAc (1)	100, 48	0
7	$Pd(OAc)_2$	5	10	Pyridine (1)	100, 48	0
8	$Pd(OAc)_2$	5	10	DTBMP[a] (1)	100, 48	0
9	$Pd(OAc)_2$	5	10	NEt_3 (1)	100, 24	39
10	$Pd(OAc)_2$	5	10	*i*-Pr_2NEt (1)	100, 24	40
11	$Pd(OAc)_2$	5	10	Cy_2NEt (1)	100, 50	48
12	$Pd(OAc)_2$	5	10	*n*-Bu_3N (1)	100, 24	48
13	$Pd(OAc)_2$	5	5	*n*-Bu_3N (1)	100, 10	54
14	$Pd(OAc)_2$	5	2.5	*n*-Bu_3N (1)	100, 10	45
15	$Pd(OAc)_2$	10	5	*n*-Bu_3N (1)	100, 8	51
16	$Pd(OAc)_2$	5	5	*n*-Bu_3N (2)	100, 10	52
17	$PdCl_2(PPh_3)_2$	5	5	*n*-Bu_3N (1)	100, 10	40
18	$PdCl_2(PhCN)_2$	5	5	*n*-Bu_3N (1)	100, 10	46
19	$Pd(PPh_3)_4$	5	5	*n*-Bu_3N (1)	100, 10	41
20	$Pd(dba)_2$	5	5	*n*-Bu_3N (1)	100, 10	41
21	$Pd(dppe)_2$	5	5	*n*-Bu_3N (1)	100, 10	51

[a] 2,6-Di-*tert*-butyl-4-methylpyridine.

However, these conditions failed to produce any of the desired β-carboline **2**. When the reaction temperature was raised to 130 °C, still no desired product was detected after 48 h (entry 2). We next examined different inorganic bases in the reaction, since the nature of the base often has a dramatic effect on these palladium-catalyzed annulation reactions.[8] All of the inorganic bases we tried, including K_2CO_3, Cs_2CO_3, NaOAc, and KOAc proved to be ineffective (entries 3-6). Two pyridine bases, namely pyridine and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) also failed to produce any of the desired product (entries 7 and 8). When the tertiary amine base triethylamine was employed, a 39% yield of the desired product was isolated (entry 9). Several other tertiary amine bases, including *N*,*N*-diisopropylethylamine (*i*-Pr_2NEt), *N*-ethyldicyclohexylamine (Cy_2NEt), and tri-*n*-butylamine (*n*-Bu_3N) generated the desired product, but in relatively low yields (entries 10-12). Comparing entries 11 and 12, we noticed that the use of *n*-Bu_3N required not only shorter reaction times, but also produced a cleaner reaction as monitored by TLC analysis than the use of Cy_2NEt. Therefore, we selected *n*-Bu_3N as the base of choice for the succeeding optimization work. We next changed the amount of PPh_3 ligand. When 5 mol % of PPh_3 was employed in the reaction, a slight increase in the yield, as well as a reduction in the reaction time, was observed (entry 13). Further reduction in the amount of PPh_3 to 2.5 mol % was accompanied by a decrease in the product yield (entry 14). Additional attempts to optimize this annulation process employed 5 mol % of PPh_3, but varied either the amount of $Pd(OAc)_2$ (entry 15) or *n*-Bu_3N (entry 16). A slight decrease in the product yield was observed in both cases. Finally, 5 mol % of five different palladium catalysts other than $Pd(OAc)_2$ were employed, but none of these reactions gave a yield higher than 54% (entry 13, where 5 mol % of $Pd(OAc)_2$, 5 mol % of PPh_3 and 1 equiv of *n*-Bu_3N were employed).

It has been reported that aryl halides and indole can undergo palladium-catalyzed amination to produce *N*-arylindoles.[20] The low yields of carboline observed under various reaction conditions may be a result of the *N*-arylation of our

N–H containing indole by another molecule of starting material to form a dimer, which may subsequently form oligomers or polymers. However, no direct evidence has been obtained during the course of our study to support this hypothesis. The easiest way to solve this problem is to employ *N*-protected indole imines. 3-Iodo-1-methylindole-2-methylene-*tert*-butylamine (**3**) was, therefore, prepared and allowed to react with diphenylacetylene under the optimal reaction conditions for the annulation of diphenylacetylene by imine **1** (Table 1, entry 13; Conditions A in Table 2). As we expected, a substantial 76% yield of the desired *β*-carboline **4** was observed (Table 2, entry 1). It is worth noting that when the conditions in our earlier isoquinoline synthesis[16] were employed, the same reaction afforded the desired product, but in a lower yield. When imine **3** and ethyl 3-phenylpropiolate are employed, the annulation reaction gives two isomers **5** and **6** in 58% and 42% isolated yields, respectively (Table 2, entry 3). Thus, we have chosen Conditions A as our general reaction procedure for the synthesis of *β*-carbolines, instead of further endlessly optimizing the reaction conditions. We then proceeded to determine the scope and limitations of this methodology by annulating a wide variety of acetylenes with imine **3** and other *N*-substituted indole imines (eq 3). The results of this study are summarized in Table 2.



(3)

The annulation of a variety of internal alkynes with imine **3** under Conditions A has afforded the desired *β*-carbolines in moderate to excellent yields (entries 1, 2, 4, 6-8, 10-13, 15 and 16). When an unsymmetrical alkyne is employed, two regioisomers have generally been observed, usually with poor regioselectivity

Table 2. Synthesis of β-Carbolines by the Palladium-Catalyzed Annulation of Internal Alkynes (eq 3)[a]

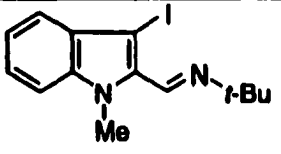
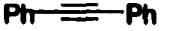
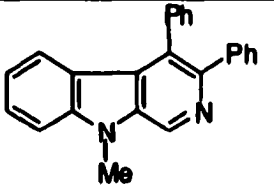
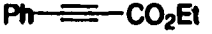
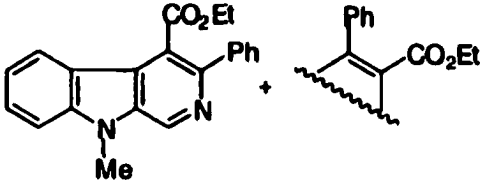
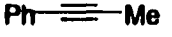
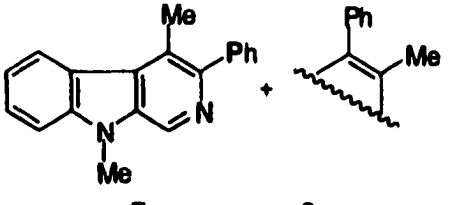
entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
1	 **3**		A	4	 **4**	76
2			A	5	 **5** **6**	58 + 42
3			B	17		99 + trace
4			A	5	 **7** **8**	49 + 42
5			B	6		64 + 22

Table 2. Continued

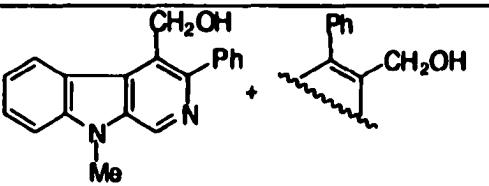
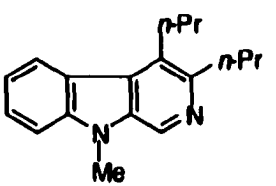
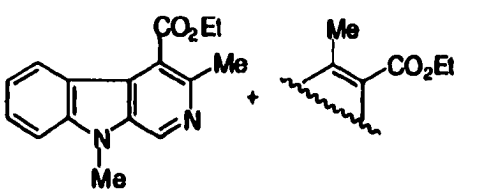
entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
6		Ph—≡—CH_2OH	A	2	 **9** + **10**	43 + 36
7		*n*-Pr—≡—*n*-Pr	A	2	 **11**	72
8		Me—≡—CO_2Et	A	2	 **12** + **13**	73 (1:1)[b]
9			B	22		62 (1:1.7)[b]

Table 2. Continued

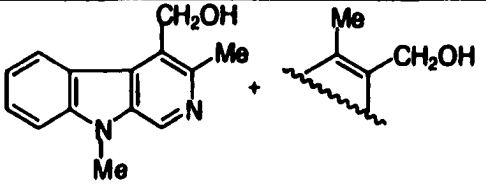
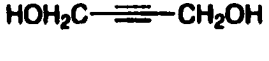
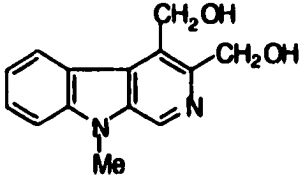
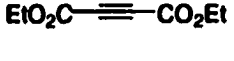
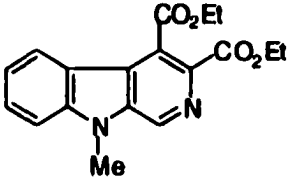
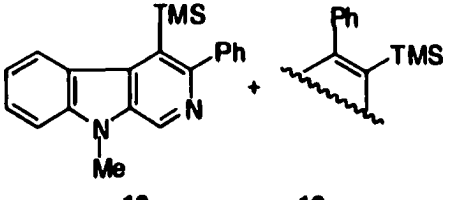
entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
10			A	2	 **14** **15**	100 (1:1)[b]
11			A	2	 **16**	96
12			A	9	 **17**	49
13			A	1.5	 **18** **19**	34 + 25

Table 2. Continued

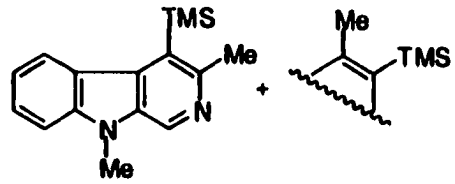
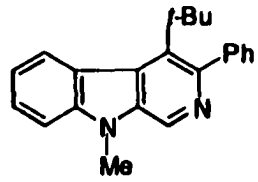
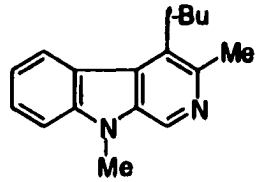
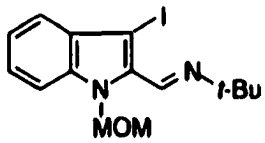
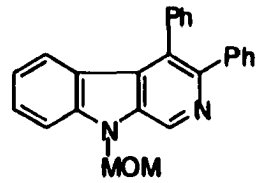
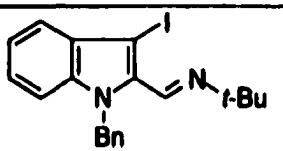
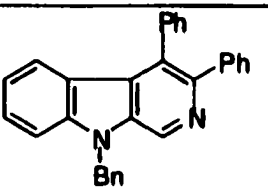
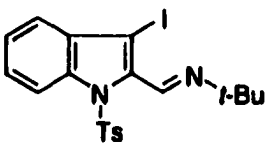
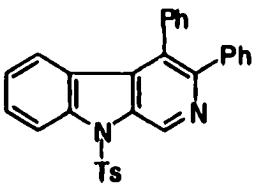
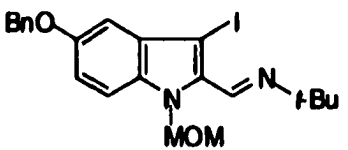
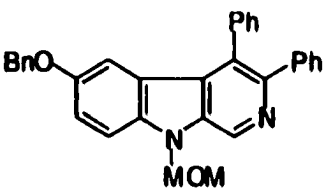
entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
14			B	24		31 + 24
15		Me—≡—TMS	A	1.5	 **20** + **21**	31 + 22
16		Ph—≡—*t*-Bu	A	1	 **22**	32
17		Me—≡—*t*-Bu	A	2	 **23**	trace
18	 **24**	Ph—≡—Ph	A	3	 **25**	80

Table 2. Continued

entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
19	 **26**	Ph—≡—Ph	A	5	 **27**	100
20	 **28**	Ph—≡—Ph	A	5	 **29**	32
21	 **30**	Ph—≡—Ph	A	1	 **31**	79

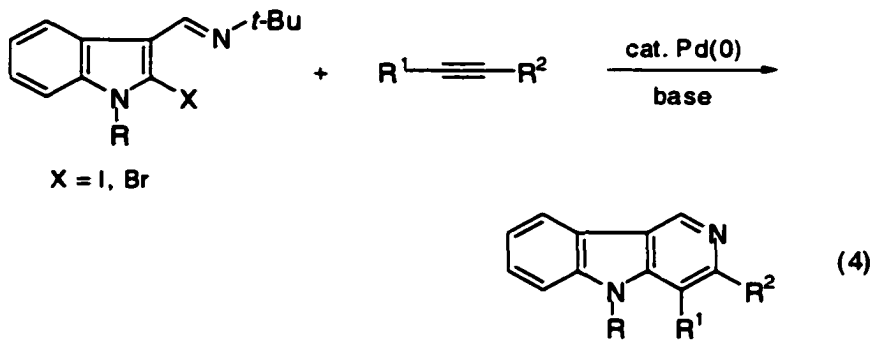
[a]Representative procedure for Conditions A: 5 mol % $Pd(OAc)_2$, 5 mol % PPh_3, *n*-Bu_3N (0.25 mmol), the acetylene (0.5 mmol), the imine (0.25 mmol), and DMF (5 mL) were placed in a 4 dram vial and heated at 100 °C for the indicated time. Conditions B: TBAC (0.25 mmol) was added to Conditions A. [b]The ratio was determined by ^1H NMR spectroscopic analysis.

(entries 2, 4, 6-8, 10, 11, 13 and 15). These results are consistent with our isoquinoline synthesis in which two regioisomers were also observed when an electron-rich imine was employed.[16] Interestingly, the poor regioselectivity can often be improved by simply adding 1 equiv of *n*-Bu_4NCl (TBAC) (Conditions B, also see the latter mechanistic discussion). For example, the annulation of imine **3** with ethyl 3-phenylpropiolate under Conditions B gave predominantly a single isomer (entry 3). The regioselectivity of reactions of imine **3** with 1-phenylpropyne and ethyl 2-butynoate improved from around 1:1 to about 3:1 and 2:1, respectively (entries 5 and 9). However, the regioselectivity of the annulation of phenyl(trimethylsilyl)acetylene by imine **3** under Conditions B remained essentially unchanged (compare entries 13 and 14). Therefore, the use of TBAC is not generally applicable for increasing the regioselectivity of this chemistry, which is believed to be highly sensitive to the nature of the internal alkyne. The annulation results from the reactions of phenyl(trimethylsilyl)acetylene or 1-trimethylsilyl-1-propyne and imine **3** (entries 13 and 15) were quite interesting, since these alkynes produced unexpected carboline products bearing the more hindered trimethylsilyl group in the 4-position as the major isomers, while the same alkynes afforded desilylated mono-substituted products in our isoquinoline synthesis.[16] This annulation chemistry also works on an alkyne bearing a bulky *tert*-butyl group. For example, 3,3-dimethyl-1-phenyl-1-butyne, which failed to afford any of the desired product in our isoquinoline synthesis,[16] produces only the unexpected isomer **22** in a 32% yield (entry 16), whose regiochemistry has been confirmed by its NOESY spectrum. When another *tert*-butyl-bearing alkyne, 4,4-dimethyl-2-pentyne, was employed in this annulation chemistry, it produced only a trace of the carboline product (entry 17). Quite possibly, the low boiling point of 4,4-dimethyl-2-pentyne (82 °C) results in loss of the acetylene from the reaction vessel under the reaction conditions and thus lowers the yield significantly.

Three other *N*-substituted indole imines were also employed in this palladium-catalyzed iminoannulation chemistry. The annulation of diphenylacetylene by the *N*-

methoxymethyl-, *N*-benzyl-, and *N*-tosyl-substituted imines **24**, **26**, and **28** under Conditions A afforded 80%, 100% and 32% yields of the desired products, respectively (entries 18-20). Finally, the annulation of diphenylacetylene by the 1-methoxymethyl-5-benzyloxy-substituted imine **30** under Conditions A was carried out, which generated the desired *β*-carboline **31** in a 79% yield (entry 21).

Encouraged by our success with the synthesis of *β*-carbolines, we have also investigated the palladium-catalyzed iminoannulation of internal acetylenes using 2-haloindole-3-methylene-*tert*-butylamines in order to synthesize substituted *γ*-carbolines (eq 4). The results of this investigation are summarized in Table 3.



(4)

The annulation reaction of the *tert*-butylimine of 2-iodo-1-methylindole-3-carboxaldehyde (**32**) and diphenylacetylene under Conditions A, which were quite successful in our *β*-carboline synthesis, was first examined. To our surprise, this reaction did not afford any of the desired product **33** (entry 1), but a 74% yield of the reduced product 1-methylindole-3-carboxaldehyde was obtained instead. This product apparently arises from the hydrolysis of 1-methylindole-3-methylene-*tert*-butylamine during the work-up. When 4-octyne was employed under the same reaction conditions, none of the desired product was observed either. Instead, the same reduced product was isolated in a 76% yield (entry 3). When the standard reaction conditions in our isoquinoline synthesis,[16] Conditions C, were employed in the annulation of diphenylacetylene by imine **32**, a messy reaction was observed and only a 24% yield of the desired product was obtained (entry 2). Surprisingly, the reaction of imine **32** with 4-octyne under Conditions C afforded a 78% yield of the

Table 3. Synthesis of γ-Carbolines by the Palladium-Catalyzed Annulation of Internal Alkynes (eq 4)[a]

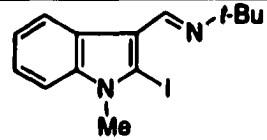
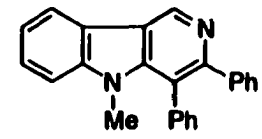
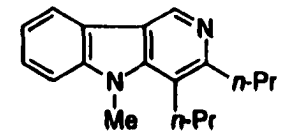
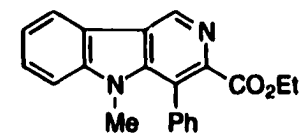
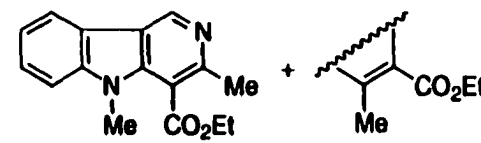
entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
1	 **32**	Ph—≡—Ph	A	24	 **33**	0[b]
2			C	48		24
3		*n*-Pr—≡—*n*-Pr	A	12	 **34**	0[c]
4			C	50		78
5		Ph—≡—CO_2Et	C	28	 **35**	72
6		Me—≡—CO_2Et	C	24	 **36** **37**	69 (1:7.5)[d]

Table 3. Continued

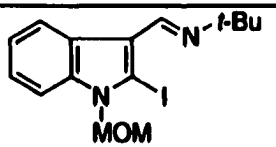
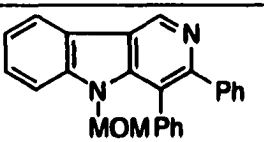
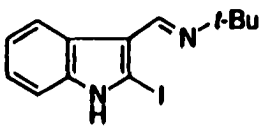
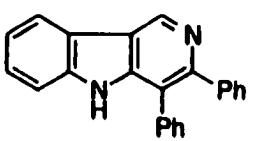
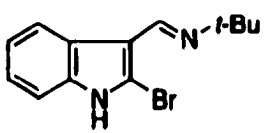
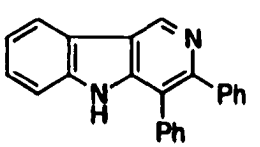
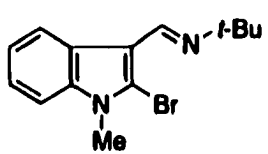
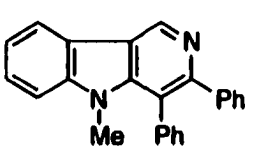
entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
7	 **38**	Ph—≡—Ph	C	96[a]	 **39**	40
8	 **40**	Ph—≡—Ph	C	96	 **41**	0
9			A	96		68
10	 **42**	Ph—≡—Ph	A	50	 **41**	41
11			C	96		0
12	 **43**	Ph—≡—Ph	A	96	 **33**	30

Table 3. Continued

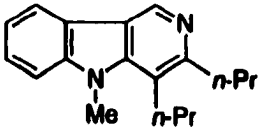
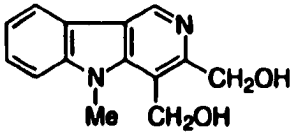
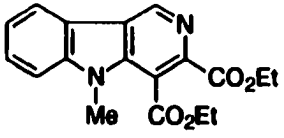
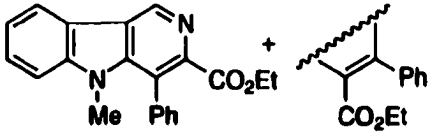
entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
13			C	96		58
14			C′	18		70
15		*n*-Pr—≡—*n*-Pr	C′	16	 **34**	67
16		HOH_2C—≡—CH_2OH	C′	20	 **44**	65
17		EtO_2C—≡—CO_2Et	C′	24	 **45**	49
18		Ph—≡—CO_2Et	C′	20	 **35** **46**	63 + 37

Table 3. Continued

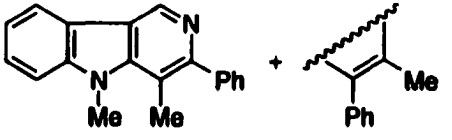
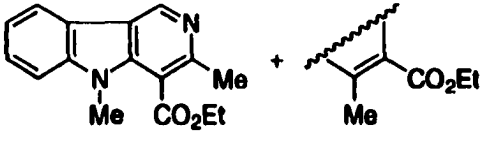
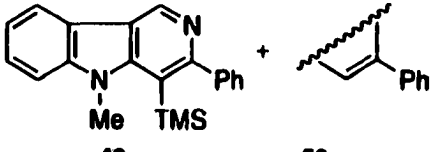
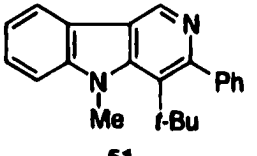
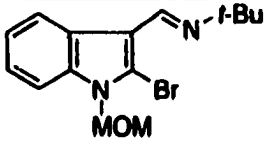
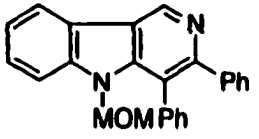
entry	imine	alkyne	Cond.	time (h)	product(s)	% isolated yield
19		Ph—≡—Me	C′	20	 **47** + **48**	49 + 51
20			C	72		44 + 45
21			C[g]	240		50 + 45
22			C[h]	20		29 + 34
23		Me—≡—CO_2Et	C′	20	 **36** + **37**	84 (1:2.4)[d]
24		Ph—≡—TMS	C′	20	 **49** + **50**	38 (1:5)[d]
25		Ph—≡—*t*-Bu	C′	45	 **51**	trace

Table 3. Continued

entry	imine	alkyne	cond.	time (h)	product(s)	% isolated yield
26	 **52**	Ph—≡—Ph	C[f]	72	 **39**	70

[a] Representative procedure for Conditions A: 5 mol % $Pd(OAc)_2$, 5 mol % PPh_3, *n*-Bu_3N (0.25 mmol), the acetylene (0.5 mmol), the imine (0.25 mmol), and DMF (5 mL) were placed in a 4 dram vial and heated at 100 °C for the indicated time. Conditions C: 10 mol % PPh_3, Na_2CO_3 as the base (0.25 mmol), everything else is the same as in Conditions A. [b] A 74% yield of the reduced product 1-methylindole-3-carboxaldehyde was isolated. [c] A 76% yield of the reduced product 1-methylindole-3-carboxaldehyde was isolated. [d] The ratio was determined by ^1H NMR spectroscopic analysis. [e] The reaction was run at 100 °C for 72 h and subsequently at 125 °C for 24 h. [f] The reaction was run at 125 °C. [g] The reaction was run at 85 °C. [h] 1 Equiv of TBAC was added and the reaction was run at 125 °C.

desired γ-carboline **34** (entry 4). Even more exciting was the observation that the annulation of ethyl 3-phenylpropiolate by imine **32** under Conditions C gave a single regioisomer bearing the phenyl group in the 4-position in a 72% yield (entry 5). When ethyl 2-butynoate was employed, two regioisomers in a 69% total yield, as well as a small amount of the corresponding reduced indolecarboxaldehyde product, were observed (entry 6). Unfortunately, when the alkynes 1-phenylpropyne, 3-phenyl-2-propyn-1-ol, diethyl acetylenedicarboxylate, phenyl(trimethylsilyl)acetylene and 3,3-dimethyl-1-phenyl-1-butyne were employed to this palladium-catalyzed iminoannulation with imine **32**, messy reactions and low yields were observed in all cases.

The annulation of diphenylacetylene by *N*-methoxymethyl-substituted imine **38** took 72 h at 100 °C and subsequently 24 h at 125 °C to reach completion and only 40% of the desired product **39** was isolated. Neither the *N*-benzyl nor the *N*-tosyl-substituted 2-iodoimines afforded any of the desired products when allowed to react with diphenylacetylene under Conditions C. Finally, the annulation reaction of the unsubstituted imine **40** and diphenylacetylene was examined under both Conditions C and A. Surprisingly, Conditions C didn't afford any recognizable product even after 96 h (entry 8). However, Conditions A, which have usually only given the reduced product, afforded a 68% yield of the desired γ-carboline **41** after 96 h (entry 9).

Since the 2-iodoindole imines **32**, **38**, and **40** didn't give very promising results in this palladium-catalyzed iminoannulation chemistry, the corresponding 2-bromoindole imines **42**, **43**, and **52** were prepared in order to examine their iminoannulation chemistry with internal alkynes. The annulation of diphenylacetylene by the unsubstituted 2-bromoindole imine **42** was first examined using Conditions A. This reaction gave the desired γ-carboline **41** in a 41% yield (entry 10). When the same reaction was run using Conditions C, none of the desired product was observed (entry 11). These results are consistent with the results from the annulation of diphenylacetylene by 2-iodoindole imine **40** (compare

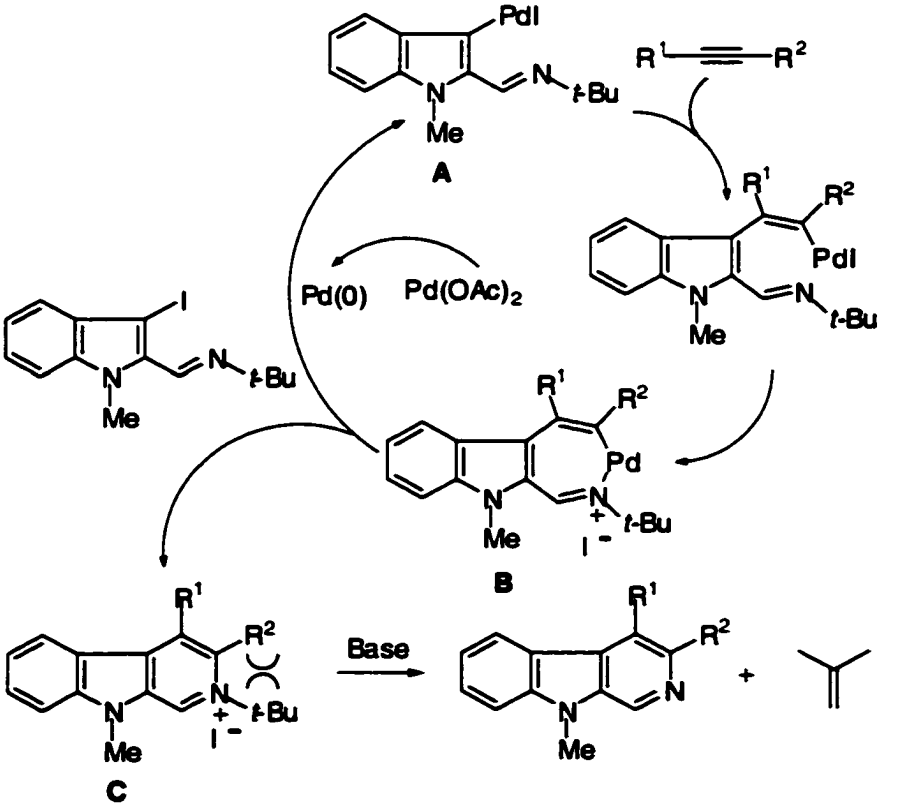
entries 8-11). Interestingly, the annulation of diphenylacetylene by 2-bromo-1-methylindole-3-methylene-*tert*-butylamine (**43**) under Conditions A gave a 30% yield of γ-carboline **33** (entry 12). The same reaction using Conditions C afforded a 58% yield of the desired product after 96 h (entry 13). When the temperature was increased to 125 °C, the reaction was complete in a much shorter time (18 h), producing a 70% yield of γ-carboline **33** (entry 14). Encouraged by this result, we examined the palladium-catalyzed iminoannulation of other internal alkynes by imine **43** under Conditions C at the elevated temperature of 125 °C. Symmetrical alkynes, such as 4-octyne, 2-butyne-1,4-diol, and diethyl acetylenedicarboxylate afforded the desired products in moderate to good yields (entries 15-17). However, when unsymmetrical alkynes were employed, this chemistry generally produced two regioisomers with poor regioselectivity (entries 18, 19, and 23). Ethyl 3-phenyl propiolate produced two regioisomers with the major isomer bearing the phenyl group in the 4-position (entry 18). 1-Phenyl-1-propyne afforded two regioisomers in approximately a 1:1 ratio (entry 19). We tried to improve the regioselectivity of the annulation of 1-phenyl-1-propyne by imine **43**, but none of our attempts gave any improved regioselectivity (entries 20-22). A screening of 88 different combinations of palladium catalysts and bases on this reaction using multiplexed capillary electrophoresis also failed to give reaction conditions, which afford both good regioselectivity and a good yield.[21] The annulation of ethyl 2-butynoate by imine **43** produced a mixture of two regioisomers in an 84% combined yield, with the major isomer having the ester group in the 3-position (entry 23). The reactions of two alkynes bearing sterically bulky groups, phenyl(trimethylsilyl)acetylene and 3,3-dimethyl-1-phenyl-1-butyne were then examined. The former alkyne gave a 1:5 mixture of γ-carboline **49** and its desilylated product **50** in a 38% combined yield (entry 24), and the latter didn't give any of the desired carboline product.

Finally, the *N*-methoxymethyl-substituted 2-bromoindole imine **52** was employed in the annulation of diphenylacetylene. The reaction gave a 70% yield of the desired product **39** (entry 26). It's noteworthy that the reaction of the

corresponding *N*-benzyl-substituted 2-bromoindole imine with diphenylacetylene didn't give a significant yield of the desired product, presumably because of the extra steric hindrance introduced by the benzyl group.

We propose a mechanism for this palladium-catalyzed iminoannulation chemistry, which is similar to our isoquinoline synthesis (Scheme 1).[16] Specifically, oxidative addition of the indole halide to Pd(0) produces an organopalladium intermediate **A**, which then undergoes alkyne insertion, producing a vinylic palladium intermediate, which then reacts with the neighboring imine substituent to form a 7-membered palladacyclic immonium salt **B**. Subsequent reductive elimination produces a *tert*-butylcarbolinium salt **C** and regenerates the catalyst Pd(0). As previously suggested by Heck,[22] the *tert*-butyl group of the *tert*-butylcarbolinium salt **C** apparently fragments to relieve the strain resulting from interaction with the substituent present in the 3-position.

Scheme 1



As mentioned earlier, the poor regioselectivity in our β-carboline synthesis can often be improved by simply adding one equiv TBAC (Table 2; entries 3, 5, and 9). Presumably, the chloride anion of the TBAC displaces the iodide in Pd(II) intermediate **A** and thus slows down the addition of intermediate **A** across the carbon-carbon triple bond of the alkyne, which was confirmed by the observation of prolonged reaction times (compare entries 2, 4, 8 and 13 with entries 3, 5, 9 and 14). Consequently, the reaction gives the more thermodynamically stable regioisomer as the major product.

It is now easy to understand why the annulation reaction of 3,3-dimethyl-1-phenyl-1-butyne by imine **3** produces only one isomer **22**. As previously mentioned, unsymmetrical alkynes usually give two regioisomers. However, in this case, this hindered alkyne is apparently unable to form the other regioisomer. To generate the other isomer, the corresponding vinylic Pd(II) intermediate has to undergo reductive elimination to generate a β-carbolinium salt having bulky *tert*-butyl groups in both the 2- and 3-positions. Apparently, the steric hindrance between these two *tert*-butyl groups disfavors formation of the anticipated β-carbolinium salt (see Figure 1).

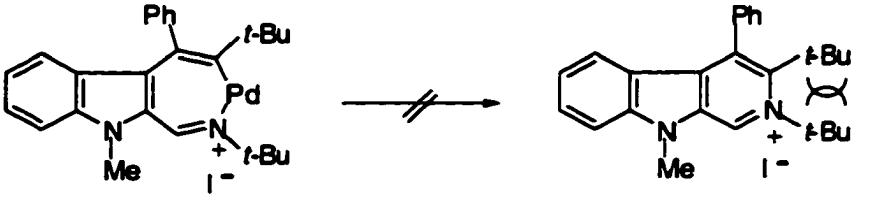


Figure 1. Formation of the β-carbolinium salt is disfavored due to steric hindrance.

It is also understandable why the reaction of 3,3-dimethyl-1-phenyl-1-butyne and imine **43** didn't afford any γ-carboline product. Very likely, the steric hindrance between the 2-*tert*-butyl, 3-phenyl, 4-*tert*-butyl and the 5-methyl groups prevents formation of the anticipated γ-carbolinium intermediate (see Figure 2).

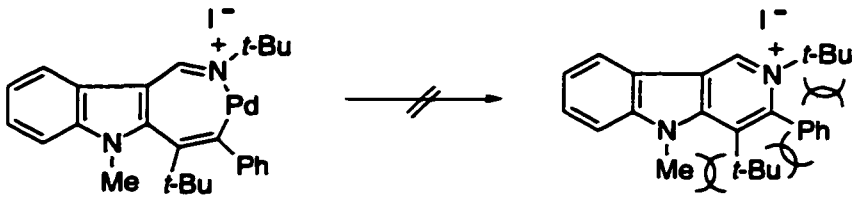


Figure 2. Formation of the γ-carbolinium salt is disfavored due to steric hindrance.

Thus far, our iminoannulation chemistry for the synthesis of β- and γ-carbolines has employed only internal alkynes. Although the palladium-catalyzed annulation of terminal alkynes has been rarely investigated,[23] we were determined to examine the palladium-catalyzed iminoannulation of terminal alkynes (Scheme 2) in order to broaden the scope and reduce the limitations of our iminoannulation chemistry. Previously, we have reported useful two-step approaches to the synthesis of β- and γ-carbolines involving the Sonogashira cross-coupling of terminal alkynes with the corresponding haloindolecarboxaldehydes, followed by imine formation with *t*-$BuNH_2$ and either CuI-catalyzed or thermal cyclization (Scheme 3).[4j,k] We hoped to be able to develop this approach into a more convenient one-step process. The results of this investigation are summarized in Table 4.

Scheme 2

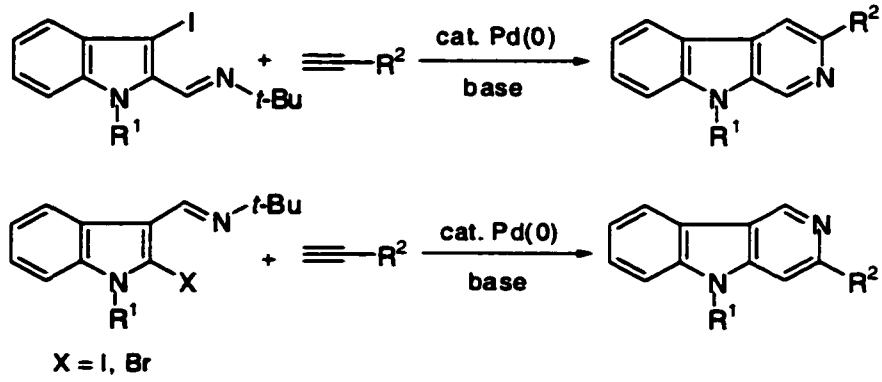


Table 4. Synthesis of β- and γ-Carbolines by the Palladium-Catalyzed Annulation of Terminal Alkynes[a]

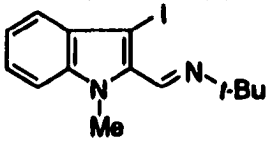
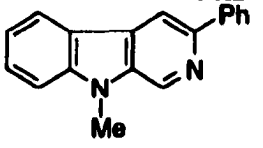
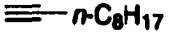
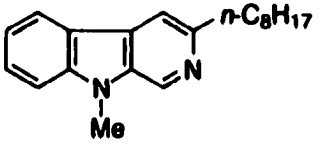
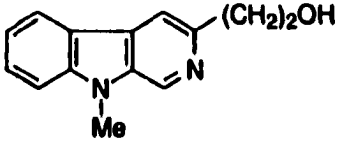
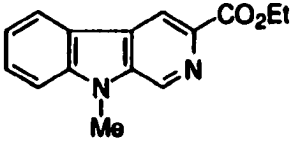
entry	imine	alkyne	cond.	time (h)	product	% isolated yield
1	 **3**		A	24	 **53**	43
2			A	24		33[b]
3			C	5		34
4			A	6	 **54**	32
5			A	7	 **55**	60
6			A	7	 **56**	trace

Table 4. Continued

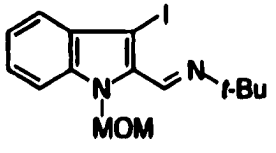
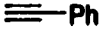
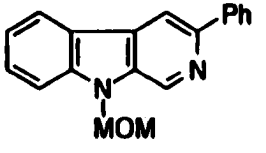
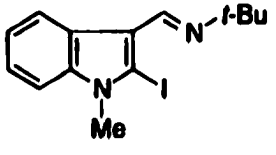
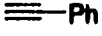
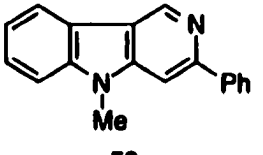
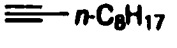
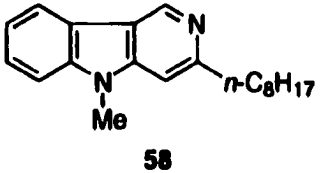
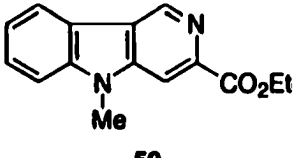
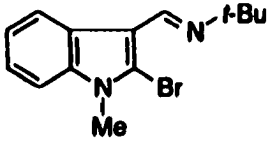
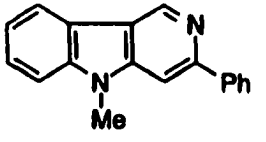
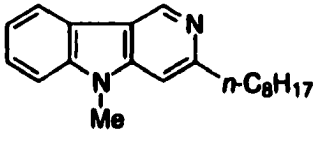
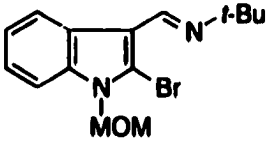
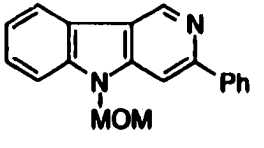
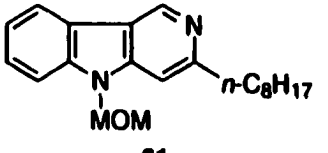
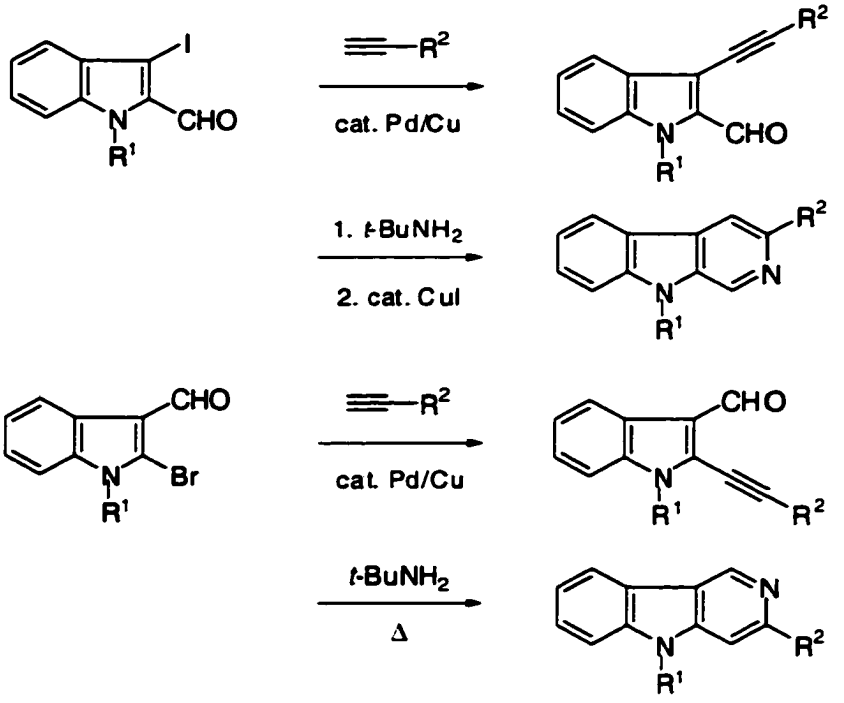
entry	imine	alkyne	cond.	time (h)	product	% isolated yield
7	 **24**		A	8	 **57**	44
8	 **32**		C	24	 **50**	56[c]
9			C	20	 **58**	42
10			C	20	 **59**	71

Table 4. Continued

entry	imine	alkyne	cond.	time (h)	product	% isolated yield
11	 **43**		C[d]	24	 **50**	70
12			C[d]	18	 **58**	64
13	 **52**		C[d]	24	 **60**	83
14			C[d]	16	 **61**	92

[a] Representative procedure for Conditions A: 5 mol % $Pd(OAc)_2$, 5 mol % PPh_3, *n*-Bu_3N (0.25 mmol), the acetylene (0.5 mmol), the imine (0.25 mmol), and DMF (5 mL) were placed in a 4 dram vial and heated at 100 °C for the indicated time. Conditions C: Na_2CO_3 (0.25 mmol) was used as the base. [b] CuI (2 mol %) was added. [c] An inseparable mixture of carboline **50** and an unidentified by-product was isolated. The yield was based on ^1H NMR spectroscopy. [d] The reaction was run at 125 °C.

Scheme 3

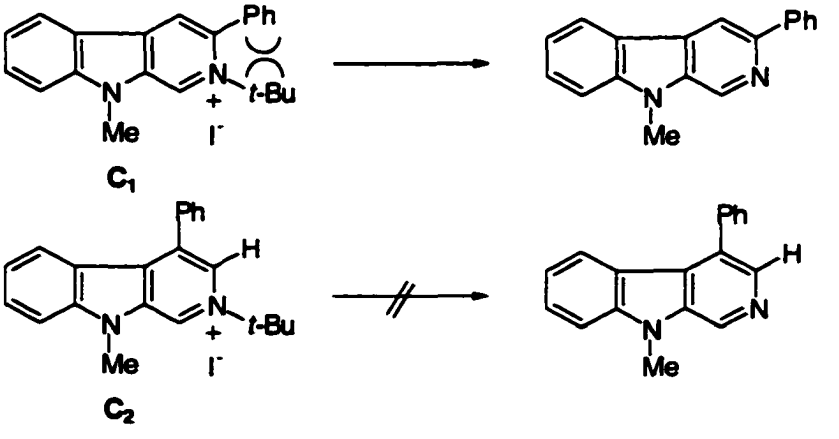


The annulation of imine **3** by phenylacetylene under our standard conditions for the synthesis of β-carbolines (Conditions A) was first examined. We were excited to see that only one regioisomer **53** was isolated, although in only a moderate 43% yield (Table 4, entry 1). Unfortunately, either adding 2 mol % of CuI to Conditions A or employing our standard conditions for the synthesis of γ-carbolines (Conditions C) afforded even lower yields of β-carboline **53** (entries 2 and 3). The reactions of 1-octyne and ethyl propiolate generated a low yield (32%) of β-carboline **54** and only a trace amount of the desired β-carboline **56**, respectively (entries 4 and 6). However, 3-butyn-1-ol afforded an appreciable 60% yield of the desired β-carboline **55** (entry 5). The annulation of phenylacetylene by the *N*-methoxymethyl protected imine **24** produced β-carboline **57** in a yield comparable to that of the methyl imine **3** (entry 7).

According to the mechanism we have proposed (Scheme 1), the annulation of imine **3** with a terminal acetylene, for example phenylacetylene, should generate two

isomeric *tert*-butylcarbolinium intermediate C_1 and C_2 (Scheme 4). As mentioned previously, the *tert*-butyl group of the *tert*-butylcarbolinium salt C_1 apparently fragments to relieve the strain resulting from interaction with the phenyl group present in the 3-position. However, the *tert*-butyl group of salt C_2 fails to fragment due to the lack of steric interaction between the *tert*-butyl group and the neighboring small hydrogen. Indeed, we have observed extremely polar and highly fluorescent compounds by TLC analysis in essentially every reaction mixture of the annulation of terminal alkynes by 3-iodoimines. These compounds were easily transferred into the aqueous layer during aqueous work-up. The evidence obtained from ^{1}H NMR spectra of the reaction mixture of imine **3** and phenylacetylene, and the contents in the aqueous layer after work-up also prove the existence of the corresponding *tert*-butylcarbolinium salt C_2. That's probably why most of the reactions of 3-iodoimines with terminal alkynes only produce moderate yields of carbolines. Moreover, terminal alkynes can undergo palladium-catalyzed homocoupling,[24] which might also decrease the yields of the annulation products.

Scheme 4



The annulation of two terminal alkynes, namely phenylacetylene and 1-octyne, by 2-iodoimine **32** only produced moderate yields of the γ-carboline products **50** and **58** under our standard γ-carboline conditions (Conditions C) (entries 8 and 9). Interestingly, ethyl propiolate afforded a 71% yield of the desired γ-carboline **59**

(entry 10). The relatively low yields might be a direct result of the 2-iodoimine **32** being reduced during the reaction, which has been observed in other reactions employing internal alkynes.

Surprisingly, when 2-bromoimine **43** was employed in the annulation reactions with phenylacetylene and 1-octyne at 125 °C, both reactions afforded reasonably good yields of the desired γ-carbolines **50** and **58** (entries 11 and 12). To our delight, the annulation of phenylacetylene and 1-decyne by *N*-methoxymethyl-substituted bromoimine **52** generated an 83% yield of γ-carboline **60** and a 92% yield of γ-carboline **61**, respectively. It is worth mentioning that we did not observe significant amounts of extremely polar and highly fluorescent compounds presumably corresponding to the isomeric *tert*-butylcarbolinium intermediates **C** (Figure 3) in the reactions employing 2-haloimines and terminal alkynes.

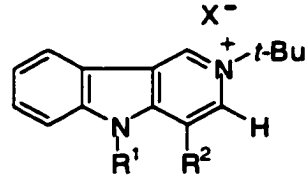


Figure 3. The isomeric *tert*-butyl-γ-carbolinium salts **C** were not observed.

As seen from the mechanism we have proposed (Scheme 1), the annulation of imine **43** and phenylacetylene should, for example, form two isomeric 7-membered palladacyclic immonium salts $\mathbf{B_1}$ and $\mathbf{B_2}$ as intermediates (Figure 4). However, salt $\mathbf{B_2}$ is more difficult to form due to steric interactions between the 4-phenyl and 5-methyl groups. Therefore, the energy difference between these two isomeric salts should be significant enough to result in the production of only one γ-carboline regioisomer. However, in the case of the annulation of imine **3** and phenylacetylene, because of the lack of steric interactions between the 4- and 5-positions, the energy difference between the two isomeric 7-membered palladacyclic immonium salts $\mathbf{B_3}$ and $\mathbf{B_4}$ should not be significant (Figure 4). Therefore, we are able to observe the *tert*-butyl-β-carbolinium salt $\mathbf{C_2}$ which arises from the reductive

elimination of Pd(0) from immonium salt $\mathbf{B_4}$ by TLC and NMR analysis, as mentioned earlier.

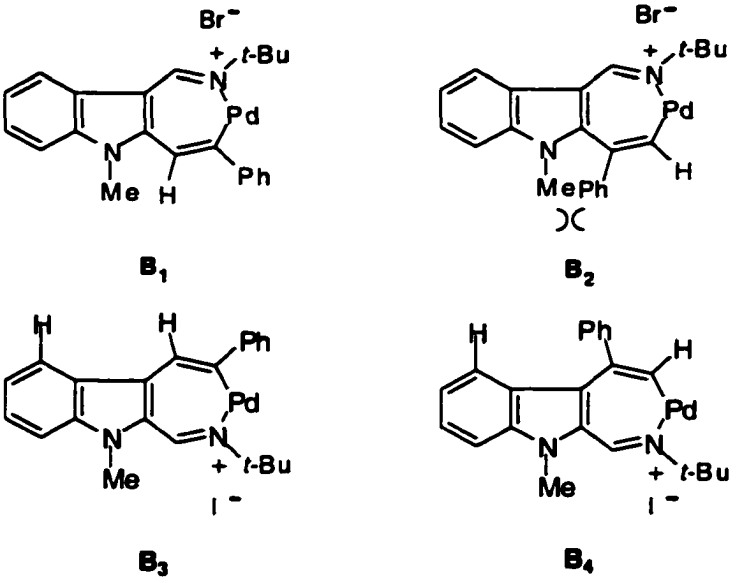
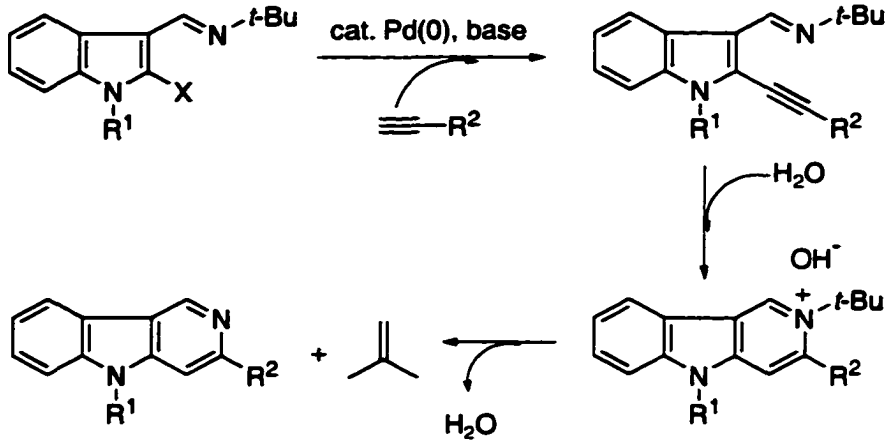


Figure 4. Salts $\mathbf{B_1}$ and $\mathbf{B_2}$ should have significantly different energy, but $\mathbf{B_3}$ and $\mathbf{B_4}$ should not.

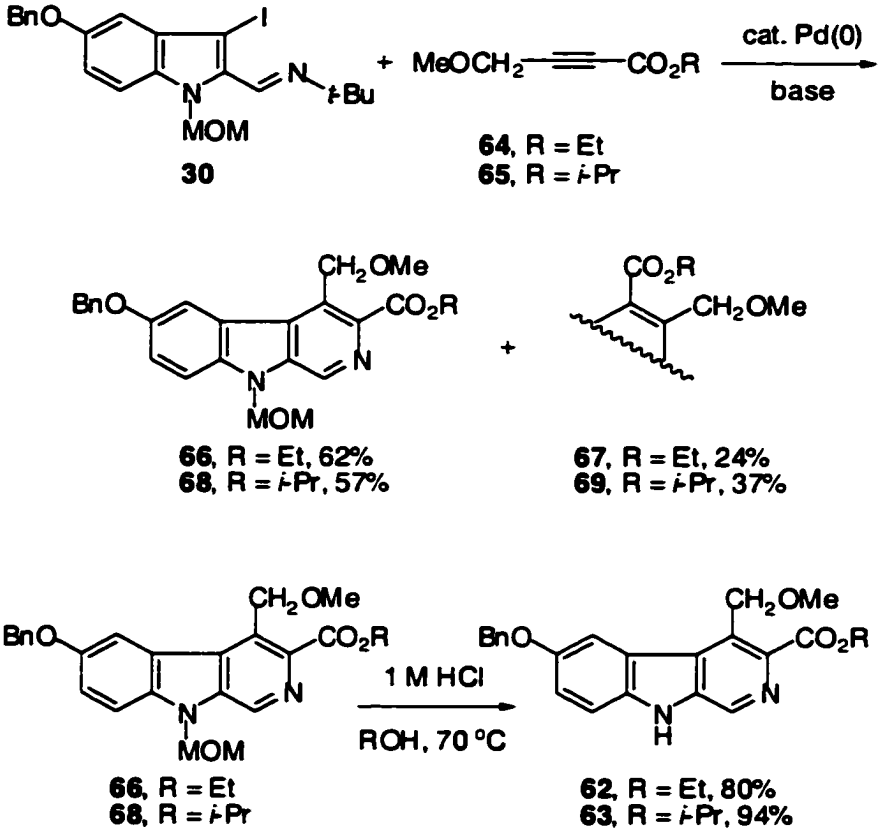
Alternatively, since only the 3-substituted γ-carboline product was observed, other mechanisms might be operating in this system. The following alternative mechanism may be envisioned for this transformation (Scheme 5). Specifically, the Sonogashira coupling of 2-haloindole imine with a terminal alkyne produces an intermediate 2-(1-alkynyl)indole imine, which can then be cyclized thermally in the presence of spurious amount of water, producing a *tert*-butylcarbolinium salt, which apparently fragments, producing the γ-carboline.[4k] Although we have been unable to observe the 2-(1-alkynyl)indole imine intermediate when the reaction of imine **52** and phenylacetylene was stopped after only 1 h, the mechanism proposed in Scheme 5 is still possible for this process and cannot be excluded.

Scheme 5



To demonstrate the versatility of this annulation chemistry, we have applied the palladium-catalyzed iminoannulation process to the synthesis of two biologically interesting *β*-carboline alkaloids ZK93423 (**62**) and abecarnil (ZK112119, **63**). ZK93423 is a full agonist at the wild type and recombinant $GABA_A$ receptor,[18] and abecarnil displays metabolically stable, anxioselective activity at benzodiazapine receptors and anticonvulsant properties.[19] Although the syntheses of ZK93423[18b,d] and abecarnil[19c] have been achieved previously, our approach may provide a useful alternative to existing methodology. Upon examination of the structures of ZK93423 and abecarnil, we felt that they could be synthesized by employing our palladium-catalyzed iminoannulation using 1-methoxymethyl-5-benzyloxy-substituted imine **30** and internal alkynes **64** and **65**, followed by acid-promoted deprotection of the *N*-methoxymethyl group (Scheme 6). Despite our concern that the annulation reactions might produce two regioisomers, we anticipated that the desired isomer would be the major one required for the synthesis of ZK93423 (**62**) and abecarnil (**63**).

Scheme 6



By employing the standard reaction conditions for our β-carboline synthesis (Conditions A), the annulation of ethyl 4-methoxy-2-butynoate (**64**) by imine **30** fortunately produced the desired β-carboline **66** in a 62% yield, along with a 24% yield of regioisomer **67**. It is noteworthy that when employing Conditions B, which contains one equiv of *n*-Bu_4NCl (TBAC), the same reaction generated a similar combined yield, but with decreased regioselectivity, presumably due to coordination of the 4-methoxy group to the palladium. Similarly, the annulation of isopropyl 4-methoxy-2-butynoate (**65**) by imine **30** under Conditions A afforded a 57% yield of the desired isomer **68**, as well as a 37% yield of regioisomer **69**. To avoid hydrolysis of the ethyl and isopropyl esters in the 3-position during acid-promoted deprotection of the *N*-methoxymethyl group, EtOH and *i*-PrOH were chosen as the solvents for deprotection of the β-carbolines **66** and **68**, respectively. The acid-promoted

deprotection proceeded smoothly at 70 °C, generating ZK93423 (**62**) in an 80% yield and abecarnil (**63**) in a 94% yield, respectively (Scheme 6).

Conclusions

An efficient, palladium-catalyzed synthesis of substituted β- and γ-carbolines from simple internal and terminal alkynes and the *tert*-butylimines of *N*-substituted 3-iodoindole-2-carboxaldehydes and 2-haloindole-3-carboxaldehydes has been developed. The best reaction conditions for the β-carboline synthesis employ 0.25 mmol of the *tert*-butylimine, 2 equiv of alkyne, 5 mol % of $Pd(OAc)_2$, 5 mol % of PPh_3 and 1 equiv of *n*-Bu_3N as the base in 5 mL of DMF at 100 °C. The preferred conditions for the γ-carboline synthesis employ 0.25 mmol of the *tert*-butylimine, 2 equiv of alkyne, 5 mol % of $Pd(OAc)_2$, 10 mol % of PPh_3 and 1 equiv of Na_2CO_3 as the base in 5 mL of DMF at 100 or 125 °C. A wide variety of aryl-, alkyl-, hydroxymethyl-, ethoxycarbonyl- and trimethylsilyl-substituted acetylenes undergo this process in moderate to excellent yields. When unsymmetrical internal alkynes are employed, mixtures of regioisomers are observed in most cases. When terminal alkynes are employed, only one regioisomer has been isolated. This annulation chemistry has also been successfully applied to the synthesis of two biologically interesting β-carboline alkaloids, ZK93423 and abecarnil (ZK112119).

Experimental Section

General. ^1H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. All reagents were used directly as obtained commercially unless otherwise noted. 3-Iodo-1-methylindole-2-carboxaldehyde, 2-bromo-1-methylindole-3-carboxaldehyde, 2-bromo-1-methoxylmethylindole-3-carboxaldehyde and compounds **1-6**, **11**, **16**, **24**, **25**, **32-35**, **39**, **43**, **44**, **46**, **50**, **52**, **53-55**, **57**, **58** and **60** have been previously

reported.[4k,17] 3-Iodo-1*H*-indole-2-carboxaldehyde,[25] 3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde,[25] and 2-bromo-1*H*-indole-3-carboxaldehyde[26] were prepared according to previous literature procedures. Following are the preparation and characterization of the starting materials 1-benzyl-3-iodoindole-2-carboxaldehyde, 3-iodo-1-tosylindole-2-carboxaldehyde, 5-benzyloxy-3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde, 2-iodo-1*H*-indole-3-carboxaldehyde, 2-iodo-1-(methoxymethyl)indole-3-carboxaldehyde, ethyl 4-methoxy-2-butynoate (**64**) and isopropyl 4-methoxy-2-butynoate (**65**).

1-Benzyl-3-iodoIndole-2-carboxaldehyde. This aldehyde was prepared as a white solid in 100% yield by the method used to prepare 3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde,[25] only employing 3-iodo-1*H*-indole-2-carboxaldehyde and benzyl iodide: mp 114-115 °C; ^{1}H NMR ($CDCl_3$) δ 5.84 (s, 2H), 7.08 (d, J = 6.8 Hz, 2H), 7.20-7.27 (m, 4H), 7.35 (d, J = 8.4 Hz, 1H), 7.43 (dt, J = 8.0, 0.4 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 10.00 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 48.0, 111.4, 122.1, 123.9, 126.6, 127.6, 128.5, 128.7, 130.0, 131.1, 137.4, 140.4, 184.5.

3-Iodo-1-tosylindole-2-carboxaldehyde. This aldehyde was prepared as a yellow solid in 73% yield by the method used to prepare 3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde,[25] only employing 3-iodo-1*H*-indole-2-carboxaldehyde and tosyl chloride: mp 155-156 °C; ^{1}H NMR ($CDCl_3$) δ 2.34 (s, 3H), 7.20 (d, J = 7.8 Hz, 2H), 7.39 (m, 1H), 7.53-7.60 (m, 2H), 7.66 (d, J = 7.8 Hz, 2H), 8.21 (d, J = 8.4 Hz, 1H), 10.42 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.9, 81.7, 115.8, 125.0, 125.6, 127.1, 130.1, 130.2, 132.5, 134.5, 134.7, 137.9, 146.1, 183.3.

5-Benzyloxy-3-iodo-1*H*-indole-2-carboxaldehyde. This aldehyde was prepared as a yellow solid in an overall 38% yield by the reaction sequence used to prepare 3-iodo-1*H*-indole-2-carboxaldehyde,[25] only starting with ethyl 5-benzyloxy-1*H*-indole-2-carboxylate:[27] mp 160-162 °C; ^{1}H NMR (acetone-d_6) δ 5.19 (s, 2H), 7.05 (d, J = 2.4 Hz, 1H), 7.16 (dd, J = 8.8, 2.4 Hz, 1H), 7.31 (t, J = 7.2 Hz, 1H), 7.39 (t, J = 7.2 Hz, 2H), 7.47 (d, J = 8.8 Hz, 1H), 7.52 (d, J = 7.2 Hz, 2H), 9.80 (s, 1H); ^{13}C

NMR (acetone-d_6) δ 70.2, 103.6, 114.5, 114.6, 120.4, 127.7, 127.8, 128.4, 130.9, 133.3, 134.2, 137.5, 154.9, 182.1.

5-Benzyloxy-3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde. This aldehyde was prepared as a yellow solid in 83% yield by the method used to prepare 3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde,[25] only employing 5-benzyloxy-3-iodo-1*H*-indole-2-carboxaldehyde and methoxymethyl chloride: mp 110-112 °C; ^{1}H NMR ($CDCl_3$) δ 3.28 (s, 3H), 5.15 (s, 2H), 5.94 (s, 2H), 7.03 (d, J = 2.4 Hz, 1H), 7.23 (dd, J = 9.0, 2.4 Hz, 1H), 7.35-7.52 (m, 6H), 9.98 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.3, 70.9, 74.9, 78.1, 104.7, 113.2, 121.5, 128.0, 128.4, 128.9, 130.9, 131.9, 136.0, 136.9, 155.5, 184.5.

2-Iodo-1*H*-indole-3-carboxaldehyde. $POCl_3$ (0.9 mL, 9.6 mmol) was added slowly by a syringe to ice-cooled dry DMF (10 mL). The solution, protected from moisture with a drying tube, was stirred for 15 min at room temperature and then recooled to around 0 °C. A solution of 2-iodoindole[28] (2.13 g, 8.76 mmol) in DMF (10 mL) was then added over 5 min. The mixture was stirred at room temperature for 3 h and then poured into ice water (50 mL). The yellow mixture was made alkaline with NaOH (1.5 g) in water (10 mL). The mixture was quickly boiled for 1 min and extracted with ether. The organic phase was washed with water and dried over Na_2SO_4. The solvent was removed under vacuum and the residue was chromatographed using 3:1 hexanes:EtOAc to afford a yellow solid (1.66 g, 70%): mp 218-219 °C (decomp); ^{1}H NMR (acetone-d_6) δ 7.24-7.32 (m, 2H), 7.45-7.48 (m, 1H), 8.17-8.19 (m, 1H), 10.11 (s, 1H), 11.75 (s, 1H); ^{13}C NMR (acetone-d_6) δ 90.0, 112.3, 113.7, 121.4, 123.7, 124.9, 125.7, 135.8, 183.9.

2-Iodo-1-(methoxymethyl)indole-3-carboxaldehyde. This aldehyde was prepared as a yellow oil in 67% yield by the method used to prepare 3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde,[25] only employing 2-iodo-1*H*-indole-3-carboxaldehyde and methoxymethyl chloride: ^{1}H NMR ($CDCl_3$) δ 3.30 (s, 3H), 5.50 (s, 2H), 7.27-7.34 (m, 2H), 7.38-7.45 (m, 1H), 8.21-8.28 (m, 1H), 10.10 (s, 1H); ^{13}C

NMR ($CDCl_3$) δ 56.8, 74.4, 110.5, 114.0, 121.5, 124.1, 124.6, 124.8, 136.0, 136.5, 184.6.

Ethyl 4-methoxy-2-butynoate (64). A hexane solution of *n*-BuLi (2.5 M, 3.6 mL) was added to a THF (20 mL) solution of methyl propargyl ether (0.526 g, 7.5 mmol) at – 78 °C under Ar and the mixture was stirred for 30 min. Ethyl chloroformate (0.977 g, 1.2 equiv) in THF (10 mL) was added. After stirring at – 78 °C for 1 h, the reaction was quenched by satd. aq. NH_4Cl and extracted by EtOAc. The organic phase was washed with brine, dried over Na_2SO_4 and evaporated. The residue was chromatographed using 7:1 hexanes/EtOAc to afford a colorless oil (0.876 g, 82%): ^1H NMR ($CDCl_3$) δ 1.32 (t, J = 7.2 Hz, 3H), 3.42 (s, 3H), 4.24 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 14.0, 58.1, 59.4, 62.1, 78.2, 83.0, 153.1.

Isopropyl 4-methoxy-2-butynoate (65). This ester was prepared as a colorless oil in 52% yield by the method used to prepare ethyl 4-methoxy-2-butynoate (**64**), only employing methyl propargyl ether and isopropyl chloroformate: ^1H NMR ($CDCl_3$) δ 1.30 (d, J = 6.4 Hz, 6H), 3.42 (s, 3H), 4.23 (s, 2H), 5.10 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 58.1, 59.4, 70.1, 78.6, 82.6, 152.7.

Imines Prepared.

1-Benzyl-3-iodoindole-2-methylene-*tert*-butylamine (26). The imine was prepared by the method used to prepare **1**,[17] only employing 1-benzyl-3-iodoindole-2-carboxaldehyde (180 mg, 0.5 mmol). Removal of the solvent afforded 210 mg (100%) of the imine as a yellow viscous oil: ^1H NMR ($CDCl_3$) δ 1.22 (s, 9H), 6.06 (s, 2H), 7.05 (d, J = 6.8 Hz, 2H), 7.15-7.22 (m, 4H), 7.27-7.31 (m, 2H), 7.51 (d, J = 8.0 Hz, 1H), 8.49 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 28.4, 47.0, 57.2, 67.4, 109.5, 119.8, 121.0, 124.0, 125.6, 125.8, 127.2, 129.0, 131.8, 137.6, 138.6, 147.7; IR (neat, cm^{-1}) 3061, 2967; HRMS calcd for $C_{20}H_{21}IN_2$: 416.0750. Found: 416.0757.

3-Iodo-1-tosylindole-2-methylene-*tert*-butylamine (28). This imine was prepared by the method used to prepare imine **1**,[17] only employing 3-iodo-1-tosylindole-2-carboxaldehyde (212 mg, 0.5 mmol). Removal of the solvent afforded

240 mg (100%) of the imine as a yellow viscous oil: ^{1}H NMR ($CDCl_3$) δ 1.44 (s, 9H), 2.30 (s, 3H), 7.15 (d, *J* = 8.0 Hz, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.37-7.43 (m, 2H), 7.60 (d, *J* = 8.0 Hz, 2H), 8.10 (d, *J* = 8.0 Hz, 1H), 8.59 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.6, 29.6, 59.2, 73.9, 114.8, 123.3, 124.6, 126.8, 126.9, 129.9, 132.8, 134.6, 135.7, 136.2, 145.3, 148.7; IR (neat, cm^{-1}) 3022, 2964; HRMS calcd for $C_{20}H_{21}IN_2O_2S$: 480.0369. Found: 480.0375.

5-Benzyloxy-3-iodo-1-(methoxymethyl)indole-2-methylene-*tert*-butylamine (30). This imine was prepared by the method used to prepare imine **1**,[17] only employing 5-benzyloxy-3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde (463 mg, 1.1 mmol). Removal of the solvent afforded 524 mg (100%) of the imine as a yellow solid: mp 97-98 °C; ^{1}H NMR ($CDCl_3$) δ 1.33 (s, 9H), 3.27 (s, 3H), 5.14 (s, 2H), 6.21 (s, 2H), 7.00 (d, *J* = 2.4 Hz, 1H), 7.08 (dd, *J* = 9.0, 2.4 Hz, 1H), 7.33-7.52 (m, 6H), 8.48 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.8, 55.8, 58.7, 70.3, 71.0, 74.7, 104.6, 112.5, 117.1, 128.0, 128.2, 128.8, 131.0, 133.9, 135.1, 137.4, 149.3, 154.9; IR (neat, cm^{-1}) 3017, 2969, 2927; HRMS calcd for $C_{22}H_{25}IN_2O_2$: 476.0961. Found: 476.0971.

2-Iodo-1-(methoxymethyl)indole-3-methylene-*tert*-butylamine (38). This imine was prepared by the method used to prepare imine **1**,[17] only employing 2-iodo-1-(methoxymethyl)indole-3-carboxaldehyde (157 mg, 0.5 mmol). Removal of the solvent afforded 185 mg (100%) of the imine as a pale yellow solid: mp 108-110 °C; ^{1}H NMR ($CDCl_3$) δ 1.34 (s, 9H), 3.29 (s, 3H), 5.55 (s, 2H), 7.22-7.30 (m, 2H), 7.40-7.43 (m, 1H), 8.50-8.54 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 30.0, 56.1, 57.4, 73.9, 109.5, 112.0, 122.3, 122.4, 123.6, 125.4, 128.9, 136.2, 148.3; IR (neat, cm^{-1}) 3054, 2964; HRMS calcd for $C_{15}H_{19}IN_2O$: 370.0542. Found: 370.0547.

2-Iodo-1*H*-indole-3-methylene-*tert*-butylamine (40). This imine was prepared by the method used to prepare imine **1**,[17] only employing 2-iodo-1*H*-indole-3-carboxaldehyde (215 mg, 0.79 mmol) for 6 h. Removal of the solvent afforded 260 mg (100%) of the imine as a pale yellow solid: mp 155-157 °C; ^{1}H NMR ($CDCl_3$) δ 1.49 (s, 9H), 7.16-7.26 (m, 2H), 7.40 (d, *J* = 6.8 Hz, 1H), 7.58 (d, *J* = 7.6 Hz, 1H), 7.76 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.1, 54.7, 117.8 (broad), 119.6 (broad), 123.0,

124.3 (broad), 144.0 (broad). The ^{13}C NMR spectrum of compound **40** gives incomplete (four sp^2 carbons missing) and unusually broad peaks for the indole ring, even when the background noise is very low; IR (neat, cm^{-1}) 3184, 3052, 2974, 1635; HRMS calcd for $C_{13}H_{15}IN_2$: 326.0280. Found: 326.0286.

2-Bromo-1*H*-indole-3-methylene-*tert*-butylamine (42). This imine was prepared by the method used to prepare imine **1**,[17] only employing 2-bromo-1-*H*-indole-3-carboxaldehyde (223 mg, 1.0 mmol) for 6 h. Removal of the solvent afforded 278 mg (100%) of the imine as a yellow solid: mp 152-153 °C; ^1H NMR ($CDCl_3$) δ 1.49, 7.15-7.26 (m, 2H), 7.44 (d, J = 6.9 Hz, 1H), 7.58-7.61 (m, 1H), 7.75 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.3, 55.0, 117.6 (broad), 119.6, 123.2, 124.4, 145.3 (broad), 145.9 (broad). The ^{13}C NMR spectrum of compound **42** gives incomplete (three sp^2 carbons missing) and unusually broad peaks for the indole ring, even when the background noise is very low, which is very similar to compound **40**; IR (neat, cm^{-1}) 3181, 3054, 2971, 1633; HRMS calcd for $C_{13}H_{15}BrN_2$: 278.0419. Found: 278.0423.

General Procedure for the Palladium-Catalyzed Formation of Carbolines. Conditions A: DMF (5 mL), $Pd(OAc)_2$ (3.0 mg, 0.013 mmol), PPh_3 (3.3 mg, 0.013 mmol), *n*-Bu_3N (47 mg, 0.25 mmol), and the alkyne (0.5 mmol) [Conditions B: *n*-Bu_4NCl (TBAC, 46 mg, 0.25 mmol), everything else is the same as in Conditions A. Conditions C: PPh_3 (6.5 mg, 0.025 mmol), Na_2CO_3 instead of *n*-Bu_3N (26.5 mg, 0.25 mmol), everything else is the same as in Conditions A] were placed in a 4 dram vial. The contents were then stirred for 1 minute and the appropriate imine (0.25 mmol) was added. The vial was flushed with Ar and heated in an oil bath at 100 or 125 °C for the indicated period of time. The completion of the reactions was established by the observation of palladium black. The reaction mixture (except entries 10 and 11 in Table 2 and entry 16 in Table 3, which afford fairly water soluble carbolines) was cooled, diluted with ether, washed with satd aq NH_4Cl, dried (Na_2SO_4), and filtered. The solvent was evaporated under reduced pressure and the product was isolated

by chromatography on a silica gel column. The reaction mixtures of entries 10 and 11 in Table 1 and entry 16 in Table 3 were filtered, the solvent was removed directly under reduced pressure, and the residue was purified by chromatography.

Carbolines Prepared

4,9-Dimethyl-3-phenyl-9*H*-pyrido[3,4-*b*]indole (7). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 34 mg (49%) of the indicated compound as a white solid: mp 179-180 °C; ^{1}H NMR (acetone-d_6) δ 2.89 (s, 3H), 4.06 (s, 3H), 7.30-7.42 (m, 2H), 7.45-7.51 (m, 2H), 7.60-7.71 (m, 4H), 8.33 (d, J = 7.8 Hz, 1H), 8.92 (s, 1H); ^{13}C NMR (acetone-d_6) δ 17.8, 110.4, 120.4, 122.8, 124.7, 124.9, 127.7, 128.3, 128.4, 128.6, 130.3, 131.0, 136.9, 142.6, 143.0, 149.3 (one sp^3 carbon missing due to overlap); IR (neat, cm^{-1}) 3058, 2924; HRMS calcd for $C_{19}H_{16}N_2$: 272.1314. Found: 272.1318.

3,9-Dimethyl-4-phenyl-9*H*-pyrido[3,4-*b*]indole (8). The reaction mixture was chromatographed using EtOAc to afford 29 mg (42%) of the indicated compound as a white solid: mp 117-119 °C; ^{1}H NMR (acetone-d_6) δ 2.42 (s, 3H), 4.02 (s, 3H), 6.85-6.95 (m, 2H), 7.40-7.85 (m, 7H), 8.89 (s, 1H); ^{13}C NMR (acetone-d_6) δ 22.3, 29.5, 110.2, 119.7, 121.7, 123.7, 127.7, 128.5, 128.6, 129.5, 129.9, 130.0, 131.2, 132.7, 139.9, 143.1, 145.2; IR (neat, cm^{-1}) 3053, 2924; HRMS calcd for $C_{19}H_{16}N_2$: 272.1314. Found: 272.1318. The regiochemistry of carbolines **7** and **8** was determined by comparison of the spectral data for these compounds with those of carboline **4**.[17] Compared to the chemical shift of 5-H in carboline **7**, the chemical shift of 5-H in carboline **8** is shifted to higher field by 0.7 ppm, which is due to the phenyl group present in the 4-position of carboline **8**.

4-Hydroxymethyl-9-methyl-3-phenyl-9*H*-pyrido[3,4-*b*]indole (9). The reaction mixture was chromatographed using 1:3 hexanes/EtOAc to afford 26 mg (36%) of the indicated compound as a white solid: mp 193-195 °C; ^{1}H NMR (DMSO-d_6) δ 3.98 (s, 3H), 4.93 (s, 1H), 5.40 (s, 1H), 7.28 (t, J = 7.2 Hz, 1H), 7.35-7.47 (m, 3H), 7.61 (t, J = 7.2 Hz, 1H), 7.69 (d, J = 7.6 Hz, 3H), 8.41 (d, J = 7.6 Hz, 1H), 9.02

(s, 1H); ^{13}C NMR (DMSO-d_6) δ 29.8, 59.4, 110.3, 120.0, 120.9, 125.4, 126.7, 127.7, 128.2, 128.3, 128.4, 130.4, 132.0, 136.5, 141.1, 142.3, 148.2; IR (neat, cm^{-1}) 3214, 3056, 2925; HRMS calcd for $C_{19}H_{16}N_2O$: 288.1263. Found: 288.1268.

3-Hydroxymethyl-9-methyl-4-phenyl-9*H*-pyrido[3,4-*b*]indole (10). The reaction mixture was chromatographed using 1:1 EtOAc/acetone to afford 31 mg (43%) of the indicated compound as a white solid: mp 278-280 °C; ^{1}H NMR (acetone-d_6) δ 4.08 (s, 3H), 4.44 (s, 1H), 4.53 (s, 2H), 6.95-7.01 (m, 2H), 7.47-7.50 (m, 2H), 7.52-7.56 (m, 1H), 7.59-7.66 (m, 4H), 9.01 (s, 1H); ^{13}C NMR (acetone-d_6) δ 62.5, 110.4, 120.1, 121.8, 124.0, 128.3, 129.0, 129.1, 129.2, 129.9, 130.1, 130.6, 137.8, 143.7, 146.6 (one sp^3 and one sp^2 carbon missing due to overlap); IR (neat, cm^{-1}) 3195, 3056, 2922; HRMS calcd for $C_{19}H_{16}N_2O$: 288.1263. Found: 288.1268. The regiochemistry of carbolines **9** and **10** was determined by comparison of the spectral data for these compounds with those of carboline **4**.[17] Compared to the chemical shift of 5-H in carboline **9**, the chemical shift of 5-H in carboline **10** is shifted to higher field by 0.7 ppm, which is due to the phenyl group present in the 4-position of carboline **10**.

Ethyl 3,9-dimethyl-9*H*-pyrido[3,4-*b*]indole-4-carboxylate (12) and ethyl 4,9-dimethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (13). The reaction mixture was chromatographed using 1:3 hexanes/EtOAc to afford 49 mg (73%) of the indicated compounds as a yellow solid (1:1 inseparable mixture of isomers). ^{1}H NMR (acetone-d_6) δ 1.41 (t, J = 7.2 Hz, 3H), 1.46 (t, J = 7.2 Hz, 3H), 2.68 (s, 3H), 3.03 (s, 3H), 4.02 (s, 3H), 4.05 (s, 3H), 4.40 (q, J = 7.2 Hz, 2H), 4.61 (q, J = 7.2 Hz, 2H), 7.25 (m, 1H), 7.35 (m, 1H), 7.65 (m, 4H), 8.09 (d, J = 8.1 Hz, 1H), 8.35 (d, J = 8.1 Hz, 1H), 8.86 (s, 1H), 8.96 (s, 1H); ^{13}C NMR (acetone-d_6) δ 14.5, 14.7, 16.5, 22.6, 29.7, 61.3, 62.2, 110.6, 110.8, 120.1, 120.4, 121.0, 121.2, 122.6, 124.1, 124.7, 125.9, 127.7, 128.7, 129.5, 130.1, 132.7, 133.6, 136.3, 138.0, 142.9, 143.3, 144.7, 168.3, 169.4; IR (neat, cm^{-1}) 3055, 2927, 1717; HRMS calcd for $C_{16}H_{16}N_2O_2$: 268.1212. Found: 268.1217.

4-Hydroxymethyl-3,9-dimethyl-9*H*-pyrido[3,4-*b*]indole (14) and 3-hydroxymethyl-4,9-dimethyl-9*H*-pyrido[3,4-*b*]indole (15). The reaction mixture was chromatographed using acetone to afford 68 mg (100%) of a 1:1 inseparable mixture of the indicated compounds as an off-white solid. ^{1}H NMR (DMSO-d_6) δ 2.70 (s, 3H), 2.82 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 4.79 (s, 2H), 5.04 (s, 2H), 5.05 (s, 1H), 5.23 (s, 1H), 7.23-7.31 (m, 2H), 7.55-7.70 (m, 4H), 8.28 (d, J = 8.0 Hz, 1H), 8.33 (d, J = 8.0 Hz, 1H), 8.78 (s, 1H), 8.81 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 15.3, 21.7, 29.6, 29.7, 58.4, 63.8, 110.1, 110.3, 119.6, 119.9, 120.6, 121.5, 124.1, 125.1, 125.5, 127.3, 127.5, 128.1, 128.2, 128.6, 130.9, 136.4, 136.6, 142.1, 142.2, 145.5, 147.6; IR (neat, cm^{-1}) 3350, 3012, 2924; HRMS calcd for $C_{14}H_{14}N_2O$: 226.1106. Found: 226.1111.

Diethyl 9-methyl-9*H*-pyrido[3,4-*b*]indole-3,4-dicarboxylate (17). The reaction was carried out under conditions A (Table 2, entry 12) and the mixture was chromatographed using 1:4 hexanes/EtOAc to afford 40 mg (49%) of the indicated compound as a white solid: mp 154-155 °C; ^{1}H NMR (acetone-d_6) δ 1.41 (t, J = 7.2 Hz, 3H), 1.43 (t, J = 7.2 Hz, 3H), 4.13 (s, 3H), 4.41 (q, J = 7.2 Hz, 2H), 4.59 (q, J = 7.2 Hz, 3H), 7.36 (t, J = 7.2 Hz, 1H), 7.69-7.77 (m, 2H), 8.12 (d, J = 8.0 Hz, 1H), 9.12 (s, 1H); ^{13}C NMR (acetone-d_6) δ 14.7, 15.0, 62.3, 62.9, 111.6, 120.7, 121.9, 124.1, 125.4, 126.0, 130.5, 133.6, 136.4, 139.0, 143.7, 166.8, 168.5; IR (neat, cm^{-1}) 2987, 1734, 1718; HRMS calcd for $C_{18}H_{18}N_2O_4$: 326.1267. Found: 326.1273.

9-Methyl-3-phenyl-4-trimethylsilyl-9*H*-pyrido[3,4-*b*]indole (18). The reaction mixture was chromatographed using 1.5:1 hexanes/EtOAc to afford 28 mg (34%) of the indicated compound as a yellow solid: mp 138-140 °C; ^{1}H NMR (acetone-d_6) δ 0.21 (s, 9H), 4.06 (s, 3H), 7.31 (m, 1H), 7.40-7.49 (m, 3H), 7.55-7.70 (m, 4H), 8.32 (dd, J = 8.1, 0.9 Hz, 1H), 9.01 (s, 1H); ^{13}C NMR (acetone-d_6) δ 1.0, 28.8, 110.0, 118.9, 121.9, 124.6, 125.8, 127.6, 127.87, 127.9, 130.7, 132.2, 134.0, 135.3, 142.6, 146.1, 156.3; IR (neat, cm^{-1}) 3057, 2932; HRMS calcd for $C_{21}H_{22}N_2Si$: 330.1552. Found: 330.1557.

9-Methyl-4-phenyl-3-trimethylsilyl-9*H*-pyrido[3,4-*b*]indole (19). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford 21 mg (25%) of the indicated compound as a yellow oil: ^{1}H NMR (acetone-d_6) δ 0.04 (s, 9H), 4.05 (s, 3H), 6.83 (d, J = 7.8 Hz, 1H), 6.94 (dt, J = 7.8, 0.9 Hz, 1H), 7.42-7.46 (m, 2H), 7.51 (dd, J = 7.2, 1.2 Hz, 1H), 7.58-7.63 (m, 4H), 9.17 (s, 1H); ^{13}C NMR (acetone-d_6) δ -0.04, 28.9, 109.6, 119.4, 121.2, 123.1, 125.2, 127.8, 128.2, 128.6, 130.1, 132.1, 136.3, 138.2, 139.9, 141.8, 151.5; IR (neat, cm^{-1}) 3055, 2953; HRMS calcd for $C_{21}H_{22}N_2Si$: 330.1552. Found: 330.1557. The regiochemistry of carbolines **18** and **19** was determined by comparison of the spectral data for these compounds with those of carboline **4**.[17] Compared to the chemical shift of 5-H in carboline **18**, the chemical shift of 5-H in carboline **19** is shifted to higher field by 0.7 ppm, which is due to the phenyl group present in the 4-position of carboline **19**.

3,9-Dimethyl-4-trimethylsilyl-9*H*-pyrido[3,4-*b*]indole (20). The reaction mixture was chromatographed using 1:3 hexanes/EtOAc to afford 21 mg (31%) of the indicated compound as a yellow solid: mp 186-187 °C; ^{1}H NMR (acetone-d_6) δ 0.61 (s, 9H), 2.80 (s, 3H), 3.99 (s, 3H), 7.22-7.28 (m, 1H), 7.56-7.64 (m, 2H), 8.27 (d, J = 8.4 Hz, 1H), 8.87 (s, 1H); ^{13}C NMR (acetone-d_6) δ 1.9, 27.4, 28.6, 109.7, 118.5, 121.3, 124.0, 126.2, 127.6, 132.3, 133.1, 135.1, 142.5, 151.6; IR (neat, cm^{-1}) 3027, 2922; HRMS calcd for $C_{16}H_{20}N_2Si$: 268.1396. Found: 268.1400.

4,9-Dimethyl-3-trimethylsilyl-9*H*-pyrido[3,4-*b*]indole (21). The reaction mixture was chromatographed using 1:1.5 hexanes/EtOAc to afford 15 mg (22%) of the indicated compound as a yellow oil: ^{1}H NMR (acetone-d_6) δ 0.43 (s, 9H), 2.97 (s, 3H), 3.99 (s, 3H), 7.28-7.32 (m, 1H), 7.58-7.65 (m, 2H), 8.27 (d, J = 8.0 Hz, 1H), 8.99 (s, 1H); ^{13}C NMR (acetone-d_6) δ -0.2, 17.8, 109.4, 119.5, 121.7, 123.7, 125.4, 127.3, 130.5, 133.3, 136.5, 141.4, 151.8 (one sp^3 carbon missing due to overlap); IR (neat, cm^{-1}) 3030, 2924; HRMS calcd for $C_{16}H_{20}N_2Si$: 268.1396. Found: 268.1400. The regiochemistry of carboline **21** was determined from its NOESY spectrum.

4-*tert*-Butyl-9-methyl-3-phenyl-9*H*-pyrido[3,4-*b*]indole (22). The reaction mixture was chromatographed using 1:2 hexanes/EtOAc to afford 25 mg (32%) of

the indicated compound as a yellow solid: mp 152-154 °C; ^{1}H NMR ($CDCl_3$) δ 1.55 (s, 9H), 3.99 (s, 3H), 7.33-7.42 (m, 6H), 7.54 (d, *J* = 8.0 Hz, 1H), 7.63 (t, *J* = 7.6 Hz, 1H), 8.48 (d, *J* = 8.4 Hz, 1H), 8.82 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.4, 32.6, 36.1, 109.3, 119.0, 121.2, 126.9, 127.2, 127.6, 127.7, 128.5, 128.9, 129.8, 136.6, 137.8, 142.1, 146.2, 148.4. The regiochemistry of carboline **22** was determined from its NOESY spectrum. IR (neat, cm^{-1}) 3010, 2926; HRMS calcd for $C_{22}H_{22}N_2$: 314.1783. Found: 314.1787.

9-Benzyl-3,4-diphenyl-9*H*-pyrido[3,4-*b*]indole (27). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 103 mg (100%) of the indicated compound as a yellow solid: mp 200-201 °C; ^{1}H NMR (acetone-d_6) δ 5.86 (s, 2H), 6.95-7.05 (m, 2H), 7.16 (m, 3H), 7.25-7.35 (m, 5H), 7.40 (m, 4H), 7.45-7.55 (m, 4H), 7.71 (d, *J* = 8.4 Hz, 1H), 9.12 (s, 1H); ^{13}C NMR (acetone-d_6) δ 46.3, 110.1, 119.5, 121.5, 123.3, 126.4, 126.9, 127.2, 127.5, 127.6, 127.7, 128.1, 128.7, 128.8, 129.4, 130.3, 130.4, 131.5, 135.8, 137.5, 138.7, 141.4, 142.0, 147.1; IR (neat, cm^{-1}) 3057, 2922; HRMS calcd for $C_{30}H_{22}N_2$: 410.1783. Found: 410.1787.

3,4-Diphenyl-9-tosyl-9*H*-pyrido[3,4-*b*]indole (29). The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford 37 mg (32%) of the indicated compound as a white solid: mp 238-239 °C; ^{1}H NMR (acetone-d_6) δ 2.35 (s, 3H), 6.77 (d, *J* = 7.8 Hz, 1H), 7.16 (t, *J* = 8.4 Hz, 1H), 7.19-7.23 (m, 3H), 7.30-7.35 (m, 2H), 7.35-7.43 (m, 4H), 7.43-7.50 (m, 3H), 7.64 (m, 1H), 7.98 (d, *J* = 8.4 Hz, 2H), 8.43 (d, *J* = 8.7 Hz, 1H), 9.70 (s, 1H); ^{13}C NMR (acetone-d_6) δ 21.5, 115.6, 124.4, 124.9, 125.4, 127.7, 128.0, 128.2, 129.0, 129.8, 130.5, 130.6, 130.9, 131.0, 131.2, 132.2, 134.4, 135.4, 136.2, 138.0, 140.0, 141.1, 147.2, 152.7; IR (neat, cm^{-1}) 3061, 2923; HRMS calcd for $C_{30}H_{22}N_2O_2S$: 474.1402. Found: 474.1409.

6-Benzyloxy-9-methoxymethyl-3,4-diphenyl-9*H*-pyrido[3,4-*b*]indole (31). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 92 mg (79%) of the indicated compound as a white solid: mp 163-164 °C; ^{1}H NMR ($CDCl_3$) δ 3.37 (s, 3H), 4.75 (s, 2H), 5.77 (s, 2H), 6.57 (d, *J* = 2.4 Hz, 1H), 7.15-7.41 (m, 16H), 7.50 (d, *J* = 8.8 Hz, 1H), 9.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.5, 70.2, 74.6,

106.8, 110.7, 119.2, 122.4, 126.7. 127.6 (2), 127.7, 127.9, 128.3, 128.5, 128.6, 129.7, 130.2, 130.4, 131.3, 136.3, 136.9, 137.0, 138.0, 140.7, 147.8, 153.1; IR (neat, cm^{-1}) 3040, 2976, 2871; HRMS calcd for $C_{32}H_{26}N_2O_2$: 470.1994. Found: 470.2000.

Ethyl 3,5-dimethyl-5*H*-pyrido[4,3-*b*]indole-4-carboxylate (36) and ethyl 4,5-dimethyl-5*H*-pyrido[4,3-*b*]indole-3-carboxylate (37). The reaction mixture was chromatographed using 1:1.5 hexanes/EtOAc to afford 56 mg (84%) of a 1:2.4 inseparable mixture of the indicated compounds as a yellow solid. **Ethyl 3,5-dimethyl-5*H*-pyrido[4,3-*b*]indole-4-carboxylate** (minor isomer): ^{1}H NMR ($CDCl_3$) δ 1.49 (t, J = 7.2 Hz), 2.78 (s), 3.81 (s), 4.56 (q, J = 7.2 Hz), 8.11 (d); all other peaks overlap with the peaks of the major isomer. **Ethyl 4,5-dimethyl-5*H*-pyrido[4,3-*b*]indole-3-carboxylate** (major isomer): ^{1}H NMR ($CDCl_3$) δ 1.48 (t, J = 7.2 Hz, 3H), 2.99 (s, 3H), 4.19 (s, 3H), 4.51 (q, J = 7.2 Hz, 2H), 7.37 (m, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.58 (m, 1H), 9.20 (s, 1H). Additional spectral data from the mixture: ^{13}C NMR ($CDCl_3$) δ 14.3, 14.4, 15.3, 22.8, 30.7, 32.8, 61.8, 61.9, 109.2, 109.3, 111.9, 117.0, 118.7, 120.3, 120.6, 120.8, 121.0, 127.0, 127.4, 140.1, 141.6, 141.9, 142.2, 142.4, 144.2, 145.4, 151.0, 167.9, 168.7. The regiochemistry of carbolines **36** and **37** was determined from the NOESY spectrum of the mixture. IR (neat, cm^{-1}) 2980, 1722; HRMS calcd for $C_{16}H_{16}N_2O_2$: 268.1212. Found: 268.1217.

3,4-Diphenyl-5*H*-pyrido[4,3-*b*]indole (41). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 54 mg (68%) of the indicated compound as a white solid: mp 316-317 °C; ^{1}H NMR ($CDCl_3$) δ 7.22 (m, 3H), 7.32-7.50 (m, 10H), 8.19 (d, J = 7.6 Hz, 1H), 8.37 (s, 1H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 111.0, 118.8, 119.1, 120.9, 121.1, 122.0, 126.9, 127.3, 127.7, 127.8, 129.2, 130.1, 130.3, 136.0, 139.8, 140.4, 141.3, 144.0 (one sp^2 carbon missing due to overlap); IR (neat, cm^{-1}) 3054, 1595; HRMS calcd for $C_{23}H_{16}N_2$: 320.1314. Found: 320.1317.

Diethyl 5-methyl-5*H*-pyrido[4,3-*b*]indole-3,4-dicarboxylate (45). The reaction was carried out under Conditions C (Table 3, entry 17) and the mixture was chromatographed using 1:1 hexanes/EtOAc to afford 40 mg (49%) of the indicated compound as a yellow solid: mp 118-119 °C; ^{1}H NMR ($CDCl_3$) δ 1.48 (q, J = 7.2 Hz,

6H), 3.90 (s, 3H), 4.53 (q, J = 7.2 Hz, 2H), 4.58 (q, J = 7.2 Hz, 2H), 7.39 (t, J = 7.6 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 8.20 (d, J = 8.0 Hz, 1H), 9.38 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 14.4, 30.5, 62.3, 62.5, 109.6, 116.1, 120.0, 121.2, 121.6, 122.4, 128.5, 140.5, 140.7, 142.2, 142.5, 165.7, 167.7; IR (neat, cm^{-1}) 2983, 1725; HRMS calcd for $C_{18}H_{18}N_2O_4$: 326.1267. Found: 326.1273.

4,5-Dimethyl-3-phenyl-5*H*-pyrido[4,3-*b*]indole (47). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 33.5 mg (49%) of the indicated compound as a white solid: mp 180-182 °C; ^{1}H NMR ($CDCl_3$) δ 2.74 (s, 3H), 4.10 (s, 3H), 7.31 (t, J = 7.6 Hz, 1H), 7.35-7.42 (m, 2H), 7.43-7.58 (m, 5H), 8.13 (d, J = 7.6 Hz, 1H), 9.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.7, 32.6, 109.1, 113.1, 118.9, 120.3, 120.6, 121.2, 126.6, 127.5, 128.1, 129.9, 140.1, 141.5, 142.1, 145.1, 155.7. The regiochemistry of carboline **47** was determined from its NOESY spectrum. IR (neat, cm^{-1}) 3054, 1582; HRMS calcd for $C_{19}H_{16}N_2$: 272.1314. Found: 272.1318.

3,5-Dimethyl-4-phenyl-5*H*-pyrido[4,3-*b*]indole (48). The reaction mixture was chromatographed using 1:2 hexanes/EtOAc to afford 34.5 mg (51%) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.43 (s, 3H), 3.17 (s, 3H), 7.30 (m, 2H), 7.34-7.38 (m, 2H), 7.44-7.53 (m, 4H), 8.14 (m, 1H), 9.20 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.2, 31.5, 109.1, 118.5, 119.4, 120.2, 120.5, 121.1, 126.4, 128.0, 128.6, 130.6, 137.3, 140.9, 141.8, 143.2, 152.3; IR (neat, cm^{-1}) 3054, 2928, 1587; HRMS calcd for $C_{19}H_{16}N_2$: 272.1314. Found: 272.1318.

5-Methyl-3-phenyl-4-trimethylsilyl-5*H*-pyrido[4,3-*b*]indole (49) and 5-methyl-3-phenyl-5*H*-pyrido[4,3-*b*]indole (50). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 25 mg (38%) of a 1:5 inseparable mixture of the indicated compounds as a yellow oil. **5-Methyl-3-phenyl-4-trimethylsilyl-5*H*-pyrido[4,3-*b*]indole** (minor compound): ^{1}H NMR ($CDCl_3$) δ 0.12 (s), 3.98 (s), 9.27 (s); all other peaks overlap with the peaks from compound **50**. Fifty mg of the above mixture (collected from two runs) was dissolved in 2 mL of methanol and 10 mg of KOH was added. The mixture was stirred at room temperature for 20 h and checked by TLC, which showed only one spot. The

solvent was removed by vacuum and the residue was chromatographed using 3:1 hexanes/EtOAc to afford 36 mg of compound **50** as a yellow solid. **5-Methyl-3-phenyl-5*H*-pyrido[4,3-*b*]indole**: mp 106-107 °C (lit.[29] mp 106-107 °C); ^{1}H NMR ($CDCl_3$) δ 3.89 (s, 3H), 7.34 (t, J = 7.6 Hz, 1H), 7.40-7.46 (m, 2H), 7.49-7.56 (m, 3H), 7.69 (s, 1H), 8.11 (d, J = 8.0 Hz, 2H), 8.17 (d, J = 8.0 Hz, 1H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.1, 100.6, 108.9, 118.7, 120.6, 120.7, 121.3, 126.7, 127.3, 128.5, 128.8, 140.6, 141.5, 142.3, 146.1, 153.6; IR (neat, cm^{-1}) 3054, 1594; HRMS calcd for $C_{18}H_{14}N_2$: 258.1157. Found: 258.1161.

Ethyl 5-methyl-5*H*-pyrido[4,3-*b*]indole-3-carboxylate (59). The reaction mixture was chromatographed using 1:2 hexanes/EtOAc to afford 45 mg (71%) of the indicated compound as a yellow solid: mp 150-151 °C; ^{1}H NMR (acetone-d_6) δ 1.42 (t, J = 7.2 Hz, 3H), 4.04 (s, 3H), 4.43 (q, J = 7.2 Hz, 2H), 7.38 (dt, J = 0.9, 7.2 Hz, 1H), 7.63 (dt, J = 0.9, 7.2 Hz, 1H), 7.71 (d, J = 8.4 Hz, 1H), 8.29 (s, 1H), 8.34 (d, J = 8.4 Hz, 1H), 9.41 (s, 1H); ^{13}C NMR (acetone-d_6) δ 13.9, 60.8, 106.4, 109.9, 120.6, 120.9, 121.2, 121.4, 127.8, 142.1, 142.3, 144.1, 144.8, 165.9 (one sp^3 carbon missing due to overlap); IR (neat, cm^{-1}) 3059, 2979, 1713; HRMS calcd for $C_{15}H_{14}N_2O_2$: 254.1055. Found: 254.1058.

5-Methoxymethyl-3-*n*-octyl-5*H*-pyrido[4,3-*b*]indole (61). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 75 mg (92%) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.87 (t, J = 8.8 Hz, 3H), 1.20-1.43 (m, 11H), 1.82 (quintet, J = 9.2 Hz, 2H), 3.29 (s, 3H), 5.63 (s, 2H), 7.26 (s, 1H), 7.30 (t, J = 10.0 Hz, 1H), 7.50 (m, 2H), 8.10 (d, J = 10.0 Hz, 1H), 9.21 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.3, 22.9, 29.5, 29.7, 29.8, 30.7, 32.1, 39.3, 56.6, 74.3, 103.1, 109.8, 118.5, 120.7, 121.5, 122.2, 126.8, 140.8, 142.3, 146.3, 159.1; IR (neat, cm^{-1}) 3027, 2986; HRMS calcd for $C_{21}H_{28}N_2O$: 324.2202. Found: 324.2206.

Ethyl 6-benzyloxy-4-methoxymethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (62, ZK93423). To a 2-dram vial were added β-carboline **66** (50 mg), hydrochloric acid (1 M, 1 mL) and EtOH (2 mL). The mixture was then heated at 70 °C for 24 h, cooled, neutralized with satd. aq. Na_2CO_3 and extracted with EtOAc.

The organic layer was washed with brine, dried over anhydrous Na_2SO_4 and filtered. The solvent was removed in vacuum and the residue was purified by chromatography on a silica gel column using 10:1 $CHCl_3$/MeOH to afford 36 mg (80%) of ZK93423 (**62**) as a white solid: mp 167-168 (lit.[18b] 187 °C); ^{1}H NMR ($CDCl_3$) δ 1.41 (t, *J* = 7.2 Hz, 3H), 3.48 (s, 3H), 4.48 (q, *J* = 7.2 Hz, 2H), 5.20 (s, 2H), 5.34 (s, 2H), 7.28-7.45 (m, 5H), 7.50 (d, *J* = 7.2 Hz, 2H), 7.87 (d, *J* = 2.4 Hz, 1H), 8.79 (s, 1H), 9.55 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 58.2, 61.8, 67.8, 71.0, 108.7, 112.6, 119.5, 121.8, 127.7, 128.0, 128.7, 128.9, 129.2, 133.0, 136.2, 137.2, 137.5, 137.7, 153.8, 167.2; IR (neat, cm^{-1}) 3234, 2981, 1712; HRMS calcd for $C_{23}H_{22}N_2O_4$: 390.1580. Found: 390.1585.

Isopropyl 6-benzyloxy-4-methoxymethyl-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (63, abecarnil). *i*-PrOH (2 mL) instead of EtOH was used as the solvent to deprotect the *N*-methoxymethyl group of β-carboline **68** (60 mg). Everything else is the same as in the case of β-carboline **66**. The mixture was chromatographed using 10:1 $CHCl_3$/MeOH to afford 51 mg (94%) of abecarnil (**63**) as a white solid: mp 148-149 °C (lit.[30] 150-151 °C); ^{1}H NMR ($CDCl_3$) δ 1.40 (d, *J* = 6.3 Hz, 6H), 3.47 (s, 3H), 5.20 (s, 2H), 5.30 (s, 2H), 5.37 (m, 1H), 7.28-7.52 (m, 7H), 7.86 (d, *J* = 2.4 Hz, 1H), 8.76 (s, 1H), 9.72 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.1, 58.3, 68.1, 69.6, 71.2, 108.8, 112.8, 119.6, 122.0, 127.9, 128.2, 128.7, 128.8 (2), 129.0, 133.3, 136.4, 137.4, 137.6, 153.9, 167.2; IR (neat, cm^{-1}) 3290, 2981, 1706; HRMS calcd for $C_{24}H_{24}N_2O_4$: 404.1736. Found: 404.1742.

Ethyl 6-benzyloxy-4,9-bis(methoxymethyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (66). The reaction mixture was chromatographed using 1:2 hexanes/EtOAc to afford 67 mg (62%) of the indicated compound as a pale yellow solid: mp 105-107 °C; ^{1}H NMR ($CDCl_3$) δ 1.49 (t, *J* = 7.2 Hz, 3H), 3.27 (s, 3H), 3.47 (s, 3H), 4.53 (q, *J* = 7.2 Hz, 2H), 5.22 (s, 2H), 5.32 (s, 2H), 5.74 (s, 2H), 7.30-7.45 (m, 4H), 7.51 (d, *J* = 6.9 Hz, 2H), 7.56 (d, *J* = 9.0 Hz, 1H), 7.90 (d, *J* = 2.4 Hz, 1H), 8.99 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.7, 56.6, 58.4, 62.0, 67.8, 71.2, 74.7, 109.3, 111.1, 119.6, 122.3, 127.8, 128.3, 128.9, 129.0, 129.3, 131.9, 137.0, 137.3, 138.2,

139.2, 154.5, 167.2. The regiochemistry of carboline **66** was determined from its NOESY spectrum in which the correlation signal between the 4-methoxymethyl group and 5-H was observed. IR (neat, cm^{-1}) 3032, 2928, 1724; HRMS calcd for $C_{25}H_{26}N_2O_5$: 434.1842. Found: 434.1850.

Ethyl 6-benzyloxy-3,9-bis(methoxymethyl)-9*H*-pyrido[3,4-*b*]indole-4-carboxylate (67). The reaction mixture was chromatographed using 1:2 hexanes/EtOAc to afford 26 mg (24%) of the indicated compound as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.46 (t, J = 7.2 Hz, 3H), 3.26 (s, 3H), 3.40 (s, 3H), 4.53 (q, J = 7.2 Hz, 2H), 4.88 (s, 2H), 5.16 (s, 2H), 5.70 (s, 2H), 7.30-7.53 (m, 7H), 7.68 (d, J = 2.4 Hz, 1H), 8.95 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 56.5, 58.6, 62.1, 71.1, 74.6, 75.0, 107.5, 111.1, 120.3, 120.7, 121.4, 126.8, 127.8, 128.2, 128.8, 132.6, 136.8, 137.3, 137.4, 145.6, 154.0, 168.4; IR (neat, cm^{-1}) 3032, 2980, 1728; HRMS calcd for $C_{25}H_{26}N_2O_5$: 434.1842. Found: 434.1850.

Isopropyl 6-benzyloxy-4,9-bis(methoxymethyl)-9*H*-pyrido[3,4-*b*]indole-3-carboxylate (68). The reaction mixture was chromatographed using 1:1.5 hexanes/EtOAc to afford 64 mg (57%) of the indicated compound as a pale yellow solid: mp 90-92 °C; ^1H NMR ($CDCl_3$) δ 1.48 (d, J = 6.4 Hz, 6H), 3.26 (s, 3H), 3.45 (s, 3H), 5.22 (s, 2H), 5.26 (s, 2H), 5.40 (m, 1H), 5.73 (s, 2H), 7.31-7.43 (m, 4H), 7.51 (d, J = 7.2 Hz, 2H), 7.55 (d, J = 9.2 Hz, 1H), 7.90 (d, J = 2.4 Hz, 1H), 8.99 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0, 56.4, 58.1, 67.8, 69.4, 71.0, 74.5, 109.1, 110.9, 119.4, 122.1, 127.7, 128.0, 128.1, 128.7, 129.0, 131.9, 136.8, 137.1, 137.9, 140.0, 154.2, 166.9. The regiochemistry of carboline **68** was determined from its NOESY spectrum in which the correlation signal between the 4-methoxymethyl group and 5-H was observed. IR (neat, cm^{-1}) 2925, 1717; HRMS calcd for $C_{28}H_{28}N_2O_5$: 448.1998. Found: 448.2003.

Isopropyl 6-benzyloxy-3,9-bis(methoxymethyl)-9*H*-pyrido[3,4-*b*]indole-4-carboxylate (69). The reaction mixture was chromatographed using 1:1.5 hexanes/EtOAc to afford 41 mg (37%) of the indicated compound as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.48 (d, J = 6.0 Hz, 6H), 3.25 (s, 3H), 3.39 (s, 3H), 4.87 (s, 2H), 5.15

(s, 2H), 5.47 (m, 1H), 5.70 (s, 2H), 7.31-7.36 (m, 2H), 7.40 (t, J = 7.2 Hz, 2H), 7.50 (m, 3H), 7.74 (d, J = 2.4 Hz, 1H), 8.94 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0, 56.5, 58.4, 69.9, 71.1, 74.6, 74.9, 107.5, 111.1, 120.1, 120.8, 121.9, 126.6, 127.8, 128.2, 128.8, 132.6, 136.8, 137.2, 145.3, 154.0, 168.0; IR (neat, cm^{-1}) 2980, 1717; HRMS calcd for $C_{26}H_{28}N_2O_5$: 448.1998. Found: 448.2003.

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Supporting Information Available. ^{1}H and ^{13}C NMR spectra for compounds **7-10**, **12-15**, **17-22**, **26-31**, **36-38**, **40-42**, **45**, **47**, **48**, **59**, **61-63** and **66-69**; and NOESY spectra for compounds **12** and **13**, **21**, **22**, **36**, **37**, **47**, **66** and **68**. This material is included in Appendix A and is also available free of charge via the Internet at http://pubs.acs.org.

References

1. (a) Hino, T.; Nakagawa, M. *J. Heterocycl. Chem.* **1994**, *31*, 625. (b) Baker, B. J. *Alkaloids: Chem. Biol. Perspect.* **1996**, *10*, 357. (c) Love, B. E. *Org. Prep. Proced. Int.* **1996**, *28*, 1. (d) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *43*, 6201. (e) Nakagawa, M. *J. Heterocycl. Chem.* **2000**, *37*, 567. (f) Ohmoto, T.; Koike, K. In *The Alkaloids*; Brossi, A., Ed.; Academic: San Diego, 1989; Vol. 36, pp. 135-170.
2. (a) Matsuura, N.; Kawachi, T.; Morino, K.; Ohgaki, H.; Sugimura, T.; Takayama, S. *Science*, **1981**, *213*, 346. (b) Hibino, S.; Sugino, E.; Ogura, N.; Shintani, Y.; Sato, K. *Heterocycles* **1990**, *30*, 271.
3. For reviews, see: (a) Gribble, G. W.; In *The Alkaloids*; Brossi, A., Ed.; Academic: San Diego, 1990; Vol. 39, Chapter 7. (b) Tan, G. T.; Pezzuto, J. M.; In *Chemistry and Toxicology of Diverse Classes of Alkaloids*; Blum, M. S., Ed.; Alaken, Inc.: 1996; pp. 1-119. For a recent report, see: (c) Nguyen, C. H.; Lavelle, F.; Riou, J. -F.; Bissery, M. -C.; Huel, C.; Bisagni, E. *Anti-Cancer Drug Design* **1992**, *7*, 235.
4. For recent examples, see: (a) Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans I* **1999**, 1505. (b) Suzuki, H.; Unemoto, M.; Murakemi, Y. *J. Chem. Soc., Perkin Trans. 1* **1999**, 1717. (c) Sakamoto, T.; Numata, A.; Saitoh, H.; Kondo, Y. *Chem. Pharm. Bull.* **1999**, *47*, 1740. (d) Snyder, S. A.; Vosburg, D. A.; Jarvis, M. G.; Markgraf, J. H. *Tetrahedron* **2000**, *56*, 5329. (e) Engler, T.; Wanner, J. *J. Org. Chem.* **2000**, *65*, 2444. (f) Kanekiyo, N.; Choshi, T.; Kuwada, T.; Sugino, E.; Hibino, S. *Heterocycles* **2000**, *53*, 1877. (g) Choshi, T.; Kumada, T.; Fukni, M.; Matsuya, Y.; Sugino, E.; Hibino, S. *Chem. Pharm. Bull.* **2000**, *48*, 108. (h) Kanekiyo, N.; Kuwada, T.; Choshi, T.; Nobuhiro, J.; Hibino, S. *J. Org. Chem.* **2001**, *66*, 8793. (i) Abbiati, G.; Beccalli, E. M.; Marchesini, A.; Rossi, E. *Synthesis* **2001**, 2477. (j) Zhang, H.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 1359. (k) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7048.

5. Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G. *Tetrahedron* **1993**, *49*, 49.

6. Rocca, P.; Marsais, F.; Godard, A.; Queguiner, G.; Adams, L.; Alo, B. *Synth. Commun.* **1995**, *25*, 3373.

7. Boger, D. L.; Duff, S. R.; Panek, J. S.; Yasuda, M. *J. Org. Chem.* **1985**, *50*, 5782.

8. For reviews, see: (a) Larock, R. C. *J. Organometal. Chem.* **1999**, *576*, 111. (b) Larock, R. C.; "Palladium-Catalyzed Annulation," in *Perspectives in Organopalladium Chemistry for the XXI Century*, Ed. J. Tsuji, Elsevier Press, Lausanne, Switzerland, 1999, pp. 111-124. (c) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1435.

9. (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.

10. (a) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1551. (b) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 412.

11. Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270.

12. Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.

13. Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713.

14. Larock, R. C.; Doty, M. J.; Cacchi, S. J. *J. Org. Chem.* **1993**, *58*, 4579.

15. (a) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002.

16. (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (b) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042.

17. Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 3083.

18. (a) Huang, Q.; He, X.; Ma, C.; Liu, R.; Yu, S.; Dayer, C. A.; Wenger, G. R.; McKernan, R.; Cook, J. M. *J. Med. Chem.* **2000**, *43*, 71. (b) Cox, E. D.; Diaz-Arauzo, H.; Huang, Q.; Reddy, M. S.; Ma, C.; Harris, B.; McKernan, R.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1998**, *41*, 2537. (c) Huang, Q.; Zhang, W.; Liu, R.; McKernan, R. M.; Cook, J. M. *Med. Chem. Res.* **1996**, *6*,

384. (d) Fryer, R. I.; Wang, C.-G.; Chia, N.-C.; Basile, A. S.; Gu, Z.-Q.; Skolnick, P. *Med. Chem. Res.* **1995**, *5*, 296. (e) Liu, R.; Zhang, P.; McKernan, R. M.; Wafford, K.; Cook, J. M. *Med. Chem. Res.* **1995**, *5*, 700. (f) Hollinshead, S. P.; Trudell, M. L.; Skolnick, P.; Cook, J. M. *J. Med. Chem.* **1990**, *33*, 1062.

19. (a) Koek, W.; Patoiseau, J.-F.; Assie, M.-B.; Cosi, C.; Kleven, M. S. *J. Pharmacol. Exp. Ther.* **1998**, *287*, 266. (b) Thompson, S.-A.; Bonnert, T. P.; Whiting, P. J.; Wafford, K. A. *Toxico. Lett.* **1998**, *100*, 233. (c) Haffer, G.; Nickisch, K.; Tilstam, U. *Heterocycles* **1998**, *48*, 993. (d) Scholze, P.; Ebert, V.; Sieghart, W. *Eur. J. Pharmacol.* **1996**, *304*, 155. (e) Witkin, J. M.; Acri, J. B.; Wong, G.; Gleeson, S.; Barrett, J. E. *J. Pharmacol. Exp. Ther.* **1996**, *277*, 87. (f) Wafford, K. A.; Thompson, S. A.; Sikela, J.; Wilcox, A. S.; Whiting, P. *J. Mol. Pharmacol.* **1996**, *50*, 670. (g) Mehta, A. K.; Shank, R. P. *Life Sci.* **1995**, *57*, 2215. (h) Mumford, G. K.; Rush, C. R.; Griffiths, R. R. *J. Pharmacol. Exp. Ther.* **1995**, *272*, 570. (i) Dazzi, L; Motzo, C.; Imperatoi, A.; Serra, M.; Gessa, G. L.; Biggio, G. *J. Pharmacol. Exp. Ther.* **1995**, *273*, 241. (j) Stephens, D. N.; Schneider, H.; Kehr, W.; Andrews, J. S.; Rettig, K. J.; Truski, L.; Schmiechen, R.; Turner, J. D.; Jensen, L. H.; Petersen, E. N.; Honore, T.; Hansen, J. B. *J. Pharmacol. Exp. Ther.* **1990**, *253*, 334. (k) Truski, L.; Stephens, D. N.; Jensen, L. H.; Petersen, E. N.; Meldrum, S. B.; Patel, S.; Hansen, J. B.; Losher, W.; Schneider, H.; Schmiechen, R. *J. Pharmacol. Exp. Ther.* **1990**, *253*, 344. (l) Krause, W.; Mengel, H.; Nordholm, L. *J. Pharm. Sci.* **1989**, *78*, 622.

20. (a) Old, D. W.; Harris, M. C.; Buchwald, S. L. *Org. Lett.* **2000**, *2*, 1403. (b) Mann, G.; Hartwig, J. F.; Driver, M. S.; Fernández-Rivas, C. *J. Am. Chem. Soc.* **1998**, *120*, 827. (c) Watanabe, M.; Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **2000**, *41*, 481.

21. Zhang, Y.; Gong, X.; Zhang, H.; Larock, R. C.; Yeung, E. S. *J. Comb. Chem.* **2000**, *2*, 450.

22. (a) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941. (b) Wu, G.; Geib, S. J.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1988**, *53*, 3238.

23. (a) Kundo, N. G.; Pal, M.; Nandi, B. *J. Chem. Soc., Perkin Trans. 1* **1998**, 561. (b) Gevorgyan, V.; Radhakrishnan, U.; Takeda, A.; Rubina, M.; Rubin, M.; Yamamoto, Y. *J. Org. Chem.* **2001**, *66*, 2835. (c) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86.

24. (a) Lei, A.; Srivastava, M.; Zhang, X. *J. Org. Chem.* **2002**, *67*, 1969. (b) Lücking, U.; Pfaltz, A. *Synlett.* **2000**, *1261.* (c) Trost, B. M.; Chan, C.; Rühter, G. *J. Am. Chem. Soc.* **1987**, *109*, 3486.

25. Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C. Sugino, E.; Hibino, S. *J. Org. Chem.* **1997**, *62*, 2535.

26. Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. *Tetrahedron* **1997**, *53*, 4447. We used ethyl acetate, instead of diethyl ether, as the extraction solvent, and were able to isolate 2-bromo-1*H*-indole-3-carboxaldehyde in 55% yield.

27. Ash, W. *J. Chem. Soc.* **1958**, 3887.

28. Bergman, J.; Venemalm, L. *J. Org. Chem.* **1992**, *57*, 2495.

29. Prikhod'ko, T.A.; Vasilevskii, S.F.; Shvartsberg, M.S. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1984**, *33*, 2383.

30. Weber, A.; Kennecke, M.; Hilscher, J. C.; Nickisch, K. *Ger. Offen.* **1992**, DE4029389; *Chem. Abstr.* **1991**, *117*, 7912.

CHAPTER 2. SYNTHESIS OF β- AND γ-CARBOLINES BY THE PALLADIUM/COPPER-CATALYZED COUPLING AND CYCLIZATION OF TERMINAL ACETYLENES

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Abstract

A variety of 3-substituted β- and γ-carbolines have been synthesized from *N*-substituted 3-iodoindole-2-carboxaldehydes and 2-bromoindole-3-carboxaldehydes respectively. The coupling of these aldehydes with various terminal acetylenes using cat. $PdCl_2(PPh_3)_2$/CuI readily affords the corresponding alkynylindole carboxaldehydes, which have subsequently been converted to the corresponding *tert*-butylimines and cyclized to β- and γ-carbolines by either copper-catalyzed or thermal processes.

Introduction

Palladium-catalyzed annulation processes have recently proven to be a powerful method for the construction of a wide variety of hetero- and carbocycles in our own laboratories.[1] In addition, the transition metal-mediated,[2] base-promoted,[3] electrophile-induced[4] and thermal[5] cyclization of alkynes, which possess a nucleophile in close proximity to the carbon-carbon triple bond, have also been shown to be very effective for the synthesis of a wide variety of hetero- and carbocycles. In our own laboratories, a variety of isoquinolines, pyridines and naphthyridines have been successfully synthesized by the copper-catalyzed,[6] the palladium-catalyzed[7] and the electrophile-induced[8] cyclization of alkynes having a *tert*-butylimino group in close proximity to the carbon-carbon triple bond.

Pyrido[3,4-*b*]indoles and pyrido[4,3-*b*]indoles, commonly known as β- and γ-carbolines, respectively, are the key structural units for a variety of biologically important alkaloids.[9] Numerous β- and γ-carbolines have been studied extensively as antitumor agents.[9] The isolation and synthesis of naturally occurring carbolines and the synthesis of β- and γ-carboline derivatives have received considerable attention in the literature[9,10] due to their biological and pharmaceutical importance.

Hibino and Sakamoto have separately reported that substituted β-carbolines and their *N*-oxides can be synthesized readily by heating the corresponding 3-(1-alkynyl)indole-2-carboxaldehydes with NH_3[5a] or NH_2OH.[5b,c] The β-carboline *N*-oxides obtained by this method have been further elaborated by Hibino in the total synthesis of naturally occurring β-carboline alkaloids pyridindolols.[5b,c] Recently, Rossi has improved Sakamoto's carboline synthesis to the synthesis of 1,3-disubstituted β-carbolines by employing 2-acyl-3-(1-alkynyl)indoles and NH_3.[5d] Similarly, γ-carbolines and their *N*-oxides have also been synthesized by heating the corresponding 2-(1-alkynyl)indole-3-carboxaldehydes with NH_3 or NH_2OH.[5a,g] The reduction of γ-carbolines *N*-oxides by PCl_3 readily affords the corresponding γ-carbolines in satisfactory yields.[5g]

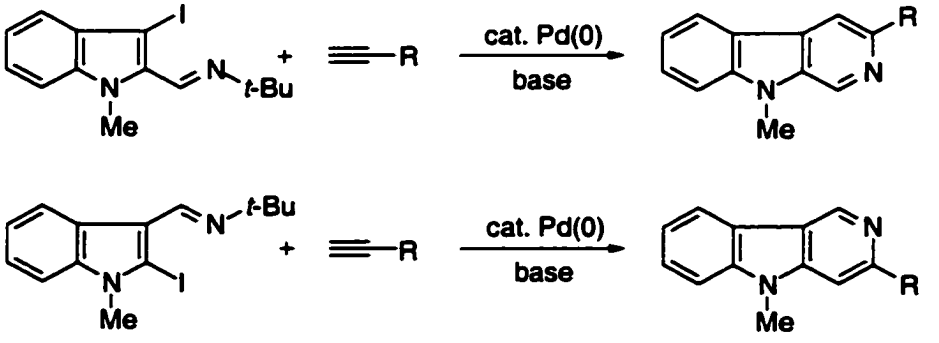
Recently, we have developed a general synthesis of 3,4-disubstituted β- and γ-carbolines by the palladium-catalyzed iminoannulation of *internal* acetylenes.[11] We have also developed a general synthesis of isoquinolines and pyridines by the palladium- and copper-catalyzed coupling and cyclization of *terminal* acetylenes.[6] Our interest in the synthesis of carbolines prompted us to examine the synthesis of a variety of 3-substituted β- and γ-carboline derivatives. Our goal during this work was to provide a clean, high yielding and general synthesis of functionalized β- and γ-carbolines, which would provide a useful alternative to Sakamoto's carboline synthesis.[5a] Preliminary studies on this project have previously been communicated.[12] Herein, we wish to report the full details of this successful

synthesis of various β- and γ-carbolines by the palladium/copper-catalyzed coupling and copper-catalyzed or thermal cyclization of *terminal* acetylenes.

Results and Discussion

During the course of our investigation of the palladium-catalyzed iminoannulation of *internal* alkynes, we also examined the palladium-catalyzed iminoannulation of *terminal* alkynes. Unfortunately, the annulation of terminal alkynes, such as phenylacetylene, 1-decyne, 3-butyn-1-ol and ethyl propiolate by the *tert*-butylimine of 3-iodo-1-methylindole-2-carboxaldehyde and 2-iodo-1-methylindole-3-carboxaldehyde (**1a** and **1b**) under our standard conditions[11] for β- and γ-carboline synthesis gave the desired β- and γ-carbolines in relatively low yields in most cases (Scheme 1). Our several attempts to increase the yields of this annulation chemistry failed to give any improved results.

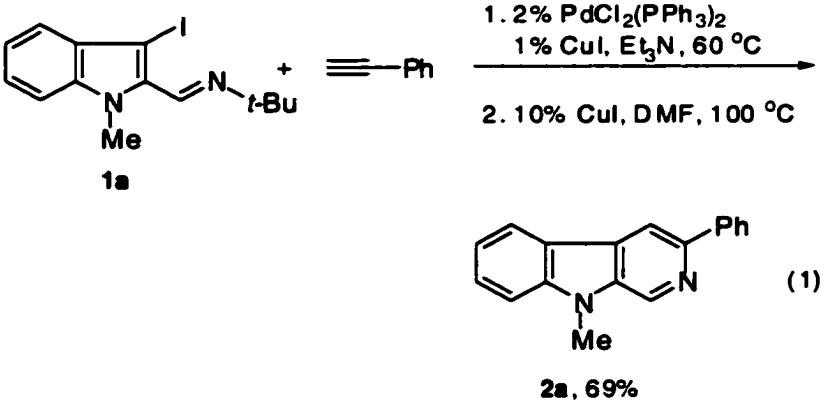
Scheme 1



R = Ph, *n*-C_8H_{17}, $(CH_2)_2OH$, CO_2Et

The reaction sequence for the synthesis of isoquinolines and pyridines by the palladium- and copper-catalyzed coupling and cyclization of terminal acetylenes[6] was then examined for the synthesis of β-carbolines by employing the *tert*-butylimine of 3-iodo-1-methylindole-2-carboxaldehyde (**1a**) and examining its coupling with several terminal alkynes. In short, the palladium/copper-catalzyed coupling of imine **1a** with a terminal acetylene was complete in a few hours as monitored by TLC analysis. The precipitate and the solvent were subsequently removed by filtration and evaporation. DMF and 10 mol % of CuI were then added to the residue. The

resulting mixture was then heated at 100 °C until the cyclization was complete. Unfortunately, only phenylacetylene gave an acceptable yield (69%) of the desired β-carboline **2a** (eq 1). When other acetylenes, such as 1-decyne, 3-butyn-1-ol and ethyl propiolate were employed, the reactions afforded low yields of the corresponding β-carbolines in all cases.



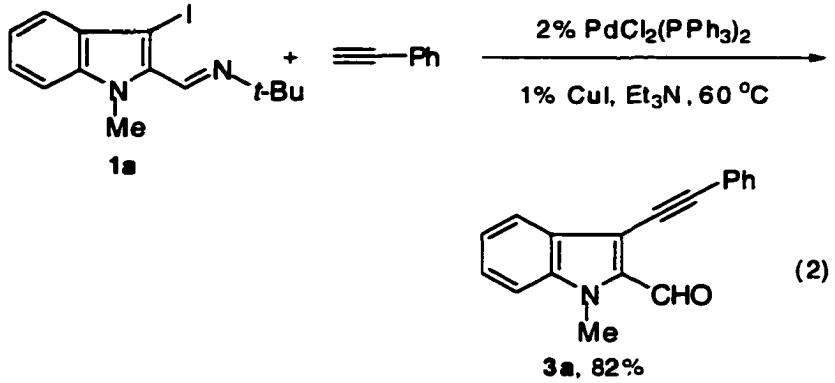
1a

2a, 69% (1)

Since the same reaction procedure has proven successful for the synthesis of isoquinolines, one wonders why this reaction procedure does not work well in the β-carboline synthesis. The reasons appear complicated. The palladium/copper-catalyzed Sonogashira coupling[13] of ethyl 3-iodo-1*H*-indole-2-carboxylate and ethyl 3-iodo-1-(methanesulfonyl)indole-2-carboxylate with terminal acetylenes has been reported previously to proceed in relatively low yields.[14] As an analogue to the above carboxylates, imine **1a** might also suffer the problem of low yields when it undergoes the coupling reaction with terminal acetylenes. Moreover, the bulky *tert*-butylimine moiety in imine **1a** might also affect the Sonogashira reaction. Furthermore, the Sonogashira coupling might produce by-products, which cannot be removed in the one-pot process and might interfere with the subsequent copper-catalyzed cyclization.

In order to investigate the major factors that cause the low yields of β-carboline products, the coupling product of imine **1a** with phenylacetylene was therefore isolated before it was employed in the subsequent copper-catalyzed cyclization. Instead of the *tert*-butylimine, the alkynylindole aldehyde **3a**, which is

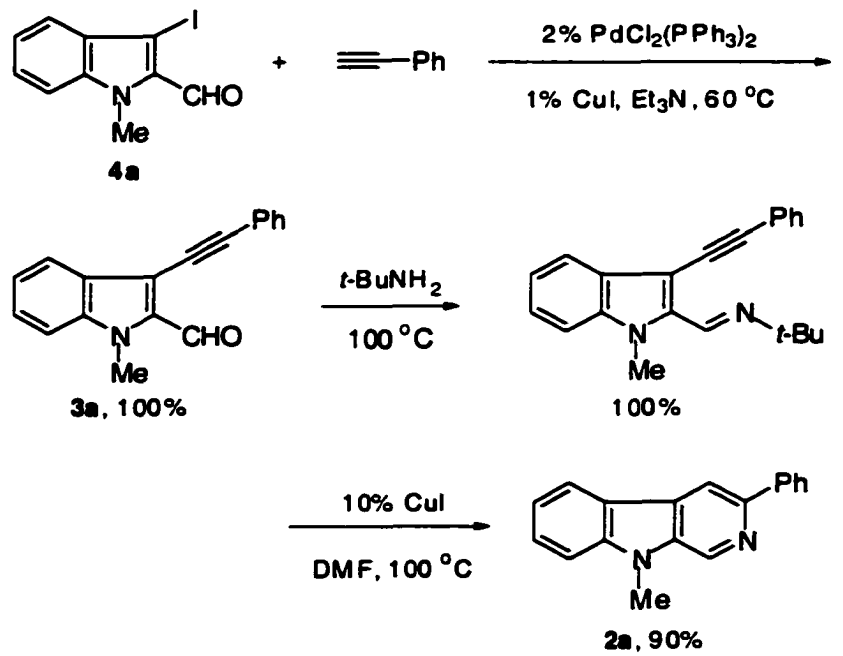
apparently arising from hydrolysis of the corresponding *tert*-butylimine during column chromatography, was isolated in an 82% yield (eq 2). As a control experiment,



(2)

the coupling of 3-iodo-1-methylindole-2-carboxaldehyde (**4a**) with phenylacetylene was performed, affording the same alkynylindole aldehyde **3a** in a 100% yield. The aldehyde **3a** was then quantitatively converted to the corresponding *tert*-butylimine, which was subsequently employed in the copper-catalyzed cyclization, which smoothly afforded the desired β-carboline **2a** in a 90% yield (Scheme 2).

Scheme 2

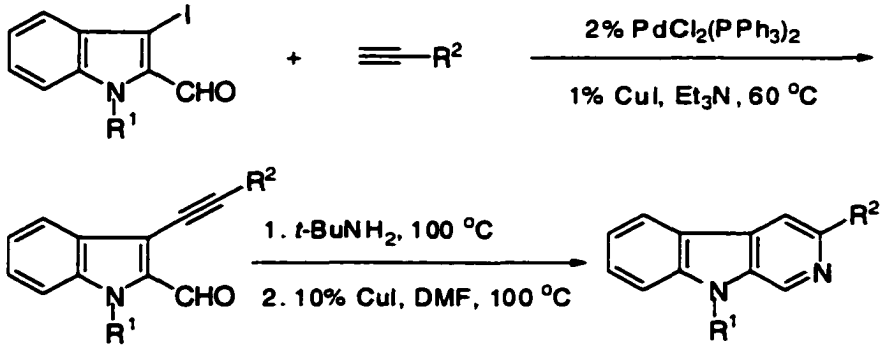


By comparing the results of eq 1 and eq 2 with those of Scheme 2, we conclude that the bulky *tert*-butylimine moiety does affect the Sonogashira coupling

of imine **1a** with phenylacetylene, and the by-products generated by the Sonogashira coupling of imine **1a** with phenylacetylene also interfere with the subsequent copper-catalyzed cyclization. These problems might also happen in the β-carboline synthesis employing other acetylenes under the standard reaction sequence of our isoquinoline synthesis, which afforded low yields of β-carbolines in all cases, as mentioned previously.

As we have seen, the control experiment employing aldehyde **4a** and phenylacetylene gave a higher total yield (90%) of the desired β-carboline **2a** (Table 1, entry 1) than the reaction employing the sequence of our earlier isoquinoline synthesis (69%). The transformation of aldehyde to the corresponding *tert*-butylimine is essentially quantitative, as observed in our previous work.[1m,1n,6,11] We have thus simply changed the reaction sequence to that of the control experiment, which requires no further purification and characterization of the *tert*-butylimines. This ensures essentially pure starting materials for each step (Scheme 3). The results of this study are summarized in Table 1.

Scheme 3



As shown in Table 1, the palladium/copper-catalyzed Sonogashira coupling of 3-iodo-1-methylindole-2-carboxaldehyde (**4a**) with a variety of terminal acetylenes afforded excellent yields of the corresponding 3-alkynyl-1-methylindole-2-carboxaldehydes **3a-g**, which were then converted into the correponding *tert*-butylimines, which were subsequently subjected to copper-catalyzed cyclization to generate the desired 3-substituted β-carbolines **2a-g** in excellent yields (entries 1-7).

Aryl-, alkenyl-, and alkyl-substituted terminal acetylenes have proven successful in this β-carboline synthesis (entries 1-4). Moreover, hydroxy-, ester-, and cyano-substituted terminal alkynes also afforded the coupling products and the corresponding β-carbolines in excellent yields (entries 5-7).

When a silyl-substituted terminal alkyne, triethylsilylacetylene, was employed, the coupling successfully afforded a 100% yield of the desired alkynylindole **3h** (entry 8). However, the copper-catalyzed cyclization didn't afford any of the desired triethylsilyl-substituted β-carboline. Instead, a 28% yield of the desilylated β-carboline **2h** was isolated by column chromatography, along with a 70% yield of the desilylated intermediate 2-*tert*-butyl-9-methyl-9*H*-pyrido[3,4-*b*]indolium hydroxide, which was confirmed by ^{1}H and ^{13}C NMR spectroscopy and mass spectrometry. The β-carbolinium salt thermally eliminates the *tert*-butyl group to form the β-carboline **2h** in a 58% yield at 130 °C after 72 h. To avoid the difficulty in isolating the highly polar β-carbolinium salt, after the copper-catalyzed cyclization reaction was complete as judged by TLC analysis, the reaction mixture was continuously heated at 130 °C for 72 h. Unfortunately, the β-carboline **2h** was isolated in only a 41% yield by this process (entry 8).

When an acetylene containing a bulky group, namely 1-ethynylcyclohexanol was employed, the coupling successfully gave the alkynylindole **3i** in a 100% yield (entry 9). Surprisingly, the cyclization didn't afford any of the desired product. Instead, the β-carboline **2h**, which had lost the cyclohexane ring, and the same β-carbolinium salt that was formed in the silyl case were detected by TLC analysis and ^{1}H NMR spectroscopy. To avoid isolation of the extremely polar β-carbolinium salt, the reaction mixture was heated at 130 °C for 72 h to eliminate the *tert*-butyl group present in the salt. Unfortunately, only a 35% yield of the β-carboline **2h** was isolated (entry 9). Again, loss of the hydroxycyclohexyl group is the predominant reaction.

Table 1. Synthesis of β-Carbolines by the Palladium/Copper-Catalyzed Coupling and Copper-Catalyzed Cyclization of Terminal Acetylenes

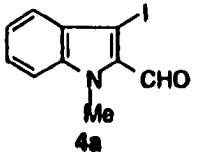
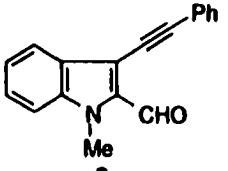
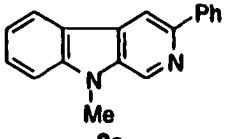
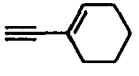
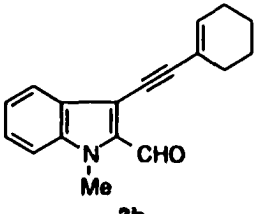
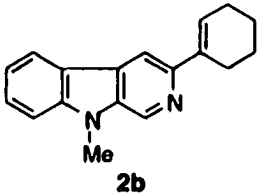
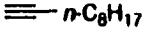
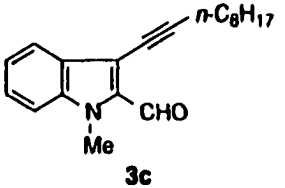
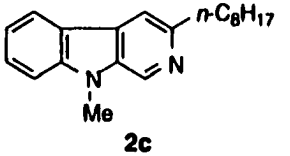
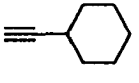
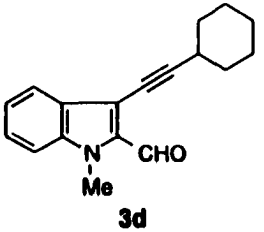
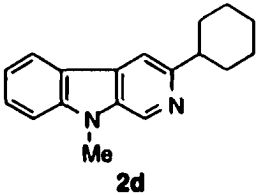
entry	aldehyde	alkyne	alkynylindole	time (h)[a]	% yield[b]	product	time (h)[a]	% yield[b]
1	 **4a**		 **3a**	3	100	 **2a**	20	90
2			 **3b**	18	98	 **2b**	24	93
3			 **3c**	16	88	 **2c**	24	93
4			 **3d**	16	96	 **2d**	40	93

Table 1. Continued

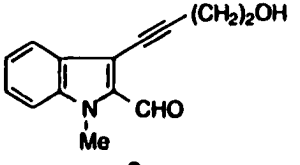
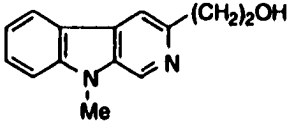
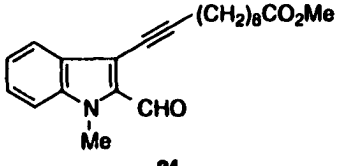
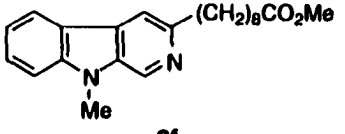
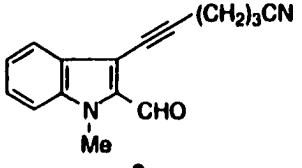
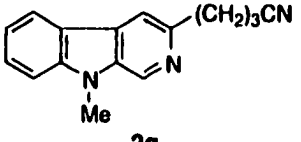
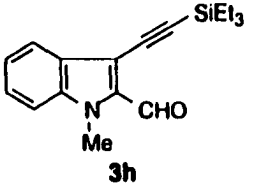
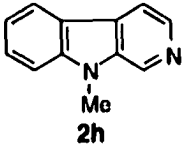
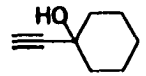
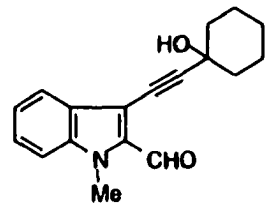
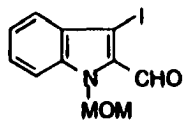
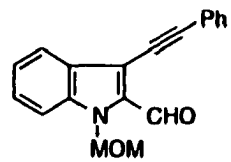
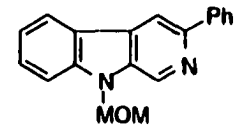
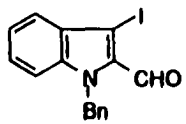
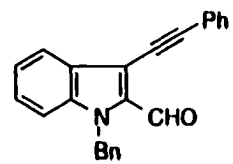
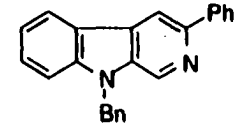
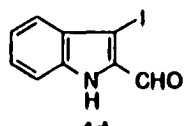
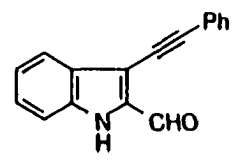
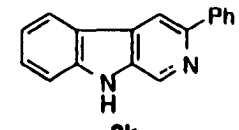
entry	aldehyde	alkyne	alkynylindole	time (h)[a]	% yield[b]	product	time (h)[a]	% yield[b]
5		≡—$(CH_2)_2OH$	 **3e**	16	87	 **2e**	15	95
6		≡—$(CH_2)_8CO_2Me$	 **3f**	16	98	 **2f**	18	95
7		≡—$(CH_2)_3CN$	 **3g**	16	82	 **2g**	20	88
8		≡—$SiEt_3$	 **3h**	16	100	 **2h**	92[c]	41

Table 1. Continued

entry	imine	alkyne	alkynylindole	time (h)[a]	% yield[b]	product	time (h)[a]	% yield[b]
9			 **3i**	18	100	**2h**	92[c]	35
10	 **4b**		 **3j**	16	95	 **2i**	20	100
11	 **4c**		 **3k**	18	89	 **2j**	18	99
12	 **4d**		 **3l**	4	93	 **2k**	24	trace[d]

[a] The reaction time was not optimized. Some of the coupling reactions in this study might be complete in a much shorter time than listed, as is the case in entries 1 and 12. [b] Isolated yields. [c] The reaction was heated at 100 °C for 20 h and subsequently at 130 °C for 72 h. [d] A 36% yield of **3l** was isolated.

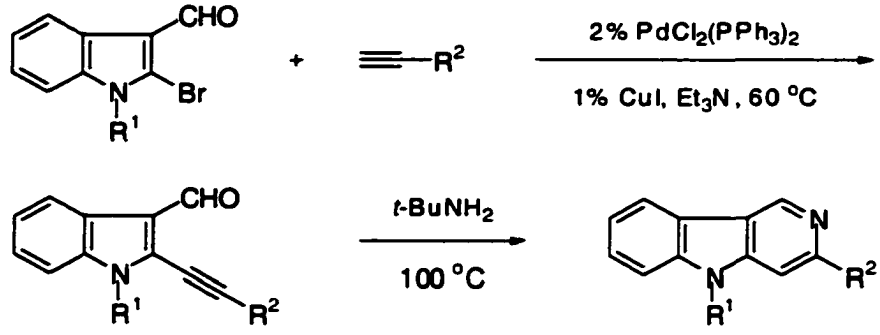
An electron-deficient terminal acetylene, ethyl propiolate, was also employed in the palladium/copper-catalyzed coupling process. Unfortunately, the reaction didn't afford any significant amount of the coupling product. Two electron-rich terminal acetylenes, ethoxyacetylene and 2-ethynylbenzofuran, also failed to produce the coupling products in decent yields. Presumably, these terminal alkynes are too reactive and thus polymerize under the coupling conditions.[15]

Finally, *N*-methoxymethyl- and *N*-benzyl-substituted iodoindoles **4b** and **4c** were employed in the palladium/copper-catalyzed coupling and copper-catalyzed cyclization of phenylacetylene. The coupling process afforded the alkynylindole aldehydes **3j** and **3k** in 95% and 89% yields, and the cyclization generated the desired β-carbolines **2i** and **2j** in 100% and 99% yields, respectively (entries 10 and 11). The unprotected iodoindole, 3-iodo-1*H*-indole-2-carboxaldehyde (**4d**) undergoes palladium-catalyzed Sonogashira coupling with phenylacetylene, producing the corresponding alkynylaldehyde **3l** in a 92% yield. Unfortunately, the subsequent cyclization only afforded a trace of the desired β-carboline **2k**. A messy reaction was observed and a 36% of the aldehyde **3l** was recovered (entry 12).

Encouraged by our success with the β-carboline synthesis, we have also investigated the palladium/copper-catalyzed coupling of terminal acetylenes using *N*-substituted 2-bromoindole-3-carboxaldehydes in order to synthesize various 3-substituted γ-carbolines. The palladium/copper-catalyzed coupling of phenylacetylene and 2-bromo-1-methylindole-3-carboxaldehyde (**5a**) was first examined. The coupling reaction proceeded smoothly, producing the desired alkynylindole **6a** in a 93% yield. The alkynylindole **6a** was then heated with *tert*-butylamine at 100 °C in a sealed tube. To our pleasant surprise, instead of the corresponding *tert*-butylimine, the γ-carboline product **7a** was detected by TLC analysis after 20 h and subsequently isolated in a 92% yield (Table 2, entry 1). This preliminary result prompted us to investigate the scope of this synthesis of 3-substituted γ-carbolines by the palladium/copper-catalyzed coupling and thermal

cyclization of terminal acetylenes (Scheme 4). The results of this study are summarized in Table 2.

Scheme 4



As shown in Table 2, the palladium/copper-catalyzed Sonogashira coupling of 2-bromo-1-methylindole-3-carboxaldehyde (**5a**) with a variety of terminal acetylenes afforded good to excellent yields of the corresponding 2-alkynyl-1-methylindole-3-carboxaldehydes, which were then converted to the *tert*-butylimines, which subsequently underwent thermal cyclization *in situ* to generate the desired 3-substituted γ-carbolines in good to excellent yields (entries 1-6). As we expected, aryl-, alkenyl-, alkyl-substituted terminal acetylenes have again proven successful in this γ-carboline synthesis (entries 1-4). Unfortunately, 3-propyn-1-ol, which was quite successful in the β-carboline synthesis, didn't give any significant yield of the coupling product. However, another hydroxy-containing acetylene, 10-undecyn-1-ol afforded Sonogashira coupling product **6e** and the corresponding γ-carboline **7e** in 61% and 72% yields, respectively (entry 5). Methyl 10-undecynoate also underwent coupling and cyclization successfully, affording an 86% yield of coupling product **6f** and an 88% yield of the γ-carboline product **7f** (entry 6). Surprisingly again, 5-cyano-1-pentyne, which proved successful in our β-carboline synthesis, failed to give any decent yield of the Sonogashira coupling product.

Triethylsilylacetylene undergoes the coupling smoothly, generating a 94% yield of alkynylindole aldehyde **6g**. However, the subsequent thermal cyclization afforded none of the desired γ-carboline. Instead, an 86% yield of the desilylated

Table 2. Synthesis of γ-Carbolines by the Palladium/Copper-Catalyzed Coupling and Thermal Cyclization of Terminal Acetylenes

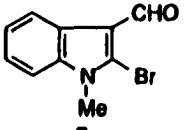
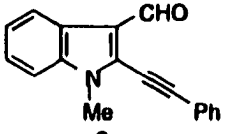
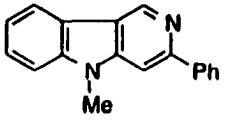
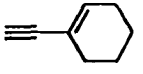
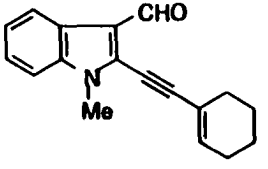
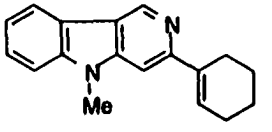
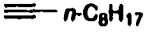
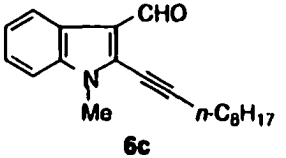
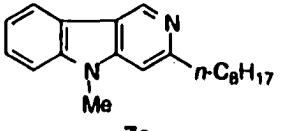
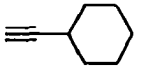
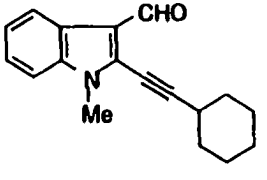
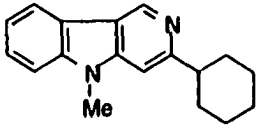
entry	aldehyde	alkyne	alkynylindole	time (h)[a]	% yield[b]	product	time (h)[a]	% yield[b]
1	 **5a**		 **6a**	24	93	 **7a**	20	92
2			 **6b**	20	98	 **7b**	40	93
3			 **6c**	20	82	 **7c**	24	87
4			 **6d**	4	89	 **7d**	40	83

Table 2. Continued

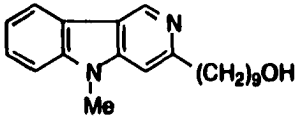
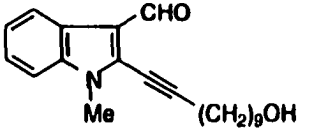
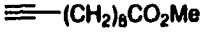
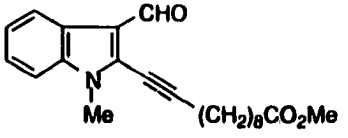
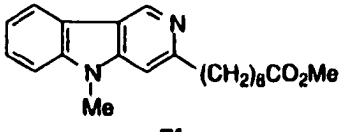
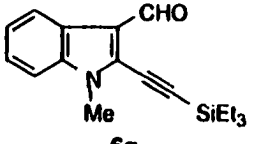
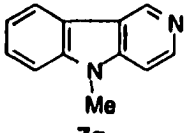
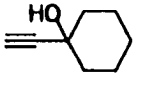
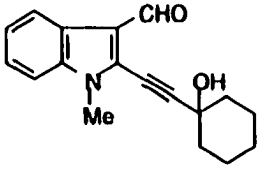
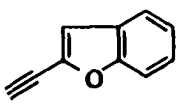
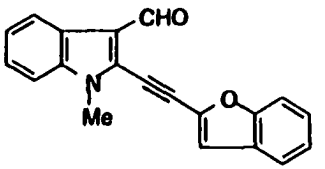
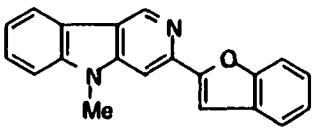
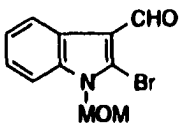
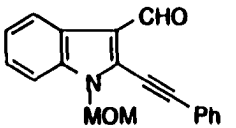
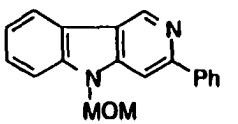
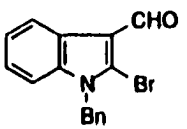
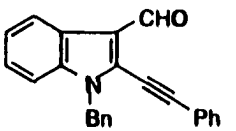
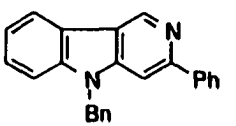
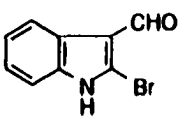
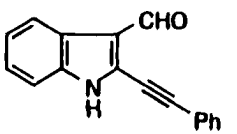
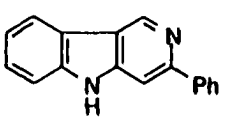
entry	aldehyde	alkyne	alkynylindole	time (h)[a]	% yield[b]	product	time (h)[a]	% yield[b]
5			 **6e**	16	61	 **7e**	20	72
6			 **6f**	16	86	 **7f**	20	88
7			 **6g**	16	94	 **7g**	92[c]	41
8			 **6h**	18	87	**7g**	92[c]	40

Table 2. Continued

entry	imine	alkyne	alkynylindole	time (h)[a]	% yield[b]	product	time (h)[a]	% yield[b]
9			 **6i**	6[d]	78[d]	 **7h**	40	95
10	 **5b**		 **6j**	20	97	 **7i**	18	80
11	 **5c**		 **6k**	18	73	 **7j**	22	90
12	 **5d**		 **6l**	14	64	 **7k**	20	49

[a] The reaction time was not optimized. Some of the coupling reactions might be complete in a much shorter time, as is the case in entries 4 and 9. [b] Isolated yields. [c] The reaction was run at 100 °C for 22 h and subsequently at 130 °C for 72 h. [d] An unseparable mixture of 67% of **6l** and 33% of **5a** was isolated after 3 h, which was subjected to another Sonogashira coupling for 3 h.

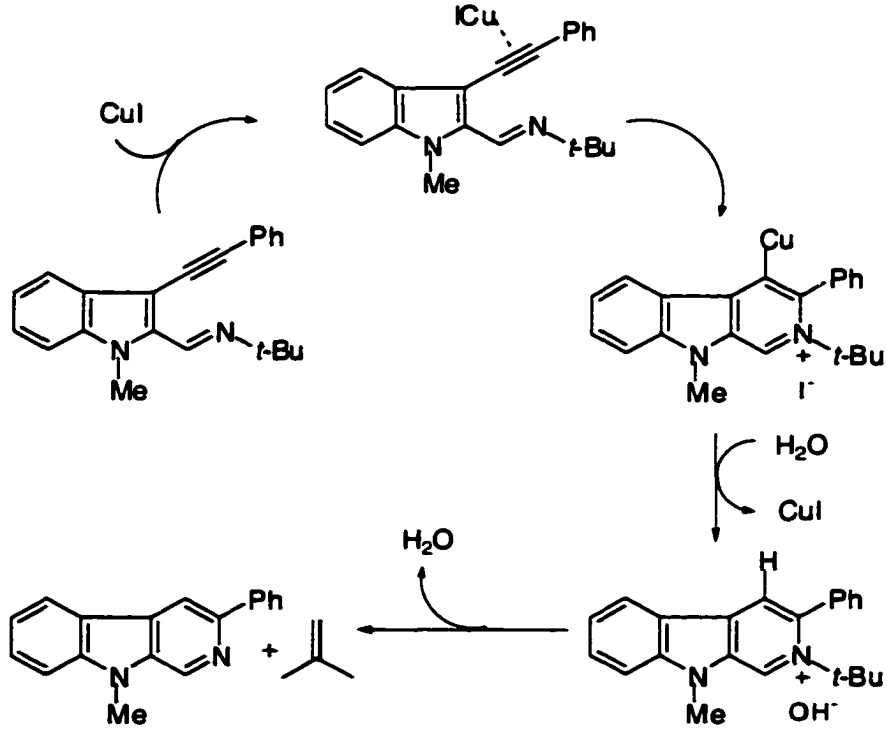
salt, 2-*tert*-butyl-5-methyl-5*H*-pyrido[4,3-*b*]indolium hydroxide, was observed and confirmed by ^{1}H NMR spectroscopy and mass spectrometry. To avoid isolation of the extremely polar γ-carbolinium salt, a process similar to that of the corresponding β-carboline system was carried out. After the cyclization was complete as judged by TLC analysis, the solvent *tert*-butylamine was removed by vacuum and DMF was added to the residue. The mixture was then heated at 130 °C for 72 h. Unfortunately, only a 41% yield of the γ-carboline **7g** was isolated (entry 7). When 1-ethynylcyclohexanol was employed, the coupling was successful, producing an 87% yield of the alkynylindole **6h**, which was then heated with *tert*-butylimine. Surprisingly, neither the desired γ-carboline, nor the γ-carboline minus the hydroxycyclohexyl group or the γ-carbolinum salt were observed. Instead, the corresponding *tert*-butylimine was detected after 24 h by TLC analysis, which was further confirmed by ^{1}H NMR spectroscopy, and the imine was isolated in a 100% yield after removal of the solvent *tert*-butylamine by vacuum. CuI (10 mol %) and DMF were then added to the *tert*-butylimine in order to facilitate the cyclization, as was done in the β-carboline synthesis. Interestingly, the *tert*-butylimine completely disappeared and the γ-carbolinium salt minus the hydroxycyclohexyl group, the same salt as we obtained earlier in the silyl case, was observed after only 2 h by TLC analysis and ^{1}H NMR spectroscopy. Apparently, CuI accelerates the fragmentation process.[16] The reaction mixture was then heated at 130 °C for 72 h, and a 40% yield of the γ-carboline **7g** was isolated (entry 8).

Similar to our observations in the β-carboline synthesis, the electron-deficient alkyne ethyl propiolate and the electron-rich alkyne ethoxyacetylene failed to afford significant amounts of the coupling products. Interestingly, another electron-rich terminal alkyne, 2-ethynylbenzofuran, produced the coupling product in a 67% yield, along with a 33% yield of the starting bromide as an unseparable mixture. This mixture was employed in another Sonogashira coupling under our standard conditions, affording cleanly the alkynylindole **6i** in a 78% total yield. Surprisingly, if the amount of 2-ethynylbenzofuran was increased from 1.2 to 3 equivs, the coupling

gave a messier reaction and a lower yield (56%) of the alkynylindole **6i**. The resulting alkynylindole **6i** was subjected to the subsequent thermal cyclization, which produced a 95% yield of the desired γ-carboline **7h** (entry 9).

Finally, *N*-methoxymethyl- and *N*-benzyl-substituted bromoindoles **5b** and **5c** were employed in the palladium/copper-catalyzed coupling and thermal cyclization of phenylacetylene. The coupling afforded the alkynylindole aldehydes **6j** and **6k** in 97% and 73% yields, and the cyclization generated the desired γ-carbolines **7i** and **7j** in 80% and 90% yields, respectively (entries 10 and 11). The unprotected indolealdehyde, 2-bromo-1*H*-indole-3-carboxaldehyde (**5d**), underwent palladium-catalyzed Sonogashira coupling with phenylacetylene, producing the corresponding alkynylaldehyde **6l** in a 64% yield. Unfortunately, the subsequent thermal cyclization only afforded a 49% yield of the desired γ-carboline **7k** (entry 12).

Scheme 5

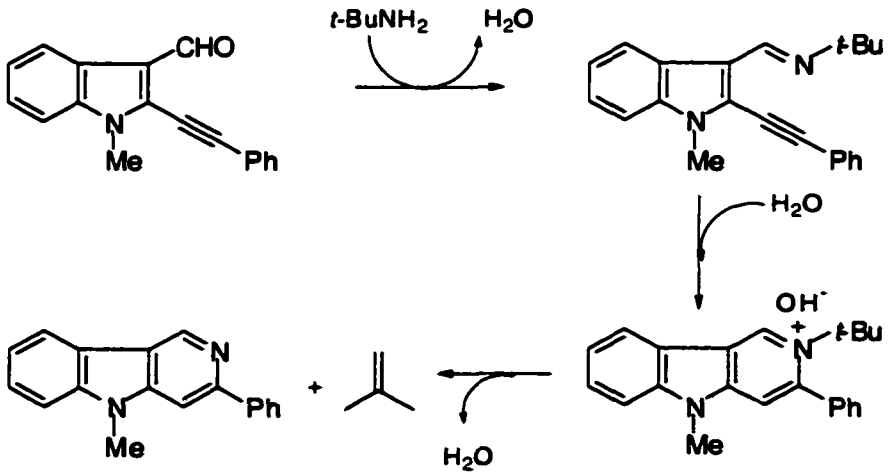


We believe that a reasonable mechanism for the synthesis of β-carbolines by the palladium/copper-catalyzed coupling and copper-catalyzed cyclization of

terminal acetylenes involves CuI coordinating to the carbon-carbon triple bond of the *tert*-butylimine, followed by intramolecular nucleophilic attack of the nitrogen of the imine moiety on the carbon-carbon triple bond forming a β-carbolinium intermediate. This copper intermediate is presumably protonated by spurious amounts of water present in the system, regenerating CuI and producing a carbolinium salt, which then relieves the strain resulting from the interaction with the substituent present on the neighboring carbon by fragmentation of the *tert*-butyl group,[17] producing the β-carboline (Scheme 5).

We also propose a mechanism for the synthesis of γ-carbolines by the palladium/copper-catalyzed coupling and thermal cyclization of terminal acetylenes (Scheme 6). Specifically, the nitrogen of the imine moiety nucleophilically attacks the carbon-carbon triple bond of the *tert*-butylimine, capturing a proton from water to form the γ-carbolinium salt. The *tert*-butyl group in the γ-carbolinium salt apparently fragments to relieve the strain resulting from the interaction with the substituent present in the 3-position.

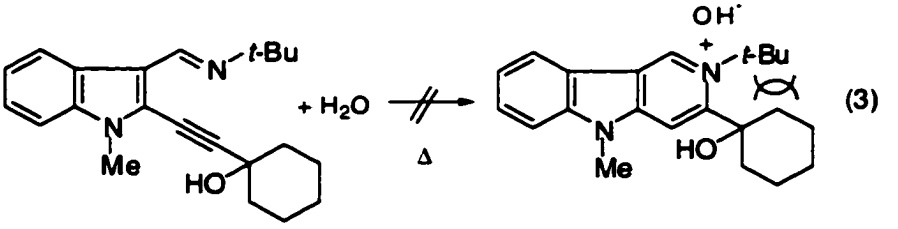
Scheme 6



It is now easy to understand why the copper-catalyzed cyclization of the *tert*-butylimine of the silyl-substituted alkynylindole **3h** and the thermal cyclization of the *tert*-butylimine of the silyl-substituted alkynylindole **6g** both afforded the corresponding desilylated carbolinium salts.[18] In these two cases, the triethylsilyl

group undergoes protodesilylation under the reaction conditions. Due to the lack of strain between the *tert*-butyl group and the hydrogen in the 3-position, the *tert*-butyl group either fragments incompletely (β-carboline synthesis), or survives without fragmentation (γ-carboline synthesis) under the standard reaction conditions. However, a higher temperature (130 °C) promotes thermal fragmentation of the *tert*-butyl group, as discussed previously.

It is also understandable that when the bulky 1-hydroxycyclohexyl substituted alkynylindole **6h** was subjected to thermal cyclization under the standard conditions, which are successful for the less bulky substituted alkynylindoles **6a-f**, the reaction produced none of the desired γ-carboline, but afforded the corresponding *tert*-butylimine instead. Apparently, the steric interaction between two neighboring bulky groups disfavors formation of the γ-carbolinium salt intermediate (eq 3). The presence of a catalytic amount of CuI



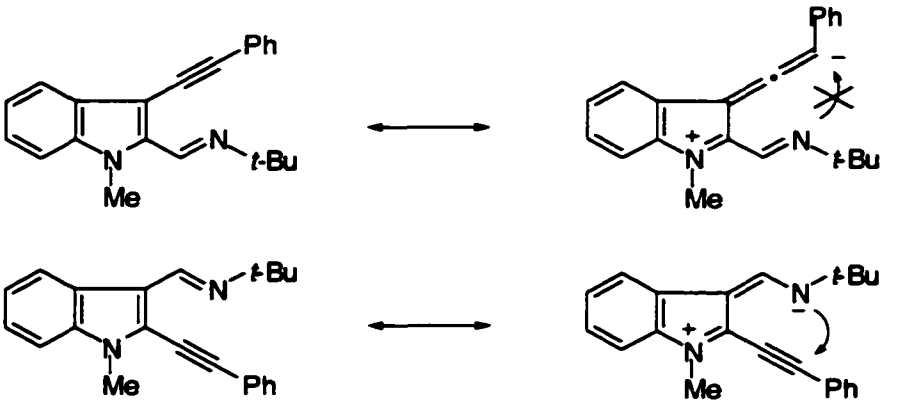
(3)

apparently accelerates loss of the hydroxycyclohexyl group,[16] as we observed disappearance of the *tert*-butylimine of alkynylindole **6h** and formation of the fragmented γ-carbolinium salt in only 2 h. As discussed previously, the fragmentation process also occurs during the corresponding β-carboline synthesis, which might also be catalyzed by the presence of CuI.

It is worth noting that the nitrogen of the indole moiety of the *tert*-butylimine of the alkynylindoles **3** can donate electrons through resonance to increase the electron density on the carbon-carbon triple bond. Therefore, the carbon-carbon triple bond is less electrophilic, and thus requires CuI coordination to decrease the electron density. On the contrary, the nitrogen of the indole moiety of the *tert*-butylimine of the alkynylindoles **5** donates electrons through resonance to the

nitrogen of the imine moiety, which consequently becomes a better nucleophile. As a result, *in situ* nucleophilic attack of the imino-nitrogen on the carbon-carbon triple bond proceeds smoothly under the thermal conditions used to produce the imine (Scheme 7).

Scheme 7



Conclusions

In conclusion, an efficient palladium/copper-catalyzed coupling and copper-catalyzed or thermal-promoted synthesis of β- and γ-carbolines has been developed. A wide variety of functionalized terminal acetylenes participate in this process to afford the desired nitrogen heterocycles in good to excellent yields. However, triethylsilyl- and 1-hydroxycyclohexyl-substituted acetylenes generate the desilylated and fragmented carbolines in moderate yields at an elevated temperature.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75 MHz or 400 and 100 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. All reagents were used directly as obtained commercially. 3-Iodo-1-(methoxymethyl)indole-2-carboxaldehyde[19] (**4b**), 3-iodo-1*H*-indole-2-carboxaldehyde[19] (**4d**), 2-bromo-1*H*-indole-3-carboxaldehyde[20] (**5d**) and methyl 1-

undecynoate[21] were prepared according to previous literature procedures. 3-Iodo-1-methylindole-2-carboxaldehyde (**4a**), 2-bromo-1-methylindole-3-carboxaldehyde (**5a**), 2-bromo-1-(methoxymethyl)indole-3-carboxaldehyde (**5b**), 3-iodo-1-methylindole-2-methylene-*tert*-butylamine and 2-iodo-1-methylindole-3-methylene-*tert*-butylamine have been reported previously.[11] Following is the preparation of the starting materials 2-ethynylbenzofuran, 1-benzyl-3-iodoindole-2-carboxaldehyde (**4c**) and 1-benzyl-2-bromoindole-3-carboxaldehyde (**5c**).

2-Ethynylbenzofuran. *tert*-Butyl lithium (6.5 mL, 1.7 M in pentane, 11 mmol) was added to a solution of benzofuran (1.18 g, 10 mmol) in dry ether (20 mL) at –78 °C. The mixture was stirred for 30 min and a solution of I_2 (2.85 g, 11 mmol) in dry ether (30 mL) was added. The mixture was stirred for another 30 min, allowed to warm to room temperature, diluted with satd aq NH_4Cl, and extracted with ether. The organic solution was washed with $Na_2S_2O_3$ and water, dried over Na_2SO_4 and the solvent evaporated under reduced pressure, affording 2.32 g (95%) of crude 2-iodobenzofuran as a yellow oil in > 90% purity, which was confirmed by ^{1}H NMR spectroscopy.

To 2.32 g of crude 2-iodobenzofuran was added CuI (19 mg, 1 mol %), $PdCl_2(PPh_3)_2$ (133 mg, 2 mol %), Et_3N (20 mL) and trimethylsilylacetylene (1.12 g, 11 mmol, 1.2 equiv). The mixture was flushed with Ar and heated at 60 °C for 3 h. The precipitate and solvent were filtered and evaporated, affording 2.24 g (100%) of crude 2-(trimethylsilylethynyl)benzofuran as a yellow oil, which was then dissolved in CH_3OH (20 mL) containing KOH (0.533 g, 9.5 mmol, 1 equiv). The mixture was stirred at room temperature for 30 min. The solvent was evaporated by vaccum and the residue was purified by column chromatography using hexanes, affording 0.86 g (64% based on benzofuran) of 2-ethynylbenzofuran as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.49 (s, 1H), 7.00 (d, J = 0.4 Hz, 1H), 7.24 (dt, J = 8.0, 1.2 Hz, 1H), 7.35 (dt, J = 8.0, 1.2 Hz, 1H), 7.46 (dd, J = 8.0, 0.8 Hz, 1H), 7.56 (dd, J = 8.0, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 74.2, 83.5, 111.4, 112.7, 121.4, 123.5, 126.0, 127.2, 137.7, 154.8.

1-Benzyl-3-iodoindole-2-carboxaldehyde (4c). This aldehyde was prepared as a white solid in 100% yield by the method used to prepare 3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde[19] only employing 3-iodo-1*H*-indole-2-carboxaldehyde and benzyl iodide: mp 114-115 °C; ^{1}H NMR ($CDCl_3$) δ 5.84 (s, 2H), 7.08 (d, J = 6.8 Hz, 2H), 7.20-7.27 (m, 4H), 7.35 (d, J = 8.4 Hz, 1H), 7.43 (dt, J = 8.0, 0.4 Hz, 1H), 7.61 (d, J = 8.4 Hz, 1H), 10.00 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 48.0, 111.4, 122.1, 123.9, 126.6, 127.6, 128.5, 128.7, 130.0, 131.1, 137.4, 140.4, 184.5.

1-Benzyl-2-bromoindole-3-carboxaldehyde (5c). This aldehyde was prepared as a pale yellow solid in 97% yield by the method used to prepare 3-iodo-1-(methoxymethyl)indole-2-carboxaldehyde[19] only employing 2-bromo-1*H*-indole-3-carboxaldehyde and benzyl iodide: mp 124-126 °C (lit.[22] mp 125 °C); the ^{1}H NMR spectral data are consistent with those previously reported;[22] ^{13}C NMR ($CDCl_3$) δ 48.9, 110.6, 121.5, 123.7, 124.5, 125.7, 126.3, 126.6, 126.7, 128.3, 129.3, 135.4, 137.3, 185.8.

General Procedure for the Synthesis of β-Carbolines by the Palladium/Copper-Catalyzed Coupling and Copper-Catalyzed Cyclization of Terminal Acetylenes. CuI (1.0 mg, 1 mol %), $PdCl_2(PPh_3)_2$ (7.0 mg, 2 mol %), the *N*-substituted 3-iodoindole-2-carboxaldehyde (0.50 mmol), and Et_3N (4 mL) were placed in a 2-dram vial. The contents were stirred for 1 min and the appropriate acetylene (0.60 mmol) was added. The vial was flushed with Ar and heated in an oil bath at 60 °C for the indicated period of time. Completion of the reactions was established by TLC analysis. The precipitate was removed by filtration. The solvent was evaporated under reduced pressure and the coupling product was isolated by chromatography on a silica gel column. A small amount of the coupling product was used for characterization. The remaining material was transferred to another 2-dram vial, and *tert*-butylamine (5 mL/mmol) was added. The mixture was flushed with Ar and the vial was carefully sealed. The mixture was heated at 100 °C for 24 h and then cooled, diluted with ether, dried over Na_2SO_4, and filtered. The solvent was

evaporated under reduced pressure, giving the corresponding *tert*-butylimine. The *tert*-butylimine was transferred to a 2-dram vial, CuI (10 mol %) and DMF (10 mL/mmol) were added. The mixture was flushed with Ar and heated at 100 °C for the indicated period of time. Completion of the reactions was established by TLC analysis. DMF was removed under reduced pressure by rotary evaporation and the β-carboline was isolated by column chromatography.

General Procedure for the Synthesis of γ-Carbolines by the Palladium/Copper-Catalyzed Coupling and Thermal Cyclization of Terminal Acetylenes. The *N*-substituted 2-bromoindole-3-carboxaldehyde (0.50 mmol), Et_3N (4 mL) and DMF (0.4 mL, to increase the solubility of the aldehyde) were used. The rest of the procedure is identical to that used for the coupling reactions in the β-carboline synthesis. A small amount of the coupling product was used for characterization. The remaining material was transferred to a 2-dram vial and *tert*-butylamine (5 mL/mmol) was added. The mixture was flushed with Ar and the vial was carefully sealed. The mixture was heated at 100 °C for the indicated period of time. Completion of the reactions was established by TLC analysis. The solvent was evaporated under reduced pressure and the γ-carboline was isolated by column chromatography.

Alkynylindoles Prepared

1-Methyl-3-(phenylethynyl)indole-2-carboxaldehyde (3a). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 130 mg (100%) of the indicated compound as a yellow solid: mp 87-89 °C; ^{1}H NMR ($CDCl_3$) δ 4.07 (s, 3H), 7.25 (m, 1H), 7.37 (m, 4H), 7.45 (t, J = 8.0 Hz, 1H), 7.59 (m, 2H), 7.89 (d, J = 8.0 Hz, 1H), 10.26 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 31.9, 80.4, 97.0, 110.6, 111.9, 121.7, 122.3, 123.1, 127.7, 127.8, 128.5, 128.6, 131.6, 135.5, 139.6, 182.3; IR (neat, cm^{-1}) 2207, 1669; HRMS calcd for $C_{18}H_{13}NO$: 259.0997. Found: 259.1001.

3-(1-Cyclohexenylethynyl)-1-methylindole-2-carboxaldehyde (3b). The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford 129 mg

(98%) of the indicated compound as a yellow solid: mp 71-73 °C; ^{1}H NMR ($CDCl_3$) δ 1.61-1.69 (m, 2H), 1.69-1.97 (m, 2H), 2.18-2.21 (m, 2H), 2.29-2.32 (m, 2H), 4.08 (s, 1H), 6.31 (m, 1H), 7.22 (m, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.45 (m, 1H), 7.82 (d, J = 8.4 Hz, 1H), 10.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.5, 21.3, 24.8, 28.3, 30.7, 76.5, 98.0, 109.4, 111.7, 119.7, 120.4, 121.2, 126.6, 126.7, 134.1, 134.8, 138.5, 181.4; IR (neat, cm^{-1}) 2935, 2178, 1668; HRMS calcd for $C_{18}H_{17}NO$: 263.1310. Found: 263.1314.

3-(1-Decynyl)-1-methylindole-2-carboxaldehyde (3c). The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford 130 mg (88%) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 6.8 Hz, 3H), 1.22-1.40 (m, 8H), 1.45-1.55 (m, 2H), 1.64-1.71 (m, 2H), 2.54 (t, J = 8.0 Hz, 2H), 4.07 (s, 3H), 7.21 (t, J = 7.2 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.44 (m, 1H), 7.81 (d, J = 8.0 Hz, 1H), 10.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.1, 18.9, 21.7, 27.8, 27.9, 28.1, 28.2, 30.7, 30.8, 70.2, 97.4, 109.3, 112.2, 120.2, 121.2, 126.6, 126.9, 134.4, 138.5, 181.5; IR (neat, cm^{-1}) 2926, 2232, 1654; HRMS calcd for $C_{20}H_{25}NO$: 295.1936. Found: 295.1939.

3-(Cyclohexylethynyl)-1-methylindole-2-carboxaldehyde (3d). The reaction mixture was chromatographed using hexanes/EtOAc 15:1 to afford 128 mg (96%) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.35-1.50 (m, 3H), 1.50-1.70 (m, 3H), 1.70-1.87 (m, 2H), 1.87-1.98 (m, 2H), 2.75 (m, 1H), 4.04 (s, 3H), 7.20 (m, 1H), 7.33 (m, 1H), 7.42 (m, 1H), 7.80 (dt, J = 8.4, 0.9 Hz, 1H), 10.25 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.4, 24.6, 28.7, 30.3, 31.3, 69.8, 101.1, 108.9, 111.9, 119.8, 120.8, 126.2, 126.4, 133.9, 138.1, 181.1; IR (neat, cm^{-1}) 2929, 2219, 1669; HRMS calcd for $C_{18}H_{19}NO$: 265.1467. Found: 265.1472.

3-(4-Hydroxy-1-butynyl)-1-methylindole-2-carboxaldehyde (3e). The reaction mixture was chromatographed using 1.5:1 hexanes/EtOAc to afford 99 mg (87%) of the indicated compound as a yellow solid: mp 109-110 °C; ^{1}H NMR ($CDCl_3$) δ 1.93 (s, 1H), 2.84 (t, J = 6.4 Hz, 2H), 3.90 (t, J = 6.4 Hz, 2H), 4.07 (s, 1H), 7.23 (m, 1H), 7.37 (d, J = 7.8 Hz, 1H), 7.45 (m, 1H), 7.81 (d, J = 7.8 Hz, 1H), 10.18 (s, 1H);

^{13}C NMR ($CDCl_3$) δ 23.3, 30.7, 60.2, 72.1, 93.2, 109.4, 111.0, 120.5, 121.0, 126.7, 126.8, 134.6, 138.4, 181.3; IR (neat, cm^{-1}) 3420, 2941, 2233, 1667; HRMS calcd for $C_{14}H_{13}NO_2$: 227.0946. Found: 227.0950.

3-(10-Methoxycarbonyl-1-decynyl)-1-methylindole-2-carboxaldehyde (3f). The reaction mixture was chromatographed using 8:1 hexanes/EtOAc to afford 173 mg (98%) of the indicated compound as a yellow solid: mp 53-55 °C; ^1H NMR ($CDCl_3$) δ 1.30-1.45 (m, 6H), 1.45-1.57 (m, 2H), 1.57-1.75 (m, 4H), 2.31 (t, J = 7.2 Hz, 2H), 2.52 (t, J = 7.2 Hz, 2H), 3.66 (s, 3H), 4.07 (s, 3H), 7.23 (m, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.43 (m, 1H), 7.81 (m, 1H), 10.16 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.9, 25.0, 28.8, 28.9, 29.0, 29.1, 29.2, 31.7, 34.1, 51.5, 71.3, 98.4, 110.4, 113.2, 121.3, 122.2, 127.7, 127.9, 135.5, 139.5, 174.4, 182.5; IR (neat, cm^{-1}) 3019, 2929, 2232, 1732, 1664; HRMS calcd for $C_{22}H_{27}NO_3$: 353.1991. Found: 353.1998.

3-(5-Cyano-1-pentynyl)-1-methylindole-2-carboxaldehyde (3g). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 103 mg (82%) of the indicated compound as a yellow oil: ^1H NMR ($CDCl_3$) δ 2.05 (quintet, J = 7.2 Hz, 2H), 2.62 (t, J = 7.2 Hz, 2H), 2.77 (t, J = 6.8 Hz, 2H), 4.08 (s, 3H), 7.24 (t, J = 6.8 Hz, 1H), 7.38 (d, J = 8.8 Hz, 1H), 7.46 (t, J = 6.8 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 10.16 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.4, 19.1, 24.7, 31.8, 73.3, 94.7, 110.6, 111.8, 119.1, 121.6, 122.0, 127.81, 127.82, 135.6, 139.5, 182.2; IR (neat, cm^{-1}) 2940, 2246, 1668; HRMS calcd for $C_{16}H_{14}N_2O$: 250.1106. Found: 250.1110.

1-Methyl-3-(triethylsilylethynyl)indole-2-carboxaldehyde (3h). The reaction mixture was chromatographed using 20:1 hexanes/EtOAc to afford 149 mg (100%) of the indicated compound as a pale yellow solid: mp 55-56 °C; ^1H NMR ($CDCl_3$) δ 0.75 (m, 6H), 1.10 (m, 9H), 4.08 (s, 3H), 7.24 (m, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.45 (m, 1H), 7.82 (dd, J = 8.0, 0.8 Hz, 1H), 10.22 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 4.5, 7.7, 31.8, 96.6, 100.4, 110.5, 112.1, 121.7, 122.2, 127.8, 128.0, 136.1, 139.4, 182.4; IR (neat, cm^{-1}) 2953, 2144, 1674; HRMS calcd for $C_{18}H_{23}NOSi$: 297.1549. Found: 297.1154.

3-(1-Hydroxycyclohexylethynyl)-1-methylindole-2-carboxaldehyde (3i). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 141 mg (100%) of the indicated compound as a yellow solid: mp 147-148 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (m, 1H), 1.50-1.90 (m, 7H), 2.10 (m, 2H), 2.55 (s, 1H), 4.03 (s, 1H), 7.22 (t, J = 7.6 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 7.43 (t, J = 7.6 Hz, 1H), 7.78 (d, J = 8.0 hz, 1H), 10.16 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.6, 25.2, 31.8, 40.2, 69.6, 75.2, 100.7, 110.5, 111.5, 121.6, 122.1, 127.7, 127.8, 135.5, 139.4, 182.3; IR (neat, cm^{-1}) 3407, 2933, 1655; HRMS calcd for $C_{18}H_{19}NO_2$: 281.1416. Found: 281.1421.

1-Methoxymethyl-3-(phenylethynyl)indole-2-carboxaldehyde (3j). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 138 mg (95%) of the indicated compound as a yellow solid: mp 81-83 °C; ^{1}H NMR ($CDCl_3$) δ 3.32 (s, 3H), 6.01 (s, 2H), 7.33 (m, 1H), 7.38-7.45 (m, 3H), 7.51 (m, 1H), 7.57-7.65 (m, 3H), 7.94 (m, 1H), 10.33 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.3, 75.1, 80.1, 98.0, 111.9, 114.4, 122.5, 122.7, 123.0, 128.3, 128.7, 128.8, 129.1, 131.9, 135.7, 139.8, 182.3; IR (neat, cm^{-1}) 2212, 1654; HRMS calcd for $C_{19}H_{15}NO_2$: 289.1103. Found: 289.1108.

1-Benzyl-3-(phenylethynyl)indole-2-carboxaldehyde (3k). The reaction mixture was chromatographed using 12:1 hexanes/EtOAc to afford 149 mg (89%) of the indicated compound as a yellow solid: mp 134-135 °C; ^{1}H NMR ($CDCl_3$) δ 5.85 (s, 2H), 7.11 (d, J = 6.8 Hz, 2H), 7.20-7.30 (m, 4H), 7.38-7.45 (m, 5H), 7.60 (m, 2H), 7.94 (d, J = 8.0 Hz, 1H), 10.32 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 48.2, 80.2, 97.4, 111.3, 112.8, 122.0, 122.4, 123.0, 126.7, 127.6, 128.0, 128.1, 128.6, 128.7, 131.6, 135.1, 137.3, 139.4, 182.1; IR (neat, cm^{-1}) 3061, 2205, 1667; HRMS calcd for $C_{24}H_{17}NO$: 335.1310. Found: 335.1315.

3-(Phenylethynyl)-1*H*-indole-2-carboxaldehyde (3l). The reaction mixture was chromatographed using 4:1 hexanes/EtOAc to afford 122 mg (100%) of the indicated compound as a yellow solid: mp 200 °C (decomp); ^{1}H NMR ($CDCl_3$) δ 7.27 (m, 1H), 7.37-7.44 (m, 3H), 7.44-7.50 (m, 2H), 7.62 (m, 2H), 7.93 (d, J = 8.0 Hz, 1H), 9.42 (s, 1H), 10.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 80.0, 96.7, 110.1, 112.7, 122.0,

122.3, 122.9, 128.2, 128.6, 128.7, 128.8, 131.7, 136.2, 137.0, 181.1; IR (neat, cm^{-1}) 3278, 1652; HRMS calcd for $C_{17}H_{11}NO$: 245.0841. Found: 245.0845.

1-Methyl-2-(phenylethynyl)indole-3-carboxaldehyde (6a). The reaction mixture was chromatographed using 4:1 hexanes/EtOAc to afford 121 mg (93%) of the indicated compound as a yellow solid: mp 118-119 °C (lit.[5g] mp 120-121 °C); ^{13}C NMR ($CDCl_3$) δ 31.3, 77.5, 101.3, 109.8, 119.9, 121.3, 122.3, 123.6, 124.5, 125.1, 128.8, 129.9, 131.9, 132.1, 137.6, 185.2. All other spectral properties are consistent with those reported previously.[5g]

2-(1-Cyclohexenylethynyl)-1-methylindole-3-carboxaldehyde (6b). The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford 130 mg (98%) of the indicated compound as a yellow solid: mp 84-85 °C; ^1H NMR ($CDCl_3$) δ 1.60-1.75 (m, 4H), 2.18-2.25 (m, 2H), 2.26-2.33 (m, 2H), 3.81 (s, 3H), 6.43 (m, 1H), 7.27-7.37 (m, 3H), 8.29 (d, J = 8.0 Hz, 1H), 10.15 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 22.1, 26.0, 28.8, 31.1, 75.1, 103.4, 109.6, 119.3, 119.7, 122.1, 123.4, 124.5, 124.8, 133.0, 137.4, 138.9, 185.3; IR (neat, cm^{-1}) 3016, 2935, 2197, 1659; HRMS calcd for $C_{18}H_{17}NO$: 263.1310. Found: 263.1314.

2-(1-Decynyl)-1-methylindole-3-carboxaldehyde (6c). The reaction mixture was chromatographed using 7:1 hexanes/EtOAc to afford 122 mg (82%) of the indicated compound as a yellow oil: ^1H NMR ($CDCl_3$) δ 0.90 (t, J = 3.2 Hz, 3H), 1.25-1.40 (m, 8H), 1.50 (m, 2H), 1.70 (m, 2H), 2.59 (t, J = 7.2 Hz, 2H), 3.83 (s, 3H), 7.28-7.36 (m, 3H), 8.30 (d, J = 8.4 Hz, 1H), 10.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.2, 19.9, 22.7, 28.3, 29.0, 29.1, 31.1, 31.9, 69.3, 103.8, 109.6, 119.5, 122.1, 123.4, 124.4, 124.7, 137.1, 185.4 (one sp^2 carbon missing due to overlap); IR (neat, cm^{-1}) 2922, 2232, 1644; HRMS calcd for $C_{20}H_{25}NO$: 295.1936. Found: 295.1939.

2-(Cyclohexylethynyl)-1-methylindole-3-carboxaldehyde (6d). The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford 119 mg (89%) of the indicated compound as a yellow solid: mp 63-65 °C; ^1H NMR ($CDCl_3$) δ 1.40-1.52 (m, 3H), 1.52-1.71 (m, 3H), 1.71-1.85 (m, 2H), 1.90-2.00 (m, 2H), 2.80 (m, 1H), 3.82 (s, 1H), 7.26-7.36 (m, 3H), 8.29 (m, 1H), 10.15 (s, 1H); ^{13}C NMR ($CDCl_3$) δ

24.9, 26.0, 30.2, 31.2, 32.4, 69.5, 107.7, 109.8, 119.6, 122.3, 123.5, 124.6, 124.8, 133.6, 137.4, 185.6; IR (neat, cm^{-1}) 2931, 2227, 1654; HRMS calcd for $C_{18}H_{19}NO$: 265.1467. Found: 265.1472.

2-(11-Hydroxy-1-undecynyl)-1-methylindole-3-carboxaldehyde (6e). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford 99 mg (61%) of the indicated compound as a yellow solid: mp 63-65 °C; ^1H NMR ($CDCl_3$) δ 1.30-1.65 (m, 14H), 1.70 (m, 2H), 2.60 (t, J = 7.2 Hz, 2H), 3.65 (t, J = 6.8 Hz, 2H), 3.83 (s, 3H), 7.28-7.37 (m, 3H), 8.30 (d, J = 8.4 Hz, 1H), 10.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.9, 25.7, 28.3, 28.9, 29.3, 29.4, 31.1, 32.8, 63.1, 69.4, 103.7, 109.6, 119.5, 122.1, 123.4, 124.4, 124.7, 133.3, 137.1, 185.4; IR (neat, cm^{-1}) 3347, 2930, 2233, 1644; HRMS calcd for $C_{21}H_{27}NO_2$: 325.2042. Found: 325.2046.

2-(10-Methoxycarbonyl-1-decynyl)-1-methylindole-3-carboxaldehyde (6f). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 153 mg (86%) of the indicated compound as a yellow solid: mp 42-44 °C; ^1H NMR ($CDCl_3$) δ 1.30-1.40 (m, 6H), 1.42-1.57 (m, 2H), 1.57-1.78 (m, 4H), 2.31 (t, J = 7.5 Hz, 2H), 2.59 (t, J = 7.2 Hz, 2H), 3.66 (s, 3H), 3.83 (s, 3H), 7.27-7.38 (m, 3H), 8.29 (dd, J = 8.4, 1.2 Hz, 1H), 10.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.0, 25.1, 28.5, 29.1, 29.30, 29.34, 31.2, 34.3, 51.7, 69.6, 103.8, 109.8, 119.7, 122.3, 123.6, 124.6, 124.9, 133.4, 137.3, 174.5, 185.6 (one sp^3 carbon missing due to overlap); IR (neat, cm^{-1}) 2932, 2231, 1736, 1644; HRMS calcd for $C_{22}H_{27}NO_3$: 353.1991. Found: 353.1998.

1-Methyl-2-(triethylsilylethynyl)indole-3-carboxaldehyde (6g). The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford 140 mg (94%) of the indicated compound as a pale yellow solid: mp 67-69 °C; ^1H NMR ($CDCl_3$) δ 0.78 (m, 6H), 1.09 (m, 9H), 3.86 (s, 3H), 7.29-7.40 (m, 3H), 8.30 (dd, J = 8.4, 1.2 Hz, 1H), 10.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 4.2, 7.6, 31.1, 93.4, 106.6, 109.8, 120.4, 122.4, 123.6, 124.2, 125.2, 132.0, 137.3, 185.3; IR (neat, cm^{-1}) 2955, 2157, 1661; HRMS calcd for $C_{18}H_{23}NOSi$: 297.1549. Found: 297.1154.

2-(1-Hydroxycyclohexylethynyl)-1-methylindole-3-carboxaldehyde (6h). The reaction mixture was chromatographed using 1.5:1 hexanes/EtOAc to afford

122 mg (87%) of the indicated compound as a yellow solid: mp 155-156 °C; ^{1}H NMR ($CDCl_3$) δ 1.25-1.40 (m, 1H), 1.51-1.65 (m, 3H), 1.72-1.88 (m, 4H), 2.08-2.15 (m, 2H), 3.30 (br s, 1H), 3.53 (s, 3H), 7.14 (d, *J* = 7.6 Hz, 1H), 7.26-7.34 (m, 2H), 8.26 (dd, *J* = 6.8, 1.6 Hz, 1H), 10.08 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 23.4, 25.1, 30.8, 39.7, 69.2, 72.3, 106.2, 109.7, 119.5, 122.1, 123.6, 124.2, 124.9, 132.2, 137.1, 185.5; IR (neat, cm^{-1}) 3390, 2934, 1642; HRMS calcd for $C_{18}H_{19}NO_2$: 281.1416. Found: 281.1421.

2-(2-Benzofurylethynyl)-1-methylindole-3-carboxaldehyde (6i). The reaction mixture was chromatographed using hexanes/EtOAc 4:1 to afford 79 mg (78%) of the indicated compound as a yellow solid: mp 147-148 °C; ^{1}H NMR ($CDCl_3$) δ 3.93 (s, 3H), 7.21 (s, 1H), 7.28-7.37 (m, 3H), 7.37-7.43 (m, 2H), 7.52 (d, *J* = 8.4 Hz, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 8.34 (m, 1H), 10.28 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 31.5, 83.4, 91.0, 109.8, 111.5, 114.3, 120.8, 121.7, 122.4, 123.8, 124.5, 125.6, 126.7, 127.3, 130.1, 137.0, 137.8, 155.4, 184.9; IR (neat, cm^{-1}) 3062, 2206, 1652; HRMS calcd for $C_{20}H_{13}NO_2$: 299.0946. Found: 299.0950.

1-Methoxymethyl-2-(phenylethynyl)indole-3-carboxaldehyde (6j). The reaction mixture was chromatographed using 4:1 hexanes/EtOAc to afford 140 mg (97%) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 3.38 (s, 3H), 5.72 (s, 2H), 7.35-7.50 (m, 5H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.63 (m, 2H), 8.35 (d, *J* = 7.8 Hz, 1H), 10.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.6, 75.6, 77.2, 101.5, 110.7, 120.9, 121.1, 122.3, 124.1, 124.8, 125.7, 128.8, 130.1, 131.8, 131.9, 137.1, 185.7; IR (neat, cm^{-1}) 2210, 1657; HRMS calcd for $C_{19}H_{15}NO_2$: 289.1103. Found: 289.1108.

1-Benzyl-2-(phenylethynyl)indole-3-carboxaldehyde (6k). The reaction mixture was chromatographed using 4.5:1 hexanes/EtOAc to afford 122 mg (73%) of the indicated compound as a yellow solid: mp 119-120 °C; ^{1}H NMR ($CDCl_3$) δ 5.56 (s, 2H), 7.22-7.35 (m, 8H), 7.35-7.45 (m, 3H), 7.56 (m, 2H), 8.36 (m, 1H), 10.34 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 48.7, 77.6, 101.4, 110.4, 120.2, 121.2, 122.3, 123.6, 124.8, 125.2, 126.9, 128.0, 128.7, 129.0, 129.9, 131.9, 136.0, 137.1, 185.4; IR (neat, cm^{-1}) 3060, 2211, 1655; HRMS calcd for $C_{24}H_{17}NO$: 335.1310. Found: 335.1315.

2-(Phenylethynyl)-1*H*-indole-3-carboxaldehyde (6l). The reaction mixture was chromatographed using 2.5:1 hexanes/EtOAc to afford 79 mg (64%) of the indicated compound as a yellow solid: mp 171-172 °C; ^{1}H NMR ($CDCl_3$) δ 7.30-7.45 (m, 6H), 7.57 (dd, J = 7.2, 1.2 Hz, 2H), 8.35 (d, J = 7.6 Hz, 1H), 9.08 (s, 1H), 10.33 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 78.2, 98.4, 111.1, 120.8, 121.2, 122.1, 123.6, 124.5, 125.5, 128.7, 129.4, 129.8, 131.9, 135.9, 185.7; IR (neat, cm^{-1}) 3198, 1637; HRMS calcd for $C_{17}H_{11}NO$: 245.0841. Found: 245.0845.

Carbolines Prepared

9-Methyl-3-phenyl-9*H*-pyrido[3,4-*b*]indole (2a). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford a 90% yield of the indicated compound as a yellow solid: mp 135-136 °C; ^{1}H NMR (acetone-d_6) δ 3.99 (s, 3H), 7.27-7.38 (m, 2H), 7.45-7.51 (m, 2H), 7.58-7.63 (m, 2H), 8.24 (m, 2H), 8.31 (dt, J = 7.8, 0.9 Hz, 1H), 8.64 (d, J = 0.9 Hz, 1H), 9.01 (d, J = 0.9 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 29.0, 109.9, 110.8, 119.7, 121.5, 122.0, 126.6, 127.6, 128.5, 128.7, 129.2, 132.0, 136.7, 140.9, 142.5, 146.9; IR (neat, cm^{-1}) 3057, 2934; HRMS calcd for $C_{18}H_{14}N_2$: 258.1157. Found: 258.1161.

3-(1-Cyclohexenyl)-9-methyl-9*H*-pyrido[3,4-*b*]indole (2b). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford a 93% yield of the indicated compound as a yellow solid: mp 110-111 °C; ^{1}H NMR (acetone-d_6) δ 1.65-1.75 (m, 2H), 1.75-1.85 (m, 2H), 2.27 (m, 2H), 2.65 (m, 2H), 3.96 (s, 3H), 6.77 (m, 1H), 7.25 (m, 1H), 7.55-7.62 (m, 2H), 8.15 (s, 1H), 8.23 (d, J = 7.8 Hz, 1H), 8.89 (s, 1H); ^{13}C NMR (acetone-d_6) δ 22.5, 23.2, 25.8, 26.5, 109.8, 119.5, 121.5, 121.8, 124.9, 128.3, 128.8, 131.1, 137.4, 142.4, 149.2 (one sp^3 carbon missing due to overlap); IR (neat, cm^{-1}) 3026, 2927; HRMS calcd for $C_{18}H_{18}N_2$: 262.1470. Found: 262.1475.

9-Methyl-3-*n*-octyl-9*H*-pyrido[3,4-*b*]indole (2c). The reaction mixture was chromatographed using 1:1 hexanes/EtOAc to afford a 93% yield of the indicated compound as a yellow oil: ^{1}H NMR (acetone-d_6) δ 0.87 (m, 3H), 1.25-1.40 (m, 10H),

1.82 (m, 2H), 2.94 (t, J = 7.8 Hz, 2H), 3.97 (s, 3H), 7.23 (m, 1H), 7.59 (dd, J = 4.5, 0.9 Hz, 2H), 7.91 (d, J = 0.9 Hz, 1H), 8.20 (dt, J = 8.1, 0.9 Hz, 1H), 8.87 (d, J = 0.9 Hz, 1H); ^{13}C NMR (acetone-d_6) δ 13.7, 28.4, 28.9, 29.4, 29.5, 29.6, 30.7, 32.0, 38.1, 109.7, 112.6, 119.3, 121.2, 121.8, 128.2, 128.8, 131.5, 135.9, 142.4, 151.4; IR (neat, cm^{-1}) 3055, 2924; HRMS calcd for $C_{20}H_{26}N_2$: 294.2096. Found: 294.2101.

3-Cyclohexyl-9-Methyl-9*H*-pyrido[3,4-*b*]indole (2d). The reaction mixture was chromatographed using 20:1 $CHCl_3/CH_3OH$ to afford an 87% yield of the indicated compound as a yellow solid: mp 129-130 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (tt, J = 12.0, 3.2 Hz, 1H), 1.48 (qt, J = 12.8, 2.4 Hz, 2H) 1.65 (qd, J = 12.4, 2.8 Hz, 2H), 1.79 (d, J = 12.8 Hz, 1H), 1.91 (d, J = 13.2 Hz, 2H), 2.08 (d, J = 11.6 Hz, 2H), 2.91 (tt, J = 12.0, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.3, 26.9, 29.4, 33.9, 46.5, 109.1, 111.1, 119.3, 121.2, 121.8, 128.2, 129.3, 130.8, 135.8, 142.2, 156.0; IR (neat, cm^{-1}) 2925, 2851; HRMS calcd for $C_{18}H_{20}N_2$: 264.1627. Found: 264.1632.

3-(2-Hydroxyethyl)-9-methyl-9*H*-pyrido[3,4-*b*]indole (2e). The reaction mixture was chromatographed using acetone to afford a 95% yield of the indicated compound as a white solid: mp 135-136 °C; ^{1}H NMR (acetone-d_6) δ 3.13 (t, J = 6.4 Hz, 2H), 3.96 (t, J = 6.4 Hz, 2H), 3.99 (s, 3H), 7.27 (m, 1H), 7.61 (d, J = 4.0 Hz, 2H), 7.96 (s, 1H), 8.22 (d, J = 8.0 Hz, 1H), 8.88 (s, 1H); ^{13}C NMR (acetone-d_6) δ 29.6, 41.2, 63.1, 110.4, 114.2, 120.1, 121.7, 122.5, 129.1, 129.6, 132.1, 136.8, 143.1, 150.0; IR (neat, cm^{-1}) 3212, 2920; HRMS calcd for $C_{14}H_{14}N_2O$: 226.1106. Found: 226.1111.

3-(8-Methoxycarbonyl-1-octyl)-9-methyl-9*H*-pyrido[3,4-*b*]indole (2f). The reaction mixture was chromatographed using 20:1 $CHCl_3/CH_3OH$ to afford a 95% yield of the indicated compound as a yellow oil, which crystallized upon standing at 0 °C overnight: mp 67-68 °C; ^{1}H NMR ($CDCl_3$) δ 1.25-1.40 (m, 8H), 1.60 (m, 2H), 1.80 (m, 2H), 2.29 (t, J = 7.5 Hz, 2H), 2.97 (t, J = 7.5 Hz, 2H), 3.65 (s, 3H), 3.90 (s, 3H), 7.26 (m, 1H), 7.42 (d, J = 7.8 Hz, 1H), 7.59 (dt, J = 7.8, 0.9 Hz, 1H), 7.80 (br s, 1H), 8.11 (d, J = 7.6 Hz, 1H), 8.79 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.2, 29.37, 29.43, 29.6, 31.0, 34.3, 51.7, 109.3, 119.5, 121.2, 122.0, 128.4, 129.4, 142.4, 174.6 (two sp^3

carbons are missing due to overlap; two unusual broad peaks are observed at 113.0 and 131.0 ppm, and two sp^2 carbons somehow are missing, even when the noise was very low. Using the 300 and 400 MHz NMR spectrometers or changing the relaxation time of the spectrometers gave similar incomplete spectra); IR (neat, cm^{-1}) 2926, 1735; Anal. calcd. for $C_{22}H_{28}N_2O_2$: C, 74.97; H, 8.01, N, 7.95. Found: C, 74.45; H, 8.13; N, 7.67; HRMS calcd for $C_{22}H_{28}N_2O_2$: 352.2151. Found: 352.2157.

3-(3-Cyanopropyl)-9-methyl-9*H*-pyrido[3,4-*b*]indole (2g). The reaction mixture was chromatographed using 20:1 $CHCl_3/CH_3OH$ to afford an 88% yield of the indicated compound as an off-white solid: mp 187-188 °C; ^1H NMR ($CDCl_3$) δ 2.20 (quintet, J = 7.2 Hz, 2H), 2.38 (t, J = 7.2 Hz, 2H), 3.10 (t, J = 7.2 Hz, 2H), 3.86 (s, 3H), 7.26 (dt, J = 8.4, 0.6 Hz, 1H), 7.41 (d, J = 8.4 Hz, 1H), 7.59 (m, 1H), 7.79 (s, 1H), 8.09 (d, J = 7.8 Hz, 1H), 8.77 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.6, 26.0, 29.4, 36.5, 109.3, 113.6, 119.6, 119.9, 120.8, 121.9, 128.5, 129.3, 131.3, 142.2, 148.3; IR (neat, cm^{-1}) 3052, 2930, 2243; HRMS calcd for $C_{16}H_{15}N_3$: 249.1266. Found: 249.1270.

9-Methyl-9*H*-pyrido[3,4-*b*]indole (2h). The reaction mixture was chromatographed using 10:1 $CHCl_3/CH_3OH$ to afford a 41% yield of the indicated compound as a yellow solid: mp 104-106 °C (lit.[23] mp 106-107 °C); ^1H NMR ($CDCl_3$) δ 3.84 (s, 3H), 7.26 (t, J = 7.6 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.58 (t, J = 8.0 Hz, 1H), 7.90 (br s, 1H), 8.09 (d, J = 7.6 Hz, 1H), 8.46 (br s, 1H), 8.86 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.3, 109.2, 119.6, 121.0, 121.8, 128.2, 128.4, 131.8, 138.8, 141.7 (one unusual broad peak is observed at 114.5 ppm and one sp^2 carbon is missing due to overlap); IR (neat, cm^{-1}) 3050, 2926; HRMS calcd for $C_{12}H_{10}N_2$: 182.0844. Found: 182.0846.

9-Methoxymethyl-3-phenyl-9*H*-pyrido[3,4-*b*]indole (2i). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford a 100% yield of the indicated compound as a white solid: mp 114-115 °C; ^1H NMR (acetone-d_6) δ 3.30 (s, 3H), 5.90 (s, 2H), 7.34 (q, J = 7.6 Hz, 2H), 7.47 (t, J = 7.6 Hz, 2H), 7.62 (t, J = 7.6 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 8.22 (d, J = 8.0 Hz, 2H), 8.34 (d, J = 8.0 Hz, 1H), 8.68 (s, 1H), 9.14 (s, 1H); ^{13}C NMR (acetone-d_6) δ 55.5, 74.1, 110.6, 110.8,

120.6, 121.9, 126.5, 127.7, 128.6, 128.7, 130.0, 132.5, 136.2, 140.4, 142.0, 147.8; IR (neat, cm^{-1}) 3062, 1461; HRMS calcd for $C_{19}H_{16}N_2O$: 288.1263. Found: 288.1267.

9-Benzyl-3-phenyl-9*H*-pyrido[3,4-*b*]indole (2j). The reaction mixture was chromatographed using 4.5:1 hexanes/EtOAc to afford a 99% yield of the indicated compound as a white solid: mp 145-146 °C; ^1H NMR ($CDCl_3$) δ 5.53 (s, 2H), 7.17-7.20 (m, 2H), 7.20-7.30 (m, 3H), 7.30-7.58 (m, 6H), 8.09 (dd, J = 7.2, 1.5 Hz, 2H), 8.19 (d, J = 7.8 Hz, 1H), 8.38 (d, J = 0.6 Hz, 1H), 8.87 (d, J = 0.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 47.3, 110.1, 111.6, 120.2, 121.9, 122.2, 126.8, 127.0, 128.0, 128.1, 128.9, 129.0, 129.2, 130.0, 132.0, 136.2, 136.7, 140.7, 142.1, 148.1; IR (neat, cm^{-1}) 3059, 3030, 2936; HRMS calcd for $C_{24}H_{18}N_2$: 334.1470. Found: 334.1476.

5-Methyl-3-phenyl-5*H*-pyrido[4,3-*b*]indole (7a). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford a 92% yield of the indicated compound as a yellow solid: mp 106-107 °C (lit.[5g] mp 106-107 °C); ^1H NMR ($CDCl_3$) δ 3.89 (s, 3H), 7.34 (t, J = 7.6 Hz, 1H), 7.40-7.46 (m, 2H), 7.49-7.56 (m, 3H), 7.69 (s, 1H), 8.11 (d, J = 8.0 Hz, 2H), 8.17 (d, J = 8.0 Hz, 1H), 9.36 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.1, 100.6, 108.9, 118.7, 120.6, 120.7, 121.3, 126.7, 127.3, 128.5, 128.8, 140.6, 141.5, 142.3, 146.1, 153.6; IR (neat, cm^{-1}) 3054, 1594; HRMS calcd for $C_{18}H_{14}N_2$: 258.1157. Found: 258.1161.

3-(1-Cyclohexenyl)-5-methyl-5*H*-pyrido[4,3-*b*]indole (7b). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford a 93% yield of the indicated compound as a pale yellow solid: mp 99-100 °C; ^1H NMR ($CDCl_3$) δ 1.72 (m, 2H), 1.85 (m, 2H), 2.32 (m, 2H), 2.63 (m, 2H), 3.78 (s, 3H), 6.85 (m, 1H), 7.25-7.30 (m, 2H), 7.36 (d, J = 8.0 Hz, 1H), 7.48 (dt, J = 8.0, 0.9 Hz, 1H), 8.10 (d, J = 8.0 Hz, 1H), 9.20 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.3, 23.1, 26.1, 26.6, 29.0, 98.8, 108.8, 118.1, 120.4, 120.5, 121.6, 126.3, 128.0, 137.1, 141.4, 141.6, 146.0, 155.4; IR (neat, cm^{-1}) 3050, 2928; HRMS calcd for $C_{18}H_{18}N_2$: 262.1470. Found: 262.1475.

5-Methyl-3-*n*-octyl-5*H*-pyrido[4,3-*b*]indole (7c). The reaction mixture was chromatographed using 20:1 $CHCl_3/CH_3OH$ to afford an 87% yield of the indicated

compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.87 (t, *J* = 6.8 Hz, 3H), 1.20-1.45 (m, 10H), 1.82 (m, 2H), 2.95 (t, *J* = 8.0 Hz, 2H), 3.79 (s, 3H), 7.11 (s, 1H), 7.29 (m, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.49 (m, 1H), 8.10 (d, *J* = 8.0 Hz, 1H), 9.19 (s, 1H); ^{13}C NMR (acetone-d_6) δ 14.2, 22.7, 29.1, 29.3, 29.6, 30.7, 31.9, 39.2, 102.2, 108.8, 117.8, 120.4, 121.6, 126.3, 141.2, 141.9, 146.1, 158.3; IR (neat, cm^{-1}) 3052, 2924; HRMS calcd for $C_{20}H_{26}N_2$: 294.2096. Found: 294.2101.

3-Cyclohexyl-5-methyl-5*H*-pyrido[4,3-*b*]indole (7d). The reaction mixture was chromatographed using 20:1 $CHCl_3/CH_3OH$ to afford an 83% yield of the indicated compound as a yellow solid: mp 134-135 °C; ^{1}H NMR ($CDCl_3$) δ 1.36 (tt, *J* = 12.0, 3.2 Hz, 1H), 1.48 (qt, *J* = 12.8, 2.4 Hz, 2H) 1.65 (qd, *J* = 12.4, 3.2 Hz, 2H), 1.79 (d, *J* = 12.4 Hz, 1H), 1.91 (dt, *J* = 13.2, 2.8 Hz, 2H), 2.07 (dd, *J* = 11.2, 1.6 Hz, 2H), 2.89 (tt, *J* = 12.0, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 26.3, 26.8, 29.1, 33.6, 47.2, 100.4, 108.8, 117.9, 120.4, 120.5, 121.6, 126.3, 141.2, 141.8, 146.2, 162.7; IR (neat, cm^{-1}) 2924, 2851; HRMS calcd for $C_{18}H_{20}N_2$: 264.1627. Found: 264.1632.

3-(9-Hydroxy-1-nonyl)-5-methyl-5*H*-pyrido[4,3-*b*]indole (7e). The reaction mixture was chromatographed using 10:1 $CHCl_3/CH_3OH$ to afford a 72% yield of the indicated compound as a white solid: mp 120-121 °C; ^{1}H NMR ($CDCl_3$) δ 1.28-1.45 (m, 10H), 1.55 (m, 2H), 1.81 (m, 2H), 1.92 (br s, 1H), 2.95 (t, *J* = 8.0 Hz, 2H), 3.63 (t, *J* = 6.8 Hz, 2H), 3.81 (s, 3H), 7.12 (s, 1H), 7.30 (t, *J* = 7.8 Hz, 1H), 7.40 (d, *J* = 8.0 Hz, 1H), 7.50 (dt, *J* = 8.0, 0.8 Hz, 1H), 8.11 (d, *J* = 8.0 Hz, 1H), 9.19 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 25.8, 29.1, 29.4, 29.50, 29.53, 29.55, 30.6, 32.9, 39.1, 62.9, 102.2, 108.8, 117.8, 120.4, 120.5, 121.5, 126.3, 141.2, 141.8, 146.1, 158.3; IR (neat, cm^{-1}) 3199, 2917; HRMS calcd for $C_{21}H_{28}N_2O$: 324.2202. Found: 324.2206.

3-(8-Methoxycarbonyl-1-octyl)-5-methyl-5*H*-pyrido[4,3-*b*]indole (7f). The reaction mixture was chromatographed using 20:1 $CHCl_3/CH_3OH$ to afford an 88% yield of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.25-1.45 (m, 8H), 1.61 (m, 2H), 1.82 (m, 2H), 2.29 (t, *J* = 7.5 Hz, 2H), 2.94 (t, *J* = 7.8 Hz, 2H), 3.65 (s, 3H), 3.80 (s, 3H), 7.11 (s, 1H), 7.29 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 7.5 Hz, 1H), 7.49 (t, *J* = 7.5 Hz, 1H), 8.10 (d, *J* = 7.5 Hz, 1H), 9.19 (s, 1H); ^{13}C NMR ($CDCl_3$)

δ 25.2, 29.2, 29.3, 29.4, 29.6, 29.7, 30.8, 34.3, 39.3, 51.7, 102.3, 109.0, 118.0, 120.5, 120.6, 121.7, 126.5, 141.3, 142.1, 146.3, 158.5, 174.6; IR (neat, cm^{-1}) 2927, 1734; HRMS calcd for $C_{22}H_{28}N_2O_2$: 352.2151. Found: 352.2157.

5-Methyl-5*H*-pyrido[4,3-*b*]indole (7g). The reaction mixture was chromatographed using 10:1 $CHCl_3/CH_3OH$ to afford a 43% yield of the indicated compound as a yellow oil: ^1H NMR ($CDCl_3$) δ 3.80 (s, 3H), 7.28 (br s, 1H), 7.32 (dt, *J* = 7.8, 0.9 Hz, 1H), 7.42 (d, *J* = 8.1 Hz, 1H), 7.53 (dt, *J* = 8.1, 0.9 Hz, 1H), 8.13 (d, *J* = 7.8 Hz, 1H), 8.60 (br s, 1H), 9.30 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.3, 109.2, 120.8, 120.9, 121.6, 127.1, 141.1, 142.7, 144.9, 145.2, 145.3 (one sp^2 carbon missing due to overlap); IR (neat, cm^{-1}) 3045, 2930; HRMS calcd for $C_{12}H_{10}N_2$: 182.0844. Found: 182.0846.

3-(2-Benzofuranyl)-5-methyl-5*H*-pyrido[4,3-*b*]indole (7h). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford a 95% yield of the indicated compound as a yellow solid: mp 167-168 °C; ^1H NMR ($CDCl_3$) δ 3.83 (s, 1H), 7.25 (t, *J* = 7.2 Hz, 1H), 7.31 (t, *J* = 7.2 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.45 (s, 1H), 7.50 (t, *J* = 8.0 Hz, 1H), 7.56 (d, *J* = 8.0 Hz, 1H), 7.64 (d, *J* = 7.8 Hz, 1H), 7.83 (s, 1H), 8.11 (d, *J* = 7.8 Hz, 1H), 9.27 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 29.2, 100.1, 104.1, 109.1, 111.3, 119.0, 120.7, 120.8, 121.4, 121.6, 123.1, 124.8, 126.9, 129.3, 141.6, 142.7, 144.9, 145.5, 155.2, 156.4; IR (neat, cm^{-1}) 3058, 2935; HRMS calcd for $C_{20}H_{14}N_2$: 298.1106. Found: 298.1111.

5-Methoxymethyl-3-phenyl-5*H*-pyrido[4,3-*b*]indole (7i). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford an 80% yield of the indicated compound as a white solid: mp 101-102 °C; ^1H NMR ($CDCl_3$) δ 3.31 (s, 3H), 5.68 (s, 2H), 7.35 (m, 1H), 7.41 (m, 1H), 7.48-7.58 (m, 4H), 7.81 (d, *J* = 0.4 Hz, 1H), 8.09 (m, 2H), 8.14 (d, *J* = 8.0 Hz, 1H), 9.35 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 56.4, 74.2, 101.3, 109.8, 119.3, 120.8, 121.6, 121.9, 127.1, 127.3, 128.6, 128.8, 140.4, 141.1, 142.6, 146.2, 154.2; IR (neat, cm^{-1}) 3057, 1596; HRMS calcd for $C_{19}H_{16}N_2O$: 288.1263. Found: 288.1267.

5-Benzyl-3-phenyl-5*H*-pyrido[4,3-*b*]indole (7j). The reaction mixture was chromatographed using 4:1 hexanes/EtOAc to afford a 90% yield of the indicated compound as a white solid: mp 154-155 °C; ^{1}H NMR ($CDCl_3$) δ 5.52 (s, 2H), 7.15 (m, 2H), 7.23-7.30 (m, 3H), 7.32-7.41 (m, 3H), 7.42-7.50 (m, 3H), 7.65 (s, 1H), 8.04 (dd, J = 7.2, 1.5 Hz, 2H), 8.18 (d, J = 7.5 Hz, 1H), 9.39 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 46.8, 101.2, 109.7, 119.1, 121.0, 121.2, 121.8, 126.6, 127.1, 127.5, 128.1, 128.7, 129.0, 129.2, 136.4, 140.7, 141.4, 142.8, 146.3, 154.1; IR (neat, cm^{-1}) 3059, 3030, 2928; HRMS calcd for $C_{24}H_{18}N_2$: 334.1470. Found: 334.1476.

3-Phenyl-5*H*-pyrido[4,3-*b*]indole (7k). The reaction mixture was chromatographed using 2:1 hexanes/EtOAc to afford a 49% yield of the indicated compound as a yellow solid: mp 272-273 °C; ^{1}H NMR (DMSO-d_6) δ 7.27 (t, J = 7.6 Hz, 1H), 7.41 (t, J = 8.0 Hz, 1H), 7.44-7.55 (m, 3H), 7.58 (d, J = 8.0 Hz, 1H), 7.96 (s, 1H), 8.18 (d, J = 7.2 Hz, 2H), 8.24 (d, J = 8.0 Hz, 1H), 9.41 (s, 1H), 11.78 (s, 1H); ^{13}C NMR (DMSO-d_6) δ 102.3, 111.5, 112.3, 118.7, 120.1, 120.7, 126.6, 126.7, 128.3, 128.7, 139.9, 140.2, 142.4, 144.9, 151.7; IR (neat, cm^{-1}) 3415, 3021; HRMS calcd for $C_{17}H_{12}N_2$: 244.1001. Found: 244.1004.

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Supporting Information

Copies of ^{1}H NMR and ^{13}C NMR for compounds **2b-j**, **3a-l**, **6a-l**, and **7a-k**. This material is included in Appendix B and is also available free of charge via the Internet at http://pubs.acs.org.

References

1. For reviews, see: (a) Larock, R. C. *J. Organometal. Chem.* **1999**, *576*, 111. (b) Larock, R. C.; "Palladium-Catalyzed Annulation," in *Perspectives in Organopalladium Chemistry for the XXI Century*, Tsuji, J., Ed.; Elsevier Press, Lausanne, Switzerland, 1999; pp 111-124. (c) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1435. For recent reports, see (d) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (e) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (f) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1551. (g) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 412. (h) Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270. (i) Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770. (j) Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713. (k) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (l) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002. (m) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (n) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042.
2. For recent leading references, see: (a) Takeda, A.; Kamijo, S.; Yamamoto, Y. *J. Am. Chem. Soc.* **2000**, *122*, 5662. (b) Gabriele, B.; Salerno, G.; Fazio, A. *Org. Lett.* **2000**, *2*, 351. (c) Roshchin, A. I.; Bumagin, N. A. *Chem. Heterocyl. Compd.* **1999**, *35*, 171. (d) Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron Lett.* **1998**, *39*, 5101. (e) Chowdhury, C.; Chaudhuri, G.; Guha, S.; Mukherjee, A. K.; Kundu, N. G. *J. Org. Chem.* **1998**, *63*, 1863. (f) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 5327. (g) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280.
3. (a) Rodriguez, A. L.; Koradin, C.; Dohle, W.; Knochel, P. *Angew. Chem., Int. Ed. Engl.* **2000**, *39*, 2488. (b) Yasuhara, A.; Kanamori, Y.; Kaneko, M.; Numata, A.; Kondo, Y.; Sakamoto, T. *J. Chem. Soc., Perkin Trans. 1* **1999**, 529.

4. (a) Larock, R. C.; Yue, D. *Tetrahedron Lett.* **2001**, *42*, 6011. (b) Flynn, B. L.; Verdier-Pinard, P.; Hamel, E. *Org. Lett.* **2001**, *3*, 651. (c) Barluenga, J.; Romanelli, G. P.; Alvarez-García, L. J.; Llorente, I.; González, J. M.; García-Rodríguez, E.; García-Granda, S. *Angew. Chem., Int. Ed. Engl.* **1998**, *37*, 3136. (d) Goldfinger, M. B.; Crawford, K. B.; Swager, T. M. *J. Am. Chem. Soc.* **1997**, *119*, 4578.

5. (a) Sakamoto, T.; Numata, A.; Saitoh, H.; Kondo, Y. *Chem. Pharm. Bull.* **1999**, *47*, 1740. (b) Kanekiyo, N.; Choshi, T.; Kuwada, T.; Sugino, E.; Hibiho, S. *Heterocycles* **2000**, *53*, 1877. (c) Kanekiyo, N.; Kuwada, T.; Choshi, T.; Nobuhiro, J.; Hibiho, S. *J. Org. Chem.* **2001**, *66*, 8793. (d) Abbiati, G.; Beccalli, E. M.; Marchesini, A.; Rossi, E. *Synthesis* **2001**, 2477. (e) Numata, A.; Kondo, Y.; Sakamoto, T. *Synthesis* **1999**, 306. (f) Sakamo, T.; Kondo, Y.; Miura, N.; Hayashi, K.; Yamanaka, H. *Heterocycles* **1986**, *24*, 2311. (g) Prikhod'ko, T. A.; Vasilevskii, S. F.; Shvartsberg, M. S. *Bull. Acad. Sci. USSR, Div. Chem. Sci.* **1984**, *33*, 2383.

6. (a) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 553. (b) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 86.

7. (a) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035. (b) Dai, G.; Larock, R. C. *Org. Lett.* **2002**, *4*, 193.

8. Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973.

9. (a) Hino, T.; Nakagawa, M. *J. Heterocycl. Chem.* **1994**, *31*, 625. (b) Baker, B. J. *Alkaloids: Chem. Biol. Perspect.* **1996**, *10*, 357. (c) Love, B. E. *Org. Prep. Proced. Int.* **1996**, *28*, 1. (d) Magnier, E.; Langlois, Y. *Tetrahedron* **1998**, *43*, 6201. (e) Nakagawa, M. *J. Heterocycl. Chem.* **2000**, *37*, 567. (f) Ohmoto, T.; Koike, K. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1989; Vol. 36, pp 135-170. (g) Matsukura, N.; Kawachi, T.; Morino, K.; Ohgaki, H.; Sugimura, T.; Takayama, S. *Science*, **1981**, *213*, 346. (h) Hibino, S.; Sugino, E.; Ogura, N.; Shintani, Y.; Sato, K. *Heterocycles* **1990**, *30*, 271. (i) Gribble, G. W.; In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1990; Vol.

39, Chapter 7. (j) Tan, G. T.; Pezzuto, J. M.; In *Chemistry and Toxicology of Diverse Classes of Alkaloids*; Blum, M. S., Ed.; Alaken, Inc.: Ft. Collins, CO, 1996; pp 1-119. (k) Nguyen, C. H.; Lavelle, F.; Riou, J.-F.; Bissery, M.-C.; Huel, C.; Bisagni, E. *Anti-Cancer Drug Des.* **1992**, *7*, 235.

10. (a) Iwaki, T.; Yasuhara, A.; Sakamoto, T. *J. Chem. Soc., Perkin Trans I* **1999**, 1505. (b) Snyder, S. A.; Vosburg, D. A.; Jarvis, M. G.; Markgraf, J. H. *Tetrahedron* **2000**, *56*, 5329. (c) Engler, T.; Wanner, J. *J. Org. Chem.* **2000**, *65*, 2444.
11. Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 3083.
12. Zhang, H.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 1359.
13. (a) Sonogashira, K. In *Metal-Catalyzed Cross-Coupling Reactions*; Diederich, F.; Stang, P. J., Eds. Perspectives in Organopalladium Chemistry for the XXI Century. Wiley-VCH: Weinheim, 1998: Chapter 5, pp 203-229. (b) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.
14. Sakamoto, T.; Nagano, T.; Kondo, Y.; Yamanaka, H. *Chem. Pharm. Bull.* **1988**, *36*, 2248.
15. Ethyl propiolate and ethoxyacetylene are prone to polymerization. For examples, see: (a) Gal, Y.-S.; Lee, W.-C.; Choi, S.-K. *Korea Polym. J.* **1997**, *5*, 10. (b) Tabata, M.; Inaba, Y.; Yokota, K.; Nozaki, Y. *J. Macromol. Sci., Pure Appl. Chem.* **1994**, *31*, 465. (c) Jacobs, T. L.; Juster, N. *J. Chem. Eng. Data* **1969**, *14*, 125.
16. The base-promoted deacetonation of α,β-acetylenic carbinols has been well studied. For representative examples, see: (a) Veliev, M. G.; Shatirova, M. I.; Chalabiev, C. A.; Mamedov, I. M.; Mustafaev, A. M. *Russ. J. Org. Chem.* **1995**, *31*, 52. (b) Havens, S. J.; Hergenrother, P. M. *J. Org. Chem.* **1985**, *50*, 1763. (c) Fowler, J. S.; *J. Org. Chem.* **1977**, *42*, 2637. The base-promoted fragmentation of a 1-hydroxycyclohexyl-substituted acetylene is also known. See: (d) Henbest, H. B.; Jones, E. R. H.; Walls, I. M. S. *J. Chem. Soc.* **1949**, 2696.

17. (a) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941. (b) Wu, G.; Geib, S. J.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1988**, *53*, 3238

18. The thermal reaction of 1-benzenesulfonyl-3-(trimethylsilylethynyl)indole-2-carboxaldehyde with NH_3 also afforded the corresponding desilylated β-carboline in a low yield (37%). See ref. 5a for details.

19. Choshi, T.; Sada, T.; Fujimoto, H.; Nagayama, C. Sugino, E.; Hibino, S. *J. Org. Chem.* **1997**, *62*, 2535.

20. Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. *Tetrahedron* **1997**, *53*, 4447. We used ethyl acetate instead of diethyl ether as the extraction solvent, and were able to isolate 2-bromo-1*H*-indole-3-carboxaldehyde in 55% yield.

21. Ranganathan, S.; Maniktala, V.; Kumar, R.; Singh, G. P. *Indian J. Chem. Sec. B* **1984**, *23*, 1197.

22. Erba, E.; Pocar, D.; Valle, M. *J. Chem. Soc., Perkin Trans. 1* **1999**, 421.

23. Abramovitch R. A. *Can. J. Chem.* **1960**, *38*, 2273.

CHAPTER 3. SYNTHESIS OF ANNULATED γ-CARBOLINES AND HETEROPOLYCYCLES BY THE PALLADIUM-CATALYZED INTRAMOLECULAR ANNULATION OF ALKYNES

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Abstract

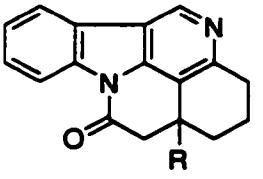
A variety of *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehydes incorporating an alkyne-containing tether on the indole nitrogen have been converted to the corresponding *tert*-butylimines, which have been subjected to palladium-catalyzed intramolecular iminoannulation, affording various γ-carboline derivatives with an additional ring fused across the 4- and 5-positions in good to excellent yields. When the tethered carbon–carbon triple bond is terminal or substituted with a triethylsilyl group, the iminoannulation generates a *tert*-butyl-γ-carbolinium salt as the major product. The palladium-catalyzed intramolecular annulations of *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehyde, methyl 2-iodo-1*H*-indole-3-carboxylate and 2-iodo-3-phenyl-1*H*-indole containing a phenylpentynyl tether produce the corresponding heteropolycycles in moderate to good yields.

Introduction

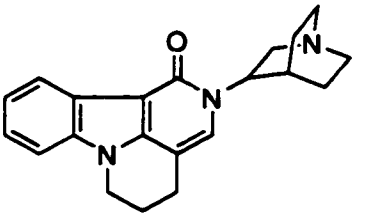
Annulation processes have proven to be very useful in organic synthesis due to the ease with which a wide variety of complex carbocycles and heterocycles can be rapidly constructed. In our own laboratories, it has been demonstrated that palladium-catalyzed annulation methodology[1] can be effectively employed for the synthesis of indoles,[2] isoindolo[2,1-*a*]indoles,[3] benzofurans,[4] benzopyrans,[4] isocoumarins,[4,5] α-pyrones,[5,6] indenones,[7] pyridines,[8] isoquinolines,[8] naphthalenes[9]

and polycyclic aromatic hydrocarbons.[10] However, intramolecular palladium-catalyzed annulation has not been well explored mainly because of the difficulty of assembling a halide, a carbon-carbon triple bond and other necessary elements into the appropriate positions into a single starting material.[11]

Pyrido[4,3-*b*]-5*H*-indoles, commonly known as γ-carbolines, which are condensed analogues of the ellipticine/olivacine anticancer agents, have been studied extensively because of their potential pharmaceutical importance.[12] However, there are relatively few synthetic studies of γ-carboline derivatives having wide scope and generality,[12,13] and the synthesis of new alkaloid derivatives of γ-carboline with an additional ring fused across the 4- and 5-positions is rare.[14] Two closely related examples of this type of heteropolycyclic system having interesting biological activity are the pentacyclic γ-carboline **1**, which is a cardiovascular agent[15] and the indolonaphthyridone **2**, which acts as a conformationally restricted 5-HT_3 receptor antagonist.[16]



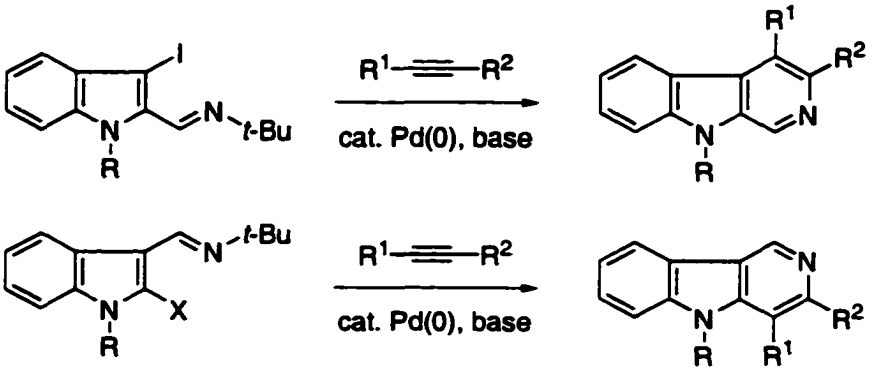
1 R = Me, Et



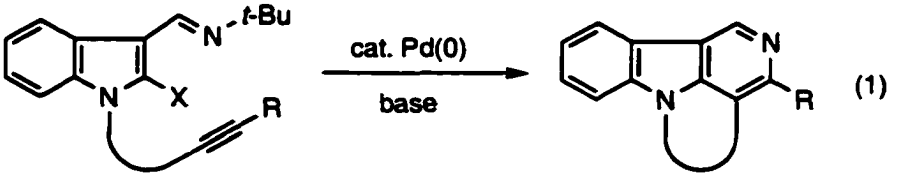
2

Syntheses of annulated γ-carboline alkaloids have typically employed electrocyclic ring closures of 1-azatrienes,[14c,d] or intramolecular Diels-Alder reactions.[14a,b,e] However, both methods afford the desired γ-carbolines in relatively low yields. Recently, we have developed a general synthesis of 3,4-disubstituted β- and γ-carbolines by the palladium-catalyzed iminoannulation of acetylenes (Scheme 1).[17] While certain β- and γ-carbolines could be prepared in good to excellent

Scheme 1



yields, the regioselectivity of the reaction was too sensitive to the nature of the alkynes to be of broad applicability.[17] Alternatively, by readily incorporating an alkyne-containing tether onto the indole nitrogen, subsequent palladium-catalyzed intramolecular iminoannulation would enable regioselective construction of two rings in a single step, and provide a well-recognized entropic advantage (eq 1). Our own



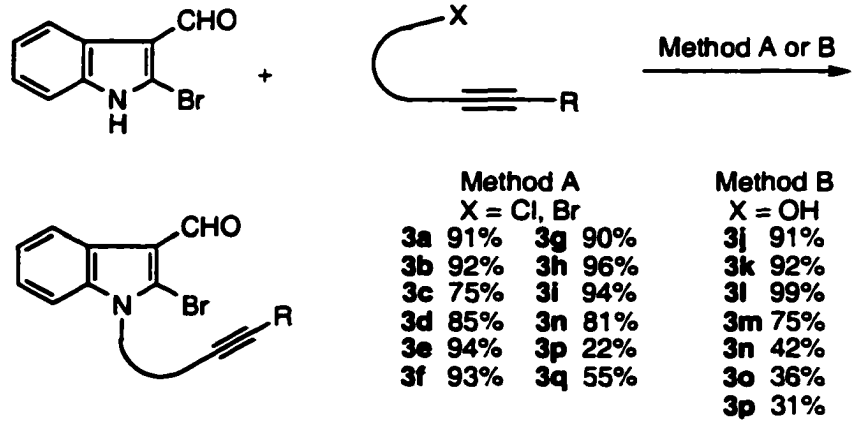
interest in carboline synthesis therefore prompted us to examine the synthesis of a variety of annulated γ-carbolines. A brief communication of this study has been reported previously.[18] Herein, we wish to report the full details of the palladium-catalyzed intramolecular iminoannulation to synthesize annulated γ-carbolines, and extension of this "intramolecular" concept to other palladium-catalyzed annulations to synthesize various complex heteropolycycles.

Results and Discussion

In the early stage of our investigation, we were focused on finding a general, high-yielding method to prepare *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehydes bearing a tether with a carbon–carbon triple bond for the

palladium-catalyzed intramolecular iminoannulation. The alkylation and acylation of 1*H*-indole-3-carboxaldehyde to prepare alkyne-tethered indole-3-carboxaldehydes have been reported previously.[14a,b] We anticipated that 2-bromo-1*H*-indole-3-carboxaldehyde[17] would undergo a similar process and were delighted to observe that 2-bromo-1*H*-indole-3-carboxaldehyde reacts readily with the appropriate chlorides or bromides bearing a carbon–carbon triple bond in the presence of NaI and K_2CO_3 in acetone, affording the desired tethered indoles **3** in excellent yields in most cases (Method A in Scheme 2, see Table 1 and the Experimental Section for details). Relatively low yields were obtained only when the halide contains a conjugated enyne, which might be unstable under the reaction conditions (compare **3c**, **3p** and **3q** with others). An alternative method employing the Mitsunobu reaction[19] of 2-bromo-1*H*-indole-3-carboxaldehyde with sterically unhindered

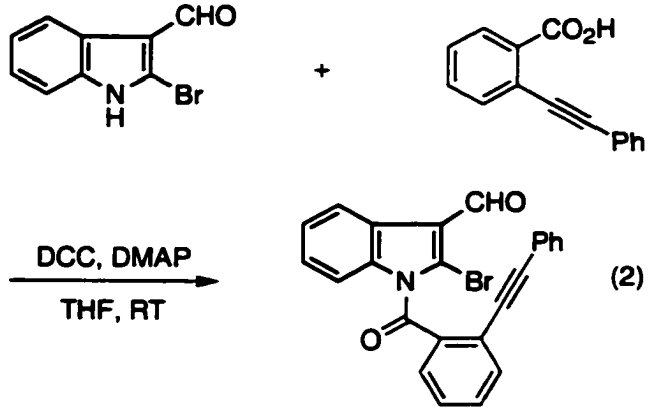
Scheme 2



Method A X = Cl, Br				Method B X = OH	
3a	91%	**3g**	90%	**3j**	91%
3b	92%	**3h**	96%	**3k**	92%
3c	75%	**3i**	94%	**3l**	99%
3d	85%	**3n**	81%	**3m**	75%
3e	94%	**3p**	22%	**3n**	42%
3f	93%	**3q**	55%	**3o**	36%
				3p	31%

alcohols containing a carbon–carbon triple bond has also generated good to excellent yields of the corresponding tethered indoles (Method B in Scheme 2, also see Table 1 and the Experimental Section for details). However, when relatively sterically hindered alcohols were employed, the corresponding Mitsunobu reaction only produced moderate yields of the desired tethered indoles (compare **3n-p** with others). The acylation of 2-bromo-1*H*-indole-3-carboxaldehyde has proven more difficult. After several unsuccessful attempts, we finally managed to couple 2-bromo-1*H*-indole-3-carboxaldehyde with 2-(phenylethynyl)benzoic acid in the

presence of DCC and DMAP,[20] which only afforded a 50% yield of the desired product **3r** (eq 2). Unfortunately, 2-(1-octynyl)benzoic acid and 5-phenylpent-4-ynoic



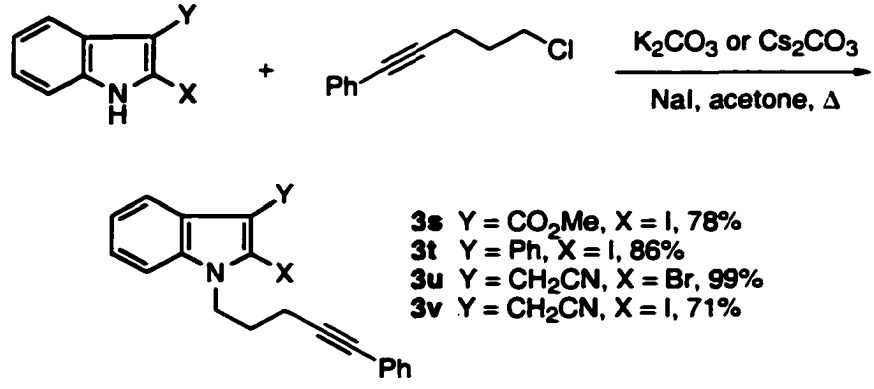
(2)

3r 50%

acid failed to give any significant amount of the products under the same reaction conditions.

Similarly, a phenylpentynyl tether has also been successfully incorporated onto the nitrogen of methyl 2-iodo-1*H*-indole-3-carboxylate, 2-iodo-3-phenyl-1*H*-indole,[21] 2-bromo-1*H*-indole-3-acetonitrile[22] and 2-iodo-1*H*-indole-3-acetonitrile by employing the corresponding 2-haloindoles and 5-chloro-1-phenyl-1-pentyne in the presence of NaI and K_2CO_3 or Cs_2CO_3 in acetone (Scheme 3).

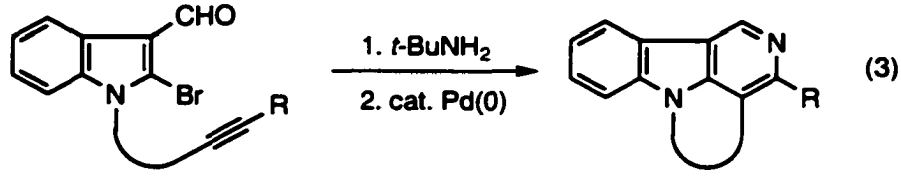
Scheme 3



3s Y = CO_2Me, X = I, 78%
3t Y = Ph, X = I, 86%
3u Y = CH_2CN, X = Br, 99%
3v Y = CH_2CN, X = I, 71%

The *tert*-butylimine of indole **3a** was first prepared and employed in the intramolecular palladium-catalyzed iminoannulation under the reaction conditions used in our earlier intermolecular γ-carboline synthesis.[17] Considering that an intramolecular reaction might provide an entropic advantage, we lowered the

reaction temperature from 125 °C to 100 °C. We were pleased to see that under these reaction conditions, the palladium-catalyzed intramolecular iminoannulation produced a 93% yield of the desired γ-carboline **4a** in only 10 h (Table 1, entry 1). It is noteworthy that the preparation of the *tert*-butylimines from the corresponding aldehydes is essentially quantitative, requiring no further purification and characterization of the starting imines used for the subsequent palladium-catalyzed annulation, as we have observed in our previous work.[17,23] Thus, by employing a two-step protocol, namely imine formation, followed by palladium-catalyzed intramolecular iminoannulation without isolation of the intermediate imine, we have been able to prepare a variety of annulated γ-carbolines and investigate the scope and limitations of this process (eq 3). The results of this investigation are summarized in Table 1.



(3)

3 **4**

As seen from Table 1, by employing *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehydes with a trimethylene tether from the indole nitrogen to the carbon-carbon triple bond, the parent isocanthine skeleton[14a] can be readily constructed (entries 1-6). This route allows easy access to a variety of substituted isocanthine derivatives and tolerates various functional groups. For example, tethered indoles **3a-f** containing aryl-, alkyl-, alkenyl-, hydroxy-, ester- and pyrimidyl functionalities all afforded the desired annulation products **4a-f** in excellent yields (entries 1-6). Unfortunately, indole **3g** containing a triethylsilyl group did not generate the desired silyl-substituted isocanthine derivative. Instead, a desilylated γ-carbolinium salt with a *tert*-butyl group on the nitrogen (**4g**) was isolated in a 53% yield, along with a 40% yield of the desilylated isocanthine **4h** (entry 7). Tethered indole **3h** with a terminal carbon–carbon triple bond also afforded the same γ-carbolinium salt **4g** as in the silyl case in a 72% yield, as well as a 10% yield of isocanthine (**4h**) as the minor product

Table 1. Synthesis of Annulated γ-Carbolines by Palladium-Catalyzed Intramolecular Iminoannulation (eq 3)[a]

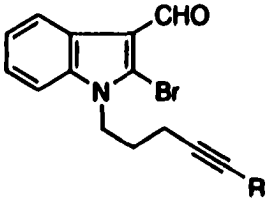
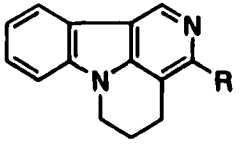
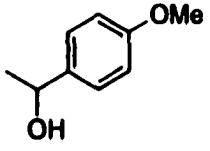
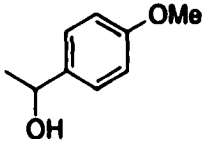
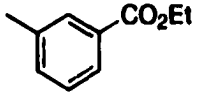
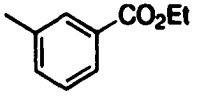
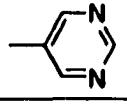
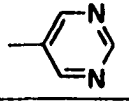
entry	aldehyde		annulation time (h)	product		% yield
						
	R			R		
1	Ph	**3a**	10	Ph	**4a**	93
2	*n*-C_6H_{13}	**3b**	24	*n*-C_6H_{13}	**4b**	95
3	(*E*)-CH=CHPh	**3c**	10	(*E*)-CH=CHPh	**4c**	94
4		**3d**	18		**4d**	95
5		**3e**	12		**4e**	93
6		**3f**	40		**4f**	99

Table 1. continued

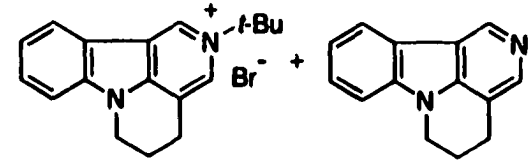
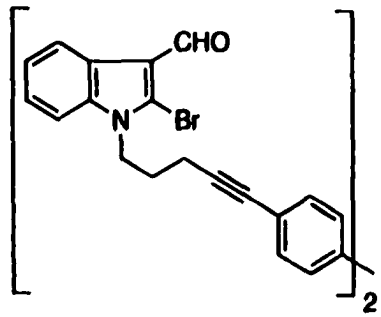
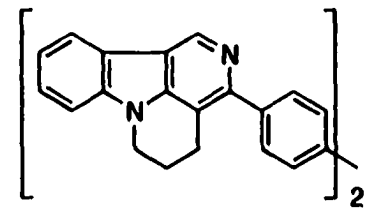
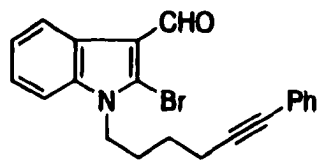
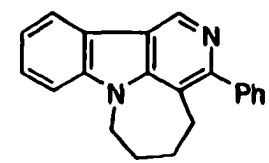
entry	aldehyde		annulation time (h)	product		% yield
7[b]	$SiEt_3$	**3g**	18		**4g + 4h**	53 + 40
8	H	**3h**	40		**4g + 4h**	72 + 10
9		**3i**	10		**4i**	91
10		**3j**	10		**4j**	90

Table 1. continued

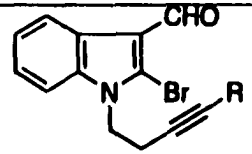
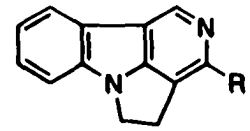
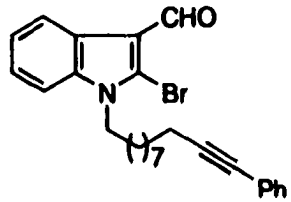
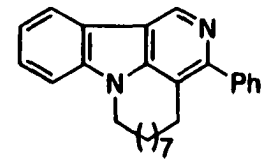
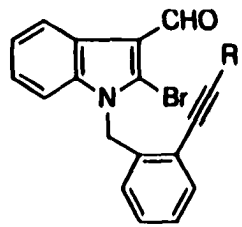
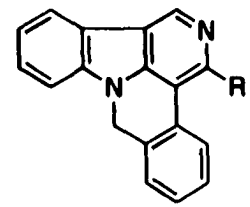
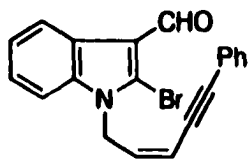
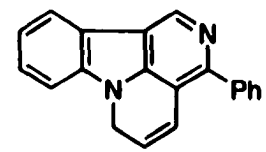
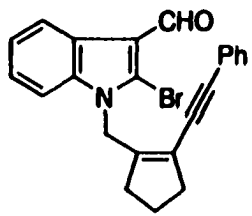
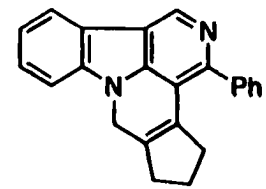
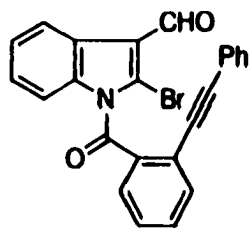
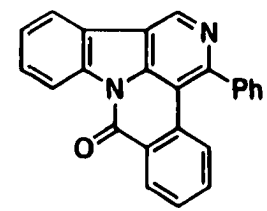
entry	aldehyde		annulation time (h)	product		% yield
						
	R			R		
11	Ph	3k	24	Ph	4k	84
12	n-C_6H_{13}	3l	12	n-C_6H_{13}	4l	91
13		3m	48		4m	trace
						
	R			R		

Table 1. continued

entry	aldehyde		annulation time (h)	product		% yield
14	Ph	**3n**	24	Ph	**4n**	88
15	*n*-Bu	**3o**	20	*n*-Bu	**4o**	75
16		**3p**	18		**4p**	57
17		**3q**	14		**4q**	94
18[c]		**3r**	-		**4r**	-

[a] Representative procedure: the aldehyde (0.25 mmol) and *tert*-butylamine (1 mL) were placed in a 2-dram vial. The vial was flushed with Ar and carefully sealed, and the mixture was heated at 100 °C for 8 h. The mixture was cooled, diluted with ether, dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was dissolved in 5 mL of DMF and transferred to a 4-dram vial containing 5 mol % $Pd(OAc)_2$, 10 mol % PPh_3 and Na_2CO_3 (0.25 mmol). The mixture was then flushed with Ar and heated at 100 °C for the indicated time. [b] *n*-Bu_3N (0.25 mmol) instead of Na_2CO_3 was used as the base. [c] The amide bond was dissociated during the imine preparation.

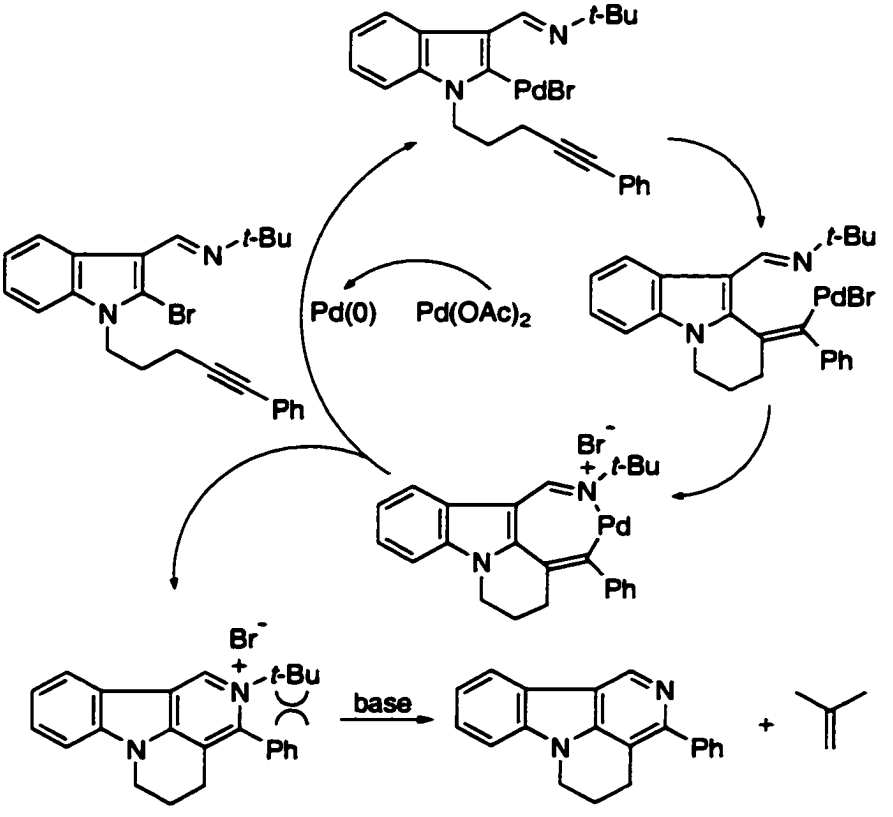
(entry 8, also see the later discussion). As we expected, tethered indole **3i** readily underwent a double intramolecular iminoannulation, generating a complex isocanthine derivative **4i** in an excellent 91% yield (entry 9).

Interestingly, by employing indole **3j** with a tetramethylene tether, we have been able to isolate an annulated γ-carboline **4j** with a seven-membered ring fused to the 4- and 5-positions in a 90% yield (entry 10). We have also been able to obtain annulated γ-carbolines **4k** and **4l** with a five-membered ring fused across the 4- and 5-positions in 84% and 91% yields, by employing indoles **3k** and **3l** with a dimethylene tether, respectively (entries 11 and 12). It is worth noting that ring systems similar to carbolines **4j** and **4k-l** have never been efficiently prepared by either an intramolecular Diels-Alder reaction[24] or the electrocyclization of a 1-azatriene,[14c] since those reactions require significant strain of the tether to achieve the necessary transition-state geometry, especially for the case of a five-five ring juncture. Unfortunately, our attempt to achieve a 12-membered ring fused γ-carboline by employing tethered indole **4m** failed to give any significant amount of the desired product (entry 13). A messy reaction with inseparable multiple products were observed. Presumably because of the entropic disadvantage of forming a 12-membered ring, the competitive intermolecular annulation in this case is significant enough to produce multiple byproducts.

Other types of tethers have also proven to be successful in this intramolecular annulation chemistry. For example, indoles **3n** and **3o** with a tether containing an aryl moiety afforded the desired annulated γ-carbolines **4n** and **4o** in 88% and 75% yields, respectively (entries 14 and 15). Indoles **3p** and **3q** with a tether incorporating an alkene moiety also afforded the desired annulated γ-carbolines **4p** and **4q** in 57% and 94% yields, respectively. The relatively low yield of γ-carboline **4p** may be attributable to the fact that the (*Z*)-enyne moiety in indole **3p** can isomerize[25] or undergo side reactions[11a-c] in the presence of a palladium catalyst. Consistent with this hypothesis is the fact that the more highly substituted enyne **3q** gives an excellent yield.

Unfortunately, indole **3r** having an amide linkage underwent transamidation during imine preparation. Therefore, this palladium-catalyzed intramolecular iminoannulation methodology is limited to those tethered indoles with a CH_2–N bond linkage. Our attempts to oxidize isocanthine **4a** to the corresponding isocanthin-6-one using benzyltriethylammonium permanganate[26] (BTAP), which has been used to oxidize amines to amides[26] and employed to oxidize canthine derivatives to their corresponding canthin-6-ones,[27] also failed to give any significant amount of the desired product.

Scheme 4



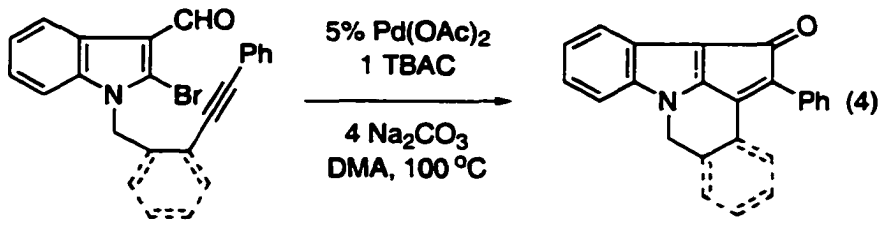
We propose a mechanism for this palladium-catalyzed intramolecular iminoannulation chemistry, which is similar to our earlier intermolecular annulation (Scheme 4).[8,17] Specifically, oxidative addition of the indole bromide to Pd(0) produces an organopalladium intermediate, which then intramolecularly adds across

the tethered carbon–carbon triple bond through an exo-dig addition, producing a vinylic palladium intermediate, which then reacts with the neighboring imine substituent to form a seven-membered palladacyclic immonium ion salt. Subsequent reductive elimination produces a *tert*-butylcarbolinium salt and regenerates Pd(0). As previously suggested by Heck,[28] the *tert*-butyl group apparently fragments to relieve the strain resulting from the interaction with the substituent present on the neighboring carbon.

Now it is easy to understand why tethered indole **3h** containing a terminal carbon–carbon produced the *tert*-butylcarbolinium salt **4g** as the major product. In this case, the *tert*-butylcarbolinium salt is unable to fragment the *tert*-butyl group due to the lack of strain between the *tert*-butyl group and the neighboring hydrogen. The observed small amount (10%) of product **4h**, absent of a *tert*-butyl group, presumably arises from thermal fragmentation of the *tert*-butyl group.

It is also understandable that tethered indole **4g** bearing a triethylsilyl-substituted carbon–carbon triple bond generated a mixture of the desilylated *tert*-butylcarbolinium salt and isocanthine **4h**. In this case, the *tert*-butylcarbolinium intermediate with a *tert*-butyl and a triethylsilyl group on adjacent atoms might undergo either protodesilylation to give the *tert*-butylcarbolinium salt **4g** (53%) without the silyl group or fragmentation of the *tert*-butyl group to give a silyl-substituted isocanthine derivative, which finally protodesilylates under the reaction conditions to give isocanthine **4h** (40%).

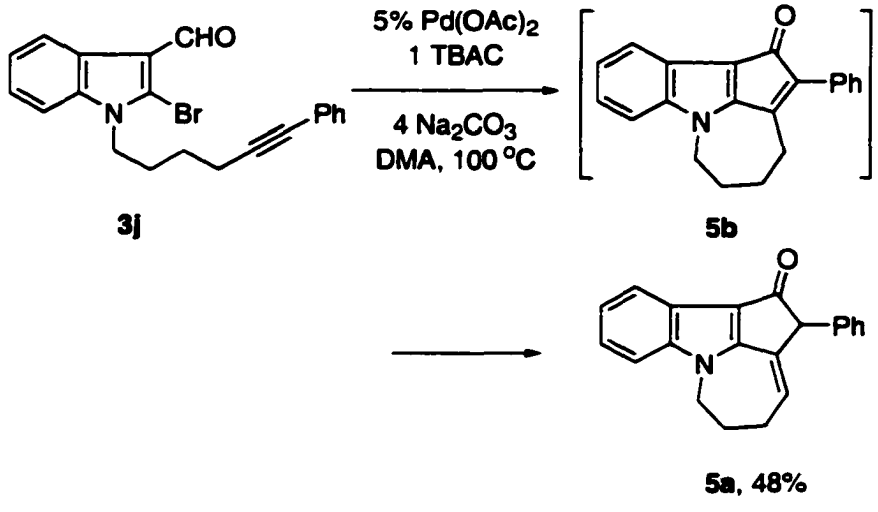
Encouraged by the success of our palladium-catalyzed intramolecular iminoannulation, we have also examined several other types of palladium-catalyzed intramolecular annulation. To our disappointment, the intramolecular annulation of aldehydes **3a** and **3n** under the conditions of our earlier indenone synthesis[7] did not generate significant amounts of the desired heterocycles (eq 4), presumably because the desired products having a five-five-six ring juncture are too strained



3a, 3n trace

to form or too unstable under the reaction conditions. Interestingly, by simply increasing the length of the linkage, the palladium-catalyzed intramolecular annulation of aldehyde **3j** has generated a 48% yield of heterocycle **5a** with a five-five-seven ring juncture, which apparently arises from tautomerization of the anticipated less stable heterocycle **5b** (Scheme 5). Similar tautomerization has also been previously observed in our indenone synthesis.[7] Unfortunately, the palladium-catalyzed intramolecular annulation of aldehyde **3j** under the conditions of Yamamoto's indenol synthesis[29] did not afford any significant yield of the desired alcohol or the tautomeric ketone.

Scheme 5



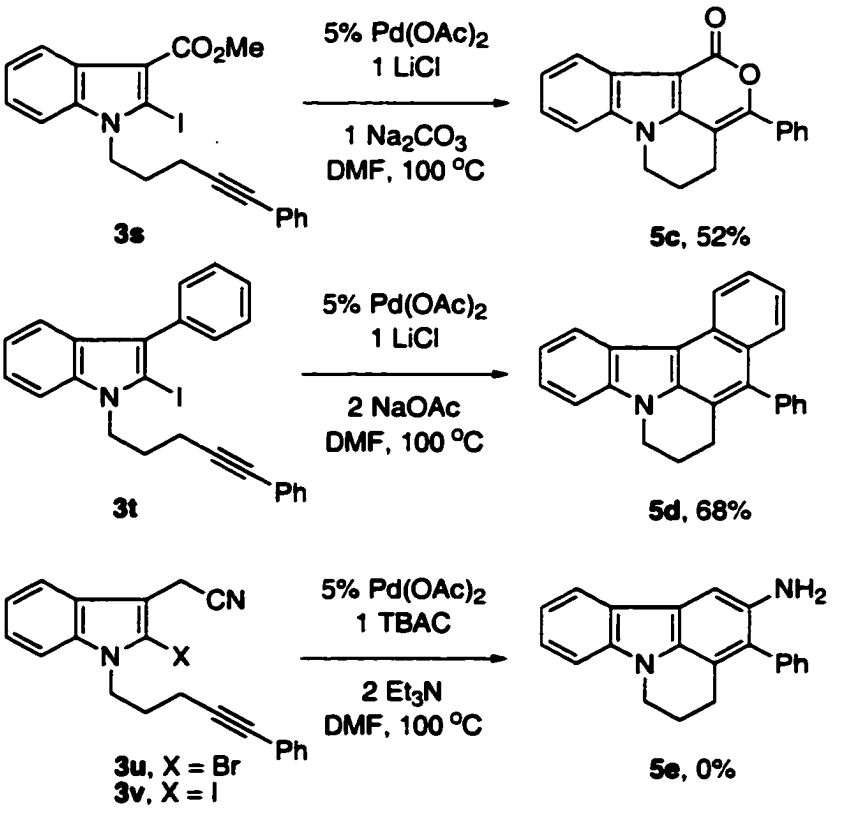
3j **5b**

5a, 48%

To our great satisfaction, the intramolecular annulation of alkyne-tethered methyl 2-iodo-1*H*-indole-3-carboxylate **3s** under the conditions of our earlier isocoumarin synthesis[4,5] smoothly produced a 52% yield of the desired heterocycle **5c** (Scheme 6). Equally exciting was the fact that the intramolecular annulation of indole **3t** under the conditions of our earlier phenanthrene synthesis[10] also generated

the desired annulation product **5d** in a 68% yield (Scheme 6). However, neither the 2-bromoindole **3u** nor 2-iodoindole **3v** containing acetonitrile functionality generated any of the desired carbazole **5e** under the conditions of our earlier palladium-catalyzed aminonaphthalene synthesis (Scheme 6).[9b] Messy reactions were observed in both cases. One possible reason is that the 2-haloindoles might be reduced to the corresponding indoles under the reaction conditions, as previously observed in our own laboratory.[30]

Scheme 6



Conclusions

In conclusion, a number of *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehydes bearing a tether with a carbon–carbon triple bond have been prepared, and an efficient synthesis of various annulated γ-carbolines by imination of these aldehydes, followed by palladium-catalyzed intramolecular iminoannulation has been developed. A wide variety of functionalized 2-bromo-1*H*-indole-3-

carboxaldehydes participate in this process to afford the desired γ-carbolines in good to excellent yields. When the tethered carbon–carbon triple bond is terminal or substituted with a silyl group, the iminoannulation generates a *tert*-butyl-γ-carbolinium salt as the major product. This chemistry has also been extended to other palladium-catalyzed intramolecular annulations. An *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehyde, 2-iodo-1*H*-indole-3-carboxylate and 2-iodo-3-phenyl-1*H*-indole containing an alkyne tether have undergone palladium-catalyzed intramolecular annulation, producing the corresponding heteropolycycles in moderate to good yields. However, none of the desired products were observed in the palladium-catalyzed intramolecular annulation of an alkyne-tethered 2-bromo-1*H*-indole-3-acetonitrile or 2-iodo-1*H*-indole-3-acetonitrile.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. All reagents were used directly as obtained commercially unless otherwise noted. Compounds **3a-b**, **3d-f**, **3j**, **3l**, **3n**, **3q**, **4a-b**, **4d-f**, **4j**, **4l**, **4n**, **4q**, and **5a** have been previously reported.[18] 2-Iodo-3-phenyl-1*H*-indole was prepared according to a literature procedure.[21] Following are the preparation and characterization of the starting materials, methyl 2-iodo-1*H*-indole-3-carboxylate, and 2-iodo-1*H*-indole-3-acetonitrile.

(*E*)-7-Chloro-1-phenylhept-1-en-3-yne. To a 4-dram vial was added (*E*)-β-iodostyrene[31] (0.230 g, 1.0 mmol), CuI (1 mol %), $PdCl_2(PPh_3)_2$ (2 mol %) and Et_3N (5 mL). The mixture was stirred for 1 min and 5-chloro-1-pentyne (1.2 mmol) was added. The mixture was flushed with Ar and stirred at 60 °C for 3 h. The completion of the reaction was monitored by TLC analysis. The reaction mixture was cooled, diluted with ether and filtered. The solvent was evaporated and the residue was

purified on a silica gel column using 50:1 hexanes/EtOAc to afford 70% yield of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.01 (quintet, J = 6.6 Hz, 2H), 2.56 (dt, J = 2.1, 6.6 Hz, 2H), 3.68 (t, J = 6.6 Hz, 2H), 6.13 (dt, J = 16.2, 2.1 Hz, 1H), 6.88 (d, J = 16.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 31.8, 44.0, 80.8, 90.2, 108.4, 126.1, 128.4, 128.7, 136.3, 140.6.

5-Chloro-1-triethylsilyl-1-pentyne. *n*-BuLi (2.5 M in hexanes, 1.1 equiv) was added dropwise to a stirred solution of 5-chloro-1-pentyne (0.513 g, 5.0 mmol) in dry THF (10 mL) at -78 °C under Ar. After 30 min, a solution of triethylsilyl chloride (0.980, 1.3 equiv) in THF (10 mL) was added dropwise. The mixture was warmed to room temperature for 3 h, quenched with satd aq NH_4Cl and extracted with ether. The organic layer was dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was purified using 100:1 hexanes/EtOAc to afford 0.97 g (90%) of the indicated compound as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 0.57 (q, J = 8.0 Hz, 6H), 0.98 (t, J = 8.0 Hz, 9H), 1.98 (quintet, J = 6.4 Hz, 2H), 2.43 (t, J = 6.4 Hz, 2H), 3.66 (t, J = 6.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 4.6, 7.5, 17.3, 31.5, 43.5, 82.8, 106.2.

4,4'-Bis-(5-chloropent-1-ynyl)biphenyl. This compound was prepared by the procedure used to synthesize (*E*)-7-chloro-1-phenylhept-1-en-3-yne, but using 4,4'-diiodobiphenyl and 5-chloro-1-pentyne (2.4 equiv). The product was purified using 10:1 hexanes/EtOAc to afford a 99% yield of the indicated compound as a pale yellow solid: mp 112-114 °C; ^{1}H NMR ($CDCl_3$) δ 2.07 (quintet, J = 6.8 Hz, 4H), 2.63 (t, J = 6.8 Hz, 4H), 3.72 (t, J = 6.8 Hz, 4H), 7.45 (d, J = 8.0 Hz, 4H), 7.51 (d, J = 8.0 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 17.0, 31.5, 43.8, 81.4, 89.1, 122.9, 126.8, 132.1, 139.7.

4-Phenylbut-3-yn-1-ol. This compound was prepared by the procedure used to synthesize (*E*)-7-chloro-1-phenylhept-1-en-3-yne, but using iodobenzene and 3-butyn-1-ol. The product was purified using 2:1 hexanes/EtOAc to afford a 93% yield of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.36 (t, J = 6.4 Hz,

1H), 2.67 (t, J = 6.4 Hz, 2H), 3.79 (m, 2H), 7.28 (m, 3H), 7.40 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 23.8, 61.2, 82.4, 86.5, 123.4, 128.0, 128.3, 131.7.

11-Phenylundec-10-yn-1-ol. This compound was prepared by the procedure used to synthesize (*E*)-7-chloro-1-phenylhept-1-en-3-yne, but using iodobenzene and 10-undecyn-1-ol. The product was purified using 3:1 hexanes/EtOAc to afford a 95% yield of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.30-1.50 (m, 10H), 1.50-1.65 (m, 5H), 2.41 (t, J = 7.2 Hz, 2H), 3.63 (t, J = 7.2 Hz, 2H), 7.25-7.30 (m, 3H), 7.35-7.42 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 19.6, 26.0, 29.0, 29.1, 29.3, 29.6, 29.7, 33.0, 63.2, 80.8, 90.7, 124.3, 127.7, 128.4, 131.8.

2-(Phenylethynyl)benzyl chloride. This compound was prepared by the procedure used to synthesize (*E*)-7-chloro-1-phenylhept-1-en-3-yne, but using 2-iodobenzyl chloride and phenylacetylene. The product was purified using 50:1 hexanes/EtOAc to afford a 100% yield of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 4.88 (s, 2H), 7.30-7.45 (m, 5H), 7.50-7.62 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 44.8, 86.5, 94.9, 123.0, 123.1, 128.5, 128.7, 128.8, 129.4, 131.7, 132.4, 132.6, 138.9.

2-(Hex-1-ynyl)benzyl alcohol. This compound was prepared by the procedure used to synthesize (*E*)-7-chloro-1-phenylhept-1-en-3-yne, but using 2-iodobenzyl alcohol and 1-hexyne. The product was purified using 5:1 hexanes/EtOAc to afford a 73% yield of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.95 (t, J = 7.2 Hz, 2H), 1.48 (m, 2H), 1.60 (m, 2H), 2.45 (t, J = 7.2 Hz, 2H), 4.78 (s, 2H), 7.21 (dt, J = 1.2, 7.6 Hz, 1H), 7.27 (dt, J = 1.2, 7.6 Hz, 1H), 7.39 (dt, J = 1.2, 7.6 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 13.7, 19.3, 22.1, 30.9, 64.2, 78.2, 95.5, 122.2, 127.2, 127.4, 128.0, 132.2, 142.4.

(*Z*)-1-Bromo-5-phenylpent-2-en-4-yne. To a solution of (*Z*)-5-phenylpent-2-en-4-yn-1-ol[32] (2.2 mmol, 0.348 g) and CBr_4 (0.948 g, 1.3 equiv) in CH_2Cl_2 (10 mL) at 0 °C was added PPh_3 (1.5 equiv, 0.866 g) portionwise. The mixture was stirred at room temperature for 2 h. The reaction mixture was flushed through a short silica gel column to remove the triphenylphosphine oxide. The solvent was evaporated

and the residue was purified using 25:1 hexanes/EtOAc to afford 0.462 g (95%) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 4.27 (d, J = 8.1 Hz, 2H), 5.85 (d, J = 10.5 Hz, 1H), 6.20 (m, 1H), 7.35 (m, 3H), 7.47 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 28.7, 84.3, 97.6, 113.6, 123.0, 128.7, 129.0, 131.9, 137.1.

Methyl 2-iodo-1-phenylsulfonyl-1*H*-indole-3-carboxylate: *n*-BuLi (2.0 mmol, 2.5 M in hexanes) was added under Ar to a mixture of diisopropylamine (4.0 mmol) and dry THF (20 mL) at -78 °C and the mixture was stirred for 30 min. Methyl 1-phenylsulfonyl-1*H*-indole-3-carboxylate[33] (0.63 g, 2.0 mmol) in dry THF (8 mL) was added to the mixture and stirring was continued at -78 °C for 30 min. I_2 (1.52 g, 6.0 mmol) in dry THF (10 mL) was added and the mixture was stirred at -78 °C for 2 h. The reaction was quenched by satd aq NH_4Cl, washed with satd aq $Na_2S_2O_3$ and extracted with EtOAc. The organic layer was dried over Na_2SO_4, and the solvent was evaporated. The residue was purified using 3:1 hexanes/EtOAc to afford 0.756 g (86%) of the indicated compound as a white solid: mp 138-140 °C; ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 3H), 7.28-7.39 (m, 2H), 7.43-7.50 (m, 2H), 7.60 (tt, J = 7.5, 1.2 Hz, 1H), 7.92-7.97 (m, 2H), 8.04 (m, 1H), 8.40 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 51.8, 85.5, 115.4, 121.1, 121.6, 124.5, 125.7, 127.5, 128.3, 129.4, 134.6, 138.2, 139.2, 164.0.

Methyl 2-iodo-1*H*-indole-3-carboxylate: To a mixture of methyl 2-iodo-1-phenylsulfonyl-1*H*-indole-3-carboxylate (0.441 g, 1.0 mmol) in methanol (15 mL) and 1,4-dioxane (5 mL) was added NaOH (0.120 g, 3.0 mmol) and the mixture was heated at 60 °C for 18 h. The solvent was evaporated and the residue was purified using 3:1 hexanes/EtOAc to afford 0.181 g (63%) of the indicated compound as a white solid: mp 159-160 °C; ^{1}H NMR ($CDCl_3$) δ 3.99 (s, 3H), 7.16-7.25 (m, 2H), 7.34-7.40 (m, 1H), 8.12 (m, 1H), 9.02 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 51.4, 86.2, 110.6, 112.3, 121.3, 122.1, 123.4, 126.6, 138.7, 165.0.

2-Iodo-1*H*-indole-3-acetonitrile: To a mixture of 1*H*-indole-3-acetonitrile (0.781 g, 5.0 mmol) and AgOTs (1.535 g, 5.5 mmol) in CH_2Cl_2 (15 mL) was added slowly a solution of I_2 (1.396 g, 5.5 mmol) in CH_2Cl_2 (50 mL) and the mixture was stirred at room temperature for 15 min. The precipitate was filtered and washed with

CH_2Cl_2. The solvent was evaporated and the residue was purified using 2:1 hexanes/EtOAc to afford 0.560 g (40%) of the indicated compound as a yellow solid: mp 116-118 °C; ^{1}H NMR ($CDCl_3$) δ 3.78 (s, 2H), 7.15-7.22 (m, 2H), 7.34 (dd, J = 2.0, 6.4 Hz, 1H), 7.64 (m, 1H), 8.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.4, 79.6, 110.7, 111.0, 117.5, 117.7, 121.0, 123.3, 126.6, 138.9.

General Procedure for the Synthesis of *N*-Substituted 2-Bromo-1*H*-indole-3-carboxaldehydes. Method A: 2-bromo-1*H*-indole-3-carboxaldehyde[17] (0.5 mmol), the alkynyl halide (0.6 mmol), NaI (0.75 mmol) and K_2CO_3 (0.75 mmol) were placed in a 4-dram vial and acetone (3 mL) was added. The vial was flushed with Ar and heated in an oil bath at 75 °C for 24 h. The mixture was cooled and diluted with ether (5 mL). The precipitate was removed by filtration and the solvent was evaporated. The residue was purified by chromatography on a silica gel column. Method B: to a mixture of 2-bromo-1*H*-indole-3-carboxaldehyde (0.5 mmol), the alkynyl alcohol (0.6 mmol), and PPh_3 (0.75 mmol) in CH_2Cl_2 (8 mL) was added diethyl azodicarboxylate (0.75 mmol) at 0 °C. The resulting mixture was flushed with Ar and stirred at room temperature for 24 h. The mixture was concentrated and the residue was purified by chromatography on a silica gel column.

***N*-Substituted 2-Bromo-1*H*-indole-3-carboxaldehydes Prepared**

2-Bromo-1-[(*E*)-7-phenylhept-6-en-4-ynyl]-1*H*-indole-3-carboxaldehyde (3c). This compound was prepared using (*E*)-7-chloro-1-phenylhept-1-en-3-yne according to Method A. The product was purified using 4:1 hexanes/EtOAc to afford 147 mg (75%) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.09 (quintet, J = 7.2 Hz, 2H), 2.48 (dt, J = 2.1, 7.2 Hz, 2H), 4.42 (t, J = 7.2 Hz, 2H), 6.16 (dt, J = 16.2, 2.1 Hz, 1H), 6.90 (d, J = 16.2 Hz, 1H), 7.25-7.46 (m, 8H), 8.33 (m, 1H), 10.04 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 17.4, 28.7, 44.5, 81.5, 90.5, 108.4, 110.1, 115.7, 121.5, 123.6, 124.4, 125.6, 125.8, 126.4, 128.8, 129.0, 136.5, 137.1, 141.2, 185.6;

IR (neat, cm^{-1}) 3017, 2926, 1654; HRMS calcd for $C_{22}H_{18}BrNO$: 391.0572. Found: 391.0579.

2-Bromo-1-[5-(triethylsilyl)pent-4-ynyl]-1*H*-indole-3-carboxaldehyde (3g). This compound was prepared using 5-chloro-1-triethylsilyl-1-pentyne and $(i\text{-Pr})_2NEt$ as the base using a modification of method A. The product was purified using 5:1 hexanes/EtOAc to afford a 90% yield of the indicated compound as a yellow oil, which solidifies upon cooling and standing: mp 59-61 °C; ^1H NMR ($CDCl_3$) δ 0.65 (m, 6H), 1.03 (m, 9H), 2.05 (quintet, J = 7.2 Hz, 2H), 2.39 (t, J = 7.2 Hz, 2H), 4.44 (t, J = 7.2 Hz, 2H), 7.27-7.33 (m, 2H), 7.48 (m, 1H), 8.33 (m, 1H), 10.05 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 4.7, 7.8, 17.6, 28.6, 44.4, 57.4, 84.1, 106.2, 110.0, 115.7, 121.5, 123.6, 124.63, 125.6, 125.7, 137.2, 185.6; IR (neat, cm^{-1}) 3056, 2954, 2805, 2172, 1653; HRMS calcd for $C_{22}H_{26}BrNOSi$: 403.0967. Found: 403.0974.

2-Bromo-1-(pent-4-ynyl)-1*H*-indole-3-carboxaldehyde (3h). This compound was prepared using 5-chloro-1-pentyne according to method A. The product was purified using 5:1 hexanes/EtOAc to afford a 96% yield of the indicated compound as a yellow solid: mp 94-96 °C; ^1H NMR ($CDCl_3$) δ 2.05 (quintet, J = 7.2 Hz, 2H), 2.11 (t, J = 2.7 Hz, 1H), 2.31 (dt, J = 2.7, 7.2 Hz, 2H), 4.40 (t, J = 7.2 Hz, 2H), 7.26-7.35 (m, 2H), 7.43 (m, 1H), 8.31 (m, 1H), 10.03 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 16.2, 28.4, 44.3, 70.3, 82.7, 110.0, 115.7, 121.5, 123.6, 124.4, 125.6, 125.8, 137.1, 185.6; IR (neat, cm^{-1}) 3223, 2926, 2806, 1648; HRMS calcd for $C_{14}H_{12}BrNO$: 289.0102. Found: 289.0106.

4,4'-Bis-[5-(2-bromo-3-formylindol-1-yl)pent-1-ynyl]biphenyl (3i). This compound was prepared using 4,4'-bis-(5-chloropent-1-ynyl)biphenyl (178 mg, 0.5 mmol), 2-bromo-1*H*-indole-3-carboxaldehyde[17] (268 mg, 1.2 mmol), K_2CO_3 (208 mg, 1.5 mmol) and NaI (224 mg, 1.5 mmol) in acetone (6 mL) at 75 °C for 48 h using a modification of method A. The product was purified using 3:2 hexanes/EtOAc to afford 343 mg (94%) of the indicated compound as a yellow solid: mp 135-137 °C; ^1H NMR ($CDCl_3$) δ 2.17 (m, 4H), 2.56 (t, J = 7.2 Hz, 4H), 4.49 (t, J = 7.2, 4H), 7.27-7.35 (m, 4H), 7.45-7.50 (m, 6H), 7.51-7.60 (m, 4H), 8.33 (m, 2H), 10.04 (s, 2H); ^{13}C

NMR ($CDCl_3$) δ 17.1, 28.5, 44.3, 82.0, 89.0, 109.9, 115.5, 121.4, 122.7, 123.5, 124.2, 125.5, 125.6, 126.9, 132.1, 136.9, 139.9, 185.5; IR (neat, cm^{-1}) 3022, 2922, 2262, 1653; HRMS calcd for $C_{40}H_{30}Br_2N_2O_2$: 730.0654. Found: 730.0667.

2-Bromo-1-(4-phenylbut-3-ynyl)-1*H*-indole-3-carboxaldehyde (3k). This compound was prepared using 4-phenylbut-3-yn-1-ol according to method B. The product was purified using 3:1 hexanes/EtOAc to afford 161 mg (92%) of the indicated compound as a yellow solid: mp 104-105 °C; ^1H NMR ($CDCl_3$) δ 2.95 (t, *J* = 7.2 Hz, 2H), 4.53 (t, *J* = 7.2 Hz, 2H), 7.24-7.33 (m, 7H), 7.46 (m, 1H), 8.34 (m, 1H), 10.05 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 20.6, 44.0, 83.6, 84.8, 110.0, 115.7, 121.4, 122.8, 123.5, 124.2, 125.4, 125.6, 128.2, 128.3, 131.5, 136.8, 185.6; IR (neat, cm^{-1}) 3055, 3017, 2807, 2237, 1652; HRMS calcd for $C_{19}H_{14}BrNO$: 351.0259. Found: 351.0265.

2-Bromo-1-(11-phenylundec-10-ynyl)indole-3-carboxaldehyde (3m). This compound was prepared using 11-phenylundec-10-yn-1-ol according to Method B. The product was purified using 8:1 hexanes/EtOAc to afford a 75% yield of the indicated compound as a yellow oil: ^1H NMR ($CDCl_3$) δ 1.25-1.50 (m, 10H), 1.59 (quintet, *J* = 7.2 Hz, 2H), 1.82 (quintet, *J* = 7.2 Hz, 2H), 2.39 (t, *J* = 7.2 Hz, 2H), 4.24 (t, *J* = 7.2 Hz, 2H), 7.22-7.40 (m, 8H), 8.32 (m, 1H), 10.03 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 19.6, 27.0, 28.9, 29.0, 29.2, 29.4, 29.5, 29.7, 45.7, 80.9, 90.6, 110.1, 115.4, 121.5, 123.5, 124.2, 124.3, 125.6, 125.9, 127.7, 128.4, 131.7, 136.9, 185.7; IR (neat, cm^{-1}) 3017, 2930, 2856, 1654; HRMS calcd for $C_{26}H_{28}BrNO$: 449.1354. Found: 449.1363.

2-Bromo-1-[2-(hex-1-ynyl)benzyl]-1*H*-indole-3-carboxaldehyde (3o). This compound was prepared using 2-(hex-1-ynyl)benzyl alcohol according to method B for 72 h. The product was purified using 7:1 hexanes/EtOAc to afford a 36% yield of the indicated compound as a yellow oil: ^1H NMR ($CDCl_3$) δ 0.98 (t, *J* = 7.2 Hz, 2H), 1.54 (sextet, *J* = 7.2 Hz, 2H), 1.67 (quintet, *J* = 7.2 Hz, 2H), 2.54 (t, *J* = 7.2 Hz, 2H), 6.52 (d, *J* = 7.8 Hz, 1H), 7.10 (t, *J* = 7.8 Hz, 1H), 7.18-7.32 (m, 4H), 7.48 (d, *J* = 7.8 Hz, 1H), 8.35 (d, *J* = 7.8 Hz, 1H), 10.09 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 13.7, 19.4, 22.2,

30.9, 47.3, 77.8, 97.3, 110.4, 115.7, 121.3, 122.2, 123.6, 124.4, 125.3, 125.4, 126.4, 127.7, 128.3, 132.5, 136.4, 137.2, 185.6; IR (neat, cm^{-1}) 3058, 2956, 2930, 2226, 1661; HRMS calcd for $C_{22}H_{20}BrNO$: 393.0728. Found: 393.0733.

2-Bromo-1-[(*Z*)-5-phenylpent-2-en-4-ynyl]-1*H*-indole-3-carboxaldehyde (3p). This compound was prepared using (*Z*)-1-bromo-5-phenylpent-2-en-4-yne according to method A for 48 h or (*Z*)-5-phenylpent-2-en-4-yn-1-ol[32] according to method B for 48 h. The product was purified using 5:1 hexanes/EtOAc to afford a 22% yield (method A) or a 31% yield (method B) of the indicated compound as a yellow solid: mp 129-131 °C; ^1H NMR ($CDCl_3$) δ 5.33 (d, J = 6.0 Hz, 2H), 5.94 (dd, J = 6.0, 8.4 Hz, 1H), 5.99 (d, J = 8.4 Hz, 1H), 7.25-7.31 (m, 2H), 7.31-7.40 (m, 3H), 7.45-7.52 (m, 3H), 8.31 (m, 1H), 10.03 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 44.9, 84.5, 97.2, 110.2, 113.8, 115.7, 121.3, 122.6, 123.5, 124.3, 125.4, 125.6, 128.6, 129.0, 131.6, 134.5, 136.9, 185.5; IR (neat, cm^{-1}) 3055, 2808, 2196, 1654; HRMS calcd for $C_{20}H_{14}BrNO$: 363.0259. Found: 363.0265.

2-Bromo-1-[2-(phenylethynyl)benzoyl]-1*H*-indole-3-carboxaldehyde (3r). To a mixture of 2-bromo-1*H*-indole-3-carboxaldehyde[17] (86 mg, 0.38 mmol) and 2-(phenylethynyl)benzoic acid[34] (111 mg, 0.5 mmol) in THF (5 mL) was added DMAP (6 mg) and DCC (105 mg), and the mixture was stirred at room temperature for 28 h. The precipitate was filtered and the solvent was evaporated and the residue was purified using 4:1 hexanes/EtOAc to afford a 50% yield of the indicated compound as a yellow solid: mp 136-138 °C; ^1H NMR ($CDCl_3$) δ 6.69 (d, J = 8.0 Hz, 2H), 7.09 (t, J = 7.8 Hz, 2H), 7.20 (m, 1H), 7.32-7.38 (m, 2H), 7.54 (m, 1H), 7.60 (m, 2H), 7.69 (m, 1H), 7.81 (d, J = 8.0 Hz, 1H), 8.24 (m, 1H), 10.05 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 84.6, 95.6, 113.7, 119.9, 121.1, 121.5, 122.2, 123.5, 125.1, 125.9, 126.1, 128.1, 128.8, 128.9, 130.5, 131.4, 132.9, 133.3, 136.3, 137.1, 168.0, 186.8; IR (neat, cm^{-1}) 3061, 2214, 1699, 1669; HRMS calcd for $C_{24}H_{14}BrNO_2$: 427.0208. Found: 427.0213.

Other Tethered Indoles Prepared

Methyl 2-iodo-1-(5-phenylpent-4-ynyl)-1*H*-indole-3-carboxylate (3s). This compound was prepared using methyl 2-iodo-1*H*-indole-3-carboxylate and 5-chloro-1-pentyne at 100 °C using a modification of method A. The product was purified using 4:1 hexanes/EtOAc to afford a 78% yield of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 2.08 (quintet, J = 7.5 Hz, 2H), 2.51 (t, J = 7.5 Hz, 2H), 3.96 (s, 3H), 4.48 (t, J = 7.5 Hz, 2H), 7.18-7.25 (m, 2H), 7.28-7.33 (m, 3H), 7.40-7.50 (m, 3H), 8.12 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 17.0, 28.6, 47.0, 51.2, 82.1, 88.4, 94.2, 110.2, 111.6, 121.8, 122.0, 123.1, 123.5, 127.5, 128.0, 128.4, 131.6, 138.2, 164.9; IR (neat, cm^{-1}) 3053, 2949, 2228, 1697; HRMS calcd for $C_{21}H_{18}INO_2$: 443.0382. Found: 443.0389.

2-Iodo-3-phenyl-1-(5-phenylpent-4-ynyl)-1*H*-indole (3t). This compound was prepared using 2-iodo-3-phenyl-1*H*-indole,[21] 5-chloro-1-pentyne and Cs_2CO_3 as the base at 100 °C for 40 h using a modification of method A. The product was purified using 10:1 hexanes/EtOAc to afford an 86% yield of the indicated compound as a yellow oil, which solidifies upon cooling and standing: mp 68-70 °C; ^{1}H NMR ($CDCl_3$) δ 2.13 (quintet, J = 7.2 Hz, 2H), 2.53 (t, J = 7.2 Hz, 2H), 4.45 (t, J = 7.2 Hz, 2H), 7.08 (t, J = 7.6, 1H), 7.21 (t, J =7.6, 1H), 7.28-7.38 (m, 4H), 7.41-7.51 (m, 5H), 7.54-7.61 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 17.1, 29.1, 46.5, 81.8, 85.8, 88.8, 109.8, 119.2, 120.2, 122.4, 123.4, 123.7, 126.9, 127.9, 128.4, 128.5, 130.1, 131.7, 135.2, 138.1 (one sp^2 carbon missing due to overlap); IR (neat, cm^{-1}) 3052, 2933, 2223; HRMS calcd for $C_{25}H_{20}IN$: 461.0641. Found: 461.0646.

2-Bromo-1-(5-phenylpent-4-ynyl)-1*H*-indole-3-acetonitrile (3u). This compound was prepared using 2-bromo-1*H*-indole-3-acetonitrile,[22] 5-chloro-1-pentyne and Cs_2CO_3 as the base at 75 °C using a modification of method A. The product was purified using 5:1 hexanes/EtOAc to afford a 99% yield of the indicated compound as a yellow oil, which solidifies upon cooling and standing: mp 68-70 °C; ^{1}H NMR ($CDCl_3$) δ 2.07 (quintet, J = 7.2 Hz, 2H), 2.46 (t, J = 7.2 Hz, 2H), 3.79 (s, 2H), 4.37 (t, J = 7.2 Hz, 2H), 7.16-7.32 (m, 5H), 7.38-7.48 (m, 3H), 7.62 (d, J = 6.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.7, 17.2, 29.1, 44.3, 82.1, 88.7, 103.6, 110.1, 114.0,

117.3, 118.1, 121.0, 123.0, 123.8, 126.3, 128.2, 128.6, 131.8, 136.6; IR (neat, cm^{-1}) 3055, 2929, 2231; HRMS calcd for $C_{21}H_{17}BrN_2$: 376.0575. Found: 376.0580.

2-Iodo-1-(5-phenylpent-4-ynyl)-1*H*-indole-3-acetonitrile (3v). This compound was prepared using 2-iodo-1*H*-indole-3-acetonitrile, 5-chloro-1-pentyne and Cs_2CO_3 as the base at 100 °C for 40 h using a modification of method A. The product was purified using 4:1 hexanes/EtOAc to afford a 71% yield of the indicated compound as a yellow oil: ^1H NMR ($CDCl_3$) δ 2.03 (quintet, J = 7.2 Hz, 2H), 2.45 (t, J = 7.2 Hz, 2H), 3.77 (s, 2H), 4.34 (t, J = 7.2 Hz, 2H), 7.14-7.22 (m, 2H), 7.25-7.32 (m, 3H), 7.40-7.45 (m, 3H), 7.62 (d, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 16.9, 17.0, 29.0, 46.6, 82.0, 87.7, 88.6, 109.8, 110.2, 117.3, 117.9, 120.5, 122.8, 123.6, 127.0, 128.0, 128.4, 131.6, 138.1; IR (neat, cm^{-1}) 3057, 2939, 2243; HRMS calcd for $C_{21}H_{17}IN_2$: 424.0437. Found: 424.0442.

General Procedure for the Synthesis of Annulated γ-Carbolines by Palladium-Catalyzed Intramolecular Iminoannulation. The *N*-substituted 2-bromo-1*H*-indole-3-carboxaldehyde (0.25 mmol) was placed in a 2-dram vial and *tert*-butylamine (1 mL) was added. The vial was flushed with Ar and carefully sealed. The mixture was heated at 100 °C for 8 h and cooled, diluted with ether, dried over anhydrous Na_2SO_4 and filtered. The solvent was evaporated and the residue was dissolved in DMF (5 mL) and transferred to a 4-dram vial containing $Pd(OAc)_2$ (5 mol %), PPh_3 (10 mol %) and Na_2CO_3 (0.25 mmol). The mixture was flushed with Ar and heated at 100 °C for the indicated time. The completion of the reaction was established by the observation of palladium black. The mixture (except for entries 4 and 6-8 in Table 1, which produce reasonably water soluble products) was diluted with EtOAc, washed with satd aq NH_4Cl and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by chromatography on a silica gel column. The solvent from the reaction mixtures of entries 4 and 6-8 was directly evaporated and the residue was purified by chromatography on a silica gel column.

Annulated γ-Carbolines Prepared

3-[(*E*)-β-Styryl]-5,6-dihydro-4*H*-indolo[3,2,1-*ij*]-1,6-naphthyridine (4c). The mixture was chromatographed using 12:1 $CHCl_3$/MeOH to afford 73 mg (94%) of the indicated compound as a yellow solid: mp 131-132 °C; ^{1}H NMR ($CDCl_3$) δ 2.35 (quintet, *J* = 7.2 Hz, 2H), 3.15 (t, *J* = 7.2 Hz, 2H), 4.16 (t, *J* = 7.2 Hz, 2H), 7.24-7.31 (m, 2H), 7.34-7.50 (m, 5H), 7.63 (d, *J* = 8.0 Hz, 2H), 7.86 (d, *J* = 15.6 Hz, 1H), 8.12 (d, *J* = 8.0 Hz, 1H), 9.14 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.3, 22.2, 40.5, 108.8, 114.0, 116.6, 120.4, 121.2, 121.7, 123.9, 126.2, 127.1, 127.9, 128.7, 132.2, 137.5, 140.3, 140.4, 142.9, 146.0; IR (neat, cm^{-1}) 3054, 2947, 2865; HRMS calcd for $C_{22}H_{18}N_2$: 310.1470. Found: 310.1476.

2-*tert*-Butyl-5,6-dihydro-4*H*-indolo[3,2,1-*ij*]-1,6-naphthyridinium bromide (4g). The mixture was chromatographed using 4:1 $CHCl_3$/MeOH to afford 46 mg (53%) of the indicated compound as a yellow solid: mp >300 °C; ^{1}H NMR ($CDCl_3$) δ 2.01 (s, 9H), 2.42 (quintet, *J* = 6.0 Hz, 2H), 3.44 (t, *J* = 6.0 Hz, 2H), 4.38 (t, *J* = 6.0 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.64 (t, *J* = 7.8 Hz, 1H), 8.78 (d, *J* = 8.0 Hz, 1H), 9.15 (s, 1H), 10.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.2, 22.2, 31.1, 41.6, 68.0, 110.2, 118.1, 119.8, 120.9, 123.3, 124.4, 129.4, 132.3, 134.1, 141.7, 143.6; IR (neat, cm^{-1}) 3016, 2980; MS *m/z* (rel intensity) 345 (21, M^+), 209 (100, MH^+-*t*-Bu-Br). Anal. Calcd for $C_{18}H_{21}BrN_2$: C, 62.62; H, 6.13; N, 8.11. Found: C, 62.16; H, 6.22; N, 8.01.

5,6-Dihydro-4*H*-indolo[3,2,1-*ij*]-1,6-naphthyridine (4h). The mixture was chromatographed using 10:1 $CHCl_3$/MeOH to afford 21 mg (40%) of the indicated compound as a yellow solid: mp 268-270 °C (lit.[14c] mp 270 °C). All other spectral properties are identical to those previously reported.[14a,c]

4,4'-Bis-{5,6-dihydro-4*H*-indolo[3,2,1-*ij*]-1,6-naphthyrid-3-yl}biphenyl (4i). The aldehyde (**3i**, 146 mg, 0.20 mmol), *tert*-butylamine (3 mL) and $CHCl_3$ (5 mL) were placed in a 2-dram vial. The vial was flushed with Ar and carefully sealed, and the mixture was heated at 100 °C for 20 h. The mixture was cooled, diluted with

ether, dried over anhydrous Na_2SO_4 and the solvent was evaporated. The residue was dissolved in 8 mL of DMF and transferred to a 4-dram vial containing 10 mol % $Pd(OAc)_2$, 20 mol % PPh_3 and Na_2CO_3 (0.40 mmol). The mixture was then flushed with Ar and heated at 100 °C for 10 h. The mixture was chromatographed using 8:1 $CHCl_3$/MeOH on a short silica gel column to afford 103 mg (91%) of the indicated compound as a yellow solid: mp >300 °C; ^{1}H NMR ($CDCl_3$) δ 2.32 (quintet, J = 5.6 Hz, 4H), 3.27 (t, J = 5.6 Hz, 4H), 4.29 (t, J = 5.6 Hz, 4H), 7.35 (t, J = 7.6 Hz, 2H), 7.45 (d, J = 7.6 Hz, 2H), 7.54 (t, J = 7.6 Hz, 2H), 7.81 (d, J = 8.4 Hz, 4H), 7.86 (d, J = 8.4 Hz, 4H), 8.19 (d, J = 7.6 Hz, 2H), 9.28 (s, 2H); the ^{13}C NMR spectrum of compound **4i** was not obtained due to its extremely poor solubility in all the solvents we tried; IR (neat, cm^{-1}) 3050, 2929, 2862; HRMS calcd for $C_{40}H_{30}N_4$: 566.2471. Found: 566.2478.

3-Phenyl-4,5-dihydrobenzo[*b*]pyrido[3,4,5-*gh*]pyrrolizine (4k). The mixture was chromatographed using 3:2 hexanes/EtOAc to afford 57 mg (84%) of the indicated compound as a yellow solid: mp 171-172 °C; ^{1}H NMR ($CDCl_3$) δ 4.06 (t, J = 7.2 Hz, 2H), 4.53 (t, J = 7.2 Hz, 2H), 7.28 (m, 1H), 7.37 (t, J = 8.0 Hz, 2H), 7.42-7.50 (m, 3H), 8.02 (m, 2H), 8.08 (d, J = 8.0 Hz, 2H), 9.07 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 35.0, 48.7, 110.5, 112.8, 116.5, 120.2, 123.0, 126.0, 127.6, 128.2, 128.7, 139.4, 140.4, 141.0, 146.8, 158.2; IR (neat, cm^{-1}) 3055, 2922, 1559; HRMS calcd for $C_{19}H_{14}N_2$: 270.1157. Found: 270.1161.

1-*n*-Butyl-9*H*-benzo[*c*]indolo[3,2,1-*ij*]-1,6-naphthyridine (4o). The mixture was chromatographed using 2:3 hexanes/EtOAc to afford 58 mg (75%) of the indicated compound as a yellow solid: mp 129-130 °C; ^{1}H NMR ($CDCl_3$) δ 1.03 (t, J = 7.2 Hz, 3H), 1.58 (m, 2H), 1.90 (m, 2H), 3.29 (t, J = 8.0 Hz, 2H), 5.40 (s, 2H), 7.30-7.37 (m, 3H), 7.38-7.45 (m, 2H), 7.50 (dt, J = 0.8, 8.0 Hz, 1H), 8.02 (d, J = 8.0 Hz, 1H), 8.08 (d, J = 8.0 Hz, 1H), 8.99 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.1, 23.1, 31.4, 38.1, 45.7, 109.2, 112.2, 116.8, 121.0, 121.2, 122.0, 126.3, 126.7, 127.8, 128.1, 128.2, 129.6, 130.9, 140.3, 140.9, 143.7; IR (neat, cm^{-1}) 3059, 2956, 2870; HRMS calcd for $C_{22}H_{20}N_2$: 312.1626. Found: 312.1630.

3-Phenyl-6*H*-indolo[3,2,1-*ij*]-1,6-naphthyridine (4p). The mixture was chromatographed using 1:2 hexanes/EtOAc to afford 40 mg (57%) of the indicated compound as a yellow solid: mp 160-161 °C; ^{1}H NMR ($CDCl_3$) δ 5.18 (t, J = 2.8 Hz, 2H), 5.97 (dt, J = 10.4, 3.2 Hz, 1H), 6.88 (dt, J = 10.4, 2.0 Hz, 1H), 7.32-7.44 (m, 3H), 7.46-7.54 (m, 3H), 7.69 (m, 2H), 8.13 (d, J = 7.8 Hz, 1H), 9.10 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 44.0, 109.0, 110.9, 116.0, 121.0, 121.4, 121.7, 122.2, 123.1, 126.2, 128.0, 129.6, 139.1, 140.3, 142.5, 142.6, 148.9; IR (neat, cm^{-1}) 3056, 2927; HRMS calcd for $C_{20}H_{14}N_2$: 282.1157. Found: 282.1160.

Heteropolycycles prepared

3-Phenyl-5,6-dihydro-1*H*,4*H*-benzo[*b*]pyrano[3,4,5-*hi*]indolizin-1-one (5c). To a 4-dram vial were added methyl 2-iodo-1-(5-phenylpent-4-ynyl)-1*H*-indole-3-carboxylate (**3s**, 0.25 mmol), $Pd(OAc)_2$ (5 mol %), Na_2CO_3 (0.25 mmol), LiCl (0.25 mmol) and DMF (5 mL). The mixture was flushed with Ar and heated at 100 °C for 24 h. The mixture was diluted with EtOAc, washed with satd aq NH_4Cl and dried over anhydrous Na_2SO_4. The solvent was evaporated and the residue was purified by chromatography on a silica gel column using 1:1 hexanes/EtOAc to afford 39 mg (52%) of the indicated compound as a white solid: mp 209-210 °C; ^{1}H NMR ($CDCl_3$) δ 2.16 (m, 2H), 2.95 (t, J = 6.0 Hz, 2H), 4.10 (t, J = 6.0 Hz, 2H), 7.27-7.31 (m, 3H), 7.31-7.46 (m, 3H), 7.65 (m, 2H), 8.15 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 22.1, 22.8, 40.9, 98.2, 103.8, 109.1, 121.4, 122.4, 124.0, 124.3, 128.3 (2), 129.4, 132.3, 138.2, 144.7, 153.4, 159.4; IR (neat, cm^{-1}) 3056, 2923, 1702; HRMS calcd for $C_{20}H_{15}NO_2$: 301.1103. Found: 301.1108; Anal. Calcd for $C_{20}H_{15}NO_2$: C, 79.73; H, 5.02; N, 4.65. Found: C, 79.43; H, 4.81; N, 4.41.

9-Phenyl-7,8-dihydro-6*H*-benzo[*c*]pyrido[1,2,3-*lm*]carbazole (5d). To a 4-dram vial were added 2-iodo-3-phenyl-1-(5-phenylpent-4-ynyl)-1*H*-indole (**3t**, 0.25 mmol), $Pd(OAc)_2$ (5 mol %), NaOAc (0.50 mmol), LiCl (0.25 mmol) and DMF (5 mL). The mixture was flushed with Ar and heated at 100 °C for 8 h. The mixture was diluted with EtOAc, washed with satd aq NH_4Cl and dried over anhydrous Na_2SO_4.

The solvent was evaporated and the residue was purified by chromatography on a silica gel column using 10:1 hexanes/EtOAc to afford 56 mg (68%) of the indicated compound as a yellow solid: mp 239-241 °C; ^{1}H NMR ($CDCl_3$) δ 2.27 (quintet, J = 6.0 Hz, 2H), 2.89 (t, J = 6.0 Hz, 2H), 4.34 (t, J = 6.0 Hz, 2H), 7.31 (m, 1H), 7.39 (m, 3H), 7.44-7.56 (m, 5H), 7.64 (m, 2H), 8.58 (d, J = 8.0 Hz, 1H), 8.76 (d, J = 8.0 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 22.6, 24.6, 41.1, 108.9, 112.2, 119.7, 120.9, 122.1, 122.4, 123.0, 123.5, 123.7, 125.7, 127.1, 127.7, 128.3, 128.9, 129.0, 130.6, 135.1, 135.5, 138.9, 139.0; IR (neat, cm^{-1}) 3050, 2944; HRMS calcd for $C_{25}H_{18}N$: 333.1518. Found: 333.1523. Anal. Calcd for $C_{25}H_{19}N$: C, 90.06; H, 5.74; N, 4.20. Found: C, 90.27; H, 5.44; N, 4.17.

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Supporting Information Available. ^{1}H and ^{13}C NMR spectra for compounds **3c**, **3g-l**, **3k**, **3m**, **3o-p**, **3r-v**, **4c**, **4g**, **4k**, **4o-p**, and **5c-d**, and ^{1}H NMR spectrum for compound **4i**. This material is included in Appendix C and is also available free of charge via the Internet at http://pubs.acs.org.

References

1. For reviews, see: (a) Larock, R. C. *J. Organometal. Chem.* **1999**, *576*, 111. (b) Larock, R. C.; "Palladium-Catalyzed Annulation," in *Perspectives in Organopalladium Chemistry for the XXI Century*, Ed. J. Tsuji, Elsevier Press, Lausanne, Switzerland, 1999, pp 111-124. (c) Larock, R. C. *Pure Appl. Chem.* **1999**, *71*, 1435.
2. (a) Larock, R. C.; Yum, E. K. *J. Am. Chem. Soc.* **1991**, *113*, 6689. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652.
3. (a) Roesch, K. R.; Larock, R. C. *Org. Lett.* **1999**, *1*, 1551. (b) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 412.
4. Larock, R. C.; Yum, E. K.; Doty, M. J.; Sham, K. K. C. *J. Org. Chem.* **1995**, *60*, 3270.
5. Larock, R. C.; Doty, M. J.; Han, X. *J. Org. Chem.* **1999**, *64*, 8770.
6. Larock, R. C.; Han, X.; Doty, M. J. *Tetrahedron Lett.* **1998**, *39*, 5713.
7. Larock, R. C.; Doty, M. J.; Cacchi, S. *J. Org. Chem.* **1993**, *58*, 4579.
8. (a) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (b) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042.
9. (a) Huang, Q.; Larock, R. C. *Org. Lett.* **2002**, *4*, 2505. (b) Tian, Q.; Pletnev, A. A.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 339.
10. (a) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **1998**, *63*, 2002.
11. For palladium-catalyzed intramolecular benzoannulations, see: (a) Kawasaki, T.; Saito, S.; Yamamoto, Y. *J. Org. Chem.* **2002**, *67*, 2653. (b) Weibel, D.; Gevorgyan, V.; Yamamoto, Y. *J. Org. Chem.* **1998**, *63*, 1217. (c) Saito, S.; Tsuboya, N.; Yamamoto, Y. *J. Org. Chem.* **1997**, *62*, 5042. For other palladium-catalyzed intramolecular annulations, see: (d) Hu, Y.; Yang, Z. *Org. Lett.* **2001**, *3*, 1387. (e) Piers, E.; Marais, P. C. *J. Org. Chem.* **1990**, *55*, 3454.
12. (a) Saxton, J. E. in *The Chemistry of Heterocyclic Compounds*; Taylor, E. D., Ed.; Wiley-Intersciences Publication: New York, 1994; Vol. 25. (b) Gribble, G.

W. In *The Alkaloids*; Brossi, A., Ed.; Academic Press: San Diego, 1990; Vol. 39, Chapter 7. (c) Tan, G. T.; Pezzuto, J. M. In *Chemistry and Toxicology of Diverse Classes of Alkaloids*; Blum, M. S., Ed.; Alaken, Inc.: 1996; pp 1-119.

13. (a) Engler, T. A.; Wanner, J. *J. Org. Chem.* **2000**, *65*, 2444. (b) Sakamoto, T.; Numata, A.; Saitoh, H.; Kondo, Y. *Chem. Pharm. Bull.* **1999**, *47*, 1740. (c) Molina, A.; Vaquero, J. J.; Garcia-Navio, J. L.; Alvarez-Builla, J.; de Pascual-Teresa, B.; Gago, F.; Rodrigo, M. M.; Ballesteros, M. *J. Org. Chem.* **1996**, *61*, 5587. (d) Hibino, S.; Sugino, E.; Kuwada, T.; Ogura, N.; Sato, K.; Choshi, T. *J. Org. Chem.* **1992**, *57*, 5917. (e) Hibino, S.; Kano, S.; Mochizuki, N.; Sugino, E. *J. Org. Chem.* **1984**, *49*, 5006. (f) Prikhod'ko, T. A.; Vasilevskii, S. F.; Shvartsberg, M. S. *J. Acad. Sci. USSR, Org. Chem.* **1984**, *11*, 2383.
14. (a) Snyder, S. A.; Vosburg, D. A.; Jarvis, M. G.; Markgraf, J. H. *Tetrahedron* **2000**, *56*, 5329. (b) Markgraf, J. H.; Snyder, S. A.; Vosburg, D. A. *Tetrahedron Lett.* **1998**, *39*, 1111. (c) Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. *Tetrahedron* **1997**, *53*, 4447. (d) Gilchrist, T. L.; Kemmitt, P. D.; Germain, A. L. *Heterocycles* **1994**, *37*, 697. (e) Shimoji, Y.; Hashimoto, T.; Furukawa, Y.; Yanagisawa, H. *Heterocycles* **1993**, *36*, 123.
15. Yanagisawa, H.; Shimoji, Y.; Hashimoto, T. Jpn. Kokai Tokkyo Koho JP 05310738, 1993, Heisei; *Chem. Abstr.* **1994**, *120*, 245056.
16. Clark, R. D.; Miller, A. B.; Berger, J.; Repke, D. B.; Weinhardt, K. K.; Kowalczyk, B. A.; Eglen, R, M.; Bonhaus, D. W.; Lee, C.–H.; Michel, A. D.; Smith, W. L.; Wong, E. H. F. *J. Med. Chem.* **1993**, *36*, 2645.
17. (a) Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 3083. (b) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9318.
18. Zhang, H.; Larock, R. C. *Org. Lett.* **2002**, *4*, 3035.
19. For recent reviews of the Mitsunobu reaction, see: (a) Dodge, J. A.; Jones, S. A. *Recent Res. Develop. Org. Chem.* **1997**, *1*, 273. (b) Simon, C.; Hosztafi, S.; Makleit, S. *J. Heterocyclic Chem.* **1997**, *34*, 349. (c) Hughes, D. L. *Org. Prep. Proced. Inter.* **1996**, *28*, 127. (d) Hughes, D. L. *Org. React.* **1992**, *42*, 335.

20. For a similar acylation of 1*H*-indole-3-carboxaldehyde, see: Kraus, G. A.; Kim. H. *Synth. Commun.* **1993**, *23*, 55.
21. Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 5616.
22. Mistry, A. G.; Smith, K.; Bye, M. R. *Tetrahedron Lett.* **1986**, *27*, 1051.
23. (a) Zhang, H.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 1359. (b) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7048.
24. Benson, S. C.; Li, J.–H.; Snyder, J. K. *J. Org. Chem.* **1992**, *57*, 5285.
25. For a recent review on the palladium-catalyzed isomerization of double bonds, see: Negishi, E.–I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.–I., Ed.; John Wiley & Sons, Inc.: 2002; Vol. 2, pp 2783-2788.
26. (a) Schmidt, H.–J.; Schaefer, H. J. *Angew. Chem., Int. Ed. Engl.* **1979**, *18*, 68. (b) Schmidt, H.–J.; Schaefer, H. J. *Angew. Chem., Int. Ed. Engl.* **1981**, *20*, 109.
27. Li, J.–H; Snyder, J. K. *Tetrahedron Lett.* **1994**, *35*, 1485.
28. (a) Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941. (b) Wu, G.; Geib, S. J.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1988**, *53*, 3238.
29. Gevorgyan, V.; Quan, L. G.; Yamamoto, Y. *Tetrahedron Lett.* **1999**, *40*, 4089.
30. (a) Pletnev, A. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9428. (b) Pletnev, A. A.; Tian, Q.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 9276.
31. Brown, H. C.; Subrahmanyan, C.; Hamaoka, T.; Ravindran, N.; Bowman, D. H.; Misumi, S.; Unni, M. K.; Somayaji, V.; Bhat, N. G. *J. Org. Chem.* **1989**, *54*, 6068.
32. Takeuchi, R.; Tanabe, K.; Tanaka, S. *J. Org. Chem.* **2000**, *65*, 1558.
33. Wenkert, E.; Moeller, P. D.; Piettre, S. R. *J. Am. Chem. Soc.* **1988**, *110*, 7188.
34. Biagetti, M.; Bellina, F.; Carpita, A.; Stabile, P.; Rossi, R. *Tetrahedron* **2002**, *58*, 5023.

CHAPTER 4. 1,4-PALLADIUM MIGRATION IN THE SUZUKI COUPLING OF *o*-IODOBIARYLS

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Abstract

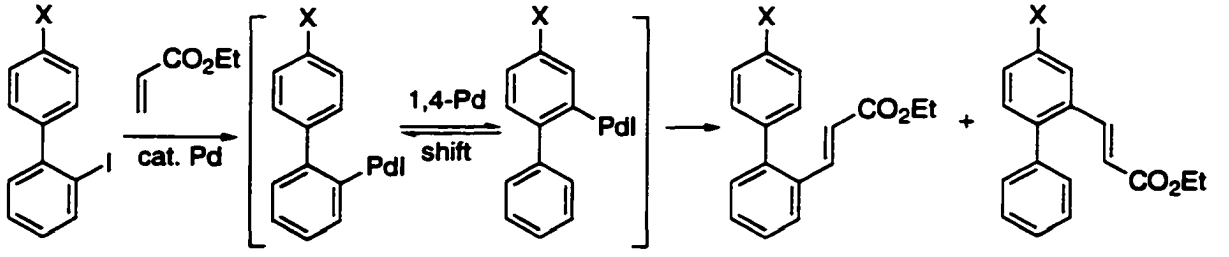
A novel 1,4-palladium migration between the *o*- and *o'*-positions of biaryls has been observed in the organopalladium intermediates derived from *o*-iodobiaryls. The organopalladium intermediates generated by this palladium migration have been trapped by way of a Suzuki coupling reaction with arylboronic acids. The molar ratios of the Suzuki products indicate that palladium has a preference to migrate from a more electron-deficient position to a more electron-rich position in the biaryl.

Introduction

Palladium has been shown to catalyze an extraordinary number of incredibly diverse reactions, making it one of the most useful of all metals for organic synthesis.[1] With the exception of alkene, alkyne and carbon monoxide insertion reactions, the palladium moiety typically stays directly attached to the carbon to which it is originally introduced. However, one of the unique features of palladium is its ability to migrate from one carbon to another.[2] We and others have reported that palladium can migrate through space in Heck coupling reactions.[2e-h] In particular, we have shown that the organopalladium intermediates derived from *o*-iodobiaryls lead to a 1,4-palladium migration, and such palladium intermediates can be trapped by Heck reactions with ethyl acrylate (Scheme 1).[2e] However, no palladium migration has been observed previously in Suzuki coupling reactions.[3] Herein, we wish to

report the first examples of palladium migration in Suzuki coupling reactions of *o*-iodobiaryls with arylboronic acids and important mechanistic implications of this chemistry.

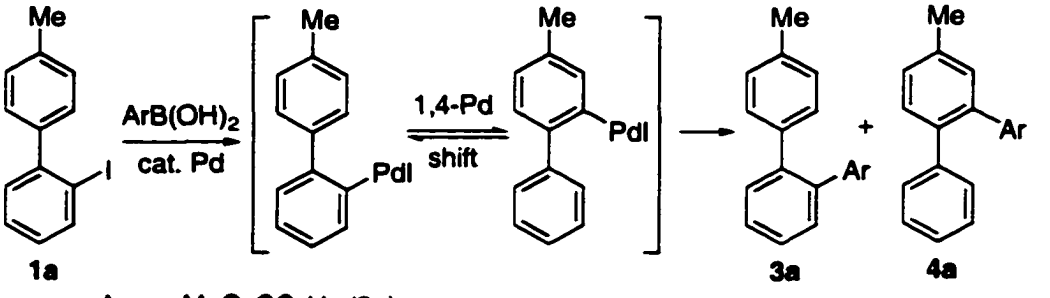
Scheme 1



Results and Discussion

In order to obtain a clear idea of what reaction conditions promote palladium migration, we have first studied the Suzuki coupling reaction of 2-iodo-4'-methylbiphenyl (**1a**) and 4-(methoxycarbonyl)phenylboronic acid (**2a**) under various reaction conditions (Scheme 2, Table 1).

Scheme 2



1a **3a** **4a**

Ar = *p*-$MeO_2CC_6H_4$ (**2a**)

The Pd-catalyzed Suzuki coupling of **1a** and **2a** under conditions described by Wright et al[4] produced methyl 4″-methyl-*o*-terphenyl-4-carboxylate (**3a**) exclusively in a 62% yield (entry 1, Table 1). Clearly under these conditions, the coupling reaction proceeds without any palladium migration. The coupling reaction of **1a** and 1 equiv of **2a** was then carried out under our standard migration conditions for the

Table 1. Pd-Catalyzed Reaction of 2-Iodo-4'-methylbiphenyl (1a) and 4-(Methoxycarbonyl)phenylboronic Acid (2a)[a]

entry	**2a** equiv	conditions[b]	time (h)	mol ratio[c] **3a:4a**	% yield
1	1.2	A	8	100:0	62
2	1.0	B	72	-	trace
3	1.0	B + 20 H_2O	8	57:43	55
4	1.0	B + 20 H_2O + 2 PA[d]	24	50:50	57
5	1.4	B + 20 H_2O + 2 PA[d]	4	51:49	78

[a] All reactions were run using 0.25 mmol of **1a**, 5 mol % $Pd(OAc)_2$, and appropriate amounts of boronic acid **2a** and base. [b] Conditions A: 10 mol % PPh_3, 2.2 equiv of CsF in 1 mL of DME at 90 °C; Conditions B: 5 mol % $(Ph_2P)_2CH_2$ (dppm), 2.0 equiv of CsPiv in 4 mL of DMF at 100 °C. [c] The mol ratio was determined by ^1H NMR spectroscopic analysis. [d] PA = pivalic acid (Me_3CCO_2H).

Heck reaction of unsymmetrical *o*-iodobiaryls and ethyl acrylate.[2e] Unfortunately, only a trace amount of coupling products was observed (entry 2). It has been reported that the addition of water facilitates Suzuki coupling reactions.[5] Therefore, we proceeded to carry out the coupling reaction of **1a** with **2a** after adding 20 equiv of H_2O to the reaction mixture. We were encouraged by obtaining a 57:43 mixture of Suzuki product **3a** and migration product **4a** in a 55% total yield (entry 3). Realizing that, in the presence of base, H_2O may serve as an OH^- source, which probably activates the arylboronic acid and facilitates the direct Suzuki coupling prior to Pd migration, we have attempted to control the concentration of OH^- by buffering the reaction mixture using a combination of 2 equiv of cesium pivalate (CsPiv) and 2 equiv of pivalic acid (PA). To our satisfaction, the reaction of **1a** and **2a** under these buffered conditions produced a 50:50 mixture of **3a** and **4a** in a 57% overall yield (entry 4). An even higher overall yield (78%) of a 51:49 mixture of **3a** and **4a** could be obtained by simply employing 1.4 equiv of arylboronic acid **2a** (entry 5, also entry 1 in Table 2). Thus, we chose this latter set of reaction conditions, described in entry 5, Table 1, which employ 1.4 equiv of boronic acid, 5 mol % $Pd(OAc)_2$, 5 mol %

$(Ph_2P)_2CH_2$ (dppm), 2 equiv of CsPiv, 2 equiv of PA and 20 equiv of H_2O in DMF at 100 °C as our standard migration conditions, for the Suzuki coupling of *o*-iodobiphenyls with arylboronic acids to further explore the scope of this palladium migration process (Scheme 3, Table 2).

Scheme 3

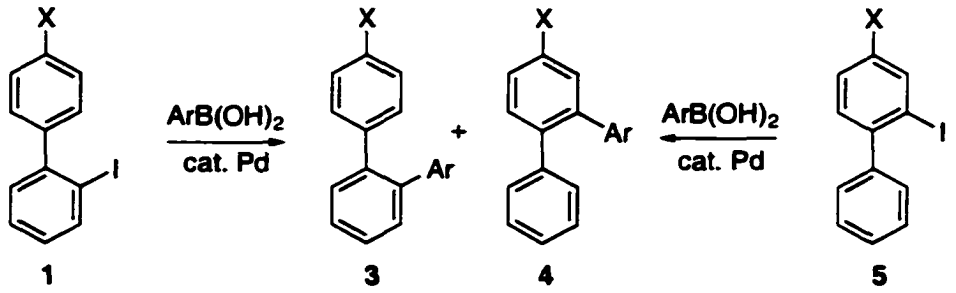


Table 2. Pd-Catalyzed Reaction of *o*-Iodobiphenyls (1 and 5) and Arylboronic Acids (2) under Standard Migration Conditions[a]

entry	*o*-iodobiphenyl X =	$ArB(OH)_2$ Ar =	time (h)	mol ratio[b] **3:4**	% yield
1	**1a**, Me	*p*-$MeO_2CC_6H_4$ (**2a**)	4	51:49	78
2	**5a**, Me	(**2a**)	6	49:51	83
3	**1a**, Me	Ph (**2b**)	3	52:48	79
4	**5a**, Me	(**2b**)	10	50:50	69
5	**1a**, Me	*p*-$MeOC_6H_4$ (**2c**)	3	52:48	93
6	**5a**, Me	(**2c**)	6	49:51	90
7	**1b**, MeO	(**2a**)	4	42:58	85
8	**5b**, MeO	(**2a**)	9	39:61	75
9	**1c**, CO_2Et	(**2a**)	10	40:60	84
10	**5c**, CO_2Et	(**2a**)	10	34:66	68

[a] All reactions were run using 0.25 mmol of the *o*-iodobiphenyl, 1.4 equiv of boronic acid, 5 mol % $Pd(OAc)_2$, 5 mol % dppm, 2.0 equiv of CsPiv, 2.0 equiv of PA and 20 equiv of H_2O in 4 mL of DMF at 100 °C. [b] The mol ratio was determined by ^1H NMR spectroscopic analysis.

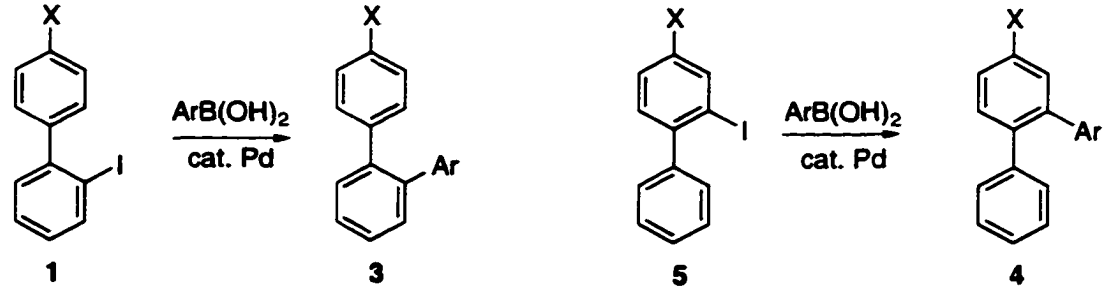
Interestingly, under our standard migration conditions, 2-iodo-4-methylbiphenyl (X = Me, **5a**) and 4-(methoxycarbonyl)phenylboronic acid (**2a**) generated a similar distribution of isomers **3a** and **4a** (49:51) as previously obtained from the reaction of **1a** and **2a** in an overall 83% yield (entry 2, Table 2). Furthermore, similar product distributions have also been observed in the reaction of **1a** and **5a** with phenylboronic acid (**2b**) and 4-methoxyphenylboronic acid (**2c**) (entries 3-6). These results seem to indicate that under our migration conditions, the arylpalladium intermediates generated from either **1a** or **5a** reach apparent equilibrium prior to transmetalation with the boronic acids, since the molar ratios of products **3a-c** to **4a-c** are essentially identical regardless of the electronic properties of the boronic acids **2a-c** employed.

The Pd-catalyzed reaction of methoxy-substituted *o*-iodobiphenyls **1b** and **5b** (X = MeO) with boronic acid **2a** under our migration conditions gave more dramatic results (entries 7 and 8). 2′-Iodo-4-methoxybiphenyl (**1b**) generated a 42:58 mixture of **3d** and **4d** in an 85% yield, while 2-iodo-4-methoxybiphenyl (**5b**) afforded **3d** and **4d** in a 75% yield in a very similar 39:61 molar ratio, indicating that palladium has a preference for the more electron-rich aromatic ring. Interestingly, under our standard migration conditions, the reaction of the ester-substituted *o*-iodobiphenyls **1c** and **5c** (X = CO_2Et) with boronic acid **2a** generated similar results to the methoxy-substituted *o*-iodobiphenyls **1b** and **5b** (entries 9 and 10). Thus, **1c** generated a 40:60 mixture of **3e** and **4e** in an 84% yield, while **5c** produced a 34:66 mixture of **3e** and **4e** in a 68% yield. In both cases, palladium seems to prefer to stay attached to the phenyl ring where the ester substituent resides. A preliminary theoretical calculation[6] of the electron densities of the 2- and 2′- positions of ethyl 4-phenylbenzoate indicates that the electron density of the 3-position is higher than that of the 2-position of the phenyl ring, which might explain our results.

It is worth noting that under the reaction conditions described by Wright et al,[4] all of the Suzuki coupling reactions of *o*-iodobiphenyls **1a-c** and **5a-c** with the boronic acids **2a-c** afforded good to excellent yields (62-98%) of the expected

Suzuki products, without any palladium migration products being observed (Scheme 4, Table 3). Thus, we can simply switch the palladium migration "on" and "off" at will in this biphenyl system by manipulating the reaction conditions.

Scheme 4



1 3 5 4

Table 3. Pd-Catalyzed Reaction of *o*-Iodobiphenyls (1 and 5) and Arylboronic Acids (2) under Non-migration Conditions[a]

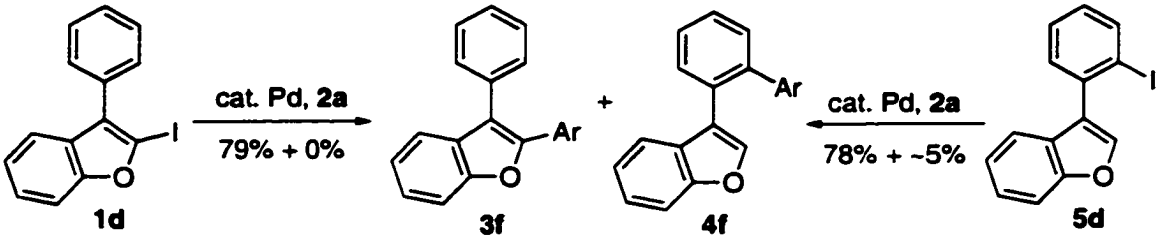
entry	*o*-iodobiphenyl X =	$ArB(OH)_2$ Ar =	time (h)	% yield
1	**1a**, Me	*p*-$MeO_2CC_6H_4$ (**2a**)	8	62
2	**5a**, Me	(**2a**)	12	90
3	**1a**, Me	Ph (**2b**)	40	85
4	**5a**, Me	(**2b**)	8	93
5	**1a**, Me	*p*-$MeOC_6H_4$ (**2c**)	18	93
6	**5a**, Me	(**2c**)	16	94
7	**1b**, MeO	(**2a**)	18	92
8	**5b**, MeO	(**2a**)	16	94
9	**1c**, CO_2Et	(**2a**)	16	98
10	**5c**, CO_2Et	(**2a**)	16	97

[a] All reactions were run using 0.25 mmol of the *o*-iodobiphenyl, 1.2 equiv of boronic acid, 5 mol % $Pd(OAc)_2$, 10 mol % PPh_3, 2.2 equiv of CsF in 1 mL of DME at 90 °C.

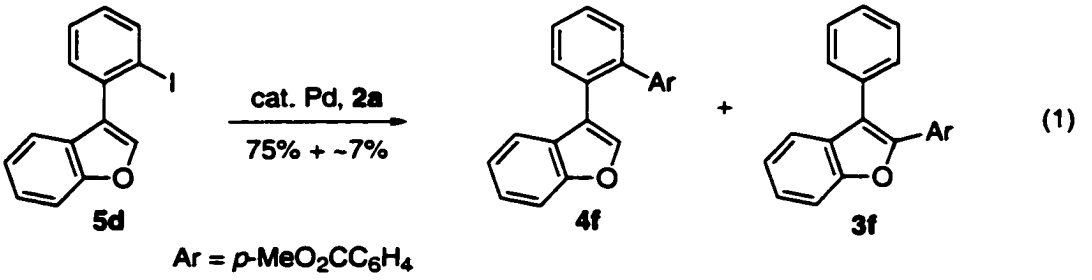
An even more marked effect on the product distribution was observed in the reaction of 2-iodo-3-phenylbenzofuran (**1d**) with 4-(methoxycarbonyl)phenylboronic

acid (**2a**), which under our standard migration conditions gives exclusively 2-[4-(methoxycarbonyl)phenyl]-3-phenylbenzofuran (**3f**) in a 79% yield in 3 h. Obviously, no palladium migration has occurred in this biaryl system. This is consistent with our Heck migration chemistry[2e] in which the reaction of **1d** with ethyl acrylate shows no palladium migration either. When 3-(2-iodophenyl)benzofuran (**5d**) was allowed to react with boronic acid **2a** under our standard migration conditions, **3f** was produced in a 78% yield in 3 h, along with only ~5% of isomer **4f** (Scheme 5), clearly showing

Scheme 5



a preference for palladium migration from the phenyl ring to the more electron-rich benzofuran ring. Furthermore, a 75% yield of **4f**, along with only ~7% of benzofuran **3f**, were obtained from **5d** when employing the reaction conditions described by Wright et al (eq 1).[4]

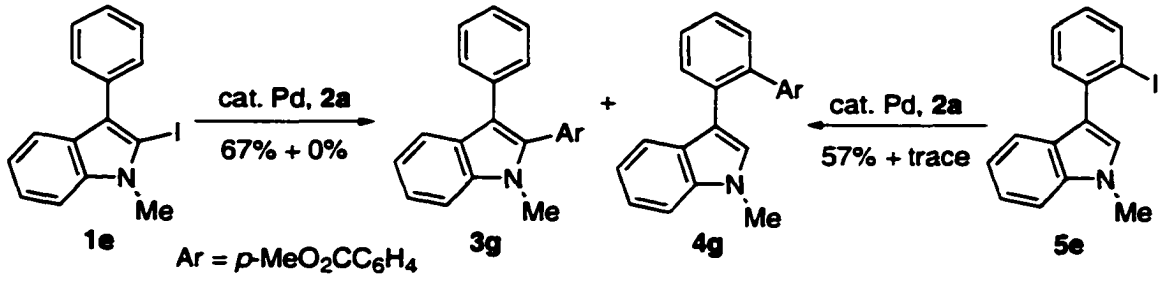


(1)

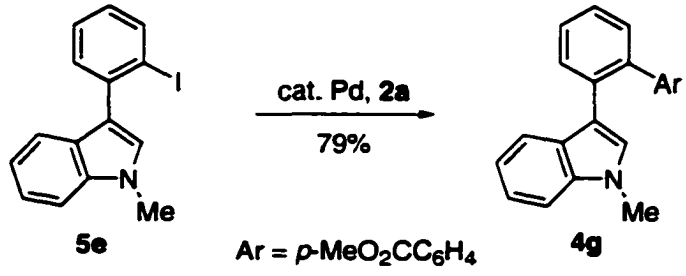
A similar remarkable effect was also observed in the reaction of 2-iodo-1-methyl-3-phenylindole (**1e**) and boronic acid **2a**, which under standard migration conditions gives exclusively the Suzuki product (**3g**) in a 67% yield in 3 h. When 3-(2-iodophenyl)-1-methylindole (**5e**) was allowed to react with boronic acid **2a** under our Pd migration conditions, **3g** was produced in a 57% yield in 6 h, along with a

trace amount of isomer **4g**, again indicating a preference for palladium migration from the phenyl ring to the more electron-rich indole ring (Scheme 6). Moreover, **4g**

Scheme 6



can be obtained exclusively in a 79% yield when **5e** is allowed to react with boronic acid **2a** under the non-migration conditions described by Wright et al (eq 2).[4]



(2)

Conclusions

In conclusion, we have observed during Suzuki cross-coupling 1,4-palladium migration in arylpalladium intermediates generated from *o*-iodobiaryls. The choice of reaction conditions is important in turning "on" and "off" the migration. There are important electronic effects controlling the distribution of the palladium intermediates, which is reflected in the isomer distribution of the Suzuki products. Further investigation of the scope, limitations and mechanism of this palladium migration chemistry is currently underway.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz or 400 and 100 MHz, respectively. Thin-layer chromatography was performed using

commercially prepared 60-mesh silica gel plates, and visualization was effected with short wavelength UV light (254 nm). All melting points are uncorrected. All reagents were used directly as obtained commercially unless otherwise noted. Compounds **1a**,[7] **1b**,[7] **1d**,[2e] **1e**,[7] **5a**,[7] **5b**,[7] and **5d**[7] have been reported before. Compounds **1c**, **5c** and **5e** were prepared as follows.

Ethyl 4-(2-iodophenyl)benzoate (1c). To a solution of 4-(2-iodophenyl)benzaldehyde[7] (0.33 g, 1.07 mmol) in ethanol (10 mL) was added activated MnO_2 (1.90 g, 20 equiv), KCN (0.35 g, 5 equiv) and HOAc (0.20 mL, 3 equiv). The mixture was stirred at room temperature for 1 d and filtered. The organic solution was diluted with EtOAc and washed with brine, dried over anhydrous Na_2SO_4, filtered and evaporated. The residue was purified on a silica gel column using 9:1 hexanes/EtOAc to afford 0.353 g (94%) of the desired compound as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 1.41 (t, J = 7.2 Hz, 3H), 4.40 (q, J = 7.2 Hz, 2H), 7.04 (dt, J = 1.8, 7.8 Hz, 1H), 7.28 (dd, J = 1.8, 7.8 Hz, 1H), 7.37-7.44 (m, 3H), 7.95 (dd, J = 0.9, 7.8 Hz, 1H), 8.11 (dt, J = 8.4, 1.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 14.7, 61.3, 98.1, 128.5, 129.5 (2), 129.6, 129.9, 130.1, 139.9, 145.9, 148.7, 166.6; IR (neat, cm^{-1}) 3042, 2970, 1726; HRMS calcd for $C_{15}H_{13}IO_2$: 351.9960. Found: 351.9966.

Ethyl 3-iodo-4-phenylbenzoate (5c). Compound **5c** was prepared from ethyl 4-iodo-3-nitrobenzoate.[8] First, a Suzuki coupling of ethyl 4-iodo-3-nitrobenzoate and $NaBPh_4$ was carried out as follows. $NaBPh_4$ (1.69 g, 4.94 mmol), ethyl 4-iodo-3-nitrobenzoate (1.38 g, 4.3 mmol), LiCl (0.182 g, 4.3 mmol), $Pd(OAc)_2$ (0.048 g, 5 mol %), and PPh_3 (0.113 g, 10 mol %) in DMF (10 mL) were stirred under Ar at 70 °C for 2d. The reaction mixture was diluted with ether and washed with brine. The organic layer was dried ($MgSO_4$), filtered and evaporated to afford a yellow oil, which is presumed to be crude ethyl 3-nitro-4-phenylbenzoate. The crude ethyl 3-nitro-4-phenylbenzoate was dissolved in a mixture of DME/EtOH/AcOH (5:4:1, 50 mL) and $SnCl_2$ (5.71 g, 30.1 mmol) was added. The resulting mixture was stirred at 60 °C under Ar for 16 h, diluted with ether and washed with 10% aq

Na_2CO_3. The organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified on a silica gel column using 3:1 hexanes/EtOAc to afford 0.93 g (90%) of ethyl 3-amino-4-phenylbenzoate as a yellow oil, which was quickly diazotized and iodinated by the following procedure. To a solution of ethyl 3-amino-4-phenylbenzoate (0.93 g, 3.86 mmol) in DME (10 mL) was added H_2O (8 mL) containing concentrated H_2SO_4 (0.7 mL). The reaction mixture was stirred at 0 °C and $NaNO_2$ (0.39 g, 5.6 mmol) in H_2O (2 mL) was added dropwise over 30 min. The mixture was stirred for another 20 min at 0 °C and then the mixture was added to NaI (3.0 g, 20.0 mmol) in H_2O (7 mL). The mixture was extracted with ether and washed with 10% aq $Na_2S_2O_3$. The organic layer was filtered, dried (Na_2SO_4) and evaporated. The residue was purified on a silica gel column using 7:1 hexanes/EtOAc to afford 1.06 g (78%) of compound **5c** as a white solid: mp 76-77 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (t, J = 7.2 Hz, 3H), 4.40 (q, J = 7.2 Hz, 2H), 7.33-7.37 (m, 3H), 7.41-7.45 (m, 3H), 8.04 (dd, J = 8.0, 1.6 Hz, 1H), 8.61 (d, J = 1.6 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 14.4, 61.4, 98.1, 128.2 (2), 129.0, 129.2, 129.9, 130.8, 140.6, 143.4, 150.9, 165.0; IR (neat, cm^{-1}) 2973, 2818, 1722; HRMS calcd for $C_{15}H_{13}IO_2$: 351.9960. Found: 351.9966. Anal. calcd for $C_{15}H_{13}IO_2$: C, 51.14; H, 3.34. Found: C, 51.16; H, 3.72.

3-(2-Iodophenyl)-1-methylindole (5e). Compound **5e** was prepared in two steps from 2-(2-iodophenyl)acetaldehyde.[9] A solution of 2-(2-iodophenyl)acetaldehyde (0.216 g, 0.88 mmol), phenylhydrazine (0.105 g, 0.97 mmol) and methanesulfonic acid (17 mg, 0.18 mmol) in ethanol (5 mL) was stirred at room temperature for 40 min under Ar. Then more methanesulfonic acid (0.152 g, 1.58 mmol) was added and the mixture was stirred at 85 °C for 1.5 d under Ar. The reaction mixture was diluted with ether, washed with satd aq NH_4Cl and the organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified on a silica gel column using 3:1 hexanes/EtOAc to afford 0.115 g (41%) of 3-(2-iodophenyl)indole as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 6.99 (m, 1H), 7.13-7.17 (m, 1H), 7.21-7.25 (m, 1H), 7.32-7.47 (m, 4H), 7.53 (d, J = 8.0 Hz, 1H), 8.00 (dd, J = 8.0, 0.8

Hz, 1H), 8.18 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 100.9, 111.4, 120.2, 122.5, 123.7, 126.6, 128.1, 128.4, 131.5, 135.7, 139.9, 140.0 (two sp^2 carbons missing due to overlap). To a suspension of NaH (0.031 g, 1.3 mmol) in DMF (2.0 mL) at 0 °C was added 3-(2-iodophenyl)indole (0.319 g, 1.0 mmol) in DMF (3.0 mL) and the mixture was stirred at room temperature for 30 min. MeI (1.42 g, 10.0 mmol) in DMF (3 mL) was added and the reaction mixture was stirred at room temperature for 14 h. The reaction mixture was diluted with ether, washed with brine and the organic layer was dried ($MgSO_4$), filtered and evaporated. The residue was purified on a silica gel column using 5:1 hexanes/EtOAc to afford 0.320 g (96%) of compound **5e** as a yellow oil: ^1H NMR ($CDCl_3$) δ 3.84 (s, 3H), 6.97-7.01 (m, 1H), 7.12-7.16 (m, 1H), 7.22-7.28 (m, 2H), 7.35-7.40 (m, 2H), 7.45 (dd, J = 7.6, 1.6 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.99 (dd, J = 7.6, 0.8 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 33.1, 100.8, 109.5, 118.5, 119.7, 120.3, 122.0, 127.0, 128.1, 128.2, 128.4, 131.5, 136.6, 139.9, 140.1; IR (neat, cm^{-1}) 3050, 2922, 1547; HRMS calcd for $C_{15}H_{12}IN$: 333.0014. Found: 333.0024.

General Procedure for the Suzuki Coupling of *o*-Iodobiaryls with Arylboronic Acids under the Conditions Described by Wright et al[4] (Non-migration Conditions): To a 2-dram vial was added the *o*-iodobiaryl (0.25 mmol), the arylboronic acid (0.30 mmol, 1.2 equiv), $Pd(OAc)_2$ (2.8 mg, 5 mol %), PPh_3 (6.5 mg, 10 mol %), CsF (84.0 mg, 2.2 equiv) and DME (1.0 mL). The mixture was flushed with Ar and stirred at 90 °C in an oil bath. The completion of the reaction was determined by the observation of palladium black. The reaction mixture was cooled and purified directly by column chromatography on a silica gel column.

General Procedure for the Suzuki Coupling of *o*-Iodobiaryls with Arylboronic Acids under Migration Conditions: To a 2-dram vial was added the *o*-iodobiaryl (0.25 mmol), the arylboronic acid (0.35 mmol, 1.4 equiv), $Pd(OAc)_2$ (2.8 mg, 5 mol %), $(Ph_2P)_2CH_2$ (dppm, 4.8 mg, 5 mol %), CsO_2CCMe_3 (CsPiv, 117 mg, 2.0 equiv), Me_3CCO_2H (PA, 51 mg, 2 equiv), H_2O (90 mg, 20 equiv) and DMF (4.0

mL). The mixture was flushed with Ar and stirred at 100 °C in an oil bath. The completion of the reaction was determined by the observation of palladium black. The reaction mixture was cooled, diluted with ether and washed with satd aq $NaHCO_3$. The organic layer was dried (Na_2SO_4), filtered and evaporated. The residue was purified by column chromatography on a silica gel column and the molar ratio of the products was determined by ^1H NMR spectroscopic analysis.

Suzuki Coupling Products Prepared

Ethyl 4"-methyl-*o*-terphenyl-4-carboxylate (3a). This compound was prepared employing **1a** and **2a** under non-migration conditions for 8 h. The reaction mixture was chromatographed using 9:1 hexanes/EtOAc to afford a 62% yield of the indicated compound as a colorless oil: ^1H NMR ($CDCl_3$) δ 2.30 (s, 3H), 3.89 (s, 3H), 6.97-7.04 (m, 4H), 7.20-7.23 (m, 2H), 7.40-7.44 (m, 4H), 7.87-7.90 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3, 52.3, 127.6, 128.3 (2), 129.0, 129.4, 129.9, 130.1, 130.6, 131.0, 136.6, 138.3, 139.7, 140.9, 146.9, 167.4; IR (neat, cm^{-1}) 3023, 2918, 1724; HRMS calcd for $C_{21}H_{18}O_2$: 302.1307. Found: 302.1313.

4-Methyl-*o*-terphenyl (3b). This compound was prepared employing **1a** and **2b** under non-migration conditions for 40 h. The reaction mixture was chromatographed using 50:1 hexanes/EtOAc to afford an 85% yield of the indicated compound as a colorless oil, which crystallizes upon cooling and standing: mp 74-75 °C (lit.[10] mp 74-75 °C); ^{13}C NMR ($CDCl_3$) δ 21.4, 126.7, 127.5, 127.7, 128.1, 128.9, 130.0, 130.2, 130.9, 136.3, 138.8, 140.78, 140.79, 142.0 (one sp^2 carbon missing due to overlap); all other spectral properties are identical to those previously reported.[10,11]

4-Methoxy-4"-methyl-*o*-terphenyl (3c). This compound was prepared employing **1a** and **2c** under non-migration conditions for 18 h. The reaction mixture was chromatographed using 40:1 hexanes/EtOAc to afford a 93% yield of the indicated compound as a colorless oil: ^{13}C NMR ($CDCl_3$) δ 21.2, 55.2, 113.4, 127.2,

127.4, 128.8, 129.8, 130.6, 130.7, 131.0, 134.2, 136.0, 138.8, 140.2, 140.5, 158.3; all other spectral properties are identical to those previously reported.[12]

Methyl 4"-methoxy-*o*-terphenyl-4-carboxylate (3d). This compound was prepared employing **1b** and **2a** under non-migration conditions for 18 h. The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford a 92% yield of the indicated compound as a colorless oil, which crystallizes upon cooling and standing: mp 113-114 °C; ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 3H), 3.89 (s, 3H), 6.74 (d, J = 8.8 Hz, 2H), 7.02 (d, J = 8.8 Hz, 2H), 7.22 (d, J = 8.4 Hz, 2H), 7.41 (m, 4H), 7.90 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 52.1, 55.2, 113.6, 127.3, 128.1, 128.2, 129.3, 129.9, 130.5, 130.7, 131.0, 133.4, 139.4, 140.3, 146.7, 158.5, 167.2; IR (neat, cm^{-1}) 3024, 2951, 1721; HRMS calcd for $C_{21}H_{18}O_3$: 318.1256. Found: 318.1261. Anal. calcd for $C_{21}H_{18}O_3$: C, 79.23; H, 5.70. Found: C, 78.90; H, 5.72.

Ethyl methyl *o*-terphenyl-4,4"-dicarboxylate (3e). This compound was prepared employing **1c** and **2a** under non-migration conditions for 16 h. The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford a 98% yield of the indicated compound as a colorless oil, which crystallizes upon cooling and standing: mp 103-104 °C; ^{1}H NMR ($CDCl_3$) δ 1.37 (t, J = 7.2 Hz, 3H), 3.89 (s, 3H), 4.35 (q, J = 7.2 Hz, 2H), 7.18 (dd, J = 2.4, 8.4 Hz, 4H), 7.45 (m, 4H), 7.89 (dd, J = 2.0, 8.4 Hz, 4H); ^{13}C NMR ($CDCl_3$) δ 14.4, 52.1, 61.0, 128.28, 128.30, 128.5, 128.8, 129.37, 129.40, 129.87, 129.92, 130.58, 130.60, 139.6, 139.7, 145.8, 145.9, 166.5, 167.0; IR (neat, cm^{-1}) 3024, 2985, 1720; HRMS calcd for $C_{23}H_{20}O_4$: 360.1362. Found: 360.1371. Anal. calcd for $C_{23}H_{20}O_4$: C, 76.65; H, 5.59. Found: C, 76.30; H, 5.64.

2-(4-Methoxycarbonylphenyl)-3-phenylbenzofuran (3f). This compound was prepared employing **1d** and **2a** under migration conditions for 3 h. The reaction mixture was chromatographed using 9:1 hexanes/EtOAc to afford a 79% yield of the indicated compound as a white solid: mp 122-123 °C; ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 7.23-7.27 (m, 1H), 7.34-7.38 (m, H), 7.43-7.51 (m, 6H), 7.56-7.58 (m, 1H), 7.71-7.73 (m, 2H), 7.96-7.98 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 52.2, 111.3, 119.6, 120.4,

123.2, 125.5, 126.6, 128.1, 129.2, 129.4, 129.7, 130.1, 132.4, 134.9, 149.3, 154.2, 166.7 (one sp^2 carbon missing due to overlap); IR (neat, cm^{-1}) 2917, 2849, 1727; HRMS calcd for $C_{22}H_{16}O_3$: 328.1099. Found: 328.1104. Anal. calcd for $C_{22}H_{16}O_3$: C, 80.47; H, 4.91. Found: C, 80.12; H, 4.81.

2-(4-Methoxycarbonylphenyl)-1-methyl-3-phenylindole (3g). This compound was prepared employing **1e** and **2a** under migration conditions for 3 h. The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford a 67% yield of the indicated compound as a white solid: mp 122-123 °C; ^1H NMR ($CDCl_3$) δ 3.71 (s, 3H), 3.94 (s, 3H), 7.19 (m, 2H), 7.27 (m, 4H), 7.32 (t, J = 7.2 Hz, 1H), 7.71 (m, 3H), 7.78 (d, J = 8.0 Hz, 1H), 8.04 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 31.2, 52.3, 109.8, 116.2, 119.9, 120.5, 122.8, 125.9, 127.0, 128.4, 129.5, 129.7, 130.0, 131.2, 134.8, 136.5, 136.7, 137.8, 166.9; IR (neat, cm^{-1}) 3053, 2950, 1723; HRMS calcd for $C_{23}H_{19}NO_2$: 341.1416. Found: 341.1421. Anal. calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.77; H, 5.53; N, 4.08.

Methyl 5'-methyl-*o*-terphenyl-4-carboxylate (4a). This compound was prepared employing **5a** and **2a** under non-migration conditions for 12 h. The reaction mixture was chromatographed using 10:1 hexanes/EtOAc to afford a 90% yield of the indicated compound as a colorless oil: ^1H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.86 (s, 3H), 7.07 (m, 2H), 7.14-7.26 (m, 7H), 7.32 (m, 1H), 7.86 (dt, J = 8.4, 1.8 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 21.3, 52.3, 126.8, 128.26, 128.34, 129.1, 129.4, 130.1, 130.2, 130.9, 131.4, 137.6, 138.1, 139.6, 141.2, 146.8, 167.3; IR (neat, cm^{-1}) 3025, 2950, 1727; HRMS calcd for $C_{21}H_{18}O_2$: 302.1307. Found: 302.1313.

5'-Methyl-*o*-terphenyl (4b). This compound was prepared employing **5a** and **2b** under non-migration conditions for 8 h. The reaction mixture was chromatographed using 50:1 hexanes/EtOAc to afford a 93% yield of the indicated compound as a colorless oil: all spectral properties are identical to those previously reported.[13]

4-Methoxy-5'-methyl-*o*-terphenyl (4c). This compound was prepared employing **5a** and **2c** under non-migration conditions for 16 h. The reaction mixture

was chromatographed using 30:1 hexanes/EtOAc to afford a 94% yield of the indicated compound as a colorless oil, which crystallizes upon cooling and standing: mp 107-108 °C; ^{1}H NMR ($CDCl_3$) δ 2.42 (s, 3H), 3.75 (s, 3H), 6.73 (m, 2H), 7.05 (m, 2H), 7.10-7.22 (m, 7H), 7.30 (d, J = 8.4 Hz, 1H); ^{13}C NMR ($CDCl_3$) δ 21.4, 55.4, 113.6, 126.4, 128.1, 130.2, 130.9, 131.2, 131.6, 134.3, 137.4, 137.9, 140.2, 141.9, 158.5 (one sp^2 carbon missing due to overlap); IR (neat, cm^{-1}) 3026, 2931, 1516; HRMS calcd for $C_{20}H_{18}O$: 274.1358. Found: 274.1362. Anal. calcd for $C_{20}H_{18}O$: C, 87.56; H, 6.61. Found: C, 87.62; H, 6.67.

Methyl 5'-methoxy-*o*-terphenyl-4-carboxylate (4d). This compound was prepared employing **5b** and **2a** under non-migration conditions for 16 h. The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford a 94% yield of the indicated compound as a colorless oil, which crystallizes upon cooling and standing: mp 113-114 °C; ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H), 3.88 (s, 3H), 6.95-7.01 (m, 2H), 7.02-7.08 (m, 2H), 7.15-7.23 (m, 5H), 7.36 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.4 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 52.3, 55.7, 113.8, 116.0, 126.6, 128.2, 128.5, 129.5, 130.09, 130.14, 132.1, 133.6, 140.9, 141.0, 146.6, 159.2, 167.3; IR (neat, cm^{-1}) 3027, 2951, 1723; HRMS calcd for $C_{21}H_{18}O_3$: 318.1256. Found: 318.1263. Anal. calcd for $C_{21}H_{18}O_3$: C, 79.23; H, 5.70. Found: C, 79.03; H, 5.76.

Ethyl methyl *o*-terphenyl-5',4-dicarboxylate (4e). This compound was prepared employing **5c** and **2a** under non-migration conditions for 16 h. The reaction mixture was chromatographed using 5:1 hexanes/EtOAc to afford a 97% yield of the indicated compound as a colorless oil, which crystallizes upon cooling and standing: mp 105-106 °C; ^{1}H NMR ($CDCl_3$) δ 1.41 (t, J = 7.2 Hz, 3H), 3.89 (s, 3H), 4.42 (q, J = 7.2 Hz, 2H), 7.11 (m, 2H), 7.20-7.24 (m, 5H), 7.51 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.4 Hz, 2H), 8.10 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 14.6, 52.3, 61.4, 127.6, 128.4, 128.8, 129.3, 129.6, 129.9, 130.0, 130.1, 131.1, 131.8, 139.9, 140.3, 145.3, 145.7, 166.5, 167.1; IR (neat, cm^{-1}) 3027, 2983, 1723; HRMS calcd for $C_{23}H_{20}O_4$: 360.1362. Found: 360.1371. Anal. calcd for $C_{23}H_{20}O_4$: C, 76.65; H, 5.59. Found: C, 76.72; H, 5.47.

Methyl 4-[2-(benzofuran-3-yl)phenyl]benzoate (4f). This compound was prepared employing **5d** and **2a** under non-migration conditions for 6 h. The reaction mixture was chromatographed using 9:1 hexanes/EtOAc to afford a 75% yield of the indicated compound as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.87 (s, 3H), 7.11-7.14 (m, 1H), 7.21-7.27 (m, 2H), 7.30-7.34 (m, 3H), 7.42-7.49 (m, 4H), 7.58-7.60 (m, 1H), 7.87-7.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 52.3, 111.7, 120.6, 121.2, 123.0, 124.6, 127.4, 128.3, 128.4, 128.8, 129.5, 129.6, 130.1, 130.8, 131.1, 140.7, 143.1, 146.4, 155.3, 167.2; IR (neat, cm^{-1}) 2973, 2850, 1723; HRMS calcd for $C_{22}H_{16}O_3$: 328.1099. Found: 328.1104.

Methyl 4-[2-(1-methylindol-3-yl)phenyl]benzoate (4g). This compound was prepared employing **5e** and **2a** under non-migration conditions for 16 h. The reaction mixture was chromatographed using 6:1 hexanes/EtOAc to afford a 79% yield of the indicated compound as a white solid: mp 147-148 °C; ^{1}H NMR ($CDCl_3$) δ 3.64 (s, 3H), 3.88 (s, 3H), 7.06 (t, J = 7.2 Hz, 1H), 7.21 (t, J = 7.2 Hz, 1H), 7.28 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.0 Hz, 2H), 7.40 (m, 1H), 7.44 (m, 2H), 7.54 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 1H), 7.85 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$) δ 32.8, 52.1, 109.3, 114.9, 119.6, 119.9, 121.8, 126.6, 127.2, 128.0, 128.6, 129.2, 129.6, 130.6, 131.3, 133.5, 136.8, 140.0, 147.4, 167.2; IR (neat, cm^{-1}) 3056, 2950, 1719; HRMS calcd for $C_{23}H_{19}NO_2$: 341.1416. Found: 341.1422. Anal. calcd for $C_{23}H_{19}NO_2$: C, 80.92; H, 5.61; N, 4.10. Found: C, 80.67; H, 5.44; N, 3.99.

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Supporting Information Available: ^{1}H and ^{13}C NMR spectra of all new compounds. This material is included in Appendix D and is also available free of charge via the Internet at http://interscience.wiley.com.

References

1. (a) Tsuji, J. In *Palladium Reagents and Catalysts. Innovations in Organic Synthesis*, John Wiley & Sons, New York, 1995. (b) Negishi, E.–I. In *Handbook of Organopalladium Chemistry for Organic Synthesis*, John Wiley & Sons, New York, 2002.
2. For palladium migration along a carbon chain, see: (a) Larock, R. C.; Wang, Y. *Tetrahedron Lett.* **2002**, *43*, 21. (b) Larock, R. C.; Wang, Y.; Lu, Y.–D.; Russell, C. E. *J. Org. Chem.* **1994**, *59*, 8107. (c) Larock, R. C.; Lu, Y.–D.; Bain, A. C.; Russell, C. E. *J. Org. Chem.* **1991**, *56*, 4589, and references therein. For palladium migration through space, see: (d) Larock, R. C.; Tian, Q. *J. Org. Chem.* **2001**, *66*, 7372. (e) Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2002**, *124*, 14326. (f) Karig, G.; Moon, M.–T.; Thasana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 3115. (g) Wang, L.; Pan, Y.; Jiang, X.; Hu, H. *Tetrahedron Lett.* **2000**, *41*, 725. (h) Heck, R. F. *J. Organomet. Chem.* **1972**, *37*, 389.
3. For recent reviews on Suzuki coupling, see: (a) Hassan, J.; Sevignon, M.; Gozzi, C.; Schulz, E.; Lemaire, M. *Chem. Rev.* **2002**, *102*, 1359. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.
4. Wright, S. W.; Hageman, D. L.; McClure, L. D. *J. Org. Chem.* **1994**, *59*, 6095.
5. (a) Bedford, R. B.; Blake, M. E.; Butts, C. P.; Holder, D. *Chem. Commun.* **2003**, 466. (b) Netherton, M. R.; Dai, C.; Neushutz, K.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 10099.
6. Campo. M. A. Ph.D. Dissertation, Iowa State University, 2002.
7. Campo, M. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 5616.
8. Murray, M. M.; Kaszynski, P.; Kaisaki, D. A.; Dougherty, D. A. *J. Am. Chem. Soc.* **1994**, *116*, 8152.
9. Gibson, S. E.; Guillo, N.; Middleton, R. J.; Thuilliez, A.; Tozer, M. J. *J. Chem. Soc., Perkin Trans. 1* **1997**, 447.

10. Ibuki, E.; Ozasa, S.; Fujioka, Y.; Yanogihara, Y. *Chem. Pharm. Bull.* **1982**, *30*, 802.
11. Trost, B. M.; Arndt, H. C. *J. Am. Chem. Soc.* **1973**, *95*, 5288.
12. Hanson, G.; Kemp, D. S. *J. Org. Chem.* **1981**, *46*, 5441.
13. Freeman, P. K.; Tafesh, A. M.; Clapp, G. E. *J. Org. Chem.* **1989**, *54*, 782.

GENERAL CONCLUSION

The isolation and synthesis of naturally occurring carbolines and the synthesis of β- and γ-carboline derivatives have received considerable attention in the literature due to their biological and pharmaceutical importance. In this dissertation, we have investigated new palladium approaches to the synthesis of a variety of β- and γ-carboline derivatives.

Chapter 1 describes the synthesis of a variety of 3,4-disubstituted β- and γ-carbolines by the palladium-catalyzed iminoannulation of internal alkynes. This chemistry tolerates various functional groups on the alkyne and can be extended to terminal alkynes to synthesize a variety of 3-substituted β- and γ-carbolines. Two biologically interesting β-carboline alkaloids, ZK93423 and abecarnil, have also been synthesized by employing this palladium-catalyzed iminoannulation methodology.

Chapter 2 describes in detail, the synthesis of 3-substituted β- and γ-carboline derivatives by the palladium/copper-catalyzed coupling and cyclization of terminal alkynes, which is complementary to our annulation chemistry described in Chapter 1. This chemistry also tolerates various functional groups on the terminal alkynes and affords good to excellent yields of the desired β- and γ-carbolines.

Chapter 3 presents an extension of our intermolecular iminoannulation chemistry described in Chapter 1 to intramolecular iminoannulation, by which a variety of annulated γ-carbolines with an additional ring fused across the 4- and 5-positions can be synthesized in good to excellent yields. This "intramolecular" concept has also been extended to other palladium-catalyzed annulations to synthesize various complex heteropolycycles.

Chapter 4 presents relatively independent chemistry involving a novel 1,4-palladium migration in the Suzuki coupling of *o*-iodobiaryls with arylboronic acids. Various *o*-iodobiaryls and arylboronic acids with different electronic properties have been examined. It has been found that palladium prefers to migrate from a more electron-deficient position to a more electron-rich position in the biaryl.

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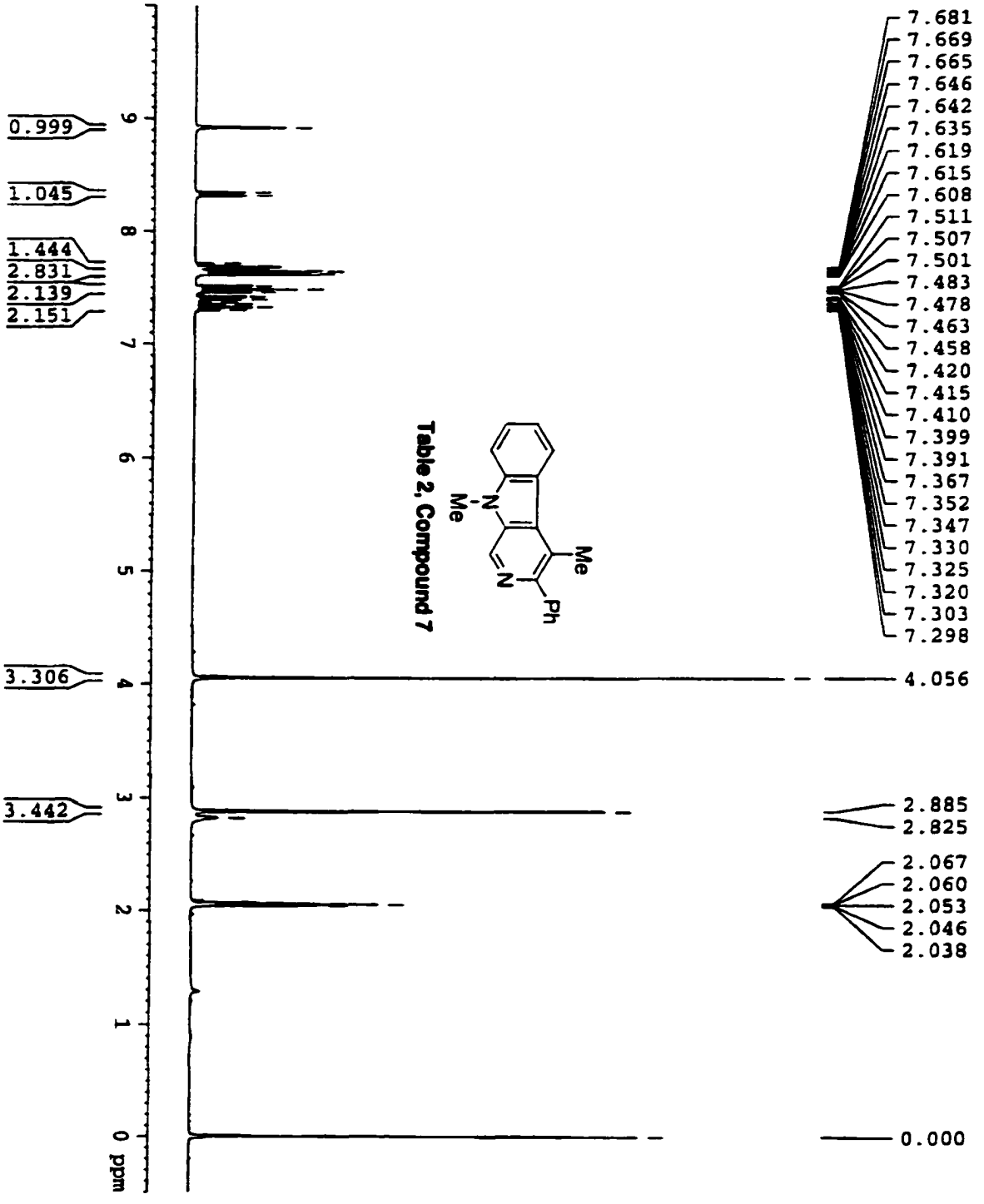
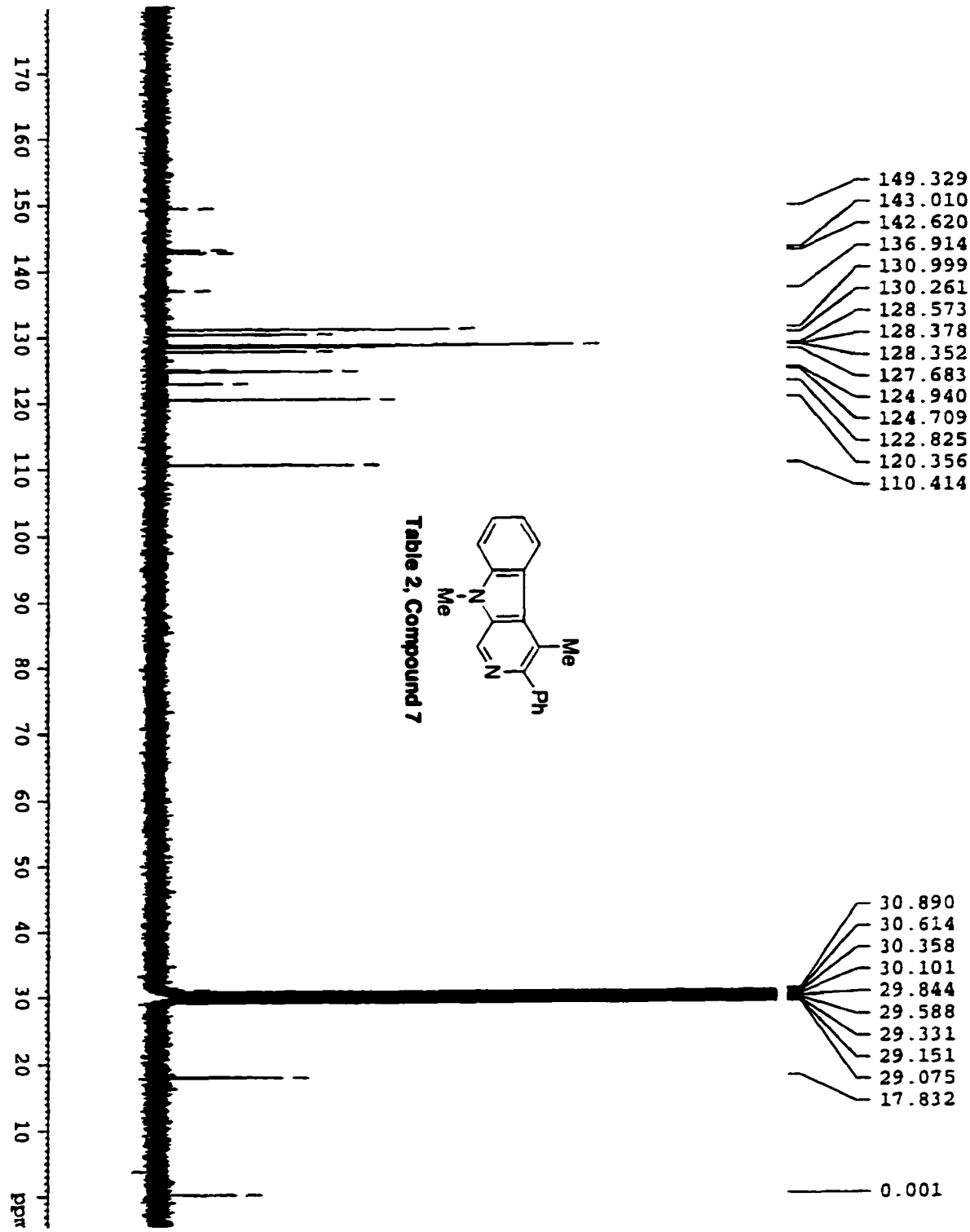
I have met so many great professors and students in the past five years at Iowa State University who have helped me through a number of things. I have to thank all the professors who have taught me fascinating chemistry; I also want to thank all my committee members for providing me both academic and personal help. I want to thank the past members of the Larock group that I have worked with: Dr. Kevin Roesch, Dr. Steve Gagnier, Dr. Dan Emrich, Dr. Alex Pletnev, Dr. Dmitry Kadnikov, Jack Hunter, Li Zhang, Hao Yin, Daohua Zhang, and especially Dr. Marino Campo, with whom I worked in the same lab for four years and from whom I received numerous exciting ideas. I can't allow myself to forget to thank the current members of the Larock group: Dr. Fengkui Li, Guangxiu Dai, Roman Rhozkov, Qinhua Huang, Dawei Yue, Xiaoxia Zhang, Tuanli Yao, Chengxiang Zhou, Zhijian Liu and Jian Zhao. Some of you guys really helped me a lot in the laboratory. Anyways, it has been my great pleasure being with all of you guys.

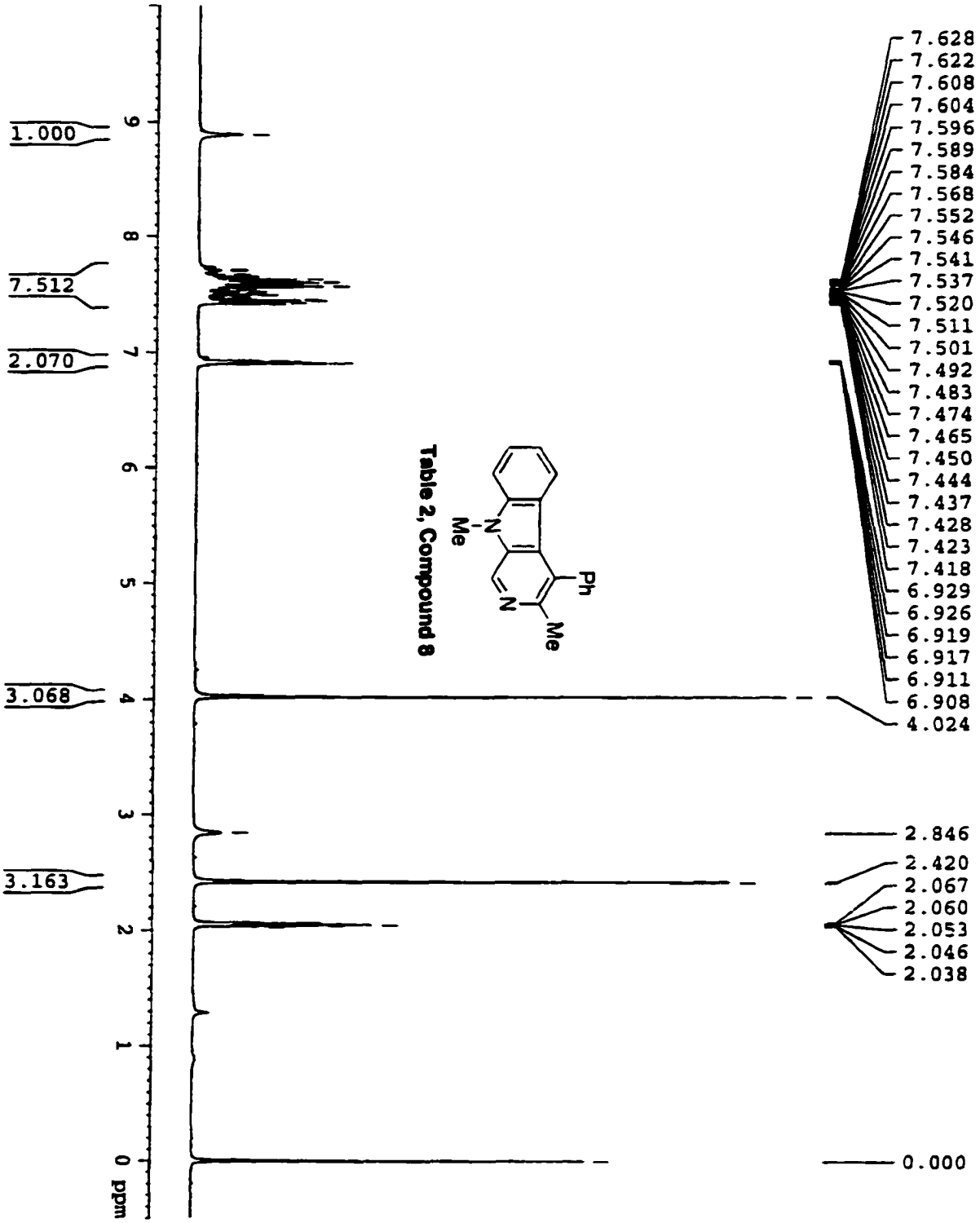
I would like to thank my parents and my parents-in-law, even though I am sure they cannot understand what I have been working on. It's been five long years that my wife and I haven't called you "dad and mom" face to face!

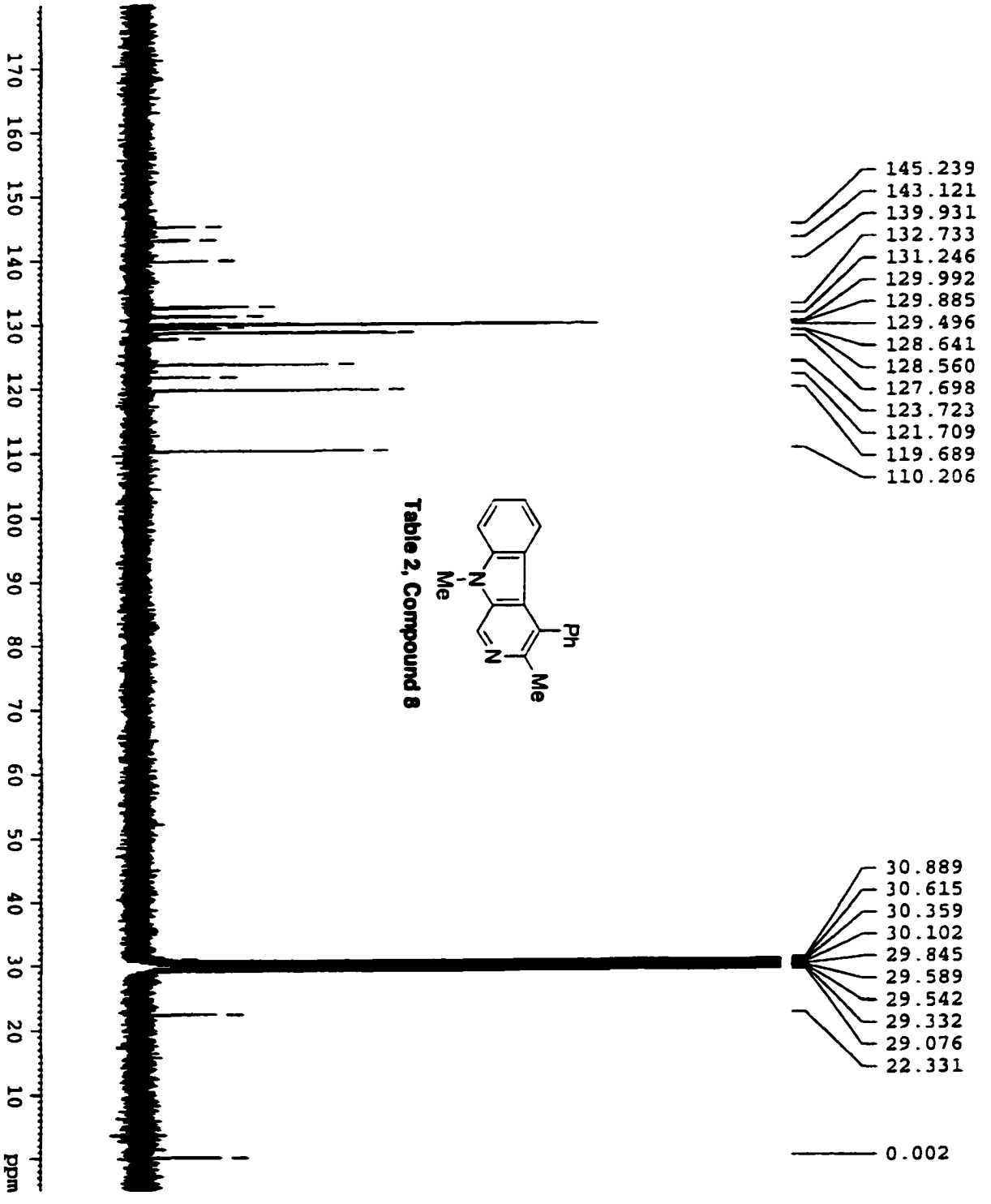
Finally, I want to thank my lovely wife, Ye Gu, for her loving support, patience, understanding, and incredible sacrifices during my five years here at Iowa State. We still need to get through the coming two years of my postdoctoral career in Pasadena.

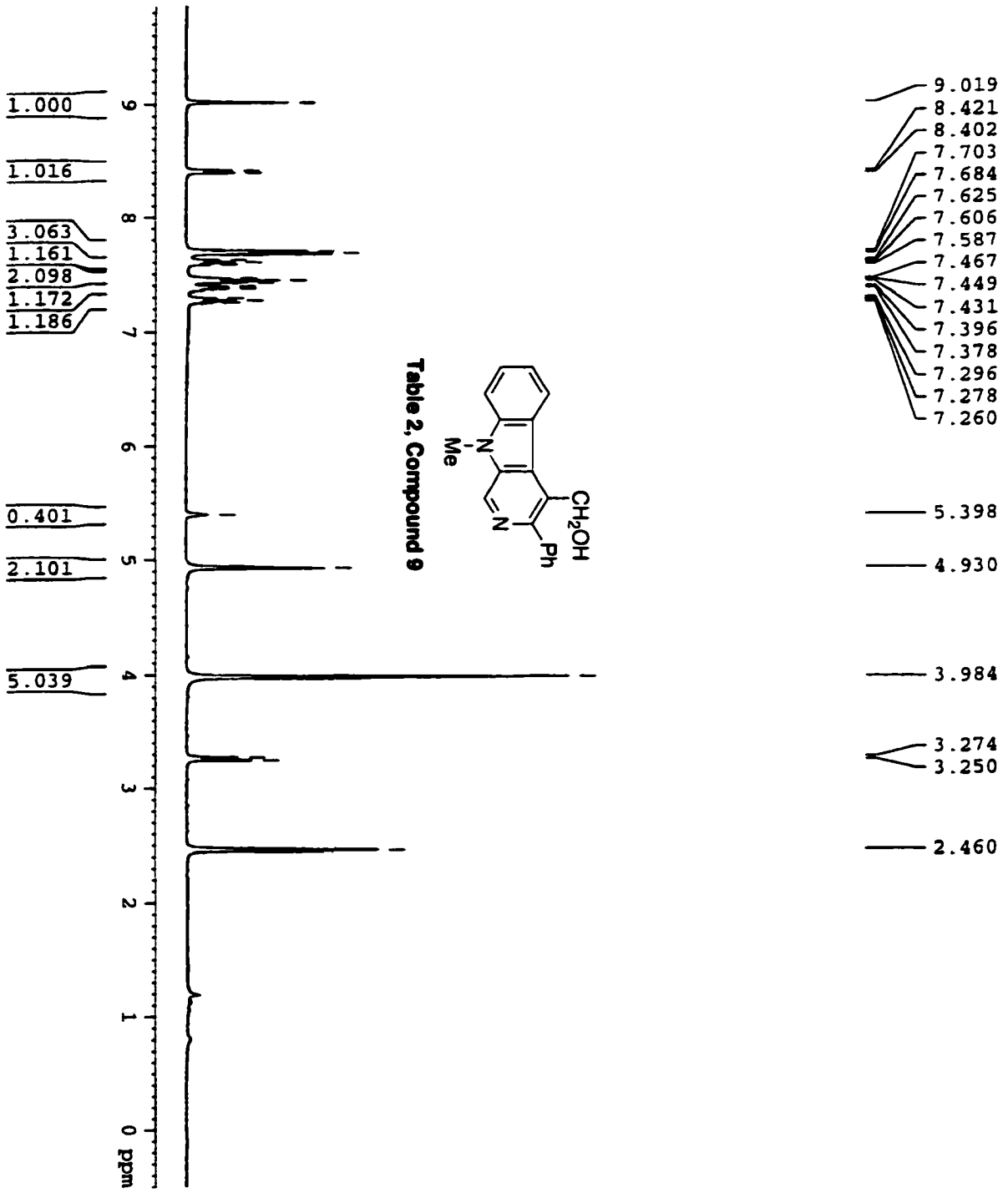
APPENDIX A. CHAPTER 1 ^{1}H AND ^{13}C NMR SPECTRA


0.999
1.045
1.444
2.831
2.139
2.151
3.306
3.442
9
8
7
6
5
4
3
2
1
0 ppm
Table 2, Compound 7
N
Me
N
Me
Ph
7.681
7.669
7.665
7.646
7.642
7.635
7.619
7.615
7.608
7.511
7.507
7.501
7.483
7.478
7.463
7.458
7.420
7.415
7.410
7.399
7.391
7.367
7.352
7.347
7.330
7.325
7.320
7.303
7.298
4.056
2.885
2.825
2.067
2.060
2.053
2.046
2.038
0.000


149.329
143.010
142.620
136.914
130.999
130.261
128.573
128.378
128.352
127.683
124.940
124.709
122.825
120.356
110.414
30.890
30.614
30.358
30.101
29.844
29.588
29.331
29.151
29.075
17.832
0.001
Table 2, Compound 7
Me
N
Me
Me
N
Ph
ppm


1.000
7.512
2.070
3.068
3.163
9
8
7
6
5
4
3
2
1
0 ppm
Table 2, Compound 8
N
Me
Ph
N
Me
7.628
7.622
7.608
7.604
7.596
7.589
7.584
7.568
7.552
7.546
7.541
7.537
7.520
7.511
7.501
7.492
7.483
7.474
7.465
7.450
7.444
7.437
7.428
7.423
7.418
6.929
6.926
6.919
6.917
6.911
6.908
4.024
2.846
2.420
2.067
2.060
2.053
2.046
2.038
0.000


145.239
143.121
139.931
132.733
131.246
129.992
129.885
129.496
128.641
128.560
127.698
123.723
121.709
119.689
110.206
30.889
30.615
30.359
30.102
29.845
29.589
29.542
29.332
29.076
22.331
0.002
Table 2, Compound 8
Me
N
Ph
N
Me
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


1.000
1.016
3.063
1.161
2.098
1.172
1.186
0.401
2.101
5.039
9.019
8.421
8.402
7.703
7.684
7.625
7.606
7.587
7.467
7.449
7.431
7.396
7.378
7.296
7.278
7.260
5.398
4.930
3.984
3.274
3.250
2.460
Me
N
N
Ph
CH2OH
Table 2, Compound 9
ppm

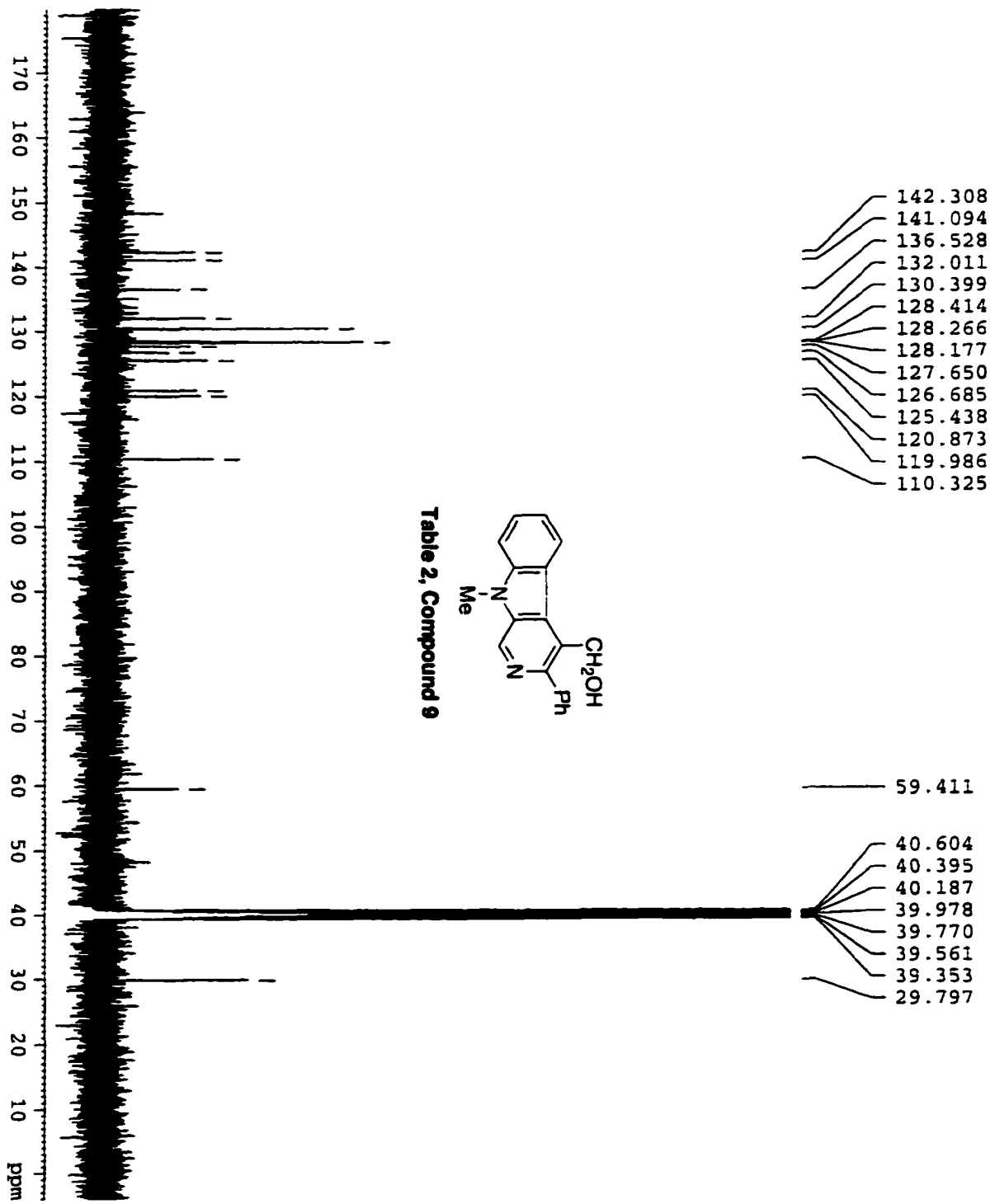
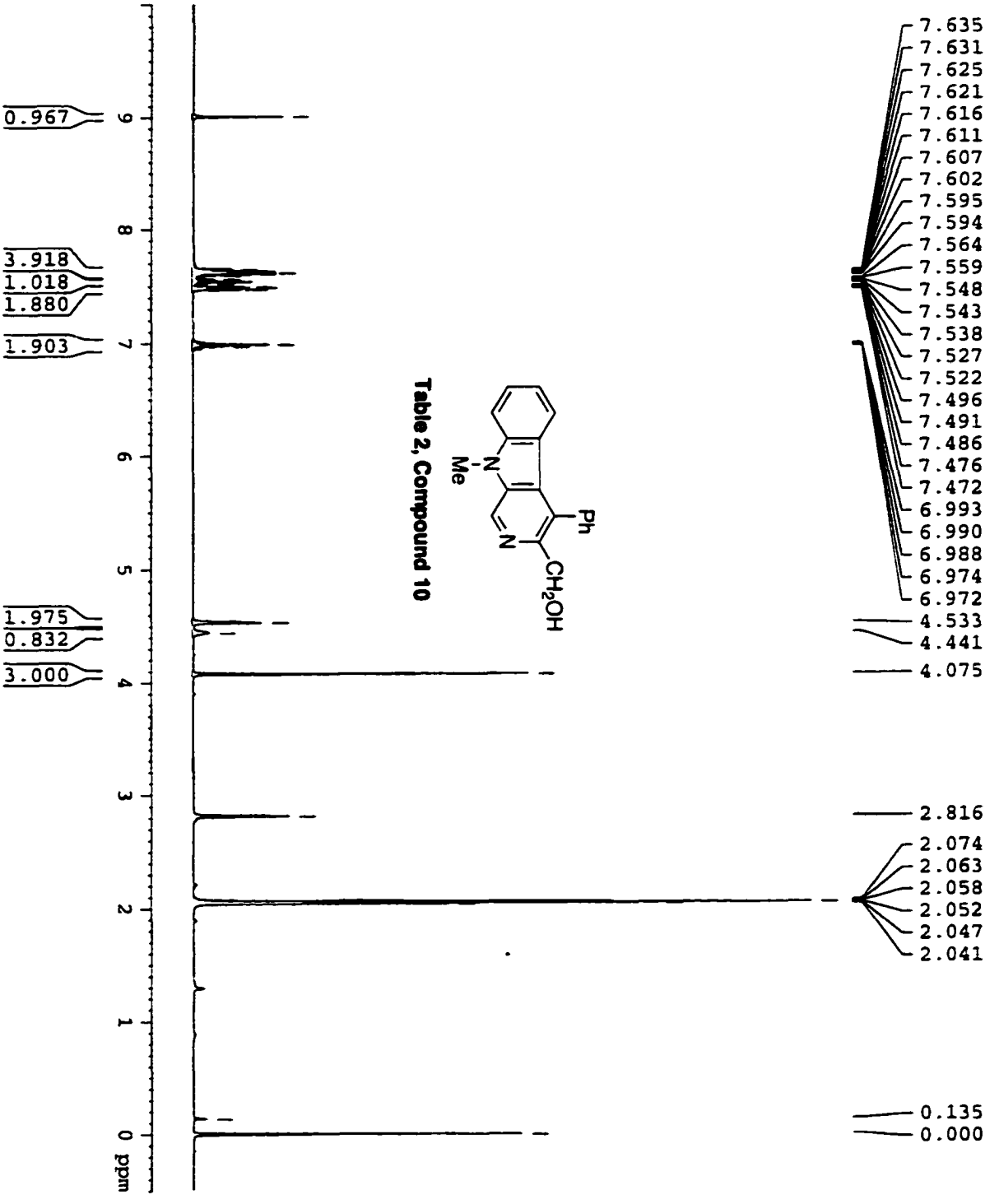
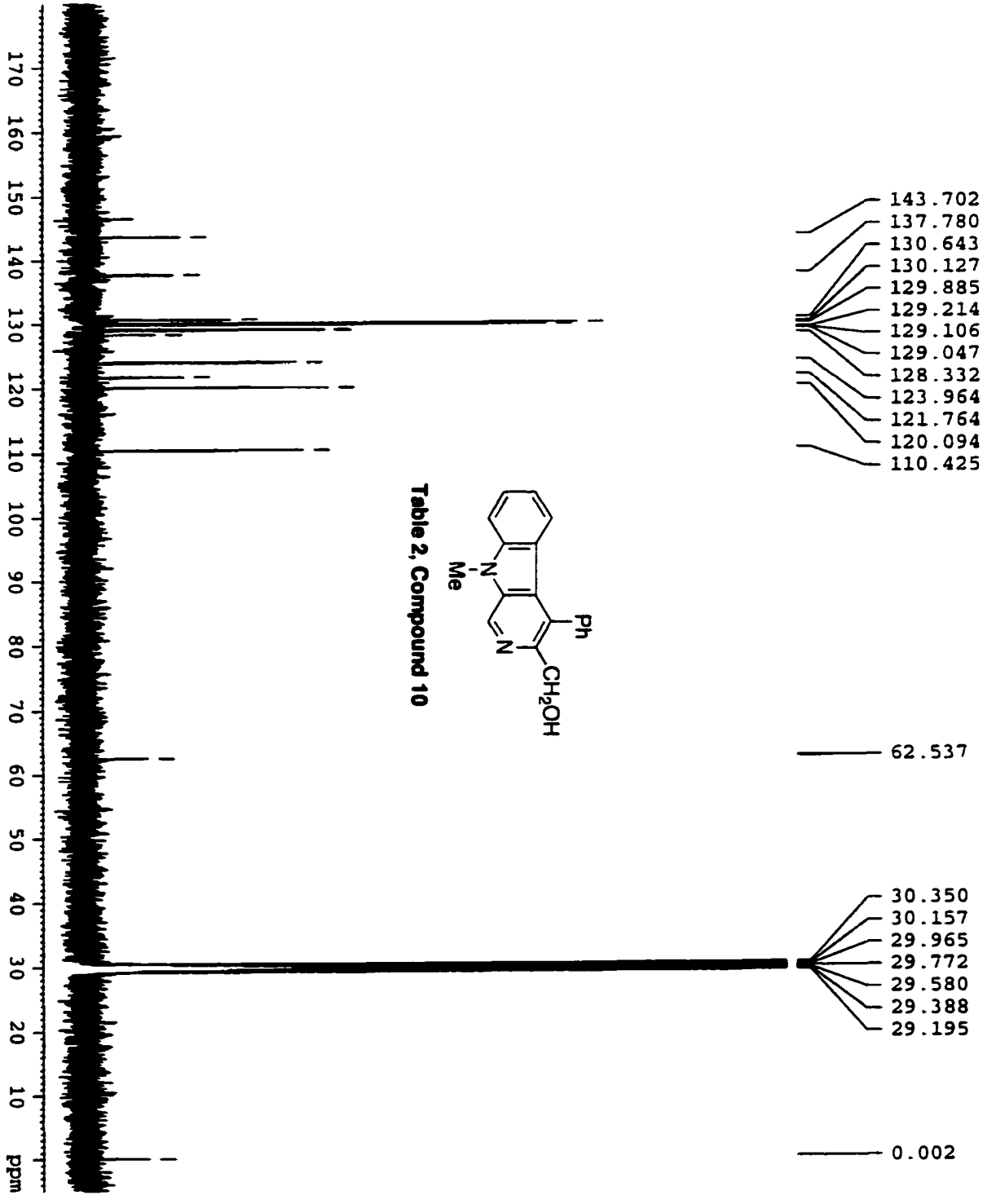
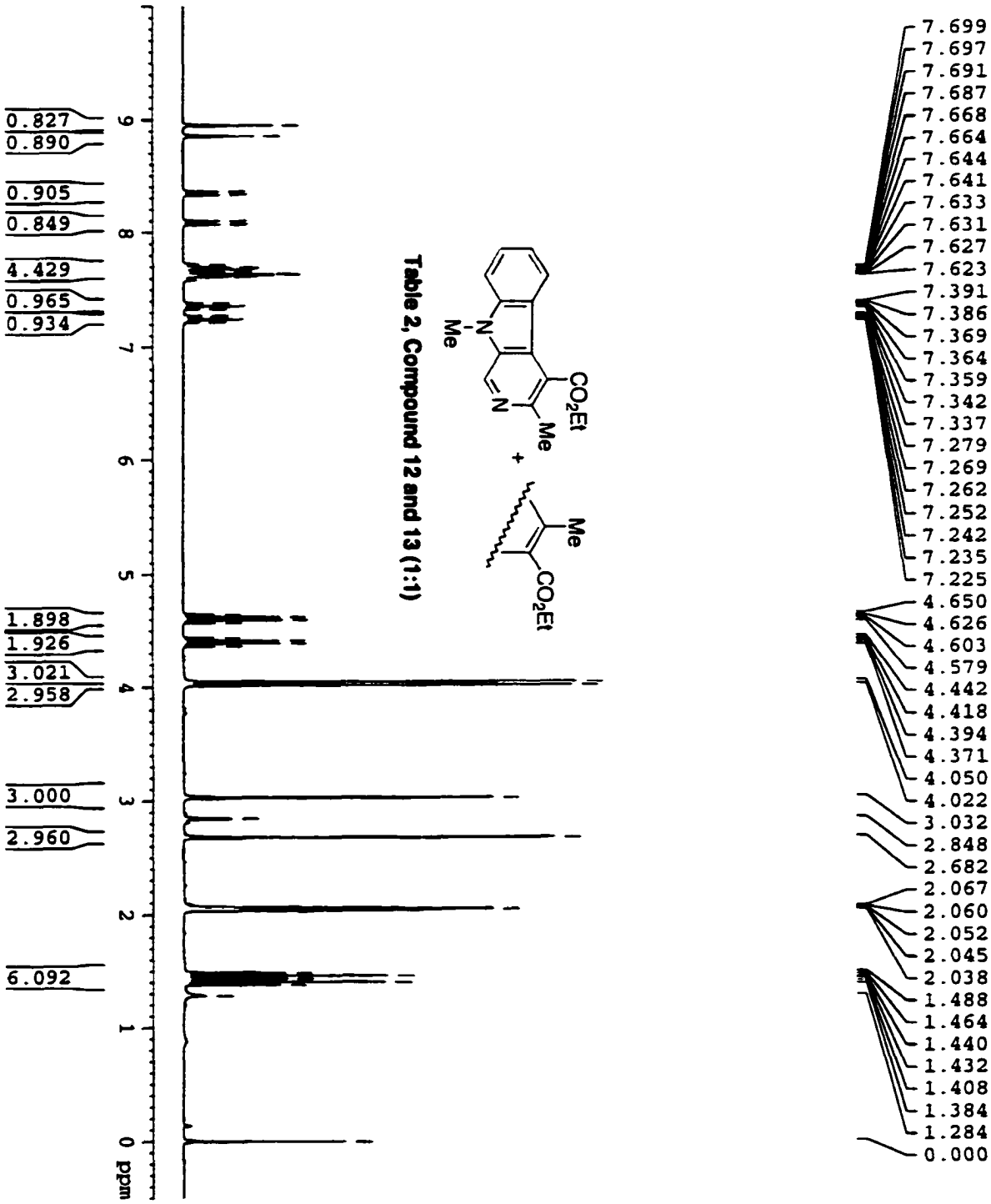


Table 2, Compound 9


0.967
3.918
1.018
1.880
1.903
1.975
0.832
3.000
9
8
7
6
5
4
3
2
1
0
ppm
Table 2, Compound 10
N
Me
N
Ph
CH2OH
7.635
7.631
7.625
7.621
7.616
7.611
7.607
7.602
7.595
7.594
7.564
7.559
7.548
7.543
7.538
7.527
7.522
7.496
7.491
7.486
7.476
7.472
6.993
6.990
6.988
6.974
6.972
4.533
4.441
4.075
2.816
2.074
2.063
2.058
2.052
2.047
2.041
0.135
0.000


143.702
137.780
130.643
130.127
129.885
129.214
129.106
129.047
128.332
123.964
121.764
120.094
110.425
62.537
30.350
30.157
29.965
29.772
29.580
29.388
29.195
0.002
ppm
Table 2, Compound 10
Me
N
N
Ph
CH2OH


0.827
0.890
0.905
0.849
4.429
0.965
0.934
1.898
1.926
3.021
2.958
3.000
2.960
6.092
9
8
7
6
5
4
3
2
1
0 ppm
Table 2, Compound 12 and 13 (1:1)
Me
N
CO2Et
Me
+
Me
CO2Et
7.699
7.697
7.691
7.687
7.668
7.664
7.644
7.641
7.633
7.631
7.627
7.623
7.391
7.386
7.369
7.364
7.359
7.342
7.337
7.279
7.269
7.262
7.252
7.242
7.235
7.225
4.650
4.626
4.603
4.579
4.442
4.418
4.394
4.371
4.050
4.022
3.032
2.848
2.682
2.067
2.060
2.052
2.045
2.038
1.488
1.464
1.440
1.432
1.408
1.384
1.284
0.000

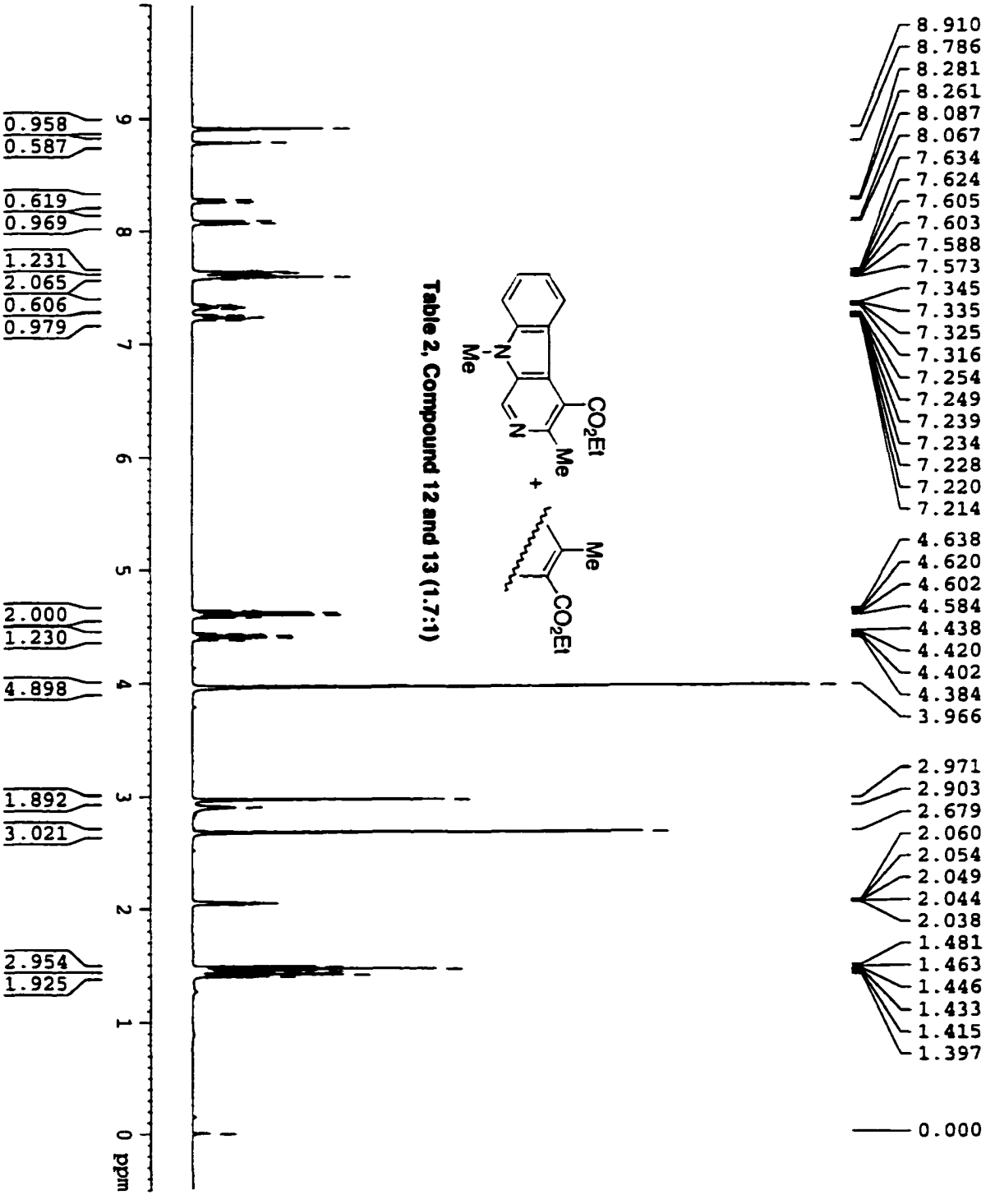


Table 2, Compound 12 and 13 (1.7:1)

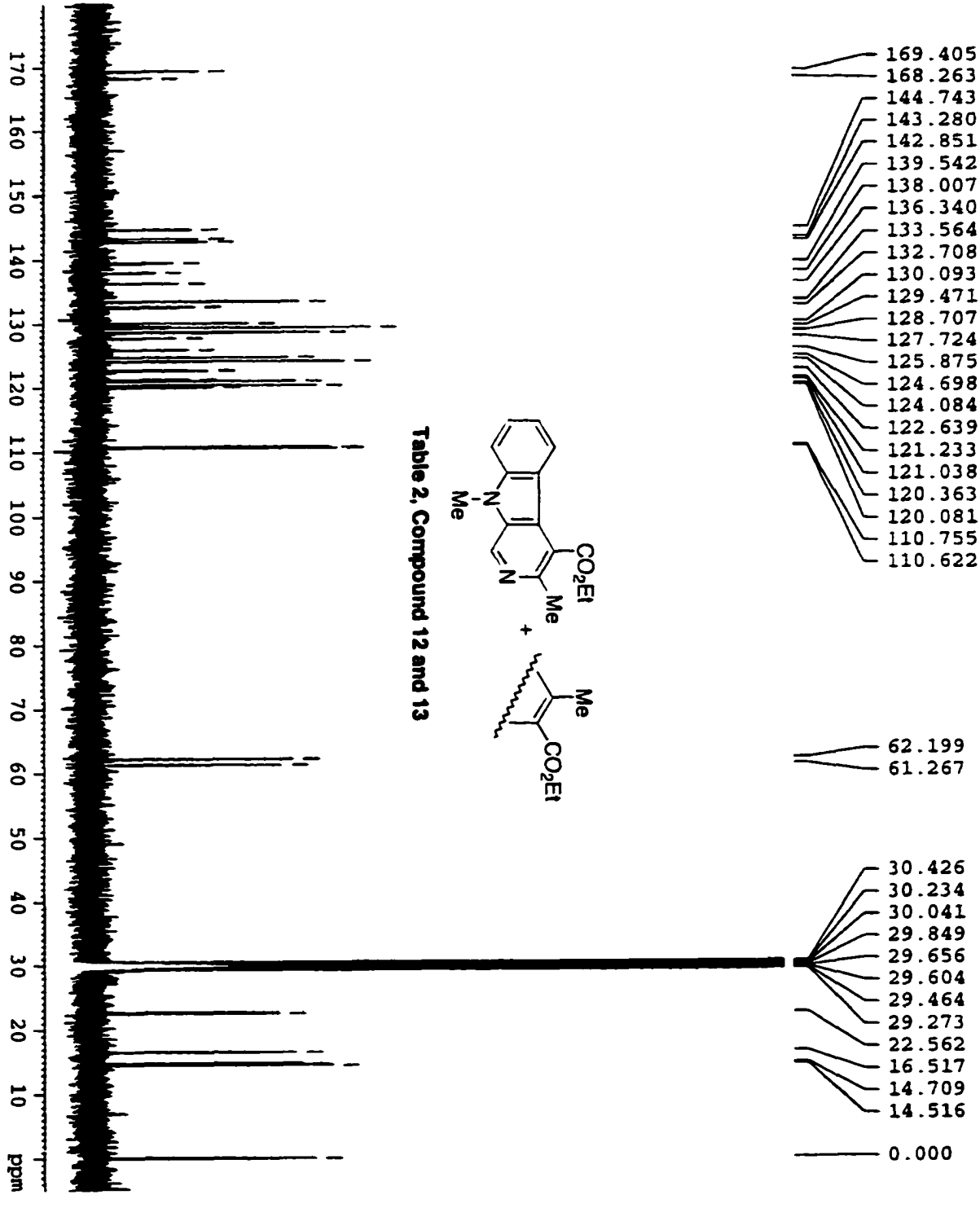
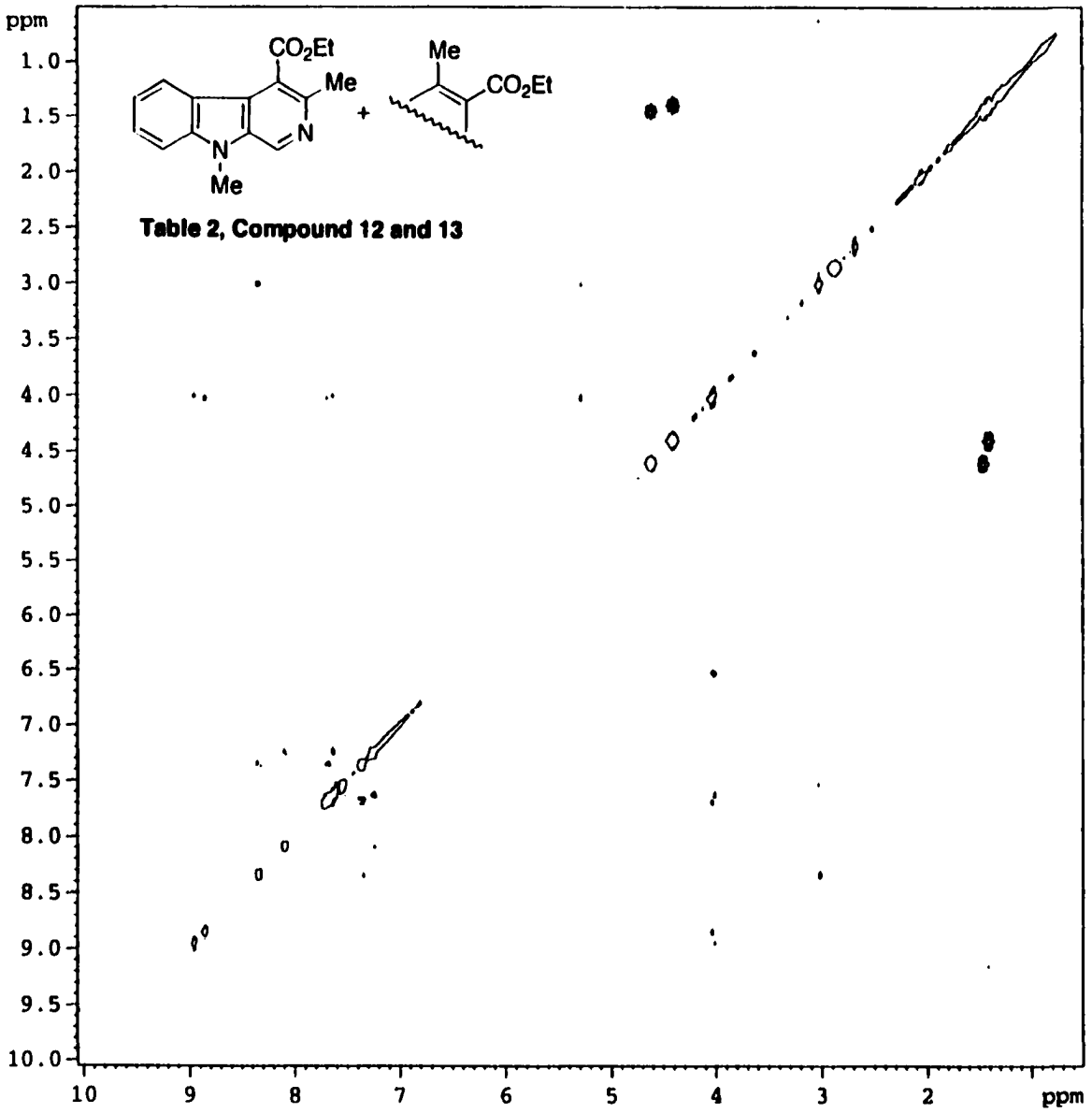


Table 2, Compound 12 and 13


ppm
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
8.0
8.5
9.0
9.5
10.0
10
9
8
7
6
5
4
3
2
ppm
CO2Et
Me
N
Me
+
Me
CO2Et
Table 2, Compound 12 and 13

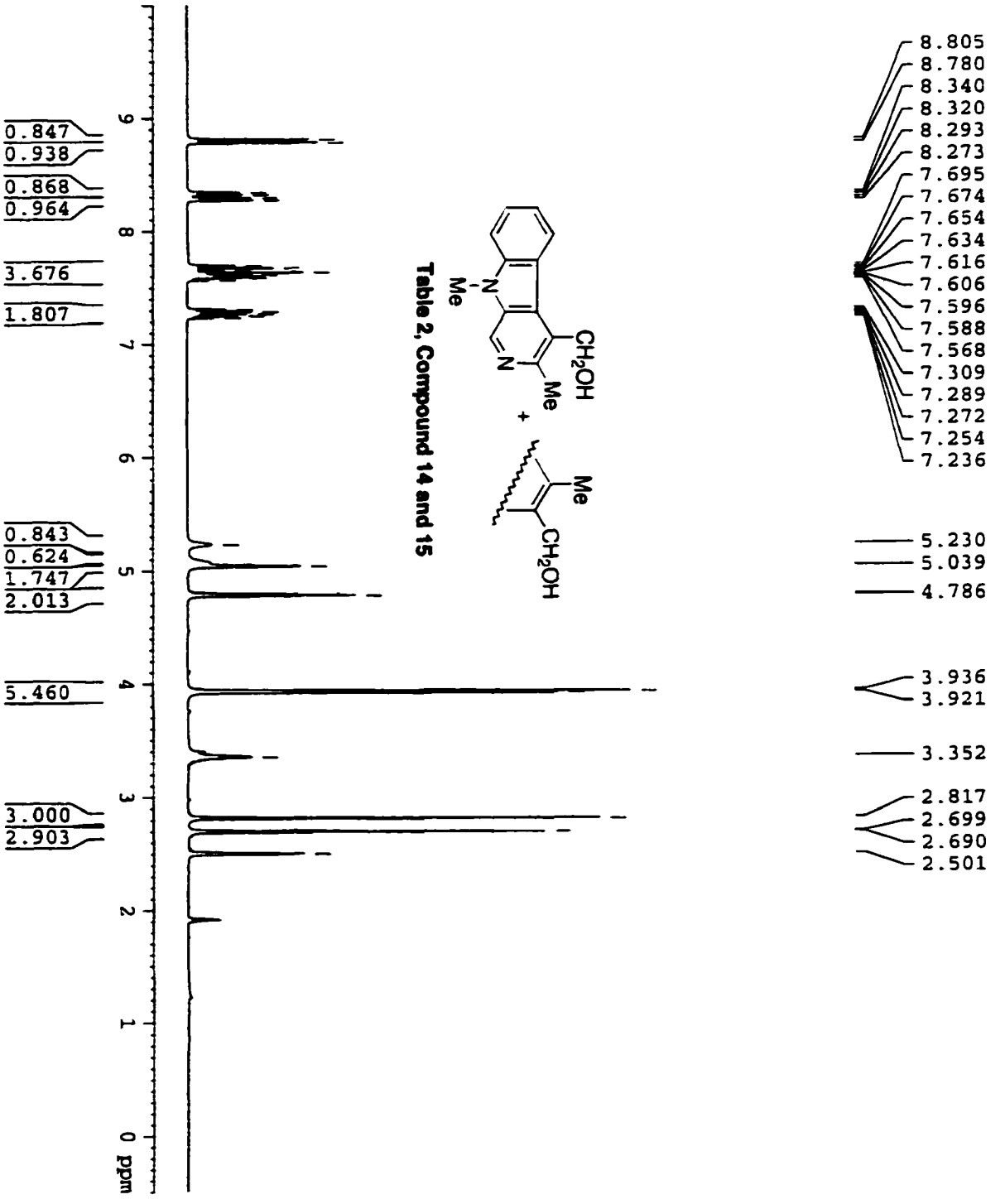


Table 2, Compound 14 and 15

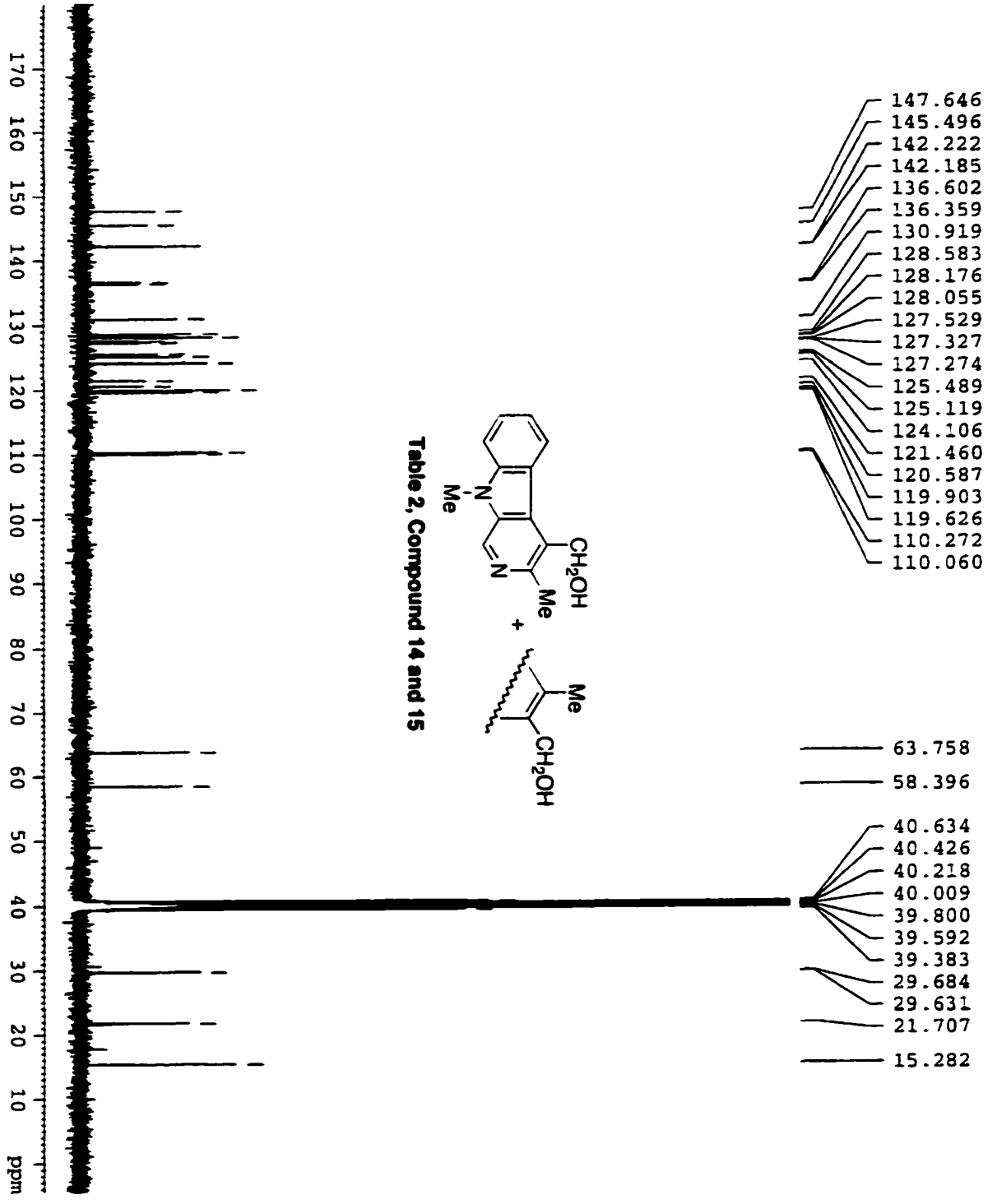
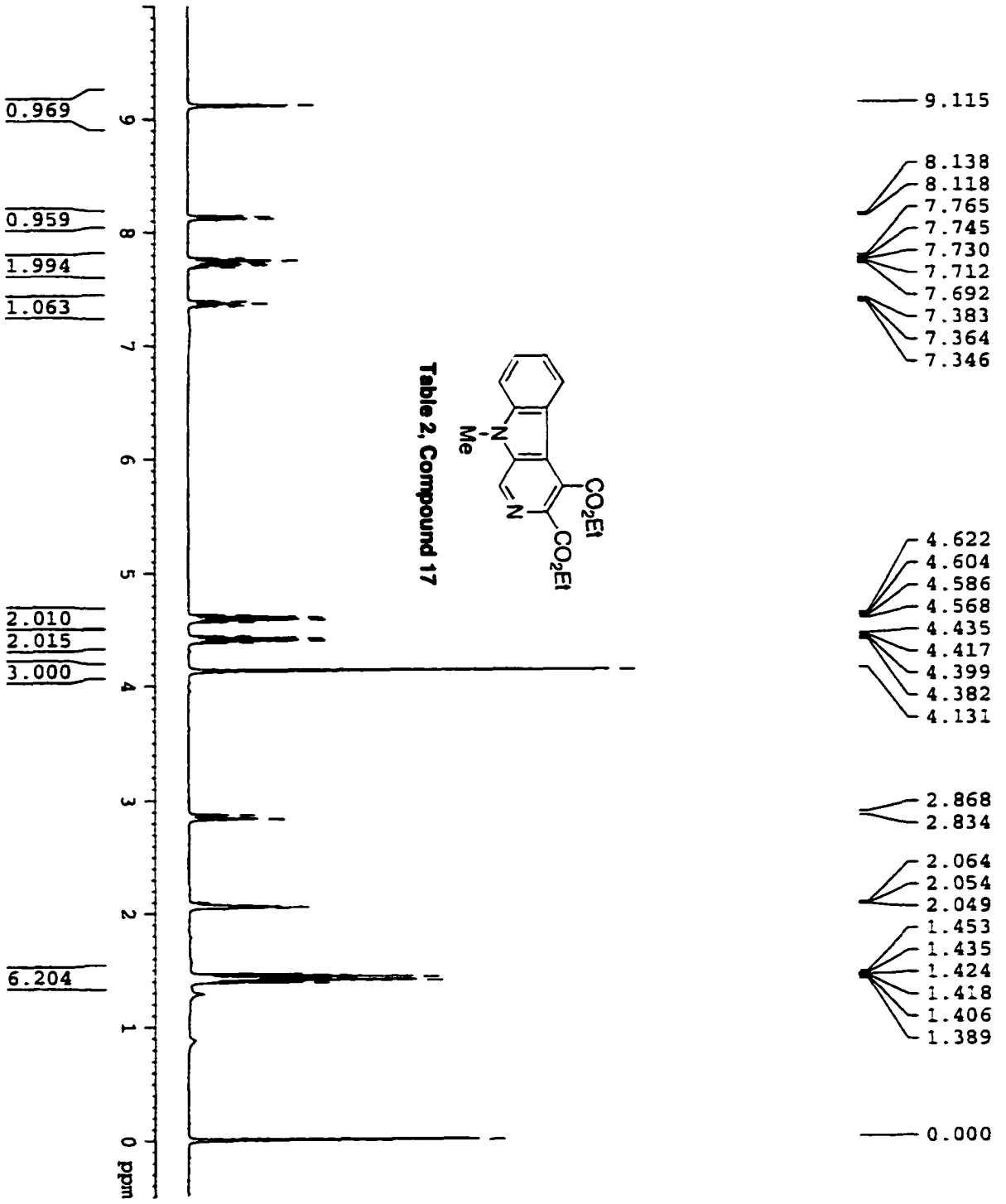
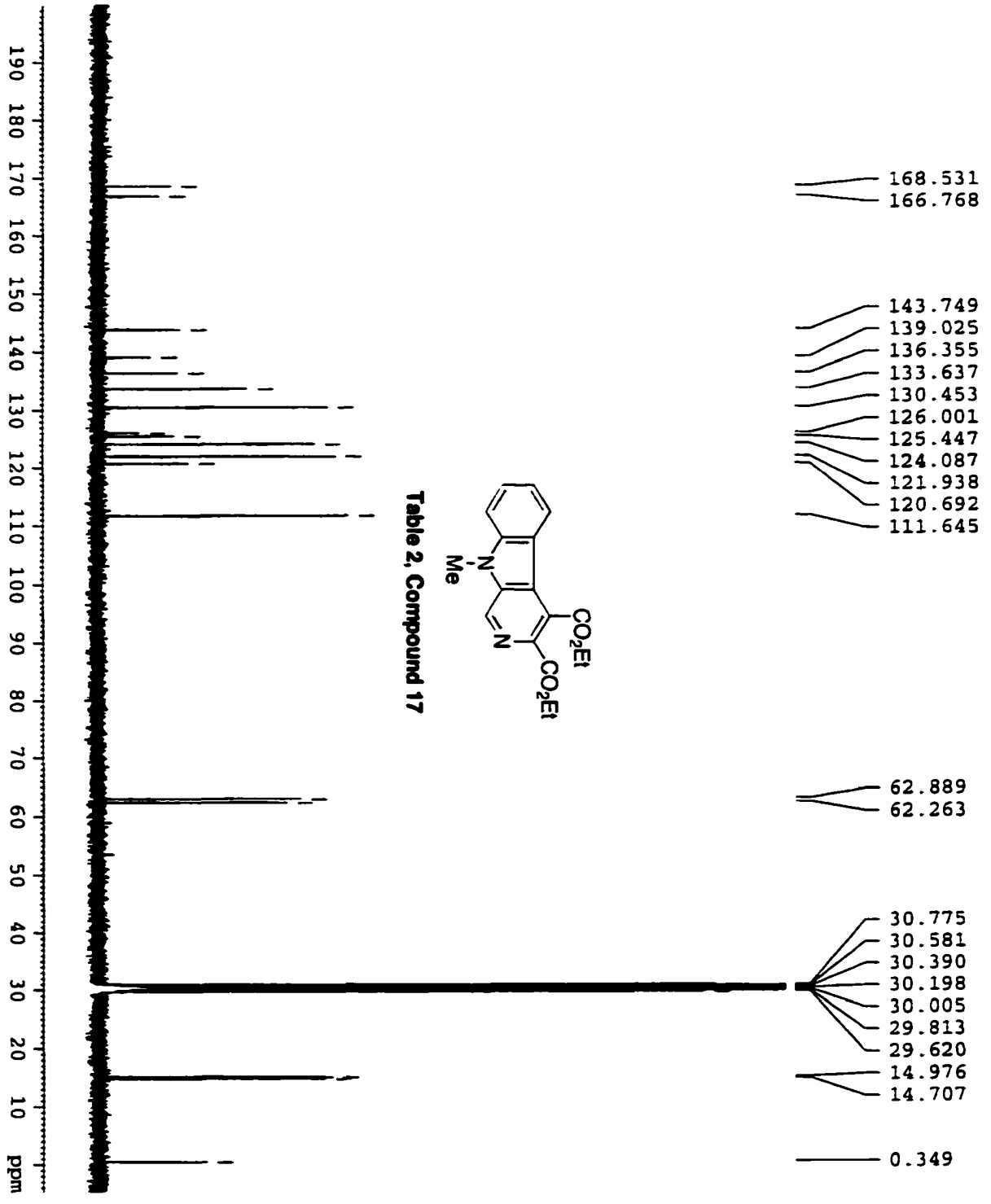


Table 2, Compound 14 and 15


0.969
0.959
1.994
1.063
2.010
2.015
3.000
6.204
9 8 7 6 5 4 3 2 1 0 ppm
Table 2, Compound 17
N
Me
N
CO2Et
CO2Et
9.115
8.138
8.118
7.765
7.745
7.730
7.712
7.692
7.383
7.364
7.346
4.622
4.604
4.586
4.568
4.435
4.417
4.399
4.382
4.131
2.868
2.834
2.064
2.054
2.049
1.453
1.435
1.424
1.418
1.406
1.389
0.000


168.531
166.768
143.749
139.025
136.355
133.637
130.453
126.001
125.447
124.087
121.938
120.692
111.645
62.889
62.263
30.775
30.581
30.390
30.198
30.005
29.813
29.620
14.976
14.707
0.349
ppm
Table 2, Compound 17
Me
N
N
CO2Et
CO2Et

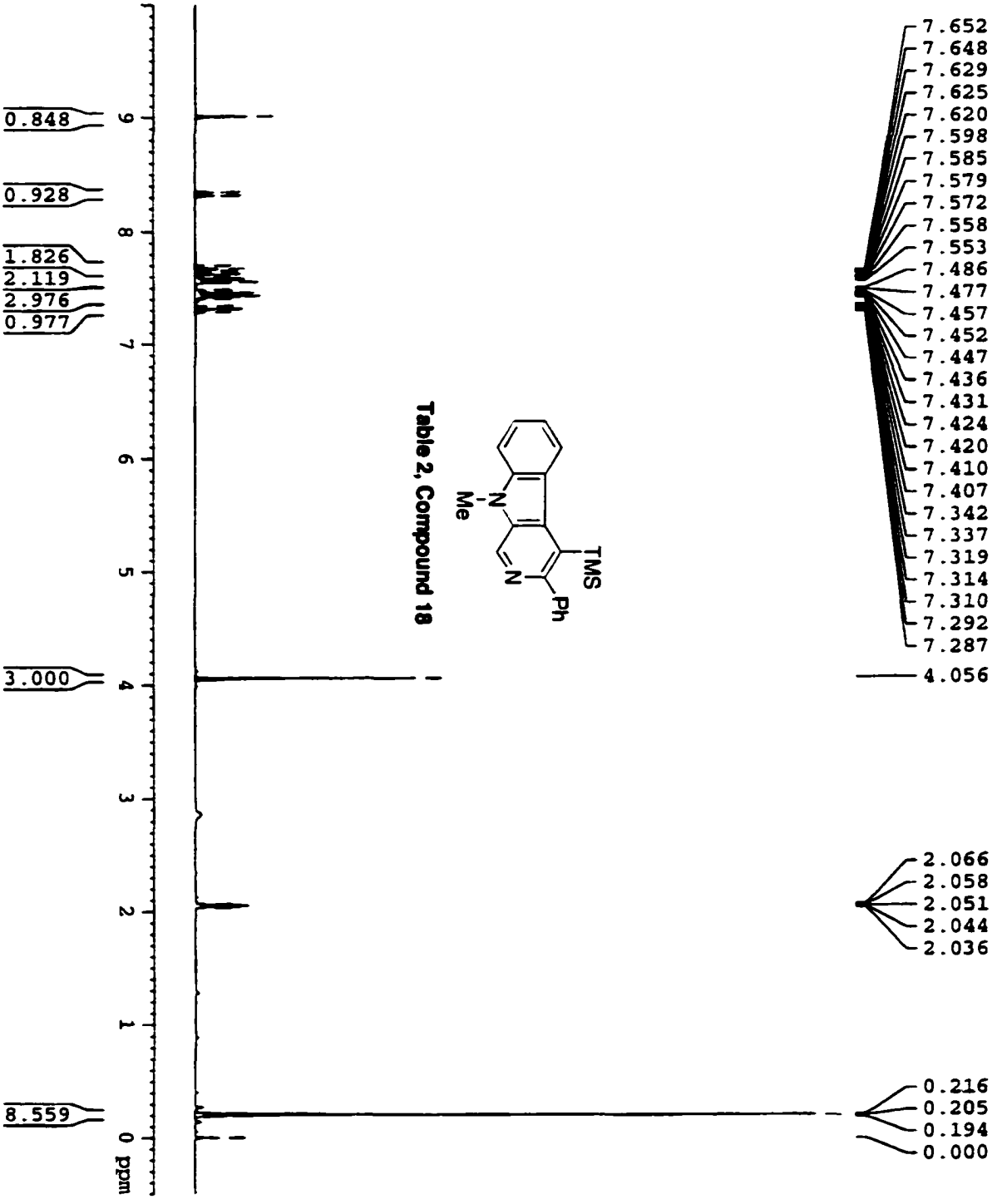
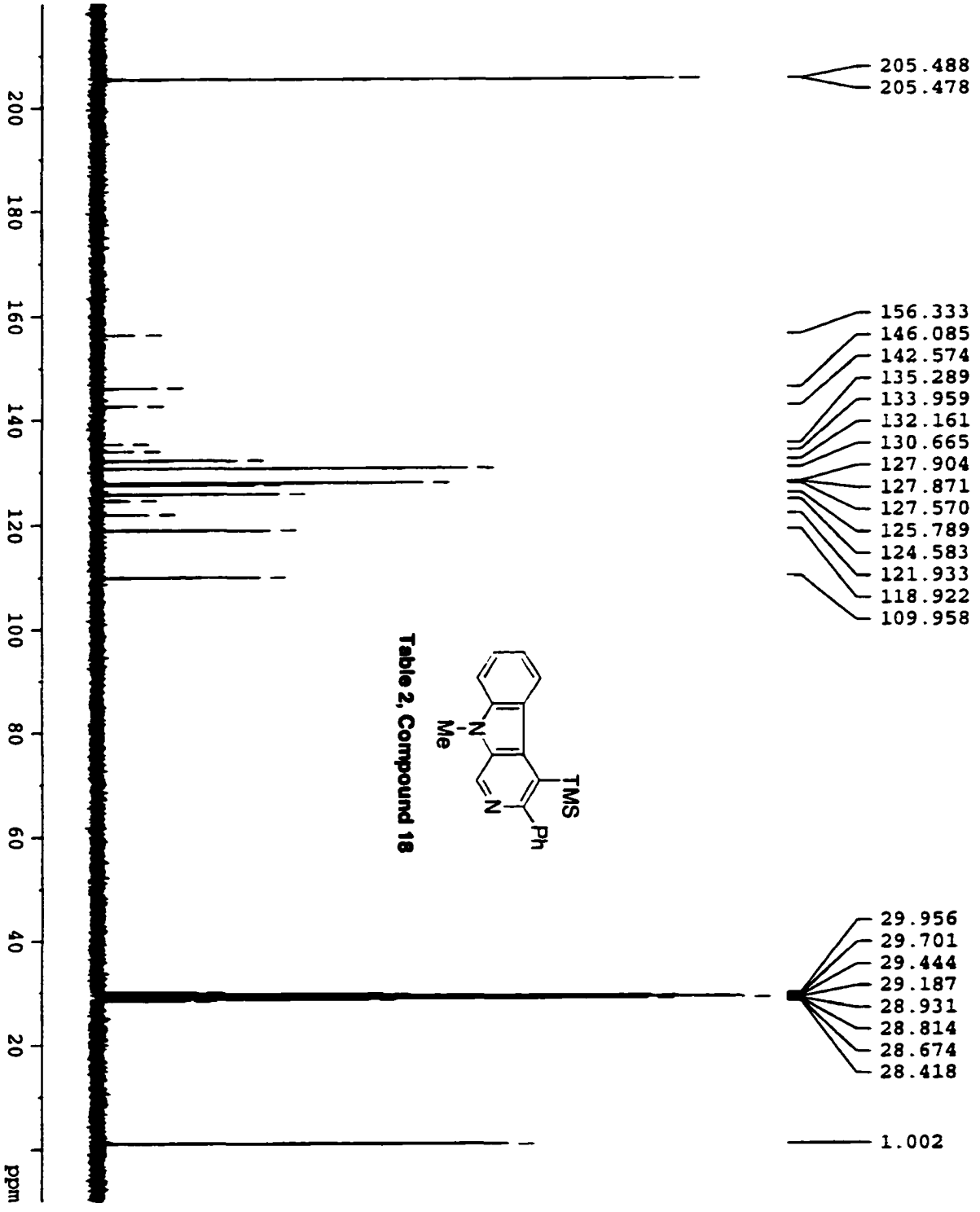
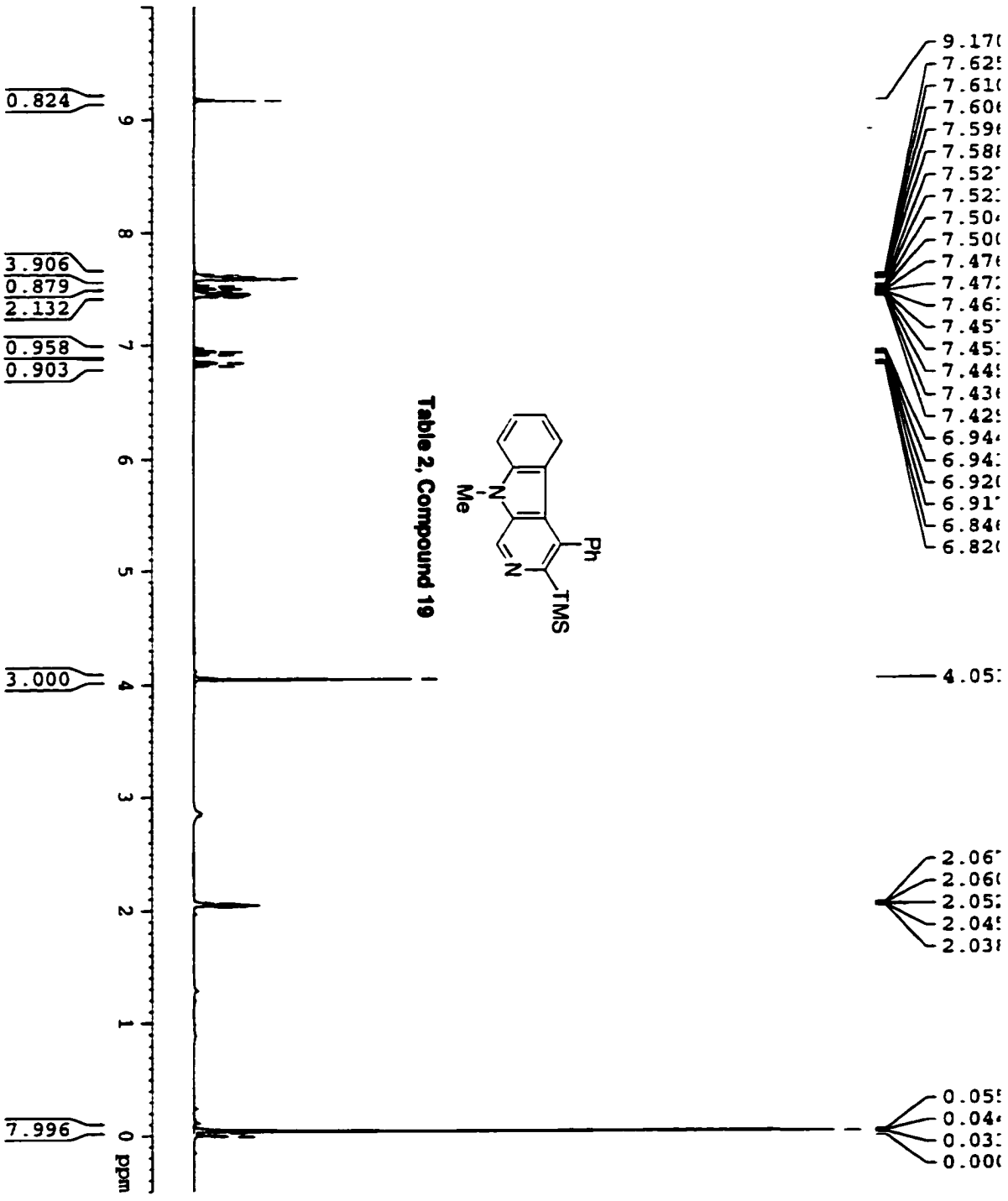


Table 2, Compound 18
Me
N
N
TMS
Ph
0.848
0.928
1.826
2.119
2.976
0.977
3.000
8.559
7.652
7.648
7.629
7.625
7.620
7.598
7.585
7.579
7.572
7.558
7.553
7.486
7.477
7.457
7.452
7.447
7.436
7.431
7.424
7.420
7.410
7.407
7.342
7.337
7.319
7.314
7.310
7.292
7.287
4.056
2.066
2.058
2.051
2.044
2.036
0.216
0.205
0.194
0.000
9
8
7
6
5
4
3
2
1
0 ppm


205.488
205.478
156.333
146.085
142.574
135.289
133.959
132.161
130.665
127.904
127.871
127.570
125.789
124.583
121.933
118.922
109.958
29.956
29.701
29.444
29.187
28.931
28.814
28.674
28.418
1.002
200
180
160
140
120
100
80
60
40
20
ppm
Table 2, Compound 18
N
Me
N
TMS
Ph


0.824
3.906
0.879
2.132
0.958
0.903
3.000
7.996
9 8 7 6 5 4 3 2 1 0 ppm
9.17(
7.62
7.61(
7.60
7.59
7.58
7.52
7.52
7.50
7.50(
7.47
7.47
7.46
7.45
7.45
7.44
7.43
7.42
6.94
6.94
6.92(
6.91
6.84
6.82(
4.05
2.06
2.06(
2.05
2.04
2.03
0.05
0.04
0.03
0.00(
Table 2, Compound 19
N
Me
Ph
N
TMS

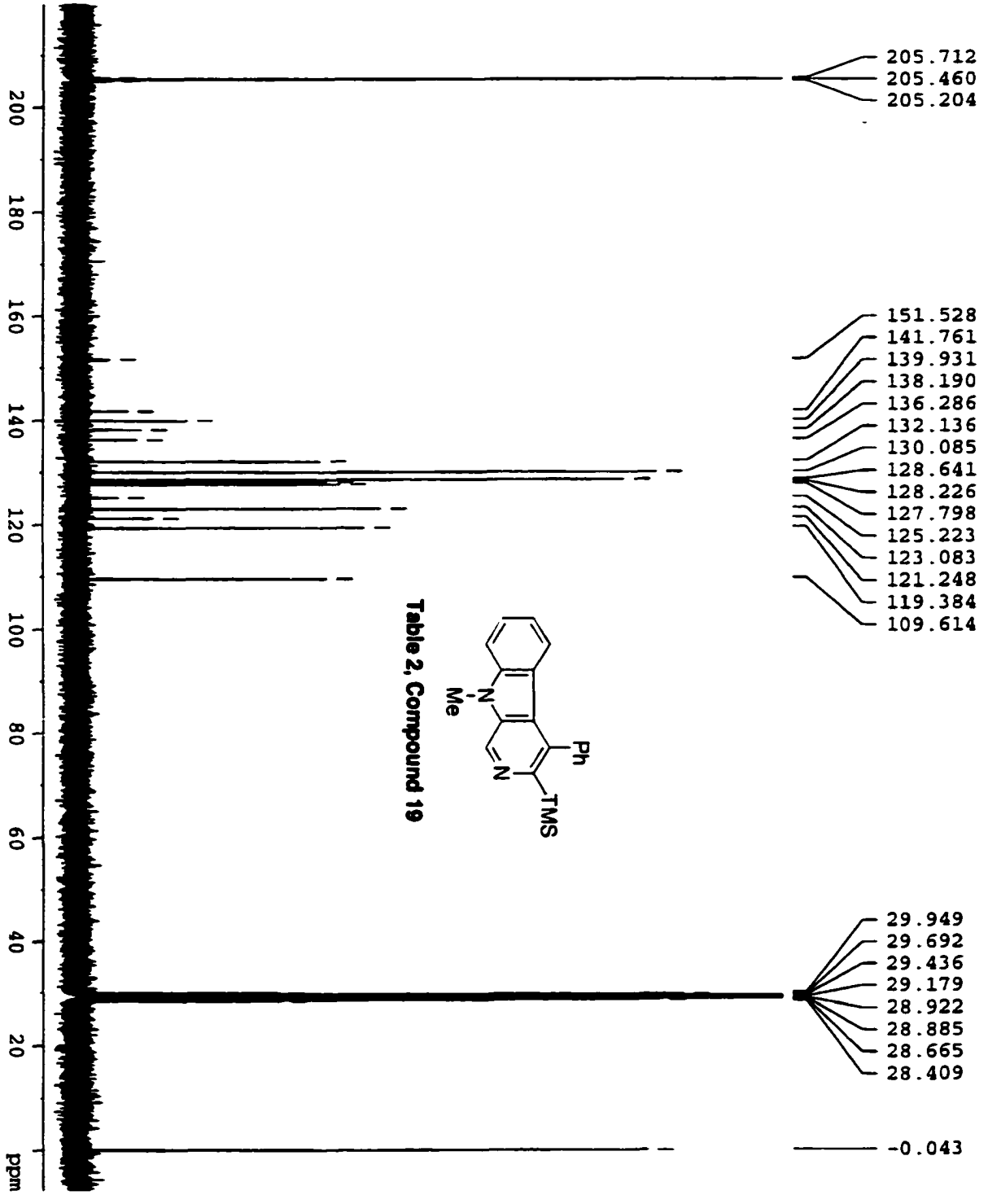
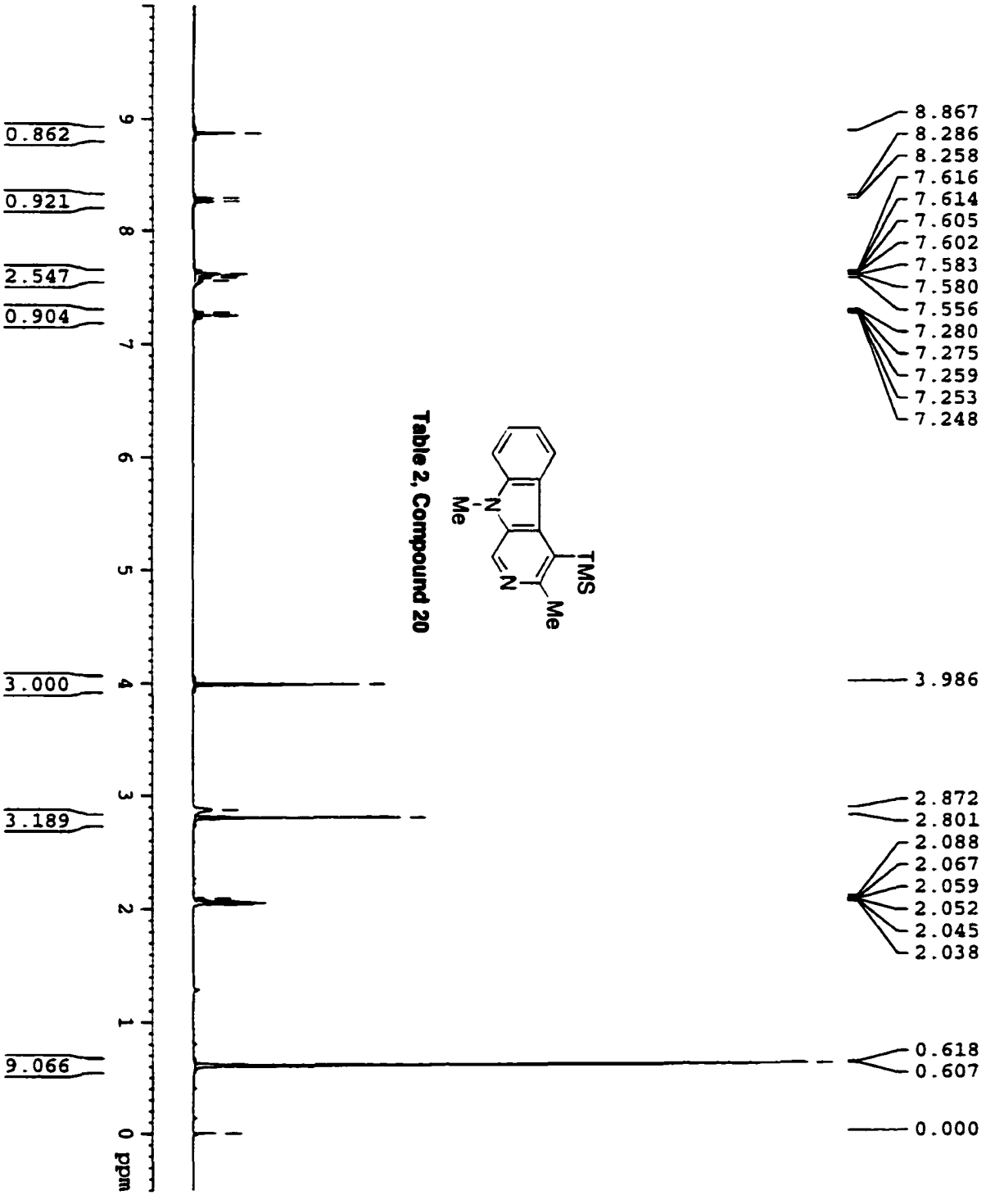
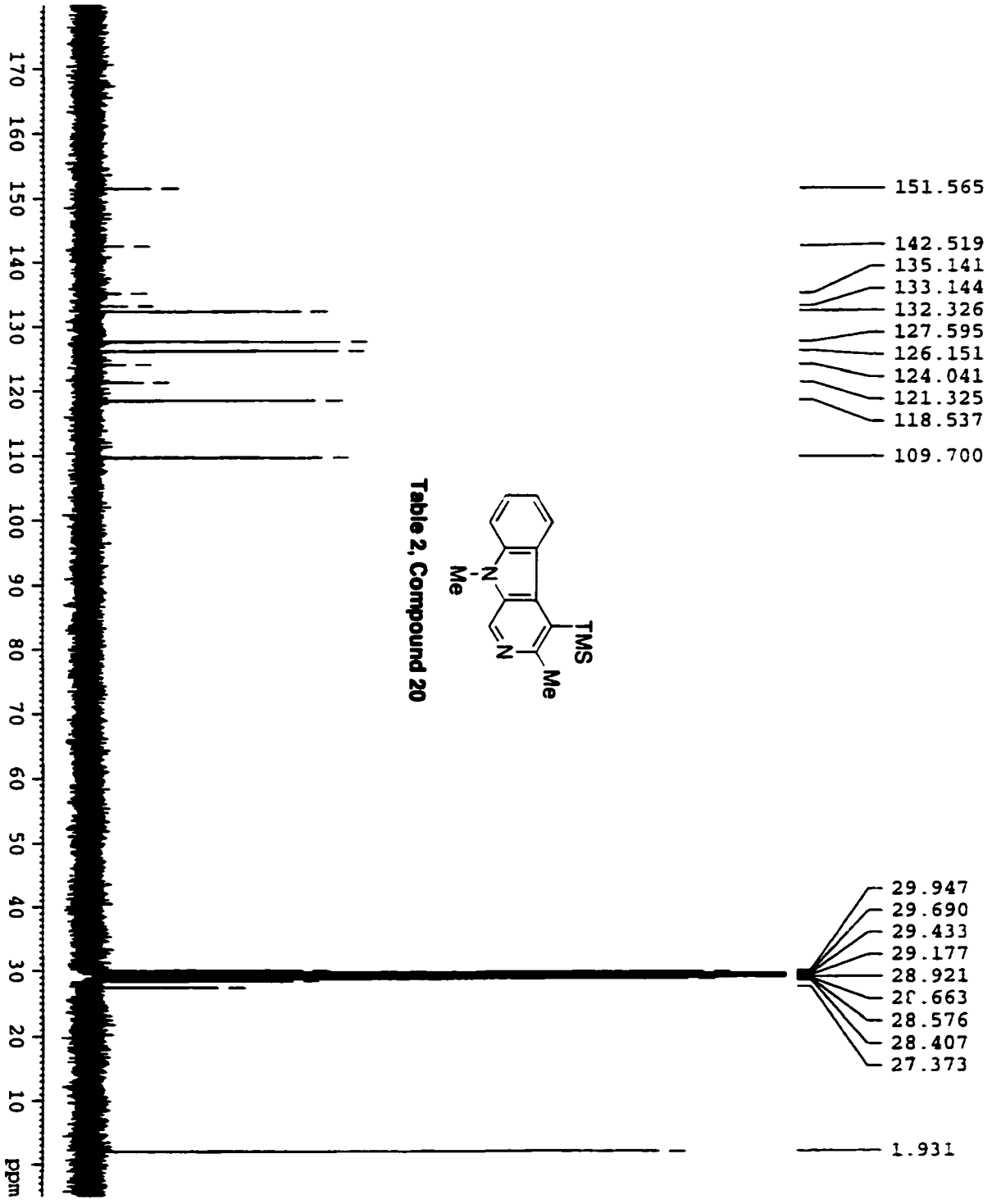


Table 2, Compound 19


8.867
8.286
8.258
7.616
7.614
7.605
7.602
7.583
7.580
7.556
7.280
7.275
7.259
7.253
7.248
3.986
2.872
2.801
2.088
2.067
2.059
2.052
2.045
2.038
0.618
0.607
0.000
0.862
0.921
2.547
0.904
3.000
3.189
9.066
ppm
Table 2, Compound 20
N
Me
TMS
Me


151.565
142.519
135.141
133.144
132.326
127.595
126.151
124.041
121.325
118.537
109.700
29.947
29.690
29.433
29.177
28.921
28.663
28.576
28.407
27.373
1.931
ppm
Table 2, Compound 20
Me
N
N
TMS
Me

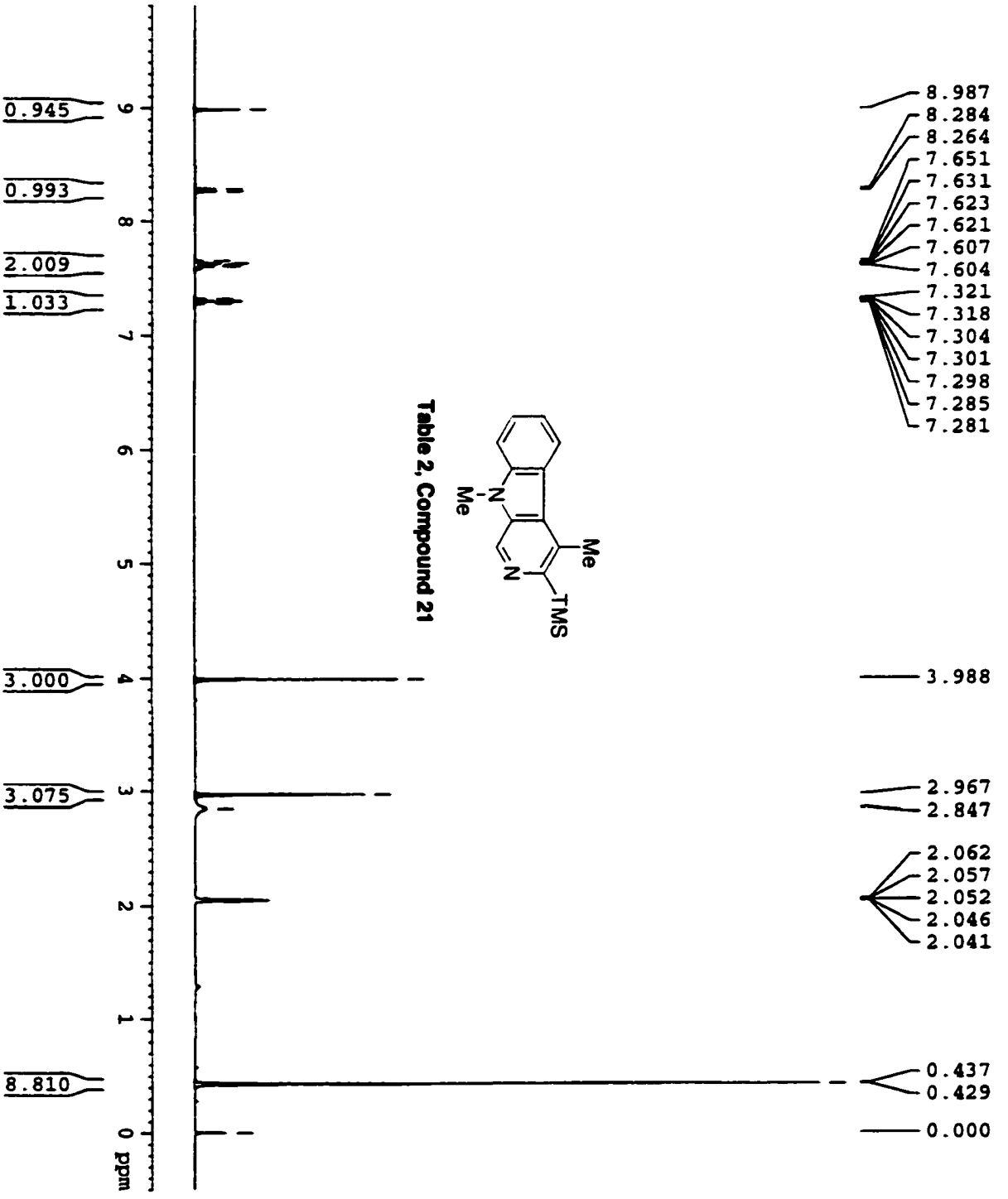
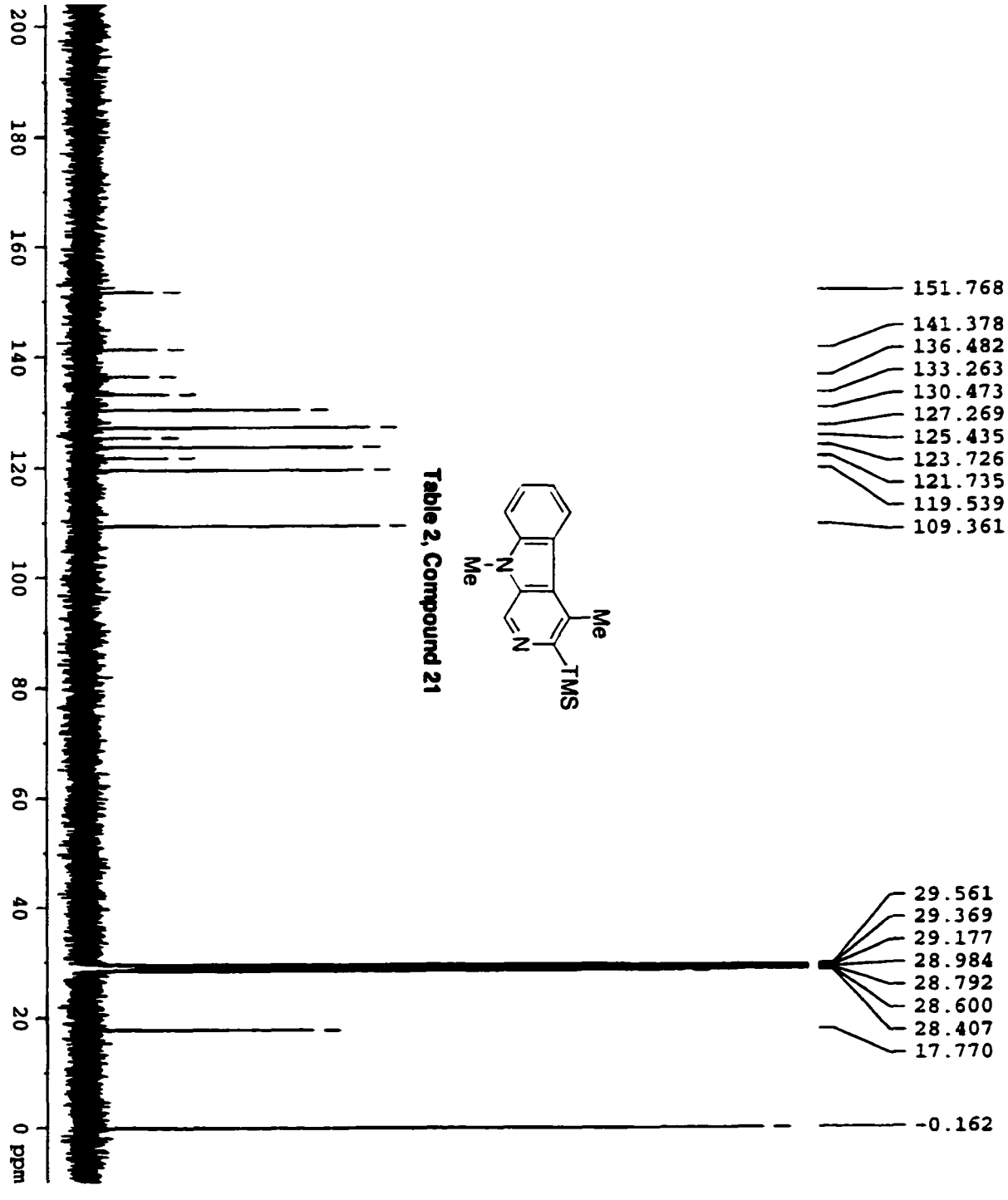


Table 2, Compound 21
Me
N
Me
N
TMS
0.945
0.993
2.009
1.033
3.000
3.075
8.810
8.987
8.284
8.264
7.651
7.631
7.623
7.621
7.607
7.604
7.321
7.318
7.304
7.301
7.298
7.285
7.281
3.988
2.967
2.847
2.062
2.057
2.052
2.046
2.041
0.437
0.429
0.000
ppm


200
180
160
140
120
100
80
60
40
20
0 ppm
151.768
141.378
136.482
133.263
130.473
127.269
125.435
123.726
121.735
119.539
109.361
29.561
29.369
29.177
28.984
28.792
28.600
28.407
17.770
-0.162
Table 2, Compound 21
N
Me
N
Me
TMS

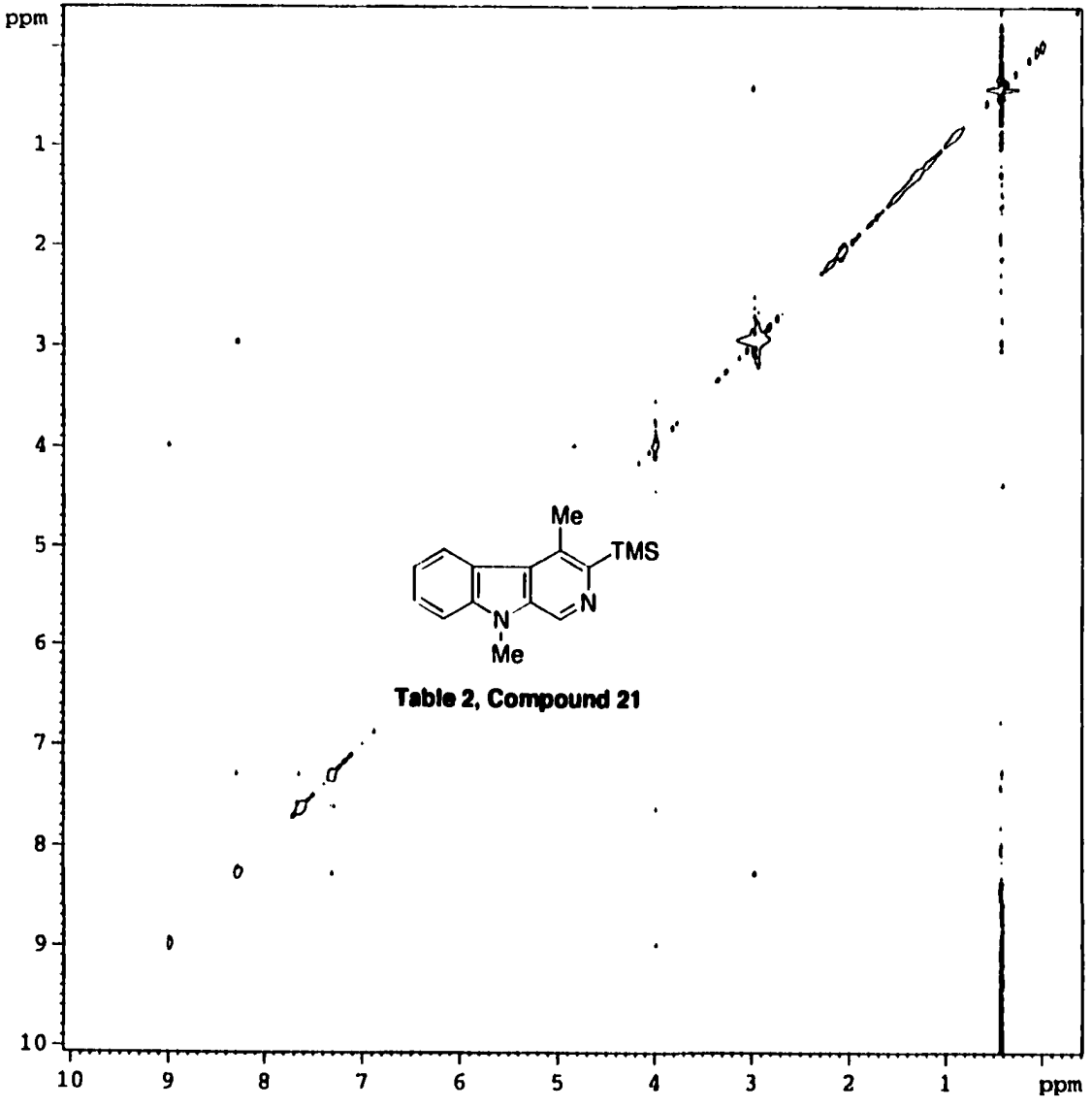


Table 2, Compound 21

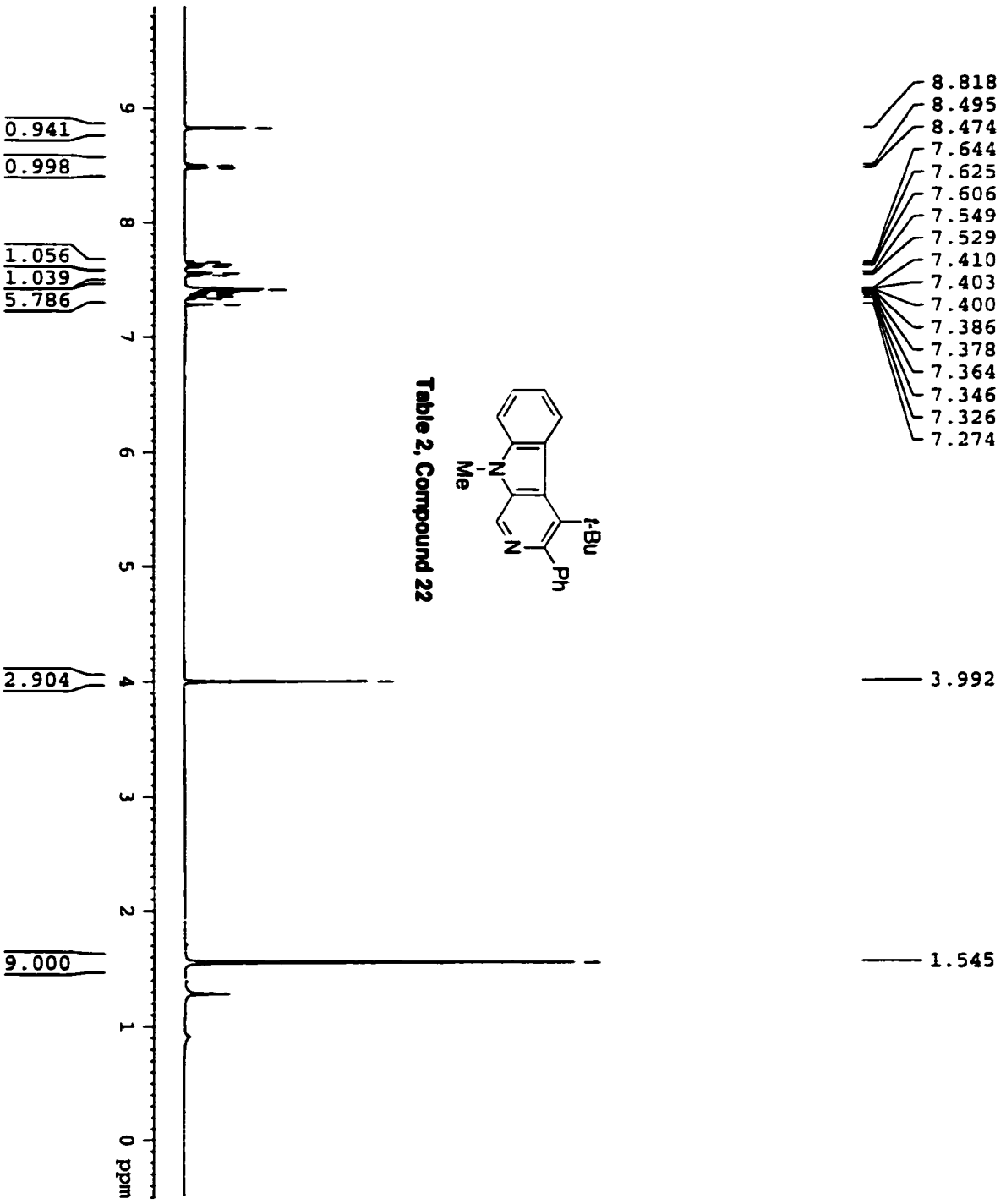


Table 2, Compound 22

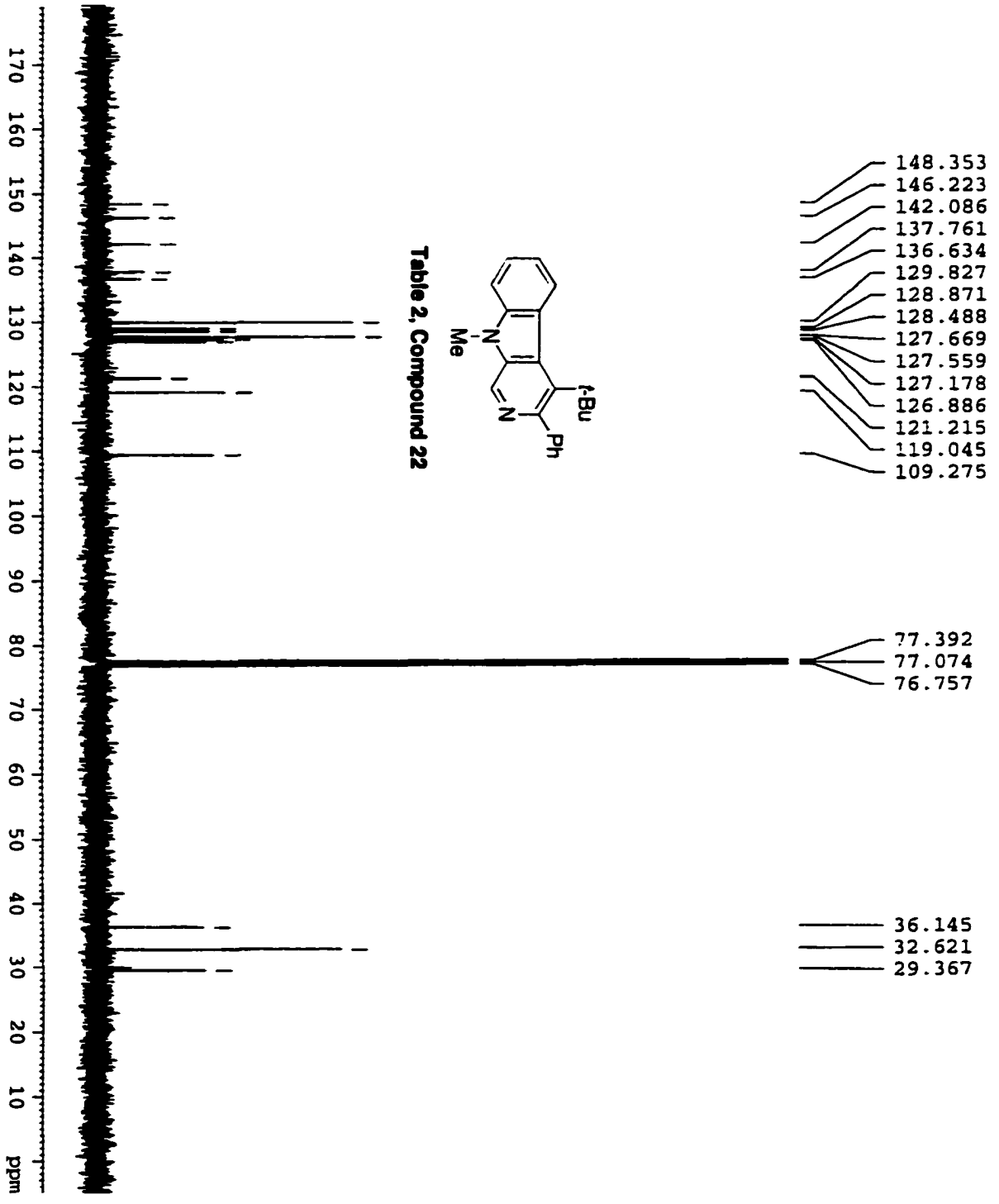


Table 2, Compound 22

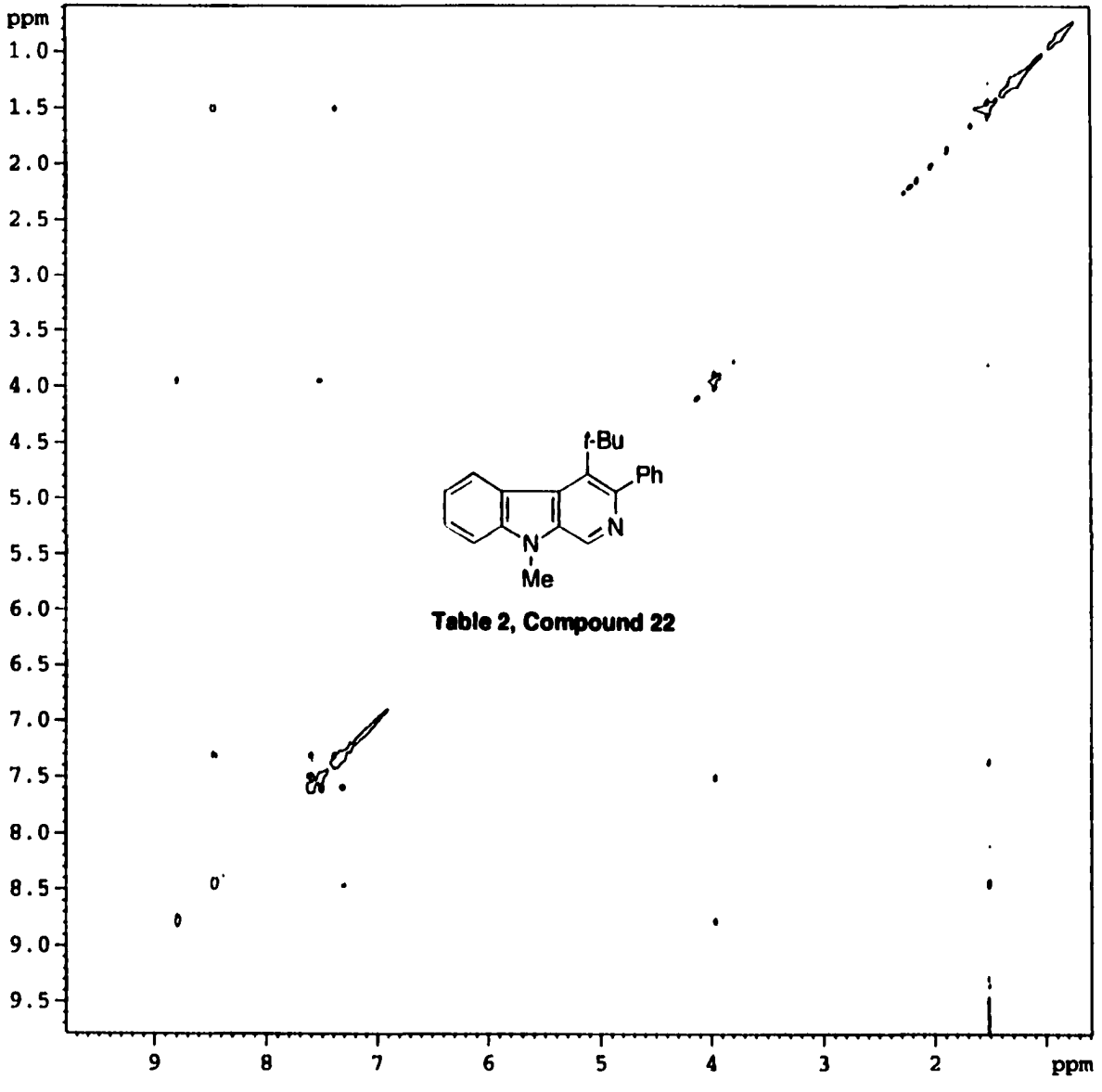


Table 2, Compound 22

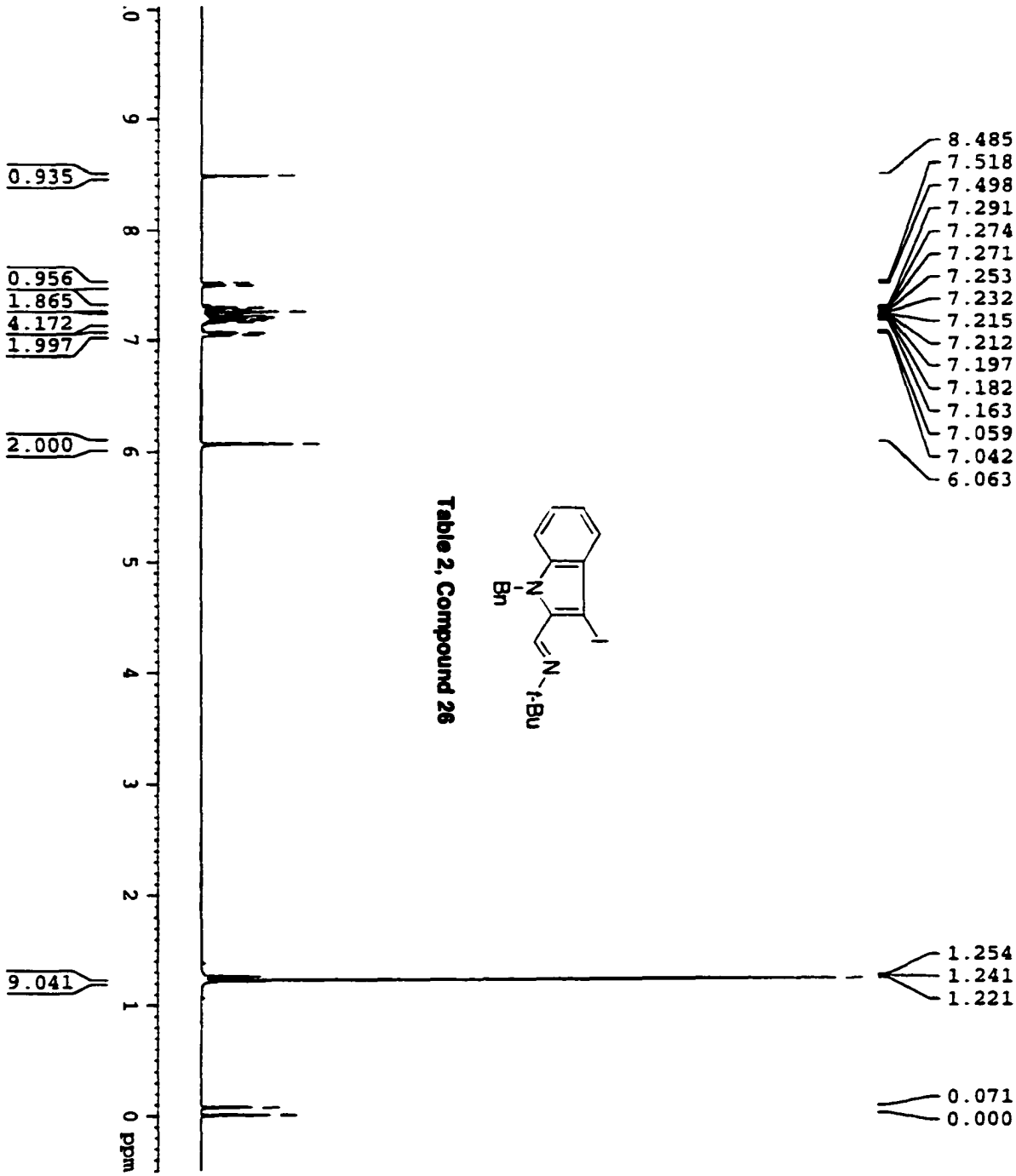
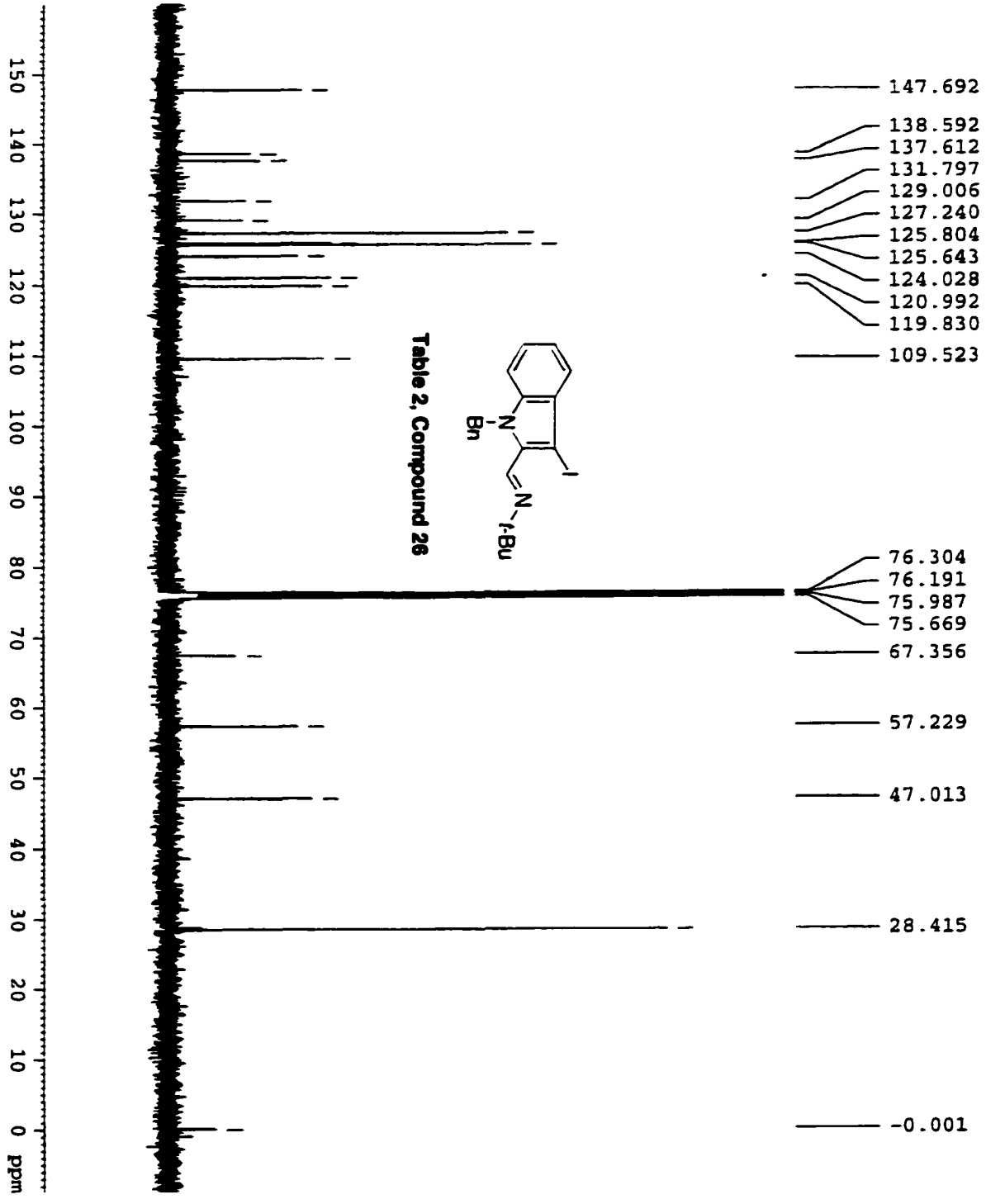
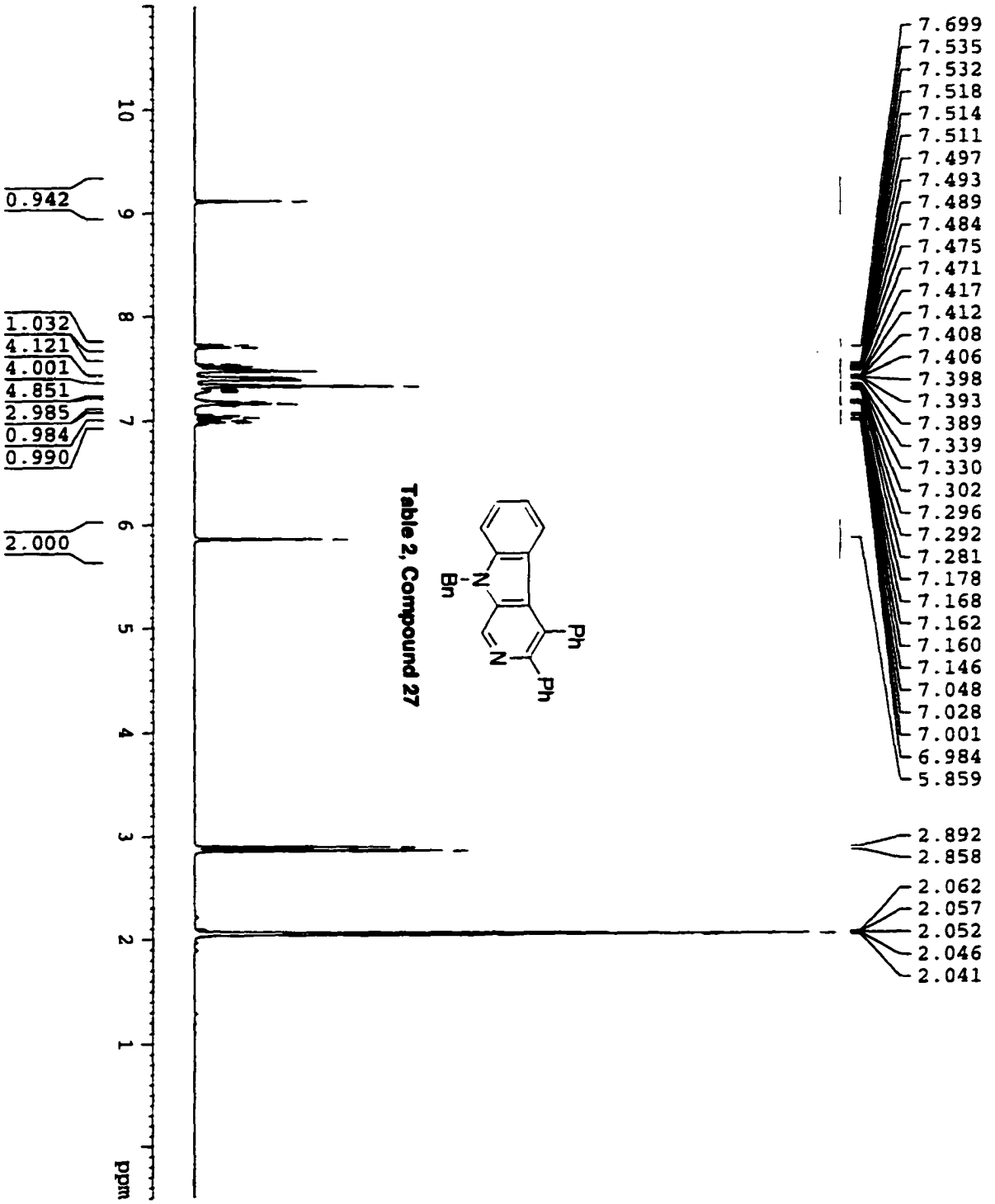
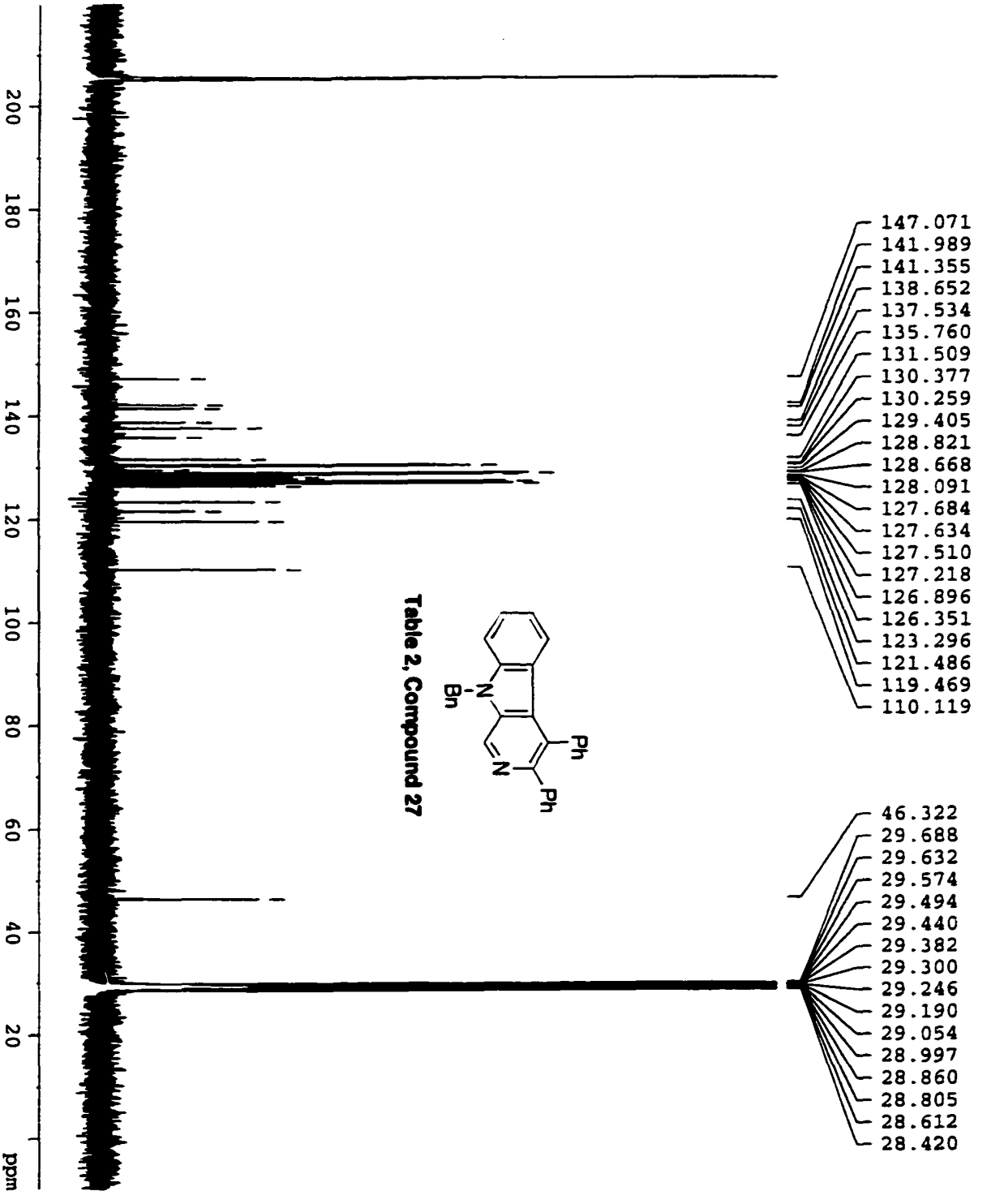


Table 2, Compound 26


147.692
138.592
137.612
131.797
129.006
127.240
125.804
125.643
124.028
120.992
119.830
109.523
76.304
76.191
75.987
75.669
67.356
57.229
47.013
28.415
-0.001
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm
Table 2, Compound 26
Bn
N
N
t-Bu
I


0.942
1.032
4.121
4.001
4.851
2.985
0.984
0.990
2.000
7.699
7.535
7.532
7.518
7.514
7.511
7.497
7.493
7.489
7.484
7.475
7.471
7.417
7.412
7.408
7.406
7.398
7.393
7.389
7.339
7.330
7.302
7.296
7.292
7.281
7.178
7.168
7.162
7.160
7.146
7.048
7.028
7.001
6.984
5.859
2.892
2.858
2.062
2.057
2.052
2.046
2.041
Bn
N
N
Ph
Ph
Table 2, Compound 27
ppm


147.071
141.989
141.355
138.652
137.534
135.760
131.509
130.377
130.259
129.405
128.821
128.668
128.091
127.684
127.634
127.510
127.218
126.896
126.351
123.296
121.486
119.469
110.119
46.322
29.688
29.632
29.574
29.494
29.440
29.382
29.300
29.246
29.190
29.054
28.997
28.860
28.805
28.612
28.420
Table 2, Compound 27
Bn
N
N
Ph
Ph
200
180
160
140
120
100
80
60
40
20
ppm

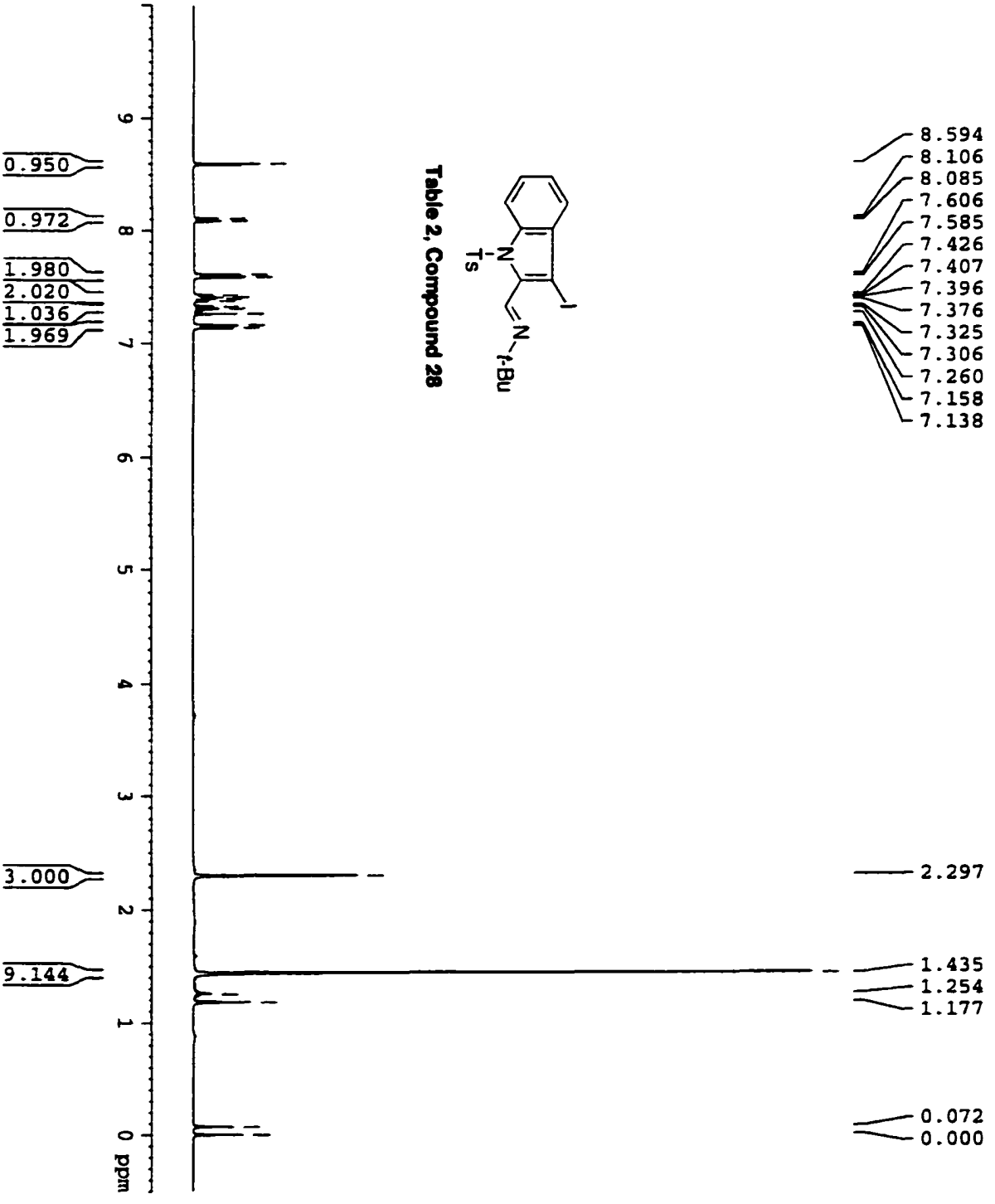


Table 2, Compound 28
Ts
N
N
t-Bu
0.950
0.972
1.980
2.020
1.036
1.969
3.000
9.144
8.594
8.106
8.085
7.606
7.585
7.426
7.407
7.396
7.376
7.325
7.306
7.260
7.158
7.138
2.297
1.435
1.254
1.177
0.072
0.000
ppm

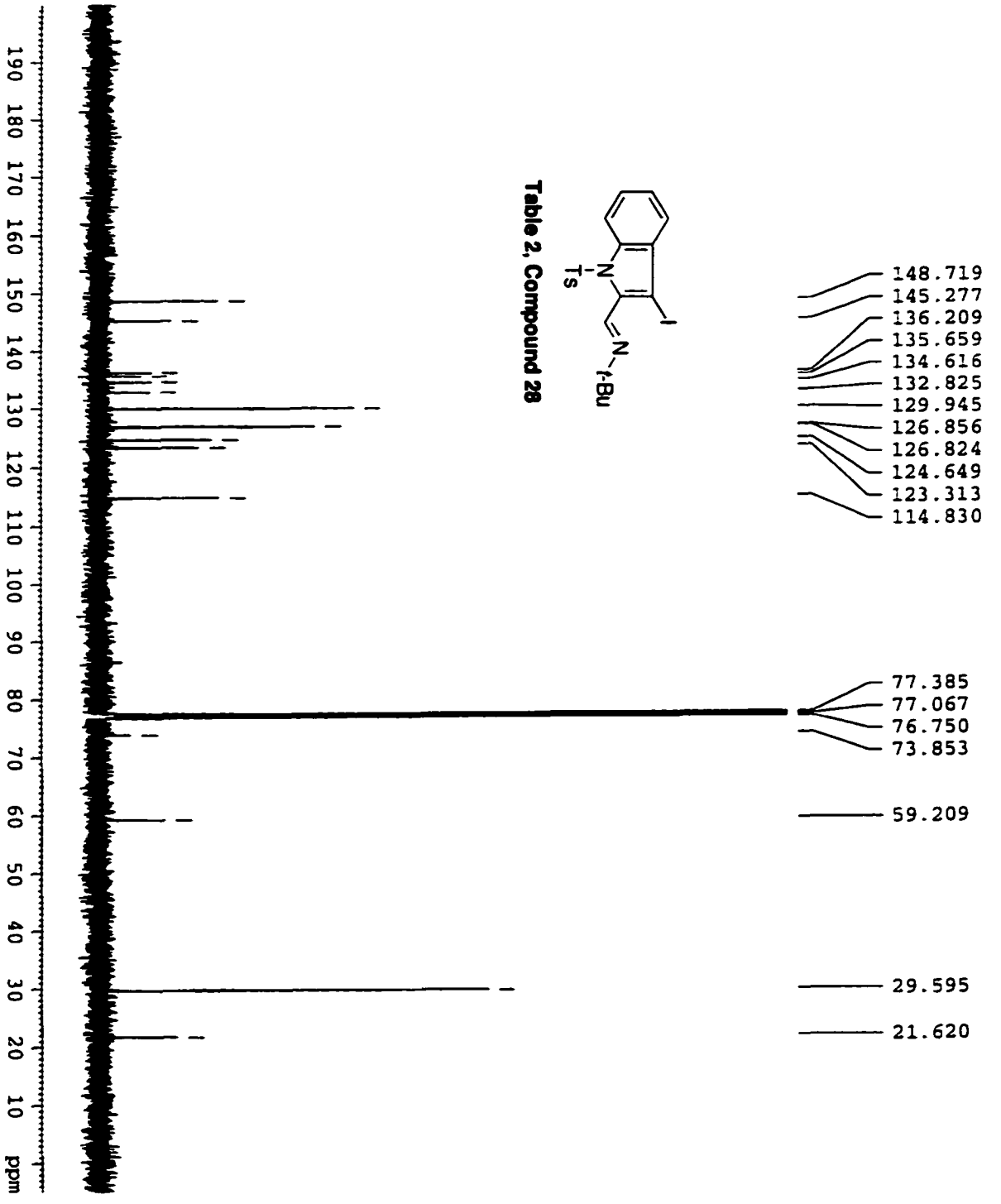


Table 2, Compound 28
Ts
N
N
t-Bu
I
148.719
145.277
136.209
135.659
134.616
132.825
129.945
126.856
126.824
124.649
123.313
114.830
77.385
77.067
76.750
73.853
59.209
29.595
21.620
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

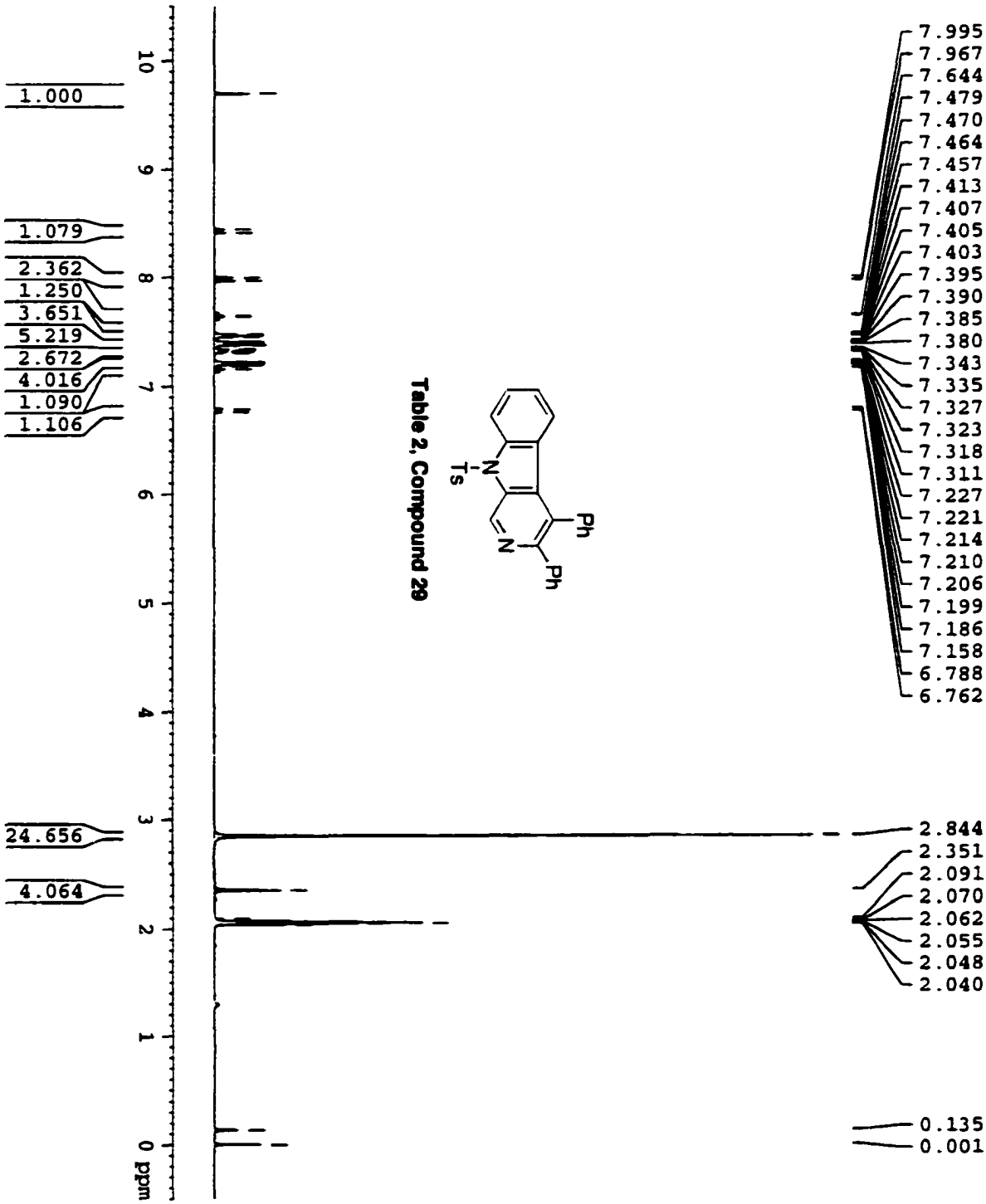
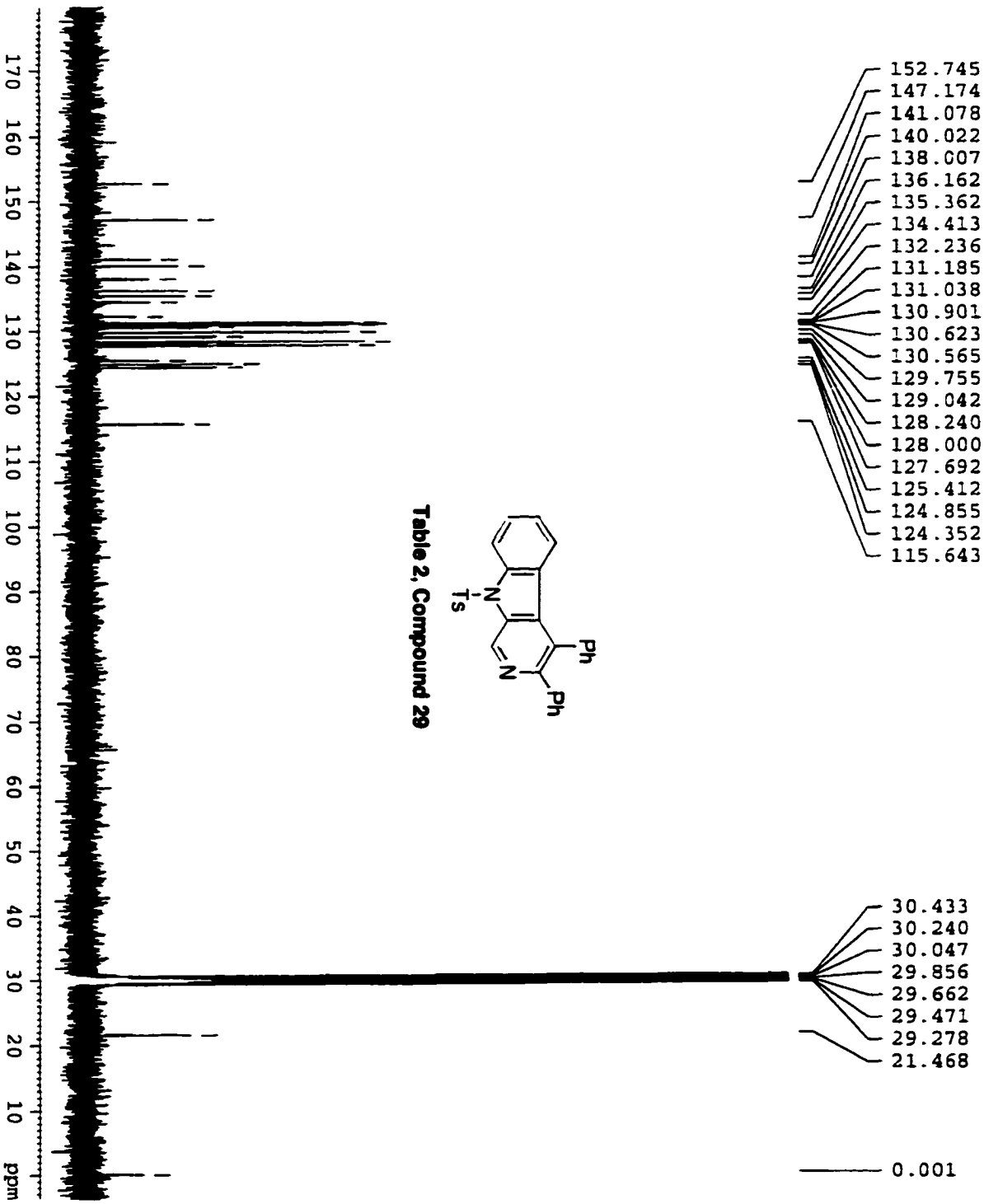


Table 2, Compound 29
Ts
N
N
Ph
Ph
1.000
1.079
2.362
1.250
3.651
5.219
2.672
4.016
1.090
1.106
24.656
4.064
7.995
7.967
7.644
7.479
7.470
7.464
7.457
7.413
7.407
7.405
7.403
7.395
7.390
7.385
7.380
7.343
7.335
7.327
7.323
7.318
7.311
7.227
7.221
7.214
7.210
7.206
7.199
7.186
7.158
6.788
6.762
2.844
2.351
2.091
2.070
2.062
2.055
2.048
2.040
0.135
0.001
10
9
8
7
6
5
4
3
2
1
0
ppm


152.745
147.174
141.078
140.022
138.007
136.162
135.362
134.413
132.236
131.185
131.038
130.901
130.623
130.565
129.755
129.042
128.240
128.000
127.692
125.412
124.855
124.352
115.643
30.433
30.240
30.047
29.856
29.662
29.471
29.278
21.468
0.001
ppm
Table 2, Compound 29
Ts
N
N
Ph
Ph

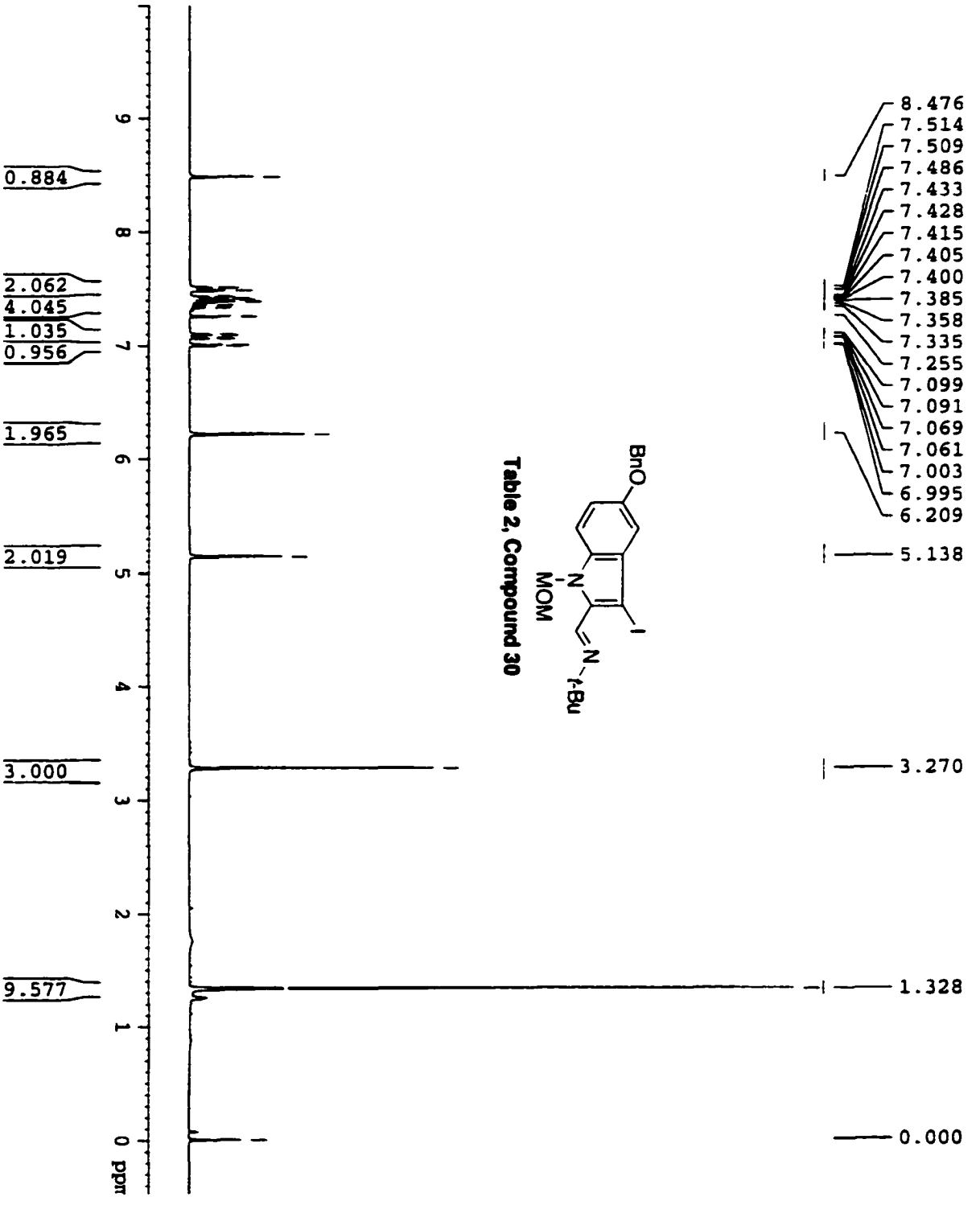
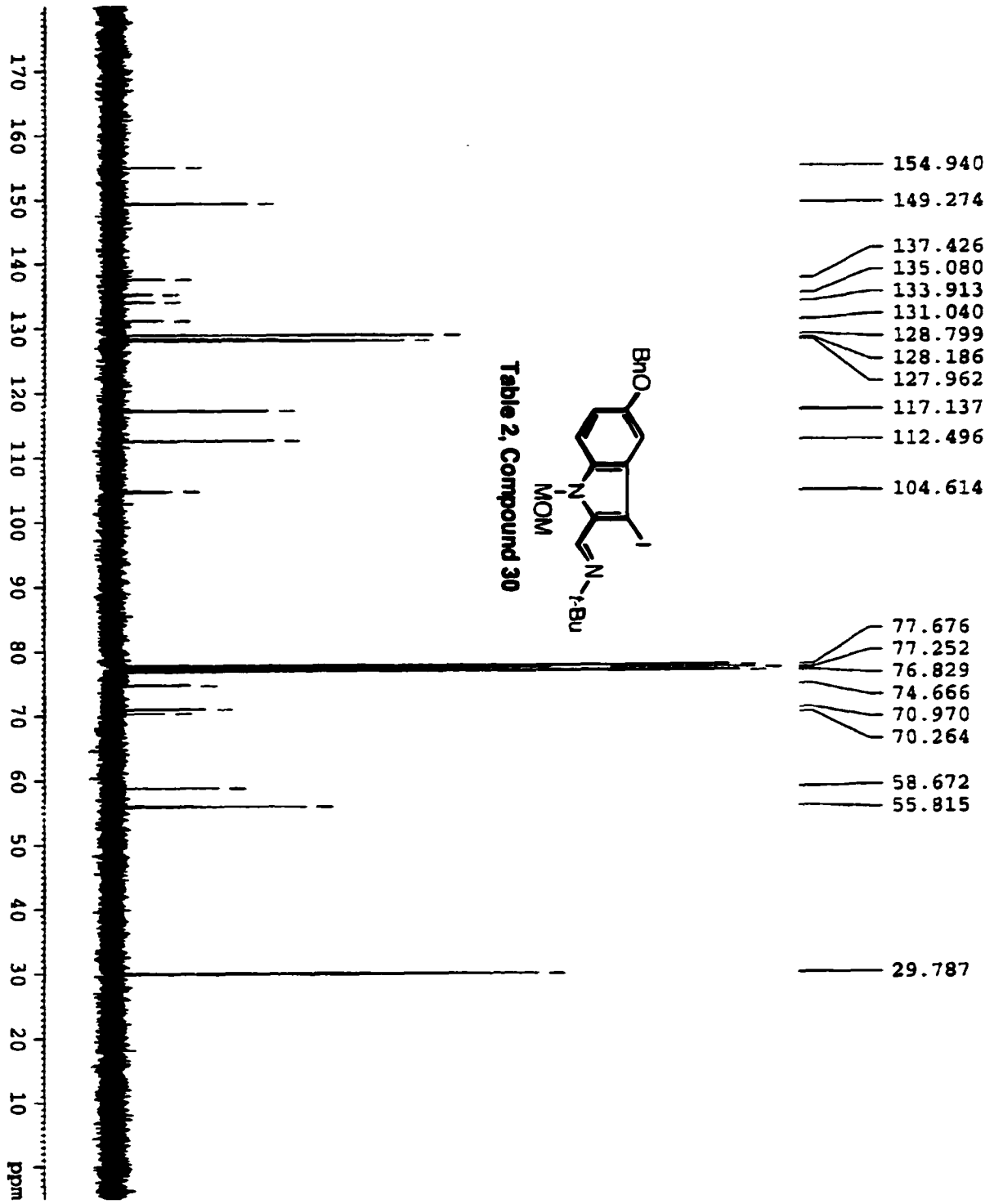


Table 2, Compound 30


154.940
149.274
137.426
135.080
133.913
131.040
128.799
128.186
127.962
117.137
112.496
104.614
77.676
77.252
76.829
74.666
70.970
70.264
58.672
55.815
29.787
BnO
MOM
N
N
t-Bu
I
Table 2, Compound 30
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

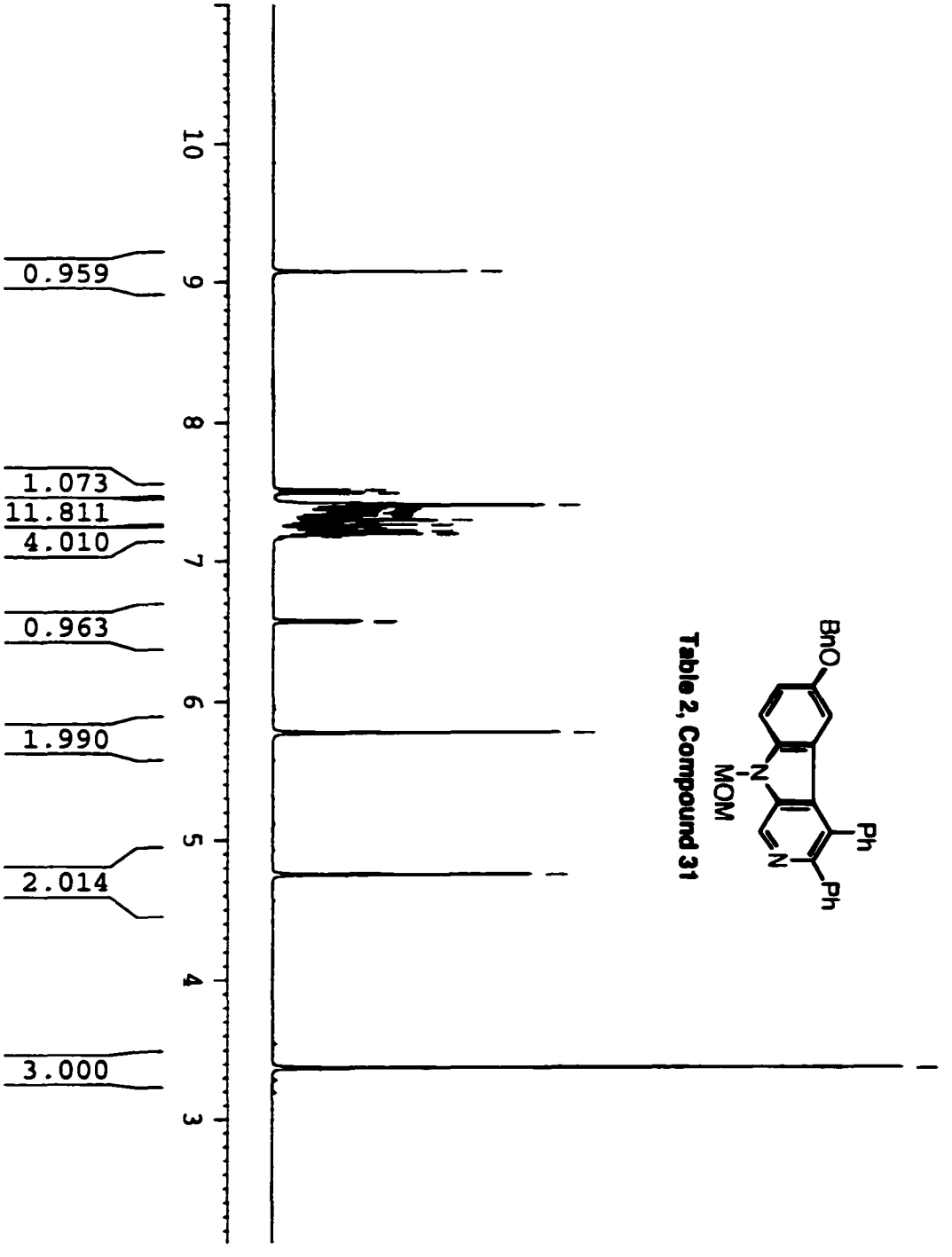
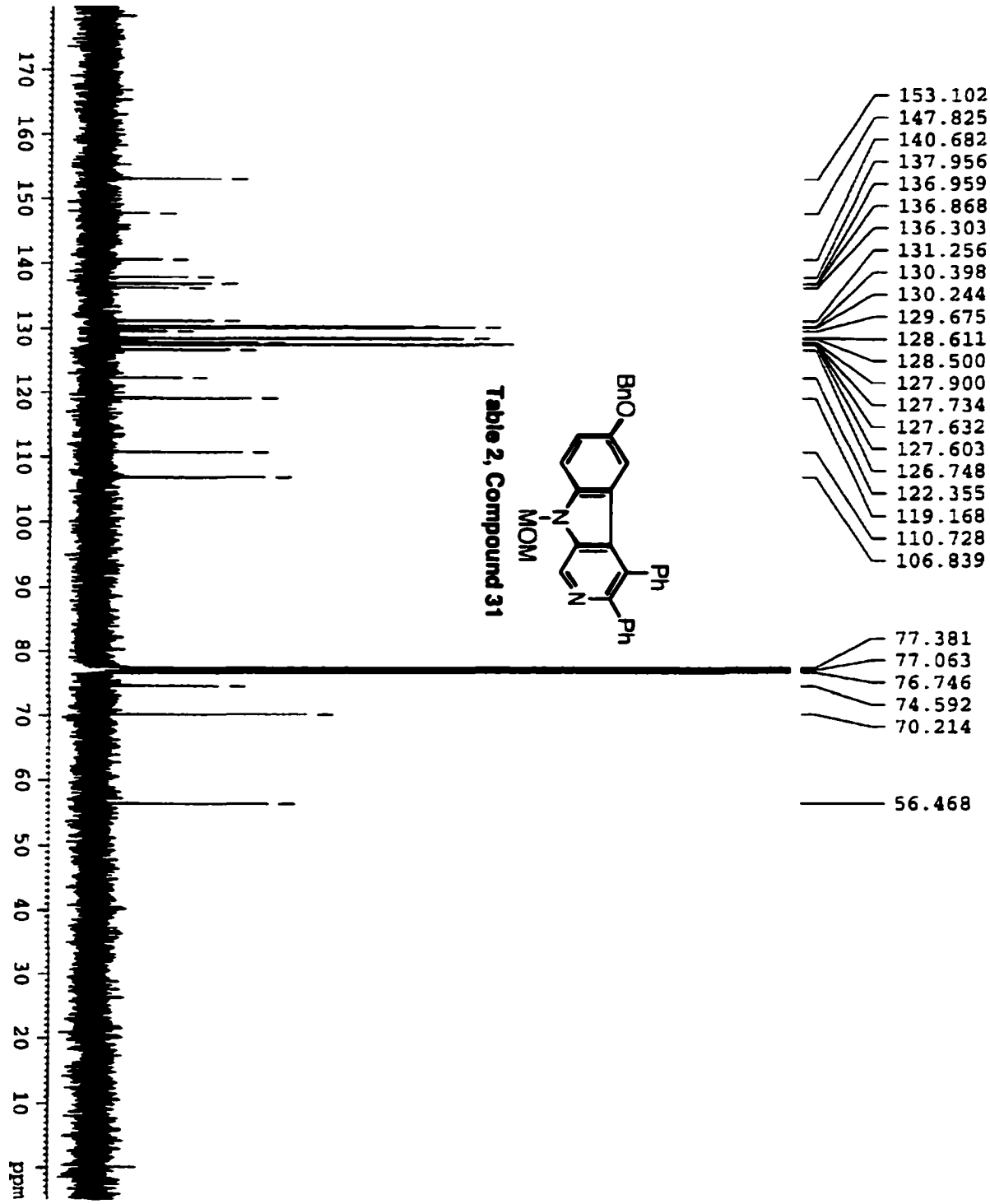
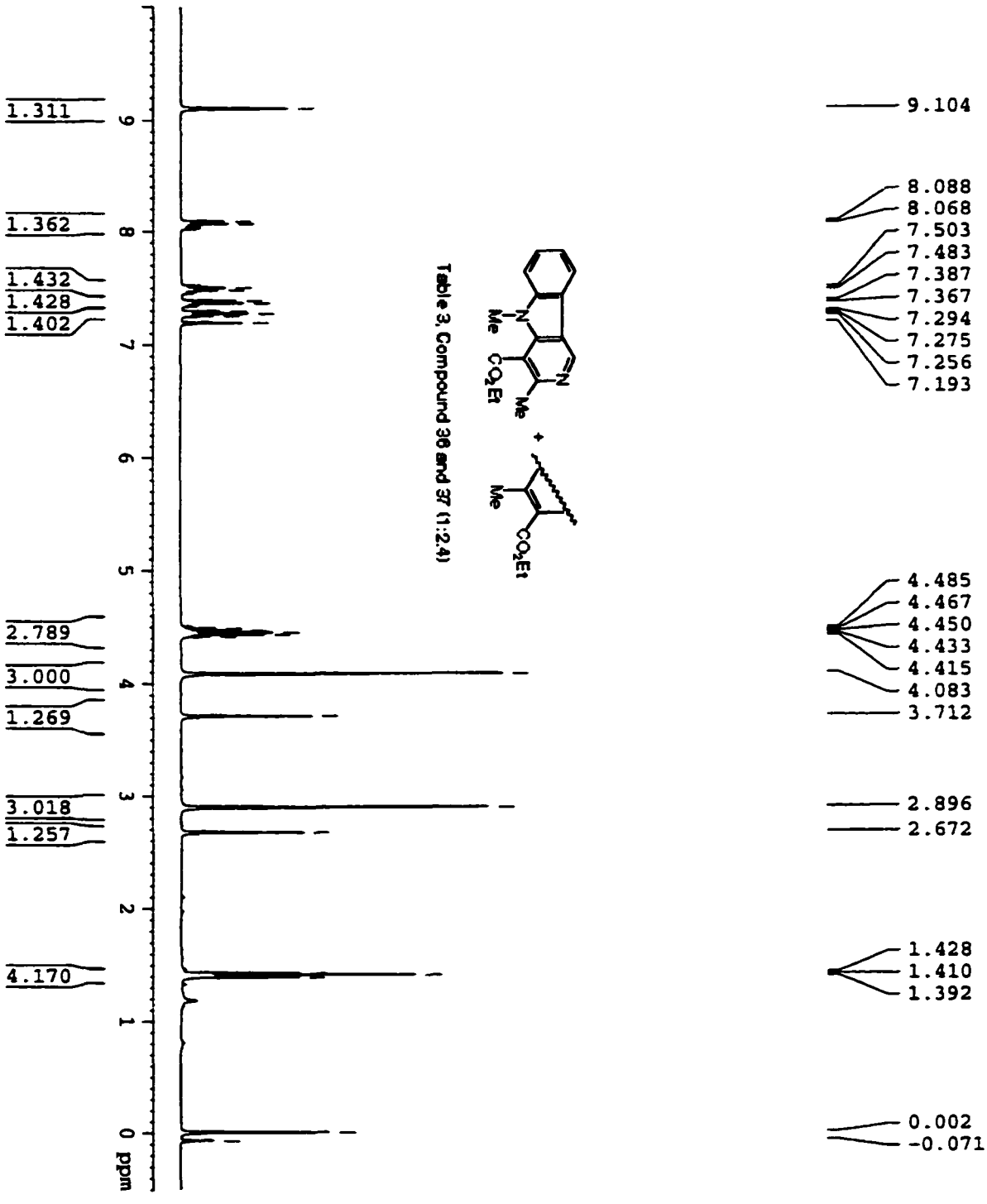


Table 2, Compound 31


153.102
147.825
140.682
137.956
136.959
136.868
136.303
131.256
130.398
130.244
129.675
128.611
128.500
127.900
127.734
127.632
127.603
126.748
122.355
119.168
110.728
106.839
77.381
77.063
76.746
74.592
70.214
56.468
BnO
N
MOM
N
Ph
Ph
Table 2, Compound 31
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10
ppm


1.311
1.362
1.432
1.428
1.402
2.789
3.000
1.269
3.018
1.257
4.170
9 8 7 6 5 4 3 2 1 0 ppm
Table 3. Compound 36 and 37 (1:2.4)
Me
CO2Et
Me
Me
CO2Et
9.104
8.088
8.068
7.503
7.483
7.387
7.367
7.294
7.275
7.256
7.193
4.485
4.467
4.450
4.433
4.415
4.083
3.712
2.896
2.672
1.428
1.410
1.392
0.002
-0.071

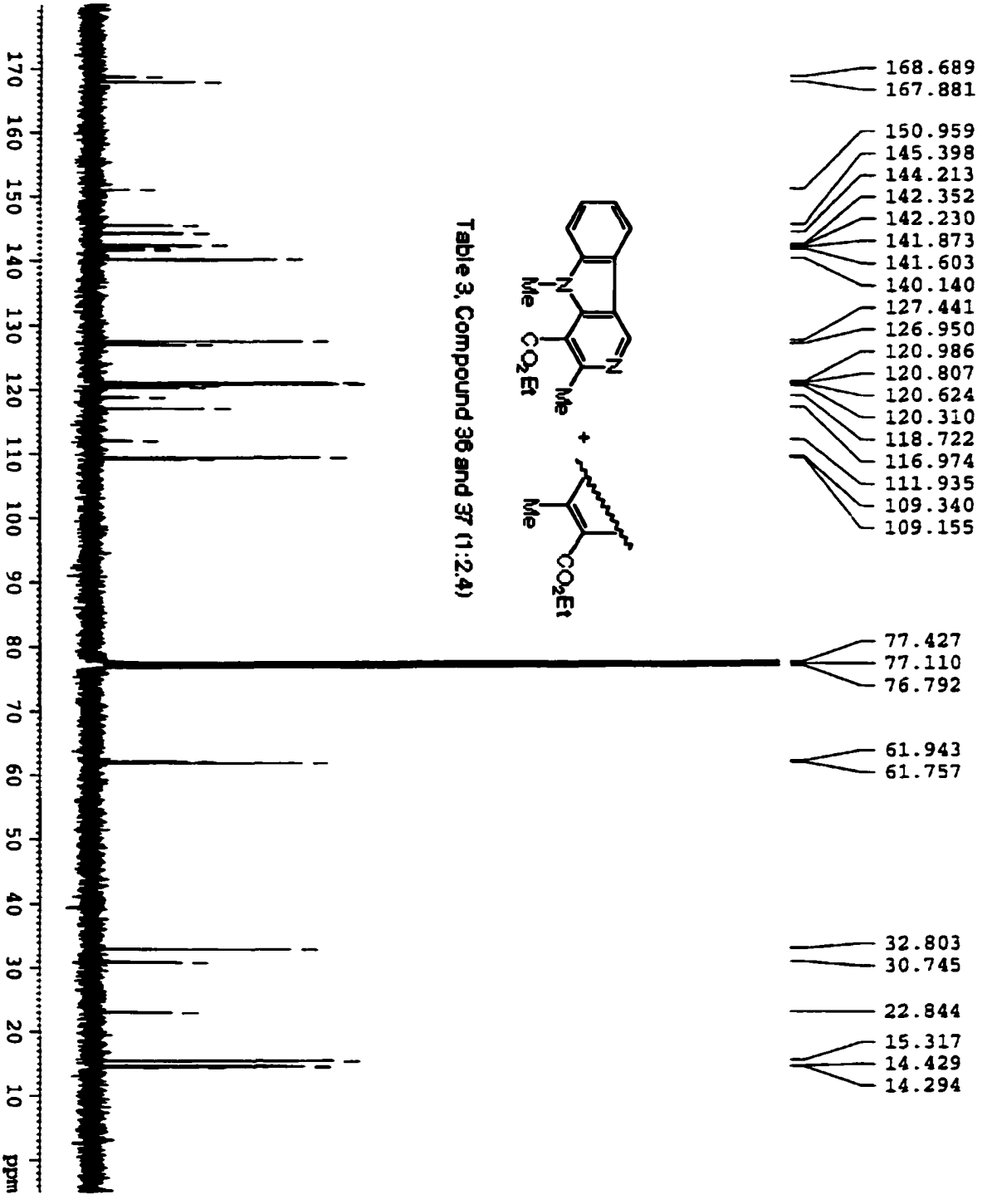


Table 3. Compound 36 and 37 (1:2.4)

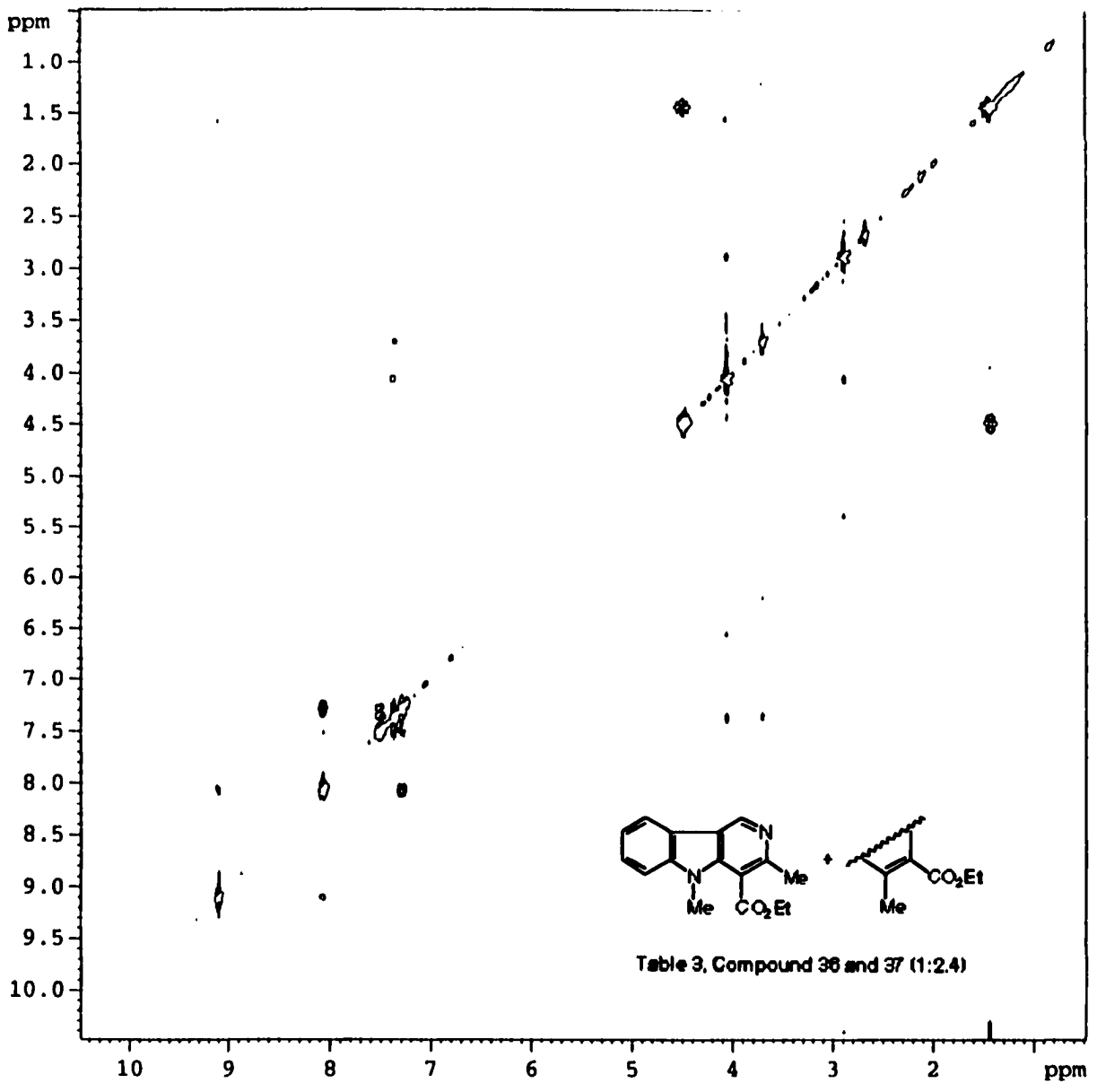
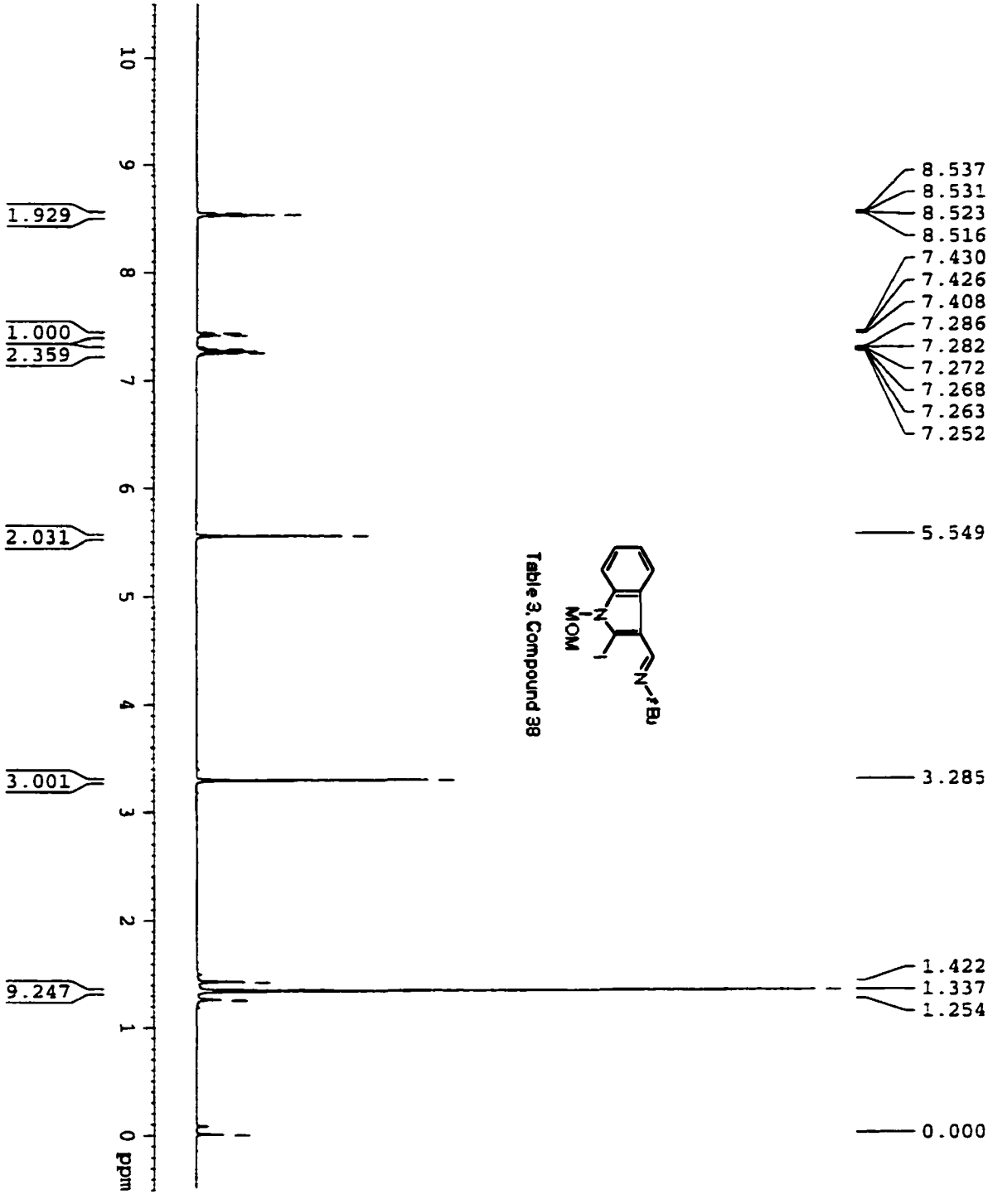
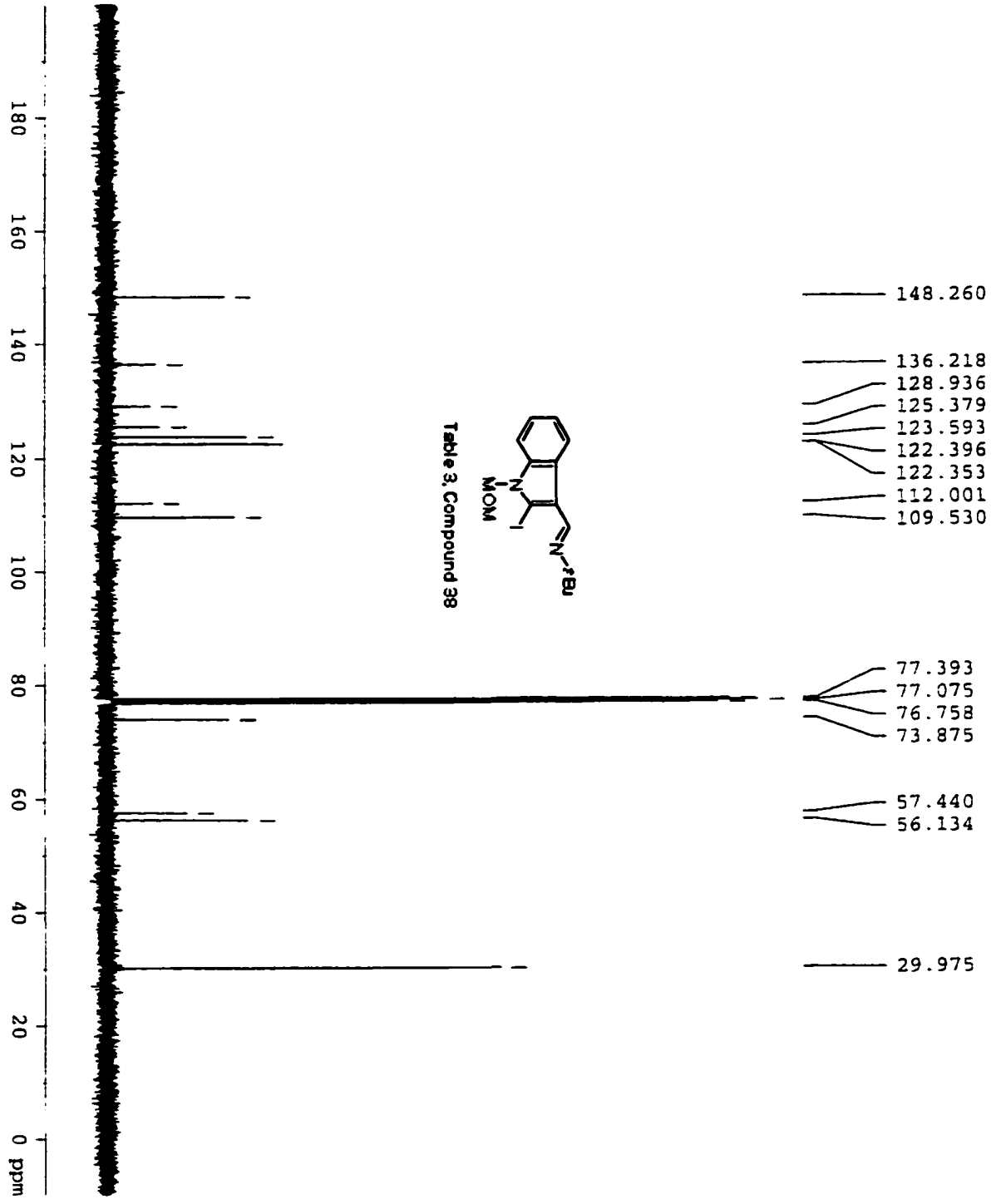
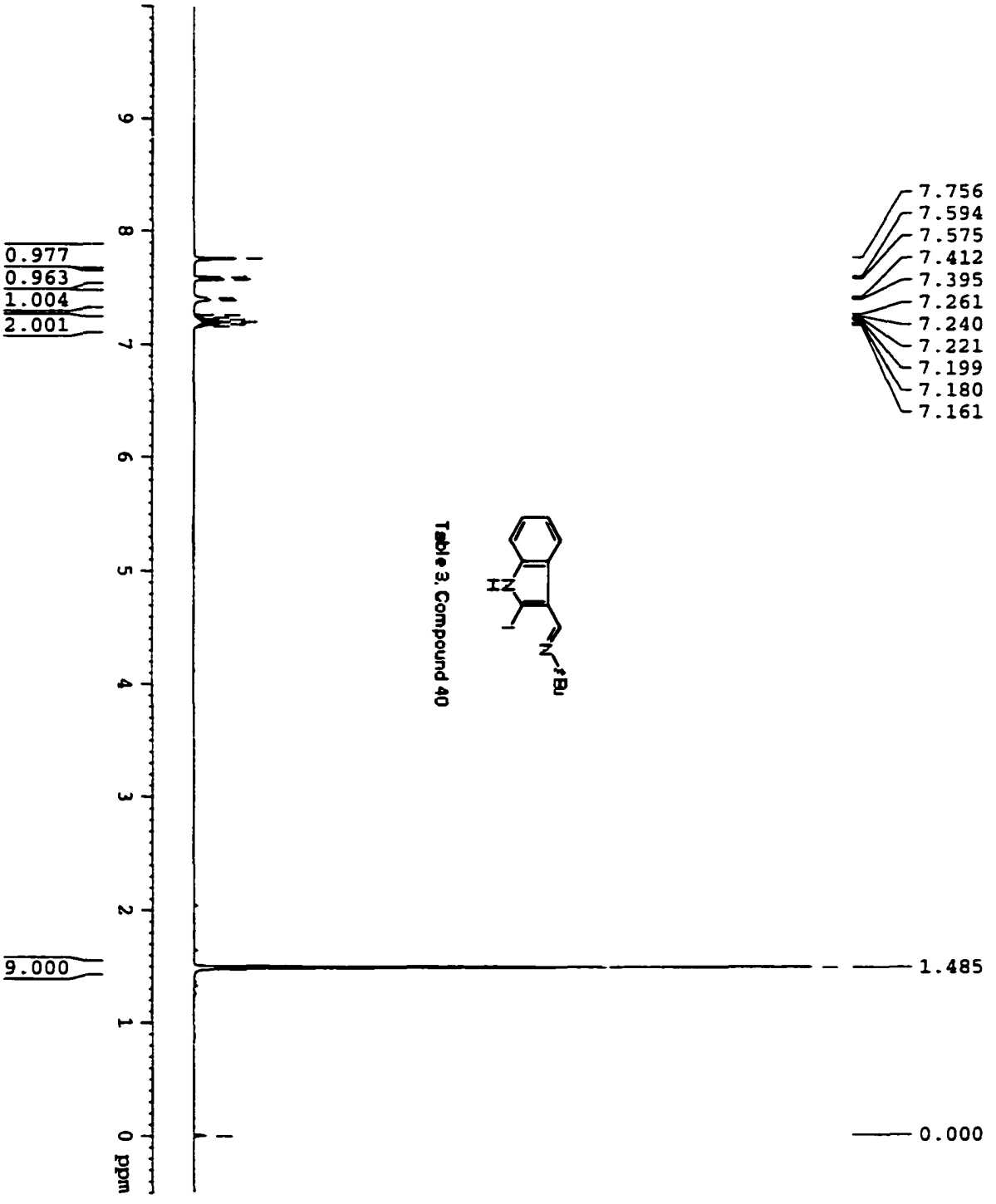
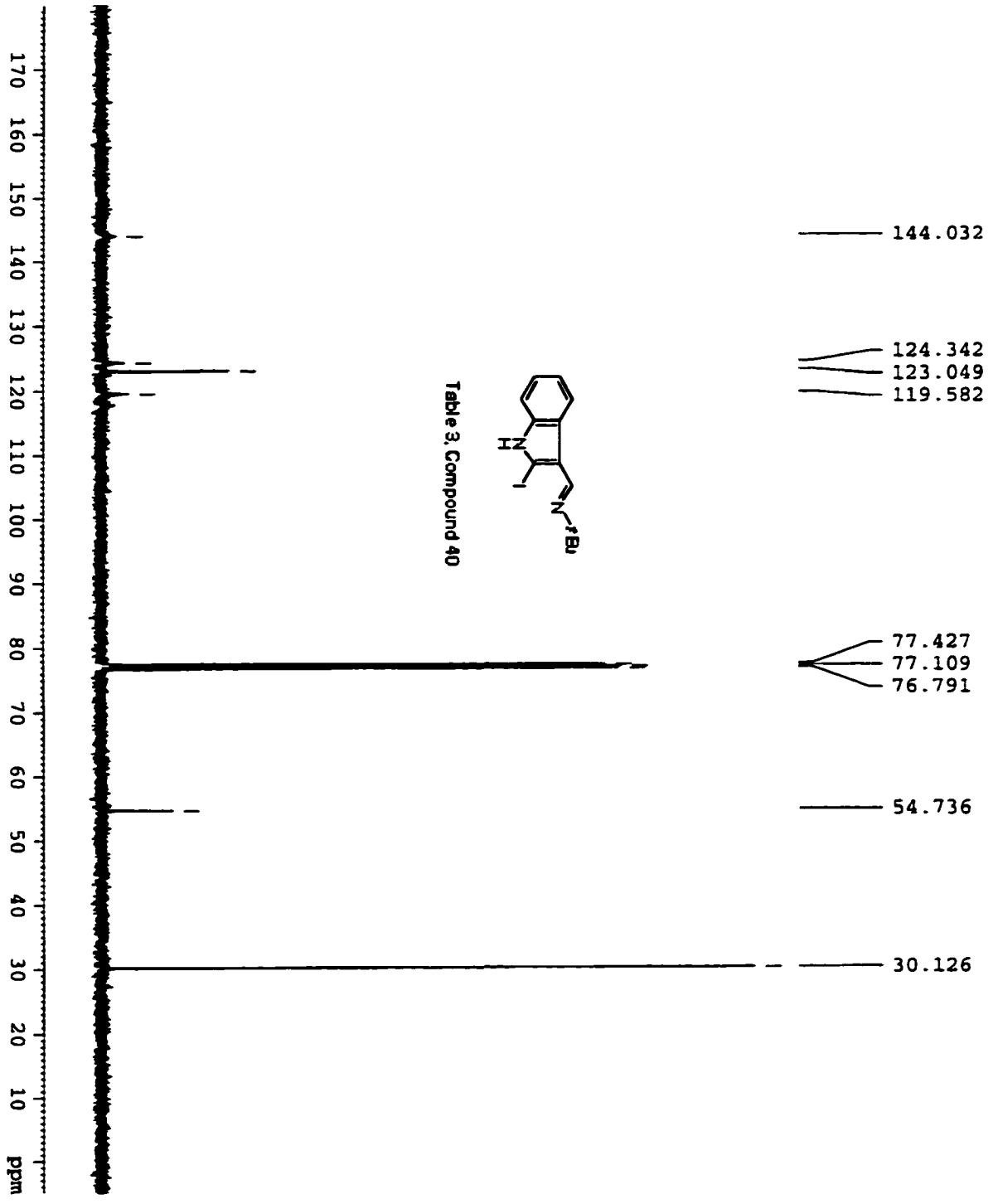


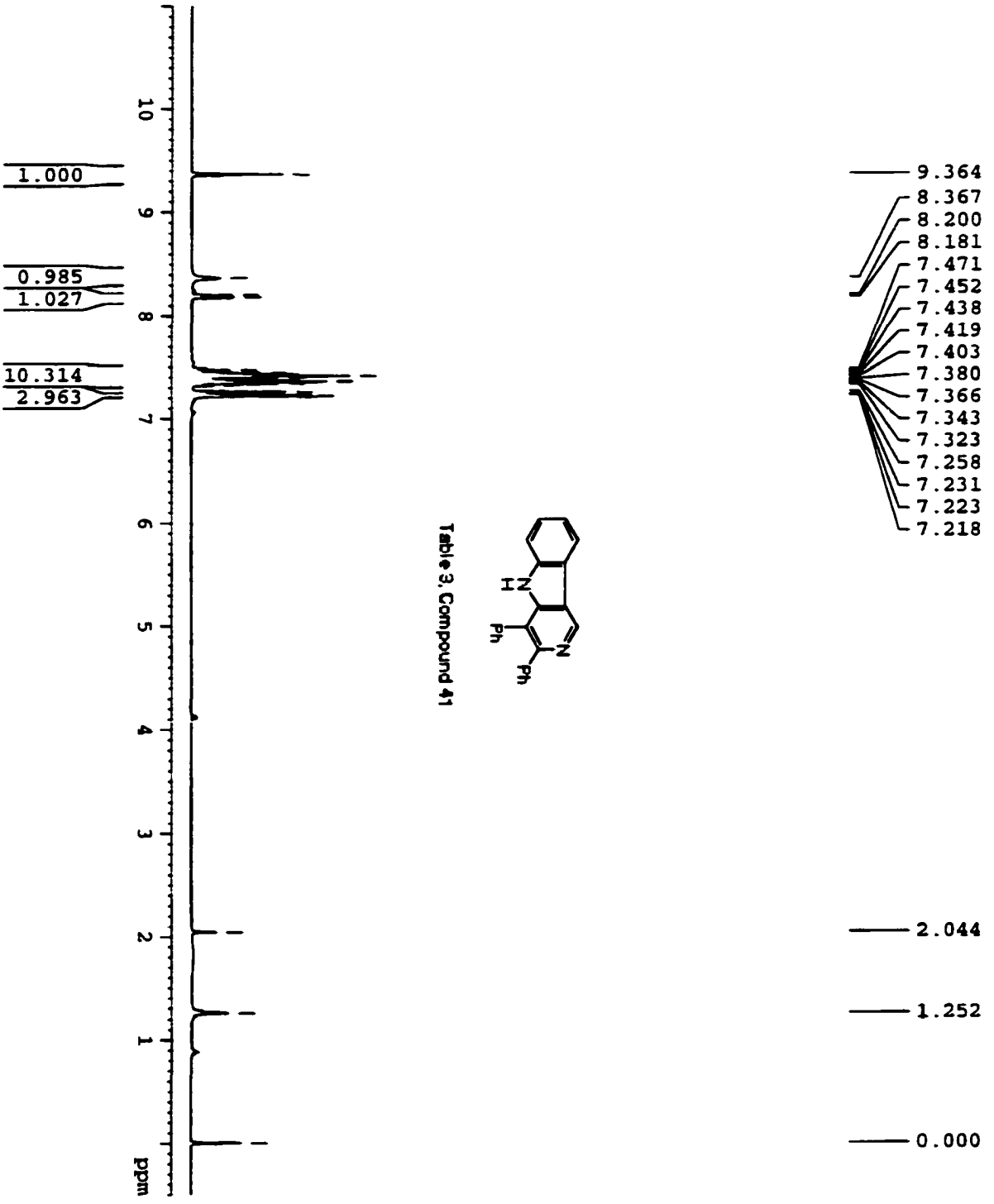
Table 3, Compound 36 and 37 (1:2.4)

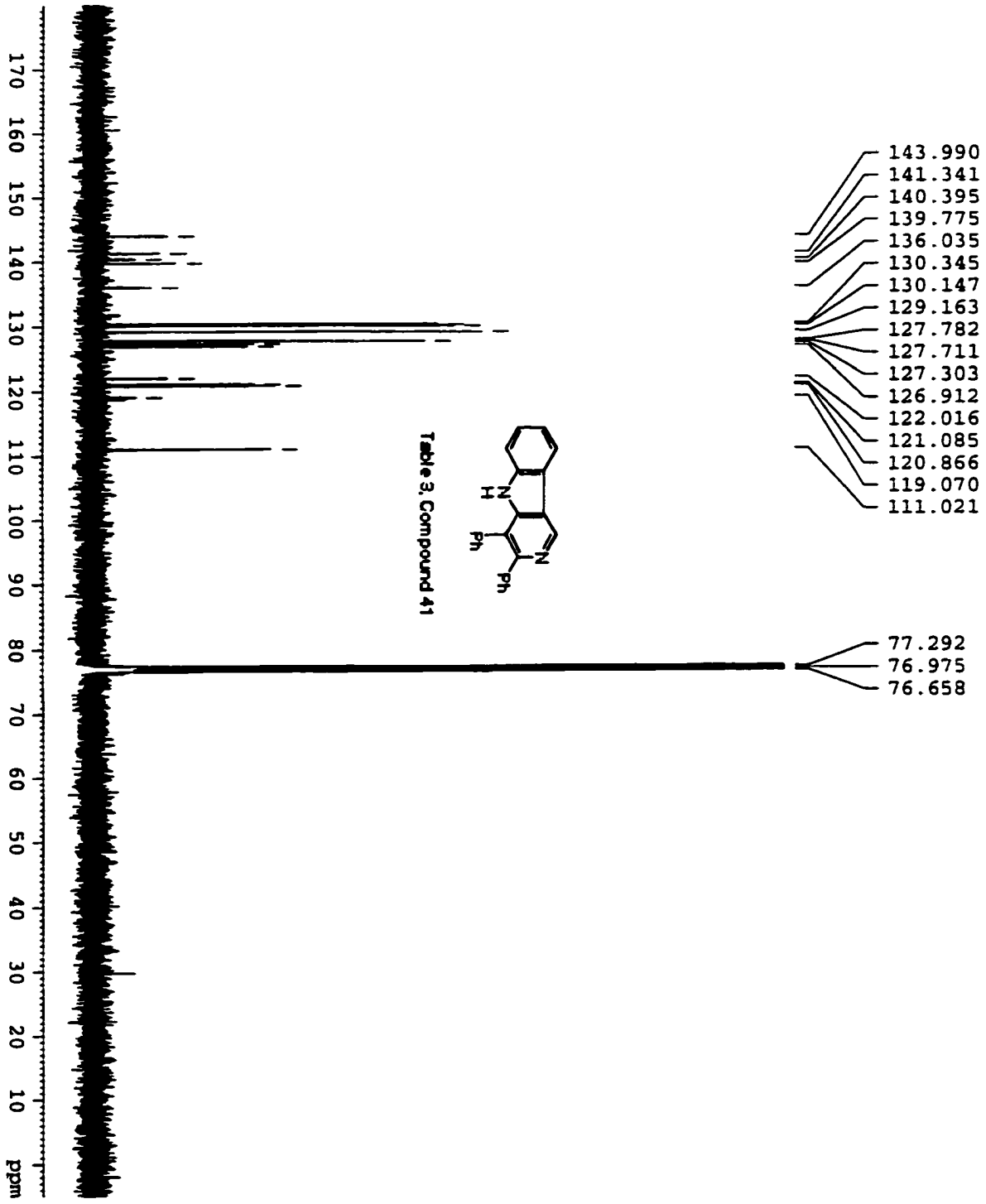

8.537
8.531
8.523
8.516
7.430
7.426
7.408
7.286
7.282
7.272
7.268
7.263
7.252
5.549
3.285
1.422
1.337
1.254
0.000
1.929
1.000
2.359
2.031
3.001
9.247
10
9
8
7
6
5
4
3
2
1
0 ppm
Table 3. Compound 38
MOM
N
tBu

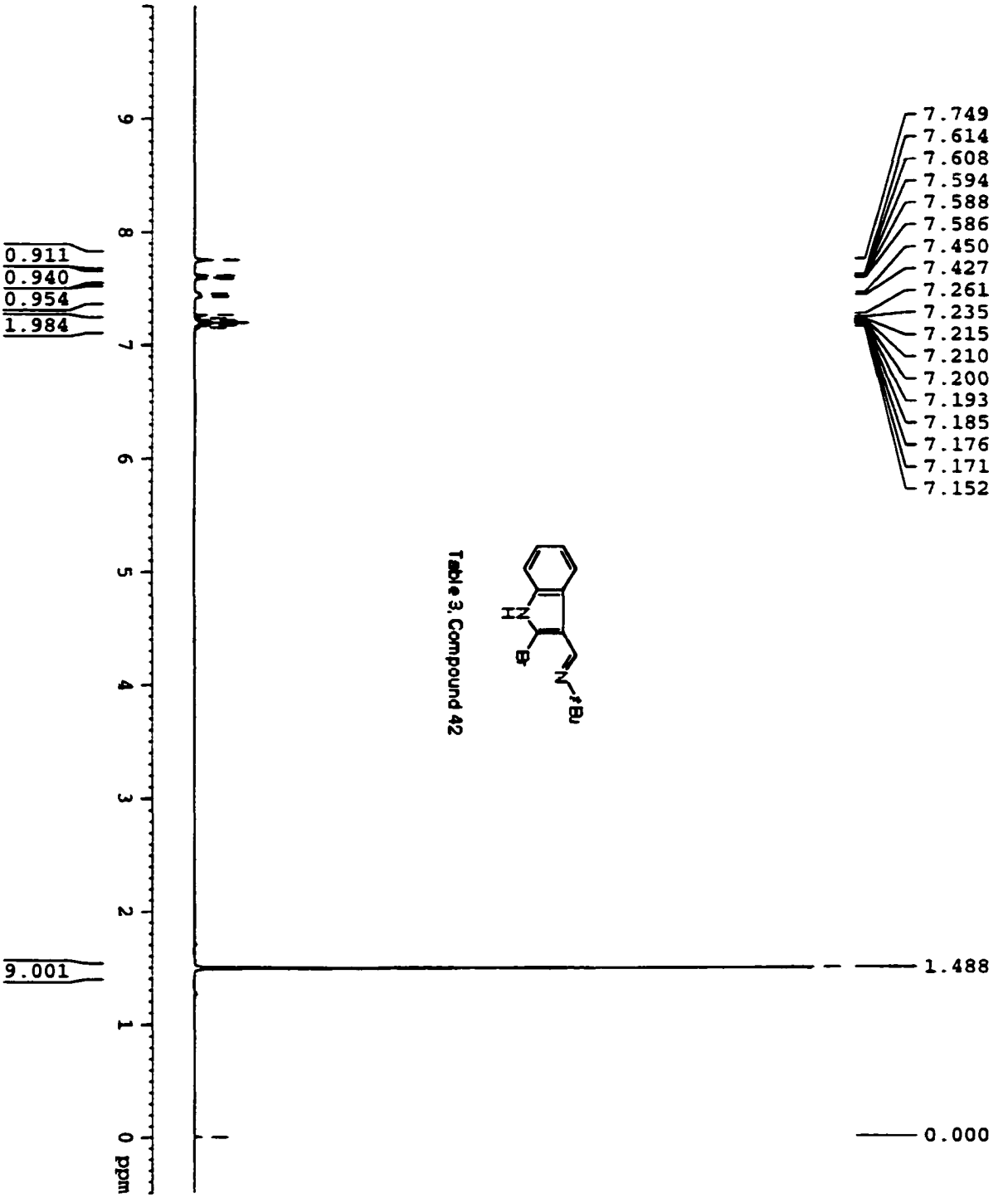

148.260
136.218
128.936
125.379
123.593
122.396
122.353
112.001
109.530
77.393
77.075
76.758
73.875
57.440
56.134
29.975
180
160
140
120
100
80
60
40
20
0 ppm
Table 3. Compound 38
MOM
N
N
tBu

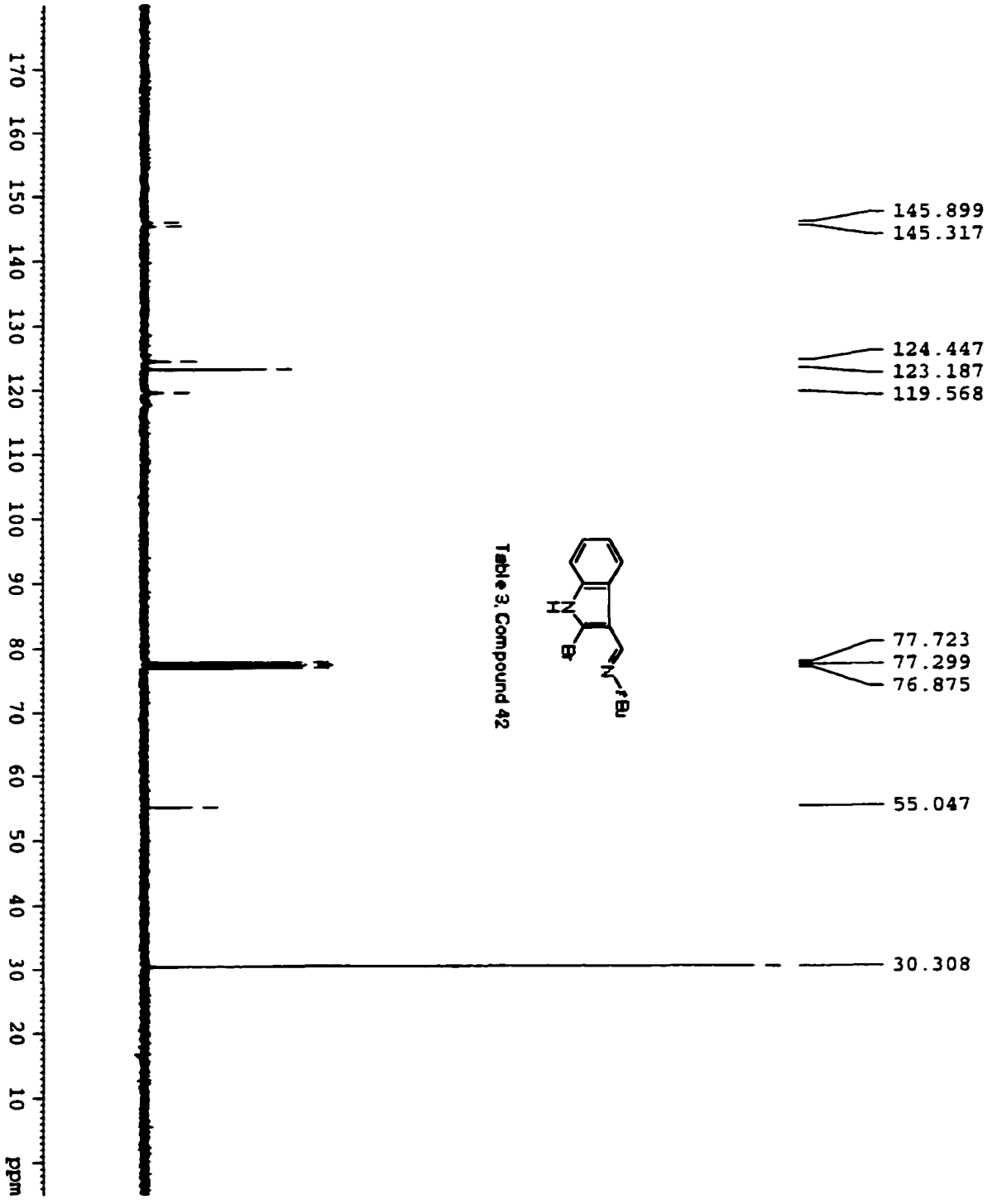

7.756
7.594
7.575
7.412
7.395
7.261
7.240
7.221
7.199
7.180
7.161
0.977
0.963
1.004
2.001
9.000
1.485
0.000
ppm
Table 3. Compound 40

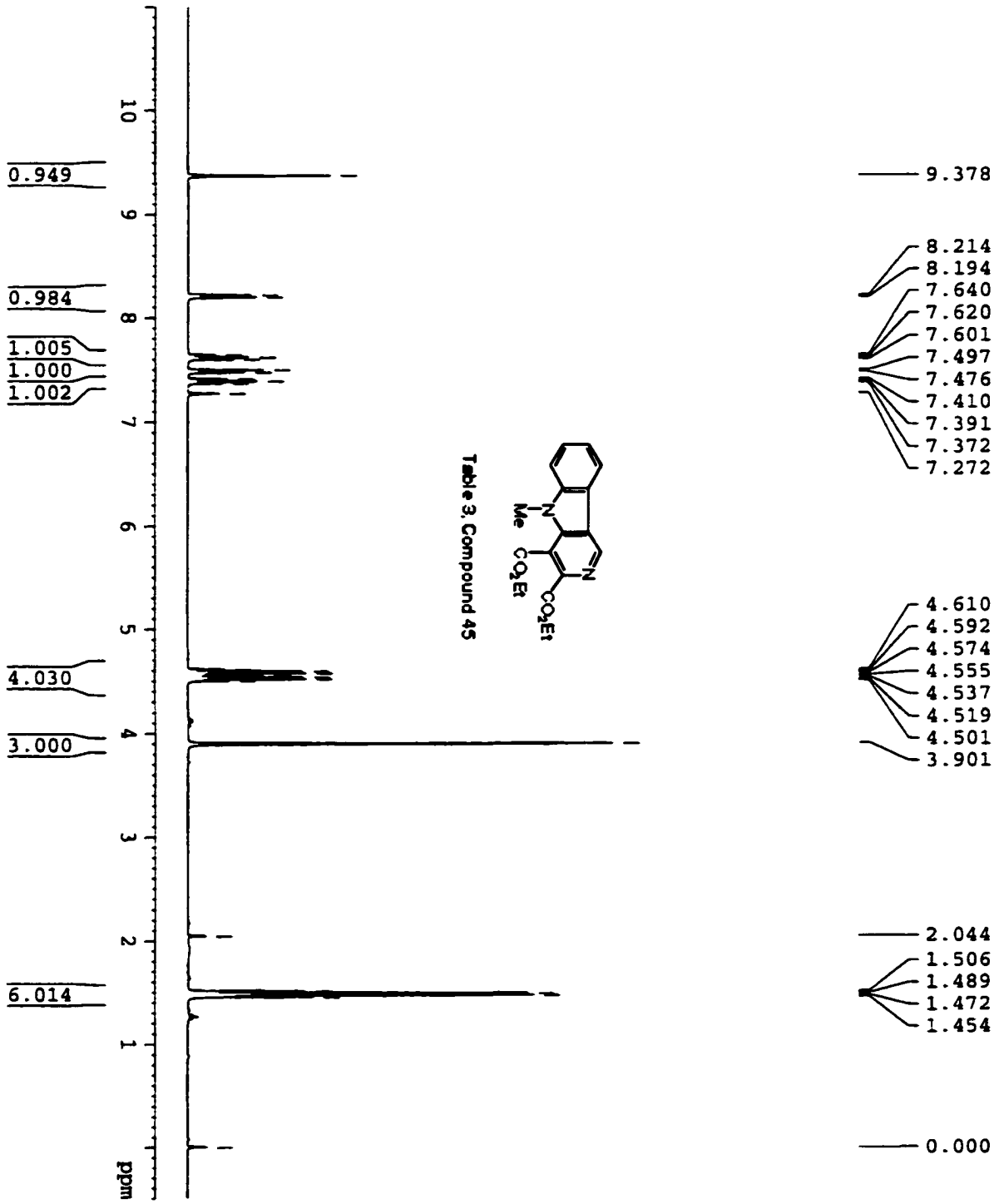

144.032
124.342
123.049
119.582
77.427
77.109
76.791
54.736
30.126
Table 3, Compound 40
ppm

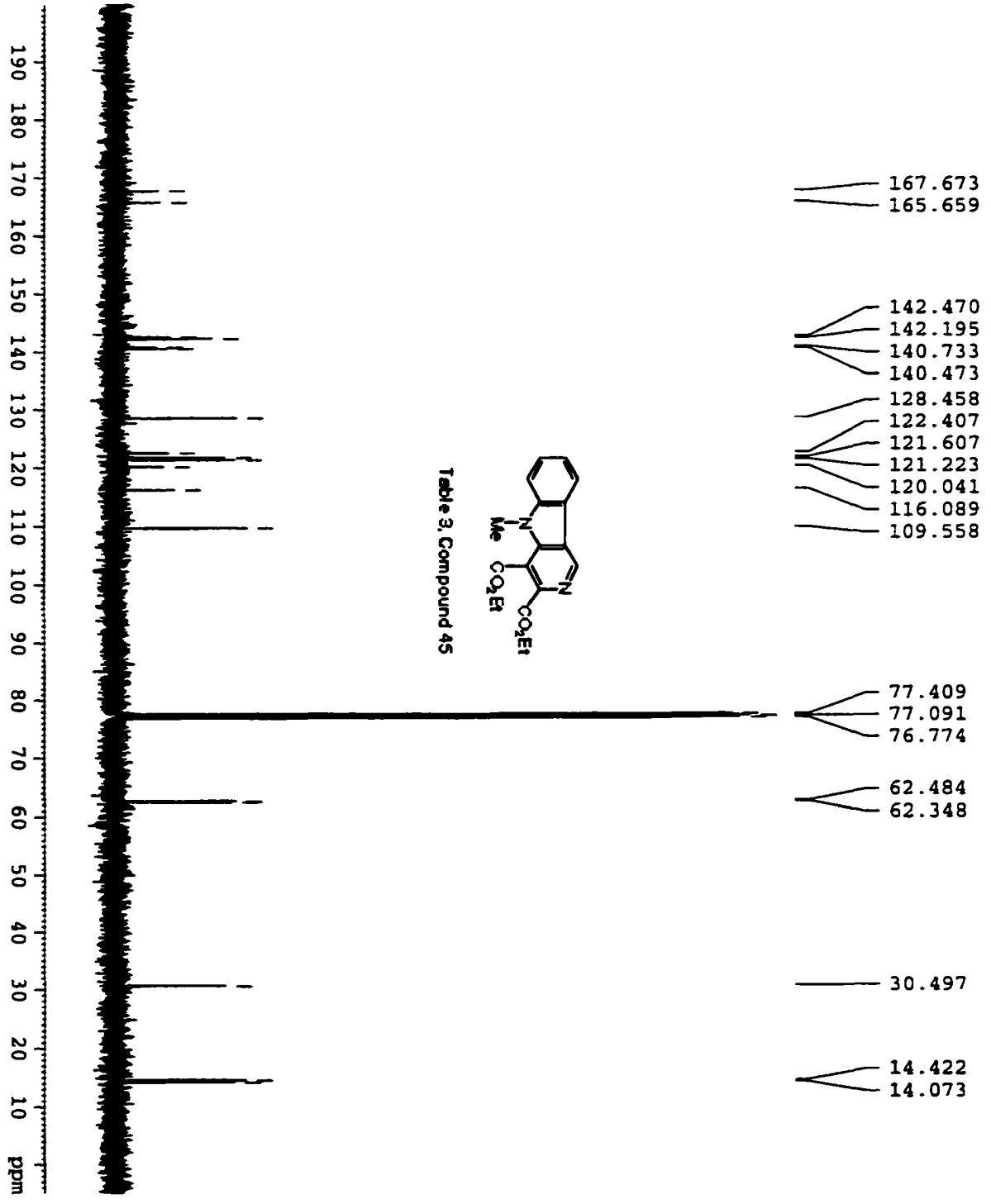

1.000
0.985
1.027
10.314
2.963
ppm
9.364
8.367
8.200
8.181
7.471
7.452
7.438
7.419
7.403
7.380
7.366
7.343
7.323
7.258
7.231
7.223
7.218
2.044
1.252
0.000
Table 3. Compound 41
N
H
Ph
N
Ph

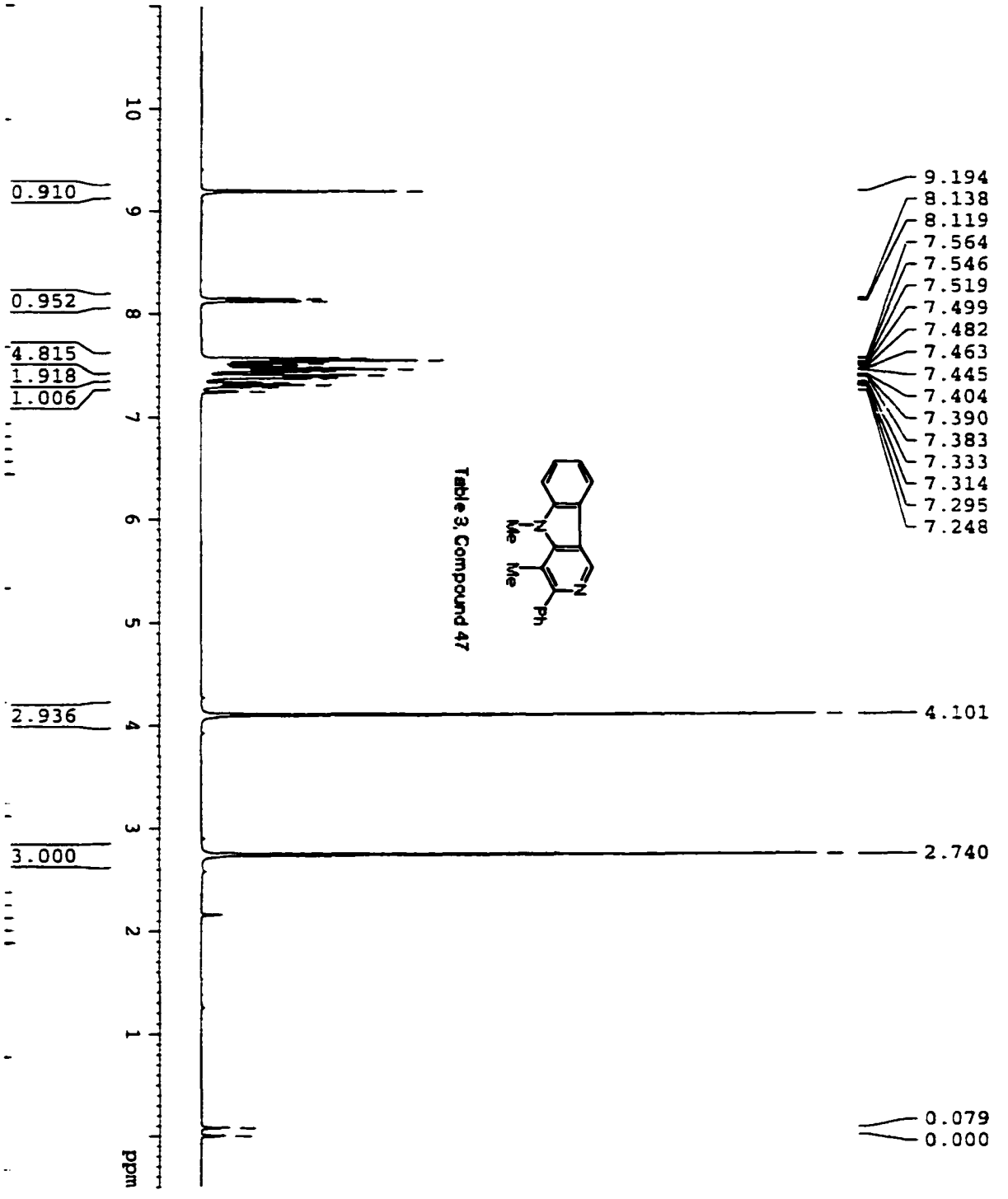

143.990
141.341
140.395
139.775
136.035
130.345
130.147
129.163
127.782
127.711
127.303
126.912
122.016
121.085
120.866
119.070
111.021
77.292
76.975
76.658
Table 3. Compound 41
H
N
Ph
N
Ph
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


7.749
7.614
7.608
7.594
7.588
7.586
7.450
7.427
7.261
7.235
7.215
7.210
7.200
7.193
7.185
7.176
7.171
7.152
0.911
0.940
0.954
1.984
9.001
1.488
0.000
ppm
Table 3. Compound 42
H
N
Br
N
tBu


145.899
145.317
124.447
123.187
119.568
77.723
77.299
76.875
55.047
30.308
ppm
Table 3. Compound 42


0.949
0.984
1.005
1.000
1.002
4.030
3.000
6.014
ppm
Table 3. Compound 45
Me
CO2Et
CO2Et
9.378
8.214
8.194
7.640
7.620
7.601
7.497
7.476
7.410
7.391
7.372
7.272
4.610
4.592
4.574
4.555
4.537
4.519
4.501
3.901
2.044
1.506
1.489
1.472
1.454
0.000


167.673
165.659
142.470
142.195
140.733
140.473
128.458
122.407
121.607
121.223
120.041
116.089
109.558
77.409
77.091
76.774
62.484
62.348
30.497
14.422
14.073
Table 3. Compound 45
Me
CO2Et
CO2Et
ppm


9.194
8.138
8.119
7.564
7.546
7.519
7.499
7.482
7.463
7.445
7.404
7.390
7.383
7.333
7.314
7.295
7.248
4.101
2.740
0.079
0.000
0.910
0.952
4.815
1.918
1.006
2.936
3.000
ppm
Table 3, Compound 47
Me
Me
Ph

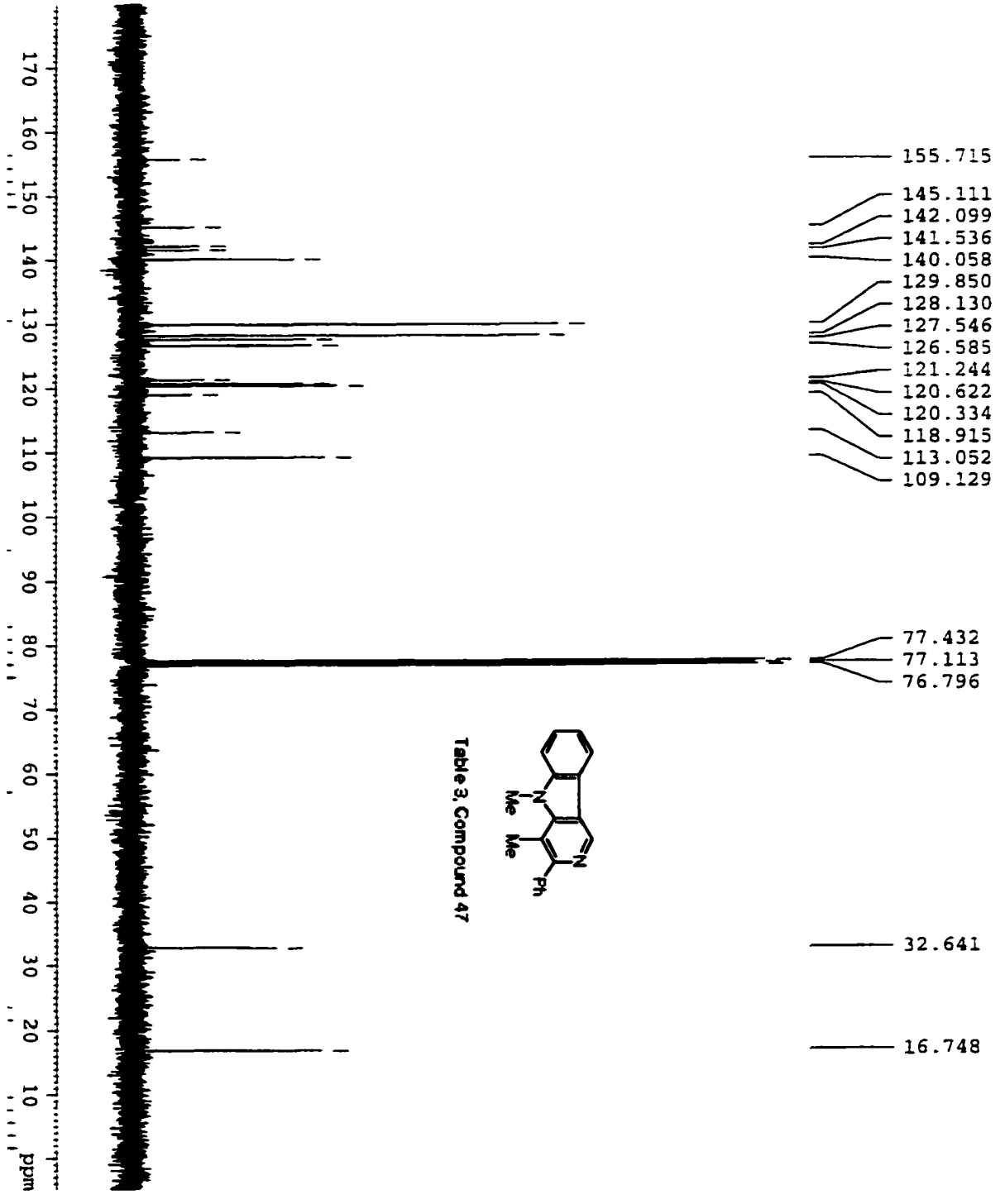


Table 3. Compound 47

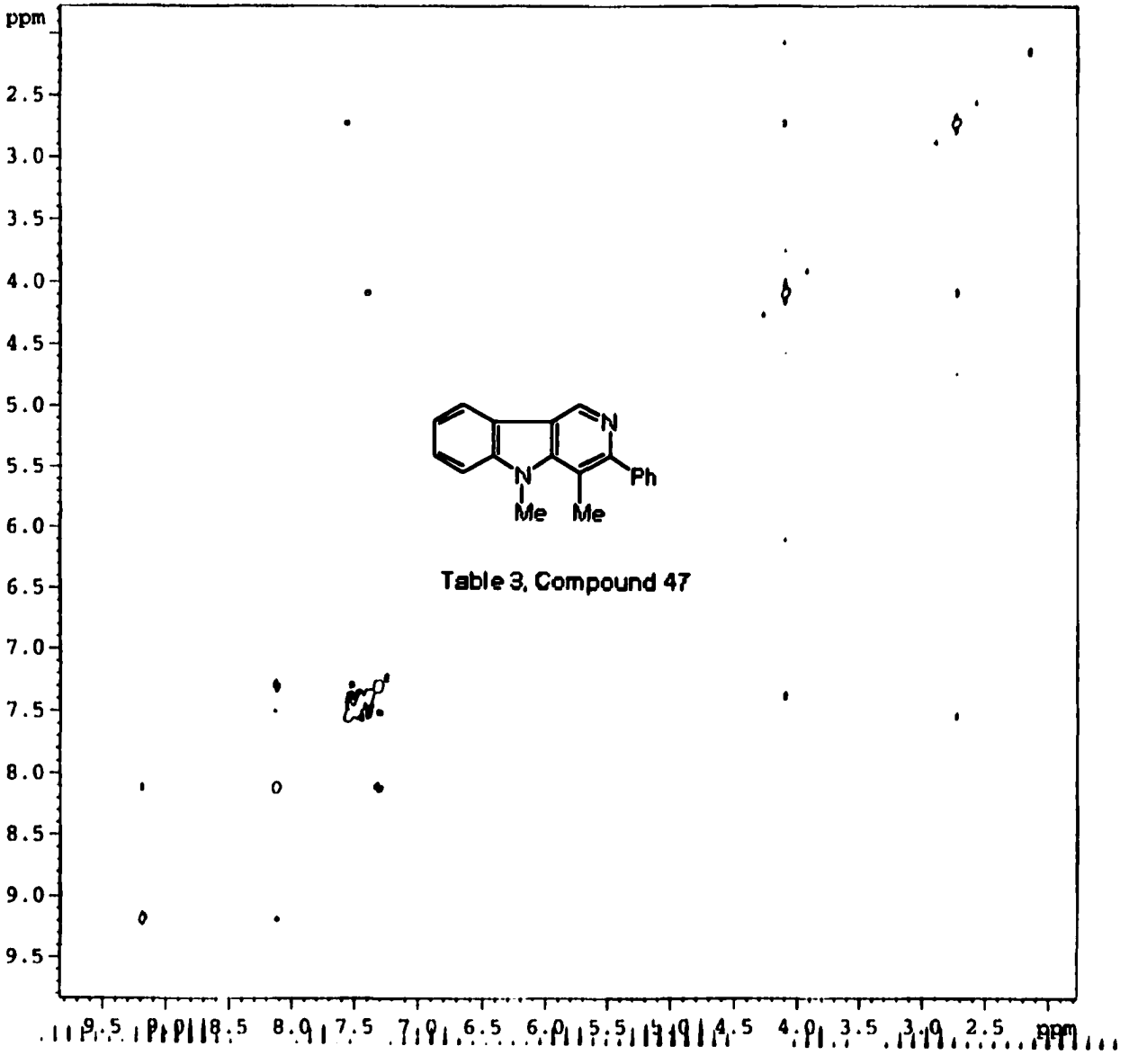
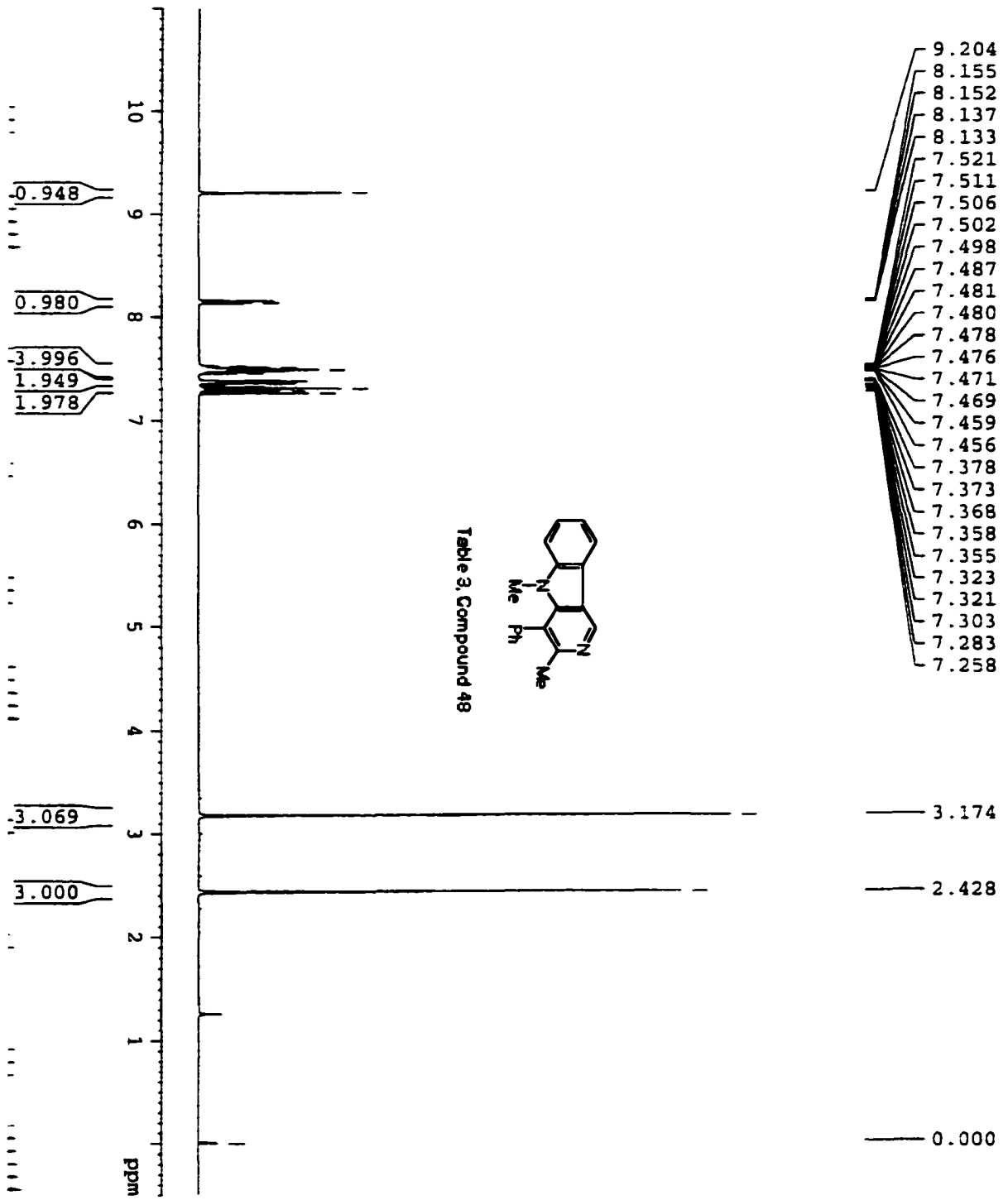
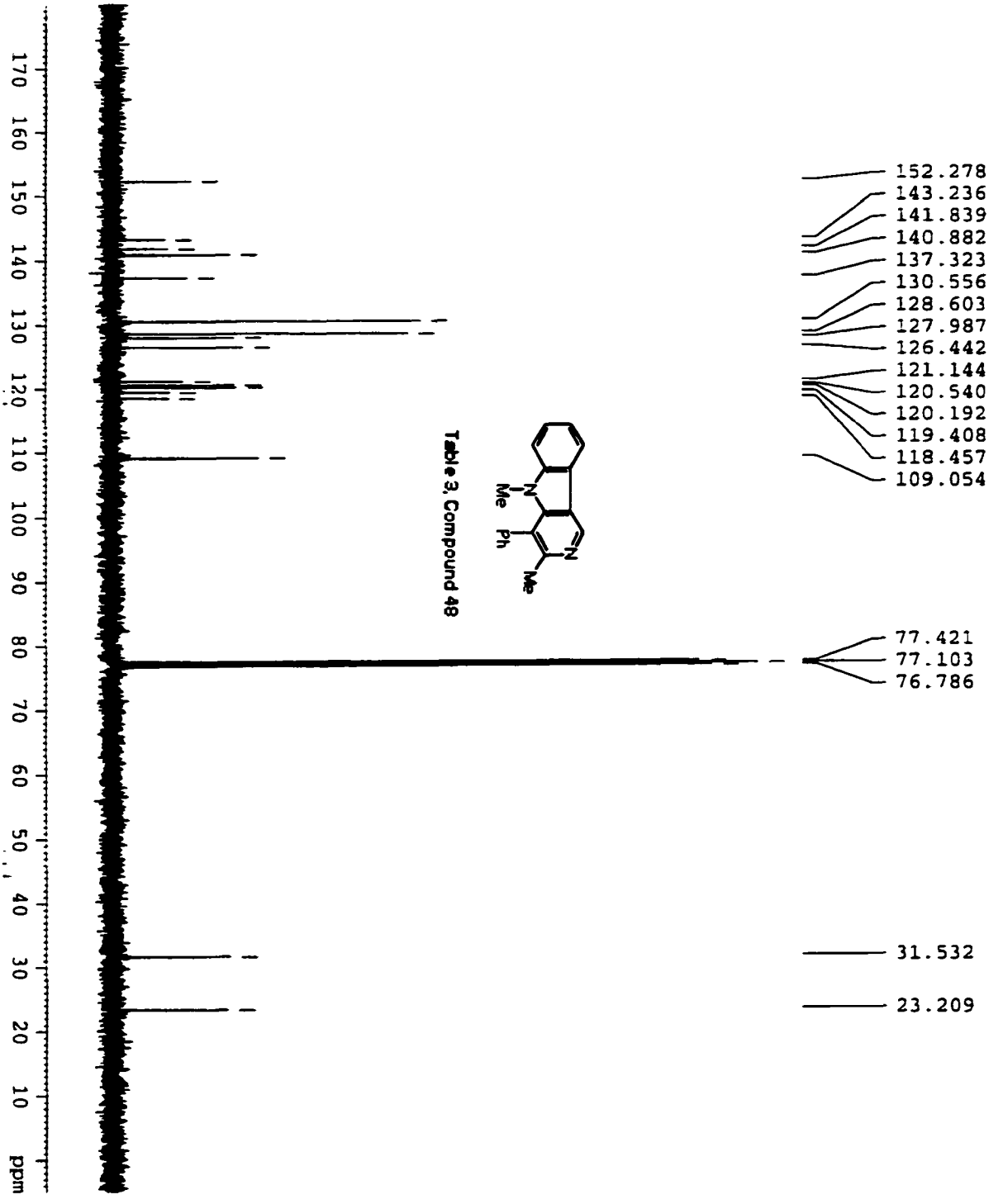


Table 3, Compound 47


9.204
8.155
8.152
8.137
8.133
7.521
7.511
7.506
7.502
7.498
7.487
7.481
7.480
7.478
7.476
7.471
7.469
7.459
7.456
7.378
7.373
7.368
7.358
7.355
7.323
7.321
7.303
7.283
7.258
3.174
2.428
0.000
0.948
0.980
3.996
1.949
1.978
3.069
3.000
ppm
Table 3, Compound 48
Me
Ph
Me


152.278
143.236
141.839
140.882
137.323
130.556
128.603
127.987
126.442
121.144
120.540
120.192
119.408
118.457
109.054
77.421
77.103
76.786
31.532
23.209
Table 3, Compound 48
Me
Ph
N
Me
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

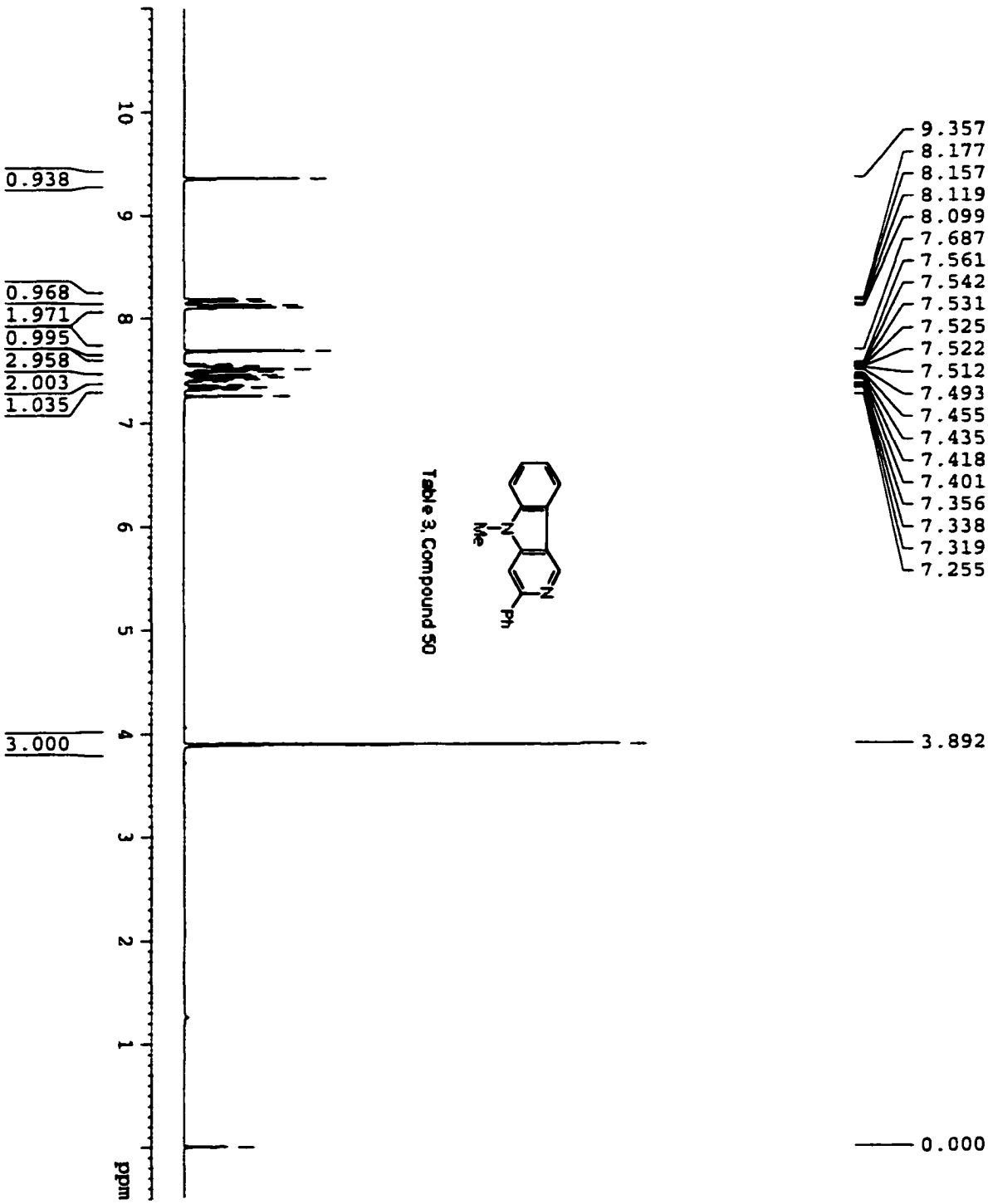
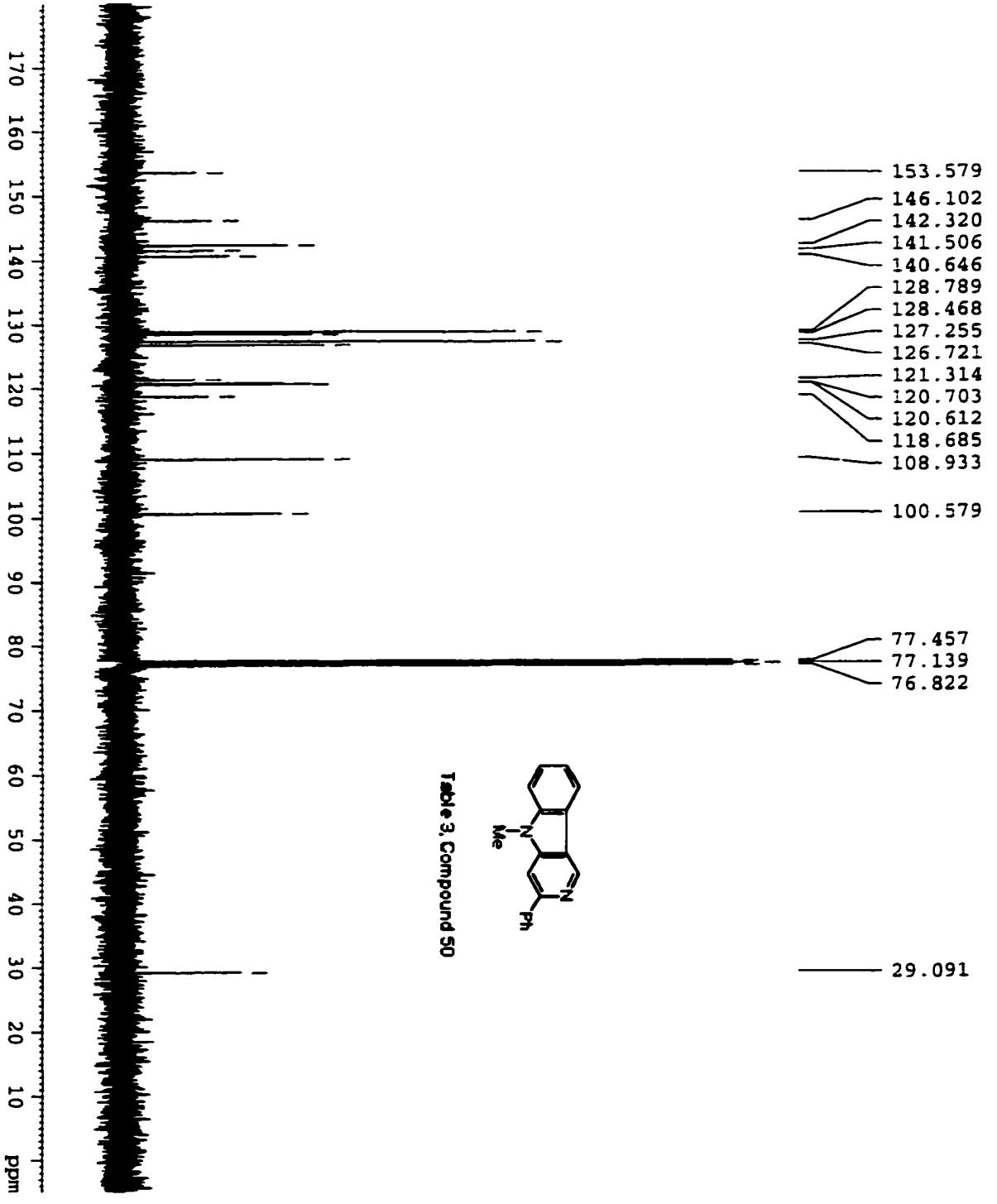
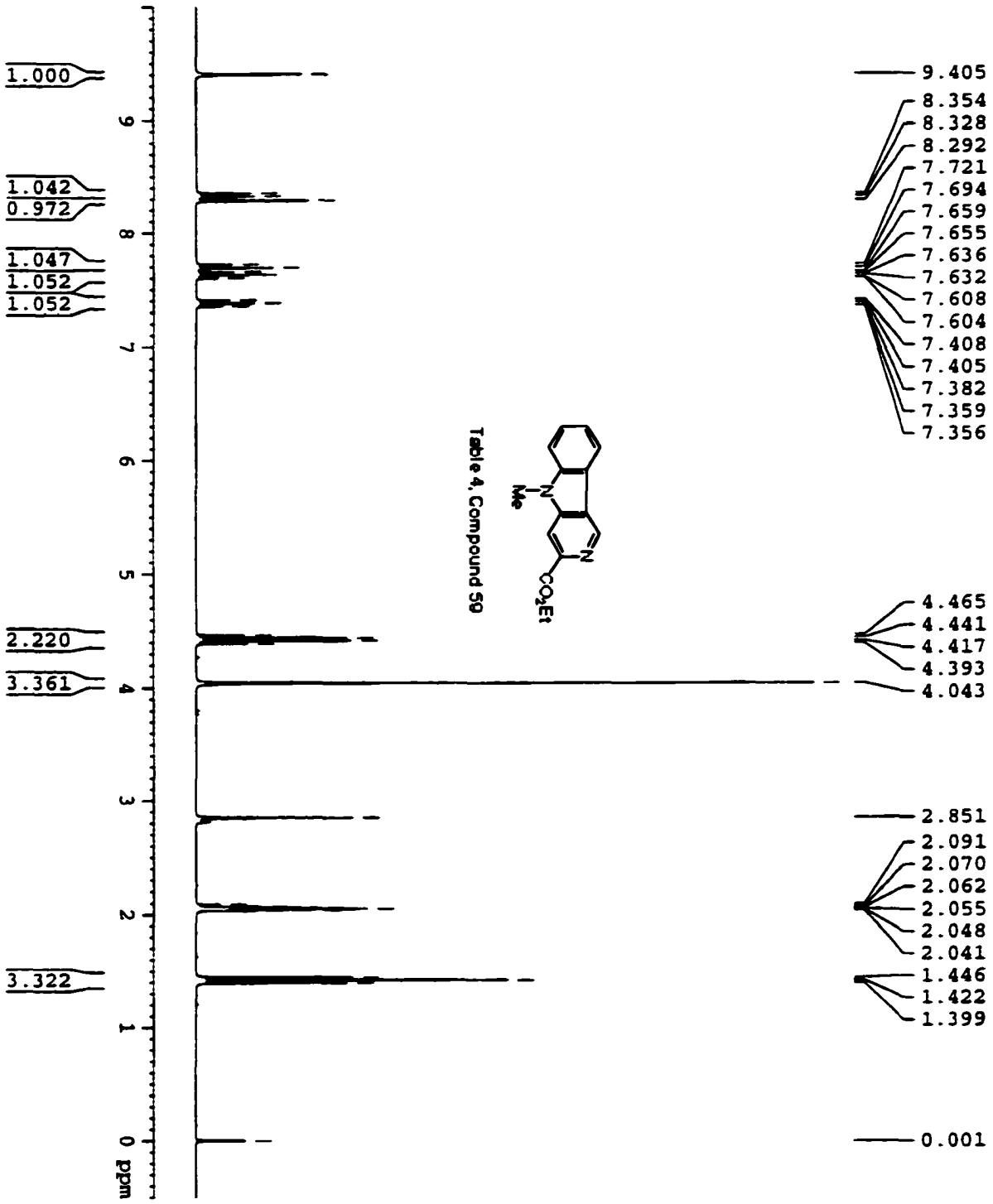
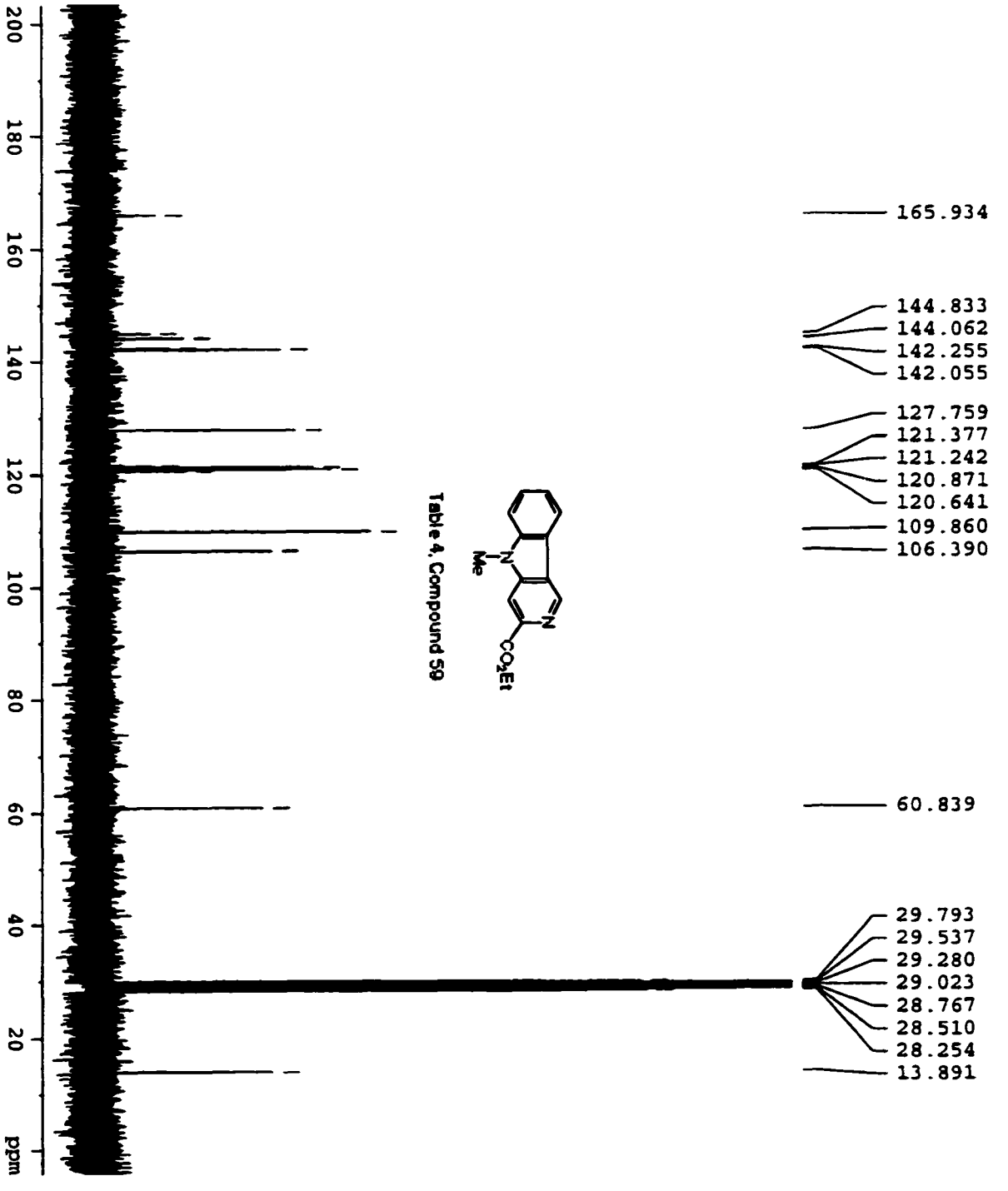
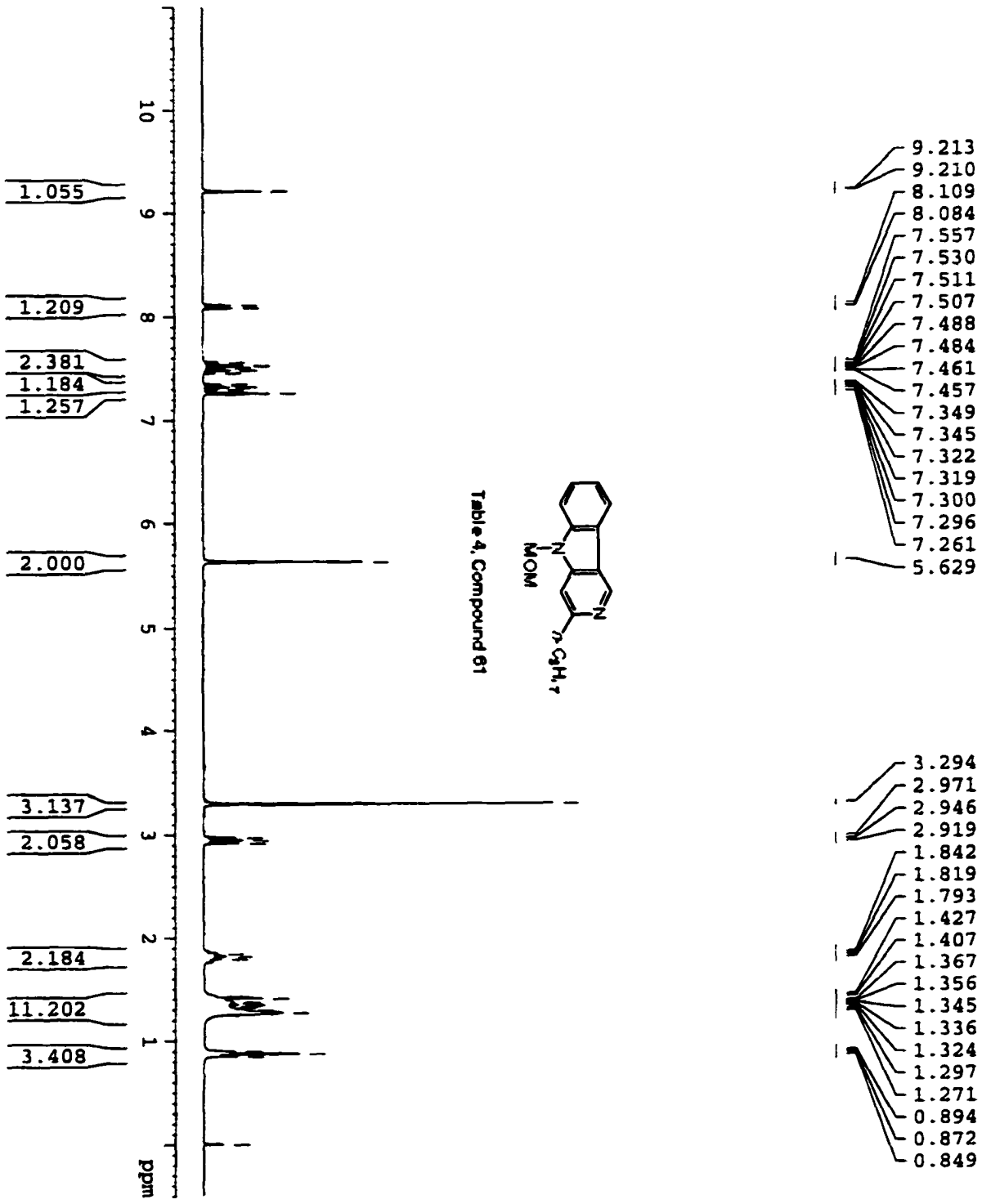


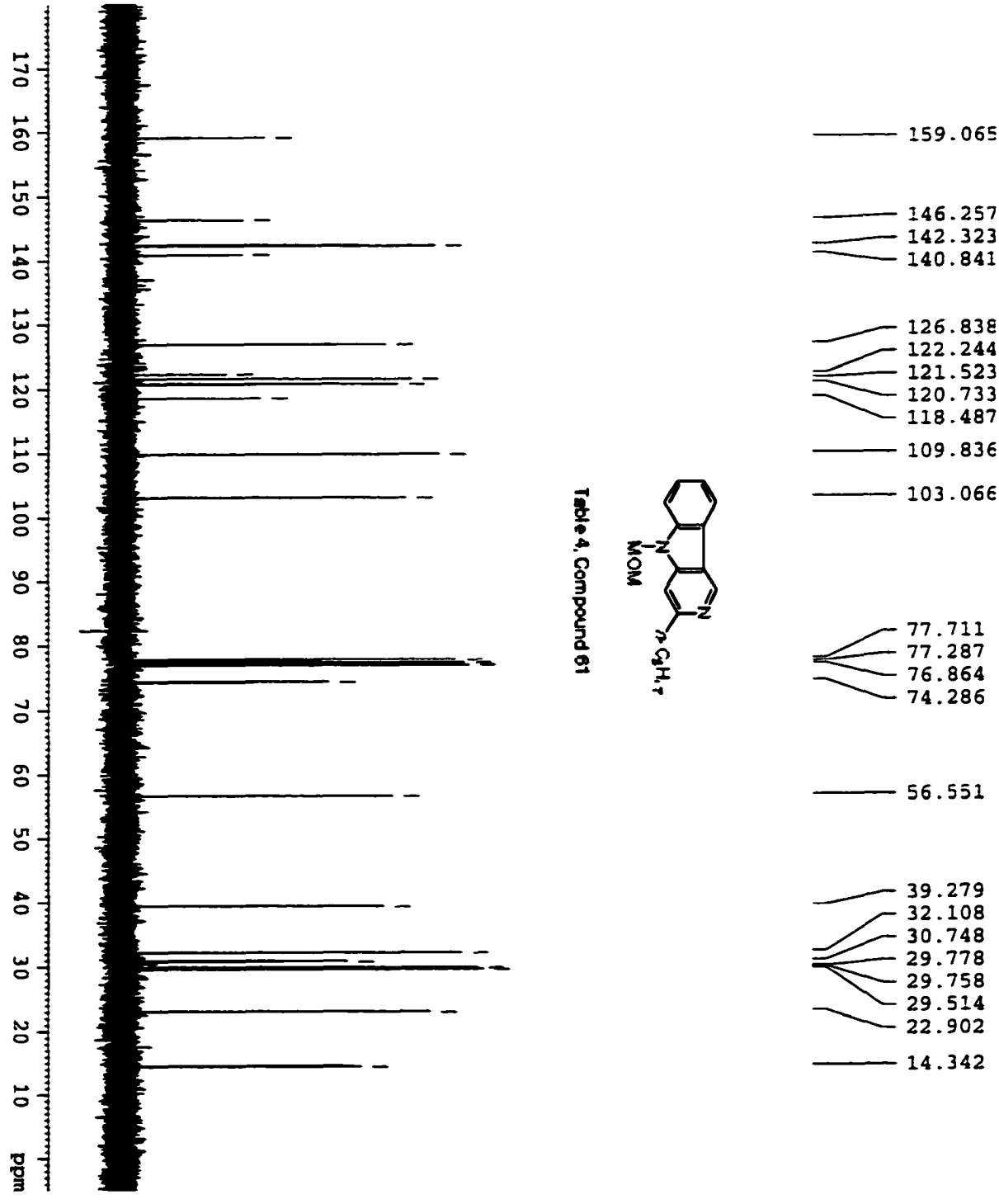
Table 3. Compound 50
Me
Ph
0.938
0.968
1.971
0.995
2.958
2.003
1.035
3.000
9.357
8.177
8.157
8.119
8.099
7.687
7.561
7.542
7.531
7.525
7.522
7.512
7.493
7.455
7.435
7.418
7.401
7.356
7.338
7.319
7.255
3.892
0.000
ppm

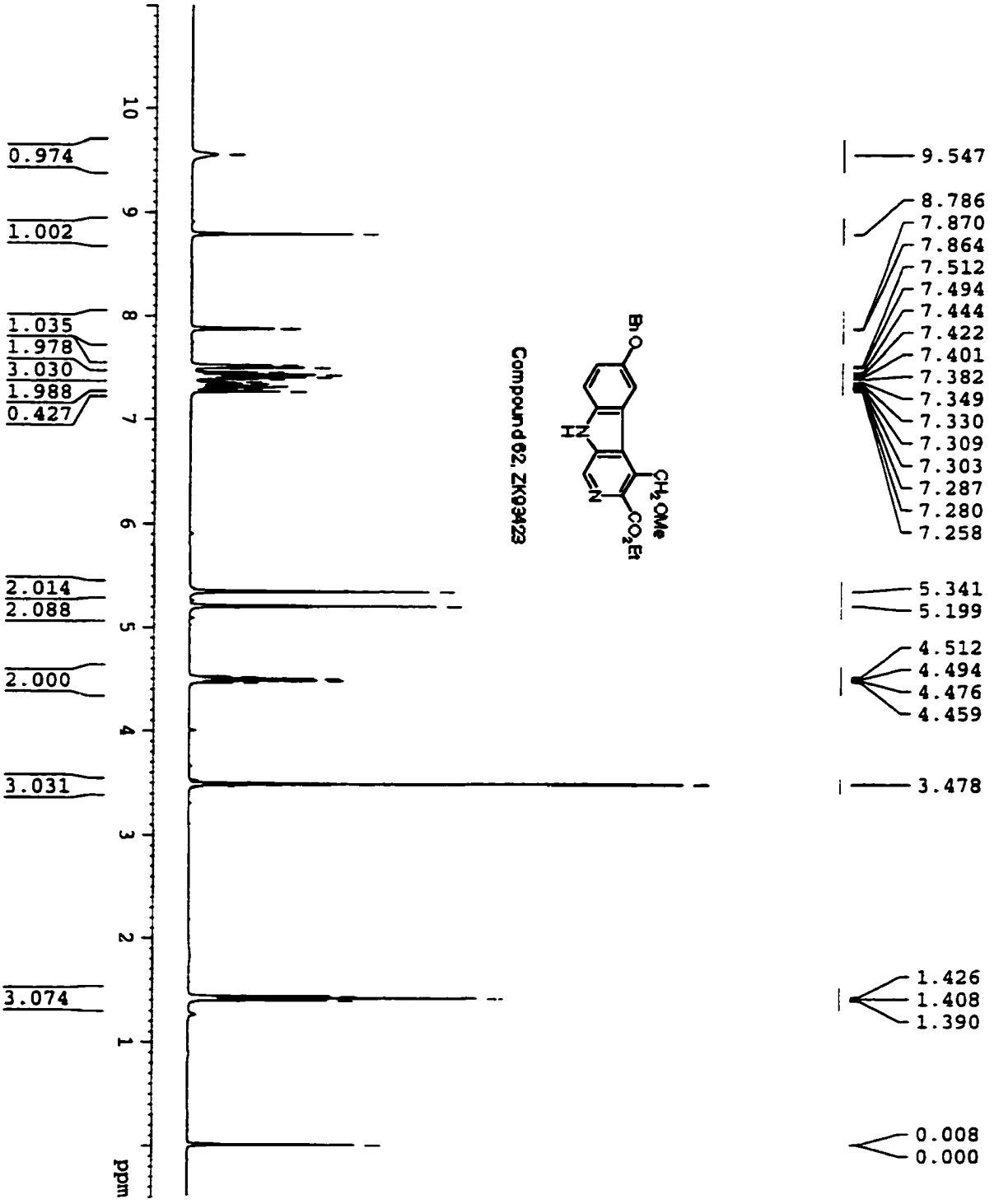

153.579
146.102
142.320
141.506
140.646
128.789
128.468
127.255
126.721
121.314
120.703
120.612
118.685
108.933
100.579
77.457
77.139
76.822
29.091
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
Table 3. Compound 50
N
Me
N
Ph

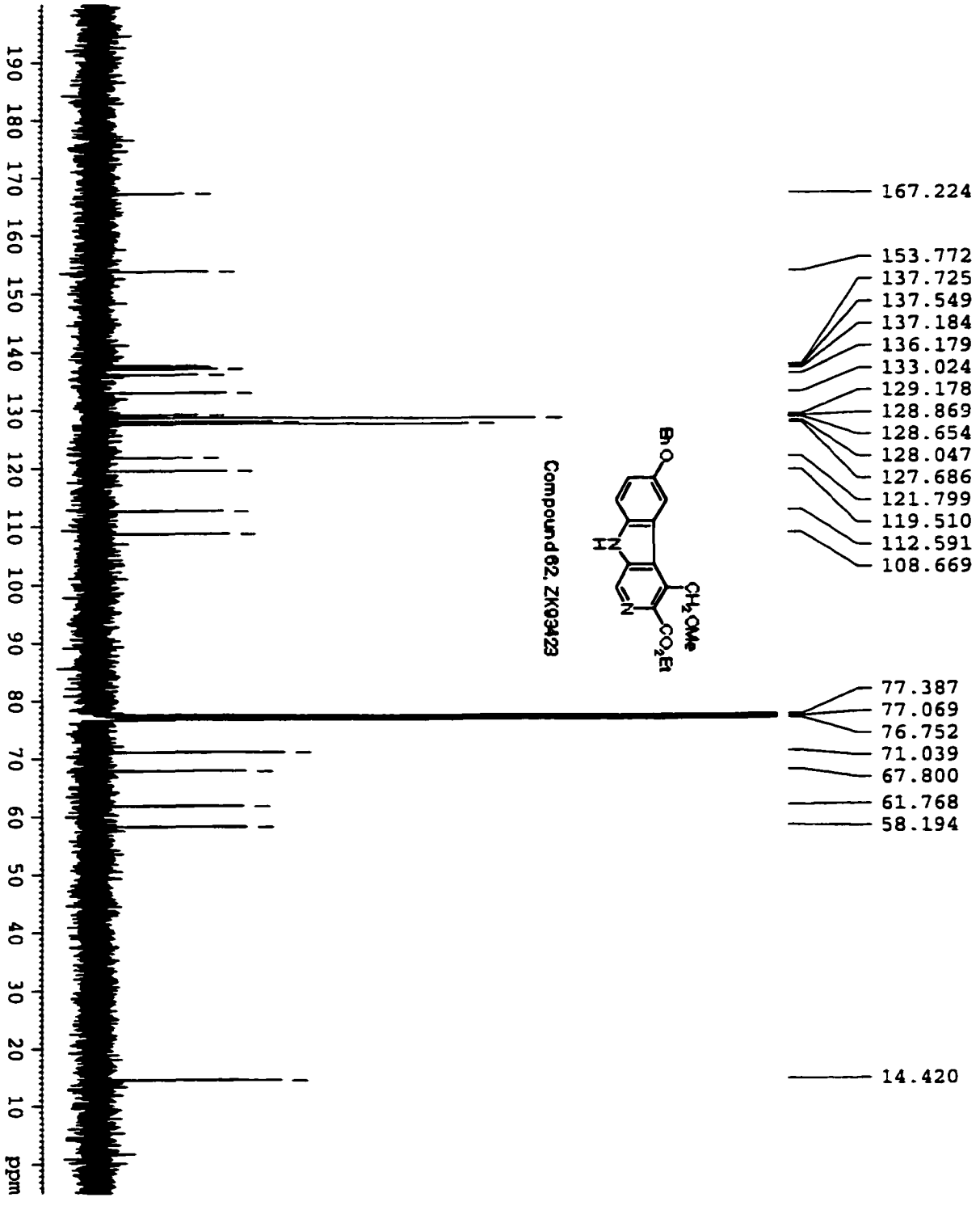

1.000
1.042
0.972
1.047
1.052
1.052
2.220
3.361
3.322
9.405
8.354
8.328
8.292
7.721
7.694
7.659
7.655
7.636
7.632
7.608
7.604
7.408
7.405
7.382
7.359
7.356
4.465
4.441
4.417
4.393
4.043
2.851
2.091
2.070
2.062
2.055
2.048
2.041
1.446
1.422
1.399
0.001
ppm
Table 4, Compound 59
Me
CO2Et

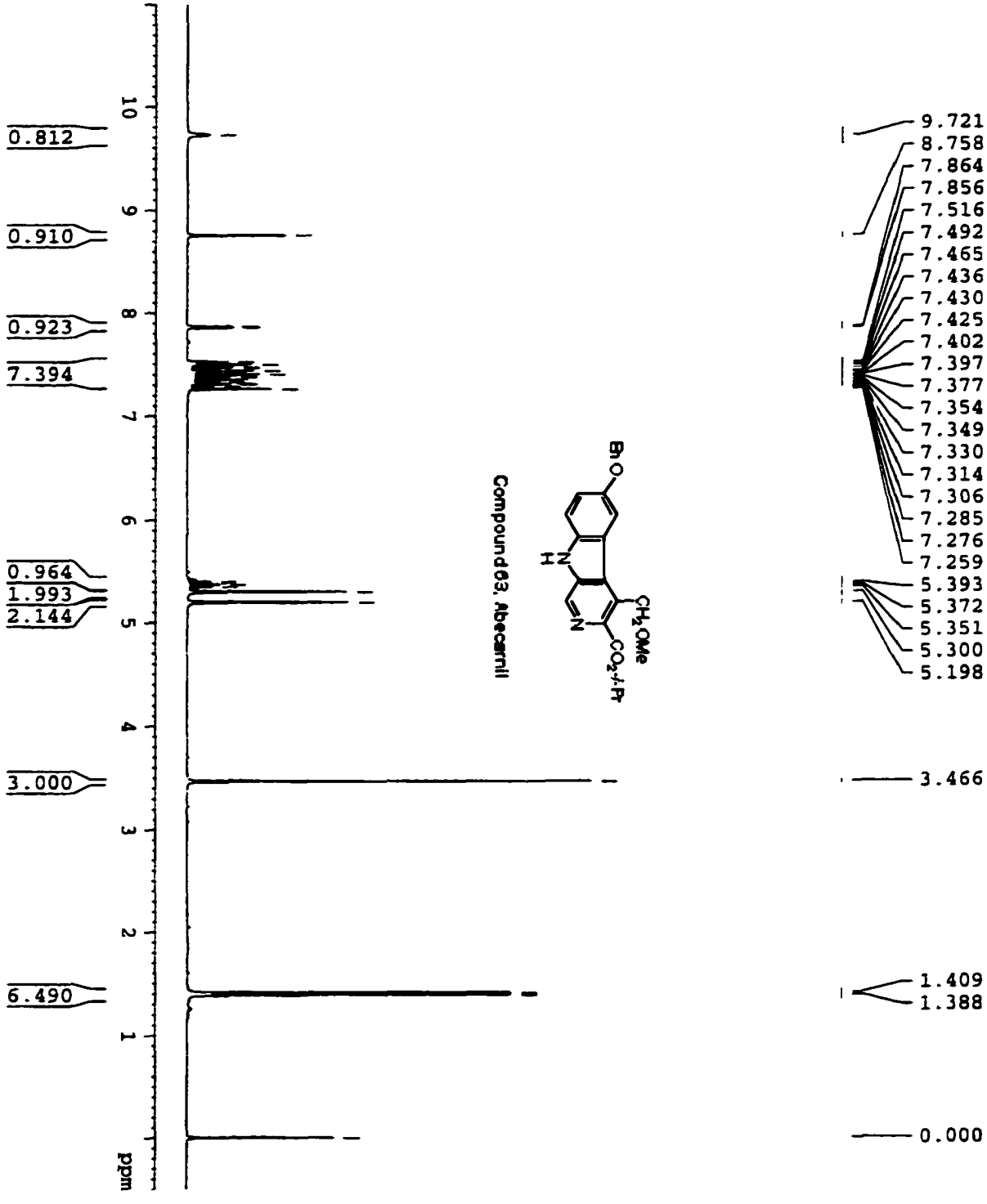

200
180
160
140
120
100
80
60
40
20
ppm
165.934
144.833
144.062
142.255
142.055
127.759
121.377
121.242
120.871
120.641
109.860
106.390
60.839
29.793
29.537
29.280
29.023
28.767
28.510
28.254
13.891
Table 4, Compound 59
N
Me
N
CO2Et

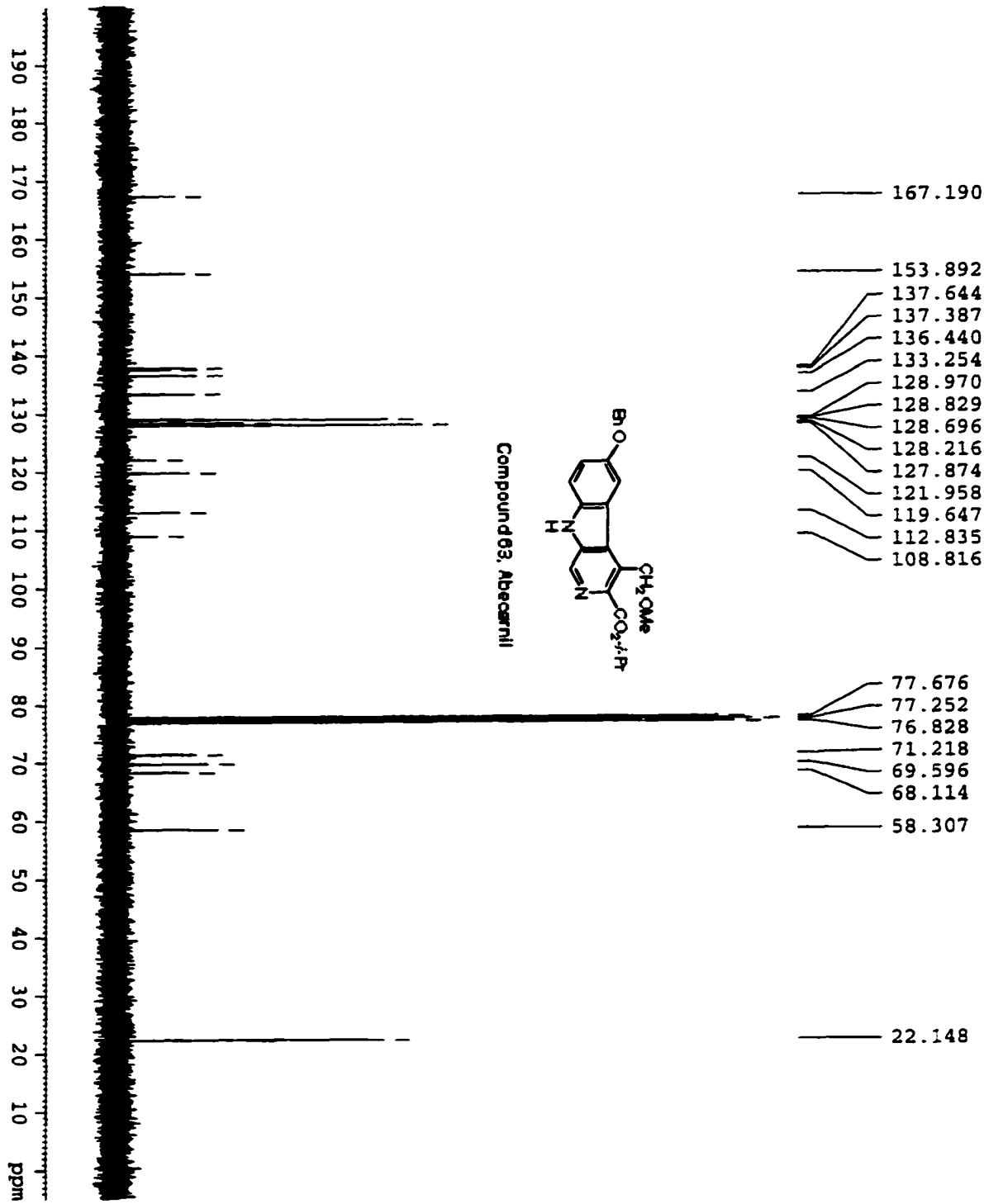

1.055
1.209
2.381
1.184
1.257
2.000
3.137
2.058
2.184
11.202
3.408
ppm
Table 4, Compound 61
MOM
n-C5H11
9.213
9.210
8.109
8.084
7.557
7.530
7.511
7.507
7.488
7.484
7.461
7.457
7.349
7.345
7.322
7.319
7.300
7.296
7.261
5.629
3.294
2.971
2.946
2.919
1.842
1.819
1.793
1.427
1.407
1.367
1.356
1.345
1.336
1.324
1.297
1.271
0.894
0.872
0.849

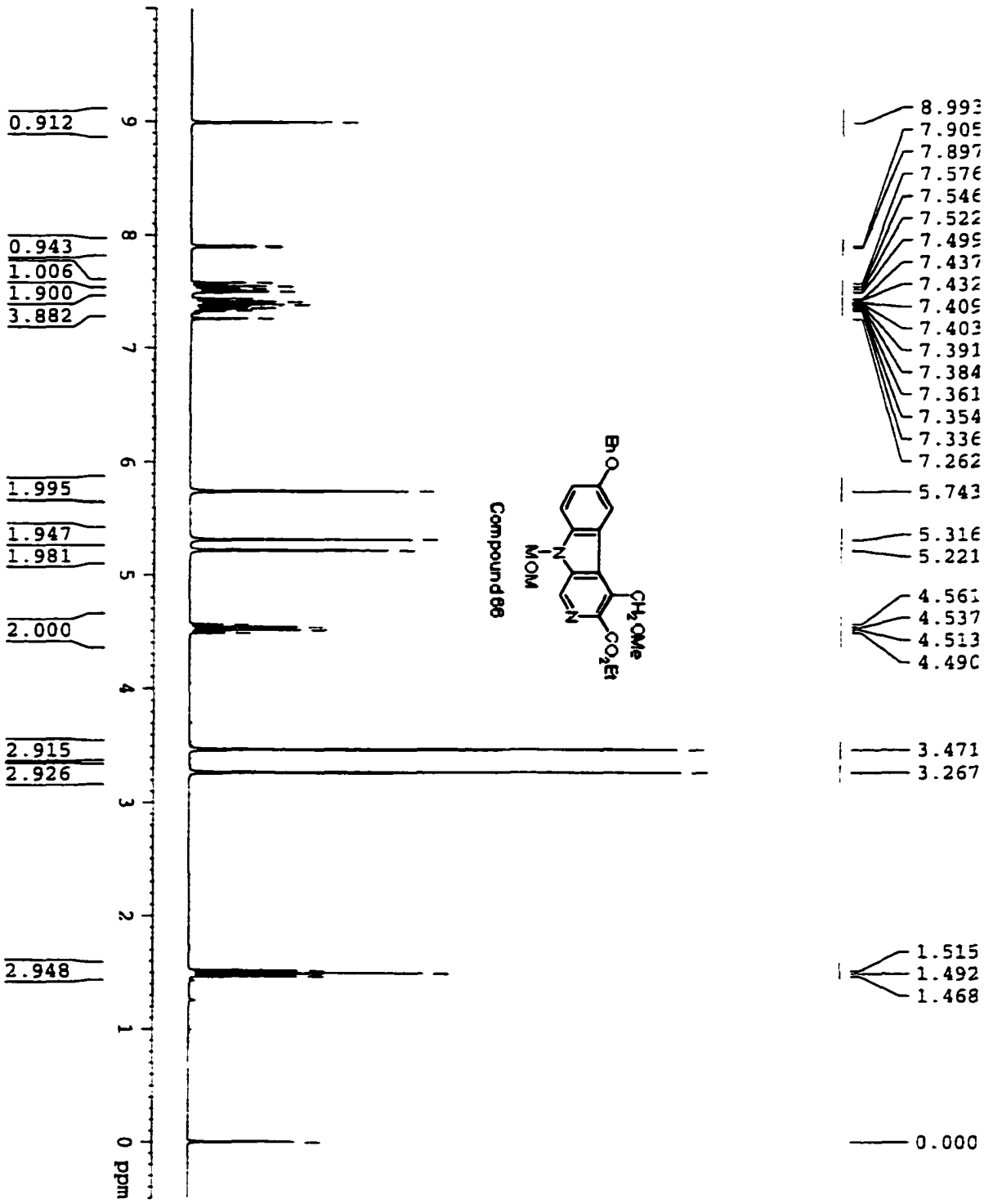

170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
159.065
146.257
142.323
140.841
126.838
122.244
121.523
120.733
118.487
109.836
103.066
77.711
77.287
76.864
74.286
56.551
39.279
32.108
30.748
29.778
29.758
29.514
22.902
14.342
MOM
Table 4, Compound 61

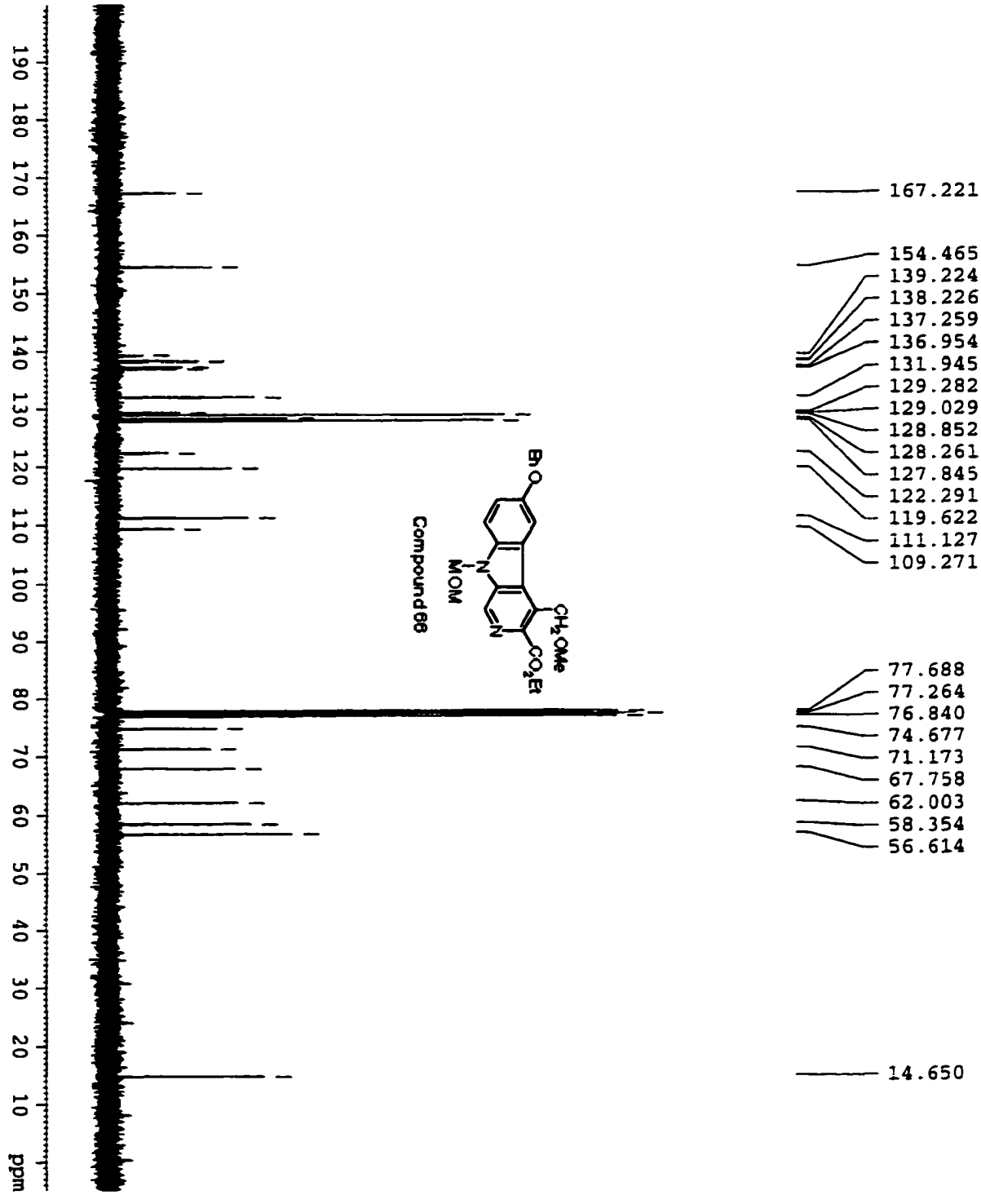

Compound 62, ZK03423
BnO
N
H
N
CH2OMe
CO2Et
0.974
1.002
1.035
1.978
3.030
1.988
0.427
2.014
2.088
2.000
3.031
3.074
9.547
8.786
7.870
7.864
7.512
7.494
7.444
7.422
7.401
7.382
7.349
7.330
7.309
7.303
7.287
7.280
7.258
5.341
5.199
4.512
4.494
4.476
4.459
3.478
1.426
1.408
1.390
0.008
0.000
ppm

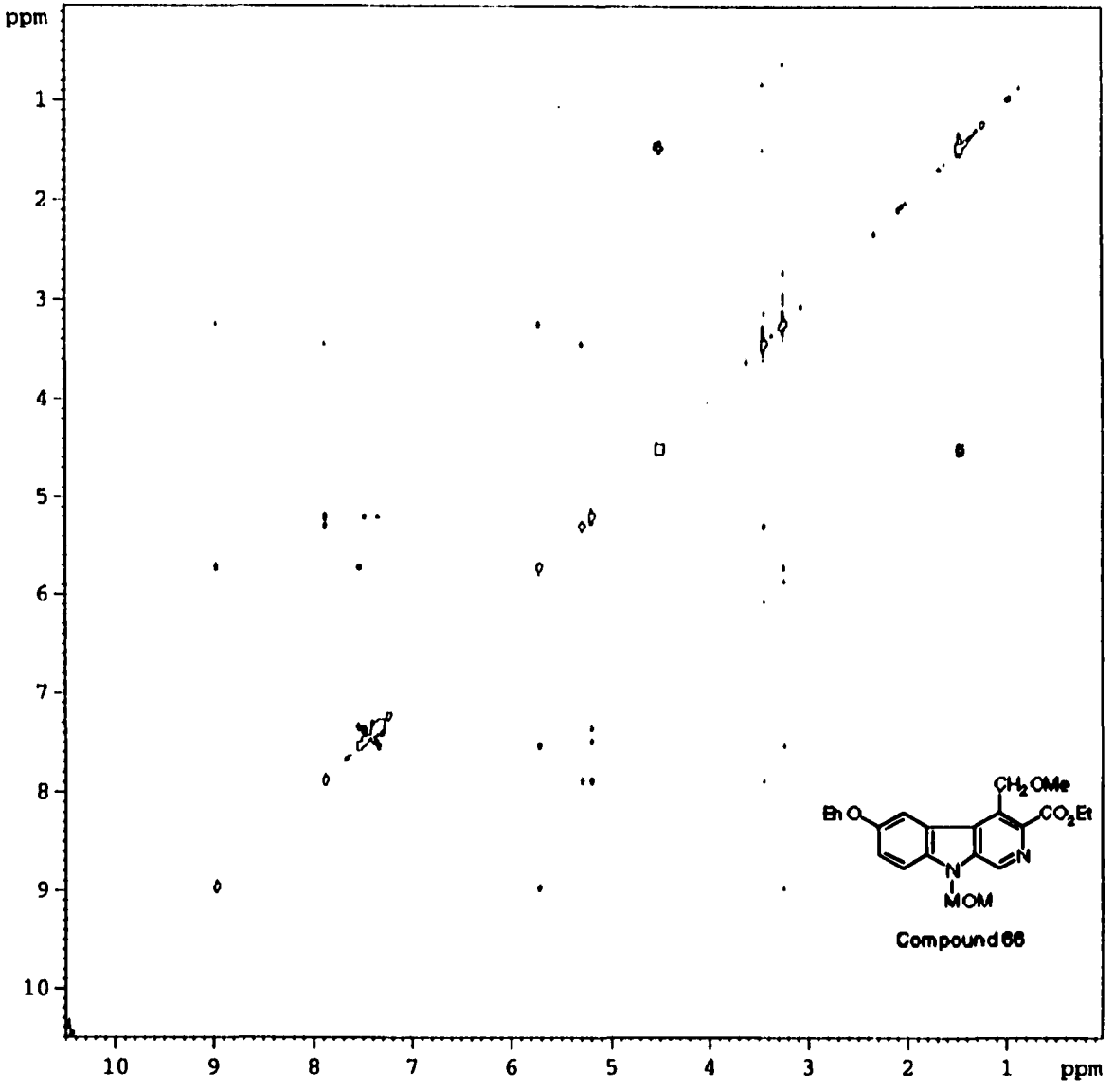

167.224
153.772
137.725
137.549
137.184
136.179
133.024
129.178
128.869
128.654
128.047
127.686
121.799
119.510
112.591
108.669
77.387
77.069
76.752
71.039
67.800
61.768
58.194
14.420
Compound 62, ZK03423
BnO
CH2OMe
CO2Et
ppm


0.812
0.910
0.923
7.394
0.964
1.993
2.144
3.000
6.490
ppm
Compound 63, Abecarnil
BnO
CH2OMe
CO2-i-Pr
9.721
8.758
7.864
7.856
7.516
7.492
7.465
7.436
7.430
7.425
7.402
7.397
7.377
7.354
7.349
7.330
7.314
7.306
7.285
7.276
7.259
5.393
5.372
5.351
5.300
5.198
3.466
1.409
1.388
0.000

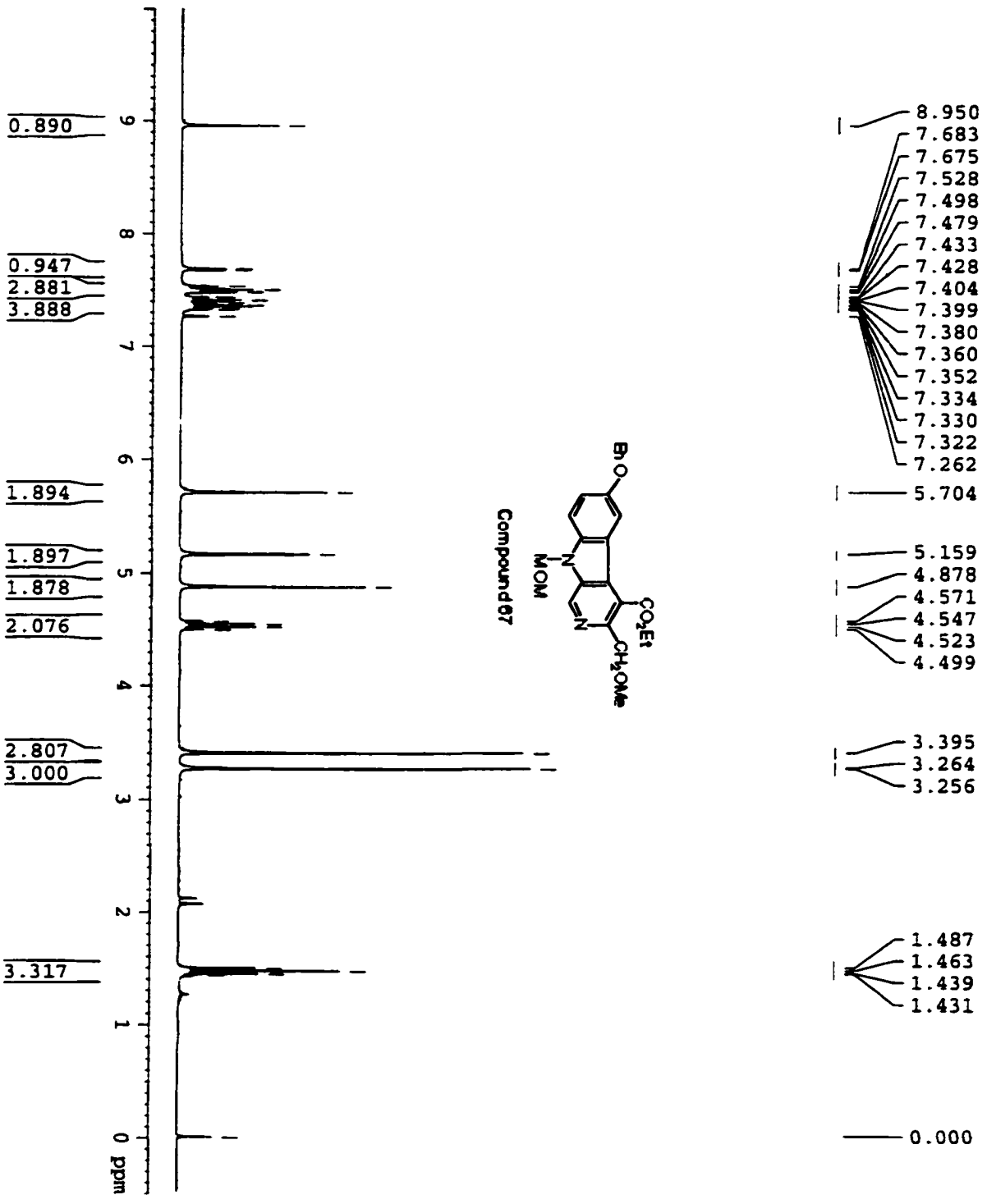

167.190
153.892
137.644
137.387
136.440
133.254
128.970
128.829
128.696
128.216
127.874
121.958
119.647
112.835
108.816
77.676
77.252
76.828
71.218
69.596
68.114
58.307
22.148
Compound 63, Abecarnil
BnO
CH2OMe
CO2-i-Pr
ppm

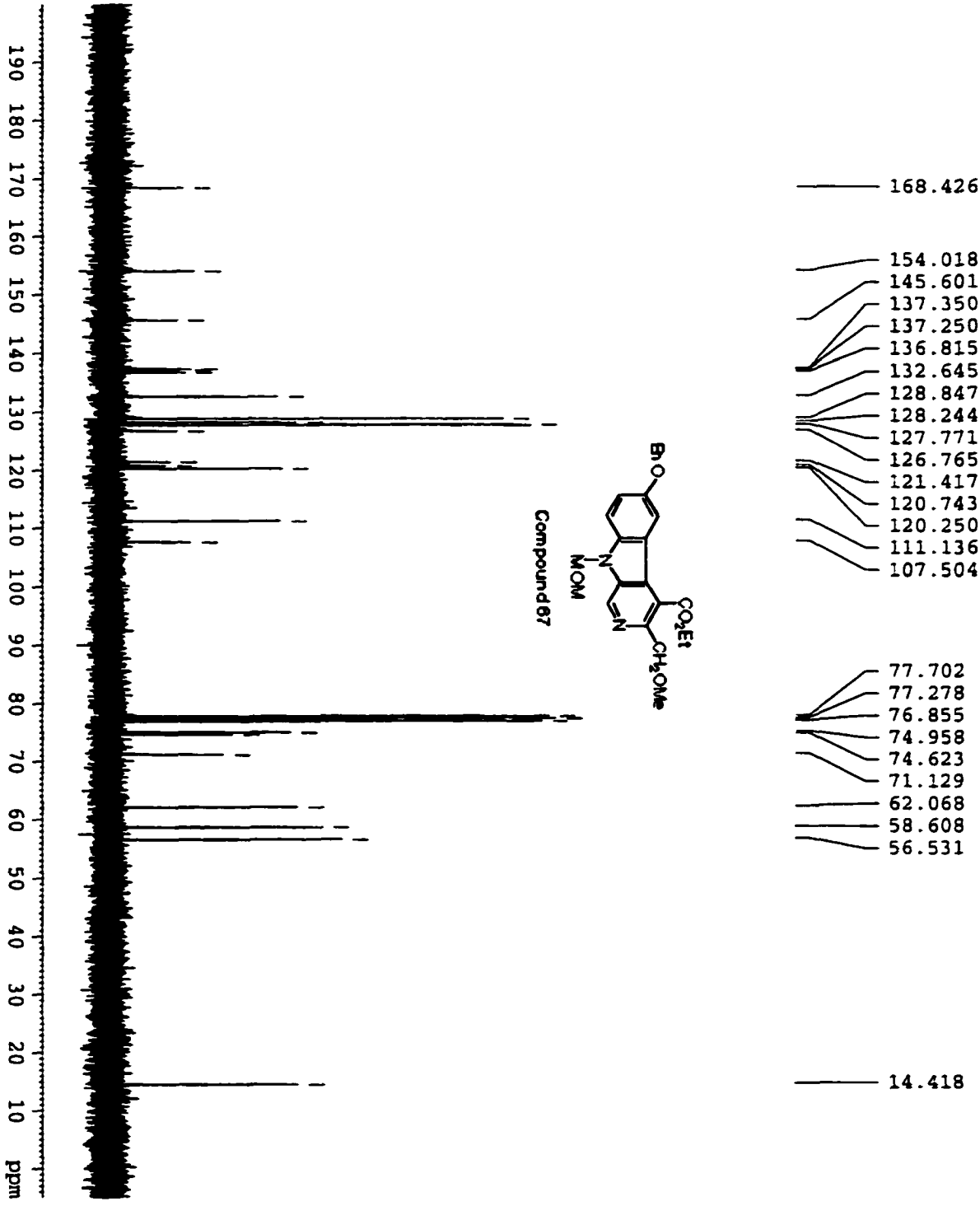

0.912
0.943
1.006
1.900
3.882
1.995
1.947
1.981
2.000
2.915
2.926
2.948
8.993
7.905
7.897
7.576
7.546
7.522
7.499
7.437
7.432
7.409
7.403
7.391
7.384
7.361
7.354
7.336
7.262
5.743
5.316
5.221
4.561
4.537
4.513
4.490
3.471
3.267
1.515
1.492
1.468
0.000
ppm
Compound 66
BnO
MOM
N
N
CH2OMe
CO2Et

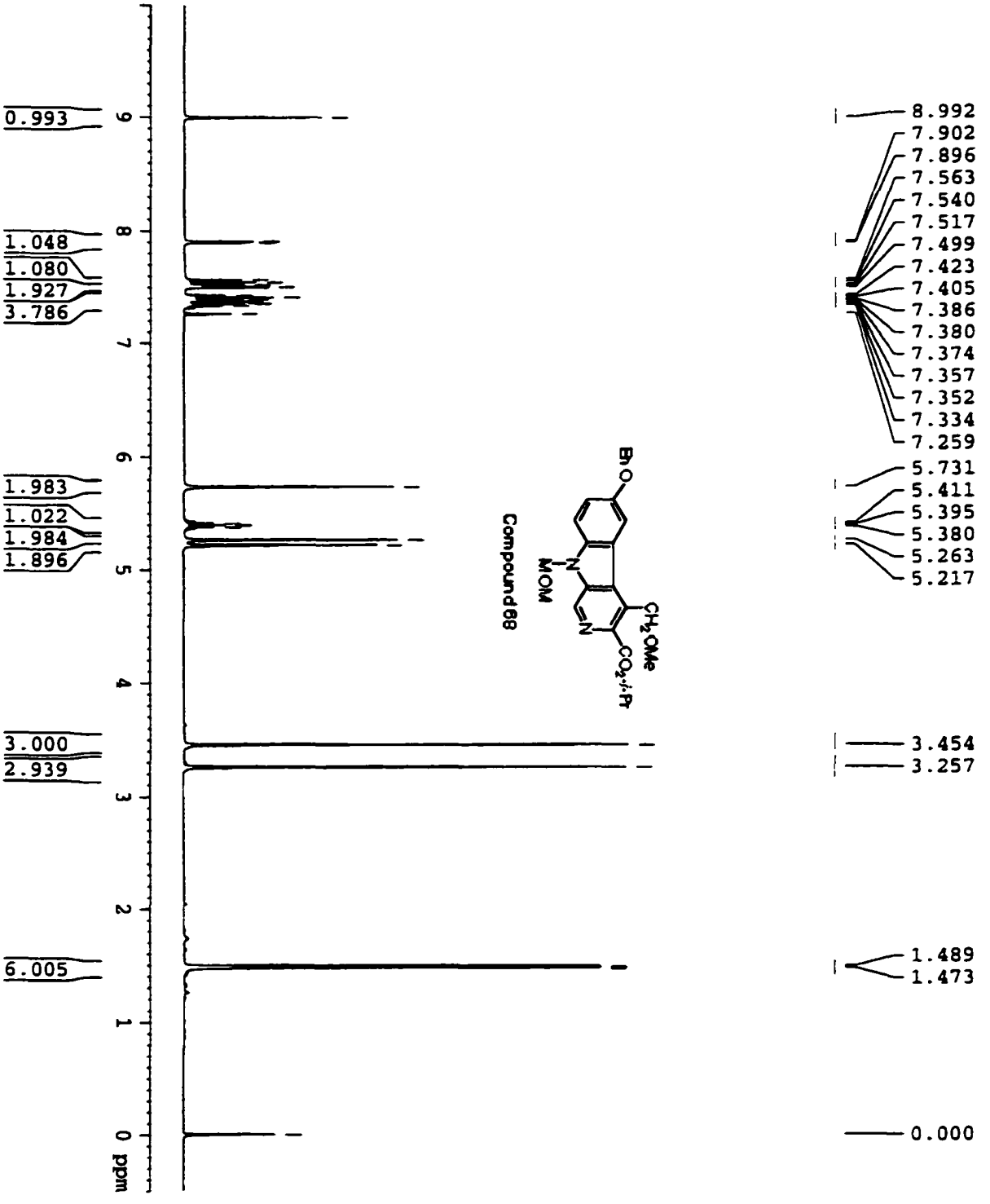

167.221
154.465
139.224
138.226
137.259
136.954
131.945
129.282
129.029
128.852
128.261
127.845
122.291
119.622
111.127
109.271
77.688
77.264
76.840
74.677
71.173
67.758
62.003
58.354
56.614
14.650
Compound 66
MOM
BnO
CH2OMe
CO2Et
ppm

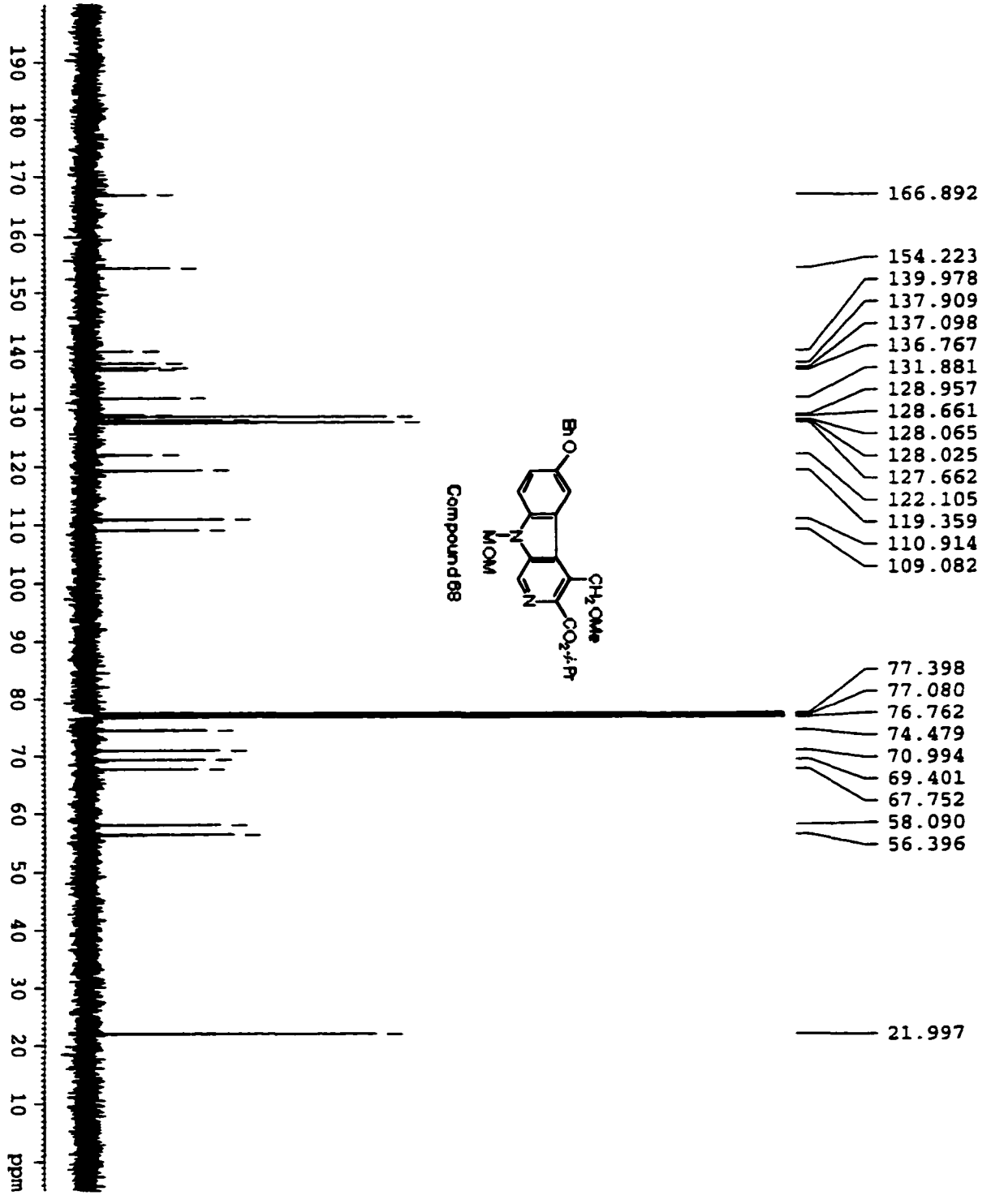


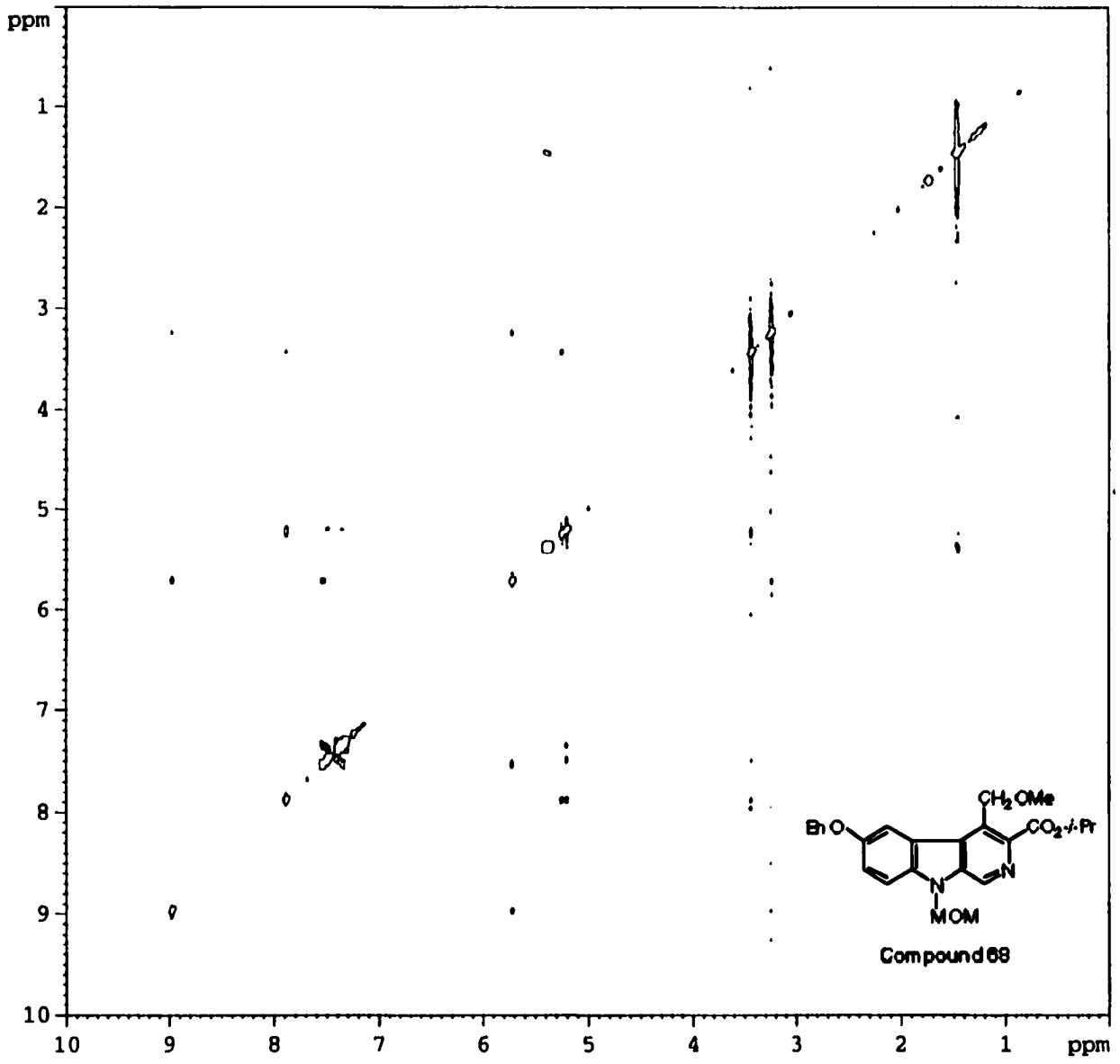
Compound 66

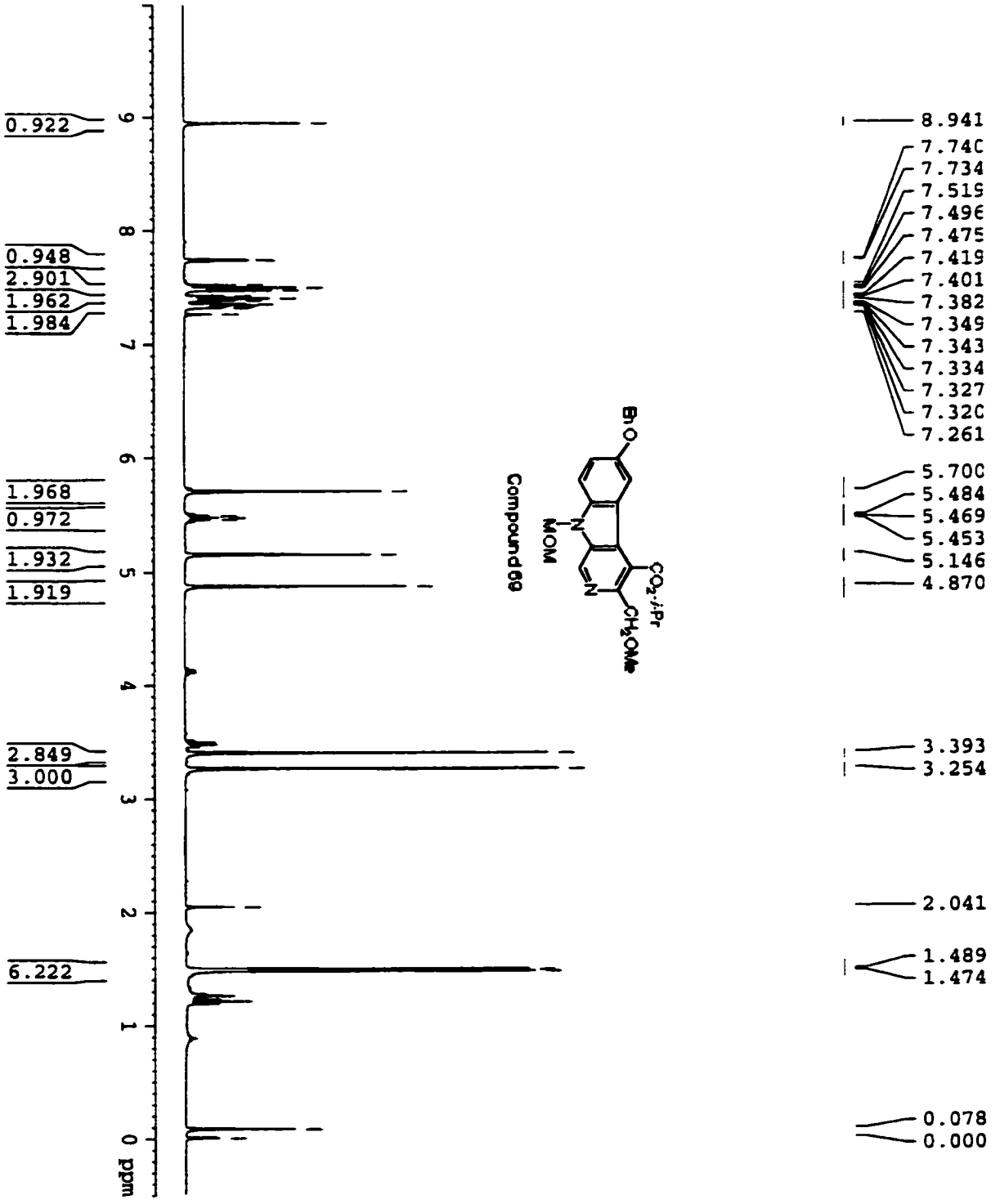

0.890
0.947
2.881
3.888
1.894
1.897
1.878
2.076
2.807
3.000
3.317
9
8
7
6
5
4
3
2
1
0 ppm
Compound 67
BnO
MOM
N
N
CO2Et
CH2OMe
8.950
7.683
7.675
7.528
7.498
7.479
7.433
7.428
7.404
7.399
7.380
7.360
7.352
7.334
7.330
7.322
7.262
5.704
5.159
4.878
4.571
4.547
4.523
4.499
3.395
3.264
3.256
1.487
1.463
1.439
1.431
0.000

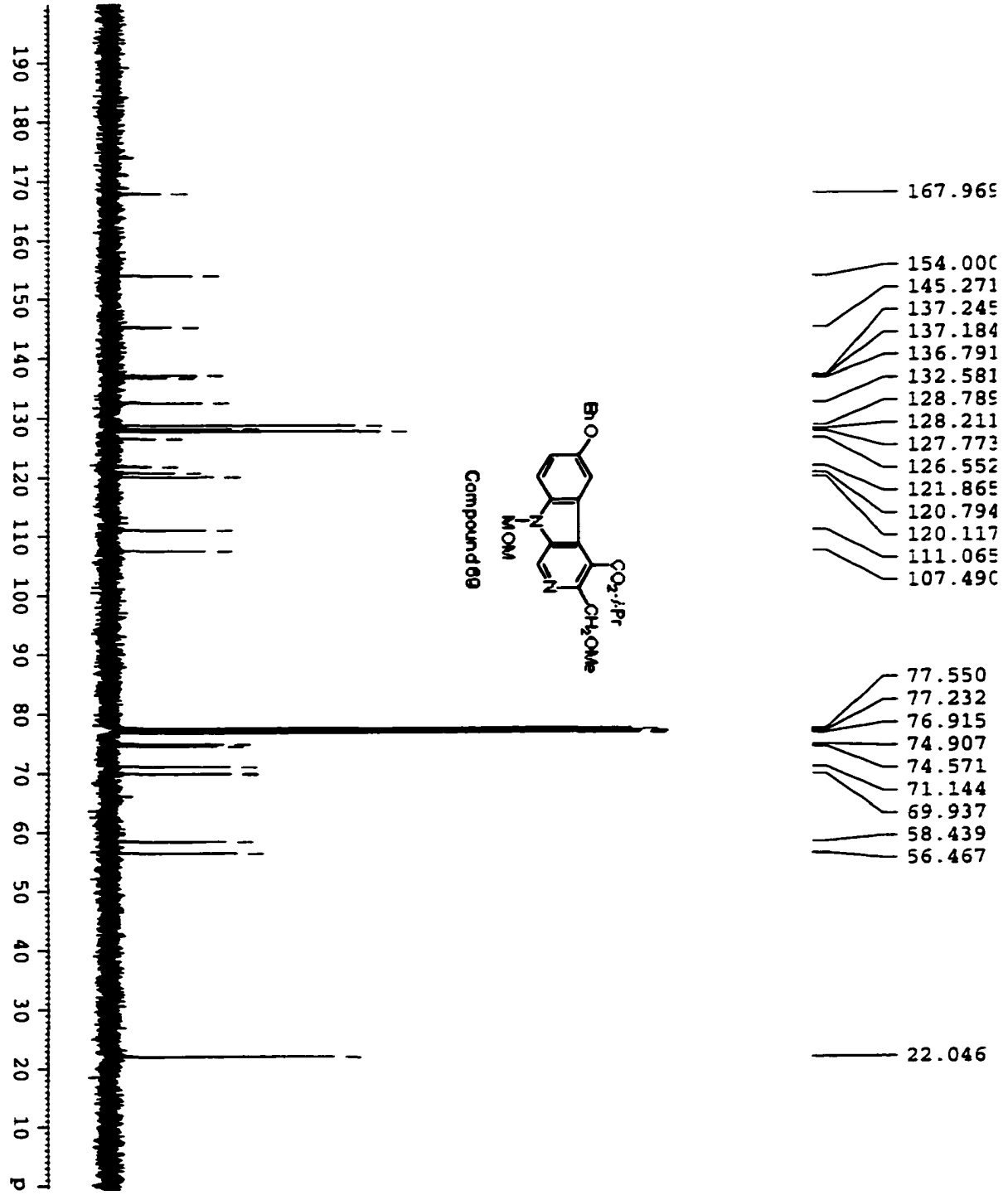

168.426
154.018
145.601
137.350
137.250
136.815
132.645
128.847
128.244
127.771
126.765
121.417
120.743
120.250
111.136
107.504
77.702
77.278
76.855
74.958
74.623
71.129
62.068
58.608
56.531
14.418
Compound 87
BnO
MOM
CO2Et
CH2OMe
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


0.993
1.048
1.080
1.927
3.786
1.983
1.022
1.984
1.896
3.000
2.939
6.005
ppm
Compound 68
BnO
MOM
CH2OMe
CO2i-Pr
8.992
7.902
7.896
7.563
7.540
7.517
7.499
7.423
7.405
7.386
7.380
7.374
7.357
7.352
7.334
7.259
5.731
5.411
5.395
5.380
5.263
5.217
3.454
3.257
1.489
1.473
0.000


166.892
154.223
139.978
137.909
137.098
136.767
131.881
128.957
128.661
128.065
128.025
127.662
122.105
119.359
110.914
109.082
77.398
77.080
76.762
74.479
70.994
69.401
67.752
58.090
56.396
21.997
Compound 88
BnO
MOM
N
N
CH2OMe
CO2-i-Pr
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
10
10
9
8
7
6
5
4
3
2
1
ppm
BnO
CH2OMe
CO2-i-Pr
N
N
MOM
Compound 68


0.922
0.948
2.901
1.962
1.984
1.968
0.972
1.932
1.919
2.849
3.000
6.222
9
8
7
6
5
4
3
2
1
0 ppm
Compound 69
BnO
MOM
CO2-iPr
CH2OMe
8.941
7.740
7.734
7.519
7.496
7.475
7.419
7.401
7.382
7.349
7.343
7.334
7.327
7.320
7.261
5.700
5.484
5.469
5.453
5.146
4.870
3.393
3.254
2.041
1.489
1.474
0.078
0.000


Compound 69
BnO
MOM
N
N
CO2-i-Pr
CH2OMe
167.969
154.000
145.271
137.245
137.184
136.791
132.581
128.785
128.211
127.773
126.552
121.865
120.794
120.117
111.065
107.490
77.550
77.232
76.915
74.907
74.571
71.144
69.937
58.439
56.467
22.046
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 p

APPENDIX B. CHAPTER 2 ^{1}H AND ^{13}C NMR SPECTRA

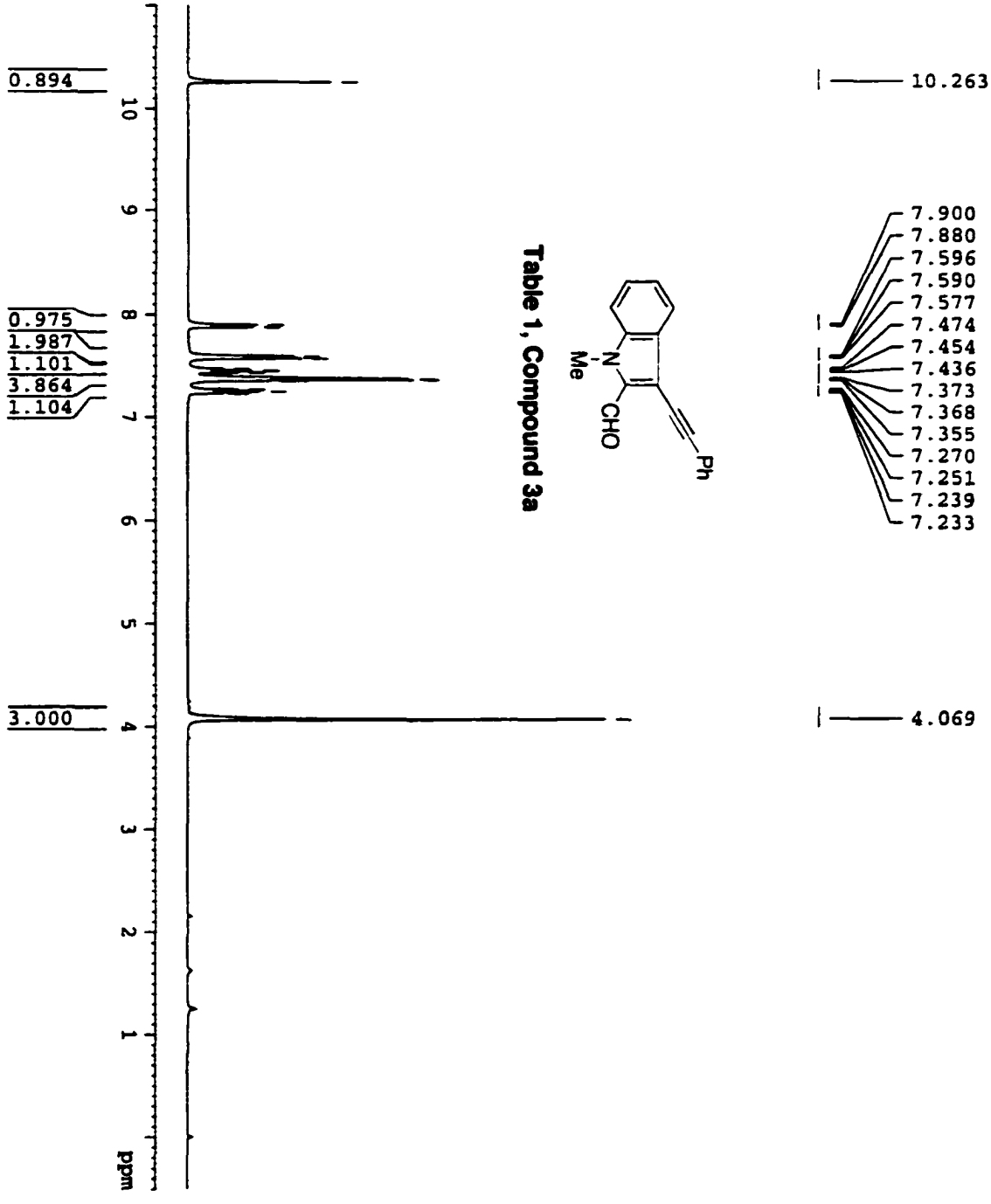


Table 1, Compound 3a

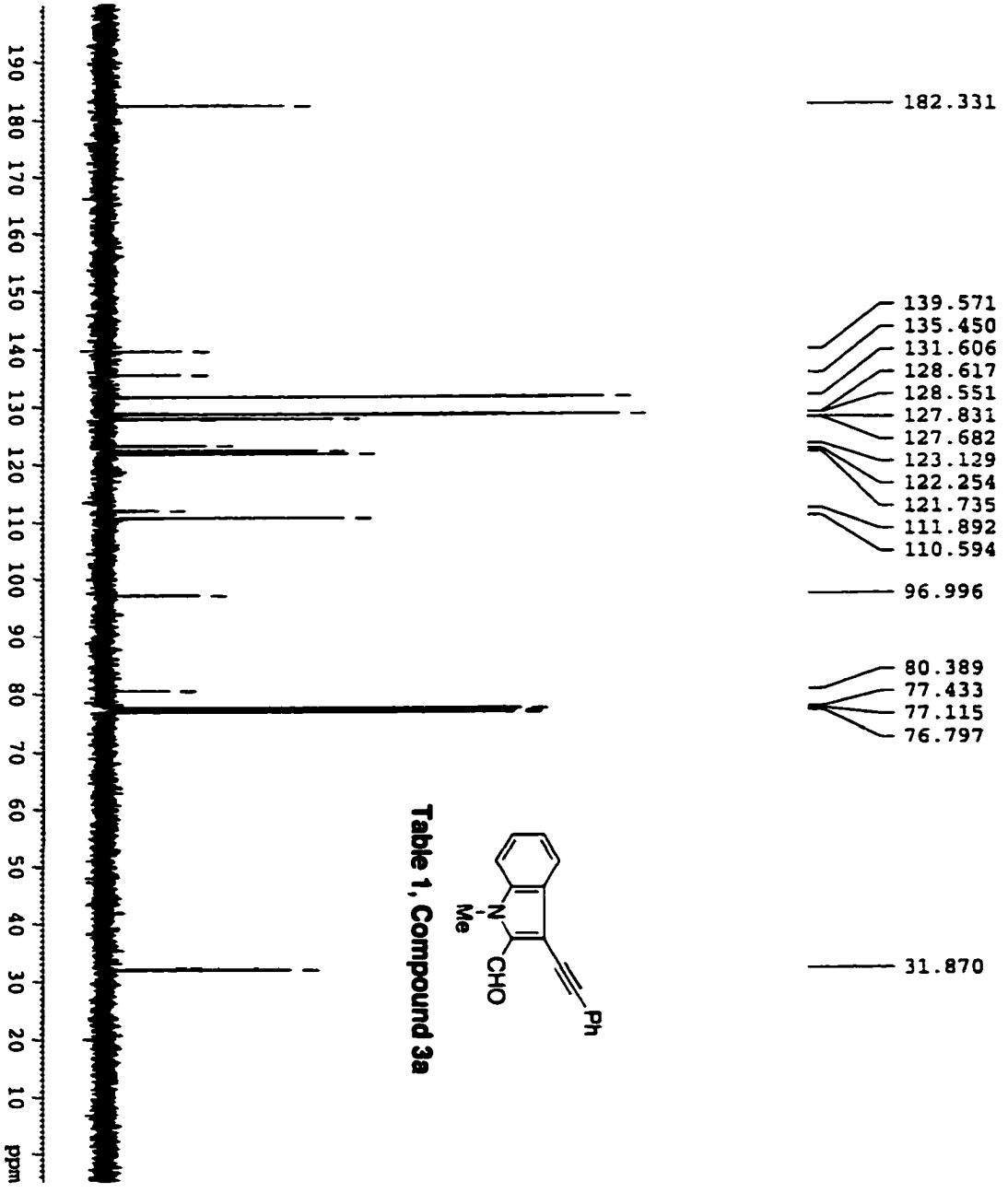


Table 1, Compound 3a

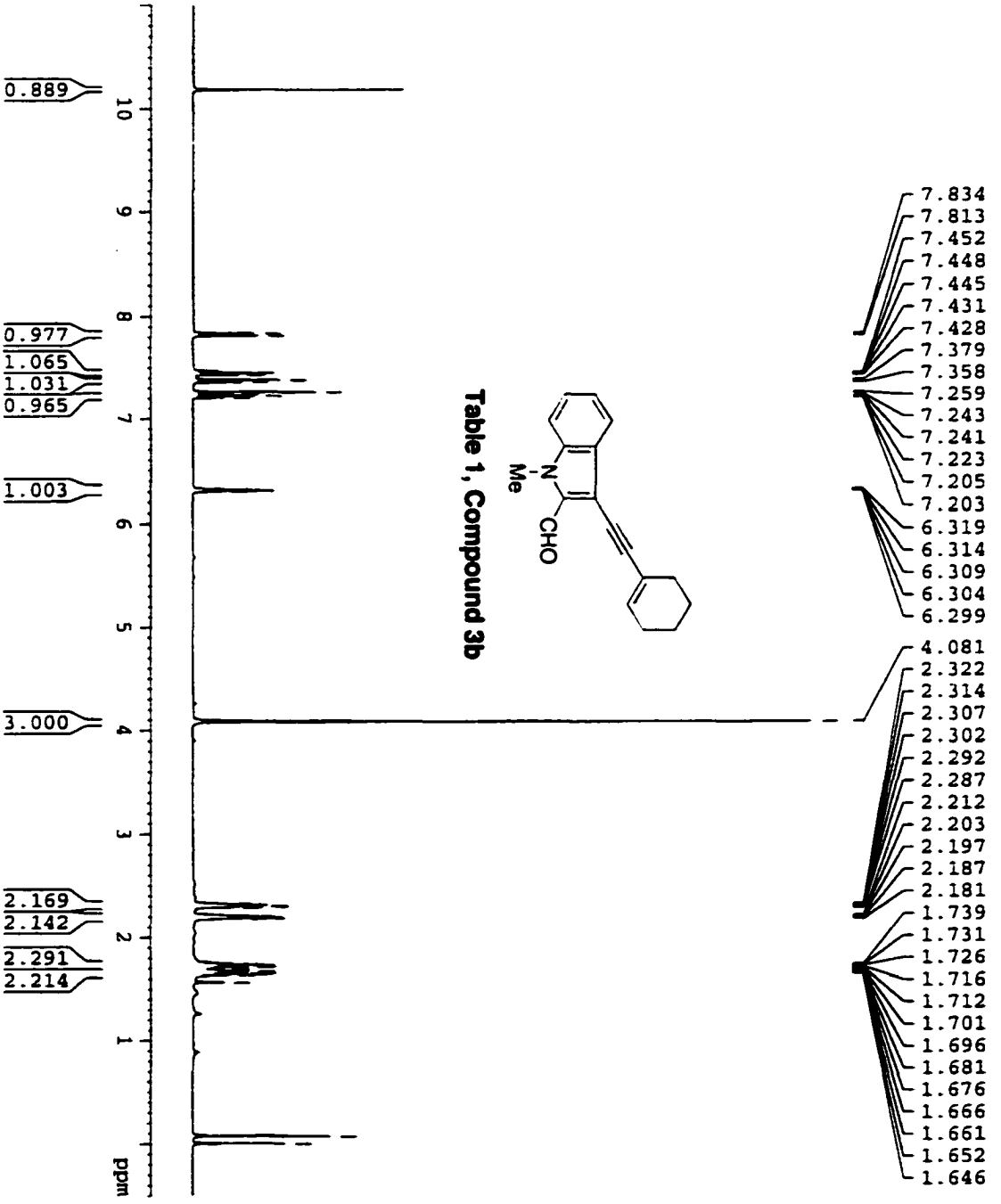


Table 1, Compound 3b

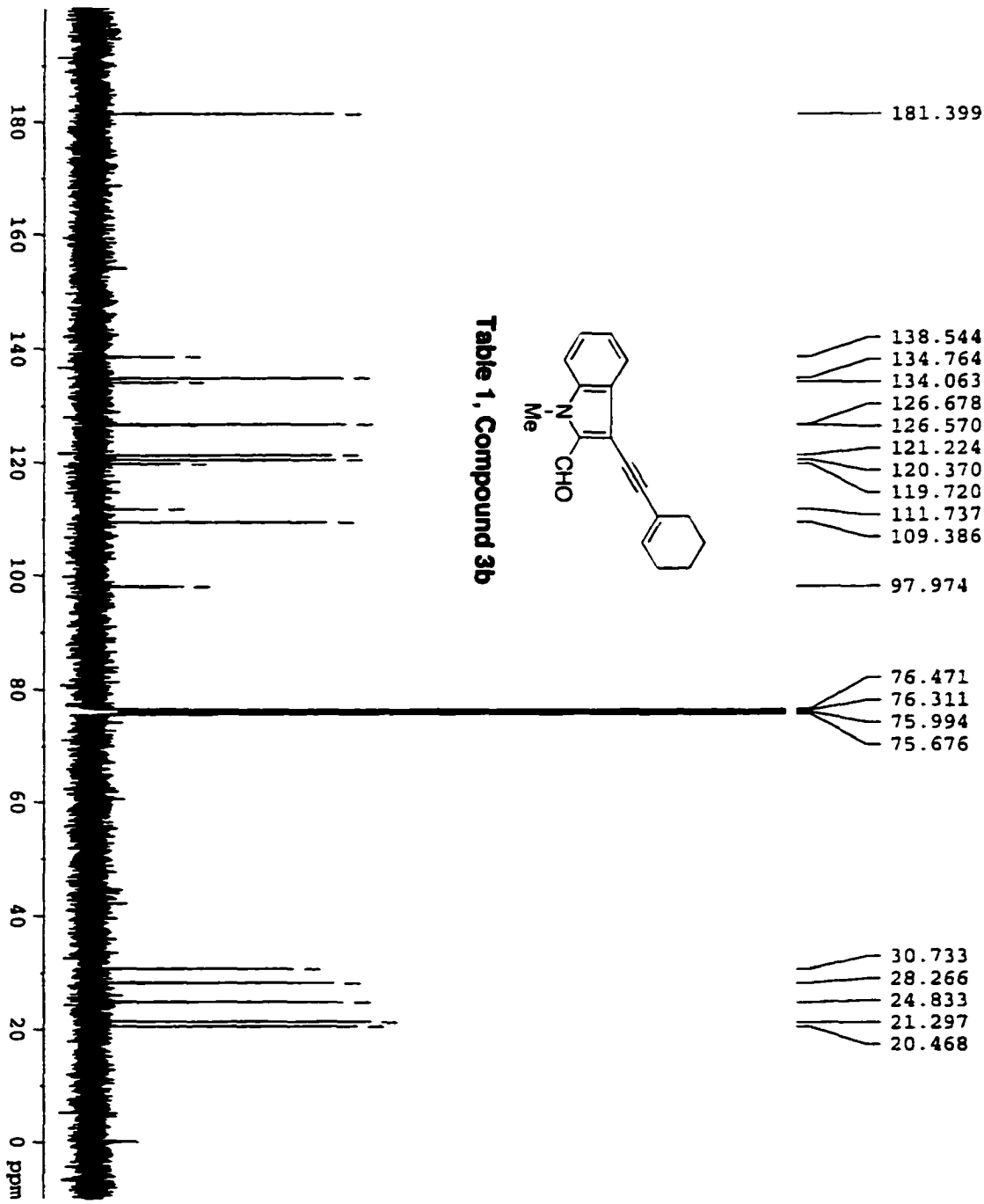
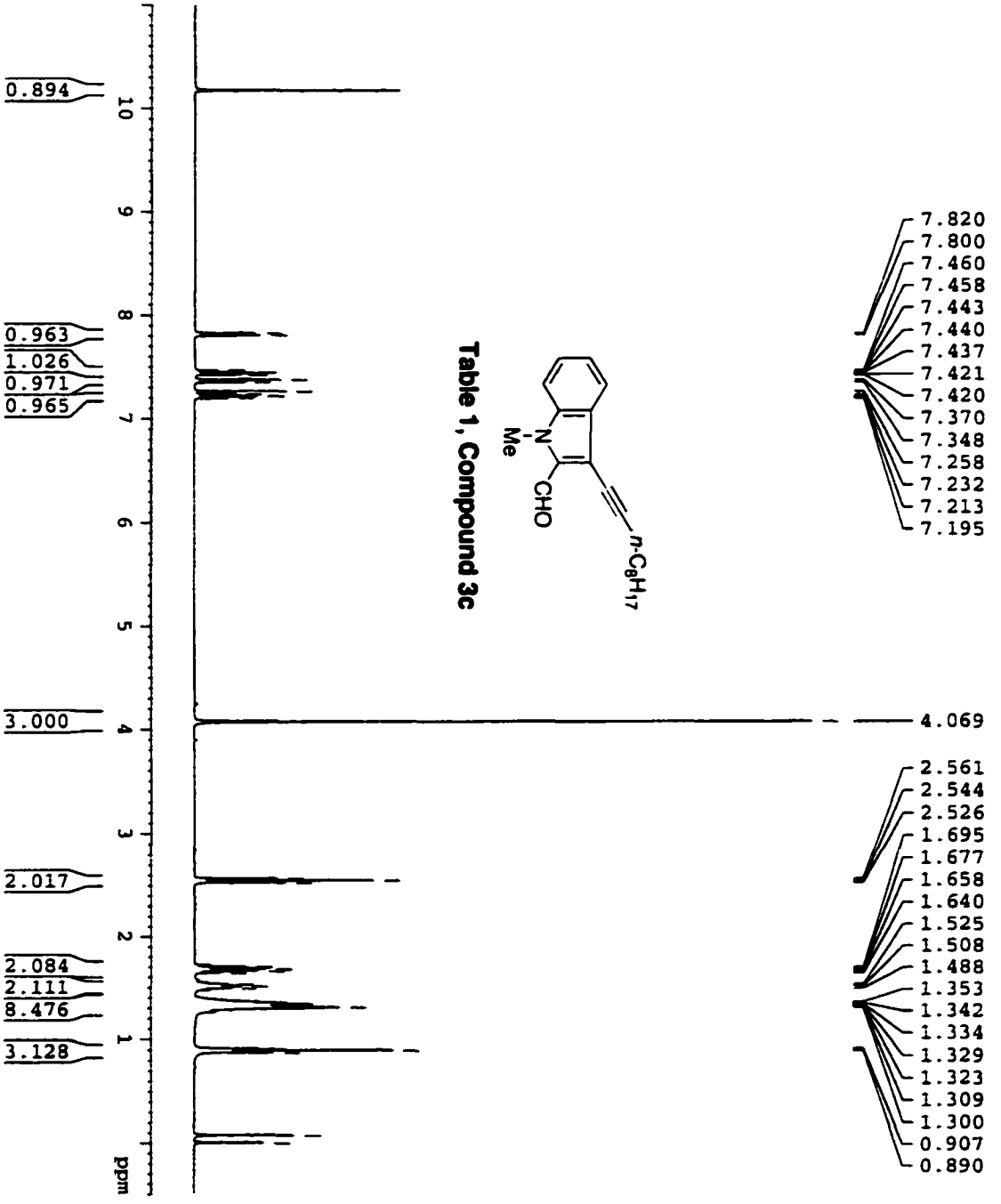
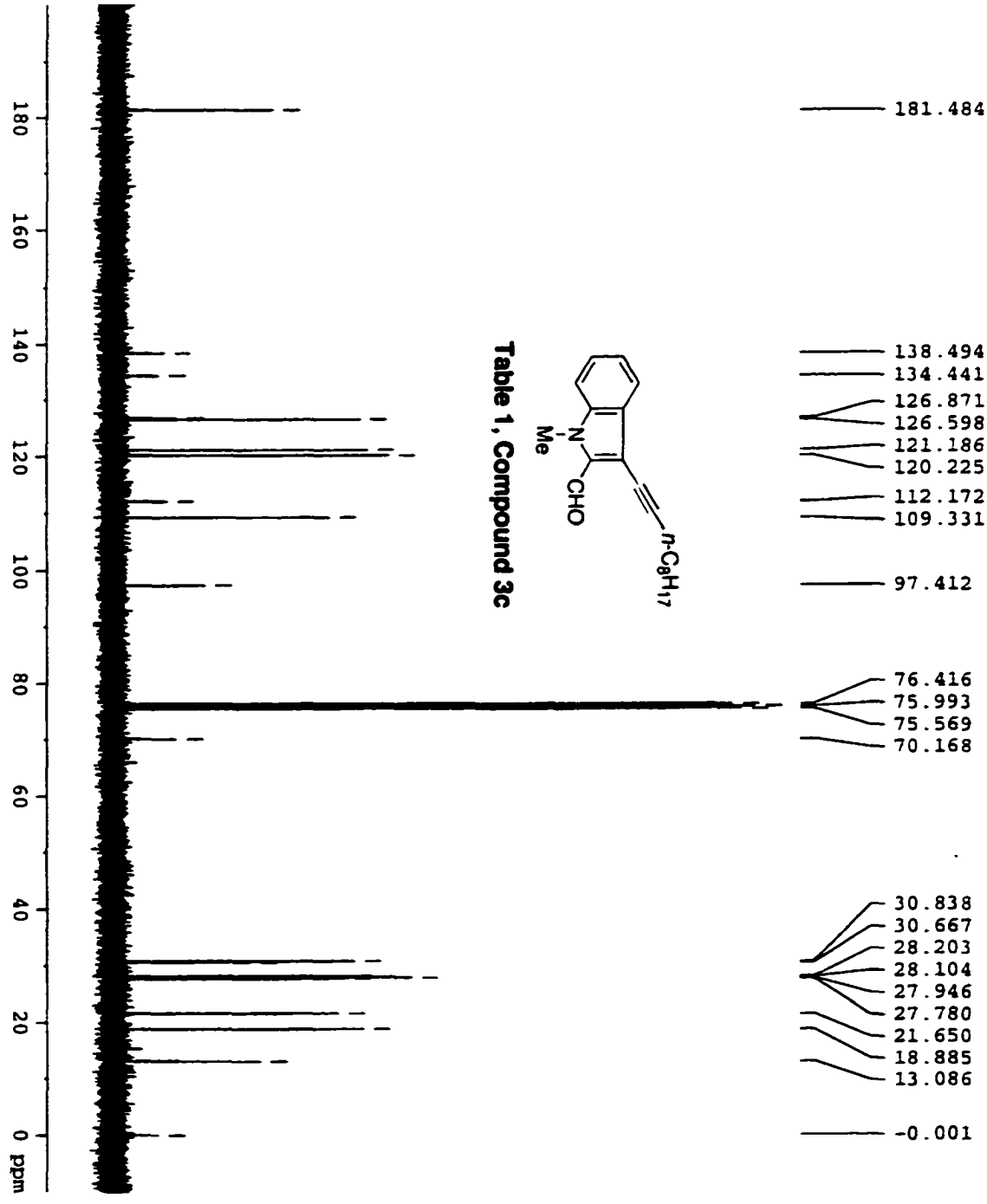
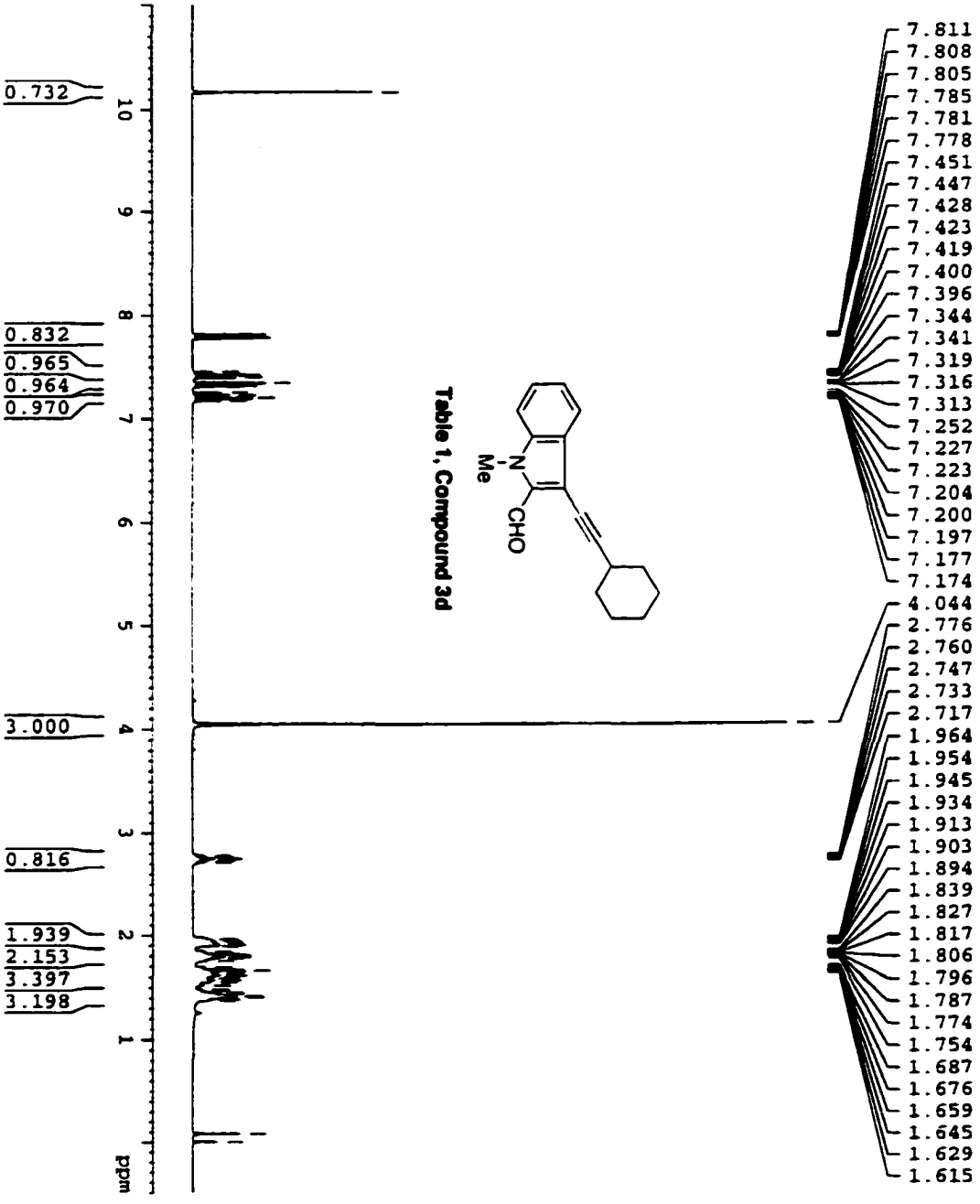
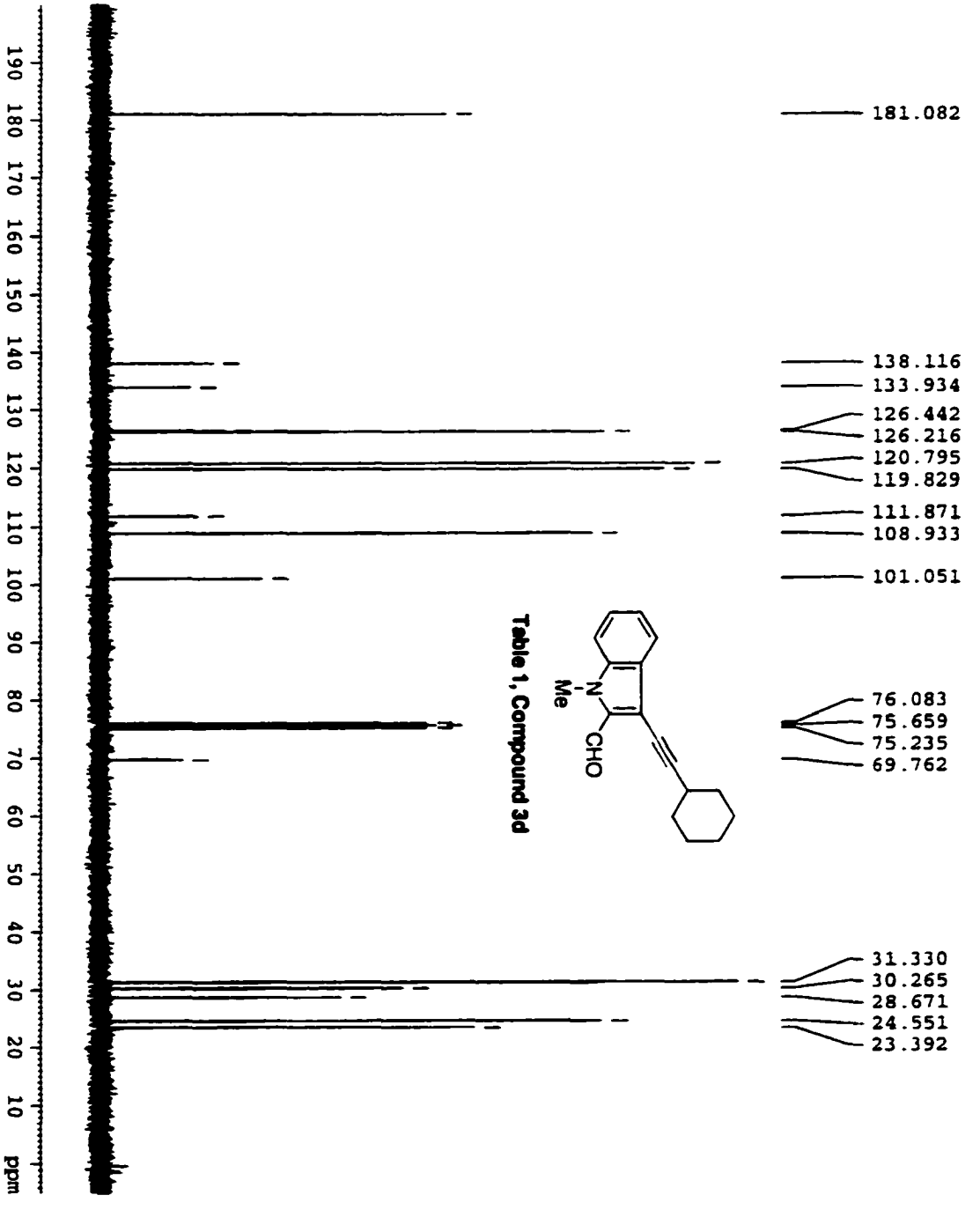


Table 1, Compound 3b
Me
N
CHO
181.399
138.544
134.764
134.063
126.678
126.570
121.224
120.370
119.720
111.737
109.386
97.974
76.471
76.311
75.994
75.676
30.733
28.266
24.833
21.297
20.468
180
160
140
120
100
80
60
40
20
0
ppm


0.894
0.963
1.026
0.971
0.965
3.000
2.017
2.084
2.111
8.476
3.128
ppm
Table 1, Compound 3c
N
Me
CHO
n-C6H17
7.820
7.800
7.460
7.458
7.443
7.440
7.437
7.421
7.420
7.370
7.348
7.258
7.232
7.213
7.195
4.069
2.561
2.544
2.526
1.695
1.677
1.658
1.640
1.525
1.508
1.488
1.353
1.342
1.334
1.329
1.323
1.309
1.300
0.907
0.890


181.484
138.494
134.441
126.871
126.598
121.186
120.225
112.172
109.331
97.412
76.416
75.993
75.569
70.168
30.838
30.667
28.203
28.104
27.946
27.780
21.650
18.885
13.086
-0.001
180
160
140
120
100
80
60
40
20
0 ppm
Table 1, Compound 3c
N
Me
CHO
n-C8H17


0.732
0.832
0.965
0.964
0.970
3.000
0.816
1.939
2.153
3.397
3.198
ppm
Table 1, Compound 3d
N
Me
CHO
7.811
7.808
7.805
7.785
7.781
7.778
7.451
7.447
7.428
7.423
7.419
7.400
7.396
7.344
7.341
7.319
7.316
7.313
7.252
7.227
7.223
7.204
7.200
7.197
7.177
7.174
4.044
2.776
2.760
2.747
2.733
2.717
1.964
1.954
1.945
1.934
1.913
1.903
1.894
1.839
1.827
1.817
1.806
1.796
1.787
1.774
1.754
1.687
1.676
1.659
1.645
1.629
1.615


181.082
138.116
133.934
126.442
126.216
120.795
119.829
111.871
108.933
101.051
76.083
75.659
75.235
69.762
31.330
30.265
28.671
24.551
23.392
Me
N
CHO
Table 1, Compound 3d
ppm

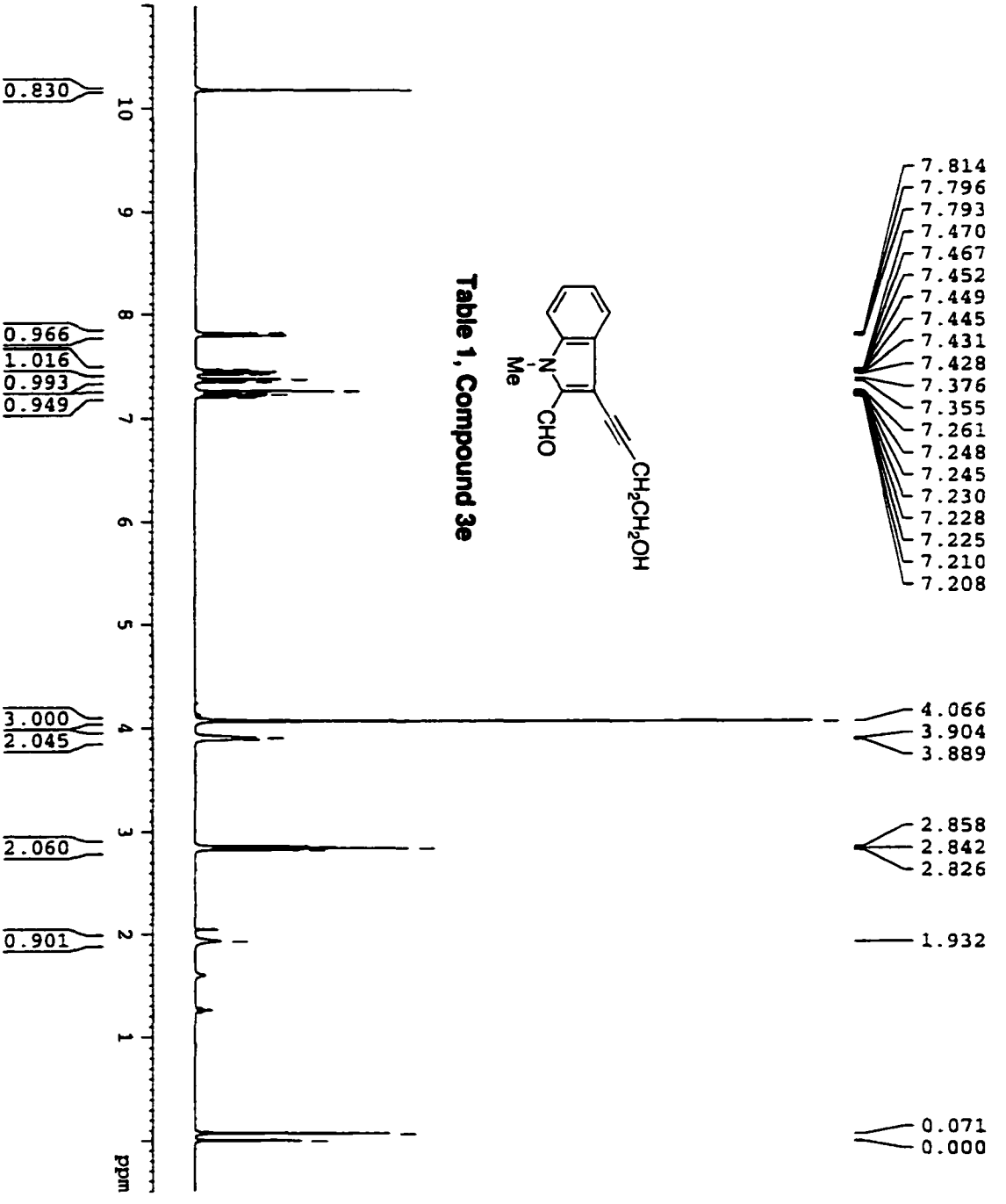
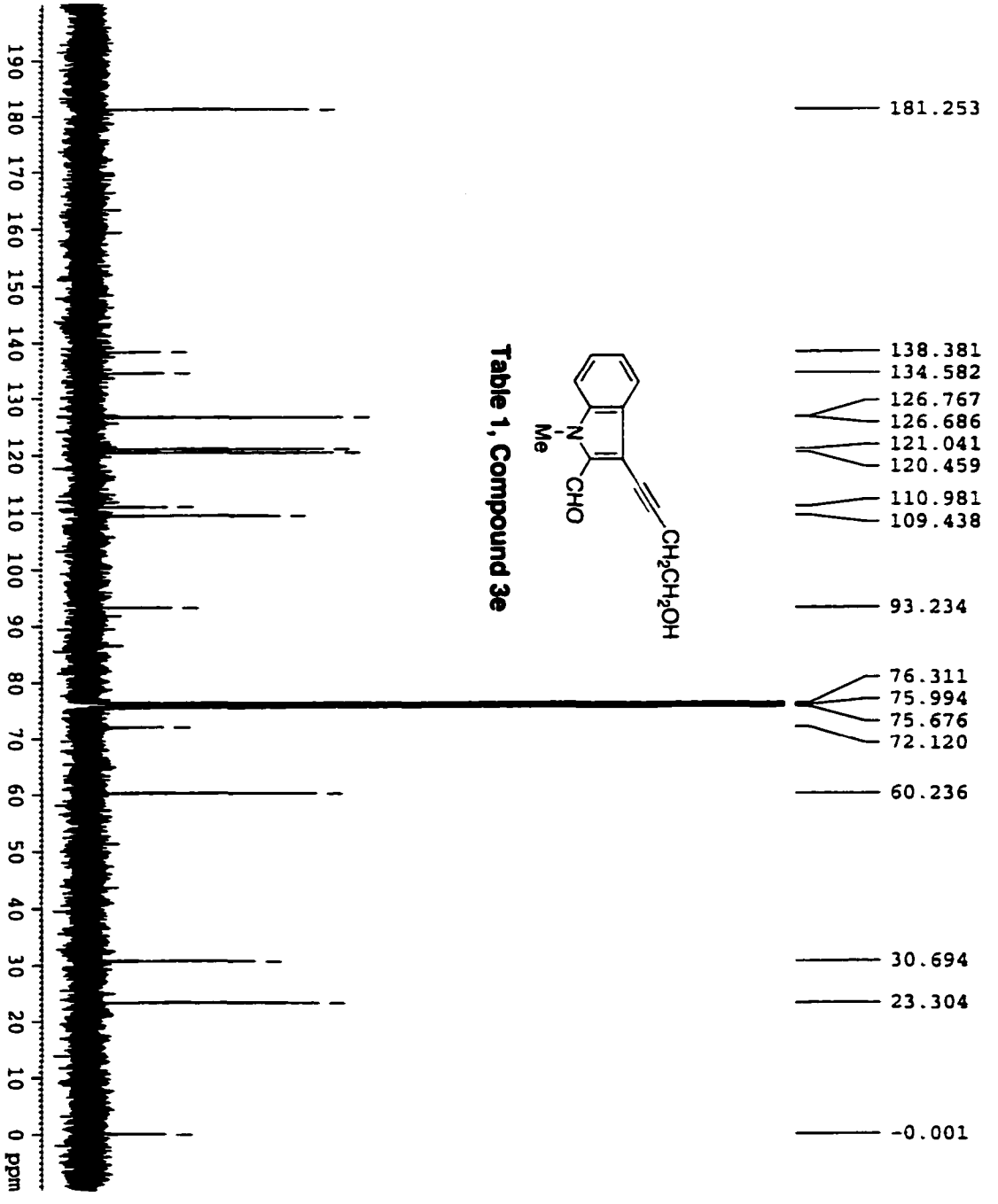


Table 1, Compound 3e
0.830
0.966
1.016
0.993
0.949
3.000
2.045
2.060
0.901
7.814
7.796
7.793
7.470
7.467
7.452
7.449
7.445
7.431
7.428
7.376
7.355
7.261
7.248
7.245
7.230
7.228
7.225
7.210
7.208
4.066
3.904
3.889
2.858
2.842
2.826
1.932
0.071
0.000
Me
N
CHO
CH2CH2OH
ppm


181.253
138.381
134.582
126.767
126.686
121.041
120.459
110.981
109.438
93.234
76.311
75.994
75.676
72.120
60.236
30.694
23.304
-0.001
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm
Table 1, Compound 3e
N
Me
CHO
CH2CH2OH

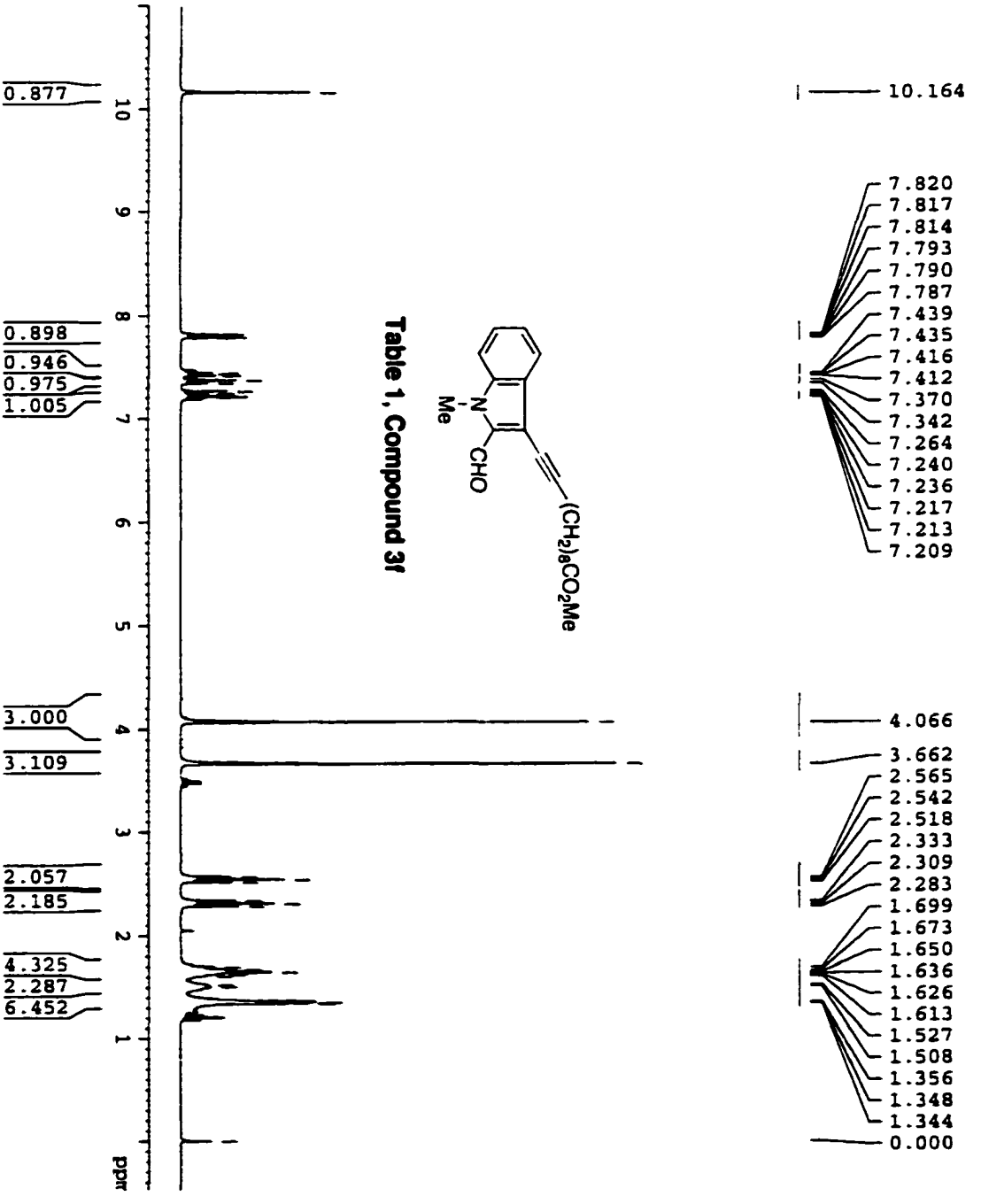
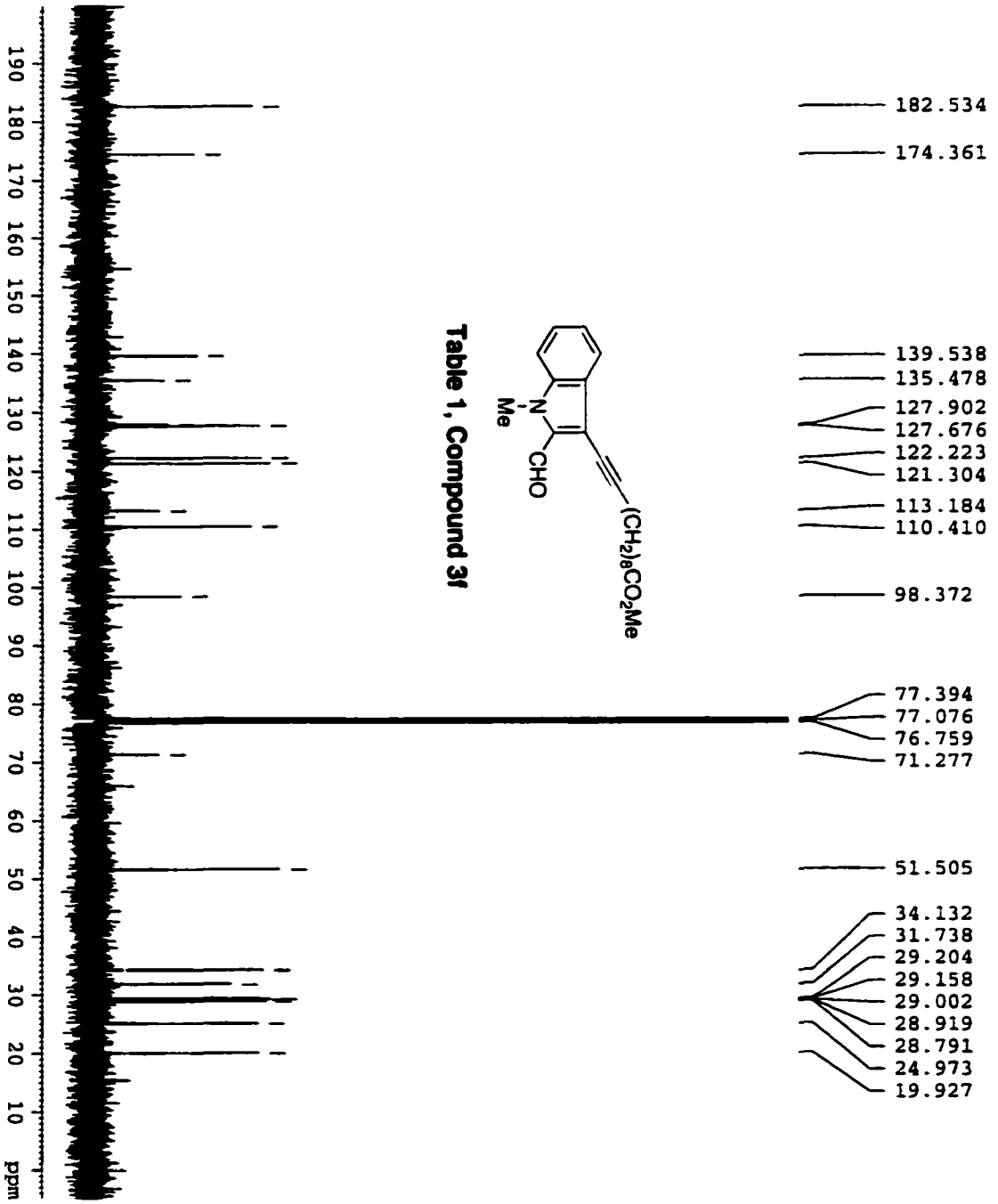
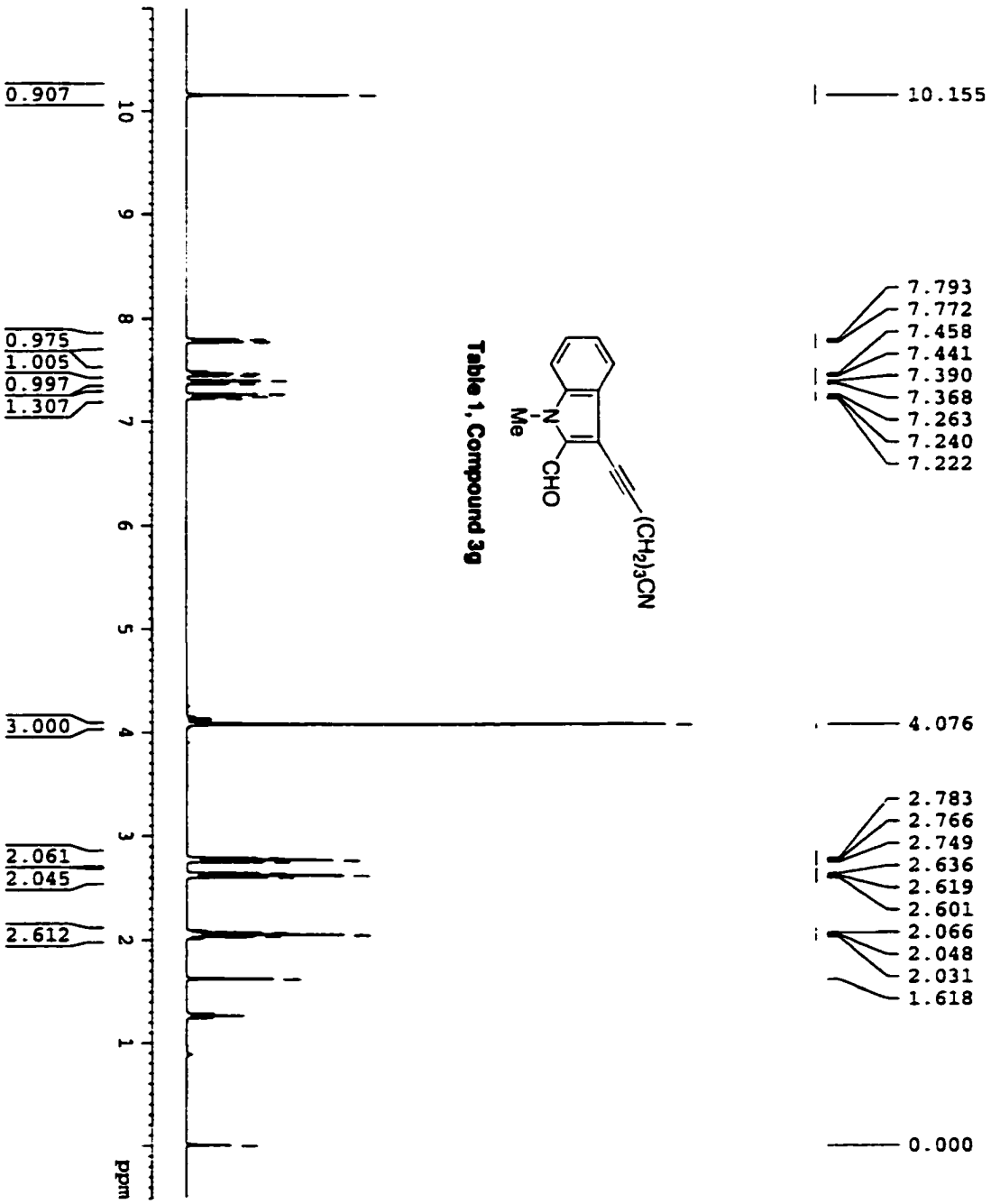
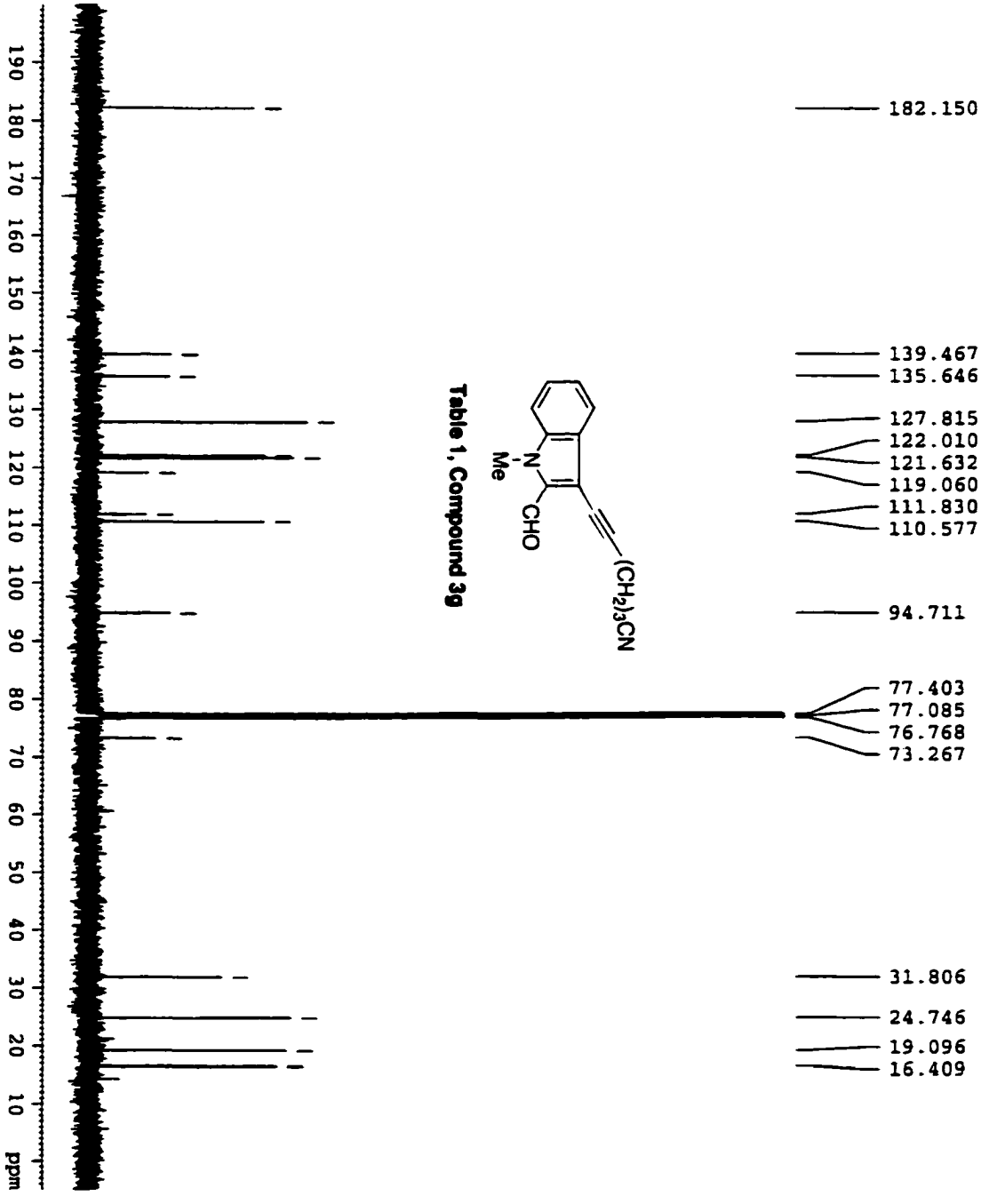
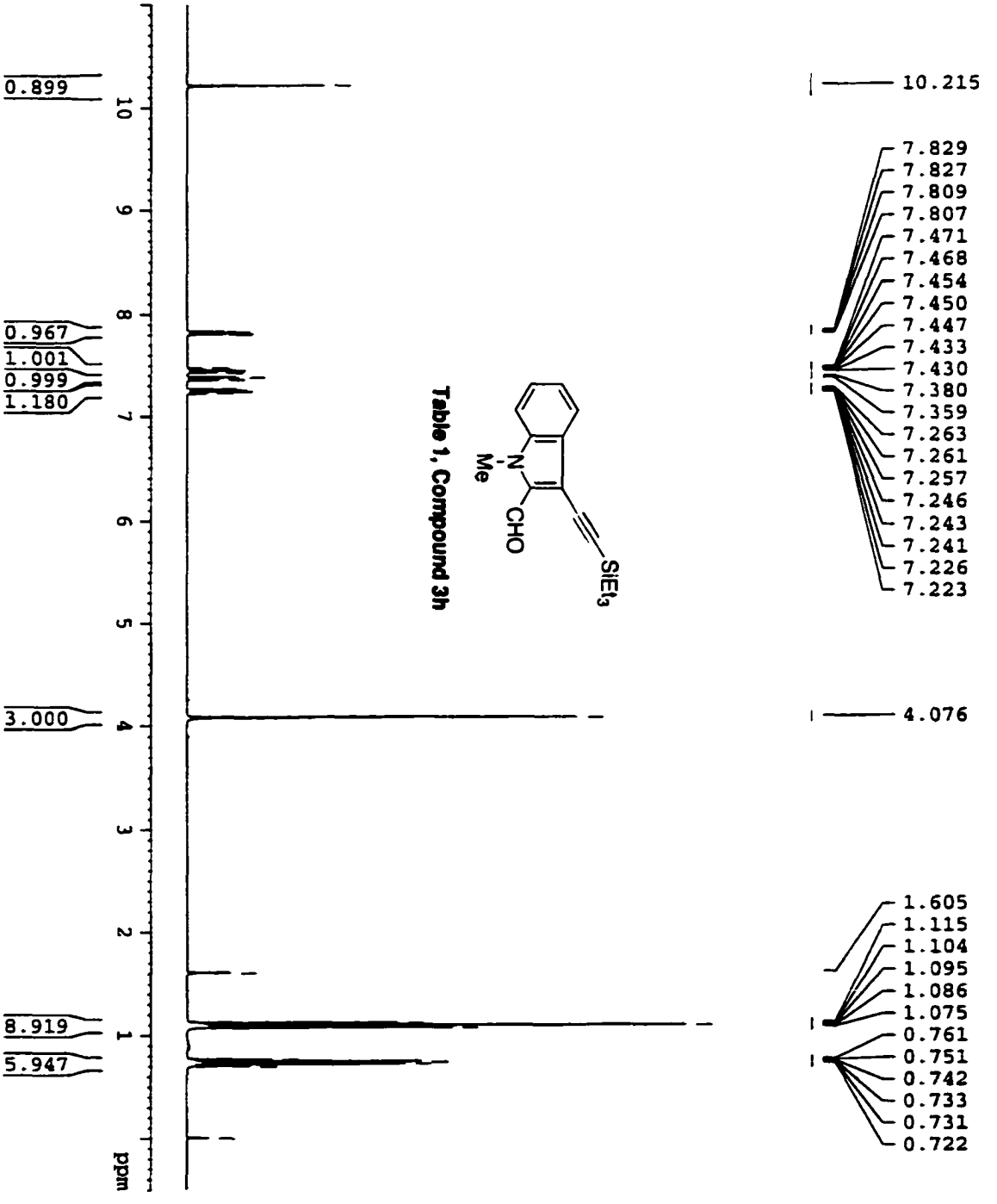


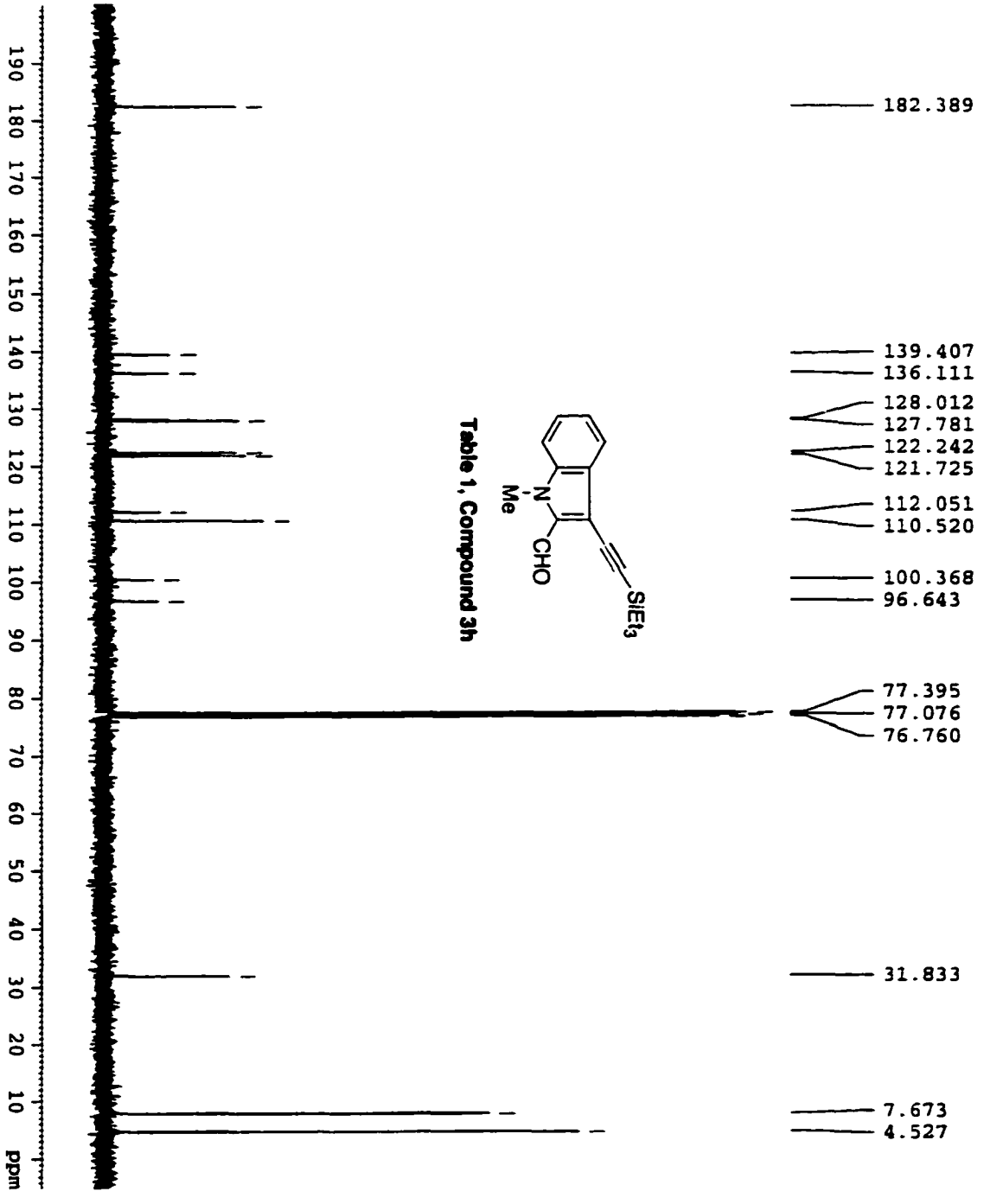
Table 1, Compound 3f
N
Me
CHO
(CH2)8CO2Me
0.877
0.898
0.946
0.975
1.005
3.000
3.109
2.057
2.185
4.325
2.287
6.452
ppm
10.164
7.820
7.817
7.814
7.793
7.790
7.787
7.439
7.435
7.416
7.412
7.370
7.342
7.264
7.240
7.236
7.217
7.213
7.209
4.066
3.662
2.565
2.542
2.518
2.333
2.309
2.283
1.699
1.673
1.650
1.636
1.626
1.613
1.527
1.508
1.356
1.348
1.344
0.000

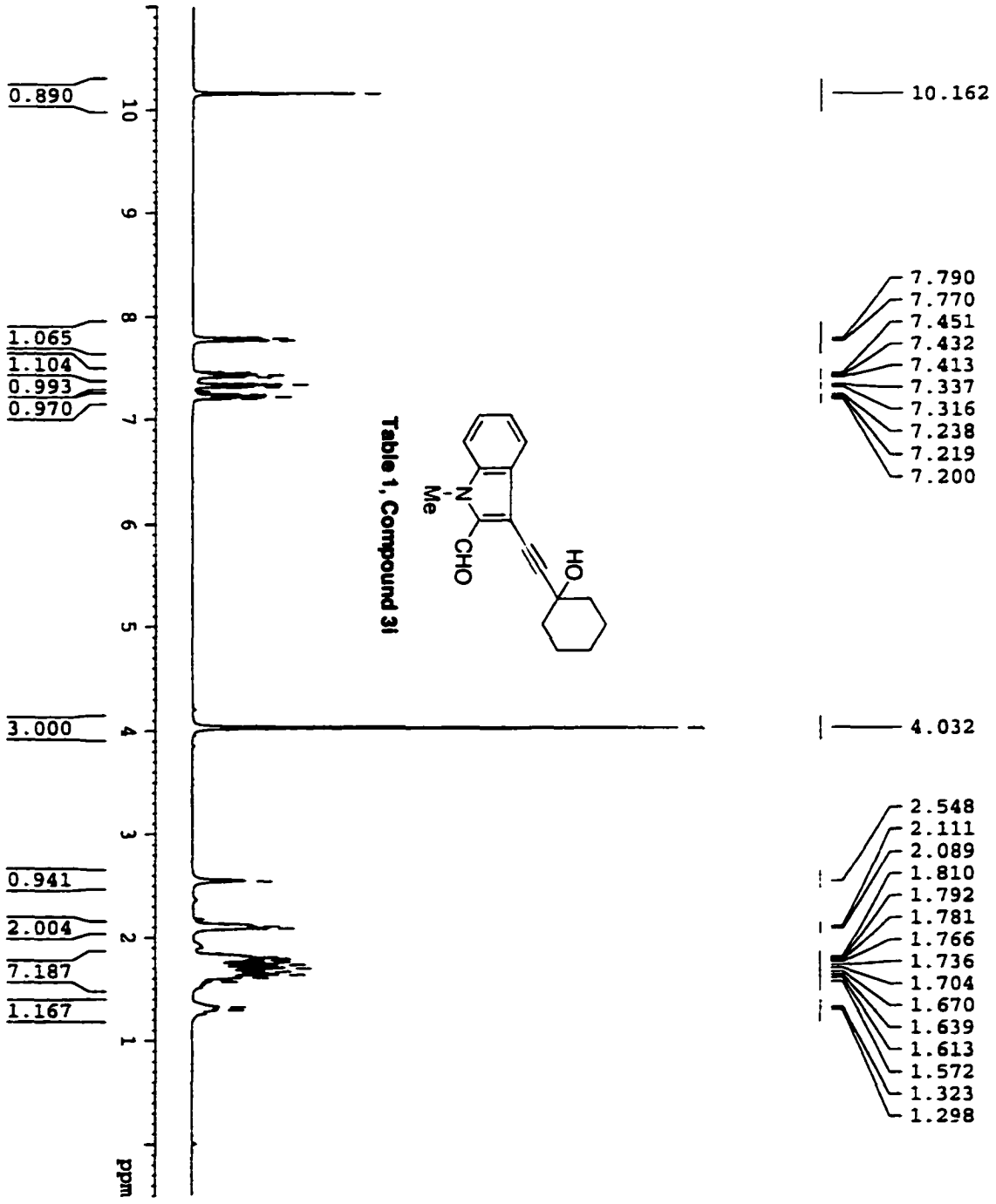

182.534
174.361
139.538
135.478
127.902
127.676
122.223
121.304
113.184
110.410
98.372
77.394
77.076
76.759
71.277
51.505
34.132
31.738
29.204
29.158
29.002
28.919
28.791
24.973
19.927
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
Table 1, Compound 3f
N
Me
CHO
(CH2)8CO2Me

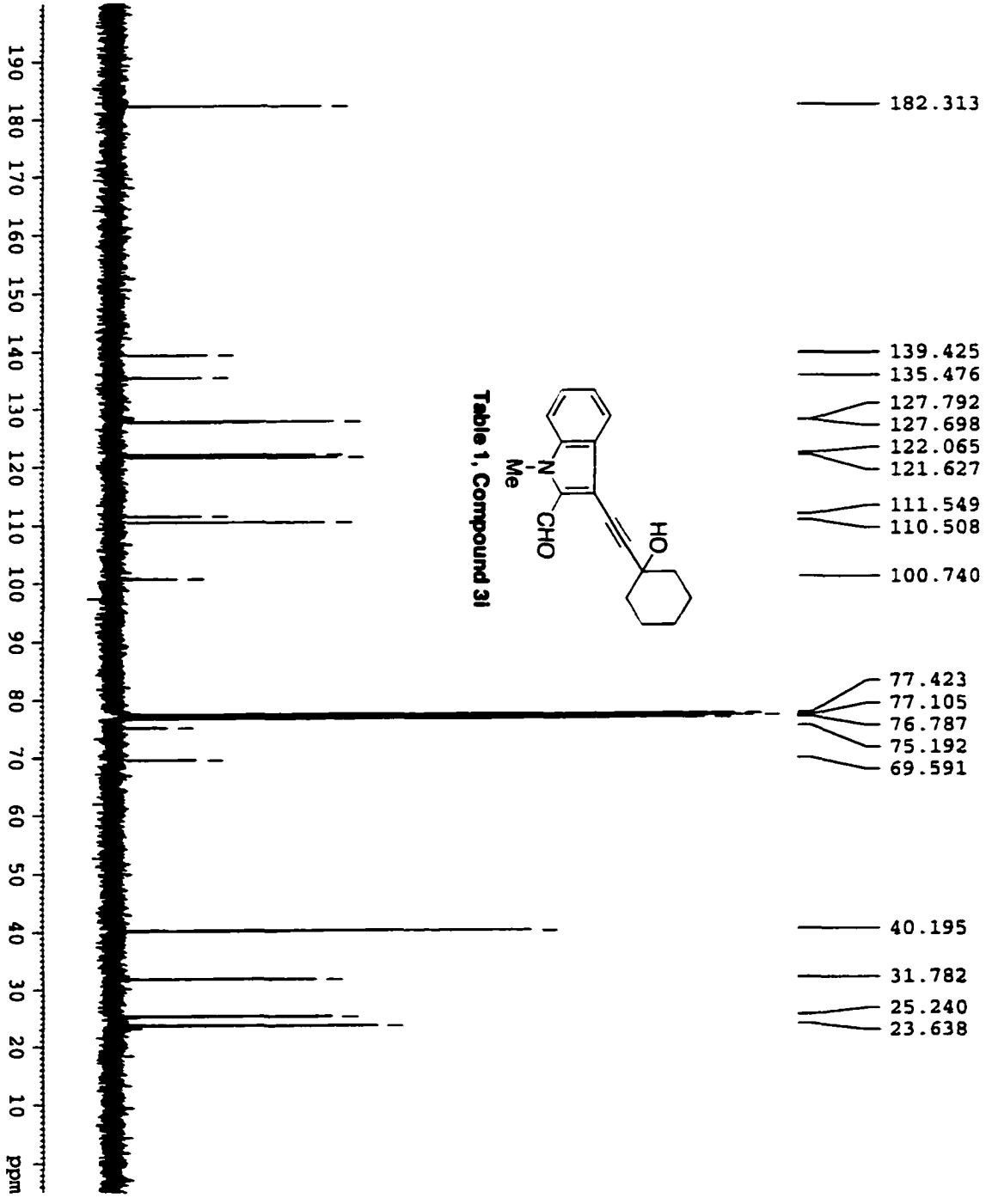

0.907
0.975
1.005
0.997
1.307
3.000
2.061
2.045
2.612
ppm
10
9
8
7
6
5
4
3
2
1
Table 1, Compound 3g
N
Me
CHO
(CH2)3CN
10.155
7.793
7.772
7.458
7.441
7.390
7.368
7.263
7.240
7.222
4.076
2.783
2.766
2.749
2.636
2.619
2.601
2.066
2.048
2.031
1.618
0.000


182.150
139.467
135.646
127.815
122.010
121.632
119.060
111.830
110.577
94.711
77.403
77.085
76.768
73.267
31.806
24.746
19.096
16.409
Table 1, Compound 3g
Me
N
CHO
(CH2)3CN
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


0.899
0.967
1.001
0.999
1.180
3.000
8.919
5.947
ppm
10.215
7.829
7.827
7.809
7.807
7.471
7.468
7.454
7.450
7.447
7.433
7.430
7.380
7.359
7.263
7.261
7.257
7.246
7.243
7.241
7.226
7.223
4.076
1.605
1.115
1.104
1.095
1.086
1.075
0.761
0.751
0.742
0.733
0.731
0.722
Table 1, Compound 3h
Me
N
CHO
SiEt3


182.389
139.407
136.111
128.012
127.781
122.242
121.725
112.051
110.520
100.368
96.643
77.395
77.076
76.760
31.833
7.673
4.527
Table 1, Compound 3h
N
Me
CHO
SiEt3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


0.890
1.065
1.104
0.993
0.970
3.000
0.941
2.004
7.187
1.167
10
9
8
7
6
5
4
3
2
1
ppm
Table 1, Compound 3l
N
Me
CHO
OH
10.162
7.790
7.770
7.451
7.432
7.413
7.337
7.316
7.238
7.219
7.200
4.032
2.548
2.111
2.089
1.810
1.792
1.781
1.766
1.736
1.704
1.670
1.639
1.613
1.572
1.323
1.298


182.313
139.425
135.476
127.792
127.698
122.065
121.627
111.549
110.508
100.740
77.423
77.105
76.787
75.192
69.591
40.195
31.782
25.240
23.638
Table 1, Compound 3i
N
Me
CHO
HO
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

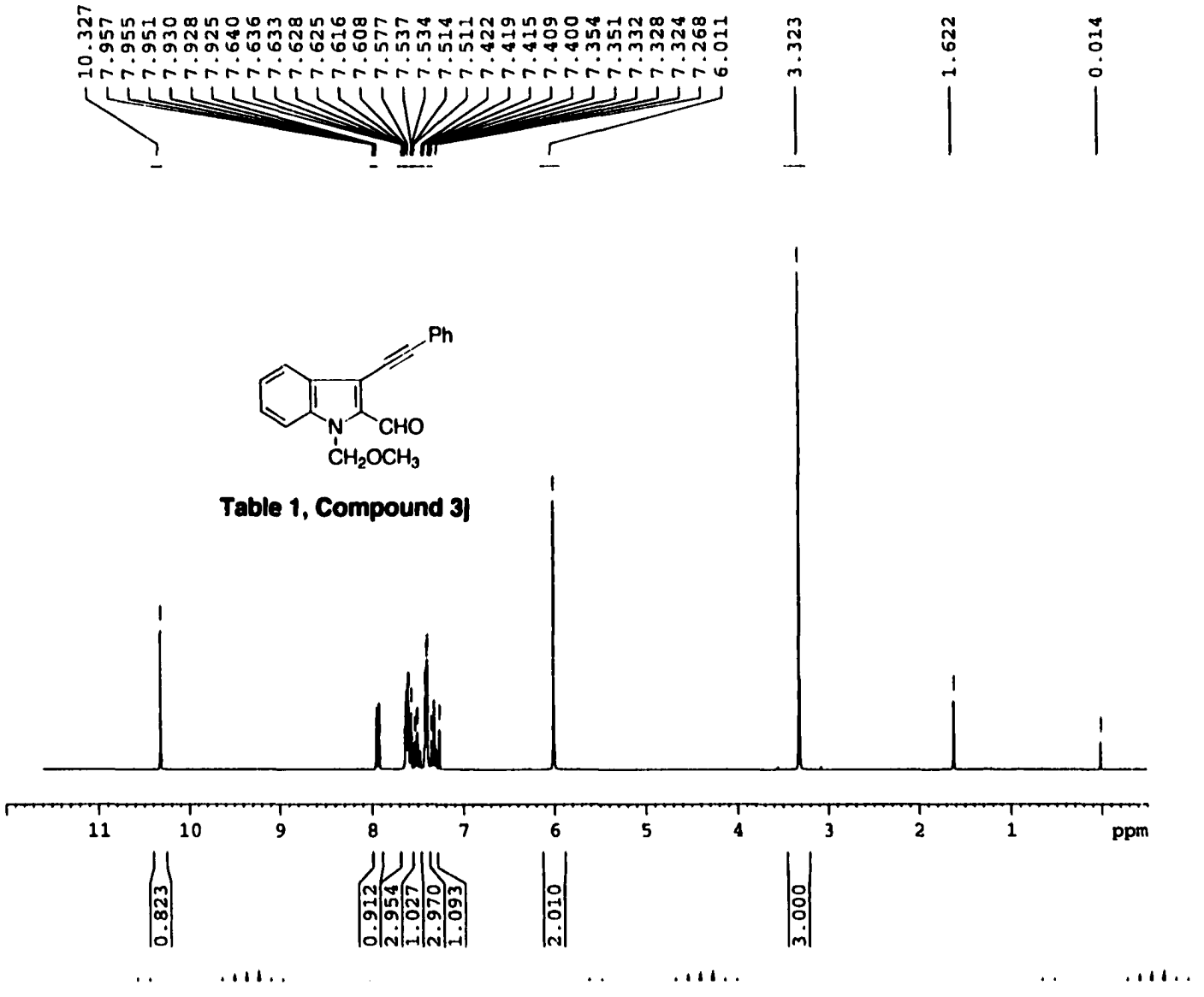


Table 1, Compound 3j

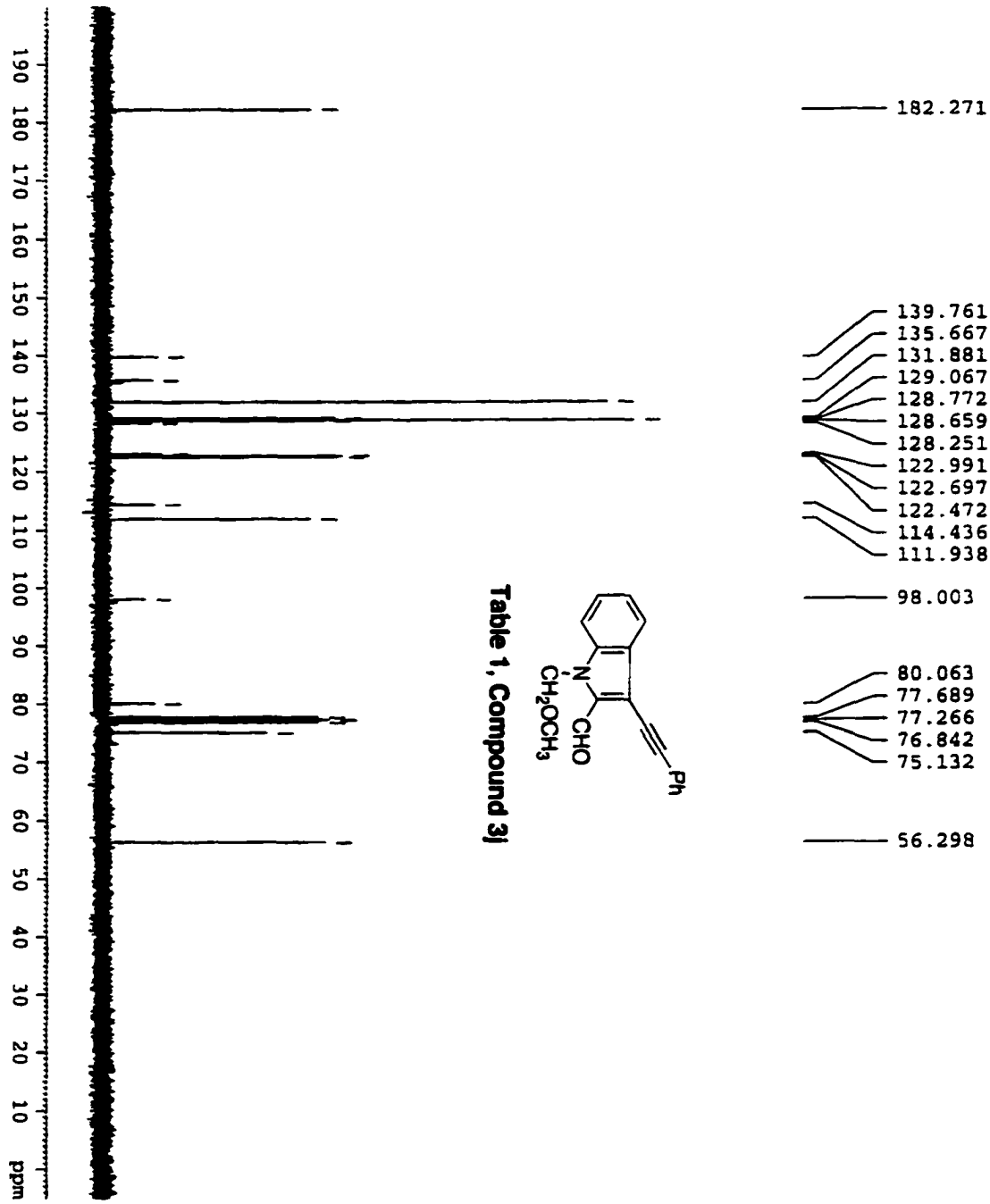


Table 1, Compound 3j

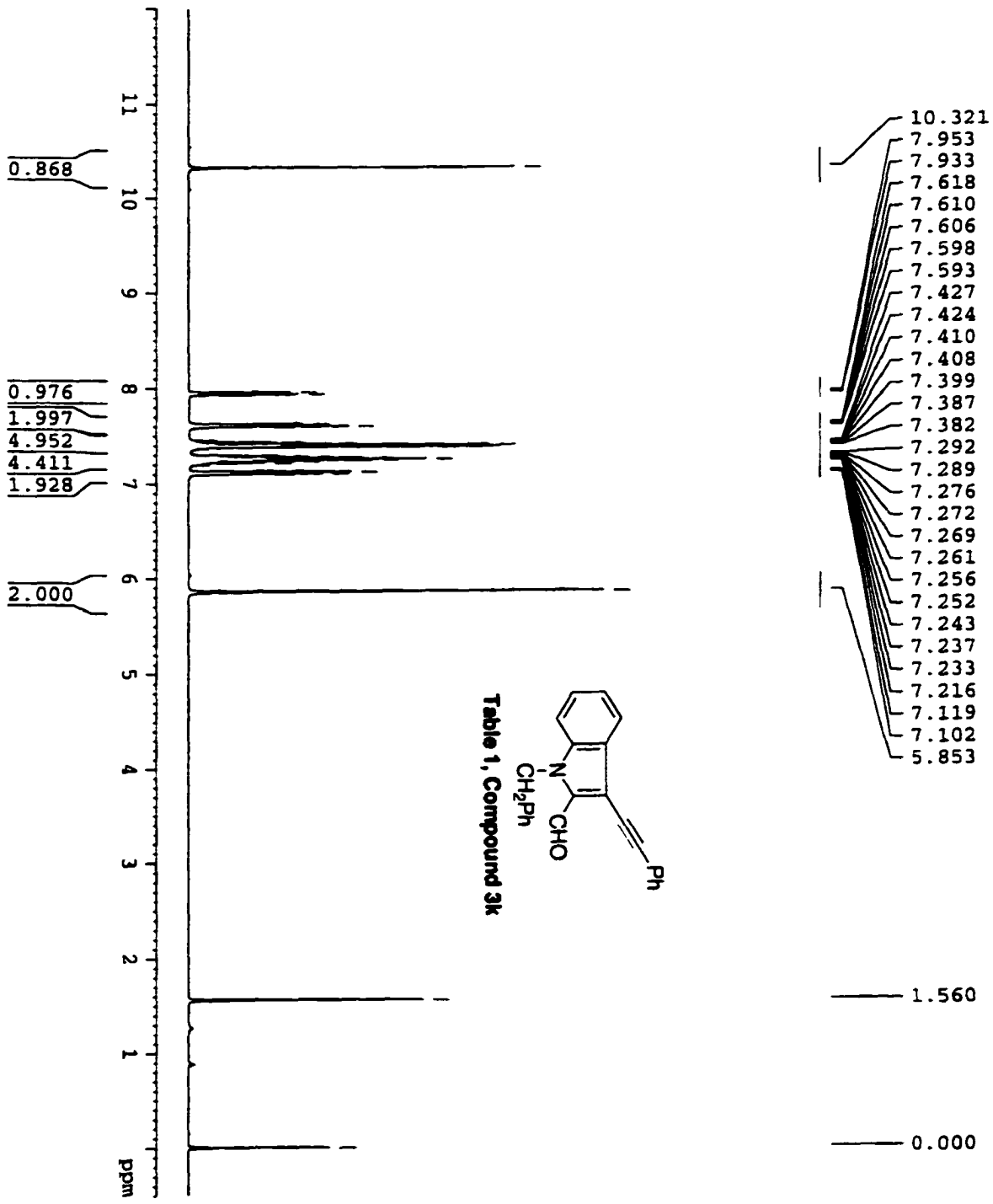


Table 1, Compound 3k

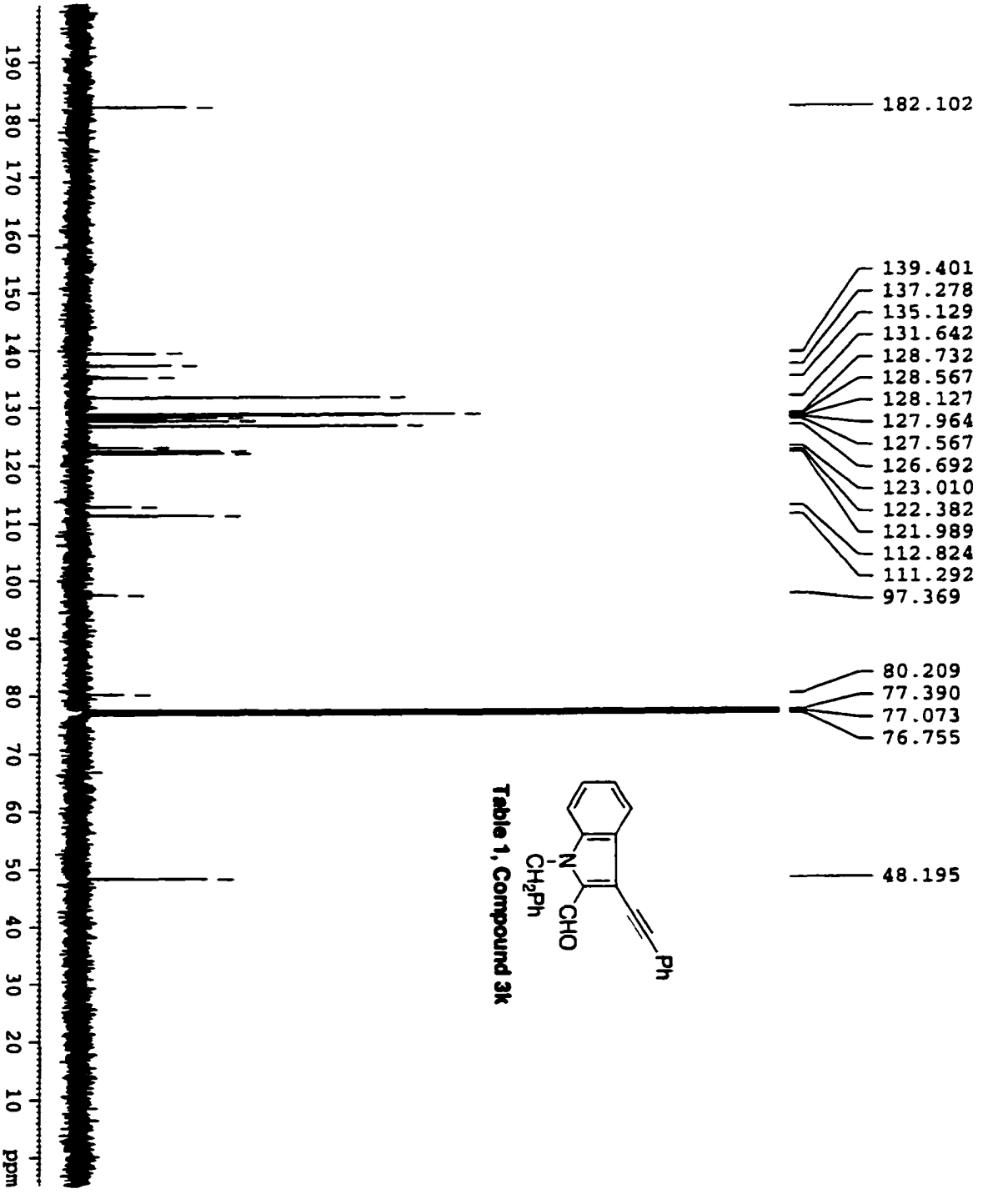


Table 1, Compound 3k

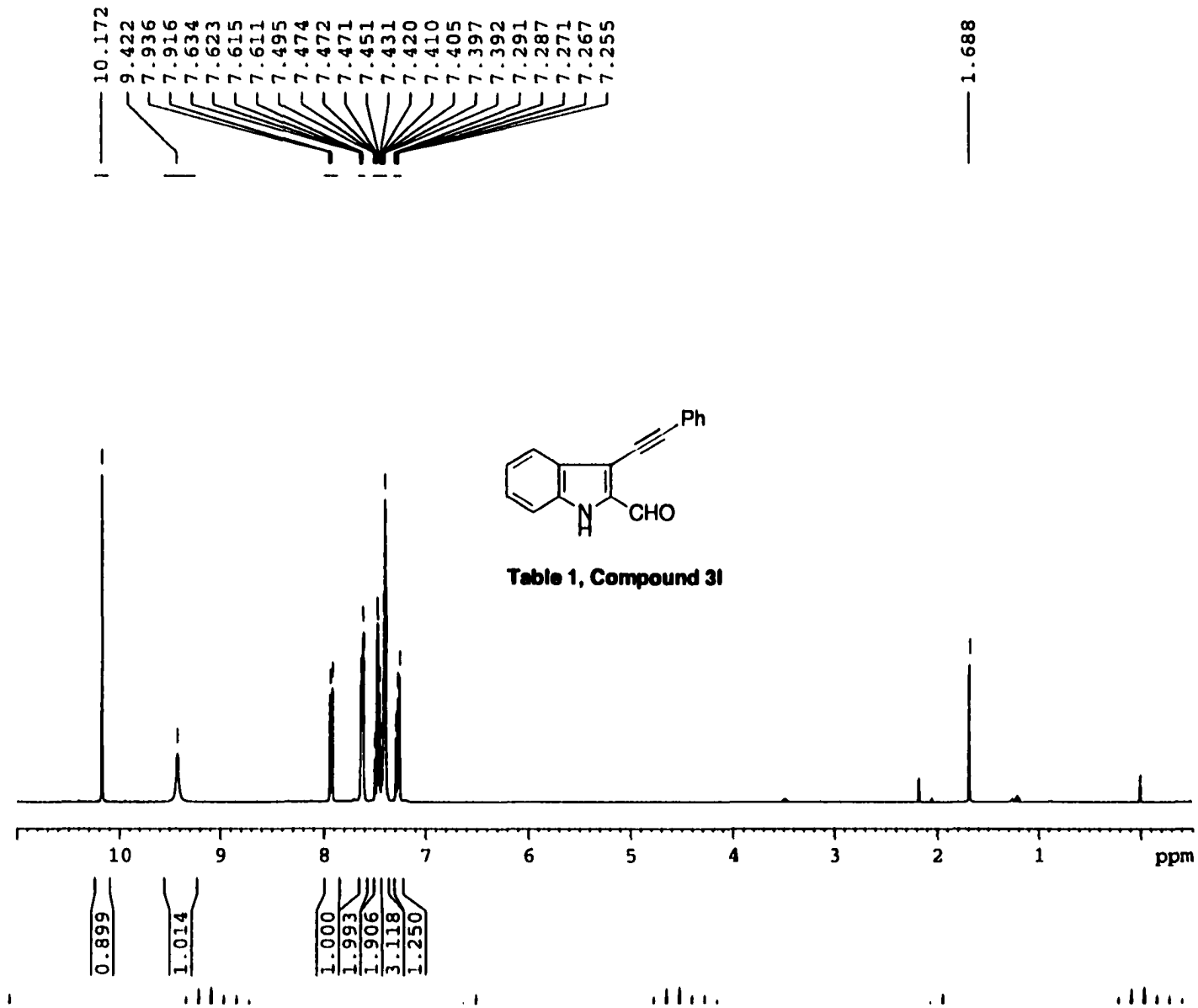


Table 1, Compound 3l

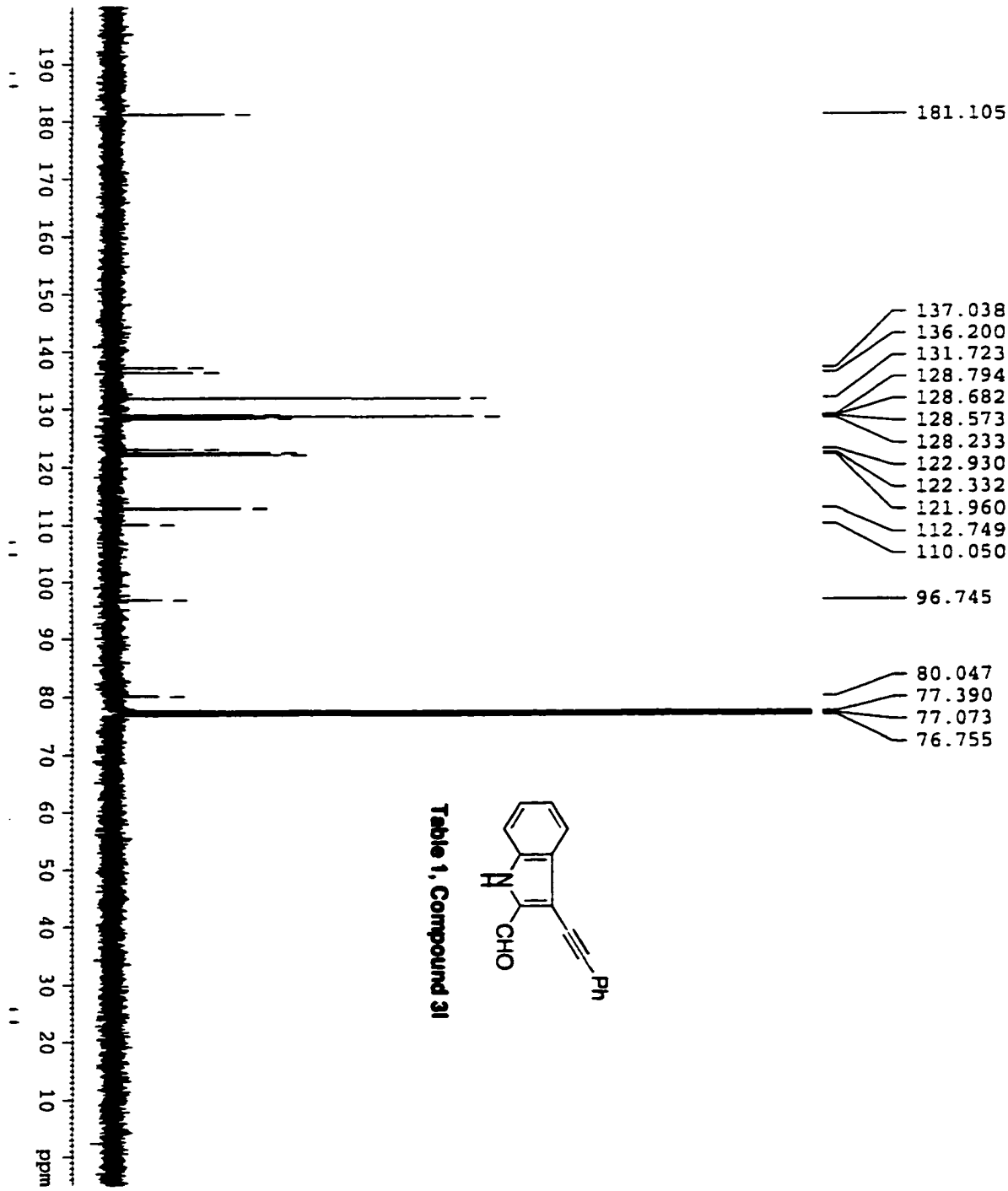


Table 1, Compound 3l

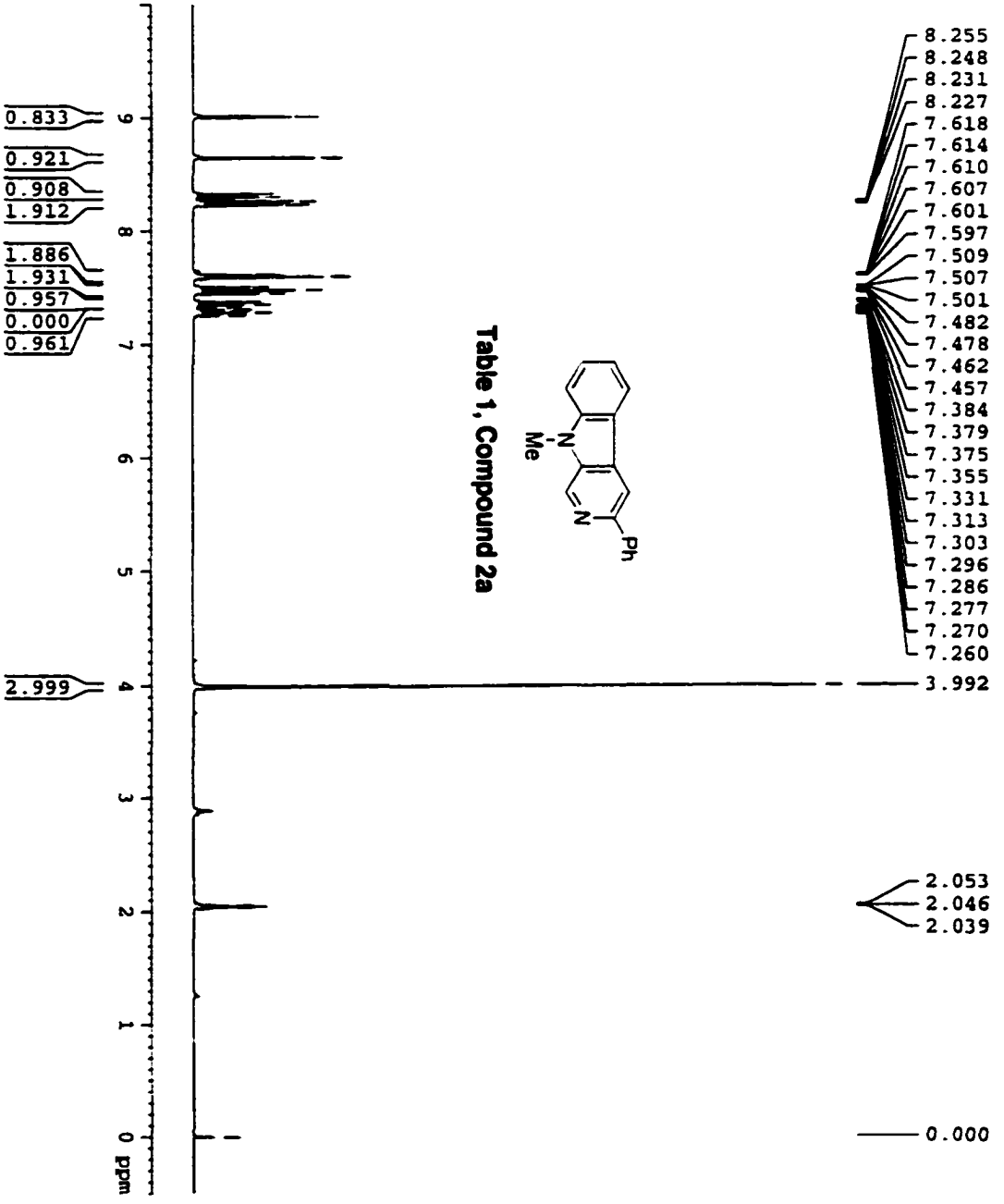


Table 1, Compound 2a

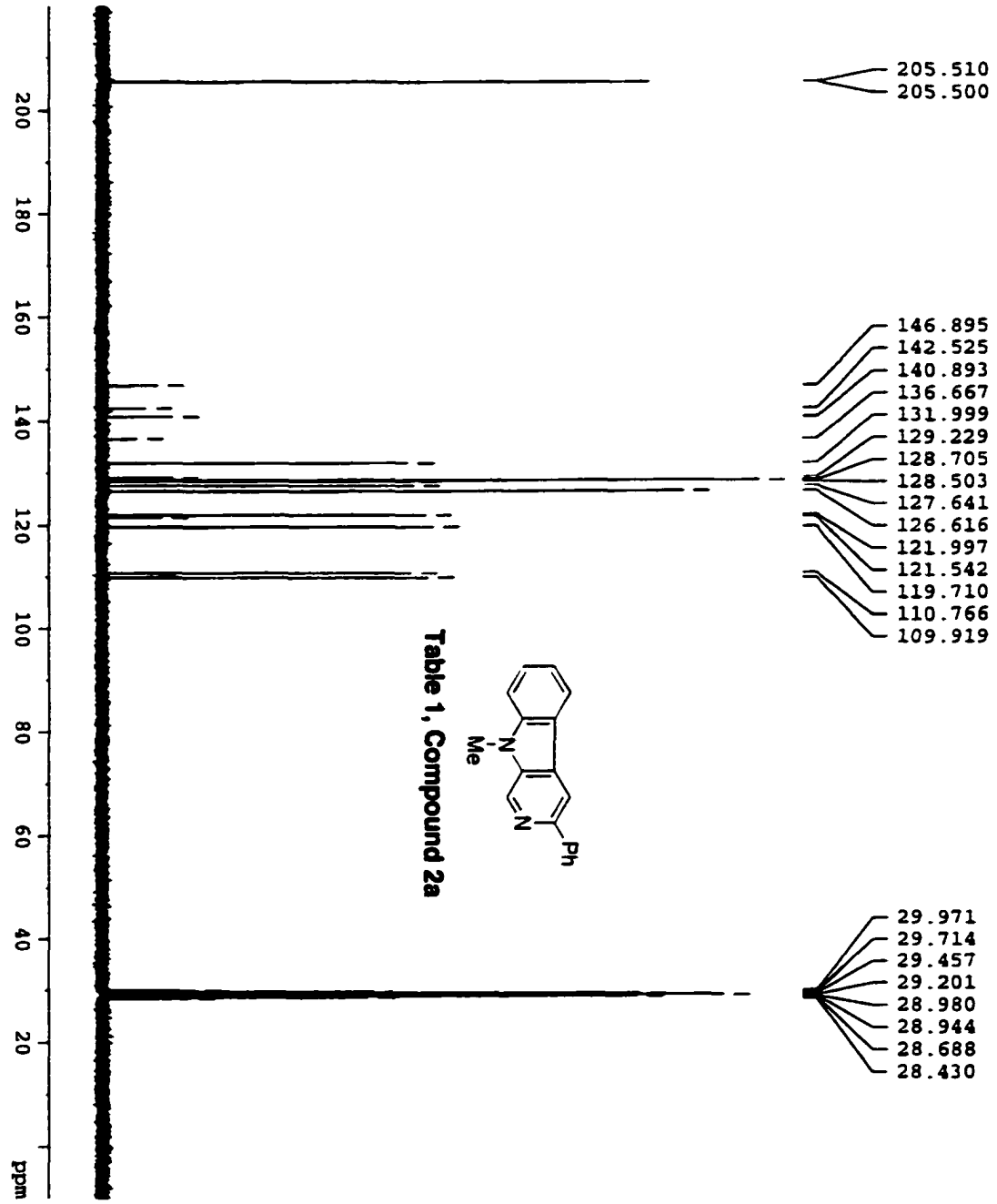
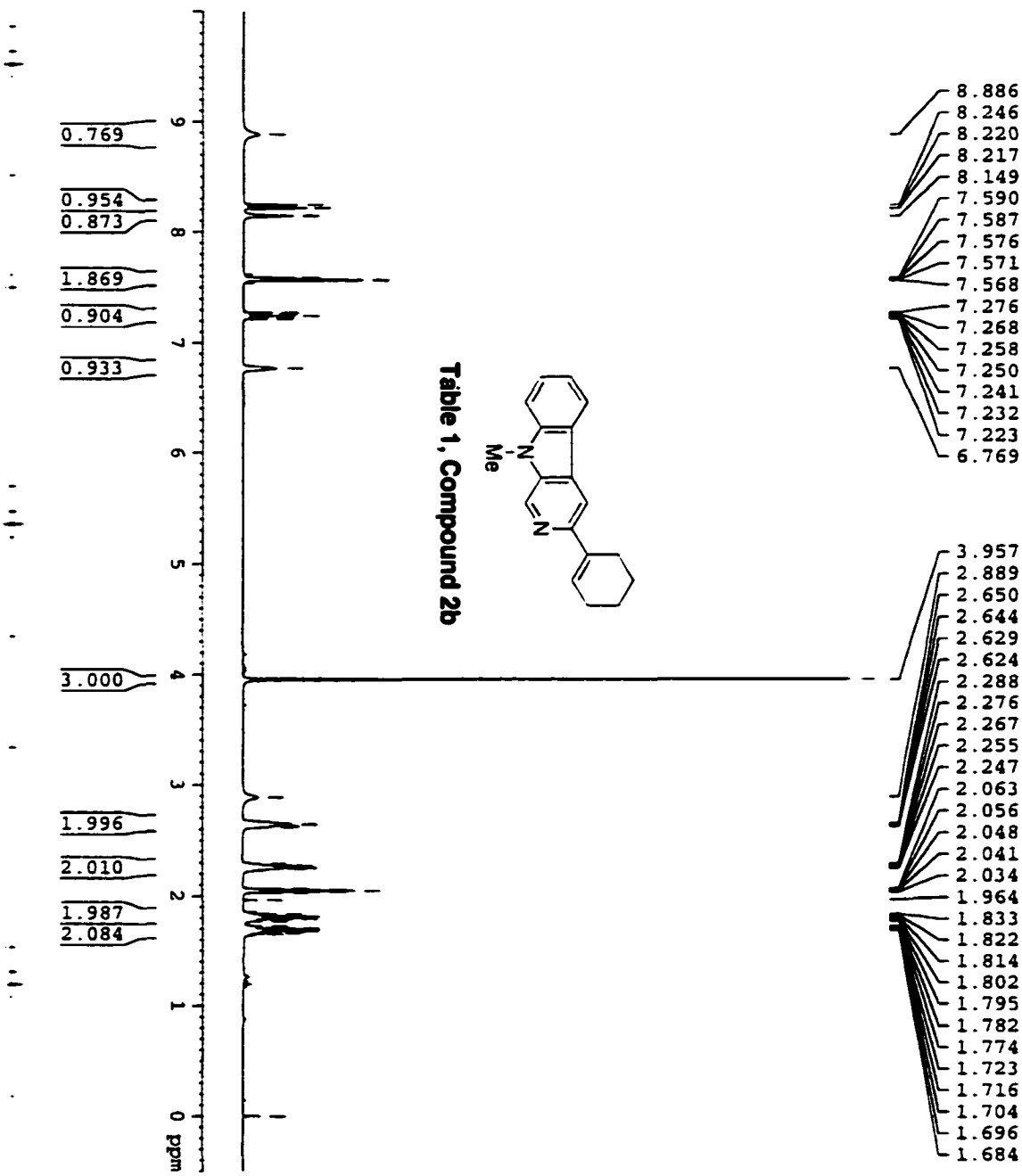


Table 1, Compound 2a


8.886
8.246
8.220
8.217
8.149
7.590
7.587
7.576
7.571
7.568
7.276
7.268
7.258
7.250
7.241
7.232
7.223
6.769
3.957
2.889
2.650
2.644
2.629
2.624
2.288
2.276
2.267
2.255
2.247
2.063
2.056
2.048
2.041
2.034
1.964
1.833
1.822
1.814
1.802
1.795
1.782
1.774
1.723
1.716
1.704
1.696
1.684
0.769
0.954
0.873
1.869
0.904
0.933
3.000
1.996
2.010
1.987
2.084
ppm
Me
N
N
Table 1, Compound 2b

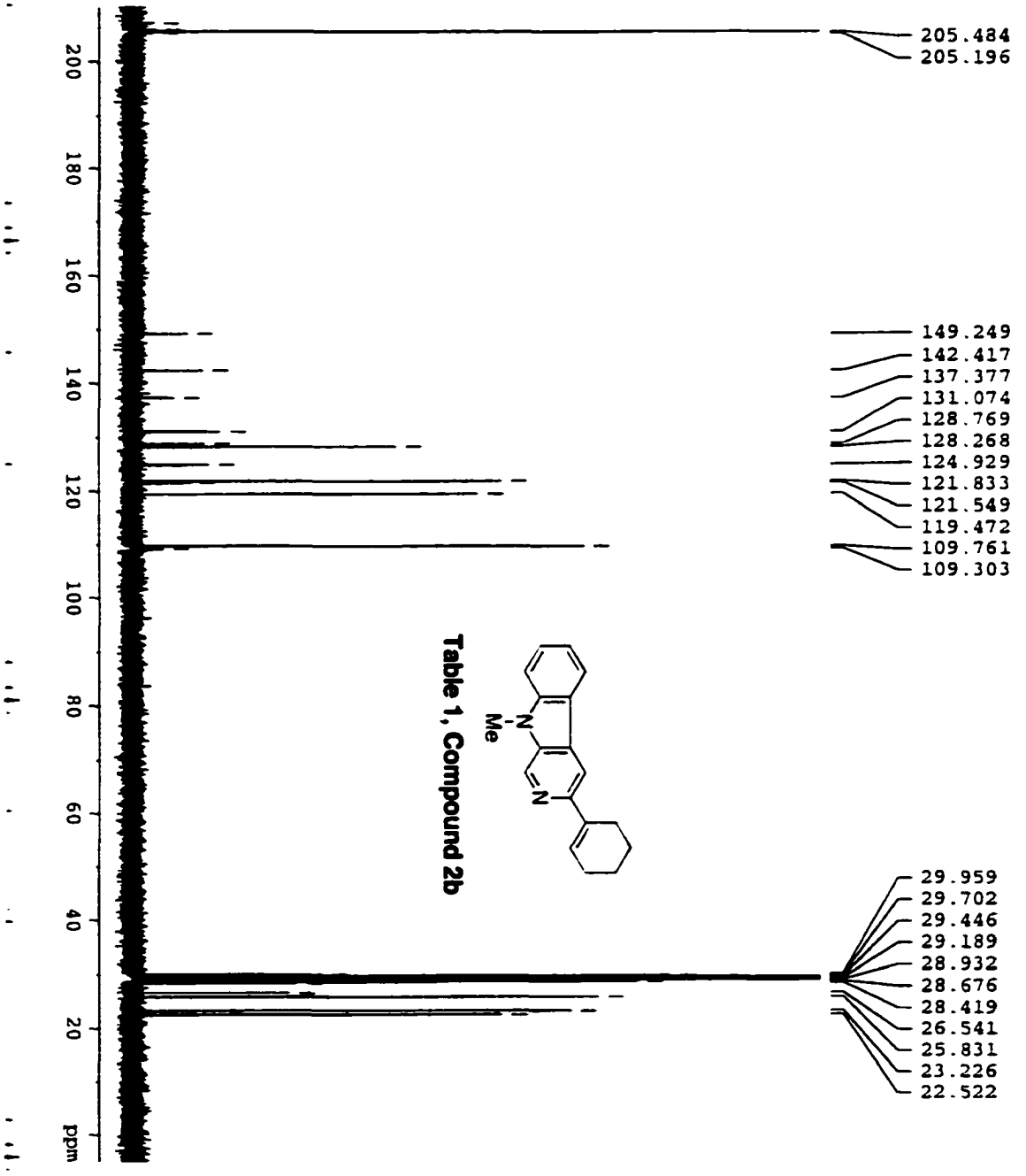


Table 1, Compound 2b

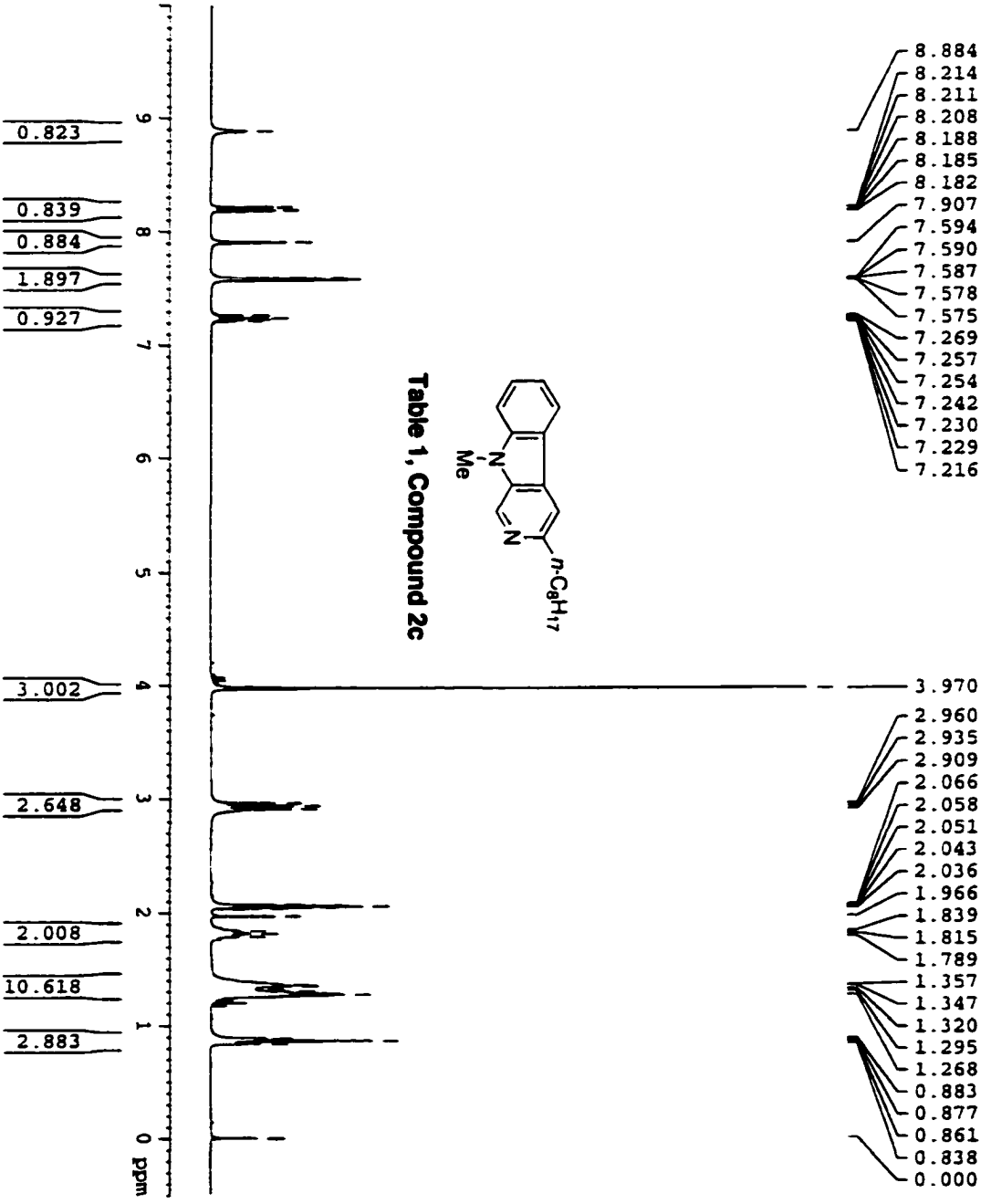


Table 1, Compound 2c

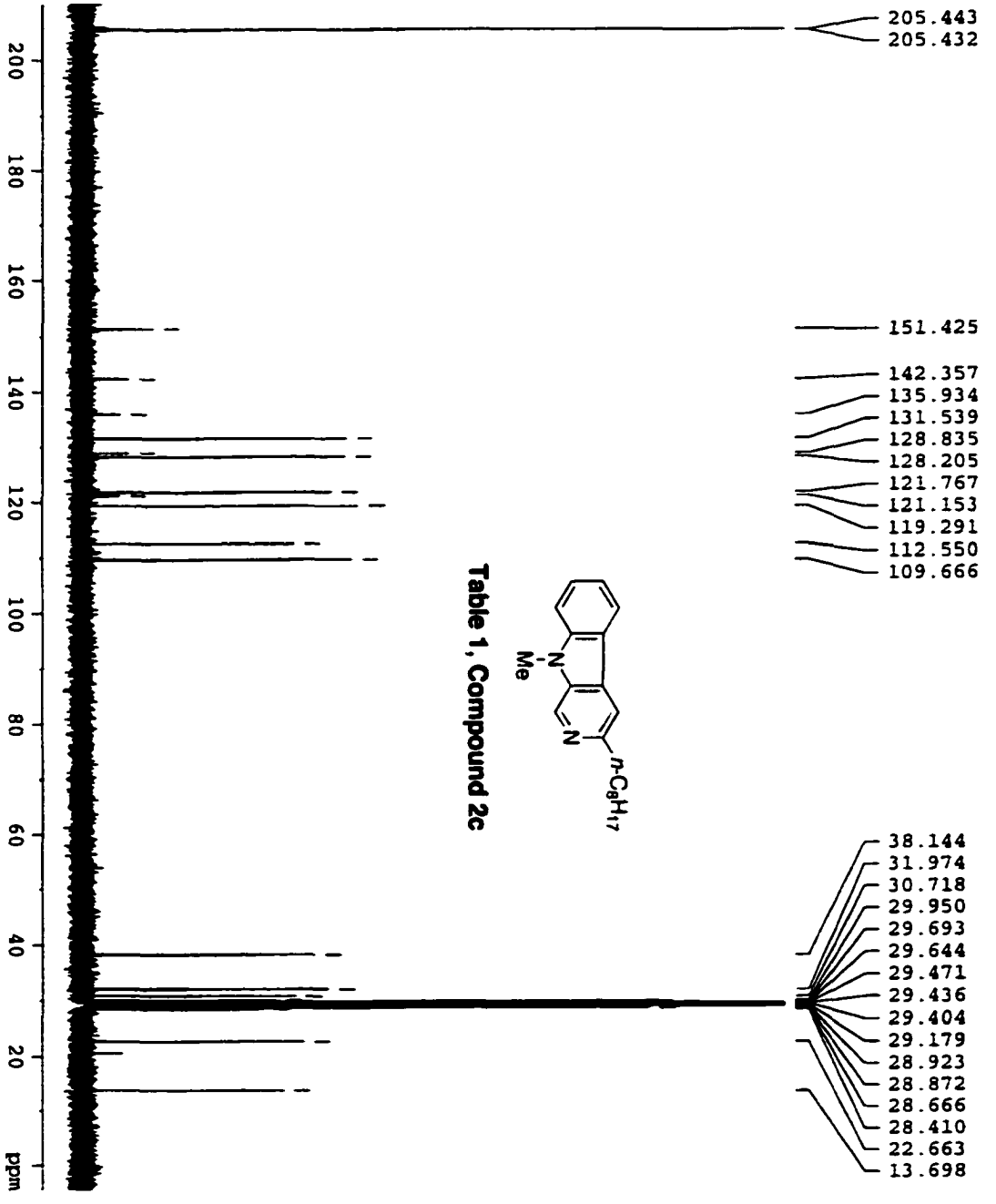
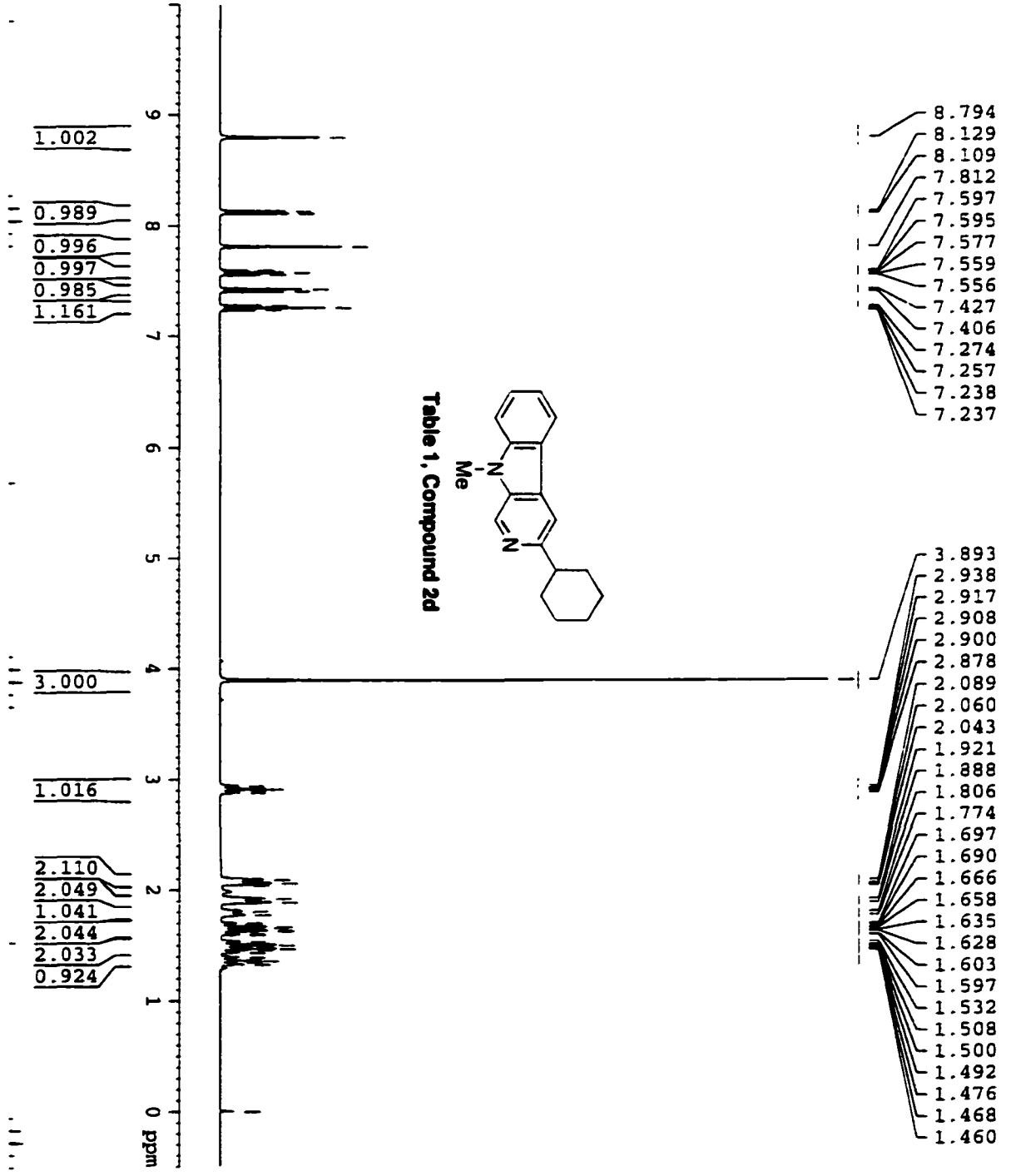


Table 1, Compound 2c


8.794
8.129
8.109
7.812
7.597
7.595
7.577
7.559
7.556
7.427
7.406
7.274
7.257
7.238
7.237
3.893
2.938
2.917
2.908
2.900
2.878
2.089
2.060
2.043
1.921
1.888
1.806
1.774
1.697
1.690
1.666
1.658
1.635
1.628
1.603
1.597
1.532
1.508
1.500
1.492
1.476
1.468
1.460
1.002
0.989
0.996
0.997
0.985
1.161
3.000
1.016
2.110
2.049
1.041
2.044
2.033
0.924
9
8
7
6
5
4
3
2
1
0
ppm
N
Me
N
Table 1, Compound 2d

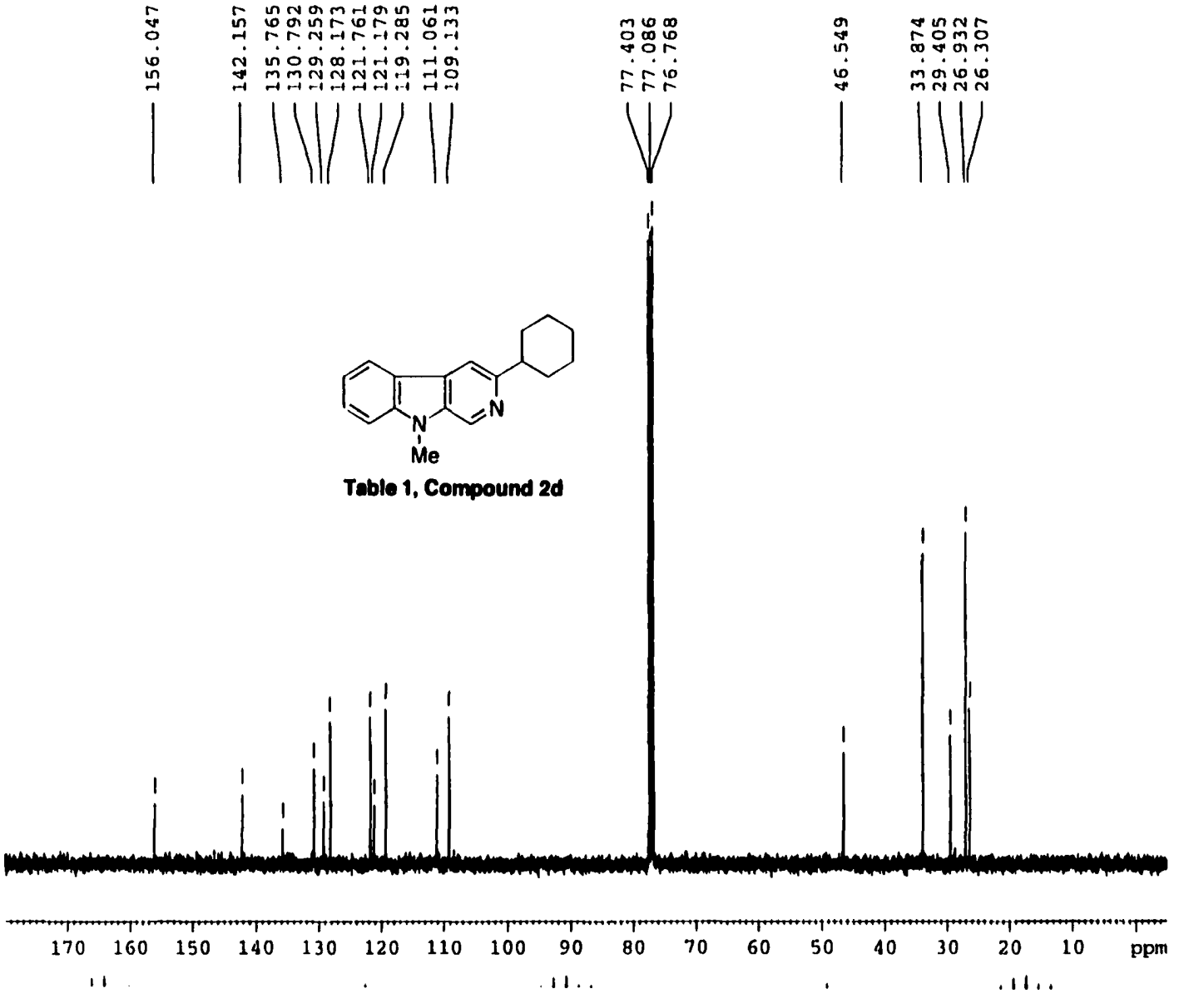
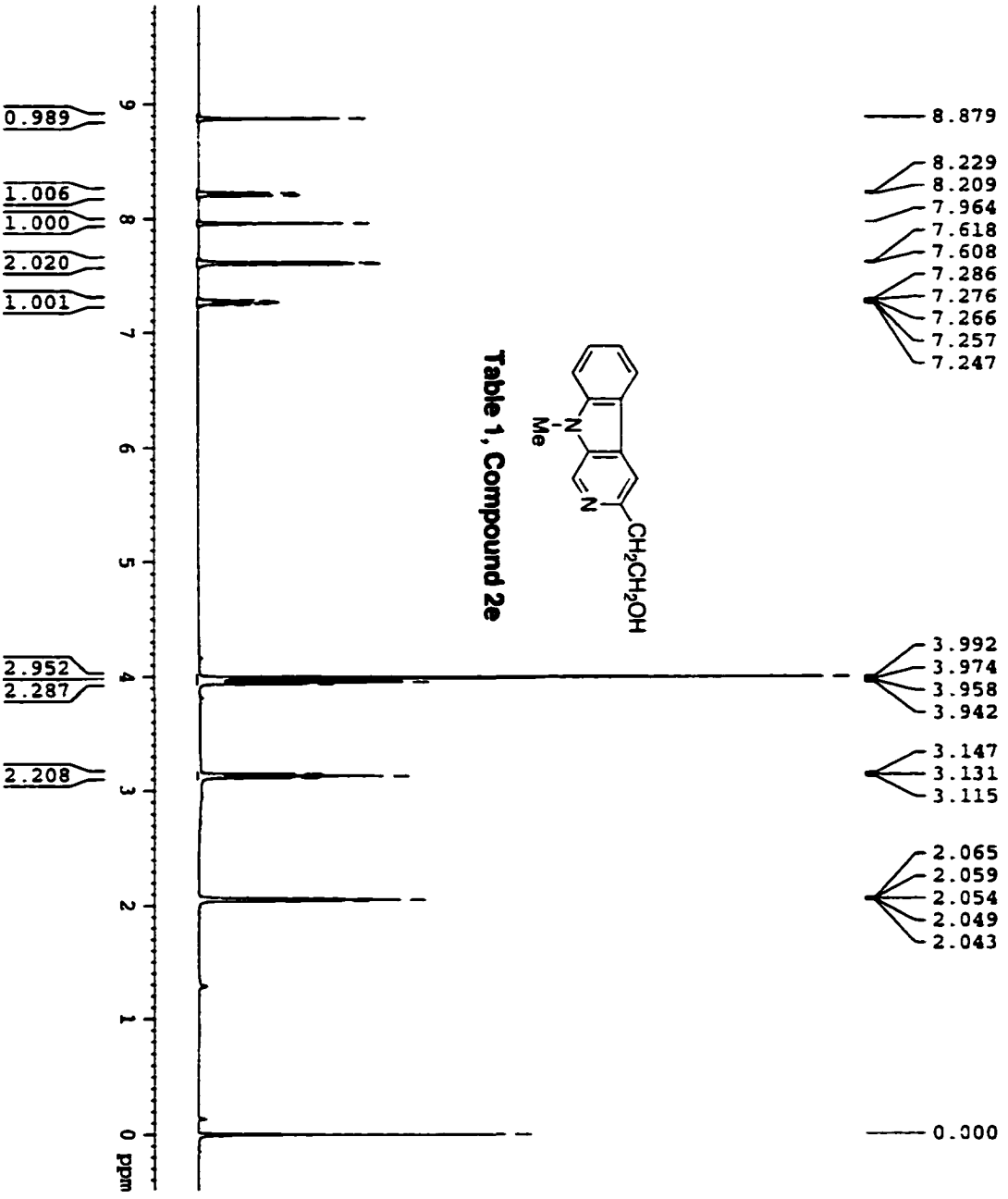
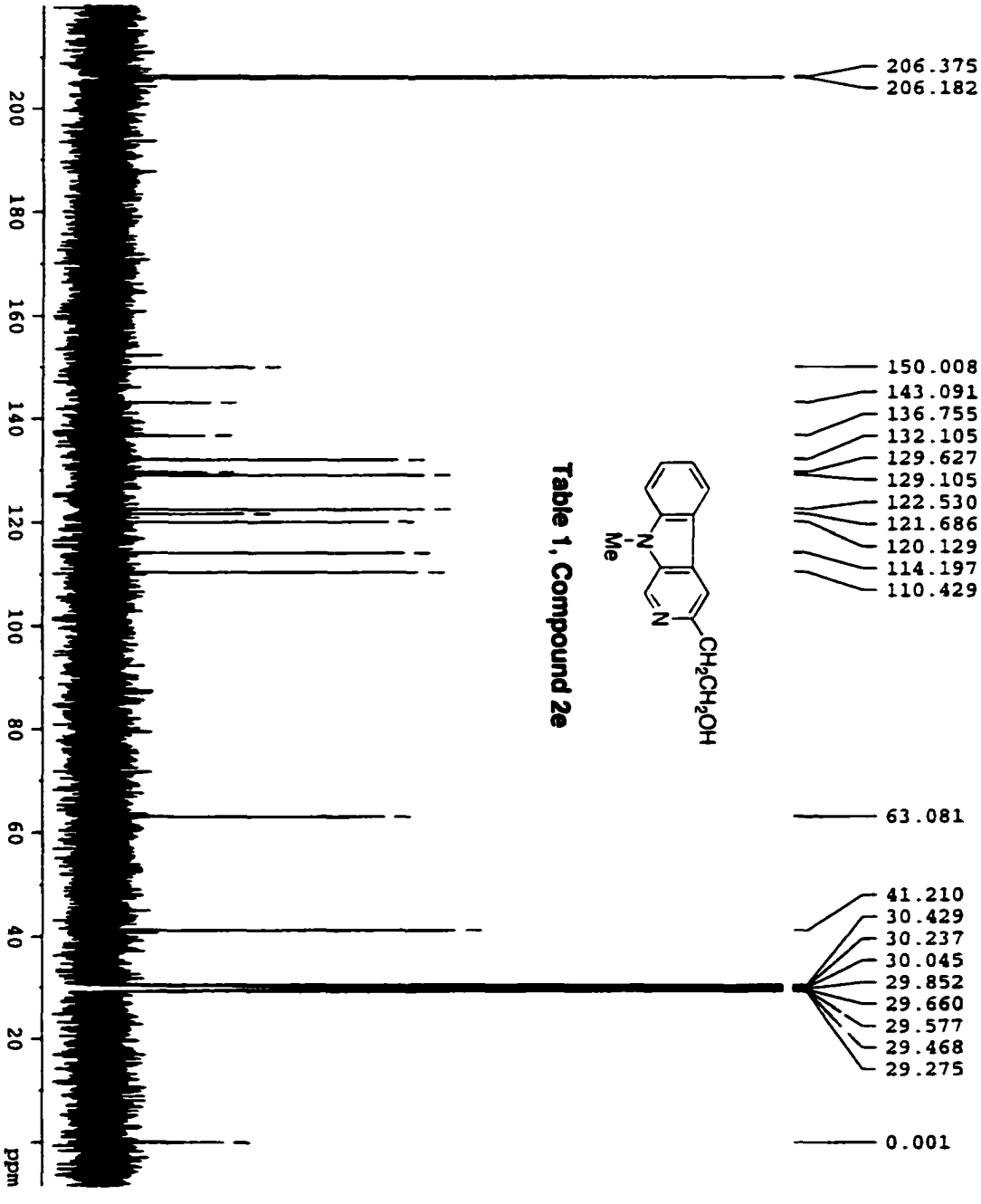


Table 1, Compound 2d


0.989
1.006
1.000
2.020
1.001
2.952
2.287
2.208
9
8
7
6
5
4
3
2
1
0 ppm
8.879
8.229
8.209
7.964
7.618
7.608
7.286
7.276
7.266
7.257
7.247
3.992
3.974
3.958
3.942
3.147
3.131
3.115
2.065
2.059
2.054
2.049
2.043
0.000
Table 1, Compound 2e
Me
N
N
CH2CH2OH


206.375
206.182
150.008
143.091
136.755
132.105
129.627
129.105
122.530
121.686
120.129
114.197
110.429
63.081
41.210
30.429
30.237
30.045
29.852
29.660
29.577
29.468
29.275
0.001
ppm
200
180
160
140
120
100
80
60
40
20
Table 1, Compound 2e
Me
N
N
CH2CH2OH

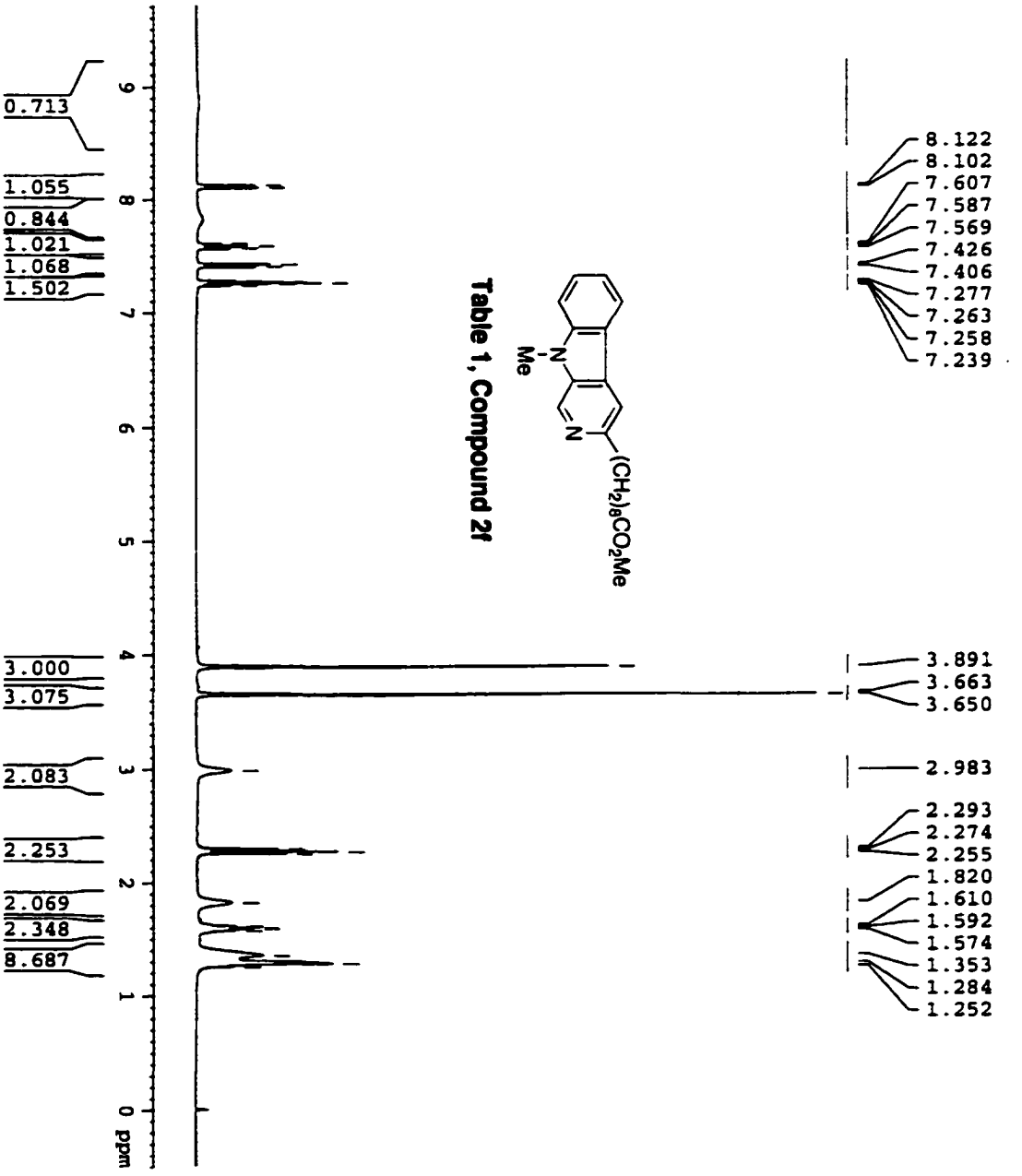


Table 1, Compound 2f

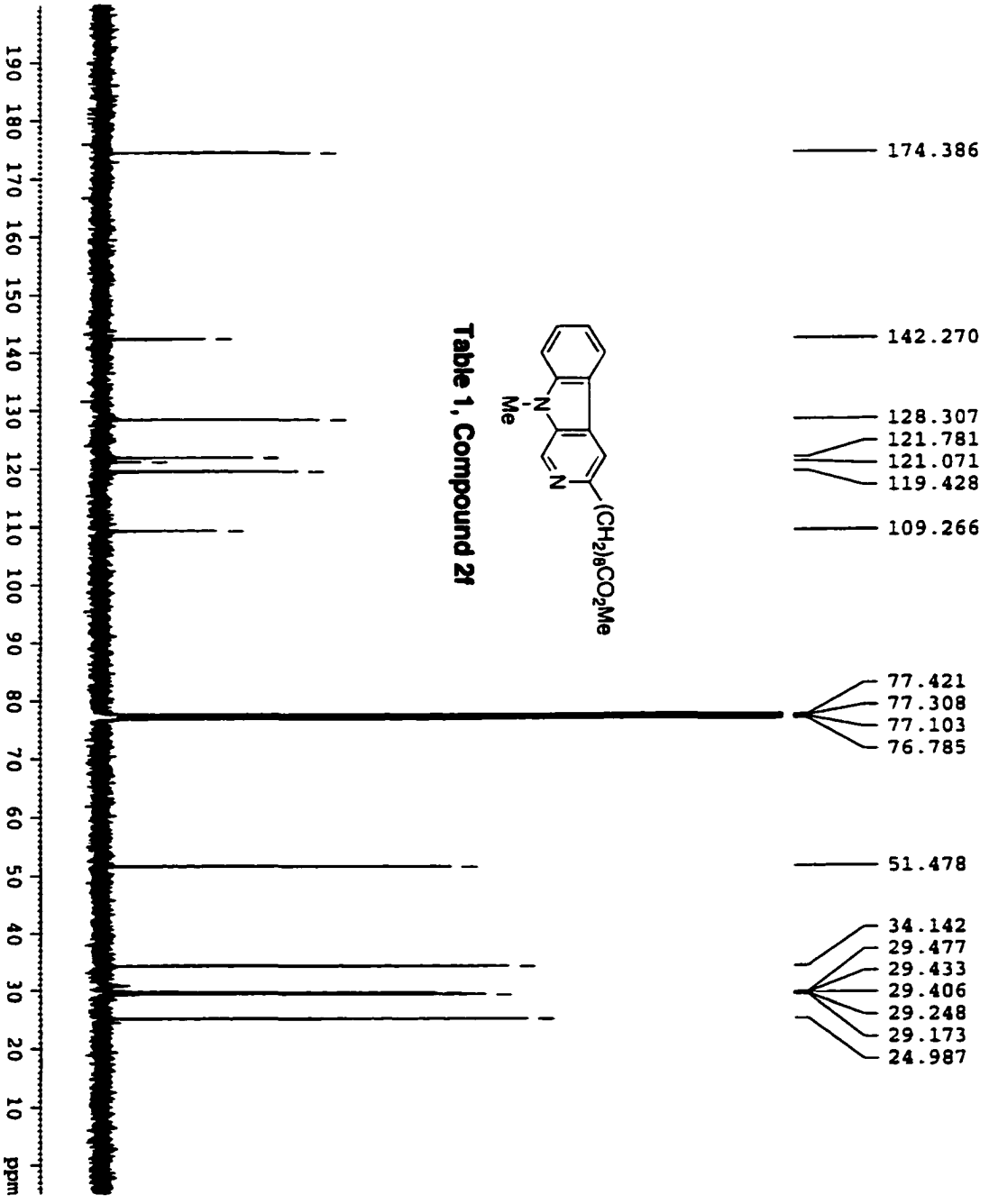


Table 1, Compound 2f

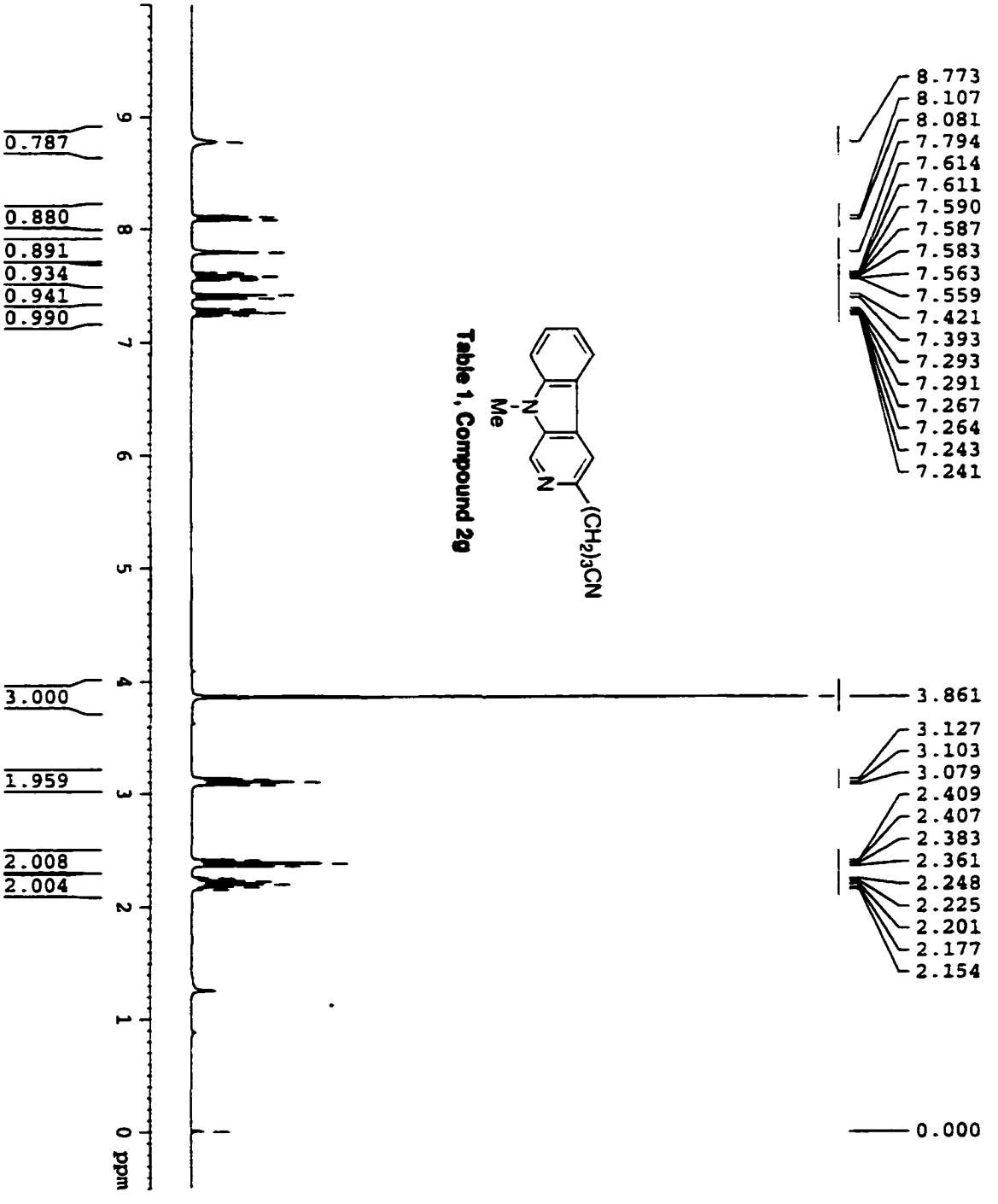


Table 1, Compound 2g

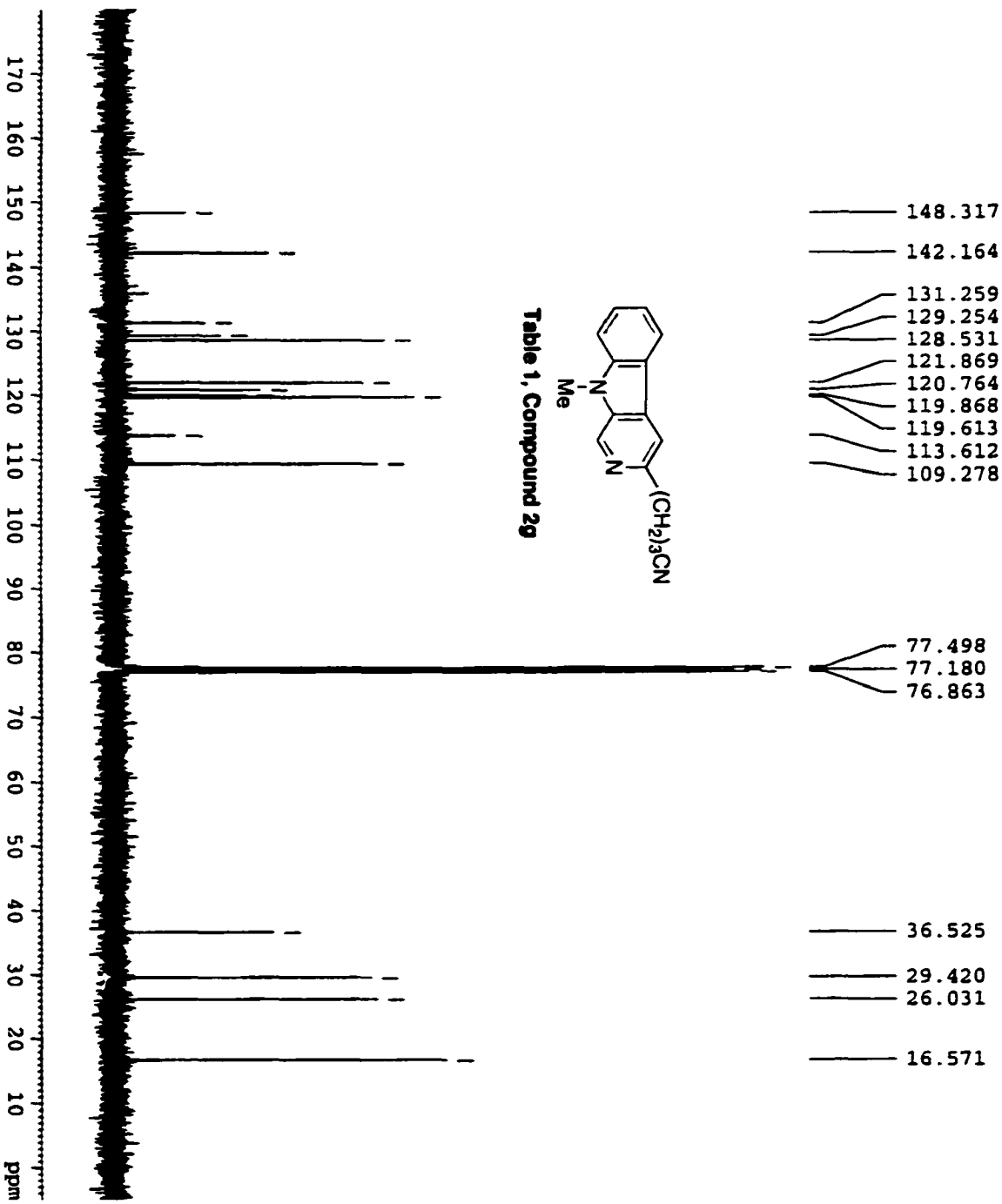
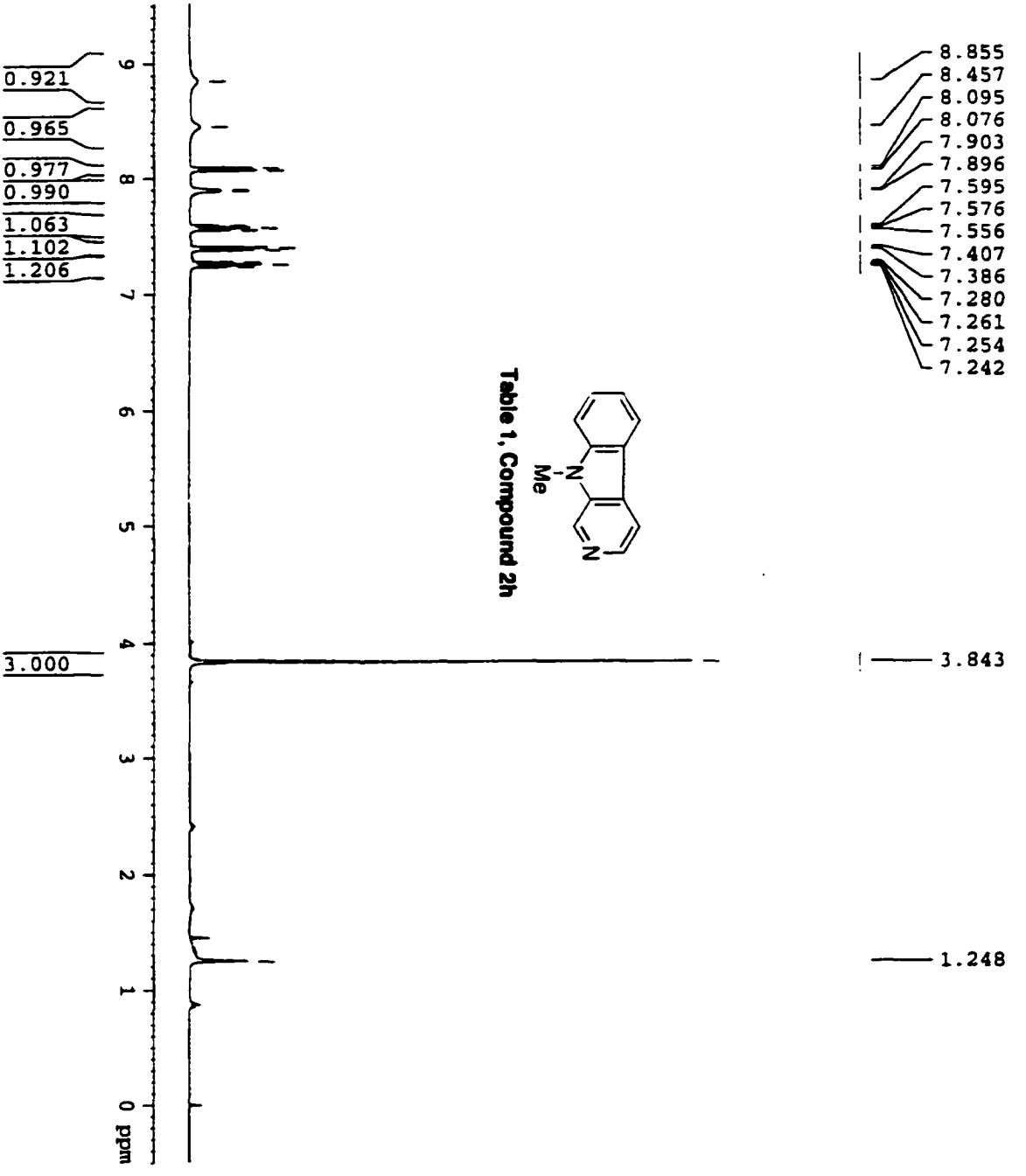
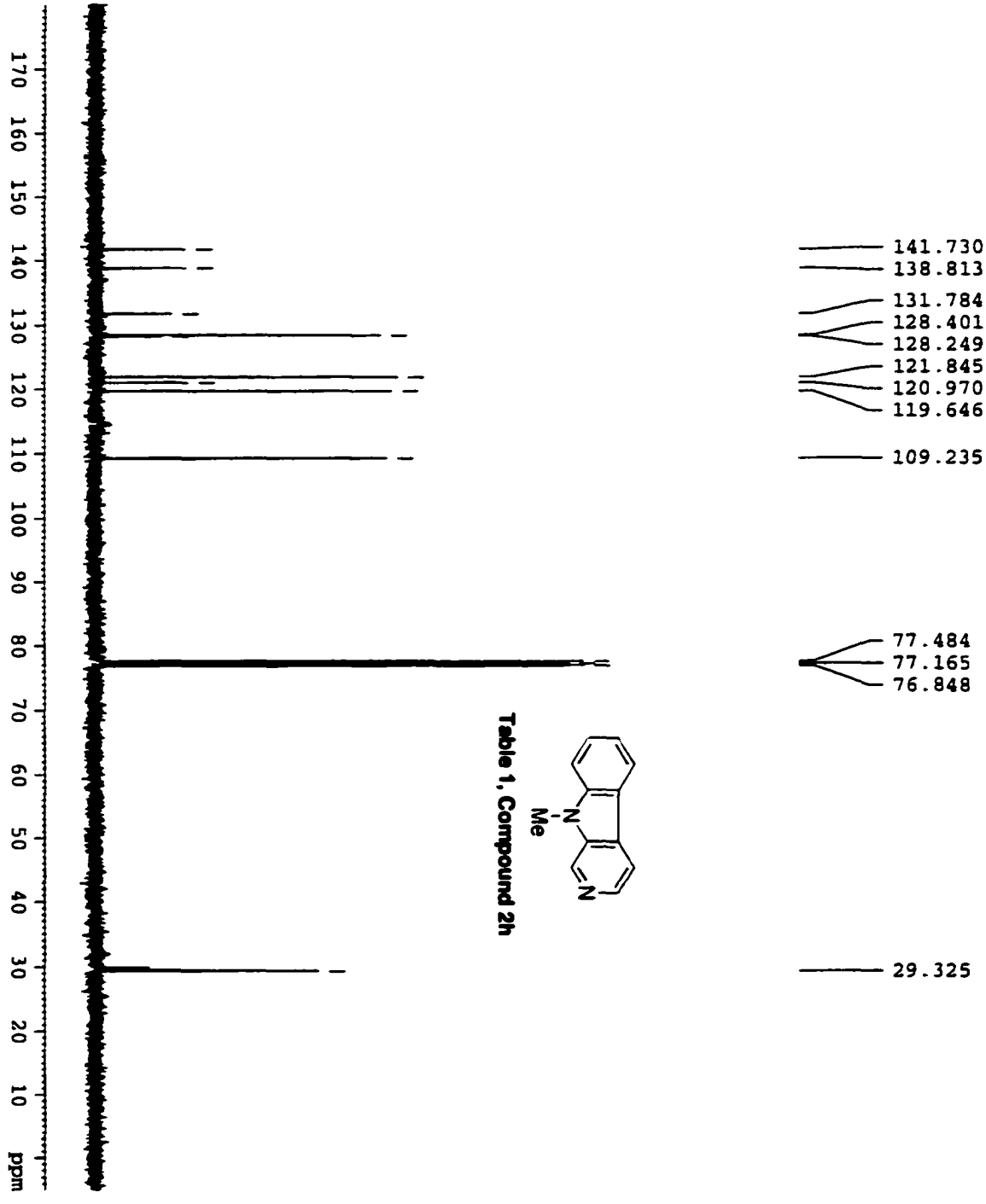
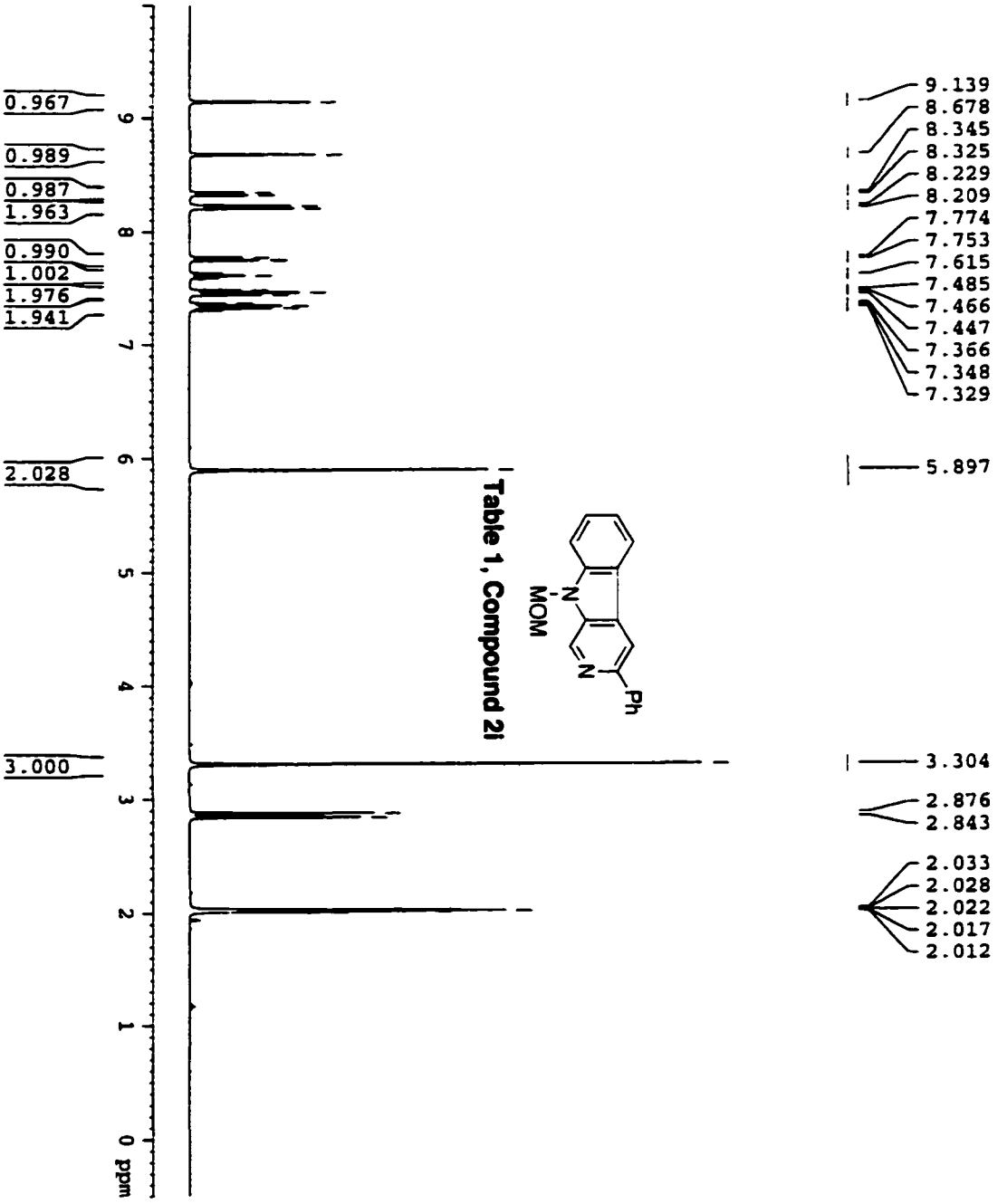


Table 1, Compound 2g


0.921
0.965
0.977
0.990
1.063
1.102
1.206
3.000
9
8
7
6
5
4
3
2
1
0
ppm
8.855
8.457
8.095
8.076
7.903
7.896
7.595
7.576
7.556
7.407
7.386
7.280
7.261
7.254
7.242
3.843
1.248
Table 1, Compound 2h
Me
N
N


141.730
138.813
131.784
128.401
128.249
121.845
120.970
119.646
109.235
77.484
77.165
76.848
29.325
Me
N
N
Table 1, Compound 2h
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


0.967
0.989
0.987
1.963
0.990
1.002
1.976
1.941
2.028
3.000
9.139
8.678
8.345
8.325
8.229
8.209
7.774
7.753
7.615
7.485
7.466
7.447
7.366
7.348
7.329
5.897
3.304
2.876
2.843
2.033
2.028
2.022
2.017
2.012
ppm
Table 1, Compound 2i
MOM
N
N
Ph

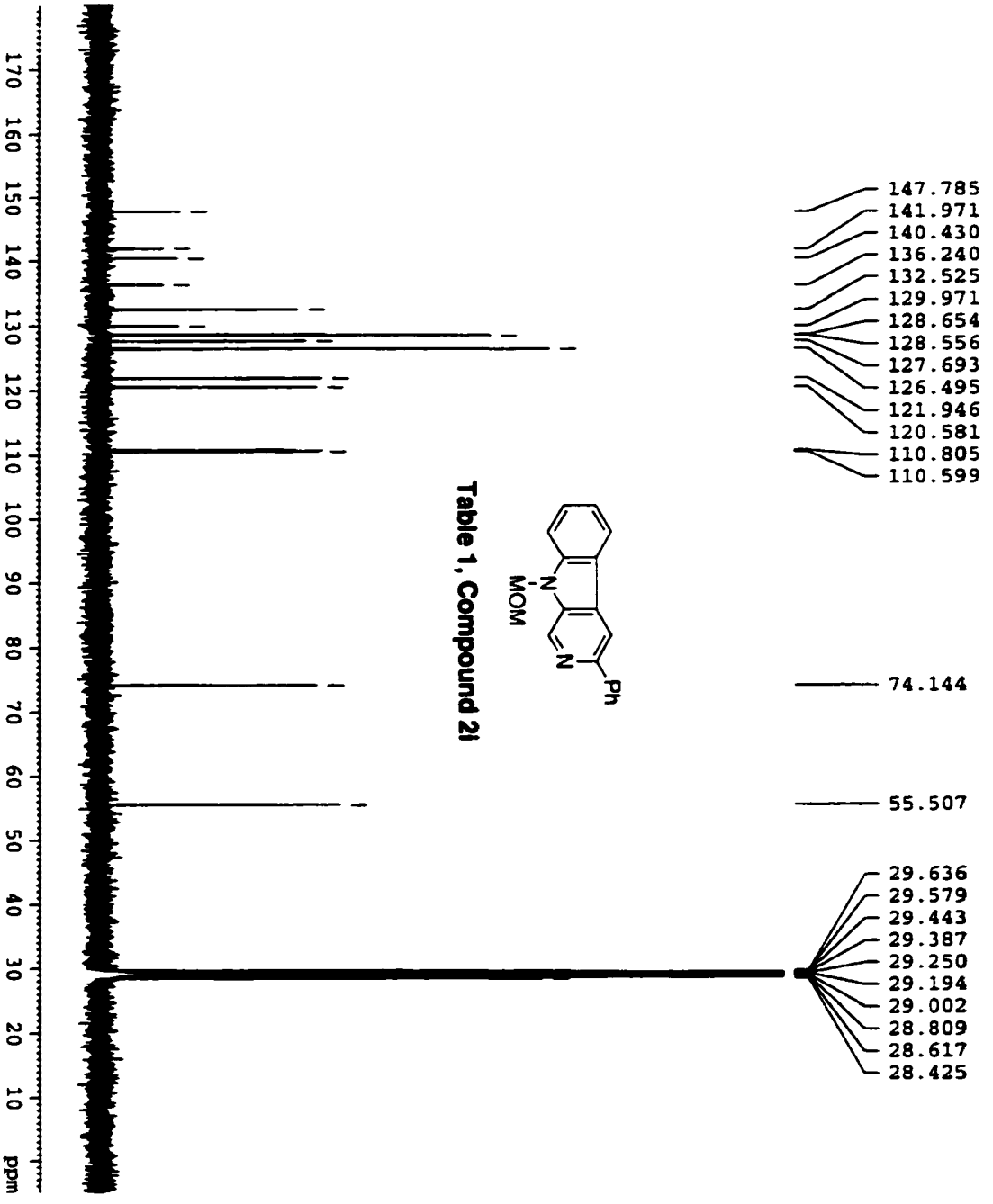


Table 1, Compound 2l

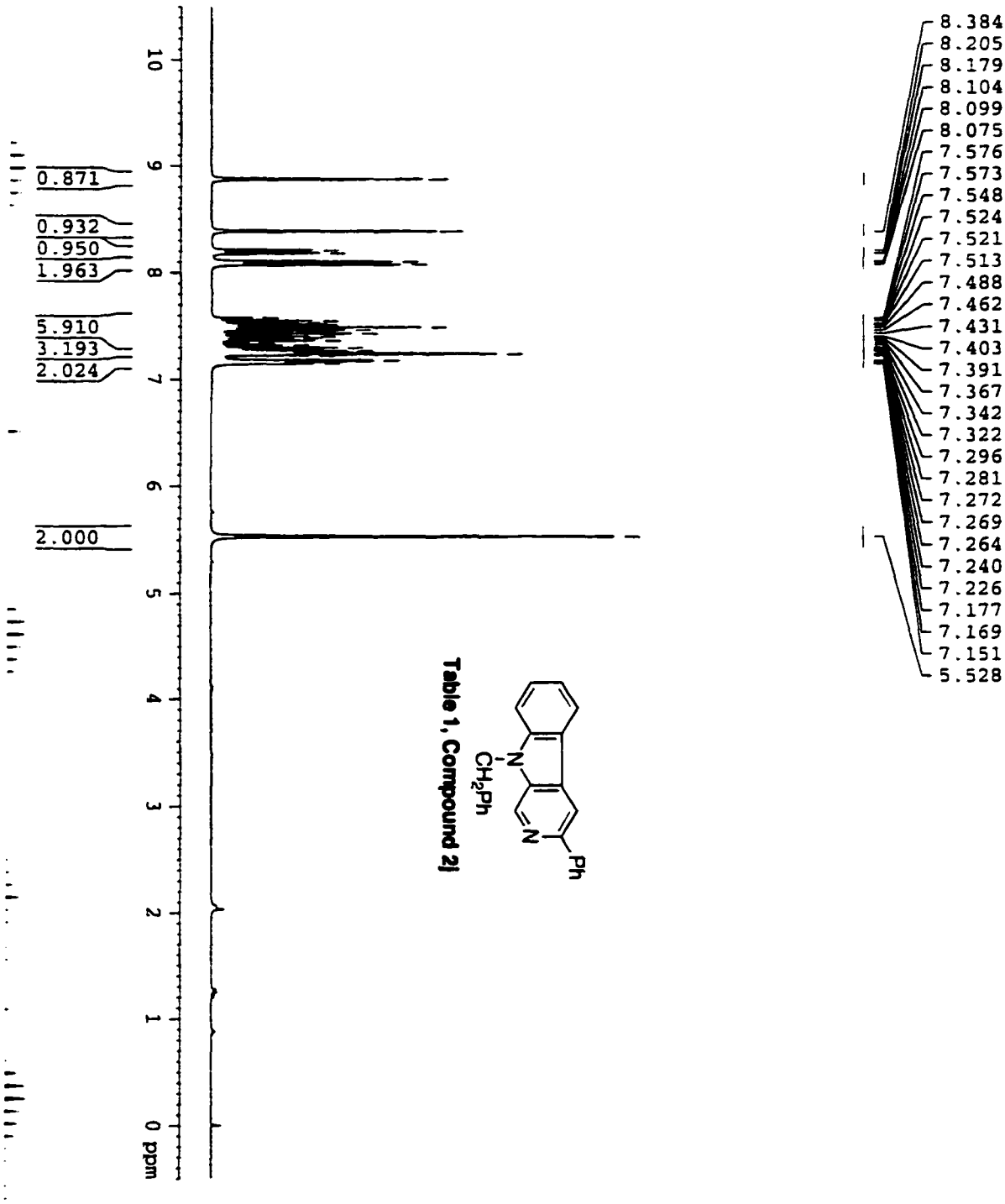
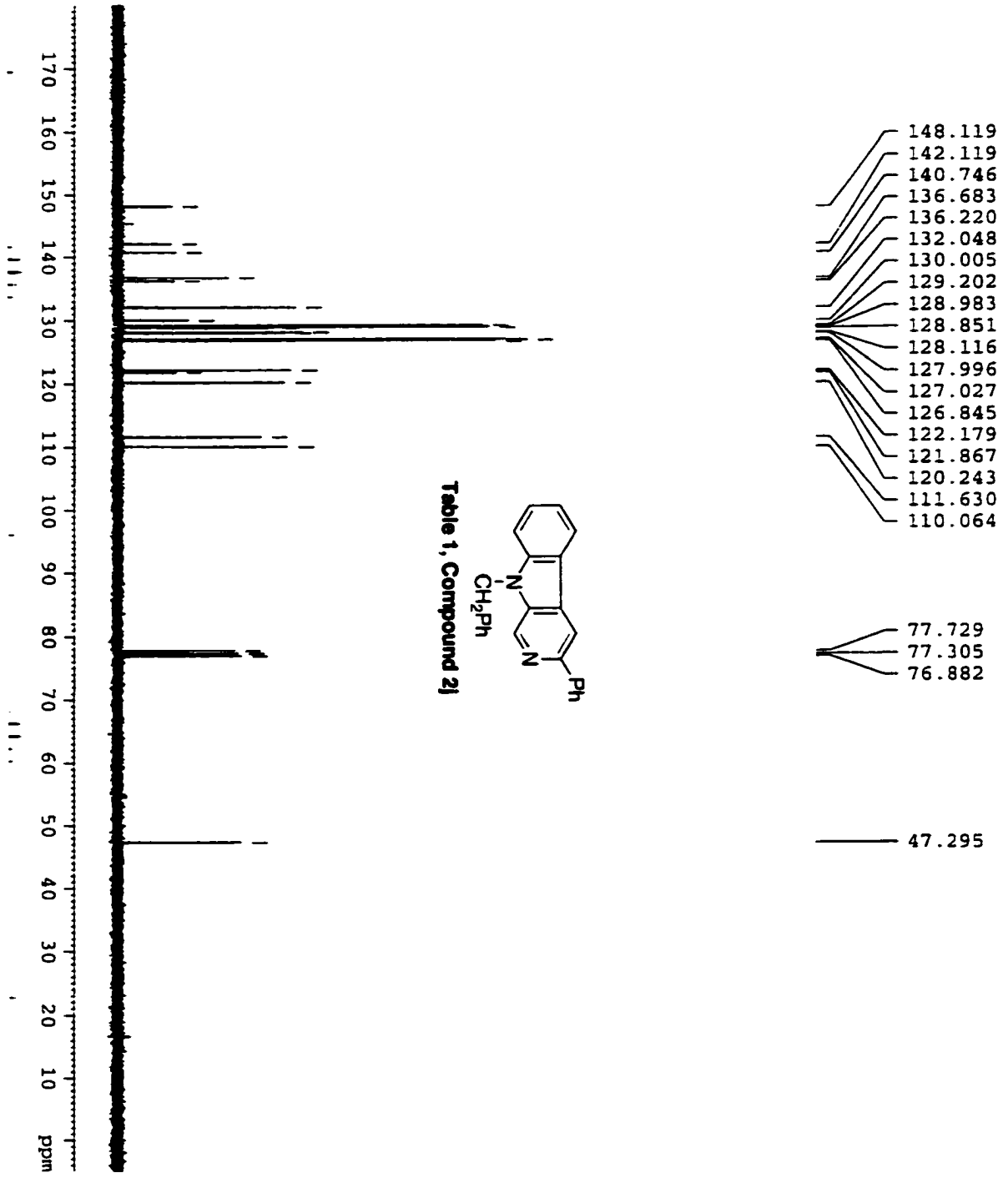
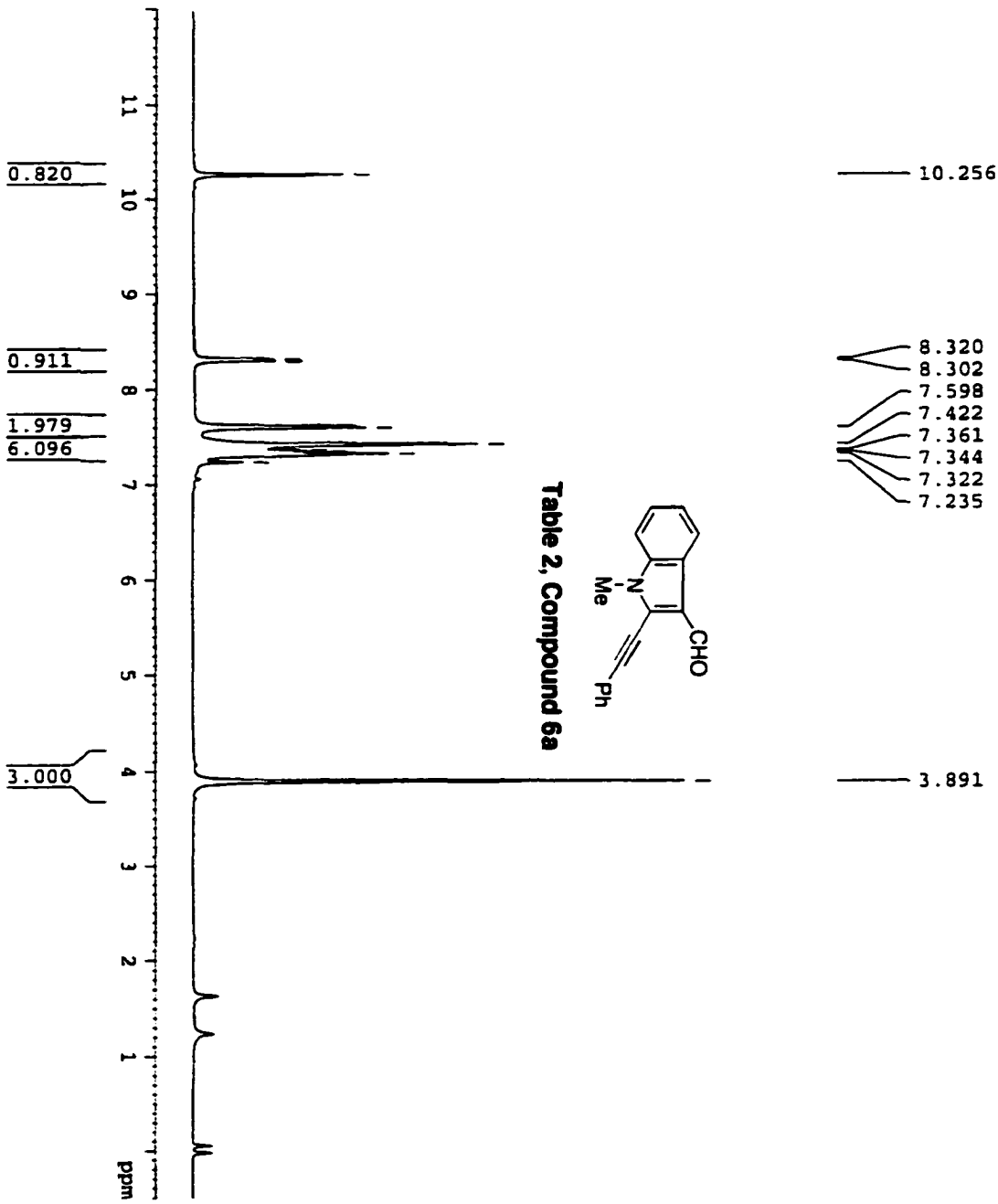
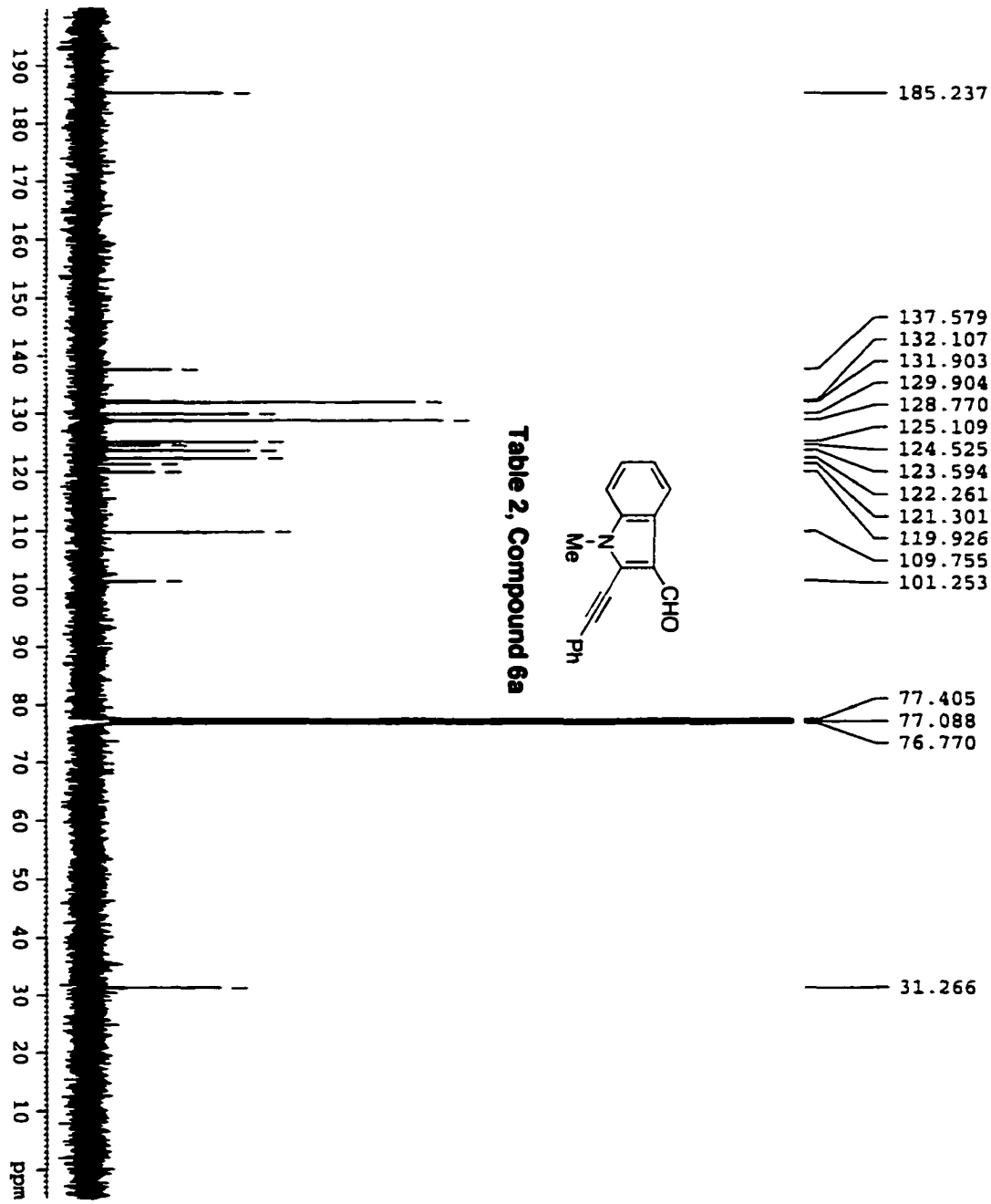


Table 1, Compound 2j


148.119
142.119
140.746
136.683
136.220
132.048
130.005
129.202
128.983
128.851
128.116
127.996
127.027
126.845
122.179
121.867
120.243
111.630
110.064
77.729
77.305
76.882
47.295
Table 1, Compound 2j
CH2Ph
N
N
Ph
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


0.820
0.911
1.979
6.096
3.000
10.256
8.320
8.302
7.598
7.422
7.361
7.344
7.322
7.235
3.891
ppm
Table 2, Compound 6a
N
Me
Ph
CHO


185.237
137.579
132.107
131.903
129.904
128.770
125.109
124.525
123.594
122.261
121.301
119.926
109.755
101.253
77.405
77.088
76.770
31.266
Table 2, Compound 6a
Me
N
CHO
Ph
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

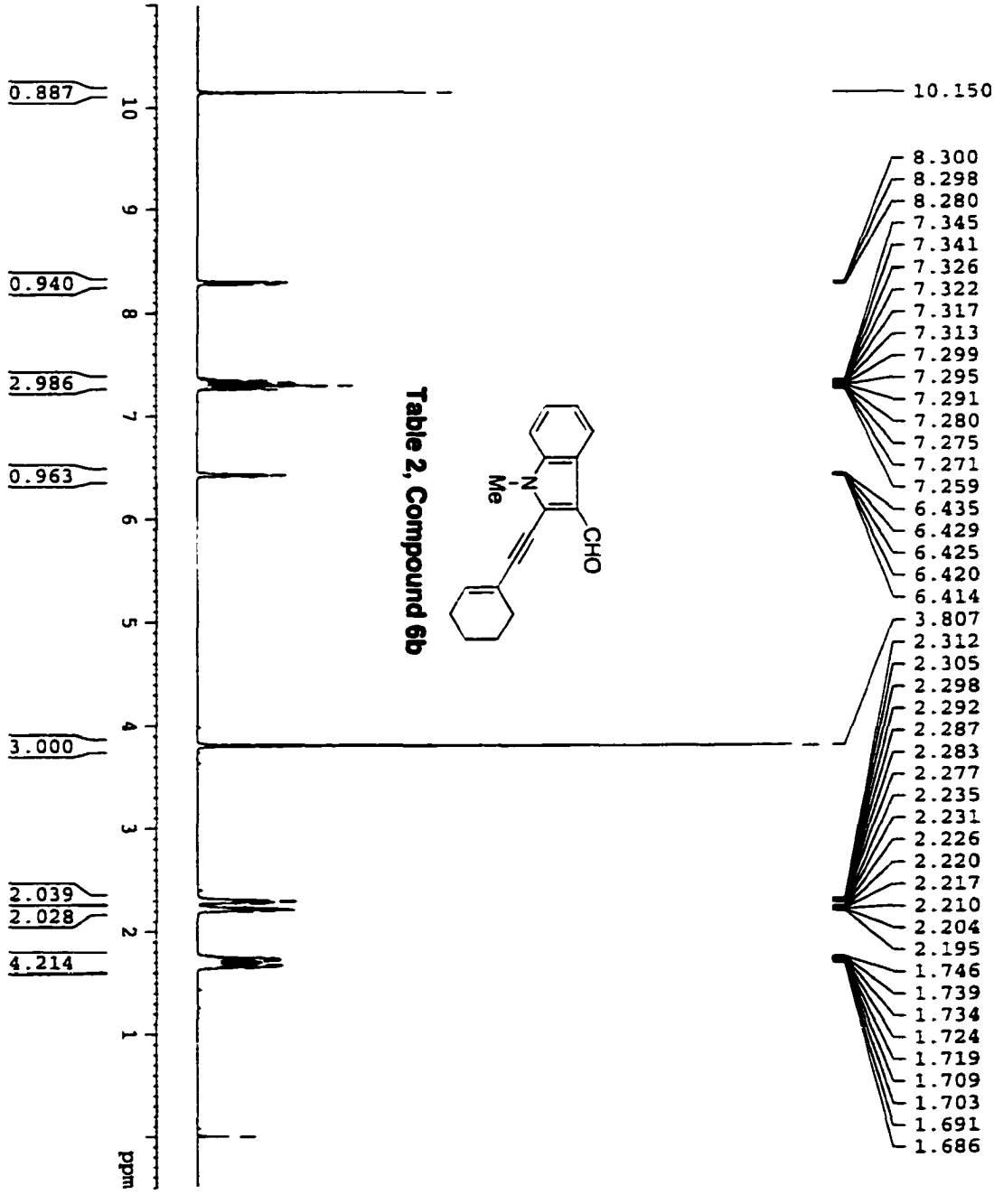


Table 2, Compound 6b
Me
N
CHO
0.887
0.940
2.986
0.963
3.000
2.039
2.028
4.214
ppm
10.150
8.300
8.298
8.280
7.345
7.341
7.326
7.322
7.317
7.313
7.299
7.295
7.291
7.280
7.275
7.271
7.259
6.435
6.429
6.425
6.420
6.414
3.807
2.312
2.305
2.298
2.292
2.287
2.283
2.277
2.235
2.231
2.226
2.220
2.217
2.210
2.204
2.195
1.746
1.739
1.734
1.724
1.719
1.709
1.703
1.691
1.686

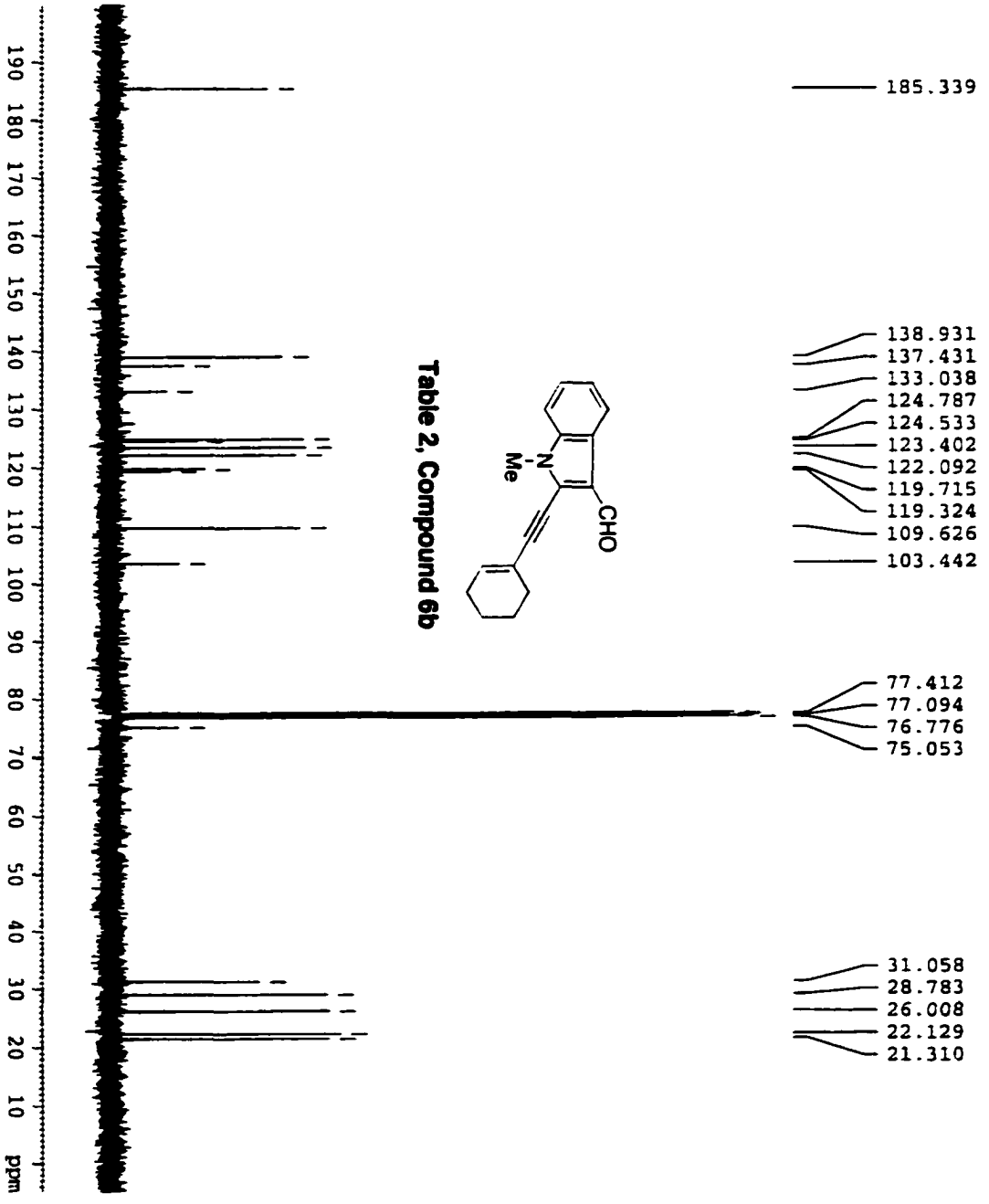


Table 2, Compound 6b

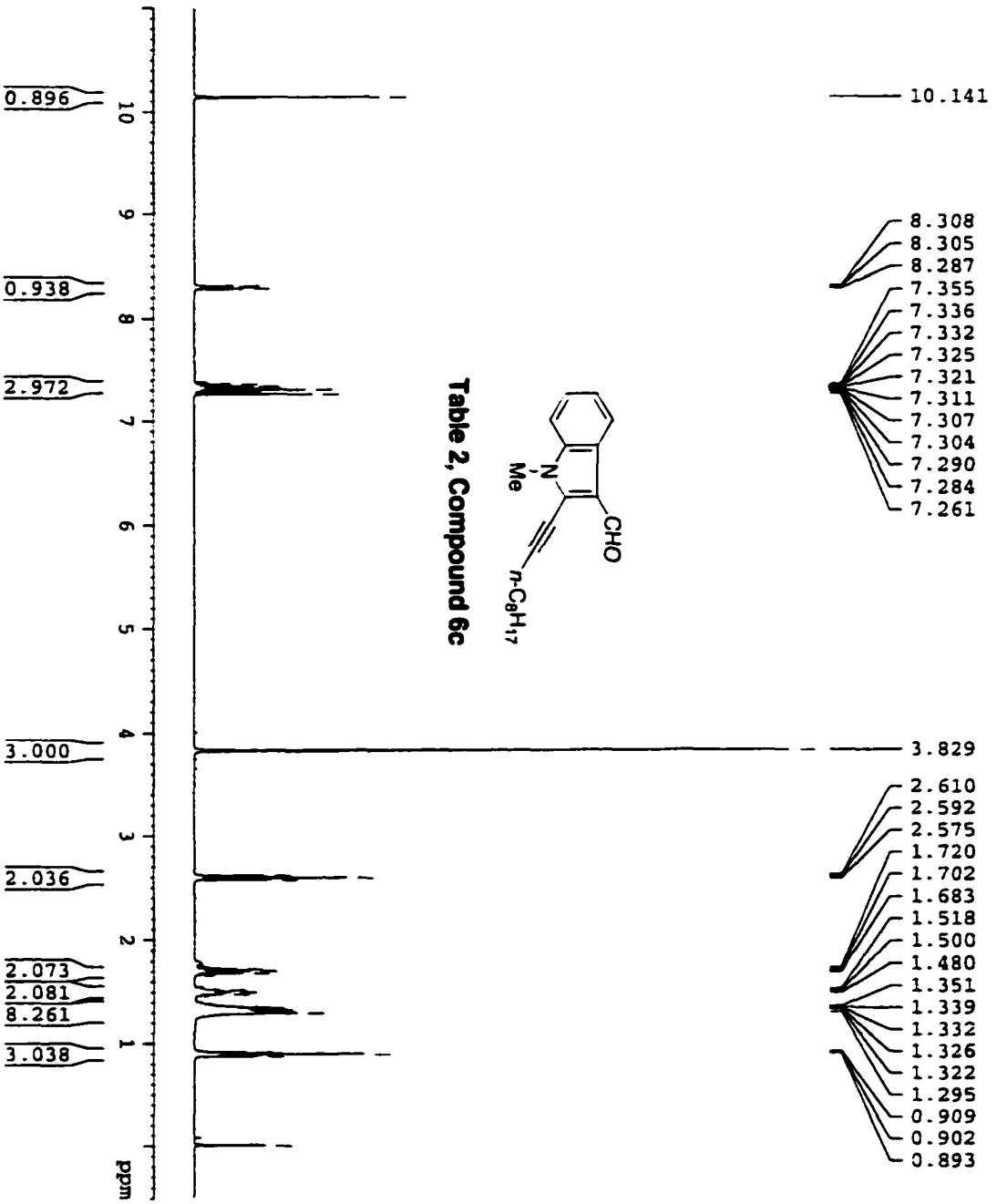


Table 2, Compound 6c
Me
N
CHO
n-C8H17
0.896
0.938
2.972
3.000
2.036
2.073
2.081
8.261
3.038
10.141
8.308
8.305
8.287
7.355
7.336
7.332
7.325
7.321
7.311
7.307
7.304
7.290
7.284
7.261
3.829
2.610
2.592
2.575
1.720
1.702
1.683
1.518
1.500
1.480
1.351
1.339
1.332
1.326
1.322
1.295
0.909
0.902
0.893
ppm

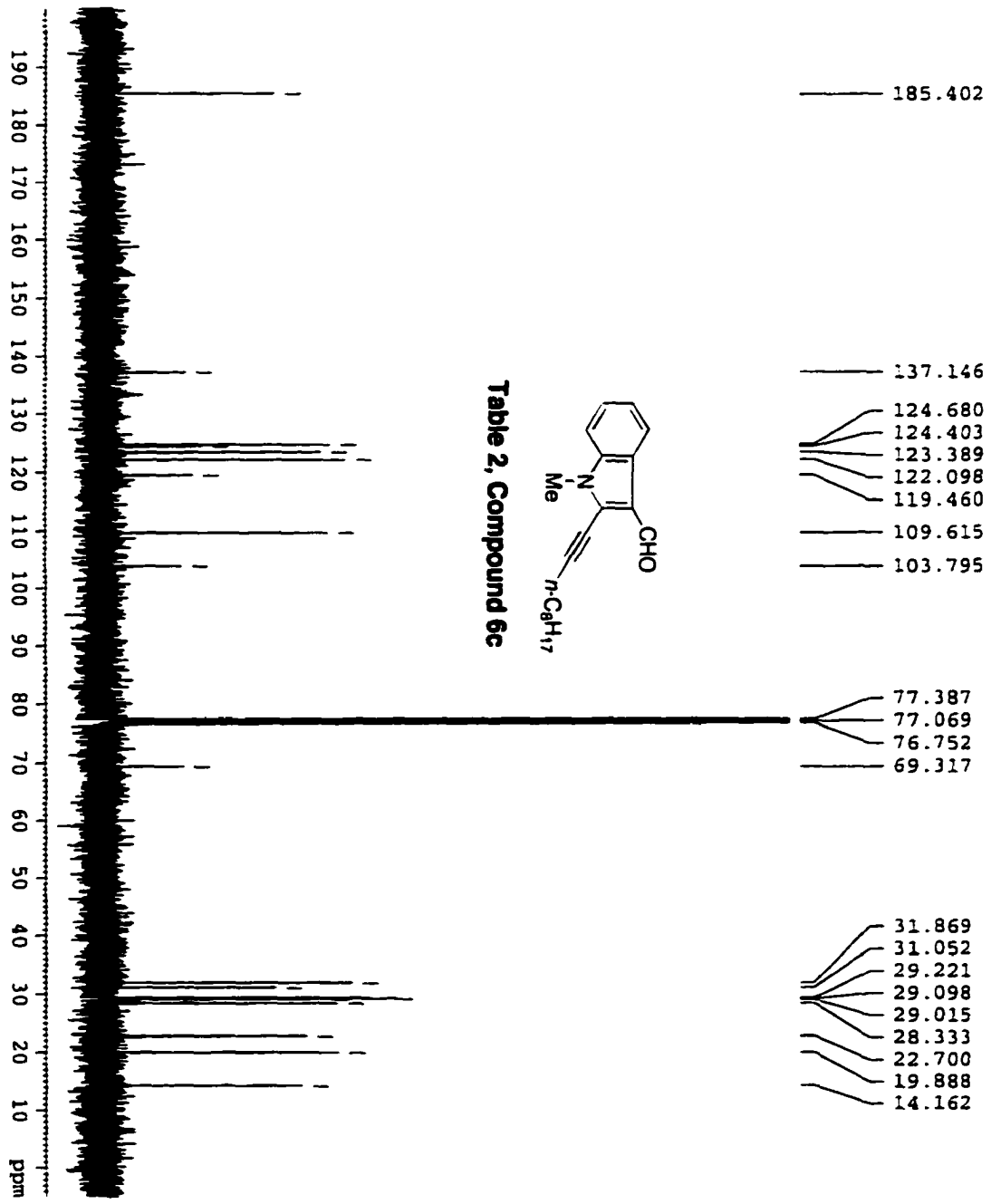
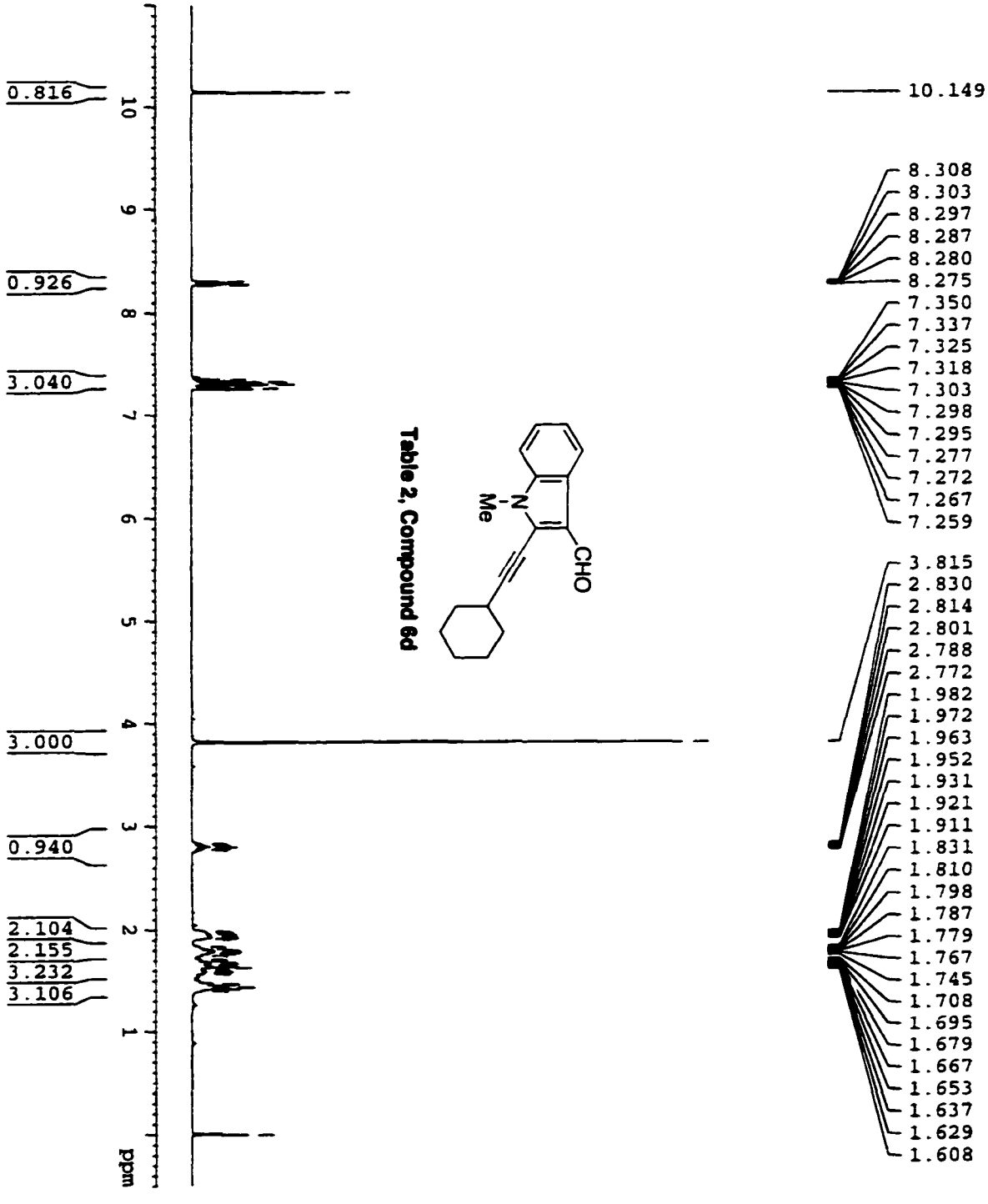


Table 2, Compound 6c


0.816
0.926
3.040
3.000
0.940
2.104
2.155
3.232
3.106
10
9
8
7
6
5
4
3
2
1
ppm
Table 2, Compound 6d
N
Me
CHO
10.149
8.308
8.303
8.297
8.287
8.280
8.275
7.350
7.337
7.325
7.318
7.303
7.298
7.295
7.277
7.272
7.267
7.259
3.815
2.830
2.814
2.801
2.788
2.772
1.982
1.972
1.963
1.952
1.931
1.921
1.911
1.831
1.810
1.798
1.787
1.779
1.767
1.745
1.708
1.695
1.679
1.667
1.653
1.637
1.629
1.608

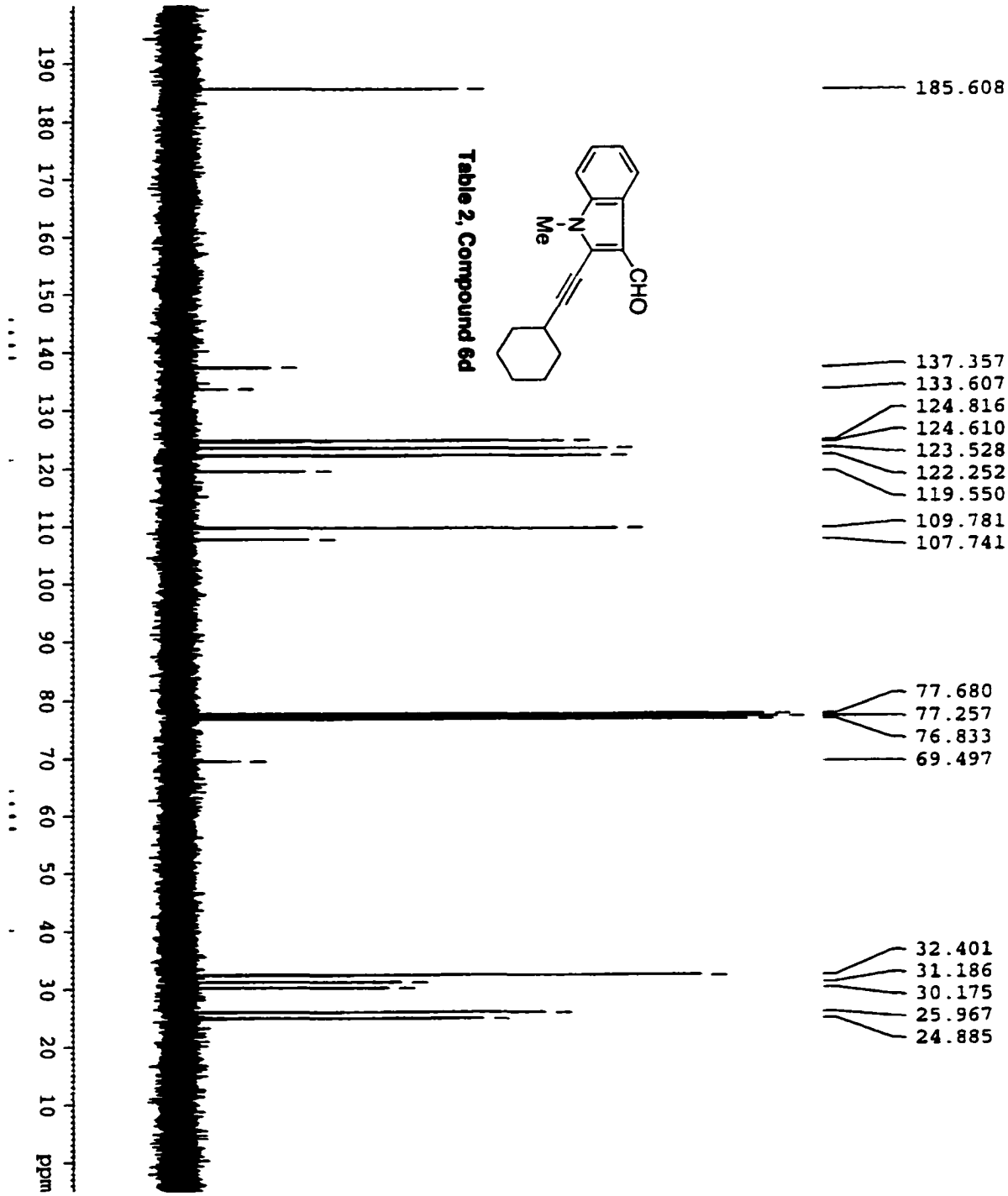


Table 2, Compound 6d
Me
N
CHO
185.608
137.357
133.607
124.816
124.610
123.528
122.252
119.550
109.781
107.741
77.680
77.257
76.833
69.497
32.401
31.186
30.175
25.967
24.885
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

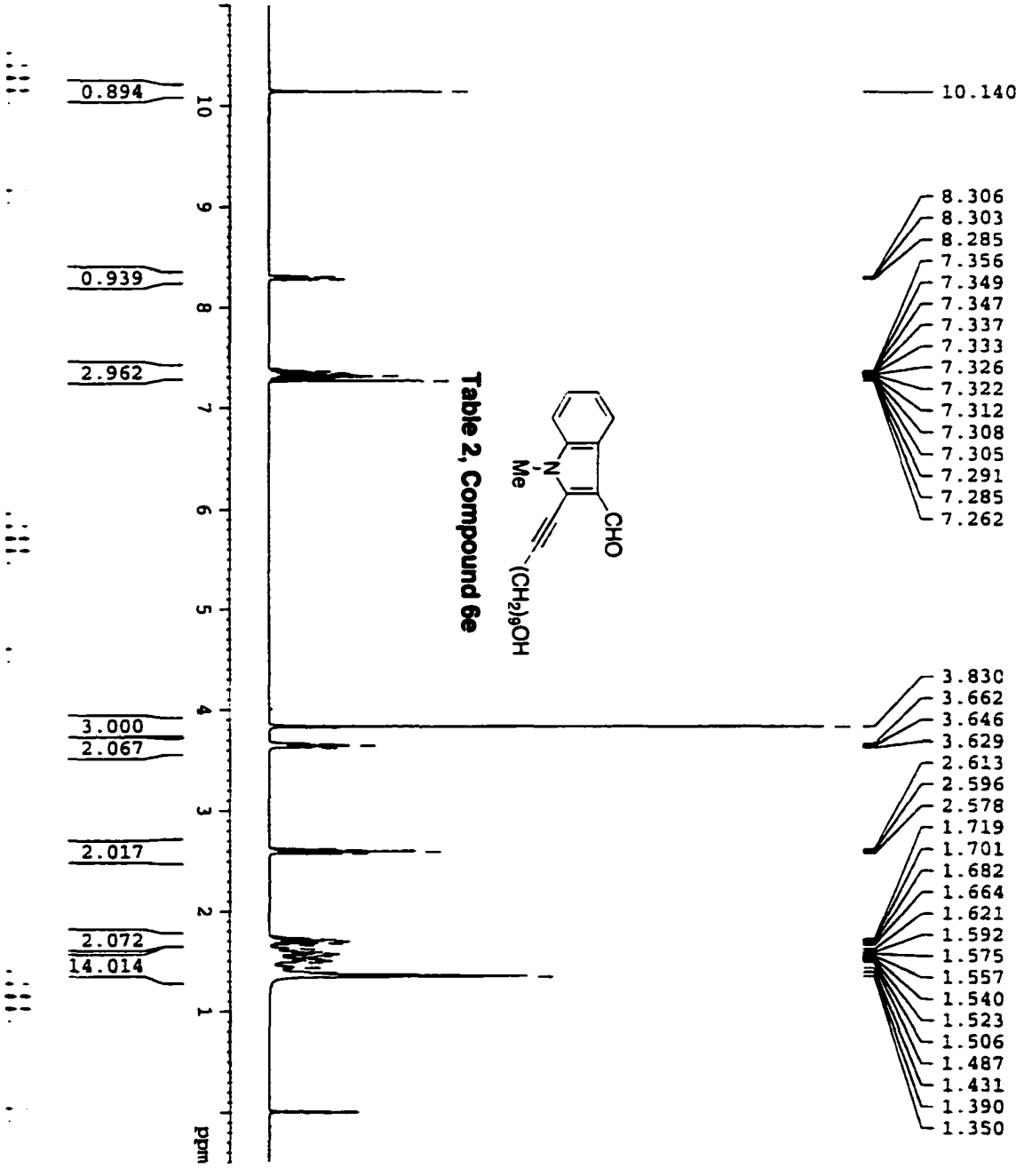


Table 2, Compound 6e
Me
N
CHO
(CH2)9OH
0.894
0.939
2.962
3.000
2.067
2.017
2.072
14.014
10.140
8.306
8.303
8.285
7.356
7.349
7.347
7.337
7.333
7.326
7.322
7.312
7.308
7.305
7.291
7.285
7.262
3.830
3.662
3.646
3.629
2.613
2.596
2.578
1.719
1.701
1.682
1.664
1.621
1.592
1.575
1.557
1.540
1.523
1.506
1.487
1.431
1.390
1.350
ppm

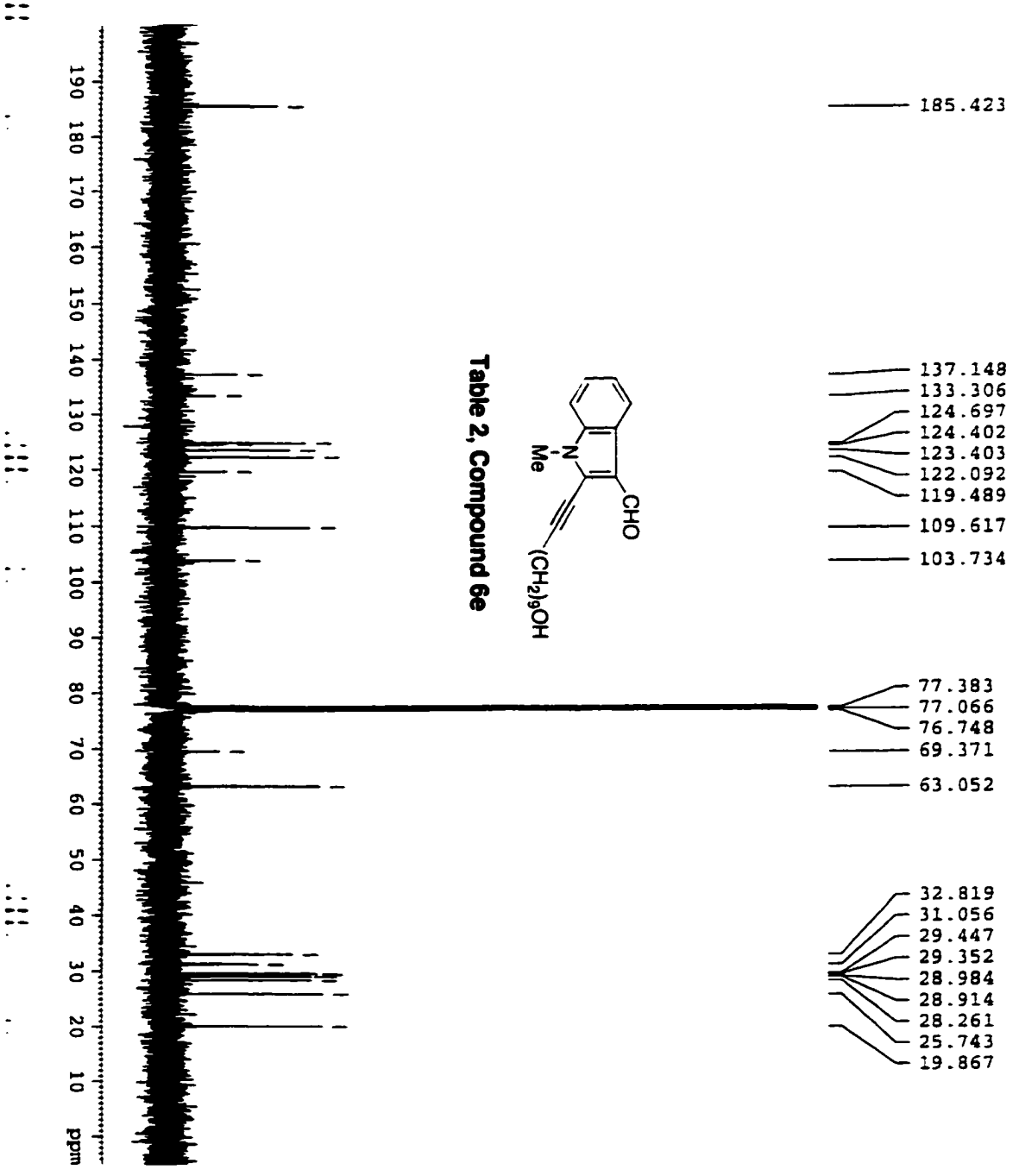


Table 2, Compound 6e

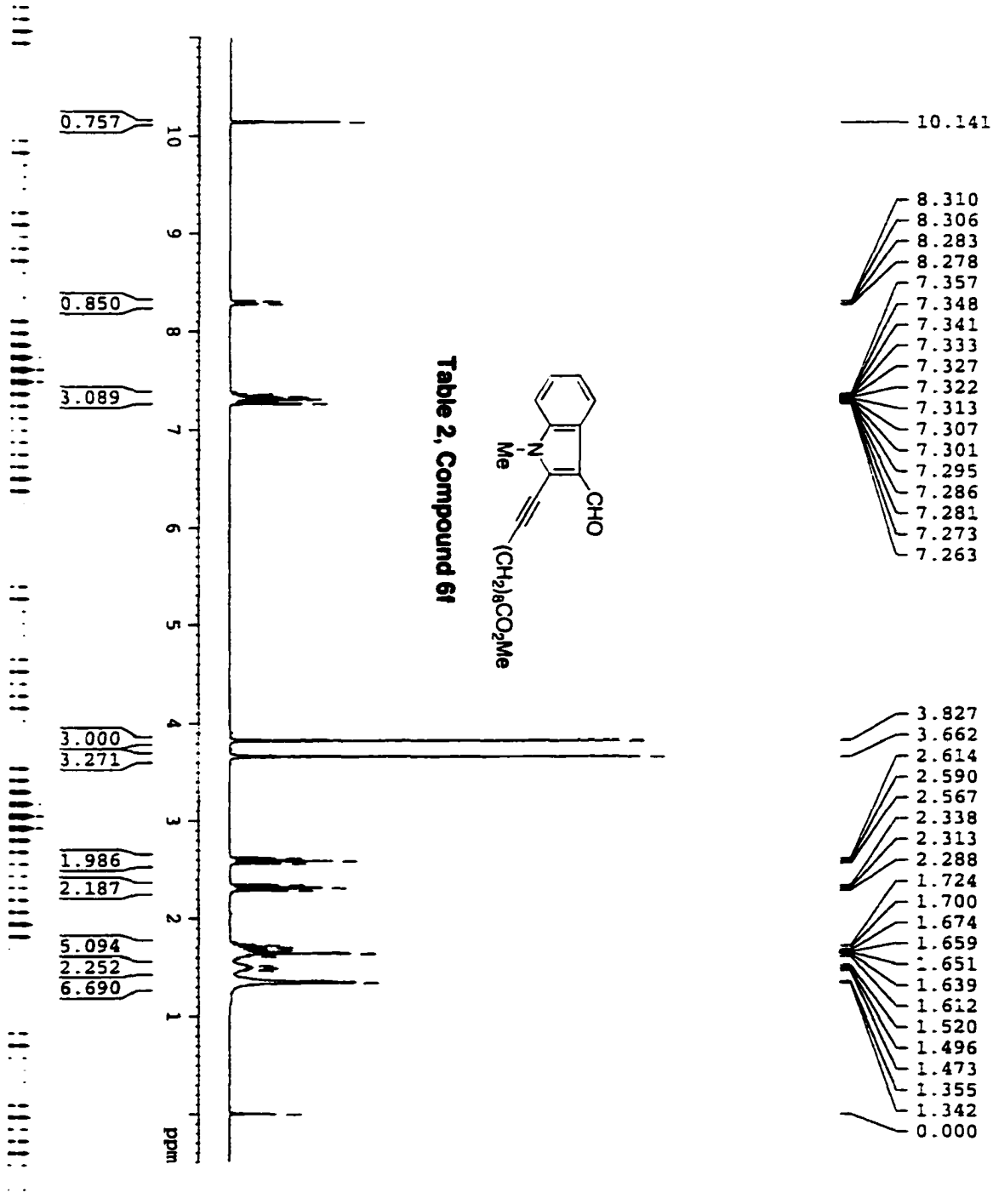


Table 2, Compound 6t
Me
N
CHO
(CH2)8CO2Me
0.757
0.850
3.089
3.000
3.271
1.986
2.187
5.094
2.252
6.690
ppm
10.141
8.310
8.306
8.283
8.278
7.357
7.348
7.341
7.333
7.327
7.322
7.313
7.307
7.301
7.295
7.286
7.281
7.273
7.263
3.827
3.662
2.614
2.590
2.567
2.338
2.313
2.288
1.724
1.700
1.674
1.659
1.651
1.639
1.612
1.520
1.496
1.473
1.355
1.342
0.000

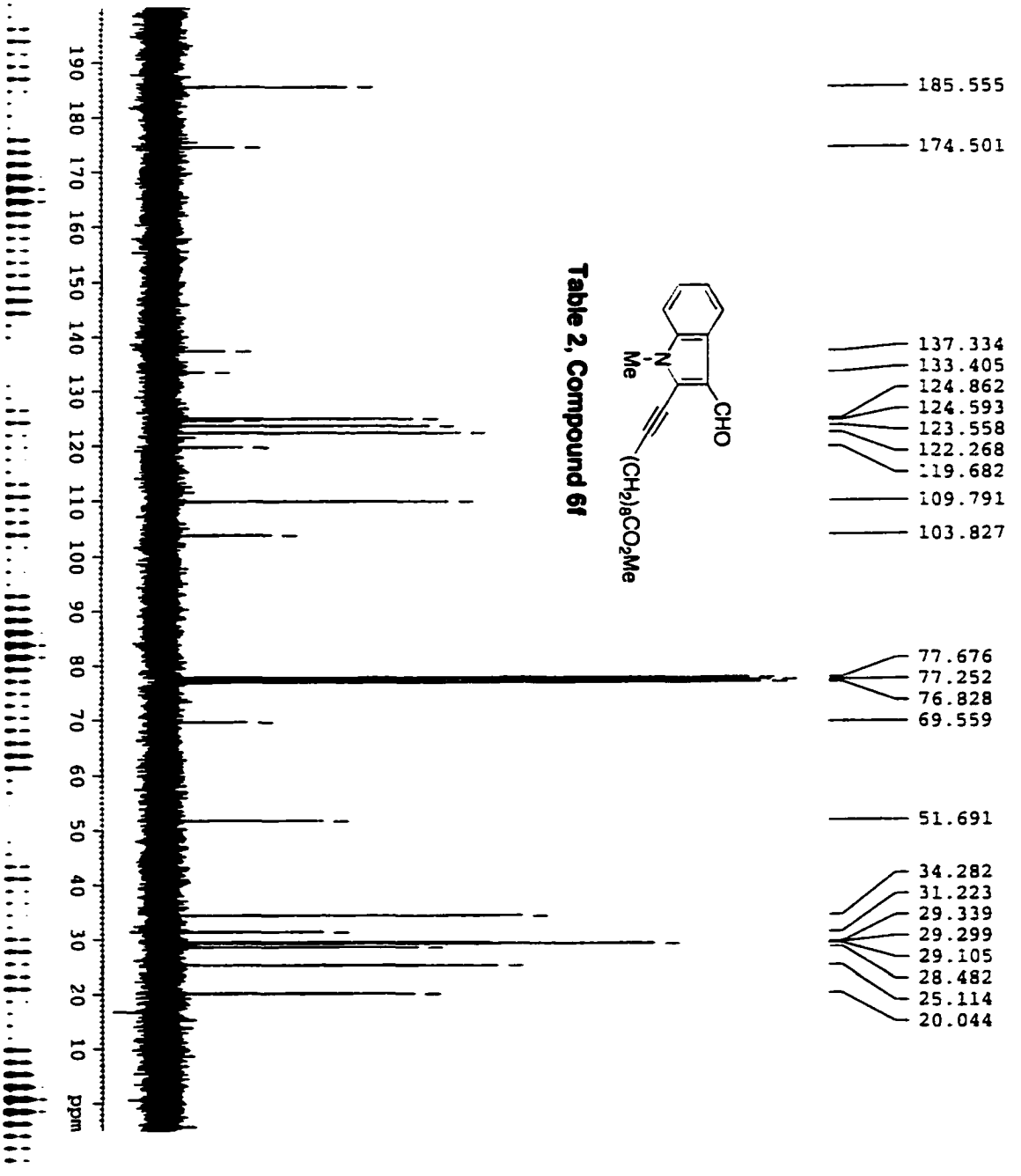
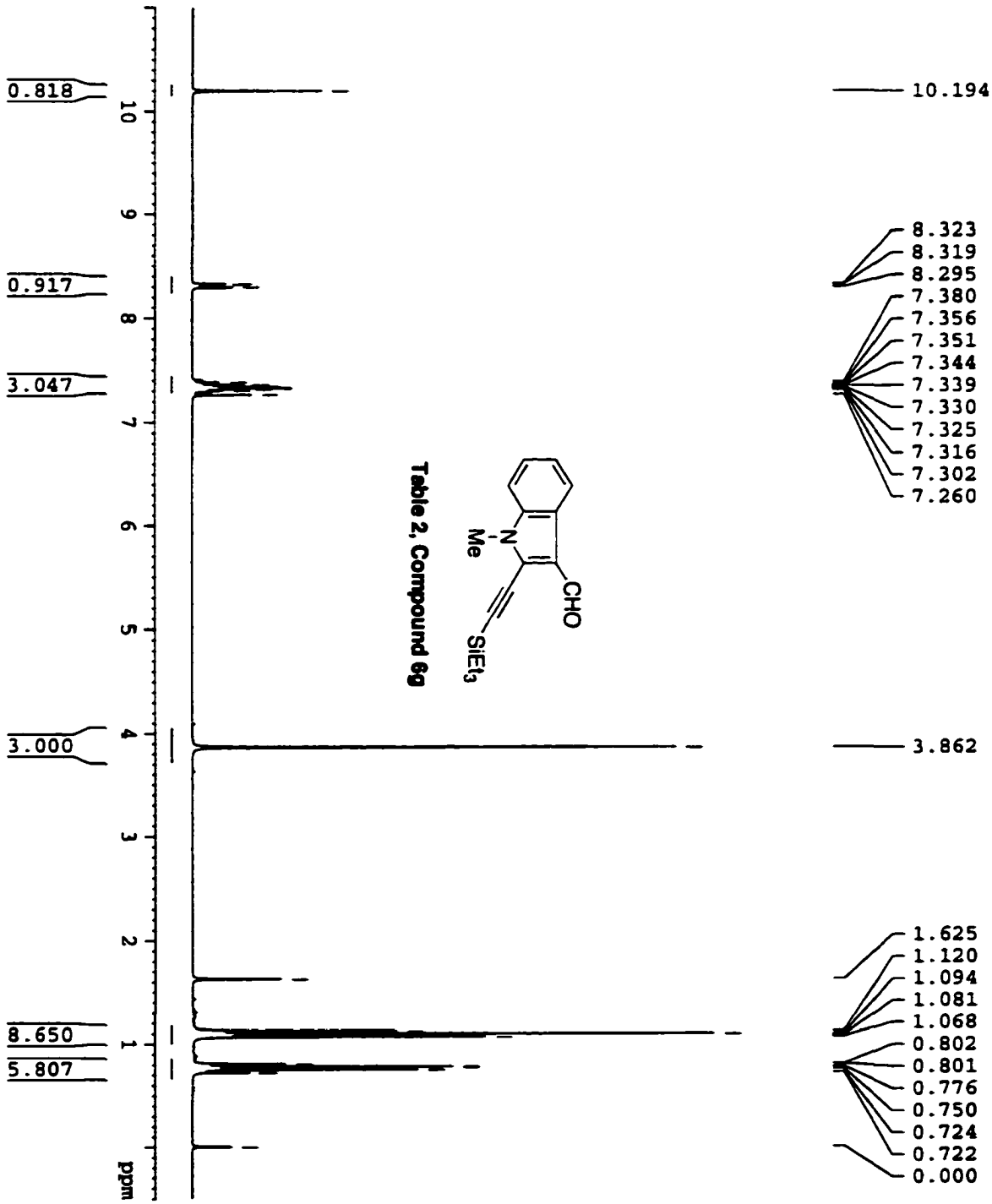
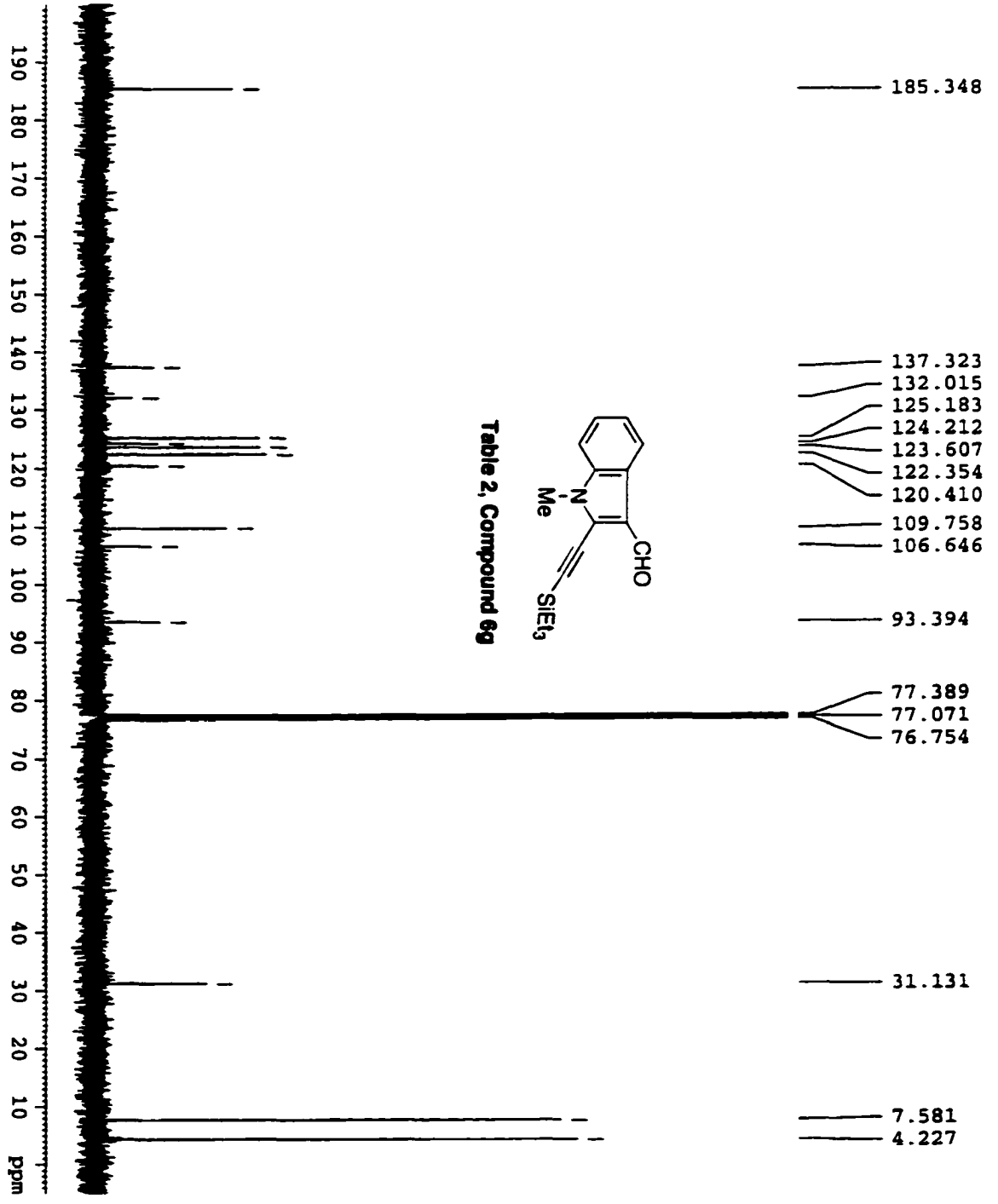
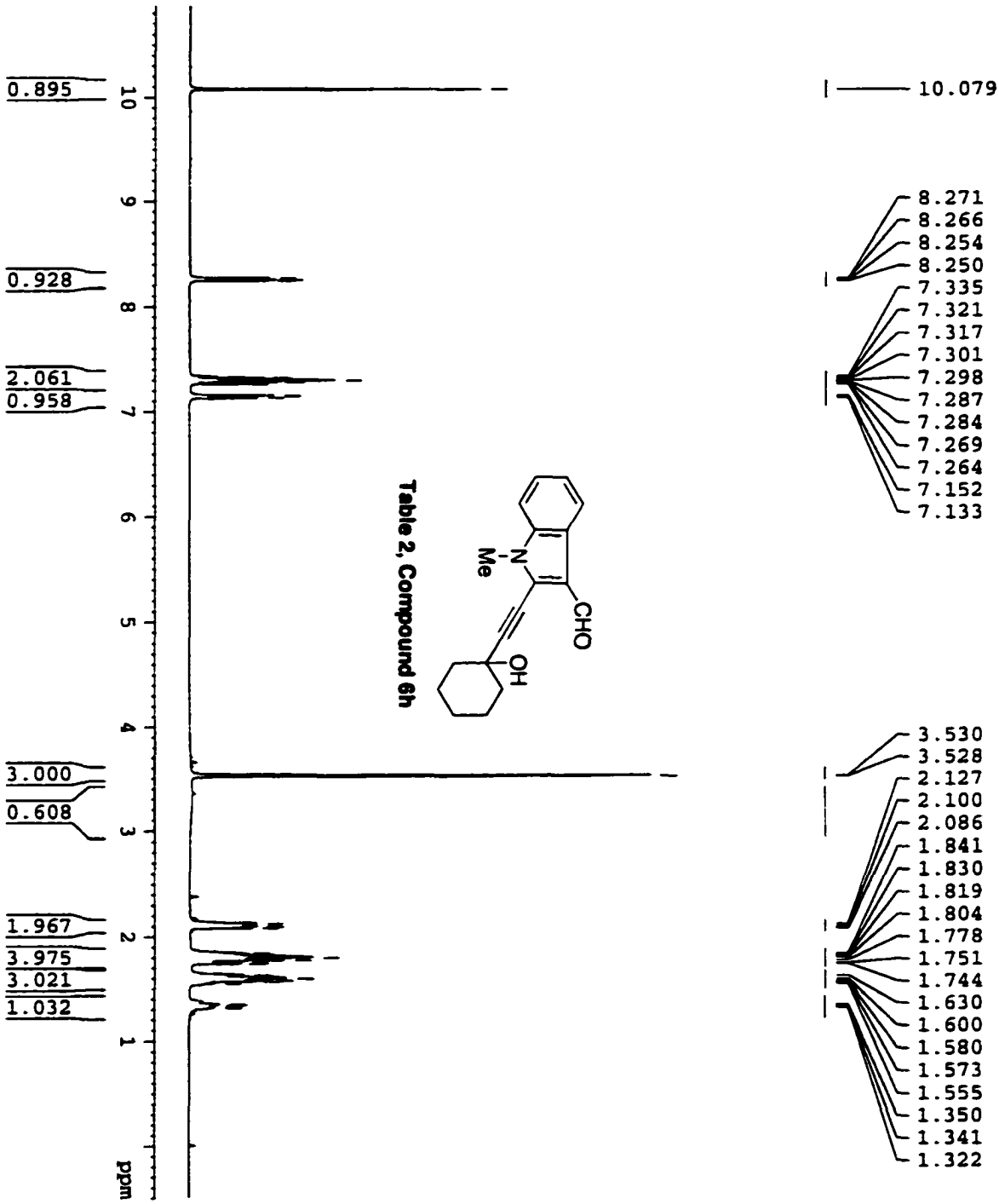
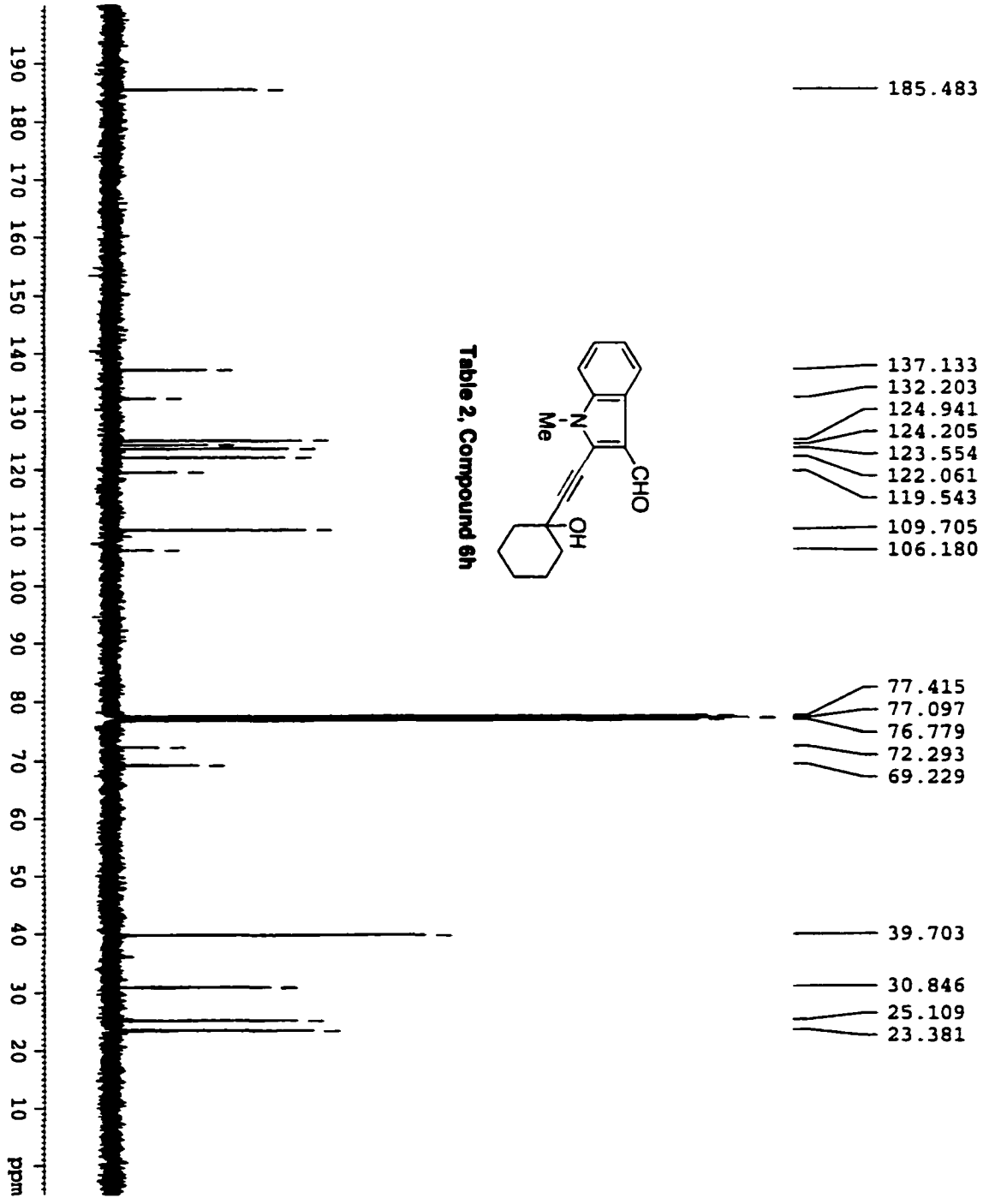


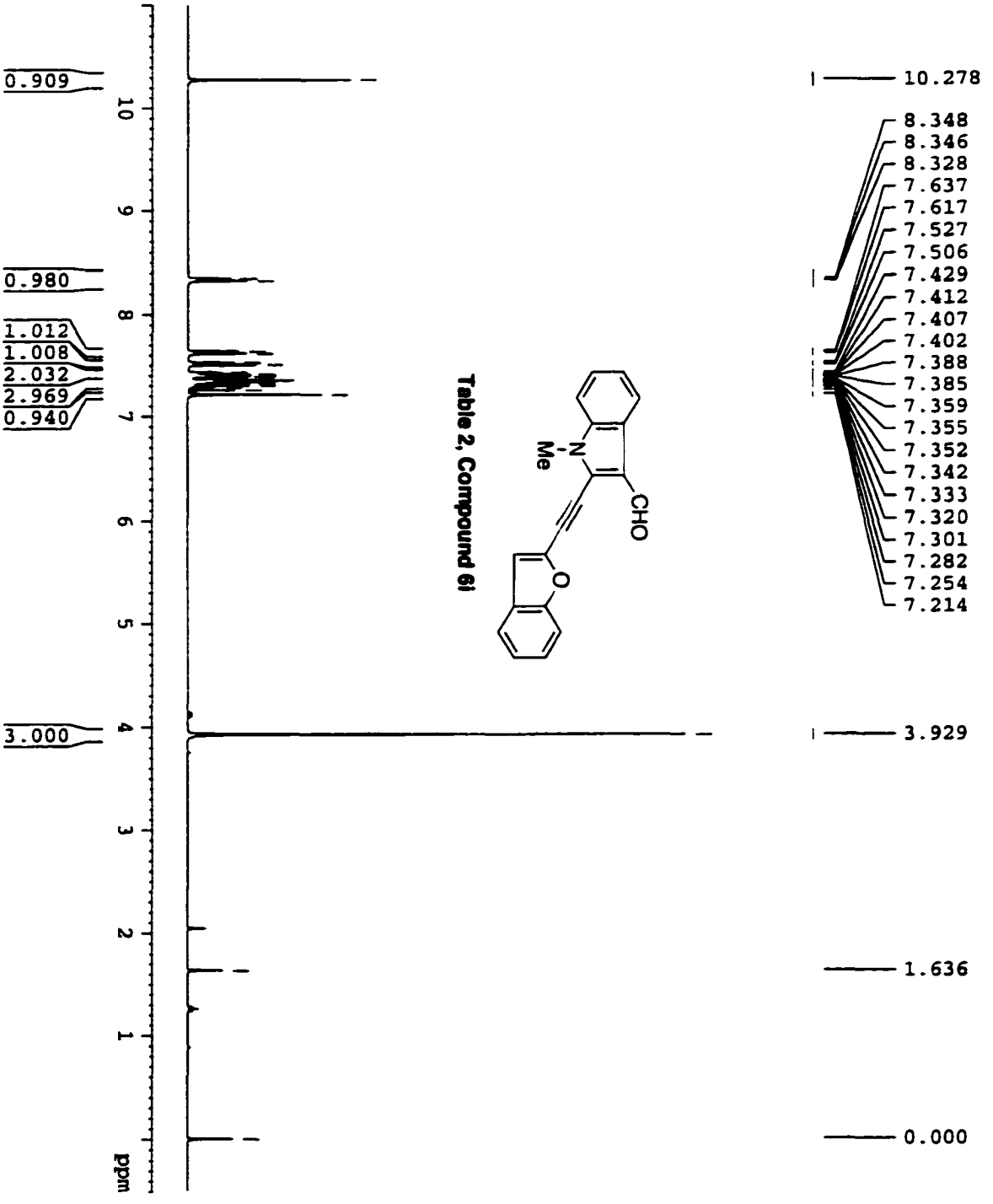
Table 2, Compound 6f

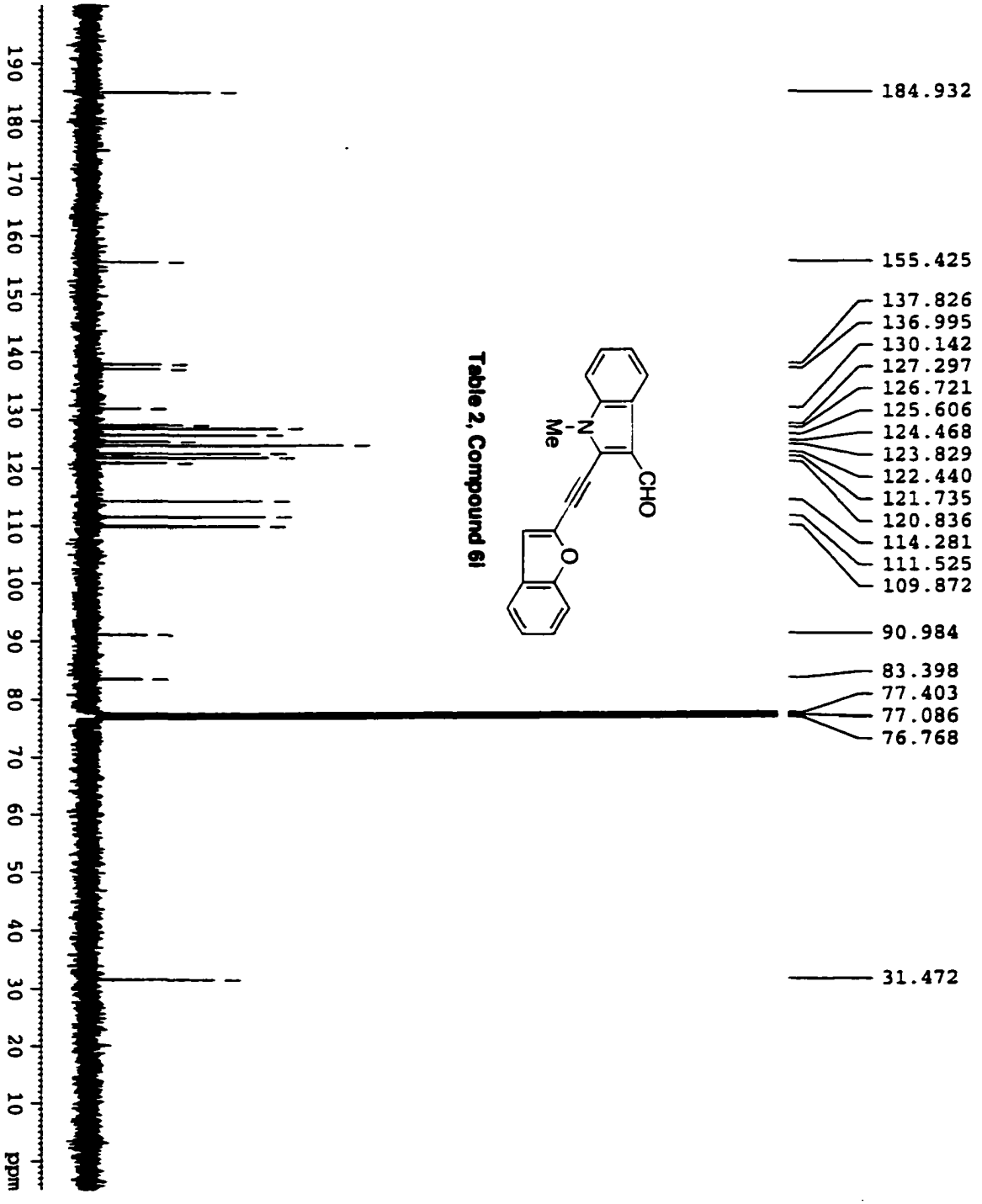

0.818
0.917
3.047
3.000
8.650
5.807
10.194
8.323
8.319
8.295
7.380
7.356
7.351
7.344
7.339
7.330
7.325
7.316
7.302
7.260
3.862
1.625
1.120
1.094
1.081
1.068
0.802
0.801
0.776
0.750
0.724
0.722
0.000
ppm
Table 2, Compound 6g
N
Me
CHO
SiEt3


185.348
137.323
132.015
125.183
124.212
123.607
122.354
120.410
109.758
106.646
93.394
77.389
77.071
76.754
31.131
7.581
4.227
Table 2, Compound 6g
Me
N
CHO
SiEt3
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


0.895
0.928
2.061
0.958
3.000
0.608
1.967
3.975
3.021
1.032
10
9
8
7
6
5
4
3
2
1
ppm
10.079
8.271
8.266
8.254
8.250
7.335
7.321
7.317
7.301
7.298
7.287
7.284
7.269
7.264
7.152
7.133
3.530
3.528
2.127
2.100
2.086
1.841
1.830
1.819
1.804
1.778
1.751
1.744
1.630
1.600
1.580
1.573
1.555
1.350
1.341
1.322
Table 2, Compound 6h
N
Me
CHO
OH


185.483
137.133
132.203
124.941
124.205
123.554
122.061
119.543
109.705
106.180
77.415
77.097
76.779
72.293
69.229
39.703
30.846
25.109
23.381
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
Table 2, Compound 6h
Me
N
CHO
OH


0.909
0.980
1.012
1.008
2.032
2.969
0.940
3.000
10.278
8.348
8.346
8.328
7.637
7.617
7.527
7.506
7.429
7.412
7.407
7.402
7.388
7.385
7.359
7.355
7.352
7.342
7.333
7.320
7.301
7.282
7.254
7.214
3.929
1.636
0.000
ppm
Table 2, Compound 6l
Me
N
CHO
O


184.932
155.425
137.826
136.995
130.142
127.297
126.721
125.606
124.468
123.829
122.440
121.735
120.836
114.281
111.525
109.872
90.984
83.398
77.403
77.086
76.768
31.472
Me
N
CHO
O
Table 2, Compound 6i
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

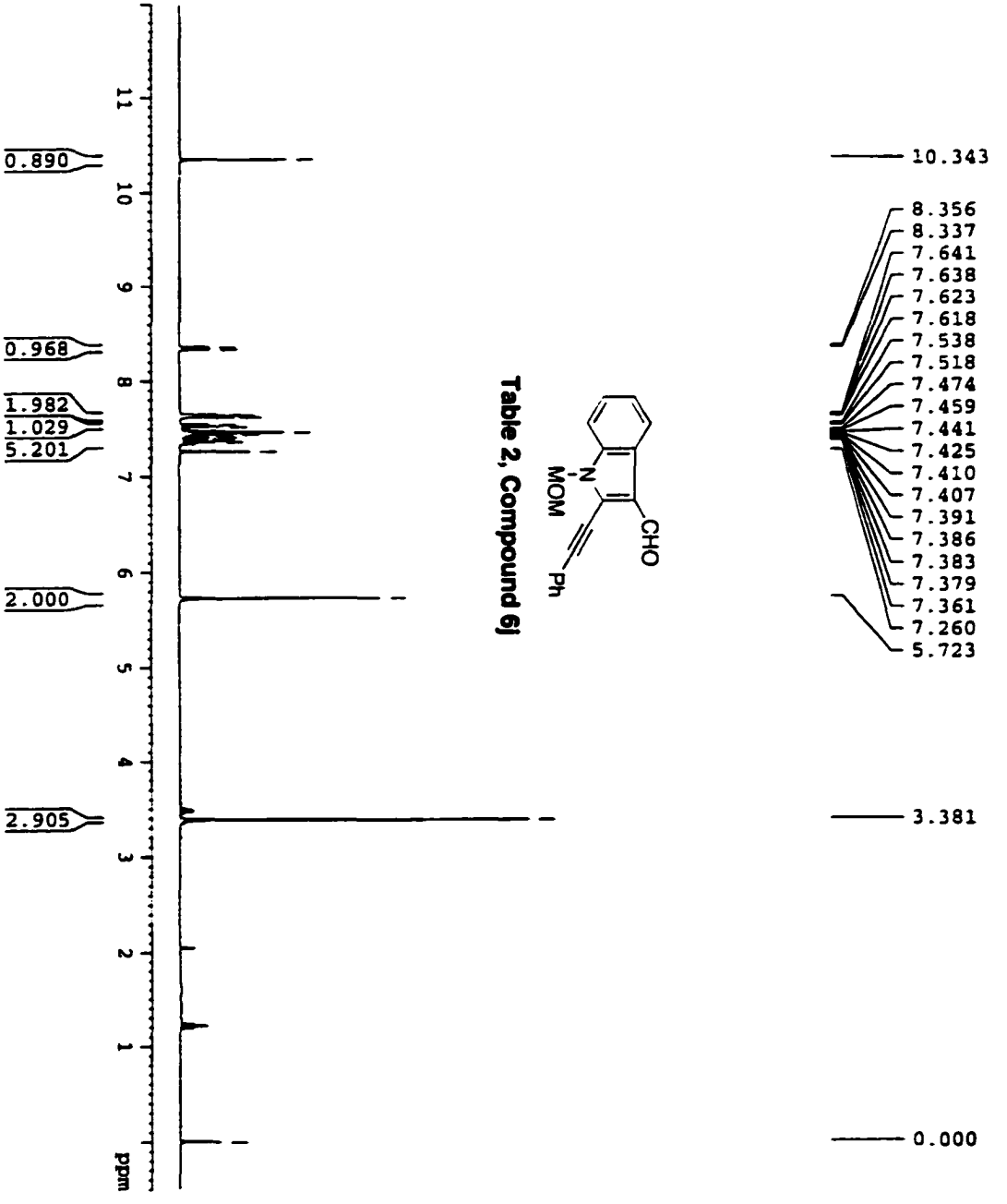


Table 2, Compound 6j

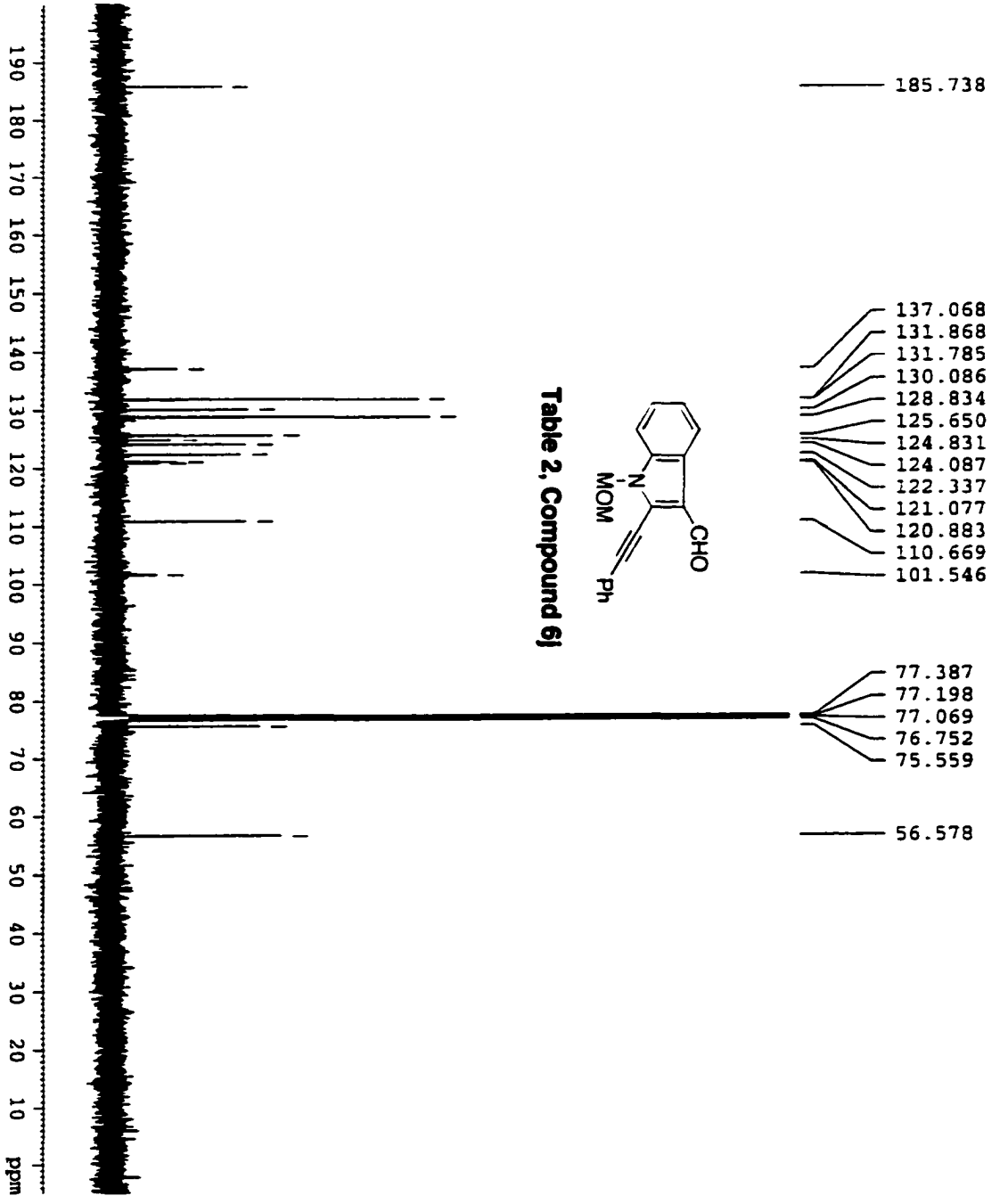
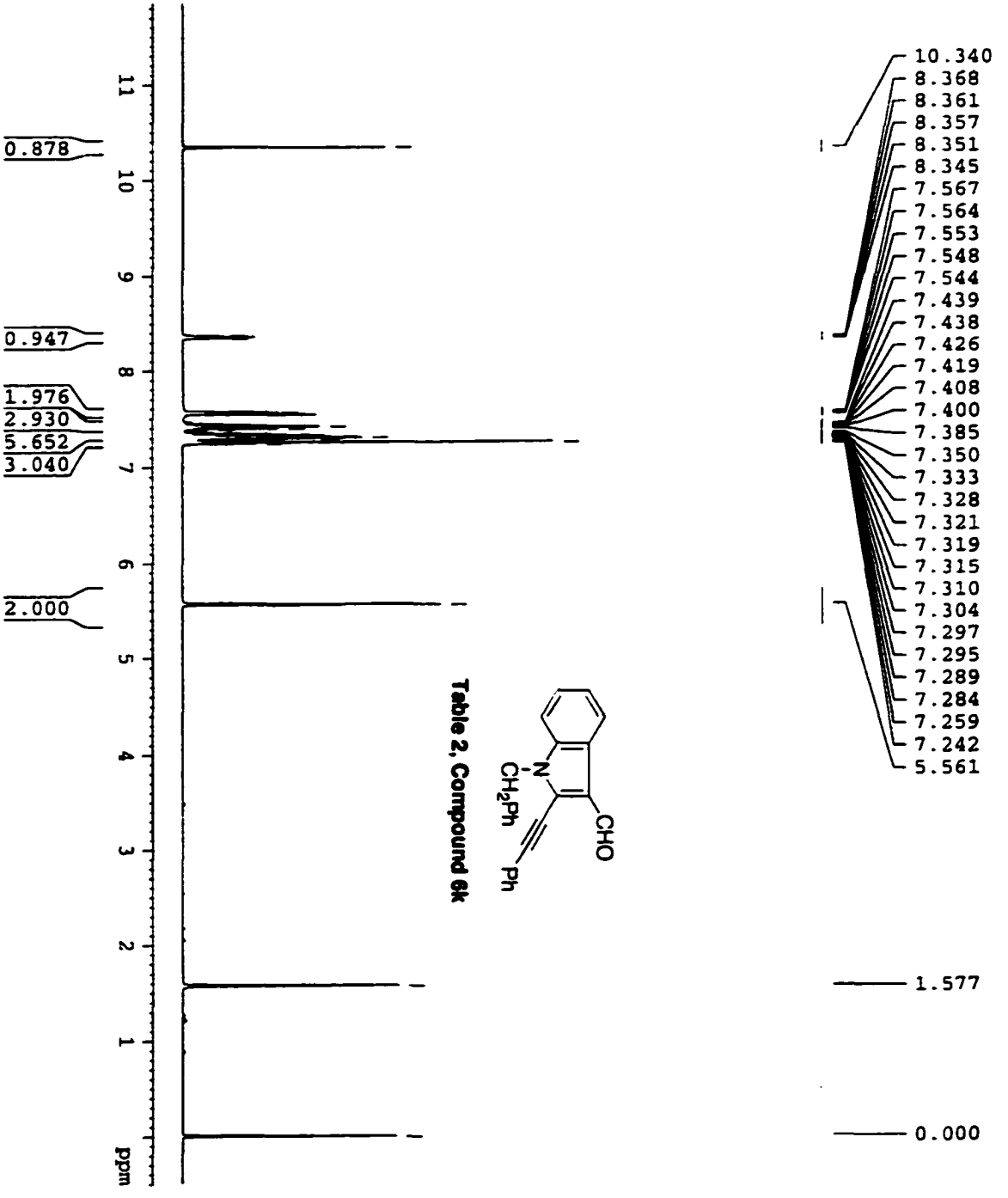


Table 2, Compound 6j


0.878
0.947
1.976
2.930
5.652
3.040
2.000
11
10
9
8
7
6
5
4
3
2
1
ppm
10.340
8.368
8.361
8.357
8.351
8.345
7.567
7.564
7.553
7.548
7.544
7.439
7.438
7.426
7.419
7.408
7.400
7.385
7.350
7.333
7.328
7.321
7.319
7.315
7.310
7.304
7.297
7.295
7.289
7.284
7.259
7.242
5.561
1.577
0.000
Table 2, Compound 6k
N
CH2Ph
Ph
CHO

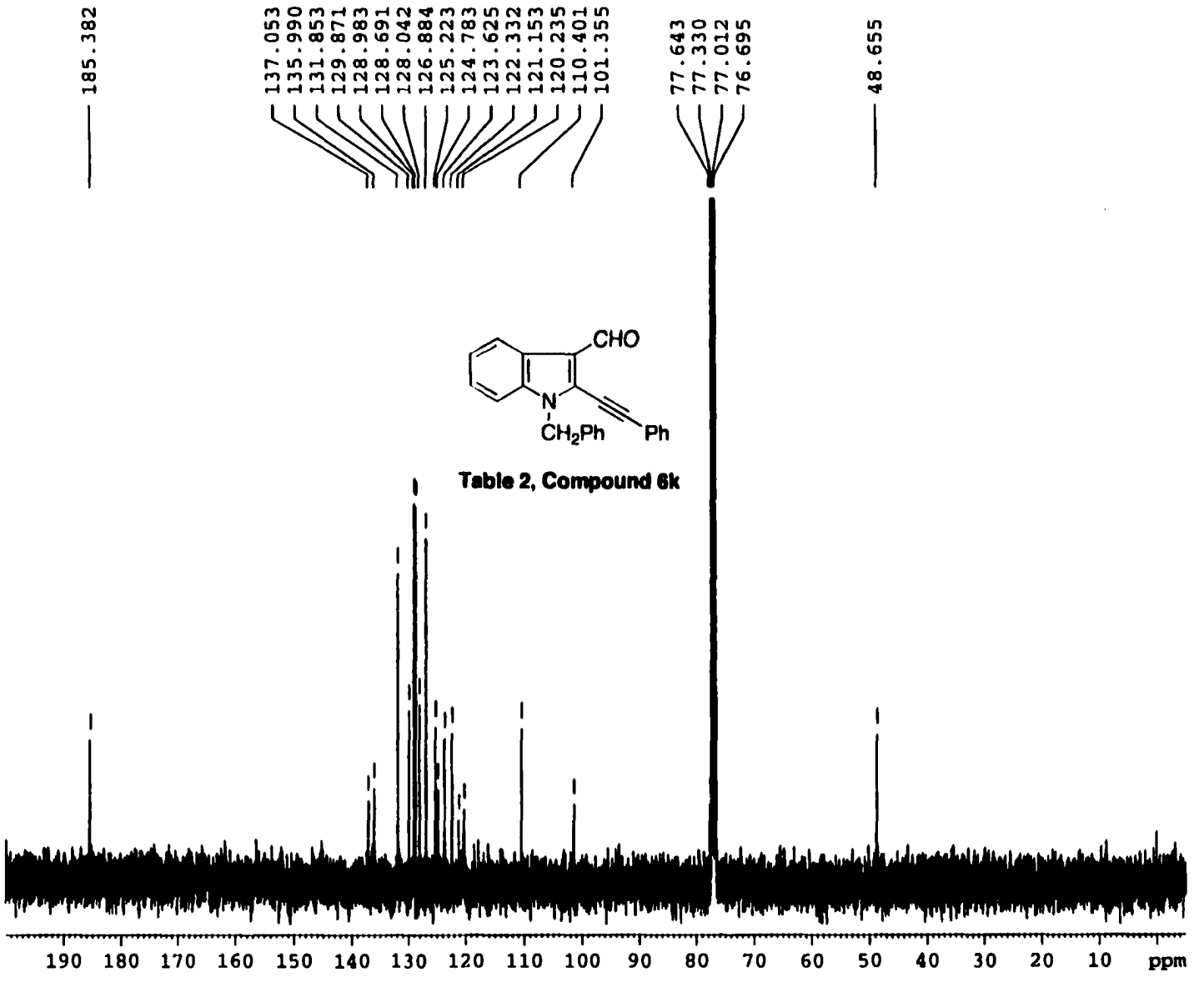


Table 2, Compound 6k

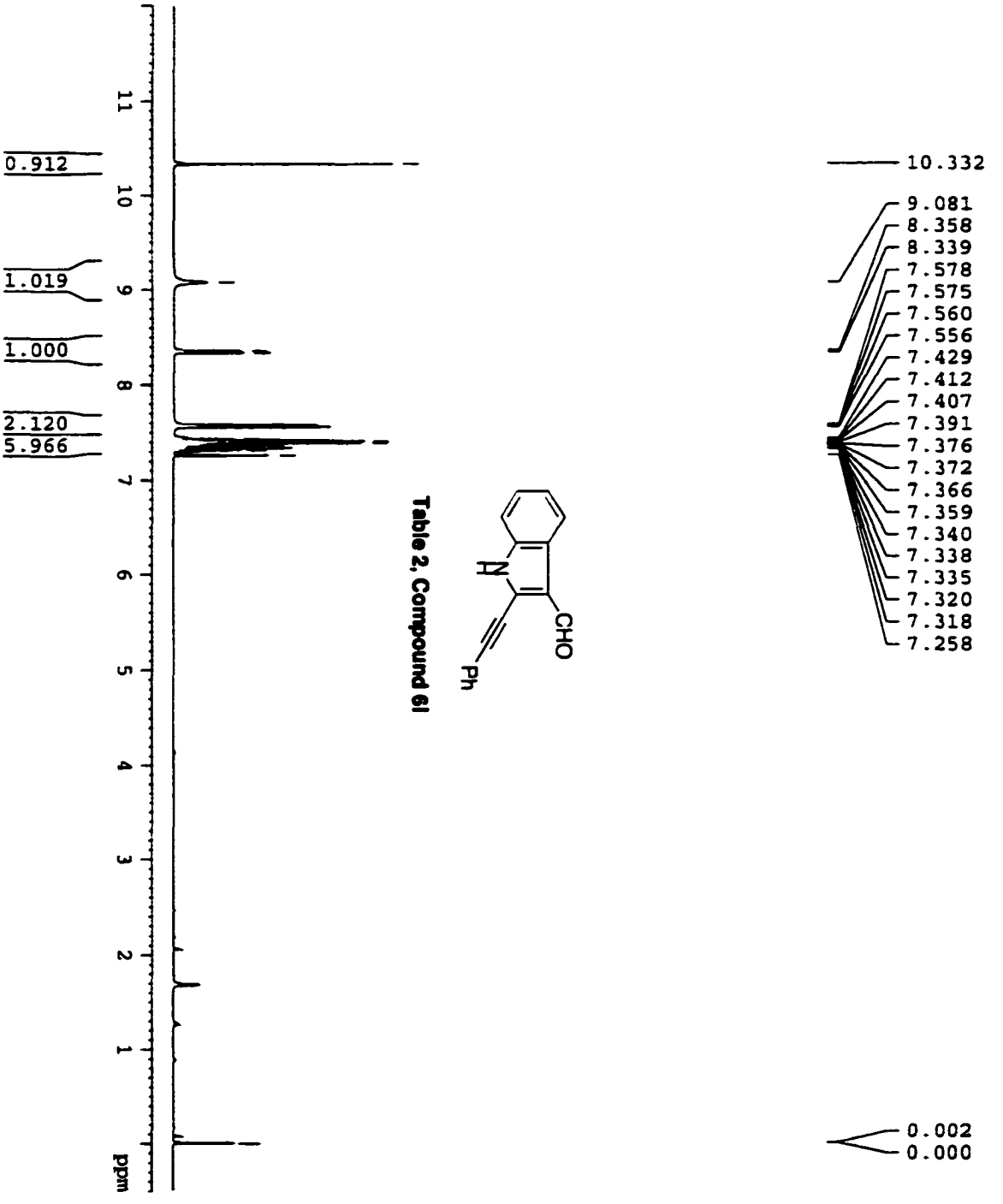
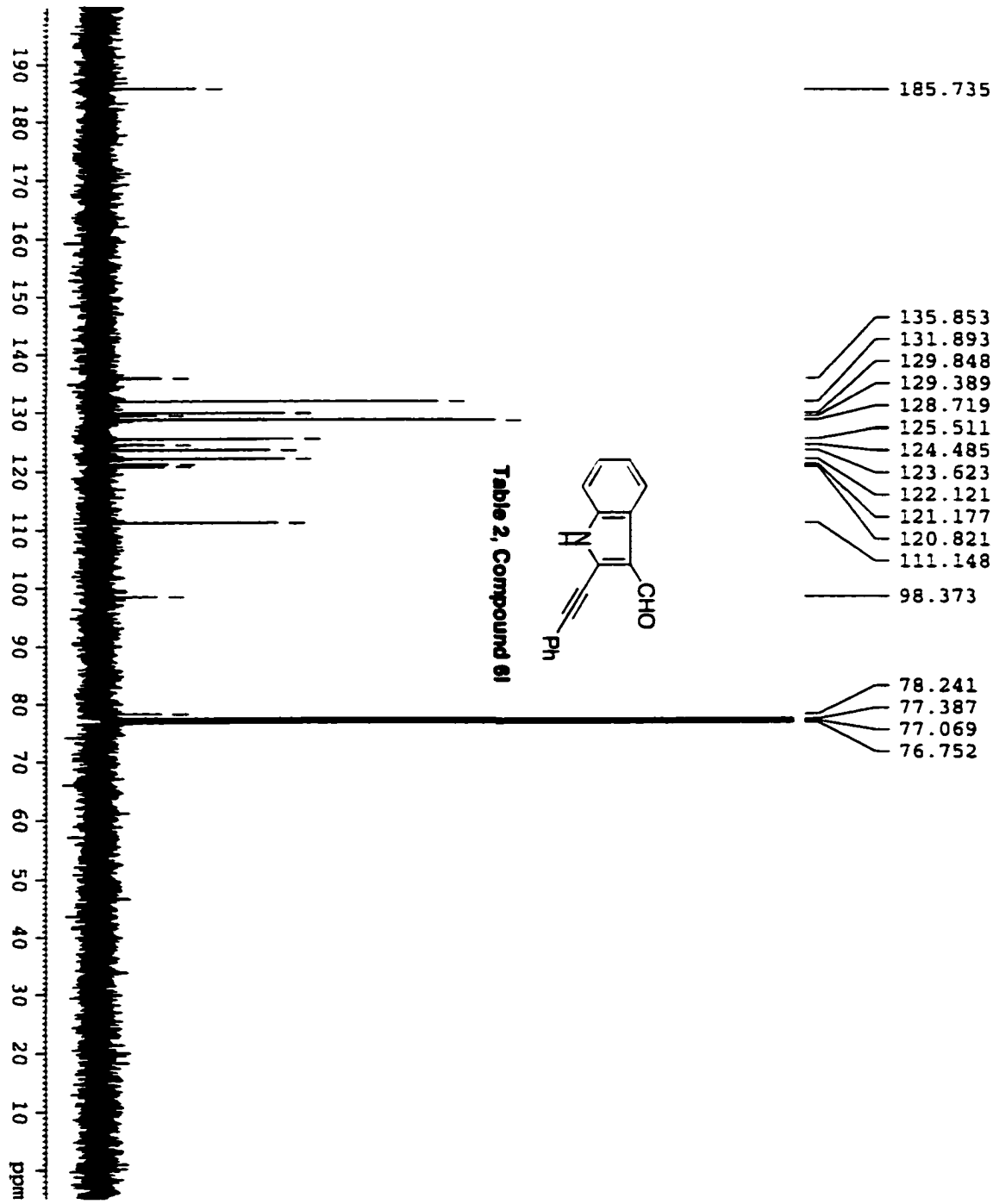
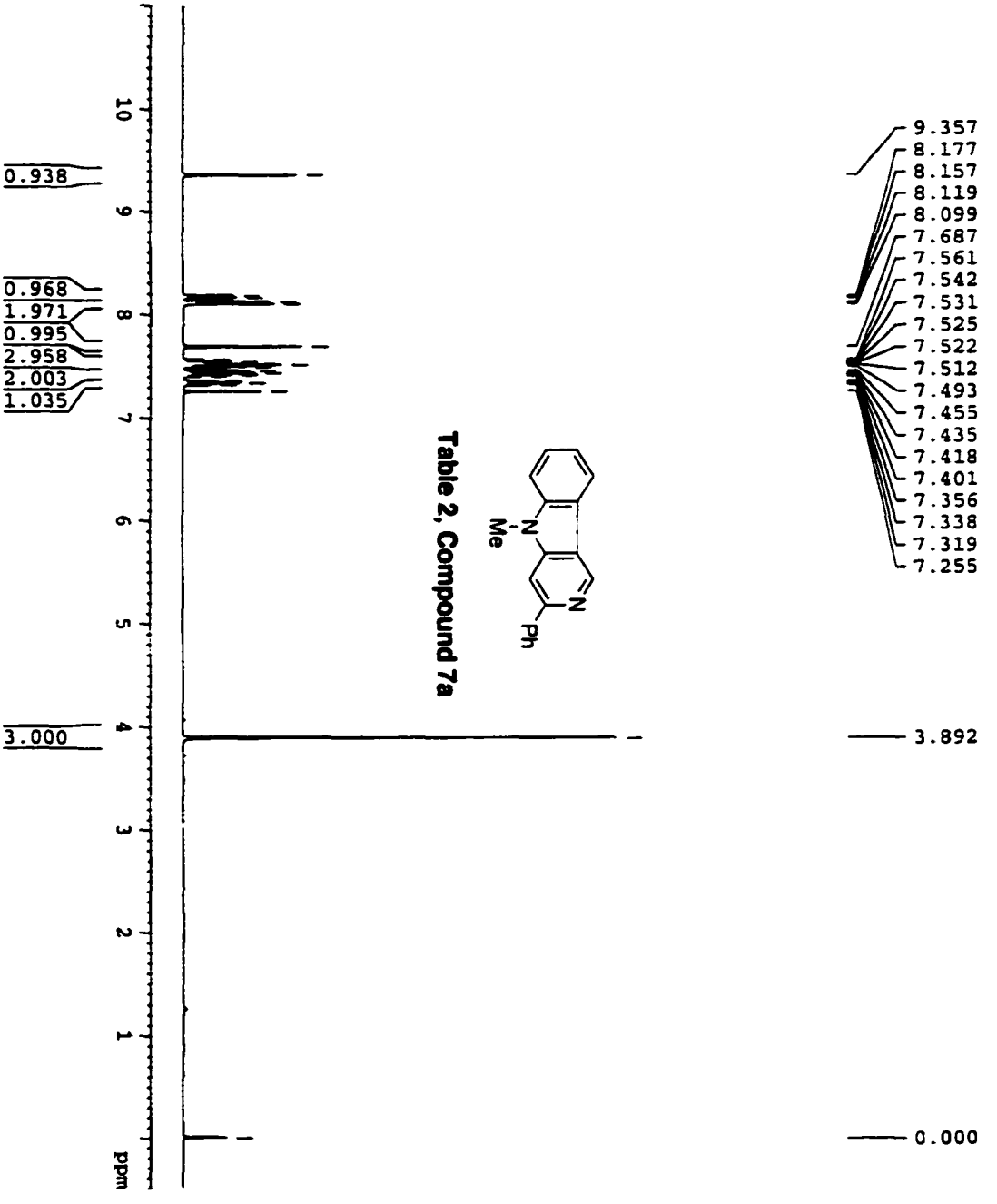


Table 2, Compound 6l


185.735
135.853
131.893
129.848
129.389
128.719
125.511
124.485
123.623
122.121
121.177
120.821
111.148
98.373
78.241
77.387
77.069
76.752
CHO
Ph
Table 2, Compound 6l
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


0.938
0.968
1.971
0.995
2.958
2.003
1.035
3.000
10
9
8
7
6
5
4
3
2
1
ppm
9.357
8.177
8.157
8.119
8.099
7.687
7.561
7.542
7.531
7.525
7.522
7.512
7.493
7.455
7.435
7.418
7.401
7.356
7.338
7.319
7.255
3.892
0.000
Table 2, Compound 7a
N
Me
N
Ph

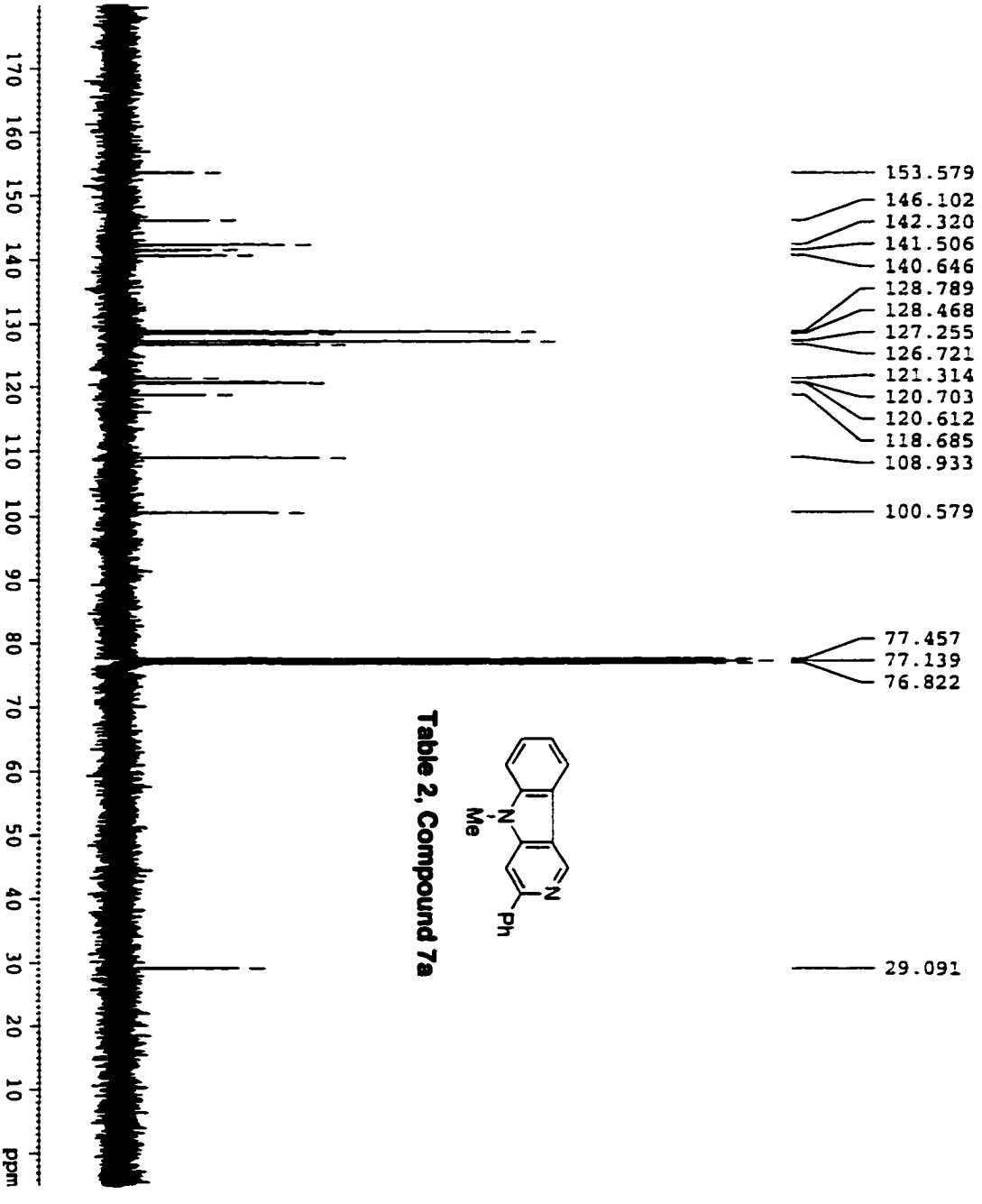


Table 2, Compound 7a

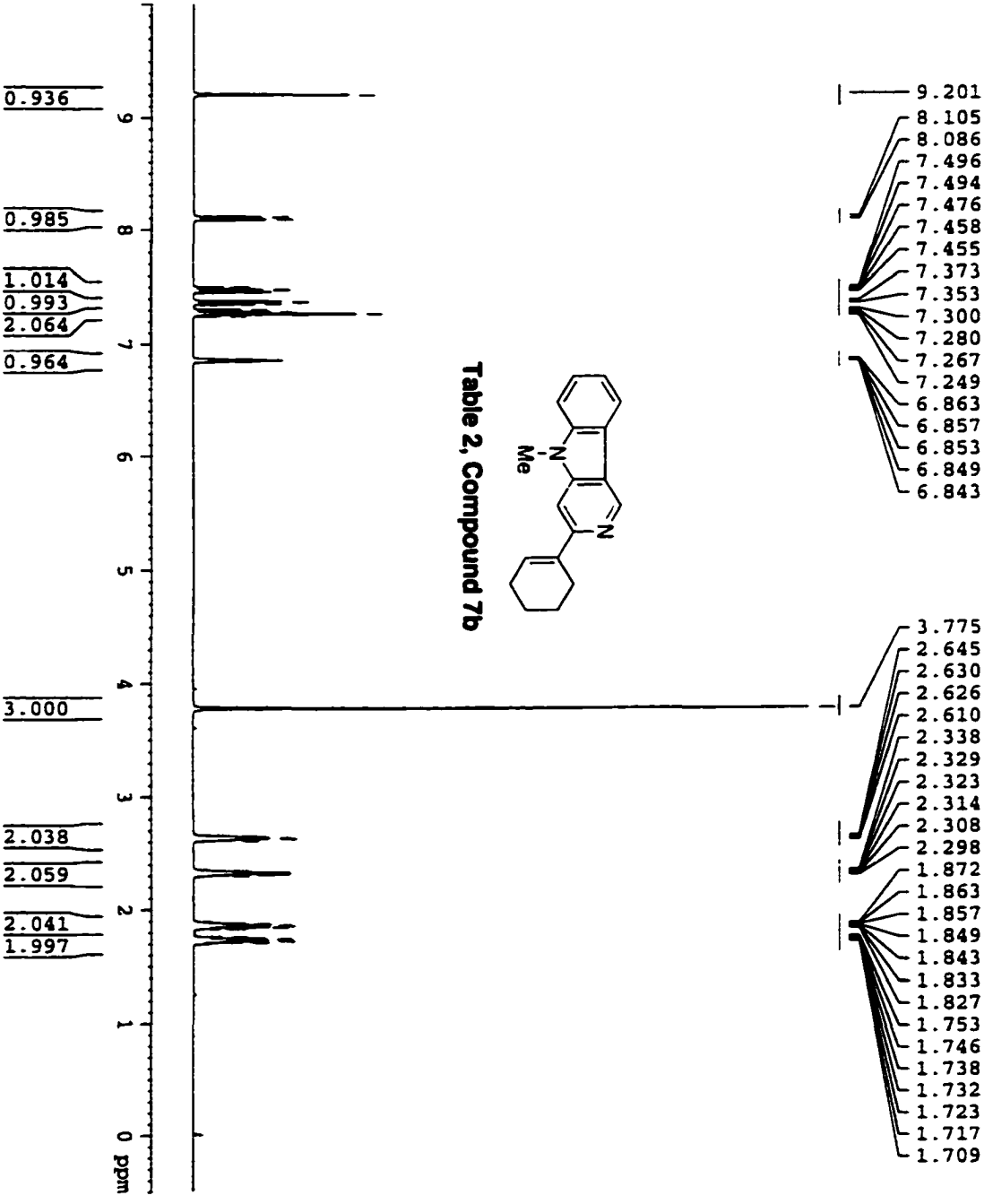
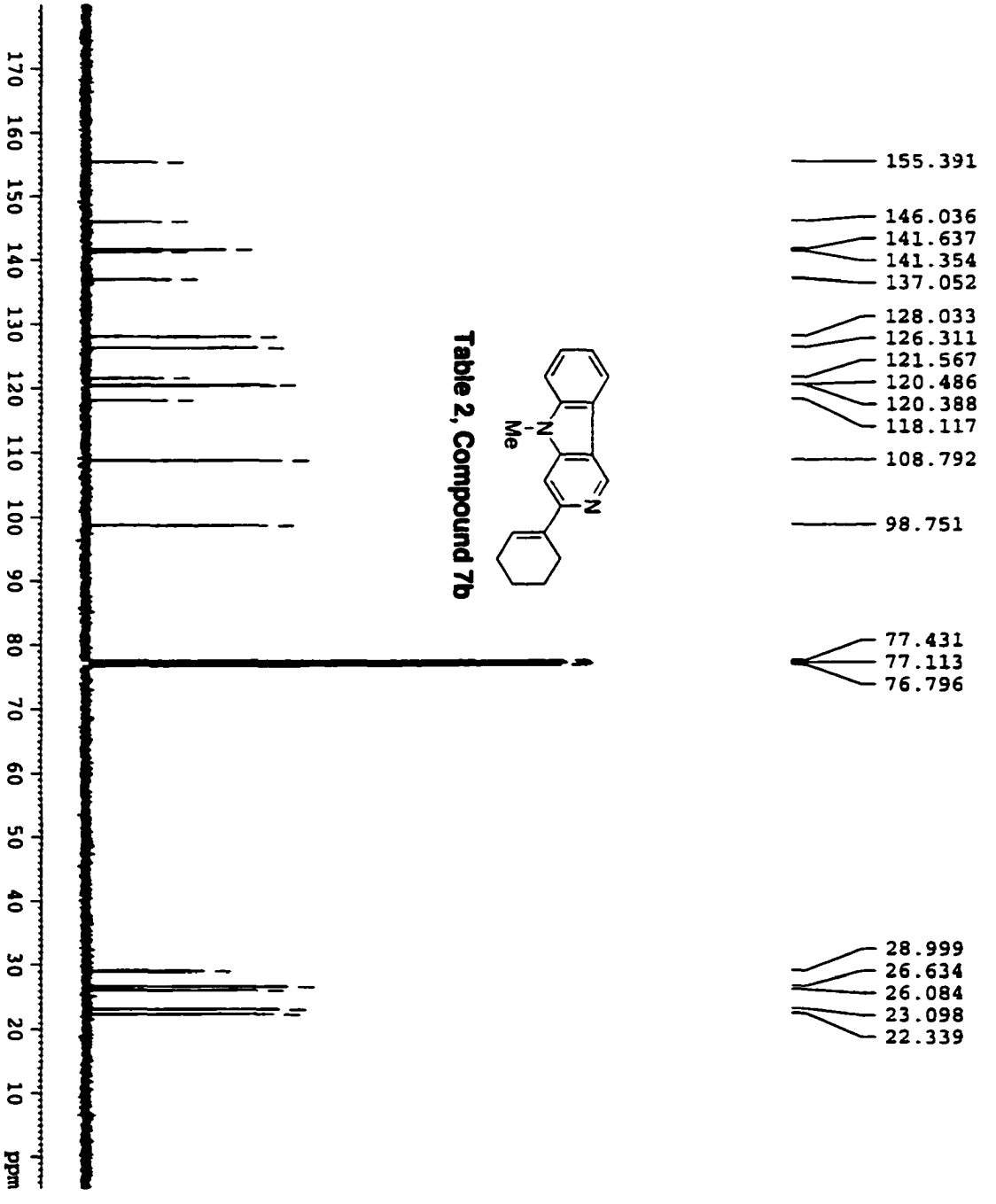


Table 2, Compound 7b


155.391
146.036
141.637
141.354
137.052
128.033
126.311
121.567
120.486
120.388
118.117
108.792
98.751
77.431
77.113
76.796
28.999
26.634
26.084
23.098
22.339
Me
N
N
Table 2, Compound 7b
ppm

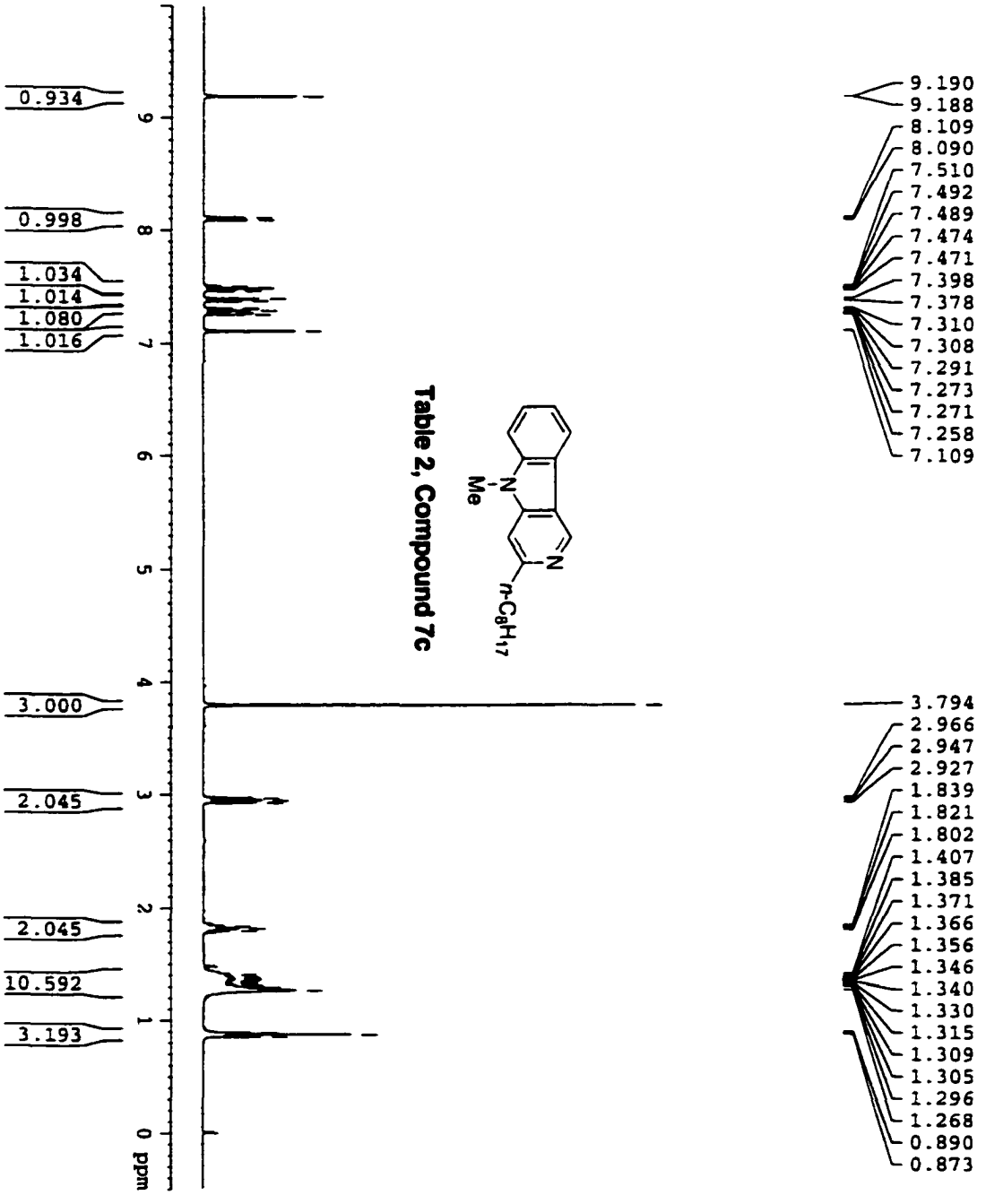


Table 2, Compound 7c
Me
n-C8H17
0.934
0.998
1.034
1.014
1.080
1.016
3.000
2.045
2.045
10.592
3.193
ppm
9.190
9.188
8.109
8.090
7.510
7.492
7.489
7.474
7.471
7.398
7.378
7.310
7.308
7.291
7.273
7.271
7.258
7.109
3.794
2.966
2.947
2.927
1.839
1.821
1.802
1.407
1.385
1.371
1.366
1.356
1.346
1.340
1.330
1.315
1.309
1.305
1.296
1.268
0.890
0.873

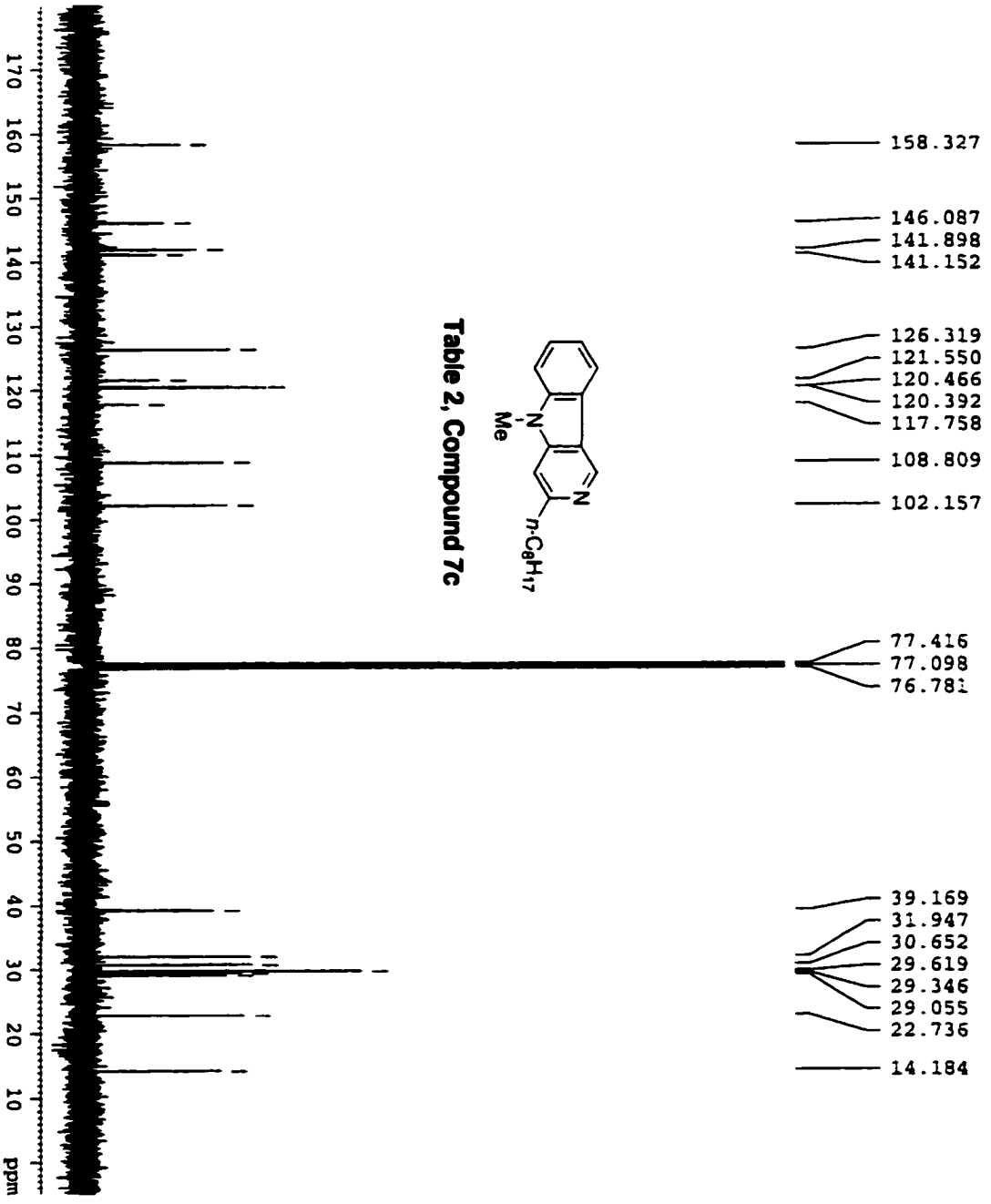


Table 2, Compound 7c

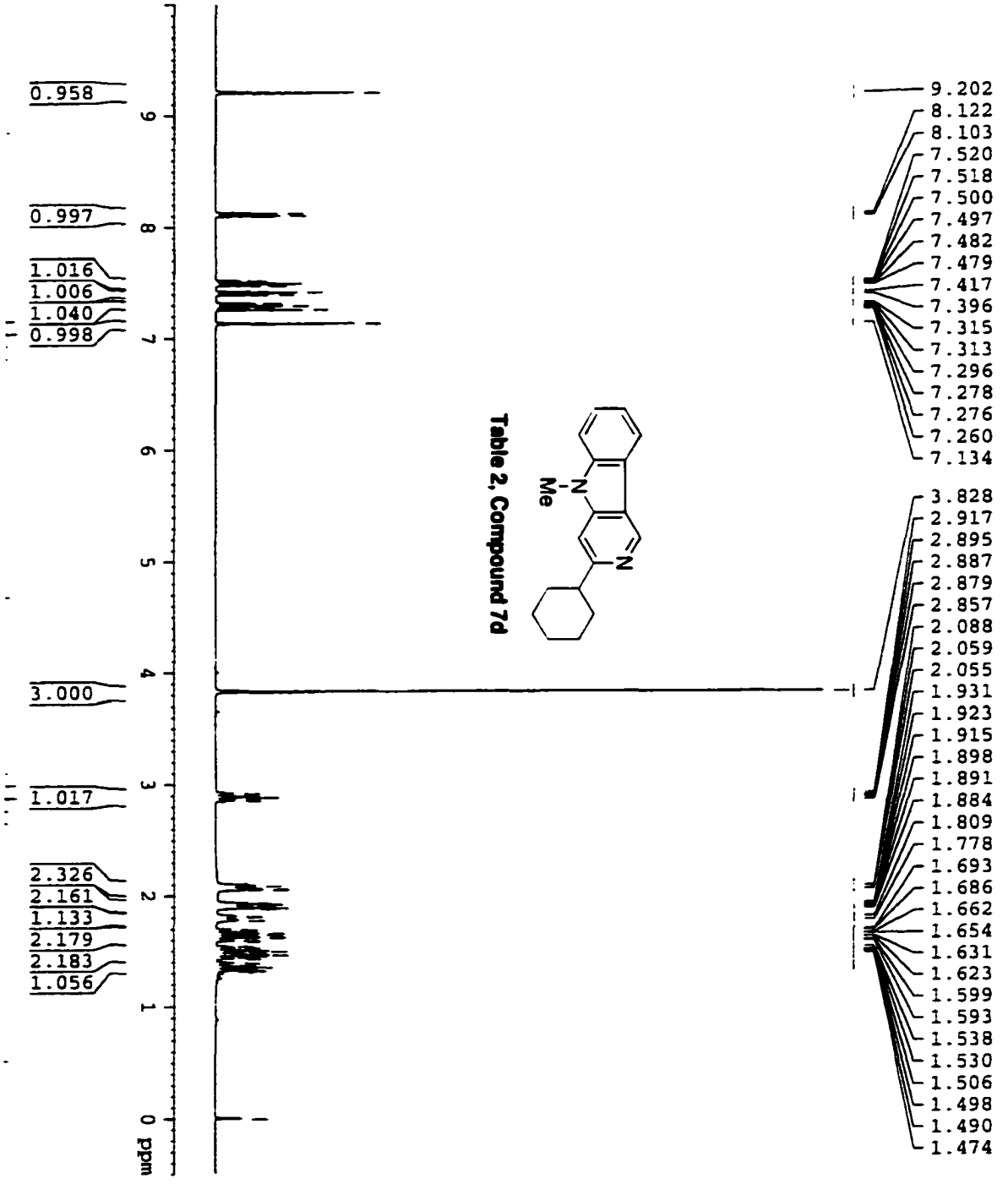


Table 2, Compound 7d

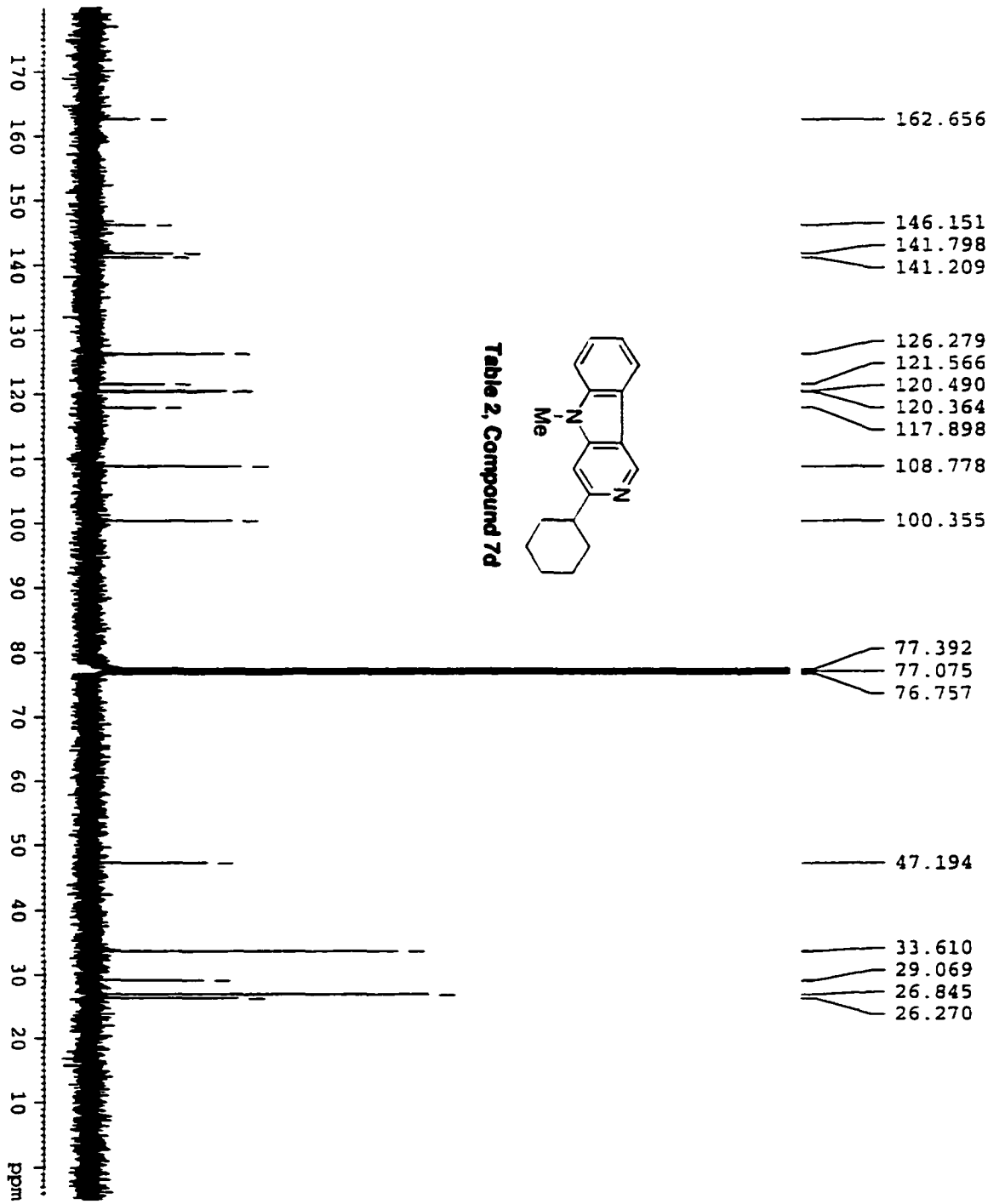


Table 2, Compound 7d
Me
N
N
162.656
146.151
141.798
141.209
126.279
121.566
120.490
120.364
117.898
108.778
100.355
77.392
77.075
76.757
47.194
33.610
29.069
26.845
26.270
ppm

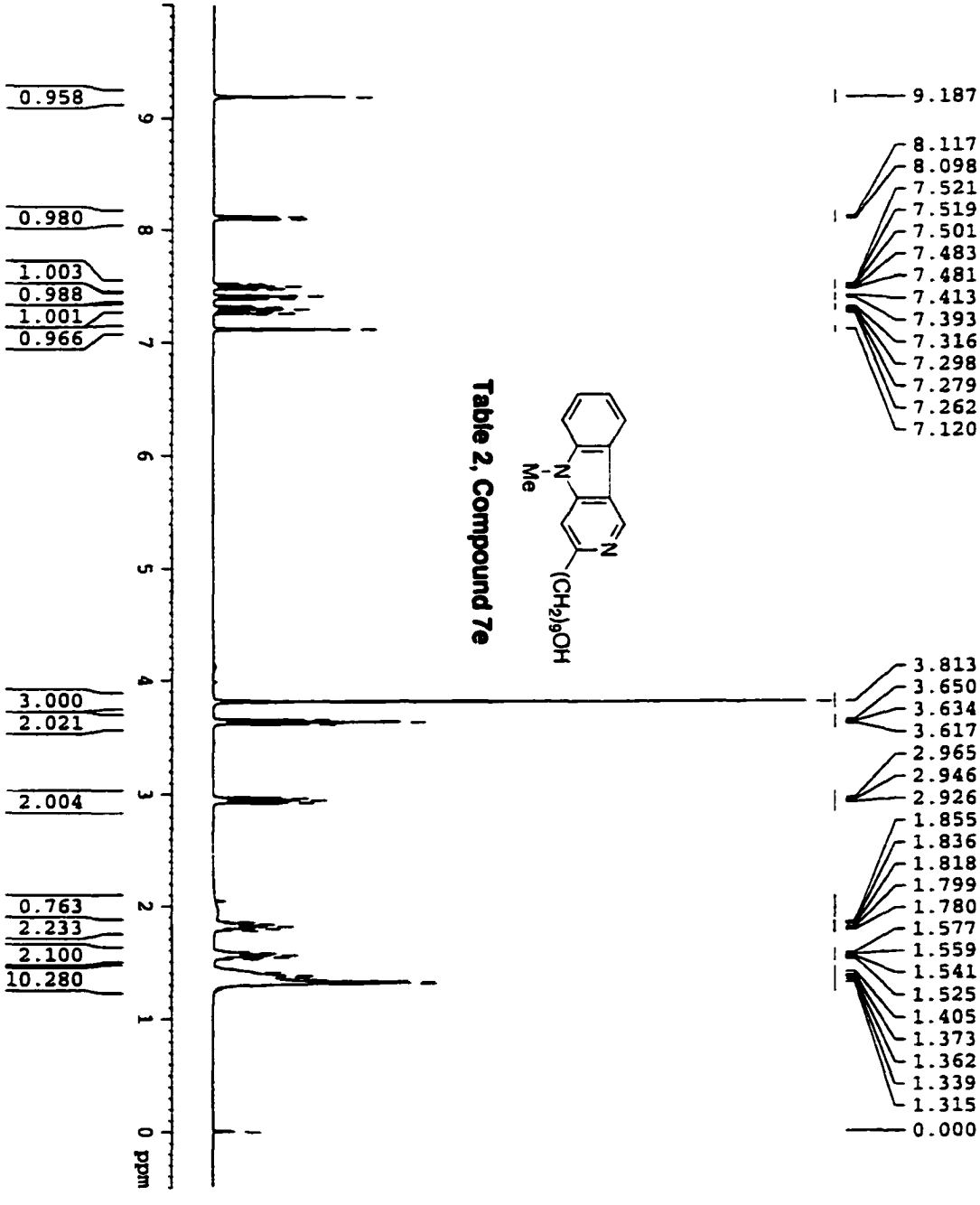


Table 2, Compound 7e

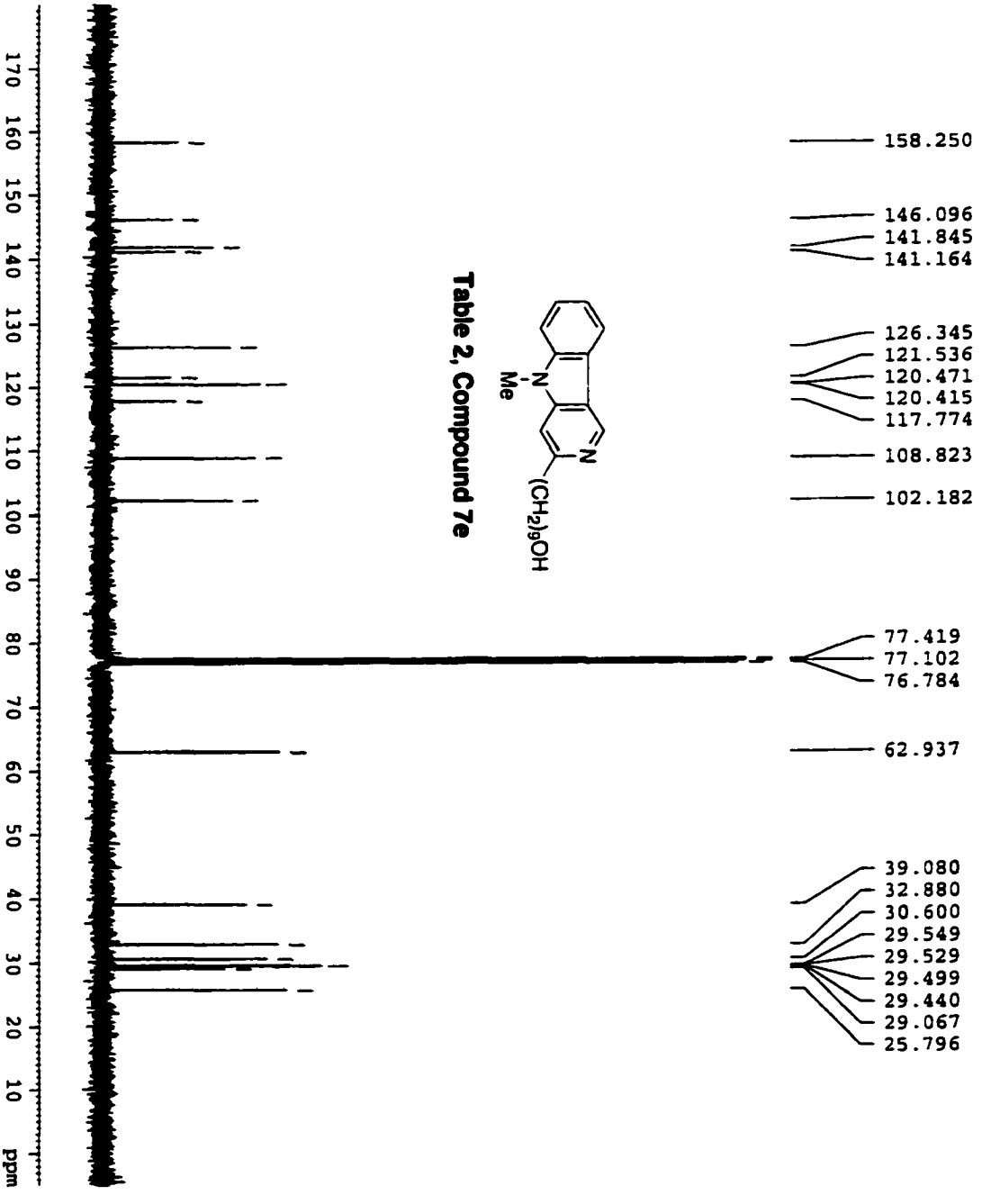


Table 2, Compound 7e

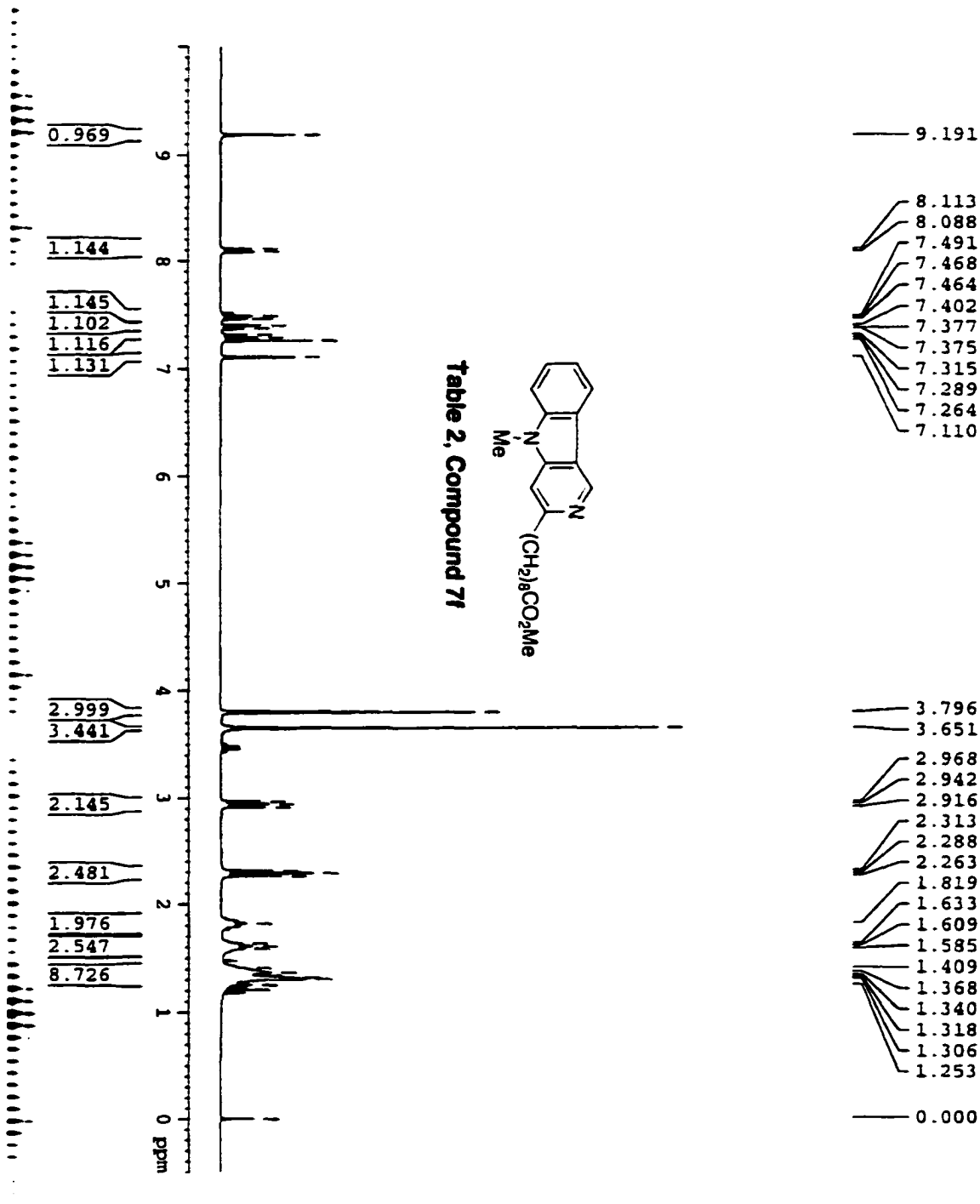


Table 2, Compound 7l
N
Me
N
(CH2)8CO2Me
0.969
1.144
1.145
1.102
1.116
1.131
2.999
3.441
2.145
2.481
1.976
2.547
8.726
9.191
8.113
8.088
7.491
7.468
7.464
7.402
7.377
7.375
7.315
7.289
7.264
7.110
3.796
3.651
2.968
2.942
2.916
2.313
2.288
2.263
1.819
1.633
1.609
1.585
1.409
1.368
1.340
1.318
1.306
1.253
0.000
9
8
7
6
5
4
3
2
1
0
ppm

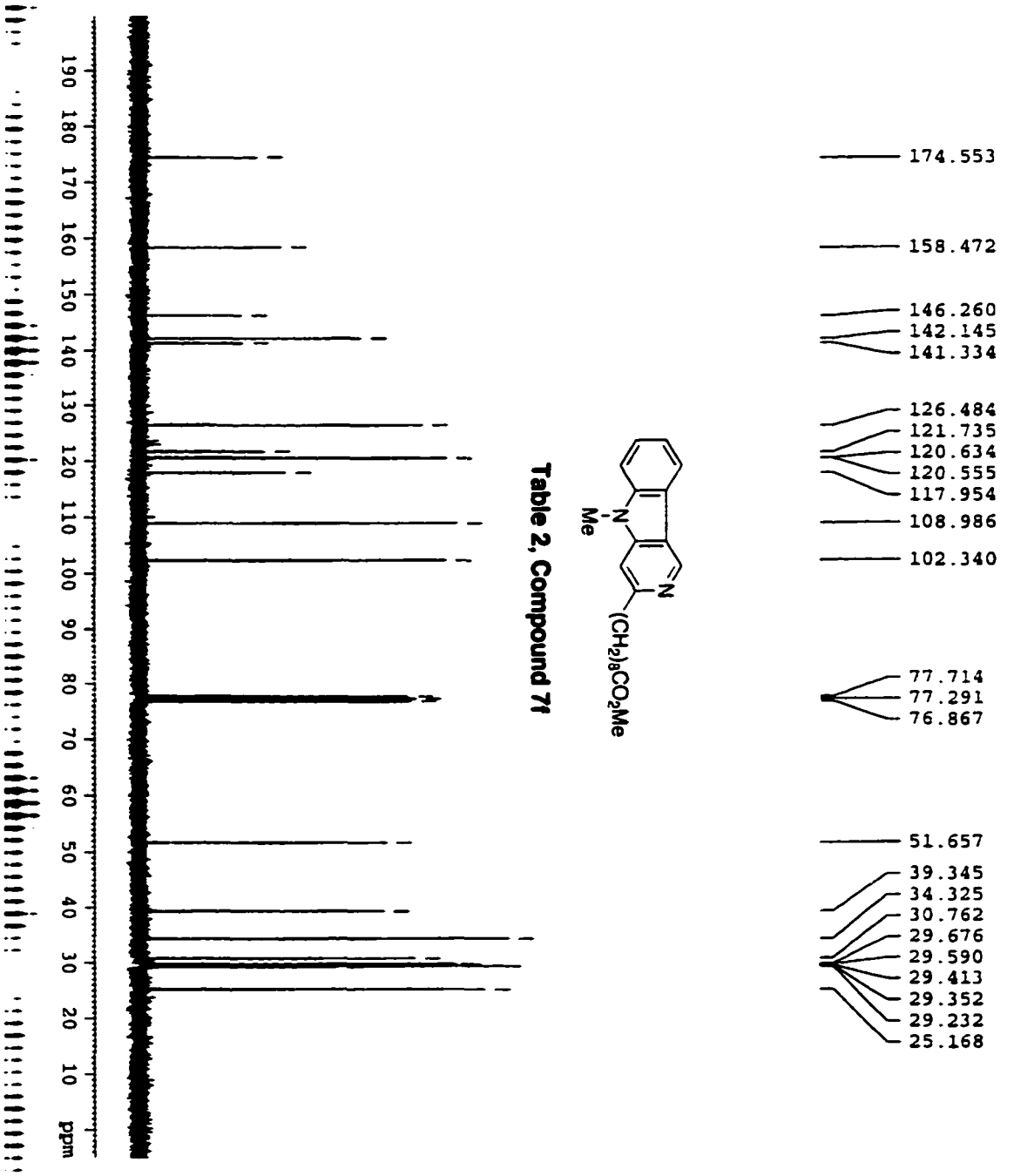
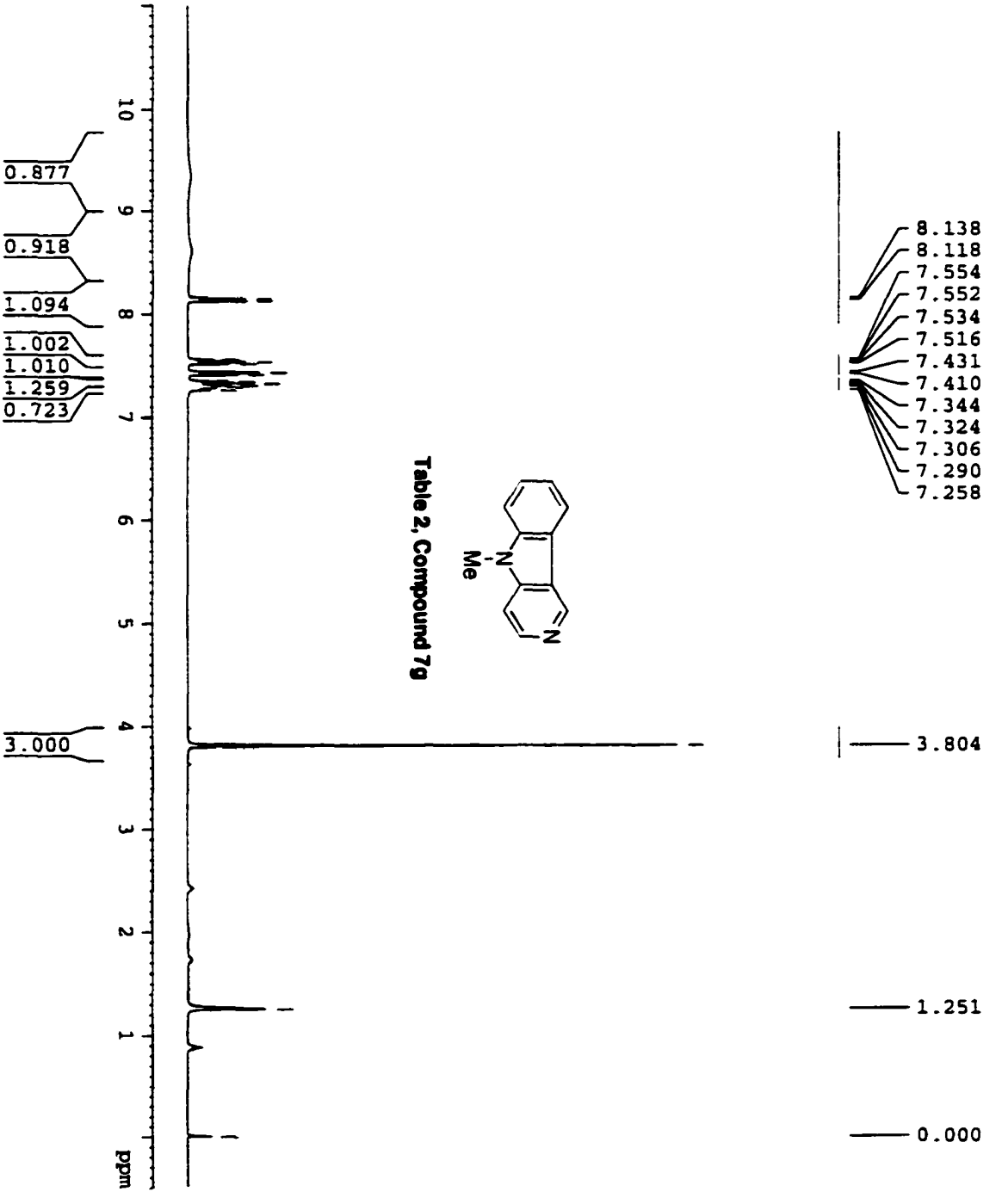
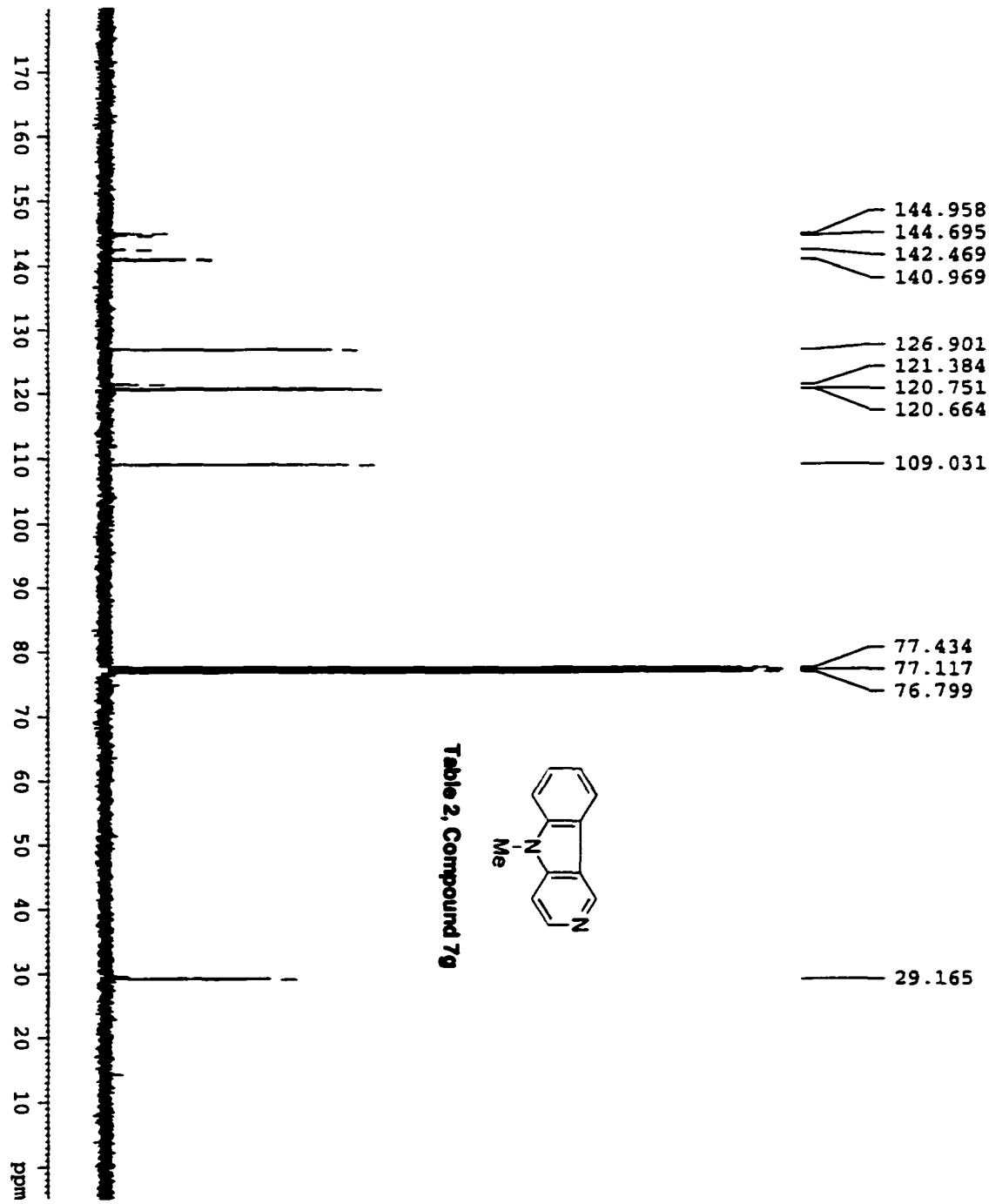
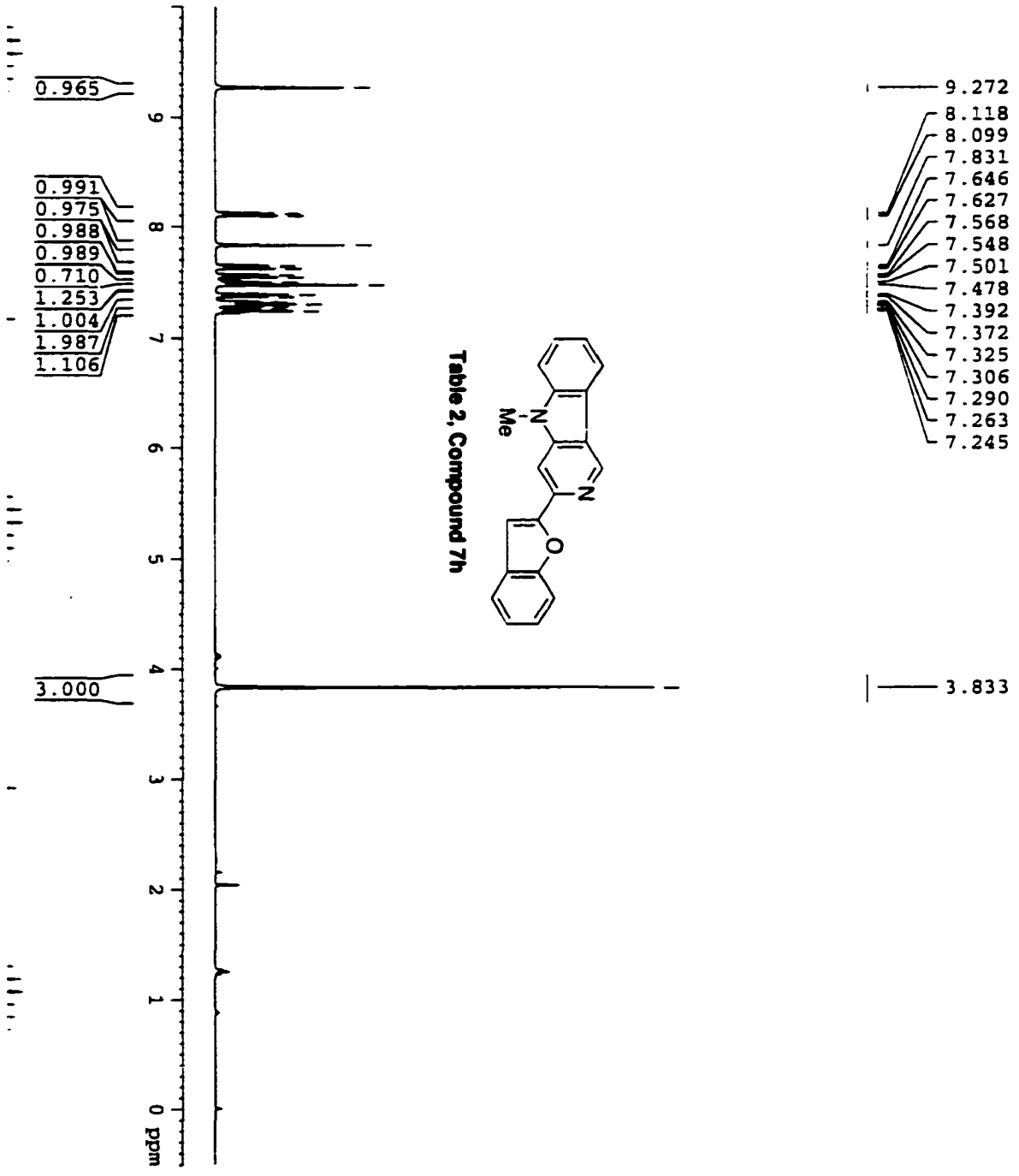


Table 2, Compound 7f


0.877
0.918
1.094
1.002
1.010
1.259
0.723
3.000
10
9
8
7
6
5
4
3
2
1
ppm
Table 2, Compound 7g
Me
N
N
8.138
8.118
7.554
7.552
7.534
7.516
7.431
7.410
7.344
7.324
7.306
7.290
7.258
3.804
1.251
0.000


144.958
144.695
142.469
140.969
126.901
121.384
120.751
120.664
109.031
77.434
77.117
76.799
29.165
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
Table 2, Compound 7g
N
Me
N


0.965
0.991
0.975
0.988
0.989
0.710
1.253
1.004
1.987
1.106
3.000
9.272
8.118
8.099
7.831
7.646
7.627
7.568
7.548
7.501
7.478
7.392
7.372
7.325
7.306
7.290
7.263
7.245
3.833
Me
N
N
O
Table 2, Compound 7h
9
8
7
6
5
4
3
2
1
0 ppm

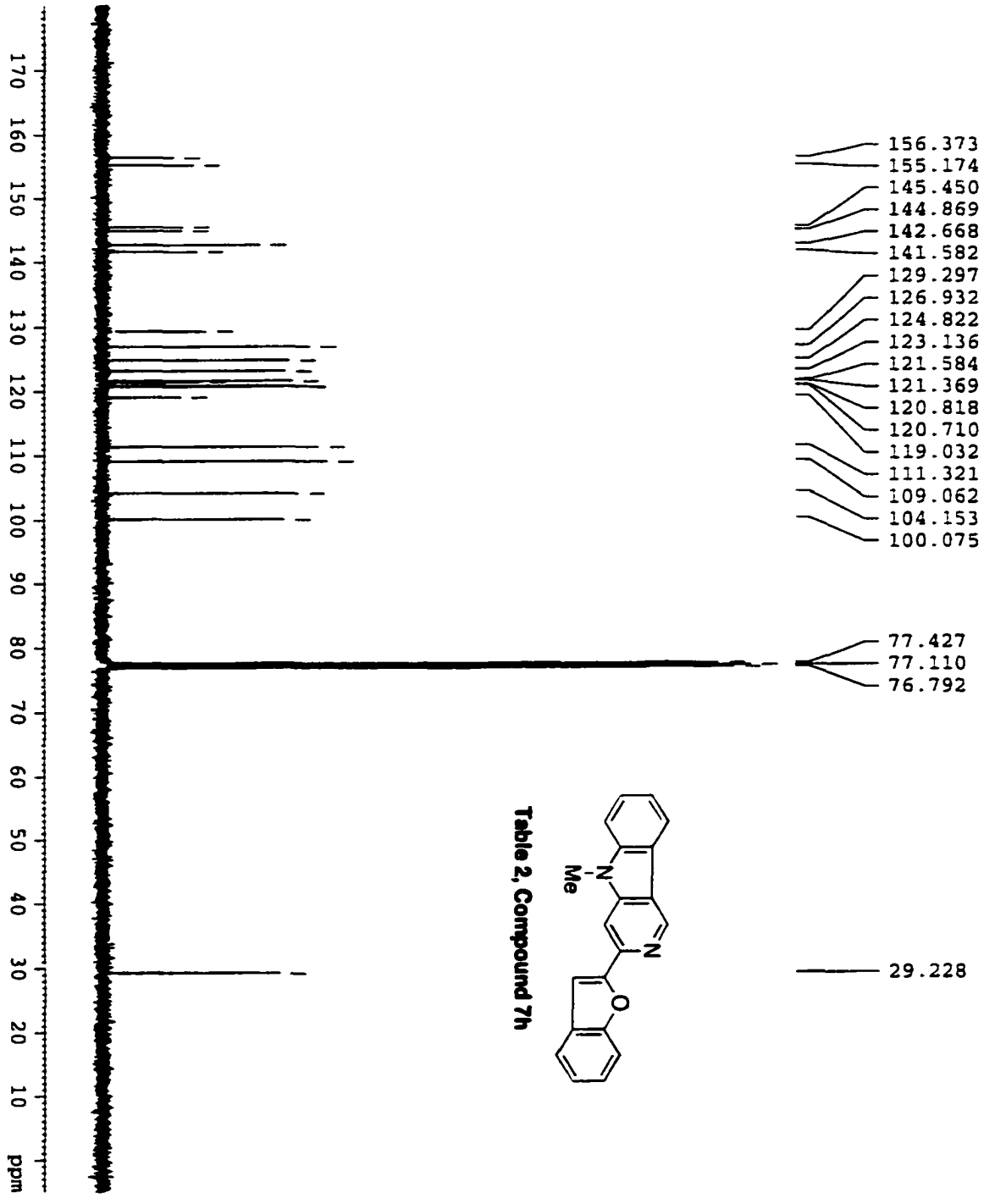


Table 2, Compound 7h

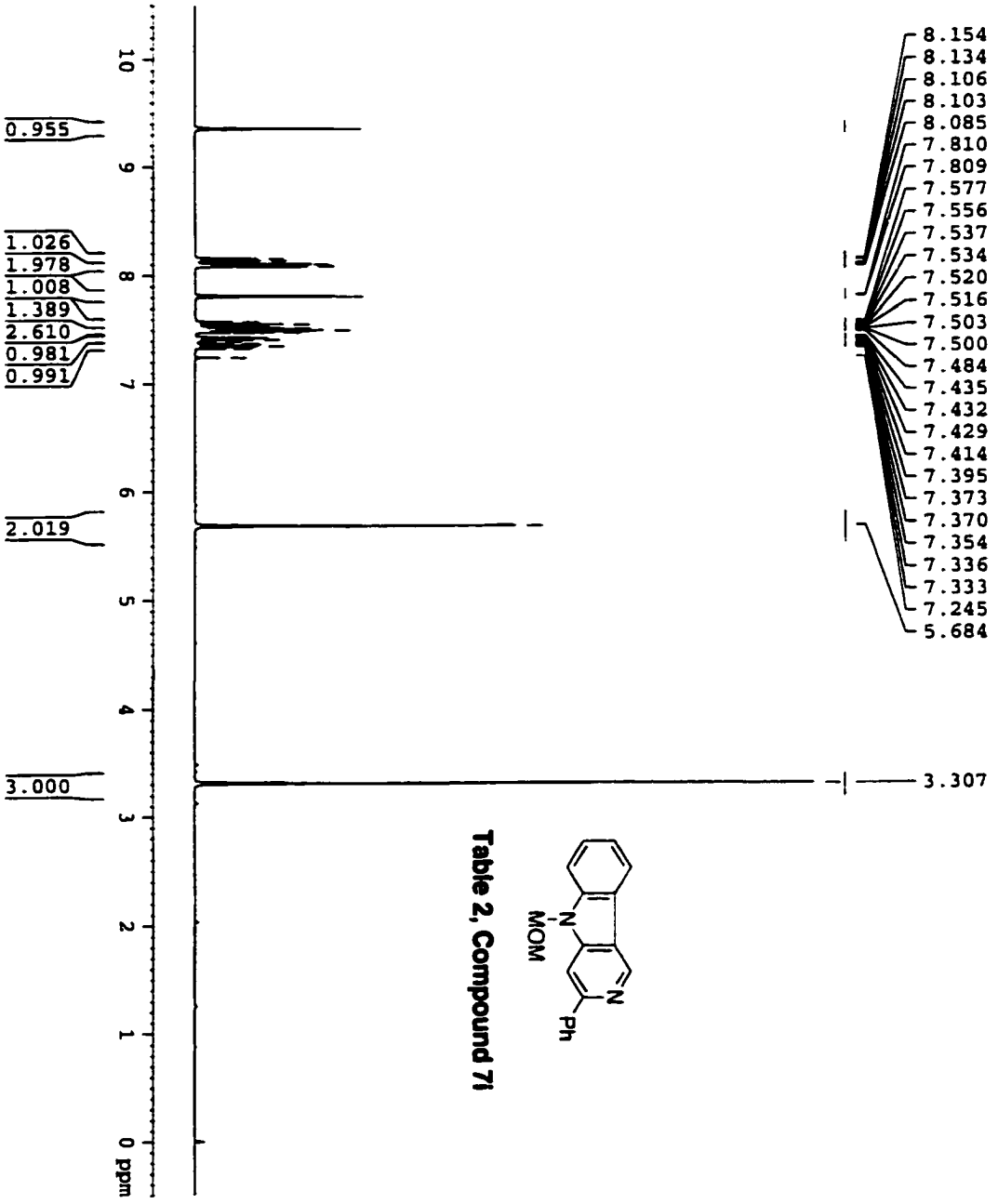


Table 2, Compound 7l

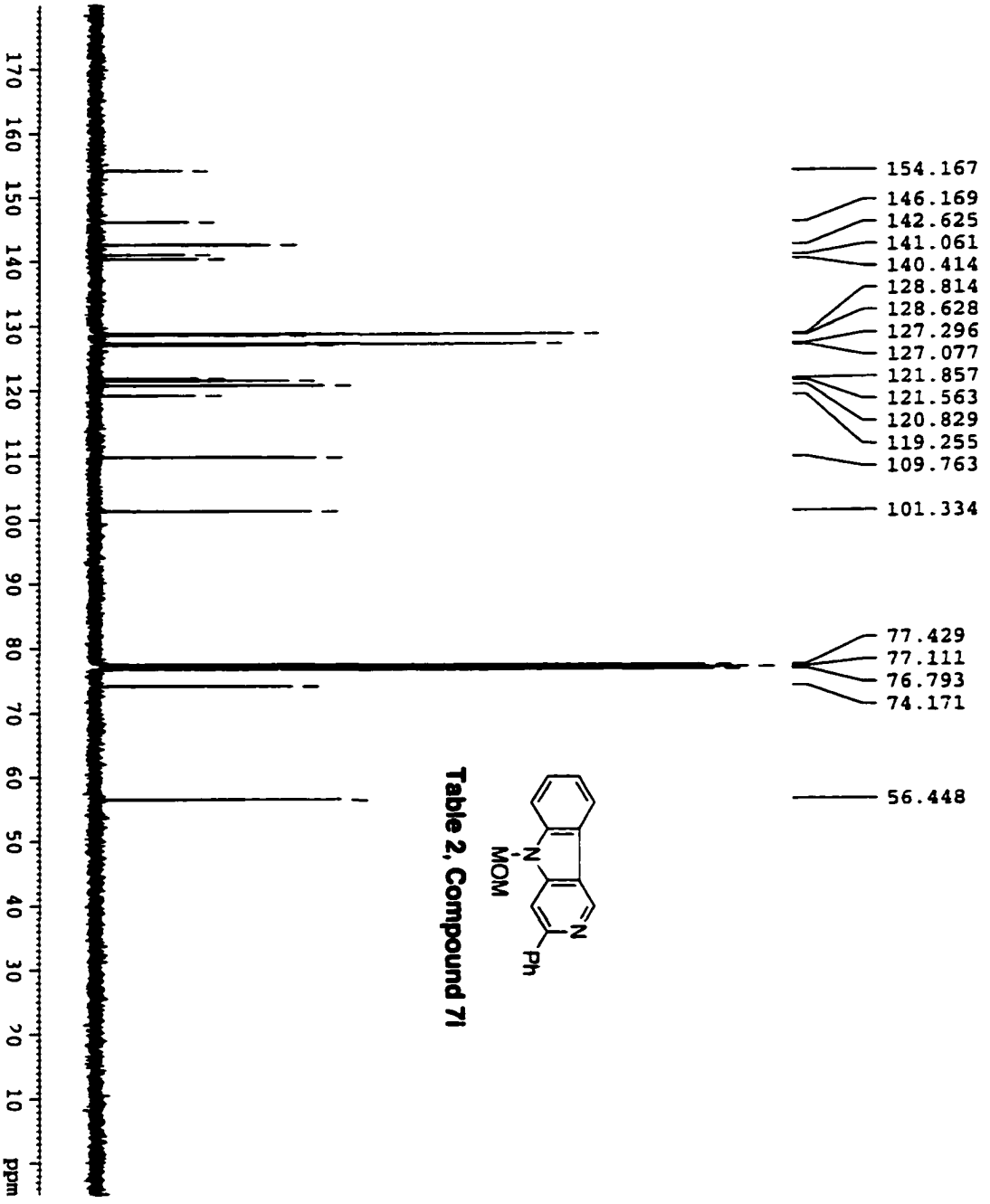


Table 2, Compound 7l

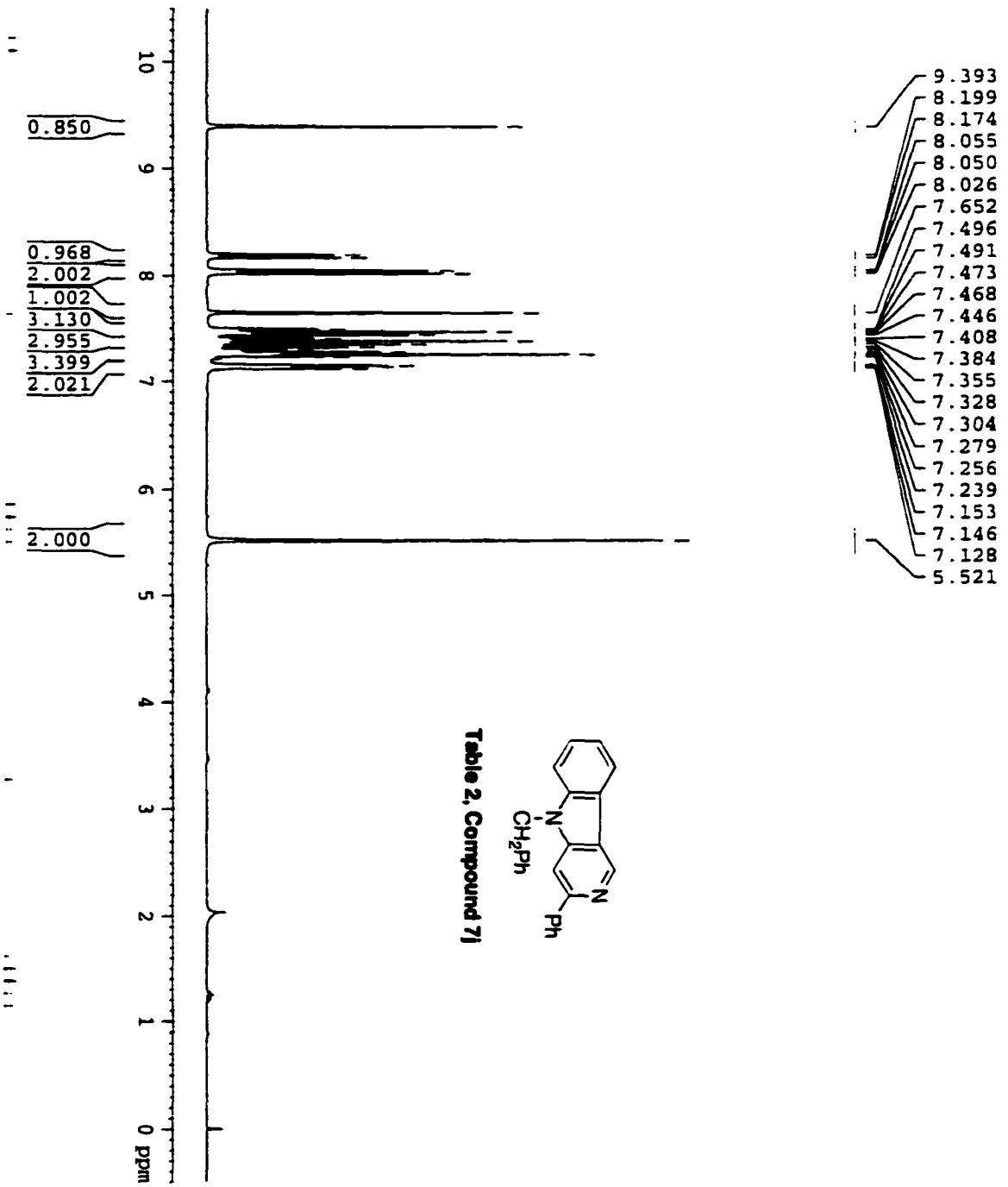


Table 2, Compound 7j

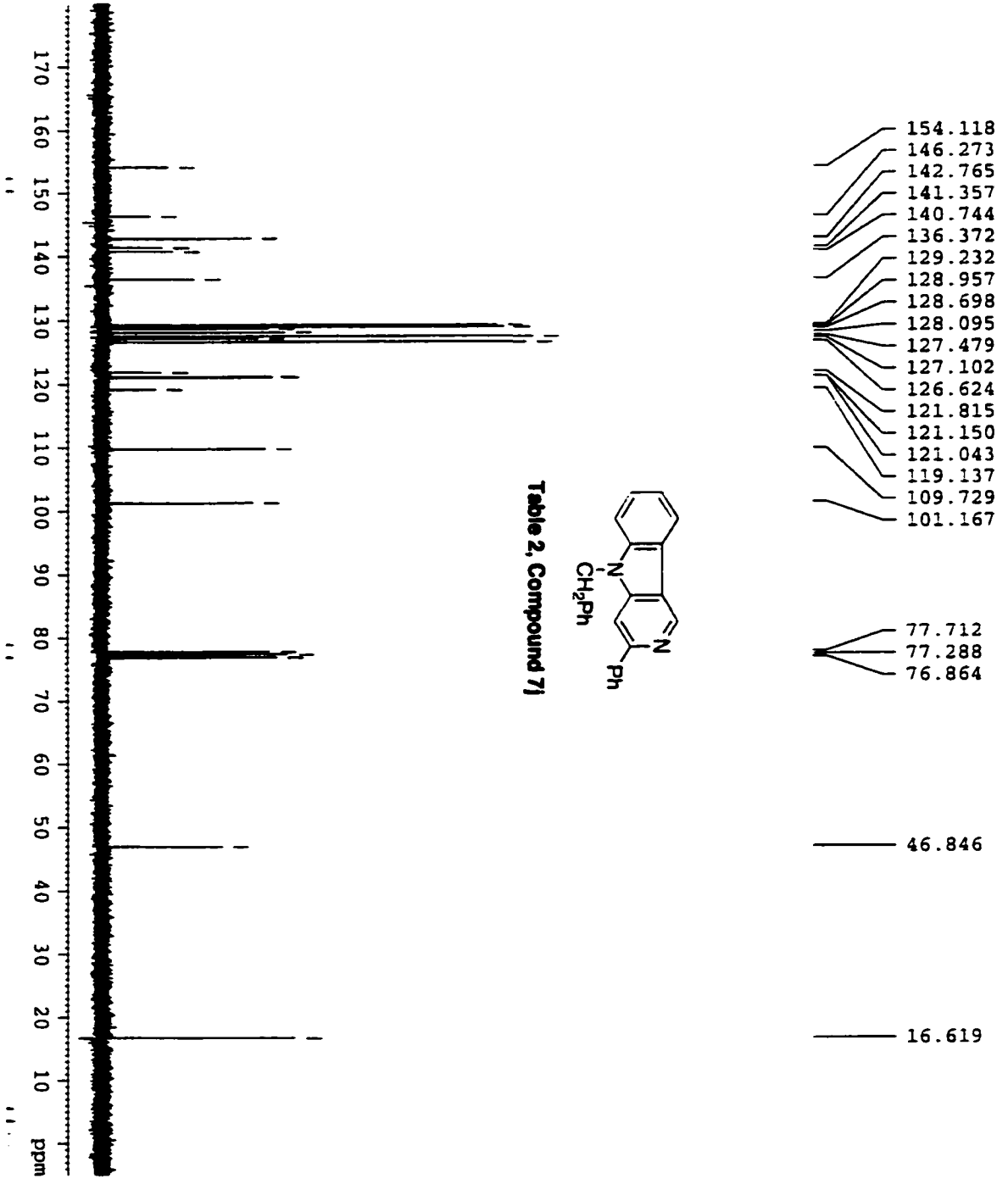
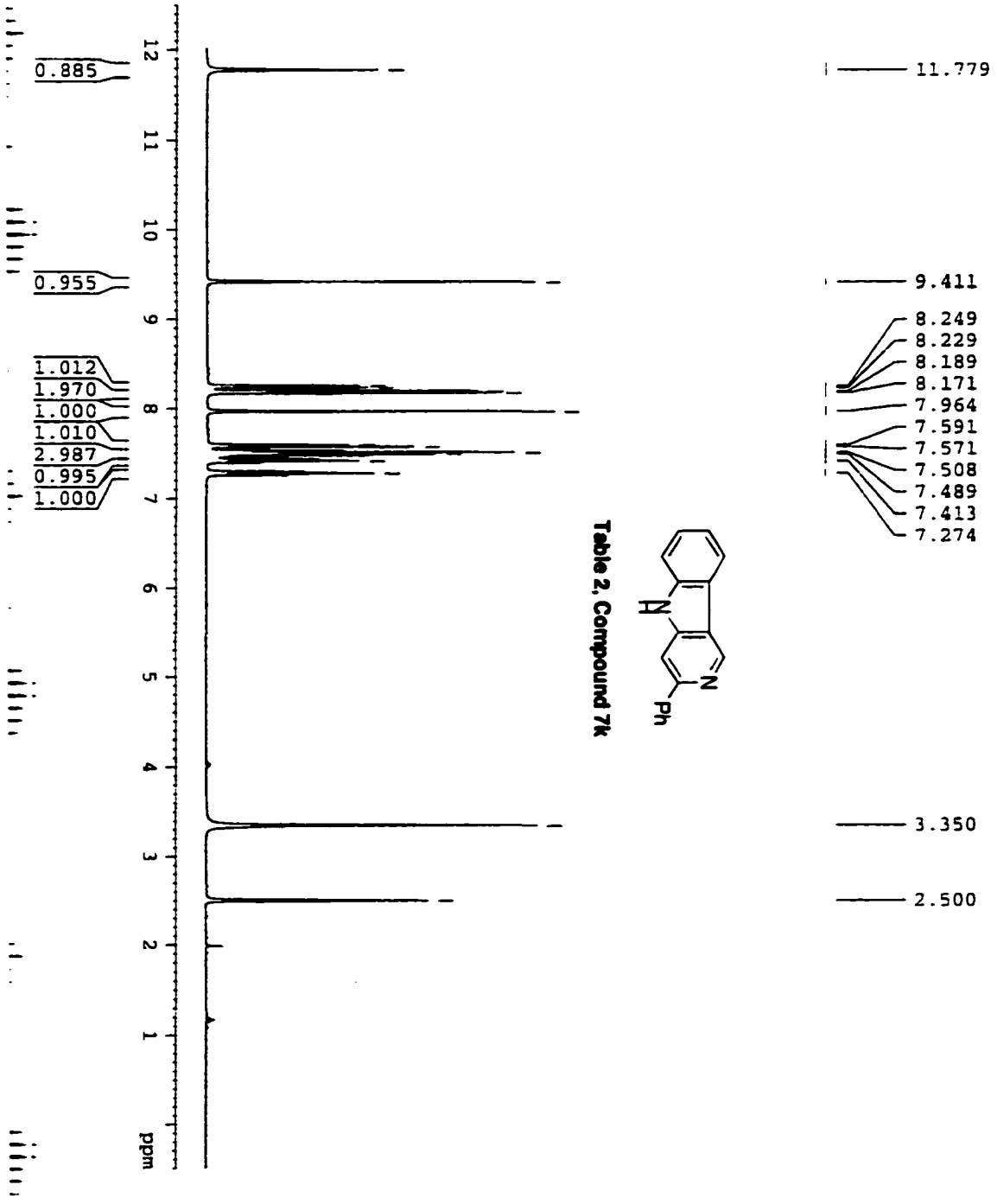
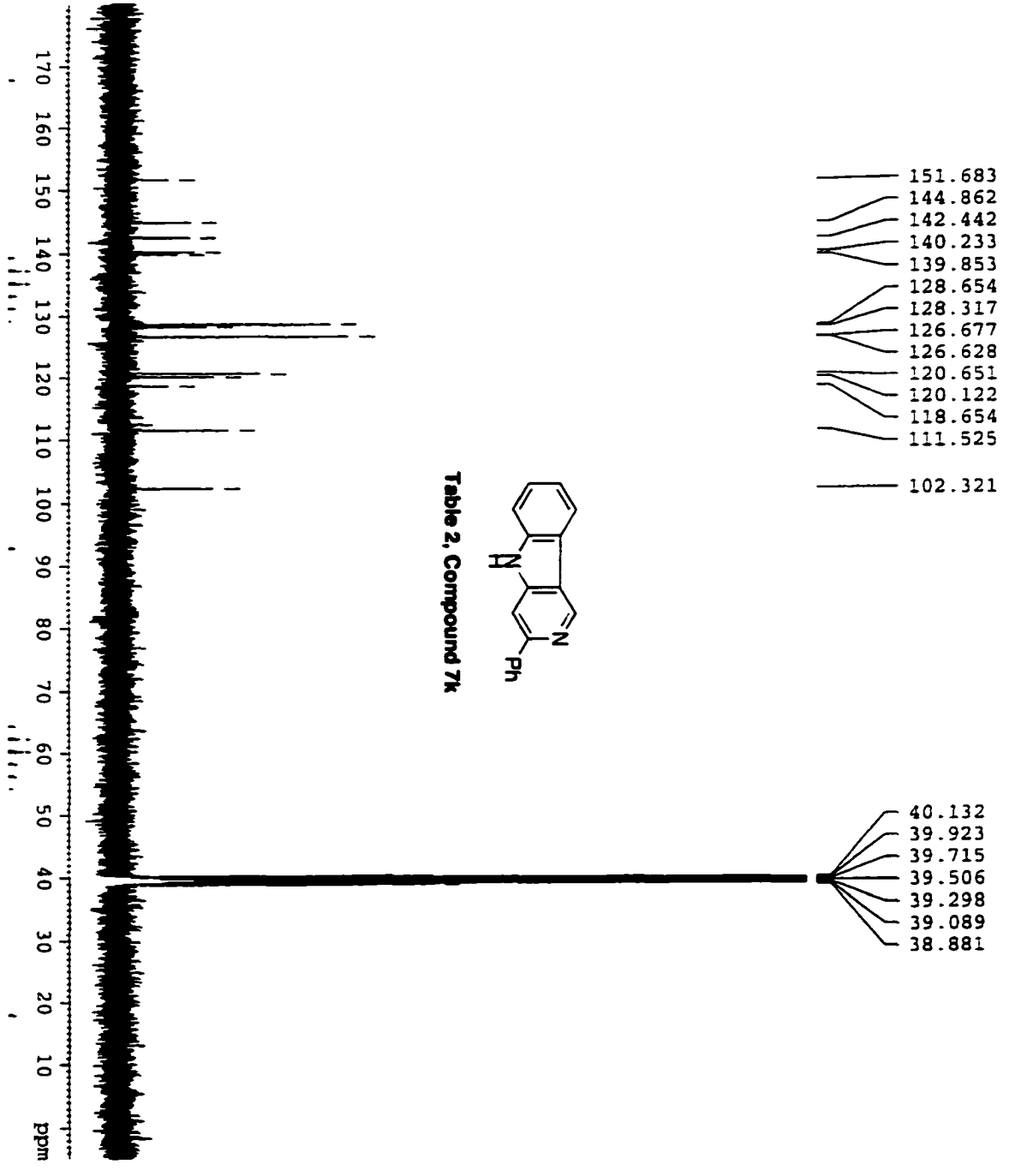
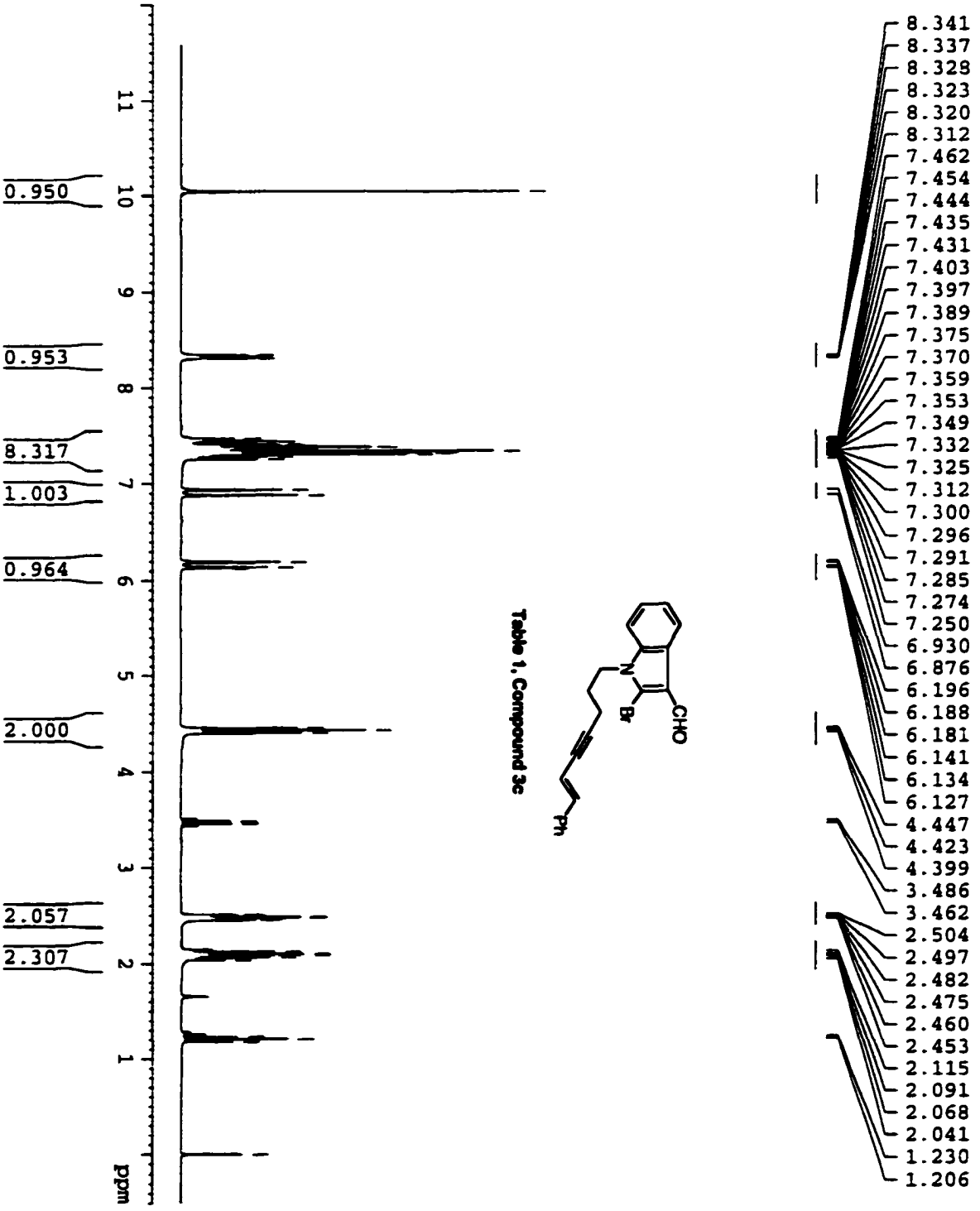


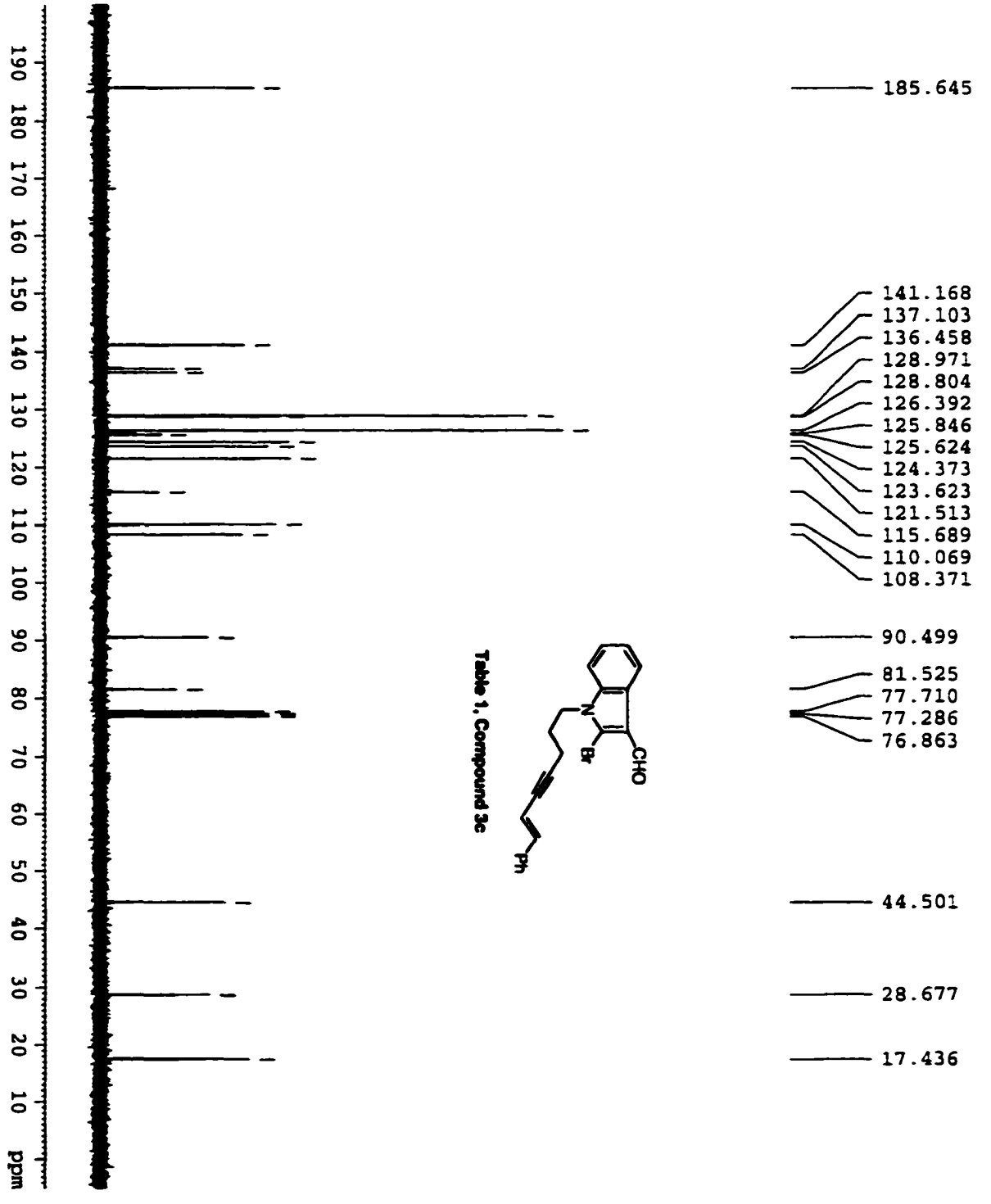
Table 2, Compound 7j

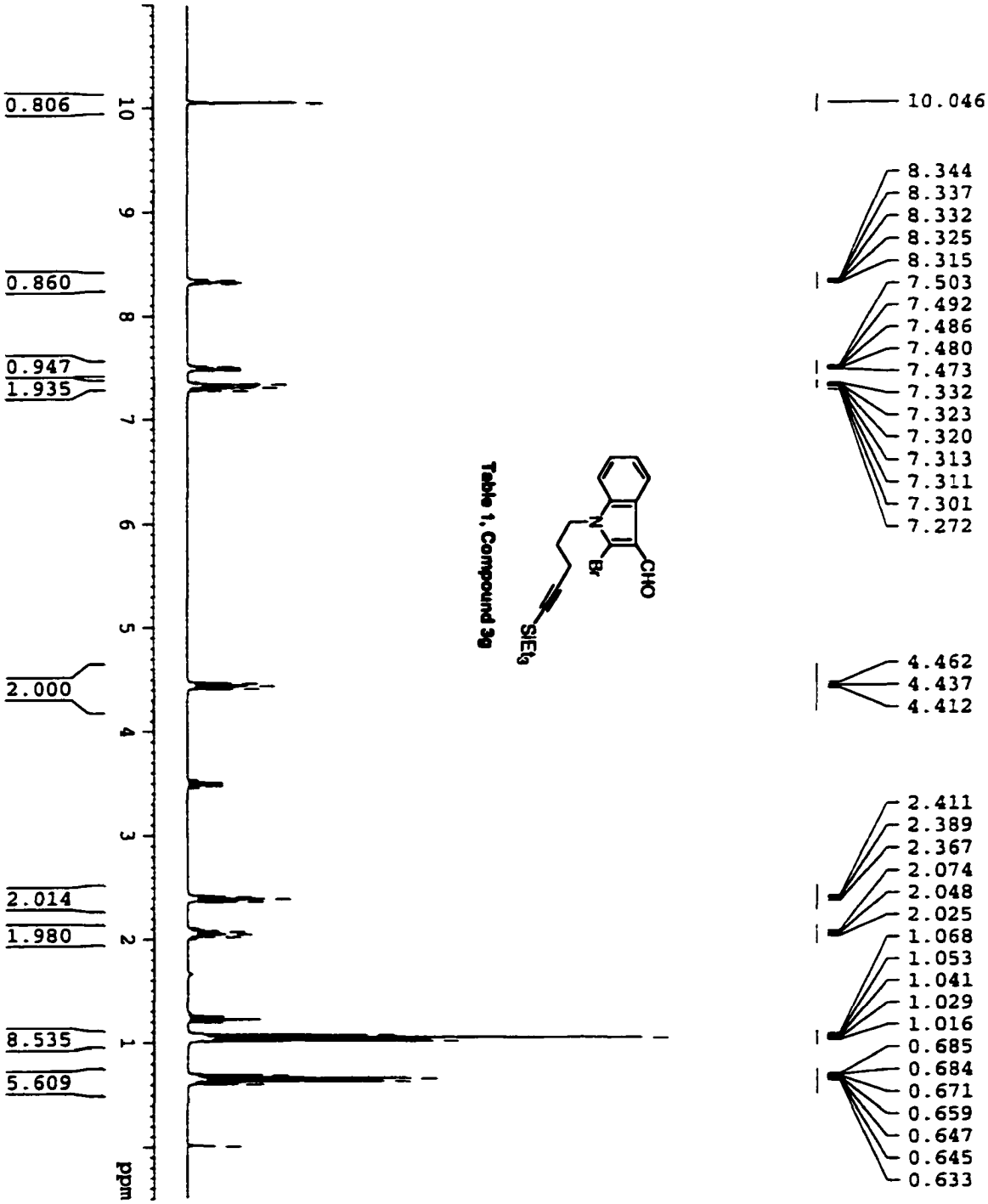

11.779
9.411
8.249
8.229
8.189
8.171
7.964
7.591
7.571
7.508
7.489
7.413
7.274
3.350
2.500
0.885
0.955
1.012
1.970
1.000
1.010
2.987
0.995
1.000
ppm
Table 2, Compound 7k
N
H
N
Ph


151.683
144.862
142.442
140.233
139.853
128.654
128.317
126.677
126.628
120.651
120.122
118.654
111.525
102.321
40.132
39.923
39.715
39.506
39.298
39.089
38.881
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
Table 2, Compound 7k
N
H
N
Ph

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


0.950
0.953
8.317
1.003
0.964
2.000
2.057
2.307
ppm
Table 1, Compound 3c
N
Br
CHO
Ph
8.341
8.337
8.328
8.323
8.320
8.312
7.462
7.454
7.444
7.435
7.431
7.403
7.397
7.389
7.375
7.370
7.359
7.353
7.349
7.332
7.325
7.312
7.300
7.296
7.291
7.285
7.274
7.250
6.930
6.876
6.196
6.188
6.181
6.141
6.134
6.127
4.447
4.423
4.399
3.486
3.462
2.504
2.497
2.482
2.475
2.460
2.453
2.115
2.091
2.068
2.041
1.230
1.206


185.645
141.168
137.103
136.458
128.971
128.804
126.392
125.846
125.624
124.373
123.623
121.513
115.689
110.069
108.371
90.499
81.525
77.710
77.286
76.863
44.501
28.677
17.436
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
Table 1, Compound 3c
N
Br
CHO
Ph


0.806
0.860
0.947
1.935
2.000
2.014
1.980
8.535
5.609
ppm
Table 1, Compound 3g
CHO
Br
SiEt3
10.046
8.344
8.337
8.332
8.325
8.315
7.503
7.492
7.486
7.480
7.473
7.332
7.323
7.320
7.313
7.311
7.301
7.272
4.462
4.437
4.412
2.411
2.389
2.367
2.074
2.048
2.025
1.068
1.053
1.041
1.029
1.016
0.685
0.684
0.671
0.659
0.647
0.645
0.633

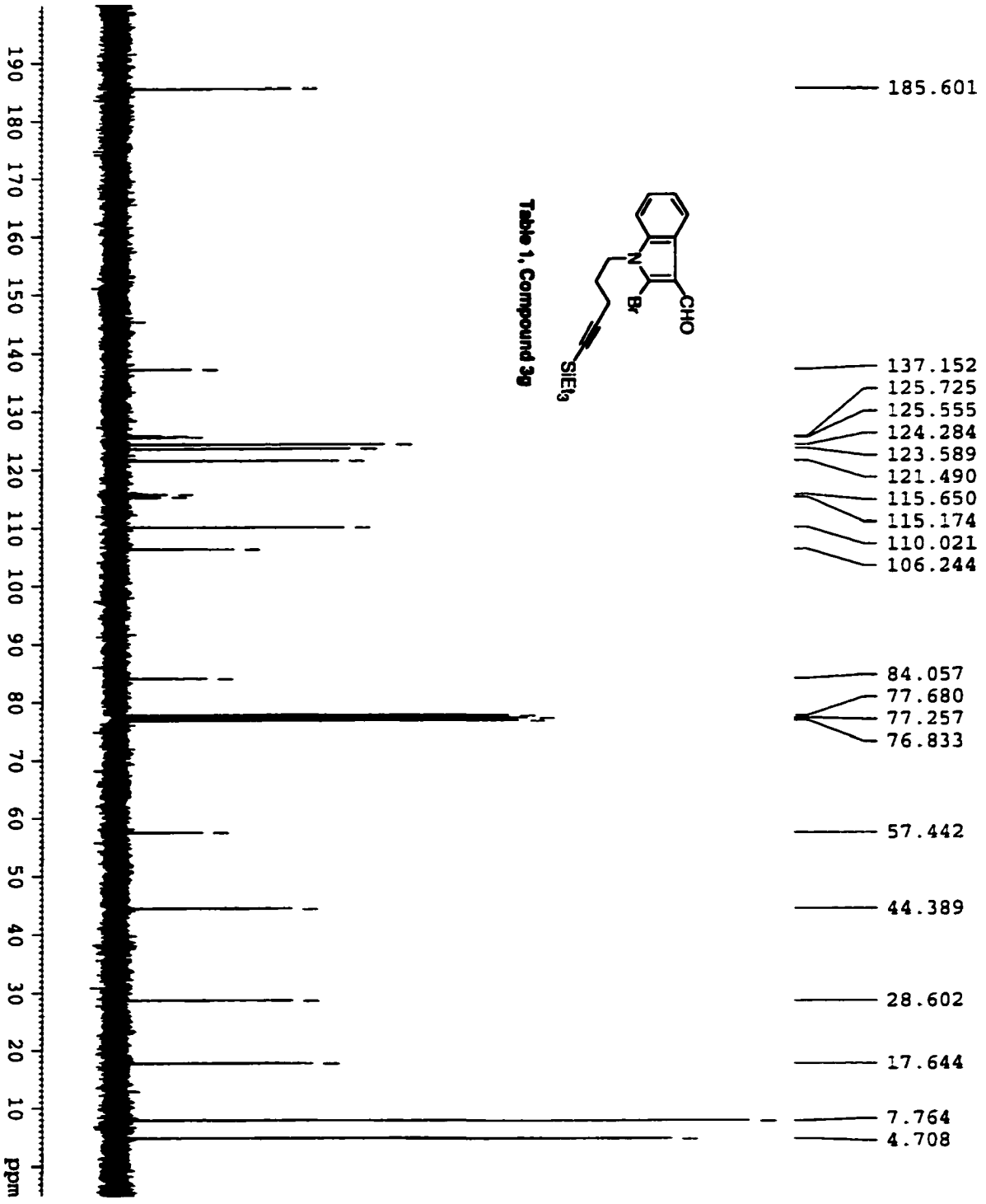
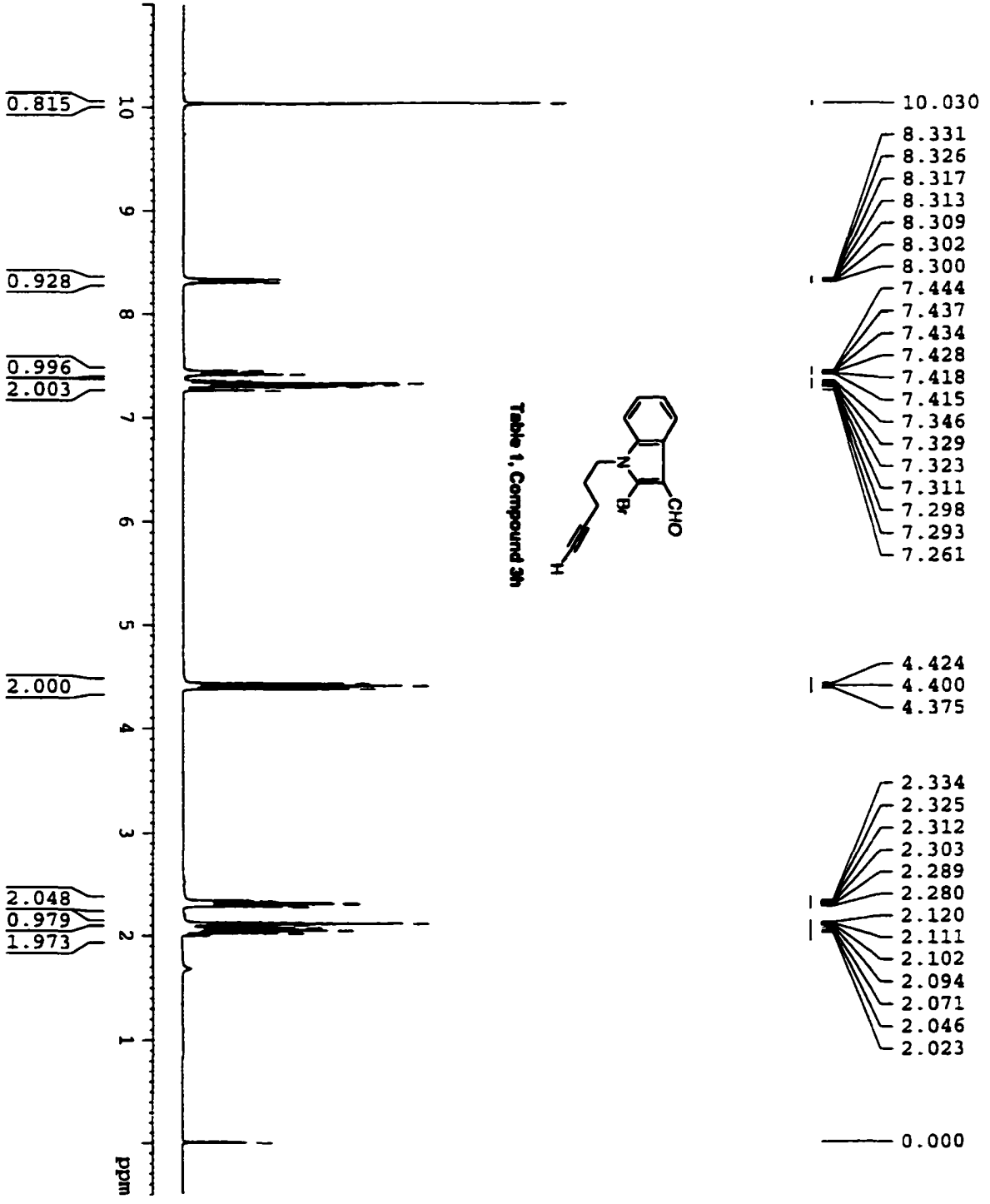


Table 1, Compound 3g
SiEt3
Br
CHO
185.601
137.152
125.725
125.555
124.284
123.589
121.490
115.650
115.174
110.021
106.244
84.057
77.680
77.257
76.833
57.442
44.389
28.602
17.644
7.764
4.708
ppm


0.815
0.928
0.996
2.003
2.000
2.048
0.979
1.973
ppm
Table 1, Compound 3h
N
Br
CHO
H
10.030
8.331
8.326
8.317
8.313
8.309
8.302
8.300
7.444
7.437
7.434
7.428
7.418
7.415
7.346
7.329
7.323
7.311
7.298
7.293
7.261
4.424
4.400
4.375
2.334
2.325
2.312
2.303
2.289
2.280
2.120
2.111
2.102
2.094
2.071
2.046
2.023
0.000

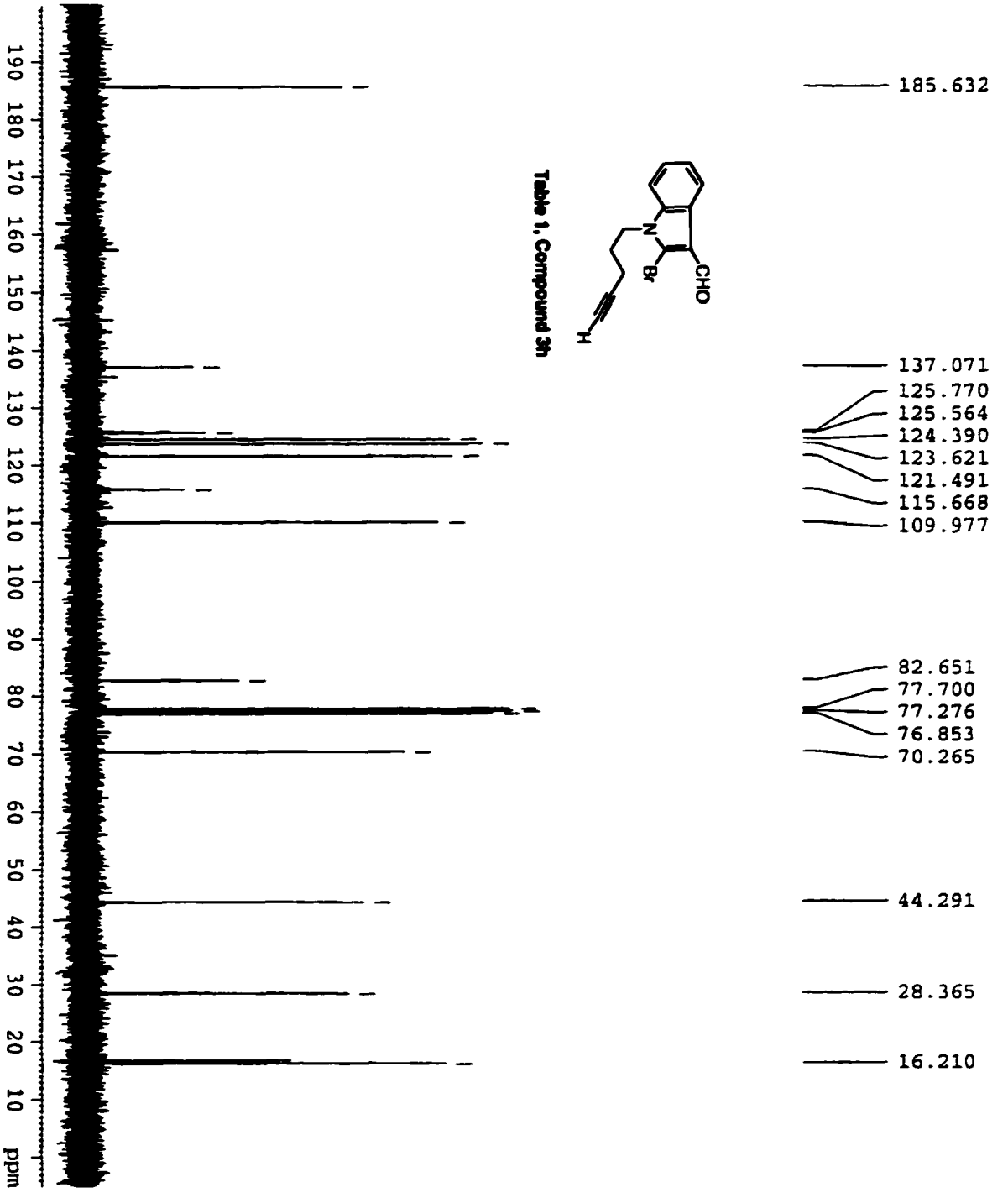
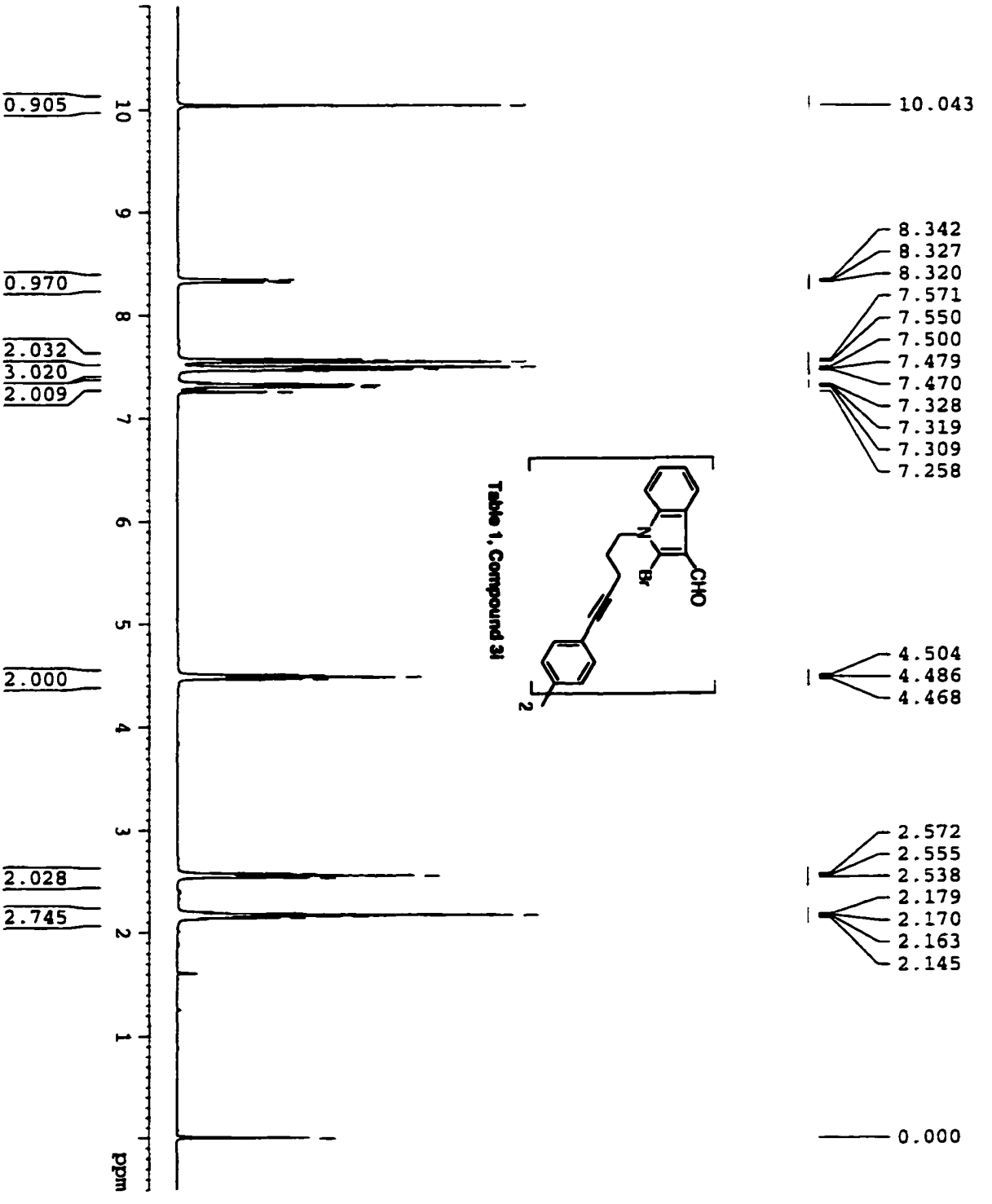


Table 1, Compound 3h
N
Br
CHO
H
185.632
137.071
125.770
125.564
124.390
123.621
121.491
115.668
109.977
82.651
77.700
77.276
76.853
70.265
44.291
28.365
16.210
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


0.905
0.970
2.032
3.020
2.009
2.000
2.028
2.745
10
9
8
7
6
5
4
3
2
1
ppm
Table 1, Compound 3l
N
Br
CHO
2
10.043
8.342
8.327
8.320
7.571
7.550
7.500
7.479
7.470
7.328
7.319
7.309
7.258
4.504
4.486
4.468
2.572
2.555
2.538
2.179
2.170
2.163
2.145
0.000

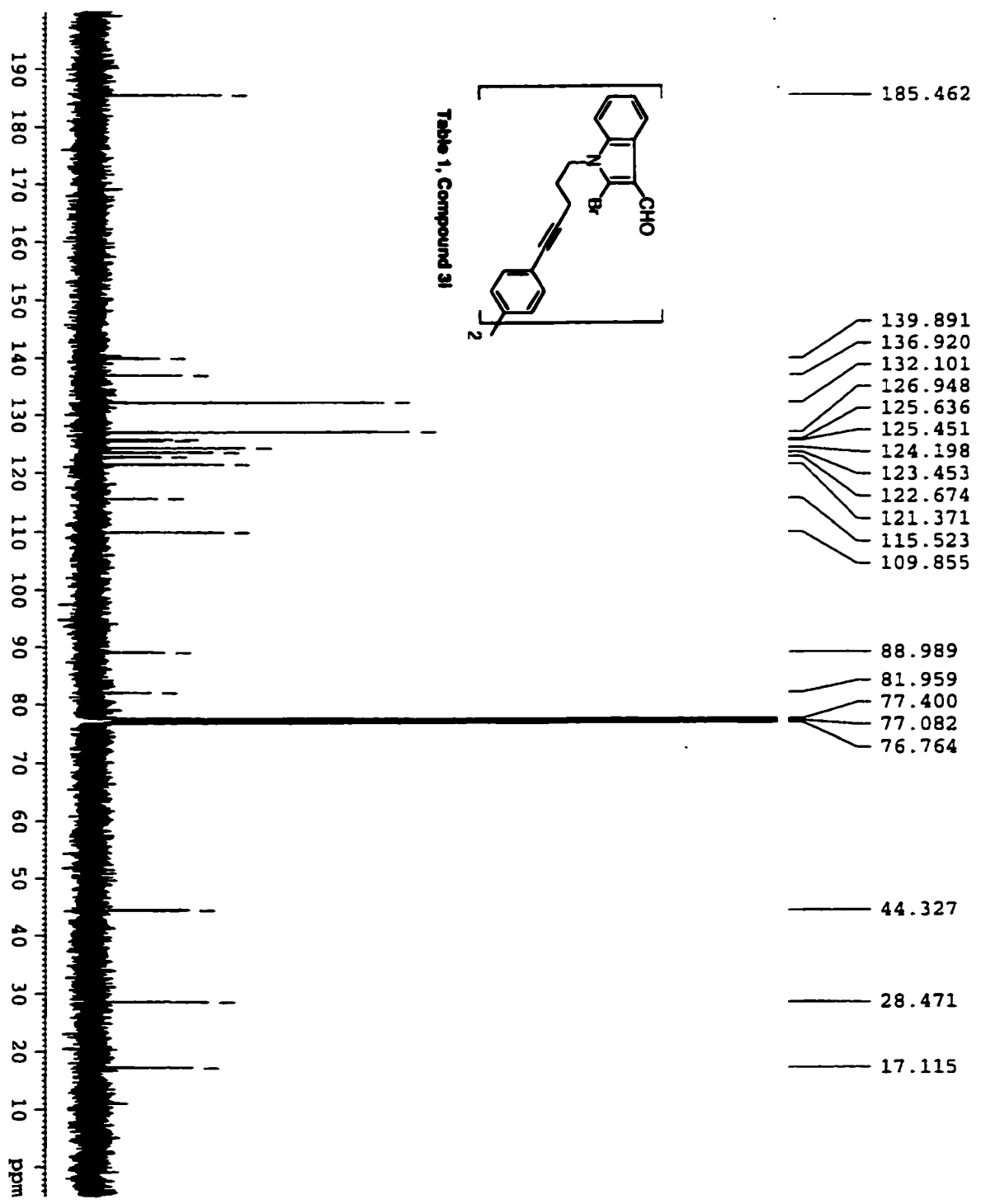
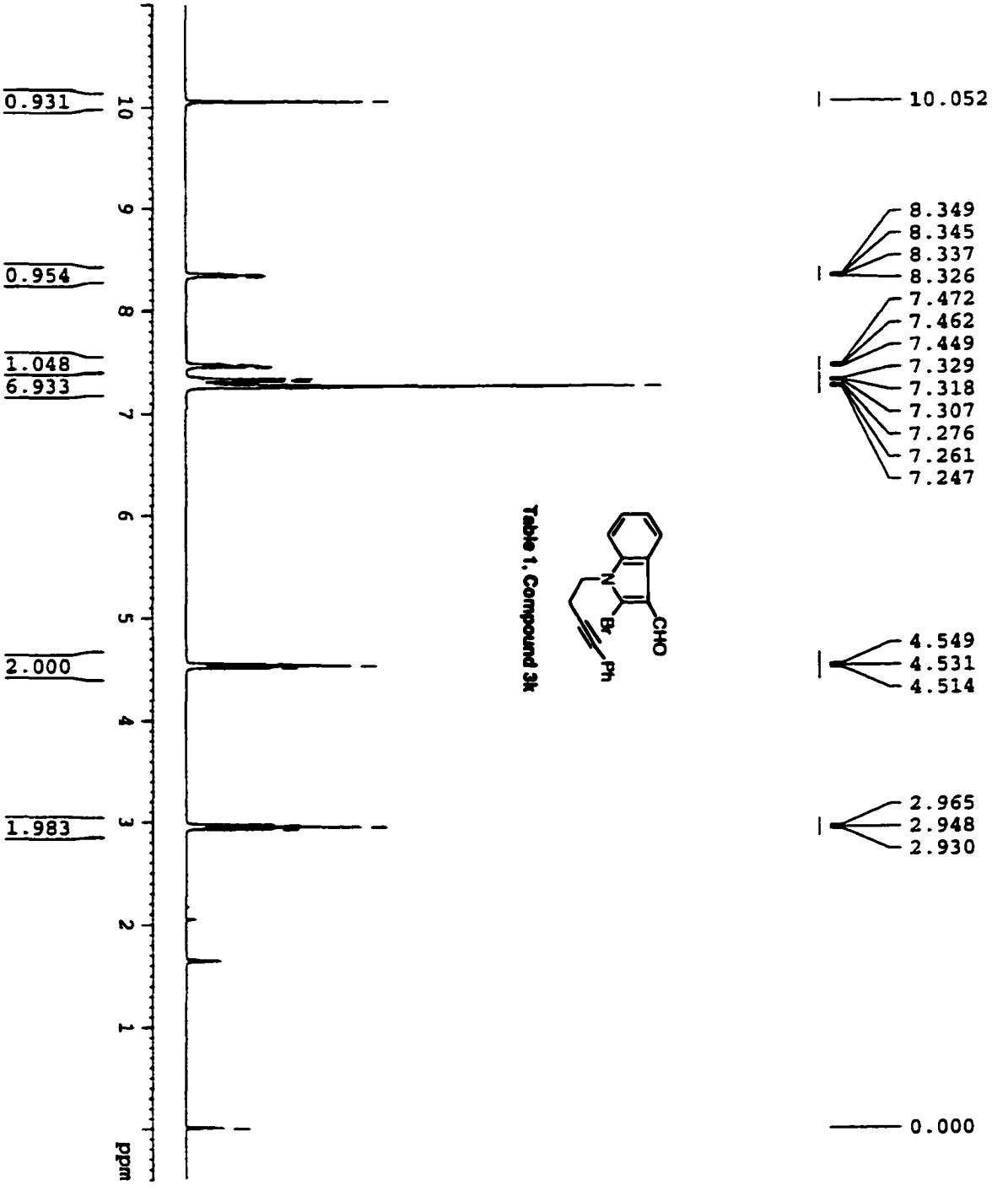


Table 1, Compound 3l
N
Br
CHO
2
185.462
139.891
136.920
132.101
126.948
125.636
125.451
124.198
123.453
122.674
121.371
115.523
109.855
88.989
81.959
77.400
77.082
76.764
44.327
28.471
17.115
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


0.931
0.954
1.048
6.933
2.000
1.983
10
9
8
7
6
5
4
3
2
1
ppm
10.052
8.349
8.345
8.337
8.326
7.472
7.462
7.449
7.329
7.318
7.307
7.276
7.261
7.247
4.549
4.531
4.514
2.965
2.948
2.930
0.000
Table 1, Compound 3k
N
Br
Ph
CHO

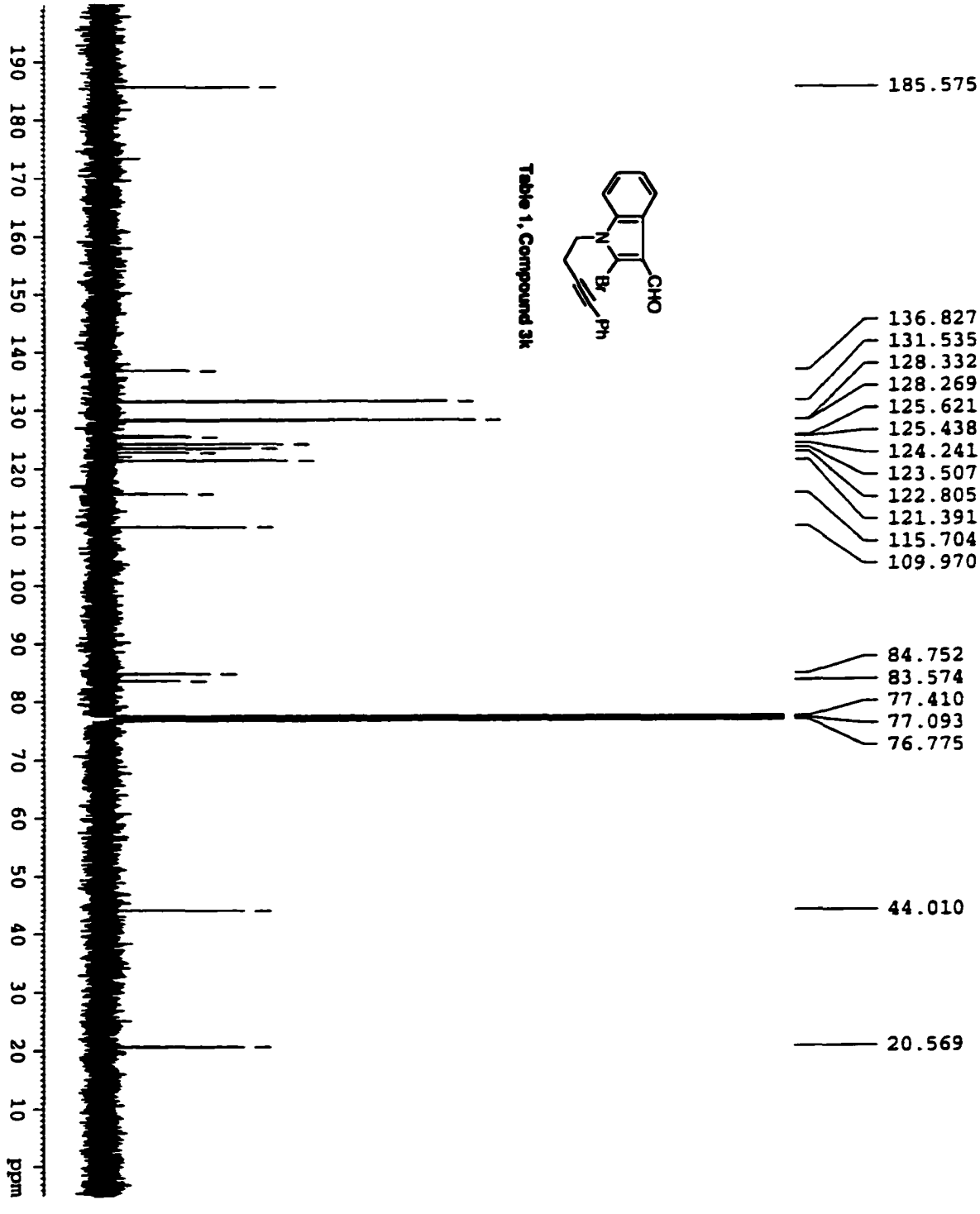
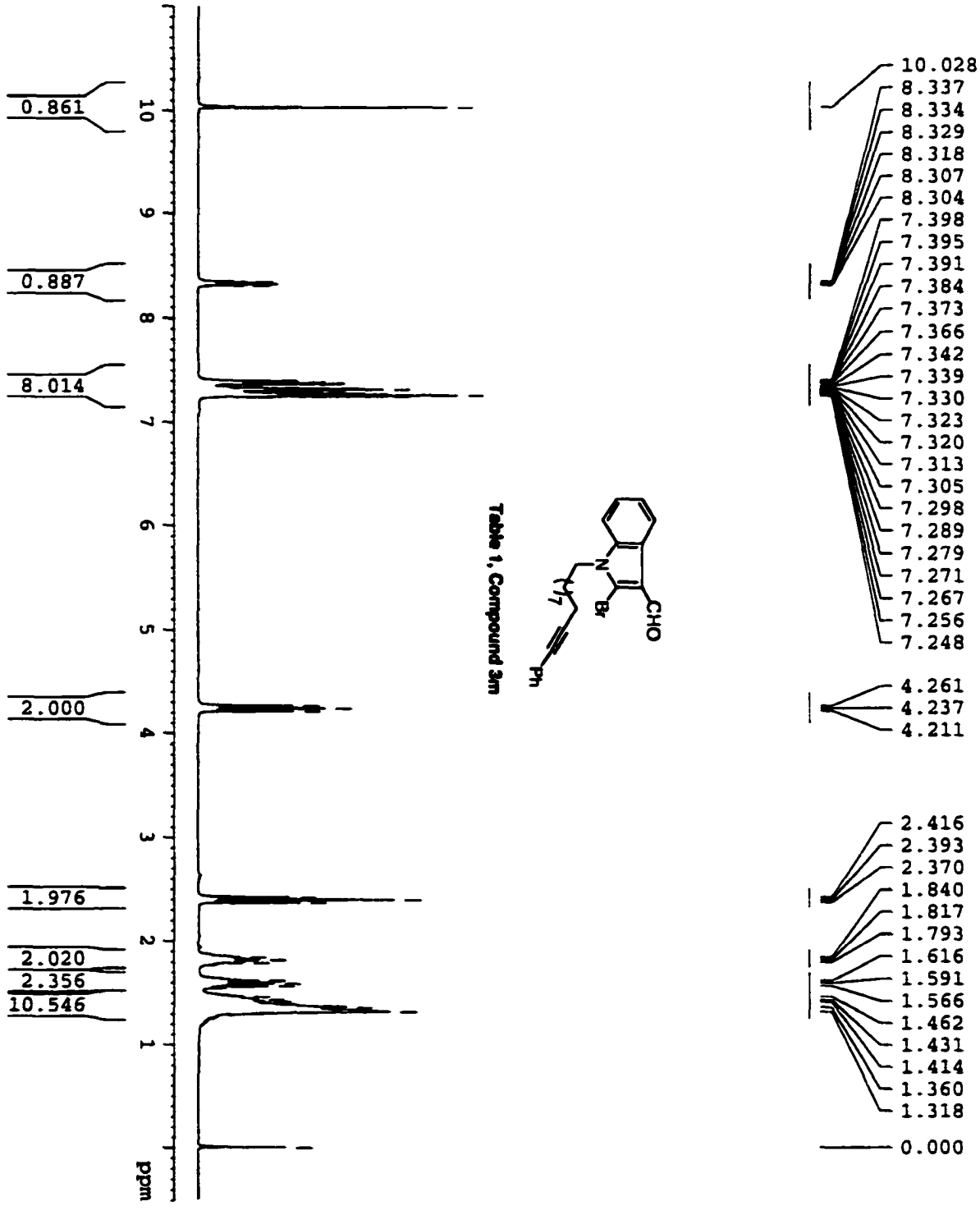


Table 1, Compound 3k
CHO
Br
Ph
185.575
136.827
131.535
128.332
128.269
125.621
125.438
124.241
123.507
122.805
121.391
115.704
109.970
84.752
83.574
77.410
77.093
76.775
44.010
20.569
ppm


0.861
0.887
8.014
2.000
1.976
2.020
2.356
10.546
ppm
Table 1, Compound 3m
Br
CHO
Ph
10.028
8.337
8.334
8.329
8.318
8.307
8.304
7.398
7.395
7.391
7.384
7.373
7.366
7.342
7.339
7.330
7.323
7.320
7.313
7.305
7.298
7.289
7.279
7.271
7.267
7.256
7.248
4.261
4.237
4.211
2.416
2.393
2.370
1.840
1.817
1.793
1.616
1.591
1.566
1.462
1.431
1.414
1.360
1.318
0.000

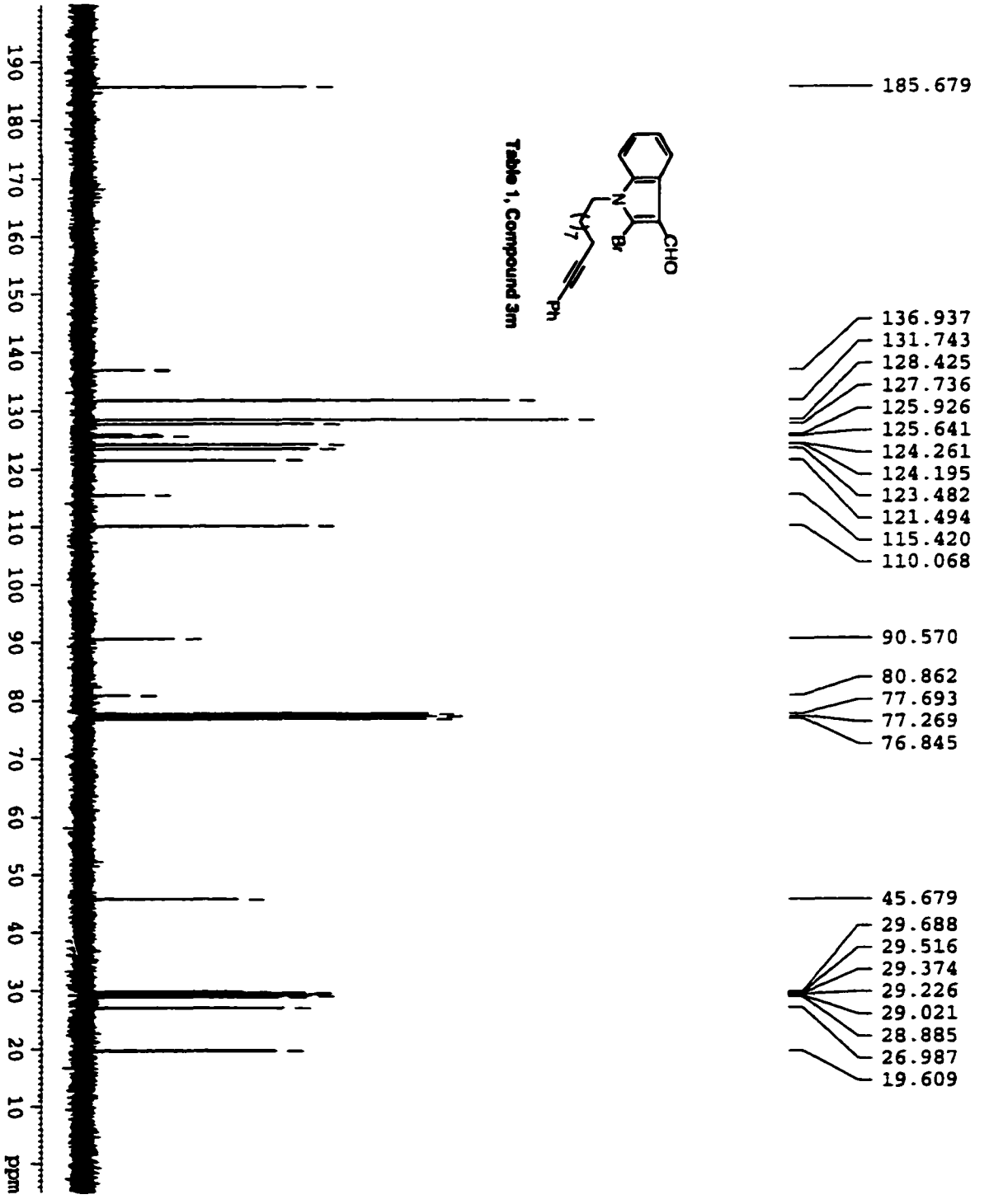
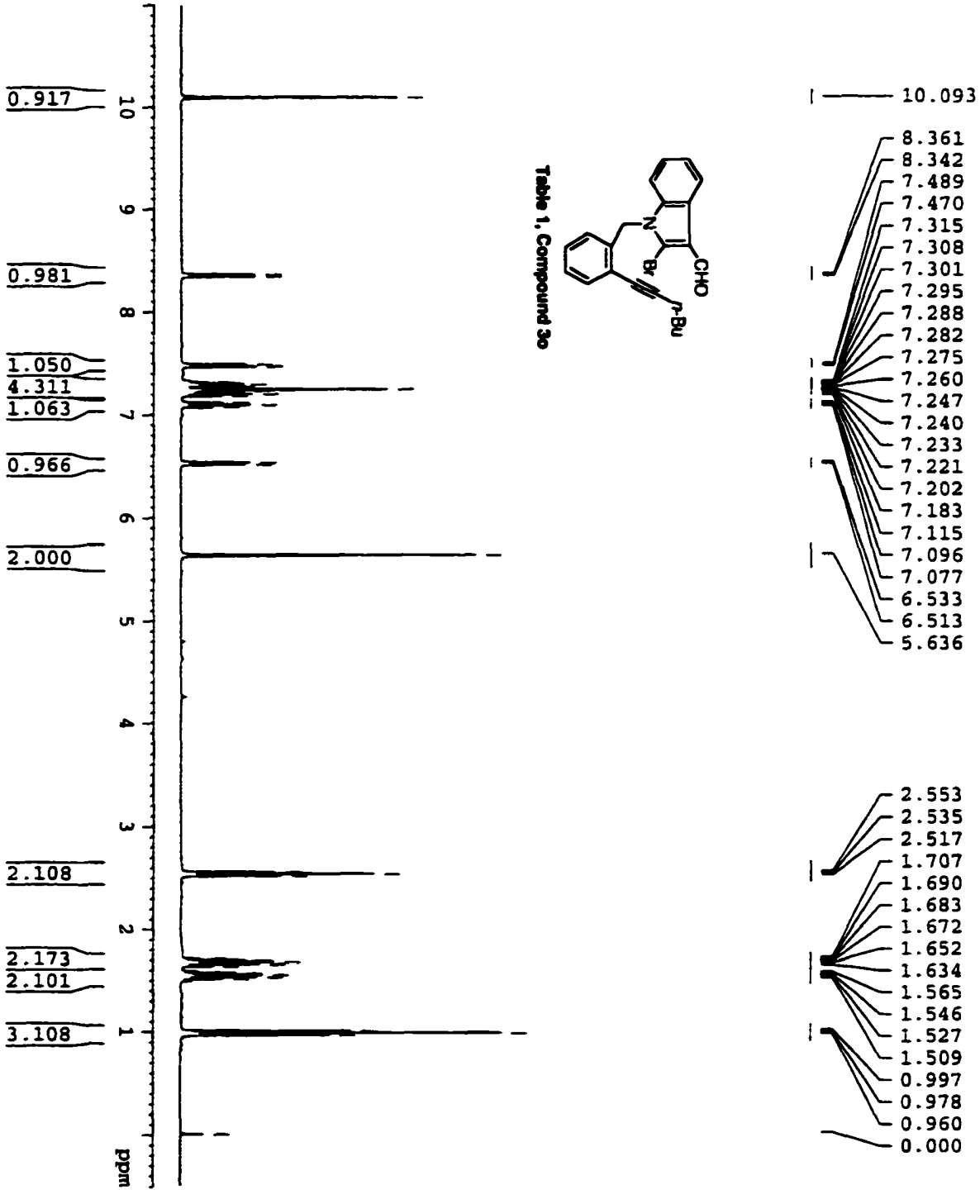


Table 1, Compound 3m
CHO
Br
N
Ph
185.679
136.937
131.743
128.425
127.736
125.926
125.641
124.261
124.195
123.482
121.494
115.420
110.068
90.570
80.862
77.693
77.269
76.845
45.679
29.688
29.516
29.374
29.226
29.021
28.885
26.987
19.609
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


0.917
0.981
1.050
4.311
1.063
0.966
2.000
2.108
2.173
2.101
3.108
ppm
Table 1, Compound 3o
CHO
Br
t-Bu
10.093
8.361
8.342
7.489
7.470
7.315
7.308
7.301
7.295
7.288
7.282
7.275
7.260
7.247
7.240
7.233
7.221
7.202
7.183
7.115
7.096
7.077
6.533
6.513
5.636
2.553
2.535
2.517
1.707
1.690
1.683
1.672
1.652
1.634
1.565
1.546
1.527
1.509
0.997
0.978
0.960
0.000

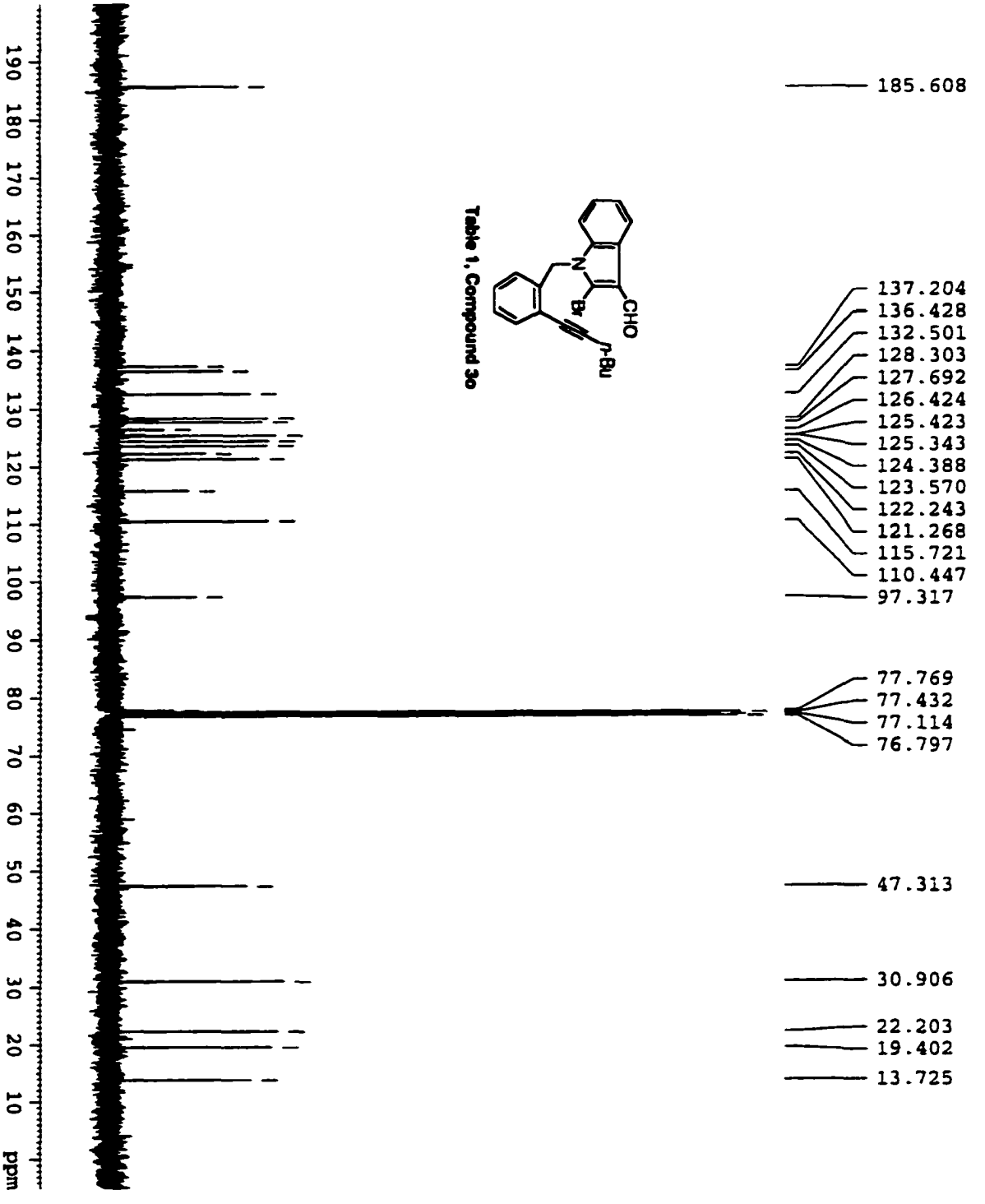
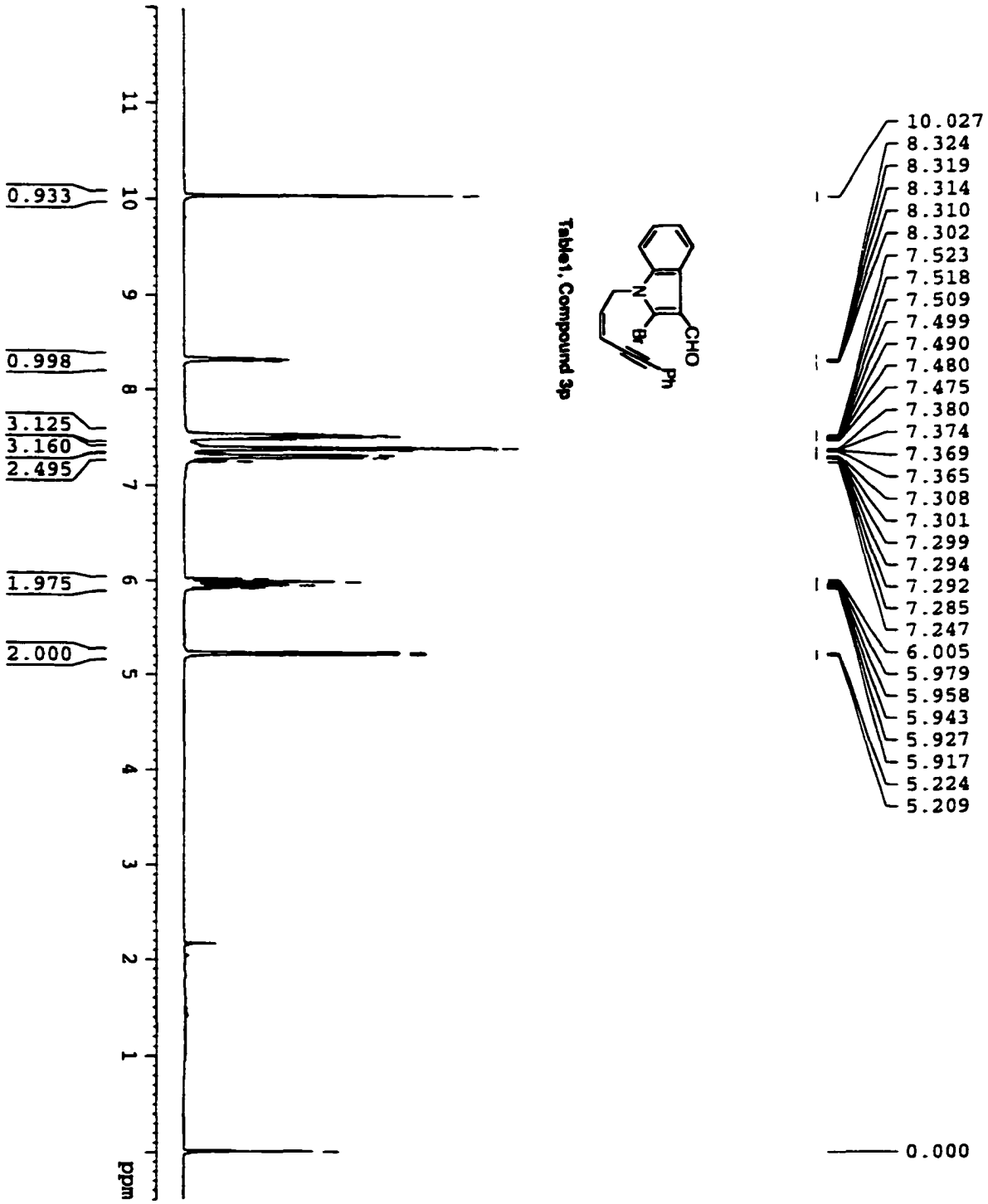


Table 1, Compound 3o
CHO
n-Bu
185.608
137.204
136.428
132.501
128.303
127.692
126.424
125.423
125.343
124.388
123.570
122.243
121.268
115.721
110.447
97.317
77.769
77.432
77.114
76.797
47.313
30.906
22.203
19.402
13.725
ppm


0.933
0.998
3.125
3.160
2.495
1.975
2.000
ppm
Table1, Compound 3p
CHO
Br
Ph
10.027
8.324
8.319
8.314
8.310
8.302
7.523
7.518
7.509
7.499
7.490
7.480
7.475
7.380
7.374
7.369
7.365
7.308
7.301
7.299
7.294
7.292
7.285
7.247
6.005
5.979
5.958
5.943
5.927
5.917
5.224
5.209
0.000

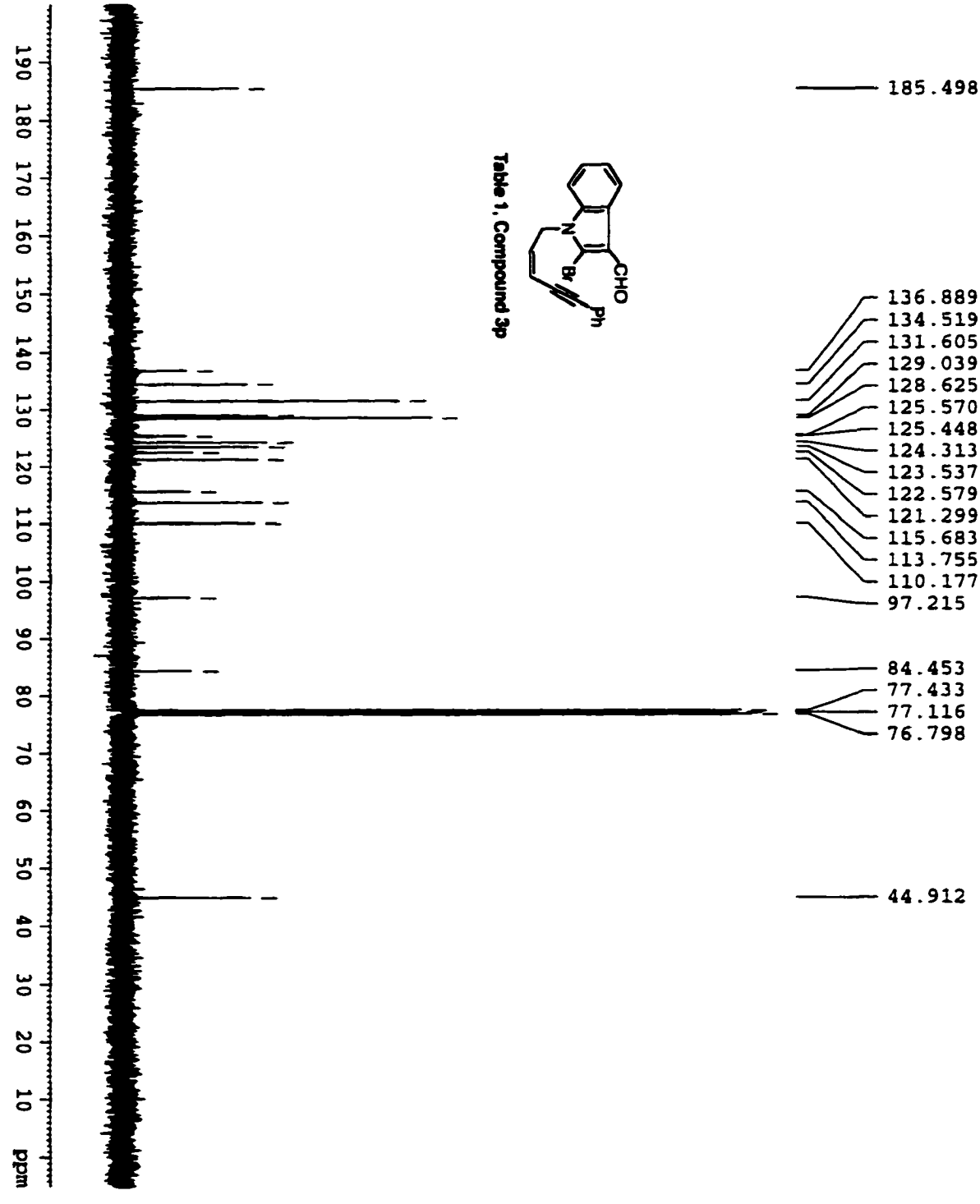


Table 1, Compound 3p
CHO
Br
Ph
185.498
136.889
134.519
131.605
129.039
128.625
125.570
125.448
124.313
123.537
122.579
121.299
115.683
113.755
110.177
97.215
84.453
77.433
77.116
76.798
44.912
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

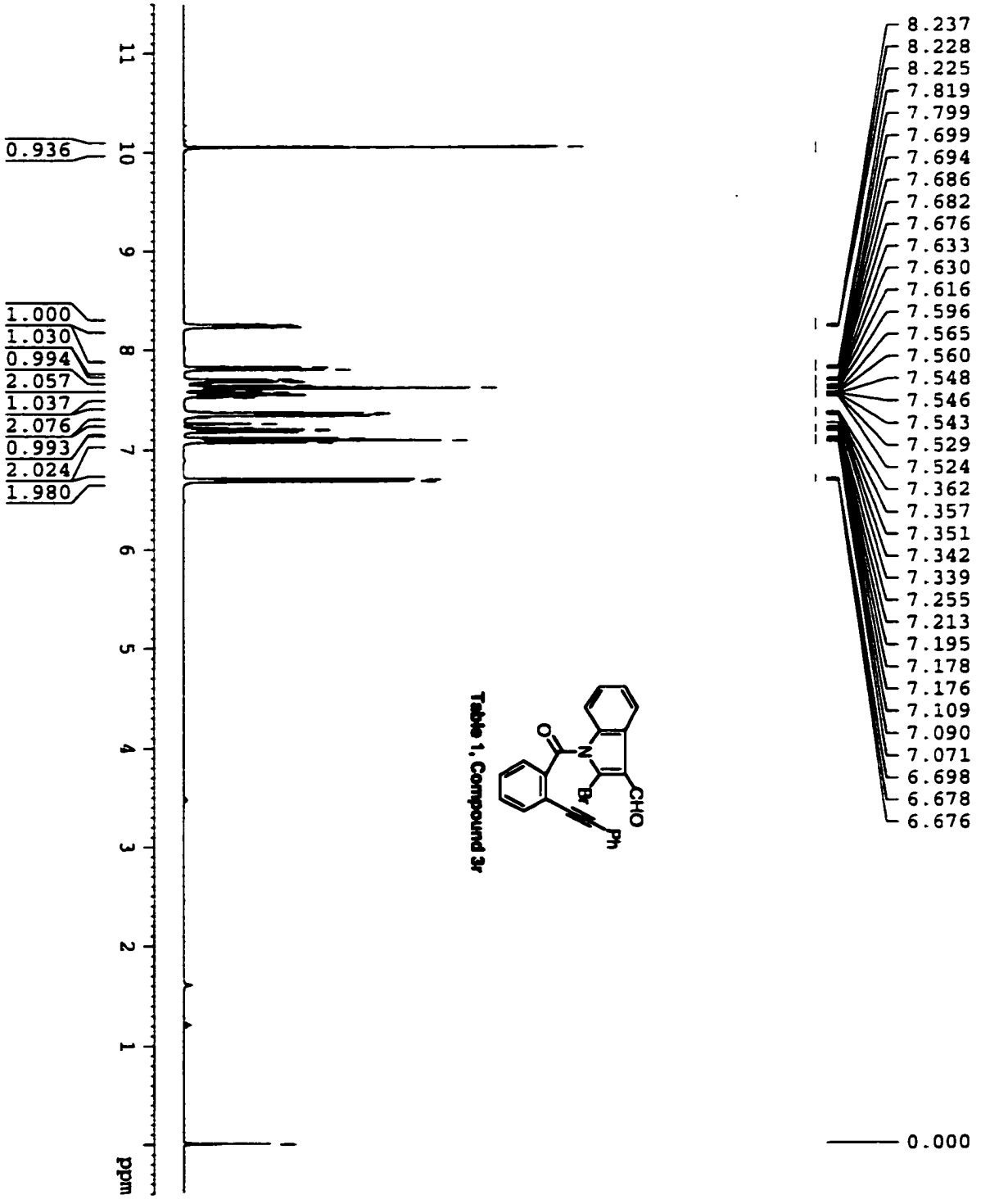


Table 1, Compound 3r

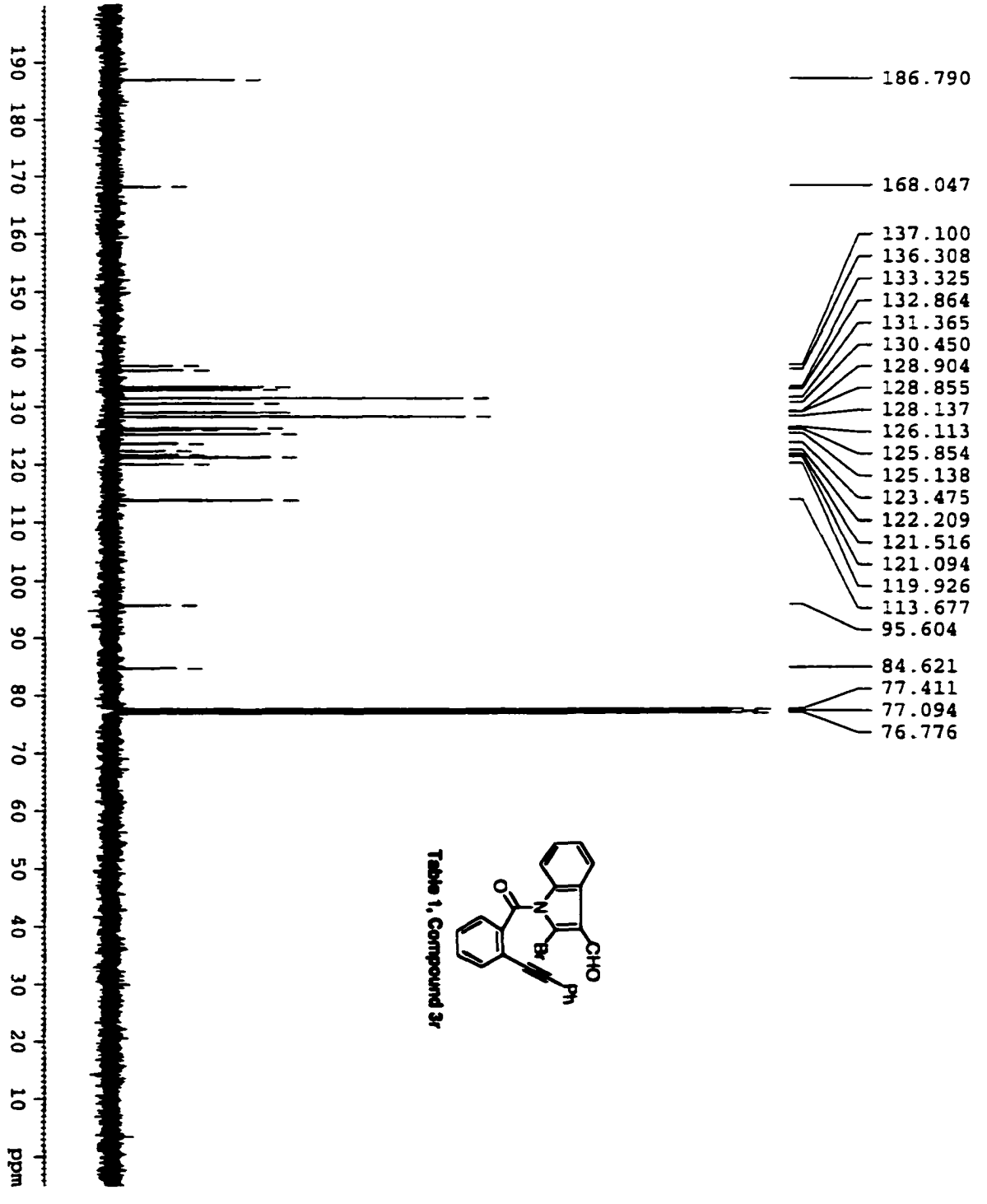
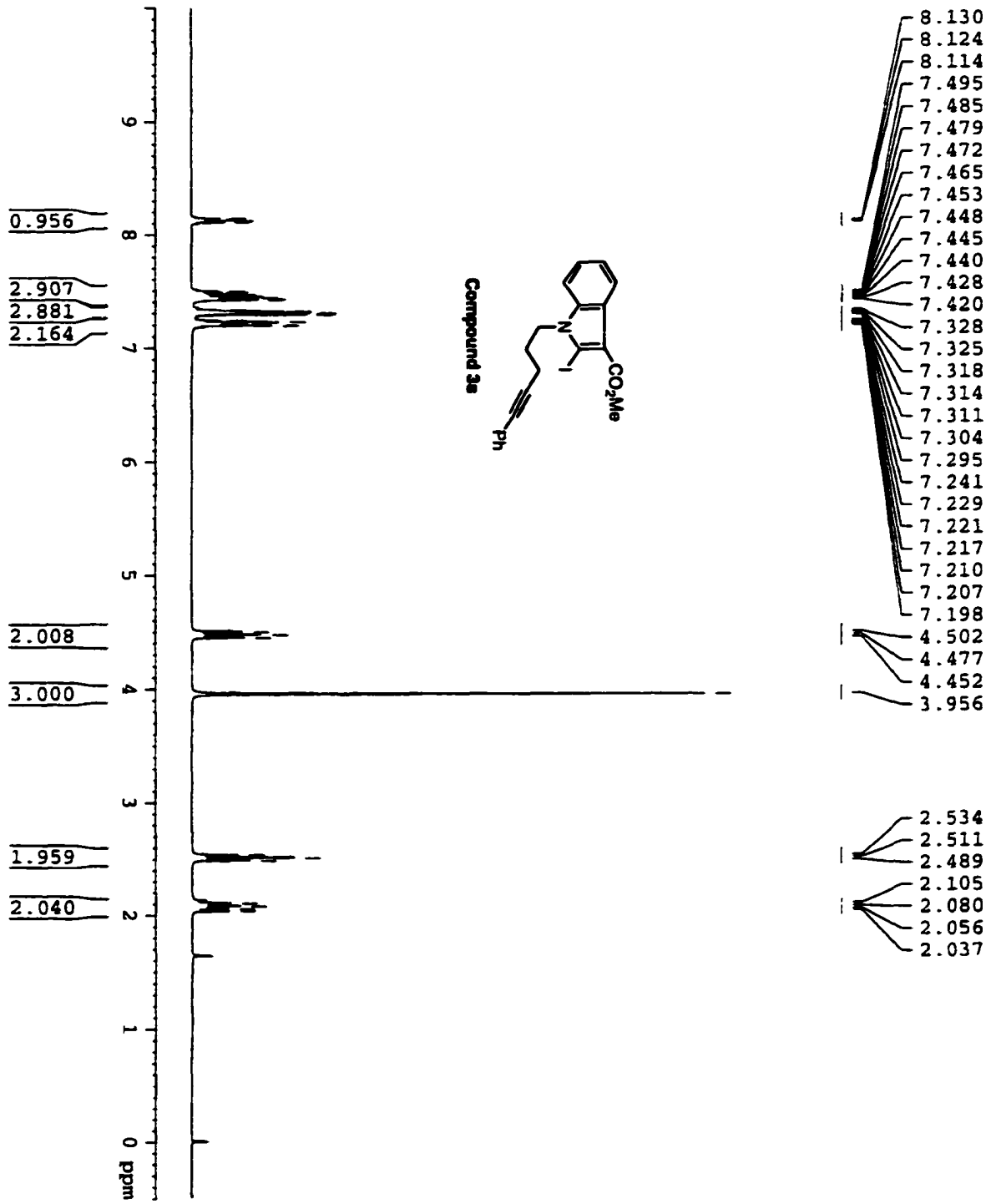
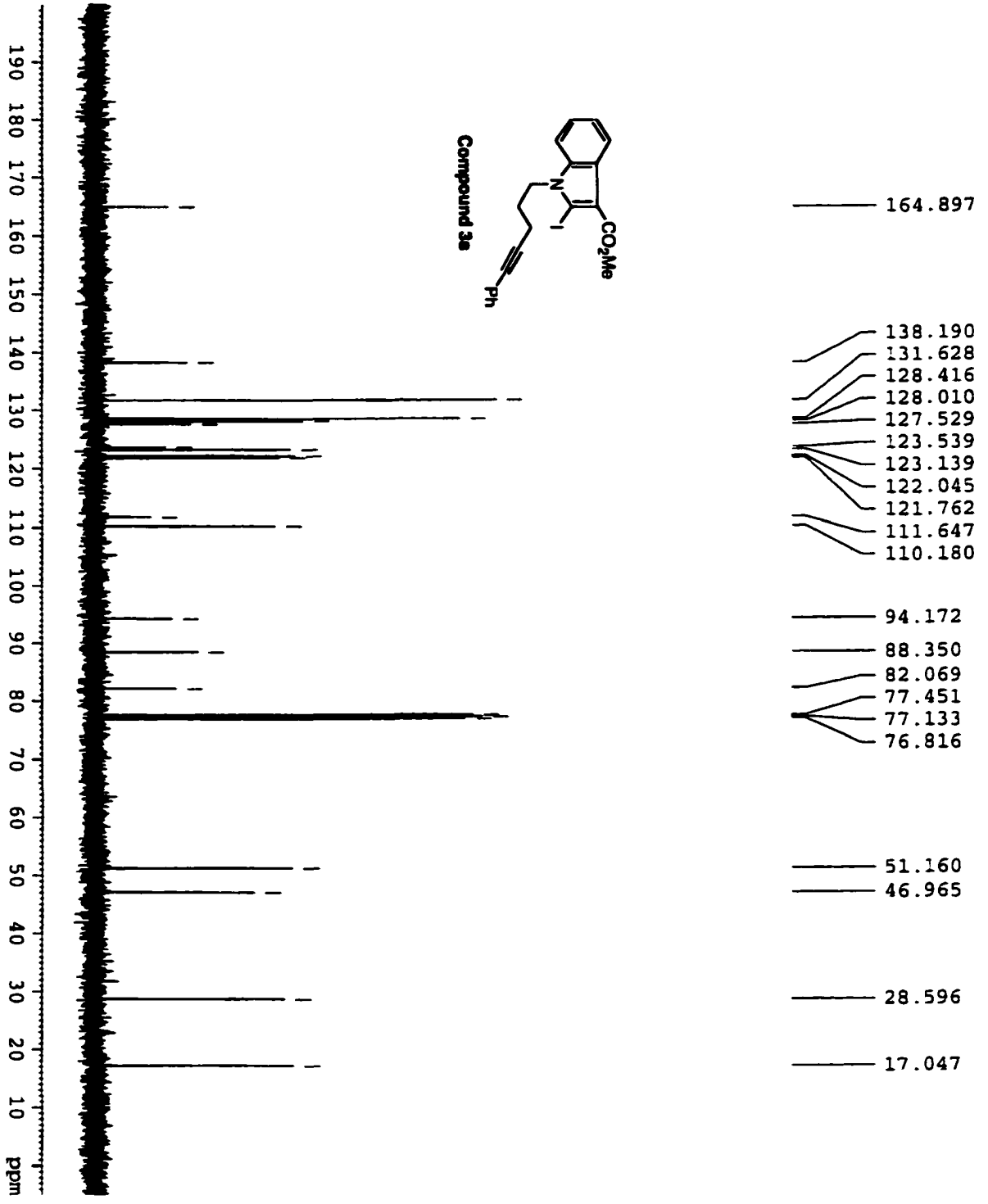
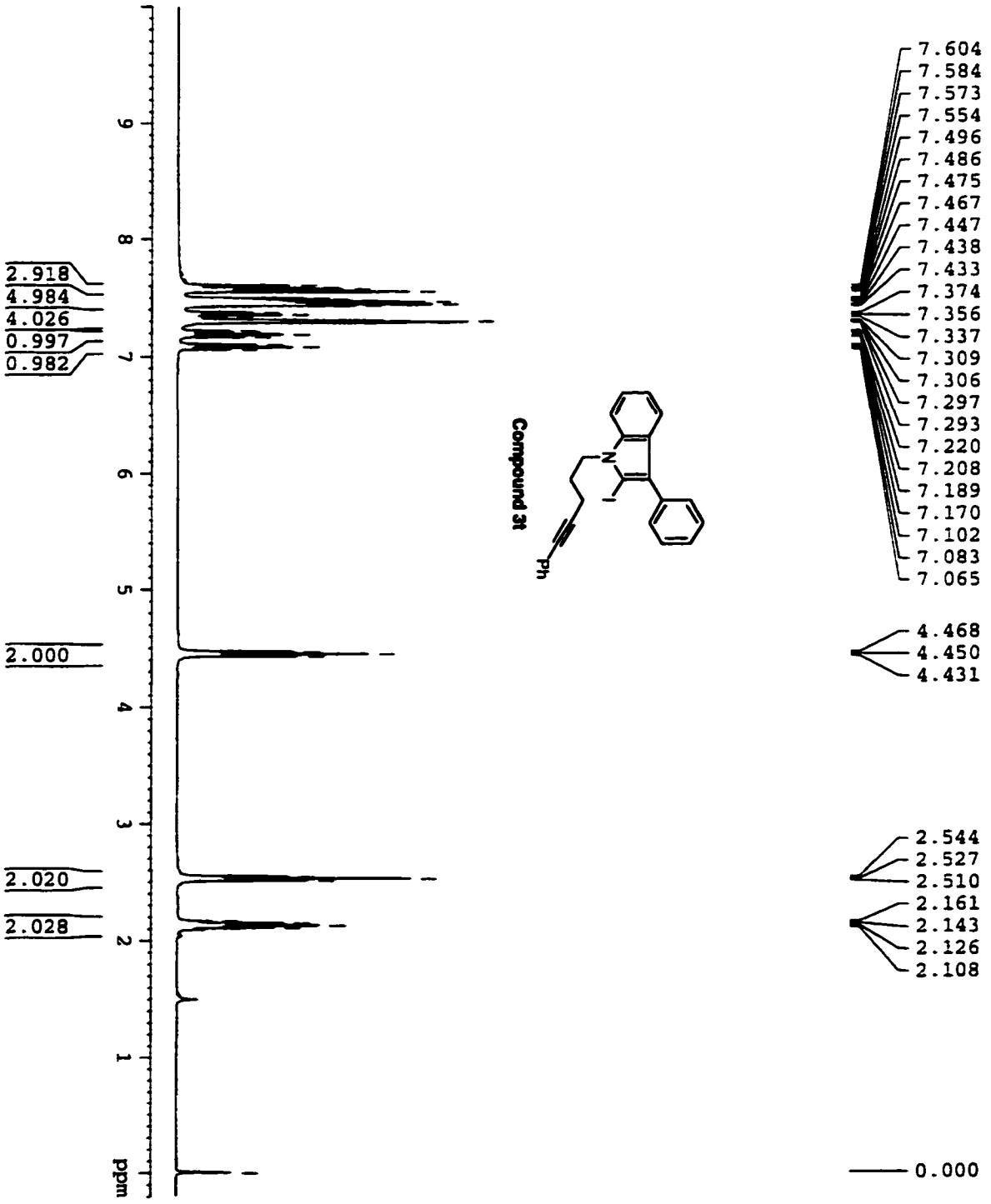
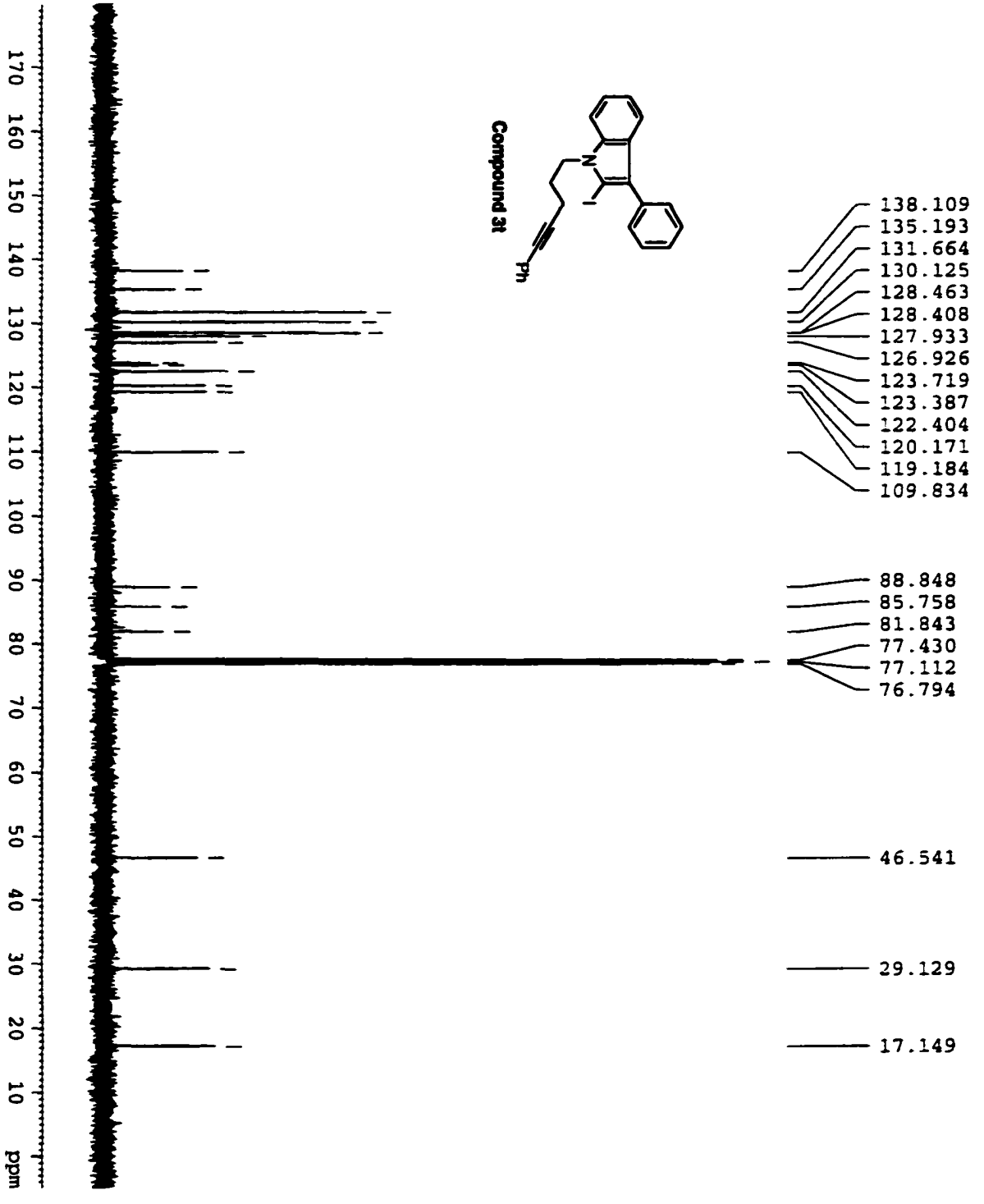


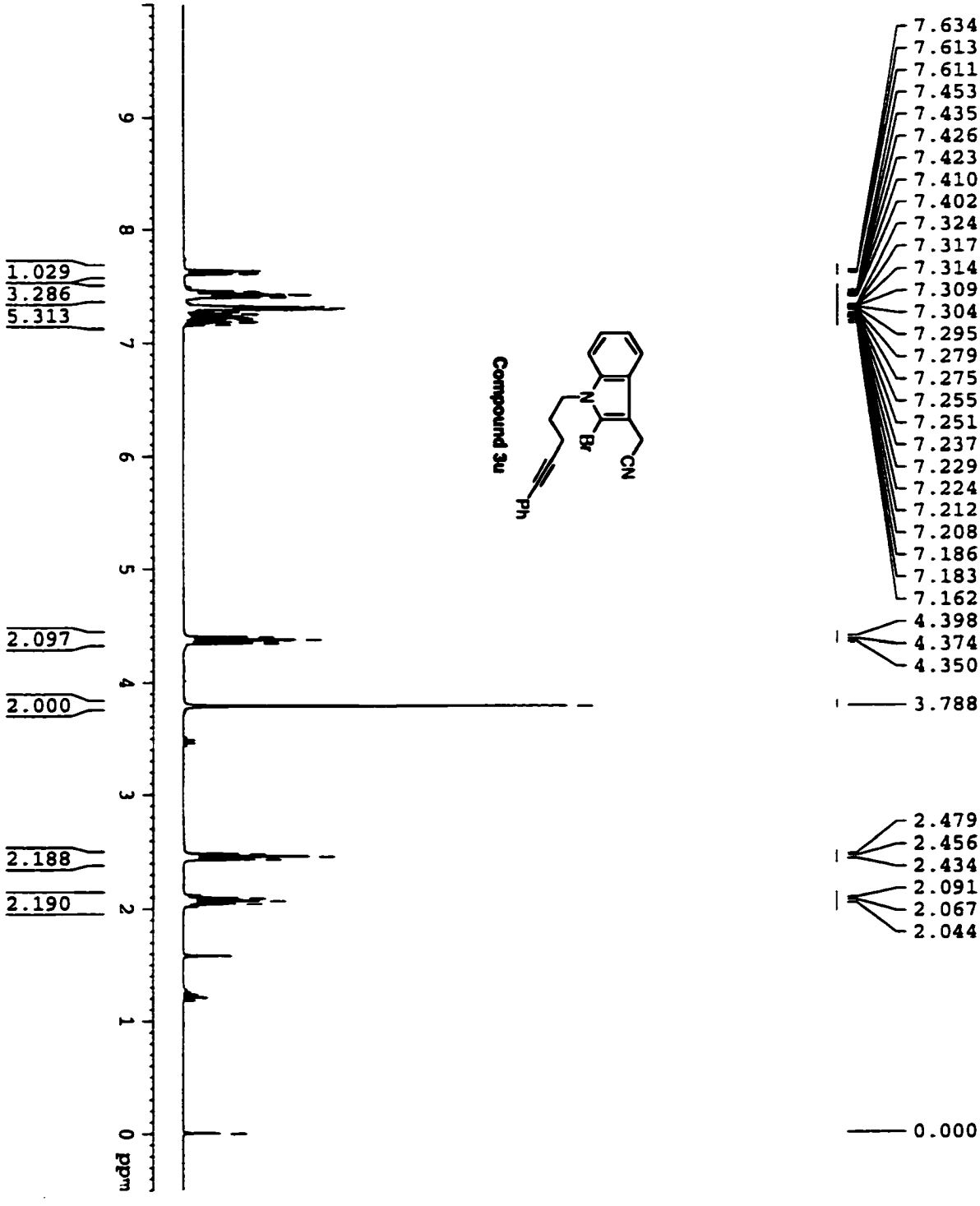
Table 1, Compound 3r

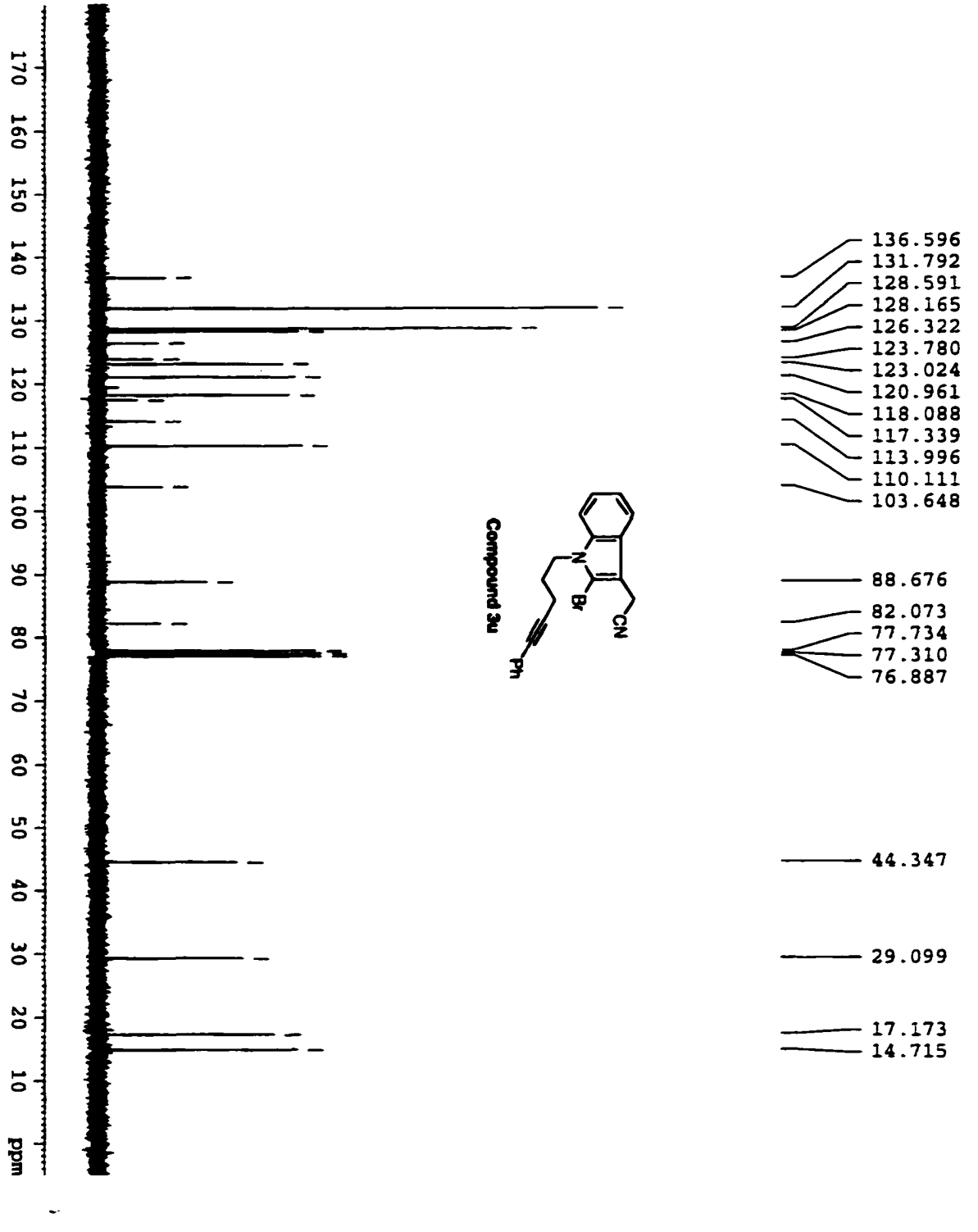

8.130
8.124
8.114
7.495
7.485
7.479
7.472
7.465
7.453
7.448
7.445
7.440
7.428
7.420
7.328
7.325
7.318
7.314
7.311
7.304
7.295
7.241
7.229
7.221
7.217
7.210
7.207
7.198
4.502
4.477
4.452
3.956
2.534
2.511
2.489
2.105
2.080
2.056
2.037
0.956
2.907
2.881
2.164
2.008
3.000
1.959
2.040
Compound 3s
CO2Me
Ph
ppm

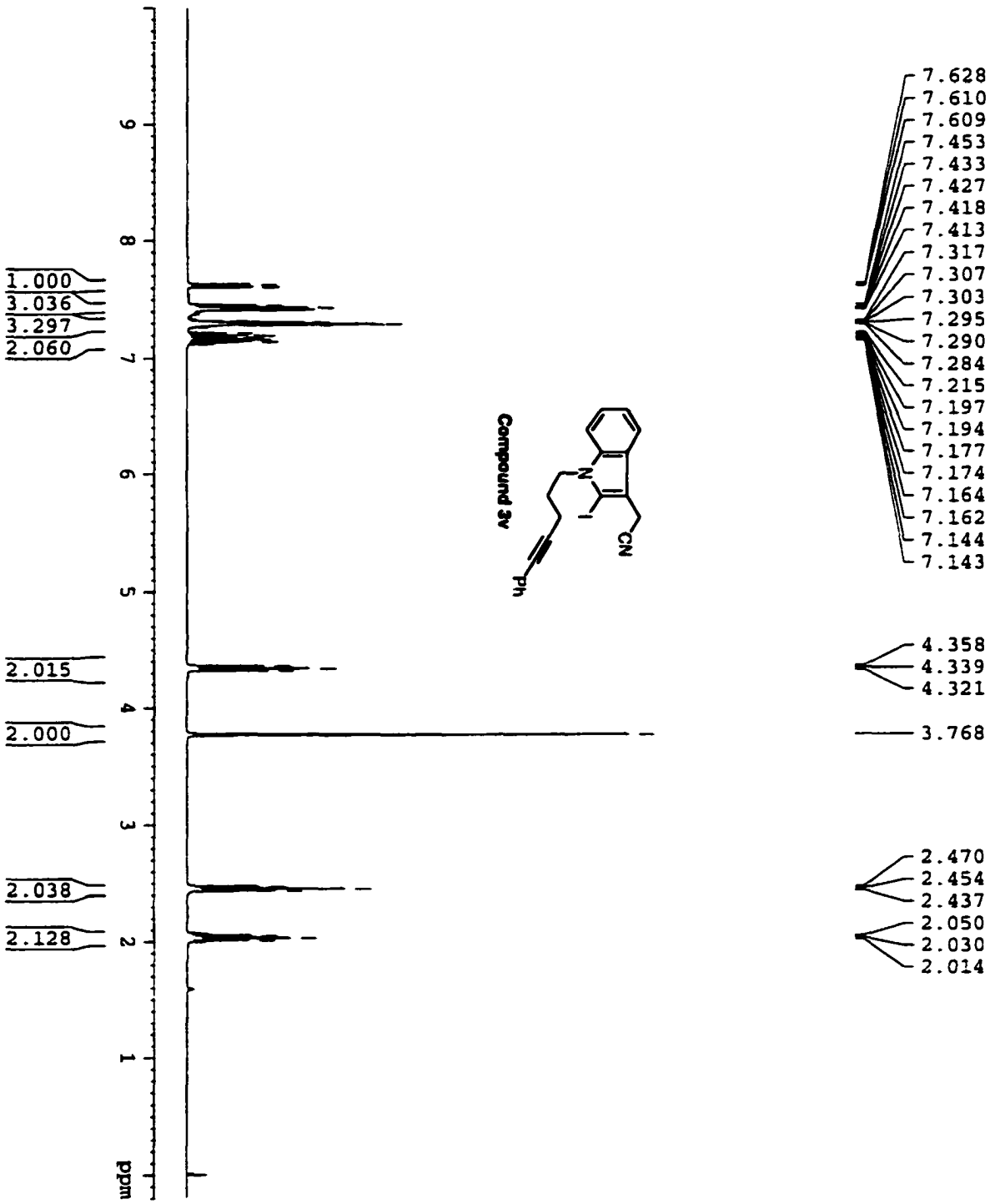

Compound 3e
Ph
CO2Me
164.897
138.190
131.628
128.416
128.010
127.529
123.539
123.139
122.045
121.762
111.647
110.180
94.172
88.350
82.069
77.451
77.133
76.816
51.160
46.965
28.596
17.047
ppm

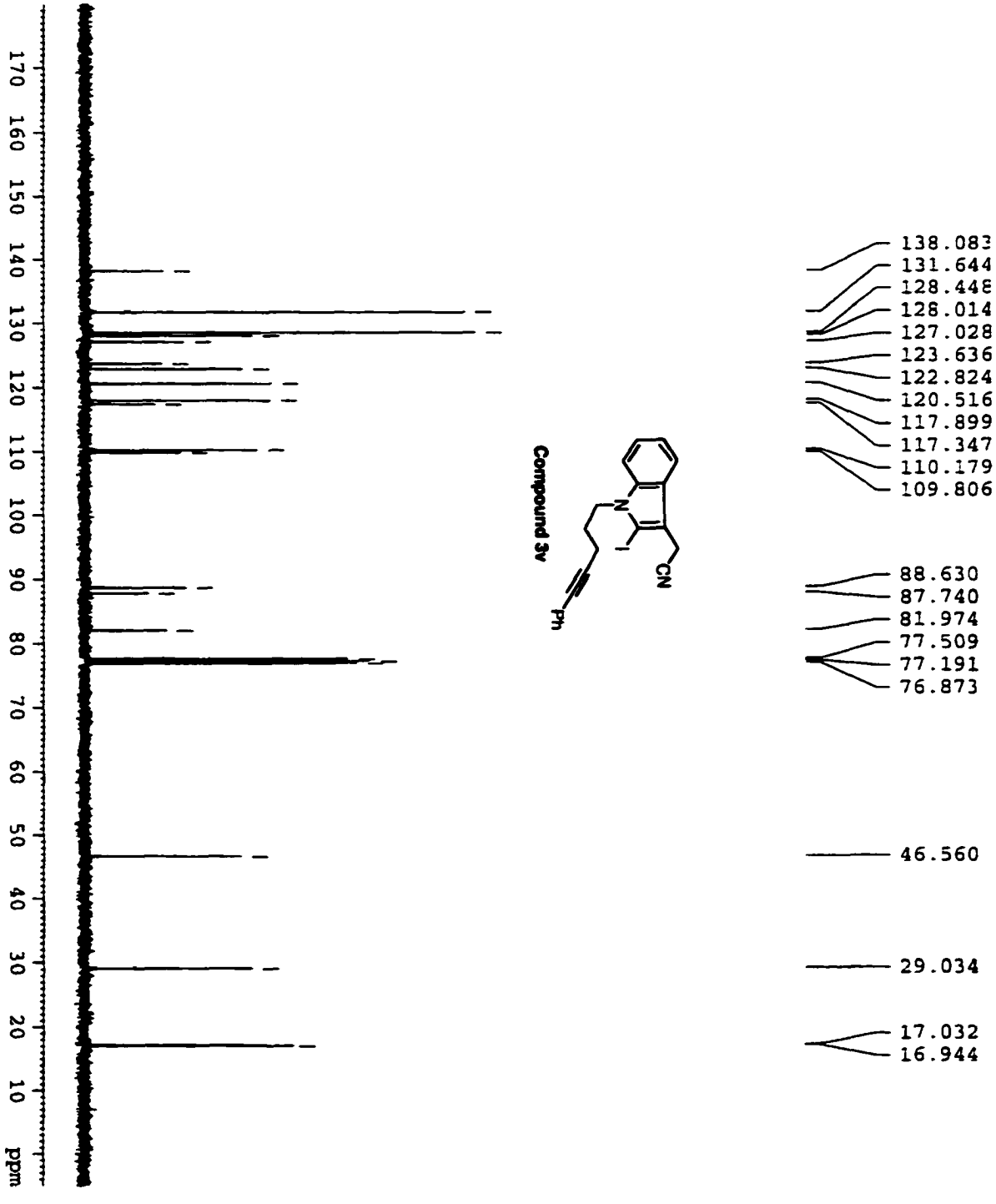

2.918
4.984
4.026
0.997
0.982
2.000
2.020
2.028
ppm
Compound 3t
Ph
7.604
7.584
7.573
7.554
7.496
7.486
7.475
7.467
7.447
7.438
7.433
7.374
7.356
7.337
7.309
7.306
7.297
7.293
7.220
7.208
7.189
7.170
7.102
7.083
7.065
4.468
4.450
4.431
2.544
2.527
2.510
2.161
2.143
2.126
2.108
0.000

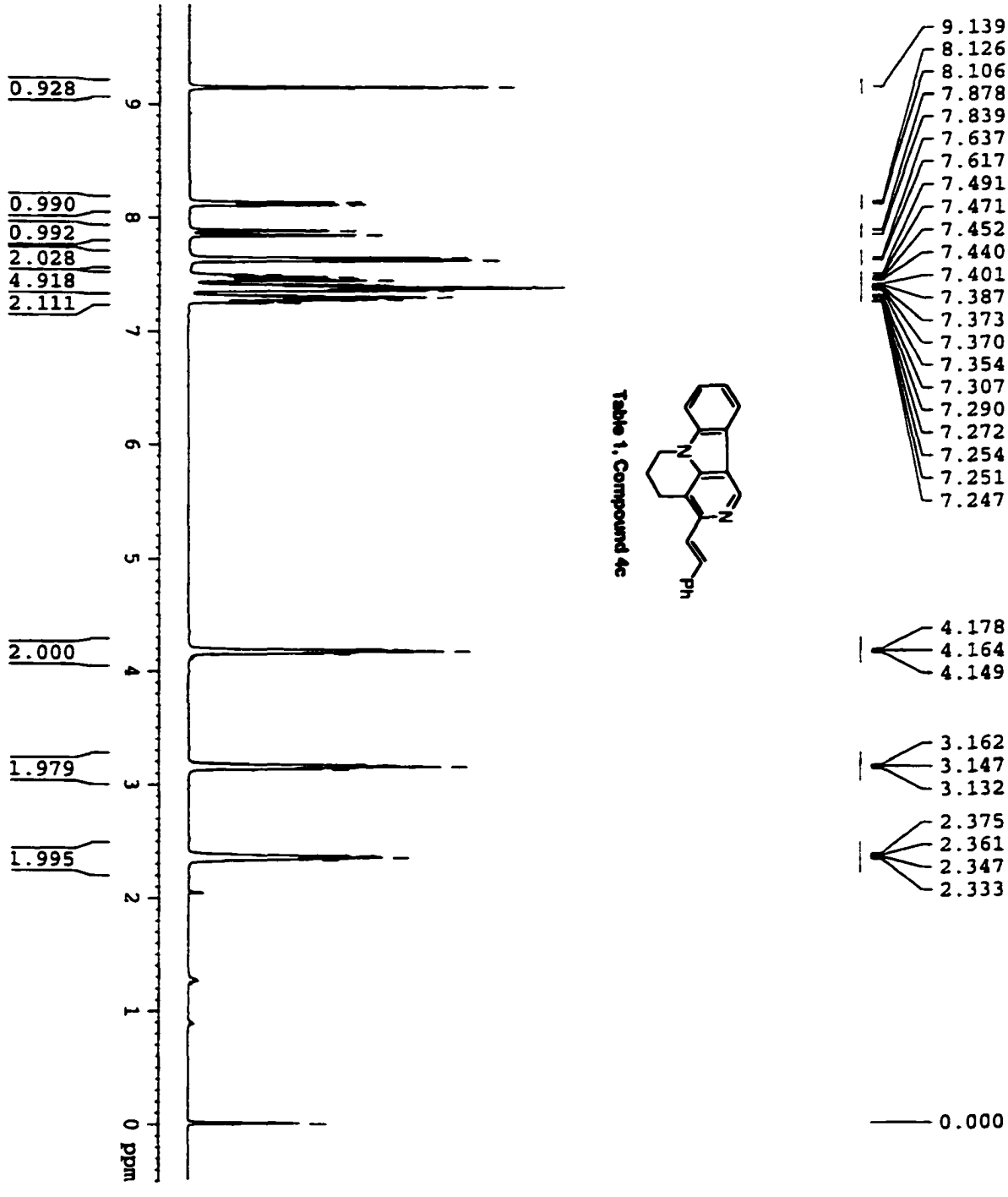

Compound 3t
Ph
138.109
135.193
131.664
130.125
128.463
128.408
127.933
126.926
123.719
123.387
122.404
120.171
119.184
109.834
88.848
85.758
81.843
77.430
77.112
76.794
46.541
29.129
17.149
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm


1.029
3.286
5.313
2.097
2.000
2.188
2.190
0 ppm
Compound 3u
N
Br
CN
Ph
7.634
7.613
7.611
7.453
7.435
7.426
7.423
7.410
7.402
7.324
7.317
7.314
7.309
7.304
7.295
7.279
7.275
7.255
7.251
7.237
7.229
7.224
7.212
7.208
7.186
7.183
7.162
4.398
4.374
4.350
3.788
2.479
2.456
2.434
2.091
2.067
2.044
0.000


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm
Compound 3u
N
Br
CN
Ph
136.596
131.792
128.591
128.165
126.322
123.780
123.024
120.961
118.088
117.339
113.996
110.111
103.648
88.676
82.073
77.734
77.310
76.887
44.347
29.099
17.173
14.715


7.628
7.610
7.609
7.453
7.433
7.427
7.418
7.413
7.317
7.307
7.303
7.295
7.290
7.284
7.215
7.197
7.194
7.177
7.174
7.164
7.162
7.144
7.143
4.358
4.339
4.321
3.768
2.470
2.454
2.437
2.050
2.030
2.014
1.000
3.036
3.297
2.060
2.015
2.000
2.038
2.128
Compound 3v
N
I
CN
Ph
ppm


170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm
Compound 3v
N
CN
Ph
138.083
131.644
128.448
128.014
127.028
123.636
122.824
120.516
117.899
117.347
110.179
109.806
88.630
87.740
81.974
77.509
77.191
76.873
46.560
29.034
17.032
16.944


0.928
0.990
0.992
2.028
4.918
2.111
2.000
1.979
1.995
ppm
Table 1, Compound 4c
Ph
9.139
8.126
8.106
7.878
7.839
7.637
7.617
7.491
7.471
7.452
7.440
7.401
7.387
7.373
7.370
7.354
7.307
7.290
7.272
7.254
7.251
7.247
4.178
4.164
4.149
3.162
3.147
3.132
2.375
2.361
2.347
2.333
0.000

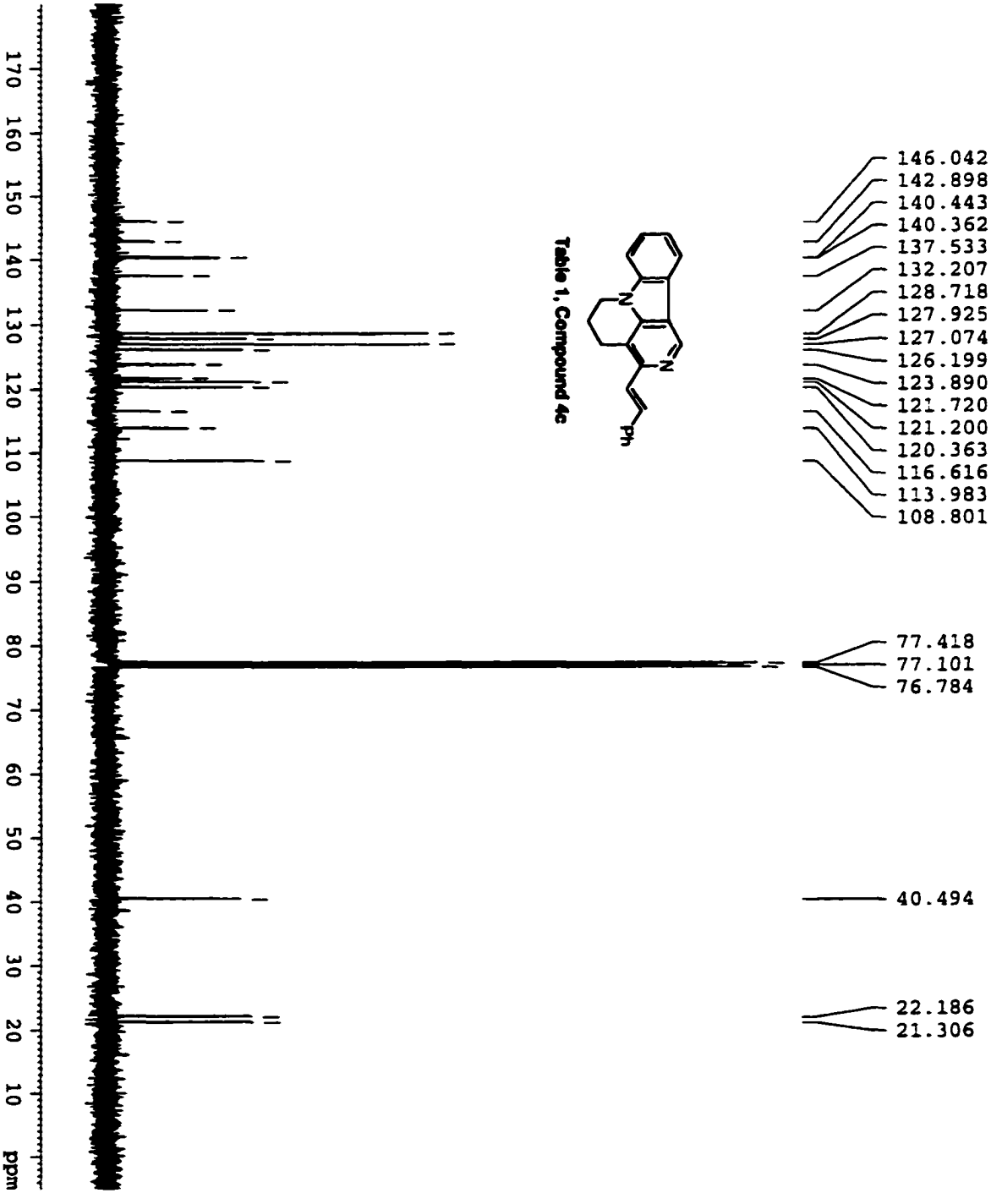
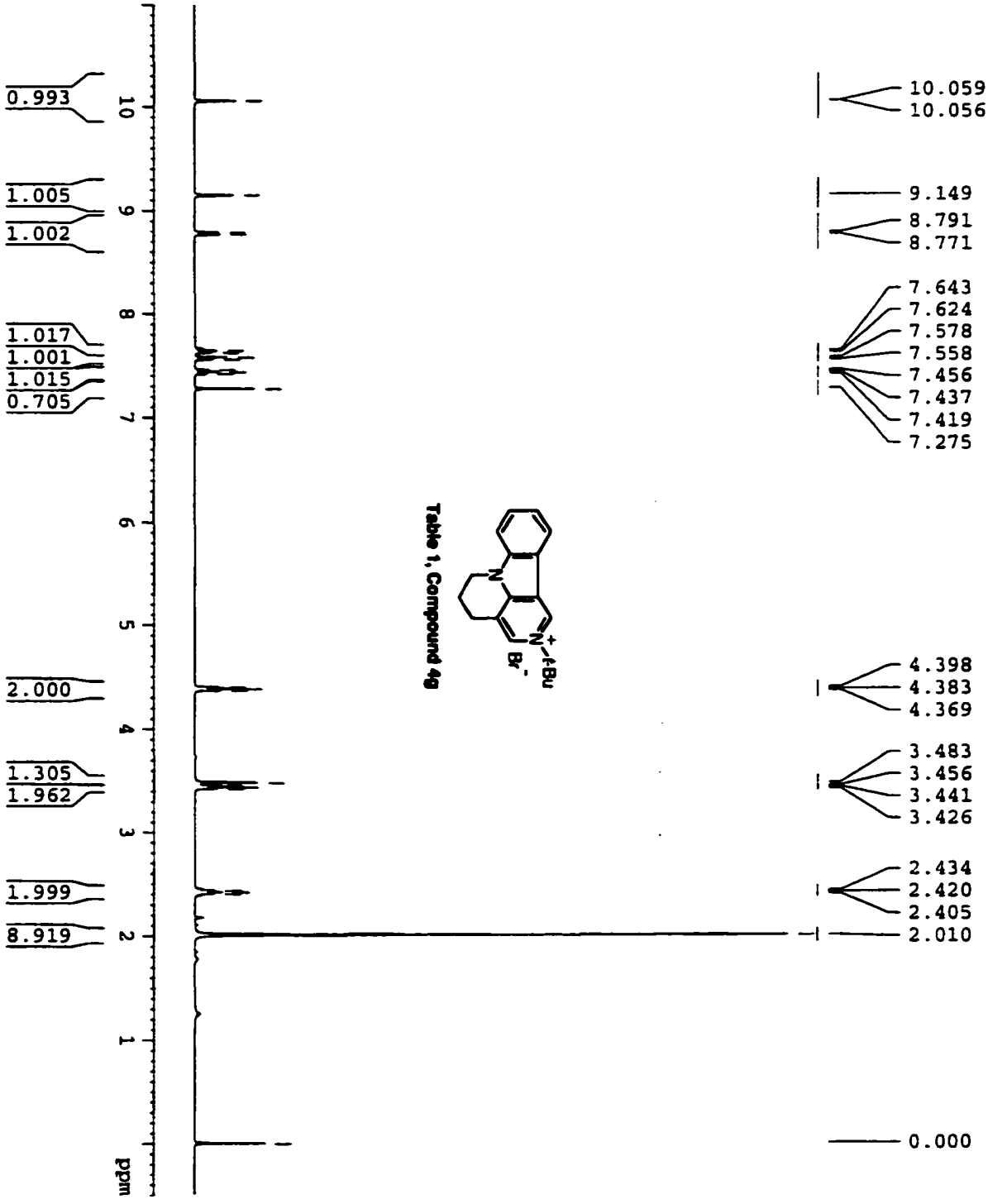


Table 1, Compound 4c
146.042
142.898
140.443
140.362
137.533
132.207
128.718
127.925
127.074
126.199
123.890
121.720
121.200
120.363
116.616
113.983
108.801
77.418
77.101
76.784
40.494
22.186
21.306
ppm


0.993
1.005
1.002
1.017
1.001
1.015
0.705
2.000
1.305
1.962
1.999
8.919
10.059
10.056
9.149
8.791
8.771
7.643
7.624
7.578
7.558
7.456
7.437
7.419
7.275
4.398
4.383
4.369
3.483
3.456
3.441
3.426
2.434
2.420
2.405
2.010
0.000
ppm
Table 1, Compound 4g
N
N
+
t-Bu
Br-

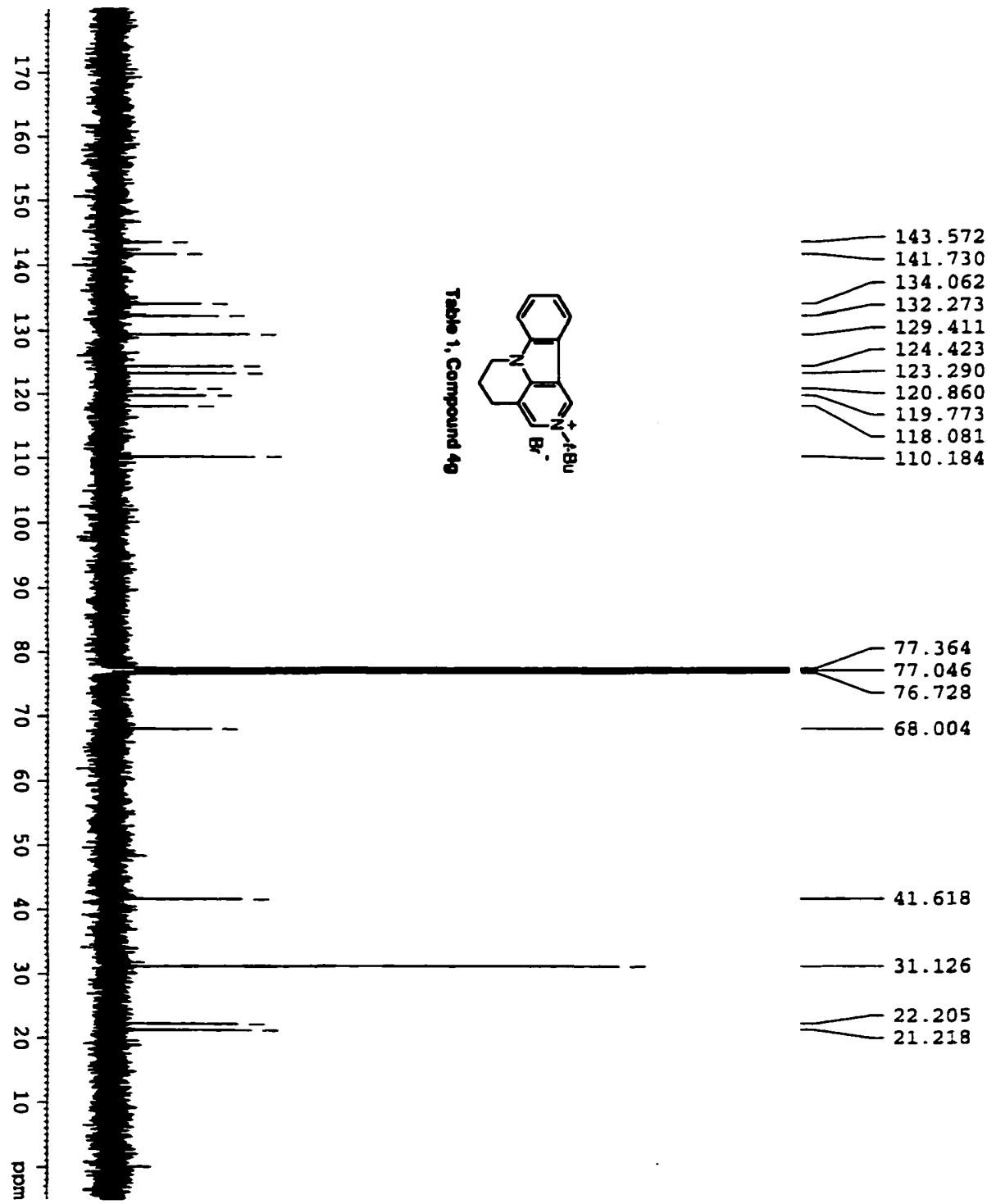


Table 1, Compound 4g
143.572
141.730
134.062
132.273
129.411
124.423
123.290
120.860
119.773
118.081
110.184
77.364
77.046
76.728
68.004
41.618
31.126
22.205
21.218
ppm

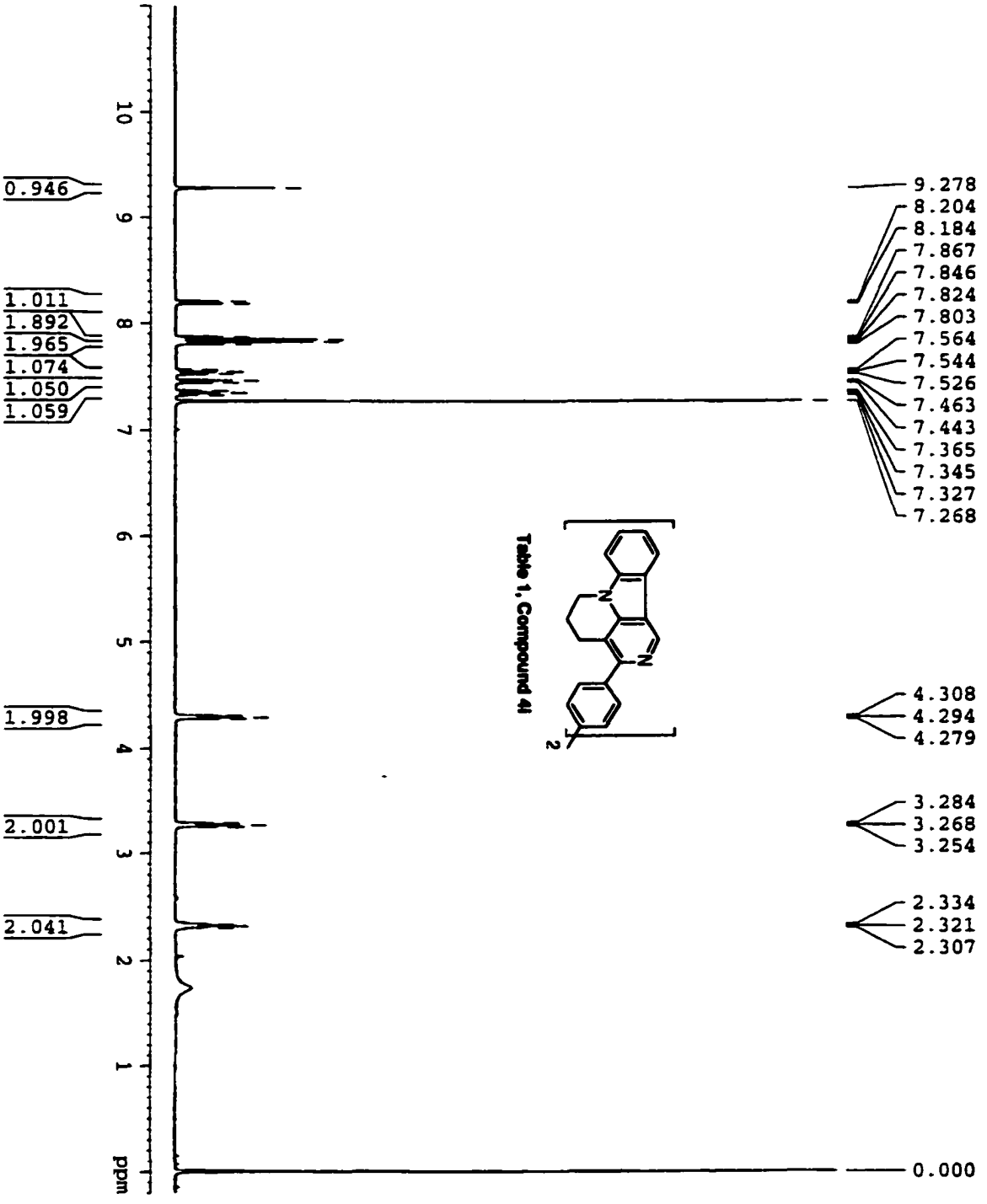
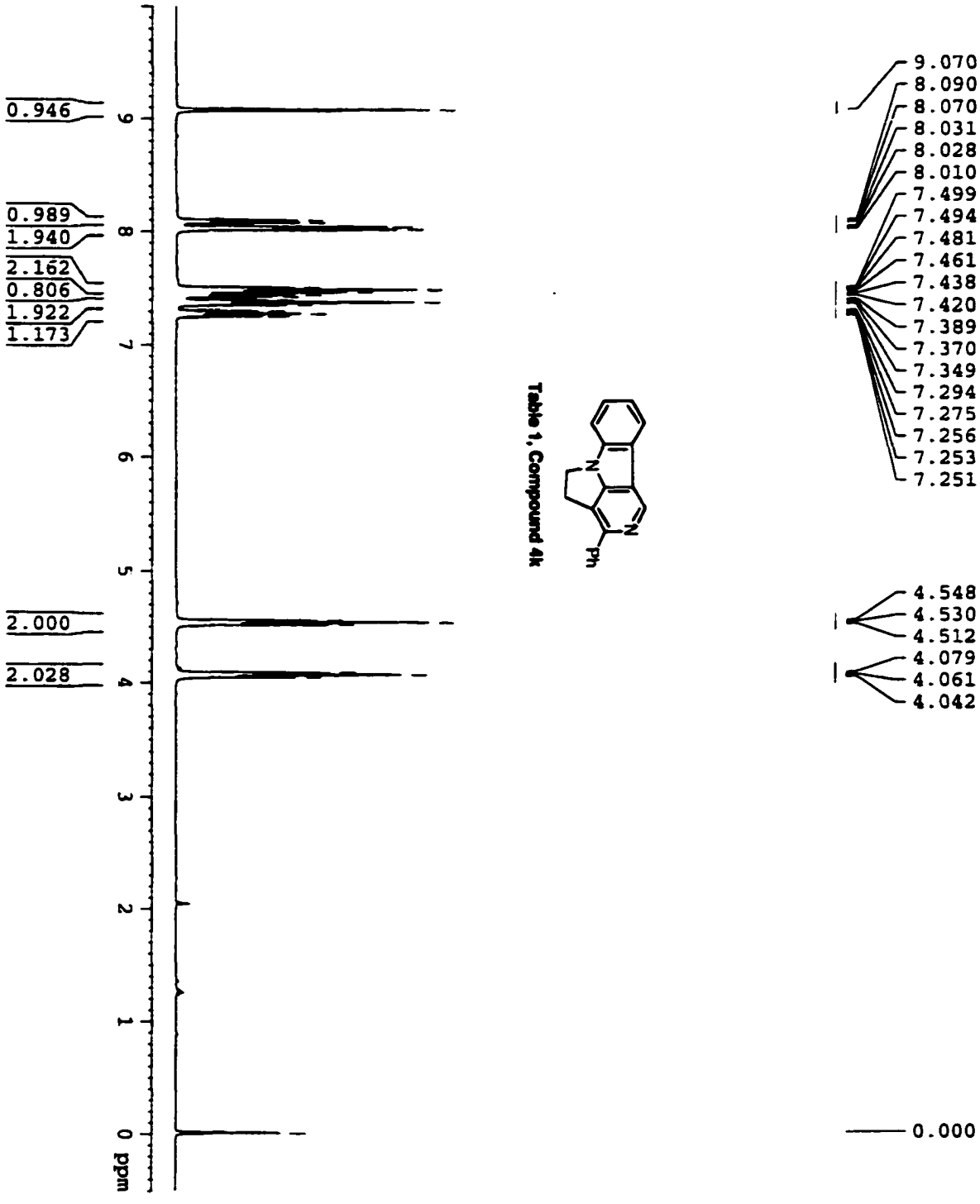
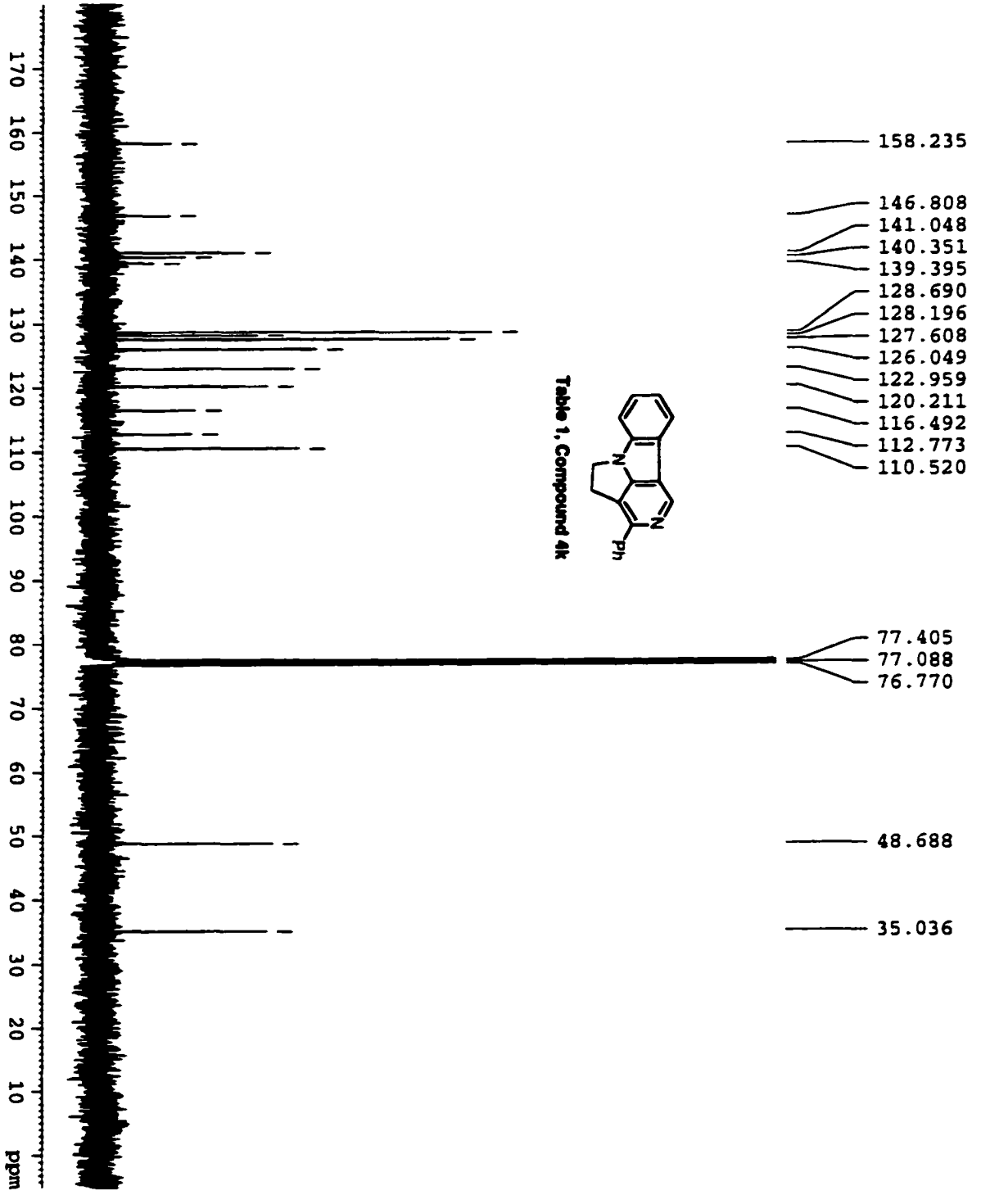


Table 1, Compound 4i
9.278
8.204
8.184
7.867
7.846
7.824
7.803
7.564
7.544
7.526
7.463
7.443
7.365
7.345
7.327
7.268
4.308
4.294
4.279
3.284
3.268
3.254
2.334
2.321
2.307
0.000
0.946
1.011
1.892
1.965
1.074
1.050
1.059
1.998
2.001
2.041
ppm


0.946
0.989
1.940
2.162
0.806
1.922
1.173
2.000
2.028
9
8
7
6
5
4
3
2
1
0 ppm
Table 1, Compound 4k
N
N
Ph
9.070
8.090
8.070
8.031
8.028
8.010
7.499
7.494
7.481
7.461
7.438
7.420
7.389
7.370
7.349
7.294
7.275
7.256
7.253
7.251
4.548
4.530
4.512
4.079
4.061
4.042
0.000


158.235
146.808
141.048
140.351
139.395
128.690
128.196
127.608
126.049
122.959
120.211
116.492
112.773
110.520
77.405
77.088
76.770
48.688
35.036
Table 1, Compound 4k
Ph
ppm

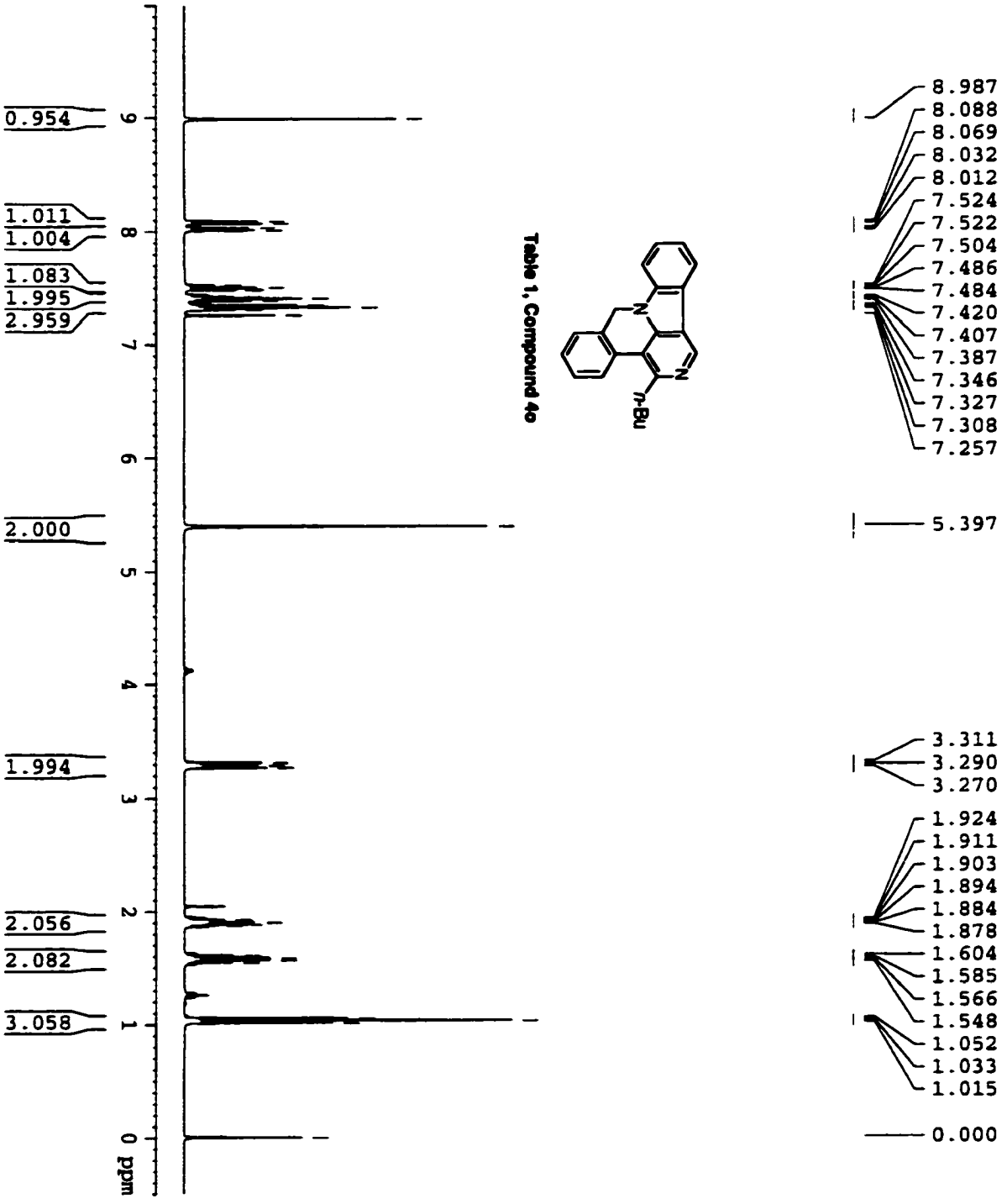


Table 1, Compound 4o
n-Bu
0.954
1.011
1.004
1.083
1.995
2.959
2.000
1.994
2.056
2.082
3.058
8.987
8.088
8.069
8.032
8.012
7.524
7.522
7.504
7.486
7.484
7.420
7.407
7.387
7.346
7.327
7.308
7.257
5.397
3.311
3.290
3.270
1.924
1.911
1.903
1.894
1.884
1.878
1.604
1.585
1.566
1.548
1.052
1.033
1.015
0.000
ppm

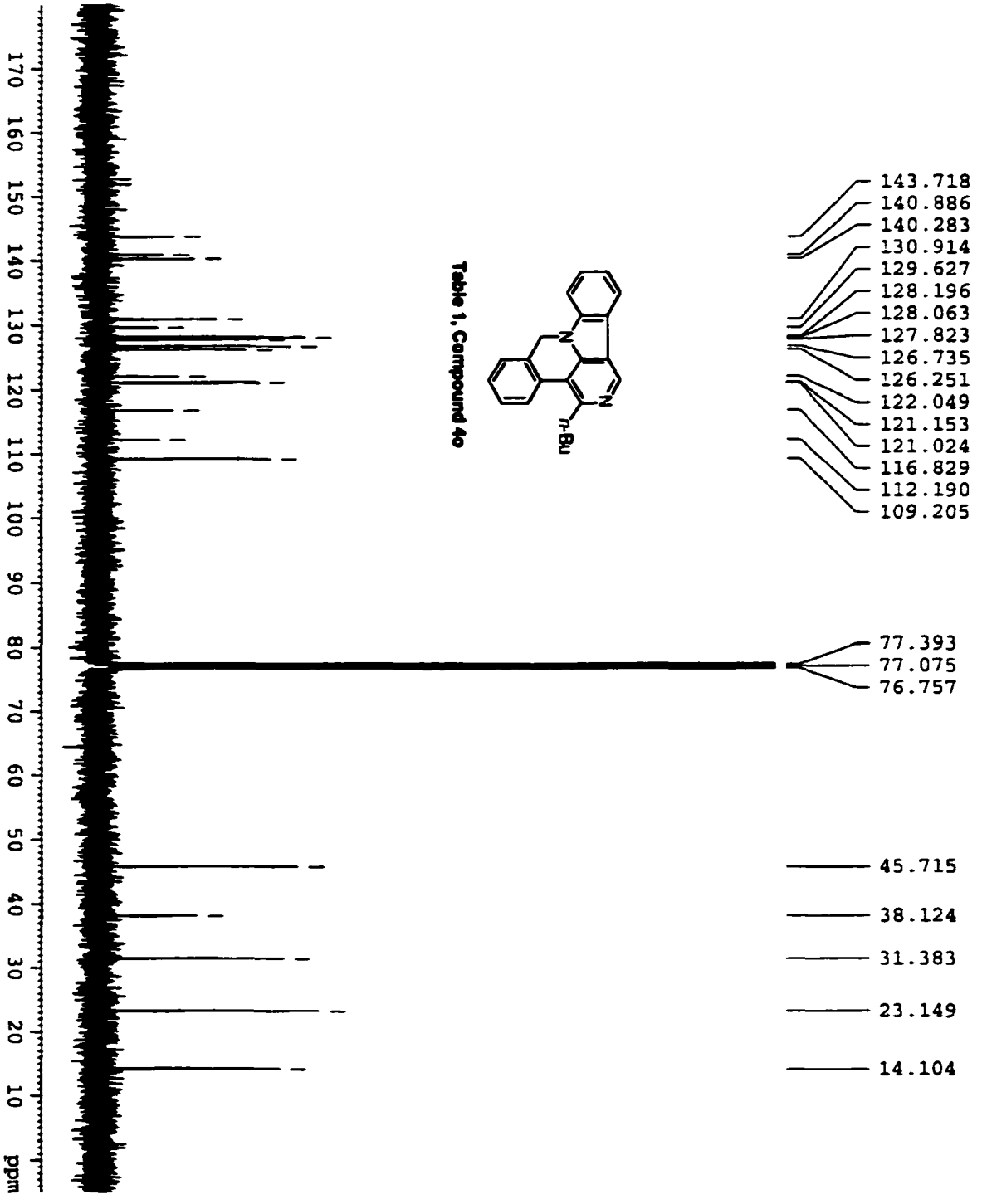


Table 1, Compound 4o
n-Bu
143.718
140.886
140.283
130.914
129.627
128.196
128.063
127.823
126.735
126.251
122.049
121.153
121.024
116.829
112.190
109.205
77.393
77.075
76.757
45.715
38.124
31.383
23.149
14.104
ppm

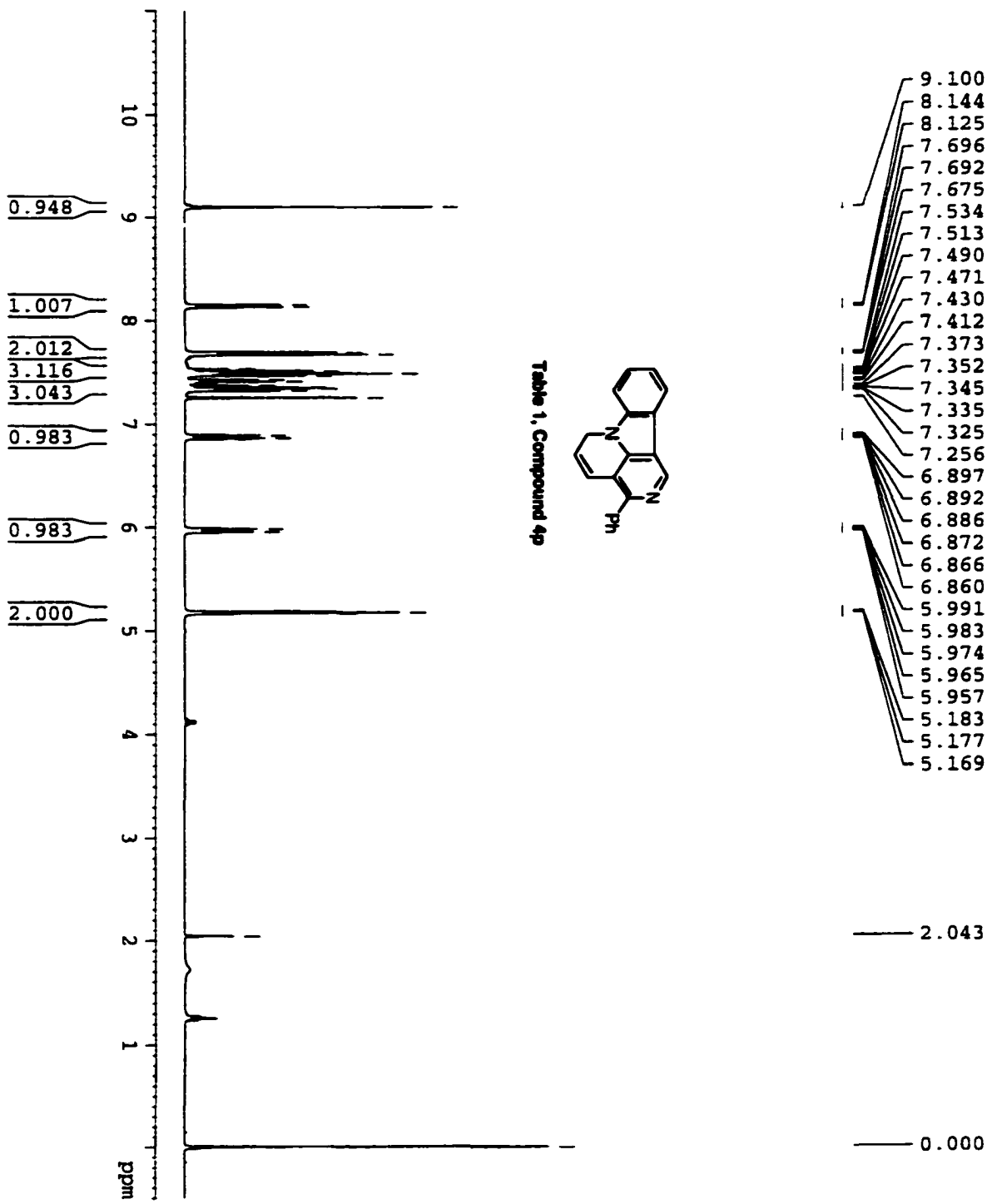


Table 1, Compound 4p
Ph
N
N
0.948
1.007
2.012
3.116
3.043
0.983
0.983
2.000
ppm
9.100
8.144
8.125
7.696
7.692
7.675
7.534
7.513
7.490
7.471
7.430
7.412
7.373
7.352
7.345
7.335
7.325
7.256
6.897
6.892
6.886
6.872
6.866
6.860
5.991
5.983
5.974
5.965
5.957
5.183
5.177
5.169
2.043
0.000

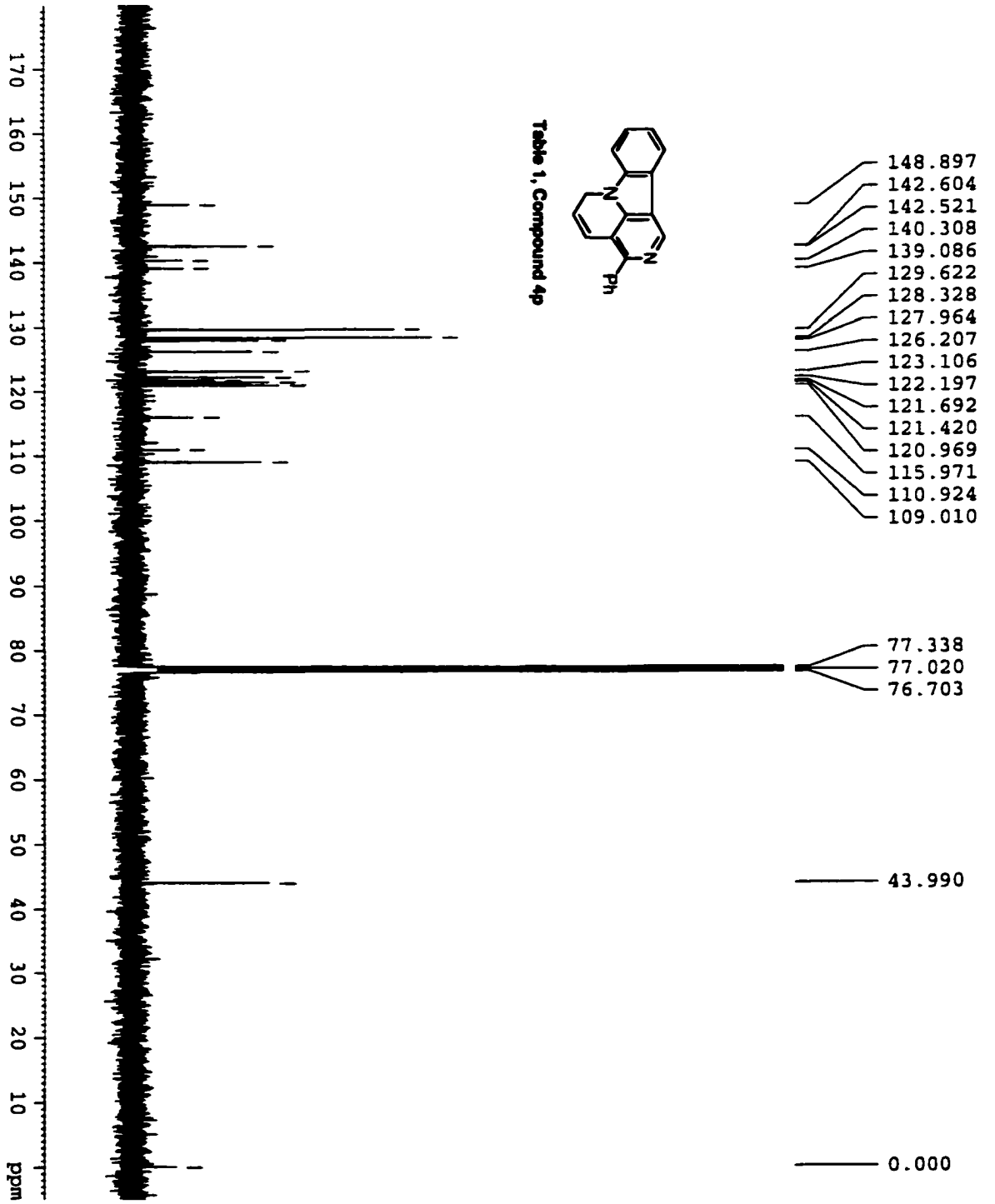
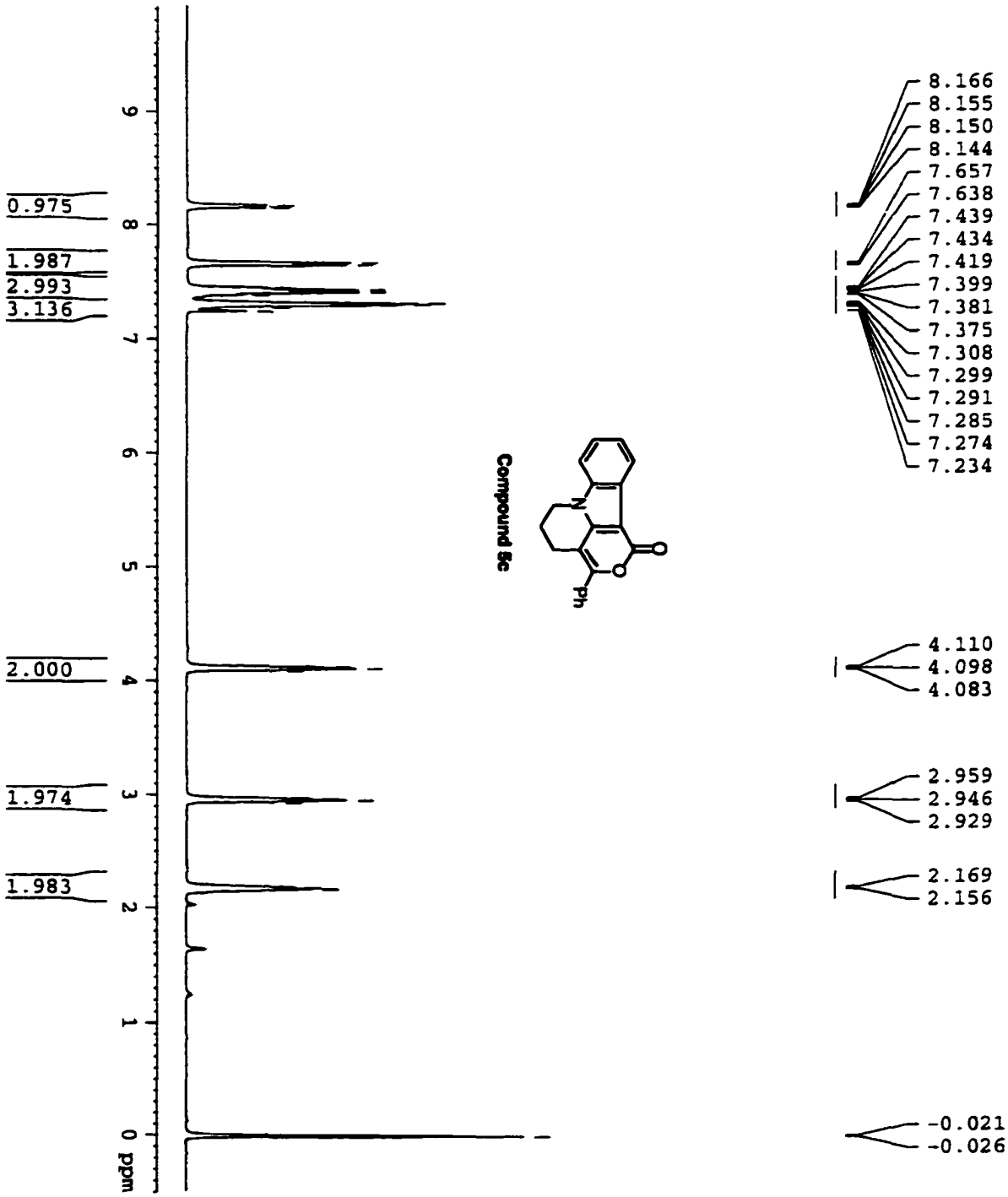
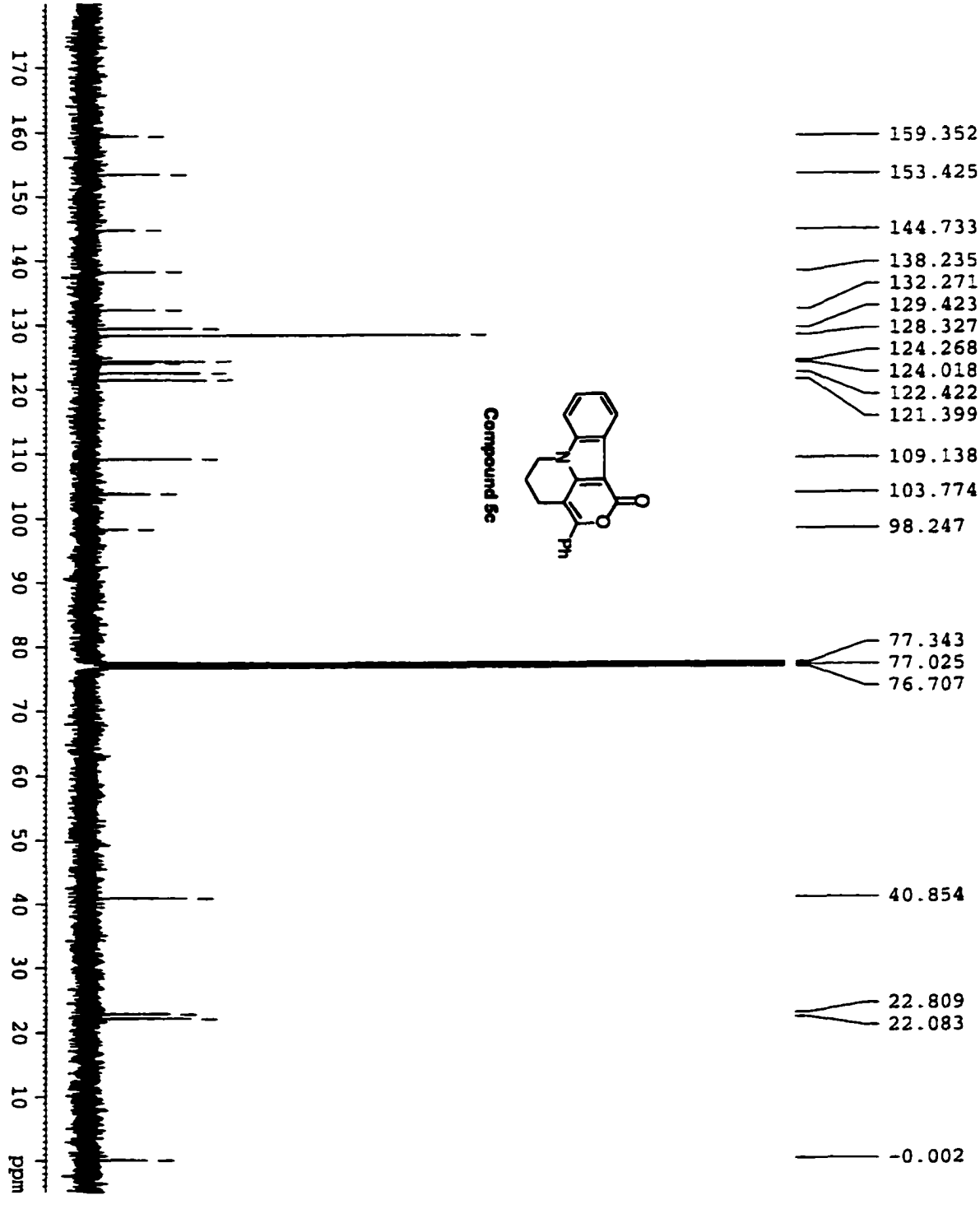
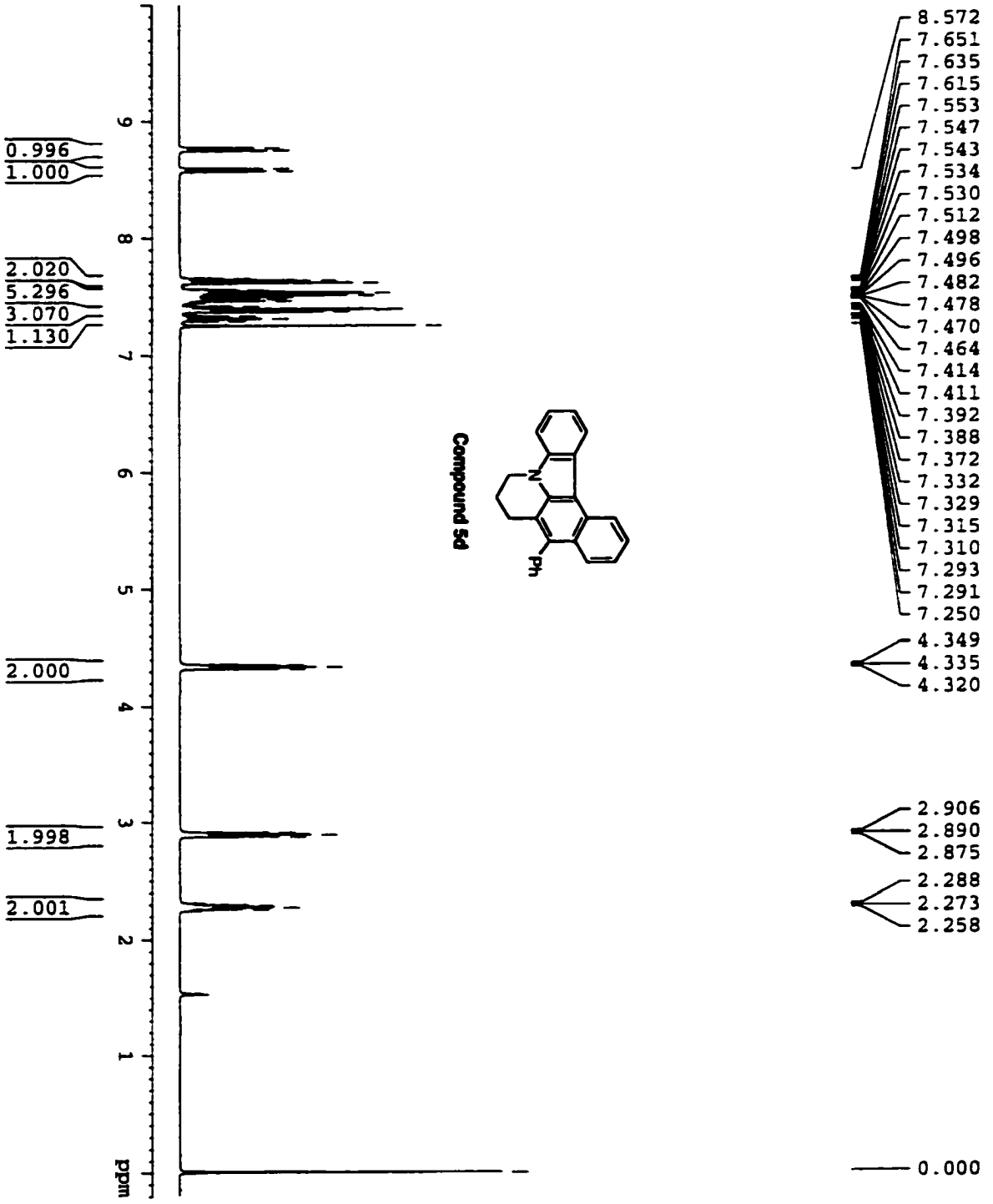
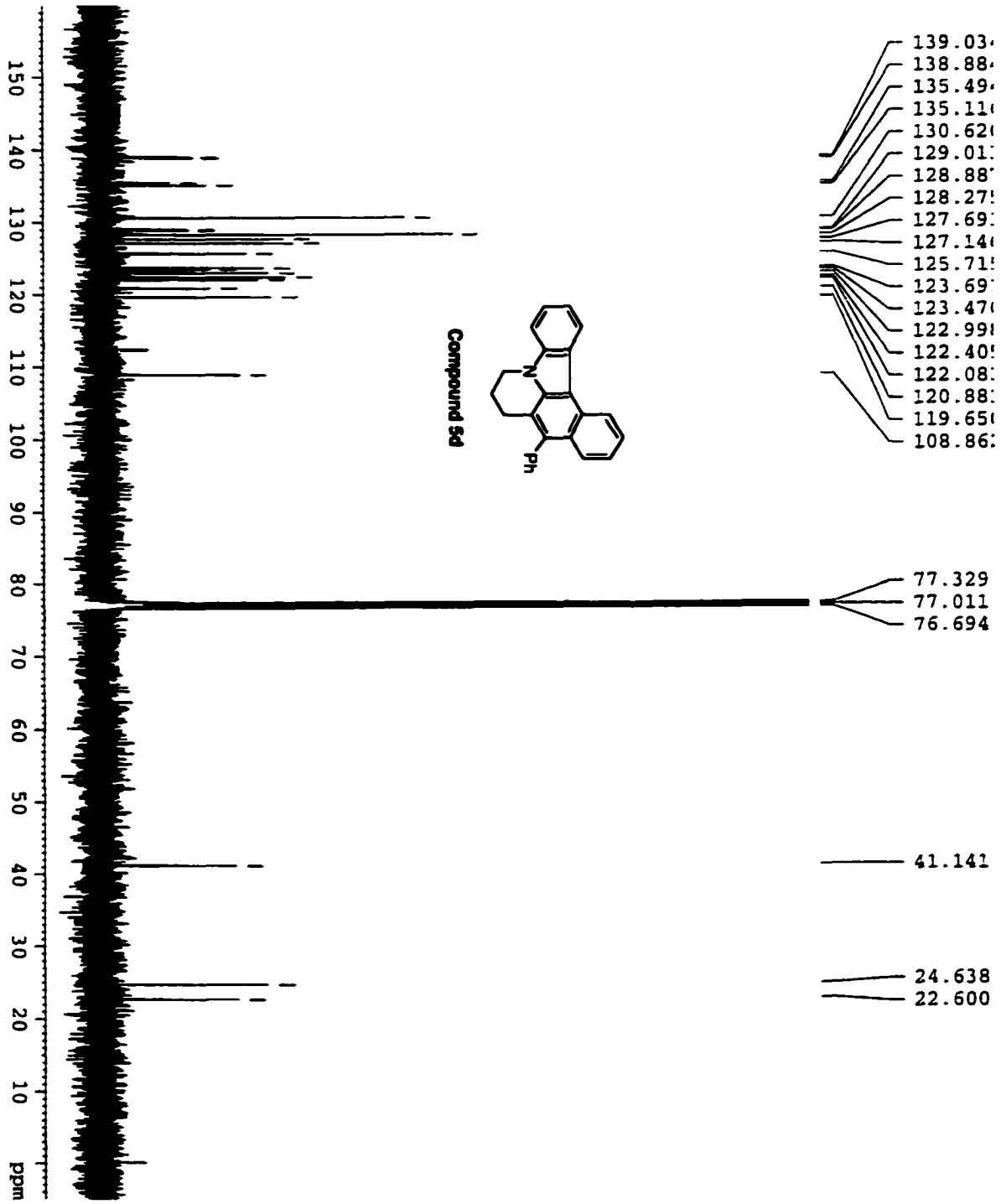


Table 1, Compound 4p
Ph
148.897
142.604
142.521
140.308
139.086
129.622
128.328
127.964
126.207
123.106
122.197
121.692
121.420
120.969
115.971
110.924
109.010
77.338
77.020
76.703
43.990
0.000
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

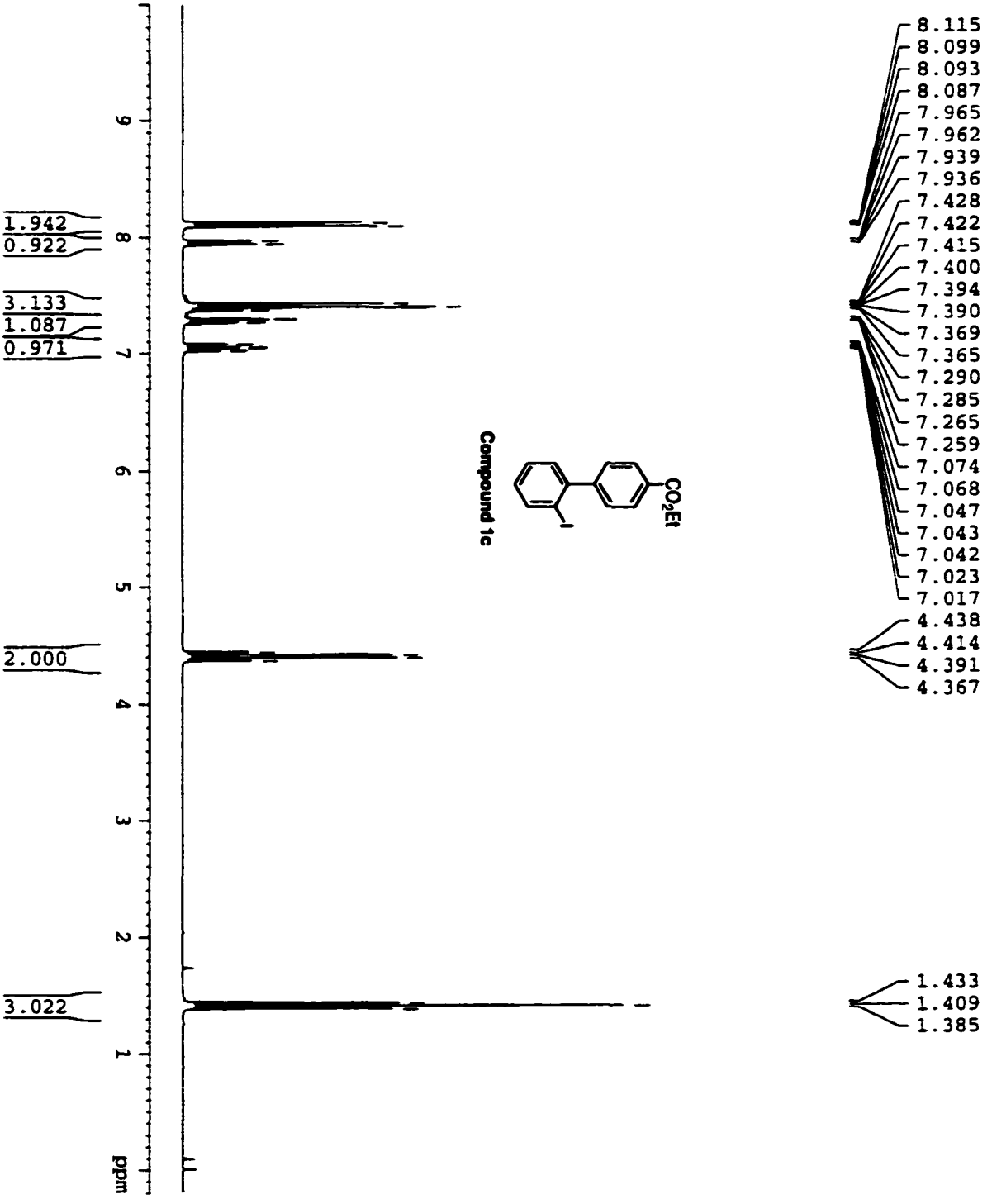

0.975
1.987
2.993
3.136
2.000
1.974
1.983
9
8
7
6
5
4
3
2
1
0 ppm
Compound 5c
Ph
8.166
8.155
8.150
8.144
7.657
7.638
7.439
7.434
7.419
7.399
7.381
7.375
7.308
7.299
7.291
7.285
7.274
7.234
4.110
4.098
4.083
2.959
2.946
2.929
2.169
2.156
-0.021
-0.026

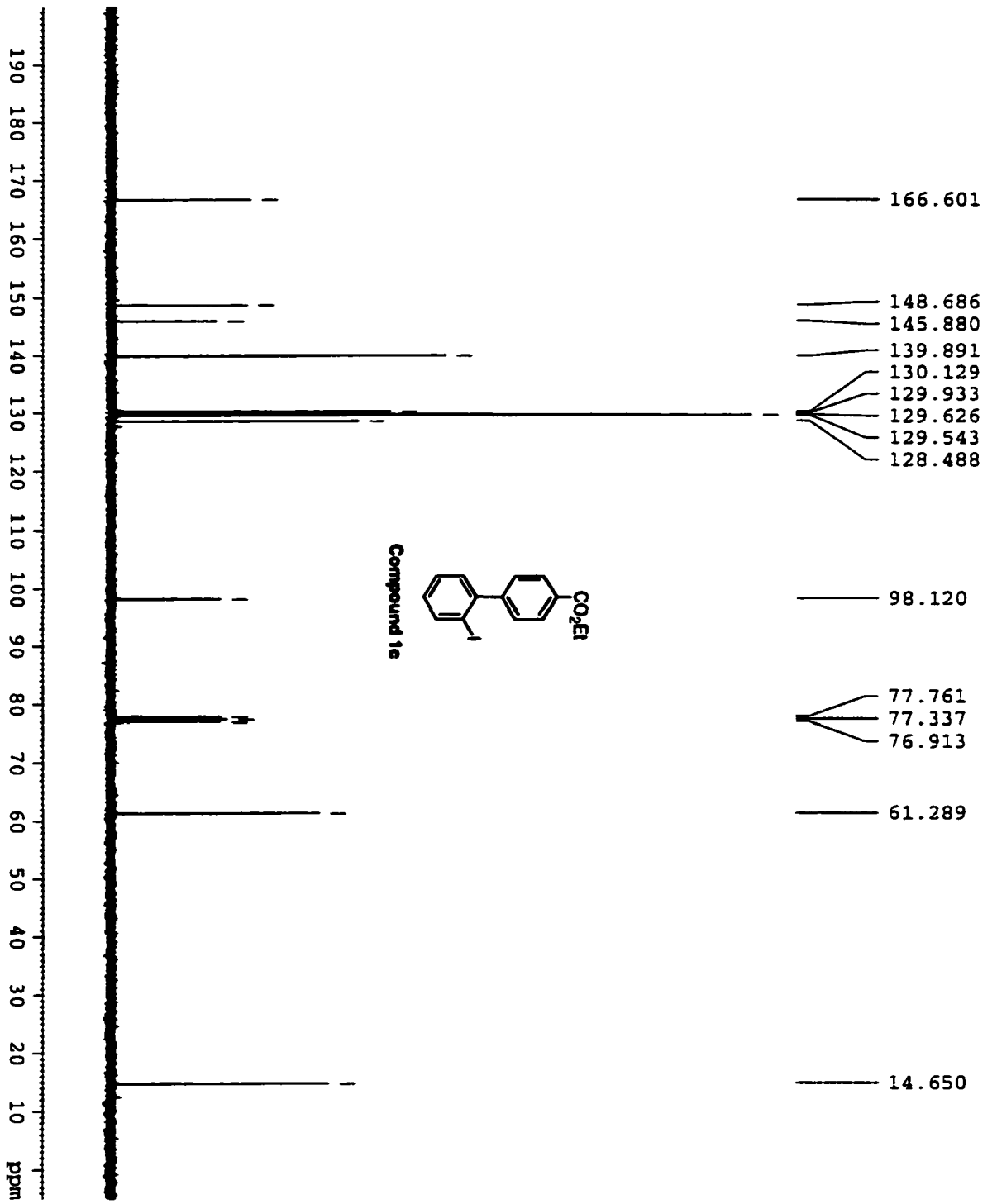

159.352
153.425
144.733
138.235
132.271
129.423
128.327
124.268
124.018
122.422
121.399
109.138
103.774
98.247
77.343
77.025
76.707
40.854
22.809
22.083
-0.002
Compound 5c
Ph
ppm

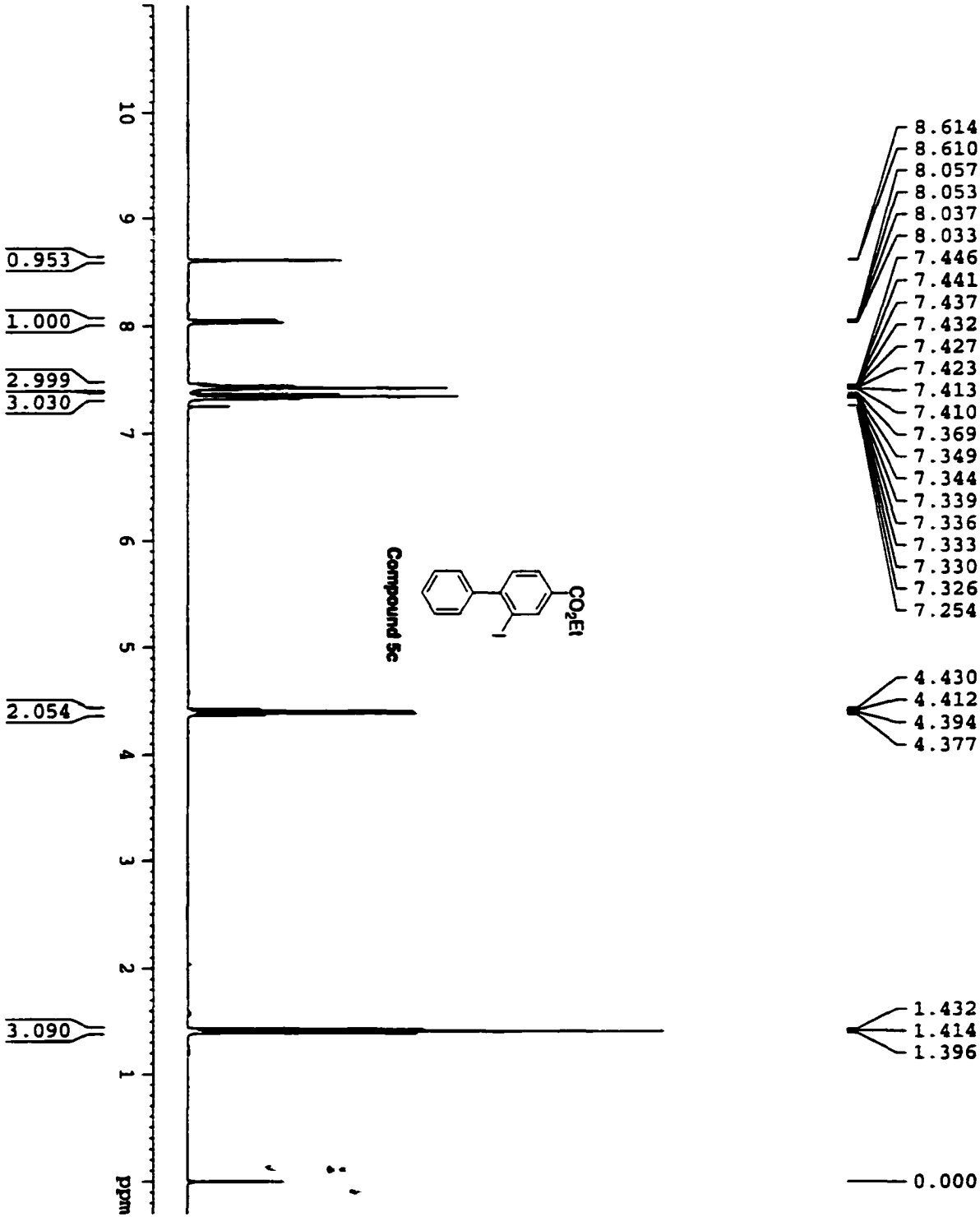

8.572
7.651
7.635
7.615
7.553
7.547
7.543
7.534
7.530
7.512
7.498
7.496
7.482
7.478
7.470
7.464
7.414
7.411
7.392
7.388
7.372
7.332
7.329
7.315
7.310
7.293
7.291
7.250
4.349
4.335
4.320
2.906
2.890
2.875
2.288
2.273
2.258
0.000
0.996
1.000
2.020
5.296
3.070
1.130
2.000
1.998
2.001
ppm
Compound 5g
N
Ph

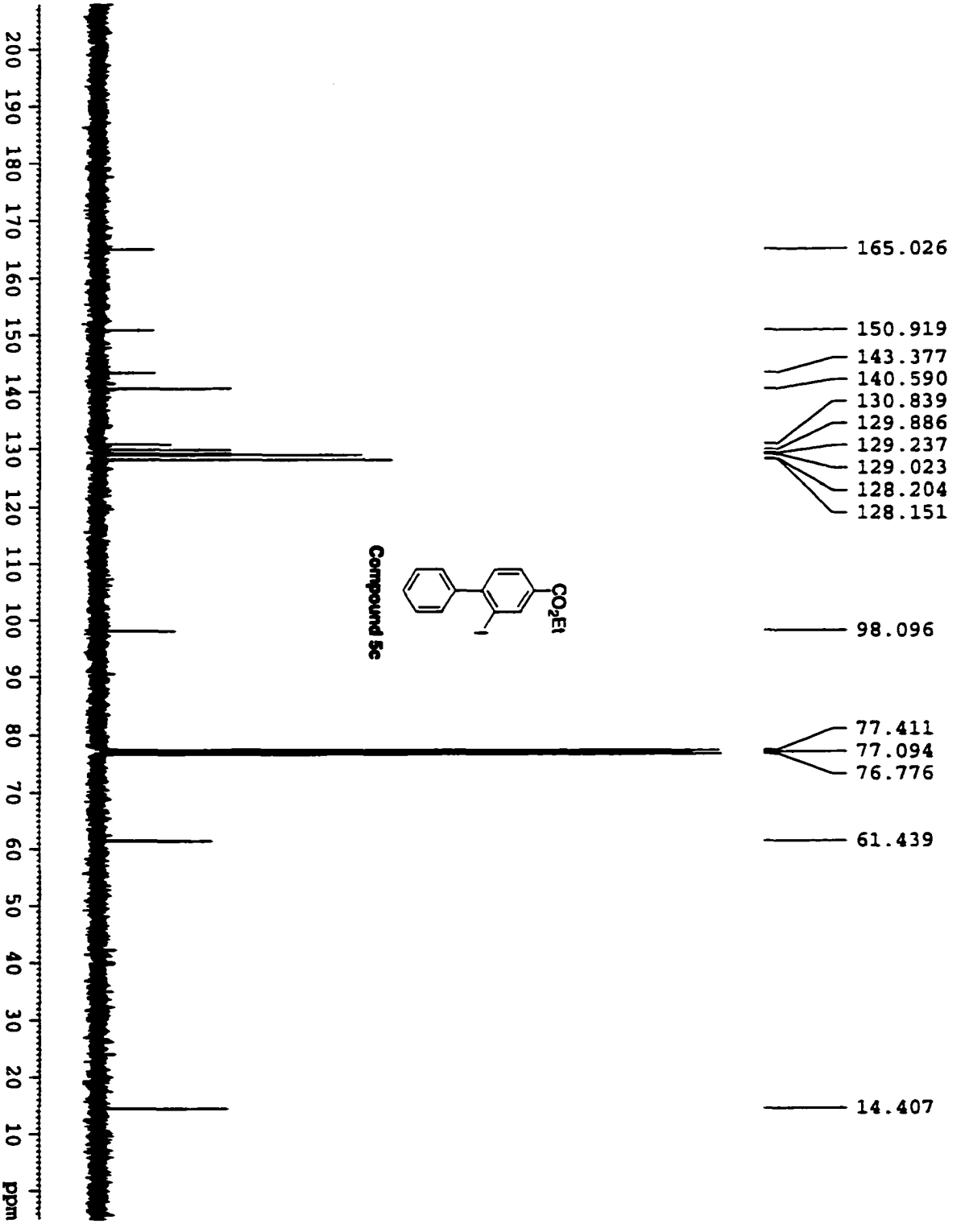

139.03
138.88
135.49
135.11
130.62
129.01
128.88
128.27
127.69
127.14
125.71
123.69
123.47
122.99
122.40
122.08
120.88
119.65
108.86
77.329
77.011
76.694
41.141
24.638
22.600
Compound 5d
N
Ph
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

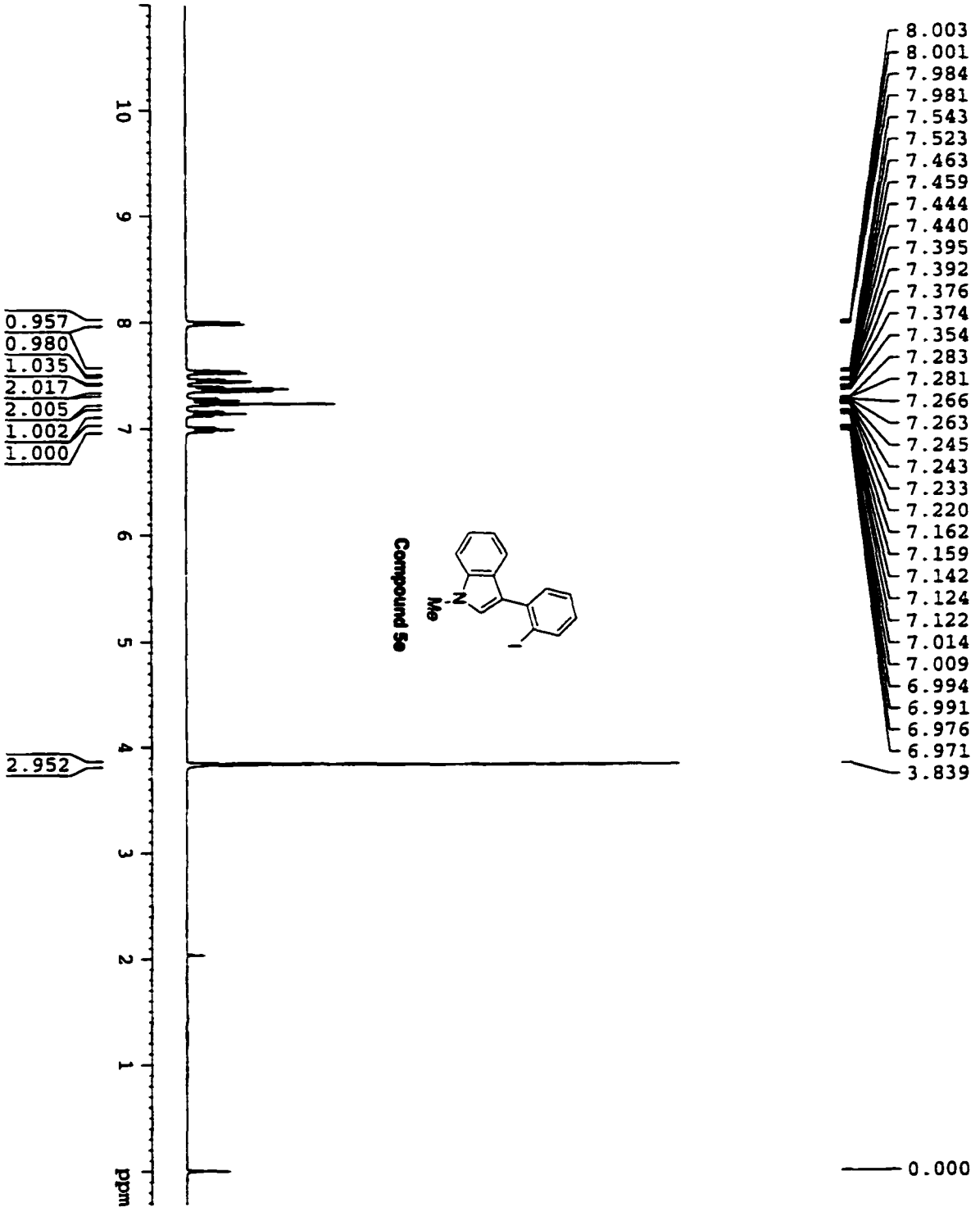
APPENDIX D. CHAPTER 4 ^{1}H AND ^{13}C NMR SPECTRA

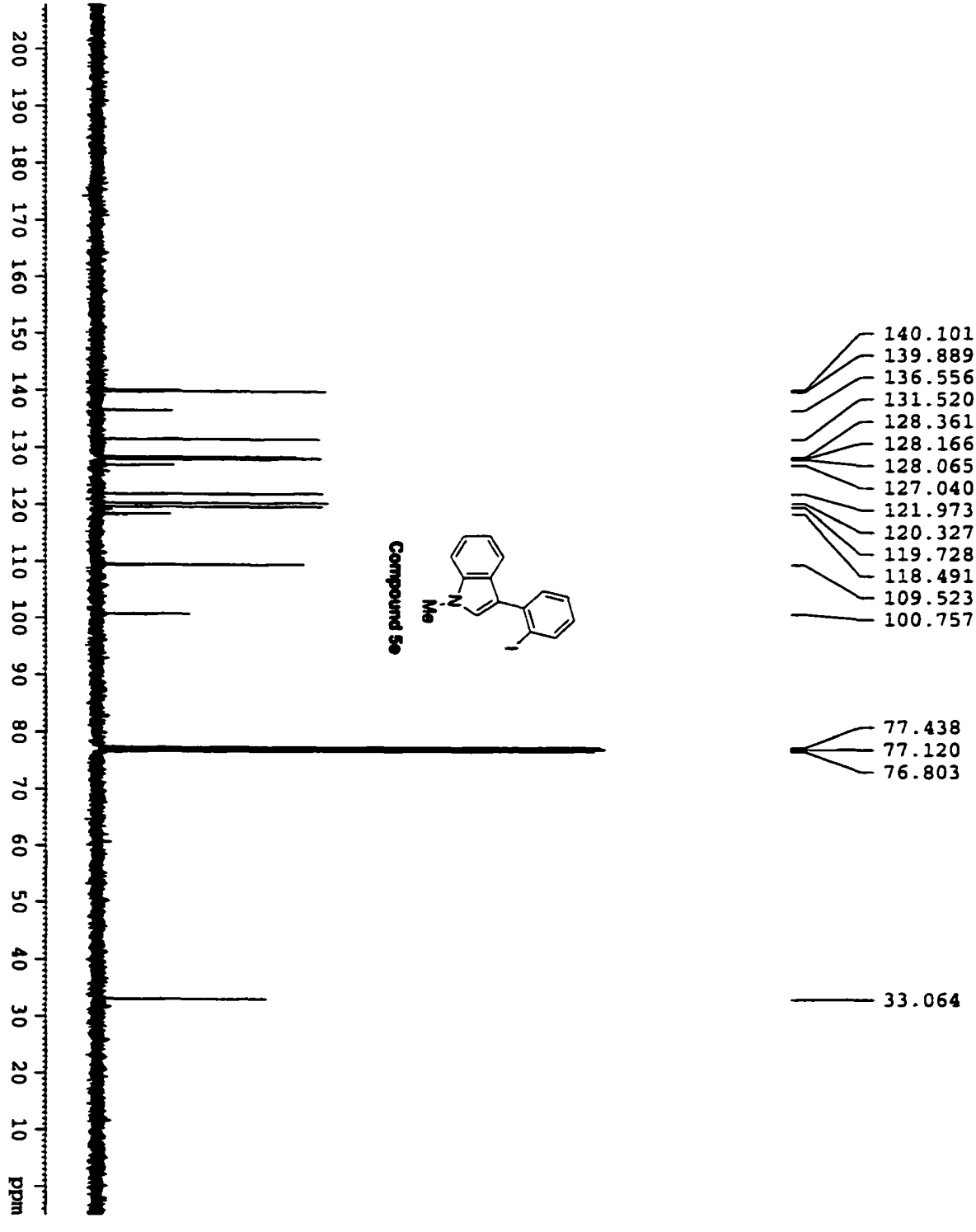

8.115
8.099
8.093
8.087
7.965
7.962
7.939
7.936
7.428
7.422
7.415
7.400
7.394
7.390
7.369
7.365
7.290
7.285
7.265
7.259
7.074
7.068
7.047
7.043
7.042
7.023
7.017
4.438
4.414
4.391
4.367
1.433
1.409
1.385
1.942
0.922
3.133
1.087
0.971
2.000
3.022
Compound 1c
CO2Et
I
ppm

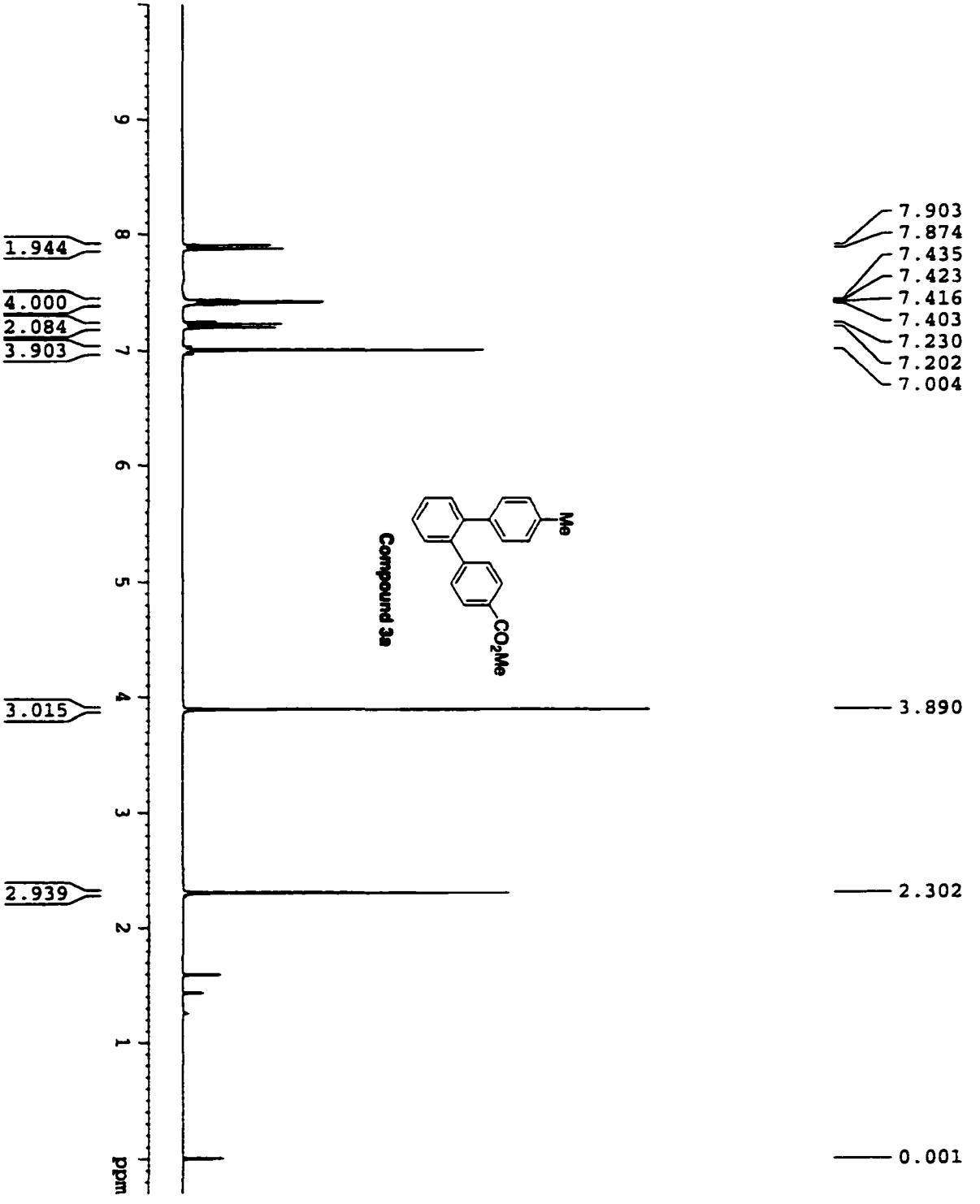

166.601
148.686
145.880
139.891
130.129
129.933
129.626
129.543
128.488
98.120
77.761
77.337
76.913
61.289
14.650
Compound 1c
CO2Et
I
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

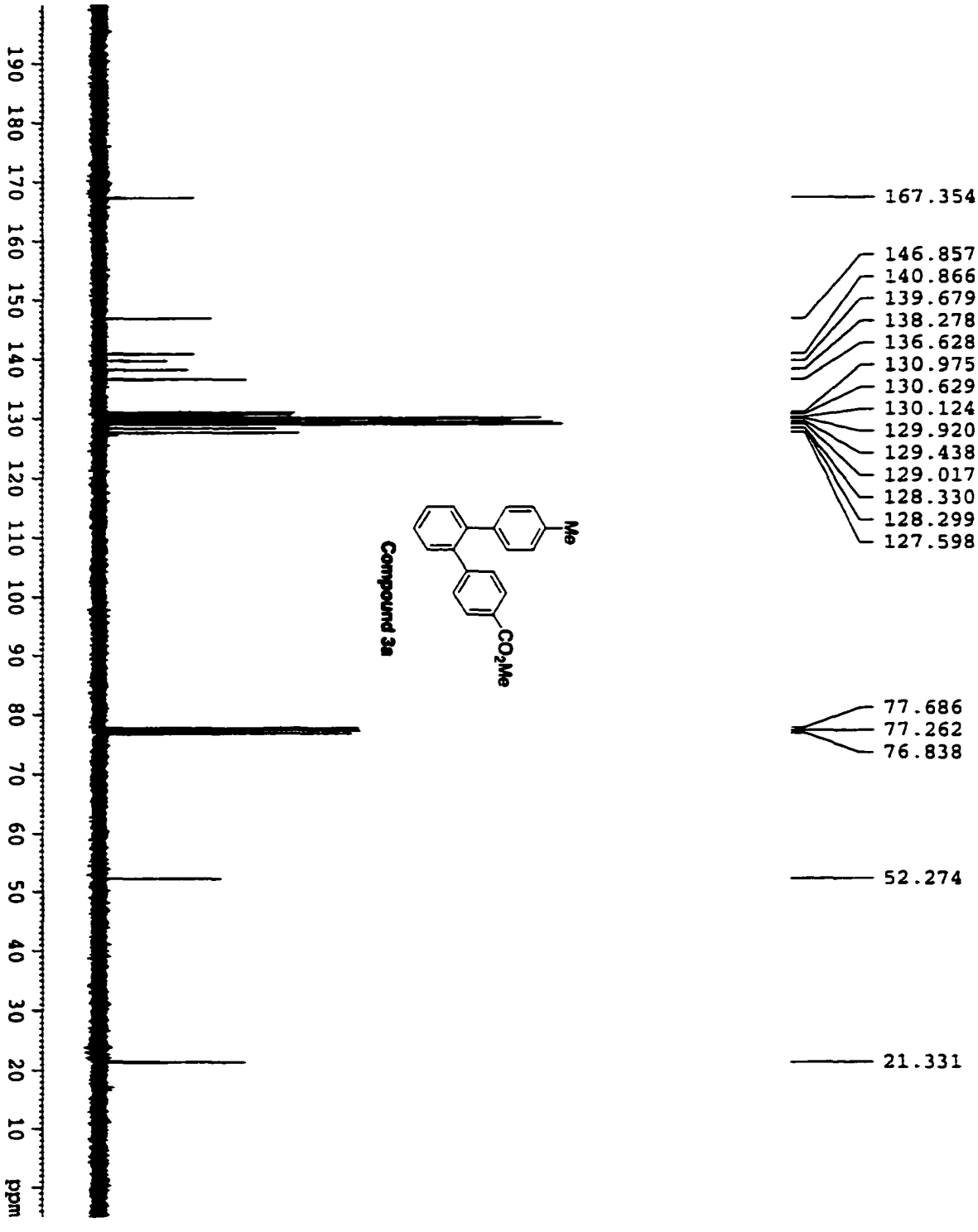

8.614
8.610
8.057
8.053
8.037
8.033
7.446
7.441
7.437
7.432
7.427
7.423
7.413
7.410
7.369
7.349
7.344
7.339
7.336
7.333
7.330
7.326
7.254
4.430
4.412
4.394
4.377
1.432
1.414
1.396
0.000
0.953
1.000
2.999
3.030
2.054
3.090
Compound 5c
CO2Et
I
ppm

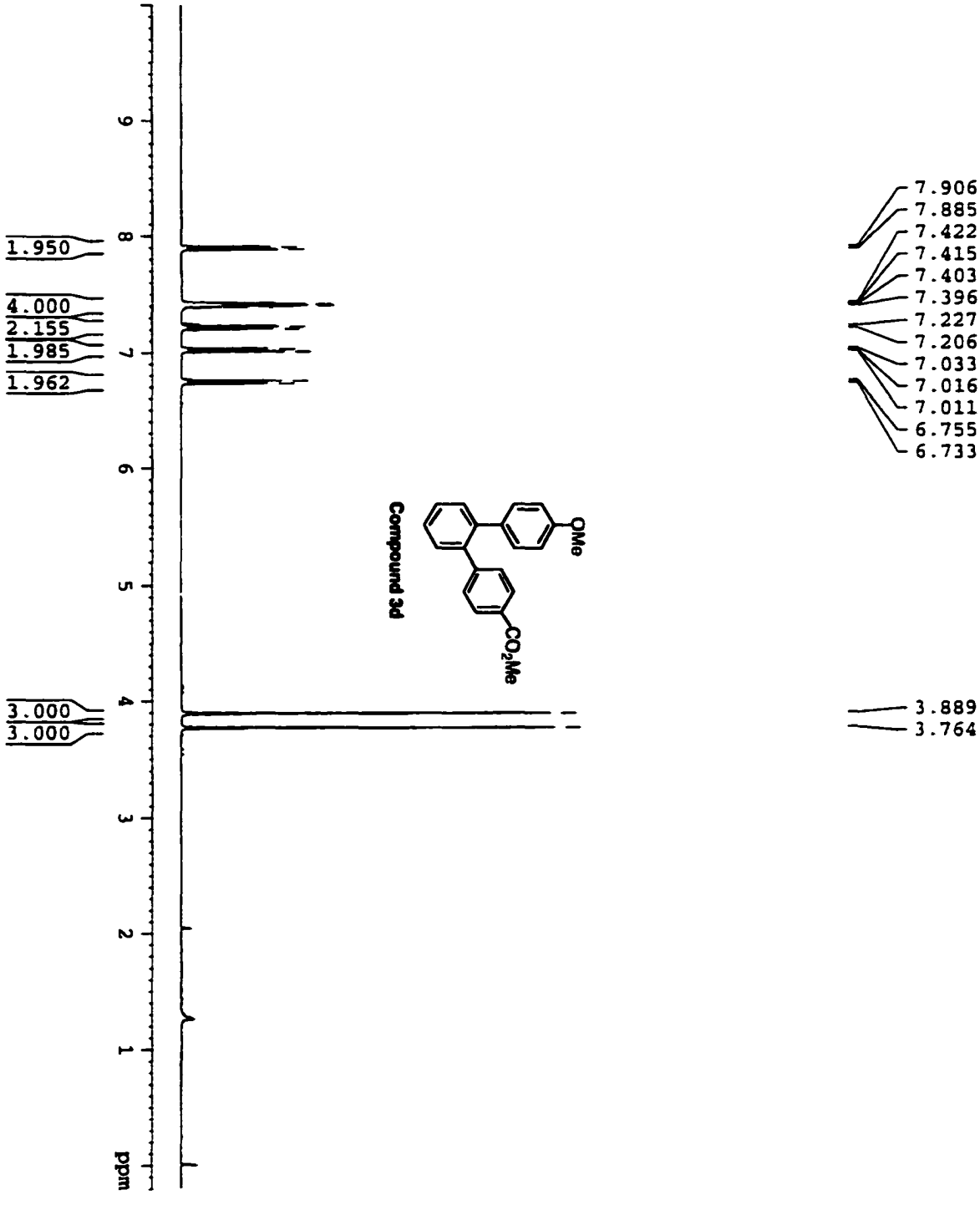

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
Compound 5c
CO2Et
165.026
150.919
143.377
140.590
130.839
129.886
129.237
129.023
128.204
128.151
98.096
77.411
77.094
76.776
61.439
14.407

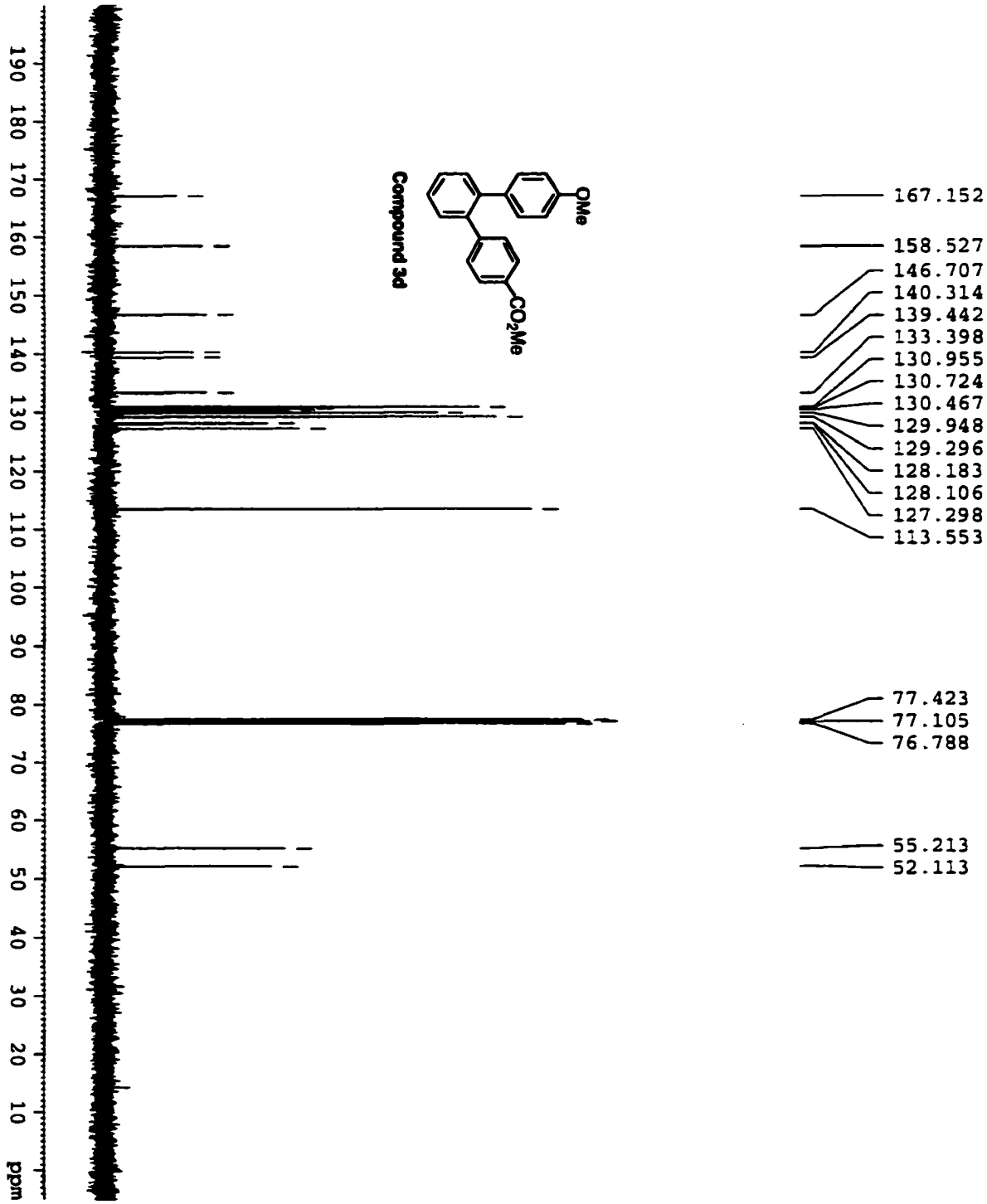

8.003
8.001
7.984
7.981
7.543
7.523
7.463
7.459
7.444
7.440
7.395
7.392
7.376
7.374
7.354
7.283
7.281
7.266
7.263
7.245
7.243
7.233
7.220
7.162
7.159
7.142
7.124
7.122
7.014
7.009
6.994
6.991
6.976
6.971
3.839
0.957
0.980
1.035
2.017
2.005
1.002
1.000
2.952
0.000
Compound 5e
Me
N
I
ppm

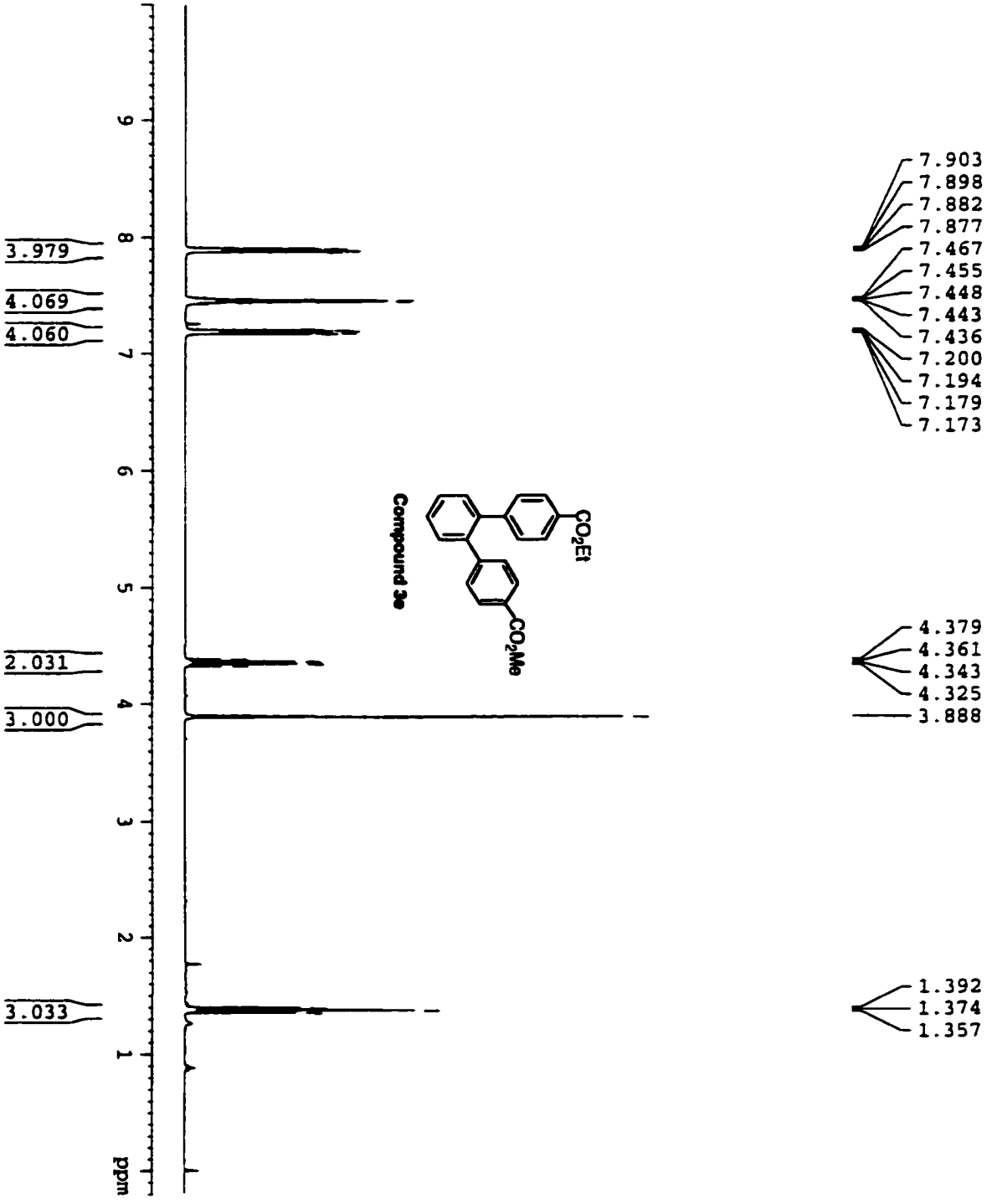

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
Compound 5e
Me
N
140.101
139.889
136.556
131.520
128.361
128.166
128.065
127.040
121.973
120.327
119.728
118.491
109.523
100.757
77.438
77.120
76.803
33.064

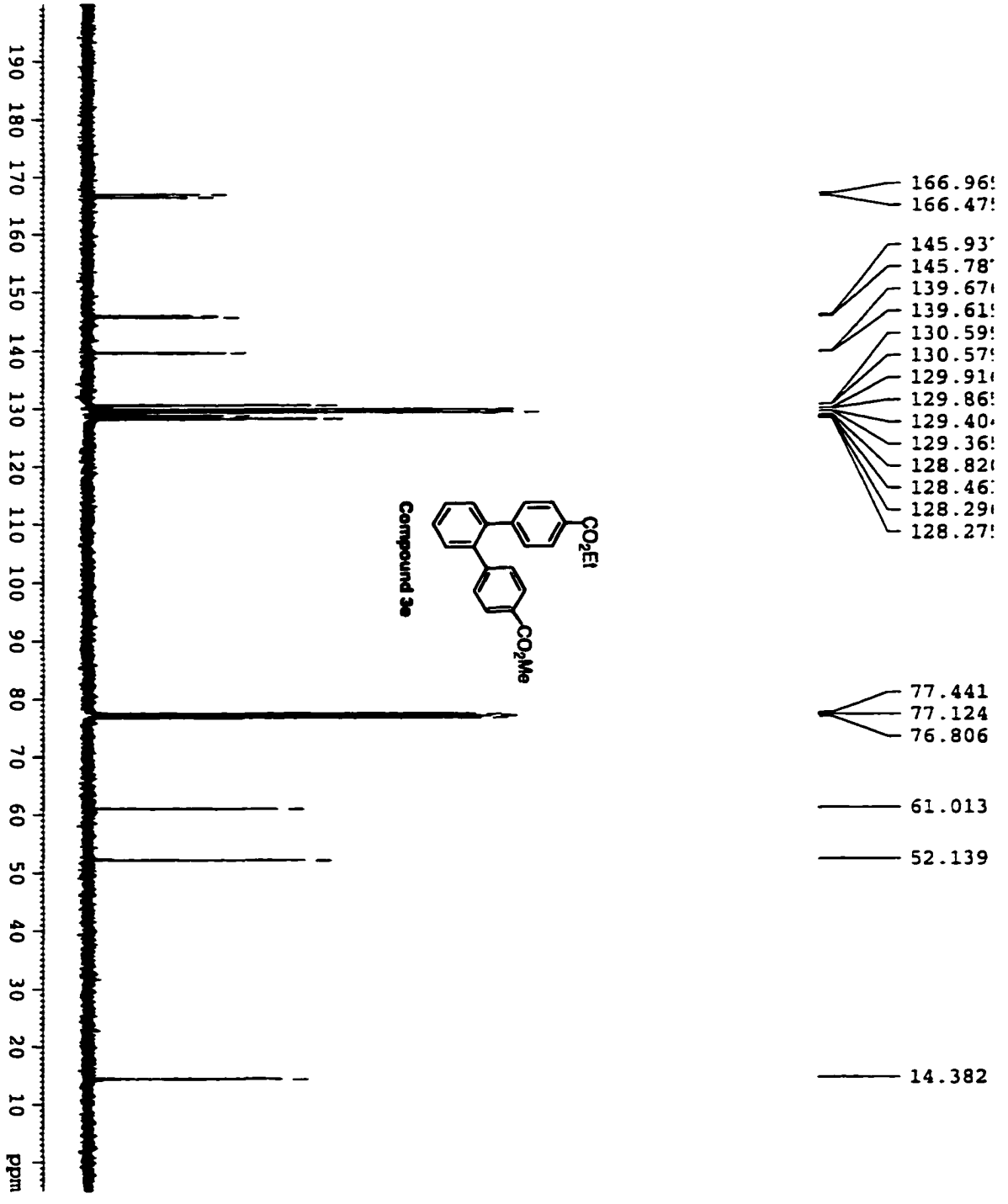

1.944
4.000
2.084
3.903
3.015
2.939
7.903
7.874
7.435
7.423
7.416
7.403
7.230
7.202
7.004
3.890
2.302
0.001
Compound 3a
Me
CO2Me
ppm

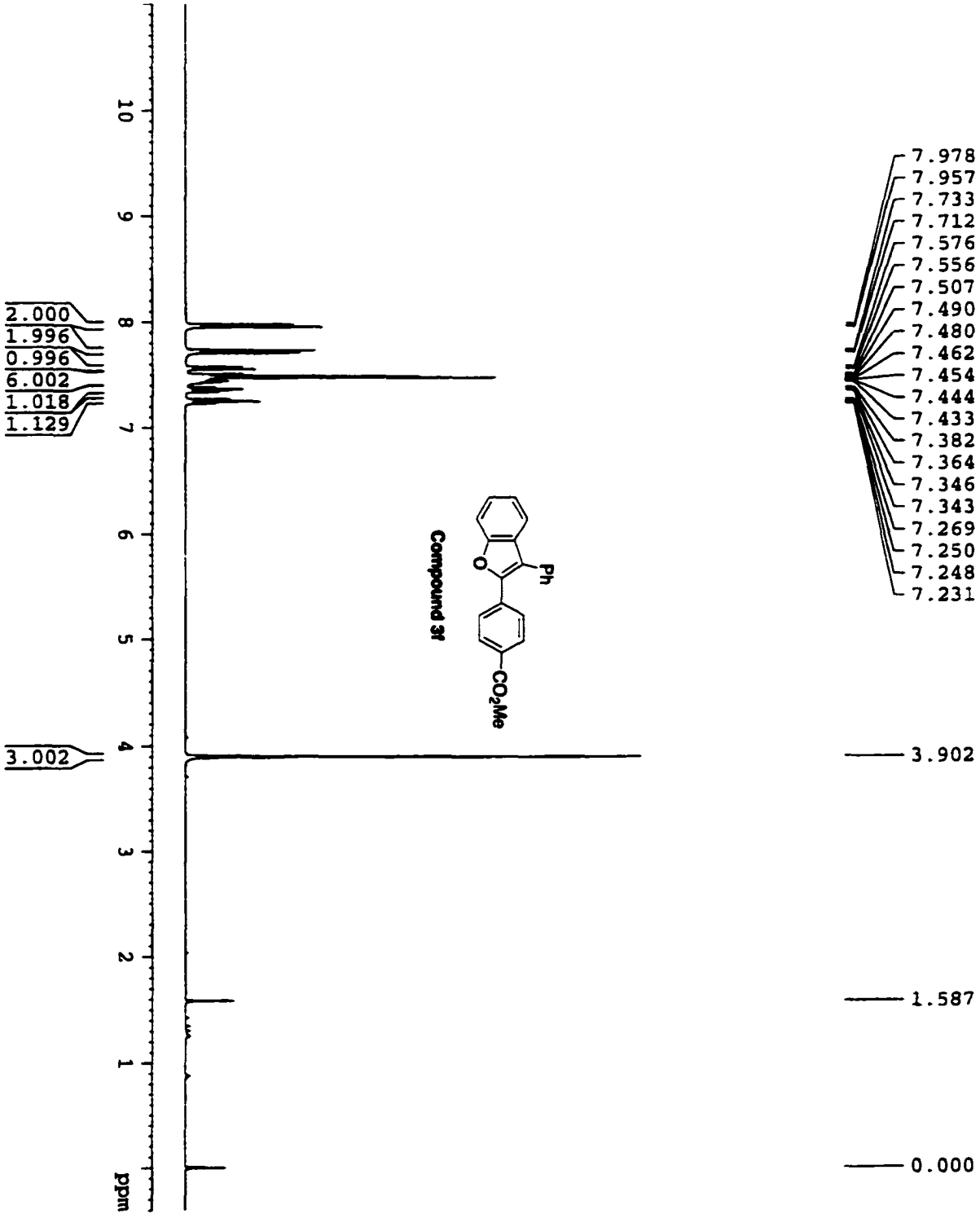

167.354
146.857
140.866
139.679
138.278
136.628
130.975
130.629
130.124
129.920
129.438
129.017
128.330
128.299
127.598
77.686
77.262
76.838
52.274
21.331
Me
CO2Me
Compound 3a
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

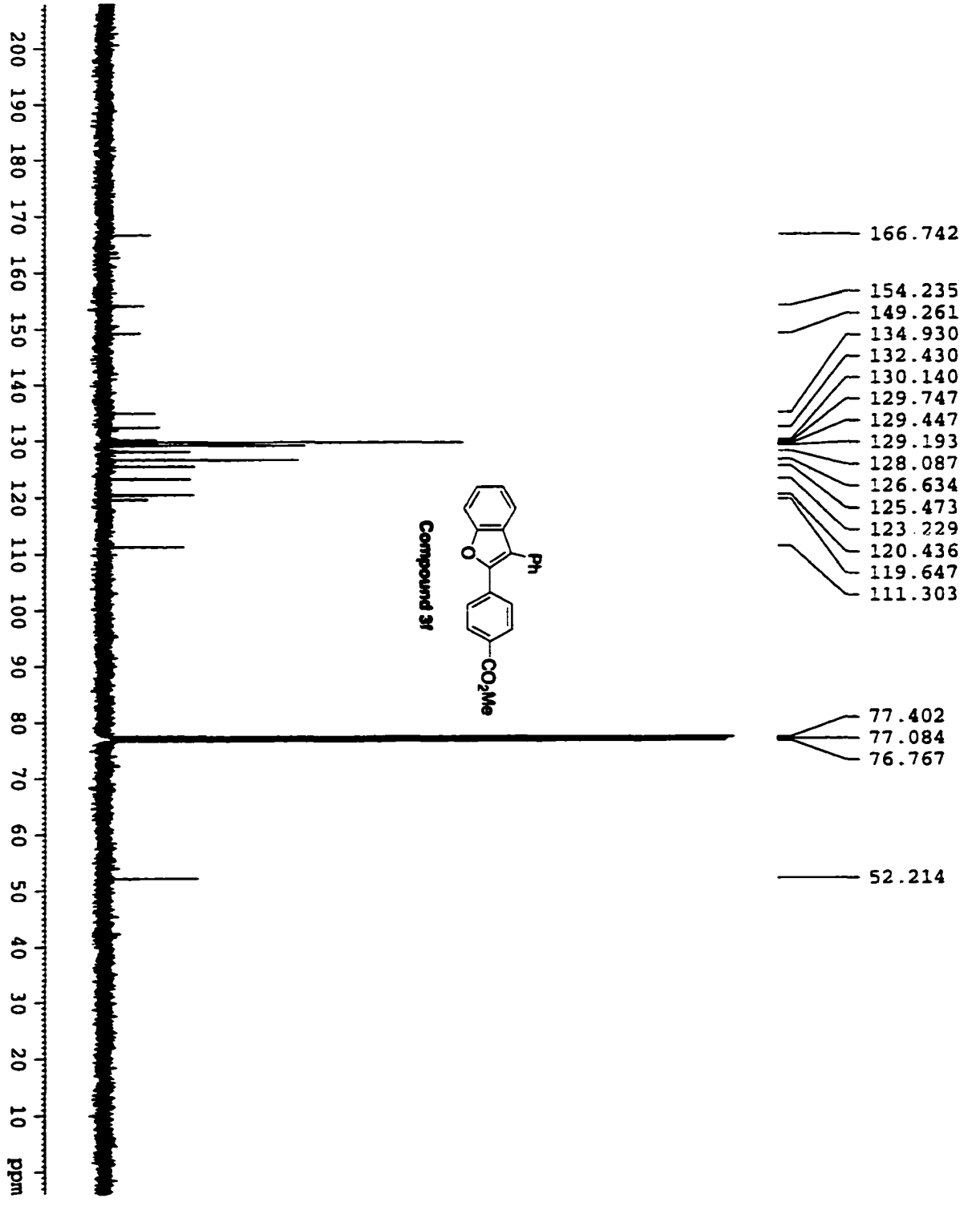

7.906
7.885
7.422
7.415
7.403
7.396
7.227
7.206
7.033
7.016
7.011
6.755
6.733
3.889
3.764
1.950
4.000
2.155
1.985
1.962
3.000
3.000
OMe
CO2Me
Compound 3d
ppm

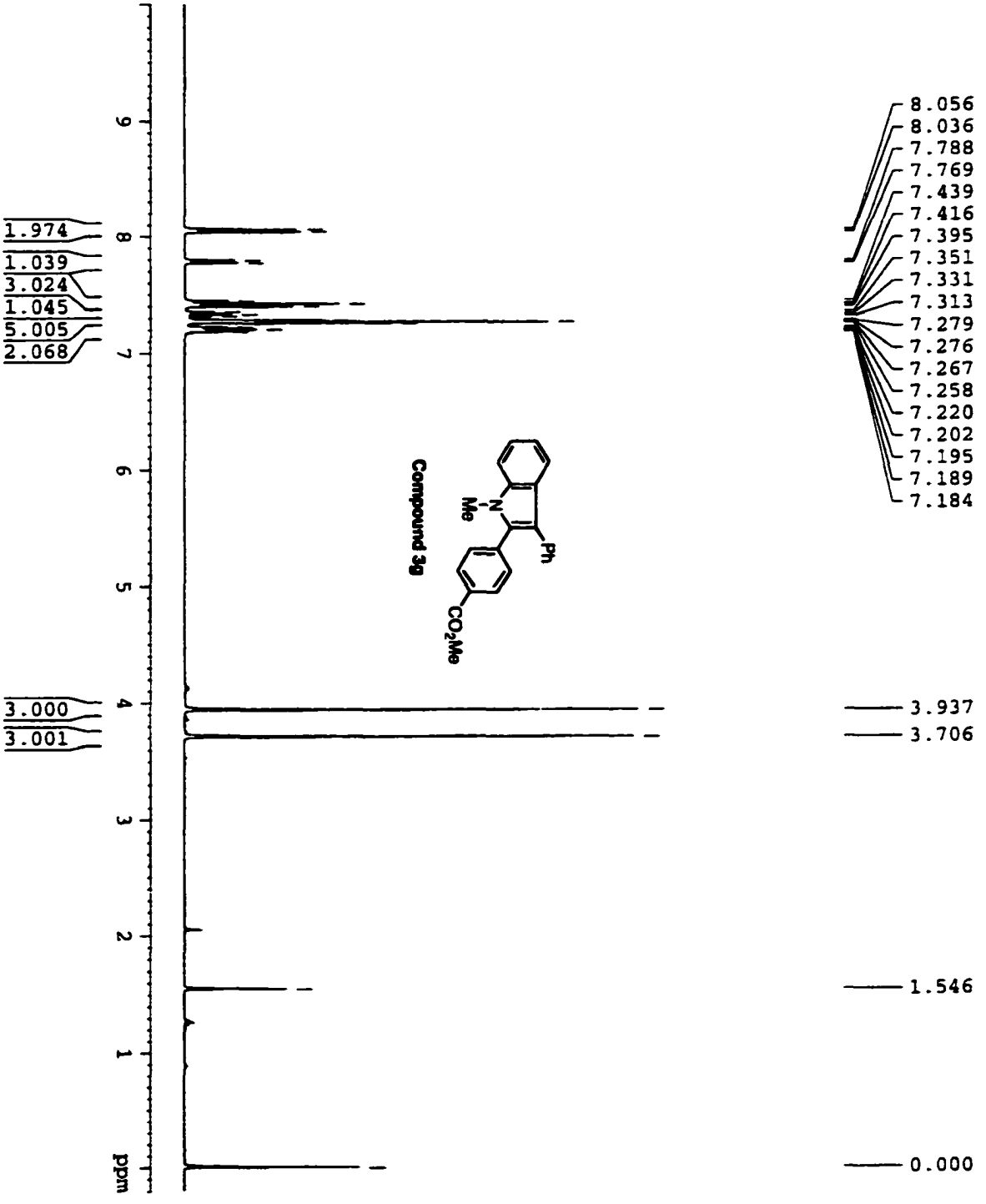

Compound 3d
OMe
CO2Me
167.152
158.527
146.707
140.314
139.442
133.398
130.955
130.724
130.467
129.948
129.296
128.183
128.106
127.298
113.553
77.423
77.105
76.788
55.213
52.113
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

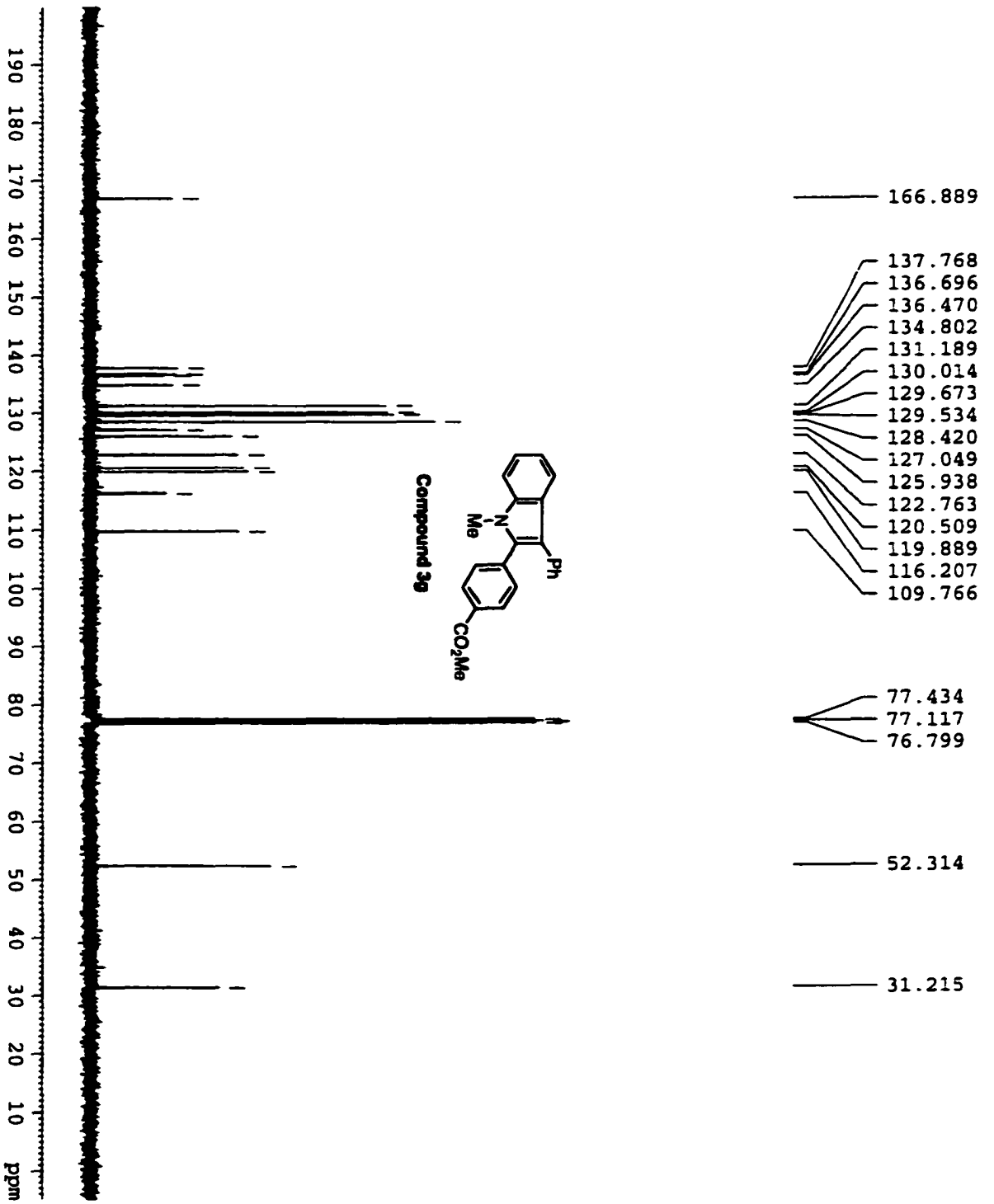

7.903
7.898
7.882
7.877
7.467
7.455
7.448
7.443
7.436
7.200
7.194
7.179
7.173
4.379
4.361
4.343
4.325
3.888
1.392
1.374
1.357
3.979
4.069
4.060
2.031
3.000
3.033
Compound 3e
CO2Et
CO2Me
ppm

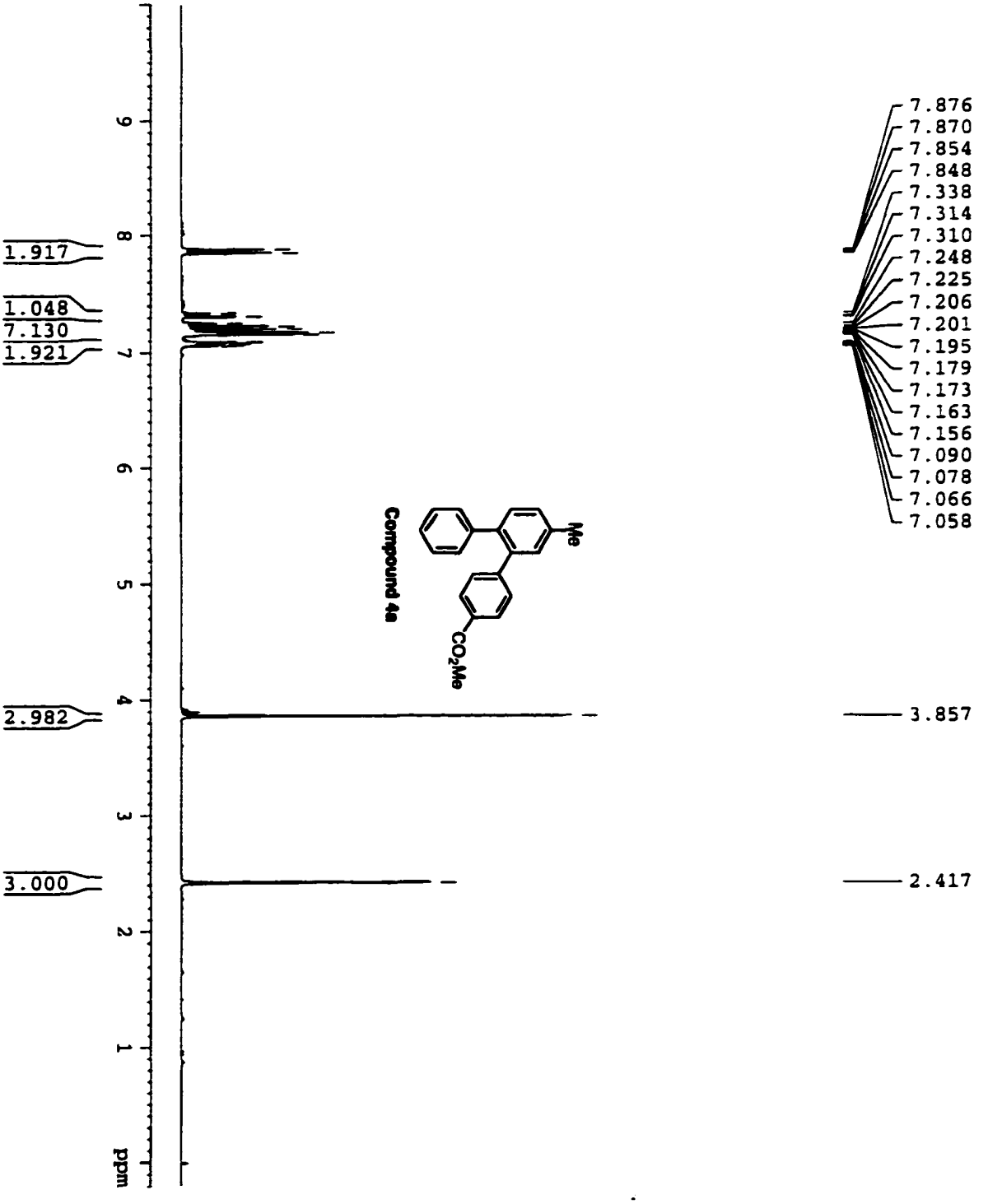

166.965
166.475
145.93
145.78
139.67
139.61
130.59
130.57
129.91
129.86
129.40
129.36
128.82
128.46
128.29
128.27
77.441
77.124
76.806
61.013
52.139
14.382
Compound 3e
CO2Et
CO2Me
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

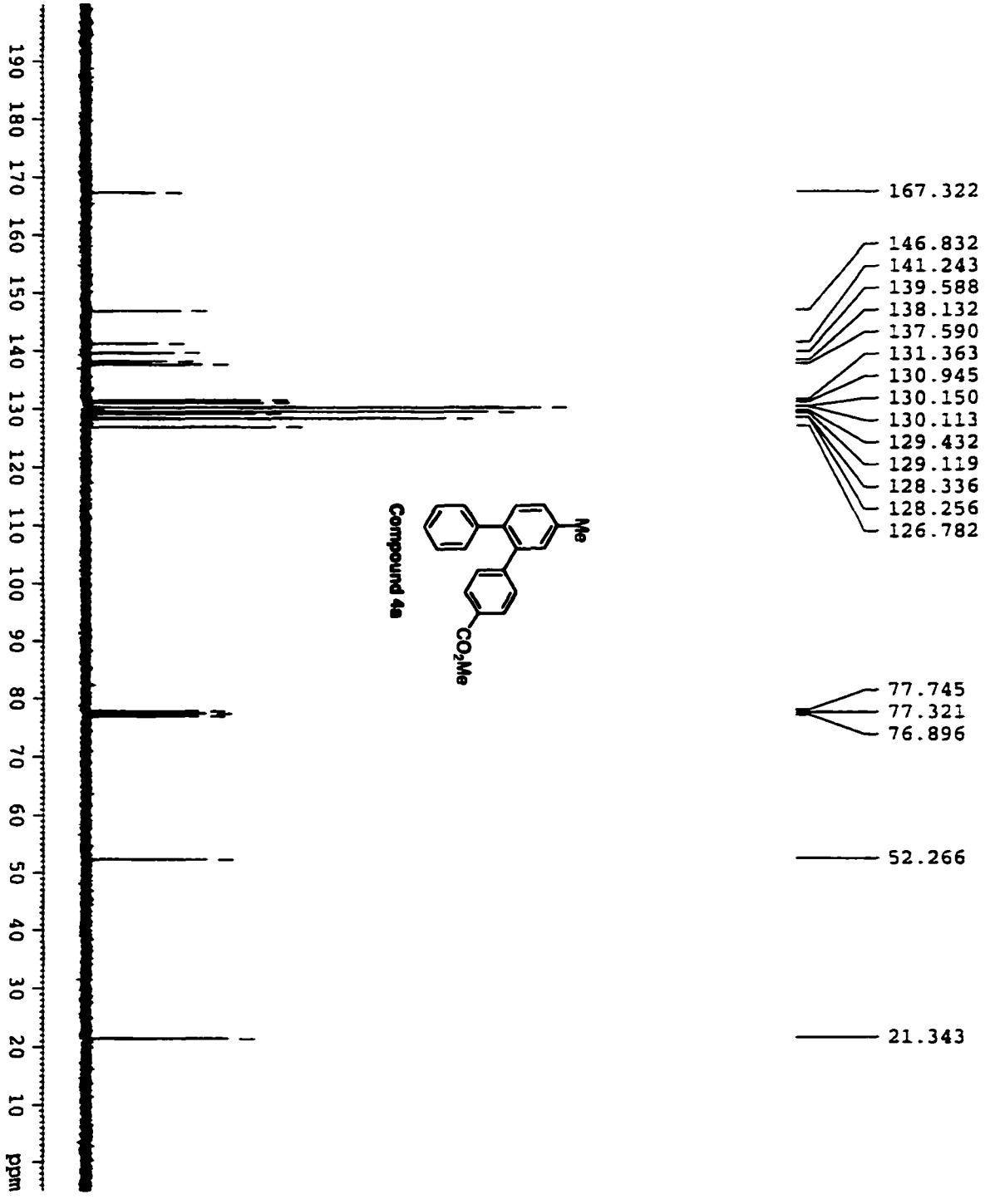

7.978
7.957
7.733
7.712
7.576
7.556
7.507
7.490
7.480
7.462
7.454
7.444
7.433
7.382
7.364
7.346
7.343
7.269
7.250
7.248
7.231
2.000
1.996
0.996
6.002
1.018
1.129
3.002
3.902
1.587
0.000
Compound 3f
Ph
CO2Me
ppm

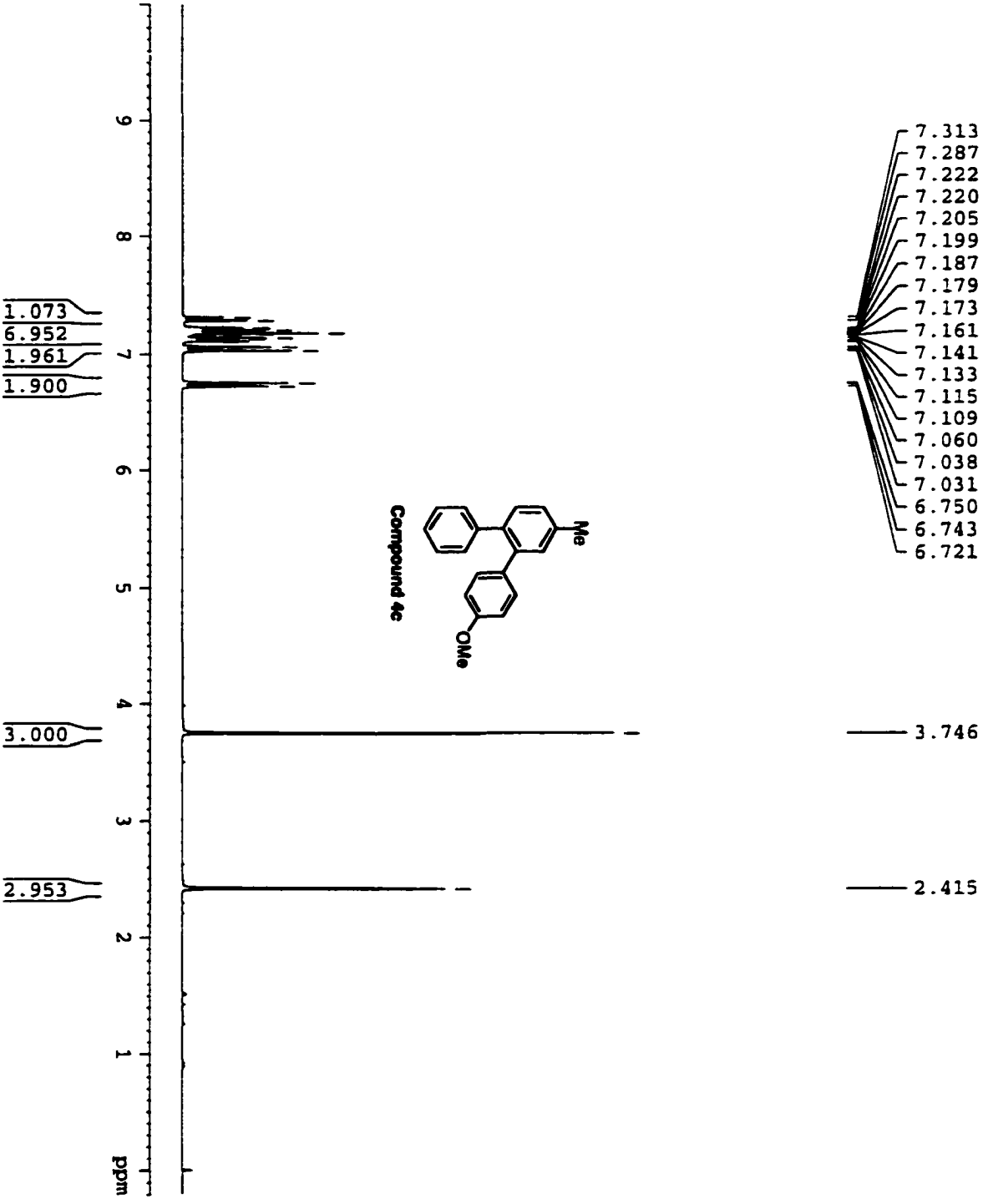

166.742
154.235
149.261
134.930
132.430
130.140
129.747
129.447
129.193
128.087
126.634
125.473
123.229
120.436
119.647
111.303
77.402
77.084
76.767
52.214
Compound 31
Ph
O
CO2Me
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

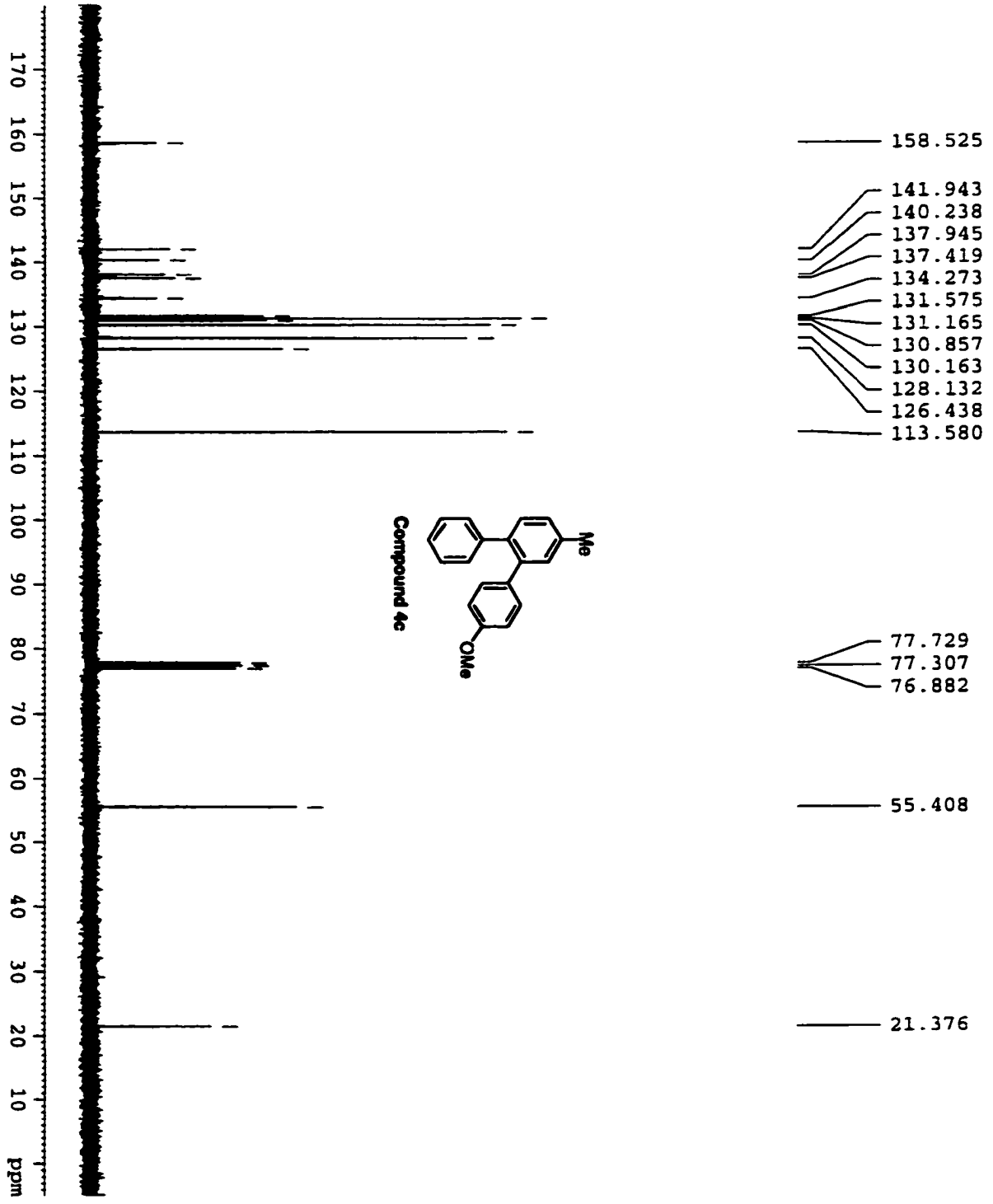

8.056
8.036
7.788
7.769
7.439
7.416
7.395
7.351
7.331
7.313
7.279
7.276
7.267
7.258
7.220
7.202
7.195
7.189
7.184
1.974
1.039
3.024
1.045
5.005
2.068
3.000
3.001
3.937
3.706
1.546
0.000
Compound 3g
Me
N
Ph
CO2Me
ppm

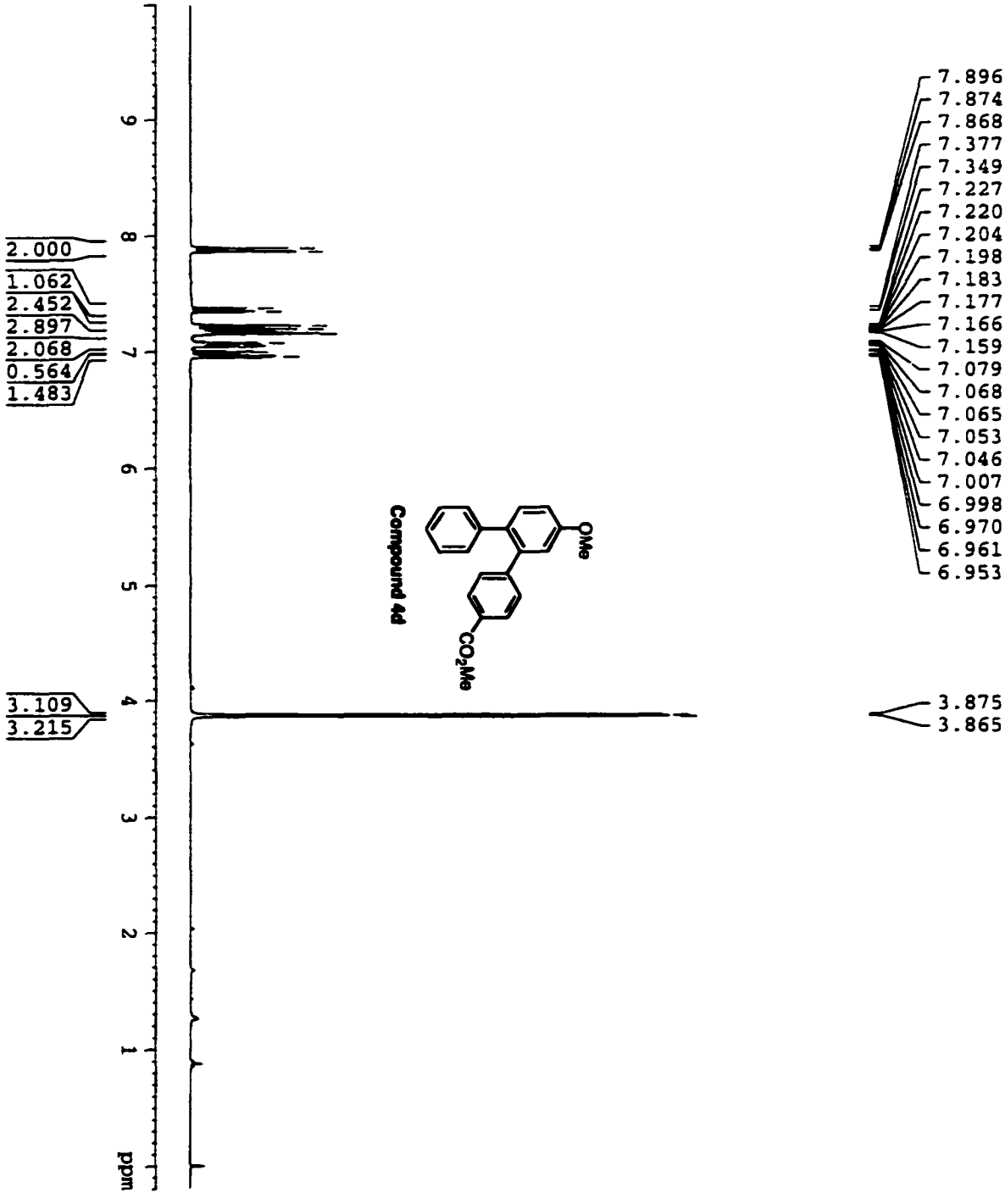

166.889
137.768
136.696
136.470
134.802
131.189
130.014
129.673
129.534
128.420
127.049
125.938
122.763
120.509
119.889
116.207
109.766
77.434
77.117
76.799
52.314
31.215
Compound 3g
Me
N
Ph
CO2Me
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

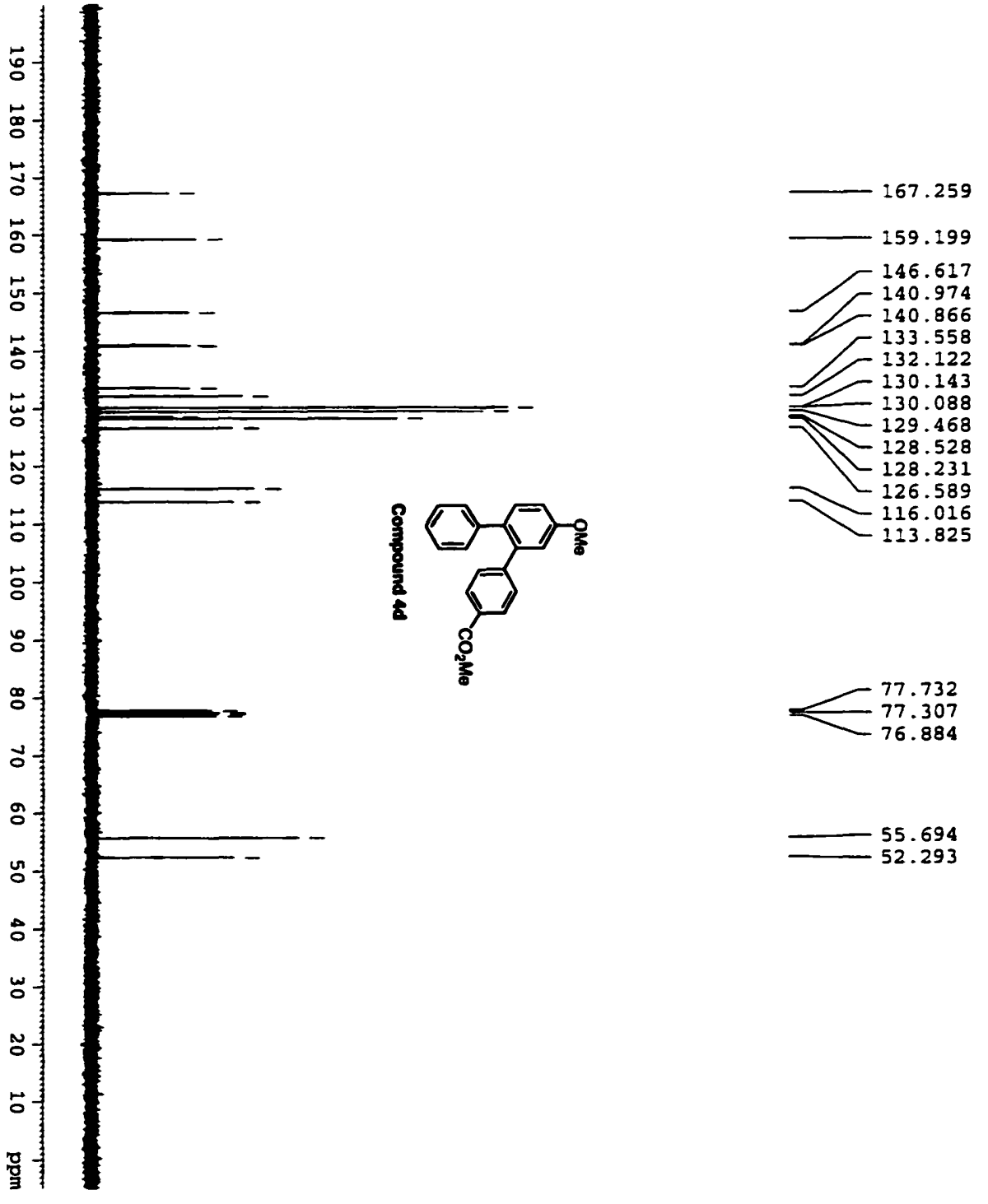

7.876
7.870
7.854
7.848
7.338
7.314
7.310
7.248
7.225
7.206
7.201
7.195
7.179
7.173
7.163
7.156
7.090
7.078
7.066
7.058
1.917
1.048
7.130
1.921
2.982
3.000
3.857
2.417
Me
CO2Me
Compound 4a
ppm

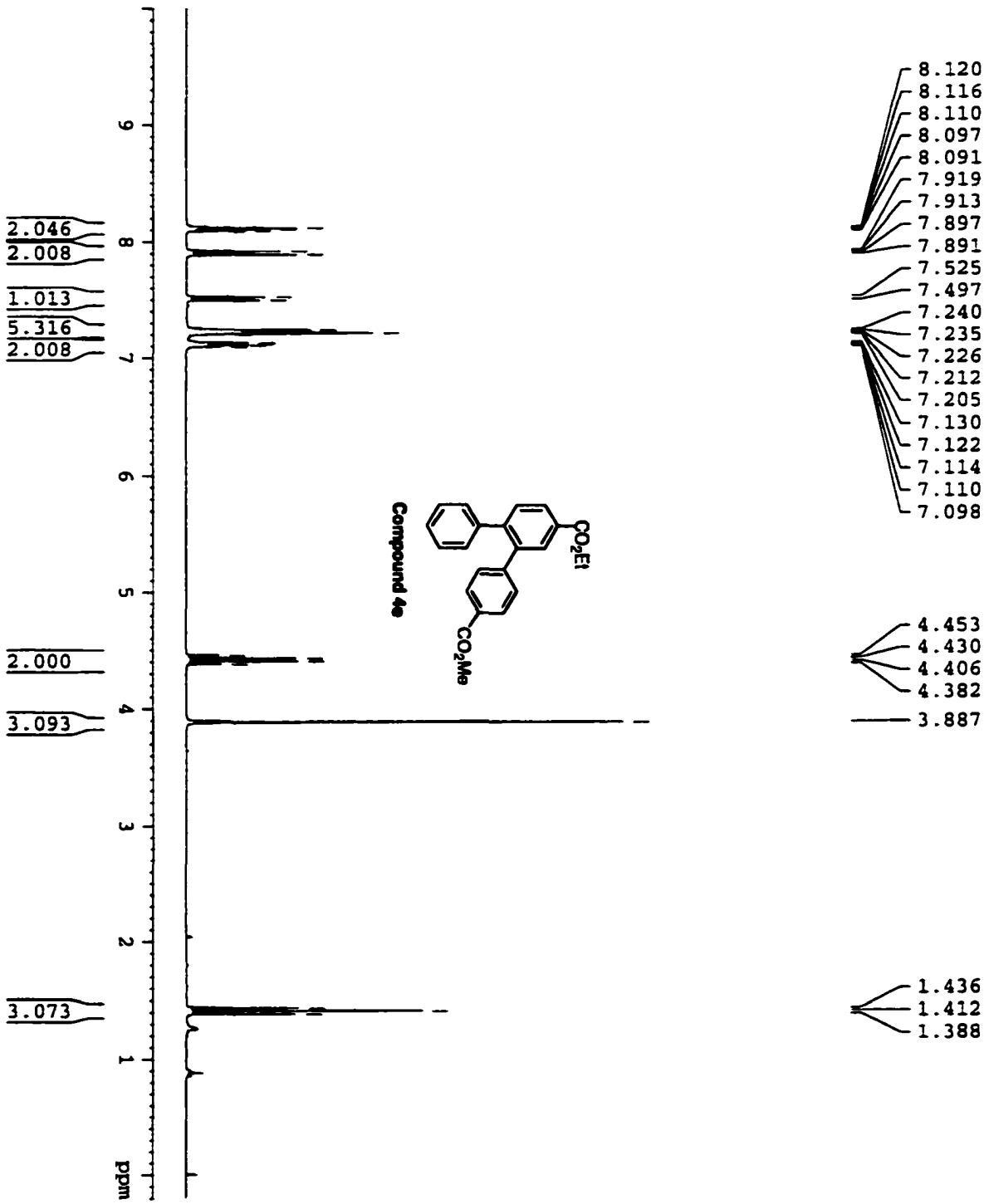

167.322
146.832
141.243
139.588
138.132
137.590
131.363
130.945
130.150
130.113
129.432
129.119
128.336
128.256
126.782
77.745
77.321
76.896
52.266
21.343
Compound 4a
Me
CO2Me
ppm

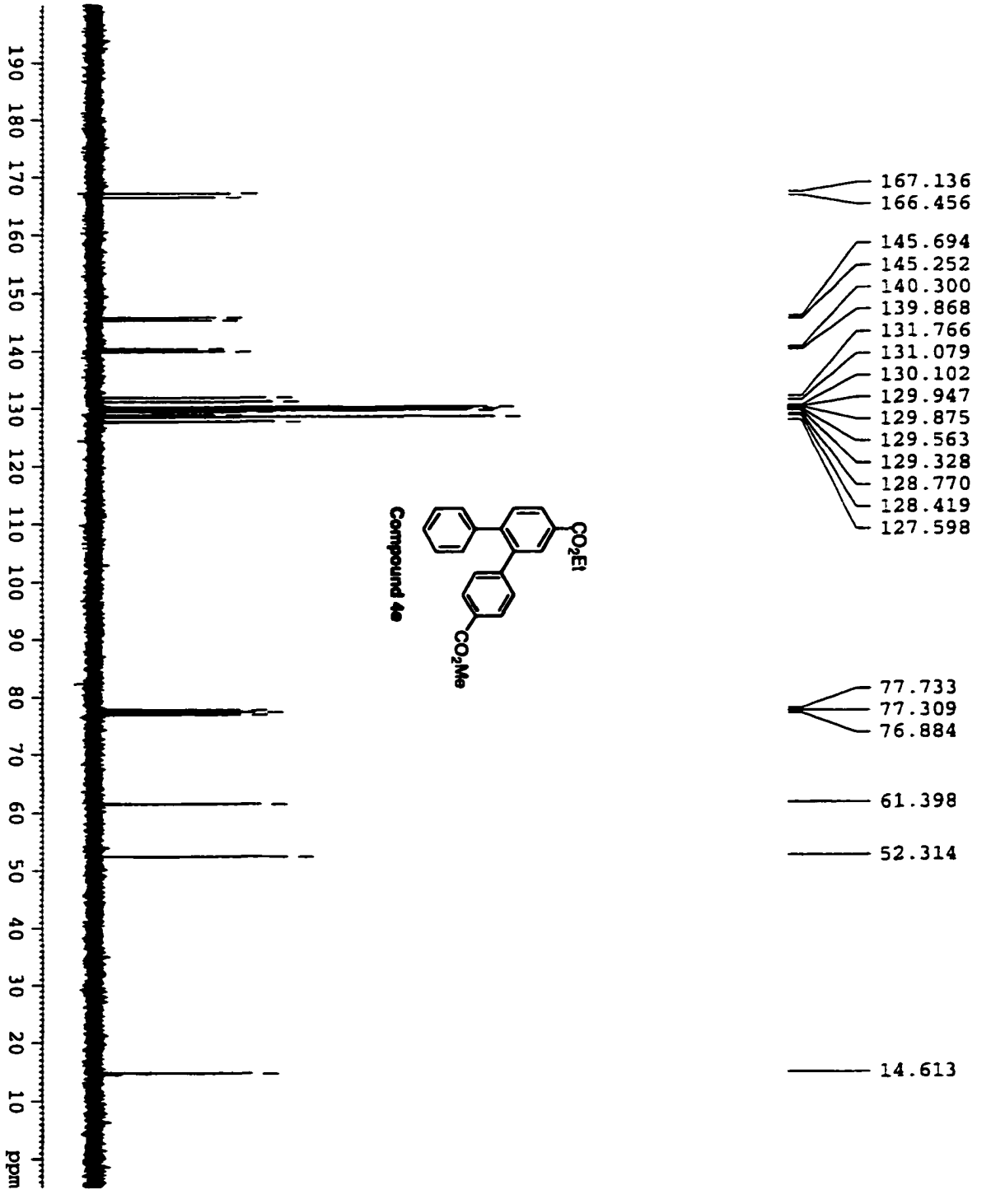

1.073
6.952
1.961
1.900
3.000
2.953
9
8
7
6
5
4
3
2
1
ppm
Compound 4c
Me
OMe
7.313
7.287
7.222
7.220
7.205
7.199
7.187
7.179
7.173
7.161
7.141
7.133
7.115
7.109
7.060
7.038
7.031
6.750
6.743
6.721
3.746
2.415

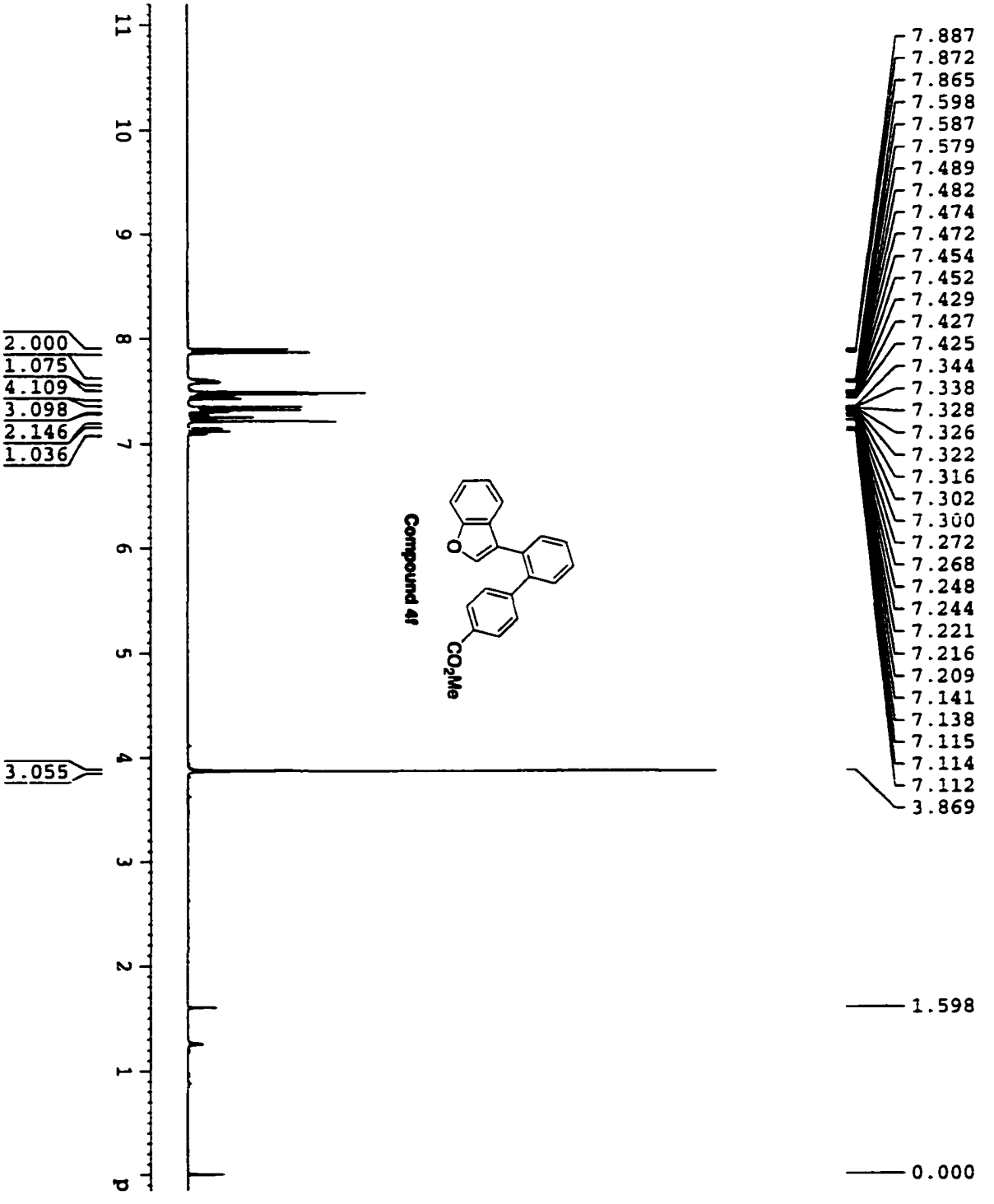

158.525
141.943
140.238
137.945
137.419
134.273
131.575
131.165
130.857
130.163
128.132
126.438
113.580
77.729
77.307
76.882
55.408
21.376
Compound 4c
Me
OMe
ppm

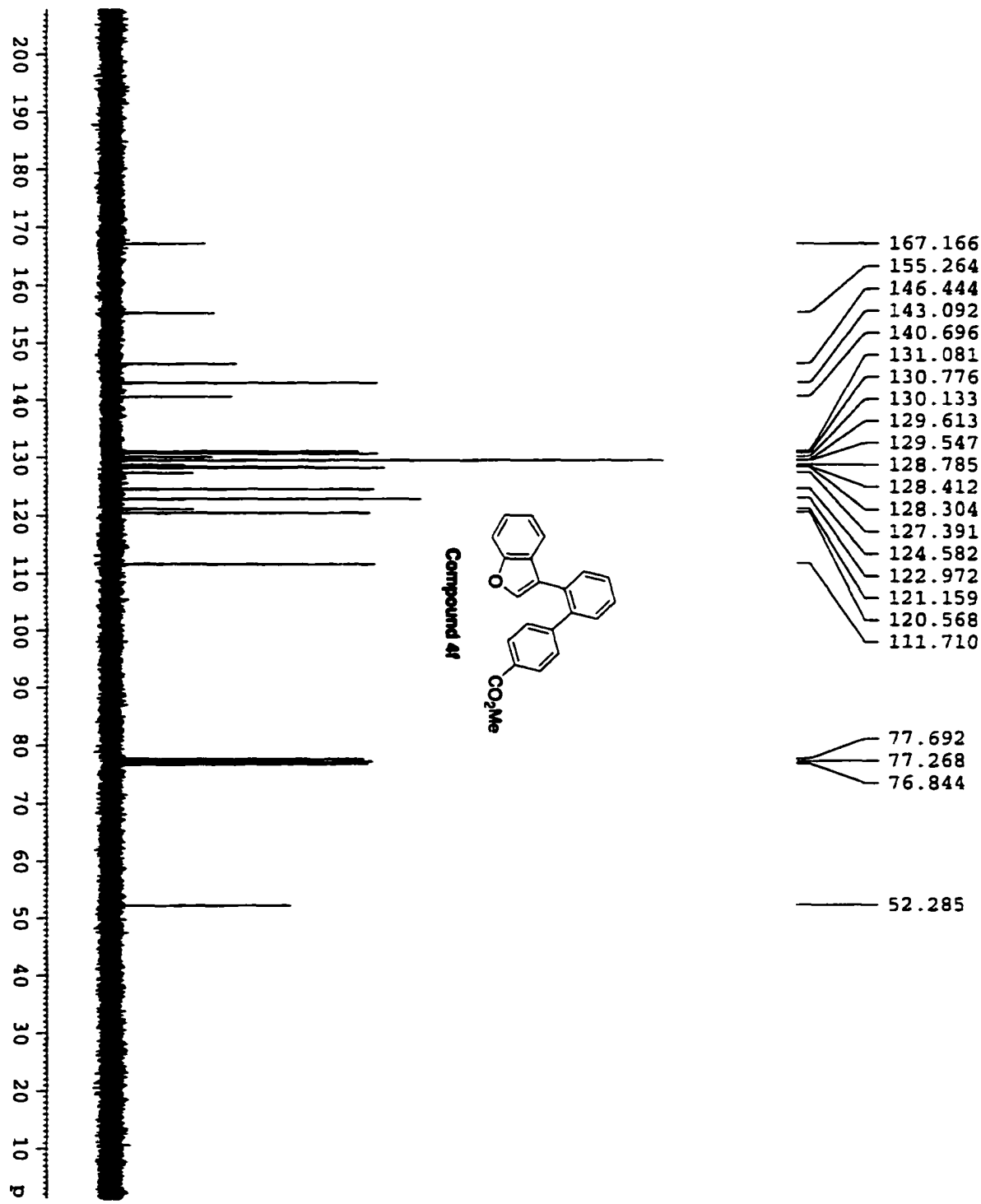

7.896
7.874
7.868
7.377
7.349
7.227
7.220
7.204
7.198
7.183
7.177
7.166
7.159
7.079
7.068
7.065
7.053
7.046
7.007
6.998
6.970
6.961
6.953
3.875
3.865
2.000
1.062
2.452
2.897
2.068
0.564
1.483
3.109
3.215
OMe
CO2Me
Compound 4d
ppm

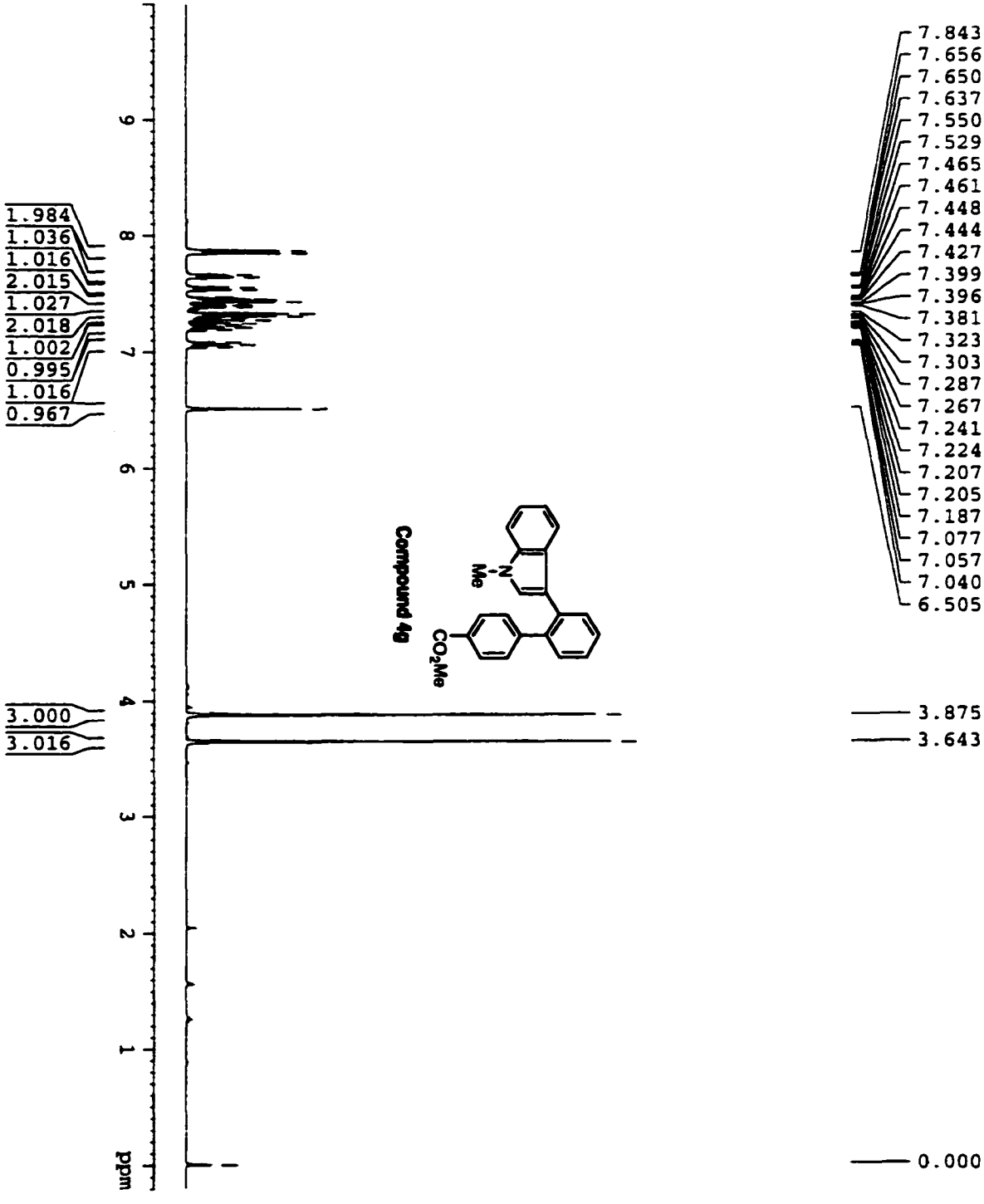

167.259
159.199
146.617
140.974
140.866
133.558
132.122
130.143
130.088
129.468
128.528
128.231
126.589
116.016
113.825
77.732
77.307
76.884
55.694
52.293
OMe
CO2Me
Compound 4d
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

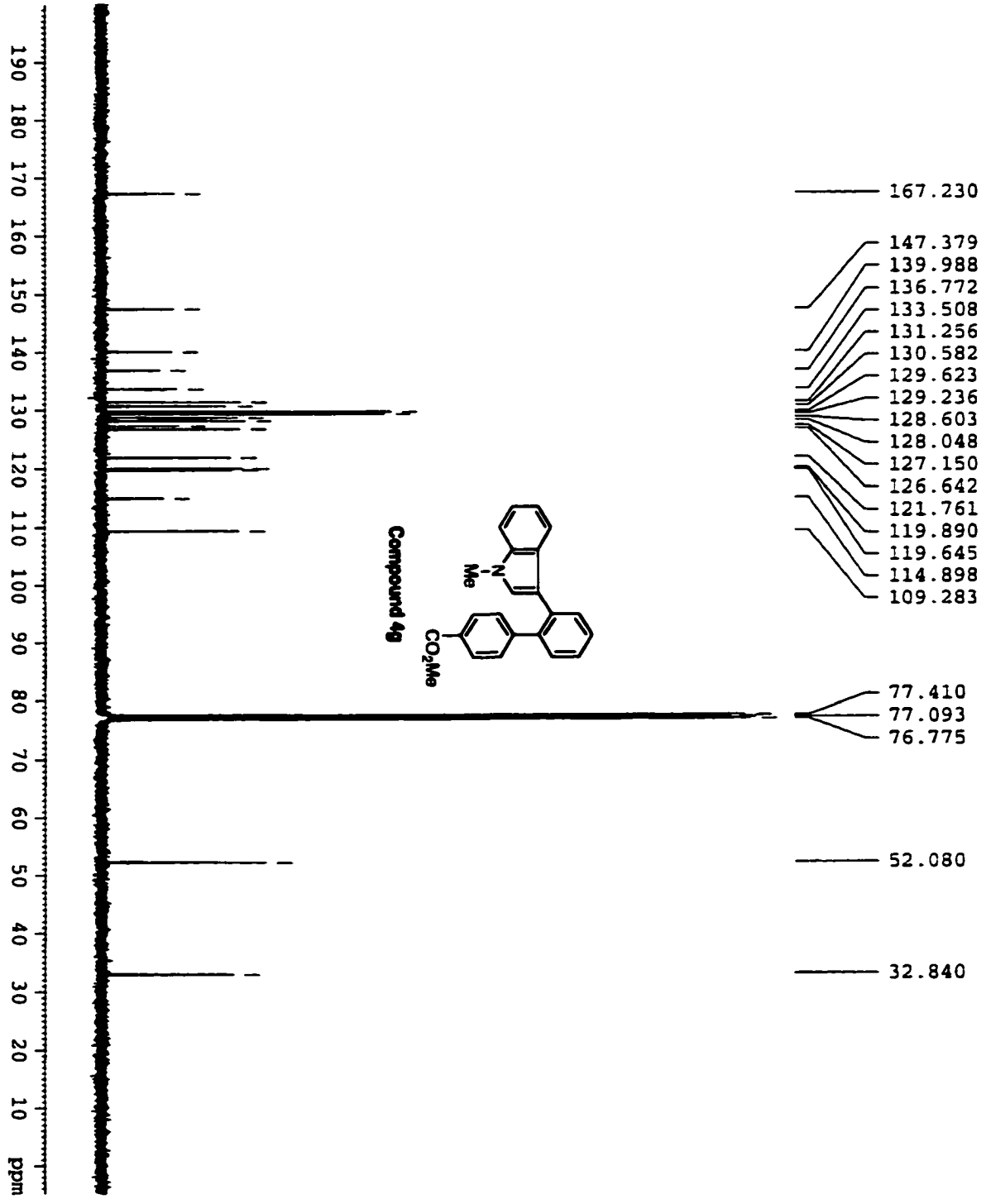

8.120
8.116
8.110
8.097
8.091
7.919
7.913
7.897
7.891
7.525
7.497
7.240
7.235
7.226
7.212
7.205
7.130
7.122
7.114
7.110
7.098
4.453
4.430
4.406
4.382
3.887
1.436
1.412
1.388
2.046
2.008
1.013
5.316
2.008
2.000
3.093
3.073
Compound 4e
CO2Et
CO2Me
ppm

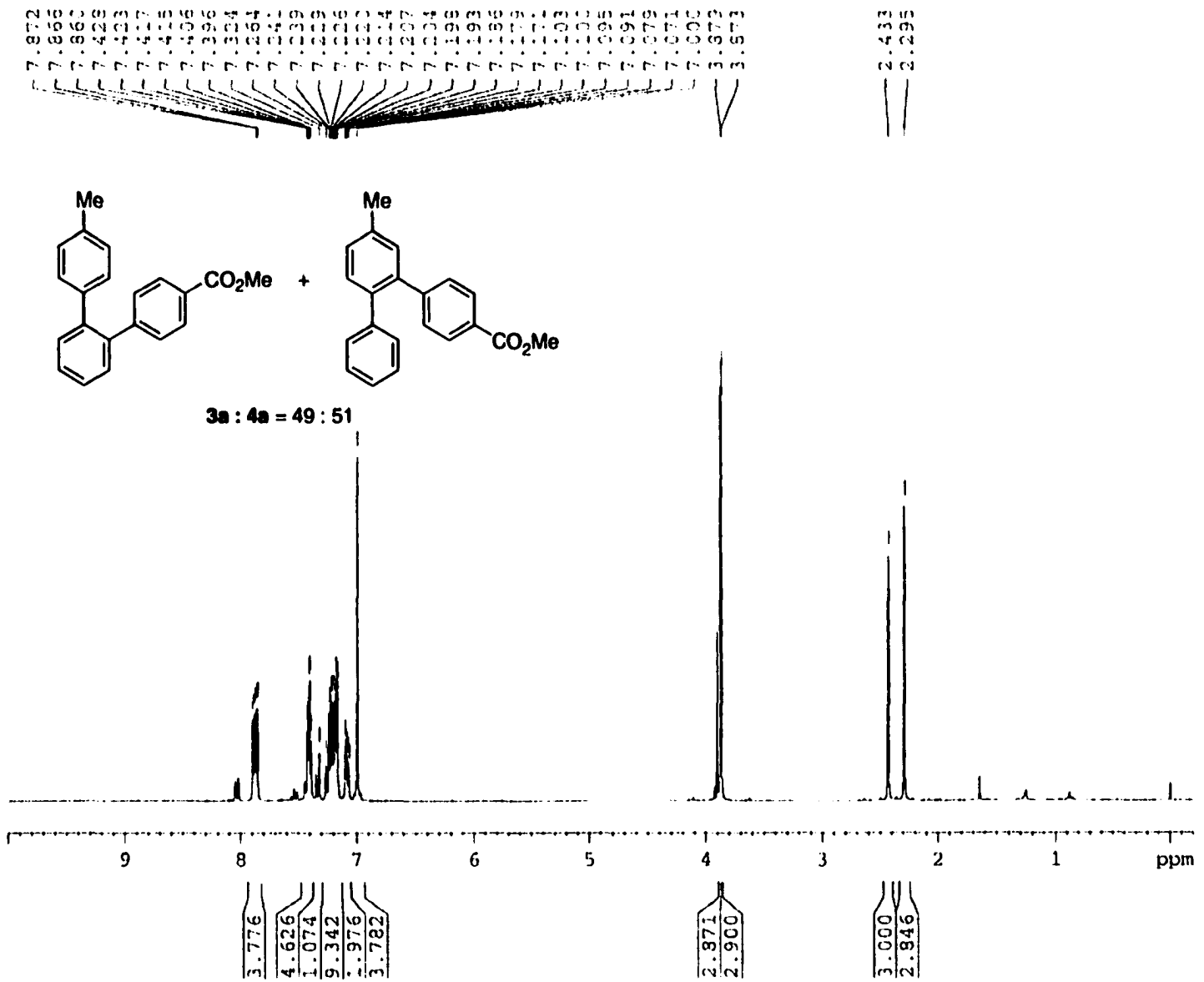

190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm
Compound 4e
CO2Et
CO2Me
167.136
166.456
145.694
145.252
140.300
139.868
131.766
131.079
130.102
129.947
129.875
129.563
129.328
128.770
128.419
127.598
77.733
77.309
76.884
61.398
52.314
14.613

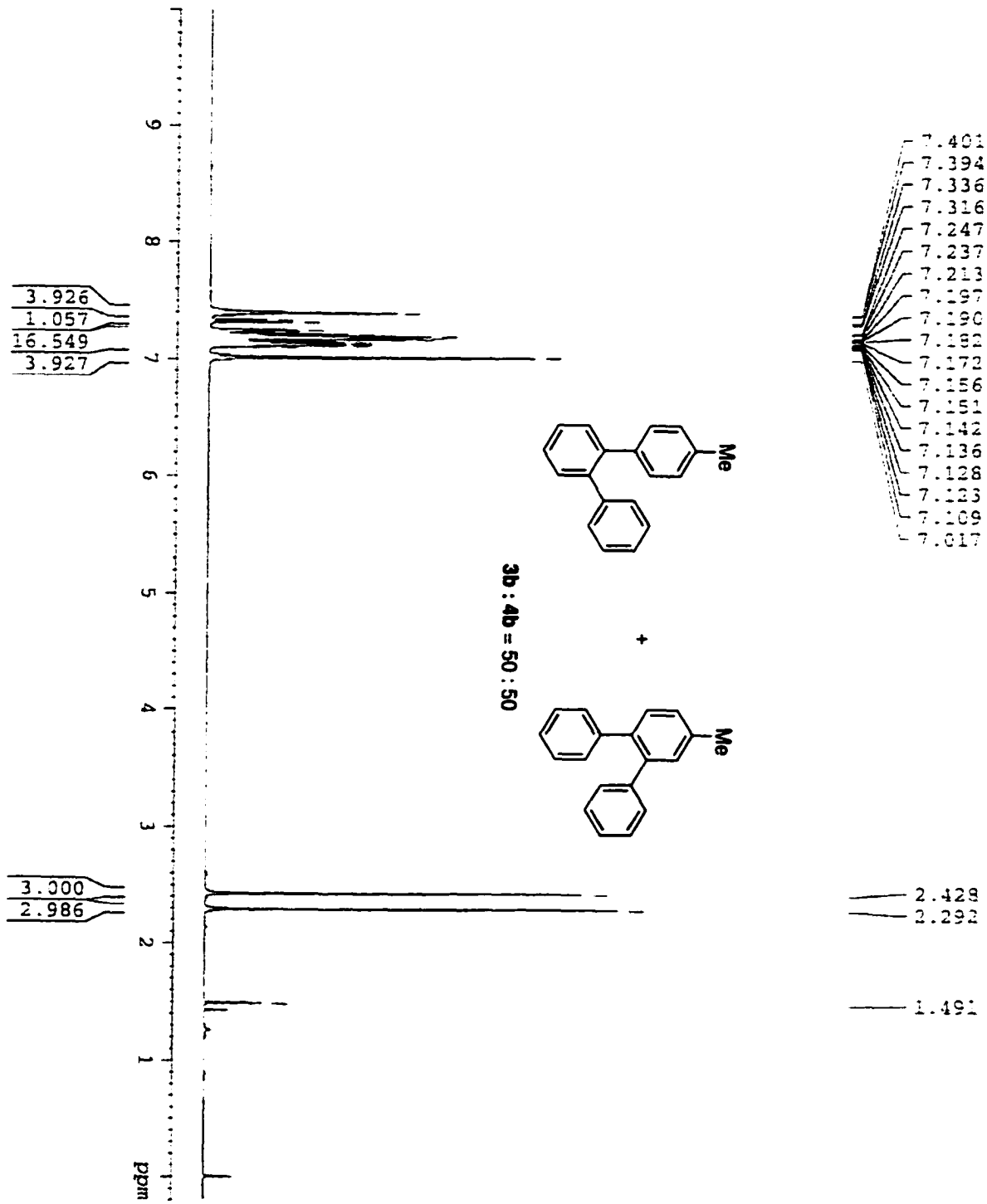

11
10
9
8
7
6
5
4
3
2
1
p
2.000
1.075
4.109
3.098
2.146
1.036
3.055
Compound 4f
O
CO2Me
7.887
7.872
7.865
7.598
7.587
7.579
7.489
7.482
7.474
7.472
7.454
7.452
7.429
7.427
7.425
7.344
7.338
7.328
7.326
7.322
7.316
7.302
7.300
7.272
7.268
7.248
7.244
7.221
7.216
7.209
7.141
7.138
7.115
7.114
7.112
3.869
1.598
0.000

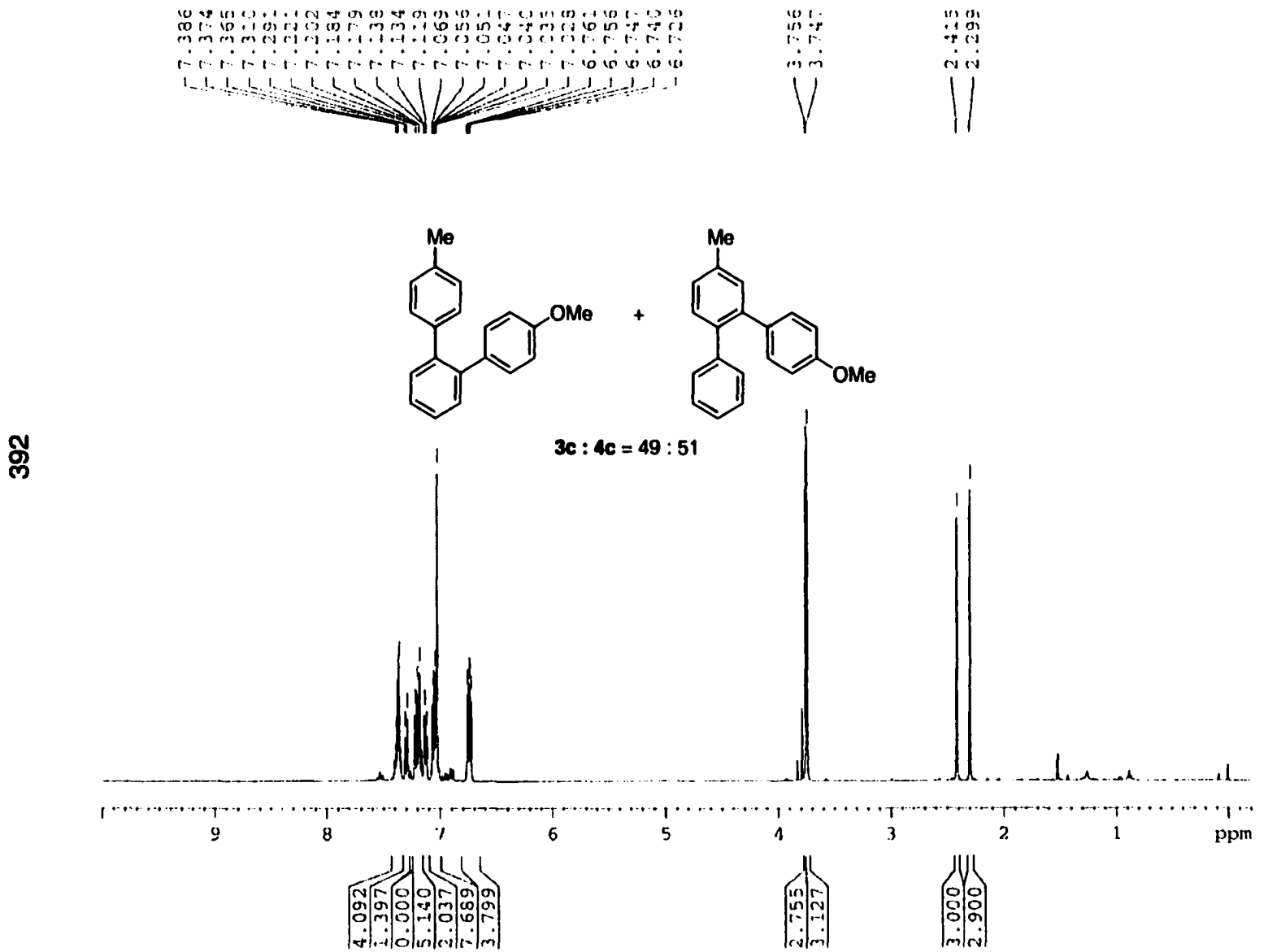

167.166
155.264
146.444
143.092
140.696
131.081
130.776
130.133
129.613
129.547
128.785
128.412
128.304
127.391
124.582
122.972
121.159
120.568
111.710
77.692
77.268
76.844
52.285
Compound 4f
O
CO2Me
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 p

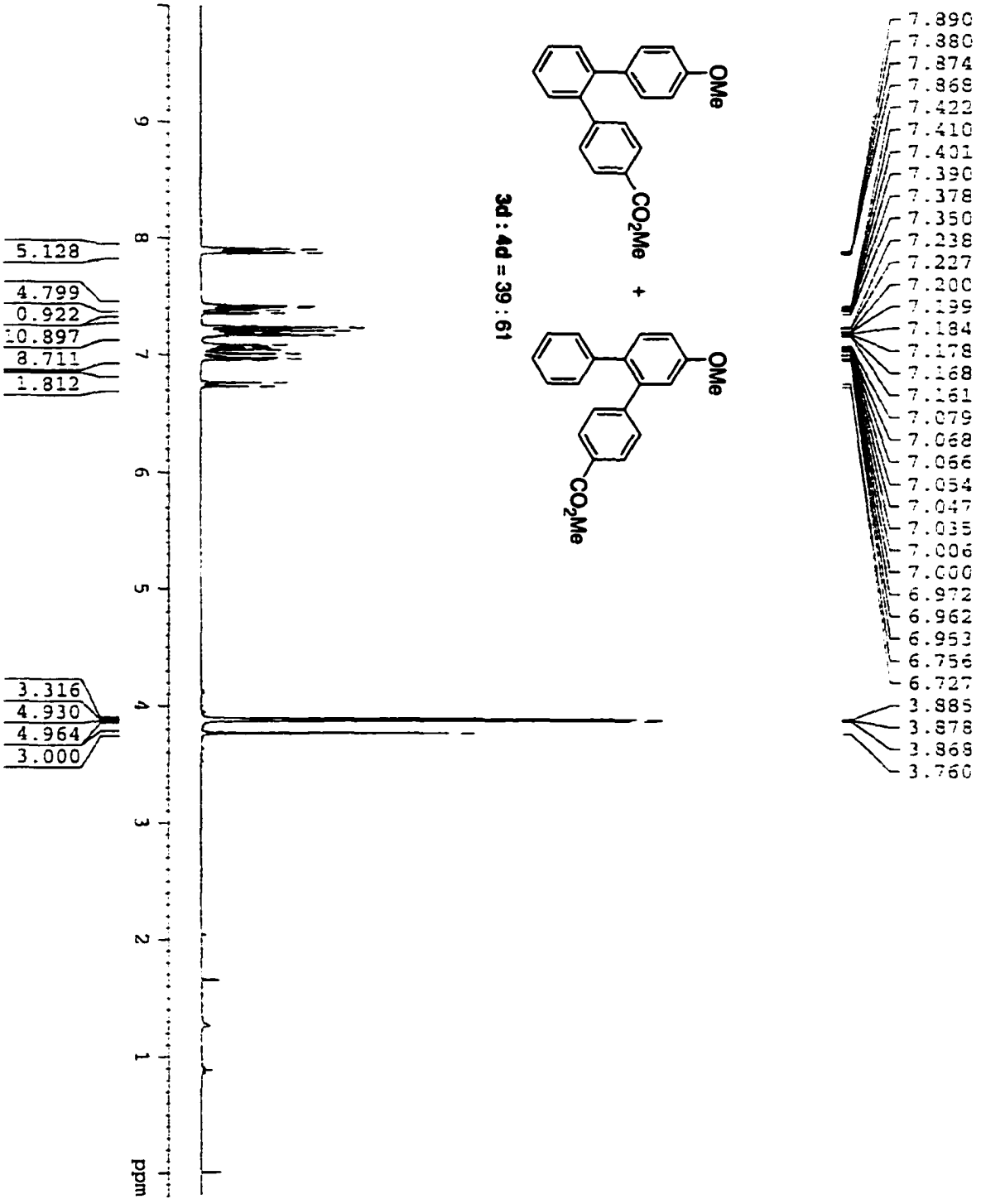

1.984
1.036
1.016
2.015
1.027
2.018
1.002
0.995
1.016
0.967
3.000
3.016
Compound 4g
Me
N
CO2Me
7.843
7.656
7.650
7.637
7.550
7.529
7.465
7.461
7.448
7.444
7.427
7.399
7.396
7.381
7.323
7.303
7.287
7.267
7.241
7.224
7.207
7.205
7.187
7.077
7.057
7.040
6.505
3.875
3.643
0.000
ppm

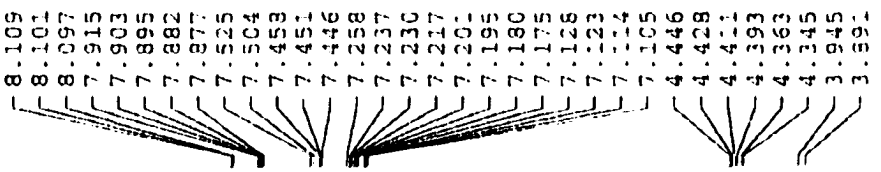

167.230
147.379
139.988
136.772
133.508
131.256
130.582
129.623
129.236
128.603
128.048
127.150
126.642
121.761
119.890
119.645
114.898
109.283
77.410
77.093
76.775
52.080
32.840
Compound 4g
Me
N
CO2Me
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

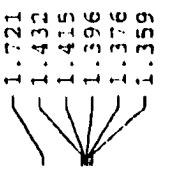

Me
CO2Me
+
Me
CO2Me
3a : 4a = 49 : 51
9
8
7
6
5
4
3
2
1
ppm
3.776
4.626
1.074
9.342
2.976
3.782
2.871
2.900
3.000
2.846

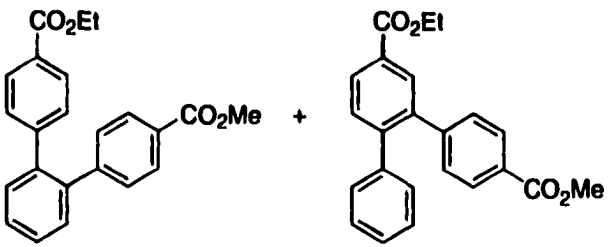

3.926
1.057
16.549
3.927
3.000
2.986
7.401
7.394
7.336
7.316
7.247
7.237
7.213
7.197
7.190
7.182
7.172
7.156
7.151
7.142
7.136
7.128
7.123
7.109
7.017
2.428
2.292
1.491
Me
Me
3b : 4b = 50 : 50
ppm


Me
OMe
+
Me
OMe
3c : 4c = 49 : 51
9
8
7
6
5
4
3
2
1
ppm
4.092
1.397
0.000
5.140
2.037
7.689
3.799
2.755
3.127
3.000
2.900


7.890
7.880
7.874
7.868
7.422
7.410
7.401
7.390
7.378
7.350
7.238
7.227
7.200
7.199
7.184
7.178
7.168
7.161
7.079
7.068
7.066
7.054
7.047
7.035
7.006
7.000
6.972
6.962
6.953
6.756
6.727
3.885
3.878
3.868
3.760
OMe
CO2Me
+
OMe
CO2Me
3d : 4d = 39 : 61
5.128
4.799
0.922
10.897
8.711
1.812
3.316
4.930
4.964
3.000
9
8
7
6
5
4
3
2
1
ppm


8.109
8.101
8.097
7.915
7.903
7.895
7.882
7.525
7.504
7.453
7.451
7.446
7.258
7.237
7.230
7.217
7.195
7.180
7.175
7.148
7.123
7.105
4.446
4.428
4.411
4.393
4.363
4.345
3.945


1.721
1.432
1.415
1.396
1.376
1.359


CO2Et
CO2Me
+
CO2Et
CO2Me

3e : 4e = 34 : 66

9
8
7
6
5
4
3
2
1
0 ppm
2.359
4.057
3.155
7.272
1.979
1.996
1.054
4.506
2.290
1.129
1.197