1-1-2000

Synthesis of isoquinolines by electrophilic ring closure of iminoalkynes

Jack Alan Hunter
Iowa State University

Synthesis of isoquinolines by electrophilic ring closure of iminoalkynes

by

Jack Alan Hunter

A thesis submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE

Major: Organic Chemistry

Major Professor: Richard C. Larock

Iowa State University

Ames, Iowa

2000

Graduate College

Iowa State University

This is to certify that the Master's thesis of

Jack Alan Hunter

has met the thesis requirements of Iowa State University

Signatures have been redacted for privacy

To my parents, Roy and Ruth, for your support

and encouragement. To my brother, Eddie, for being there.

Thank you all for believing in me.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS v

ABSTRACT vii

GENERAL INTRODUCTION 1

Thesis Organization 1

SYNTHESIS OF ISOQUINOLINES BY ELECTROPHILIC RING CLOSURE OF IMINOALKYNES 3

Abstract 3
Introduction 3
Results and Discussion 6
Experimental Section 36
Acknowledgment 46
References 47

GENERAL CONCLUSIONS 49

APPENDIX. ^{1}H AND ^{13}C NMR SPECTRA 50

ACKNOWLEDGMENTS 87

LIST OF ABBREVIATIONS

br	broad
br s	broad singlet
t-Bu	*tert*-butyl
cat.	catalytic
d	doublet
dd	doublet of doublets
ddd	doublet of doublets of doublets
dddd	doublet of doublets of doublets of doublets
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
dt	doublet of triplets
eq	equation
equiv	equivalent
EtOAc	ethyl acetate
g	gram(s)
h	hour(s)
HRMS	high resolution mass spectroscopy
Hz	Hertz
IR	infrared
m	multiplet
mL	milliliters

mmol	millimole
mol	mole
mp	melting point
MS	mass spectrometry
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance
o	ortho
OAc	acetate
o-tol	*o*-tolyl
p	para
Ph	phenyl
PPh_3	triphenylphosphine
q	quartet
s	singlet
sat	saturated
t	triplet
TBAC	tetra-*n*-butylammonium chloride
tert	tertiary
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet

ABSTRACT

A variety of substituted isoquinolines have been synthesized in good to excellent yields by the electrophilic ring closure of iminoalkynes in the presence of various external electrophiles. The best results were obtained with an excess of the electrophile, plus 3 equiv of sodium bicarbonate as a base when needed, at room temperature with either acetonitrile or methylene chloride as the solvent. This electrophilic ring closure is highly effective when an aryl- or alkenyl-substituted alkyne is utilized. Other acetylenes fail to undergo this ring closure.

Mono-substituted isoquinolines have been prepared in good to excellent yields by the silver-catalyzed cyclization of various iminoalkynes. The best results were obtained using 5 mol % silver nitrate at 50 °C in chloroform. Aryl-, vinylic-, and alkyl-substituted iminoalkynes undergo this silver-catalyzed cyclization in excellent yields.

GENERAL INTRODUCTION

In recent years, the isoquinoline ring system has received a lot of attention in organic synthesis. That interest arises from the fact that numerous natural products contain the isoquinoline ring system in their backbone.[1]

The Larock group has previously shown that disubstituted isoquinolines and pyridine heterocycles can be synthesized by the palladium-catalyzed annulation of the *tert*-butyl imines of *o*-iodobenzaldehyde and 3-halo-2-alkenals respectively onto internal alkynes.[2] Also it has been shown by Larock and Roesch that mono-substituted isoquinolines and pyridines can be synthesized by the palladium-catalyzed coupling of terminal acetylenes onto the *tert*-butyl imine of *o*-iodobenzaldehyde and 3-halo-2-alkenals, followed by subsequent copper-catalyzed cyclization.[3]

The synthesis of disubstituted isoquinolines has led us to investigate another method for their synthesis. This approach involves the electrophilic ring closure of iminoalkynes by various external electrophiles. Along with this method, a silver-catalyzed cyclization has also been investigated as a route to mono-substituted isoquinoline derivatives. The author of this manuscript was the primary investigator and the author of the paper reported in this thesis.

Thesis Organization

This thesis is composed of one main chapter. The chapter presented herein is written following the guidelines for a full paper in the *Journal of Organic*

Chemistry and is composed of an abstract, introduction, results and discussion, conclusion, experimental, acknowledgment, and references.

The paper presents within it the synthesis of substituted isoquinolines by electrophilic ring closure reactions. The overall synthetic process involves the coupling of a terminal acetylene with *o*-bromobenzaldehyde by a palladium-catalyzed coupling reaction[4], followed by *tert*-butyl imine formation. An external electrophile or silver catalyst is then added to the iminoalkyne intermediate, which promotes ring closure to the desired isoquinolines.

Finally, all of the ^{1}H and ^{13}C NMR spectra for the aldehyde and imine starting materials and the electrophilic and silver-catalyzed products have been compiled in the appendix following the conclusions for this thesis.

References

1. (a) Fitzgerald, J. J.; Micheal, F. E.; Olofson, R. A. *Tetrahedron* **1994**, *49*, 9191. (b) Bringmann, G.; Holenz, J.; Weirich, R.; Rubenacker, M.; Funke, C. *Tetrahedron* **1998**, *54*, 497. (c) Xu, X.; Qin, G.; Xu, R.; Zhu, X. *Tetrahedron* **1998**, *54*, 14179. (d) Buske, A.; Busemann, S.; Muhlbacker, J.; Schmidt, J.; Porzel, A.; Bringmann, G.; Adam, G. *Tetrahedron* **1999**, *55*, 1079. (e) Brossi, A. *Heterocycles* **1988**, *12*, 2905.
2. Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306.
3. Roesch, K. R.; Larock, R. C., manuscript in preparation.
4. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, *16*, 4467.

SYNTHESIS OF ISOQUINOLINES BY ELECTROPHILIC RING CLOSURE OF IMINOALKYNES

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

Jack A. Hunter, Kevin R. Roesch, Richard C. Larock*

Department of Chemistry, Iowa State University, Ames, IA 50011

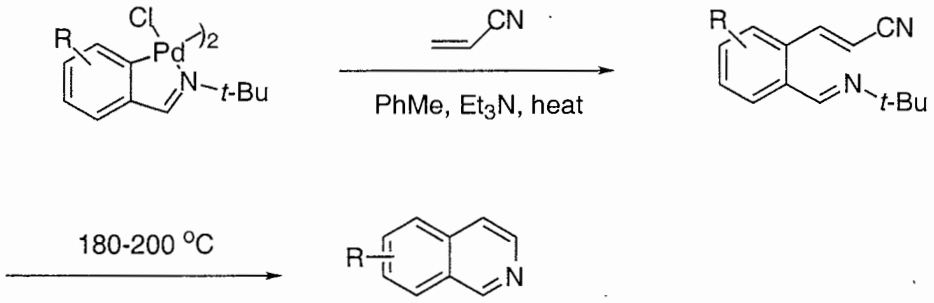
Abstract

A variety of substituted isoquinolines have been synthesized in good to excellent yields by two distinct methods. The *tert*-butylimines of 2-(1-alkynyl)benzaldehydes have been cyclized by Br_2, I_2, ArSCl, and ArSeCl to give the corresponding 3,4-disubstituted isoquinoline derivatives. This electrophilic ring closure chemistry works very well when aryl- and alkenyl-substituted alkynes are used. Other acetylenes fail to undergo this ring closure. Mono-substituted isoquinolines have been synthesized by a silver(I)-catalyzed ring closure of the *tert*-butylimines of 2-(1-alkynyl)benzaldehydes. This silver-catalyzed ring closure is highly effective in cyclizing aryl-, alkenyl-, and alkyl-substituted iminoalkynes.

Introduction

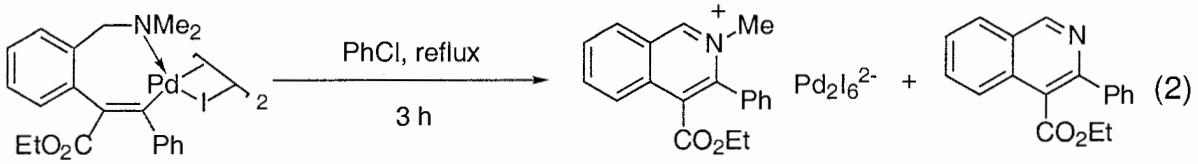
The synthesis of isoquinolines has received much attention in the literature due to the fact that the isoquinoline backbone appears in numerous natural products.[1] Substituted isoquinolines have been synthesized by utilizing palladium

methods[2-5] and by more classical, but harsher conditions.[6] Widdowson has published a synthesis of isoquinolines based on cyclopalladated *N-tert*-butylarylaldimines (eq 1).[2] This synthesis suffers from the use of stoichiometric amounts of palladium salts and a final pyrolysis step at 180-200 °C.



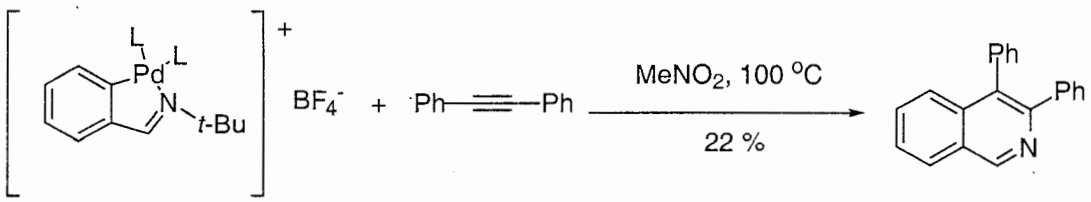
(1)

Pfeffer has reported the synthesis of disubstituted isoquinolines by using *N,N*-dimethylbenzylamine palladium complexes (eq 2).[3] This synthesis is also disadvantageous due to the use of stoichiometric palladium salts.



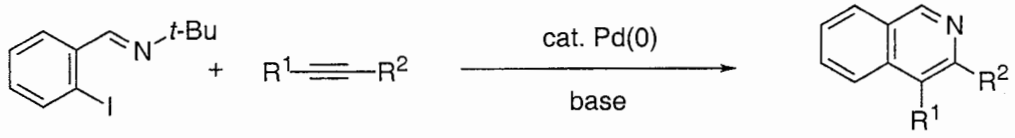
(2)

Heck has reported the formation of 3,4-diphenylisoquinoline by the reaction of diphenylacetylene and a cyclopalladated *N-tert*-butylbenzaldimine tetrafluoroborate complex (eq 3).[4] This Heck synthesis also utilizes stoichiometric palladium salts, which is not very practical in organic synthesis.

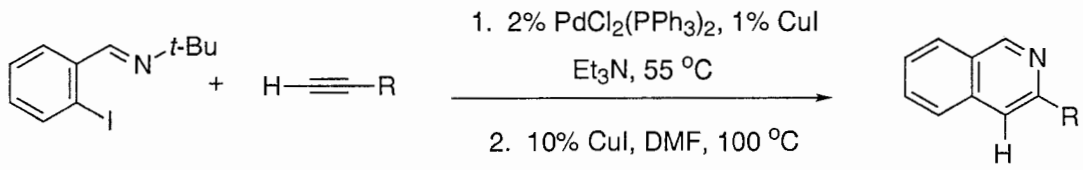


(3)

In our own group, Roesch reported the formation of numerous 3,4-disubstituted isoquinolines by the palladium-catalyzed annulation of internal alkynes (eq 4)[5] and also 3-substituted isoquinoline derivatives by a copper(I)-catalyzed ring closure (eq 5).[7] One drawback to this synthesis of disubstituted isoquinolines is the need for a disubstituted. The copper-catalyzed synthesis uses a relatively high temperature of 100 °C, which could lead to problems for thermally unstable substituents.

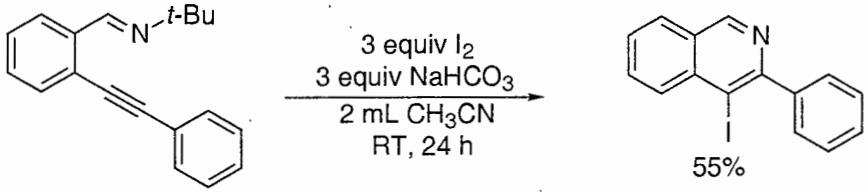


(4)



(5)

Roesch has also discovered one reaction which utilizes an external electrophile, iodine, to ring close an iminoalkyne to give the 3,4-disubstituted isoquinoline in a modest yield (eq 6).[8]

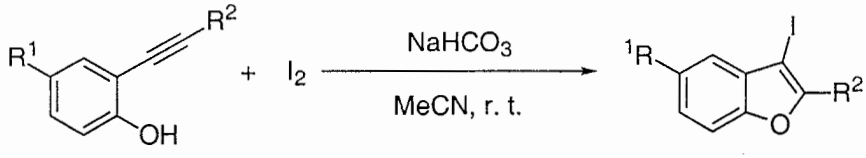


(6)

The classical methods for the synthesis of isoquinolines rely on much harsher reaction conditions.[6] The Bischler-Napieralski,[6a] Pictet-Spengler,[6b] and

Pomeranz-Fritsch[6c] all require relatively strong acids to cyclize β-phenethylamines to the nitrogen-containing ring system of the isoquinoline. Also, the Bischler-Napieralski[6a] and the Pictet-Spengler[6b] reactions require the additional step of dehydrogenating a dihydro- and tetrahydroisoquinoline, respectively.

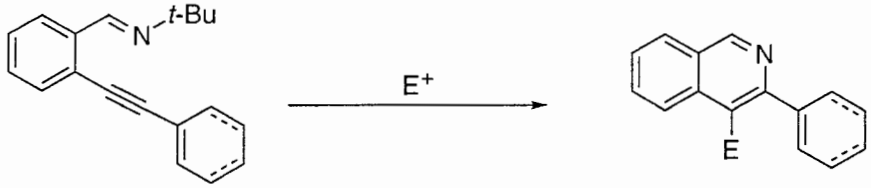
It has been reported by Cacchi that iodine can be used to electrophilically close *o*-(2-alkynyl)phenols to 2,3-disubstituted benzofuran derivatives (eq 7).[9] We have found simultaneously that this type of electrophilic cyclization can be very useful for the synthesis of isoquinolines.



(7)

Results and Discussion

Our research on the synthesis of disubstituted isoquinolines led us to investigate an electrophilic ring closure methodology involving the electrophilic cyclization of the *tert*-butylimines of 2-(1-alkynyl)benzaldehydes (eq 8). Our preliminary results are summarized in Table 1.



(8)

This methodology was begun by Dr. Kevin Roesch. He began by attempting to electrophilically close *N*-(2-phenylethynylbenzylidene)-*tert*-butyl amine using iodine as the electrophile to give 4-iodo-3-phenylisoquinoline (eq 9).

Table 1. Electrophilic ring closure to 3,4-disubstituted isoquinolines[a]

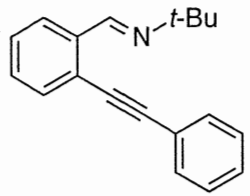
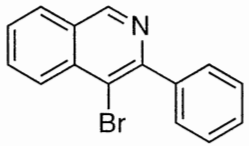
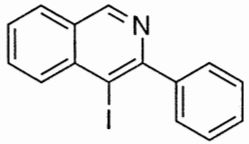
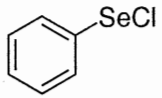
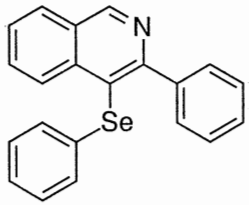
entry	imine	electrophile	time (h)	solvent	product	% yield
1	 **1**	Br_2[b]	24	CH_3CN	 **9**	46
2		I_2[b]	3	CH_3CN	 **10**	80
3			24	CH_2Cl_2	 **11**	78[c]

Table 1. (continued)

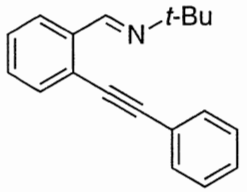
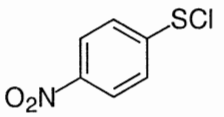
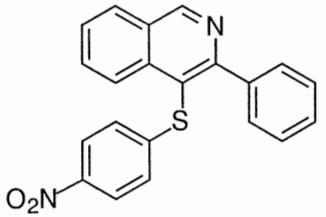
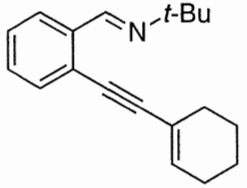
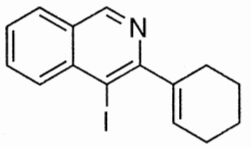
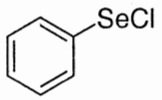
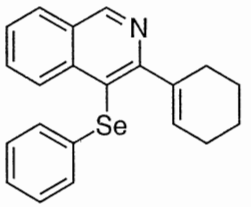
entry	imine	electrophile	time (h)	solvent	product	% yield
4			48	CH_2Cl_2	 **12**	57[c]
5	 **2**	I_2[b]	3	CH_3CN	 **13**	87
6			24	CH_2Cl_2	 **14**	89[c]

Table 1. (continued)

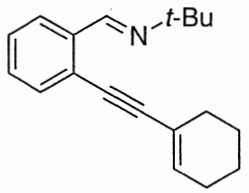
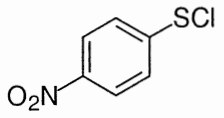
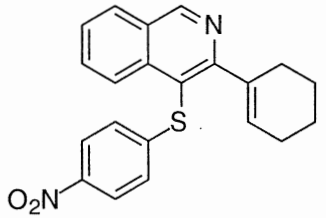
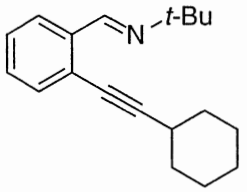
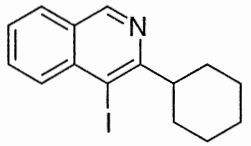
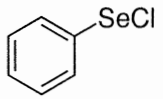
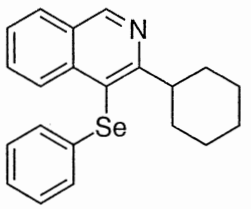
entry	imine	electrophile	time (h)	solvent	product	% yield
7			48	CH_2Cl_2	 **15**	33
8	 **3**	I_2[b]	120[d]	CH_3CN	 **16**	0
9			120[d]	CH_2Cl_2	 **17**	0

Table 1. (continued)

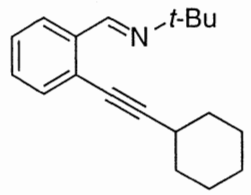
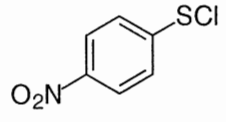
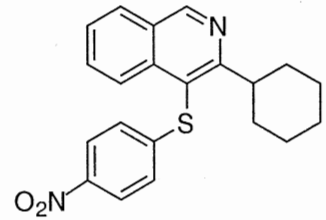
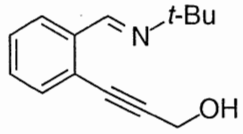
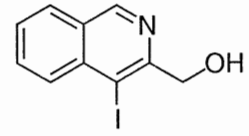
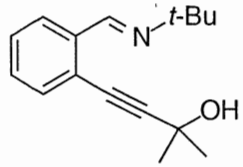
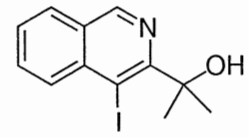
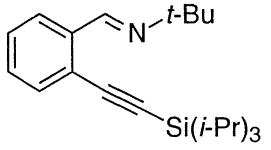
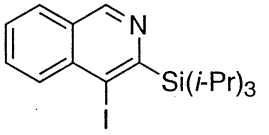
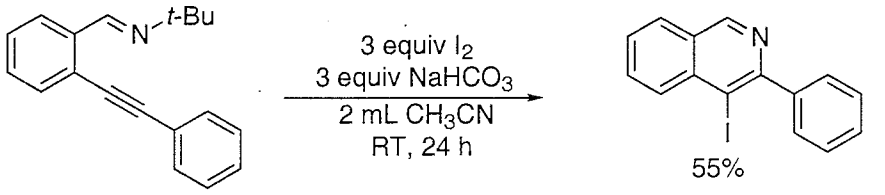
entry	imine	electrophile	time (h)	solvent	product	% yield
10			120[d]	CH_2Cl_2	 **18**	0
11	 **4**	I_2[b]	120[d]	CH_3CN	 **19**	0
12	 **5**	I_2[b]	120[d]	CH_3CN	 **20**	0

Table 1. (continued)

entry	imine	electrophile	time (h)	solvent	product	% yield
13		I_2[b]	120[d]	CH_3CN		0
	6				**21**	

[a]All reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of the imine, 2 equiv of the electrophile, 7 mL of the solvent, 3 equiv of $NaHCO_3$, run at room temperature. [b]6 Equiv of the electrophile were used. [c]No base was added. [d]Reactions were allowed to run for one week at which time they were stopped if no new products were observed by thin layer chromatographic analysis.



(9)

Research was begun on optimization of this reaction and subsequent extension to other electrophiles and starting iminoalkynes. The first variation of the reaction shown in eq 9 was variation of the solvent (Table 2, entries 1-5). As can be seen, varying the solvent did indeed affect the reaction. When methylene chloride, tetrahydrofuran (THF), and *N,N*-dimethylformamide (DMF) were used as the solvent (Table 2, entries 3-5, respectively), the desired isoquinoline was not observed. However, acetonitrile afforded a 55% yield and methanol was almost as effective (51%) (Table 2, entries 1 and 2). Next, the reaction temperature was examined (Table 2, entries 6-10). A slight elevation in temperature caused no increase in the yield and actually lowered it in the acetonitrile case (Table 2, entry 6). The use of a base in the reaction was inspected to see if it was truly necessary. As seen in entries 11 and 12 of Table 2, the absence of a base resulted in no observable reaction. Next, the amount of solvent was changed from 2 mL to 7 mL (Table 2, entry 13). A modest drop in yield was observed. With an increase in the amount of solvent, the amount of iodine was increased (Table 2, entry 14). An increase in the amount of iodine and the amount of solvent caused the reaction to proceed in 80% yield. The reaction was rerun and a yield of 78% was obtained (Table 2, entry 15). From this work, the standard reaction conditions for iodination

are as follows: 0.25 mmol of the imine, 6 equiv of I_2, 3 equiv of $NaHCO_3$, 7 mL of CH_3CN stirred at room temperature.

Once the optimal conditions were obtained for iodination, we next examined other electrophiles. A bromine source was the next choice to see if it could be used to electrophilically ring close the iminoalkynes to the corresponding bromoisoquinolines. *N*-Bromosuccinimide (NBS) was chosen as the bromine source. Reactions were run in acetonitrile and methylene chloride with no reaction being observed (Table 3, entries 1-4). Next, bromine was utilized, since iodine had worked. It was found that bromine would effect the electrophilic ring closure, although the yield was much lower than that of iodine (Table 3, entries 6 and 7). Again the use of base was investigated to see if it was necessary (Table 3, entries 2, 4, and 5). It was found that the optimal yield of the desired isoquinoline was obtained when the same reaction conditions used for the iodine-promoted cyclization were employed (Table 3, entries 6 and 7).

Table 2. Optimization of the Iodine Reaction (eq 9)[a]

entry	I_2 equiv	solvent	temperature (°C)	$NaHCO_3$ equiv	% yield
1	3	2 mL CH_3CN	RT	3	55
3	3	2 mL CH_3OH	RT	3	51
3	3	2 mL CH_2Cl_2	RT	3	0
4	3	2 mL THF	RT	3	0

Table 2. (continued)

entry	I_2 equiv	solvent	temperature (°C)	$NaHCO_3$ equiv	% yield
5	3	2 mL DMF	RT	3	0
6	3	2 mL CH_3CN	35	3	30
7	3	2 mL CH_3OH	35	3	50
8	3	2 mL CH_2Cl_2	35	3	0
9	3	2 mL THF	35	3	0
10	3	2 mL DMF	35	3	0
11	3	2 mL CH_3CN	RT	0	0
12	3	2 mL CH_3OH	RT	0	0
13	3	7 mL CH_3CN	RT	3	49
14	6	7 mL CH_3CN[b]	RT	3	80
15	6	7 mL CH_3CN[b]	RT	3	78

[a] All reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of the imine, I_2, solvent, stirred for 24 hours at the reported temperature.

[b] The reaction was complete in 3 hours.

The next electrophile chosen was phenylselenyl chloride (PhSeCl). Very similar yields of aryl selenide product were obtained using one or two equivalents of PhSeCl (Table 4, entries 1 and 2). Upon using 2 equiv of the PhSeCl in 7 mL of methylene chloride, a 78 % yield of the desired isoquinoline was obtained (Table

Table 3. Bromination[a]

entry	Brominating agent	equiv	solvent	temperature (°C)	$NaHCO_3$ equiv	% yield
1	NBS	3	CH_3CN	RT	3	0
2	NBS	3	CH_3CN	RT	0	0
3	NBS	3	CH_2Cl_2	RT	3	0
4	NBS	3	CH_2Cl_2	RT	0	0
5	Br_2	6	CH_3CN	RT	0	0
6	Br_2	6	CH_3CN	RT	3	41
7	Br_2	6	CH_3CN	RT	3	46

[a] All reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of the imine, 6 equiv of the electrophile, 7 mL of the solvent, stirring at the indicated temperature for 24 hours.

1, entry 2). The concentration of the reaction also seems to play little role in this reaction. A more concentrated reaction gave a slightly lower yield (Table 4, entry 3). Also, the choice of the selenium electrophile is critical. As can be seen in Table 4, entry 4, when diphenyl diselenide is used, no product was obtained.

The use of *p*-nitrobenzenesulfinyl chloride as the electrophile has also been examined using the reaction conditions found optimal for PhSeCl. The desired isoquinoline was obtained although in a somewhat lower yield (Table 1, entry 4).

Upon obtaining the desired isoquinolines with the phenyl-substituted

iminoalkyne, we next employed other iminoalkynes to see how general these reactions were. The cyclohexenyl-substituted iminoalkyne was used and the desired disubstituted isoquinolines were obtained (Table 1, entries 5-7). The yields for the cyclohexenyl-substituted iminoalkyne are consistant with those obtained with the phenyl-substituted iminoalkyne. Both the iodine and PhSeCl ring

Table 4. Optimization of the PhSeCl Reaction[a]

entry	PhSeCl equiv	temperature	% yield
1	1	RT	74
2	2	RT	77
3	2[b]	RT	70
4	2[c]	RT	0

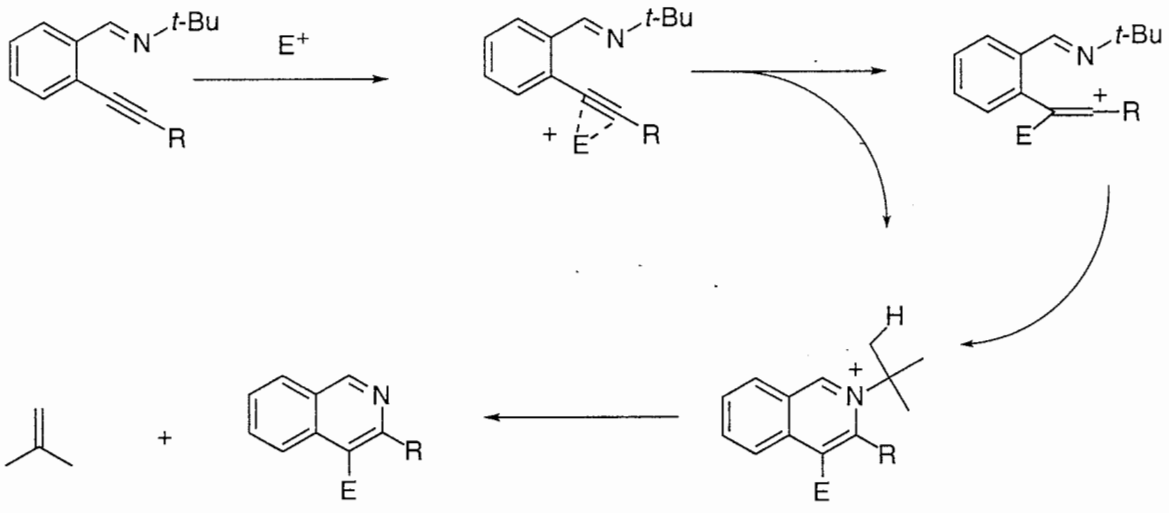
[a] All reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of the imine, 7 mL of CH_2Cl_2, stirring for 24 hours. [b] 2 mL of CH_2Cl_2 was used. [c] 2 Equiv of PhSeSePh were used as the electrophile.

closures proceed in relatively high yields (Table 1, entries 5 and 6), while the *p*-nitrobenzenesulfinyl chloride reaction again goes in a lower yield (Table 1, entry 7).

Next, we looked at reactions with alkyl- and silyl-substituted iminoalkynes. In these cases, the reaction did not occur (Table 1, entries 8-13). The reason for this, we believe, lies in the mechanism of the reaction.

The mechanism we propose is electrophilic addition onto the triple bond to give a cyclopropenyl type intermediate, which can go to either a vinylic cation or directly to the isoquinolinium salt, Scheme 1. At this stage, loss of a proton and isobutene gives the desired isoquinoline. The reason the alkyl- and silyl-substituted iminoalkynes fail is probably due to the inability of the alkyl or silyl groups to stabilize the neighboring vinylic cation. This likely intermediate is stabilized through resonance by the phenyl- and cyclohexenyl-substituted iminoalkynes, but in the case of the silyl- and alkyl-substituted reactions this stabilization cannot occur.

Scheme 1



After obtaining the desired isoquinoline products with the above electrophiles, we next turned our attention to nitrogen and carbon electrophiles. Attempts at nitrogen electrophiles were challenging do to the fact that we felt we

needed to utilize a nitrogen bearing a positive charge. In our attempts we have tried nitrosonium tetrafluoroborate and a diazonium tetrafluoroborate salt (Table 5). As can be seen, we were unable to form disubstituted isoquinolines using these two electrophiles.

The use of carbon electrophiles was a simpler task than that of the nitrogen electrophiles, but no more successful. Carbon electrophiles can be generated *in situ* by the treatment of carbonyl compounds with a Lewis acid (Table 6, entries 1-13), or halogen-containing or oxygenated compounds and a Lewis Acid or a silver salt (Table 6, entries 14-32), or by adding an appropriate carbon-containing salt directly to the reaction mixture (Table 6, entries 33-37).

Table 5. Nitrogen electrophiles examined[a]

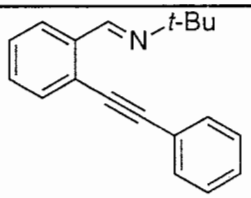
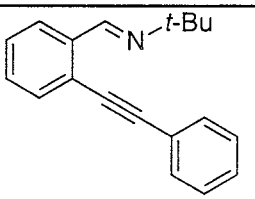
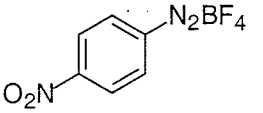
entry	imine	electrophile	solvent	temperature (°C)	% yield
1		$NOBF_4$	CH_3CN	RT	0
2			CH_3CN	50°	0
3		$NOBF_4$	$CHCl_3$	RT	0
4			$CHCl_3$	50	0

Table 5. (continued)

entry	imine	electrophile	solvent	temperature (°C)	% yield
5			CH_3CN	RT	0
6			CH_3CN	50	0
7			$CHCl_3$	RT	0
8			$CHCl_3$	50	0

[a] All reactions were run under the following conditions: 0.25 mmol of the imine, 2 equiv of the electrophile, 7 mL of solvent, at the temperature noted for 1 week.

In attempting to obtain the desired isoquinoline from *t*-BuI (Table 6, entry 21), a slight variation gave an unexpected product. The solvent was changed from methylene chloride to chloroform and the reaction was run at 50 °C, instead of at room temperature. Silver nitrate was the salt used to remove the iodide from the carbon electrophile as in the previous table (Table 6, entries 21 and 22). The product was not the expected 4-*tert*-butyl-3-phenylisoquinoline but 3-phenylisoquinoline in a modest yield of 43% (Table 7, entry 1). Next, we set out to optimize this unexpected product and see if we could extend this reaction to other

Table 6. Carbon electrophiles examined[a]

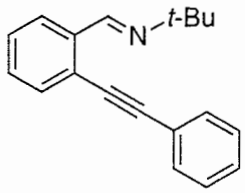
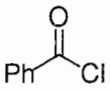
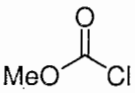
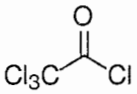
entry	imine	electrophile	Lewis acid	solvent	temperature (°C)	% yield
1			$AlCl_3$	CH_2Cl_2	RT	0
2			$AlCl_3$	CH_2Cl_2	RT	0
3			$AlCl_3$	CH_3CN	RT	0
4			$AlCl_3$	CH_2Cl_2	RT	0
5			$AlCl_3$	CH_3CN	RT	0
6		Ac_2O	$AlCl_3$	CH_3CN	RT	0
7			$AlCl_3$	CH_2Cl_2	RT	0
8			$BF_3 \bullet OEt_2$	CH_3CN	RT	0
9			$BF_3 \bullet OEt_2$	CH_2Cl_2	RT	0
10			$AlCl_3$	CH_3CN	50	0

Table 6. (continued)

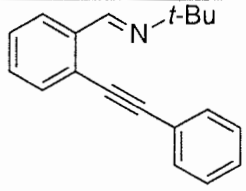
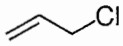
entry	imine	electrophile	Lewis acid	solvent	temperature (°C)	% yield
11		Ac_2O	$BF_3 \bullet OEt_2$	CH_3CN	50	0
12			$BF_3 \bullet OEt_2$	$CHCl_3$	50	0
13			$AlCl_3$	CH_2Cl_2	RT	0
14		$ClCH_2CH(OMe)_2$	$AlCl_3$	CH_2Cl_2	RT	0
15			$BF_3 \bullet OEt_2$	CH_2Cl_2	RT	0
16		$BrCH_2CH(OMe)_2$	$AlCl_3$	CH_2Cl_2	RT	0
17			$BF_3 \bullet OEt_2$	CH_2Cl_2	RT	0
18		Ph_3CCl	$AlCl_3$	CH_2Cl_2	RT	0
19			$BF_3 \bullet OEt_2$	CH_2Cl_2	RT	0
20		$(CH_3)_3CCl$	$AgNO_3$	CH_2Cl_2	RT	0

Table 6. (continued)

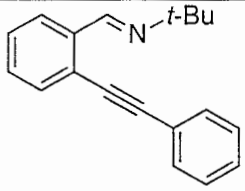
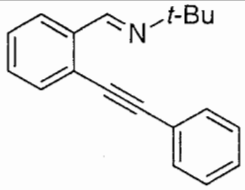
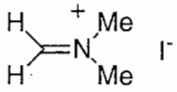
entry	imine	electrophile	Lewis acid	solvent	temperature (°C)	% yield
21		$(CH_3)_3CCl$	$AgNO_3$	CH_2Cl_2	RT	0
22		$PhCH(OMe)_2$	$AlCl_3$	CH_3CN	RT	0
23			$AlCl_3$	CH_2Cl_2	RT	0
24			$AlCl_3$	$CHCl_3$	RT	0
25			$AlCl_3$	CH_3CN	50	0
26			$AlCl_3$	$CHCl_3$	50	0
27			$BF_3 \bullet OEt_2$	CH_3CN	RT	0
28			$BF_3 \bullet OEt_2$	CH_2Cl_2	RT	0
29			$BF_3 \bullet OEt_2$	$CHCl_3$	RT	0
30			$BF_3 \bullet OEt_2$	CH_3CN	50	0

Table 6. (continued)

entry	imine	electrophile	Lewis acid	solvent	temperature (°C)	% yield
31		$PhCH(OMe)_2$	$BF_3 \bullet OEt_2$	$CHCl_3$	50	0
32			-	CH_2Cl_2	RT	0
33		Ph_3CBF_4	-	CH_3CN	RT	0
34			-	$CHCl_3$	RT	0
35			-	CH_3CN	50	0
36			-	$CHCl_3$	50	0

[a] All reactions were run under the following conditions, unless otherwise noted: 0.25 mmol of the imine, 2 equiv of the electrophile, 2 equiv of the Lewis acid, 7 mL of solvent, stirred at the specified temperature for 1 week.

iminoalkyne derivatives. The first thing investigated was the source of the hydrogen, which ended up in the four position of the isoquinoline. In an effort to find this out, a number of reactions were run to see if the source could be narrowed down (Table 7, entries 2 and 3). After running these reactions, we came to the

conclusion that the hydrogen was coming from the *tert*-butyl group of the imine starting material. If the hydrogen were coming from the solvent, the use of deuterated chloroform (Table 7, entry 3) would have resulted in the deuterated product. This was not the case as indicated by ^{1}H NMR spectroscopy. It can also be observed that the *t*-BuI is not the source of the hydrogen (Table 7, entry 2). The reaction proceeds much better once the *t*-BuI is removed from the reaction. Once the proton source was narrowed down, we then turned our attention to seeing if we could possibly make this process catalytic in the silver salt (Table 7, entries 4-7). The silver catalyst used was also looked at and there appears to be no difference (Table 7, entries 9, 11, and 14). Both silver nitrate and silver acetate give approximately the same yields for this ring closure. After optimization of the conditions, we chose the following as our standard conditions for future experiments: 0.25 mmol of the imine, 5 mol % silver salt, 7 mL of chloroform, stirred at 50 ° C for the specified time. Our preliminary results are summarized in Table 7.

The mechanism we propose is quite similar to our other electrophilic ring closure mechanism, Scheme 2. First, the silver salt electrophilically adds to the triple bond to give a metalacyclopropenyl cation; this then can either go to the vinylic cation or directly to the isoquinolinium salt. At this step, loss of a proton and isobutene gives the isoquinoline with a silver substituent in the 4-position. Next, we propose that the silver is removed by the acid that is produced during removal of the *tert*-butyl group. This gives the desired 3-substituted isoquinoline and the silver salt reenters the catalytic cycle.

Table 7. Silver-catalyzed ring closure to mono-substituted isoquinolines[a]

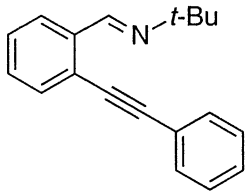
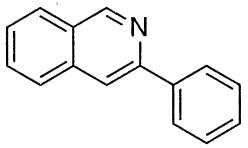
entry	imine	silver salt	time (h)	solvent	product	% yield
1	 **1**	2 $AgNO_3$[b]	24	$CHCl_3$	 **22**	43
2		2 $AgNO_3$	24	$CHCl_3$		90
3		2 $AgNO_3$	24	$CDCl_3$		69
4		0.1 $AgNO_3$	24	$CHCl_3$		80

Table 7. (continued)

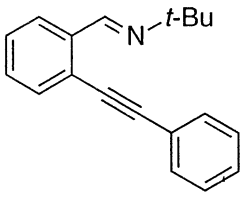
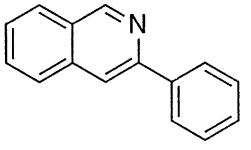
entry	imine	silver salt	time (h)	solvent	product	% yield
5		0.5 $AgNO_3$	24	$CHCl_3$		82
6		0.02 $AgNO_3$	24	$CHCl_3$		0[c]
7		0.01 $AgNO_3$	24	$CHCl_3$		0[c]
8		0.05 AgOAc	24	$CHCl_3$		80

Table 7. (continued)

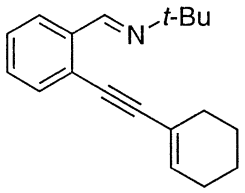
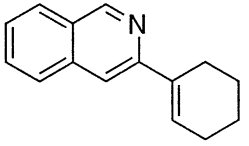
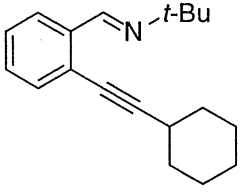
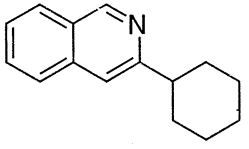
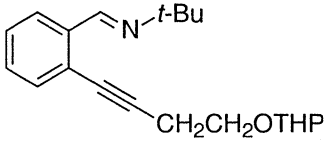
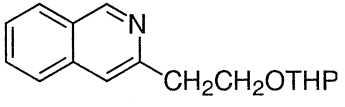
entry	imine	silver salt	time (h)	solvent	product	% yield
9	 **2**	0.05 $AgNO_3$	24	$CHCl_3$	 **23**	79
10		0.05 AgOAc	24	$CHCl_3$		78
11	 **3**	0.05 $AgNO_3$	24	$CHCl_3$	 **24**	75
12	 **7**	0.05 $AgNO_3$	24	$CHCl_3$	 **25**	62

Table 7. (continued)

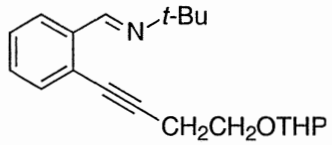
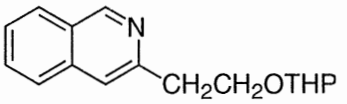
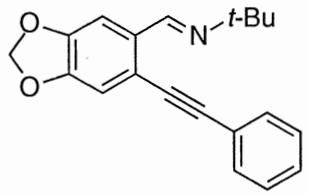
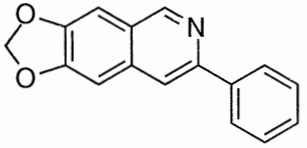
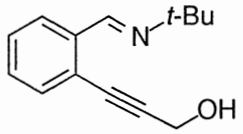
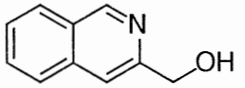
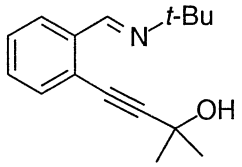
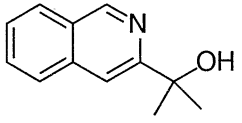
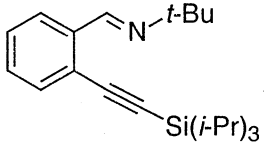
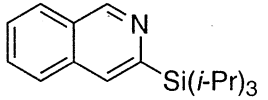
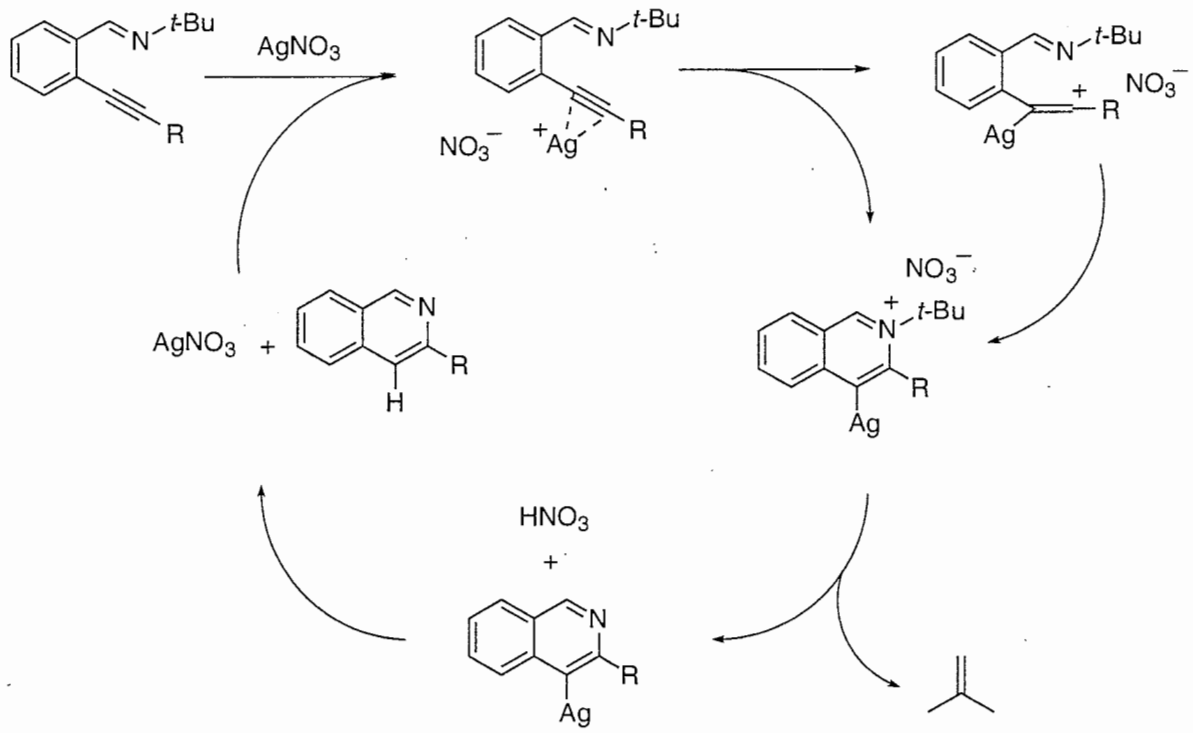
entry	imine	silver salt	time (h)	solvent	product	% yield
13		0.05 AgOAc	24	$CHCl_3$		56
14	 **8**	0.05 $AgNO_3$	24	$CHCl_3$	 **26**	56
15	 **4**	0.05 $AgNO_3$	120[d]	$CHCl_3$	 **27**	0
16		0.05 AgOAc	120[d]	$CHCl_3$		0

Table 7. (continued)

entry	imine	silver salt	time (h)	solvent	product	% yield
17	 **5**	0.05 $AgNO_3$	120[d]	$CHCl_3$	 **28**	0
18		0.05 AgOAc	120[d]	$CHCl_3$		0
19	 **6**	0.05 $AgNO_3$	120[d]	$CHCl_3$	 **29**	0

[a]All reactions were run under the following conditions unless otherwise specified: 0.25 mmol of the imine, 7 mL of the solvent, run at 50°C. [b]2 Equiv of *tert*-butyl iodide were used. [c]After 24 hours, there was only a minimal amount of the desired product present by thin-layer chromatography. [d]Reactions were allowed to run for one week at which time they were stopped if no new products were observed by thin layer chromatographic analysis.

Scheme 2



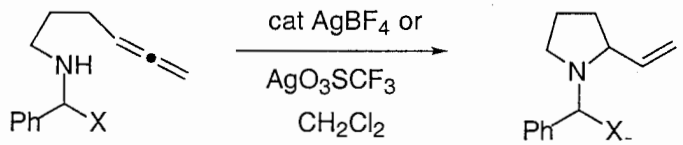
The reason for the unprotected alcohol iminoalkynes (Table 7, entries 16-19) failing to give the desired isoquinolines is unclear. It may be due to the alcohol coordinating the silver salt more readily than the triple bond. By doing this, the silver is not available for the reaction with the alkyne as needed, thus killing the reaction.

The silver-catalyzed ring closure reported above is similar to the copper-catalyzed synthesis of 3-substituted isoquinolines found previously in the Larock group.[7] There are advantages of the silver over the copper-catalyzed reactions. The major advantage is the use of a much lower reaction temperature. Roesch

used 100 °C in his copper reactions, while the silver-catalyzed reactions proceed quite nicely at only 50 °C. Also, the use of 5 mol % of the silver catalyst over 10 mol % of the copper salt is favorable. The major disadvantage of the silver promoted ring closure is the use of a chlorinated solvent, $CHCl_3$.

As for the types of iminoalkynes that undergo cyclization, it seems that what works for the copper reactions also works for the silver reactions. Also, the iminoalkynes which fail to produce the desired isoquinolines by the copper-catalyzed ring closure also fail in the silver-catalyzed methodology. There is no case where the silver works and the copper fails and vice-versa.

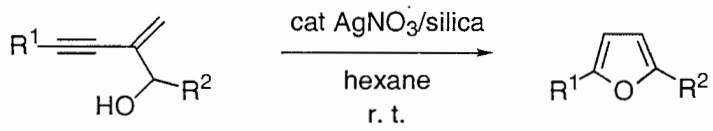
This type of silver-catalyzed ring closure is not new in organic synthesis. It has previously been shown that silver will cyclize allenic amines to the corresponding pyrrolidines (eq 10).[10]



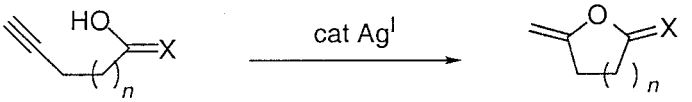
(10)

X= Me, CO_2Me, CH_2OH, CONHMe, CH_2NHMe

Also, furan,[11] tetrahydrofuran,[12] and lactone[12] derivatives have been synthesized utilizing analogous silver-catalyzed cyclizations of alkynes (eqs 11 and 12, respectively).



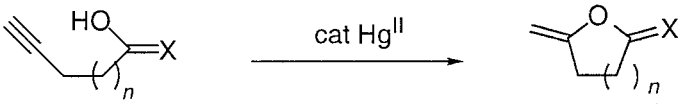
(11)



(12)

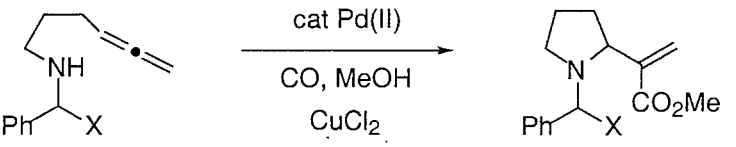
X = H_2, O
n = 1

Besides these silver-catalyzed cyclizations, other metals have been found to facilitate this type of ring closure. Mercury has been utilized for the intramolecular cyclization of carboxylic acids and alcohols onto alkynes (eq 13).[12, 13] Palladium has been used catalytically to electrophilically form pyrrolidine derivatives from allenic amines (eq 14).[10, 14]



(13)

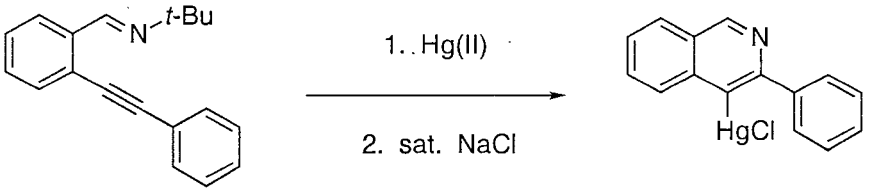
X = H_2, O
n = 1



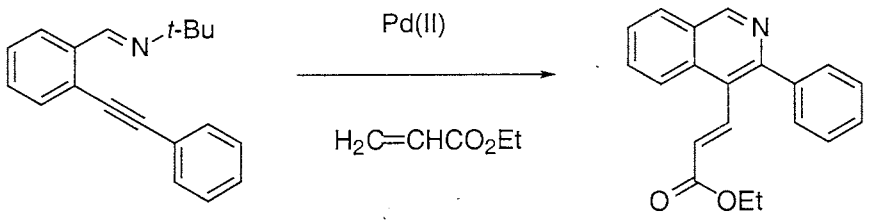
(14)

X = Me, CO_2Me, CH_2OH
CONHMe, CH_2NHMe

In attempts to further our own electrophilic ring closure to disubstituted isoquinolines, these two metals, mercury (eq 15) and palladium (eq 16), have been looked at to see if they would allow us to form the desired isoquinolines. The results are summarized in Tables 8 and 9.



(15)



(16)

The mercury and palladium electrophiles were unsuccessful in cyclizing the iminoalkyne (Tables 8 and 9). In the mercury case, the reactions were quenched with 25 mL of saturated sodium chloride solution after the 24 hour reaction time. A ^{1}H NMR spectrum was taken of the crude product after extraction with ether and none of the desired isoquinoline was observed. The palladium reactions were also quenched with 25 mL of saturated sodium chloride solution after the 24 hour reaction time and again a ^{1}H NMR spectrum was taken of the crude product after extraction with ether. Again, none of the desired isoquinoline was observed.

Table 8. Mercury salts examined[a]

entry	mercury salt	solvent	% yield
1	$Hg(OAc)_2$[b]	CH_3CN	0
2	$Hg(OAc)_2$	CH_3CN	0
3	$Hg(OAc)_2$	CH_2Cl_2	0
4	$Hg(OAc)_2$	HOAc	0
5	$Hg(O_2CCF_3)_2$[b]	CH_2Cl_2	0
6	$Hg(O_2CCF_3)_2$	CH_2Cl_2	0
7	$Hg(O_2CCF_3)_2$	HOAc	0
8	$HgCl_2$	HOAc	0

Table 8. (continued)

entry	mercury salt	solvent	% yield
9	$HgCl_2$	CH_2Cl_2	0
10	$HgBr_2$	HOAc	0
11	$HgBr_2$	CH_2Cl_2	0
12	HgI_2	HOAc	0
13	HgI_2	CH_2Cl_2	0

[a] All reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of the imine *N*-(2-phenylethynylbenzylidene)-*tert*-butyl amine, 2 equivs of the mercury salt, 7 mL of the solvent at room temperature for 24 hours. [b] 1 Equiv of the mercury salt was used.

Table 9. Attempted synthesis of isoquinolines by palladium addition followed by a subsequent Heck reaction.[a]

entry	Pd salt	phosphine	base	TBAC	solvent	% yield
1	$Pd(OAc)_2$	-	$NaHCO_3$	1 equiv	DMF	0
2	$Pd(OAc)_2$	-	$NaHCO_3$	1 equiv	CH_3CN	0
3	$Pd(OAc)_2$	-	$NaHCO_3$	1 equiv	DMF	0
4	$Pd(OAc)_2$	-	$NaHCO_3$	1 equiv	DMF[b]	0
5	$Pd(OAc)_2$	$(o\text{-tol})_3P$	$NaHCO_3$	1 equiv	DMF	0
6	$Pd(OAc)_2$	$(o\text{-tol})_3P$	$NaHCO_3$	1 equiv	CH_3CN	0

Table 9. (continued)

entry	Pd salt	phosphine	base	TBAC	solvent	% yield
7	$Pd(OAc)_2$	(*o*-tol)$_3$P	-	1 equiv	CH_3CN	0
8	$Pd(OAc)_2$	(*o*-tol)$_3$P	-	1 equiv	DMF	0
9	$Pd(OAc)_2$	-	-	1 equiv	CH_3CN	0
10	$Pd(OAc)_2$	-	-	1 equiv	DMF	0
11	$Pd(OAc)_2$	-	-	-	DMF[b]	0
12	$Pd(OAc)_2$	-	-	-	CH_3CN	0

[a] All reactions were run under the following conditions, unless otherwise specified: 0.25 mmol of the imine *N*-(2-phenylethynylbenzylidene)-*tert*-butyl amine, 1 equiv of $Pd(OAc)_2$, 1 equiv of ethyl acrylate, 3 equivs of sodium bicarbonate, 1 equiv of TBAC, 1 equiv of P(*o*-tol)$_3$, in 7 mL of solvent at room temperature for 24 hours. [b] 100 °C was the reaction temperature.

Conclusions

Herein we have reported the synthesis of isoquinolines, both di- and mono-substituted derivatives. The reaction conditions are extremely mild and utilize readily available starting materials. The reactions which work best seem to employ a soft electrophile to effect ring closure. In the silver-catalyzed ring closure reactions, it seems the methodology is only limited by the use of unprotected alcohols and is quite mild.

Experimental Section

General. ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica get plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) and basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of K_2CO_3 + 5 mL of NaOH (5%) + 300 mL of H_2O]. All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI 70 eV.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of DMF, THF, methanol, chloroform, DMSO, methylene chloride, acetonitrile, acetic acid, ethyl ether, hexanes, ethyl acetate, sodium bicarbonate, iodine, bromine, benzoyl chloride, acetic anhydride, aluminum chloride, silver nitrate, silver acetate, mercuric acetate, mercuric chloride, mercuric bromide, mercuric iodide, and mercuric trifluoroacetate were purchased from Fisher Scientific Co. $Pd(OAc)_2$ and $PdCl_2$ were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. PPh_3 was donated by Kawaken Fine Chemicals Co. Ltd. 2-Bromobenzaldehyde, phenylacetylene, propargyl alcohol, 2-methyl-3-butyn-2-ol, 2-(3-butynyloxy)tetrahydro-2*H* -pyran, 1-ethynylcyclohexene, (trimethylsilyl)acetylene, *tert*-butylamine, cupric iodide, *tert*-butyl iodide, trityl chloride, benzaldehyde dimethyl acetal, Eschenmoser's salt, 4-

nitrobenzenediazonium tetrafluoroborate, phenylselenyl chloride, 4-nitrobenzenesulfenyl chloride, ethyl acrylate, allyl chloride, boron trifluoride-diethyletherate, methyl chloroformate, chloroacetaldehyde dimethyl acetal, bromoacetaldehyde dimethyl acetal, nitrosonium tetrafluoroborate, *N*-bromosuccinimide, triphenylmethyl tetrafluoroborate, and Et_3N were purchased from Aldrich Chemical Co., Inc. Cyclohexylacetylene was purchased from Farchan Chemical Co. The following starting materials were prepared as indicated.

Aldehydes Prepared

2-(2-Phenylethynyl)benzaldehyde. To a solution of 2-bromobenzaldehyde (1.85 g, 10.0 mmol) and phenylacetylene (1.23 g, 12.0 mmol) in Et_3N (40 mL) was added $PdCl_2(PPh_3)_2$ (0.140 g, 2 mol %). The mixture was stirred for 5 min and CuI (0.020 g, 1 mol %) was added. The resulting mixture was then heated under an argon atmosphere at 50 °C for 6 hours. The reaction was monitored by TLC to establish completion. The reaction mixture was allowed to cool to room temperature, and the ammonium salt was removed by filtration. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography on silica gel using 20:1 hexanes:EtOAc to afford 1.90 g (92%) of the compound as a yellow oil. All spectral data matched those previously reported.[12]

2-(2-Cyclohex-1-enylethynyl)benzaldehyde. The aldehyde was prepared by the same manner used above, but employing 2-bromobenzaldehyde and 1-ethynylcyclohexene (1.27 g, 12.0 mmol) for 4 hours. Column

chromatography using 25:1 hexanes/EtOAc afforded 1.8 g (86%) of the compound as a yellow oil. All spectral data matched those previously reported.[12]

2-(2-Cyclohexylethynyl)benzaldehyde. The aldehyde was prepared by the same manner used above, but employing 2-bromobenzaldehyde and cyclohexyl acetylene (1.29 g, 12.0 mmol) for 4 hours. Column chromatography using 25:1 hexanes/EtOAc afforded 2 g (94%) of the compound as a yellow oil. All spectral data matched those previously reported.[12]

2-[4-(Tetrahydropyran-2-yloxy)but-1-ynyl]benzaldehyde. The aldehyde was prepared by the same manner used above, but employing 2-bromobenzaldehyde and 2-(3-butynyloxy)tetrahydro-2*H*-pyran (1.85 g, 12.0 mmol) for 4 hours. Column chromatography using 10:1 hexanes/EtOAc afforded 1.9 g (74%) of the compound as a yellow oil. All spectral data matched those previously reported.[12]

2-(3-Hydroxyprop-1-ynyl)benzaldehyde. The aldehyde was prepared by the same manner used above, but employing 2-bromobenzaldehyde and propargyl alcohol (0.67 g, 12.0 mmol) for 6 hours. Column chromatography using 1:1 hexanes/EtOAc afforded 1.5 g (94%) of the compound as a yellow oil. All spectral data matched those previously reported.[12]

2-(3-Hydroxy-3-methylbut-1-ynyl)benzaldehyde. The aldehyde was prepared by the same manner used above, but employing 2-bromobenzaldehyde and 2-methyl-3-butyn-2-ol (1.01 g, 12.0 mmol) for 4 hours. Column chromatography using 1:1 hexanes/EtOAc afforded 1.6 g (84%) of the compound as a yellow oil. All spectral data matched those previously reported.[12]

2-(2-Triisopropylsilylethynyl)benzaldehyde. The aldehyde was prepared by the same manner used above, but employing 2-bromobenzaldehyde and (triisopropylsilyl)acetylene (2.19 g, 12.0 mmol) for 4 hours. Column chromatography using 35:1 hexanes/EtOAc afforded 2.7 g (95%) of the compound as a yellow oil. All spectral data matched those previously reported.[12]

4,5-Methylenedioxy-2-(2-phenylethynyl)benzaldehyde. The aldehyde was prepared by the same manner used above, but employing 2-bromo-4,5-(methylenedioxy)benzaldehyde (2.29 g, 10 mmol) and phenylacetylene (1.23 g, 12.0 mmol) for 6 hours. Column chromatography using 35:1 hexanes/EtOAc afforded 2.0 g (80%) of the compound as a yellow solid: mp 98-101 °C; ^{1}H NMR ($CDCl_3$) δ 6.09 (s, 1H), 7.03 (s, 1H), 7.26 (s, 1H), 7.37-7.39 (m, 3H), 7.53-7.55 (m, 2H), 10.49 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 85.0, 95.4, 102.6, 106.3, 112.2, 122.5, 123.9, 128.8, 129.2, 131.8, 132.4, 148.9, 152.6, 190.3.

Imines Prepared

***N*-(2-Phenylethynylbenzylidene)-*tert*-butylamine (1).** To a mixture of 2-(2-phenylethynyl)benzaldehyde (1.90 g, 9.2 mmol) and H_2O (0.25 mL/mmol) was added *tert*-butylamine (2.0 g, 3 equiv). The mixture was then stirred under an argon atmosphere at room temperature for 12 hours. The excess *tert*-butylamine was removed under reduced pressure and the resulting mixture was extracted with ether. The combined organic layers were dried (Na_2SO_4) and filtered. Removal of

the solvent produced 2.3 g (95%) of the imine as a yellow oil, which solidified upon cooling. All spectral data matched those previously reported.[12]

***N*-(2-Cyclohex-1-enylethynylbenzylidene)-*tert*-butylamine (2).** The imine was prepared by the same method used for **1**, but employing 2-(2-cyclohex-1-enylethynyl)benzaldehyde (1.7 g, 8.1 mmol). Removal of the solvent afforded 2 g (95%) of the imine as a yellow oil. All spectral data matched those previously reported.[12]

***N*-(2-Cyclohexylethynylbenzylidene)-*tert*-butylamine (3).** The imine was prepared by the same method used for **1**, but employing 2-(2-cyclohexylethynyl)benzaldehyde (1.9 g, 9.0 mmol). Removal of the solvent afforded 2.3 g (96%) of the imine as a yellow oil. All spectral data matched those previously reported.[12]

***N*-[2-(3-Hydroxyprop-1-ynyl)benzylidene]-*tert*-butylamine (4).** The imine was prepared by the same method used for **1**, but employing 2-(3-hydroxyprop-1-ynyl)benzaldehyde (1.4 g, 9 mmol). Removal of the solvent afforded 1.6 g (84%) of the imine as a brown solid. All spectral data matched those previously reported.[12]

***N*-[2-(3-Hydroxy-3-methylbut-1-ynyl)benzylidene]-*tert*-butylamine (5).** The imine was prepared by the same method used for **1**, but employing 2-(3-hydroxy-3-methylbut-1-ynyl)benzaldehyde (1.5 g, 8 mmol). Removal of the solvent afforded 1.8 g (90%) of the imine as a yellow oil. All spectral data matched those previously reported.[12]

***N*-(2-Triisopropylsilylethynylbenzylidene)-*tert*-butylamine (6).** The imine was prepared by the same method used for **1**, but employing 2-(2-triisopropylsilylethynyl)benzaldehyde (2.6 g, 9 mmol). Removal of the solvent afforded 2.8 g (93%) of the imine as a colorless oil. All spectral data matched those previously reported.[12]

***N*-[4-(Tetrahydropyran-2-yloxy)but-1-ynylbenzylidene]-*tert*-butylamine (7).** The imine was prepared by the same method used for **1**, but employing 2-[4-(tetrahydropyran-2-yloxy)but-1-ynyl]benzaldehyde (1.8 g, 7 mmol). Removal of the solvent afforded 2.0 g (91%) of the imine as a yellow oil. All spectral data matched those previously reported.[12]

***N*-[4,5-Methylenedioxy-2-(2-phenylethynyl)benzylidene]-*tert*-butylamine (8).** The imine was prepared by the same method used for **1**, but employing 4,5-methylenedioxy-2-(2-phenylethynyl)benzaldehyde (2.0 g, 8 mmol). Removal of the solvent afforded 2.4 g (98%) of the imine as a white solid: mp 72-75 °C; ^{1}H NMR ($CDCl_3$) δ 1.30 (s, 9H), 6.00 (s, 2H), 6.96 (s, 1H), 7.35-7.37 (m, 3H), 7.49-7.52 (m, 2H), 7.56 (s, 1H), 8.84 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 30.0, 57.8, 86.9, 93.9, 101.9, 106.0, 111.3, 123.4, 128.6, 128.7, 128.8, 131.6, 131.8, 148.8, 153.71 (one sp^2 carbon missing due to overlap); IR ($CHCl_3$, cm^{-1}) 3017, 2972, 1684; HRMS Calcd for $C_{20}H_{19}NO_2$: 305.1416. Found: 305.1420.

General Procedure for the Electrophilic Cyclization of Iminoalkynes. The electrophile (6 or 2 equiv), the solvent (5 mL), the base,

where required (3 equiv), were placed in a 2 dram vial. The imine (0.25 mmol) in 2 mL of the solvent was added dropwise to the vial. The vial was then flushed with argon and the reaction stirred at room temperature for the indicated time period. The reaction was monitored by TLC to establish completion. The reaction mixture was then diluted with 25 mL of ether, washed with either 25 mL of saturated $Na_2S_2O_3$ or saturated NaCl, 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.

General Procedure for the Silver-Catalyzed Cyclization of Iminoalkynes. CH_2Cl_2 (5 mL) and 5 mol % of the silver salt were placed into a 2 dram vial. The imine (0.25 mmol) in 2 mL of CH_2Cl_2 was added dropwise to the vial. The vial was then flushed with argon and heated at 50 °C for the indicated period of time. The reaction was monitored by TLC to establish completion. The reaction was cooled, diluted with 25 mL of ether, washed with 25 mL of saturated NaCl, dried (Na_2SO_4), and filtered. The solvent was removed under reduced pressure and the product was isolated by chromatography on a silica gel column.

Compounds Prepared

4-Bromo-3-phenylisoquinoline (9). To a mixture of bromine (0.24 g, 6 equiv) and $NaHCO_3$ (0.063 g, 0.75 mmol) in CH_3CN (5 mL) was added dropwise a solution of *N*-(2-phenylethynylbenzylidene)-*tert*-butylamine (0.065 g, 0.25 mmol) in CH_3CN (2 mL). The resulting mixture was stirred at room temperature for 24 hours.

Saturated NaCl (25 mL) was added and the product was extracted with ether, and the extract dried (Na_2SO_4) and filtered. The solvent was evaporated under reduced pressure and the product was isolated by column chromatography on silica gel using 3:1 hexanes/EtOAc to afford 0.033 g (46 %) of the indicated compound as a orange oil: ^{1}H NMR ($CDCl_3$) δ 7.45-7.53 (m, 3H), 7.67-7.75 (m, 3H). 7.86 (d, J = 1.8, 3.9 Hz, 1H), 8.03 (d, J = 2.3 Hz), 8.35 (d, J = 2.3 Hz), 9.24 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 127.0, 127.2, 128.0, 128.2, 128.6, 128.8, 129.5, 130.2, 132.2, 136.2, 140.9, 151.4, 152.6; IR (neat, cm^{-1}) 3018, 2926, 1620, 1572; HRMS Calcd for $C_{15}H_{10}BrN$: 284.1547. Found: 284.1539.

4-Iodo-3-phenylisoquinoline (10). The product was isolated by column chromatography on silica gel using 3:1 hexanes/EtOAc to afford 0.066 g (80 %) of the indicated compound as a dark brown viscous oil. Filtration through charcoal gave a yellow solid: mp 84-85 °C; ^{1}H NMR ($CDCl_3$) δ 7.45-7.53 (m, 3H), 7.61-7.71 (m, 3H), 7.83 (ddd, J = 1.5, 6.9, 8.4 Hz, 1H), 7.96 (d, J = 8.1 Hz, 1H), 8.24 (d, J = 8.4, Hz, 1H), 9.17 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 98.2, 128.0, 128.1, 128.1, 128.4, 129.9, 132.4, 132.5, 138.7, 143.7, 152.1, 157.1 (one sp^2 carbon missing due to overlap); IR (neat, cm^{-1}) 3055, 1630, 1549; HRMS Calcd for $C_{15}H_{10}IN$: 330.9858. Found: 330.9852.

3-Phenyl-4-phenylselenylisoquinoline (11). The product was isolated by column chromatography on silica gel using 3:1 hexanes/EtOAc to afford 0.07 g (78 %) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.04-

7.08 (m, 5H), 7.39-7.42 (m, 3H), 7.55-7.65 (m, 3H), 7.71 (ddd, J = 1.2, 6.9, 8.1 Hz, 1H), 8.02 (d, J = 7.5 Hz, 1H), 8.45 (d, J = 8.1 Hz, 1H), 9.35 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 121.7, 126.4, 127.8, 127.9, 128.3, 128.4, 128.4, 128.9, 129.4, 129.9, 130.1, 132.0, 133.3, 138.9, 142.2, 153.4, 158.6; IR ($CHCl_3$, cm^{-1}) 3056, 2924, 1575; HRMS Calcd for $C_{21}H_{15}NSe$: 361.0370. Found: 361.0378

3-Phenyl-4-(4-nitrobenzene)sufinylisoquinoline (12). The product was isolated by column chromatography on silica gel using 3:1 hexanes/EtOAc to afford 0.51 g (57 %) of the indicated compound as a oil: ^{1}H NMR ($CDCl_3$) δ 6.96-6.99 (m, 2H)), 7.34-7.41 (m, 2H), 7.57-7.60 (m, 3H), 7.68-7.80 (m, 2H), 7.95-7.99 (m, 2H), 8.12 (d, J = 8.4Hz, 1H), 8.27 (d, J = 8.4Hz, 1H), 9.46 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 124.4, 125.6, 126.1, 126.6, 128.2, 128.3, 128.5, 128.9, 128.9, 129.8, 132.8, 138.1, 140.3, 145.5, 147.8, 154.6, 159.1; IR ($CHCl_3$, cm^{-1}) 3019, 2926, 1518; HRMS Calcd for $C_{21}H_{14}N_2O_2S$: 358.0776. Found: 358.0781.

3-(Cyclohex-1-enyl)-4-iodoisoquinoline (13). The product was isolated by column chromatography on silica gel using 3:1 hexanes/EtOAc to afford 0.073 g (87 %) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.73-1.92 (m, 4H), 2.25-2.30 (m, 2H), 2.40-2.45 (m, 2H), 7.57-7.63 (m, 1H), 7.73-7.78 (m, 1H), 7.87 (d, J = 8.1 Hz, 1H), 8.14 (d, J = 8.4 Hz, 1H), 9.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.9, 22.9, 25.3, 28.4, 97.6, 127.5, 127.9, 128.0, 129.5, 131.9, 132.1, 138.6, 141.8, 152.1, 159.6; IR (neat, cm^{-1}) 3019, 2936, 1618; HRMS Calcd for $C_{15}H_{14}IN$: 335.0165. Found: 335.0168.

3-(Cyclohex-1-enyl)-4-phenylselenylisoquinoline (14). The product was isolated by column chromatography on silica gel using 3:1 hexanes/EtOAc to afford 0.081 g (89 %) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.69-1.82 (m, 4H), 2.15-2.21 (m, 2H), 2.44-2.48 (m, 2H), 5.67-5.70 (m, 1H), 7.08-7.14 (m, 5H), 7.52-7.65 (m, 2H), 7.94 (d, J = 8.1 Hz, 1H), 8.30 (d, J = 8.4 Hz, 1H), 9.23 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 22.0, 22.9, 25.4, 29.0, 120.8, 126.1, 127.0, 128.1, 128.2, 128.4, 129.2, 129.3, 129.8, 129.9, 131.4, 133.7, 138.4, 140.0, 153.1; IR ($CHCl_3$, cm^{-1}) 3019, 2936, 1571; HRMS Calcd for $C_{21}H_{19}NSe$: 365.0684. Found: 365.0690.

3-(Cyclohex-1-enyl)-4-(4-nitrobenzene)sulfinylisoquinoline (15). The product was isolated by column chromatography on silica gel using 3:1 hexanes/EtOAc to afford 0.03 g (33 %) of the indicated compound as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.67-1.77 (m, 4H), 2.13 (d, J = 0.45 Hz), 2.41 (d, J = 0.45 Hz), 5.78 (s, 1H), 6.98-7.01 (m, 2H), 7.59-7.74 (m, 2H), 7.98-8.16 (m, 3H), 8.18-8.20 (m, 1H), 9.35 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.9, 22.8, 25.5, 28.9, 118.8, 124.3, 125.4, 126.1, 126.6, 127.8, 128.3, 128.8, 129.8, 132.5, 138.1, 138.4, 148.7, 154.4, 161.9; IR ($CHCl_3$, cm^{-1}) 3019, 2932, 1517; HRMS Calcd for $C_{21}H_{18}N_2O_2S$: 362.1089. Found: 362.1094.

3-Phenylisoquinoline (22). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 0.042 g (82 %) of the indicated compound with spectral properties identical to those previously reported.[12]

3-(Cyclohex-1-enyl)isoquinoline (23). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 0.041 g (79 %) of the indicated compound with spectral properties identical to those previously reported.[12]

3-Cyclohexylisoquinoline (24). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 0.040 g (75 %) of the indicated compound with spectral properties identical to those previously reported.[12]

3-[2-(Tetrahydropyran-2-yloxy)ethyl]isoquinoline (25). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 0.040 g (62 %) of the indicated compound with spectral properties identical to those previously reported.[12]

3-Phenyl-6,7-(methylenedioxy)isoquinoline (26). The reaction mixture was chromatographed using 3:1 hexanes/EtOAc to afford 0.035 g (56 %) of the indicated compound as a yellow paste; ^{1}H NMR ($CDCl_3$) δ 6.10 (s, 1H), 7.16 (d, J = 7.1 Hz) 7.37-7.51 (m, 3H), 7.89 (s, 1H), 8.07 (d, J = 1.8 Hz), 9.06 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 101.9, 103.0, 103.4, 116.6, 125.3, 127.0, 128.5, 129.0, 135.3, 139.9, 148.6, 150.4, 150.8, 151.4; IR ($CHCl_3$, cm^{-1}) 3019, 2925, 1600, 1458; HRMS Calcd for $C_{16}H_{11}NO_2$: 249.0789. Found: 249.0793.

Acknowledgment. We gratefully acknowledge the donors of the Petroleum Research Fund, administered by the American Chemical Society, for

partial support of this research and Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for donation of the palladium salts.

References

1. (a) Fitzgerald, J. J.; Michael, F. E.; Olofson, R. A. *Tetrahedron* **1994**, *49*, 9191. (b) Bringmann, G.; Holenz, J.; Weirich, R.; Rubenacker, M.; Funke, C. *Tetrahedron* **1998**, *54*, 497. (c) Xu, X.; Qin, G.; Xu, R.; Zhu, X. *Tetrahedron* **1998**, *54*, 14179. (d) Buske, A.; Busemann, S.; Muhlbacker, J.; Schmidt, J.; Porzel, A.; Bringmann, G.; Adam, G. *Tetrahedron* **1999**, *55*, 1079. (e) Brossi, A. *Heterocycles* **1988**, *12*, 2905.
2. Girling, I. R.; Widdowson, D. A. *Tetrahedron Lett.* **1982**, *41*, 4281.
3. Maassarani, F.; Pfeffer, M.; Le Borgne, G. *J. Chem. Soc., Chem. Commun.* **1987**, 565.
4. (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.
5. Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306.
6. (a) Whaley, W. M.; Govindachari, T. R. In *Organic Reactions*; Adams, R., Ed.; Wiley, New York, 1951, Vol. 6, pp. 74-150. (b) Whaley, W. M.; Govindachari, T. R. In *Organic Reactions*; Adams, R., Ed.; Wiley, New York, 1951, Vol. 6, pp. 151-190. (c) Gensler, W. J. In *Organic Reactions*; Adams, R., Ed., Wiley, New York, 1951, Vol. 6, pp. 191-206.

7. Roesch, K. R.; Larock, R. C. manuscript in preparation.

8. Roesch, K. R. Ph.D. Dissertation, Iowa State University, **1999**.

9. Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L. *Synlett* **1999**, 1432.

10. Fox, D. N. A.; Gallagher, T. *Tetrahedron* **1990**, *46*, 4679.

11. Marshall, J. A.; Sehon, C. A. *J. Org. Chem.* **1995**, *60*, 5966.

12. Pale, P.; Chuche, J. *Tetrahedron Lett.* **1987**, *28*, 6447.

13. Krafft, G. A.; Katzenellenbogen, J. A. *J. Am. Chem. Soc.* **1981**, *103*, 5459.

14. Lathbury, D.; Vernon, P.; Gallagher, T. *Tetrahedron Lett.* **1986**, *27*, 6009.

GENERAL CONCLUSIONS

In this thesis, the scope and limitations of several electrophilic ring closure processes have been presented for the synthesis of substituted isoquinolines. A variety of iminoalkynes have been shown to undergo this cyclization in moderate to good yields using readily available electrophiles and iminoalkynes under very mild conditions. It seems that the softer the electrophile, the better the reaction proceeds. This methodology adds to the already growing number of methods to synthesize isoquinolines and offers advantages over palladium and classical methods already reported. While attempting to utilize carbon electrophiles, an interesting synthesis of monosubstituted isoquinolines was observed. Preliminary results show this method is catalyzed by silver salts. This process seems to be quite general and similar to the findings of Roesch.[7]

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

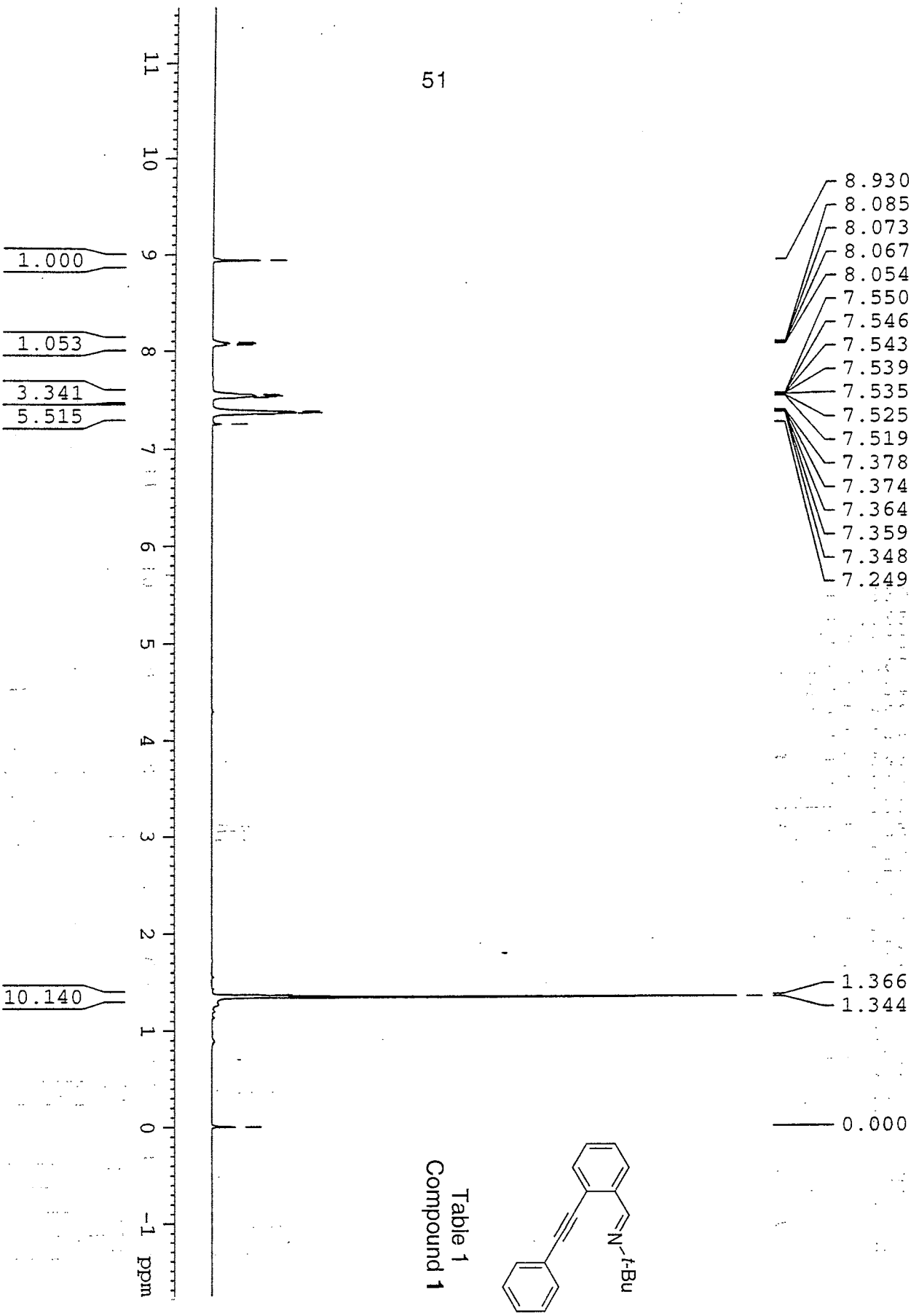


Table 1
Compound **1**

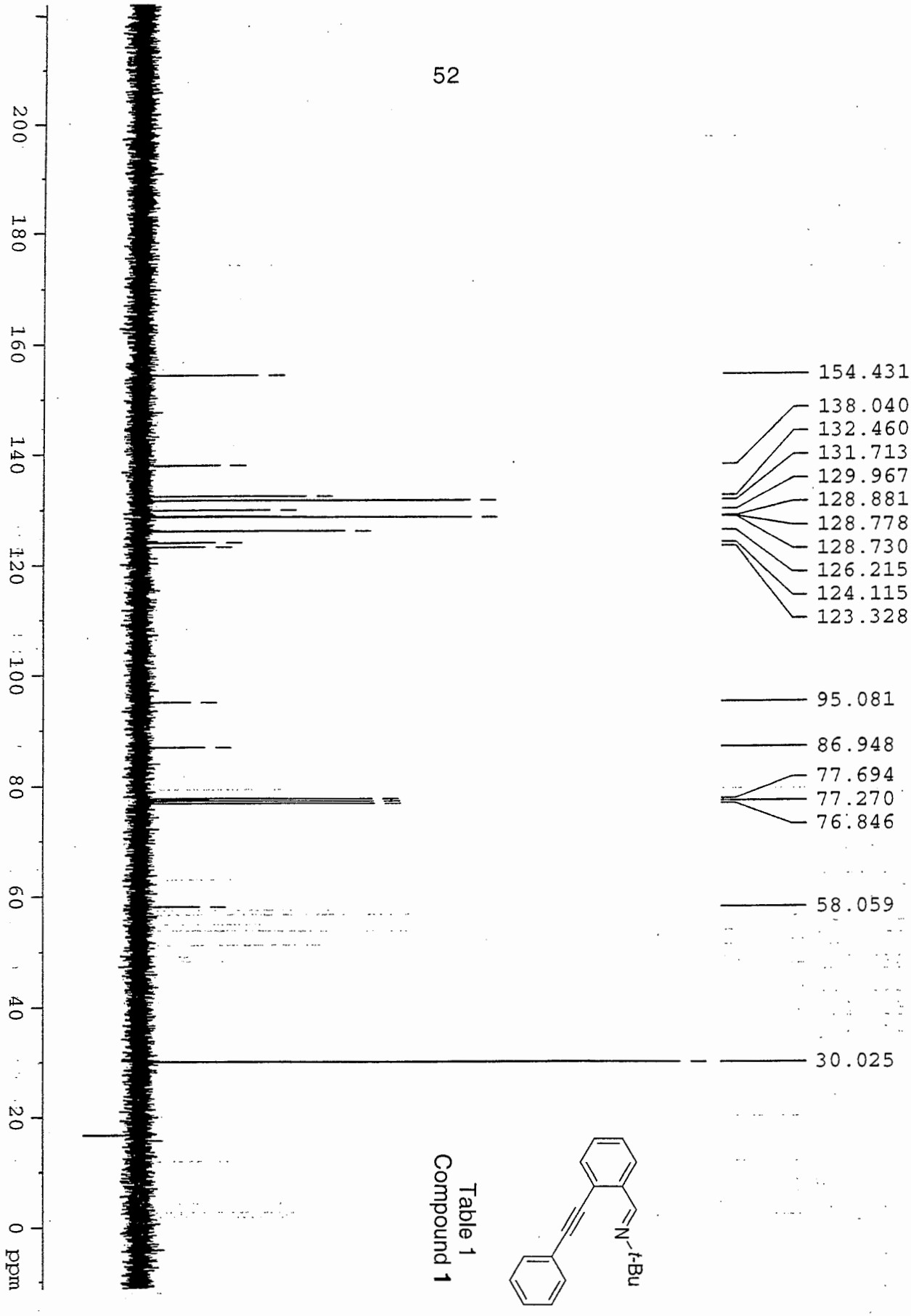
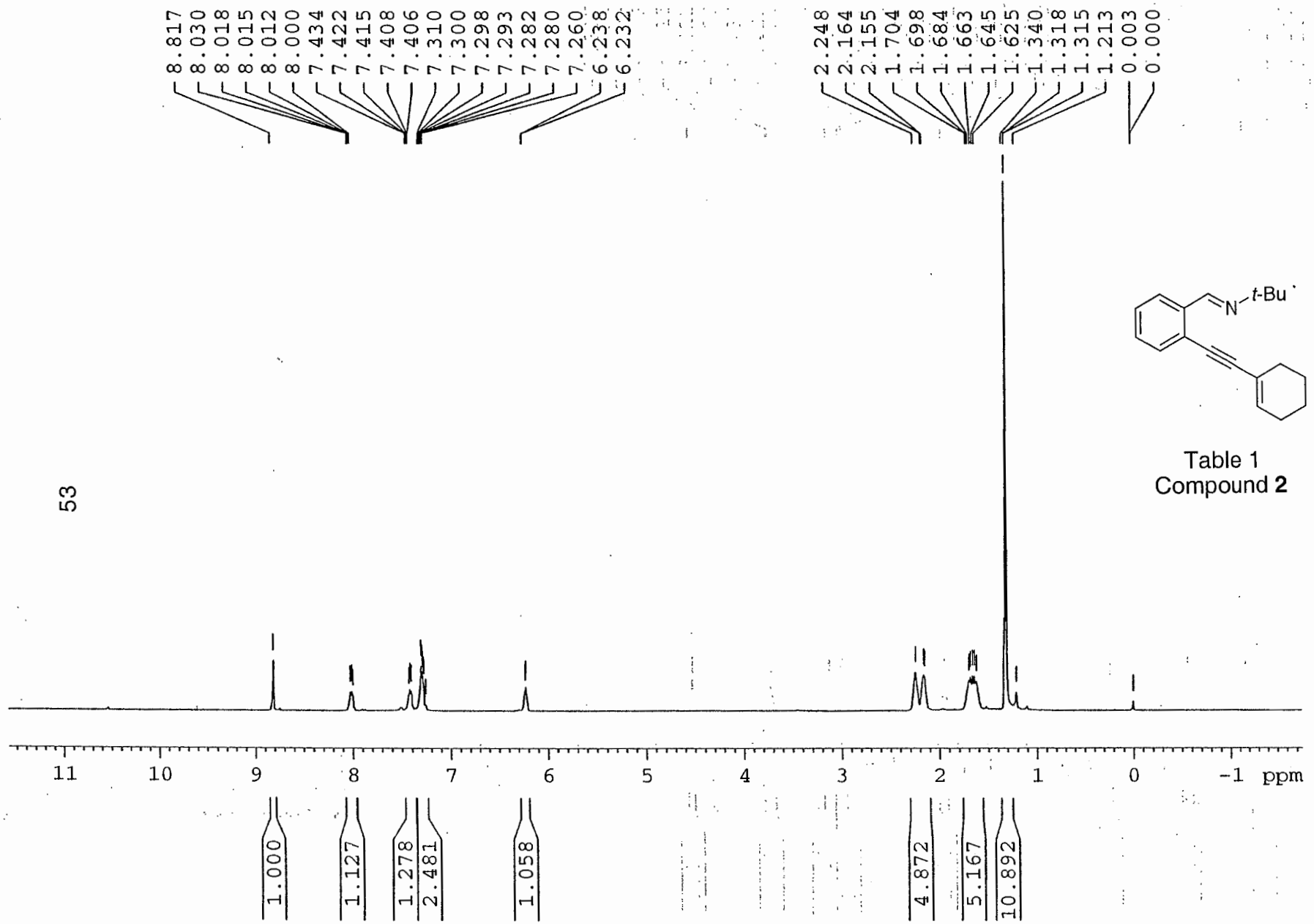


Table 1
Compound **1**



53

Table 1
Compound **2**

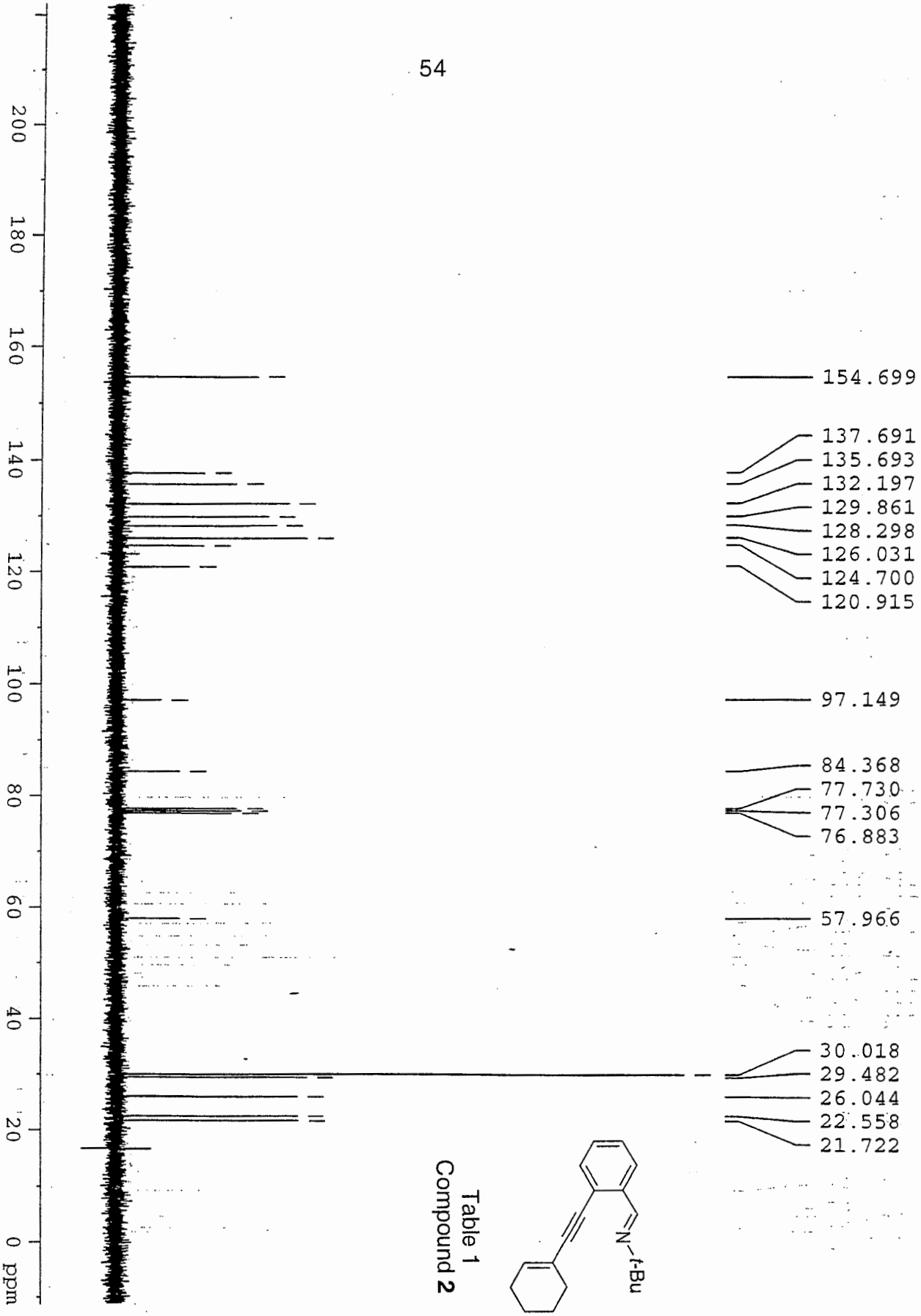


Table 1
Compound **2**

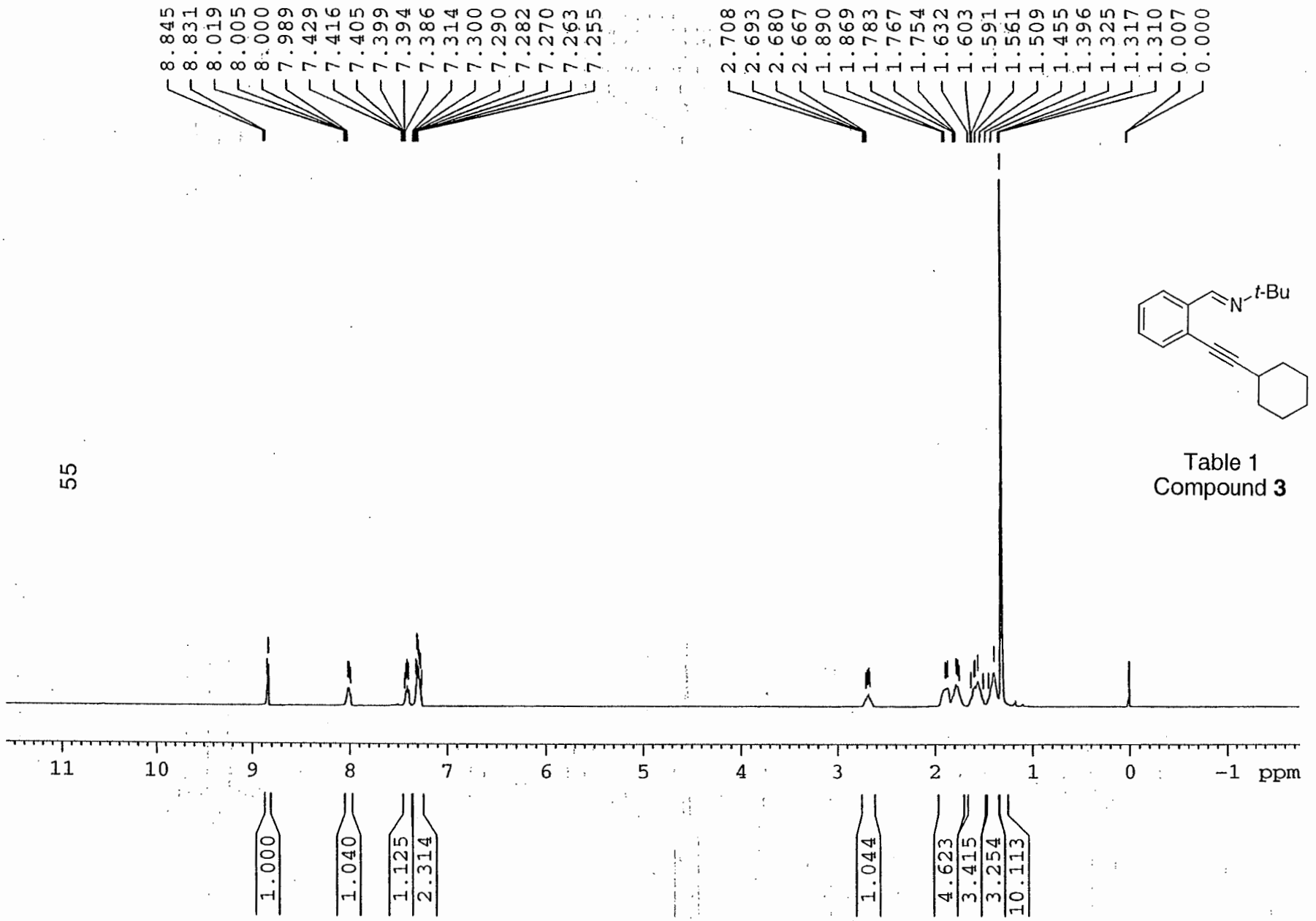


Table 1
Compound **3**

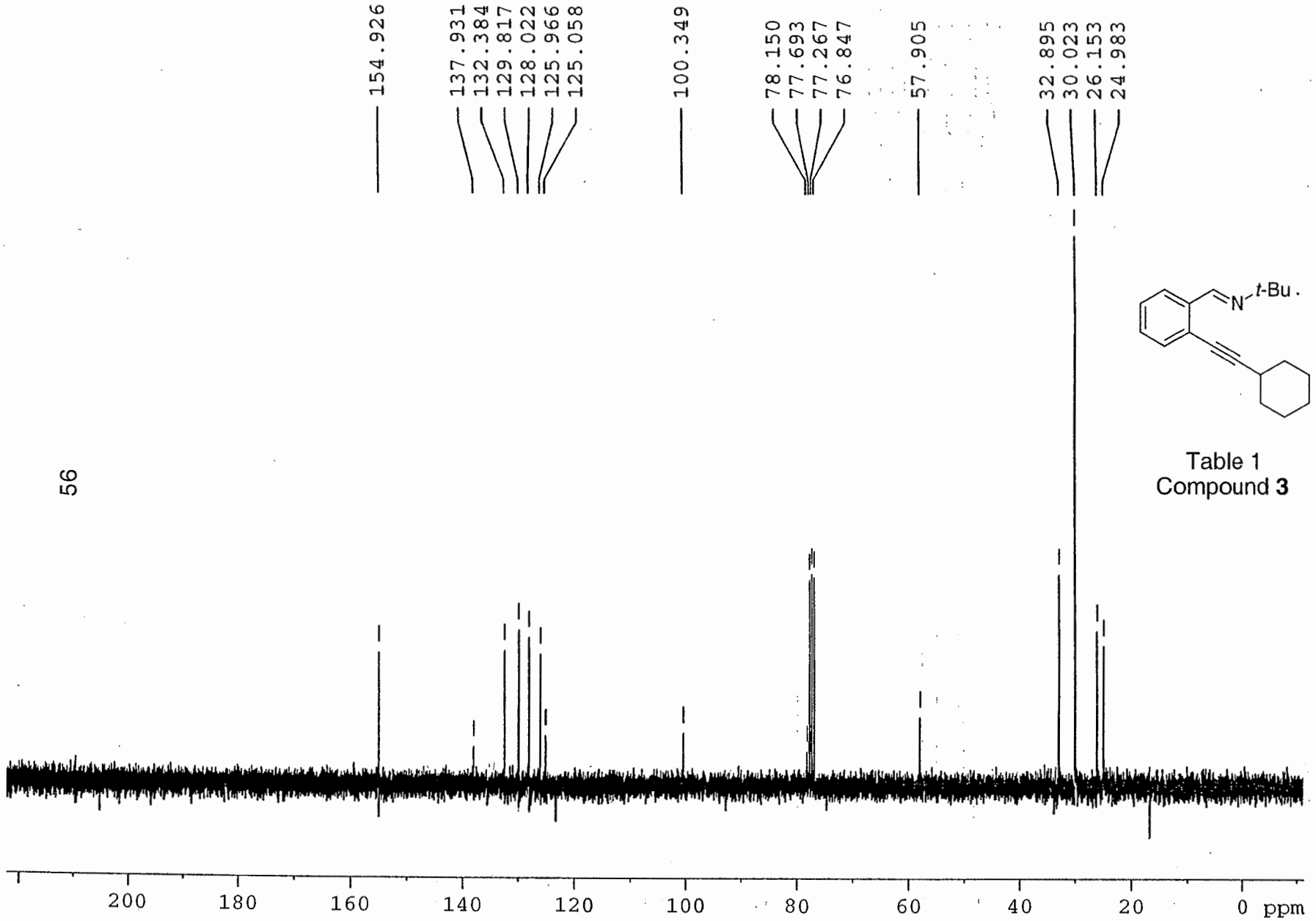


Table 1
Compound **3**

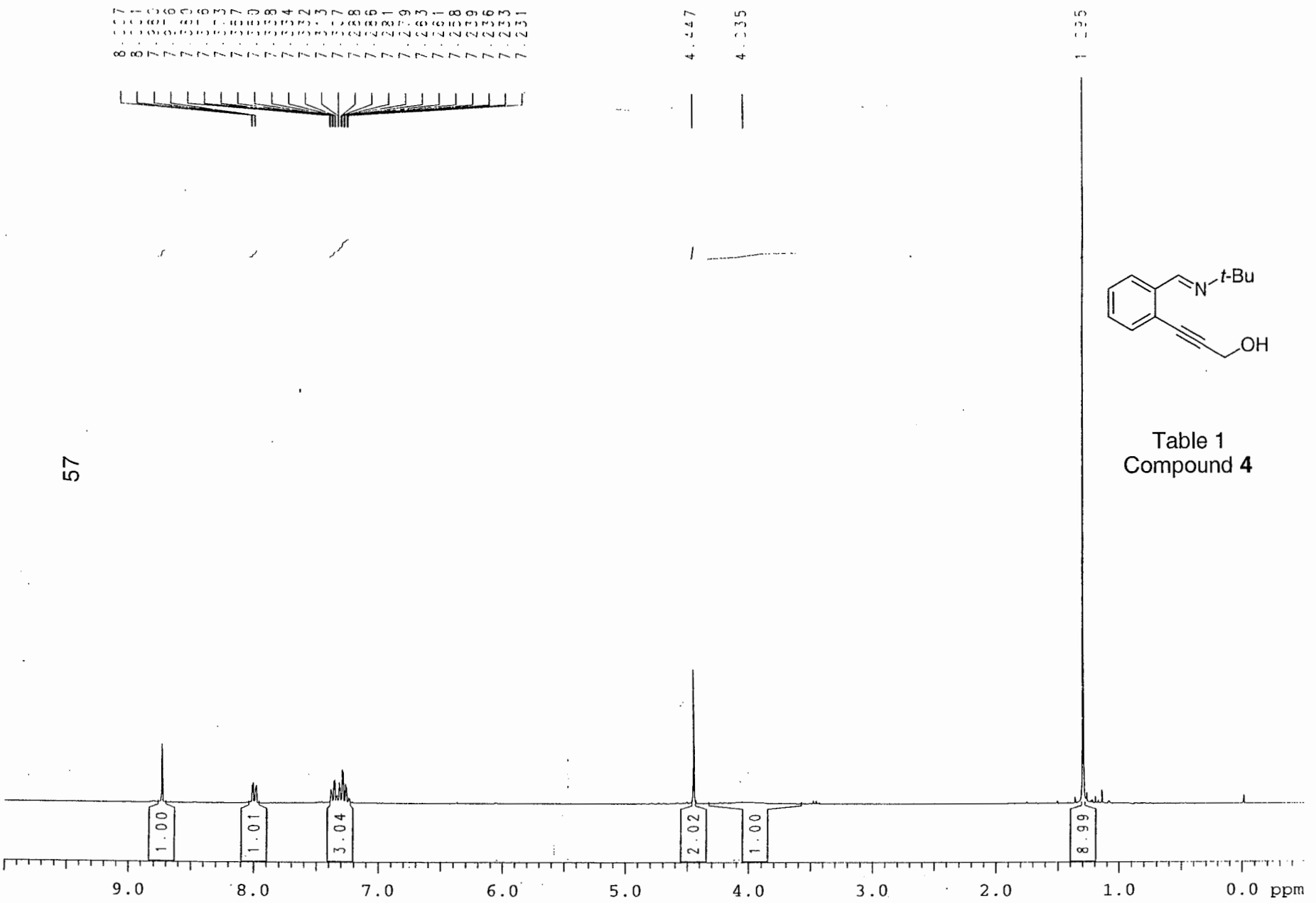
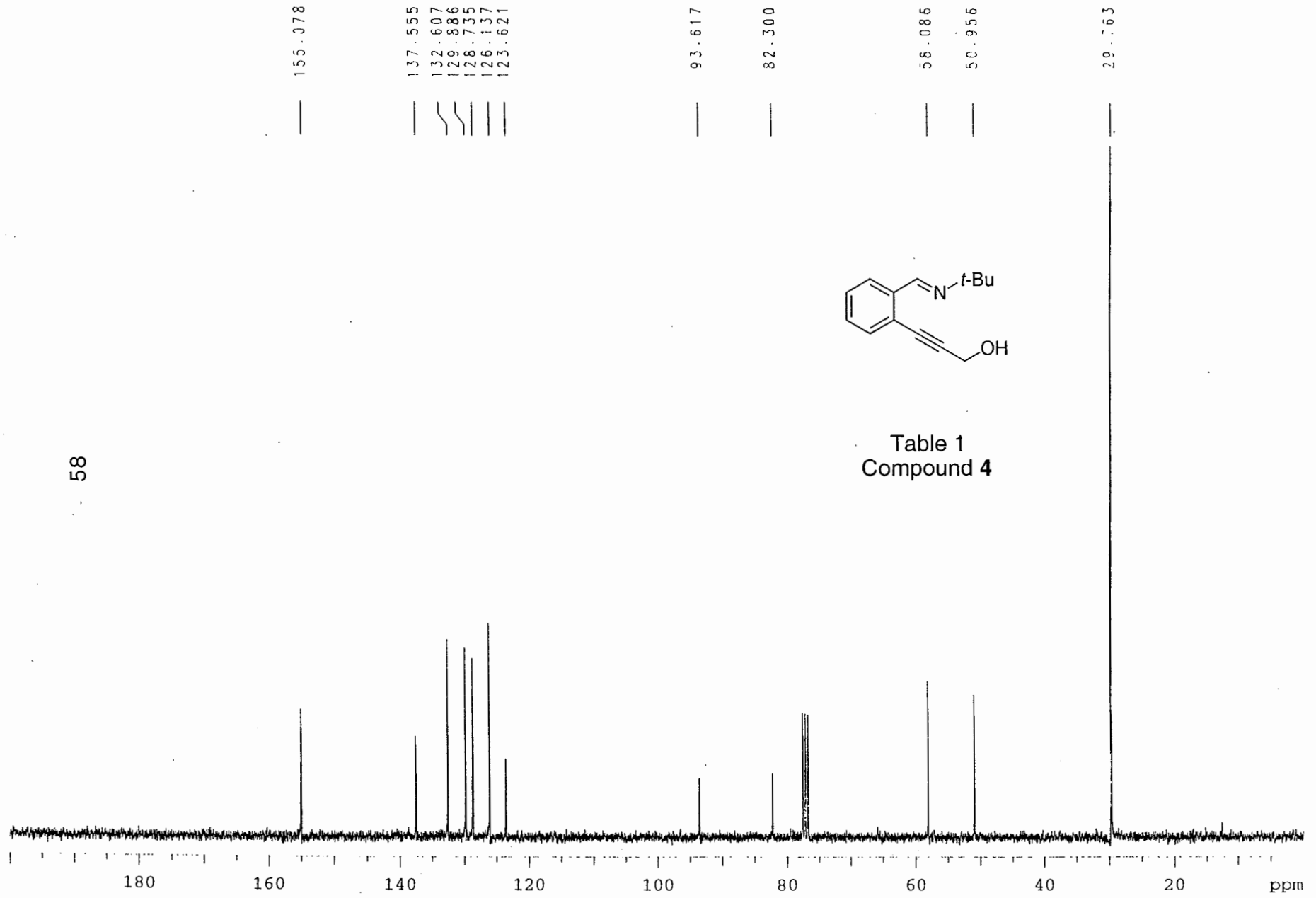
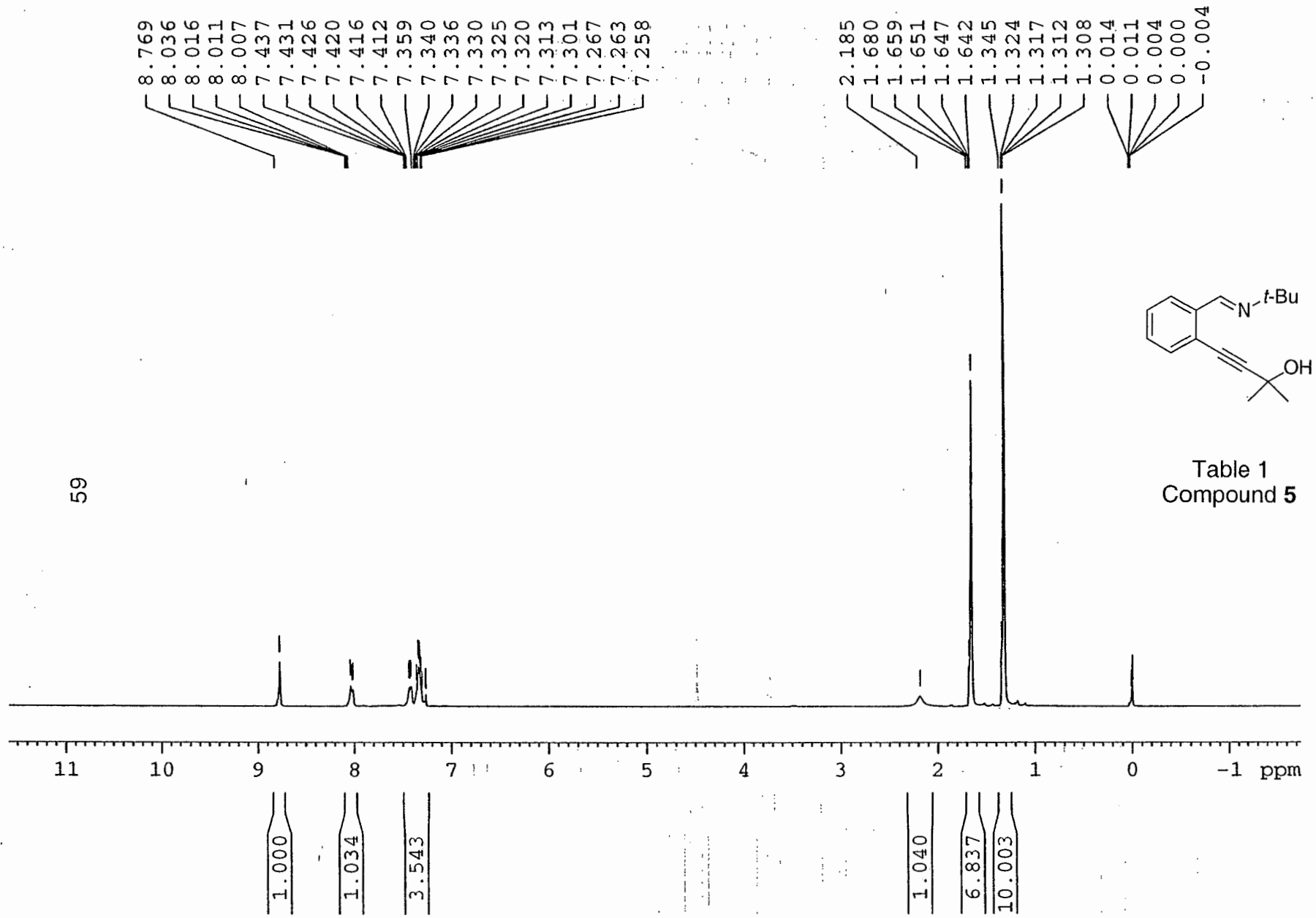


Table 1
Compound **4**



58

Table 1
Compound **4**



59

Table 1
Compound **5**

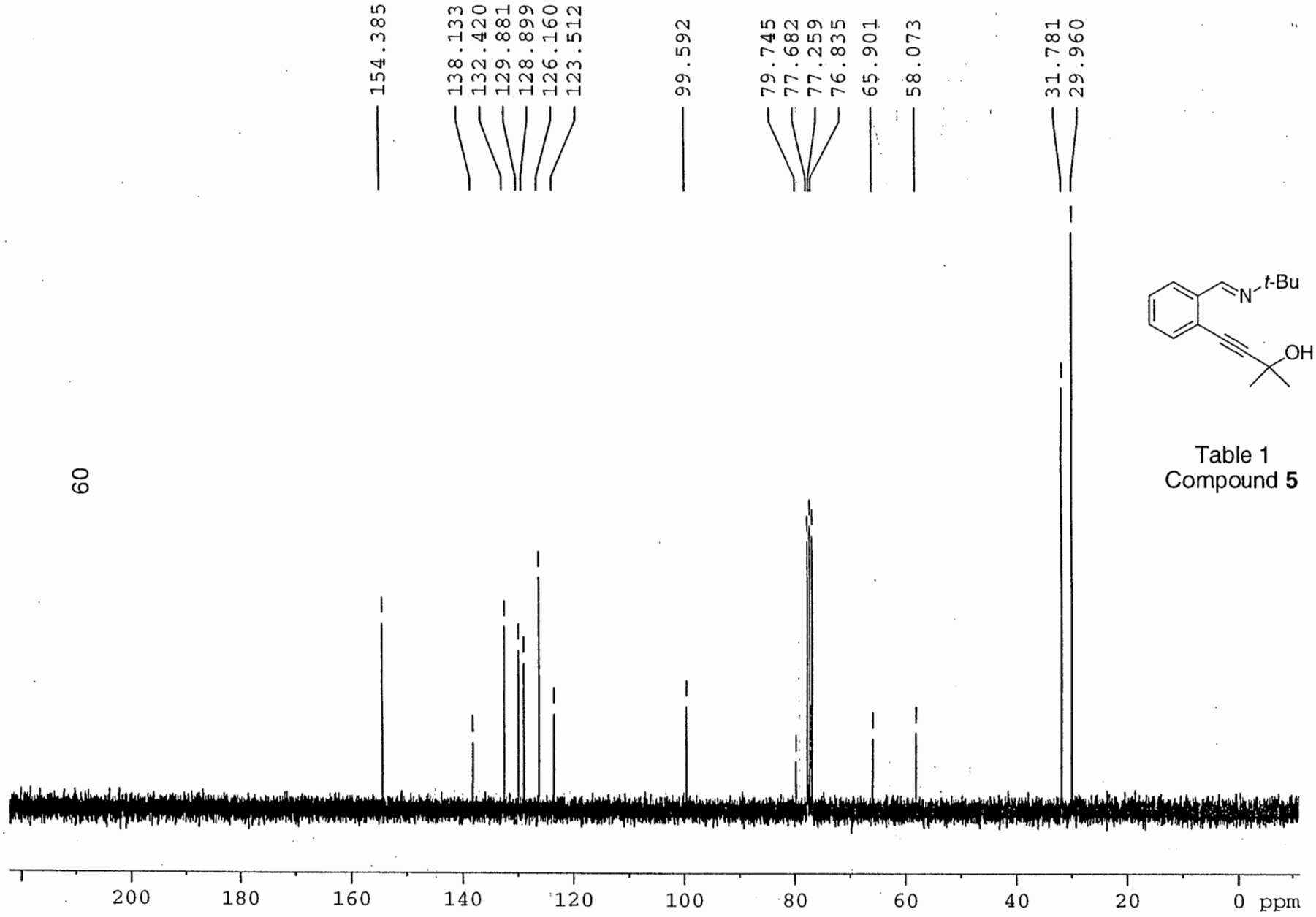
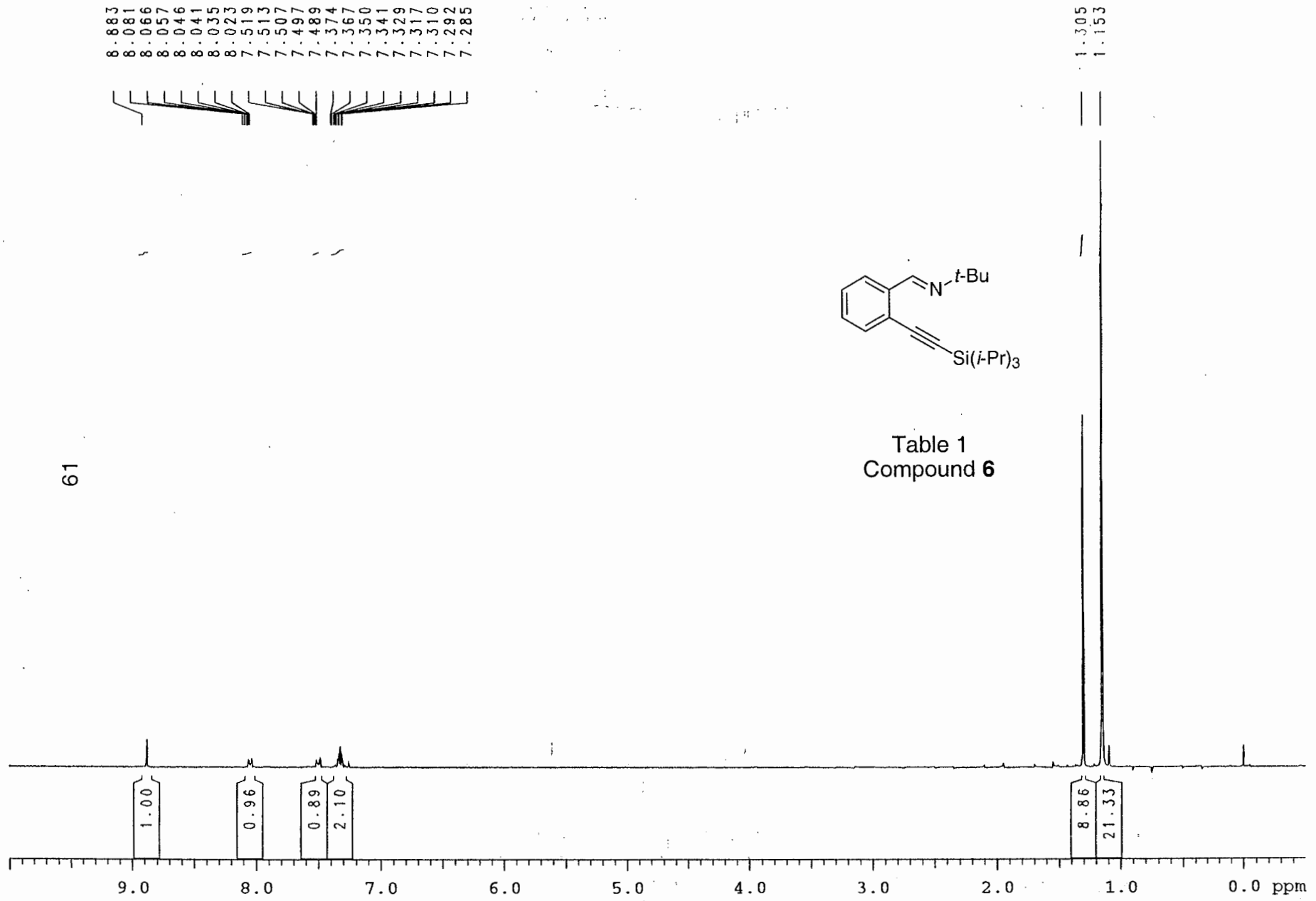


Table 1
Compound **5**



61

Table 1
Compound **6**

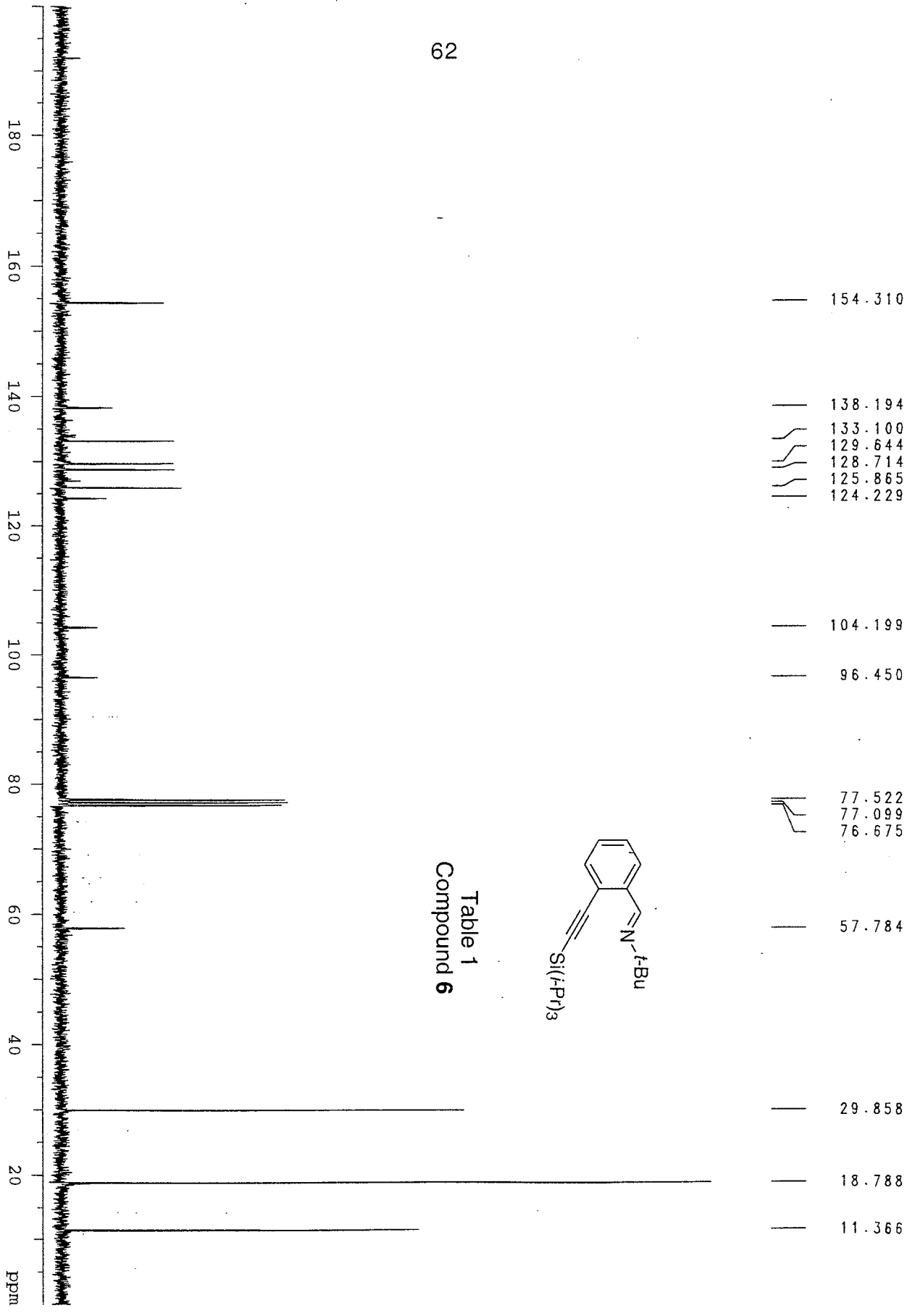


Table 1
Compound **6**

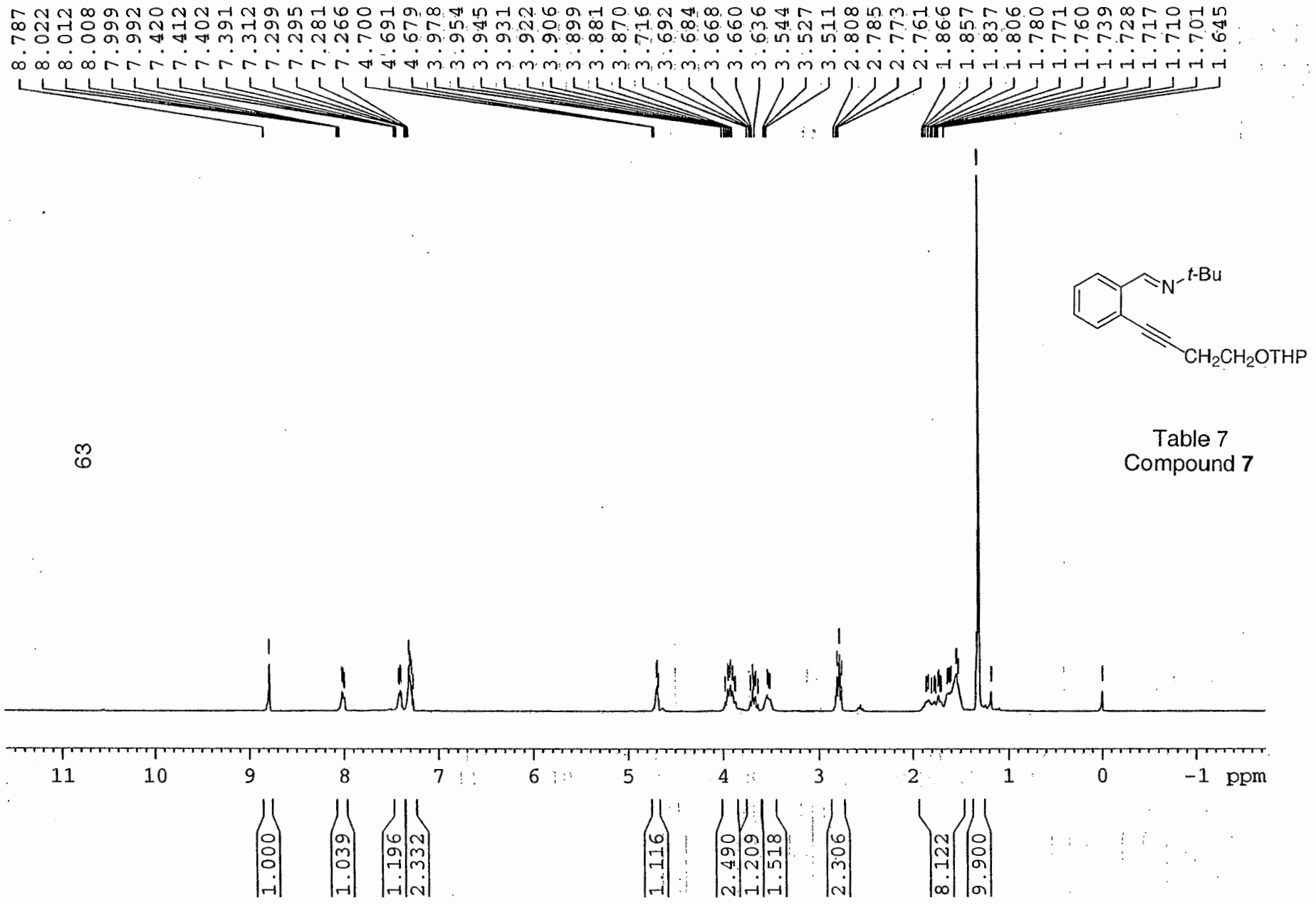


Table 7
Compound **7**

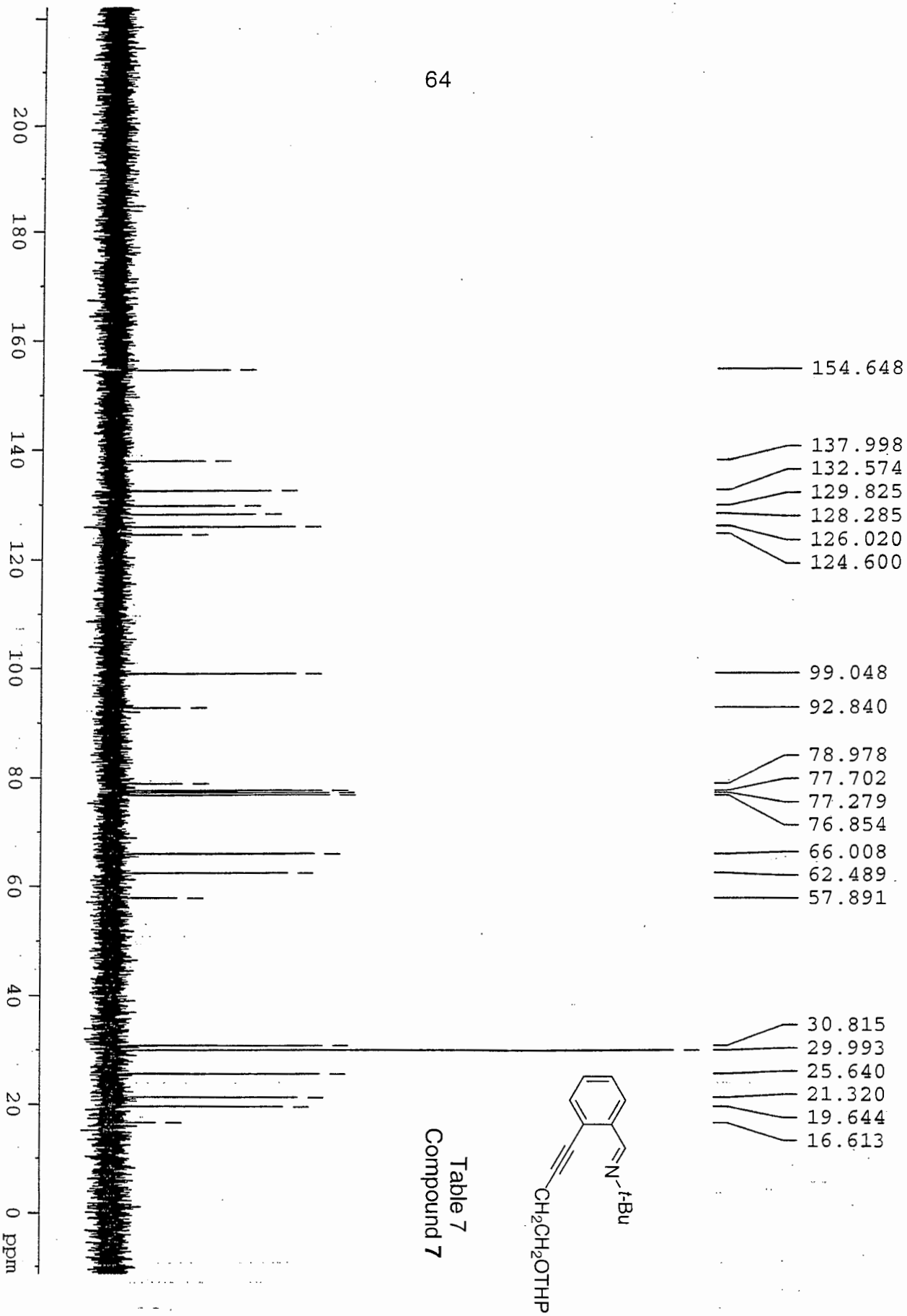
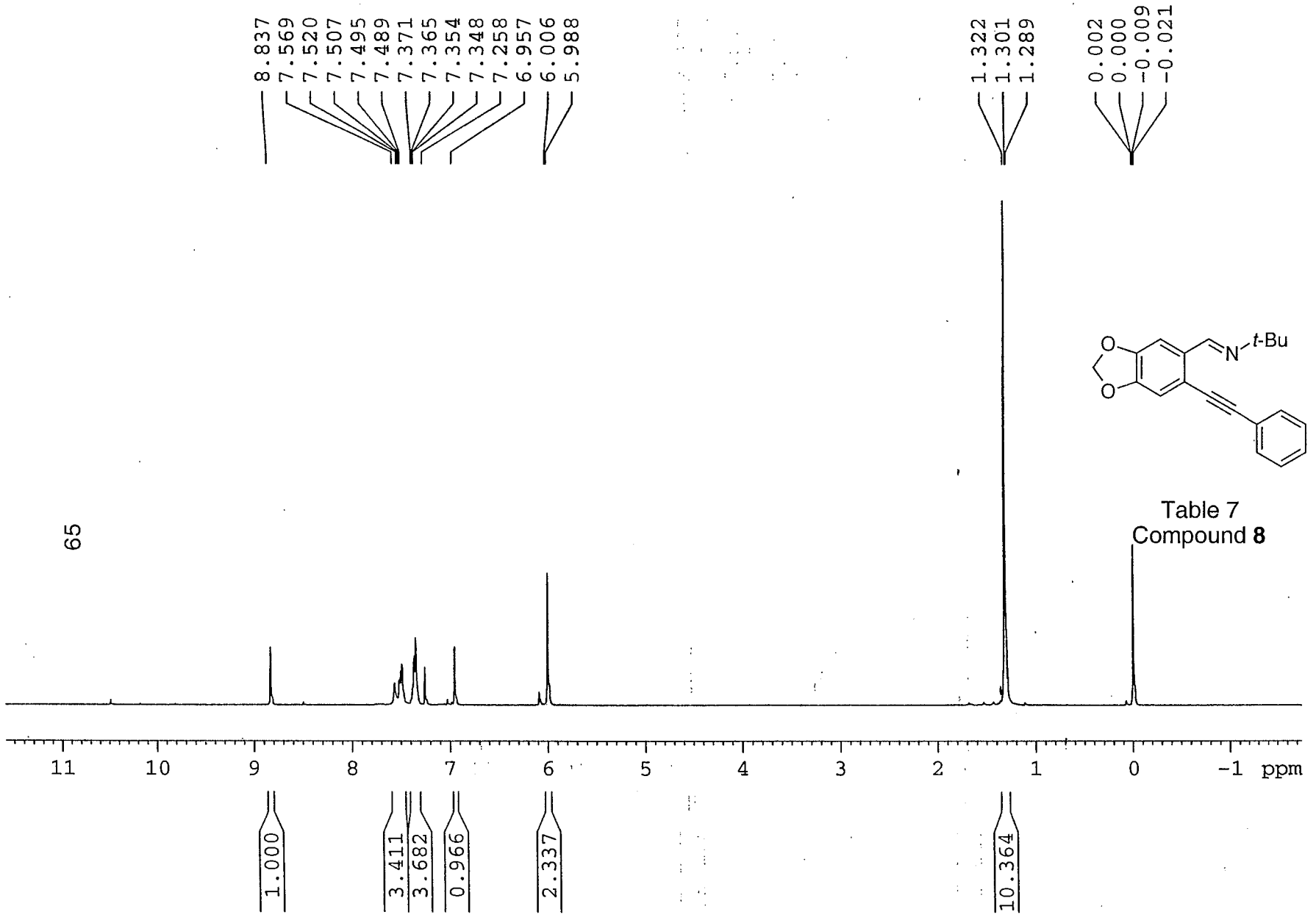


Table 7
Compound **7**


8.837
7.569
7.520
7.507
7.495
7.489
7.371
7.365
7.354
7.348
7.258
6.957
6.006
5.988
1.322
1.301
1.289
0.002
0.000
-0.009
-0.021
O
O
O
N
t-Bu
65
Table 7
Compound 8
11
10
9
8
7
6
5
4
3
2
1
0
-1
ppm
1.000
3.411
3.682
0.966
2.337
10.364

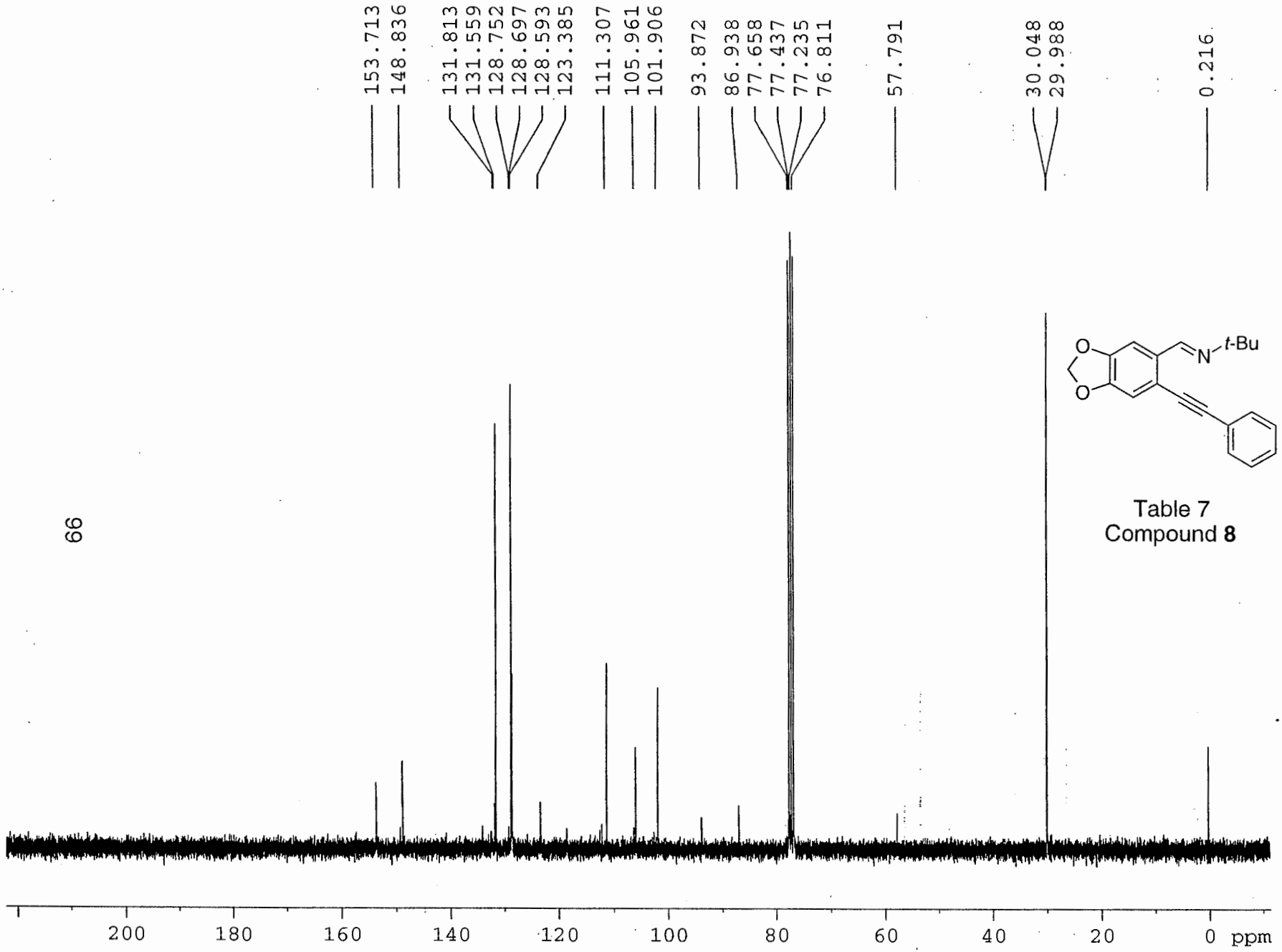


Table 7
Compound **8**

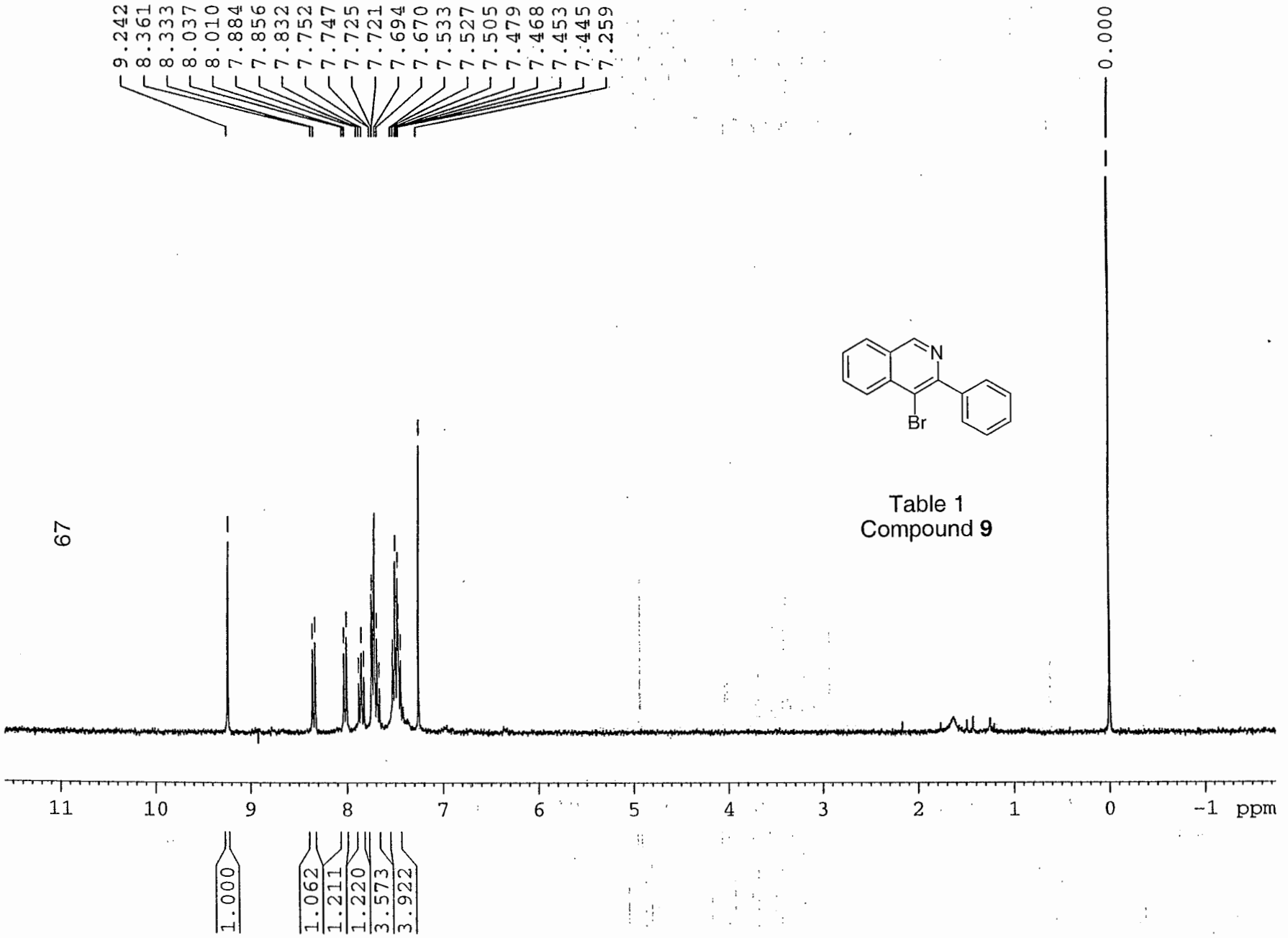


Table 1
Compound **9**

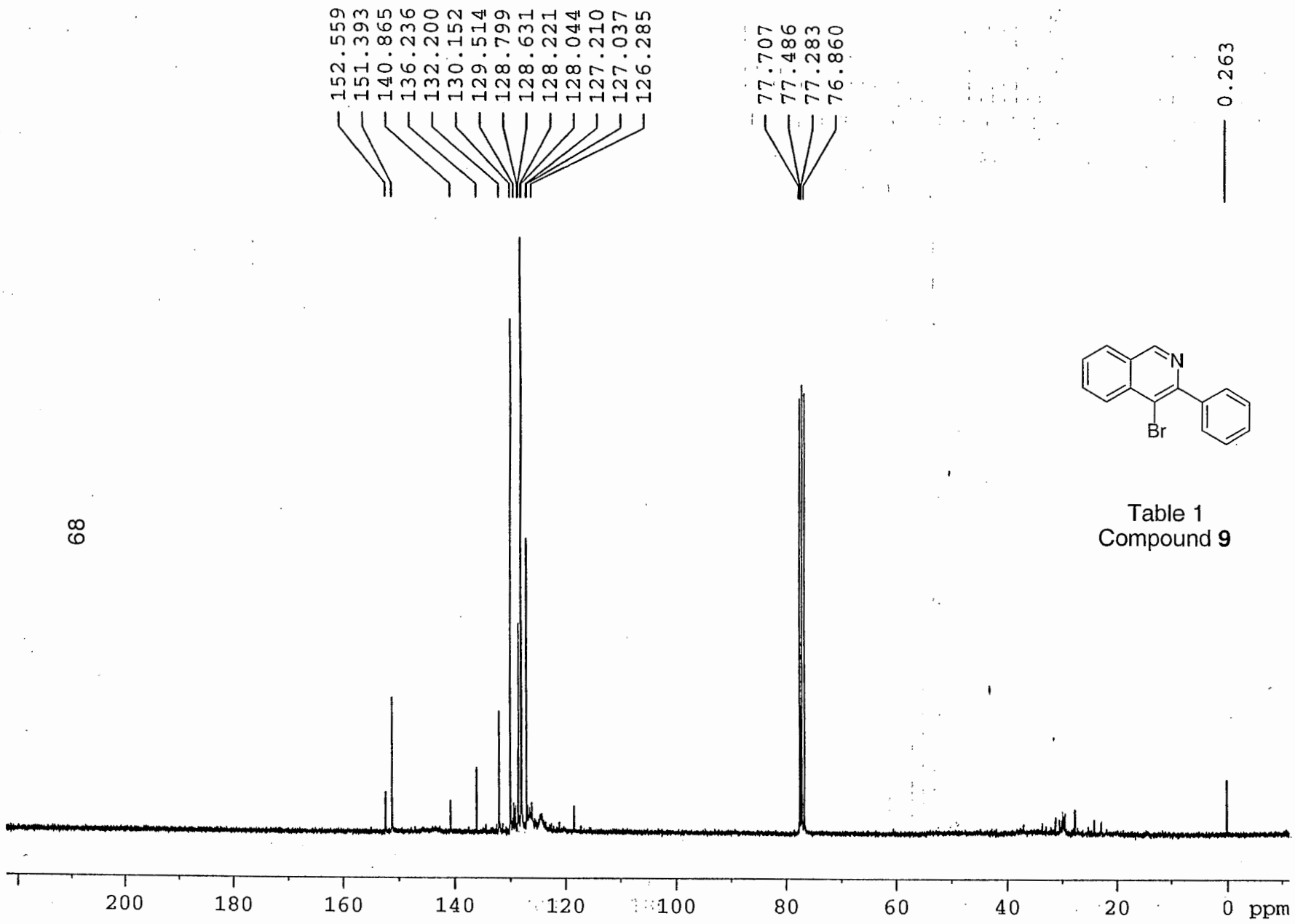


Table 1
Compound **9**

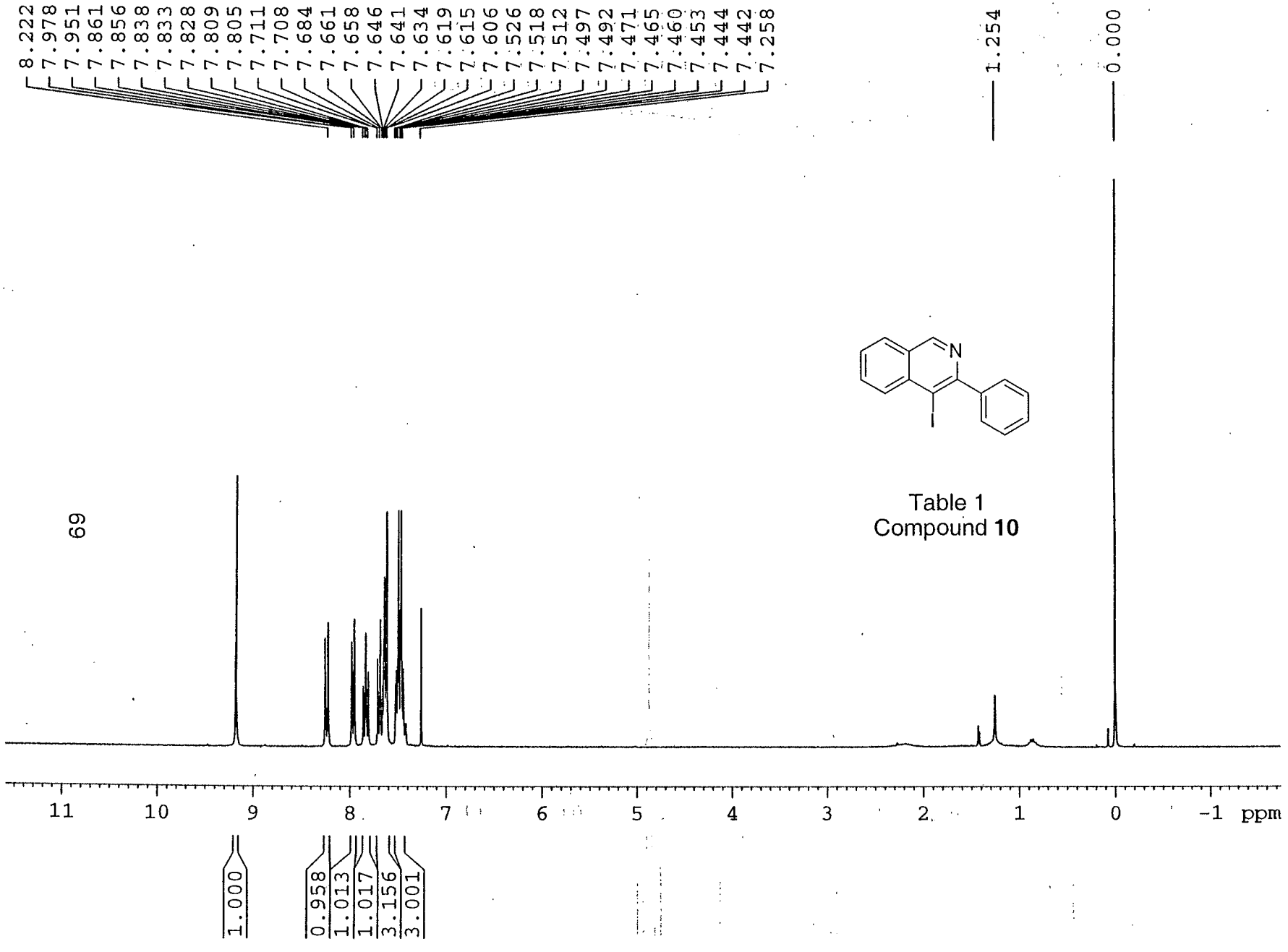


Table 1
Compound **10**

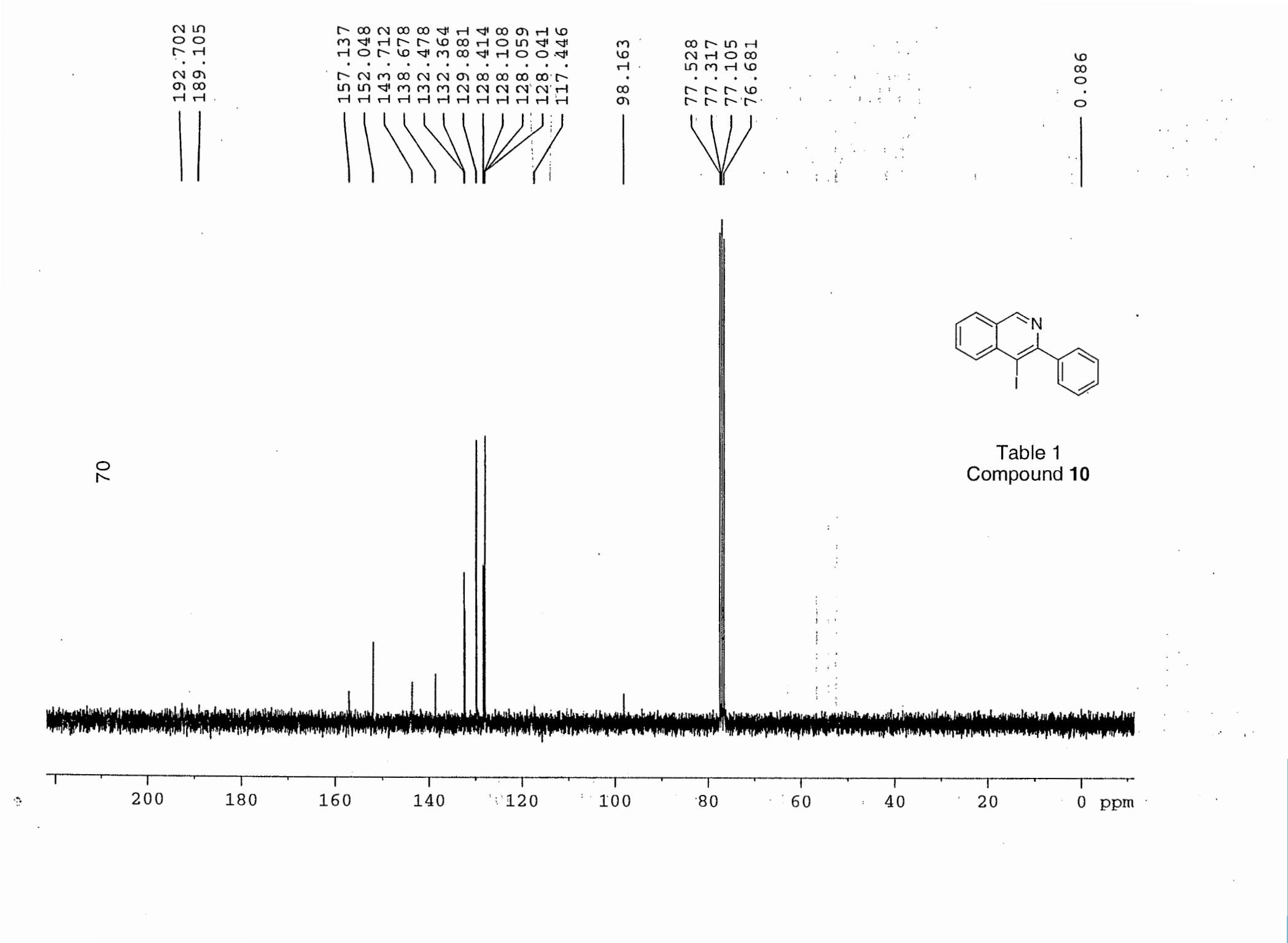
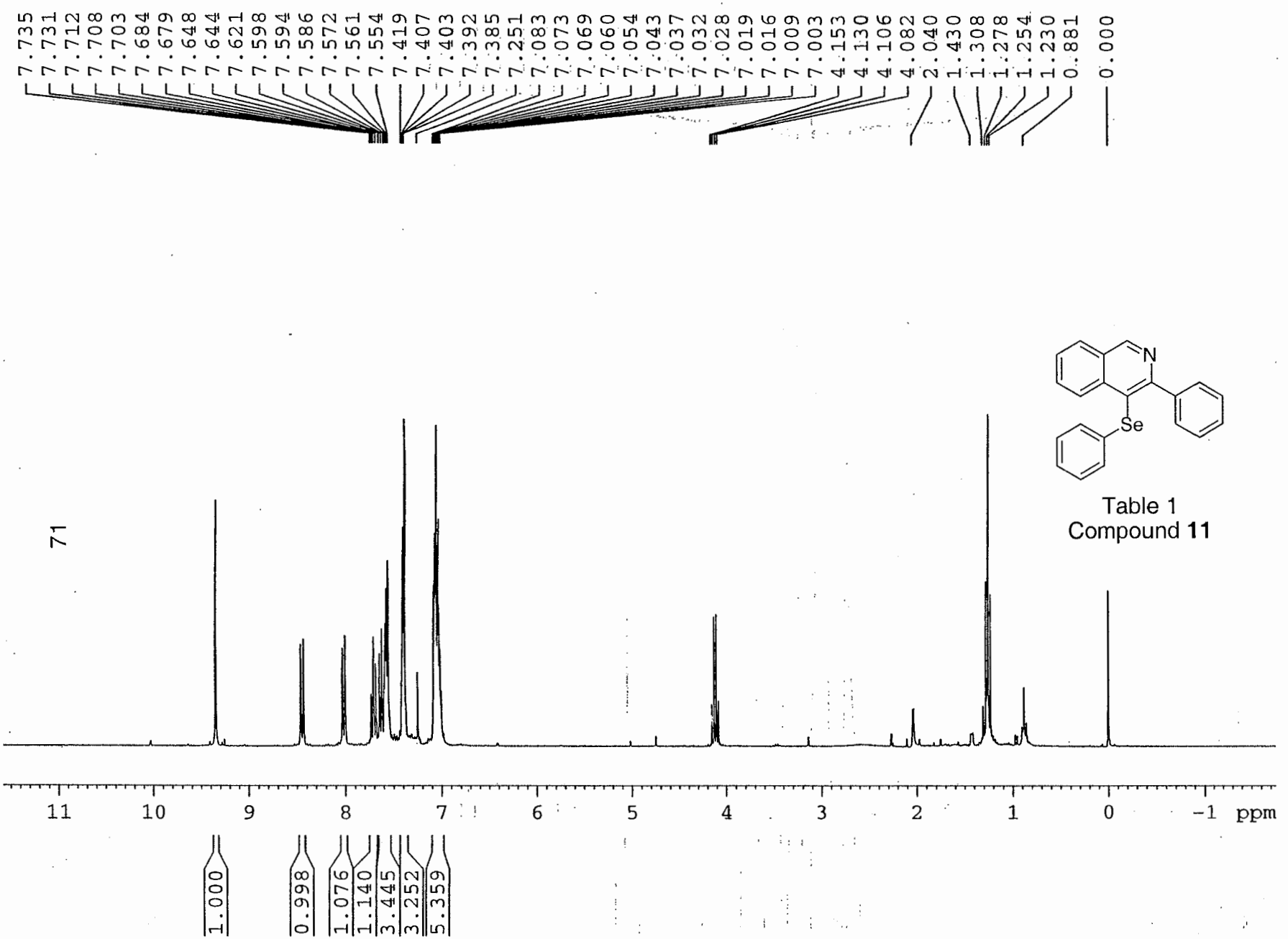


Table 1
Compound **10**


7.735
7.731
7.712
7.708
7.703
7.684
7.679
7.648
7.644
7.621
7.598
7.594
7.586
7.572
7.561
7.554
7.419
7.407
7.403
7.392
7.385
7.251
7.083
7.073
7.069
7.060
7.054
7.043
7.037
7.032
7.028
7.019
7.016
7.009
7.003
4.153
4.130
4.106
4.082
2.040
1.430
1.308
1.278
1.254
1.230
0.881
0.000
71
N
Se
Table 1
Compound 11
11
10
9
8
7
6
5
4
3
2
1
0
−1
ppm
1.000
0.998
1.076
1.140
3.445
3.252
5.359

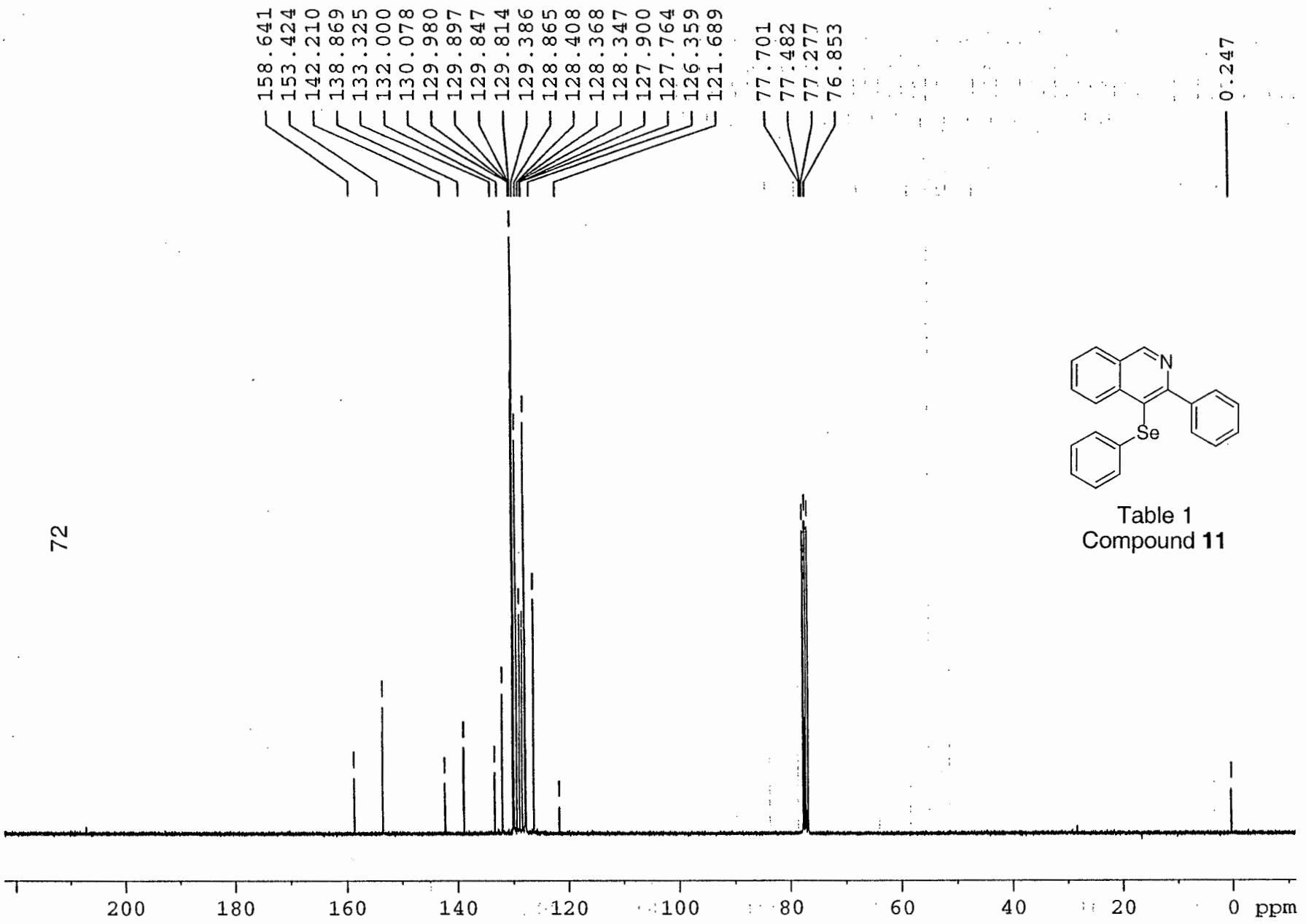
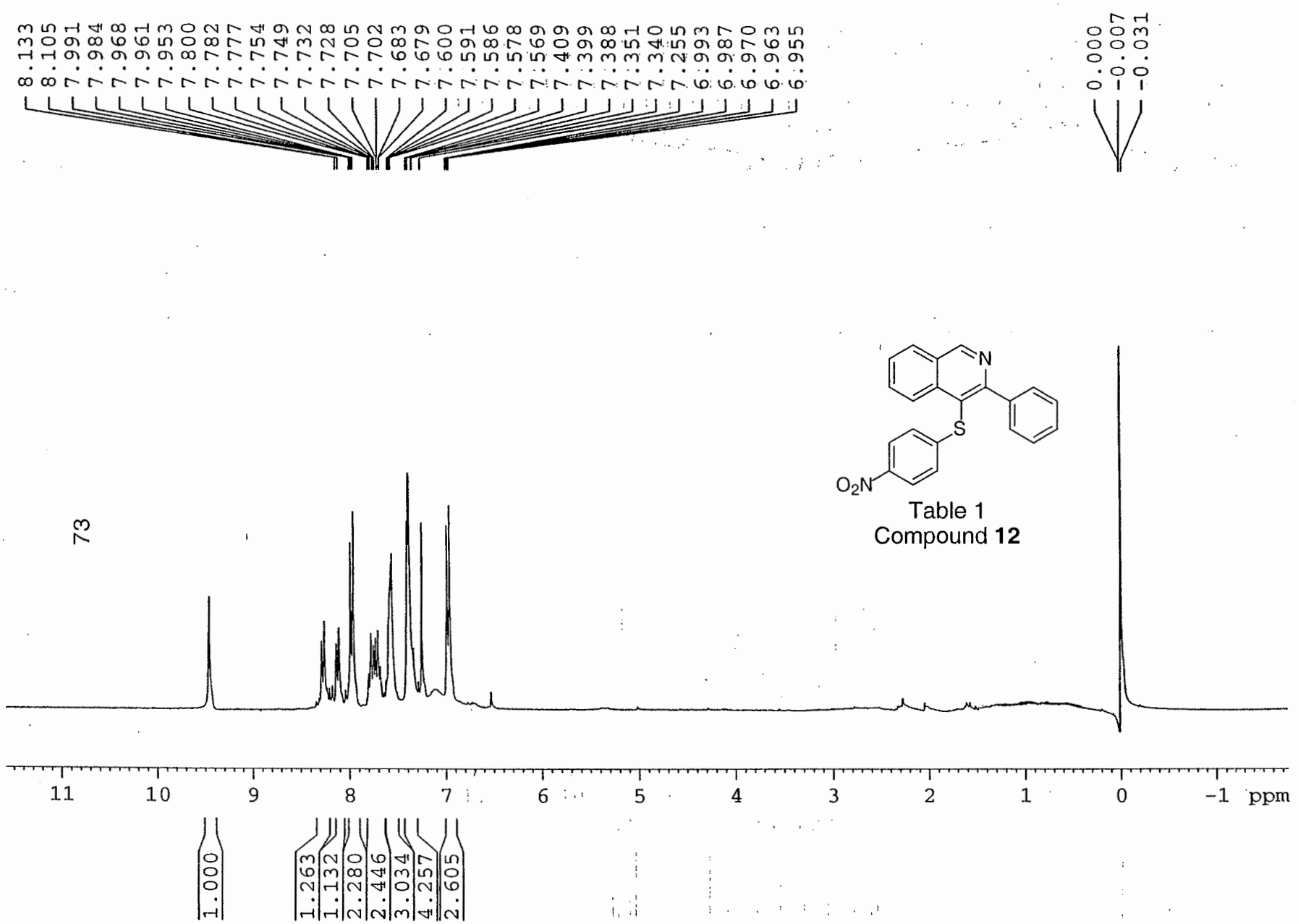


Table 1
Compound **11**


8.133
8.105
7.991
7.984
7.968
7.961
7.953
7.800
7.782
7.777
7.754
7.749
7.732
7.728
7.705
7.702
7.683
7.679
7.600
7.591
7.586
7.578
7.569
7.409
7.399
7.388
7.351
7.340
7.255
6.993
6.987
6.970
6.963
6.955
0.000
-0.007
-0.031
73
N
S
O_2N
Table 1
Compound **12**
11
10
9
8
7
6
5
4
3
2
1
0
-1 ppm
1.000
1.263
1.132
2.280
2.446
3.034
4.257
2.605

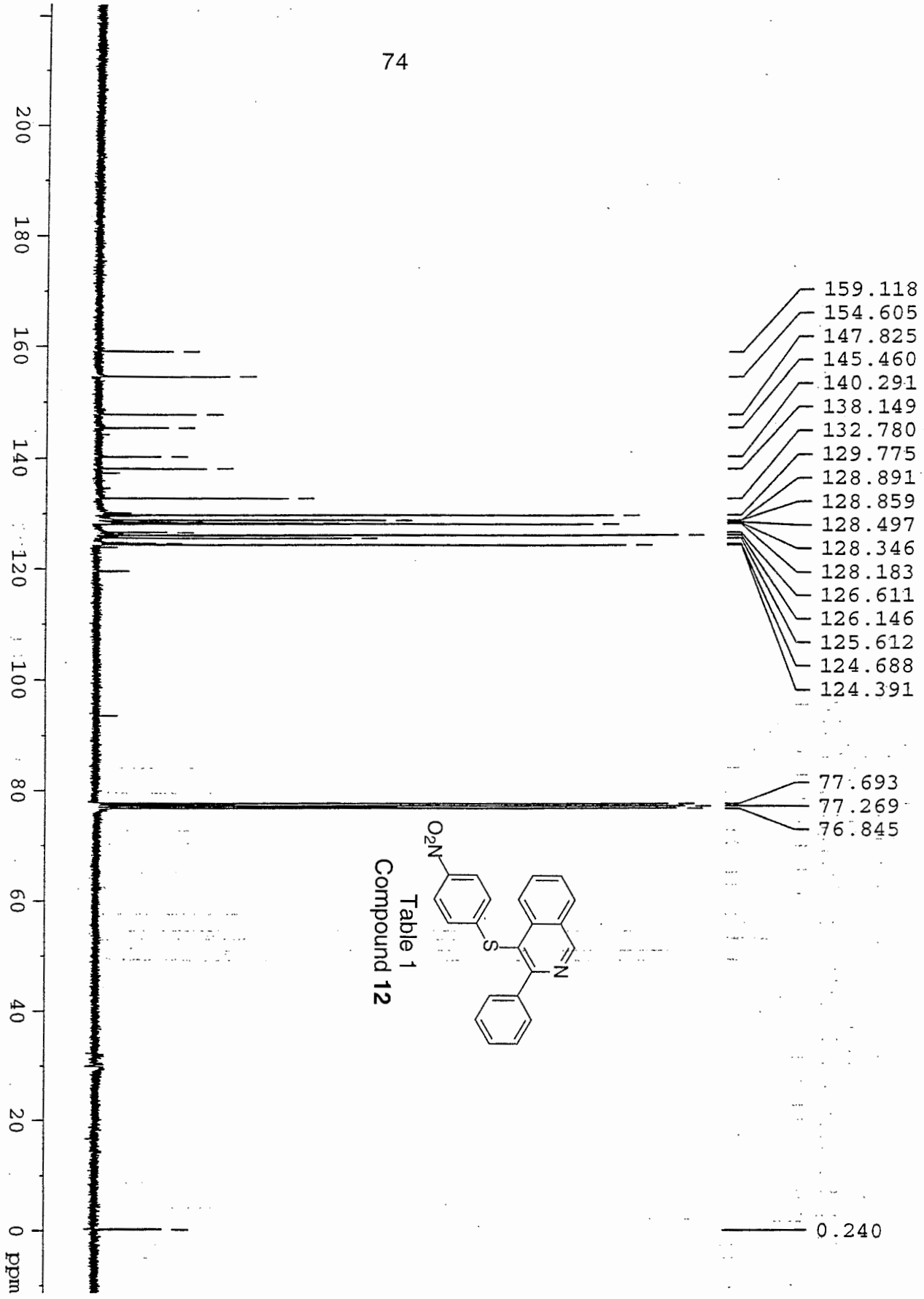


Table 1
Compound **12**

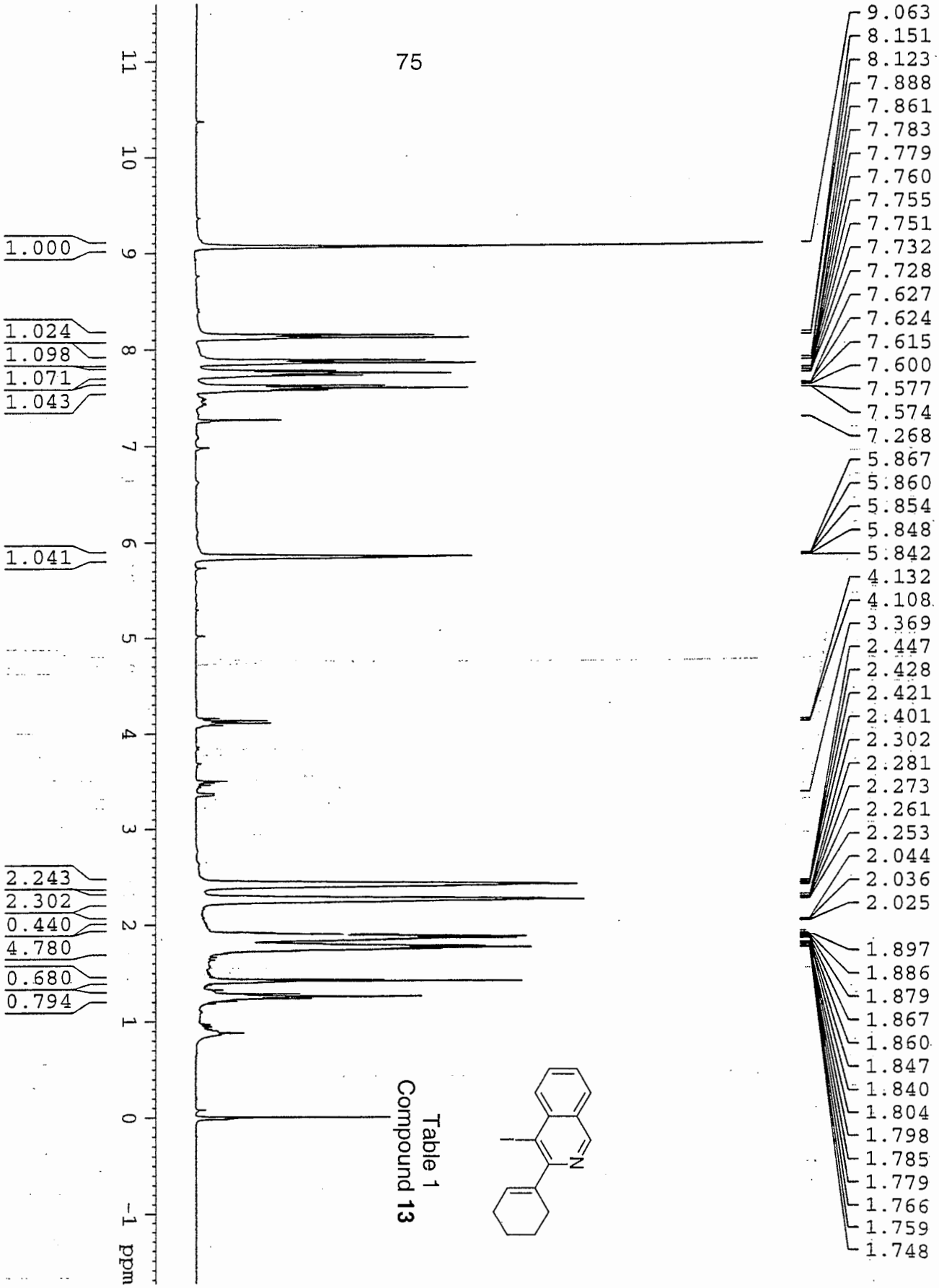


Table 1
Compound **13**

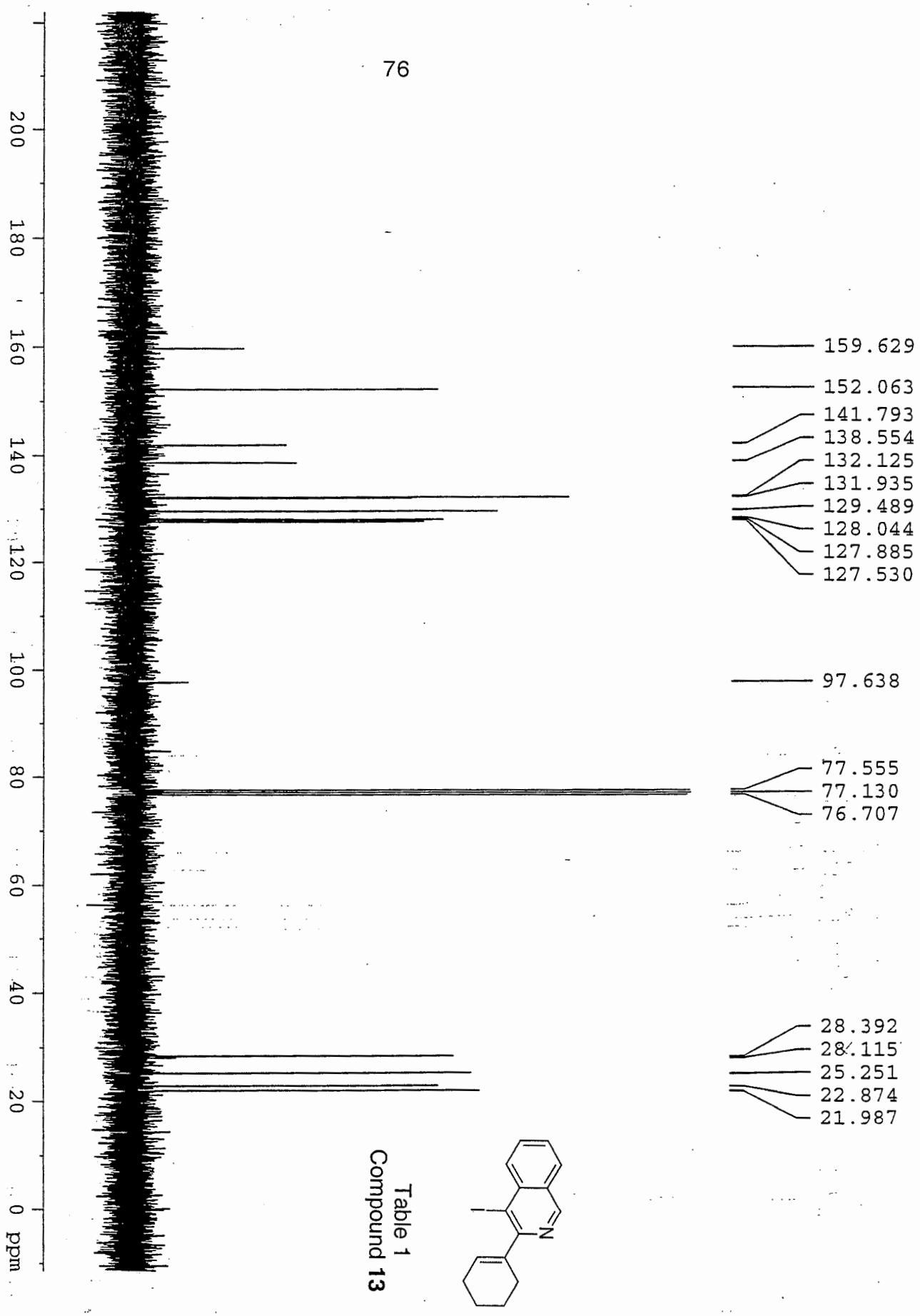


Table 1
Compound **13**

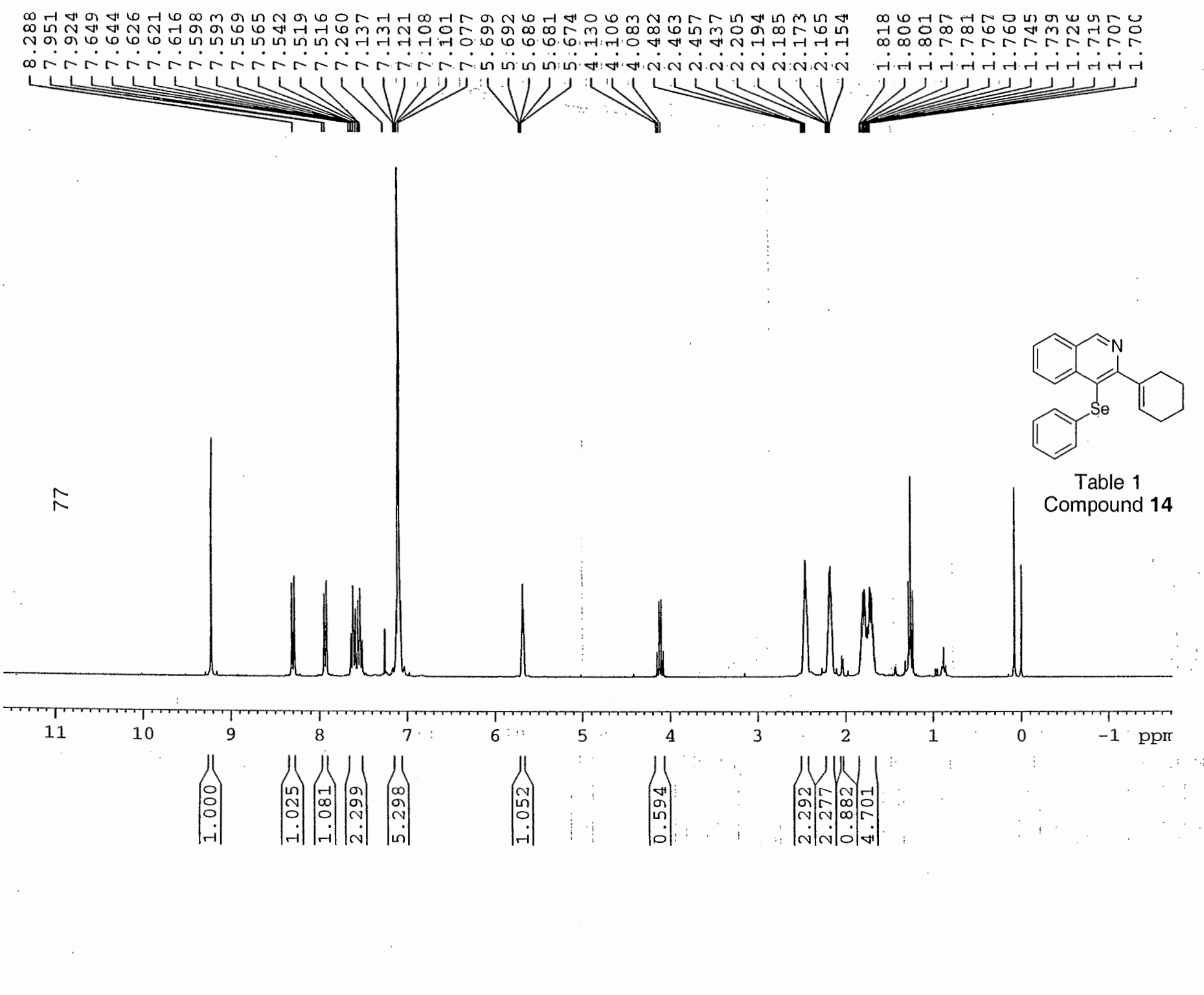


Table 1
Compound **14**

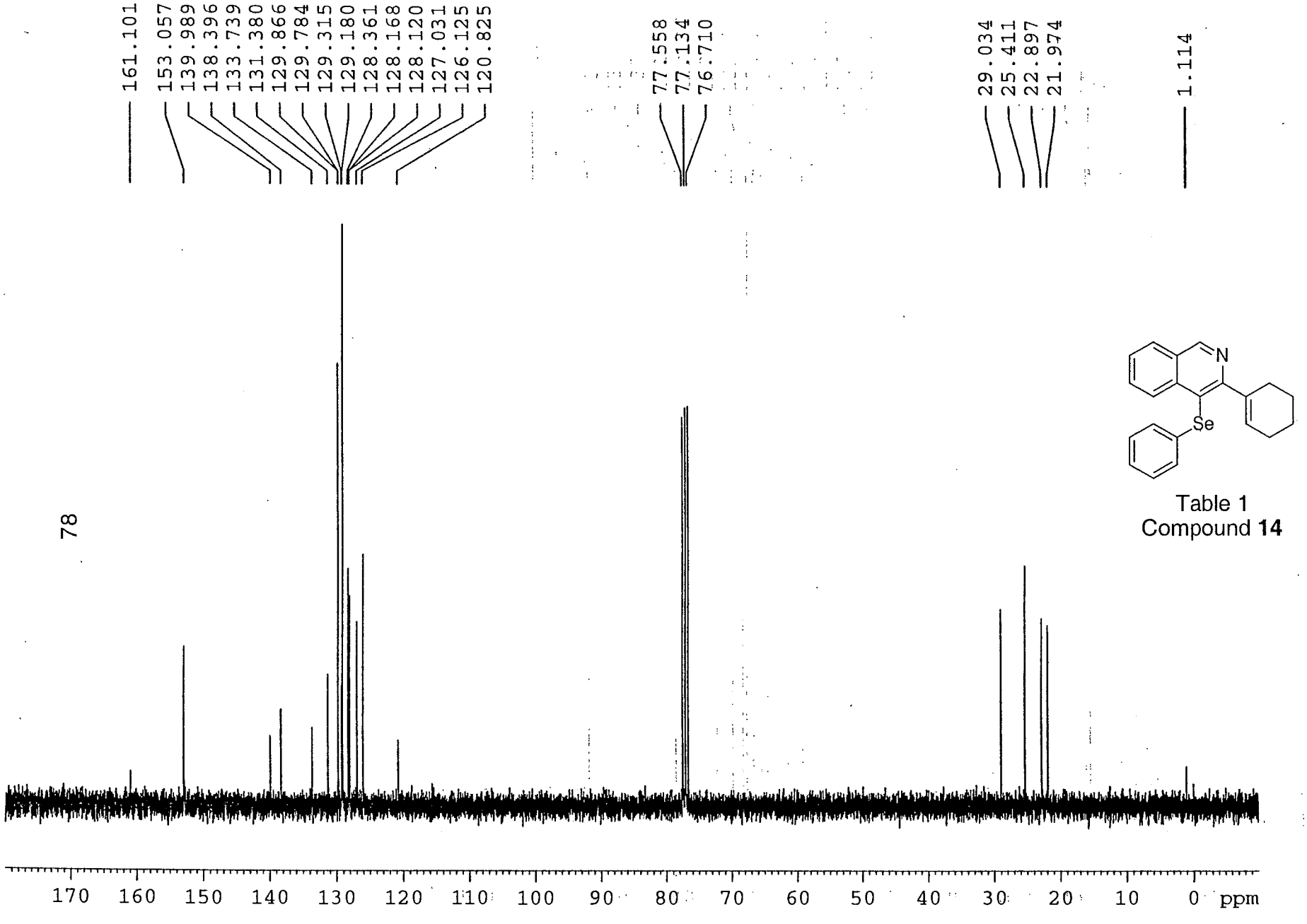


Table 1
Compound **14**

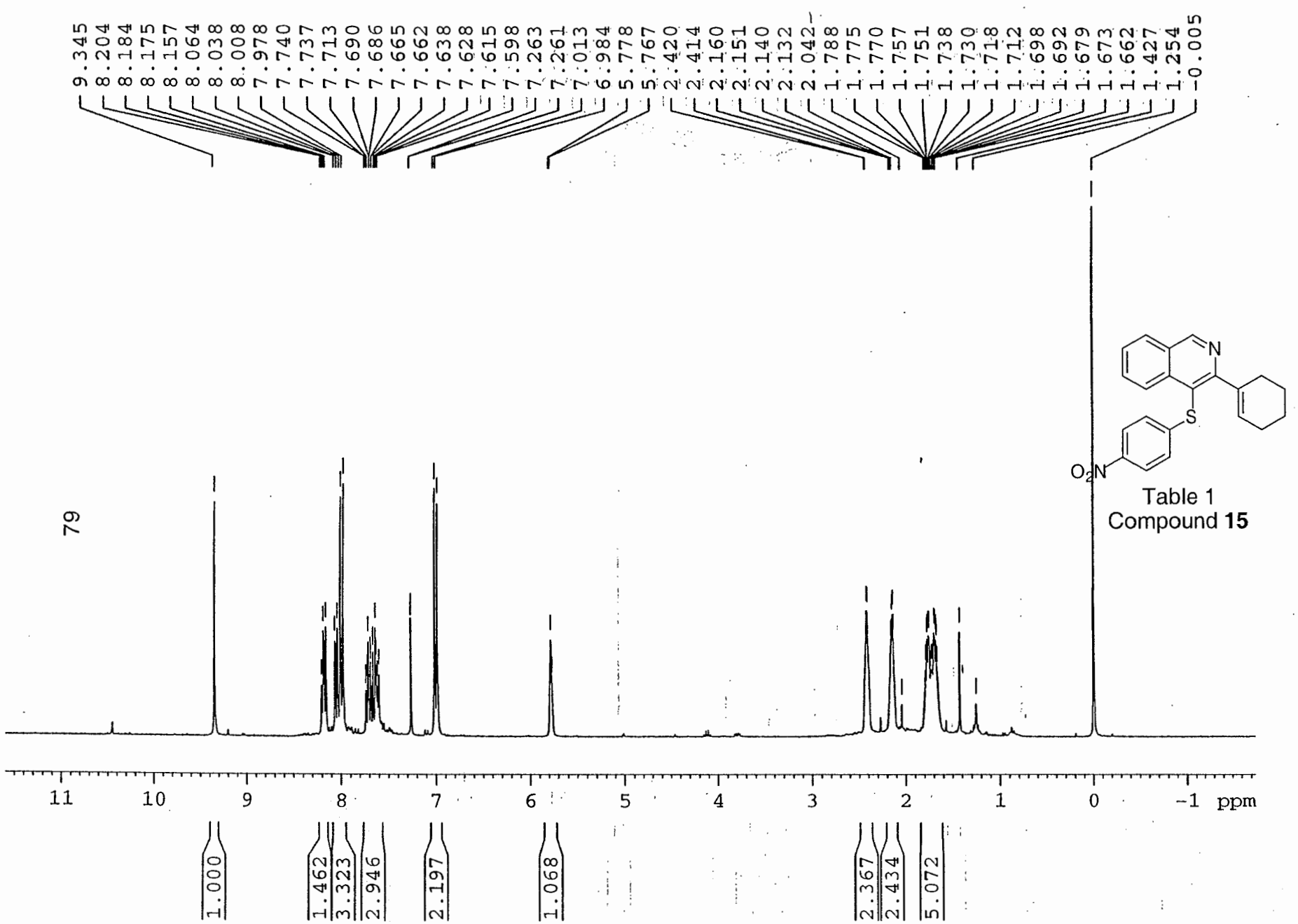


Table 1
Compound **15**

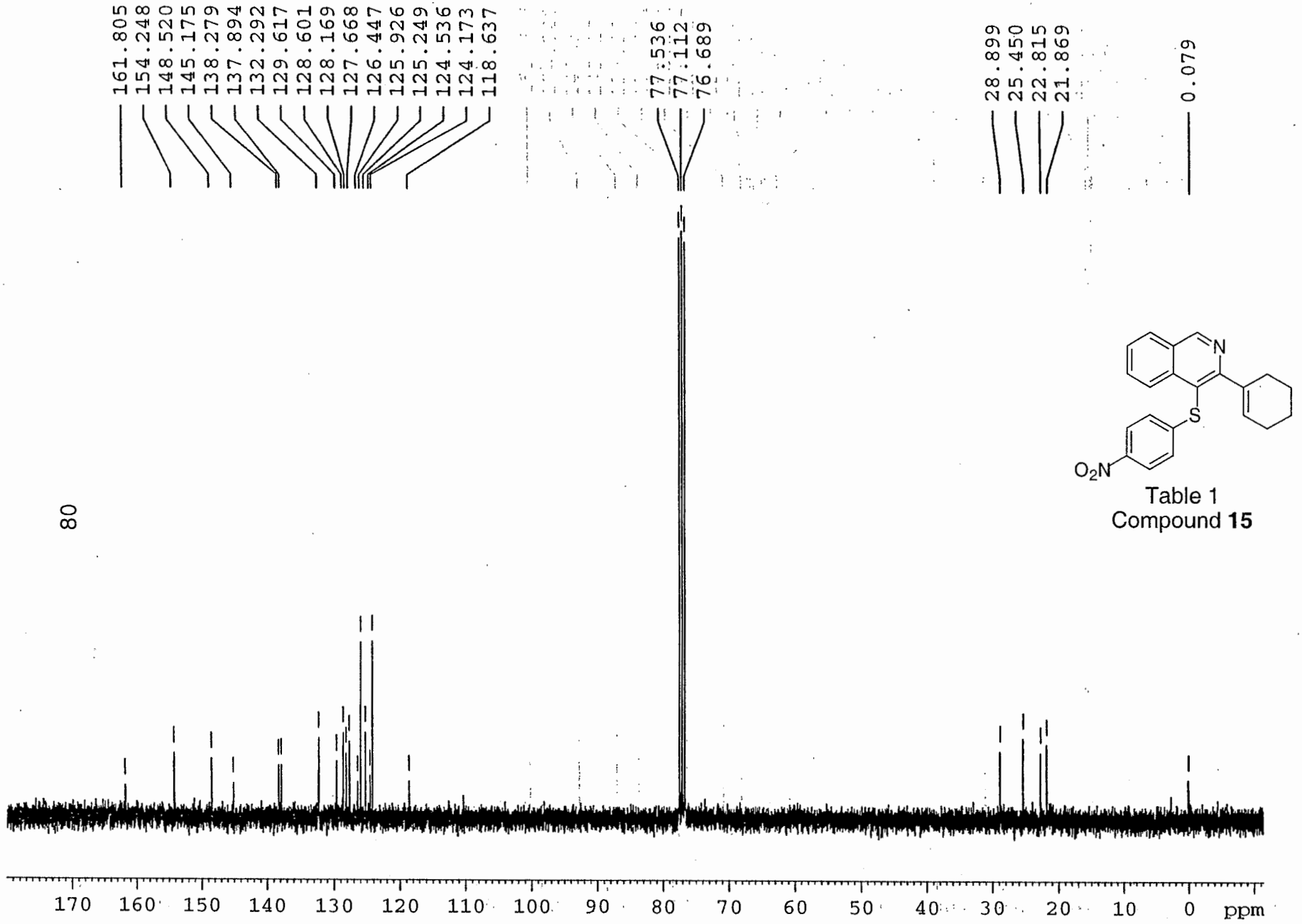


Table 1
Compound **15**

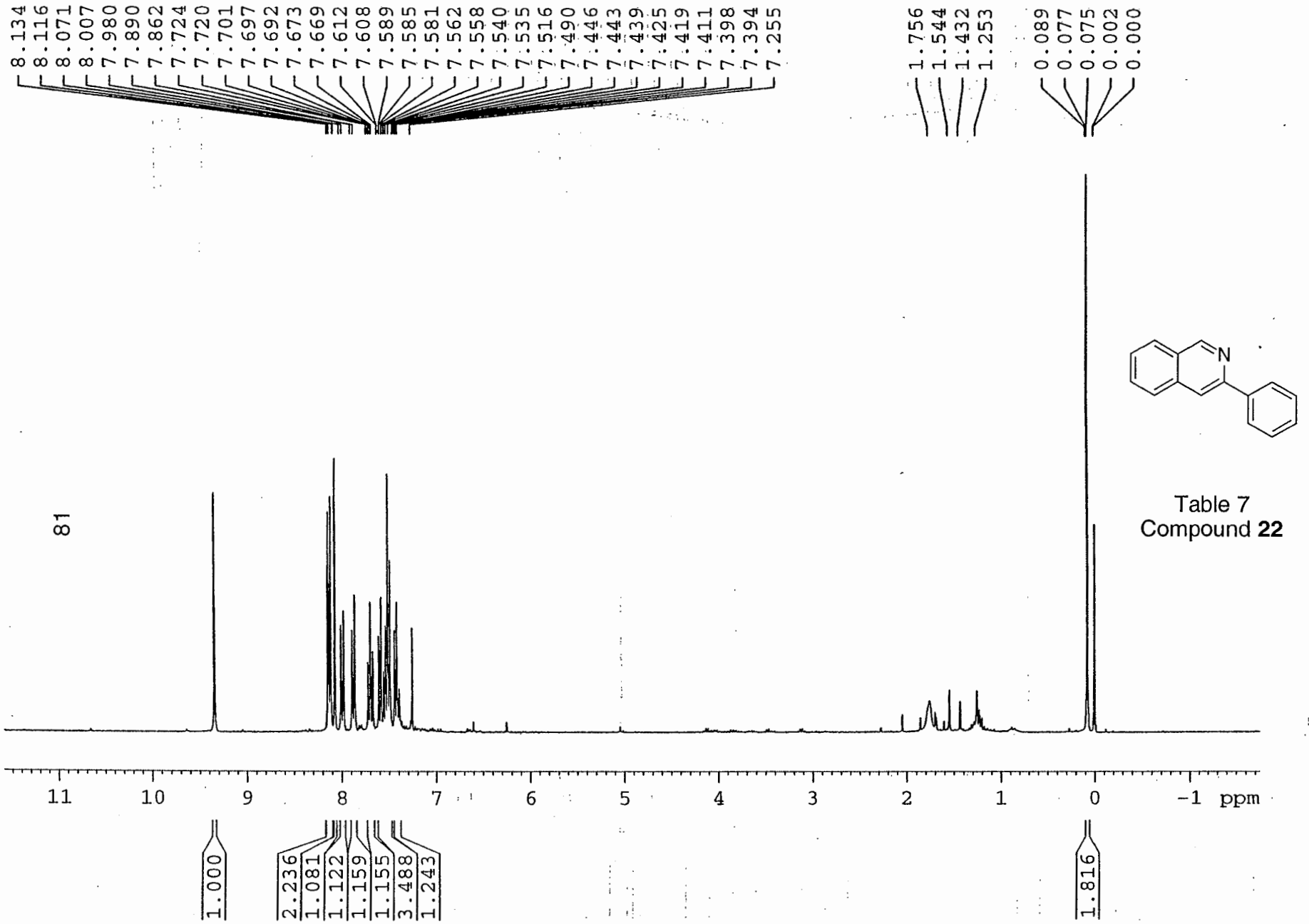


Table 7
Compound **22**

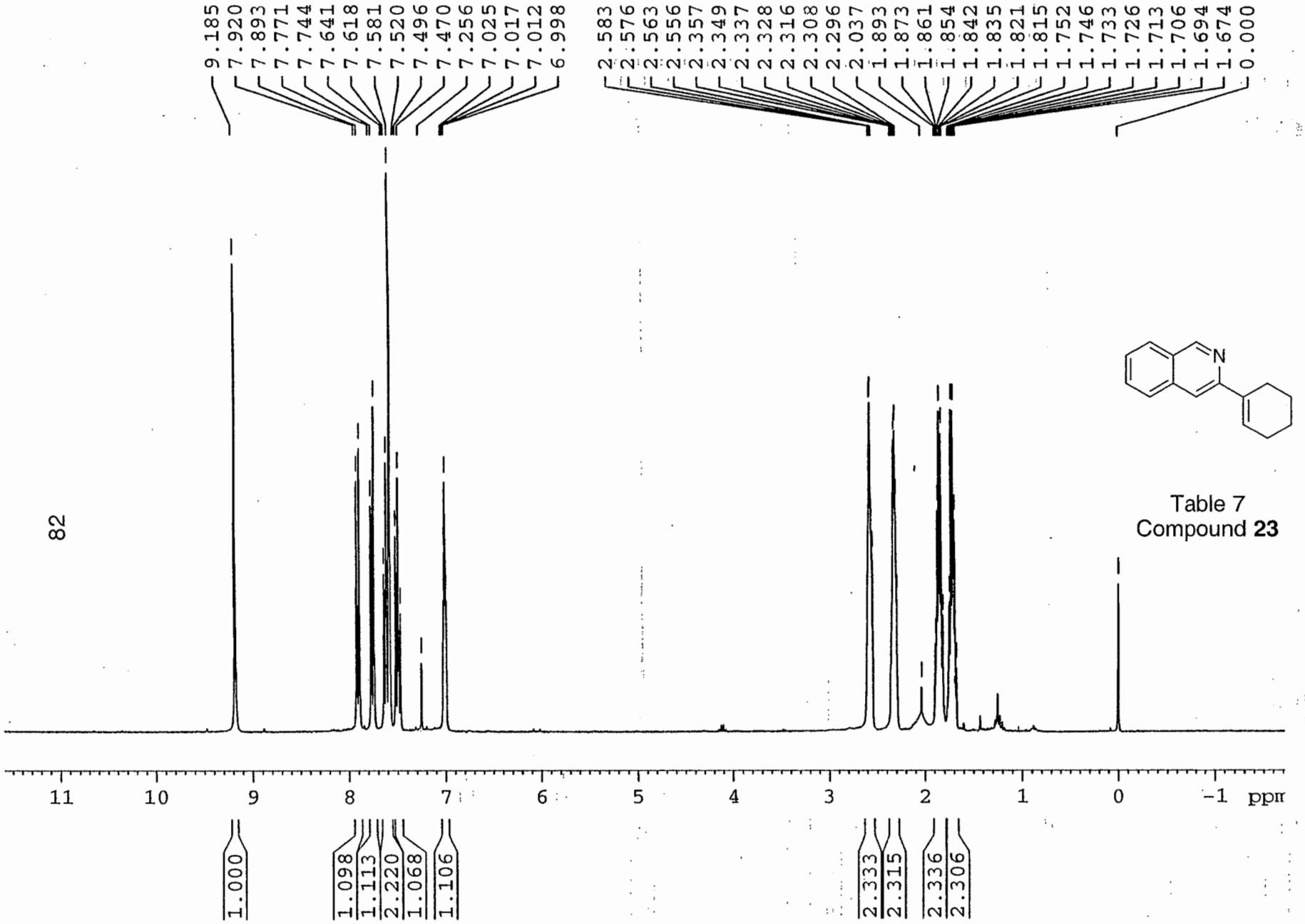


Table 7
Compound **23**

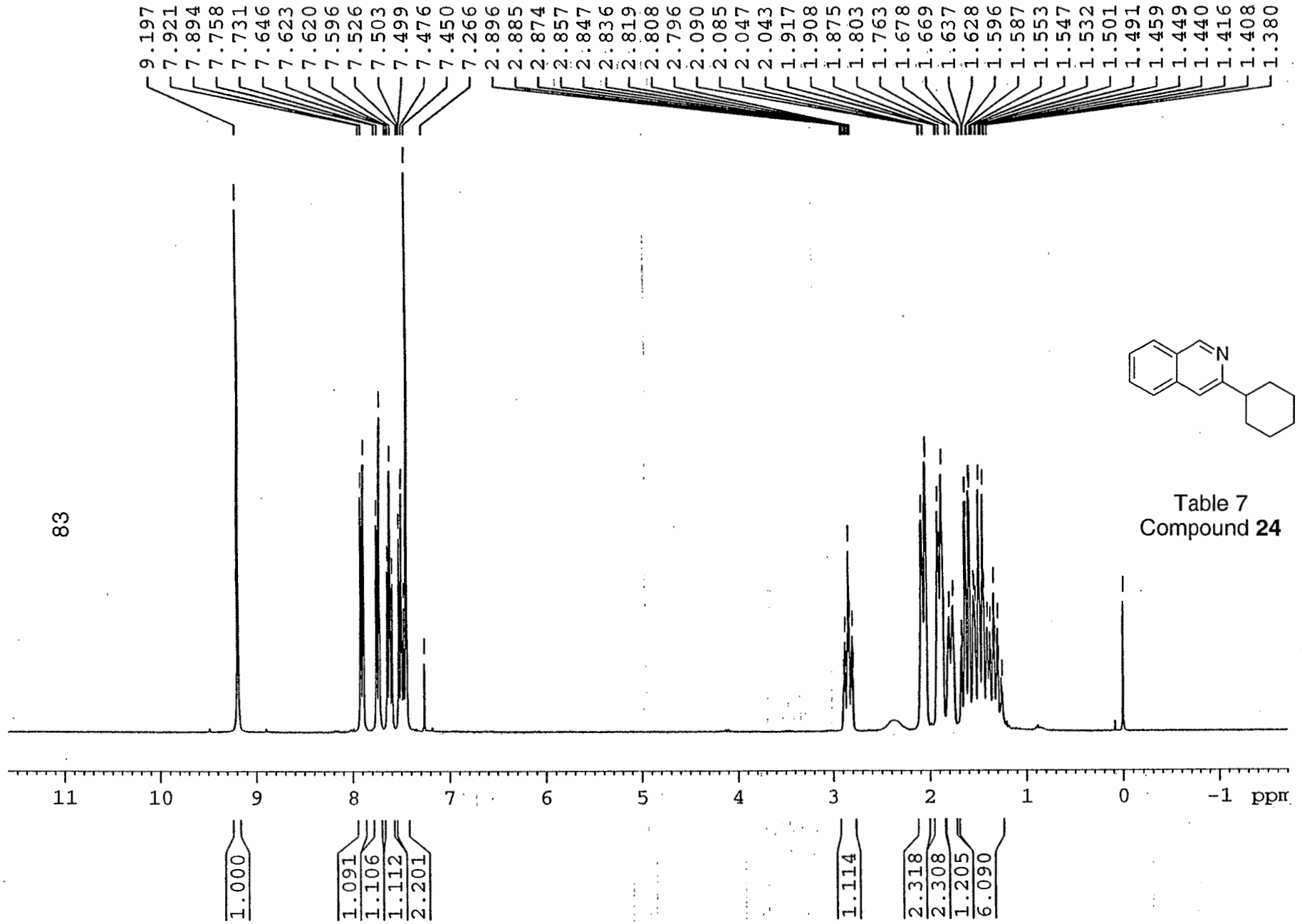
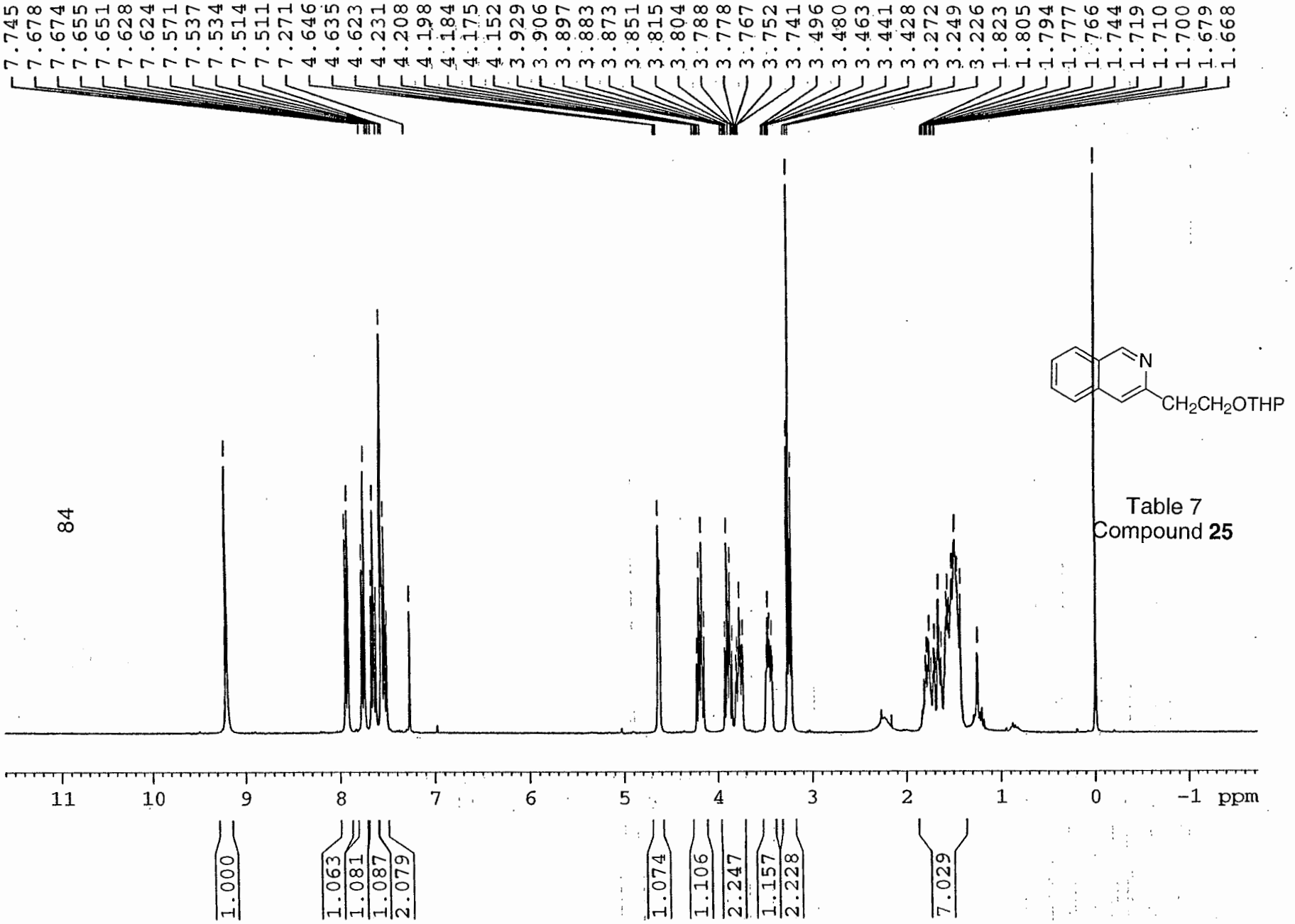


Table 7
Compound **24**


7.745
7.678
7.674
7.655
7.651
7.628
7.624
7.571
7.537
7.534
7.514
7.511
7.271
4.646
4.635
4.623
4.231
4.208
4.198
4.184
4.175
4.152
3.929
3.906
3.897
3.883
3.873
3.851
3.815
3.804
3.788
3.778
3.767
3.752
3.741
3.496
3.480
3.463
3.441
3.428
3.272
3.249
3.226
1.823
1.805
1.794
1.777
1.766
1.744
1.719
1.710
1.700
1.679
1.668
N
CH2CH2OTHP
84
Table 7
Compound 25
11
10
9
8
7
6
5
4
3
2
1
0
−1
ppm
1.000
1.063
1.081
1.087
2.079
1.074
1.106
2.247
1.157
2.228
7.029

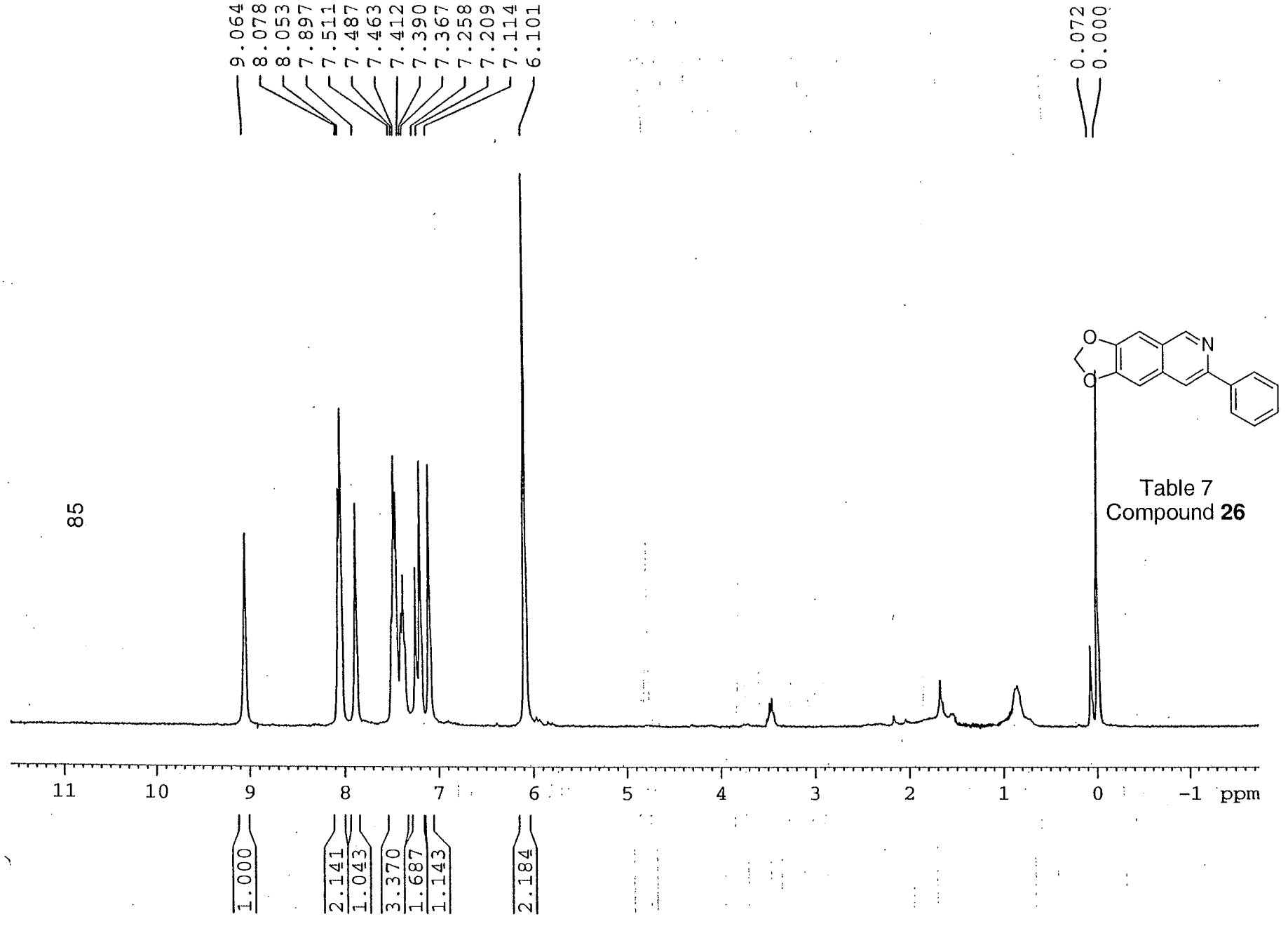


Table 7
Compound **26**

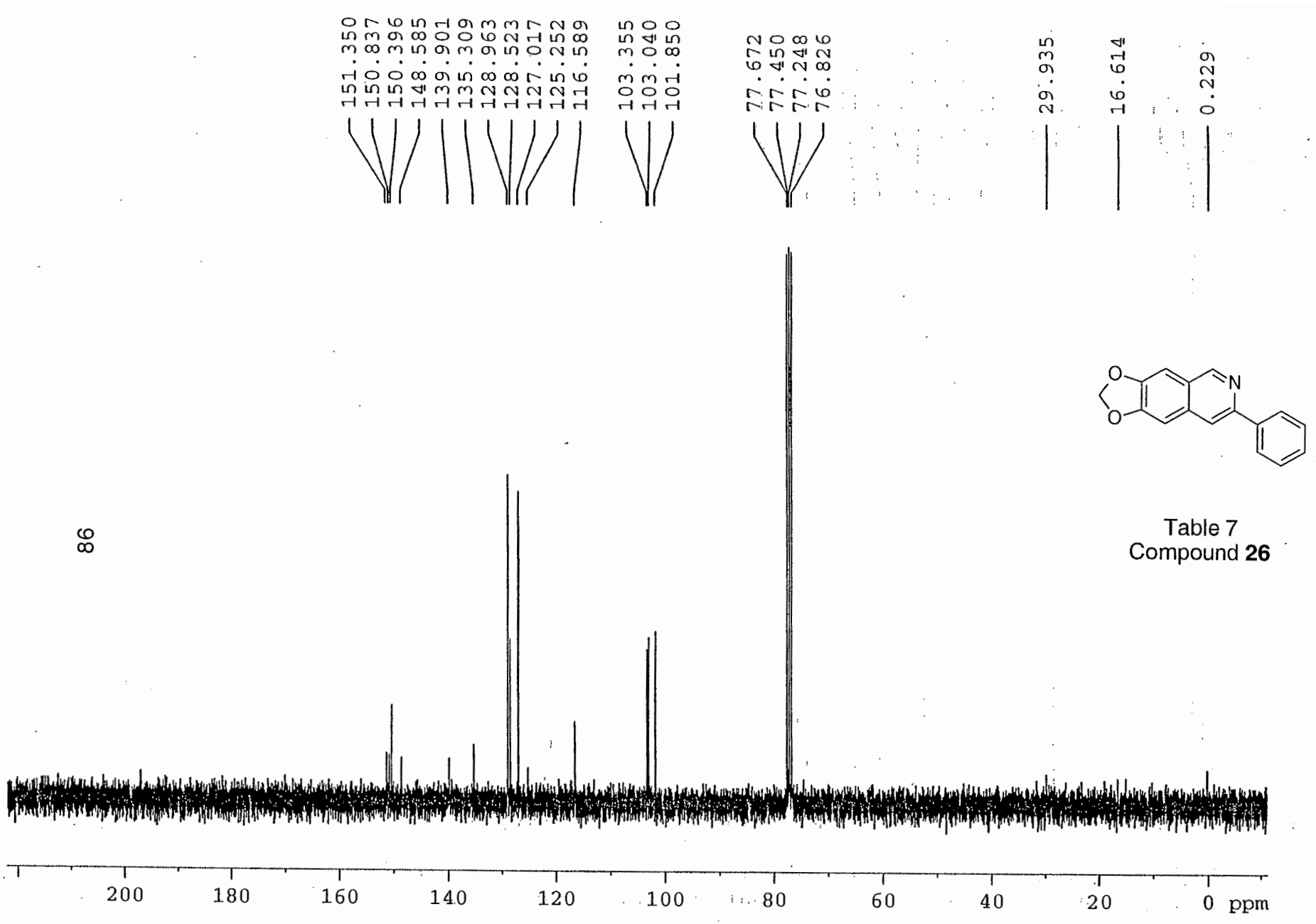


Table 7
Compound **26**

ACKNOWLEDGMENTS

I must begin this section with a sincere word of thanks to my major professor, Richard C. Larock, for his exceptional guidance, patience, understanding, and financial support throughout the course of this work. I also have to acknowledge his willingness to help, allowing me to learn from my mistakes, and to offer advice on the best ways to carry out ideas I had.

Also, I would like to thank the person who gave me my start in organic chemistry, Dr. Colleen Fried of Hiram College. I thank you for turning me onto organic chemistry, for listening to me complain, and for showing me that hard work does indeed pay off.

Throughout my career here at Iowa State, I have had the opportunity to meet so many people who's own ideas helped me to make it through the rough times. I have to give special thanks to Dr. Kevin Roesch and his wife, Julie, for whom I owe a great deal. He was instrumental in showing me techniques, answering my numerous questions, and for the project's beginning. I will always remember our talks, even the ones about chemistry, and lunches on Saturdays (don't eat off that plate, you ain't at home, and the S-10). I would like to thank Julie for dinners, lunches, and letting Kevin hang out with me.

I also would like to thank Dan Emrich, Steve Gagnier, and Marino Campo. I thank Dan for turning down my radio and the "swear jar," Steve for complaining constantly and for the "double wide" crack, and Marino for "Rocko and for being "oneademdam..."

This section could not end without a very special thanks to Mike, Kathy, and Emily Serby. Where do I start with you three? You all have helped me through so much that if I wrote everything, it would be another chapter. I thank Mike for listening when things were not going right, both in and out of chemistry, golf, being like a brother, and for showing me that there is more, a lot more, to life than chemistry. Kathy, thank you for putting up with me even when sometimes you could have done without it, the numerous dinners, and for being like a sister/mother when I needed either one. Emily, you have no idea how you have helped me through the past 3 years. You made me see life through your eyes, the eyes of a child, and showed me that nothing was as bad as it really seemed. No matter how down or depressed I was, you could always cheer me up with "a hug, a kiss, and a smackaroony," a hat, a story, or a "knuckle sandwich." You better be good or else... All three of you have made me feel like I had a home away from home and as a part of your family and for that, I thank you most of all.

Finally, this section would be incomplete without thanking those closest to me, my family. Dick and Lilly, thank you making me feel welcome. Uncle Jim (WUSS) and Aunt Loretta (Auntie), thank you for the recipes (especially spatzels), talking about fishing, and for being there. Chris (Meathead) and Tonya, I thank you for being there always. Matt, thanks for all the "checks" you sent me in the mail, I am still waiting though. Jennifer (Blondie), thanks for listening to me babble about what to do and not do in life when I had had a few, "Field of Dreams," and for our time together at Hiram. Vickie (Podunk), thanks for the care-packages, cookies, and "Marvin."

Now, time for the three people I owe my success to most of all. Bro, what can I say. I can count on you for just about anything. No matter what it was, you did it. Luckily we were never caught. You always treated me like a brother and a friend. As a brother, you knew when to praise and when to pick on me and did both equally well. As a friend, you would listen and tell me the truth and not what you thought I wanted to hear. Thanks for our week at camp, keeping my bed warm, and for believing in me even when I had doubts. Mom and Dad (Red and the Old Man), I thank you most of all. Without the support and love of you both, I definitely would not have made it through. I know I have caused you some worry, but I hope there was some feeling of pride in there as well. Mom, thanks for our talks, letting me win on Monday nights every now and then, and for always being there to cheer me up (by locking yourself in or out), when I was down. Dad, thanks for coming to see me, telling me what mom had done each week, driving me to do better, and making up for lost time together, which means the most of all to me. Thank you both for treating me like a man, but allowing me to be a child when I needed your help. You both always believed in me and supported my decisions, even though you had no idea what you were believing in, even when I was unsure of my own abilities. It meant and will always mean the most to me. Mom and Dad, without the two of you, none of this would have been possible or as worthwhile. Now it is my turn to help you out. I only have one thing left to say, **I MADE IT!**