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# Palladium-catalyzed approaches to carbo- and heterocyclic compounds

Steve Vencil Gagnier
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# Palladium-catalyzed approaches to carbo- and heterocyclic compounds

by

Steve Vencil Gagnier

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

DOCTOR OF PHILOSOPHY

Major: Organic Chemistry

Major Professor: Richard C. Larock

Iowa State University

Ames, Iowa

2001

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Major Professor

Signature was redacted for privacy.

For the Major Program

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For the Graduate College

To my wife Mary Kate, for her love, patience,

and encouragement. Thank you for believing in me.

# TABLE OF CONTENTS

## LIST OF ABBREVIATIONS

| | |
|---|---|
| aq | aqueous |
| br s | broad singlet |
| Bu | butyl |
| *t*-Bu | *tert*-butyl |
| cat. | catalytic |
| calcd | calculated |
| d | doublet |
| dba | dibenzylideneacetone |
| dd | doublet of doublets |
| ddd | doublet of doublets of doublets |
| DMA | *N,N*-dimethylacetamide |
| DMF | *N,N*-dimethylformamide |
| DMSO | dimethyl sulfoxide |
| DPPE | 1,2-bis(diphenylphosphino)ethane |
| DPPF | 1,1'-bis(diphenylphosphino)ferrocene |
| dq | doublet of quartets |
| dt | doublet of triplets |
| D$^t$BPF | (di-*tert*-butylphosphino)ferrocene |
| eq | equation |
| equiv | equivalent |
| Et | ethyl |

| | |
|---|---|
| h | hours |
| HRMS | high resolution mass spectrometry |
| Hz | Hertz |
| IR | infrared |
| m | multiplet |
| Me | methyl |
| mL | milliliters |
| mol | mole(s) |
| mp | melting point |
| NMR | nuclear magnetic resonance |
| *o* | ortho |
| Ph | phenyl |
| q | quartet |
| s | singlet |
| soln | solution |
| t | triplet |
| TBAC | tetra-*n*-butylammonium chloride |
| TBDMS | *t*-butyl(dimethyl)silyl |
| *tert* | tertiary |
| Tf | trifluoromethanesulfonyl |
| TMS | trimethylsilyl |
| tt | triplet of triplets |

# GENERAL INTRODUCTION

Palladium-catalyzed organic transformations have become indispensable for many common and state-of-the-art syntheses. In recent years, a variety of palladium-based methodologies have been developed which demonstrate palladium's ability to produce a wide range of carbo- and heterocycles. These reactions have proven to be general in scope and often react with a high degree of regio- and stereospecificity. Palladium catalysts have also been shown to be tolerant of functionality and are not generally moisture or air sensitive.

The Larock group has recently developed new palladium-catalyzed annulations onto alkenes, dienes, and alkynes which have proven to be efficient routes to many different carbo- and heterocyclic systems. This dissertation serves to expand the scope and synthetic utility of earlier methodologies and is organized into four different papers that are suitable for publication. The author of this dissertation was the primary investigator and author of each of the papers reported in this thesis.

## Dissertation Organization

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

Chapter 1 is a publication that describes the synthesis of α-alkylidene-γ-butyrolactones by the palladium-catalyzed heteroannulation of acyclic and cyclic

1,3-dienes by α-iodo and α-bromo acrylic acids. This process has proven to be highly regio- and stereoselective. Annulation predominately occurs at the less hindered end of the diene, and with acyclic dienes the *E*-isomer is the major product. The success of this process is dependent upon the use of the sterically hindered, electron-rich phosphine ligand D$^t$BPF.

Chapter 2 presents the synthesis of indanones and 2-cyclopentenones via the palladium-catalyzed carbonylative cyclization of unsaturated aryl iodides and dienyl triflates, iodides, and bromides. This cyclization is particularly effective on substrates that contain a terminal olefin. It is likely that this palladium transformation forms an indenone intermediate, which is coordinated to a palladium hydride species. This palladium hydride then adds back across the carbon-carbon double bond to form a palladium enolate, which is protonated by $H_2O$.

Chapter 3 examines the synthesis of quinolines through a palladium-catalyzed iminoannulation of internal alkynes. In order to achieve a quinoline product, this annulation process needs to proceed through a 6-endo ring closure. However, this process is in competition with the more favorable 5-exo ring closure, which leads to an isoindole system. While the yields and generality for the synthesis of quinolines are only moderate, the optimization results have proven to be interesting from a mechanistic point of view.

Chapter 4 concerns the synthesis of α,β-unsaturated ketones from the corresponding enol silyl ethers using a catalytic palladium(II) strategy. This

palladium(II) procedure is performed using catalytic amounts of $Pd(OAc)_2$ in DMSO at room temperature and uses $O_2$ as an efficient reoxidant.

Finally, all of the $^1H$ and $^{13}C$ NMR spectra for the starting materials and the palladium-catalyzed reaction products have been compiled in appendices A-D following the general conclusions for this dissertation.

# CHAPTER 1. PALLADIUM-CATALYZED HETEROANNULATION OF 1,3-DIENES TO FORM α-ALKYLIDENE-γ-BUTYROLACTONES

A paper submitted to the *Journal of Organic Chemistry*

Steve V. Gagnier and Richard C. Larock*

*Department of Chemistry, Iowa State University, Ames, Iowa 50010*

## Abstract

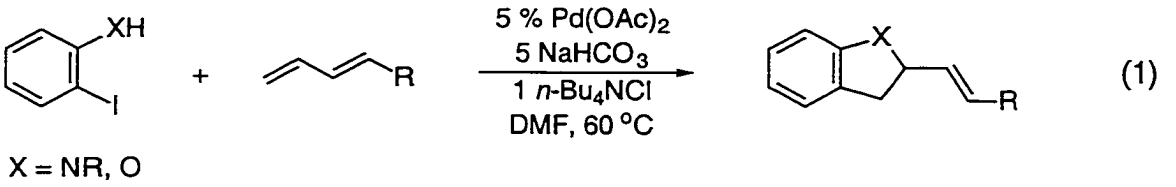
α-Alkylidene-γ-butyrolactones are readily prepared by the palladium-catalyzed heteroannulation of a variety of 1,3-dienes by α-iodo and α-bromo acrylic acids. The best results are obtained by employing a catalytic amount of the sterically hindered chelating alkyl phosphine D$^t$BPF [(di-*tert*-butylphosphino)-ferrocene]. In most cases, this process is highly regioselective. The reaction is believed to proceed via (1) oxidative addition of the vinylic halide to Pd(0), (2) organopalladium addition to the less hindered end of the 1,3-diene to form a π-allylpalladium intermediate, and (3) nucleophilic displacement of the palladium by the carboxylate ion.

## Introduction

The synthesis of α-methylene-γ-lactone derivatives has been of great interest due to their biological activity and occurrence in numerous natural

products.[1-3] Several of these compounds display antiinflammatory activity, as well as prostaglandin synthetase inhibitory activity.[2] Past progress in the synthesis of these heterocycles has involved multi-step procedures,[4,5] which in some cases involves preparing the γ-lactone first, before transforming it into the corresponding α-methylene- or α-alkylidene-γ-lactone.[6-8]

Recently, it has been shown that palladium is an efficient catalyst for the heteroannulation of 1,3-dienes (eq 1).[9-11] This process proceeds through a π-




(1)

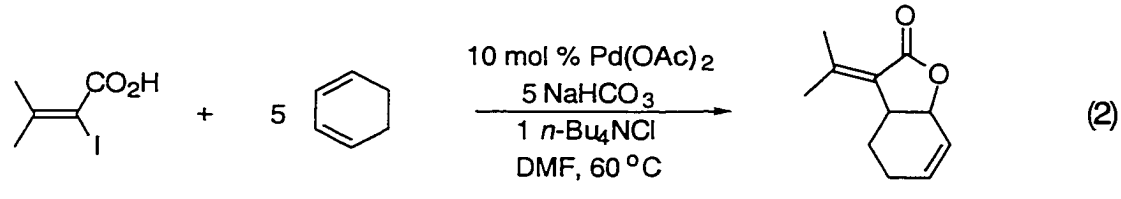
allylpalladium intermediate, which is formed by the addition of an arylpalladium complex to the 1,3-diene. This π-allylpalladium intermediate closes to the five-membered ring by internal nucleophilic attack on the π-allyl system. It has been observed, however, that these palladium conditions are ineffective for annulation with α-iodo or α-bromo acrylic acids. Possible problems with this system are the low reactivity of these vinylic halides towards oxidative addition and the possibility that the vinylpalladium species may coordinate too strongly with the neighboring carboxylate. This coordination could deactivate the vinylpalladium intermediate towards diene addition.

In congruence with our effort to prepare α-alkylidene-γ-butyrolactones through a palladium-catalyzed heteroannulation of 1,3-dienes by α-iodo and α-

bromo acrylic acids, an Indian group published a communication which reported a few examples of this type of annulation, which resulted in modest to poor yields.[12] It is not clear form this work what reaction conditions were actually utilized or whether catalytic amounts of palladium were even employed. In this paper, we report reaction conditions under which the palladium-catalyzed regioselective heteroannulation of 1,3-dienes by α-iodo and α-bromo acrylic acids provides α-alkylidene-γ-butyrolactones in good yields. The major advantages that our system offers over recently reported results are improved yields and the use of catalytic amounts of palladium.

## Results and Discussion

Our initial work was aimed at developing a set of palladium conditions which would work well for a variety of substrates in the production of α-alkylidene-γ-butyrolactones. The original reaction conditions examined for this system included $Pd(OAc)_2$ (0.05 mmol), vinylic halide (0.5 mmol), diene (2.5 mmol), $NaHCO_3$ (2.5 mmol), *n*-$Bu_4NCl$ (0.5 mmol), DMF (2 mL) as the solvent, a 60 °C reaction temperature, and a 3 day reaction time (eq 2). Unfortunately, these conditions only produced the desired γ-lactones in modest yields (30-40%). Further optimization




(2)

was carried out focusing on the use of various phosphine ligands. Triphenylphosphine was explored first, because of its commercial availability and success in other organopalladium transformations (entry 1, Table 1). However, this ligand, as well as some bidentate derivatives (entries 2-4), did not appear to improve the reaction significantly. Recently, there have been reports of the use of more hindered, electron-rich phosphine ligands, such as P(*t*-Bu)$_3$,[13] PCy$_3$,[14] 2-(dicyclohexylphosphino)biphenyl (**1**),[15,16] 2-(di-*t*-butylphosphino)biphenyl (**2**),[15,16] D$^t$BPF [(di-*tert*-butylphosphino)ferrocene], and bis(di-*tert*-butylphosphino)ferrocene,[17,18] activating aryl chlorides in palladium-catalyzed processes. When P(*t*-Bu)$_3$ was employed in our system, there was no evidence of the desired lactone

**Table 1. Effect of Phosphine Ligands**[a]

| entry | ligand | time (h) | % yield |
|---|---|---|---|
| 1 | 20 mol % $PPh_3$ | 72 | 31 |
| 2 | 10 mol % DPPE | 72 | 5 |
| 3 | 10 mol % DPPF | 24 | 20 |
| 4 | 20 mol % DPPF | 24 | 46 |
| 5 | 20 mol % P(*t*-Bu)$_3$ | 72 | 0 |
| 6 | 20 mol % **1** | 24 | 50 |
| 7 | 20 mol % **2** | 24 | 53 |
| 8 | 20 mol % D$^t$BPF | 24 | 70 |

[a]The reaction conditions are the same as those in eq 2.

(entry 5). However, since P(*t*-Bu)$_3$ is highly reactive towards oxygen, it is possible that the ligand could have been oxidized to the corresponding phosphine oxide along the way. Ligands **1** and **2** did show improvements in the reaction time and product yield (entries 6 and 7). However, the yields still remained modest, near 50%. Hartwig et al. have shown that mono- and di-phosphine substituted ferrocene derivatives accelerate the arylation of ketones and malonates with bromo- and chloroarenes as effectively as P(*t*-Bu)$_3$.[17,18] Therefore, D$^t$BPF was prepared by the monolithiation of ferrocene, followed by quenching with ClP(*t*-Bu)$_2$.[19] This ligand is less oxygen sensitive and can easily be handled in the presence of air for fairly long periods of time. When 20 mol % of D$^t$BPF was added to the previously optimized palladium conditions for the synthesis of α-alkylidene-γ-butyrolactones, the yields were increased greatly and the reaction times were reduced to 24 h (entry 8). The ligand D$^t$BPF offers two advantages. First, because alkylphosphines bind more strongly to palladium than arylphosphines, the electron density at the metal center is increased, which may accelerate the reaction rate. Second, this sterically hindered ligand may help break up any unwanted coordination of the vinylpalladium species and the neighboring carboxylic acid. Therefore, our best present reaction conditions for the preparation of α-alkylidene-γ-butyrolactones are found in equation 2, with the addition of 20 mol % D$^t$BPF.

Upon examining the heteroannulation of a variety of 1,3-dienes under our optimized conditions (Table 2), it was found that the best results were obtained using acyclic dienes, bearing a monosubstituted terminal double bond (entries 2-6, 19, 20, and 22). This can be explained by steric arguments and the ability of the

**Table 2. Synthesis of α-Alkylidene-γ-butyrolactones[a]**

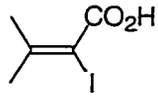
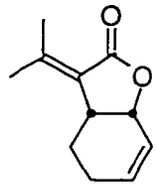
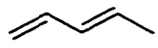
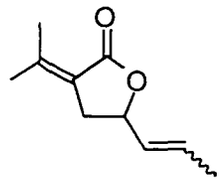
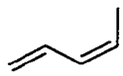
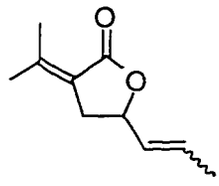
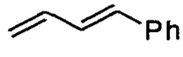
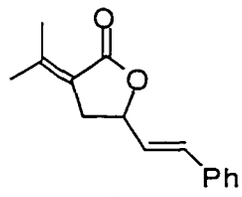
| entry | carboxylic acid | diene | product(s) | % yield |
|---|---|---|---|---|
| 1 |  **3** |  |  **4** | 70 |
| 2 | |  |  **5** (9:1 *E/Z*) | 96 |
| 3 | |  |  **5** (9:1 *E/Z*) | 99 |
| 4 | |  |  **6** | 74 |

**Table 2. (continued)**

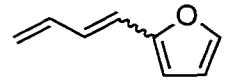
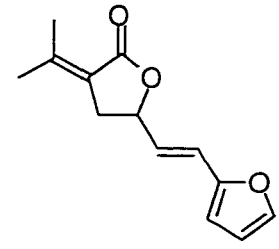
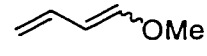
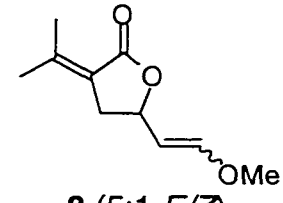
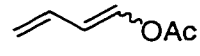
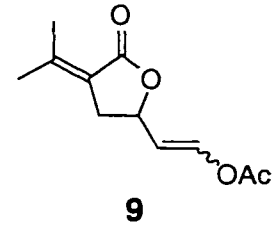
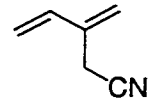
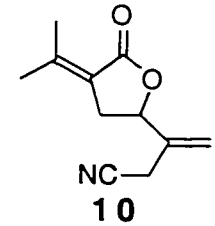
| entry | carboxylic acid | diene | product(s) | % yield |
|---|---|---|---|---|
| 5 | |  1:1 *E/Z* |  **7** | 73 |
| 6 | |  3:1 *E/Z* |  **8** (5:1 *E/Z*) | 74 |
| 7 | |  3:1 *E/Z* |  **9** | 0 |
| 8 | |  |  **10** | 0 |

**Table 2 (continued)**

| entry | carboxylic acid | diene | product(s) | % yield |
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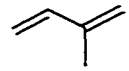
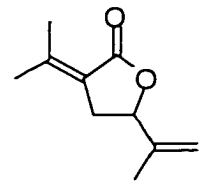
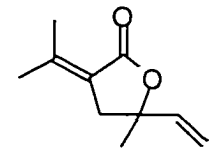
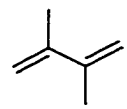
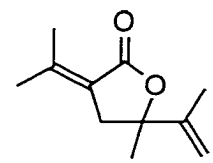
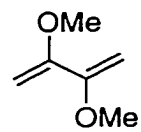
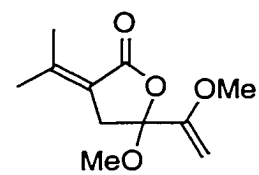
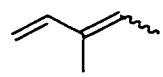
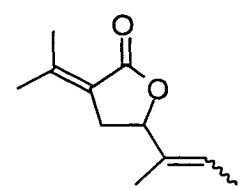
| 9 | |  |  **11**  **12** | 70 (10:1) |
| 10 | |  |  **13** | 0 |
| 11 | |  |  **14** | 0 |
| 12 | |  2:1 *E/Z* |  **15** (2.4:1 *E/Z*) | 66 |

**Table 2. (continued)**

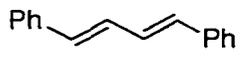
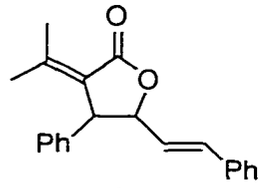
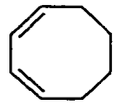
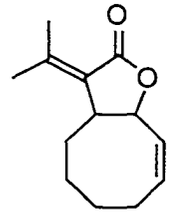
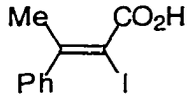
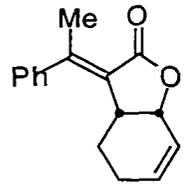
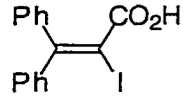
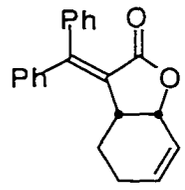
| entry | carboxylic acid | diene | product(s) | % yield |
|---|---|---|---|---|
| 13 | |  |  **16** | 0 |
| 14 | |  |  **17** | 0 |
| 15 |  **18** |  |  **19** | 65 |
| 16 |  **20** |  |  **21** | 60 |

**Table 2 (continued)**

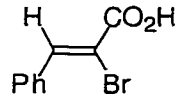
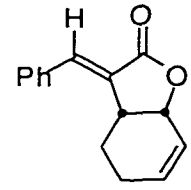
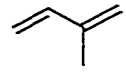
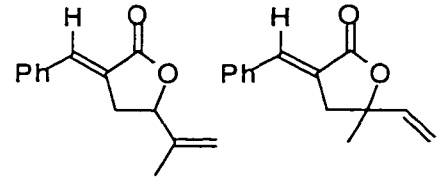
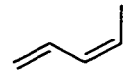
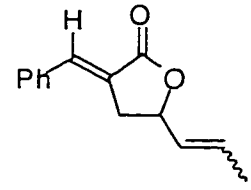
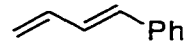
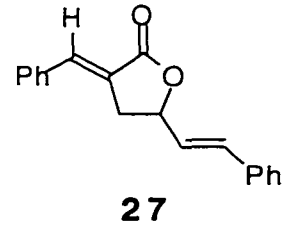
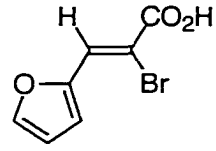
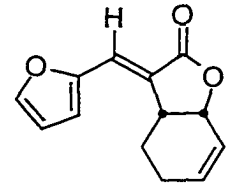
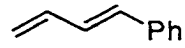
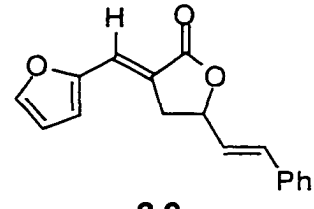
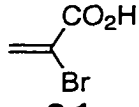
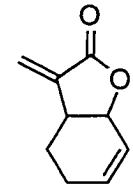
| entry | carboxylic acid | diene | product(s) | % yield |
|---|---|---|---|---|
| 17 |  **22** |  |  **23** | 85 |
| 18 |  |  **24** **25** | | 66 (3:1) |
| 19 |  |  **26** (10:1 *E/Z*) | | 78 |
| 20 |  |  **27** | | 99 |

**Table 2 (continued)**

| entry | carboxylic acid | diene | product(s) | % yield |
|---|---|---|---|---|
| 21 |  **28** |  |  **29** | 64 |
| 22 | |  |  **30** | 50 |
| 23 |  **31** |  |  **32** | 0 |

[a]The palladium-catalyzed conditions include $Pd(OAc)_2$ (0.05 mmol), *n*-$Bu_4NCl$ (0.5 mmol), $NaHCO_3$ (2.5 mmol), D$^t$BPF (0.1 mmol), diene ( 2.5 mmol), vinyl iodide or bromide (0.5 mmol), and DMF (2 mL) placed in an argon flushed 2 dram vial.

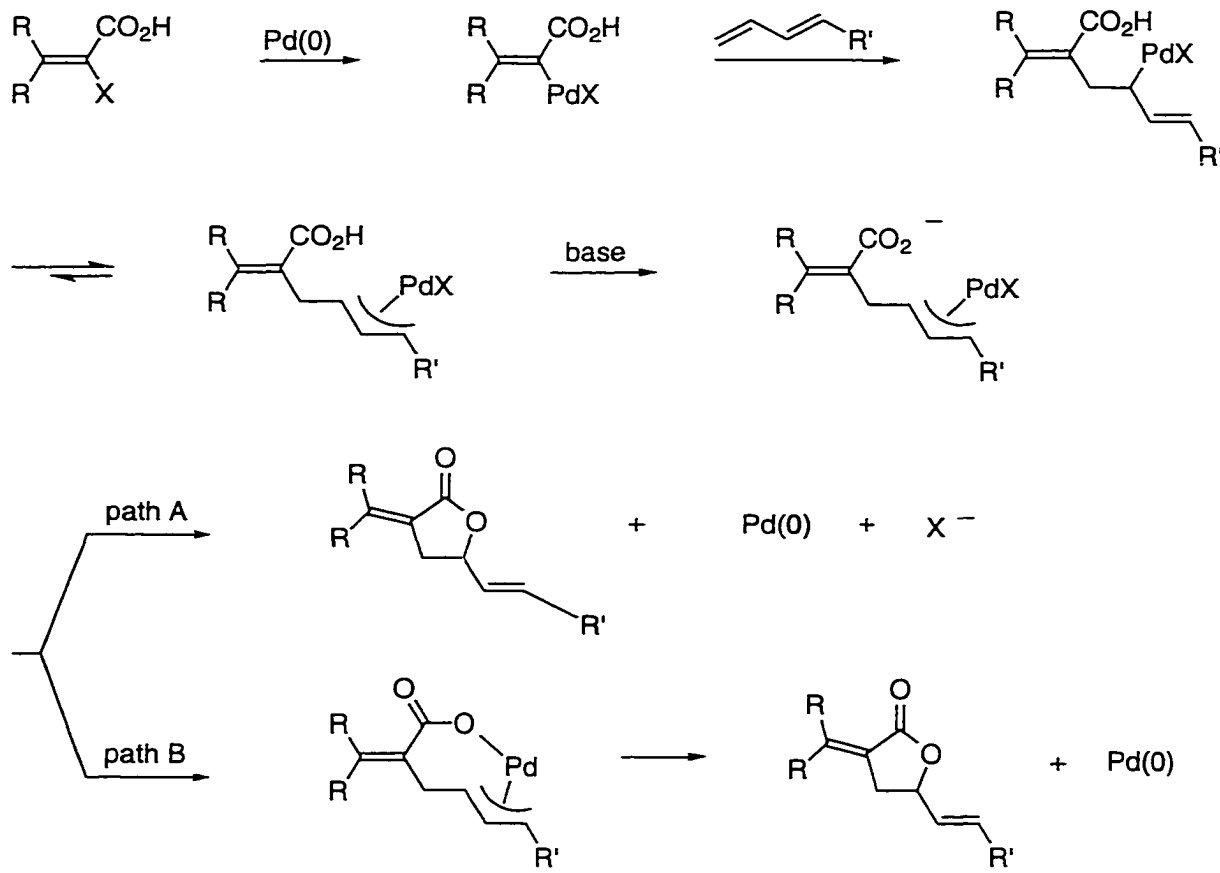
palladium catalyst to better coordinate to the terminal double bond of the diene. When the single substituent on the diene is small, such as a methyl or methoxy group, the product was obtained as a mixture of *cis* and *trans* isomers (entries 2, 3, 6, and 19). When the terminal group is larger and aryl, such as a phenyl or furyl group, only the *trans* isomer has been obtained (entries 4, 5, 20, and 22). Dienes that are substituted on an internal position on only one double bond also give good yields (entries 9, 12, and 18). However, when isoprene was used, a mixture of regioisomers were obtained arising from vinylpalladium addition to both ends of the diene (entries 9 and 18). 3-Methylenepent-4-enenitrile did not cyclize to the corresponding butyrolactone (entry 8). This failure could be caused by an unwanted chelation of the nearby nitrile to the palladium metal or the instability of this diene towards bases and elevated temperatures. Surprisingly, 1,3-dienes which were substituted in both of the internal positions, such as 2,3-dimethyl-1,3-butadiene and 2,3-dimethoxy-1,3-butadiene, failed to produce any of the expected lactone (entries 10 and 11). Also, 1,4-diphenyl-1,3-butadiene did not react under our standard palladium conditions, due to unfavorable steric interactions (entry 13). Simple cyclic dienes, such as 1,3-cyclohexadiene, produced the desired lactone in modest to good yields (entries 1, 15-17, and 21). However, 1,3-cyclooctadiene did not annulate to give the corresponding lactone (entry 14).

A variety of acrylic acids were used in this study to better determine the scope and limitations of this annulation. It was first discovered that acrylic acids with alkyl substituents in the $\beta$-position reacted in a similar fashion to those with aryl substituents. However, acid **28**, which has a 2-furyl group *cis* to the bromine,

produced lower yields than acid **22**, which has a phenyl group *cis* to the bromine (entries 17, 20, 21, and 22). A possible explanation for the difference in yields is that the furyl group is coordinating to the vinylpalladium species, thus reducing its reactivity towards diene addition. It has also been discovered that vinylic bromides are as reactive as vinylic iodides. This result is somewhat surprising in that previous work has generally shown that vinylic and aryl iodides are much more reactive than the corresponding bromides. However, it should be noted that the ligand used in this palladium-catalyzed reaction was originally designed to activate aryl chlorides and bromides towards oxidative addition by palladium(0).[17,18] Lastly, this palladium-catalyzed annulation did not proceed with α-bromoacrylic acid to produce the corresponding α-methylene-γ-butyrolactone derivative (entry 23).

This heteroannulation process most likely proceeds through a π-allyl-palladium intermediate as shown in Scheme 1. The key steps are (1) $Pd(OAc)_2$ reduction to the active palladium(0) catalyst, (2) oxidative addition of the vinylic iodide or bromide to Pd(0), (3) organopalladium addition to the less hindered end of the 1,3-diene to form a π-allylpalladium intermediate, and (4) displacement of palladium by the neighboring carboxylate ion. The exact nature of this substitution process for acyclic dienes is uncertain. The carboxylate ion could effect direct backside displacement of palladium (path A). Alternatively, the carboxylate ion could proceed through frontside attack on palladium to produce a palladacycle that subsequently undergoes reductive elimination to the five-membered ring lactone. Since the annulation onto 1,3-cyclohexadiene produces only the *cis* ring fusion, pathway B is believed to be the dominant process, at least with cyclic dienes.

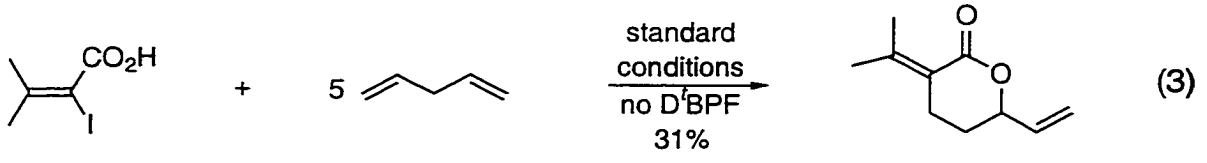
**Scheme 1**




The annulation of acyclic dienes produces primarily the *trans* stereoisomer. This can be easily explained by the π-allylpalladium intermediate conforming mainly to the more stable syn-$\eta^3$-allyl complex.[20] *Cis*- and *trans*-1,3-pentadiene both produce the same mixture of lactones in a 9:1 *E/Z* ratio. Dienes which have a bulkier substituent in the 1-position, such as 1-phenyl-1,3-butadiene and 2-(1,3-butadienyl)furan, only produce the *trans* isomer.

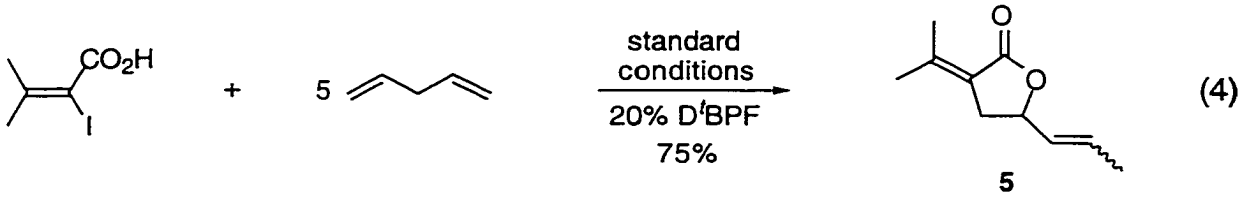
In an attempt to broaden the scope of this chemistry, similar hetero-annulations were performed on 1,4-dienes. When carboxylic acid **1** was reacted

with 1,4-pentadiene using the optimized palladium conditions excluding D$^t$BPF, the predicted six-membered ring lactone was obtained in a 31% yield (eq 3). However, it was discovered that reactions which contained D$^t$BPF apparently isomerize the 1,4-diene to the corresponding 1,3-diene. When 20 mol % of D$^t$BPF




(3)

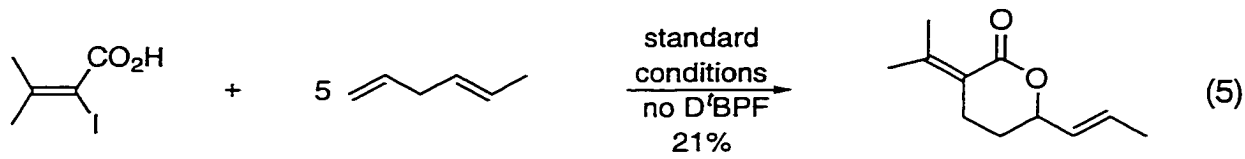
was added to the palladium reaction, the five-membered ring lactone **5** was recovered in a 75% yield as a 9:1 *trans/cis* mixture (eq 4). The production of the five-membered ring lactone can be explained by isomerization of the 1,4-pentadiene to 1,3-pentadiene and subsequent annulation. When 1,4-hexadiene



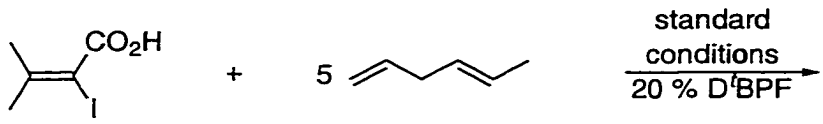

(4)

**5**

and no D$^t$BPF are utilized, the anticipated six-membered ring lactone is obtained in a 21% yield (eq 5). However, in the presence of 20 mol % D$^t$BPF, no annulation product was observed (eq 6). This occurs because the corresponding isomerized 2,3-hexadiene is sterically hindered at both ends and is less reactive towards vinylpalladium addition.




(5)




(6)

## Conclusion

The palladium-catalyzed heteroannulation of acyclic and cyclic 1,3-dienes by α-iodo and α-bromo acrylic acids has been proven to be a useful route for the synthesis of α-alkylidene-γ-butyrolactones. For most substrates, this process is highly regio- and stereoselective. Annulation predominately occurs at the less hindered end of the diene, and with acyclic dienes the *E*-isomer is the major product. The success of this process is dependent upon the use of the sterically hindered, electron-rich phosphine ligand D$^t$BPF. The exact role of this ligand is uncertain, but it is likely breaking up any unwanted coordination between the vinylpalladium species and the neighboring carboxylic acid.

## Experimental Section

**General Procedures.** All $^1$H and $^{13}$C NMR spectra were recorded at 400 and 100.5 MHz, respectively. Thin-layer chromatography (TLC) was performed using commercially prepared 60 mesh silica plates (Whatman K6F), and

visualization was effected with short wavelength UV light (254 nm) or basic $KMnO_4$ solution [3 g of $KMnO_4$ + 20 g of $K_2CO_3$ + 5 mL of NaOH (5%) + 300 mL $H_20$].

**Regents**. All reagents were used directly as obtained commercially unless otherwise stated. $KMnO_4$, $K_2CO_3$, NaOH, $NaHCO_3$ and *N,N*-dimethylformamide were obtained from Fischer Scientific. Anhydrous *n*-$Bu_4NCl$ was purchased from Lancaster Synthesis Inc. Palladium acetate was donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. Isoprene, 1,3-cyclohexadiene, (*E/Z*)-1,3-pentadiene, 3-methyl-1,3-pentadiene, and 1-methoxy-1,3-butadiene were purchased from Aldrich Chemical Co., Inc. (*E*)-1-Phenyl-1,3-butadiene,[21] 2-(1,3-butadienyl)furan,[22] 2-bromo-3-(furan-2-yl)-acrylic acid,[23] and 2-bromo-3-phenylacrylic acid[24] were prepared according to previous literature procedures.

**(Di-*tert*-butylphosphino)ferrocene**. (Di-*tert*-butylphosphino)ferrocene was prepared by a procedure provided by the Hartwig group.[19] Into a 250 mL Schlenk flask under Ar was added ferrocene (50 mmol) and THF (25 mL). *tert*-Butyllithium (95 mmol) was added dropwise into the Schlenk flask via an addition funnel. After the addition (ca. 30 min) the reaction was allowed to stir at room temp for 2 h, and an orange precipitate collected at the bottom of the flask. Di(*tert*-butyl)chlorophosphine (132 mmol) was added dropwise to the reaction mixture at room temperature via an addition funnel. After 4 h, MeOH (6 mL) was added to the flask and the mixture was allowed to stir for 0.5 h. The solvent was removed under vacuum and the resulting deep orange solid was dissolved in pentane (75 mL) and the mixture was filtered through a medium fritted funnel. The orange solution was concentrated under vacuum and cooled to -35 $^{o}$C overnight. An orange solid was

obtained, which was sublimed twice, to give the product in a 51% yield. $^1$H NMR ($^{31}$P decoupled, $CDCl_3$) δ 1.23 (s, 18 H), 4.04 (s, 5 H), 4.09 (s, 2 H), 4.09 (s, 2 H).

**2-Iodo-3-methyl-2-butenoic acid (3)** was prepared according to a modified literature procedure.[25] A 250 mL round bottom flask was charged with MeLi (20 mL, 1.5 M ether solution) and a magnetic stir bar. The ether was removed by water aspiration and THF (100 mL) was added. The solution was cooled to 0 °C and CuI (15 mmol) was added in one portion. The solution was cooled further to -78 °C and ethyl 2-butynoate (10 mmol) was added dropwise, and the mixture stirred for 5 h at -78 °C. Iodine (50 mmol) was added as a THF solution and stirred further for 15 min. The mixture was poured into a separatory funnel containing ice and HCl (7.5 mL). Ether (100 mL) was added and the organic layer was washed first with aqueous $Na_2S_2O_3$ (50 mL) and then aqueous $NaHCO_3$ (50 mL).

The organic layer was concentrated and acetone (100 mL) and LiOH (100 mL 1 M aqueous solution) were added. The mixture was refluxed for 4 h and the acetone was removed under vacuo. The resulting mixture was poured onto ice and HCl (7.5 mL) and extracted with three portions of ether (50 mL). The organic solvent was concentrated and the resulting oil was taken up into hot $H_2O$ (50 mL). The aqueous mixture was cooled and 2-iodo-3-methyl-2-butenoic acid (**3**) crystallized out to give white crystals in a 60% yield: mp 79-80 °C; $^1$H NMR ($CDCl_3$) δ 2.18 (s, 3 H), 2.25 (s, 3 H), 10.36 (br s, 1 H); $^{13}$C NMR ($CDCl_3$) δ, 23.40, 33.39, 84.66, 156.91, 170.64; IR (neat) 3485, 3056, 2975, 1674 cm$^{-1}$; HRMS for $C_5H_7IO_2$ calcd 225.9491, found 225.9494.

**(Z)-2-Iodo-3-phenyl-2-butenoic acid (18)** was prepared using the same general procedure as described for **3**, but starting with ethyl phenylpropiolate. Yellow crystals, 64% yield: mp 141-142 °C; $^1$H NMR ($CDCl_3$) δ 2.59 (s, 3 H), 7.17-7.29 (m, 2 H), 7.34-7.45 (m, 3 H), 11.25 (br s, 1 H); $^{13}$C NMR ($CDCl_3$) δ 24.60, 84.98, 126.47, 128.20, 128.61, 146.57, 158.61, 171.59; IR (neat) 3480, 3020, 2977, 1670 cm$^{-1}$; HRMS for $C_{10}H_9IO_2$ calcd 287.9647, found 287.9653.

**2-Iodo-3,3-diphenyl-2-propenoic acid (20)** was prepared using the same general procedure as described for **3**, but starting with ethyl phenylpropiolate and phenyllithium. Red crystals, 55% yield: mp 170-171 °C; $^1$H NMR ($CDCl_3$) δ 7.18-7.20 (m, 2 H), 7.24-7.40 (m, 8 H), 10.19 (br s, 1 H); $^{13}$C NMR ($CDCl_3$) δ 85.13, 128.35, 128.44, 128.58, 128.79, 128.92, 128.95, 140.05, 143.66, 157.42, 172.35; IR (neat) 3420, 3030, 2980, 1680 cm$^{-1}$; HRMS for $C_{15}H_{11}IO_2$ calcd 349.9804, found 349.9809.

**General Procedure for the Palladium-Catalyzed Reactions.** $Pd(OAc)_2$ (0.05 mmol), *n*-$Bu_4NCl$ (0.5 mmol), $NaHCO_3$ (2.5 mmol), D$^t$BPF (0.1 mmol), diene (2.5 mmol), vinylic iodide or bromide (0.5 mmol), and DMF (2 mL) were added to an argon flushed 2 dram vial. The vial was flushed further with argon for 2 min and heated at 60 °C for 24 h. The reaction mixture was cooled, diluted with saturated $NaHCO_3$, extracted with ether, dried over anhydrous $MgSO_4$, and filtered. The organic solvent was evaporated in vacuo, and the product was isolated by flash chromatography (10:1 hexanes/EtOAc) on a silica gel column. The following compounds were prepared by the above procedure, and the results are summarized in Table 2.

***cis*-3-Isopropylidene-3a,4,5,7a-tetrahydro-3*H*-benzofuran-2-one (4)** (entry 1, Table 2). Slightly yellow oil: $^1$H NMR ($CDCl_3$) δ 1.27 (dq, $J$ = 12.8, 4.4 Hz, 1 H), 1.76-1.82 (m, 1 H), 1.93 (s, 3 H), 1.96-2.04 (m, 1 H), 2.11-2.19 (m, 1 H), 2.24 (s, 3 H), 2.99 (dt, $J$ = 12.8, 5.6 Hz, 1 H), 4.56 (m, 1 H), 5.95 (dt, $J$ = 10.0, 2.8 Hz, 1 H), 6.17 (t, $J$ = 7.2 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 20.09, 23.56, 23.74, 38.98, 71.23, 123.20, 125.98, 134.36, 149.78, 169.89 (one $sp^3$ carbon missing due to overlap); IR (neat) 3034, 2926, 1747 (C=O) $cm^{-1}$; HRMS for $C_{11}H_{14}O_2$ calcd 178.0994, found 178.0997.

**3-Isopropylidene-5-(1-propenyl)dihydrofuran-2-one (5)** (entries 2 and 3, Table 2). The reaction product was obtained as a slightly yellow oil and an inseparable mixture of two stereoisomers (9:1, *E/Z*): $^1$H NMR ($CDCl_3$) δ 1.70 (d, $J$ = 7.6 Hz, 3.45 H), 1.84 (s, 3.49 H), 2.23 (t, $J$ = 2.4 Hz, 3.46 H), 2.52-2.58 (m, 1.19 H), 3.00 (ddt, $J$ = 16.0, 8.0, 1.2 Hz, 1.06 H), 4.78 (q, $J$ = 7.6 Hz, 1 H), 5.20 (q, $J$ = 7.2, 0.11 H), 5.49 (ddd, $J$ = 15.2, 7.6, 1.6 Hz, 1 H), 5.67-5.72 (m, 0.09 H), 5.78 (dq, $J$ = 15.2, 6.4 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 13.40, 17.67, 19.82, 24.50, 24.53, 34.42, 34.77, 71.39, 76.43, 119.31, 129.23, 129.56, 129.84, 129.97, 149.98, 170.09; IR (neat) 3002, 2917, 1748 (C=O) $cm^{-1}$; HRMS for $C_{10}H_{14}O_2$ calcd 166.0994, found 166.0997.

**3-Isopropylidene-5-(*E*)-styryldihydrofuran-2-one (6)** (entry 4, Table 2). Slightly yellow oil: $^1$H NMR ($CDCl_3$) δ 1.81 (s, 3 H), 2.20 (s, 3 H), 2.62 (m, 1 H), 3.05 (dd, $J$ = 16.0, 8.0 Hz, 1 H), 4.96 (q, $J$ = 6.8 Hz, 1 H), 6.13 (dd, $J$ = 16.0, 6.8 Hz, 1 H), 6.59 (d, $J$ = 16.0 Hz, 1 H), 7.19 (t, $J$ = 7.2 Hz, 1 H), 7.25 (t, $J$ = 7.2 Hz, 2 H), 7.31 (d, $J$ = 7.6 Hz, 2 H); $^{13}$C NMR ($CDCl_3$) δ 19.93, 24.63, 34.52, 76.09, 118.87,

126.74, 127.78, 128.27, 128.72, 132.33, 135.93, 150.72, 170.00; IR (neat) 2933, 1744 (C=O) $cm^{-1}$; HRMS for $C_{15}H_{16}O_2$ calcd 228.1150, found 228.1151.

**3-Isopropylidene-5-(*E*-2-furan-2-ylethenyl)dihydrofuran-2-one (7)** (entry 5, Table 2). Slightly yellow oil: $^1H$ NMR ($CDCl_3$) δ 1.86 (s, 3 H), 2.50 (s, 3 H), 2.64-2.68 (m, 1 H), 3.09 (dd, *J* = 16.0, 7.6 Hz, 1 H), 4.99 (q, *J* = 6.8 Hz, 1 H), 6.12 (dd, *J* = 15.6, 6.4 Hz, 1 H), 6.27 (d, *J* = 2.8 Hz, 1 H), 6.36, (d, *J* = 1.2 Hz, 1 H), 6.46 (d, *J* = 15.6 Hz, 1 H), 7.34 (s, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 19.90, 24.59, 34.48, 75.53, 109.40, 111.49, 118.70, 120.19, 126.16, 142.51, 150.83, 151.61, 169.93; IR (neat) 3050, 2980, 1747 (C=O) $cm^{-1}$; HRMS for $C_{13}H_{14}O_3$ calcd 218.0943, found 218.0948.

**3-Isopropylidene-5-(2-methoxyethenyl)dihydrofuran-2-one (8)** (entry 6, Table 2). The reaction product was obtained as a slightly yellow oil and an inseparable mixture of two stereoisomers (5:1, *E/Z*): $^1H$ NMR ($CDCl_3$) δ 1.85 (s, 3.79 H), 2.24 (t, *J* = 2.0 Hz, 3.76 H), 2.48-2.60 (m, 1.28 H), 3.02-3.06 (m, 1.29 H), 3.56 (s, 3.14 H), 3.63 (s, 0.67 H), 4.51 (dd, *J* = 8.4, 6.4 Hz, 0.22 H), 4.74-4.81 (m, 2.03 H), 5.32 (q, *J* = 7.2 Hz, 0.22 H), 6.04 (d, *J* = 6.4 Hz, 0.22 H), 6.59-6.65 (m, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 19.80, 19.87, 24.47, 24.50, 35.08, 35.60, 56.23, 60.25, 70.10, 75.03, 102.26, 105.77, 119.70, 119.76, 149.49, 149.69, 149.83, 151.93, 170.06; IR (neat) 2920, 2837, 1760 (C=O) $cm^{-1}$; HRMS for $C_{10}H_{14}O_3$ calcd 182.0943, found 182.0945.

**3-Isopropylidene-5-isopropenyldihydrofuran-2-one (11)** and **3-isopropylidene-5-methyl-5-vinyldihydrofuran-2-one (12)** (entry 9, Table 2). The reaction product was obtained as a slightly yellow oil and an inseparable

mixture of two regioisomers (10:1, **11/12**): $^1$H NMR ($CDCl_3$) δ 1.47 (s, 0.31 H), 1.60-1.70 (br s, 0.09 H), 1.73 (s, 3.00 H), 1.84 (s, 0.10 H), 1.87 (s, 2.42 H), 2.26 (s, 3.32 H), 2.61 (d, *J* = 14.4 Hz, 1.02 H), 2.71-2.83 (m, 0.06 H), 3.01 (dd, *J* = 16.0, 8.8 Hz, 1.09 H), 4.81 (t, *J* = 7.6 Hz, 0.90 H), 4.90 (s, 1 H), 5.04 (s, 0.91 H), 5.09 (d, *J* = 11.2 Hz, 0.02 H), 5.27 (d, *J* = 17.2 Hz, 0.09 H), 7.55 (dd, *J* = 16.8, 10.4 Hz, 0.08 H); $^{13}$C NMR ($CDCl_3$) δ 17.06, 19.88, 24.56, 32.95, 78.11, 112.24, 119.07, 143.18, 150.41, 170.09; IR (neat) 2983, 2925, 1765 (C=O), cm$^{-1}$; HRMS for $C_{10}H_{14}O_2$ calcd 166.0994, found 166.0995.

**3-Isopropylidene-5-(1-methyl-1-propenyl)dihydrofuran-2-one (15)** (entry 12, Table 2). The reaction product was obtained as a slightly yellow oil and an inseparable mixture of two stereoisomers (2.4:1, *E/Z*). *E*-isomer: $^1$H NMR ($CDCl_3$) δ 1.58 (s, 3 H), 1.64 (d, *J* = 6.0 Hz, 3 H), 1.85 (s, 3 H), 2.25 (s, 3 H), 2.57-2.63 (m, 1 H), 2.91-2.97 (m, 1 H), 4.77 (t, *J* = 7.6 Hz, 1 H), 5.57 (q, *J* = 6.8 Hz, 1 H); *Z*-isomer: $^1$H NMR ($CDCl_3$) δ 1.62 (s, 3 H), 1.66 (d, *J* = 6.8 Hz, 3 H), 1.87 (s, 3 H), 2.26 (s, 3 H), 2.57-2.63 (m, 1 H), 2.91-2.97 (m, 1 H), 5.35 (t, *J* = 8.0 Hz, 1 H), 5.39-5.44 (m, 1 H); $^{13}$C NMR ($CDCl_3$) mixture of *E/Z* isomers δ 10.56, 12.96, 13.15, 16.91, 19.85, 24.54, 24.58, 32.45, 32.68. 73.17, 80.45, 119.60, 119.92, 122.87, 123.59, 133.74, 133.94, 149.87, 149.90, 170.36; IR (neat) 2975, 2918, 1747 (C=O) cm$^{-1}$; HRMS for $C_{11}H_{16}O_2$ calcd 180.1150, found 180.1151;

***cis*-3-(*E*-1-Phenylethylidene)-3a,4,5,7a-tetrahydro-3*H*-benzofuran-2-one (19)** (entry 15, Table 2). White solid: mp 95-97 $^{o}$C; $^1$H NMR ($CDCl_3$) δ 1.10-1.23 (m, 1 H), 1.37 (dq, *J* = 13.2, 4.8 Hz, 1 H), 1.61-1.71 (m, 1 H), 1.88-1.93 (m, 1 H), 2.46 (s, 3 H), 2.85 (dt, *J* = 12.4, 5.6 Hz, 1 H), 4.54-4.56 (m, 1 H),

5.81-5.85 (m, 1 H), 6.00-6.04 (m, 1 H), 7.14-7.16 (m, 2 H), 7.24-7.35 (m, 3 H); $^{13}C$ NMR ($CDCl_3$) δ 21.10, 23.50, 24.06, 38.94, 71.85, 122.98, 126.43, 127.82, 127.94, 128.64, 134.8, 142.50, 152.11, 170.31; IR (neat) 3030, 2915, 1746 (C=O) $cm^{-1}$; HRMS for $C_{16}H_{16}O_2$ calcd 240.1150, found 240.1153.

***cis*-3-Diphenylmethylene-3a,4,5,7a-tetrahydro-3*H*-benzofuran-2-one (21)** (entry 16, Table 2). White solid: mp 164-166 °C; $^1H$ NMR ($CDCl_3$) δ 1.34-1.44 (m, 1 H), 1.61 (dq, *J* = 13.2, 4.4 Hz, 1 H), 1.71-1.80 (m, 1 H), 1.98 (dq, *J* = 17.6, 4.4 Hz, 1 H), 3.08 (dt, *J* = 12.0, 4.8 Hz, 1 H) 4.68 (br s, 1 H), 5.83-5.86 (m, 1 H), 6.03-6.06 (m, 1 H), 7.12-7.17 (m, 4 H), 7.23-7.32 (m, 6 H); $^{13}C$ NMR ($CDCl_3$) δ 23.26, 24.06, 40.17, 72.03, 123.45, 127.89, 128.46, 128.50, 128.52, 128.55, 128.69, 129.27, 134.17, 139.11, 141.04, 153.19, 169.06; IR (neat) 3040, 2975, 1740 (C=O) $cm^{-1}$; HRMS for $C_{21}H_{18}O_2$ calcd 302.1307, found 302.1307.

***cis*-3-(*E*-Phenylmethylene)-3a,4,5,7a-tetrahydro-3*H*-benzofuran-2-one (23)** (entry 17, Table 2). Slightly yellow oil: $^1H$ NMR ($CDCl_3$) δ 1.38 (dq, *J* = 12.8, 6.0 Hz, 1 H), 2.06-2.24 (m, 3 H), 3.51 (dt, *J* = 12.8, 4.8 Hz, 1 H), 4.73 (br s, 1 H), 6.02-6.05 (m, 1 H), 6.23-6.27 (m, 1 H), 7.38-7.46 (m, 3 H), 7.52 (d, *J* = 5.2 Hz, 2 H), 7.55 (s, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 22.56, 23.71, 38.13, 72.69, 122.92, 129.10, 129.85, 129.91, 130.95, 134.21, 134.70, 136.54, 171.83; IR (neat) 3080, 2932, 1748 (C=O) $cm^{-1}$; HRMS for $C_{15}H_{14}O_2$ calcd 226.0994, found 226.0996.

**3-(*E*-Phenylmethylene)-5-isopropenyldihydrofuran-2-one (24)** and **3-(*E*-phenylmethylene)-5-methyl-5-vinyldihydrofuran-2-one (25)** (entry 18, Table 2). The reaction product was obtained as a slightly yellow oil and an inseparable mixture of two regioisomers (3:1, **24/25**): $^1H$ NMR ($CDCl_3$) δ 1.56

(s, 1 H), 1.65 (s, 0.32 H), 1.76 (s, 3 H), 2.95 (dd, $J$ = 7.6, 4.0 Hz, 0.44 H), 3.01 (m, 0.67 H), 3.09 (d, $J$ = 3.6 Hz, 0.22 H), 3.16 (d, $J$ = 3.6 Hz, 0.23 H), 3.22 (d, $J$ = 3.6 Hz, 0.09 H), 3.38 (dd, $J$ = 11.2, 3.6 Hz, 0.57 H), 3.43 (dd, $J$ = 11.2, 4.0 Hz, 0.42 H), 4.96 (s, 1 H), 5.01 (dd, $J$ = 11.6, 7.6 Hz, 1 H), 5.11 (s, 1 H), 5.14 (d, $J$ = 14.4 Hz, 0.30 H), 5.33 (d, $J$ = 22.8 Hz, 0.31 H), 5.97 (dd, $J$ = 22.8, 14.4 Hz, 0.27 H), 7.37-7.51 (m, 6.40 H), 7.58 (t, $J$ = 3.6 Hz, 1.17 H); $^{13}$C NMR ($CDCl_3$) δ 16.92, 27.12, 32.88, 40.49, 79.71, 82.56, 113.03, 113.89, 124.21, 125.12, 128.95, 128.98, 129.88, 129.94, 129.98, 130.06, 134.64, 134.68, 136.75, 137.05, 140.65, 142.67, 171.51, 172.05; IR (neat) 3050, 2975, 1747 (C=O) cm$^{-1}$; HRMS for $C_{14}H_{14}O_2$ calcd 214.0994, found 214.09941.

**3-(*E*-Phenylmethylene)-5-(1-propenyl)dihydrofuran-2-one (26)** (entry 19, Table 2). The reaction product was obtained as a white solid and an inseparable mixture of two stereoisomers (10:1, *E/Z*): mp 57 °C; $^1$H NMR ($CDCl_3$) δ 1.72 (s, 0.13 H), 1.74 (dd, $J$ = 6.8, 1.6 Hz, 3 H), 1.77 (d, $J$ = 2.0 Hz, 0.13 H), 2.88 (dd, $J$ = 6.0, 3.2 Hz, 0.03 H), 2.94 (ddd, $J$ = 17.2, 5.6, 2.8 Hz, 1 H), 3.40 (ddd, $J$ = 17.6, 8.4, 2.8 Hz, 1 H), 3.47 (dd, $J$ = 8.0, 2.8 Hz, 0.04 H), 4.98 (q, $J$ = 7.2 Hz, 1H), 5.38 (q, $J$ = 7.6 Hz, 0.11 H), 5.55 (ddq, $J$ = 15.2, 7.2, 1.6 Hz, 1 H), 5.74-5.80 (m, 0.09 H), 5.87 (ddq, $J$ = 15.2, 6.4, 0.8 Hz, 1 H), 7.37-7.45 (m, 3 H), 7.47-7.49 (m, 2 H), 5.55 (t, $J$ = 2.8 Hz, 1.06 H); $^{13}$C NMR ($CDCl_3$) δ 13.51, 17.72, 34.37, 34.67, 72.98, 78.04, 124.60, 128.95, 128.99, 129.47, 129.85, 130.01, 130.68, 134.74, 136.49, 172.02; IR (neat) 3050, 2980, 1750 (C=O) cm$^{-1}$; HRMS for $C_{14}H_{14}O_2$ calcd 214.0994, found 214.0996.

**3-(*E*-Phenylmethylene)-5-(*E*-styryl)dihydrofuran-2-one (27)** (entry 20, Table 2). White solid: mp 97 °C; $^1$H NMR ($CDCl_3$) δ 3.07 (d, $J$ = 17.2 Hz, 1 H), 3.52 (dd, $J$ = 17.2, 7.2 Hz, 1 H), 5.23 (q, $J$ = 6.4 Hz, 1 H), 6.24 (dd, $J$ = 16.0, 7.2 Hz, 1 H), 6.73 (d, $J$ = 15.6 Hz, 1 H), 7.26-7.51 (m, 10 H), 7.61 (s, 1 H); $^{13}$C NMR ($CDCl_3$) δ 34.49, 77.73, 124.06, 126.81, 127.06, 128.48, 128.76, 129.00, 129.98, 130.07, 133.13, 134.64, 135.66, 137.10, 171.92; IR (neat) 3040, 2980, 1738 (C=O) cm$^{-1}$; HRMS for $C_{19}H_{16}O_2$ calcd 276.1150, found 276.1150.

**3-(*E*-Furan-2-ylmethylene)-3a,4,5,7a-tetrahydro-3*H*-benzofuran-2-one (29)** (entry 21, Table 2). White solid: mp 94-95 °C; $^1$H NMR ($CDCl_3$) δ 1.23-1.34 (m, 1 H), 2.07-2.23 (m, 3 H), 3.51-3.60 (m, 1 H), 4.68-4.72 (m, 1 H), 5.99-6.04 (m, 1 H), 6.22-6.28 (m, 1 H), 6.52 (dd, $J$ = 3.3, 1.8 Hz, 1 H), 6.67 (d, $J$ = 3.6 Hz, 1 H), 7.24 (d, $J$ = 1.5 Hz, 1 H), 7.57 (d, $J$ = 1.8 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 23.83, 38.50, 72.97, 112.53, 116.64, 122.28, 122.90. 128.33, 134.89, 145.29, 150.91, 171.69 (one sp$^3$ carbon missing due to overlap); IR (neat) 3080, 2990, 1732 (C=O) cm$^{-1}$; HRMS for $C_{13}H_{12}O_3$ calcd 216.0786, found 216.0791.

**3-(*E*-Furan-2-ylmethylene)-5-(*E*-styryl)dihydrofuran-2-one (30)** (entry 22, Table 2). White solid: mp 103-104 °C; $^1$H NMR ($CDCl_3$) δ 3.09 (ddd, $J$ = 18.6, 5.7, 2.7 Hz, 1 H), 3.57 (ddd, $J$ = 18.6, 8.1, 2.7 Hz, 1 H), 5.22 (dddd, $J$ = 8.1, 6.9, 5.7, 0.9 Hz, 1 H), 6.24 (dd, $J$ = 15.9, 6.9 Hz, 1 H), 6.53 (dd, $J$ = 3.3, 1.8 Hz, 1 H), 6.67 (d, $J$ = 3.3 Hz, 1 H), 6.72 (d, $J$ = 17.4 Hz, 1 H), 7.25-7.42 (m, 6 H), 7.57 (d, $J$ = 1.2 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 34.30, 77.89, 112.58, 116.58, 121.52, 123.10, 126.10, 127.33, 128.40, 128.74, 132.85, 135.78, 145.36, 151.30, 171.76; IR (neat) 3054, 2980, 1738 (C=O) cm$^{-1}$; HRMS for $C_{17}H_{14}O_3$ calcd 266.0943, found 266.0947.

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# CHAPTER 2. PALLADIUM-CATALYZED CARBONYLATIVE CYCLIZATION OF UNSATURATED ARYL IODIDES AND DIENYL TRIFLATES, IODIDES AND BROMIDES

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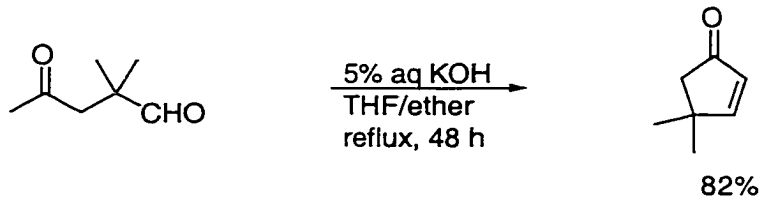
## Abstract

Indanones and 2-cyclopentenones have been successfully prepared in good to excellent yields by the palladium-catalyzed carbonylative cyclization of unsaturated aryl iodides and dienyl triflates, iodides, and bromides respectively. The best results are obtained by employing 10 mol % of $Pd(OAc)_2$, 2 equiv of pyridine, 1 equiv of *n*-$Bu_4NCl$, an atmosphere of CO, a reaction temperature of 100 $^oC$, and DMF as the solvent. This carbonylative cyclization is particularly effective on substrates that contain a terminal olefin. The proposed mechanism for this annulation includes (1) $Pd(OAc)_2$ reduction to the active palladium(0) catalyst, (2) oxidative addition of the organic halide or triflate to Pd(0), (3) coordination and insertion of carbon monoxide to produce an acylpalladium intermediate, (4) addition across the carbon-carbon double bond, (5) β-hydride elimination and readdition to form a palladium enolate, and (6) protonation by $H_2O$ to produce the desired indanone or 2-cyclopentenone derivative.

## Introduction

2-Cyclopentenones can be found in many natural products or used as building blocks for the development of other biological systems. For instance, tetrahydrodicranenone B has shown antimicrobial and antihypertensive properties,[1] while indanocine has been identified as having antiproliferative activity.[2] Because of the importance of 2-cyclopentenones[3-6] and indanones,[7-11] numerous synthetic methods for their preparation have been developed. One early approach involves an intramolecular aldol reaction (eq 1).[12] This method proved to

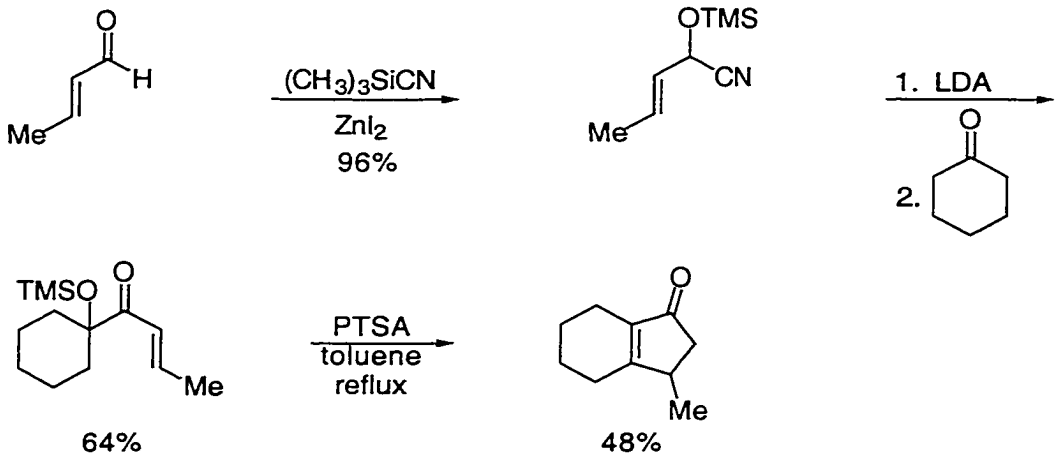



(1)

be effective for specific reactions, but is limited by its generality and requires starting materials which are not readily available.

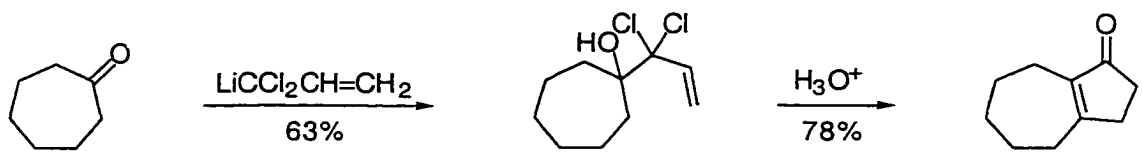
Jacobson and coworkers have developed a three-carbon annulation process through the addition of anions of protected cyanohydrins to ketones, the products of which are closed to a 2-cyclopentenone by a Nazarov cyclization.[13-15] This approach leads to the synthesis of a number of 2-cyclopentenones. However, most of the results have been obtained using crotonaldehyde, which affords 2-methyl-2-cyclopentenone derivatives (Scheme 1).

**Scheme 1**




Hiyama and coworkers have also developed a three-carbon annulation approach, which involves the reaction of 1,1-dichloroallyllithium and ketones to produce 2-cyclopentenone derivatives.[16,17] This procedure involves two separate steps. The first step involves the synthesis of a dichlorohomoallylic alcohol (Scheme 2). This alcohol is closed to a 2-cyclopentenone through an acid-catalyzed thermal conrotatory ring-closure. A disadvantage of this chemistry is that the starting ketone cannot contain other functional groups that might react with the organolithium reagent.

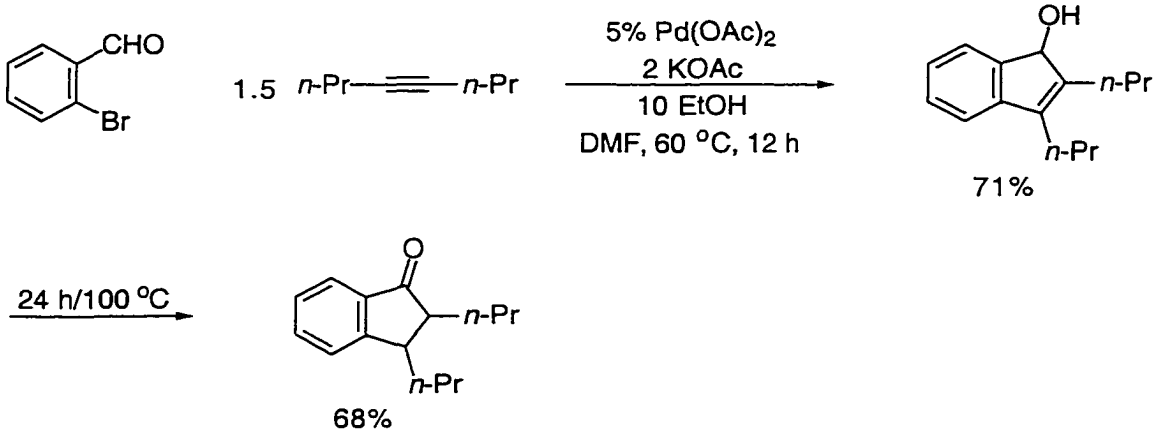
**Scheme 2**



More recently 2-cyclopentenones have been synthesized through a [2+2+1] cycloaddition known as the Pauson-Khand reaction.[18-20] This metal-mediated transformation was originally promoted by $Co_2(CO)_8$, and involved the coupling of an alkyne, an alkene and CO. Negishi et al. have reported similar results using zirconium,[21,22] Buchwald et al. have reported similar results using titanium,[23,24] and Heathcock et al. have used a palladium-catalyzed procedure.[25]

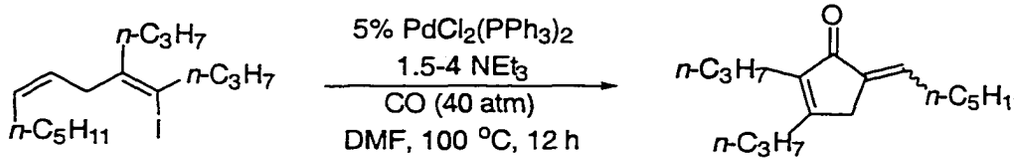
A number of palladium-catalyzed annulation processes have been reported for the synthesis of carbo- and heterocycles.[19,26-28] Yamamoto et al. have synthesized indenols and indanones through a palladium-catalyzed annulation of internal alkynes by aromatic aldehydes (Scheme 3).[29] A number of substituted indenol derivatives have been prepared by treating *o*-bromobenzaldehydes with various internal alkynes in the presence of a palladium catalyst. Upon further heating, these indenol derivatives isomerize to the corresponding indanones. The

**Scheme 3**



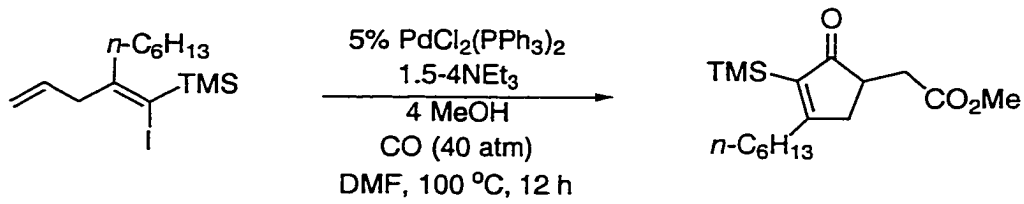
synthesis of indenones has also been reported by Larock et al. using similar starting materials and slightly modified palladium conditions.[30,31]

Negishi and coworkers have extensively explored palladium-catalyzed carbonylative cyclization reactions which produce a variety of cyclic ketones. They were able to produce 2-cyclopentenones through a palladium-catalyzed carbonylation of 1-iodo-1,4-alkadienes.[32] Two different palladium conditions were employed. One procedure employed 5 mol % of the palladium catalyst $Pd(PPh_3)_4$, $PdCl_2(PPh_3)_2$, or $Pd(OAc)_2$, 1-40 atm of CO, 1.5-4 equiv of $NEt_3$, a reaction temperature of 60 or 100 °C, and THF, DMF, benzene or acetonitrile as the solvent. This procedure produced cyclopentenone **2** in an 82% yield, starting with diene **1** (eq 2). Another procedure included an additional 4 equiv of MeOH. The products



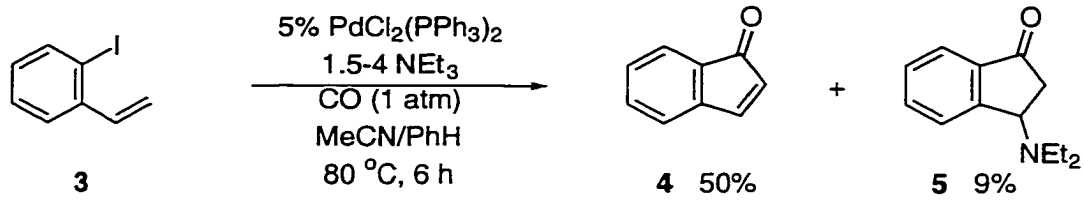

**1** **2** (2)

produced using this procedure contain a second inserted CO, which is esterified by MeOH (eq 3). The exact palladium procedure is different for each substrate run and in some cases large amounts of the palladium catalyst were needed to produce good yields. This palladium-catalyzed carbonylative cyclization was also applied to 1-(2-iodoaryl)-1-alkenes.[33] When *o*-iodostyrene (**3**) was reacted under



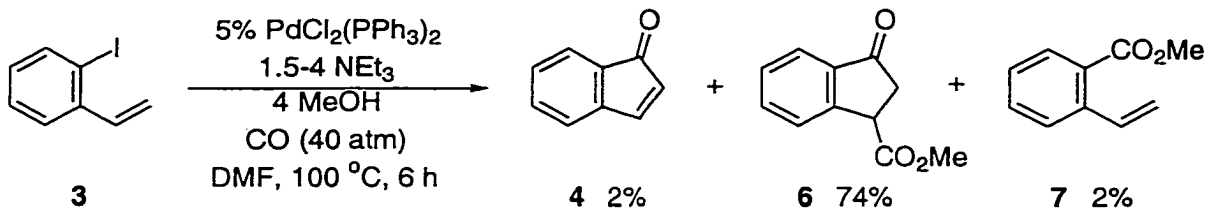

(3)

the palladium conditions without MeOH, indenone **4** and indanone **5** were produced in 50% and 9% yields respectively (eq 4). When MeOH was added to the palladium conditions and the amount of CO was increased to 40 atm, **4** was produced in a 2% yield along with a 74% yield of indanone **6** and a 2% yield of ester **7** (eq 5).




**3** **4** 50% **5** 9%

(4)



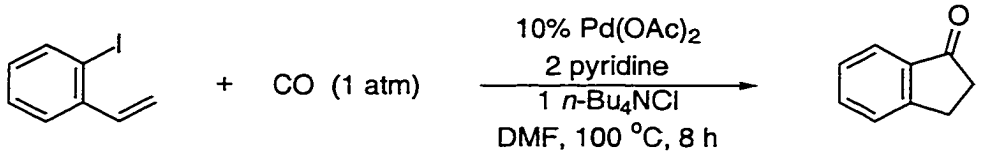

**3** **4** 2% **6** 74% **7** 2%

(5)

We wish to report at this time a novel palladium-catalyzed carbonylative cyclization of unsaturated aryl iodides and dienyl triflates, iodides, and bromides which provides a highly efficient new route to indanones and 2-cyclopentenones respectively.

## Results and Discussion

Our initial work was aimed at developing a set of palladium conditions that would work well for a variety of substrates to produce 2-cyclopentenones and indanones. The original set of palladium conditions used included 10 mol % $Pd(OAc)_2$, 2 equiv of pyridine, 1 equiv of *n*-$Bu_4NCl$, 1 atm of CO, DMF as the solvent, and a reaction temperature of 100 °C. These carbonylative palladium conditions were developed within the Larock group by Dmitry Kadnikov for the synthesis of coumarins.[34] Using *o*-iodostyrene as the model system, it was discovered that indanone was produced in a quantitative yield after an 8 h reaction time (eq 6). A few experiments were performed to examine the effect of each key




**3** **8** 100% (6)

reagent on the yield, beginning with the chloride source. When *n*-$Bu_4NCl$ was removed from the reaction mixture, the reaction time increased to 18 h and the yield of indanone decreased to 66%. In a second experiment, the amount of pyridine was lowered to 1 equiv, which lowered the yield of **8** to 93%. Also, when the pyridine base was replaced by $NEt_3$, only a trace amount of indanone was seen, with no evidence of any other products. Lastly, the palladium catalyst was reduced to 5 mol %, which increased the reaction time to 18 h and lowered the yield of **8** to 76%. Therefore, the standard conditions for this palladium

transformation are those employed in equation 6 (henceforth identified as procedure A).

This palladium-catalyzed carboannulation was extended to other aryl systems, in order to explore the generality of this reaction and produce substituted indanone derivatives (Table 1). Styryl derivatives that are substituted in the 2-position by either an aryl or alkyl group proved to work well. Aryl iodides **9** and **11** both reacted under the standard palladium conditions to provide the desired indanone products **10** and **12** in 100% and 60% yields respectively (entries 2 and 3). Unfavorable steric interactions between the phenyl group and the organopalladium intermediate may occur during the cyclization accounting for the lower yield with starting material **11**. Styryl derivatives that contain heteroatom substituents in the 2-position did not produce any indanone products (entries 4-6). It is possible that indanones **14**, **16**, and **18** are unstable at the elevated temperatures under which the reaction is run. Styryl derivative **19**, which contains an internal carbon-carbon double bond, also failed to cyclize to the desired indanone (entry 7). Presumably steric interactions between the aryl- or acylpalladium intermediate and the methyl group do not allow the palladium to add across the carbon-carbon double bond (see the later mechanistic discussion).

Starting materials, which contain electron-donating methoxy groups on the arene, did cyclize to the desired indanones (entries 8 and 9). However, when a methoxy group was placed *ortho* to the iodide, the yield dropped substantially, presumably due to steric hindrance to oxidative addition. This was observed

**Table 1. Synthesis of cyclic ketones.[a]**

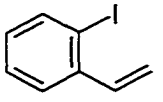
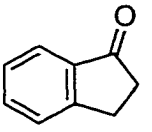
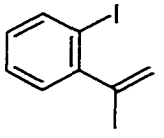
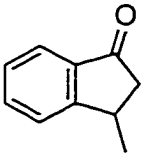
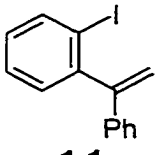
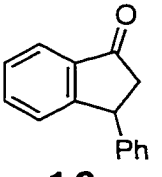
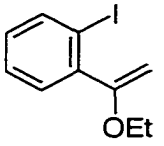
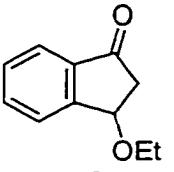
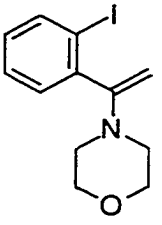
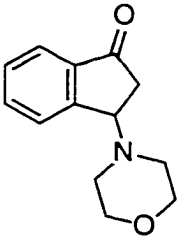
| entry | organic substrate | ketone | procedure | time (h) | % yield[b] |
|---|---|---|---|---|---|
| 1 |  **3** |  **8** | A | 8 | 100 |
| 2 |  **9** |  **10** | A | 12 | 100 |
| 3 |  **11** |  **12** | A | 72 | 60 |
| 4 |  **13** |  **14** | A | 72 | 0 |
| 5 |  **15** |  **16** | A | 72 | 0 |

**Table 1 (continued)**

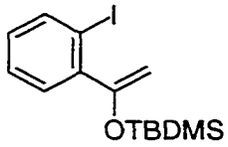
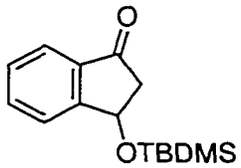
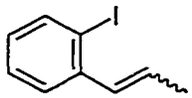
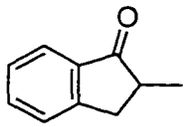
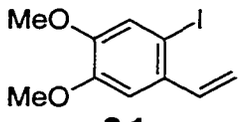
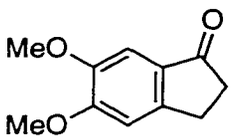
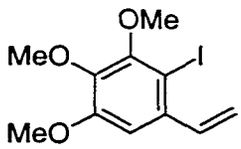
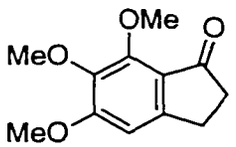
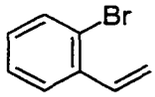
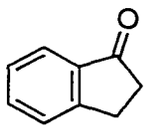
| entry | organic substrate | ketone | procedure | time (h) | % yield[b] |
|---|---|---|---|---|---|
| 6 |  **17** |  **18** | A | 72 | 0 |
| 7 |  3:1 *E/Z* **19** |  **20** | A | 72 | 0 |
| 8 |  **21** |  **22** | A | 24 | 82 |
| 9 |  **23** |  **24** | A | 24 | 45 |
| 10 |  **25** |  **8** | A | 72 | 0 |

**Table 1 (continued)**

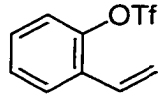
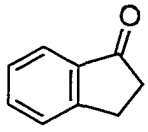
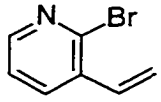
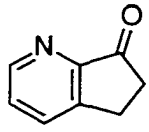
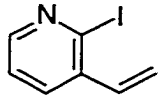
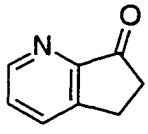
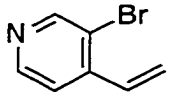
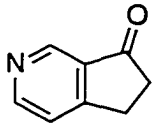
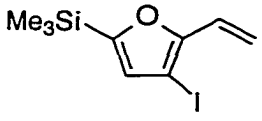
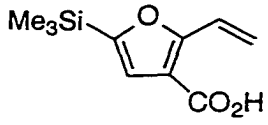
| entry | organic substrate | ketone | procedure | time (h) | % yield[b] |
|---|---|---|---|---|---|
| 11 |  **26** |  **8** | A | 72 | 0 |
| 12 |  **27** |  **28** | A | 72 | 0 |
| 13 |  **29** |  **28** | A | 72 | 0 |
| 14 |  **30** |  **31** | A | 72 | 0 |
| 15 |  **32** |  **33** | A | 24 | 61 |

**Table 1 (continued)**

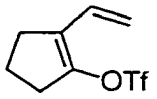
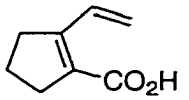
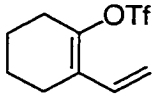
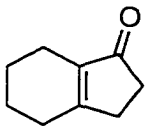
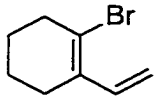
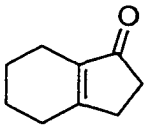
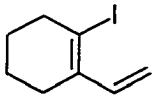
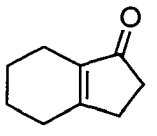
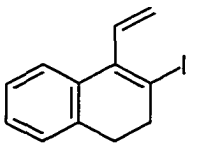
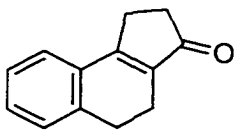
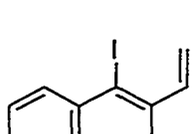
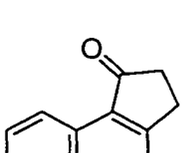
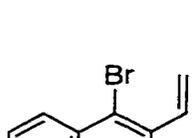
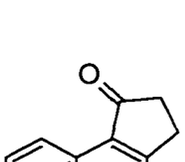
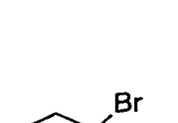
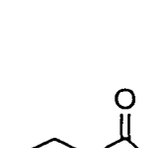
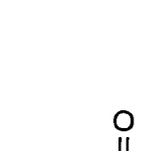
| entry | organic substrate | ketone | procedure | time (h) | % yield[b] |
|---|---|---|---|---|---|
| 16 |  **34** |  **35** | A | 24 | 89 |
| 17 |  **36** |  **37** | A | 12 | 95 |
| 18 |  **38** |  **37** | B | 72 | 87 |
| 19 |  **39** |  **37** | A | 72 | 86 |
| 20 |  **40** |  **41** | A | 72 | 85 |

**Table 1 (continued)**

| entry | organic substrate | ketone | procedure | time (h) | % yield[b] |
|---|---|---|---|---|---|
| 21 |  **42** |  **43** | A | 72 | 98 |
| 22 |  **44** |  **45** | B | 72 | 0 |
| 23 |  **46** |  **47** | B | 48 | 98 |
| 24 |  **48** |  **49** | A | 24 | 70 |

[a] Procedure A includes 10 mol % of $Pd(OAc)_2$, 2 equiv of pyridine, 1 equiv of *n*-$Bu_4NCl$, one atmosphere of CO, a reaction temperature of 100 °C, and DMF as the solvent. Procedure B replaces the 10 mol % $Pd(OAc)_2$ in procedure A with $Pd(dba)_2$. [b]All reported yields are for isolated products.

when aryl iodide **23** was utilized. The resulting indanone **24** was obtained in only a 45% yield (entry 9).

The corresponding aryl bromide **25** and aryl triflate **26** were also reacted under the standard palladium conditions. Unfortunately, neither substrate produced any product (entries 10 and 11). In each case, the starting material still remained after 72 h and there was no evidence of any products.

A couple of pyridine-containing substrates were prepared and reacted under the standard palladium conditions. Compounds **27** and **28**, which contain a bromide and an iodide in the 2-position of the pyridine ring, did not cyclize to the corresponding cyclopentenone (entries 12 and 13). It has been reported by Heck that 2- and 4-bromopyridines react poorly with styrene when performing palladium-catalyzed vinylic substitution reactions.[35] However, compound **30**, which contains a bromide in the 3-position, does not produce the desired cyclopentenone either (entry 14). In all of the pyridine examples, the starting materials disappeared after 72 h and there was no evidence of any products being formed.

In addition to reactions which form 5,6 ring-fused ketones, a few examples were tried which would presumably lead to a 5,5 ring-fused system. However, both aryl iodide **32** and vinylic triflate **34** produced non-cyclized carboxylic acid derivatives (entries 15 and 16). The failure of these substrates to cyclize to the ketone can be attributed to the ring strain introduced in trying to form a 5,5 ring-fused system. The acylpalladium intermediate may not be able to properly coordinate to the nearby olefin and subsequently add across the carbon-carbon double bond.

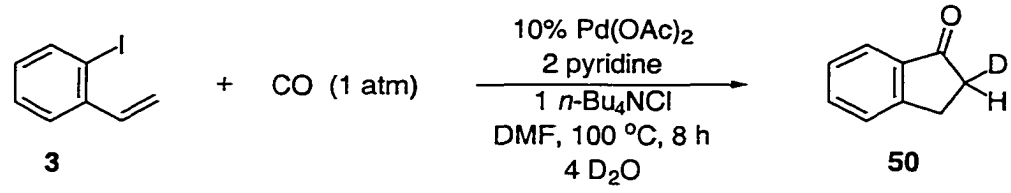
Vinylic derivatives which contain a triflate, bromide or iodide and are able to cyclize to a 5,6 ring-fused cyclopentenone efficiently. Vinylic triflate **36** reacted under the standard palladium conditions to produce cyclopentenone **37** in a 95% yield after a 12 h reaction time (entry 17). The corresponding vinylic bromide **38** and vinylic iodide **39** also gave high 87% and 86% yields of cyclopentenone **37** (entries 18 and 19). However, the reaction times for both **38** and **39** increased to 72 h. It should also be noted that vinylic bromide **38** required 10 mol % of $Pd(dba)_2$, instead of 10 mol % $Pd(OAc)_2$, as the palladium catalyst (procedure B). When **38** was reacted using $Pd(OAc)_2$ as the catalyst, palladium black precipitated out of solution after only 1 h and only a trace amount of indanone **37** was detected after 72 h. Precipitated palladium black was only found when reacting vinylic bromides and no other starting materials. Vinylic iodides **40** and **42**, which were synthesized from α- and β-tetralone, also produced high 85% and 98% yields of the corresponding cyclopentenones (entries 20 and 21). However, vinylic bromide **44**, which was prepared from 4-chromanone, did not cyclize using procedure B (entry 22). The starting material disappeared after 72 h, but there were no products detected by TLC or GC-MS. The reason for the failure of this reaction is not understood, since it is similar to other starting materials that have worked well.

Lastly, a 5,7 ring-fused cyclopentenone was prepared from vinylic bromide **46** in a 98% yield (entry 23). Also, acyclic vinylic iodide **48** afforded cyclopentenone **49** in a 70% yield after a 24 h reaction time (entry 24).

From these results, it appears that indanone derivatives can be prepared in moderate to excellent yields from *o*-iodostyrenes. However, this cyclization does

not occur with starting materials that contain more hindered internal carbon-carbon double bonds. This process also works well on dienyl bromides, iodides and triflates to produce 2-cyclopentenone derivatives. Limitations have been discovered when attempting to form 5,5 ring-fused systems. In this latter case, carboxylic acids are produced by palladium-catalyzed carbonylation of the aryl iodide or vinylic triflate.

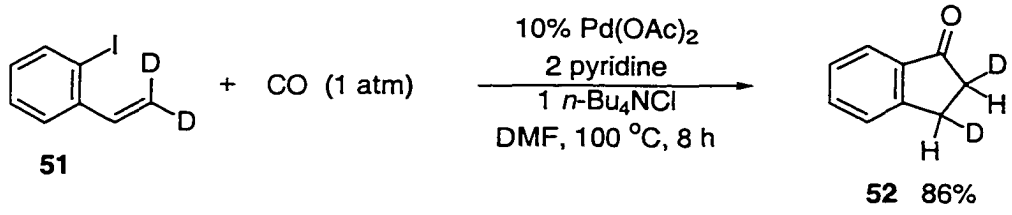
The mechanism for this process was not clearly understood initially, since the products differed significantly from Negishi's earlier work.[33] Negishi's products were presumably derived from the β-hydride elimination of a palladium intermediate to form indenones or insertion of a second CO under high pressures to form ester derivatives. In our system, a proton is incorporated into the product to form the indanone or 2-cyclopentenone. One possible source of this proton is the solvent DMF. Therefore, an experiment was carried out replacing DMF with DMA under the standard palladium conditions and employing **3** as the starting material. It was discovered that indanone was still produced in a near quantitative yield in the same 8 h reaction time. A second possible proton source is water. Water could be introduced into the system by either *n*-$Bu_4NCl$ or DMF, since both of these materials are hygroscopic. Another experiment was carried out with **3**, in which 4 equiv of $D_2O$ were added to a reaction employing the standard palladium conditions (eq 7). The indanone product recovered contained 55% deuterium in the 2-position and no deuterium incorporation was found in the 3-position. In a separate experiment, it was found that indanone itself will incorporate 55% deuterium at the 2-position under the standard palladium conditions when 4 equiv




3 50 (7)

of $D_2O$ are added. Therefore, the results from the experiment in equation 7 only suggest that the palladium intermediate formed after addition across the carbon-carbon double bond does not directly incorporate a proton from water. The deuterium is apparently only introduced later, after the indanone product has been formed.

In another mechanistic reaction, styryl derivative **51**, which contains two deuteria at the terminal positions of the olefin, was reacted under the standard palladium conditions (eq 8). It was found that 35% deuterium was incorporated



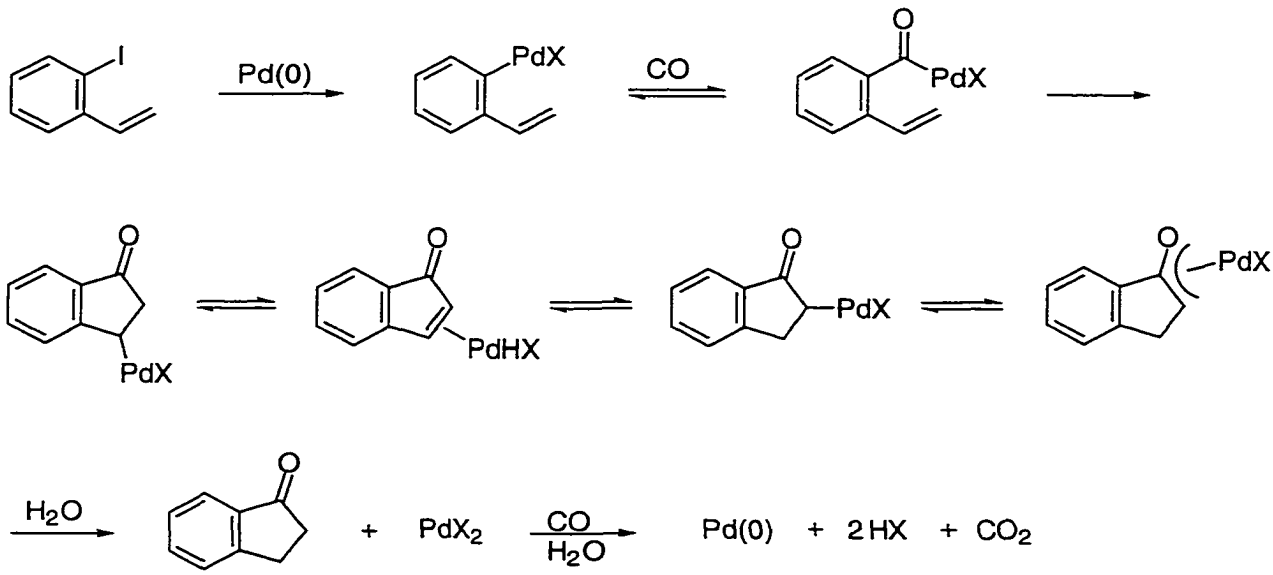

51 52 86% (8)

into the 3-position and 12% deuterium was incorporated into the 2-position with an 86% overall yield. The deuterium incorporation in the 3-position shows that a deuterium is migrating from the 2-position. The relatively low percentage of deuterium at the 2-position can be explained by deuterium-proton exchange occurring with $H_2O$, present in the reaction conditions, after the 2,3-dideutero-

indanone is formed. From these mechanistic studies, the following mechanism for this transformation is proposed: (1) $Pd(OAc)_2$ reduction to the active palladium(0) catalyst; (2) oxidative addition of the aryl iodide to Pd(0); (3) coordination and insertion of carbon monoxide to produce an acylpalladium intermediate; (4) addition across the carbon-carbon double bond; (5) palladium β-hydride elimination and readdition to form a palladium enolate; and (6) protonation by $H_2O$ to produce indanone and a Pd(II) salt, which is once again reduced to Pd(0) (Scheme 4).

Indenone was also prepared and reacted under the standard palladium conditions to see if it can be reduced to indanone. After a 12 h reaction time, the only material found in the reaction mixture was indenone itself, which was

**Scheme 4**



recovered in 80% yield. This reaction supports the idea that after the palladium β-hydride elimination, the palladium hydride never dissociates from the indenone, but rather readds rapidly to form the palladium enolate.

## Conclusion

Indanones and 2-cyclopentenones have been successfully prepared by a palladium-catalyzed carbonylative cyclization of unsaturated aryl iodides and dienyl triflates, iodides, and bromides in moderate to excellent yields. A number of ketone derivatives have been prepared. However, it has been observed that a terminal olefin is required in order to obtain high yields; presumably this is due to steric hindrance to alkene insertion by the more hindered olefin. Several bicyclic cyclopentenones containing 5,6 and 5,7 fused-rings have been prepared in excellent yields. However, 5,5 ring-fused products cannot be obtained.

Several mechanistic experiments employing $D_2O$ have been performed which help explain the mechanism for this process. It is likely that this palladium transformation is forming an indenone intermediate, which is coordinated to a palladium hydride species. This palladium hydride adds back across the carbon-carbon double bond to form a palladium enolate, which is protonated by $H_2O$.

## Experimental

**General.** $^1H$ and $^{13}C$ NMR spectra were recorded at 300 and 75.5 MHz respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected

with short wavelength UV light (254 nm) and basic $KMnO_4$ solution (3 g of $KMnO_4$ + 20 g of $K_2CO_3$ + 5 mL of NaOH (5%) + 300 mL of $H_2O$). All melting points are uncorrected. Low resolution mass spectra were recorded on a Finnigan TSQ700 triple quadrupole mass spectrometer (Finnigan MAT, San Jose, CA). High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV.

**Reagents.** All reagents were used directly as obtained commercially unless otherwise noted. Pyridine, DMF, DMA, THF, hexanes, ethyl acetate, and ethyl ether were purchased from Fisher Scientific Co. *n*-$Bu_4NCl$ was purchased from Lancaster Synthesis, Inc. 1-Indanone, 3,4,5-trimethoxybenzyl alcohol, 3,4-dimethoxybenzaldehyde, cyclohexanone, α-tetralone, β-tetralone, 4-chromanone, cycloheptanone, ethyl 2-cyclohexanonecarboxylate, ethyl 2-cyclopentanonecarboxylate, 2-furoic acid, 4-octyne, 2-bromopyridine, 3-bromopyridine, salicylaldehyde, methyltriphenylphosphonium bromide, iodomethane-$d_3$, and *n*-BuLi were purchased from Aldrich Chemical Co., Inc. 2-Iodobenzaldehyde,[36] 1-iodo-2-vinylbenzene, 1-iodo-2-isopropenylbenzene,[33] 1-iodo-2-propenylbenzene,[33] 4,5-dimethoxy-2-iodobenzaldehyde,[37] 2-iodo-3,4,5-trimethoxybenzaldehyde,[38] 1-bromo-2-vinylbenzene,[39] 4-iodo-3-*n*-propylhepta-1,3-diene,[40] 2-bromopyridine-3-carbaldehyde,[41] 3-bromopyridine-4-carbaldehyde,[41] indenone[42] and (methyl-$d_3$)triphenylphosphonium iodide[43] were prepared according to previous literature procedures.

**Starting materials prepared**

**1-(2-Iodophenyl)-1-phenylethene (11).** Methyltriphenylphosphonium bromide (5.5 mmol) was suspended in THF (10 mL) and *n*-BuLi (5.5 mmol of a 2.5 M soln) was added dropwise with stirring under nitrogen at 0 °C. After 30 min at 0 °C, 2-iodobenzophenone (5 mmol) in THF (5 mL) was added dropwise and stirred for 1 h. The reaction was quenched with $H_2O$ (20 mL) and extracted with ether (3 x 20 mL). The extracts were dried ($Na_2SO_4$), concentrated under vacuum and chromatographed on a silica gel column using 10:1 hexane/ethyl acetate to afford **11** as a clear oil in an 84% yield: $^1$H NMR ($CDCl_3$) δ 5.28 (s, 1 H), 5.89 (s, 1 H), 7.07 (dt, *J* = 2.0, 7.6 Hz, 1 H), 7.33-7.77 (m, 7 H), 7.93 (dd, *J* = 0.8, 7.6 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 99.16, 116.09, 126.96, 127.89, 128.19, 128.48, 129.04, 130.77, 139.32, 139.56, 146.70, 151.63; IR (neat) 3080, 3027, 1493 cm$^{-1}$; HRMS calcd for $C_{14}H_{11}I$ 305.99113, found 305.99113.

**1-Iodo-4,5-dimethoxy-2-vinylbenzene (21).** This compound was prepared by the same method used for the preparation of **11**, but 4,5-dimethoxy-2-iodobenzaldehyde was employed. Removal of the solvent afforded a 90% yield of compound **21** as a clear oil: $^1$H NMR ($CDCl_3$) δ 3.84 (s, 3 H), 3.87 (s, 3 H), 5.20 (dd, *J* = 0.9, 10.3 Hz, 1 H), 5.50 (dd, *J* = 0.9, 17.4 Hz, 1 H), 6.79 (dd, *J* = 10.8, 17.4 Hz, 1 H), 7.00 (s, 1 H), 7.20 (s, 1 H); $^{13}$C NMR ($CDCl_3$) δ 56.18, 56.38, 88.65, 108.71, 115.10, 121.55, 133.34, 140.46, 149.63, 149.71; IR (neat) 3053, 2985, 1594 cm$^{-1}$; HRMS calcd for $C_{10}H_{11}IO_2$ 289.98038, found 289.98079.

**2-Iodo-3,4,5-trimethoxy-1-vinylbenzene (23).** This compound was prepared by the same method used for the preparation of **11**, but 2-iodo-3,4,5-trimethoxybenzaldehyde was employed. Removal of the solvent afforded a 66% yield of compound **23** as a clear oil: $^1$H NMR ($CDCl_3$) δ 3.84 (s, 3 H), 3.85 (s, 3 H), 3.86 (s, 3 H), 5.23 (dd, $J$ = 0.8, 10.8 Hz, 1 H), 5.50 (d, $J$ = 17.2 Hz, 1 H), 6.88 (s, 1 H), 6.91 (dd, $J$ = 10.8, 17.2 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 56.19, 60.77, 61.09, 88.05, 105.65, 116.06, 136.62, 140.82, 141.99, 153.04, 153.84; IR (neat) 3050, 2950, 1555 cm$^{-1}$; HRMS calcd for $C_{11}H_{13}IO_3$ 319.99095, found 319.99136.

**2-Vinylphenyl trifluoromethanesulfonate (26).** Methyltriphenylphosphonium bromide (22 mmol) was suspended in THF (15 ml) and *n*-BuLi (22 mmol of a 2.5 M soln) was added dropwise with stirring under nitrogen at 0 °C. After 30 min at 0 °C, salicylaldehyde (10 mmol) in THF (10 mL) was added dropwise and stirred for 1 h. The reaction was quenched with $H_2O$ (20 mL) and extracted with ether (3 x 20 mL). The extracts were dried ($Na_2SO_4$), concentrated under vacuum and chromatographed on a silica gel column using 10:1 hexane/ethyl acetate to afford 2-vinylphenol as a clear oil in a 40% yield.

To a solution of 2-vinylphenol (4.7 mmol) in $CH_2Cl_2$ (60 mL) was added *i*-$Pr_2NEt$ (9 mmol) in $CH_2Cl_2$ (7 mL) and TfCl (13.5 mmol) in $CH_2Cl_2$ (7 mL) at -78 °C. The reaction was stirred for an hour at -78 °C and then allowed to warm up to room temp and stirred overnight. The reaction was quenched by adding satd aq $NaHCO_3$ and the mixture was extracted with EtOAc (3 x 25 mL). The combined extracts were washed with brine, dried ($Na_2SO_4$), and concentrated under vacuum. The resulting residue was chromatographed on a silica gel column using 10:1

hexane/ethyl acetate to afford **26** as a clear oil in a 90% yield: $^1$H NMR ($CDCl_3$) δ 5.50 (d, $J$ = 11.1 Hz, 1 H), 5.86 (d, $J$ = 17.4 Hz, 1 H), 6.94 (dd, $J$ = 11.1, 17.4 Hz, 1 H), 7.26-7.39 (m, 3 H), 7.64-7.67 (m, 1 H); $^{13}$C NMR ($CDCl_3$) δ 118.82, 118.85 (q, $J$ = 320.6 Hz), 121.87 (q, $J$ = 0.91 Hz), 127.48, 128.62, 129.08, 129.50, 131.29, 147.09; IR (neat) 3095, 2950, 1484 cm$^{-1}$; HRMS calcd for $C_9H_7F_3O_3S$ 252.00680, found 252.00712.

**2-Bromo-3-vinylpyridine (27).** Methyltriphenylphosphonium bromide (5.5 mmol) was suspended in THF (10 mL) and *n*-BuLi (5.5 mmol of a 2.5 M soln) was added dropwise with stirring under nitrogen at 0 °C. After 30 min at 0 °C, 2-bromopyridine-3-carbaldehyde (5 mmol) in THF (5 mL) was added dropwise and stirred for 1 h. The reaction was quenched with $H_2O$ (20 mL) and extracted with ether (3 x 20 mL). The extracts were dried ($Na_2SO_4$), concentrated under vacuum and chromatographed on a silica gel column using 10:1 hexane/ethyl acetate to afford **27** as a clear oil in an 80% yield: $^1$H NMR ($CDCl_3$) δ 5.41 (d, $J$ = 11.2 Hz, 1 H), 5.69 (d, $J$ = 17.6 Hz, 1 H), 6.90 (dd, $J$ = 11.2, 17.6 Hz, 1 H), 7.19 (dd, $J$ = 4.4, 7.6 Hz, 1 H), 7.74 (dd, $J$ = 2.0, 7.6 Hz, 1 H), 8.19 (dd, $J$ = 2.0, 4.8 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 118.85, 123.07, 134.11, 134.66, 134.74, 142.92, 148.97; IR (neat) 3080, 2985, 1510 cm$^{-1}$; HRMS calcd for $C_7H_6BrN$ 184.96836, found 184.96875.

**2-Iodo-3-vinylpyridine (29).** In a 50 mL round bottom flask, *n*-BuLi (4.4 mmol) was added dropwise to 2-bromo-3-vinylpyridine (4 mmol) in ether (10 mL) at -30 °C. The mixture was stirred for 20 min at -30 °C at which time $I_2$ (8 mmol) in ether (5 mL) was added dropwise. The solution was stirred 30 min, quenched with $H_2O$ (50 mL) and extracted with ether (3 x 25 mL). The extracts were dried

($Na_2SO_4$), concentrated under vacuum and chromatographed on a silica gel column using 10:1 hexane/ethyl acetate to afford **29** as a yellow oil in a 50% yield: $^1$H NMR ($CDCl_3$) δ 5.41 (dd, $J$ = 0.8, 11.2 Hz, 1 H), 5.65 (dd, $J$ = 0.4, 17.2 Hz, 1 H), 6.78 (dd, $J$ = 10.8, 17.2 Hz, 1 H), 7.20 (ddd, $J$ = 0.8, 4.8, 8.0 Hz, 1 H), 5.41 (dd, $J$ = 0.8, 11.2 Hz, 1 H), 5.65 (dd, $J$ = 0.4, 17.2 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 118.93, 123.20, 123.39, 133.25, 138.19, 138.41, 149.55; IR (neat) 3091, 3052, 2985, 1568 cm$^{-1}$; HRMS calcd for $C_7H_6IN$ 230.95450, found 230.95485.

**3-Bromo-4-vinylpyridine (30).** This compound was prepared by the same method used for the preparation of **27**, but 3-bromopyridine-4-carbaldehyde was employed: $^1$H NMR ($CDCl_3$) δ 5.53 (d, $J$ = 10.8 Hz, 1 H), 5.88 (d, $J$ = 17.2 Hz, 1 H), 6.92 (dd, $J$ = 10.8, 17.6 Hz, 1 H), 7.35 (d, $J$ = 4.8, 1 H), 8.4 (d, $J$ = 5.2 Hz, 1 H), 8.64 (s, 1 H); $^{13}$C NMR ($CDCl_3$) δ 120.68, 120.83, 121.40, 133.61, 144.38, 148.28, 152.48; IR (neat) 3080, 2985, 1510 cm$^{-1}$; HRMS calcd for $C_7H_6BrN$ 184.96836, found 184.96875.

**3-Iodo-5-trimethylsilyl-2-vinylfuran (32).** 3-Iodo-5-trimethylsilyl-2-furoic acid (8 mmol) was dissolved in dry THF (135 mL) and treated with $BH_3$•THF (16 mmol). The resulting cloudy white soln was heated at reflux for 4 h, cooled and carefully quenched with $H_2O$ (270 mL). The mixture was extracted with ether (3 x 25 mL). The combined organic layers were washed with $NaHCO_3$ (2 x 100 mL), $H_2O$ (100 mL), dried ($Na_2SO_4$), concentrated under vacuum and chromatographed on a silica gel column using 10:1 hexane/ethyl acetate to afford 3-iodo-5-trimethylsilyl-2-(hydroxymethyl)furan as a clear oil in a 90% yield.

3-Iodo-5-trimethylsilyl-2-(hydroxymethyl)furan (5 mmol), $MnO_2$ (100 mmol), and $CH_2Cl_2$ (75 mL) were placed in a 250 mL round bottom flask and flushed with Ar. The mixture was stirred overnight and filtered through Celite. The solvent was evaporated affording 3-iodo-5-(trimethylsilyl)furan-2-carbaldehyde as a clear oil in a 91% yield.

Methyltriphenylphosphonium bromide (4.4 mmol) was suspended in THF (10 mL) and *n*-BuLi (4.4 mmol of a 2.5 M soln) was added dropwise with stirring under nitrogen at 0 °C. After 30 min at 0 °C, 3-iodo-5-(trimethylsilyl)furan-2-carbaldehyde (4 mmol) in THF (5 mL) was added dropwise and stirred for 1 h. The reaction was quenched with $H_2O$ (20 mL) and extracted with ether (3 x 20 mL). The extracts were dried ($Na_2SO_4$), concentrated under vacuum and chromatographed on a silica gel column using 10:1 hexane/ethyl acetate to afford **32** as a clear oil in a 61% yield: $^1$H NMR ($CDCl_3$) $\delta$ 0.28 (s, 9 H), 5.25-5.30 (m, 1 H), 5.78-5.84 (m, 1 H), 6.61 (ddd, $J$ = 0.6, 11.4, 17.4 Hz, 1 H), 6.67 (d, $J$ = 0.6 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 1.52, 65.92, 115.08, 123.88, 128.17, 156.28, 161.72; IR (neat) 3053, 2985, 1422 cm$^{-1}$; HRMS calcd for $C_9H_{13}IOSi$ 291.97805, found 291.97866.

**2-Vinyl-1-cyclohexenyl trifluoromethanesulfonate (36).** To a soln of ethyl 2-oxocyclohexanecarboxylate (20 mmol), in $CH_2Cl_2$ (50 mL) was added *i*-$Pr_2NEt$ (17.5 mL) at -78 °C. The mixture was stirred for 10 min during which $Tf_2O$ (24 mmol) was added dropwise, followed by slow warming to room temp overnight. The mixture was washed with $H_2O$ (50 mL) and a 10% aq citric acid soln (2 x 75 mL). The organic layer was dried ($Na_2SO_4$), concentrated under vacuum, and chromatographed on a silica gel column with 10:1 hexane/ethyl acetate to produce

ethyl 2-trifluoromethanesulfonyloxy-1-cyclohexenecarboxylate as a clear oil in a 99% yield.

To a cold (0 °C) magnetically stirred solution of ethyl 2-trifluoromethanesulfonyloxy-1-cyclohexenecarboxylate (8 mmol) in anhydrous ether (20 mL) was added DIBAl-H (24 mmol, 1 M soln in hexanes). The reaction was stirred at 0 °C for 30 min and quenched with ethyl acetate (20 mL), followed by sufficient HCl (1 M aq soln) to dissolve all of the precipitated solid. The separated aq phase was extracted with ether (3 x 50 mL) and the combined organic extracts were washed with 1 M HCl (3 x 50 mL), dried ($Na_2SO_4$), and concentrated under vacuum. The resulting residue was chromatographed on a silica gel column with 10:1 hexane/ethyl acetate to produce 2-(hydroxymethyl)cyclohex-1-enyl trifluoromethanesulfonate as a clear oil in an 85% yield.

2-(Hydroxymethyl)cyclohex-1-enyl trifluoromethanesulfonate (5 mmol), $MnO_2$ (100 mmol), and $CH_2Cl_2$ (75 mL) were placed in a 250 mL round bottom flask and flushed with Ar. The mixture was stirred overnight and filtered through Celite. The solvent was evaporated giving 2-trifluoromethanesulfonyloxy-1-cyclohexenecarbaldehyde as a pale yellow oil in an 85% yield. The aldehyde formed decomposes rapidly. Therefore, it was immediately used in the next step.

Methyltriphenylphosphonium bromide (6.6 mmol) was suspended in THF (15 mL) and *n*-BuLi (6.6 mmol of a 2.5 M soln) was added dropwise with stirring under nitrogen at 0 °C. After 30 min at 0 °C, 2-trifluoromethanesulfonyloxy-1-cyclohexenecarbaldehyde (6 mmol) in THF (10 mL) was added dropwise and stirred for 1 h. The reaction was quenched with $H_2O$ (20 mL) and extracted with

ether (3 x 20 mL). The extracts were dried ($Na_2SO_4$), concentrated under vacuum and chromatographed on a silica gel column using 10:1 hexane/ethyl acetate to yield 2-vinyl-1-cyclohexenyl trifluoromethanesulfonate as a clear oil in a 25% yield: $^1H$ NMR ($CDCl_3$) δ 1.65-1.82 (m, 4 H), 2.31-2.36 (m, 2 H), 2.42-2.44 (m, 2 H), 5.24 (d, $J$ = 11.1 Hz, 1 H), 5.34 (dt, $J$ = 0.9, 17.4 Hz, 1 H), 6.78 (dd, $J$ = 10.8, 17.4 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 21.53, 23.06, 24.52, 28.36, 116.52, 120.69, 127.17, 129.90, 145.90; IR (neat) 3099, 2945, 1664 $cm^{-1}$; HRMS calcd for $C_9H_{11}F_3O_3S$ 256.03810, found 256.03848.

**2-Vinyl-1-cyclopentenyl trifluoromethanesulfonate (34).** This compound was prepared by the same method used for the preparation of **36**, but ethyl 2-oxocyclopentanecarboxylate was employed (20 mmol): $^1H$ NMR ($CDCl_3$) δ 1.98-2.08 (m, 2 H), 2.49-2.56 (m, 2 H), 2.73 (t, $J$ = 7.5 Hz, 2 H), 5.21-5.31 (m, 2 H), 6.60 (dd, $J$ = 10.8, 17.4 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 19.42, 27.76, 31.67, 118.62, 118.66 (q, $J$ = 320.6 Hz), 126.86, 129.86, 144.75; IR (neat) 3110, 2955, 1664 $cm^{-1}$; HRMS calcd for $C_8H_9F_3O_3S$ 242.07245, found 242.02280.

**1-Bromo-2-vinylcyclohexene (38).** Dry DMF (150 mmol) was cooled to 0 °C in dry $CHCl_3$ (220 mL) and $PBr_3$ (125 mmol) was added dropwise. The mixture was stirred at 0 °C for 1 h to give a yellow suspension. A soln of cyclohexanone (50 mmol) in $CHCl_3$ (50 mL) was added and the mixture was heated under reflux for 1 h. The reaction was cooled to 0 °C and aq $NaHCO_3$ was added slowly until the effervescence subsided. The mixture was extracted with $CH_2Cl_2$ (3 x 50 mL). The extracts were dried ($Na_2SO_4$), concentrated under vacuum

and chromatographed on a silica gel column using 10:1 hexane/ethyl acetate to afford 2-bromocyclohex-1-enecarbaldehyde as a yellow oil in a 30% yield.

Methyltriphenylphosphonium bromide (11 mmol) was suspended in THF (15 mL) and *n*-BuLi (11 mmol of a 2.5 M soln) was added dropwise with stirring under nitrogen at 0 °C. After 30 min at 0 °C, 2-bromocyclohex-1-enecarbaldehyde (10 mmol) in THF (10 mL) was added dropwise and stirred for 1 h. The reaction was quenched with $H_2O$ (20 mL) and extracted with ether (3 x 20 mL). The extracts were dried ($Na_2SO_4$), concentrated under vacuum and chromatographed on a silica gel column using 10:1 hexane/ethyl acetate to afford 1-bromo-2-vinylcyclohexene as a clear oil in an 82% yield: $^1$H NMR ($CDCl_3$) δ 1.70-1.74 (m, 4 H), 2.25-2.29 (m, 2 H), 2.62-2.64 (m, 2 H), 5.13 (dq, $J$ = 0.6, 8.1 Hz, 1 H), 5.25 (dq, $J$ = 0.6, 12.9 Hz, 1 H), 6.91 (dd, $J$ = 8.1, 12.9 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 22.31, 24.97, 27.01, 37.81, 114.60, 125.39, 132.45, 137.28; IR (neat) 3050, 2975, 1421 $cm^{-1}$. The remaining spectral properties match those previously reported in the literature.[44]

**1-Iodo-2-vinylcyclohexene (39).** To a 25 mL round bottom flask was added 1-bromo-2-vinylcyclohexene (3.5 mmol), Mg (4.2 mmol), dry THF (6 mL), and one drop of $CH_3I$. The mixture was refluxed for 2 h, at which time a soln of $I_2$ (7 mmol) in THF (10 mL) was added and stirred for 1 h at room temperature. The reaction mixture was hydrolyzed with 2 N HCl and the product was extracted with ether. The ethereal soln was washed with satd aq NaCl, dried ($Na_2SO_4$), concentrated under vacuum, and chromatographed on a silica gel column using 10:1 hexane/ethyl acetate to afford **39** as a pale yellow oil in a 63% yield (95%

percent pure, 5% of the corresponding bromide remained): $^1$H NMR ($CDCl_3$) δ 1.64-1.70 (m, 2 H), 1.74-1.80 (m, 2 H), 2.30-2.34 (m, 2 H), 2.78-2.81 (m, 2 H), 5.10 (dq, $J$ = 0.6, 8.1 Hz, 1 H), 5.25 (dq, $J$ = 0.6, 12.9 Hz, 1 H), 6.69 (dd, $J$ = 8.1,12.9 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 22.45, 26.17, 27.50, 43.15, 105.28, 115.28, 137.30, 142.8; IR (neat) 3053, 2986, 1421 cm$^{-1}$; HRMS calcd for $C_8H_{11}I$ 233.99055, found 233.98562.

**1-Vinyl-2-iodo-3,4-dihydronaphthalene (40).** This compound was prepared by the same method used for the preparation of **39**, but β-tetralone was employed: $^1$H NMR ($CDCl_3$) δ 2.81-2.84 (m, 2 H), 2.92-2.96 (m, 2 H), 5.42 (dd, $J$ = 0.8, 17.9 Hz, 1 H), 5.51 (dd, $J$ = 1.2, 11.2 Hz, 1 H), 6.59 (dd, $J$ = 11.6, 18.0 Hz, 1 H), 7.14-7.21 (m, 3 H), 7.42-7.44 (m, 1 H); $^{13}$C NMR ($CDCl_3$) δ 30.22, 40.33, 100.44, 120.61, 125.92, 126.38, 127.43, 127.62, 133.45, 136.22, 139.00, 140.07; IR (neat) 3010, 2950, 1450 cm$^{-1}$; HRMS calcd for $C_{12}H_{11}I$ 281.99055, found 281.99094.

**2-Vinyl-1-iodo-3,4-dihydronaphthalene (42).** This compound was prepared by the same method used for the preparation of **39**, but α-tetralone was employed: $^1$H NMR ($CDCl_3$) δ 2.60-2.63 (m, 2 H), 2.82-2.87 (m, 2 H), 5.37 (d, $J$ = 11.1 Hz, 1 H), 5.54 (d, $J$ = 17.1 Hz, 1 H), 7.01-7.30 (m, 4 H), 7.70 (d, J = 7.5 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 26.38, 28.31, 117.67, 126.77, 126.96, 127.12, 128.29, 132.51, 136.62, 136.73, 141.27, 142.99; IR (neat) 3086, 2945, 2885, 2829, 1480 cm$^{-1}$; HRMS calcd for $C_{12}H_{11}I$ 281.99055, found 281.99094.

**4-Bromo-3-vinyl-2*H*-chromene (44).** This compound was prepared by the same method used for the preparation of **38**, but 4-chromanone was employed: $^1$H NMR ($CDCl_3$) δ 4.95 (s, 2 H), 5.32 (d, $J$ = 17.6 Hz, 1 H), 5.40 (d, $J$ = 11.2 Hz, 1 H),

6.85 (dd, $J$ = 0.8, 8.0 Hz, 1 H), 6.91-7.01 (m, 2 H), 7.19 (dt, $J$ = 1.6, 8.0 Hz, 1 H), 7.55, (d, $J$ = 7.6 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 66.57, 115.63, 116.91, 118.60, 121.91, 122.93, 127.86, 128.61, 130.28, 133.50, 154.31; IR (neat) 3080, 2885, 1480 $cm^{-1}$; HRMS calcd for $C_{11}H_9BrO$ 235.98368, found 235.98416.

**1-Bromo-2-vinylcycloheptene (46).** This compound was prepared by the same method used for the preparation of **38**, but cycloheptanone was employed: $^1$H NMR ($CDCl_3$) δ 1.45-1.51 (m, 2 H), 1.53-1.62 (m, 2 H), 1.72-1.80 (m, 2 H), 2.39-2.43 (m, 2 H), 2.85-2.88 (m, 2 H), 5.14 (dd, $J$ = 0.9, 11.1 Hz, 1 H), 5.26 (d, $J$ = 17.4 Hz, 1 H), 6.81 (dd, $J$ = 10.8, 17.1 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 25.28, 25.39, 27.95, 31.53, 41.78, 114.44, 127.68, 137.85, 138.76; IR (neat) 3085, 2880, 1480 $cm^{-1}$; HRMS calcd for $C_9H_{13}Br$ 200.02006, found 200.02036.

**2-(2,2-Dideuteriovinyl)-1-iodobenzene (51).** (Methyl-$d_3$)triphenylphosphonium iodide (5.5 mmol) was suspended in THF (10 mL) and *n*-BuLi (5.5 mmol of a 2.5 M soln) was added dropwise with stirring under nitrogen at 0 °C. After 30 min at 0 °C, 2-iodobenzaldehyde (5 mmol) in THF (5 mL) was added dropwise and stirred for 1 h. The reaction was quenched with $H_2O$ (20 mL) and extracted with ether (3 x 20 mL). The extracts were dried ($Na_2SO_4$), concentrated under vacuum and chromatographed on a silica gel column using 10:1 hexane/ethyl acetate to afford **51** as a clear oil in an 60% yield with 93% deuterium incorporation: $^1$H NMR ($CDCl_3$) δ 5.31-5.35 (m, 0.07 H), 5.61-5.66 (m, 0.07 H), 6.91 (s, 1 H), 6.96 (dt, $J$ = 1.6, 7.6 Hz, 1 H), 7.31-7.35 (m, 1 H), 7.53 (dd, $J$ = 1.6, 7.6 Hz, 1 H), 7.86 (dd, $J$ = 1.2, 8.0 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 99.77, 126.43, 128.46,

129.33, 139.49, 140.51, 140.79 (one $sp^2$ carbon mixing due to overlap); IR (neat) 3055, 2985, 1485 $cm^{-1}$; HRMS calcd for $C_8H_5D_2I$ 231.97181, found 231.97230.

**General procedure for the palladium-catalyzed carbonylative cyclization of unsaturated aryl iodides and dienyl triflates, iodides and bromides.** The appropriate aryl iodide, dienyl triflate, dienyl bromide, or dienyl iodide (0.5 mmol), $Pd(OAc)_2$ (0.05 mmol), pyridine (1.0 mmol), *n*-$Bu_4NCl$ (0.5 mmol), and DMF (5 mL) were placed in a 4 dram vial. The reaction mixture was placed under a CO atmosphere *via* balloon and allowed to stir at 100 °C for the designated time. The reaction was diluted with satd aq $NH_4Cl$ (50 mL), extracted with diethyl ether (3 x 25 mL), and dried ($Na_2SO_4$). The solvent was evaporated under reduced pressure and the product was isolated by column chromatography. The following compounds were prepared using this procedure.

**1-Indanone (8).** The product was isolated in a 100% yield as a yellow oil after an 8 h reaction time The spectral properties match those previously reported in the literature.[45,46]

**3-Methylindan-1-one (10).** The product was isolated in a 100% yield as a yellow oil after a 12 h reaction time. The spectral properties match those previously reported in the literature.[47]

**3-Phenylindan-1-one (12).** The product was isolated in a 60% yield as a yellow oil after a 72 h reaction time. The spectral properties match those previously reported in the literature.[48-51]

**5,6-Dimethoxyindan-1-one (22).** The product was isolated in an 82% yield as a pale yellow solid after a 24 h reaction time: lit mp[52] 114-116 °C, found

110-113 °C. The spectral properties match those previously reported in the literature.[53]

**5,6,7-Trimethoxyindan-1-one (24).** The product was isolated in a 45% yield as a pale yellow solid after a 24 h reaction time: lit mp[54] 75-77 °C, found 74-75 °C. The spectral properties match those previously reported in the literature.[53]

**5-Trimethylsilyl-2-vinyl-3-furoic acid (33).** The product was isolated in a 61% yield as a pale yellow solid after a 24 h reaction time: mp 100-103 °C; $^1$H NMR ($CDCl_3$) δ 0.27 (s, 9 H), 5.47 (dd, $J$ = 1.2, 11.2 Hz, 1 H), 6.02 (dd, $J$ = 1.2, 17.6 Hz, 1 H), 6.93 (s, 1 H), 7.25 (dd, $J$ = 11.2, 17.6 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ -1.76, 113.80, 118.48, 121.39, 124.38, 160.38, 161.09, 169.30; IR (neat) 3500, 3053, 1683 cm$^{-1}$; HRMS calcd for $C_{10}H_{14}O_3Si$ 210.07122, found 210.07159.

**2-Vinylcyclopent-1-enecarboxylic acid (35).** The product was isolated in an 89% yield as a pale yellow solid after a 24 h reaction time: lit mp[55] 98-101 °C, found 100 °C; HRMS calcd for $C_8H_{10}O_2$ 138.06808, found 138.06828. The remaining spectral properties match those previously reported in the literature.[55]

**4,5,6,7-Tetrahydroindan-1-one (37).** The product was isolated in a 95% yield as a clear oil after a 12 h reaction time: $^{13}$C NMR ($CDCl_3$) δ 20.24, 21.92, 22.35, 28.79, 30.29, 34.69, 138.94, 173.85, 209.36. The remaining spectral properties match those previously reported in the literature.[15]

**1,2,4,5-Tetrahydrocyclopenta[*a*]naphthalen-3-one (41).** The product was isolated in an 85% yield as a pale yellow solid after a 72 h reaction

time: lit mp[56] 75-78 °C, found 78-79 °C; $^1$H NMR ($CDCl_3$) δ 2.49 (tt, $J$ = 1.8, 6.3, 12.3 Hz, 2 H), 2.59-2.61 (m, 2 H), 2.87-2.93 (m, 4 H), 7.24-7.40 (m, 4 H); $^{13}$C NMR ($CDCl_3$) δ 18.39, 25.16, 28.16, 35.50, 124.39, 127.04, 128.45, 131.02, 132.22, 137.87, 138.83, 166.14, 207.97; IR (neat) 3053, 2937, 2595, 1688, 1630 cm$^{-1}$; HRMS calcd for $C_{13}H_{12}O$ 184.08882, found 184.08922.

**2,3,4,5-Tetrahydrocyclopenta[*a*]naphthalen-1-one (43).** The product was isolated in a 98% yield as a pale yellow solid after a 72 h reaction time: mp 112-113 °C; $^1$H NMR ($CDCl_3$) δ 2.55-2.58 (m, 2 H), 2.62-2.67 (m, 4 H), 2.94 (t, $J$ = 6.0 Hz, 2 H), 7.16-7.26 (m, 3 H), 8.23 (d, $J$ = 5.7 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 27.29, 27.85, 29.49, 36.13, 124.13, 126.94, 127.76, 128.02, 129.34, 134.65, 135.09, 175.32, 206.41; IR (neat) 3053, 2985, 1696 cm$^{-1}$; HRMS calcd for $C_{13}H_{12}O$ 184.08882, found 184.08972.

**3,4,5,6,7,8-Hexahydro-2*H*-azulen-1-one (47).** The product was isolated in a 98% yield as a yellow oil after a 48 h reaction time. The spectral properties match those previously reported in the literature.[57]

**2,3-Di-*n*-propylcyclopent-2-enone (49).** The product was isolated in a 70% yield as a yellow oil after a 24 h reaction time: HRMS calcd for $C_{11}H_{18}O$ 166.13577, found 166.13600. The spectral properties match those previously reported in the literature.[58]

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# CHAPTER 3. SYNTHESIS OF QUINOLINES VIA PALLADIUM-CATALYZED IMINOANNULATION OF INTERNAL ALKYNES

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

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## Abstract

Substituted quinolines have been prepared through the annulation of internal alkynes by imines derived from *o*-iodoanilines in the presence of a palladium catalyst. The optimized palladium conditions provide for a 6-endo ring closure. The mechanism of this annulation appears to involve (1) reduction of $Pd(OAc)_2$ to the actual Pd(0) catalyst, (2) oxidative addition of the aryl iodide to Pd(0), (3) coordination and subsequent insertion of the acetylene to produce a vinylic palladium species, (4) a 6-endo addition of the vinylic palladium intermediate across the carbon-nitrogen double bond, (5) beta hydride elimination to form the quinoline, and (6) regeneration of the Pd(0) catalyst by reductive elimination of HPdI. This annulation, however, is limited in its generality and suffers from poor yields. A common side product is an isoindole derivative, which is formed by 5-exo ring closure of the vinylic palladium intermediate.

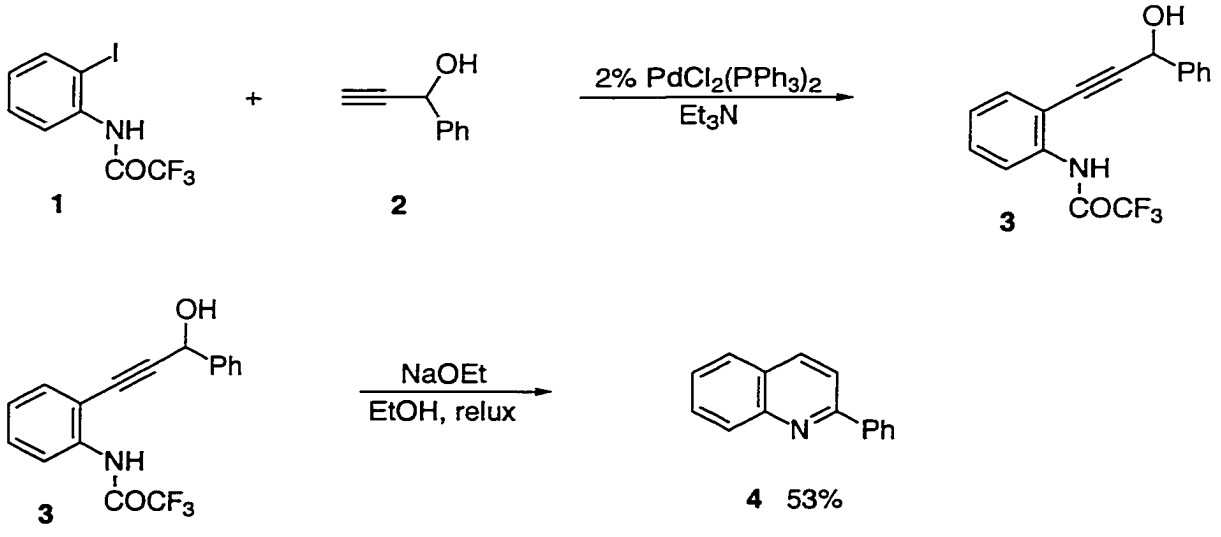
## Introduction

The synthesis of quinolines has received a considerable amount of attention in the literature, because the quinoline ring system is found in numerous biologically active natural and synthetic compounds.[1] Many of the early syntheses are limited in their generality and the harsh reaction conditions required.[1,2] This has led to the development of several palladium-catalyzed heteroannulation strategies, which employ relatively mild reaction conditions.

Kundu and coworkers have developed a palladium-catalyzed system, which involves the coupling of *ortho*-iodoanilides or *ortho*-iodoanilines with terminal acetylenic carbinols. Two general procedures have been used, the first of which contains a one-pot, two step approach.[3] *ortho*-Iodoanilide **1** and acetylenic carbinol **2** have been reacted with $PdCl_2(PPh_3)_2$ (2 mol %) in $Et_3N$ to produce compound **3** in a 61% yield (Scheme 1). Then, without isolating alkyne **3**, $Et_3N$ was removed under reduced pressure and the residue was refluxed with NaOEt in ethanol to obtain quinoline **4**. The disadvantages of this first approach include the conversion of *ortho*-iodoaniline into the *ortho*-iodotrifluoroacetanilide using costly trifluoroacetic anhydride, and the cyclization procedure in step two requires a strong base.

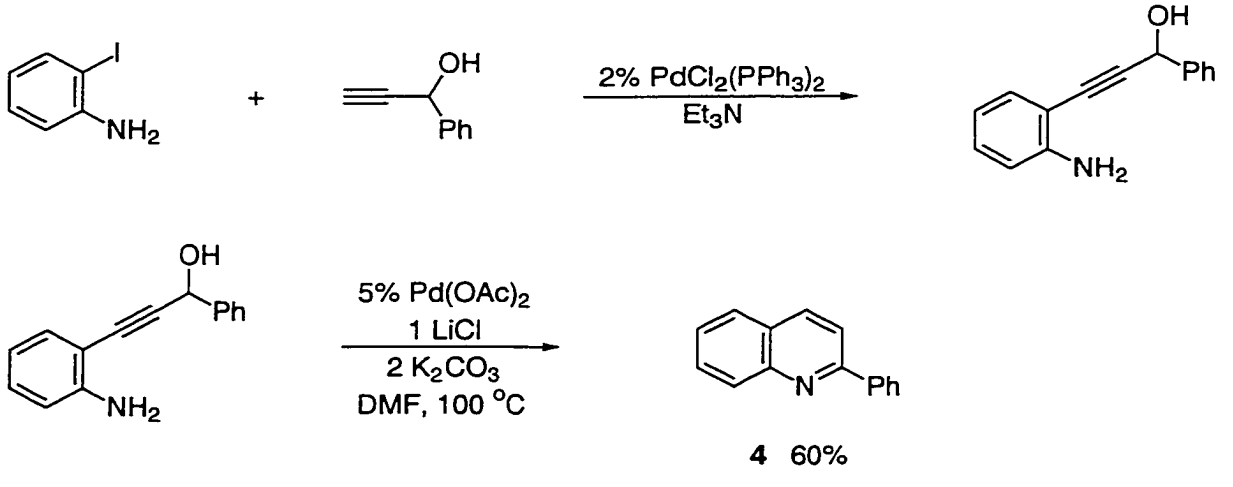
The second general procedure used by Kundu involves a palladium(II)-catalyzed annulation of *ortho*-aminoarylacetylenic carbinols.[4] This procedure requires two separate steps. The first step is the coupling of a terminal acetylene with *ortho*-iodoaniline. The second step is a palladium(II)-catalyzed heteroannulation to produce the quinoline ring structure (Scheme 2). The

**Scheme 1**

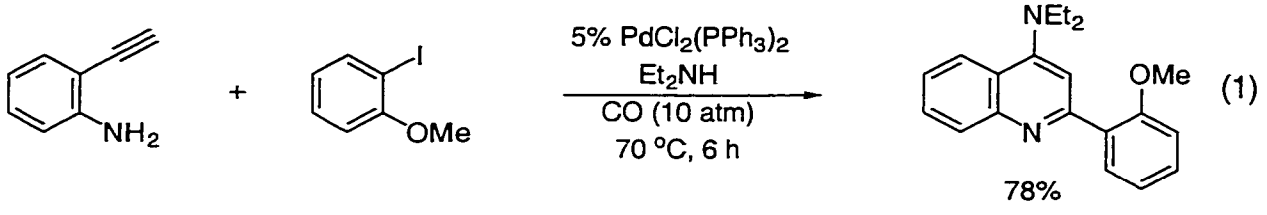



limitations of Kundu's second procedure for producing quinolines include (1) the requirement for a multiple step synthesis, and (2) this palladium-catalyzed annulation is limited to terminal alkynes, which does not allow for substitution at the 3- and 4-positions.

**Scheme 2**



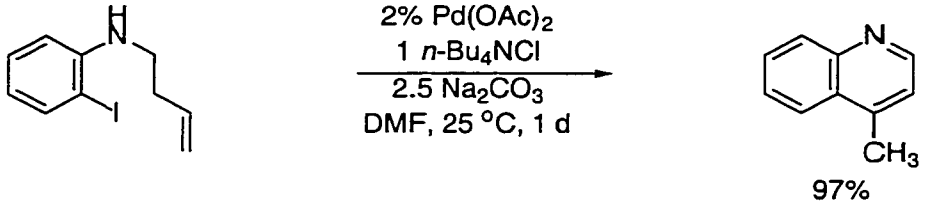
Another palladium-catalyzed method for the preparation of quinolines has been reported by Torii et al.[5] Their procedure includes a carbonylative coupling of 2-aminophenylacetylenes and aryl iodides in dialkylamines under a carbon monoxide atmosphere (eq 1). This procedure, like Kundu's, is limited by the




(1)

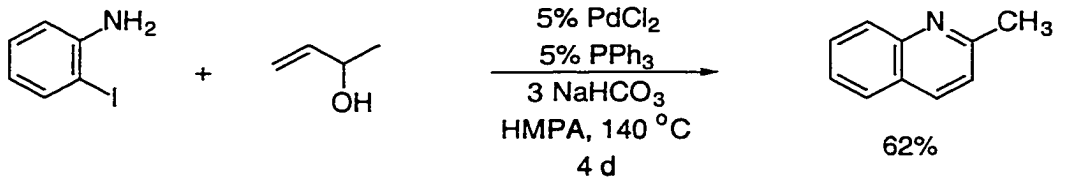
generality of the reaction and also requires starting materials which are not readily available.

A more general route to the synthesis of quinolines, based on palladium chemistry, is through the cyclization of *N*-(3-alkenyl)-*o*-iodoanilines. Larock and coworkers have developed a palladium-catalyzed process, which involves the oxidative addition of *N*-(3-alkenyl)-*o*-iodoanilines to palladium(0), followed by a Heck reaction with the neighboring olefin to close to the quinoline ring system (eq 2).[6] This procedure is performed under relatively mild conditions.




(2)

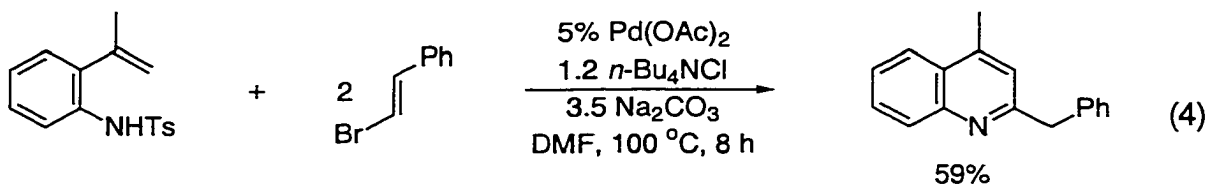
Larock and coworker have also developed a palladium-catalyzed method which couples *ortho*-iodoanilines and allylic alcohols to produce quinolines (eq 3).[7] The initial Heck reaction of the aryl iodide and the allylic alcohol produces the corresponding aryl ketone or aldehyde. This newly formed carbonyl compound




(3)

reacts with the neighboring amine through an intramolecular condensation reaction to produce an imine. The quinoline is then generated in a palladium-catalyzed dehydrogenation. This system, however, produces only low yields of quinolines and high reaction temperatures and HMPA are required.

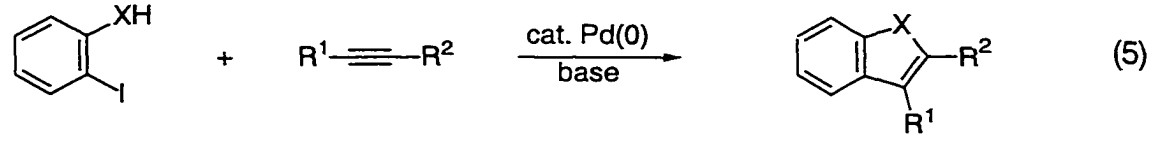
A third palladium-catalyzed approach to the synthesis of quinolines, developed by Larock and coworkers, takes advantage of an unusual palladium hydride rearrangement.[8,9] It was discovered that the cross coupling of *N*-tosyl-2-isopropenylaniline and vinylic halides produces quinolines (eq 4). However, this system suffers from poor yields. There are also several reports of the palladium-




(4)

catalyzed synthesis of indoles in which quinolines are seen as by-products in low yields.[10-13]

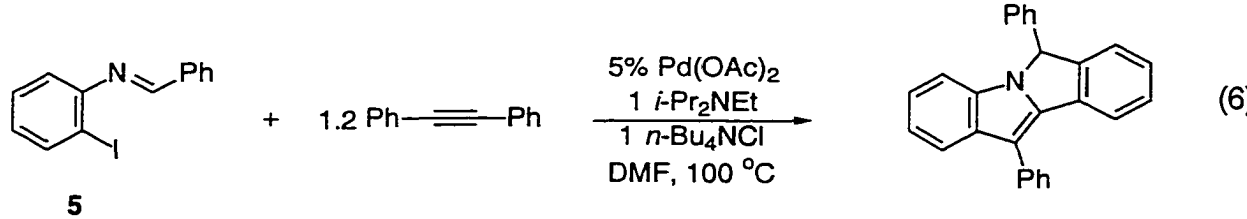
Palladium-catalyzed heteroannulations onto internal alkynes have proven to be an effective method within our laboratories for the synthesis of indoles,[14,15] benzofurans,[16] benzopyrans,[16] isocoumarins,[16] indenones,[17] polycyclic aromatic hydrocarbons,[18,19] and α-pyrones[20] (eq 5). Recently it has been discovered that




(5)

XH = $CH(CO_2Et)_2$, NHR, OH, CHO, $CO_2Et$
$R^1$, $R^2$ = alkyl, aryl, silyl, alkenyl

imine **5**, prepared form *ortho*-iodoaniline and benzaldehyde, and diphenylacetylene couple together to produce a unique tetracyclic compound when reacted under catalytic palladium conditions (eq 6).[21] The mechanism of this heteroannulation apparently involves (1) oxidative addition of the aryl iodide to palladium(0), (2) organopalladium addition to diphenylacetylene, (3) 5-exo addition of the vinylpalladium intermediate across the carbon-nitrogen double



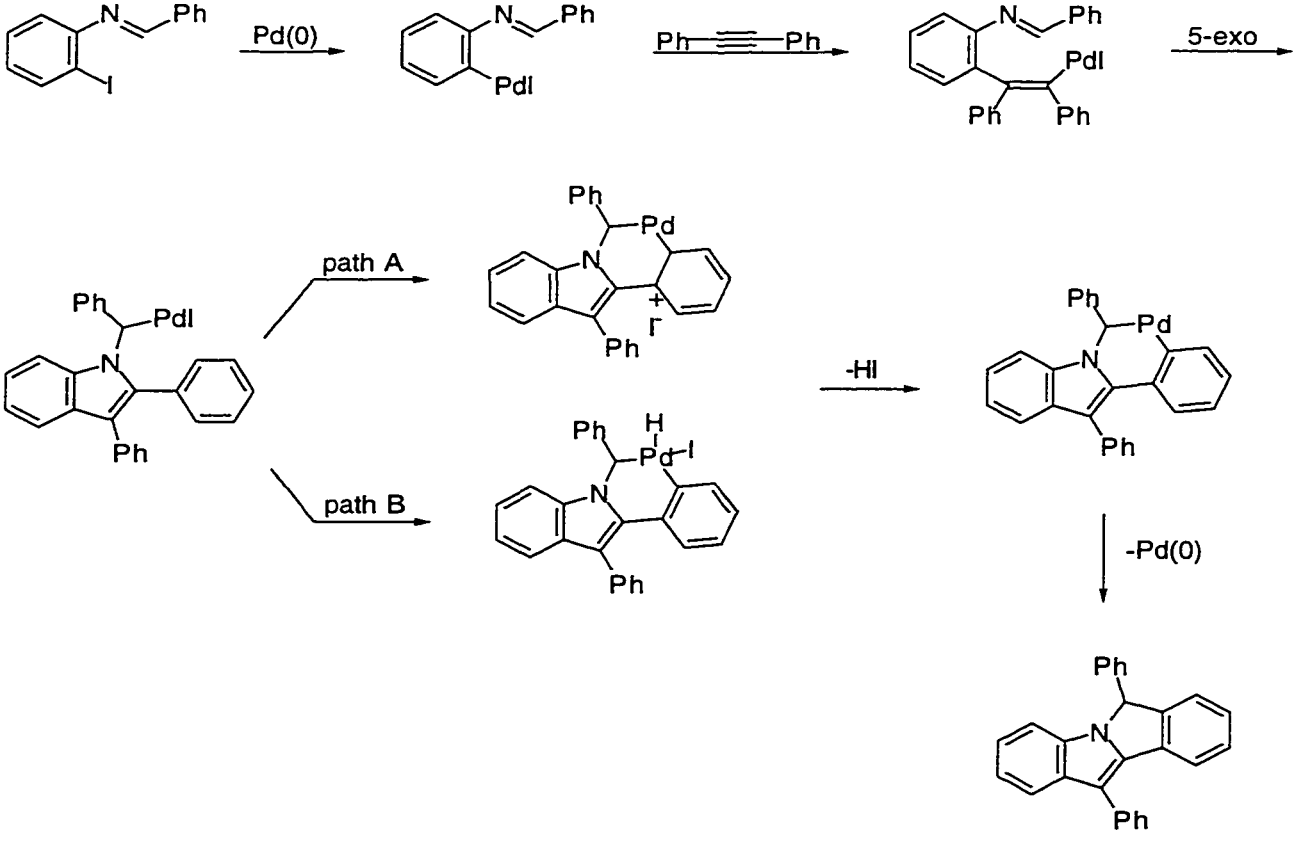

**5**

**6** 94%

(6)

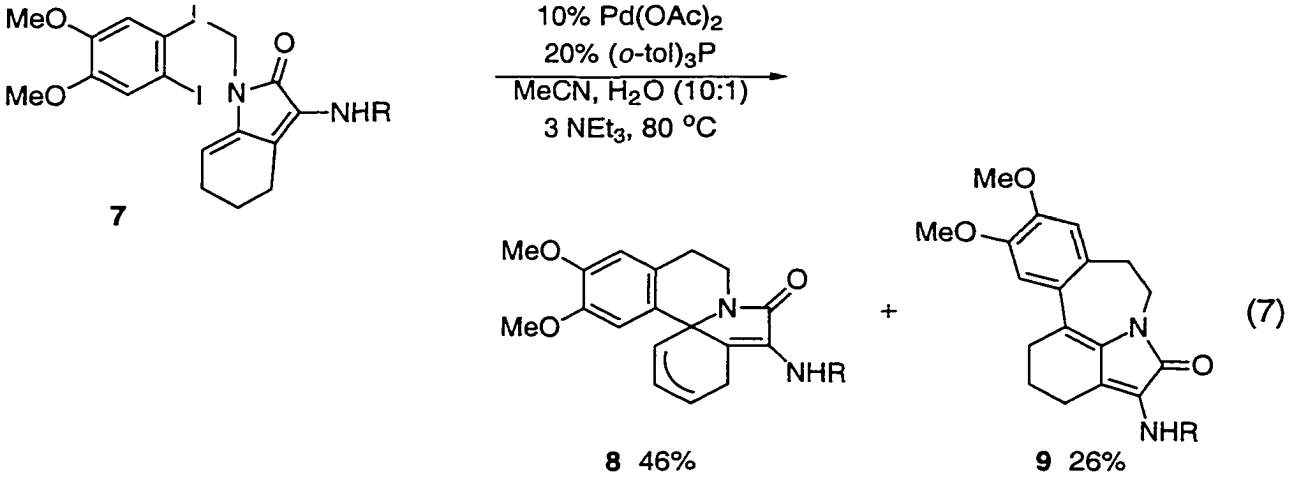
bond, (4) either electrophilic palladation of the σ-palladium intermediate onto the adjacent aromatic ring (path A), or oxidative addition of the neighboring aryl carbon-hydrogen bond of the aromatic ring to the σ-palladium intermediate to form a palladium(IV) intermediate (path B), and subsequent elimination of HI by base, and (6) regeneration of the palladium(0) catalyst by reductive elimination to form the tetracyclic product (Scheme 3). This palladium-catalyzed procedure produced tetracyclic isoindole derivatives in good to excellent yields. The formation of this

**Scheme 3**



tetracyclic product depends on the 5-exo ring closure onto the nitrogen atom of the nitrogen-carbon double bond.

There have been several examples reported in the literature in which palladium intermediates can cyclize selectively either exo or endo during a Heck-type reaction. Although the dominate mode of cyclization is usually exo, there are reported cases of the less favored endo mode of cyclization.[22-25] For example, Rigby and coworkers applied two different palladium conditions for the cyclization of hydroindolinone **7**.[24] It was discovered that standard Heck-type conditions produced a mixture of both the exo **8** and endo **9** ring closure products (eq 7).

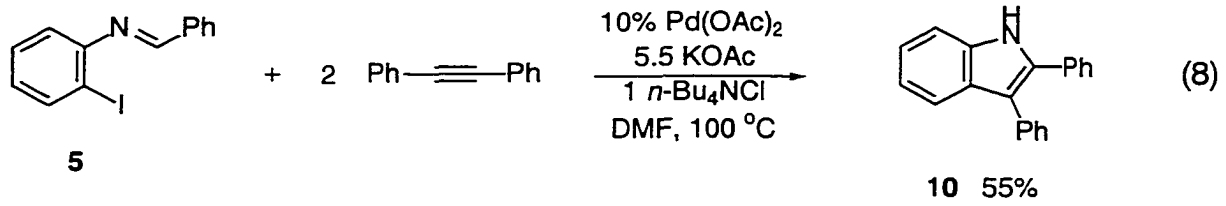



Rigby modified the palladium conditions using $Pd(OAc)_2$ (10 mol %), *n*-$Bu_4NCl$ (2 equiv), KOAc (5.5 equiv), DMF as the solvent, and a reaction temperature of 100 °C. These new conditions produced endocyclic product **9** in a 48% yield with no evidence of exocyclic product **8**. We now wish to report palladium conditions

which produce substituted quinoline products, presumably by a 6-endo ring closure.

## Results and Discussion

The palladium-catalyzed reaction of imine **5** and diphenylacetylene was chosen as the model system for our initial investigation into the synthesis of quinolines. As mentioned earlier, this type of starting material has been used in a palladium-catalyzed reaction to produce isoindoles through a 5-exo ring closure.[21] We anticipated that modifications to the palladium conditions used in this system might produce the corresponding substituted quinoline through a 6-endo cyclization. We began our investigation by applying Rigby's 6-endo palladium conditions to our system. What was discovered was a third product, 2,3-diphenylindole **10** (eq 8). After 24 hours, all of the imine **5** was gone and the only

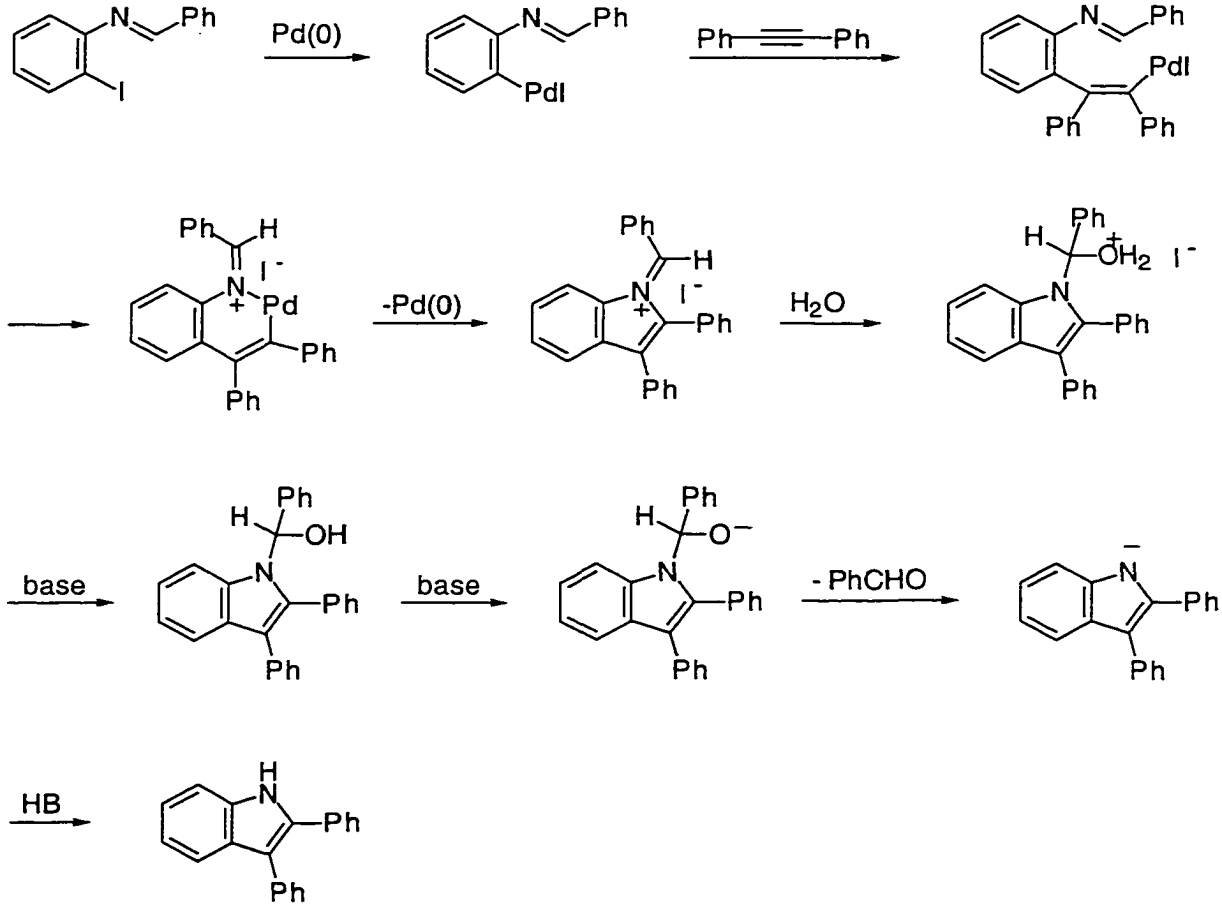



**5** **10** 55% (8)

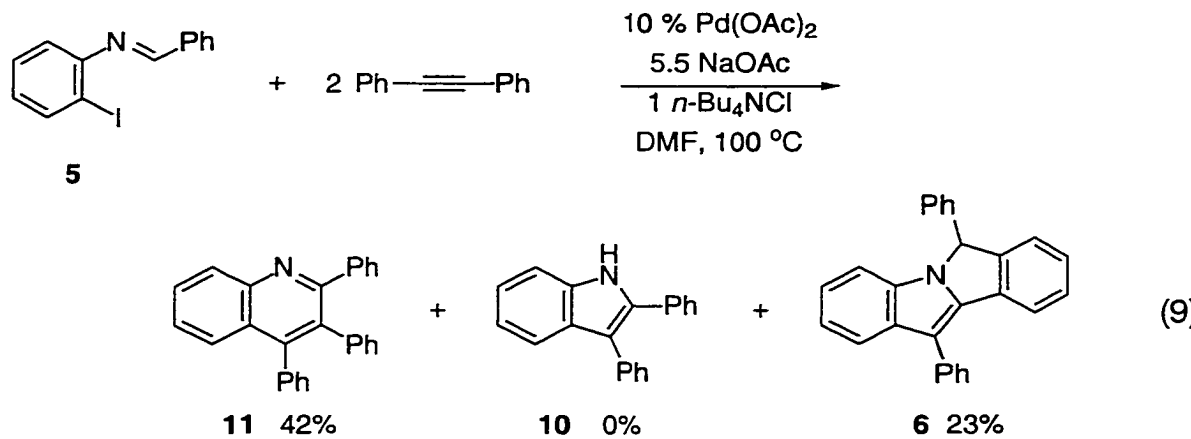
product found was indole **10** in a 55% isolated yield. The simplest explanation for the appearance of **10** is that the starting imine decomposes to *o*-iodoaniline, and couples with diphenylacetylene to produce 2,3-diphenylindole through a palladium-catalyzed heteroannulation.[14,15] A second mechanism is also proposed,

because *o*-iodoaniline has never been detected in any of the optimization reactions and may not, therefore, be an intermediate in this process (Scheme 4). This alternative mechanism involves (1) oxidative addition of the aryl iodide to palladium(0), (2) attack by the nitrogen atom of the imine on the organopalladium intermediate to form a palladacycle, (3) this palladacycle reductively eliminates to produce an indolium salt, which eventually hydrolyzes to the corresponding indole.

**Scheme 4**



Rigby's original palladium conditions were modified for the synthesis of substituted quinolines. Optimization began with the addition of different bases, keeping all other conditions constant. It was discovered that the type of base used greatly affected the reaction yield and the products formed. Other potassium bases, such as $K_2CO_3$ and $KHCO_3$, as well as CsOAc, predominantly gave indole **10** (Table 1, entries 2-4). With sodium bases, such as NaOAc, $NaHCO_3$, and $Na_2CO_3$, quinoline product **11** was seen for the first time (entries 5-7). However, large amounts of isoindole **6** were also produced, along with small amounts of indole **10** in some cases (eq 9). The lithium bases LiOAc and $LiCO_3$ produced the




isoindole **6** in 62% and 67% yields respectively (entries 8 and 9). Amine bases, such as $NEt_3$ and *i*-$Pr_2NEt$, again produced primarily isoindole **6** in moderate to good yields (entries 10 and 11). Other nontraditional bases, like $Mg(OAc)_2$, $Ba(OAc)_2$, $Zn(OAc)_2$, $Fe(OAc)_2$, TlOAc, and *n*-$Bu_4NOAc$, did not produce the desired quinoline product (entries 12-17).

**Table 1. Effect of base on the product distribution (eq 9).**[a]

| entry | base (5.5 equiv) | % yield of **11** | % yield of **10** | % yield of **6** |
|---|---|---|---|---|
| 1 | KOAc | 0 | 55 | 0 |
| 2 | $KHCO_3$ | 0 | 35 | 7 |
| 3 | $K_2CO_3$ | 0 | 32 | 0 |
| 4 | CsOAc | 0 | 44 | 0 |
| 5 | NaOAc | 42 | 0 | 23 |
| 6 | $NaHCO_3$ | 26 | 0 | 19 |
| 7 | $Na_2CO_3$ | 13 | 9 | 30 |
| 8 | LiOAc | 15 | 1 | 62 |
| 9 | $Li_2CO_3$ | 0 | 6 | 67 |
| 10 | $NEt_3$ | 0 | 0 | 63 |
| 11 | *i*-$Pr_2NEt$ | 0 | 10 | 79 |
| 12 | $Mg(OAc)_2$ | 0 | 0 | 63 |
| 13 | $Ba(OAc)_2$ | 0 | <2 | 83 |
| 14 | $Zn(OAc)_2$ | 0 | 0 | 35 |
| 15 | $Fe(OAc)_2$ | 0 | 0 | 19 |

**Table 1. (continued)**

| entry | base (5.5 equiv) | % yield of **11** | % yield of **10** | % yield of **6** |
|---|---|---|---|---|
| 16 | TlOAc | 0 | 17 | 5 |
| 17 | *n*-$Bu_4NOAc$ | 0 | 27 | 0 |

[a] All reactions were run with imine **5** (0.5 mmol), diphenylacetylene (2 equiv), $Pd(OAc)_2$ (10 mol %), *n*-$Bu_4NCl$ (2 equiv), base (5.5 equiv), DMF (10 mL), a 100 °C reaction temperature, and a 24 h reaction time.

Because quinoline **11** was only seen when sodium bases were used under the palladium conditions, several other sodium bases were also investigated (Table 2). It has already been reported in Table 1 that NaOAc produced quinoline **11** in a 42% yield, along with a 23% yield of isoindole **6**. Therefore, $NaOAc{\cdot}3H_2O$ and sodium trifluoroacetate were examined under the palladium conditions (entries 2 and 3). However, in both experiments isoindole **6** was found as the major product and quinoline **11** was produced in much lower yields compared to NaOAc. Sodium bases, such as sodium benzoate and sodium formate, produced isoindole **6** in 16% and 14% yields respectively and quinoline **11** in 19% and 0% yields respectively (entries 6 and 7). Phosphorous bases also proved to be worse, with no quinoline product detected (entries 8-10). Lastly, NaH and $Na_2B_4O_7$ failed to produce quinoline **11** in significant yields (entries 11 and 12).

Thus, NaOAc proved to be the best base for this palladium-catalyzed annulation to form substituted quinolines. However, the yield of quinoline **11** was poor and there was always a significant amount of isoindole **6** produced as a by-

**Table 2. Effect of sodium bases on the product distribution.**[a]

| entry | base (5.5 equiv) | % yield of **11** | % yield of **10** | % yield of **6** |
|---|---|---|---|---|
| 1 | NaOAc | 42 | 0 | 23 |
| 2 | $NaOAc{\cdot}3H_2O$ | 21 | 3 | 31 |
| 3 | $CF_3CO_2Na$ | 0 | 0 | 22 |
| 4 | $NaHCO_3$ | 26 | 0 | 19 |
| 5 | $Na_2CO_3$ | 13 | 9 | 30 |
| 6 | $PhCO_2Na$ | 19 | 0 | 16 |
| 7 | $NaO_2CH$ | 0 | 7 | 14 |
| 8 | $Na_3PO_4{\cdot}12H_2O$ | 0 | 29 | 9 |
| 9 | $Na_2HPO_4$ | 0 | 7 | 14 |
| 10 | $NaH_2PO_4{\cdot}H_2O$ | 0 | 7 | 12 |
| 11 | NaH | 0 | 7 | 0 |
| 12 | $Na_2B_4O_7$ | 4 | 0 | 46 |

[a] All reactions were run with imine **5** (0.5 mmol), diphenylacetylene (2 equiv), $Pd(OAc)_2$ (10 mol %), *n*-$Bu_4NCl$ (2 equiv), base (5.5 equiv), DMF (10 mL), a 100 °C reaction temperature, and a 24 h reaction time.

product. Several optimization experiments were performed varying the concentration of the NaOAc. The amount of NaOAc was reduced to 4, 2 and 1 equivalents in a series of experiments. It was discovered that the amount of isoindole **6** produced remained constant at a 27-28% yield, while the amount of quinoline **11** decreased as the amount of NaOAc decreased, affording 32%, 23%, and 29% yields respectively. Therefore, 5.5 equivalents of NaOAc were used under the standard palladium conditions. However, the yield of the desired quinoline **11** remains modest at 42% and there still is a 23% yield of the isoindole product **6**.

In many palladium-catalyzed transformations, the addition or absence of a chloride source has a profound affect on the reaction results. The standard palladium conditions used for our annulation contains two equivalents of *n*-$Bu_4NCl$. The concentration, as well as the type of chloride source, has been investigated in a series of experiments, which it was hoped would lead to a higher yield of quinoline **11** and eliminate the isoindole product (Table 3). The concentration of *n*-$Bu_4NCl$ was found to have little affect on the percent yield of isoindole **6**. In each case **6** was recovered in a 23-30% yield (entries 1-3). The concentration of *n*-$Bu_4NCl$ did, however, have an affect on the percent yield of quinoline **11**. When only one equivalent of *n*-$Bu_4NCl$ was used, the yield dropped to 32% (entry 3). Removing the chloride source completely only produced **11** in a trace amount (entry 1). Switching the chloride source to LiCl lowered the yields of **11** to 16% and 14% when one and two equivalents were added respectively (entries 4 and 5). It appears that two equivalents of *n*-$Bu_4NCl$ is the optimum chloride source and

**Table 3. Optimization of the chloride source.**[a]

| entry | chloride source (equiv) | % yield of **11** | % yield of **6** |
|---|---|---|---|
| 1 | — | 2 | 30 |
| 2 | TBAC (2) | 42 | 23 |
| 3 | TBAC (1) | 32 | 24 |
| 4 | LiCl (2) | 14 | 26 |
| 5 | LiCl (1) | 16 | 32 |

[a] All reactions were run with imine **5** (0.5 mmol), diphenylacetylene (2 equiv), $Pd(OAc)_2$ (10 mol %), base (5.5 equiv), DMF (10 mL), a 100 °C reaction temperature, and a 24 h reaction time.

concentration. However, the yield of quinoline **11** is poor and there still is a significant amount of isoindole **6** produced. Therefore, further optimization work has been carried out.

Next, the addition of phosphine ligands was explored. The addition of triphenylphosphine (26%), 1,2-bis(diphenylphosphino)ethane (15%), tetraphenylphosphonium chloride (15%), and diphenyl-2-pyridylphosphine (28%) to the palladium reaction did not improve the yield of quinoline **11**. In each experiment the yield of **11** was significantly lower and **6** still appeared in the product mixture.

Next, the use of other palladium(II) catalysts was tried. The palladium salts $PdCl_2$ and $Pd(NO_3)_2$ produced quinoline **11** in 48% and 25% yields respectively, along with 16-19% yields of isoindole **6**. The palladium(0) catalyst $Pd(dba)_2$ gave

nearly the same results as $Pd(OAc)_2$, producing **11** in a 45% yield and **6** in a 23% yield. $Pd(PPh_3)_4$ produced **6** in a 15% yield and indole **10** in a 14% yield.

Lastly, the final optimization experiments were performed using different solvents. DMA gave a yield (45%) comparable to DMF. However, less polar solvents, such as toluene (22%), THF (25%), and acetonitrile (19%), all produced lower yields of quinoline **11** and high yields of isoindole **6**.

With completion of the optimization work, the best yield of quinoline **11** was still only 42%, yield along with a 23% yield of isoindole **6**. The conditions used for this reaction involved imine **5** (0.5 mmol), diphenylacetylene (2 equiv), $Pd(OAc)_2$ (10 mol %), *n*-$Bu_4NCl$ (2 equiv), NaOAc (5.5 equiv), DMF (10 mL), a 100 °C reaction temperature, and a 24 h reaction time.

We proceeded to investigate the annulation of imine **5** with alkynes of differing functionality to hopefully expand the scope of this quinoline synthesis (Table 4). Alkynes that do not have an aryl group attached to the triple bond will not be able to form an isoindole product. The isoindole product is formed by a tandem palladium-catalyzed annulation, which eventually cyclizes onto the arene of the alkyne. 4,4-Dimethyl-2-pentyne produced quinoline **12** in a 31% yield when reacted with imine **5** under the standard palladium conditions (entry 2). No other products were produced in this reaction. Ethyl phenylpropiolate undergoes reaction to give only isoindole **13** in a 31% yield (entry 3). Alkynes, such as 4-octyne, 2,5-dimethyl-3-hexyne-2,5-diol, and 4-phenyl-2-methyl-3-butyn-2-ol did not afford any recognizable products (entries 4-6).

**Table 4. Palladium-catalyzed reaction of *ortho*-iodoimines with internal alkynes.[a]**

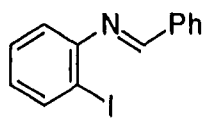
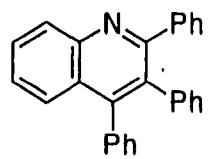
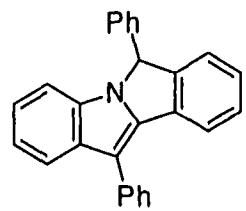
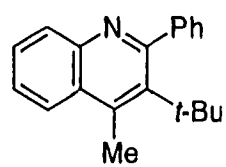
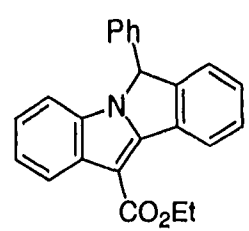
| entry | imine | alkyne | % yield of quinoline | % yield of indole **10** | % yield of isoindole |
|---|---|---|---|---|---|
| 1 |  **5** | Ph—≡—Ph |  42% **11** | 0 |  23% **6** |
| 2 | | Me—≡—*t*-Bu |  31% **12** | 0 | 0 |
| 3 | | Ph—≡—$CO_2Et$ | 0 | 0 |  31% **13** |
| 4 | | *n*-$C_3H_7$—≡—*n*-$C_3H_7$ | 0 | 0 | 0 |

**Table 4. (continued)**

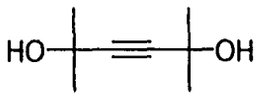
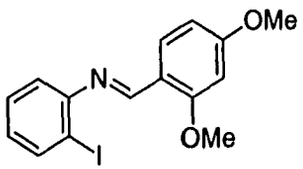
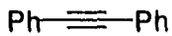
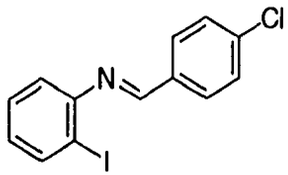
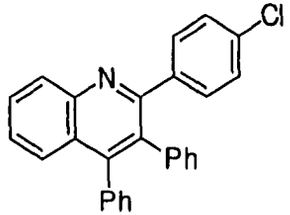
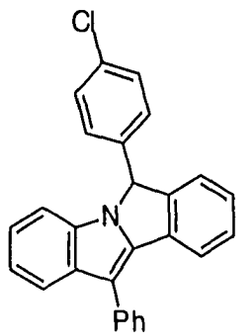
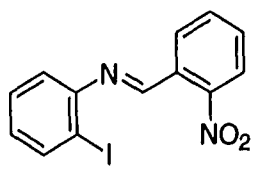
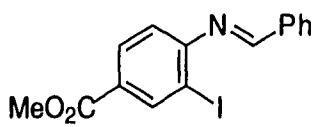
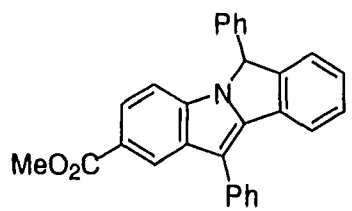
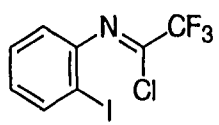
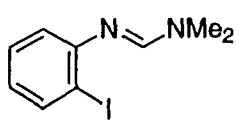
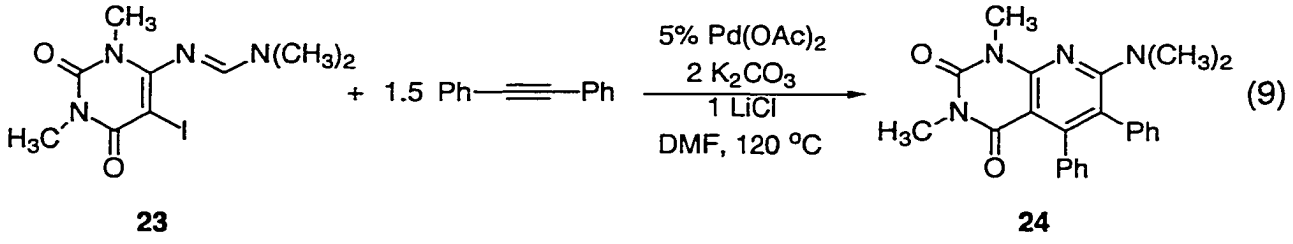
| entry | imine | alkyne | % of yield quinoline | % yield of indole **10** | % yield of isoindole |
|---|---|---|---|---|---|
| 5 | |  | 0 | 0 | 0 |
| 6 | |  | 0 | 0 | 0 |
| 7 |  **14** |  | 0 | 0 | 0 |
| 8 |  **15** |  31% **16** | 0 |  10% **17** | |

**Table 4. (continued)**

| entry | imine | alkyne | % yield of quinoline | % yield of indole **10** | % yield of isoindole |
|---|---|---|---|---|---|
| 9 |  **18** | | 0 | 28 | 0 |
| 10 |  **19** | | 0 | 0 |  6% **20** |
| 11 |  **21** | | 0 | 13 | 0 |
| 12 |  **22** | | 0 | 20 | 0 |

[a] The reaction conditions include imine (0.5 mmol), acetylene (2 equiv), $Pd(OAc)_2$ (10 mol %), *n*-$Bu_4NCl$ (2 equiv), NaOAc (5.5 equiv), DMF (10 mL), a 100 °C reaction temperature, and a 24 h reaction time.

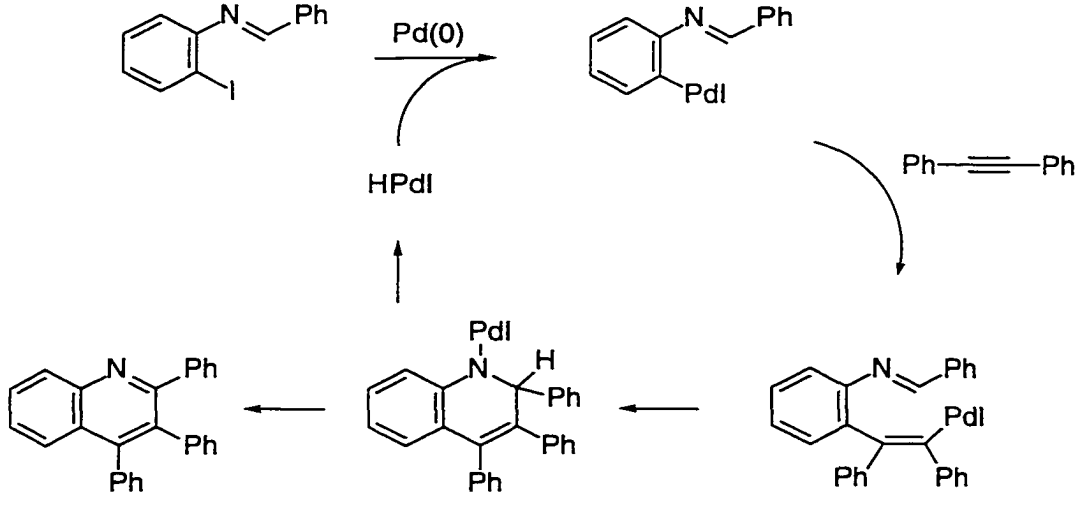
Finally, the annulation of functionalized imines was examined to see if changing the electronics of the imine would affect the annulation process and ultimately the product selectivity. The addition of electron-donating methoxy groups to the arene had a profound negative effect. Imine **14** did not react and no recognizable products were seen (entry 7). Imine **15** that contains a weak electron-withdrawing chloro group behaved similar to the model system, producing quinoline **16** in a 31% yield, along with isoindole **17** in a 10% yield (entry 8). With a stronger electron-withdrawing nitro group attached to the arene of the imine, only indole **10** was recovered (entry 9). Imine **21** that contains a chloro and trifluoromethyl group on the carbon atom of the imine was also reacted with diphenylacetylene (entry 11). Again, no quinoline product was seen and only indole **10** was found in a 13% yield. Lastly, imine **22** that has a dimethylamino group attached to the carbon atom of the imine was reacted with diphenylacetylene (entry 12). Again, no quinoline product was seen and indole **10** was recovered in a 20% yield. Imine **22** was also reacted under palladium conditions developed by Yoon and coworkers for the palladium-catalyzed reaction of iodouracils with acetylenes (eq 9).[26] Uracil **23** is very similar to imine **22**. However, **22** failed to provide any of the quinoline product using Yoon's palladium conditions.




**23** **24** (9)

The proposed mechanism for the synthesis of substituted quinolines by the palladium-catalyzed annulation of internal alkynes presumably involves (1) reduction of $Pd(OAc)_2$ to the actual Pd(0) catalyst, (2) oxidative addition of the aryl iodide to Pd(0), (3) coordination and subsequent insertion of the acetylene to produce a vinylic palladium species, (4) a 6-endo addition of the vinylic palladium intermediate across the carbon-nitrogen double bond, (5) beta hydride elimination to form the quinoline, and (6) regeneration of the Pd(0) catalyst by reductive elimination of HPdI (Scheme 5).

**Scheme 5**



## Conclusions

The palladium-catalyzed synthesis of substituted quinolines from the iminoannulation of internal acetylenes has proven to be difficult. The optimized palladium conditions for the model system produced the desired quinoline in only a 42% yield, along with a 23% yield of a tetracyclic isoindole product. The annulation process to achieve the quinoline product needs to proceed through a 6-endo ring closure. However, this process is in competition with the more favored 5-exo ring closure, which leads to the isoindole system. When other imines and alkynes were employed in the palladium reaction, the yields suffered greatly, and in many cases the quinoline product was not seen at all.

This palladium-catalyzed annulation has proven to be interesting from a mechanistic point of view. Varying the palladium conditions, primarily the base, has a profound affect on the products formed. The quinoline product was seen only when sodium bases, such as NaOAc and $NaHCO_3$, were employed. Potassium bases, such as KOAc, $KHCO_3$, and $K_2CO_3$, all produced the corresponding indole as the major product. Lastly, lithium bases, such as LiOAc and $Li_2CO_3$, as well as amine bases, such as $NEt_3$ and *i*-$Pr_2NEt$, all gave a tetracyclic isoindole heterocycle as the major product. One purpose for the base in these reactions is to neutralize the acid generated during the reaction. However, it appears that the cation present in these bases has a profound effect on the palladium transformation. This affect is not clearly understood here and does not appear in the generally accepted palladium mechanisms commonly proposed in the literature.

## Experimental

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

**Reagents.** All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of LiOAc, NaOAc, KOAc, CsOAc, $Li_2CO_3$, $Na_2CO_3$, $NaHCO_3$, $K_2CO_3$, $KHCO_3$, $NaO_2Ph$, $NaO_2CH$, $Na_3PO_4 \cdot 12H_2O$, $Na_2HPO_4$, $NaH_2PO_4 \cdot H_2O$, $Na_2B_4O_7$, $CF_3CO_2Na$, NaH, $Mg(OAc)_2$, $Ba(OAc)_2$, TlOAc, *n*-$Bu_4NOAc$, LiCl, DMF, DMA, THF, $CH_3CN$, toluene, hexanes, and ethyl acetate were purchased from Fischer Scientific Co. All palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. $PPh_3$ was donated by Kawaken Fine Chemicals Co. Ltd. 2-Iodoaniline, benzaldehyde, 4-chlorobenzaldehyde, 2-nitrobenzaldehyde, 2,4-dimethoxybenzaldehyde, diphenylacetylene, 4,4-dimethyl-2-pentyne, ethyl phenylpropiolate, 4-octyne, 2,5-dimethyl-3-hexyne-2,5-diol, 4-phenyl-2-methyl-3-butyn-2-ol, $NEt_3$, and *i*-$Pr_2NEt$ were purchased from Aldrich Chemical Co., Inc. *n*-$Bu_4NCl$ was purchased from

Lancaster Synthesis, Inc. The following starting materials were prepared as indicated.

**Imines Prepared**

**Benzylidene(2-iodophenyl)amine (5).** A mixture of 2-iodoaniline (2.19 g, 10 mmol), benzaldehyde (1.06 g, 10 mmol), and *p*-toluenesulfonic acid monohydrate (1 crystal) in benzene (40 mL) was refluxed with the aid of a Dean-Stark apparatus to remove the water produced. The reaction was monitored by TLC to establish completion. The reaction mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The oily residue was then dissolved in a minimal amount of 100% ethanol and cooled. The resulting solid was collected to afford 2.15 g (70%) of imine **5** as a white solid: mp 56-57 $^{o}$C; $^{1}$H NMR ($CDCl_3$) $\delta$ 6.92 (dt, $J$ = 1.8, 7.8 Hz, 1 H), 7.00 (dd, $J$ = 1.5, 7.8 Hz, 1 H), 7.36 (dt, $J$ = 1.2, 7.5 Hz, 1 H), 7.47-7.52 (m, 3 H), 7.89 (dd, $J$ = 1.5, 7.8 Hz, 1 H), 7.95-7.98 (m, 2 H), 8.29 (s, 1 H); $^{13}$C NMR ($CDCl_3$) $\delta$ 95.0, 118.6, 127.2, 129.0, 129.3, 129.5, 131.9, 135.9, 139.2, 153.1, 161.1; IR ($CHCl_3$, $cm^{-1}$) 3052, 3001, 1626, 1573; HRMS calcd for $C_{13}H_{10}IN$ 306.9858, found 306.9863.

**2,4-Methoxybenzylidene(2-iodophenyl)amine (14).** This compound was prepared using the same procedure as described for **5**, except 2,4-dimethoxybenzaldehyde was substituted for benzaldehyde. Crystallization from 100% ethanol afforded **14** in a 77% yield as a white solid: mp 102 $^{o}$C; $^{1}$H NMR ($CDCl_3$) $\delta$ 3.87 (s, 6 H), 6.47 (d, $J$ = 2.0 Hz, 1 H), 6.62 (dd, $J$ = 2.0, 8.8 Hz, 1 H), 6.88

(t, $J$ = 7.6 Hz, 1 H), 7.01 (d, $J$ = 8.0 Hz, 1 H), 7.34 (t, $J$ = 7.6 Hz, 1 H), 7.87 (d, $J$ = 7.6 Hz, 1 H), 8.25 (d, $J$ = 8.8 Hz, 1 H), 8.65 (s, 1 H); $^{13}$C NMR ($CDCl_3$) δ 55.62, 95.34, 98.03, 105.92, 117.86, 118.78, 126.46, 129.32, 129.58, 138.86, 154.00, 156.37, 161.10, 164.13 (one $sp^3$ carbon missing due to overlap); IR ($CHCl_3$, $cm^{-1}$) 3010, 2907, 2834, 1603; HRMS calcd for $C_{15}H_{14}INO_2$ 367.0070, found 367.0076.

**4-Chlorobenzylidene(2-iodophenyl)amine (15).** This compound was prepared using the same procedure as described for **5**, except 4-chlorobenzaldehyde was substituted for benzaldehyde. Crystallization from 100% ethanol afforded **15** in a 72% yield as a yellow solid: mp 44-45 °C; $^1$H NMR ($CDCl_3$) δ 6.94 (dt, $J$ = 1.2, 7.6 Hz, 1 H), 7.00 (dd, $J$ = 1.6, 8.0 Hz, 1 H), 7.37 (dt, $J$ = 1.2, 8.0 Hz, 1 H), 7.46-7.48 (m, 2 H), 7.90-7.92 (m, 3 H), 8.26 (s, 1 H); $^{13}$C NMR ($CDCl_3$) δ 95.0, 118.32, 127.35, 129.24, 129.43, 130.31, 134.33, 137.86, 139.17, 152.68, 159.46; IR ($CHCl_3$, $cm^{-1}$) 3056, 2997, 1628, 1569; HRMS calcd for $C_{13}H_9ClIN$ 340.9468, found 340.9472.

**2-Nitrobenzylidene(2-iodophenyl)amine (18).** This compound was prepared using the same procedure as described for **5**, except 2-nitrobenzaldehyde was substituted for benzaldehyde. Crystallization from 100% ethanol afforded **18** in a 77% yield as a yellow solid: mp 58 °C; $^1$H NMR ($CDCl_3$) δ 6.984 (t, $J$ = 7.6 Hz, 1 H), 7.13 (d, $J$ = 7.6 Hz, 1 H), 7.41 (t, $J$ = 7.6 Hz, 1 H), 7.66 (t, $J$ = 8.0 Hz, 1 H), 7.79 (t, $J$ = 7.6 Hz, 1 H), 7.91 (d, $J$ = 8.0 Hz, 1 H), 8.11 (d, $J$ = 8.0 Hz, 1 H), 8.46 (d, $J$ = 7.6 Hz, 1 H), 8.81 (s, 1 H); $^{13}$C NMR ($CDCl_3$) δ 94.9, 118.79, 124.65, 127.98, 129.62, 130.53, 130.90, 131.57, 133.96, 139.13, 149.14, 152.16,

157.06; IR ($CHCl_3$, $cm^{-1}$) 3053, 2980, 1623; HRMS calcd for $C_{13}H_9IN_2O_2$ 351.9709, found 351.9715.

**4-Benzylideneamino-3-iodobenzoic acid methyl ester (19).** This compound was prepared using the same procedure as describe for **5**, except methyl 3-iodo-4-aminobenzoate was substituted for 2-iodoaniline. Crystallization from 100% ethanol afforded **19** in a 40% yield as a white solid: mp 64-65 °C; $^1H$ NMR ($CDCl_3$) δ 3.93 (s, 3 H), 7.00 (d, $J$ = 8.4 Hz, 1 H), 7.51-7.55 (m, 3 H), 7.98 (d, $J$ = 6.0 Hz, 2 H), 8.04 (d, $J$ = 8.1 Hz, 1 H), 8.30 (s, 1 H), 8.56 (s, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 52.37, 93.62, 118.19, 128.53, 129.03, 129.42, 131.01, 132.32, 135.50, 140.45, 157.21, 161.95, 165.56; IR ($CHCl_3$, $cm^{-1}$) 3060, 2949, 1720, 1631, 1585; HRMS calcd for $C_{15}H_{12}INO_2$ 364.9913, found 364.9921.

***N*-(2-Iodophenyl)-2,2,2-trifluoroacetimidoyl chloride (21).** This compound was prepared using a modified literature procedure.[27] A 100 mL flask equipped with a water jacketed condenser and a Teflon coated magnetic stir bar was charged with $Ph_3P$ (16.57 g, 63.16 mmol), $Et_3N$ (3.53 mL, 25.36 mmol), $CCl_4$ (10.1 mL), and TFA (1.62 mL, 21.05 mmol). After the solution was stirred for 10 min at 0 °C 2-iodoaniline (25.36 mmol) dissolved in $CCl_4$ (10.1 mL) was added. The mixture was then stirred and refluxed for 3 h. Solvents were removed under reduced pressure and the residue was diluted with hexane and filtered. Residual solid $Ph_3PO$, $Ph_3P$, and $Et_3NHCl$ were washed with hexane several times. The filtrate was concentrated under reduced pressure and the residue was distilled to afford the desired imine **21** as clear oil in a 43% yield: $^1H$ NMR ($CDCl_3$) δ 6.94 (d, $J$ = 8.1 Hz, 1 H), 6.93-7.03 (m, 1 H), 7.39-7.45 (m, 1 H), 7.92 (d, $J$ = 8.1 Hz, 1 H), $^{13}C$

NMR ($CDCl_3$) δ 88.73, 116.75 (q, $J$ = 277.2 Hz), 119.17, 128.20, 129.01, 135.15 (q, $J$ = 43.3 Hz), 139.53, 146.16; IR ($CHCl_3$, $cm^{-1}$) 3064, 1702; HRMS calcd for $C_8H_4ClF_3IN$ 332.9029, found 332.9034.

***N'*-(2-Iodophenyl)-*N,N*-dimethylformamidine (22).** This compound was prepared using a modified literature procedure.[28] $POCl_3$ (20 mmol) in diethyl ether (4 mL) was added dropwise to DMF (20 mmol) in diethyl ether (4 mL) at 15 °C. The reaction mixture was allowed to warm to room temperature and an oil separates out. The top ether layer was decanted and the oil was rinsed with ether (3 x 20 mL). At this point 2-iodoaniline (10 mmol) in diethyl ether (4 mL) was added dropwise and stirred for 30 min. The resulting salt was placed in $H_2O$ (100 mL) and benzene (100 mL). NaOH (1 M soln) was added until the solution became basic and the organic layer separated. The aqueous layer was extract with ether (3 x 20 mL) and the combined extracts were dried ($MgSO_4$) and concentrated under vacuum to give the desired imine **22** in a 72% yield as a yellow oil: $^1H$ NMR ($CDCl_3$) δ 3.02 (s, 3 H), 3.07 (s, 3 H), 6.70 (dt, $J$ = 1.6, 7.6 Hz, 1 H), 6.82 (dd, $J$ = 1.6, 7.6 Hz, 1 H), 7.22 (dt, $J$ = 1.2, 7.2 Hz, 1 H), 7.39 (s, 1 H), 7.80 (dd, $J$ = 1.6, 8.0 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 34.63, 40.19, 96.68, 118.95, 123.86, 129.17, 138.85, 152.68, 153.06; IR ($CHCl_3$, $cm^{-1}$) 2957, 2870, 1684; HRMS calcd for $C_9H_{11}IN_2$ 273.9967, found 273.9971.

**General procedure for the palladium-catalyzed annulation.** Into a 25 mL round bottom flask was placed the appropriate imine (0.50 mmol), the alkyne (2 equiv), $Pd(OAc)_2$ (10 mol %), a base (5.5 equiv), *n*-$Bu_4NCl$ (2 equiv), and

DMF (10 mL). The reaction mixture was flushed with argon and allowed to stir for 24 h at 100 °C. The reaction mixture was then diluted with satd aq $NH_4Cl$ (50 mL) and extracted with diethyl ether (3 x 25 mL). The ether fractions were combined, dried ($MgSO_4$) and concentrated under vacuum to yield the crude product. The crude product was purified by flash chromatography on silica gel.

**6,11-Diphenylisoindolo[2,1-*a*]indole (6).** The product was obtained as a white solid: lit mp[21] 168-169 °C, found 168-169 °C; $^1$H NMR ($CDCl_3$) δ 6.20 (s, 1 H), 7.02 (dt, $J$ = 0.6, 8.1 Hz, 1 H), 7.16 (dddd, $J$ = 1.5, 7.2, 7.2, 22.2 Hz, 2 H), 7.25-7.49 (m, 9 H), 7.63 (t, $J$ = 7.5 Hz, 2 H), 7.87-7.94 (m, 4 H); $^{13}$C NMR ($CDCl_3$) δ 64.5, 109.8, 110.3, 120.3, 120.5, 121.1, 122.4, 124.1, 126.5, 127.3, 127.7, 128.4, 128.6, 128.9, 129.3, 129.5, 131.9, 132.0, 133.7, 135.1, 138.9, 139.5, 147.5; IR ($CHCl_3$, $cm^{-1}$) 3065, 3028, 1602, 1450; MS *m/z* (rel intensity) 358 (28, M+1), 357 (100, $M^+$), 356 (26), 280 (78). Anal. Calcd for $C_{27}H_{19}N$: C, 90.72; H, 5.36; N, 3.92. Found: C, 90.39; H, 5.61; N, 3.94.

**2,3-Diphenylindole (10).** The product was obtained as a yellow oil:[29] $^1$H NMR ($CDCl_3$) δ 7.08 (t, $J$ = 8.0 Hz, 1 H), 7.15-7.38 (m, 12 H), 7.61 (d, $J$ = 8.0 Hz, 1 H), 8.15 (s, 1 H); $^{13}$C NMR ($CDCl_3$) δ 110.94, 115.11, 119.76, 120.49, 122.77, 126.29, 127.75, 128.22, 128.58, 128.75, 128.81, 130.22, 132.75, 134.13, 135.10, 135.94; IR ($CHCl_3$, $cm^{-1}$) 3450, 3020; HRMS calcd for $C_{20}H_{15}N$ 269.1205, found 269.1210.

**2,3,4-Triphenylquinoline (11).** The product was obtained as a white solid: literature mp[30] 189-190 °C, found 190-192 °C; $^1$H NMR ($CDCl_3$) δ 6.87-6.90 (m, 2 H), 6.98-7.01 (m, 3 H), 7.12-7.14 (m, 2 H), 7.19-7.23 (m, 3 H), 7.23-7.27 (m, 3

H), 7.35-7.39 (m, 2 H), 7.42-7.46 (m, 1 H), 7.57-7.59 (m, 1 H), 7.70-7.74 (m, 1 H), 8.25 (dd, J = 0.4, 8.4 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 126.37, 126.63, 126.68, 126.71, 127.33, 127.40, 127.64, 127.74, 127.85, 129.42, 129.78, 129.98, 130.36, 131.43, 133.00, 137.01, 138.41, 141.24, 147.39, 147.71, 159.07; IR ($CHCl_3$, $cm^{-1}$) 3053, 2985, 1265; HRMS calcd for $C_{27}H_{19}N$ 357.1524, found 357.1518.

**3-*tert*-Butyl-4-methyl-2-phenylquinoline (12).** The product was obtained as a white solid: mp 60-62 °C; $^1H$ NMR ($CDCl_3$) δ 8.94 (s, 9 H), 2.47 (s, 3 H), 7.41-7.49 (m, 4 H), 7.55-7.58 (m, 3 H), 8.08 (dd, *J* = 1.2, 8.4 Hz, 1 H), 8.38 (d, *J* = 8.8 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 23.56, 33.85, 39.52, 124.19, 126.71, 127.07, 127.35, 127.53, 128.19, 128.57, 129.35, 130.65, 142.52, 147.31, 154.86, 162.81; IR ($CHCl_3$, $cm^{-1}$) 3022, 2928, 1558; HRMS calcd for $C_{20}H_{21}N$ 275.1674, found 275.1679.

**Ethyl 6-phenylisoindolo[2,1-*a*]indole-11-carboxylate (13).** The product was obtained as a white solid: lit mp[21] 181-182 °C, found 181-182 °C; $^1H$ NMR ($CDCl_3$) δ 1.57 (t, *J* = 7.2 Hz, 3 H), 4.55 (q, *J* = 7.2 Hz, 2 H), 6.02 (s, 1 H), 6.90 (d, *J* = 8.1 Hz, 1 H), 7.06-7.13 (m, 3 H), 7.24 (dt, *J* = 0.9, 14.4 Hz, 2 H), 7.30-7.37 (m, 4 H), 7.49 (dt, *J* = 0.6, 14.7 Hz, 1 H), 8.28 (d, *J* = 8.1 Hz, 1 H), 8.78 (d, *J* = 7.5 Hz, 1 H); $^{13}C$ NMR ($CDCl_3$) δ 14.9, 60.0, 64.9, 99.9, 110.4, 122.0, 122.9, 123.4, 125.7, 127.2, 128.8, 129.2, 129.3, 130.7, 131.2, 133.1, 137.5, 148.3, 148.6, 165.8 (two $sp^2$ carbons missing due to overlap); IR ($CHCl_3$, $cm^{-1}$) 3056, 2980, 1688, 1559; HRMS Calcd for $C_{24}H_{19}NO_2$ 353.1416, found 353.1416.

**2-*p*-Chlorophenyl-3,4-diphenylquinoline (16).** The product was obtained was a white solid: mp 151-154 °C; $^1$H NMR ($CDCl_3$) δ 6.86-6.88 (m, 2 H), 7.00-7.03 (m, 2 H), 7.10-7.12 (m, 4 H), 7.17 (d, *J* = 8.4 Hz, 2 H), 7.24-7.28 (m, 2 H), 7.32 (d, *J* = 8.4 Hz, 2 H), 7.45 (t, *J* = 7.2 Hz, 1 H), 7.57 (d, *J* = 8.4 Hz, 1 H), 7.72 (dt, *J* = 0.8, 6.8 Hz, 1 H), 8.22 (d, *J* = 8.4 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 126.60, 126.71, 126.76, 126.83, 127.41, 127.62, 127.88, 127.96, 129.57, 129.72, 130.30, 131.35, 131.38, 132.79, 133.84, 136.82, 138.13, 139.70, 147.39, 147.97, 157.68; IR ($CHCl_3$, $cm^{-1}$) 2977, 2864, 1382; HRMS calcd for $C_{27}H_{18}ClN$ 391.1128, found 391.1133.

**11-Phenyl-6-(3-chlorophenyl)isoindolo[2,1-*a*]indole (17).** The product was obtained as white solid:[21] literature mp 165-166 °C, found 165-166 °C; $^1$H NMR ($CDCl_3$) δ 6.11 (s, 1 H), 6.99 (dd, *J* = 1.2, 7.2 Hz, 1 H), 7.13-7.39 (m, 9 H), 7.47 (t, *J* = 7.5 Hz, 1 H), 7.63 (t, *J* = 7.5 Hz, 2 H), 7.86-7.93 (m, 4 H); $^{13}$C NMR ($CDCl_3$) δ 63.7, 110.0, 110.2, 120.5, 120.6, 121.2, 122.5, 123.9, 126.6, 127.8, 128.6, 128.7, 129.0, 129.5, 129.5, 131.8, 132.0, 133.6, 134.4, 134.9, 137.5, 139.3, 147.0; IR ($CHCl_3$, $cm^{-1}$) 3051, 3016, 1602, 1489; HRMS Calcd for $C_{27}H_{18}ClN$ 391.1128, found 391.1121.

**Methyl 6,11-diphenylisoindolo[2,1-*a*]indole-2-carboxylate (20).** The product was obtained as a white solid: lit mp[21] 170-171 °C, found 170-171 °C; $^1$H NMR ($CDCl_3$) δ 3.90 (s, 3 H), 6.22 (s, 1 H), 6.95 (d, *J* = 8.7 Hz, 1 H), 7.21-7.47 (m, 9 H), 7.60 (t, *J* = 7.5 Hz, 2 H), 7.77-7.88 (m, 4 H), 8.55 (d, *J* = 1.8 Hz, 1 H); $^{13}$C NMR ($CDCl_3$) δ 51.9, 64.5, 109.8, 110.9, 121.3, 122.2, 123.3, 123.8, 124.1, 126.9, 127.2, 128.2, 128.5, 128.7, 129.1, 129.3, 129.5, 131.2, 131.6, 134.1, 136.0, 138.4, 140.7,

147.3, 168.2; IR ($CDCl_3$, $cm^{-1}$) 3063, 2947, 1711, 1621, 1437; HRMS Calcd for $C_{29}H_{21}NO_2$ 415.1572, found 415.1574.

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# CHAPTER 4. SYNTHESIS OF α,β-UNSATURATED KETONES USING A CATALYTIC PALLADIUM(II) STRATEGY

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

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## Abstract

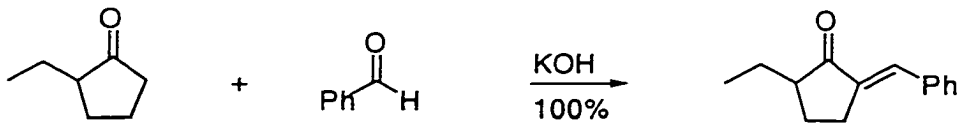
α,β-Unsaturated ketones have been successfully synthesized from the corresponding enol silyl ethers using a catalytic palladium(II) strategy. This palladium(II) procedure is performed using catalytic amounts of $Pd(OAc)_2$ in DMSO at room temperature and uses $O_2$ as an efficient reoxidant. The mechanism of this transformation apparently involves (1) Pd(II) coordination to the enol silyl ether, (2) rearrangement to a σ-complex, (3) β-hydride elimination of the palladium to form the desired enone, and (4) reoxidation of palladium by $O_2$. A limitation of this transformation is the formation of the corresponding saturated ketone.

## Introduction

The importance of α,β-unsaturated ketones in organic synthesis has encouraged the development of many different strategies for their synthesis. α,β-Unsaturated ketones are found in many biological systems and are widely used

in the total synthesis of many natural products. This demand for enones has encouraged work on methodology, which is aimed at creating α,β-unsaturated ketones through a general procedure using mild reaction conditions.[1]

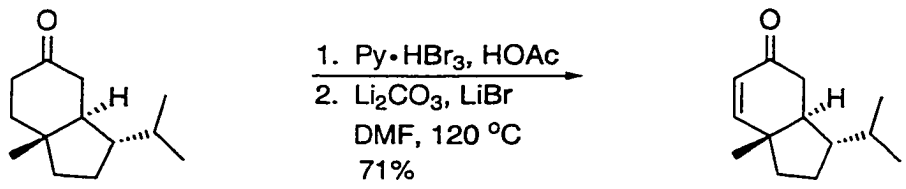
An early method for creating α,β-unsaturated ketones utilizes the aldol condensation reaction (eq 1).[2] This method, however, requires the reaction of two




(1)

carbonyl compounds, which limits the generality of this process. Also, the starting materials cannot be base sensitive, because this reaction requires a strong base.

A second method for the preparation of α,β-unsaturated is the elimination of α-haloketones.[3,4] For example, this procedure has been used by Paquette and coworkers in the total synthesis of 18-oxo-3-virgene.[4] Compound **1** was first treated with pyridinium hydrobromide perbromide in acetic acid to afford the α-bromoketone *in situ* (eq 2). The mixture was then treated with $Li_2CO_3$/LiBr in hot DMF to form the desired enone **2** in a 71% yield. This elimination procedure has



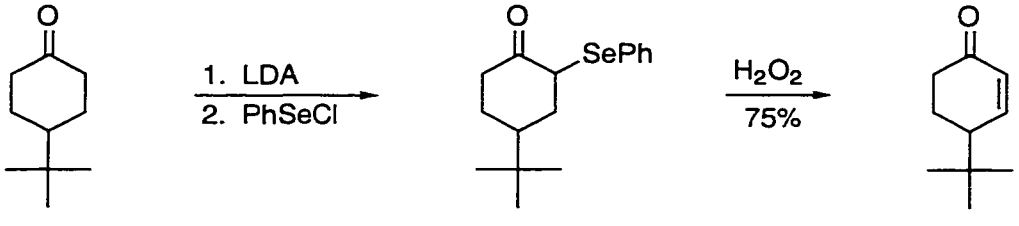

**1** **2**

(2)

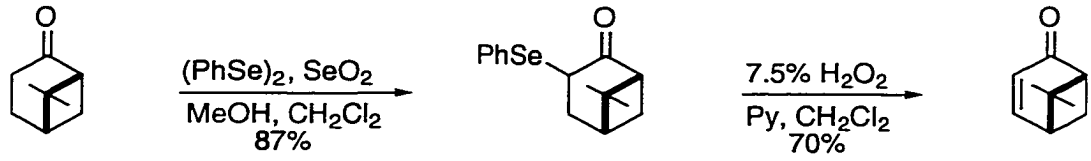
also been performed with α-chloroketones, utilizing such bases as DBU and KOH.[5] A limitation of this procedure is the rather harsh reaction conditions, which require starting materials and products to tolerate high reaction temperatures.

Another method of forming α,β-unsaturated ketones developed by Sharpless involves the use of organoselenium reagents.[6] It has been established that alkyl phenyl selenides can be easily oxidized to selenoxides, which readily undergo *syn* elimination to produce olefins. Alkyl phenyl selenides can be prepared by nucleophilic reaction of an enolate with the electrophilic selenium reagents PhSeCl or PhSeBr. The resulting alkyl phenyl selenides can then be oxidized to the corresponding selenoxides using standard oxidizing agents, such as $H_2O_2$, $CH_3CO_3H$, or $NaIO_4$, which subsequently eliminate at room temperature to give the desired α,β-unsaturated ketones (Scheme 1). This procedure to obtain α,β-unsaturated ketones is undesirable, because of the high toxicity of selenium and the fact that the compounds used need to tolerate rather strong oxidizing agents. Other selenium reagents, such as $(PhSe)_2$ and $SeO_2$, have been used in place of PhSeCl to give similar results. For example, Kato and coworkers have used this

**Scheme 1**

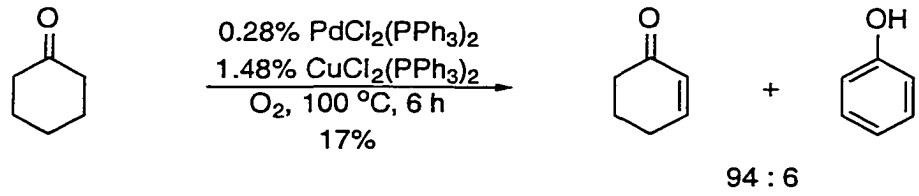


**Scheme 2**




strategy in their synthesis of (1*S*,5*S*)-4-alkyl-6,6-dimethylbicyclo[3.1.1]hept-3-en-2-ones (Scheme 2).[7]

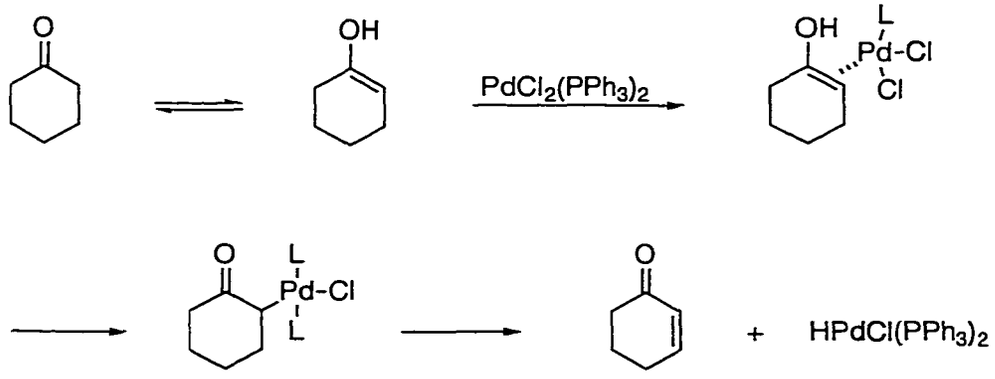
The use of palladium catalysts has become an attractive method for the conversion of carbonyl compounds to their corresponding enones, because of the low toxicity of palladium and the mild reaction conditions involved. Earlier work demonstrated that $PdCl_2(PPh_3)_2$ could be used directly with cyclic and acyclic ketones to provide the desired enones (eq 3).[8-10] The proposed mechanism for this




(3)

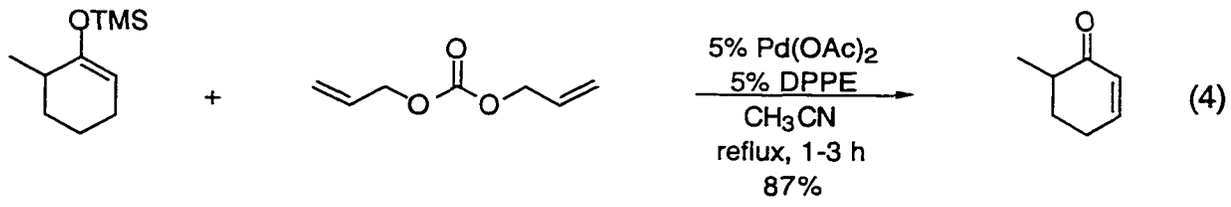
reaction involves (1) Pd(II) coordination to the enol form of the ketone, (2) rearrangement to a σ-palladium complex, (3) β-hydride elimination of the palladium to form the desired enone, and (4) reoxidation of palladium by the copper cocatalyst and oxygen (Scheme 3).[8] The limitations of this procedure include poor yields and unwanted side products.

**Scheme 3**




Saegusa and coworkers have investigated the preparation of α,β-unsaturated ketones and aldehydes from saturated ketones and aldehydes via their enol silyl ethers.[11] Their reaction conditions utilize 50 mol % of $Pd(OAc)_2$ and 50 mol % of *p*-benzoquinone. The yields of their reactions are good. However, their procedure requires large amounts of $Pd(OAc)_2$.

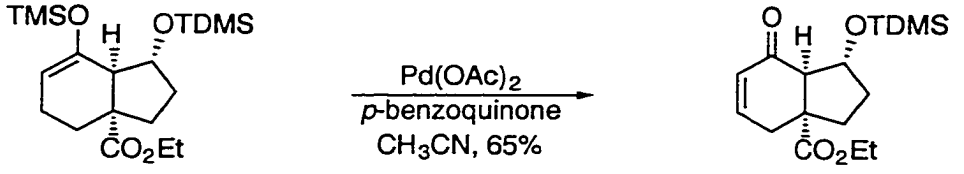
Tsuji and coworkers have also reported a palladium(II) transformation of enol silanes to the corresponding α,β-unsaturated ketones.[12-14] Their reaction conditions require an equivalent of diallyl carbonate (eq 4). The palladium catalyst first reacts with diallyl carbonate to form a π-allylpalladium species, which serves as the active catalyst. This palladium(II) catalyst can further react with enol silyl




(4)

ethers to produce α,β-unsaturated ketones and aldehydes. Tsuji's procedure provides the desired enones in good yields under relatively mild conditions. However, this procedure requires an equivalent of diallyl carbonate to produce the active palladium(II) catalyst.

Other reoxidants, such as benzoquinone and oxygen, have been utilized in the conversion of palladium(0) to palladium(II).[15-17] Cossy and coworkers have used benzoquinone as a reoxidant during their synthesis of ptaquilosin (eq 5).[17]

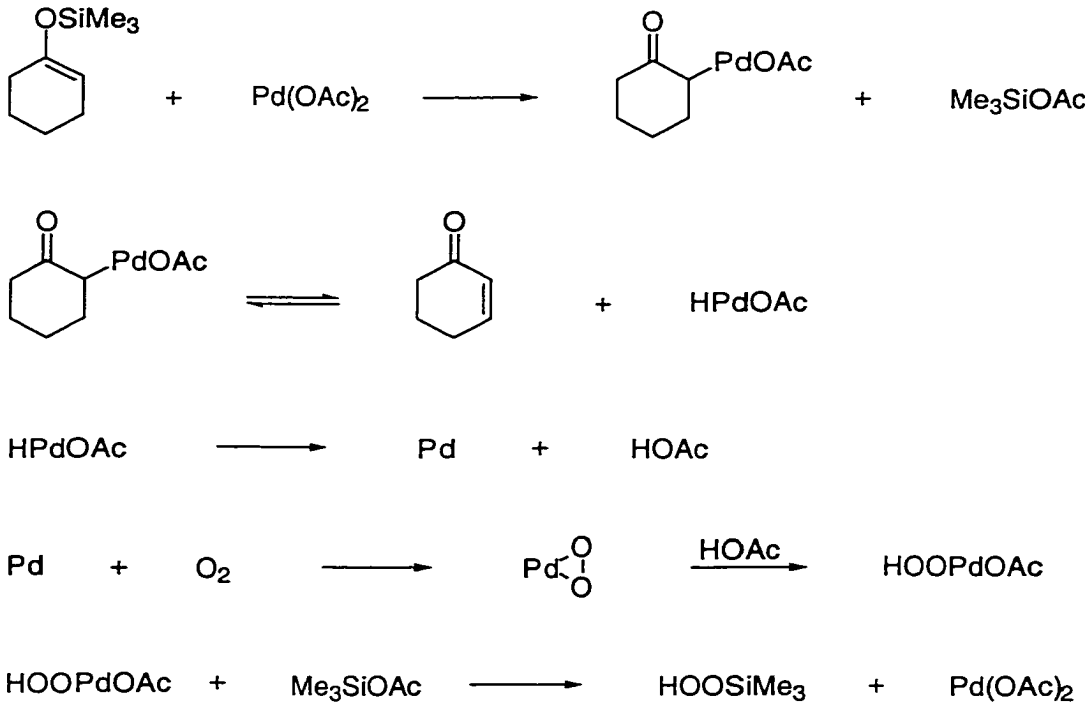



(5)

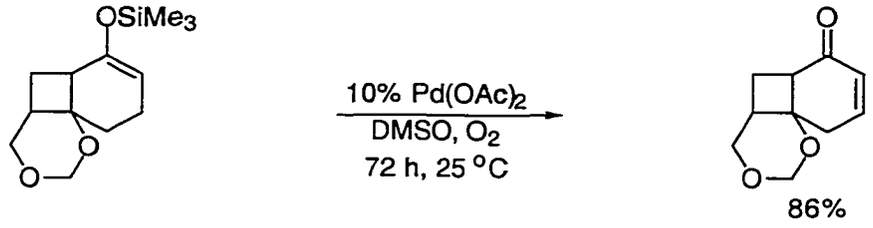
The main disadvantage is the requirement of a stoichiometric amount of benzoquinone. Neither Tsuji's or Cossy's procedures would be practical on a large industrial scale, because of the cost and the waste generated by the reoxidant.

Several groups have reported palladium(II) procedures that use molecular oxygen as a reoxidant.[18-24] Oxygen is more cost efficient and does not produce large amounts of waste like benzoquinone. The general reaction conditions for this procedure include 10 mol % $Pd(OAc)_2$, DMSO as the solvent, 1 atmosphere of $O_2$, and a reaction temperature of 25 $^{o}$C. The mechanism is similar to Tsuji's with respect to the formation of the enone. However, the reoxidation of palladium is achieved by molecular oxygen (Scheme 4). It is proposed that palladium(0) forms

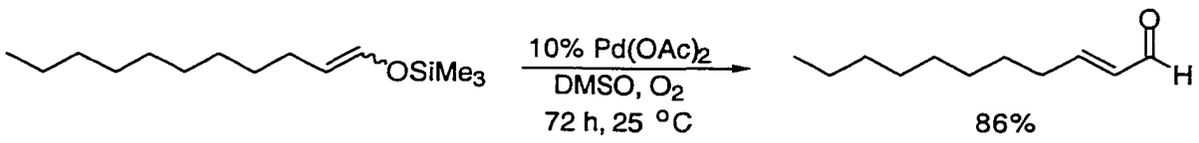
**Scheme 4**




a three membered peroxide with oxygen. This peroxide is cleaved by HOAc, produced earlier in the reaction, to generate a hydroperoxypalladium acetate. This species could react with the trimethylsilyl acetate, generated in the first step of the process, to regenerate $Pd(OAc)_2$. This process works most effectively when DMSO is used as the solvent. However, it is unclear what role DMSO plays during the reoxidation of palladium(0).[23] This palladium(II) procedure works for simple ketones, aldehydes and esters (eqs 6-8).[25] The limitations of this procedure include long reaction times and unwanted side products in some systems. Some starting enol silyl ethers produce large amounts of the corresponding saturated carbonyl compounds, which are the precursors to the enol silanes (eqs 8 and 9).




(6)

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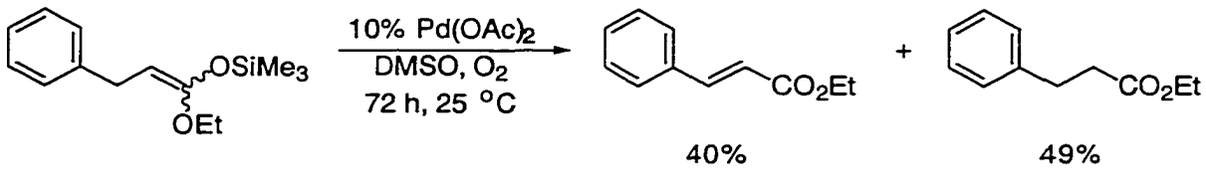


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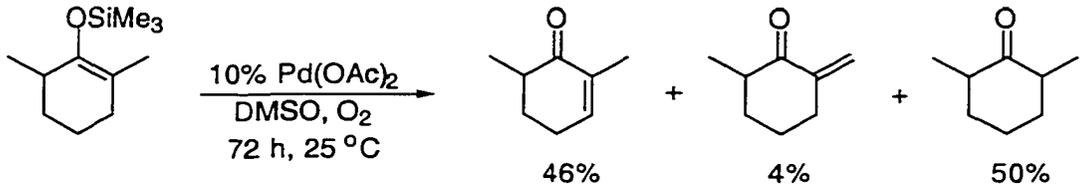


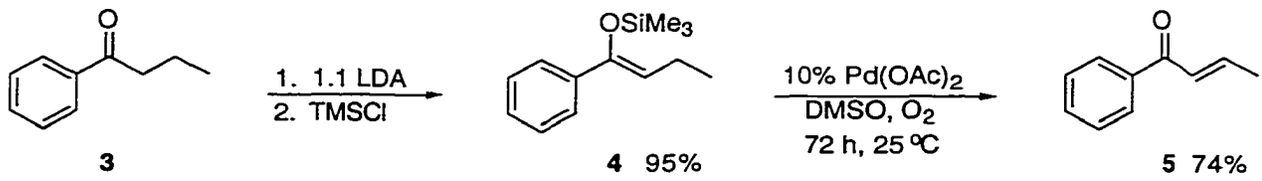

(9)

It was our desire to develop a palladium(II)-catalyzed procedure for the synthesis of enones, which used $O_2$ as the sole reoxidant and eliminated by-products, such as the corresponding saturated ketone.

## Results and Discussion

Our initial studies focused on optimization of the reaction conditions developed earlier by Larock and Hightower for the palladium(II)-catalyzed conversion of enol silanes to enones. This system is unique in that oxygen is used as the sole reoxidant. However, in many examples the saturated ketone is formed as an unwanted side product. This side product is presumably coming from hydrolysis of the enol silane by water. Optimization began with enol silyl ether **4** produced from butyrophenone (**3**).[26] This substrate was previously run by Hightower using his standard conditions of $Pd(OAc)_2$ (10 mol %), DMSO (10 mL), enol silyl ether (0.50 mmol), $O_2$ (1 atm), and a reaction time of 72 h (Scheme 5). He obtained a 74% yield of enone **5**.

**Scheme 5**




**3** **4** 95% **5** 74%

It was first discovered that reducing the amount of palladium catalyst to 5 mol % under the standard reaction conditions did not effect the yield of enone produced (72%). Decreasing the amount of palladium catalyst further to 2.5 mol % decreased the enone yield to 63%, with 5% of the saturated product **3** also present in the product mixture. Since optimization of this reaction was the main objective, the remainder of the reactions reported use 2.5 mol % of the palladium catalyst. It

should also be noted that the reaction time of 72 h reported by Hightower was unnecessary. It was found that 24 h is sufficient. It was necessary, however, to increase the reaction time to 48 h when 2.5 mol % $Pd(OAc)_2$ was used. Changing to other palladium(II) catalysts, such as palladium(II) trifluoroacetate or palladium(II) nitrate, did not prove beneficial. Palladium(II) trifluoroacetate produced enone **5** in a 74% yield, along with a 17% yield of saturated ketone **3**. Palladium(II) nitrate only produced enone **5** in a 4% yield, along with a 95% yield of **3**.

The use of DMSO as the solvent in this palladium(II) process was found to be crucial for the reoxidation step involving oxygen. The original procedure called for 10 mL of solvent per 0.5 mmol of enol silyl ether used. This large amount of solvent would not be practical or economical for a large scale reaction. Therefore, a series of reactions were performed reducing the amount of DMSO from 10 mL to 2 and 0.5 mL. It was discovered that the concentration of the reaction did not affect the reaction yield. In each experiment, enone **5** was produced in a 63-64% yield. For practical reasons, 2 mL of DMSO per 0.5 mmol of substrate was adopted as the standard reaction conditions for this palladium(II) transformation.

With the new procedure employing 2.5 mol % of $Pd(OAc)_2$, 0.5 mmol of enol silyl ether, 2 mL of DMSO, 1 atm of $O_2$, and a reaction temperature of 25 °C, we began to expiore the effect of adding various drying agents and Lewis acids to our model reaction. These reagents would hopefully increase the yield of enone and eliminate the saturated ketone product. The formation of the saturated ketone is presumably coming from hydrolysis of the enol silyl ether. Several drying agents were investigated with the idea that they would react with the water and retard

hydrolysis of the starting material. Table 1 displays the results for several drying agents.

In each experiment, one equiv of the drying agent was added to the standard palladium conditions and substrate **4**. Typical drying salts, such as $Na_2SO_4$, $MgSO_4$, $MgCO_3$, and $CaCO_3$, did provide good yields of **5**. However, in each case a small amount of the saturated product **3** was produced (entries 2-5). Compounds, such as triethyl orthoacetate and triethyl orthoformate, were used as drying agents, because of their high reactivity with water (entries 6 and 7). Triethyl orthoacetate did show some improvement providing a higher yield of the desired enone **5** and only a 2% yield of the saturated product **3**. However, for this palladium procedure to be considered superior to other chemical methods already reported, the formation of ketone **3** would have to be eliminated. *Bis*-trimethylsilyl amine produced only the saturated ketone, and acetic anhydride provided enone **3** in a 58% yield, along with an 8% yield of ketone **5** (entries 8 and 9). Trimethylsilyl acetate was also employed, because of its hydroscopic properties, and also because it is believed to play a role in the reoxidation of palladium(0). Addition of this reagent did not show an improvement in the yield of the desired enone and there was still a significant amount of saturated ketone formed (entry 10). Compounds, such as trimethylsilyl chloride and *N,O*-bis(trimethylsilyl)acetamide, are known silylating agents, and are also very reactive in the presence of water. It was discovered, however, that both of these additives produced only the saturated ketone (entries 11 and 12). Therefore, the most effective drying agents were $MgSO_4$, $CaCO_3$, and trimethyl orthoacetate (entries 3, 5, and 6). In all three

**Table 1. Effect of drying agents.**[a]

| entry | drying agent | reaction time (h) | % yield of enone **5** | % yield of ketone **3** |
|---|---|---|---|---|
| 1 | none | 48 | 63 | 8 |
| 2 | $Na_2SO_4$ | 48 | 68 | 3 |
| 3 | $MgSO_4$ | 48 | 78 | 5 |
| 4 | $MgCO_3$ | 48 | 54 | 15 |
| 5 | $CaCO_3$ | 48 | 79 | 4 |
| 6 | $CH_3C(OC_2H_5)_3$ | 48 | 78 | 2 |
| 7 | $HC(OC_2H_5)_3$ | 48 | 40 | 49 |
| 8 | $(Me_3Si)_2NH$ | 48 | 0 | 74 |
| 9 | $Ac_2O$ | 48 | 58 | 8 |
| 10 | $Me_3SiOAc$ | 48 | 61 | 18 |
| 11 | TMSCl | 48 | 0 | 79 |
| 12 | $CH_3(OSiMe_3)C{=}NSiMe_3$ | 72 | 0 | 14 |

[a]All reactions were run with 0.5 mmol of **4**, 2.5 mol % of $Pd(OAc)_2$, 1 atm of $O_2$, 2 mL of DMSO, 1 equiv of drying agent, and a reaction temperature of 25 °C.

experiments, the yield of enone **5** was increased. However, small amounts of the saturated ketone were still observed.

The addition of Lewis acids to the standard palladium conditions has also been explored. The idea was to create a more reactive palladium(II) catalyst, which would decrease the reaction time and retard hydrolysis of the enol silyl ether

to the saturated ketone. Table 2 summarizes the results for the addition of several Lewis acids to the standard palladium(II) reaction conditions.

In each experiment, one equiv of Lewis acid was added. It was discovered that copper(II) salts had the most positive effect. $Cu(OAc)_2$ increased the yield of enone **5** to 86% and lowered the amount of saturated ketone **3** to 3% (entry 2). A similar improvement was seen with CuO. The addition of one equiv of CuO increased the yield of **5** to 74% and lowered the yield of **3** to 2% (entry 3). Zinc salts did not improve the overall reaction, and in most cases a large amount of saturated ketone was recovered (entries 5-7). It was also found that magnesium, iron and calcium salts did not improve the reaction (entries 8-10). Lastly, $BF_3 \cdot OEt_2$ produced the saturated ketone **3** in a 47% yield and provided only a 21% yield of the desired enone. Many of the additives tried may have acted as a base under the reaction conditions. It was discovered by Hightower that the addition of a base to his palladium conditions lowered the yield of enone product.[25] The addition of one equivalent of NaOAc to our new standard conditions produced a 64% yield of the saturated ketone and none of the enone product. The standard palladium conditions did, however, prove to be tolerant of acidic conditions. When one equivalent of acetic acid was introduced into the reaction, a 72% yield of the enone was recovered, along with a 2% yield of the saturated ketone.

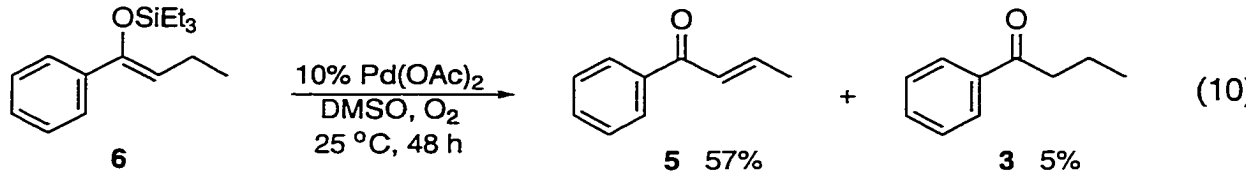
This palladium(II) transformation was also performed on enol silyl ethers, which contain bulkier silyl groups. A bulkier silyl group would presumably be more stable towards hydrolysis and still allow for the palladium transformation. Enol silyl ethers **6** and **7** were prepared by deprotonation of butyrophenone with LDA,

**Table 2. Effect of Lewis acids.**[a]

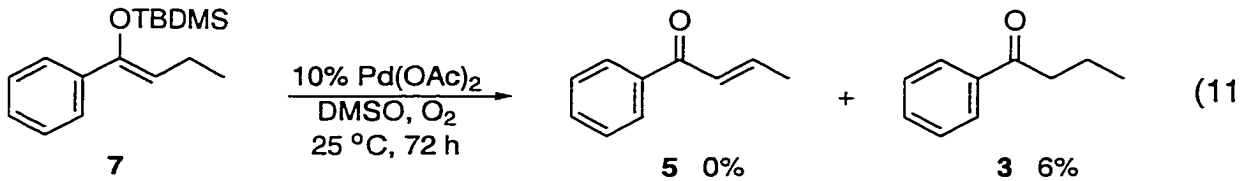
| entry | Lewis acid | reaction time (h) | % yield of enone **5** | % yield of ketone **3** |
|---|---|---|---|---|
| 1 | none | 48 | 63 | 8 |
| 2 | $Cu(OAc)_2$ | 48 | 86 | 3 |
| 3 | CuO | 48 | 74 | 2 |
| 4 | $CuCO_3 \cdot Cu(OH)_2$ | 48 | 6 | 17 |
| 5 | $Zn(OAc)_2$ | 48 | 60 | 8 |
| 6 | ZnO | 48 | 23 | 60 |
| 7 | $ZnCO_3 \cdot Zn(OH)_2 \cdot H_2O$ | 48 | 35 | 41 |
| 8 | $Mg(OAc)_2$ | 48 | 7 | 68 |
| 9 | $Fe(OAc)_2$ | 48 | 39 | 46 |
| 10 | CaO | 72 | 56 | 14 |
| 11 | $BF_3 \cdot OEt_2$ | 48 | 21 | 47 |

[a]All reactions were run with 0.5 mmol of **4**, 2.5 mol % of $Pd(OAc)_2$, 1 atm of $O_2$, 2 mL of DMSO, 1 equiv of Lewis acid, and a reaction temperature of 25 °C.

followed by the addition of triethylchlorosilane or *tert*-butyldimethylsilyl chloride.[26] When reacted under the standard palladium(II) conditions, enol silane **6** produced the desired product in only a 57% yield, along with 5% of the saturated ketone (eq 10). After 72 h, the starting compound **7** remained mostly unreacted with only 6% of saturated ketone **3** being formed (eq 11). None of the desired enone **5** was ever observed. Compound **7** was also allowed to react at 80 °C, which produced only 2% of enone **5** and 51% of the saturated ketone **3**. It was, therefore, concluded



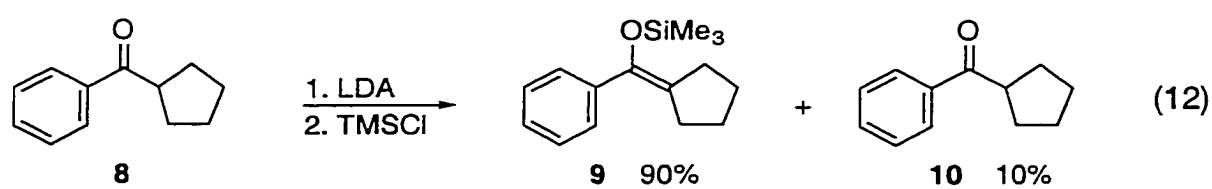

**6** **5** 57% **3** 5% (10)



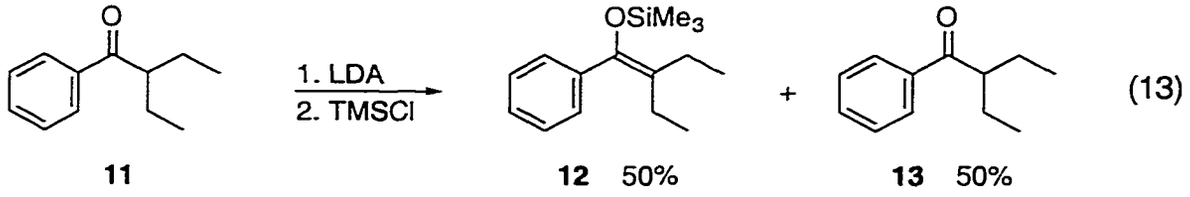

**7** **5** 0% **3** 6% (11)

that enol silanes with bulkier silyl groups do not react well with the palladium(II) catalyst.

Our next challenge for this palladium(II) transformation was to apply it to the synthesis of more substituted enones. The first obstacle was the synthesis of the corresponding enol silyl ethers. In our hands, attempts to prepare enol silyl ethers that contain a tetrasubstituted carbon-carbon double bond always produced an appreciable amount of the starting ketone in the product mixture. Efforts to separate such mixtures only led to a higher ratio of the starting ketone, which was caused by hydrolysis of the enol silyl ether (eqs 12 and 13). This led to the synthesis of enol silane **14**, which was prepared as a pure compound and should provide a trisubstituted enone after the palladium(II) transformation. Using our

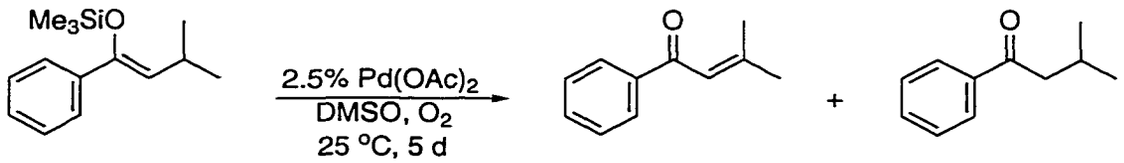



**8** **9** 90% **10** 10% (12)




**11** **12** 50% **13** 50% (13)

standard palladium(II) conditions, compound **14** afforded only a 23% yield of enone **15** and a 60% yield of saturated ketone **16** (eq 14). Several experiments were then carried out with **14**, which employed the best Lewis acids and drying agents discovered in our previous work (Table 3). Copper(II) salts that provided




**14** **15** 23% **16** 60% (14)

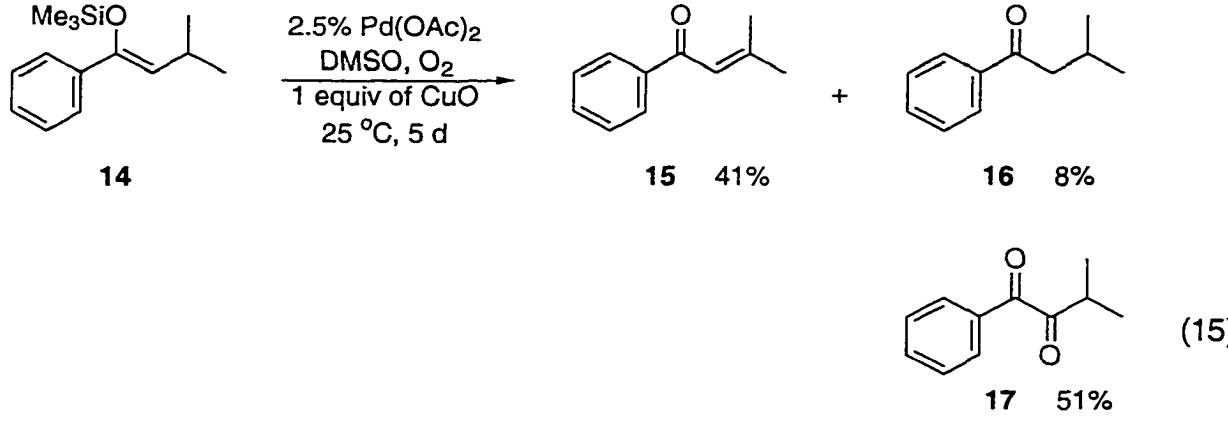
improved results with enol silyl ether **4** also improved the results obtained using enol silyl ether **14**. Copper(II) acetate and copper oxide increased the yield of **15** to 53% and 41% respectively and lowered the yield of **16** to 7% and 8% respectively (entries 2 and 3). However, the addition of these copper salts to the palladium(II) conditions caused the appearance of a new byproduct. When one equiv of copper oxide was added to the palladium(II) reaction conditions, a 51% yield of diketone **17** was recovered, along with the enone **15** and saturated ketone **16** (eq 15). The mechanism for the formation of **17** is not clear. However, **17** is

**Table 3. Optimization using compound 14.**[a]

| entry | additive | reaction time (d) | % yield of **15** | % yield of **16** | % yield of **17** |
|---|---|---|---|---|---|
| 1 | none | 5 | 23 | 60 | 0 |
| 2 | CuO | 3 | 41 | 8 | 51 |
| 3 | $Cu(OAc)_2$ | 3 | 53 | 7 | 39 |
| 4 | 2.5% $Cu(OAc)_2$ | 5 | 40 | 9 | 51 |
| 5 | $CH_3C(OC_2H_5)_3$ | 5 | 14 | 85 | 0 |

[a]All reactions were run with 0.5 mmol of **14**, 2.5 mol % of $Pd(OAc)_2$, 1 atm of $O_2$, 2 mL of DMSO, and a reaction temperature of 25 °C.

only seen when copper(II) salts are added to the palladium reaction. When one equiv of triethyl orthoacetate was added to the standard conditions as a drying agent, only a 14% yield of enone **15** was obtained, along with an 85% yield of the saturated ketone **16** (entry 5).




**14** **15** 41% + **16** 8%

**17** 51% (15)

## Conclusions

The palladium-catalyzed conversion of enol silyl ethers to enones using molecular oxygen as the reoxidant and DMSO as the solvent has been improved upon. Based on previous work by Hightower, the amount of $Pd(OAc)_2$ has been reduced from 10 mol % to 2.5 mol %, the amount of solvent has been reduced, and the reaction time has been shortened. It has also been discovered that Lewis acids, such as copper(II) salts, and drying agents, such as triethyl orthoacetate, increase the yield of enone product and depress the amount of saturated ketone by-product. This procedure, however, is limited to the synthesis of less substituted olefins. The production of trisubstituted enones leads to substantial amounts of the saturated ketone and in some cases substantial amounts of a diketone product.

## Experimental Section

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

**Reagents**. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of $Na_2SO_4$, $MgSO_4$, $MgCO_3$, $CaCO_3$, $Cu(OAc)_2$, CuO, $CuCO_3 \cdot Cu(OH)_2$, $Zn(OAc)_2$, ZnO, $ZnCO_3 \cdot Zn(OH)_2 \cdot H_2O$, $Mg(OAc)_2$, $Fe(OAc)_2$, CaO, DMSO, ethyl ether, hexanes, and ethyl acetate were purchased from Fisher Scientific Co. All palladium salts were donated by Johnson Matthey Inc. and Kawaken Fine Chemicals Co. Ltd. $PPh_3$ was also donated by Kawaken Fine Chemicals Co. Ltd. Triethyl orthoacetate, triethyl orthoformate, trimethylsilyl chloride, triethylsilyl chloride, *tert*-butyldimethylsilyl chloride, *N,O*-bis(trimethylsilyl)-acetamide, trimethylsilyl acetate, acetic anhydride, $BF_3 \cdot OEt_2$, 1,1,1,3,3-hexamethyl-disilazane, and butyrophenone were purchased from Aldrich Chemical Co., Inc.

**1-Phenyl-1-trimethylsiloxy-1-butene (4)**. This enol silane was prepared using a modified literature procedure.[26] Into a dry 150 mL round bottom flask was placed $LiN(i\text{-}Pr)_2$ (11.0 mmol) in THF (20 mL) at -78 °C. A solution of $Me_3SiCl$ (75 mmol) in THF (20 mL) was added, followed by the dropwise addition of butyrophenone (10.0 mmol) in THF (20 mL). After 5 min, dry $Et_3N$ (20 mL) was added, followed by quenching with a satd aq $NaHCO_3$ solution. The product was extracted with petroleum ether (3 x 30 mL) and the ether extracts were washed first with water (50 mL) and then with 0.1 N citric acid (50 mL). The organic solution was dried over $Na_2SO_4$ and concentrated under reduced pressure to yield the desired product as a clear oil in 95% yield: $^1H$ NMR ($CDCl_3$) $\delta$ 0.15 (s, 9 H), 1.05 (t, $J$ = 6.0 Hz, 3 H), 2.22 (p, $J$ = 6.0 Hz, 2 H), 5.24 (t, $J$ = 9.0 Hz, 1 H), 7.23-7.32 (m, 3 H), 7.46-7.49 (m, 2 H); $^{13}C$ NMR ($CDCl_3$) $\delta$ 0.05, 14.3, 19.6, 113.4, 125.4, 127.4,

128.1, 139.3, 148.5; IR (neat, $cm^{-1}$) 3075, 2910, 1650; HRMS calcd for $C_{13}H_{20}OSi$ 220.12834, found 220.12875.

**1-Phenyl-1-triethylsiloxy-1-butene (6).** This compound was prepared using the procedure described for enol silane **4**, except $Et_3SiCl$ was substituted for $Me_3SiCl$. After work-up, the product mixture was purified by column chromatography using 10:1 hexane/ethyl acetate to afford a 44% yield of the desired enol silyl ether as a clear oil: $^1H$ NMR ($CDCl_3$) δ 0.58-0.66 (m, 6 H), 0.92-0.97 (m, 9 H), 1.05 (t, $J$ = 7.5 Hz, 3 H), 2.25 (p, $J$ = 7.5 Hz, 2 H), 5.13 (t, $J$ = 7.2 Hz, 1 H), 7.26-7.30 (m, 3 H), 7.45-7.49 (m, 2 H); $^{13}C$ NMR ($CDCl_3$) δ 5.36, 6.75, 14.30, 19.45, 113.28, 125.55, 127.35, 127.98, 139.74, 148.92; IR (neat $cm^{-1}$) 2957, 2877, 1683; HRMS calcd for $C_{16}H_{26}OSi$ 262.1753, found 262.1758.

**3-Methyl-1-phenyl-1-trimethylsiloxy-1-butene (14).** This compound was prepared using the procedure described for enol silane **4**. The desired enol silyl ether was recovered in a 90% yield as a clear oil: $^1H$ NMR ($CDCl_3$) δ 0.16 (s, 9 H), 1.07 (d, $J$ = 6.9 Hz, 6 H), 2.76-2.92 (m, 1 H), 5.10 (d, $J$ = 9.6 Hz, 1 H), 7.21-7.34 (m, 3 H), 7.46-7.50 (m, 2 H); $^{13}C$ NMR ($CDCl_3$) δ 0.60, 23.28, 25.58, 119.24, 125.55, 127.39, 128.08, 139.48, 147.22; IR (neat, $cm^{-1}$) 3082, 2957, 2867, 1647; HRMS calcd for $C_{14}H_{22}OSi$ 234.14399, found 234.14446.

**3-Methyl-1-phenylbutan-1-one (16).** This compound was prepared using a modified literature procedure.[27] A suspension of zinc (99.99% purity, 26 mmol) in THF (2 mL) containing 1,2-dibromoethane (1.0 mmol) was heated to 65 °C for a minute and cooled to 25 °C, and $Me_3SiCl$ (0.1 mL, 0.8 mmol) was added. After 15 min at 25 °C, a solution of 1-iodo-2-methylpropane (25 mmol) in THF (10

mL) was added and the reaction mixture was stirred for 12 h at 25 °C. The clear solution was then cooled to -10 °C, and a solution of CuCN (22 mmol) and LiCl (44 mmol, dried at 150 °C for 1 h) in THF (22 mL) was rapidly added. The mixture was cooled to -25 °C and benzoyl chloride (18.7 mmol) was added slowly and stirred for 3 h at 0 °C. The resulting mixture was poured into satd aq $NH_4Cl$ (75 mL) and extracted with ether (3 x 25 mL). The organic extracts were combined dried and reduced under vacuum. The resulting oil was purified by column chromatography to produce the desired ketone as a clear oil. $^1H$ NMR ($CDCl_3$) δ 1.00 (d, $J$ = 6.8 Hz, 6 H), 2.25-2.35 (m, 1 H), 2.83 (d, $J$ = 6.8 Hz, 2 H), 7.43-7.56 (m, 3 H), 7.94-7.96 (m, 2 H); $^{13}C$ NMR ($CDCl_3$) δ 22.81, 25.19, 47.54, 128.14, 128.58, 132.89, 137.43, 200.31; IR (neat, $cm^{-1}$) 2950, 3050; HRMS calcd for $C_{11}H_{14}O$ 162.1045, found 162.1047.

**General Procedure for the Palladium(II)-catalyzed Reactions of Enol Silanes.** The appropriate enol silyl ether (0.50 mmol) was added to a solution of $Pd(OAc)_2$ (0.0125 mmol) and DMSO (2 mL). The reaction mixture was placed under an $O_2$ atmosphere via balloon and allowed to stir for the designated time and temperature. The reaction mixture was diluted with satd aq $NH_4Cl$ (50 mL) and extracted with diethyl ether (3 x 25 mL). The ether fractions were combined, dried ($MgSO_4$) and concentrated under vacuum to yield the crude product. The crude product was purified by flash chromatography on silica gel.

**1-Phenylbut-2-en-1-one (5).** The spectral properties matched those previously reported in the literature.[28,29]

**3-Methyl-1-phenylbut-2-en-1-one (15).** The spectral properties matched those previously reported in the literature.[30,31]

**3-Methyl-1-phenylbutane-1,2-dione (17).** The spectral properties matched those previously reported in the literature.[32-34]

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## GENERAL CONCLUSIONS

In this dissertation the scope and limitations of several palladium-catalyzed processes have been presented. In particular, palladium-catalyzed methodologies have been developed for a variety of carbo- and heterocycles, including α-alkylidene-γ-butyrolactones, indanones, 2-cyclopentenones, and quinolines. In addition, the scope and limitations of a palladium(II) process are presented in which α,β-unsaturated ketones are formed from the corresponding enol silyl ethers.

Chapter 1 describes the synthesis of α-alkylidene-γ-butyrolactones by the palladium-catalyzed heteroannulation of acyclic and cyclic 1,3-dienes using α-iodo and α-bromo acrylic acids. This process has proven to be highly regio- and stereoselective. Annulation predominately occurs at the less hindered end of the diene, and with acyclic dienes the *E*-isomer is the major product. The success of this process is dependent upon the use of the sterically-hindered, electron-rich phosphine ligand D$^t$BPF. The exact role of this ligand is uncertain, but it is likely that it is breaking up any unwanted coordination between the vinylpalladium species and the neighboring carboxylic acid

Chapter 2 presents a synthesis of indanones and 2-cyclopentenones by the palladium-catalyzed carbonylative cyclization of unsaturated aryl iodides and dienyl triflates, iodides, and bromides. This cyclization is particularly effective on substrates that contain a terminal olefin. Several bicyclic cyclopentenones containing 5,6 and 5,7 fused-rings have been prepared in excellent yields. It is likely that this palladium transformation is forming an indenone intermediate, which is coordinated to a palladium hydride species. This palladium hydride apparently

adds back across the carbon-carbon double bond to form a palladium enolate, which is protonated by $H_2O$.

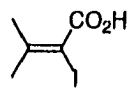
Chapter 3 describes a synthesis of quinolines through a palladium-catalyzed iminoannulation of internal alkynes. In order to achieve a quinoline product, this annulation process needs to proceed through a 6-endo ring closure. However, this process is in competition with the more favorable 5-exo ring closure, which leads to an isoindole system. While the yields and generality of this synthesis of quinolines are only moderate, the optimization results have proven to be interesting from a mechanistic point of view. Varying the palladium conditions, particularly the base, has a profound effect on the products formed.

Chapter 4 describes a synthesis of $\alpha,\beta$-unsaturated ketones from the corresponding enol silyl ethers using a catalytic palladium(II) strategy. This palladium(II) procedure is performed using catalytic amounts of $Pd(OAc)_2$ in DMSO at room temperature and uses $O_2$ as an efficient reoxidant. Significant improvements have been made in this transformation which was reported earlier by Timothy Hightower. The amount of $Pd(OAc)_2$ has been reduced from 10 mol % to 2.5 mol %, the amount of solvent has been reduced, and the reaction time has been shortened. Limitations of this procedure have been discovered for the synthesis of trisubstituted enones. In these latter examples, substantial amounts of saturated ketone or diketone by-products have been produced.

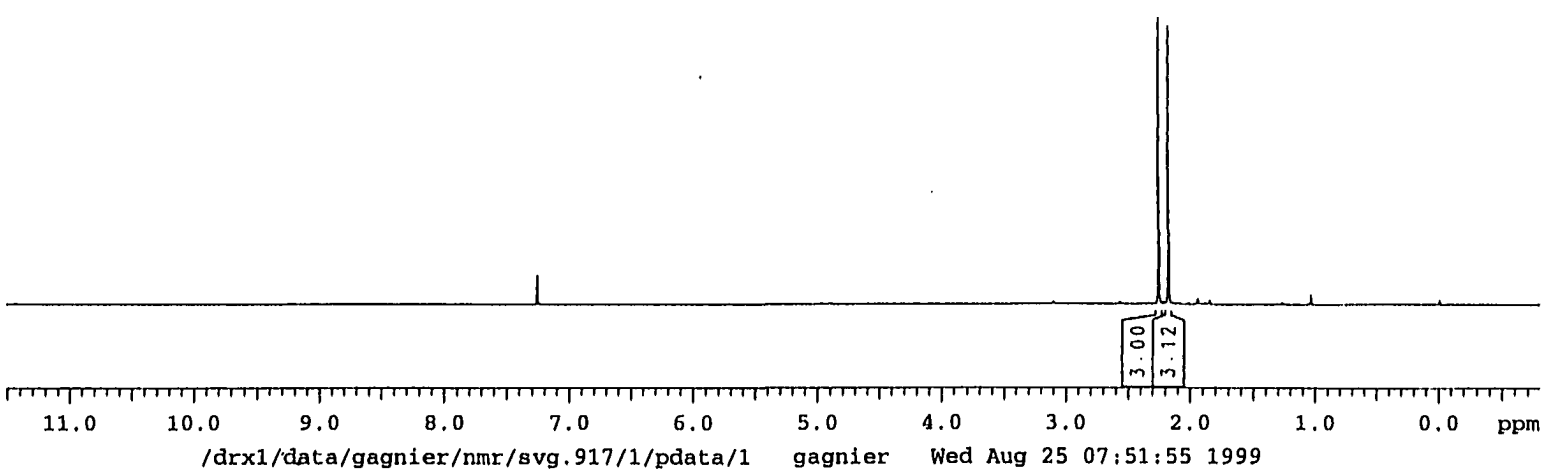
# APPENDIX A. CHAPTER 1 $^{1}H$ AND $^{13}C$ NMR SPECTRA

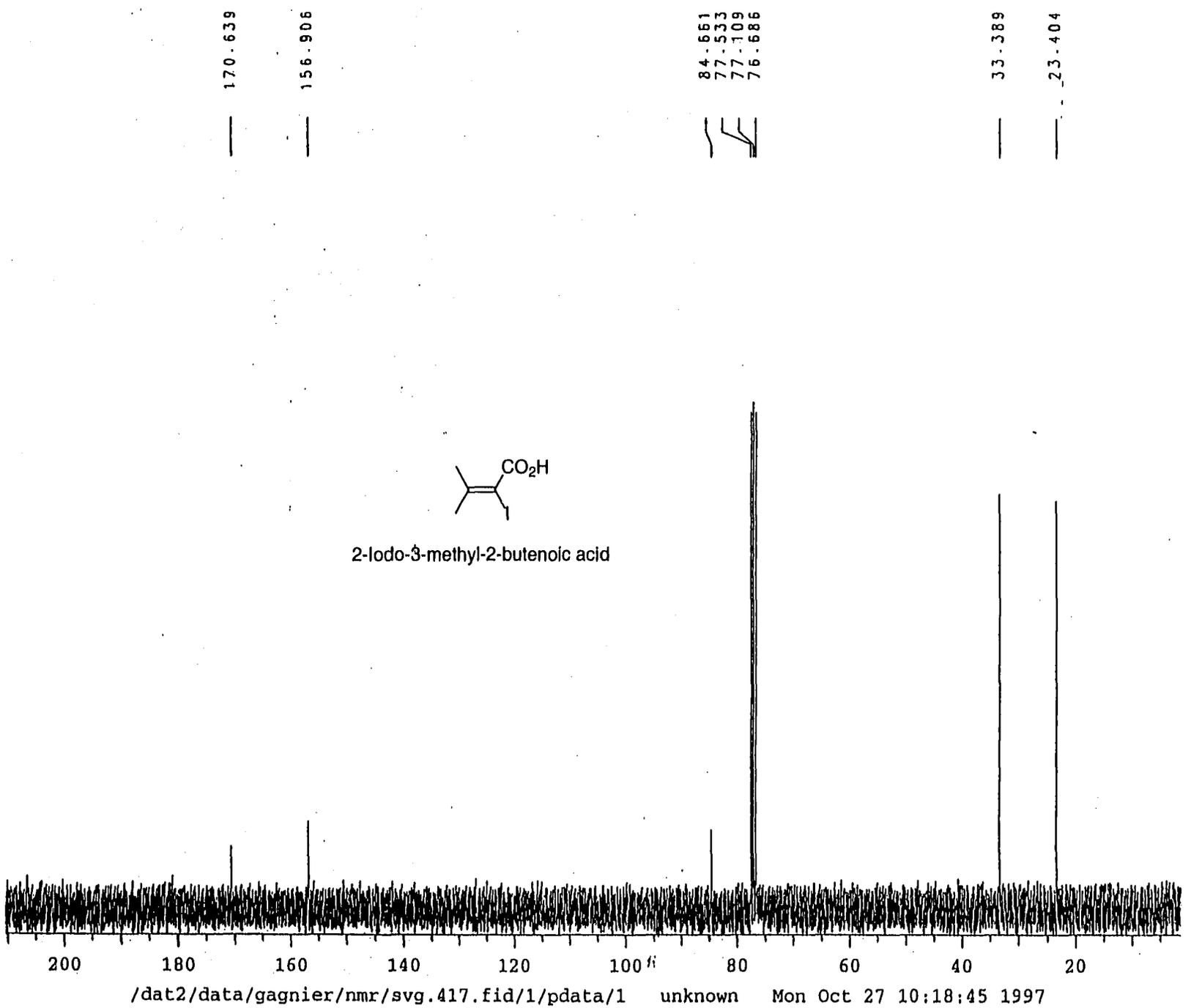
10.364

2.254
2.176




2-Iodo-3-methyl-2-butenoic acid

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156.906
84.661
77.533
77.109
76.686
33.389
23.404
CO2H
2-Iodo-3-methyl-2-butenoic acid
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180
160
140
120
100
80
60
40
20
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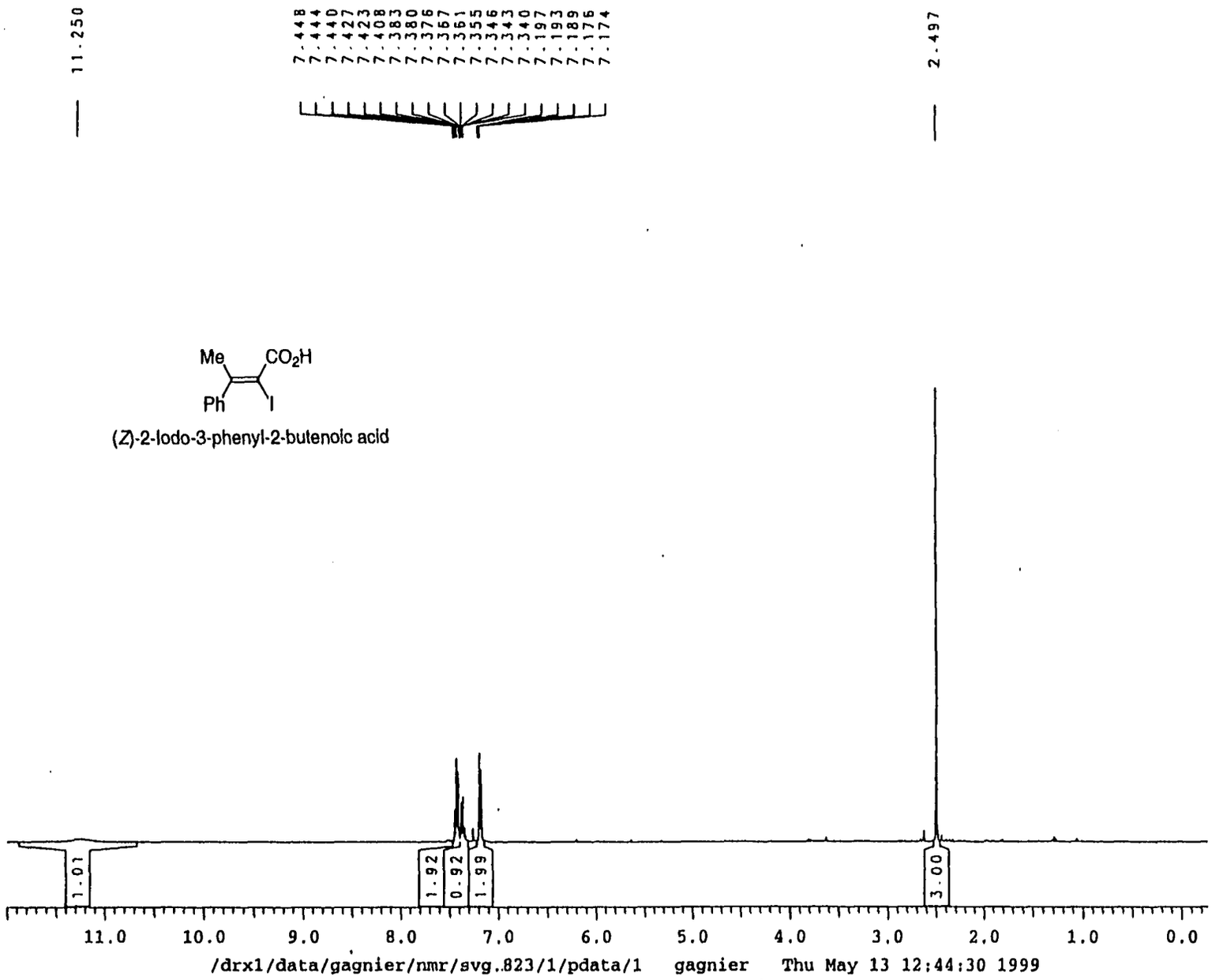
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7.448
7.444
7.440
7.427
7.423
7.408
7.383
7.380
7.376
7.367
7.361
7.355
7.346
7.343
7.340
7.197
7.193
7.189
7.176
7.174
2.497
Me
CO2H
Ph
I
(Z)-2-Iodo-3-phenyl-2-butenoic acid
1.01
1.92
0.92
1.99
3.00
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
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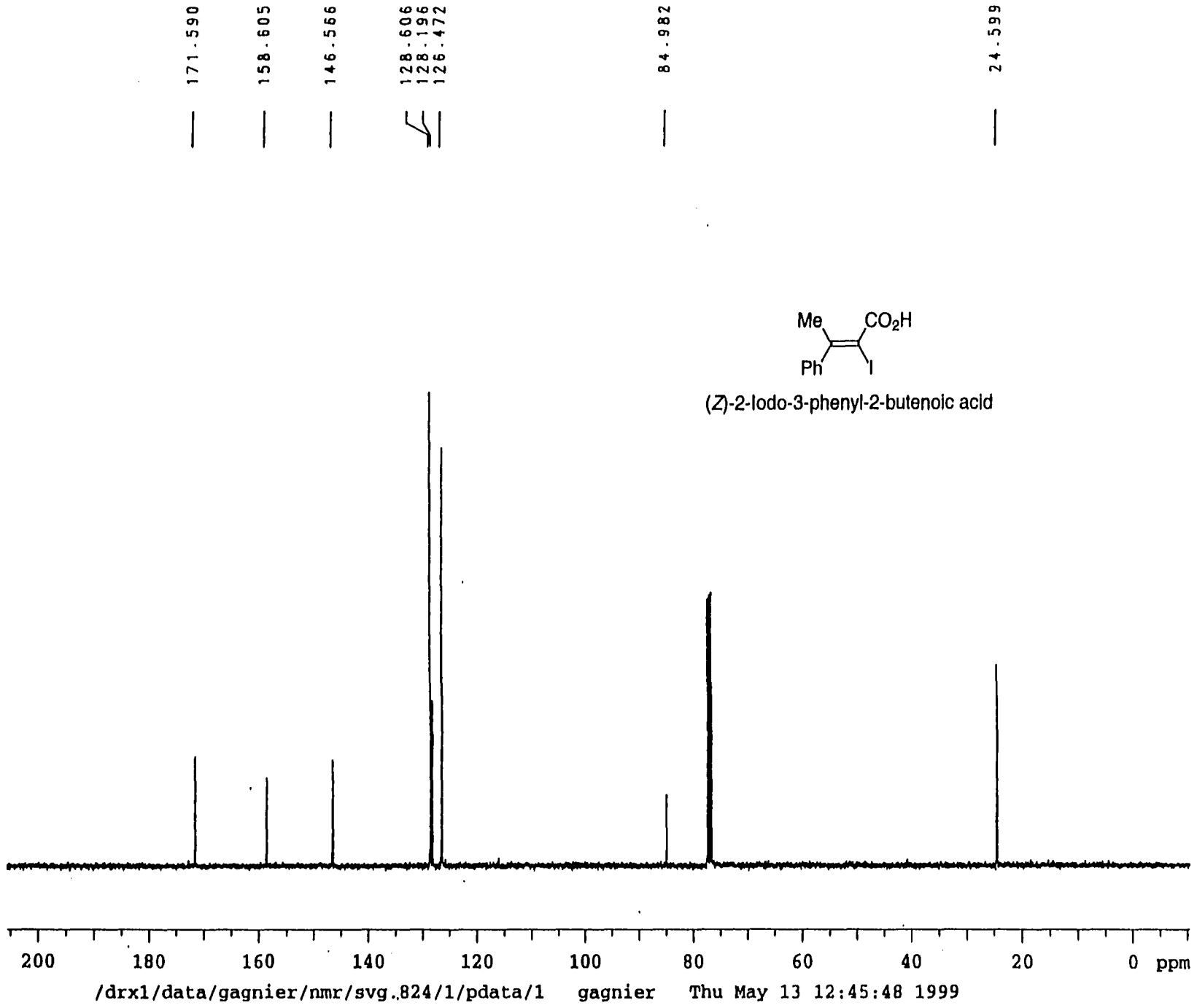
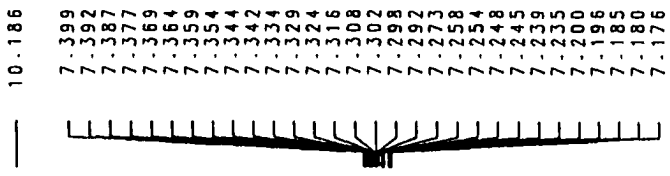



(*Z*)-2-Iodo-3-phenyl-2-butenoic acid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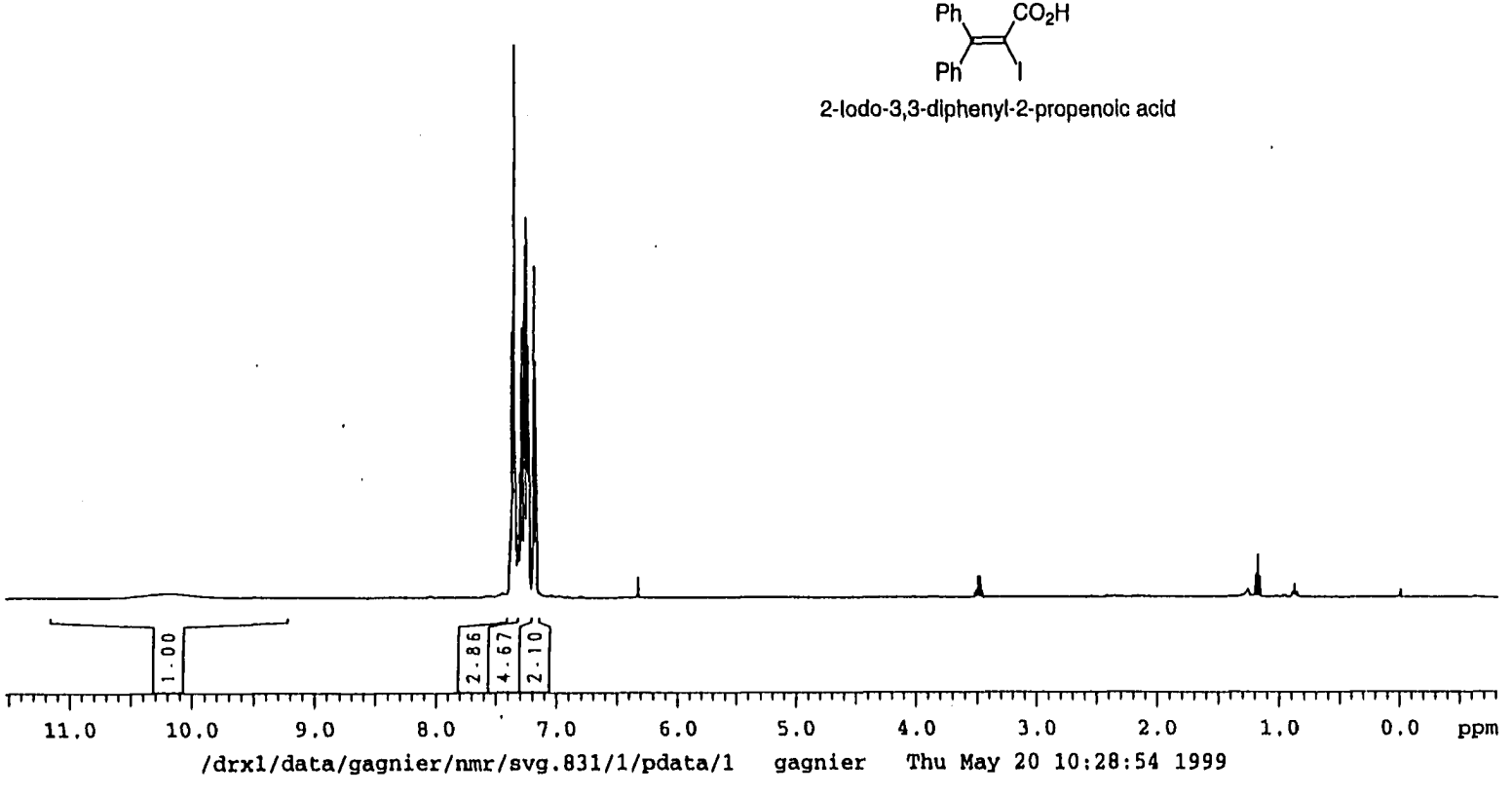
7.399
7.392
7.387
7.377
7.369
7.364
7.359
7.354
7.344
7.342
7.334
7.329
7.324
7.316
7.308
7.302
7.298
7.292
7.273
7.258
7.254
7.248
7.245
7.239
7.235
7.200
7.196
7.185
7.180
7.176


Ph
CO2H
Ph
I
2-Iodo-3,3-diphenyl-2-propenoic acid
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2.86
4.67
2.10
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm
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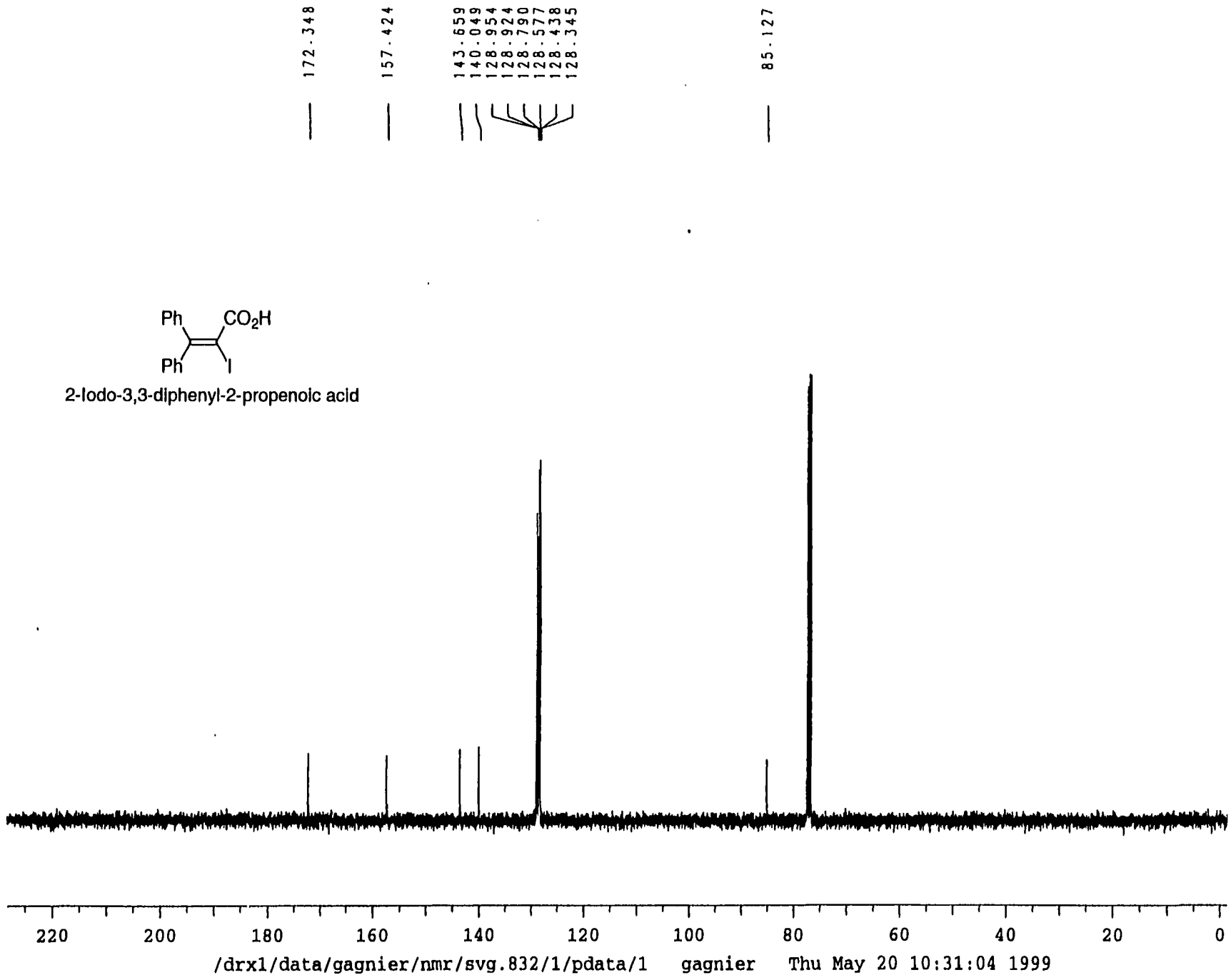
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157.424
143.659
140.049
128.954
128.924
128.790
128.577
128.438
128.345
85.127
Ph
CO2H
Ph
I
2-Iodo-3,3-diphenyl-2-propenoic acid
220
200
180
160
140
120
100
80
60
40
20
0
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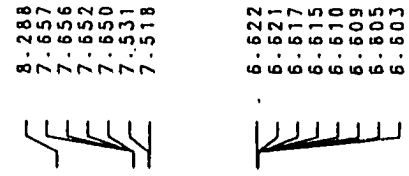
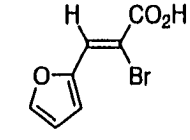
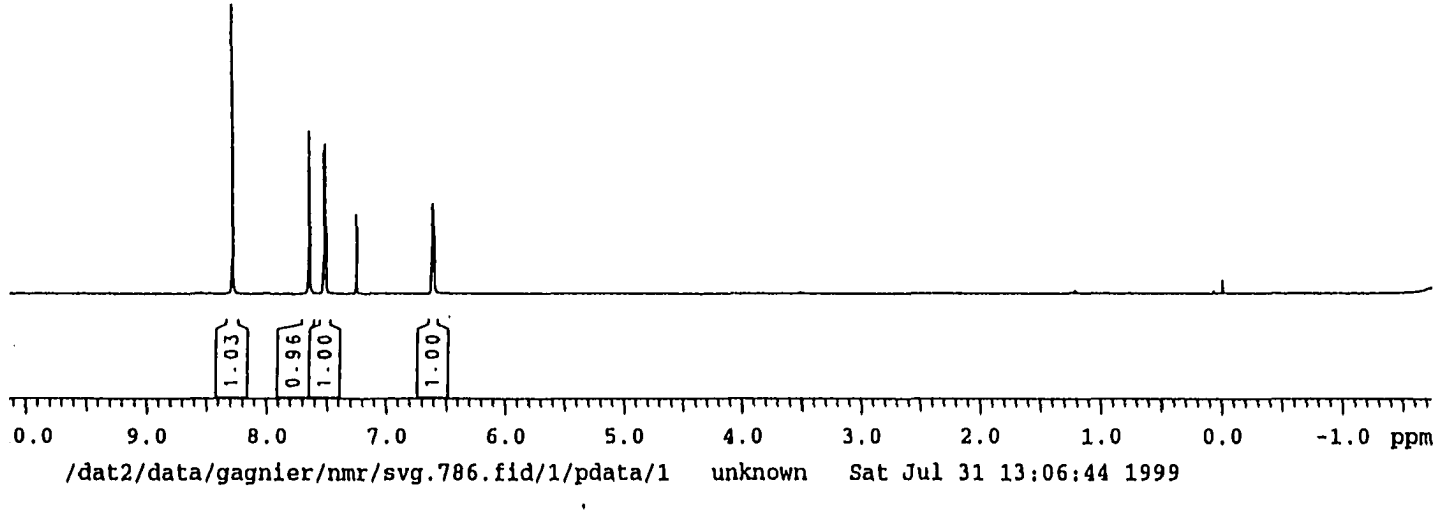
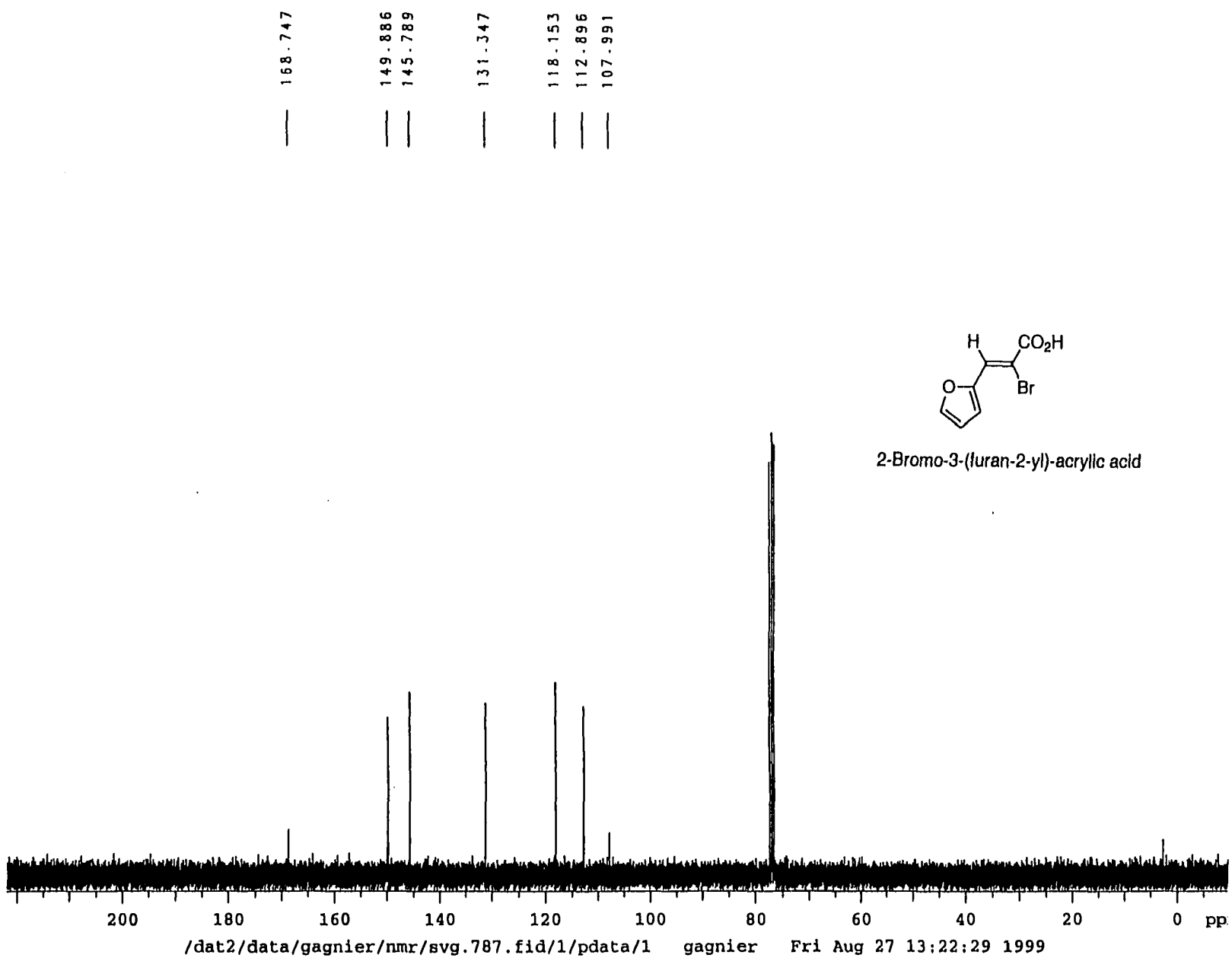



2-Bromo-3-(furan-2-yl)-acrylic acid

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149.886
145.789
131.347
118.153
112.896
107.991
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CO2H
O
Br
2-Bromo-3-(furan-2-yl)-acrylic acid
200
180
160
140
120
100
80
60
40
20
0
pp
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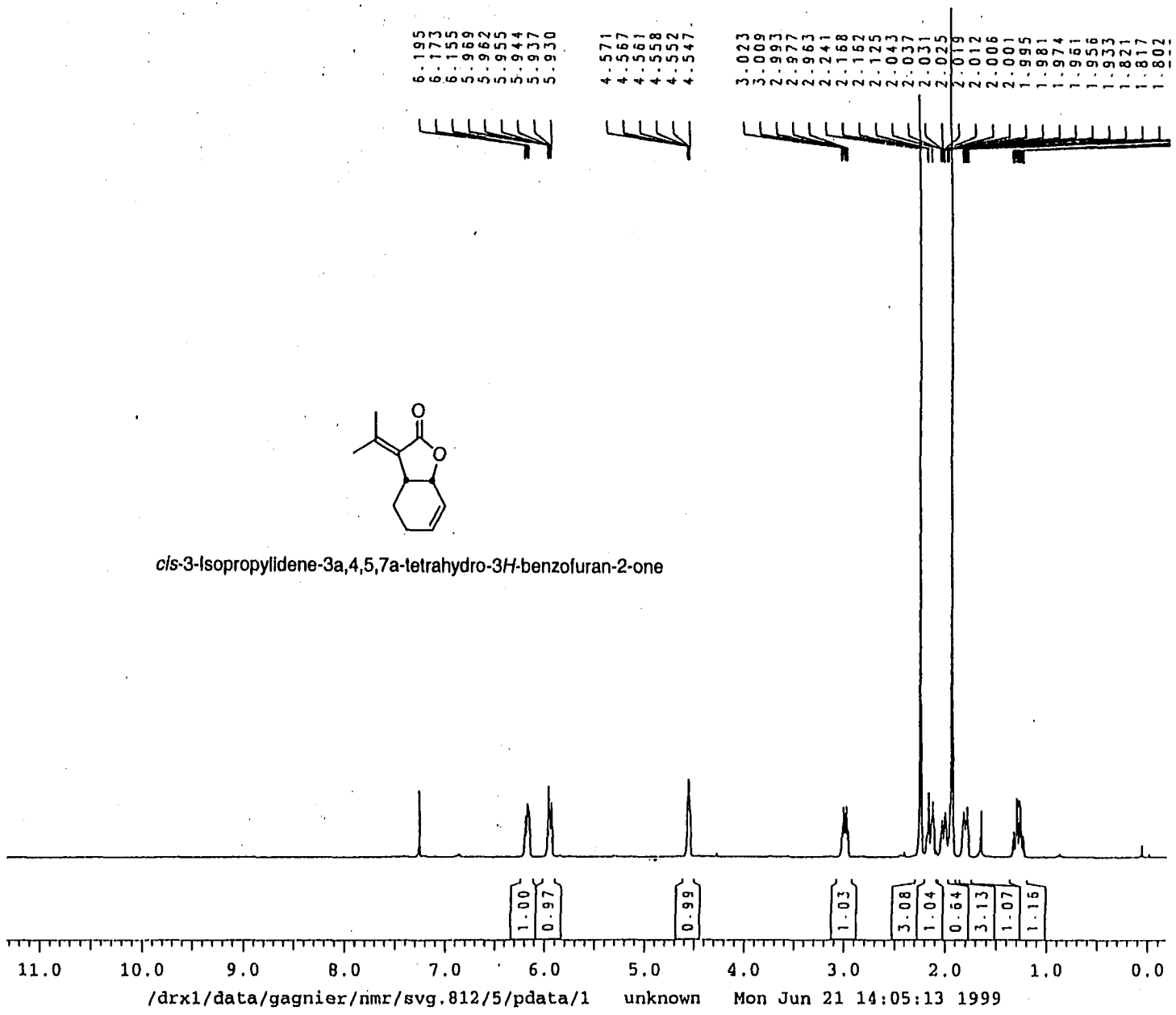


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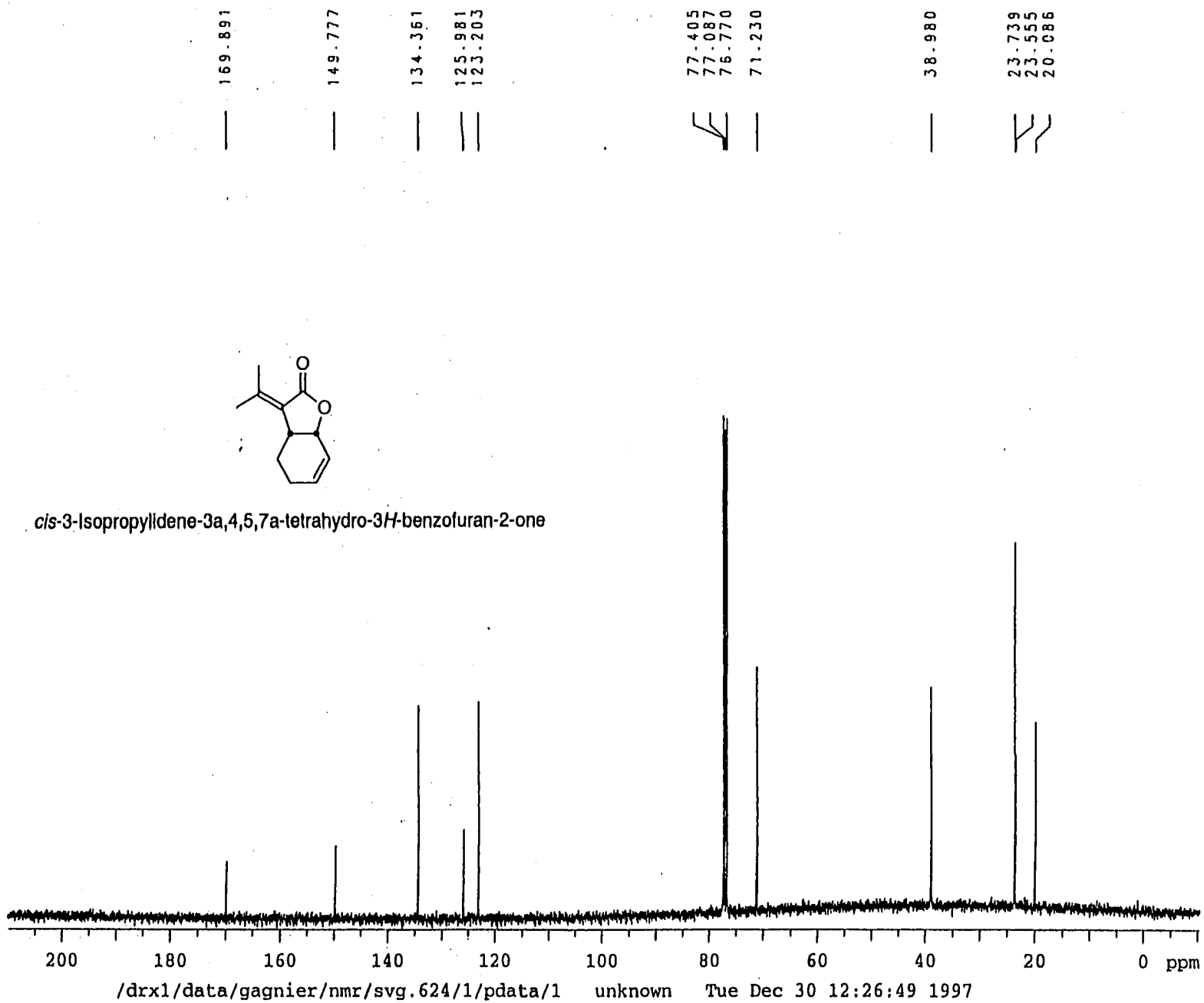


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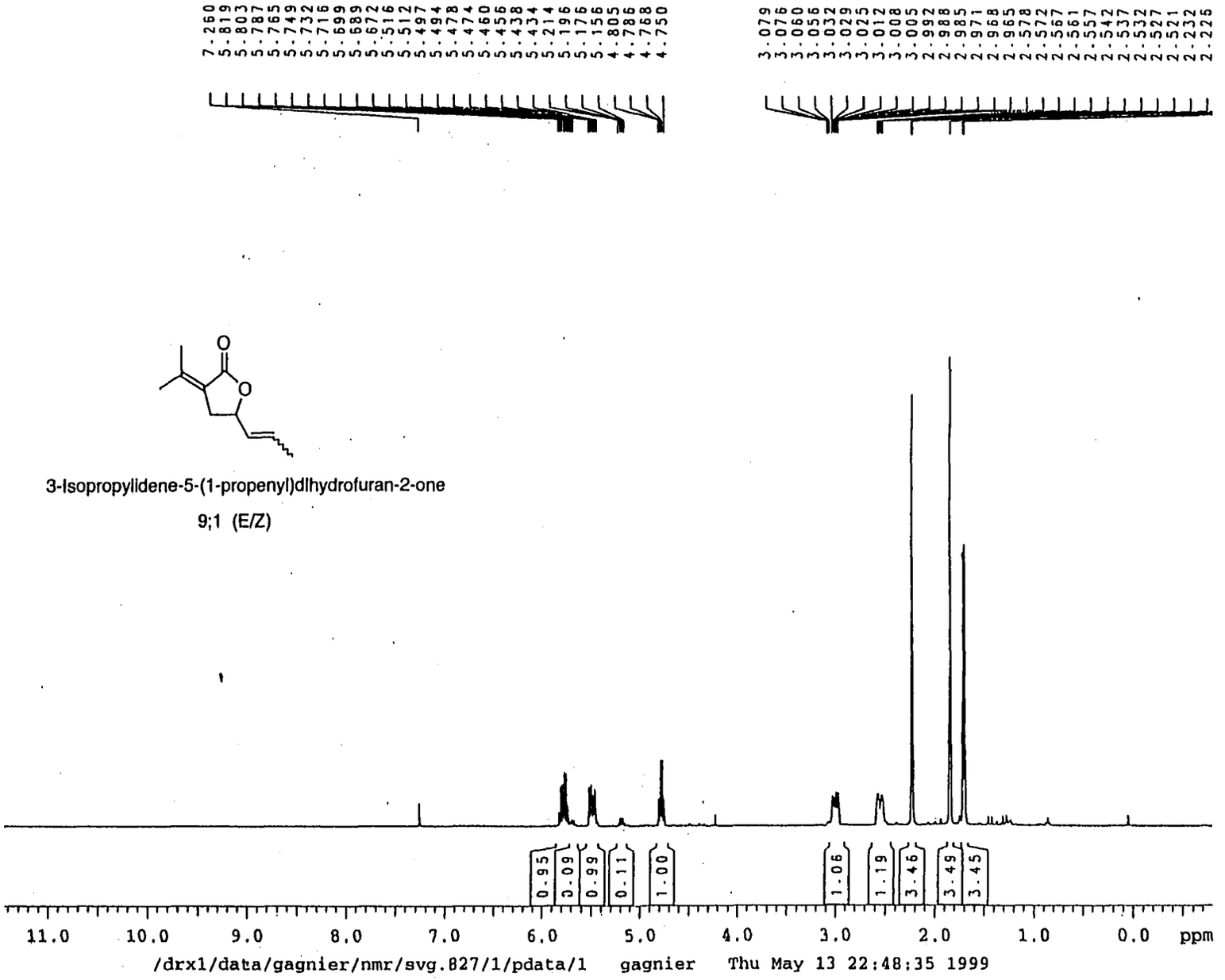
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5.732
5.716
5.699
5.689
5.672
5.516
5.512
5.497
5.494
5.478
5.474
5.460
5.456
5.438
5.434
5.214
5.196
5.176
5.156
4.805
4.786
4.768
4.750
3.079
3.076
3.060
3.056
3.032
3.029
3.025
3.012
3.008
3.005
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2.985
2.971
2.968
2.965
2.578
2.572
2.567
2.561
2.557
2.542
2.537
2.532
2.527
2.521
2.232
2.225
O
O
3-Isopropylidene-5-(1-propenyl)dlhydrofuran-2-one
9;1 (E/Z)
0.95
3.09
0.99
0.11
1.00
1.06
1.19
3.46
3.49
3.45
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
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ppm
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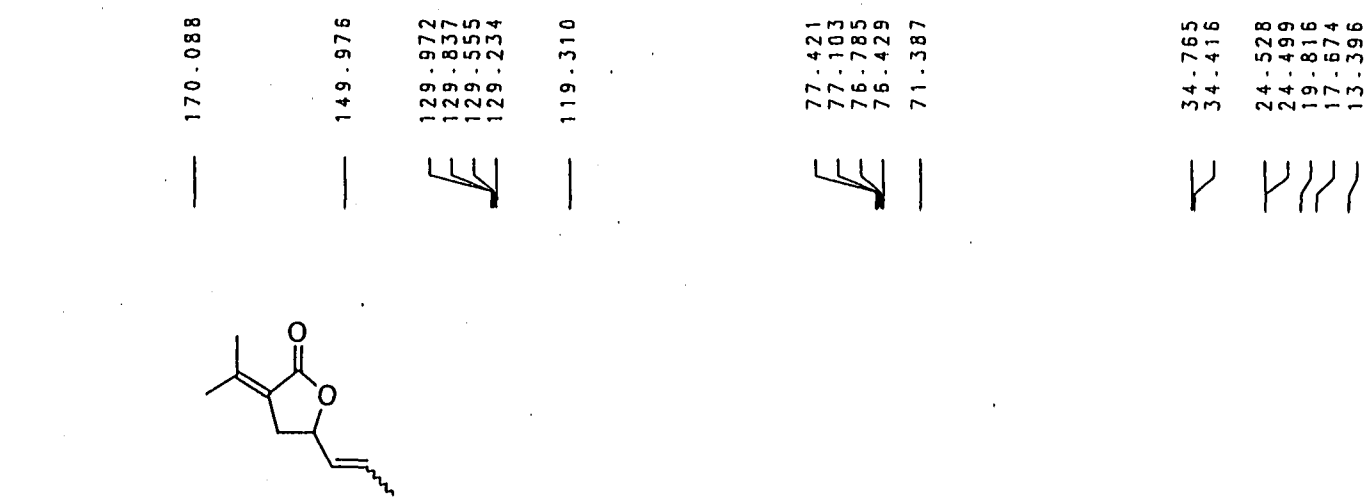
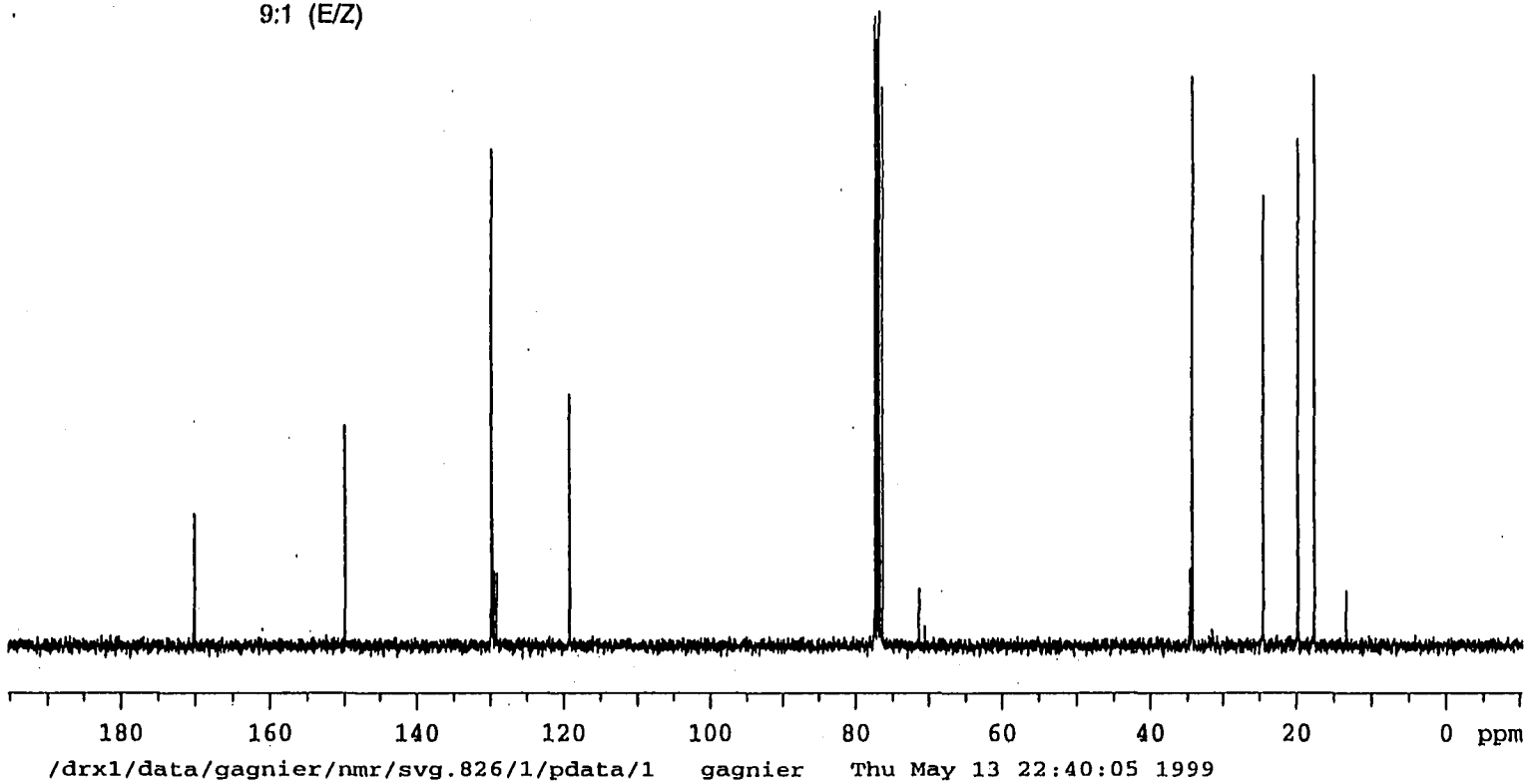
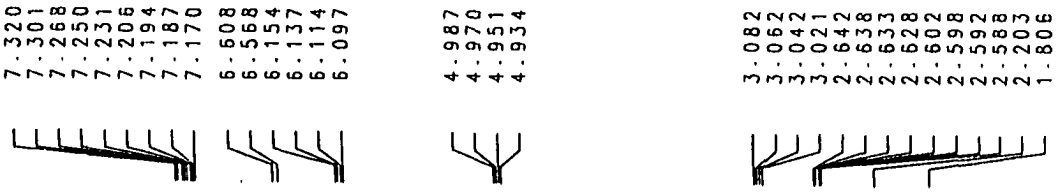
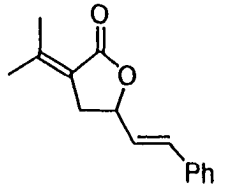



3-Isopropylidene-5-(1-propenyl)dihydrofuran-2-one

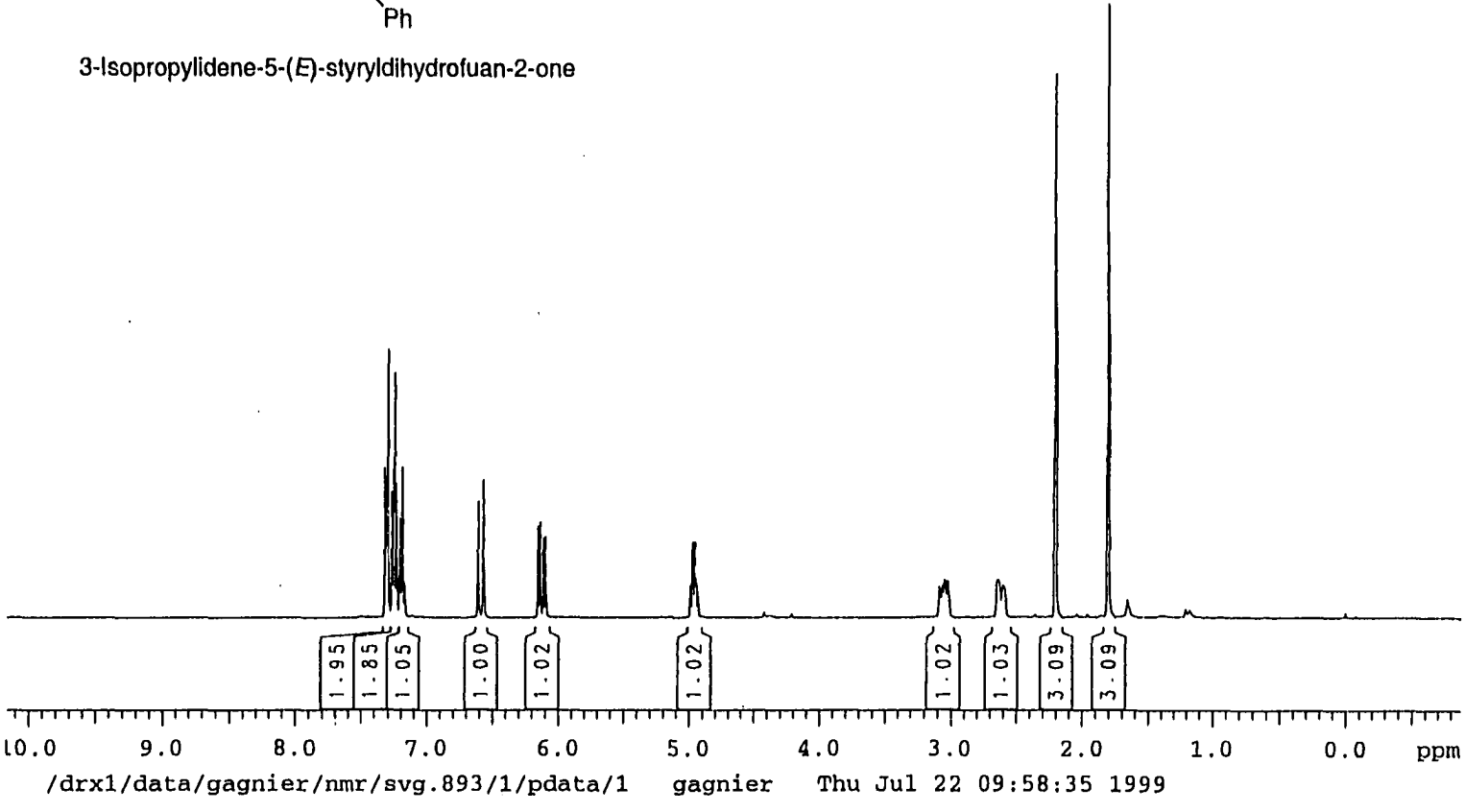
9:1 (E/Z)

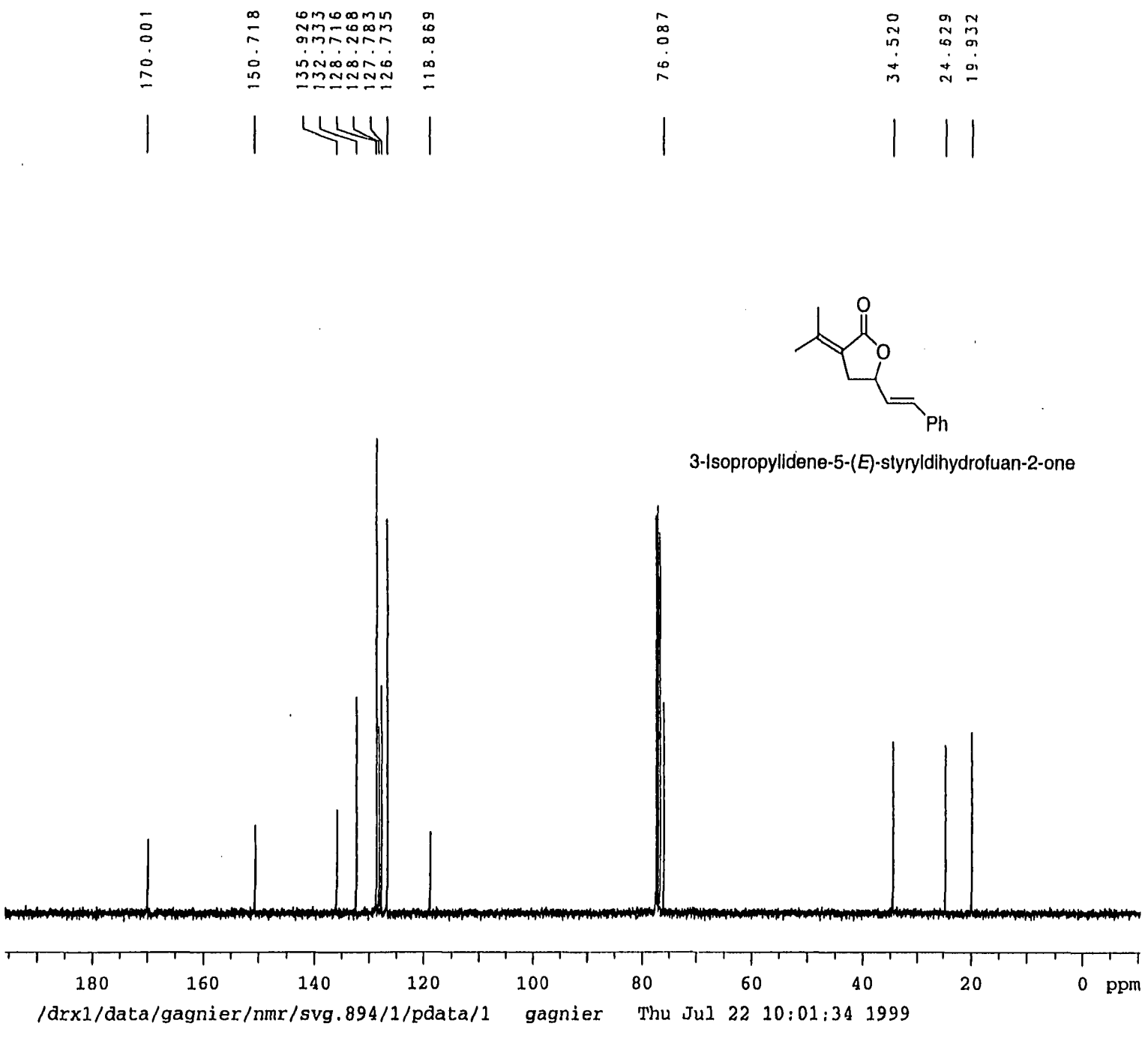





3-Isopropylidene-5-(*E*)-styryldihydrofuan-2-one

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132.333
128.716
128.268
127.783
126.735
118.869
76.087
34.520
24.629
19.932
O
O
Ph
3-Isopropylidene-5-(E)-styryldihydrofuan-2-one
180
160
140
120
100
80
60
40
20
0 ppm
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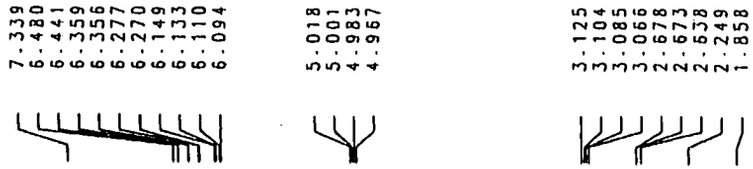
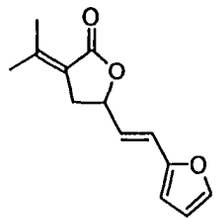
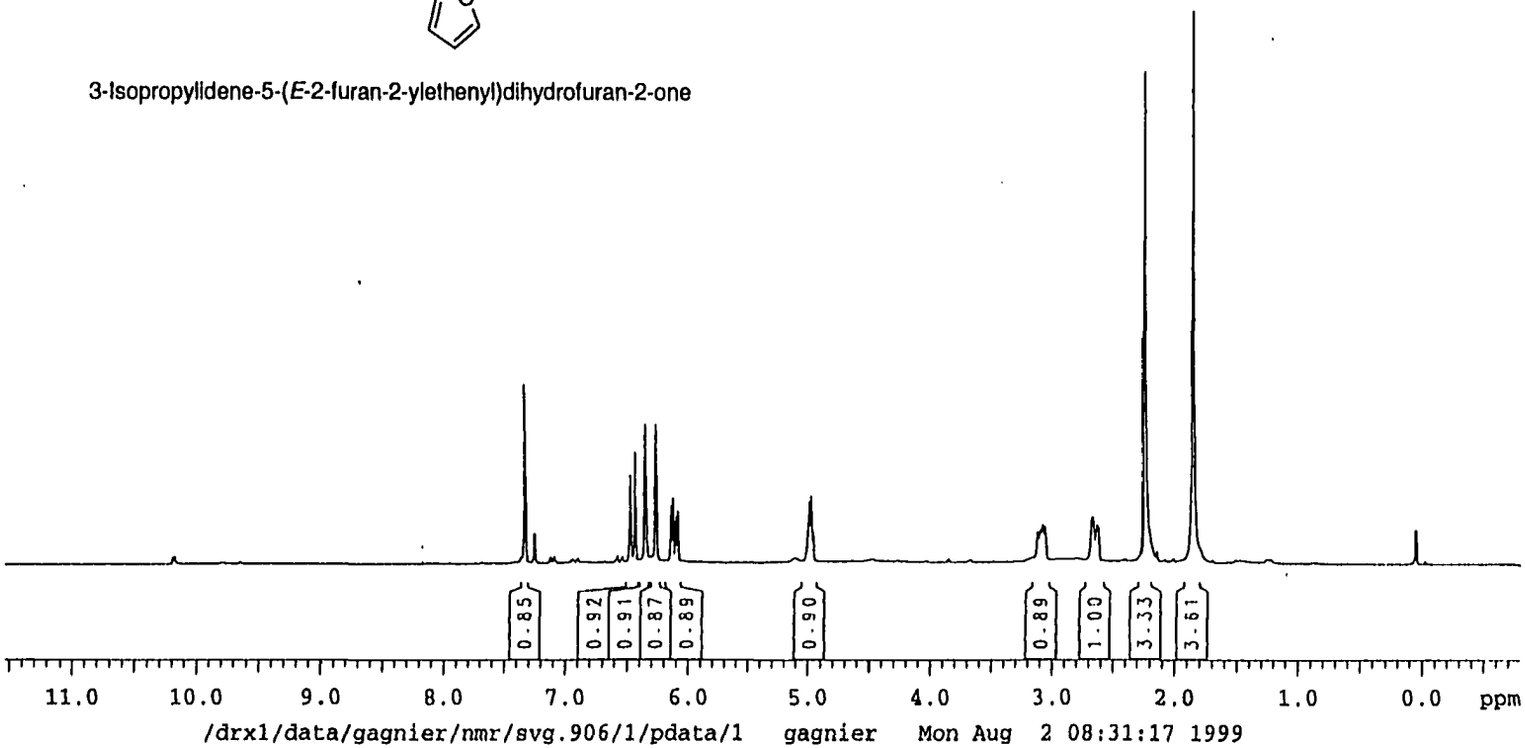
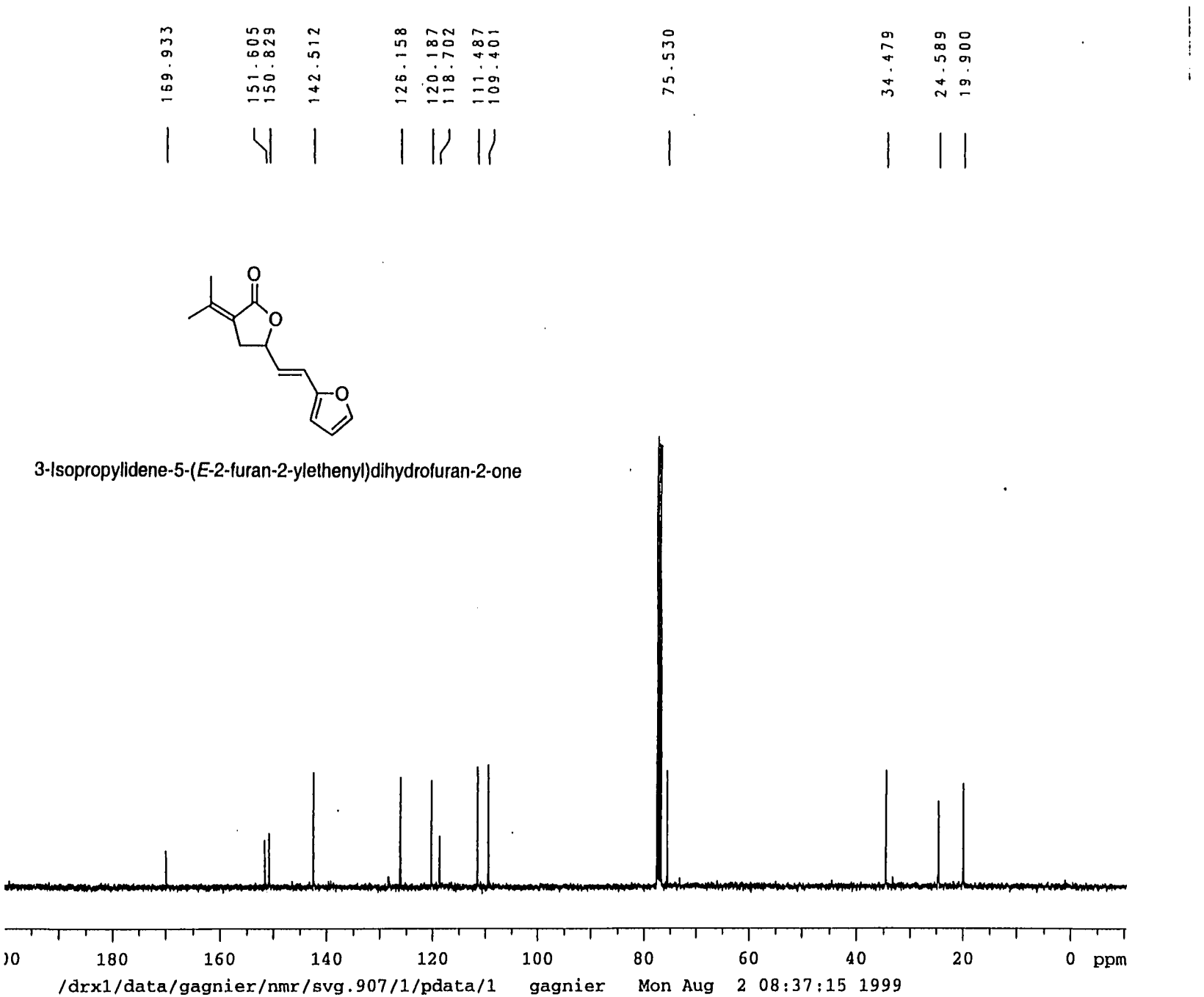


3-Isopropylidene-5-(*E*-2-furan-2-ylethenyl)dihydrofuran-2-one

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150.829
142.512
126.158
120.187
118.702
111.487
109.401
75.530
34.479
24.589
19.900
O
O
O
3-Isopropylidene-5-(E-2-furan-2-ylethenyl)dihydrofuran-2-one
)0
180
160
140
120
100
80
60
40
20
0 ppm
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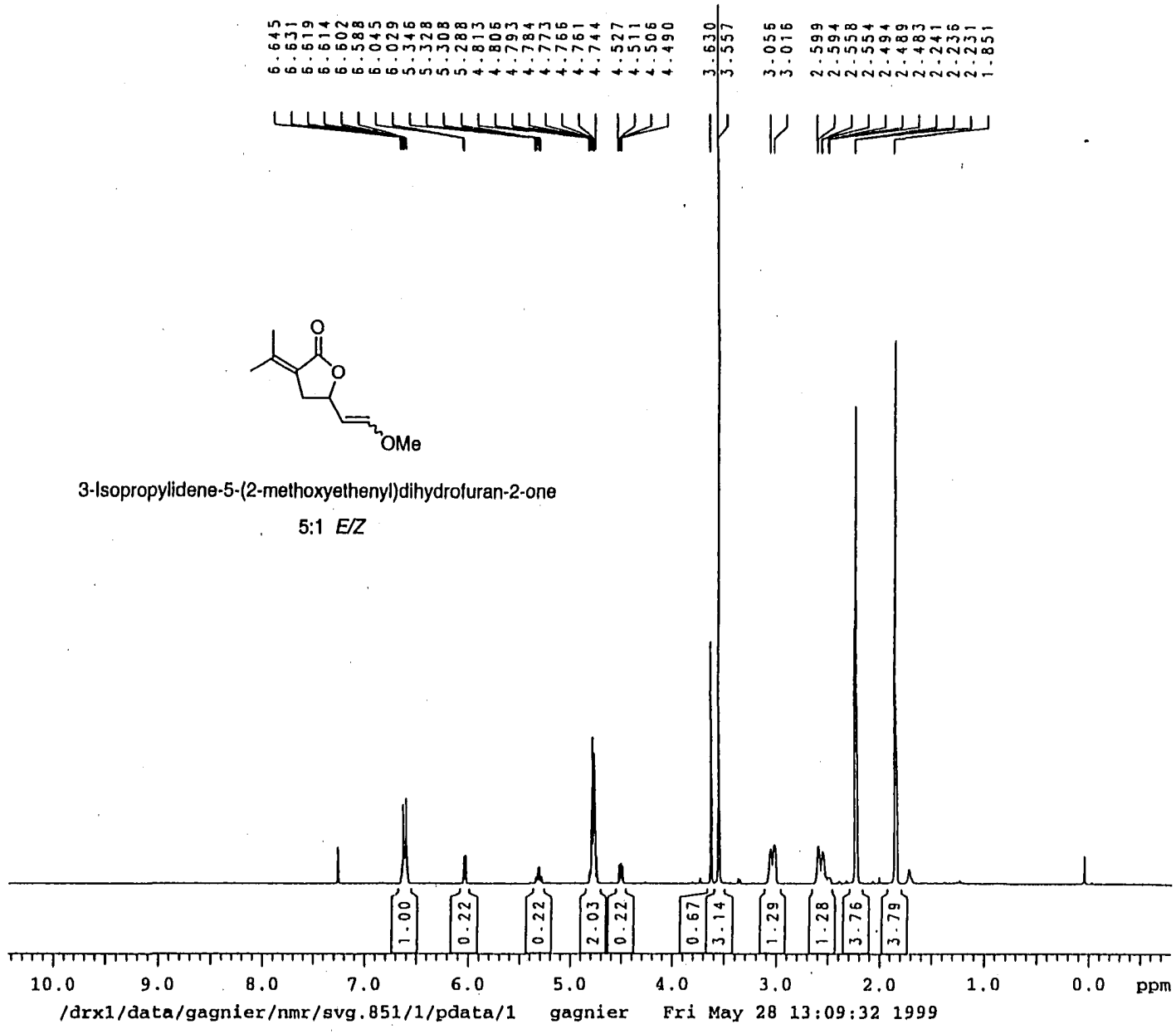
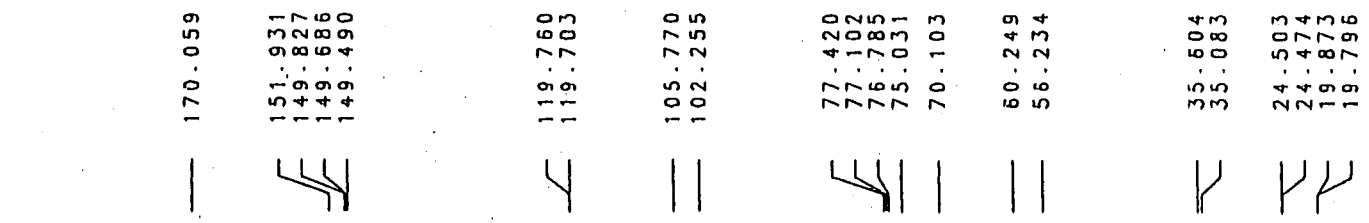
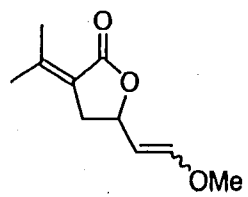



3-Isopropylidene-5-(2-methoxyethenyl)dihydrofuran-2-one

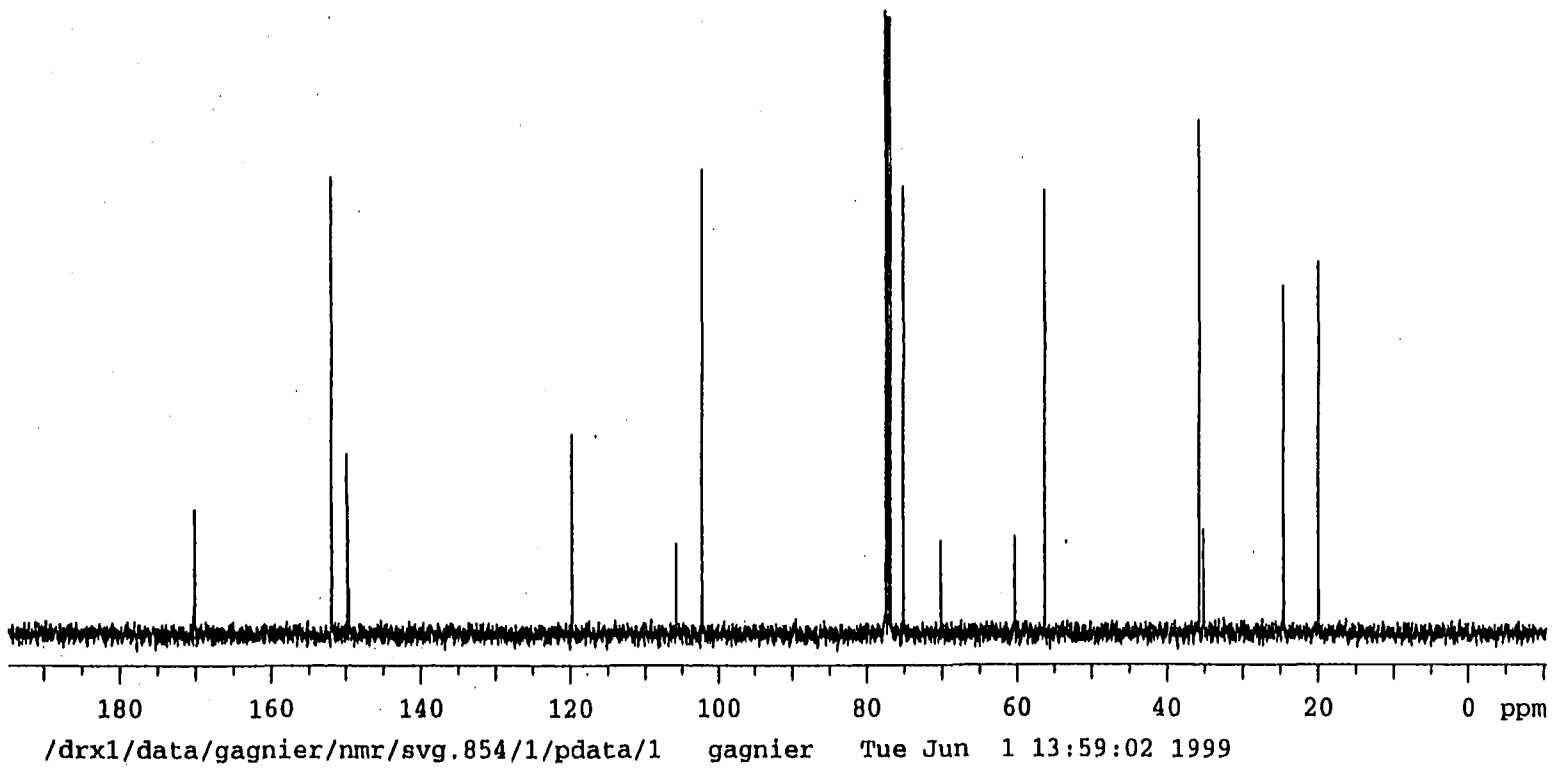
5:1 *E/Z*

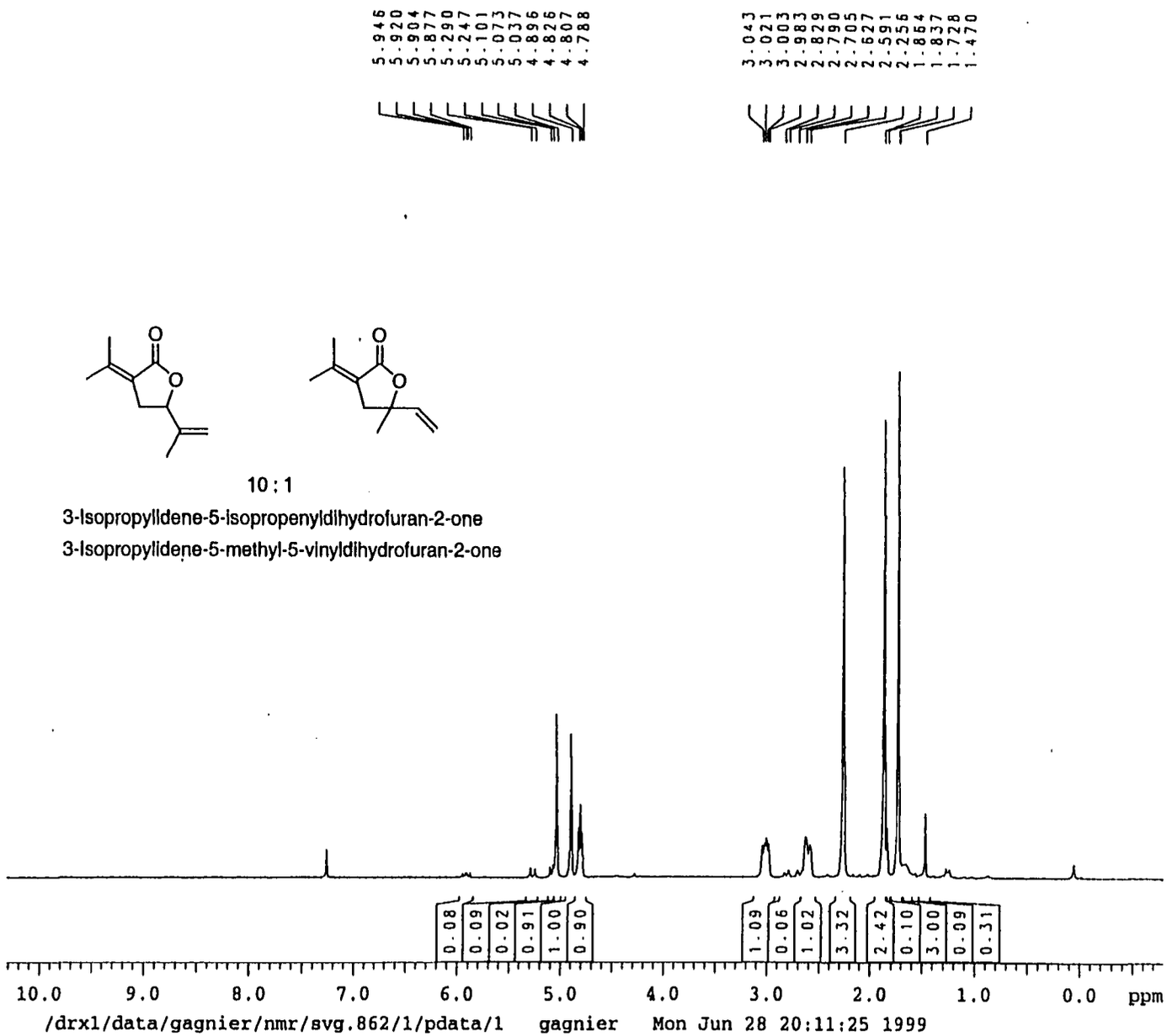



3-Isopropylidene-5-(2-methoxyethenyl)dihydrofuran-2-one

5:1 *E/Z*

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5.877
5.290
5.247
5.101
5.073
5.037
4.896
4.826
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4.788
3.043
3.021
3.003
2.983
2.829
2.790
2.705
2.627
2.591
2.256
1.864
1.837
1.728
1.470
10 : 1
3-Isopropylidene-5-isopropenyldihydrofuran-2-one
3-Isopropylidene-5-methyl-5-vinyldihydrofuran-2-one
0.08
0.09
0.02
0.91
1.00
0.90
1.09
0.06
1.02
3.32
2.42
0.10
3.00
0.09
0.31
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
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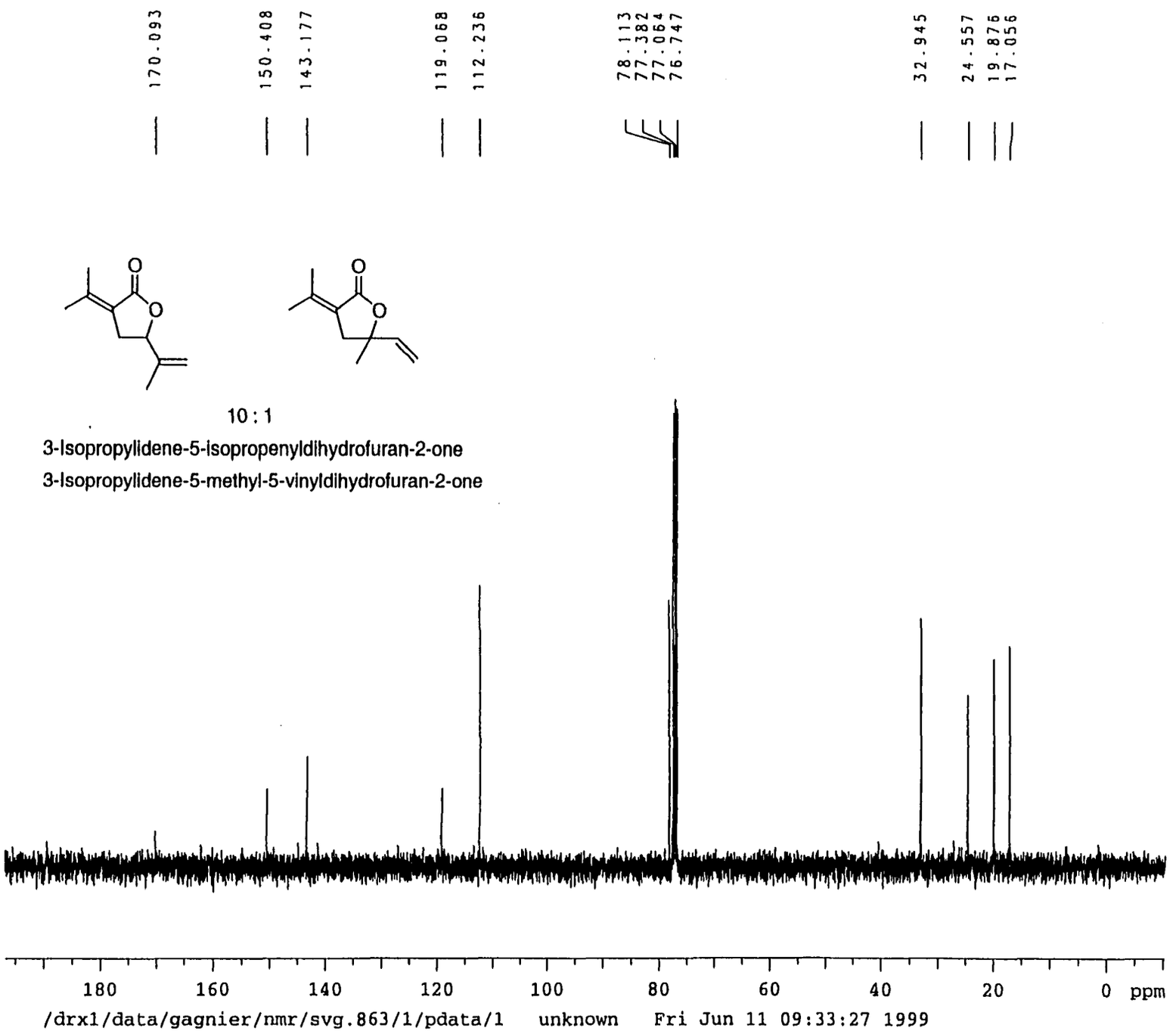
170.093
150.408
143.177
119.068
112.236
78.113
77.382
77.064
76.747
32.945
24.557
19.876
17.056
O
O
O
O
10 : 1
3-Isopropylidene-5-isopropenyldihydrofuran-2-one
3-Isopropylidene-5-methyl-5-vinyldihydrofuran-2-one
180
160
140
120
100
80
60
40
20
0 ppm
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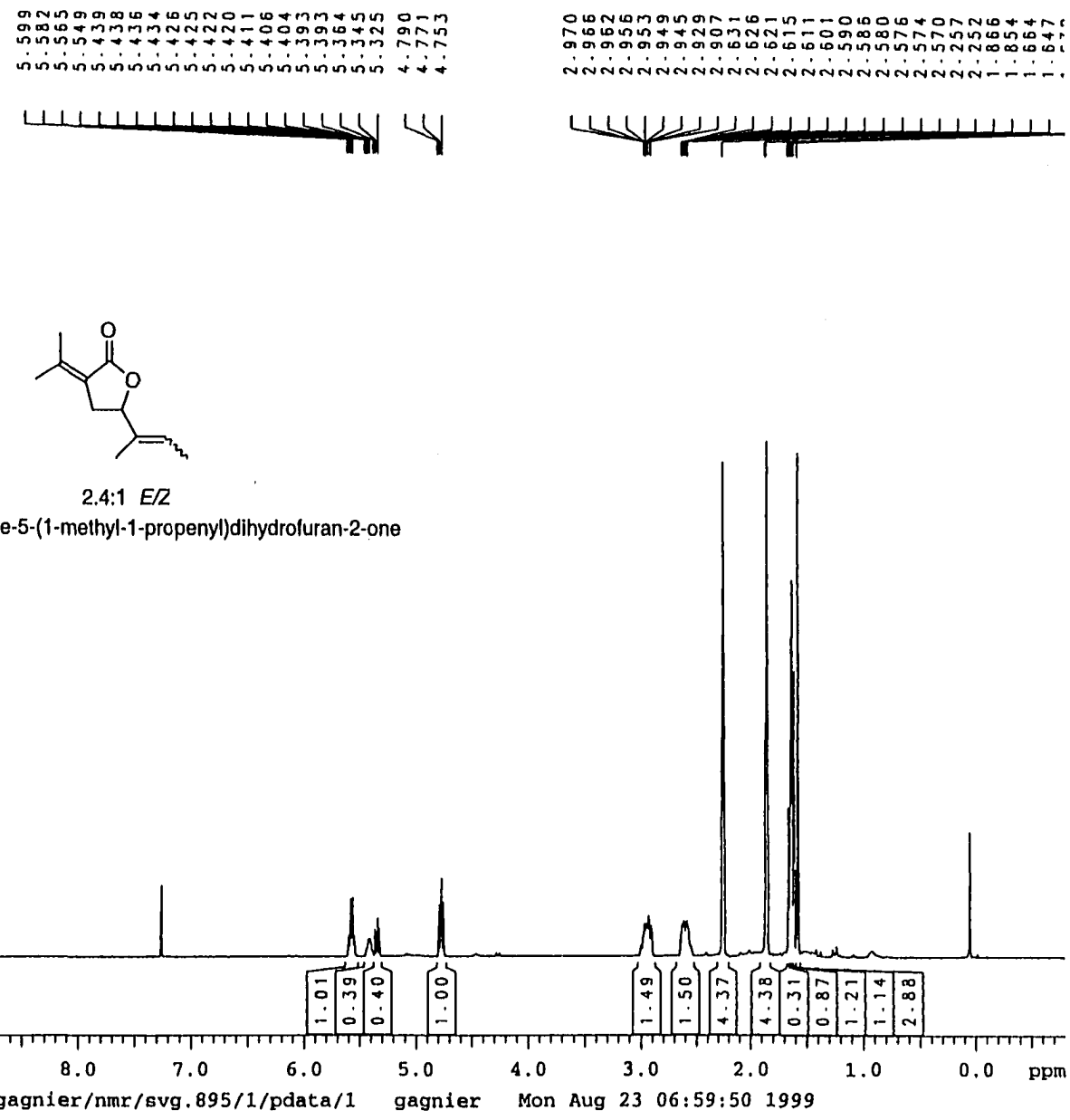
5.599
5.582
5.565
5.549
5.439
5.438
5.436
5.434
5.426
5.425
5.422
5.420
5.411
5.406
5.404
5.393
5.393
5.364
5.345
5.325
4.790
4.771
4.753
2.970
2.966
2.962
2.956
2.953
2.949
2.945
2.929
2.907
2.631
2.626
2.621
2.615
2.611
2.601
2.590
2.586
2.580
2.576
2.574
2.570
2.257
2.252
1.866
1.854
1.664
1.647
O
O
2.4:1 E/Z
3-Isopropylidene-5-(1-methyl-1-propenyl)dihydrofuran-2-one
1.01
0.39
0.40
1.00
1.49
1.50
4.37
4.38
0.31
0.87
1.21
1.14
2.88
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm
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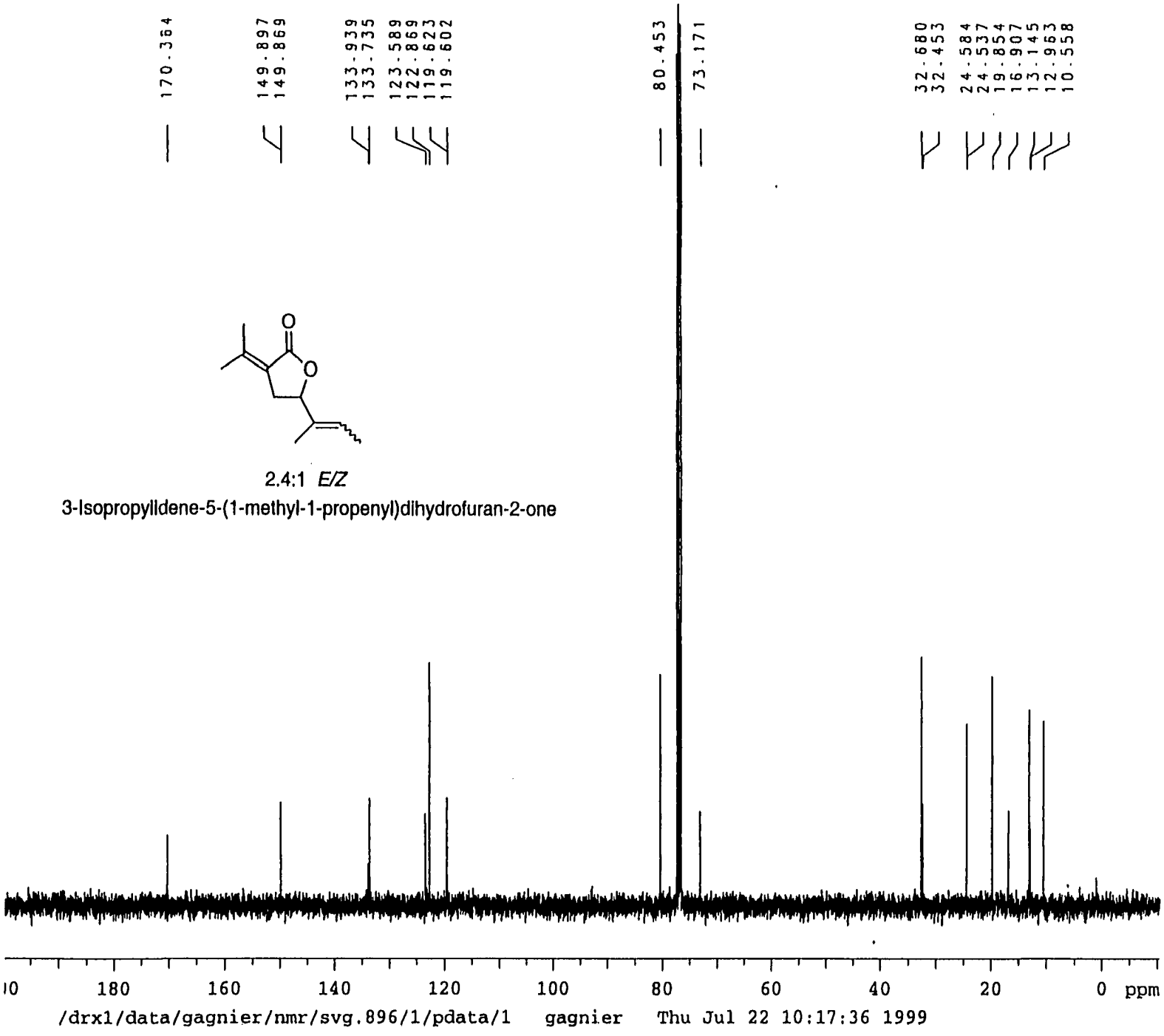
170.364
149.897
149.869
133.939
133.735
123.589
122.869
119.623
119.602
80.453
73.171
32.680
32.453
24.584
24.537
19.854
16.907
13.145
12.963
10.558
O
O
2.4:1 E/Z
3-Isopropylidene-5-(1-methyl-1-propenyl)dihydrofuran-2-one
180
160
140
120
100
80
60
40
20
0 ppm
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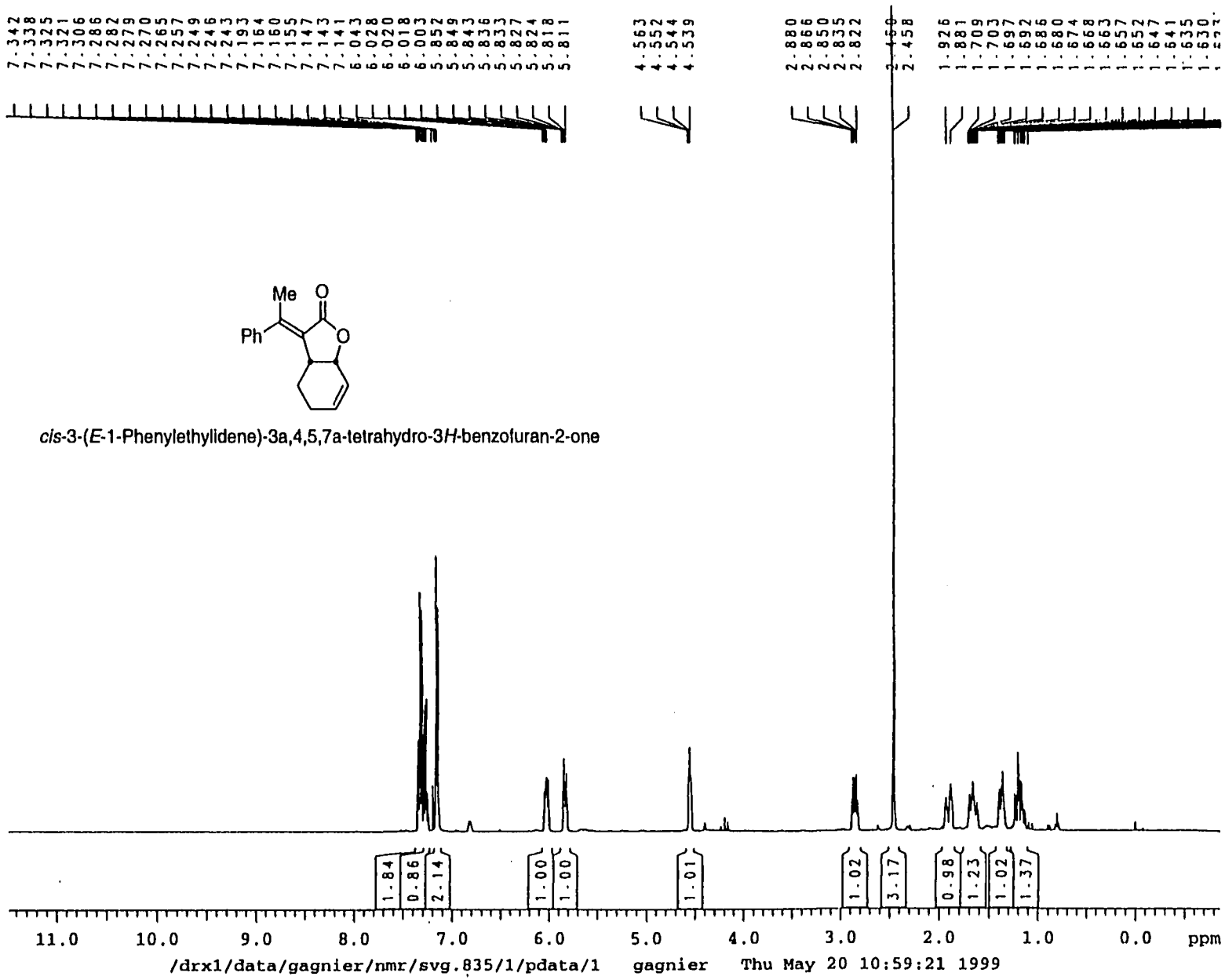
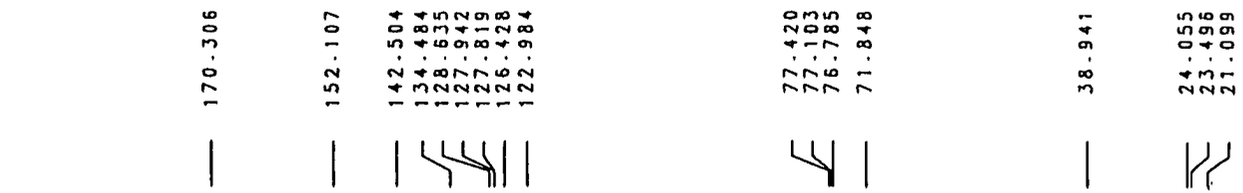
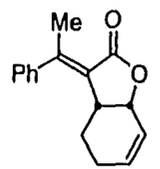
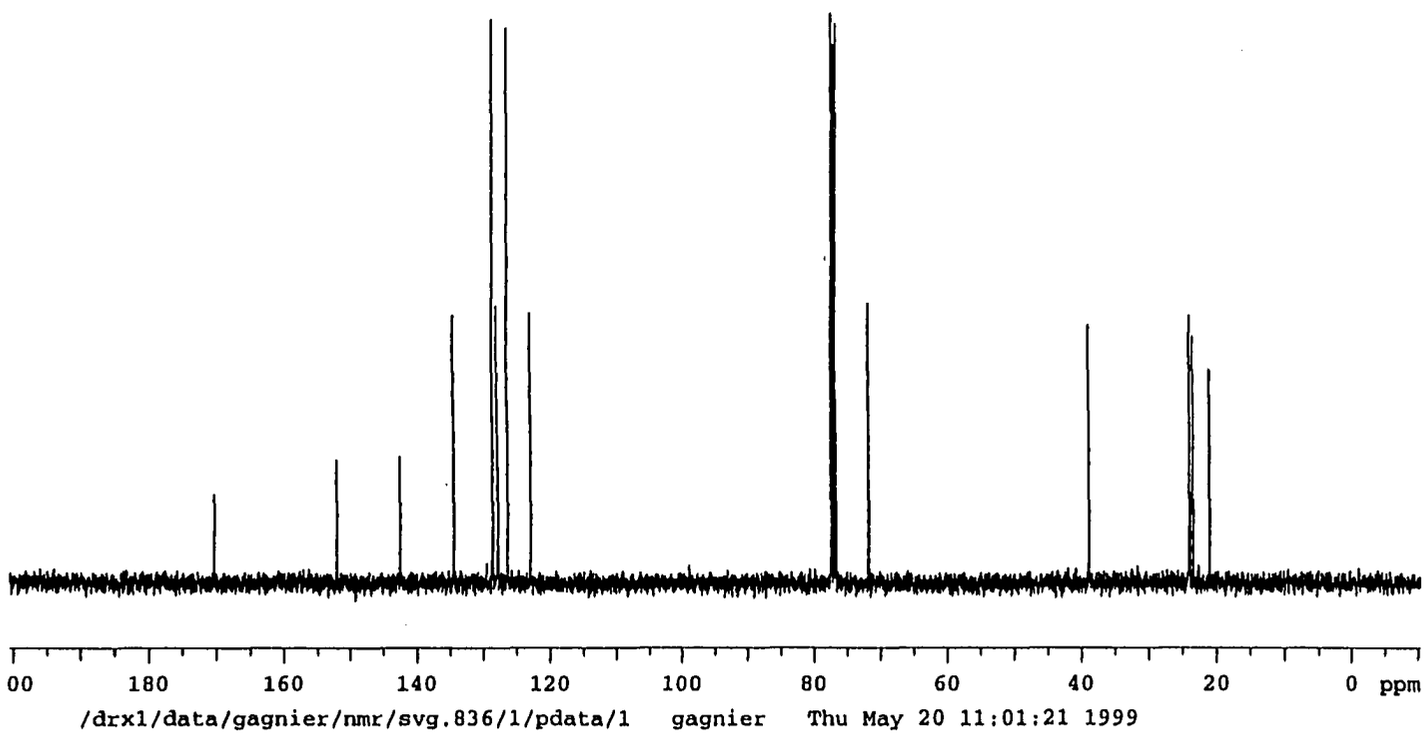


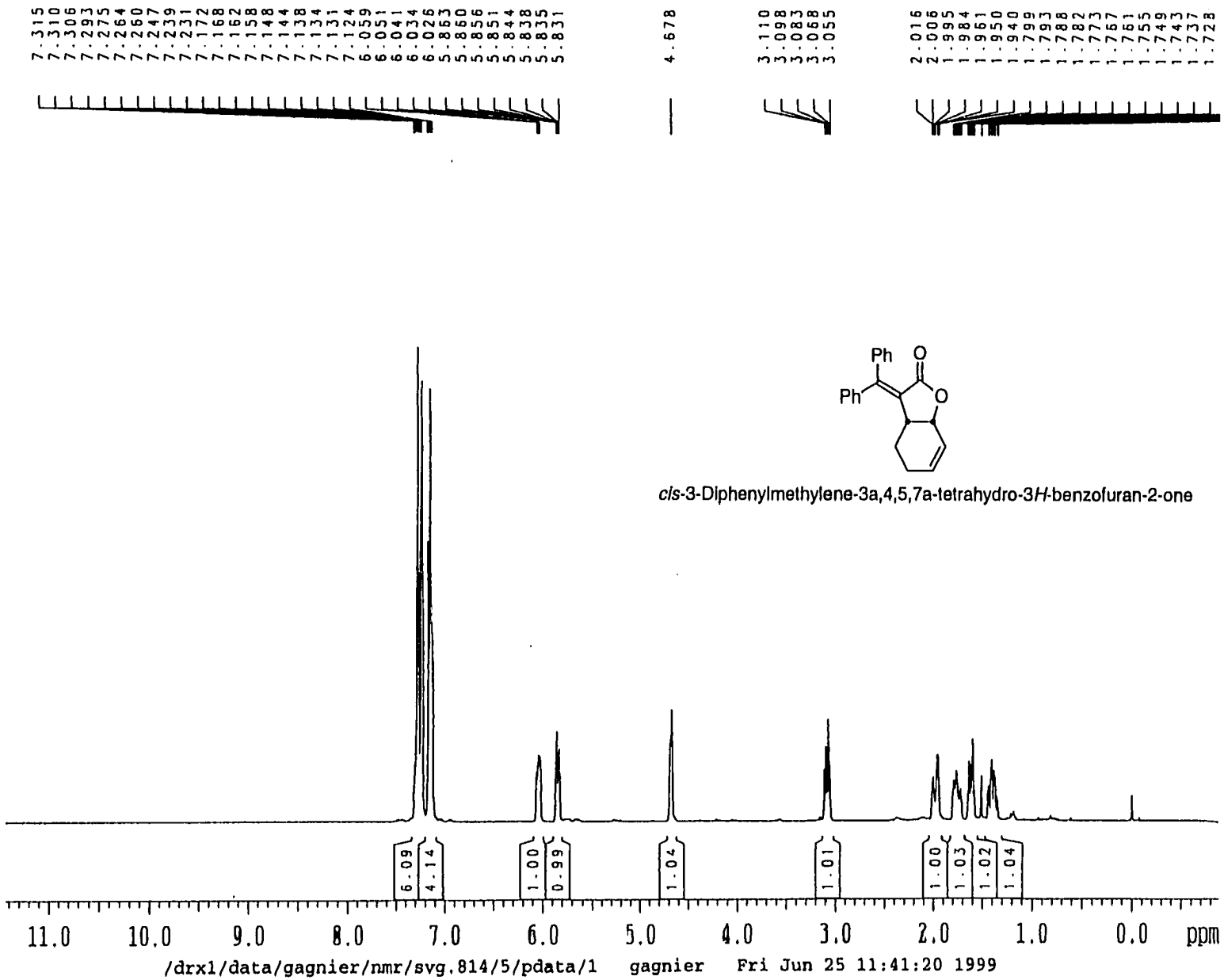

*cis*-3-(*E*-1-Phenylethylidene)-3a,4,5,7a-tetrahydro-3*H*-benzofuran-2-one



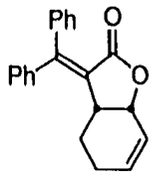




*cis*-3-(*E*-1-Phenylethylidene)-3a,4,5,7a-tetrahydro-3*H*-benzofuran-2-one

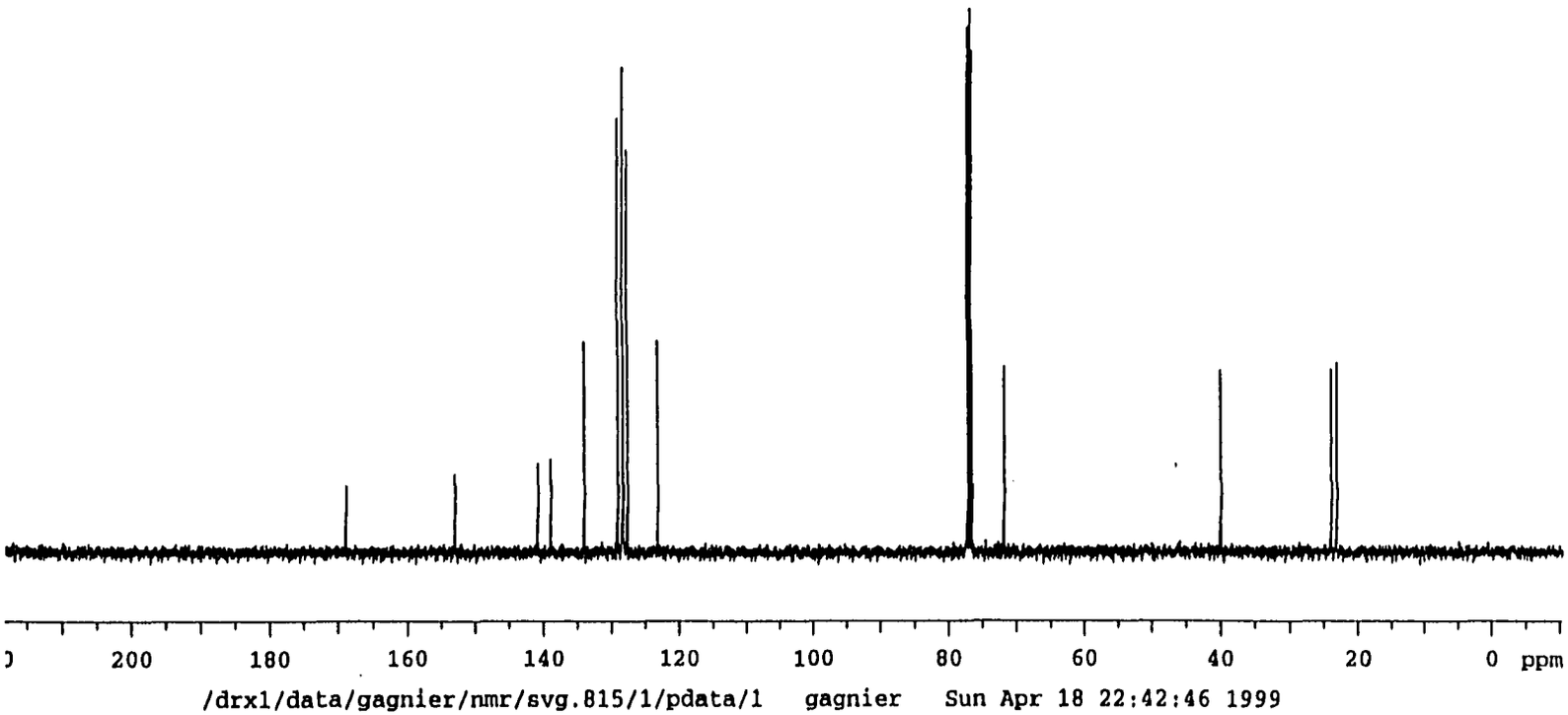


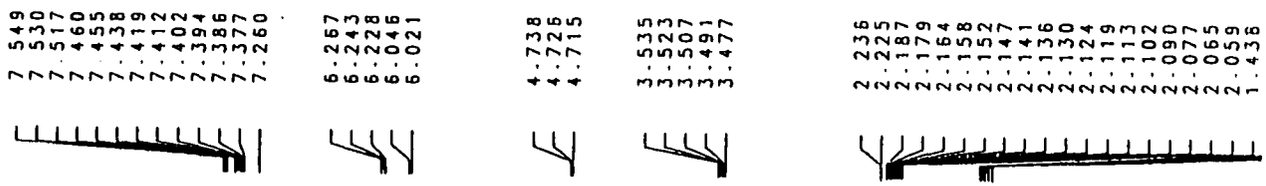


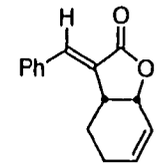

*cis*-3-Diphenylmethylene-3a,4,5,7a-tetrahydro-3*H*-benzofuran-2-one

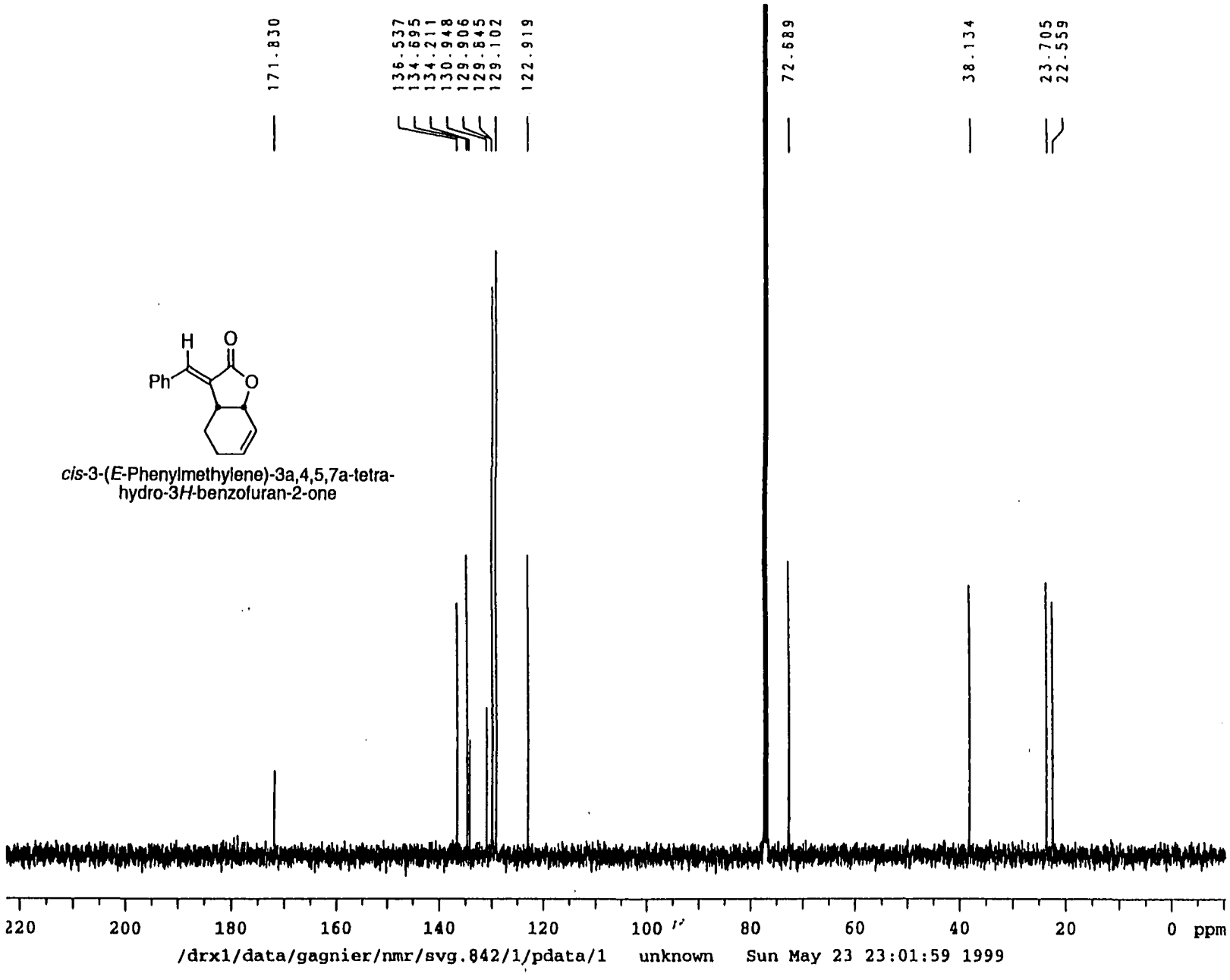

*cis*-3-Diphenylmethylene-3a,4,5,7a-tetrahydro-3*H*-benzofuran-2-one



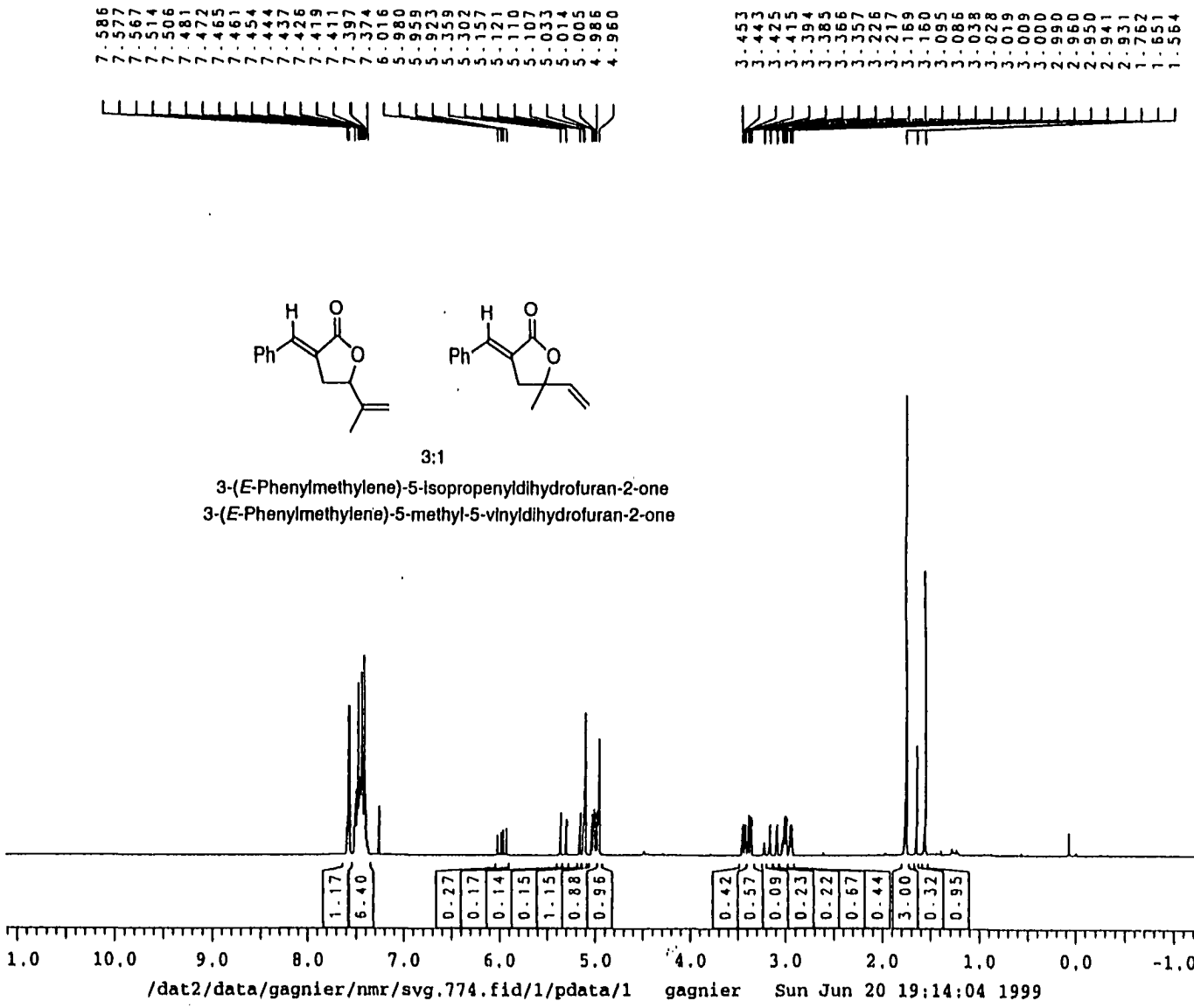



*cis*-3-(*E*-Phenylmethylene)-3a,4,5,7a-tetrahydro-3*H*-benzofuran-2-one




*cis*-3-(*E*-Phenylmethylene)-3a,4,5,7a-tetra-hydro-3*H*-benzofuran-2-one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7.577
7.567
7.514
7.506
7.481
7.472
7.465
7.461
7.454
7.444
7.437
7.426
7.419
7.411
7.397
7.374
6.016
5.980
5.959
5.923
5.359
5.302
5.157
5.121
5.110
5.107
5.033
5.014
5.005
4.986
4.960
3.453
3.443
3.425
3.415
3.394
3.385
3.366
3.357
3.226
3.217
3.169
3.160
3.095
3.086
3.038
3.028
3.019
3.009
3.000
2.990
2.960
2.950
2.941
2.931
1.762
1.651
1.564
H
O
Ph
O
H
O
Ph
O
3:1
3-(E-Phenylmethylene)-5-Isopropenyldihydrofuran-2-one
3-(E-Phenylmethylene)-5-methyl-5-vinyldihydrofuran-2-one
1.17
6.40
0.27
0.17
0.14
0.15
1.15
0.88
0.96
0.42
0.57
0.09
0.23
0.22
0.67
0.44
3.00
0.32
0.95
1.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0 ppm
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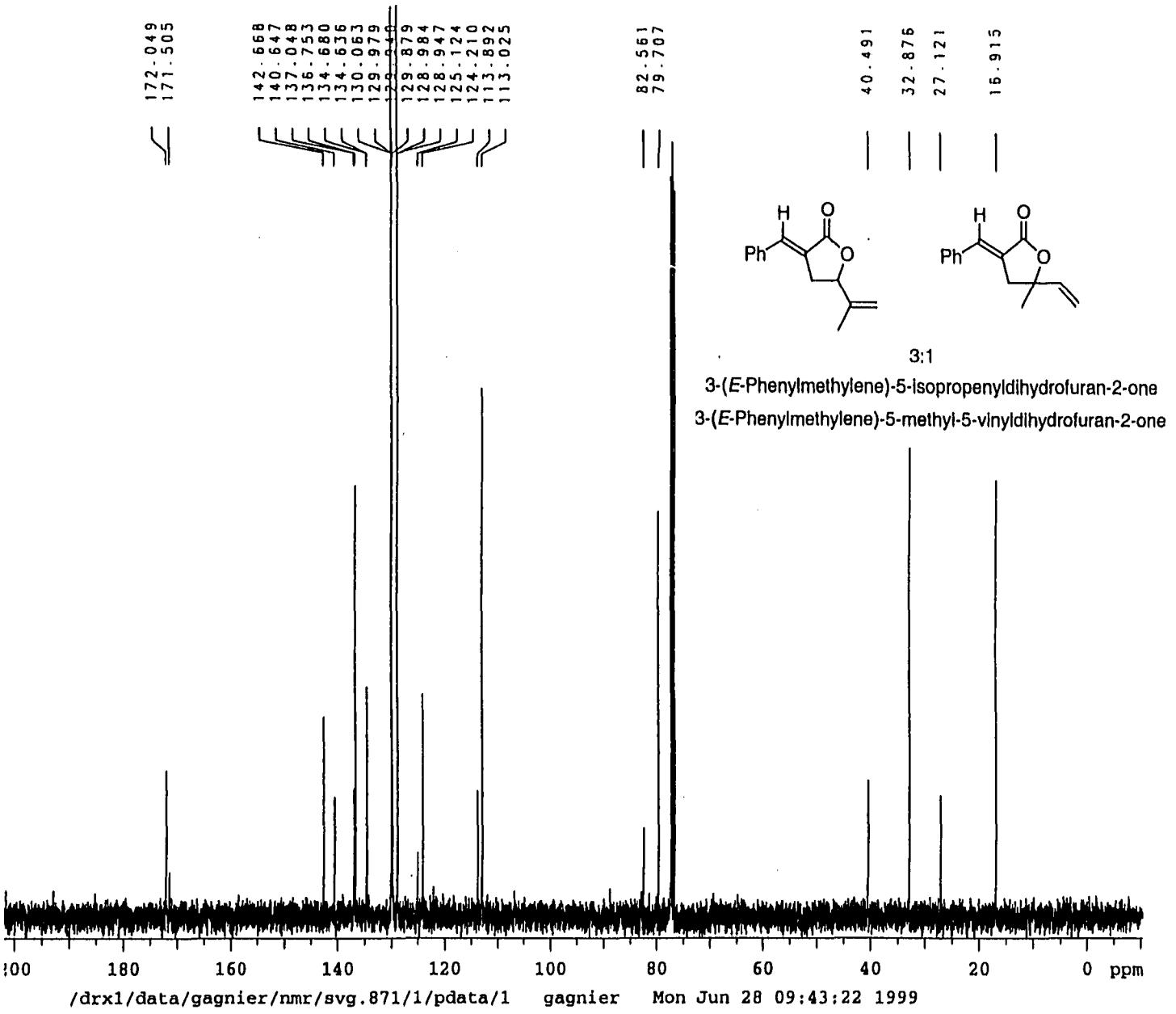
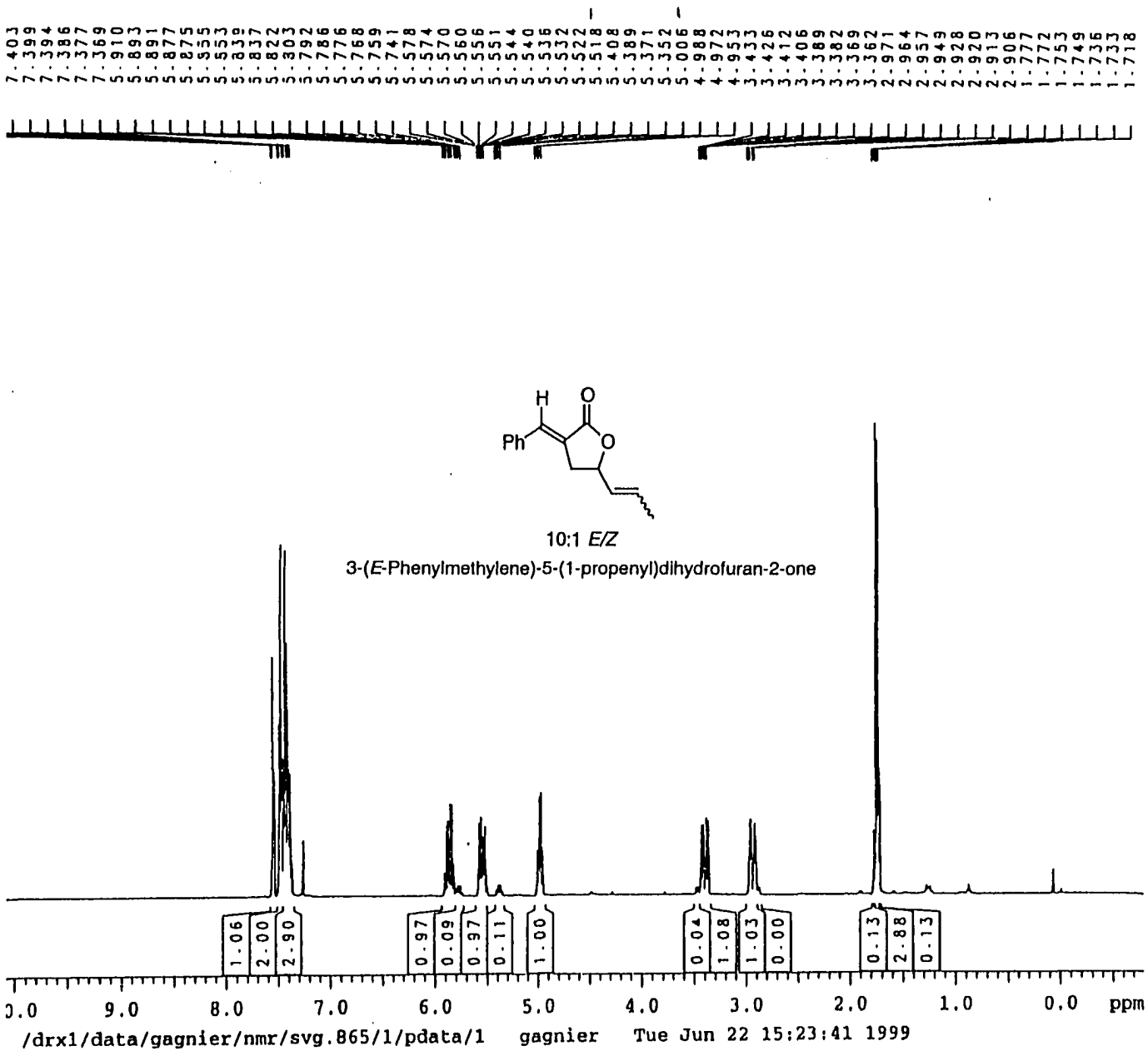

172.049
171.505
142.668
140.647
137.048
136.753
134.680
134.636
130.063
129.979
129.879
128.984
128.947
125.124
124.210
113.892
113.025
82.561
79.707
40.491
32.876
27.121
16.915
H
O
Ph
O
H
O
Ph
O
3:1
3-(E-Phenylmethylene)-5-isopropenyldihydrofuran-2-one
3-(E-Phenylmethylene)-5-methyl-5-vinyldihydrofuran-2-one
200
180
160
140
120
100
80
60
40
20
0 ppm
/drx1/data/gagnier/nmr/svg.871/1/pdata/1 gagnier Mon Jun 28 09:43:22 1999


7.403
7.399
7.394
7.386
7.377
7.369
5.910
5.893
5.891
5.877
5.875
5.555
5.553
5.839
5.837
5.822
5.303
5.792
5.786
5.776
5.768
5.759
5.741
5.578
5.574
5.570
5.560
5.556
5.551
5.544
5.540
5.536
5.532
5.522
5.518
5.408
5.389
5.371
5.352
5.006
4.988
4.972
4.953
3.433
3.426
3.412
3.406
3.389
3.382
3.369
3.362
2.971
2.964
2.957
2.949
2.928
2.920
2.913
2.906
1.777
1.772
1.753
1.749
1.736
1.733
1.718
H
O
Ph
O
10:1 E/Z
3-(E-Phenylmethylene)-5-(1-propenyl)dihydrofuran-2-one
1.06
2.00
2.90
0.97
0.09
0.97
0.11
1.00
0.04
1.08
1.03
0.00
0.13
2.88
0.13
0.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm
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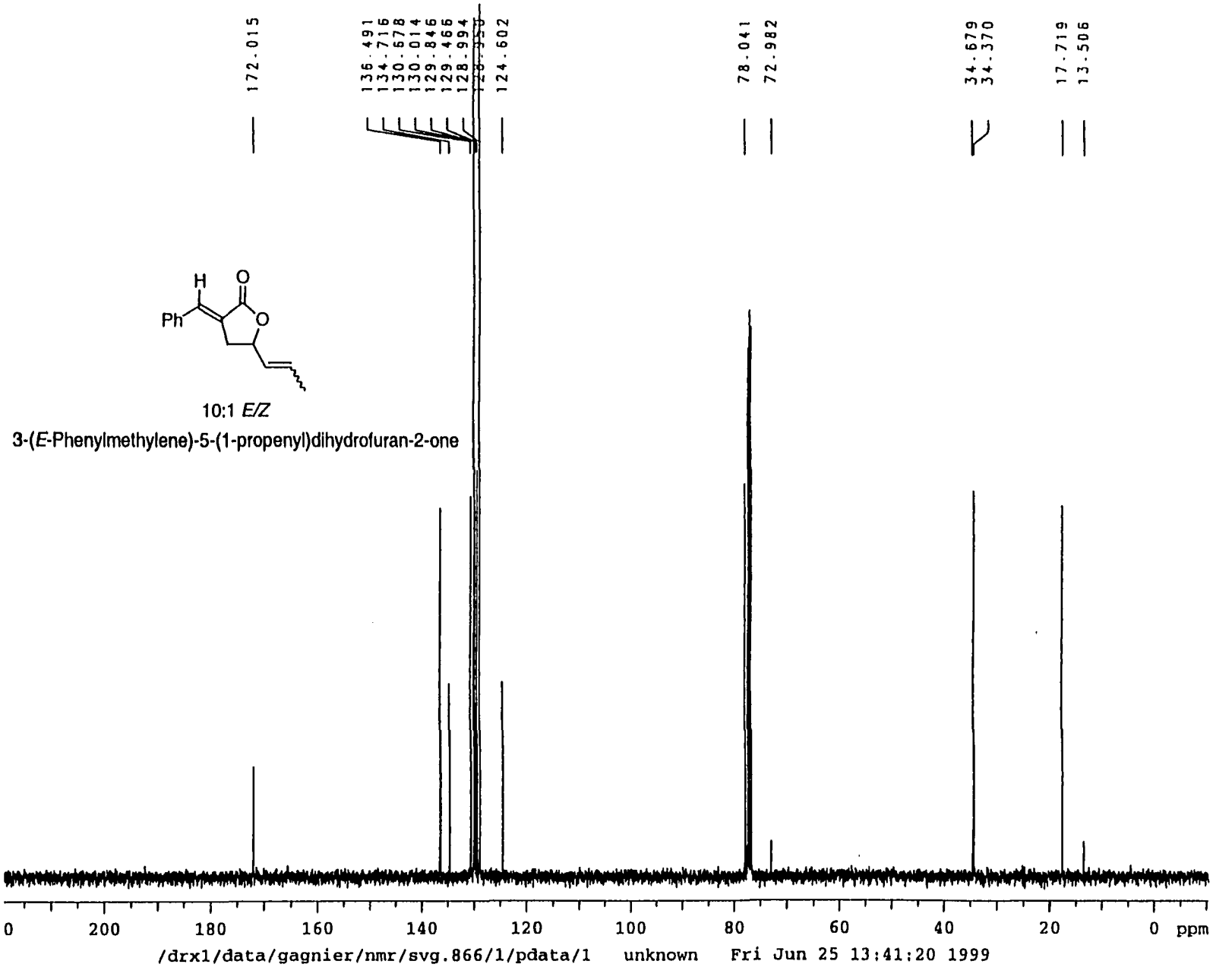
172.015
136.491
134.716
130.678
130.014
129.846
129.466
128.994
124.602
78.041
72.982
34.679
34.370
17.719
13.506
H
O
Ph
O
10:1 E/Z
3-(E-Phenylmethylene)-5-(1-propenyl)dihydrofuran-2-one
0
200
180
160
140
120
100
80
60
40
20
0 ppm
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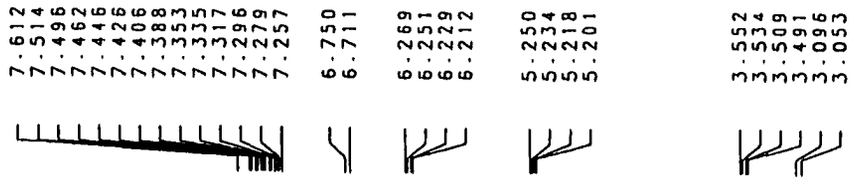
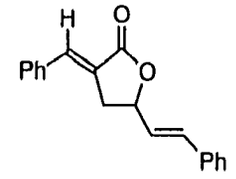
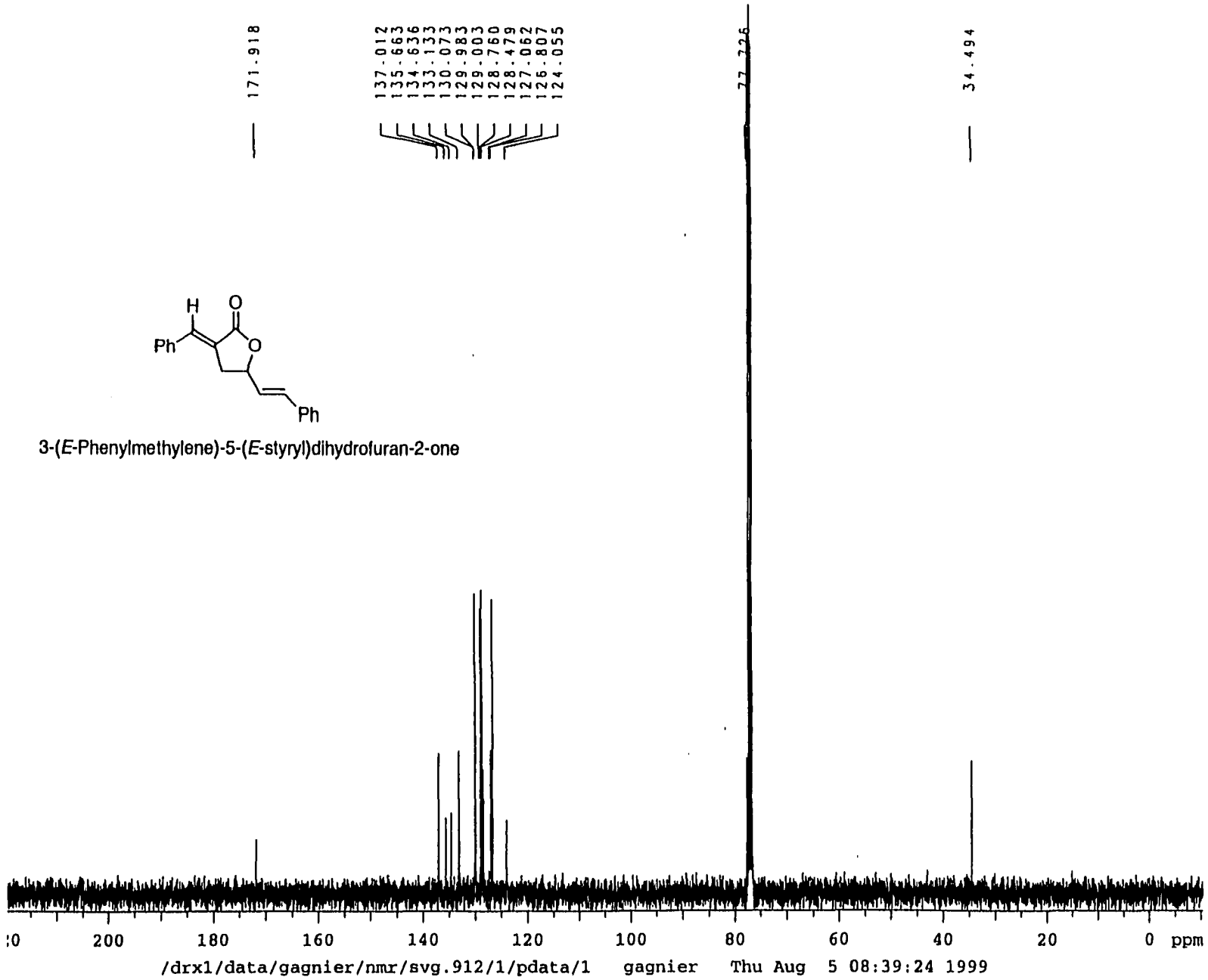
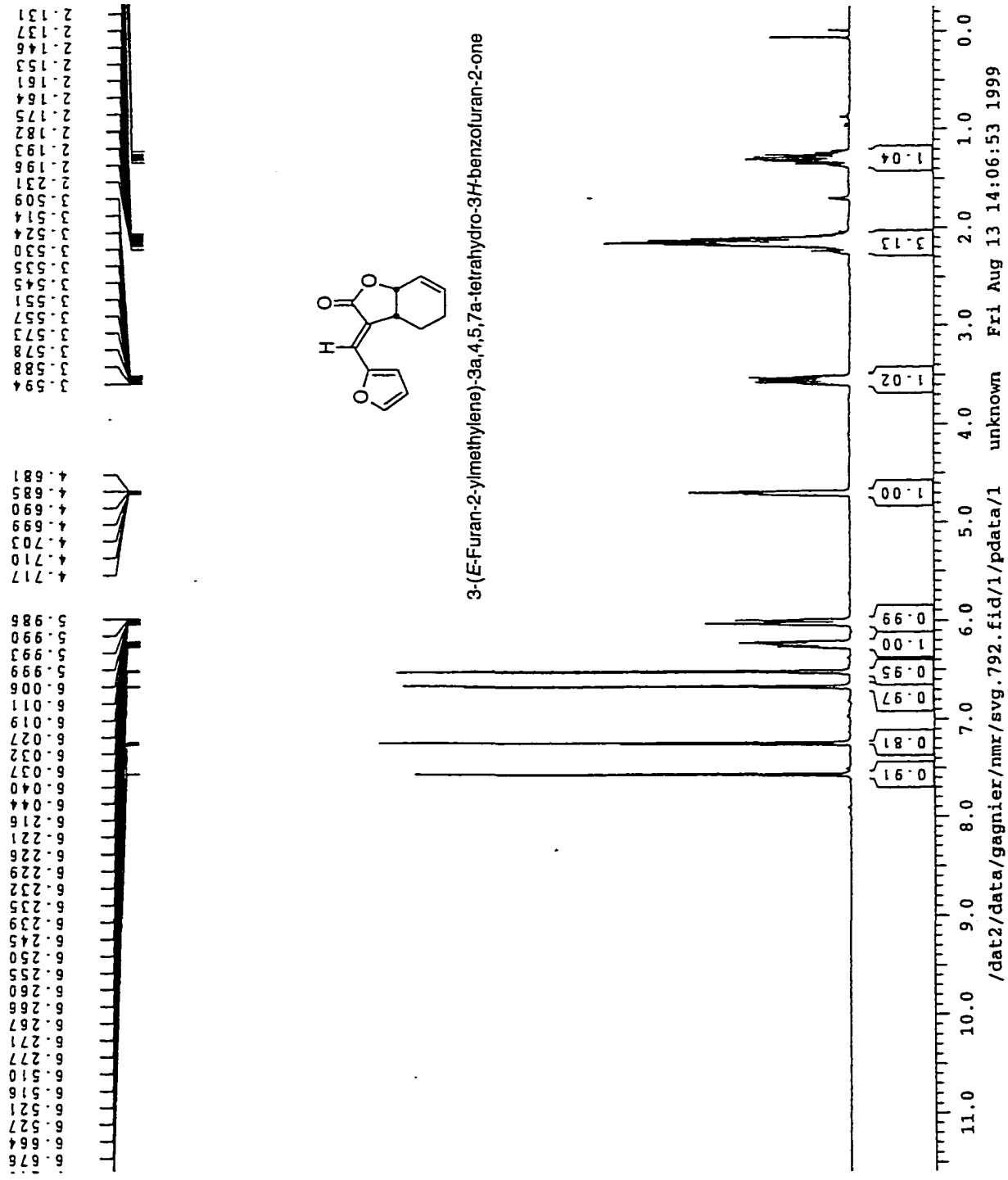



3-(*E*-Phenylmethylene)-5-(*E*-styryl)dihydrofuran-2-one




3-(*E*-Phenylmethylene)-5-(*E*-styryl)dihydrofuran-2-one


3-(E-Furan-2-ylmethylene)-3a,4,5,7a-tetrahydro-3H-benzofuran-2-one
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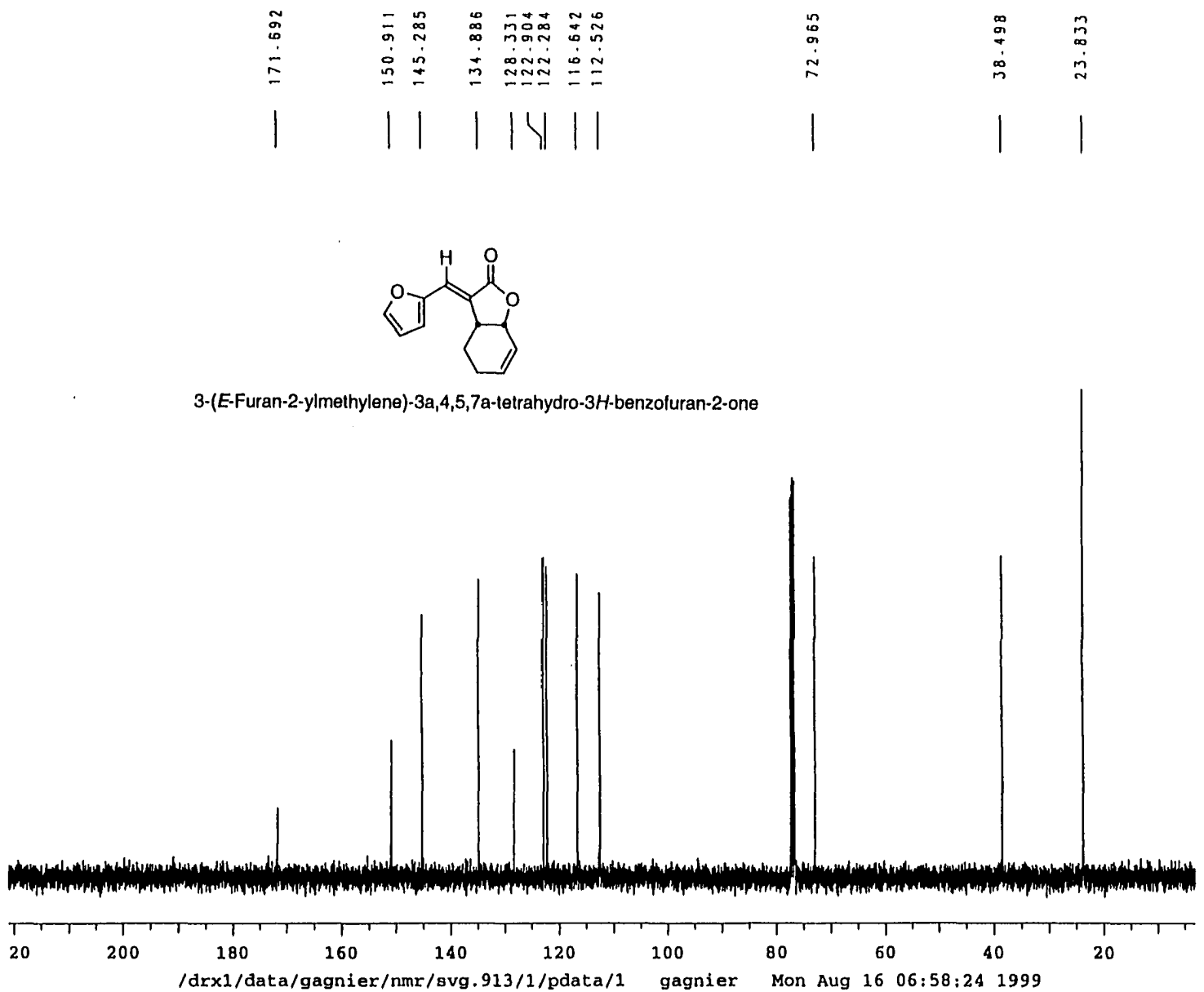
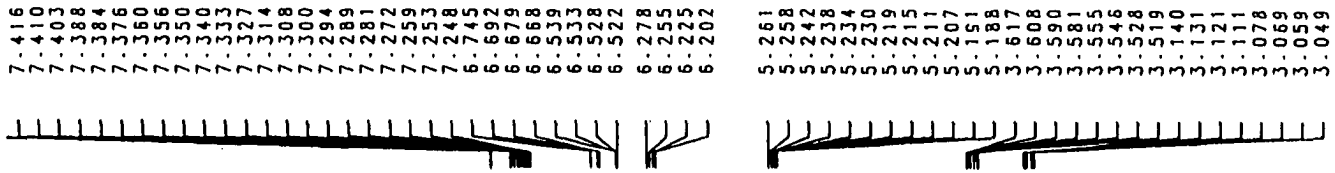
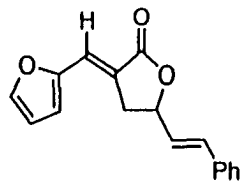
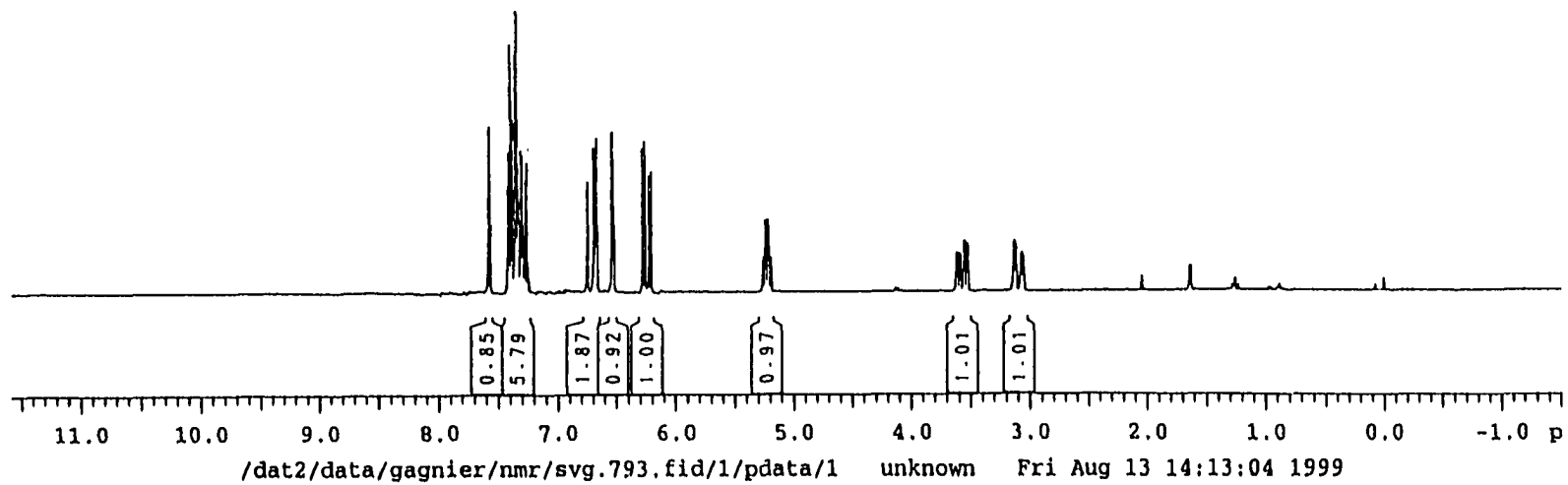
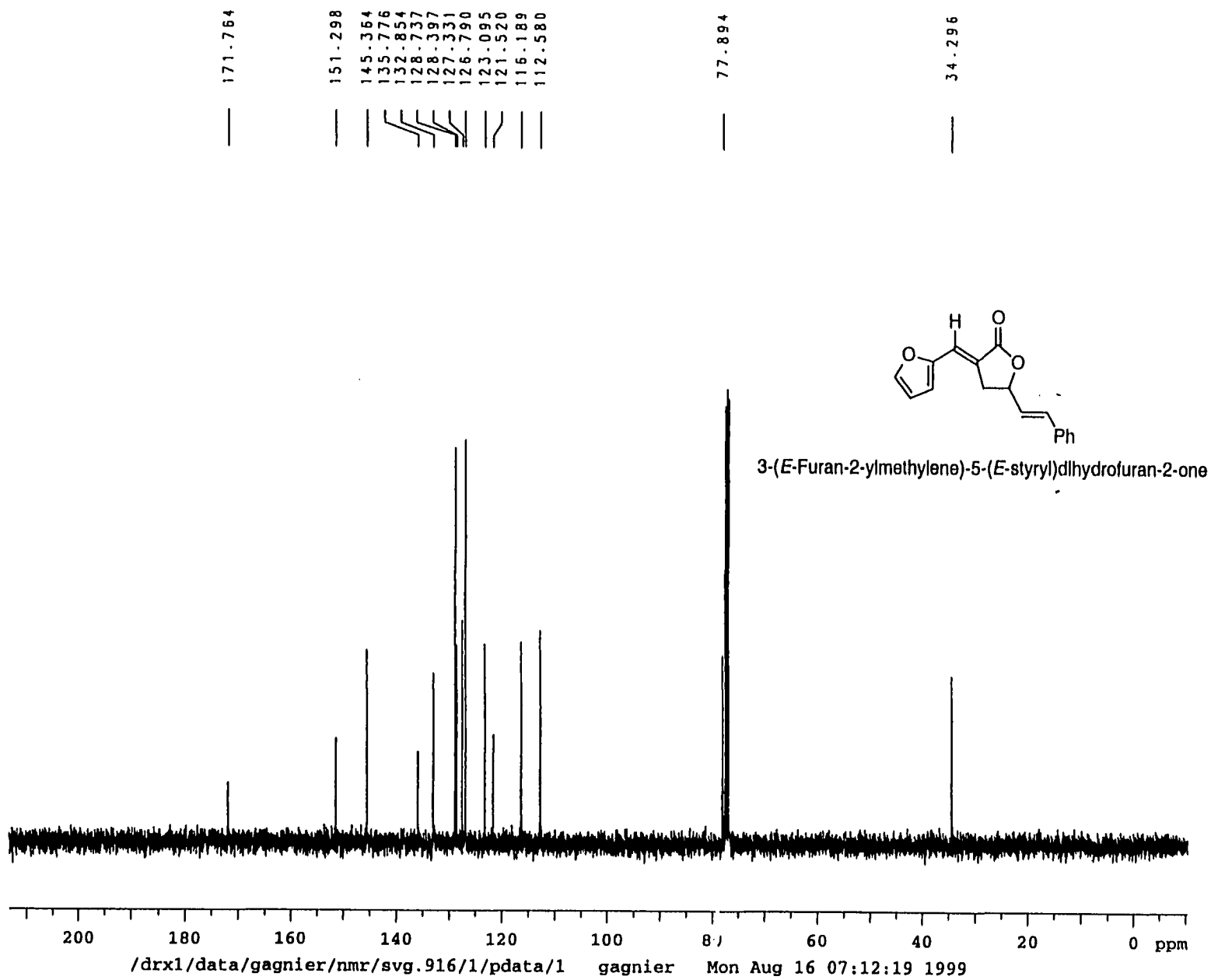

171.692
150.911
145.285
134.886
128.331
122.904
122.284
116.642
112.526
72.965
38.498
23.833
H
O
O
O
3-(E-Furan-2-ylmethylene)-3a,4,5,7a-tetrahydro-3H-benzofuran-2-one
20
200
180
160
140
120
100
80
60
40
20
/drx1/data/gagnier/nmr/svg.913/1/pdata/1 gagnier Mon Aug 16 06:58:24 1999



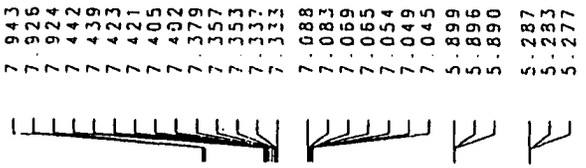



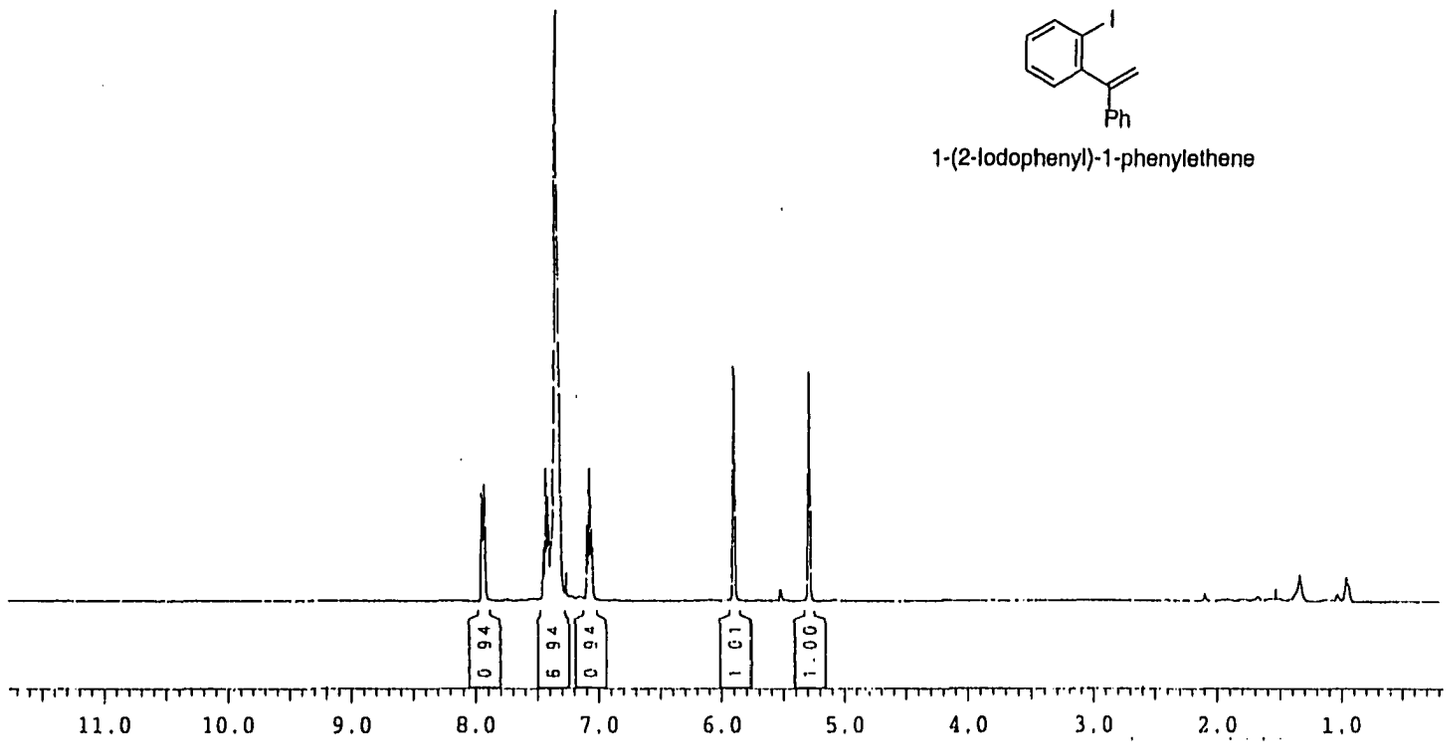

3-(*E*-Furan-2-ylmethylene)-5-(*E*-styryl)dihydrofuran-2-one




171.764
151.298
145.364
135.776
132.854
128.737
128.397
127.331
126.790
123.095
121.520
116.189
112.580
77.894
34.296
H
O
O
O
Ph
3-(E-Furan-2-ylmethylene)-5-(E-styryl)dihydrofuran-2-one
200
180
160
140
120
100
80
60
40
20
0 ppm
/drx1/data/gagnier/nmr/svg.916/1/pdata/1 gagnier Mon Aug 16 07:12:19 1999

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

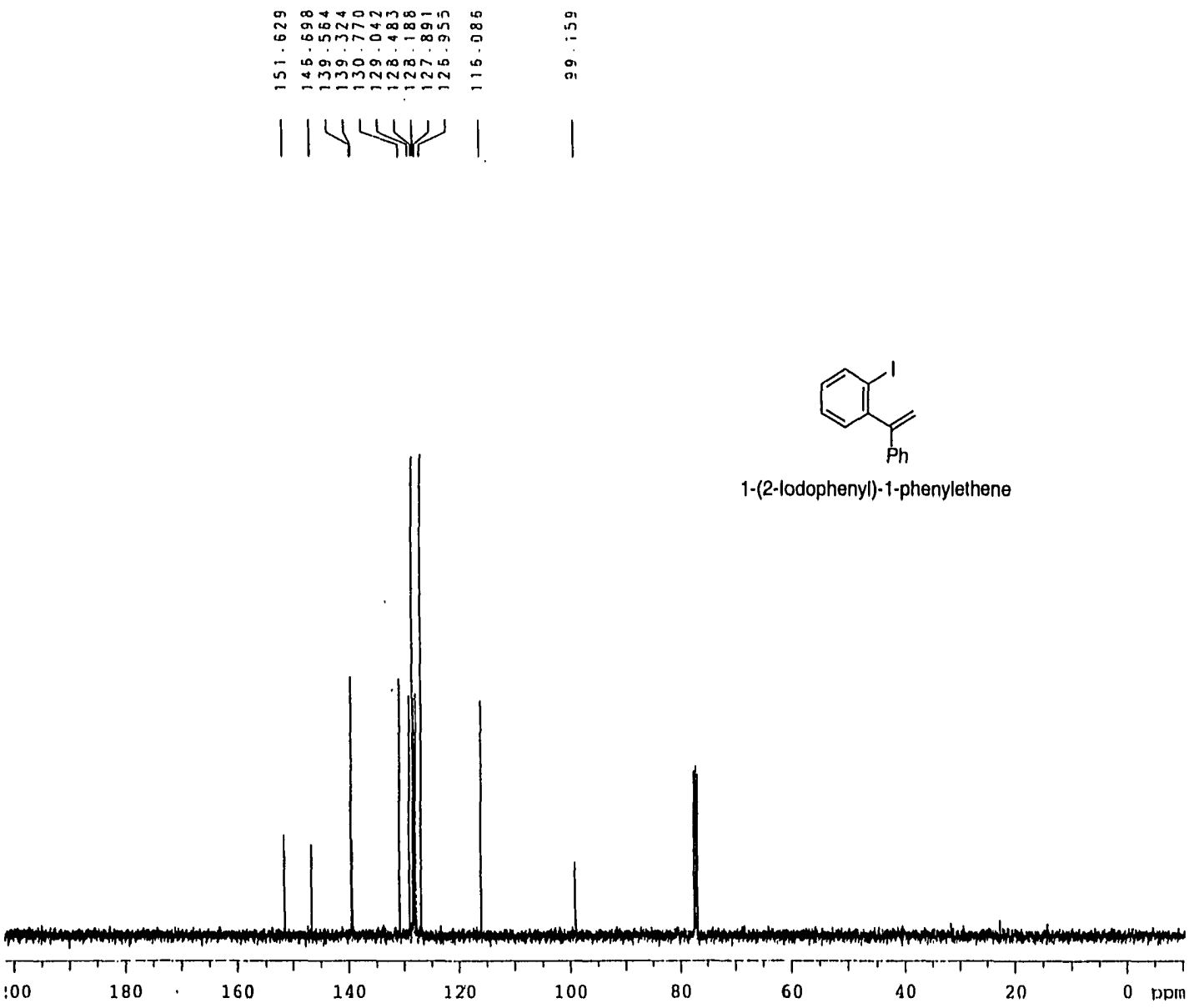


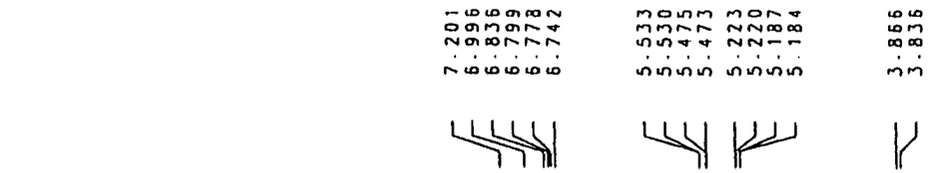



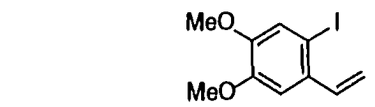




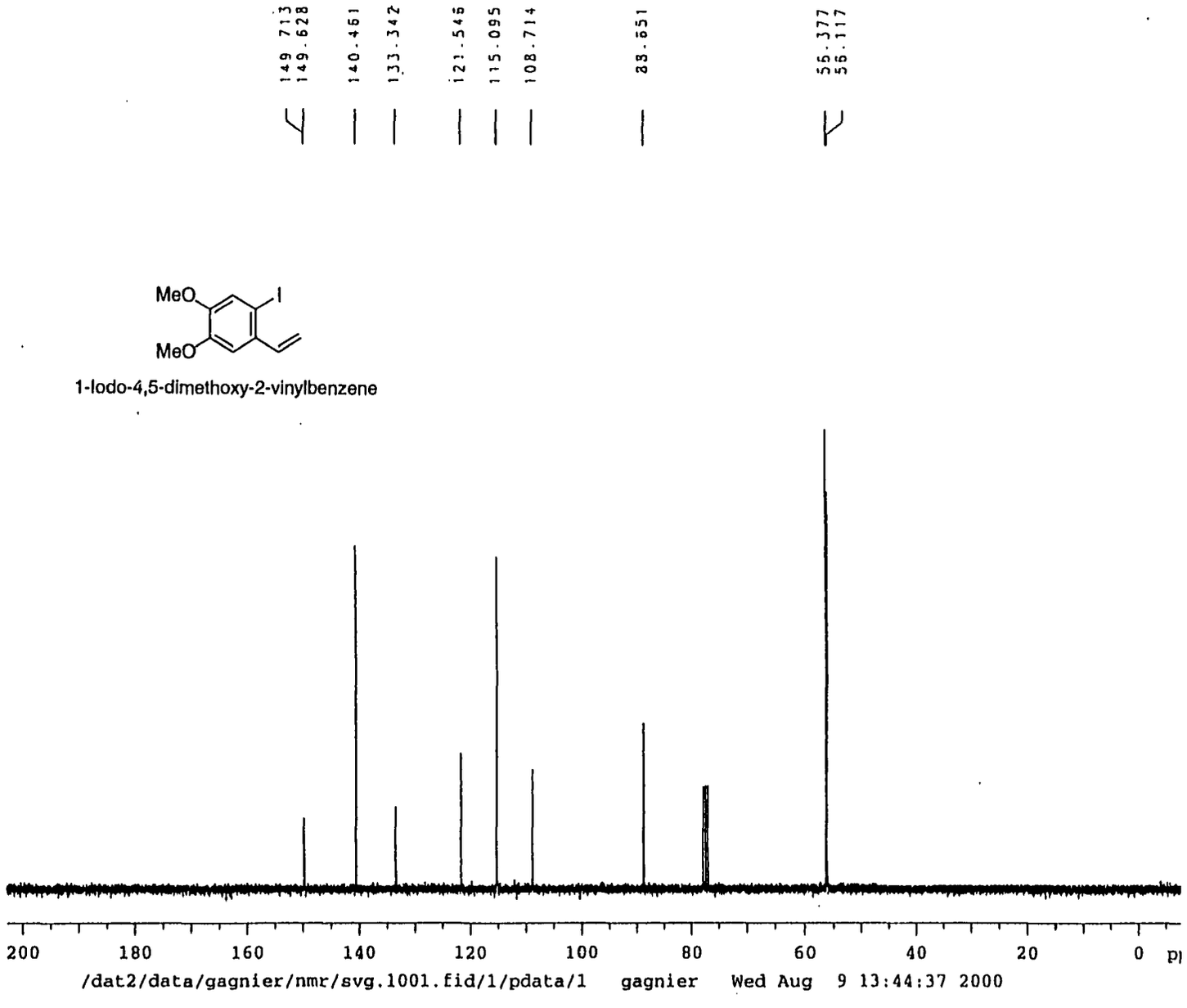
1-(2-Iodophenyl)-1-phenylethene

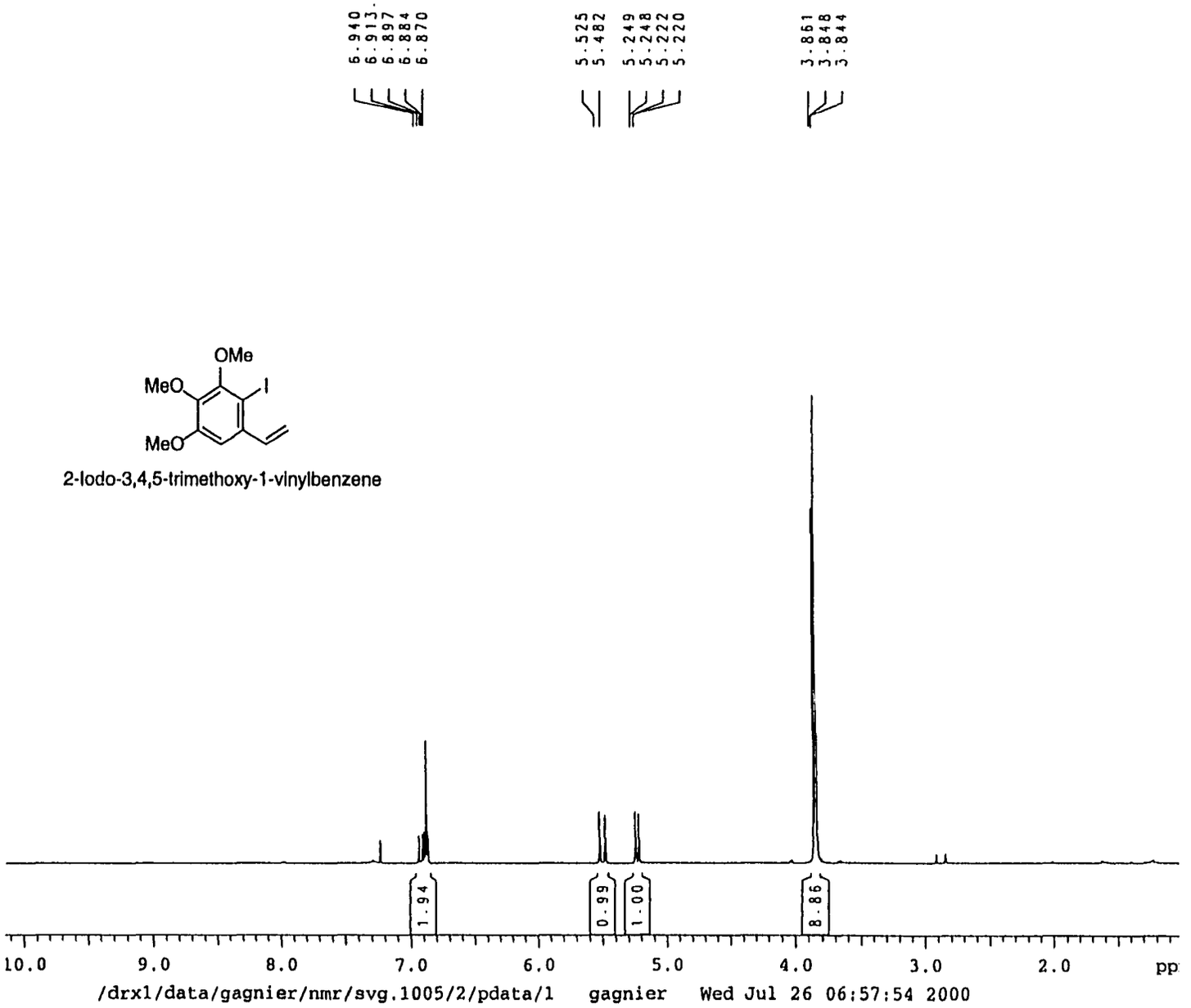

151.629
145.698
139.564
139.324
130.770
129.042
128.483
128.188
127.891
126.955
116.086
99.159
I
Ph
1-(2-Iodophenyl)-1-phenylethene
:00
180
160
140
120
100
80
60
40
20
0 ppm

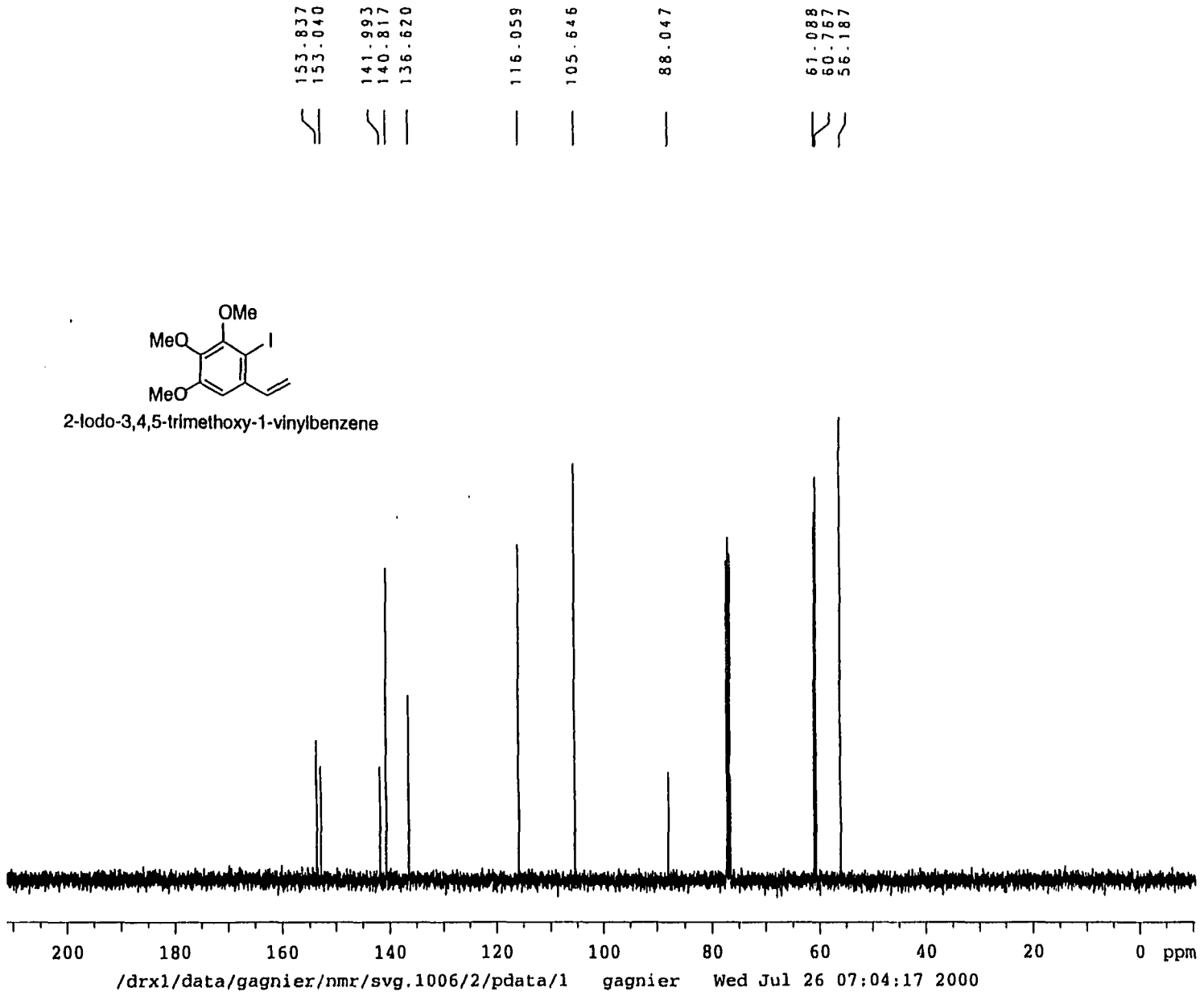


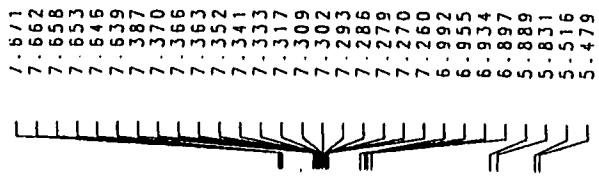



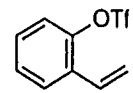

1-Iodo-4,5-dimethoxy-2-vinylbenzene


149.713
149.628
140.461
133.342
121.546
115.095
108.714
83.651
56.377
56.117
MeO
I
MeO
1-Iodo-4,5-dimethoxy-2-vinylbenzene
200
180
160
140
120
100
80
60
40
20
0
/dat2/data/gagnier/nmr/svg.1001.fid/1/pdata/1 gagnier Wed Aug 9 13:44:37 2000

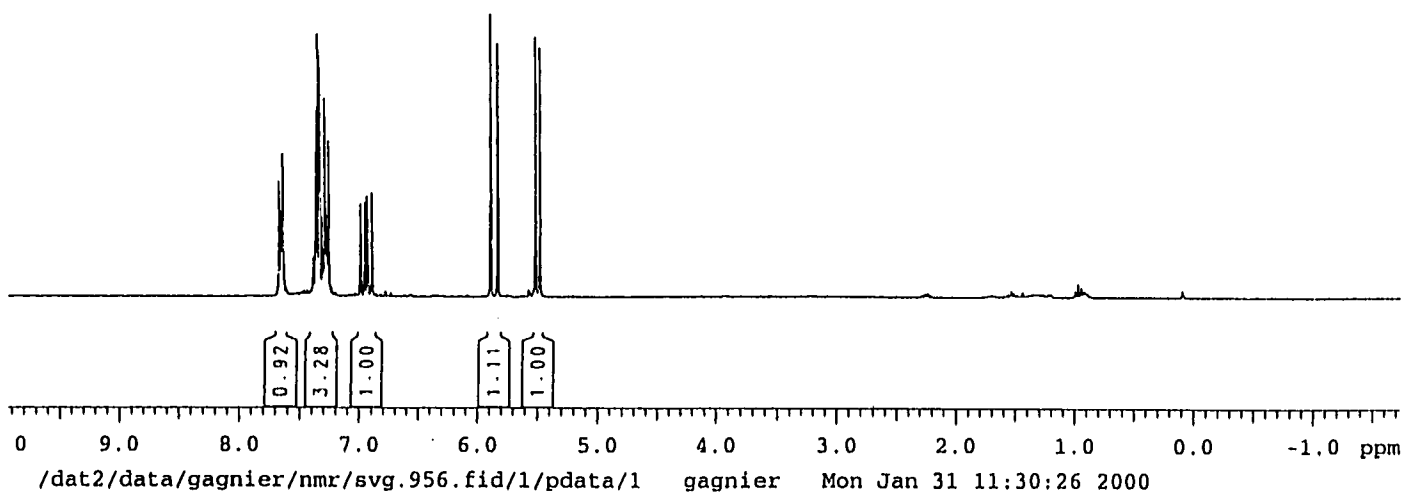

6.940
6.913
6.897
6.884
6.870
5.525
5.482
5.249
5.248
5.222
5.220
3.861
3.848
3.844
OMe
MeO
I
MeO
2-Iodo-3,4,5-trimethoxy-1-vinylbenzene
1.94
0.99
1.00
8.86
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
ppm
/drx1/data/gagnier/nmr/svg.1005/2/pdata/1 gagnier Wed Jul 26 06:57:54 2000


153.837
153.040
141.993
140.817
136.620
116.059
105.646
88.047
61.088
60.767
56.187
OMe
MeO
I
MeO
2-Iodo-3,4,5-trimethoxy-1-vinylbenzene
200
180
160
140
120
100
80
60
40
20
0 ppm
/drx1/data/gagnier/nmr/svg.1006/2/pdata/1 gagnier Wed Jul 26 07:04:17 2000

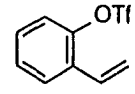


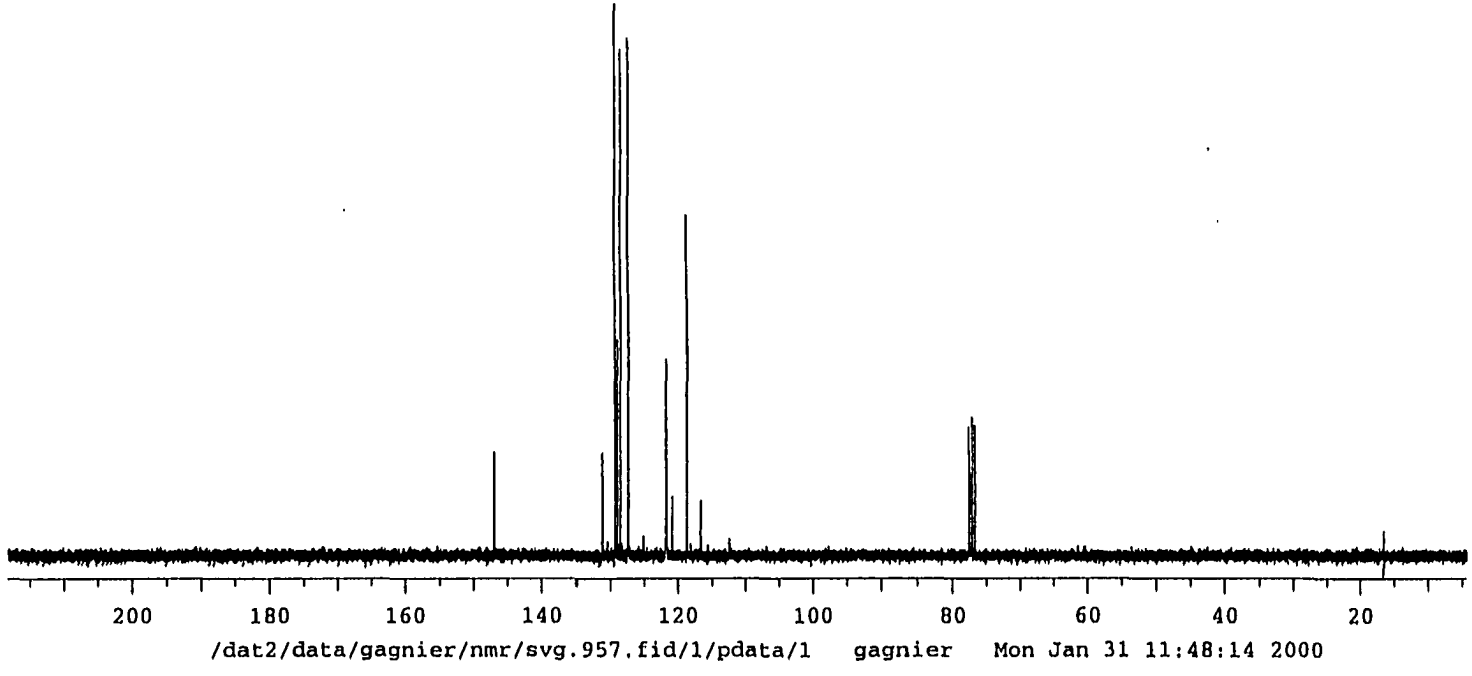

2-Vinylphenyl trifluoromethanesulfonate

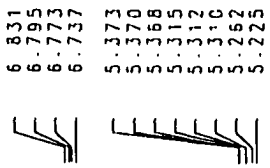


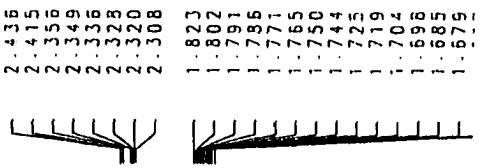
147.094
131.285
129.496
129.081
128.622
127.479
125.213
121.887
121.875
121.865
120.969
118.815
116.723
112.476

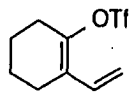



2-Vinylphenyl trifluoromethanesulfonate

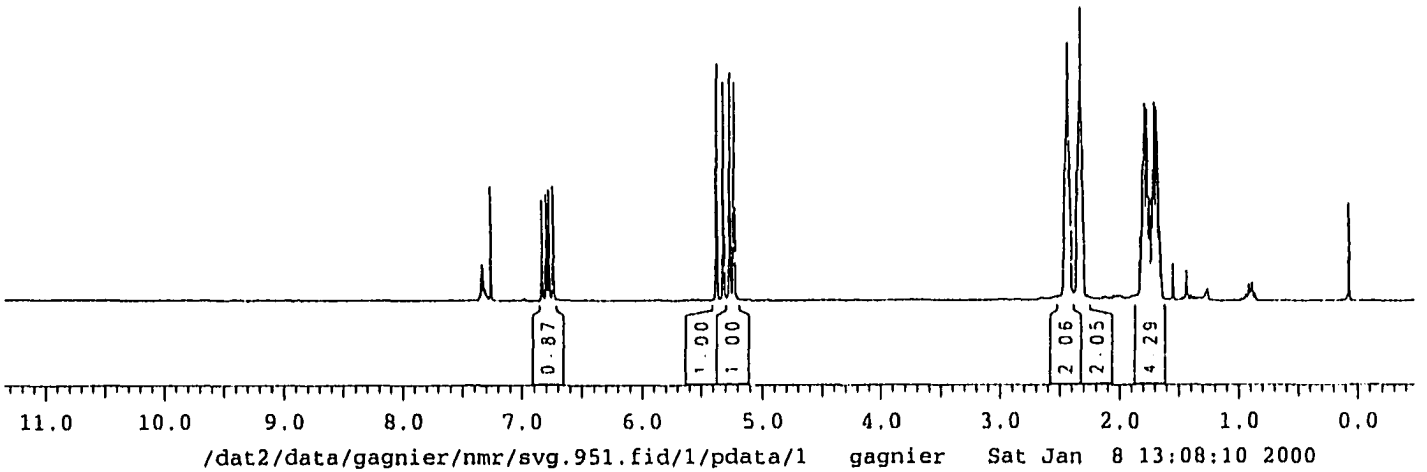


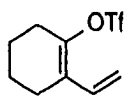


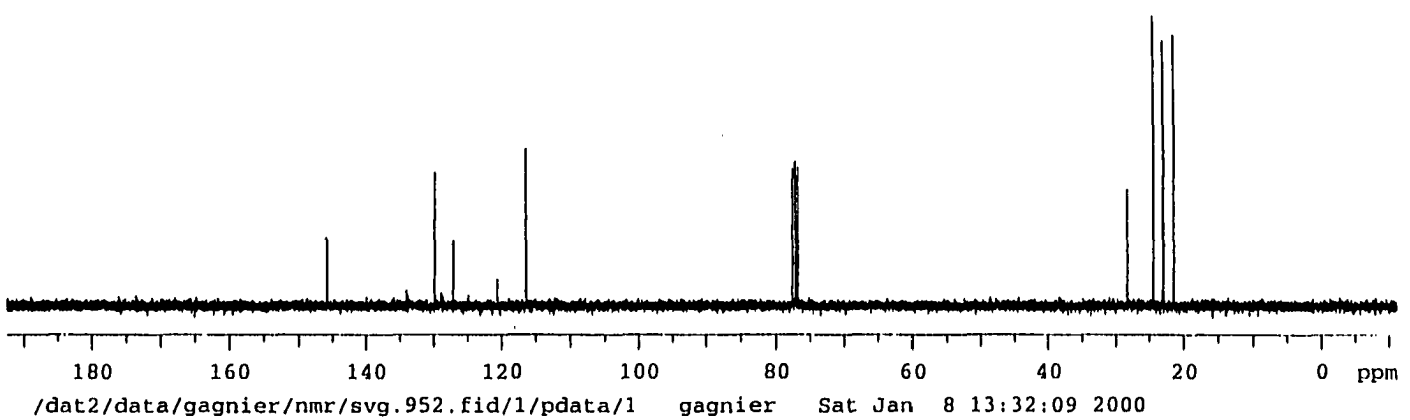



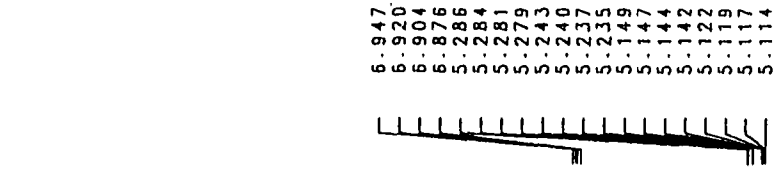

2-Vinylcyclohexenyl trifluoromethanesulfonate

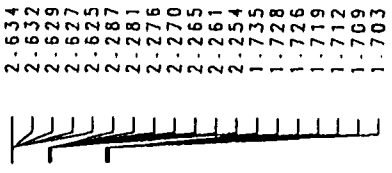


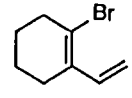




2-Vinylcyclohexenyl trifluoromethanesulfonate

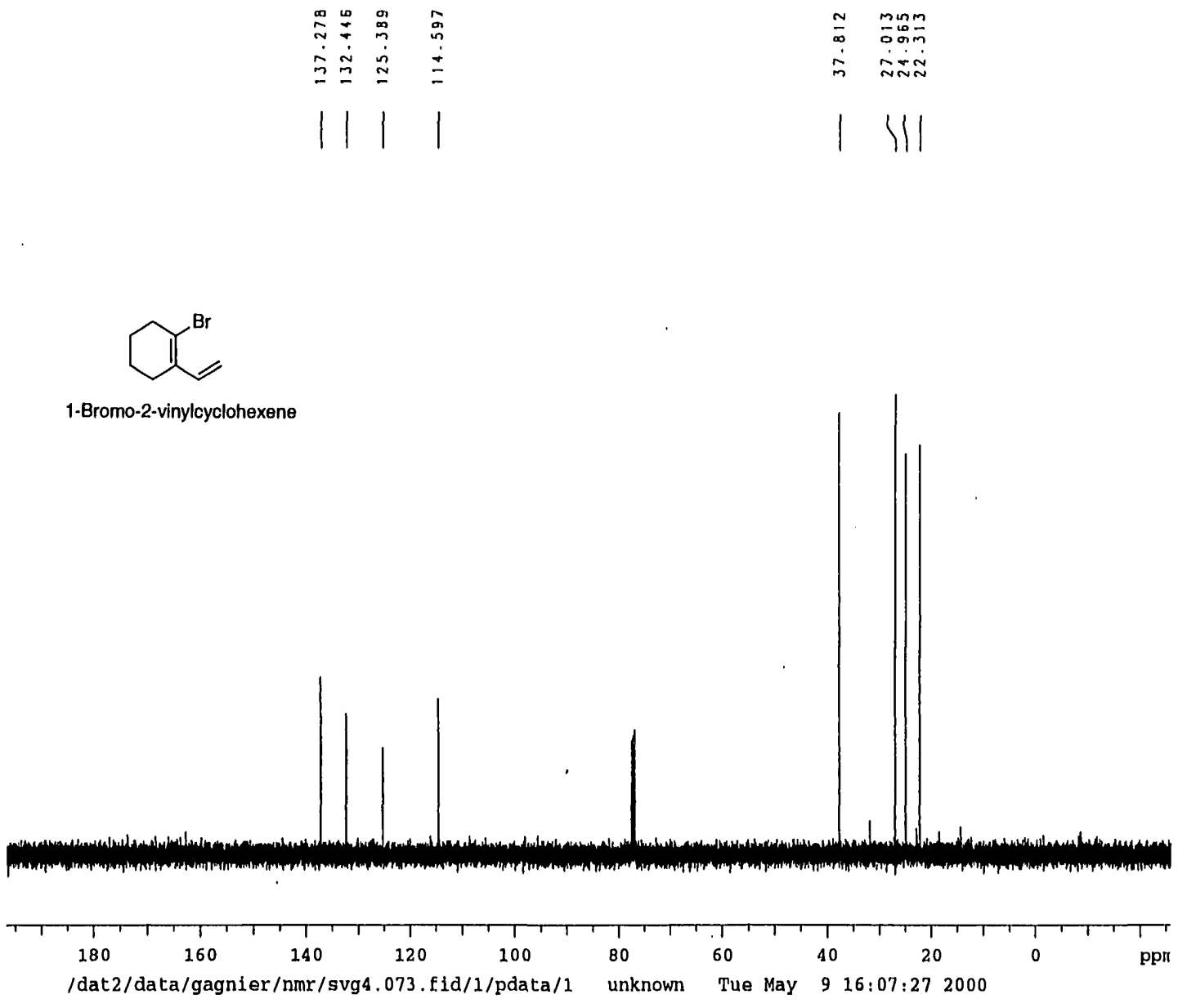


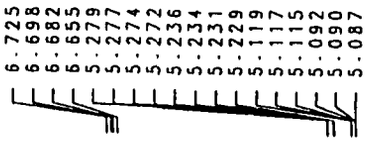


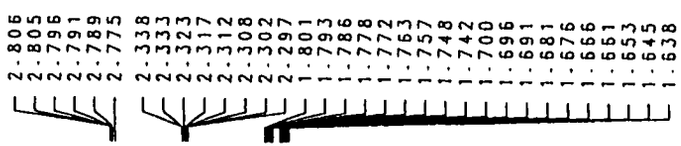



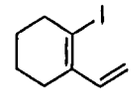




1-Bromo-2-vinylcyclohexene


137.278
132.446
125.389
114.597
37.812
27.013
24.965
22.313
Br
1-Bromo-2-vinylcyclohexene
180
160
140
120
100
80
60
40
20
0
ppm
/dat2/data/gagnier/nmr/svg4.073.fid/1/pdata/1 unknown Tue May 9 16:07:27 2000

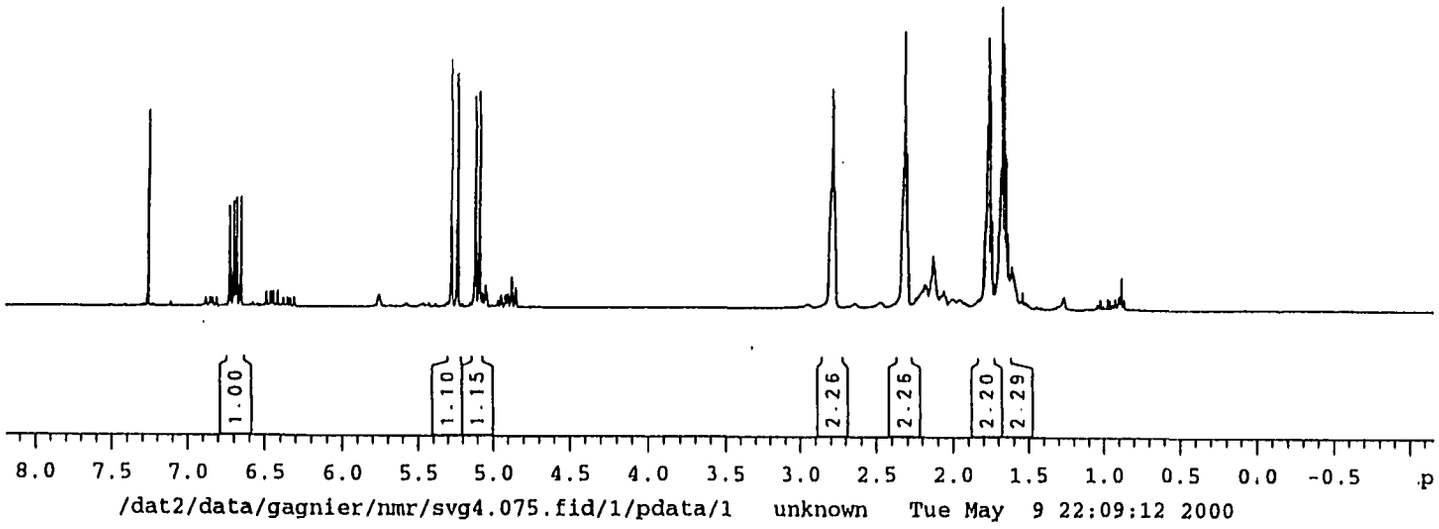


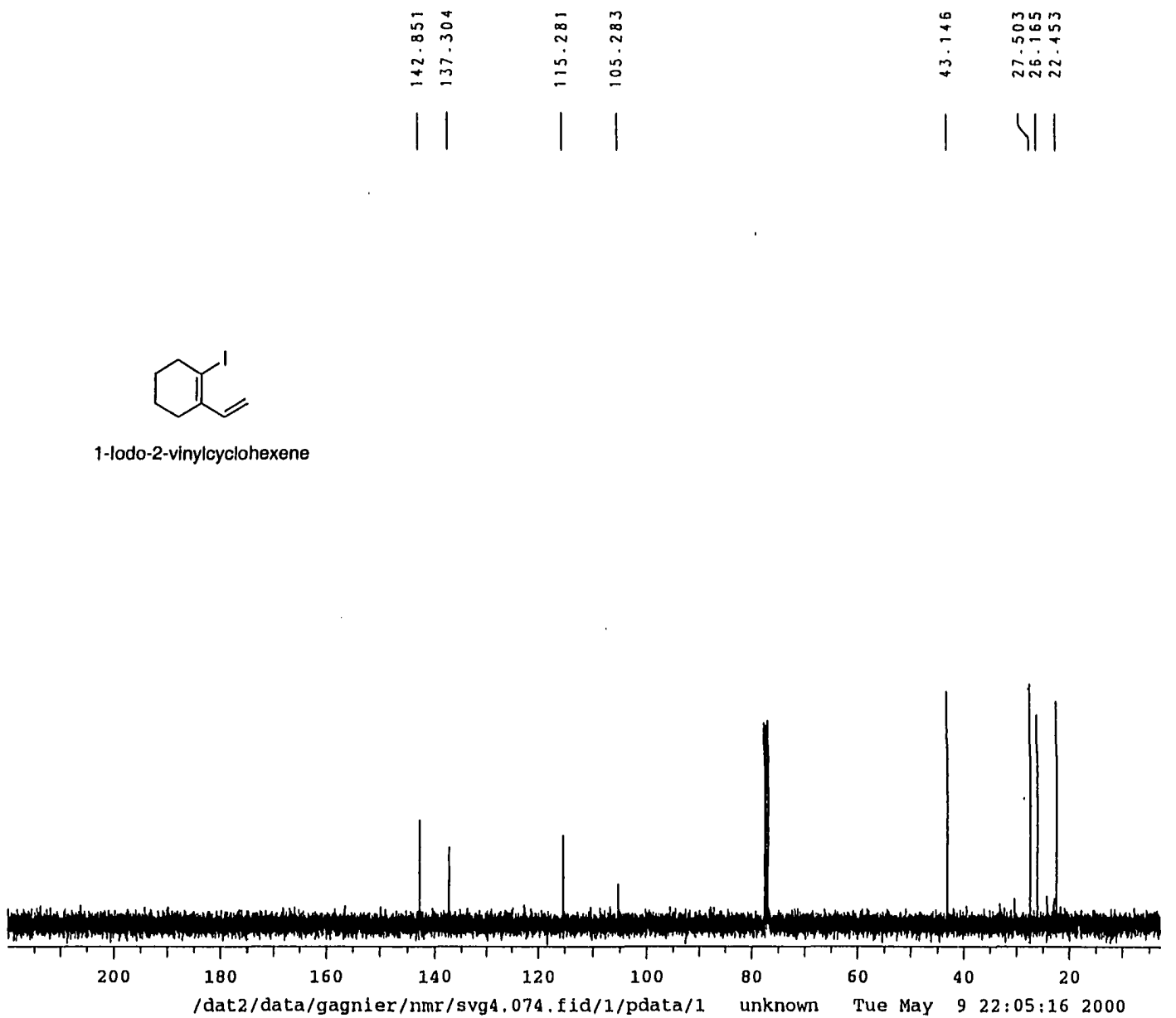



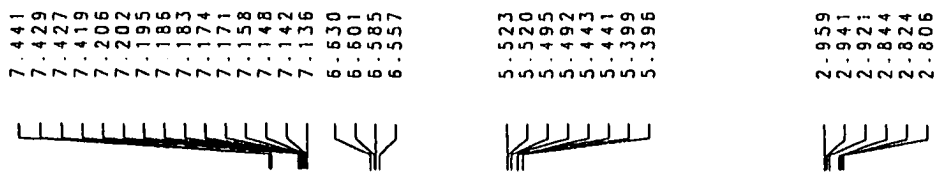



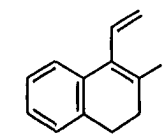
1-Iodo-2-vinylcyclohexene



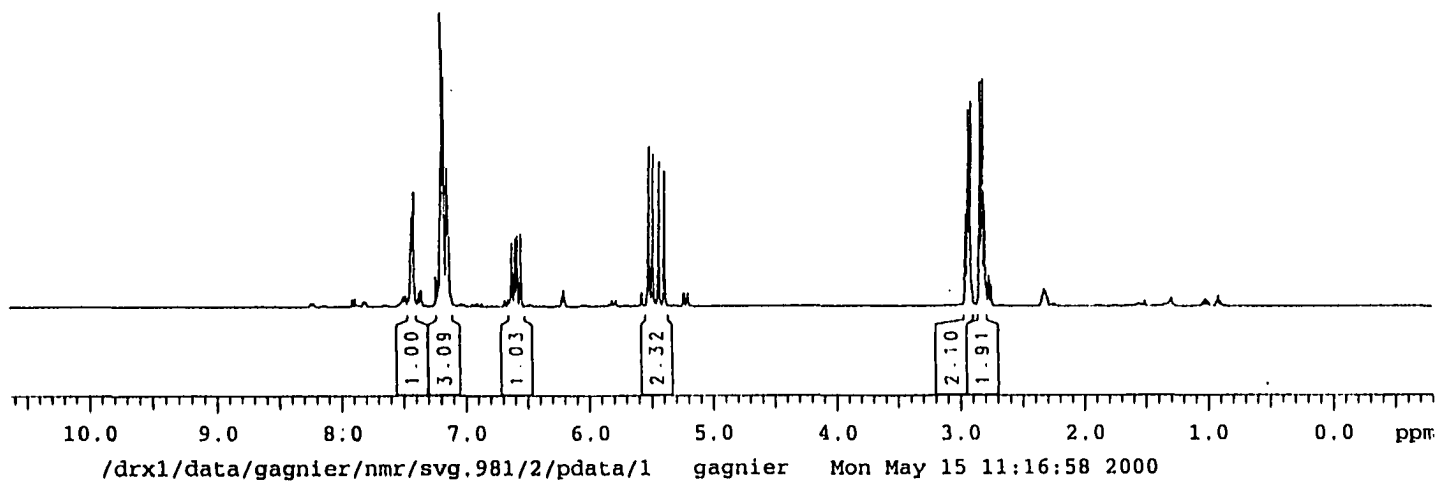


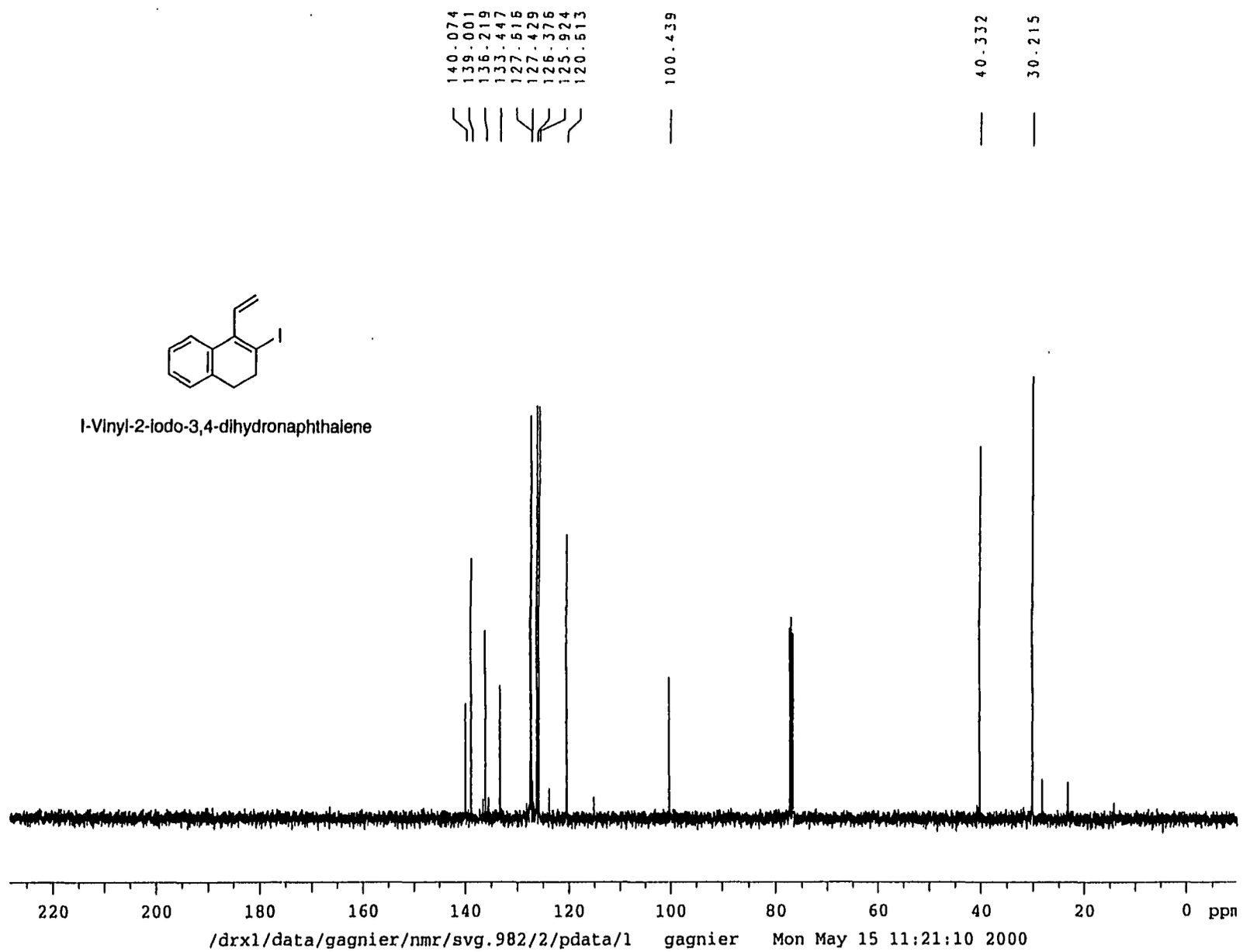

142.851
137.304
115.281
105.283
43.146
27.503
26.165
22.453
I
1-Iodo-2-vinylcyclohexene
200
180
160
140
120
100
80
60
40
20
/dat2/data/gagnier/nmr/svg4.074.fid/1/pdata/1 unknown Tue May 9 22:05:16 2000

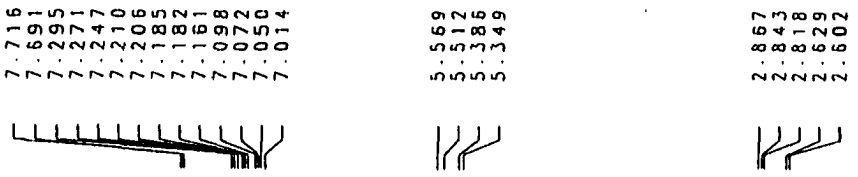


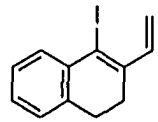



1-Vinyl-2-Iodo-3,4-dihydronaphthalene

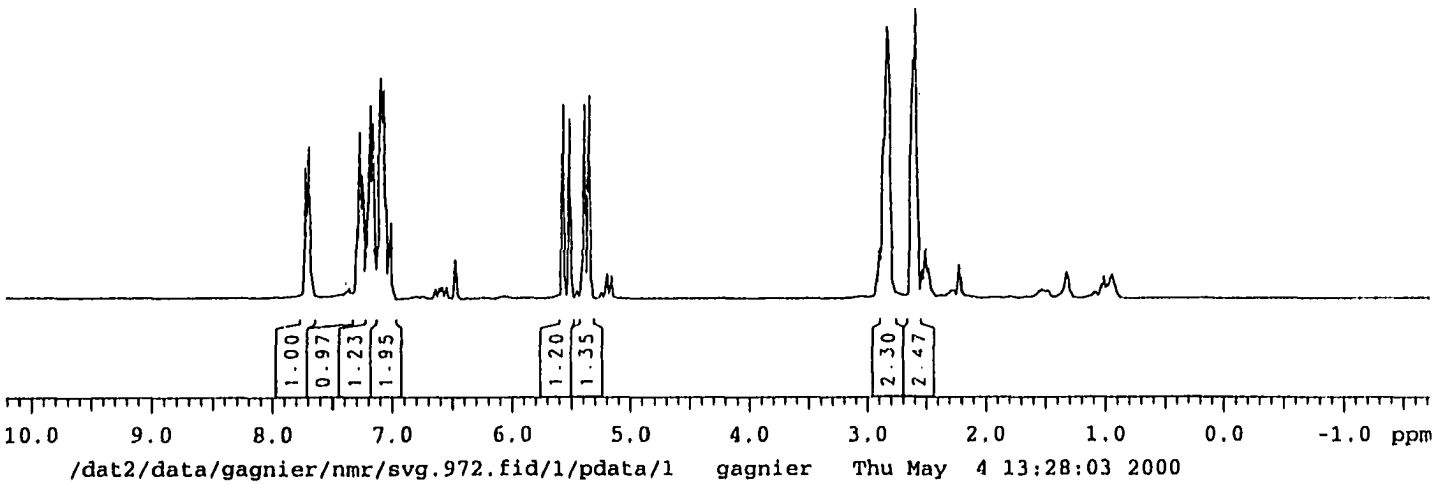



140.074
139.001
136.219
133.447
127.616
127.429
126.376
125.924
120.513
100.439
40.332
30.215
I
1-Vinyl-2-iodo-3,4-dihydronaphthalene
220
200
180
160
140
120
100
80
60
40
20
0
ppm
/drx1/data/gagnier/nmr/svg.982/2/pdata/1 gagnier Mon May 15 11:21:10 2000



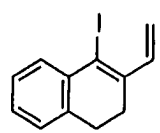



2-Vinyl-1-Iodo-3,4-dihydronaphthalene

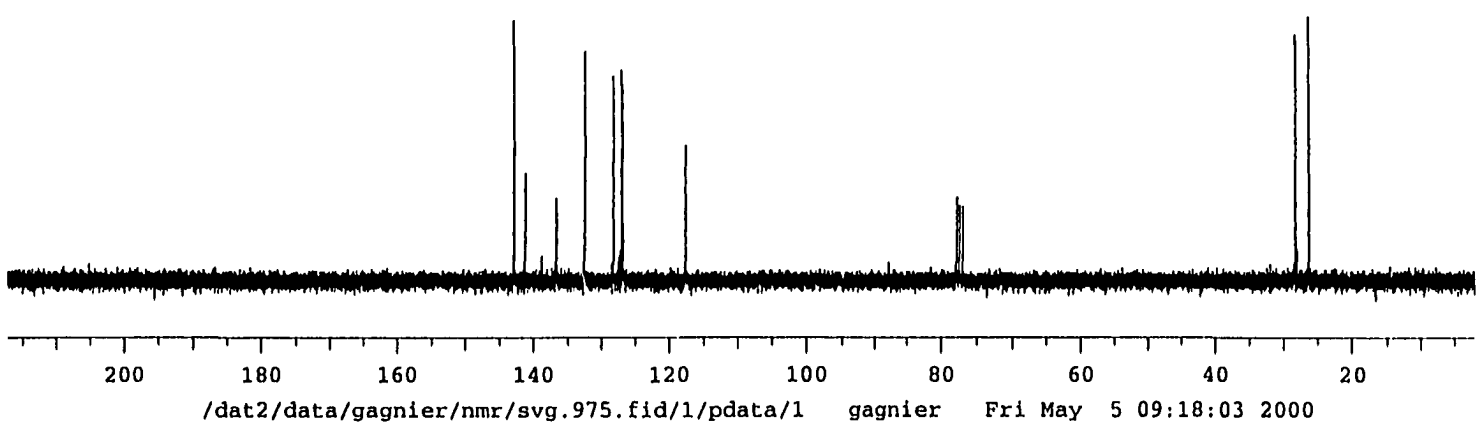


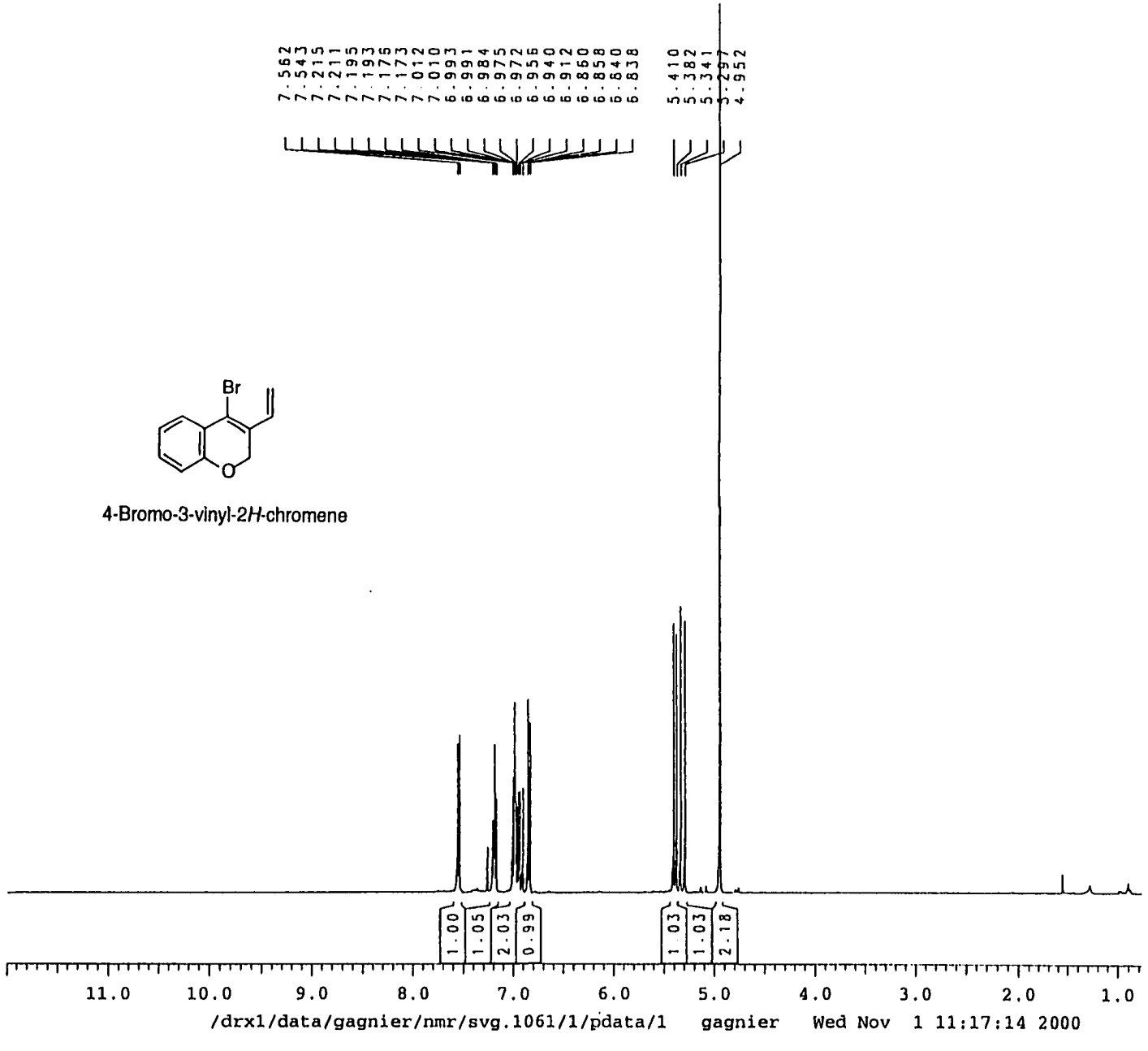
142.990
141.270
136.725
136.618
132.508
128.294
127.118
126.961
126.773
117.673

28.312
26.382



2-Vinyl-1-iodo-3,4-dihydronaphthalene




7.562
7.543
7.215
7.211
7.195
7.193
7.175
7.173
7.012
7.010
6.993
6.991
6.984
6.975
6.972
6.956
6.940
6.912
6.860
6.858
6.840
6.838
5.410
5.382
5.341
5.297
4.952
Br
O
4-Bromo-3-vinyl-2H-chromene
1.00
1.05
2.03
0.99
1.03
1.03
2.18
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
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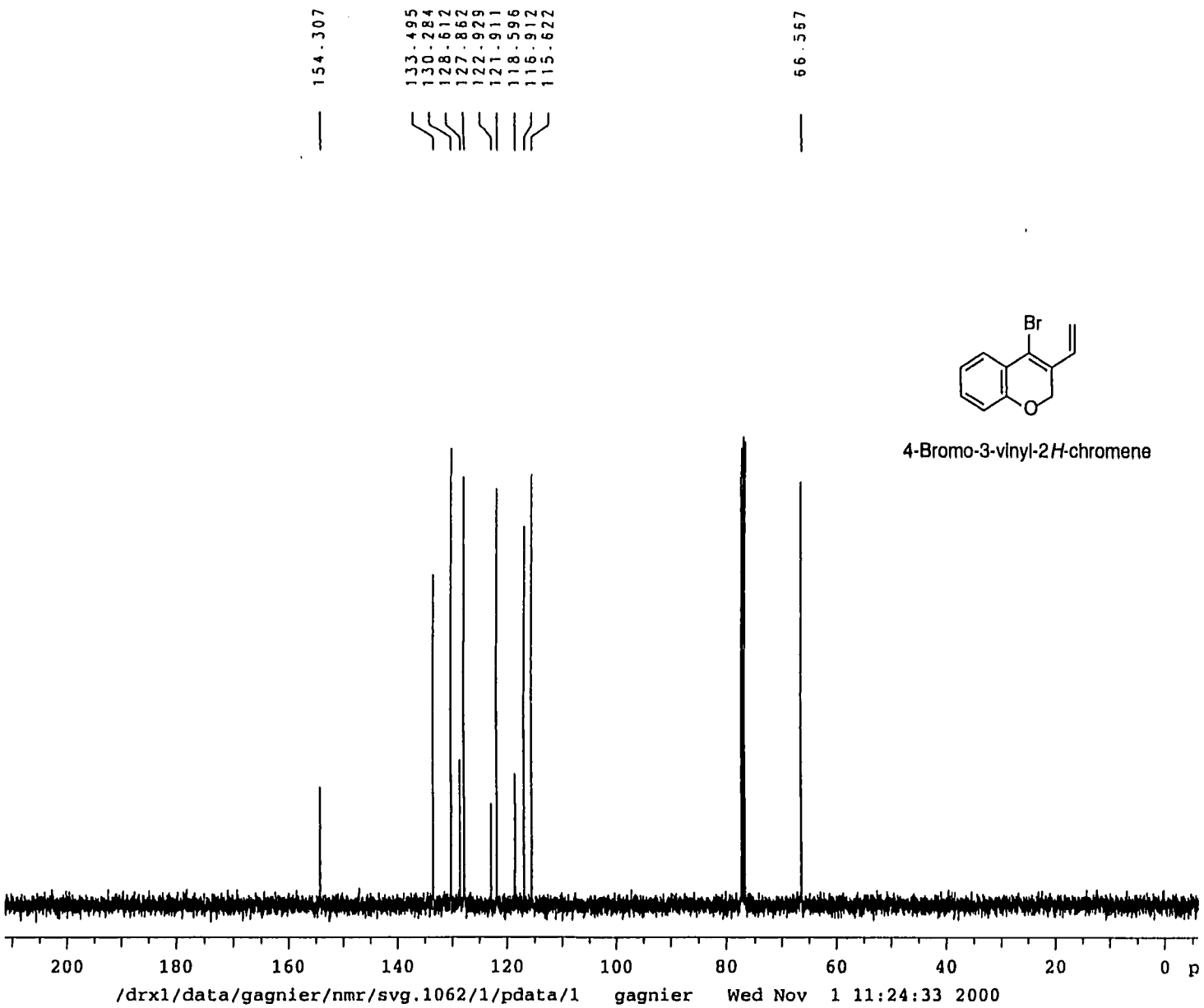
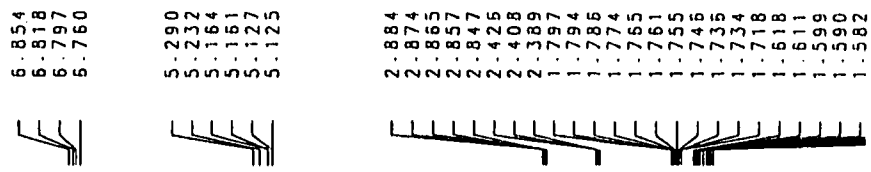
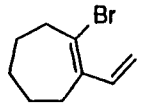
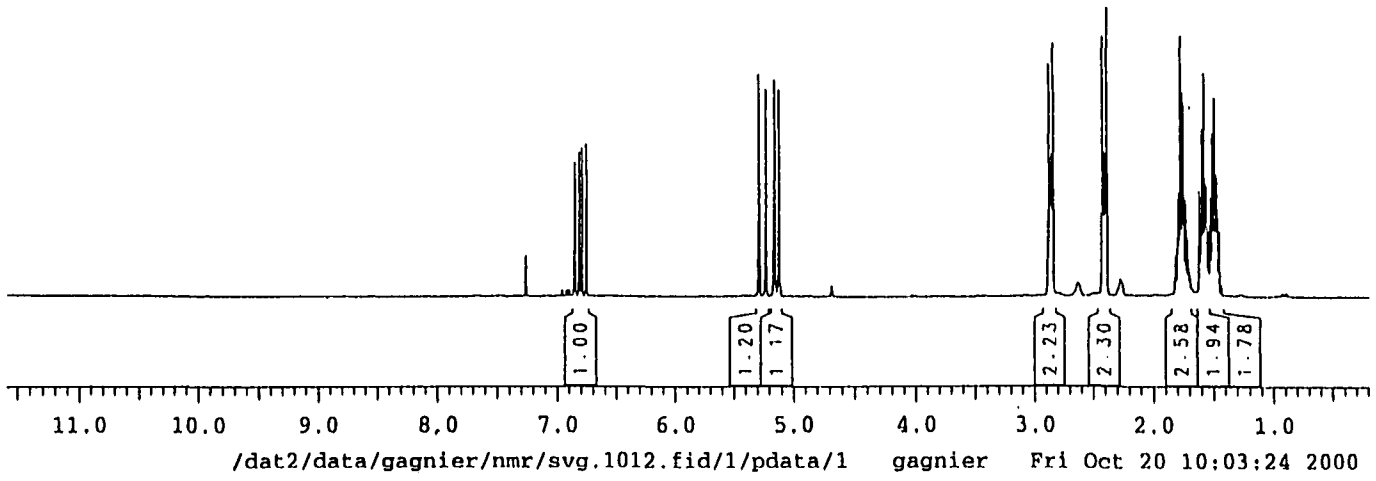
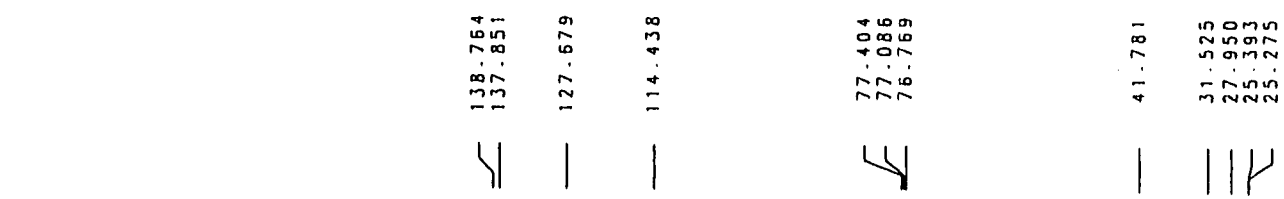

154.307
133.495
130.284
128.612
127.862
122.929
121.911
118.596
116.912
115.622
66.567
Br
O
4-Bromo-3-vinyl-2H-chromene
200
180
160
140
120
100
80
60
40
20
0 p
/drx1/data/gagnier/nmr/svg.1062/1/pdata/1 gagnier Wed Nov 1 11:24:33 2000

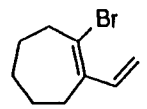


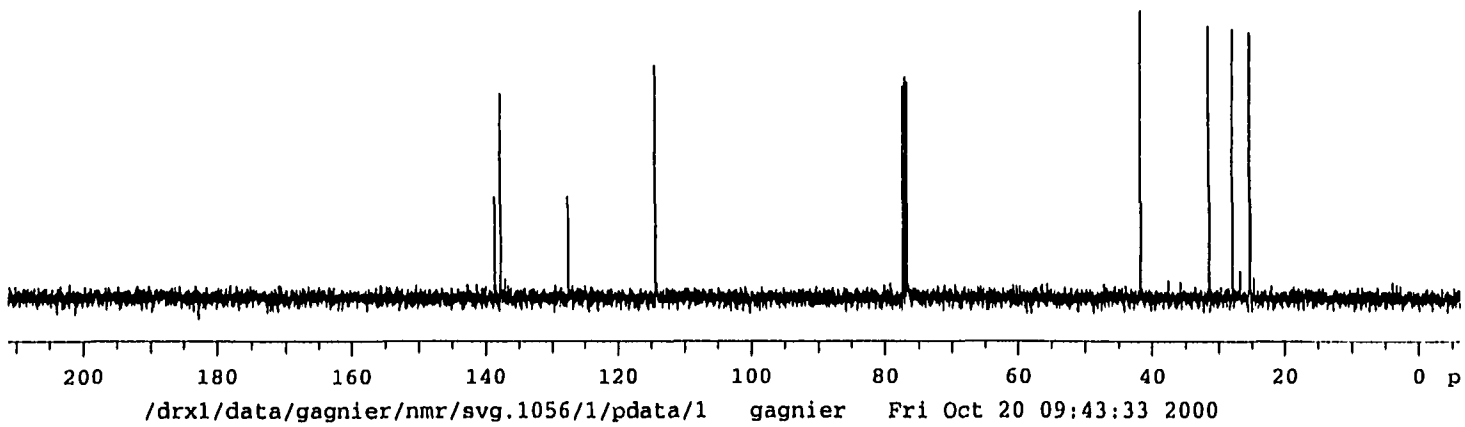

1-Bromo-2-vinylcycloheptene

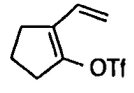




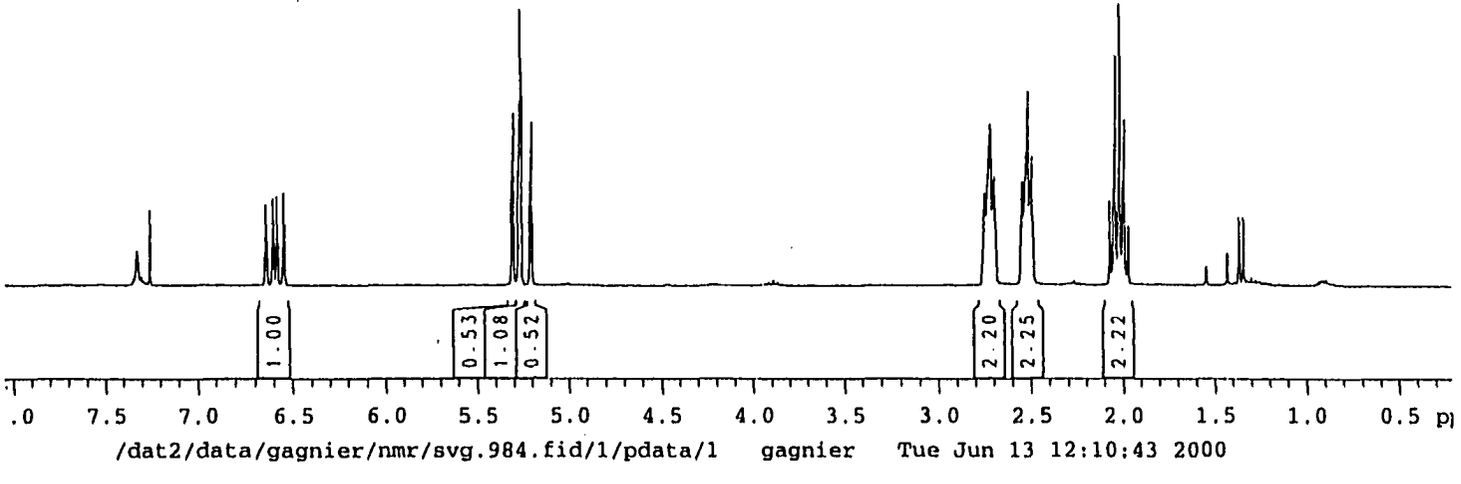



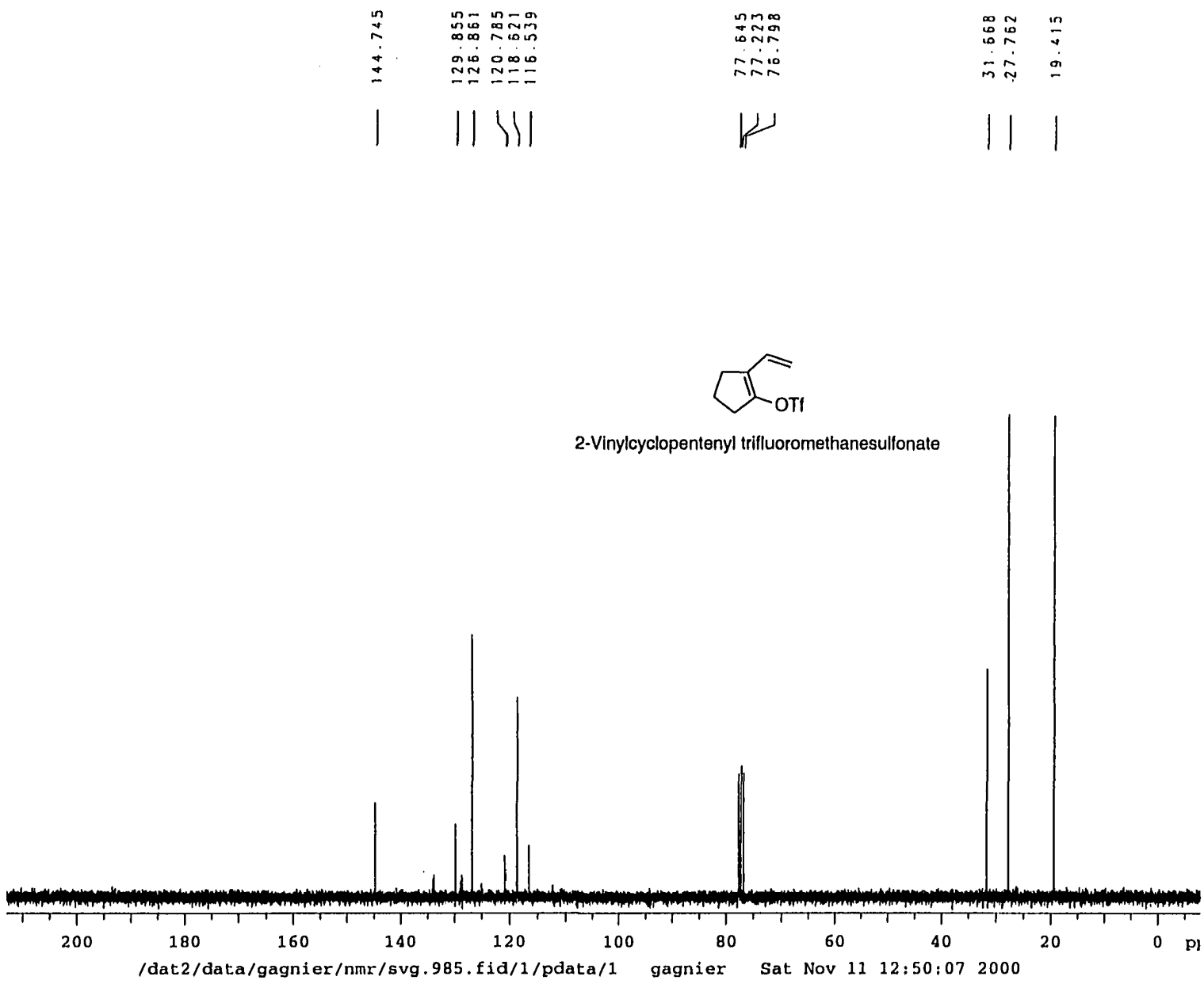

1-Bromo-2-vinylcycloheptene

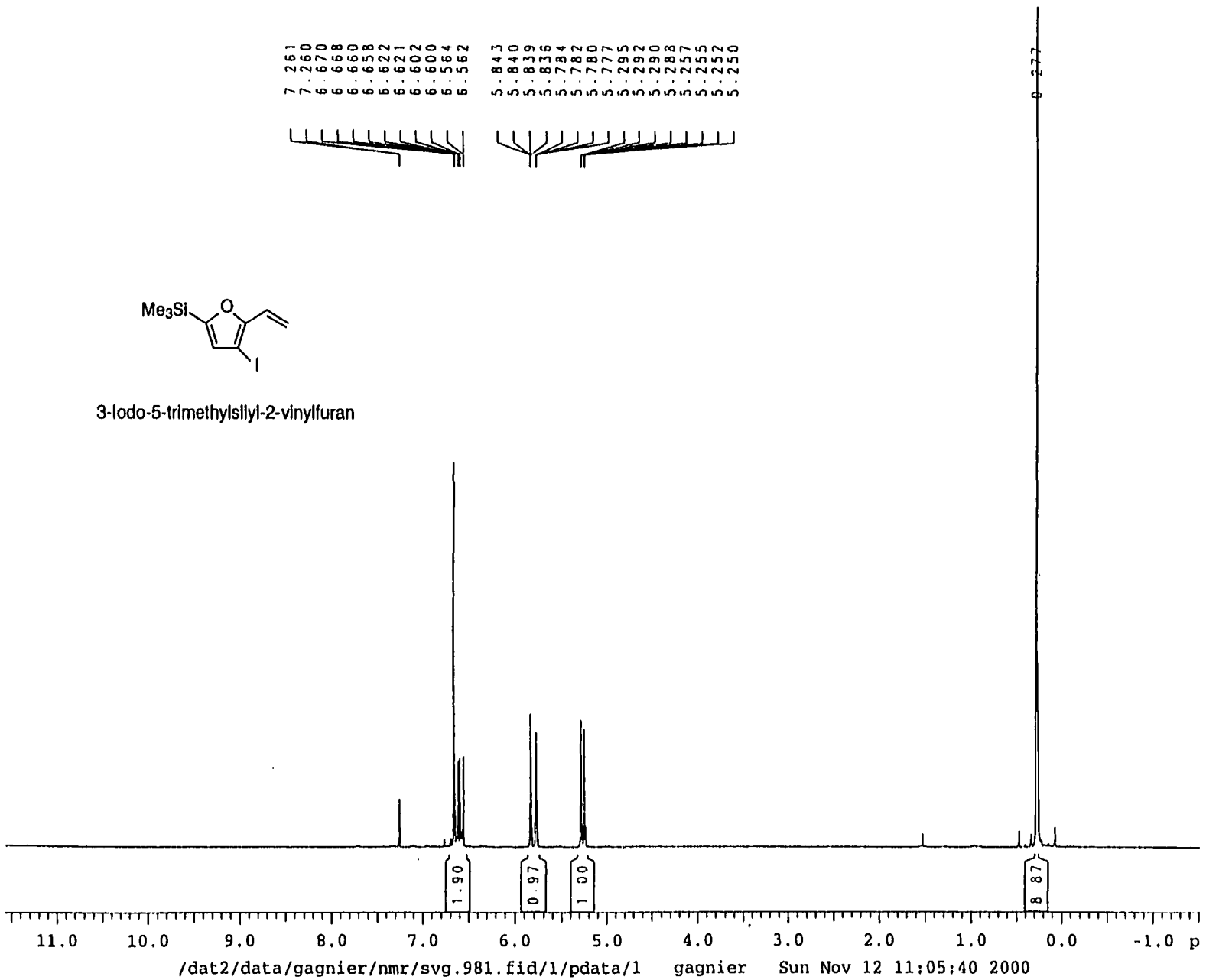


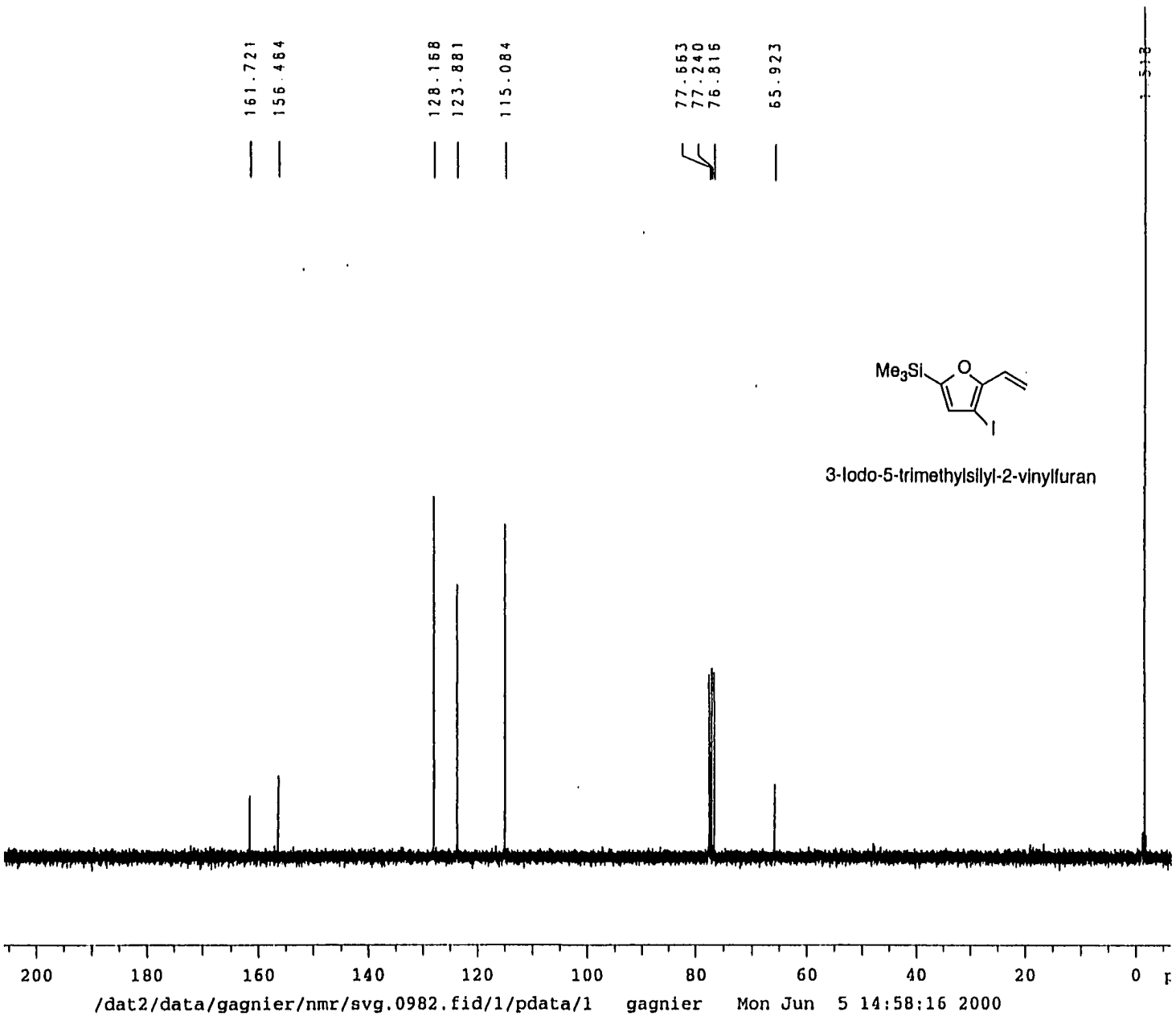

2-Vinylcyclopentenyl trifluoromethanesulfonate

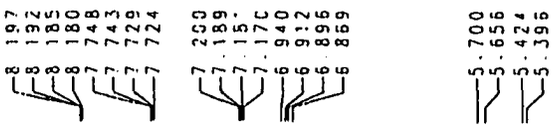


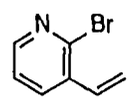

144.745
129.855
126.861
120.785
118.621
116.539
77.645
77.223
76.798
31.668
27.762
19.415
OTf
2-Vinylcyclopentenyl trifluoromethanesulfonate
200
180
160
140
120
100
80
60
40
20
0
/dat2/data/gagnier/nmr/svg.985.fid/1/pdata/1 gagnier Sat Nov 11 12:50:07 2000



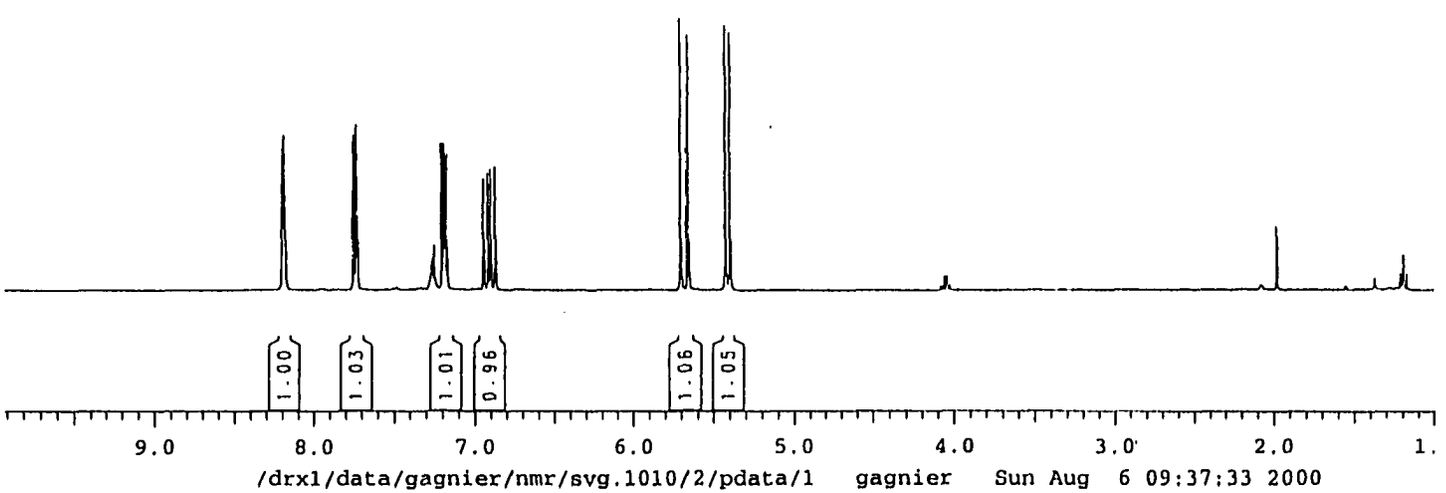

3-Iodo-5-trimethylsilyl-2-vinylfuran


161.721
156.464
128.168
123.881
115.084
77.663
77.240
76.816
65.923
1.518
Me3Si
O
I
3-Iodo-5-trimethylsilyl-2-vinylfuran
200
180
160
140
120
100
80
60
40
20
0
/dat2/data/gagnier/nmr/svg.0982.fid/1/pdata/1 gagnier Mon Jun 5 14:58:16 2000

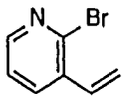


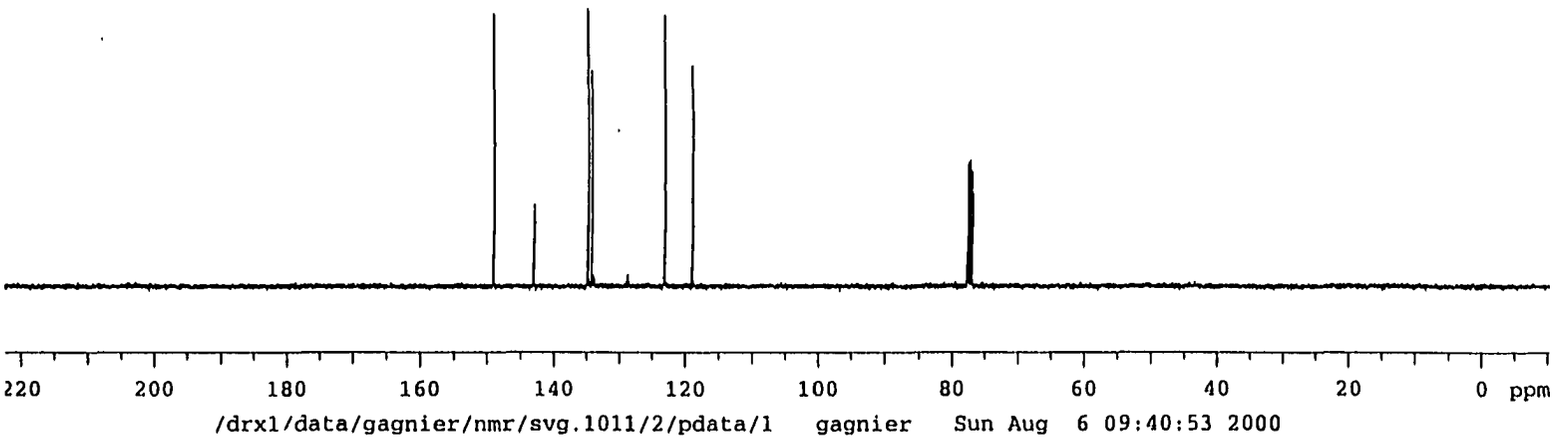

2-Bromo-3-vinylpyridine

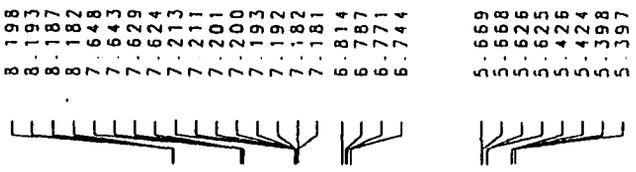


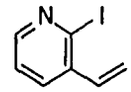
148.353
142.919
134.744
134.659
134.112
123.071
118.848



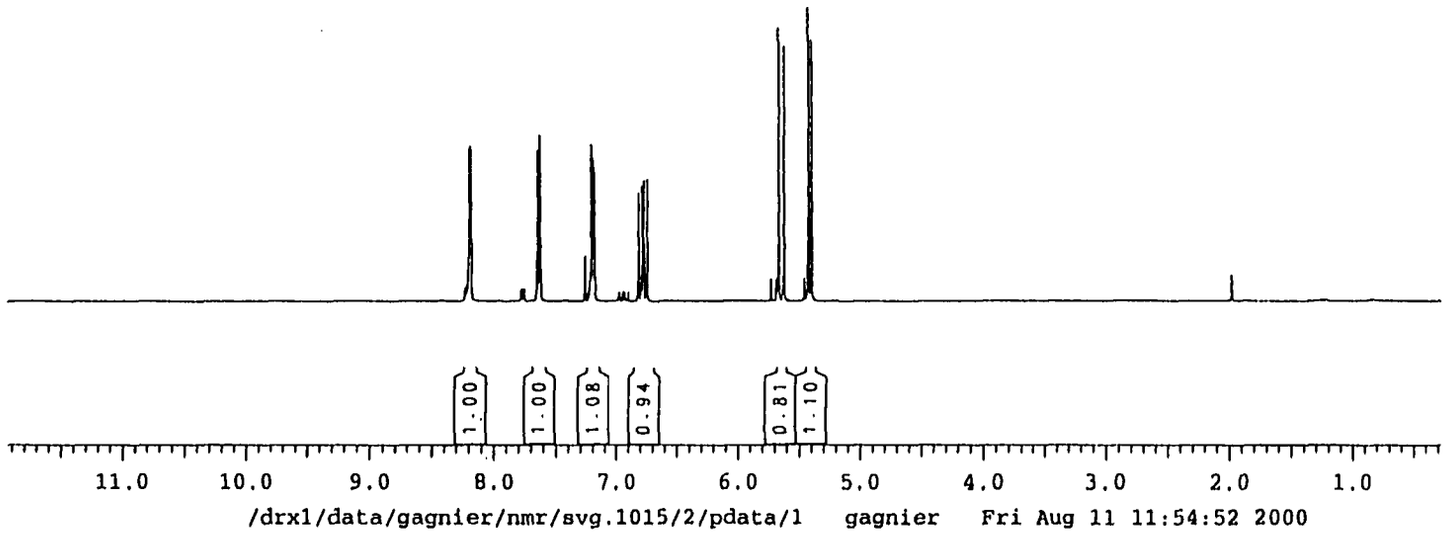

2-Bromo-3-vinylpyridine

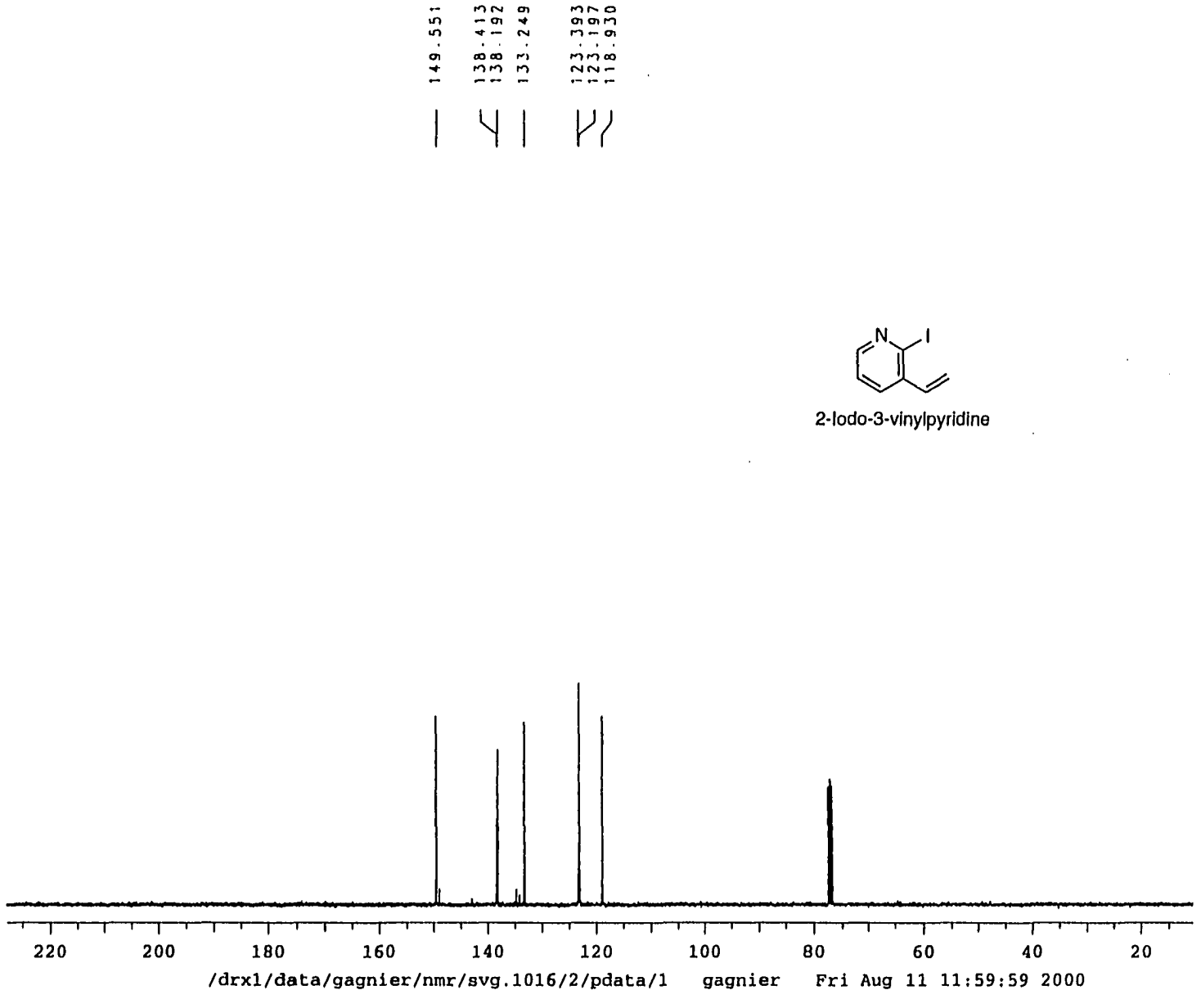


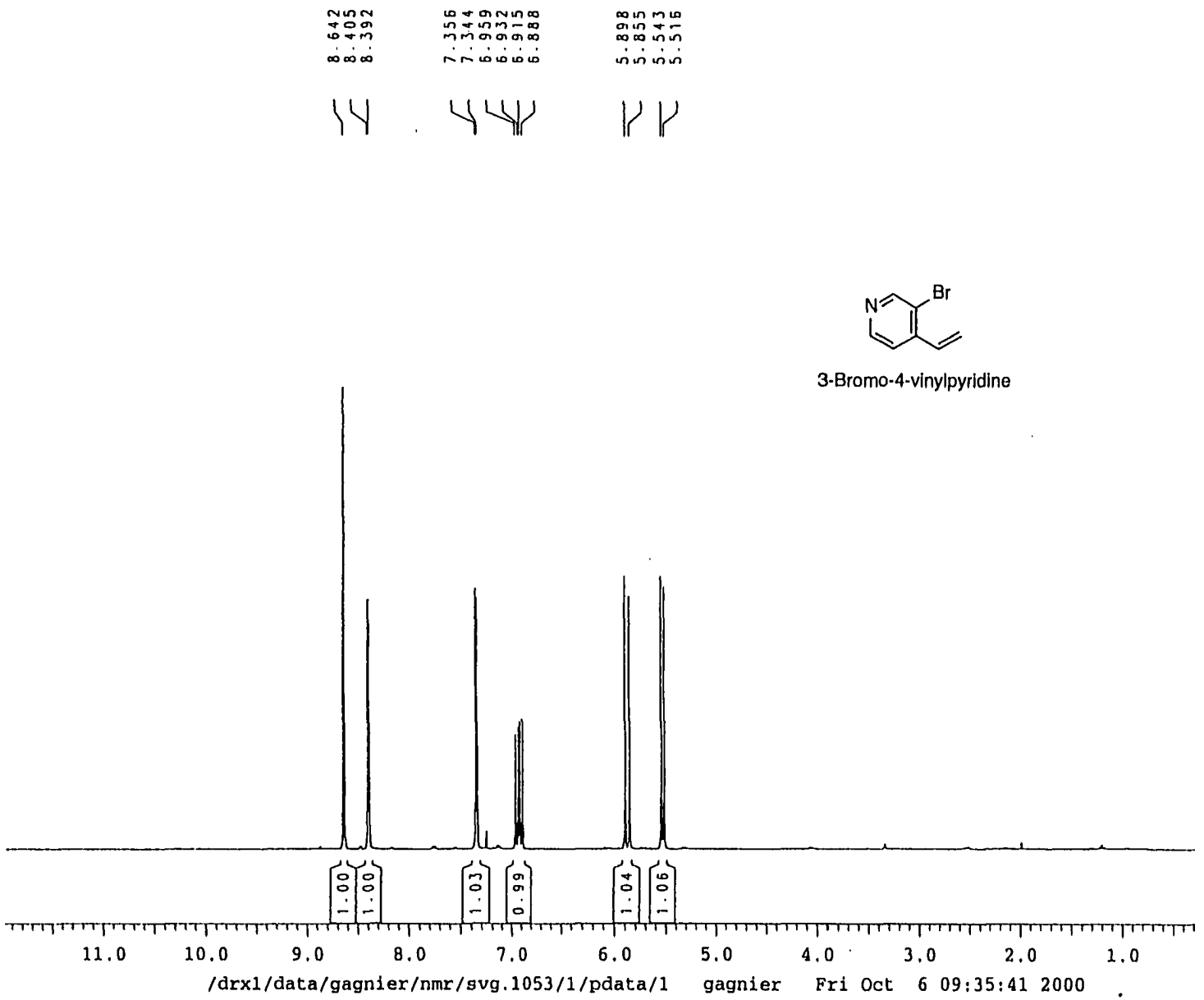


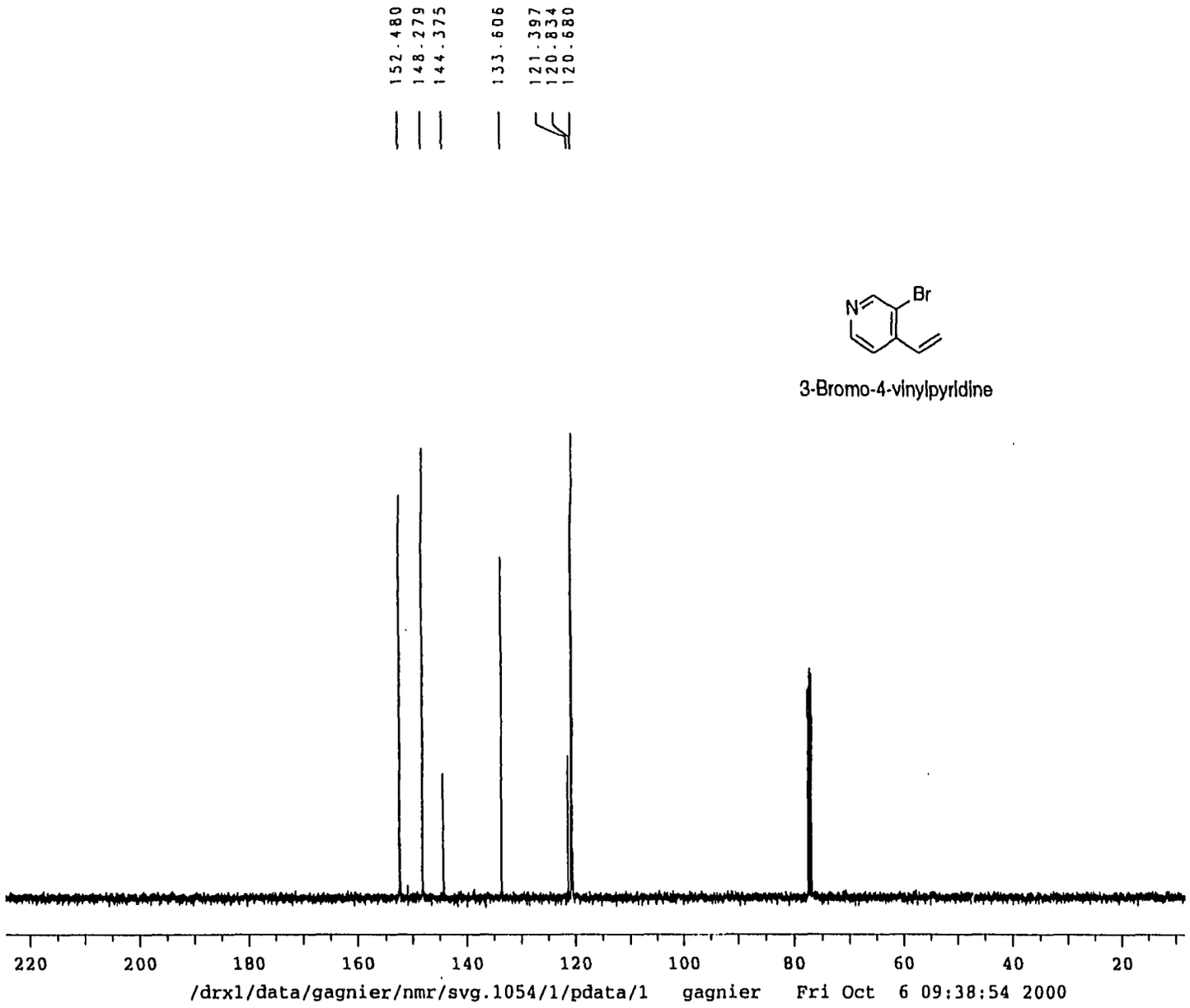



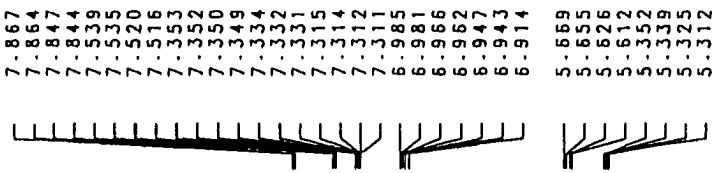

2-Iodo-3-vinylpyridine

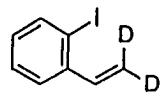



149.551
138.413
138.192
133.249
123.393
123.197
118.930
N
I
2-Iodo-3-vinylpyridine
220
200
180
160
140
120
100
80
60
40
20
/drx1/data/gagnier/nmr/svg.1016/2/pdata/1 gagnier Fri Aug 11 11:59:59 2000

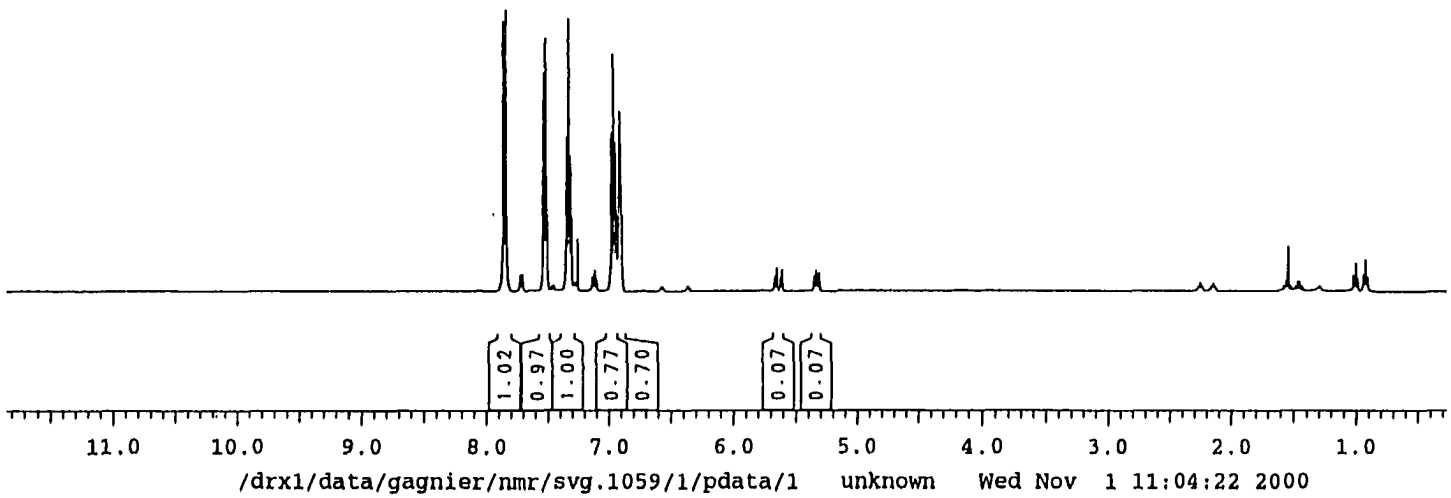

8.642
8.405
8.392
7.356
7.344
6.959
6.932
6.915
6.888
5.898
5.855
5.543
5.516
N
Br
3-Bromo-4-vinylpyridine
1.00
1.00
1.03
0.99
1.04
1.06
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
/drx1/data/gagnier/nmr/svg.1053/1/pdata/1 gagnier Fri Oct 6 09:35:41 2000

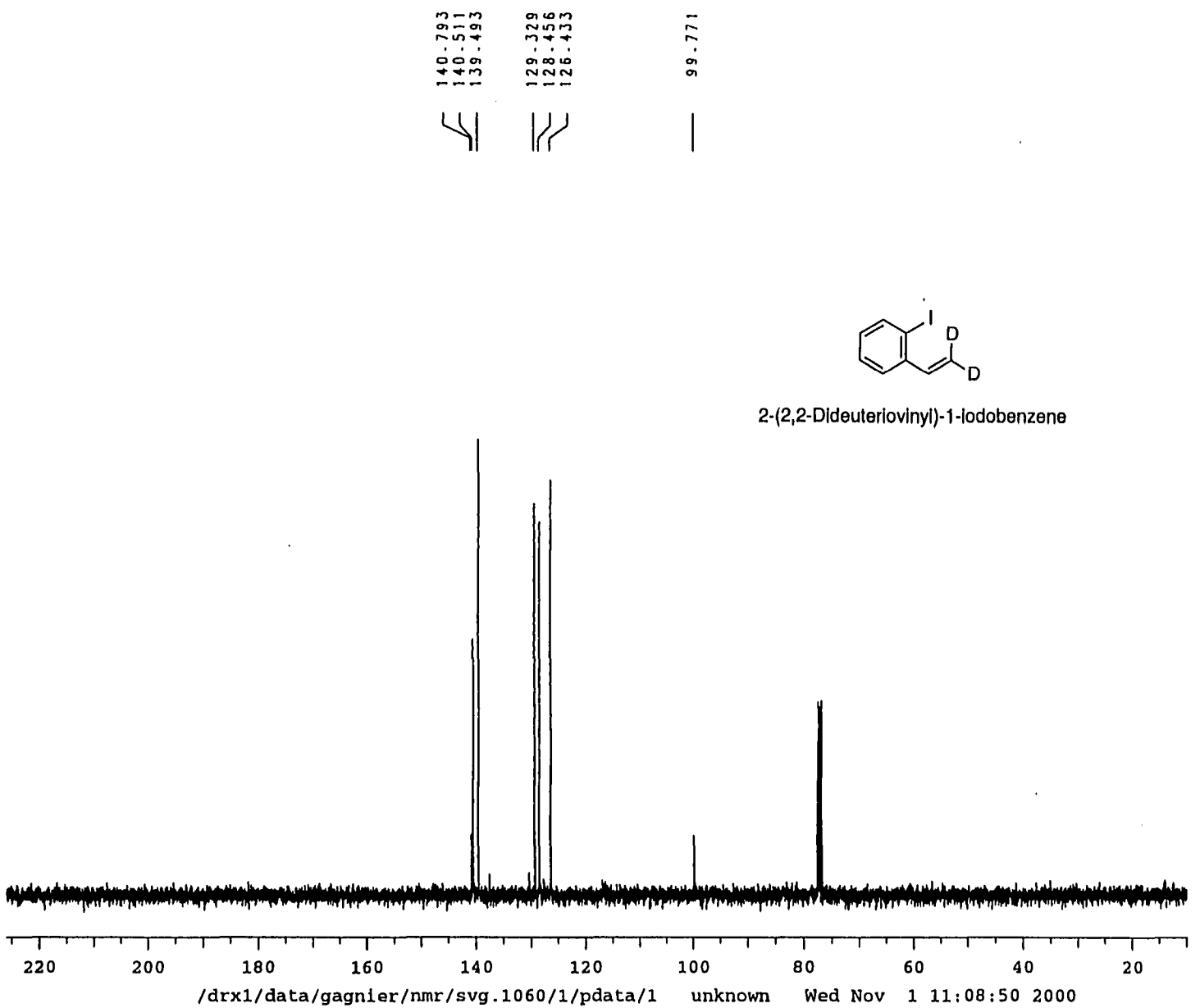

152.480
148.279
144.375
133.606
121.397
120.834
120.680
Br
N
3-Bromo-4-vinylpyridine
220
200
180
160
140
120
100
80
60
40
20
/drx1/data/gagnier/nmr/svg.1054/1/pdata/1 gagnier Fri Oct 6 09:38:54 2000

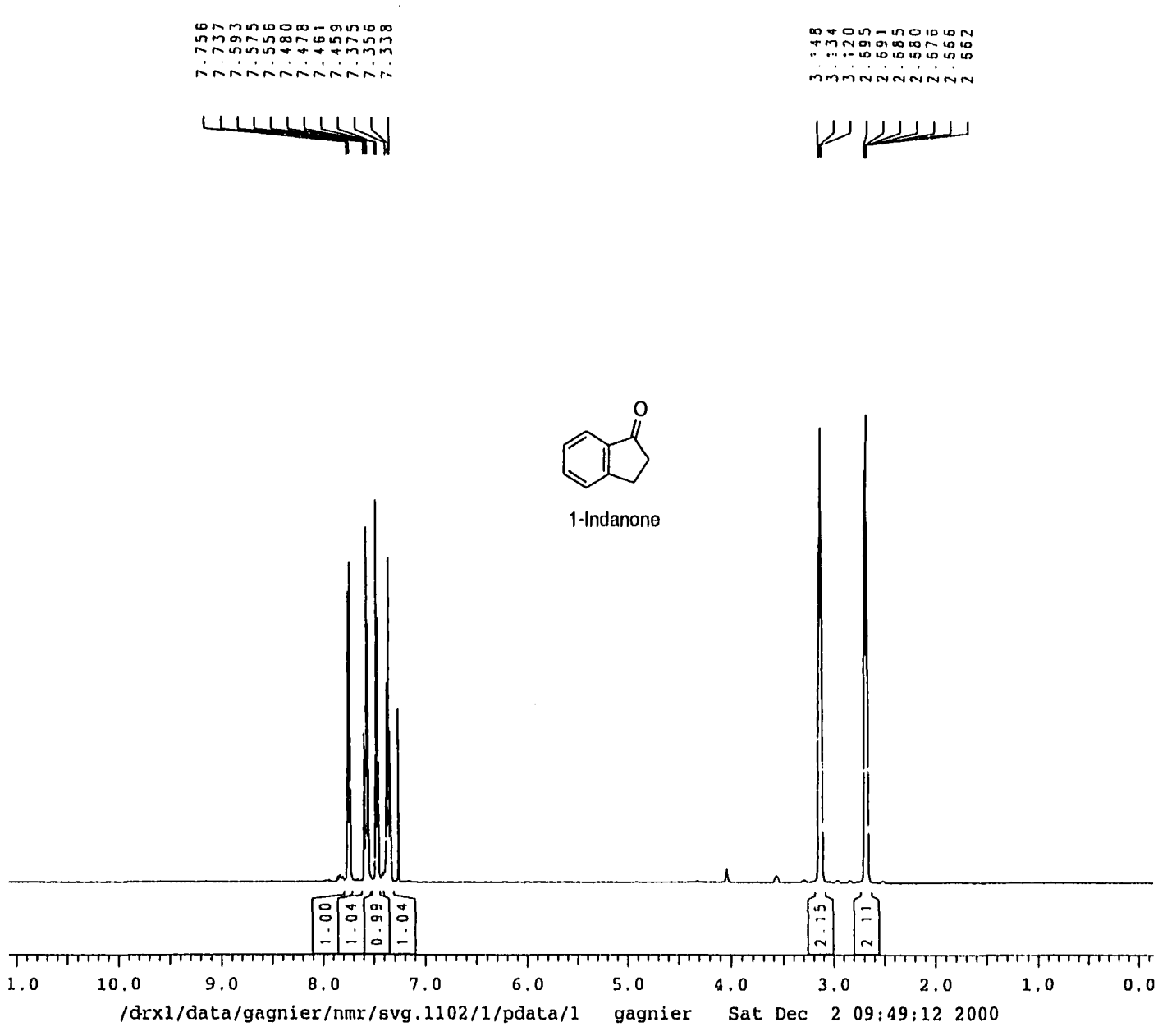



2-(2,2-Dideuteriovinyl)-1-iodobenzene




140.793
140.511
139.493
129.329
128.456
126.433
99.771
I
D
D
2-(2,2-Dideuteriovinyl)-1-Iodobenzene
220
200
180
160
140
120
100
80
60
40
20
/drx1/data/gagnier/nmr/svg.1060/1/pdata/1 unknown Wed Nov 1 11:08:50 2000


7.756
7.737
7.593
7.575
7.556
7.480
7.478
7.461
7.459
7.375
7.356
7.338
3.148
3.134
3.120
2.695
2.691
2.685
2.580
2.576
2.566
2.562
O
1-Indanone
1.00
1.04
0.99
1.04
2.15
2.11
1.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
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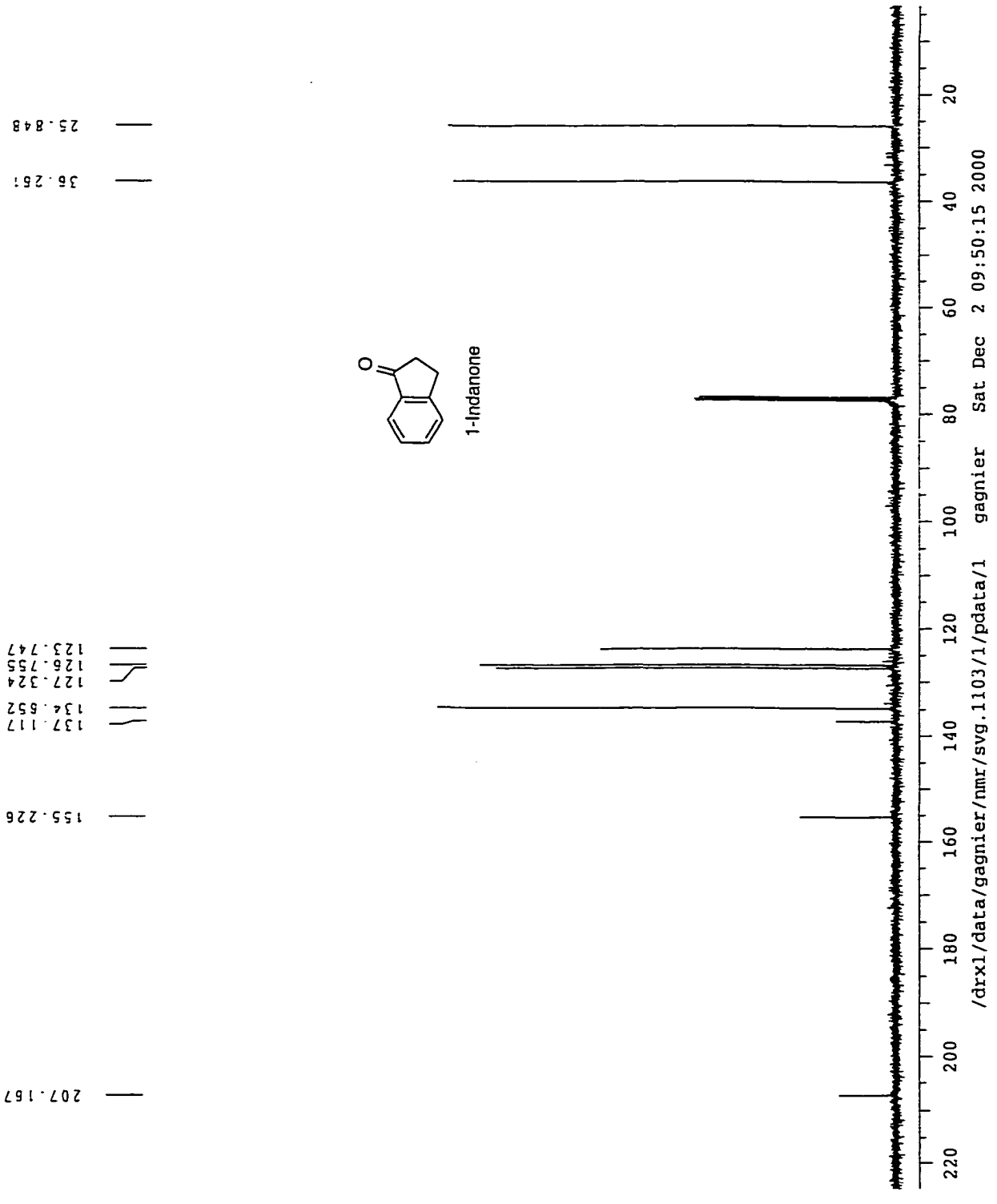
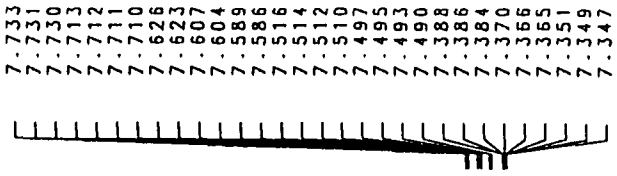
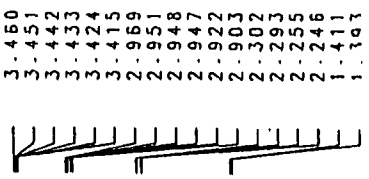
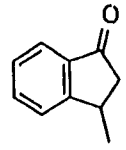
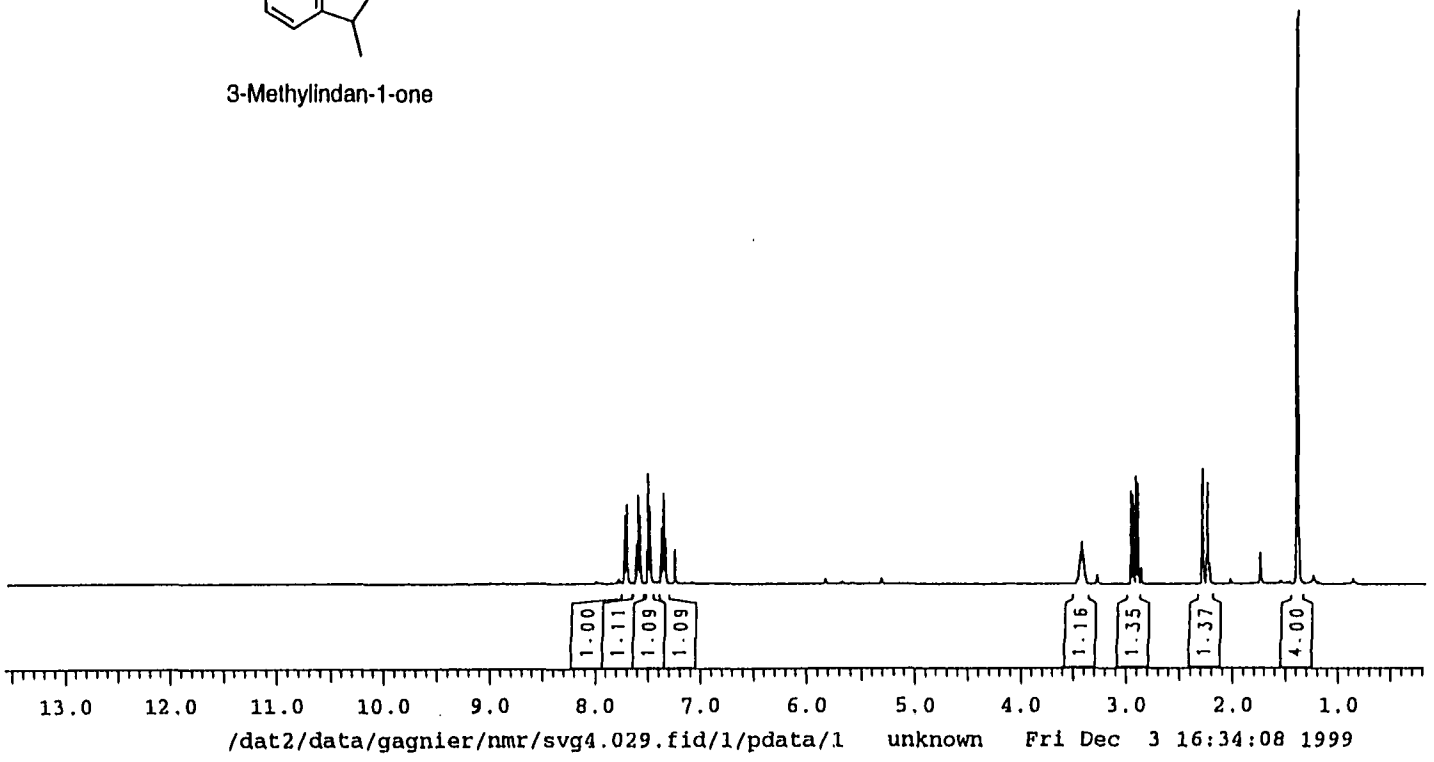

25.848
36.261
123.747
126.755
127.324
134.652
137.117
155.226
207.167
1-Indanone
/drx1/data/gagnier/nmr/svg.1103/1/pdata/1 gagnier Sat Dec 2 09:50:15 2000
220
200
180
160
140
120
100
80
60
40
20

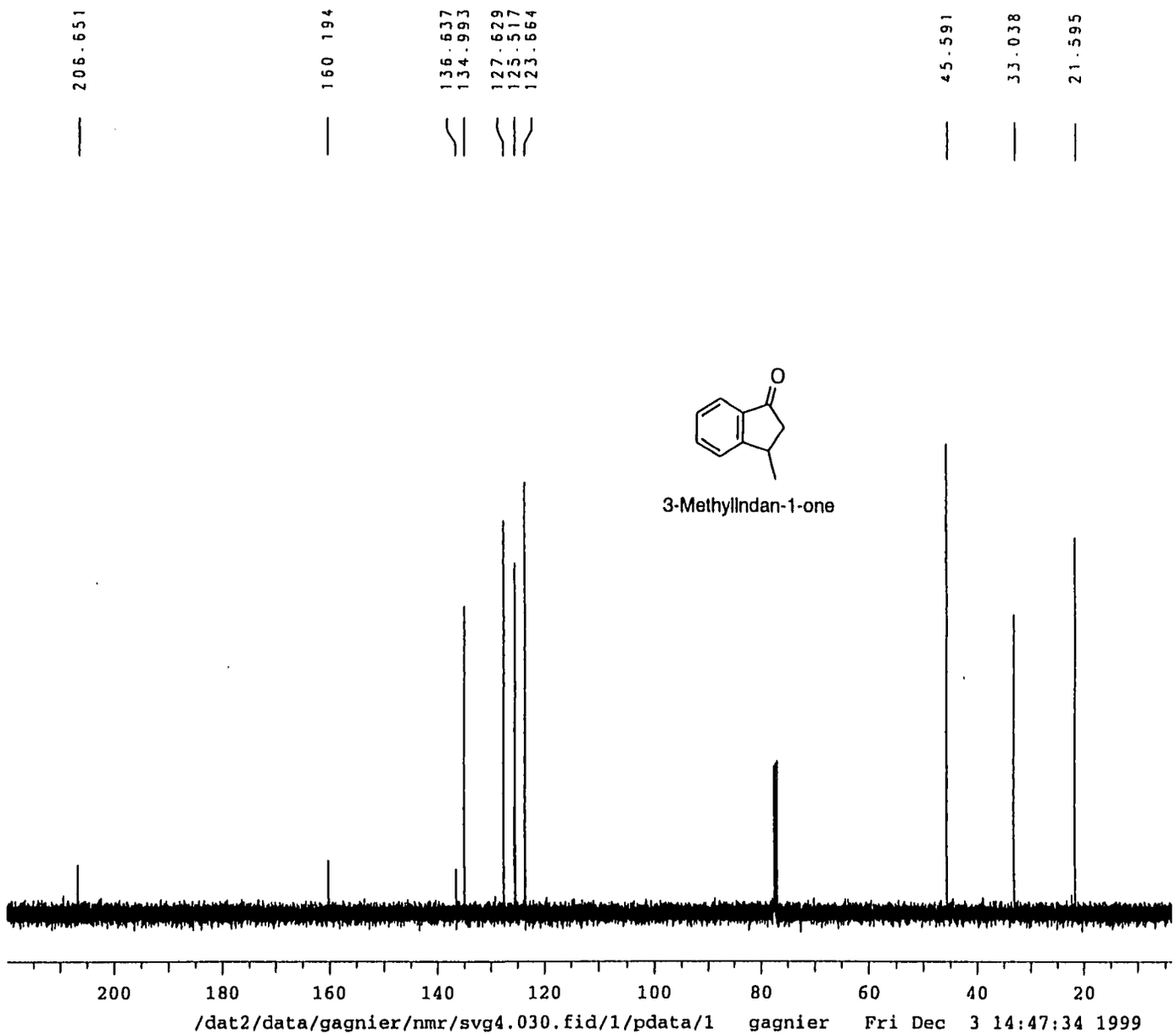



3-Methylindan-1-one




206.651
160.194
136.637
134.993
127.629
125.517
123.664
45.591
33.038
21.595
O
3-Methylindan-1-one
200
180
160
140
120
100
80
60
40
20
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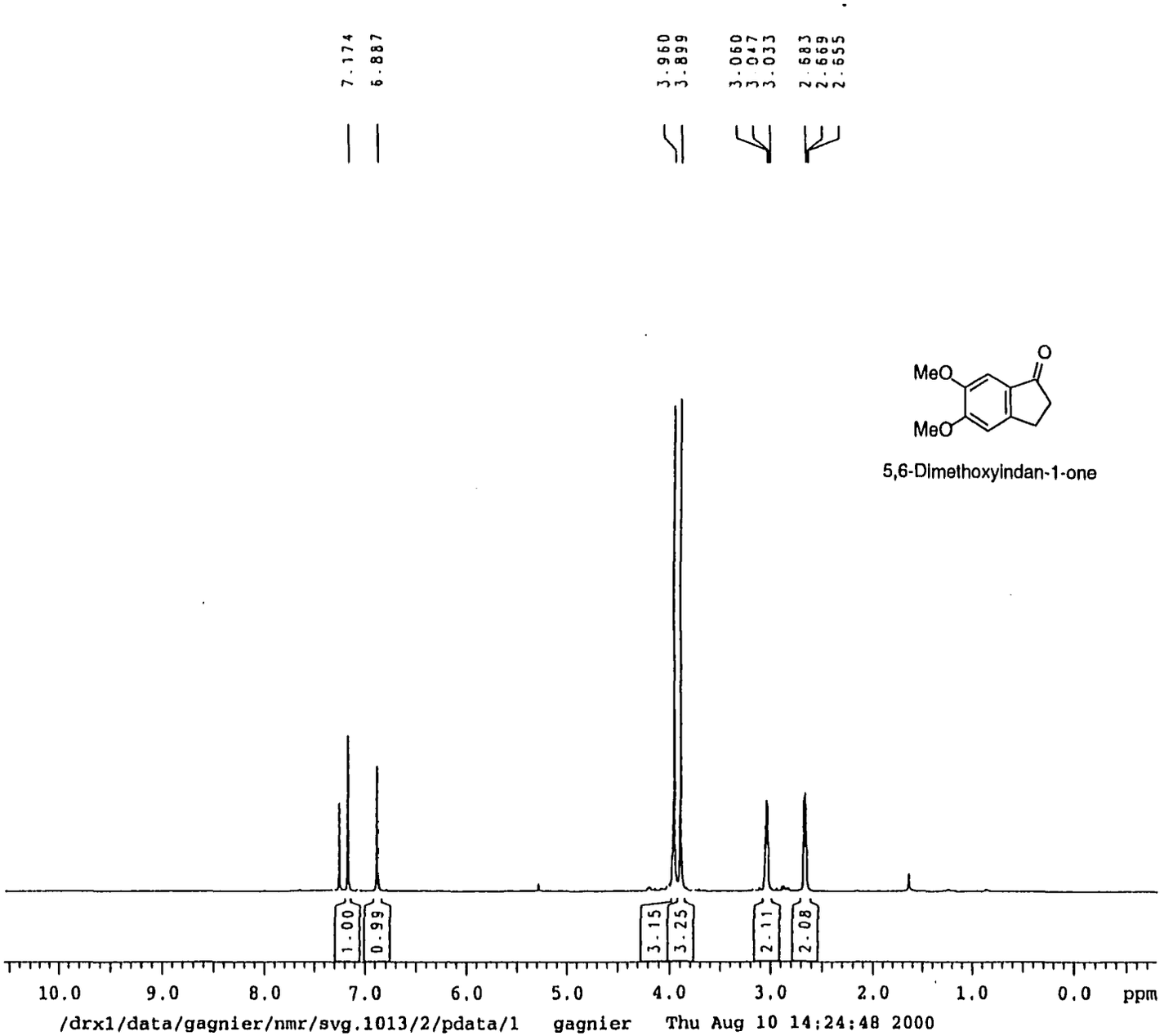
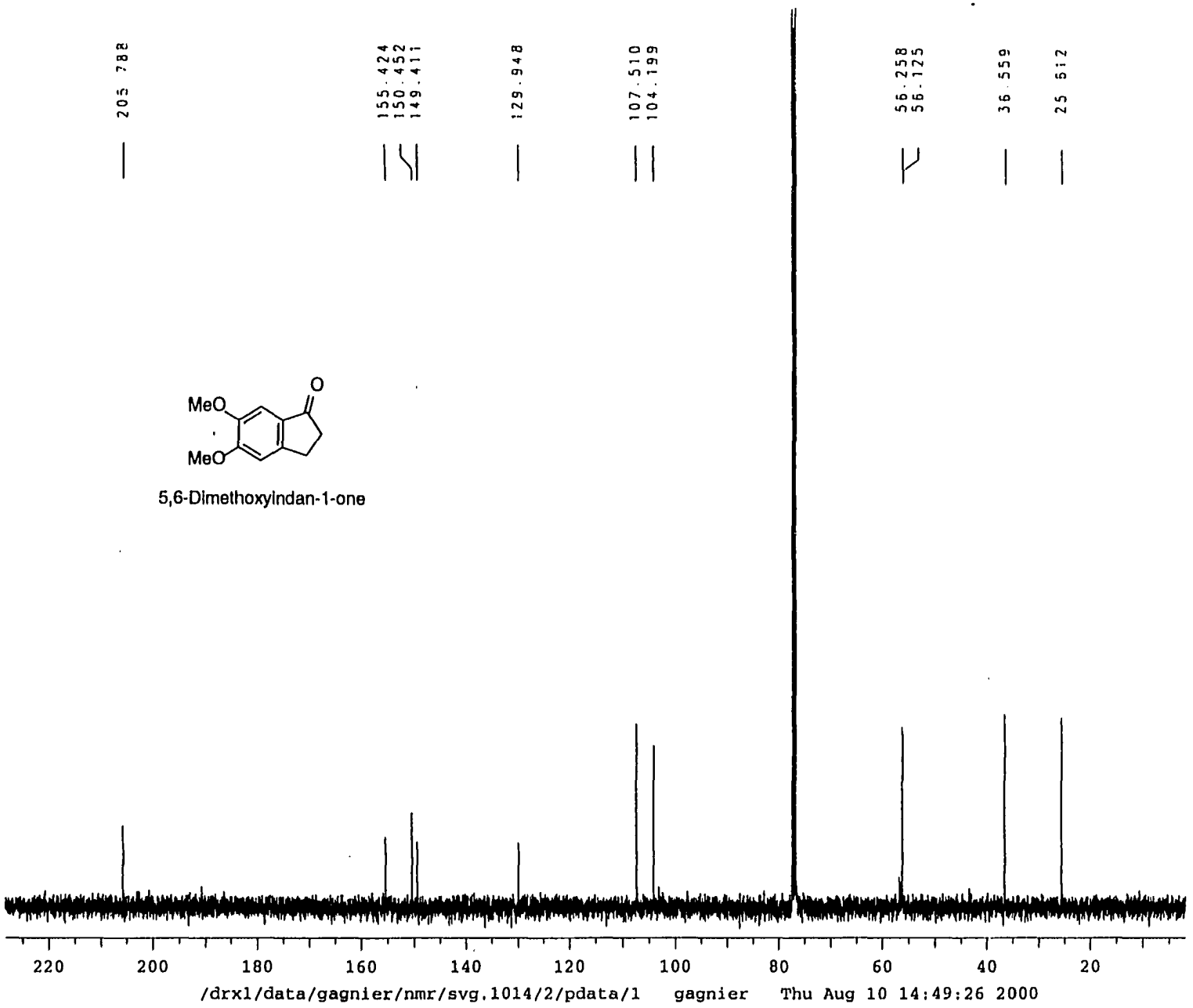
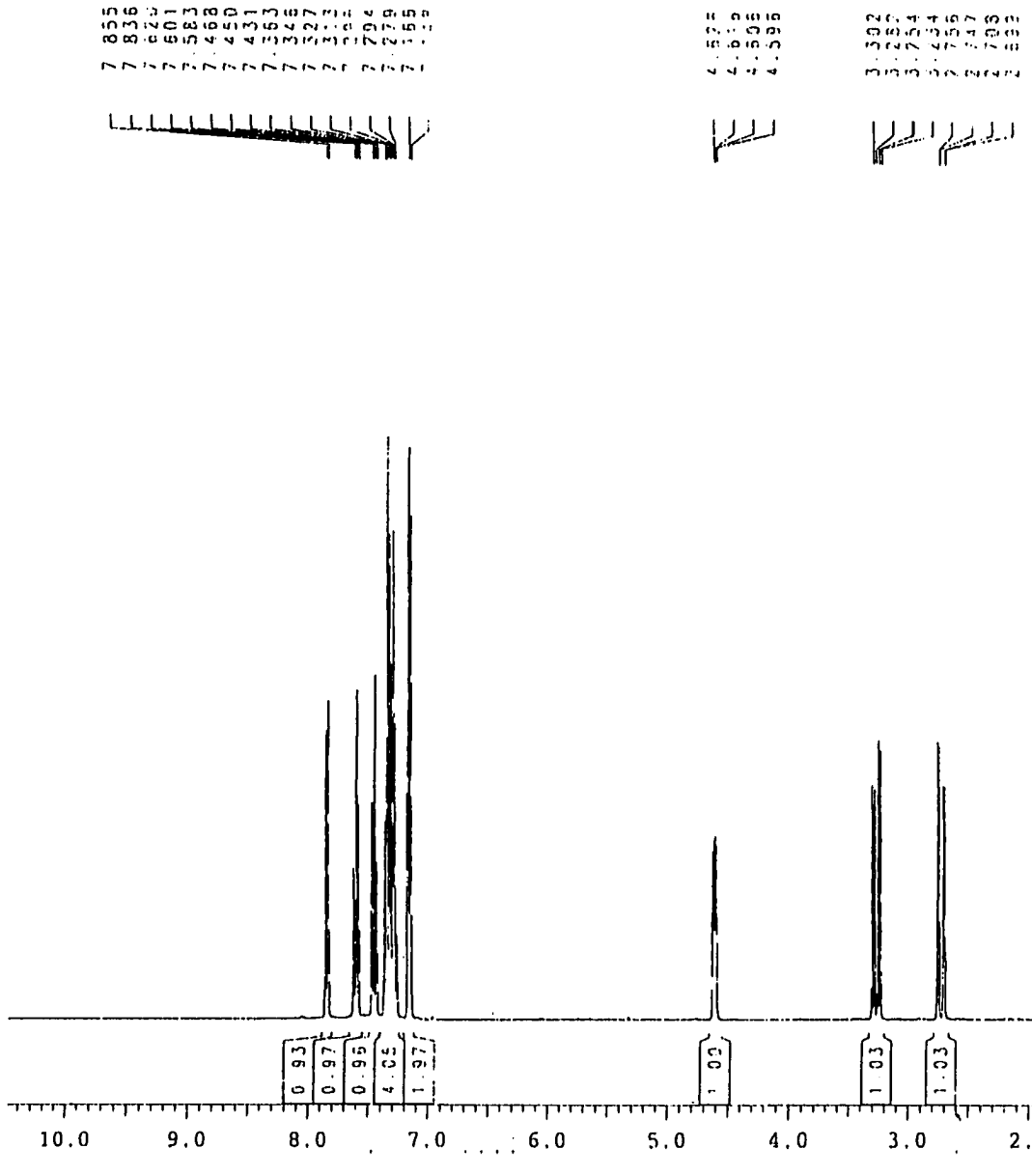
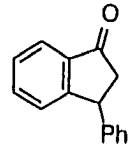

7.174
6.887
3.960
3.899
3.060
3.047
3.033
2.683
2.669
2.655
MeO
MeO
O
5,6-Dimethoxyindan-1-one
1.00
0.99
3.15
3.25
2.11
2.08
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm
/drx1/data/gagnier/nmr/svg.1013/2/pdata/1 gagnier Thu Aug 10 14:24:48 2000

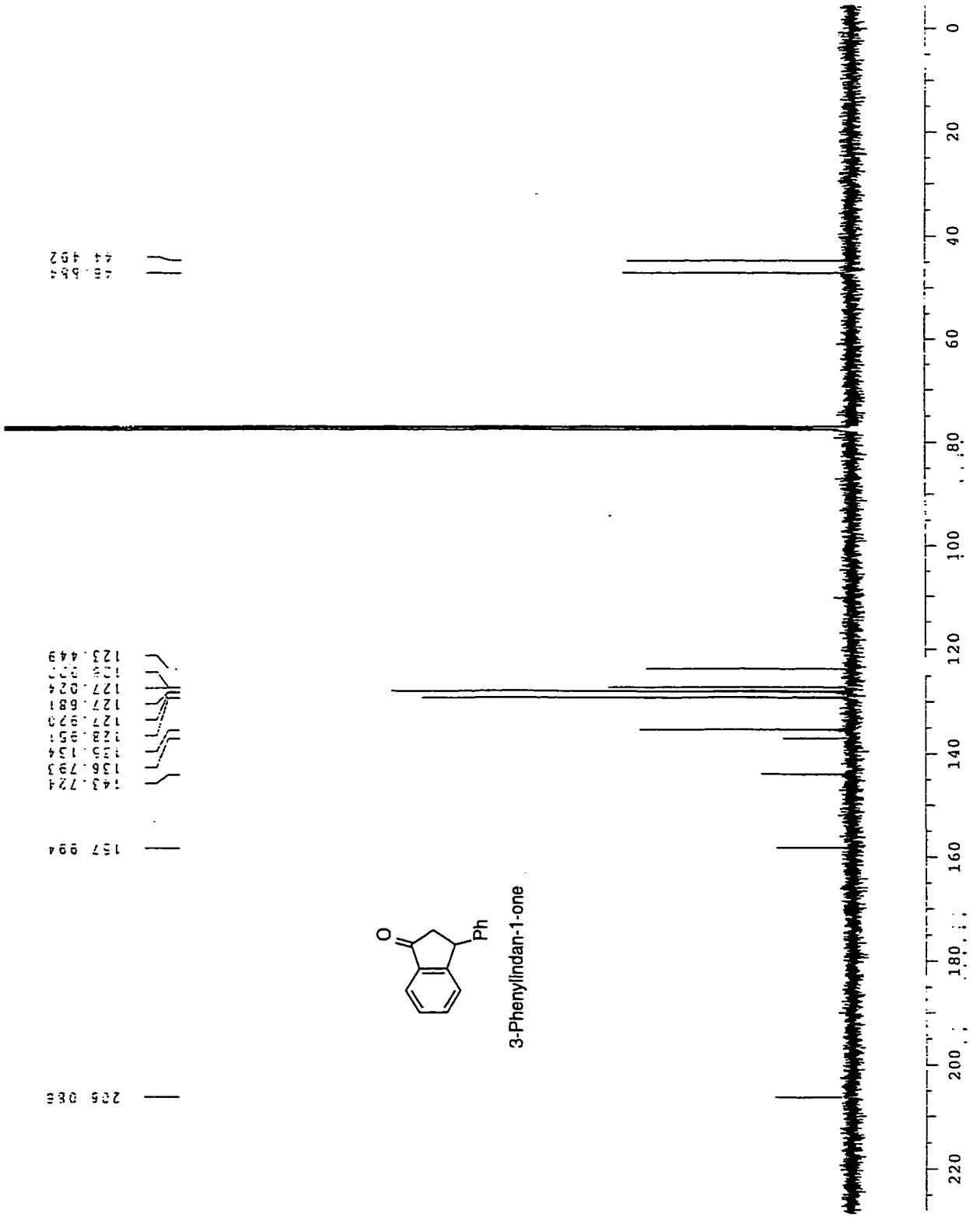


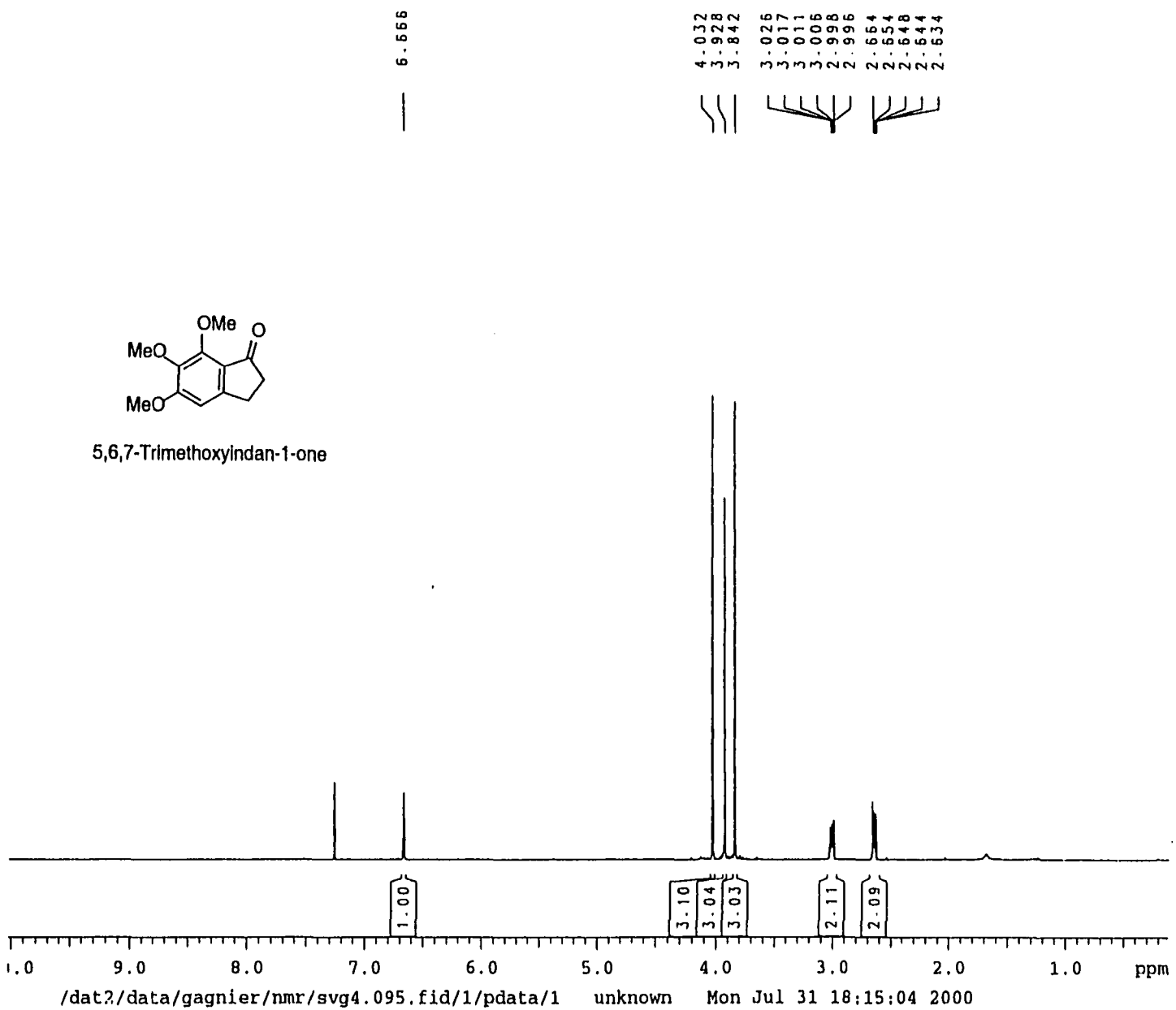

5,6-Dimethoxyindan-1-one

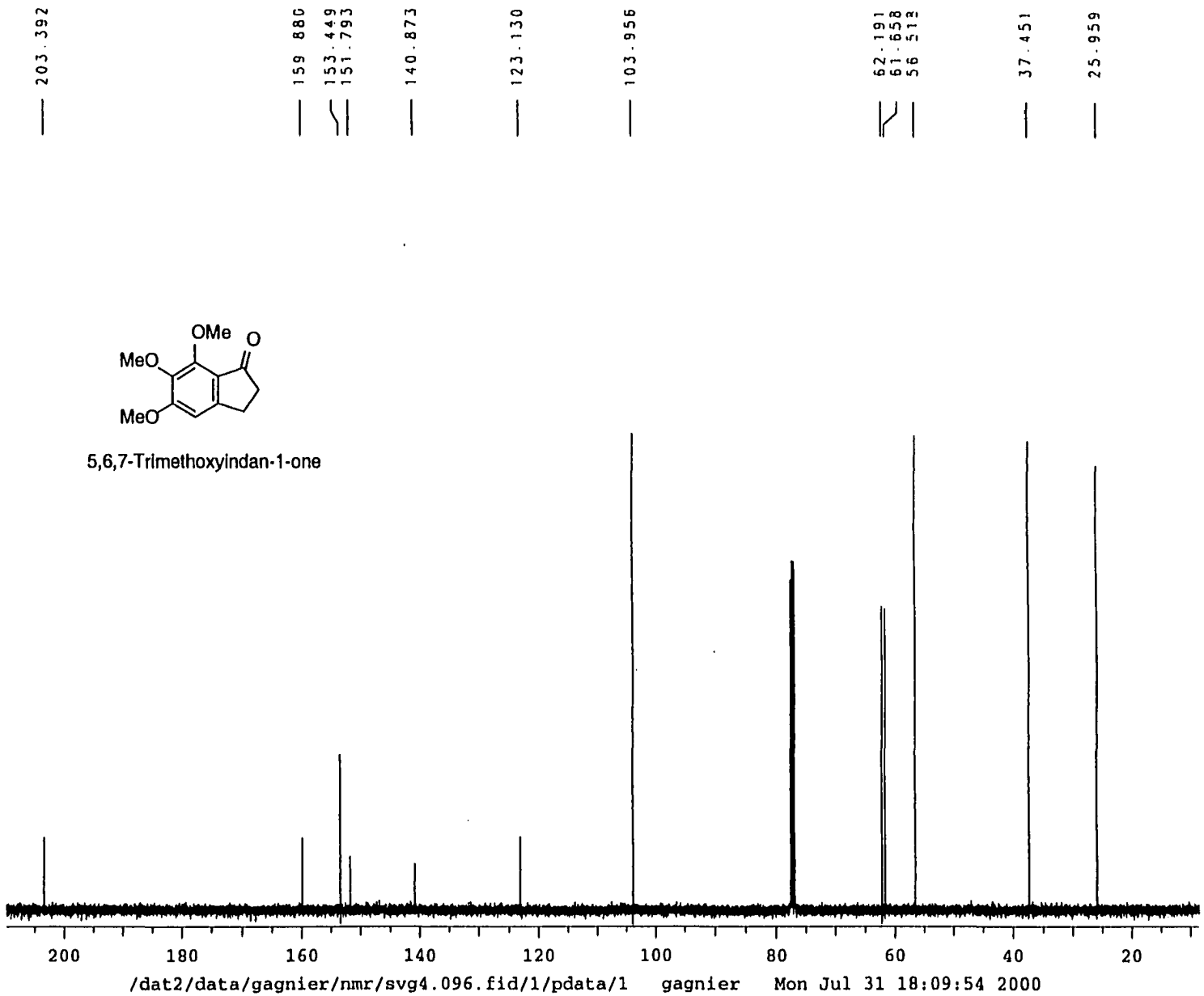


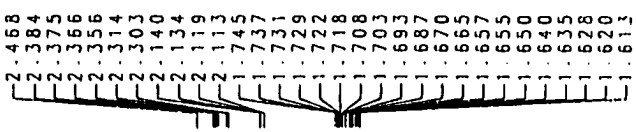



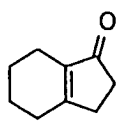

3-Phenylindan-1-one


44.492
46.664
123.449
125.999
127.024
127.681
127.979
128.951
135.154
136.793
143.724
157.994
206.986
O
Ph
3-Phenylindan-1-one
0
20
40
60
80
100
120
140
160
180
200
220

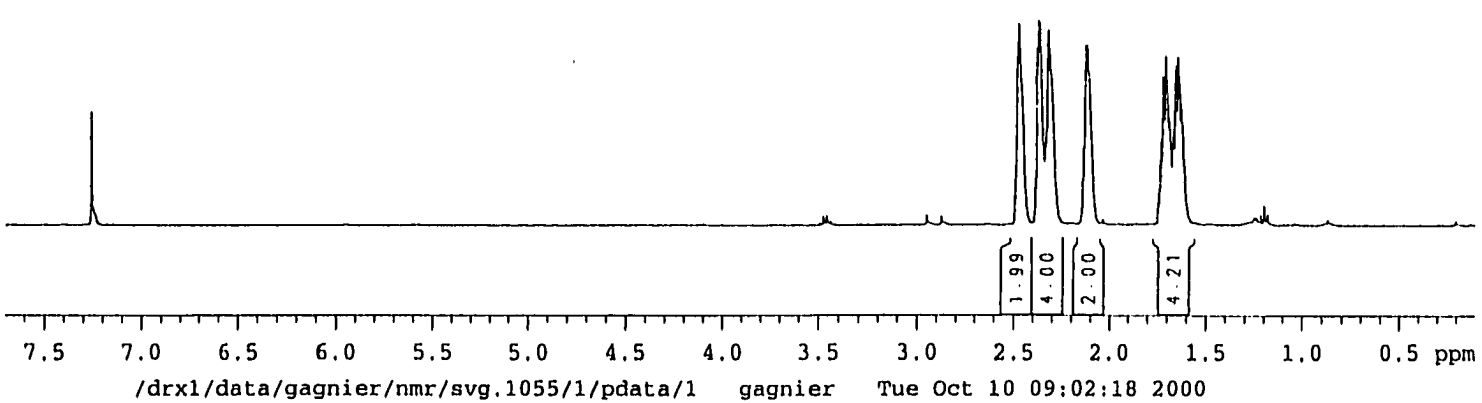

6.666
4.032
3.928
3.842
3.026
3.017
3.011
3.006
2.998
2.996
2.664
2.654
2.648
2.644
2.634
OMe
O
MeO
MeO
5,6,7-Trimethoxyindan-1-one
1.00
3.10
3.04
3.03
2.11
2.09
1.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm
/dat2/data/gagnier/nmr/svg4.095.fid/1/pdata/1 unknown Mon Jul 31 18:15:04 2000

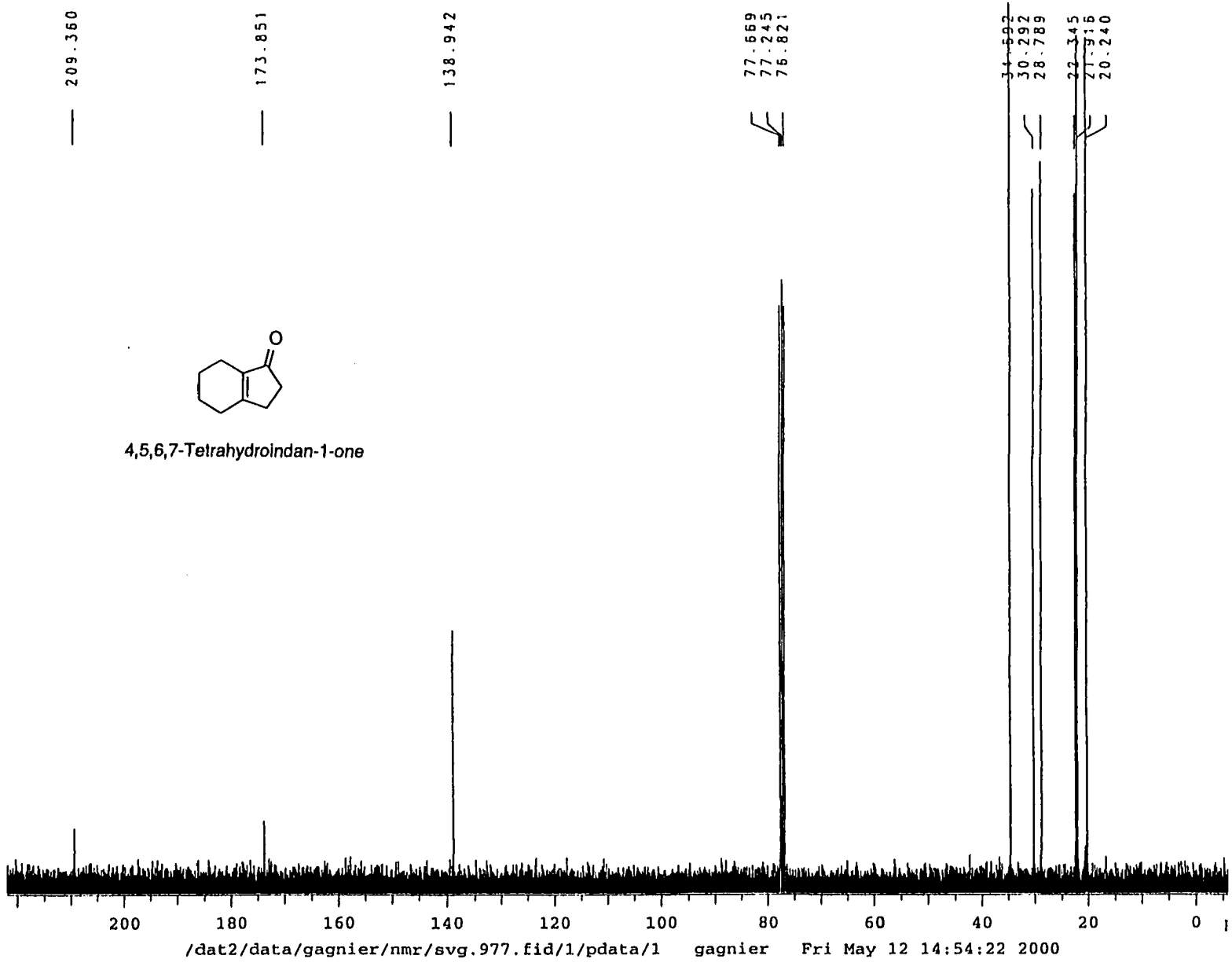

203.392
159.880
153.449
151.793
140.873
123.130
103.956
62.191
61.658
56.512
37.451
25.959
OMe
O
MeO
MeO
5,6,7-Trimethoxyindan-1-one
200
180
160
140
120
100
80
60
40
20
/dat2/data/gagnier/nmr/svg4.096.fid/1/pdata/1 gagnier Mon Jul 31 18:09:54 2000

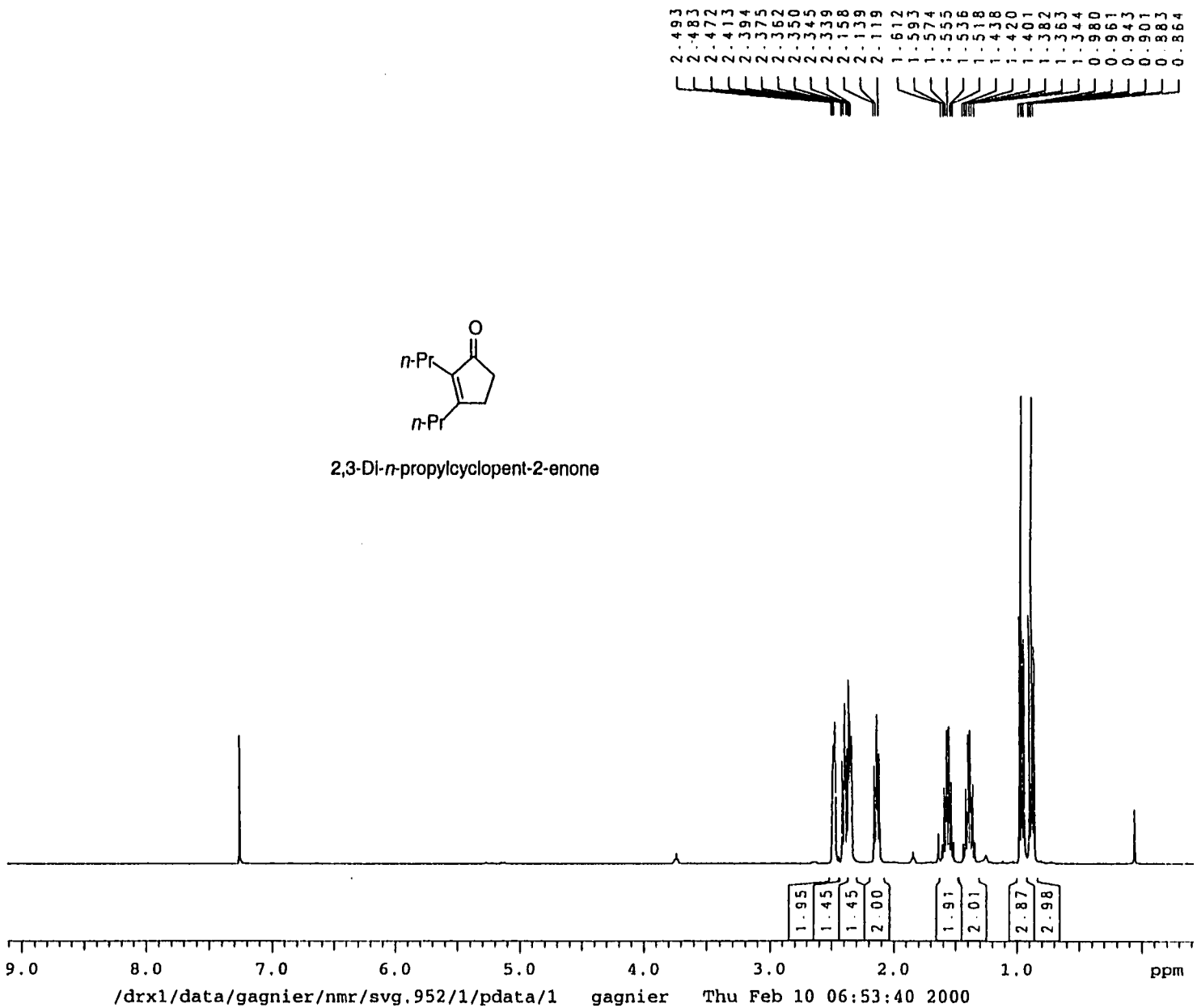


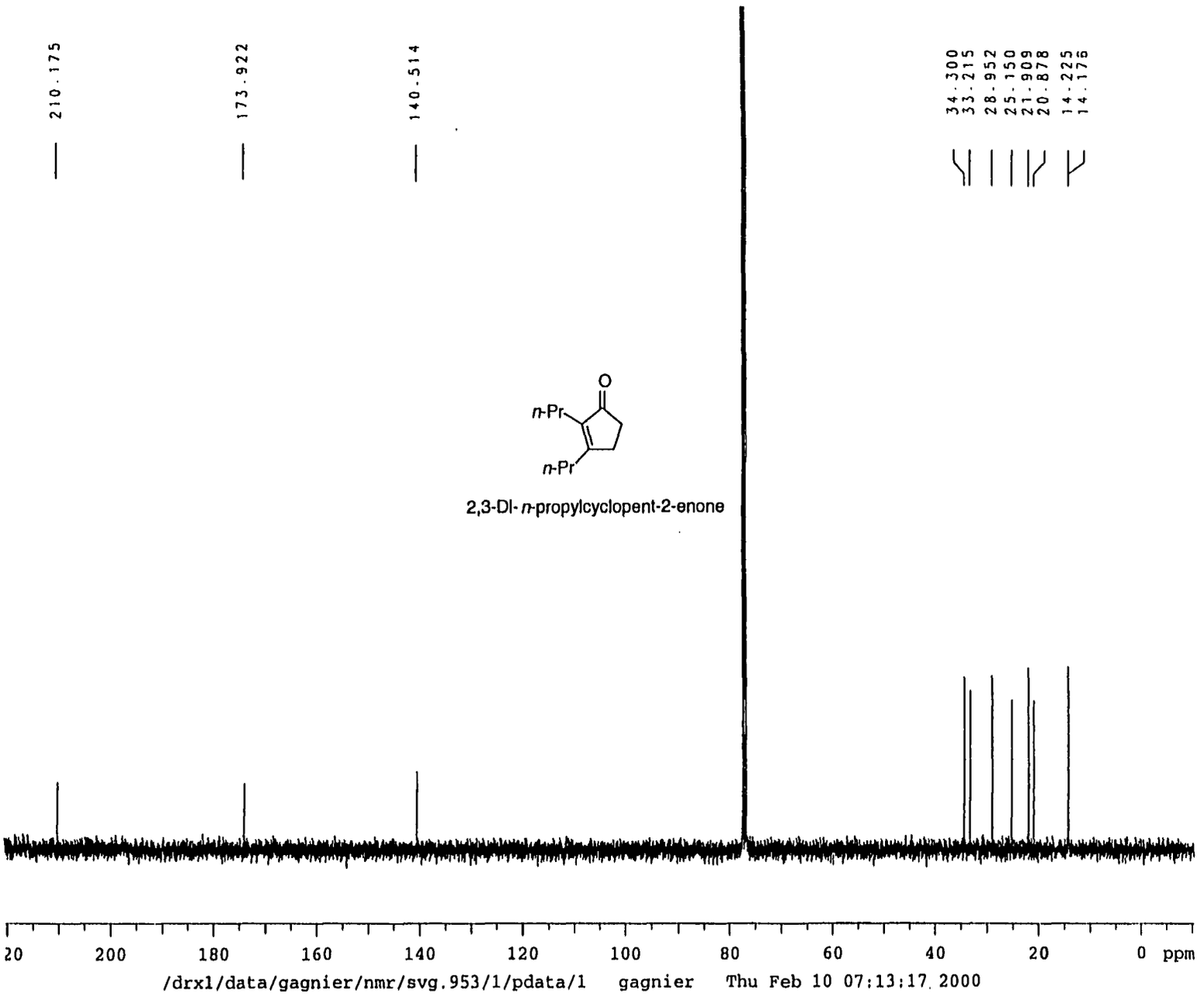



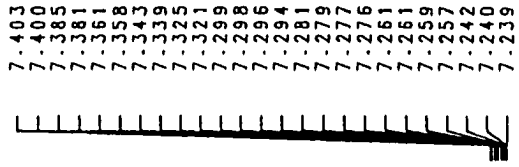

4,5,6,7-Tetrahydroindan-1-one

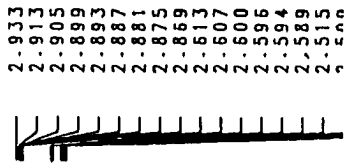


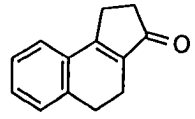

209.360
173.851
138.942
77.669
77.245
76.821
31.592
30.292
28.789
22.345
21.916
20.240
O
4,5,6,7-Tetrahydroindan-1-one
200
180
160
140
120
100
80
60
40
20
0
/dat2/data/gagnier/nmr/svg.977.fid/1/pdata/1 gagnier Fri May 12 14:54:22 2000


2.493
2.483
2.472
2.413
2.394
2.375
2.362
2.350
2.345
2.339
2.158
2.139
2.119
1.612
1.593
1.574
1.555
1.536
1.518
1.438
1.420
1.401
1.382
1.363
1.344
0.980
0.961
0.943
0.901
0.883
0.864
O
n-Pr
n-Pr
2,3-Di-n-propylcyclopent-2-enone
1.95
1.45
1.45
2.00
1.91
2.01
2.87
2.98
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm
/drx1/data/gagnier/nmr/svg.952/1/pdata/1 gagnier Thu Feb 10 06:53:40 2000

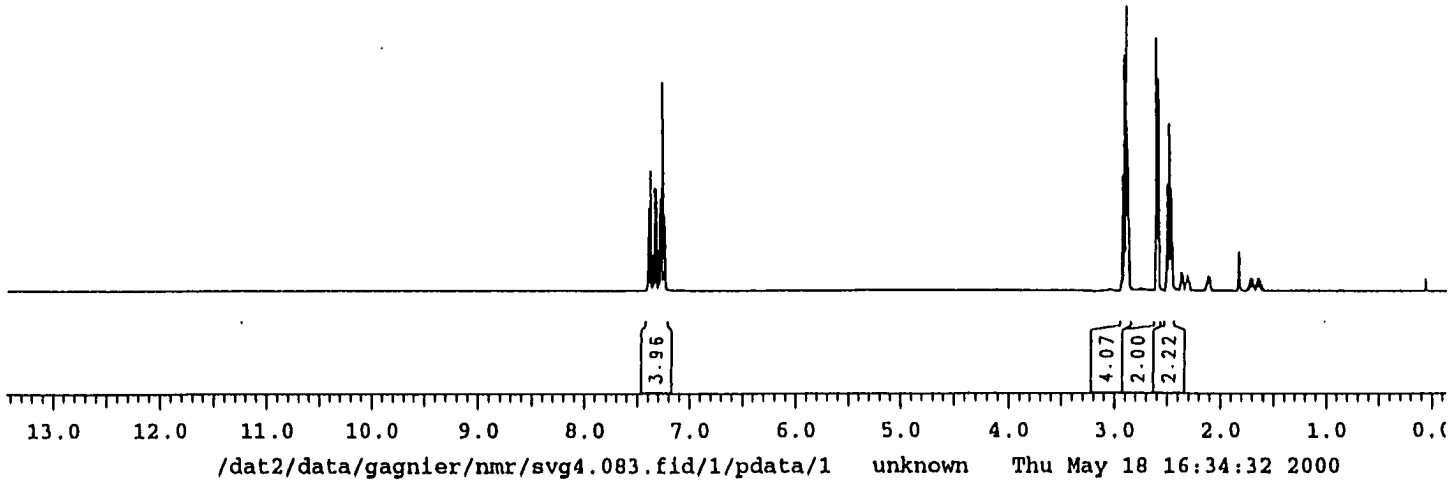

210.175
173.922
140.514
34.300
33.215
28.952
25.150
21.909
20.878
14.225
14.176
O
n-Pr
n-Pr
2,3-Di-n-propylcyclopent-2-enone
20
200
180
160
140
120
100
80
60
40
20
0 ppm
/drx1/data/gagnier/nmr/svg.953/1/pdata/1 gagnier Thu Feb 10 07:13:17 2000




1,2,4,5-Tetrahydrocyclopenta[*a*]naphthalen-3-one



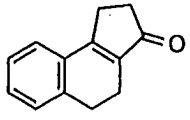
166.143

138.832
137.870
132.219
131.019
128.448
127.044
124.389

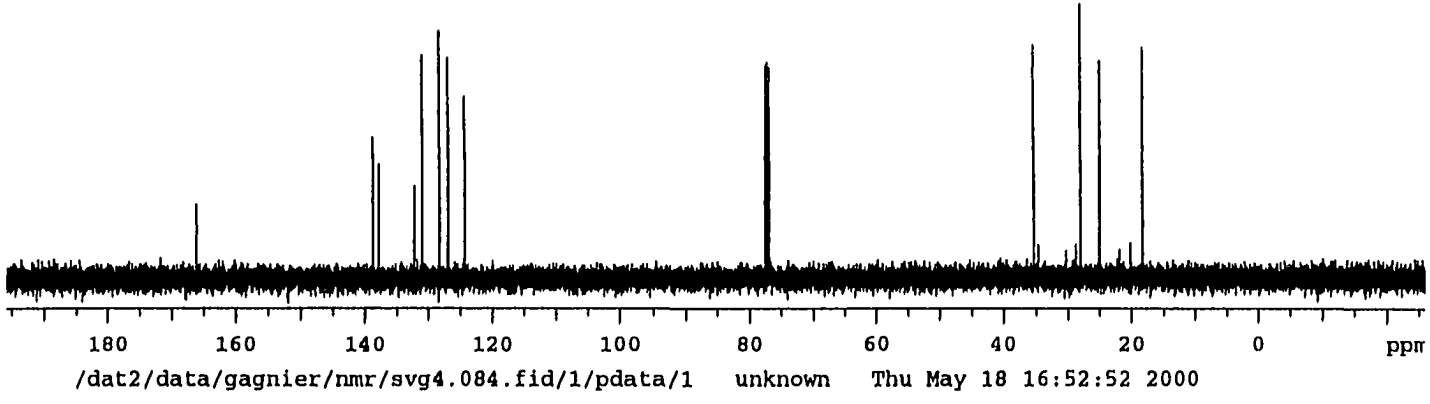
35.498

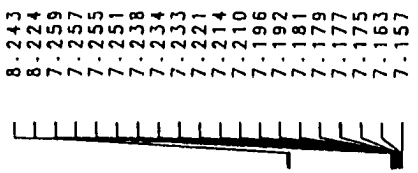
28.162
25.160

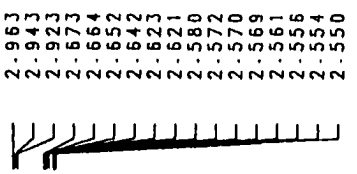
18.392

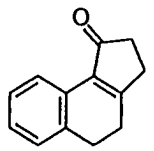



1,2,4,5-Tetrahydrocyclopenta[*a*]naphthalen-3-one

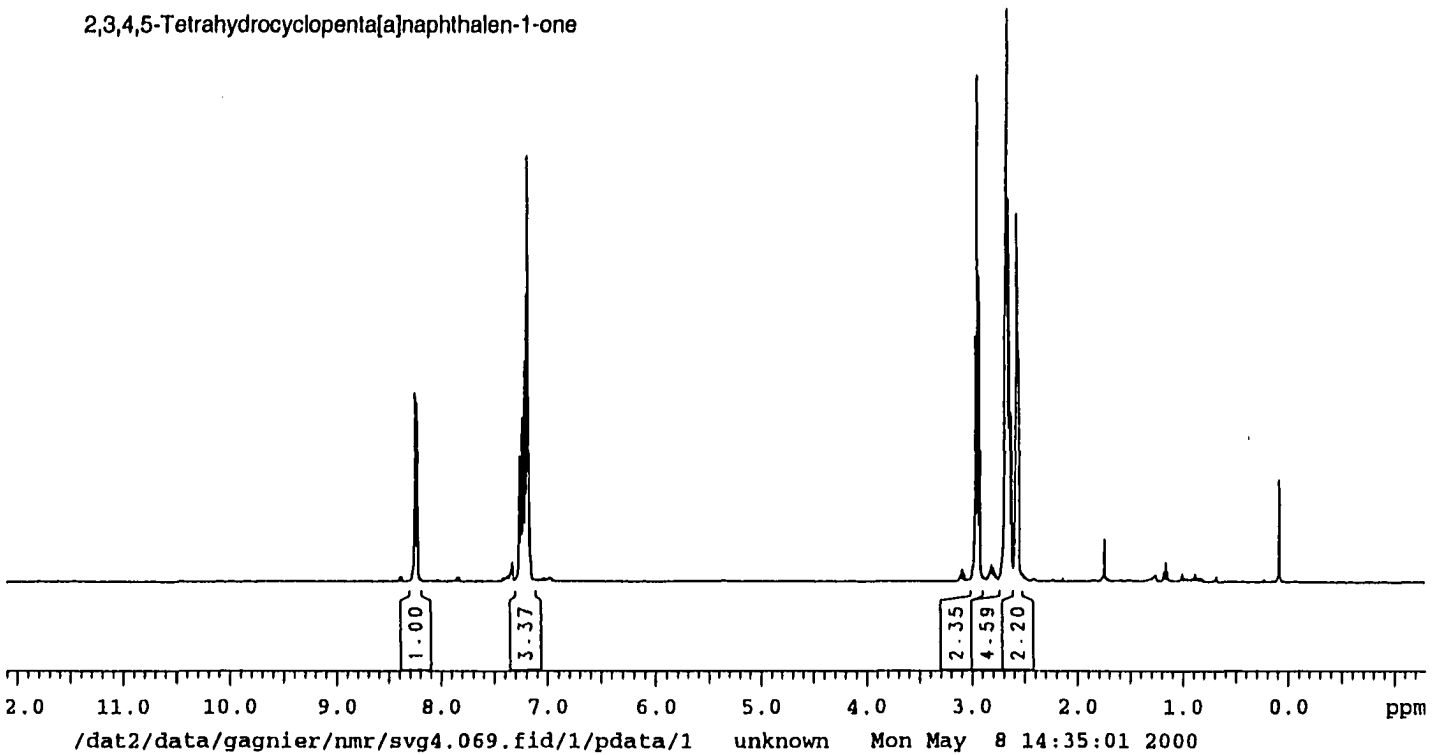





2,3,4,5-Tetrahydrocyclopenta[a]naphthalen-1-one

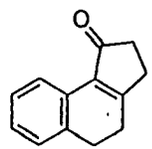


175.322

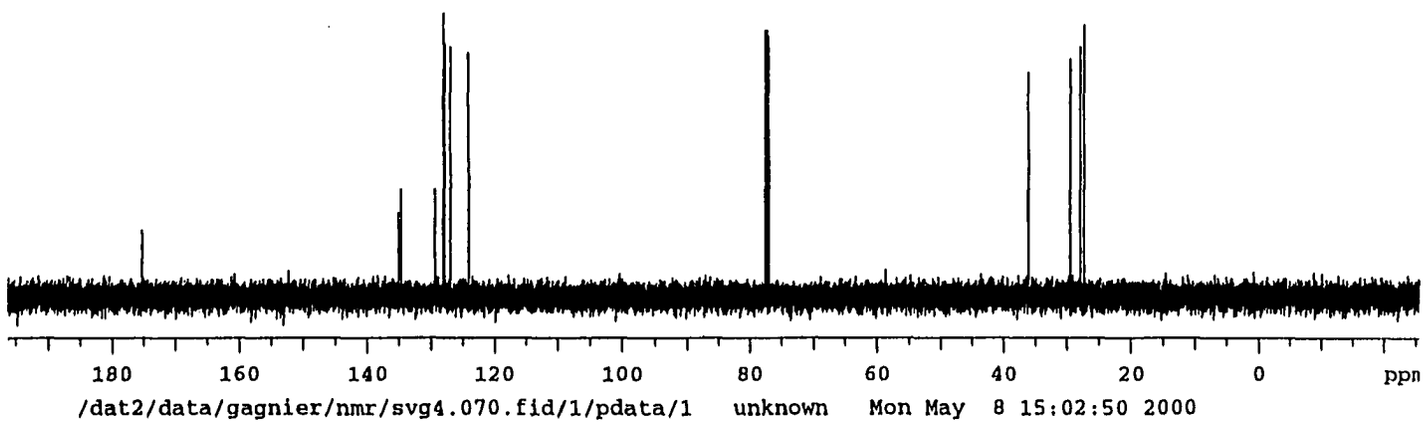
135.087
134.654
129.343
128.016
127.759
126.942
124.126

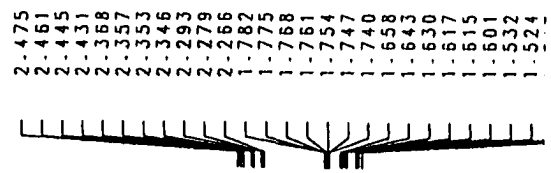
36.126

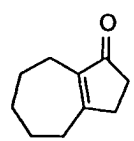
29.494
27.852
27.294



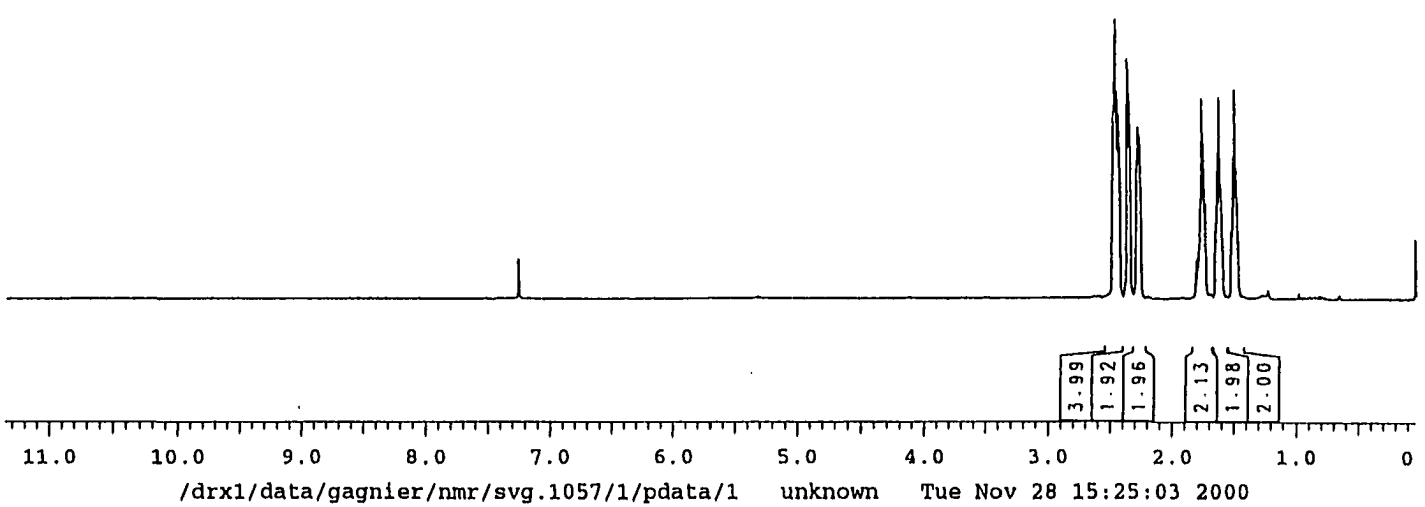
2,3,4,5-Tetrahydrocyclopenta[a]naphthalen-1-one

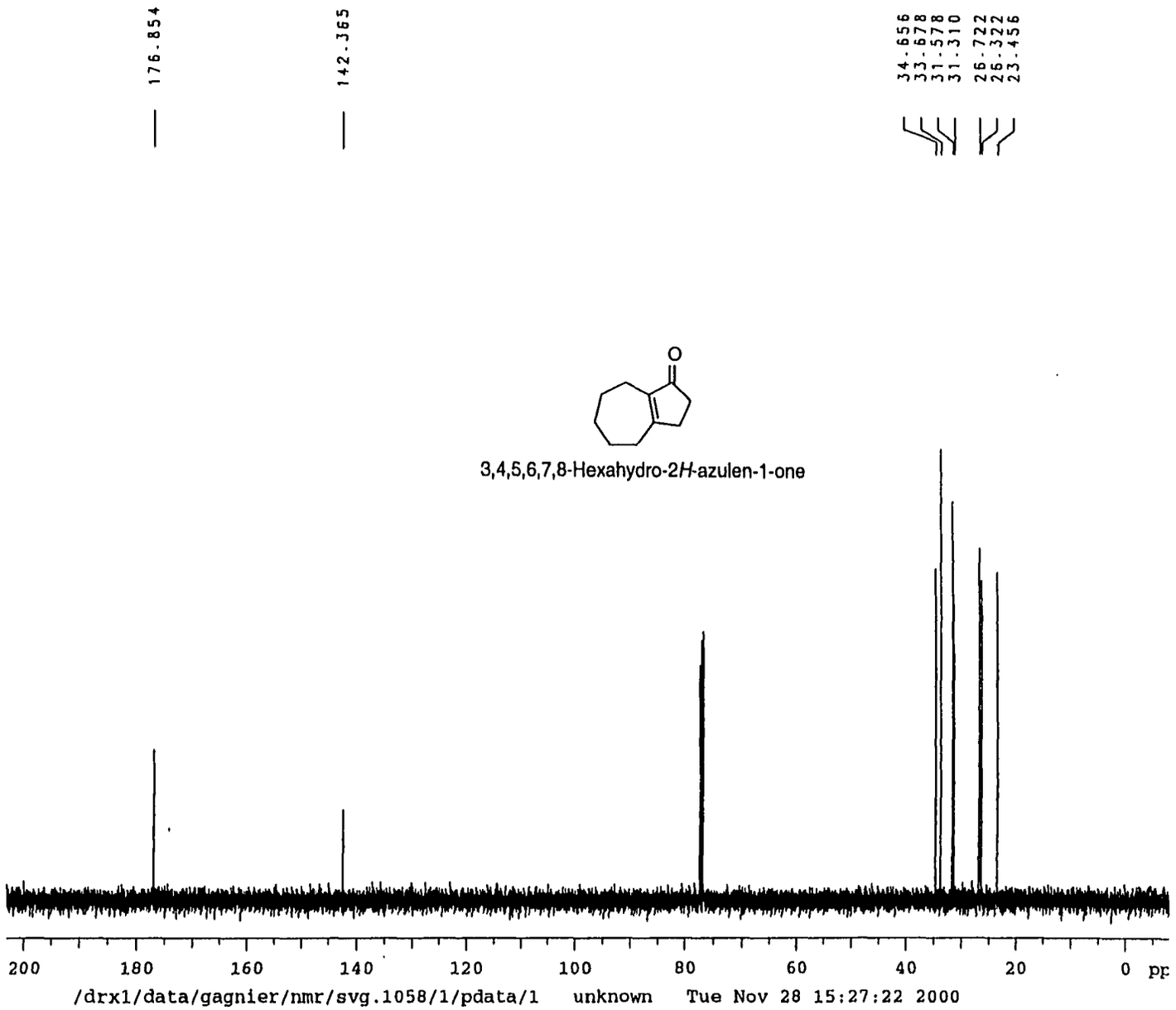


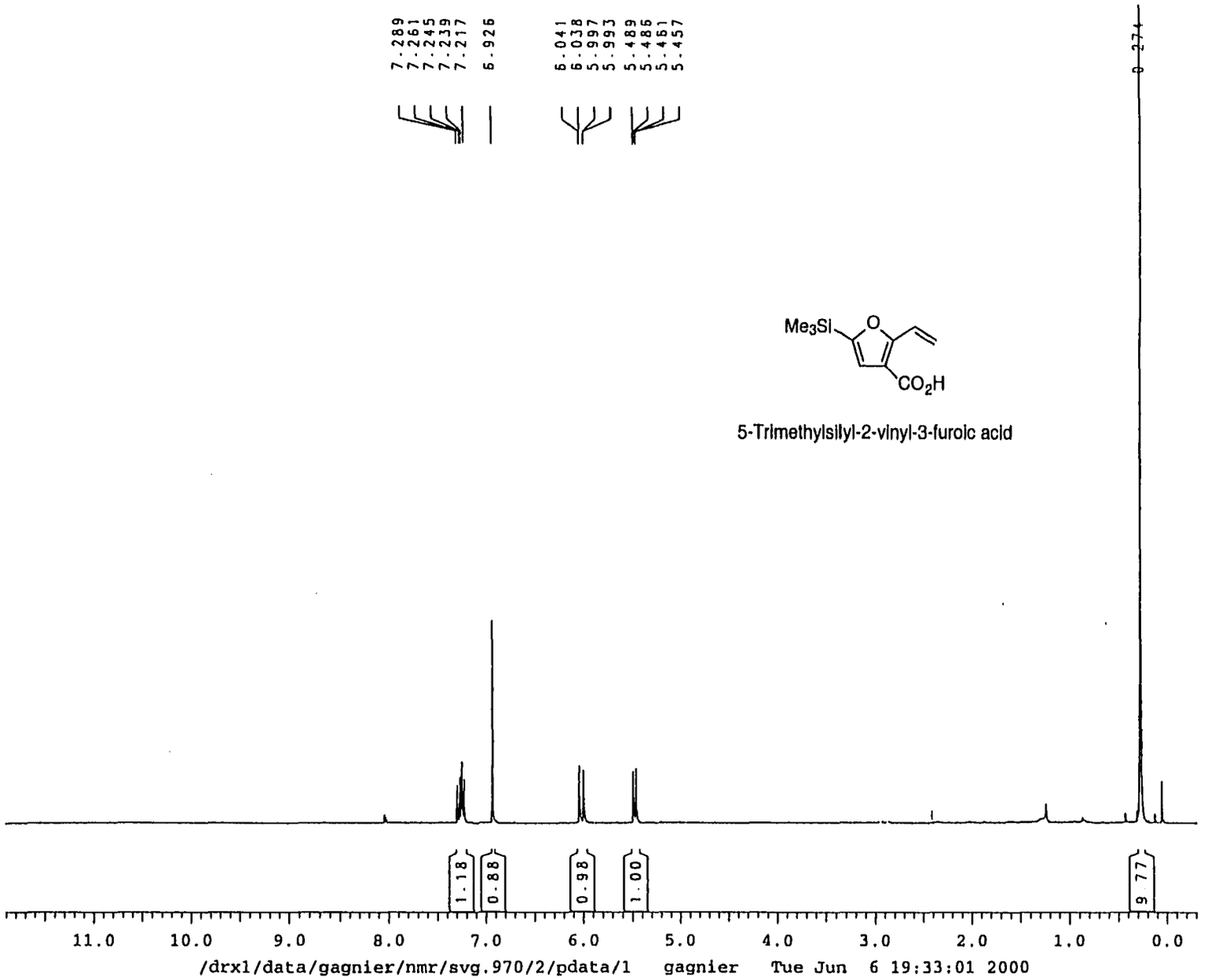



3,4,5,6,7,8-Hexahydro-2*H*-azulen-1-one




176.854
142.365
34.656
33.678
31.578
31.310
26.722
26.322
23.456
O
3,4,5,6,7,8-Hexahydro-2H-azulen-1-one
200
180
160
140
120
100
80
60
40
20
0
/drx1/data/gagnier/nmr/svg.1058/1/pdata/1 unknown Tue Nov 28 15:27:22 2000


7.289
7.261
7.245
7.239
7.217
6.926
6.041
6.038
5.997
5.993
5.489
5.486
5.461
5.457
0.274
Me3Si
O
CO2H
5-Trimethylsilyl-2-vinyl-3-furoic acid
1.18
0.88
0.98
1.00
9.77
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
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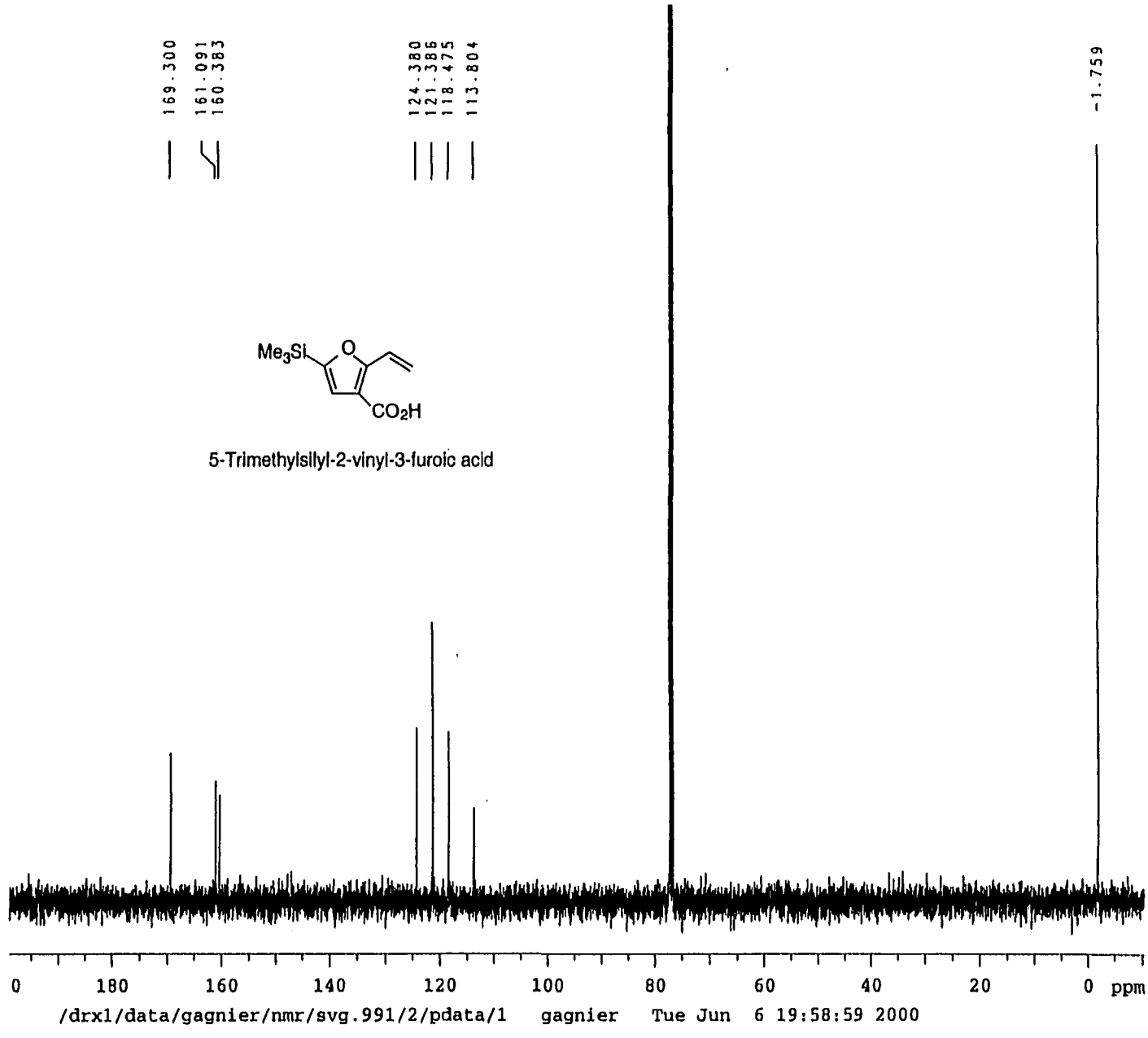
169.300
161.091
160.383
124.380
121.386
118.475
113.804
-1.759
Me3Si
O
CO2H
5-Trimethylsilyl-2-vinyl-3-furoic acid
0
180
160
140
120
100
80
60
40
20
0 ppm
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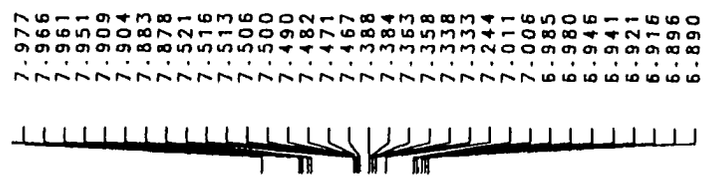
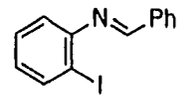
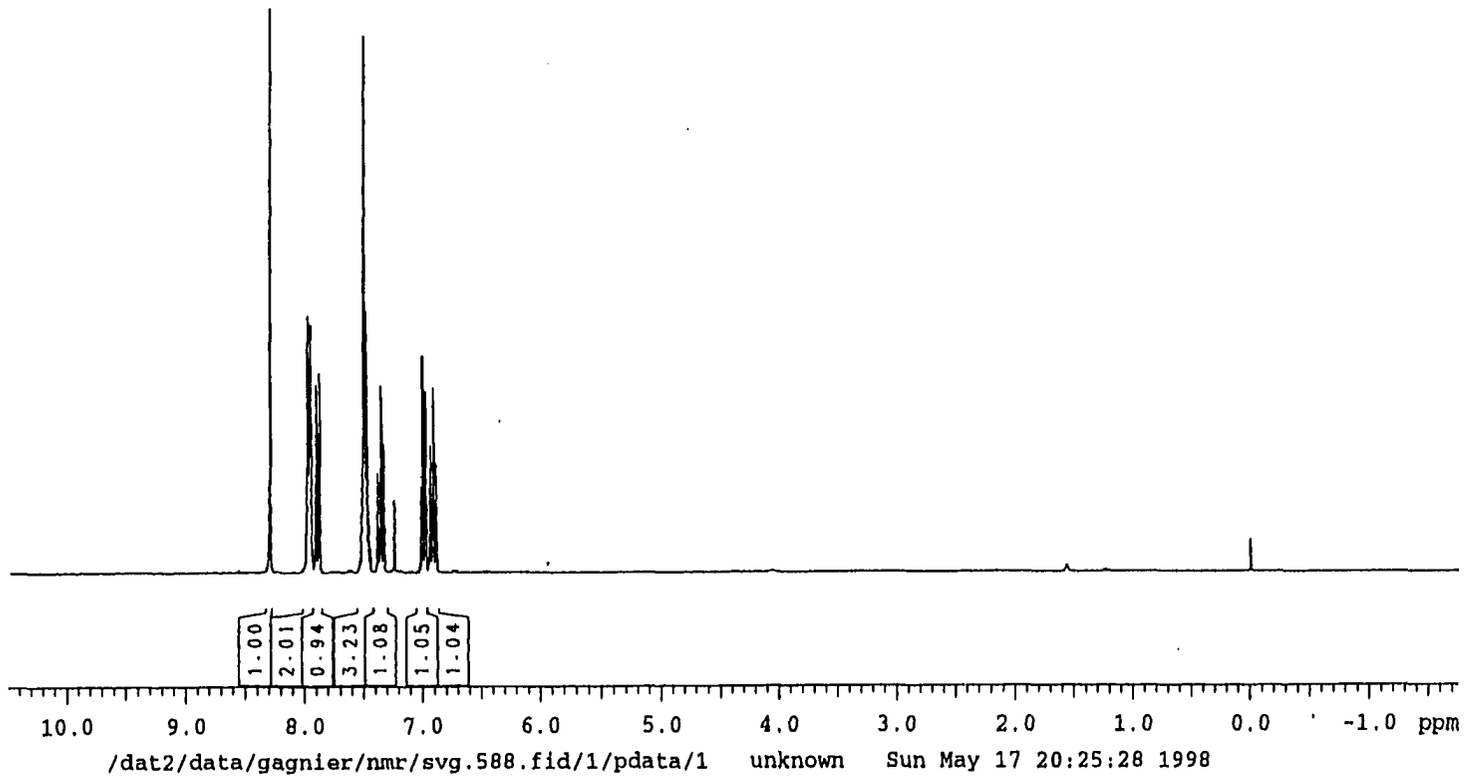
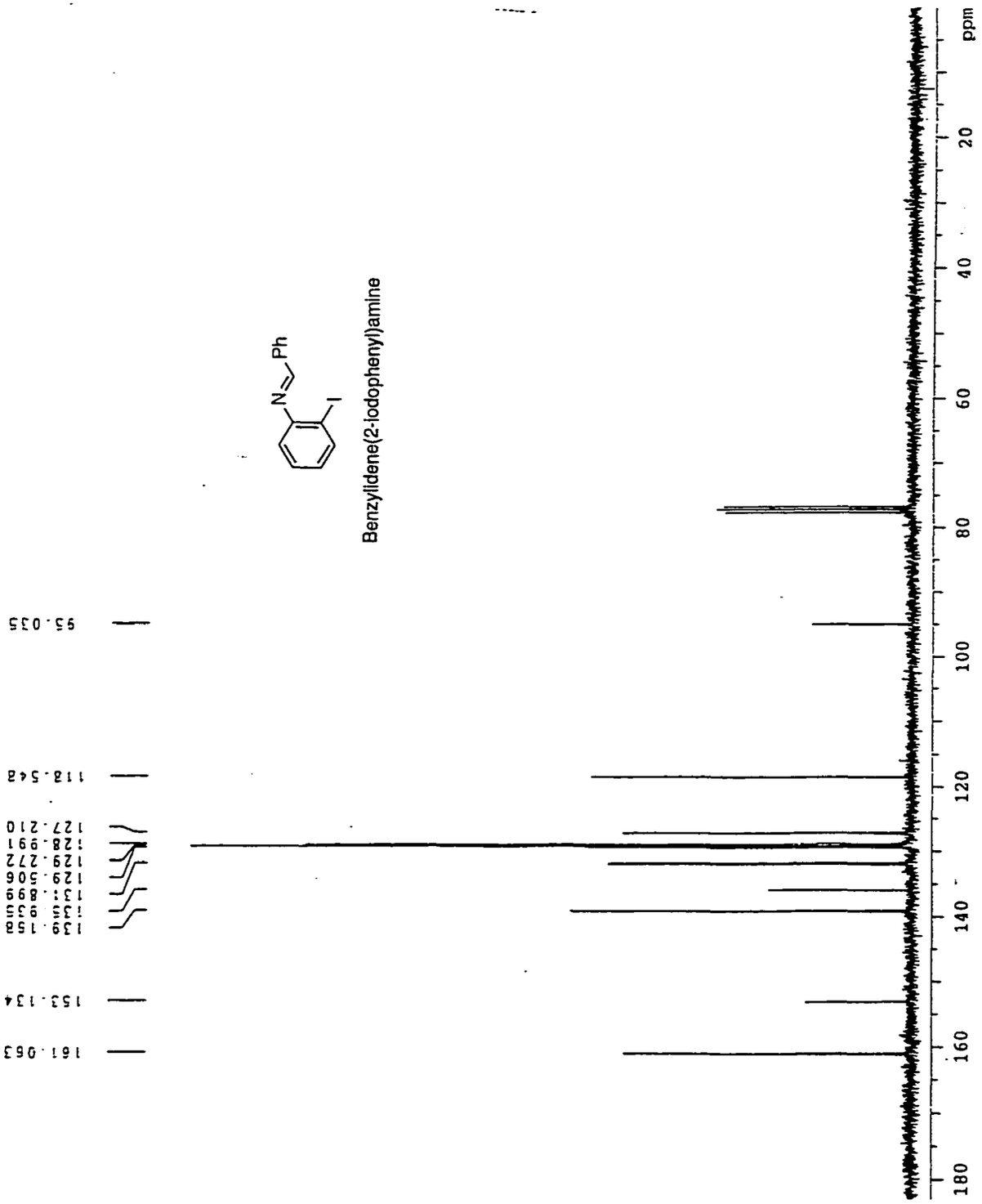
# APPENDIX C. CHAPTER 3 $^{1}H$ AND $^{13}C$ NMR SPECTRA

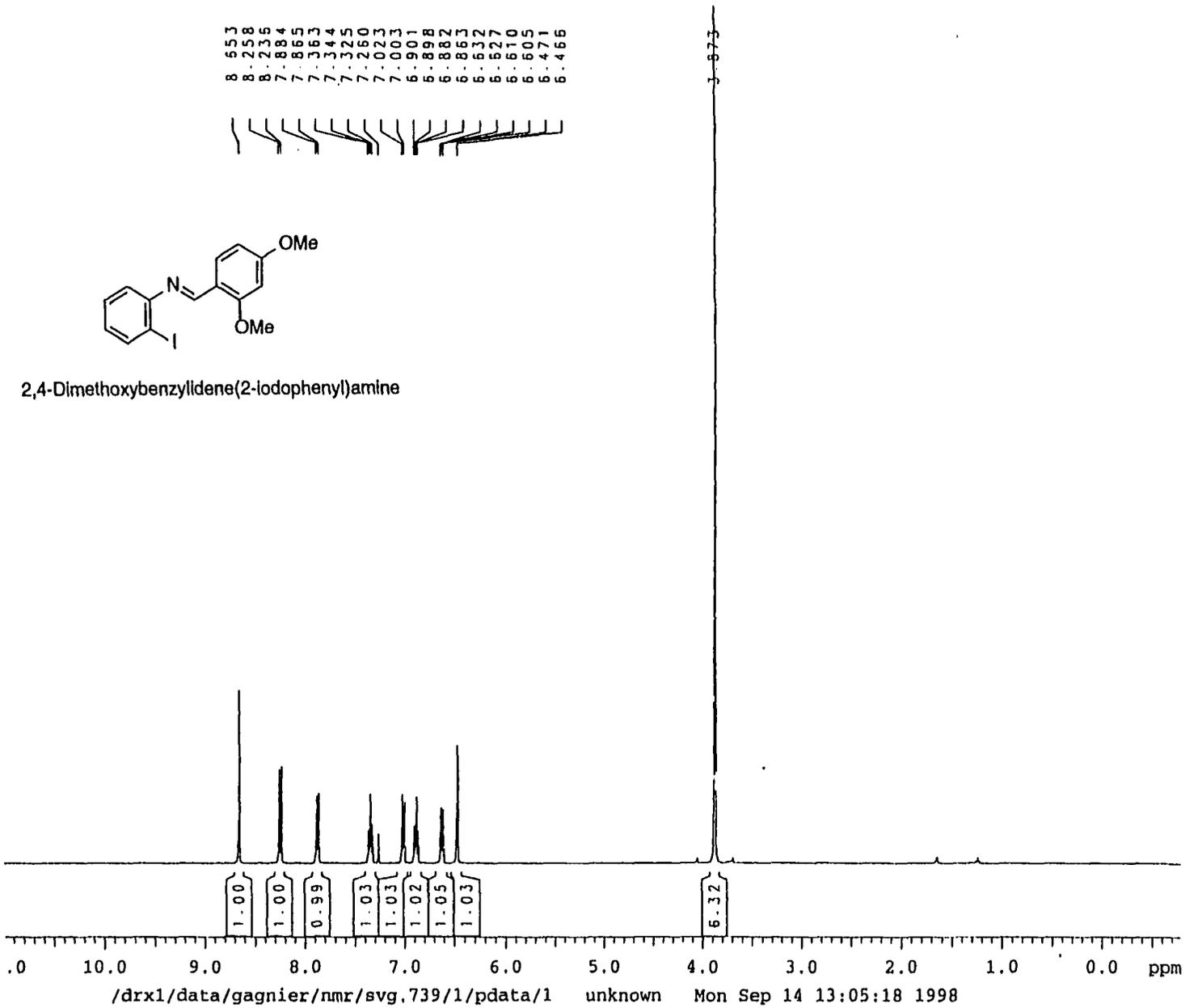


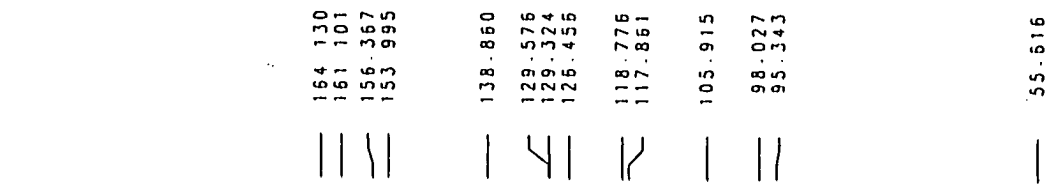

Benzylidene(2-iodophenyl)amine

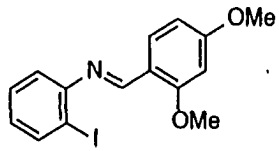



Benzylidene(2-iodophenyl)amine
N
Ph
I
161.063
153.134
139.158
135.935
131.899
129.506
129.272
128.991
127.210
118.548
93.035
ppm
20
40
60
80
100
120
140
160
180

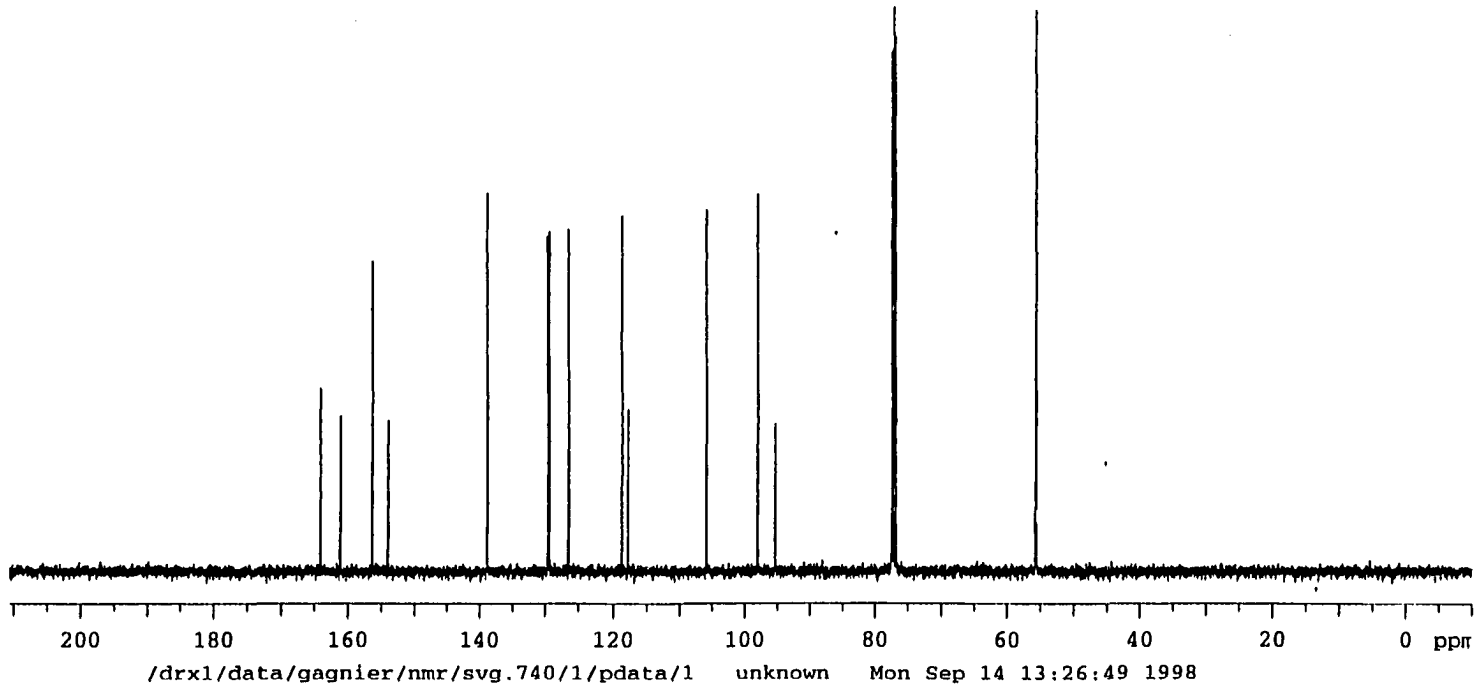


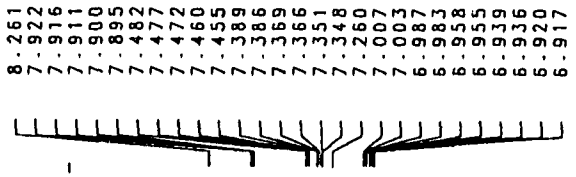

2,4-Dimethoxybenzylidene(2-iodophenyl)amine

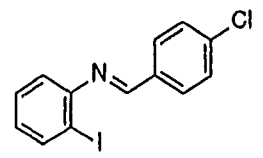


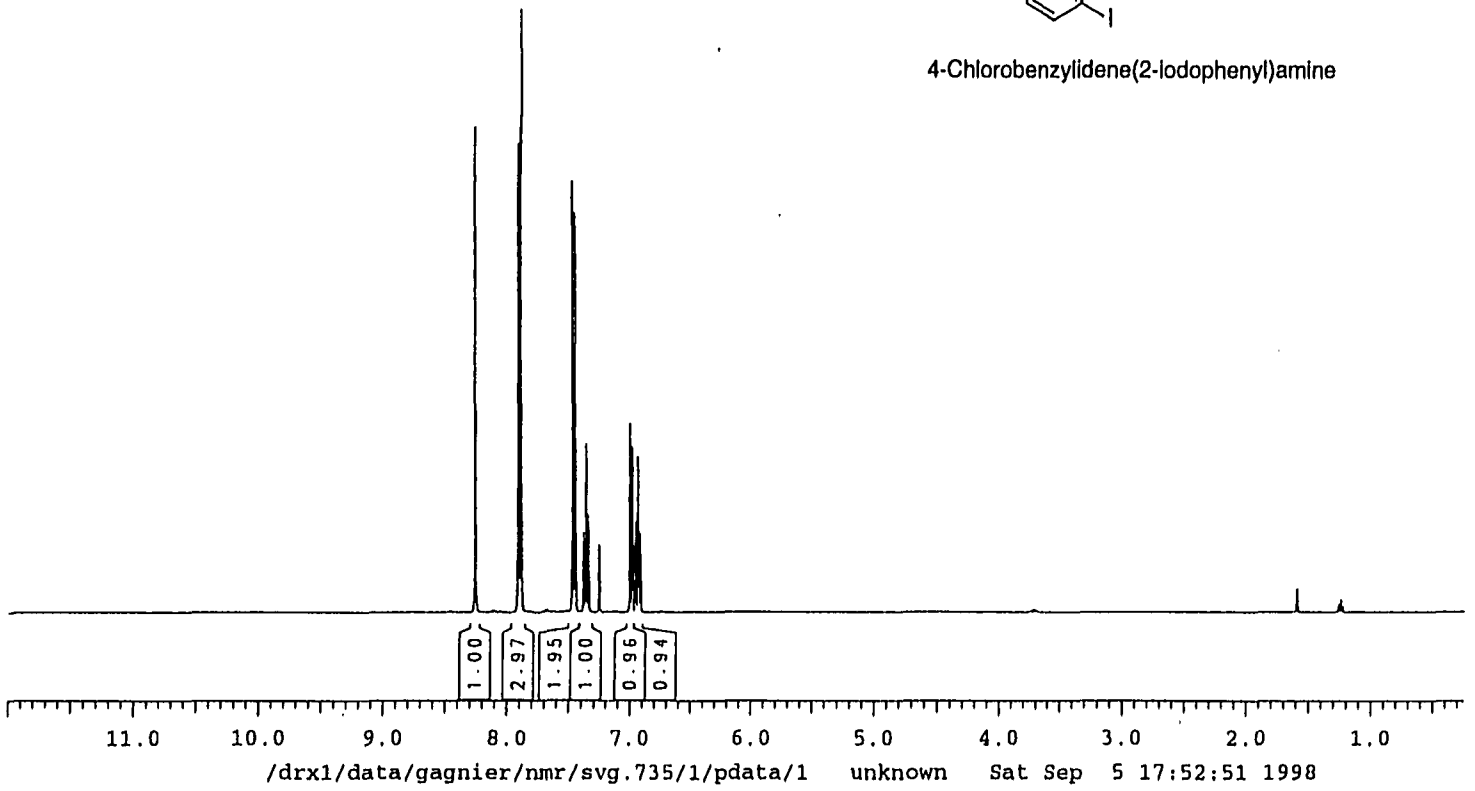

2,4-Dimethoxybenzylidene(2-iodophenyl)amine



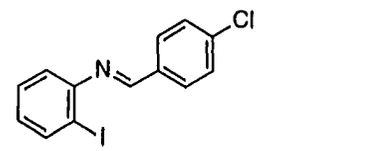


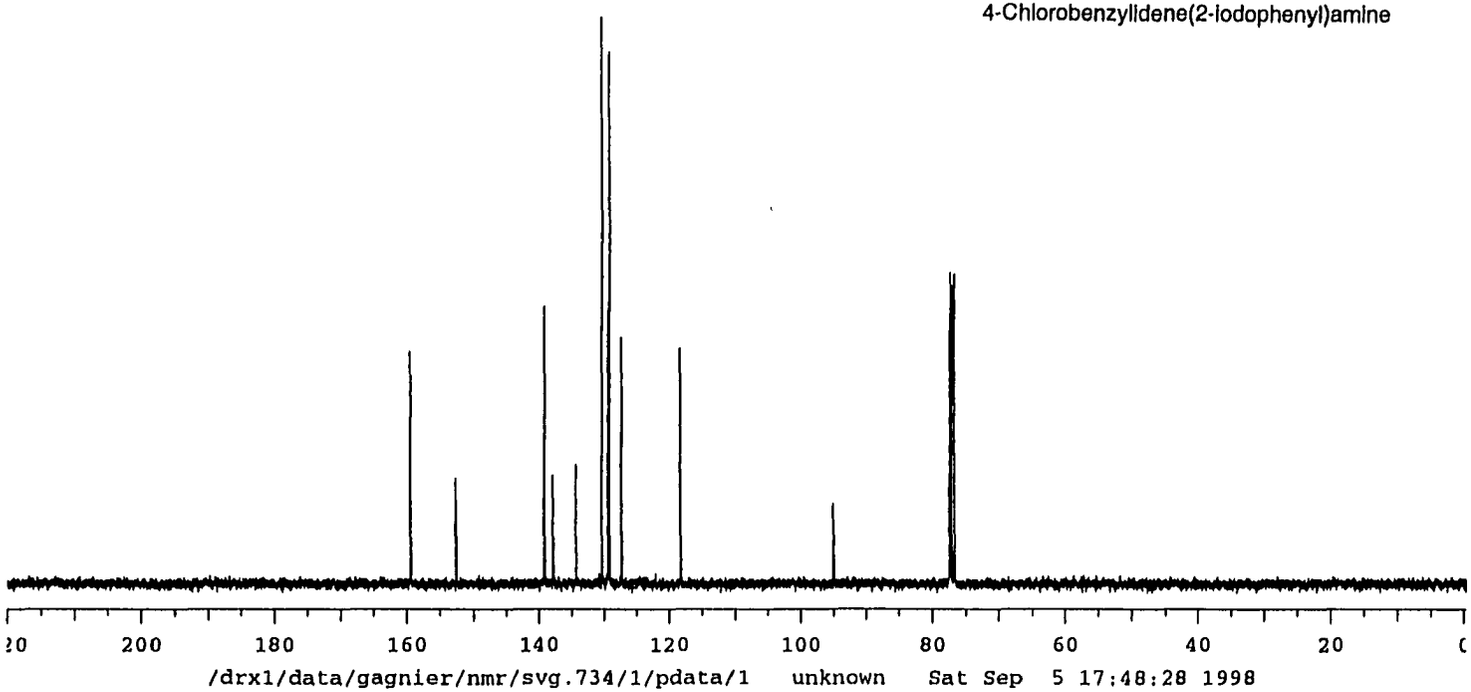

4-Chlorobenzylidene(2-Iodophenyl)amine

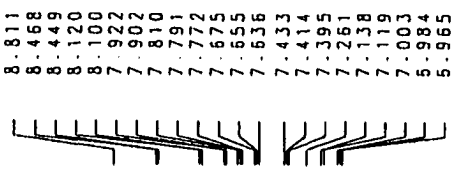


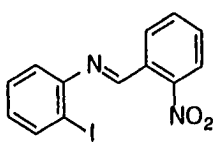
159.464
152.683
139.171
137.867
134.331
130.312
129.431
129.235
127.351
118.321
95.008



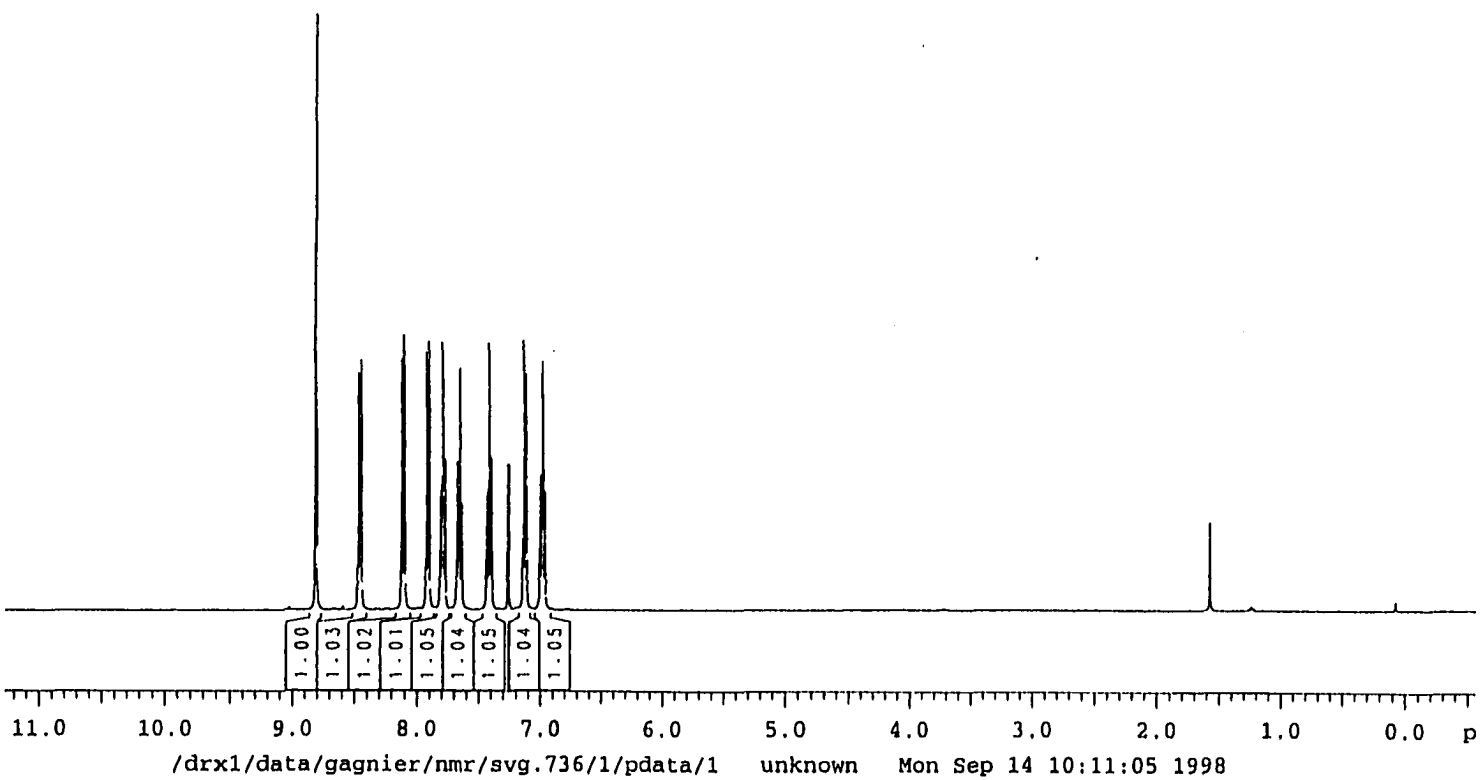

4-Chlorobenzylidene(2-iodophenyl)amine

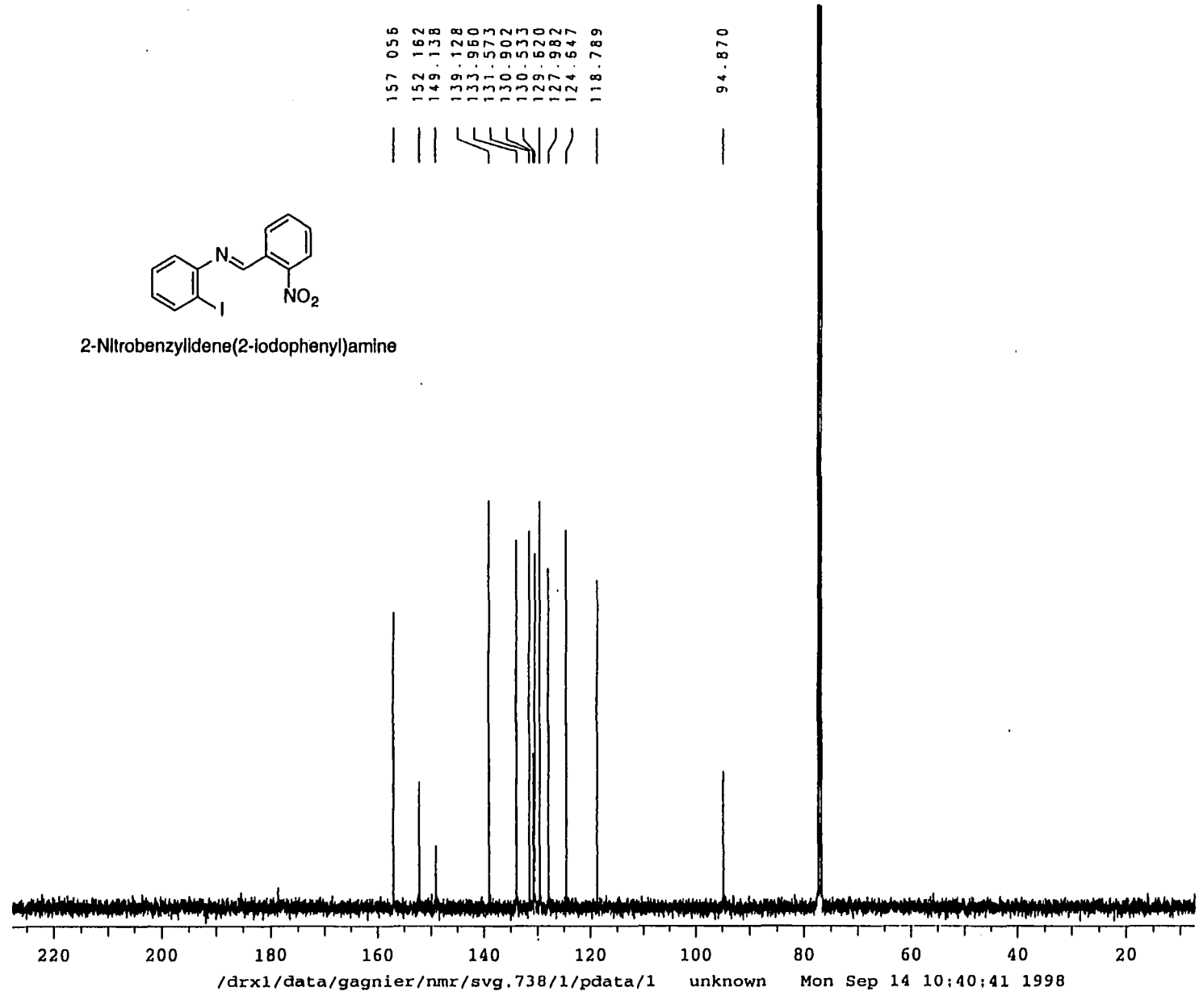




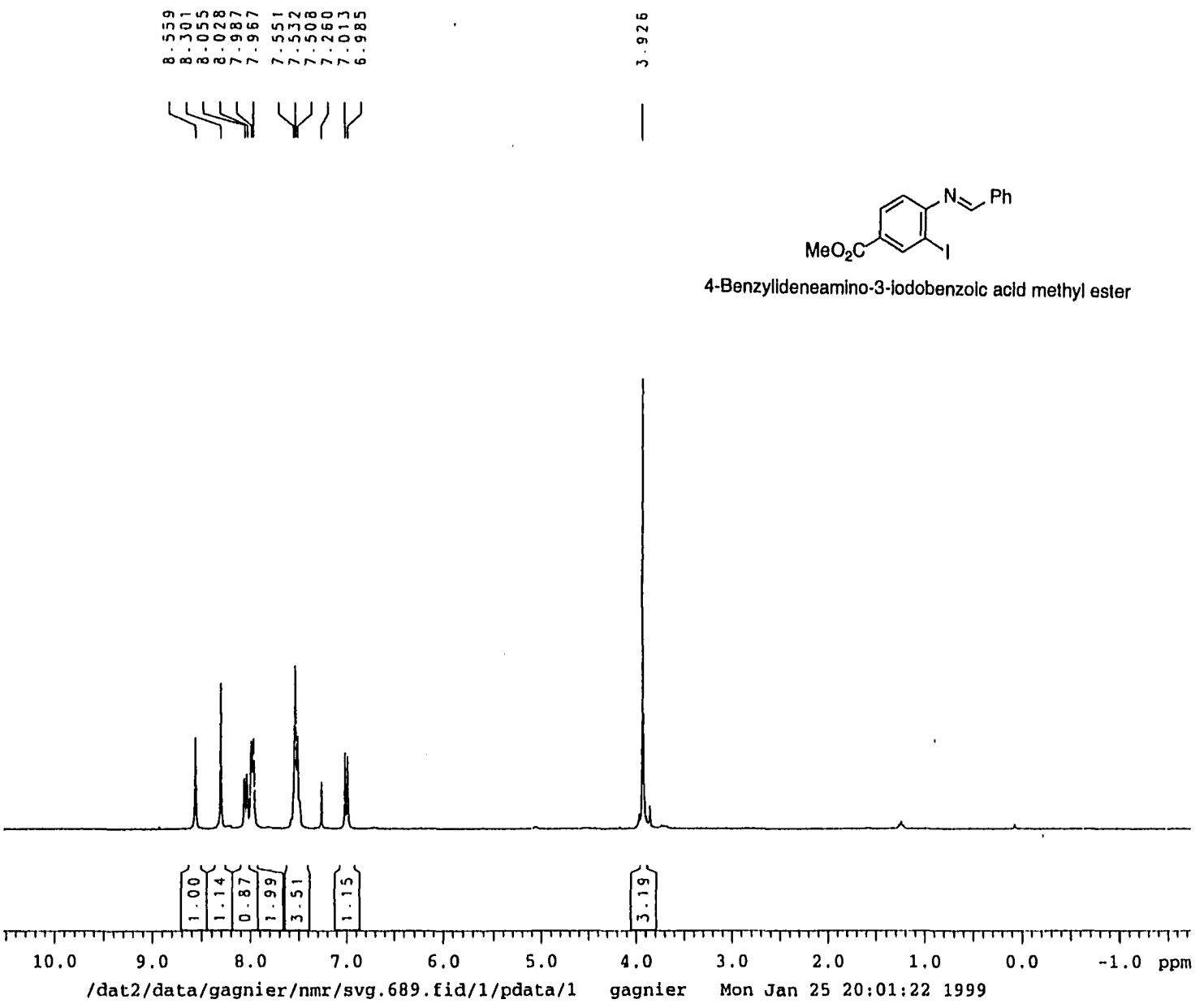




2-Nitrobenzylidene(2-iodophenyl)amine

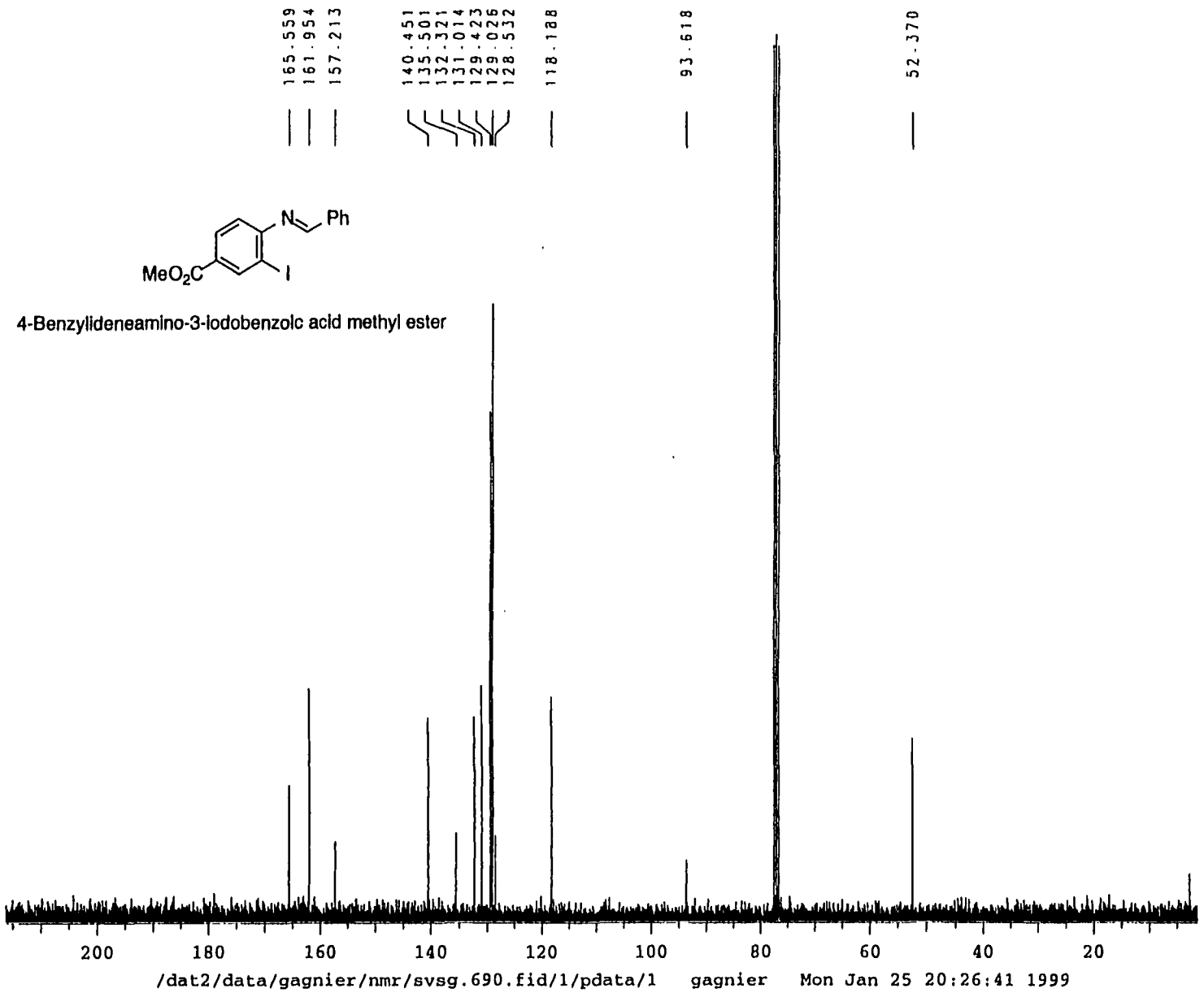





2-Nitrobenzylidene(2-iodophenyl)amine




4-Benzylideneamino-3-iodobenzoic acid methyl ester


165.559
161.954
157.213
140.451
135.501
132.321
131.014
129.423
129.026
128.532
118.188
93.618
52.370
N
Ph
MeO2C
I
4-Benzylideneamino-3-iodobenzoic acid methyl ester
200
180
160
140
120
100
80
60
40
20
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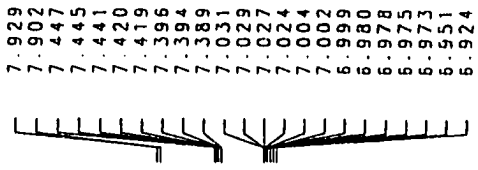
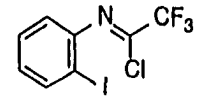
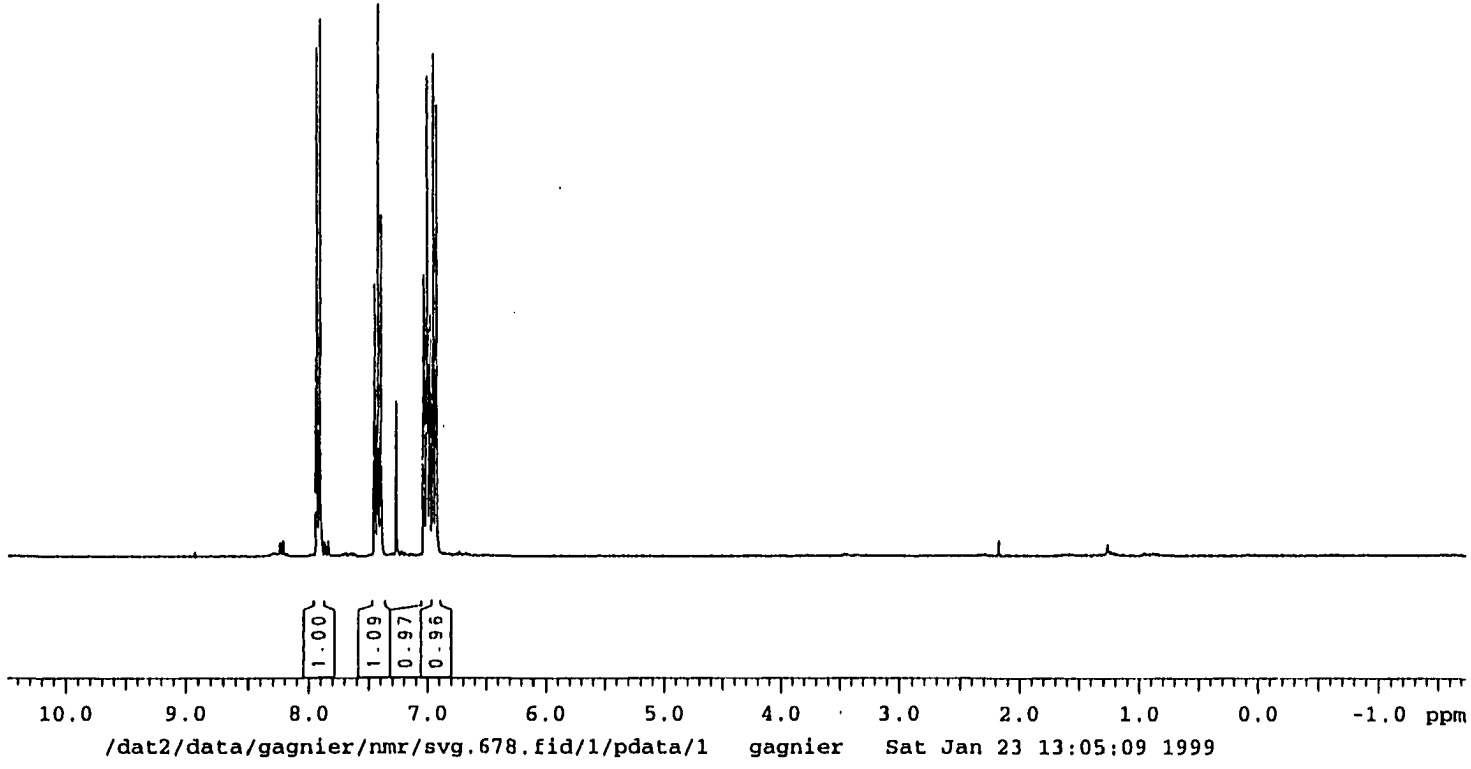
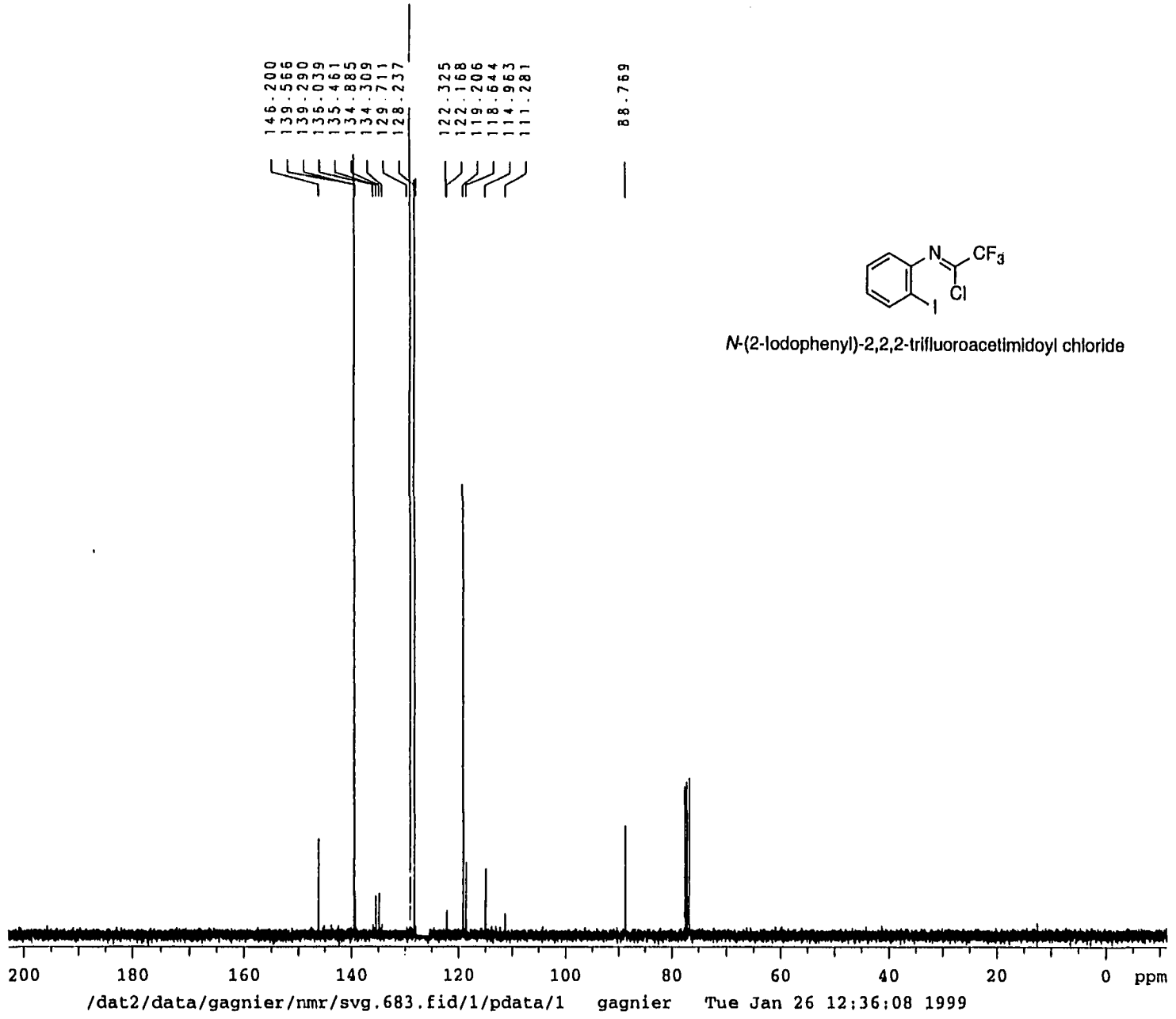


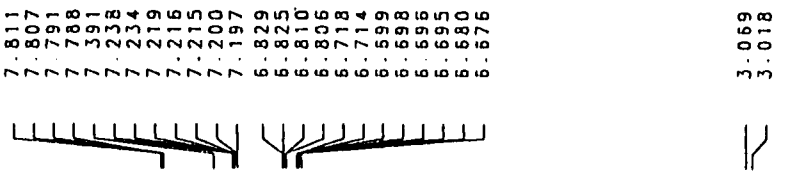



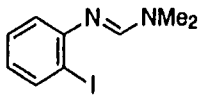

*N*-(2-Iodophenyl)-2,2,2-trifluoroacetimidoyl chloride



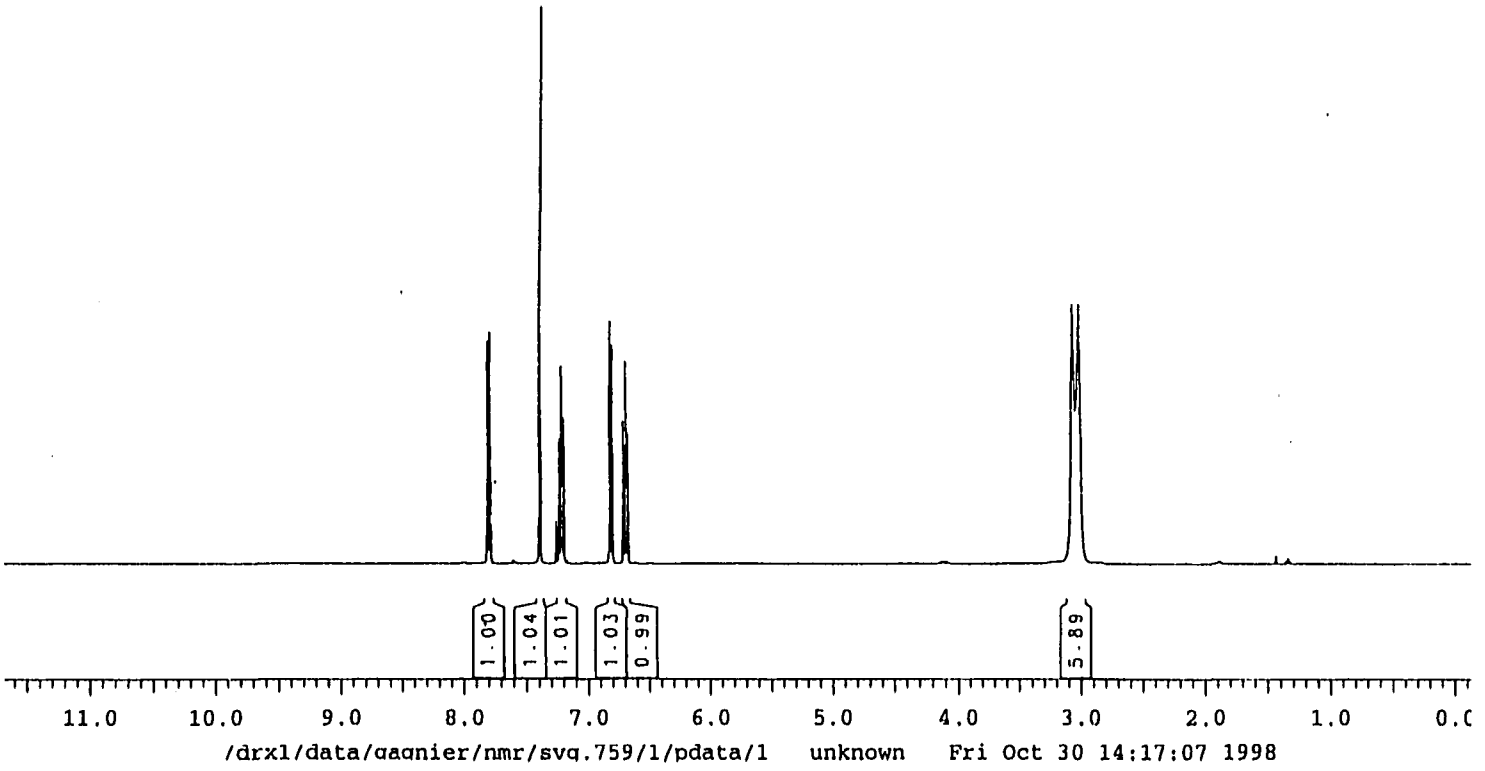


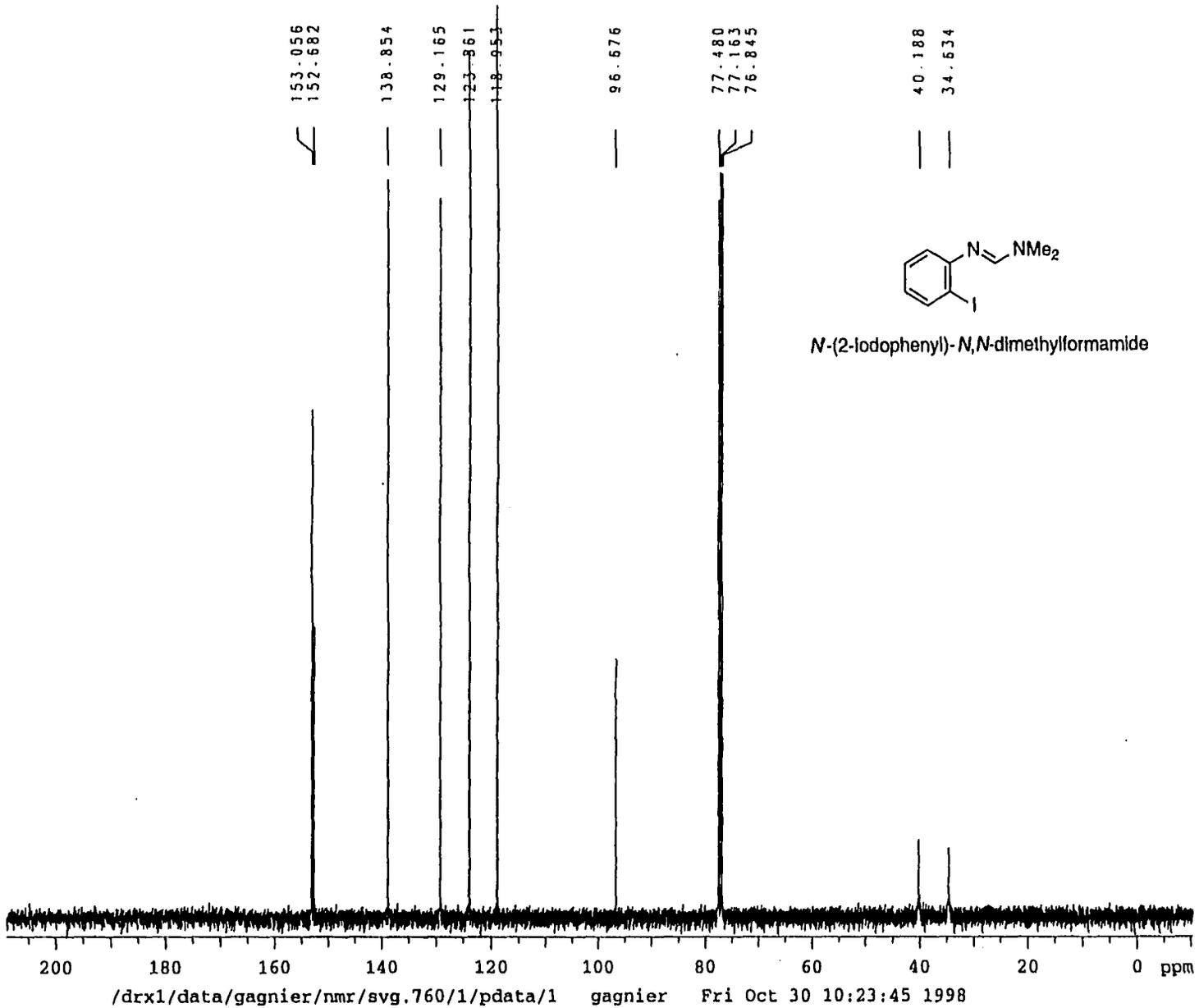

*N*-(2-Iodophenyl)-2,2,2-trifluoroacetimidoyl chloride




*N*-(2-Iodophenyl)-*N*,*N*-dimethylformamide




153.056
152.682
138.854
129.165
123.861
118.953
96.676
77.480
77.163
76.845
40.188
34.634
N
NMe2
I
N-(2-Iodophenyl)-N,N-dimethylformamide
200
180
160
140
120
100
80
60
40
20
0 ppm
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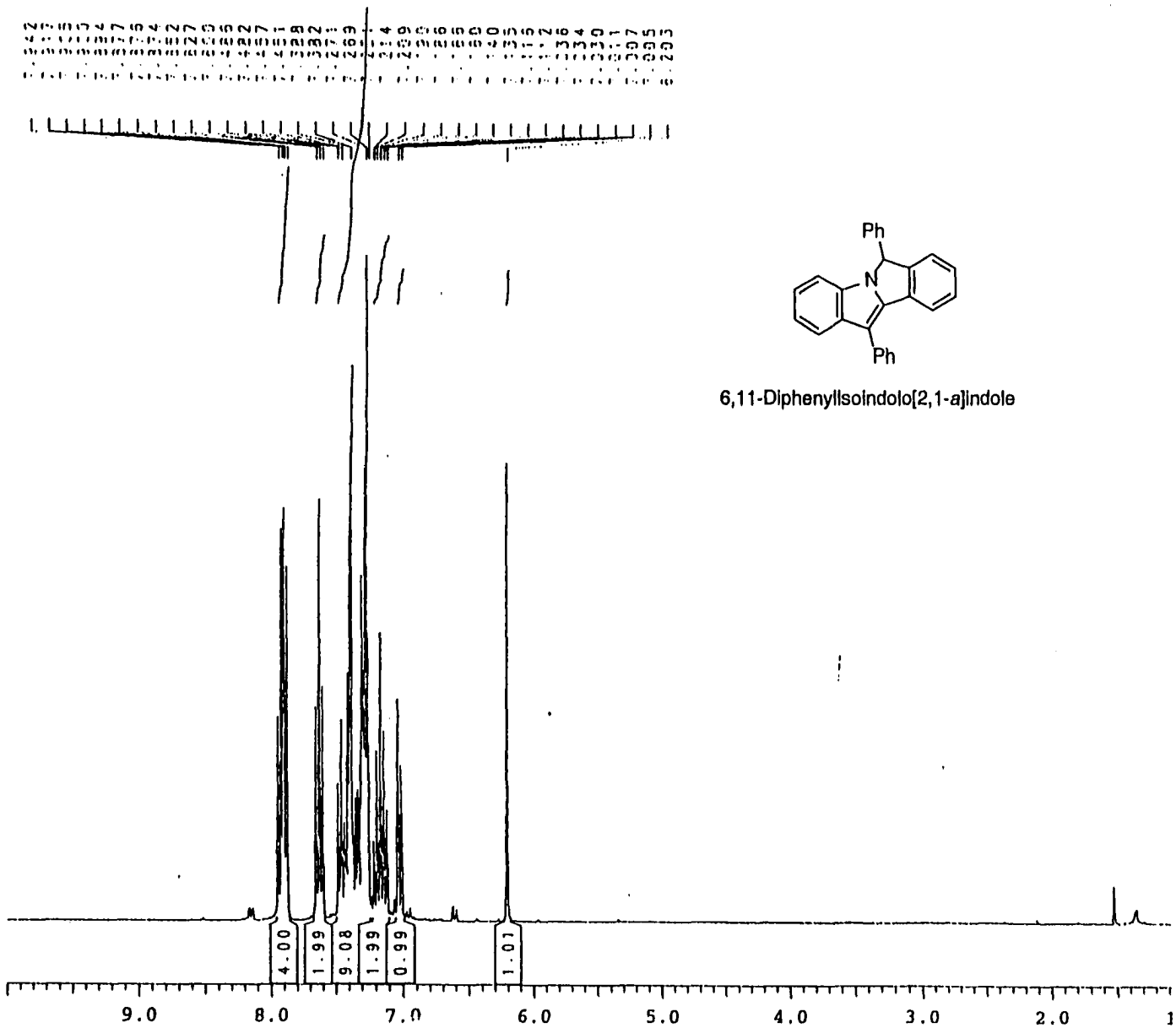
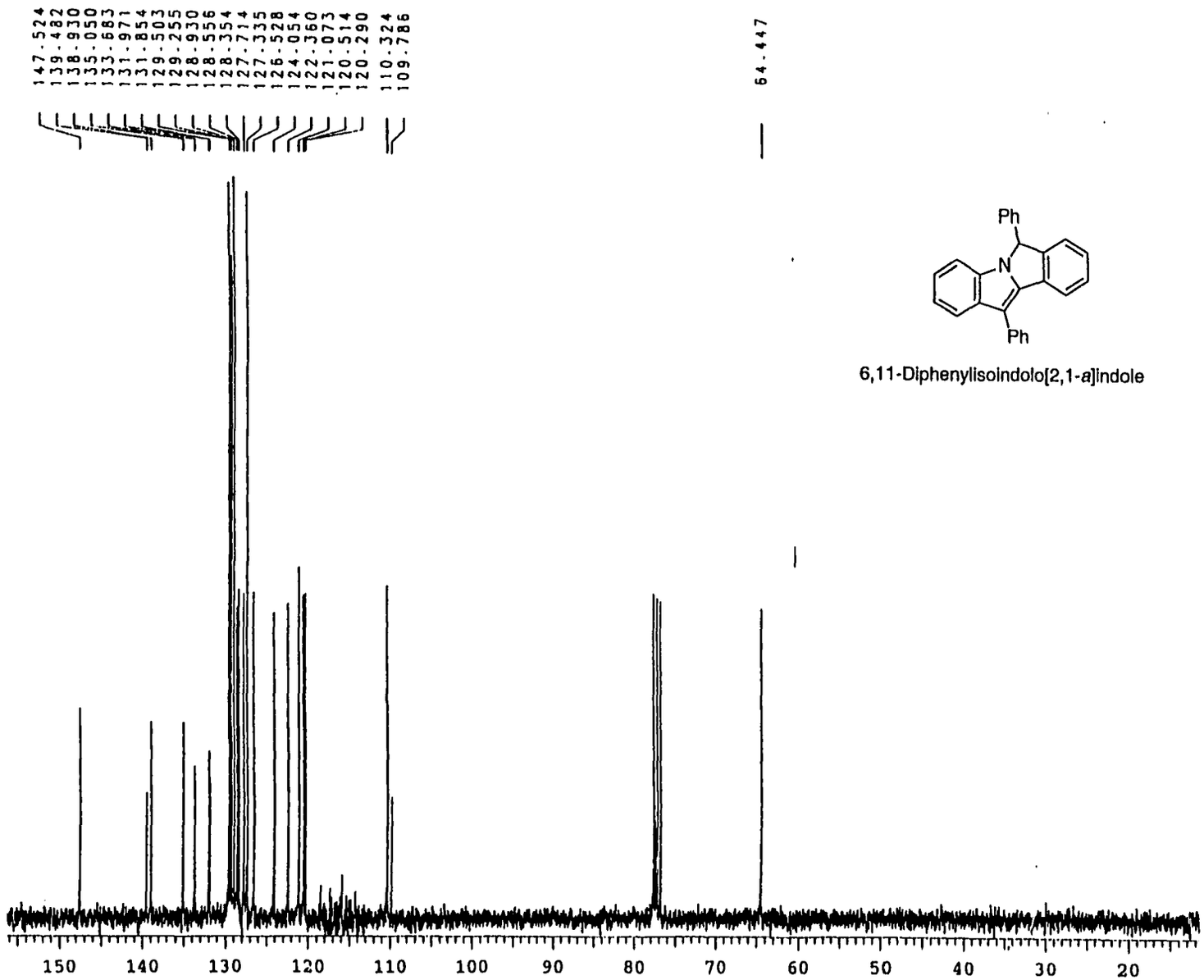






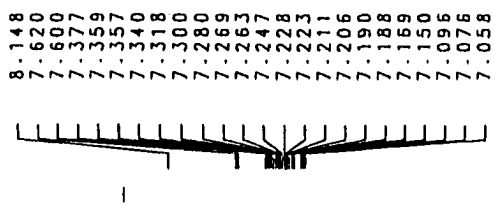
6,11-Diphenylisoindolo[2,1-*a*]indole

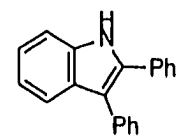




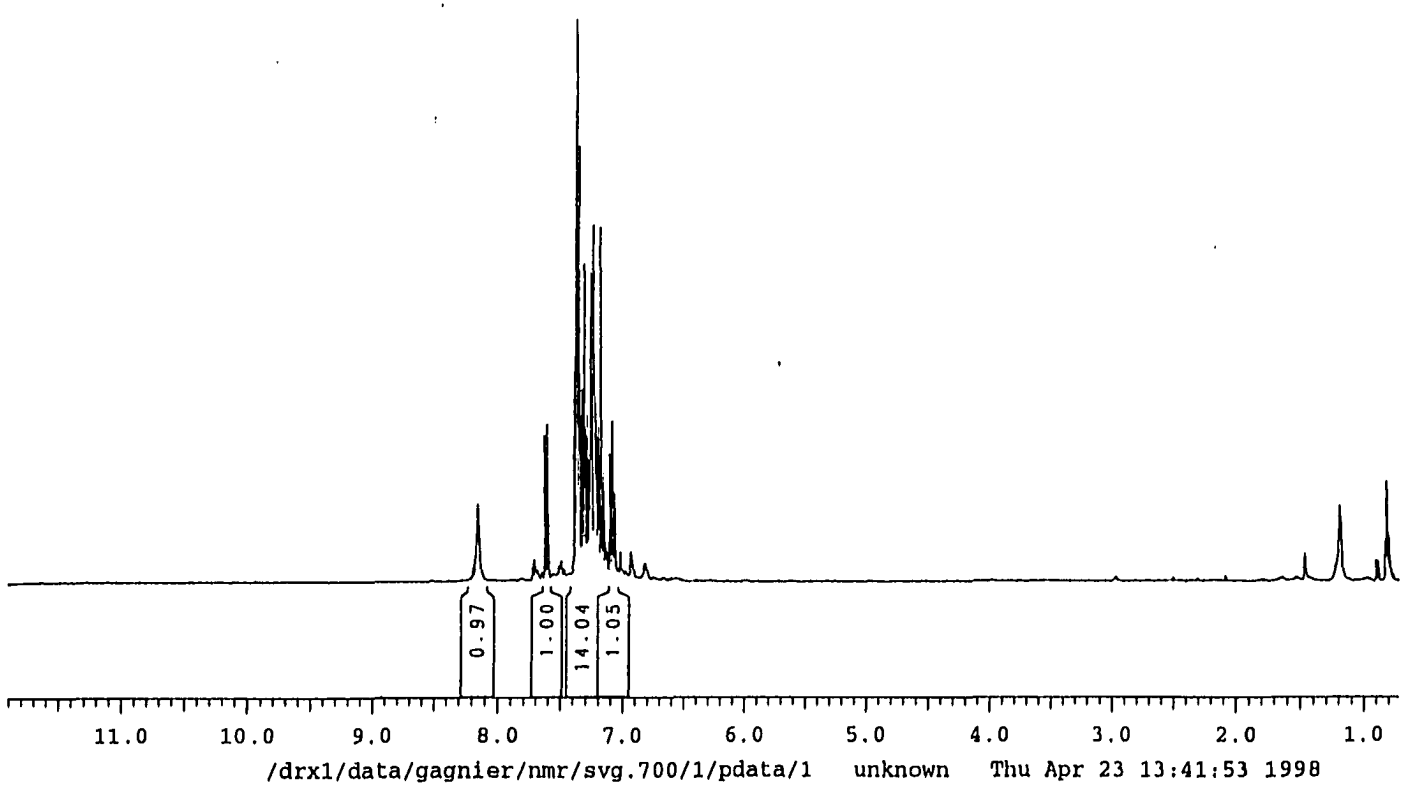


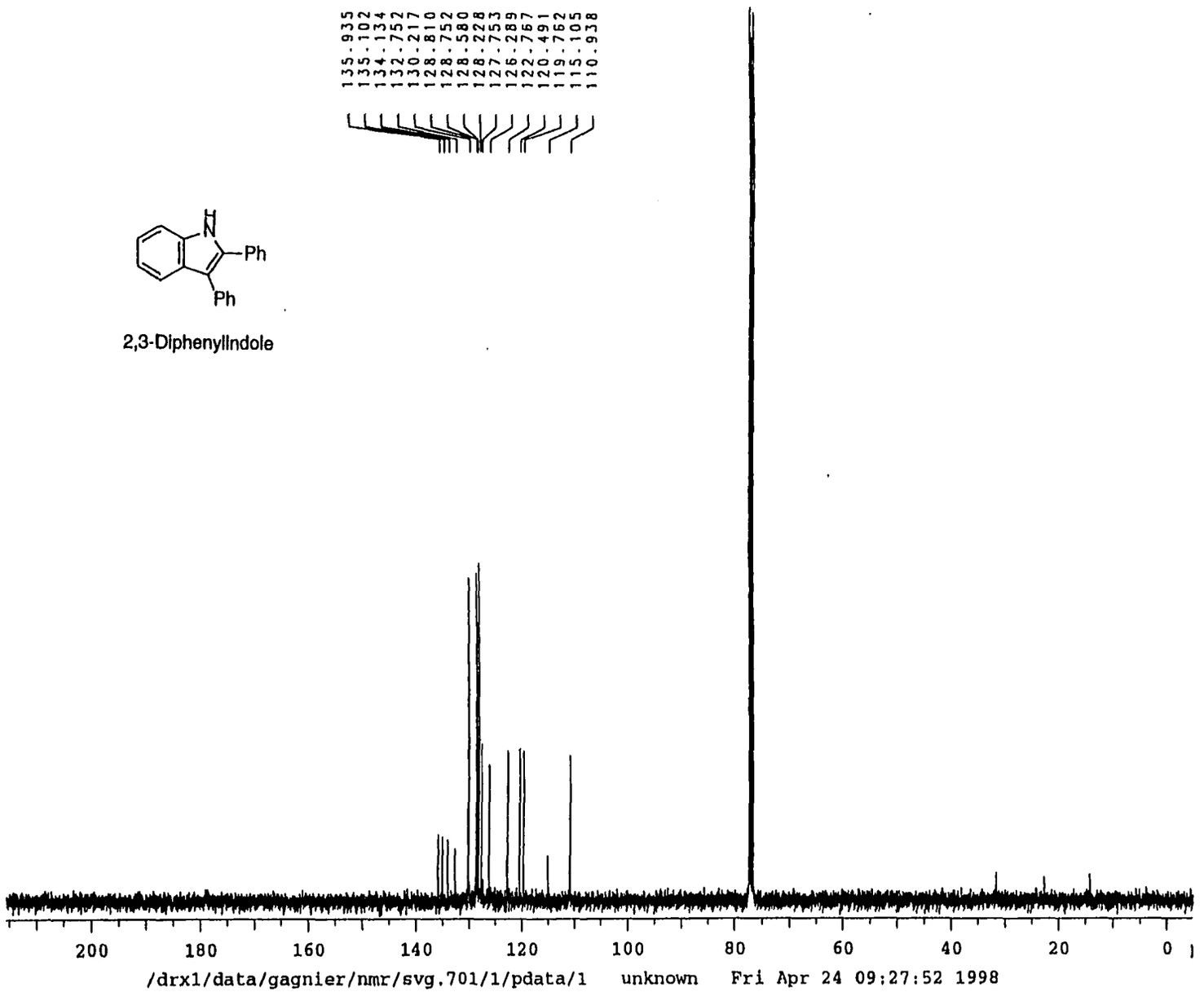
6,11-Diphenylisoindolo[2,1-*a*]indole




2,3-Diphenylindole




135.935
135.102
134.134
132.752
130.217
128.810
128.752
128.580
128.228
127.753
126.289
122.767
120.491
119.762
115.105
110.938
Ph
Ph
2,3-Diphenylindole
200
180
160
140
120
100
80
60
40
20
0
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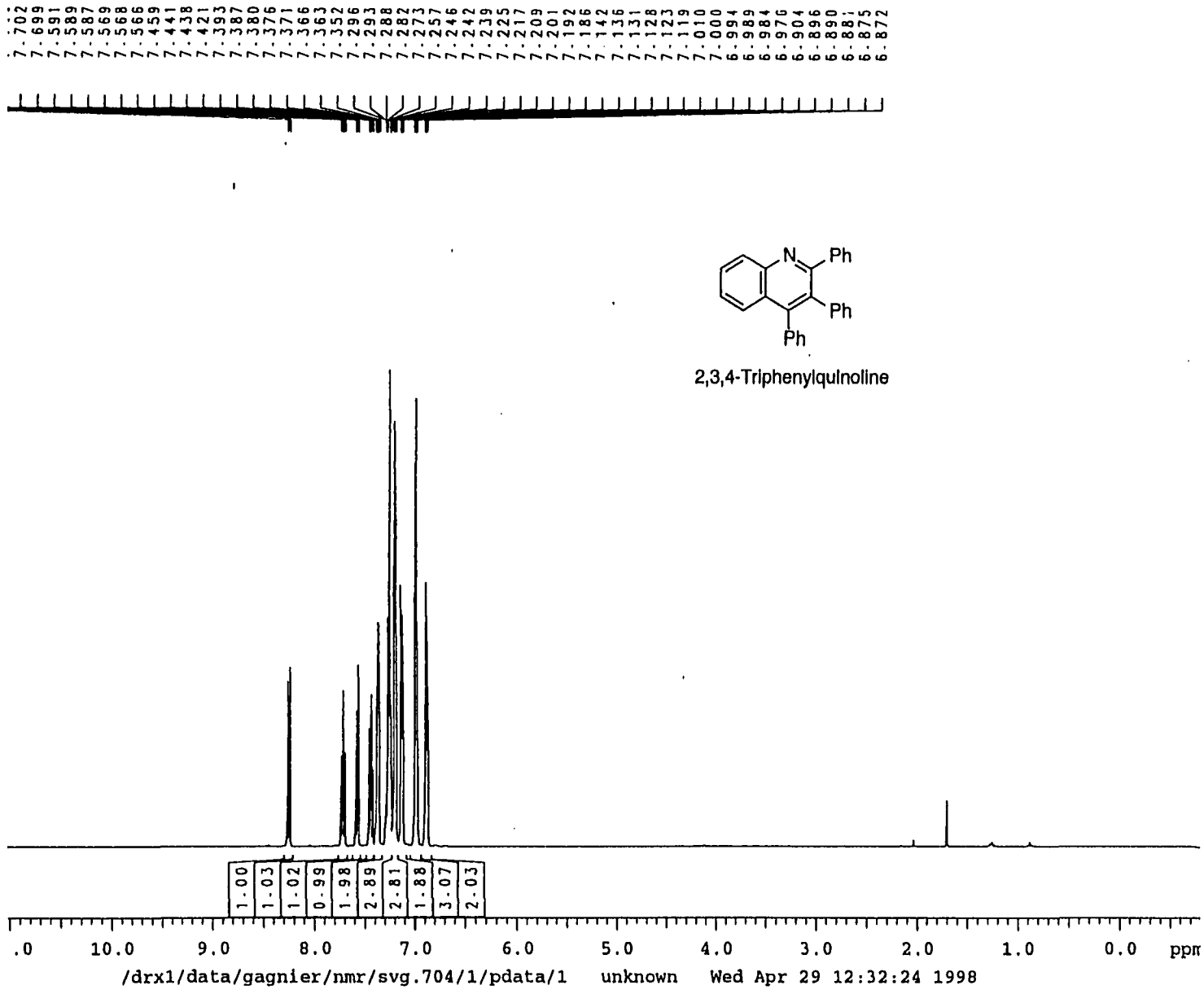
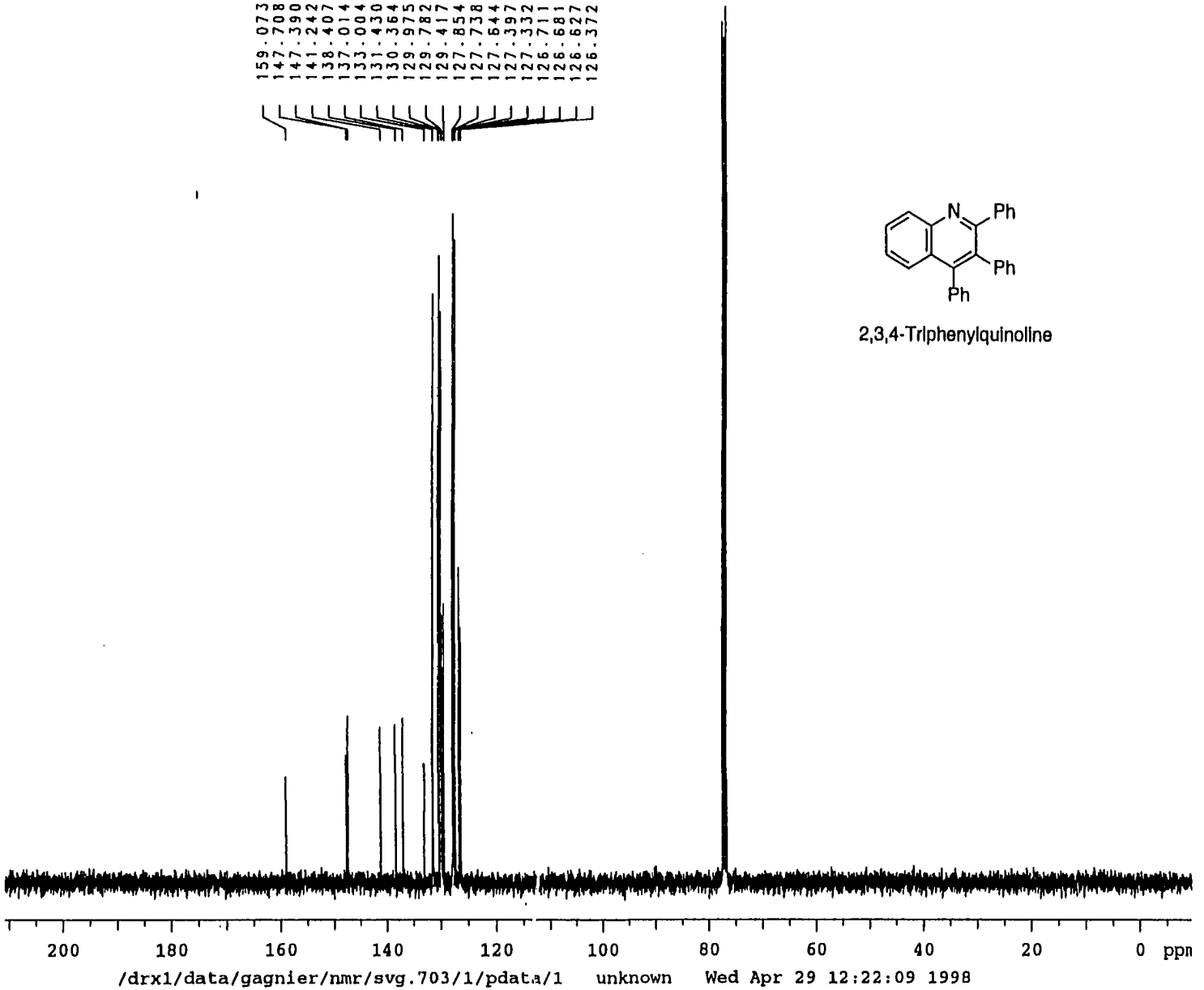
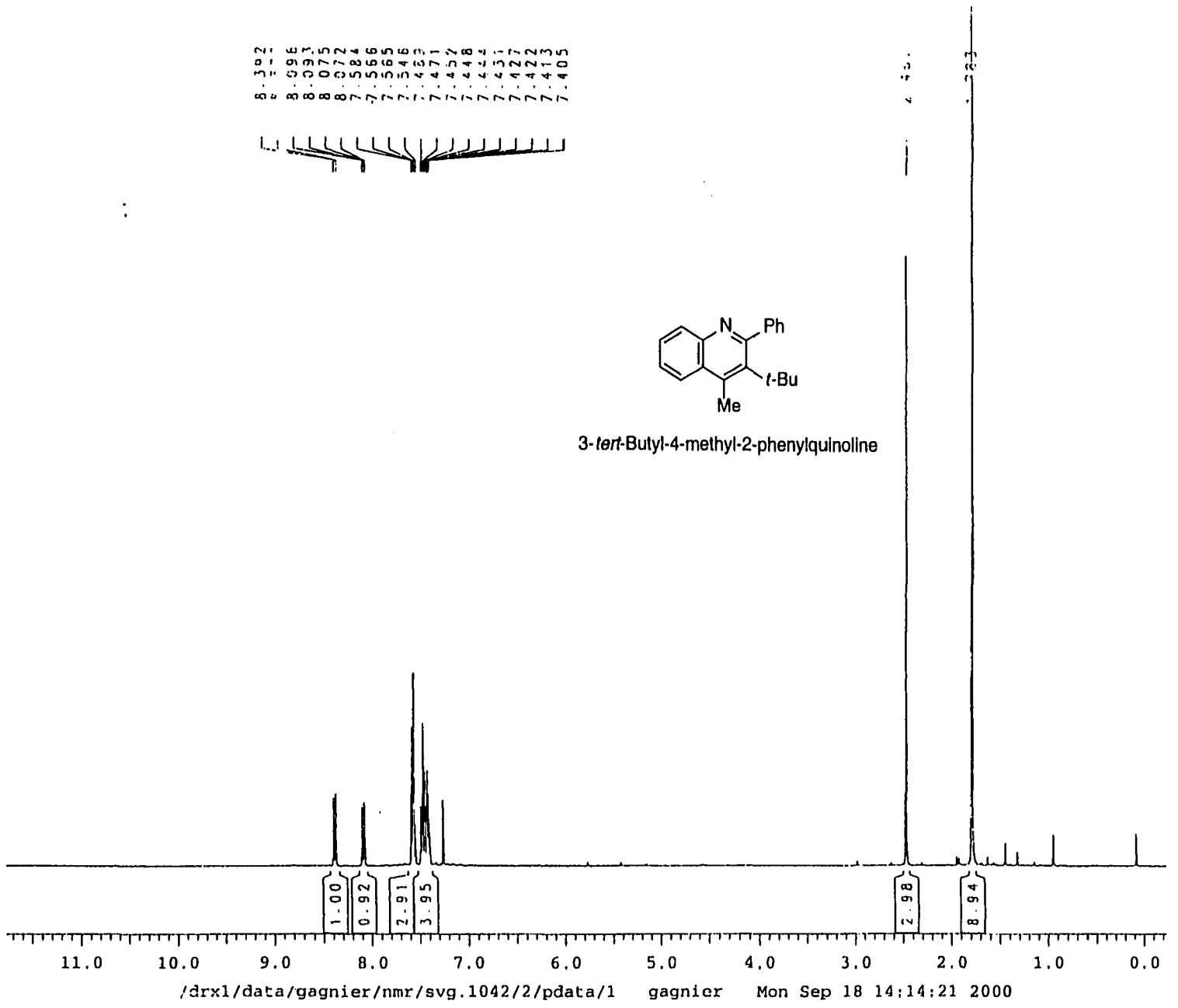


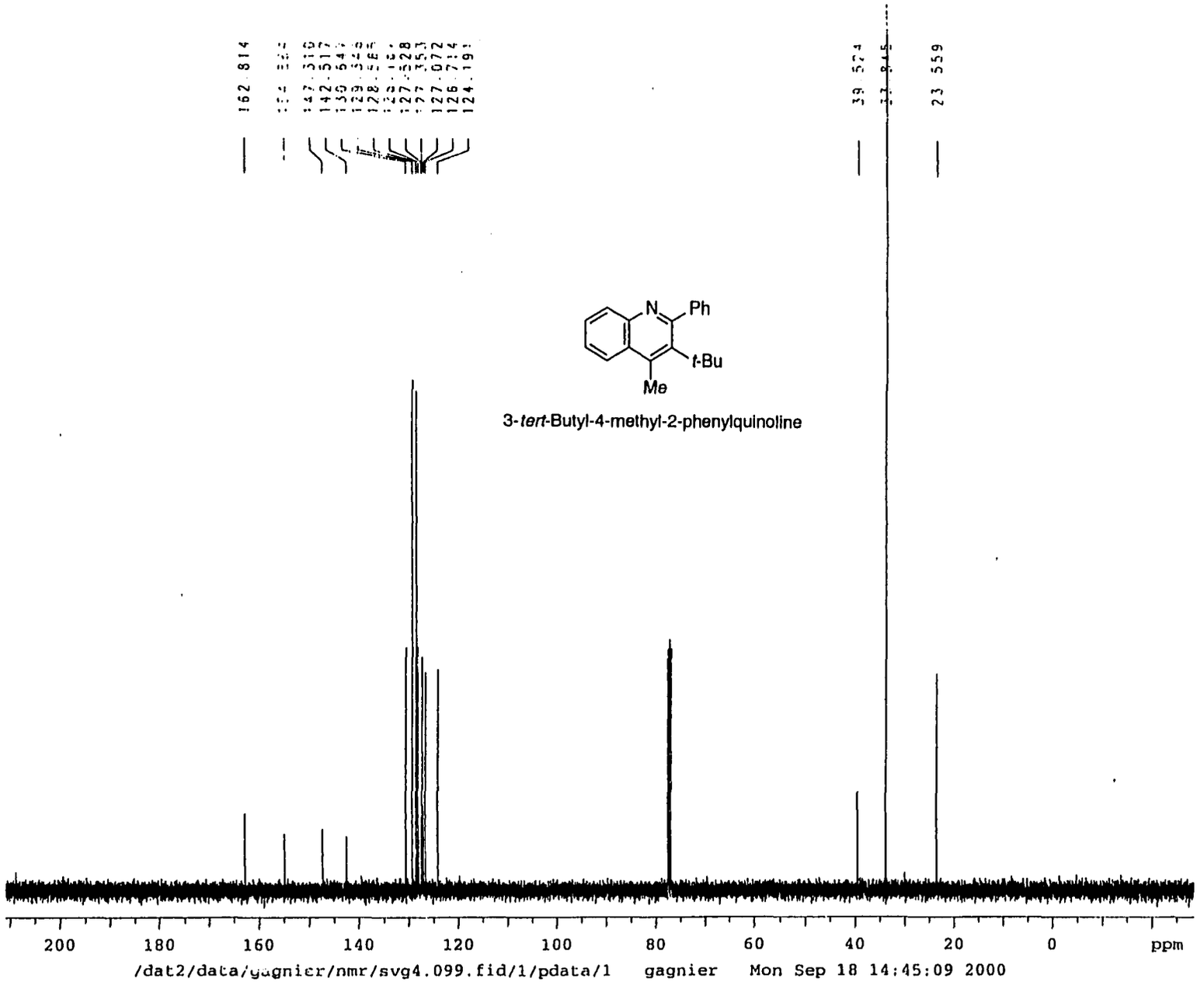

2,3,4-Triphenylquinoline



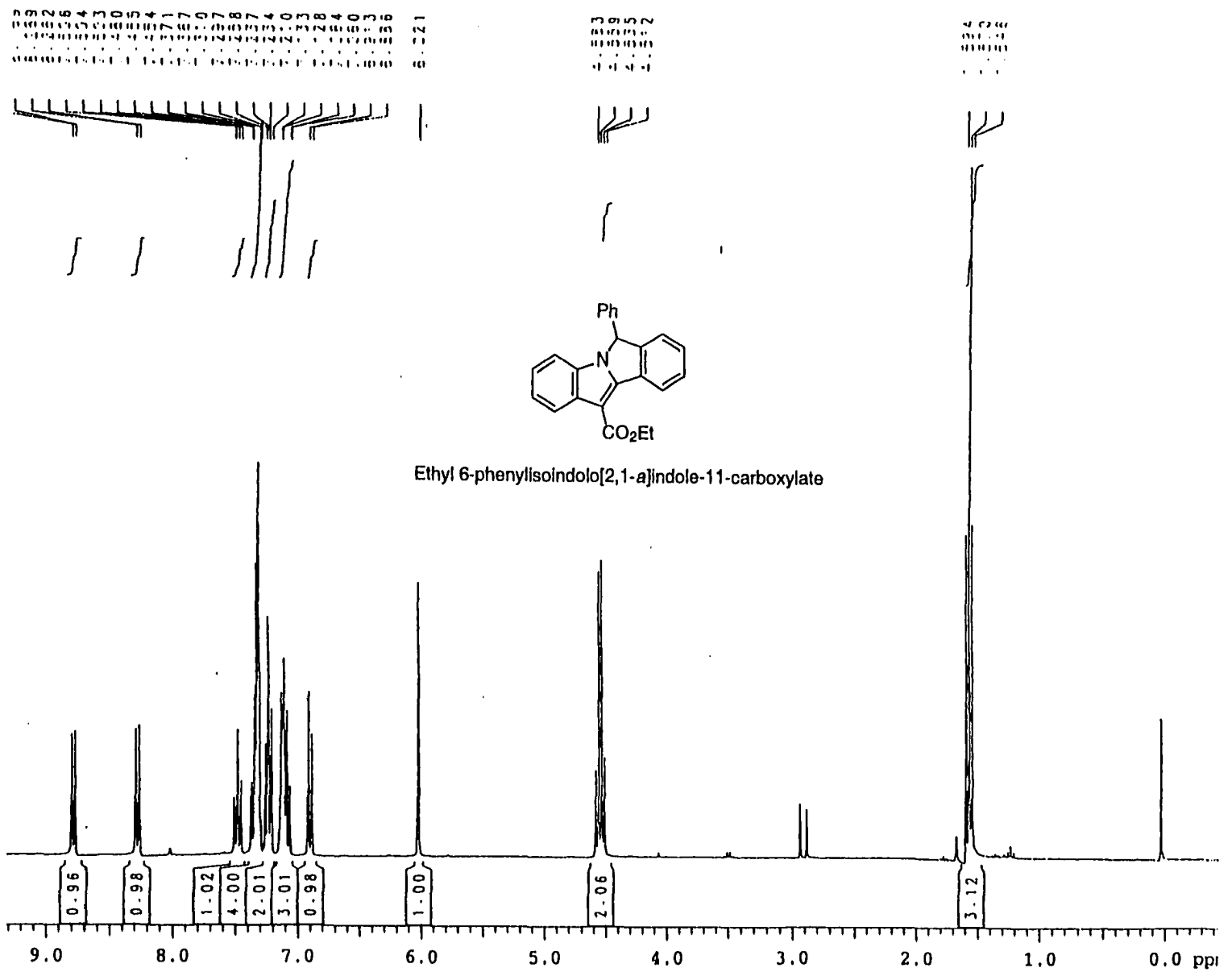

2,3,4-Triphenylquinoline



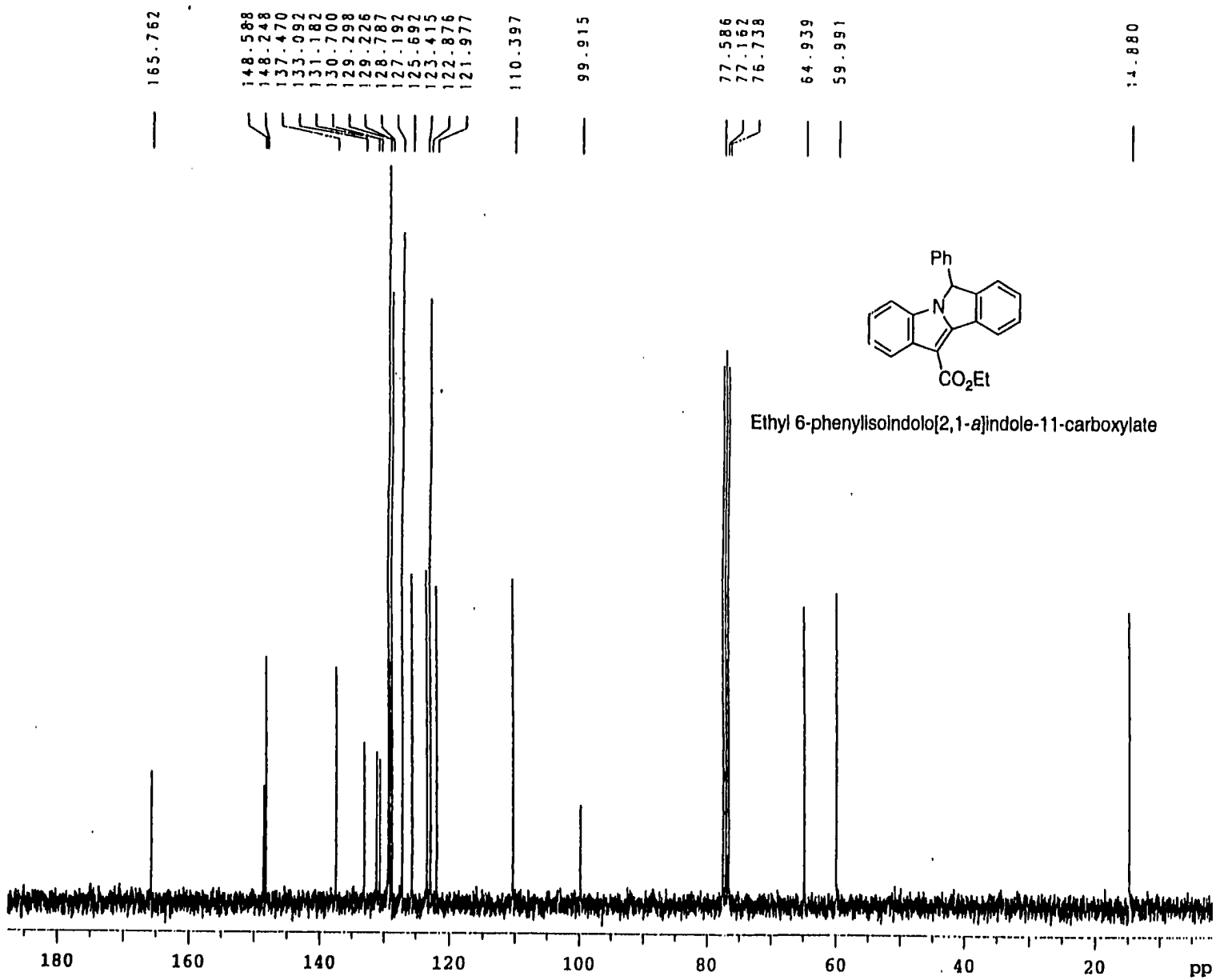

3-*tert*-Butyl-4-methyl-2-phenylquinoline

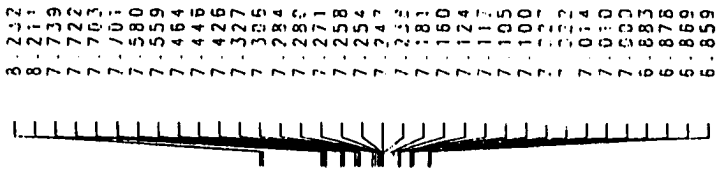


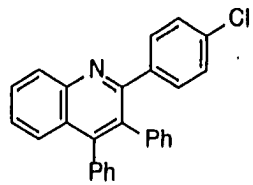

3-*tert*-Butyl-4-methyl-2-phenylquinoline



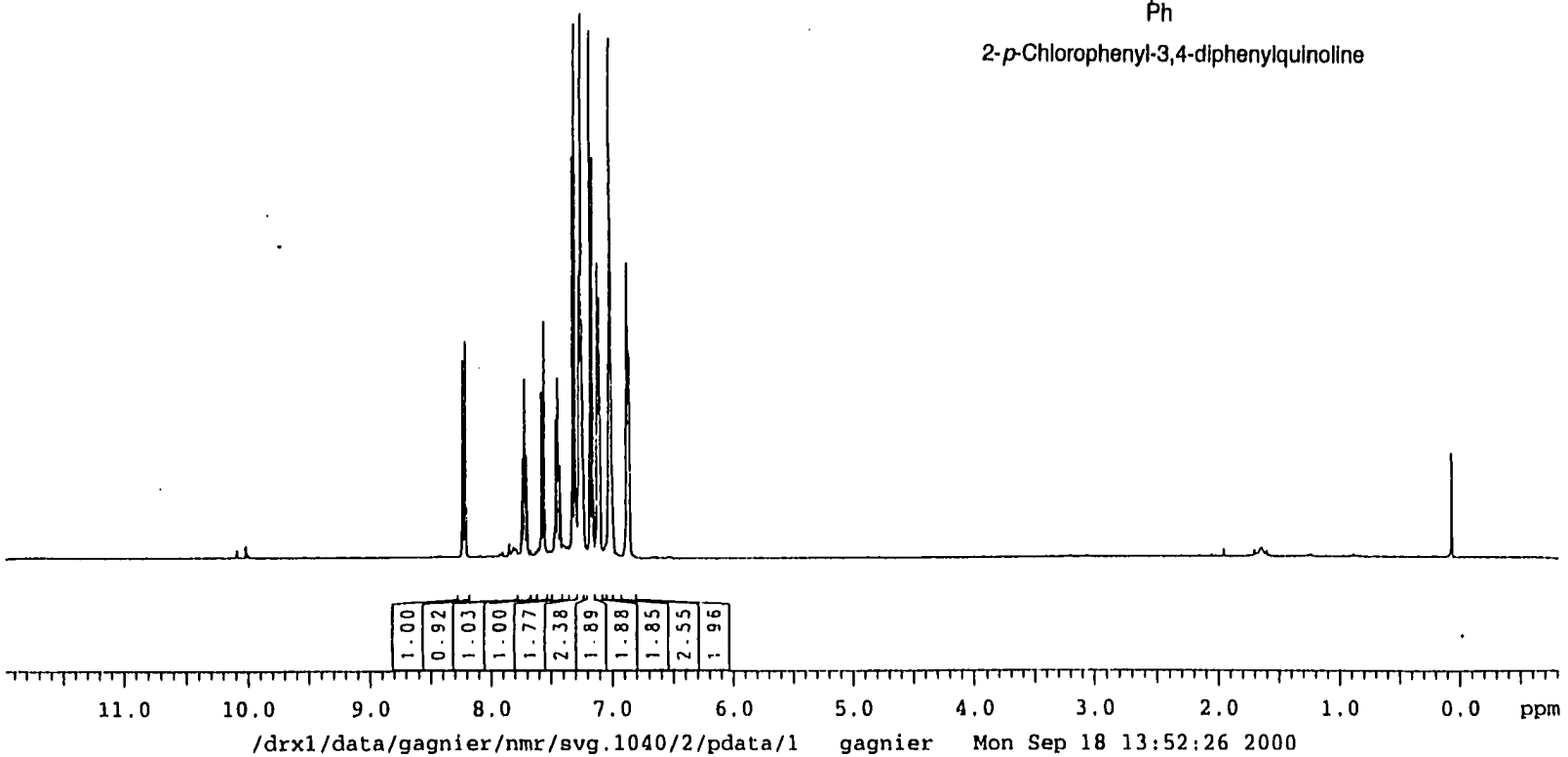

Ethyl 6-phenylisoindolo[2,1-*a*]indole-11-carboxylate

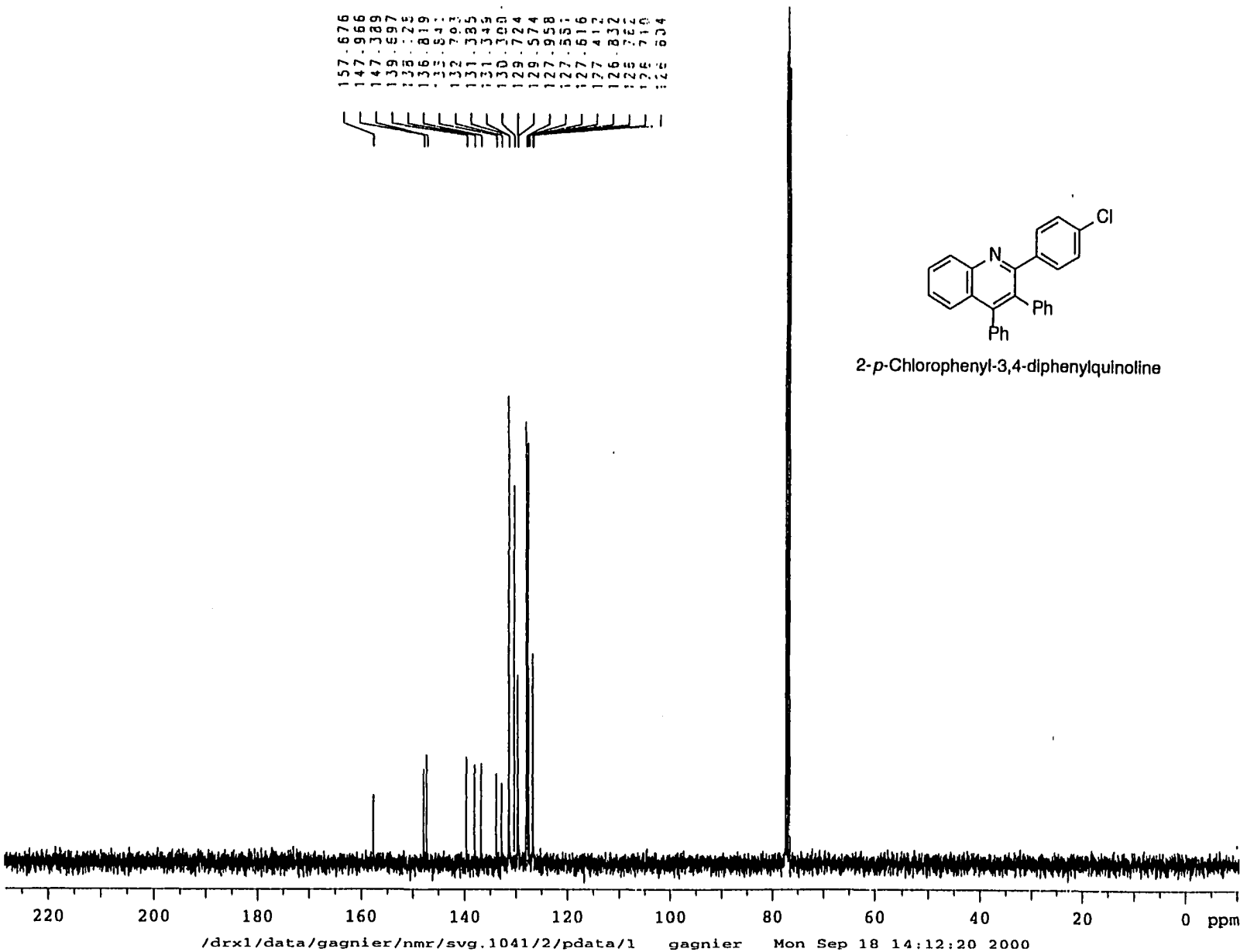

165.762
148.588
148.248
137.470
133.092
131.182
130.700
129.298
129.226
128.787
127.192
125.692
123.415
122.876
121.977
110.397
99.915
77.586
77.162
76.738
64.939
59.991
14.880
Ph
N
CO2Et
Ethyl 6-phenylisoindolo[2,1-a]indole-11-carboxylate
180
160
140
120
100
80
60
40
20
pp



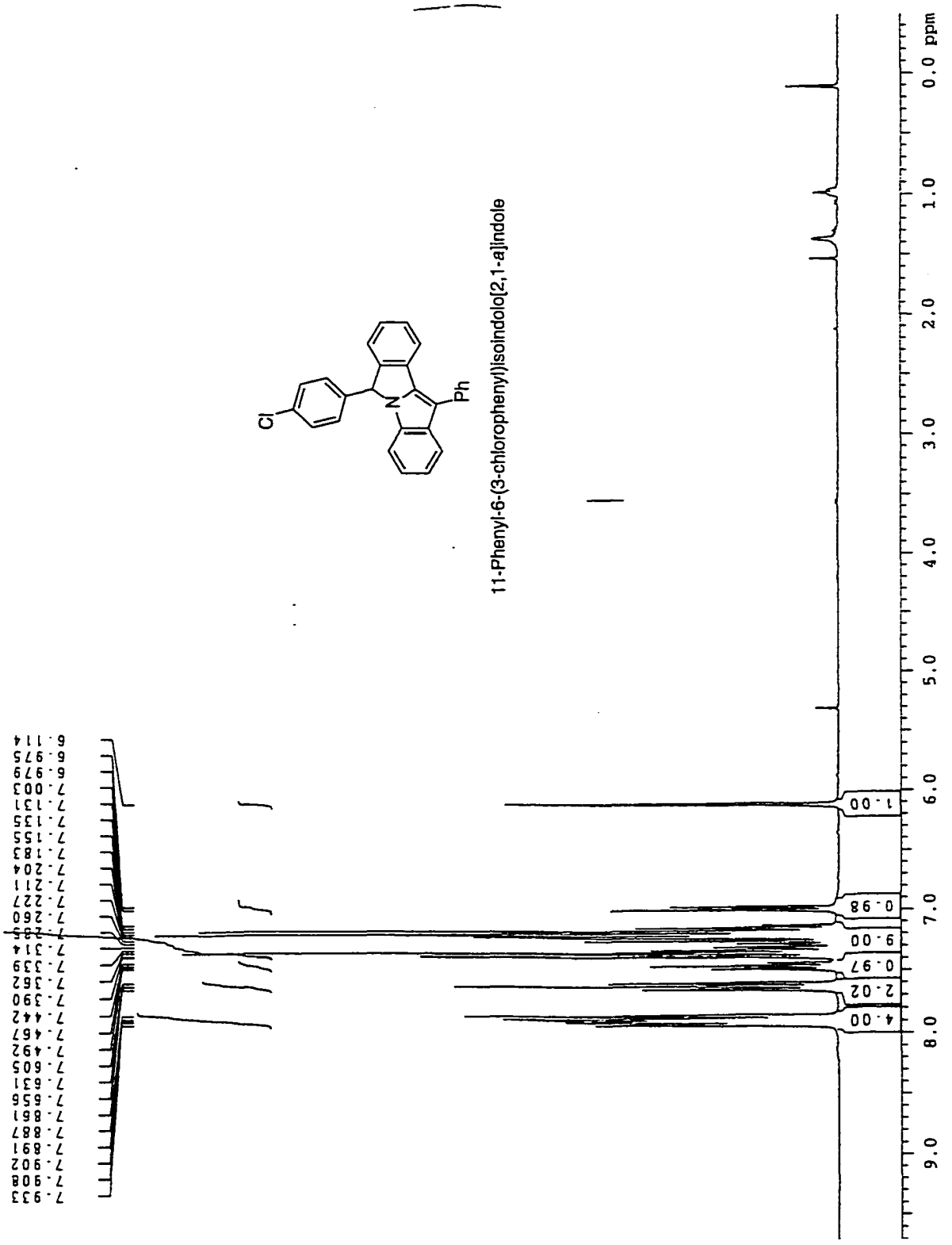


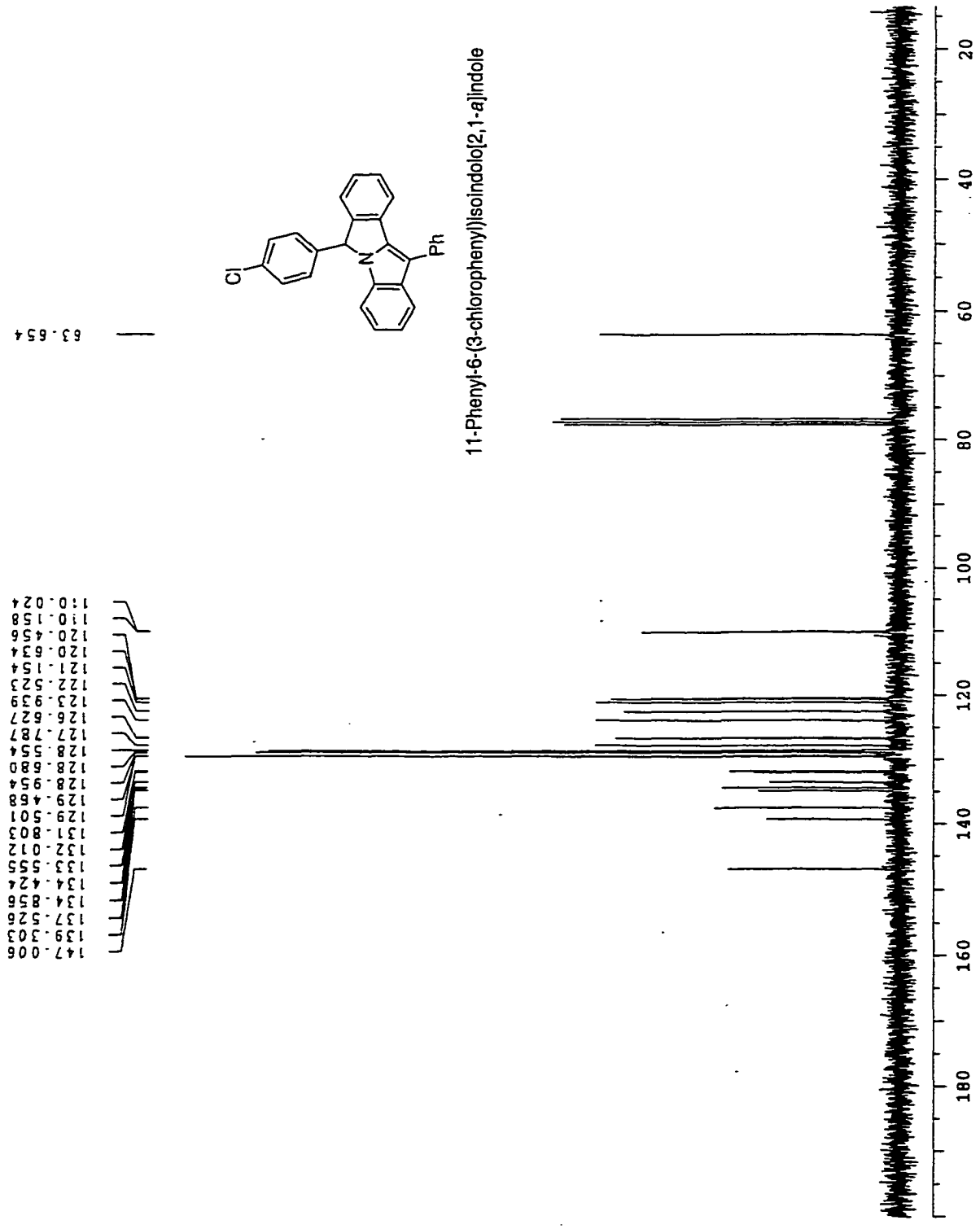

2-*p*-Chlorophenyl-3,4-diphenylquinoline

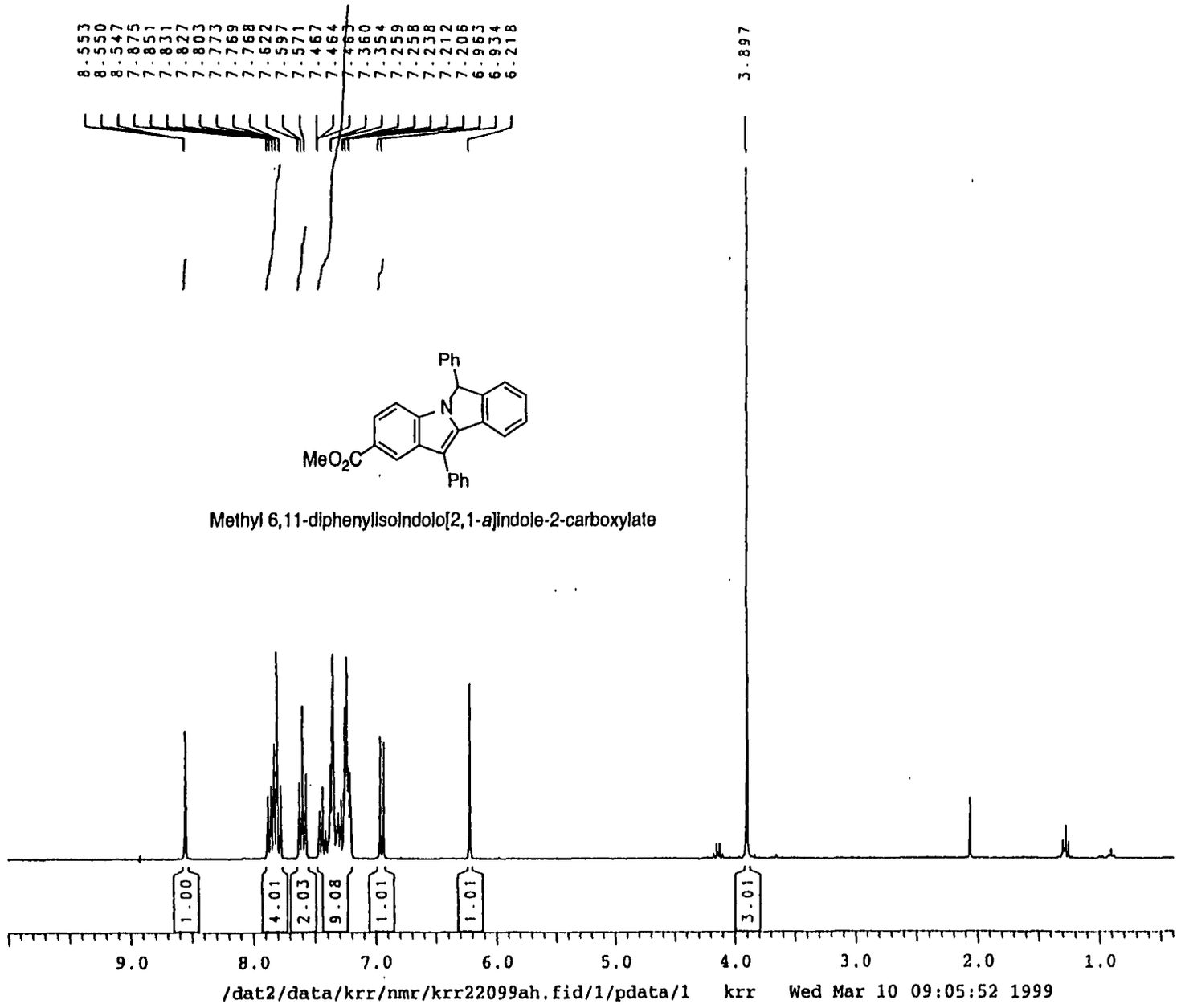




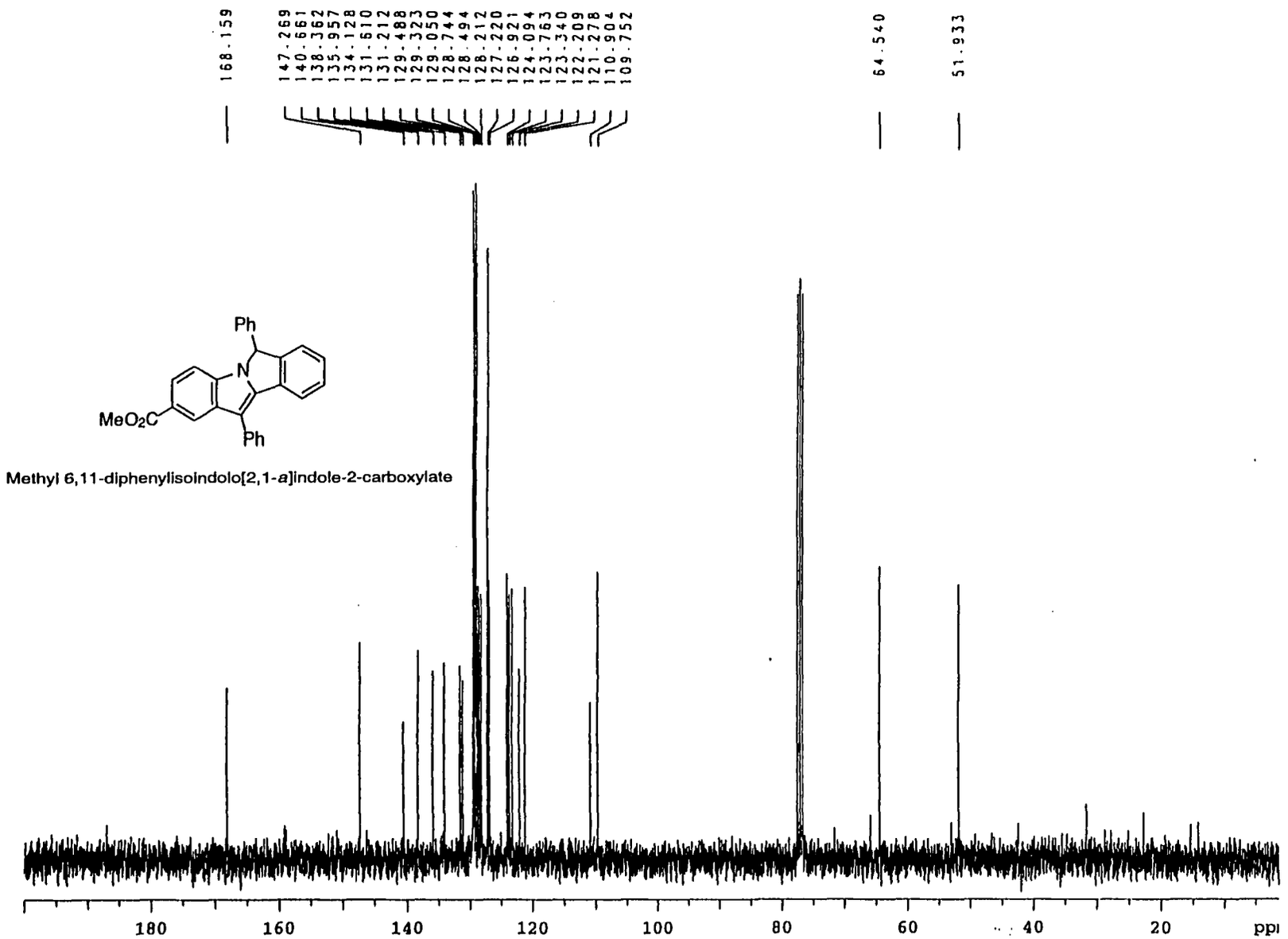

2-*p*-Chlorophenyl-3,4-diphenylquinoline


11-Phenyl-6-(3-chlorophenyl)isoindolo[2,1-a]indole
Cl
N
Ph
7.933
7.908
7.902
7.891
7.887
7.861
7.656
7.631
7.605
7.492
7.467
7.442
7.390
7.362
7.339
7.314
7.285
7.260
7.227
7.211
7.204
7.183
7.155
7.135
7.131
7.003
6.979
6.975
6.114
1.00
0.98
9.00
0.97
2.02
4.00
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0 ppm


11-Phenyl-6-(3-chlorophenyl)isoindolo[2,1-a]indole
Cl
N
Ph
63.654
147.006
139.303
137.526
134.856
134.424
133.555
132.012
131.803
129.501
129.468
128.954
128.680
128.554
127.787
126.627
123.939
122.523
121.154
120.634
120.456
110.158
110.024
20
40
60
80
100
120
140
160
180

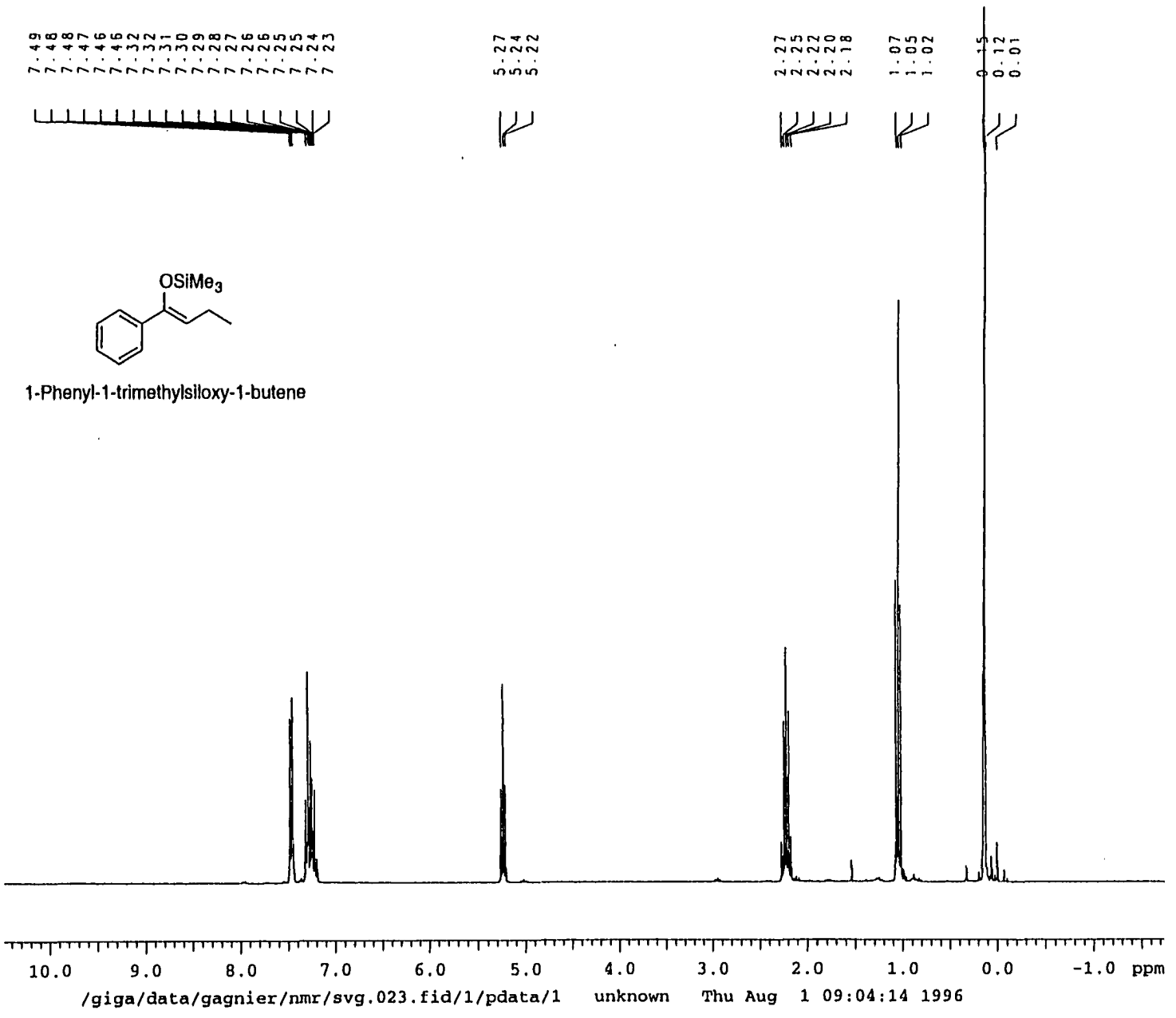


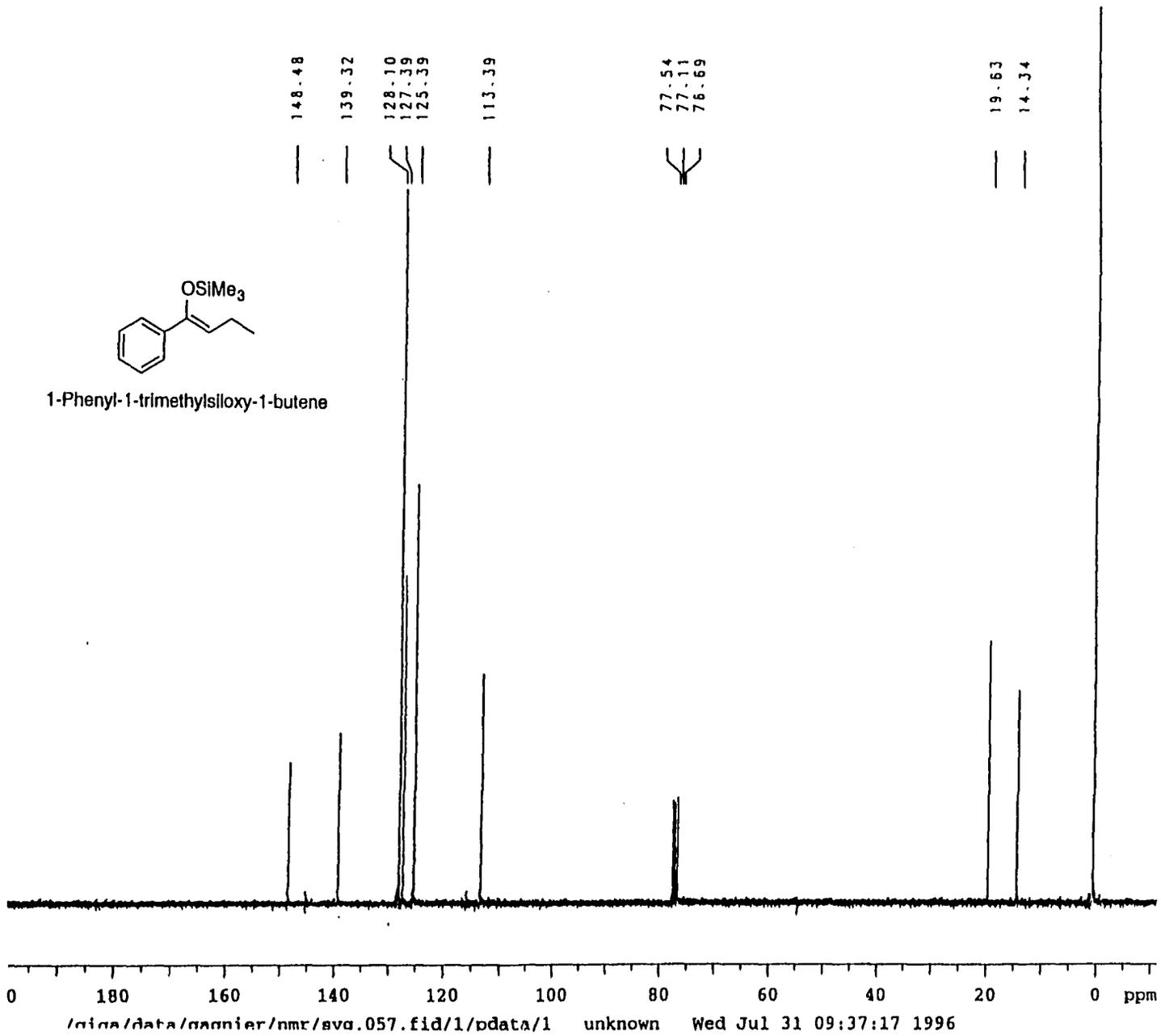

Methyl 6,11-diphenylisoindolo[2,1-*a*]indole-2-carboxylate




Methyl 6,11-diphenylisoindolo[2,1-*a*]indole-2-carboxylate

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


7.49
7.48
7.48
7.47
7.46
7.46
7.32
7.32
7.31
7.30
7.29
7.28
7.27
7.26
7.26
7.25
7.25
7.24
7.23
5.27
5.24
5.22
2.27
2.25
2.22
2.20
2.18
1.07
1.05
1.02
0.15
0.12
0.01
OSiMe3
1-Phenyl-1-trimethylsiloxy-1-butene
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
-1.0 ppm
/giga/data/gagnier/nmr/svg.023.fid/1/pdata/1 unknown Thu Aug 1 09:04:14 1996


148.48
139.32
128.10
127.39
125.39
113.39
77.54
77.11
76.69
19.63
14.34
OSiMe3
1-Phenyl-1-trimethylsiloxy-1-butene
0
180
160
140
120
100
80
60
40
20
0
ppm
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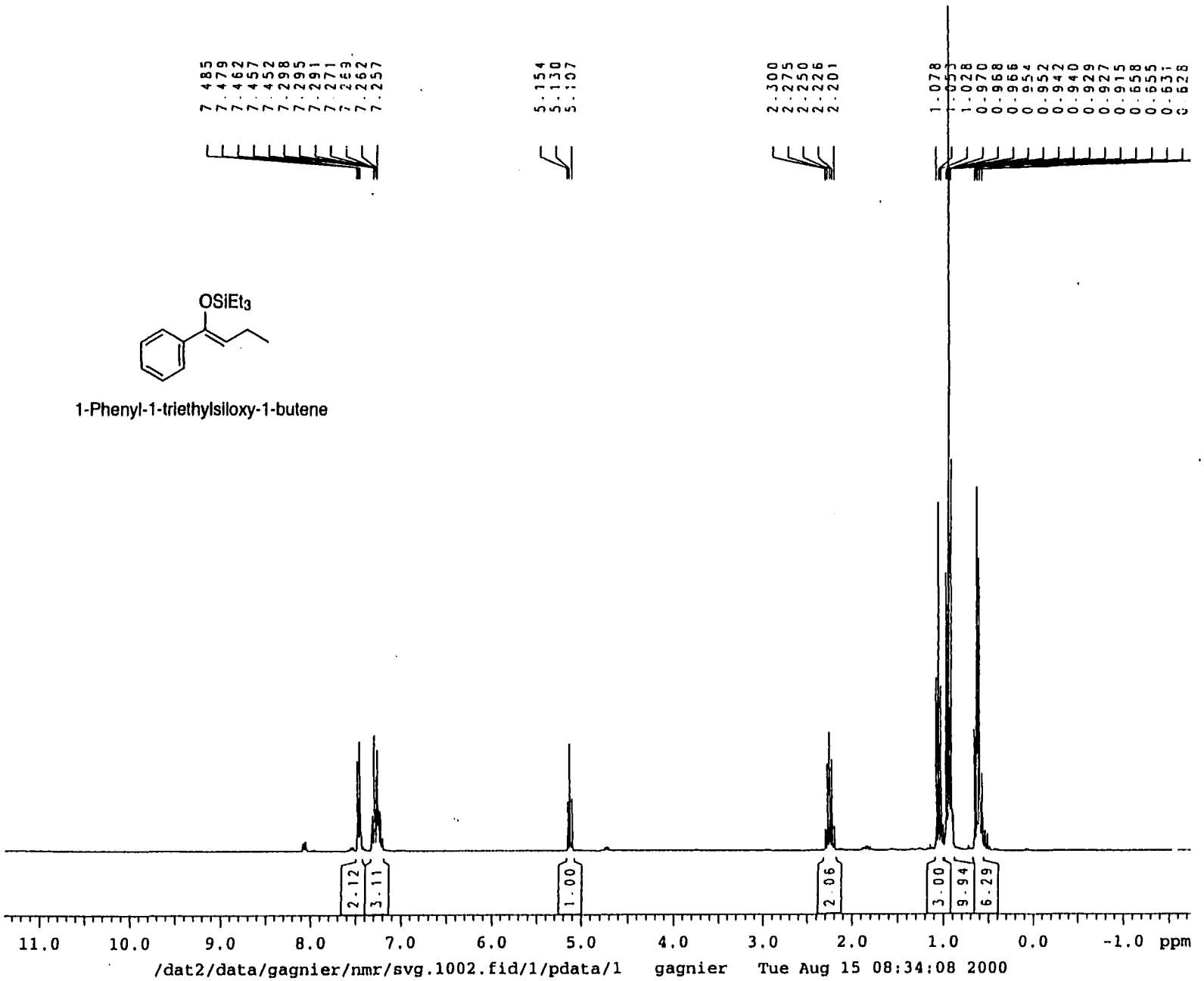
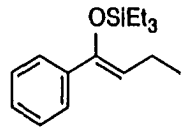
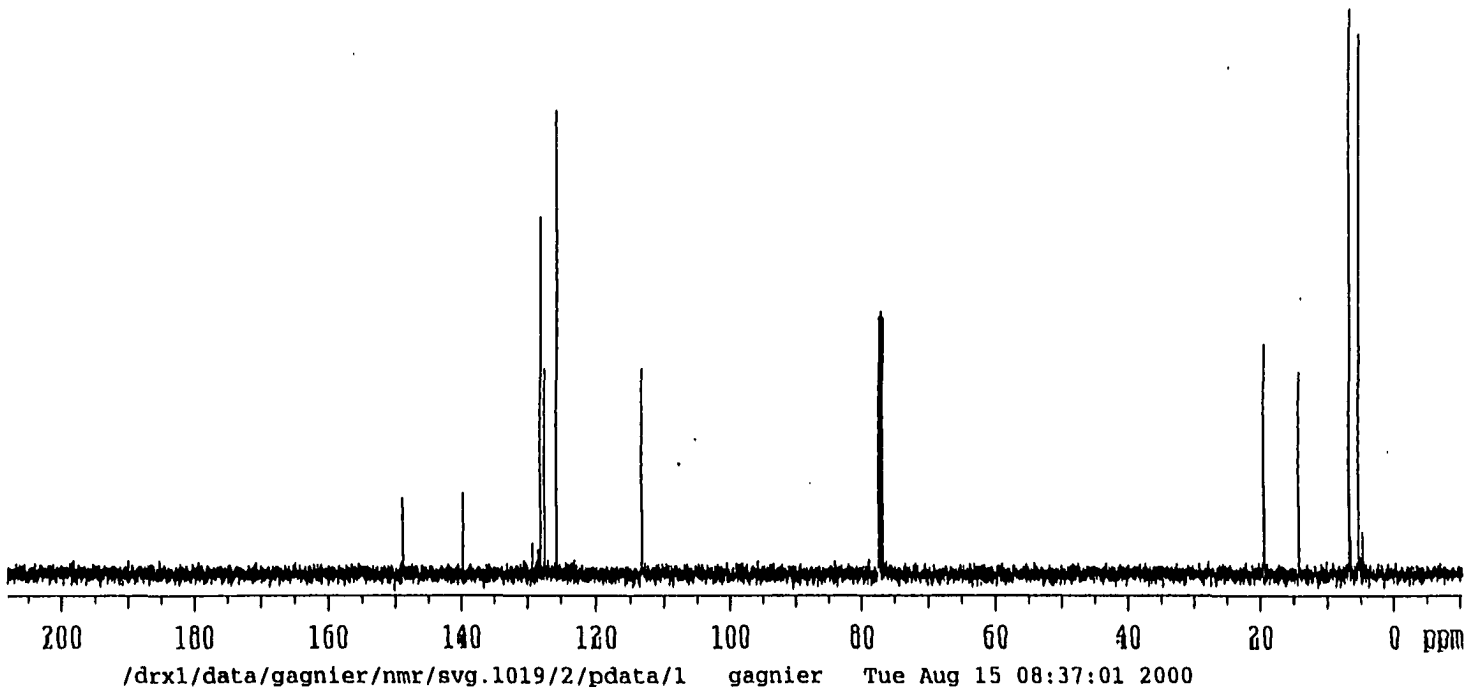


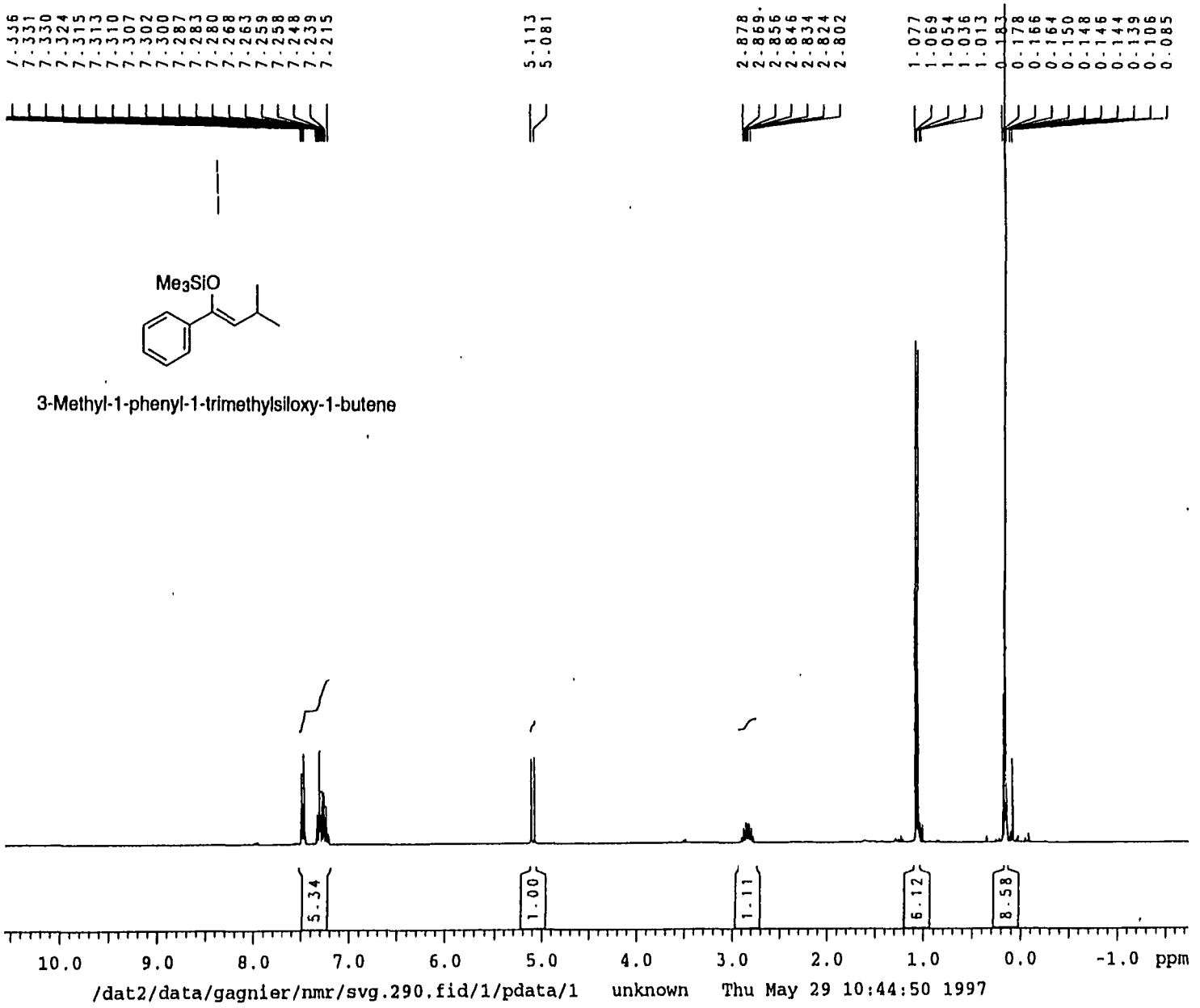

1-Phenyl-1-triethylsiloxy-1-butene

148.914
139.741
127.976
127.351
125.544
113.272
19.446
14.297
6.750
5.355

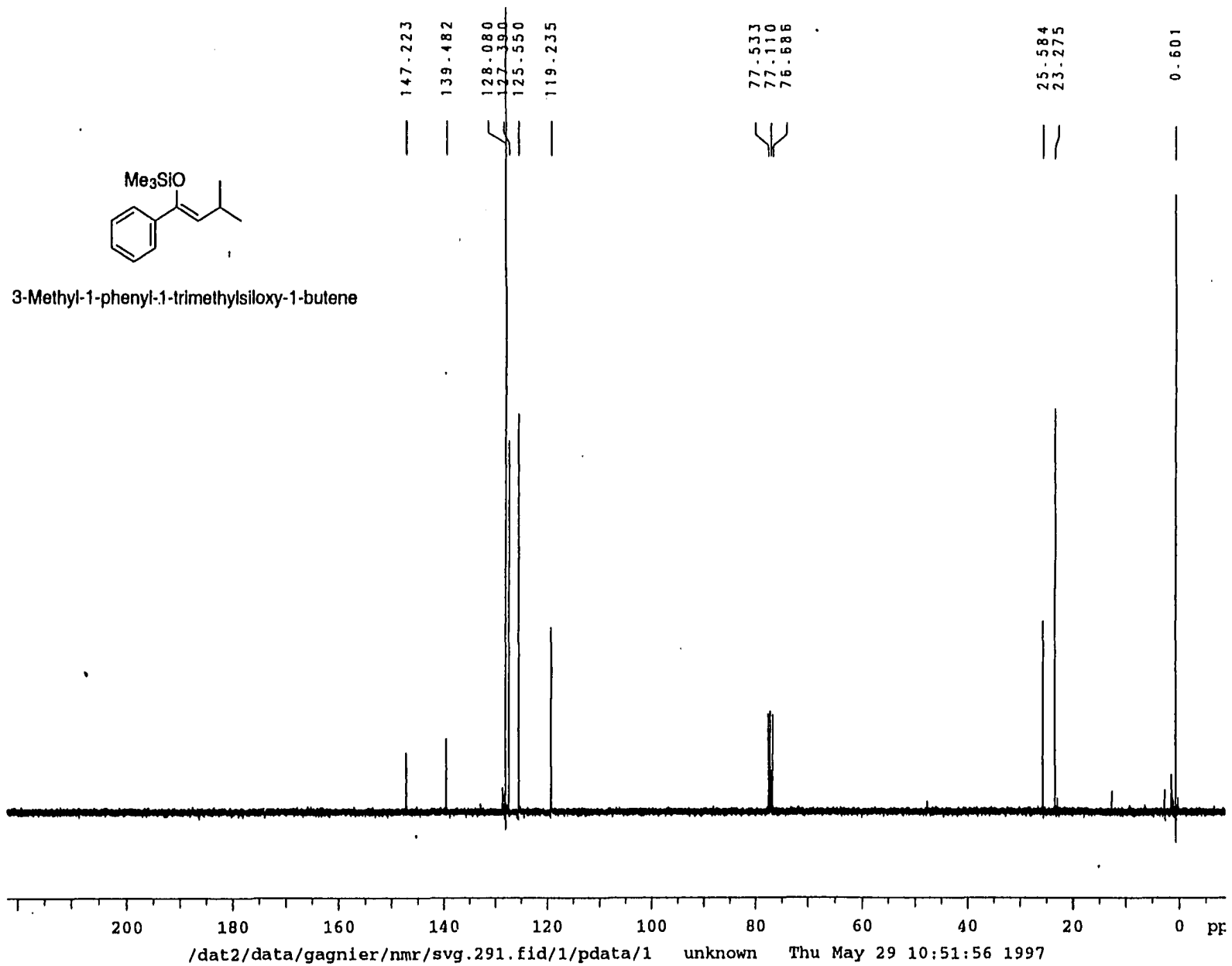



1-Phenyl-1-triethylsiloxy-1-butene






3-Methyl-1-phenyl-1-trimethylsiloxy-1-butene


147.223
139.482
128.080
127.390
125.550
119.235
77.533
77.110
76.686
25.584
23.275
0.601
Me3SiO
3-Methyl-1-phenyl-1-trimethylsiloxy-1-butene
200
180
160
140
120
100
80
60
40
20
0
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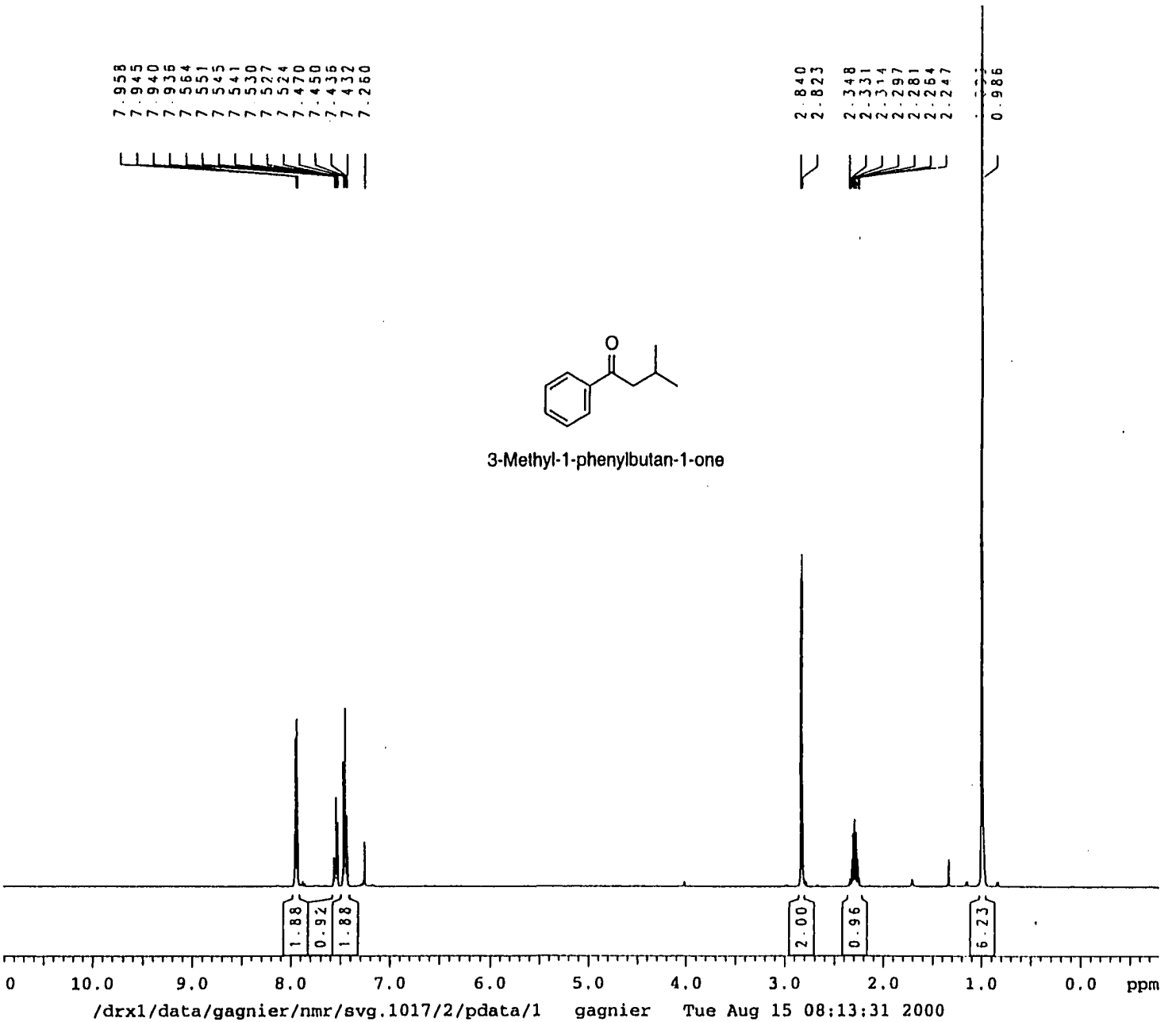
7.958
7.945
7.940
7.936
7.564
7.551
7.545
7.541
7.530
7.527
7.524
7.470
7.450
7.436
7.432
7.260
2.840
2.823
2.348
2.331
2.314
2.297
2.281
2.264
2.247
0.986
O
3-Methyl-1-phenylbutan-1-one
1.88
0.92
1.88
2.00
0.96
6.23
0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm
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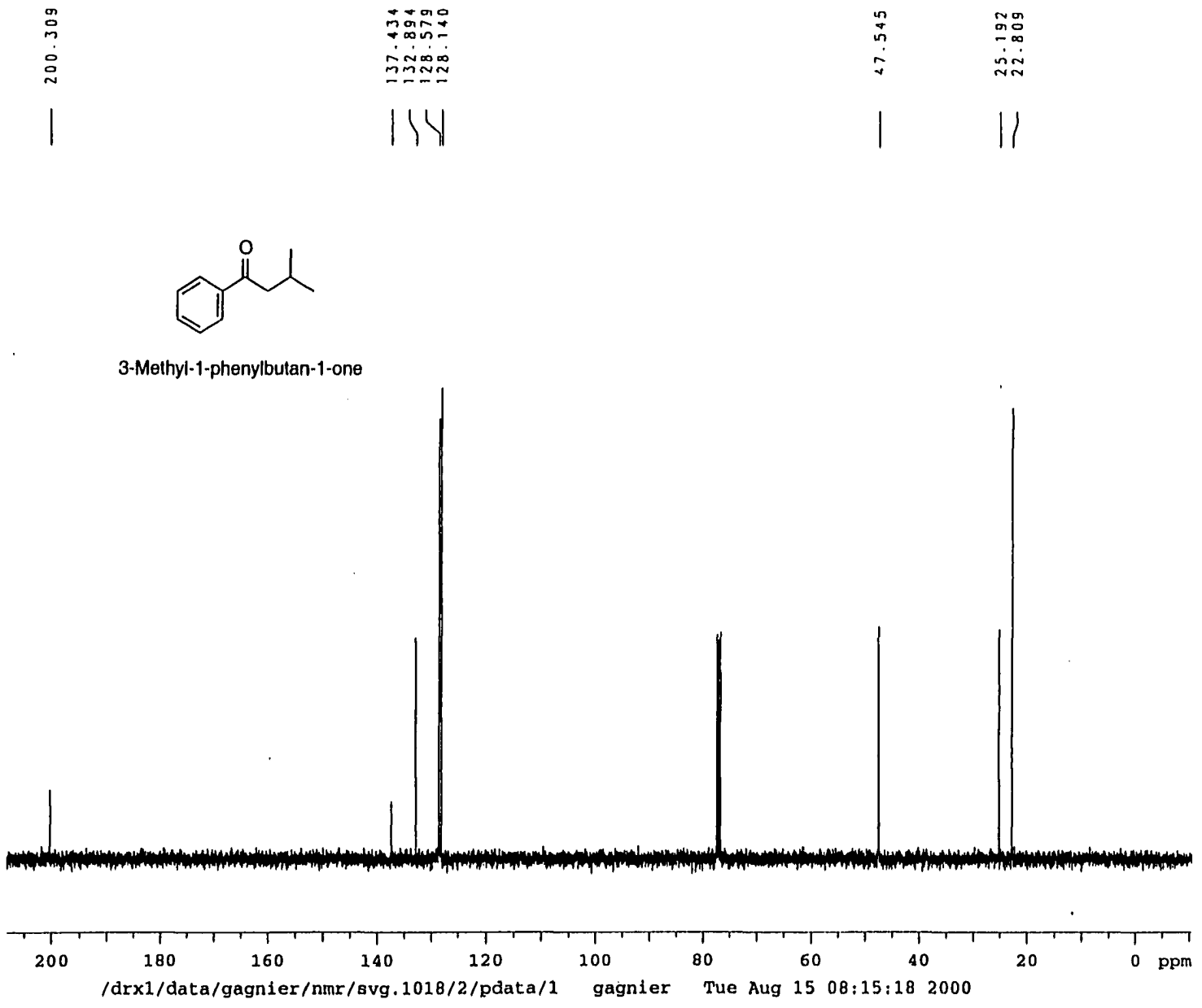
200.309
137.434
132.894
128.579
128.140
47.545
25.192
22.809
O
3-Methyl-1-phenylbutan-1-one
200
180
160
140
120
100
80
60
40
20
0 ppm
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## ACKNOWLEDGMENTS

I would like to express my sincere gratitude and appreciation to Professor Richard C. Larock. I am indebted to him for his patience, understanding, and financial support.

I would like to thank the past and present members of the Larock group that I have worked with. In particular, I would like to thank Karl Peterson for taking the time and teaching me how to do palladium chemistry in the early days.

I would like to thank my parents, Dennis and Dorothy Gagnier, for their prayers and support. Even though you may have not understood what I was working on, you never doubted for a minute that I could do it.

Finally, I would like to thank my wife Mary Kate, whose loving support and incredible sacrifices made all of this possible. WE DID IT!