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New palladium-catalyzed approaches to heterocycles and carbocycles

Guangxiu Dai
Iowa State University

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New palladium-catalyzed approaches to heterocycles and carbocycles

by

Guangxiu Dai

A dissertation submitted to the graduate faculty
in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Program of Study Committee:
Richard C. Larock (Major Professor)
George A. Kraus
William S. Jenks
Victor S. Lin
John Kozak

Iowa State University

Ames, Iowa

2003

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Guangxiu Dai

has met the dissertation requirement of Iowa State University

Signature was redacted for privacy.

Major Professor

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For the Major Program

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LIST OF ABBREVIATIONS

Ac	acetyl
aq	aqueous
br	benzyl
br m	broad multiplet
br s	broad singlet
Bu	butyl
<i>t</i> -Bu	<i>tert</i> -butyl
cat.	catalytic
concd	concentrated
d	doublet
dba	dibenzylideneacetone
dd	doublet of doublet
DMF	<i>N,N</i> -dimethylformamide
DMSO	dimethyl sulfoxide
eq	equation
equiv	equivalent
Et	ethyl
h	hour(s)
HRMS	high resolution mass spectrometry
Hz	Hertz
IR	infrared
m	multiplet

Me	methyl
mL	milliter(s)
mol	mole(s)
mp	melting point
Ms	methanesulfonyl
MS	mass spectrometry
NMR	nuclear magnetic resonance
<i>o</i>	ortho
<i>p</i>	para
Ph	phenyl
q	quartet
s	singlet
t	triplet
TBAC	tetra- <i>n</i> -butylammonium chloride
<i>tert</i>	tertiary
THF	tetrahydrofuran
TLC	thin-layer chromatography
Ts	<i>p</i> -toluenesulfonyl

ABSTRACT

A wide variety of 3,4-disubstituted isoquinolines containing an aryl, allylic, benzylic, alkynyl and vinylic group at the 4 position have been prepared via cross-coupling of 2-(1-alkynyl)benzaldimines with organic halides in the presence of a palladium catalyst. The best results are obtained by employing 5 mol % Pd(PPh₃)₄, 5 equiv of K₂CO₃ in DMF at 100 °C. The electronic effect of the imine substrates and organic halides on the yields has been discussed.

3-Substituted 4-aryloisoquinolines have been prepared in high yields via carbonylative cross-coupling of 2-(1-alkynyl)benzaldimines with aromatic iodides or aryl chlorides in the presence of a palladium catalyst under 1 atm of CO pressure. Imine substrates having an aryl, vinylic or alkyl substituent on the distal end of the triple bond all undergo this palladium-catalyzed carbonylative cross-coupling cyclization in high yields.

The palladium(II)-catalyzed oxidative carbonylation of 2-(1-alkynyl)-benzaldimines for synthesis of the corresponding isoquinoline-4-carboxylates has been studied and the optimal reaction conditions have been investigated. Although this methodology study has not provided an efficient route to synthesize methyl 3-substituted isoquinoline-4-carboxylates in synthetically useful yields, it provides an insight into the nature of the palladium-catalyzed cyclization reactions promoted by organopalladium intermediates.

A novel intramolecular alkyl-to-aryl palladium rearrangement has been observed by trapping the arylpalladium intermediate with an olefin by a Heck

reaction. The reaction conditions have been optimized and the reaction scope has been extensively studied. In all of the successful examples, migration products were isolated exclusively. In addition, this alkyl-to-aryl palladium migration can be controlled by simply modifying the reaction conditions.

GENERAL INTRODUCTION

Transition metal-catalyzed processes have proved to be extremely effective in organic synthesis. More specifically, palladium-catalyzed methodology has been extensively utilized in recent years.¹ The ability to create multiple carbon-carbon bonds from simple starting materials, the regio- and stereospecificity of the reactions, the exceptional tolerance for functionality, the insensitivity to air or moisture, and the procedural ease with which the reactions can be carried out have all contributed to the success of palladium in organic synthesis.

The Larock group has shown in a series of recent papers that palladium-catalyzed cyclization or annulation methods² can be effectively employed for the synthesis of isoquinolines and derivatives with a wide variety of substituent patterns. In this dissertation, the scope of the isoquinoline synthesis methodology has been expanded by employing 2-(1-alkynyl)benzaldimines to provide access to a variety of 3,4-disubstituted isoquinolines and 3-substituted 4-aryloisoquinolines.³

A newly discovered palladium migration reaction interests us as both an opportunity to study the behavior of palladium and an unusual pathway to construct cyclic compounds.

The author of this manuscript was the primary investigator and the author of each of the papers reported in this dissertation.

Dissertation Organization

This dissertation is divided into four chapters. Each of the chapters presented herein is written by following the guidelines for a full paper in the *Journal of Organic Chemistry* and is composed of an abstract, introduction, results and discussion, conclusion, experimental, acknowledgement and references.

Chapter 1 discusses the synthesis of 3,4-disubstituted isoquinolines by the palladium-catalyzed cross-coupling cyclization of 2-(1-alkynyl)benzaldimines and organic halides. Various imine substrates and organic halides have been investigated. A mechanism for this transformation is proposed.

Chapter 2 presents an extension of the cross-coupling methodology described in Chapter 1. The palladium-catalyzed carbonylative cross-coupling of 2-(1-alkynyl)benzaldimines and organic halides affords a variety of 4-aryl-isoquinoline heterocycles in high yields.

Chapter 3 describes an attempt to synthesize methyl isoquinoline-4-carboxylates via palladium-catalyzed oxidative carbonylative cross-coupling of 2-(1-alkynyl)benzaldimines in the presence of carbon monoxide.

Chapter 4 shows an intramolecular alkyl-to-aryl palladium migration reaction that has been observed in the Larock group. This reaction is both mechanically and synthetically interesting to us because it involves multiple mechanistic steps but still generates the products exclusively in good yields and it provides an unusual pathway for the synthesis of heterocyclic and carbocyclic compounds.

Finally, all of the ^1H and ^{13}C spectra for the imine starting materials and the palladium-catalyzed reaction products have been compiled in appendices A-C

following the general conclusions for this dissertation.

References

1. (a) Tsuji, J. *Palladium Reagents and Catalysis*; Wiley: Chichester, 1995 and references therein. (b) Heck, R. F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985 and references therein.
 2. For the Pd-catalyzed olefination of 2-(1-alkynyl)benzaldimines, see: (a) Huang, Q.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 3557. For the electrophile-promoted cyclization of 2-(1-alkynyl)benzaldimines, see: (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973. (c) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437. For the Pd-catalyzed annulation of internal alkynes by 2-iodobenzaldimines, see: (d) Roesch, K. R.; Larock, R. C. *J. Org. Chem.* **1998**, *63*, 5306. (e) Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042.
 3. For the Pd-catalyzed cross-coupling cyclization of 2-(1-alkynyl)benzaldimines, see: (a) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035. (b) Dai, G.; Larock, R. C. *J. Org. Chem.* **2003**, *68*, 920. For the Pd-catalyzed carbonylative cyclization of 2-(1-alkynyl)benzaldimines, see: (c) Dai, G.; Larock, R. C. *Org. Lett.* **2002**, *4*, 193. (d) Dai, G.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7042.
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**Chapter 1. Synthesis of 3,4-Disubstituted Isoquinolines via
Palladium-Catalyzed Cross-Coupling of 2-(1-Alkynyl)benzaldimines
and Organic Halides**

Two papers published in *Organic Letters* and the *Journal of Organic Chemistry*

Guangxiu Dai and Richard C. Larock

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

Abstract

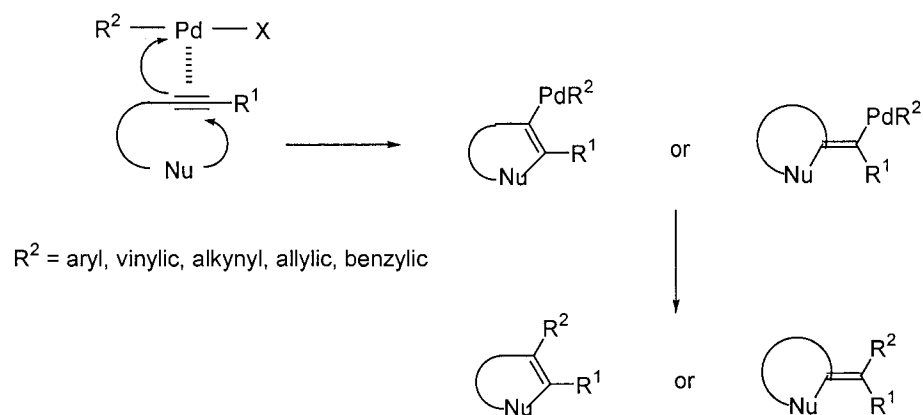
The palladium-catalyzed cross-coupling of readily available *N*-*tert*-butyl-2-(1-alkynyl)benzaldimines and aryl, allylic, benzylic, and alkynyl halides, as well as a vinylic halide, provides a valuable new route to 3,4-disubstituted isoquinolines with aryl, allylic, benzylic, 1-alkynyl and vinylic substituents respectively in the 4 position. The reaction appears to require an aryl group on the end of the acetylene furthest from the imine functionality. The reaction conditions have been optimized and reasonably good yields have been obtained.

Introduction

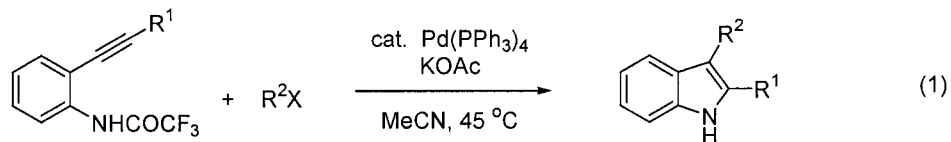
The cyclization of alkynes containing proximate nucleophilic centers promoted by organopalladium complexes is currently of great interest and developing into a most effective strategy for heterocyclic ring construction.¹ This chemistry provides a straightforward approach to the synthesis of functionalized carbo- and heterocycles through the regio- and stereoselective addition of a

nucleophile and an unsaturated carbon unit across the carbon-carbon triple bond (Scheme 1).

Scheme 1



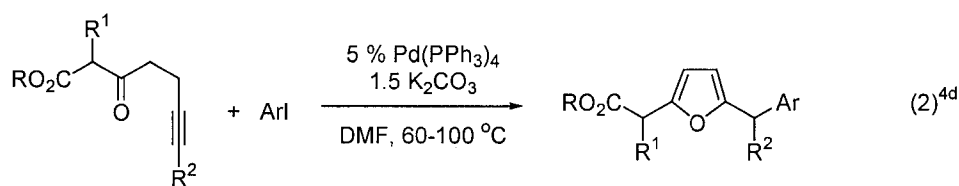
Successful examples of this process have been reported for the synthesis of 2,3-disubstituted indoles (eq 1),² 2,3-disubstituted benzofurans³ and other cyclic compounds (for an example see in eq 2).⁴ However, no one has thus far employed this chemistry to synthesize isoquinolines.



R¹ = alkyl, aryl, vinylic

R² = aryl, vinylic, allylic, benzylic

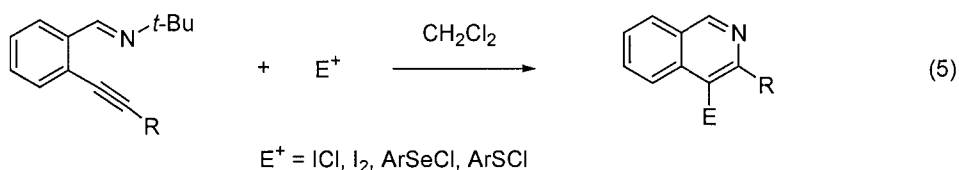
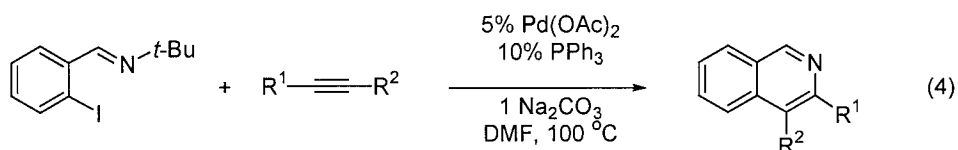
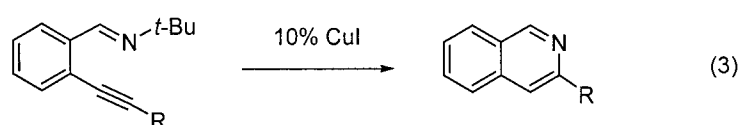
X = halide, triflate

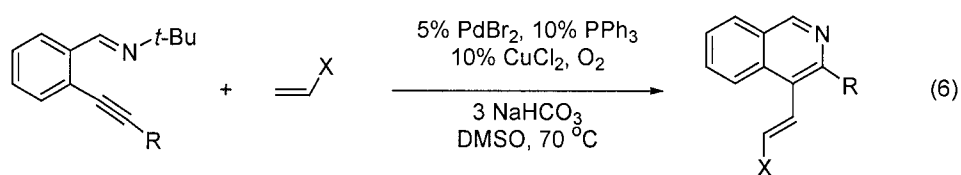


The isoquinoline ring system is present in many natural alkaloids and drug candidates that possess interesting biological activities,⁵ encouraging the development of a variety of classical approaches⁶ for isoquinoline synthesis, including the Bischler-Napieralski, the Pictet-Spengler and the Pomeranz-Fritsch reactions. However, these methods employ either strong acidic conditions for the ring closure (Bischler-Napieralski and Pomeranz-Fritsch) or the tedious preparation of appropriately substituted phenethylamines as starting materials (Pictet-Spengler).

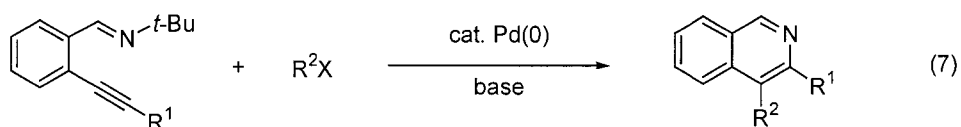
Palladium-catalyzed methods have been employed more and more for the synthesis of substituted isoquinolines in recent years. For instance, Pfeffer and co-workers reported the formation of a disubstituted isoquinoline derivative from cyclopalladated *N,N*-dimethylbenzylamine complexes in yields ranging from 10-56%.⁷ Heck and co-workers observed the formation of 3,4-diphenylisoquinoline in a 22% yield from the reaction of cyclopalladated *N-tert*-butylbenzaldimine tetrafluoroborate with diphenylacetylene.⁸ Widdowson has also reported an isoquinoline synthesis based on cyclopalladated *N-tert*-butylaryldimines.⁹ These approaches to isoquinolines, however, suffer the major disadvantage that they are stoichiometric with respect to palladium, and a final pyrolysis step greatly limits the synthetic utility.

In our own laboratories, we have carried out systematic studies on the synthesis of isoquinolines, including the copper-catalyzed cyclization of 2-(1-alkynyl)aryaldimines to 3-substituted isoquinolines (eq 3),¹⁰ the palladium-catalyzed iminoannulation of internal alkynes (eq 4),¹¹ the electrophile-promoted cyclization of 2-(1-alkynyl)aryaldimines (eq 5)¹² and the Pd(II)-catalyzed olefination of 2-(1-alkynyl)aryaldimines followed by Heck reactions (eq 6).¹³ This chemistry provides simple approaches to 3-monosubstituted and 3,4-disubstituted isoquinolines, which generally proceed in excellent yields. Despite the broad applicability of these processes, there are still many 3,4-disubstituted isoquinolines that cannot be directly prepared by these approaches.





Therefore, we have examined the possibility of preparing 3,4-disubstituted isoquinolines by a more general process involving the palladium-catalyzed cross coupling of *N-tert-butyl-2-(1-alkynyl)benzaldimines* and organic halides (eq 7). Hopefully, this approach might avoid the problem of regioselectivity that exists in the synthesis of isoquinolines by the iminoannulation of internal alkynes,¹¹ and may offer a new way to construct the isoquinoline ring. Herein, we report a full investigation of this intriguing reaction.¹⁴

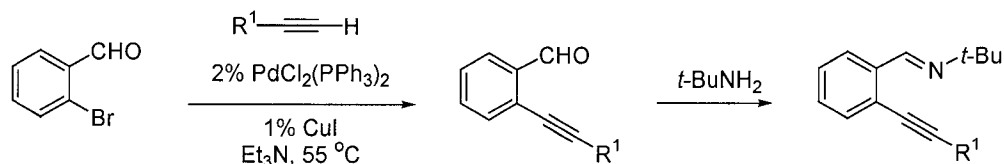


Results and Discussion

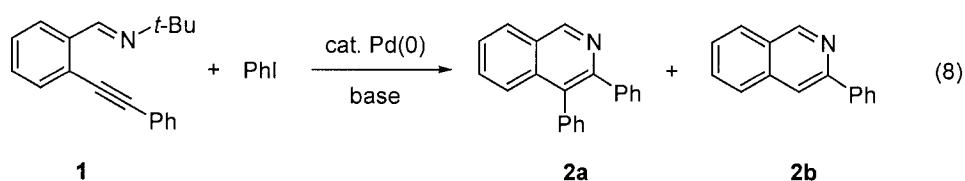
Starting Materials. The preparation of the starting materials for this chemistry is quite simple and straightforward. The appropriate imines are readily available in two steps from 2-bromoarene-carboxaldehydes and terminal alkynes. The first step is the Sonogashira coupling¹⁵ of the aryl halide and a terminal alkyne catalyzed by 2 mol % of PdCl₂(PPh₃)₂ and 1 mol % of CuI in Et₃N at 55 °C. This step generally gives yields of the coupled product above 90%. The second step of the sequence involves reaction of the 2-(1-alkynyl)arene-carboxaldehyde and

excess *tert*-butylamine at room temperature and proceeds in almost quantitative yields (Scheme 2).

Scheme 2



Optimization. Our first attempt to explore the reaction of *N-tert*-butyl-2-(phenylethynyl)benzaldimine (**1**) and 3 equiv of phenyl iodide employed 5 mol % Pd(dba)₂, 10 mol % of PPh₃, 3 equiv of Na₂CO₃ in 5 ml of DMF at 100 °C (eq 8). Although the desired product, 3,4-diphenylisoquinoline (**2a**) was formed, the generation of another product, 3-phenylisoquinoline (**2b**) was also observed. The 3-phenylisoquinoline (**2b**) is believed to be formed by either the thermal or Pd(II)-catalyzed cyclization of imine **1**.¹⁰



We have, thus, attempted to optimize formation of the disubstituted isoquinoline **2a** (eq 8). Using Pd(dba)₂ as the catalyst plus 2 equiv of PPh₃ per palladium as the ligand, and raising the temperature from 80 to 100 °C significantly increased the yields of the 3,4-diphenylisoquinoline (**2a**) and the selectivity for **2a**

Table 1. Optimization of the Reaction of *N*-tert-Butyl-2-(phenylethynyl)-benzaldimine (1**) and Phi (eq 8).^a**

	Pd catalyst	Phi (equiv)	base (equiv)	temp (°C)	time (h) ^b	% yield ^c 2a : 2b
1	Pd(dba) ₂ /2 PPh ₃	3	Na ₂ CO ₃ (3)	80	9	26 : 21
2	Pd(dba) ₂ /2 PPh ₃	5	Na ₂ CO ₃ (3)	80	9	20 : 23
3	Pd(dba) ₂ /2 PPh ₃	3	Na ₂ CO ₃ (3)	100	9	49 : 25
4	Pd(dba) ₂ /2 PPh ₃	5	Na ₂ CO ₃ (3)	100	9	61 : 10
5	Pd(dba) ₂ /2 PPh ₃	5	Na ₂ CO ₃ (3)	120	9	62 : 9
6	Pd(PPh ₃) ₄	5	KOAc (5)	50	10	36 : <2
7	Pd(PPh ₃) ₄	5	KOAc (5)	75	10	27 : 5
8	Pd(PPh ₃) ₄	5	KOAc (5)	100	10	29 : 49
9	Pd(PPh ₃) ₄	5	K ₂ CO ₃ (5)	50	12	17 : 0
10	Pd(PPh ₃) ₄	5	K ₂ CO ₃ (5)	100	12	49 : <2
11	Pd(PPh ₃) ₄	5	Na ₂ CO ₃ (5)	100	12	48 : <2
12	Pd(PPh ₃) ₄	5	Cs ₂ CO ₃ (5)	100	24	22 : 0
13	Pd(PPh ₃) ₄	5	Li ₂ CO ₃ (5)	100	24	28 : 36
14 ^d	Pd(PPh ₃) ₄	5	K ₂ CO ₃ (5)	100	24	36 : 12
15 ^e	Pd(PPh ₃) ₄	5	K ₂ CO ₃ (5)	100	24	24 : 45

^a All reactions were carried out in 5 ml of DMF as the solvent, using 0.25 mmol of imine **1** and 5 mol % of the palladium catalyst unless otherwise specified. ^b In most cases, monitoring by TLC showed that the reaction had reached completion in less time than the time specified. ^c Yields are given for isolated products and refer to single runs. ^d The reaction was run in 5 ml of CH₃CN. ^e The reaction was run in 5 ml of DMSO.

over **2b** (Table 1, entries 1-4). Further raising the temperature from 100 to 120 °C did not help much (entry 5). Increasing the amount of the PhI from 3 to 5 equiv favored formation of the desired product **2a** at 100 °C (compare entries 3 and 4). The best result obtained was a 61% yield of **2a** and 10% of **2b**, acquired using 5 equiv of PhI, 5 mol % of Pd(dba)₂, 10 mol % of PPh₃, 3 equiv of Na₂CO₃ in 5 ml of DMF at 100 °C (entry 4).

The replacement of Pd(dba)₂ plus Ph₃P by Pd(PPh₃)₄ and 3 equiv of Na₂CO₃ by 5 equiv of KOAc at 50 °C (entry 6) reduced the amount of the side product **2b** to only a trace, but the yield of **2a** was not high enough to be synthetically useful. Increasing the temperature from 50 °C to 75 °C to 100 °C only reduced the selectivity between **2a** and **2b** and did not significantly improve the yield of **2a** (entries 6-8). The side product isoquinoline **2b** was not observed using K₂CO₃ as the base at 50 °C (entry 9), and a higher yield of **2a** and relatively low yield of **2b** were obtained when the temperature was further raised to 100 °C (entry 10). Using lithium, sodium and cesium carbonate as bases failed to improve the yield of **2a** (entries 11-13). Changing the solvent from DMF to acetonitrile or DMSO did not enhance the yield of **2a** or the selectivity between the two isoquinoline products (entries 14 and 15).

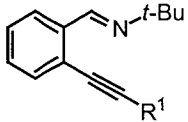
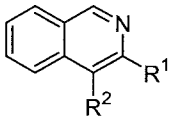
The procedure summarized in Table 1, entry 10, is thought to give the best result, because of the distribution of the two products and the ease with which one can isolate pure product, although the yield of the desired product **2a** suffers compared to the results described in Table 1, entry 4.

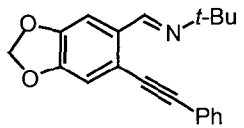
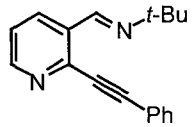
Cross-coupling of *N*-tert-Butyl-2-(1-alkynyl)aryldimines with Aryl Halides and Triflates. When the optimized reaction conditions reported above in

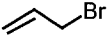
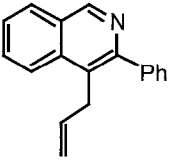
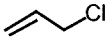
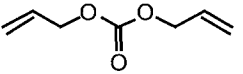
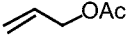
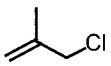
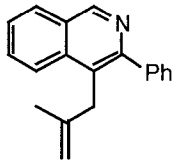
entry 10 were applied to the reaction of *N*-*tert*-butyl-2-(phenylethynyl)benzaldimine (**1**) and phenyl triflate, which is assumed to form the corresponding PhPdOTf intermediate, no desired product, 3,4-diphenylisoquinoline (**2a**), was observed even after 48 h. A 40% yield of monosubstituted isoquinoline **2b** was obtained as the only product.

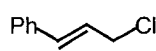
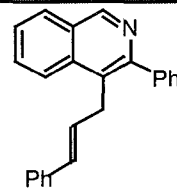
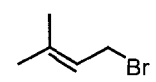
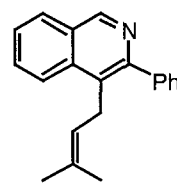
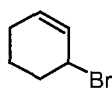
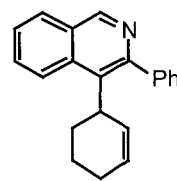
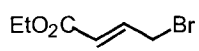
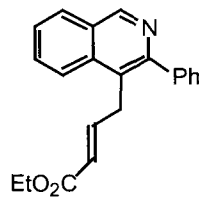
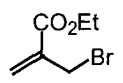
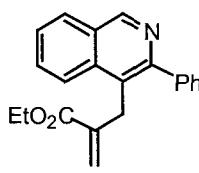
Under the optimized reaction conditions above, the reactions of imine **1** with a variety of aryl iodides afforded reasonable yields of the corresponding 3,4-disubstituted isoquinolines (eq 7; Table 2, entries 1-14). Aryl halides bearing an electron-withdrawing group in the *para* or *meta* positions usually lead to good to high yields of the 3,4-disubstituted isoquinoline products and low yields of the side product 3-phenylisoquinoline (**2b**) (entries 2, 4, 6, 7 and 9-11). Aryl iodides with an *ortho* electron-withdrawing group, such as ethyl 2-iodobenzoate and 2-iodonitrobenzene, do not react well with imine **1** (entries 5 and 8). These two reactions afforded only the monosubstituted isoquinoline **2b**. This is apparently the result of a steric problem with the ArPdX intermediate, since electron-withdrawing groups elsewhere in the aryl halides generally give good results. Reactions with aryl halides containing electron-donating groups, like *o*- and *p*-iodotoluene and 4-iodoanisole, only afford low yields of the corresponding 3,4-disubstituted products and poor ratios of di- to mono-substituted isoquinoline products (entries 12-14). The best yield obtained with imine **1** was 75%, which was afforded by 4-iodonitrobenzene (entry 2). The corresponding bromide, 4-bromonitrobenzene, affords the 3,4-disubstituted isoquinoline product **3** in a 48% yield (entry 3). The relatively low yield indicates that the lower reactivity of an aryl bromide toward

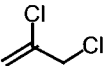
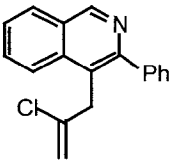
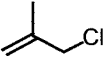
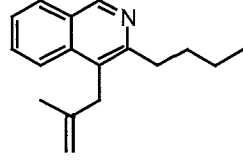
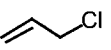
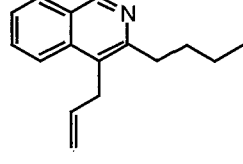
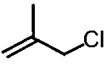
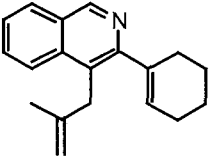
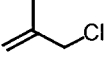
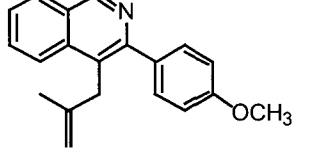
Table 2. Synthesis of 3,4-Disubstituted Isoquinolines by the Pd-Catalyzed Cross-Coupling of *N*-*tert*-Butyl-2-(1-alkynyl)benzaldimines and Organic Halides (eq 8).^a

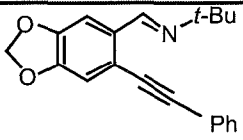
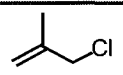
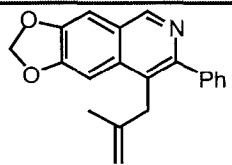
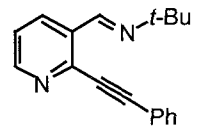
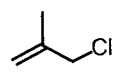
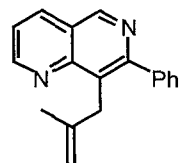
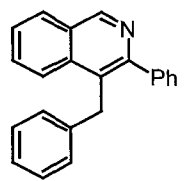
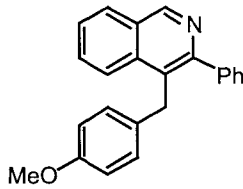
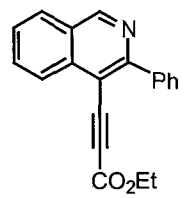
	alkynyl imine		R ² X	time (h)	Isoquinoline	% yield ^b
						
1	R ¹ = C ₆ H ₅	1	C ₆ H ₅ I	12	R ² = C ₆ H ₅	2a 49 (<2)
2	1	1	<i>p</i> -O ₂ NC ₆ H ₄ I	12	R ² = <i>p</i> -O ₂ NC ₆ H ₄	3 75 (0)
3	1	1	<i>p</i> -O ₂ NC ₆ H ₄ Br	24	R ² = <i>p</i> -O ₂ NC ₆ H ₄	3 48 (0)
4	1	1	<i>m</i> -O ₂ NC ₆ H ₄ I	8	R ² = <i>m</i> -O ₂ NC ₆ H ₄	4 49 (0)
5	1	1	<i>o</i> -O ₂ NC ₆ H ₄ I	48	R ² = <i>o</i> -O ₂ NC ₆ H ₄	5 0 (42)
6	1	1	<i>p</i> -EtO ₂ CC ₆ H ₄ I	7	R ² = <i>p</i> -EtO ₂ CC ₆ H ₄	6 67 (<2)
7	1	1	<i>m</i> -EtO ₂ CC ₆ H ₄ I	11	R ² = <i>m</i> -EtO ₂ CC ₆ H ₄	7 55 (<2)
8	1	1	<i>o</i> -EtO ₂ CC ₆ H ₄ I	11	R ² = <i>o</i> -EtO ₂ CC ₆ H ₄	8 0 (48)
9	1	1	<i>p</i> -F ₃ CC ₆ H ₄ I	8	R ² = <i>p</i> -F ₃ CC ₆ H ₄	9 65 (0)

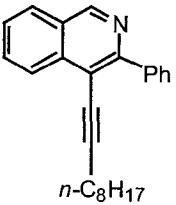
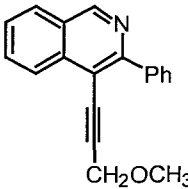
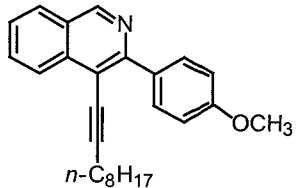
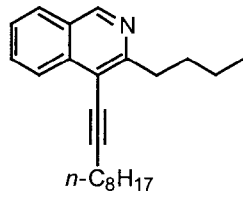
10	1		<i>m</i> -F ₃ CC ₆ H ₄ l	10	R ² = <i>m</i> -F ₃ CC ₆ H ₄	10	51 (<2)
11	1		3-iodopyridine	12	R ² = 3-pyridyl	11	48 (0)
12	1		<i>p</i> -H ₃ CC ₆ H ₄ l	10	R ² = <i>p</i> -CH ₃ C ₆ H ₄	12	48 (1)
13	1		<i>o</i> -H ₃ CC ₆ H ₄ l	24	R ² = <i>o</i> -CH ₃ C ₆ H ₄	13	29 (16)
14	1		<i>p</i> -H ₃ COC ₆ H ₄ l	24	R ² = <i>p</i> -CH ₃ OC ₆ H ₄	14	13 (14)
15	R ¹ = <i>n</i> -Bu	15	<i>p</i> -O ₂ NC ₆ H ₄ l	6	R ² = <i>p</i> -O ₂ NC ₆ H ₄	16	35 (0)
16	R ¹ = 1-cyclohexenyl	17	<i>p</i> -O ₂ NC ₆ H ₄ l	12	R ² = <i>p</i> -O ₂ NC ₆ H ₄	18	60 (0)
17	17		<i>p</i> -EtO ₂ CC ₆ H ₄ l	12	R ² = <i>p</i> -EtO ₂ CC ₆ H ₄	19	61 (0)
18	R ¹ = <i>p</i> -MeOC ₆ H ₄	20	<i>p</i> -O ₂ NC ₆ H ₄ l	10	R ² = <i>p</i> -O ₂ NC ₆ H ₄	21	80 (0)
19	20		<i>p</i> -CH ₃ OC ₆ H ₄ l	48	R ² = <i>p</i> -CH ₃ OC ₆ H ₄	22	30 (19)
20		23	<i>p</i> -O ₂ NC ₆ H ₄ l	10	R ² = <i>p</i> -O ₂ NC ₆ H ₄	24	59 (0)
21		25	<i>p</i> -O ₂ NC ₆ H ₄ l	10	R ² = <i>p</i> -O ₂ NC ₆ H ₄	26	23 (11)

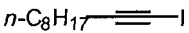
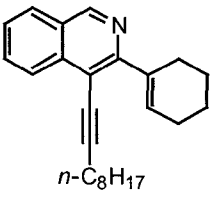
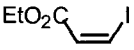
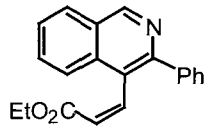
22	1		18		27	65 (0)
23	1		18	27	27	69 (0)
24	1		19	27	27	68 (0) ^c
25	1		120	27	27	28 (13)
26	1		24		28	71 (0)

27	1		20		29	48 (1)
28	1		42		30	0 (49)
29	1		72		31	0
30	1		24		32	0 (51)
31	1		48		33	59 (18)

32	1			21		34	0 (39)
33	R ¹ = <i>n</i> -Bu	15		48		35	62 (0)
34	15			48		36	55 (0)
35	R ¹ = 1-cyclohexenyl	17		48		37	30 (<3)
36	R ¹ = <i>p</i> -MeOC ₆ H ₄	20		24		38	88 (0)

37		23		72		39	59 (0)
38		25		24		40	42 (0)
39	1	1	PhCH ₂ Cl	24		41	45 (0)
40	1	1	<i>p</i> -MeOC ₆ H ₄ CH ₂ Cl	24		42	52 (0)
41	1	1	EtO ₂ C-C≡C-I	4		43	38 (0) ^d

42	1	$n\text{-C}_8\text{H}_{17}\text{-}\equiv\text{I}$	6		44	56 (0)
43	1	$\text{CH}_3\text{OCH}_2\text{-}\equiv\text{I}$	10		45	53 (0)
44	$\text{R}^1 = p\text{-MeOC}_6\text{H}_4$	$n\text{-C}_8\text{H}_{17}\text{-}\equiv\text{I}$	11		46	56 (0)
45	$\text{R}^1 = n\text{-Bu}$	$n\text{-C}_8\text{H}_{17}\text{-}\equiv\text{I}$	10		47	0 (<2)

46	R ¹ = 1-cyclohexenyl	17		10		48	0 (0)
47	1			24		49	55 (0)

^a The reaction conditions are specified in the text. ^b Yields are given for isolated products and refer to single runs. The numbers in parentheses are the yields of the corresponding 3-substituted isoquinolines. ^c Only 2.5 equiv of K₂CO₃ were used as the base. ^d 4-Iodo-3-phenylisoquinoline was isolated in an 8% yield.

formation of the organopalladium ArPdX intermediate does affect the outcome of the reaction.

A variety of imines have also been tested using 4-iodonitrobenzene. According to the results in Table 2, the R¹ group of the imine (eq 8) also plays an important role in the reaction. When R¹ is an aryl group, the reactions work well with electron-deficient aryl halides. However, when R¹ is an alkyl or vinylic group, the yields drop significantly (entries 15-17), even when using 4-iodonitrobenzene. It is important to note, however, that the monosubstituted isoquinolines are not observed in these reactions.

In addition to the strong dependence of the reaction on the aryl halides employed, the electronic nature of the substituents attached to the aromatic ring of the imine significantly affects the outcome of the reactions with aryl halides. The electron-rich imine *N-tert-butyl-2-[(4-methoxyphenyl)ethynyl]benzaldimine* (**20**) affords slightly higher yields of 3,4-disubstituted isoquinoline products than imine **1** when allowed to react with 4-iodonitrobenzene and 4-iodoanisole (entries 18 and 19). However, placing a methylenedioxy moiety on the imine-bearing aryl ring (**23**) leads to a somewhat lower yield (entry 20). Using an electron-deficient pyridine-containing imine **25** and 4-iodonitrobenzene leads to the 3,4-disubstituted product **26** in only a 23% yield and the 3-monosubstituted product was isolated in an 11% yield (entry 21).

Cross-coupling of *N-tert-Butyl-2-(1-alkynyl)arylaldimines with Allylic Halides and Esters.* Allylpalladium complexes have been used to promote the cyclization of alkynes containing proximate nucleophiles (N and O) to afford 3-allylic indoles,^{2c,g,h} 3-allylic benzo[*b*]furans^{3a,b} and 3-allylic furans.^{4a,b} We here report

that π -allylpalladium complexes can be successfully employed in the synthesis of 4-allylic 3-substituted isoquinolines.

First, we have investigated the reaction of our model imine **1** with allyl bromide under our optimized cross-coupling conditions. We were pleased to observe a 65% yield of the 4-allyl-3-phenylisoquinoline (**27**) and no 3-phenylisoquinoline (**2b**) (entry 22). This reaction took 18 h to complete, showing the lower reactivity of the allylpalladium complex compared to the arylpalladium complex. When allyl chloride was used in the reaction (entry 23), it afforded a slightly higher yield, 69%, of product **27** and no side product **2b** at all. Although allylic bromides usually possess higher reactivities than allylic chlorides in π -allylpalladium chemistry, the stability of the halides must be taken into account in this case where there are 5 equiv of K_2CO_3 present in the reaction mixture.

We were also interested in investigating diallyl carbonate in this reaction (entry 24). In this case, only 2.5 equiv of K_2CO_3 were employed, because one equiv of base is formed when both allyl groups are released from each equiv of carbonate. This reaction proceeded well and afforded a 68% yield of **27** after 18 h.

Then we turned to allyl acetate, another important source of π -allylpalladium intermediates. After 120 h, only 28% of the desired product **27** and 13% of the side product **2b** were isolated, and 17% of the starting material **1** was recovered (entry 25). Considering the fact that allyl acetate might not be very stable with so much base present in the reaction, we carried out another reaction in which only a stoichiometric amount of K_2CO_3 was employed. This reaction took 30 hours to reach completion and gave only a 13% yield of **27** and 34% of the side product **2b**.

Based on this observation, the extra base is considered to play an important role in improving the selectivity between the two competing processes.

The reactions of imine **1** with methallyl chloride and cinnamyl chloride both proceeded smoothly to generate the corresponding 4-allylic 3-phenylisoquinolines **28** and **29** in good yields, and the side product **2b** in only 0-1% yields (entries 26 and 27). Thus, the reactions of allylic chlorides exhibit excellent product selectivity. However, with 3,3-dimethylallyl bromide and 3-bromocyclohexene, two other allylic halides with hydrogens next to the π -allylic moiety, the reactions of imine **1** afforded none of the desired products **30** and **31** and produced only 3-phenylisoquinoline (**2b**) in the former case (entries 28 and 29).

The reactions of imine **1** and two electron-deficient allylic bromides displayed completely different reactivities. Ethyl 4-bromo-2-butenate did not produce any of the desired product **32**, but instead a significant amount of the cyclization product **2b** was generated (entry 30). Ethyl 2-(bromomethyl)propenoate, however, did afford the desired product **33** in a 59% yield and **2b** was produced in only an 18% yield (entry 31). The reaction between imine **1** and 2,3-dichloropropene did not generate any of the expected 4-allylic-3-phenylisoquinoline (**34**) for reasons that are not obvious (entry 32).

Unlike the reactions of imines with aryl halides, the reactions of imine **15** with $R^1 = n$ -butyl provided good yields when methallyl chloride and allyl chloride were employed (entries 33 and 34). However, the reaction of imine **17** with $R^1 = 1$ -cyclohexenyl afforded only a 30% yield of the desired product after 48 h (entry 35).

Since the highest yield from allylic halides was obtained in the reaction of imine **1** with methallyl chloride, other imines were all examined with this allylic

chloride. The influence of electronic factors present in the imines on the reactions is obvious. Generally the electron-rich imine substrates **20** and **23** result in better yields than their electron-deficient pyridine counterpart **25** (entries 36-38). The problem here might also be that the pyridine moiety in imine **25** could also be reacting directly with the allylic chloride (entry 38).

Besides the allylic halides and esters, benzyl chloride and 4-methoxybenzyl chloride have also been successfully employed in the isoquinoline cyclization and afford reasonably good yields of the corresponding cross-coupling products **41** and **42**, respectively (entries 39 and 40). However, the reaction with 4-nitrobenzyl chloride failed.

Cross-coupling of *N*-tert-Butyl-2-(1-alkynyl)aryldimines with Alkynyl Halides. Inspired by the success of the reactions of imines with electron-poor aryl halides, we examined the cross-coupling of ethyl 3-iodopropiolate. This alkynyl halide gave a 38% yield of the desired product **43** after only 4 h (entry 41). Although we did not observe 3-phenylisoquinoline (**2b**) as a side product this time, we isolated another side product, 4-iodo-3-phenylisoquinoline (**2c**) in an 8% yield. At the same time, a significant amount of I₂ appeared to be generated during the reaction.¹⁶ The decomposition of ethyl 3-iodopropiolate to I₂ could account for the formation of the side product **2c**¹² and the low yield of the 3-substituted 4-(1-alkynyl)isoquinoline **43**.

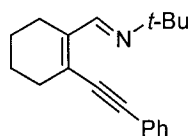
Encouraged by this preliminary result, we next examined the reactions of two different alkynyl iodides that do not possess any electron-withdrawing groups. Both of them produced the desired products in yields of 53% and 56% (entries 42 and 43).

Different imine substrates have been investigated in the reactions with 1-iodo-1-decyne. While the electron-donating group in the imine substrate **20** did not affect the yield of the product **46** (entry 44), the presence of the R² groups *n*-butyl in **15** and 1-cyclohexenyl in **17** both had a very strong negative influence on the outcome. No 3,4-disubstituted isoquinoline products were observed in these latter two reactions (entries 45 and 46). The possible 3-monosubstituted isoquinoline side products were not observed either.

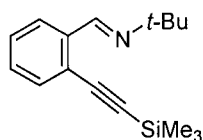
Cross-coupling of *N*-tert-Butyl-2-(1-alkynyl)aryaldimines with Vinylic Halides. Several vinylic halides have been utilized in this chemistry. Only ethyl *cis*-3-iodoacrylate produced the expected 4-vinylic substituted isoquinoline in a good yield (entry 47). Ethyl *trans*-3-iodoacrylate, *cis*- β -iodostyrene, (iodomethylene)cyclohexane, 3-iodo-2-cyclohexen-1-one, and 2-iodo-2-cyclohexen-1-one all failed to generate the expected isoquinolines.

We also tried *N*-tert-butyl-2-(phenylethynyl)cyclohex-1-enecarbox-aldimine (**50**) as a non-aromatic imine substrate in this chemistry with 4-iodonitrobenzene, methallyl chloride and 1-iodo-1-decyne. None of these experiments succeeded in producing the desired isoquinolines.

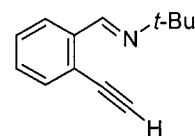
We intended to prepare *N*-tert-butyl-2-(trimethylsilylethynyl)benzaldimine (**51**)¹⁸ and *N*-tert-butyl-2-ethynylbenzaldimine (**52**).¹⁹ However, our attempts to prepare these two imines from their corresponding aldehydes failed.



50



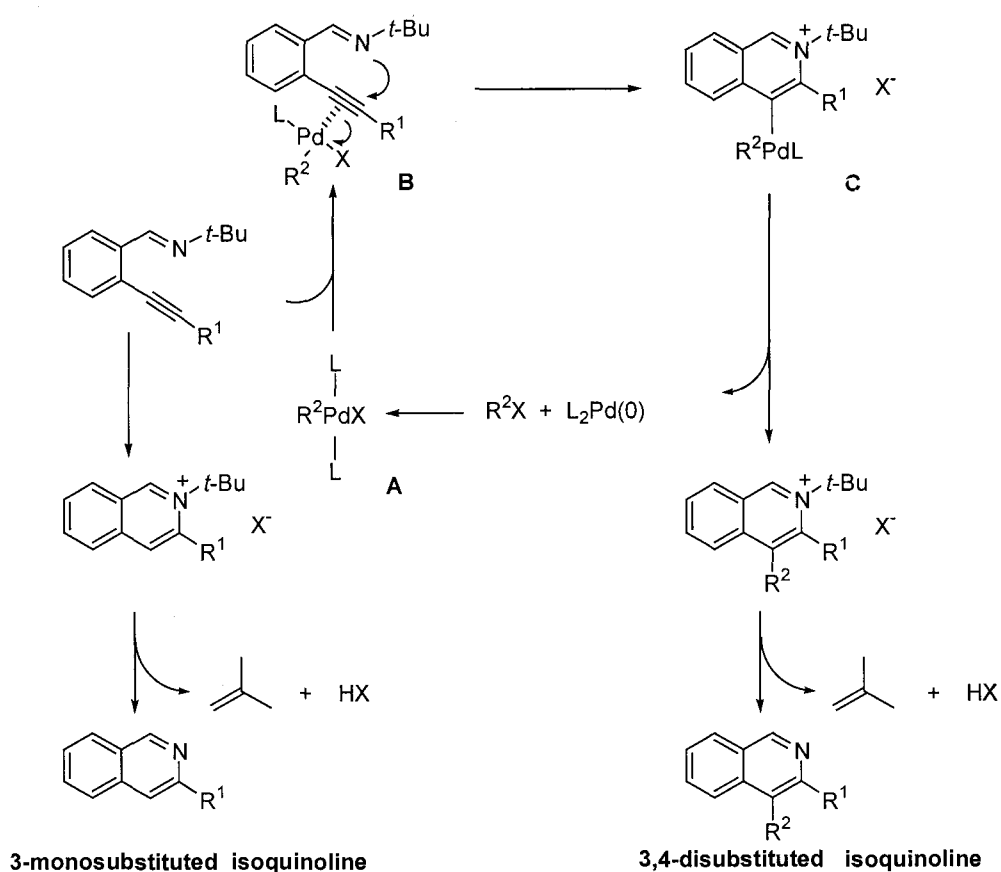
51



52

Mechanism. The present synthesis of 3,4-disubstituted isoquinolines is believed to proceed as outlined in Scheme 3, which is similar to previously reported Pd-catalyzed syntheses of benzofurans,^{1h,13a,b} indoles,^{3c} and other heterocyclic compounds.^{4i,j} The process consists of the following key steps: (1) oxidative addition of the organic halide to the Pd(0) catalyst,²⁰ (2) coordination of the resulting palladium intermediate **A** to the triple bond of the imine forming complex **B**, which activates the triple bond towards nucleophilic attack,^{1h} (3) intramolecular

Scheme 3



nucleophilic attack of the nitrogen atom of the imine on the activated carbon-carbon triple bond to afford intermediate **C**,^{1h} (4) reductive elimination to form the carbon-carbon bond between R² and the carbon of the isoquinoline ring with simultaneous regeneration of the Pd(0) catalytic species,²¹ (5) cleavage of the *tert*-butyl group from the N atom to generate the 3,4-disubstituted isoquinoline and also release the strain between the *tert*-butyl group and the group R¹.¹⁰⁻¹³

If the 2-(1-alkynyl)benzaldimine does not coordinate well to the palladium(II) intermediate **A**, cyclization by either thermal or Pd(II) catalysis to the monosubstituted isoquinoline can occur. This latter chemistry can also be accomplished by employing a catalytic amount of CuI.¹⁰ Therefore, the selectivity between the mono- and disubstituted isoquinolines is determined by whether the triple bond of the 2-alkynyl imine coordinates the R²Pd^{II}X intermediate **A**.

In the reactions of imines and aryl halides R²X, we observed a significant effect of the electronic nature of the substituents present in R²X on the yields of 3,4-disubstituted isoquinolines and the ratios of the di- and monosubstituted isoquinolines. The strong dependence of the reaction yields on the electronic nature of the aryl halides used provides useful mechanistic data. For the aryl iodides containing a *para* or *meta* electron-withdrawing substituent, the more electron-deficient intermediate **A** would be expected to coordinate more strongly to the triple bond in the imine substrate producing complex **B**. The coordination step therefore may be crucial in formation of the 3,4-disubstituted isoquinoline, because without it the imine substrate may cyclize by either a thermal or Pd(II)-catalyzed process to form the side product with no incorporation of the R² group onto the isoquinoline ring.¹⁰

This assumption is supported by the results from the electron-rich imine **20** and electron-deficient imine **25**. Imine **20** possesses a higher electron density on the carbon carbon triple bond than imine **1**, and imine **25** has decreased electron density on the triple bond. The experiments show that the higher electron density in imine **20** affords a slightly improved 80% yield of the corresponding 3,4-disubstituted isoquinoline product **21** when using 4-iodonitrobenzene, compared to the 75% yield obtained from imine **1** and the same aryl iodide (Table 1, entries 2 and 18). On the other hand, the corresponding reaction of imine **25** with lower electron density on the triple bond results in a significant decrease in the yield of the 3,4-disubstituted isoquinoline product **26** (23%) and 11% of the monosubstituted side product was also isolated (Table 1, entry 21).

Conclusions

In conclusion, we have developed a new, efficient, palladium-catalyzed synthesis of 3,4-disubstituted isoquinolines from readily available *N*-*tert*-butyl-2-(1-alkynyl)aryldimines and various organic halides. This synthetic strategy exhibits considerable structural flexibility in both the types of iminoalkynes and organic halides that can be employed. The overall yields are reasonably good. Despite some limitations, such as electron-rich and *o*-substituted aryl halides giving lower yields, the process holds promise as a useful tool for the construction of complex heterocycles containing the isoquinoline unit.

Experimental Section

General. All ^1H and ^{13}C NMR spectra were recorded at 300 and 400, and 75.5 and 100.7 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) and a 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. Lower resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV.

Procedure for synthesis of the 2-(1-alkynyl)benzaldehydes and the *N*-*tert*-butyl-2-(1-alkynyl)arylaldimines.

***N*-*tert*-Butyl-2-(phenylethynyl)benzaldimine (1).** 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 $\text{PdCl}_2(\text{PPh}_3)_2$ (140 mg, 2 mol %). The mixture was stirred for 5 min and CuI (20.0 mg, 1 mol %) was added. The resulting mixture was then heated under a nitrogen atmosphere at 50 °C for 4 h. 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 residue was purified by column chromatography on silica gel using 20:1 hexanes/ EtOAc to afford 1.88 g (91%) of the compound 2-(phenylethynyl)benzaldehyde as a yellow oil: ^1H NMR (CDCl_3) δ 7.37-7.40 (m, 3H), 7.45 (t, J = 7.2 Hz, 1H), 7.54-7.65 (m, 4H), 7.95 (dd, J = 0.8, 7.6 Hz, 1H), 10.65 (d, J = 0.8 Hz, 1H); ^{13}C NMR (CDCl_3) δ 85.1, 96.5, 122.4,

126.9, 127.3, 128.6, 128.7, 129.2, 131.8, 133.3, 133.9, 135.9, 191.7. To a mixture of the prepared 2-(phenylethynyl)benzaldehyde (0.80 g, 3.88 mmol) and H₂O (0.25 mL/mmol) was added *tert*-butylamine (11.64 mmol, 3 equiv). The mixture was then stirred under a nitrogen atmosphere at room temperature for 12 h. The excess *tert*-butylamine was removed under reduced pressure and the resulting mixture was extracted with ether. The combined organic layers were dried (Na₂SO₄) and filtered. Removal of the solvent afforded 1.00 g (97%) of the indicated compound **1** with spectral properties identical to those previously reported:^{10,12,13} mp 52-53 °C (lit.^{10,12} mp 52-53 °C).

***N*-tert-Butyl-2-(1-hexynyl)benzaldimine (15).** The corresponding aldehyde was prepared by the same method used for 2-(phenylethynyl)benzaldehyde, but employing 1-hexyne (0.4920 g, 1.2 equivalents). Column chromatography using 15:1 hexanes/EtOAc afforded 1.01 g (96%) of 2-(1-hexynyl)benzaldehyde as a yellow oil: ¹H NMR (CDCl₃) δ 0.96 (t, *J* = 7.2 Hz, 3H), 1.43-1.58 (m, 2H), 1.60-1.68 (m, 2H), 2.49 (t, *J* = 7.2 Hz, 2H), 7.34-7.40 (m, 1H), 7.48-7.52 (m, 2H), 7.88 (dt, *J* = 0.9, 7.8 Hz, 1H), 10.54 (d, *J* = 0.9 Hz, 1H); ¹³C NMR (CDCl₃) δ 13.79, 19.48, 22.27, 30.77, 76.51, 98.35, 127.08, 128.03, 128.17, 133.48, 133.86, 136.17, 192.40. The imine was prepared by the same method used for **1**, but employing 2-(1-hexynyl)benzaldehyde (0.74 g, 4.0 mmol). Removal of the solvent afforded 0.92 g (95%) of the indicated compound **21** as a yellow oil: ¹H NMR (CDCl₃) δ 0.96 (t, *J* = 6.9 Hz, 3H), 1.31 (s, 9H), 1.47-1.64 (m, 4H), 2.47 (t, *J* = 6.9 Hz, 2H), 7.25-7.31 (m, 2H), 7.37-7.41 (m, 1H), 7.98-8.03 (m, 1H), 8.81 (s, 1H); ¹³C NMR (CDCl₃) δ 13.79, 19.41, 22.19, 29.93, 30.99, 57.79, 76.80, 96.17, 124.96, 125.94, 127.97, 129.75,

132.42, 137.88, 154.68; IR (CHCl₃) 2210, 1632 cm⁻¹; HRMS: *m/z* 249.1831 (calcd for C₁₇H₂₃N, 249.1830).

***N*-tert-Butyl-2-(1-cyclohexenylethynyl)benzaldimine (17).** The corresponding aldehyde was prepared by the same method used for 2-(phenylethynyl)benzaldehyde, but employing 1-cyclohexenylacetylene (0.6360 g, 1.2 equiv). Column chromatography using 15:1 hexanes/EtOAc afforded 1.01 g (96%) of 2-(1-cyclohexenylethynyl)benzaldehyde as a yellow oil: ¹H NMR (CDCl₃) δ 1.61-1.73 (m, 4H), 2.11-2.20 (m, 2H), 2.23-2.27 (m, 2H), 6.29-6.32 (m, 1H), 7.37-7.42 (m, 1H), 7.51-7.56 (m, 2H), 7.90 (d, *J* = 8.0 Hz, 1H), 10.54 (s, 1H); ¹³C NMR (CDCl₃) δ 21.61, 22.42, 26.05, 29.19, 82.58, 98.69, 120.53, 127.26, 127.82, 128.26, 133.22, 133.91, 135.82, 137.09, 192.25. The imine was prepared by the same method used for **1**, but employing 2-(1-cyclohexenylethynyl)benzaldehyde (0.84 g, 4.0 mmol). Removal of the solvent afforded 0.98 g (95%) of the indicated compound **19** as a yellow oil: ¹H NMR (CDCl₃) δ 1.31 (s, 9H), 1.61-1.73 (m, 4H), 2.14-2.27 (m, 4H), 6.22-6.25 (m, 1H), 7.29-7.33 (m, 2H), 7.41-7.43 (m, 1H), 8.00-8.02 (m, 1H), 8.81 (s, 1H); ¹³C NMR (CDCl₃) δ 21.70, 22.54, 26.02, 29.46, 29.99, 57.96, 84.33, 97.12, 120.90, 124.68, 126.01, 128.29, 129.84, 132.19, 135.69, 137.67, 154.73; IR (CHCl₃) 3062, 2200, 1636 cm⁻¹; HRMS: *m/z* 265.1831 (calcd for C₁₉H₂₃N, 265.1830).

***N*-tert-Butyl-2-(4-methoxyphenylethynyl)benzaldimine (20).** The corresponding aldehyde was prepared by the same method used for 2-(phenylethynyl)benzaldehyde, but employing 2-bromobenzaldehyde (1.85 g, 10 mmol) and 1-ethynyl-4-methoxybenzene for 4 h. Column chromatography using 5:1 hexanes/ethyl acetate afforded 2.24 g (95%) of the compound 2-(4-

methoxyphenylethynyl)benzaldehyde as a yellow solid: mp 50-51 °C; ^1H NMR (CDCl_3) δ 3.86 (s, 3H), 6.93 (d, J = 8.8 Hz, 2H), 7.44 (t, J = 7.6 Hz, 1H), 7.52 (d, J = 8.8 Hz, 2H), 7.56-7.64 (m, 2H), 7.95 (d, J = 8.0 Hz, 1H), 10.66 (s, 1H); ^{13}C NMR (CDCl_3) δ 55.57, 83.97, 96.78, 114.37, 114.55, 127.38, 127.54, 128.42, 133.22, 133.42, 133.97, 135.80, 160.40, 192.09. The imine was prepared by the same method used for **1**, but employing 2-(4-methoxyphenylethynyl)benzaldehyde (0.92 g, 3.88 mmol). Removal of the solvent afforded 1.04 g (95% yield) of the indicated compound **16** as a bright yellow oil: ^1H NMR (CDCl_3) δ 1.36 (s, 9H), 3.85 (s, 3H), 6.92 (dt, J = 2.1, 9.0 Hz, 2H), 7.34-7.38 (m, 2H), 7.49 (dt, J = 2.1, 9.0 Hz, 2H), 7.52-7.55 (m, 1H), 8.06-8.09 (m, 1H), 8.94 (s, 1H); ^{13}C NMR (CDCl_3) δ 30.05, 55.59, 58.06, 85.67, 95.20, 114.37, 115.37, 124.50, 126.14, 128.53, 129.97, 132.25, 133.17, 137.72, 154.66, 160.04; IR (CHCl_3) 2963, 2200, 1699 cm^{-1} ; HRMS m/z 291.1626 (calcd for $\text{C}_{20}\text{H}_{21}\text{NO}$, 291.1623).

***N*-tert-Butyl-6-(phenylethynyl)piperonaldimine (23).** The corresponding aldehyde was prepared by the same method used to prepare 2-(phenylethynyl)benzaldehyde, but employing 5-bromopiperonal (1.145 g, 5.0 mmol) and phenylacetylene (0.6128 g, 1.2 equiv). Column chromatography using 5:1 hexanes/ethyl acetate afforded 1.172 g (94%) of 5-(phenylethynyl)piperonal as a yellow solid: mp 98-101 °C; ^1H NMR (CDCl_3) δ 6.10 (s, 2H), 7.03 (s, 1H), 7.34-7.39 (m, 4H), 7.53-7.55 (m, 2H), 10.49 (s, 1H); ^{13}C NMR (CDCl_3) δ 84.98, 95.36, 102.62, 106.32, 112.21, 122.54, 123.85, 128.74, 129.20, 131.80, 132.36, 148.93, 152.62, 190.27. The imine **23** was prepared by the same method used for **1**, but employing 6-(phenylethynyl)piperonal (1.002 g, 4 mmol). Removal of the solvent afforded

1.091 g (87%) of the indicated compound **23** as a yellow solid: 88-90 °C; ¹H NMR (CHCl₃) δ 1.32 (s, 9H), 6.01 (s, 2H), 6.96 (s, 1H), 7.35-7.38 (m, 3H), 7.49-7.52 (m, 2H), 7.56 (s, 1H), 8.84 (s, 1H); ¹³C NMR (CDCl₃) δ 30.04, 57.77, 86.93, 93.85, 101.89, 105.93, 111.29, 118.57, 123.37, 128.58, 128.68, 131.54, 134.05, 148.82, 149.22, 153.70; IR (CHCl₃) 3018, 2970, 1612 cm⁻¹; HRMS: m/z 305.1420 (calcd for C₁₈H₁₈N₂, 305.1416).

N-tert-Butyl-2-phenylethynyl-3-pyridinecarboxaldimine (25). The corresponding aldehyde was prepared by the same method used for 2-(phenylethynyl)benzaldehyde, but employing 2-bromo-3-pyridinecarboxaldehyde (0.93 g, 5.0 mmol) and phenylacetylene (0.6128 g, 1.2 equiv). Column chromatography using 3:1 hexanes/ethyl acetate afforded 0.88 g (85%) of 2-phenylethynyl-3-pyridinecarboxaldehyde as a white solid²²: ¹H NMR (CDCl₃) δ 7.37-7.45 (m, 4H), 7.64-7.67 (m, 2H), 8.22 (dd, *J* = 1.6, 8.0 Hz, 1H), 8.83 (dd, *J* = 2.0, 5.6 Hz, 1H), 10.68 (d, *J* = 0.8 Hz, 1H); ¹³C NMR (CDCl₃) δ 84.90, 96.29, 121.48, 123.43, 128.82, 130.08, 132.06, 132.41, 135.03, 146.32, 154.73, 191.02. The imine **21** was prepared by the same method used for **1**, but employing 2-phenylethynyl-3-pyridinecarboxaldehyde (0.83 g, 4.0 mmol). Removal of the solvent afforded 1.00 g (95%) of the indicated compound **21** as a white solid: mp 71-72 °C; ¹H NMR (CHCl₃) δ 1.35 (s, 9H), 7.30 (d, *J* = 7.2 Hz, 1H), 7.38-7.41 (m, 3H), 7.60-7.62 (m, 2H), 8.37 (dd, *J* = 2.0, 8.0 Hz, 1H), 8.64 (dd, *J* = 2.0, 4.8 Hz, 1H), 8.88 (s, 1H); ¹³C NMR (CDCl₃) δ 29.82, 58.44, 86.36, 94.57, 122.27, 123.34, 128.73, 129.46, 132.14, 133.96, 134.19, 143.55, 151.37, 152.56; IR (CHCl₃) 3057, 2969, 2218, 1635 cm⁻¹; HRMS: m/z 262.1476 (calcd for C₁₈H₁₈N₂, 262.1470).

***N*-tert-Butyl-2-(phenylethynyl)cyclohex-1-enecarboxaldimine (50).** The corresponding aldehyde was prepared by the same method used for 2-(phenylethynyl)benzaldehyde, but employing 2-bromocyclohex-1-enecarbaldehyde (this aldehyde is not stable at room temperature and should be used right away or stored in the refrigerator)²³ (0.946 g, 5.0 mmol) and phenylacetylene (0.6128 g, 1.2 equiv). Column chromatography using 25:1 hexanes/ethyl acetate afforded 0.98 g (93%) of 2-(phenylethynyl)cyclohex-1-enecarbaldehyde as a yellow oil: ¹H NMR (CDCl₃) δ 1.58-1.76 (m, 4H), 2.30-2.33 (m, 2H), 2.50-2.53 (m, 2H), 10.32 (s, 1H); ¹³C NMR (CDCl₃) δ 21.28, 22.10, 22.31, 32.55, 86.48, 98.73, 122.53, 128.70, 129.29, 131.85, 140.12, 142.80, 193.07. The imine **50** was prepared by the same method used for **1**, but employing 2-(phenylethynyl)cyclohex-1-enecarbaldehyde (0.84 g, 4.0 mmol). Removal of the solvent afforded 1.00 g (94%) of the indicated compound **50** as a yellow oil: ¹H NMR (CHCl₃) δ 1.25 (s, 9H), 1.68-1.69 (m, 4H), 2.42 (br s, 4H), 7.32-7.35 (m, 3H), 7.43-7.45 (m, 2H), 8.70 (s, 1H); ¹³C NMR (CDCl₃) δ 21.94, 22.58, 24.73, 30.08, 31.53, 57.55, 88.56, 95.92, 123.63, 127.23, 128.44, 128.61, 131.56, 142.68, 156.75; IR (CHCl₃) 3042, 2972, 2221, 1620 cm⁻¹; HRMS: m/z 265.3938 (calcd for C₁₉H₂₃N, 265.3934).

Typical Procedure for the Palladium-Catalyzed Formation of 3,4-Disubstituted Isoquinolines.

3,4-Diphenylisoquinoline (2a). A mixture of DMF (5.0 mL), Pd(PPh₃)₄ (14.4 mg, 0.0125 mmol), K₂CO₃ (0.1725 g, 1.25 mmol), *N*-tert-butyl-2-(phenylethynyl)benzaldimine (**1**) (0.0653 g, 0.25 mmol), and phenyl iodide (0.2551 g, 1.25 mmol) was flushed with Ar at room temperature for 5 min and then heated to 100 °C with stirring for 12 h. The reaction mixture was cooled to room

temperature, diluted with diethyl ether (30 mL) and washed with brine (30 mL). The aqueous layer was reextracted with diethyl ether (15 mL). The organic layers were combined, dried (MgSO_4), filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on a silica gel column using 10:1 hexanes/EtOAc to afford 34 mg (49%) of the indicated compound: mp 154-155 °C (lit¹⁷ mp 154-155 °C). The spectral properties were identical to those previously reported.¹⁷

4-(4-Nitrophenyl)-3-phenylisoquinoline (3). The reaction mixture was chromatographed using 3:1 hexanes/ethyl acetate to afford 62 mg (75%) of the indicated compound as a yellow solid: mp 133-134 °C; ^1H NMR (CDCl_3) δ 7.24-7.25 (m, 3H), 7.30-7.33 (m, 2H), 7.46 (dt, $J = 1.5, 6.6$ Hz, 2H), 7.55-7.57 (m, 1H), 7.65-7.69 (m, 2H), 8.10-8.12 (m, 1H), 8.25 (dt, $J = 1.5, 6.6$ Hz, 2H), 9.43 (s, 1H); ^{13}C NMR (CDCl_3) δ 123.80, 124.85, 127.47, 127.60, 127.92, 128.20, 128.24, 128.67, 130.41, 131.47, 132.52, 135.31, 140.12, 144.94, 147.32, 151.09, 152.98; IR (CHCl_3) 3059, 1521 cm^{-1} ; HRMS m/z 326.1059 (calcd for $\text{C}_{21}\text{H}_{14}\text{N}_2\text{O}_2$, 326.1055).

4-(3-Nitrophenyl)-3-phenylisoquinoline (4). The reaction mixture was chromatographed using 5:1 hexanes/ethyl acetate to afford 39 mg (49%) of the indicated compound as a yellow solid: mp 131-132 °C; ^1H NMR (CDCl_3) δ 7.22-7.25 (m, 3H), 7.30-7.33 (m, 2H), 7.52-7.58 (m, 3H), 7.65-7.71 (m, 2H), 8.10-8.13 (m, 1H), 8.19 (s, 1H), 8.23 (dt, $J = 1.5, 6.9$ Hz, 1H), 9.43 (s, 1H); ^{13}C NMR (CDCl_3) δ 122.66, 124.77, 126.30, 127.49, 127.53, 127.78, 128.18, 128.29, 129.61, 130.44, 131.44, 135.44, 137.64, 139.42, 140.09, 148.36, 151.41, 152.88; IR (CHCl_3) 3032, 2969, 1532 cm^{-1} ; HRMS m/z 326.1059 (calcd for $\text{C}_{21}\text{H}_{14}\text{N}_2\text{O}_2$, 326.1055).

Ethyl 4-(3-phenylisoquinolin-4-yl)benzoate (6). The reaction mixture was chromatographed using 5:1 hexanes/ethyl acetate to afford 59 mg (67%) of the indicated compound as a yellow solid: mp 149-150 °C; ¹H NMR (CDCl₃) δ 1.42 (t, *J* = 5.4 Hz, 3H), 4.41 (q, *J* = 5.4 Hz, 2H), 7.20-7.23 (m, 3H), 7.33-7.36 (m, 4H), 7.59-7.65 (m, 3H), 8.05-8.09 (m, 3H), 9.40 (s, 1H); ¹³C NMR (CDCl₃) δ 14.33, 61.07, 125.14, 127.06, 127.27, 127.32, 127.71, 127.81, 129.44, 129.52, 129.63, 130.78, 131.32, 135.48, 140.34, 142.28, 150.65, 152.20, 166.41; IR (CHCl₃) 3019, 1711, 1619 cm⁻¹; HRMS *m/z* 353.1420 (calcd for C₂₄H₁₉NO₂, 353.1416).

4-(3-Ethoxycarbonylphenyl)-3-phenylisoquinoline (7). The reaction mixture was chromatographed using 5:1 hexanes/ethyl acetate to afford 48 mg (55%) of the indicated compound as a yellow oil: ¹H NMR (CDCl₃) δ 1.37 (t, *J* = 3.9 Hz, 3H), 4.38 (q, *J* = 3.9 Hz, 2H), 7.19-7.25 (m, 3H), 7.33-7.45 (m, 4H), 7.58-7.66 (m, 3H), 8.03-8.09 (m, 3H), 9.40 (s, 1H); ¹³C NMR (CDCl₃) δ 140.25, 61.07, 125.22, 127.0, 127.21, 127.31, 127.67, 127.74, 128.50, 128.54, 129.57, 130.28, 130.54, 130.77, 135.57, 135.70, 137.59, 140.37, 150.89, 152.08, 166.38; IR (CHCl₃) 3061, 2984, 1712 cm⁻¹; HRMS *m/z* 353.1422 (calcd for C₂₄H₁₉NO₂, 353.1416).

3-Phenyl-4-(4-trifluoromethylphenyl)isoquinoline (9). The reaction mixture was chromatographed using 5:1 hexanes/ethyl acetate to afford 52 mg (65%) of the indicated compound as a yellow solid: mp 128-129 °C; ¹H NMR (CDCl₃) δ 7.22-7.23 (m, 3H), 7.32-7.34 (m, 2H), 7.40 (d, *J* = 5.7 Hz, 2H), 7.57-7.65 (m, 5H), 8.08 (d, *J* = 5.7 Hz, 1H), 9.41 (s, 1H); ¹³C NMR (CDCl₃) δ 125.24, 125.50 (q, *J* = 3.8 Hz, 1C, including 125.43, 125.48, 125.53, 125.58), 127.37, 127.51, 127.64, 128.00, 128.07, 129.38, 130.00, 130.44, 131.14, 131.87, 135.69, 140.43,

141.52, 151.03, 152.58 (one sp^2 carbon is missing due to overlap); IR ($CHCl_3$) 3060, 3019, 2929, 1619 cm^{-1} ; HRMS m/z 349.1083 (calcd for $C_{22}H_{14}F_3N$, 349.1078).

3-Phenyl-4-(3-trifluoromethylphenyl)isoquinoline (10). The reaction mixture was chromatographed using 7:1 hexanes/ethyl acetate to afford 45 mg (51%) of the indicated compound as a yellow oil: 1H NMR ($CDCl_3$) δ 7.21-7.25 (m, 3H), 7.28-7.32 (m, 2H), 7.43 (d, $J = 7.6$ Hz, 1H), 7.49 (t, $J = 7.6$ Hz, 1H), 7.55 (s, 1H), 7.59-7.69 (m, 4H), 8.08-8.10 (m, 1H), 9.41 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 126.59 (q, $J = 272.6$ Hz, 1C, including 122.37, 125.98), 124.41 (q, $J = 3.8$ Hz, 1C, including 124.33, 124.38, 124.43, 124.48), 125.16, 127.38, 127.57, 127.60, 128.28 (q, $J = 3.8$ Hz, 1C, including 128.04, 128.26, 128.31, 128.41), 129.07, 129.30, 130.39, 130.75, 131.18, 131.23, 134.83 (d, $J = 1.2$ Hz, 1C, including 134.82, 134.84), 135.71, 138.38, 140.38, 151.33, 152.55 (one sp^2 carbon is missing due to overlap); IR ($CHCl_3$) 3061, 3018, 2972, 1619 cm^{-1} ; HRMS m/z 349.1083 (calcd for $C_{22}H_{14}F_3N$, 349.1078).

3-Phenyl-4-(3-pyridyl)isoquinoline (11). The reaction mixture was chromatographed using 3:1 hexanes/ethyl acetate to afford 34 mg (48%) of the indicated compound as a yellow solid: mp 149-150 $^{\circ}C$; 1H NMR ($CDCl_3$) δ 7.22-7.24 (m, 3H), 7.29-7.34 (m, 3H), 7.55-7.62 (m, 2H), 7.63-7.69 (m, 2H), 8.08-8.12 (m, 1H), 7.55 (d, $J = 1.5$, 1H), 8.60 (dd, $J = 4.8, 1.5$ Hz, 1H), 9.42 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 123.39, 125.00, 127.06, 127.42, 127.50, 127.66, 128.05, 128.12, 130.54, 131.26, 135.89, 138.81, 140.26, 148.71, 151.76, 151.81, 152.69 (one sp^2 C is missing due to overlap); IR ($CHCl_3$) 3020, 1672 cm^{-1} ; HRMS m/z 282.1158 (calcd for $C_{20}H_{14}N_2$, 282.1157).

4-(4-Methylphenyl)-3-phenylisoquinoline (12). The reaction mixture was chromatographed using 10:1 hexanes/ethyl acetate to yield a yellow solid: mp 120-121 °C (hexanes); ^1H NMR (CDCl_3) δ 2.30 (s, 3H), 7.07 (d, $J = 8.0$ Hz, 2H), 7.21-7.29 (m, 3H), 7.58 (d, $J = 8.0$ Hz, 2H), 7.63-7.68 (m, 4H), 7.72, (d, $J = 7.2$ Hz, 1H), 8.07-8.09 (m, 1H), 9.45 (s, 1H); ^{13}C NMR (CDCl_3) δ 21.86, 124.76, 127.09, 127.72, 128.09, 128.43, 128.55, 129.08, 129.45, 129.67, 129.92, 131.57, 134.33, 135.17, 139.82, 144.87, 149.82, 153.43; IR (CHCl_3) 3018, 2956, 1610 cm^{-1} ; HRMS 323.1315 (calcd for $\text{C}_{22}\text{H}_{17}\text{N}$ 323.1310).

4-(2-Methylphenyl)-3-phenylisoquinoline (13). The reaction mixture was chromatographed using 10:1 hexanes/ethyl acetate to yield a yellow solid: mp 99-100 °C (hexanes); ^1H NMR (CDCl_3) δ 2.58 (s, 3H), 6.90 (t, $J = 5.7$ Hz, 1H), 7.06 (d, $J = 5.7$ Hz, 1H), 7.10 (d, $J = 5.7$ Hz, 1H), 7.18-7.28 (m, 4H), 7.51-7.53 (m, 2H), 7.67 (td, $J = 6.0, 0.9$ Hz, 1H), 7.73 (td, $J = 6.0, 0.9$ Hz, 1H), 7.92 (d, $J = 6.0$ Hz, 1H), 8.10 (d, $J = 8.0$ Hz, 1H), 9.44 (s, 1H); ^{13}C NMR (CDCl_3) δ 21.84, 124.77, 125.58, 127.26, 127.81, 128.19, 128.31, 128.53, 129.55, 130.59, 131.84, 131.87, 132.08, 132.52, 134.51, 137.47, 140.15, 140.37, 150.67, 153.54; IR (CHCl_3) 3058, 3012, 1612 cm^{-1} ; HRMS 323.1315 (calcd for $\text{C}_{22}\text{H}_{17}\text{N}$ 323.1310).

4-(4-Methoxyphenyl)-3-phenylisoquinoline (14). The reaction mixture was chromatographed using 5:1 hexanes/ethyl acetate to afford 10 mg (13%) of the indicated compound as a white solid: mp 141-142 °C; ^1H NMR (CDCl_3) δ 3.85 (s, 3H), 6.91 (d, $J = 6.3$ Hz, 2H), 7.16 (d, $J = 6.3$ Hz, 2H), 7.22 (t, $J = 5.4$ Hz, 3H), 7.39 (d, $J = 5.4$ Hz, 2H), 7.59-7.65 (m, 2H), 7.72 (d, $J = 6.0$ Hz, 1H), 8.05 (d, $J = 5.4$ Hz, 1H), 9.36 (s, 1H); ^{13}C NMR (CDCl_3) δ 55.45, 114.01, 125.87, 127.03, 127.18,

127.66, 127.76, 127.90, 129.52, 130.47, 130.52, 130.64, 132.53, 136.48, 141.17, 151.76, 159.04 (one sp^2 carbon missing due to overlap); IR ($CHCl_3$) 3057, 1261 cm^{-1} ; HRMS m/z 311.3779 (calcd for $C_{22}H_{17}NO$, 311.3775).

3-Butyl-4-(4-nitrophenyl)isoquinoline (16). The reaction mixture was chromatographed using 5:1 hexanes/ethyl acetate to afford 27 mg (35%) of the indicated compound as a yellow solid: mp 105-107 °C; 1H NMR ($CDCl_3$) δ 0.82 (t, $J = 7.2$ Hz, 3H), 1.26 (sextet, $J = 7.5$ Hz, 2H), 1.62-1.72 (m, 2H), 2.68 (t, $J = 7.8$ Hz, 2H), 7.23-7.25 (m, 1H), 7.52 (dt, $J = 2.4, 8.7$ Hz, 2H), 7.55-7.61 (m, 2H), 7.99-8.03 (m, 1H), 8.40 (dt, $J = 2.1, 9.0$ Hz, 2H), 9.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 14.08, 22.87, 32.58, 35.65, 123.98, 124.54, 126.73, 126.77, 127.94, 128.47, 130.98, 131.61, 135.35, 145.19, 147.71, 152.81, 152.91; IR ($CHCl_3$) 3019, 1522, 1349 cm^{-1} ; HRMS m/z 306.1372 (calcd for $C_{19}H_{18}N_2O_2$, 306.1368).

3-(1-Cyclohexenyl)-4-(4-nitrophenyl)isoquinoline (18). The reaction mixture was chromatographed using 3:1 hexanes/ethyl acetate to afford 49 mg (60%) of the indicated compound as an orange solid: mp 130-132 °C; 1H NMR ($CDCl_3$) δ 1.47-1.54 (m, 2H), 1.58-1.66 (m, 2H), 1.94-1.99 (m, 2H), 2.19-2.22 (m, 2H), 5.58-5.61 (m, 1H), 7.44-7.48 (m, 1H), 7.52 (dt, $J = 2.1, 9.0$ Hz, 2H), 5.57-7.65 (m, 2H), 8.02-8.05 (m, 1H), 8.34 (dt, $J = 2.1, 9.0$ Hz, 2H), 9.30 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 21.96, 22.92, 25.69, 29.26, 123.56, 124.76, 127.05, 127.22, 127.66, 128.08, 131.10, 131.85, 131.89, 135.27, 137.68, 145.60, 147.32, 152.52, 154.11; IR ($CHCl_3$) 3005, 2928, 1522, 1360 cm^{-1} ; HRMS m/z 330.1372 (calcd for $C_{21}H_{18}N_2O_2$, 330.1368).

Ethyl 4-[3-(1-cyclohexenyl)isoquinolin-4-yl]benzoate (19). The reaction mixture was chromatographed using 5:1 hexanes/ethyl acetate to afford 54.4 mg

(61%) of the indicated compound as a yellow solid: mp 128-129 °C; ^1H NMR (CDCl_3) δ 1.45 (t, $J = 7.2$ Hz, 3H), 1.48-1.52 (m, 2H), 1.56-1.61 (m, 2H), 1.95-1.97 (m, 2H), 2.16-2.18 (m, 2H), 4.44 (q, $J = 7.2$ Hz, 2H), 5.63-5.66 (m, 1H), 7.41 (dd, $J = 7.2, 1.6$ Hz, 2H), 7.49-7.51 (m, 1H), 7.54-7.58 (m, 2H), 7.99-8.01 (m, 1H), 8.15 (dd, $J = 7.2, 1.6$ Hz, 2H), 9.27 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.61, 22.03, 23.00, 25.71, 29.20, 61.32, 125.26, 126.76, 127.28, 127.85, 128.89, 129.51, 129.56, 130.71, 130.98, 131.22, 135.66, 137.93, 143.09, 151.95, 154.02, 166.79; IR (CHCl_3) 3019, 1725 cm^{-1} ; HRMS m/z 357.1734 (calcd for $\text{C}_{24}\text{H}_{23}\text{NO}_2$, 357.1729).

3-(4-Methoxyphenyl)-4-(4-nitrophenyl)isoquinoline (21). The reaction mixture was chromatographed using 2:1 hexanes/ethyl acetate to afford 74 mg (80%) of the indicated compound as an orange solid: mp 181-182 °C; ^1H NMR (CDCl_3) δ 3.78 (s, 3H), 6.77 (dt, $J = 2.7, 8.7$ Hz, 2H), 7.27 (dt, $J = 2.7, 8.7$ Hz, 2H), 7.47 (dt, $J = 2.1, 9.0$ Hz, 2H), 7.52-7.55 (m, 1H), 7.62-7.67 (m, 2H), 8.07-8.10 (m, 1H), 8.27 (dt, $J = 2.1, 9.0$ Hz, 2H), 9.40 (s, 1H); ^{13}C NMR (CDCl_3) δ 55.35, 113.63, 123.82, 124.65, 127.19, 127.27, 128.03, 128.19, 131.31, 131.73, 132.48, 135.32, 145.22, 147.21, 150.65, 152.84, 159.30 (one sp^2 carbon missing due to overlap); IR (CHCl_3) 3019, 1518, 1215 cm^{-1} ; HRMS m/z 356.1167 (calcd for $\text{C}_{22}\text{H}_{16}\text{N}_2\text{O}_3$, 356.1161).

3,4-Di(4-methoxyphenyl)isoquinoline (22). The reaction mixture was chromatographed using 2:1 hexanes/ethyl acetate to afford 27 mg (30%) of the indicated compound as a white solid: mp 164-165 °C; ^1H NMR (CDCl_3) δ 3.77 (s, 3H), 3.85 (s, 3H), 6.76 (dt, $J = 6.9, 1.8$ Hz, 2H), 6.93 (dt, $J = 6.6, 1.8$ Hz, 2H), 7.17 (dt, $J = 6.9, 1.8$ Hz, 2H), 7.34 (dt, $J = 6.6, 1.8$ Hz, 2H), 7.55-7.61 (m, 2H), 7.69 (d, J

= 6.0 Hz, 1H), 8.00-8.03 (m, 1H), 9.33 (s, 1H); ^{13}C NMR (CDCl_3) δ 55.37, 55.45, 113.36, 114.11, 125.73, 126.75, 127.44, 127.73, 129.82, 129.92, 130.53, 131.73, 132.48, 133.63, 136.57, 150.59, 151.68, 158.83, 158.99; IR (CHCl_3) 3019, 1514 cm^{-1} ; HRMS m/z 341.1422 (calcd for $\text{C}_{23}\text{H}_{19}\text{NO}_2$, 341.1416).

8-(4-Nitrophenyl)-7-phenyl-[1,3]dioxolo[4,5-g]isoquinoline (24). The reaction mixture was chromatographed using 3.5:1 hexanes/ethyl acetate to afford 56 mg (59%) of the indicated compound as a yellow solid: mp 169-170 $^\circ\text{C}$; ^1H NMR (CDCl_3) δ 6.11 (s, 2H), 6.78 (s, 1H), 7.18-7.24 (m, 3H), 7.25-7.29 (m, 2H), 7.31 (s, 1H), 7.41 (dt, $J = 8.7, 2.1$ Hz, 2H), 8.23 (dt, $J = 8.7, 2.1$ Hz, 2H), 9.14 (s, 1H); ^{13}C NMR (CDCl_3) δ 101.26, 102.17, 103.55, 123.86, 124.99, 127.73, 128.15, 128.47, 130.27, 132.40, 133.79, 140.22, 145.33, 147.28, 148.61, 150.46, 150.56, 152.07; IR (CHCl_3) 3019, 2926, 1642 cm^{-1} ; HRMS m/z 370.0959 (calcd for $\text{C}_{22}\text{H}_{14}\text{N}_2\text{O}_4$, 370.0954).

4-Allyl-3-phenylisoquinoline (27). The reaction mixture was chromatographed using 7:1 hexanes/ethyl acetate to afford 42 mg (69%) of the indicated compound as a yellow oil: ^1H NMR (CDCl_3) δ 3.80-3.81 (m, 2H), 4.88 (dd, $J = 1.6, 17.6$ Hz, 1H), 5.15 (dd, $J = 1.6, 11.2$ Hz, 1H), 6.10-6.19 (m, 1H), 7.39-7.48 (m, 3H), 7.58-7.62 (m, 3H), 7.73 (dt, $J = 1.2, 8.0$ Hz, 1H), 8.01 (t, $J = 8.0$ Hz, 2H), 9.24 (s, 1H); ^{13}C NMR (CDCl_3) δ 33.38, 116.98, 124.55, 125.72, 126.90, 127.89, 128.01, 128.31, 128.39, 129.51, 130.66, 136.06, 137.15, 141.37, 151.18, 152.87; IR (CHCl_3) 3059, 3014, 1621, 1572 cm^{-1} ; HRMS m/z 245.1206 (calcd for $\text{C}_{18}\text{H}_{15}\text{N}$, 245.1204).

4-Methallyl-3-phenylisoquinoline (28). The reaction mixture was chromatographed using 8:1 hexanes/ethyl acetate to afford 46mg (71%) of the indicated compound as a yellow oil: ^1H NMR (CDCl_3) δ 1.87 (s, 3H), 3.67 (s, 2H), 4.33 (s, 1H), 4.90 (d, $J = 1.5$ Hz, 1H), 7.40-7.46 (m, 3H), 7.47-7.49 (m, 4H), 7.57-7.74 (m, 4H), 7.93 (d, $J = 8.7$ Hz, 1H), 8.00 (d, $J = 7.5$ Hz, 1H), 9.25 (s, 1H); ^{13}C NMR (CDCl_3) δ 23.63, 37.31, 112.63, 124.56, 125.70, 126.60, 127.52, 127.75, 127.97, 128.05, 129.04, 130.32, 136.18, 141.13, 144.81, 150.99, 152.57; IR (CHCl_3) 2928, 1621 cm^{-1} ; HRMS m/z 259.1363 (calcd for $\text{C}_{19}\text{H}_{17}\text{N}$, 259.1361).

3-Phenyl-4-(*E*-3-phenyl-2-propenyl)isoquinoline (29). The reaction mixture was chromatographed using 7:1 hexanes/ethyl acetate to afford 39 mg (48%) of the indicated compound as a yellow oil: ^1H NMR (CDCl_3) δ 3.97 (d, $J = 4.4$ Hz, 2H), 6.22 (d, $J = 16.0$ Hz, 1H), 6.52 (dt, $J = 16.0, 5.6$ Hz, 1H), 7.18-7.27 (m, 5H), 7.41-7.48 (m, 3H), 7.59-7.64 (m, 3H), 7.73 (t, $J = 5.7$ Hz, 1H), 8.03 (d, $J = 8.0$ Hz, 1H), 8.08 (d, $J = 8.8$ Hz, 1H), 9.28 (s, 1H); ^{13}C NMR (CDCl_3) δ 32.41, 124.23, 125.60, 126.04, 126.72, 127.22, 127.69, 127.81, 128.13, 128.20, 128.48, 128.88, 129.32, 130.61, 131.63, 135.82, 137.25, 141.04, 151.05, 152.67; IR (CHCl_3) 3019, 1673 cm^{-1} ; HRMS m/z 321.1521 (calcd for $\text{C}_{24}\text{H}_{19}\text{N}$, 321.1518).

Ethyl 2-[(3-phenylisoquinolin-4-yl)methyl]propenoate (33). The reaction mixture was chromatographed using 3:1 hexanes/ethyl acetate to afford 47 mg (59%) of the indicated compound as an orange oil: ^1H NMR (CDCl_3) δ 1.34 (t, $J = 9.6$ Hz, 3H), 4.06 (t, $J = 2.8$ Hz, 2H), 4.28 (q, $J = 9.6$ Hz, 2H), 6.30 (d, $J = 0.8$ Hz, 1H), 7.40-7.47 (m, 3H), 7.54-7.57 (m, 2H), 7.61 (td, $J = 9.2, 1.6$ Hz, 1H), 7.72 (td, $J = 9.2, 1.6$ Hz, 2H), 7.83 (d, $J = 11.2$ Hz, 1H), 8.03 (d, $J = 10.8$ Hz, 1H), 9.29 (s, 1H);

^{13}C NMR (CDCl_3) δ 29.89, 31.43, 61.28, 124.44, 124.58, 126.70, 127.04, 127.84, 128.17, 128.42, 129.04, 130.94, 135.82, 140.02, 140.96, 151.64, 153.38, 166.99 (one sp^2 carbon is missing due to overlap); IR (CHCl_3) 2982, 1710 cm^{-1} ; HRMS m/z 317.1420 (calcd for $\text{C}_{21}\text{H}_{19}\text{NO}_2$, 317.1416).

3-Butyl-4-methallylisoquinoline (35). The reaction mixture was chromatographed using 10:1 hexanes/ethyl acetate to afford 37 mg (62%) of the indicated compound as a yellow oil: ^1H NMR (CDCl_3) δ 0.97 (t, $J = 7.2$ Hz, 3H), 1.45 (pentet, $J = 7.2$ Hz, 2H), 1.71-1.79 (m, 2H), 1.90 (s, 3H), 2.93 (t, $J = 8.0$ Hz, 2H), 3.71 (s, 2H), 4.24 (s, 1H), 4.78 (t, $J = 1.2$ Hz, 1H), 7.49 (td, $J = 0.8, 8.0$ Hz, 1H), 7.63 (td, $J = 1.6, 6.8$ Hz, 1H), 7.85 (d, $J = 8.8$ Hz, 1H), 7.90 (d, $J = 8.4$ Hz, 1H), 9.12 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.25, 23.20, 23.68, 32.50, 35.40, 35.74, 112.02, 123.65, 125.13, 125.90, 127.27, 128.16, 130.21, 136.19, 143.68, 150.90, 154.50; IR (CHCl_3) 3077, 2957, 1624 cm^{-1} ; HRMS m/z 239.1678 (calcd for $\text{C}_{17}\text{H}_{21}\text{N}$, 239.1674).

4-Allyl-3-butylisoquinoline (36). The reaction mixture was chromatographed using 10:1 hexanes/ethyl acetate to afford 34 mg (55%) of the indicated compound as a pale yellow oil: ^1H NMR (CDCl_3) δ 0.97 (t, $J = 7.2$ Hz, 3H), 1.47 (sextet, $J = 7.5$ Hz, 2H), 1.70-1.81 (m, 2H), 2.96 (t, $J = 8.1$ Hz, 2H), 3.82 (dt, $J = 5.4, 1.2$ Hz, 2H), 4.93 (dq, $J = 22.8, 2.4$ Hz, 1H), 5.06 (dq, $J = 13.2, 2.4$ Hz, 1H), 5.98-6.11 (m, 1H), 7.49-7.69 (m, 1H), 7.64-7.69 (m, 1H), 7.91-7.95 (m, 2H), 9.12 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.27, 23.22, 31.91, 32.63, 35.47, 116.29, 123.41, 124.92, 125.97, 127.39, 128.32, 130.32, 135.78, 136.10, 150.93, 154.13; IR (CHCl_3) 3011, 1628 cm^{-1} ; HRMS m/z 225.1521 (calcd for $\text{C}_{16}\text{H}_{19}\text{N}$, 225.1518).

3-(1-Cyclohexenyl)-4-methallylisoquinoline (37). The reaction mixture was chromatographed using 10:1 hexanes/ethyl acetate to afford 20 mg (30%) of the indicated compound as a yellow oil: $^1\text{H NMR}$ (CDCl_3) δ 1.71-1.86 (m, 4H), 1.88 (d, $J = 0.3$ Hz, 3H), 2.18-2.24 (m, 2H), 2.39-2.44 (m, 2H), 3.74 (s, 2H), 4.22 (q, $J = 0.9$ Hz, 1H), 4.80 (pentet, $J = 1.5$ Hz, 1H), 5.85 (pentet, $J = 1.8$ Hz, 1H), 7.52 (td, $J = 1.2, 7.5$ Hz, 1H), 7.65 (td, $J = 1.5, 7.8$ Hz, 1H), 7.81 (dd, $J = 0.6, 8.4$ Hz, 1H), 7.92 (d, $J = 8.4$ Hz, 1H), 9.14 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3) δ 22.34, 23.26, 25.63, 29.26, 37.08, 112.29, 117.66, 124.69, 125.04, 126.31, 127.38, 127.44, 128.12, 130.27, 136.45, 138.32, 145.09, 150.80, 155.54; IR (CHCl_3) 3017, 2926, 1620 cm^{-1} ; HRMS m/z 263.1678 (calcd for $\text{C}_{19}\text{H}_{21}\text{N}$, 263.1674).

4-Methallyl-3-(4-methoxyphenyl)isoquinoline (38). The reaction mixture was chromatographed using 5:1 hexanes/ethyl acetate to afford 67 mg (88%) of the indicated compound as a yellow solid: mp 81-82 $^\circ\text{C}$; $^1\text{H NMR}$ (CDCl_3) δ 1.90 (s, 3H), 3.67 (s, 2H), 3.86 (s, 3H), 4.33 (d, $J = 0.8$ Hz, 1H), 4.91 (t, $J = 1.2$ Hz, 1H), 6.99 (dt, $J = 9.2, 2.4$ Hz, 2H), 7.56 (td, $J = 8.4, 0.8$ Hz, 1H), 7.62 (dt, $J = 9.2, 2.4$ Hz, 2H), 7.69 (td, $J = 8.4, 0.8$ Hz, 1H), 7.89 (dd, $J = 8.4, 0.8$ Hz, 1H), 7.97 (d, $J = 8.0$ Hz, 1H), 9.23 (s, 1H); $^{13}\text{C NMR}$ (CDCl_3) δ 23.88, 37.65, 55.48, 112.80, 113.64, 124.68, 125.52, 126.58, 127.52, 128.12, 130.46, 130.51, 133.80, 136.46, 145.07, 151.10, 152.37, 159.50; IR (CHCl_3) 3019, 2970, 1609 cm^{-1} ; HRMS m/z 289.1471 (calcd for $\text{C}_{20}\text{H}_{19}\text{NO}$, 289.1467).

8-Methallyl-7-phenyl-[1,3]dioxolo[4,5-g]isoquinoline (39). The reaction mixture was chromatographed using 4:1 hexanes/ethyl acetate to afford 48 mg (59%) of the indicated compound as a yellow solid: mp 145-147 $^\circ\text{C}$; $^1\text{H NMR}$ (CDCl_3) δ 1.84 (s, 3H), 3.55 (s, 2H), 4.36 (d, $J = 0.6$ Hz, 1H), 4.90 (t, $J = 1.5$ Hz,

1H), 6.10 (s, 2H), 7.16 (s, 1H), 7.21 (s, 1H), 7.38-7.46 (m, 3H), 7.59-7.62 (m, 2H), 8.98 (s, 1H); ^{13}C NMR (CDCl_3) δ 23.74, 38.00, 101.30, 101.80, 103.51, 112.74, 125.13, 125.54, 127.82, 128.20, 129.16, 134.85, 141.45, 144.61, 148.01, 148.95, 151.39, 152.30; IR (CHCl_3) 3018, 2970, 1616, 1583 cm^{-1} ; HRMS m/z 303.1264 (calcd for $\text{C}_{20}\text{H}_{17}\text{NO}_2$, 303.1259).

8-Methallyl-7-phenyl[1,6]naphthyridine (40). The reaction mixture was chromatographed using 3:1 hexanes/ethyl acetate to afford 27 mg (42%) of the indicated compound as a yellow solid: mp 66-67 °C; ^1H NMR (CDCl_3) δ 1.88 (d, J = 0.4 Hz, 3H), 3.90 (s, 2H), 4.11 (dd, J = 1.6, 0.8 Hz, 1H), 4.82 (dt, J = 3.2, 1.2 Hz, 1H), 7.41-7.50 (m, 3H), 7.52 (dd, J = 8.0, 4.0 Hz, 1H), 7.69 (dt, J = 6.8, 1.6 Hz, 2H), 8.30 (dd, J = 6.8, 1.6 Hz, 1H), 9.16 (dd, J = 4.0, 1.6 Hz, 1H), 9.28 (s, 1H); ^{13}C NMR (CDCl_3) δ 24.11, 35.48, 111.62, 122.19, 122.29, 128.24, 128.28, 129.15, 129.24, 135.90, 140.83, 146.11, 150.51, 151.02, 154.53, 156.35; IR (CHCl_3) 3019, 1606 cm^{-1} ; HRMS m/z 260.1318 (calcd for $\text{C}_{18}\text{H}_{16}\text{N}_2$, 260.1314).

4-Benzyl-3-phenylisoquinoline (41). The reaction mixture was chromatographed using 4:1 hexanes/ethyl acetate to afford 33 mg (45%) of the indicated compound as a pale yellow solid: mp 133-4 °C; ^1H NMR (CDCl_3) δ 4.49 (s, 2H), 7.05 (d, J = 5.7 Hz, 2H), 7.17 (t, J = 5.4 Hz, 1H), 7.21-7.25 (m, 2H), 7.34-7.41 (m, 3H), 7.52-7.63 (m, 4H), 7.84 (d, J = 6.0 Hz, 1H), 8.02 (d, J = 6.0 Hz, 1H), 9.30 (s, 1H); ^{13}C NMR (CDCl_3) δ 35.10, 124.79, 125.92, 126.21, 126.84, 128.01, 128.31, 128.39, 128.77, 129.48, 130.84, 141.02, 141.16, 151.48, 153.28 (one sp^2 carbon missing due to overlap); IR (CHCl_3) 3019, 1639, 1216 cm^{-1} ; HRMS m/z 295.1366 (calcd for $\text{C}_{22}\text{H}_{17}\text{N}$, 295.1361).

4-(4-Methoxybenzyl)-3-phenylisoquinoline (42). The reaction mixture was chromatographed using 3:1 hexanes/ethyl acetate to afford 41 mg (51%) of the indicated compound as a white solid: mp 136-137 °C; ^1H NMR (CDCl_3) δ 3.76 (s, 3H), 4.43 (s, 2H), 6.79 (d, $J = 8.4$ Hz, 2H), 6.96 (d, $J = 8.4$ Hz, 2H), 7.36-7.42 (m, 3H), 7.52-7.56 (m, 2H), 7.57-7.64 (m, 2H), 7.86 (d, $J = 8.4$ Hz, 1H), 8.02 (d, $J = 5.7$ Hz, 1H), 9.30 (s, 1H); ^{13}C NMR (CDCl_3) δ 34.20, 55.39, 114.16, 124.82, 126.24, 126.89, 127.97, 128.02, 128.34, 128.35, 129.22, 129.48, 130.77, 133.06, 136.27, 141.24, 151.42, 153.19, 158.02; IR (CHCl_3) 3019, 1510 cm^{-1} ; HRMS m/z 325.1473 (calcd for $\text{C}_{23}\text{H}_{19}\text{NO}$, 325.1467).

Ethyl 3-(3-phenylisoquinolin-4-yl)prop-2-ynoate (43). The reaction mixture was chromatographed using 5:1 hexanes/ethyl acetate to afford 29 mg (38%) of the indicated compound as a yellow solid: mp 92-93 °C; ^1H NMR (CDCl_3) δ 1.36 (t, $J = 7.2$ Hz, 3H), 4.30 (q, $J = 7.2$ Hz, 2H), 7.45-7.56 (m, 3H), 7.69 (td, $J = 7.5, 0.9$ Hz, 1H), 7.86 (td, $J = 7.2, 1.2$ Hz, 1H), 8.04-8.08 (m, 3H), 8.39 (d, $J = 8.7$ Hz, 1H), 9.34 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.34, 62.43, 82.66, 90.04, 109.27, 125.52, 126.54, 128.28, 128.33, 128.44, 129.43, 130.05, 132.37, 137.40, 139.21, 153.75, 154.04, 157.31; IR (CHCl_3) 2208, 1701 cm^{-1} ; HRMS m/z 301.1104 (calcd for $\text{C}_{20}\text{H}_{15}\text{NO}_2$, 301.1103).

4-(1-Decynyl)-3-phenylisoquinoline (44). The reaction mixture was chromatographed using 8:1 hexanes/ethyl acetate to afford 47 mg (56%) of the indicated compound as a brown oil: ^1H NMR (CDCl_3) δ 0.89 (t, $J = 6.8$ Hz, 3H), 1.26-1.44 (m, 10H), 1.63 (quintet, $J = 2.8$ Hz, 2H), 2.51 (t, $J = 7.2$ Hz, 2H), 7.41 (tt, $J = 2.4, 7.2$ Hz, 1H), 7.47 (t, $J = 7.6$ Hz, 2H), 7.62 (t, $J = 7.2$ Hz, 1H), 7.77 (td, $J =$

1.2, 6.8 Hz, 1H), 7.98 (d, $J = 8.0$ Hz, 1H), 8.07 (dd, $J = 0.8, 8.0$ Hz, 2H), 8.38 (d, $J = 8.4$ Hz, 1H), 9.23 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.33, 20.19, 22.89, 28.69, 29.23, 29.39, 29.43, 32.07, 76.70, 101.31, 113.55, 126.07, 126.84, 127.53, 127.92, 128.00, 128.42, 130.00, 131.15, 137.37, 140.43, 150.90, 154.29; IR (CHCl_3) 3009, 2928, 2218 cm^{-1} ; HRMS m/z 341.2150 (calcd for $\text{C}_{25}\text{H}_{27}\text{N}$, 341.2144).

4-(3-Methoxy-1-propynyl)-3-phenylisoquinoline (45). The mixture was chromatographed using 6:1 hexanes/ethyl acetate to afford 36 mg (53%) of the indicated compound as a yellow oil: ^1H NMR (CDCl_3) δ 3.42 (s, 3H), 4.41 (s, 2H), 7.41-7.44 (m, 1H), 7.49 (t, $J = 7.2$ Hz, 2H), 7.65 (td, $J = 8.0, 0.8$ Hz, 1H), 7.80 (td, $J = 7.6, 1.2$ Hz, 1H), 8.00-8.05 (m, 3H), 8.38 (d, $J = 8.4$ Hz, 1H), 9.28 (s, 1H); ^{13}C NMR (CDCl_3) δ 58.01, 60.82, 82.59, 95.39, 112.17, 125.81, 126.75, 127.79, 128.05, 128.16, 128.70, 129.96, 131.57, 137.14, 140.12, 151.86, 155.03; IR (CHCl_3) 3019, 2219, 1619 cm^{-1} ; HRMS m/z 273.1158 (calcd for $\text{C}_{19}\text{H}_{15}\text{NO}$, 273.1154).

4-(1-Decynyl)-3-(4-methoxyphenyl)isoquinoline (46). The reaction mixture was chromatographed using 10:1 hexanes/ethyl acetate to afford 52 mg (56%) of the indicated compound as a brown oil: ^1H NMR (CDCl_3) δ 0.89 (t, $J = 6.8$ Hz, 3H), 1.29-1.31 (m, 8H), 1.42-1.49 (m, 2H), 1.66 (sextet, $J = 3.2$ Hz, 2H), 2.54 (t, $J = 6.8$ Hz, 2H), 3.88 (s, 3H), 7.01 (d, $J = 8.8$ Hz, 2H), 7.59 (td, $J = 7.6, 0.8$ Hz, 1H), 7.75 (td, $J = 6.8, 1.2$ Hz, 1H), 7.96 (d, $J = 8.0$ Hz, 1H), 8.07 (d, $J = 8.8$ Hz, 2H), 8.36 (d, $J = 8.4$ Hz, 1H), 9.20 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.32, 20.21, 22.88, 28.76, 29.27, 29.41, 29.46, 32.07, 55.49, 76.94, 101.08, 112.70, 113.39, 125.93, 126.60, 127.23, 127.89, 131.08, 131.34, 132.96, 137.50, 150.81, 153.81, 159.92; IR

(CHCl₃) 3009, 2928, 2218, 1607 cm⁻¹; HRMS *m/z* 371.2253 (calcd for C₂₆H₂₉NO, 371.2249).

Ethyl (Z)-3-(3-phenylisoquinolin-4-yl)propenoate (49). The mixture was chromatographed using 7:1 hexanes/ethyl acetate to afford 42 mg (55%) of the indicated compound as a red oil: ¹H NMR (CDCl₃) δ 0.78 (t, *J* = 7.2 Hz, 3H), 3.83 (t, *J* = 7.2 Hz, 2H), 6.30 (d, *J* = 12.0 Hz, 1H), 7.25 (d, *J* = 12.0 Hz, 1H), 7.38-7.47 (m, 3H), 7.58-7.72 (m, 4H), 7.91 (d, *J* = 8.4 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 9.30 (s, 1H); ¹³C NMR (CDCl₃) δ 13.78, 60.39, 124.56, 125.63, 125.90, 127.70, 127.13, 128.18, 128.19, 128.23, 160.26, 130.84, 134.42, 140.08, 140.75, 149.93, 152.09, 165.54; IR (CHCl₃) 3020, 2980, 1720, 1620 cm⁻¹; HRMS *m/z* 303.1265 (calcd for C₂₀H₁₇NO₂, 303.1259).

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References

1. For recent leading references, see: (a) Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron Lett.* **1998**, *39*, 5101 and references therein. (b) Chaudhuri, G.; Chowdhury, C.; Kundu, N. G. *Synlett* **1998**, 1273. (c) Montiero, N.; Balme, G. *Synlett* **1998**, 746. (d) Chowdhury, C.; Chaudhuri, G.; Guha, S.; Mukherjee, A. K.; Kundu, N. G. *J. Org. Chem.* **1998**, *63*, 1863. (e) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 5327. (f) Khan, M. W.; Kundu, N. G. *Synlett* **1997**, 1435. (g) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace,

- P. *Synlett* **1997**, 1363. (h) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280. (i) Chowdhury, C.; Kundu, N. G. *J. Chem. Soc., Chem. Commun.* **1996**, 1067. (j) Kundu, N. G.; Pal, M. *J. Chem. Soc., Chem. Commun.* **1993**, 86. (k) Candiani, I.; DeBernardinis, S.; Cabri, W.; Marchi, M.; Bedeschi, A.; Penco, S. *Synlett* **1993**, 269. (l) Zhang, H.; Brumfield, K. K.; Jaroskova, L.; Maryanoff, B. E. *Tetrahedron Lett.* **1998**, *39*, 4449. (m) Fancelli, D.; Fagnola, M. C.; Severino, D.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2311. (n) Fagnola, M. C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307. (o) Gabriele, B.; Salerno, G.; Fazio, A.; Bossio, M. *Tetrahedron Lett.* **2001**, *42*, 1339. (p) Monteiro, N.; Arnold, A.; Balme, G. *Synlett* **1998**, 1111. (q) Larock, R. C.; Pace, P.; Yang, H.; Russell, C. E. *Tetrahedron* **1998**, *54*, 9961. (r) Cacchi, S.; Fabrizi, G.; Moro, L. *Synlett* **1998**, 741. (s) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 527 and references therein. (t) Balme, G.; Bouyssi, D. *Tetrahedron* **1994**, *50*, 403.
2. (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2000**, 394. (b) Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. *Synlett* **1999**, 620. (c) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001. (d) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, 1363. (e) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437. (f) Mandai, T.; Ohat, K.; Baba, N.; Kawada, M.; Tsuji, J. *Synlett* **1992**, 671. (g) Tsuda, T.; Ohashi, Y.; Nagahama, M.; Sumiya, R.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 2650.
-

3. (a) Monteiro, N.; Balme, G. *Synlett* **1998**, 746. (b) Cacchi, S.; Fabrizi, G.; Moro, L. *Synlett* **1998**, 741. (c) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280 and references therein.
 4. (a) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1985**, *41*, 3655. (b) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, *56*, 5816. (c) Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. R. *J. Org. Chem.* **1992**, *57*, 976. (d) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 5327. (e) Cavicchioli, M.; Decortiat, S.; Bouyssi, D.; Gore, J.; Balme, G. *Tetrahedron* **1996**, *52*, 11463. (f) Bouyssi, D.; Cavicchioli, M.; Balme, G. *Synlett* **1997**, 944. (g) Arcadi, A. *Synlett* **1997**, 941. (h) Arcadi, A.; Anacardio, R.; D'Anniballe, G.; Gentile, M. *Synlett* **1997**, 1315. (i) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett* **1992**, *33*, 3915. (j) Arcadi, A.; Cacchi, S.; Larock, R. C.; Marinelli, F. *Tetrahedron Lett* **1993**, *34*, 2813.
 5. (a) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic: Australia, Canada, 1998; Vol 1. (b) Croisy-Delcey, M.; Croisy, A.; Carrez, D.; Huel, C.; Chiaroni, A.; Ducrot, P.; Bisagni, E.; Jin, L.; Leclercq, G. *Bioorg. Med. Chem.* **2000**, *8*, 2629.
 6. *Organic Reactions*, John Wiley & Sons: London, Sydney, 1951; Vol. VI, Chapters 2-4.
 7. Maassarani, F.; Pfeffer, M.; Le Borgne, G. *J. Chem. Soc., Chem. Commun.* **1987**, 565.
 8. Wu, G.; Geib, S. J.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1988**, *53*, 3288.
-

9. Girling, I. R.; Widdowson, D. A. *Tetrahedron Lett.* **1982**, 23, 4281.
 10. (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.
 11. (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.
 12. (a) Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, 3, 2973. (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, 67, 3437.
 13. Huang, Q.; Larock, R. C. *Tetrahedron Lett.* **2002**, 43, 3557.
 14. Dai, G.; Larock, R. C. *Org. Lett.* **2001**, 3, 4035. (b) Dai, G.; Larock, R. C. *J. Org. Chem.* **2002**, 67, in press.
 15. Sonogashira, K. *Comprehensive Organic Synthesis*, Vol. 3, p. 251, Pergamon Press, 1990.
 16. During the work-up procedure described in the experimental section, the reaction mixture in diethyl ether solution could be decolorized by the addition of $\text{Na}_2\text{S}_2\text{O}_3$.
 17. Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, 6, 1941.
 18. For the preparation and characterization of 2-(trimethylsilylethynyl)-benzaldehyde, see: (a) Shindo, M.; Sato, Y.; Shishido, K. *J. Org. Chem.* **2001**, 66, 7818. (b) Tovar, J. D.; Swager, T. M. *J. Org. Chem.* **1999**, 64, 6499.
 19. For the preparation and characterization of 2-ethynylbenzaldehyde, see: Wang, X.; Silverman, R. B. *J. Org. Chem.* **1998**, 63, 7357.
 20. Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, 10, 434.
-

21. Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 4387.
 22. Numata, A.; Kondo, Y.; Sakamoto, T. *Synthesis* **1999**, 2, 306.
 23. Gilchrist, T.; Kemmitt, P. D. *Tetrahedron* **1995**, 51, 9119.
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Chapter 2. Synthesis of 3-Substituted 4-Aroylisoquinolines via Palladium-Catalyzed Carbonylative Cyclization of 2-(1-Alkynyl)benzaldimines and Aryl Halides

Two papers published in *Organic Letters* and the *Journal of Organic Chemistry*

Guangxiu Dai and Richard C. Larock

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

Abstract

A number of 3-substituted 4-aryloisoquinolines have been prepared in good yields by treating *N-tert-butyl-2-(1-alkynyl)benzaldimines* with aryl halides in the presence of CO and a palladium catalyst. Synthetically the methodology provides a simple and convenient route to isoquinolines containing an aryl, alkyl or vinylic group at C-3 and an aroyl group at C-4 of the isoquinoline ring. The reaction is believed to proceed via cyclization of the alkyne containing a proximate nucleophilic center promoted by an acylpalladium complex.

Introduction

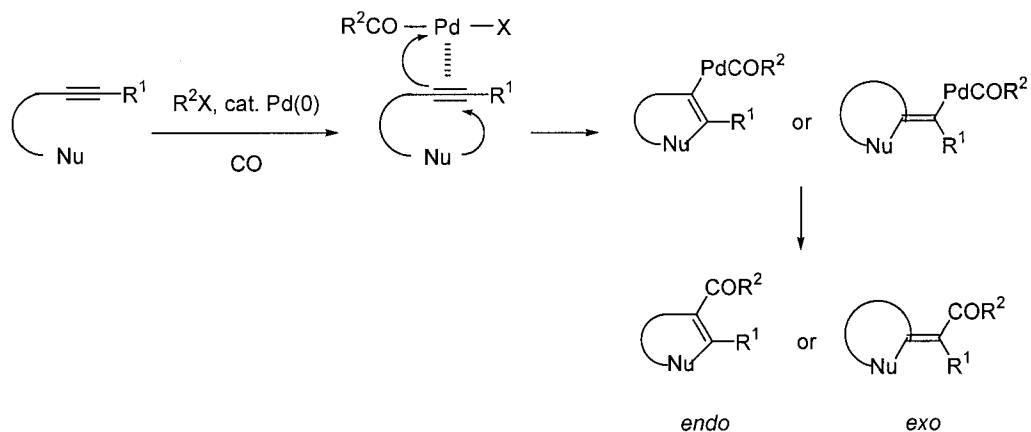
Alkyne-based palladium-catalyzed reactions provide some of the most versatile and efficient routes to heterocyclic derivatives (Scheme 1).¹ A variety of heterocycles have been prepared through *in situ* hydroarylation (hydrovinylation)/cyclization reactions,² *in situ* coupling/cyclization reactions,³ and annulation reactions promoted by σ -vinyl- and σ -arylpalladium complexes.^{1,4}

Heterocyclization promoted by σ -vinyl- and σ -arylpalladium complexes is extremely valuable, since generation of the heterocyclic skeleton accommodates functionalities amenable to further functional group manipulation and affords a rapid increase in molecular complexity.

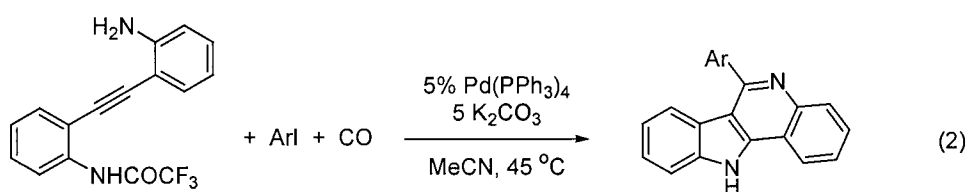
When such reactions are carried out in the presence of carbon monoxide, activation of the carbon-carbon triple bond appears to involve the intervention of σ -acylpalladium complexes. During the process, one carbon-heteroatom bond and two carbon-carbon bonds are generated in a single synthetic operation.

There are two pathways for carbonylative cyclization that have been discovered. The first pathway involves coordination of the *in situ* formed acylpalladium complex (R^2COPdX) to the carbon carbon triple bond, followed by nucleophilic attack in either an *endo* or *exo* manner on the triple bond and subsequent reductive elimination (Scheme 1). Cacchi and co-workers have reported the Pd-catalyzed carbonylative cyclization of 2-(1-alkynyl)trifluoroacetanilides by employing this strategy. It was shown that 2-substituted 3-acylindoles could be produced regioselectively from the palladium-catalyzed reaction of 2-(1-alkynyl)trifluoroacetanilides and aryl halides or vinylic triflates (eq 1).^{5a} In addition to this example, this methodology has been employed in the synthesis of 2-substituted 3-acylbenzo[*b*]furans.¹ Moreover, as an extension of this synthetic method, a tandem reaction of functionalized alkynes with organopalladium complexes has been reported (eq 2).^{5b}

Scheme 1



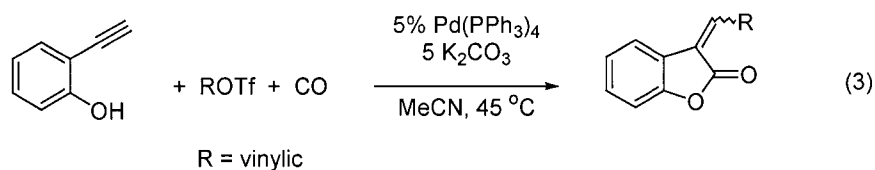
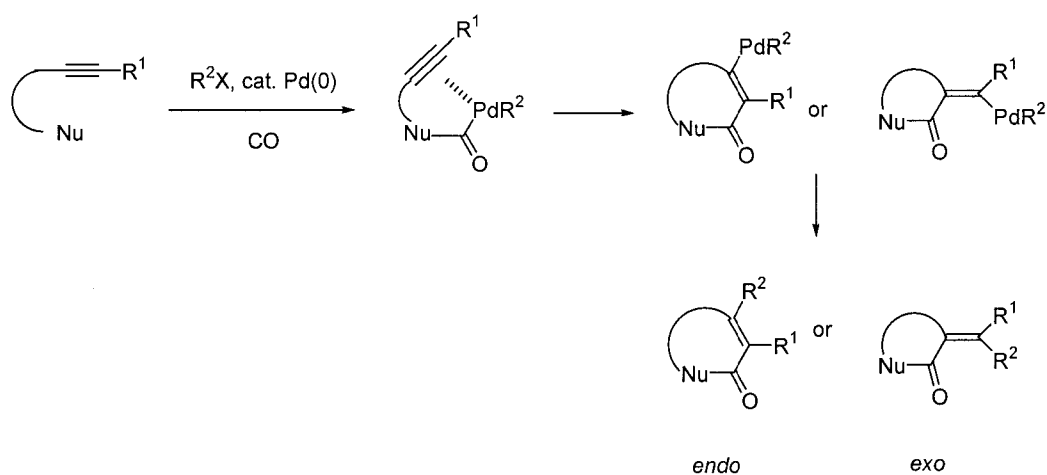
R^1 = alkyl, aryl
 R^2 = aryl, vinylic
 X = I, OTf



The second pathway for carbonylative cyclization involves nucleophilic displacement of one ligand from the palladium complex $[\text{R}^2\text{PdXL}(\text{CO})]$, while the Pd coordinates to the alkyne triple bond at the same time. This is followed by intramolecular addition of the organopalladium intermediate to the triple bond and

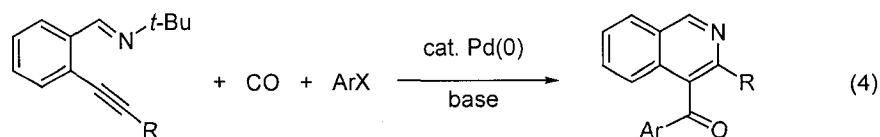
reductive elimination as depicted in Scheme 2. Although numerous examples of related reactions suggest that this addition proceeds with *syn* stereochemistry,⁶ Cacchi and co-workers have found that it is possible to get both stereoisomers (eq 3).⁷

Scheme 2



Since the acylpalladation of alkynes containing oxygen and nitrogen nucleophiles near the carbon-carbon triple bond has been employed in the synthesis of ketone-containing indoles⁵ and benzo[*b*]furans,^{1,6} we thought that analogous chemistry might be used to generate the isoquinoline skeleton. We have recently reported convenient methods for the preparation of 3-

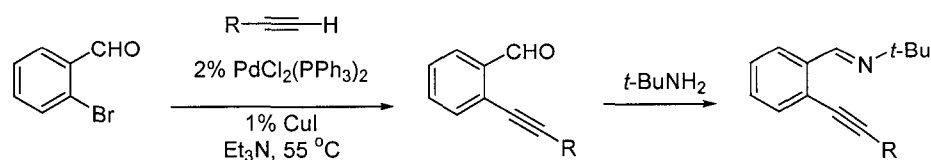
monosubstituted⁸ and 3,4-disubstituted isoquinolines,⁹ disubstituted β - and γ -carbolines¹⁰ and monosubstituted β - and γ -carbolines¹¹ by the palladium-promoted cyclization of alkynylimines. Herein we report analogous acylpalladation chemistry of *N-tert-butyl-2-(1-alkynyl)benzaldimines* for the synthesis of 3-substituted 4-aryloisoquinolines (eq 4).¹²



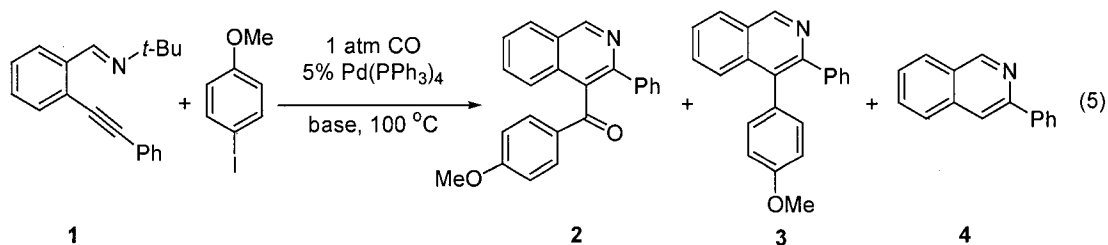
Results and Discussion

Starting Materials. The starting material *N-tert-butyl-2-(1-alkynyl)benzaldimines* can be easily prepared by the Sonogashira coupling of a 2-bromoarenecarboxaldehyde and a terminal acetylene in the presence of 2 mol % $\text{PdCl}_2(\text{PPh}_3)_2$, 1 mol % CuI and Et_3N at $55\text{ }^\circ\text{C}$,¹³ followed by condensation with *tert*-butylamine (Scheme 3). Both steps proceed smoothly in high yields.

Scheme 3



Optimization. Our first attempt to explore the reaction of *N-tert*-butyl-2-(phenylethynyl)benzaldimine (**1**) and 5 equiv of 4-iodoanisole under 1 atm of CO employed 5 mol % Pd(PPh₃)₄ and 5 equiv of K₂CO₃ in DMF at 100 °C (eq 5), reaction conditions that were used in our earlier Pd-catalyzed synthesis of 3,4-disubstituted isoquinolines.^{9c,d} The desired ketone product **2** was formed in only a 40% isolated yield. Two other isoquinoline products, **3** and **4**, were also isolated in 14% and 11% yields, respectively (Table 1, entry 1). 4-(4-Methoxybenzoyl)-3-phenylisoquinoline (**3**) is formed without incorporation of CO by a process reported previously by us.^{9c,d} The formation of 3-phenylisoquinoline (**4**) is assumed to proceed by the thermal or Pd(II)-catalyzed cyclization of the 2-(1-alkynyl)benzaldimines **1**.⁸



Decreasing the amount of the aryl iodide from 5 equiv to 3 equiv and thus increasing the ratio of CO to aryl iodide in the reaction did not improve the yield (entry 2). The use of KOAc failed to afford any of the desired ketone product (entry 3) presumably due to acetate attack on the acylpalladium intermediate (see the later mechanistic discussion).

Vastly improved yields were obtained by substitution of the inorganic base K₂CO₃ by the organic amine bases Et₃N and (*n*-Bu)₃N. Both of these bases led to cleaner reactions, affording the desired product **2** in greater than 70% yields with

none of the side product **3** and very little of the side product **4** (entries 4 and 5). Lower yields were observed by using a more hindered amine, *N,N*-diisopropylethylamine, or the less basic organic amines pyridine and *N,N*-dimethylaniline (entries 6-8). Between Et₃N and (*n*-Bu)₃N, the two best amines for this reaction, we chose (*n*-Bu)₃N over Et₃N, because (*n*-Bu)₃N has a higher boiling point than Et₃N and is less easily lost during the reaction at 100 °C.

Table 1. Optimization of the Pd-Catalyzed Cross-Coupling of *N*-*tert*-Butyl-2-(phenylethynyl)benzaldimine (1) and 4-Iodoanisole (eq 5).^a

	base (equiv)	temp (°C)	time (h)	% 2	% 3	% 4
1	K ₂ CO ₃ (5)	100	20	40	14	11
2 ^b	K ₂ CO ₃ (5)	100	7	36	13	14
3 ^c	KOAc (5)	100	11	0	0	5
4	Et ₃ N (5)	100	10	73	0	7
5	(<i>n</i> -Bu) ₃ N (5)	100	12	74	0	5
6	(<i>i</i> -Pr) ₂ NEt (5)	100	9	64	0	11
7	pyridine (5)	100	48	45	0	12
8	<i>N,N</i> -dimethylaniline (5)	100	48	52	0	27
9	(<i>n</i> -Bu) ₃ N (1.5)	100	8	56	0	4
10	(<i>n</i> -Bu) ₃ N (5)	80	40	74	0	3
11	(<i>n</i> -Bu) ₃ N (5)	120	12	50	16	23

^a All of the reactions were run employing **1** (0.0653 g, 0.25 mmol), 4-iodoanisole (0.2925 g, 1.25 mmol), Pd(PPh₃)₄ (14.4 mg, 0.0125 mmol), and the base (1.25 mmol) in the presence of 1 atm of CO in 5 ml of DMF. ^b 3 Equiv of 4-iodoanisole were employed. ^c A 65% yield of 2-(phenylethynyl)benzaldehyde was also obtained.

The optimal amount of the organic amine base has been studied. While 5 equiv of (*n*-Bu)₃N were initially employed, mechanistically only 1 equiv of the base is required. We therefore examined the reaction using less base. However, a significantly lower yield of **2** was observed when only 1.5 equiv of (*n*-Bu)₃N were employed (entry 9).

The temperature of the reaction has also been investigated. At 80 °C, the reaction takes a longer time, 40 h, to reach completion, but the results are comparable to those obtained at 100 °C (compare entries 10 and 5). At the higher temperature of 120 °C, the reaction displays poorer selectivity between the three cyclization products **2**, **3** and **4** (entry 11).

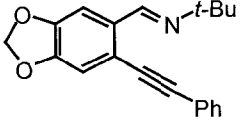
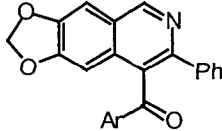
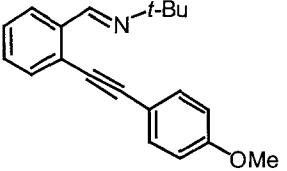
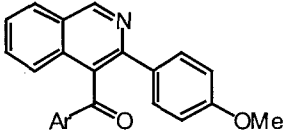
By optimization, the combination of *N*-*tert*-butyl-2-(phenylethynyl)-benzalimine (**1**, 0.25 mmol), 5 equiv of 4-iodoanisole, 5 mol % of Pd(PPh₃)₄, 5 equiv of tri-*n*-butylamine in 5 mL of DMF at 100 °C under 1 atm of CO gave the best results. This procedure provided the three isoquinolines **2**, **3** and **4** in 74%, 0% and 5% yields, respectively (Table 1, entry 5).

Carbonylative Cross-Coupling of *N*-*tert*-Butyl-2-(1-alkynyl)benzalimines with Aryl Halides. We next investigated the reaction scope employing different aryl halides under the optimal reaction conditions reported above. Aryl iodides with a methoxy group in the *para*, *meta* and *ortho* positions afforded the corresponding ketone products **2**, **5** and **6** in 74%, 76%, and 50% yields, respectively (Table 2, entries 1-3).

Table 2. Synthesis of 3-Substituted 4-Aroylisoquinolines by the Pd-Catalyzed Carbonylative Cyclization of *N*-*tert*-Butyl-2-(1-alkynyl)benzaldimines and Aryl Halides (eq 4).^a

	alkynyl imine		ArX /ArCOCl	time (h)	isoquinoline ketone	% yield ^b	
1	R = C ₆ H ₅	1	<i>p</i> -MeOC ₆ H ₄ I	12	Ar = <i>p</i> -MeOC ₆ H ₄	2	74 (0, 5)
2		1	<i>m</i> -MeOC ₆ H ₄ I	48	Ar = <i>m</i> -MeOC ₆ H ₄	5	76 (0, 5)
3		1	<i>o</i> -MeOC ₆ H ₄ I	48	Ar = <i>o</i> -MeOC ₆ H ₄	6	50 (9, 6)
4		1	<i>p</i> -MeOC ₆ H ₄ Br	24	Ar = <i>p</i> -MeOC ₆ H ₄	2	0 (0, 20)
5		1	<i>p</i> -MeC ₆ H ₄ I	24	Ar = <i>p</i> -MeC ₆ H ₄	7	77 (9,6)
6		1	<i>m</i> -MeC ₆ H ₄ I	48	Ar = <i>m</i> -MeC ₆ H ₄	8	83 (0,6)
7		1	<i>o</i> -MeC ₆ H ₄ I	72	Ar = <i>o</i> -MeC ₆ H ₄	9	66 (0, 4)
8		1	C ₆ H ₅ I	24	Ar = C ₆ H ₅	10	84 (9, 4)
9		1	1-iodonaphthalene	48	Ar = 1-naphthyl	11	73 (0, 0)
10		1	2-iodothiophene	24	Ar = 2-thienyl	12	61 (0, 0)
11		1	3-iodothiophene	24	Ar = 3-thienyl	13	69 (0, 0)
12		1	<i>p</i> -BrC ₆ H ₄ I	24	Ar = <i>p</i> -BrC ₆ H ₄	14	74 (0, 7)

13	1		<i>m</i> -EtO ₂ CC ₆ H ₄ I	48	Ar = <i>m</i> -EtO ₂ CC ₆ H ₄	15	68 (0, 7)
14	1		<i>o</i> -MeO ₂ CC ₆ H ₄ I	24	Ar = <i>o</i> -EtO ₂ CC ₆ H ₄	16	0 (0, 42)
15	1		<i>m</i> -F ₃ CC ₆ H ₄ I	48	Ar = <i>m</i> -F ₃ CC ₆ H ₄	17	63 (5, 5)
16	1		<i>p</i> -F ₃ CC ₆ H ₄ I	24	Ar = <i>p</i> -F ₃ CC ₆ H ₄	18	52 (0, 11)
17	1		<i>p</i> -O ₂ NC ₆ H ₄ I	12	Ar = <i>p</i> -O ₂ NC ₆ H ₄	19	31 (37, 7)
18 ^c	1		<i>p</i> -O ₂ NC ₆ H ₄ I	12	Ar = <i>p</i> -O ₂ NC ₆ H ₄	19	56 (11, 4)
19 ^d	1		<i>p</i> -O ₂ NC ₆ H ₄ I	48	Ar = <i>p</i> -O ₂ NC ₆ H ₄	19	52 (10, 5)
20 ^e	1		<i>p</i> -O ₂ NC ₆ H ₄ I	24	Ar = <i>p</i> -O ₂ NC ₆ H ₄	19	66 (7, 0)
21	1		<i>m</i> -O ₂ NC ₆ H ₄ I	72	Ar = <i>m</i> -O ₂ NC ₆ H ₄	21	40 (13, 10)
22	1		<i>o</i> -O ₂ NC ₆ H ₄ I	24	Ar = <i>o</i> -O ₂ NC ₆ H ₄	22	0 (0, 60)
23	1		<i>p</i> -O ₂ NC ₆ H ₄ Br	24	Ar = <i>p</i> -O ₂ NC ₆ H ₄	19	28 (22, 16)
24	R = 1-cyclohexenyl	23	<i>m</i> -EtO ₂ CC ₆ H ₄ I	24	Ar = <i>m</i> -EtO ₂ CC ₆ H ₄	24	55 (0, 0)
25	R = <i>n</i> -butyl	25	<i>m</i> -EtO ₂ CC ₆ H ₄ I	24	Ar = <i>m</i> -EtO ₂ CC ₆ H ₄	26	64 (0, 0)
26	R = 3-cyanopropyl	27	C ₆ H ₅ I	24	Ar = C ₆ H ₅	28	62 (0, 0)
27	R = CH ₂ OMe	29	C ₆ H ₅ I	24	Ar = C ₆ H ₅	30	57 (0, 0)

							
28	31	<i>p</i> -MeOC ₆ H ₄ l	15	Ar = <i>p</i> -MeOC ₆ H ₄	32	75 (0, 0)	
29	31	<i>m</i> -F ₃ CC ₆ H ₄ l	24	Ar = <i>m</i> -F ₃ CC ₆ H ₄	33	69 (0, 0)	
							
30	34	<i>p</i> -MeOC ₆ H ₄ l	24	Ar = <i>p</i> -MeOC ₆ H ₄	35	79 (0, 0)	
31	34	<i>m</i> -EtO ₂ CC ₆ H ₄ l	48	Ar = <i>m</i> -EtO ₂ CC ₆ H ₄	36	73 (8, 4)	
32	1	PhCOCl	48	Ar = C ₆ H ₅	10	62 (0, 13)	
33 ^f	1	PhCOCl	48	Ar = C ₆ H ₅	10	42 (0, 20)	

^a See the text for the procedure used. ^b The numbers in parentheses are the isolated yields of the corresponding 3-substituted 4-arylisquinolines and 3-monosubstituted isoquinolines in that order. ^c The reaction was run under 3.5 atm of CO. ^d The reaction was run at 80 °C. ^e The reaction was run under 3.5 atm of CO at 80 °C. ^f The reaction was run with no CO present. A 12 % yield of 2-(phenylethynyl)benzaldehyde was also isolated.

Steric hindrance due to an *ortho* substituent thus appears to lower the yield significantly. Employing 4-bromoanisole generated none of the desired ketone product (entry 4). A pattern similar to that of the iodoanisoles has been observed for the isomeric iodotoluenes, although a smaller drop in yield was observed (entries 5-7). Phenyl iodide and 1-iodonaphthalene also afforded good yields (entries 8 and 9), as did two isomeric iodothiophenes (entries 10 and 11). In most of these reactions, only a very small amount of or no 4-aryl 3-substituted isoquinoline was isolated. Thus, these reactions exhibit good reaction selectivities.

The lower yield from 2-iodoanisole versus the *meta* and *para* isomers and the relatively long reaction time show the negative effect of the steric hindrance of the *o*-OMe on the reaction (entry 3). Since 2-iodotoluene gave a higher yield (entry 7) than 2-iodoanisole, this suggests that besides the steric effect of the *ortho*-substituent, possible chelation of the *ortho* methoxy substituent to the Pd(0) catalyst could also perhaps have a negative effect on the yield.

Because aryl bromides do not react with the imine substrate under the optimal reaction conditions, 4-bromoiodobenzene was employed (entry 12). The bromide-containing product was cleanly produced in a 74% yield.

The reactions of **1** and aryl iodides with electron-withdrawing groups, such as CO₂Et and CF₃ groups in the *meta* or *para* positions, afforded the corresponding 4-aryl-3-phenylisoquinolines in reasonable yields, although we did generally observe a slight decrease in the yields compared to aryl iodides with no electron-withdrawing groups (entries 13, 15 and 16). An aryl iodide containing a CO₂Me group in the *ortho* position afforded none of the desired ketone product (entry 14).

The reaction of **1** and 4-iodonitrobenzene afforded a low yield of the 4-(4-nitrobenzoyl)-3-phenylisoquinoline (**19**) and a slightly higher yield of the 4-(4-nitrophenyl)-3-phenylisoquinoline (**20**) (entry 17). Because the *p*-nitro group has a strong electron-withdrawing effect and 4-iodonitrobenzene gave the best result of any aryl iodide in the palladium-catalyzed cross-coupling of *N*-*tert*-butyl-2-(phenylethynyl)benzaldimine (**1**) and aryl halides without CO to form 4-(4-nitrophenyl)-3-phenylisoquinoline (**20**),^{9c,d} this result was not unexpected. The low yield of 4-(4-nitrobenzoyl)-3-phenylisoquinoline (**19**) and the poor selectivity between **19** and **20** apparently result from the very similar reactivities of the ArPdI and ArCOPdI intermediates towards the *o*-alkynyl imine, both of which promote cyclization to isoquinolines. In an attempt to improve the selectivity of the reaction and the yield of the desired ketone, we carried out three further experiments in which we increased the CO pressure¹² and decreased the reaction temperature (entries 18-20). We were pleased to observe that these experiments provided higher yields of the desired product **19** and better selectivity between the two 3,4-disubstituted isoquinolines **19** and **20**. Using both a lower temperature and higher CO pressure improved the yield of the ketone product **19** to 66 % and afforded an improved ratio of **19/20/4** (entry 20). While 3-iodonitrobenzene gave a modest yield of ketone under our usual reaction conditions (entry 21), 2-iodonitrobenzene did not afford any of the desired ketone-containing isoquinoline (entry 22). Contrary to the electron-rich 4-bromoanisole, which failed to produce any of the CO-incorporated product **2**, 4-bromonitrobenzene gave a 28% yield of the corresponding 4-aryloisoquinoline **19**, 22% of **20** and 16 % of **4** (entry 23).

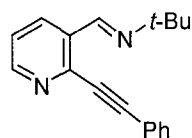
The 2-(1-alkynyl)benzaldimines containing a 1-cyclohexenyl (**23**), *n*-butyl (**25**), 3-cyanopropyl (**27**) and CH₂OMe (**29**) group as R afforded good yields when allowed to react with ethyl 3-iodobenzoate or phenyl iodide (entries 24-27).

The electron-rich imine substrates **31** and **34** displayed good reactivities toward 4-iodoanisole, 3-iodobenzotrifluoride and ethyl 3-iodobenzoate, affording high yields of the desired 4-aryloisoquinolines (entries 28-31).

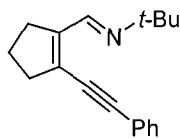
Carbonylative Cross-Coupling of an *N*-tert-Butyl-*o*-(1-alkynyl)-benzaldimine with Benzoyl Chloride. Acyl halides readily undergo oxidative addition to Pd(0) to form acylpalladium intermediates, RCOPdX, which subsequently undergo a wide range of useful transformations.¹⁴ We have, therefore, studied the utility of benzoyl chloride in our chemistry. Under 1 atm of CO (Table 2, entry 32) and with no CO present (entry 33), neither reaction afforded any 3,4-diphenylisoquinoline (**3**) at all, indicating that the initially formed acylpalladium intermediate PhCOPdX does not undergo decarbonylation to the corresponding arylpalladium species very easily.¹⁵ However, whether there is external CO or not does make a difference in the yields of the product **10** and the reaction rates. The reaction was complete after 48 h under 1 atm of CO, and was not complete after the same amount of time without CO. Better results were obtained using 1 atm of CO, in which case a 62% yield of ketone **10** was obtained. With no CO present, only a 42% yield was obtained.

Attempts to react the 2-(1-alkynyl)benzaldimine **1** with diallyl carbonate, 3-bromocyclohexene, benzyl chloride, ethyl *cis*-3-iodoacrylate, 1-iodo-1-decyne and *p*-tosyl chloride under 1 atm of CO failed to afford any recognizable ketone-containing products.

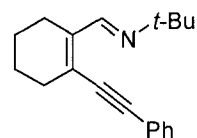
The electron-deficient *N-tert*-butyl-2-phenylethynyl-3-pyridinecarboxaldimine (**37**), non-aromatic *N-tert*-butyl-2-phenylethynyl-1-pentenecarboxaldimine (**38**) and *N-tert*-butyl-2-phenylethynyl-1-hexene-carboxaldimine (**39**) did not react with 4-iodoanisole under our “optimal” reaction conditions to afford the desired ketone.



37



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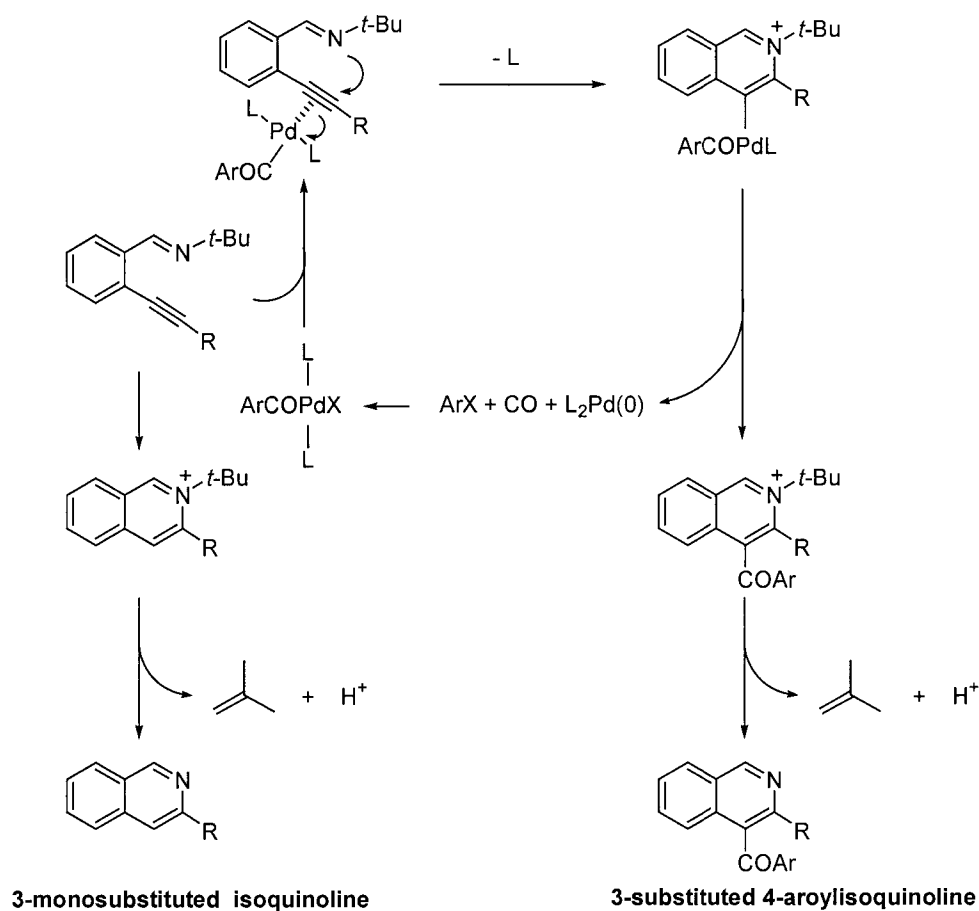


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Mechanism. The mechanism shown in Scheme 4 is proposed for this process. It is similar to mechanisms proposed in previously reported Pd-catalyzed syntheses of furans,¹⁶ benzofurans¹ and indoles.⁵ It consists of the following key steps: (1) oxidative addition of the aryl halide to the Pd(0) catalyst, followed by CO insertion,¹⁷ (2) the resulting acylpalladium intermediate **A** coordinates to the alkyne triple bond to form complex **B**, which activates the triple bond towards nucleophilic attack,⁵ (3) intramolecular nucleophilic attack of the nitrogen atom of the imine on the activated carbon-carbon triple bond to afford intermediate **C**,^{5,16,17} (4) reductive elimination to form a carbon-carbon bond between the carbonyl group and the isoquinoline ring in **D** and simultaneous regeneration of the Pd(0) catalyst,^{5,16,19} and (5) cleavage of the *tert*-butyl group from the nitrogen to release the strain between the *tert*-butyl group and the 3-phenyl group with simultaneous generation of the 3-substituted 4-aryloisoquinoline.⁸⁻¹¹ Two competing processes are (1) cyclization of the starting material by a thermal or Pd(II)-catalyzed process to afford the 3-monosubstituted product,⁸ and (2) cyclization of the imine starting material

promoted by an arylpalladium intermediate to afford a 3-substituted 4-arylisquinoline.^{9c,d}

Scheme 4



The yields of ketones obtained by this process are less dependent on the nature of the substituents present in the aryl iodide than the yields of 4-arylisquinolines obtained from arylation of these same alkynyl imines.^{9c,d} This is easily understood when one considers that the key step in the present synthesis apparently involves attack of an electron-deficient acylpalladium species on the carbon-carbon triple bond. The nature of the substituents present in the

arylpalladium intermediate is not going to change their electronics as profoundly as they would the electronics of the corresponding arylpalladium species.

The presence of steric hindrance in the aryl iodide is also less likely to affect the yield in the carbonylative cyclization, because of the presence of the carbonyl group in the arylpalladium intermediates. However, possible chelation of the *o*-substituent could prevent the reaction from proceeding as desired.

Conclusions

In summary, we have developed an efficient synthetic approach for the carbonylative cyclization of *N-tert*-butyl-2-(1-alkynyl)benzaldimines and aryl halides to the corresponding 3-substituted 4-arylisquinolines. The reaction utilizes readily available starting materials, employs mild reaction conditions and tolerates a variety of functional groups. It also works with a wide variety of substituents on the remote end of the alkyne triple bond.

Experimental Section

General. All ^1H and ^{13}C NMR spectra were recorded at 300 and 400, and 75.5 and 100.7 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) and a 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. Lower resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan

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

For the procedure for the synthesis of the *N-tert-butyl-2-(1-alkynyl)imines* (compound **1**, **23**, **25**, **31**, **34**, **37**, **38** and **39**), see the Experimental Section in Chapter 1. The following new 2-(1-alkynyl)benzaldimines were prepared using the same procedure.

N-tert-Butyl-2-(5-cyano-1-pentynyl)benzaldimine (27). A yellow oil: ^1H NMR (CDCl_3) δ 1.32 (s, 9H), 2.00 (quintet, $J = 6.8$ Hz, 2H), 2.59 (t, $J = 6.8$ Hz, 2H), 2.68 (t, $J = 6.8$ Hz, 2H), 7.31-7.34 (m, 2H), 7.40-7.43 (m, 1H), 8.01-8.03 (m, 1H), 8.75 (s, 1H); ^{13}C NMR (CDCl_3) δ 16.49, 18.88, 24.90, 29.93, 57.91, 79.97, 92.62, 119.12, 123.96, 126.16, 128.58, 129.88, 132.65, 137.97, 154.08; IR (CHCl_3) 3031, 2963, 2312, 2200, 1699 cm^{-1} ; HRMS 252.1262 (calcd $\text{C}_{17}\text{H}_{20}\text{N}_2$ 252.1259).

N-tert-Butyl-2-(3-methoxy-1-propynyl)benzaldimine (29). A yellow oil: ^1H NMR (CDCl_3) δ 1.31 (s, 9H), 3.48 (s, 3H), 4.39 (s, 2H), 7.31-7.37 (m, 2H), 7.46-7.48 (m, 1H), 8.03-8.05 (m, 1H), 8.79 (s, 1H); ^{13}C NMR (CDCl_3) δ 29.93, 57.85, 57.96, 60.62, 83.97, 90.59, 123.42, 126.15, 128.98, 129.86, 132.73, 138.16, 154.12; IR (CHCl_3) 3027, 2983, 2200, 1695 cm^{-1} ; HRMS 229.1145 (calcd $\text{C}_{15}\text{H}_{19}\text{NO}$, 229.1142).

General Procedure for the Synthesis of 3-Substituted 4-Aroylisoquinolines. DMF (5 mL), $\text{Pd}(\text{PPh}_3)_4$ (14.4 mg, 0.0125 mmol), $(n\text{-Bu})_3\text{N}$ (0.2317 g, 1.25 mmol), the *N-tert-butyl-2-(1-alkynyl)benzaldimine* (0.25 mmol) and the aryl halide (1.25 mmol) were stirred at room temperature for 5 min. The mixture was flushed with CO and fitted with a CO filled balloon (cautious!). The reaction mixture was heated to 100 $^\circ\text{C}$ with vigorous stirring for the specified time

and then cooled to room temperature, diluted with diethyl ether (25 mL) and washed with brine (20 mL). The aqueous layer was reextracted with diethyl ether (15 mL). The organic layers were combined, dried (MgSO_4), filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on a silica gel column.

4-(4-Methoxybenzoyl)-3-phenylisoquinoline (2). The reaction mixture was chromatographed using 2:1 hexanes/ethyl acetate to afford 63.0 mg (74%) of the indicated compound as a yellow solid: mp 124-125 °C; ^1H NMR (CDCl_3) δ 3.78 (s, 3H), 6.75 (d, $J = 9.2$ Hz, 2H), 7.24-7.31 (m, 4H), 7.65-7.67 (m, 3H), 7.68-7.69 (m, 2H), 7.73-7.75 (m, 1H), 8.08-8.10 (m, 1H), 9.45 (d, $J = 0.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 55.57, 113.97, 124.83, 127.12, 127.70, 128.05, 128.43, 128.55, 129.13, 129.63, 130.76, 131.54, 132.22, 134.35, 139.86, 149.68, 153.35, 164.10, 196.54; IR (CHCl_3) 3019, 1655, 1597 cm^{-1} ; HRMS m/z 339.1264 (calcd for $\text{C}_{23}\text{H}_{17}\text{NO}_2$, 339.1259).

4-(3-Methoxybenzoyl)-3-phenylisoquinoline (5). The reaction mixture was chromatographed using 2:1 hexanes/ethyl acetate to afford 63.8 mg (76%) of the indicated compound as a yellow solid: mp 116-117 °C; ^1H NMR (CDCl_3) δ 3.76 (s, 3H), 6.96-7.00 (m, 1H), 7.12-7.15 (m, 2H), 7.23-7.29 (m, 2H), 7.31-7.33 (m, 2H), 7.61-7.69 (m, 4H), 7.71-7.76 (m, 1H), 8.08-8.11 (m, 1H), 9.46 (s, 1H); ^{13}C NMR (CDCl_3) δ 55.60, 113.27, 120.62, 123.10, 124.75, 127.13, 127.82, 128.18, 128.53, 128.68, 128.96, 129.71, 129.74, 131.71, 134.38, 138.97, 139.85, 150.11, 153.63, 159.86, 198.04; IR (CHCl_3) 3019, 1663 cm^{-1} ; HRMS m/z 339.1264 (calcd for $\text{C}_{23}\text{H}_{17}\text{NO}_2$, 339.1259).

4-(2-Methoxybenzoyl)-3-phenylisoquinoline (6). The reaction mixture was chromatographed using 2.5:1 hexanes/ethyl acetate to afford 39.1 mg (50%) of the indicated compound as a yellow solid: mp 108-109 °C; ¹H NMR (CDCl₃) δ 3.43 (s, 3H), 6.68 (d, *J* = 8.0 Hz, 1H), 6.79 (t, *J* = 7.6 Hz, 1H), 7.20-7.26 (m, 3H), 7.30 (td, *J* = 0.8, 8.0 Hz, 1H), 7.50 (dd, *J* = 0.8, 8.0 Hz, 1H), 7.53-7.55 (m, 2H), 7.64 (t, *J* = 7.2 Hz, 1H), 7.70 (td, *J* = 0.8, 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 9.39 (s, 1H); ¹³C NMR (CDCl₃) δ 55.74, 111.90, 120.44, 124.75, 127.25, 127.46, 128.04, 128.18, 128.31, 129.79, 131.48, 131.77, 132.02, 134.00, 134.70, 140.06, 149.80, 152.89, 159.21, 196.87 (one sp² carbon is missing due to overlap); IR (CHCl₃) 3019, 1665 cm⁻¹; HRMS *m/z* 339.1264 (calcd for C₂₃H₁₇NO₂, 339.1259).

4-(4-Methylbenzoyl)-3-phenylisoquinoline (7). The reaction mixture was chromatographed using 4:1 hexanes/ethyl acetate to yield a yellow solid: mp 120-121 °C (hexanes); ¹H NMR (CDCl₃) δ 2.30 (s, 3H), 7.07 (d, *J* = 8.0 Hz, 2H), 7.21-7.29 (m, 3H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.63-7.68 (m, 4H), 7.72 (d, *J* = 7.2 Hz, 1H), 8.07-8.09 (m, 1H), 9.45 (s, 1H); ¹³C NMR (CDCl₃) δ 21.86, 124.76, 127.09, 127.72, 128.09, 128.43, 128.55, 129.08, 129.45, 129.67, 129.92, 131.57, 134.33, 135.17, 139.82, 144.87, 149.82, 153.43, 197.76; IR (CHCl₃) 3018, 1658 cm⁻¹; HRMS 323.1315 (calcd for C₂₃H₁₇NO 323.1310).

4-(3-Methylbenzoyl)-3-phenylisoquinoline (8). The reaction mixture was chromatographed using 4:1 hexanes/ethyl acetate to yield a yellow solid: mp 124-125 °C (hexanes); ¹H NMR (CDCl₃) δ 2.26 (s, 3H), 7.14 (t, *J* = 7.6 Hz, 1H), 7.20-7.30 (m, 4H), 7.42 (d, *J* = 8.0 Hz, 1H), 7.54 (s, 1H), 7.61-7.63 (m, 2H), 7.65-7.70 (m,

2H), 7.73-7.75 (m, 1H), 8.09-8.11 (m, 1H), 9.47 (s, 1H); ^{13}C NMR (CDCl_3) δ 21.38, 124.80, 127.16, 127.33, 127.81, 128.19, 128.48, 128.58, 128.62, 129.11, 129.72, 130.08, 131.71, 134.40, 134.71, 137.58, 138.52, 139.83, 150.05, 153.56, 198.38; IR (CHCl_3) 3019, 1659 cm^{-1} ; HRMS 323.1315 (calcd for $\text{C}_{23}\text{H}_{17}\text{NO}$ 323.1310).

4-(2-Methylbenzoyl)-3-phenylisoquinoline (9). The reaction mixture was chromatographed using 4:1 hexanes/ethyl acetate to yield a yellow solid: mp 99-100 °C (hexanes); ^1H NMR (CDCl_3) δ 2.58 (s, 3H), 6.90 (t, $J = 5.7$ Hz, 1H), 7.06 (d, $J = 5.7$ Hz, 1H), 7.10 (d, $J = 5.7$ Hz, 1H), 7.18-7.28 (m, 4H), 7.51-7.53 (m, 2H), 7.67 (td, $J = 6.0, 0.9$ Hz, 1H), 7.73 (td, $J = 6.0, 0.9$ Hz, 1H), 7.92 (d, $J = 6.0$ Hz, 1H), 8.10 (d, $J = 8.0$ Hz, 1H), 9.44 (s, 1H); ^{13}C NMR (CDCl_3) δ 21.84, 124.77, 125.58, 127.26, 127.81, 128.19, 128.31, 128.53, 129.55, 130.59, 131.84, 131.87, 132.08, 132.52, 134.51, 137.47, 140.15, 140.37, 150.67, 153.54, 199.84; IR (CHCl_3) 3019, 1659 cm^{-1} ; HRMS 323.1315 (calcd for $\text{C}_{23}\text{H}_{17}\text{NO}$ 323.1310).

4-Benzoyl-3-phenylisoquinoline (10). The reaction mixture derived from phenyl iodide was chromatographed using 3:1 hexanes/ethyl acetate to afford 65.1 mg (84%) of the indicated compound as a yellow solid: mp 124-125 °C; ^1H NMR (CDCl_3) δ 7.20-7.29 (m, 5H), 7.42 (t, $J = 7.2$ Hz, 1H), 7.62 (dd, $J = 1.2, 8.0$ Hz, 2H), 7.64-7.71 (m, 4H), 7.74 (d, $J = 8.0$ Hz, 1H), 8.10 (dd, $J = 2.0, 8.4$ Hz, 1H), 9.47 (s, 1H); ^{13}C NMR (CDCl_3) δ 124.73, 127.15, 127.83, 128.19, 128.49, 128.65, 128.68, 128.88, 129.75, 129.77, 131.74, 133.82, 134.35, 137.59, 139.71, 150.16, 153.64, 198.26; IR (CHCl_3) 3019, 1669 cm^{-1} ; HRMS m/z 309.1159 (calcd for $\text{C}_{22}\text{H}_{15}\text{NO}$, 309.1154).

4-(1-Naphthoyl)-3-phenylisoquinoline (11). The reaction mixture was chromatographed using 3:1 hexanes/ethyl acetate to yield a yellow solid: mp 160-161 °C (hexanes); ^1H NMR (CDCl_3) δ 7.01 (t, $J = 7.6$ Hz, 1H), 7.08-7.16 (m, 3H), 7.35 (d, $J = 7.2$ Hz, 1H), 7.53-7.60 (m, 3H), 7.67-7.74 (m, 3H), 7.80 (d, $J = 8.4$ Hz, 1H), 7.85 (d, $J = 8.0$ Hz, 1H), 7.87 (d, $J = 8.0$ Hz, 1H), 8.12 (d, $J = 8.0$ Hz, 1H), 9.12 (d, $J = 8.4$ Hz, 1H), 9.48 (s, 1H); ^{13}C NMR (CDCl_3) δ 124.21, 124.82, 126.22, 126.74, 127.24, 127.83, 128.16, 128.27, 128.31, 128.54, 128.75, 129.53, 130.80, 131.10, 131.96, 132.42, 133.90, 134.50, 134.80, 135.00, 139.98, 150.89, 153.66, 199.79; IR (CHCl_3) 3019, 1657, 1216 cm^{-1} ; HRMS 359.1315 (calcd $\text{C}_{26}\text{H}_{17}\text{NO}$, 359.1310).

3-Phenyl-4-(2-thienylcarbonyl)isoquinoline (12). The reaction mixture was chromatographed using 4:1 hexanes/ethyl acetate to yield a yellow solid: mp 117-118 °C (hexanes); ^1H NMR (CDCl_3) δ 6.84 (dd, $J = 5.2, 3.6$ Hz, 1H), 7.11 (dd, $J = 3.6, 1.2$ Hz, 1H), 7.24-7.28 (m, 1H), 7.30-7.34 (m, 2H), 7.55 (dd, $J = 5.2, 1.2$ Hz, 1H), 7.65 (td, $J = 8.0, 1.2$ Hz, 1H), 7.71-7.73 (m, 3H), 7.87 (d, $J = 8.0$ Hz, 1H), 8.08 (d, $J = 8.0$ Hz, 1H), 9.45 (s, 1H); ^{13}C NMR (CDCl_3) δ 124.62, 129.09, 127.86, 128.10, 128.30, 128.57, 128.71, 128.74, 129.67, 131.80, 134.08, 135.42, 135.61, 139.83, 145.09, 149.89, 153.78, 190.03; IR (CHCl_3) 3019, 1640, 1216 cm^{-1} ; HRMS 315.0723 (calcd $\text{C}_{20}\text{H}_{13}\text{NOS}$ 315.0718).

3-Phenyl-4-(3-thienylcarbonyl)isoquinoline (13). The reaction mixture was chromatographed using 4:1 hexanes/ethyl acetate to yield a yellow solid: mp 153-154 °C (hexanes); ^1H NMR (CDCl_3) δ 7.16 (dd, $J = 5.4, 3.0$ Hz, 1H), 7.24-7.35 (m, 3H), 7.41 (dd, $J = 5.1, 1.2$ Hz, 1H), 7.57 (dd, $J = 3.0, 1.2$ Hz, 1H), 7.64-7.70 (m,

4H), 7.73 (dd, $J = 6.9, 1.5$ Hz, 1H), 7.84 (d, $J = 7.8$ Hz, 1H), 8.08-8.11 (m, 1H), 9.45 (s, 1H); ^{13}C NMR (CDCl_3) δ 124.71, 126.69, 127.18, 127.42, 127.87, 128.16, 128.60, 128.74, 129.56, 129.71, 131.79, 134.08, 135.62, 139.88, 143.19, 149.84, 153.67, 191.63; IR (CHCl_3) 3019, 1641, 1216 cm^{-1} ; HRMS 315.0723 (calcd $\text{C}_{20}\text{H}_{13}\text{NOS}$ 315.0718).

4-(4-Bromobenzoyl)-3-phenylisoquinoline (14). The reaction mixture was chromatographed using 3:1 hexanes/ethyl acetate to yield a yellow solid: mp 139-140 $^{\circ}\text{C}$ (hexanes); ^1H NMR (CDCl_3) δ 7.25-7.32 (m, 3H), 7.41 (d, $J = 8.8$ Hz, 2H), 7.52 (d, $J = 8.4$ Hz, 2H), 7.61 (d, $J = 6.4$ Hz, 2H), 7.66-7.53 (m, 3H), 8.12 (d, $J = 7.2$ Hz, 1H), 9.48 (s, 1H); ^{13}C NMR (CDCl_3) δ 124.52, 127.18, 127.97, 128.28, 128.30, 128.63, 128.90, 129.20, 129.75, 131.14, 131.93, 132.07, 134.24, 136.36, 139.64, 150.24, 153.89, 197.22; IR (CHCl_3) 3019, 1658, 1216 cm^{-1} ; HRMS 387.0266 (calcd for $\text{C}_{22}\text{H}_{14}\text{BrNO}$ 387.0259).

4-(3-Ethoxycarbonylbenzoyl)-3-phenylisoquinoline (15). The reaction mixture was chromatographed using 2:1 hexanes/ethyl acetate to afford 64.3 mg (68%) of the indicated compound as a yellow solid: mp 138-139 $^{\circ}\text{C}$; ^1H NMR (CDCl_3) δ 1.35 (t, $J = 7.2$ Hz, 3H), 4.33 (q, $J = 7.2$ Hz, 2H), 7.20-7.23 (m, 2H), 7.25-7.28 (m, 1H, DCCl_3 also present), 7.33 (t, $J = 7.8$ Hz, 1H), 7.58-7.62 (m, 2H), 7.67-7.74 (m, 2H), 7.77-7.82 (m, 2H), 8.08 (td, $J = 1.5, 7.8$ Hz, 1H), 8.11-8.14 (m, 1H), 8.31 (t, $J = 1.5$ Hz, 1H), 9.49 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.41, 61.46, 124.45, 127.20, 127.90, 128.18, 128.29, 128.52, 128.77, 129.75, 130.61, 131.08, 131.88, 133.65, 134.21, 134.35, 137.63, 139.72, 150.43, 153.96, 165.61, 197.29 (one sp^2

carbon missing due to overlap); IR (CHCl₃) 3019, 1719, 1671, 1216 cm⁻¹; HRMS *m/z* 381.1370 (calcd for C₂₅H₁₉NO₃, 381.1365).

3-Phenyl-4-(3-trifluoromethylbenzoyl)isoquinoline (17). The reaction mixture was chromatographed using 3:1 hexanes/ethyl acetate to yield a yellow solid: mp 130-131 °C; ¹H NMR (CDCl₃) δ 7.20-7.28 (m, 3H), 7.37 (t, *J* = 8.0 Hz, 1H), 7.55-7.58 (m, 2H), 7.64 (d, *J* = 7.6 Hz, 1H), 7.69-7.78 (m, 3H), 7.83 (d, *J* = 8.0 Hz, 1H), 7.90 (s, 1H), 8.15 (dd, *J* = 3.2, 1.2 Hz, 1H), 9.51 (s, 1H); ¹³C NMR (CDCl₃) δ 127.23 (q, *J* = 273.1, 1C, including 121.804, 125.421, 129.034), 124.39, 126.33 (q, *J* = 3.9 Hz, 1C, including 126.26, 126.31, 126.36, 126.41), 127.26, 127.79, 128.07, 128.41, 128.62, 128.96, 129.25, 129.82, 129.90 (q, *J* = 3.6 Hz, 1C, including 129.881, 129.928, 129.975), 131.16 (q, *J* = 33.1 Hz, 1C, including 130.50, 130.94, 131.38, 131.81), 132.12, 132.71-132.73 (m, 1C, including 132.71, 132.73), 134.22, 138.04, 139.64, 150.78, 154.25, 196.80; IR (CHCl₃) 3019, 1671, 1323, 1216 cm⁻¹; HRMS *m/z* 377.1031 (calcd for C₂₃H₁₄F₃NO, 377.1028).

3-Phenyl-4-(4-trifluoromethylbenzoyl)isoquinoline (18). The reaction mixture was chromatographed using 3:1 hexanes/ethyl acetate to afford 48.9 mg (52%) of the indicated compound as a yellow solid: mp 132-133 °C; ¹H NMR (CDCl₃) δ 7.21-7.29 (m, 3H), 7.51 (d, *J* = 8.0 Hz, 2H), 7.58 (d, *J* = 8.0 Hz, 2H), 7.68-7.77 (m, 5H), 8.13 (d, *J* = 8.0 Hz, 1H), 9.49 (s, 1H); ¹³C NMR (CDCl₃) δ 123.60 (q, *J* = 273.08 Hz, 1C), 124.38, 125.70 (q, *J* = 32.92 Hz, 1C), 127.19, 128.07, 128.39, 128.68, 129.01, 129.82, 129.90, 130.43, 132.09, 134.20, 134.95 (q, *J* = 3.78 Hz, 1C), 139.58, 140.25, 150.58, 154.14, 197.27; IR (CHCl₃) 3019, 1671, 1323, 1216 cm⁻¹; HRMS *m/z* 377.1031 (calcd for C₂₃H₁₄F₃NO, 377.1028).

4-(4-Nitrobenzoyl)-3-phenylisoquinoline (19). The reaction mixture was chromatographed using 2:1 hexanes/ethyl acetate to afford 27.6 mg (31%) of the indicated compound as a yellow solid: mp 115-116 °C; ¹H NMR (CDCl₃) δ 7.19-7.28 (m, 3H), 7.56 (dd, *J* = 1.2, 8.0 Hz, 2H), 7.68-7.77 (m, 4H), 7.81 (d, *J* = 8.4 Hz, 1H), 8.05 (d, *J* = 8.8 Hz, 2H), 8.14 (d, *J* = 7.6 Hz, 1H), 9.50 (s, 1H); ¹³C NMR (CDCl₃) δ 123.73, 124.14, 127.16, 127.51, 128.16, 128.44, 128.71, 129.16, 129.87, 130.38, 132.26, 134.05, 139.46, 142.06, 150.28, 150.82, 154.43, 196.59; IR (CHCl₃) 3022, 1671, 1526 cm⁻¹; HRMS *m/z* 354.1008 (calcd for C₂₂H₁₄N₂O₃, 354.1004). The yield can be improved to 66 % by lowering the temperature to 80 °C and raising the CO pressure to 3.5 atm (see entry 11 in Table 2).

4-(3-Nitrobenzoyl)-3-phenylisoquinoline (21). The reaction mixture was chromatographed using 2:1 hexanes/ethyl acetate to yield a yellow solid: mp 128-129 °C; ¹H NMR (CDCl₃) δ 7.18-7.27 (m, 3H), 7.43 (t, *J* = 8.0 Hz, 1H), 7.57 (d, *J* = 7.6 Hz, 2H), 7.70-7.79 (m, 2H), 7.84 (d, *J* = 8.4 Hz, 1H), 7.93 (d, *J* = 7.6 Hz, 1H), 8.16 (d, *J* = 8.0 Hz, 1H), 8.22 (dt, *J* = 8.0, 1.2 Hz, 1H), 8.40 (s, 1H), 9.54 (s, 1H); ¹³C NMR (CDCl₃) δ 124.19, 124.26, 127.30, 127.31, 127.69, 128.28, 128.55, 128.73, 129.15, 129.80, 129.87, 132.34, 134.14, 134.87, 138.83, 139.51, 148.27, 150.89, 154.53, 195.86; IR (CHCl₃) 3021, 1667, 1619, 1534 cm⁻¹; HRMS *m/z* 354.1008 (calcd for C₂₂H₁₄N₂O₃, 354.1004).

3-(1-Cyclohexenyl)-4-(3-ethoxycarbonylbenzoyl)isoquinoline (24). The reaction mixture was chromatographed using 3:1 hexanes/ethyl acetate to afford 53.5 mg (55%) of the indicated compound as a yellow solid: mp 108-109 °C; ¹H NMR (CDCl₃) δ 1.16-1.25 (br m, 2H), 1.35-1.40 (m, 5H), 1.87 (s, 2H), 2.35 (s, 2H),

4.37 (q, $J = 7.2$ Hz, 2H), 5.80-5.82 (m, 1H), 7.50 (t, $J = 7.8$ Hz, 1H), 7.64 (t, $J = 7.2$ Hz, 1H), 7.71 (td, $J = 1.5, 7.2$ Hz, 1H), 7.90 (tt, $J = 1.5, 7.5$ Hz, 2H), 8.06 (d, $J = 7.8$ Hz, 1H), 8.22 (dt, $J = 1.5, 7.8$ Hz, 1H), 8.30 (t, $J = 1.8$ Hz, 1H), 9.34 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.48, 21.59, 22.45, 25.95, 27.76, 61.57, 124.56, 127.06, 127.31, 127.54, 128.32, 128.82, 129.75, 131.12, 131.86, 132.76, 133.92, 134.44, 134.69, 138.72, 139.49, 153.76, 154.28, 165.89, 197.18; IR (CHCl_3) 3019, 1662 cm^{-1} ; HRMS m/z 385.1683 (calcd for $\text{C}_{25}\text{H}_{23}\text{NO}_3$ 385.1678).

3-Butyl-4-(3-ethoxycarbonylbenzoyl)isoquinoline (26). The reaction mixture was chromatographed using 2:1 hexanes/ethyl acetate to afford 57.8 mg (64%) of the indicated compound as a yellow liquid: ^1H NMR (CDCl_3) δ 0.81 (t, $J = 7.2$ Hz, 3H), 1.27 (sextet, $J = 7.2$ Hz, 2H), 1.38 (t, $J = 7.2$ Hz, 3H), 1.72 (quintet, $J = 7.8$ Hz, 2H), 2.72 (t, $J = 7.8$ Hz, 2H), 4.38 (q, $J = 7.2$ Hz, 2H), 7.44-7.48 (m, 1H), 7.51-7.62 (m, 3H), 7.95 (d, $J = 7.8$ Hz, 1H), 8.01-8.06 (m, 1H), 8.29 (dt, $J = 1.2, 7.8$ Hz, 1H), 8.54 (s, 1H), 9.34 (s, 1H); ^{13}C NMR (CDCl_3) δ 14.00, 14.46, 22.83, 32.17, 36.25, 61.66, 123.99, 126.67, 127.18, 128.17, 128.23, 129.32, 130.59, 131.46, 131.77, 133.88, 134.03, 135.01, 137.96, 152.27, 153.62, 165.71, 197.76; IR (CHCl_3) 3019, 1664 cm^{-1} ; HRMS m/z 361.1682 (calcd for $\text{C}_{23}\text{H}_{23}\text{NO}_3$ 361.1678).

4-Benzoyl-3-(3-cyanopropyl)isoquinoline (28). The reaction mixture was chromatographed using 1:1 hexanes/ethyl acetate to yield a yellow oil: ^1H NMR (CDCl_3) δ 2.15 (quintet, $J = 7.2$ Hz, 2H), 2.36 (t, $J = 7.2$ Hz, 2H), 2.86 (t, $J = 7.2$ Hz, 2H), 7.45-7.50 (m, 3H), 7.59-7.66 (m, 3H), 7.82 (d, $J = 7.2$ Hz, 2H), 8.01-8.06 (m, 1H), 9.32 (s, 1H); ^{13}C NMR (CDCl_3) δ 16.88, 25.39, 34.69, 119.62, 124.34, 126.88, 127.58, 128.14, 129.28, 129.59, 129.95, 131.57, 133.87, 134.67, 137.38, 149.34,

153.49, 198.14; IR (CHCl₃) 3064, 2234, 1667 cm⁻¹; HRMS *m/z* 300.1266 (calcd for C₂₀H₁₆N₂O, 300.1263).

4-Benzoyl-3-(methoxymethyl)isoquinoline (30). The reaction mixture was chromatographed using 1:1 hexanes/ethyl acetate to yield a white solid: mp 99-100 °C; ¹H NMR (CDCl₃) δ 3.18, (s, 3H), 4.66 (s, 2H), 7.45 (t, *J* = 8.0 Hz, 2H), 7.58-7.64 (m, 4H), 7.82 (d, *J* = 7.2 Hz, 2H), 8.04-8.06 (m, 1H), 9.34 (s, 1H); ¹³C NMR (CDCl₃) δ 58.80, 124.58, 127.70, 127.88, 128.19, 128.98, 129.32, 129.56, 131.61, 133.93, 134.14, 137.99, 148.30, 153.24, 197.01; IR (CHCl₃) 3064, 1659 cm⁻¹; HRMS *m/z* 277.1106 (calcd for C₁₈H₁₅NO₂, 277.1103).

8-(4-Methoxybenzoyl)-7-phenyl-[1,3]dioxolo[4,5-g]isoquinoline (32). The reaction mixture was chromatographed using 1:1 hexanes/ethyl acetate to yield a yellow solid: mp 160-161 °C; ¹H NMR (CDCl₃) δ 3.75 (s, 3H), 6.06 (s, 2H), 6.73 (d, *J* = 8.8 Hz, 2H), 7.00 (s, 1H), 7.19-7.27 (m, 3H), 7.59-7.64 (m, 4H), 9.15 (s, 1H); ¹³C NMR (CDCl₃) δ 55.57, 101.23, 102.08, 103.47, 113.94, 124.73, 128.34, 128.91, 129.50, 130.68, 132.20, 132.66, 139.99, 148.72, 149.14, 150.94, 152.05, 164.07, 196.75; IR (CHCl₃) 3019, 1654 cm⁻¹; HRMS *m/z* 383.1164 (calcd for C₂₄H₁₇NO₃, 383.1158).

7-Phenyl-8-(3-trifluoromethylbenzoyl)-[1,3]dioxolo[4,5-g]iso-quinoline (33). The reaction mixture was chromatographed using 1:1 hexanes/ethyl acetate to yield a yellow solid: mp 139-140 °C; ¹H NMR (CDCl₃) δ 7.10 (s, 1H), 7.17-7.26 (m, 3H), 7.32-7.37 (m, 2H), 7.49-7.52 (m, 2H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.84 (s, 1H), 9.21 (s, 1H); ¹³C NMR (CDCl₃) δ 100.89, 102.30, 103.77, 124.93, 127.23 (q, *J* = 272.9 Hz, 1C, including 121.81, 125.43), 126.35 (q, *J* = 3.85

Hz, 1C, including 126.727, 126.32, 126.37, 126.42), 127.54, 128.54, 128.76, 129.19, 129.71, 129.82 (q, $J = 3.62$ Hz, 1C, including 129.75, 129.79, 129.84, 129.89), 130.65 (q, $J = 33.0$ Hz, 1C, including 130.87, 131.30), 132.65-132.70 (m, 1C, including 132.65, 132.70), 138.12, 139.80, 145.29, 149.00, 150.25, 151.78, 152.62, 197.08; IR (CHCl₃) 3019, 1654 cm⁻¹; HRMS m/z 383.1164 (calcd for C₂₄H₁₄F₃NO₃, 383.1158).

4-(4-Methoxybenzoyl)-4-(4-methoxyphenyl)isoquinoline (35). The reaction mixture was chromatographed using 1:1 hexanes/ethyl acetate to yield a yellow solid: mp 141-142 °C; ¹H NMR (CDCl₃) δ 3.77 (s, 3H), 3.80 (s, 3H), 6.77 (d, $J = 8.4$ Hz, 2H), 6.83 (d, $J = 8.4$ Hz, 2H), 7.61-7.73 (m, 7H), 8.08 (d, $J = 7.6$ Hz, 1H), 9.44 (s, 1H); ¹³C NMR (CDCl₃) δ 55.37, 55.61, 113.96, 114.02, 124.70, 126.92, 127.46, 128.11, 128.45, 130.75, 131.02, 131.52, 132.26, 132.48, 134.48, 149.37, 153.29, 159.94, 164.13, 196.87; IR (CHCl₃) 3019, 1654, 1216 cm⁻¹; HRMS m/z 369.1370 (calcd for C₂₄H₁₉NO₃, 369.1365).

4-(4-Ethoxycarbonylbenzoyl)-4-(4-methoxyphenyl)isoquinoline (36). The reaction mixture was chromatographed using 1:1 hexanes/ethyl acetate to yield a yellow solid: mp 152-153 °C; ¹H NMR (CDCl₃) δ 1.38 (t, $J = 7.2$ Hz, 3H), 3.72 (s, 3H), 4.33 (q, $J = 7.2$ Hz, 2H), 6.78 (dt, $J = 8.8, 2.4$ Hz, 2H), 7.33 (t, $J = 8.0$ Hz, 1H), 7.66 (dt, $J = 8.8, 2.4$ Hz, 2H), 7.64 (td, $J = 8.0, 1.2$ Hz, 1H), 7.69 (td, $J = 8.0, 1.2$ Hz, 1H), 7.76 (d, $J = 8.4$ Hz, 1H), 7.79 (dt, $J = 8.0, 1.2$ Hz, 1H), 8.09 (dd, $J = 8.0, 1.2$ Hz, 2H), 8.34 (t, $J = 1.2$ Hz, 1H), 9.46 (s, 1H); ¹³C NMR (CDCl₃) δ 14.43, 55.34, 61.47, 114.02, 124.30, 126.96, 127.46, 127.63, 128.30, 128.82, 130.61, 131.11, 131.15, 131.82, 132.34, 133.70, 134.31, 134.37, 137.64, 150.11, 153.88,

160.07, 165.68, 197.54; IR (CHCl₃) 3064, 1720, 1667 cm⁻¹; HRMS *m/z* 411.1478 (calcd for C₂₆H₂₁NO₄, 411.1471).

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References

1. Arcadi, A.; Cacchi, S.; Rosario, M. D.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280 and references therein.
2. (a) Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B.; *Tetrahedron* **1988**, *44*, 481. (b) Arcadi, A.; Bernocchi, E.; Burini, A.; Cacchi, S.; Marinelli, F.; Pietroni, B. *Tetrahedron Lett.* **1989**, *26*, 3465. (c) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Tetrahedron* **1996**, *52*, 10225.
3. (a) Saito, R.; Morimoto, M.; Akiyama, C.; Matsumoto, T.; Suzuki, K. *J. Am. Chem. Soc.* **1995**, *117*, 10757. (b) Shin, K.; Ogasawara, K. *Synlett* **1995**, 859. (c) Liao, H.-Y.; Cheng, C.-H. *J. Org. Chem.* **1995**, *60*, 3771. (d) Bates, R. W.; Rama-Devi, T. *Synlett* **1995**, 1151. (e) Amatore, C.; Blart, E.; Genet, J. P.; Jutand, A.; Lemaire-Audoir, S.; Savignac, M. *J. Org. Chem.* **1995**, *60*, 6829. (f) Chowdhury, C.; Kundu, N. G. *J. Chem. Soc., Chem. Commun.* **1996**, 1067. (g) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, 1363. (h) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 5327. (i) Khan, M. W.; Kundu, N. G. *Synlett* **1997**, 1435. (j) Fancelli, D.;

- Fagnola, M. C.; Severino, D.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2311.
- (k) Fagnola, M. C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307. (l) Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron Lett.* **1998**, *39*, 5101. (m) Chowdhury, C.; Chaudhuri, G.; Guha, S.; Mukherjee, A. K.; Kundu, N. G. *J. Org. Chem.* **1998**, *63*, 1863.
- (n) Montiero, N.; Balme, G. *Synlett* **1998**, 746. (o) Chaudhuri, G.; Chowdhury, C.; Kundu, N. G. *Synlett* **1998**, 1273. (p) Gabriele, B.; Solerno, G.; Fazio, A.; Bossio, M. *Tetrahedron Lett.* **2001**, *42*, 1339.
4. (a) Fournet, G.; Balme, G.; Van Hemelryck, B.; Gore, J. *Tetrahedron Lett.* **1990**, *31*, 5147. (b) Fournet, G.; Balme, G.; Gore, J. *Tetrahedron* **1991**, *47*, 6293. (c) Bouyssi, D.; Balme, G.; Gore, J. *Tetrahedron Lett.* **1991**, *32*, 6541. (d) Balme, G.; Bouyssi, D. *Tetrahedron* **1994**, *50*, 403. (e) Saulnier, M. G.; Frennesson, D. B.; Deshpande, M. S.; Vyas, D. M. J.; Balme, G. *Tetrahedron Lett.* **1996**, *37*, 1429. (f) Arcadi, A.; Anacardio, R.; D'Anniballe, G.; Gentile, M. *Synlett* **1997**, 1315. (g) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 527. (h) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, 1363. (i) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 5327. (j) Cacchi, S.; Fabrizi, G.; Moro, L. *Synlett* **1998**, 741. (k) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, *63*, 1001. (l) Larock, R. C.; Pace, P.; Yang, H.; Russell, C. E. *Tetrahedron* **1998**, *54*, 9961. (m) Monteiro, N.; Arnold, A.; Balme, G. *Synlett* **1998**, 1111. (n) Monteiro, N.; Balme, G. *Synlett* **1998**, 746. (o) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2000**, *3*, 394.

5. (a) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, *50*, 437. (b) Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. *Synlett* **1999**, *5*, 620.
6. For a recent leading reference to *syn* intramolecular carbopalladation of carbon carbon triple bonds, see: (a) Meyer, F. E.; Brandenburg, J.; Parsons, P. J.; de Meijere, A.; *J. Chem. Soc., Chem. Commun.* **1992**, 390. (b) Meyer, F. E.; Henniges, H.; de Meijere, A. *Tetrahedron Lett.* **1992**, *33*, 8039. (c) Coperet, S.; Ma, S.; Sugihara, T.; Negishi, E. *Tetrahedron* **1996**, *52*, 11529. (d) Grigg, R.; Loganathan, V.; Sridharan, V.; *Tetrahedron Lett.* **1996**, *37*, 3399. (e) Grigg, R.; Sansano, J. M.; Santhakumar, V.; Sridharan, V.; Thangavelanthum, R.; Thornton-Pett, M.; Wilson, D. *Tetrahedron* **1997**, *53*, 11803.
7. Arcadi, A.; Cacchi, S.; Fabrizi, G.; Moro, L. *Eur. J. Org. Chem.* **1999**, *64*, 1137.
8. (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.
9. For the annulation of internal alkynes by 2-iodobenzaldimines, see: (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. For the cyclization of alkynylimines by carbopalladation, see: (c) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035. (d) Dai, G.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, in press. For the cyclization of alkynylimines by acylpalladation, see: (e) Dai, G.; Larock, R. C. *Org. Lett.* **2002**, *4*, 193. (f) Dai, G.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7042. For the electrophile-promoted cyclization of alkynyl imines, see: (g) Huang, Q.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973.

- (h) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437.
For catalytic Pd(II)-promoted cyclization of alkynylimines, followed by a Heck reaction, see: (i) Huang, Q.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 3557 and full paper in press.
10. (a) Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 3083. (b) Zhang, H.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7048. (c) Zhang, H.; Larock, R. C. *Org. Lett.* **2001**, *3*, 3035.
11. Zhang, H.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 1359.
12. (a) Dai, G.; Larock, R. C. *Org. Lett.* **2002**, *4*, 193. (b) Dai, G.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 7042.
13. Sonogashira, K. *Comprehensive Organic Synthesis*, Vol. 3, p. 251, Pergamon Press, 1990.
14. Tsuji, J. *Palladium Reagents and Catalysts*: John Wiley & Sons: Chichester, New York, 1999, p. 253.
15. (a) Tsuji, J.; Ohno, K. *J. Am. Chem. Soc.* **1968**, *90*, 94. (b) Blaser, J. J. *J. Organomet. Chem.* **1982**, *233*, 267. (c) Spencer, A. J. *J. Organomet. Chem.* **1982**, *240*, 209. (d) Spencer, A. J. *J. Organomet. Chem.* **1984**, *265*, 323.
16. Arcadi, A.; Cacchi, S.; Larock, R. C.; Marinelli, F. *Tetrahedron Lett.* **1993**, *34*, 2813.
17. Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434.
18. Tsuda, T.; Ohashi, Y.; Nagahama, S.; Sumiya, S.; Saegusa, T. *J. Org. Chem.* **1988**, *53*, 2650.
19. Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 4387.
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Chapter 3. Palladium-Catalyzed Oxidative Carbonylation of 2-(1-Alkynyl)benzaldimines

Guangxiu Dai and Richard C. Larock*

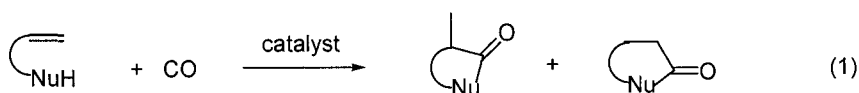
Department of Chemistry, Iowa State University, Ames, Iowa 50011

Abstract

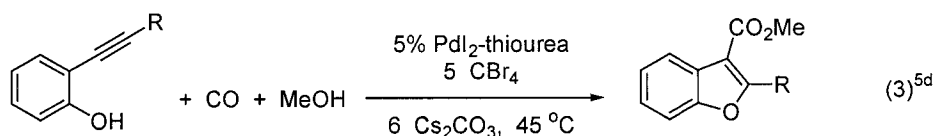
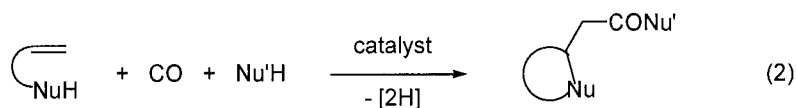
The Pd(II)-catalyzed oxidative carbonylation of 2-(1-alkynyl)benzaldimines has been studied and the optimal reaction conditions have been investigated for formation of the corresponding isoquinoline-4-carboxylates. Unfortunately, this methodology study has not provided an efficient route to synthesize methyl 3-substituted isoquinoline-4-carboxylates in synthetically useful yields.

Introduction

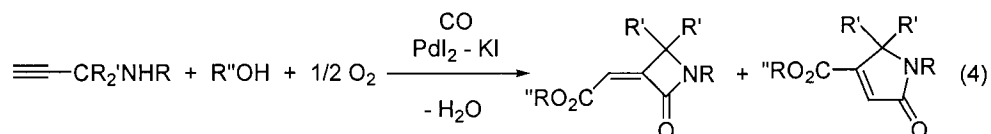
The carbonylation of unsaturated compounds containing a suitably placed nucleophilic group is an important method for the synthesis of functionalized heterocyclic compounds.¹ When carbon monoxide inserts between the nucleophile and the unsaturated moiety of the substrate, an endocyclic carbonyl group is obtained in the final cyclocarbonylation products (eq 1).²



In other cases, however, carbonylation is accompanied by ring closure without CO incorporation into the cycle, so that an external carbonyl group is obtained in the final products, as depicted, for example, in eq 2. This kind of reactivity has been observed in the oxidative cyclization-alkoxycarbonylation of 4-alken-1-ols, 5-alken-1-ols, 4-alken-1-amines, 5-alken-1-amines, unsaturated ureas, and carbamates.³ The ring closure of functionalized alkynes, followed by carbonylation, has also been reported using 2-(1-alkynyl)anilines,⁴ 2-(1-alkynyl)phenols and their derivatives (eq 3),^{4,5} prop-3-ynylamides⁶, prop-3-ynylureas⁷ and (Z)-2-alken-4-yn-1-ols⁸ to afford heterocycles.

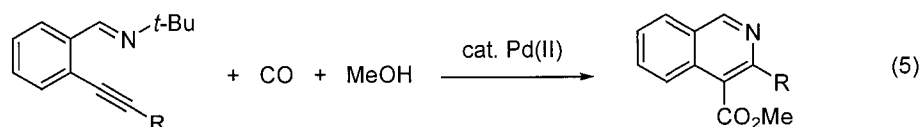


The sequential oxidative carboxylation-cyclization-alkoxycarbonylation of prop-3-ynylamines gives 5-[(alkoxycarbonyl)methylene]oxazolidin-2-ones (eq 4).⁹



It is important that most examples of oxidative carbonylation have been carried out cyclizing a four- or five-membered ring. The only attempt to cyclize a

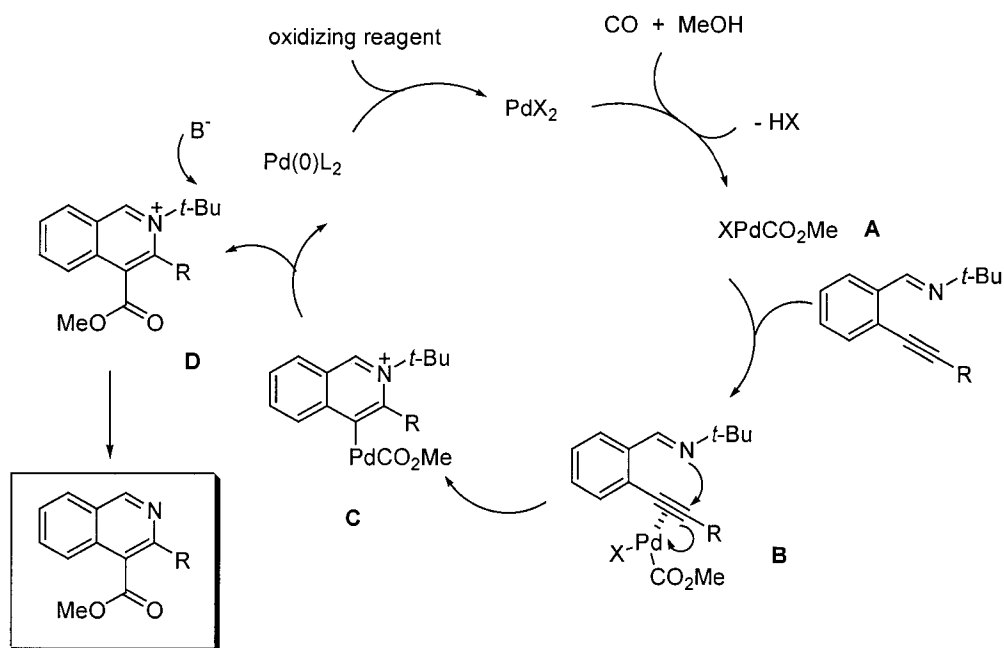
six-membered ring failed.^{4b} Our success in preparing 3-monosubstituted¹⁰ and 3,4-disubstituted isoquinolines¹¹ from 2-(1-alkynyl)benzaldimines prompted us to explore the oxidative carbonylation of a 2-(1-alkynyl)benzalimine to form the six-membered isoquinoline ring (eq 5).



Results and Discussion

The mechanism for this process is expected to be similar to that of other oxidative carbonylation processes⁴ (Scheme 1), which involve (1) a methoxycarbonylpalladium(II) species **A**, generated from carbon monoxide insertion into PdX_2 followed by methoxylation, attacks the alkyne triple bond of the 2-(1-alkynyl)benzalimine to form complex **B**. The triple bond in **B** is activated towards nucleophilic attack by coordination of XPdCO_2Me (**A**); (2) nucleophilic attack of the neighboring imine nitrogen on the triple bond generates the six-membered ring and forms the isoquinolinium salt **C**; (3) reductive elimination affords intermediate **D** and releases the $\text{Pd}(0)$ species, which is then reoxidized to $\text{Pd}(\text{II})$ and returns to the catalytic cycle; (4) the resulting intermediate **D** undergoes fragmentation of the *tert*-butyl group from the nitrogen and leads to the methyl 3-substituted isoquinoline-4-carboxylate as the desired product.

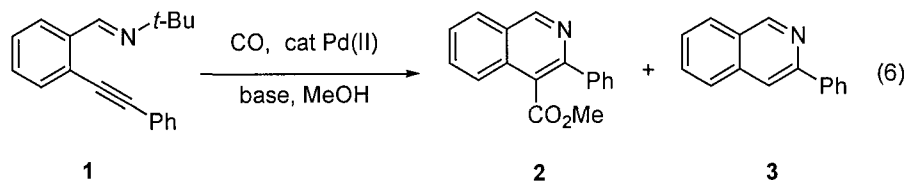
Scheme 1



In this catalytic cycle, the nature of the base (B^-), the Pd(II) catalyst and the oxidizing agent (OA) are all paramount to the success of the reaction. The base should allow the desired catalytic cycle to proceed, while minimizing the unwanted direct cyclization of the 2-(1-alkynyl)benzaldimine to a 3-monosubstituted isoquinoline. The intermediate $XPdCO_2Me$ complex (**A**) has to be active enough to coordinate to the acetylene to form complex **B**, in which the C-C triple bond is therefore activated towards nucleophilic attack. The reoxidizing agent (OA) has to efficiently promote the turnover of the palladium catalyst from Pd(0) to Pd(II) without disrupting the carbonylative cyclization.^{5c}

We have carried out a systematic study using *N*-*tert*-butyl-2-(phenylethynyl)benzaldimine (**1**) as the substrate to identify the appropriate base

(B⁻), Pd(II) catalyst, and oxidative agent (OA) that are best for the carbonylative heterocyclization (eq 6).



We first employed the reaction conditions that promoted the carbonylative cyclization of 2-(1-alkynyl)phenols to 2,3-disubstituted benzo[*b*]furans (eq 3).^{5d} Those conditions include 5 mol % PdI₂, 5 mol % thiourea as a ligand and 5 equiv of CBr₄ as the oxidant in methanol at 45 °C under 1 atm of CO.

Base. When 3 equiv of the base Cs₂CO₃ were employed, the ester product **2** was isolated in a 36% yield, alongside a 10% yield of 3-phenylisoquinoline (**3**) as a by-product (Table 1, entry 1). Other carbonate bases, such as Na₂CO₃, K₂CO₃, Li₂CO₃, NaHCO₃ and NaOCO₂Me did not improve the results at all (entries 2-6). When CsOAc was utilized, a 41% yield of 2-(phenylethynyl)benzaldehyde, was recovered after hydrolysis and a 30% yield of the side product **3** was isolated after 22 h (entry 7). No ester product **2** was observed. NaOAc did promote the formation of the ester product **2**, although the yield was low (entry 8). Organic bases, such as triethylamine and pyridine, completely inhibited formation of the ester (entries 9 and 10).

After several inorganic and organic bases were examined, Cs₂CO₃ was considered the base of choice, although we hoped to be able to further optimize the yield of product **2**.

Table 1. Carbonylative Cyclization of *N*-*tert*-Butyl-2-(phenylethynyl)-benzaldimine (1**) Under 1 atm of CO in Methanol (eq 6).^a**

	base (3 equiv)	time (h)	% 2	% 3	% 1 ^b
1	Cs ₂ CO ₃	39	36	10	0
2	Na ₂ CO ₃	22	33	14	0
3	K ₂ CO ₃	48	26	20	22
4	Li ₂ CO ₃	24	0	30	48
5	NaHCO ₃	24	0	trace	-
6	NaOCO ₂ Me	24	0	trace	-
7	CsOAc	22	0	30	41
8	NaOAc	48	26	46	0
9	Et ₃ N	28	0	trace	-
10	pyridine	24	0	12	70

^a All reactions were run using substrate **1** (0.0653 g, 0.25 mmol), PdI₂ (4.5 mg, 0.0125 mmol), thiourea (0.9 mg, 0.0125 mmol), CBr₄ (0.4147 g, 1.25 mmol) and the base indicated in 5 ml of methanol under 1 atm of CO. ^b This is actually the percent yield of 2-(phenylethynyl)benzaldehyde obtained by hydrolysis of **1** upon work-up.

We then continued to examine the amount of the base that is best for the reaction. We selected Cs₂CO₃ and Na₂CO₃ as the preferred bases based on the results shown in Table 1. When no base was used in the reaction, no ester product was detected. Only 3-phenylisoquinoline (**3**) was isolated in a yield of 65% (Table 2, entry 1). With 6 equiv of Cs₂CO₃, the yield of **2** was slightly improved to 41%

(entry 2), while 3 equiv or 10 equiv of Cs_2CO_3 (entries 2 and 4) slightly lowered the yield of **2**. Using different amounts of Na_2CO_3 did not increase the yield at all (entries 5-8). Thus, we chose to use 6 equiv of Cs_2CO_3 as the base for the rest of this project.

Table 2. Carbonylative Cyclization of *N*-tert-Butyl-2-(phenylethynyl)-benzaldimine (1**) Under 1 atm of CO in Methanol.^a**

	base	time (h)	% 2	% 3	% 1 ^b
1	none	21	0	65	10
2	Cs_2CO_3 (3)	39	36	10	0
3	Cs_2CO_3 (6)	39	41	12	trace
4	Cs_2CO_3 (10)	24	37	17	20
5	Na_2CO_3 (1)	21	0	trace	-
6	Na_2CO_3 (3)	22	33	14	0
7	Na_2CO_3 (6)	22	32	15	0
8	Na_2CO_3 (10)	24	11	0	68

^a All reactions were run using substrate **1** (0.0653 g, 0.25 mmol), PdI_2 (4.5 mg, 0.0125 mmol), thiourea (0.9 mg, 0.0125 mmol), CBr_4 (0.4147 g, 1.25 mmol) and the base indicated in 5 ml of methanol under 1 atm of CO. ^b This is the percent yield of 2-(phenylethynyl)benzaldehyde obtained by hydrolysis of **1** upon work-up.

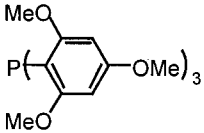
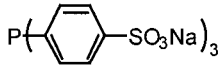
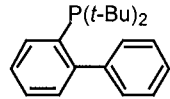
Ligand. Next, we set out to investigate the effect of different ligands on the reaction to prevent the Pd(0) formed from precipitating out. The ligand that was

used in the optimization up to this point was thiourea, a ligand that has been employed in several other carbonylation reactions.¹² With 5 mol % of thiourea combined with the rest of the reaction conditions shown in Table 3, entry 2, we were able to obtain the ester product **2** in a 41% yield. Without any thiourea, while keeping everything else the same, the reaction went faster and afforded the same yield of product **2** (Table 3, entry 1). With 17.5 mol % of thiourea¹³ present in the reaction, none of the desired ester was formed. Neither product **2** nor **3** was observed (entry 3).

Changing the thiourea to a phosphine as the ligand, including PPh_3 (entry 4), the bidentate phosphines dppf and dppe (entries 5 and 6), electron-rich and electron-deficient phosphines (entries 7 and 8), and highly electron-rich, extremely bulky phosphines (entries 9 and 10), did not improve the yield.

KI has also been an effective ligand in some carbonylation reactions.^{7,8,9a} However, KI did not improve the yield of **2** (entry 11). Using urea, instead of thiourea, did not produce any ester product **2** (entry 12). $\text{P}(\text{OEt})_3$ did not increase the yield of **2** either (entry 13).

Table 3. Carbonylative Cyclization of *N*-*tert*-Butyl-2-(phenylethynyl)-benzalimine (1) Under 1 atm of CO in Methanol Using Different Ligands.

	ligand	time (h)	% 2	% 3	% 1 ^a
1	none	24	42	12	0
2	thiourea (5 mol %)	39	41	12	-
3	thiourea (17.5 mol %)	10	0	0	-
4	PPh ₃ (10 mol %)	24	39	20	trace
5	dppf (5 mol %)	20	37	14	0
6	dppe (5 mol %)	20	32	12	0
7	 (10 mol %)	24	38	14	0
8	 (10 mol %)	24	42	7	0
9	PCy ₃ (10 mol %)	36	17	22	0
10	 (10 mol %)	24	24	12	trace
11	KI (10 mol %)	24	32	10	0
12	urea (10 mol %)	22	trace	30	-
13	P(OEt) ₃ (10 mol %)	18	32	10	0

^a All reactions were run using substrate 1 (0.0653 g, 0.25 mmol), PdI₂ (4.5 mg, 0.0125 mmol), Cs₂CO₃ (0.4887 g, 0.15 mmol), CBr₄ (0.4147 g, 1.25 mmol) and the ligand indicated in 5 ml of methanol under 1 atm of CO.

Reoxidizing Agent. In our initial studies, we relied on CBr_4 as the reoxidant to promote the turnover of Pd(0) to Pd(II) and complete the catalytic cycle (Table 4, entry 1). After examining the base and the ligand, we started to work on the next important factor mentioned earlier in the introduction, the oxidizing agent (OA). In all of the reactions shown in Table 4, 6 equiv of the reoxidizing agent were utilized to be consistent.

We examined three organic halides as possible reoxidizing agents.^{1a,14} Unfortunately, none of these oxidants worked as well in our carbonylative cyclization (Table 4, entries 2-4). It is assumed that iodobenzene is not applicable to the catalytic process owing to a possible competitive pathway leading to 3,4-diphenylisoquinoline.^{5d,11a,b}

Cu(II) salts are good oxidants for the conversion of Pd(0) to Pd(II) *in situ*.^{4,5a,b,12b} However, both $\text{Cu}(\text{OAc})_2$ and CuCl_2 gave low yields as oxidizing agents (entries 5 and 6). It is suspected that the reason why Cu(II) did not work well as an oxidizing agent in this reaction is that Cu^{2+} can be reduced by the I^- that exists in the palladium catalyst. In the presence of CuCl_2 , 4-chloro-3-phenylisoquinoline was also isolated in a 15% yield. 1,4-Benzoquinone did not promote the cyclization at all (entry 7).

Although silver salts are good at oxidizing Pd(0) to Pd(II), they are also known for their ability to catalyze the cyclization of *N-tert*-butyl-2-(1-alkynyl)-benzaldimines to 3-monosubstituted isoquinolines.^{11g,h} This is presumably the reason why the major product from this reaction was **3**, the side product without incorporation of CO (entry 8). Therefore, we have settled on CBr_4 as the oxidizing

agent.

Table 4. Carbonylative Cyclization of *N*-*tert*-Butyl-2-(phenylethynyl)-benzaldimine (1) Under 1 atm of CO in Methanol Using Different Reoxidizing Agents.

	OA	time (h)	% 2	% 3	% 1 ^a
1	CBr ₄	39	41	12	trace
2	CHI ₃	18	15	20	-
3	Mel	18	0	trace	-
4	PhI	18	0	0	-
5	Cu(OAc) ₂	24	15	trace	62
6 ^b	CuCl ₂	24	26	24	30
7	benzoquinone	23	0	0	-
8 ^c	Ag ₂ CO ₃	23	trace	49	trace

^a All reactions were run using substrate 1 (0.0653 g, 0.25 mmol), PdI₂ (4.5 mg, 0.0125 mmol), thiourea (0.9 mg, 0.0125 mmol), Cs₂CO₃ (0.4886 g, 1.5 mmol) and the reoxidizing agent indicated in 5 ml of methanol under 1 atm of CO. ^b

4-Chloro-3-phenylisoquinoline was also isolated in a 15% yield. ^c At 45 °C, an extremely polar spot was observed within the indicated time period and no ester product 2 was observed when the reaction was monitored by TLC. After the reaction mixture was heated up to 100 °C for another 24 h, 3-phenylisoquinoline (3) was isolated in a 49% yield.

Palladium Catalyst. Next we turned our attention to the palladium catalyst. Although PdX₂ (X = Cl, Br, I) often show very different reactivities in Pd(II)

chemistry,^{5c,11e} they perform very similarly (Table 5, entries 1, 2, 4 and 5) in this chemistry, even when twice as much PdI₂ was employed in the reaction (entry 2). Surprisingly, with stoichiometric amounts of PdI₂ and no oxidizing agent, none of the desired ester **2** was formed (entry 3).

Table 5. Carbonylative Cyclization of *N*-tert-Butyl-2-(phenylethynyl)-benzaldimine (1**) Under 1 atm of CO in Methanol Using Different Pd(II) Catalysts.**

	Pd reagent (5 %)	time (h)	% 2	% 3	% 1 ^a
1	PdI ₂	24	42	12	0
2 ^b	PdI ₂	18	39	10	0
3 ^c	PdI ₂	24	0	0	-
4	PdBr ₂	24	36	6	10-15
5	PdCl ₂	24	34	7	10-15
6	Pd(OAc) ₂	72	16	56	-
7	PdCl ₂ (PPh ₃) ₂	72	21	48	-

^a All reactions were run using substrate **1** (0.0653 g, 0.25 mmol), thiourea (0.9 mg, 0.0125 mmol), CBr₄ (0.4147 g, 1.25 mmol), Cs₂CO₃ (0.4886 g, 1.5 mmol) and the palladium catalyst indicated in 5 ml of methanol under 1 atm of CO. ^b 10 Mol % PdI₂ was employed in the reaction. ^c A stoichiometric amount of PdI₂ and thiourea and no oxidizing agent were used.

Although it has been claimed in the palladium-catalyzed carbonylative

cyclization of 2-(1-alkynyl)anilines that the reaction proceeds more smoothly when X^- is OAc^- than when X^- is halide,⁴ this is not the case in this chemistry. With $Pd(OAc)_2$ as the catalyst, the reaction proceeded slowly and compound **3** was isolated as the major product (entry 6). The complex $PdCl_2(PPh_3)_2$ also provided unfavorable results (entry 7).

CO Pressure. We next turned to the pressure of CO, hoping that a higher CO pressure would enhance the CO insertion and eventually favor formation of the ester product **2**, since higher CO pressures improved similar reactions described in references 11c and 11d. However, this proved not to be the case. Using 3.5 atm of CO, we isolated compound **2** in only a yield of 30% and compound **3** in a yield of 25%. It is assumed that under a higher CO pressure it is easier to form methyl formate with CO and methanol, which would not benefit the carbonylative cyclization. These results perhaps suggest that the lower yield of the oxidative carbonylation of 2-(1-alkynyl)benzaldimines is not due to slow CO insertion.

Solvent. In all of the previous experiments, methanol was employed as both one of the reactants and the solvent. When the reaction was run in four different solvents, DMF, DMSO, CH_3CN and THF with only 10 mmol of methanol, none of the desired ester was observed. We did not observe formation of either of the isoquinolines **2** or **3**, as determined by TLC analysis.

Temperature. Using methanol as the solvent limited the range of reaction temperatures under which the reaction could be run using a balloon filled with CO. At room temperature, the reaction afforded a much lower yield of product **2**, indicating that the transformation requires a higher temperature.

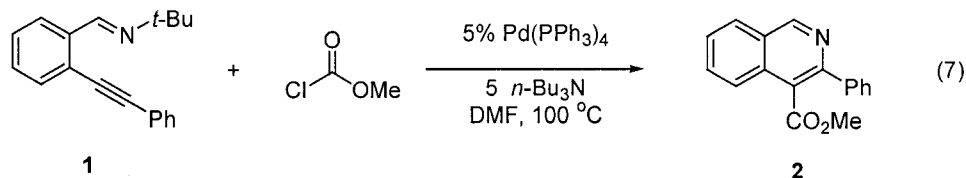
In order to employ a higher reaction temperature, we tried the reaction at 65 °C in ethanol as a reagent and also as the solvent. However, ethanol did not afford any of the desired ethyl ester product.

After extensive experimentation, we had to settle for the reaction conditions first employed, namely 5 mol % PdI₂, 5 mol % of thiourea, 5 equiv of CBr₄, and 6 equiv of Cs₂CO₃ at 45 °C in methanol under 1 atm of CO, although the best yield of product **2** we obtained was only 41%.

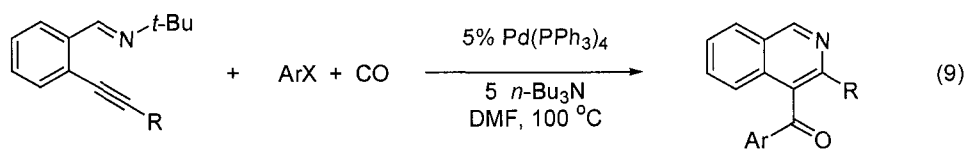
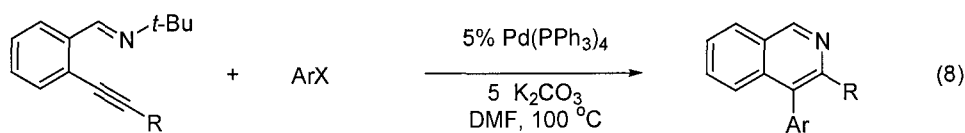
We also investigated other reaction conditions, in which 2-(1-alkynyl)phenols and 2-(1-alkynyl)anilines were successfully converted to methyl benzo[*b*]furan-3-carboxylates and methyl indole-3-carboxylates respectively.⁴ Those conditions are 6.3 mol % PdCl₂, 2 equiv of CuCl₂, 2 equiv of NaOAc, 2 equiv of K₂CO₃ at 1 atm of CO in methanol at room temperature. Under these conditions, the reaction of *N*-*tert*-butyl-2-(phenylethynyl)benzaldimine (**1**) and CO in methanol afforded product **2** in only an 11% yield. Increasing the temperature to 45 °C did not improve the yield of product **2**, and led to formation of another side product, 4-chloro-3-phenylisoquinoline, which was also observed in a Pd(II)-catalyzed olefination reaction of *N*-*tert*-butyl-2-(phenylethynyl)benzadimine (**1**) when CuCl₂ was employed as a reoxidant.^{11e} Changing the reoxidant to Cu(OAc)₂ only afforded the side product **3**, without any formation of **2**.

We have also tried an alternative route to prepare methyl 3-phenylisoquinoline-4-carboxylate (**2**) using methyl chloroformate (eq 7). This Pd(0)-catalyzed transformation is similar to our previous research employing imine **1** and benzoyl chloride to synthesize 4-benzoyl-3-phenylisoquinoline.^{11c,d} In this

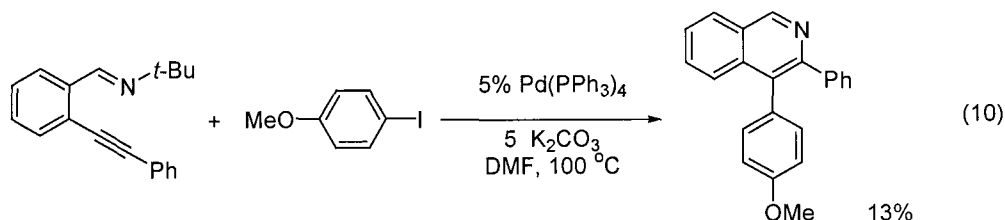
case, Pd(0) and methyl chloroformate might be expected to generate ClPdCO_2Me *in situ*,¹⁵ which is expected to promote the cyclization leading to the ester product. However, this approach did not work. Only compound **3** was isolated from this experiment.

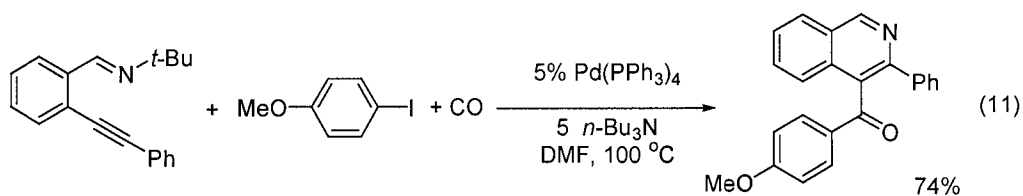


Organopalladium Intermediate. We were interested in looking into the reasons for the poor yields obtained in this project from the perspective of the nature of the organopalladium promoted cyclization of alkynes. The reactions in these three isoquinoline projects carried out by us (see thesis Chapters 1, 2 and 3) basically proceed by the same mechanism. In these transformations, the cyclization of a 2-(1-alkynyl)benzaldimine is promoted by an organopalladium complex. In Chapter 1, this is RPdX (R = aryl, allylic, benzyl, alkynyl and vinylic; X = I, Br, Cl) (eq 8). In Chapter 2, this is ArCOPdX (X = I, Cl) (eq 9), and in the current chapter this is XPdCO_2Me (eq 6). Thus, the reactivity of the organopalladium complex most likely determines the success of the reaction. Assuming that all of these intermediate organopalladium complexes (RPdX , ArCOPdX and XPdCO_2Me) are successfully generated *in situ* under their respective reaction conditions,¹⁶ based on the results that we have obtained during the three projects, it is clear that the intermediate organopalladium complexes indeed have different reactivities in this chemistry.

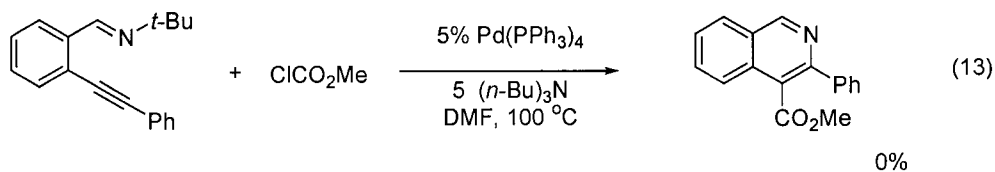
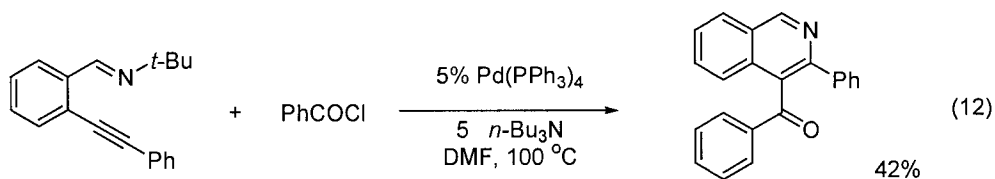


For example, the reaction of **1** and 4-iodoanisole (eq 10) in the first project generated the 3,4-disubstituted isoquinoline in only a 13% yield (see the discussion in Chapter 1).^{11a,b} On the other hand, the reaction of **1** and 4-iodoanisole in the presence of CO (eq 11) in the second chapter produced the 4-acylisoquinoline in a much higher yield, 74%.^{11c,d} The ArCOPdI complex is apparently more reactive than ArPdI based on the two results. Their different reactivities can be explained by their electrophilicity. Having a carbonyl group between the Pd and the Ar significantly increases the electrophilicity of the Pd. The resulting electron-deficient ArCOPdI complex should be more likely to coordinate the triple bond in the imine substrate to form the resulting heterocyclic palladium complex. The coordination step is presumably crucial to the cyclization, because, without it, the triple bond is not activated towards nucleophilic attack by the imine nitrogen, and therefore no organic substituent is incorporated into the 4 position of the isoquinoline ring.





The reactivity difference between ArCOPdX and XPdCO_2Me is exemplified by the results shown in eqs 12 and 13. ArCOPdX is more effective than XPdCO_2Me in promoting the cyclization of compound **1**. The low reactivity of $\text{XPdCO}_2\text{Me}^{15}$ might be the reason for the poor performance in this reaction, which by nature is very sensitive towards the strength of the organopalladium alkyne complex.^{11a,b}



It has been our experience in working on the cyclization of benzaldimines to isoquinolines that the transformation of a 2-(1-alkynyl)benzaldimine to an isoquinoline usually requires an elevated temperature (above 80 °C) in order to initiate the oxidative addition step. During the optimization work discussed in Chapters 1 and 2, it was established that at lower temperatures, the reactions usually proceed much more slowly and sometimes afford much lower yields.

However, employing methanol as the solvent basically limited us from using a higher temperature. This is assumed to be another reason for the consistently lower yields.

Conclusions

In summary, we have carefully investigated the reaction of a 2-(1-alkynyl)benzaldimine under carbon monoxide in the presence of a Pd(II) catalyst to form an isoquinoline-4-carboxylate. Although this has not proven to be an efficient way to synthesize disubstituted isoquinolines containing an ester group in the 4 position, our work has provided some insight into the nature of the Pd-catalyzed cyclization reactions promoted by organopalladium intermediates.

Experimental Section

General. All ^1H and ^{13}C NMR spectra were recorded at 300 and 400, and 75.5 and 100.7 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) and a 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. Lower resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos

MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV.

N-tert-Butyl-2-(phenylethynyl)benzaldimine (1). For the preparation of this compound, see the Experimental Section in Chapter 1.^{11a-d}

Methyl 3-phenylisoquinoline-4-carboxylate (2). The following is a representative procedure for the reactions carried out in this chapter. A mixture of PdI₂ (4.5 mg, 0.0125 mmol), thiourea (1.0 mg, 0.0125 mmol), CBr₄ (0.4146 g, 1.25 mmol), Cs₂CO₃ (0.4885 g, 1.5 mmol), *N-tert-butyl-2-(phenylethynyl)benzaldimine (1)* (0.0653 g, 0.25 mmol) in 5 mL of methanol was flushed with CO at room temperature for 5 min, fitted with a CO filled balloon (cautious!), and then heated to 100 °C with stirring for 12 h (Table 2, entry 3). The reaction mixture was cooled to room temperature, diluted with diethyl ether (30 mL) and washed with brine (30 mL). The aqueous layer was reextracted with diethyl ether (15 mL). The organic layers were combined, dried (MgSO₄), filtered and the solvent removed under reduced pressure. The residue was purified by column chromatography on a silica gel column using 3:1 hexanes/ethyl acetate to afford 27.6 mg (41%) of the indicated compound. For the full characterization of ester **2**, see reference 17.

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References

1. For recent leading references, see: (a) Cacchi, S.; Fabrizi, G.; Moro, L. *Tetrahedron Lett.* **1998**, *39*, 5101 and references therein. (b) Chaudhuri, G.; Chowdhury, C.; Kundu, N. G. *Synlett* **1998**, 1273. (c) Montiero, N.; Balme, G. *Synlett* **1998**, 746. (d) Chowdhury, C.; Chaudhuri, G.; Guha, S.; Mukherjee, A. K.; Kundu, N. G. *J. Org. Chem.* **1998**, *63*, 1863. (e) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 5327. (f) Khan, M. W.; Kundu, N. G. *Synlett* **1997**, 1435. (g) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, 1363. (h) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, *61*, 9280. (i) Chowdhury, C.; Kundu, N. G. *J. Chem. Soc., Chem. Commun.* **1996**, 1067. (j) Kundu, N. G.; Pal, M. *J. Chem. Soc., Chem. Commun.* **1993**, 86. (k) Candiani, I.; DeBernardinis, S.; Cabri, W.; Marchi, M.; Bedeschi, A.; Penco, S. *Synlett* **1993**, 269. (l) Zhang, H.; Brumfield, K. K.; Jaroskova, L.; Maryanoff, B. E. *Tetrahedron Lett.* **1998**, *39*, 4449. (m) Fancelli, D.; Fagnola, M. C.; Severino, D.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2311. (n) Fagnola, M. C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307. (o) Gabriele, B.; Salerno, G.; Fazio, A.; Bossio, M. *Tetrahedron Lett.* **2001**, *42*, 1339. (p) Monteiro, N.; Arnold, A.; Balme, G. *Synlett* **1998**, 1111. (q) Larock, R. C.; Pace, P.; Yang, H.; Russell, C. E. *Tetrahedron* **1998**, *54*, 9961. (r) Cacchi, S.; Fabrizi, G.; Moro, L. *Synlett* **1998**, 741. (s) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, *62*, 527 and references therein. (t) Balme, G.; Bouyssi, D. *Tetrahedron* **1994**, *50*, 403.

2. (a) Arcadi, A.; Cacchi, S.; Fabrizi, G.; Marinelli, F. *Synlett* **2000**, 394. (b) Cacchi, S.; Fabrizi, G.; Pace, P.; Marinelli, F. *Synlett* **1999**, 620. (c) Cacchi, S.; Fabrizi, G.; Pace, P. *J. Org. Chem.* **1998**, 63, 1001. (d) Cacchi, S.; Fabrizi, G.; Marinelli, F.; Moro, L.; Pace, P. *Synlett* **1997**, 1363. (e) Arcadi, A.; Cacchi, S.; Carnicelli, V.; Marinelli, F. *Tetrahedron* **1994**, 50, 437. (f) Mandai, T.; Ohat, K.; Baba, N.; Kawada, M.; Tsuji, J. *Synlett* **1992**, 671. (g) Tsuda, T.; Ohashi, Y.; Nagahama, M.; Sumiya, R.; Saegusa, T. *J. Org. Chem.* **1988**, 53, 2650.
 3. (a) Monteiro, N.; Balme, G. *Synlett* **1998**, 746. (b) Cacchi, S.; Fabrizi, G.; Moro, L. *Synlett* **1998**, 741. (c) Arcadi, A.; Cacchi, S.; Del Rosario, M.; Fabrizi, G.; Marinelli, F. *J. Org. Chem.* **1996**, 61, 9280 and references therein.
 4. (a) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *Tetrahedron* **1985**, 41, 3655. (b) Fukuda, Y.; Shiragami, H.; Utimoto, K.; Nozaki, H. *J. Org. Chem.* **1991**, 56, 5816. (c) Arcadi, A.; Burini, A.; Cacchi, S.; Delmastro, M.; Marinelli, F.; Pietroni, B. R. *J. Org. Chem.* **1992**, 57, 976. (d) Cacchi, S.; Fabrizi, G.; Moro, L. *J. Org. Chem.* **1997**, 62, 5327. (e) Cavicchioli, M.; Decortiat, S.; Bouyssi, D.; Gore, J.; Balme, G. *Tetrahedron* **1996**, 52, 11463. (f) Bouyssi, D.; Cavicchioli, M.; Balme, G. *Synlett* **1997**, 944. (g) Arcadi, A. *Synlett* **1997**, 941. (h) Arcadi, A.; Anacardio, R.; D'Anniballe, G.; Gentile, M. *Synlett* **1997**, 1315. (i) Arcadi, A.; Cacchi, S.; Marinelli, F. *Tetrahedron Lett* **1992**, 33, 3915. (j) Arcadi, A.; Cacchi, S.; Larock, R. C.; Marinelli, F. *Tetrahedron Lett* **1993**, 34, 2813.
 5. (a) Bentley, K. W. *The Isoquinoline Alkaloids*; Harwood Academic: Australia,
-

- Canada, 1998; Vol 1. (b) Croisy-Delcey, M.; Croisy, A.; Carrez, D.; Huel, C.; Chiaroni, A.; Ducrot, P.; Bisagni, E.; Jin, L.; Leclercq, G. *Bioorg. Med. Chem.* **2000**, *8*, 2629.
6. *Organic Reactions*, John Wiley & Sons: London, Sydney, 1951; Vol. VI, Chapters 2-4.
7. Maassarani, F.; Pfeffer, M.; Le Borgne, G. *J. Chem. Soc., Chem. Commun.* **1987**, 565.
8. Wu, G.; Geib, S. J.; Rheingold, A. L.; Heck, R. F. *J. Org. Chem.* **1988**, *53*, 3288.
9. Girling, I. R.; Widdowson, D. A. *Tetrahedron Lett.* **1982**, *23*, 4281.
10. (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.
11. (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.
12. (a) Huang, Q.; Hunter, J. A.; Larock, R. C. *Org. Lett.* **2001**, *3*, 2973. (b) Huang, Q.; Hunter, J. A.; Larock, R. C. *J. Org. Chem.* **2002**, *67*, 3437.
13. Huang, Q.; Larock, R. C. *Tetrahedron Lett.* **2002**, *43*, 3557.
14. (a) Dai, G.; Larock, R. C. *Org. Lett.* **2001**, *3*, 4035. (b) Dai, G.; Larock, R. C. *J. Org. Chem.* **2002**, *68*, 920.
15. Sonogashira, K. *Comprehensive Organic Synthesis*, Vol. 3, p. 251, Pergamon Press, 1990.
16. During the work-up procedure described in the experimental section, the reaction mixture in diethyl ether solution could be decolorized by the addition of
-

$\text{Na}_2\text{S}_2\text{O}_3$.

17. Wu, G.; Rheingold, A. L.; Geib, S. J.; Heck, R. F. *Organometallics* **1987**, *6*, 1941.
 18. For the preparation and characterization of 2-(trimethylsilylethynyl)-benzaldehyde, see: (a) Shindo, M.; Sato, Y.; Shishido, K. *J. Org. Chem.* **2001**, *66*, 7818. (b) Tovar, J. D.; Swager, T. M. *J. Org. Chem.* **1999**, *64*, 6499.
 19. For the preparation and characterization of 2-ethynylbenzaldehyde, see: Wang, X.; Silverman, R. B. *J. Org. Chem.* **1998**, *63*, 7357.
 20. Stille, J. K.; Lau, K. S. Y. *Acc. Chem. Res.* **1977**, *10*, 434.
 21. Tsuji, J.; Takahashi, H.; Morikawa, M. *Tetrahedron Lett.* **1965**, 4387.
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Chapter 4. Observation of a Novel Intramolecular Alkyl-to-Aryl Palladium Rearrangement

A paper to be submitted to the *Journal of the American Chemical Society*

Guangxiu Dai, Marino A. Campo and Richard C. Larock

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

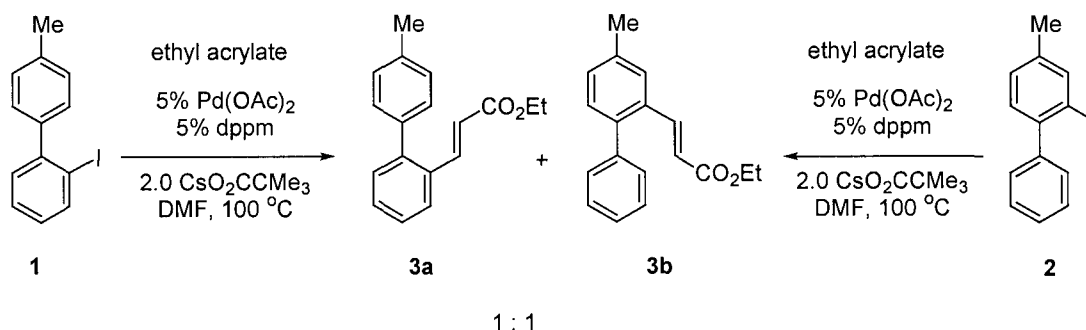
Abstract

The reaction of ethyl acrylate or methyl vinyl ketone plus an aryl halide bearing an olefin side chain affords unique 1,2,3,4-tetrahydronaphthalenes and heterocyclic analogues in which a novel intramolecular alkyl-to-aryl palladium shift has been observed by trapping the arylpalladium intermediate by an olefin in a Heck reaction. The reaction conditions have been optimized and the reaction scope has been extensively studied. The mechanism appears to involve: (1) oxidative addition of the aryl iodide to Pd(0), (2) intramolecular addition of the resulting arylpalladium intermediate to the double bond of an alkene affording an alkylpalladium intermediate with no β -hydrogen, (3) intramolecular palladium shift from an alkyl to an aryl position transforming an alkylpalladium intermediate to an arylpalladium intermediate, and (4) olefination of the resulting arylpalladium leading to the isolated product. This is the first time that a clean intramolecular alkyl-to-aryl palladium shift has been observed.

Introduction

Like carbon migration that has been reported in a multitude of reactions,¹ palladium has also been shown to migrate from carbon to carbon within a molecule given appropriate reaction conditions. In our own laboratory, it has been established that palladium is able to migrate intramolecularly between two aromatic positions (Scheme 1).² When 2-iodo-4'-methylbiphenyl (**1**) was employed in a Heck reaction with ethyl acrylate, a 1:1 mixture of two regioisomeric Heck products,

Scheme 1

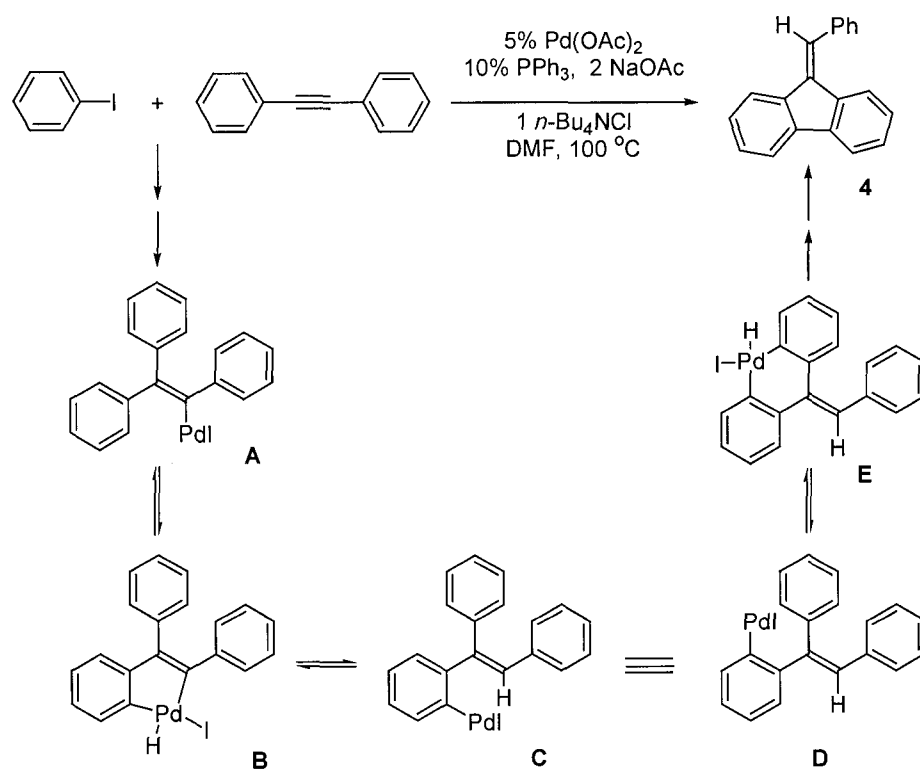


3a and **3b**, were obtained in an overall yield of 88%. Apparently, the originally formed 2-biphenylpalladium intermediate undergoes Pd migration to the 2' position to form the Heck product **3b**. What is even more interesting is the fact that the corresponding reaction with the isomeric 2-iodo-4-methylbiphenyl (**2**) affords the same two Heck products, **3a** and **3b**, in the same 1:1 ratio. Similar results have been observed when the methyl substituent was replaced by OMe, NMe₂, CO₂Et and NO₂. Gallagher and co-workers observed minor amounts of similar intramolecular palladium migration products involving migration from a pyridine ring

to another aromatic ring under different reaction conditions.³

In our own laboratory, palladium has also been observed to rearrange from a vinylic to an aryl carbon during the Pd-catalyzed reaction of phenyl iodide and diphenylacetylene to generate 9-benzylidene-9*H*-fluorene (**4**) under the reaction conditions illustrated in Scheme 2.⁴

Scheme 2

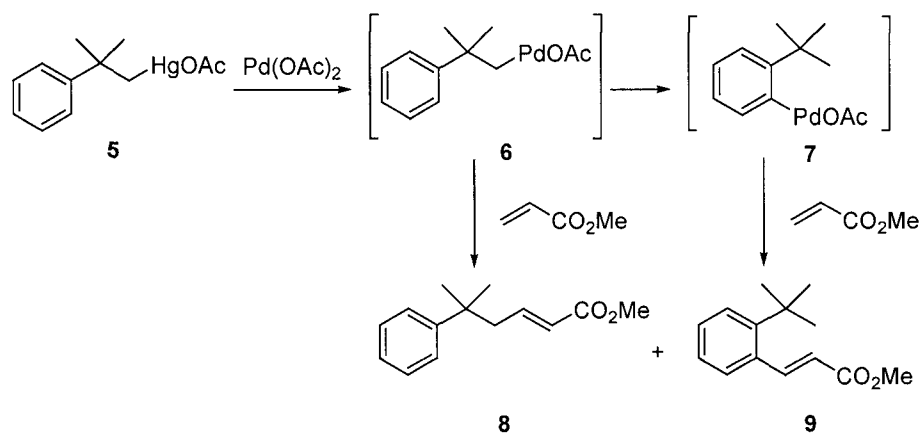


The vinylpalladium intermediate **A**, formed from the carbopalladation of diphenylacetylene by an arylpalladium iodide, apparently undergoes oxidative addition to the neighboring aryl C-H bond to generate a Pd(IV) intermediate **B**,

followed by reductive elimination leading to arylpalladium(II) intermediate **C**. Intermediate **C** eventually cyclizes to the fluorene product **4**, which confirms the formation of intermediate **C**. During this process, palladium migrates from a vinylic to an aryl position.

An intramolecular alkyl-to-aryl migration of a palladium intermediate was first reported by Heck in 1972.⁵ When 2-methyl-2-phenylpropylmercury acetate (**5**) was allowed to react with methyl acrylate in the presence of a stoichiometric amount of Pd(OAc)₂, a 65:35 mixture of two isomeric Heck products **8** and **9** respectively were isolated (Scheme 3).

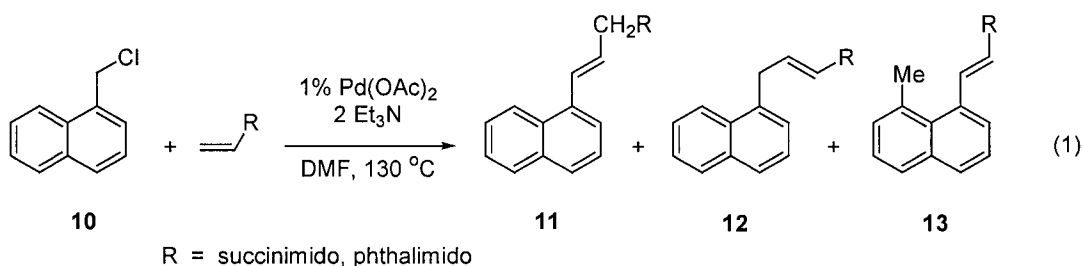
Scheme 3



The major product was the expected methyl *E*-5-methyl-5-phenyl-2-hexenoate (**8**), generated by transmetalation of **5**, followed by Heck coupling. The other product was found to be methyl *E*-*o*-*tert*-butylcinnamate (**9**). This product was assumed to arise from a rearrangement of the alkylpalladium

intermediate **6** to the arylpalladium intermediate **7**. This was the first time that an alkyl-to-aryl palladium shift has been described. No detailed mechanism was proposed or discussed to explain the migration process.

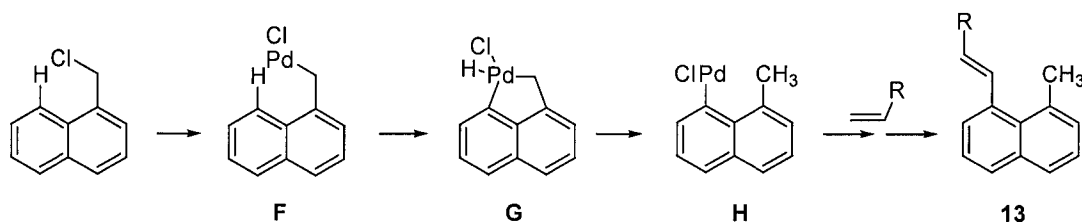
Hu and co-workers discovered the first example of a catalytic alkyl-to-aryl palladium rearrangement while investigating the Heck reaction of α -(chloromethyl)-naphthalene (**10**) with olefins (eq 1).⁶ Most of the reactions reported proceeded normally to produce products **11** and **12**. When R = succinimido, the reaction afforded the unexpected rearrangement product **13** in a yield of 25%, besides the isomerized, thermally more stable Heck product **11** isolated in a 20% yield. No normal Heck product **12** was isolated. Analogous products were also obtained in the same yields when R = phthalimido. However, no rearrangement was found when R = CO₂Et, Ph, CONH₂, CN, *p*-MeOC₆H₄, or OCOMe.⁶



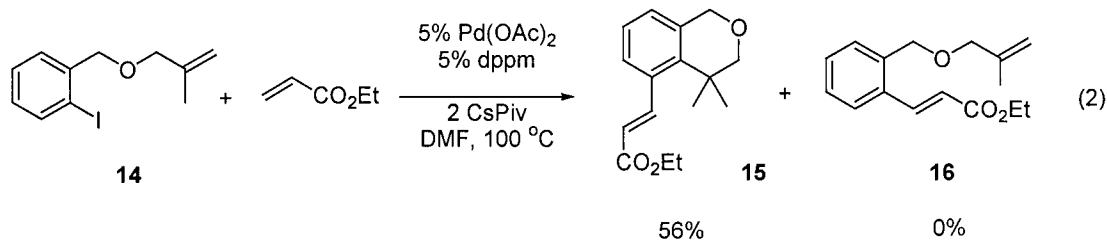
Migration in this system was considered to happen as depicted in Scheme 4. The *in situ* formed benzylic palladium chloride **F** inserts into the C-H bond at the 8 position of the naphthalene. Reductive elimination of the Pd(IV) intermediate **G** then selectively takes place between the H and methylene, affording the intermediate **H**, followed by a Heck reaction. The fact that the unusual

rearrangement happened only in the reactions of the two *N*-vinylimides suggests that the nitrogen may be involved as a coordinating ligand in stabilization of the intermediates to ensure that the intermediate **F** has time to undergo cyclopalladation. In these two literature examples of alkyl-to-aryl Pd rearrangements, both rearrangement and non-rearrangement products were formed, and the rearrangement products were always obtained in low yields, which is not synthetically useful.

Scheme 4



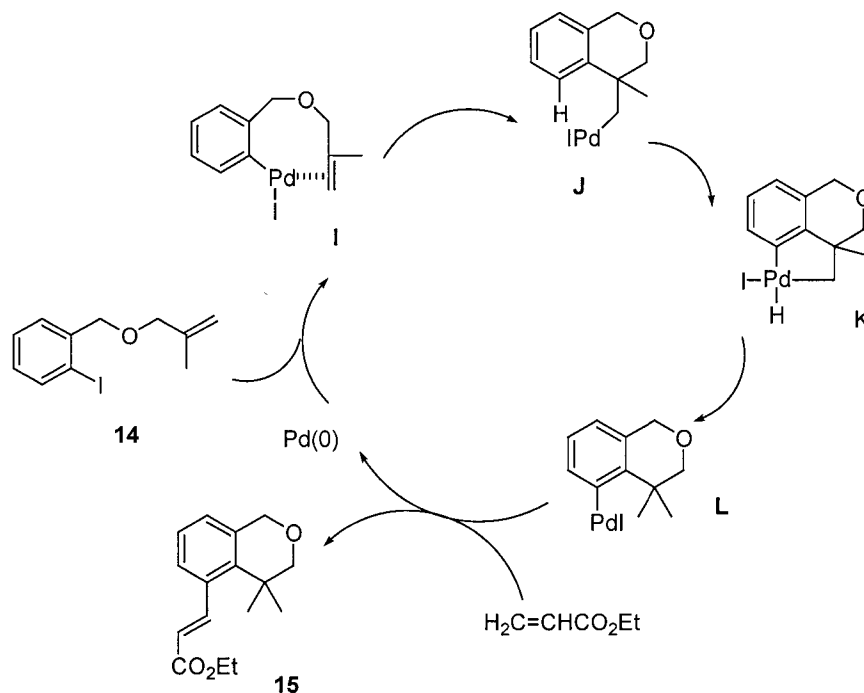
In our independent research, a new reaction was discovered employing 2-iodobenzyl methallyl ether (**14**), ethyl acrylate and a palladium catalyst (eq 2).^{2b} We did not observe any of the direct Heck coupling product **16**. Compound **15** was obtained exclusively in a 56% yield. This appeared to us to be a novel example of an intramolecular alkyl-to-aryl palladium rearrangement, which proceeds cleanly in synthetically useful yields (see the later mechanistic discussion). The exclusive formation of a single rearrangement product facilitated identification of the product and our mechanistic understanding of the reaction.



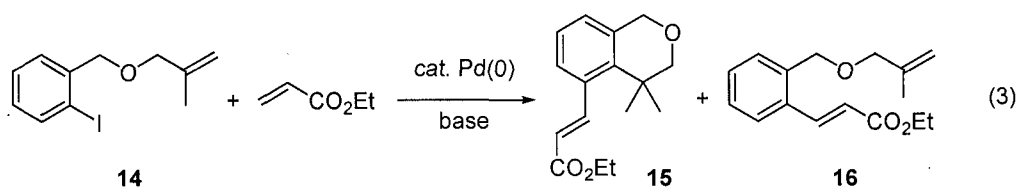
Results and Discussion

Mechanism. The overall process shown in equation 2 is believed to proceed mechanistically by the following steps as illustrated in Scheme 5: (1) oxidative addition of the aryl iodide to Pd(0) produces arylpalladium intermediate **I**, in which the palladium also coordinates to the C=C bond, (2) subsequent intramolecular carbopalladation affords a six-membered ring and generates the alkylpalladium intermediate **J**, (3) palladium then inserts into the neighboring C-H bond forming the organopalladium(IV) intermediate **K**, (4) intermediate **K** undergoes reductive elimination affording a new C-H bond and arylpalladium intermediate **L**, (5) the resulting arylpalladium species **L** is trapped by the olefin, ethyl acrylate, affording the Heck product **15** and simultaneously regenerating Pd(0). During this process, an alkylpalladium intermediate rearranges to an arylpalladium intermediate.

Scheme 5



Optimization. We started our research on this reaction by optimizing the reaction conditions with 2-iodobenzyl methallyl ether (**14**) and ethyl acrylate (eq 3). The conditions shown in Table 1, entry 1, utilizing 5 mol % Pd(OAc)₂, 5 mol % dppm, 2 equiv of CsPiv in 4 ml of DMF at 100 °C, generated the rearrangement product **15** in a 56 % yield. No direct Heck coupling product **16** was isolated. Replacing the diphosphine dppm with PPh₃ gave very similar results (entry 2). Changing the 10 mol % of PPh₃ to 5 mol % of PPh₃, 5 mol % of dppe or 10 mol % 2-(di-*t*-butylphosphino)biphenyl did not make a significant difference in terms of either the yield of **15** or the ratio of **15** to **16** (entries 3-5). Thus, the nature of the phosphine ligand appears to have no profound effect on the reaction.



Tabel 1. Optimization of the Reaction of 2-Iodobenzyl Methallyl Ether (14) and Ethyl Acrylate (eq 3).^a

	ligand	base	% yield of 15
1	5 % dppm	2 CsPiv	56
2	10 % PPh ₃	2 CsPiv	54
3	5 % PPh ₃	2 CsPiv	49
4	5 % dppe	2 CsPiv	48
5	10 % 2-(di- <i>t</i> -butylphosphino)biphenyl	2 CsPiv	48
6 ^b	10 % PPh ₃	2 CsPiv	43
7 ^c	10 % PPh ₃	2 CsPiv	35
8	10 % PPh ₃	2 CsOAc	30
9 ^d	10 % PPh ₃	2 Cs ₂ CO ₃	18
10	10 % PPh ₃	2 Et ₃ N	none ^e

^a All of the reactions were carried out employing **14** (0.0719 g, 0.25 mmol), ethyl acrylate (0.0375 g, 0.375 mmol),

Pd(OAc)₂ (2.8 mg, 0.0125 mmol) in 4 ml of DMF under 100 °C unless otherwise specified. ^b The reaction was carried

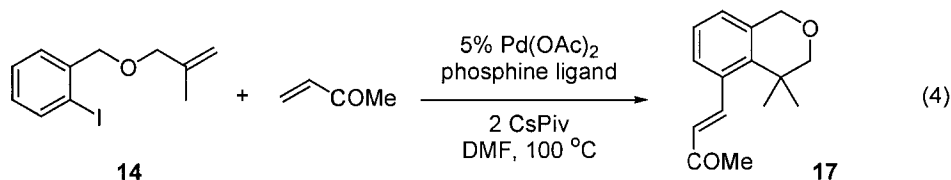
out with 0.075 g of ethyl acrylate (0.75 mmol). ^c The reaction was carried out with 0.025 g of ethyl acrylate (0.25 mmol).

^d Compound **16** was isolated in a 44% yield. ^e Product **16** was isolated in a 17% yield.

We next investigated the amount of ethyl acrylate used in the reaction. In all previous experiments, 1.5 equiv of ethyl acrylate were employed. When the amount was raised to 3 equiv, we were able to obtain **15** in only a 43% yield, and the reaction became more complicated, although we were unable to isolate and identify any of the minor side products formed (entry 6). Reducing the amount of the ethyl acrylate to 1.0 equiv significantly lowered the yield (entry 7). This might be caused by the high volatility of ethyl acrylate, resulting in a significant loss of ethyl acrylate during the reaction and hence a lower yield.

Since the nature of the base can be critical in this type of reaction,⁴ we examined a variety of bases. While CsOAc still promoted a clean reaction, affording **15** as the single product in a significantly lower yield (entry 8), Cs₂CO₃ afforded compound **16** instead as the major product, albeit in a rather low yield (entry 9). With Et₃N as the base, the reaction failed to produce any of the migration product **15**, and produced a 17% yield of Heck product **16**.

Although dppm and PPh₃ performed similarly when using ethyl acrylate as the olefin, a difference between dppm and PPh₃ was apparent when methyl vinyl ketone was utilized as the olefin (eq 4). Using 5 mol % dppm gave a 50 % yield, but 10 mol % PPh₃ gave only a 40% yield. Thus, we have employed dppm as the ligand for the rest of this investigation.



We next investigated a variety of olefins in this reaction (eq 5). To our surprise, not all olefins performed as well as ethyl acrylate and methyl vinyl ketone. As shown in Table 2, the reactions of many other olefins which usually give good results in traditional Heck reactions gave rather messy reactions and the isolated products were often hard to purify and identify.

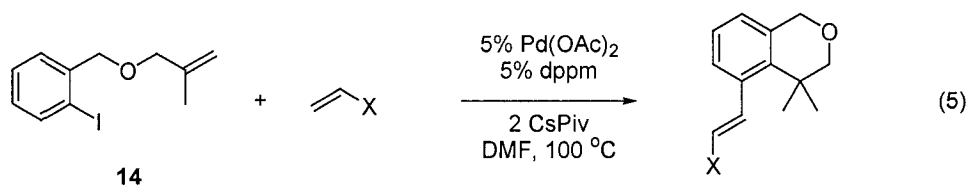


Table 2. Reactions of Compound 14 with Different Olefins (eq 5).

	olefin	% yield
1	$\text{H}_2\text{C}=\text{CHCO}_2\text{Et}$	56
2	$\text{H}_2\text{C}=\text{CHCOMe}$	50
3	$\text{H}_2\text{C}=\text{CHCO}_2\text{Bu-}t$	ca 30
4	$\text{H}_2\text{C}=\text{CHCO}_2\text{Bu-}n$	ca 25
5	$\text{H}_2\text{C}=\text{CHPh}$	ca 20
6	$\text{H}_2\text{C}=\text{CHCN}$	0
7	$\text{H}_2\text{C}=\text{CHCHO}$	0
8	$\text{H}_2\text{C}=\text{CHCH(OH)Me}$	0

Next we proceeded to define the scope and limitations of the rearrangement reaction utilizing different substrates and olefins under the optimal reaction

conditions summarized in Table 1, entry 1. The reaction of 2-bromobenzyl methallyl ether (**18**) with ethyl acrylate was much slower and afforded a lower yield of **15** (Table 3, entry 3) than the corresponding iodide **14**, presumably due to slow oxidative addition of the aryl bromide to Pd(0).

We studied the reaction of 2-iodobenzyl allyl ether (**19**) with ethyl acrylate in order to determine if the methyl group on the carbon-carbon double bond is necessary (entry 4). The reaction afforded no migration product. Instead, compound **20** was formed in a good yield. This discovery confirmed the significance of the substituent on the double bond. Also it indicates that β -hydride elimination is faster than the palladium migration (Scheme 6).

Scheme 6

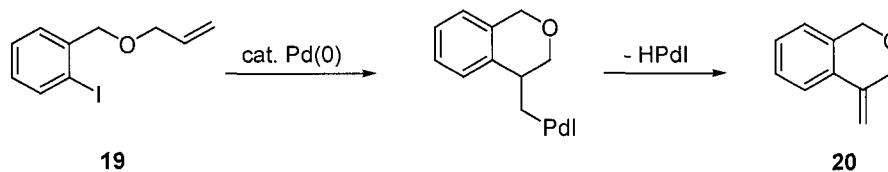
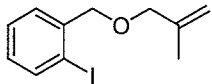
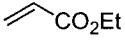
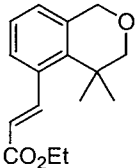
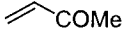
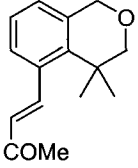
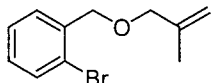
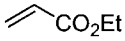
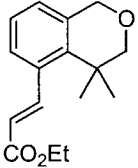
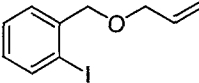
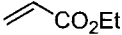
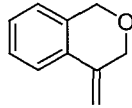
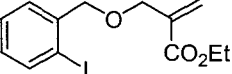
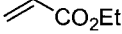
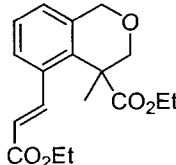
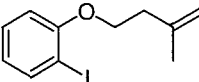
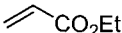
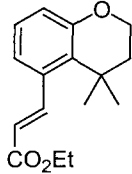
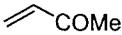
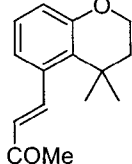
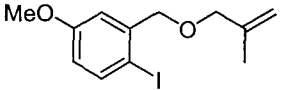
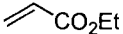
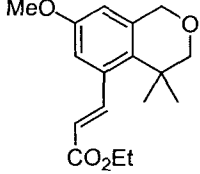
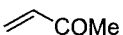
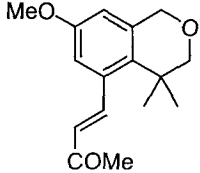
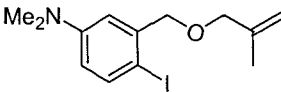
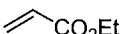
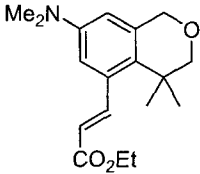
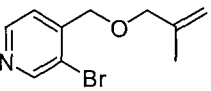
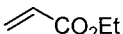
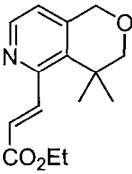


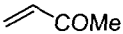
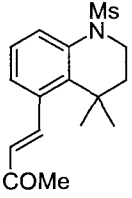
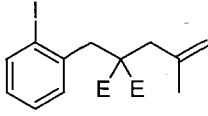
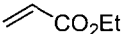
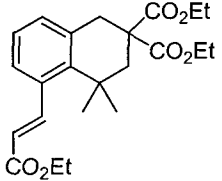
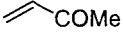
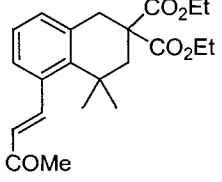
Table 3. Intramolecular Alkyl-to-Aryl Pd Rearrangement.^a

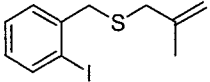
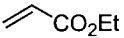
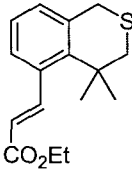
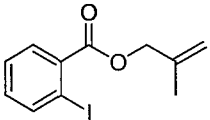
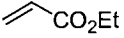
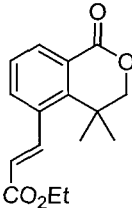
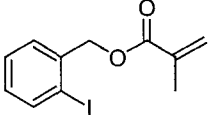
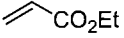
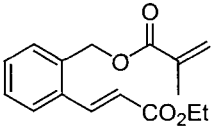
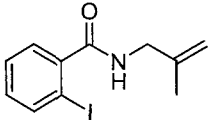
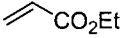
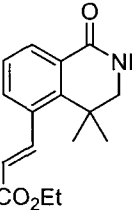
	substrate	olefin	time (h)	product	% yield
1			24		56
2	14		24		50
3 ^b			72		25

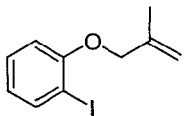
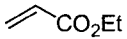
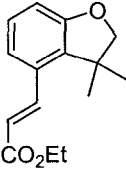
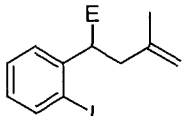
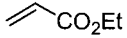
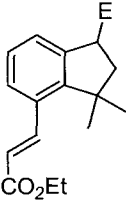
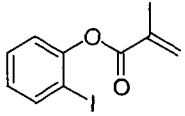
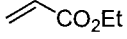
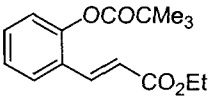
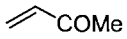
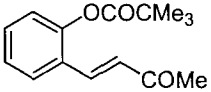
4		19		24		20	84
5		21		12		22	0
6		23		18		24	62
7	23			18		25	73

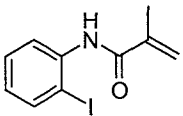
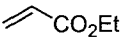
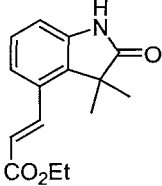
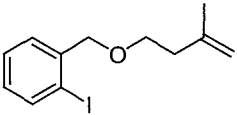
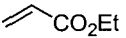
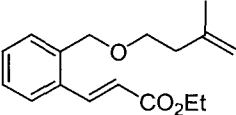
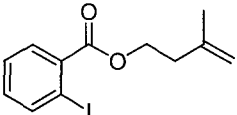
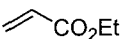
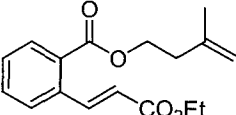
8		26		24		27	53
9	26			24		28	57
10		29		24		30	46
11		31		24		32	0

12		33		18		34	ca 30
13		35		12		36	64
14	35			15		37	67
15		38		15		39	58

16	38		16		40	63	
17	 E = CO ₂ Et	41		18		42	62
18	41		18		43	64	

19		44		24		45	0
20		46		24		47	0
21		48		18		49	75
22		50		18		51	0

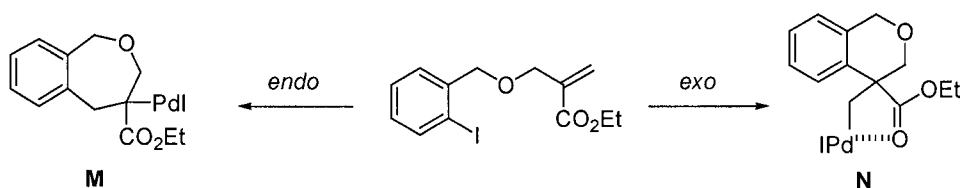
23		52		24		53	0
24	 E = CO ₂ Et	54		18		55	0
25		56		17		57	47
26	56			22		58	47

27		59		21		60	0
28		61		18		62	91
29		63		18		64	66

^a All reactions were run under the conditions summarized in Table 1, entry 1. ^b Fifteen percent of compound **18** was recovered.

The reaction of compound **21** and ethyl acrylate was not ideal and did not afford the desired product **22** (entry 5). There are two possible reasons for this disappointing result. (1) Palladium migration requires an *exo* cyclization of the arylpalladium intermediate to the carbon-carbon double bond, but the Heck reaction of this electron-deficient olefin is more likely to occur in an *endo* manner resulting in a seven-membered ring product **M** (Scheme 7). Thus, formation of a six-membered ring in this case is not easy or favored. Should *endo* cyclization occur, the palladium intermediate **M** formed is incapable of migration and would be expected to undergo β -hydrogen elimination. (2) Once the six-membered ring is formed, the palladium intermediate **N** (Scheme 7) might be stabilized via chelation of the neighboring carbonyl group. It might be difficult for the stabilized palladium intermediate to migrate.

Scheme 7



Compound **23** was prepared and allowed to react with ethyl acrylate and methyl vinyl ketone (entries 6 and 7). Structurally the rearrangement should happen, but the increased electron density on the arene would be expected to slow the oxidative addition, which is not good for the overall reaction. The results show

that the increased electron density caused by the oxygen attached to the aromatic ring does not hurt the reactions. In fact, it may facilitate Pd migration.

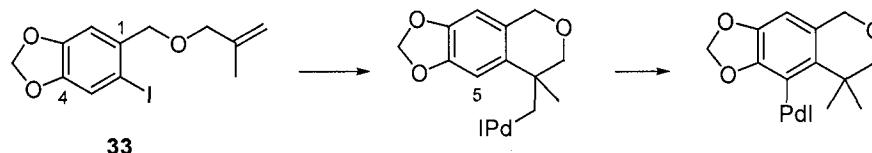
In an attempt to further investigate the influence of electronic effects on the reaction, compounds **26** and **29** were employed (entries 8-10). The reactions proceeded in decent yields. The migration products **27**, **28** and **30** were isolated as a single product from each of these reactions in reasonable yields. This again indicates that electron-rich substituents on the arene do not negatively impact the migration.

The electron-deficient substrate **31** did not afford any migration or direct Heck product at all (entry 11). Gallagher's results indicate that a pyridyl bromide will undergo palladium migration chemistry.³ Therefore, we considered that the failure of substrate **31** to afford any migration product was mainly due to its electron-deficient nature.

The reaction of another electron-rich substrate **33** was very messy (entry 12). The product **34** was isolated in a low yield and it proved difficult to purify. Two factors may account for this disappointing result. (1) Introduction of a second oxygen on the aromatic ring further increases the electron-density of the aryl iodide and therefore further slows down the oxidative addition step. (2) Introduction of the second oxygen at the 4 position causes steric hindrance to the migration. The migration terminus, the 5 position, is crowded with a methylenedioxy moiety and a tertiary carbon, making migration more difficult. When migration does occur, the arylpalladium intermediate formed is sterically hindered and may fail to undergo the Heck coupling (Scheme 8). According to another ongoing study of this type of

palladium rearrangement, it has been observed that the palladium migration can be completely inhibited by steric hindrance.²

Scheme 8

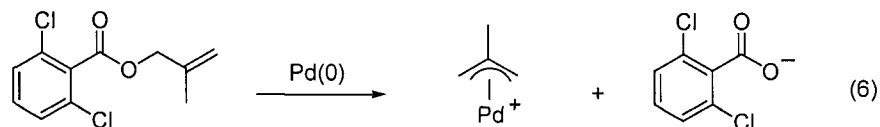


The reactions of *N*-2-iodobenzyl-*N*-(methallyl)methanesulfonamide (**35**) with ethyl acrylate and methyl vinyl ketone afforded the migration products **36** and **37** in 64% and 67% yields respectively under the standard reaction conditions (entries 13 and 14). The electron-rich isomeric compound **38** also gave good yields of migration products (entries 15 and 16). When compound **41** containing a 2-iodobenzyl and a methallyl moiety linked by a carbon was employed, the rearrangement products **42** and **43** were also cleanly isolated in good yields (entries 17 and 18).

However, 2-iodobenzyl methallyl thioether (**44**) did not afford any of the desired product **45** or the direct Heck product (entry 19). Eighty six percent of the starting material **44** was recovered after 24 h. The failure to react might be because the sulfur atom in the substrate can strongly chelate the palladium moiety in the initial arylpalladium intermediate and prevent further reaction.

The reaction of the carboxylic acid derivative **46** has also been examined (entry 20). Unfortunately, this compound failed to give the expected migration

product. Compound **46** may react to form a π -allylpalladium intermediate in the presence of a Pd(0) catalyst. It is well established that in the presence of a Pd(0) catalyst, allylic benzoates can form a π -allylpalladium intermediate after losing a benzoate ion (eq 6).⁷



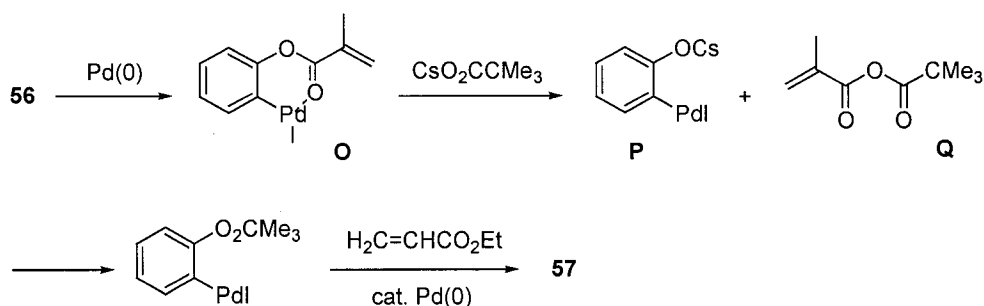
Compounds **48** and **50** are expected to be stable in the presence of a Pd(0) catalyst, but they did not produce the expected rearrangement products (entries 21 and 22). Compound **48** afforded the Heck product **49** in a 75% yield. The existence of a carbonyl group in the side chain can completely change the electronic and conformational properties of the intermediate analogous to intermediate **I** (Scheme 5). The carbonyl group may chelate the Pd moiety in the arylpalladium intermediate derived from **46**, **48** or **50** and presumably this reduces its reactivity.

We next extended our investigation to rearrangements involving five- and seven-membered ring systems. Compounds **52**, **54**, **56** and **59** were synthesized to study the migration in a five-membered ring system (entries 23-27). Compounds **52** and **54** (entries 23 and 24) did not afford any recognizable product under our "optimal" migration conditions. Compound **52** may not be stable at 100 °C because of a possible Claisen rearrangement. Alternatively, this substrate might react with Pd(0) to again form a π -allylpalladium intermediate, since a phenoxy group is a pretty good leaving group.⁸ However, no similar problems are

possible with substrate **54** and it too failed to afford any of the anticipated rearrangement product.

2-Iodophenyl methacrylate (**56**) generated surprising products with ethyl acrylate and methyl vinyl ketone (entries 25 and 26). The major products, **57** and **58**, were both direct Heck coupling products. However, the methacrylate moiety in these substrates was replaced by a pivalate group from the base. It is assumed that **57** is generated mechanistically as shown in Scheme 9 by the following steps:

Scheme 9



(1) oxidative addition of the aryl iodide to Pd(0) in **56** produces intermediate **O**, in which palladium chelates the carbonyl group and therefore enhances the electrophilicity of the carbonyl group, (2) addition/elimination of cesium pivalate to the carboxylate **O** affords intermediate phenolate **P** and anhydride **Q**, (3) reaction of **P** with the anhydride followed by a Heck reaction generates the isolated product **57**. Alternatively, it is highly possible that the Heck coupling of the arylpalladium intermediate precedes the ester exchange. No migration product was isolated. The ester exchange was further confirmed by isolating product **58** from the reaction

of substrate **56** and methyl vinyl ketone. *N*-2-Iodobenzyl methacrylamide (**59**) failed to afford any recognizable products when allowed to react with ethyl acrylate (entry 27).

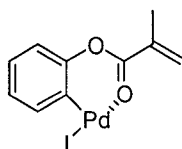
Compounds **61** and **63** were examined in order to determine if cyclization to a seven-membered ring could take place. No intramolecular cyclization products were obtained (entries 28 and 29). Only direct Heck products **62** and **64** were isolated in good yields.

Based on our present studies, the intramolecular palladium migration from an alkyl to an aryl position requires certain key structural features:

- (1) Migration occurs only when the cyclization involves formation of a six-membered ring. So far, no migration has been observed when a five or seven-membered ring is formed.
- (2) The rearrangement of an alkylpalladium to an arylpalladium intermediate is negatively affected when the migration terminus is sterically hindered.
- (3) No carboxylate derivatives have been observed to produce migration products no matter whether a five, six or seven-membered ring is being formed, even though the corresponding non-carbonyl substrates work well. This may indicate that the carbonyl group is somehow involved in a process that prevents the rearrangement from proceeding. For example, the carbonyl group might coordinate with the initial arylpalladium intermediate as depicted in Figure 1. If this intermediate is formed, it would direct the C=C bond away from the palladium and make it impossible for the palladium to add across the internal C=C bond. According to our proposed mechanism

(Scheme 5), when carbopalladation of the internal C=C bond by the arylpalladium intermediate cannot occur, no palladium rearrangement can take place either.

Figure 1



- (4) In no case have we observed products resulting from cyclization to an alkylpalladium intermediate which then undergoes coupling with the external olefin. Apparently palladium migration occurs faster than the Heck reaction of this hindered alkylpalladium intermediate under our reaction conditions.

Although we have clearly shown that palladium migration from an alkyl to an aryl position does occur, we also hoped to be able to find reaction conditions that would prevent migration and produce the product of cross-coupling between an alkylpalladium intermediate like **J** (Scheme 5) and the external olefin or perhaps the direct Heck coupling product like ester **16**. During earlier optimization studies of this type of palladium migration, we found that the nature of the base is very important in preventing migration (eq 7). Also, to enhance the direct Heck coupling at the expense of the migration process, the concentration of the olefin ethyl acrylate needs to be increased by raising the amount of ethyl acrylate and decreasing the amount of the solvent used. The results of our efforts to affect direct Heck coupling are summarized in Table 4. It is clear that employing Et₃N as

the base only afforded the non-migration product **16** and none of the cyclization/migration product **15**. No products derived from cyclization and subsequent alkylpalladium cross-coupling with the ethyl acrylate were ever observed. Therefore, we can control the migration by simply modifying the reaction conditions reported in Table 1, entry 1 to those shown in Table 4, entry 3.

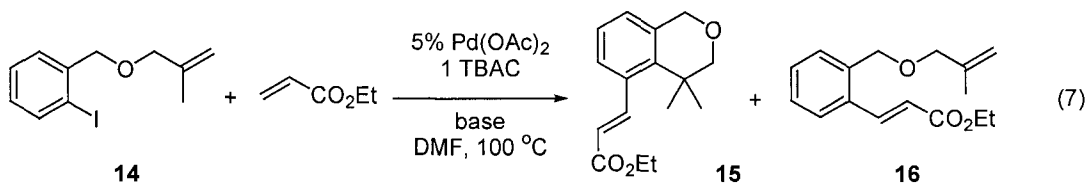


Table 4. Effect of the Base on the Heck Coupling of Substrate 14 (eq 7).^a

	base	% 15	% 16
1	NaHCO ₃	13	41
2	Cs ₂ CO ₃	20	59
3	Et ₃ N	0	64

^a All reactions were run with **14** (0.072 g, 0.25 mmol) and ethyl acrylate (0.10 g, 1.0 mmol) in the presence of 5 mol % Pd(OAc)₂ (2.8 mg, 0.0125 mmol), 1 equiv of TBAC (0.069 g, 0.25 mmol), and 2 equiv of the base indicated in 1 ml of DMF at 100 °C.

Conclusions

We have discovered and developed a new catalytic intramolecular alkyl-to-aryl palladium rearrangement involving the formation of a new 6-membered

ring and 2 new carbon-carbon bonds in a single reaction. After we optimized the reaction conditions and the olefins that can be employed in these Heck reactions, substrates with wide structural variety have been examined so we might better understand the reaction mechanism and the factors that affect the reaction.

Experimental Section

General. All ^1H and ^{13}C NMR spectra were recorded at 300 and 400, and 75.5 and 100.7 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) and a 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. Lower resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV.

2-Iodobenzyl methallyl ether (14). 2-Iodobenzyl chloride (0.2360 g, 1.0 mmol) was added to a suspension of NaH (60% suspension in mineral oil, 0.0676 g, 1.3 mmol) in 10 mL of DMF at 0 °C. The mixture was stirred for 10 min at 0 °C, followed by the addition of methallyl chloride (0.13 mL, 1.35 mmol). The resulting mixture was stirred at room temperature overnight, then diluted with diethyl ether, and washed with water. The combined organic layers were dried over anhydrous Na_2SO_4 , concentrated and purified by flash chromatography (12:1 hexanes/ethyl acetate) affording 0.2601 g (91%) of the indicated compound as a colorless oil: ^1H

NMR (CDCl₃) δ 1.80 (s, 3H), 4.20 (s, 2H), 4.47 (s, 2H), 4.95 (s, 1H), 5.05 (s, 1H), 6.98 (dt, J = 8.0, 1.2 Hz, 1H), 7.35 (t, J = 8.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.81 (dd, J = 8.0, 1.2 Hz, 1H); ¹³C NMR (CDCl₃) δ 19.84, 74.86, 75.93, 97.82, 112.71, 128.41, 128.86, 129.27, 139.31, 140.90, 142.22; IR (CHCl₃) 3022, 1610 cm⁻¹; HRMS: m/z 273.9860 (calcd for C₁₁H₁₃O, 273.9855).

General procedure for the Pd-catalyzed coupling. Ethyl (2E)-3-(4,4-dimethyl-3,4-dihydro-1H-isochromen-5-yl)propenoate (15). A 4-dram vial filled with **14** (0.0719 g, 0.25 mmol), Pd(OAc)₂ (2.8 mg, 0.0125 mmol), dppm (4.8 mg, 0.0125 mmol), CsPiv (0.1170 g, 0.5 mmol), ethyl acrylate (0.0375 g, 0.375 mmol) and DMF (4 mL) was quickly flushed with argon and heated up to 100 °C in an oil bath for 24 h. The reaction mixture was then diluted with ethyl ether, washed with satd NaHCO₃, dried over Na₂SO₄, concentrated, and purified by flash chromatography to afford **15** (36.4 mg, 56%) as a colorless oil: ¹H NMR (CDCl₃) δ 1.35 (t, J = 7.2 Hz, 3H), 1.39 (s, 6H), 3.54 (s, 2H), 4.28 (q, J = 7.2 Hz, 2H), 4.81 (s, 2H), 6.19 (d, J = 15.6 Hz, 1H), 6.98 (d, J = 7.2 Hz, 1H), 7.16 (t, J = 7.6 Hz, 1H), 7.31 (d, J = 7.6 Hz, 1H), 8.30 (d, J = 15.6 Hz, 1H); ¹³C NMR (CDCl₃) δ 14.50, 26.52, 34.05, 60.70, 69.64, 78.90, 119.78, 126.10, 126.32, 127.50, 134.89, 134.96, 141.50, 145.70, 167.03; IR (CHCl₃) 3056, 2962, 1711 cm⁻¹; HRMS: m/z 260.1416 (calcd for C₁₆H₂₀O₃, 260.1412).

(3E)-4-(4,4-Dimethyl-3,4-dihydro-1H-isochromen-5-yl)but-3-en-2-one (17). A yellow oil: ¹H NMR (CDCl₃) δ 1.40 (s, 6H), 2.40 (s, 3H), 3.55 (s, 2H), 4.81 (s, 2H), 6.49 (d, J = 15.6 Hz, 1H), 7.00 (d, J = 7.6 Hz, 1H), 7.18 (d, J = 7.6 Hz, 1H), 7.33 (d, J = 7.6 Hz, 1H), 8.16 (d, J = 15.6 Hz, 1H); ¹³C NMR (CDCl₃) δ 26.67, 28.12,

34.06, 69.66, 78.86, 126.38, 126.42, 127.49, 128.49, 134.83, 135.07, 141.75, 144.30, 198.34; IR (CHCl₃) 3056, 2966, 1707 cm⁻¹; HRMS: *m/z* 230.1311 (calcd for C₁₅H₁₈O₂, 230.1307).

2-Bromobenzyl methallyl ether (18). This compound was prepared by the same method used for 2-iodobenzyl methallyl ether (**14**), but employing 2-bromobenzyl alcohol and methallyl chloride. The resulting product is a colorless oil: ¹H NMR (CDCl₃) δ 1.79 (d, *J* = 0.6 Hz, 3H), 4.02 (s, 2H), 4.56 (s, 2H), 4.94-4.95 (m, 1H), 5.04-5.05 (m, 1H), 7.14 (m, 1H), 7.32 (td, *J* = 7.5, 1.2 Hz, 1H), 7.50-7.55 (m, 2H); ¹³C NMR (CDCl₃) δ 19.77, 71.42, 74.89, 112.66, 122.78, 127.58, 128.99, 129.14, 132.65, 138.04, 142.23; IR (CHCl₃) 3022, 1610 cm⁻¹; HRMS: *m/z* 240.0152 (calcd for C₁₁H₁₃BrO, 240.0150).

Allyl 2-iodobenzyl ether (19).⁹ This compound was prepared by the same method used for 2-iodobenzyl methallyl ether (**14**), but employing 2-iodobenzyl alcohol and allyl chloride. It was obtained as a colorless oil: ¹H NMR (CDCl₃) δ 4.11 (dt, *J* = 5.4, 1.2 Hz, 2H), 4.50 (s, 2H), 5.23 (dd, *J* = 10.2, 1.2 Hz, 1H), 5.35 (qt, *J* = 17.4, 1.5 Hz, 1H), 5.93-6.04 (m, 1H), 6.98 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.45 (d, *J* = 7.5 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H); ¹³C NMR (CDCl₃) δ 71.87, 76.08, 97.89, 117.53, 128.41, 128.88, 129.32, 134.72, 139.33, 140.78. See reference 7 for full characterization.

4-Methylene-3,4-dihydro-1*H*-isochroman (20). A colorless oil: ¹H NMR (CDCl₃) δ 4.45 (t, *J* = 1.2 Hz, 2H), 4.82 (s, 2H), 5.02 (s, 1H), 5.61 (s, 1H), 7.02-7.05 (m, 1H), 7.22-7.24 (m, 2H), 7.67-7.70 (m, 1H); ¹³C NMR (CDCl₃) δ 69.15, 71.18, 107.09, 123.62, 124.84, 127.15, 128.25, 131.23, 134.75, 138.48; IR (CHCl₃) 3010,

1613 cm^{-1} ; HRMS: m/z 146.1866 (calcd for $\text{C}_{10}\text{H}_{10}\text{O}$, 146.1863).

Ethyl 2-(2-iodobenzyloxymethyl)propenoate (21). A colorless oil: ^1H NMR (CDCl_3) δ 1.31 (t, $J = 7.2$ Hz, 3H), 4.24 (q, $J = 7.2$ Hz, 2H), 4.33 (s, 2H), 4.56 (s, 2H), 5.97 (s, 1H), 6.35 (s, 1H), 6.99-7.01 (m, 1H), 7.35 (t, $J = 7.2$ Hz, 1H), 7.46 (d, $J = 7.2$ Hz, 1H), 7.82 (d, $J = 8.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.42, 60.98, 76.72, 97.76, 126.12, 128.45, 128.82, 129.41, 137.42, 139.38, 140.53, 166.02; IR (CHCl_3) 3015, 1726 cm^{-1} ; HRMS: m/z 346.0071 (calcd for $\text{C}_{14}\text{H}_{15}\text{IO}_2$, 346.0066).

2-Iodophenyl 3-methyl-3-butenyl ether (23). This compound was prepared by the same method used for 2-iodobenzyl methallyl ether (**14**), but employing 2-iodophenol and 3-methyl-3-butenyl tosylate (see the following procedure for the preparation). It was obtained as a colorless oil: ^1H NMR (CDCl_3) δ 1.84 (s, 3H), 2.57 (t, $J = 6.9$ Hz, 2H), 4.12 (t, $J = 6.9$ Hz, 2H), 4.84-4.85 (m, 1H), 4.85-4.86 (m, 1H), 6.70 (td, $J = 7.5, 1.5$ Hz, 1H), 6.81 (dd, $J = 8.4, 1.2$ Hz, 1H), 7.25-7.31 (m, 1H), 7.76 (dd, $J = 7.8, 1.5$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 23.22, 37.31, 68.19, 86.89, 112.31, 112.60, 122.65, 129.57, 139.70, 142.29, 157.68; IR (CHCl_3) 3021, 1610 cm^{-1} ; HRMS: m/z 273.9860 (calcd for $\text{C}_{11}\text{H}_{13}\text{IO}$, 273.9855).

3-Methyl-3-butenyl tosylate.¹⁰ To a mixture of Et_3N (2.026 g, 20 mmol) and 3-methyl-3-buten-1-ol (0.8620 g, 10 mmol) in CH_2Cl_2 at 0 °C in an ice bath was slowly added *p*-tosyl chloride (1.909 g, 10 mmol). The reaction mixture was stirred at 0 °C for 3 h, then diluted with CH_2Cl_2 , washed by 10% aq HCl solution, 10% aq NaHCO_3 solution, and water and then concentrated, dried over anhydrous Na_2SO_4 to afford the indicated compound (2.015 g, 84%) as a yellow oil, used without further purification.

Ethyl (2E)-3-(4,4-dimethyl-3,4-dihydro-2H-chromen-5-yl)propenoate (24).

A yellow oil: ^1H NMR (CDCl_3) δ 1.34 (t, $J = 7.2$ Hz, 3H), 1.46 (s, 6H), 1.84 (t, $J = 7.2$ Hz, 2H), 4.15 (t, $J = 7.2$ Hz, 1H), 4.27 (q, $J = 7.2$ Hz, 2H), 6.18 (d, $J = 15.6$ Hz, 1H), 6.84 (dd, $J = 7.5, 1.5$ Hz, 1H), 6.98-7.10 (m, 2H), 8.32 (d, $J = 15.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.52, 30.42, 31.64, 41.12, 60.68, 62.54, 119.50, 119.64, 121.62, 127.40, 129.92, 136.03, 146.28, 154.69, 169.18; IR (CHCl_3) 3018, 2966, 1712 cm^{-1} ; HRMS: m/z 260.1416 (calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3$, 260.1412).

(3E)-4-(4,4-Dimethyl-3,4-dihydro-2H-chromen-5-yl)but-3-en-2-one (25).

A yellow oil: ^1H NMR (CDCl_3) δ 1.47 (s, 6H), 1.85 (t, $J = 5.2$ Hz, 2H), 2.38 (s, 3H), 4.15 (t, $J = 5.2$ Hz, 2H), 6.47 (d, $J = 15.0$ Hz, 1H), 6.86 (dd, $J = 6.0, 0.9$ Hz, 1H), 7.01 (dd, $J = 5.7, 1.2$ Hz, 1H), 7.09 (t, $J = 5.7$ Hz, 1H), 8.17 (d, $J = 15.0$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 28.23, 30.53, 31.64, 41.09, 62.50, 119.77, 121.58, 127.46, 128.30, 130.06, 135.95, 144.81, 154.74, 198.32; IR (CHCl_3) 3020, 2964, 1705 cm^{-1} ; HRMS: m/z 230.1311 (calcd for $\text{C}_{15}\text{H}_{18}\text{O}_2$, 230.1307).

2-Iodo-5-methoxybenzyl methallyl ether (26). This compound was prepared by the same method used for 2-iodobenzyl methallyl ether (14), but employing 2-iodo-5-methoxybenzyl alcohol¹¹ and methallyl chloride. It was obtained as a colorless oil: ^1H NMR (CDCl_3) δ 1.80 (s, 3H), 3.80 (s, 3H), 4.02 (s, 2H), 4.43 (s, 2H), 4.95 (s, 1H), 5.05 (d, $J = 0.8$ Hz, 1H), 6.59 (dd, $J = 8.4, 3.2$ Hz, 1H), 7.08 (d, $J = 3.2$ Hz, 1H), 7.66 (d, $J = 8.4$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.86, 55.57, 74.83, 75.72, 85.74, 112.69, 114.44, 115.38, 139.65, 141.91, 142.14, 160.24; IR (CHCl_3) 3032, 1640, 1210 cm^{-1} ; HRMS: m/z 318.0123 (calcd for $\text{C}_{12}\text{H}_{15}\text{O}_2$, 318.0117).

Ethyl (2E)-3-(7-methoxy-4,4-dimethyl-3,4-dihydro-1H-isochromen-5-yl)-propenoate (27). A colorless oil: ^1H NMR (CDCl_3) δ 1.34-1.37 (m, 9H), 3.52 (s, 2H), 3.79 (s, 3H), 4.28 (q, $J = 7.2$ Hz, 2H), 4.78 (s, 2H), 6.19 (d, $J = 15.6$ Hz, 1H), 6.51 (d, $J = 2.4$ Hz, 1H), 6.86 (d, $J = 2.8$ Hz, 1H), 8.27 (d, $J = 7.2$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.55, 26.77, 33.61, 55.48, 60.82, 69.85, 79.15, 110.80, 113.20, 119.96, 133.95, 136.18, 136.34, 145.60, 157.45, 167.01; IR (CHCl_3) 3020, 2952, 1712 cm^{-1} ; HRMS: m/z 290.1524 (calcd for $\text{C}_{17}\text{H}_{22}\text{O}_4$, 290.1518).

(3E)-4-(7-Methoxy-4,4-dimethyl-3,4-dihydro-1H-isochromen-5-yl)but-3-en-2-one (28). A yellow oil: ^1H NMR (CDCl_3) δ 1.36 (s, 6H), 2.40 (s, 3H), 3.53 (s, 2H), 3.79 (s, 3H), 4.77 (s, 2H), 6.48 (d, $J = 15.6$ Hz, 1H), 6.53 (d, $J = 2.1$ Hz, 1H), 6.88 (d, $J = 2.1$ Hz, 1H), 8.12 (d, $J = 15.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 26.91, 28.10, 33.60, 55.50, 69.86, 79.11, 111.06, 113.20, 128.69, 134.20, 136.14, 136.48, 144.18, 157.53, 198.38; IR (CHCl_3) 3020, 2954, 1707 cm^{-1} ; HRMS: m/z 260.1416 (calcd for $\text{C}_{16}\text{H}_{20}\text{O}_3$, 260.1412).

5-Dimethylamino-2-iodobenzyl methallyl ether (29). This compound was prepared by the same method used to prepare 2-iodobenzyl methallyl ether (**14**), but employing 5-dimethylamino-2-iodobenzyl alcohol¹² and methallyl chloride. It was obtained as a colorless oil: ^1H NMR (CDCl_3) δ 1.80 (s, 3H), 2.93 (s, 6H), 4.00 (s, 2H), 4.43 (s, 2H), 4.94 (d, $J = 0.4$ Hz, 1H), 5.05 (d, $J = 1.2$ Hz, 1H), 6.38 (dd, $J = 8.8, 3.2$ Hz, 1H), 6.87 (d, $J = 3.2$ Hz, 1H), 7.65 (d, $J = 8.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.88, 40.63, 74.64, 76.02, 80.90, 112.50, 113.75, 139.16, 139.18, 140.64, 142.32, 150.80; IR (CHCl_3) 3020, 1625 cm^{-1} ; HRMS: m/z 331.0441 (calcd for $\text{C}_{14}\text{H}_{18}\text{INO}$, 331.0433).

Ethyl (2E)-3-[7-(dimethylamino)-4,4-dimethyl-3,4-dihydro-1H-isochromen-5-yl]propenoate (30). A colorless oil: ^1H NMR (CDCl_3) δ 1.34-1.37 (m, 9H), 2.93 (s, 6H), 3.51 (s, 2H), 4.28 (q, $J = 7.2$ Hz, 2H), 4.77 (s, 2H), 6.20 (d, $J = 15.6$ Hz, 1H), 6.33 (d, $J = 3.2$ Hz, 1H), 8.30 (d, $J = 15.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.55, 26.87, 33.30, 40.66, 60.71, 70.10, 79.35, 109.44, 111.81, 119.34, 129.75, 135.50, 135.65, 146.72, 148.51, 167.16; IR (CHCl_3) 3022, 1712 cm^{-1} ; HRMS: m/z 303.1842 (calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_3$, 303.1834).

6-Iodopiperonyl methallyl ether (33). This compound was prepared by the same method used for 2-iodobenzyl methallyl ether (**14**), but employing (6-iodo-1,3-benzodioxo-5-yl)methanol¹³ and methallyl chloride. It was obtained as a colorless oil: ^1H NMR (CDCl_3) δ 1.79 (s, $J = 0.3$ Hz, 3H), 3.98 (s, 2H), 4.94-4.95 (m, 1H), 5.02-5.03 (m, 1H), 5.96 (s, 2H), 7.00 (s, 1H), 7.23 (s, 1H); ^{13}C NMR (CDCl_3) δ 19.84, 74.67, 75.79, 85.68, 101.79, 109.34, 112.72, 118.62, 134.42, 142.19, 147.94, 148.68; IR (CHCl_3) 3032, 1620 cm^{-1} ; HRMS: m/z 331.9914 (calcd for $\text{C}_{12}\text{H}_{13}\text{IO}_3$, 331.9910).

N-2-Iodobenzyl-N-(methallyl)methanesulfonamide (35). This compound was prepared by the same method used for 2-iodobenzyl methallyl ether (**14**), but employing 2-iodobenzyl chloride and *N*-(methallyl)methanesulfonamide (see the following procedure for the preparation). It was obtained as a colorless oil: ^1H NMR (CDCl_3) δ 1.71 (s, 3H), 2.96 (s, 3H), 3.82 (s, 2H), 4.56 (s, 2H), 4.89 (s, 1H), 4.92 (s, 1H), 6.98 (td, $J = 7.5, 1.5$ Hz, 1H), 7.37 (dd, $J = 7.8, 0.9$ Hz, 1H), 7.50 (dd, $J = 7.5, 1.5$ Hz, 1H), 7.81 (dd, $J = 7.8, 0.9$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 20.36, 40.22, 53.86, 55.92, 98.64, 114.70, 128.70, 129.13, 129.44, 138.30, 139.64, 139.66; IR

(CHCl₃) 3020, 1620, 1352 cm⁻¹; HRMS: *m/z* 364.9773 (calcd for C₁₂H₁₆INO₂S, 364.9769).

***N*-(Methallyl)methanesulfonamide.**¹⁴ Methallylamine (0.2240 g, 3.15 mmol) was placed in a 25-ml flame-dried, round bottom flask, sealed with a rubber septum, and maintained under a slight flow of N₂. Dry CH₂Cl₂ (5 ml) was added, followed by Et₃N (0.44 ml, 3.15 mmol), and the solution was cooled to -78 °C. Methanesulfonyl chloride (0.24 ml, 3.17 mmol) was added dropwise by a syringe. The reaction was stirred at -78 °C under N₂ for 1 h, and then quenched by pouring onto ice. After extraction with ether, the combined ether solution was washed with water, 10% aq NaHCO₃ solution, and water and then dried over Na₂SO₄. *N*-(Methallyl)methanesulfonamide (0.4188 g, 89%) was obtained as a colorless oil: ¹H NMR (CDCl₃) δ 1.79 (d, *J* = 0.3 Hz, 3H), 2.97 (s, 3H), 3.69 (m, 2H), 4.64 (br s, 1H), 4.93-4.95 (m, 1H), 4.99-5.00 (m, 1H); ¹³C NMR (CDCl₃) δ 20.24, 41.06, 49.12, 112.96, 141.12. See reference 14 for full characterization.

Ethyl (2*E*)-3-(4,4-dimethyl-2-methanesulfonyl-1,2,3,4-tetrahydroisoquinolin-5-yl)propenoate (36). A pale yellow solid: mp 108-109 °C; ¹H NMR (CDCl₃) δ 1.35 (t, *J* = 7.2 Hz, 3H), 1.48 (s, 6H), 2.89 (s, 3H), 3.14 (s, 2H), 4.29 (q, *J* = 7.2 Hz, 2H), 4.42 (s, 2H), 6.18 (d, *J* = 15.6 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 7.20 (t, *J* = 7.5 Hz, 1H), 7.33 (d, *J* = 6.9 Hz, 1H), 8.28 (d, *J* = 15.6 Hz, 1H); ¹³C NMR (CDCl₃) δ 14.48, 27.54, 34.87, 36.39, 49.23, 58.25, 60.80, 120.25, 126.76, 128.32, 128.43, 131.94, 135.26, 141.18, 145.69, 166.88; IR (CHCl₃) 3040, 2985, 1712, 1360 cm⁻¹; HRMS: *m/z* 337.1353 (calcd for C₁₇H₂₃NO₄S, 337.1348).

(3*E*)-4-(4,4-Dimethyl-2-methanesulfonyl-1,2,3,4-tetrahydroisoquinolin-5-

yl)but-3-en-2-one (37). A white solid: mp 149-150 °C; ^1H NMR (CDCl_3) δ 1.49 (s, 6H), 2.40 (s, 3H), 2.90 (s, 3H), 3.15 (s, 2H), 4.43 (s, 2H), 6.48 (d, $J = 15.6$ Hz, 1H), 7.10 (d, $J = 7.5$ Hz, 1H), 7.22 (t, $J = 7.5$ Hz, 1H), 7.34 (dd, $J = 7.5, 0.6$ Hz, 1H), 8.14 (d, $J = 15.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 27.68, 28.23, 34.89, 36.41, 49.26, 58.24, 126.85, 128.42, 128.57, 128.80, 132.07, 135.25, 141.42, 144.20, 198.13; IR (CHCl_3) 3032, 2984, 1707, 1360 cm^{-1} ; HRMS: m/z 307.1246 (calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3\text{S}$, 307.1242).

***N*-2-iodophenyl-*N*-(3-methyl-3-butenyl)methanesulfonamide (38).** This compound was prepared by the same method used to prepare 2-iodobenzyl methallyl ether (14), but employing *N*-(2-iodobenzyl)methanesulfonamide (see the following procedure for the preparation) and 4-iodo-2-methylbut-1-ene¹⁰ (3-methyl-3-butenyl tosylate did not work). It was obtained as a colorless oil: ^1H NMR (CDCl_3) δ 1.69 (s, 3H), 2.29 (t, $J = 8.1$ Hz, 2H), 3.07 (s, 3H), 3.59-3.92 (m, 2H), 4.69 (s, 1H), 4.78 (s, 1H), 7.05-7.11 (m, 1H), 7.38-7.46 (m, 2H), 7.94 (dd, $J = 7.8$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 22.68, 36.83, 40.91, 50.00, 101.60, 112.26, 129.31, 130.30, 132.48, 140.60, 141.05, 142.09; IR (CHCl_3) 3056, 1620, 1350 cm^{-1} ; HRMS: m/z 364.9773 (calcd for $\text{C}_{12}\text{H}_{16}\text{INO}_2\text{S}$, 364.9769).

***N*-(2-iodophenyl)methanesulfonamide.**¹⁵ Methanesulfonyl chloride (0.6 ml, 6.0 mmol), 2-iodoaniline (1.096 g, 5.0 mmol) and 4-(dimethylamino)pyridine (0.062 g, 0.5 mmol) were dissolved in Et_3N (10 ml), and the resulting mixture was heated under reflux for 12 h. The reaction mixture was allowed to cool, diluted with CH_2Cl_2 and washed with 2 M aq HCl and 2 M aq NaOH. The combined aqueous extracts were acidified with conc HCl and then extracted with CH_2Cl_2 . The

combined organic extracts were dried over MgSO_4 and then concentrated, affording the indicated compound in a 70% yield (1.043 g). See reference 15 for full characterization.

Ethyl (2E)-3-(4,4-dimethyl-1-methanesulfonyl-1,2,3,4-tetrahydroisoquinolin-5-yl)propenoate (39). A pale yellow solid: mp 120-121 °C; ^1H NMR (CDCl_3) δ 1.35 (t, $J = 7.2$ Hz, 3H), 1.47 (s, 6H), 1.85-1.87 (m, 2H), 2.92 (s, 3H), 3.80-3.83 (m, 2H), 4.28 (q, $J = 7.2$ Hz, 2H), 6.15 (d, $J = 15.2$, 1H), 7.16-7.23 (m, 2H), 7.74 (dd, $J = 8.0, 1.6$ Hz, 1H), 8.36 (d, $J = 15.2$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.50, 30.44, 33.96, 39.88, 41.16, 42.90, 60.82, 120.70, 125.20, 126.73, 126.95, 139.30, 136.34, 136.78, 146.49, 166.91; IR (CHCl_3) 2956, 1712, 1355 cm^{-1} ; HRMS: m/z 337.1353 (calcd for $\text{C}_{17}\text{H}_{23}\text{NO}_4\text{S}$, 337.1348).

(3E)-4-(4,4-Dimethyl-1-methanesulfonyl-1,2,3,4-tetrahydroisoquinolin-5-yl)but-3-en-2-one (40). A white solid: mp 135-137 °C; ^1H NMR (CDCl_3) δ 1.48 (s, 6H), 1.86-1.89 (m, 2H), 2.39 (s, 3H), 2.94 (s, 3H), 3.80-3.83 (m, 2H), 6.46 (d, $J = 15.6$ Hz, 1H), 7.18-7.24 (m, 2H), 7.75 (dd, $J = 7.6, 1.6$ Hz, 1H), 8.22 (d, $J = 15.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 28.46, 30.51, 33.93, 39.89, 41.12, 42.83, 125.36, 126.64, 126.97, 129.05, 136.24, 136.49, 136.82, 144.90, 198.04; IR (CHCl_3) 2960, 1707, 1355 cm^{-1} ; HRMS: m/z 307.1246 (calcd for $\text{C}_{16}\text{H}_{21}\text{NO}_3\text{S}$, 307.1242).

Diethyl 2-(2-iodobenzyl)-2-(methallyl)malonate (41). This compound was prepared by the same method used for 2-iodobenzyl methallyl ether (**14**), but employing diethyl 2-(2-iodobenzyl)malonate and methallyl chloride. It was obtained as a colorless oil: ^1H NMR (CDCl_3) δ 1.16 (t, $J = 7.2$ Hz, 6H), 1.71 (s, 3H), 2.81 (s, 2H), 3.53 (s, 2H), 4.06-4.17 (m, 4H), 4.75 (m, 1H), 4.88 (t, $J = 1.5$ Hz, 1H),

6.87 (td, $J = 7.5, 1.5$ Hz, 1H), 7.23 (td, $J = 7.2, 1.2$ Hz, 1H), 7.35 (dd, $J = 7.8, 1.8$ Hz, 1H), 7.81 (dd, $J = 8.1, 1.2$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.02, 23.83, 42.30, 43.11, 58.36, 61.63, 103.19, 115.53, 128.15, 128.47, 130.38, 139.89, 140.49, 141.07, 171.24; IR (CHCl_3) 2969, 1760, 1741 cm^{-1} ; HRMS: m/z 430.0652 (calcd for $\text{C}_{18}\text{H}_{19}\text{IO}_4$, 430.0641).

Diethyl 5-[(1E)-3-ethoxy-3-oxoprop-1-enyl]-4,4-dimethyl-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (42). A colorless oil: ^1H NMR (CDCl_3) δ 1.25 (t, $J = 7.2$ Hz, 6H), 1.34 (t, $J = 7.2$ Hz, 3H), 1.41 (s, 6H), 2.33 (s, 2H), 3.24 (s, 2H), 4.12-4.30 (m, 6H), 6.10 (d, $J = 15.3$ Hz, 1H), 7.11-7.27 (m, 3H), 8.37 (d, $J = 15.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.14, 14.50, 31.15, 35.12, 36.76, 46.28, 51.28, 60.64, 61.60, 120.09, 126.56, 128.41, 131.24, 134.32, 135.10, 141.79, 147.44, 167.12, 171.76; IR (CHCl_3) 1760, 1740, 1712 cm^{-1} ; HRMS: m/z 402.2042 (calcd for $\text{C}_{23}\text{H}_{30}\text{O}_6$, 402.2053).

Diethyl 4,4-dimethyl-5-[(1E)-(3-oxobut-1-enyl)-3,4-dihydronaphthalene-2,2(1H)-dicarboxylate (43). A colorless oil: ^1H NMR (CDCl_3) δ 1.25 (t, $J = 7.2$ Hz, 6H), 1.42 (s, 6H), 2.34 (s, 2H), 2.37 (s, 3H), 3.25 (s, 2H), 4.13-4.23 (m, 4H), 6.41 (d, $J = 15.6$ Hz, 1H), 7.12-7.26 (m, 3H), 8.23 (d, $J = 15.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.13, 28.16, 31.29, 35.14, 36.74, 46.28, 51.80, 61.63, 126.62, 128.36, 128.86, 131.49, 134.44, 135.03, 141.99, 146.03, 171.72, 198.36; IR (CHCl_3) 1760, 1740, 1707 cm^{-1} ; HRMS: m/z 372.1941 (calcd for $\text{C}_{22}\text{H}_{19}\text{O}_5$, 372.1937).

2-Iodobenzyl methallyl sulfide (44). This compound was prepared by the same method used for 2-iodobenzyl methallyl ether (**14**), but employing 2-iodobenzyl thiol (see the following procedure for the preparation) and methallyl

chloride. It was obtained as a colorless oil: ^1H NMR (CDCl_3) δ 1.85 (t, $J = 0.9$ Hz, 3H), 3.10 (d, $J = 0.9$ Hz, 2H), 3.71 (s, 2H), 4.89 (q, $J = 0.9$ Hz, 1H), 4.92 (t, $J = 1.5$ Hz, 1H), 6.93 (dt, $J = 7.5, 1.5$ Hz, 1H), 7.26-7.36 (m, 2H), 7.84 (dd, $J = 7.8, 1.2$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 21.12, 39.51, 40.69, 101.03, 114.19, 128.40, 128.82, 130.23, 140.04, 140.99, 141.31; IR (CHCl_3) 3055, 1624 cm^{-1} ; HRMS: m/z 303.9789 (calcd for $\text{C}_{11}\text{H}_{13}\text{IS}$, 303.9783).

2-Iodobenzyl thiol.¹⁶ 2-Iodobenzyl chloride (1.008 g, 4.30 mmol) was added to a solution of thiourea (0.6321 g, 8.3 mmol) in dioxane (10 ml). The mixture was slowly warmed to 95 °C. An oily phase separated and the reaction mixture was refluxed for an additional 3 h. After the mixture was allowed to cool, aq NaOH (1.07 g in 3 ml of water) was added. After refluxing an additional 3 h, the solution was acidified with dilute H_2SO_4 and extracted with hexanes. The organic layer was washed with water, dried over anhydrous Na_2SO_4 and concentrated, affording a crude product suitable for use without further purification.

Methallyl 2-iodobenzoate (46). Methallyl alcohol (0.2480 g, 3.44 mmol) in dry pyridine was cooled to 0 °C. 2-Iodobenzoyl chloride (0.8304 g, 3.16 mmol) was added and stirred for 6 h at room temperature. The reaction mixture was quenched by adding ice, and extracted using dichloromethane. The organic layer was then washed successively with cold 5% aq HCl solution, 5% aq NaHCO_3 solution and brine, and dried over Na_2SO_4 and concentrated, affording the indicated compound (0.8314 g, 87 %) as a colorless oil: ^1H NMR (CDCl_3) δ 1.86 (s, 3H), 4.76 (s, 2H), 5.01 (s, 1H), 5.10 (s, 1H), 7.16 (td, $J = 7.8, 1.8$ Hz, 1H), 7.41 (td, $J = 7.8, 1.2$ Hz, 1H), 7.84 (dd, $J = 7.8, 1.8$ Hz, 1H), 8.01 (dd, $J = 7.8, 1.2$ Hz, 1H); ^{13}C NMR

(CDCl₃) δ 19.99, 69.12, 94.35, 113.97, 128.12, 131.17, 132.88, 135.28, 139.77, 141.60, 166.37; IR (CHCl₃) 1727, 1622 cm⁻¹; HRMS: m/z 301.9810 (calcd for C₁₁H₁₁O₂, 301.9804).

2-Iodobenzyl methacrylate (48). To 1.0 g of powdered 3 Å molecular sieves and 2-iodobenzyl alcohol (0.7018 g, 3.0 mmol) in a stirred solution of 5 ml of CCl₄ was added methacryloyl chloride (0.37 ml, 3.75 mmol). The reaction mixture was heated to reflux for 24 h. The mixture was then filtered. The filtrate was concentrated, and then chromatographed (6:1 hexanes/ethyl acetate), affording the indicated compound (0.6825 g, 75%) as a colorless oil: ¹H NMR (CDCl₃) δ 1.99 (dd, J = 1.5, 1.5 Hz, 3H), 5.20 (s, 2H), 5.62 (qt, J = 1.5 Hz, 1H), 6.21 (dd, J = 1.5, 1.5 Hz, 1H), 7.03 (td, J = 6.6, 2.1 Hz, 1H), 7.35-7.41 (m, 2H), 7.86 (dd, J = 7.8, 0.9 Hz, 1H); ¹³C NMR (CDCl₃) δ 18.58, 70.30, 98.43, 126.36, 128.51, 129.60, 129.99, 136.24, 138.70, 139.72, 167.11; IR (CHCl₃) 1724, 1610 cm⁻¹; HRMS: m/z 301.9810 (calcd for C₁₁H₁₁O₂, 301.9804).

2-[(1E)-3-Ethoxy-3-oxoprop-1-enyl]benzyl 2-methylpropenoate (49). A colorless oil: ¹H NMR (CDCl₃) δ 1.34 (t, J = 7.2 Hz, 3H), 1.95 (q, J = 0.9 Hz, 3H), 4.27 (q, J = 7.2 Hz, 2H), 5.32 (s, 2H), 5.58 (quintet, J = 1.5 Hz, 1H), 6.14 (m, 1H), 6.39 (d, J = 15.9 Hz, 1H), 7.36-7.45 (m, 3H), 7.61-7.64 (m, 1H), 8.01 (d, J = 15.9 Hz, 1H); ¹³C NMR (CDCl₃) δ 14.46, 18.45, 60.75, 64.43, 120.89, 126.26, 127.04, 129.06, 130.12, 130.20, 134.20, 135.03, 136.18, 141.29, 166.74, 167.08; IR (CHCl₃) 1724, 1711, 1620 cm⁻¹; HRMS: m/z 274.3129 (calcd for C₁₆H₁₈O₄, 274.3125).

2-Iodophenyl methallyl ether (52).¹⁷ This compound was prepared by the

same method used for 2-iodobenzyl methallyl ether (**14**), but employing 2-iodophenol and methallyl chloride. It was obtained as a colorless oil: ^1H NMR (CDCl_3) δ 1.87 (s, 3H), 4.48 (s, 2H), 5.02 (s, 1H), 5.20 (s, 1H), 6.71 (td, $J = 7.6, 1.2$ Hz, 1H), 6.80 (dd, $J = 7.6, 0.8$ Hz, 1H), 7.26-7.30 (m, 1H), 7.78 (dd, $J = 7.6, 1.6$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 19.67, 72.72, 86.77, 112.49, 113.13, 122.77, 129.55, 139.70, 140.43, 157.36. See reference 17 for full characterization.

Ethyl 2-(2-iodophenyl)-4-methylpent-4-enoate (54). This compound was prepared by the same method used for 2-iodobenzyl methallyl ether (**14**), but employing ethyl (2-iodophenyl)acetate (see the following procedure for the preparation) and methallyl chloride. It was obtained as a colorless oil: ^1H NMR (CDCl_3) δ 1.21 (t, $J = 7.2$ Hz, 3H), 1.78 (s, 3H), 2.38-2.44 (m, 1H), 2.69-2.77 (m, 1H), 4.04-4.20 (m, 2H), 4.26 (dd, $J = 9.1, 4.5$ Hz, 1H), 4.73 (s, 1H), 4.77 (s, 1H), 6.94 (td, $J = 7.5, 1.5$ Hz, 1H), 7.31 (td, $J = 7.5, 1.2$ Hz, 1H), 7.40 (dt, $J = 8.4, 1.8$ Hz, 1H), 7.85 (dd, $J = 8.4, 1.5$ Hz, 1H); ^{13}C NMR (CDCl_3) δ 14.34, 22.91, 41.41, 53.65, 61.12, 101.71, 112.65, 128.05, 128.76, 129.04, 139.99, 141.83, 142.53, 173.15; IR (CHCl_3) 1743, 1640 cm^{-1} ; HRMS: m/z 344.0279 (calcd for $\text{C}_{14}\text{H}_{17}\text{IO}_2$, 344.0273).

Ethyl (2-iodophenyl)acetate.¹⁸ To a 50-ml round-bottom flask was added (2-iodophenyl)acetic acid (0.8652 g, 3.30 mmol), ethanol (10 ml) and conc H_2SO_4 (0.3 ml). The mixture was refluxed for 3 h, then poured into 30 ml of 5% aq NaHCO_3 solution, extracted with ethyl ether, dried over Na_2SO_4 , and concentrated, affording the indicated compound (0.8577 g, 90%) as a colorless oil: ^1H NMR (CDCl_3) δ 1.28 (t, $J = 7.2$ Hz, 3H), 3.79 (s, 3H), 4.19 (q, $J = 7.2$ Hz, 2H), 6.96 (td, $J =$

7.2, 2.0 Hz, 1H), 7.27-7.34 (m, 2H), 7.85 (d, $J = 7.6$ Hz, 1H). See reference 18 for full characterization.

2-Iodophenyl methacrylate (56). This compound was prepared by the same method used for 2-iodobenzyl methacrylate (48), but employing 2-iodophenol and methacryloyl chloride. It was obtained as a colorless oil: ^1H NMR (CDCl_3) δ 2.11 (s, 3H), 5.82 (t, $J = 1.2$ Hz, 1H), 6.46 (s, 1H), 6.98 (td, $J = 7.6$, 1.2 Hz, 1H), 7.15 (dd, $J = 8.0$, 1.2 Hz, 1H), 7.38 (td, $J = 8.0$, 1.2 Hz, 1H), 7.84 (dd, $J = 7.6$, 1.2 Hz, 1H); ^{13}C NMR (CDCl_3) δ 18.64, 90.52, 123.29, 127.71, 128.35, 129.59, 135.71, 139.62, 151.47, 165.14; IR (CHCl_3) 1725, 1615 cm^{-1} ; HRMS: m/z 287.9651 (calcd for $\text{C}_{10}\text{H}_9\text{IO}_2$, 287.9647).

Ethyl (2E)-3-{2-[(2,2-dimethylpropanoyl)oxy]phenyl}propenoate (57). A colorless oil: ^1H NMR (CDCl_3) δ 1.32 (t, $J = 7.2$ Hz, 1H), 1.42 (s, 9H), 4.25 (q, $J = 7.2$ Hz, 2H), 6.42 (d, $J = 16.0$ Hz, 1H), 7.07 (d, $J = 8.0$ Hz, 1H), 7.24-7.27 (m, 1H), 7.38-7.42 (m, 1H), 7.64 (dd, $J = 8.0$, 1.6 Hz, 1H), 7.77 (d, $J = 16.0$ Hz, 1H); IR (CHCl_3) 1722, 1714 cm^{-1} ; HRMS: m/z 276.1366 (calcd for $\text{C}_{16}\text{H}_{20}\text{O}_4$, 276.1362). Insufficient material was available to obtain a good ^{13}C NMR spectrum.

2-[(1E)-3-Oxo-1-butenyl]phenyl pivalate (58). A colorless oil: ^1H NMR (CDCl_3) δ 1.43 (s, 9H), 2.35 (s, 3H), 6.69 (d, $J = 16.2$ Hz, 1H), 7.08 (dd, $J = 8.1$, 1.2 Hz, 1H), 7.26 (t, $J = 7.2$ Hz, 1H), 7.42 (dt, $J = 7.5$, 1.5 Hz, 1H), 7.60 (d, $J = 16.5$ Hz, 1H), 7.66 (dd, $J = 7.8$, 1.8 Hz, 1H); ^{13}C NMR (CDCl_3) δ 27.22, 27.40, 27.56, 39.56, 123.21, 126.46, 127.36, 129.01, 131.53, 136.68, 150.03, 176.86, 198.18; IR (CHCl_3) 1736, 1725 cm^{-1} ; HRMS: m/z 246.1256 (calcd for $\text{C}_{15}\text{H}_{18}\text{IO}_2$, 246.1251).

N-(2-Iodophenyl)methacrylamide (59).¹⁹ 2-Iodoaniline (0.6572 g, 3.0

mmol) was dissolved in 10 mL of pyridine. The solution was cooled to 0 °C in an ice bath. Methacryloyl chloride (0.3139 g, 3.0 mmol) was added dropwise to the mixture and the mixture was stirred for another 2 h. The precipitated salts were filtered and the filtrate was washed with water, extracted using ethyl ether, concentrated, and dried over anhydrous Na₂SO₄. Removal of the solvent afforded a yellow solid: mp 48-49 °C. All spectral data were consistent with those reported in reference 19.

2-Iodobenzyl 3-methyl-3-butenyl ether (61). This compound was prepared by the same method used to prepare 2-iodobenzyl methallyl ether (**14**), but employing 2-iodobenzyl chloride and 3-methyl-3-buten-1-ol. It was obtained as a colorless oil: ¹H NMR (CDCl₃) δ 1.77 (s, 3H), 2.39 (t, *J* = 6.9 Hz, 2H), 3.67 (t, *J* = 6.9 Hz, 2H), 4.50 (s, 2H), 4.77-4.78 (m, 1H), 4.80-4.81 (m, 1H), 6.97 (td, *J* = 7.8, 1.8 Hz, 1H), 7.34 (td, *J* = 7.5, 0.9 Hz, 1H), 7.44 (dt, *J* = 6.0, 0.9 Hz, 1H), 7.81 (dd, *J* = 7.8, 0.9 Hz, 1H); ¹³C NMR (CDCl₃) δ 22.99, 38.03, 69.55, 76.80, 97.82, 111.82, 128.41, 128.80, 129.25, 139.28, 140.92, 142.98; IR (CHCl₃) 3062, 2985, 1622 cm⁻¹; HRMS: *m/z* 302.0172 (calcd for C₁₂H₁₅IO, 302.0168).

Ethyl (2E)-3-[2-(3-methyl-3-butenyloxymethyl)phenyl]propenoate (62). A colorless oil: ¹H NMR (CDCl₃) δ 1.34 (t, *J* = 7.2 Hz, 3H), 1.75 (s, 3H), 2.36 (t, *J* = 6.9 Hz, 2H), 3.64 (t, *J* = 6.9 Hz, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 4.62 (s, 2H), 4.75 (q, *J* = 0.9 Hz, 1H), 4.78 (s, 1H), 6.37 (d, *J* = 15.9 Hz, 1H), 7.29-7.42 (m, 3H), 7.57-7.60 (m, 1H), 8.00 (d, *J* = 15.9 Hz, 1H); ¹³C NMR (CDCl₃) δ 14.49, 22.88, 37.92, 60.63, 69.35, 70.86, 111.74, 120.24, 126.87, 128.35, 129.51, 130.00, 133.78, 137.45, 141.82, 142.87, 167.01; IR (CHCl₃) 1711, 1625 cm⁻¹; HRMS: *m/z* 274.1573

(calcd for C₁₇H₂₂O₃, 274.1569).

3-Methyl-3-butenyl 2-iodobenzoate (63). This compound was prepared by the same method used for methallyl 2-iodobenzoate (**35**), but employing 2-iodobenzoyl chloride and 3-methyl-3-buten-1-ol. It was obtained as a colorless oil: ¹H NMR (CDCl₃) δ 1.81 (s, 3H), 2.50 (t, *J* = 6.9 Hz, 2H), 4.46 (t, *J* = 6.9 Hz, 2H), 4.82 (m, 1H), 4.85 (s, 1H), 7.41 (td, *J* = 7.5, 1.5 Hz, 1H), 7.39 (td, *J* = 7.5, 1.2 Hz, 1H), 7.79 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.99 (dd, *J* = 8.4, 0.9 Hz, 1H); ¹³C NMR (CDCl₃) δ 22.71, 36.85, 63.95, 94.30, 112.79, 128.09, 131.11, 132.76, 141.50, 141.66, 166.68; IR (CHCl₃) 2960, 1727 cm⁻¹; HRMS: *m/z* 315.9960 (calcd for C₁₂H₁₃I O₂, 315.9969).

Ethyl (2E)-3-[2-(3-methyl-3-butenyloxycarbonyl)phenyl]propenoate (64).

A colorless oil: ¹H NMR (CDCl₃) δ 1.33 (t, *J* = 7.2 Hz, 3H), 1.80 (s, 3H), 2.49 (t, *J* = 6.9 Hz, 2H), 4.27 (q, *J* = 7.2 Hz, 2H), 4.45 (t, *J* = 6.9 Hz, 2H), 4.80 (s, 1H), 4.83 (s, 1H), 6.28 (d, *J* = 15.9 Hz, 1H), 7.42 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.51 (dt, *J* = 7.5, 1.2 Hz, 1H), 7.57 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.94 (dd, *J* = 7.8, 1.5 Hz, 1H), 8.42 (d, *J* = 15.9 Hz, 1H); ¹³C NMR (CDCl₃) δ 14.51, 22.61, 36.93, 60.72, 63.70, 112.74, 121.24, 128.06, 129.48, 130.276, 130.92, 132.43, 136.56, 141.68, 143.94, 166.70, 166.89; IR (CHCl₃) 1727, 1711 cm⁻¹; HRMS: *m/z* 288.1367 (calcd for C₁₇H₂₀O₄, 288.1362).

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References

1. Trost, B. M. *Comprehensive Organic Synthesis: Selectivity, Strategy & Efficiency in Modern Organic Chemistry*; Pergamon: Oxford, New York, 1991; Vol. 5, p 785.
2. (a) Campo, M. A.; Larock, R. C. *J. Am. Chem. Soc.* **2002**, *124*, 14326. (b) Campo, M. A., Ph.D. thesis, Iowa State University, Ames, Iowa.
3. Karig, G.; Moon, M.-T.; Thasana, N.; Gallagher, T. *Org. Lett.* **2002**, *4*, 3115.
4. (a) Tian, Q.; Larock, R. C. *Org. Lett.* **2000**, *2*, 3329. (b) Larock, R. C.; Tian, Q. *J. Org. Chem.* **2001**, *66*, 7372.
5. Heck, R. F. *J. Organomet. Chem.* **1972**, *37*, 389.
6. Wang, L.; Pan, Y.; Jiang, X.; Hu, H. *Tetrahedron Lett.* **2000**, *41*, 725.
7. Stork, G.; Poirier, J. M. *J. Am. Chem. Soc.* **1983**, *105*, 1073.
8. (a) Tsuji, J.; Kobayashi, Y.; Kataoka, H.; Takahashi, T. *Tetrahedron Lett.* **1980**, *21*, 1475. (b) Trost, B. M.; Runge, T. A.; Jungheim, L. N. *J. Am. Chem. Soc.* **1980**, *102*, 2840. (c) Trost, B. M.; Runge, T. A.; Jungheim, L. N. *J. Am. Chem. Soc.* **1981**, *103*, 2485. (d) Tsuji, J.; Okumoto, H.; Kobayashi, Y.; Takahashi, T. *Tetrahedron Lett.* **1981**, *22*, 1357. (e) Yamamoto, Y.; Tsuji, J. *Tetrahedron Lett.* **1982**, *23*, 3089.
9. Beckwith, A. L. J.; Gara, W. B. *J. Chem. Soc., Perkin Trans. 2* **1975**, 795.
10. Alderdice, M.; Spino, C.; Welder, L. *Can. J. Chem.* **1993**, *71*, 1955.
11. Dang, Q.; Brown, B. S.; van Poelje, P. D.; Colby, T. J.; Erion, M. D. *Bioorg. Med. Chem. Lett.* **1999**, *9*, 1506.
12. Roesch, K. R.; Zhang, H.; Larock, R. C. *J. Org. Chem.* **2001**, *66*, 8042.

13. Olivera, R.; SanMartin, R.; Dominguez, E. *J. Org. Chem.* **2000**, *65*, 6398.
 14. Iyer, S.; Liebeskind, L. S. *J. Am. Chem. Soc.* **1987**, *109*, 2759.
 15. Kizil, M.; Patro, B.; Callaghan, O.; Murphy, J. A.; Hursthouse, M. B.; Hibbs, D. *J. Org. Chem.* **1999**, *64*, 7856.
 16. Biellmann, J.-F.; d'Orchymont, H. *J. Org. Chem.* **1982**, *47*, 2882.
 17. Casaschi, A.; Grigg, R.; Sansano, J. M. *Tetrahedron* **2001**, *57*, 607.
 18. Zhang, D. M.S. Thesis, Iowa State University, Ames, Iowa.
 19. Casaschi, A.; Grigg, R.; Sansano, J. M.; Wilson, D.; Redpath, J. *Tetrahedron* **2000**, *56*, 7541.
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GENERAL CONCLUSION

In this dissertation, the scope and limitations of several palladium-catalyzed processes have been presented. Specifically, the scope of the palladium-catalyzed cross-coupling of 2-(1-alkynyl)benzaldimines has been investigated for the synthesis of 3,4-disubstituted isoquinolines with organic halides, for the synthesis of 3-substituted 4-aryloisoquinolines with carbon monoxide and aryl halides, and 3-substituted isoquinoline-4-carboxylates with carbon monoxide and methanol.

Chapter 1 describes the synthesis of a wide variety of 3,4-disubstituted isoquinolines containing an aryl, allylic, benzylic, alkynyl or vinylic substituent at the 4 position of the isoquinoline. These isoquinolines have been prepared in moderate to high yields by employing mild reaction conditions, short reaction times and starting materials that are easily available. The electronic and steric effects of the organic halides on the reaction yields are discussed. A mechanism is proposed for this process.

Chapter 2 describes the synthesis of 3-substituted 4-aryloisoquinolines in high yields and excellent chemical selectivities under mild reaction conditions. The success of the palladium-catalyzed carbonylative cyclization of 2-(1-alkynyl)benzaldimines expands the application of this methodology.

Chapter 3 describes our efforts in a methodology study of the palladium-catalyzed oxidative carbonylative cyclization for the synthesis of methyl 3-substituted isoquinoline-4-carboxylates employing 2-(1-alkynyl)benzaldimines, carbon monoxide and methanol. Although it has not been fully developed into a

useful synthetic method, it enables us to look into the nature of palladium-catalyzed cross-coupling cyclization reactions.

Chapter 4 describes a new palladium migration reaction that has been recently discovered in the Larock group. A mechanism involving a palladium migration step is proposed. The reaction scope has been studied. In addition, preliminary results indicate that the occurrence of this palladium migration is highly dependent on the reaction conditions.

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

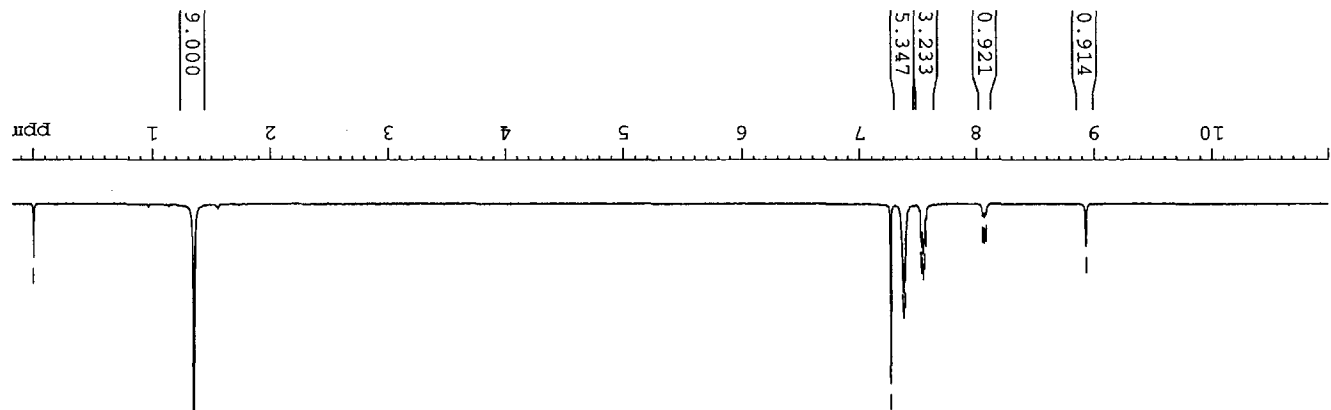
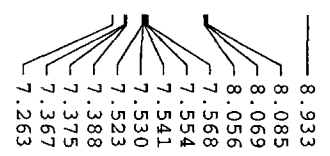
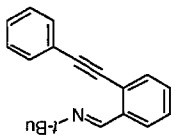
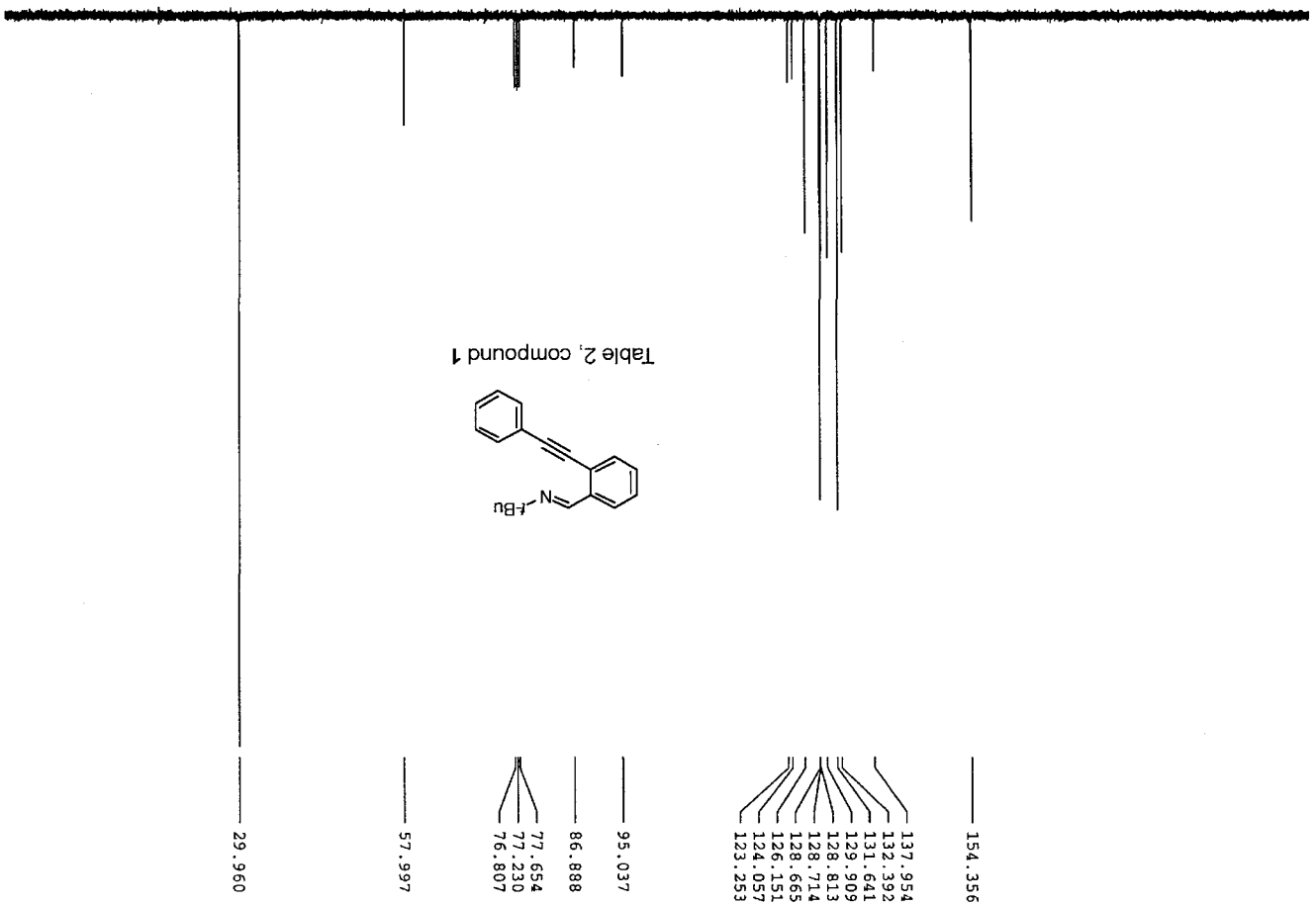
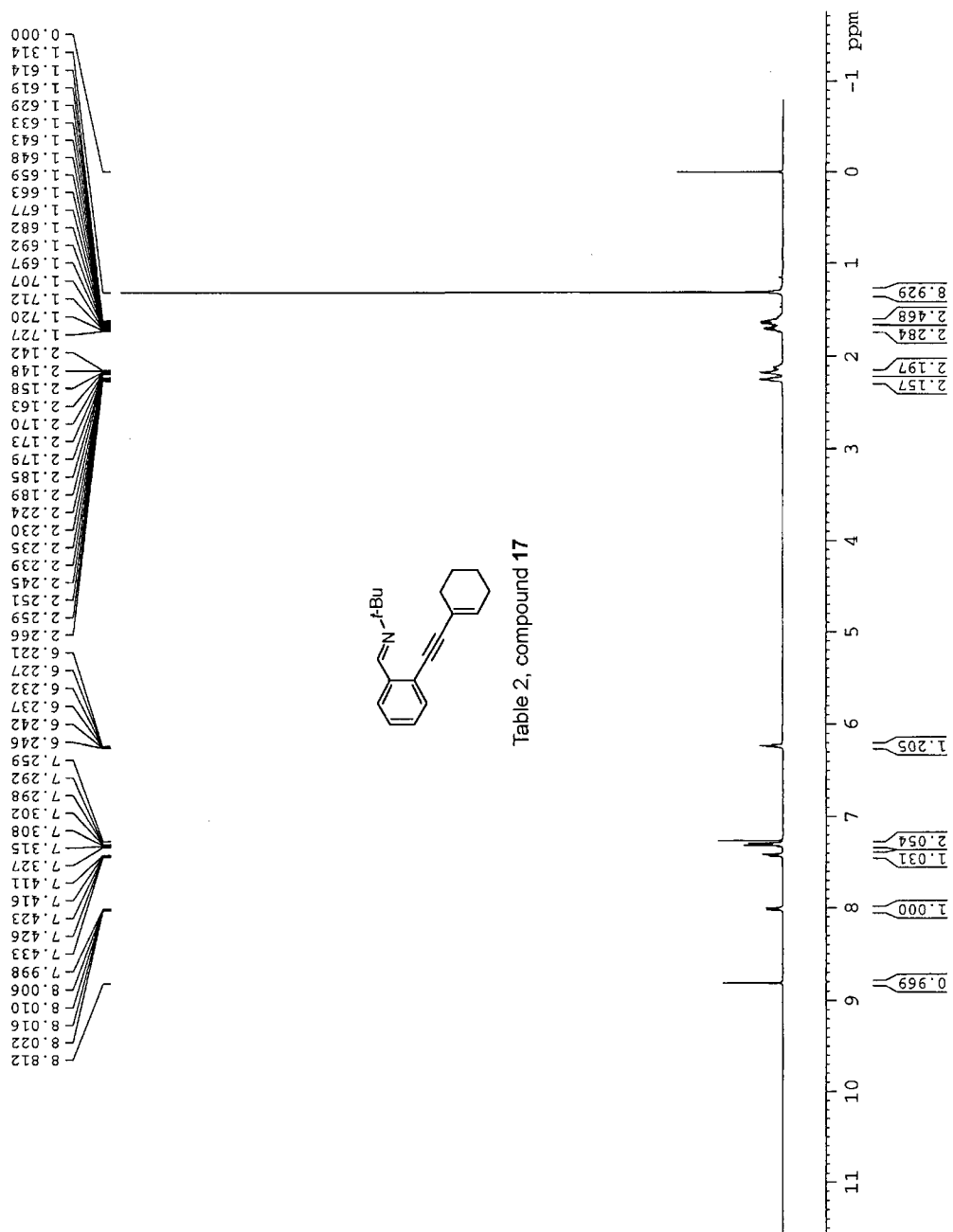


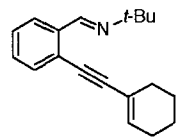
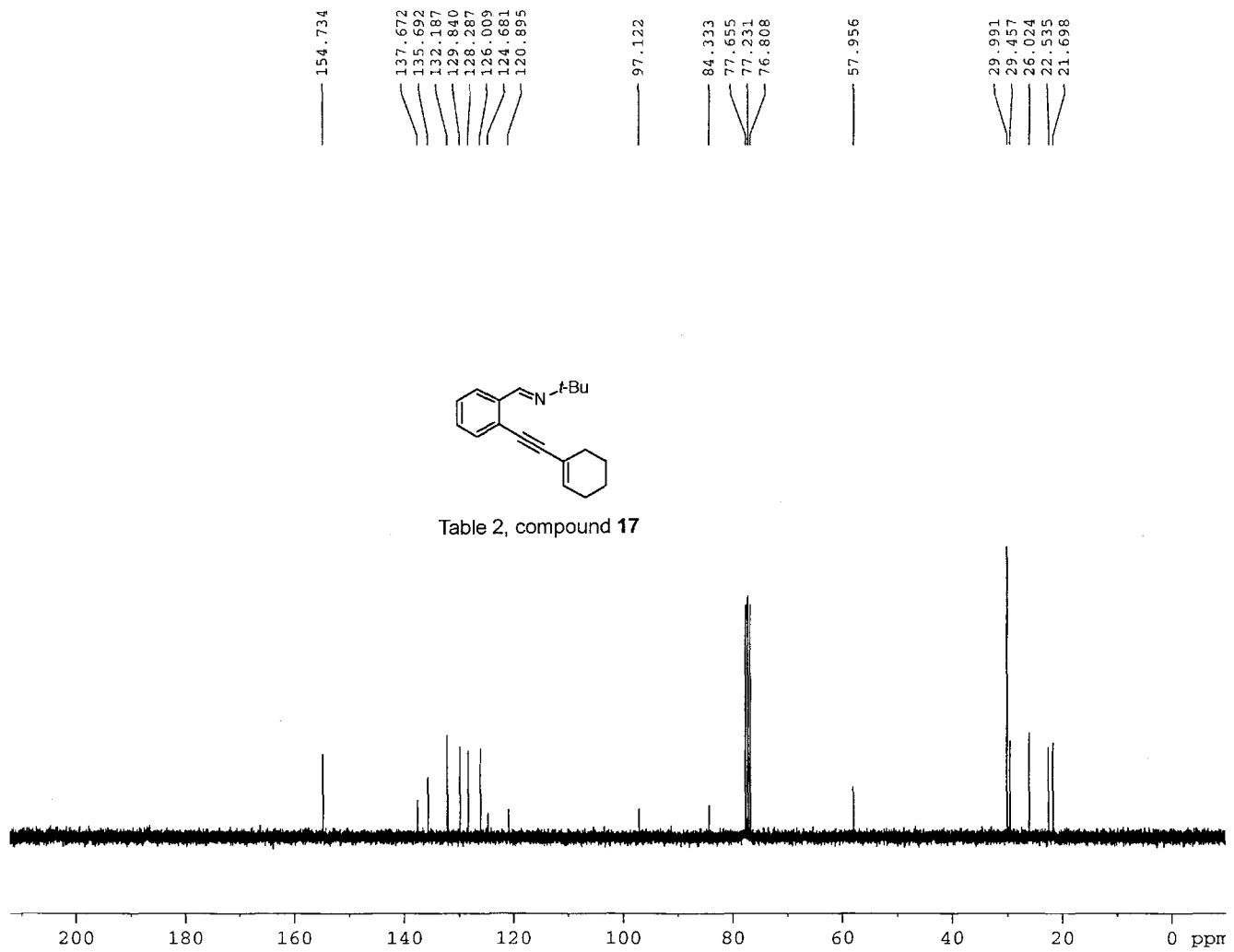
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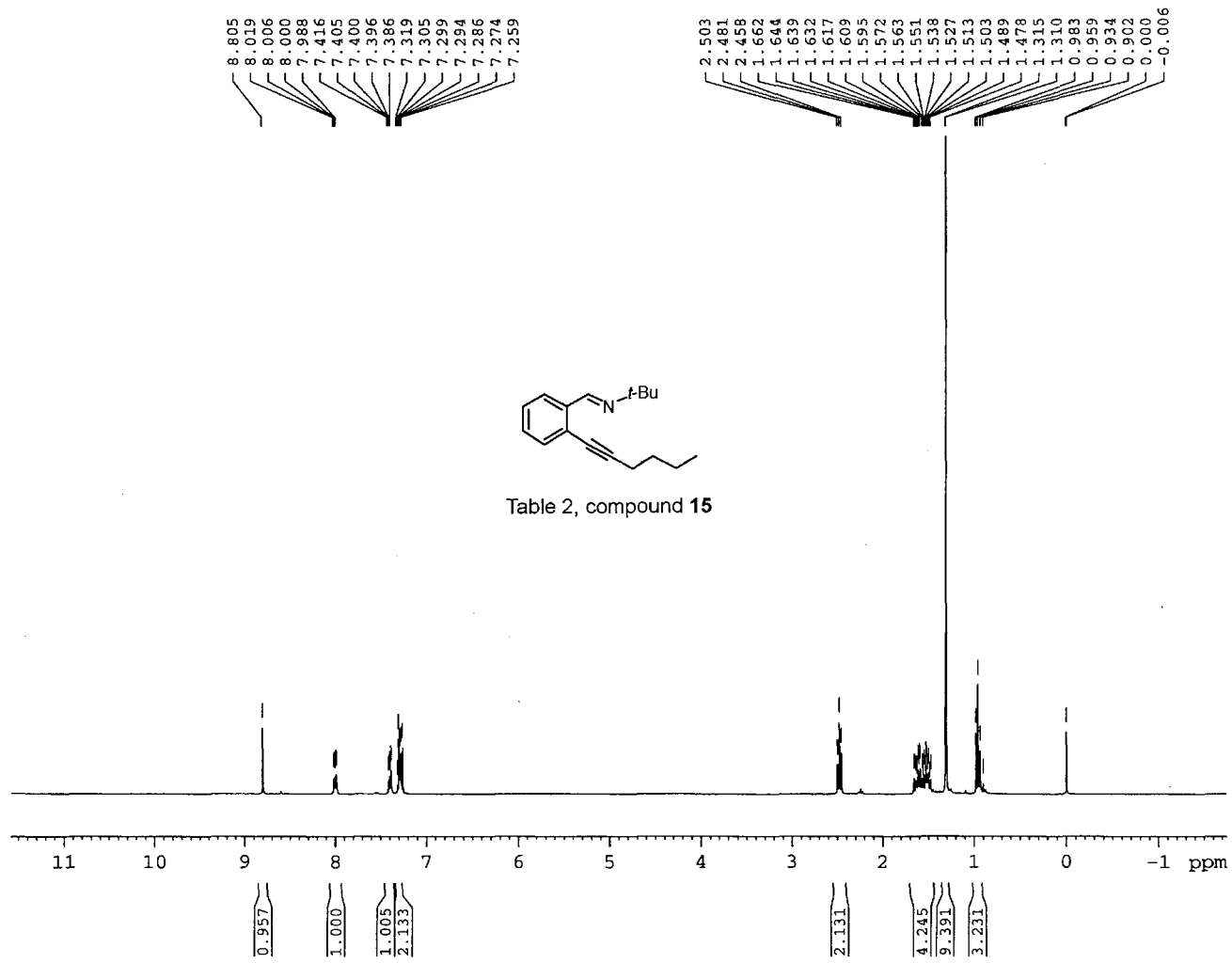


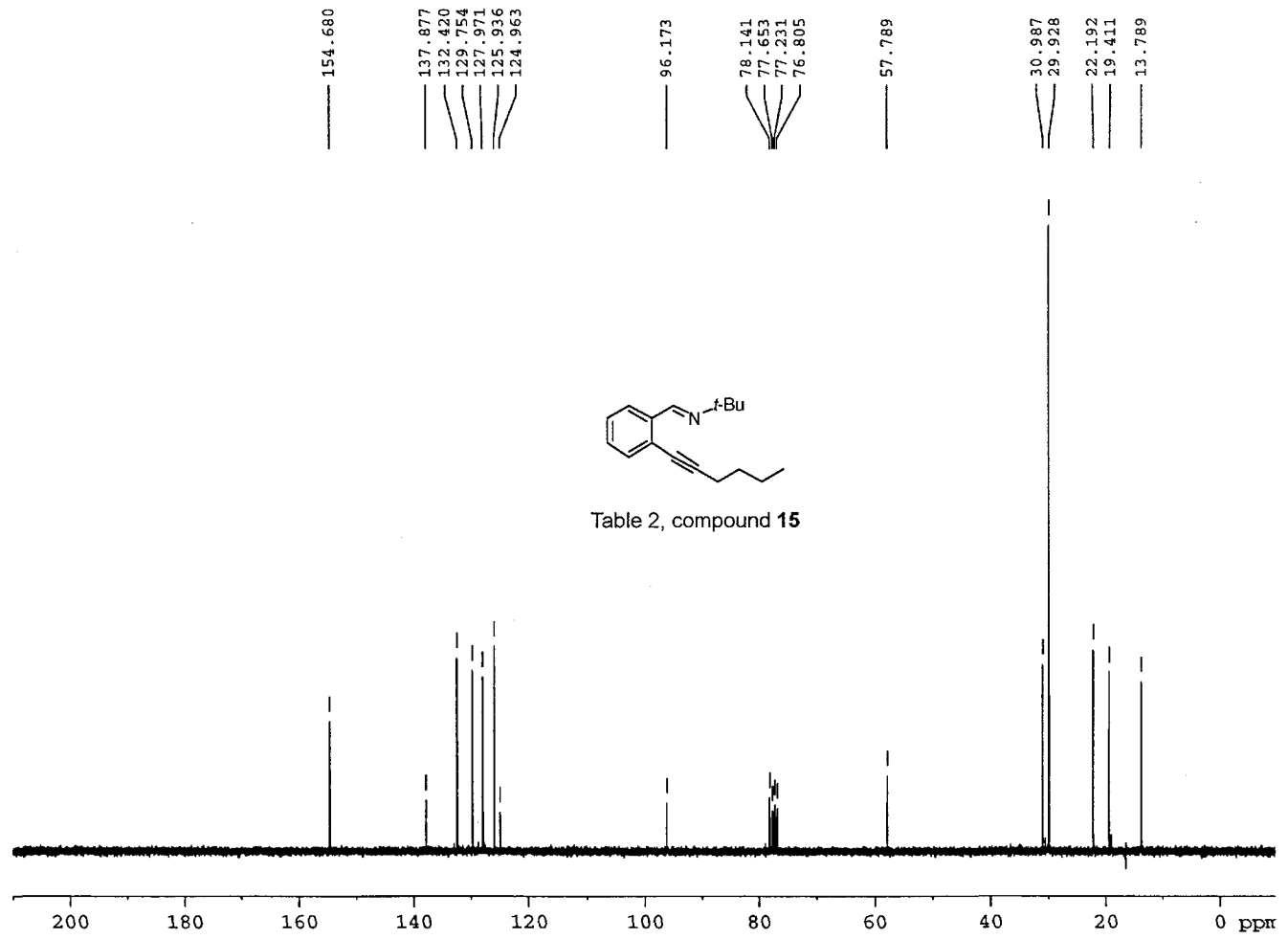
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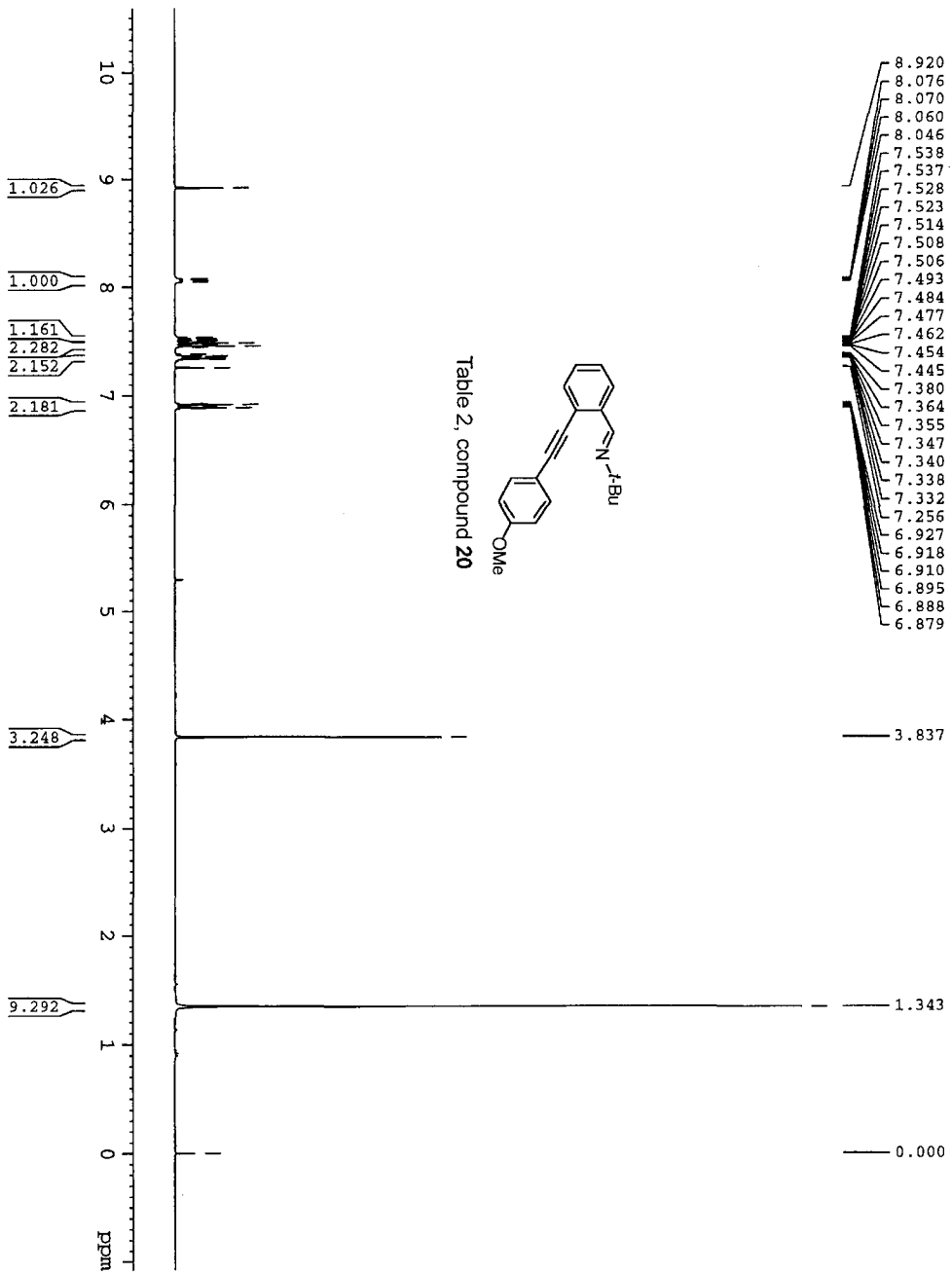


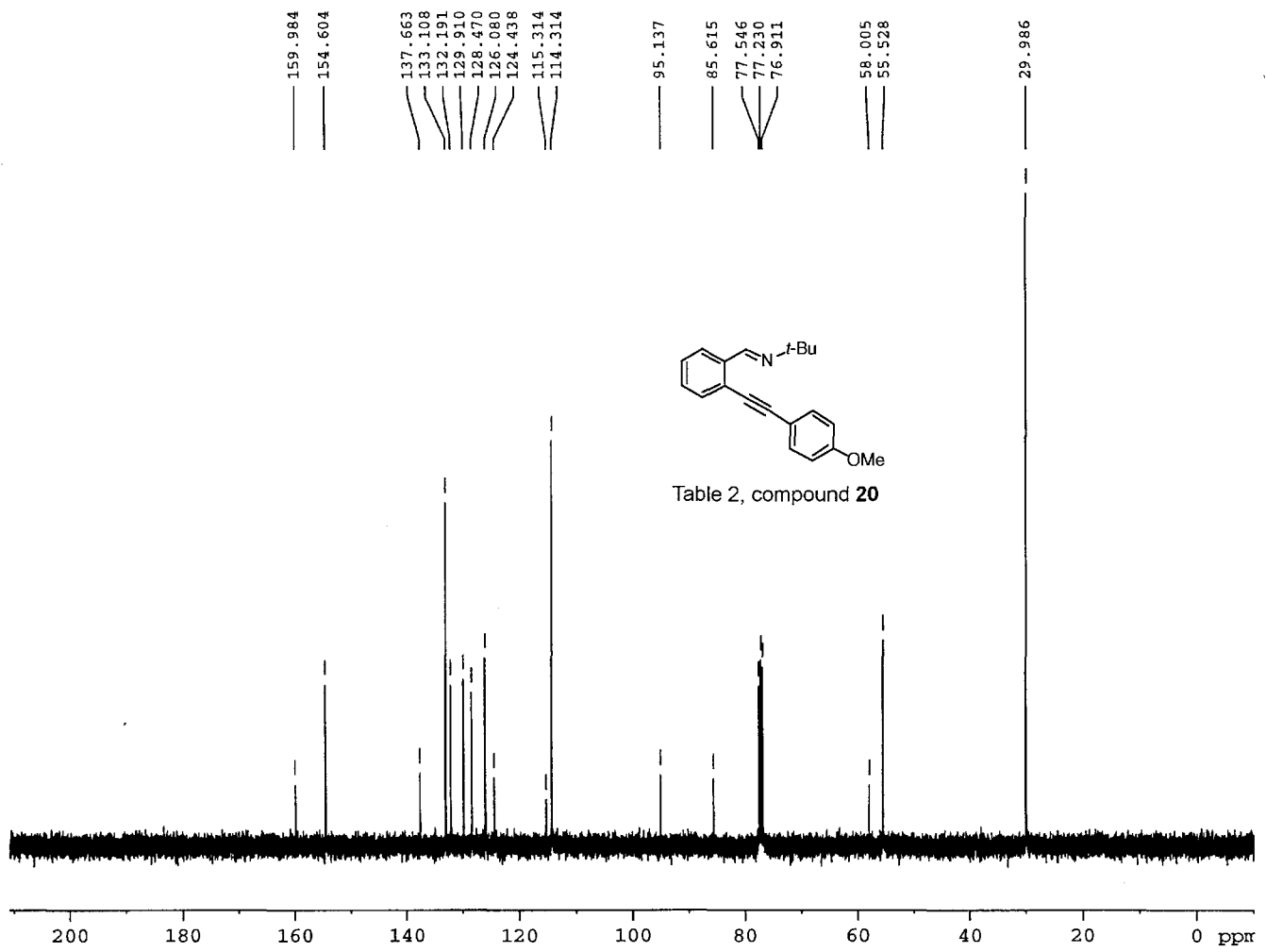












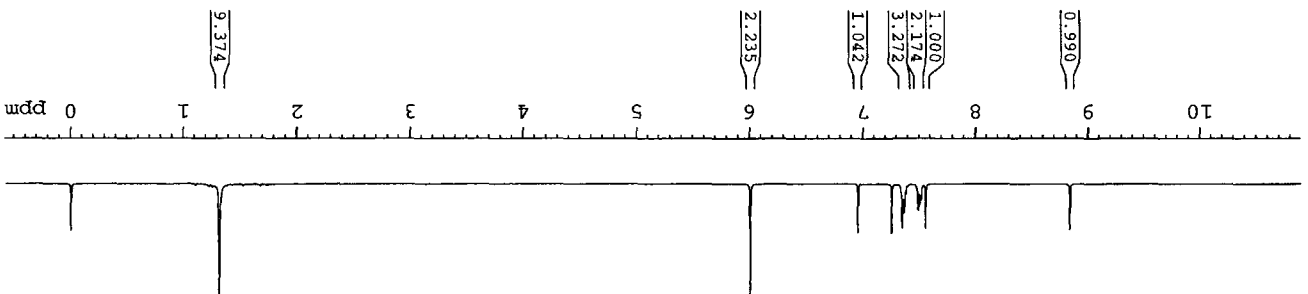
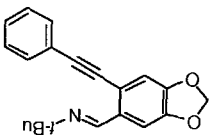


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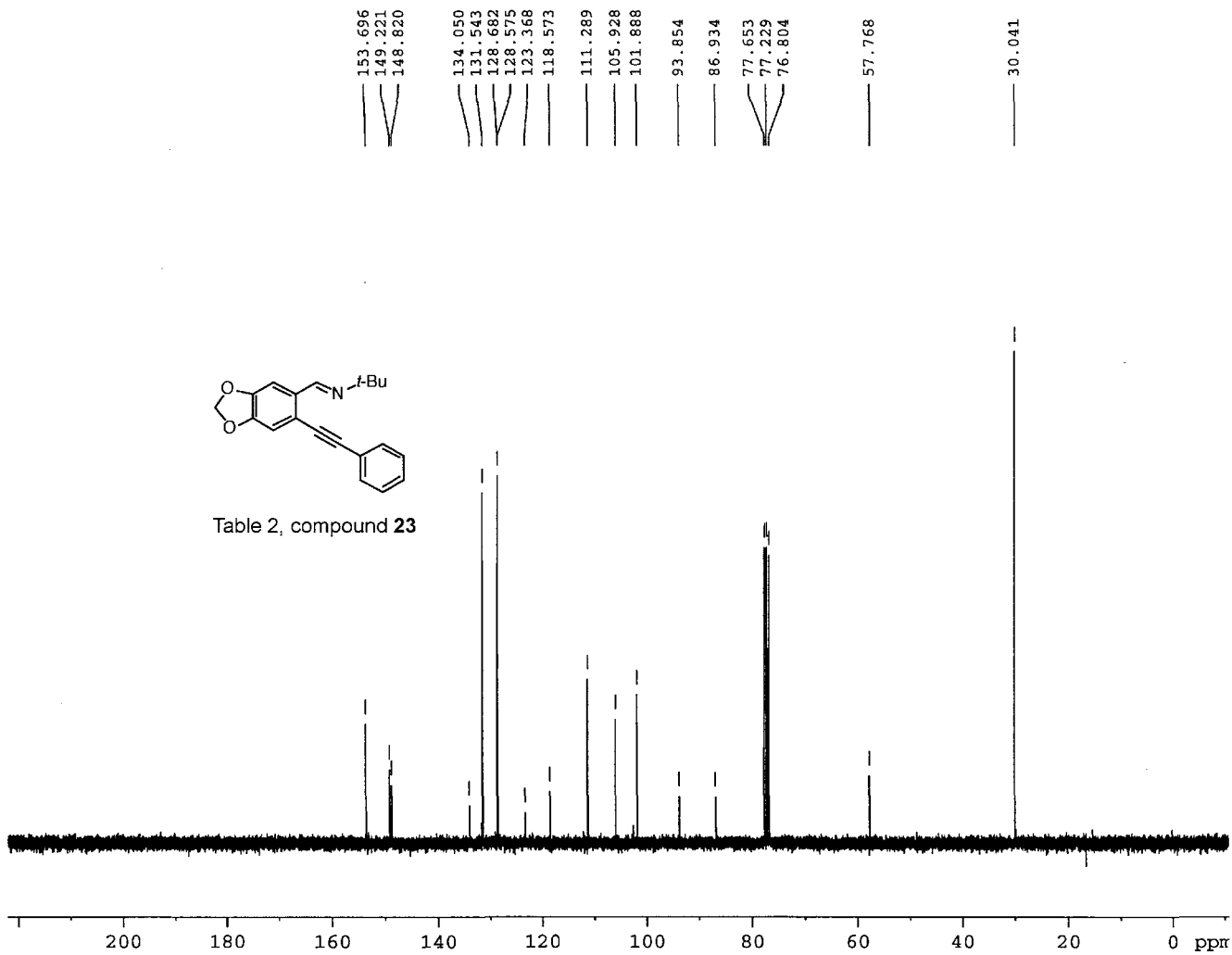


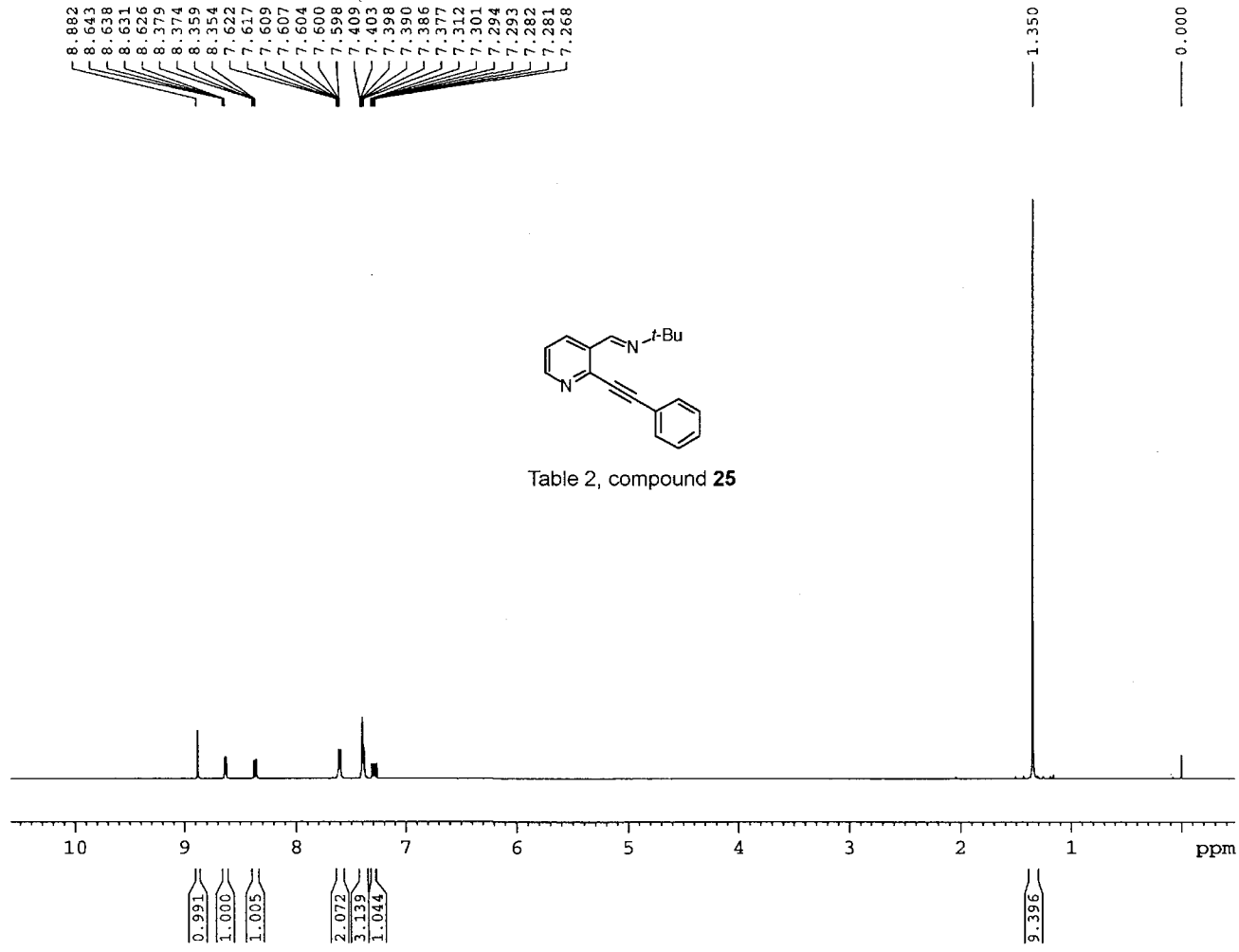
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 7.488
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 7.371
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 6.956

6.007

1.318

0.000





200 180 160 140 120 100 80 60 40 20 0 ppm

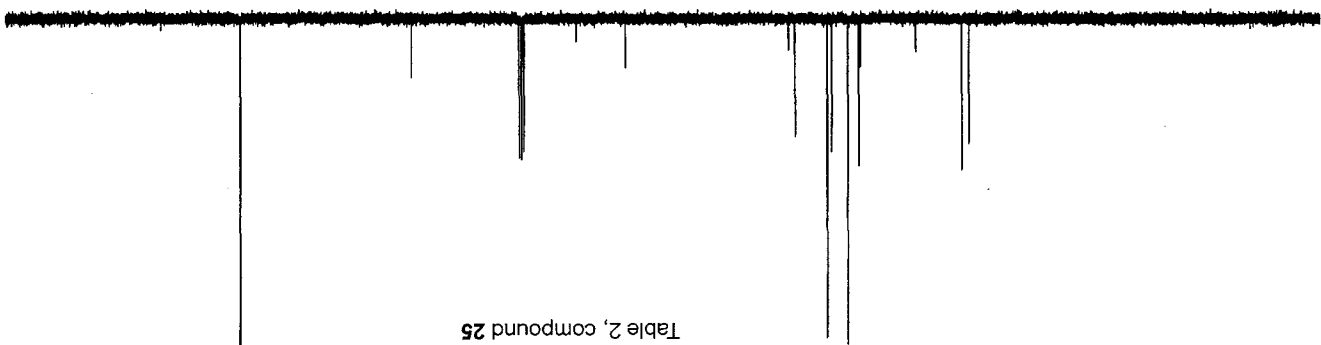
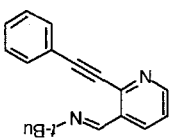


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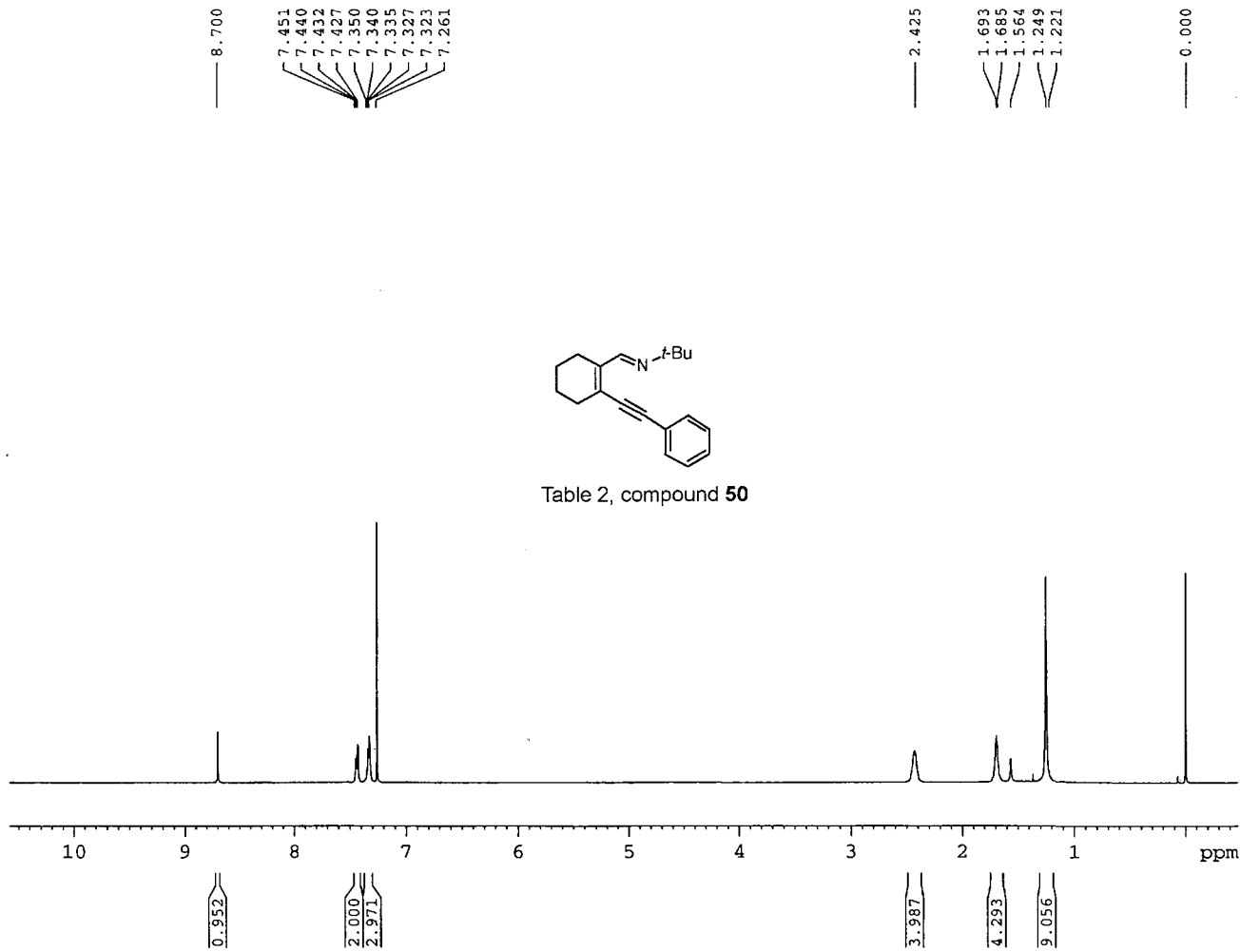


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77.652
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76.805

58.442

29.818



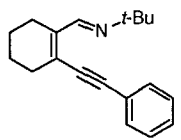
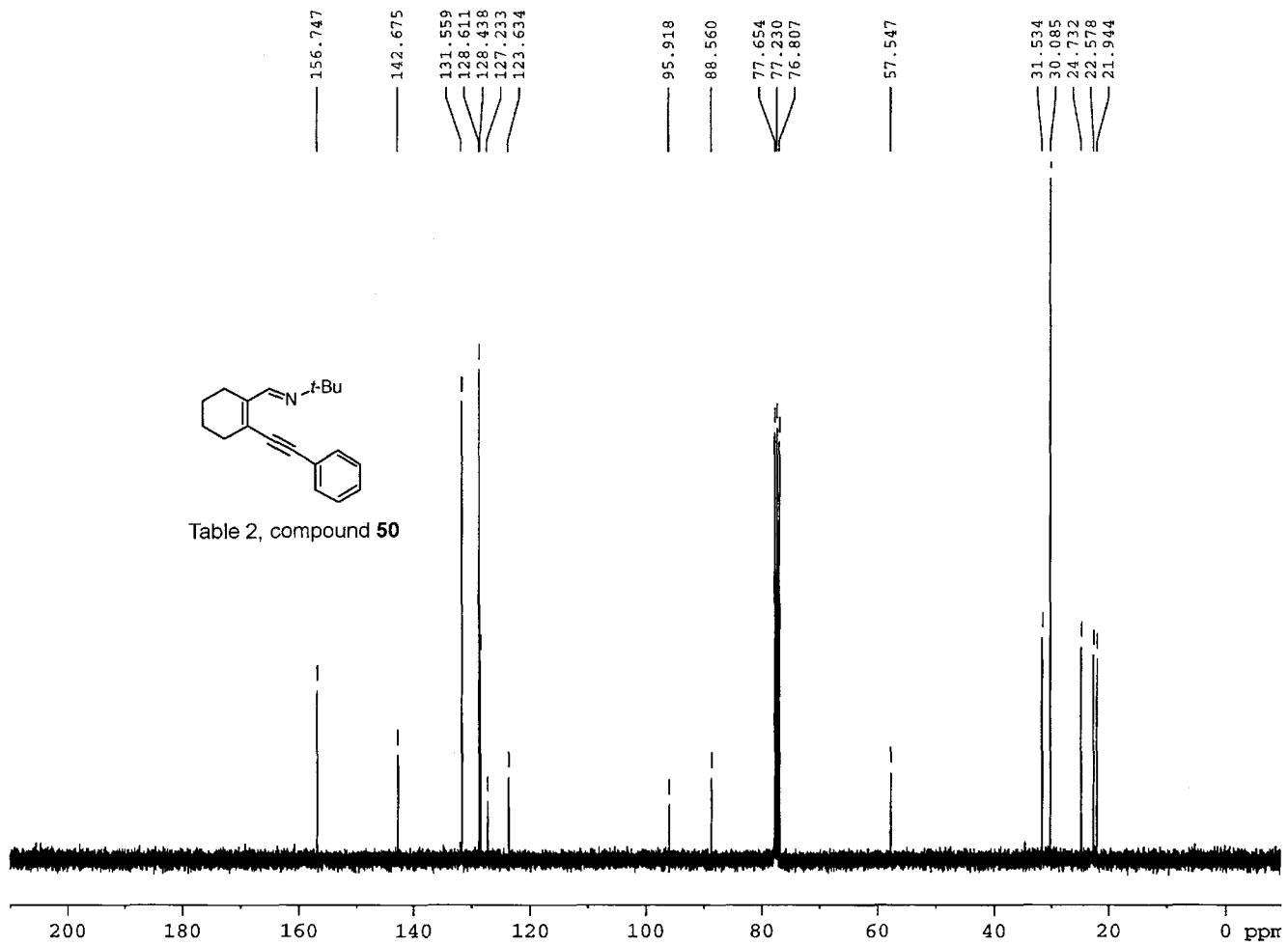
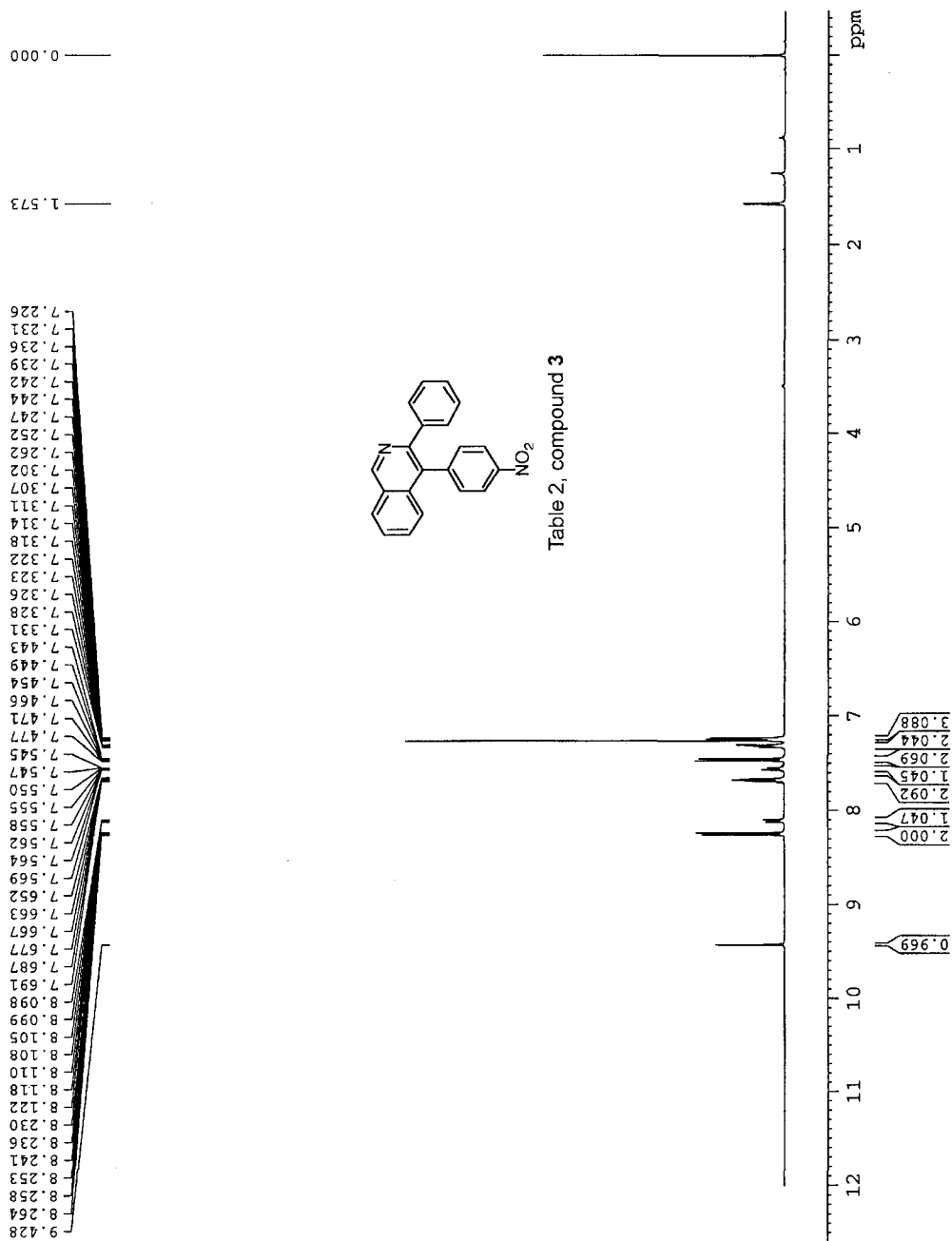
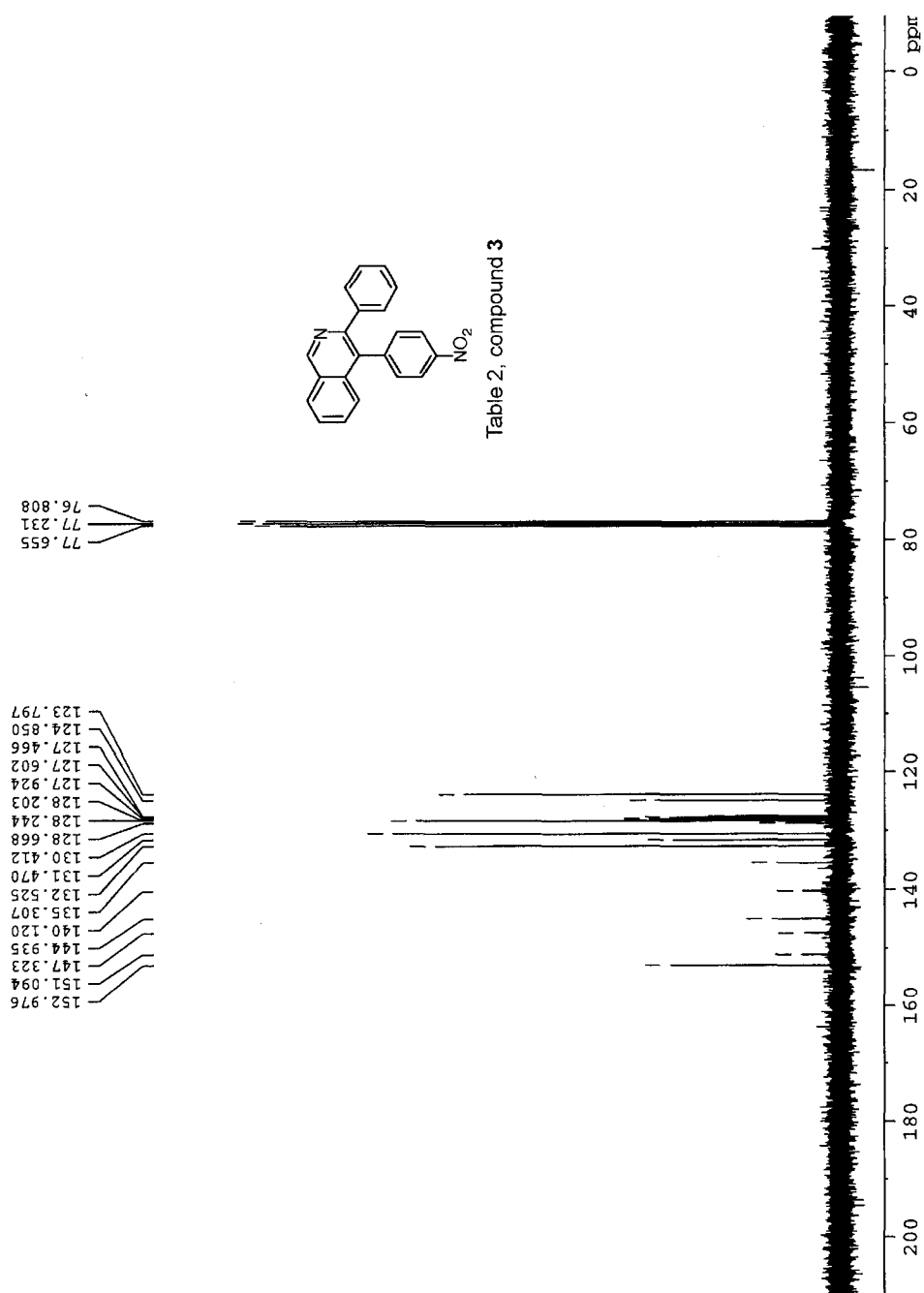


Table 2, compound 50





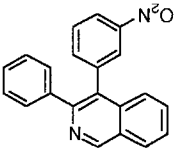
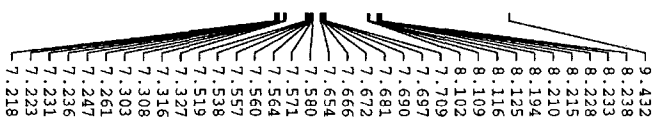
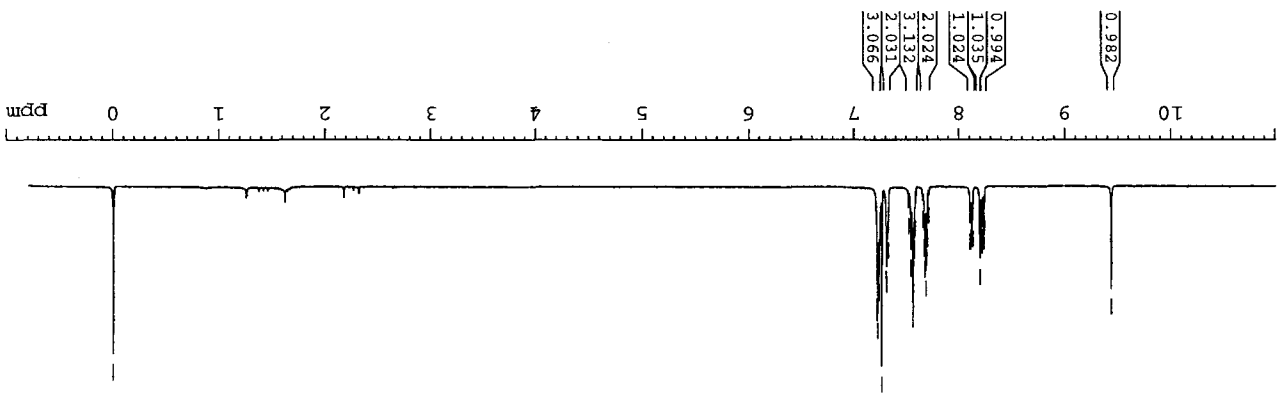
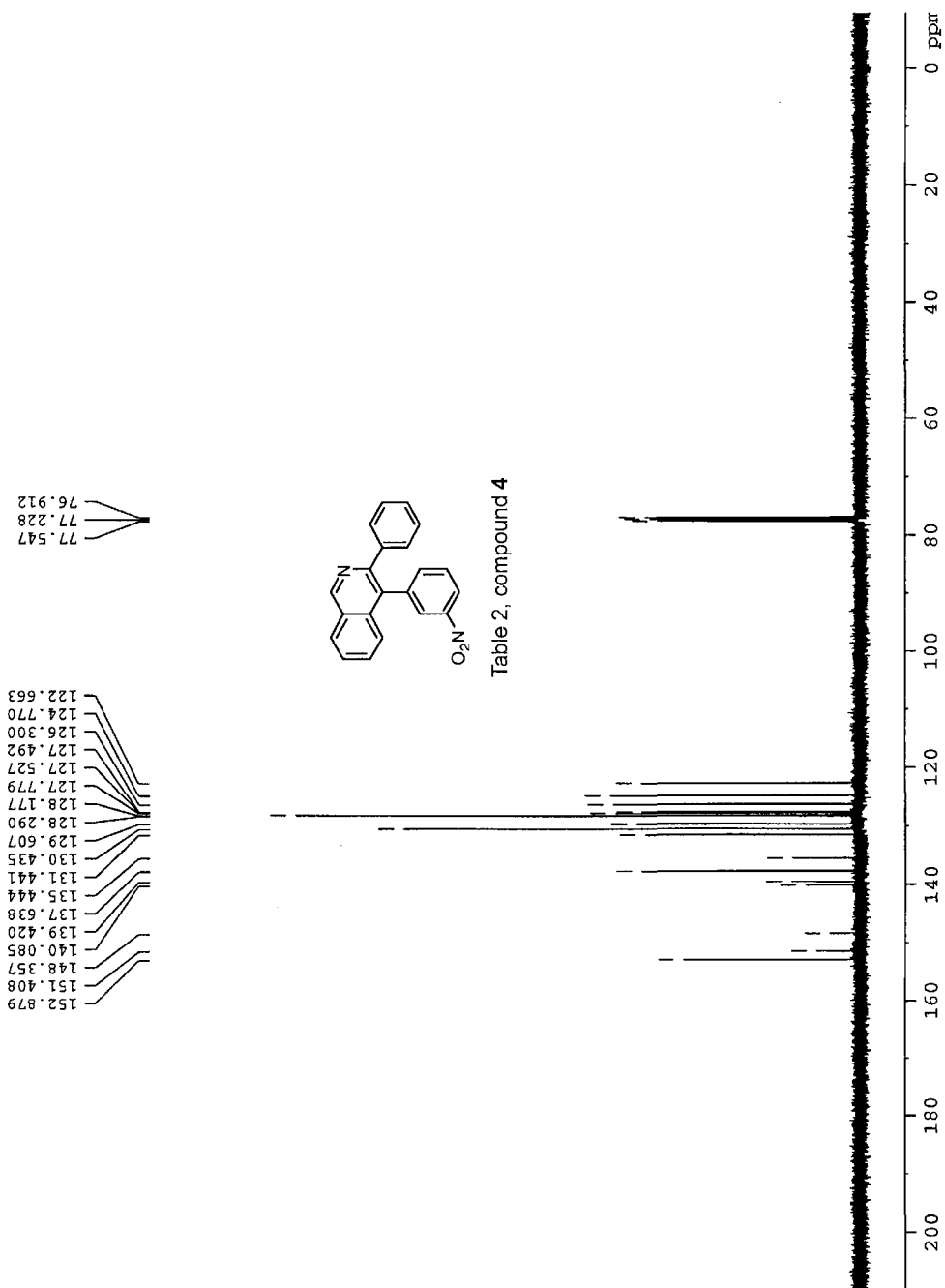
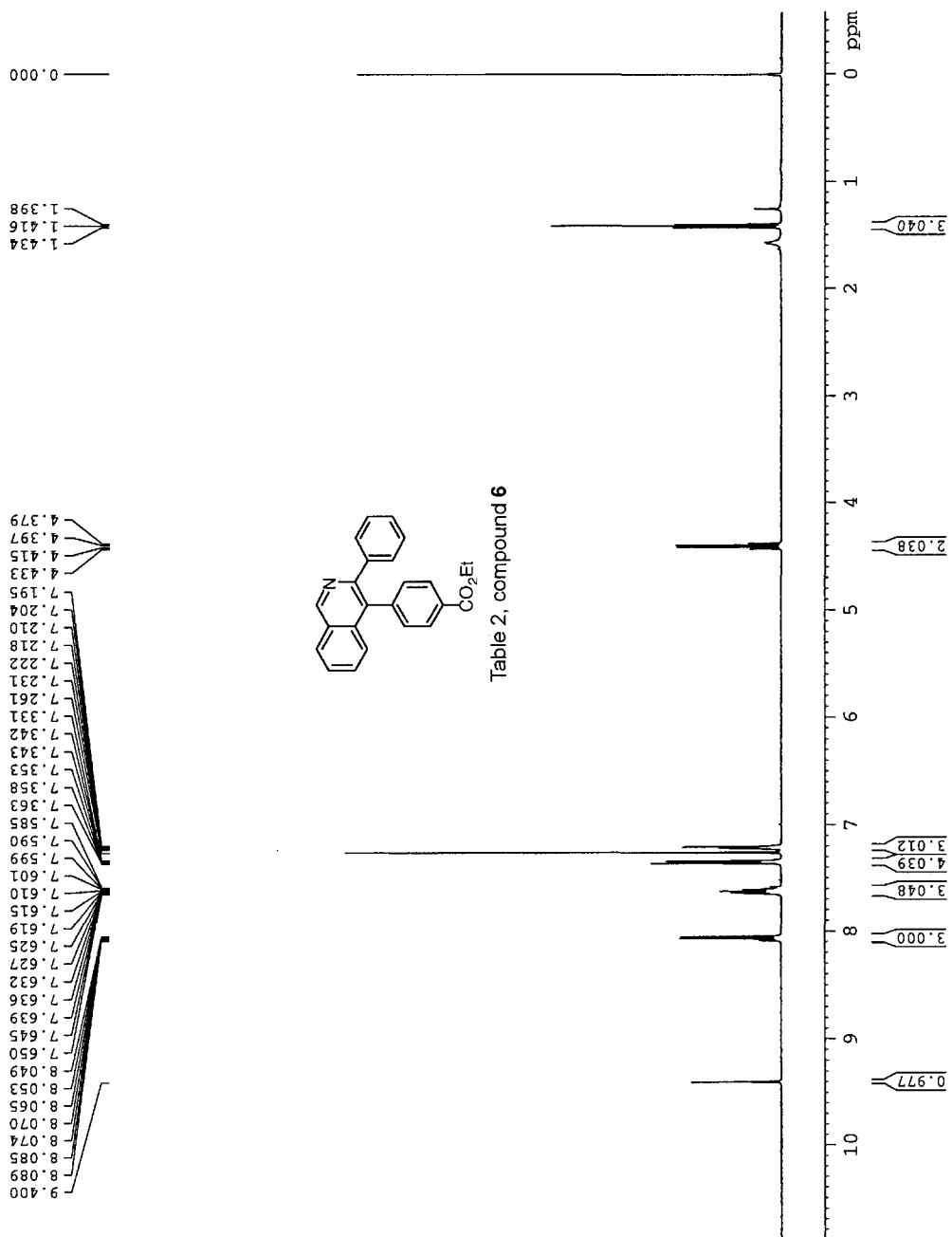


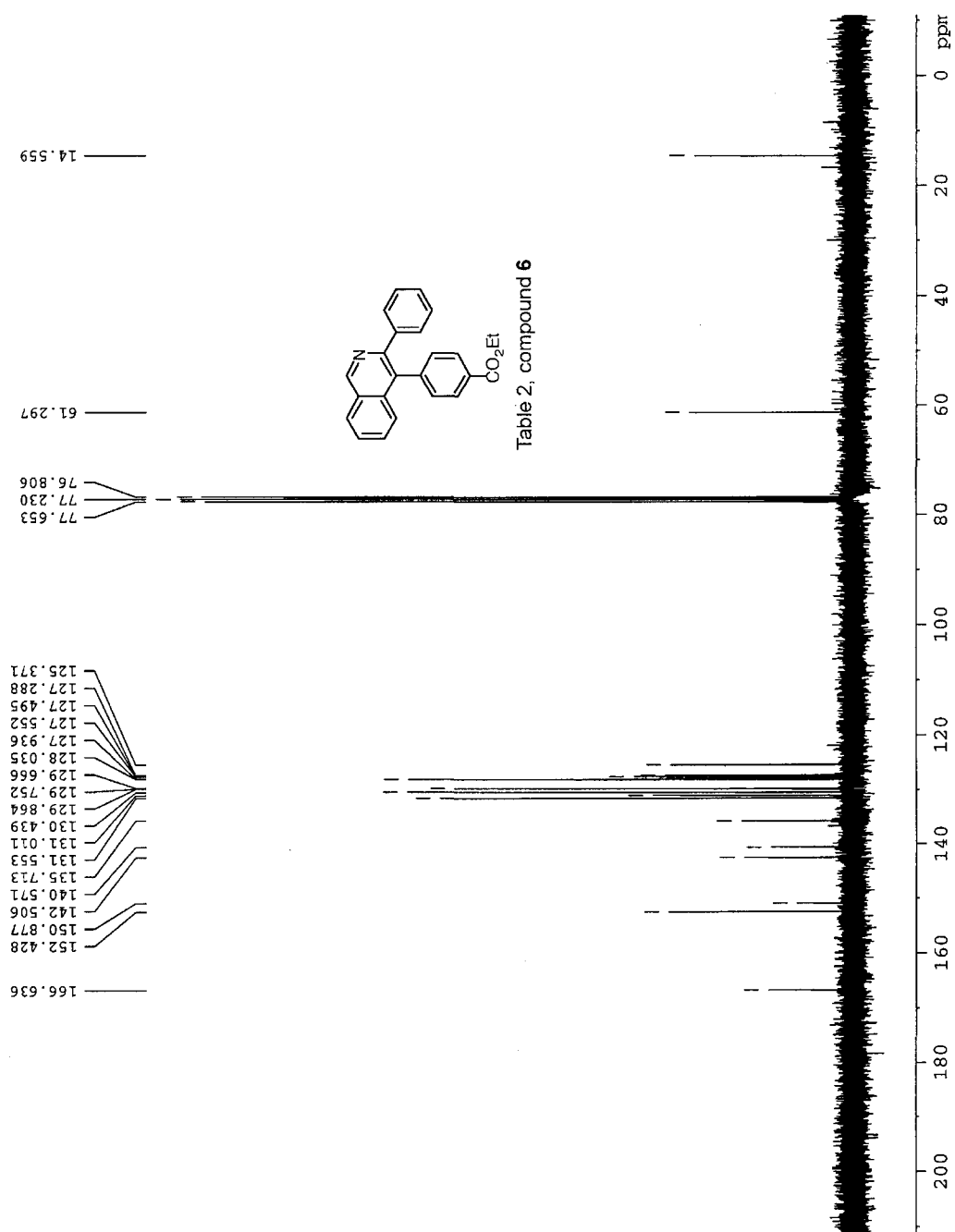
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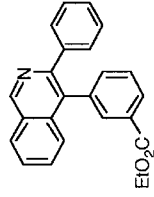
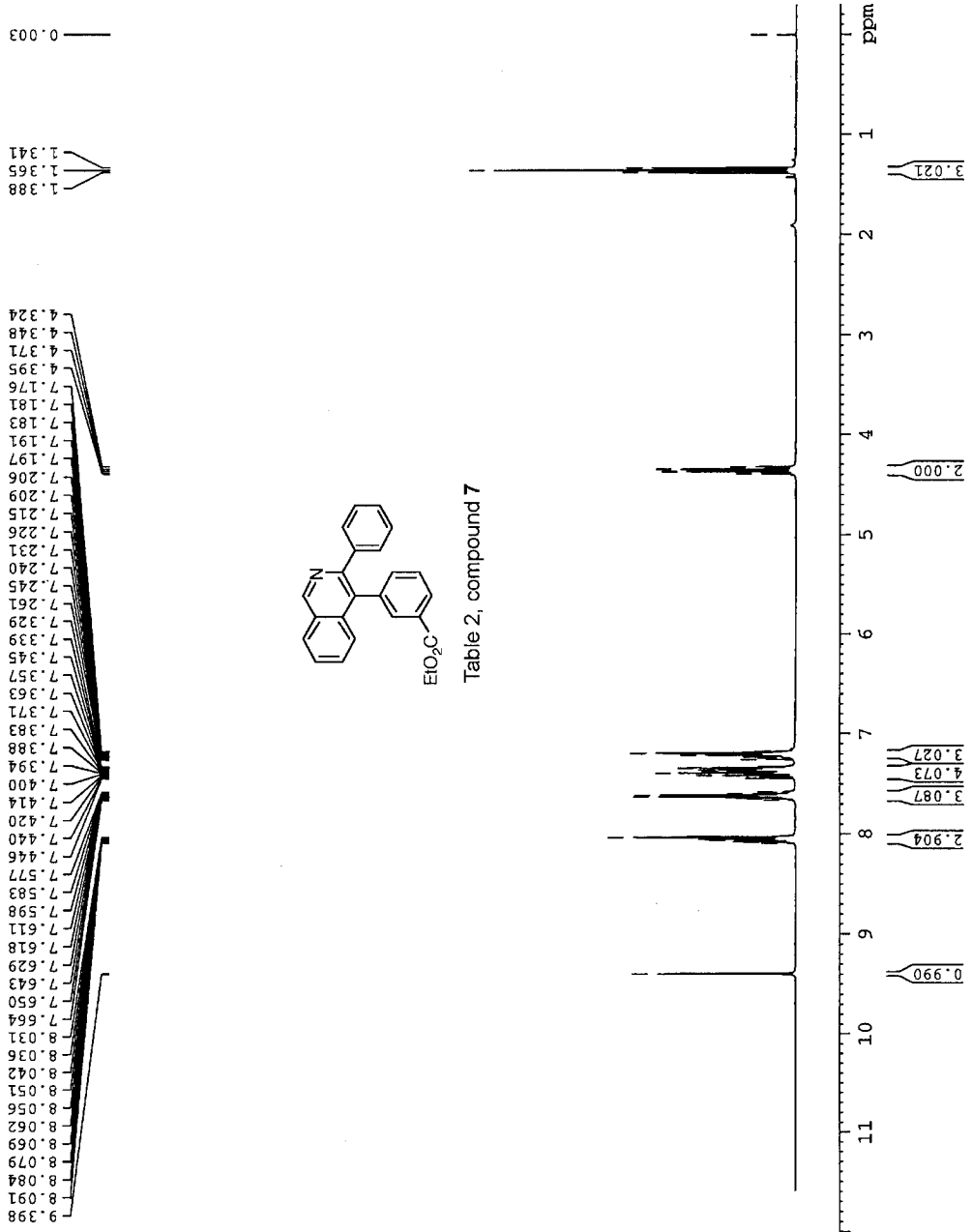
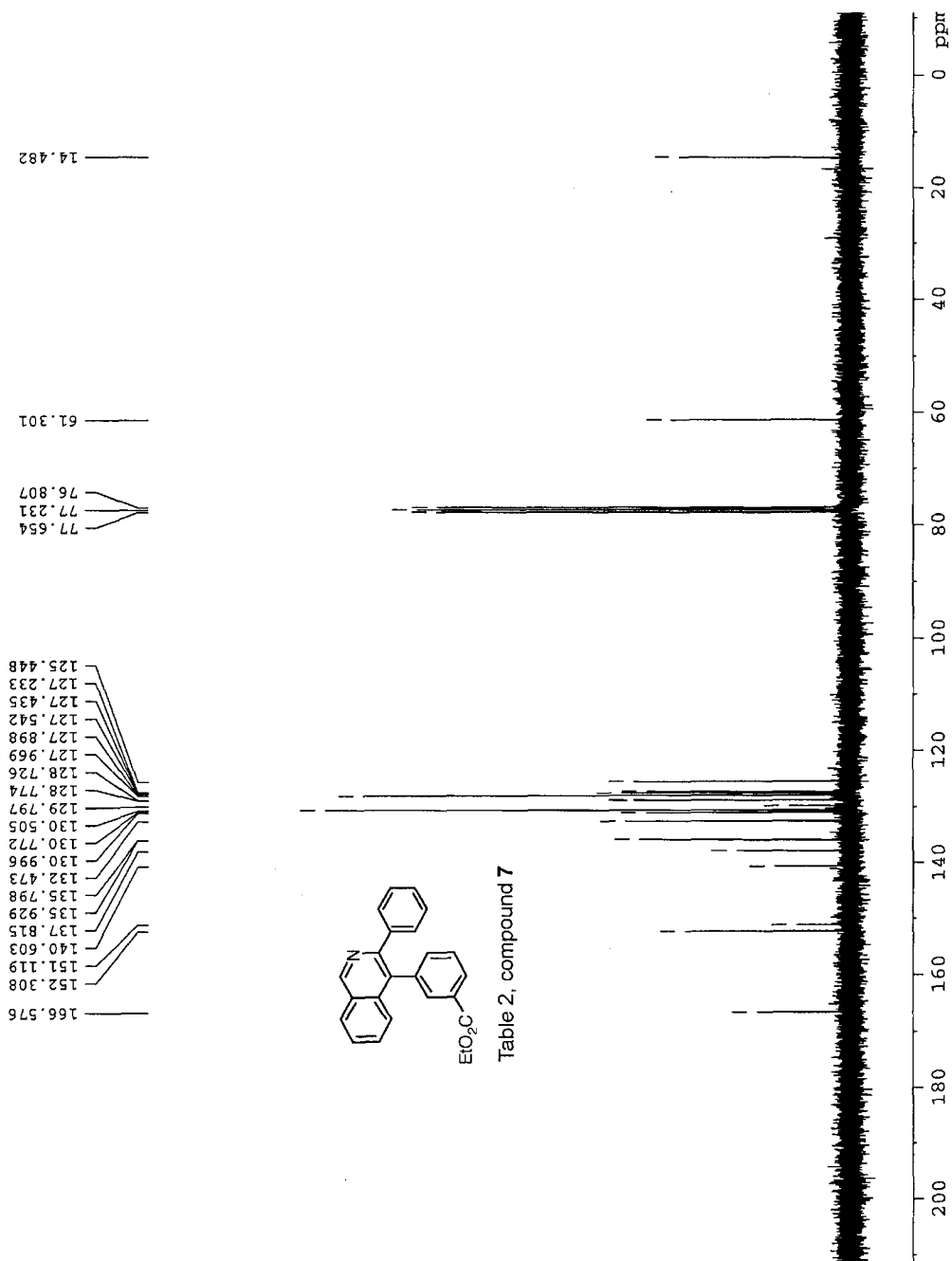
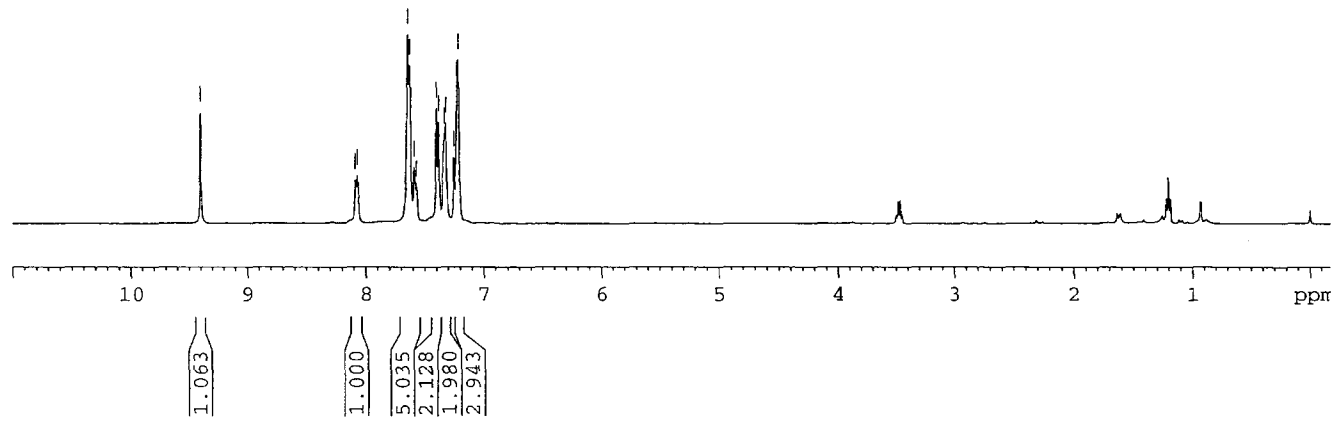


Table 2, compound 7







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7.219

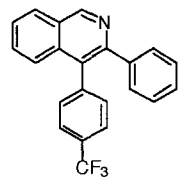
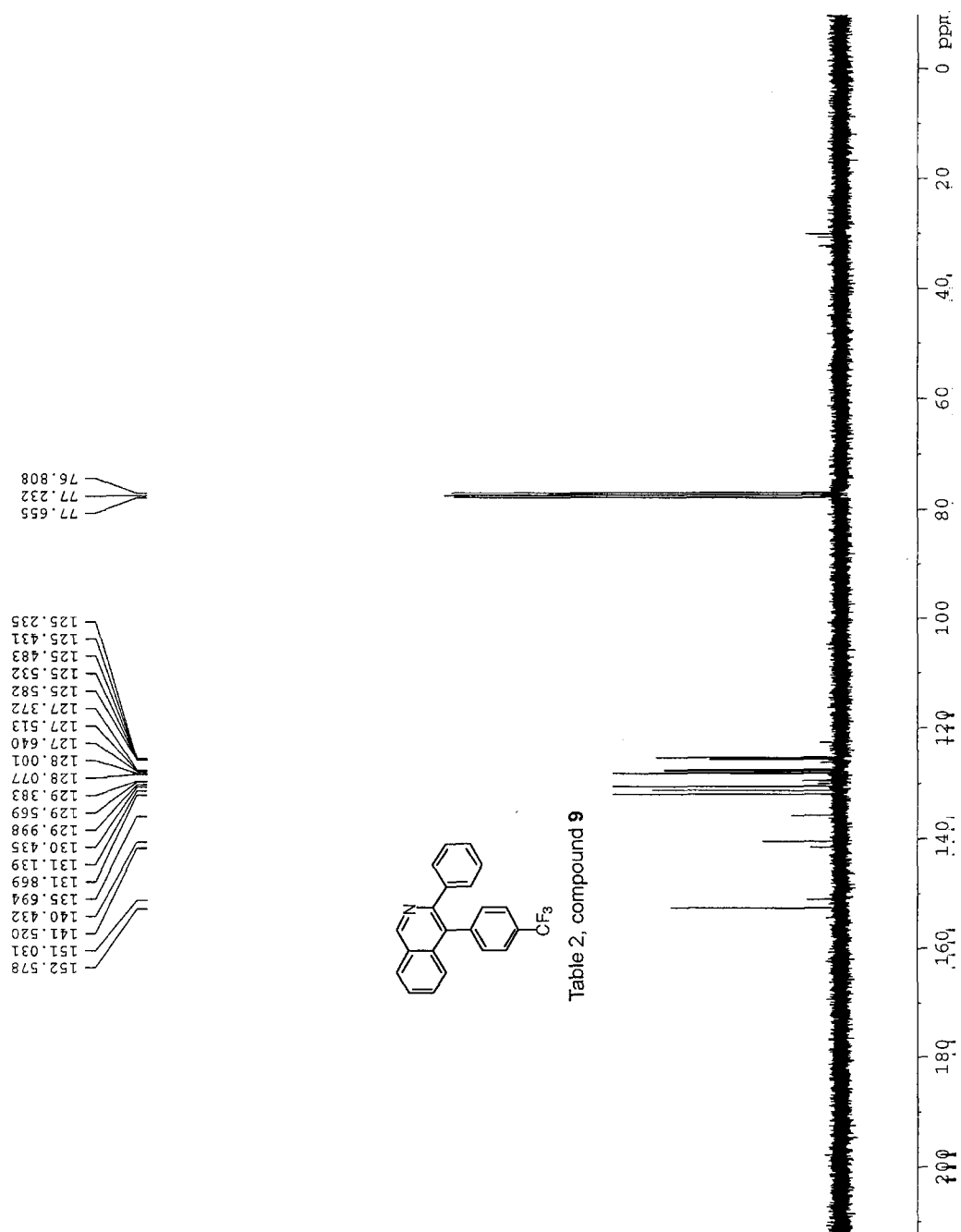
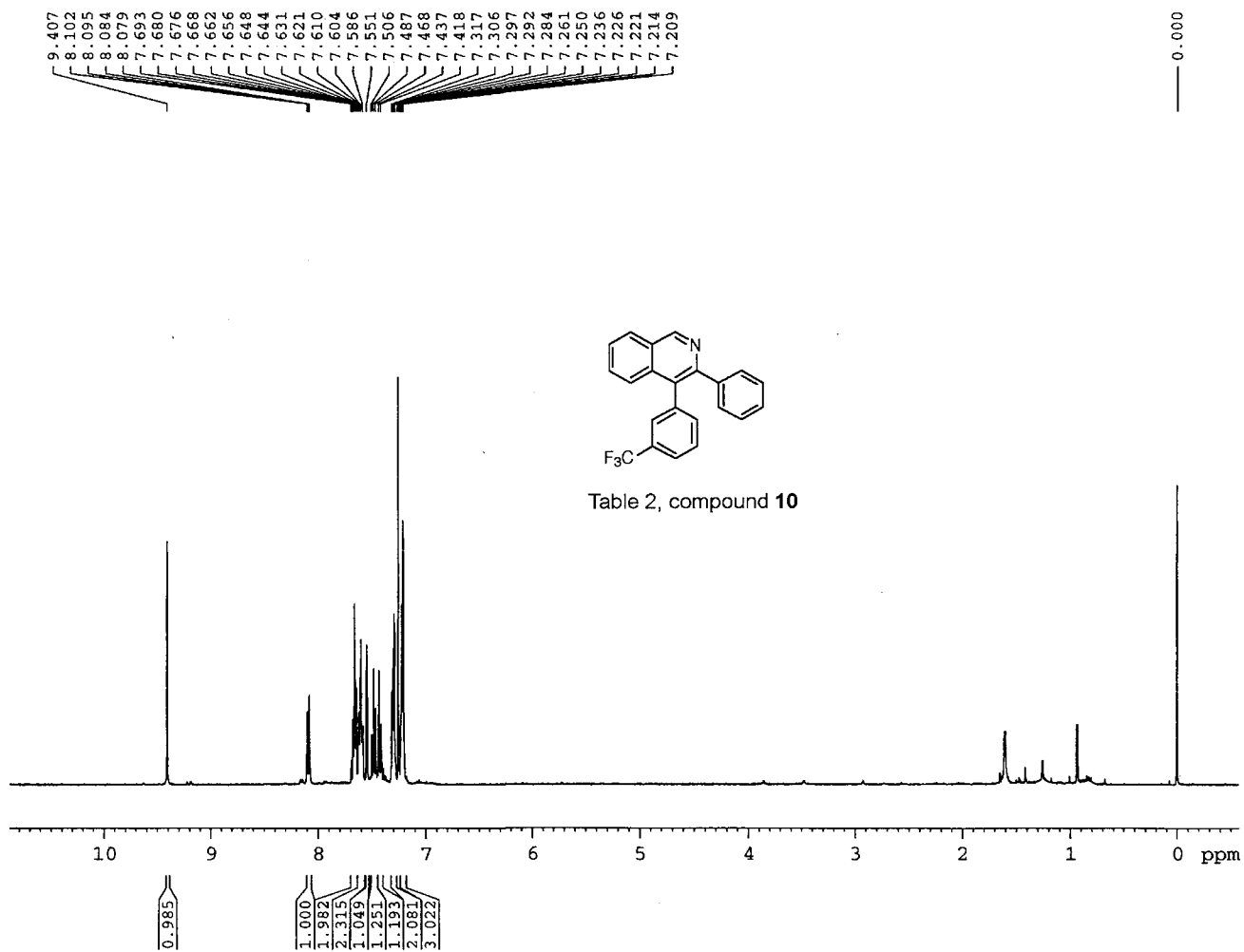
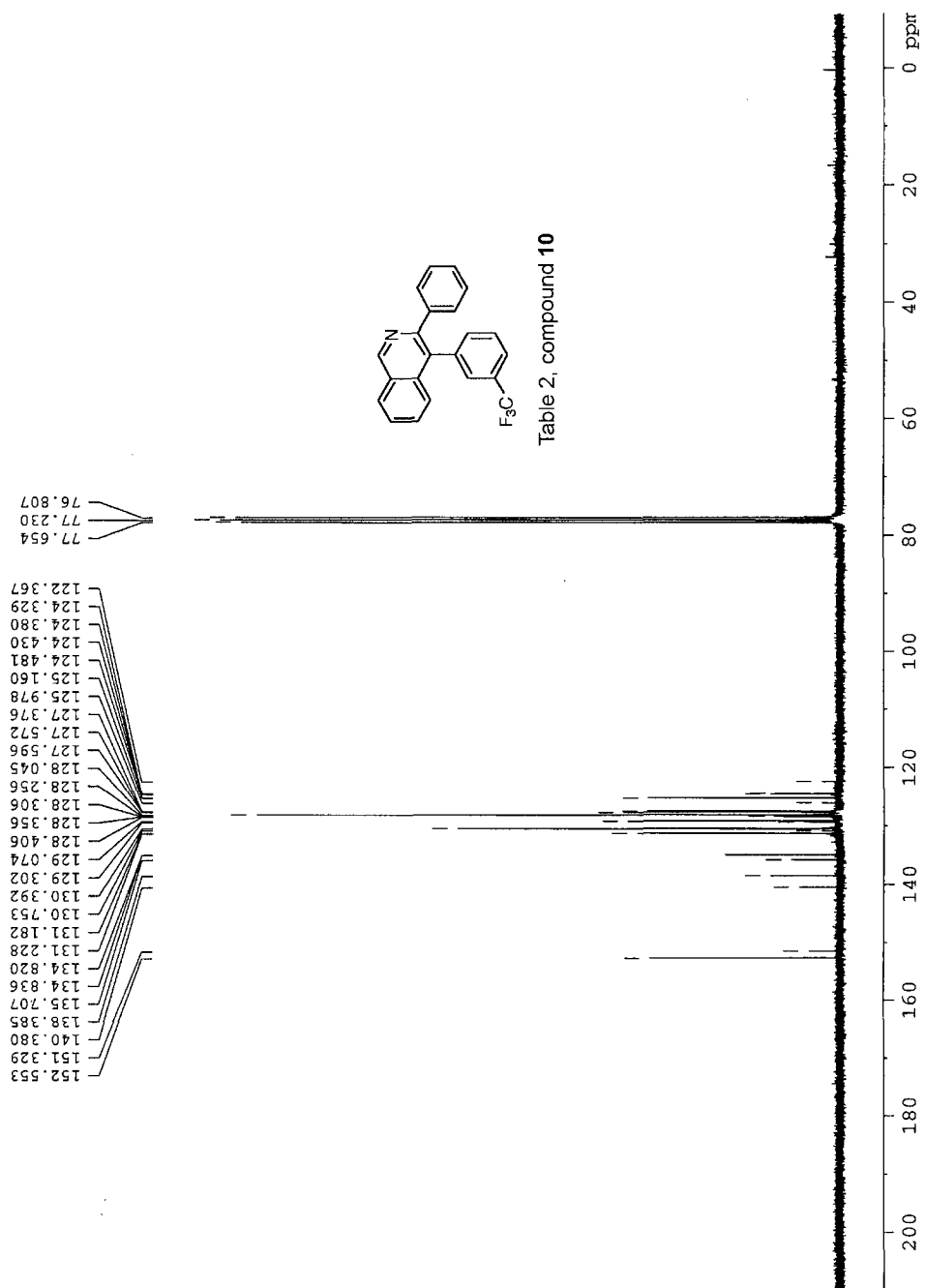
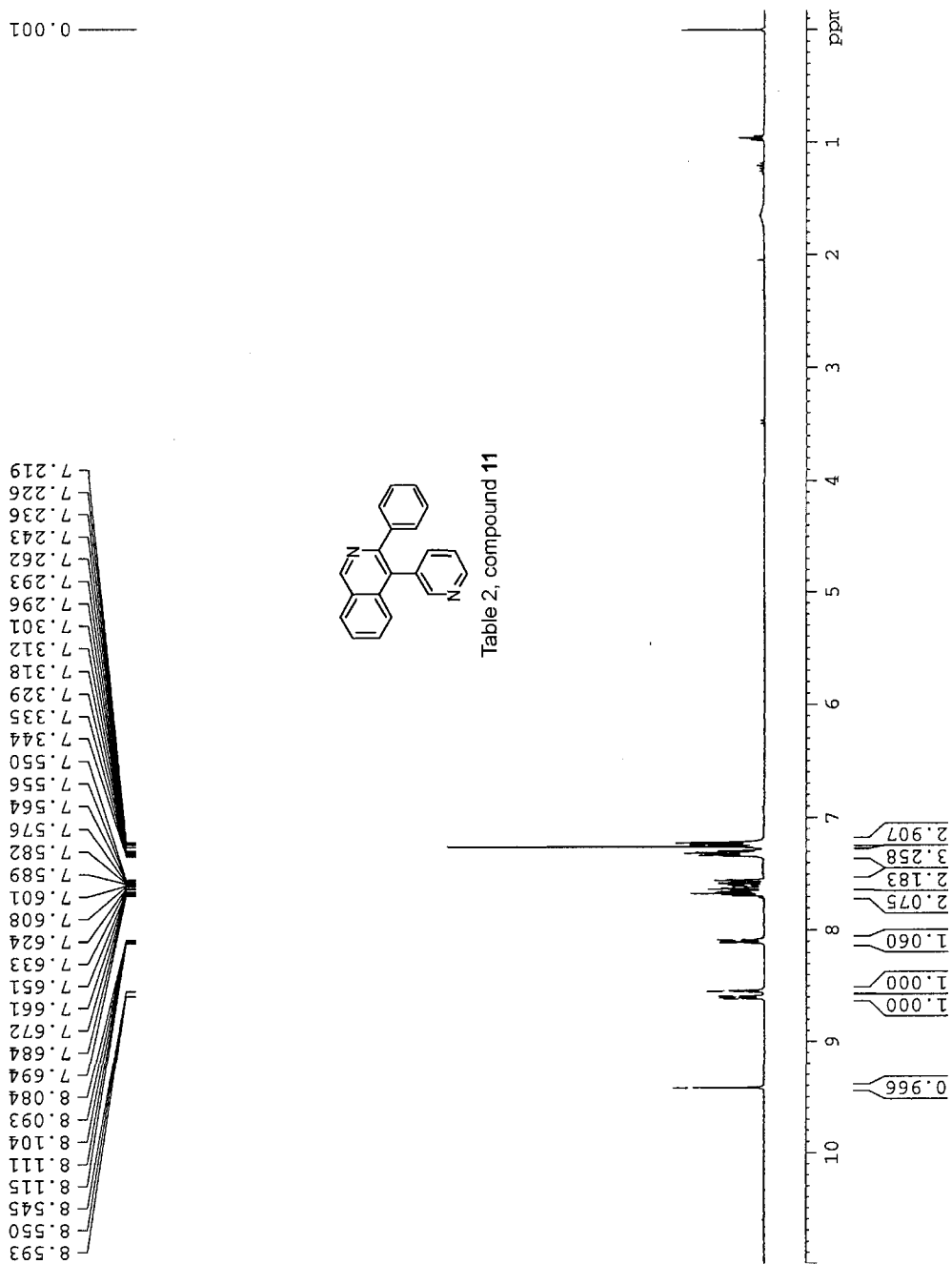


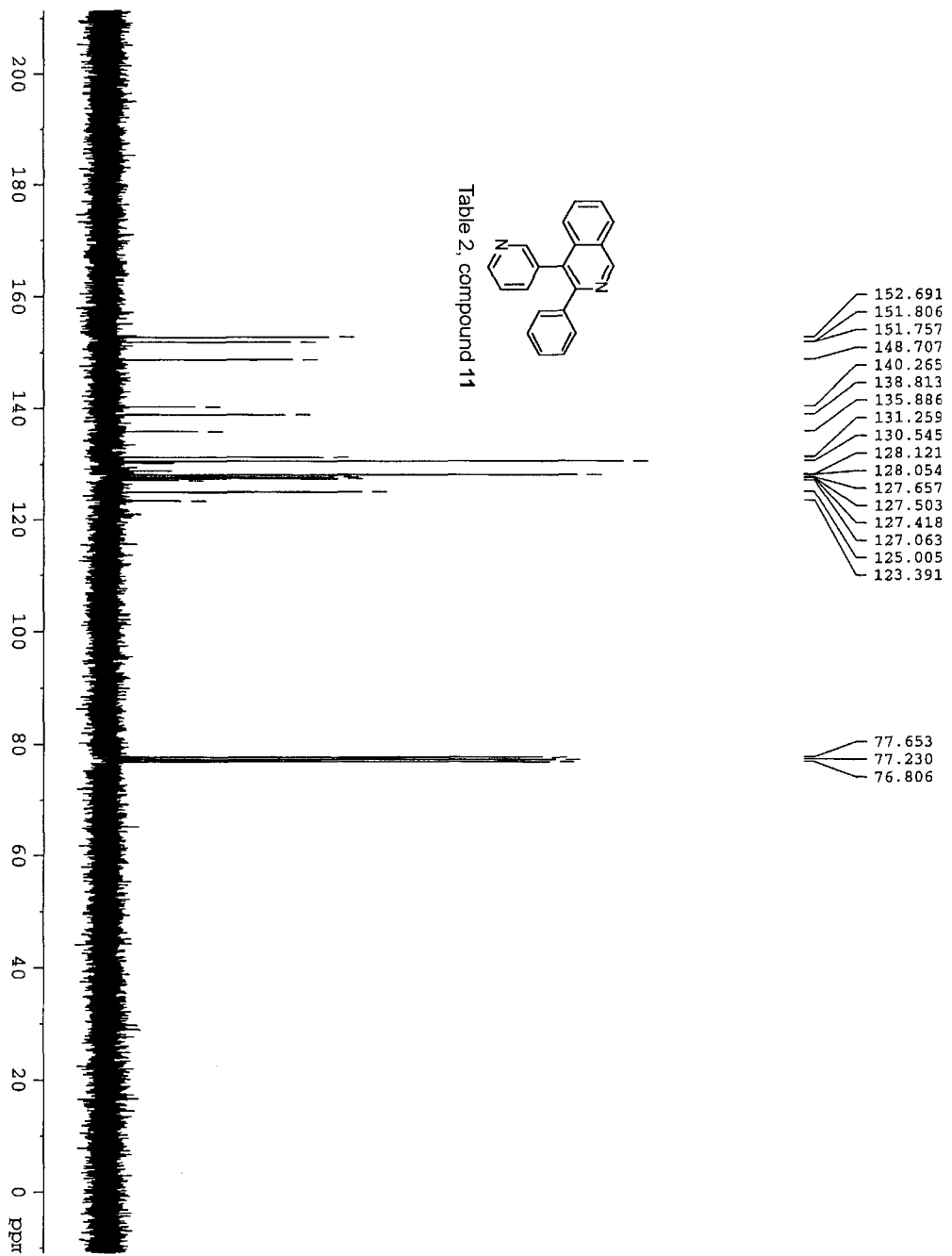
Table 2, compound 9

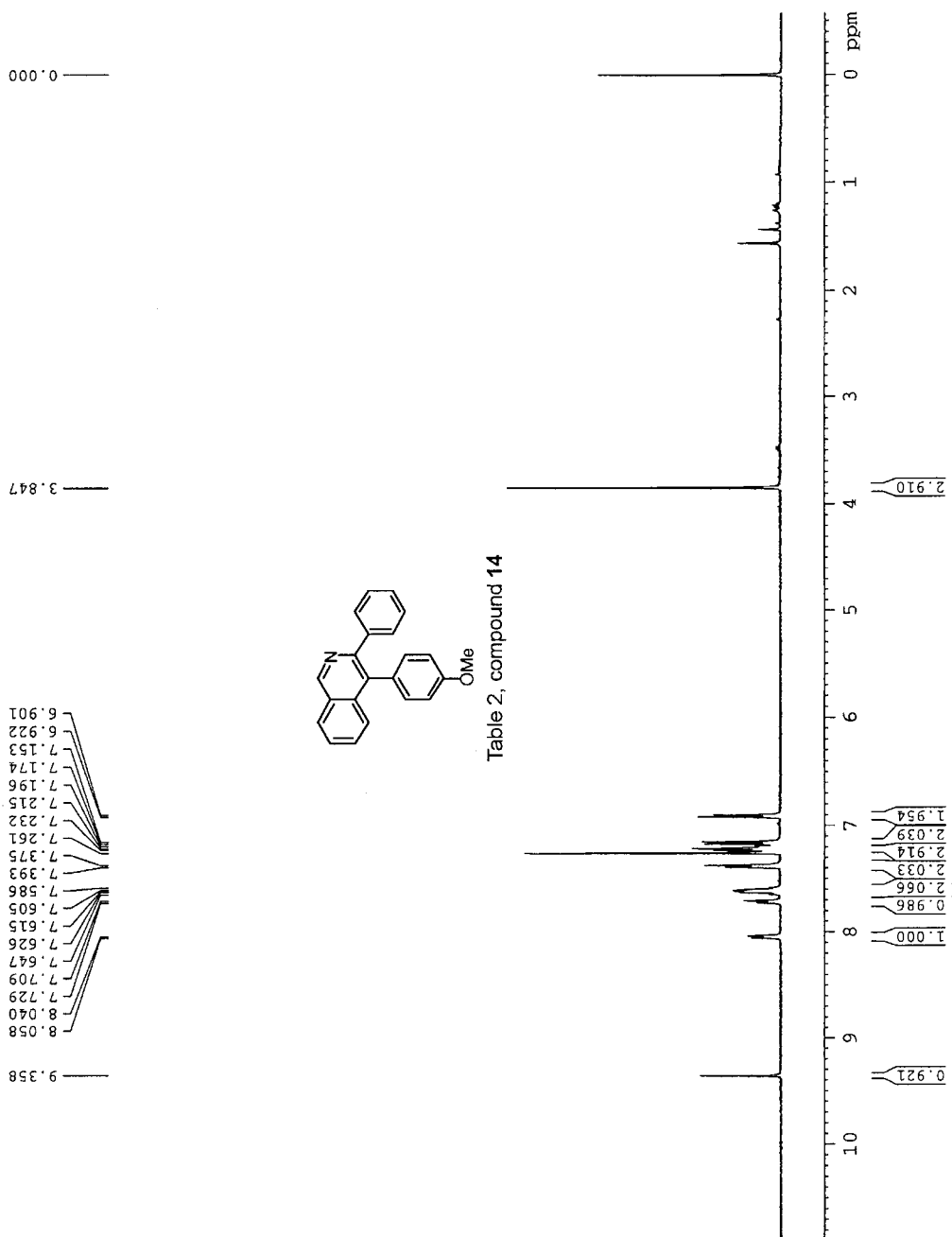












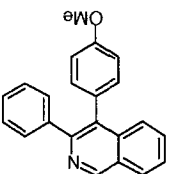
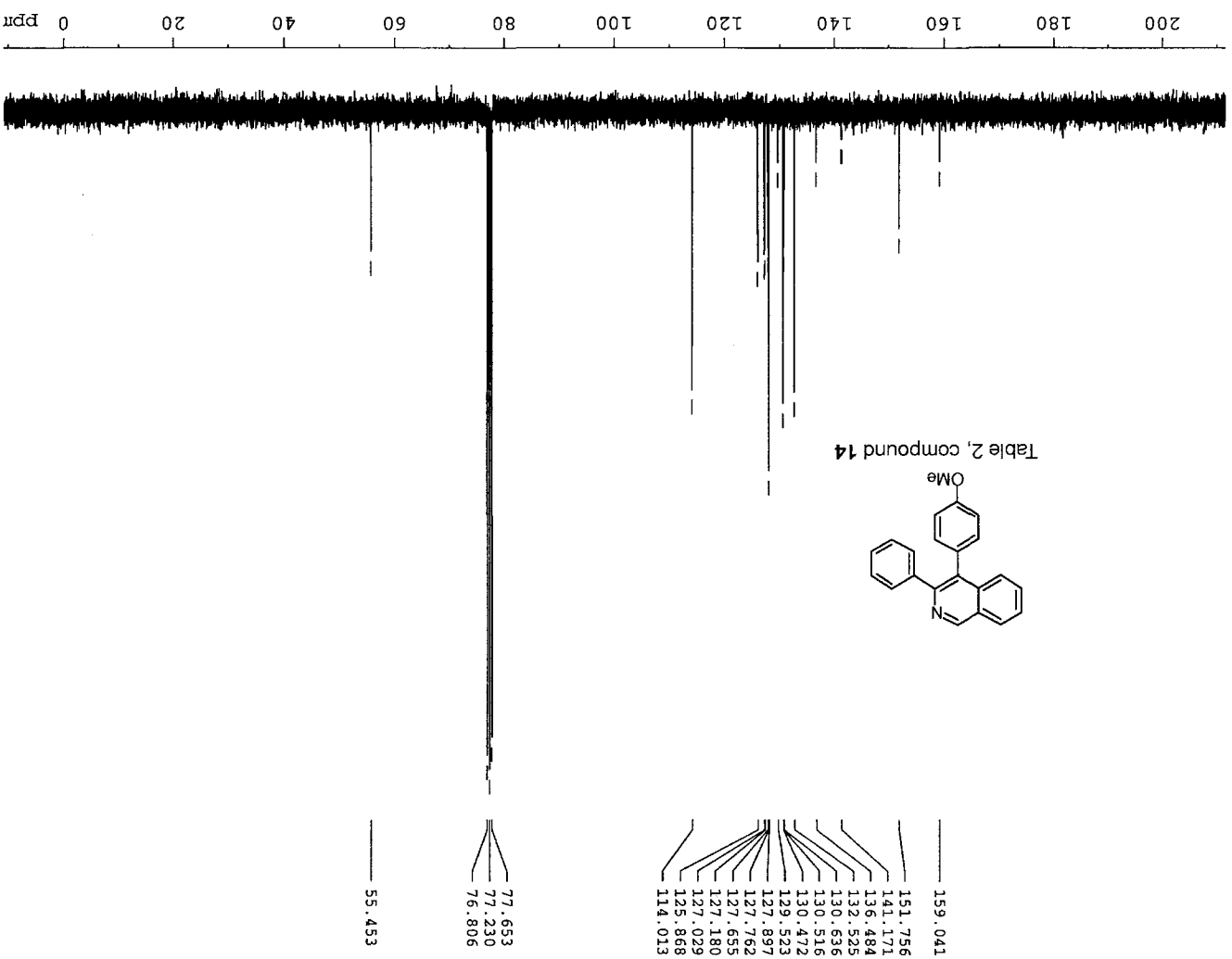
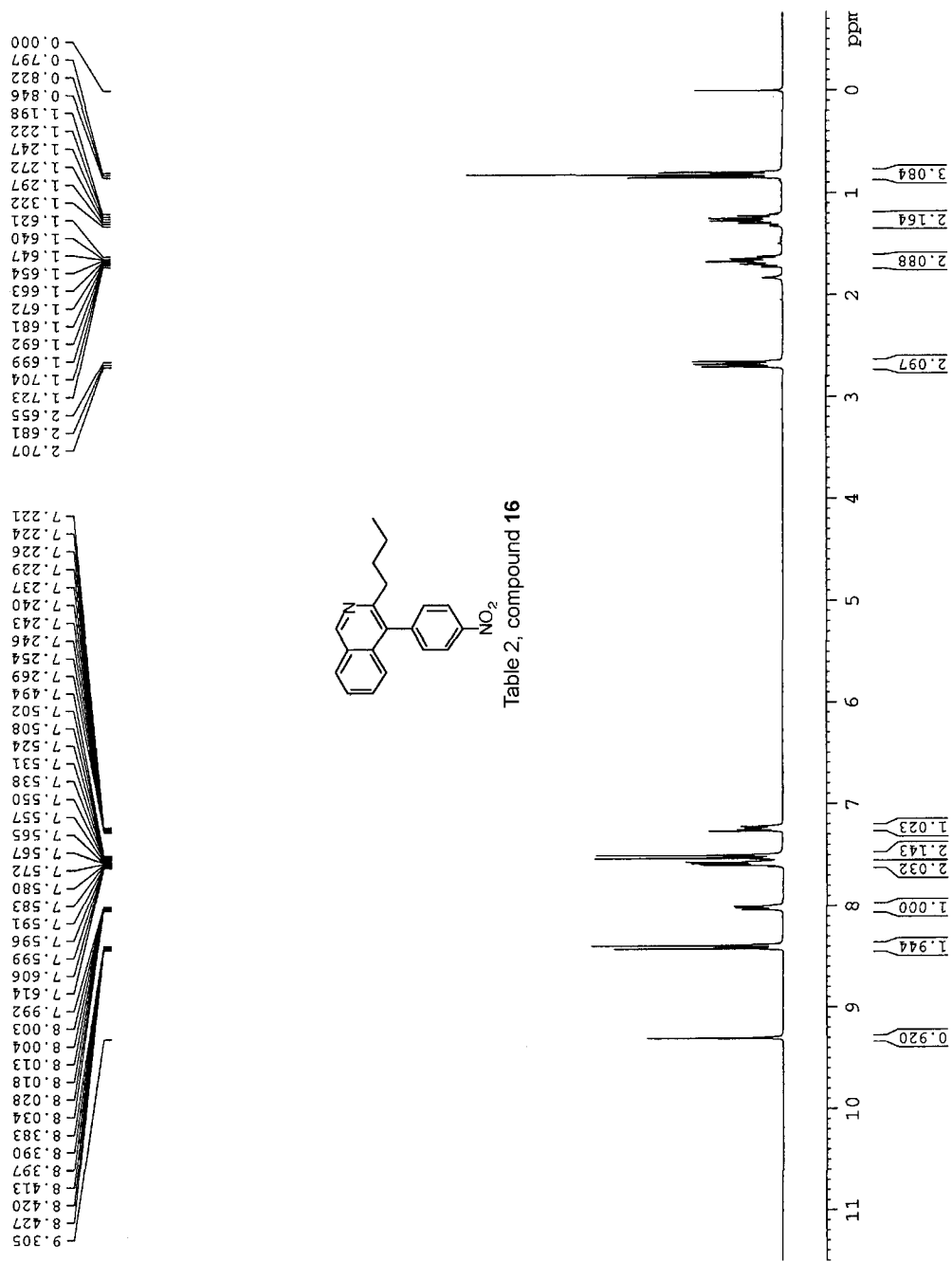


Table 2, compound 14





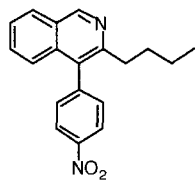
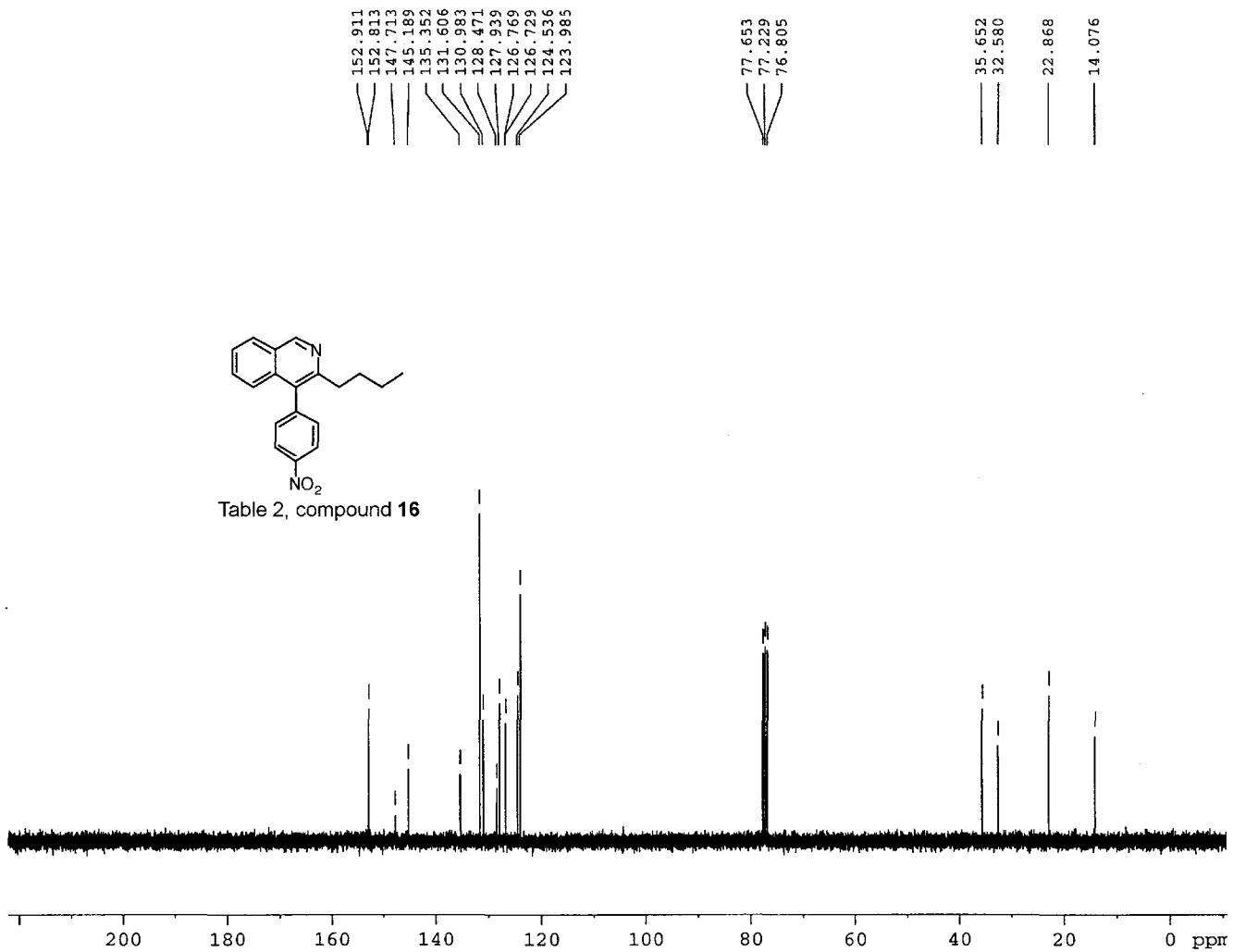
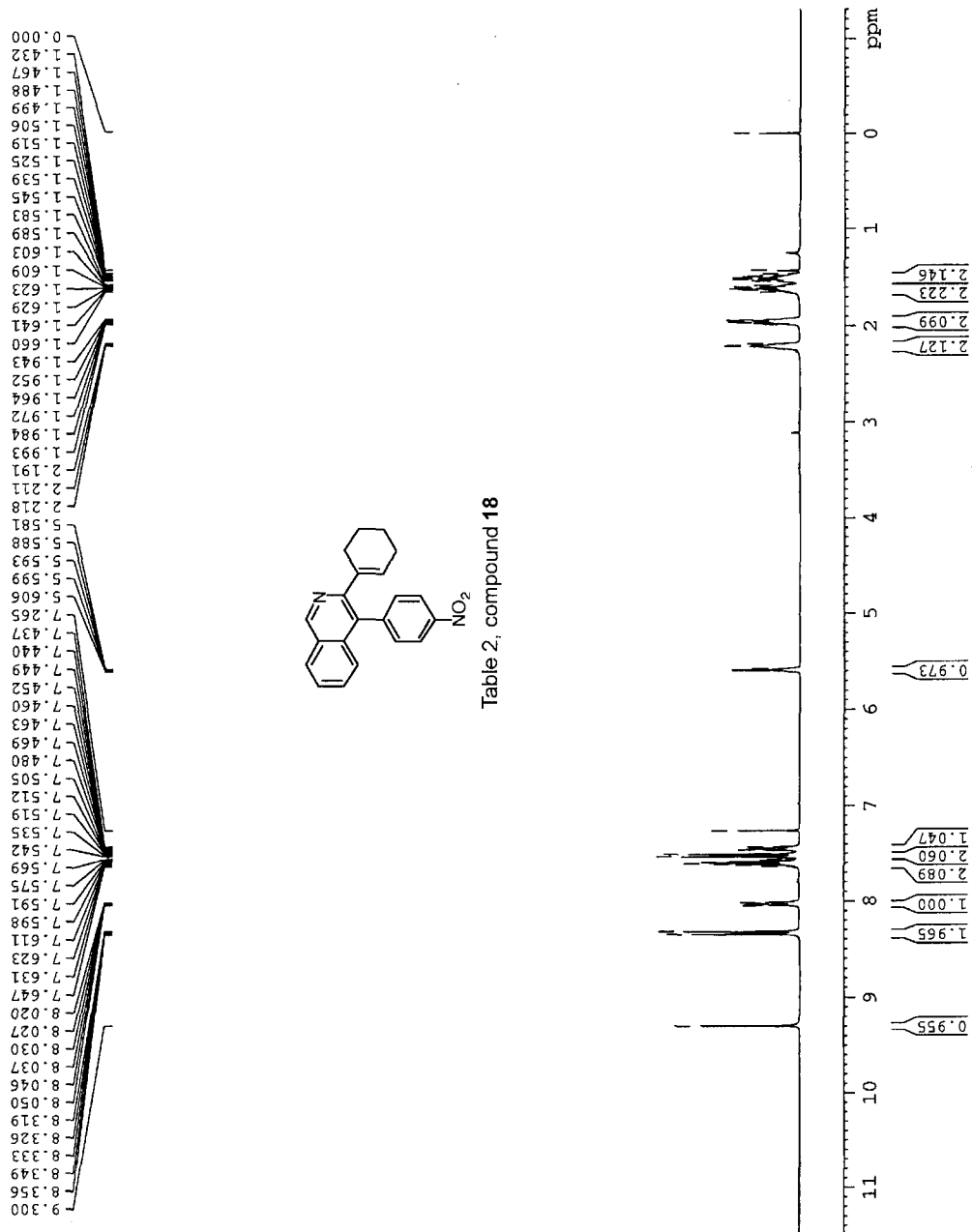


Table 2, compound 16





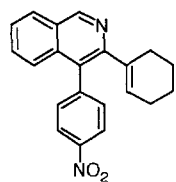
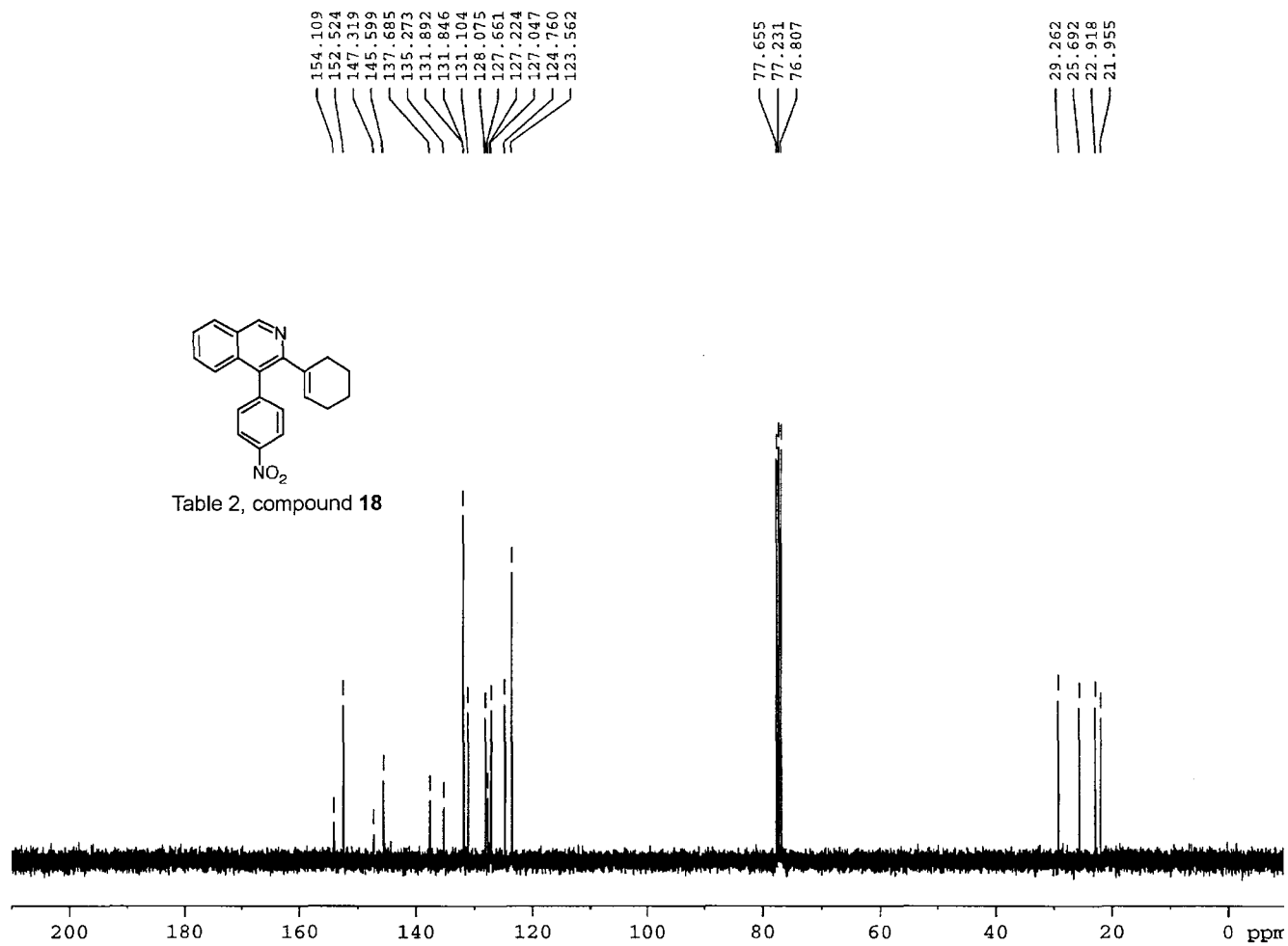
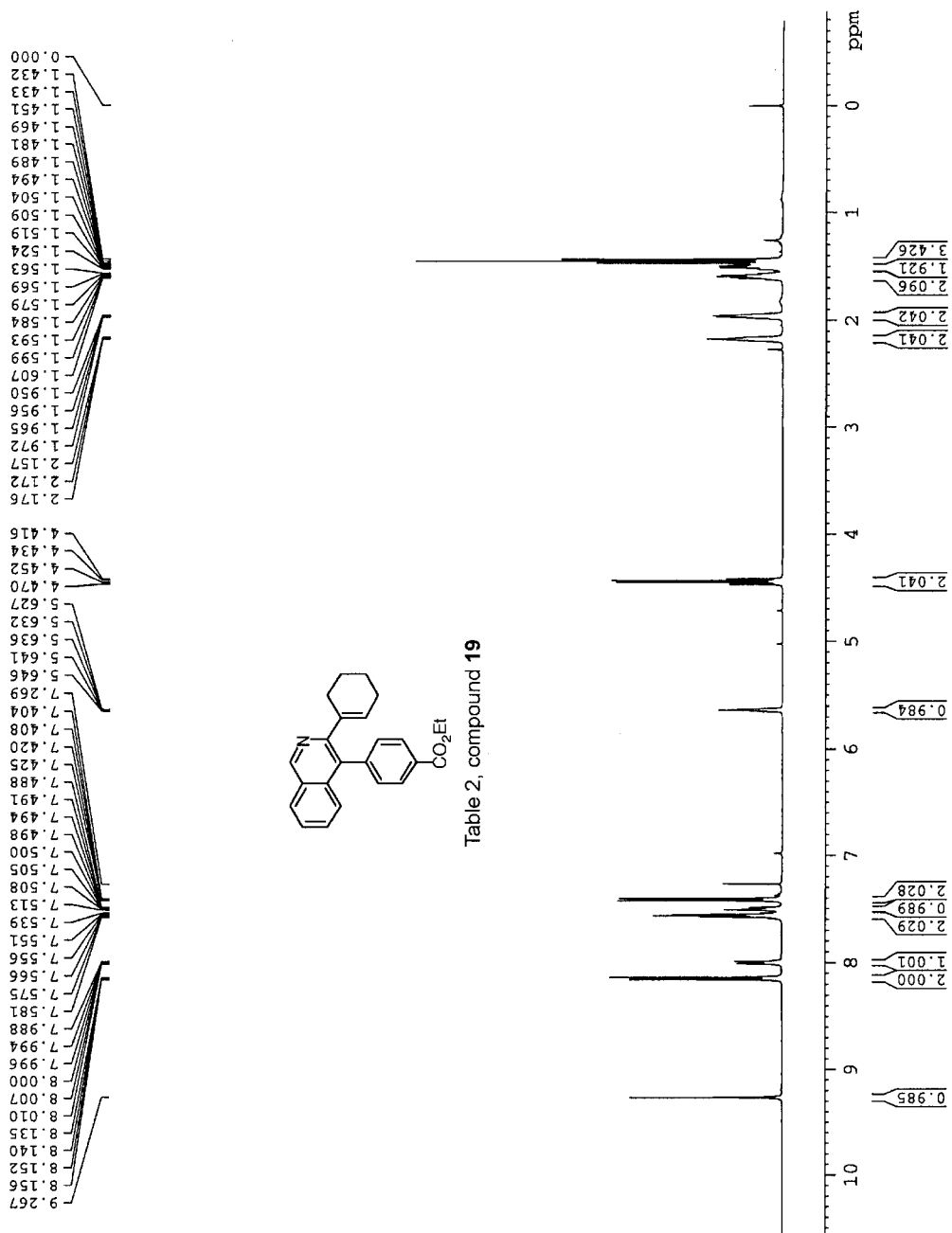


Table 2, compound 18





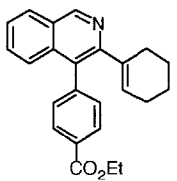


Table 2, compound 19

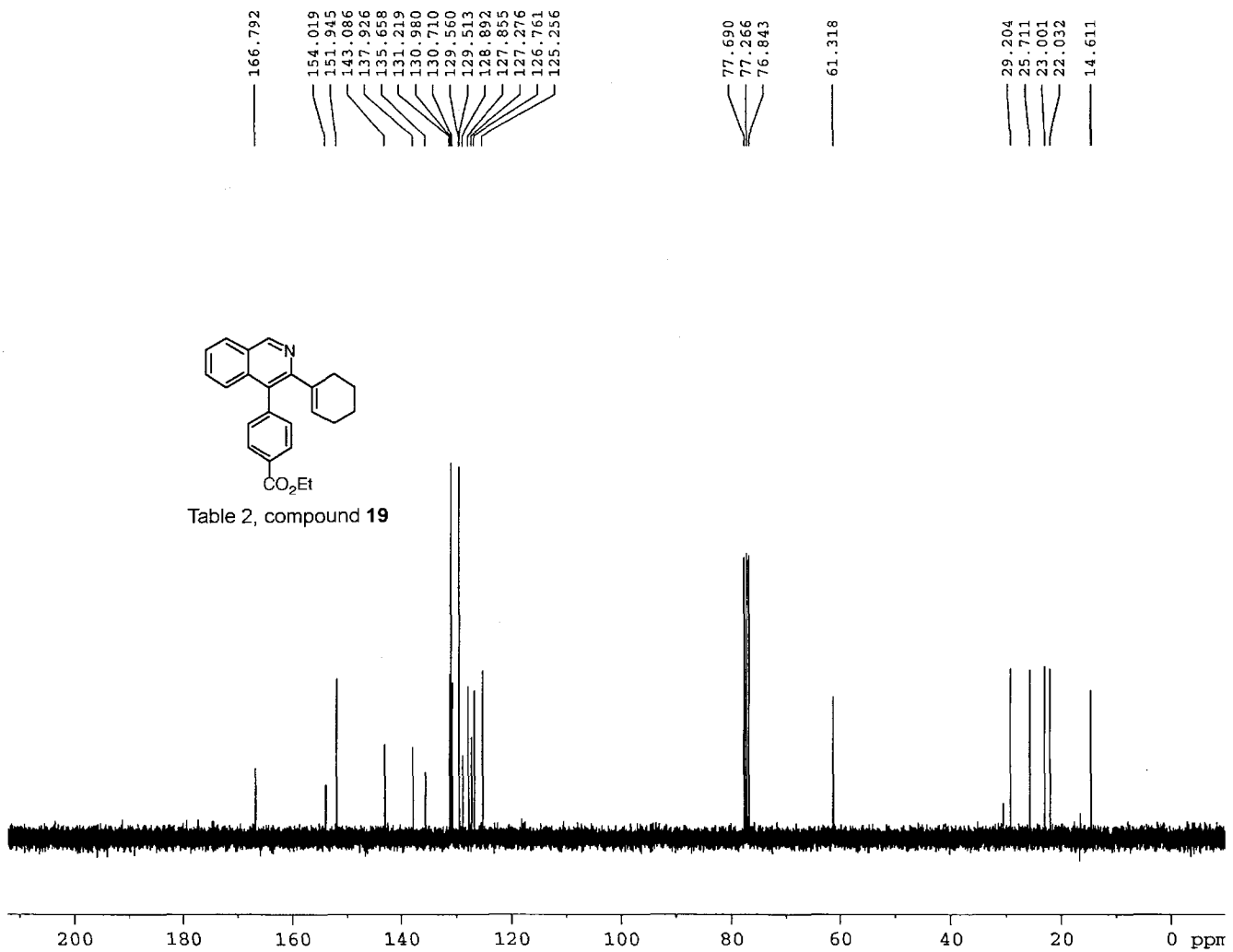
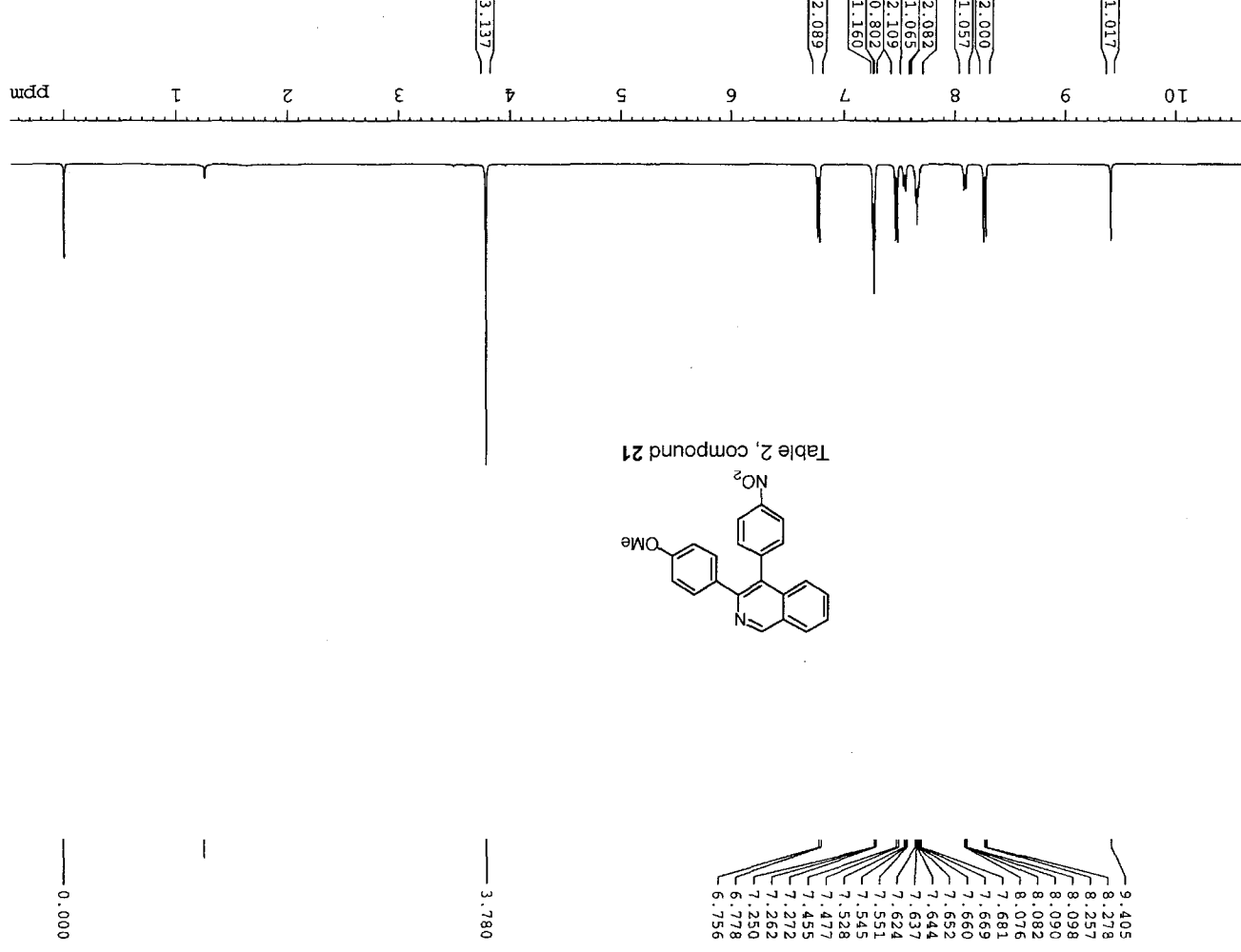
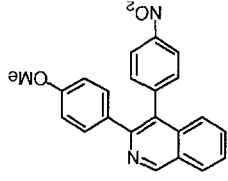


Table 2, compound 21



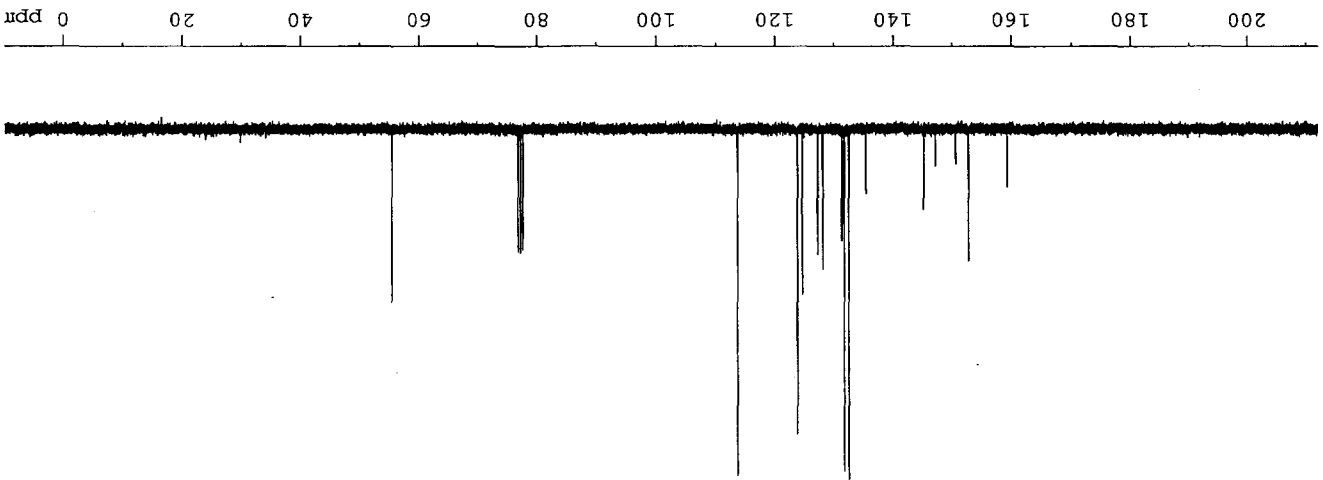
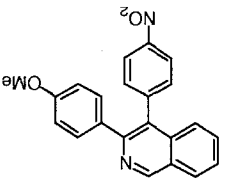


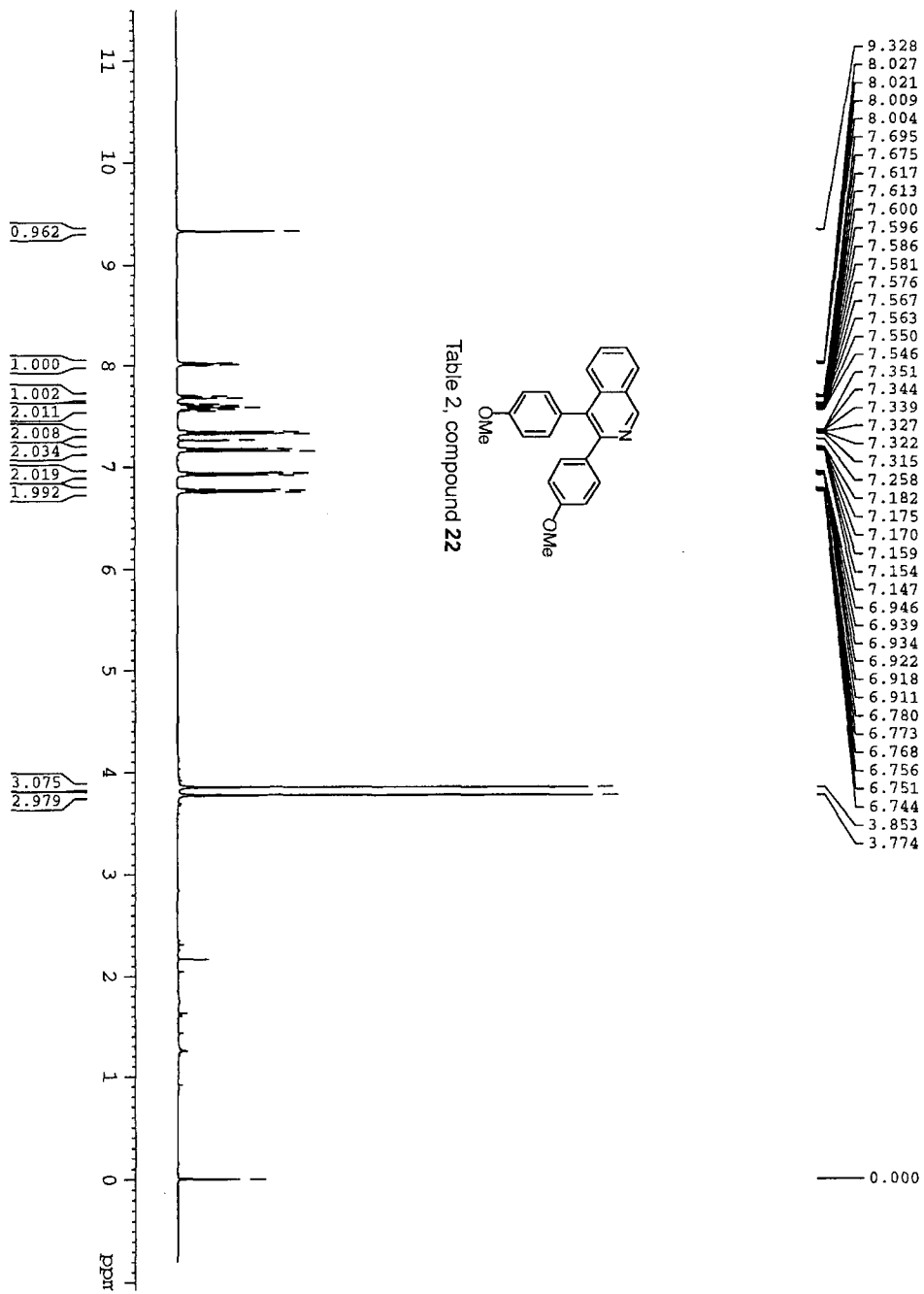
Table 2, compound 21

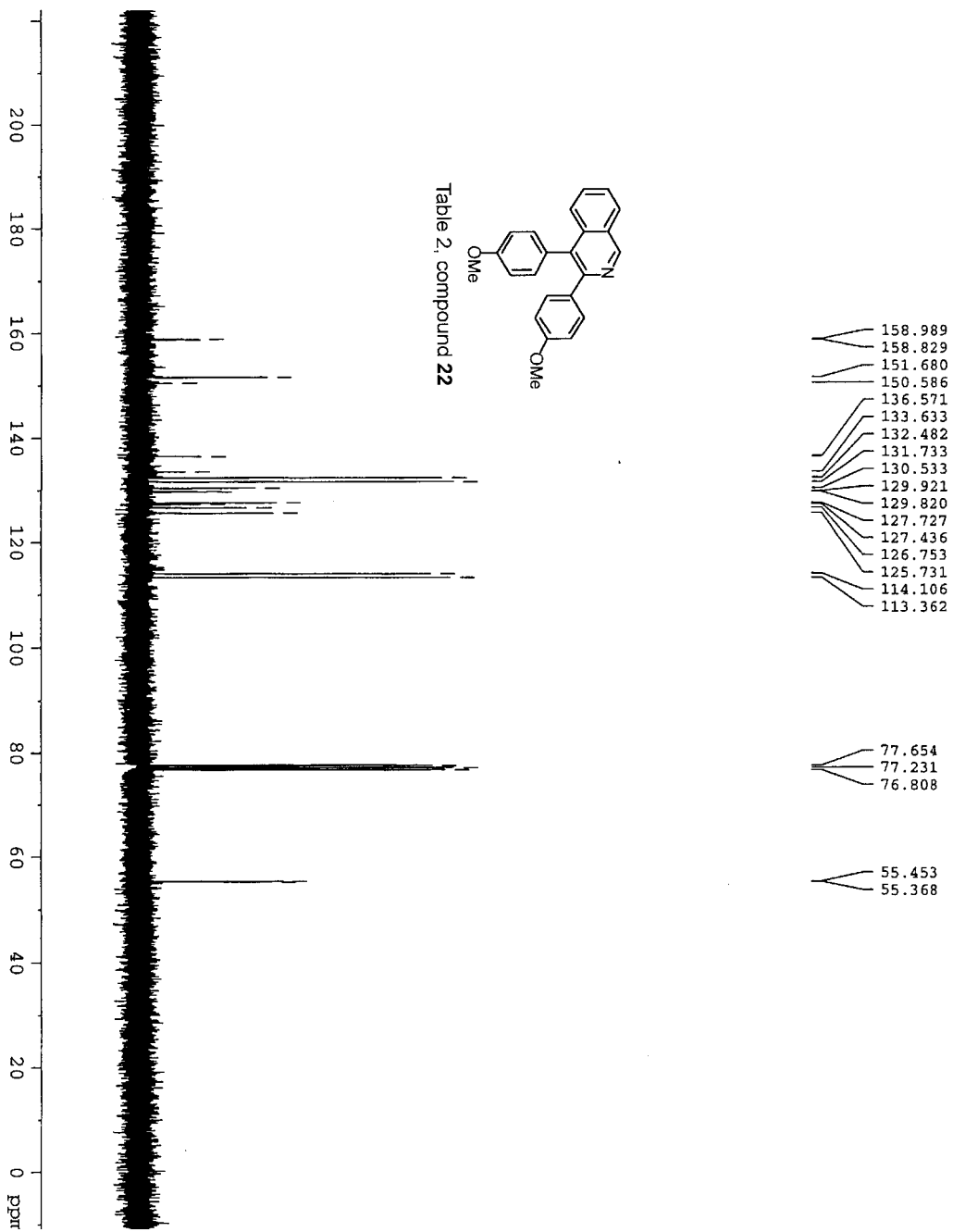


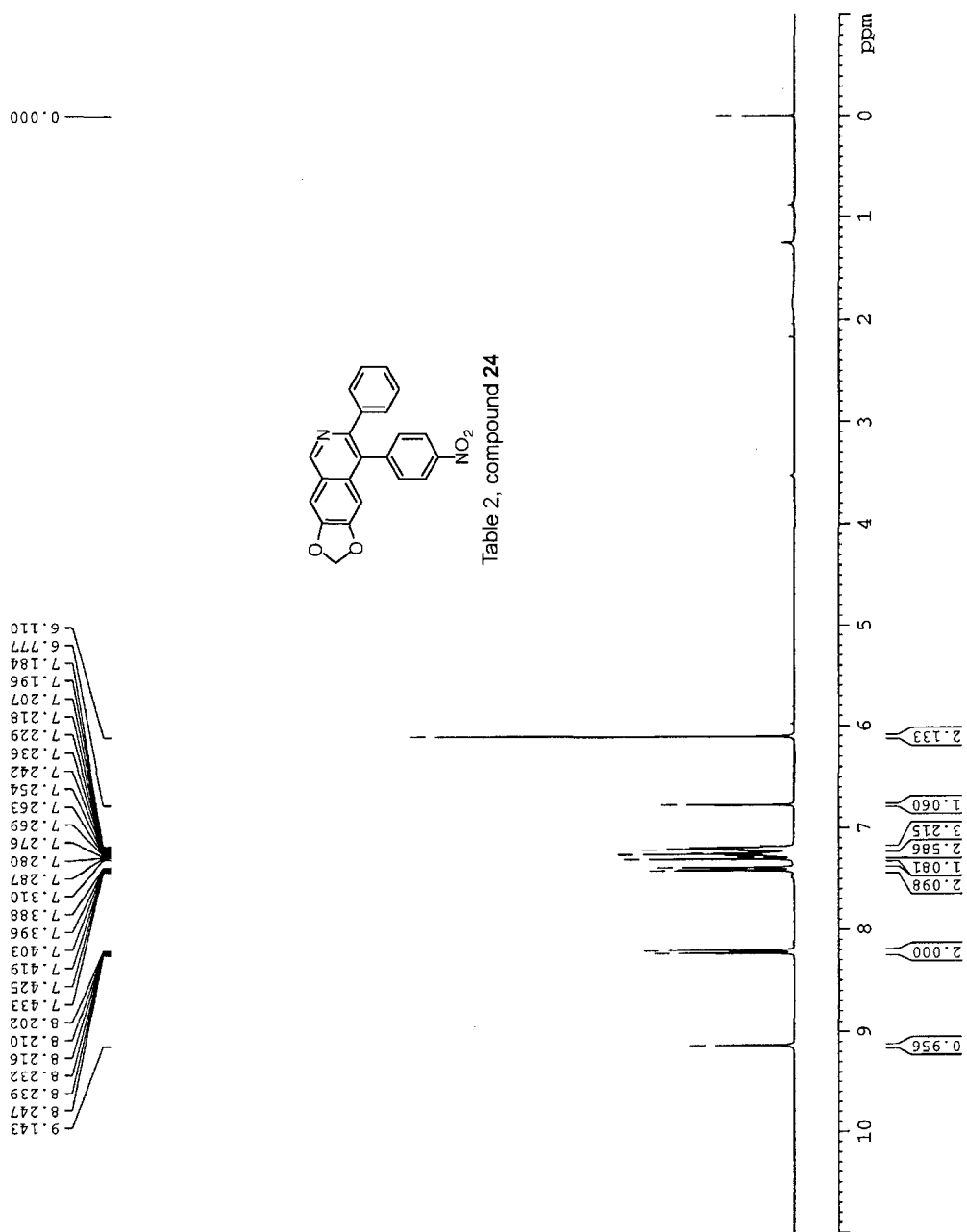
- 159.299
- 152.842
- 150.647
- 147.207
- 145.224
- 135.321
- 132.481
- 131.725
- 131.306
- 128.118
- 128.032
- 127.269
- 127.190
- 124.645
- 123.824
- 113.632

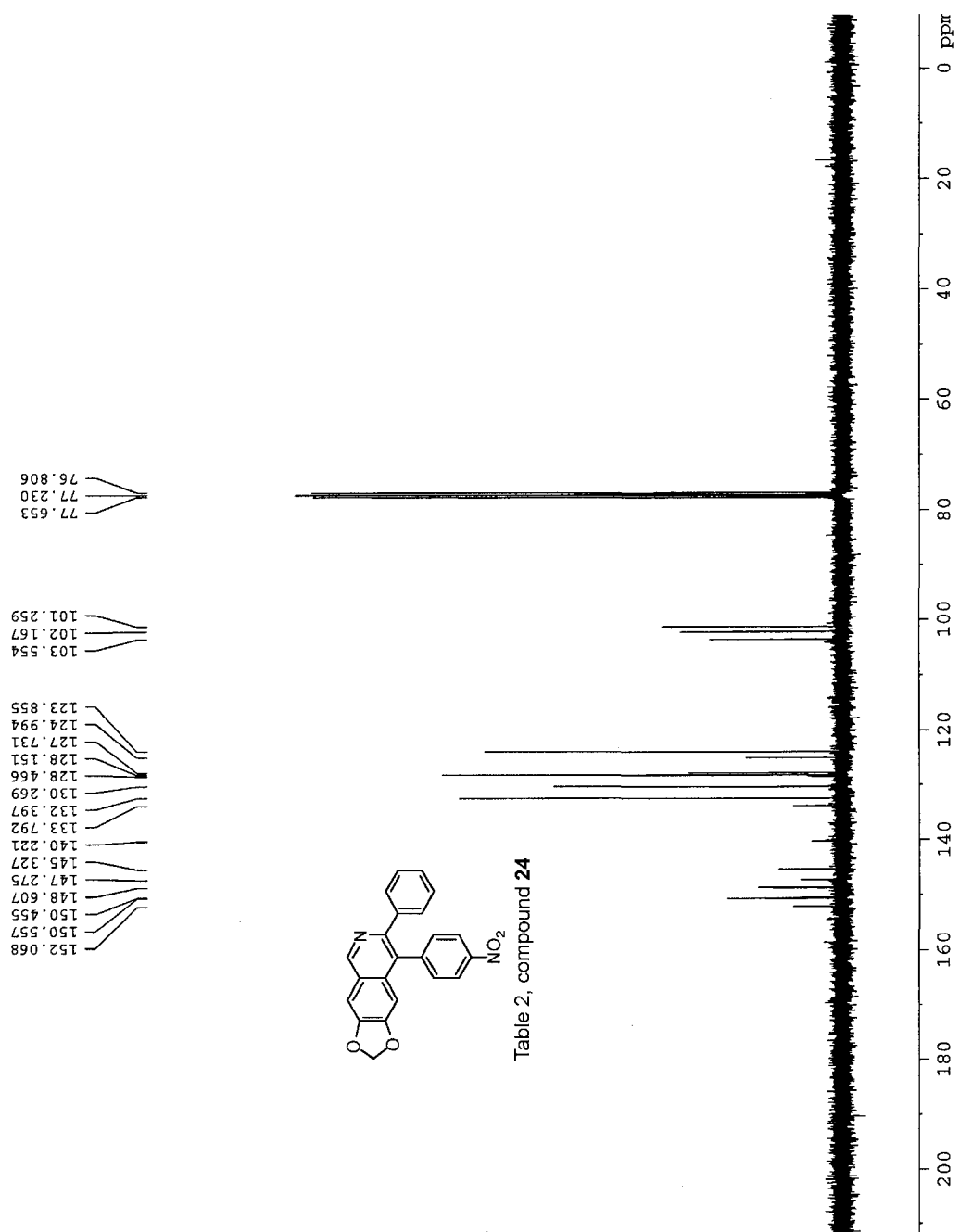
- 77.657
- 77.233
- 76.809

- 55.349









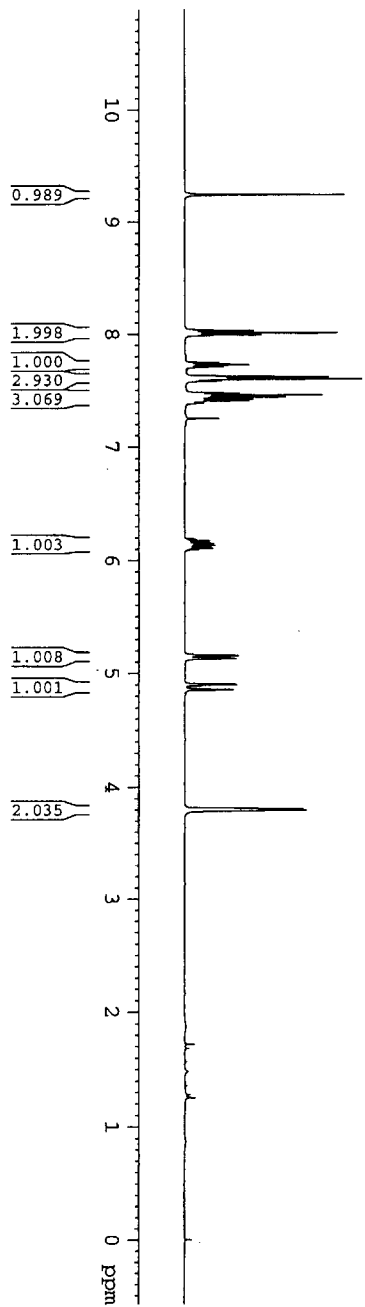
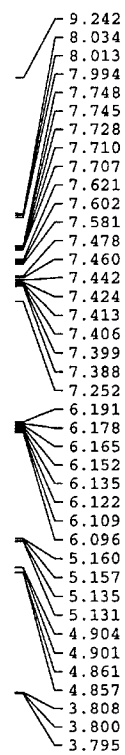
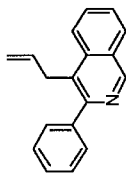
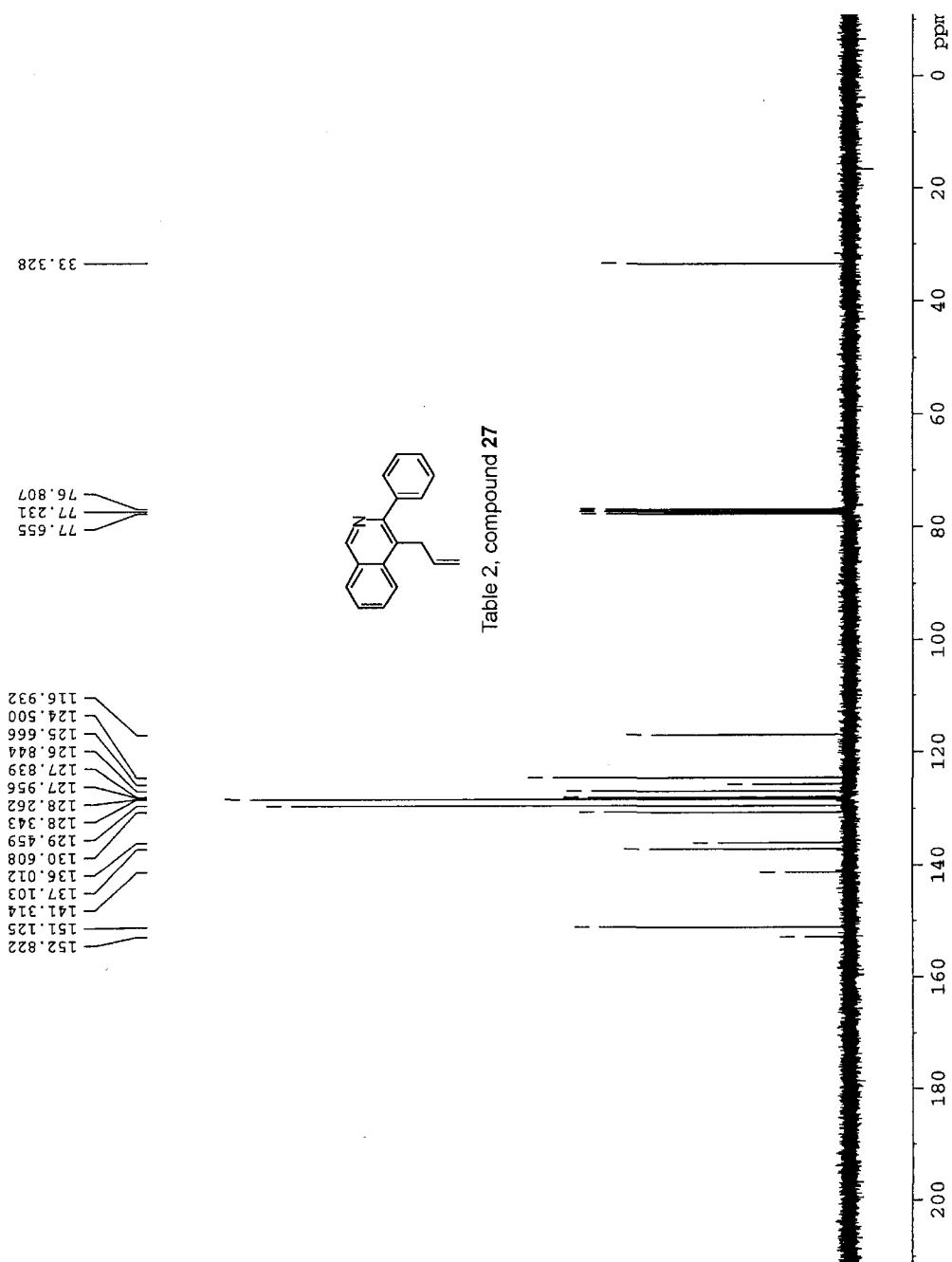
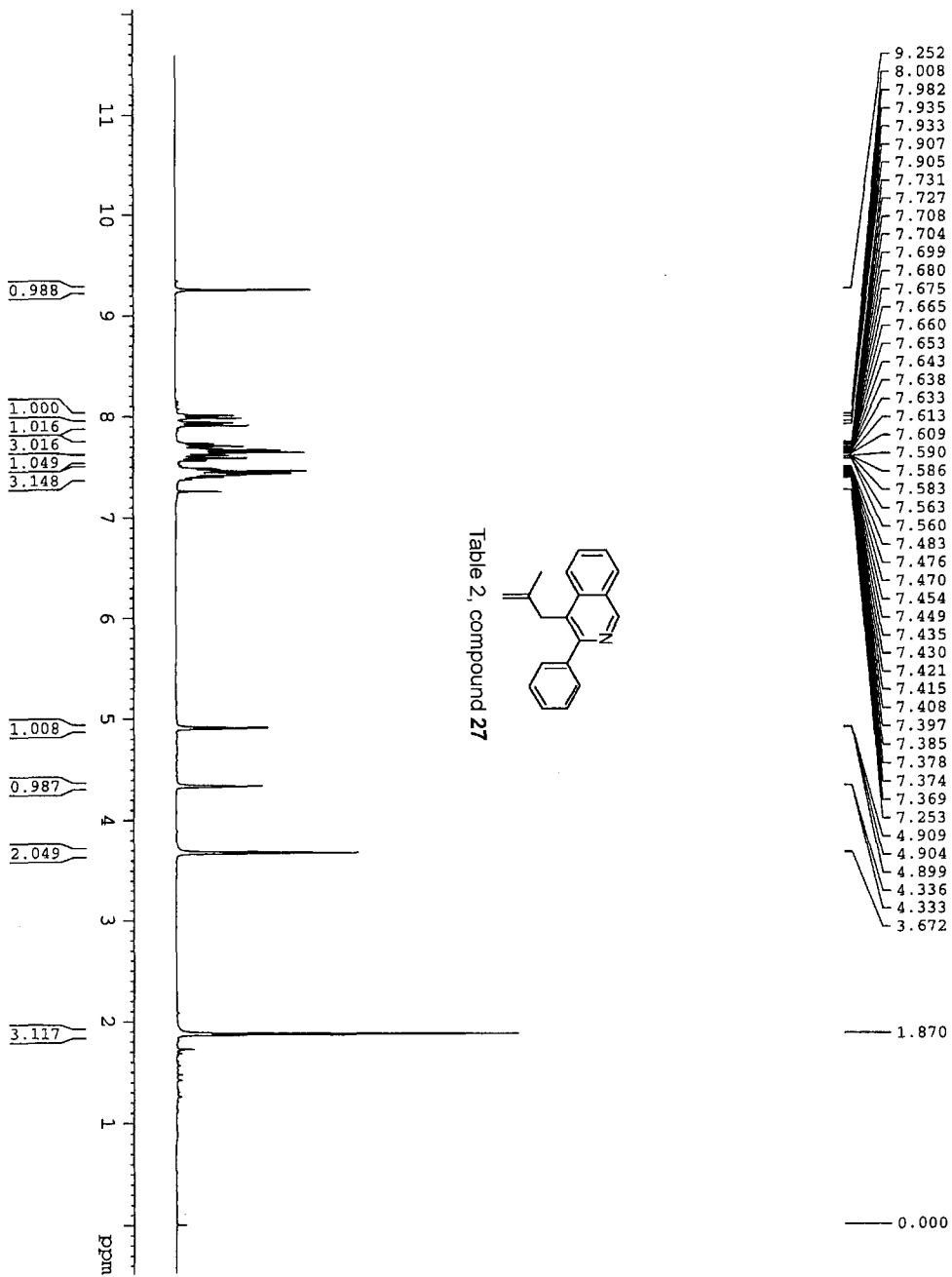


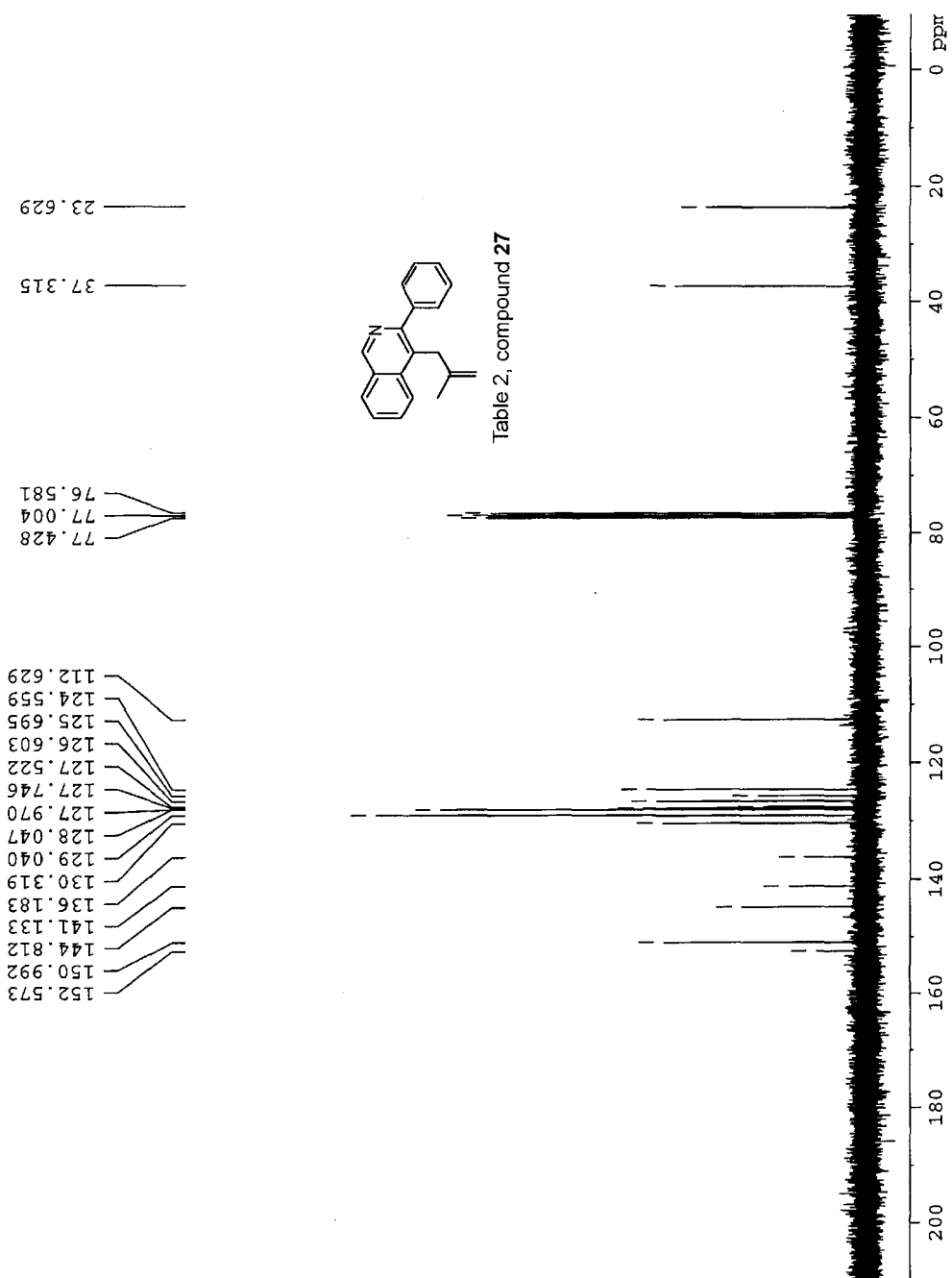
Table 2, compound 27

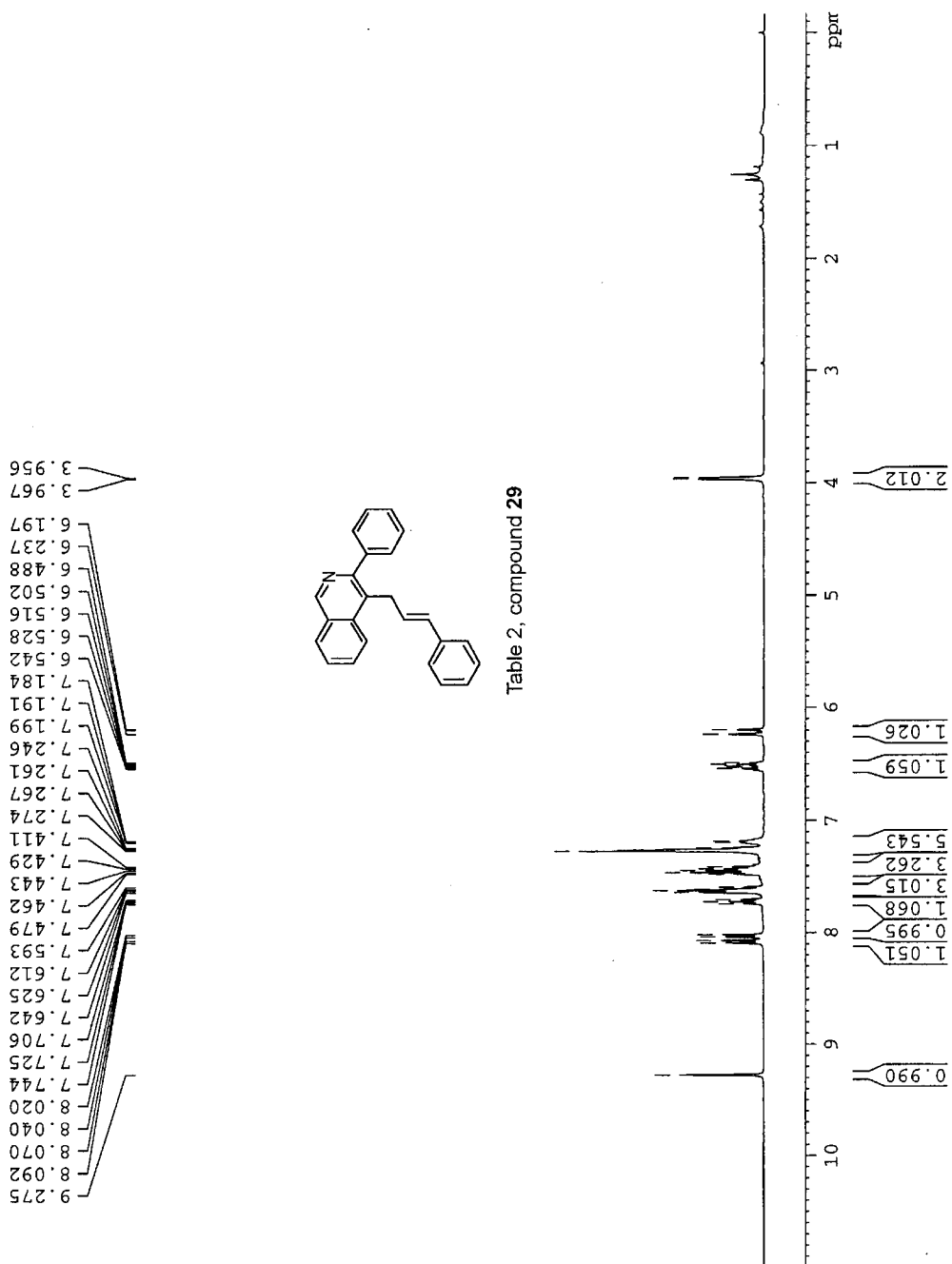


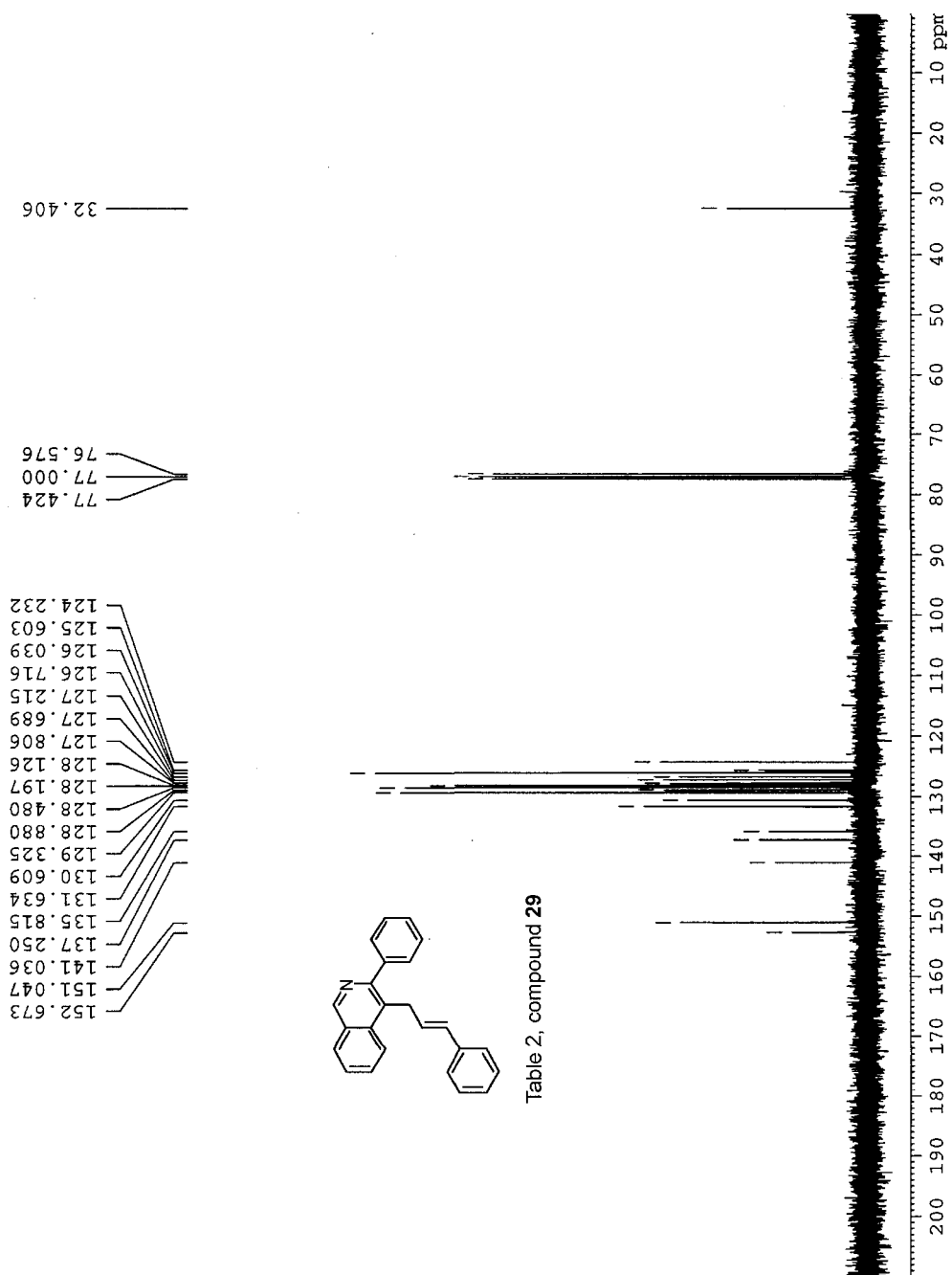
0.000

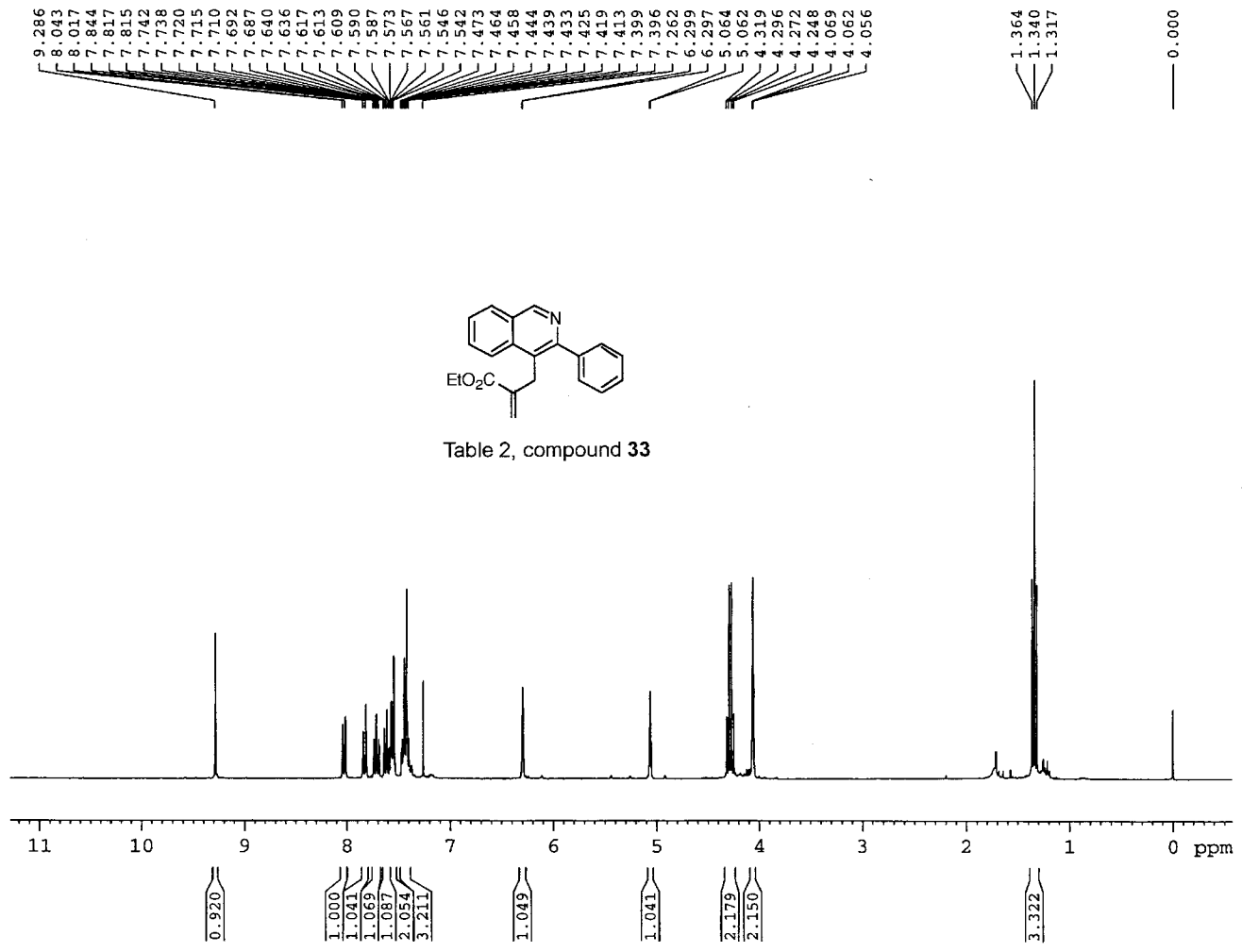


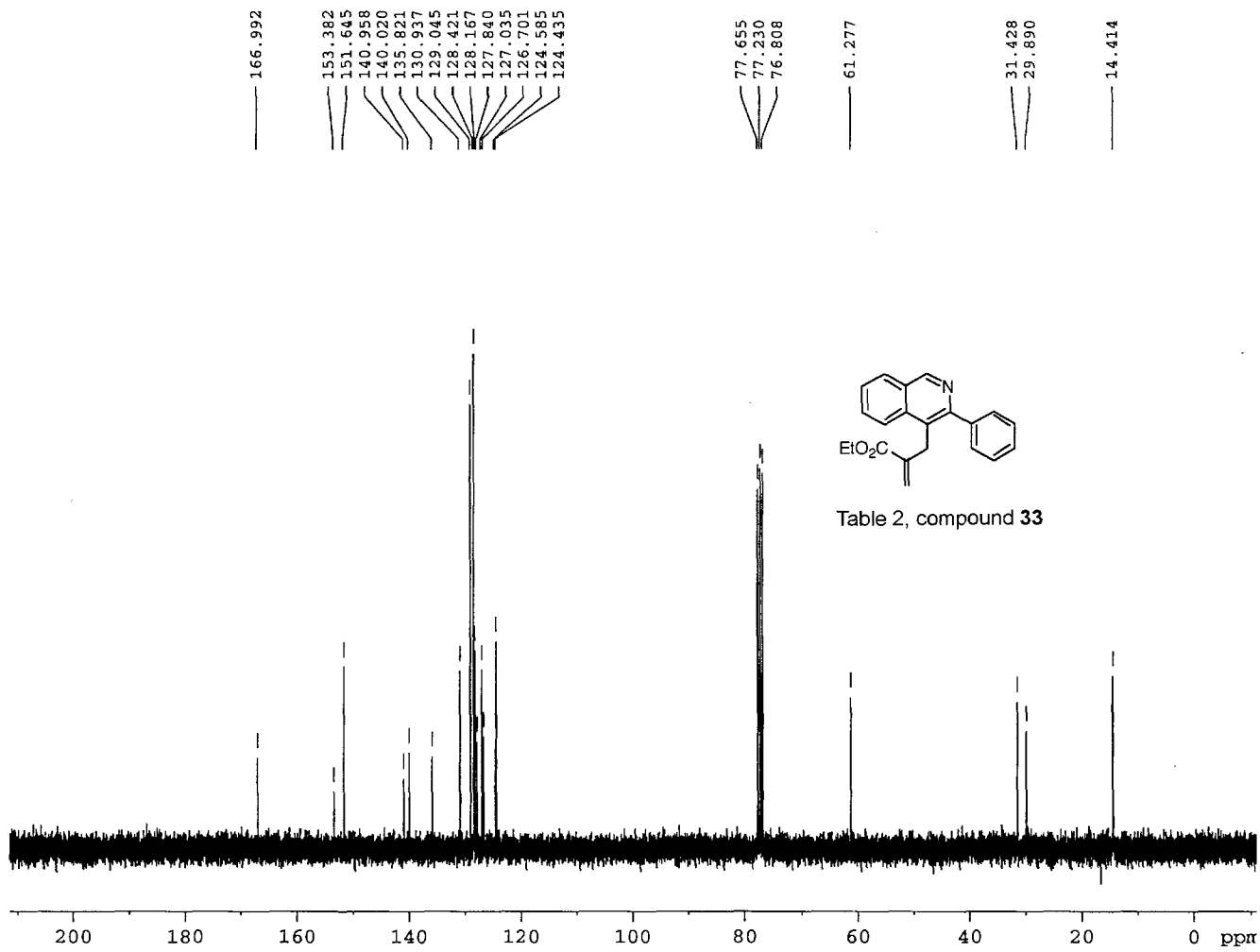


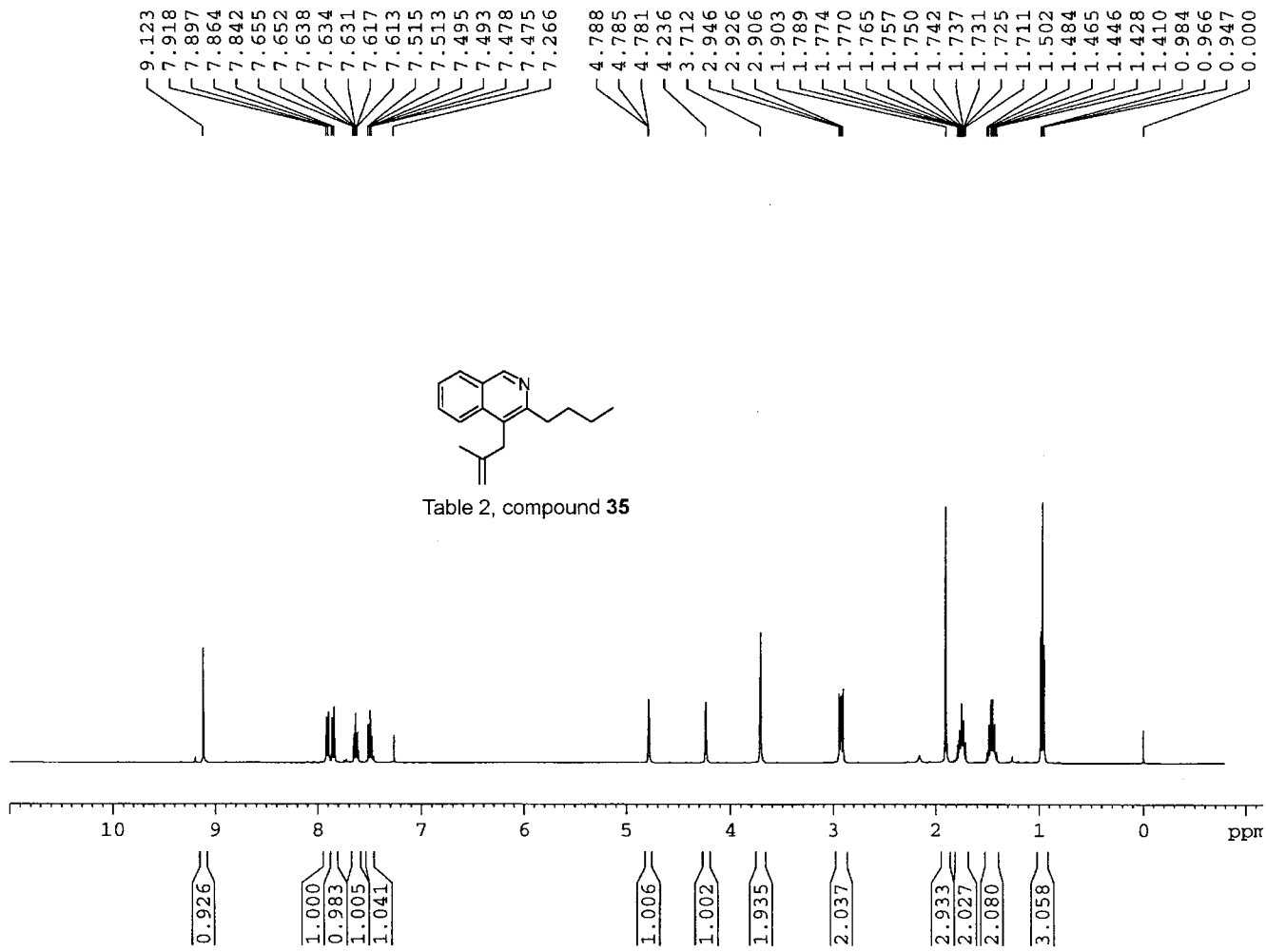












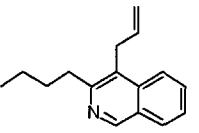
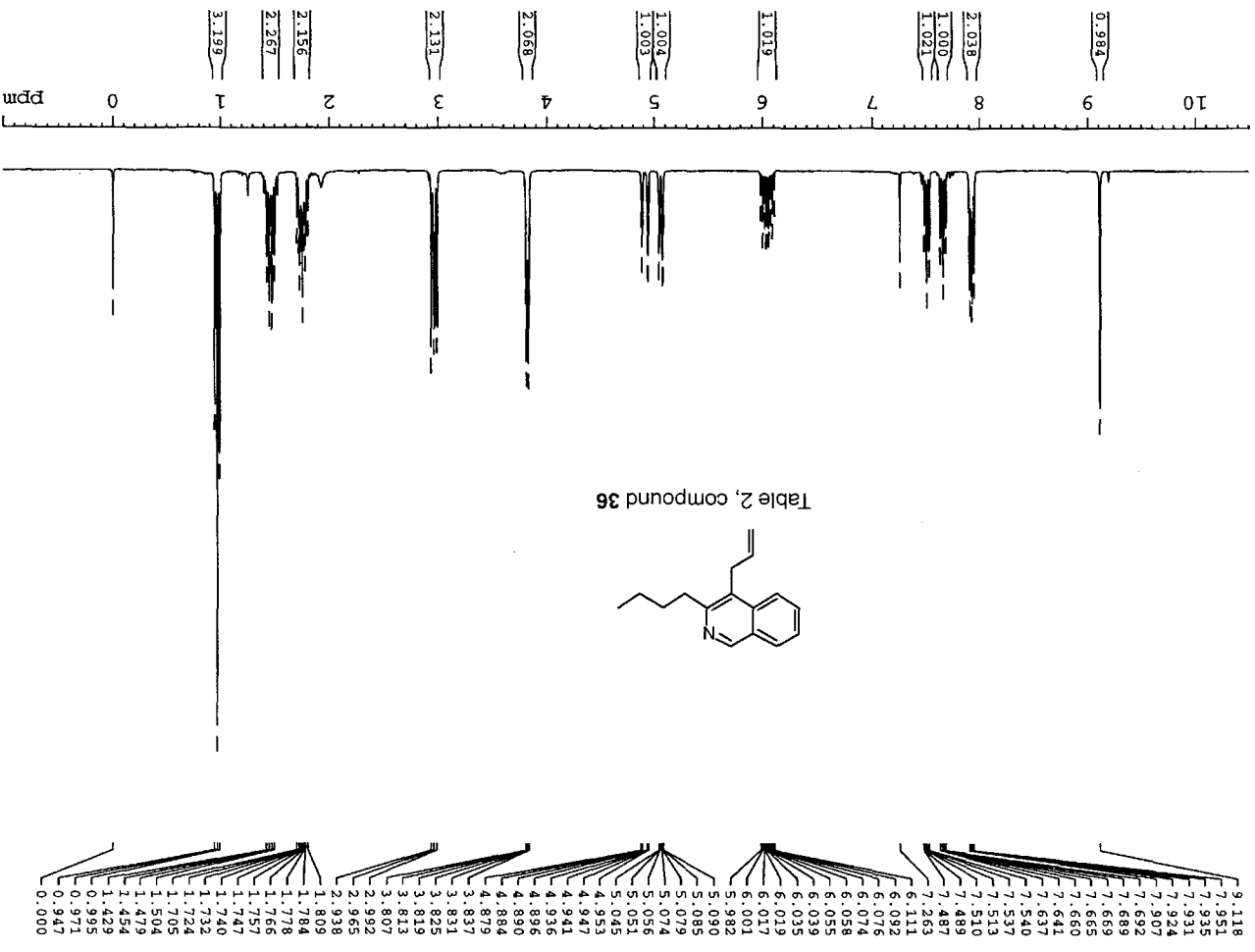


Table 2, compound 36



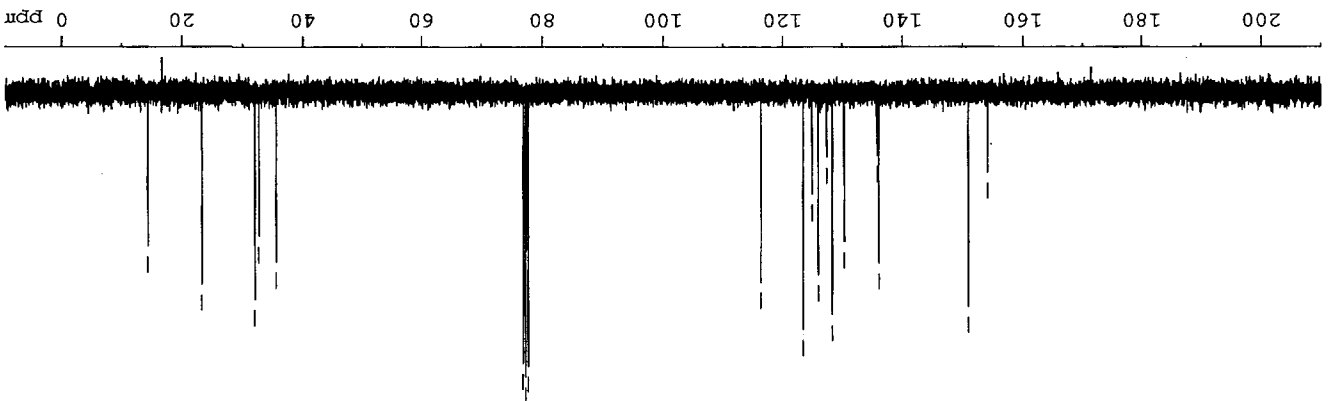
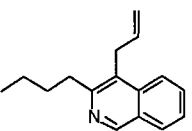
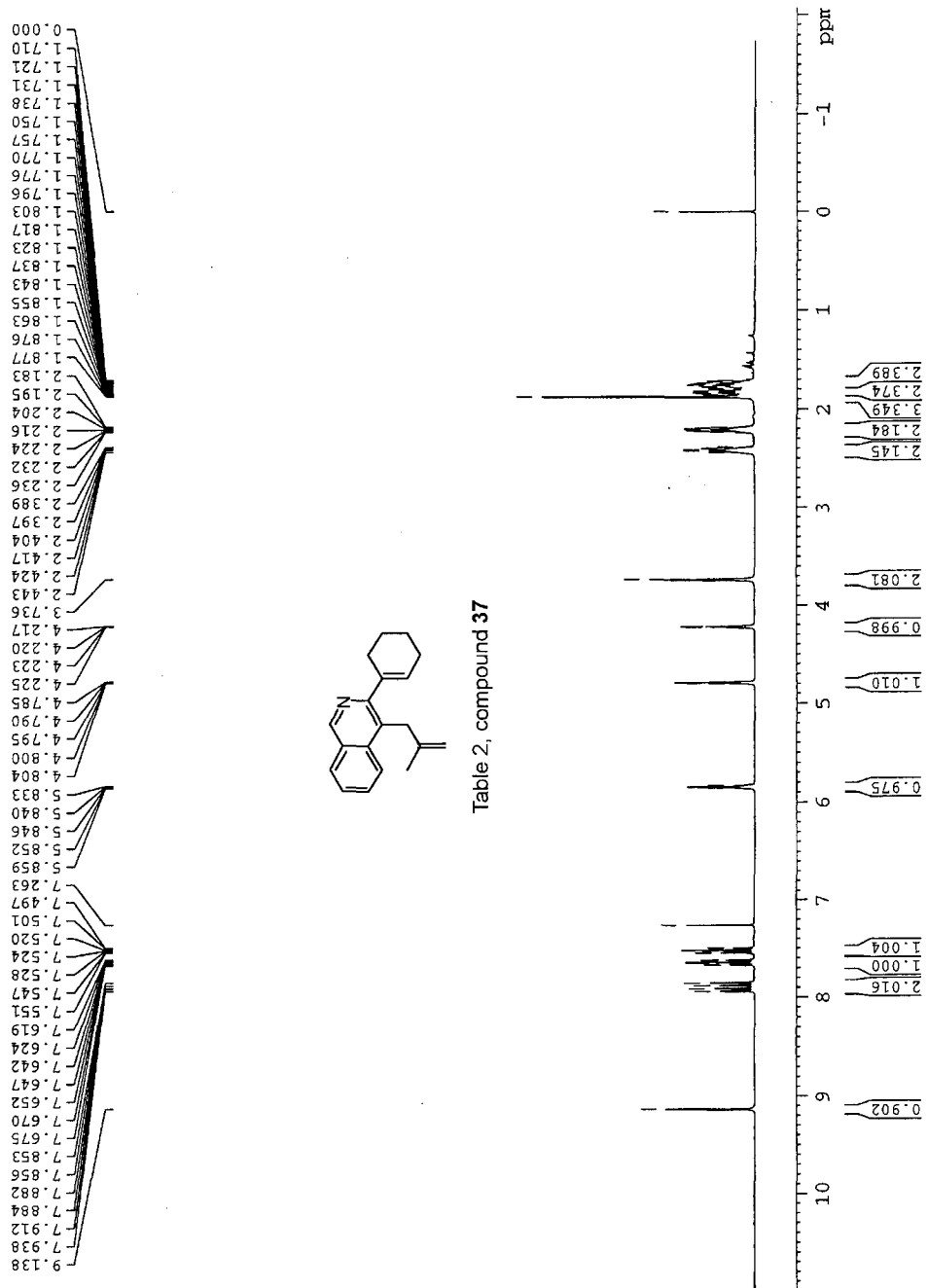


Table 2, compound 36



154.129	77.655
150.927	77.231
136.103	76.808
135.781	
130.322	
128.316	
127.390	
125.967	
124.924	
123.409	
116.293	
	35.471
	32.628
	31.909
	23.219
	14.265



200 180 160 140 120 100 80 60 40 20 0 ppm

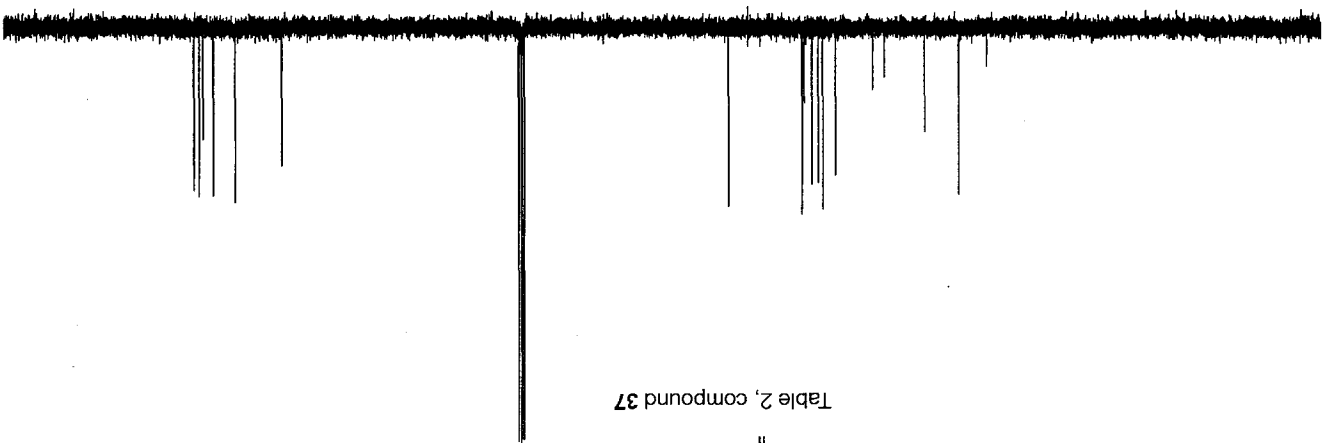
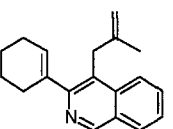


Table 2, compound 37



155.537
150.800
145.089
138.317
136.445
130.226
128.124
127.445
127.375
126.309
125.043
124.691
117.660
112.290

77.653
77.230
76.806

37.085
29.255
25.626
23.890
23.259
22.339

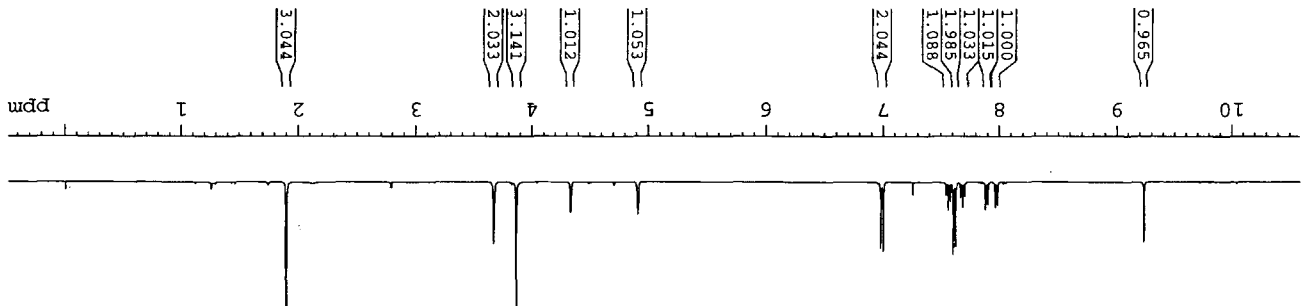
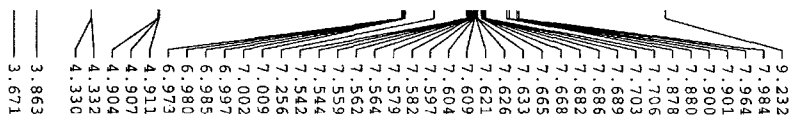
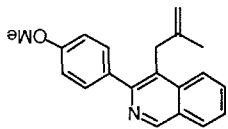


Table 2, compound 38



— 1.897

— 0.000

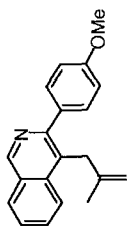
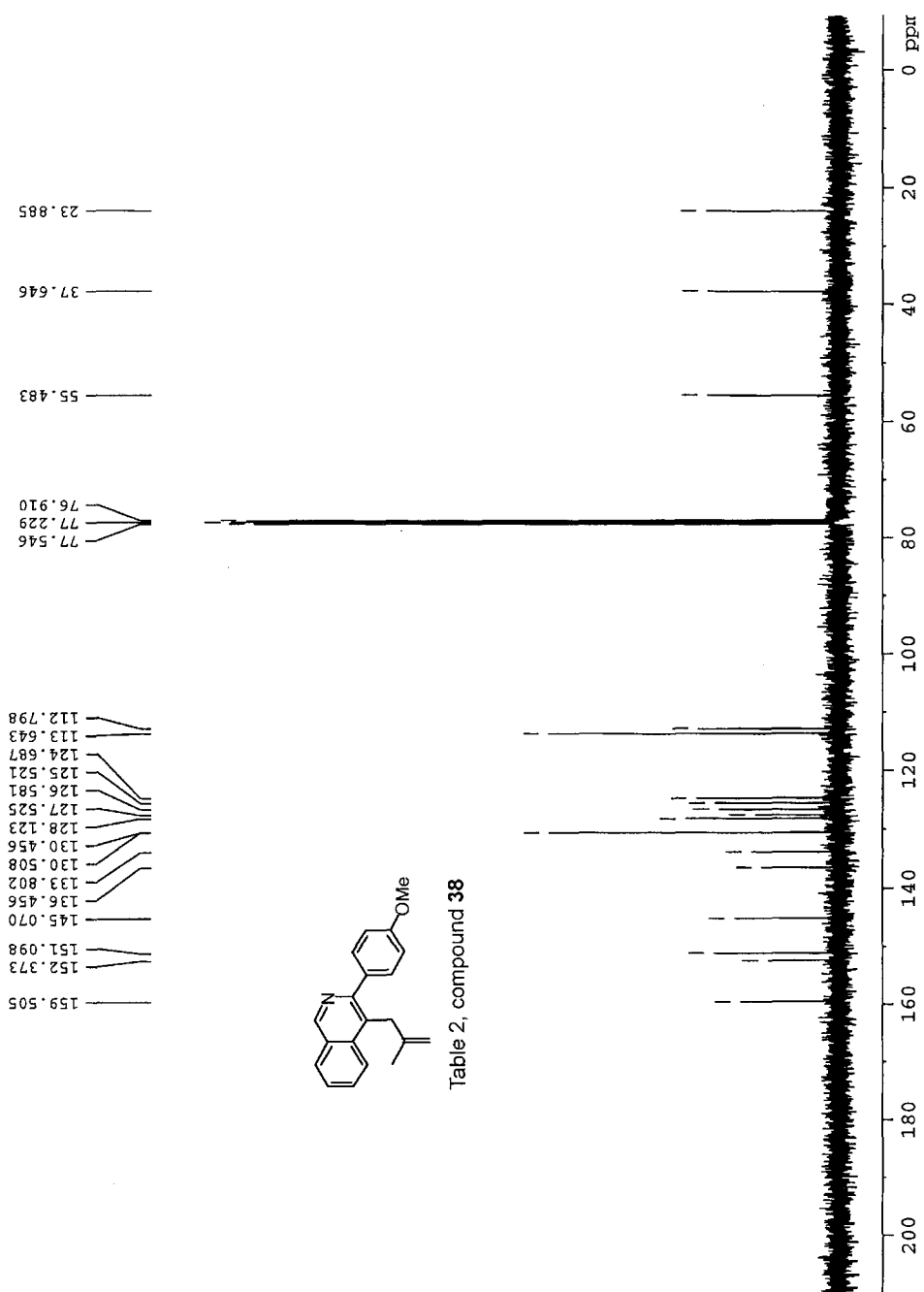


Table 2, compound 38

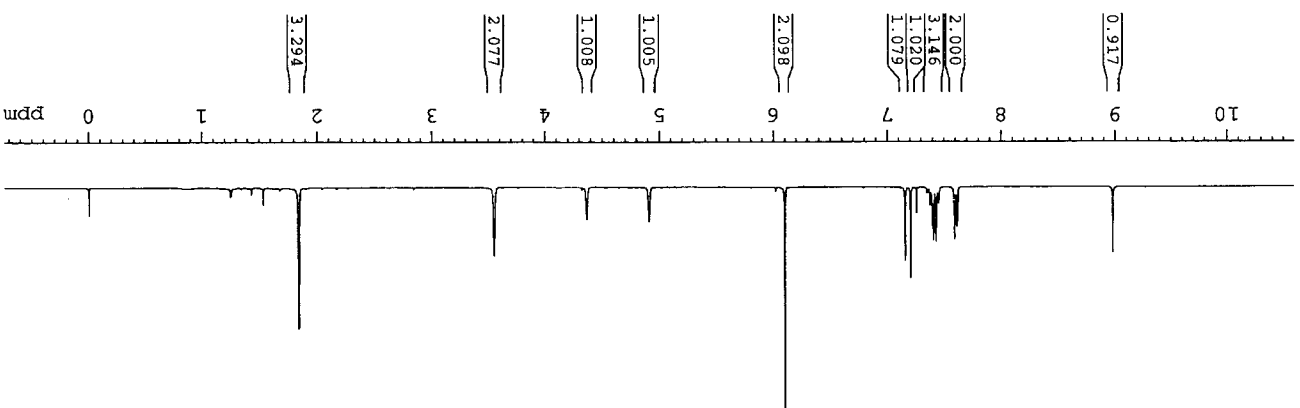
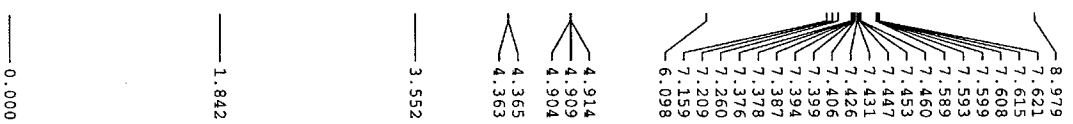
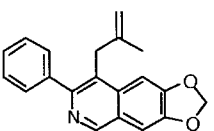


Table 2, compound 39



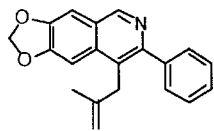
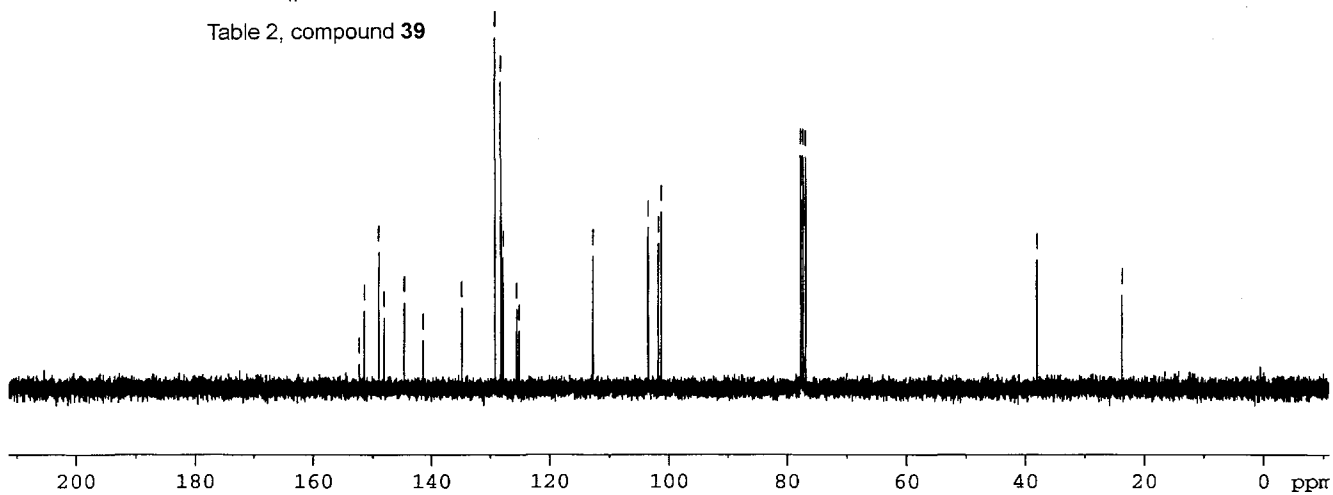


Table 2, compound 39



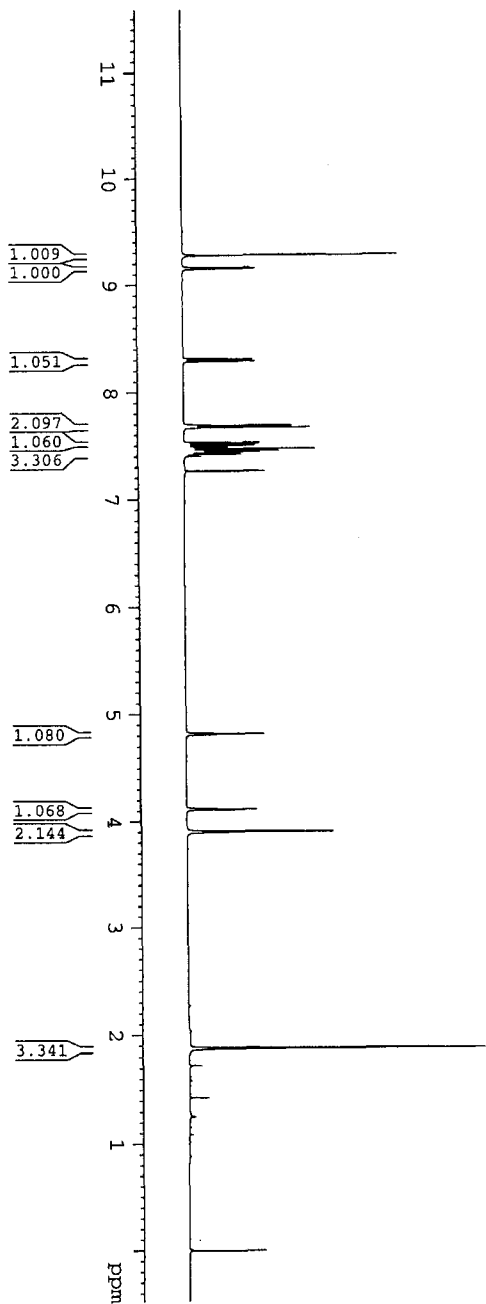
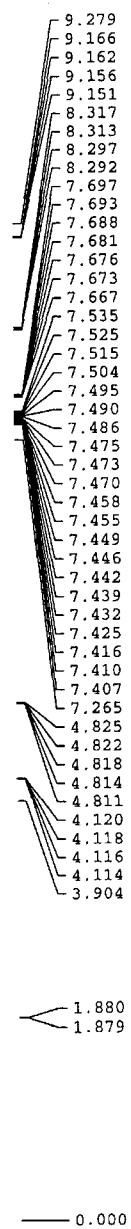
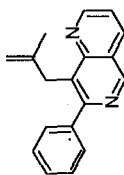
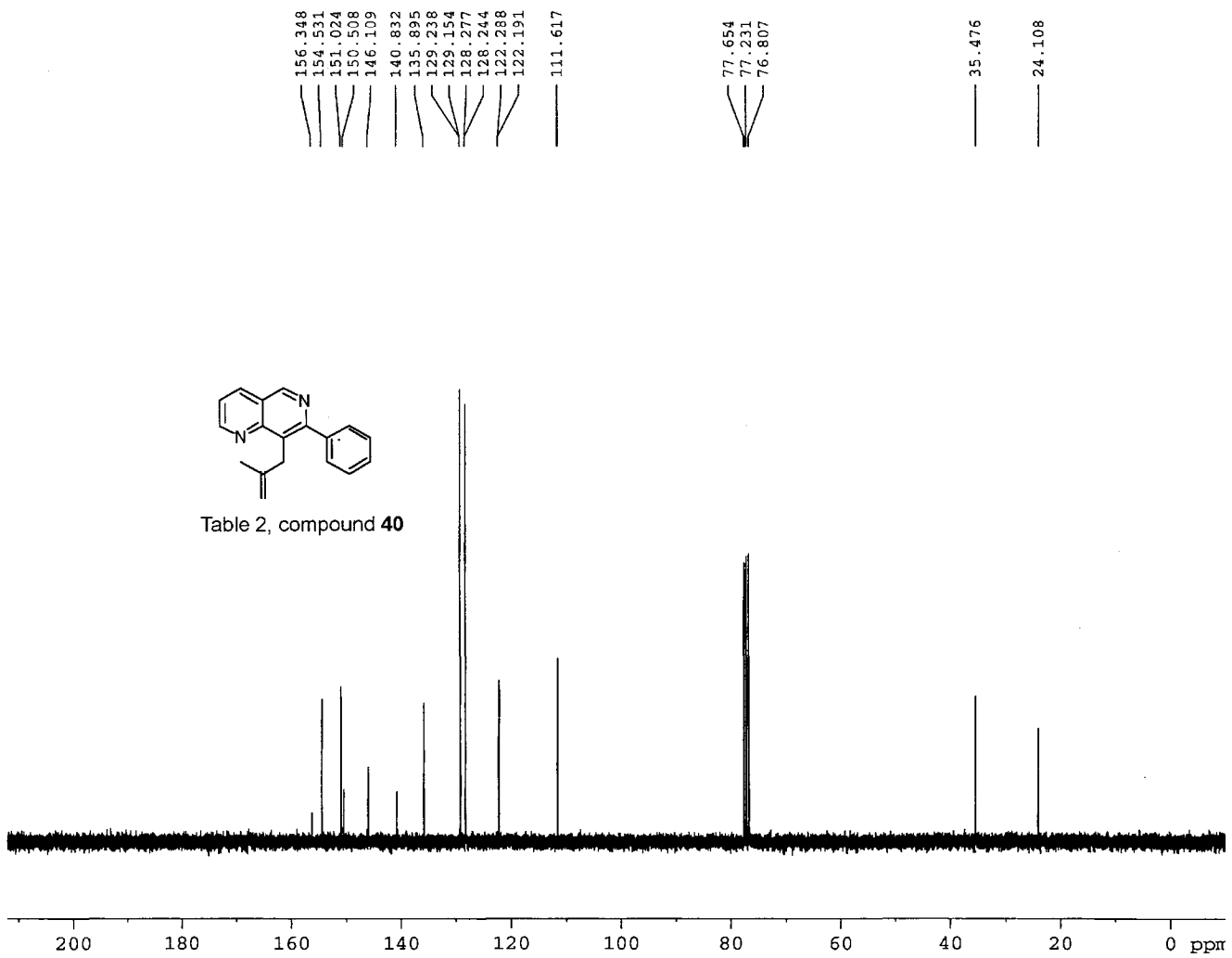
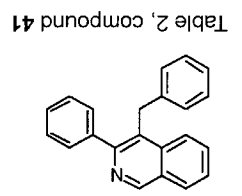
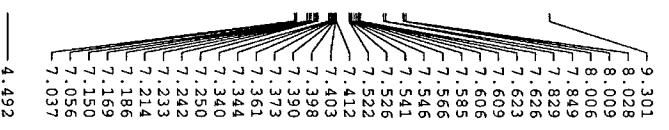
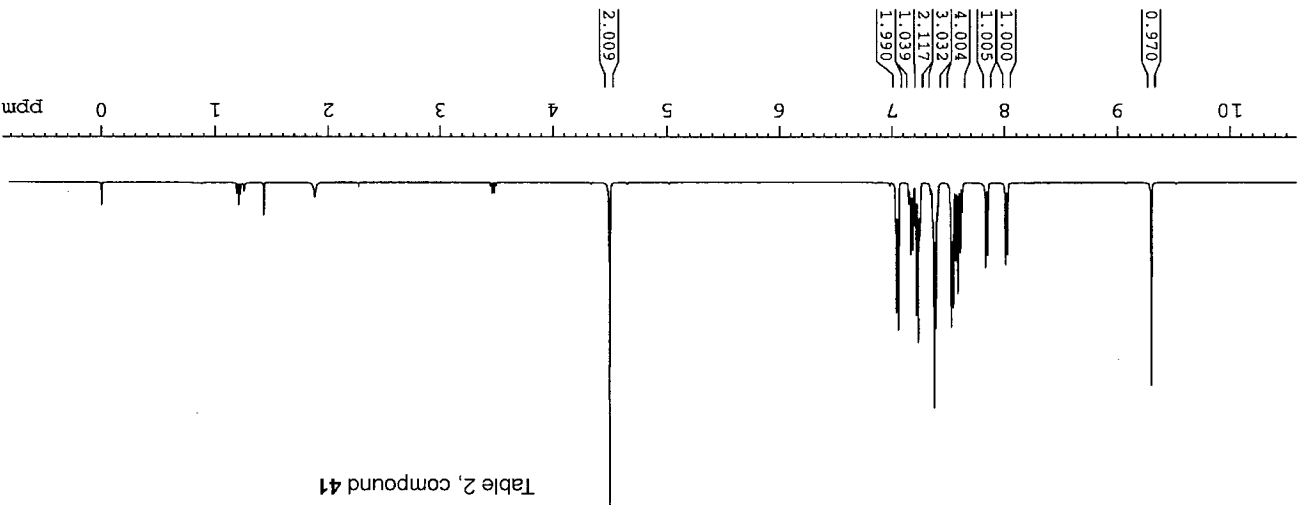


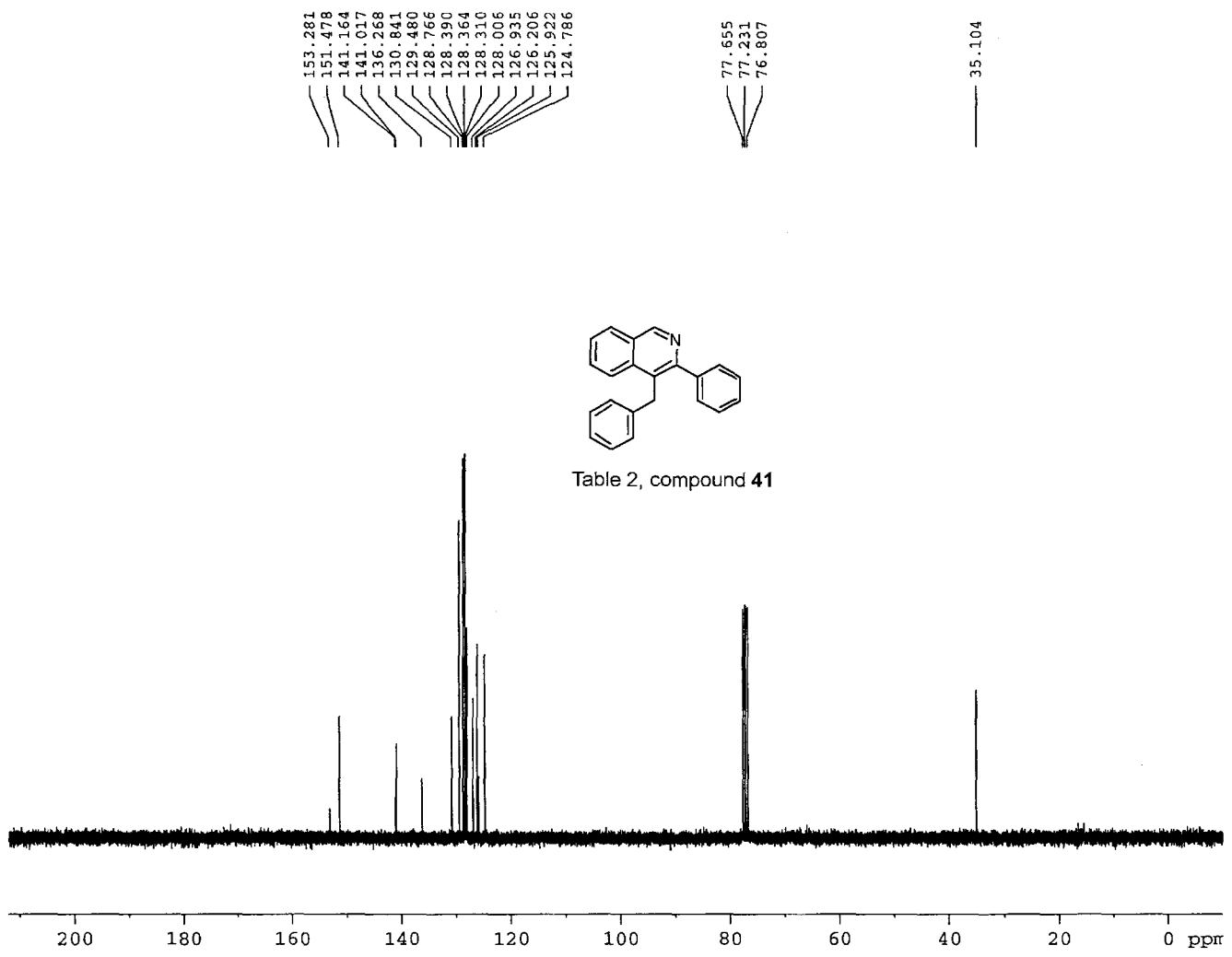
Table 2. compound 40

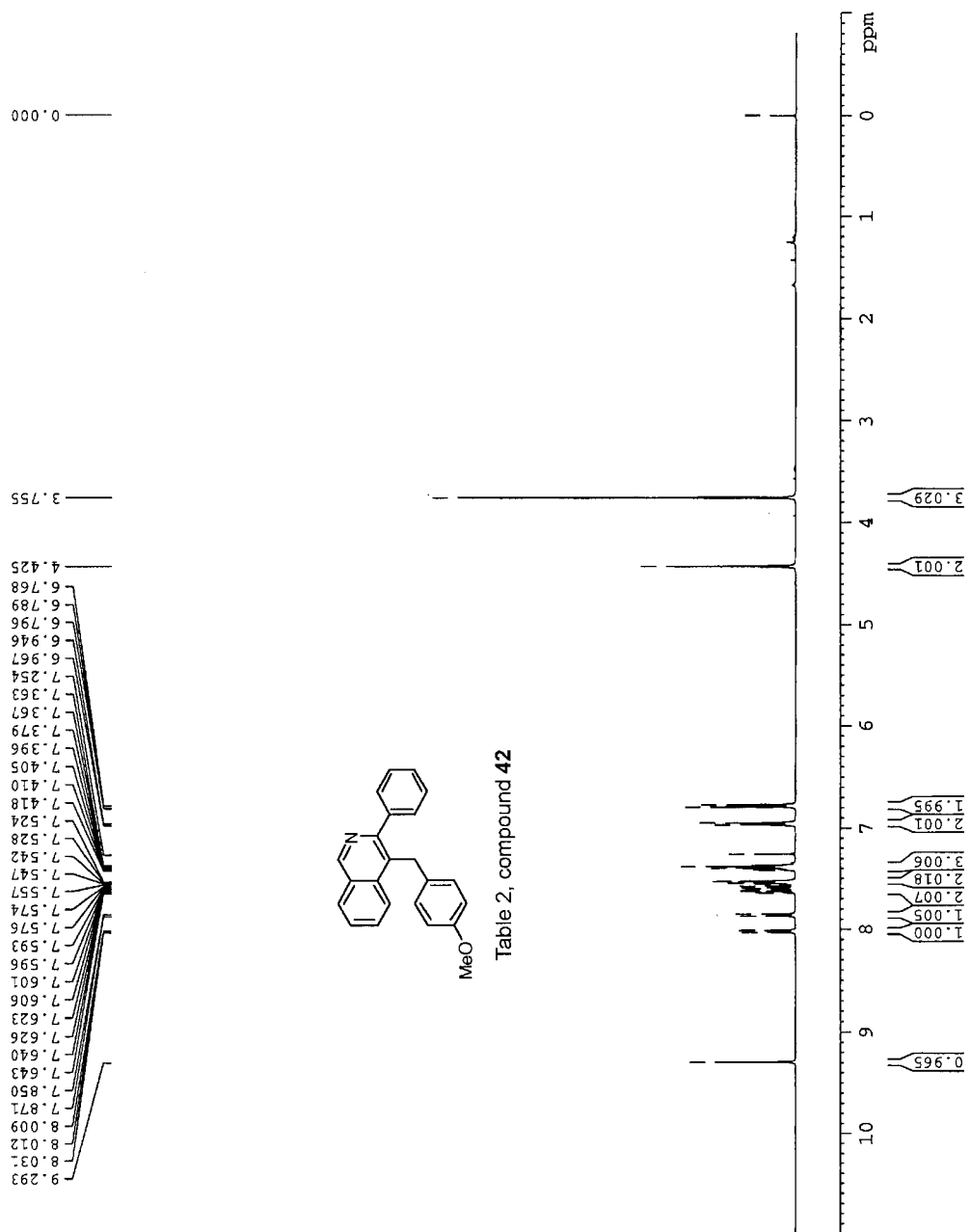


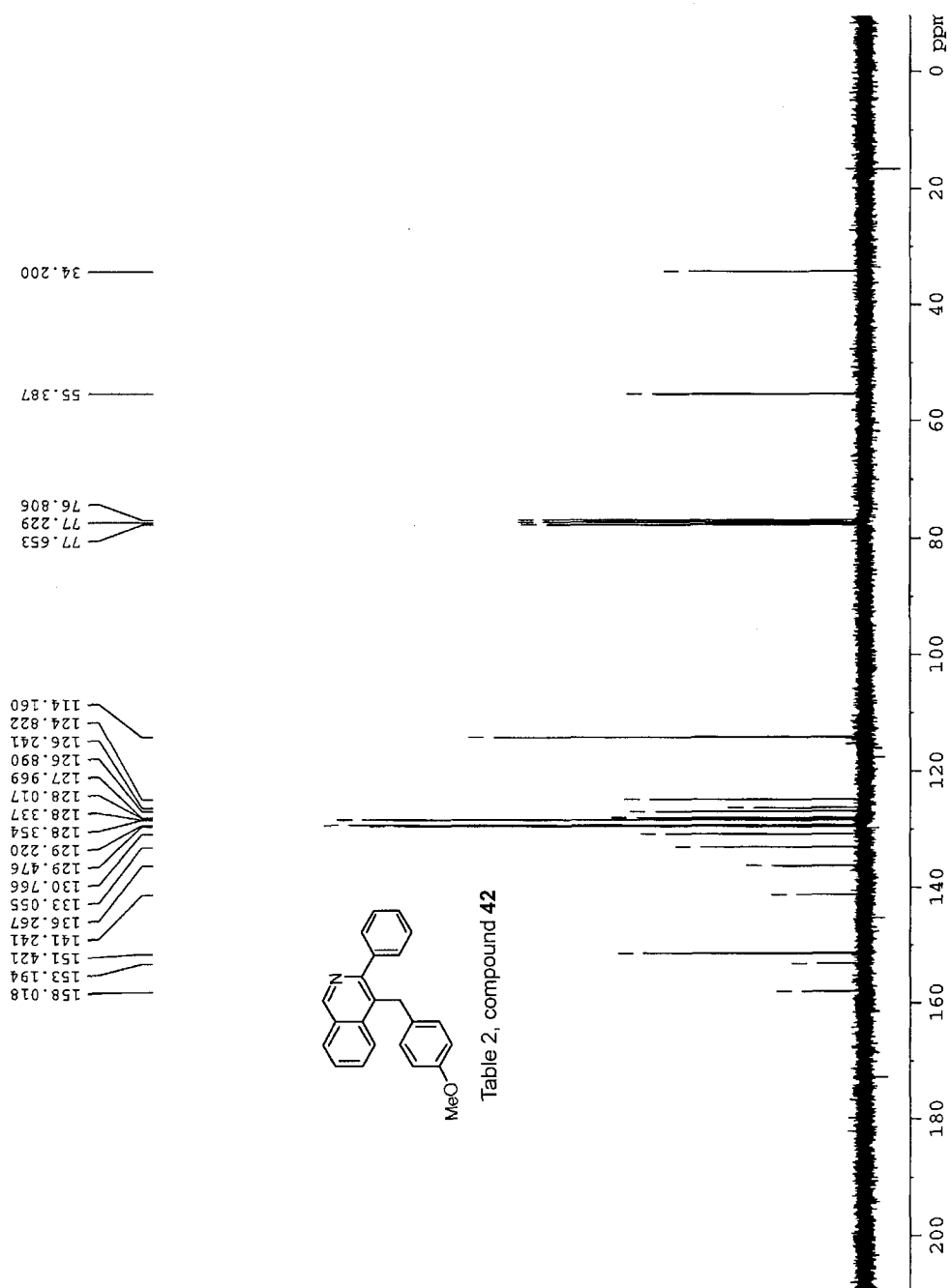


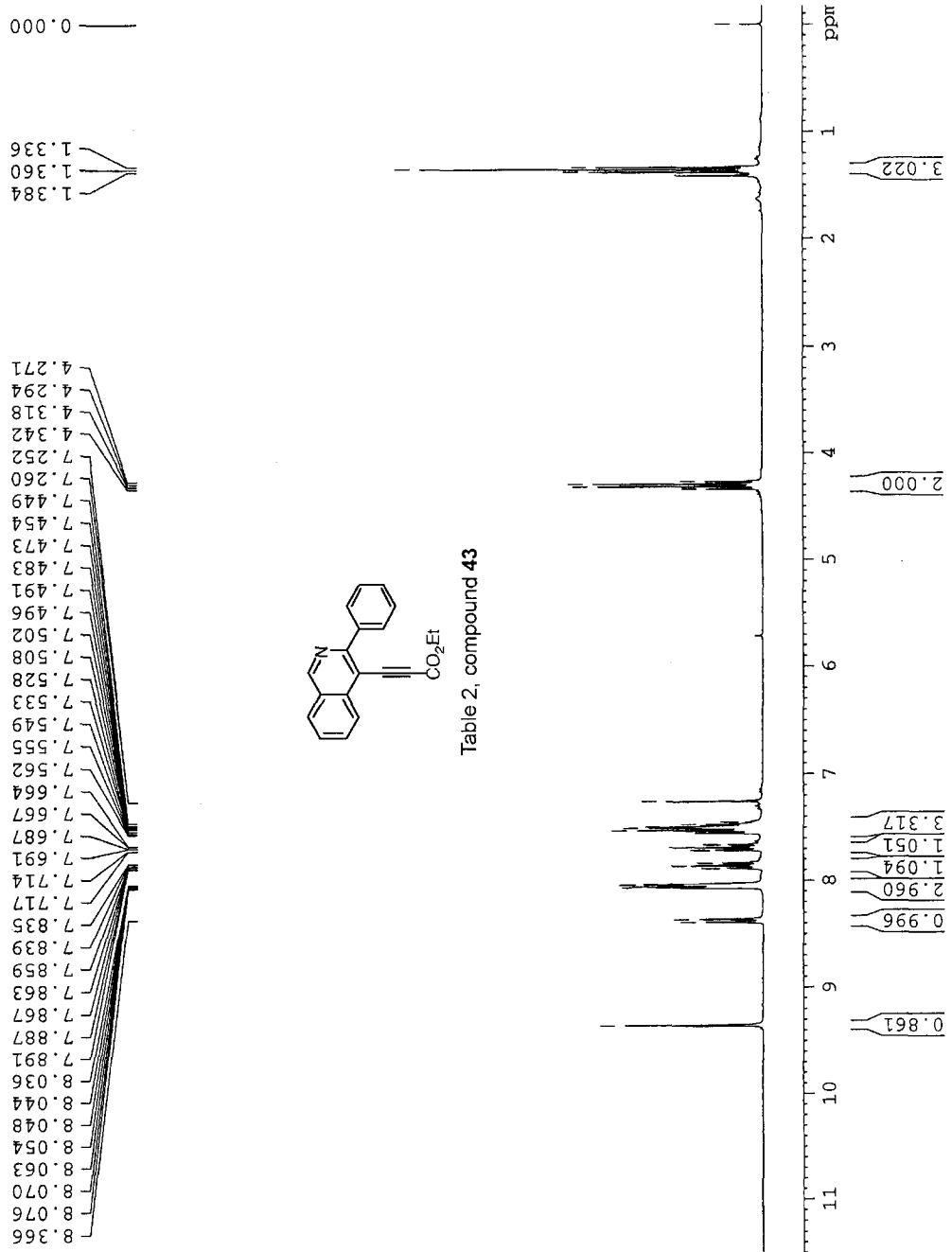


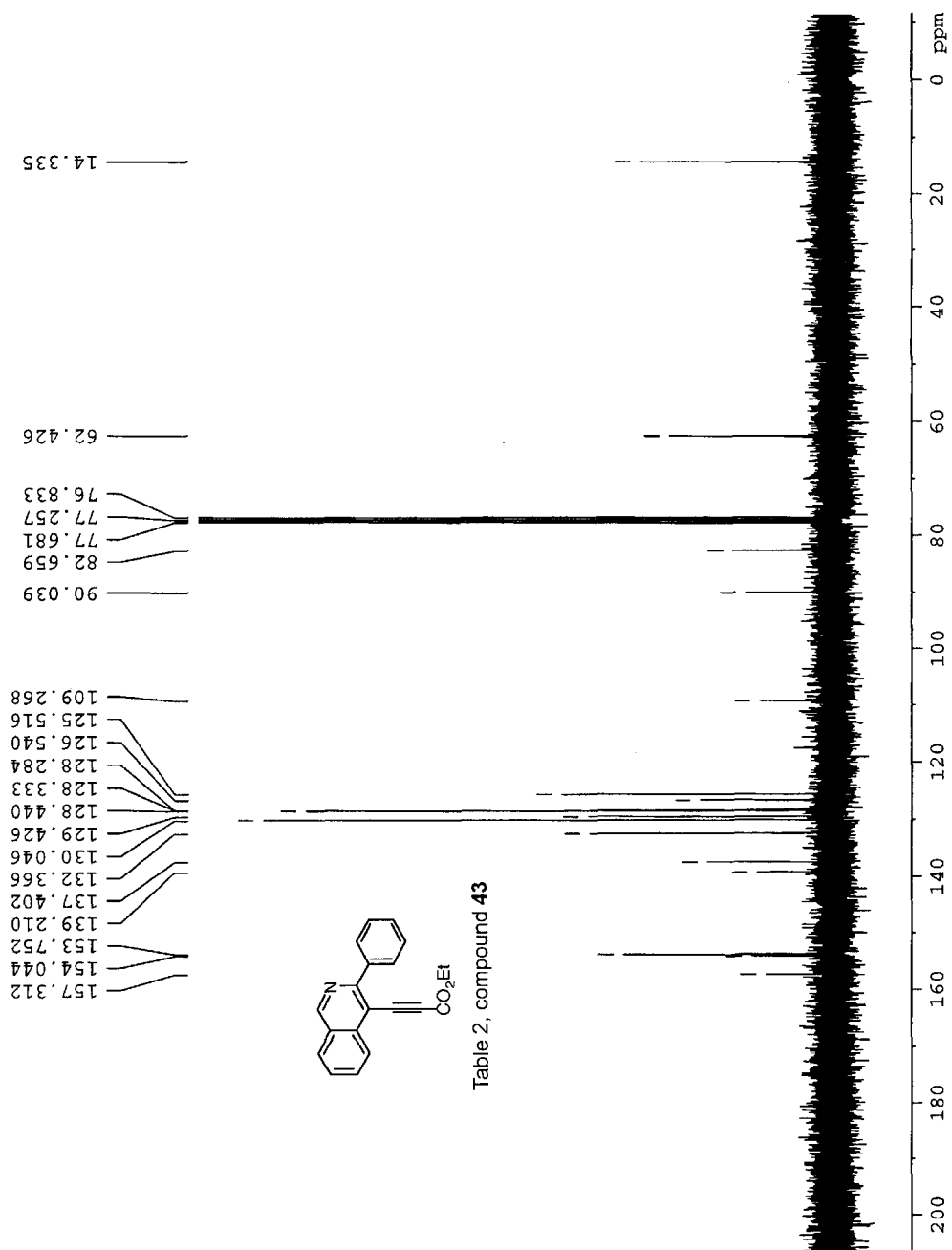
0.000

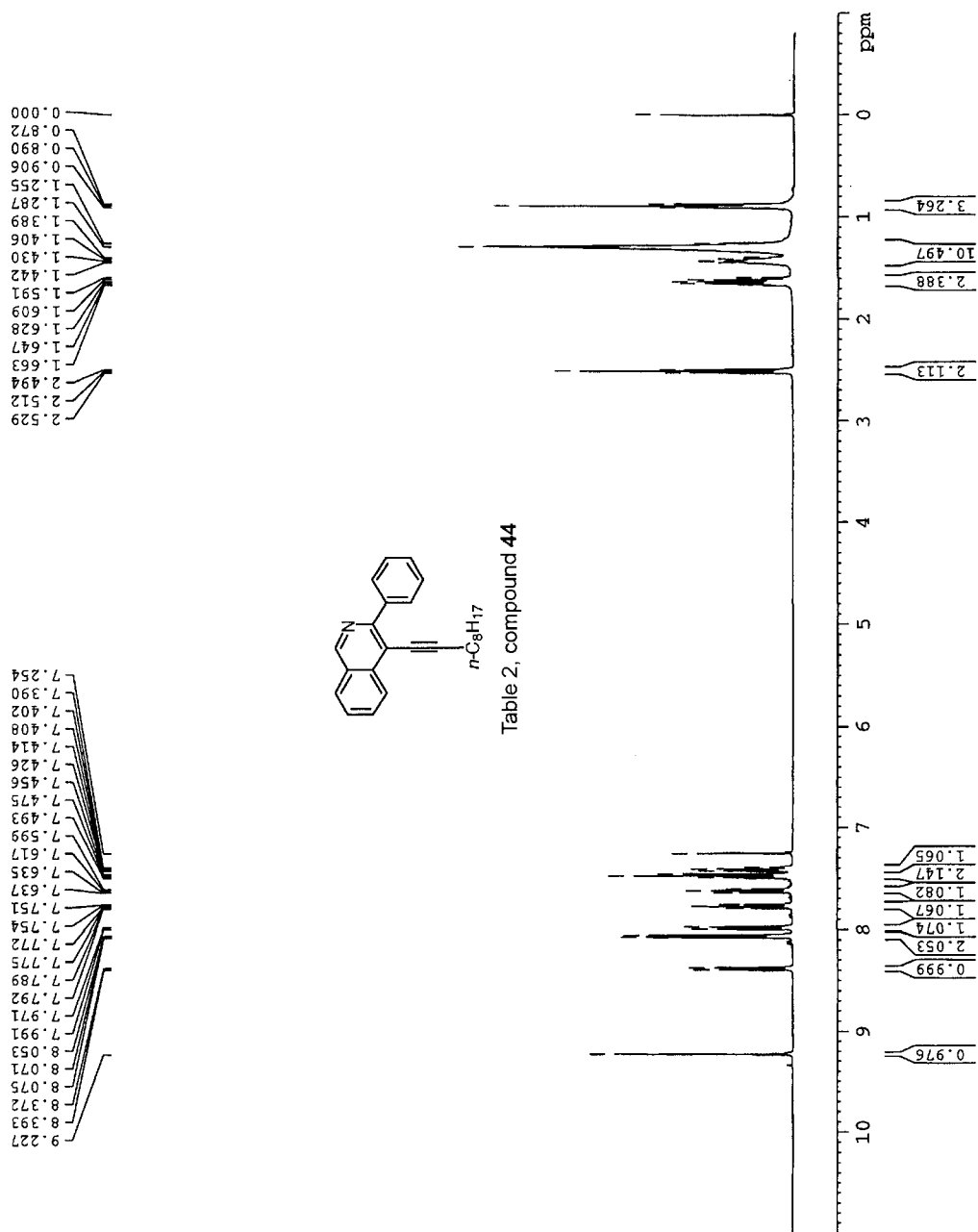


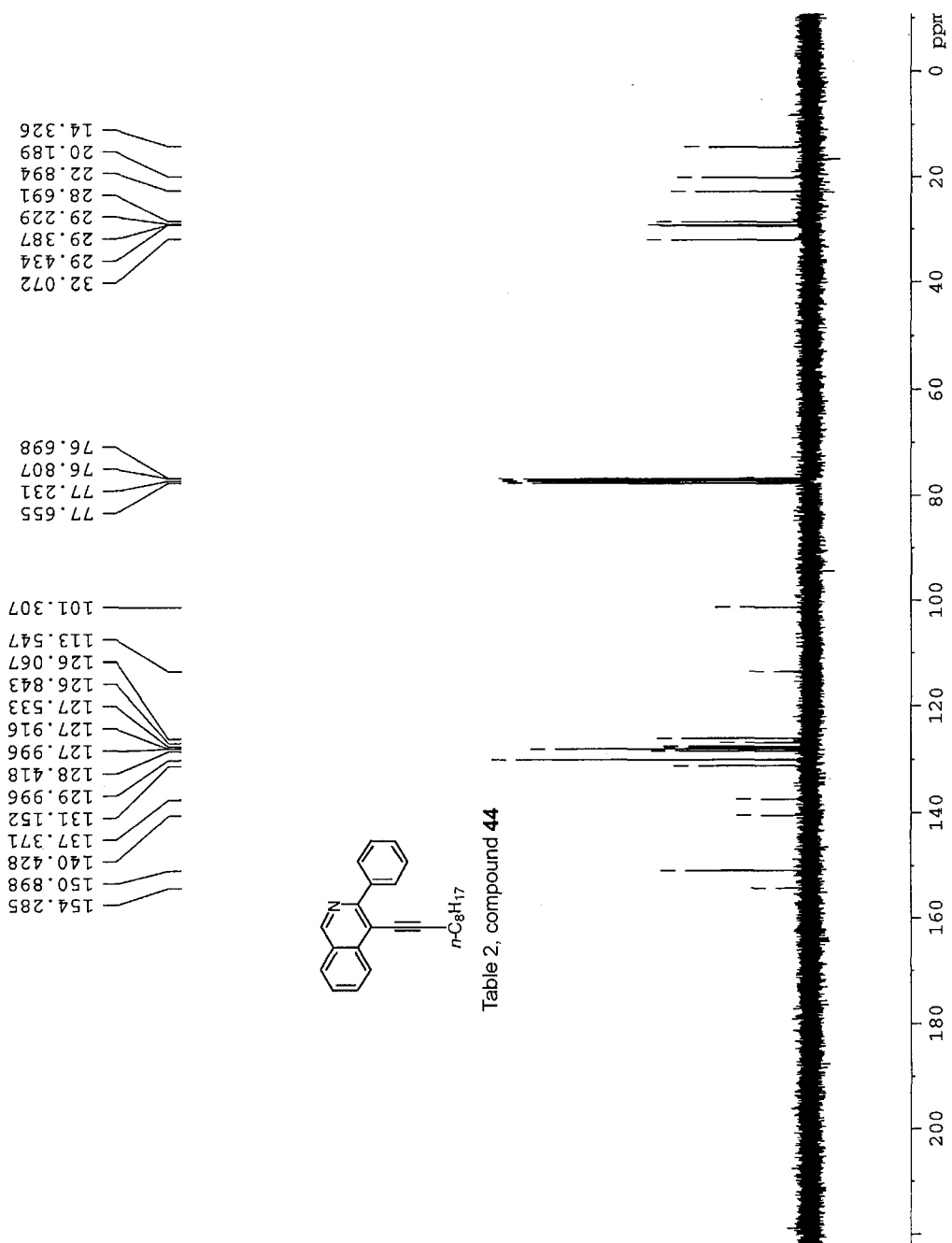












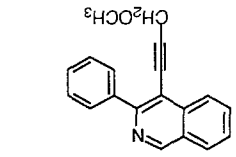
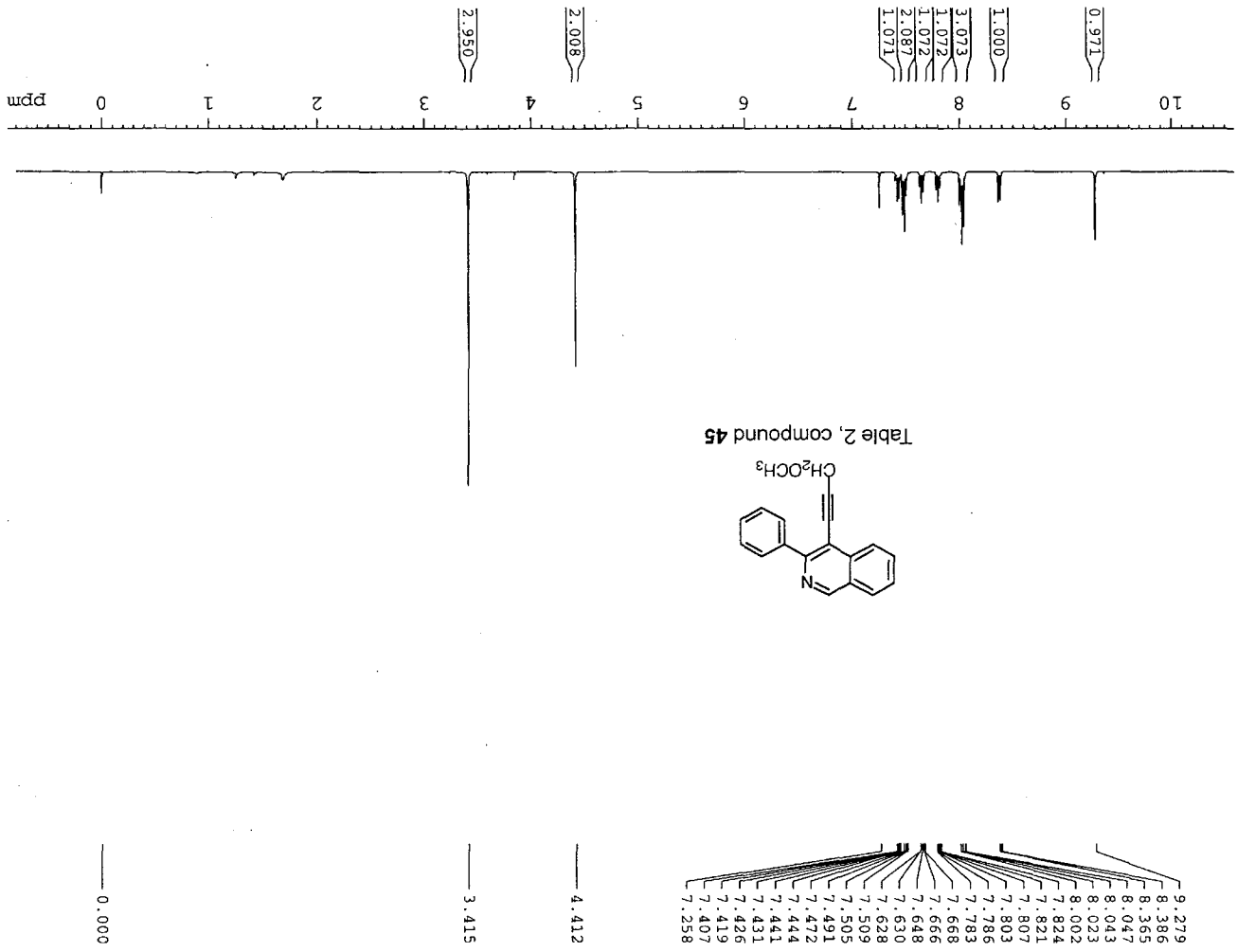


Table 2, compound 45



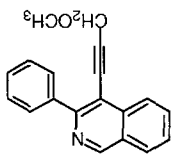
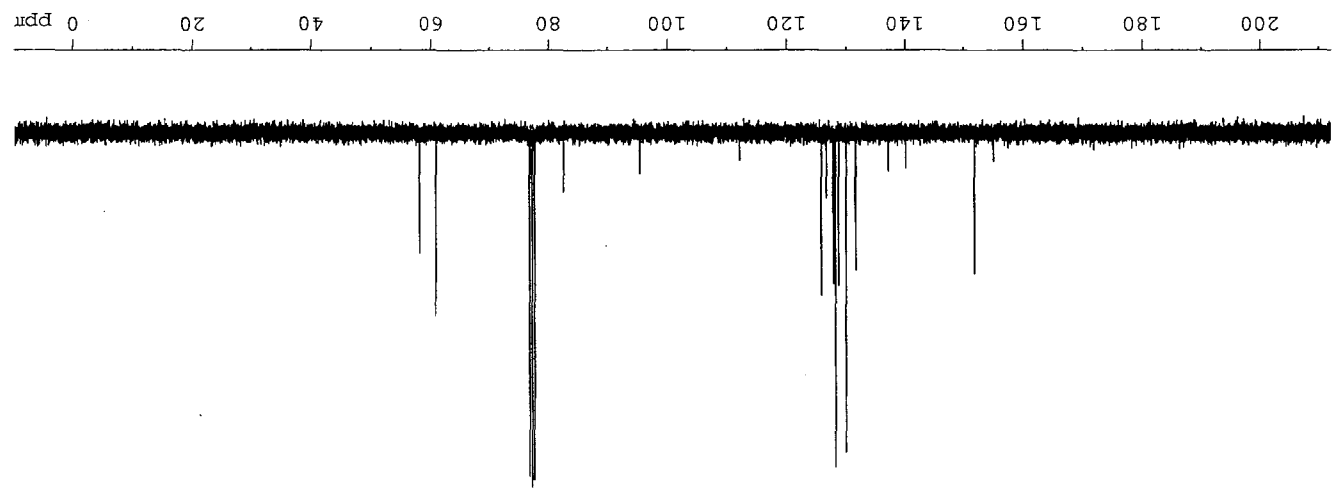


Table 2, compound 45



155.038
151.863

140.119
137.140
131.567
129.962
128.705
128.162
128.051
127.791
126.750
125.810
112.170

95.392

82.590
77.654
77.230
76.807

60.817
58.011

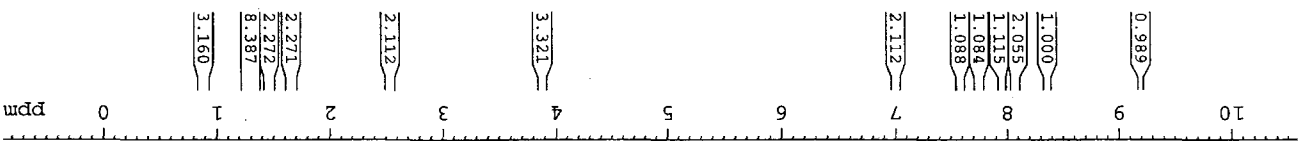
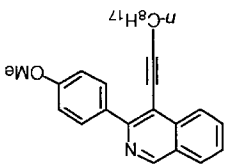


Table 2, compound 46



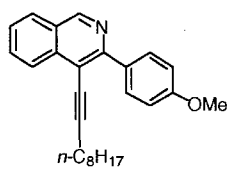
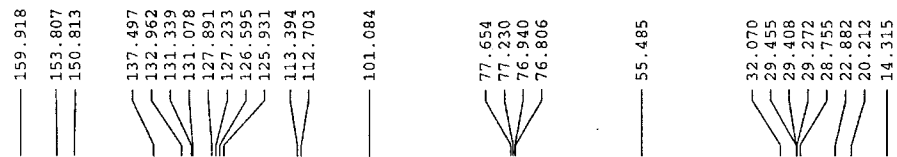
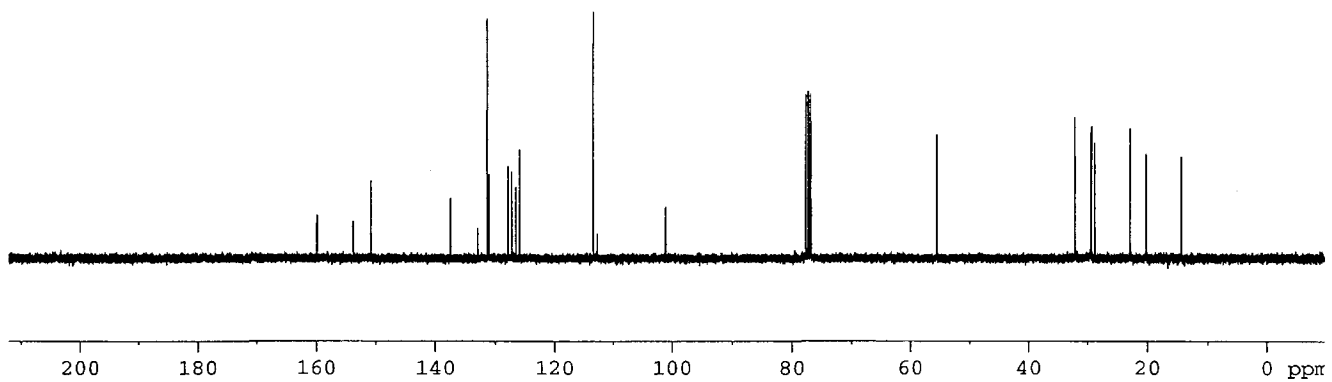
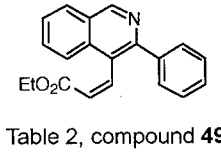
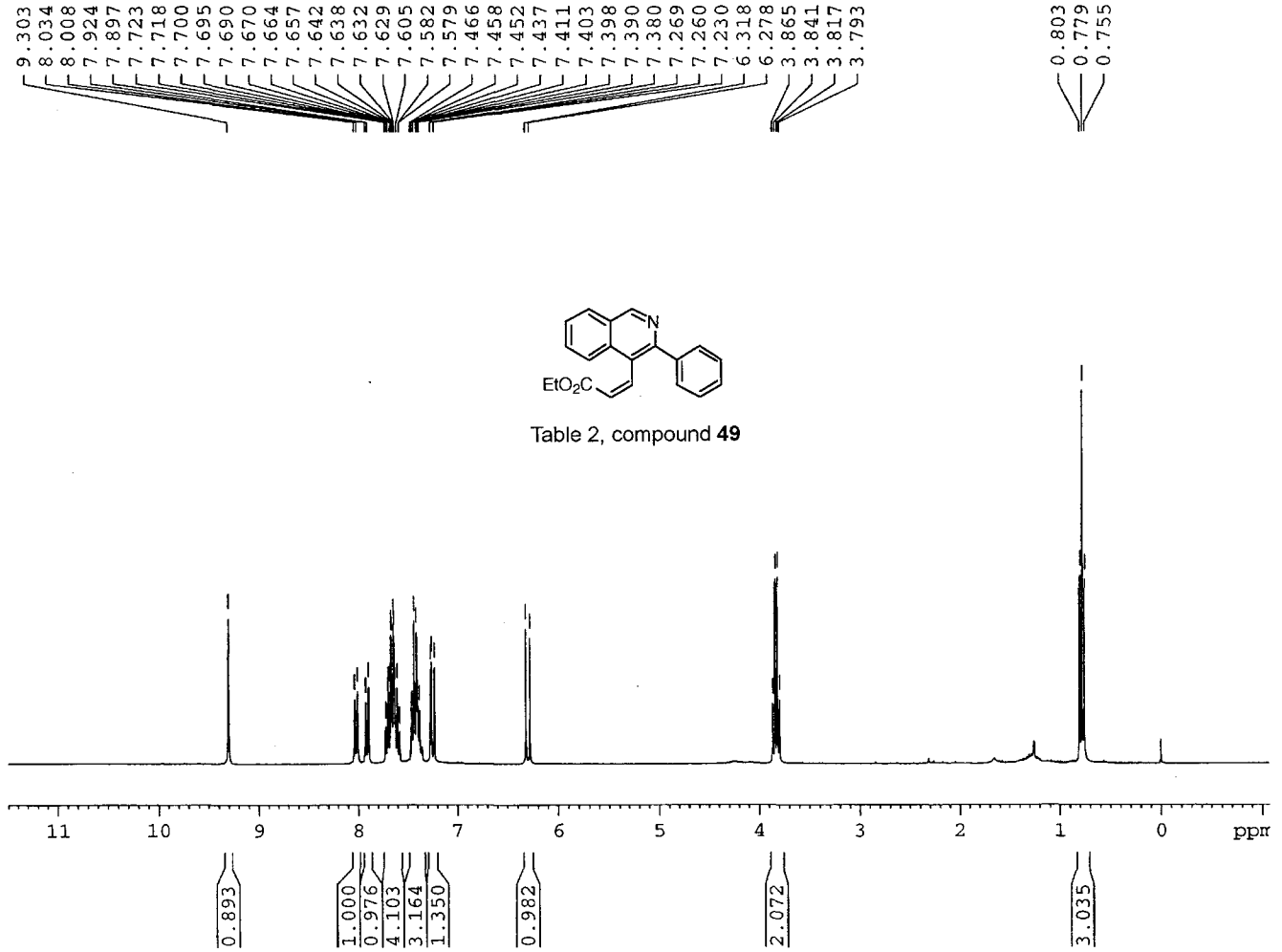
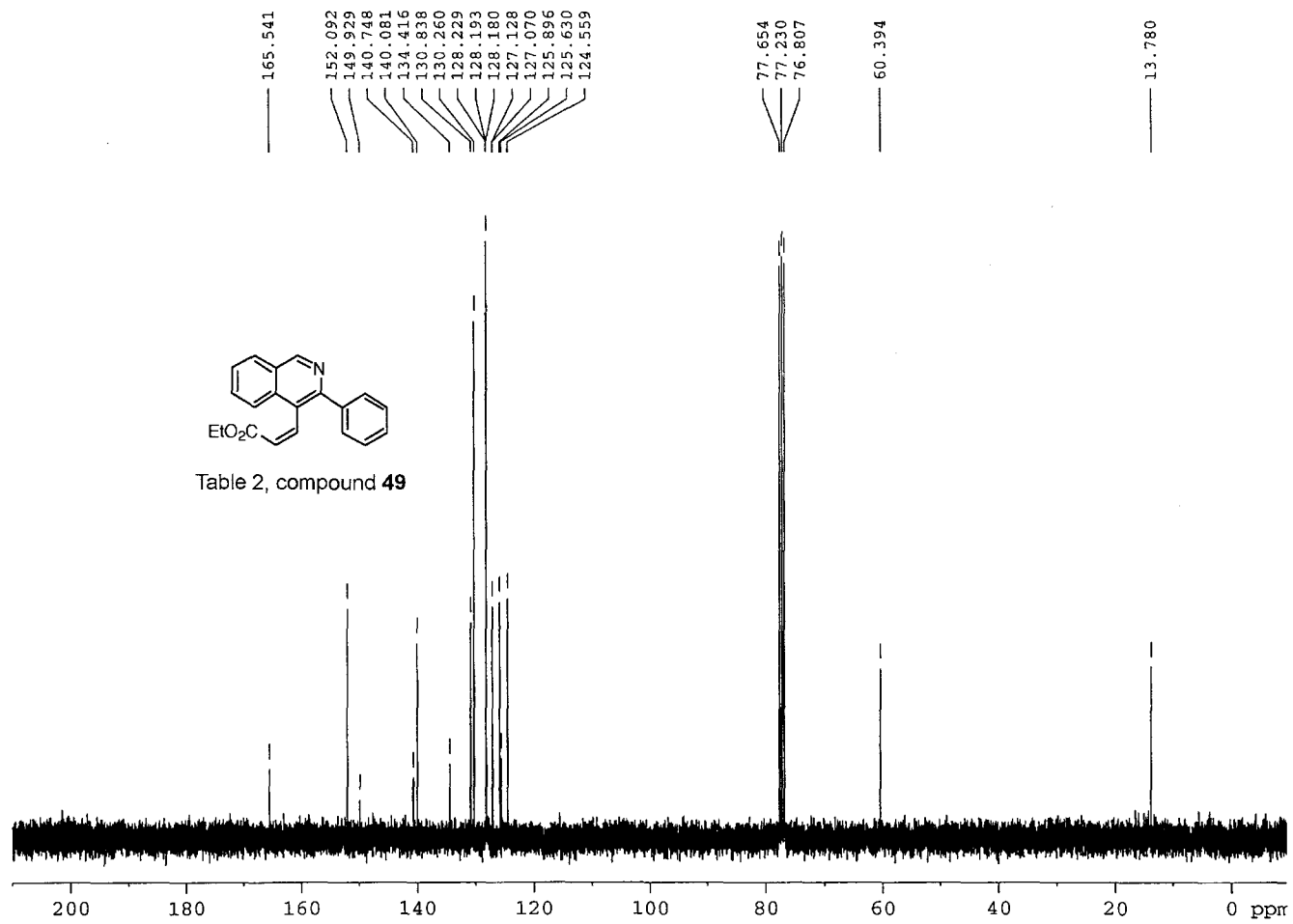


Table 2, compound 46

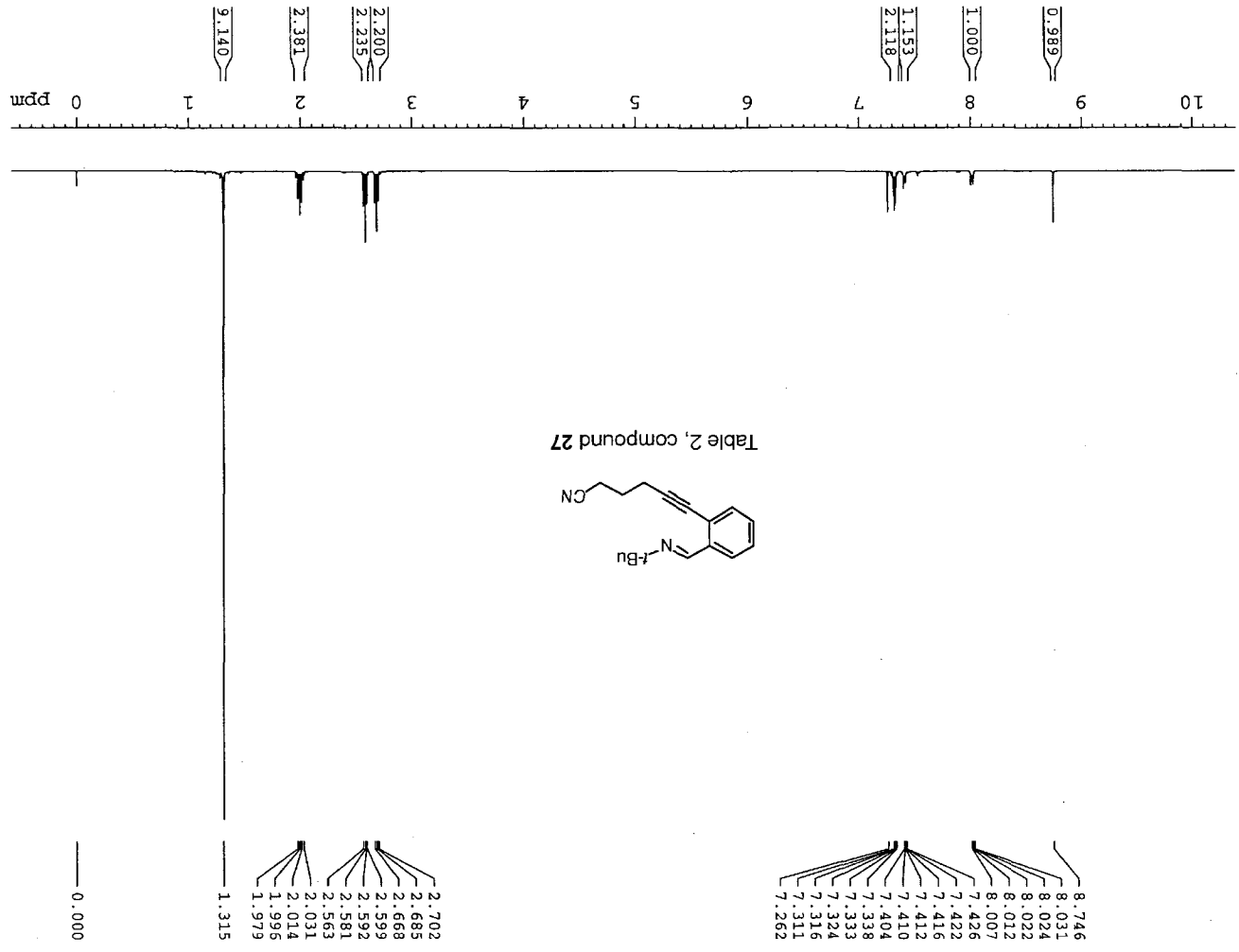
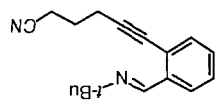


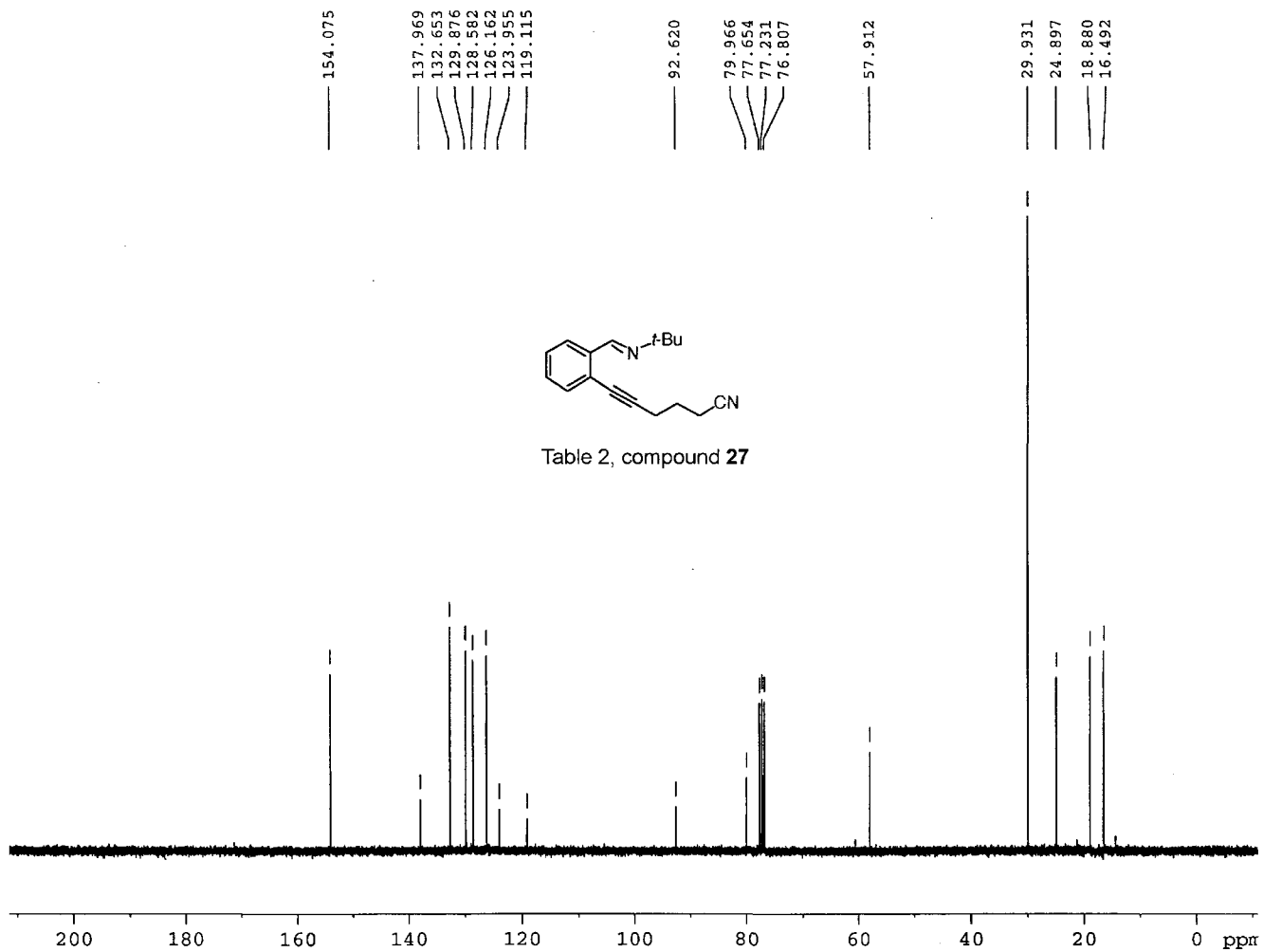




APPENDIX B. CHAPTER 2 ^1H AND ^{13}C NMR SPECTRA

Table 2, compound 27





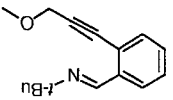
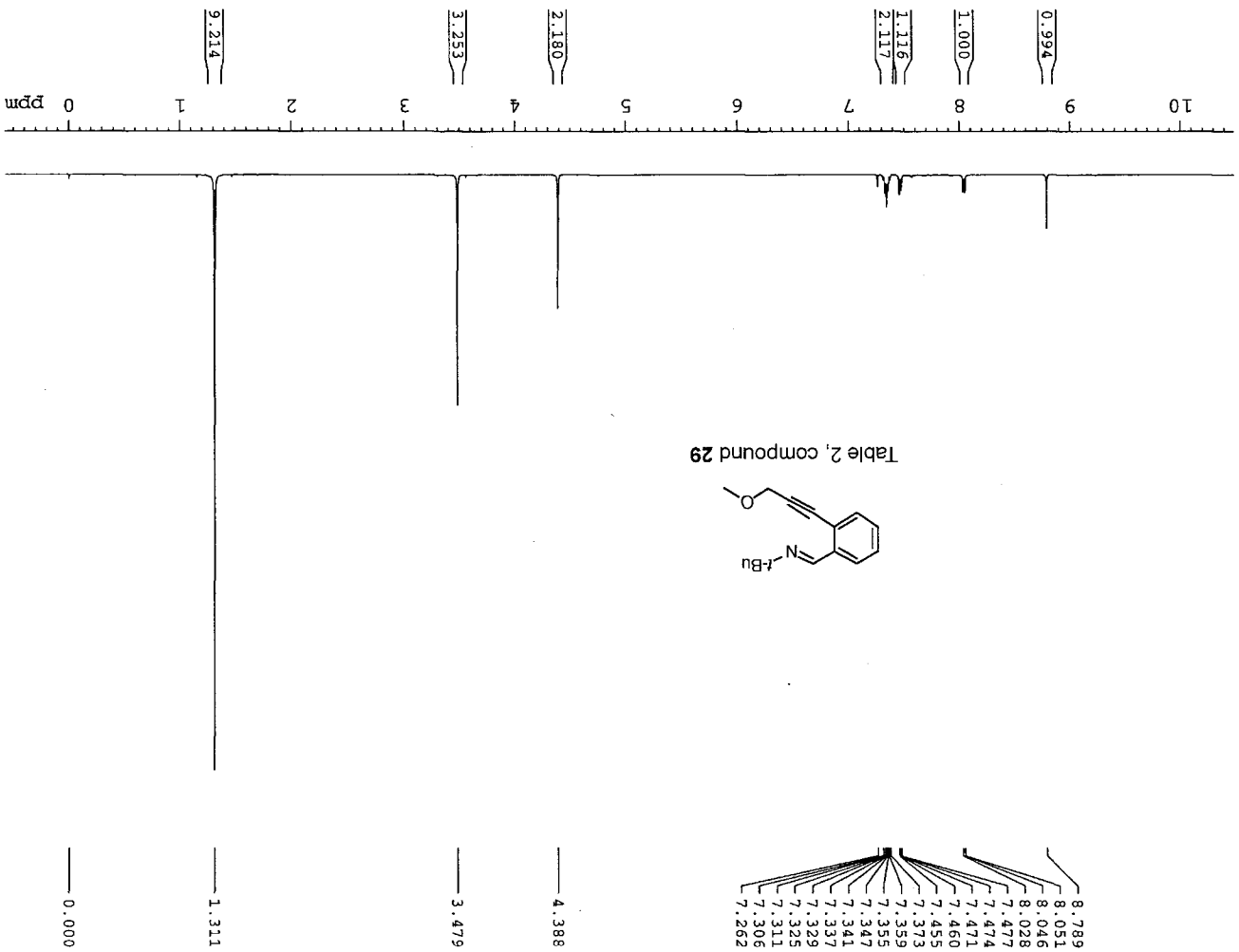
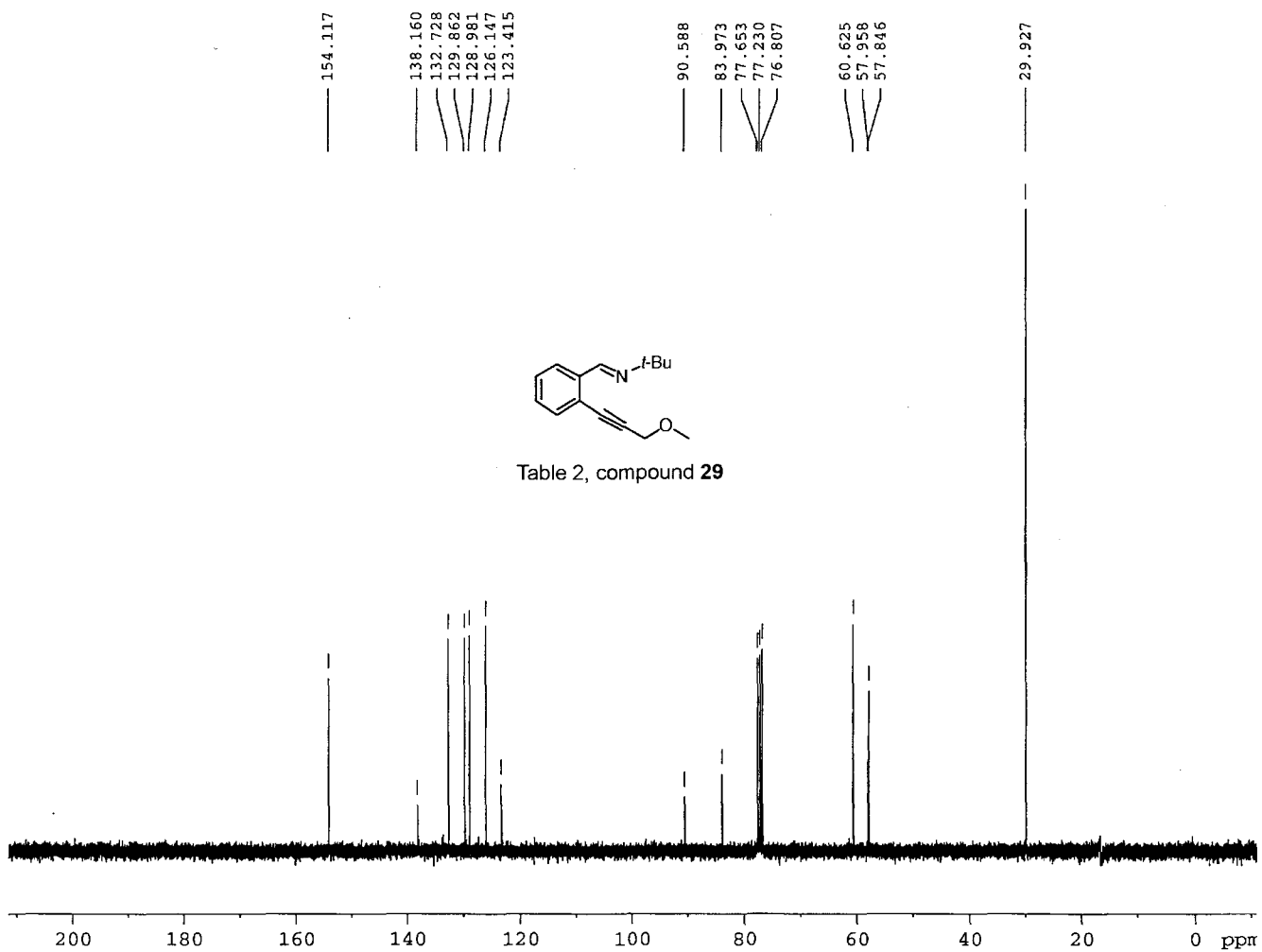
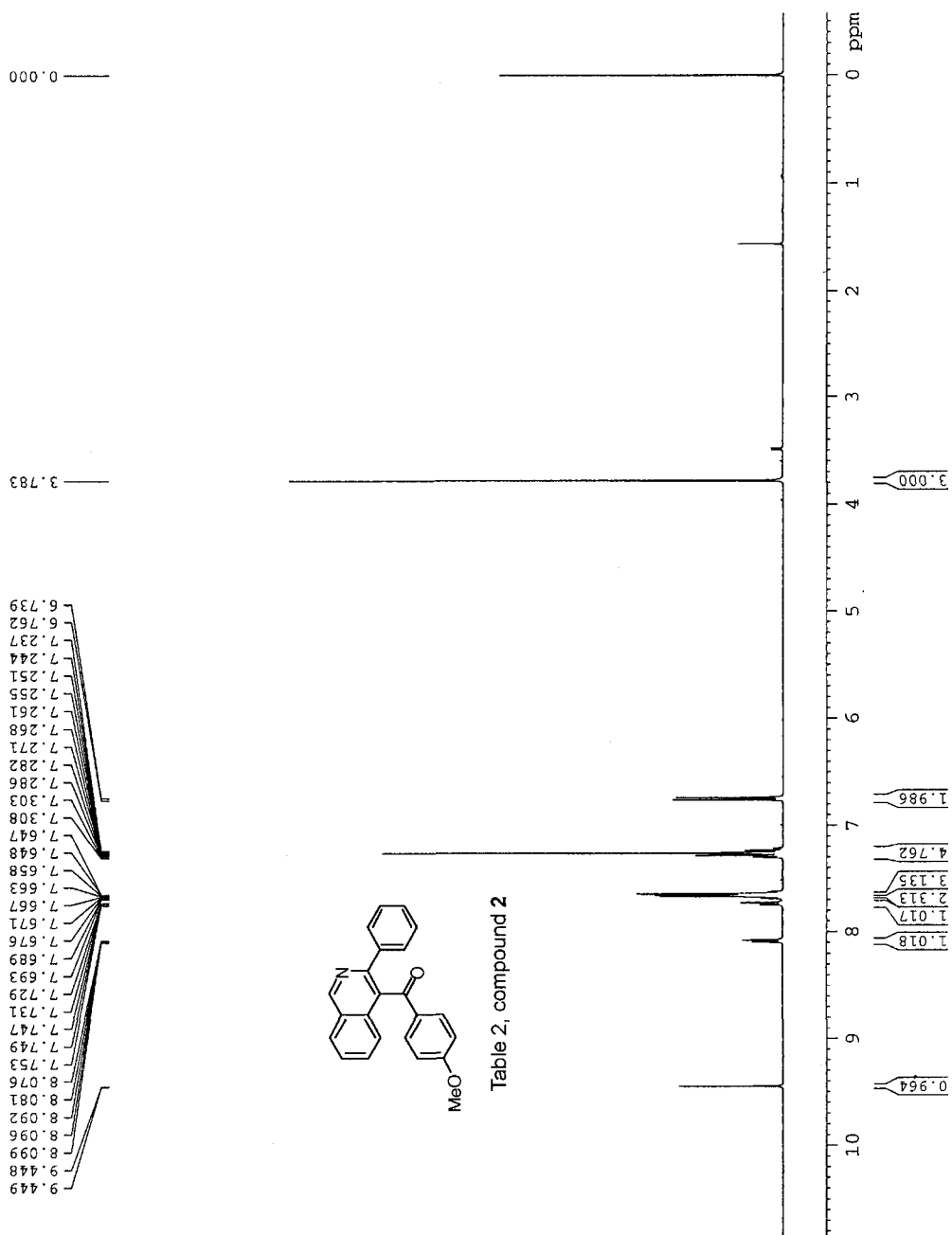
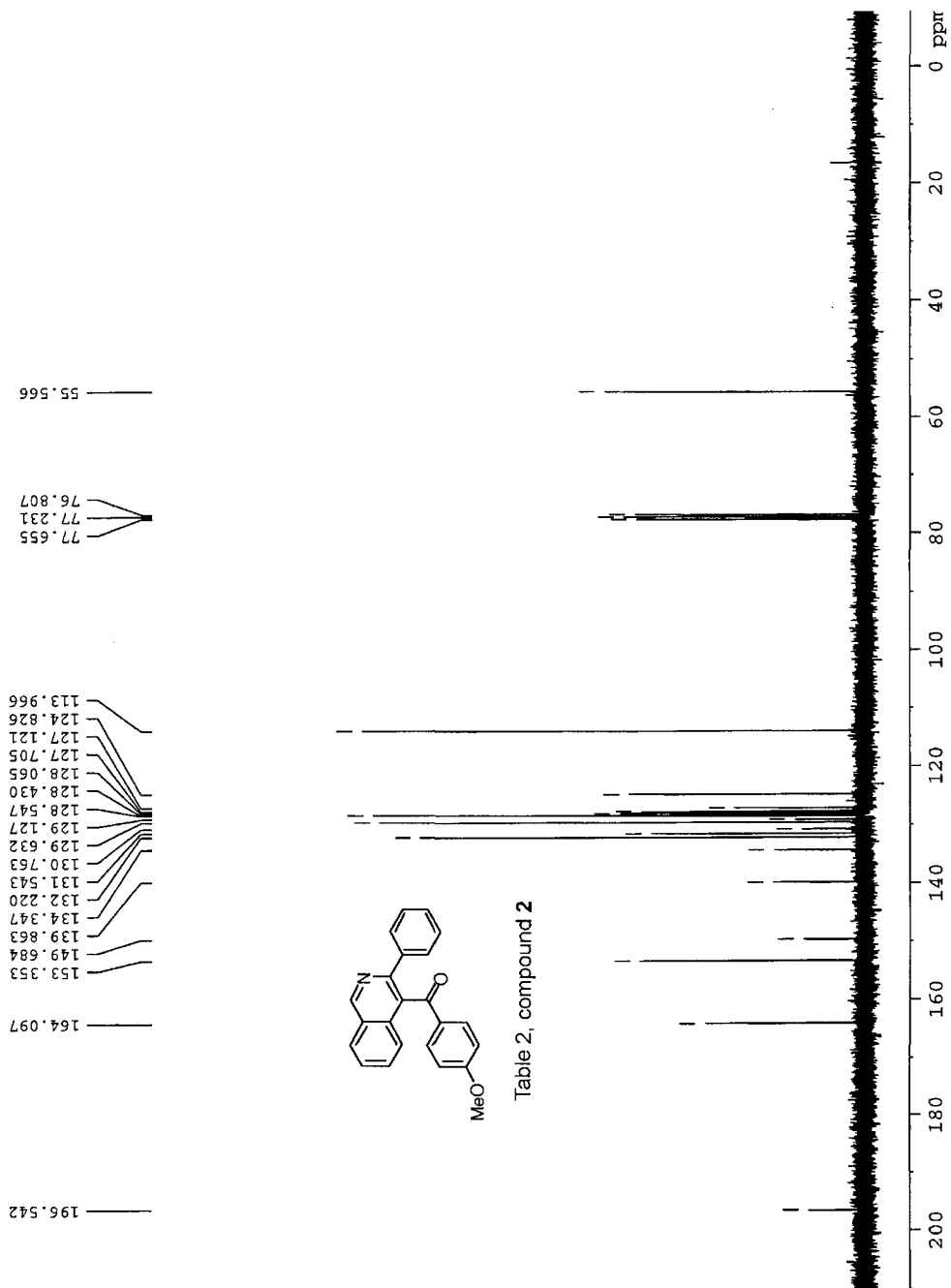


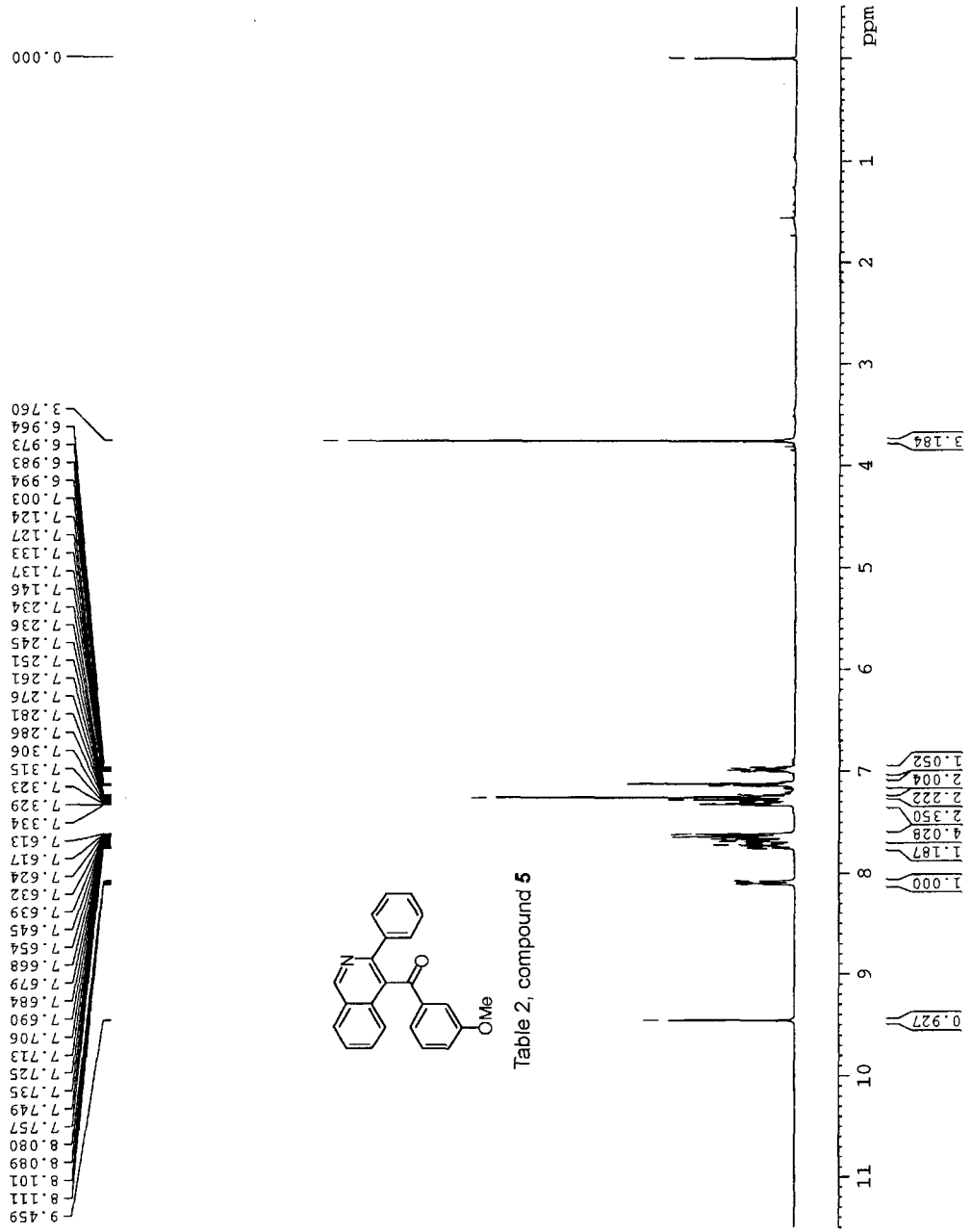
Table 2, compound 29











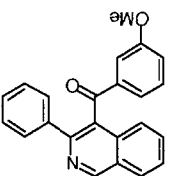
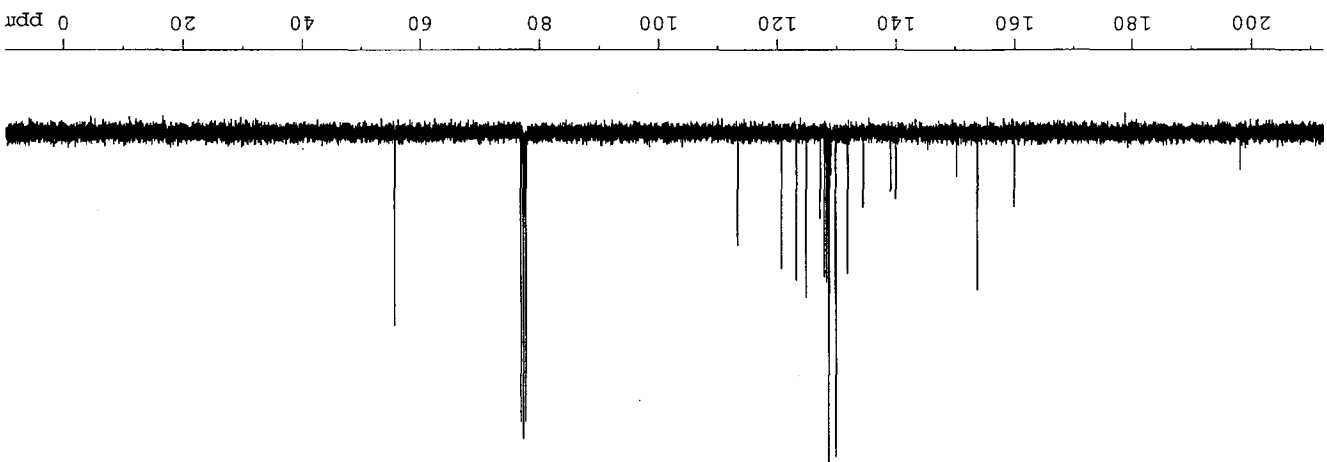


Table 2, compound 5

198.044

159.862
 153.632
 150.106
 139.848
 138.971
 134.377
 131.711
 129.745
 129.708
 128.965
 128.678
 128.531
 128.181
 127.822
 127.131
 124.746
 123.097
 120.615
 113.273

77.654
 77.230
 76.807

55.599

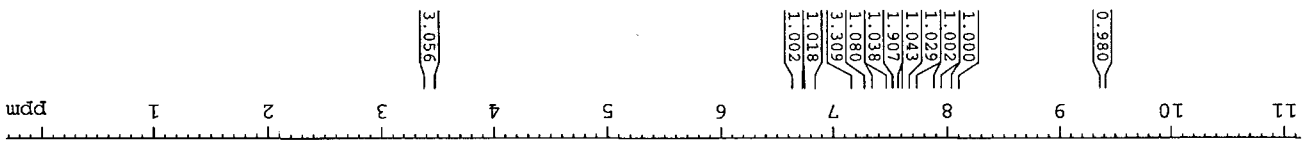
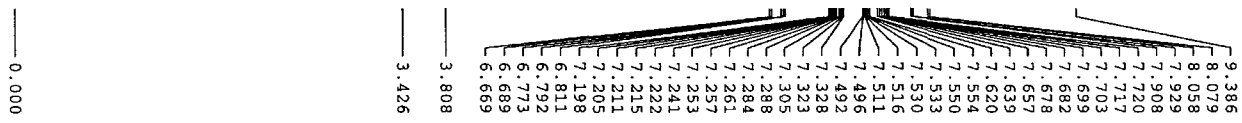
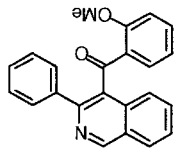


Table 2, compound 6



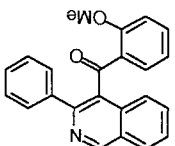
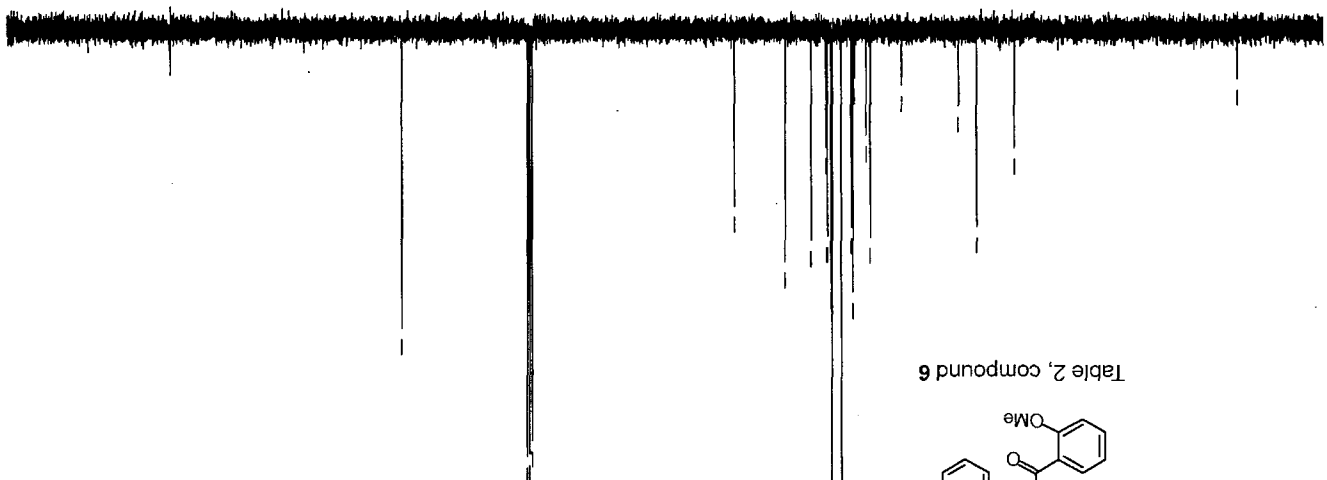


Table 2, compound 6

200 180 160 140 120 100 80 60 40 20 0 ppm

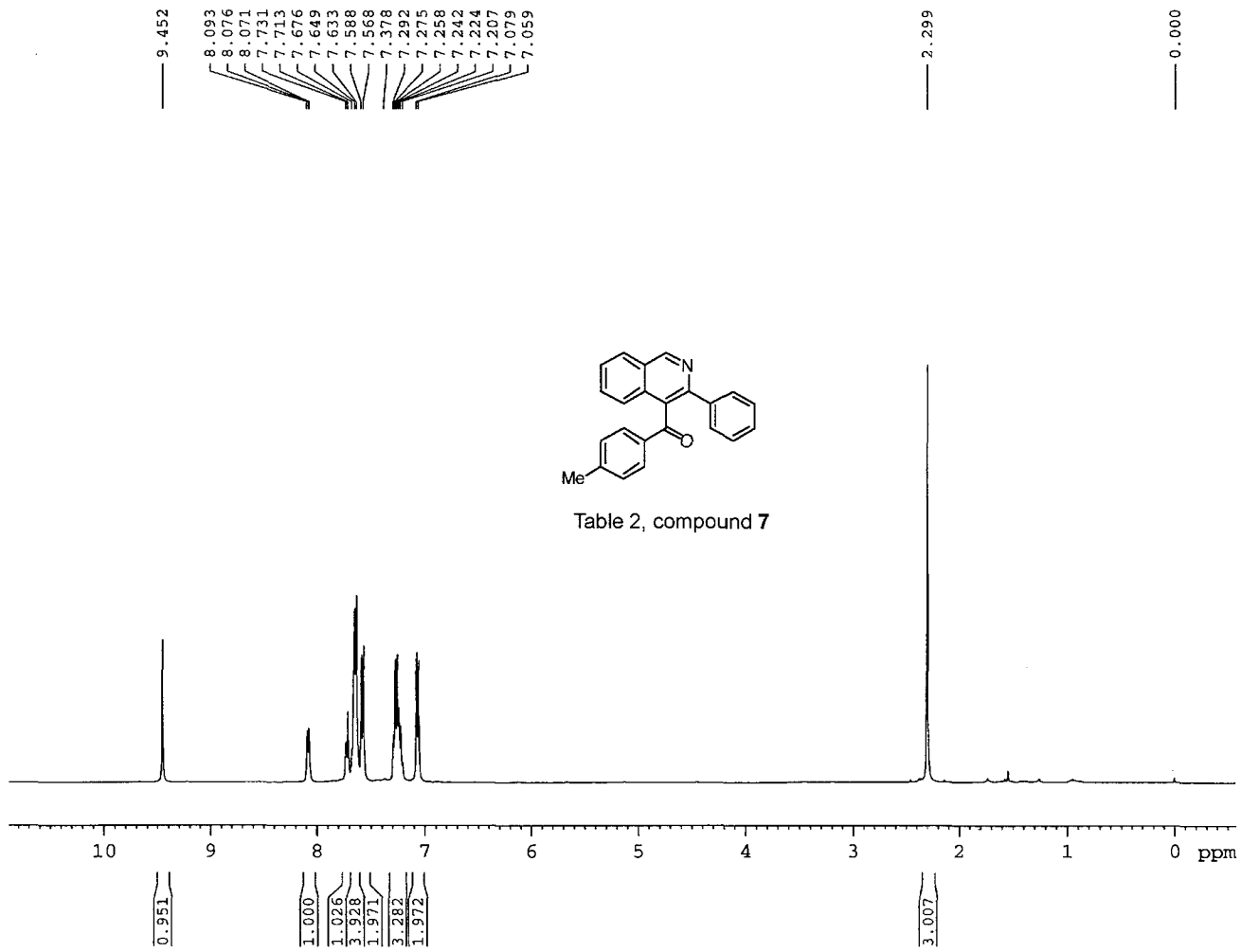


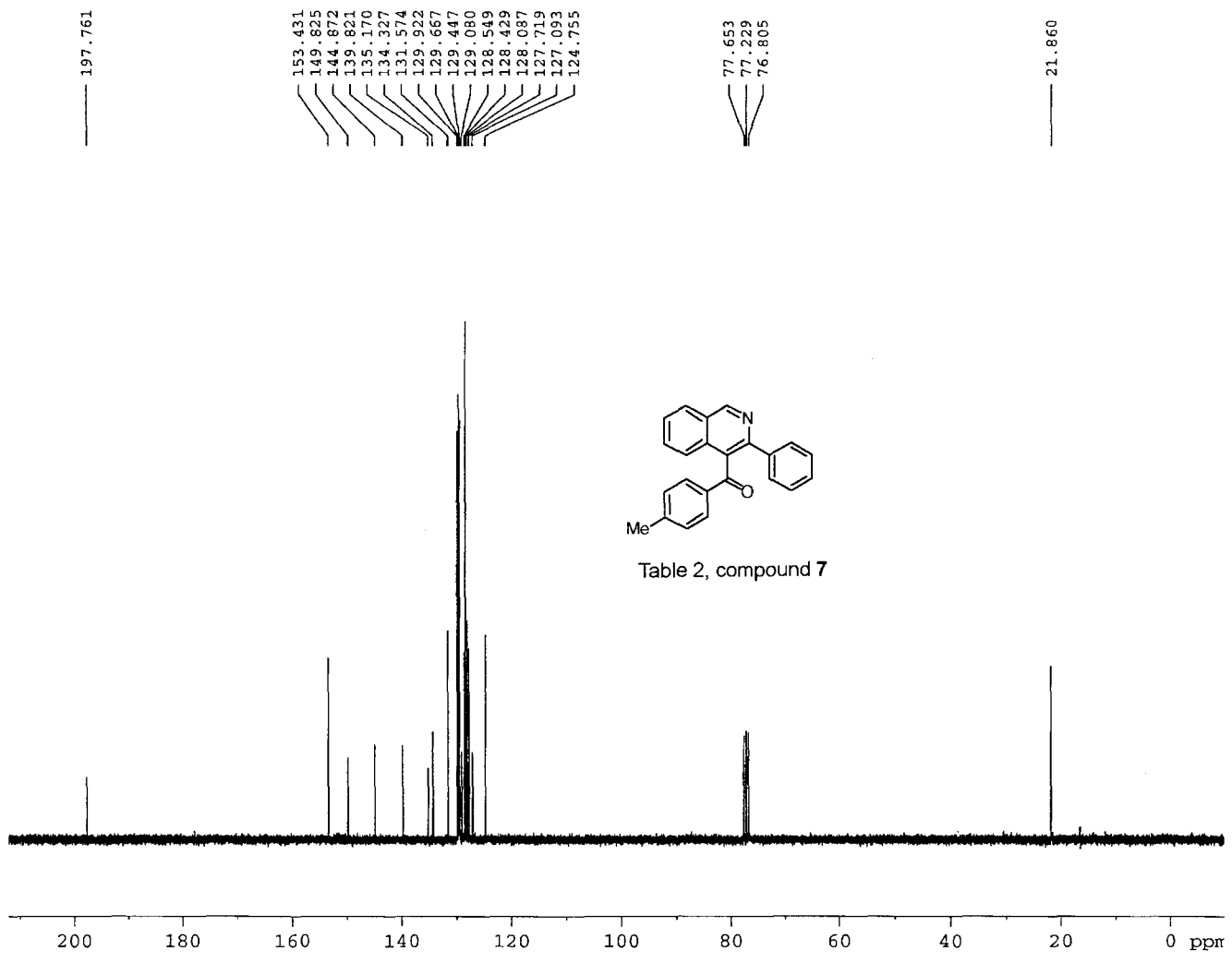
196.870

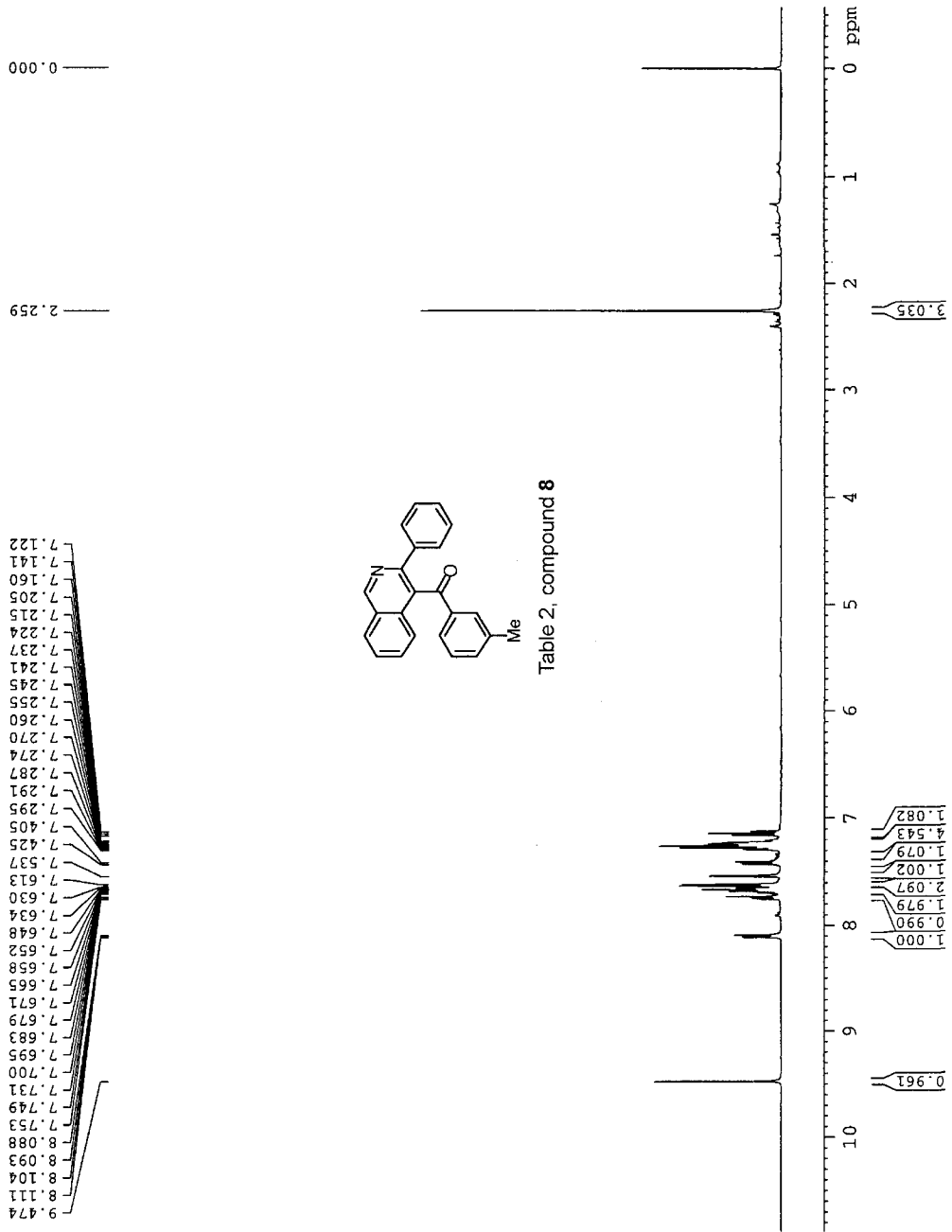
159.211
152.893
149.803
140.057
134.704
134.003
132.023
131.765
131.478
129.790
128.311
128.177
128.043
127.465
127.246
124.751
120.437
111.903

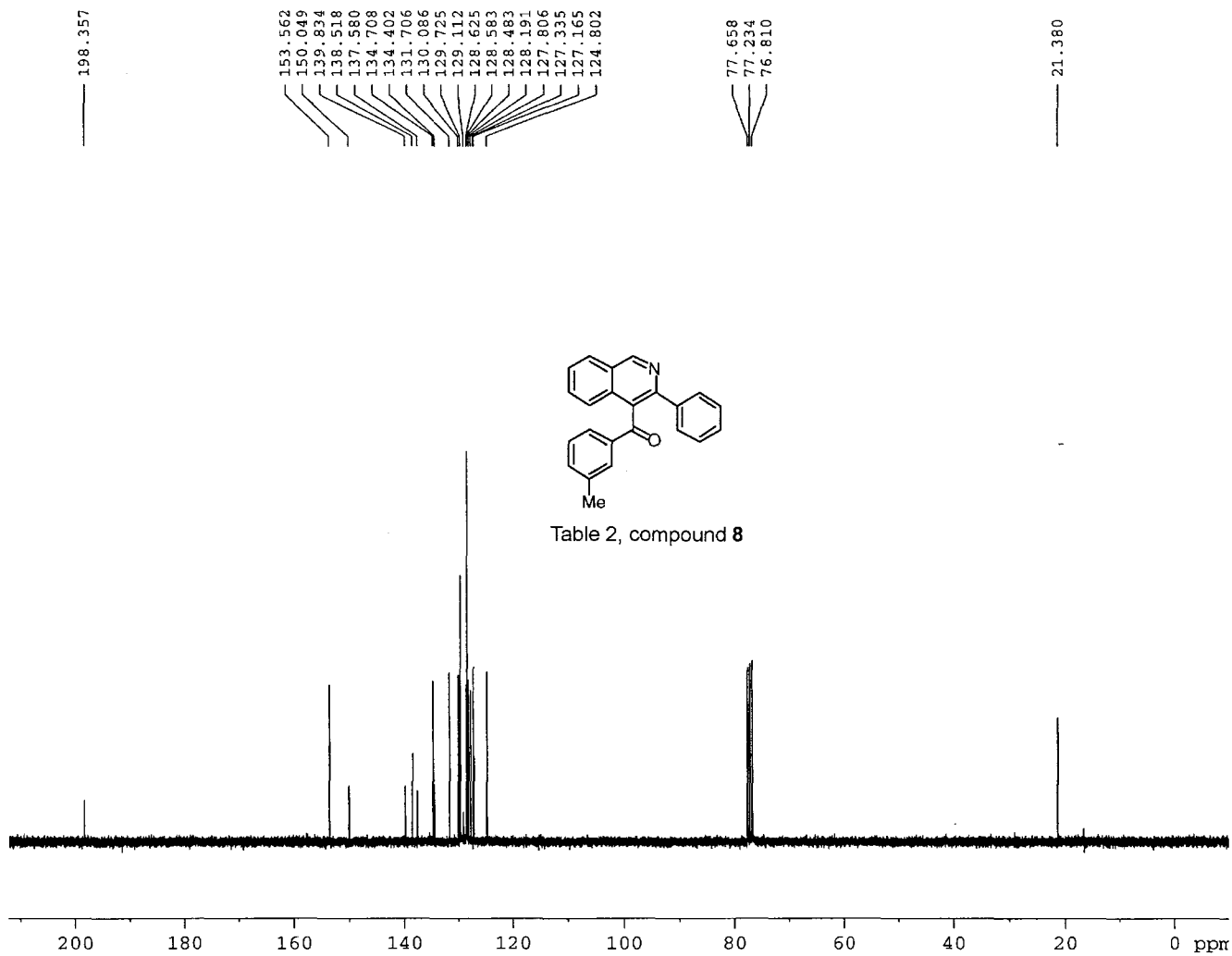
77.654
77.230
76.806

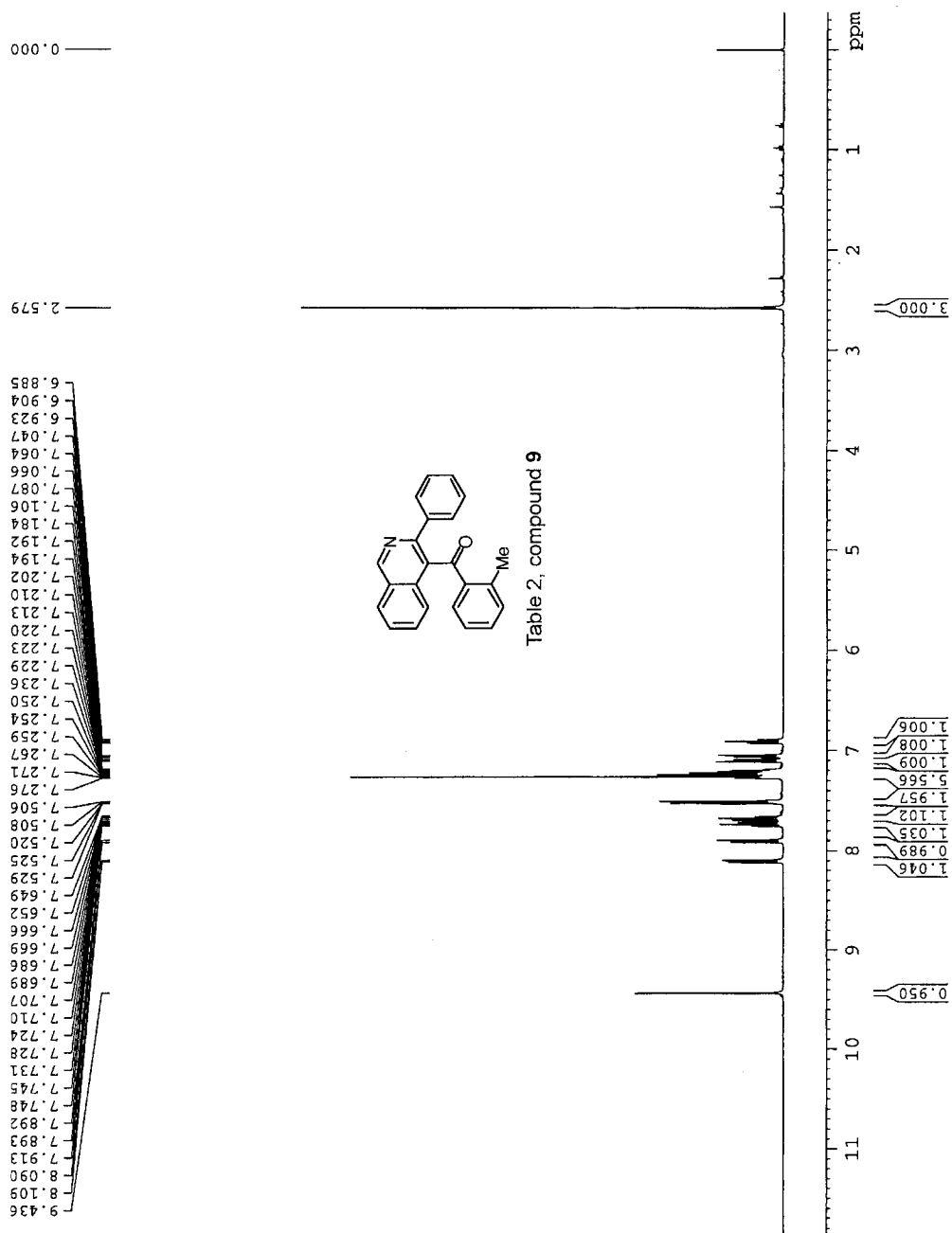
55.738











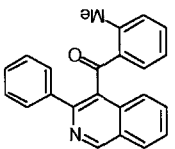


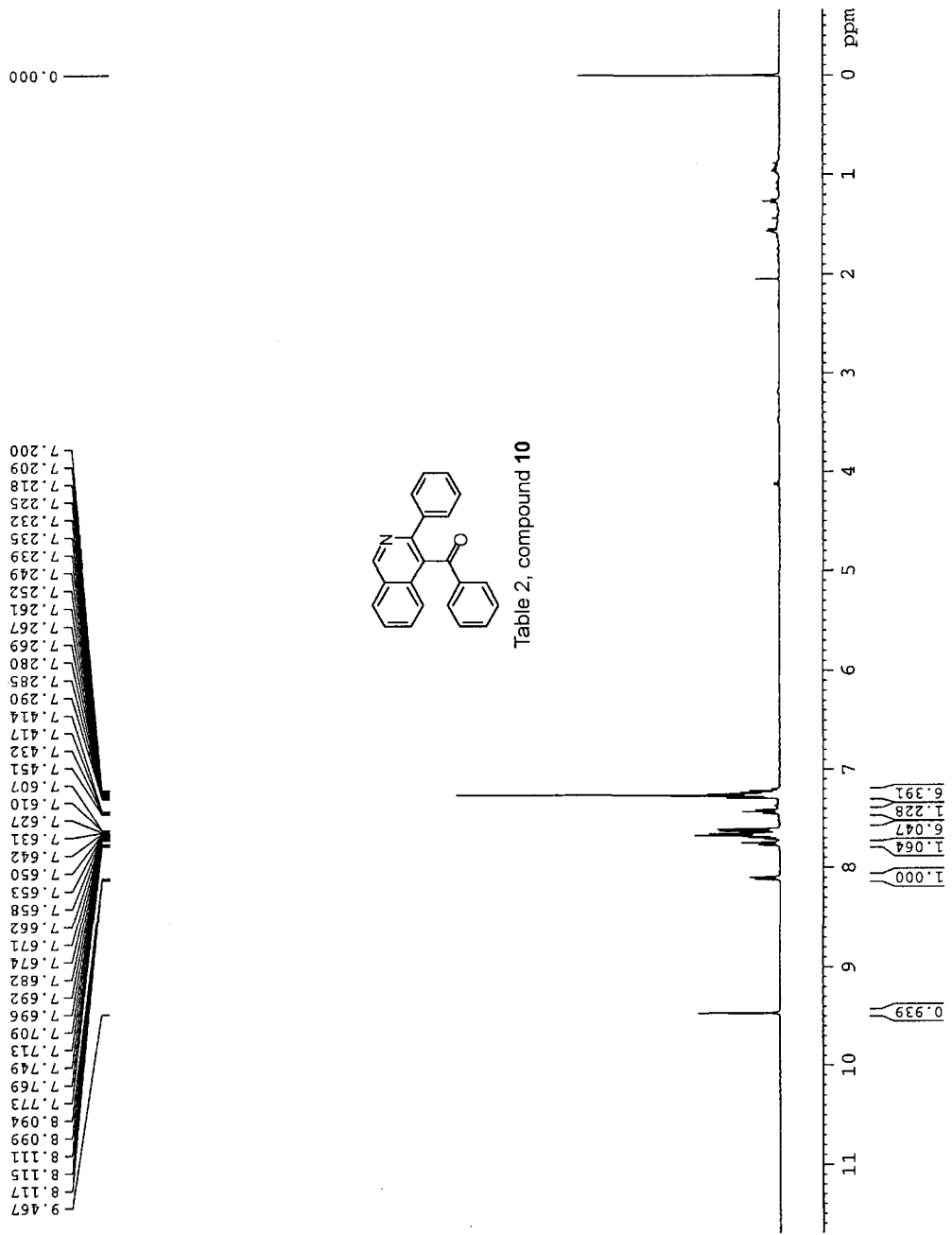
Table 2, compound 9

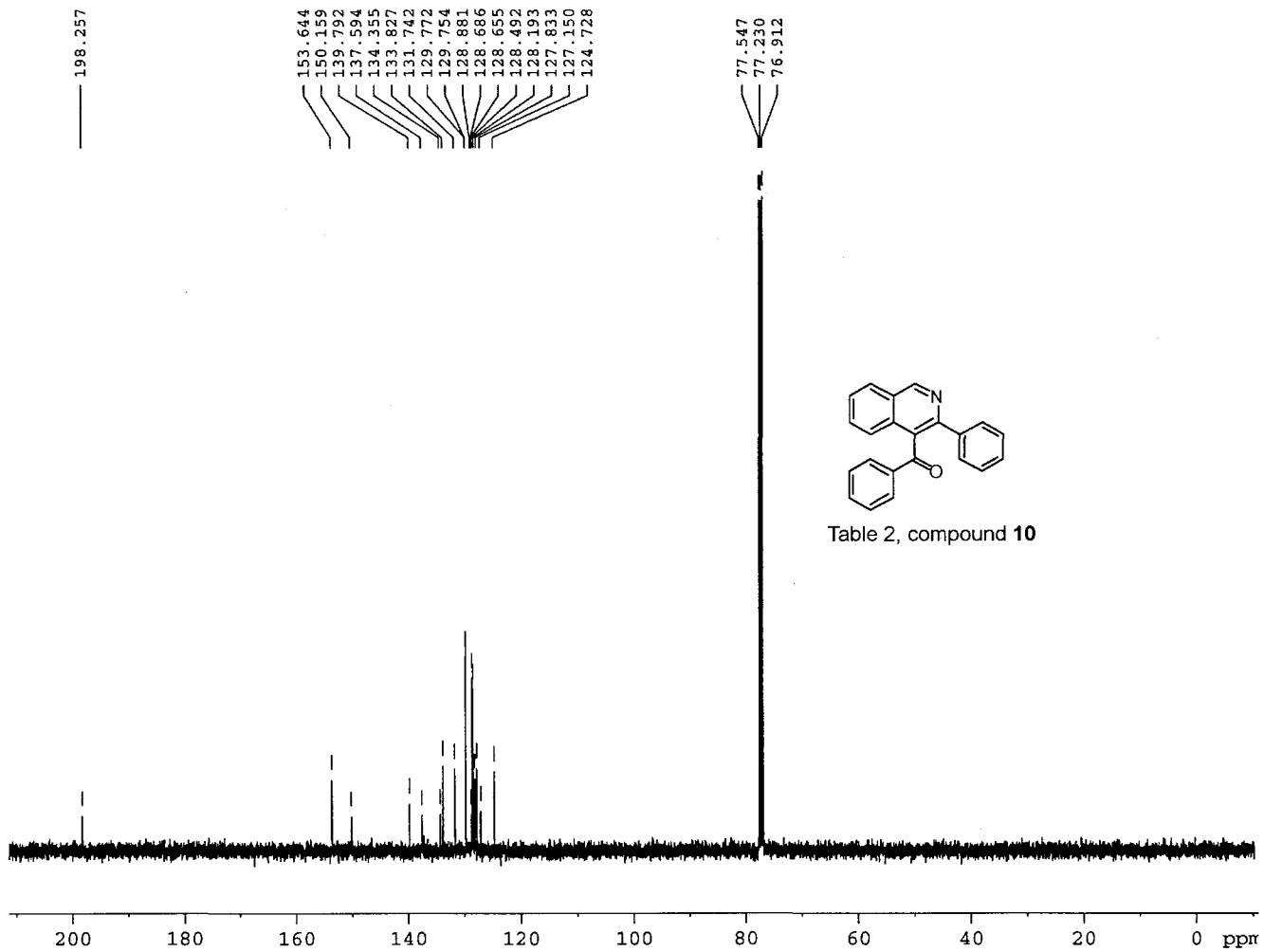
153.536
150.674
140.369
140.152
137.473
134.510
134.524
133.075
131.886
131.840
130.591
128.549
128.530
128.308
128.190
127.806
127.265
125.580
124.774

77.660
77.236
76.812

21.838

200 180 160 140 120 100 80 60 40 20 0 ppm





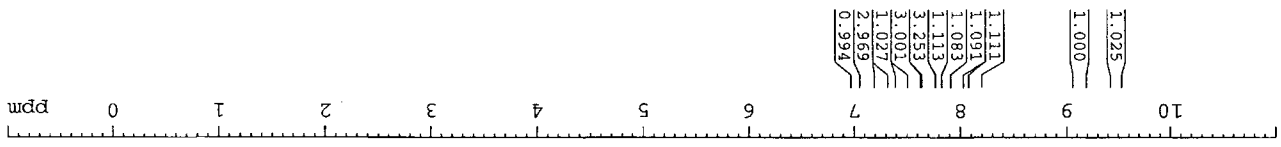
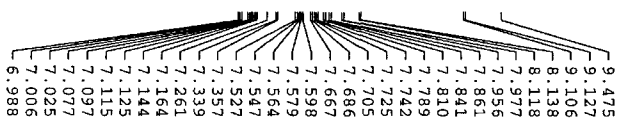
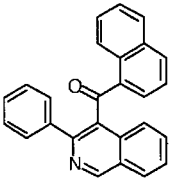
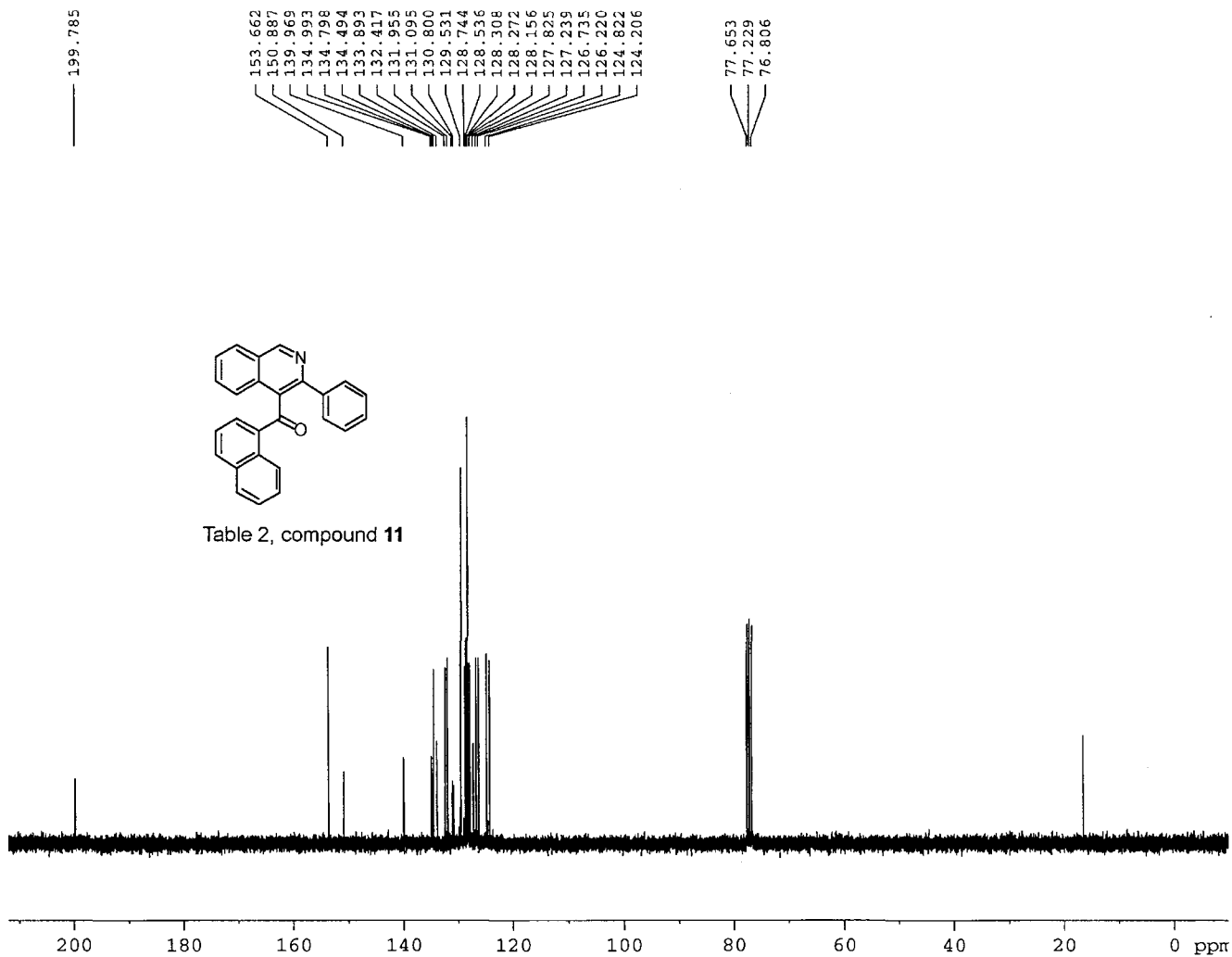
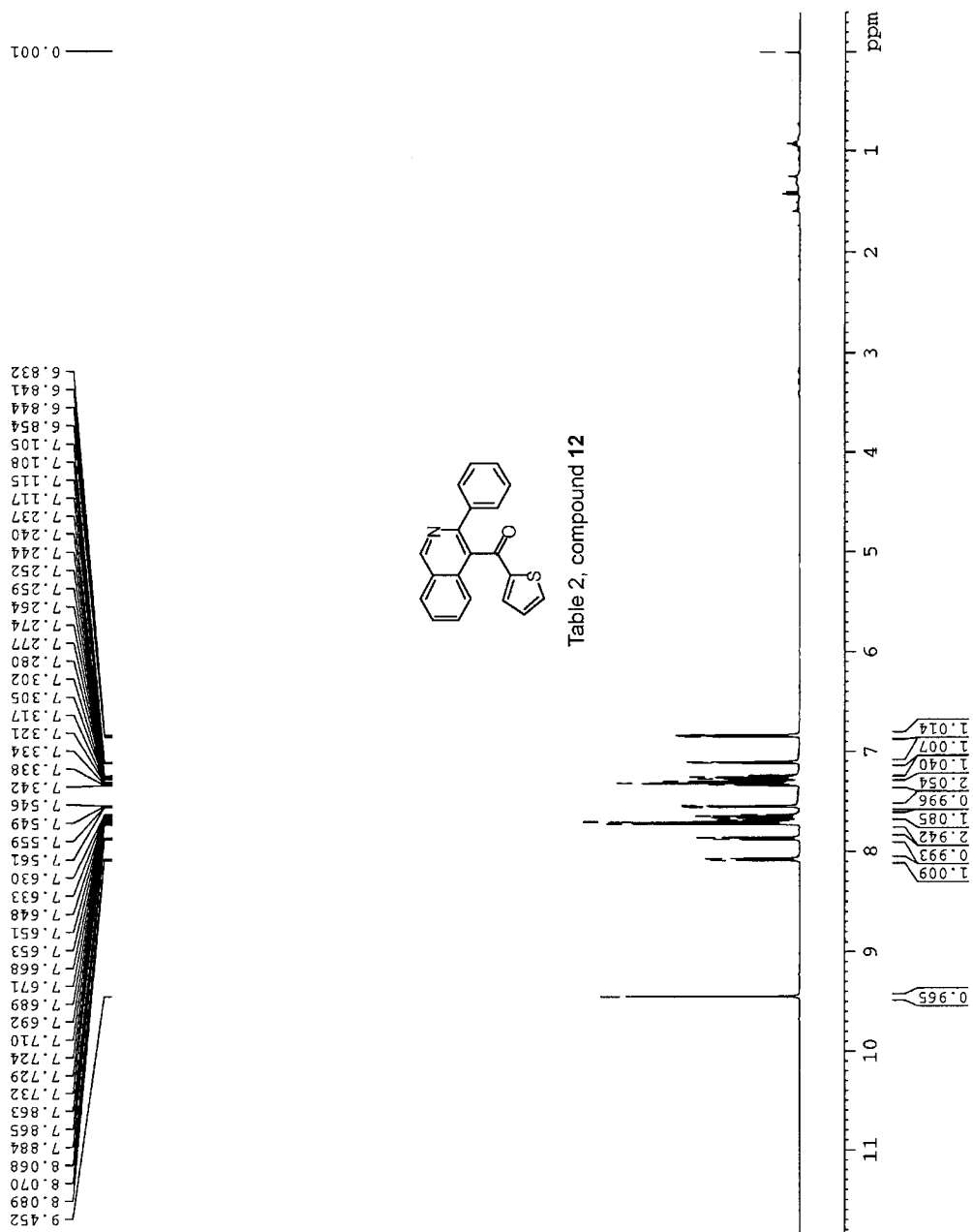


Table 2, compound 11



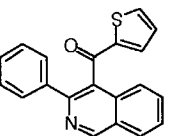




200 180 160 140 120 100 80 60 40 20 0 ppm



Table 2, compound 12



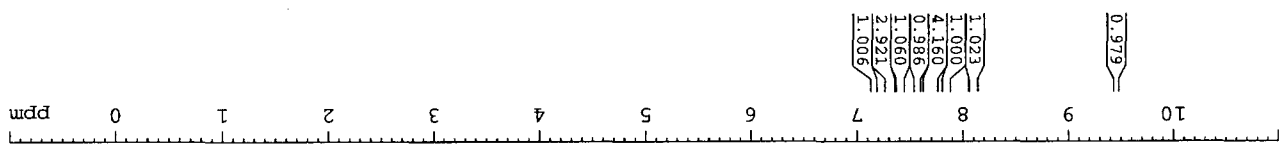
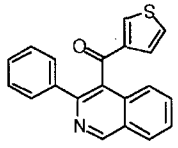
- 153.775
- 149.893
- 145.088
- 139.834
- 135.610
- 135.417
- 134.085
- 131.795
- 129.670
- 128.738
- 128.714
- 128.574
- 128.305
- 128.101
- 127.865
- 127.087
- 124.621

130.033

- 77.653
- 77.239
- 76.805

8.084
7.852
7.824
7.745
7.740
7.722
7.717
7.695
7.686
7.681
7.673
7.664
7.659
7.654
7.641
7.576
7.572
7.566
7.562
7.419
7.415
7.402
7.398
7.346
7.338
7.332
7.316
7.292
7.283
7.278
7.261
7.247
7.241
7.236
7.174
7.165
7.157
7.147

Table 2, compound 13



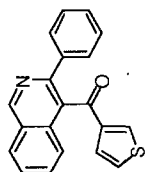
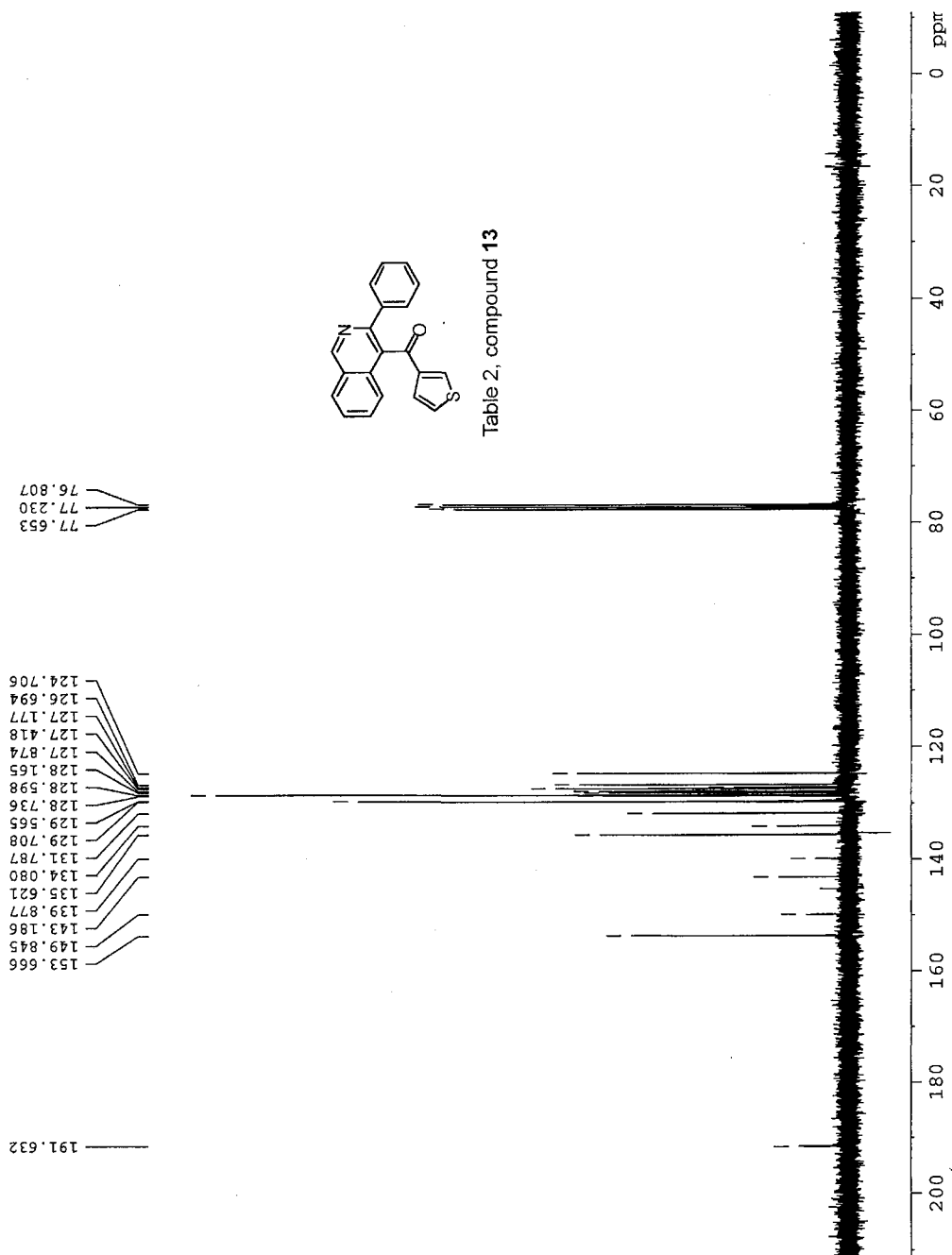
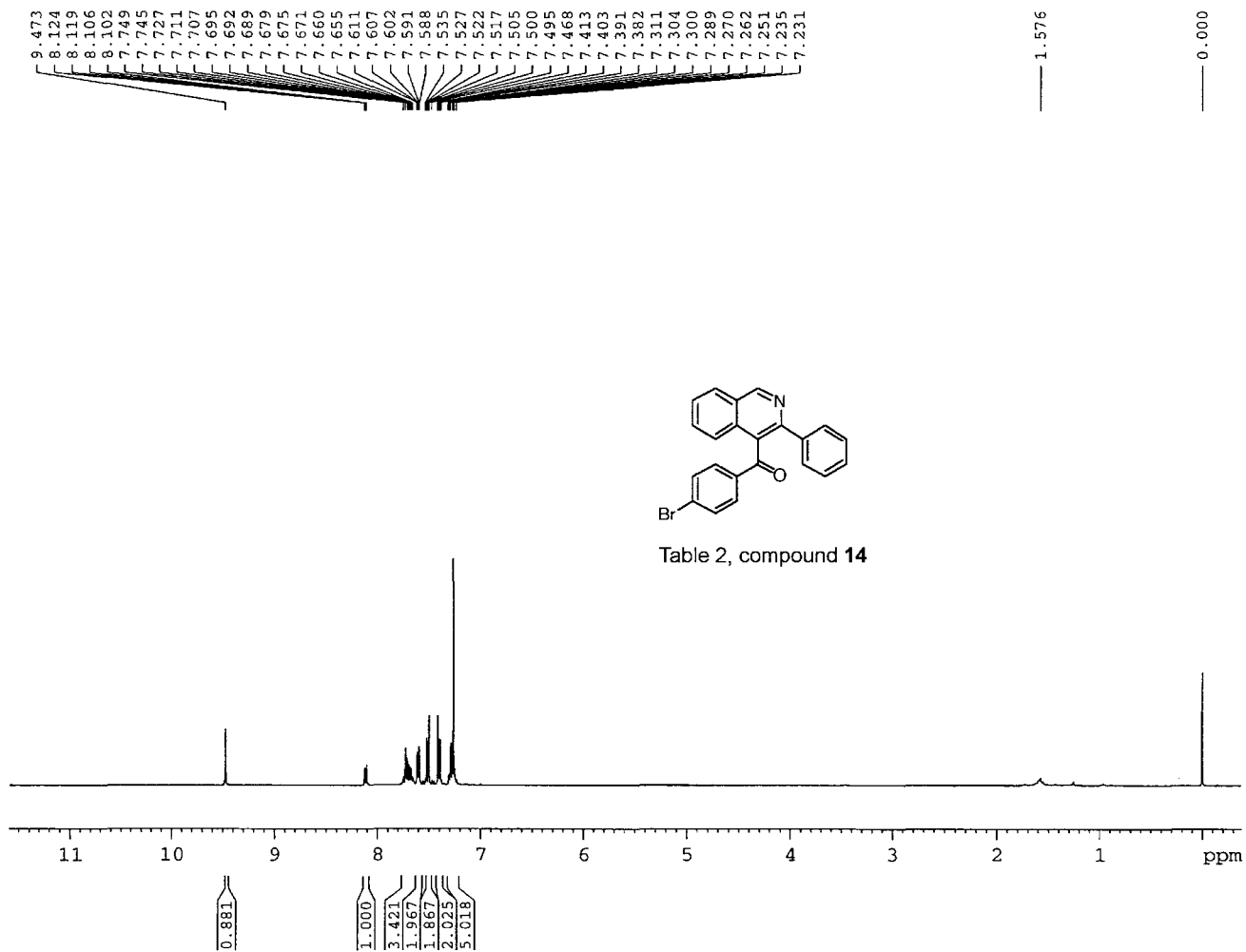
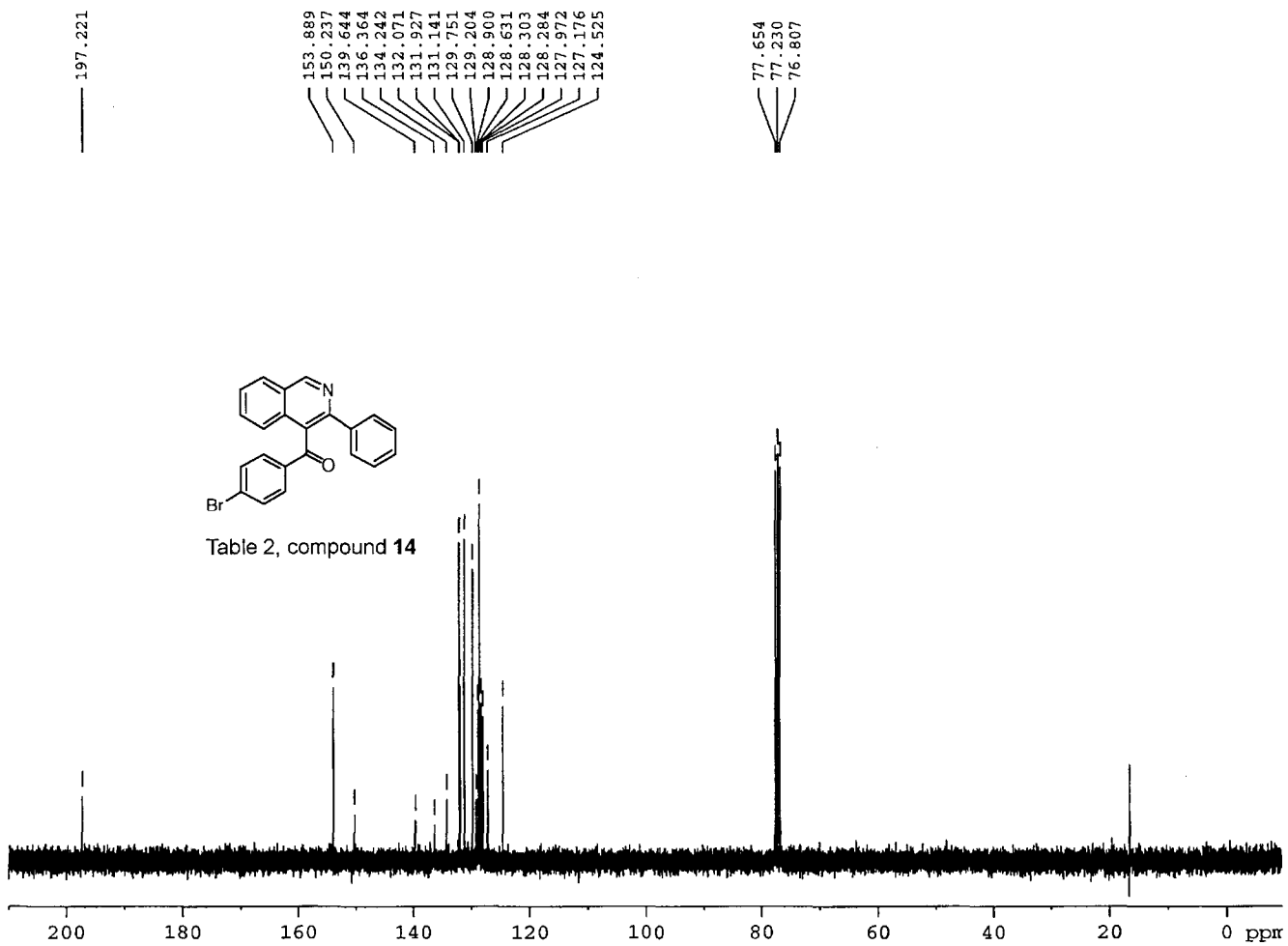
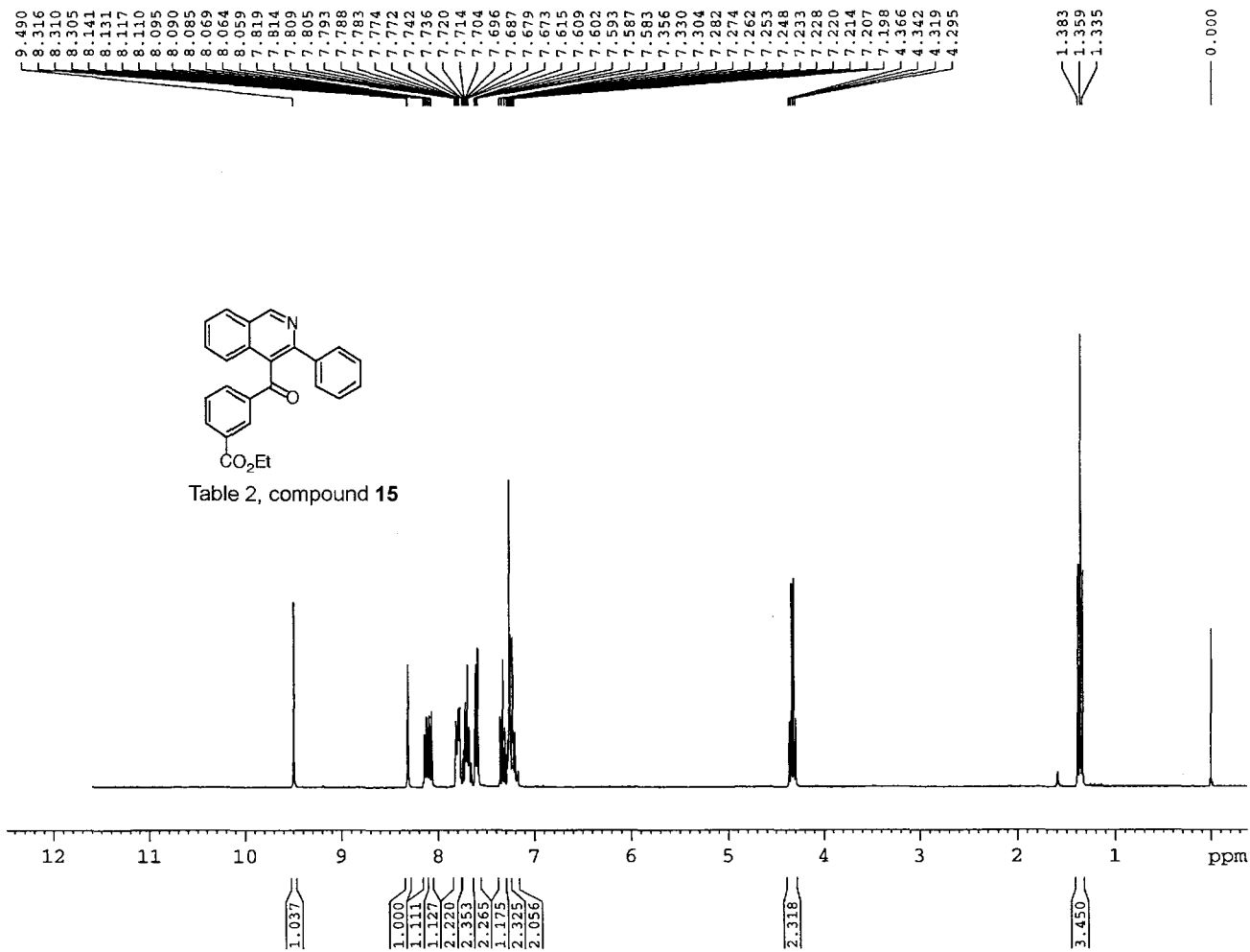


Table 2, compound 13









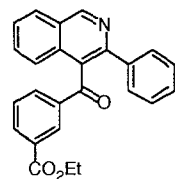
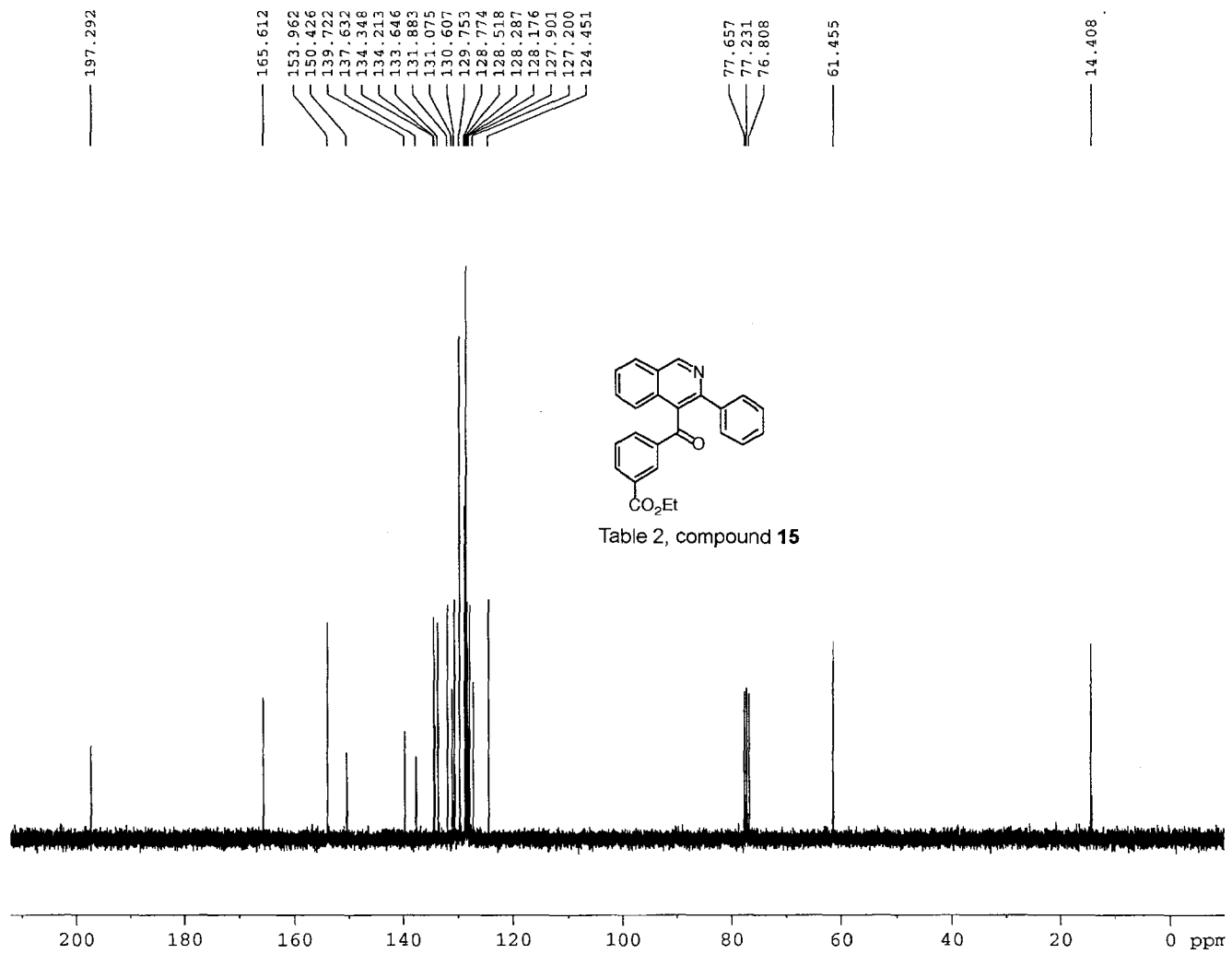
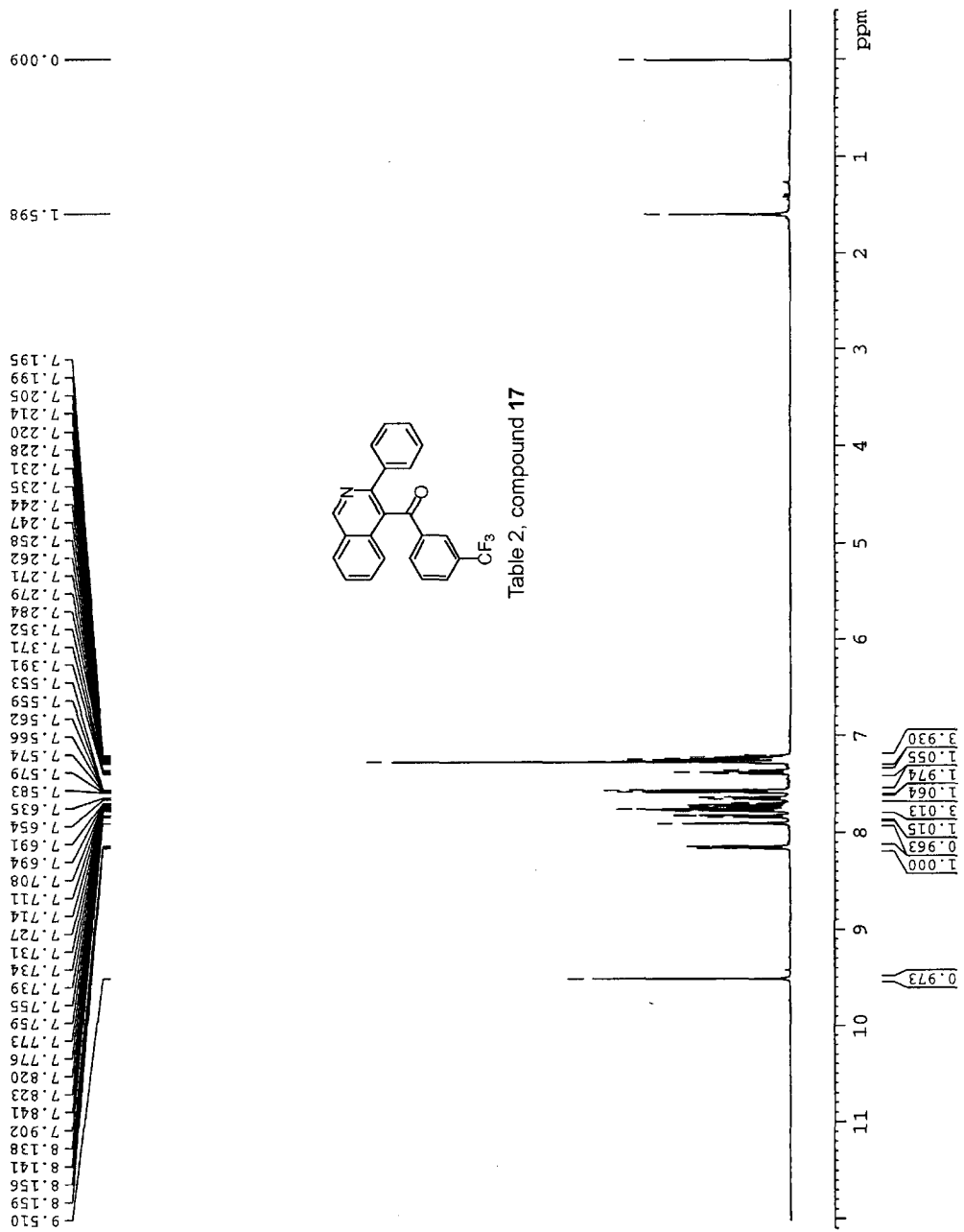
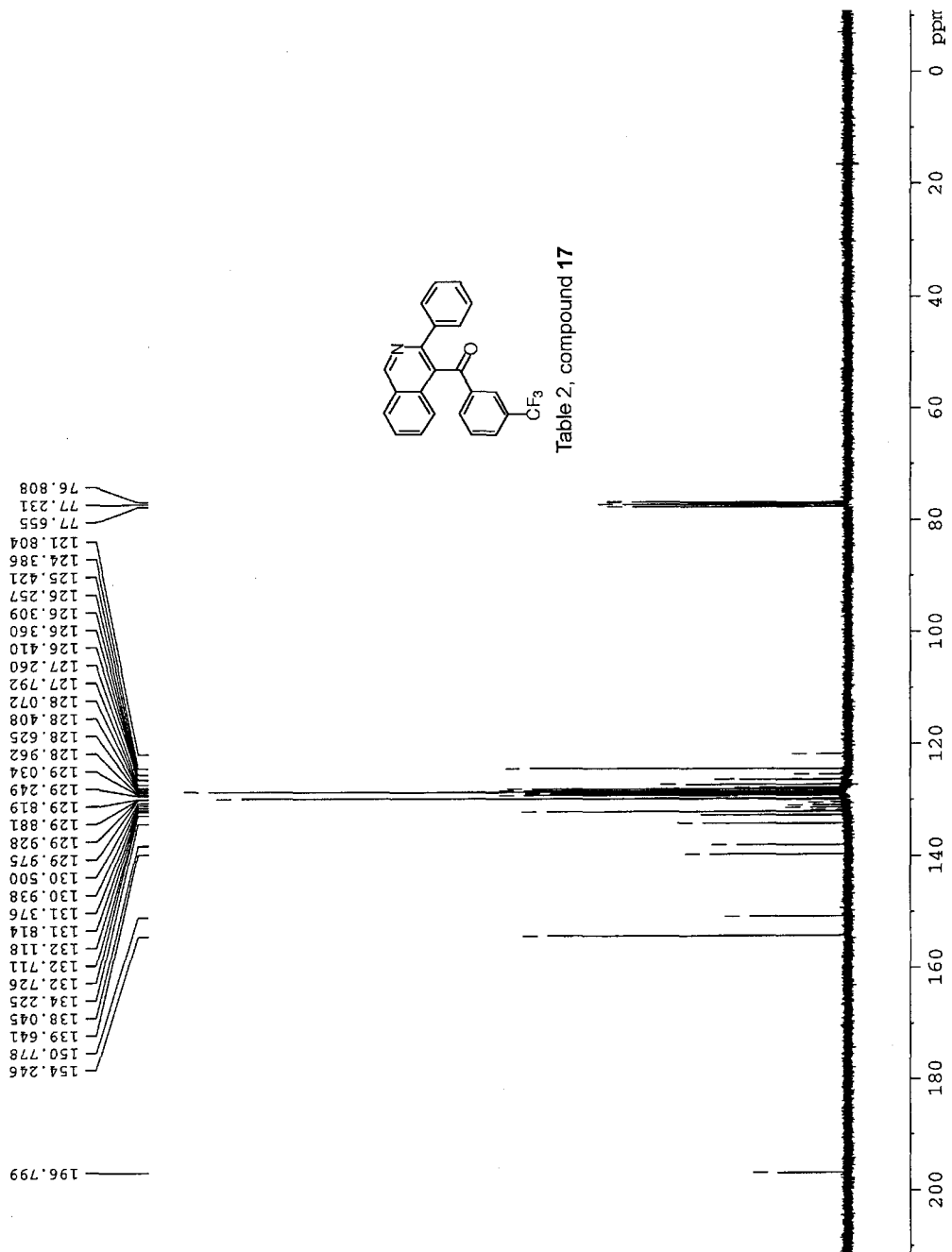


Table 2, compound 15





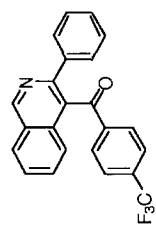
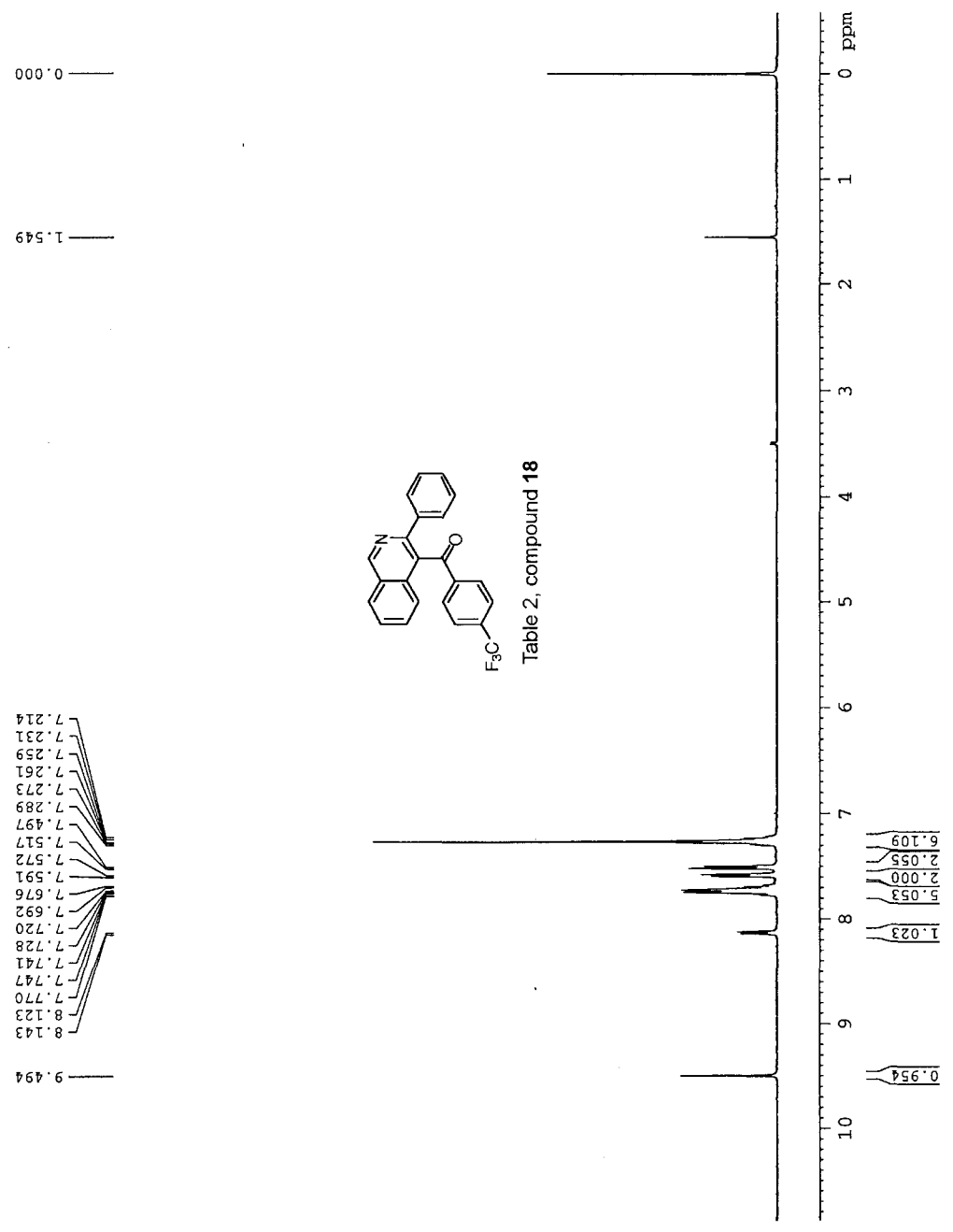


Table 2, compound 18



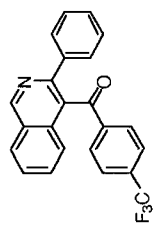
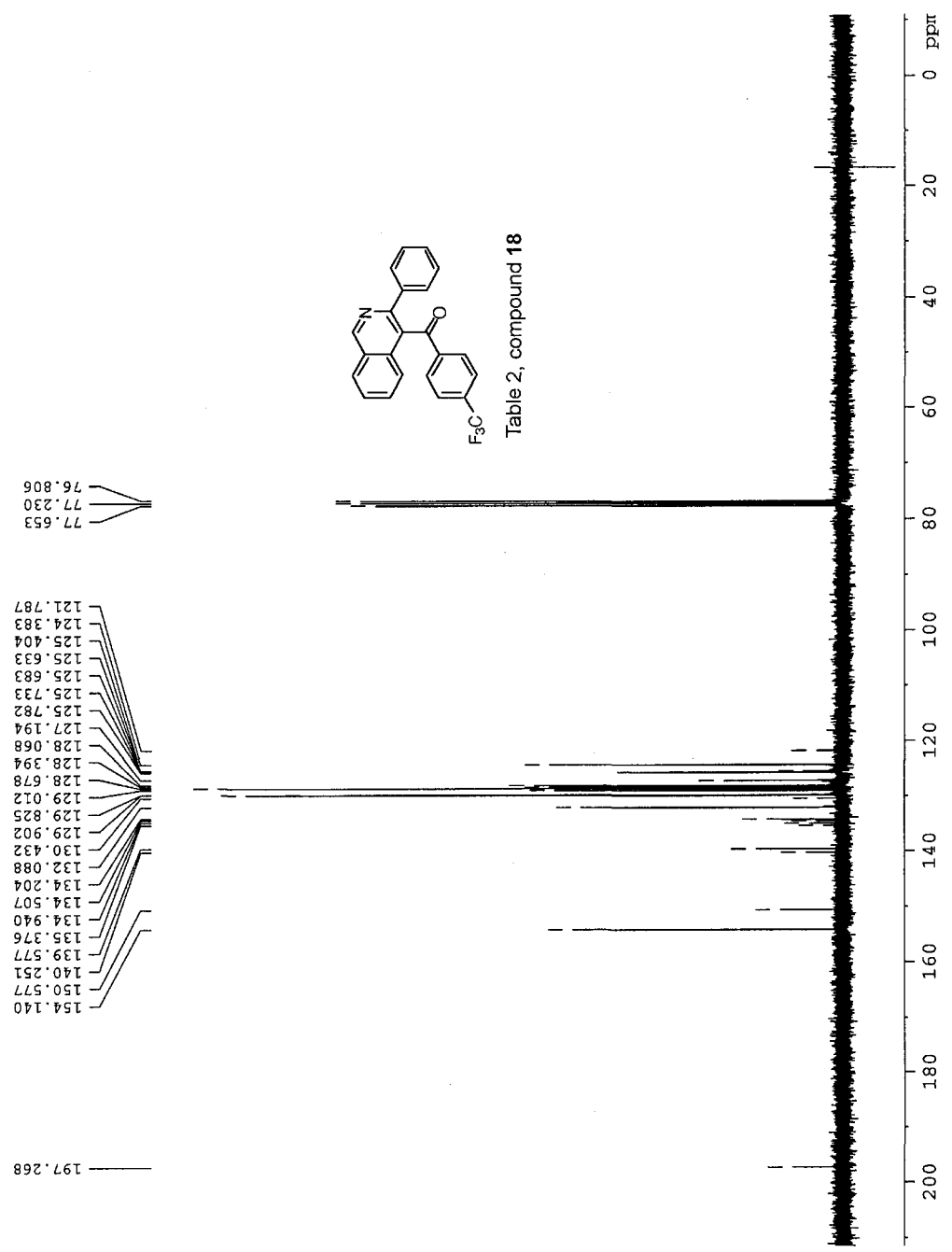


Table 2, compound 18



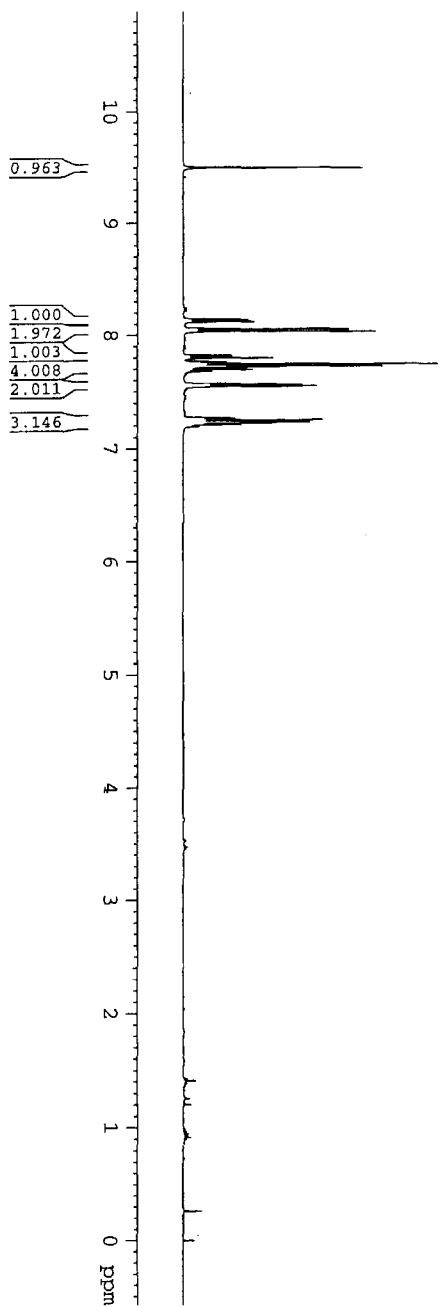
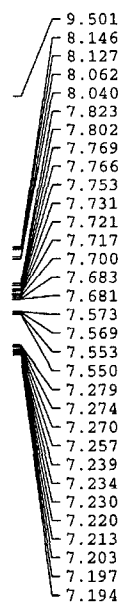
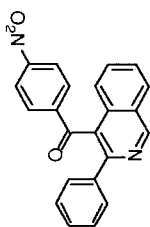
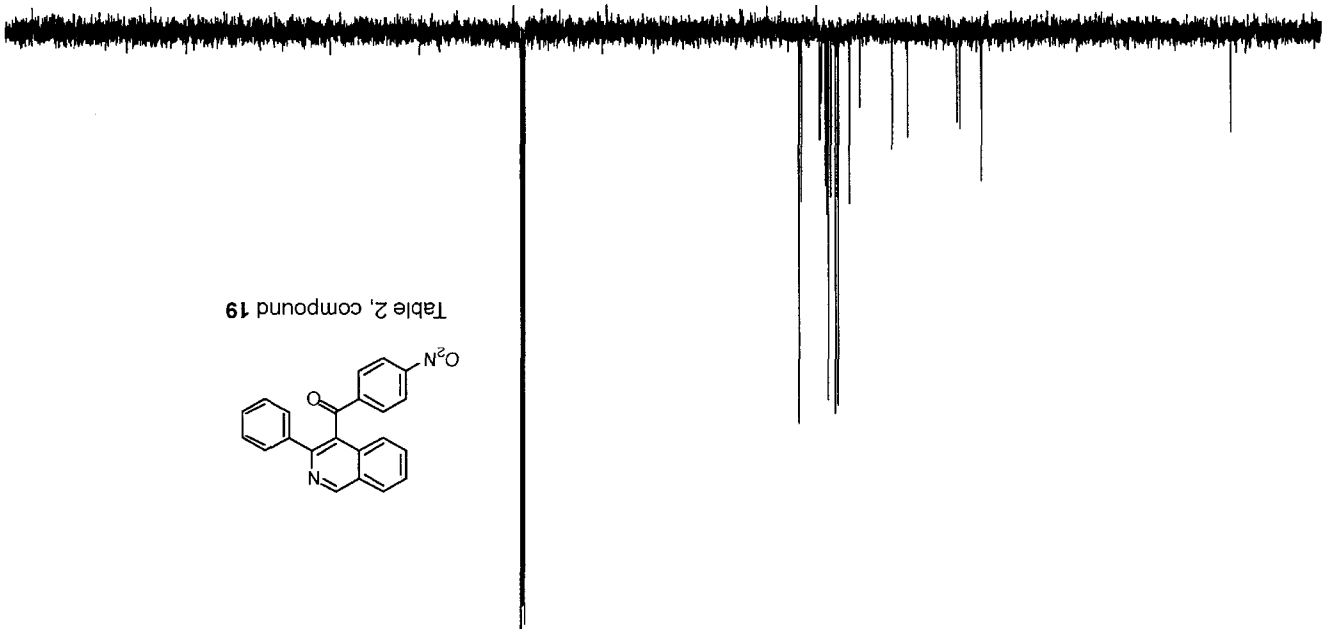


Table 2, compound 19



0.000

200 180 160 140 120 100 80 60 40 20 0 ppm

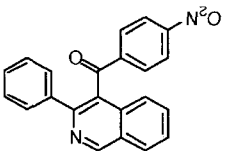


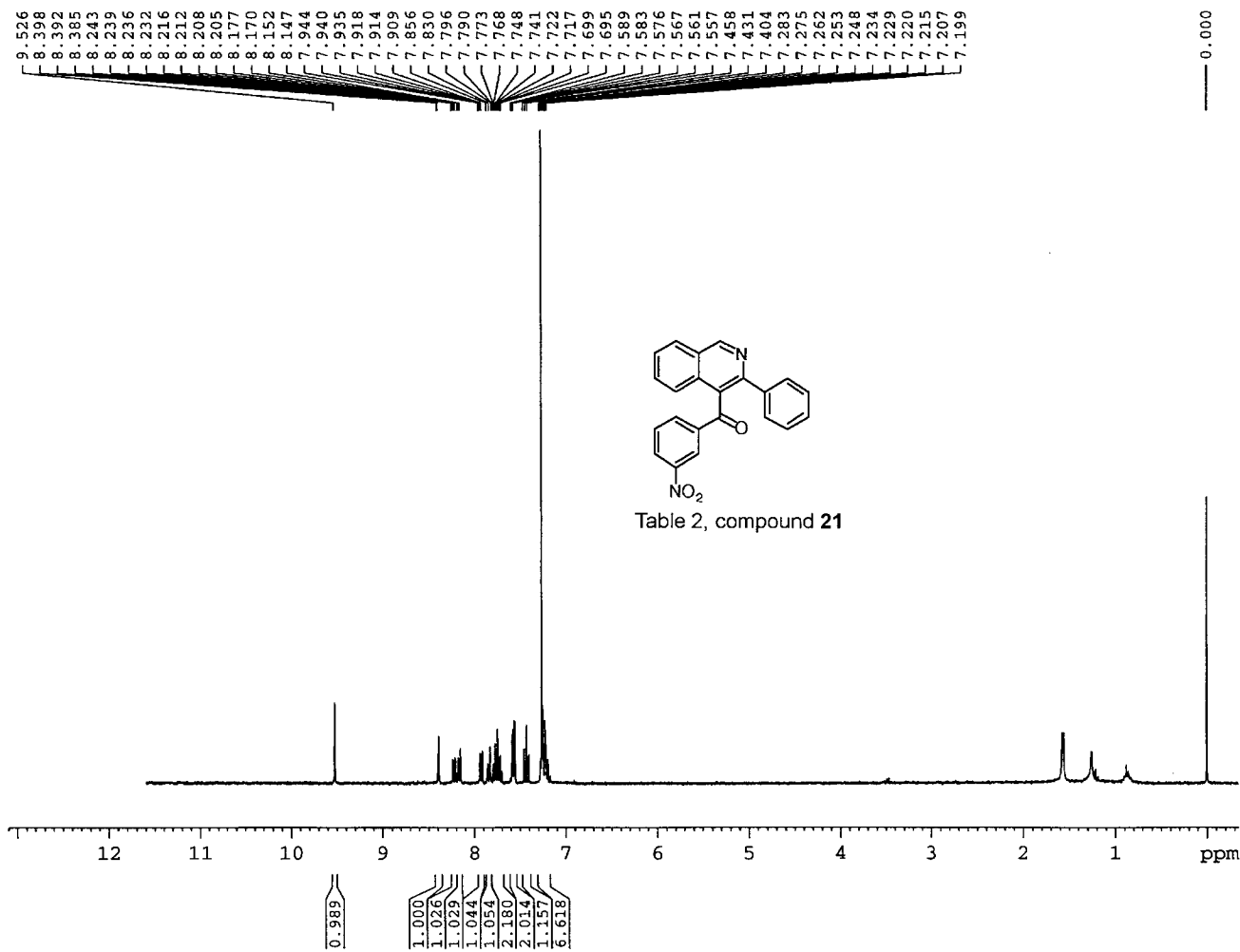
196.588

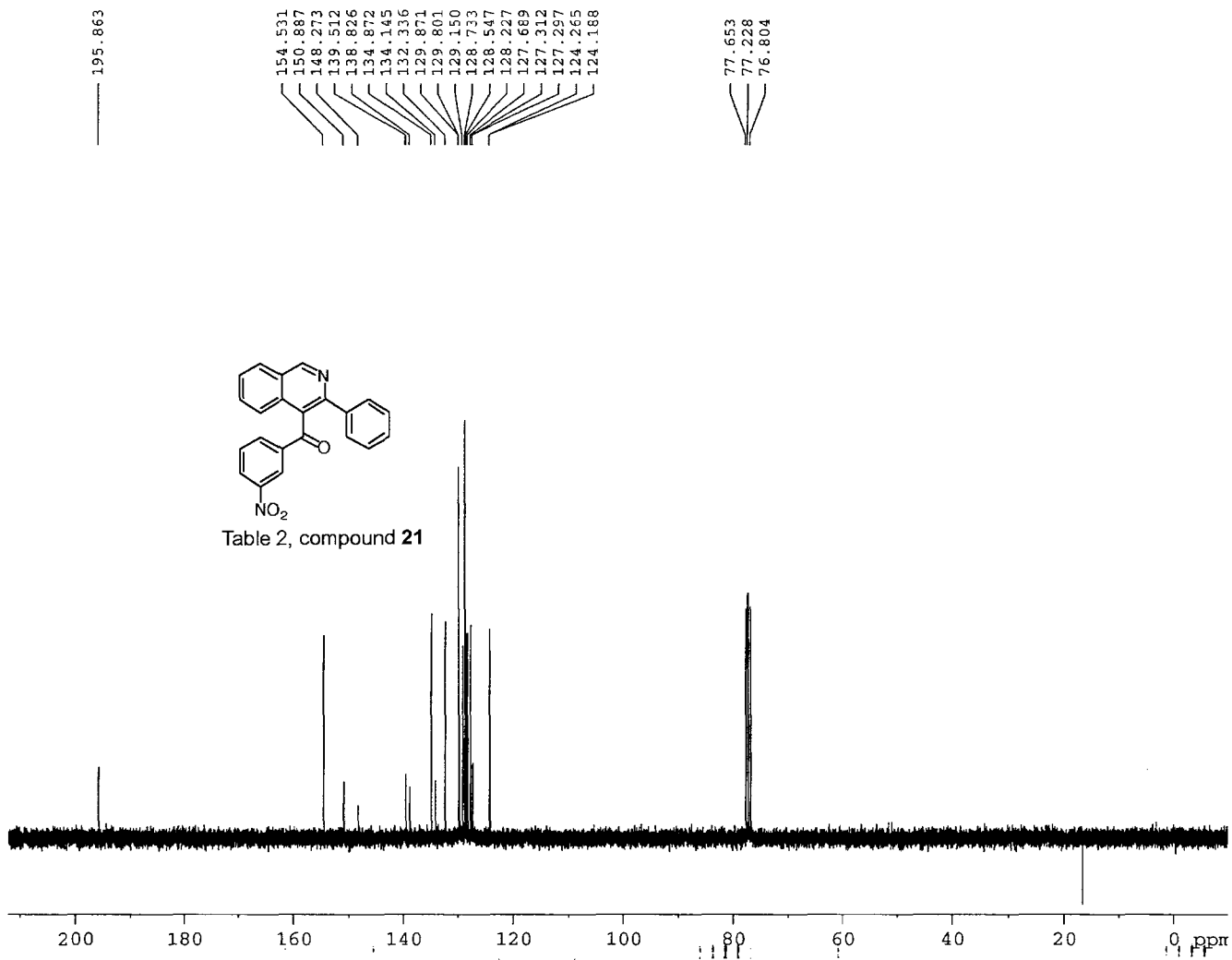
154.427
150.821
150.283
142.055
139.461
134.054
132.256
130.382
129.866
129.160
128.714
128.444
128.164
127.506
127.162
124.137
123.734

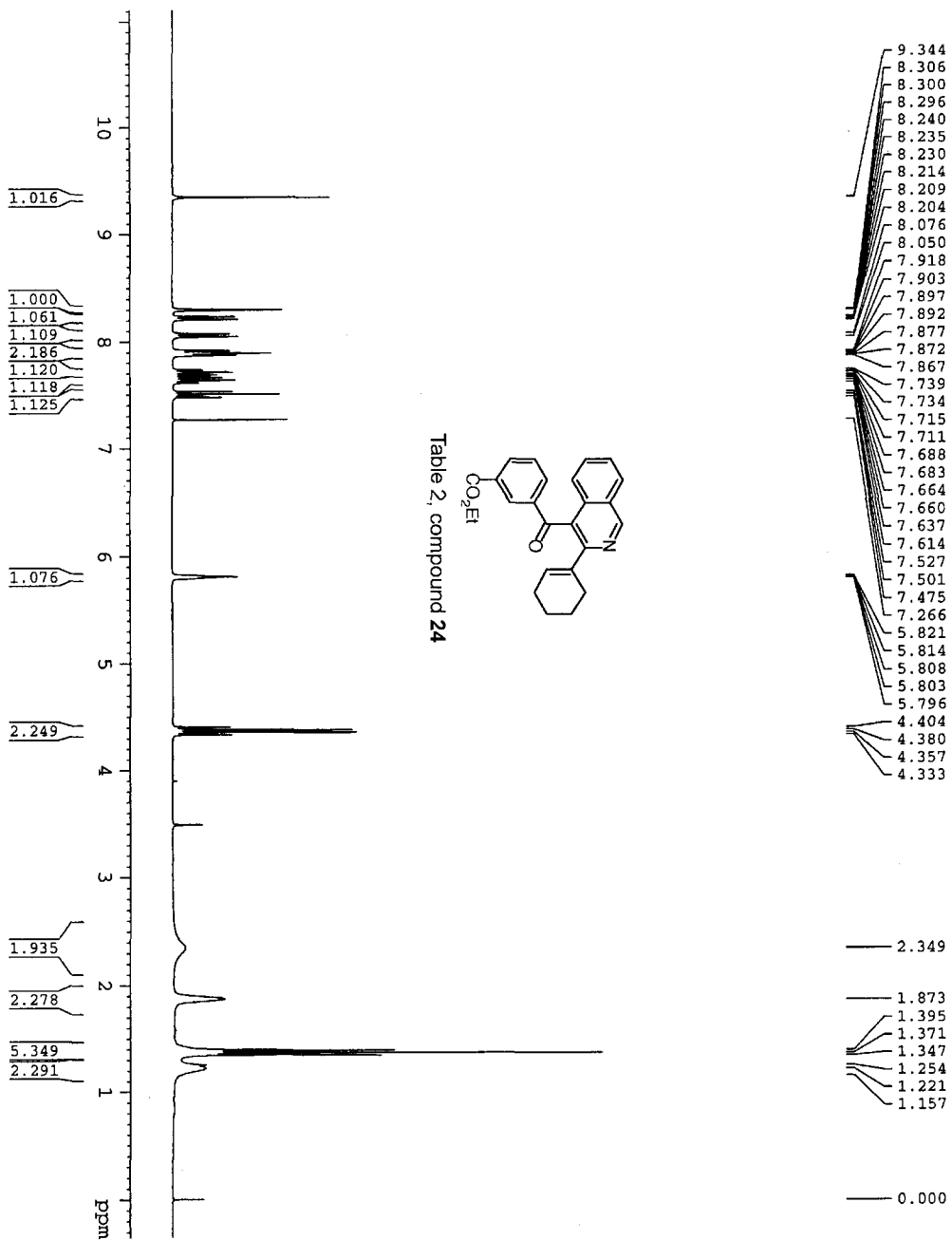
77.551
77.233
76.915

Table 2, compound 19









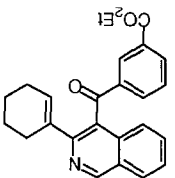
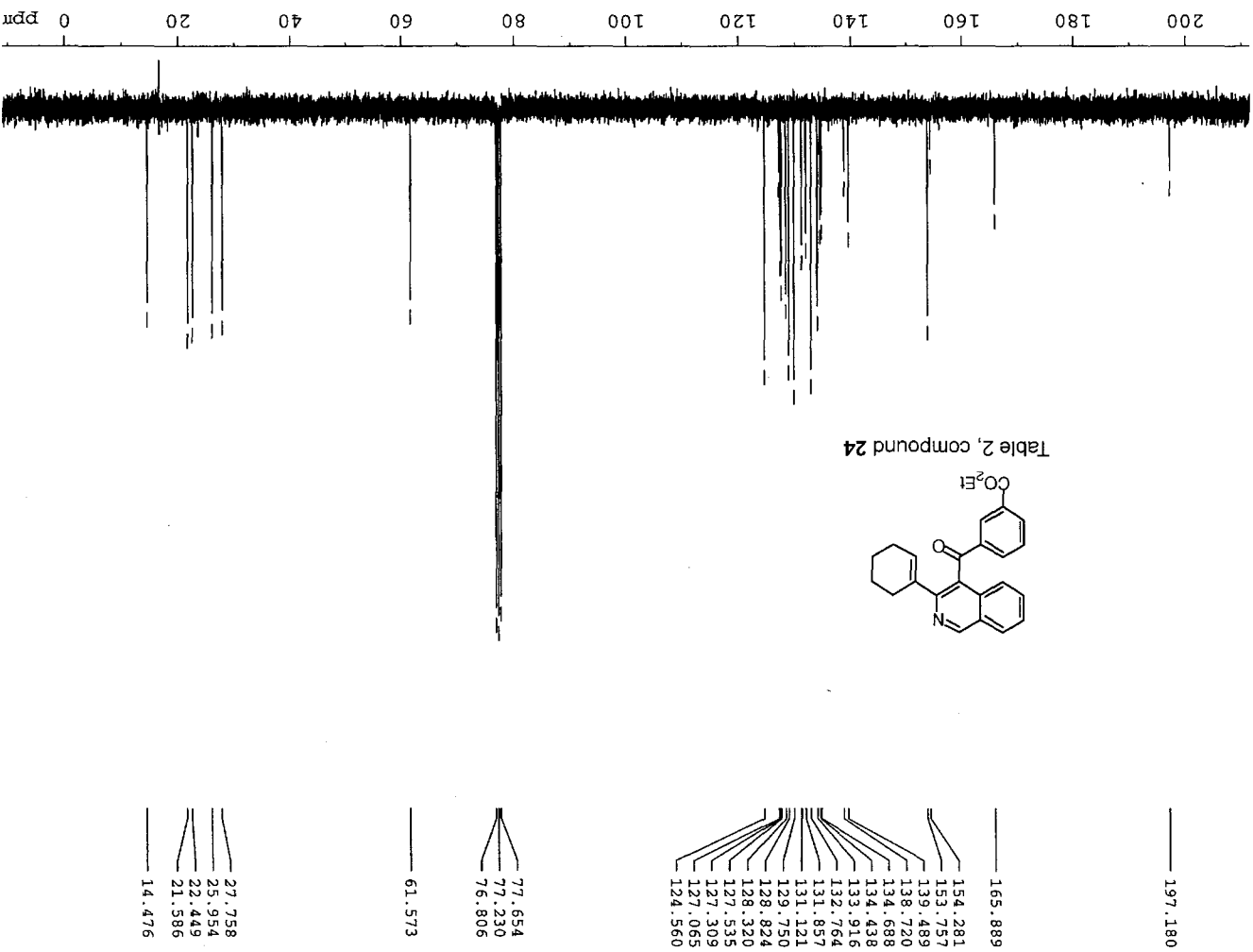
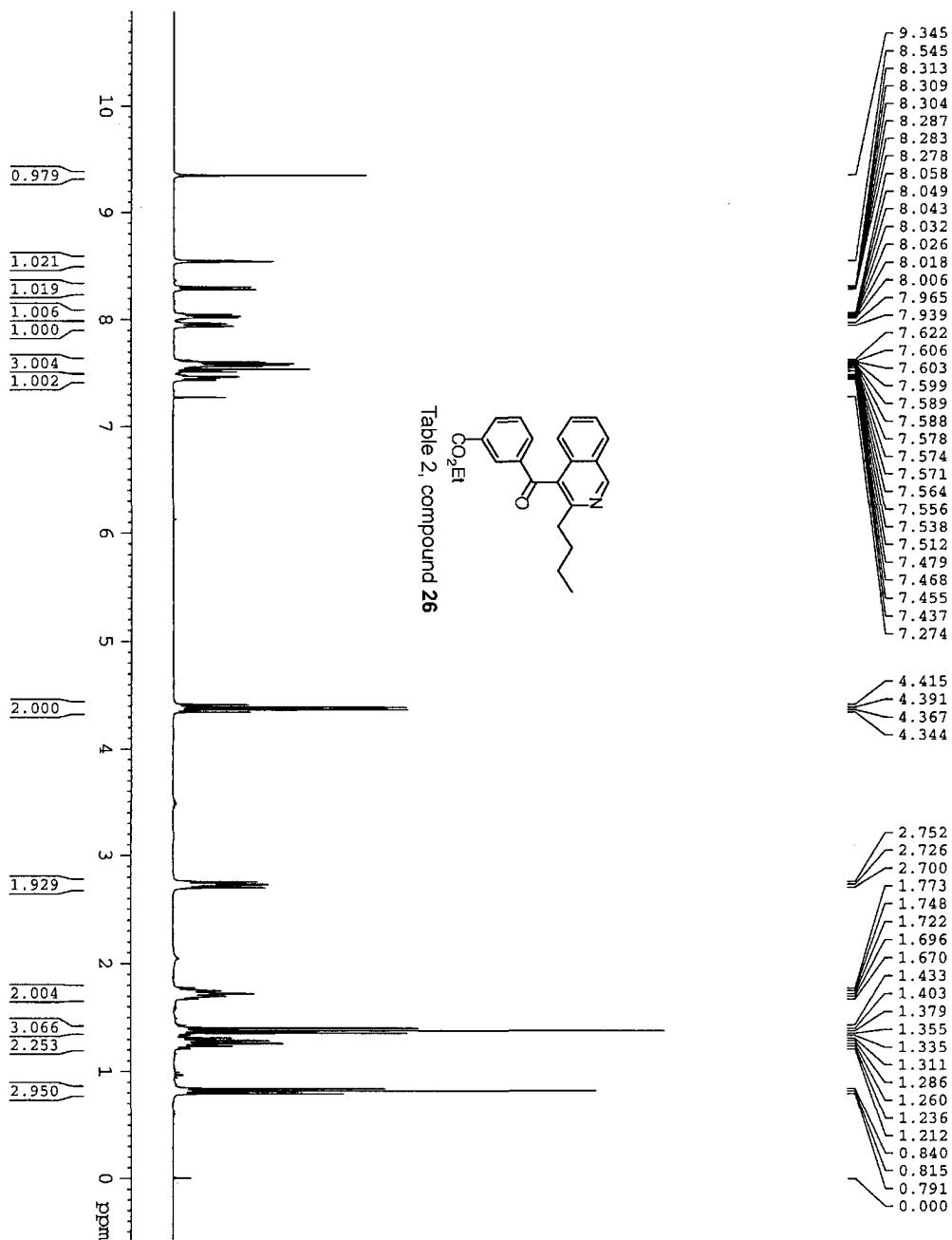
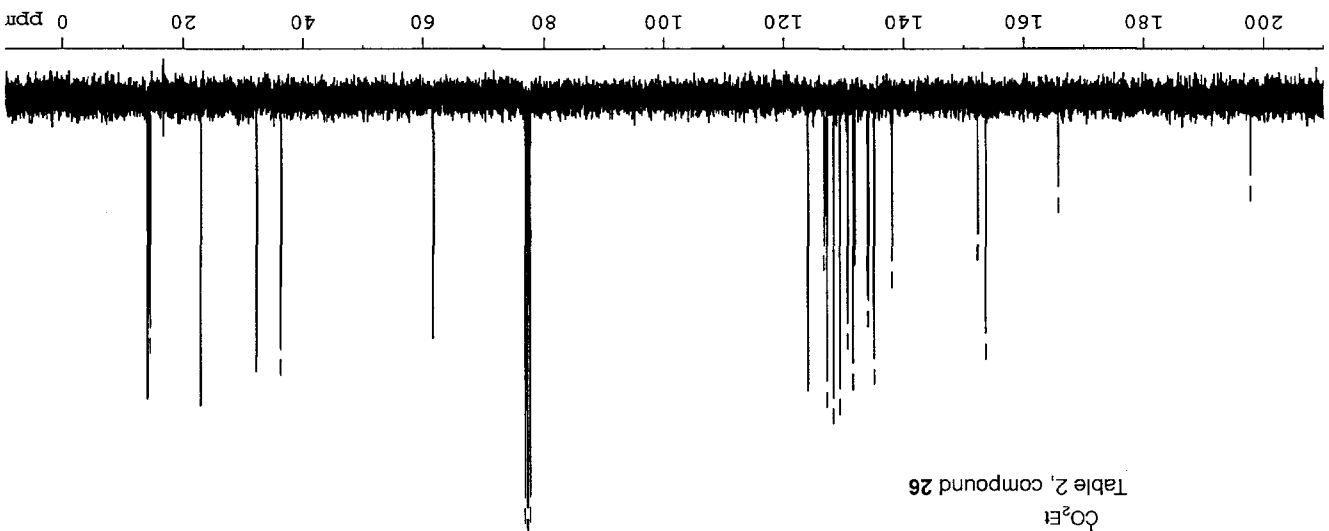
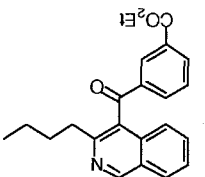


Table 2, compound 24







197.763

165.712

153.617
152.267
137.955
135.013
134.032
133.881
131.767
131.464
130.593
129.324
128.227
128.156
127.184
126.573
123.987

77.657
77.233
76.809

61.655

36.249
32.170
22.830
14.458
13.999

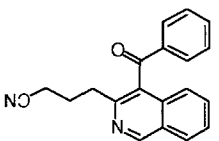
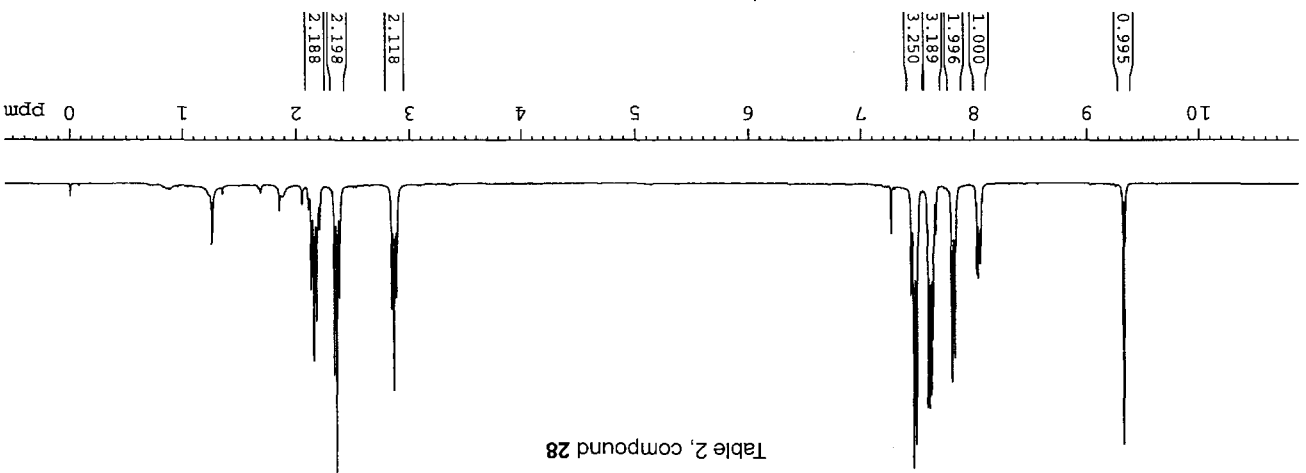


Table 2, compound 28



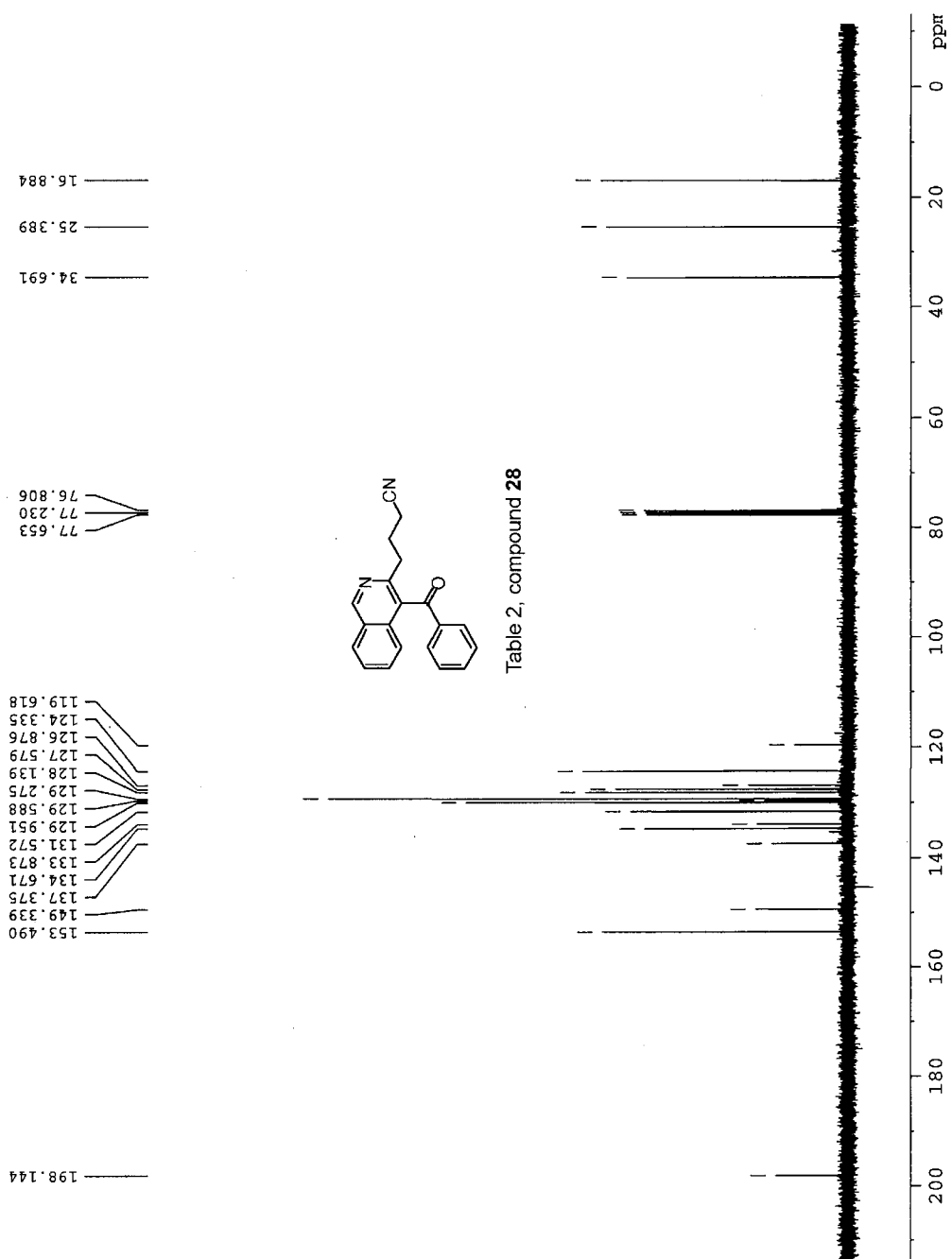
Chemical shift values (ppm) for the 1H NMR spectrum:

- 9.323
- 8.058
- 8.049
- 8.044
- 8.037
- 8.027
- 8.014
- 7.832
- 7.808
- 7.664
- 7.640
- 7.628
- 7.615
- 7.608
- 7.596
- 7.585
- 7.543
- 7.536
- 7.498
- 7.489
- 7.472
- 7.446
- 7.270

Chemical shift values (ppm) for the 1H NMR spectrum:

- 2.885
- 2.861
- 2.837
- 2.382
- 2.357
- 2.333
- 2.203
- 2.179
- 2.154
- 2.130
- 2.106

Reference peak at 0.000 ppm.



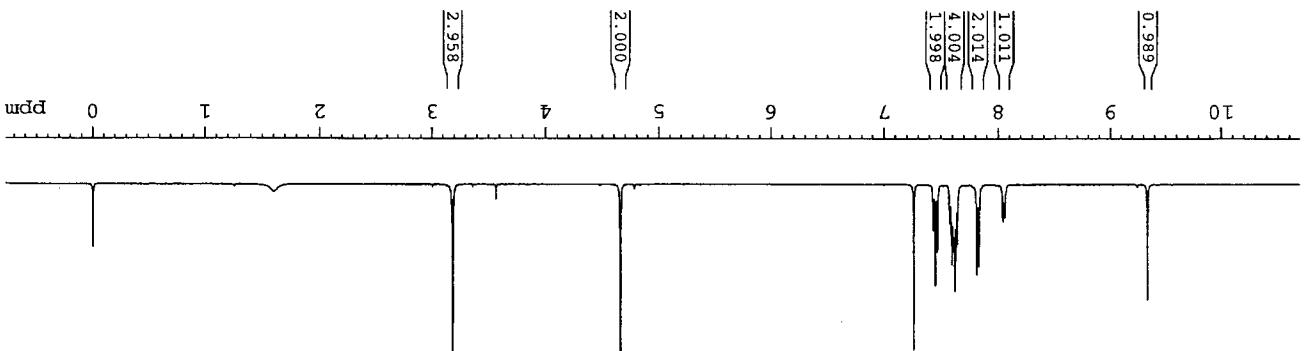
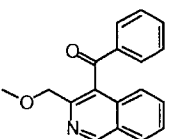


Table 2, compound 30



- 9.336
- 8.064
- 8.058
- 8.049
- 8.041
- 7.831
- 7.813
- 7.644
- 7.634
- 7.629
- 7.620
- 7.613
- 7.605
- 7.595
- 7.580
- 7.577
- 7.471
- 7.451
- 7.432
- 7.262

4.656

3.184

0.000

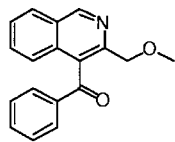
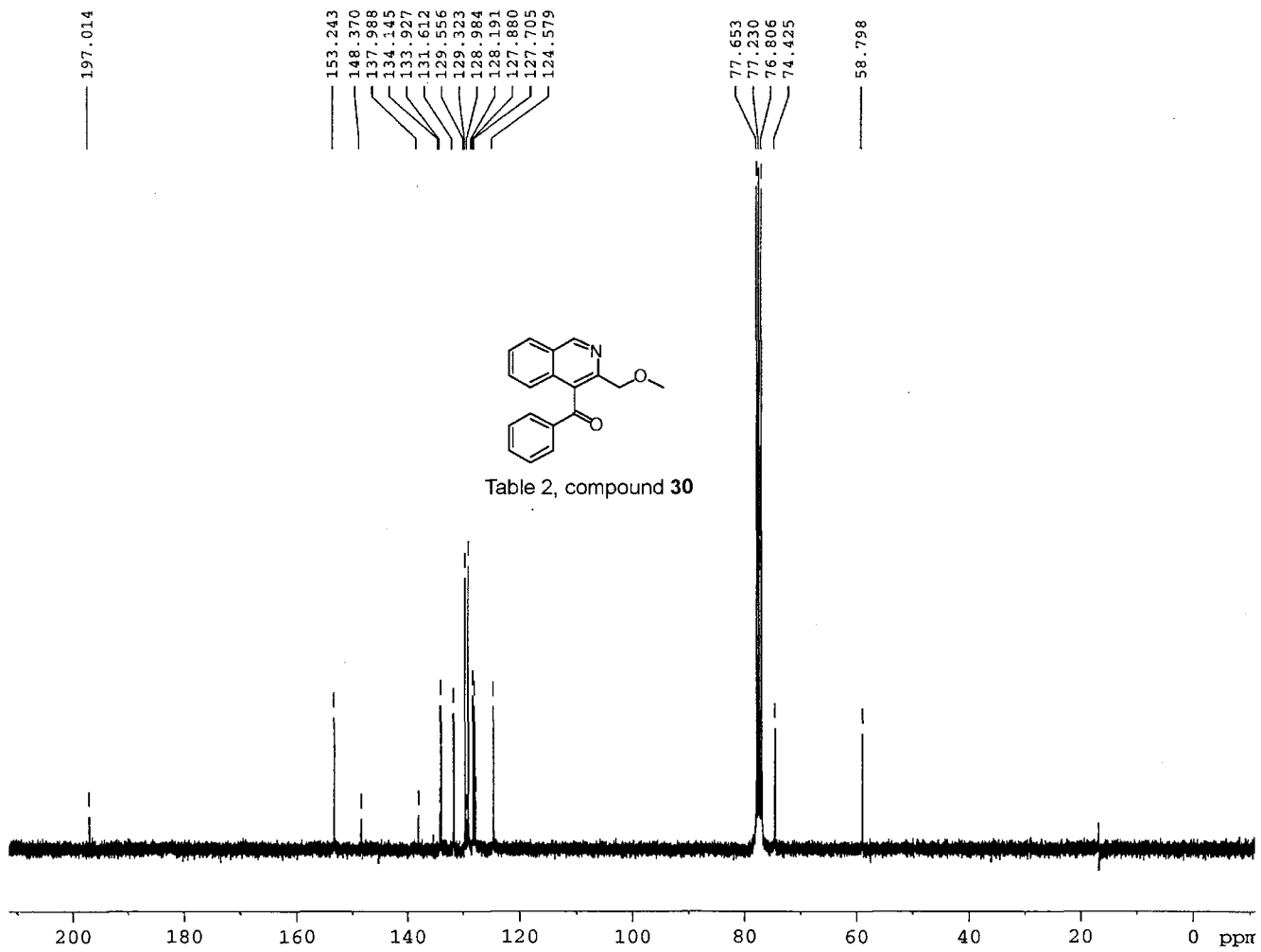


Table 2, compound 30

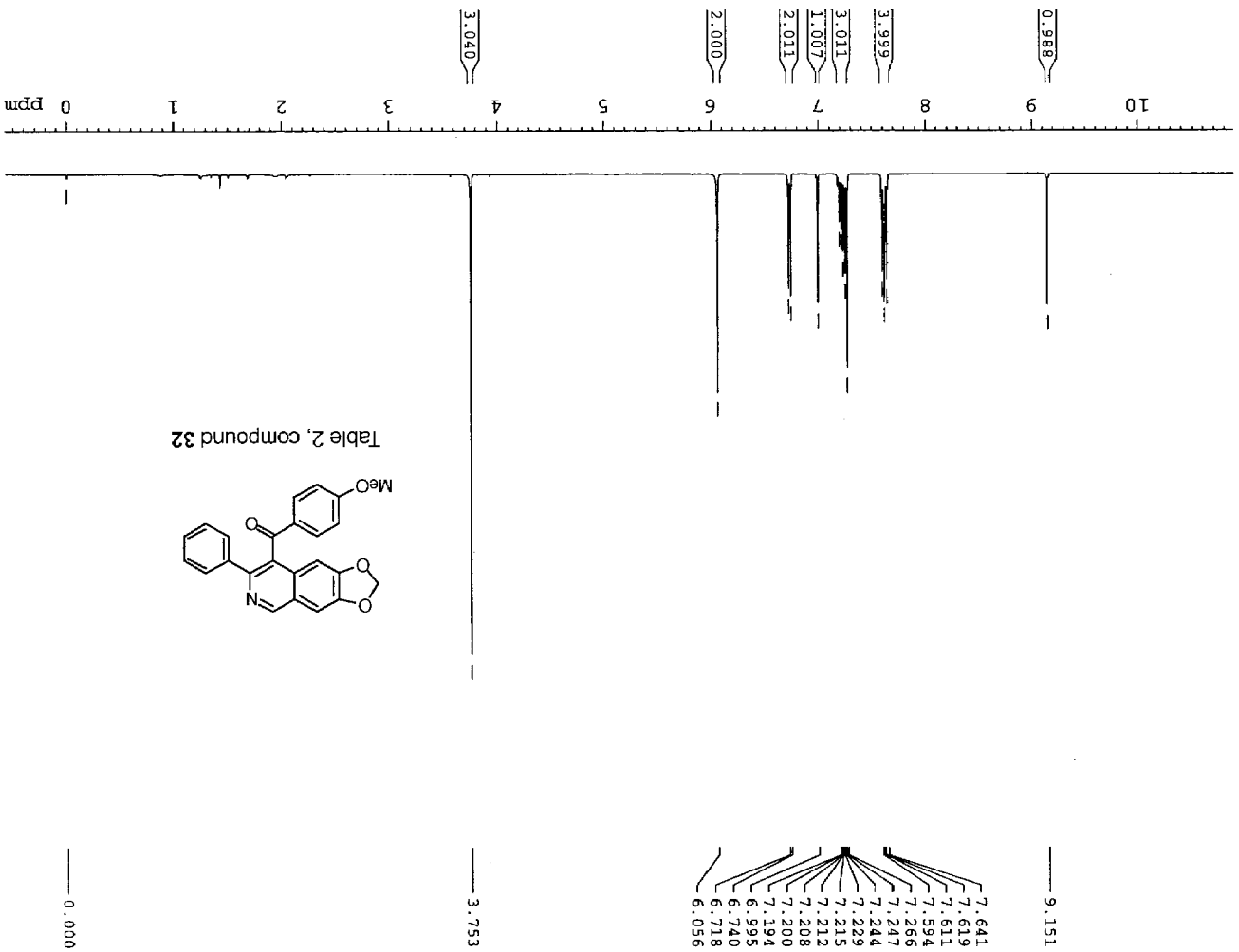
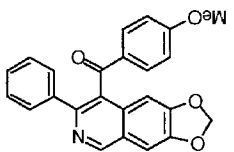


Table 2, compound 32



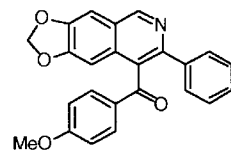
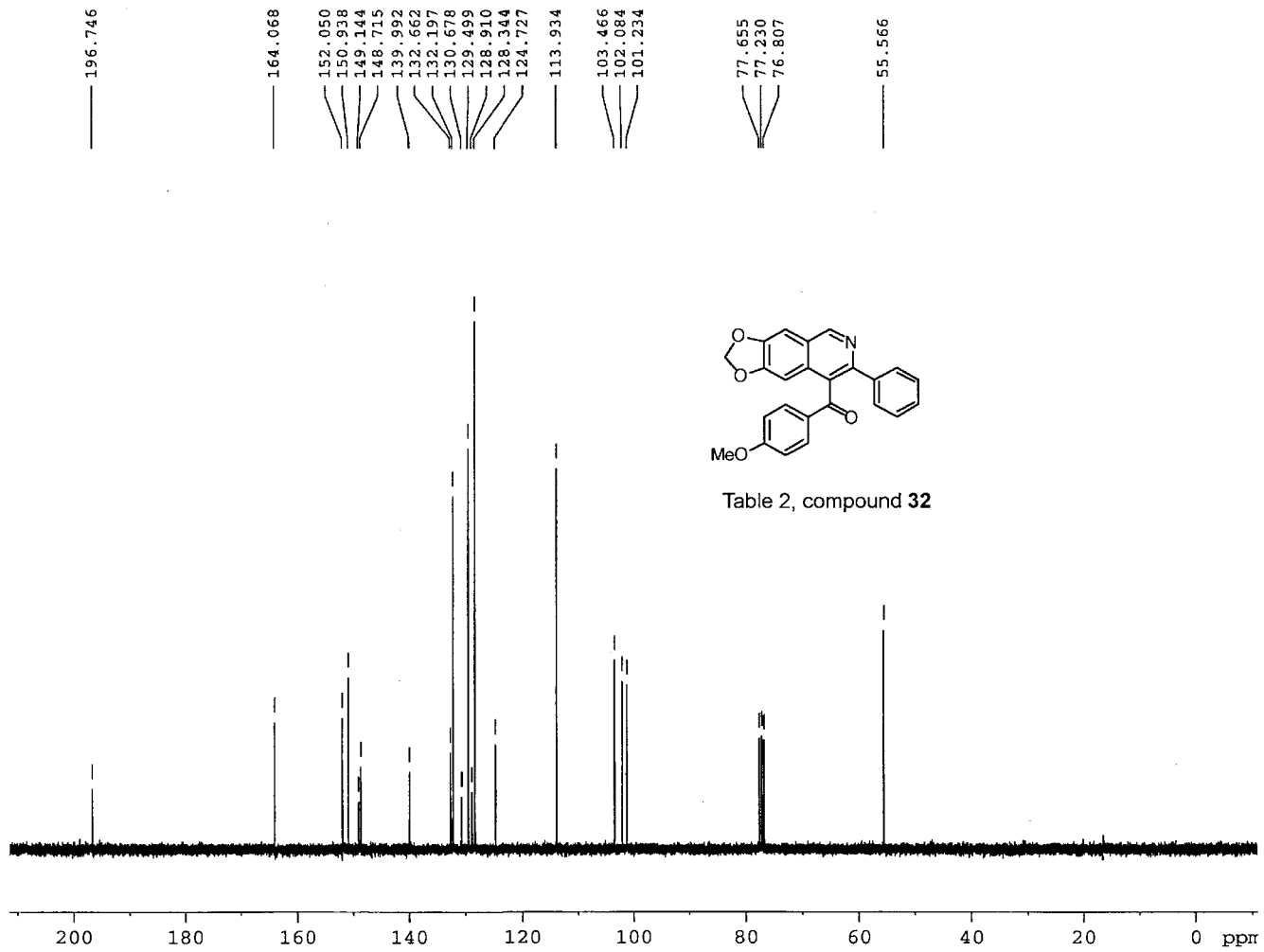


Table 2, compound 32

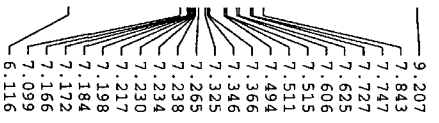
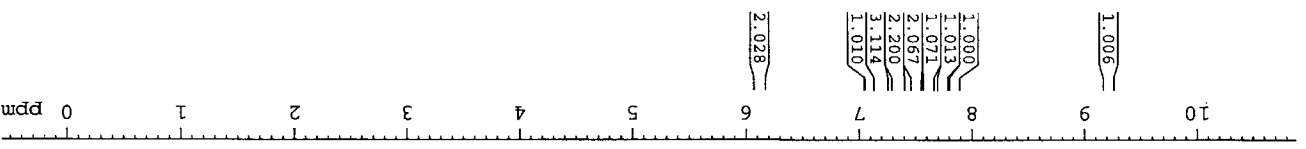
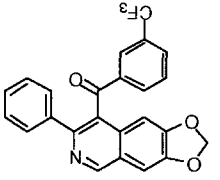


Table 2, compound 33



0.000

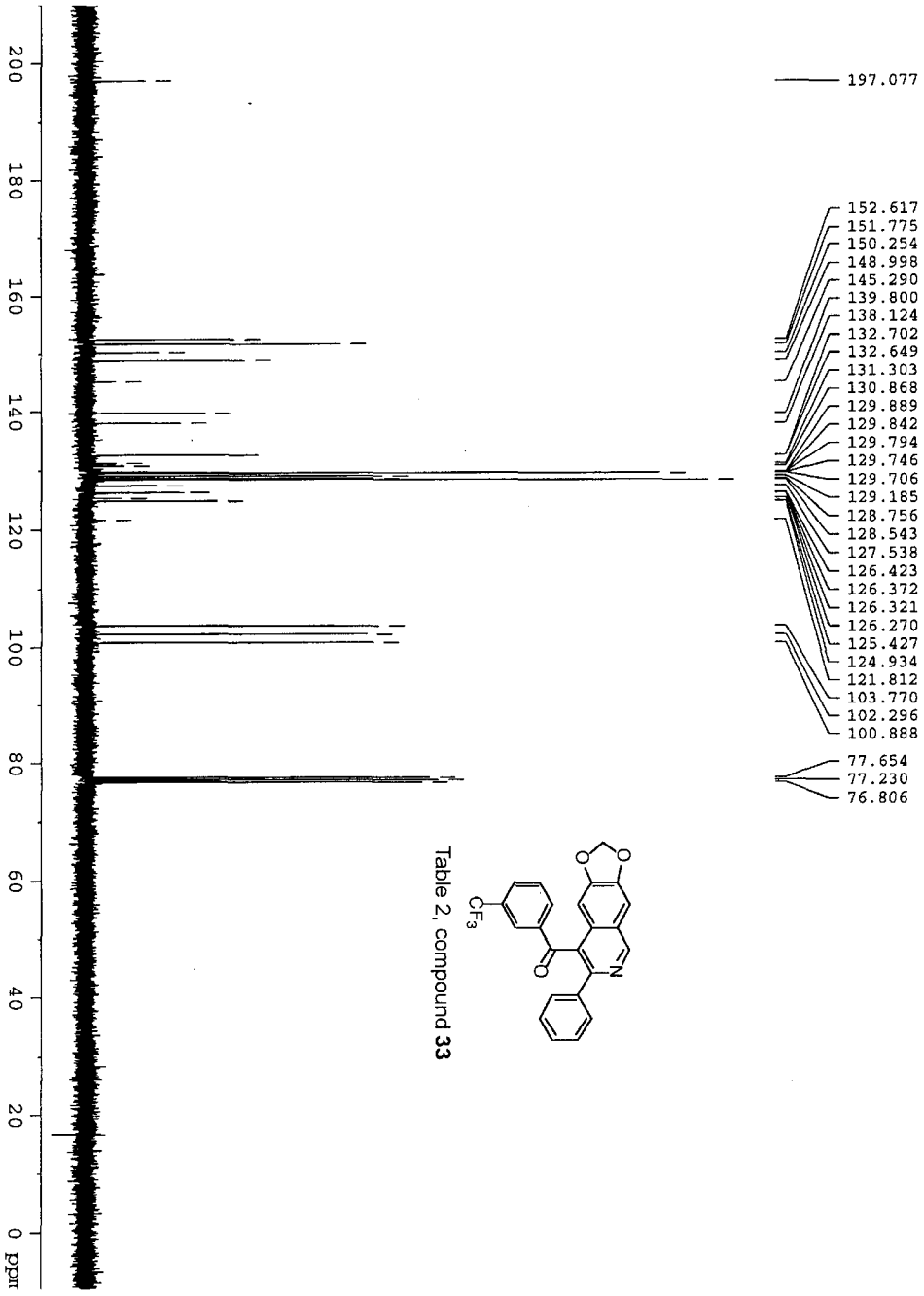
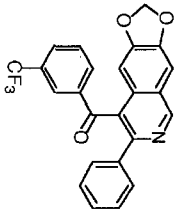


Table 2, compound 33



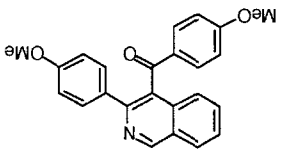
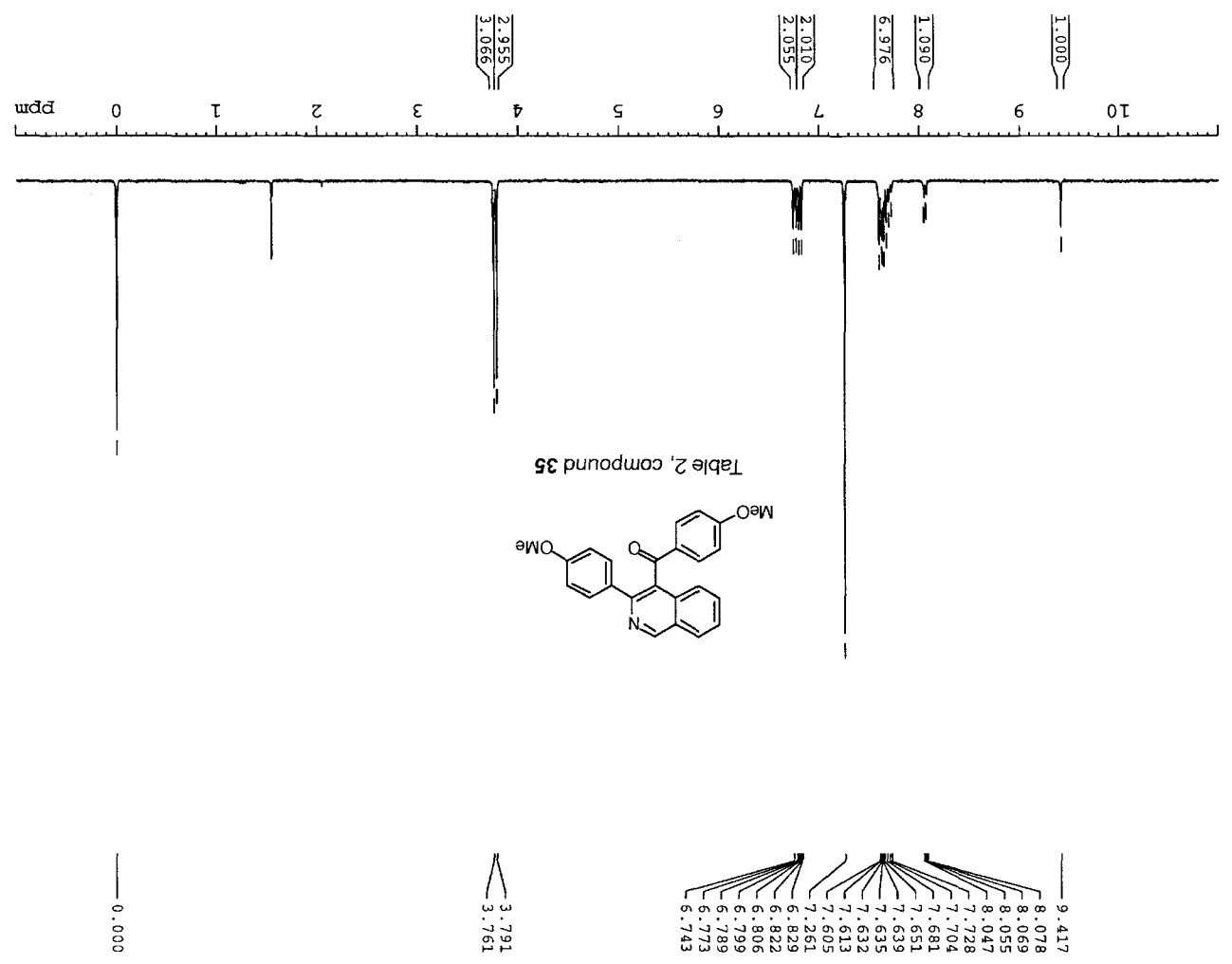
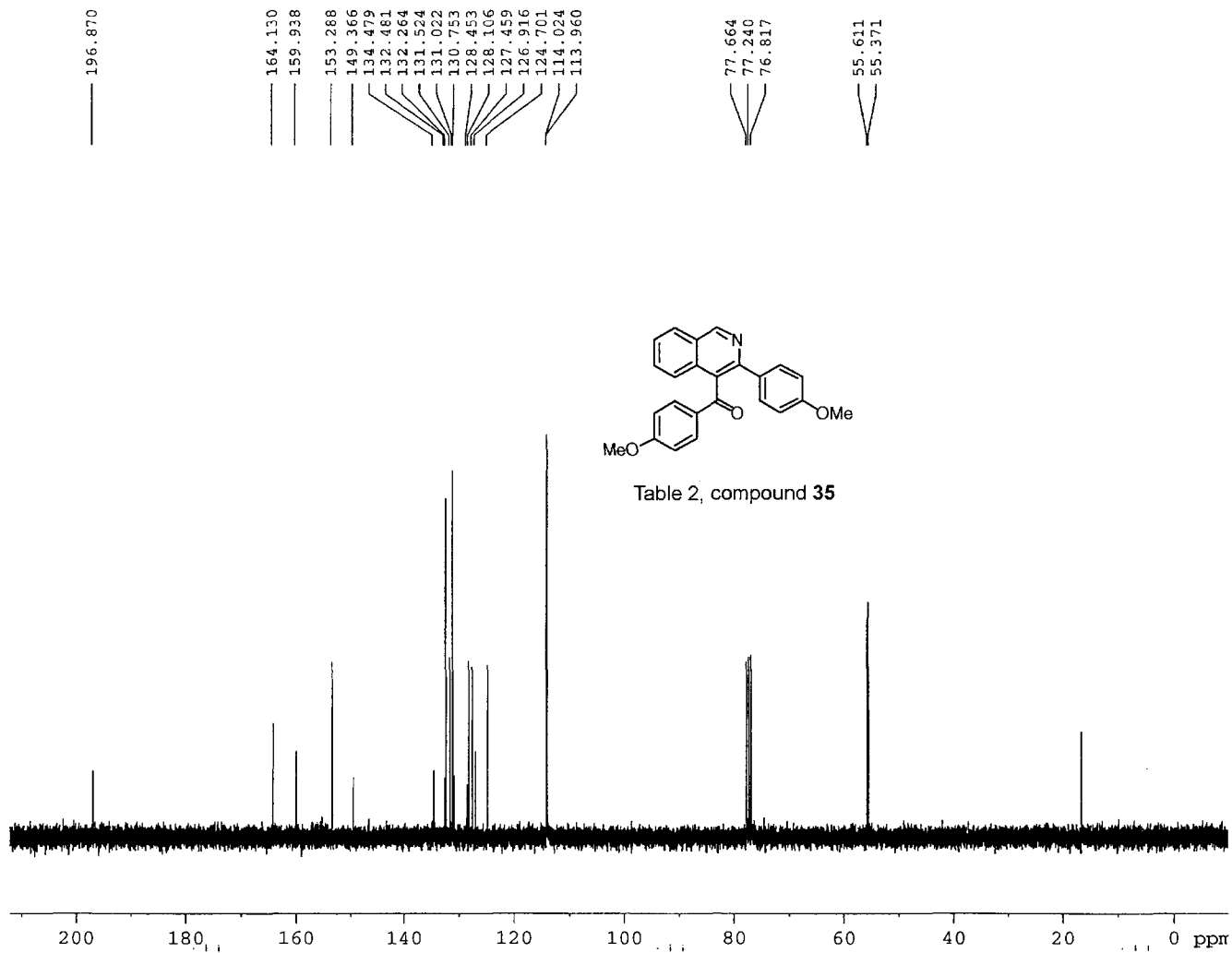
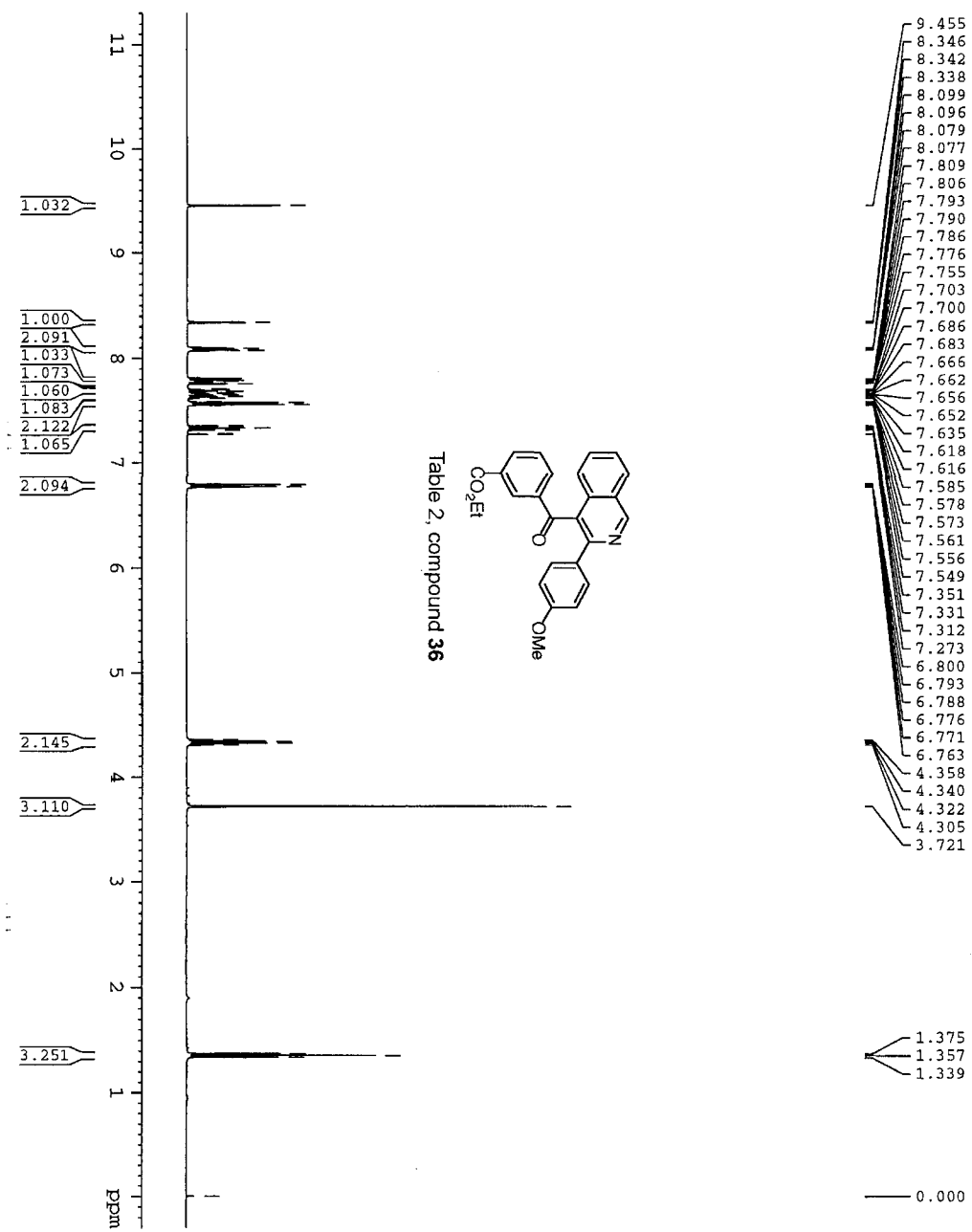


Table 2, compound 35







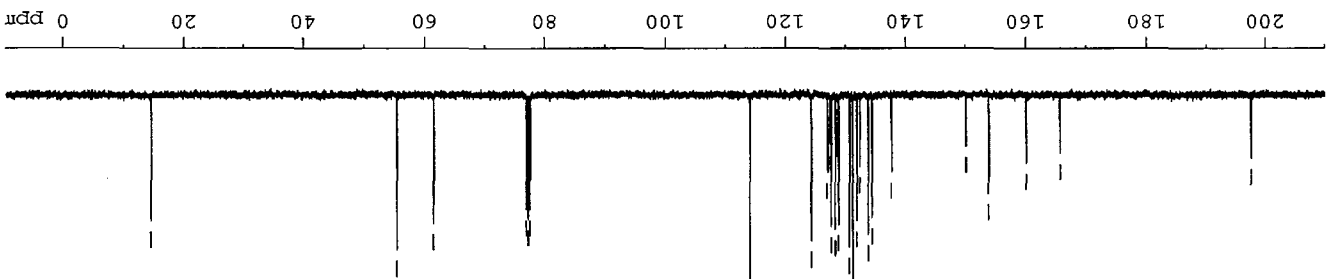
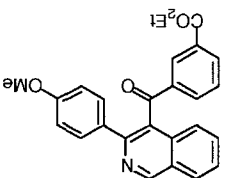


Table 2, compound 36



- 165.681
- 160.072
- 153.876
- 150.113
- 137.638
- 134.369
- 134.307
- 133.701
- 133.338
- 131.824
- 131.154
- 131.114
- 130.809
- 128.817
- 128.296
- 127.626
- 127.460
- 126.963
- 124.285
- 114.022

- 77.548
- 77.230
- 76.912

- 61.466
- 55.342

- 14.428

197.544

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

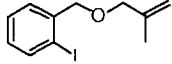
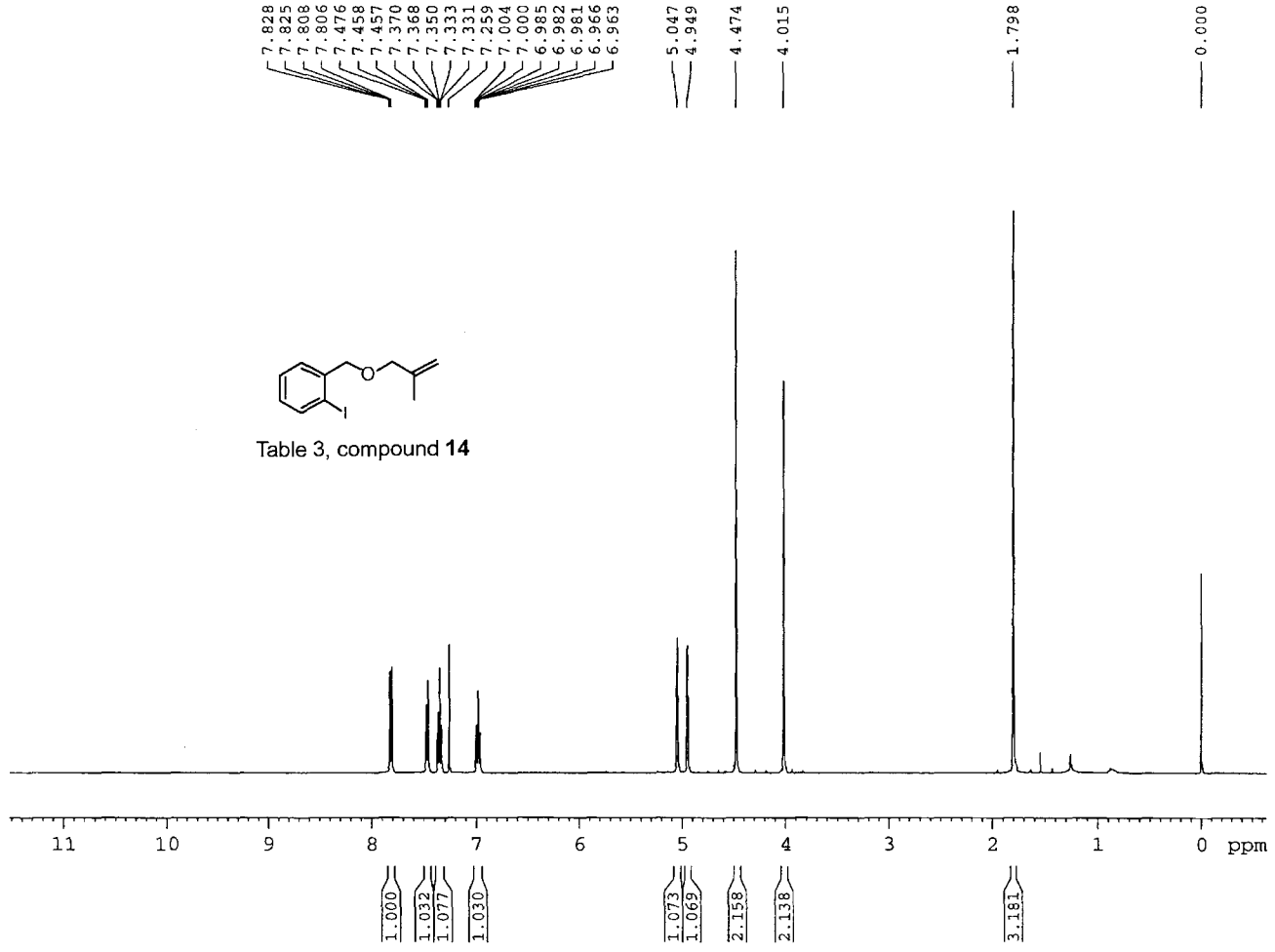


Table 3, compound 14



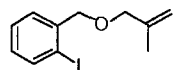
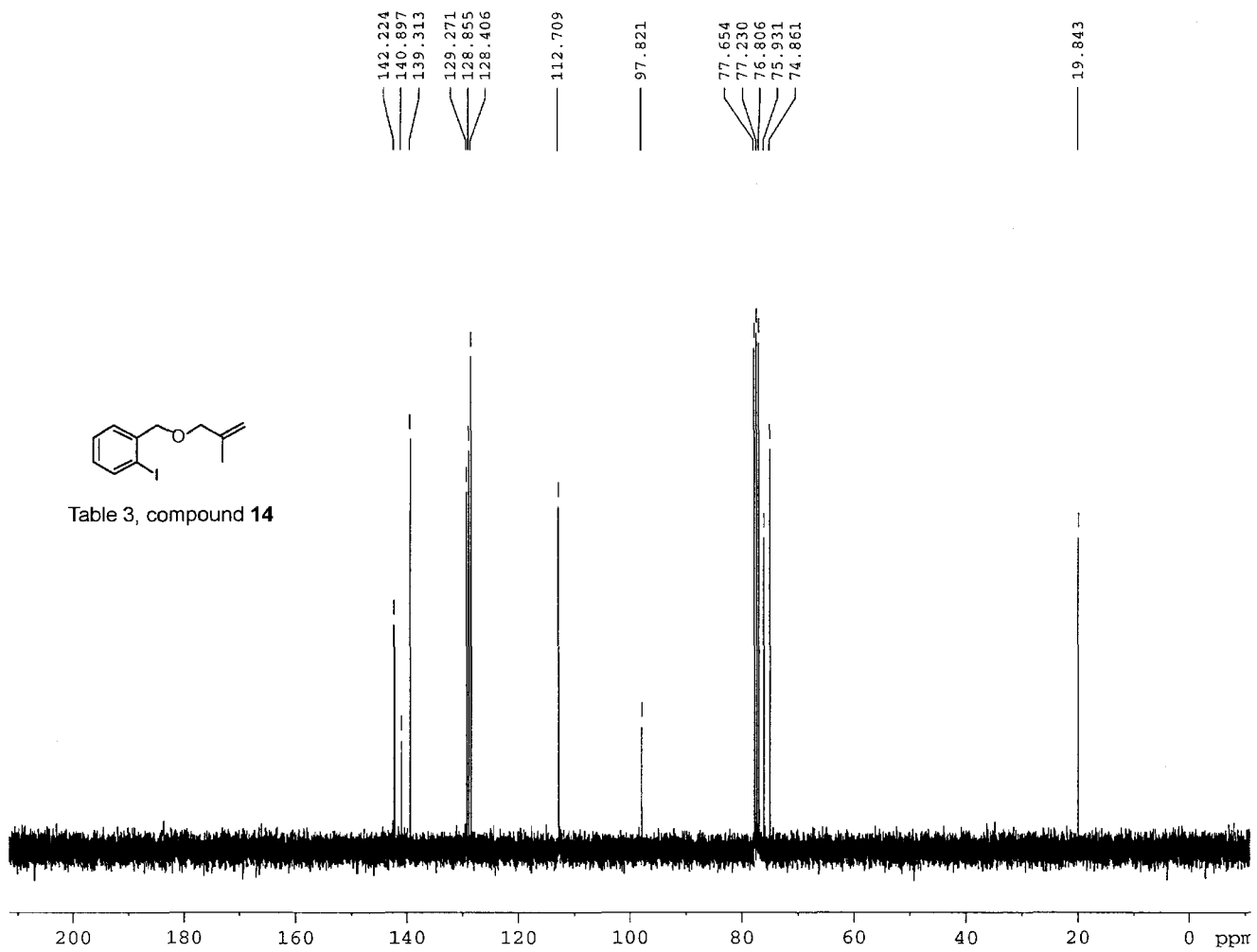


Table 3, compound **14**



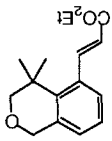
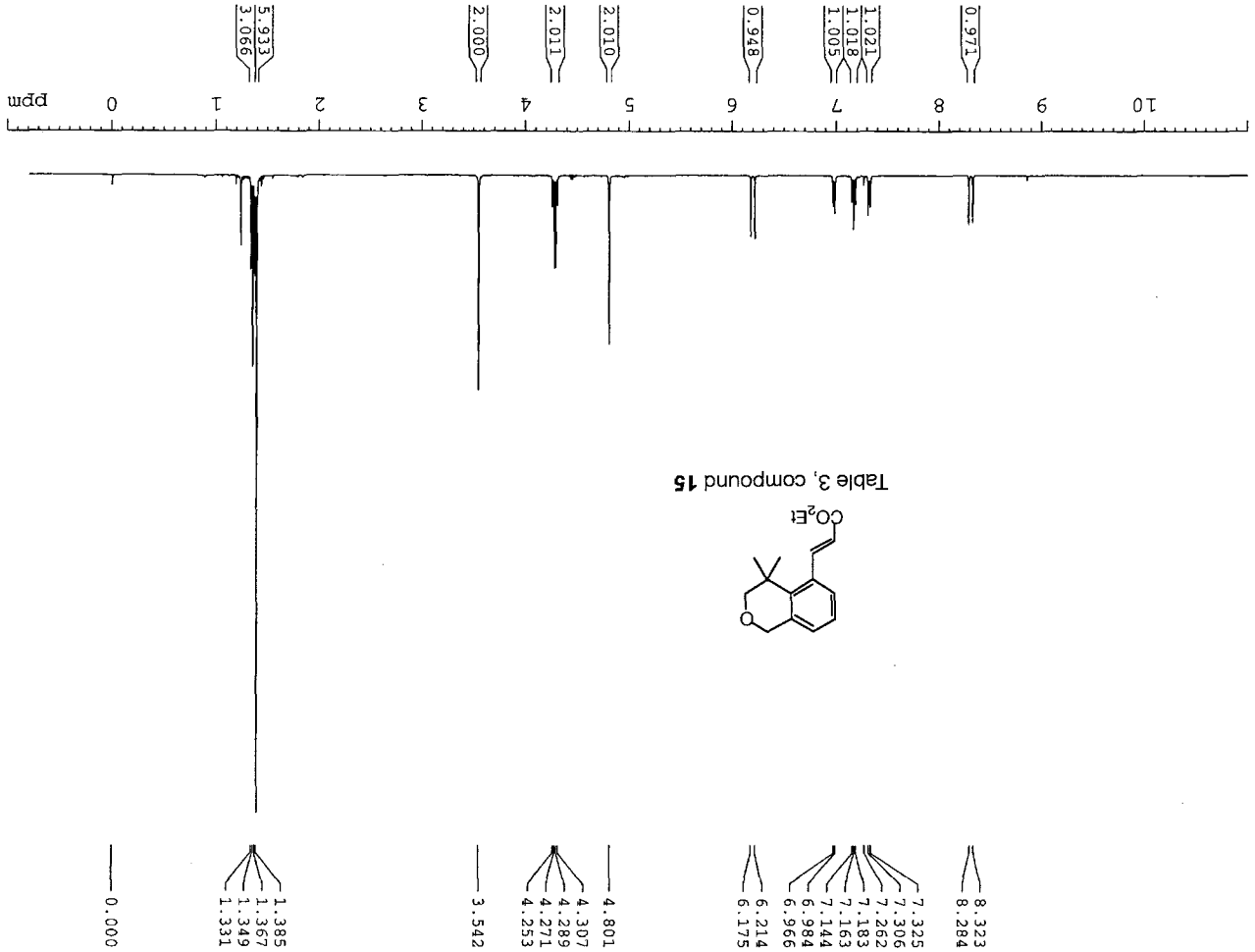


Table 3, compound 15



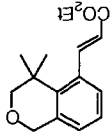


Table 3, compound 15

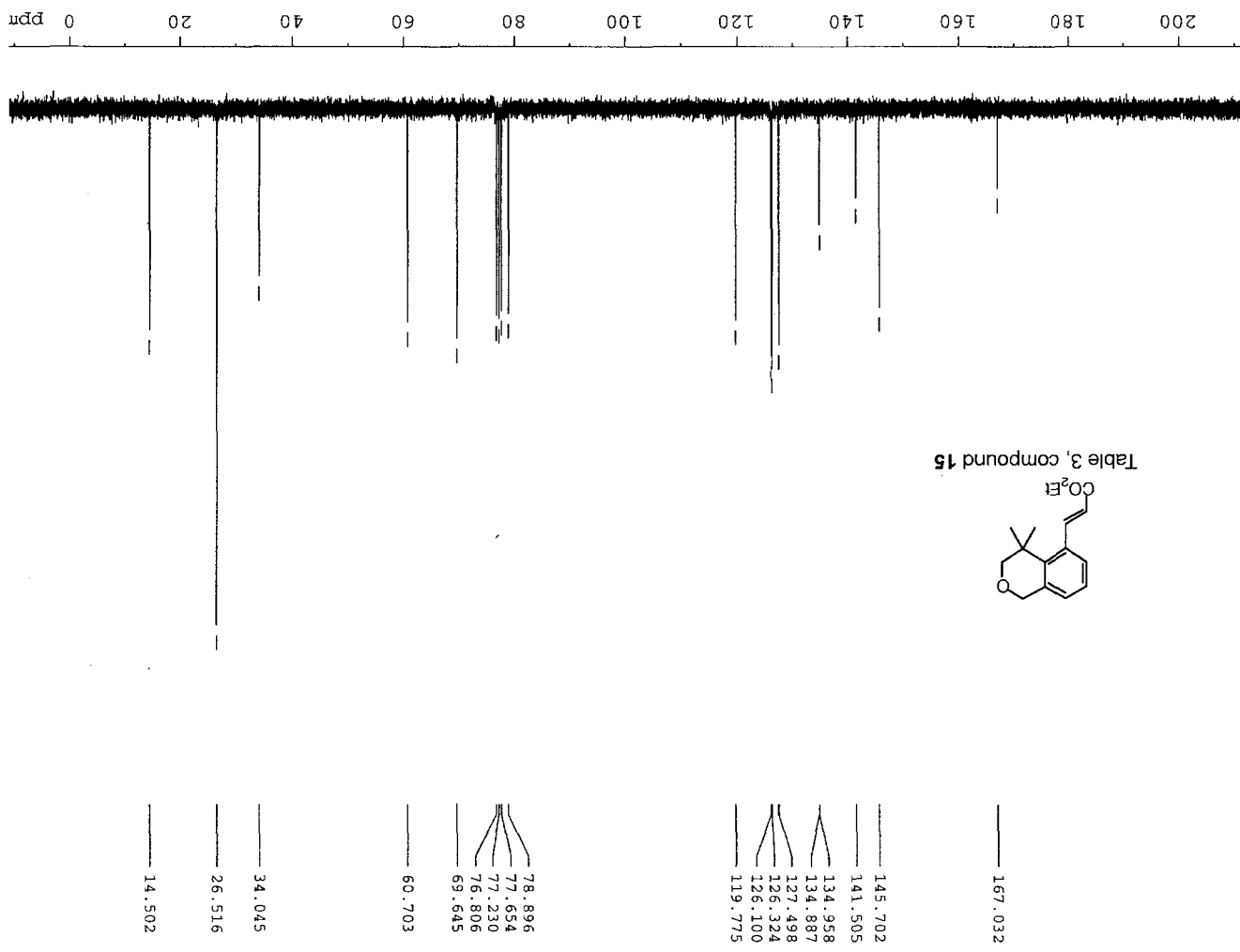
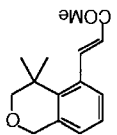


Table 3, compound 17



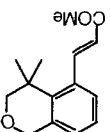


Table 3, compound 17

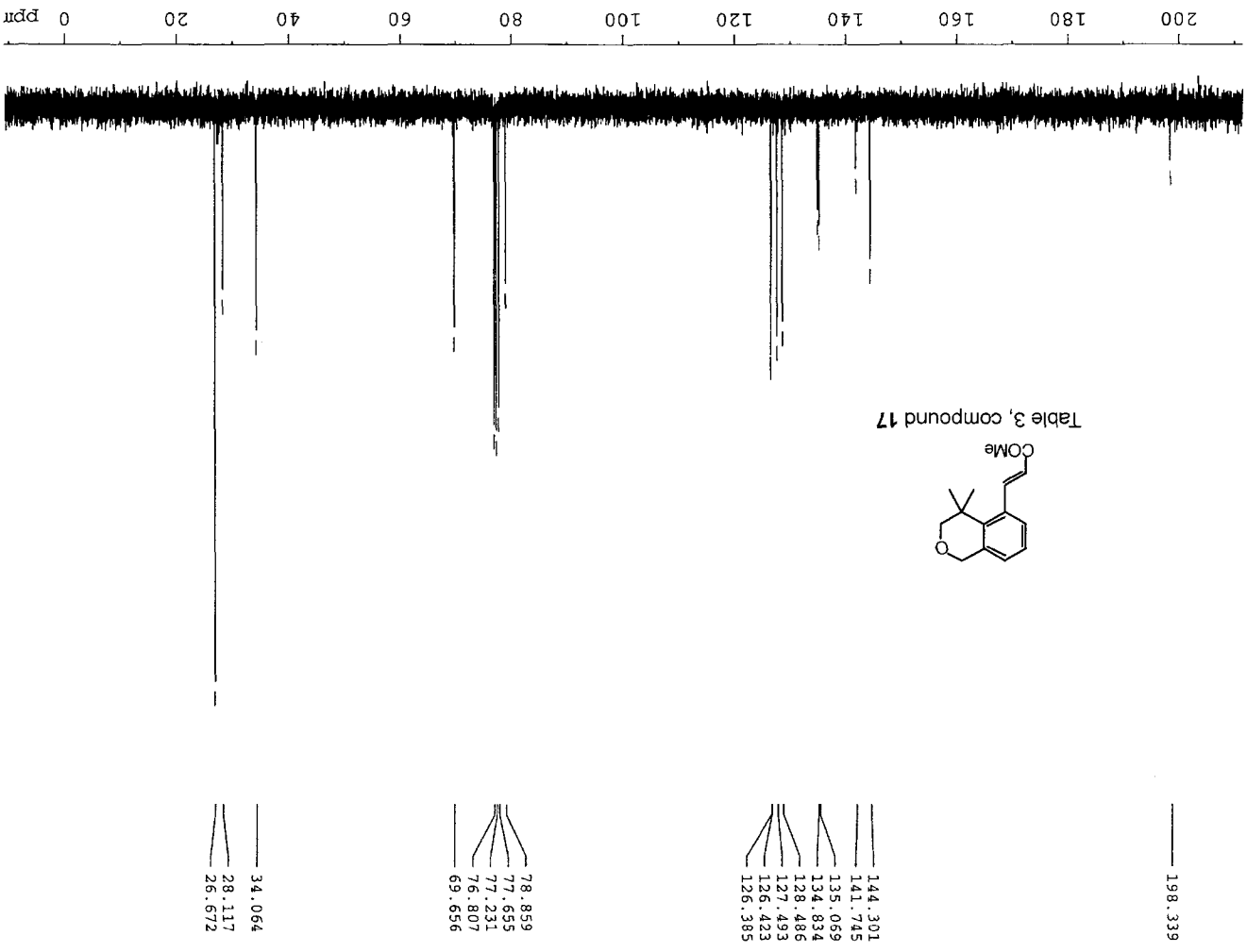
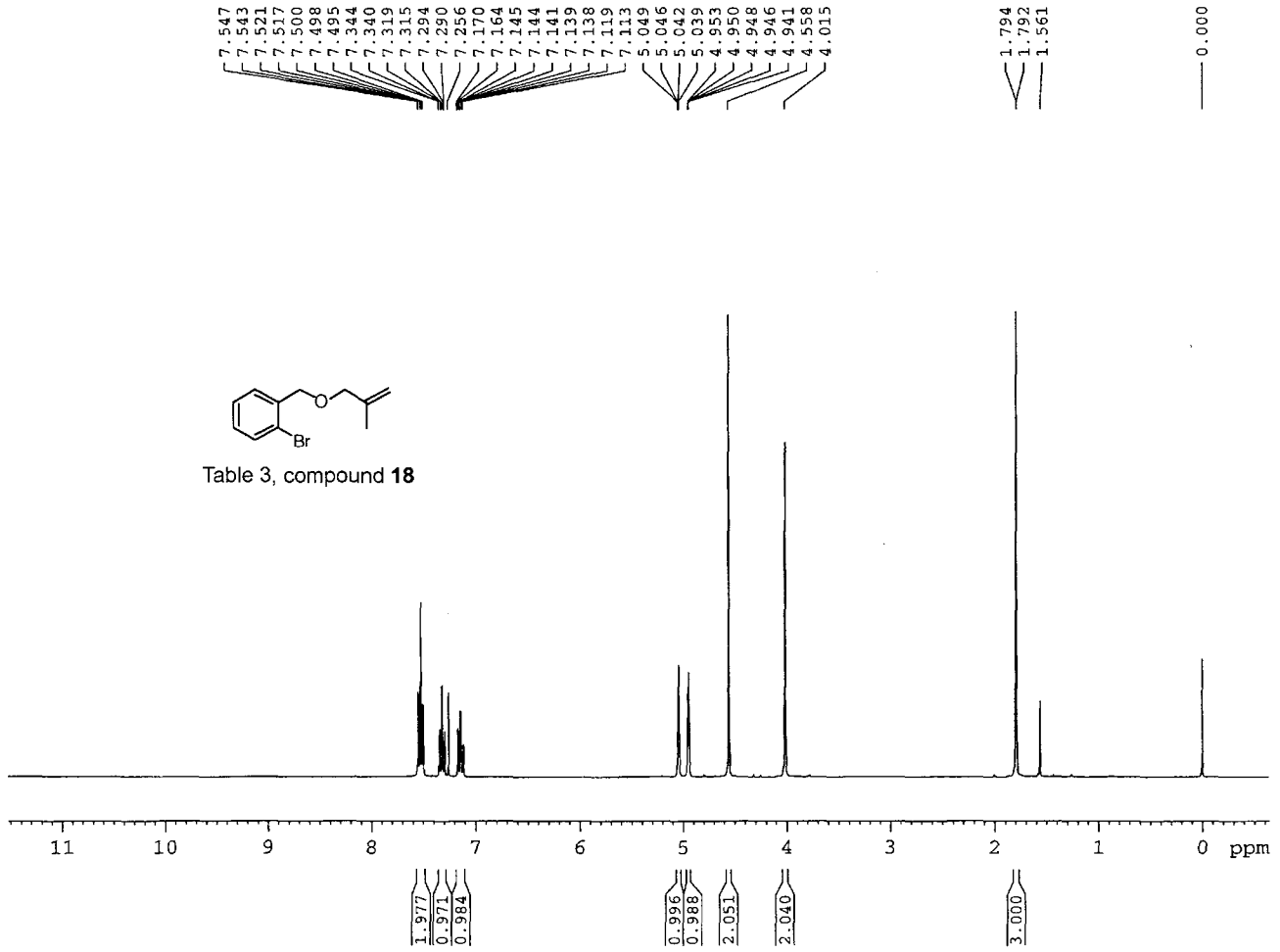
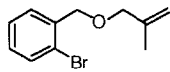


Table 3, compound 18



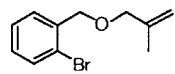
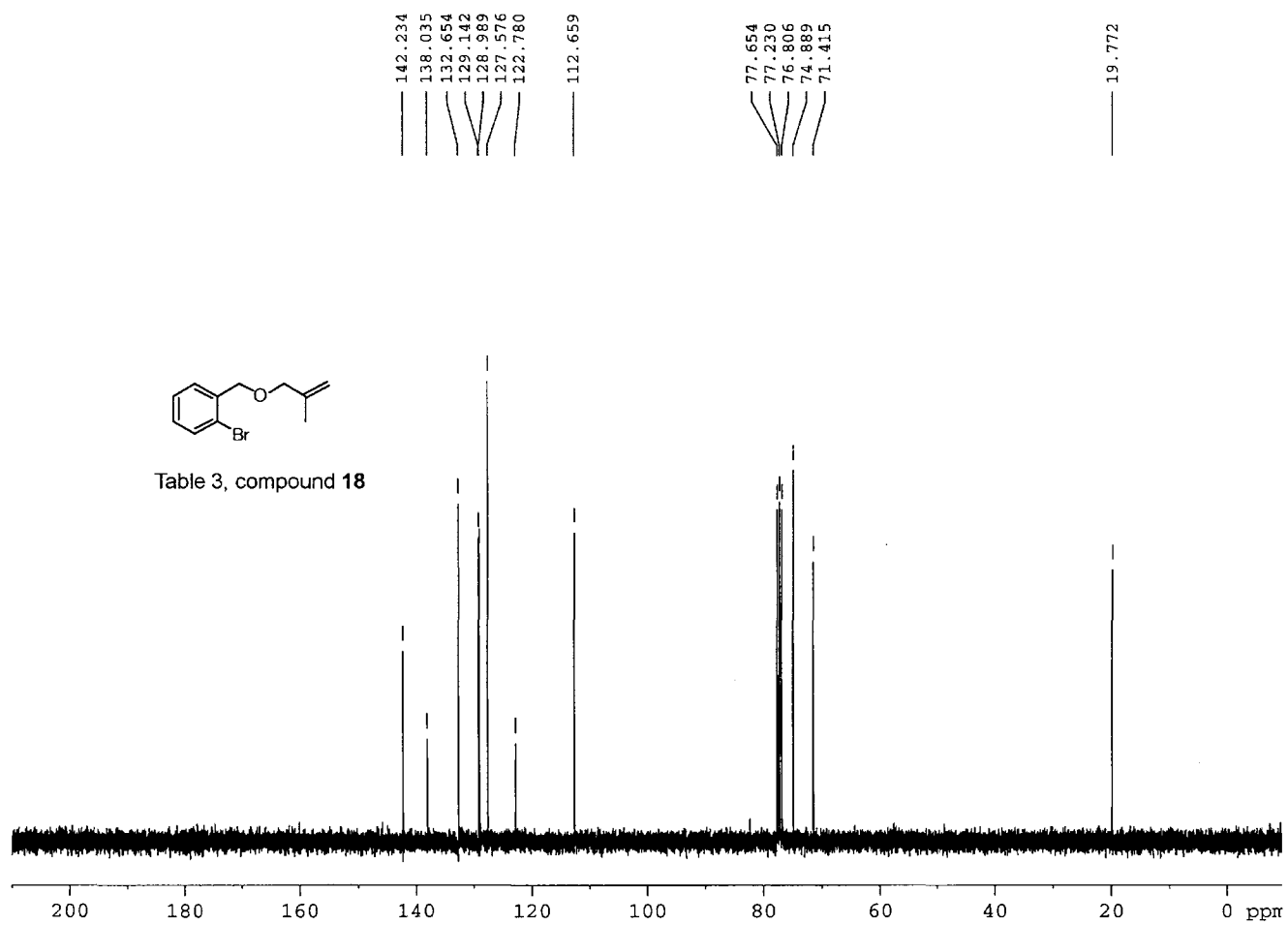
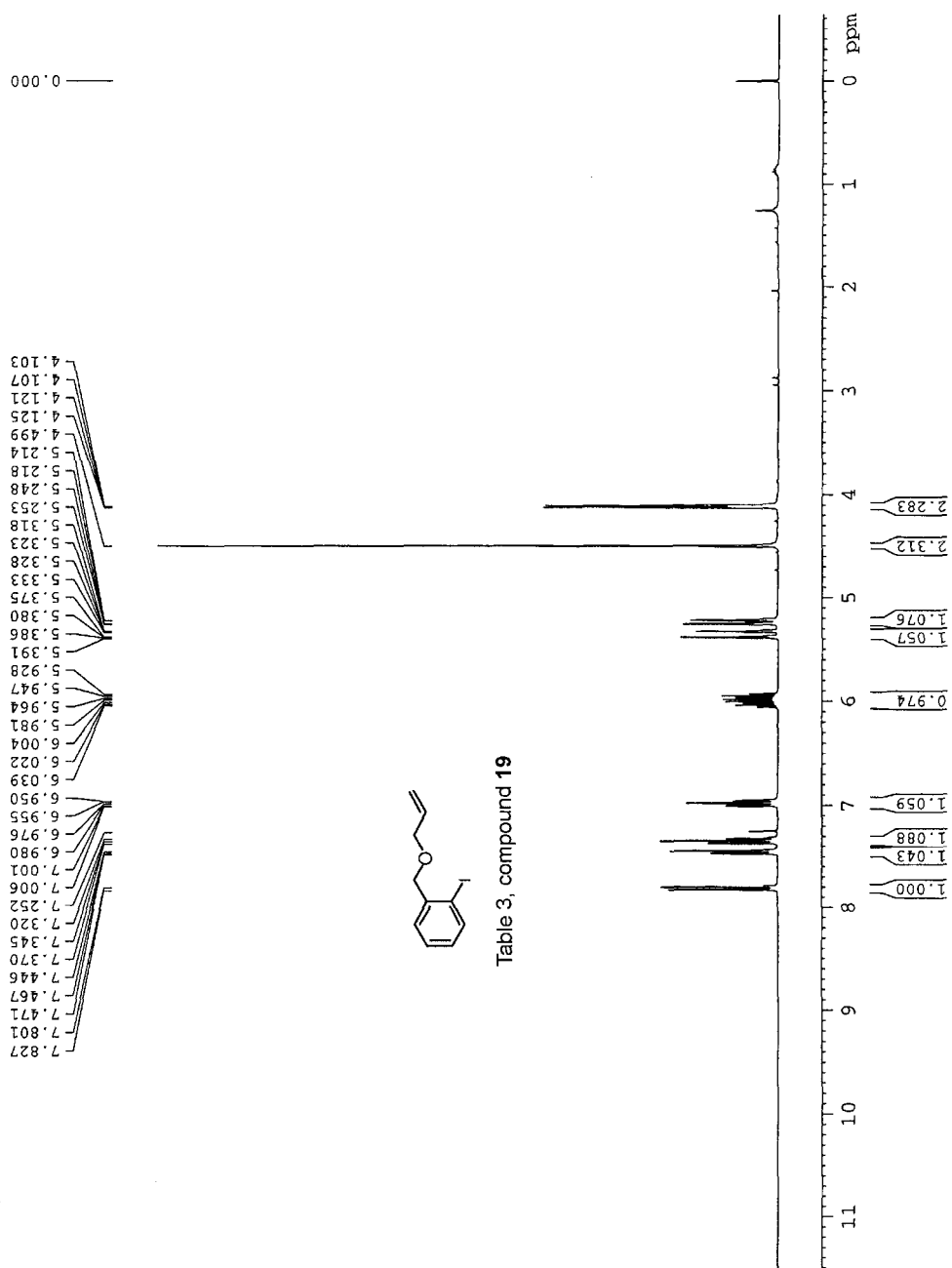


Table 3, compound 18





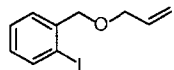
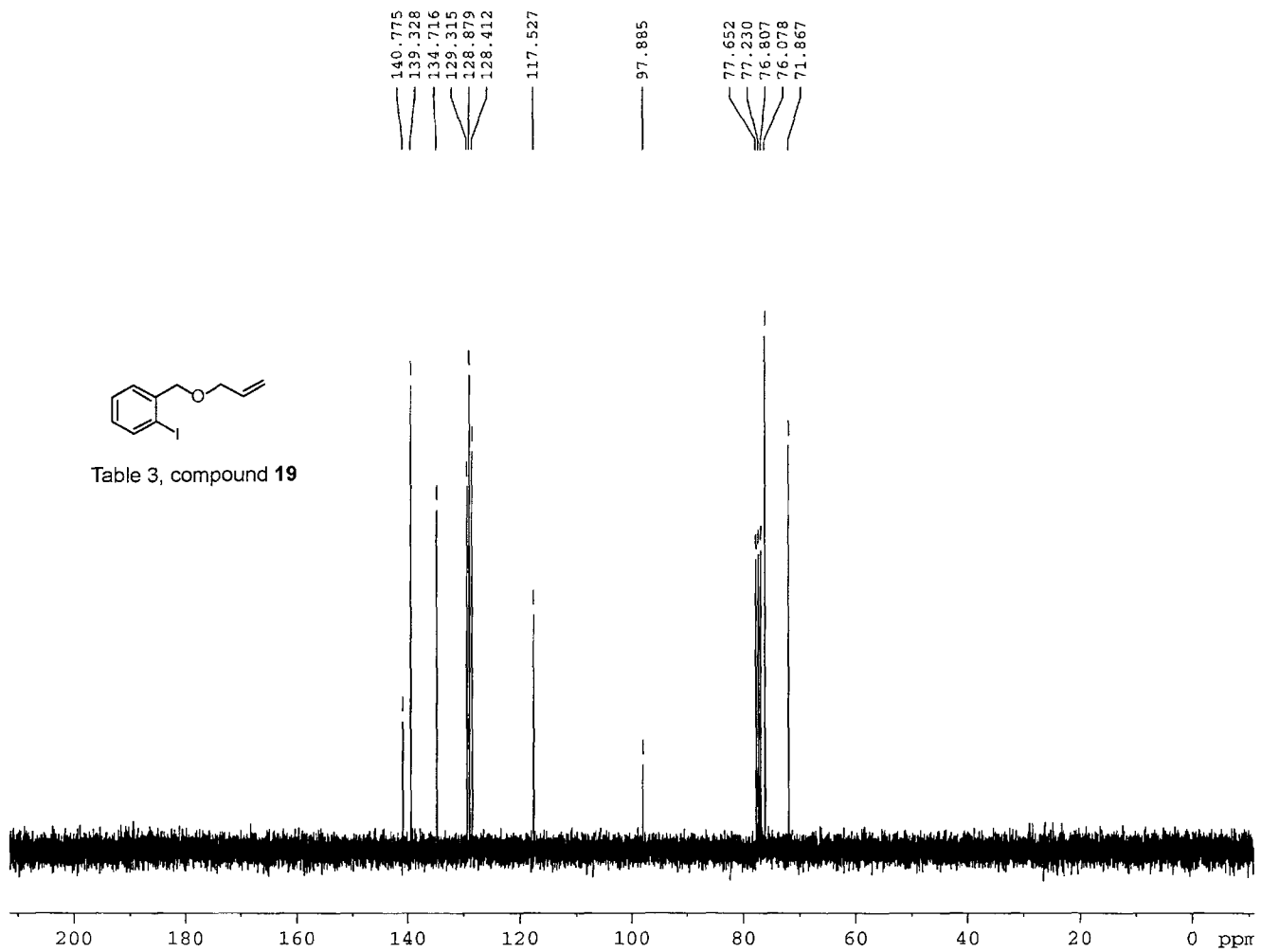


Table 3, compound **19**



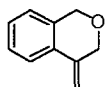
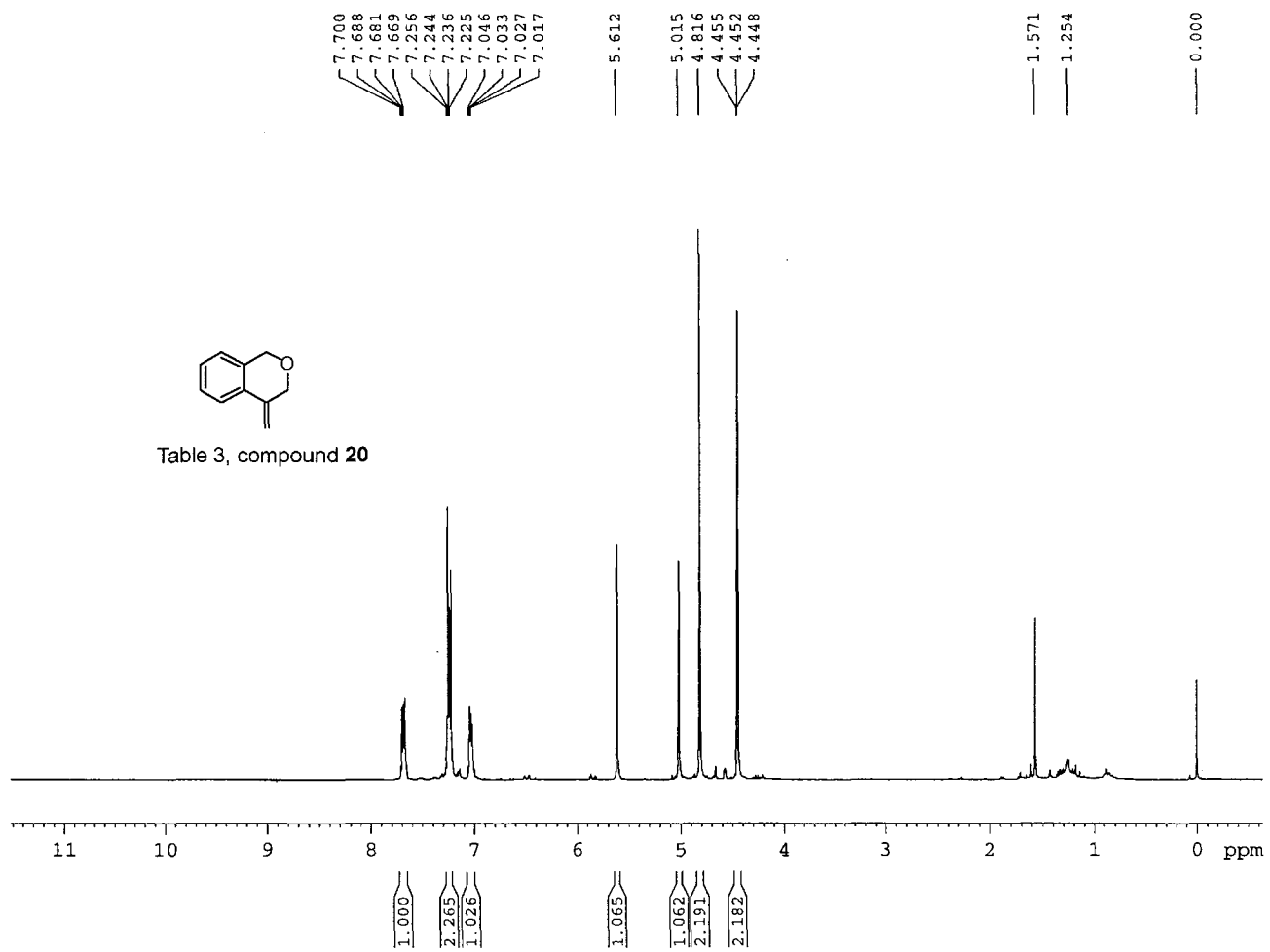


Table 3, compound 20



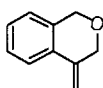
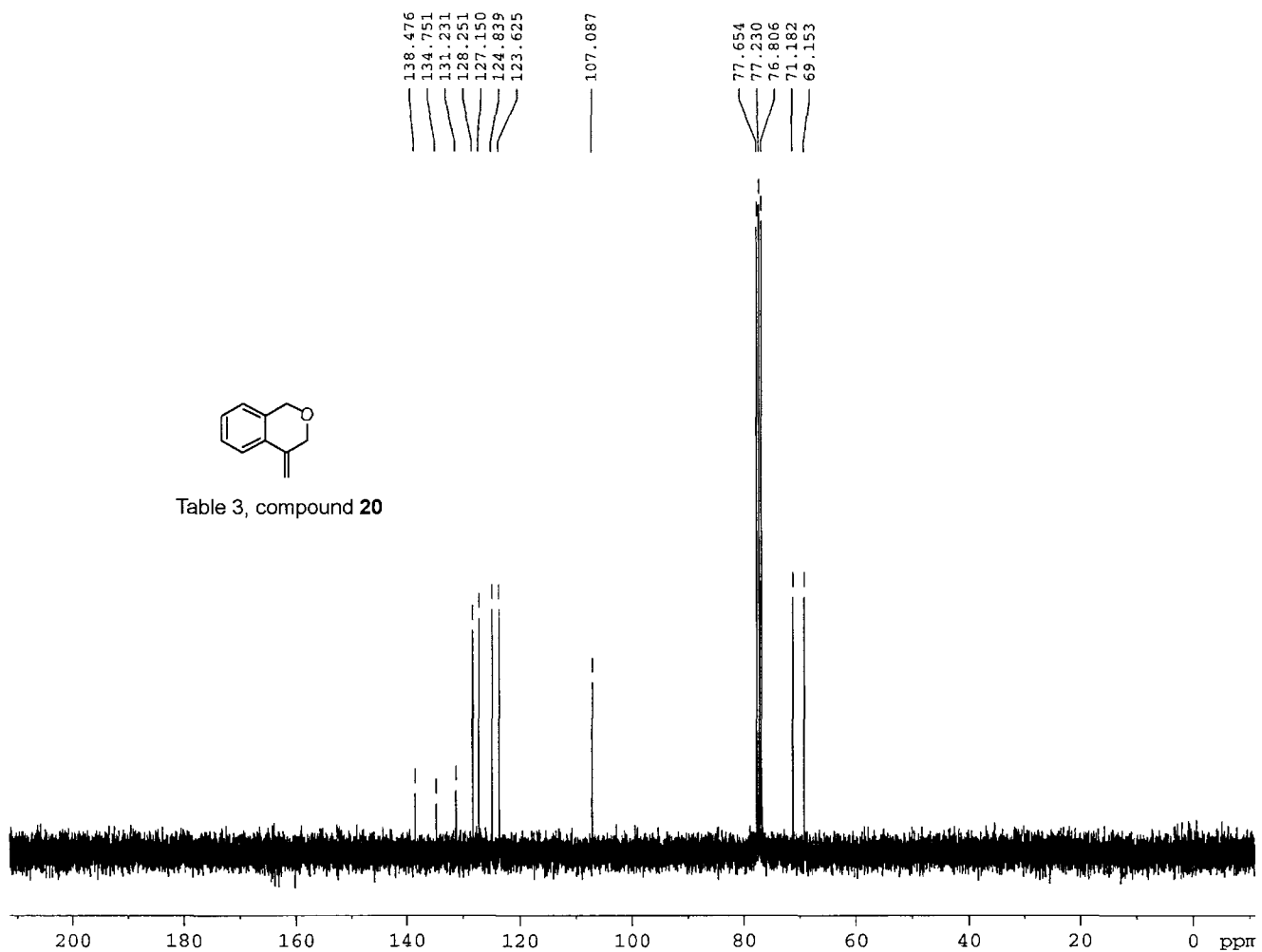


Table 3, compound 20



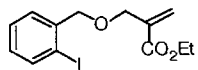
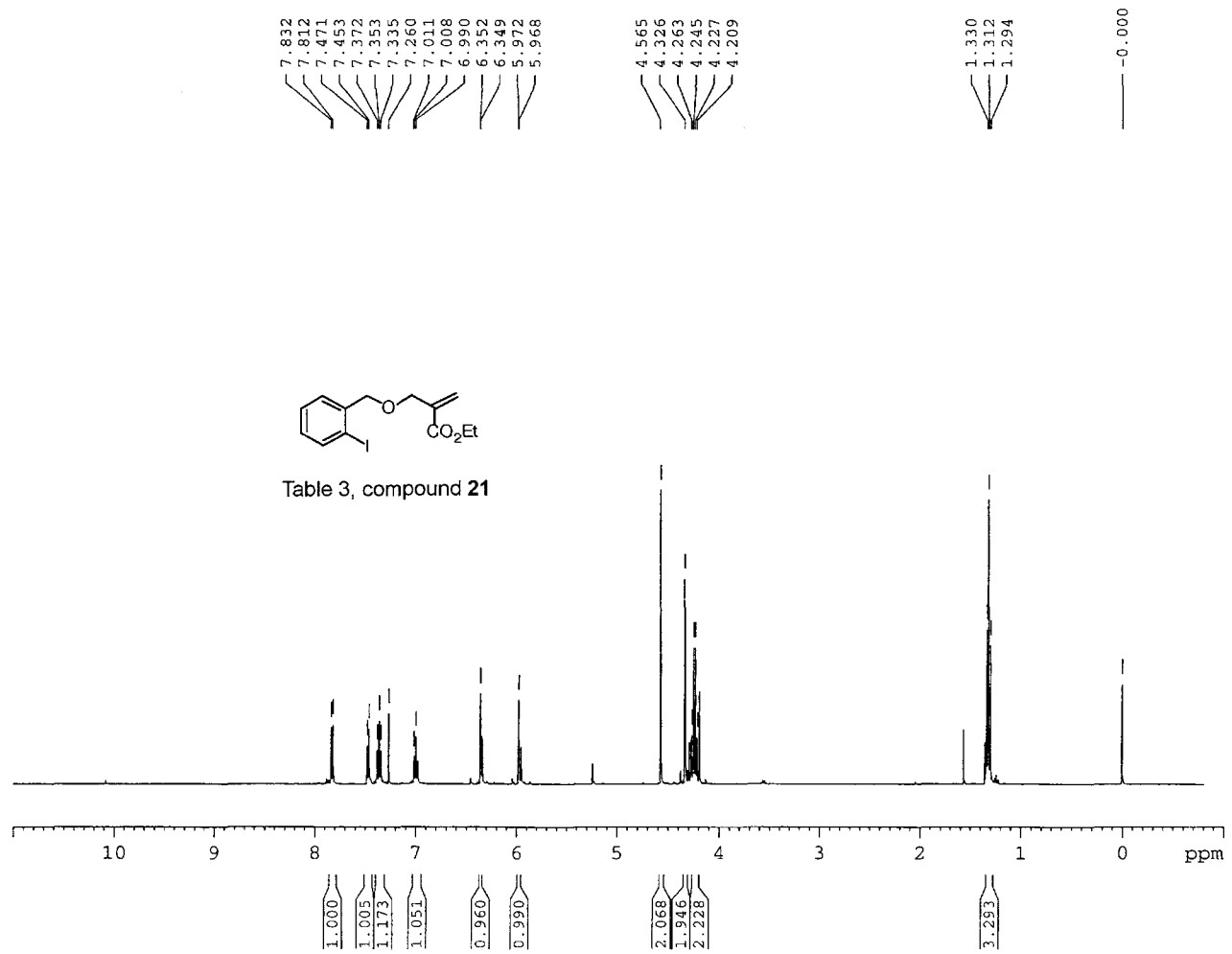


Table 3, compound 21



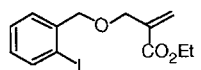
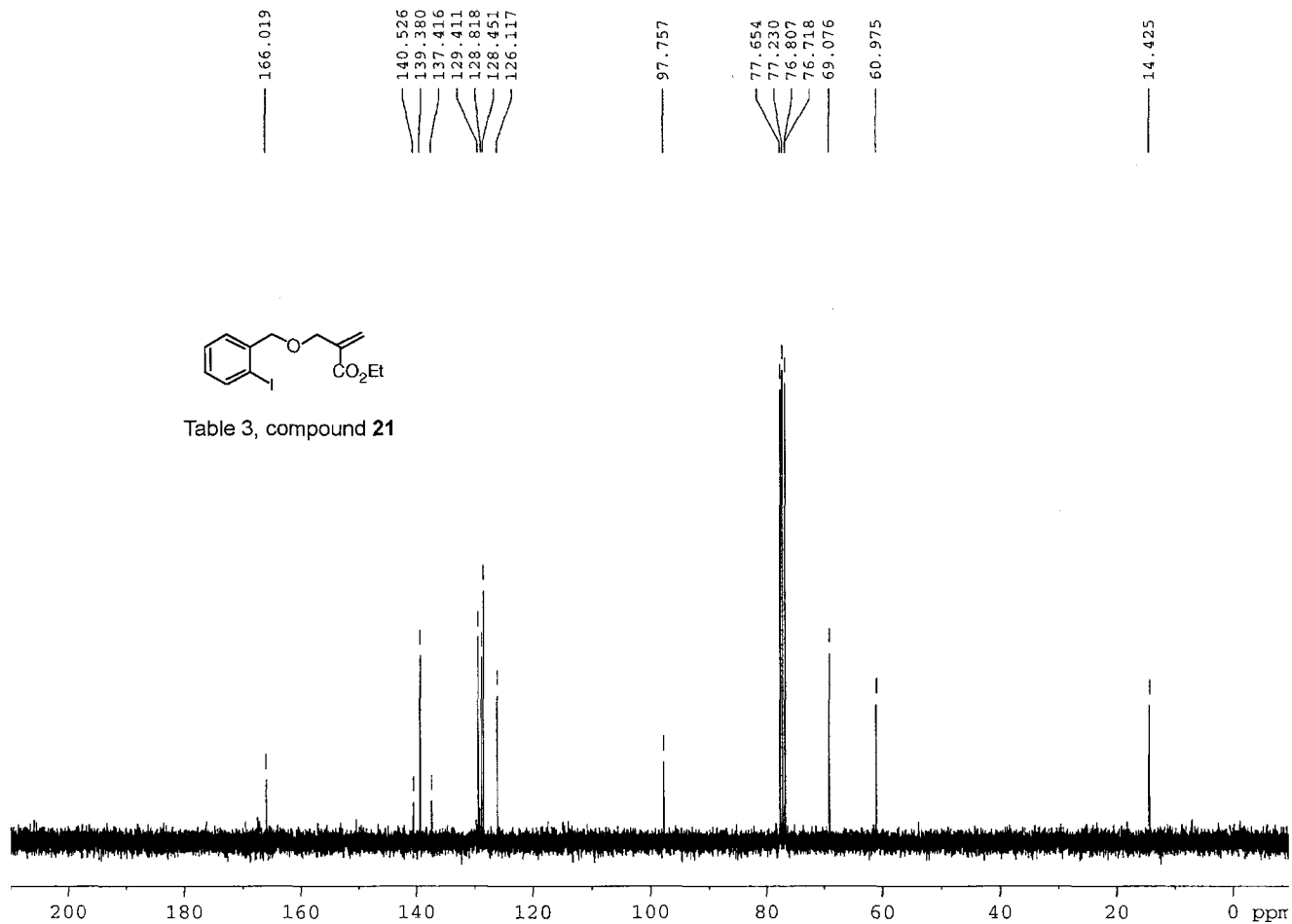


Table 3, compound 21



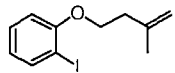
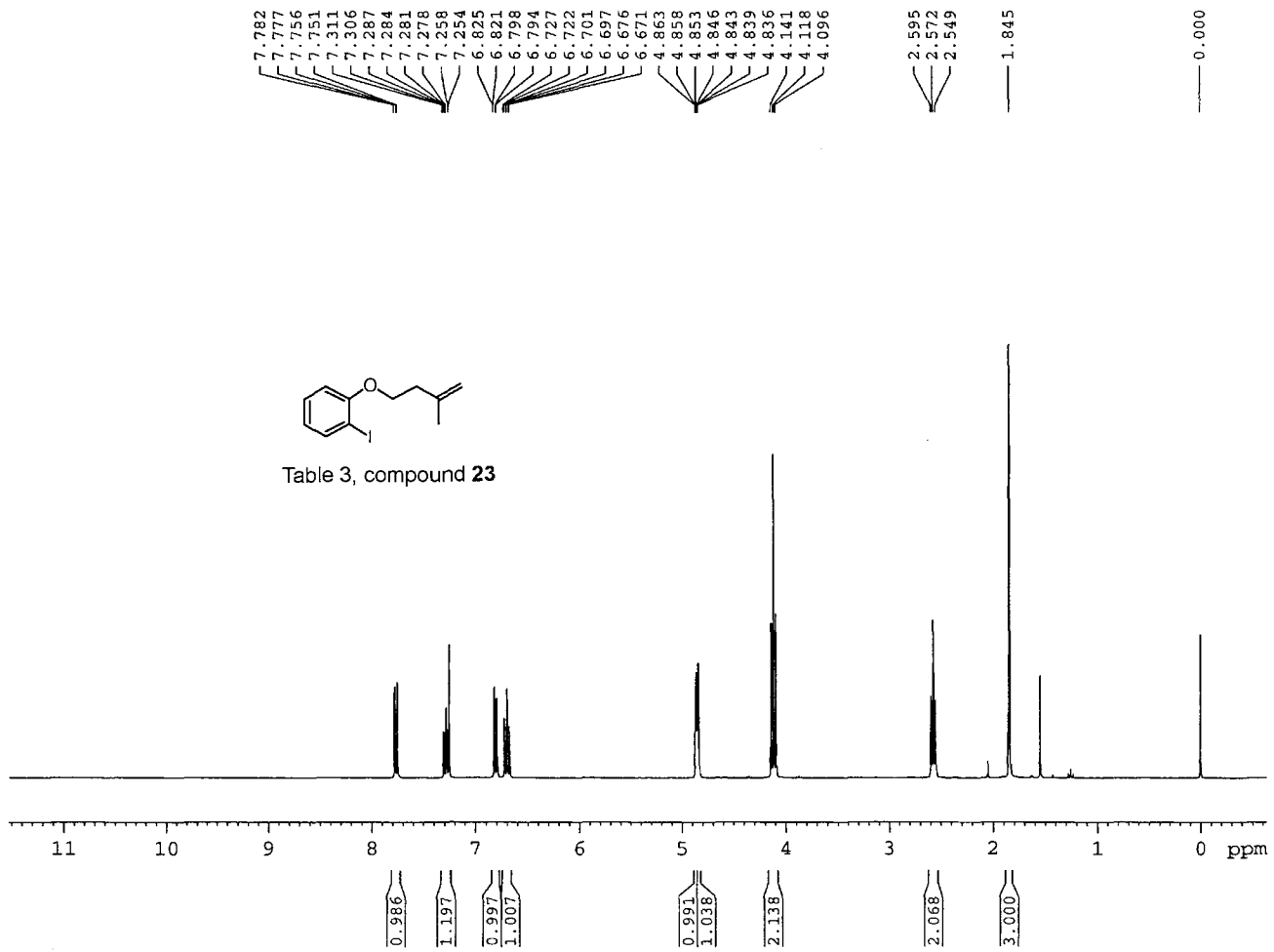


Table 3, compound 23



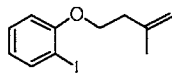


Table 3, compound **23**

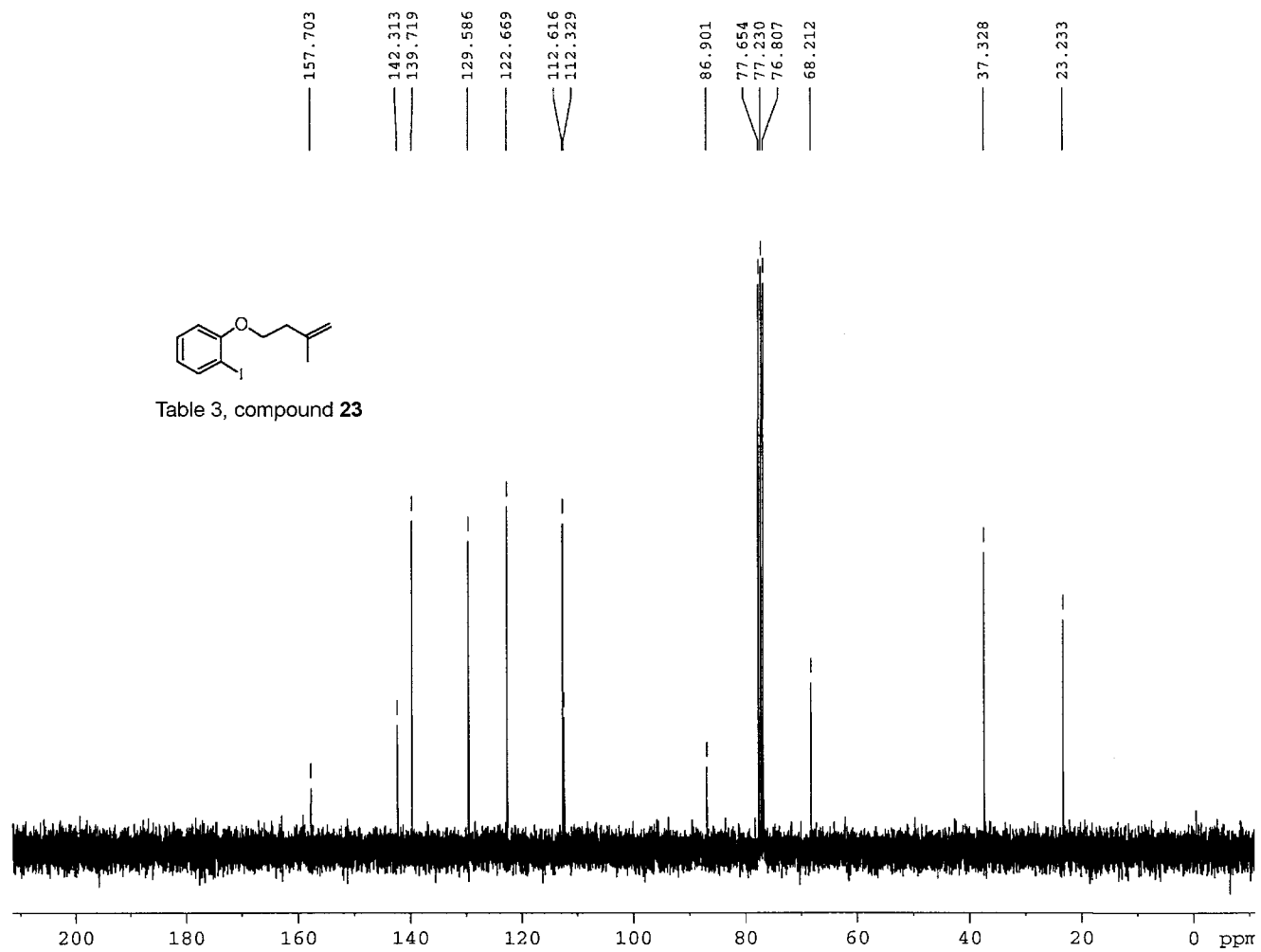
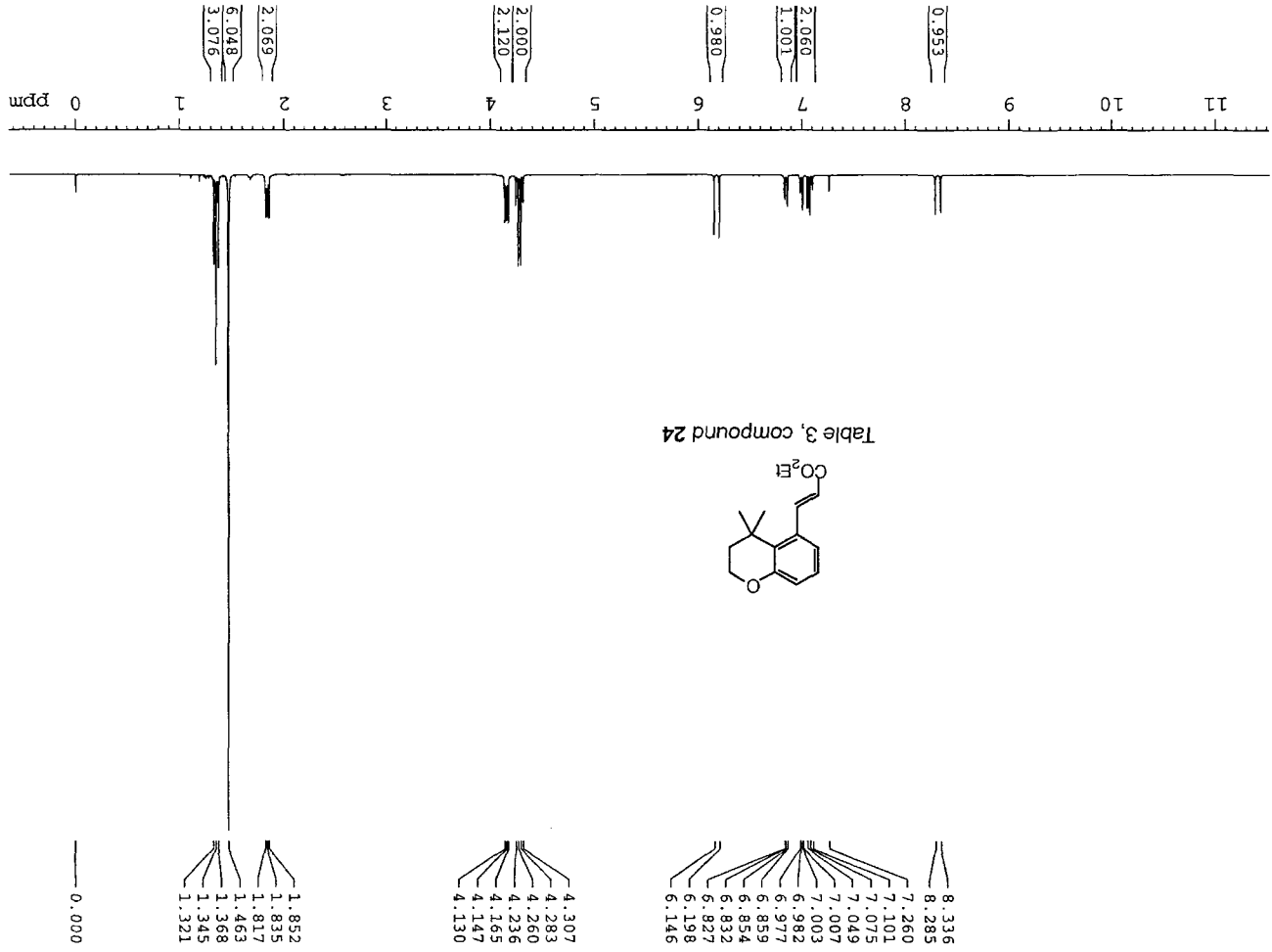
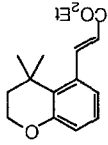


Table 3, compound 24



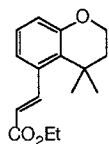
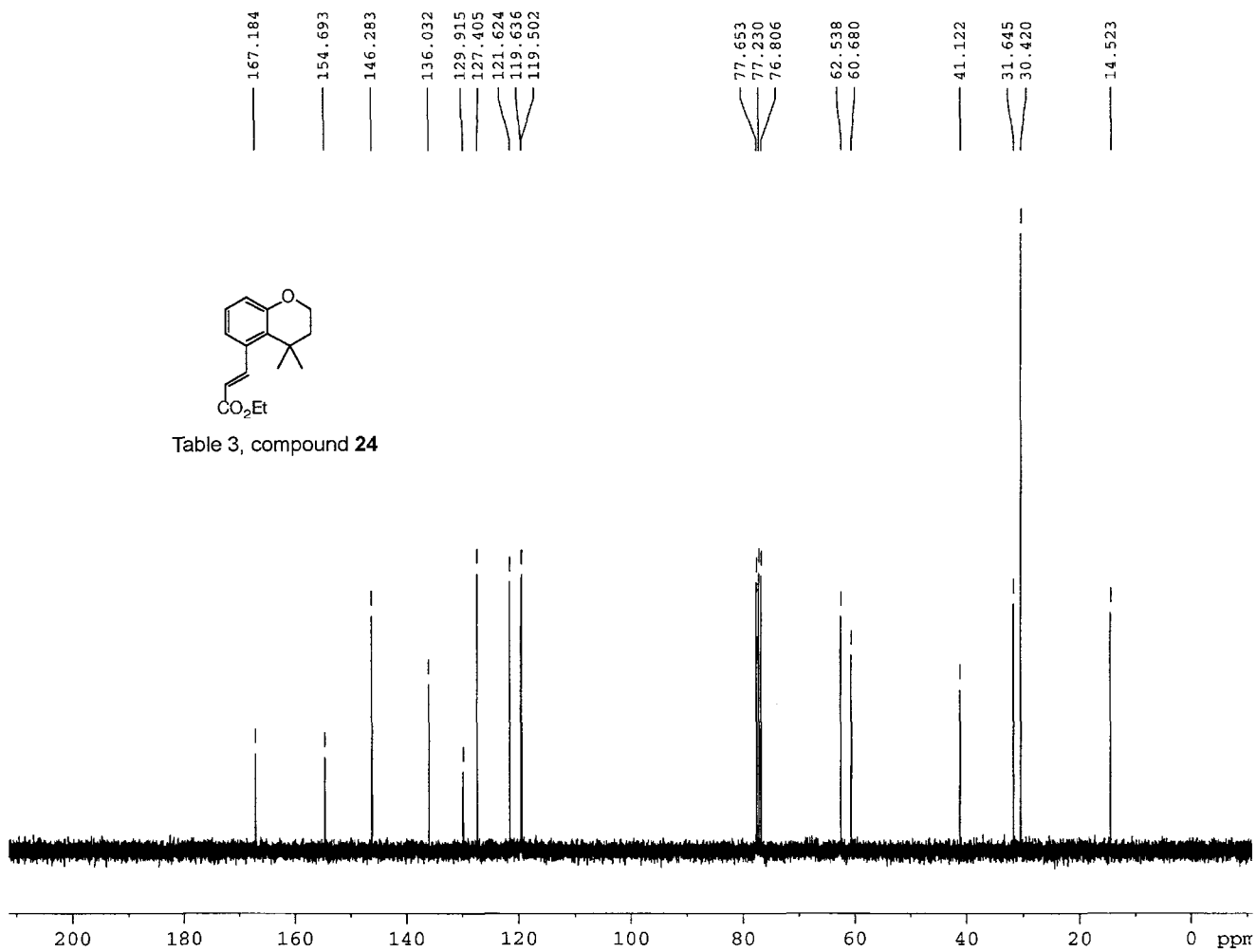
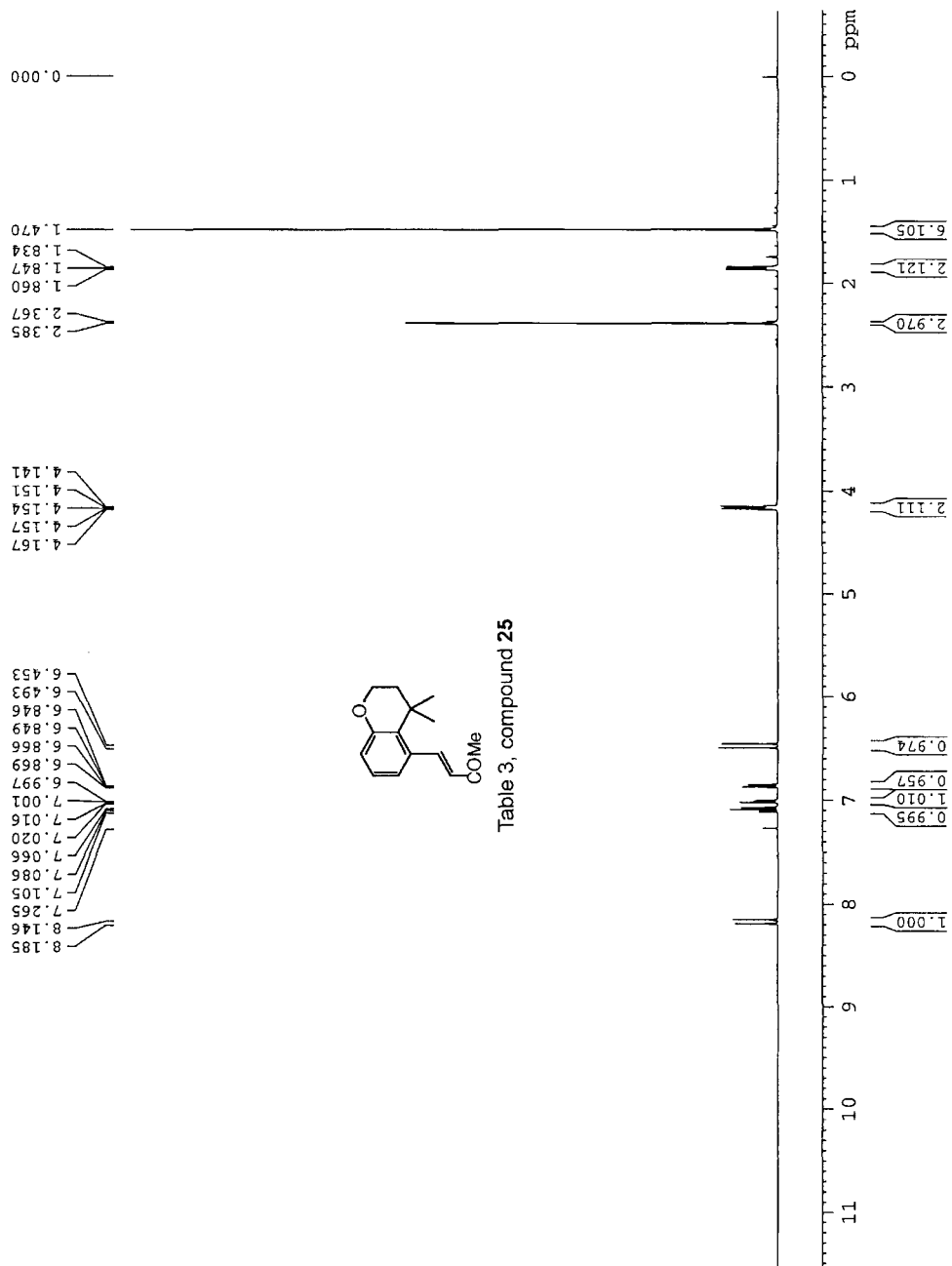


Table 3, compound 24





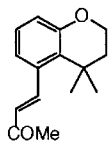
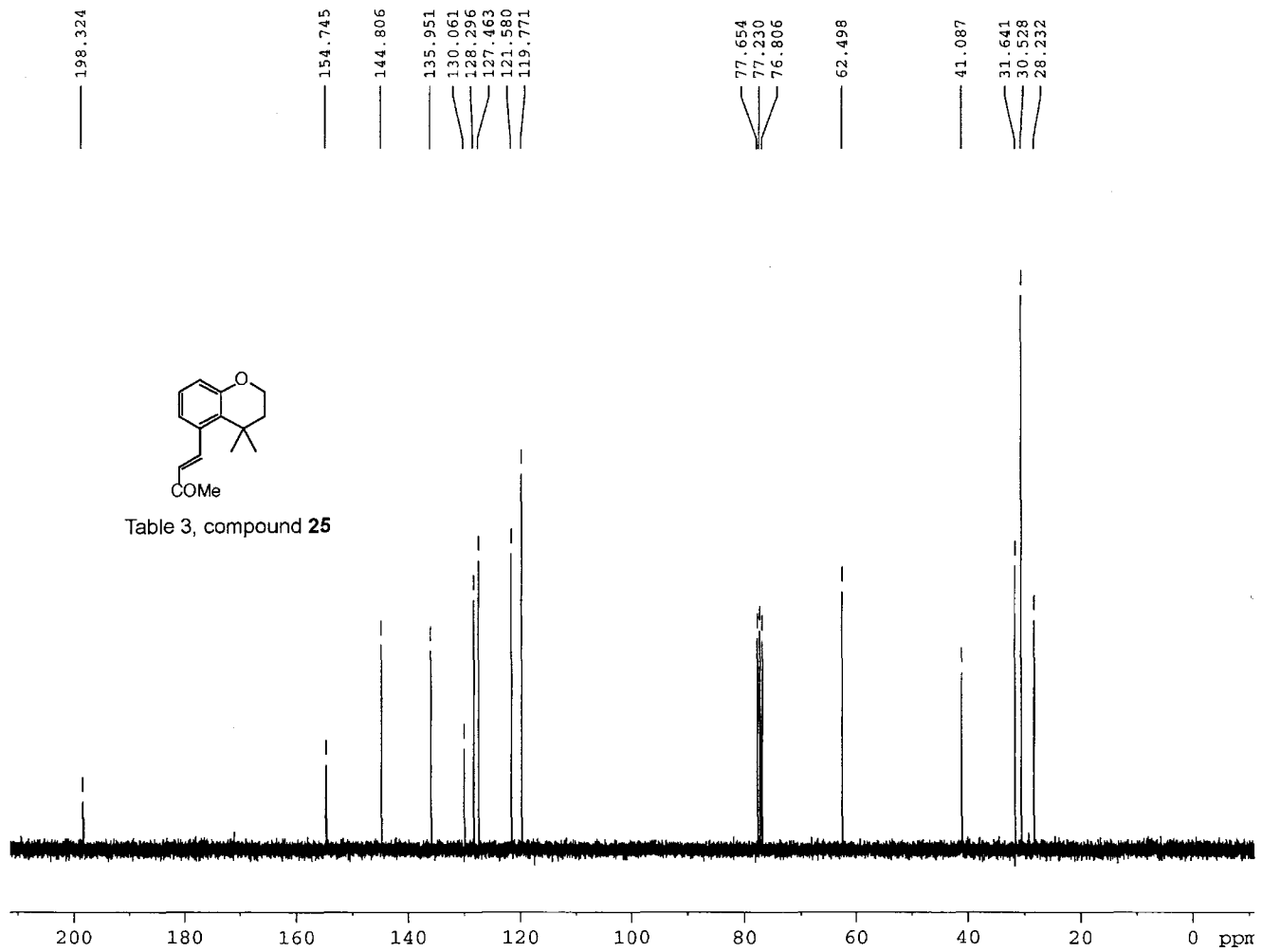
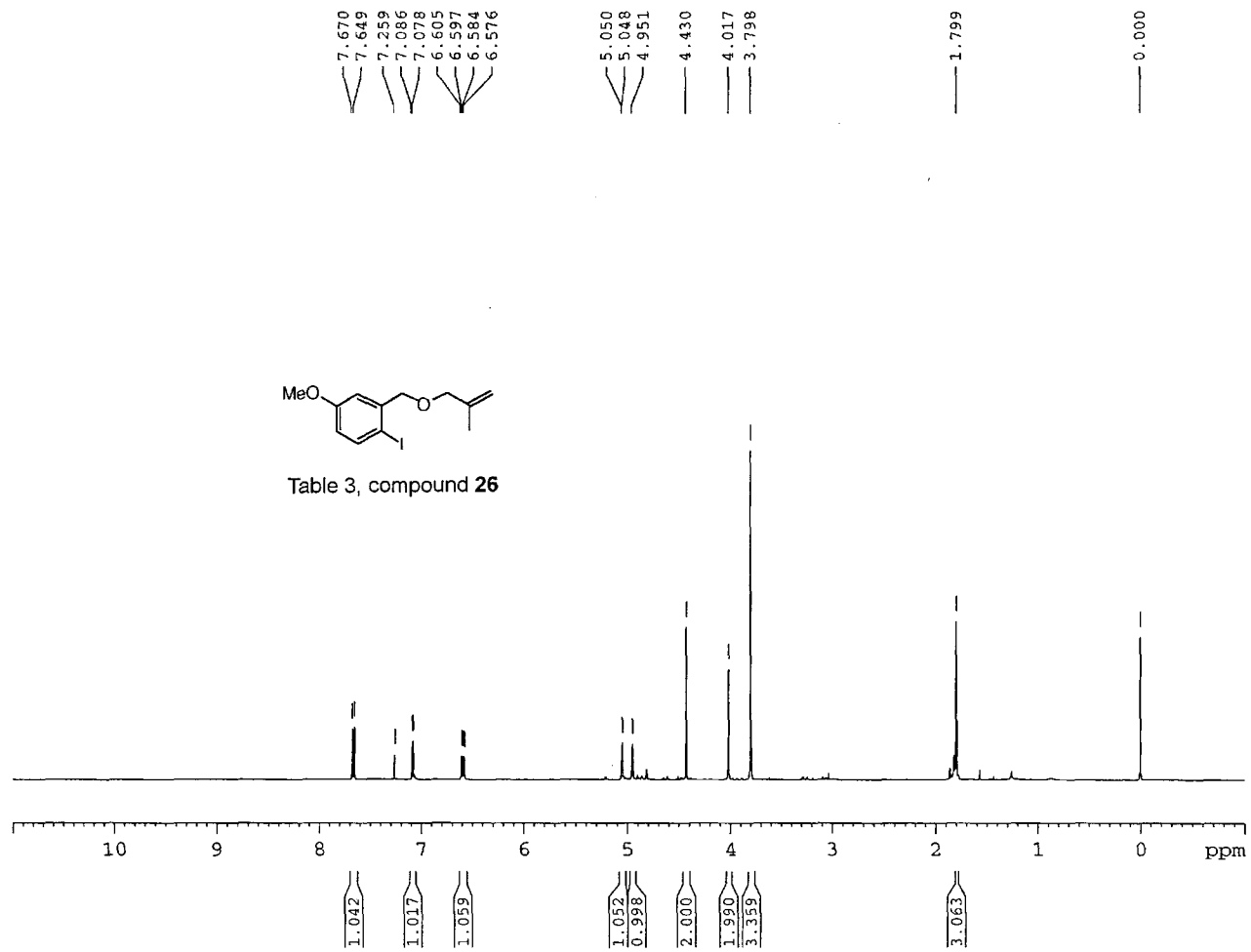
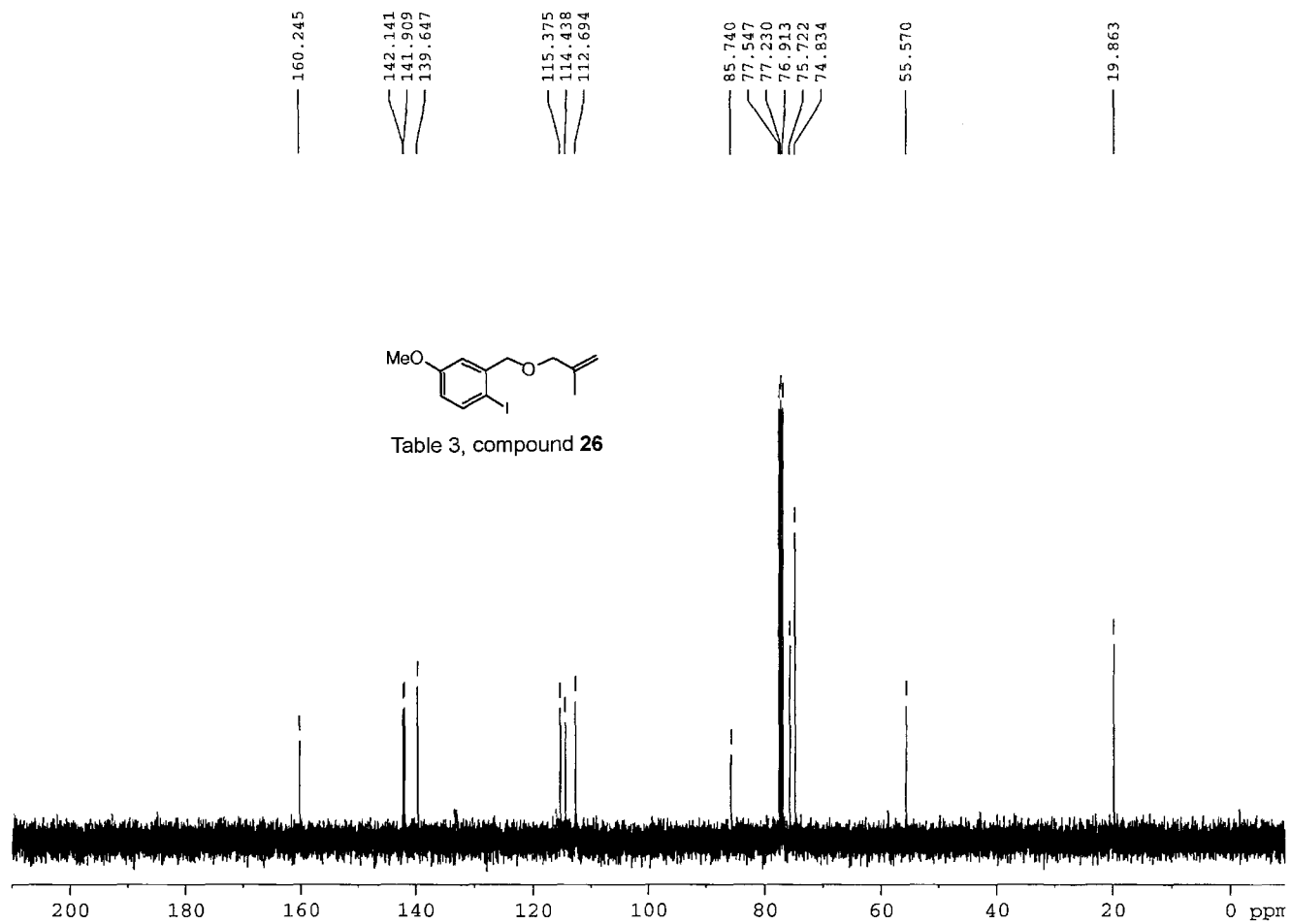
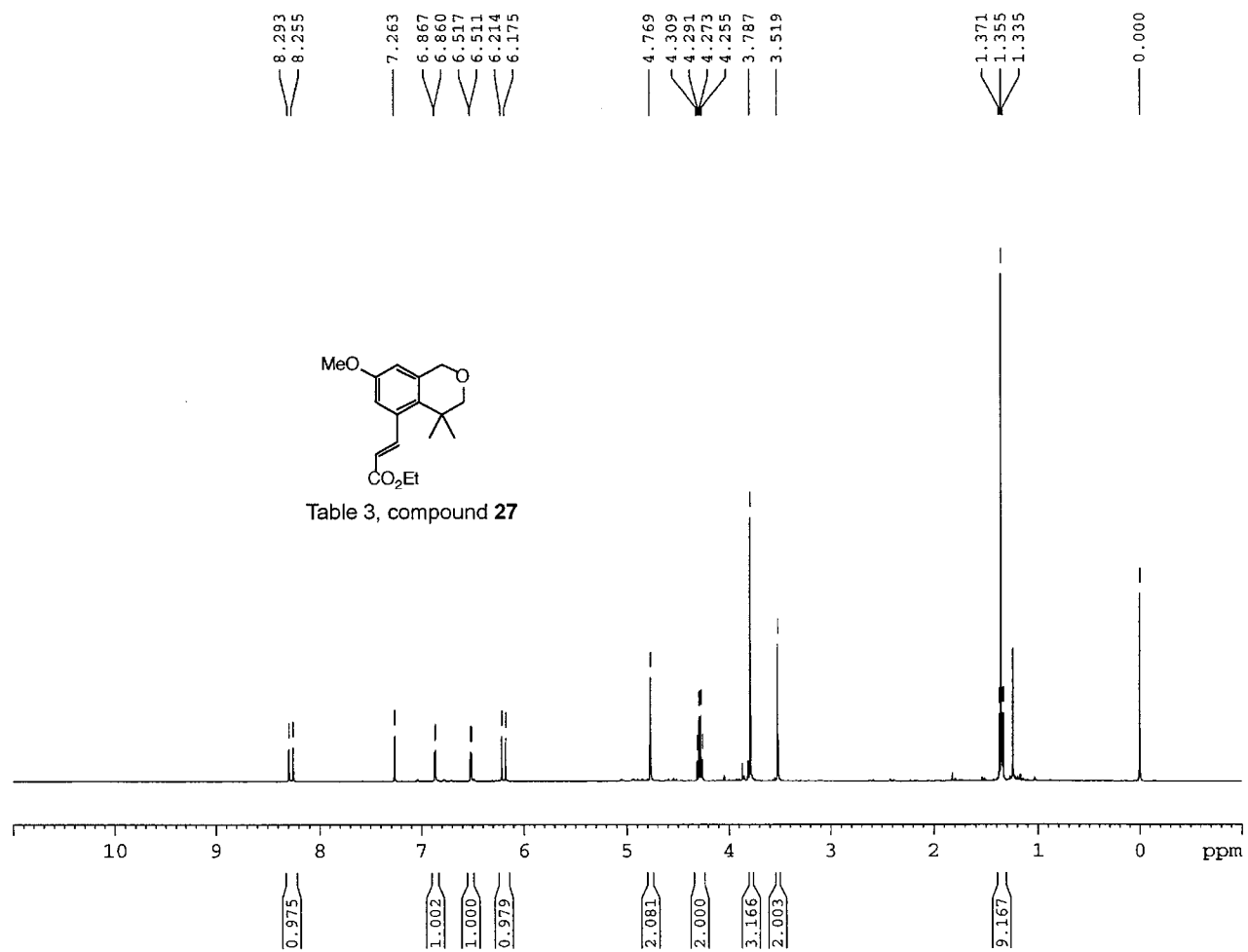


Table 3, compound 25







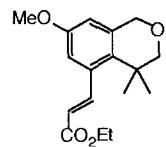
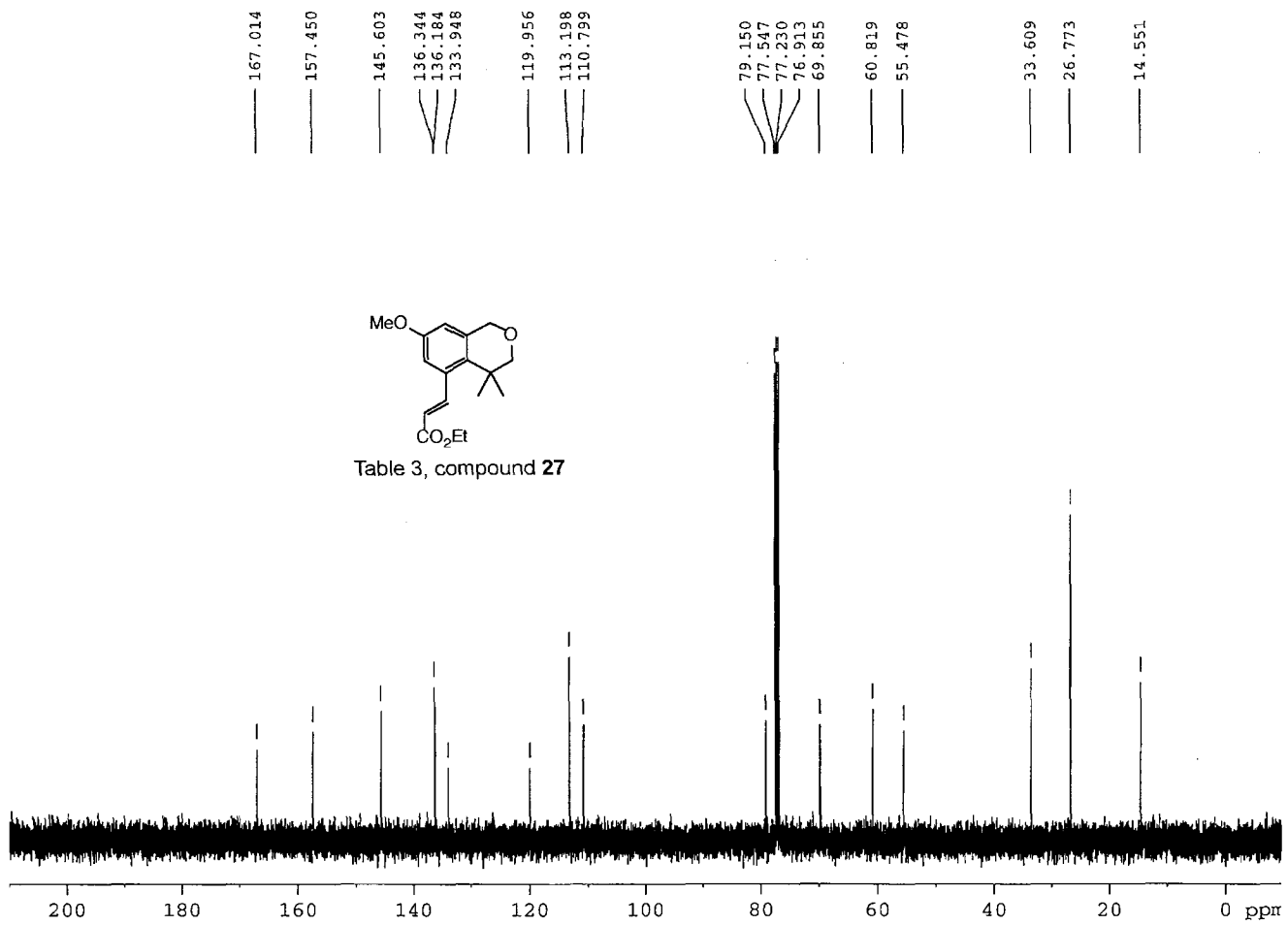
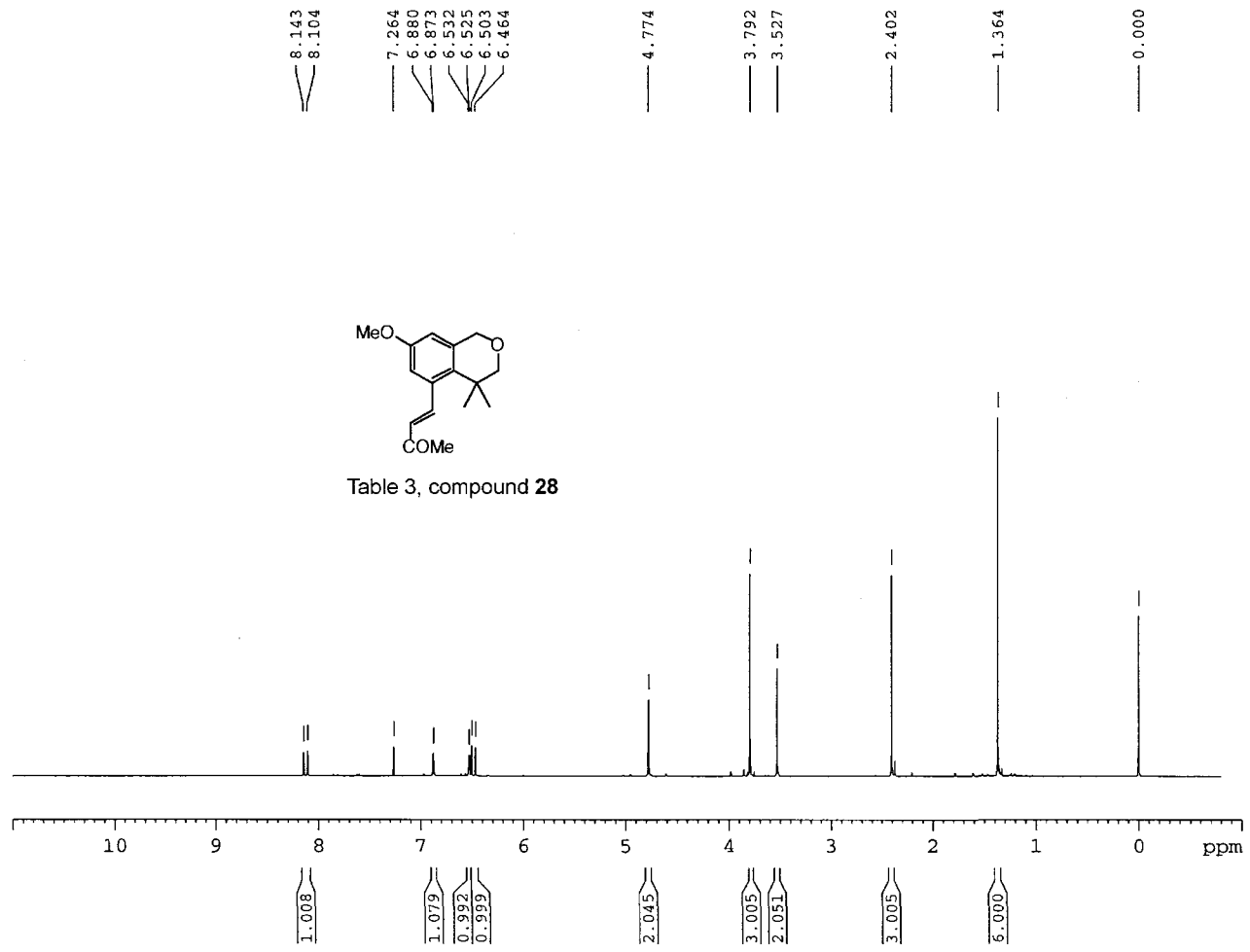


Table 3, compound 27



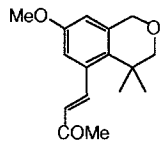
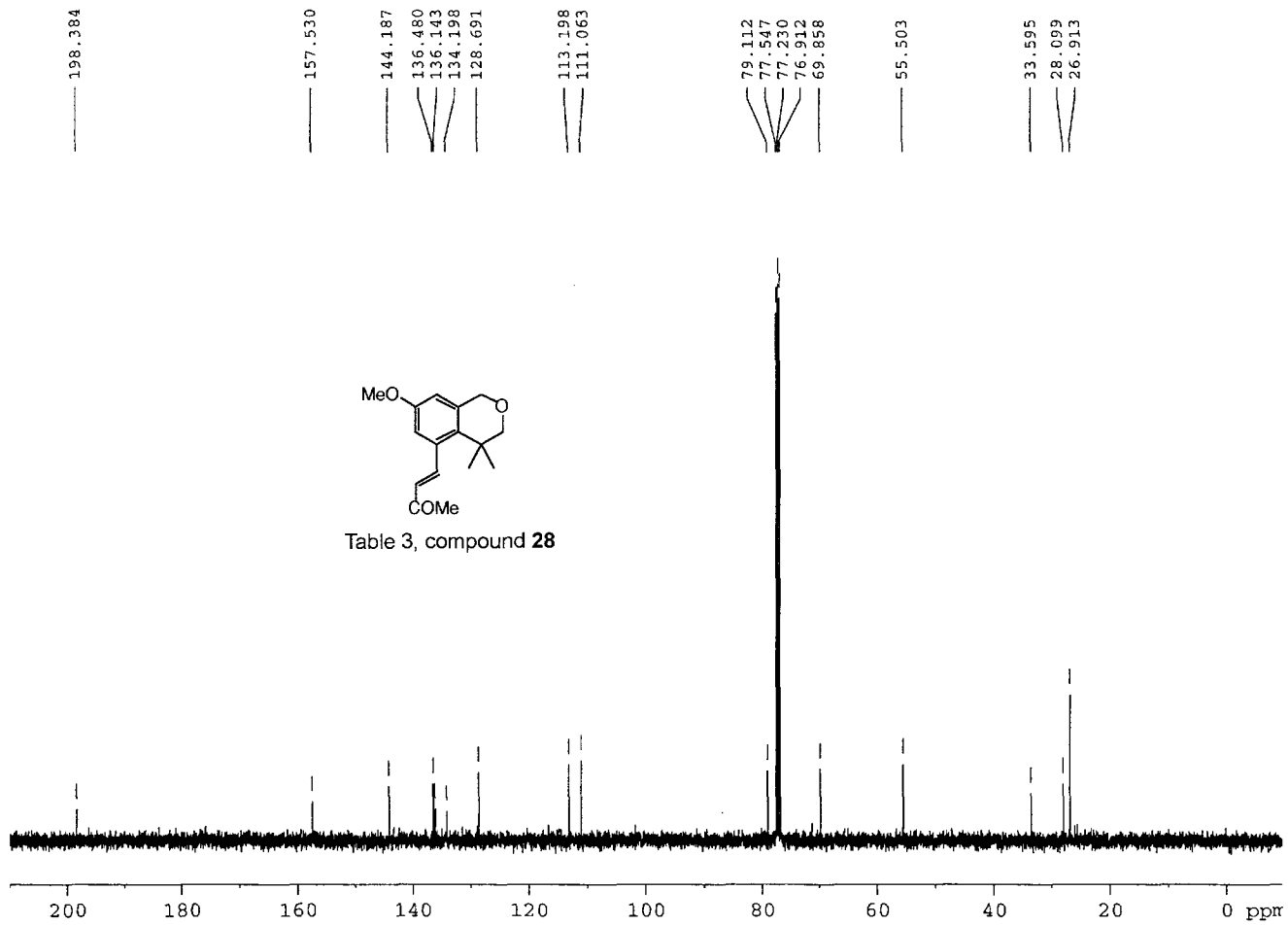
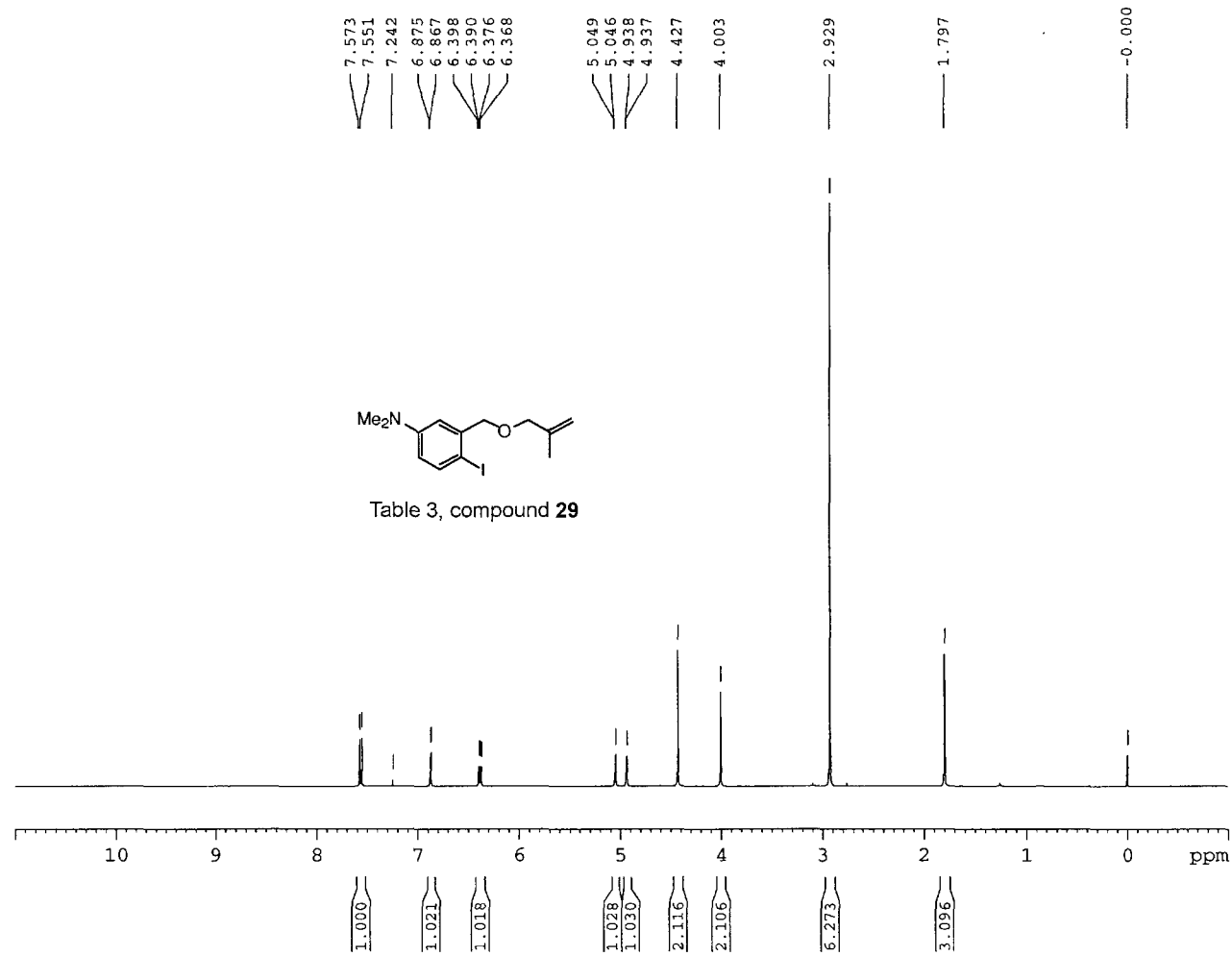


Table 3, compound **28**



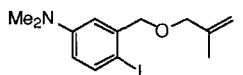
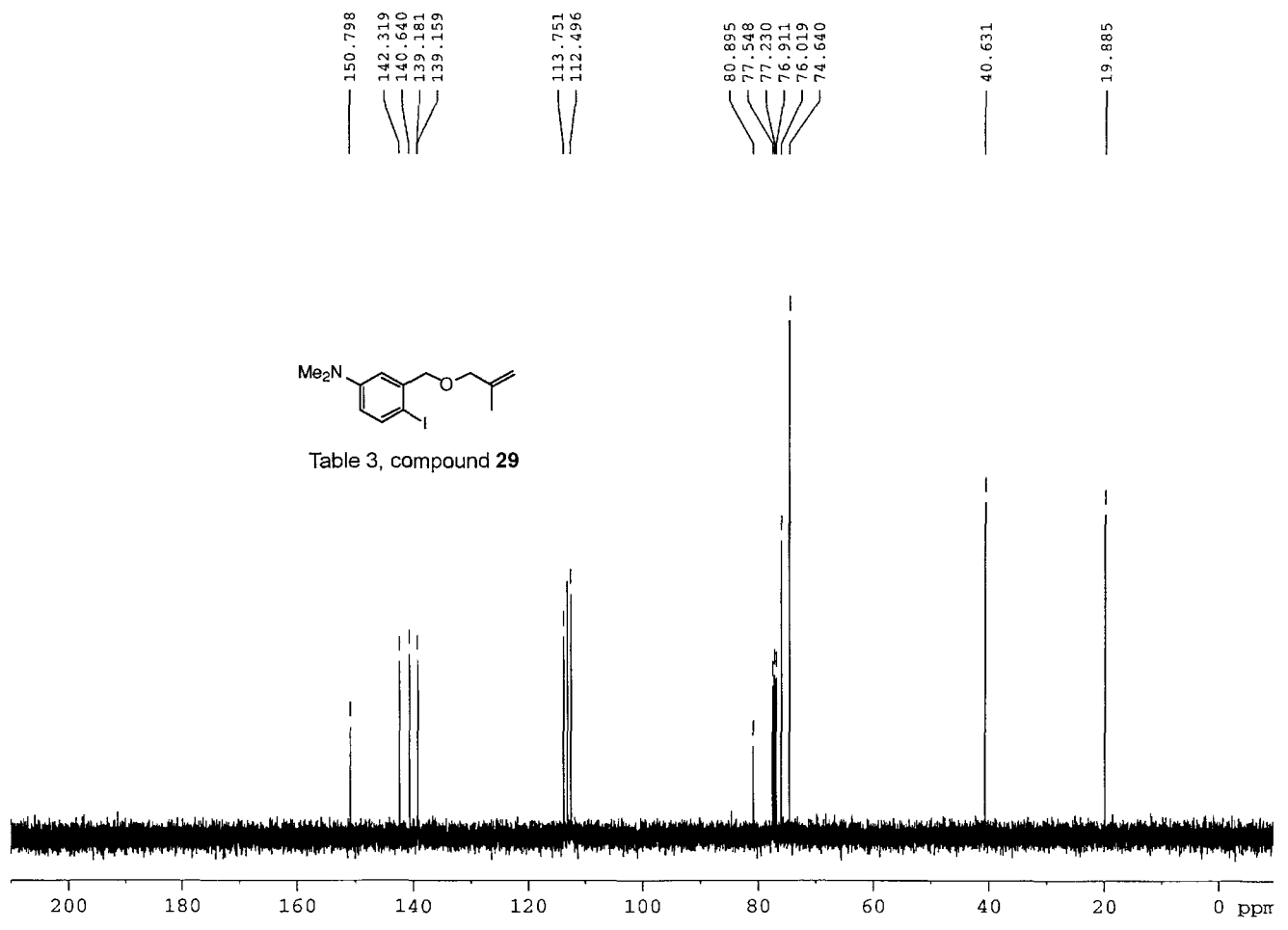
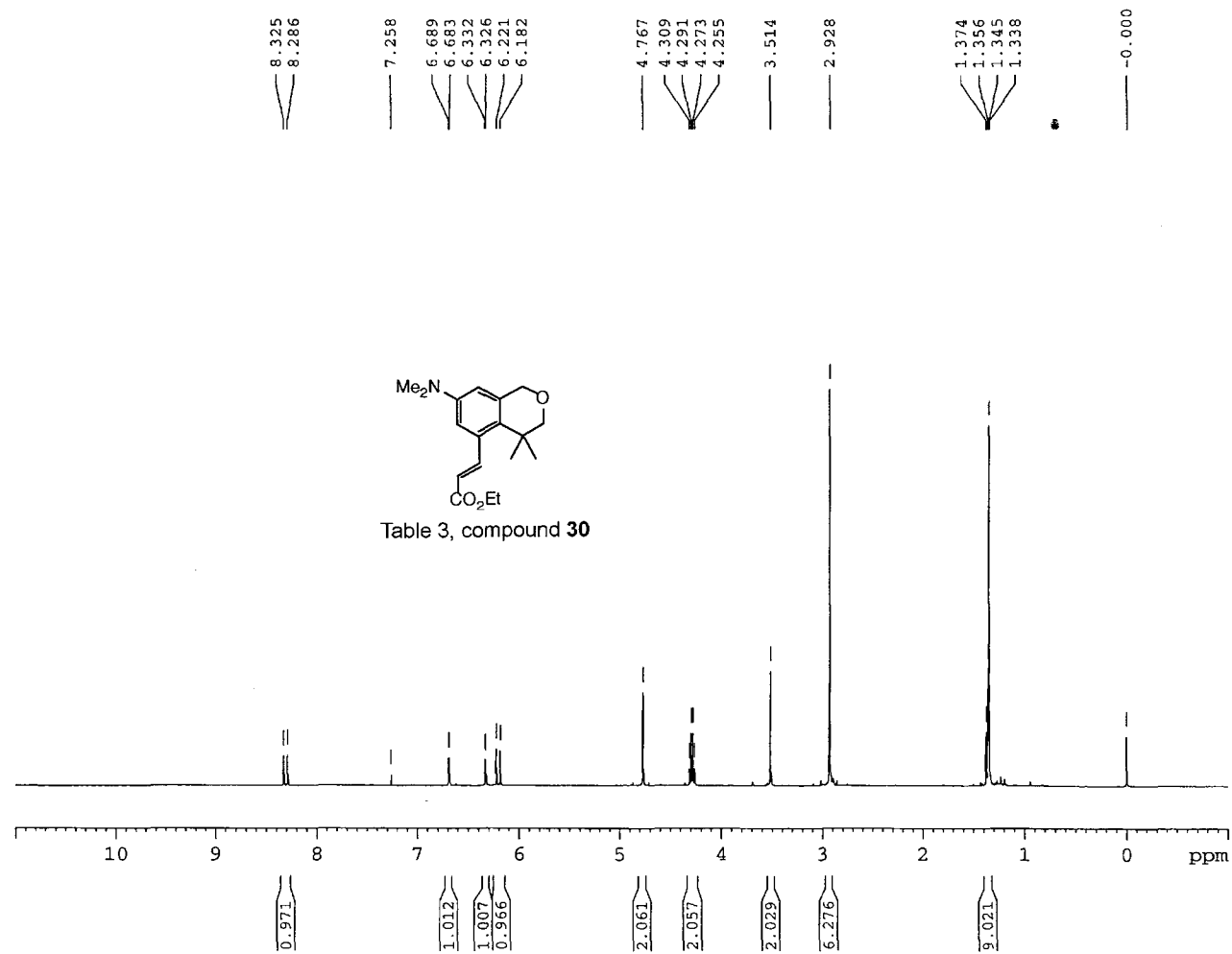


Table 3, compound 29





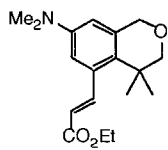
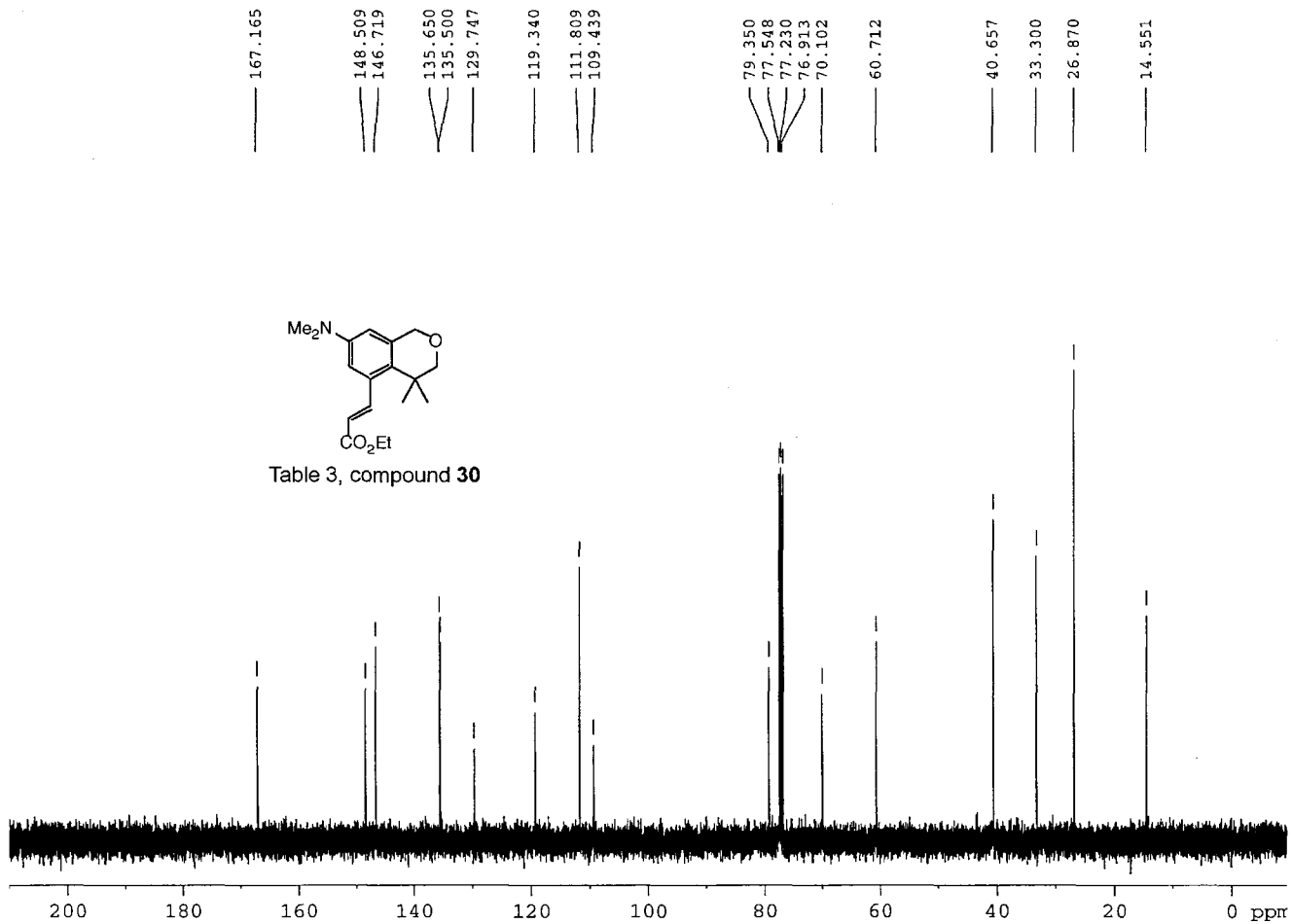


Table 3, compound 30



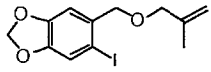
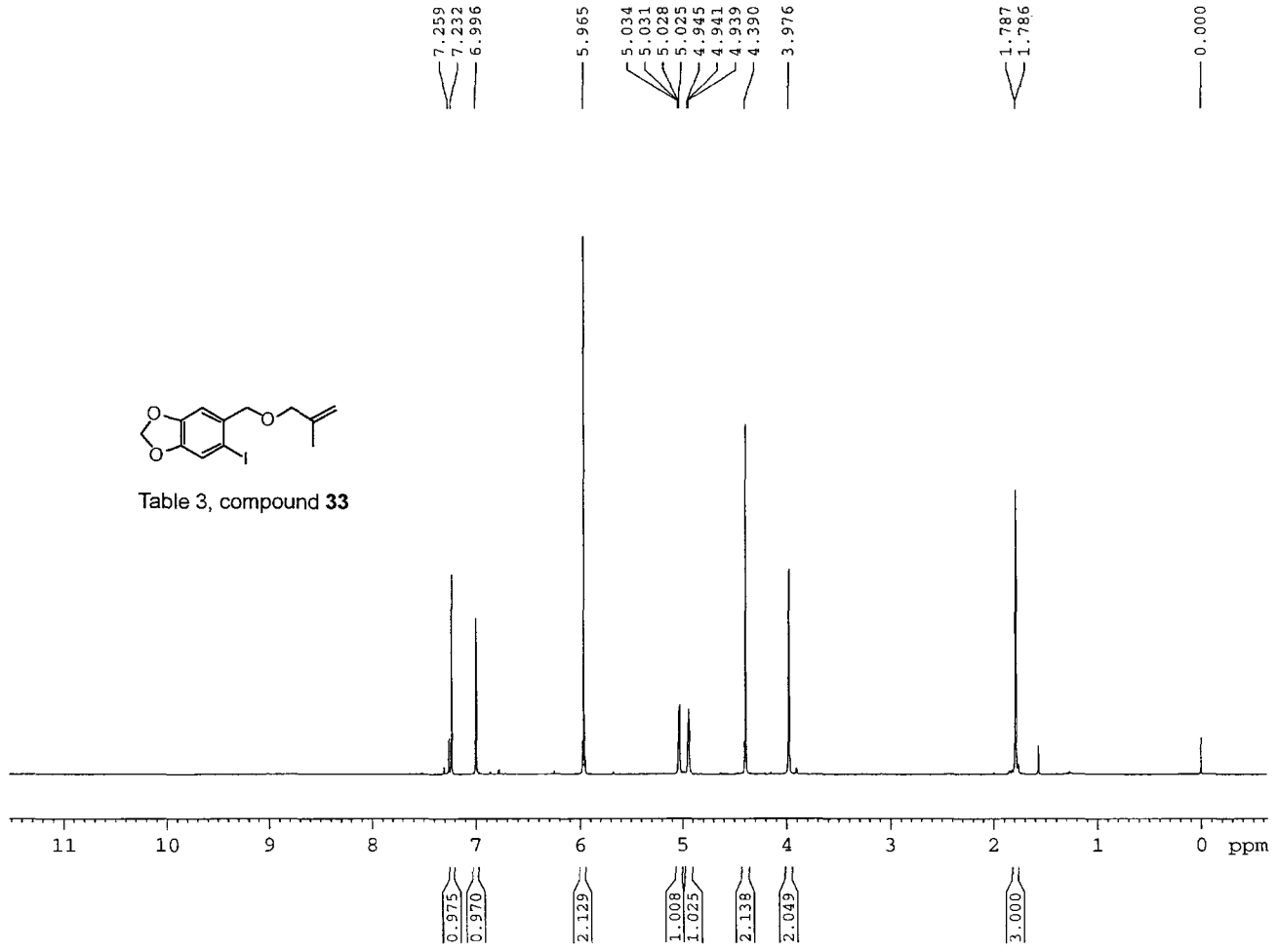
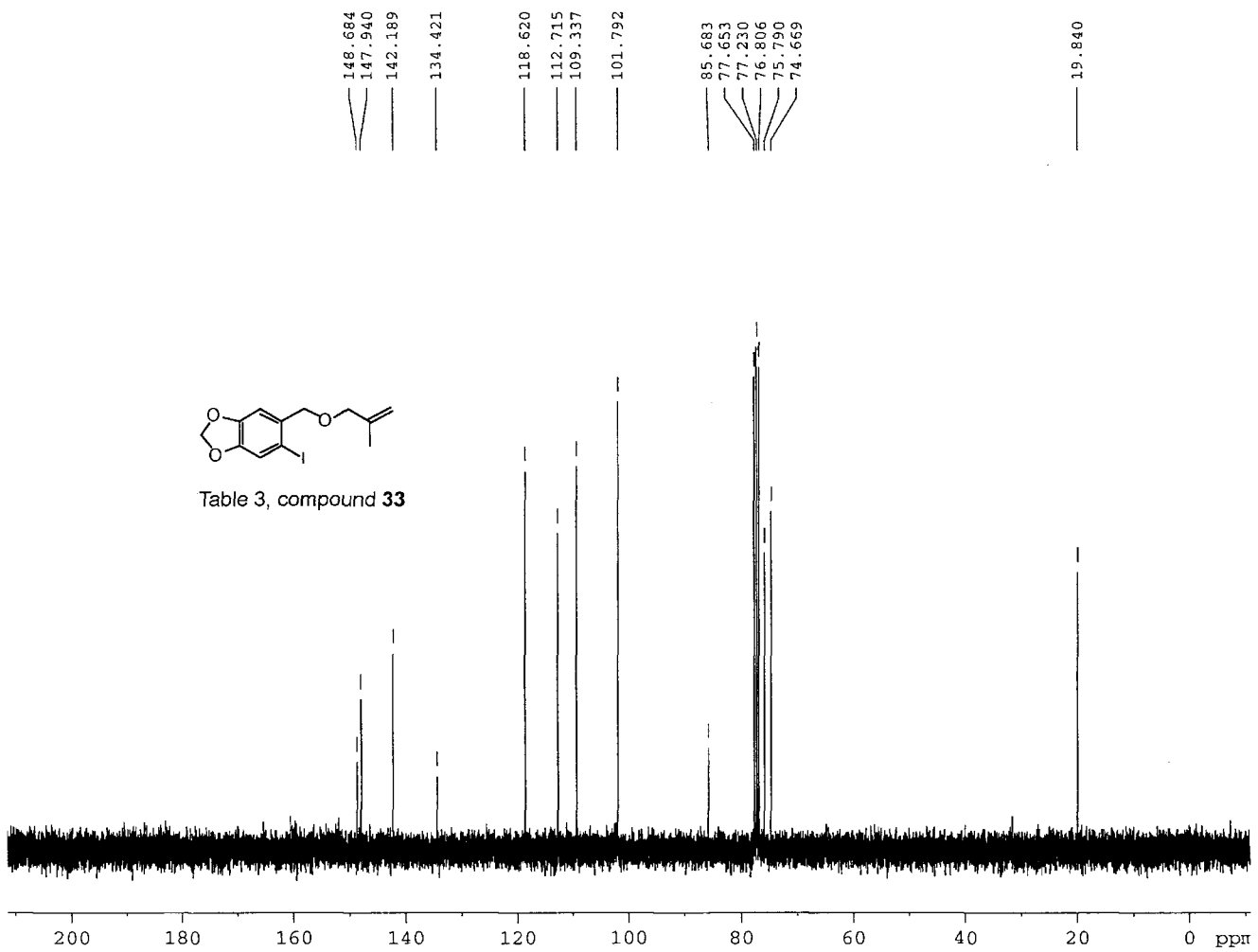


Table 3, compound **33**





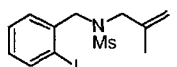
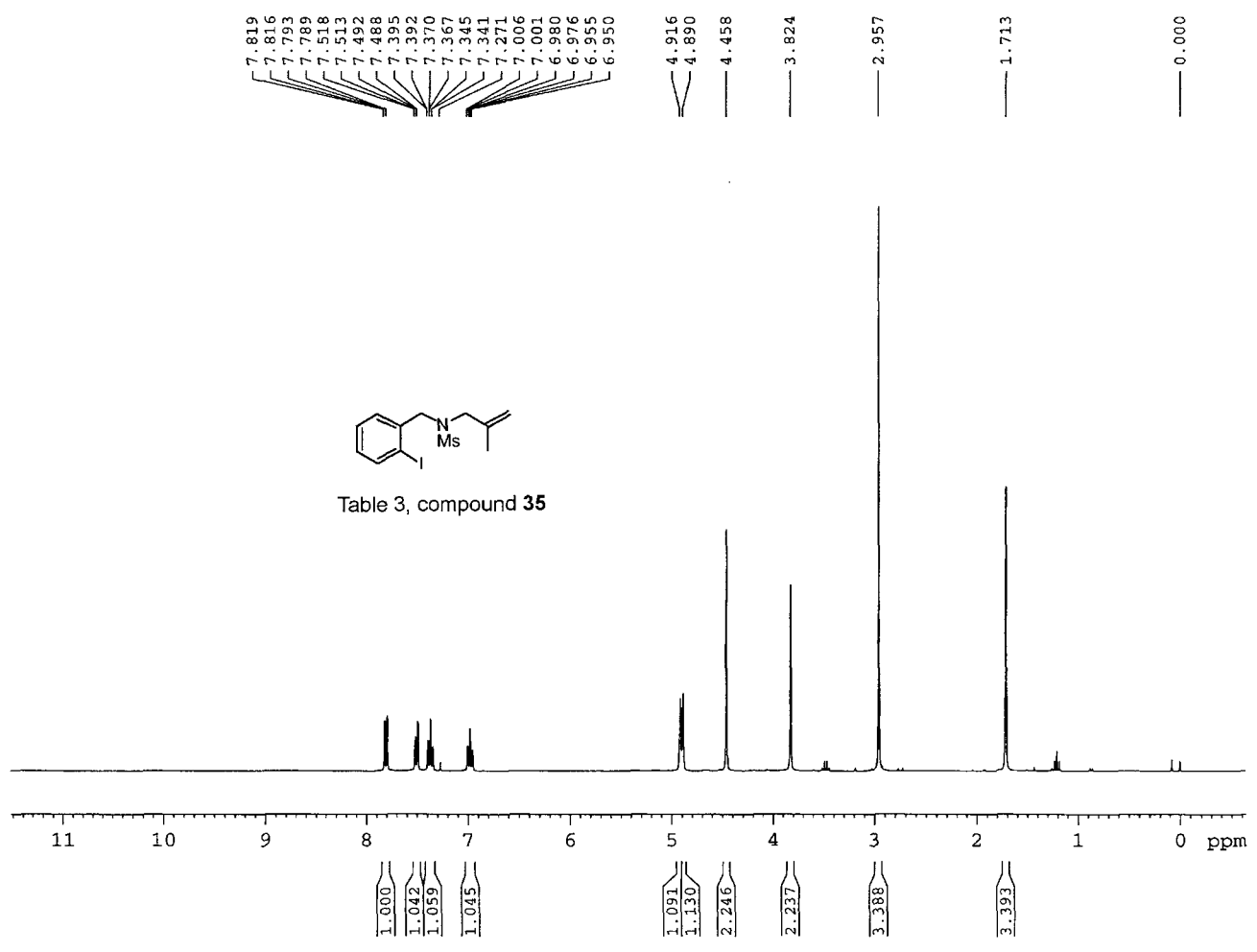


Table 3, compound 35



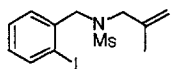
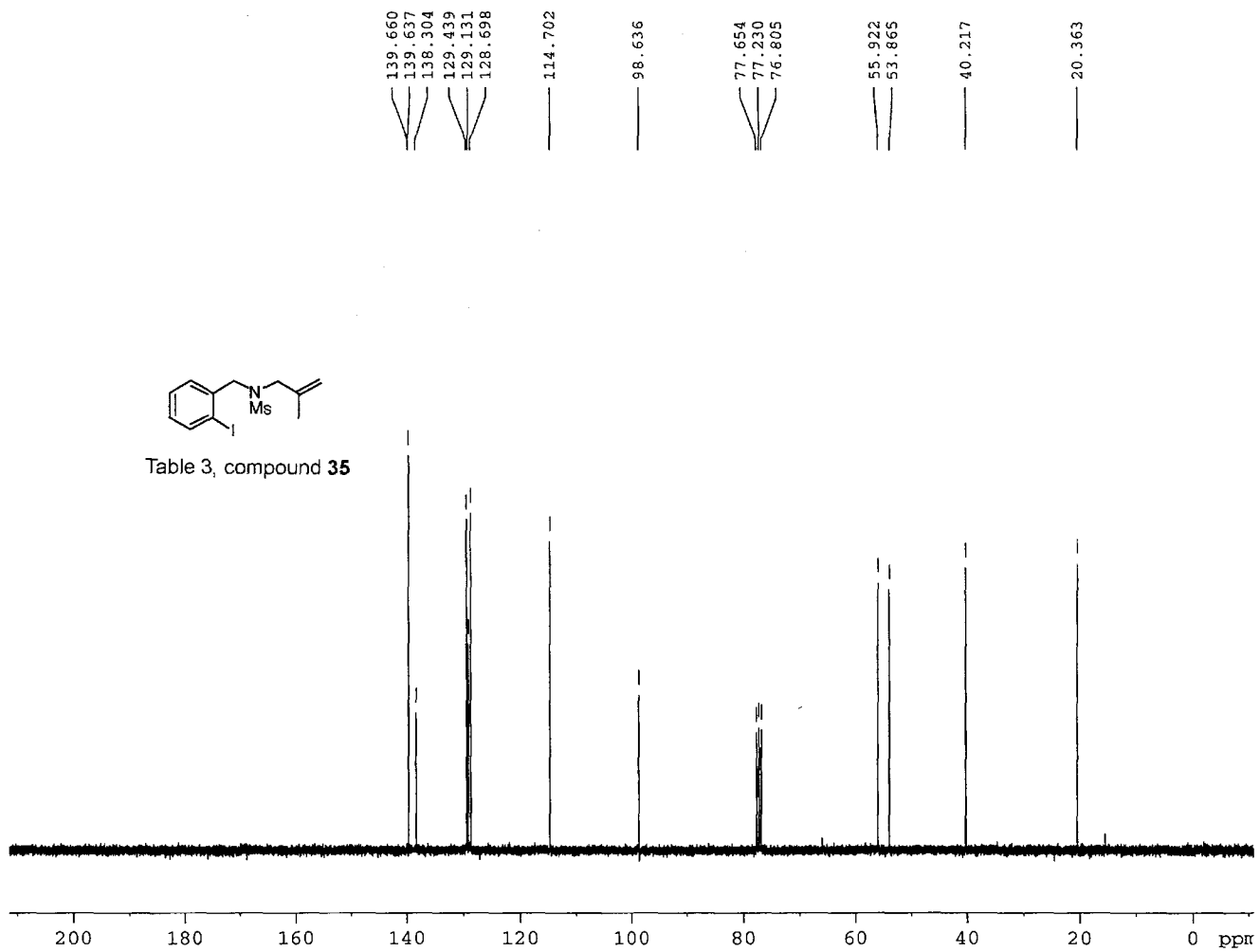
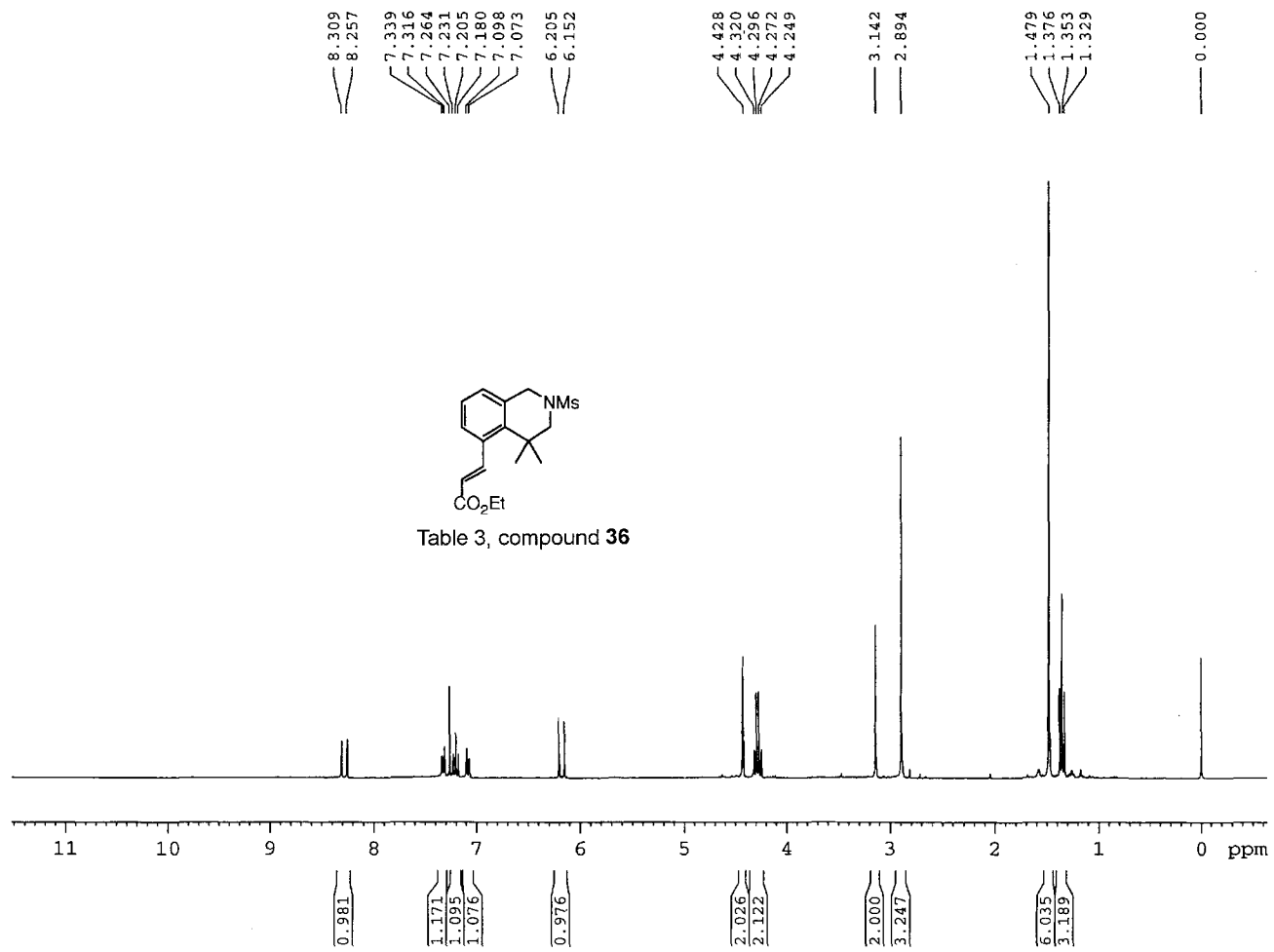


Table 3, compound 35





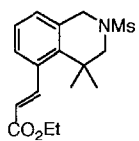
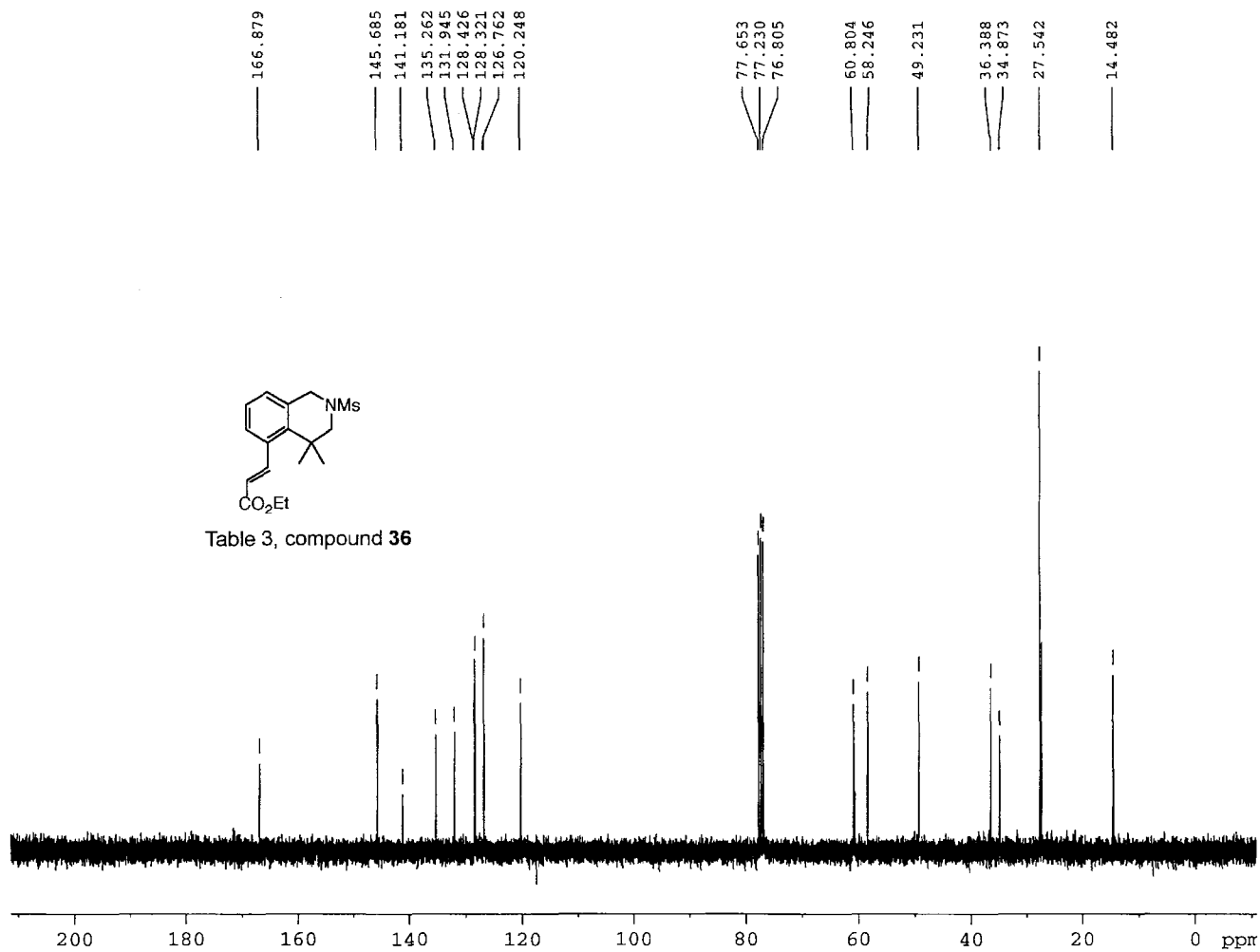


Table 3, compound 36



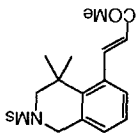
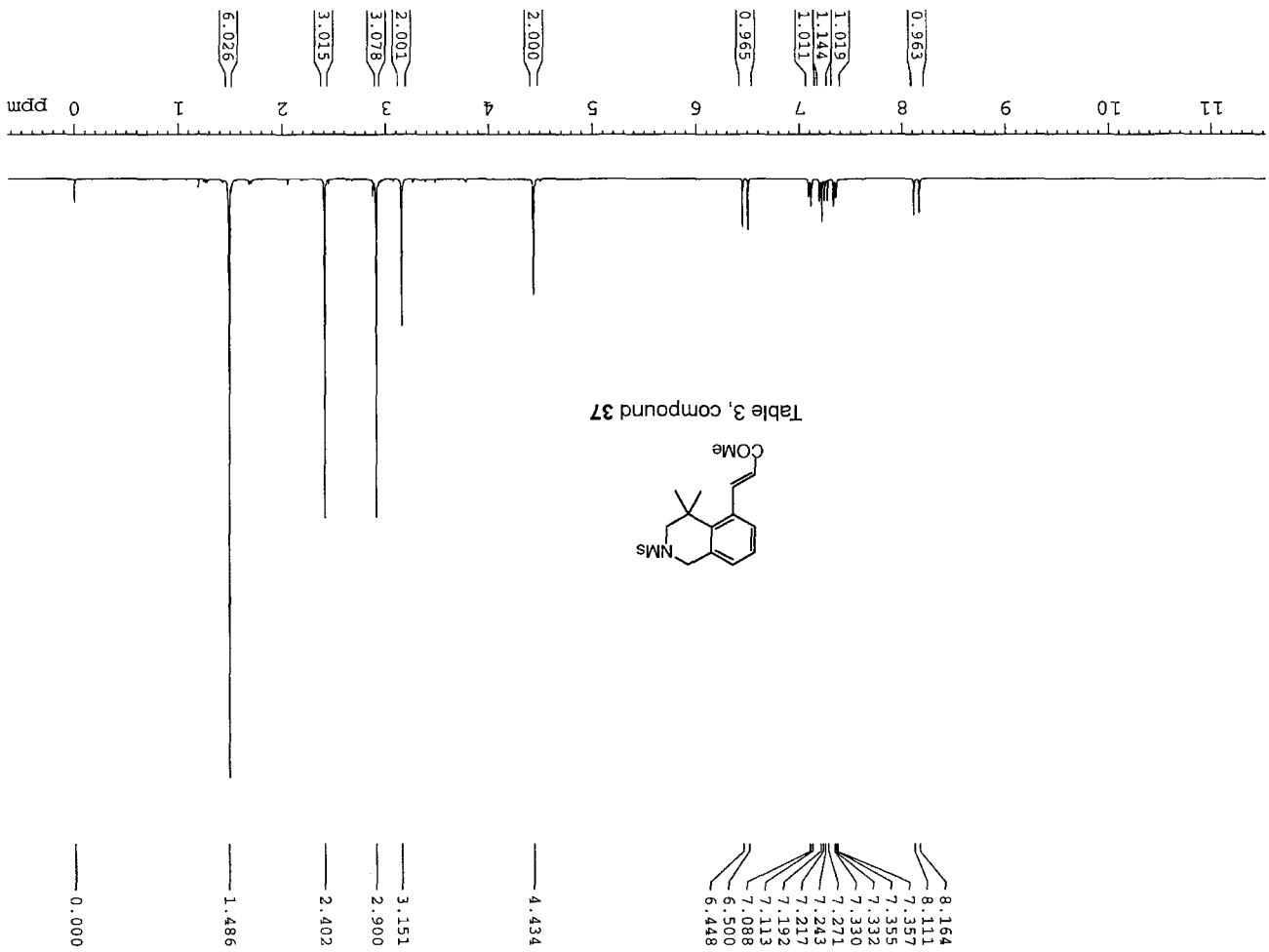
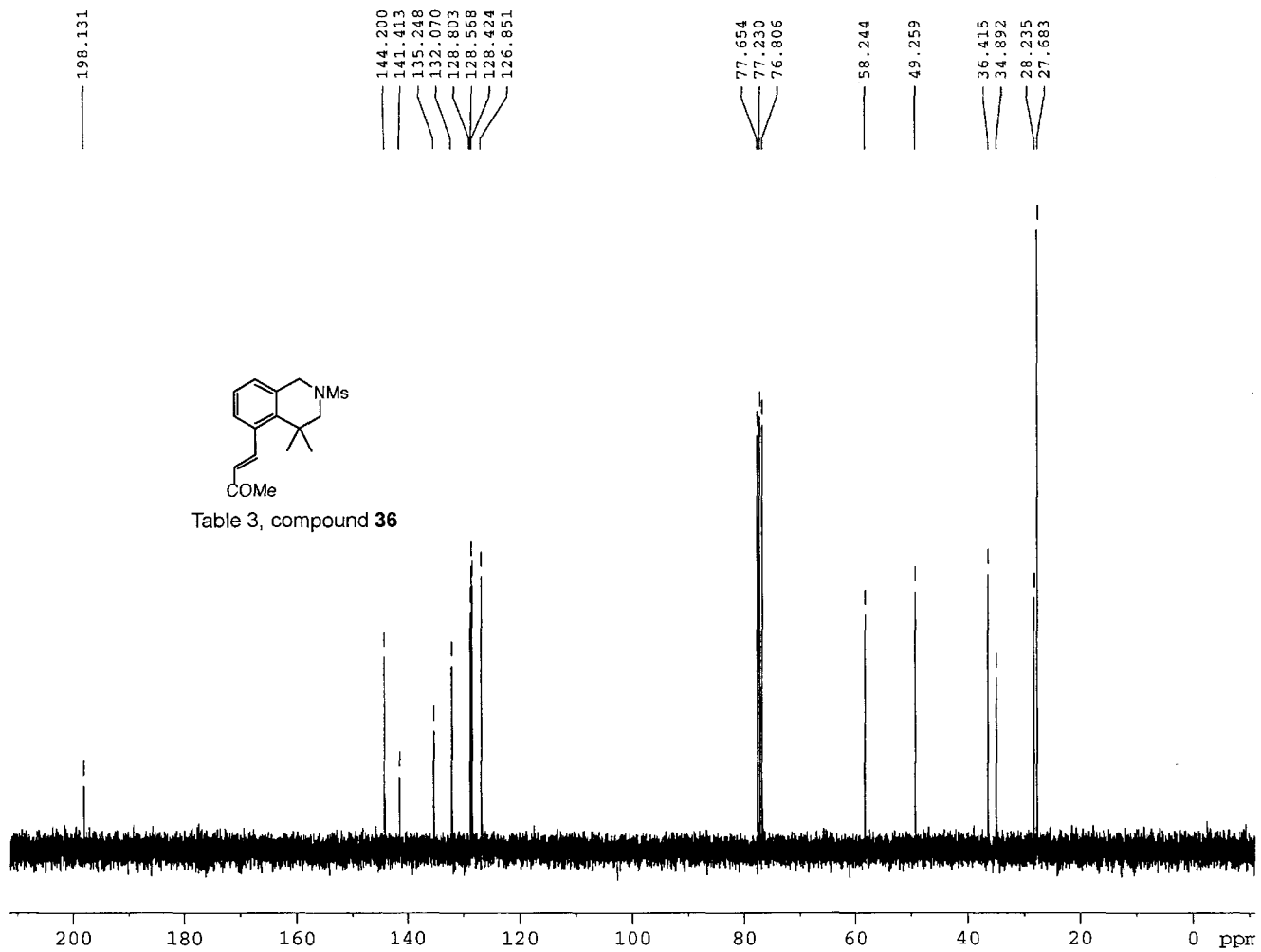


Table 3, compound 37





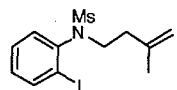


Table 3, compound **38**

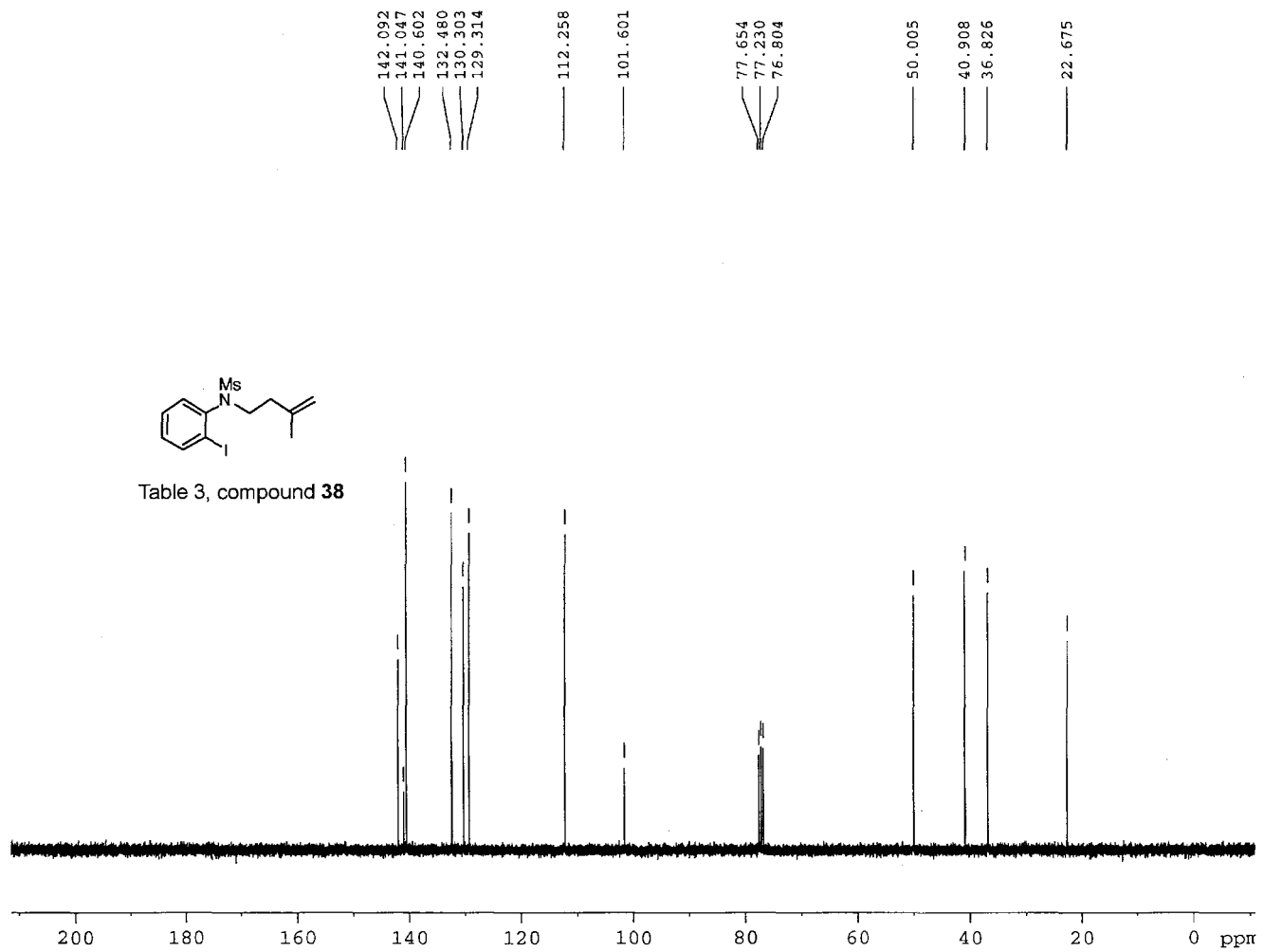
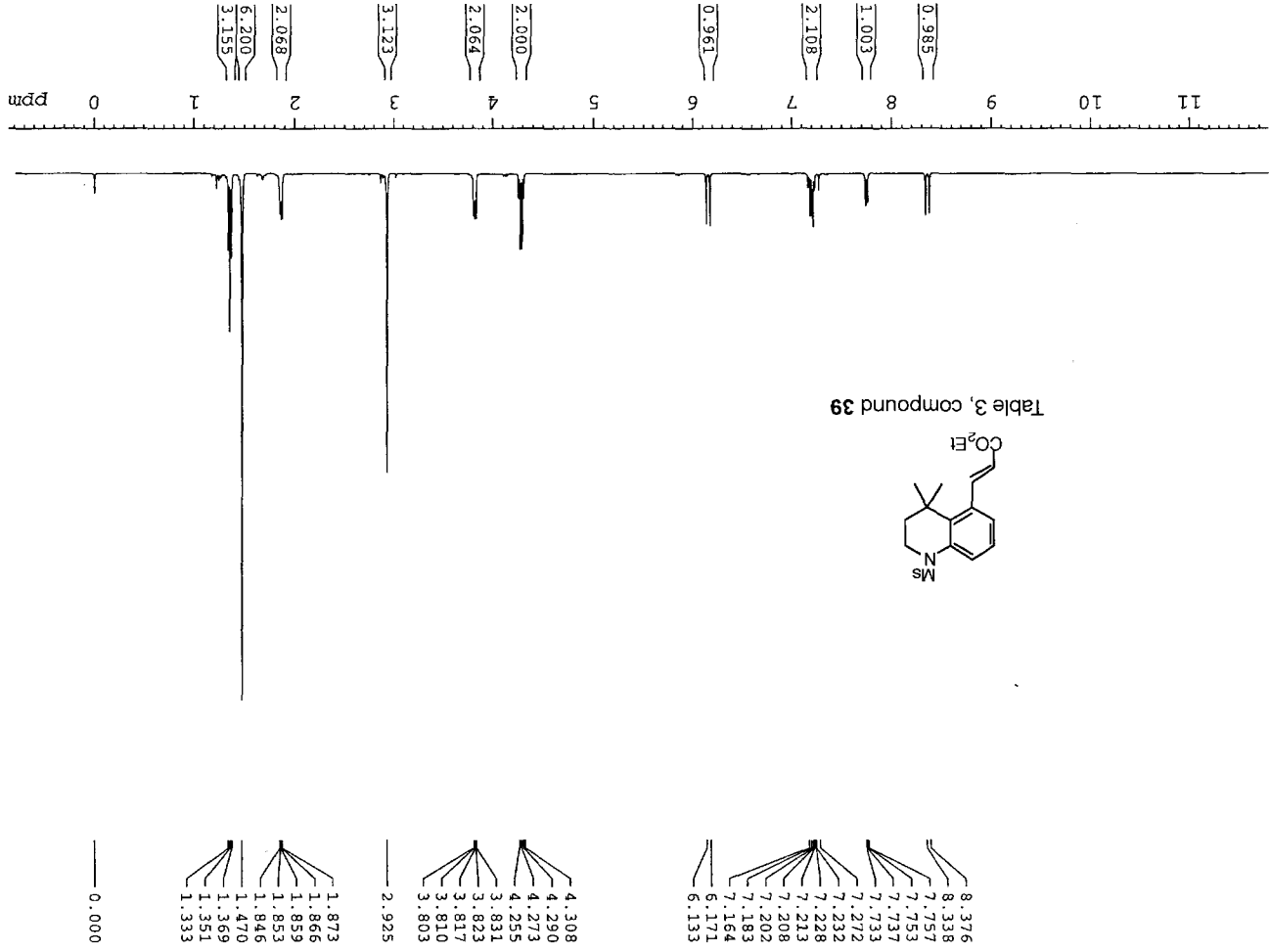
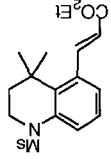


Table 3, compound 39



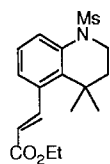
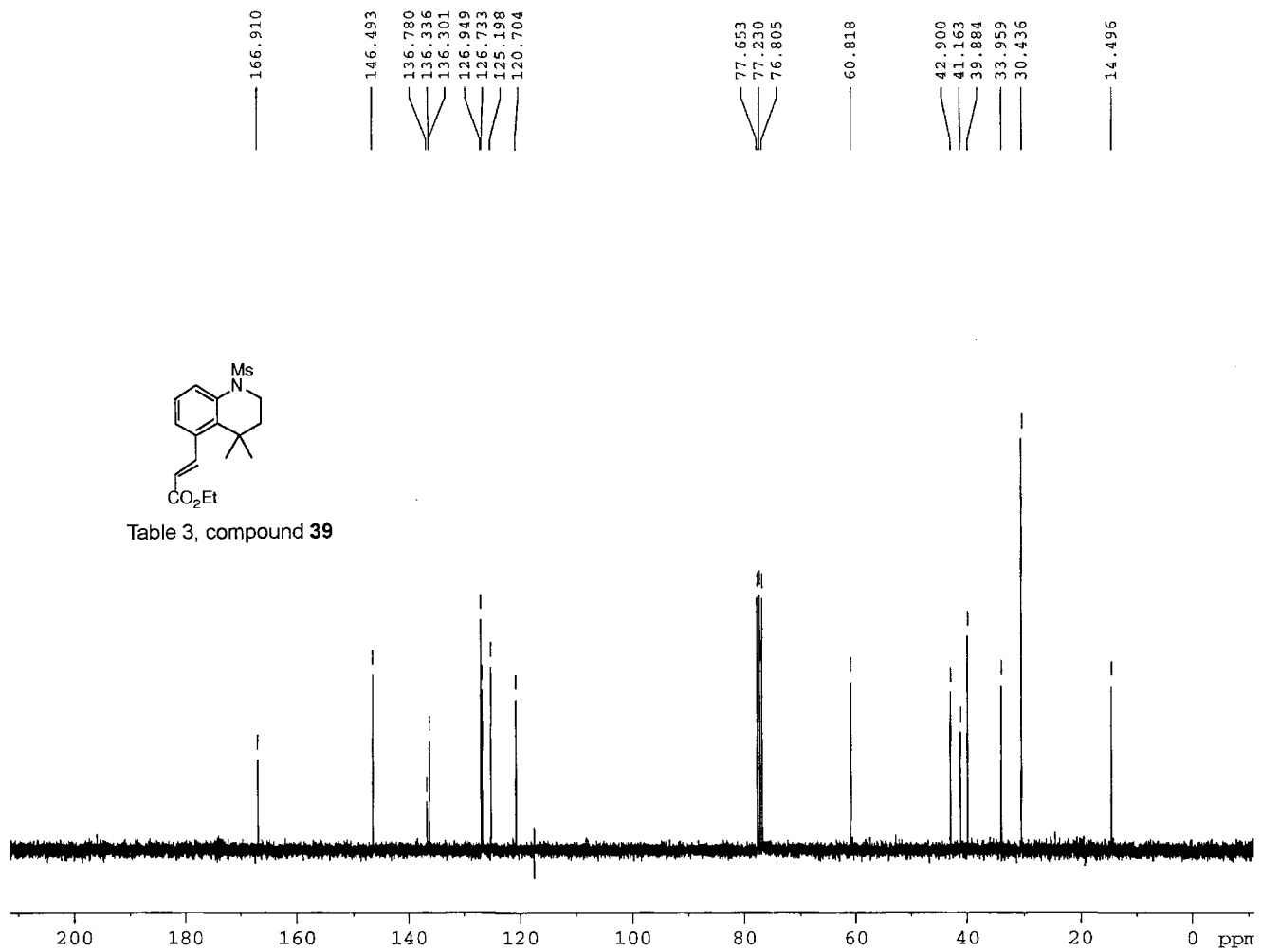


Table 3, compound **39**



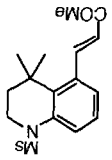
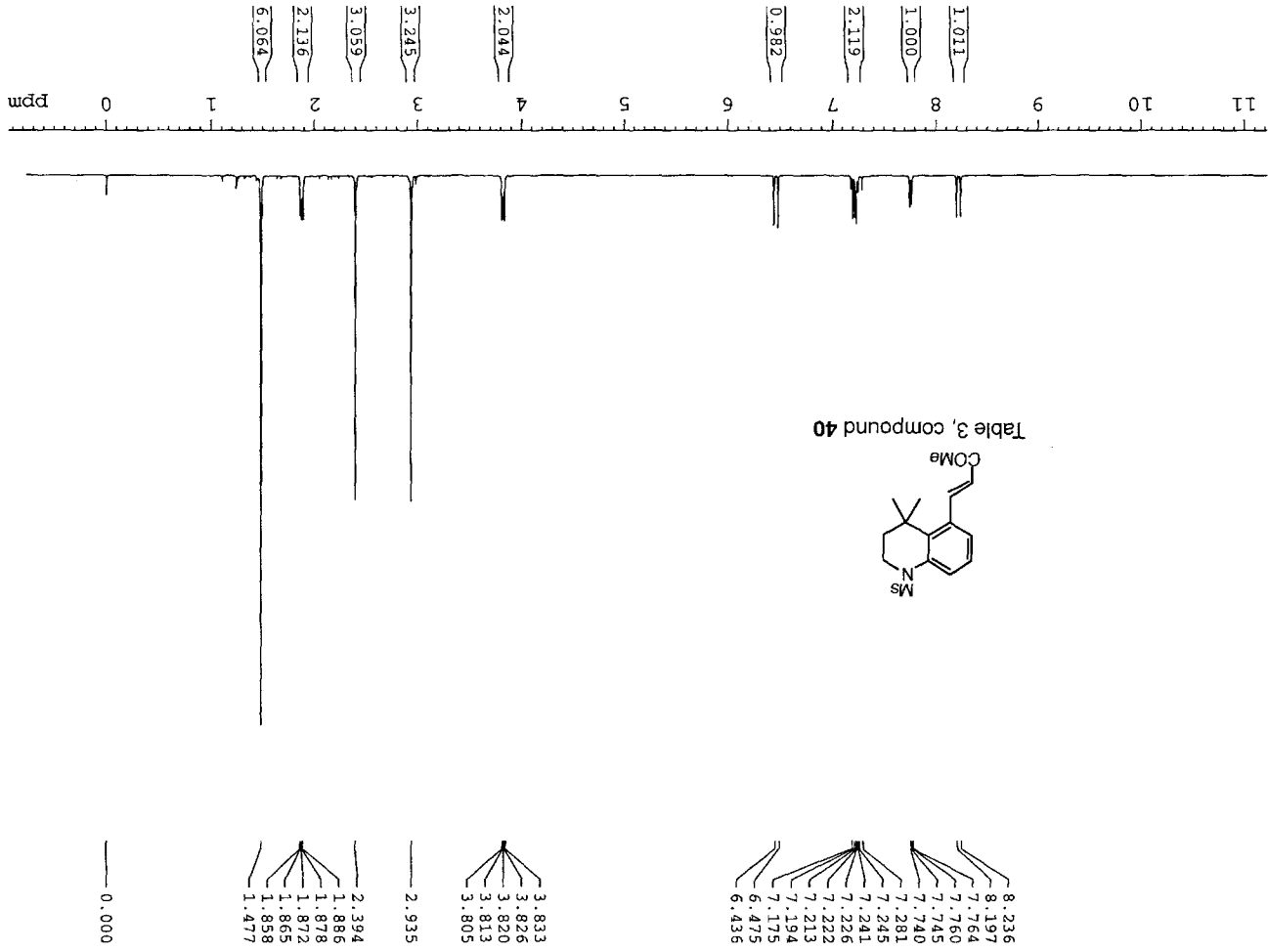
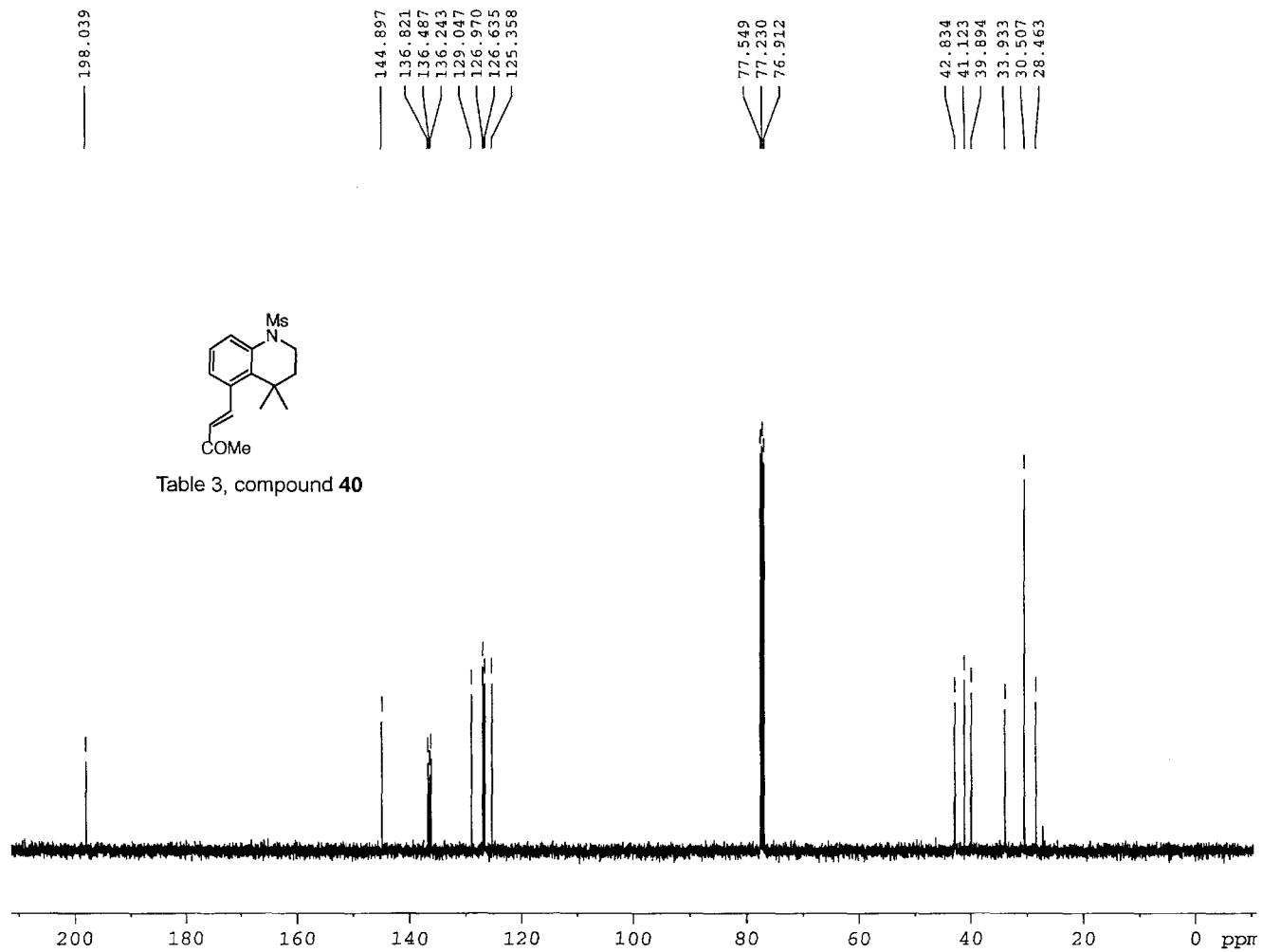
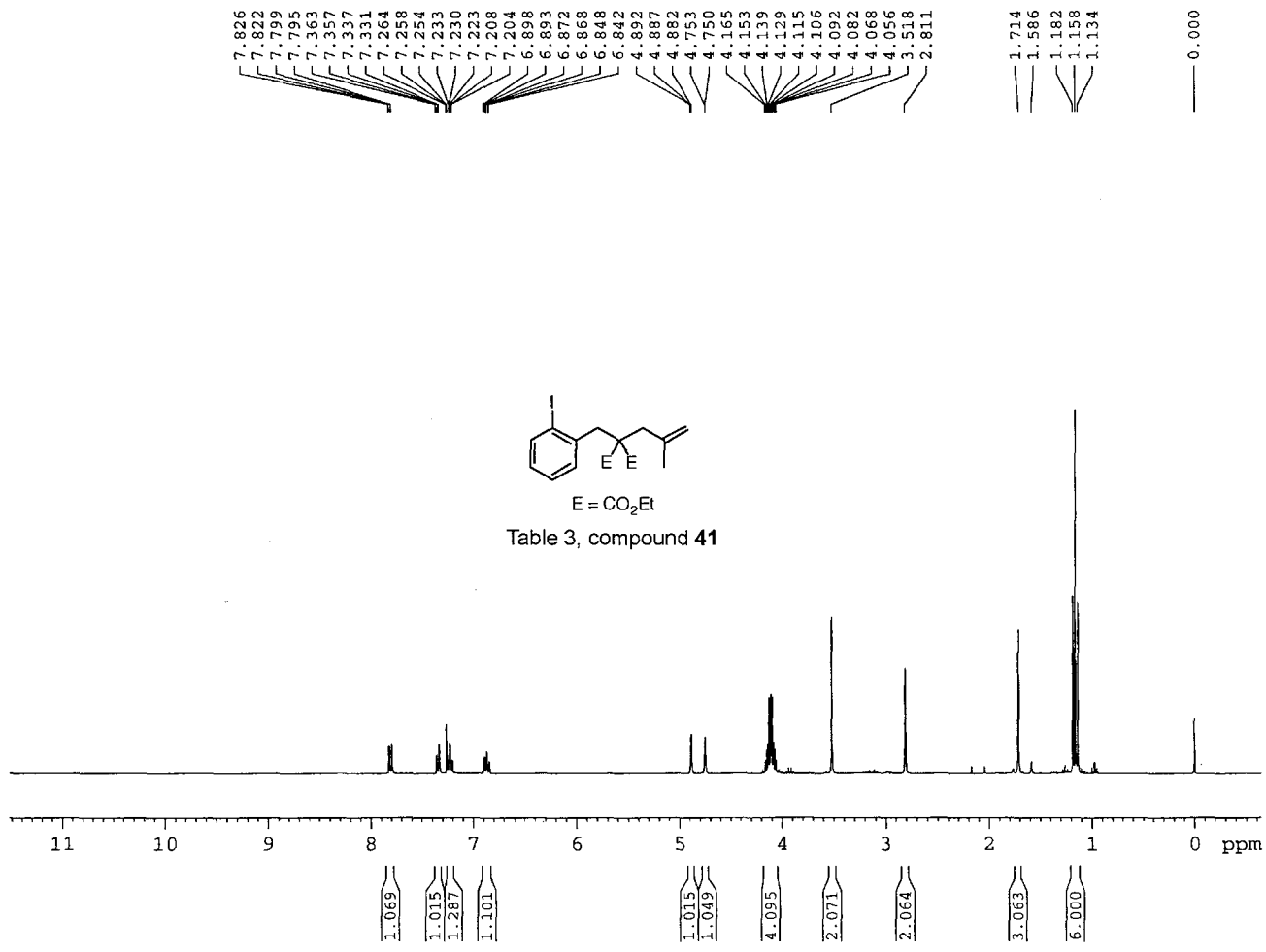
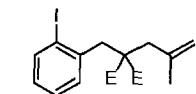


Table 3, compound 40



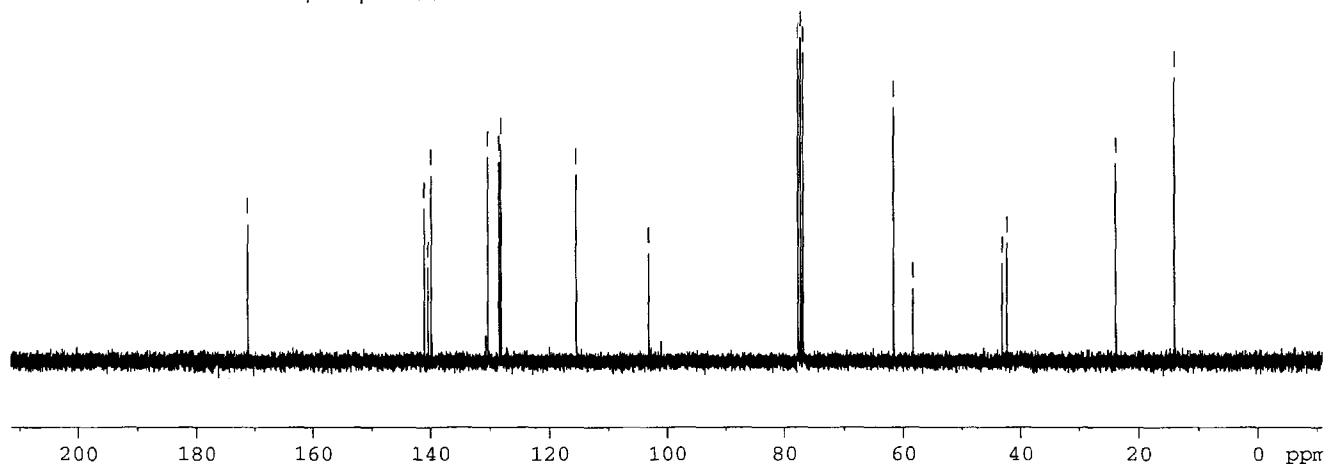






E = CO₂Et

Table 3, compound 41



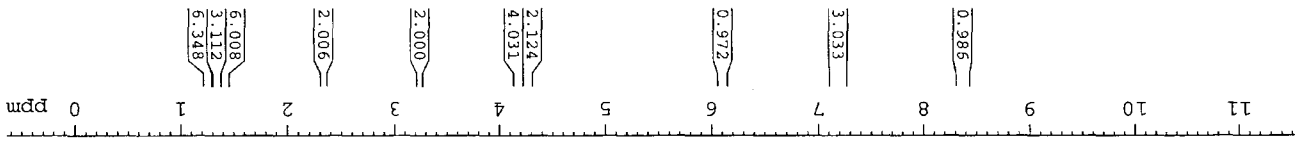
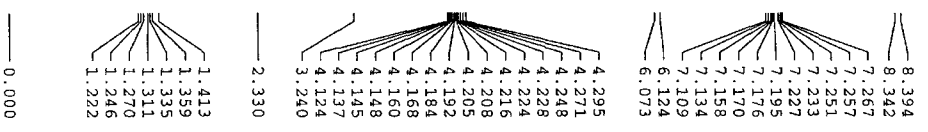
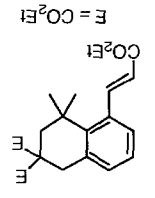
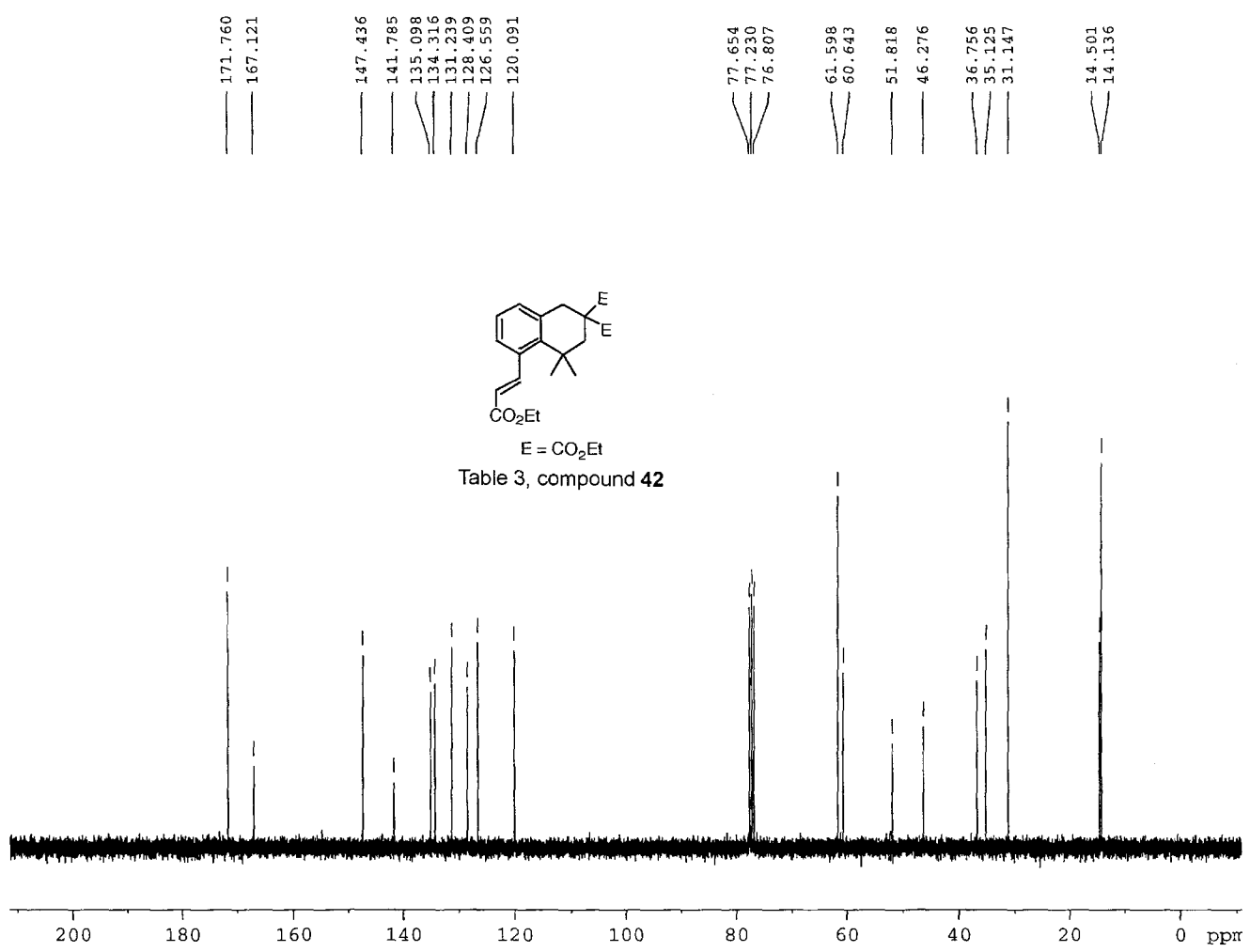


Table 3, compound 42





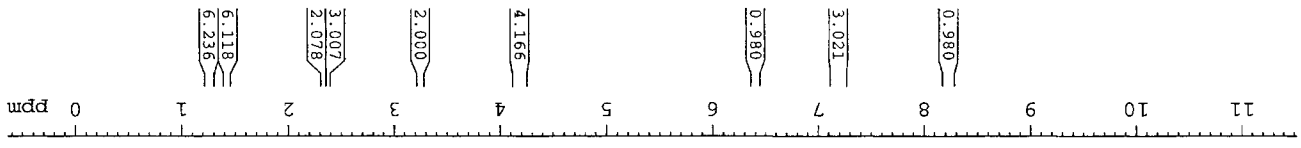
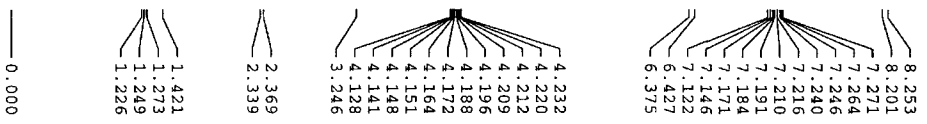
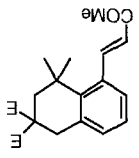
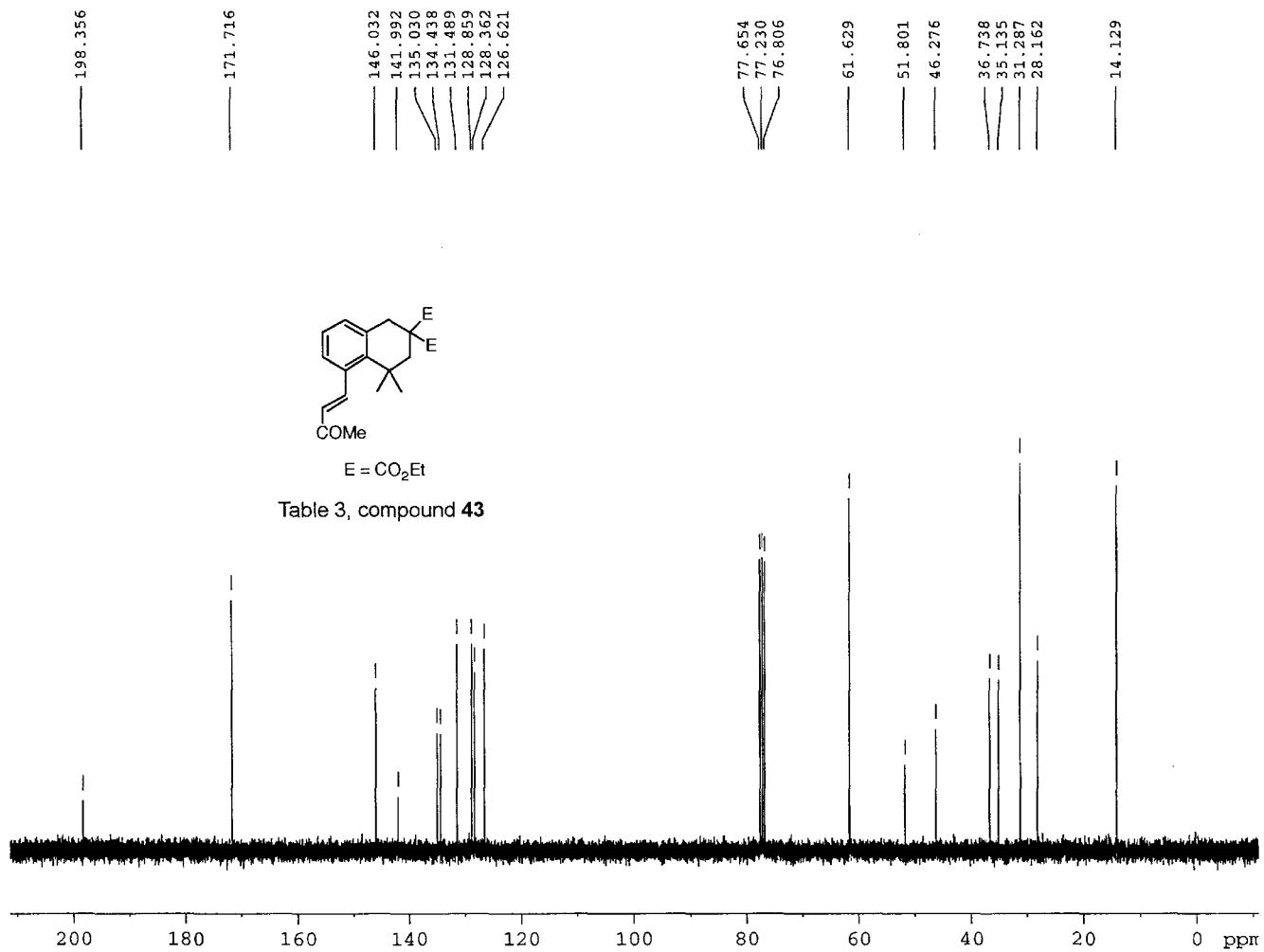


Table 3, compound 43





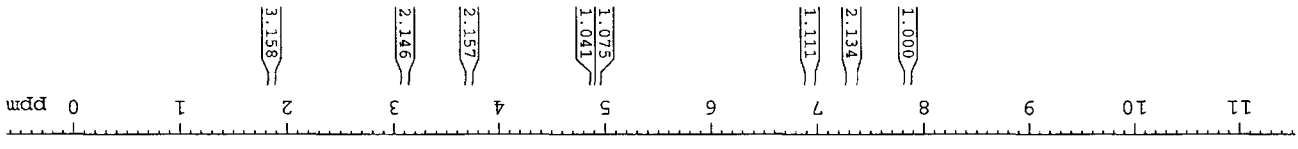
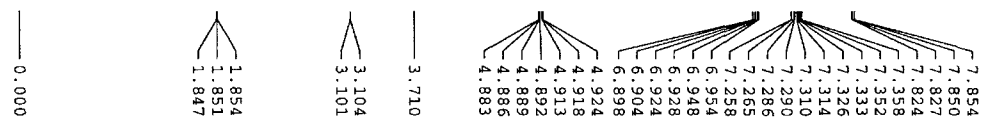
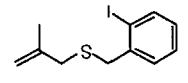


Table 3, compound 44



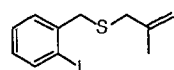
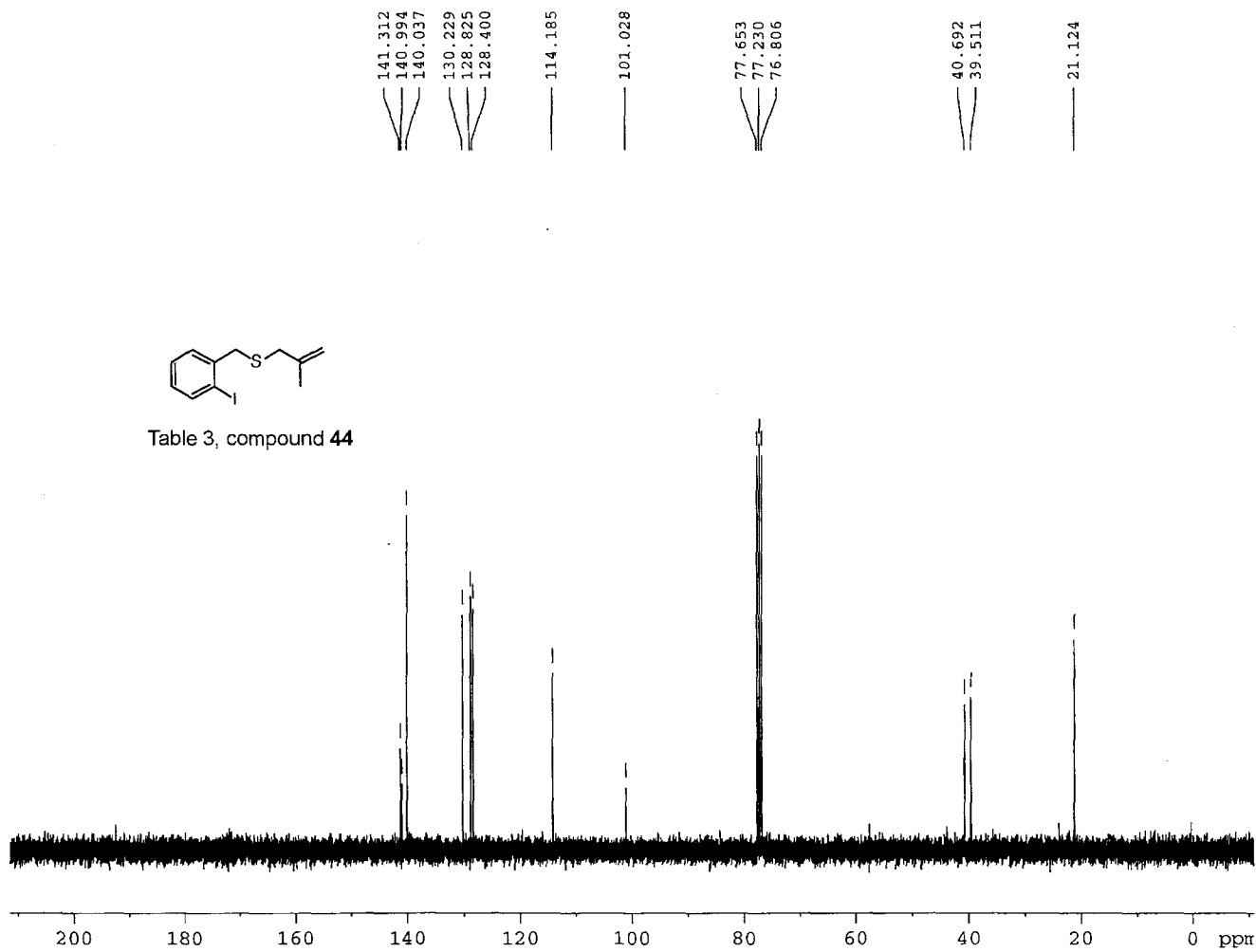


Table 3, compound 44



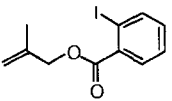
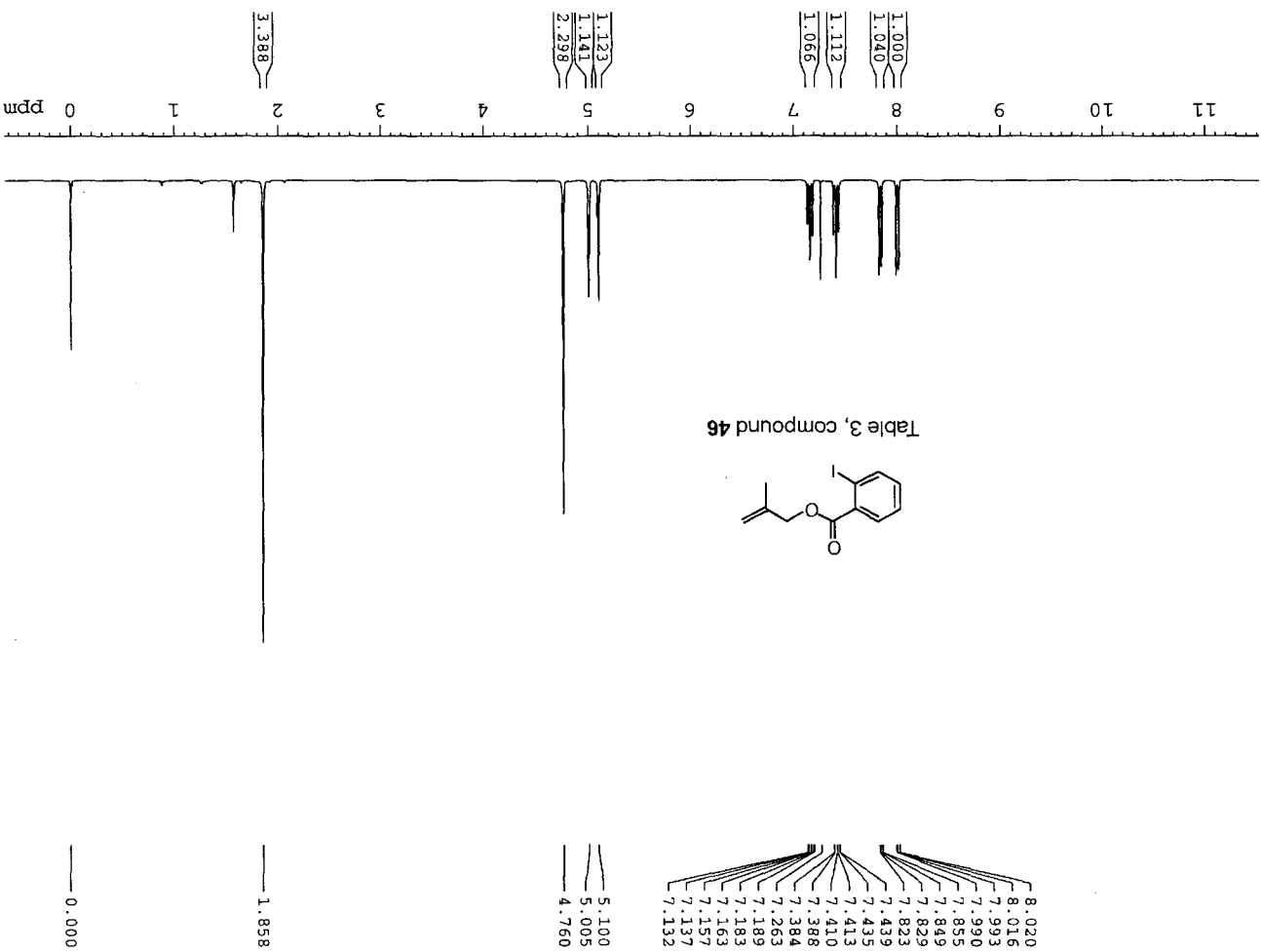


Table 3, compound 4b



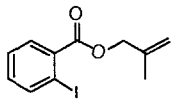
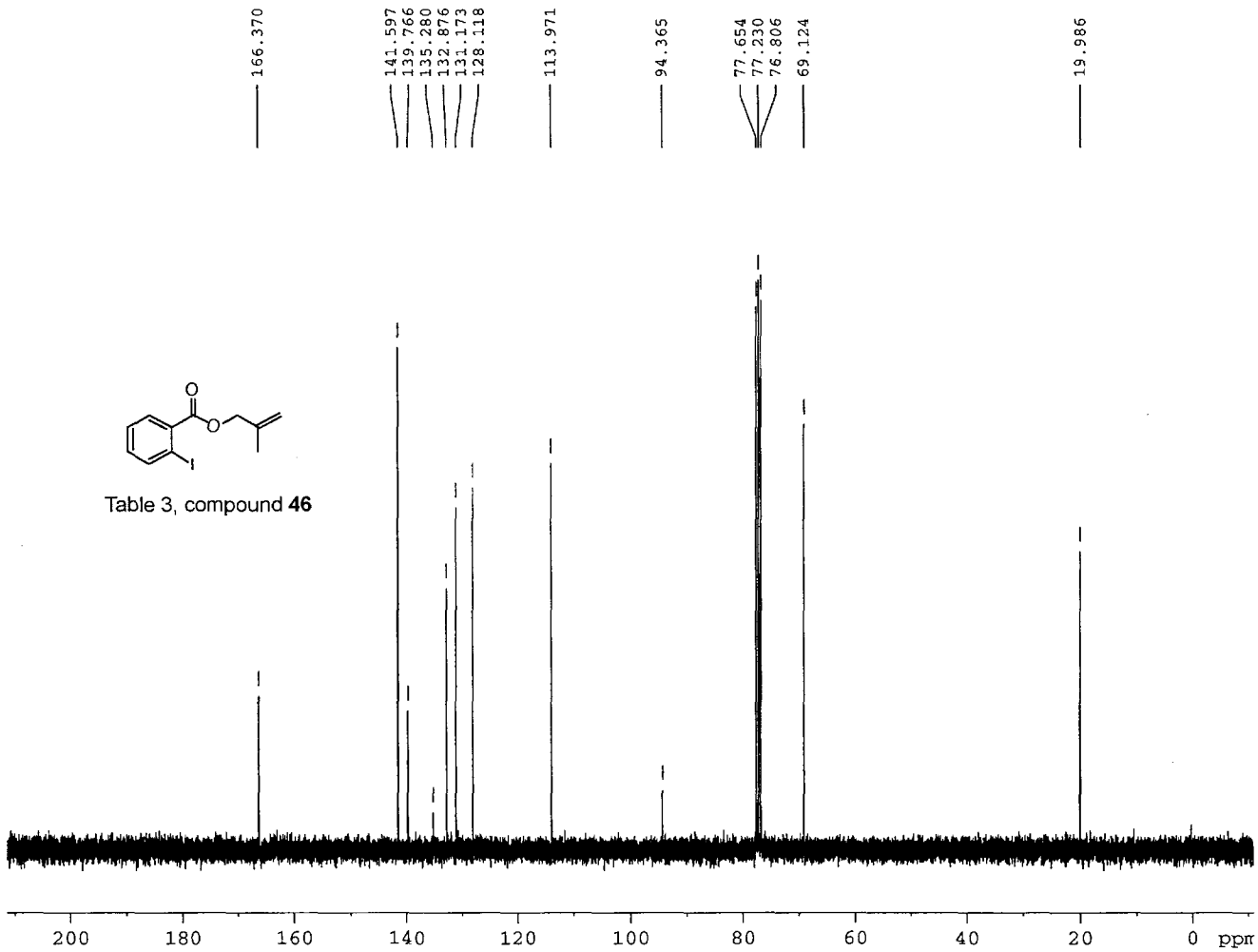


Table 3, compound 46



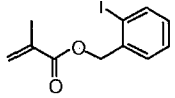
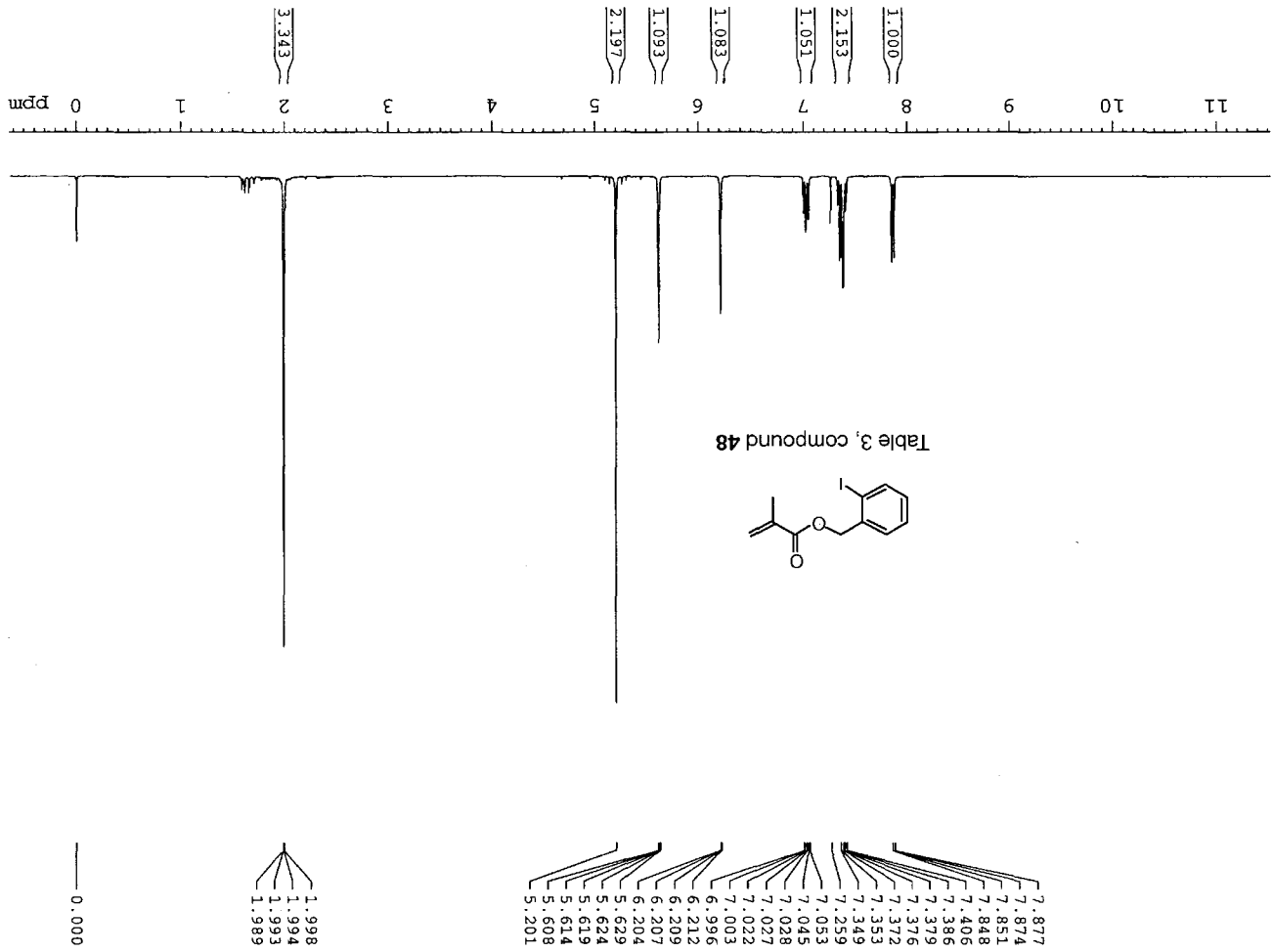


Table 3, compound 48



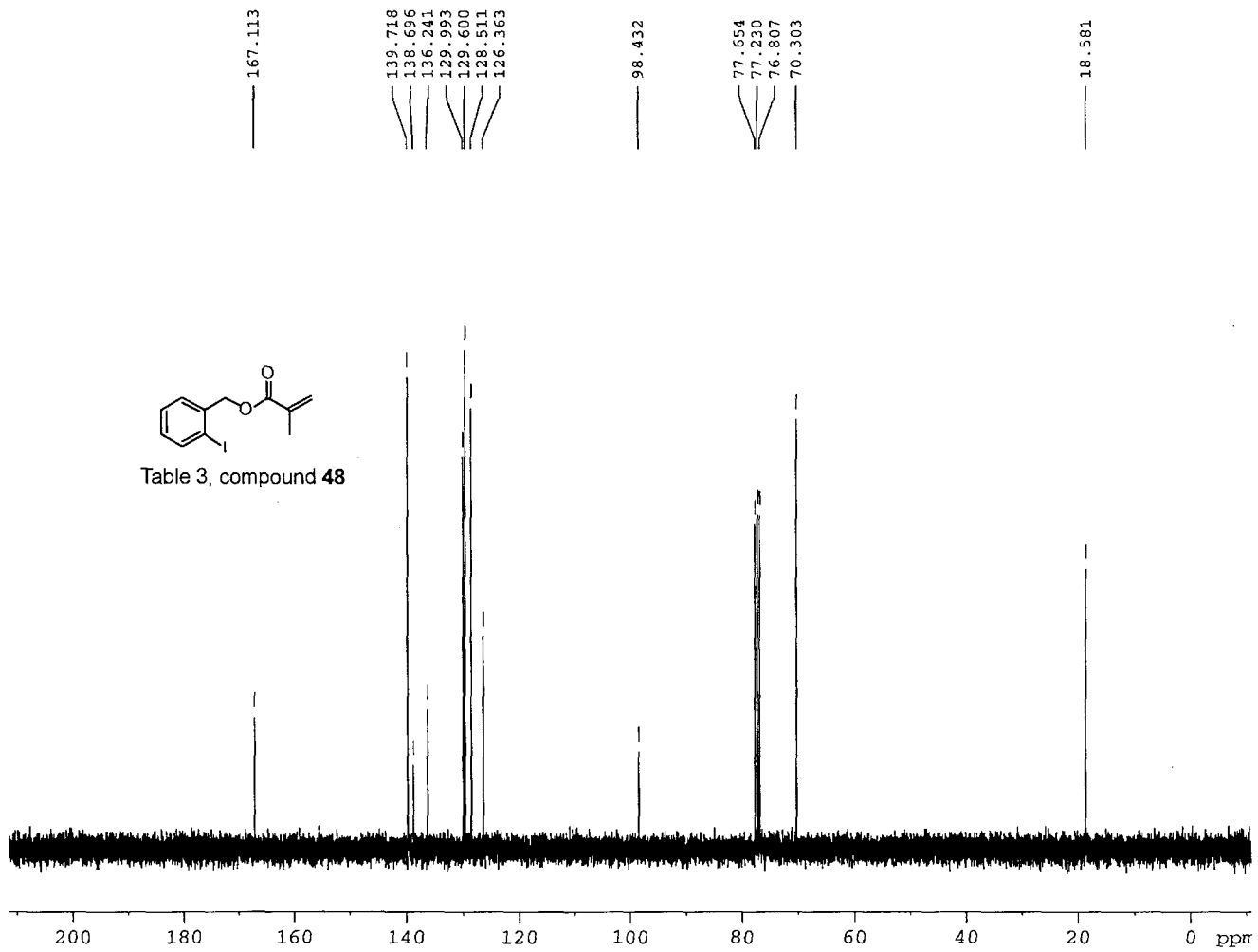
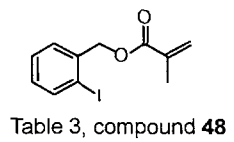
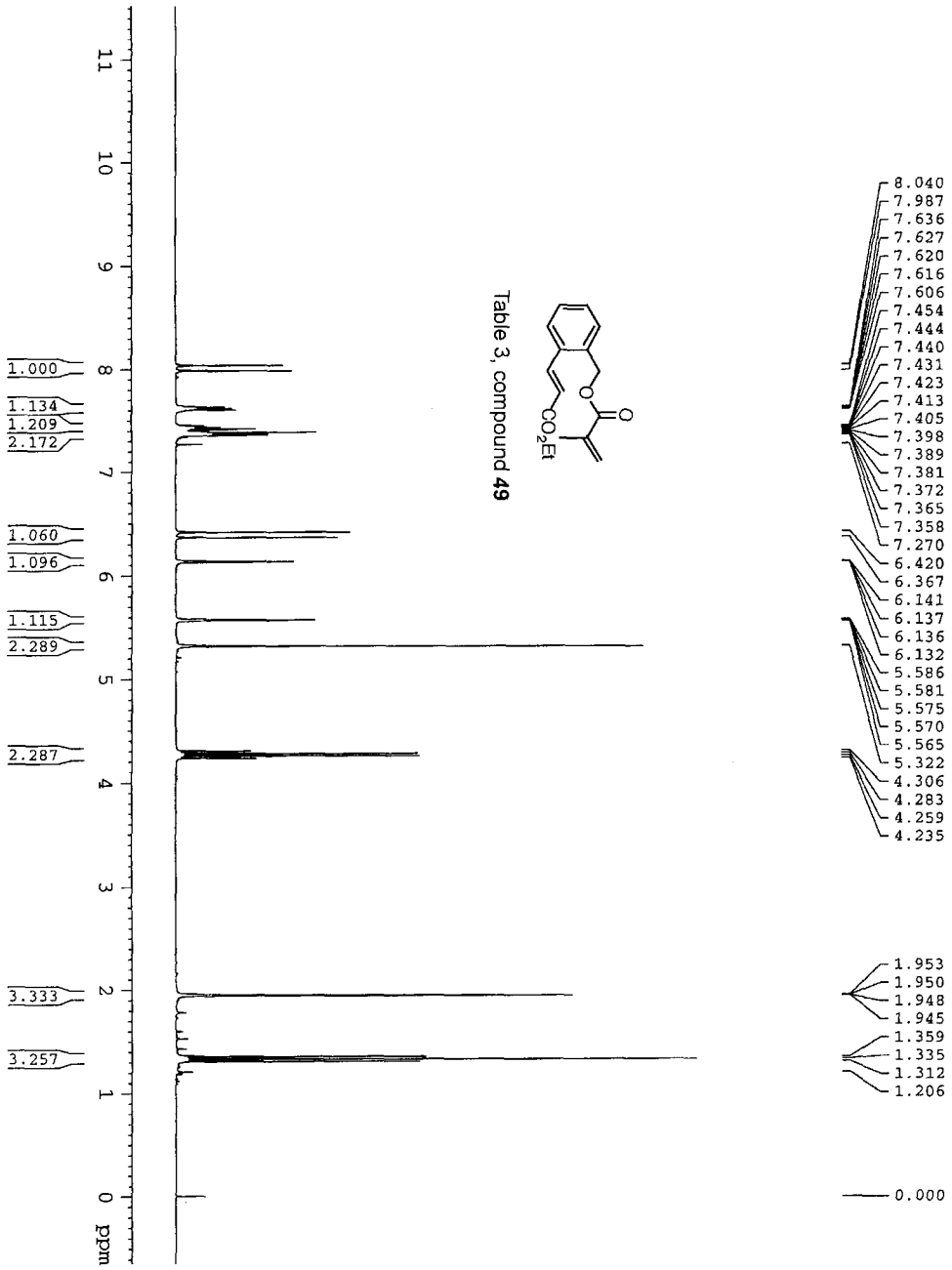
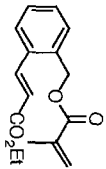


Table 3, compound 49



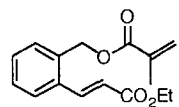
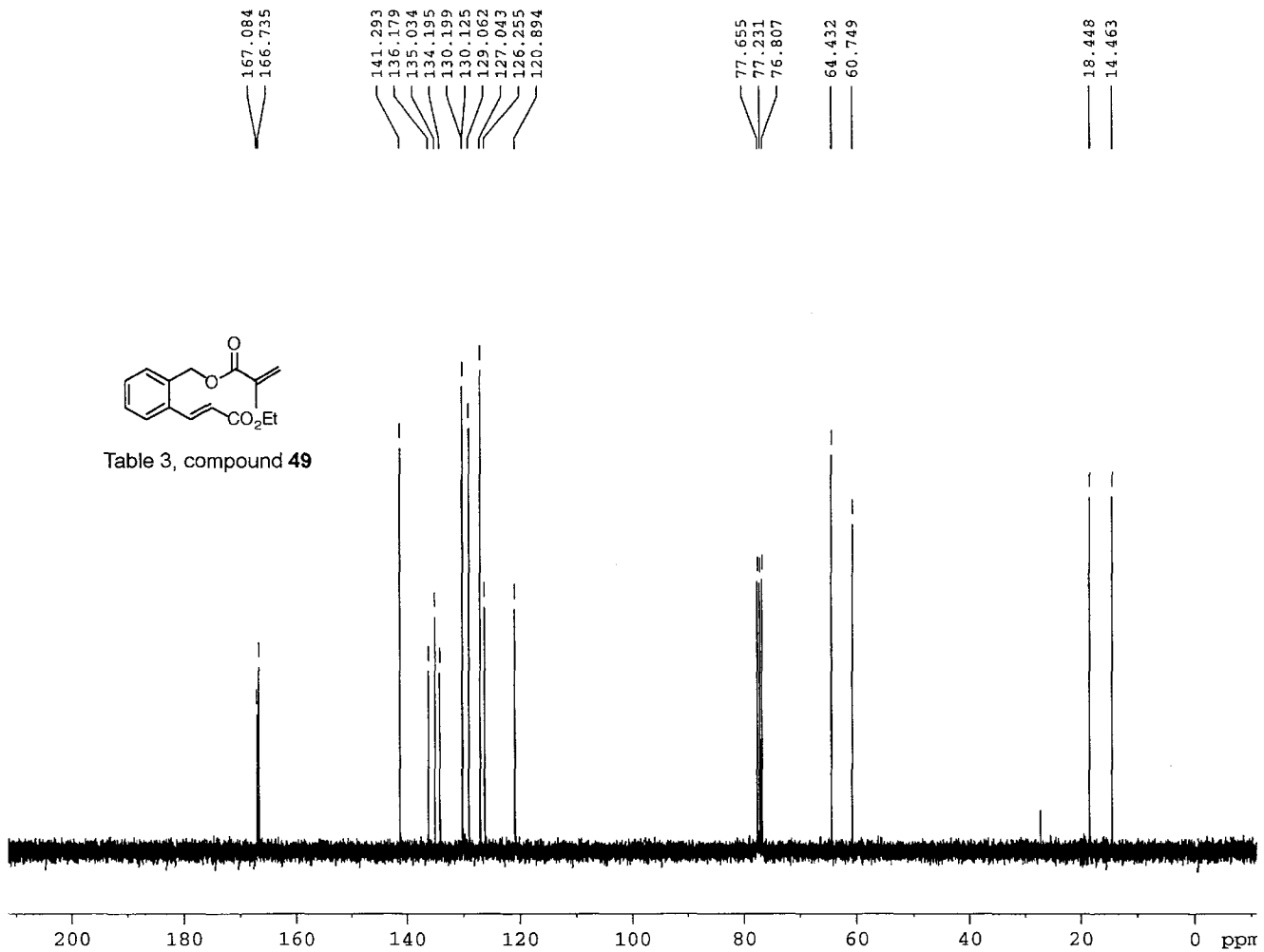
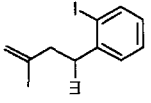


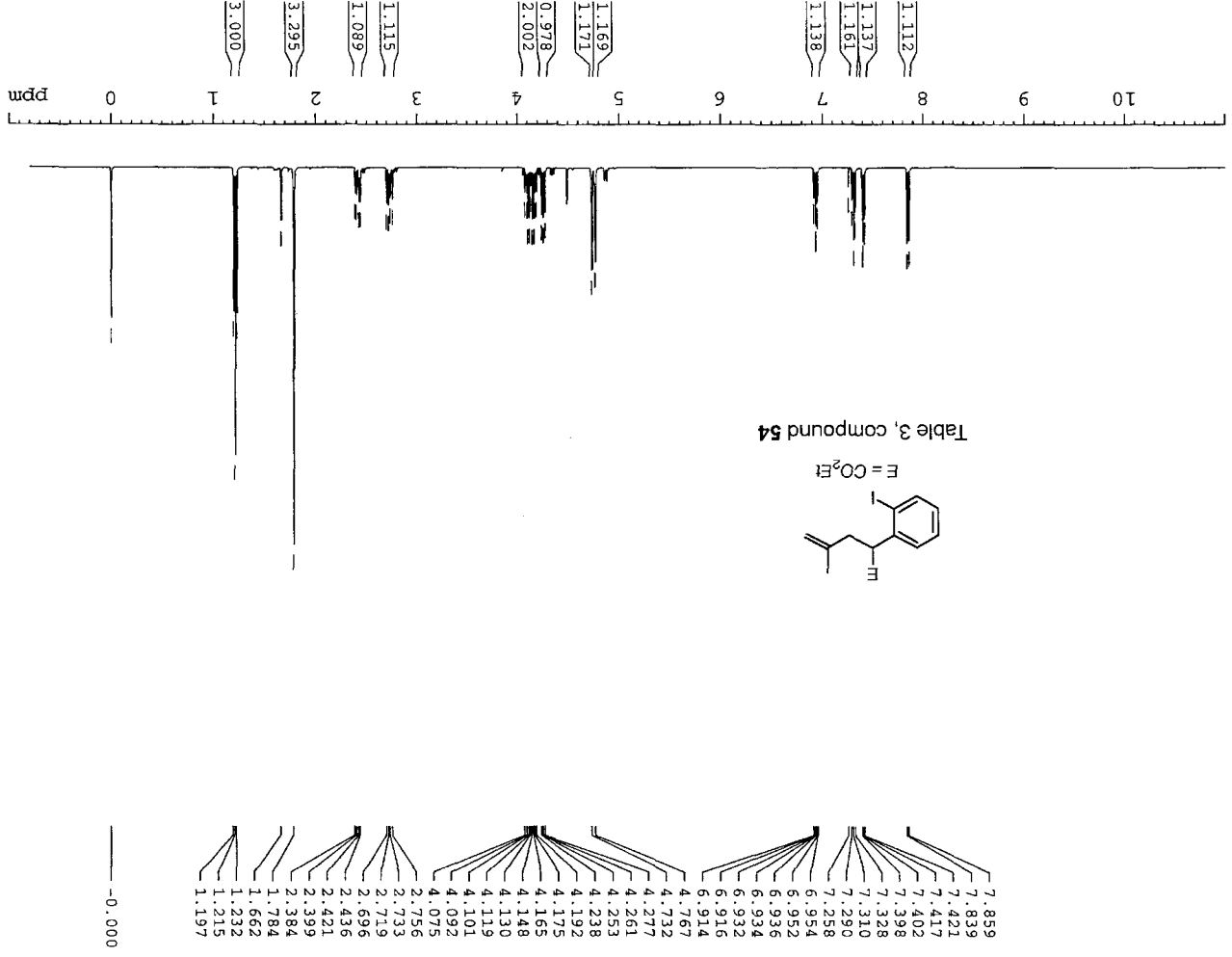
Table 3, compound 49

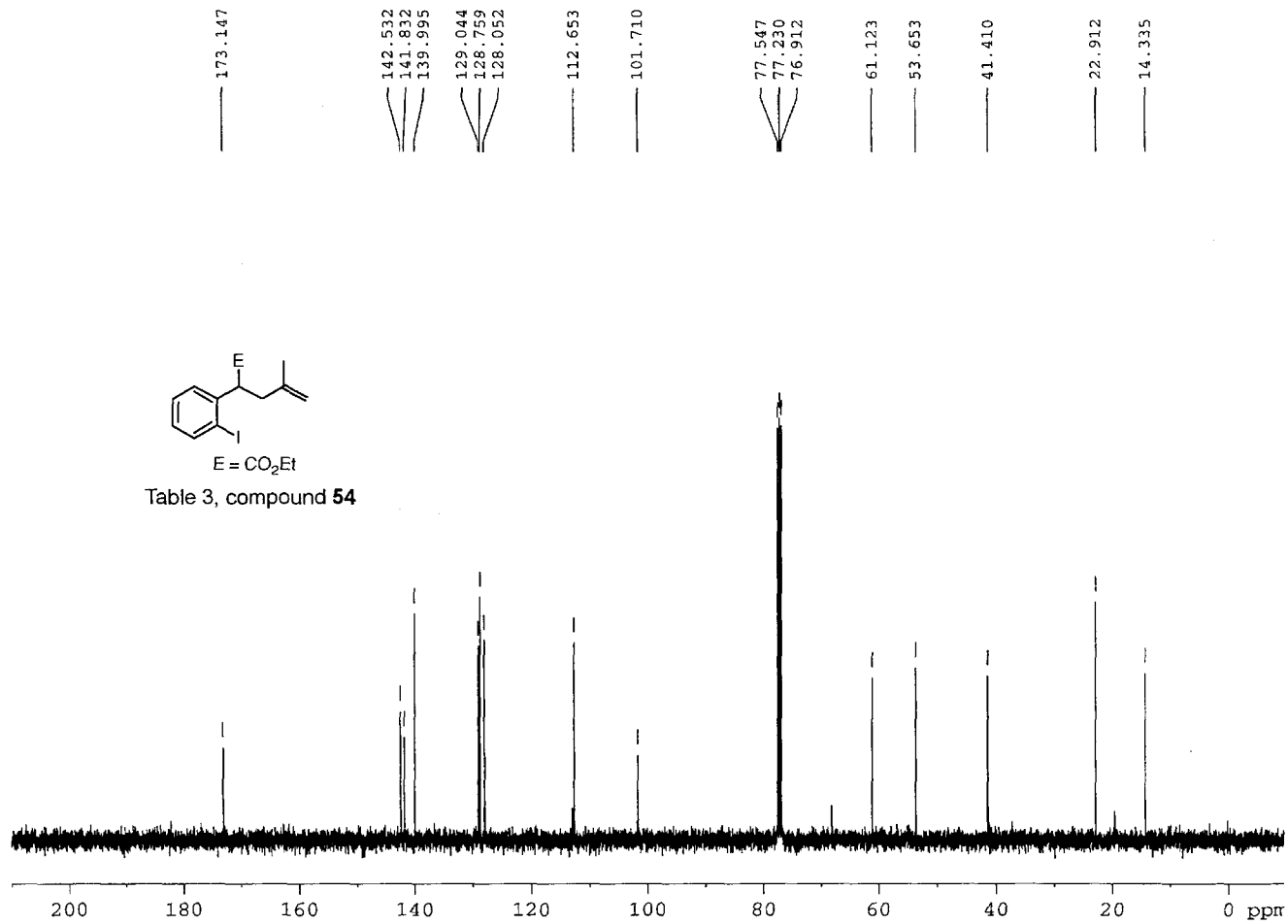


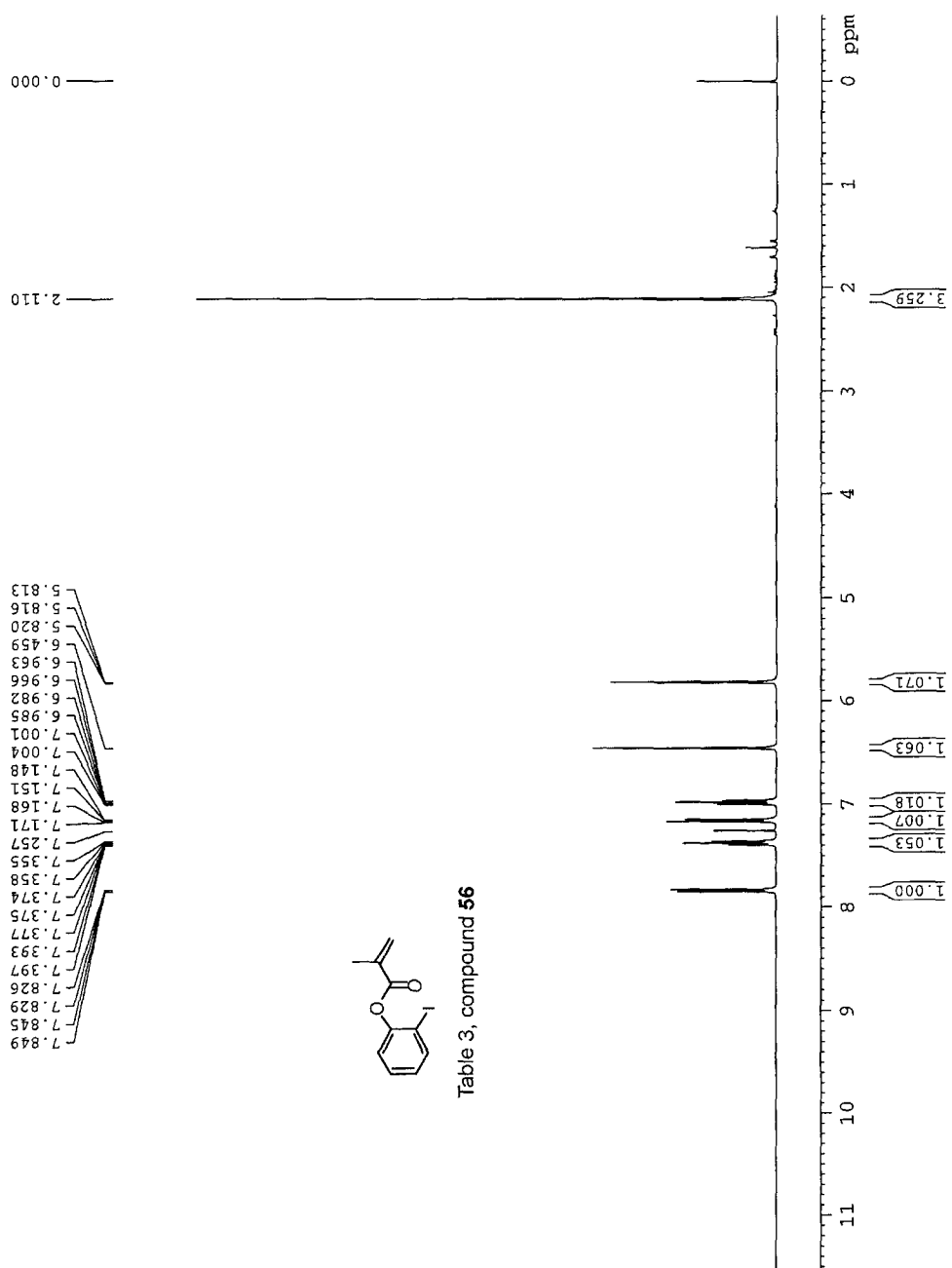


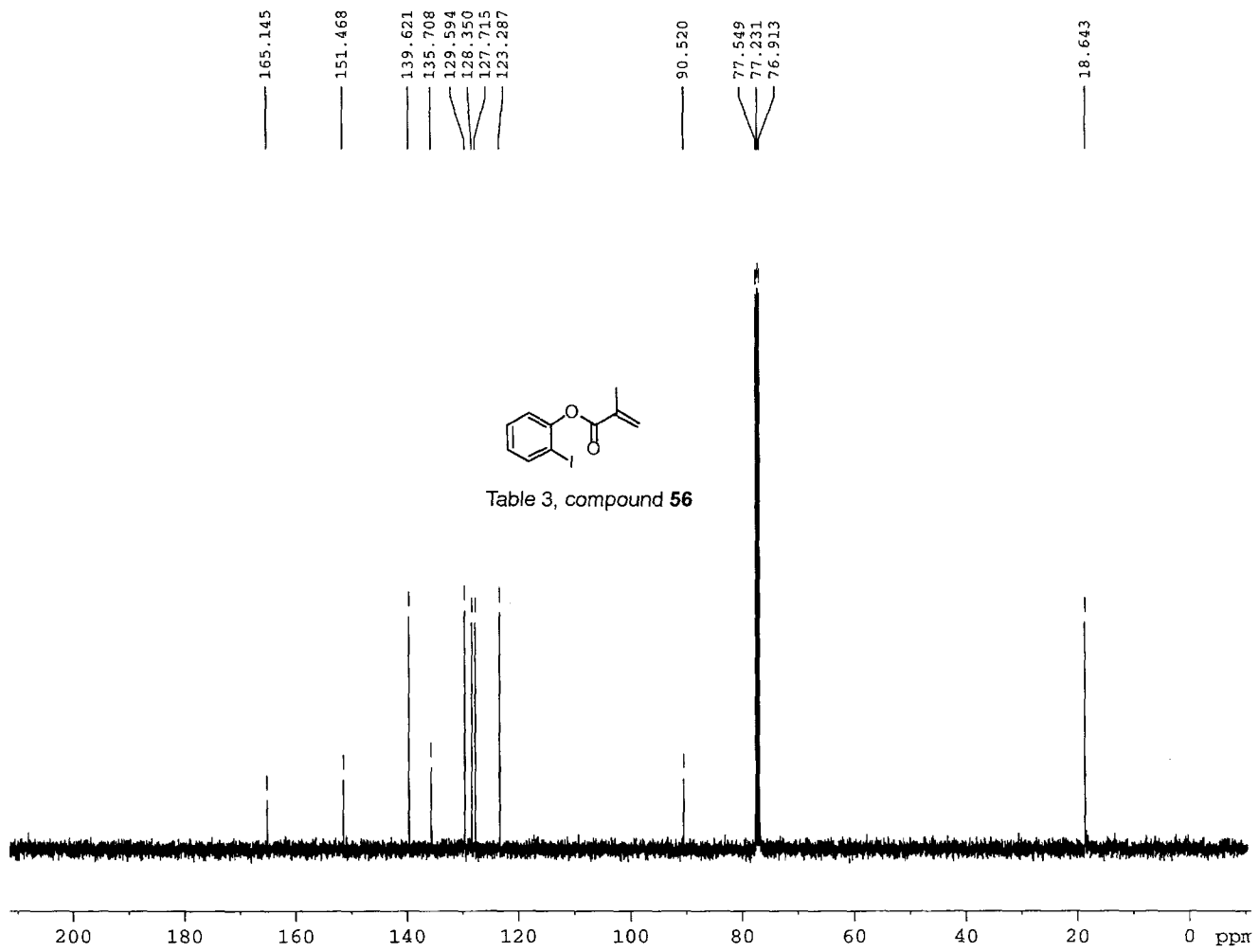
E = CO₂Et

Table 3, compound 54









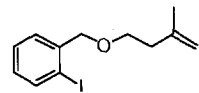
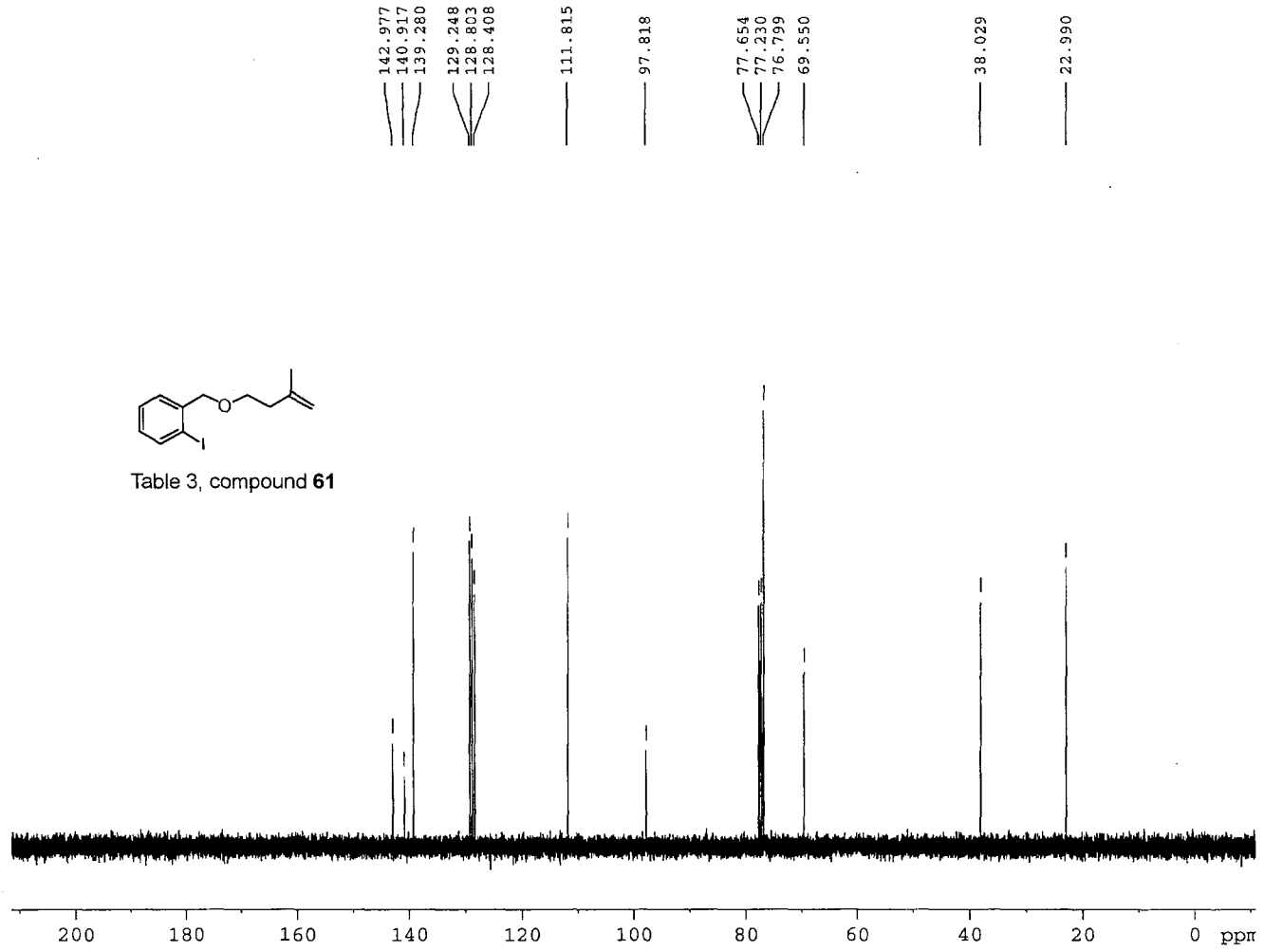
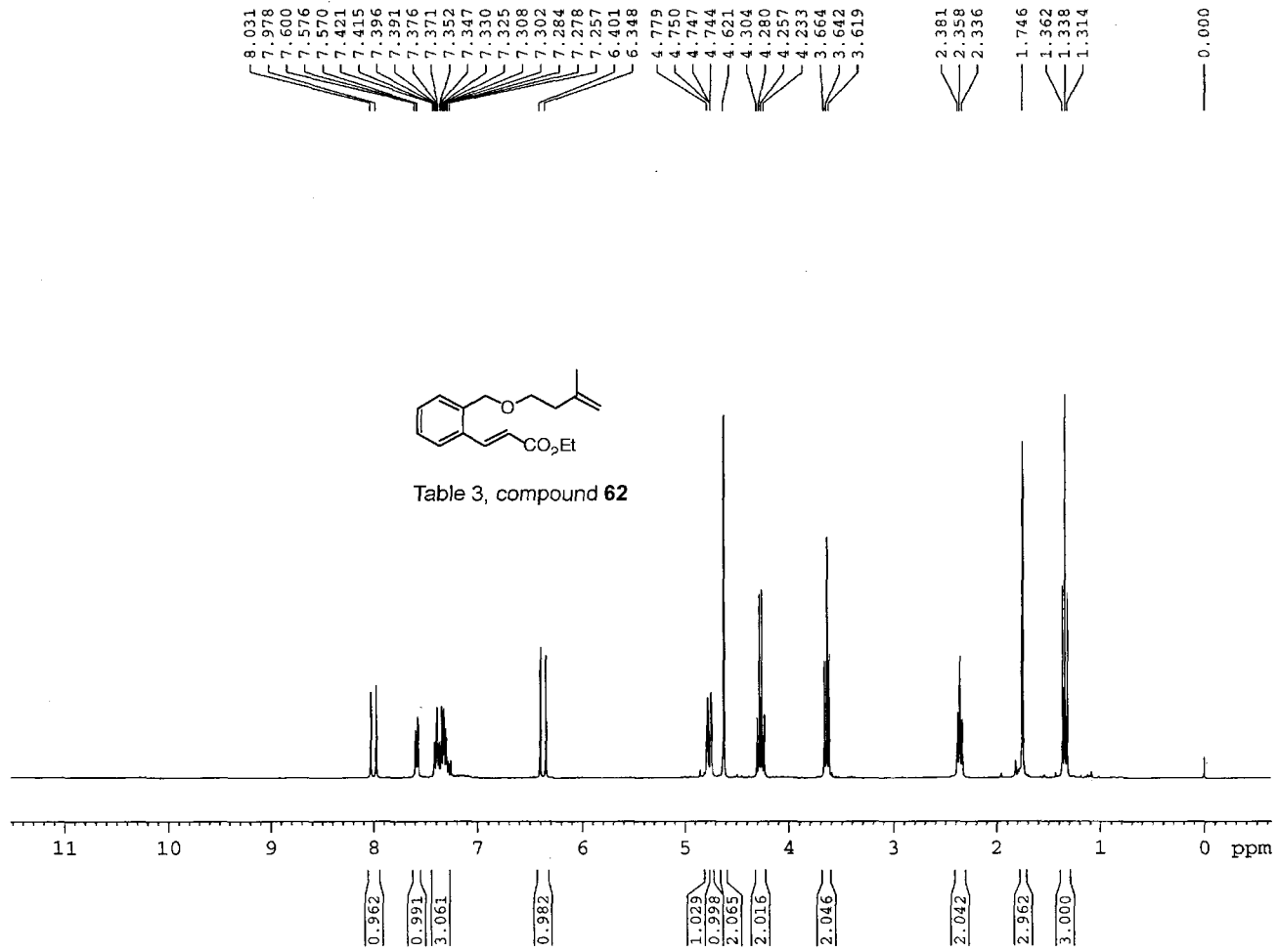


Table 3, compound **61**





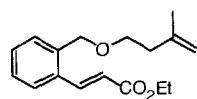
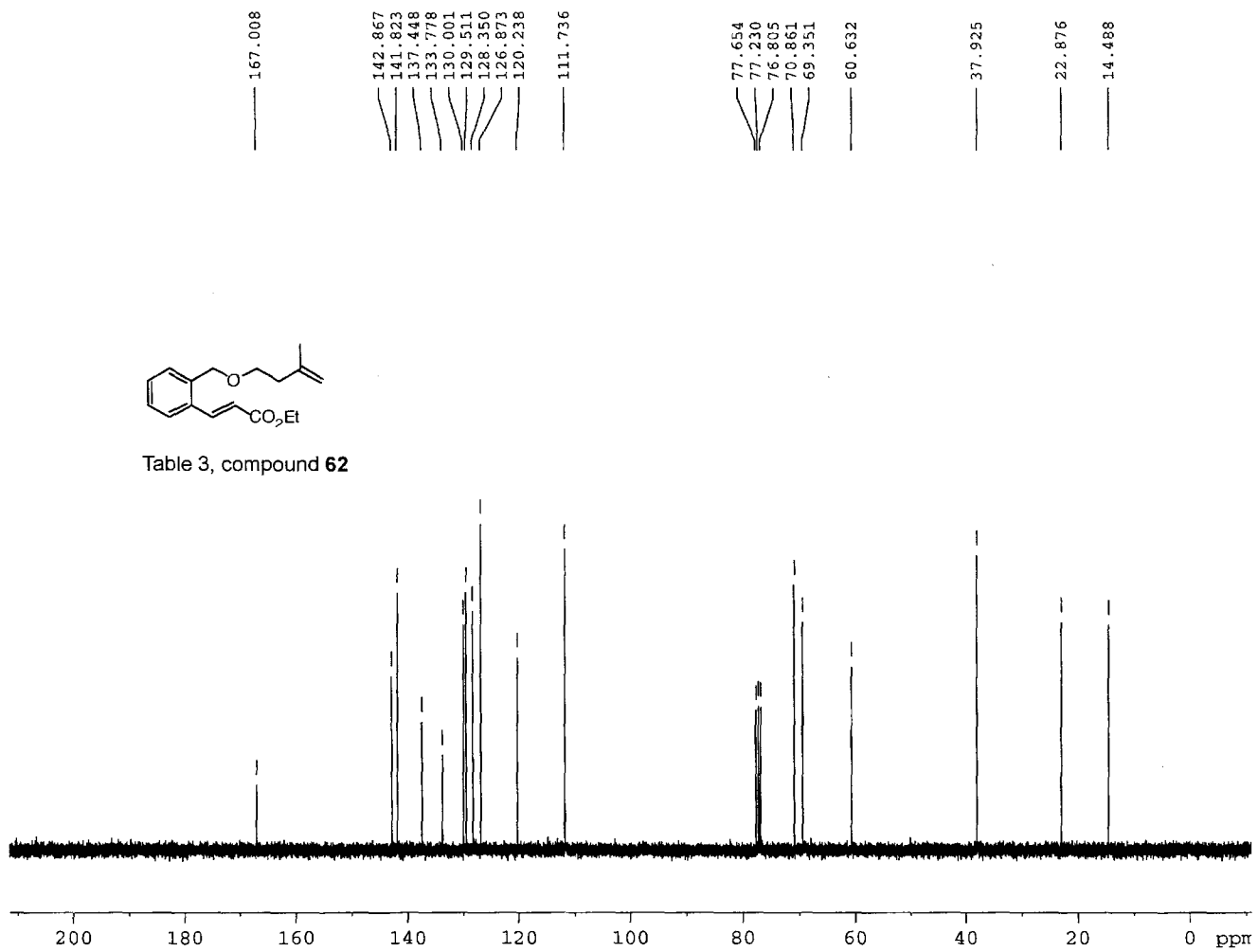


Table 3, compound 62



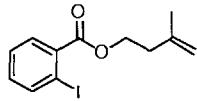
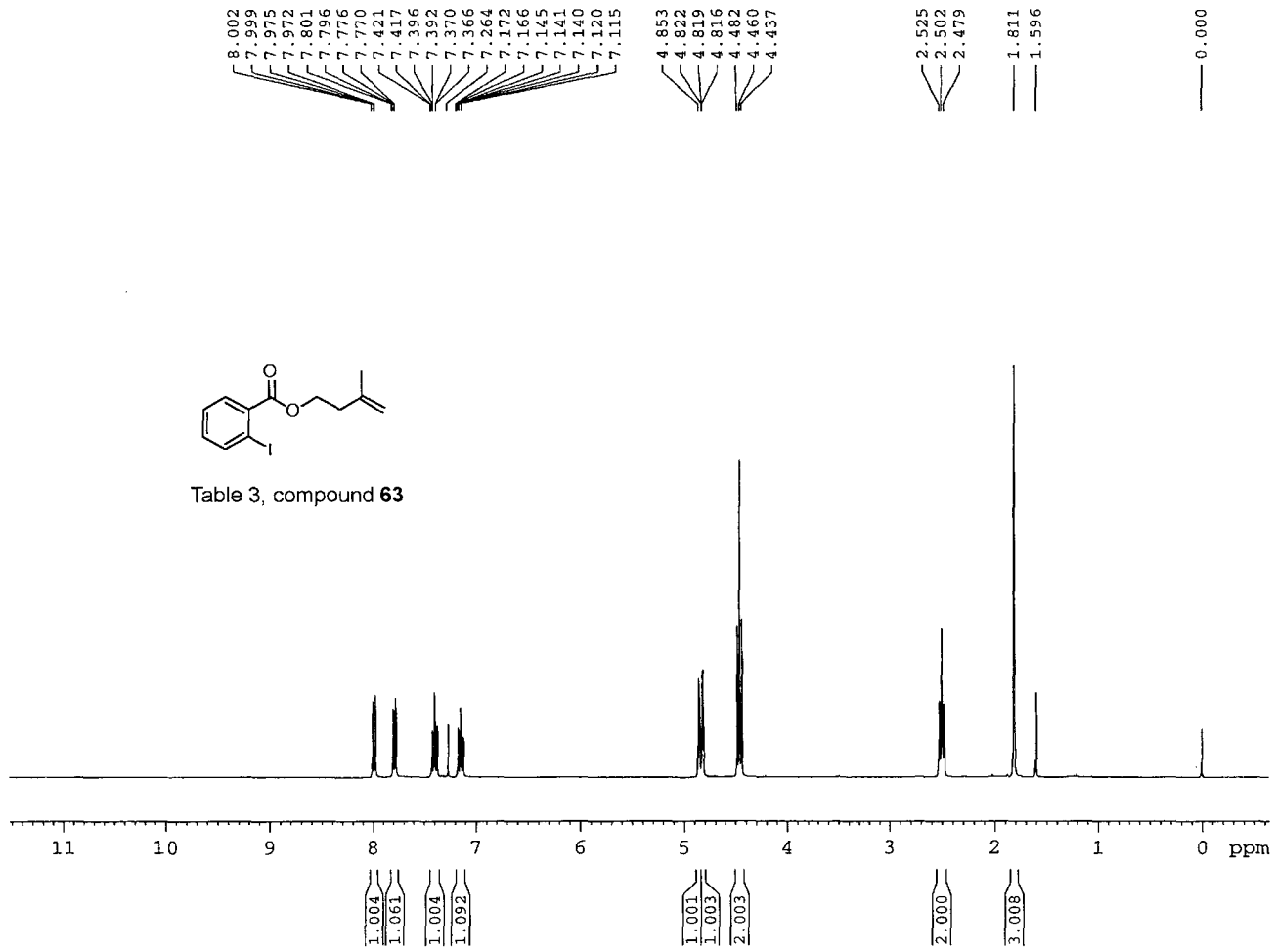


Table 3, compound **63**



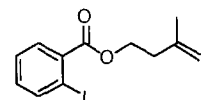
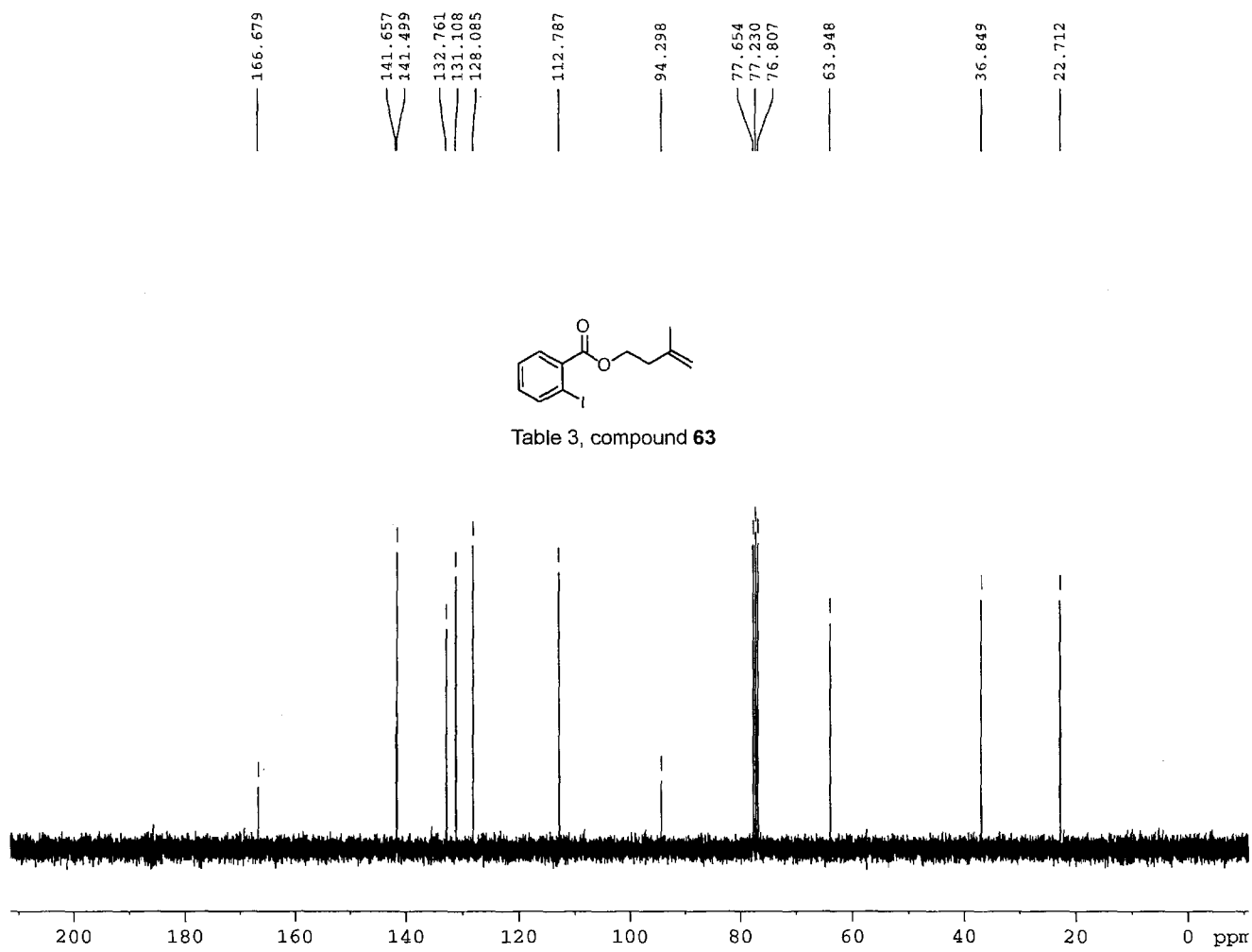
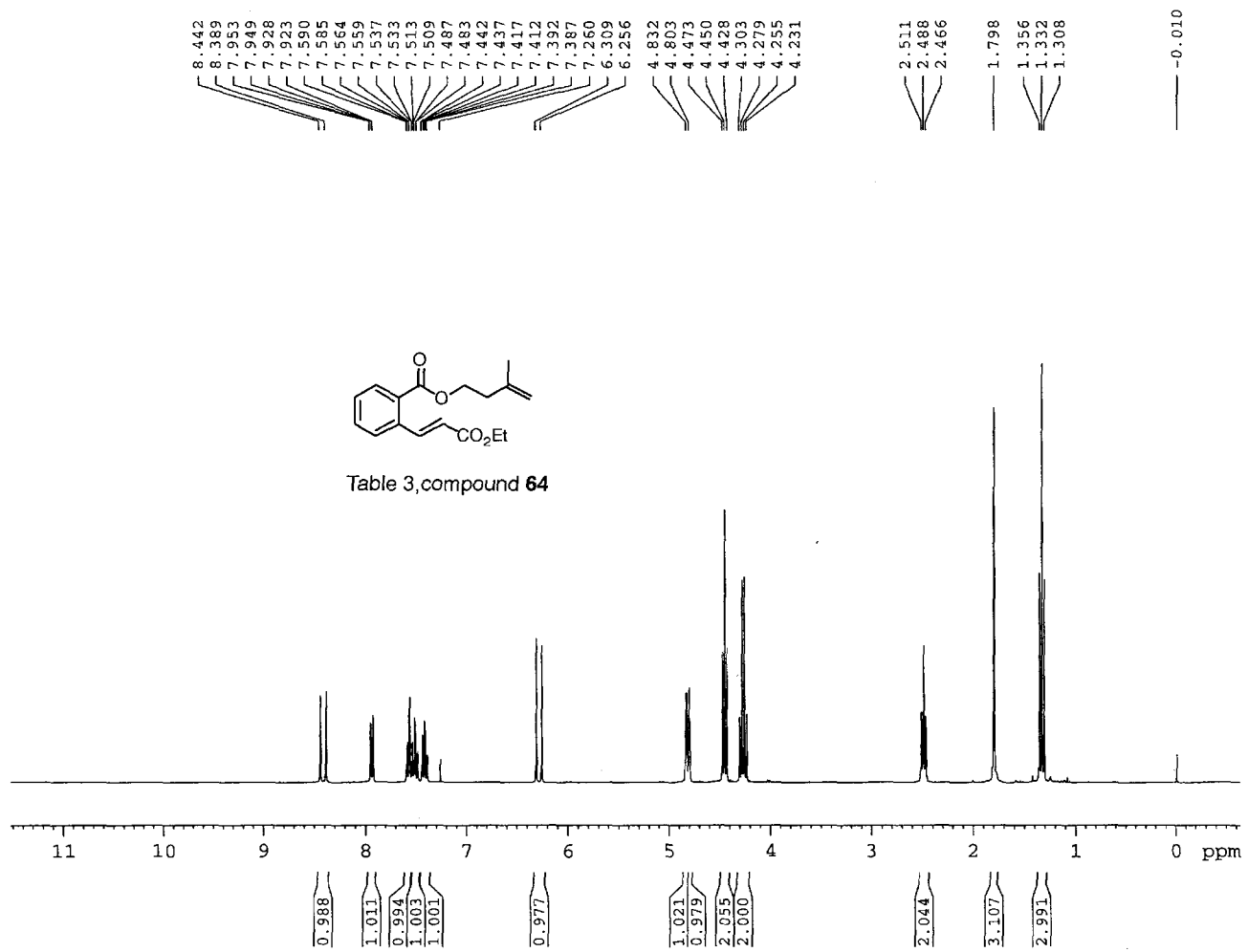


Table 3, compound 63



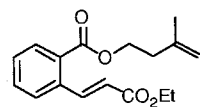
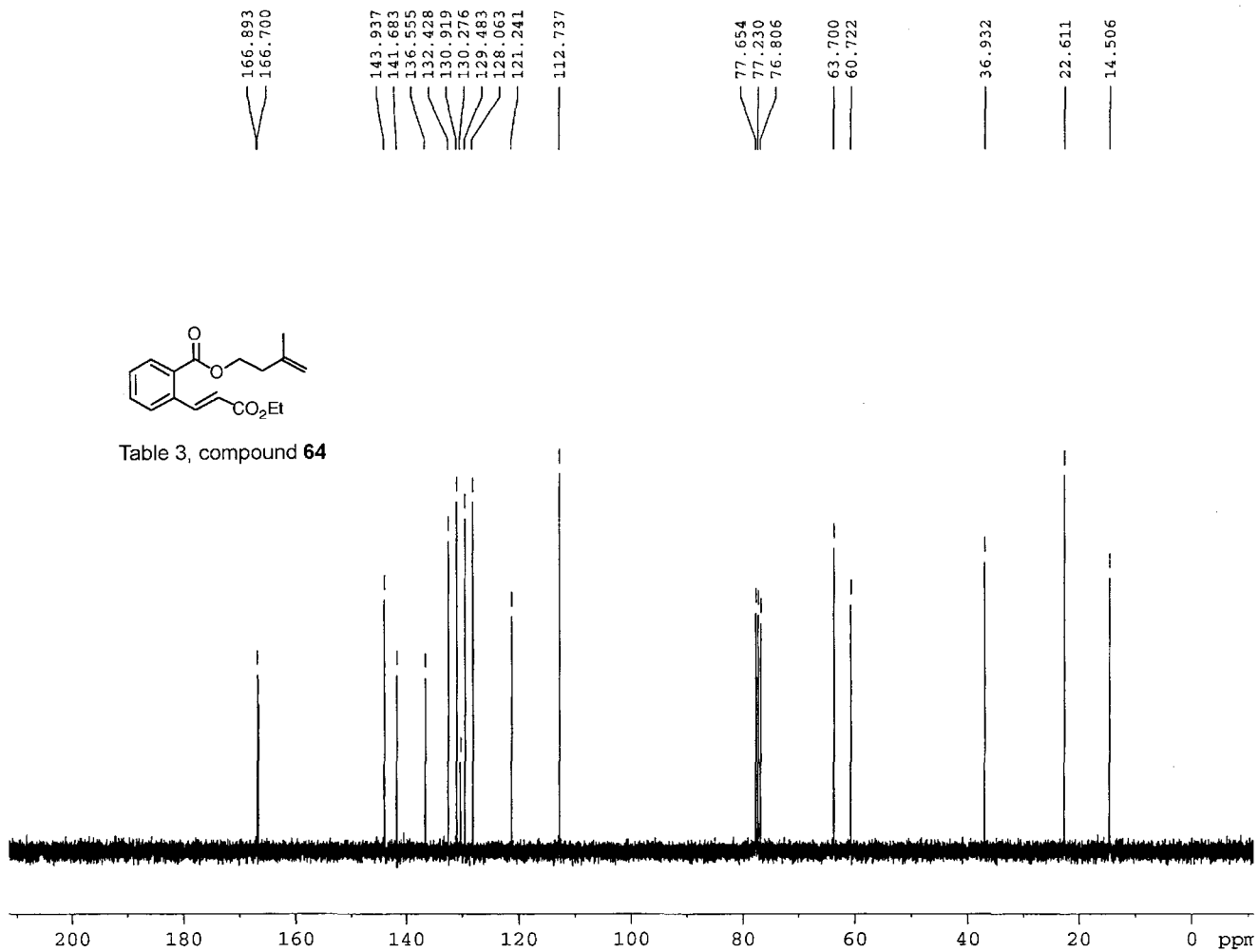


Table 3, compound **64**



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I want to take this opportunity to thank my major professor, Dr. Richard C. Larock, for his professional and personal guidance, his patience, his encouragement of creativity, his willingness to listen and help, and his financial and spiritual support throughout my years at Iowa State University.

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