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# Carbocycle synthesis via novel organopalladium addition to nitriles

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# Carbocycle synthesis via novel organopalladium addition to nitriles

by

Alexandre A. Pletnev

A dissertation submitted to the graduate faculty

in partial fulfillment of the requirements for the degree of

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Major Professor

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For the Major Program

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# LIST OF ABBREVIATIONS

| | |
|---|---|
| Ac | acetyl |
| Ar | aryl |
| aq | aqueous |
| br | broad (spectral) |
| Bu | butyl |
| °C | degrees Celsius |
| calcd | calculated |
| cat. | catalytic |
| concd | concentrated |
| d | day(s); doublet (spectral) |
| DMA | *N*,*N*-dimethylacetamide |
| DMF | *N*,*N*-dimethylformamide |
| eq | equation |
| equiv | equivalent(s) |
| Et | ethyl |
| g | gram(s) |
| GC | gas chromatorgaphy |
| h | hour(s) |
| HRMS | high-resolution mass spectrum |
| Hz | hertz |
| IR | infrared |
| LDA | lithium diisopropylamide |
| LiTMP | lithium 2,2,6,6-tetramethylpiperidide |
| m | multiplet (spectral) |
| M | moles per liter |
| Me | methyl |
| min | minute(s) |

| | |
|---|---|
| mL | milliliter(s) |
| mol | mole(s) |
| mp | melting point |
| MS | mass spectrometry |
| NMR | nuclear magnetic resonance |
| Ph | phenyl |
| *i*-Pr | isopropyl |
| q | quartet (spectral) |
| r.t. | room temperature |
| s | singlet (spectral) |
| satd. | saturated |
| t | triplet (spectral) |
| THF | tetrahydrofuran |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |

# ABSTRACT

Rarely observed carbopalladation of the cyano group has been investigated. Synthetic methodology for 2,3-diarylindenones by the palladium-catalyzed annulation of alkynes with 2-iodoarenenitriles has been developed. This methodology has also been adapted to the annulation of bicyclic olefins. The reaction affords 2,3-diarylindenones and polycyclic aromatic ketones in very good to excellent yields and tolerates a number of functional groups, making it an efficient synthetic route to these compounds. The reaction is believed to proceed via (1) oxidative addition of the aryl iodide to Pd(0), (2) arylpalladium addition to the carbon-carbon multiple bond, (3) addition of the resulting vinylic or alkylpalladium species across the triple bond of the cyano group to produce an iminopalladium moiety, and (4) hydrolysis of the imine intermediate. A model accounting for the electronic effects of substituents on the aromatic ring of the nitrile has also been proposed.

The palladium-catalyzed annulation of alkynes with iodoarenes containing a cyano group has been extended to the synthesis of 3,4-disubstituted 2-aminonaphthalenes. (2-Iodophenyl)acetonitrile reacts with a variety of internal alkynes to afford 2-aminonaphthalenes in high yields. In many cases, the regioselectivity of this reaction is excellent. The scope and limitations of this process, which proceeds via a mechanism similar to the reaction between 2-iodoarenenitriles and alkynes, have been studied. When introduced into the reaction, certain hindered propargylic alcohols have been found to afford 1,3-benzoxazine derivatives rather than the expected 2-aminonaphthalenes. The involvement of trialkylamine bases in the formation of these heterocyclic compounds has been established and a mechanism for this transformation has been proposed.

A general and efficient procedure for the synthesis of 2,2-disubstituted indanones by the palladium-catalyzed cyclization of 3-(2-iodoaryl)propanenitriles has been developed. This process is also based on intramolecular carbopalladation of the cyano group. A variety of indanones have been prepared in high yields from readily available starting materials containing various functional groups that are compatible with the reaction conditions. The reaction is not limited to the synthesis of indanones as other benzocyclic ketones, as well as a number of substituted cyclopentenones, have been synthesized by this methodology.

# GENERAL INTRODUCTION

The carbon-nitrogen triple bond represents one of the classical functional groups of organic chemistry. A unique combination of unsaturation, polarizability and low steric demand has made nitriles extremely attractive for synthetic purposes. The cyano group can be easily transformed into other functionalities. Hydrolysis and alcoholysis of nitriles can lead to amides, esters and carboxylic acids; reduction can afford aldehydes and amines; imines and ketones are produced when nitriles are treated with organometallic reagents. Even when the cyano group itself is not modified in the reaction, its presence in the molecule allows for such synthetically useful procedures as halogenations and alkylations of the α-carbon in aliphatic nitriles, or directed *o*-metallation in aromatic nitriles.

Adding to the attractiveness of the cyano group is its ease of introduction into molecules. Alkanenitriles are prepared via nucleophilic substitution in halides, sulfonates, alcohols and amines, addition of HCN and related reagents to carbon-carbon or carbon-heteroatom multiple bonds, elimination from carbonyl and carboxylic acid derivatives, as well as nitro and amino compounds. The acidity of the protons adjacent to the cyano group provides an easy opportunity to convert a relatively simple aliphatic nitrile into a more complex one via alkylation and related reactions. The synthesis of aromatic nitriles can be accomplished by the cyanation of aromatic halides (e.g., Rosenmund-von Braun reaction) or arenediazonium salts (Sandmeyer reaction). Other routes to arenenitriles include transformations of aromatic carbonyl or carboxy compounds, as well as the functionalization of benzonitrile and its derivatives.

The utility of the cyano group in heterocyclic synthesis is probably surpassed only by the amino group. The high electron density present in the cyano group makes it an excellent candidate for a variety of electrophilic additions, whereas its strong dipole moment allows for facile nucleophilic additions. Thus, nitriles have been used in the synthesis of a wide variety of hetero- and carbocyclic systems. Many of these syntheses are catalyzed by various transition metals and involve addition of organometallic species across the triple bond of the nitrile. However, examples of carbo*palladation* of the cyano group are extremely rare.

The Larock group has recently developed a number of palladium-catalyzed annulations of internal alkynes by aryl iodides containing a functional group in the *ortho* position. In this dissertation, the intramolecular addition of organopalladium species to the cyano group has been investigated and developed into efficient synthetic methodology for the construction of carbocyclic systems.

## Dissertation Organization

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

Chapter 1 describes the synthesis of 2,3-diarylindenones and related aromatic ketones by the palladium-catalyzed annulation of alkynes and bicyclic alkenes with 2-iodoarenenitriles. The scope and limitations of this methodology, based on carbopalladation of the cyano group, are explored. The effect of substituents on the aromatic ring of the nitrile on the success of the annulation is explained by the requirement that the intermediate organopalladium species possess sufficient nucleophilic character for attack on the cyano group. A reaction mechanism consistent with this effect is proposed.

Chapter 2 deals with the palladium-catalyzed reaction of internal alkynes with (2-iodophenyl)acetonitrile. This annulation is related mechanistically to the process examined in Chapter 1, but results in the formation of 3,4-disubstituted 2-aminonaphthalenes. The preparation of various 2-aminonaphthalenes in good yields is described and regioselectivity issues are discussed. Annulation of hindered propargylic alcohols in the presence of trialkylamines unexpectedly affords 1,3-benzoxazine derivatives. A mechanism for this transformation is proposed, which involves participation of the trialkylamine base employed in the reaction.

Chapter 3 extends the scope of the nitrile carbopalladation methodology to the cyclization of ω-(2-iodoaryl)alkanenitriles. 2,2-Disubstituted benzocyclic ketones are synthesized in high yields from readily prepared starting materials. The reaction is also applicable to the

synthesis of substituted cyclopentenones from appropriate vinylic substrates bearing a cyano group. The limitations of this methodology are discussed.

Finally, following some general conclusions, the $^{1}H$ and $^{13}C$ NMR spectra of all previously unknown starting materials and palladium-catalyzed reaction products are compiled in Appendices A-C of this dissertation.

# CHAPTER 1. SYNTHESIS OF 2,3-DIARYLINDENONES AND POLYCYCLIC AROMATIC KETONES VIA Pd-CATALYZED ANNULATION OF 2-IODOARENENITRILES

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

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## Abstract

Convenient and efficient syntheses of 2,3-diarylindenones and polycyclic aromatic ketones have been developed employing the carbopalladation of nitriles. The reaction represents one of the first examples of the addition of an organopalladium moiety to the carbon-nitrogen triple bond of a nitrile. 2-Iodobenzonitrile, its derivatives, and various heterocyclic analogues undergo palladium(0)-catalyzed annulation onto diarylacetylenes or bicyclic alkenes to afford 2,3-diarylindenones and polycyclic aromatic ketones in very good to excellent yields. The reaction is compatible with a number of functional groups. A reaction mechanism, as well as a model accounting for the electronic effects of substituents on the aromatic ring of the nitrile, is proposed.

## Introduction

The development of new annulation processes is one of the most challenging and important quests in organic synthesis. Annulation is one of the most efficient and economical ways of creating cyclic molecules.[1] Combining two or more independent acyclic moieties to form several bonds in one process potentially provides an opportunity to rapidly synthesize complex molecules without having to spend time and resources on the isolation of intermediates and their reintroduction into subsequent steps. This opportunity is especially

attractive in this age of high-throughput and combinatorial chemistry.[2] Equally important is the minimization of waste brought about by a decrease in the amounts of reagents and solvents required for a single-step operation as opposed to a multi-step endeavor.[3]

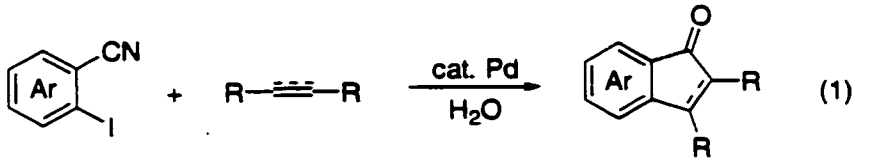
Among many transition metals used in organic synthesis, palladium is particularly useful as it offers the most versatile possibilities for carbon-carbon bond formation.[4] Palladium reagents have been used extensively to prepare various carbo- and heterocyclic compounds,[5] both by cyclic carbopalladation and annulation.[6] One of the most important factors contributing to such widespread application of palladium catalysts is their tolerance of most important organic functional groups.[4] However, as more research in palladium-mediated organic methodology is being conducted, new reaction conditions are being discovered that lead to previously unknown palladium-catalyzed reactions with "unreactive" functional groups.[7]

The cyano group has long been considered inert toward organopalladium reagents. Palladium chloride bis-acetonitrile and bis-benzonitrile are widely used catalysts, and acetonitrile is one of the most commonly employed solvents in palladium-mediated reactions.[4a,8] In most such reactions, the nitriles are not incorporated into the molecular structure of the products.[9] In many cases, substrates bearing a cyano group can undergo palladium-mediated processes that lead to products in which the cyano group remains intact. In fact, the palladium-catalyzed cyanation of aryl halides is a widely used synthetic approach to arenenitriles, which, once formed in the reaction, are not modified in any way despite the presence of organopalladium intermediates.[10] Other examples of the palladium-catalyzed introduction of a cyano group into a product include the cyanocarbonylation of iodobenzene,[11] cyanosilylation of alkynes,[12] and numerous reactions of nitrile-containing organic substrates, e.g., the cross-coupling of aryl halides with terminal acetylenes[13] or organometallic reagents,[14] α-allylation[15] and decarboxylation of α-cyanoesters.[16]

Palladium-mediated reactions that do modify the nitrile functionality[9,17] usually do not involve carbopalladation of the cyano group. However, there are rare examples of the carbopalladation of nitriles. Thus, Yang *et al.* have described the palladium-catalyzed arylation of a cyano group in the intramolecular cyclization of 2-bromoarylalkenenitriles,[18a,b]

and Cheng has reported the cyano group transfer from solvents to aryl halides mediated by palladium and zinc species.[18c]

We have recently reported that the intramolecular carbopalladation of the cyano group in 2-iodobenzonitrile and 2-iodophenylacetonitrile provides a new synthetic route to indenones, 2-aminonaphthalenes and related compounds.[19] At this time, we wish to report the full details of our investigation of the carboannulation of internal alkynes and bicyclic alkenes by 2-iodoarenenitriles that leads to 2,3-diarylindenones and related polycyclic aromatic ketones (eq 1).



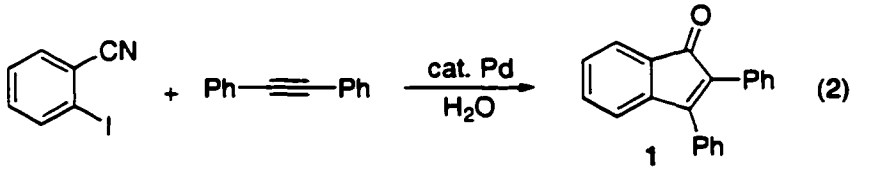

(1)

Indenones and their derivatives have been employed as fungicides and fermentation activators.[20] Their potentially useful biological activity as binding agents for estrogen receptors has been used to study the structure of the receptor's binding site and the orientation of the site's nonsteroidal ligands.[21] Indenones also serve as valuable precursors and intermediates in the synthesis of natural products (e.g. steroids and gibberellins), indanones, indenes, naphthols and other compounds.[20,22]

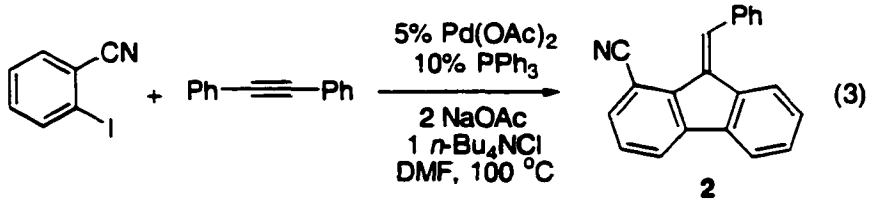
Traditionally, indenones have been synthesized via Friedel-Crafts-type cyclizations or addition of organometallic reagents to 1,3-indandiones.[21a,23] Many transition metal reagents and catalysts have been employed in indenone preparations in recent years.[20,22a] Palladium-catalyzed reactions leading to indenones (including annulation approaches) have also found a place in synthetic organic methodology.[24] One such procedure developed in this laboratory involves the annulation of internal alkynes with 2-halobenzaldehydes.[20] Although effective and reasonably general, this procedure could still be improved if more stable starting materials could be used in place of easily oxidized aldehydes.

## Results and Discussion

Ongoing research in our group on palladium-catalyzed annulation methodology[6a,25] prompted us to examine 2-iodobenzonitrile as a possible substrate for annulation onto diphenylacetylene to produce 2,3-diphenyl-1-indenone (**1**, eq 2). Encouraged by the success of the intramolecular reaction of an aldehyde, a group normally inert toward organopalladium species,[7] we envisioned that a cyano group might serve as a neighboring functional group in this reaction and that the vinylpalladium intermediate might add across the carbon-nitrogen triple bond (see the later mechanistic discussion).

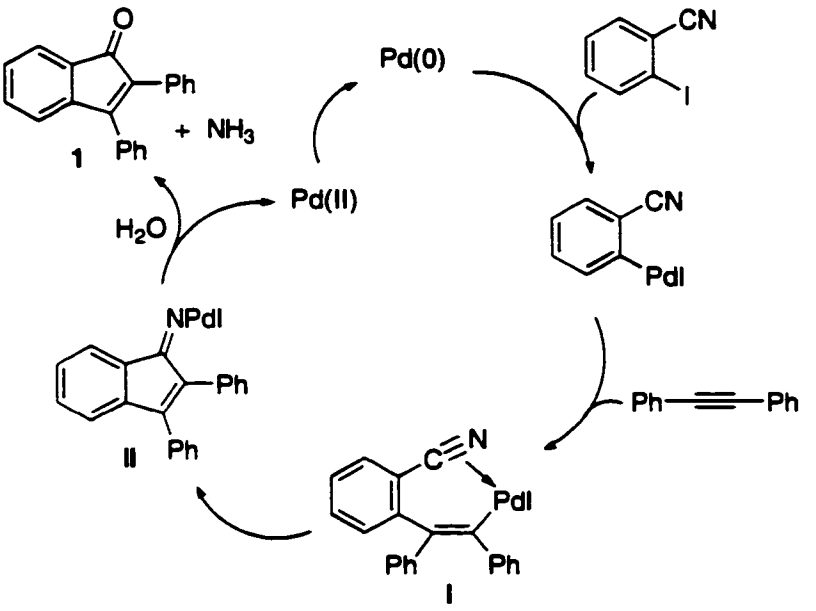



Under our standard reaction conditions developed for the synthesis of fluorenes,[26] 2-iodobenzonitrile reacted with diphenylacetylene to afford the fluorene product **2** in 63% yield (eq 3). In the absence of $PPh_3$, the reaction furnished **2** in 56% yield. When the solvent was changed from DMF to 9:1 DMF-water, to our delight, the major product (28%) was found to be the target indenone **1** (eq 2).




Based on our previous research on alkyne annulation chemistry,[6a,25a] we propose the following mechanism for the formation of **1** from 2-iodobenzonitrile and diphenylacetylene (Scheme 1). Oxidative addition of 2-iodobenzonitrile to Pd(0), formed *in situ* from Pd(II), is followed by diphenylacetylene insertion that leads to the vinylpalladium intermediate **I**. The latter then adds across the carbon-nitrogen triple bond of the neighboring cyano group to produce the iminopalladium intermediate **II**,[27] which hydrolyzes to the indenone **1**.

**Scheme 1**




Reduction of the Pd(II) species produced is required to afford a catalytic process and occurs at some point in the reaction.

Since the yield of the reaction was low, substantial optimization efforts were undertaken to improve the yield of this annulation (Table 1). Drawing on the findings of concurrent work on the optimization of a similar annulation of 2-iodophenylacetonitrile,[19] the details of which will be reported in due course, we ran the reaction using catalytic $Pd(OAc)_2$ under conditions described in Table 1, entry 1. This procedure led to a 30% yield of **1**. The yield did not improve upon addition of two equivs of water, nor upon reducing the amount of the base (entries 2 and 3, respectively). Using aqueous DMF as a solvent resulted in higher yields of **1** (entries 4 and 5). The addition of triphenylphosphine, intended to facilitate the initial reduction of Pd(II) to Pd(0), as well as to serve as a ligand for palladium, had no effect on the reaction (entry 6). We then decided to use a Pd(0) catalyst. Employing 10% $Pd(dba)_2$ raised the yield of **1** to 62% (entry 7). An almost identical yield was obtained when *n*-$Bu_4NCl$ was omitted, proving that a chloride source was unnecessary for the annulation (entry 8). Since one equiv of ammonia was supposedly forming in the reaction (Scheme 1), we questioned whether using two equivalents of triethylamine was required, and studied the effect of the amount of base on the reaction yield (entries 9-13). The best results were

**Table 1. Optimization of the Pd-Catalyzed Annulation of Diphenylacetylene by 2-Iodobenzonitrile (eq 2)[a]**

| entry | catalyst | additive (equiv) | $Et_3N$ equiv | solvent | time (h) | % isolated yield of 1[b] |
|---|---|---|---|---|---|---|
| 1 | 5% $Pd(OAc)_2$ | *n*-$Bu_4NCl$ (1) | 3 | DMF | 48 | 30 |
| 2 | 5% $Pd(OAc)_2$ | *n*-$Bu_4NCl$ (1) | 3 | DMF | 48 | 25[c] |
| 3 | 5% $Pd(OAc)_2$ | *n*-$Bu_4NCl$ (1) | 2 | DMF | 48 | 30 |
| 4 | 5% $Pd(OAc)_2$ | *n*-$Bu_4NCl$ (1) | 2 | 4:1 DMF-$H_2O$ | 24 | 45 |
| 5 | 5% $Pd(OAc)_2$ | *n*-$Bu_4NCl$ (1) | 2 | 9:1 DMF-$H_2O$ | 24 | 42 |
| 6 | 5% $Pd(OAc)_2$ | *n*-$Bu_4NCl$ (1), $PPh_3$ (0.2) | 2 | 9:1 DMF-$H_2O$ | 24 | 42 |
| 7 | 10% $Pd(dba)_2$ | *n*-$Bu_4NCl$ (1) | 2 | 9:1 DMF-$H_2O$ | 24 | 62 |
| 8 | 10% $Pd(dba)_2$ | - | 2 | 9:1 DMF-$H_2O$ | 24 | 60 |
| 9 | 10% $Pd(dba)_2$ | - | - | 9:1 DMF-$H_2O$ | 48 | 11[d] |
| 10 | 10% $Pd(dba)_2$ | - | 0.5 | 9:1 DMF-$H_2O$ | 24 | 10 |
| 11 | 10% $Pd(dba)_2$ | - | 1 | 9:1 DMF-$H_2O$ | 24 | 74 |
| 12 | 10% $Pd(dba)_2$ | - | 2 | 9:1 DMF-$H_2O$ | 72 | 59 |
| 13 | 10% $Pd(dba)_2$ | - | 3 | 9:1 DMF-$H_2O$ | 24 | 48 |
| 14 | 10% $Pd(dba)_2$ | - | 1 | 9:1 DMF-$H_2O$ | 13 | 61(71)[d] |
| 15 | 10% $Pd(dba)_2$ | - | 1 | 9:1 DMF-$H_2O$ | 17 | 66(70)[d] |
| 16 | 10% $Pd(dba)_2$ | - | 1 | 9:1 DMF-$H_2O$ | 48 | 38[e] |
| 17 | 10% $Pd(dba)_2$ | $Ag_3PO_4$ (0.4) | 1 | 9:1 DMF-$H_2O$ | 24 | trace |
| 18 | 10% $Pd(dba)_2$ | $AgNO_3$ (1.2) | 1 | 9:1 DMF-$H_2O$ | 24 | trace |
| 19 | 10% $Pd(dba)_2$ | $TlPF_6$ (1.2) | 1 | 9:1 DMF-$H_2O$ | 24 | 25(40)[d] |
| 20 | 10% $Pd(dba)_2$ | $PPh_3$ (0.2) | 1 | 9:1 DMF-$H_2O$ | 24 | 62 |
| 21 | 10% $Pd(dba)_2$ | TPPTS (0.2)[f] | 1 | 9:1 DMF-$H_2O$ | 24 | 66 |

[a] All reactions were run with 3 equivs of diphenylacetylene at 100 °C unless specified otherwise. [b] All yields in parentheses are corrected for unreacted starting material. [c] Two equivs of water were added to the reaction mixture. [d] Incomplete conversion of 2-iodobenzonitrile. [e] This reaction was run at 80 °C. [f] TPPTS = tris(3-sulfonatopheny!)phosphine, sodium salt.

obtained when we employed only one equiv of triethylamine (entry 11), whereas using both lesser and greater amounts was detrimental to the success of the annulation. It was also established that the reaction required a full 24 hours, since using shorter reaction times resulted in incomplete consumption of the 2-iodobenzonitrile (entries 14 and 15). Lowering the reaction temperature slowed the annulation considerably and led to only a 38% yield of **1** after 48 h (entry 16). Finally, we studied the effect of some additives on the reaction (entries 17-21). Hoping that a cationic palladium intermediate similar to **I** (Scheme 1) might coordinate to the carbon-nitrogen bond more strongly and thus affect the carbopalladation step favorably, we employed silver and thallium salts known to sequester halide anions from palladium complexes (entries 17-19),[28] only to find that their use decreased the yield of the indenone **1**. Using phosphine ligands resulted in lower yields compared to the phosphine-free annulation (entries 20 and 21).

We also conducted several experiments designed to elucidate the identity of the reagent responsible for the reduction of Pd(II) back to Pd(0) (Table 2). After analysis of the reaction conditions, we focused on two possibilities. Under our reaction conditions, it seemed plausible that DMF could react with water to produce formic acid, which is known to reduce Pd(II) species.[29] Alternatively, the reduction could be effected by triethylamine since alkylamines containing α-carbon-hydrogen bonds are also capable of reducing Pd(II) complexes.[30] Substitution of triethylamine by collidine, a non-reducing amine, using our best reaction conditions resulted in a sharply lower yield of the annulation product (Table 2, entry 2). However, when we employed DMA instead of DMF (entry 3), the yield of **1**

**Table 2. Effect of the Solvent and Base on the Annulation (eq 2)**[a]

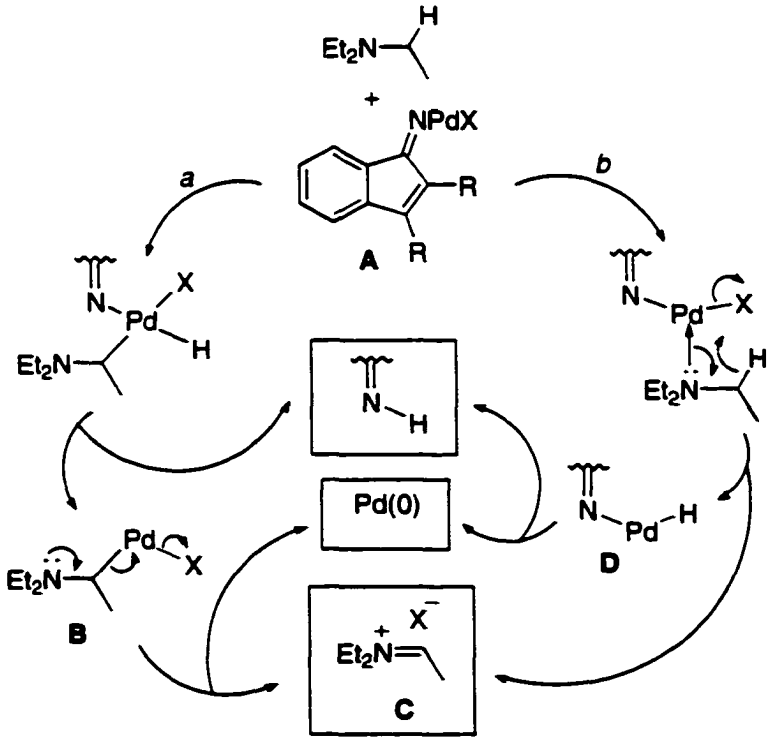
| entry | base | solvent | time (h) | % yield of **1** |
|---|---|---|---|---|
| 1 | $Et_3N$ | DMF | 24 | 74 |
| 2 | collidine | DMF | 48 | 11 |
| 3 | $Et_3N$ | DMA | 24 | 69 |
| 4 | *i*-$Pr_2NEt$ | DMF | 24 | 57 |

[a] Reactions were run with 3 equivs of diphenylacetylene, 10 mol % of $Pd(dba)_2$, and 1 equiv of the base in 9:1 solvent-water mixture at 100 °C.

remained virtually unaffected, which strongly discounts the possible role of DMF in the reduction. Obtaining **1** in a 57% yield in the experiment using *i*-$Pr_2NEt$ instead of $Et_3N$ (entry 4) seems to support our hypothesis that the alkylamine base may be the reagent actually reducing Pd(II) to Pd(0) in the catalytic cycle in Scheme 1. The lower yield in entry 4 is presumably caused by fewer α-C-H bonds available for the reduction in *i*-$Pr_2NEt$ compared to $Et_3N$ or simply the greater difficulty Pd(II) is going to have in coordinating to this more hindered amine.

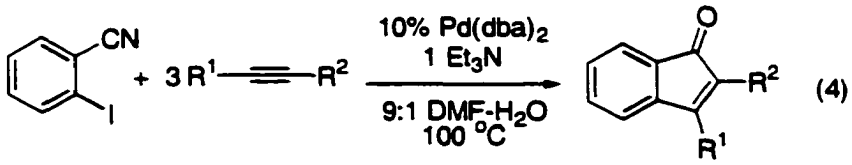
We propose the following two tentative mechanisms for the reduction of Pd(II) by triethylamine (Scheme 2). A palladium(II) species, such as **A**, may undergo insertion into the α-C-H bond activated by the nitrogen in $Et_3N$ (pathway *a*). Examples of such insertion have been reported.[31] Following reductive elimination of the organic product, the (α-aminoalkyl)palladium complex **B** is formed. Fragmentation of **B** leads to a Pd(0) species, which returns to the catalytic cycle, and an iminium salt **C**, generation of which has also been proposed as the key step in Pd-catalyzed transformations of trialkylamines.[31] Alternatively,

**Scheme 2**



**A** could coordinate to the nitrogen in $Et_3N$ and then undergo *pseudo* β-hydride elimination to afford **C** and an organopalladium species **D**, which produces Pd(0) upon reductive elimination (pathway *b*).[32]

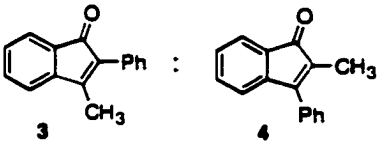
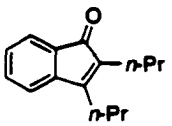
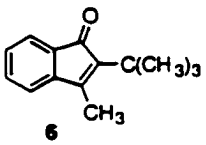
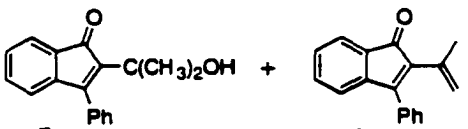
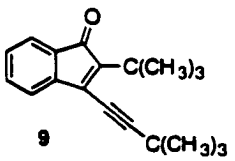
Using our best reaction conditions (Table 1, entry 11), we proceeded to test the applicability of our procedure to the annulation of other alkynes (eq 4). The annulation of 2-iodobenzonitrile onto 1-phenyl-1-propyne resulted in the formation of an inseparable 1:1 mixture of regioisomeric indenones **3** and **4** in a combined 32% yield after a 48 h reaction period (Table 3, entry 1). Only a trace amount of 2,3-di-*n*-propyl-1-indenone (**5**) was detected in the reaction of 4-octyne (entry 2), with about 40% of the starting 2-iodobenzonitrile still present after 48 h. Indenone **6** was formed in low yield when 2-iodobenzonitrile was annulated onto 4,4-dimethyl-2-pentyne (entry 3). The annulation of 2-methyl-4-phenyl-3-butyn-2-ol afforded the expected indenone **7** in an 8% yield along with 3-phenyl-2-(2-propenyl)-1-indenone (**8**), which was apparently derived from **7** (entry 4). This reaction also suffered from low conversion of the starting nitrile. Finally, we were able to obtain 2-*tert*-butyl-3-(*tert*-butylethynyl)-1-indenone (**9**) in a 16% yield from the reaction between 2-iodobenzonitrile and 2,2,7,7-tetramethyl-3,5-octadiyne (entry 5). The reasons behind the poor yields in the annulation of alkynes other than diphenylacetylene are unclear considering that these alkynes have readily participated in many other palladium-mediated annulation reactions.[6a,20,25a] Although we have made no attempt to do so, we believe that it should be possible to optimize the reaction conditions for each individual alkyne and get significantly improved yields.



(4)

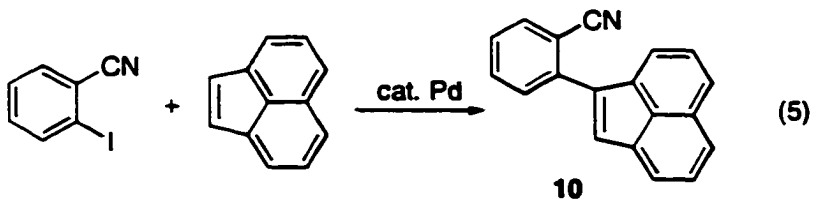
We have also screened a large number of different olefins in an attempt to extend the nitrile annulation methodology to include alkenes and dienes. No annulation products were observed in the reactions of 2-iodobenzonitrile with *cis*-stilbene, indene, 3,4-dihydronaphthalene, 2,3-dioxene, *N*-phenylmaleimide, undeca-1,2-diene, 1-phenylpropa-1,2-diene, 1,3-cyclohexadiene, and 1,4-cyclohexadiene. However, the reaction of 2-iodobenzonitrile

**Table 3. Annulation of 2-Iodobenzonitrile onto Various Alkynes (eq 4)**[a]

| entry | alkyne | time (h) | product(s) | % yield |
|---|---|---|---|---|
| 1 | Ph—≡—$CH_3$ | 48 |  **3** : **4** | 32[b] |
| 2 | *n*-Pr—≡—*n*-Pr | 48 |  **5** | trace[c] |
| 3 | $H_3C$—≡—$C(CH_3)_3$ | 48 |  **6** | 7 |
| 4 | Ph—≡—$C(CH_3)_2OH$ | 48 |  **7** + **8** | 8 + 6[c] |
| 5 | $(H_3C)_3C$—≡—≡—$C(CH_3)_3$ | 24 |  **9** | 16 |

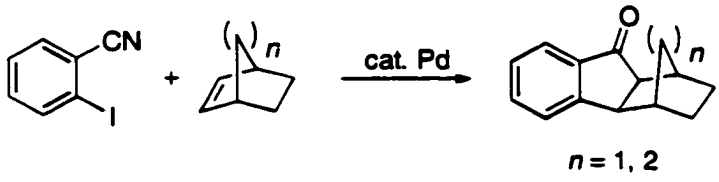
[a] All reactions were run with 3 equivs of the alkyne, 10 mol % of $Pd(dba)_2$ and 1 equiv of $Et_3N$ in a 9:1 DMF-water mixture at 100 °C. [b] Isolated as a 1:1 inseparable mixture of isomers **3** to **4**. [c] Incomplete conversion of 2-iodobenzonitrile.

with acenaphthylene afforded a Heck type product **10** in 57 % yield (eq 5). We believe that the latter reaction follows our proposed annulation mechanism, but the benzylic palladium intermediate formed undergoes solvolysis faster than it can add to the cyano group. The driving force behind this solvolysis is probably the formation of a stable, highly delocalized benzylic cation, which, upon losing a proton, leads to **10**.




**10** (5)

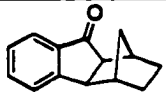
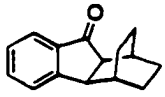
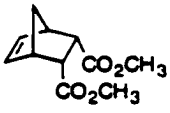
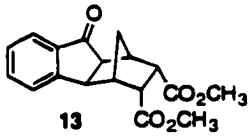
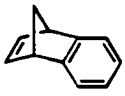
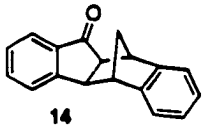
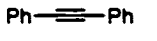
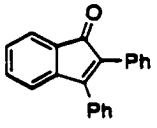
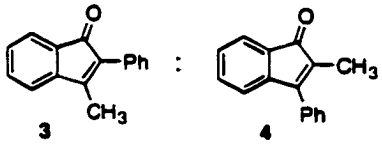
During the course of our study of the scope of the nitrile annulation chemistry, we have found that bicyclic alkenes undergo facile annulation by 2-iodobenzonitrile (eq 6). Palladium hydride elimination during annulation, which is likely the major factor in the failure of other olefins and alkylacetylenes, is prevented in bicyclic alkenes by the inability of palladium to align in a *cis*-fashion with the bridgehead hydrogen. Such elimination would also produce a very strained bridgehead olefin.




$n = 1, 2$ (6)

We have also observed the beneficial effect of increasing the temperature on the yields of this reaction (Table 4). Thus, polycyclic ketone **11** was obtained in 85% yield when the annulation was run at 100 °C. The yield improved to 93% when the temperature was raised to 130 °C (entry 1). The expected *exo* stereochemistry of **11** was confirmed by comparing its $^1$H NMR spectrum to the literature data.[33] A high reaction temperature proved even more beneficial for the annulation of 2-iodobenzonitrile onto bicyclo[2.2.2]octene (entry 2). Not only did it increase the yield of the product ketone **12**, it also enhanced the reaction rate, which was sluggish at 100 °C, presumably because of steric hindrance around the double bond of the olefin. Functionalized polycyclic ketone **13** was obtained from the corresponding norbornene derivative in 89% yield (entry 3), demonstrating the nitrile annulation's tolerance of the ester functionality. The reaction of benzonorbornadiene (prepared from benzyne and cyclopentadiene by a Diels-Alder cycloaddition)[34] at 100 °C was slow, but this problem was rectified by raising the temperature (entry 4). Repeated attempts to carry out a double annulation of 2-iodobenzonitrile onto norbornadiene failed as the nitrile was recovered even at a high temperature and after a prolonged reaction time. We believe that norbornadiene may have formed a strong complex with the palladium catalyst, thus removing the latter from the reaction.[35] This could also explain the low reactivity of benzonorbornadiene (entry 4), which is capable of forming a similar complex with Pd.

**Table 4. Effect of the Temperature on the Annulation of Bicyclic Alkenes and Alkynes (eqs 4 and 6)[a]**

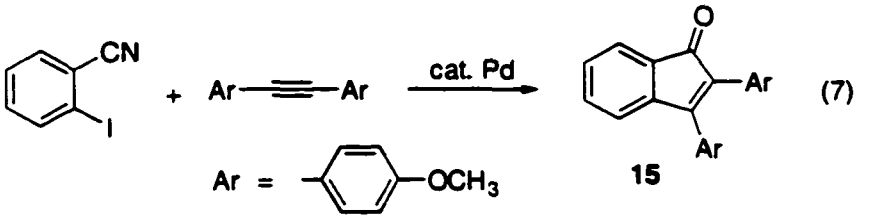
| entry | substrate | product(s) | % yield | |
|---|---|---|---|---|
| | | | at 100 °C | at 130 °C |
| 1 |  |  **11** | 85 | 93 |
| 2 |  |  **12** | 55[b] | 82 |
| 3 |  |  **13** | 70 | 89 |
| 4 |  |  **14** | -[c] | 59 |
| 5 |  |  **1** | 74 | 96 |
| 6 |  |  **3** : **4** | 32[d] | 34[d] |

[a] See the Experimental Section for the reaction conditions. [b] The reaction time was 72 h. [c] The yield was not determined due to the low conversion of the 2-iodobenzonitrile after 48 h. [d] Isolated as a 1:1 inseparable mixture of isomers **3** to **4**.

Similarly, elevating the reaction temperature improved the yield of 2,3-diphenylindenone (**1**), which was previously obtained in 74% yield using our original reaction conditions (Table 1, entry 11), to almost a quantitative yield (Table 4, entry 5). However, no improvement was observed when 2-iodobenzonitrile was allowed to react with 1-phenyl-1-propyne. The annulation at 130 °C afforded an inseparable 1:1 mixture of the two possible

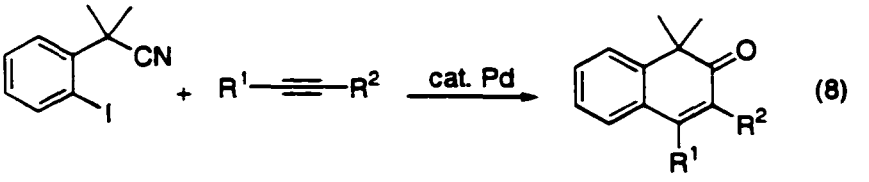
regioisomers **3** and **4** (entry 5) in a yield almost identical to that obtained at a lower temperature (Table 3, entry 1).

Based on the aforementioned results, our optimal annulation conditions are as follows: 0.25 mmol of 2-iodobenzonitrile, 3 equivs of diphenylacetylene or bicyclic alkene, 10 mol % of $Pd(dba)_2$, 1 equiv of $Et_3N$, and 5 ml of 9:1 DMF-water as the solvent at 130 °C for 24 h. This procedure is expected to be a useful method for the synthesis of various 2,3-diarylindenones other than **1**, as illustrated by the 79% yield of indenone **15** we have obtained (eq 7).




(7)

We have also found that the analogous annulation of 2-(2-iodophenyl)-2-methylpropanenitrile onto diphenylacetylene affords a high yield of the expected six-membered ring aromatic ketone **16** (eq 8). Mirroring our observations in the indenone synthesis, regioisomeric naphthenones **17** and **18** are formed in 18 and 11 % yields, respectively, when the unsymmetrical alkyne 1-phenyl-1-propyne is used in the annulation.

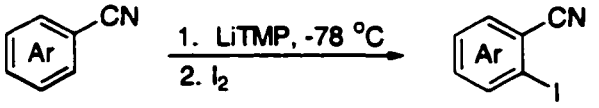



(8)

**16** ($R^1$, $R^2$ = Ph) 96%
**17** ($R^1$ = Ph, $R^2$ = $CH_3$) 18%
**18** ($R^1$ = $CH_3$, $R^2$ = Ph) 11%

Having established the alkyne and olefin limitations of the nitrile annulation methodology, we set out to explore the range of nitrile-containing components we might employ. Several strategies were used to synthesize a series of aromatic *o*-iodoarenenitrile starting materials.

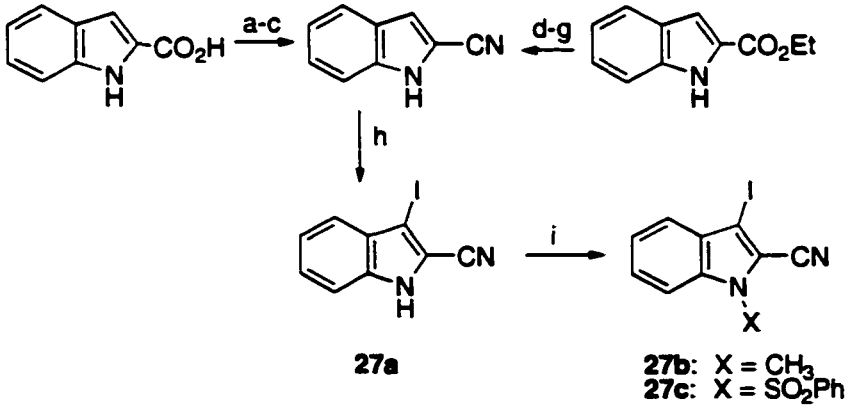
Using the synthetically underutilized ability of the cyano group to direct *o*-lithiation,[36] we successfully adopted the procedure of Fraser and Savard for the synthesis of *o*-iodoarenenitriles (eq 9).[37] Nitrile-containing substrates **19-23** were prepared in good yields by *o*-lithiation of the corresponding arenenitriles with lithium tetramethylpiperidide (LiTMP), followed by quenching with iodine (Table 5, entries 1-5). 2,3-Dicyano-1,4-diiodobenzene (**23**) was obtained from sequential introduction of each iodine substituent into the molecule (entry 5). The procedure was also applicable to the synthesis of heterocyclic *o*-iodoarenenitriles **24-26** (entries 6 and 7). *o*-Lithiation-iodination of 3-cyanopyridine produced a hard-to-separate mixture of regioisomeric **24** and **25** that were partially isolated by column chromatography.




(9)

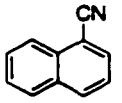
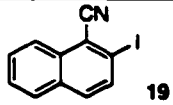
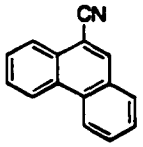
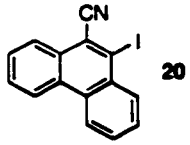
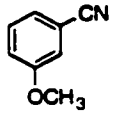
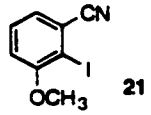
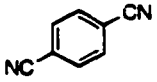
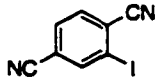
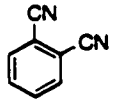
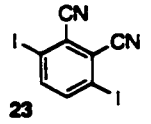
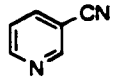
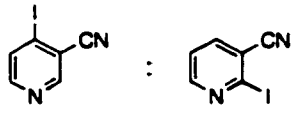
We also prepared two series of regioisomeric heterocyclic substrates designed to probe the effect of steric hindrance and electron density in the indole ring on the nitrile annulation. Substituted iodoindolecarbonitriles **27** and **28** were synthesized as shown in Schemes 3 and 4, respectively. Depending on the immediate availability of the starting materials, 2-cyano-

**Scheme 3**




(a) $SOCl_2$, ether, r.t.; (b) $NH_3$, ether, r.t.; (c) $POCl_3$, reflux; (d) LAH, ether, r.t.; (e) $MnO_2$, ether, r.t.; (f) $H_2NNMe_2$, benzene, reflux; then MeI; (g) MeONa, MeOH, reflux; (h) KOH, $I_2$, DMF, r.t.; (i) NaH, DMF, 0 °C; then MeI or $PhSO_2Cl$, r.t.

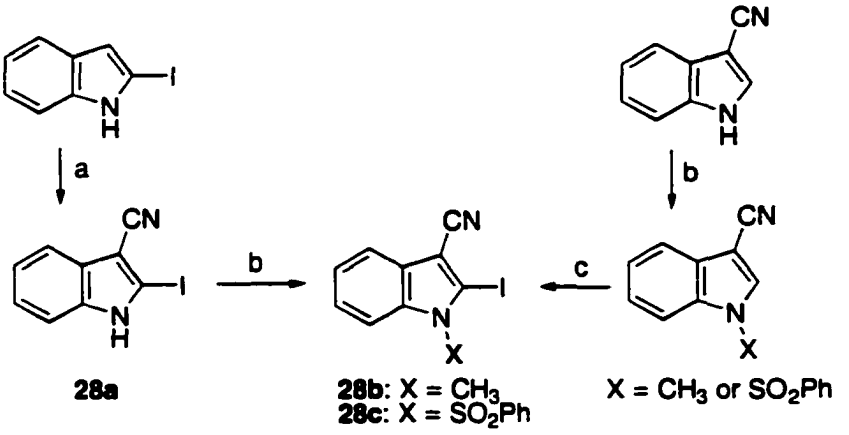
**Table 5. Preparation of *o*-Iodoarenenitriles by Nitrile-Directed *o*-Lithiation (eq 9)[a]**

| entry | substrate | product(s) | % yield |
|---|---|---|---|
| 1 |  |  **19** | 63 |
| 2 |  |  **20** | 60 |
| 3 |  |  **21** | 50 |
| 4 |  |  **22** | 72 |
| 5 |  |  **23** | 74[b] |
| 6 |  |  **24** : **25** | 50[c] |
| 7 |  |  **26** | 87 |

[a] See the Experimental Section for the reaction conditions. [b] A two-step reaction sequence was employed here. [c] Isolated as a 1:1 hard-to-separate mixture of isomers **24** to **25**.

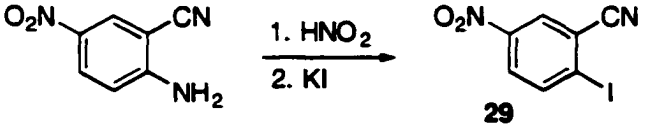
indole was obtained in good yield from either indole-2-carboxylic acid or ethyl indole-2-carboxylate and then iodinated to afford **27a**, which was derivatized at the nitrogen atom to give **27b** and **27c** (Scheme 3). 2-Iodoindole-3-carbonitrile **28a** was prepared from 2-iodoindole and was then functionalized to produce indoles **28b** and **28c** (Scheme 4). An alternative method starting with indole-3-carbonitrile worked well for the *N*-methyl compound, but *o*-lithiation-iodination of the *N*-sulfonylated precursor to hopefully produce **28c** afforded a mixture of products that had to be separated.

**Scheme 4**



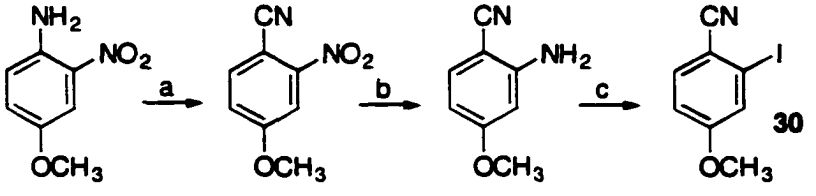

(a) $ClSO_2NCO$, MeCN, 0 °C; then $Et_3N$, r.t.; (b) NaH, DMF, 0 °C; then MeI or $PhSO_2Cl$, r.t.; (c) LiTMP, THF, -78 °C; then $I_2$, -78 °C to r.t.

Finally, we synthesized substituted 2-iodobenzonitriles **29** and **30** for a study of the electronic effect of substituents on the benzene ring. 2-Iodo-5-nitrobenzonitrile (**29**) was obtained in 65% yield by iodination of the diazonium salt prepared from 5-nitroanthranilonitrile (eq 10). A three-step synthesis based on variations of the Sandmeyer reaction afforded the electron-rich 2-iodo-4-methoxybenzonitrile (**30**) in 30% overall yield (Scheme 5).



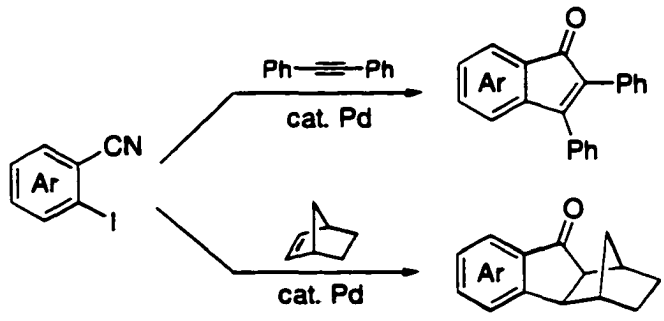

(10)

**Scheme 5**




(a) $NaNO_2$, $H_2SO_4$, 0 °C; then CuCN, NaCN, $H_2O$; (b) $SnCl_2$, AcOH, DME, 60 °C; (c) $NaNO_2$, $H_2SO_4$, 0 °C; then KI, $H_2O$, r.t.

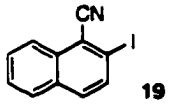
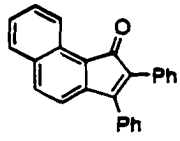
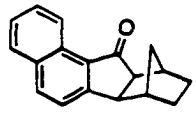
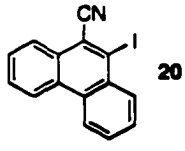
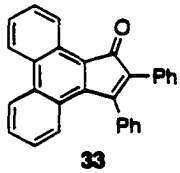
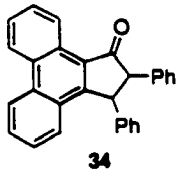
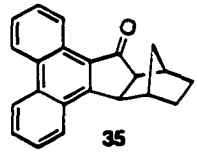
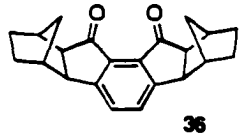
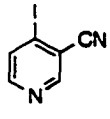
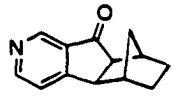
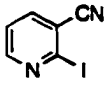
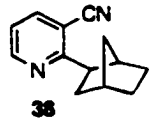
**Scheme 6**




With various *o*-iodoarenenitriles in hand, we proceeded to explore their annulation onto diphenylacetylene and norbornene (Scheme 6). 1-Cyano-2-iodonaphthalene (**19**) readily participated in both reactions, affording polycyclic ketones **31** and **32** in excellent yields identical to those obtained with 2-iodobenzonitrile (Table 6, entry 1). To our surprise, the annulation of 9-cyano-10-iodophenanthrene (**20**) onto diphenylacetylene produced not only the expected fully conjugated ketone **33**, but also its dihydro derivative **34**, which apparently is formed from **33** so as to relieve the former compound's anti-aromaticity (Table 6, entry 2). This phenomenon has been previously observed in an unrelated synthesis of **33**.[38] The reaction of **20** with norbornene proceeded smoothly and led to polycyclic ketone **35** in high yield (entry 2). An attempted double annulation of 2,3-dicyano-1,4-diiodobenzene (**23**) onto diphenylacetylene afforded a complex reaction mixture, in which we were unable to identify any individual annulation products (entry 3). However, the double annulation succeeded in the case of norbornene, and polycyclic dione **36** was obtained as a mixture of several diastereomers (entry 3).

Somewhat surprisingly, no annulation products were observed when *o*-iodonicotinonitriles **24** and **25** were allowed to react with diphenylacetylene (entries 4 and 5). The failure may possibly be caused by competing coordination of the pyridines and alkynes with palladium. Yet, no problems were encountered in the annulation of **24** onto norbornene, which produced the heterocyclic ketone **37** in a good yield (entry 4). We found, however, that the reaction between **25** and norbornene did not lead to the expected annulation product, but rather to 2-(2-norbornyl)pyridine-3-carbonitrile (**38**, entry 5). It seems quite likely that the nitrogen atom of the pyridine ring chelates to the palladium center in the intermediate

**Table 6. Annulation of 2-Iodoarenenitriles (Scheme 6)[a]**

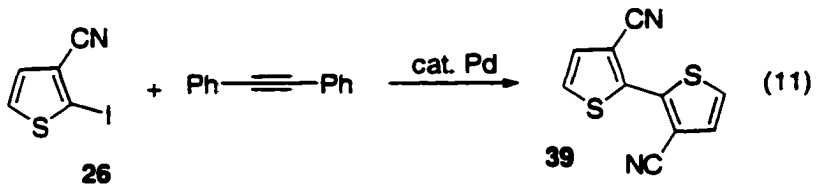
| entry | nitrile | from diphenylacetylene | | from norbornene | |
|---|---|---|---|---|---|
| | | product(s) | % yield[b] | product(s) | % yield[b] |
| 1 |  **19** |  **31** | 96 |  **32** | 93 |
| 2 |  **20** |  **33** +  **34** | 22<br>45 |  **35** | 91 |
| 3 |  **23** | -[c] | - |  **36** | 33[d] |
| 4 |  **24** | -[c] | - |  **37** | 52 |
| 5 |  **25** | - | - |  **38** | 40 |

[a] See the Experimental Section for the reaction conditions. [b] Isolated yield. [c] A complex product mixture is formed. [d] Isolated as a mixture of diastereomers.

corresponding to **I** in Scheme 1, thus preventing the norbornylpalladium species from adding to the cyano group and eventually leading to reduction of the C-Pd bond in this intermediate.

An obstacle of a different kind was encountered in the attempted annulation of 2-iodothiophene-3-carbonitrile (**26**). Instead of incorporating diphenylacetylene into the product structure, this reaction afforded the homocoupling product **39** in 85% yield (eq 11).

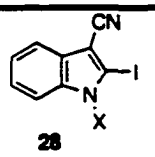
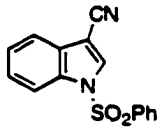
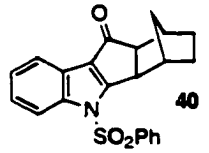
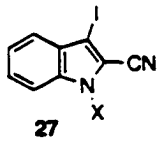
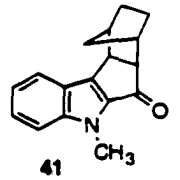
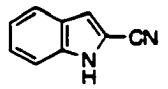
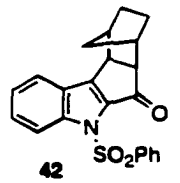
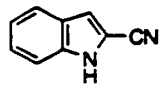
Presumably, the palladium catalyst is ligated by the sulfur atom in **26**, making coordination to the alkyne less favorable.




After no annulation was observed in the reaction between several indolecarbonitriles (**27a**, **27c**, **28b**) and diphenylacetylene, compounds **27** and **28** were subjected to annulation onto norbornene (Table 7). The more electron-rich *N*-methyl-2-iodo-3-indolecarbonitrile (**28b**) and the parent cyanoindole **28a** furnished no annulation products (entries 1 and 2). Considering the possibility that sluggish oxidative addition of the electron-rich **28a** and **28b** to the palladium catalyst may be responsible for these disappointing results, we annulated norbornene with the more electron-poor **28c**. This reaction afforded mostly *N*-(benzenesulfonyl)indole-3-carbonitrile. However, the annulation product **40** was also obtained, albeit only in a modest 16% yield (entry 3). Steric hindrance around the reaction site probably accounts for the large amount of the reduced starting material in this reaction.

To separate sterics from electronic effects, a series of indolecarbonitriles with a different substitution pattern was studied. The electron-rich **27b** furnished a 77% yield of the heterocyclic annulation product **41** (entry 4), whose skeleton is related to that of a key intermediate in the synthesis of a natural product yuehchukene and its analogs.[39] The unprotected indolecarbonitrile **27a** afforded 2-cyanoindole in a high yield with no annulation product (entry 5). This result is likely caused by the ease of nitrogen deprotonation in **27a**, which leads to the formation of a negatively charged arylpalladium intermediate and impedes its coordination and subsequent addition to norbornene. The annulation of *N*-benzenesulfonyl-3-iodoindole-2-carbonitrile (**27c**) was far more successful, the target product **42** being formed in a 69% isolated yield (entry 6). Desulfonylation and subsequent reduction of the C-I bond in **27c** accounted for 20% of the starting material, which brings the corrected yield of **42** to 86%. Interestingly, no desulfonylated annulation products were detected in the reactions of either **27c** or **28c** (entries 3 and 6).

**Table 7. Annulation of Norbornene with Indolecarbonitriles**[a]

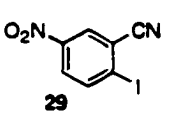
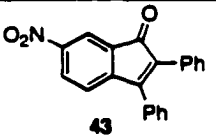
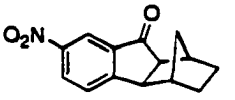
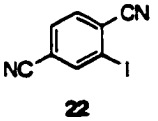
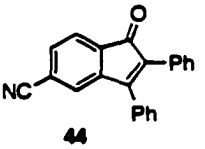
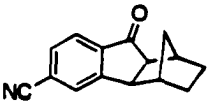
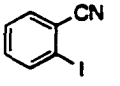
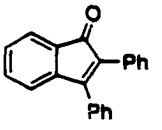
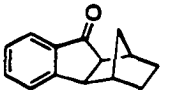
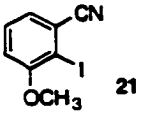
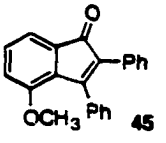
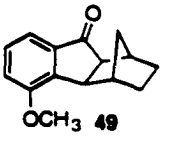
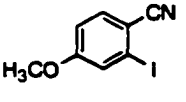
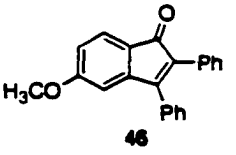
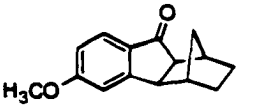
| entry | indolecarbonitrile | X | product(s) | % isolated yield |
|---|---|---|---|---|
| 1 |  **28** | $CH_3$ (**28b**) | - | - |
| 2 | | H (**28a**) | - | - |
| 3 | | $SO_2Ph$ (**28c**) |  +  **40** | 52<br>16 |
| 4 |  **27** | $CH_3$ (**27b**) |  **41** | 77 |
| 5 | | H (**27a**) |  | 81 |
| 6 | | $SO_2Ph$ (**27c**) |  **42** +  | 69(86)[b]<br>20 |

[a] See the Experimental Section for the reaction conditions. [b] The yield in parentheses is corrected for the diverted starting material.

The steric hindrance around the reaction site appears to have a pronounced effect on the annulation of indolecarbonitriles (compare entries 3 and 6, and 1 and 4), although other factors cannot be excluded. However, the success of the annulation of both the electron-rich **27b** and the electron-poor **27c** suggests that the electronic density of the indole ring does not play a significant role in this reaction.

In contrast, the electronic effects of the substituents in the benzene ring appear to have a major influence on the alkyne annulation with substituted 2-iodobenzonitriles (Table 8). Thus, electron-deficient benzonitrile derivatives **29** and **22** when annulated onto diphenylacetylene afford only moderate yields of indenones **43** and **44** (entries 1 and 2)

**Table 8. Annulation of Substituted 2-Iodobenzonitriles (Scheme 6)**[a]

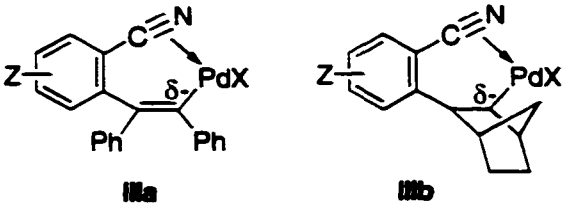
| entry | nitrile | from diphenylacetylene | | from norbornene | |
|---|---|---|---|---|---|
| | | product | % yield | product | % yield |
| 1 |  **29** |  **43** | 53 |  **47** | 81 |
| 2 |  **22** |  **44** | 47 |  **48** | 85[b] |
| 3 |  |  | 96 |  **11** | 93 |
| 4 |  **21** |  **45** | 58 |  **49** | 75 |
| 5 |  **30** |  **46** | 81[b] |  **50** | 84[b,c] |

[a] See the Experimental Section for the reaction conditions. [b] The reaction time was 48 h. [c] A byproduct, 4-methoxybenzonitrile, was isolated in 16% yield.

compared to the reaction with the parent system (entry 3). The electron-rich 2-iodo-3-methoxybenzonitrile (**21**) also produced indenone **45** in a modest yield (entry 4). On the other hand, the annulation of diphenylacetylene by the less sterically hindered **30** resulted in the formation of indenone **46** in a much higher yield (entry 5).

Both electron-deficient and electron-rich benzonitriles gave equally good results when used in the annulation of norbornene (Table 8). The yields of the polycyclic ketones **47-50** were as good as, or better than, the yields of the corresponding indenones. Electron-withdrawing substituents did not have nearly as big an effect on the annulation of norbornene with **29** and **22** (entries 1 and 2), although the yields of **47** and **48** were still lower than those obtained with 2-iodobenzonitrile itself (entry 3). Annulation of the relatively hindered **21** onto norbornene gave a higher yield compared to the corresponding reaction with diphenylacetylene (entry 4), most probably due to the reduced steric demands of the double bond in the bicyclic system. A reduction product, 4-methoxybenzonitrile, was formed in 16% yield from **30**, diverting some starting material from the annulation and lowering the otherwise excellent yield of **50** (entry 5).

We propose the following model to account for the electronic effects of the substituent on the aromatic ring on the annulation onto alkynes and alkenes (Fig 1). In order for the organopalladium intermediate **III** to successfully add to the cyano group, there has to be a sufficient partial negative charge (δ-) on the carbon atom of the Pd-C bond, as well as reasonable electron density in the carbon-nitrogen triple bond in order for the nitrile to effectively coordinate to palladium. When the annulation involves an alkyne, intermediate **IIIa** is formed, in which an electron-withdrawing substituent Z directly reduces, via conjugation, both the electron density of the cyano group and the partial negative charge




IIIa IIIb

**Figure 1.** Electronic effects of substituent Z on annulations involving 2-iodobenzonitriles.

on the carbon bearing the palladium moiety, thus inhibiting vinylpalladium attack on the CN and lowering the yield of the annulation.[40] In the case of norbornene, Z has no direct effect on the partial negative charge δ- (intermediate **IIIb**) and only affects the coordinating ability of the cyano group. It is also possible that the nitrile carbopalladation in **IIIb** is promoted by the steric interactions between the Pd and the bridging methylene unit of the norbornyl system as it relieves the steric congestion. As a result, norbornene annulation by electron-poor substrates furnishes higher yields than the corresponding diphenylacetylene reactions. An electron-donating Z group should not interfere with the annulation, except perhaps by slowing down the initial oxidative addition, as observed in the case of **30** (entry 5, Table 8).

## Conclusions

The carbon-nitrogen triple bond of aryl and heteroaryl nitriles has been observed to readily participate in organopalladium annulation reactions. An efficient procedure for the synthesis of 2,3-diarylindenones and polycyclic aromatic ketones from readily prepared *o*-iodoarenenitriles has been developed. The reaction is compatible with a variety of functional groups and affords products in good to excellent yields. We have also gained some insights into the mechanism of nitrile carbopalladation through variation of the base and a study of electronic and steric effects in substituted 2-iodobenzonitriles and indolecarbonitriles. This chemistry illustrates that there may be other organopalladium reactions which will occur intramolecularly that normally do not occur by intermolecular processes.

## Experimental Section

**General.** $^{1}H$ and $^{13}C$ NMR spectra were recorded at 300 and 75 MHz or 400 and 100 MHz, respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) 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. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass

spectrometer using EI at 70 eV. IR spectra were measured on a Bomem Michelson MB-102 FT-IR spectrometer. All reagents were used directly as obtained commercially unless otherwise noted. $Pd(OAc)_2$ was donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. $PPh_3$ was also donated by Kawaken Fine Chemicals Co., Ltd. $Pd(dba)_2$ was prepared according to a published procedure.[41] 2-Iodobenzonitrile was obtained from Trans World Chemicals, Inc. Diphenylacetylene, acenaphthylene, norbornene, tetramethylpiperidine, 5-nitroanthranilonitrile, indole-2-carboxylic acid, ethyl indole-2-carboxylate, indole-3-carbonitrile, 4-methoxy-2-nitroaniline, triethylamine, 4-octyne, 2,2,7,7-tetramethyl-3,5-octadiyne, 1-cyanonaphthalene, 9-cyanophenanthrene, 3-methoxybenzonitrile, 1,2-dicyanobenzene, 1,4-dicyanobenzene, and 3-cyanopyridine were obtained from Aldrich Chemical Co., Inc. Bicyclo[2.2.2]octene was obtained from Wiley Organics. Tetra-*n*-butylammonium chloride, 2-iodophenylacetonitrile, 4,4-dimethyl-2-pentyne, and thiophene-3-carbonitrile were obtained from Lancaster Synthesis, Inc. 1-Phenyl-1-propyne and 2-methyl-4-phenyl-3-butyn-2-ol were obtained from Farchan Laboratories, Inc.

**Starting materials**. Dimethyl *cis,endo*-5-norbornene-2,3-dicarboxylate,[42] benzonorbornadiene,[34] and 2-iodoindole[43] were prepared according to published procedures.

**General Procedure for the Preparation of 2-Iodoarenecarbonitriles via Nitrile-Directed *o*-Lithiation - Iodination.** To a solution of 2,2,6,6-tetramethylpiperidine (0.85 g, 6.0 mmol) in 25 mL of anhydrous THF at 0 °C under Ar was added 4 mL of 1.5 M solution of MeLi (6 mmol) in hexane. The resulting solution was stirred at 0 °C for 30 min, cooled to –78 °C, and 6 mmol of an aromatic nitrile (as a solution in THF, if solid) was added slowly. The dark solution was stirred for 35-60 min at –78 °C, after which a solution of $I_2$ (1.68 g, 6.6 mmol) in 2.5 mL of THF was added. After stirring for 2 h at –78 °C, the mixture was allowed to warm up to room temperature and stirred for 1 h. Then, 20 mL of ice-water was added, the mixture was extracted with ether, the ethereal extracts were combined, and washed with dilute HCl, water, aq $Na_2S_2O_3$, and brine. After drying over $MgSO_4$, the ether was removed, and the product was purified by column chromatography or recrystallization.

The following compounds, prepared by the above procedure, have been previously reported: 1-cyano-2-iodonaphthelene (**19**),[37] 9-cyano-10-iodophenanthrene (**20**),[44] 1,4-dicyano-2-iodobenzene (**22**),[45] and 2-iodothiophene-3-carbonitrile (**26**).[46]

**2-Iodo-3-methoxybenzonitrile (21).** Obtained in a 50% yield from 3-methoxybenzonitrile under the indicated conditions after recrystallization from hexanes: white solid, mp 121-122 °C (hexanes); $^1$H NMR ($CDCl_3$) δ 3.93 (s, 3H), 7.00 (dd, $J$ = 8.4, 0.8 Hz, 1H), 7.23 (dd, $J$ = 7.6, 1.2 Hz, 1H), 7.42 (t, $J$ = 8.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 56.8, 91.1, 114.4, 119.4, 122.1, 126.3, 129.9, 159.1; IR (neat) 2228, 2840, 3082 cm$^{-1}$; HRMS *m/z* 258.94988 (calcd for $C_8H_6INO$, 258.94942).

**2,3-Dicyano-1,4-diiodobenzene (23).** Obtained in a 74% yield from two consecutive lithiations of 1,2-dicyanobenzene under the indicated conditions after recrystallization from acetone: light yellow solid, mp (dec.) 230-232 °C (acetone); $^1$H NMR ($CDCl_3$) δ 7.80 (s, 2H); $^{13}$C NMR ($CDCl_3$) δ 98.6, 115.8, 125.5, 143.5; IR (neat) 2225 cm$^{-1}$; HRMS *m/z* 379.83123 (calcd for $C_8H_2I_2N_2$, 379.83075).

**3-Cyano-4-iodopyridine (24)** and **3-cyano-2-iodopyridine (25).** Obtained in a 50% combined yield from the reaction of 3-cyanopyridine under the indicated conditions. The mixture of **24** and **25** was partially separated by column chromatography using 1:2 hexanes/EtOAc. Nitrile **24**: light yellow solid, mp (dec.) 114-119 °C (hexanes/EtOAc); $^1$H NMR ($CDCl_3$) δ 7.91 (d, $J$ = 5.6 Hz, 1H), 8.39 (d, $J$ = 5.2 Hz, 1H), 8.73 (s, 1H); $^{13}$C NMR ($CDCl_3$) δ 109.6, 115.3, 134.0, 141.1, 152.1, 153.1; IR (neat) 2231 cm$^{-1}$; HRMS *m/z* 229.93441 (calcd for $C_6H_3IN_2$, 229.93410). Nitrile **25**: beige solid, mp (dec.) 120-122 °C (hexanes/EtOAc); $^1$H NMR ($CDCl_3$) δ 7.43 (m, 1H), 7.82 (m, 1H), 8.54 (dd, $J$ = 4.8, 2.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 117.7, 119.9, 121.0, 122.5, 141.2, 152.9; IR (neat) 2228 cm$^{-1}$; HRMS *m/z* 229.93441 (calcd for $C_6H_3IN_2$, 229.93410).

**3-Iodoindole-2-carbonitrile (27a).** *From indole-2-carboxylic acid*: the acid was converted to indole-2-carbonitrile by a published procedure.[47] To a cooled solution of indole-2-carboxylic acid (2.0 g, 12.4 mmol) in 60 mL of anhydrous $Et_2O$ was added 1.9 mL of $SOCl_2$ (26 mmol). After stirring for 40 min at room temperature, the ether was removed under reduced pressure at a temperature not exceeding 35 °C. The obtained acyl chloride was dissolved in 40 mL of anhydrous $Et_2O$ and the resulting solution was added immediately

to a stirred solution of liquid ammonia in 80 ml of $Et_2O$. The reaction mixture was stirred at room temperature for 24 h. The solvent was then evaporated under reduced pressure, and the white indole-2-carboxamide was crystallized from 50% aq EtOH and dried in air, after which it was dissolved in $POCl_3$ and heated under reflux for 5 min. The cooled solution was poured onto crushed ice and aq $NH_4OH$ was added to maintain a basic pH. The aqueous mixture was extracted with $Et_2O$, the extracts were dried over $Na_2SO_4$ and evaporated. The brown indole-2-carbonitrile (68% overall yield from indole-2-carboxylic acid) was recrystallized from 33% aq EtOH, dried, and iodinated according to the procedure of Chashi *et al.*[48] A cold solution of $I_2$ (0.72 g, 2.8 mmol) in 6 mL of DMF was added to a solution of indole-2-carbonitrile (0.4 g, 2.8 mmol) and powdered KOH (0.56 g, 10 mmol) in 6 mL of DMF. After stirring at room temperature for 4 h, the reaction mixture was poured into 600 mL of water containing 40 mL of 30% aq $NH_4OH$. The precipitate was collected by filtration and dried to afford 0.56 g (75%) of **27a**, whose spectral properties matched those previously reported.[49]

**3-Iodoindole-2-carbonitrile (27a).** *From ethyl indole-2-carboxylate*: the ester (1.5 g, 7.93 mmol) was quantitatively reduced with $LiAlH_4$ (0.553 g, 14.55 mmol) in ether at room temperature, and the resulting 2-(hydroxymethyl)indole was oxidized to indole-2-carbaldehyde with $MnO_2$.[50] The aldehyde was converted into indole-2-carbonitrile as follows:[51] a solution of the crude indole-2-carbaldehyde (0.9 g, 6.2 mmol) and $H_2NNMe_2$ (1.116 g, 18.6 mmol) in 35 mL of dry benzene was refluxed with a Dean-Stark separator for 4 h, concentrated to half the volume with the trap open, cooled to room temperature, and MeI (1.16 mL, 18.6 mmol) was added. The reaction mixture was refluxed for 2 h, cooled, diluted with $Et_2O$ and filtered to collect the white precipitate, which was dried in a dessicator and added to a freshly prepared solution of NaOMe (made from 6.52 mmol of Na and 20 mL of MeOH). The resulting mixture was refluxed for 4 h, after which MeOH was evaporated to afford crude indole-2-carbonitrile (66% yield), which was converted into **27a** as described above.[48]

***N*-Methyl-3-iodoindole-2-carbonitrile (27b).** A solution of **27a** (1.03 g, 3.83 mmol) in 1 mL of DMF was slowly added to a suspension of NaH (0.184 g, 7.66 mmol) in 2 mL of DMF at 0 °C under Ar. After stirring for 30 min at room temperature, MeI (0.36 mL, 5.75 mmol) was added over a few minutes. The mixture was then stirred for 1 h at room

temperature, cooled in ice, diluted with aq $NH_4OH$ and extracted with $Et_2O$. The ethereal extracts were combined, dried over $Na_2SO_4$, evaporated and chromatographed (2:1 hexanes-EtOAc) to afford **27b** in 84% yield: light yellow solid, mp 106-107 °C (hexanes-EtOAc); $^1H$ NMR ($CDCl_3$) δ 3.88 (s, 3H), 7.23-7-29 (m, 2H), 7.41-7.45 (m, 2H); $^{13}C$ NMR ($CDCl_3$) δ 32.4, 69.1, 110.3, 113.1, 122.1, 122.7, 126.7, 129.2, 137.6 (1 $sp^2$ carbon missing due to overlap); IR (neat) 2219, 2926, 3065 $cm^{-1}$; HRMS *m/z* 281.96592 (calcd for $C_{10}H_7IN_2$, 281.96540).

***N*-Benzenesulfonyl-3-iodoindole-2-carbonitrile (27c).** Obtained in 96% yield following the procedure for **27b** using $PhSO_2Cl$ instead of MeI after extraction with EtOAc and column chromatography with 2:1 hexanes-EtOAc: off-white solid, mp 210-211 °C (hexanes-EtOAc); $^1H$ NMR ($CDCl_3$) δ 7.42-7.44 (m, 2H), 7.50-7.54 (m, 2H), 7.58-7.64 (m, 2H), 8.03-8.05 (m, 2H), 8.20 (d, $J$ = 8.4 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 85.6, 112.2, 114.5, 123.6, 125.4, 127.2, 129.7, 129.8, 130.7, 135.0, 135.9, 137.0 (1 $sp^2$ carbon missing due to overlap); IR (neat) 1184, 1379, 2231, 3086 $cm^{-1}$; HRMS *m/z* 407.94341 (calcd for $C_{15}H_9IN_2O_2S$, 407.94295).

**2-Iodoindole-3-carbonitrile (28a)** was obtained according to a modified procedure of Vorbrüggen.[52] To a solution of 2-iodoindole (0.24 g, 1 mmol) in 2 mL of MeCN, kept in an ice-water bath, was slowly added 0.09 mL (1.05 mmol) of $ClSO_2NCO$. The reaction mixture was stirred for 2 h at 0 °C, after which $Et_3N$ (0.146 mL, 1.05 mmol) was added dropwise. After stirring for another 2 h at room temperature, the mixture was poured into ice water and extracted with $Et_2O$. The extracts were dried with $Na_2SO_4$ and chromatographed using 1:1 hexanes-EtOAc to afford **28a** in 40% yield: white solid, mp 185-186 °C (hexanes-EtOAc); $^1H$ NMR ($CDCl_3$) δ 7.24-7.29 (m, 2H), 7.41-7.43 (m, 1H), 7.68-7.70 (m, 1H), 8.82 (br s, 1H); $^{13}C$ NMR (DMSO-$d_6$) δ 92.5, 94.0, 112.0, 116.5, 117.5, 121.9, 123.5, 128.2, 138.0; IR (neat) 2217, 3246 $cm^{-1}$; HRMS *m/z* 267.95012 (calcd for $C_9H_5IN_2$, 267.94975).

***N*-Methyl-2-iodoindole-3-carbonitrile (28b).** Indole-3-carbonitrile was methylated according to the procedure for **27b**, and the *N*-methyl derivative was converted into crude **28b** by nitrile-directed *o*-lithiation-iodination as described above. Recrystallization from 2:1 hexanes-EtOAc afforded **28b** in 91% yield: beige solid, mp 148-149 °C (hexanes-EtOAc); $^1H$ NMR ($CDCl_3$) δ 3.76 (s, 3H), 7.18-7.25 (m, 2H), 7.31 (d, $J$ = 7.6 Hz, 1H), 7.59 (d, $J$ = 7.2

Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 35.1, 94.9, 95.8, 110.6, 116.2, 118.5, 122.2, 123.8, 128.6, 137.3; IR (neat) 2213, 2932, 3058 $cm^{-1}$; HRMS *m/z* 281.96601 (calcd for $C_{10}H_7IN_2$, 281.96540). Alternatively, **28b** was obtained from **28a** by methylation according to the procedure for **27b**.

***N*-Benzenesulfonyl-2-iodoindole-3-carbonitrile (28c)** was obtained from **28a** by sulfonylation according to the procedure for **27c** and recrystallized from 2:1 hexanes-EtOAc, 95% yield: white solid, mp 191-192 °C (hexanes-EtOAc); $^1$H NMR ($CDCl_3$) δ 7.35-7.43 (m, 2H), 7.50-7.55 (m, 2H), 7.60-7.68 (m, 2H), 7.97-8.00 (m, 2H), 8.32-8.35 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ 87.0, 114.5, 115.5, 119.1, 125.1, 126.6, 127.4, 129.3, 129.6, 130.1, 135.0, 137.6 (1 $sp^2$ carbon missing due to overlap); IR (neat) 1194, 1378, 2228 $cm^{-1}$; HRMS *m/z* 407.94341 (calcd for $C_{15}H_9IN_2O_2S$, 407.94295). Nitrile-directed *o*-lithiation-iodination of *N*-benzenesulfonyl indole-3-carbonitrile led to a hard-to-separate mixture of **28c**, unreacted starting material, and 2-iodoindole-3-carbonitrile.

**2-Iodo-5-nitrobenzonitrile (29)** was prepared by the procedure of Clive *et al.*[53] A solution of $NaNO_2$ (0.56 g, 8.1 mmol) in 2.5 ml of water was added, with stirring, to a cold (0 °C) solution of 5-nitroanthranilonitrile (1.2 g, 7.35 mmol) in 10 ml of concentrated HCl and 15 g of ice. The mixture was stirred at 0 °C for 30 min and the cold solution, maintained at 0 °C, was added dropwise over 20-30 min to a stirred solution (room temperature) of KI (12.2 g, 73 mmol) in 15 ml of water. The resulting mixture was stirred at room temperature overnight and extracted with $CH_2Cl_2$. The extracts were washed with 10% aq NaOH solution, 5% aq $NaHCO_3$, and water, and dried over $MgSO_4$. 2-Iodo-5-nitrobenzonitrile (**29**) was obtained in 65% yield upon column chromatography with 1:1 hexanes-$CH_2Cl_2$: yellowish solid, mp 116-117 °C (EtOH); $^1$H NMR ($CDCl_3$) δ 8.11 (dd, $J$ = 8.4, 2.4 Hz, 1H), 8.19 (d, $J$ = 8.4 Hz, 1H), 8.44 (d, $J$ = 2.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 106.9, 117.4, 122.2, 127.6, 128.6, 128.9, 141.0; IR (neat) 1360, 1502, 2233 $cm^{-1}$; HRMS *m/z* 273.92429 (calcd for $C_7H_3IN_2O_2$, 273.92393).

**2-Iodo-4-methoxybenzonitrile (30)**. 2-Nitroanisidine was converted into 4-methoxy-2-nitrobenzonitrile by the procedure of Rapaport.[54] 2-Nitroanisidine (1.68 g, 10 mmol) was diazotized at 0 °C as described in the procedure for **29**. The solution of the resulting diazonium salt was neutralized by addition of solid $Na_2CO_3$ and added slowly, with stirring,

to a suspension of CuCN (0.94 g, 10.5 mmol) and NaCN (1.03 g, 21 mmol) in 6 mL of $H_2O$ at 0 °C. The reaction mixture was stirred for 1 h at room temperature, the precipitate was dissolved in $CH_2Cl_2$, the aqueous layer was discarded, and the organic layer was washed with water, dried over $Na_2SO_4$ and evaporated to afford 4-methoxy-2-nitrobenzonitrile (73% yield), which was used without further purification. 4-Methoxy-2-nitrobenzonitrile (0.7 mmol) was dissolved in 3 mL of a 5:4:1 DME-EtOH-AcOH mixture, a solution of $SnCl_2$ (5.5 mmol) in the same solvent mixture was added dropwise with stirring, the reaction mixture was stirred at room temperature for 5 min, then at 65 °C for 3 h, and worked up to afford a quantitative yield of 2-amino-4-methoxybenzonitrile. Using the procedure for **29**, 2-amino-4-methoxybenzonitrile was converted into **30**, which was obtained in 61% yield after column chromatography with 1:1 hexanes-$CH_2Cl_2$: yellow solid, mp 76-78 °C (EtOH); $^1$H NMR ($CDCl_3$) δ 3.86 (s, 3H), 6.95 (dd, $J$ = 8.4, 2.4 Hz, 1H), 7.40 (d, $J$ = 2.4 Hz, 1H), 7.50 (d, $J$ = 8.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 55.8, 99.2, 112.1, 114.4, 119.6, 124.9, 135.1, 162.4; IR (neat) 2218, 2841, 3090 cm$^{-1}$; HRMS *m/z* 258.94988 (calcd for $C_8H_6INO$, 258.94942).

**General Procedure for the Palladium-Catalyzed Annulation of Alkynes and Bicyclic Alkenes with 2-Iodoarenenitriles.** Palladium bis(dibenzylideneacetone) (14.4 mg, 0.025 mmol), $Et_3N$ (25.3 mg, 0.25 mmol), the 2-iodoarenenitrile (0.25 mmol), the alkyne or bicyclic alkene (0.75 mmol), and 5 mL of a 9:1 DMF-water mixture were placed in a 4 dram vial, which was heated in an oil bath at 130 °C for the appropriate period of time. The reaction mixture was cooled, diluted with ether, washed with saturated aq $NH_4Cl$, dried over anhydrous $Na_2SO_4$, and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column.

The following compounds, prepared by the above procedure, have been previously reported by us: indenones **1**, **3-7** and **9**, polycyclic aromatic ketones **11** and **12**, and naphthenone **16**.[19,20] Also, 2,3-diphenyl-1*H*-benz[*g*]inden-1-one (**31**),[55] 1-oxo-2,3-diphenyl-1*H*-cyclopenta[*l*]phenanthrene (**33**),[38] 1-oxo-2,3-dihydro-2,3-diphenyl-1*H*-cyclopenta[*l*]-phenanthrene (**34**),[38,56] 3,3'-dicyano-2,2'-bithiophene (**39**),[57] 4-methoxy-2,3-diphenyl-1-indenone (**45**),[58] and 5-methoxy-2,3-diphenyl-1-indenone (**46**)[58] have been described elsewhere.

**3-Phenyl-2-(2-propenyl)-1-indenone (8).** Obtained in a 6% yield from the reaction of 2-methyl-4-phenyl-3-butyn-2-ol and 2-iodobenzonitrile according to the general procedure at 100 °C after purification by column chromatography using 20:1 hexanes/EtOAc: orange solid, mp 104-106 °C (hexanes-EtOAc); $^1$H NMR ($CDCl_3$) δ 1.71 (s, 3H), 5.23-5.24 (m, 1H), 5.26-5.28 (m, 1H), 7.05 (d, $J$ = 7.2 Hz, 1H), 7.24-7.26 (m, 1H), 7.30-7.33 (m, 1H), 7.45-7.53 (m, 6H); $^{13}$C NMR ($CDCl_3$) δ 22.5, 120.1, 121.1, 122.8, 128.0, 128.5, 128.6, 128.7, 129.2, 130.8, 133.2, 133.3, 134.9, 145.3, 154.5, 196.2; IR (neat) 1703, 2970, 3033 cm$^{-1}$; HRMS *m/z* 246.10475 (calcd for $C_{18}H_{14}O$, 246.10447).

**1-(2-Cyanophenyl)acenaphthylene (10).** Obtained in a 57% yield from the reaction of acenaphthylene and 2-iodobenzonitrile according to the general procedure at 100 °C after purification by column chromatography using 20:1 hexanes/EtOAc: bright yellow solid, mp 168-170 °C (benzene); $^1$H NMR ($CDCl_3$) δ 7.42-7.48 (m, 1H), 7.50 (s, 1H), 7.57-7.64 (m, 2H), 7.65-7.71 (m, 1H), 7.72-7.84 (m, 4H), 7.86-7.90 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ 111.5, 119.0, 124.3, 125.5, 127.6, 127.7, 128.0, 128.1, 128.3, 128.6, 128.8, 129.9, 130.4, 132.7, 134.3, 138.3, 138.5, 138.9, 139.5; IR (neat) 2223, 3043, 3062 cm$^{-1}$; HRMS *m/z* 253.08946 (calcd for $C_{19}H_{11}N$, 253.08915).

**Dimethyl 1,2,3,4,4a,9a-hexahydro-1,4-methano-9-oxofluorene-*cis,endo*-2,3-dicarboxylate (13).** Obtained in an 89% yield from the reaction of dimethyl *cis,endo*-5-norbornene-2,3-dicarboxylate and 2-iodobenzonitrile according to the general procedure after purification by column chromatography using 2:1 hexanes/EtOAc: off-white solid, mp 142-144 °C (hexanes-EtOAc); $^1$H NMR ($CDCl_3$) δ 0.96-1.04 (m, 2H), 2.63-2.65 (m, 1H), 2.87-2.92 (m, 2H), 3.00-3.06 (m, 1H), 3.13-3.19 (m, 1H), 3.64 (s, 6H), 3.94 (d, $J$ = 6.0 Hz, 1H), 7.27-7.32 (m, 1H), 7.49-7.56 (m, 2H), 7.63-7.66 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ 33.5, 41.6, 43.8, 44.4, 46.0, 46.7, 50.5, 51.6, 51.9, 123.3, 126.3, 127.5, 135.2, 139.2, 142.6, 156.7, 172.2, 207.3; IR (neat) 1702, 1728, 1743, 2923, 2985, 3078 cm$^{-1}$; HRMS *m/z* 314.11597 (calcd for $C_{18}H_{18}O_5$, 314.11542).

**4b,5,10,10a-Tetrahydro-5,10-methanobenz[*b*]fluoren-11-one (14).** Obtained in a 59% yield from the reaction of benzonorbornadiene and 2-iodobenzonitrile according to the general procedure after purification by column chromatography using 4:1 hexanes/EtOAc: white solid, mp 86-87 °C (hexanes); $^1$H NMR ($CDCl_3$) δ 1.31-1.36 (m, 1H), 1.63-1.67 (m,

1H), 2.70-2.73 (m, 1H), 3.37 (d, $J$ = 5.7 Hz, 1H), 3.43 (s, 1H), 3.66 (s, 1H), 7.12-7.15 (m, 2H), 7.26-7.35 (m, 2H), 7.41-7.44 (m, 1H), 7.63-7.68 (m, 2H), 7.77 (d, $J$ = 7.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 42.8, 46.8, 48.2, 48.3, 55.5, 121.3, 121.4, 123.7, 126.1, 126.2, 127.9, 135.2, 140.7, 147.3, 148.0, 156.0, 206.7 (1 $sp^2$ carbon missing due to overlap); IR (neat) 1703, 2966, 3026 cm$^{-1}$; HRMS *m/z* 246.10475 (calcd for $C_{18}H_{14}O$, 246.10447).

**2,3-Di(4-methoxyphenyl)-1-indenone (15).** Obtained in a 79% yield from the reaction of bis(4-methoxyphenyl)acetylene and 2-iodobenzonitrile according to the general procedure after purification by column chromatography using 4:1 hexanes/EtOAc: dark red solid, mp 118-119 °C (hexanes-EtOAc); $^1$H NMR ($CDCl_3$) δ 3.79 (s, 3H), 3.85 (s, 3H), 6.82 (dd, $J$ = 7.2, 2.0 Hz, 2H), 6.94 (dd, $J$ = 7.2, 2.0 Hz, 2H), 7.16 (d, $J$ = 7.2 Hz, 1H), 7.22-7.27 (m, 3H), 7.33-7.37 (m, 3H), 7.55 (dd, $J$ = 6.8, 0.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 55.2, 55.3, 113.6, 114.1, 120.9, 122.6, 123.4, 125.0, 128.6, 130.1, 130.9, 131.1, 131.2, 133.2, 145.4, 153.7, 159.0, 160.2, 196.9; IR (neat) 1705, 2834, 2957, 3066 cm$^{-1}$; HRMS *m/z* 342.12611 (calcd for $C_{23}H_{18}O_3$, 342.12559).

**1,1,3-Trimethyl-4-phenyl-1,2-dihydronaphthalen-2-one (17).** Obtained (along with **18**) in an 18% yield from the reaction of 1-phenyl-1-propyne and 2-(2-iodophenyl)-2-methylpropanenitrile according to the general procedure after purification by column chromatography using 20:1 hexanes/EtOAc: pink solid, mp 61-62 °C (hexanes-EtOAc); $^1$H NMR ($CDCl_3$) δ 1.56 (s, 6H), 1.76 (s, 3H), 6.83 (dd, $J$ = 8.0, 0.8 Hz, 1H), 7.10 (td, $J$ = 8.0, 0.8 Hz, 1H), 7.19-7.20 (m, 2H), 7.32 (td, $J$ = 8.0, 0.8 Hz, 1H), 7.41-7.45 (m, 1H), 7.47-7.52 (m, 3H); $^{13}$C NMR ($CDCl_3$) δ 13.9, 28.3, 46.8, 125.8, 126.2, 127.7, 128.2, 128.5, 128.6, 128.7, 129.2, 130.8, 137.9, 146.5, 150.9, 204.3; IR (neat) 1657, 2971, 3064 cm$^{-1}$; HRMS *m/z* 262.13625 (calcd for $C_{19}H_{18}O$, 262.13577).

**1,1,4-Trimethyl-3-phenyl-1,2-dihydronaphthalen-2-one (18).** Obtained (along with **17**) in an 11% yield from the reaction of 1-phenyl-1-propyne and 2-(2-iodophenyl)-2-methylpropanenitrile according to the general procedure after purification by column chromatography using 20:1 hexanes/EtOAc: pink solid, mp 67-68 °C (hexanes-EtOAc); $^1$H NMR ($CDCl_3$) δ 1.55 (s, 6H), 2.24 (s, 3H), 7.15 (dd, $J$ = 8.4, 1.6 Hz, 2H), 7.32-7.37 (m, 2H), 7.39-7.45 (m, 3H), 7.51 (dd, $J$ = 7.6, 0.8 Hz, 1H), 7.65 (d, $J$ = 8.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 18.2, 27.9, 47.2, 125.8, 126.0, 126.6, 127.2, 128.0, 129.4, 130.0, 130.7, 134.9,

136.5, 146.6, 202.5 (1 $sp^2$ carbon missing due to overlap); IR (neat) 1652, 2924, 2970, 3054 $cm^{-1}$; HRMS *m/z* 262.13625 (calcd for $C_{19}H_{18}O$, 262.13577).

**6b,7,8,9,10,10a-Hexahydro-7,10-methano-11*H*-benz[*a*]fluoren-11-one (32).** Obtained in a 93% yield from the reaction of norbornene and 1-cyano-2-iodonaphthalene (**19**) according to the general procedure after purification by column chromatography using 10:1 hexanes/EtOAc: white solid, mp 79-81 °C (ether); $^1H$ NMR ($CDCl_3$) δ 0.83-0.96 (m, 2H), 1.38-1.55 (m, 2H), 1.61-1.80 (m, 2H), 2.46 (d, *J* = 3.6 Hz, 1H), 2.59 (d, *J* = 5.7 Hz, 1H), 2.65 (d, *J* = 3.6 Hz, 1H), 3.19 (d, *J* = 6.0 Hz, 1H), 7.52-7.58 (m, 2H), 7.63-7.69 (m, 1H), 7.88 (dd, *J* = 8.1, 0.6 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 9.18 (dd, *J* = 8.4, 0.6 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 28.6, 29.1, 31.8, 40.2, 40.5, 48.0, 56.3, 123.4, 124.1, 126.6, 128.0, 128.9, 129.0, 132.6, 133.1, 136.0, 160.0, 209.2; IR (neat) 1691, 2954, 3056 $cm^{-1}$; HRMS *m/z* 248.120143 (calcd for $C_{18}H_{16}O$, 248.120115).

**13-Oxo-1,2,3,4,4a,13a-hexahydro-1,4-methano-1*H*-indeno[2,1-*l*]phenanthrene (35).** Obtained in a 91% yield from the reaction of norbornene and 9-cyano-10-iodophenanthrene (**20**) according to the general procedure after purification by column chromatography using 10:1 hexanes/EtOAc: white solid, mp 195-196 °C (ether); $^1H$ NMR ($CDCl_3$) δ 0.90-1.02 (m, 2H), 1.48-1.85 (m, 4H), 2.67-2.69 (m, 3H), 3.51 (d, *J* = 5.7 Hz, 1H), 7.66-7.73 (m, 3H), 7.78-7.84 (m, 1H), 8.24 (dd, *J* = 7.8, 0.9 Hz, 1H), 8.62-8.73 (m, 2H), 9.33-9.36 (m, 1H); $^{13}C$ NMR ($CDCl_3$) δ 28.6, 29.5, 32.3, 39.5, 40.4, 46.4, 56.3, 122.5, 123.6, 124.9, 126.0, 127.0, 127.1, 127.2, 128.1, 128.6, 129.8, 130.1, 132.1, 133.8, 159.9, 209.2; IR (neat) 1687, 2954, 3087 $cm^{-1}$; HRMS *m/z* 298.136302 (calcd for $C_{22}H_{18}O$, 298.135765).

**1,2,3,4,4a,6b,7,8,9,10,10a,12a-Dodecahydro-{1,4},{7,10}-dimethano-11*H*,12*H*-indeno[2,1-*a*]fluoren-11,12-dione (36).** Obtained in a 33% yield from the reaction of norbornene and 2,3-dicyano-1,4-diiodobenzene (**23**) according to the general procedure (the amount of all reagents except **23** was doubled) after purification by column chromatography using 1:1 hexanes/EtOAc: off-white solid, mp (dec.) 278-280 °C (hexanes-EtOAc); $^1H$ NMR ($CDCl_3$) δ 0.79-0.83 (m, 2H), 0.92-0.96 (m, 2H), 1.34-1.50 (m, 4H), 1.59-1.76 (m, 4H), 2.39 (d, *J* = 3.0 Hz, 2H), 2.53 (d, *J* = 4.5 Hz, 2H), 2.65 (d, *J* = 2.4 Hz, 2H), 3.17 (d, *J* = 4.5 Hz, 2H), 7.72 (s, 2H); $^{13}C$ NMR ($CDCl_3$) δ 28.5, 28.9, 31.9, 40.8, 41.3, 48.1, 55.8, 132.2, 136.2,

158.6, 205.8; IR (neat) 1716, 2870, 2949 $cm^{-1}$; HRMS *m/z* 318.162625 (calcd for $C_{22}H_{22}O_2$, 318.161980).

**7-Aza-1,2,3,4,4a,9a-hexahydro-1,4-methanofluoren-9-one (37).** Obtained in a 52% yield from the reaction of 4-iodopyridine-3-carbonitrile (**24**) and norbornene under the indicated conditions after purification by column chromatography using 1:2 hexanes/EtOAc: light yellow solid, mp 53-54 °C (hexanes/EtOAc); $^1H$ NMR ($CDCl_3$) δ 0.75-0.82 (m, 1H), 0.98-1.05 (m, 1H), 1.33-1.54 (m, 2H), 1.62-1.84 (m, 2H), 2.46 (d, *J* = 3.9 Hz, 1H), 2.54 (d, *J* = 6.3 Hz, 1H), 2.65 (d, *J* = 3.6 Hz, 1H), 3.19 (d, *J* = 6.3 Hz, 1H), 7.48 (dt, *J* = 5.1, 0.9 Hz, 1H), 8.74 (d, *J* = 5.1 Hz, 1H), 8.87 (d, *J* = 0.9 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 28.7, 29.1, 32.7, 40.8, 41.3, 48.2, 55.9, 121.7, 134.8, 146.3, 154.3, 164.9, 207.8; IR (neat) 1714, 2954 $cm^{-1}$; HRMS *m/z* 199.09995 (calcd for $C_{13}H_{13}NO$, 199.099714).

*exo*-**2-(2-Norbornyl)pyridine-3-carbonitrile (38).** Obtained in a 40% yield from the reaction of norbornene and 3-cyano-2-iodopyridine (**25**) according to the general procedure after purification by column chromatography using 4:1 hexanes/EtOAc: yellow oil; $^1H$ NMR ($CDCl_3$) δ 1.14-1.20 (m, 1H), 1.30-1.36 (m, 1H), 1.47-1.75 (m, 4H), 2.13-2.21 (m, 1H), 2.41-2.45 (m, 2H), 3.25-3.30 (m, 1H), 7.17-7.22 (m, 1H), 7.88 (dd, *J* = 7.8, 1.8 Hz, 1H), 8.70 (dd, *J* = 4.8, 1.8 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 28.9, 30.2, 35.7, 36.7, 43.7, 47.7, 108.9, 117.1, 120.4, 140.2, 151.7, 168.5 (1 $sp^3$ carbon missing due to overlap); IR (neat) 2228, 2959, 3052 $cm^{-1}$; HRMS *m/z* 198.11606 (calcd for $C_{13}H_{14}N_2$, 198.11570).

***N*-Benzenesulfonyl-10-oxo-5b,6,7,8,9,9a-hexahydro-6,9-methano-10*H*-indeno[1,2-*b*]indole (40).** Obtained in a 16% yield from the reaction of norbornene and *N*-benzenesulfonyl-2-iodoindole-3-carbonitrile (**28c**) according to the general procedure after purification by column chromatography using 2:1 hexanes/EtOAc: white solid, mp 175-177 °C (hexanes); $^1H$ NMR ($CDCl_3$) δ 1.06-1.17 (m, 2H), 1.33-1.40 (m, 1H), 1.50-1.57 (m, 1H), 1.64-1.84 (m, 2H), 2.64 (d, *J* = 3.6 Hz, 1H), 2.82 (d, *J* = 5.1 Hz, 1H), 2.89 (d, *J* = 3.6 Hz, 1H), 3.37 (d, *J* = 5.1 Hz, 1H), 7.29-7.39 (m, 2H), 7.47-7.52 (m, 2H), 7.59-7.65 (m, 1H), 7.84-7.93 (m, 3H), 7.96-7.99 (m, 1H); $^{13}C$ NMR ($CDCl_3$) δ 28.2, 29.2, 31.8, 39.3, 39.8, 46.3, 61.6, 114.3, 121.3, 122.1, 125.0, 125.8, 126.8, 128.7, 129.7, 134.6, 138.0, 140.7, 167.5, 198.2; IR (neat) 1194, 1356, 1695, 2955 $cm^{-1}$; HRMS *m/z* 377.109143 (calcd for $C_{22}H_{19}NO_3S$, 377.108386).

***N*-Methyl-6-oxo-6a,7,8,9,10,10a-hexahydro-7,10-methano-6*H*-indeno[2,1-*b*]indole (41).** Obtained in a 77% yield from the reaction of *N*-methyl-3-iodoindole-2-carbonitrile (**27b**) and norbornene under the indicated conditions after purification by column chromatography using 4:1 hexanes/EtOAc: light yellow oil; $^1$H NMR ($CDCl_3$) δ 0.94-1.03 (m, 2H), 1.33-1.37 (m, 1H), 1.41-1.45 (m, 1H), 1.62-1.77 (m, 2H), 2.46 (d, $J$ = 2.7 Hz, 1H), 2.54 (d, $J$ = 2.7 Hz, 1H), 2.76 (d, $J$ = 3.6 Hz, 1H), 3.11 (d, $J$ = 3.6 Hz, 1H), 3.90 (s, 3H), 7.16-7.20 (m, 1H), 7.34-7.43 (m, 2H), 7.73-7.75 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ 28.7, 28.9, 30.0, 32.0, 38.6, 38.8, 42.3, 62.0, 110.9, 120.1, 121.8, 122.5, 126.6, 140.9, 145.2, 146.2, 196.3; IR (neat) 1682, 2952, 3054 cm$^{-1}$; HRMS *m/z* 251.131315 (calcd for $C_{17}H_{17}NO$, 251.131014).

***N*-Benzenesulfonyl-6-oxo-6a,7,8,9,10,10a-hexahydro-7,10-methano-6*H*-indeno[2,1-*b*]indole (42).** Obtained in a 69% yield from the reaction of norbornene and *N*-benzenesulfonyl-3-iodoindole-2-carbonitrile (**27c**) according to the general procedure after purification by column chromatography using 2:1 hexanes/EtOAc: white solid, mp 147-149 °C (hexanes); $^1$H NMR ($CDCl_3$) δ 0.79-0.84 (m, 1H), 0.93-0.97 (m, 1H), 1.33-1.43 (m, 2H), 1.63-1.73 (m, 2H), 2.41 (d, $J$ = 3.0 Hz, 1H), 2.56 (d, $J$ = 3.0 Hz, 1H), 2.79 (d, $J$ = 5.1 Hz, 1H), 3.03 (d, $J$ = 5.1 Hz, 1H), 7.33-7.39 (m, 1H), 7.42-7.48 (m, 2H), 7.52-7.59 (m, 2H), 7.67-7.71 (m, 1H), 8.08-8.11 (m, 2H), 8.36 (d, $J$ = 8.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 28.5, 29.0, 31.9, 38.2, 39.3, 41.7, 61.7, 115.9, 121.8, 124.1, 124.6, 127.5, 129.3, 129.4, 134.1, 138.6, 140.3, 143.9, 155.7, 192.0; IR (neat) 1188, 1380, 1699, 2954 cm$^{-1}$; HRMS *m/z* 377.1091428 (calcd for $C_{22}H_{19}NO_3S$, 377.108566).

**6-Nitro-2,3-diphenyl-1-indenone (43).** Obtained in a 53% yield from the reaction of diphenylacetylene and 2-iodo-5-nitrobenzonitrile (**29**) according to the general procedure after purification by column chromatography using $CH_2Cl_2$: red solid, mp 224-226 °C ($CH_2Cl_2$-hexanes); $^1$H NMR ($CDCl_3$) δ 7.30-7.48 (m, 12H), 8.33 (dd, $J$ = 7.8, 2.1 Hz, 1H), 8.39 (d, $J$ = 2.1 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 117.9, 121.3, 128.3, 128.4, 128.7, 129.2, 129.3, 129.7, 130.0, 131.6, 131.7, 136.2, 148.6, 151.1, 153.9, 193.4 (1 sp$^2$ carbon missing due to overlap); IR (neat) 1335, 1519, 1707, 3080 cm$^{-1}$; HRMS *m/z* 327.0896467 (calcd for $C_{21}H_{13}NO_3$, 327.089543).

**5-Cyano-2,3-diphenyl-1-indenone (44).** Obtained in a 47% yield from the reaction of 1,4-dicyano-2-iodobenzene (**22**) and diphenylacetylene under the indicated conditions after purification by column chromatography using 1:2 hexanes/EtOAc: red solid, mp 179-181 °C (hexanes); $^1$H NMR ($CDCl_3$) δ 7.25-7.31 (m, 5H), 7.35-7.41 (m, 3H), 7.45-7.47 (m, 3H), 7.63-7.67 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ 116.6, 118.2, 122.9, 123.6, 128.3, 128.4, 128.5, 128.9, 129.2, 129.7, 129.9, 130.0, 131.6, 133.8, 133.9, 146.0, 154.4, 194.6; IR (neat) 1716, 2229, 3053 cm$^{-1}$; HRMS *m/z* 307.100183 (calcd for $C_{22}H_{13}NO$, 307.099714).

**7-Nitro-1,2,3,4,4a,9a-hexahydro-1,4-methanofluoren-9-one (47).** Obtained in an 81% yield from the reaction of norbornene and **29** according to the general procedure after purification by column chromatography using 4:1 hexanes/EtOAc: yellow oil; $^1$H NMR ($CDCl_3$) δ 0.76-0.81 (m, 1H), 1.02-1.06 (m, 1H), 1.37-1.50 (m, 2H), 1.52-1.83 (m, 2H), 2.50 (d, $J$ = 4.2 Hz, 1H), 2.63-2.68 (m, 2H), 3.28 (d, $J$ = 6.0 Hz, 1H), 7.70 (d, $J$ = 8.1 Hz, 1H), 8.45-8.52 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ 28.4, 28.8, 32.4, 40.8, 41.4, 48.2, 56.4, 118.5, 127.3, 129.2, 140.0, 147.8, 162.7, 206.6; IR (neat) 1341, 1527, 1718, 2954, 3098 cm$^{-1}$; HRMS *m/z* 243.089638 (calcd for $C_{14}H_{13}NO_3$, 243.089543).

**6-Cyano-1,2,3,4,4a,9a-hexahydro-1,4-methanofluoren-9-one (48).** Obtained in an 85% yield from the reaction of norbornene and 4-cyano-2-iodobenzonitrile (**22**) according to the general procedure (reaction time – 48 h) after purification by column chromatography using 4:1 hexanes/EtOAc: white solid, mp 135-137 °C (hexanes-EtOAc); $^1$H NMR ($CDCl_3$) δ 0.71-0.78 (m, 1H), 0.99-1.05 (m, 1H), 1.37-1.54 (m, 2H), 1.62-1.81 (m, 1H), 2.45 (d, $J$ = 3.6 Hz, 1H), 2.58 (d, $J$ = 6.0 Hz, 1H), 2.64 (d, $J$ = 3.6 Hz, 1H), 3.22 (d, $J$ = 6.0 Hz, 1H), 7.62-7.66 (m, 1H), 7.77-7.84 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ 28.7, 29.0, 32.6, 41.0, 41.6, 48.1, 56.1, 118.2, 118.4, 124.1, 130.7, 131.3, 142.2, 157.2, 207.6; IR (neat) 1711, 2227, 2965 cm$^{-1}$; HRMS *m/z* 223.100031 (calcd for $C_{15}H_{13}NO$, 223.099714).

**5-Methoxy-1,2,3,4,4a,9a-hexahydro-1,4-methanofluoren-9-one (49).** Obtained in a 75% yield from the reaction of norbornene and 2-iodo-3-methoxybenzonitrile (**21**) according to the general procedure after purification by column chromatography using 4:1 hexanes/EtOAc: beige solid, mp 82-83 °C (hexanes-EtOAc); $^1$H NMR ($CDCl_3$) δ 0.75-0.83 (m, 1H), 0.91-0.96 (m, 1H), 1.36-1.39 (m, 1H), 1.43-1.47 (m, 1H), 1.61-1.70 (m, 2H), 2.46 (d, $J$ = 6.0 Hz, 1H), 2.57-2.61 (m, 2H), 3.15 (d, $J$ = 6.0 Hz, 1H), 3.92 (s, 3H), 7.02-7.06 (m,

1H), 7.29-7.33 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ 28.6, 29.0, 32.3, 38.6, 40.2, 45.6, 55.4, 55.8, 114.8, 115.2, 129.0, 140.7, 145.4, 157.1, 209.2; IR (neat) 1707, 2871, 2959 cm$^{-1}$; HRMS *m/z* 228.1151534 (calcd for $C_{15}H_{16}O_2$, 228.115030).

**6-Methoxy-1,2,3,4,4a,9a-hexahydro-1,4-methanofluoren-9-one (50).** Obtained in an 84% yield from the reaction of norbornene and 2-iodo-4-methoxybenzonitrile (**30**) according to the general procedure after purification by column chromatography (note: the $R_f$ of the byproduct, 4-methoxybenzonitrile, is very close to that of **50**) using 4:1 hexanes/EtOAc: colorless oil; $^1$H NMR ($CDCl_3$) δ 0.83-0.86 (m, 1H), 0.93-0.97 (m, 1H), 1.39-1.45 (m, 2H), 1.59-1.75 (m, 2H), 2.40 (d, $J$ = 4.0 Hz, 1H), 2.49 (d, $J$ = 6.0 Hz, 1H), 2.58 (d, $J$ = 4.0 Hz, 1H), 3.09 (d, $J$ = 6.0 Hz, 1H), 3.89 (s, 3H), 6.87-6.92 (m, 2H), 7.65 (d, $J$ = 8.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 28.8, 32.2, 40.1, 41.3, 48.0, 55.6, 56.2, 109.2, 115.3, 124.9, 132.4, 160.1, 162.8, 165.5, 192.4; IR (neat) 1702, 2871, 2954 cm$^{-1}$; HRMS *m/z* 228.11549 (calcd for $C_{15}H_{16}O_2$, 228.11503).

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# CHAPTER 2. SYNTHESIS OF 3,4-DISUBSTITUTED 2-AMINONAPHTHALENES AND 1,3-BENZOXAZINE DERIVATIVES BY THE Pd-CATALYZED ANNULATION OF ALKYNES BY (2-IODOPHENYL)ACETONITRILE

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## Abstract

Intramolecular carbopalladation of the cyano group has been employed for the synthesis of 3,4-disubstituted 2-aminonaphthalenes. (2-Iodophenyl)acetonitrile reacts with a variety of internal alkynes to afford 2-aminonaphthalenes in high yields with good regioselectivity. The scope and limitations of this process, which proceeds by an intramolecular addition of a vinylpalladium species to the triple bond of the cyano group, have been studied. The annulation of certain hindered propargylic alcohols affords 1,3-benzoxazine derivatives, rather than the expected 2-aminonaphthalenes. The involvement of trialkylamine bases in the formation of these heterocyclic compounds has been established. A proposed mechanism for the synthesis of 1,3-benzoxazine derivatives involves the formation of the expected 2-amino-3-(1-hydroxyalkyl)naphthalenes, followed by their condensation with an iminium ion species formed from the trialkylamine base used in the reaction.

## Introduction

The preparation of amines is of considerable importance in organic synthesis owing to the vast possibilities available for their further conversion into other functionalities. Aminonaphthalenes have been employed as precursors to a variety of substances that have

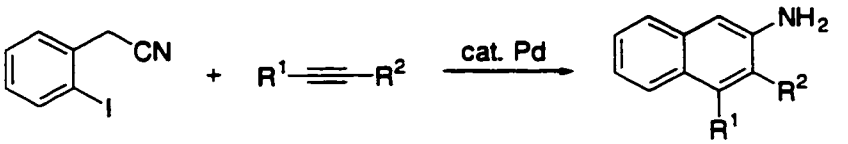
interesting industrial and pharmaceutical uses. For example, such complex heterocyclic systems as benzo[*c*]phenothiazines,[1] benzo[*f*]quinazolines,[2] benzindoles,[3] benz[*a*]- and benz[*c*]acridines,[4] naphtho[1,2-*d*]imidazoles,[5] and others have been synthesized from naphthylamines. For over a century, aminonaphthalenes have been a staple of the dyestuffs industry, serving as diazo and coupling components in the preparation of azo dyes.[6] Despite the significant carcinogenic and mutagenic activity of 1- and 2-naphthylamines,[6b,7] their derivatives have been explored as spasmolytic, emetic and antitumor agents.[8]

With the emergence of asymmetric synthesis, 2-aminonaphthalenes have found new uses as starting materials for the synthesis of binaphthyl $C_2$-symmetric chiral ligands.[9] In particular, 1,1'-binaphthyl-2,2'-diamine chiral auxiliaries have been used for enantioselective reduction of ketones, asymmetric synthesis of lactones, asymmetric hydrogenation of α-acylaminoacrylic acids and asymmetric alkylation of aromatic aldehydes.[10] Additional substituents at positions 3 and 3' of binaphthyl systems have been recognized to impose further steric interactions, which often results in a remarkable increase in asymmetric induction.[9] This underscores the importance of developing effective and practical routes to 3-substituted 2-aminonaphthalenes. In another asymmetric application, 2-naphthylamines have been used for the synthesis of naphthyl-Troger's base, a representative of a class of chiral structures that have both theoretical and practical interest as molecular receptors, chiral solvating agents (e.g., in host-guest complexes) and chiral modifiers in enantioselective reactions.[11]

Naphthylamines can be prepared from naphthalene and its derivatives by a number of traditional synthetic organic methods available for the synthesis of aromatic amines.[12] Classical routes to aminonaphthalenes include the treatment of naphthols with bisulfites and ammonia (Bucherer reaction)[13] and the acid-catalyzed transformation of tetralone oximes (Semmler-Wolff reaction).[14] To the best of our knowledge, there is no general and efficient methodology for the synthesis of aminonaphthalenes by alkyne annulation.[15] Yet, such an approach could be extremely valuable, as it would allow for rapid construction of a fairly complex functionalized cyclic system from two independent components.

Recently, useful palladium-alkyne annulation methodology has been developed in this group, which offers convenient routes to various carbo- and heterocyclic compounds.[16]

These reactions involve the insertion of an internal alkyne into an arylpalladium intermediate and subsequent cyclization onto a functional group present in the *ortho* position. In 1999, Qingping Tian started investigating the possibility that a cyanomethyl group might serve as the neighboring functional group and that the vinylpalladium intermediate might add across the carbon-nitrogen triple bond to produce 2-aminonaphthalenes (eq 1).[17]



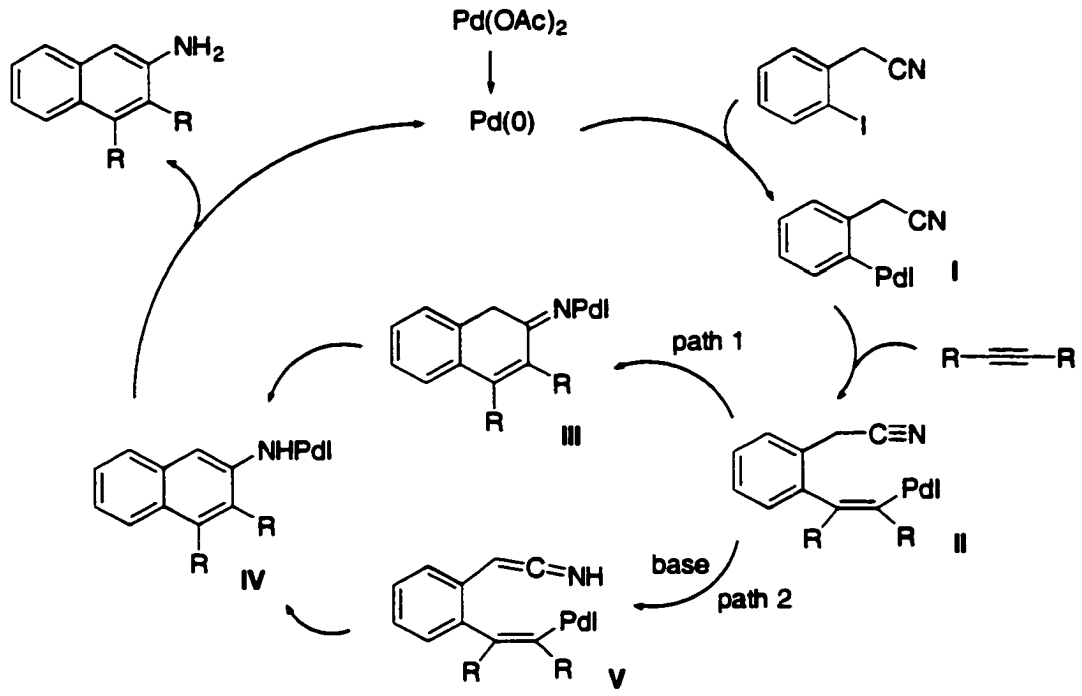

(1)

Using the annulation of diphenylacetylene by 2-iodophenylacetonitrile (eq 1; $R^1$,$R^2$ = Ph) as a model system, Tian conducted extensive optimization of the reaction conditions and arrived at the following optimized procedure: 5 mol % of $Pd(OAc)_2$, 3 equiv of diphenylacetylene, 2 equiv of $Et_3N$, 1 equiv of *n*-$Bu_4NCl$ in DMF is heated at 100 °C for 48 h. He explored the scope and limitations of this annulation by employing several other alkynes (see below). Here, we wish to report full details of our work on developing the Pd-catalyzed alkyne annulation of internal alkynes by (2-iodophenyl)acetonitrile into useful methodology for the synthesis of 3,4-disubstituted 2-aminonaphthalenes.[18]

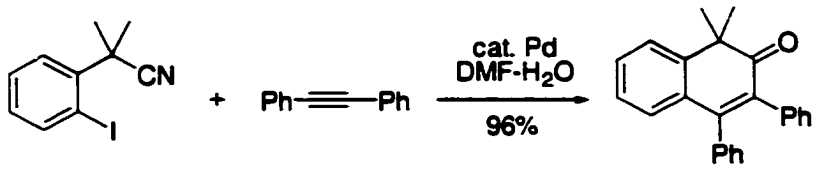
## Results and Discussion

The mechanism of 2-aminonaphthalene formation proposed by Tian[17] is shown in Scheme 1. This process presumably starts with reduction of the $Pd(OAc)_2$ to the actual catalyst Pd(0). The oxidative addition of (2-iodophenyl)acetonitrile to Pd(0) produces an arylpalladium intermediate **I**, which rapidly adds across the triple bond of the alkyne to afford a vinylic palladium species **II**. A priori, two different paths for intramolecular carbopalladation of the cyano group in **II** appear plausible. The vinylic palladium moiety **II** may undergo addition to the neighboring CN triple bond to generate the iminopalladium intermediate **III**, which undergoes rapid tautomerization to the aminopalladium species **IV** (path 1). An alternative path might involve base-induced formation of ketenimine **V**[19] and subsequent *syn* addition of the vinylpalladium moiety to the C-N double bond to generate **IV**

**Scheme 1**

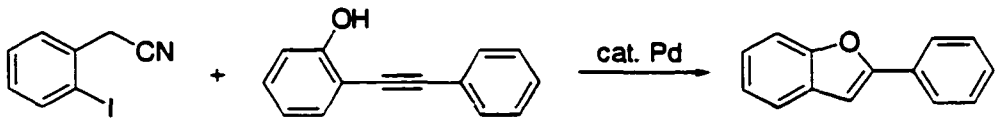



(path 2). Based on the success of our previous annulation of diphenylacetylene with 2-(2-iodophenyl)-2-methylpropanenitrile (eq 2),[20] which presumably proceeds via a very similar mechanism, we favor path 1. In the next step, aminopalladium complex **IV** is reduced to the final product, accompanied by regeneration of the Pd(0) catalyst. Although we have evidence indicating that the Pd(II) moiety in **IV** is reduced by $Et_3N$ (vide infra),[21] we cannot exclude some involvement of DMF, since the yield of the annulation product was sharply reduced when other solvents, such as DMSO and DMA, were used in the reaction.[17] Also, traces of water inadvertently present in DMF or *n*-$Bu_4NCl$ may be the hydrogen source in the reduction[22] or simple protonation of **IV** to generate Pd(II), which is subsequently reduced to Pd(0) by other species.




(2)

To study the scope of this annulation, a variety of internal alkynes have been introduced into the reaction (Table 1). 2-Amino-3,4-diarylnaphthalenes **1** and **2** were obtained in very good yields from annulation of the corresponding diarylacetylenes (entries 1 and 2). The current methodology is expected to be readily applicable to the synthesis of various 2-amino-3,4-diarylnaphthalenes from symmetrical diarylacetylenes. An excellent overall yield of the annulation product was also obtained in the reaction of an unsymmetrical alkyne, 2-(phenylethynyl)toluene (entry 3). However, both possible regioisomers **3** and **4** were isolated in approximately equal amounts. Apparently, the difference between steric demands of the two aryl substituents in this diarylacetylene is not large enough to command better regioselectivity in arylpalladium addition across the triple bond of the alkyne (see below). Applying our reaction conditions to the attempted annulation of 2-(phenylethynyl)phenol was found to afford 2-phenylbenzofuran instead of the target aminonaphthalene (eq 3). Examples of this Pd-catalyzed cyclization are well known in the literature.[23]




(3)

The annulation works reasonably well for internal alkynes other than diarylacetylenes. Thus, 2-amino-4-methyl-3-phenylnaphthalene (**5**) was isolated in a 65% yield as a single isomer from the reaction of (2-iodophenyl)acetonitrile and 1-phenyl-1-propyne (entry 4). The regioselectivity of this reaction can be nicely explained by addition of the aryl group of the arylpalladium intermediate **I** (Scheme 1) to the less hindered end of the alkyne, placing the palladium moiety on the more hindered end of the original triple bond. Such regioselectivity for the addition has been frequently observed in our previous research.[24] As a result, the more sterically hindered group present in the alkyne ends up in the 3 position of the naphthalene product and the less hindered group in the 4 position, which is indeed observed. However, for this regioselectivity to be pronounced, the two groups must be significantly different sterically (entries 4, 10, 11, 14 and 19). In other cases, formation of both possible regioisomers may be expected (entries 3 and 5). When 1-phenyl-1-butyne was employed as the alkyne, the anticipated aminonaphthalene **6** was isolated in a 37% yield

**Table 1. The Pd-Catalyzed Annulation of Internal Alkynes by (2-Iodoaryl)acetonitriles (eq 1)[a]**

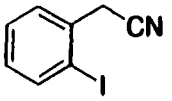
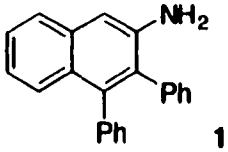
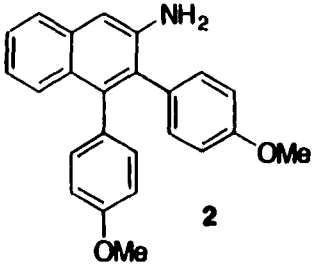
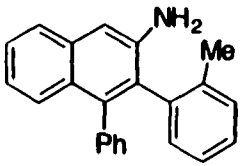
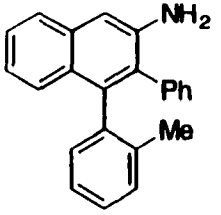
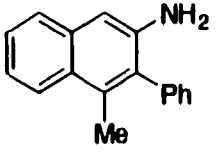
| entry | nitrile | alkyne $R^1$ | alkyne $R^2$ | product(s) | % isolated yield |
|---|---|---|---|---|---|
| 1 |  | Ph | Ph |  **1** | 83[b] |
| 2 | | *p*-$MeOC_6H_4$ | *p*-$MeOC_6H_4$ |  **2** | 80 |
| 3 | | Ph | *o*-$MeC_6H_4$ |  +  **3** **4** | 44 + 45 |
| 4 | | Me | Ph |  **5** | 65[b] |

**Table 1. (continued)**

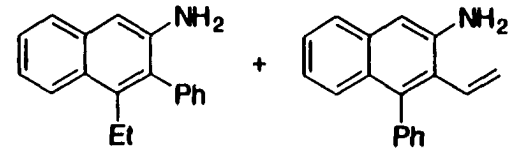
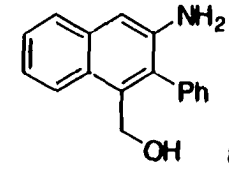
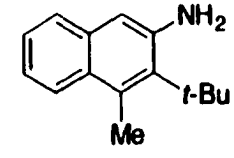
| entry | nitrile | alkyne $R^1$ | alkyne $R^2$ | product(s) | % isolated yield |
|---|---|---|---|---|---|
| 5 | | Et | Ph |  **6** + **7** | 37 + 17[b] |
| 6 | | $CH_2OH$ | Ph |  **8** | 29 |
| 7 | | $CH_2OH$ | $CH_2OH$ | - | - |
| 8 | | $CMe_2OH$ | $CMe_2OH$ | - | - |
| 9 | | $CH_2OMe$ | $CH_2OMe$ | - | - |
| 10 | | Me | *t*-Bu |  **9** | 75[b,c] |

**Table 1. (continued)**

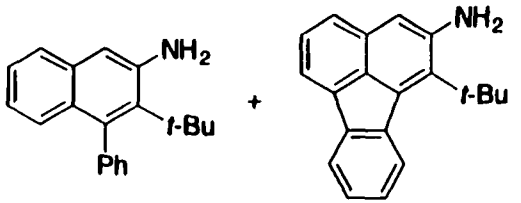
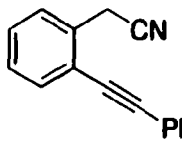
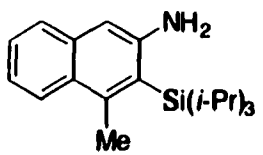
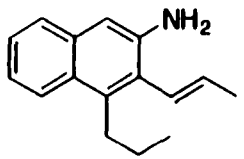
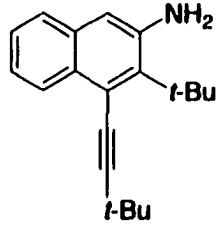
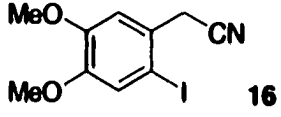
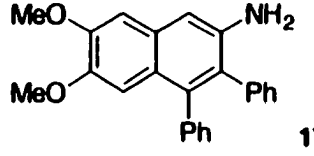
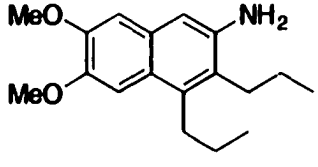
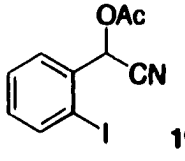
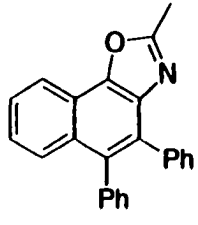
| entry | nitrile | alkyne $R^1$ | alkyne $R^2$ | product(s) | % isolated yield |
|---|---|---|---|---|---|
| 11 | | Ph | *t*-Bu |  **10** + **11** | 27 + 15[b] |
| 12 | | Ph | $SiMe_3$ |  **12** | 58[b] |
| 13 | | Ph | H | | 51 |
| 14 | | Me | $Si(i\text{-}Pr)_3$ |  **13** | 54 |
| 15 | | *n*-Pr | *n*-Pr |  **14** | 30[b] |
| 16 | | Ph | C(O)Me | - | - |
| 17 | | Me | $CH(OEt)_2$ | - | - |

**Table 1. (continued)**

| entry | nitrile | alkyne $R^1$ | alkyne $R^2$ | product(s) | % isolated yield |
|---|---|---|---|---|---|
| 18 | | Ph-C≡C | Ph | - | - |
| 19 | | *t*-Bu-C≡C | *t*-Bu |  **15** | 91[d] |
| 20 |  **16** | Ph | Ph |  **17** | 81 |
| 21 | | *n*-Pr | *n*-Pr |  **18** | 62 |
| 22 |  **19c** | Ph | Ph |  **20** | 53 |

[a] See the Experimental Section for the reaction conditions. [b] Reference 17. [c] Two equivs of $H_2O$ were employed in the reaction; without water, the yield was 61%. [d] Isolated as an inseparable mixture with about 6% of the other regioisomer as determined by $^1H$ NMR spectral analysis.

along with an unexpected product **7**, which obviously arose from the second regioisomer (entry 5).[17] While we observed only a single isomer **8** in the annulation of 3-phenyl-2-propyn-1-ol (entry 6), we cannot rule out the possibility that an aldehyde or carboxylic acid product similar to **7** was formed in the reaction, but was subsequently lost to side reactions, such as oxidation or condensation.

Surprisingly, symmetrical propargylic diols failed to afford annulation products (entries 7 and 8). Protecting the hydroxy groups in 2-butyne-1,4-diol did not rectify the problem, as the corresponding dimethoxy derivative did not undergo annulation either (entry 9). The reasons behind these results are unclear and may include coordination of these electron-rich functionalized alkynes to the palladium catalyst prior to the oxidative addition step, which diverts the catalyst from the annulation process.

Internal alkynes bearing a bulky *t*-butyl group led to the expected 2-aminonaphthalenes **9** and **10** with good regioselectivity (entries 10 and 11). The regiochemistry of these and other products in Table 1 could be determined by 1D and 2D $^1$H NMR spectral analysis.[17] We also observed the formation of the tetracyclic amine **11** from the *in situ* cyclization of **10** by a mechanism that is unclear (entry 11).[17] The reaction of 1-phenyl-2-(trimethylsilyl)acetylene afforded the simple coupling product **12** in a 58% yield (entry 12). None of the desired aminonaphthalene product was observed. This reaction presumably proceeds by the desilylation of the alkyne to produce phenylacetylene, which undergoes coupling with (2-iodophenyl)acetonitrile to give **12**. The same product **12** was also obtained in a similar yield when phenylacetylene was used as the alkyne (entry 13). A significant amount of 1,4-diphenylbutadiyne was also detected by GC-MS in this reaction mixture. The more hindered silyl group in 1-(triisopropylsilyl)-1-propyne was stable to desilylation as this alkyne afforded a 54% yield of the aminonaphthalene **13** (entry 14).

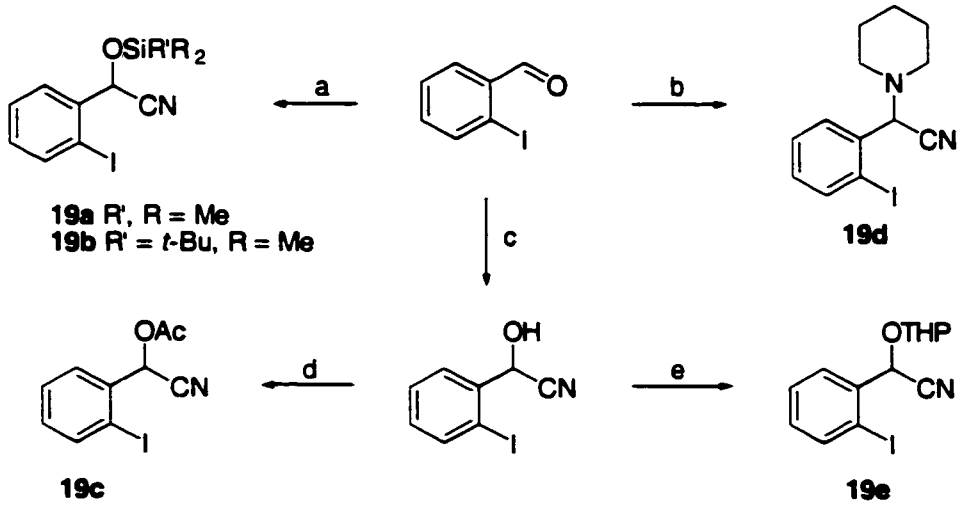
The unusual product **14** was formed as the sole product in the reaction of 4-octyne (entry 15). The (*E*)-stereochemistry of **14** was established by Tian from $^1$H NMR coupling constants between the olefinic hydrogens ($J$ = 16.2 Hz), and fully confirmed by 2D NOESY spectroscopy.[17] Internal alkynes bearing electron-withdrawing groups did not undergo annulation, possibly because of competing Michael addition-like processes (entries 16 and 17). Also unsuccessful was the annulation of 1,4-diphenylbutadiyne (entry 18). It has been

reported, however, that diarylbutadiynes may easily undergo Pd-catalyzed formation of 1,2,3-butatriene derivatives under conditions similar to ours.[25] Another 1,3-diyne, 2,2,7,7-tetramethyl-3,5-octadiyne, afforded the expected annulation product **15** in excellent yield and with very good regioselectivity (entry 19).

An electron-rich (2-iodophenyl)acetonitrile derivative **16** was prepared and used in the annulation of diphenylacetylene and 4-octyne (entries 20 and 21). In both cases, the corresponding 2-aminonaphthalenes **17** and **18** were obtained in good yields. Interestingly, we did not observe any unsaturated product similar to **14** in the reaction of 4-octyne (entry 21). No electron-poor derivatives of (2-iodophenyl)acetonitrile were examined in the annulation, since our previous research on nitrile carbopalladation indicated that arylpalladium and vinylpalladium intermediates (**I** and **II**, Scheme 1) formed from electron-deficient substrates are usually not nucleophilic enough for successful attack on the cyano group.[20,26]

We have also prepared a number of protected cyanohydrins **19** (Scheme 2) in order to investigate the possibility of synthesizing 3,4-disubstituted 2-amino-1-naphthols by this methodology. Unfortunately, only 2-acetoxy-2-(2-iodophenyl)acetonitrile (**19c**) proved stable enough to survive our reaction conditions, cleanly affording the oxazole derivative **20**

**Scheme 2**

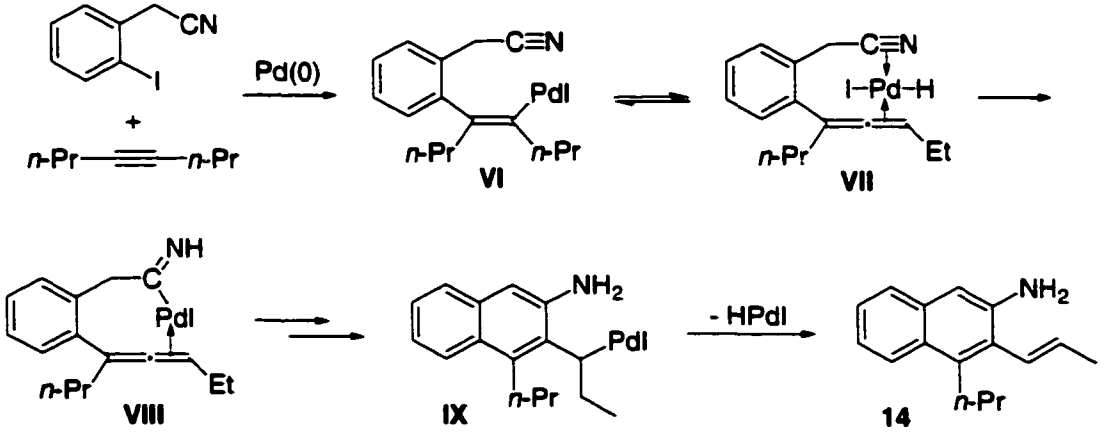



(a) $R'R_2SiCN$, cat. KCN, cat. 18-crown-6, $CH_2Cl_2$, r.t.; (b) NaCN, piperidine, aq $NaHSO_3$, 0 °C to r.t.; (c) KCN, aq $NaHSO_3$, 0 °C to r.t.; (d) $Ac_2O$, pyridine, r.t.; (e) 3,4-dihydropyran, cat. *p*-TsOH, $CH_2Cl_2$, r.t.

in a 53% yield (entry 22). An almost identical yield (52%) of **20** was achieved when the reaction was run at 130 °C. Silyl-protected cyanohydrins **19a** and **19b** underwent a retro-reaction to produce 2-iodobenzaldehyde as the major product. Even the piperidine derivative **19d** was hydrolyzed to 2-iodobenzaldehyde, presumably by traces of water present in the DMF or *n*-$Bu_4NCl$. Attempted annulation of the THP-protected cyanohydrin **19e** afforded a messy reaction mixture containing numerous products that could not be identified.

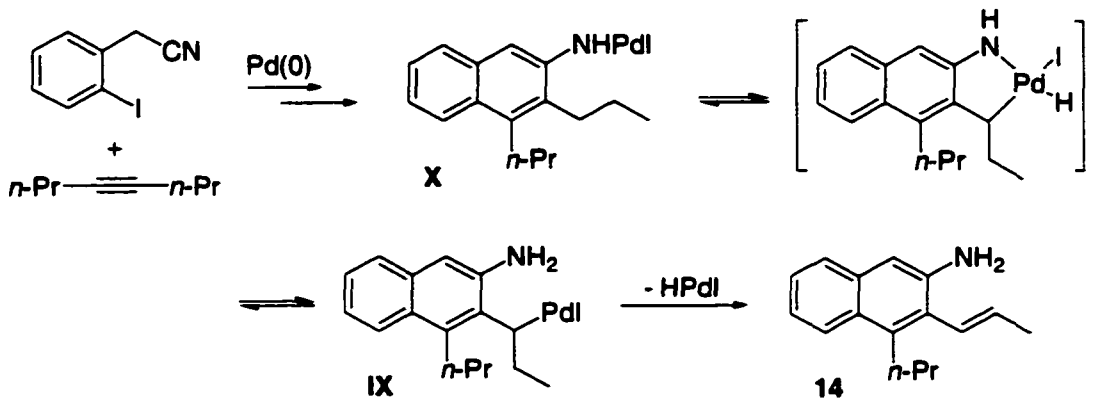
A possible mechanism for the formation of unsaturated products **7** and **14** has been proposed by Tian (Scheme 3).[17] Oxidative addition of (2-iodophenyl)acetonitrile to Pd(0) and subsequent insertion of 4-octyne furnishes intermediate **VI**. This species may undergo β-hydrogen elimination to produce an allene intermediate **VII**. Addition of the Pd-H to the cyano group will generate an acyl-like organopalladium intermediate **VIII**, which in turn can add to the allene to furnish (after imine tautomerization) a σ- or π-benzylic intermediate **IX**, which might be expected to eliminate HPdX to generate the new carbon-carbon double bond and eventually regenerate the Pd(0) catalyst.

**Scheme 3**



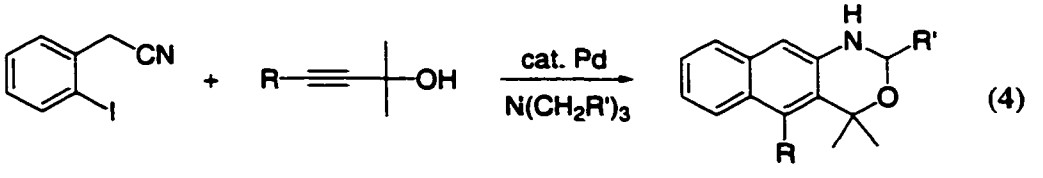

We also propose an alternative mechanism shown in Scheme 4. Upon formation of the aminopalladium intermediate **X** during the normal annulation cycle (Scheme 1), the palladium moiety may insert into a benzylic C-H bond of the alkyl substituent in the 3 position of the naphthalene and eventually migrate to the alkyl chain to furnish an

**Scheme 4**




alkylpalladium intermediate **IX** by a mechanism that differs from the one in Scheme 3. After a palladium β-hydrogen elimination, **IX** can produce the product **14**. We have no evidence that allows us to choose between these two mechanisms.

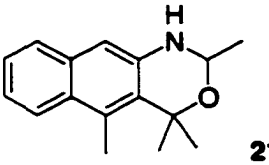
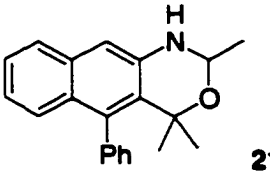
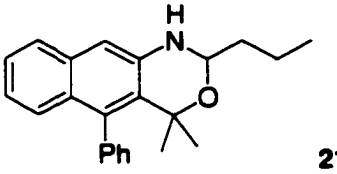
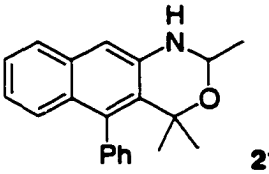
Using hindered propargylic alcohols for the annulation with (2-iodophenyl)acetonitrile, we have made an unusual observation that 1,3-benzoxazine derivatives **21** are produced instead of the anticipated 2-aminonaphthalenes (eq 4, R = Ph or Me). Thus, annulation of (2-iodophenyl)acetonitrile onto 2-methyl-3-pentyn-2-ol afforded 2,4,4,5-tetramethyl-1,4-dihydro-2*H*-naphtho[2,3-*d*][1,3]oxazine (**21a**) in a 25% isolated yield (entry 1, Table 2). Analogous 1,3-benzoxazine derivative **21b** was obtained from 2-methyl-4-phenyl-3-butyn-2-ol in a 35% yield under our original annulation conditions. When the reaction was run at 130 °C, the yield of **21b** increased to 50% (entry 2). Substituting triethylamine for another base, tri-*n*-butylamine, led to the formation of 4,4-dimethyl-5-phenyl-2-propyl-1,4-dihydro-2*H*-naphtho[2,3-*d*][1,3]oxazine (**21c**) in a 38% yield (entry 3). This result provides clear and unambiguous evidence that the C2-carbon of the 1,3-oxazine ring comes from the trialkylamine base, one of the alkyl groups of which is incorporated into the structure of the final product. It has also been established that primary alkyl groups are transferred




(4)

**21**

**Table 2. Synthesis of 1,3-Benzoxazine Derivatives (eq 4)**[a]

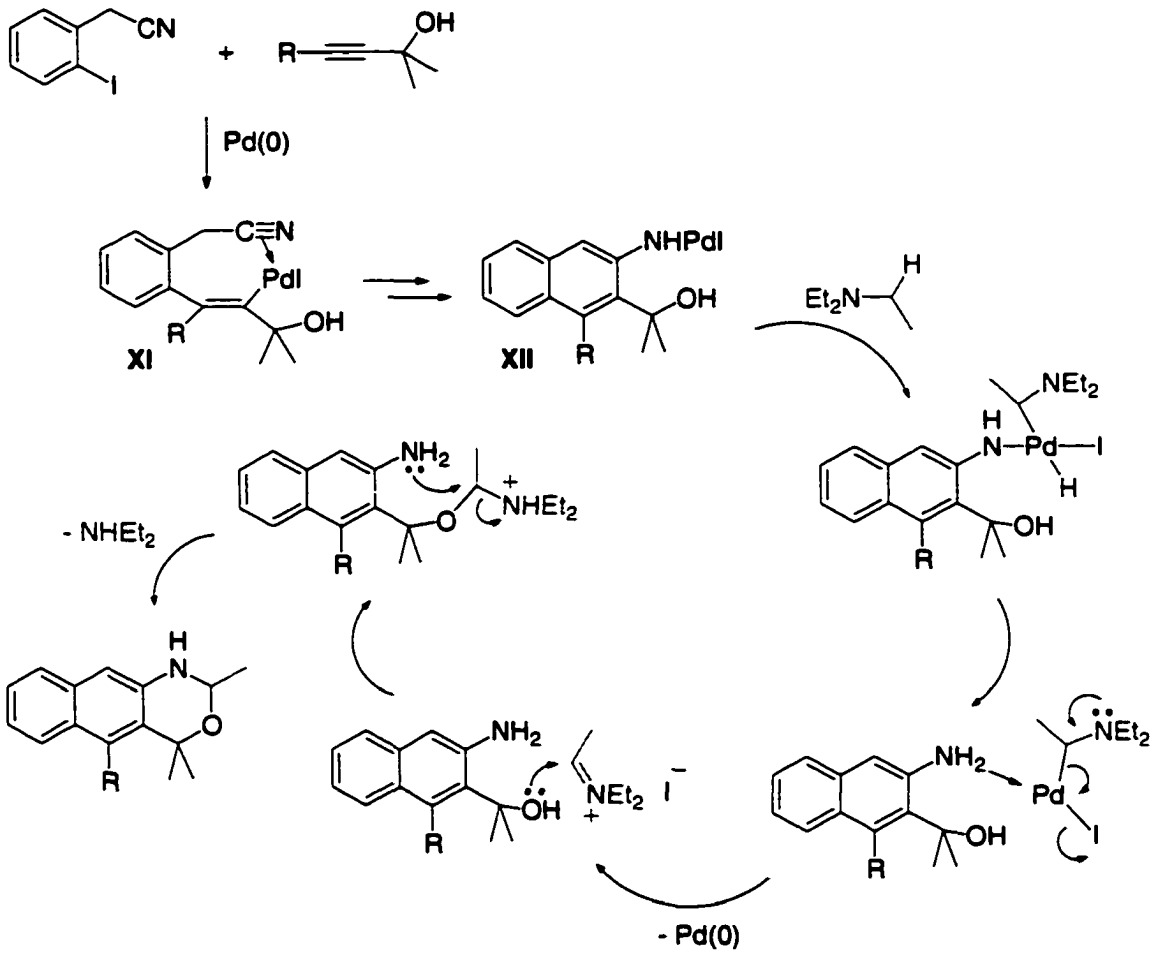
| entry | R | amine (2 equiv) | product | % isolated yield |
|---|---|---|---|---|
| 1 | Me | $Et_3N$ |  **21a** | 25 |
| 2 | Ph | $Et_3N$ |  **21b** | 50[b] |
| 3 | Ph | $n$-$Bu_3N$ |  **21c** | 38 |
| 4 | Ph | $i$-$Pr_2NEt$ |  **21b** | 16[c] |

[a] See the Experimental Section for the reaction conditions. [b] This reaction was run at 130 °C; the yield at 100 °C was 35%. [c] 96% Conversion of the starting material after 48 h.

preferentially from the trialkylamine as no incorporation of the isopropyl unit was found when diisopropylethylamine was employed (entry 4).

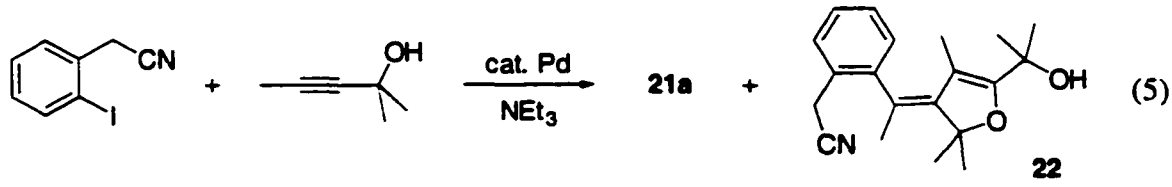
The following mechanism accounts for the Pd-catalyzed synthesis of 1,3-benzoxazine derivatives from (2-iodophenyl)acetonitrile, hindered propargylic alcohols and trialkylamines (Scheme 5). The marked difference in steric bulk between the two substituents on the triple bond of the alkyne causes regioselective formation of the vinylpalladium intermediate **XI** shown in Scheme 5, which proceeds to add to the cyano group and eventually form the aminopalladium species **XII**. It is possible that the Pd(II) in **XII** is reduced at this point by the trialkylamine via a mechanism proposed in Chapter 1. This reduction involves Pd(II) insertion into the activated α-C-H bond of the amine, reductive elimination and fragmentation of the resulting (α-aminoalkyl)palladium species, which leads to regeneration

**Scheme 5**




of Pd(0) and formation of the anticipated 2-aminonaphthalene product and an iminium moiety (Scheme 5). It is also possible that this iminium intermediate, which has been proposed in other Pd-catalyzed transformations of triethylamine,[21b,27] may be formed from triethylamine and a Pd(II) species at some other point in the reaction. The iminium intermediate then undergoes nucleophilic attack by the two nucleophilic groups present in the aminonaphthalene, which results in formation of the 1,3-oxazine ring. This mechanism may explain the exclusive transfer of primary alkyl groups from the amine (entry 4, Table 2), as the iminium ion species formed from a secondary alkylamine may be too hindered for facile condensation with the bulky alcohol moiety.

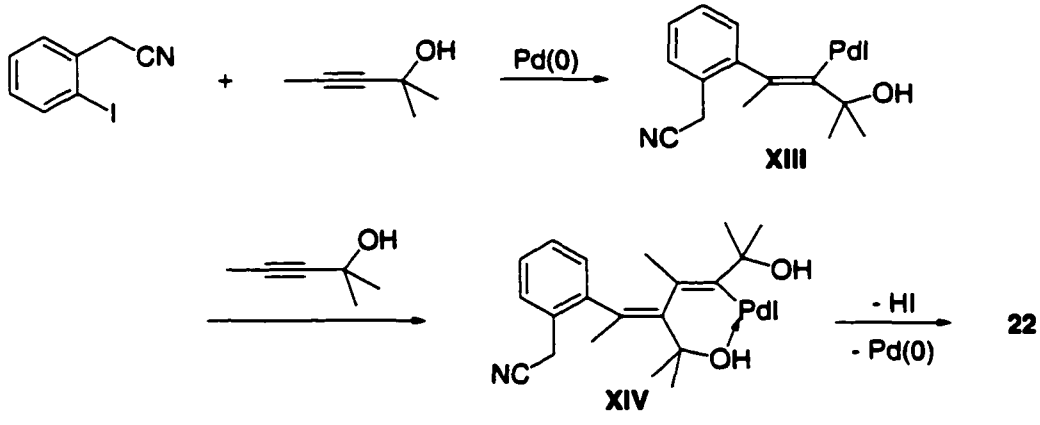
The reaction between (2-iodophenyl)acetonitrile and 2-methyl-3-pentyn-2-ol afforded another unusual product besides **21a** (eq 5). A complex furan derivative **22** was isolated




(5)

in a 26% yield. This compound is clearly a product of a double alkyne insertion, which presumably proceeds by the mechanism shown in Scheme 6. Instead of adding to the C-N triple bond of the cyano group, the vinylpalladium intermediate **XIII** apparently inserts a second molecule of the alkyne to furnish dienylpalladium species **XIV**. Intramolecular attack of an OH group then leads to the final product **22**.

**Scheme 6**




## Conclusions

The palladium-catalyzed annulation of alkynes with (2-iodophenyl)acetonitrile has been studied. This process represents a general approach to 3,4-disubstituted 2-aminonaphthalenes, which are formed in moderate to very good yields from a variety of internal alkynes. In many cases, the annulation exhibits excellent regioselectivity. The unusual formation of 1,3-benzoxazine derivatives from certain hindered propargylic alcohols has also been observed. This reaction apparently proceeds with involvement of the trialkylamine bases present in the reaction, which transfer one of their alkyl groups to the final product.

## Experimental Section

**General.** $^{1}H$ and $^{13}C$ NMR spectra were recorded at 300 and 75 MHz or 400 and 100 MHz, respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) 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. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. IR spectra were measured on a Bomem Michelson MB-102 FT-IR spectrometer. All reagents were used directly as obtained commercially unless otherwise noted. $Pd(OAc)_2$ was donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd.

**Reagents.** Diphenylacetylene, triethylamine, tri-*n*-butylamine, 4-octyne, 2,2,7,7-tetramethyl-3,5-octadiyne, phenylacetylene, 1-phenyl-2-(trimethylsilyl)acetylene and 1-triisopropylsilyl-1-propyne were obtained from Aldrich Chemical Co., Inc. Tetra-*n*-butylammonium chloride, (2-iodophenyl)acetonitrile and 4,4-dimethyl-2-pentyne were obtained from Lancaster Synthesis, Inc. 1-Phenyl-1-propyne, 1-phenyl-1-butyne, 3-phenyl-2-propyn-1-ol, 2-methyl-3-pentyn-2-ol and 2-methyl-4-phenyl-3-butyn-2-ol were obtained from Farchan Laboratories, Inc. 3,3-Dimethyl-1-phenyl-1-butyne was prepared according to a previous literature procedure.[24b]

**(2-Iodo-4,5-dimethoxyphenyl)acetonitrile (16)** was prepared from 2-iodo-4,5-dimethoxybenzyl bromide (prepared in two steps from 4,5-dimethoxybenzyl alcohol)[28] according to a published procedure.[29] A solution of 2-iodo-4,5-dimethoxybenzyl bromide (0.853 g, 2.39 mmol) and 18-crown-6 (0.053 g, 0.2 mmol) in 5 mL of MeCN was placed over solid KCN (0.338 g, 5.2 mmol). The reaction mixture was stirred vigorously for 24 h, after which it was filtered and the amount of solvent was reduced on a rotary evaporator. The mixture was diluted with water, extracted with $CH_2Cl_2$, dried ($Na_2SO_4$), evaporated and the residue was purified by column chromatography using 1:1 hexanes/ethyl acetate to produce 0.605 g (84%) of **16**: white solid, mp 110-111 °C (hexanes/ethyl acetate); $^{1}H$ NMR

($CDCl_3$) δ 3.76 (s, 2H), 3.87 (s, 3H), 3.90 (s, 3H), 6.98 (s, 1H), 7.24 (s, 1H); $^{13}C$ NMR ($CDCl_3$) δ 29.2, 55.9, 56.1, 86.8, 111.5, 117.4, 121.5, 125.1, 149.1, 149.5; IR (neat) 3086, 2967, 2916, 2845, 2257 $cm^{-1}$; HRMS *m/z* 302.97609 (calcd for $C_{10}H_{10}INO_2$, 302.97563).

**2-Acetoxy-2-(2-iodophenyl)acetonitrile (19c).** To a cold (0 °C) solution of 2-iodobenzaldehyde (1.469 g, 6.33 mmol) in aq 2M $NaHSO_3$ (15 mL) was added a solution of KCN (1.645 g, 25.3 mmol) in 3.25 mL of water. The reaction mixture was stirred for 1.5 h at room temperature, then extracted with ether. The organic extracts were washed with water, dried ($Na_2SO_4$) and evaporated to afford 1.245 g (76%) of 2-hydroxy-2-(2-iodophenyl)acetonitrile,[30] 0.39 g (1.5 mmol) of which was dissolved in a mixture of 7 mL of $Ac_2O$ and 7 mL of pyridine and stirred overnight at room temperature.[31] The reaction mixture was then poured into water and extracted with ether. The organic extracts were washed with aq HCl, aq $NaHCO_3$, and water, dried ($Na_2SO_4$), evaporated and the residue was purified by column chromatography using 4:1 hexanes/ethyl acetate to afford 0.42 g (93%) of **19c**: white solid, mp 57-59 °C (hexanes/ethyl acetate); $^1H$ NMR ($CDCl_3$) δ 2.21 (s, 3H), 6.52 (s, 1H), 7.19 (td, *J* = 7.8, 1.5 Hz, 1H), 7.48 (td, *J* = 7.8, 1.2 Hz, 1H), 7.73 (dd, *J* = 7.8, 1.5 Hz, 1H), 7.92 (dd, *J* = 7.8, 1.2 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 20.2, 67.0, 97.9, 115.4, 129.0, 129.3, 131.9, 134.1, 140.2, 168.6; IR (neat) 3064, 2935, 2845, 2246, 1756 $cm^{-1}$; HRMS *m/z* 300.96058 (calcd for $C_{10}H_8INO_2$, 300.95998).

**General Procedure for the Palladium-Catalyzed Reaction of (2-Iodophenyl)-acetonitrile and Internal Alkynes.** Palladium acetate (0.0028 g, 0.0125 mmol), $Et_3N$ (0.070 mL, 0.5 mmol), *n*-$Bu_4NCl$ (0.070 g, 0.25 mmol), (2-iodophenyl)acetonitrile (0.061 g, 0.25 mmol), the alkyne (0.75 mmol), and 5 mL of DMF were placed in a 4 dram vial, which was heated in an oil bath at 100 °C for 48 h unless indicated otherwise. The reaction mixture was cooled, diluted with ether, washed with satd aq $NH_4Cl$, dried over $Na_2SO_4$ or $MgSO_4$, and filtered. The solvent was removed on a rotary evaporator and the product was isolated by column chromatography on silica gel. The following compounds, prepared by the above procedure, have been previously described by us:[18] 2-amino-3,4-diphenylnaphthalene (**1**), 2-amino-4-methyl-3-phenylnaphthalene (**5**), 2-amino-3-*tert*-butyl-4-methylnaphthalene (**9**), and 2 amino-3-((*E*)-1-propenyl)-4-*n*-propylnaphthalene (**14**).

The following new compounds were prepared by the above procedure:

**2-Amino-3,4-di(4-methoxyphenyl)naphthalene (2).** Obtained as a yellow solid in an 80% yield from the reaction of (2-iodophenyl)acetonitrile and bis(4-methoxyphenyl)-acetylene after purification by column chromatography using 2:1 hexanes/ethyl acetate: mp 194-196 °C (EtOH); $^1$H NMR ($CDCl_3$) δ 3.76 (s, 3H), 3.77 (br s, 2H), 3.78 (s, 3H), 6.73-6.79 (m, 4H), 7.00-7.05 (m, 4H), 7.10-7.12 (m, 2H), 7.35-7.41 (m, 2H), 7.64 (d, $J$ = 8.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 55.1, 108.0, 112.9, 113.8, 122.3, 125.5, 126.0, 126.9, 127.6, 129.8, 131.5, 131.6, 131.9, 134.3, 139.7, 142.7, 157.9, 158.2 (1 $sp^3$ carbon missing due to overlap); IR (neat) 3465, 3365, 3052, 3012, 2957, 2837 1613, 1240 $cm^{-1}$; HRMS *m/z* 355.14795 (calcd for $C_{24}H_{21}NO_2$, 355.15723).

**2-Amino-3-(2-methylphenyl)-4-phenylnaphthalene (3).** Obtained as a brown solid in a 44% yield from the reaction of (2-iodophenyl)acetonitrile and 2-(phenylethynyl)toluene after purification by column chromatography using 4:1 hexanes/ethyl acetate ($R_f$ = 0.44): mp 172-174 °C (hexanes/ethyl acetate); $^1$H NMR ($CDCl_3$) δ 1.93 (s, 3H), 3.75 (br s, 2H), 7.01-7.25 (m, 12H), 7.36 (t, $J$ = 8.0 Hz, 1H), 7.66 (d, $J$ = 8.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 20.0, 108.2, 122.5, 124.8, 125.6, 126.1, 126.5, 126.9, 127.0, 128.1, 128.3, 128.9, 129.3, 129.6, 130.7, 131.1, 134.3, 136.5, 138.5, 142.4 (1 $sp^2$ carbon missing due to overlap); IR (neat) 3469, 3368, 3043, 3024, 2928, 1617, 1435 $cm^{-1}$; HRMS *m/z* 309.15227 (calcd for $C_{23}H_{19}N$, 309.15175). NOE was detected between the $NH_2$ (3.75 ppm) and $CH_3$ (1.93 ppm) groups in the 2D NOESY spectrum of **3**.

**2-Amino-4-(2-methylphenyl)-3-phenylnaphthalene (4).** Obtained as an amber oil in a 45% yield from the reaction of (2-iodophenyl)acetonitrile and 2-(phenylethynyl)toluene after purification by column chromatography using 4:1 hexanes/ethyl acetate ($R_f$ = 0.48): $^1$H NMR ($CDCl_3$) δ 2.08 (s, 3H), 3.66 (br s, 2H), 7.00-7.26 (m, 11H), 7.33-7.38 (m, 2H), 7.67 (d, $J$ = 7.6 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 19.8, 107.9, 122.3, 125.6, 125.7, 126.0, 126.5, 126.8, 127.2, 127.3, 127.4, 127.5, 129.3, 129.9, 131.0, 131.1, 134.5, 136.8, 139.1, 139.4, 142.3; IR (neat) 3476, 3380, 3058, 3019, 2923, 1616 $cm^{-1}$; HRMS *m/z* 309.15227 (calcd for $C_{23}H_{19}N$, 309.15175). No NOE was detected between the $NH_2$ (3.66 ppm) and $CH_3$ (2.08 ppm) groups.

**2-Amino-4-hydroxymethyl-3-phenylnaphthalene (8).** Obtained as a yellow oil in a 29% yield from the reaction of (2-iodophenyl)acetonitrile and 3-phenyl-2-propyn-1-ol after

purification by column chromatography using 2:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.60 (br s, 1H), 3.80 (br s, 2H), 4.79 (s, 2H), 7.09 (s, 1H), 7.31-7.36 (m, 3H), 7.40-7.47 (m, 2H), 7.50-7.54 (m, 2H), 7.65 (d, $J$ = 8.0 Hz, 1H), 8.12 (d, $J$ = 8.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 59.8, 109.2, 123.2, 124.4, 126.2, 126.3, 128.0, 128.9, 129.1, 129.8, 131.2, 134.4, 134.8, 137.0, 142.2; IR (neat) 3450, 3390, 3063, 3025, 2929, 2851, 1621 cm$^{-1}$; HRMS *m/z* 249.11577 (calcd for $C_{17}H_{15}NO$, 249.11536).

**2-Amino-4-methyl-3-(triisopropylsilyl)naphthalene (13).** Obtained as a green oil in a 54% yield from the reaction of (2-iodophenyl)acetonitrile and 1-triisopropylsilyl-1-propyne after purification by column chromatography using 10:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.16 (d, $J$ = 7.5 Hz, 18H), 1.65 (heptet, $J$ = 7.5 Hz, 3H), 2.79 (s, 3H), 3.97 (br s, 2H), 6.84 (d, $J$ = 1.2 Hz, 1H), 7.24 (td, $J$ = 8.4, 1.5 Hz, 1H), 7.35 (td, $J$ = 8.1 Hz, 1H), 7.52 (dd, $J$ = 8.1, 0.6 Hz, 1H), 7.91 (d, $J$ = 8.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 14.1, 19.4, 21.8, 108.2, 122.0, 124.2, 125.7, 126.4, 127.7, 135.1, 144.1, 149.6 (1 sp$^2$ carbon missing due to overlap); IR (neat) 3490, 3381, 3062, 2948, 2871, 1615 cm$^{-1}$; HRMS *m/z* 313.22300 (calcd for $C_{20}H_{31}NSi$, 313.22258).

**2-Amino-3-*tert*-butyl-4-(*tert*-butylethynyl)naphthalene (15).** Obtained as an inseparable mixture with the other regioisomer (about 6%) as a brown oil in a 91% yield from the reaction of (2-iodophenyl)acetonitrile and 2,2,7,7-tetramethyl-3,5-octadiyne after column chromatography using 4:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.78 (s, 9H), 4.05 (br s, 2H), 6.92 (s, 1H), 7.24-7.34 (m, 2H), 7.46-7.49 (m, 1H), 8.34-8.37 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ 29.3, 30.6, 32.3, 38.0, 79.2, 110.6, 113.3, 120.6, 123.2, 125.0, 125.9, 126.4, 130.1, 132.5, 138.0, 143.7; IR (neat) 3510, 3392, 3067, 2969, 2923, 2866, 2207, 1619 cm$^{-1}$; HRMS *m/z* 279.19915 (calcd for $C_{20}H_{25}N$, 279.19870).

**2-Amino-6,7-dimethoxy-3,4-diphenylnaphthalene (17).** Obtained as an off-white solid in an 81% yield from the reaction of **16** and diphenylacetylene after purification by column chromatography using 2:1 hexanes/ethyl acetate: mp 177-179 °C (EtOH); $^1$H NMR ($CDCl_3$) δ 3.64 (br s, 2H), 3.66 (s, 3H), 4.00 (s, 3H), 6.70 (s, 1H), 6.98 (s, 1H), 7.04 (s, 1H), 7.09-7.26 (m, 10H); $^{13}$C NMR ($CDCl_3$) δ 55.6, 55.8, 104.4, 106.2, 107.9, 122.3, 126.3, 126.7, 127.5, 128.2, 130.2, 130.7, 130.8, 137.9, 138.4, 139.4, 141.1, 146.9, 149.8 (1 sp$^2$ carbon missing

due to overlap); IR (neat) 3460, 3366, 3059, 3000, 2962, 2934, 2834, 1614, 1495 $cm^{-1}$; HRMS *m/z* 355.15787 (calcd for $C_{24}H_{21}NO_2$, 355.15723).

**2-Amino-6,7-dimethoxy-3,4-di-*n*-propylnaphthalene (18).** Obtained as an amber oil in a 62% yield from the reaction of **16** and 4-octyne after purification by column chromatography using 1:1 hexanes/ethyl acetate: $^1H$ NMR ($CDCl_3$) δ 1.09 (t, *J* = 7.6 Hz, 3H), 1.11 (t, *J* = 7.6 Hz, 3H), 1.57-1.70 (m, 4H), 2.64-2.69 (m, 2H), 2.93-2.97 (m, 2H), 3.70 (br s, 2H), 3.96 (s, 3H), 3.97 (s, 3H), 6.84 (s, 1H), 6.88 (s, 1H), 7.17 (s, 1H); $^{13}C$ NMR ($CDCl_3$) δ 14.8, 14.9, 22.9, 24.0, 30.2, 31.3, 55.7, 55.8, 104.0, 105.2, 108.1, 122.1, 125.7, 129.4, 135.7, 141.7, 146.9, 148.9; IR (neat) 3457, 3370, 3004, 2956, 2869, 2826, 1627 $cm^{-1}$; HRMS *m/z* 287.18906 (calcd for $C_{18}H_{25}NO_2$, 287.18853).

**2-Methyl-4,5-diphenylnaphtho[2,1-*d*]oxazole (20).** Obtained as a white solid in a 53% yield from the reaction of **19c** and diphenylacetylene after purification by column chromatography using 2:1 hexanes/ethyl acetate: mp 222-224 °C (hexanes/ethyl acetate); $^1H$ NMR ($CDCl_3$) δ 2.03 (s, 3H), 7.01-7.02 (m, 1H), 7.06-7.10 (m, 3H), 7.16-7.28 (m, 5H), 7.35-7.40 (m, 1H), 7.44-7.46 (m, 1H), 7.49-7.54 (m, 1H), 8.50 (d, *J* = 8.8 Hz, 1H), 9.56 (s, 1H); $^{13}C$ NMR ($CDCl_3$) δ 23.5, 117.9, 123.1, 125.6, 126.3, 126.4, 126.5, 126.9, 127.5, 127.6, 128.5, 130.6, 131.3, 131.6, 131.9, 132.7, 136.8, 138.6, 144.2, 170.3; IR (neat) 3060, 1646, 1513, 1494, 1277 $cm^{-1}$; HRMS *m/z* 335.13157 (calcd for $C_{24}H_{17}NO$, 335.13101).

**2,4,4,5-Tetramethyl-1,4-dihydro-2*H*-naphtho[2,3-*d*][1,3]oxazine (21a).** Obtained as a light brown solid in a 25% yield from the reaction of (2-iodophenyl)acetonitrile and 2-methyl-3-pentyn-2-ol after purification by column chromatography using 4:1 hexanes/ethyl acetate ($R_f$ = 0.44): mp 95-97 °C; $^1H$ NMR ($CDCl_3$) δ 1.44 (d, *J* = 5.6 Hz, 3H), 1.75 (s, 3H), 1.83 (s, 3H), 2.73 (s, 3H), 4.30 (br s, 1H), 4.92 (q, *J* = 5.6 Hz, 1H), 6.89 (s, 1H), 7.24-7.28 (m, 1H), 7.32-7.36 (m, 1H), 7.55 (d, *J* = 8.4 Hz, 1H), 7.92 (d, *J* = 8.4 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 17.7, 21.8, 28.4, 30.2, 73.3, 76.2, 109.9, 122.7, 123.9, 125.7, 126.1, 128.6, 130.5, 133.0, 140.7 (1 $sp^2$ carbon missing due to overlap); IR (neat) 3375, 3056, 2983, 2934, 2875, 1618 $cm^{-1}$; HRMS *m/z* 241.14703 (calcd for $C_{16}H_{19}NO$, 241.14666).

**3-*E*-{1-[2-cyanomethylphenyl]ethylidene}-5-{1-hydroxy-1-methylethyl}-2,2,4-trimethyl-2,3-dihydrofuran (22).** Obtained as a yellow oil in a 26% yield from the reaction of (2-iodophenyl)acetonitrile and 2-methyl-3-pentyn-2-ol after purification by column

chromatography using 4:1 hexanes/ethyl acetate ($R_f$ = 0.26): $^1$H NMR ($CDCl_3$) δ 1.03 (s, 3H), 1.40 (s, 6H), 1.57 (s, 3H), 1.62 (s, 3H), 2.04 (s, 3H), 2.10 (s, 1H), 3.55-3.70 (m, 2H), 7.16-7.19 (m, 1H), 7.23-7.28 (m, 2H), 7.36-7.38 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ 10.6, 21.3, 22.4, 26.1, 26.2, 28.7, 29.0, 70.9, 85.7, 104.3, 116.5, 118.2, 127.3, 127.8, 128.0, 128.2, 130.1, 144.1, 161.9; IR (neat) 3334, 2978, 2930, 2875, 2253 cm$^{-1}$; HRMS *m/z* 311.18908 (calcd for $C_{20}H_{25}NO_2$, 311.18853).

**2,4,4-Trimethyl-5-phenyl-1,4-dihydro-2*H*-naphtho[2,3-*d*][1,3]oxazine (21b).** Obtained as a white solid in a 50% yield from the reaction (conducted at 130 °C) of (2-iodophenyl)acetonitrile and 2-methyl-4-phenyl-3-butyn-2-ol after purification by column chromatography using 4:1 hexanes/ethyl acetate: mp 179-180 °C (EtOH); $^1$H NMR ($CDCl_3$) δ 1.22 (s, 3H), 1.44 (d, *J* = 5.4 Hz, 3H), 1.54 (s, 3H), 4.43 (br s, 1H), 5.07 (q, *J* = 5.4 Hz, 1H), 6.86 (d, *J* = 8.7 Hz, 1H), 6.97-7.02 (m, 2H), 7.25-7.32 (m, 3H), 7.43-7.46 (m, 3H), 7.55 (d, *J* = 8.1 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 16.4, 22.2, 29.6, 30.4, 73.5, 110.4, 122.3, 125.1, 125.8, 126.9, 127.3, 127.4, 127.6, 130.9, 132.4, 132.9, 137.2, 140.2, 140.3; IR (neat) 3398, 3062, 3026, 2982, 2931, 1618 cm$^{-1}$; HRMS *m/z* 303.16293 (calcd for $C_{21}H_{21}NO$, 303.16231).

**4,4-Dimethyl-5-phenyl-2-*n*-propyl-1,4-dihydro-2*H*-naphtho[2,3-*d*][1,3]oxazine (21c).** Obtained as a light yellow solid in a 38% yield from the reaction of (2-iodophenyl)-acetonitrile, 2-methyl-4-phenyl-3-butyn-2-ol and *n*-$Bu_3N$ after purification by column chromatography using 4:1 hexanes/ethyl acetate: mp 142-144 °C (EtOH); $^1$H NMR ($CDCl_3$) δ 1.00 (t, *J* = 7.4 Hz, 3H), 1.21 (s, 3H), 1.52 (s, 3H), 1.46-1.73 (m, 4H), 4.41 (br s, 1H), 4.87 (m, 1H), 6.85 (d, *J* = 8.4 Hz, 1H), 6.97-7.02 (m, 2H), 7.24-7.32 (m, 3H), 7.42-7.46 (m, 3H), 7.55 (d, *J* = 8.0 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 14.0, 17.7, 29.5, 30.4, 37.9, 76.2, 110.4, 122.3, 125.1, 125.8, 126.9, 127.3, 127.4, 127.5, 128.9, 130.1, 130.9, 132.4, 132.9, 137.1, 140.2, 140.5; IR (neat) 3381, 3057, 3021, 2969, 2933, 2871, 1619 cm$^{-1}$; HRMS *m/z* 331.19399 (calcd for $C_{23}H_{25}NO$, 331.19361).

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# CHAPTER 3. SYNTHESIS OF BENZOCYCLIC KETONES AND CYCLOPENTENONES VIA Pd-CATALYZED CYCLIZATION OF ω-(2-IODOARYL)ALKANENITRILES AND RELATED COMPOUNDS

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

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## Abstract

An efficient procedure for the synthesis of 2,2-disubstituted benzocyclic ketones by intramolecular carbopalladation of nitriles has been developed. The cyclization of substituted 3-(2-iodoaryl)propanenitriles affords indanones in high yields. The reaction is compatible with a wide variety of functional groups. This methodology has been extended to the synthesis of tetralones and cyclopentenones.

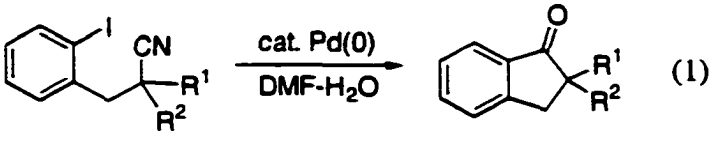
## Introduction

Benzocyclic ketones are versatile and useful synthetic intermediates in the agrochemical and pharmaceutical industries.[1] The 2-alkyl-1-indanone core is prominently featured in many pharmaceutical products, such as the antihypertensive drug (+)-Indacrinone, the diuretic MK473, and the β-blocker Spirendolol.[1a] Some indanone derivatives also exhibit bronchodilatory activity.[2] Indanones serve as important building blocks in the synthesis of steroids, gibberellic acid, fredericamycin A, and other natural products,[2,3] and are frequently used as precursors to medicinal substances, such as non-steroidal 5α-reductase inhibitors, 5-hydroxytryptamine-receptor agonists, dopamine-receptor antagonists and other agents against Alzheimer's disease.[4]

α-Tetralones have been used as precursors to chiral benzocyclic amines that provide key intermediates for a number of pharmaceutical preparations with neurotropic and psychotropic activity.[1d] Other biologically active substances synthesized from tetralones include lignans (such as podophyllotoxin and Justicidins A-F) and diterpenes (heliosporin E and the aglycon moiety of various pseudopterosins),[5] antitumor and antileukemic HIV reverse transcriptase-inhibiting benzo[*c*]phenanthridine alkaloids,[6] angucyclin antibiotics,[7] anthracyclins, tetracyclins and estrone derivatives.[8]

Traditionally, benzocyclic ketones have been synthesized by the intramolecular Friedel-Crafts acylation of β-arylpropionic and γ-arylbutyric acids and their derivatives.[6a,9] The need for strongly acidic conditions required by this method, especially when the aromatic ring is deactivated, restricts the variety of functional groups that are tolerated. There can also be problems with the regioselectivity of the cyclization. Intermolecular routes to benzocyclic ketones include the Vilsmeier-Haack cyclization of substituted styrenes,[1c] the tandem Knoevenagel condensation-cycloaddition,[3a] the Wittig-Horner reaction of phthalide-3-phosphonates and ketones,[3b] and various carbonylation processes.[10] Complex benzocyclic ketones may be synthesized by derivatization of simple indanones and tetralones, but this approach often suffers from poor yields.[11] Specific indanone targets have also been prepared via indirect, highly specific routes.[8,12]

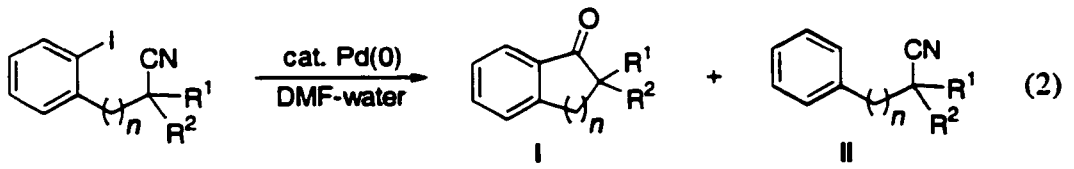
In a continuation of our work on developing useful, new synthetic organic methodology based on the carbopalladation of nitriles,[13] we decided to explore the possibility of synthesizing indanones by the Pd-catalyzed cyclization of 3-(2-iodoaryl)propanenitriles (eq 1).[14] Here, we wish to report the full details of our investigation of the scope and limitations of this process, which has been found to afford 2,2-disubstituted benzocyclic ketones in high yields.




(1)

## Results and Discussion

2,2-Dimethyl-3-(2-iodophenyl)propanenitrile (**1a**, $R^1$,$R^2$ = Me, $n$ = 1, eq 2) was chosen as the model system for the cyclization. We began the optimization work by first attempting to apply our previous carbopalladation reaction conditions (Table 1, entry 1).[13] The target, 2,2-dimethyl-1-indanone (**2a**), was formed in a moderate yield accompanied by a considerable amount of unreacted **1a** even after a long reaction time.




(2)

We then turned our attention to a catalytic system consisting of $Pd(OAc)_2$ and $PPh_3$,[15] and also employed 1.2 equivs of triethylamine as a base and a possible reducing agent for Pd(II). Under these conditions, we detected the formation of two products (eq 2), the target indanone **I** and a minor product **II**, which apparently resulted from reduction of the carbon-iodine bond

**Table 1. Optimization of the Pd-Catalyzed Cyclization of 2,2-Dimethyl-3-(2-iodophenyl)propanenitrile (eq 2, $n$ = 1, $R^1$,$R^2$ = Me)**[a]

| entry | catalyst | phosphine | argon | $NEt_3$ (equiv) | time (h) | % yield[b] | |
|---|---|---|---|---|---|---|---|
| | | | | | | **I** | **II** |
| 1 | 10% $Pd(dba)_2$ | - | - | 1 | 72 | 34[c] | 0 |
| 2 | 10% $Pd(OAc)_2$ | 20% $PPh_3$ | + | 1.2 | 10 | 89[d] | 9 |
| 3 | 10% $Pd(OAc)_2$ | 20% $PPh_3$ | + | 1.2 | 12 | 88 | 12 |
| 4 | 10% $Pd(OAc)_2$ | 20% $PPh_3$ | - | 1.2 | 12 | 80 | 9 |
| 5 | 10% $Pd(OAc)_2$ | 20% $PPh_3$ | + | 1 | 12 | 60 | 10 |
| 6 | 10% $Pd(OAc)_2$ | 20% $PPh_3$ | - | 1 | 12 | 72 | 12 |

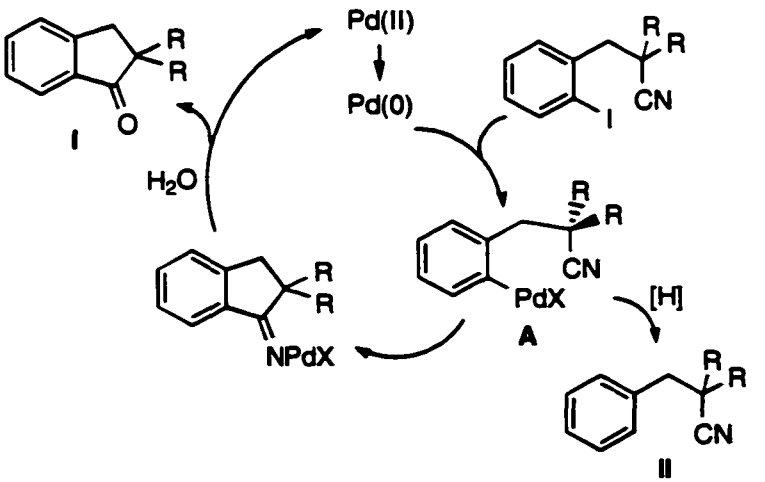
[a] All reactions were run at 130 °C in 9:1 DMF-water. [b] Yields determined by GC-MS and $^1$H NMR spectral analysis. [c] Only 62% conversion of the starting material. [d] 95% Conversion of the starting material.

of the starting material. Such reduction is a well-known process that has been observed in many other palladium-catalyzed reactions of organic halides.[16]

Since a small amount of the starting material was detected in the reaction mixture after 10 h (Table 1, entry 2), we allowed the reaction to proceed until all of **1a** was consumed (entry 3). After 12 h, the reaction was complete and the results were comparable to those reported in entry 1. It was also established that an inert atmosphere is not essential for the success of the cyclization as the target product was obtained in a high yield when the reaction was conducted in air (entry 4). Reducing the amount of triethylamine decreased the yield of the indanone (entries 5 and 6). Based on the results of our optimization, the following reaction conditions were adopted as the general procedure for the palladium-catalyzed cyclization of 3-(2-iodoaryl)propanenitriles:[17] 0.25 mmol of the substrate, 10 mol % $Pd(OAc)_2$, 20 mol % $PPh_3$, and 1.2 equiv of $NEt_3$ in 5 mL of a 9:1 DMF-water mixture are stirred at 130 °C under Ar until consumption of the starting material is complete.

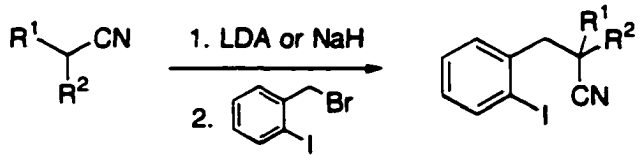
We propose the following mechanism for this cyclization (Scheme 1). Oxidative addition of the aryl iodide to a Pd(0) species, produced by reduction of $Pd(OAc)_2$, leads to the arylpalladium intermediate **A**. Intramolecular addition of the arylpalladium species across the cyano group in **A** affords an iminopalladium intermediate, which is then hydrolyzed to the corresponding indanone **I**. The Pd(II) species is then reduced again to Pd(0), which returns to the catalytic cycle. Alternatively, the arylpalladium intermediate **A**

**Scheme 1**



may undergo a reduction process, which results in the formation of the byproduct **II**. The exact mechanism of this reduction, as well as the identity of the reducing agent, is unknown at this time (vide infra).

Having established a procedure for the cyclization, we synthesized a variety of substituted 3-(2-iodoaryl)propanenitriles in order to investigate the scope and limitations of our methodology. One of the advantages of this process is in fact the ease of preparation of the starting materials from commercially available precursors. Thus, a number of alkanenitriles were alkylated with 2-iodobenzyl bromide to produce representative substrates **1a-i** (eq 3). A similar procedure utilizing the ability of the cyano group to stabilize the neighboring carbanion was the key step in the preparation of 3-(2-iodophenyl)propanenitriles functionalized at the benzylic position (**1j-n**, Scheme 2).

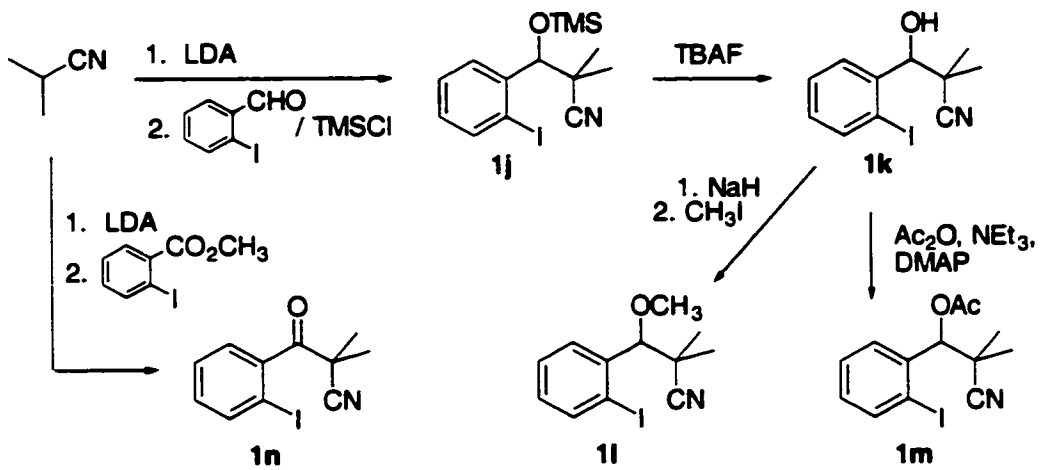



(3)

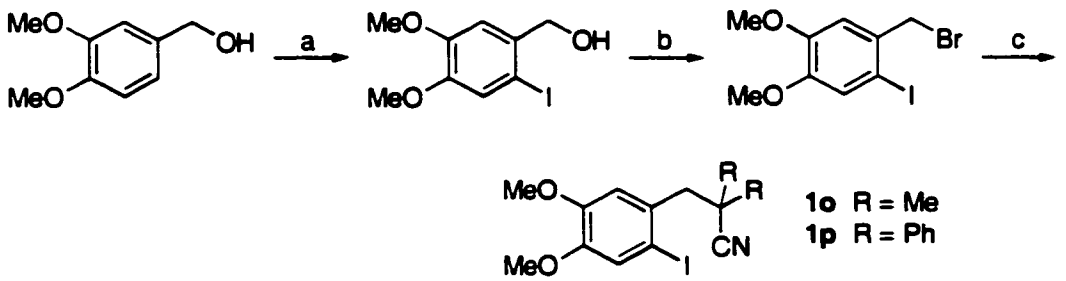
| | $R^1$ | $R^2$ |
|---|---|---|
| **1a** | Me | Me |
| **1b** | $-(CH_2)_5-$ | |
| **1c** | $-(CH_2)_3-$ | |
| **1d** | $-(CH_2)_2-$ | |
| **1e** | Me | Ph |
| **1f** | Ph | Ph |
| **1g** | H | Et |
| **1h** | Me | $CO_2Me$ |
| **1i** | Me | CN |

3-(2-Iodoaryl)propanenitriles **1o-q** were prepared via alkylation of the appropriate alkanenitriles with substituted 2-iodobenzylic bromides derived from the corresponding *o*-iodobenzylic alcohols as shown in Schemes 3 and 4. A different approach was implemented for the synthesis of electron-poor substrates **1r** and **1s**, which were obtained from nitration of the parent compound **1a** (Scheme 5). Compound **1r** was further transformed into 3-(2-iodo-4-cyanophenyl)-2,2-dimethylpropanenitrile (**1t**) by a reduction-Sandmeyer reaction sequence.

**Scheme 2**

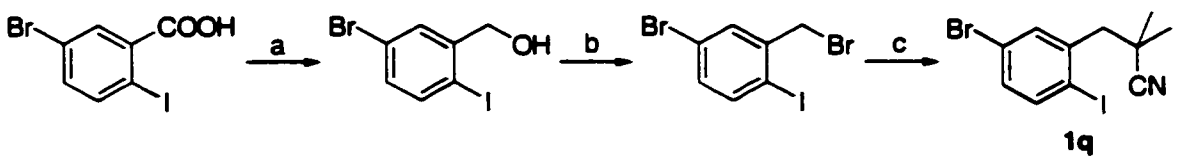



**Scheme 3**



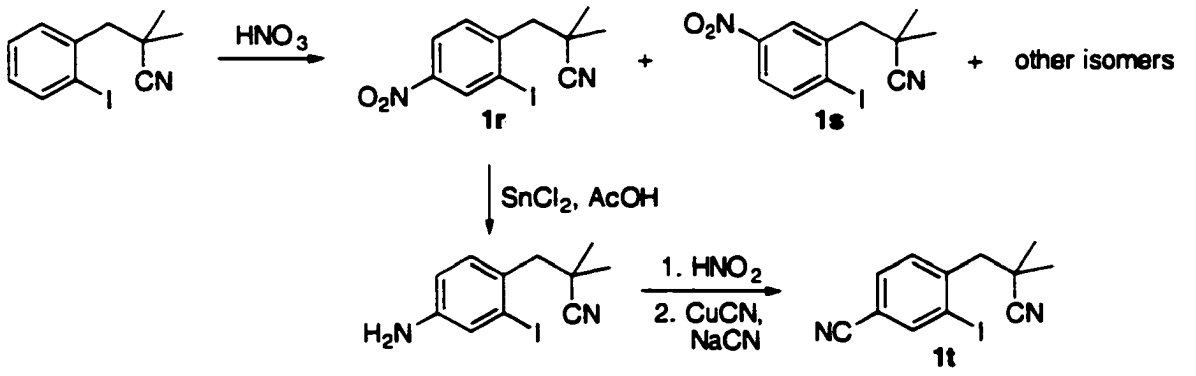

(a) $CF_3COOAg$, $I_2$, $CH_2Cl_2$, r.t.; (b) $CBr_4$, $PPh_3$, $CH_2Cl_2$, 0 °C; (c) alkylation of isobutyronitrile or diphenylacetonitrile.

**Scheme 4**




(a) $BH_3{\cdot}SMe_2$, THF, 0 °C to r.t.; (b) $CBr_4$, $PPh_3$, $CH_2Cl_2$, 0 °C; (c) alkylation of isobutyronitrile.

**Scheme 5**




With various 3-(2-iodoaryl)propanenitriles **1** in hand, we explored the scope and limitations of their palladium-catalyzed cyclization to indanones. The results of this study are presented in Table 2. In most cases, the corresponding indanones were obtained in very good yields. As we observed during the optimization studies with **1a** (entry 1), minor amounts of reduction byproducts were often formed in the cyclization of other 2,2-disubstituted 3-(2-iodoaryl)propanenitriles. Given the small scale on which this reaction has usually been run, it has sometimes proven difficult to separate the two products by column chromatography, so the yields of all known products were determined by analysis of the GC-MS and $^1$H NMR spectral data obtained from the reaction mixtures. Several of the reactions were also performed on a larger scale and the isolated yields of the products were found to be consistent with the yields that were determined spectroscopically.

As expected, cycloalkanecarbonitriles **1b** and **1c** underwent successful cyclization and afforded spirocyclic indanones **2b** and **2c**, the skeletons of which are related to several pharmaceutical and biologically active substances (Table 2, entries 2 and 3).[1a,3b,4a] 2-Methyl-2-phenyl-1-indanone (**2e**) and 2,2-diphenyl-1-indanone (**2f**) were obtained in high yields (entries 4 and 5) despite our concern that organopalladium species **A** (Scheme 1), derived from 2-aryl-3-(2-iodophenyl)propanenitriles, might undergo intramolecular attack on the aryl substituent, resulting in the formation of a dihydrophenanthrene derivative.[18] Cyclization of the secondary nitrile **1g** resulted in only a modest yield of the target, 2-monosubstituted indanone **2g**, with the major product being the dehalogenated starting material (entry 6). This represents a limitation of the current protocol (see discussion below). However, this

**Table 2. Synthesis of Indanones by the Pd-Catalyzed Cyclization of 3-(2-Iodoaryl)-propanenitriles (eq 2, $n$ = 1)[a]**

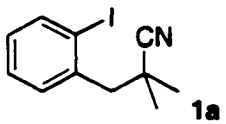
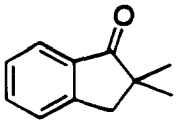
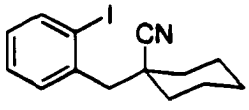
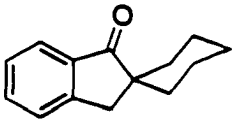
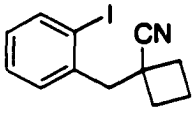
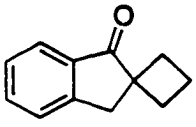
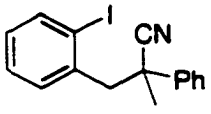
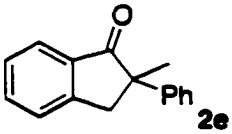
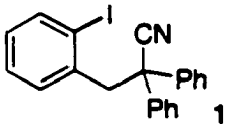
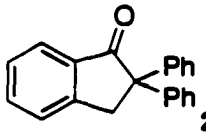
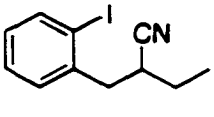
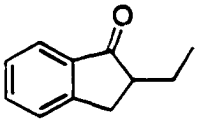
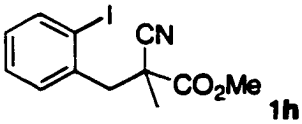
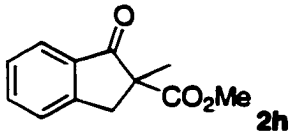
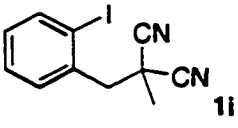
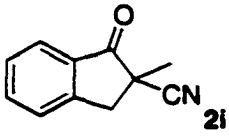
| entry | nitrile | time (h) | indanone (I) | % yield[b] | |
|---|---|---|---|---|---|
| | | | | I | II |
| 1 |  **1a** | 12 |  **2a** | 88 | 12 |
| 2 |  **1b** | 12 |  **2b** | 86 | 8 |
| 3 |  **1c** | 12 |  **2c** | 83[c] | 17 |
| 4 |  **1e** | 12 |  **2e** | 82 | 6 |
| 5 |  **1f** | 15 |  **2f** | 92 | 7 |
| 6 |  **1g** | 12 |  **2g** | 30 | 50 |
| 7 |  **1h** | 12 |  **2h** | 78, 73[c] | trace |
| 8 |  **1i** | 12 |  **2i** | 89[c] | 0 |

**Table 2. (continued)**

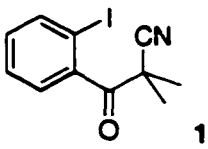
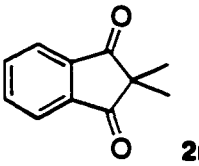
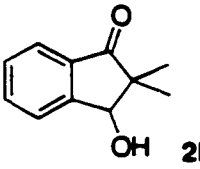
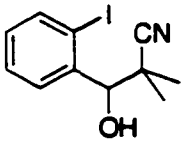
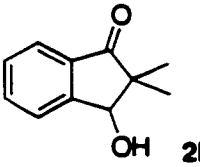
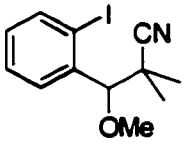
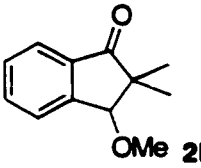
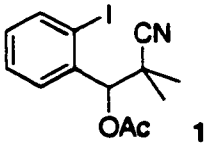
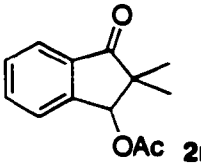
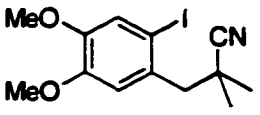
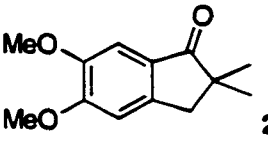
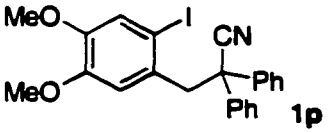
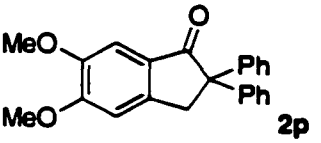
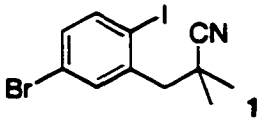
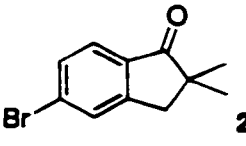
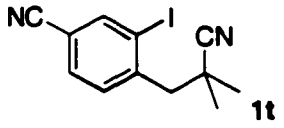
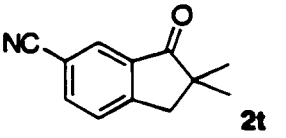
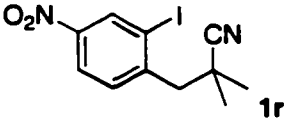
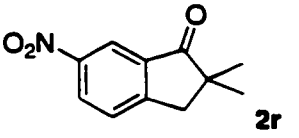
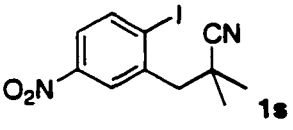
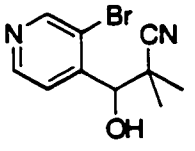
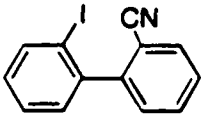
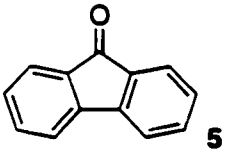
| entry | nitrile | time (h) | indanone (I) | % yield[b] | |
|---|---|---|---|---|---|
| | | | | I | II |
| 9 |  1n | 15 |  2n | 83 | 6 |
| 10 |  1j | 15 |  2k | 80 | trace |
| 11 |  1k | 12 |  2k | 80 | 5 |
| 12 |  1l | 36 |  2l | 77(79)[d] | 19(19) |
| 13 |  1m | 40 |  2m | 80[c,e] | 14 |
| 14 |  1o | 29 |  2o | 75[c] | trace |
| 15 |  1p | 18 |  2p | 84[c] | 0 |
| 16 |  1q | 15 |  2q | 64(68)[c,f] | trace |

**Table 2. (continued)**

| entry | nitrile | time (h) | indanone (**I**) | % yield[b] | |
|---|---|---|---|---|---|
| | | | | **I** | **II** |
| 17 |  **1t** | 12 |  **2t** | 43 | 48 |
| 18 |  **1r** | 12 |  **2r** | 35 | 64 |
| 19 |  **1s** | 12 | - | 0 | 98 |
| 20 |  **3** | 12 | - | 0 | 99 |
| 21 |  **4** | 12 |  **5** | 56 | 24 |

[a] See the Experimental Section for the reaction conditions. [b] Yields determined by $^1$H NMR spectral analysis unless specified otherwise. Yields in parentheses are corrected for unreacted starting material. [c] Isolated yield. [d] 97% Conversion of the starting material. [e] 87% Conversion after 36 h. [f] Approximately 5% of the starting material and 3% of 2,2-dimethylindanone were also isolated.

limitation can be overcome by the decarboalkoxylation of 1-indanone-2-carboxylate esters,[19a] such as **2h**, which is readily prepared from methyl 2-cyano-3-(2-iodophenyl)-2-methylpropanoate (**1h**) using our cyclization procedure (entry 7). Another α-functionalized propanenitrile, **1i**, also cyclized efficiently and afforded indanone **2i** without formation of the reduction byproduct (entry 8).

The cyclization has been found to tolerate a wide variety of functional groups (entries 7-18). 1,3-Indandione derivatives **2k-n** were readily obtained from β-functionalized 3-(2-iodoaryl)propanenitriles **1j-n** containing keto, hydroxy, ether and ester groups (entries 9-13). Only the trimethylsilyloxy group of **1j** did not survive the cyclization conditions, affording

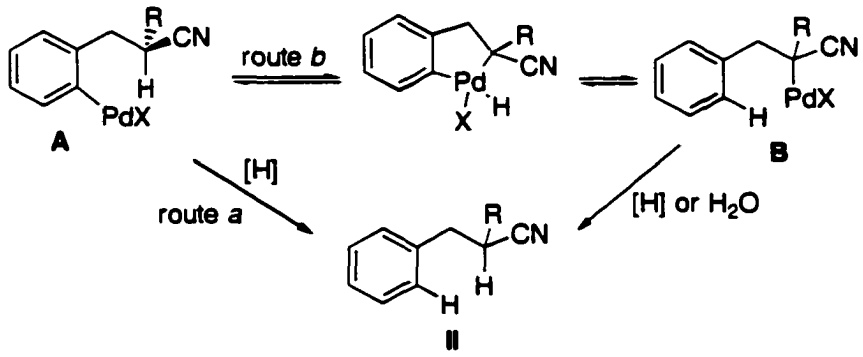
instead the deprotected hydroxyindanone **2k** (entry 10). Since the silyl derivative of **2k** was never detected in the reaction mixture during GC-MS monitoring, it appears that **1j** underwent deprotection before engaging in the palladium-catalyzed cyclization, either due to the ease of desilylation under our reaction conditions or because the bulk of the trimethylsilyl group inhibited the oxidative addition of **1j** to the Pd(0) catalyst. The long reaction times reported in entries 12 and 13 are probably caused by intramolecular chelation of the methoxy and acetoxy groups to the palladium moiety in the arylpalladium intermediates produced from **1l** and **1m**.

Substituents on the arene ring appear to have a pronounced effect on the success of the carbopalladation. The electron-rich substrates **1o** and **1p** easily produced the corresponding indanones **2o** and **2p** (entries 14 and 15), although these two reactions required longer reaction times than those of the parent systems, most probably due to the more sluggish oxidative addition of **1o** and **1p** to the Pd(0) catalyst. The slightly electron-deficient **1q** afforded only a modest yield of 5-bromo-2,2-dimethyl-1-indanone (**2q**), demonstrating the chemoselectivity of our procedure and resulting in an aryl bromide poised for other palladium-catalyzed processes. Strong electron-withdrawing groups, on the other hand, inhibited the carbopalladation considerably, making reduction of the arylpalladium intermediate the predominant reaction (entries 17-19). As we have proposed previously,[14,20] the palladium center in intermediate **A** (Scheme 1) must have sufficient electron density to be able to add to the carbon-nitrogen triple bond. Obviously, the nucleophilicity of the arylpalladium species suffers with the introduction of electron-withdrawing groups on the arene ring. We have found that the yields of the corresponding indanones decrease with the increase in electron-withdrawing ability of the substituent in the aromatic ring of the 3-(2-iodoaryl)propanenitrile as quantified by the Hammett parameter $\sigma$ (entries 17-19).[21] Heterocyclic 3-(2-haloaryl)propanenitrile **3** also failed to furnish any cyclization product, probably because of the electron-poor nature of the pyridine system (entry 20).

9-Fluorenone (**5**) was obtained in a 56% yield from 2-cyano-2'-iodobiphenyl (**4**) in what we believe to be the first example of the addition of an *aryl*palladium to an *arene*nitrile (entry 21). The modest yield is most probably caused by steric factors that hinder coordination of the arylpalladium to the carbon-nitrogen triple bond prior to the carbopalladation step.

The low yield and the considerable amount of reduction byproduct in the cyclization of 2-(2-iodobenzyl)butanenitrile (**1g**, Table 2, entry 6) prompted us to look closer at our proposed mechanism (Scheme 1). The oxidative addition of **1g** to the Pd(0) catalyst is evidently successful, but the intermediate **A** is apparently reduced faster than it cyclizes. Presumably, intermediate **A** adopts a conformation where the palladium center is oriented towards the smallest substituent on the α-carbon of the nitrile. In tertiary nitriles, the smallest substituent on the α-carbon of the nitrile is the cyano group itself, so the conformation of **A** is close to the one shown in Scheme 1, which is favorable for the cyclization. However, when formed from secondary nitriles like **1g**, intermediate **A** prefers the conformation shown in Scheme 6, where the palladium is oriented towards the hydrogen, which is now the smallest group on the α-carbon of the nitrile. Obviously, the cyano group in such a conformation is too far away from the palladium for successful intramolecular attack, and **A** is eventually reduced to the byproduct **II** (route *a*, Scheme 6).

**Scheme 6**




We also considered the possibility that the α-hydrogen plays a more active role in the reduction (route *b*). It seemed conceivable that the palladium species **A** could insert into the activated α-C-H bond of the alkanenitrile and then migrate to the α-position and furnish intermediate **B**, which could later be reduced or hydrolyzed. This would account for the reduction of the original carbon-iodine bond in **1g**. However, such a mechanism is not possible for the tertiary nitriles **1r** and **1s**, where the reduction predominates (Table 2, entries 18 and 19). To test this idea, we prepared an α-deuterated version of **1g** and carried out the cyclization under our standard conditions. No deuterium incorporation into the benzene ring

was observed in the reduction product, nor was any of the deuterium label lost from the α-position of the nitrile. These results strongly discount the likelihood of route *b* (Scheme 6).

Using the cyclization of 2-(2-iodobenzyl)butanenitrile as a model system, we attempted to find reaction conditions that would substantially increase the yield of the 2-monosubstituted indanone (Table 3). Different phosphine ligands were tried in order to stabilize the arylpalladium intermediate **A** (Scheme 1) or make it more nucleophilic, thus promoting its attack on the cyano group. However, no improvement over the use of $PPh_3$ was observed (entries 1-14). Omitting the phosphine altogether resulted in a significant increase in the reaction time, but failed to improve the indanone-to-byproduct ratio (entry 15). Using tricyclohexylphosphine, which was employed by Yamamoto in a mechanistically similar intramolecular addition of an arylpalladium intermediate to ketones,[16a] with several organic and inorganic bases was also explored to no avail (entries 16-20). Especially surprising was the almost complete absence of the cyclization product in reactions using $Na_2CO_3$ and NaOAc since these were the bases used successfully by Yamamoto for the ketone cyclization. Two other Pd catalysts gave poorer results than did $Pd(OAc)_2$ (entries 21 and 22). No advantage was obtained when we tried using a chloride source (entries 23 and 24).

Since alkylamine bases having α-C-H bonds can be a source of reduction of the Pd(II) intermediates,[22] we decided to explore different organic bases (entries 25-31). First, we reduced the amount of triethylamine in hopes that this would lead to a decrease in the amount of the reduction byproduct, but the only result of this modification was an increase in the reaction time (entry 25). Using diisopropylamine, which has fewer α-C-H bonds than $Et_3N$ and therefore can be expected to be less reducing, seemed to improve the indanone-to-byproduct ratio. However, the overall yield of **2g** remained unsatisfactory (entry 26). The use of several other amines with no α-hydrogens, as well as *i*-$Pr_2NEt$, only led to an increase in the amount of reduction (entries 27-30). From these results, it appears that our standard base of choice, triethylamine, may not be responsible for reduction of the arylpalladium intermediate **A** (Scheme 6).

Finally, we considered the possibility that **A** may be reduced by formate anion,[23] formed under our reaction conditions from DMF and water. Reactions run in the absence of water

**Table 3. Optimization of the Pd-Catalyzed Cyclization of 2-(2-Iodobenzyl)butanenitrile (eq 2, $n = 1$, $R^1 = H$, $R^2 = Et$)[a]**

| entry | catalyst (10 mol %) | phosphine or arsine | base (equiv) | % yield (GC ratio I/II)[b] | |
|---|---|---|---|---|---|
| | | | | I | II |
| 1 | $Pd(OAc)_2$ | 20% $PPh_3$ | $NEt_3$ (1.2) | 30 | 50 |
| 2 | $Pd(OAc)_2$ | 20% P(*o*-Tol)$_3$ | $NEt_3$ (1.2) | 30 | 49 |
| 3 | $Pd(OAc)_2$ | 20% $AsPh_3$ | $NEt_3$ (1.2) | 14 | 51 |
| 4 | $Pd(OAc)_2$ | 20% P(2-furyl)$_3$ | $NEt_3$ (1.2) | (1:9.3)[c] | |
| 5 | $Pd(OAc)_2$ | 20% dppf | $NEt_3$ (1.2) | 22[d] | 39 |
| 6 | $Pd(OAc)_2$ | 10% dppf | $NEt_3$ (1.2) | 24 | 38 |
| 7 | $Pd(OAc)_2$ | 10% dppe | $NEt_3$ (1.2) | 16 | 55 |
| 8 | $Pd(OAc)_2$ | 20% dppe | $NEt_3$ (1.2) | 23 | 58 |
| 9 | $Pd(OAc)_2$ | 20% BINAP | $NEt_3$ (1.2) | 20 | 40 |
| 10 | $Pd(OAc)_2$ | 20% dppp | $NEt_3$ (1.2) | 10 | 55 |
| 11 | $Pd(OAc)_2$ | 20% TPPTS[e] | $NEt_3$ (1.2) | 16 | 57 |
| 12 | $Pd(OAc)_2$ | 20% TTMPP[f] | $NEt_3$ (1.2) | (1:1.8) | |
| 13 | $Pd(OAc)_2$ | 20% (di-*t*-butyl-phosphino)ferrocene | $NEt_3$ (1.2) | 32 | 44 |
| 14 | $Pd(OAc)_2$ | 20% 2-(di-*t*-butyl-phosphino)biphenyl | $NEt_3$ (1.2) | 16 | 23 |
| 15 | $Pd(OAc)_2$ | - | $NEt_3$ (1.2) | (1:2.2)[g] | |
| 16 | $Pd(OAc)_2$ | 20% $PCy_3$ | $NEt_3$ (1.2) | 27 | 69 |
| 17 | $Pd(OAc)_2$ | 20% $PCy_3$ | pyridine (1.2) | 26 | 51[c] |
| 18 | $Pd(OAc)_2$ | 20% $PCy_3$ | 2,6-di-*t*-butyl-4-methylpyridine (1.2) | 10 | 67[c] |
| 19 | $Pd(OAc)_2$ | 20% $PCy_3$ | $Na_2CO_3$ (2) | 0 | 34 |
| 20 | $Pd(OAc)_2$ | 20% $PCy_3$ | NaOAc (2) | trace | 34 |
| 21 | $PdCl_2$ | 20% $PPh_3$ | $NEt_3$ (1.2) | 15 | 55 |

**Table 3. (continued)**

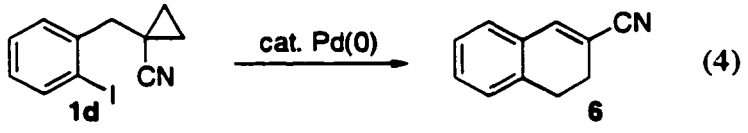
| entry | catalyst (10 mol %) | phosphine or arsine | base (equiv) | % yield (GC ratio I/II)[b] | |
|---|---|---|---|---|---|
| | | | | I | II |
| 22 | $PdCl_2(PPh_3)_2$ | - | $NEt_3$ (1.2) | 17 | 58 |
| 23 | $Pd(OAc)_2$ | 20% $PPh_3$ | $NEt_3$ (1.2) | 20[h] | 54 |
| 24 | $Pd(OAc)_2$ | 20% $PPh_3$ | $NEt_3$ (1.2) | 7[i] | 80 |
| 25 | $Pd(OAc)_2$ | 20% $PPh_3$ | $NEt_3$ (0.5) | 24[j] | 33 |
| 26 | $Pd(OAc)_2$ | 20% $PPh_3$ | *i*-$Pr_2NH$ (1.2) | 48 | 51 |
| 27 | $Pd(OAc)_2$ | 20% $PPh_3$ | 2,2,6,6-tetramethyl-piperidine (1.2) | (1:4.8)[k] | |
| 28 | $Pd(OAc)_2$ | 20% $PPh_3$ | $Ph_2NH$ (1.2) | 16[l] | 77 |
| 29 | $Pd(OAc)_2$ | 20% $PPh_3$ | $NPh_3$ (1.2) | 12[m] | 79 |
| 30 | $Pd(OAc)_2$ | 20% $PPh_3$ | *i*-$Pr_2NEt$ (1.2) | 9 | 53 |
| 31 | $Pd(OAc)_2$ | 20% $PPh_3$ | pyridine (1.2) | 29 | 38[c] |
| 32 | $Pd(OAc)_2$ | 20% $PPh_3$ | $NEt_3$ (1.2) | trace[n,o] | 48 |
| 33 | $Pd(OAc)_2$ | 20% $PPh_3$ | $NPh_3$ (1.2) | trace[n,p] | 11 |
| 34 | $Pd(OAc)_2$ | 20% $PPh_3$ | $NEt_3$ (1.2) | 31[q] | 24 |

[a] All reactions were run at 130 °C under Ar in 9:1 DMF-water unless specified otherwise. [b] All yields have been determined by $^1H$ NMR spectral analysis whenever practical. GC ratios were obtained straight from the reaction mixtures. [c] The reaction time was 36 h. [d] The same result was obtained at 100 °C. [e] TPPTS = tris(3-sulfonatophenyl)phosphine, sodium salt. [f] TTMPP = tris(2,4,6-trimethoxyphenyl)phosphine. [g] The reaction time was 84 h. [h] 1 Equiv of *n*-$Bu_4NCl$ was employed in the reaction. [i] 1 Equiv of LiCl was employed in the reaction. [j] The reaction time was 24 h. [k] Low conversion after 12 h. [l] The reaction time was 48 h. [m] The reaction time was 29 h. [n] This reaction was run for 7 days in dry DMA. [o] 76% Conversion of the starting material. [p] 12% Conversion of the starting material. [q] This reaction was run for 5 days in 9:1 DMA-water; 85% conversion of the starting material.

using DMA as a solvent were extremely slow and produced only traces of the desired compound **2g** (entries 32 and 33). A reaction using a 9:1 DMA-water mixture required an unreasonably long time and afforded **2g** in only a very modest yield (entry 34). Even though not using DMF seemed to somewhat suppress the reduction (entries 32-34), the formation of the reduced starting material indicated the presence of another reducing agent, the identity of which remains unknown. The role of DMF was further discounted when we found no

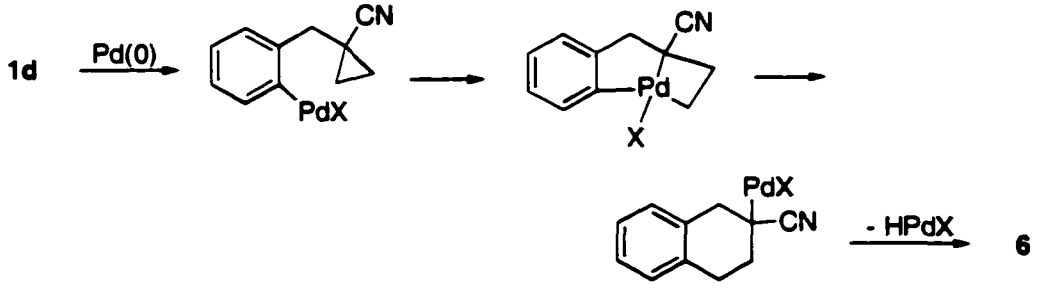
deuterium incorporation into the reduction byproduct after the reaction was conducted in a mixture of DMF-$d_7$ and $D_2O$.

An interesting process was observed in the attempted cyclization of 1-(2-iodobenzyl)cyclopropanecarbonitrile (**1d**). Instead of the expected spirocyclic indanone, this reaction produced 2-cyano-3,4-dihydronaphthalene (**6**) in a 58% yield (eq 4). The identity of the product was confirmed by synthesizing it independently from β-tetralone and TMSCN. Evidently, instead of attacking the cyano group, the arylpalladium intermediate formed from **1d** induces cyclopropane ring-opening perhaps by a process like that illustrated in Scheme 7. Examples of such ring-opening are well documented in cases where it leads to stable π-allylpalladium complexes.[24] In our case, the process is probably driven by the eventual formation of a conjugated system.




(4)

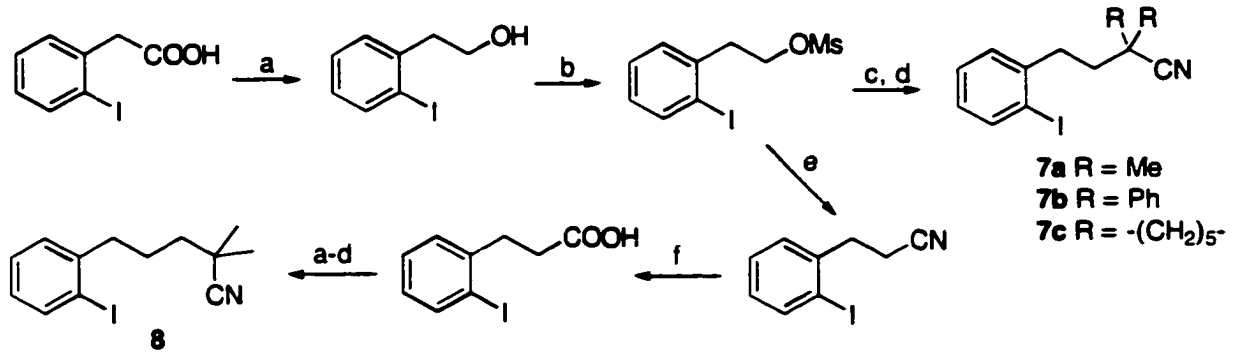
**Scheme 7.** Proposed mechanism for the formation of **6**




Encouraged by the success of the cyclization of 2,2-disubstituted 3-(2-iodoaryl)-propanenitriles, we decided to investigate the possibility of synthesizing benzocyclic ketones other than indanones. The starting materials for the six- and seven-membered ring cyclization were prepared from commercially available 2-iodophenylacetic acid as shown in Scheme 8, and introduced into the reaction under our standard conditions.

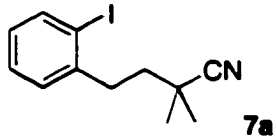
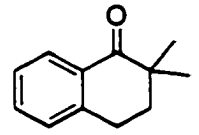
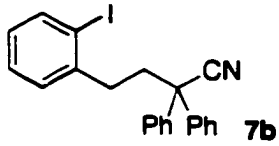
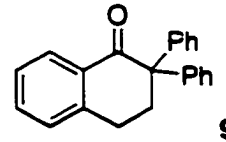
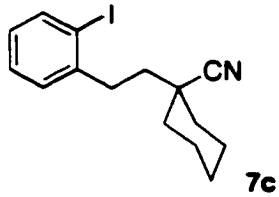
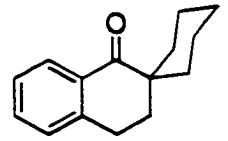
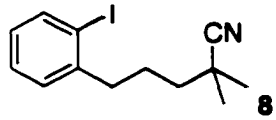
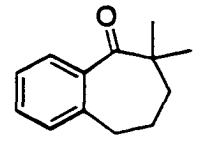
Subsequent cyclization proceeded in reasonable yields. Thus, 4-(2-iodophenyl)-2,2-dimethylbutanenitrile (**7a**) afforded tetralone **9a** in a 69% yield (Table 4, entry 1).

**Scheme 8**




(a) $BH_3{\cdot}SMe_2$, THF, 0 °C to r.t.; (b) MsCl, $Et_3N$, $CH_2Cl_2$, 0 °C to r.t.; (c) NaI, acetone, reflux; (d) alkylation of corresponding alkanenitrile; (e) KCN, 18-crown-6, acetone, reflux; (f) aq KOH, reflux; then $H_3O^+$.

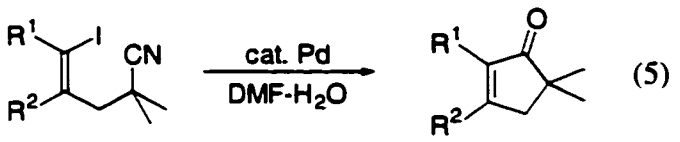
**Table 4. Synthesis of Tetralones and a Benzosuberone by the Pd-Catalyzed Cyclization of ω-(2-Iodophenyl)alkanenitriles (eq 2)[a]**

| entry | nitrile | time (h) | benzocyclic ketone (I) | % yield[b] | |
|---|---|---|---|---|---|
| | | | | I | II |
| 1 |  **7a** | 24 |  **9a** | 69 | 16 |
| 2 |  **7b** | 24 |  **9b** | 55[c] | 18 |
| 3 |  **7c** | 24 |  **9c** | 64 | 15 |
| 4 |  **8** | 36 |  **10** | 41 | 45 |

[a] See the Experimental Section for the reaction conditions. [b] All yields were determined by $^1H$ NMR spectral analysis unless specified otherwise. [c] Isolated yield.

Cyclization of other 4-(2-iodophenyl)butanenitriles was also reasonably successful (entries 2 and 3). Surprisingly, even 5-(2-iodophenyl)pentanenitrile (**8**) cyclized to produce a benzosuberone derivative **10** (entry 4). The efficacy of this six- and seven-membered ring formation is remarkable considering that the greater conformational flexibility present in these longer-chain substrates must significantly reduce the likelihood of achieving the conformation necessary for intramolecular addition of the arylpalladium species to the cyano group. This difficulty in achieving the favorable conformation is undoubtedly responsible for the increased reaction times compared to the five-membered ring cyclizations.

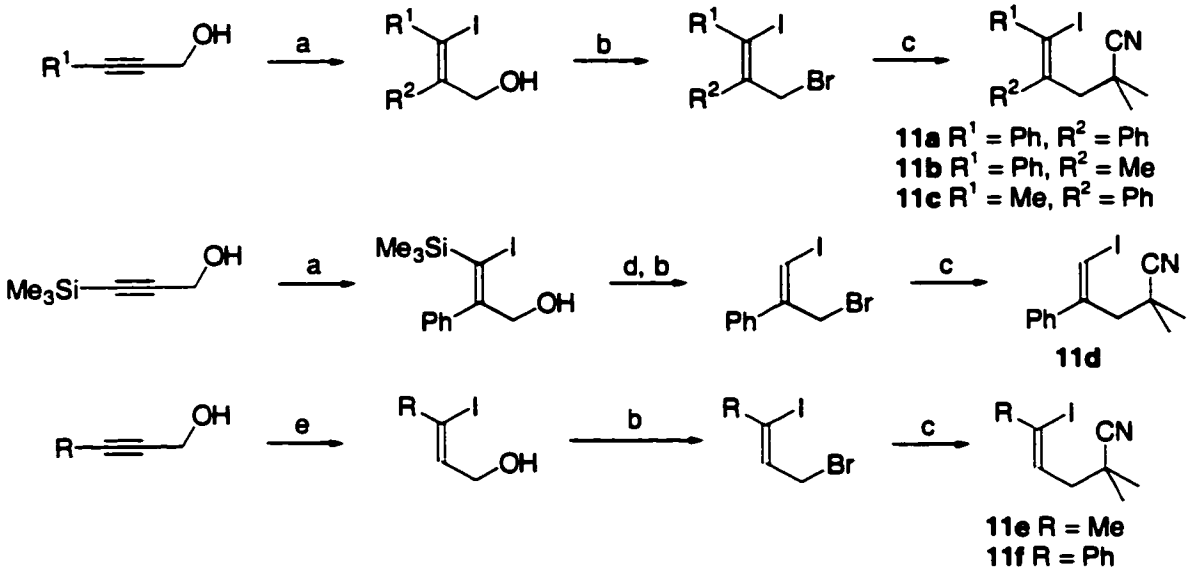
We have also extended the scope of this methodology to the synthesis of cyclopentenones (eq 5). Cyclopentenones are common carbon skeletal structures in many natural products, such as jasmonates, muscones, rethrolones, prostaglandins, etc.[25] They are also important in the pharmaceutical industry as many exhibit very useful biological activity, including antitumor, antiviral and antimicrobial properties.[26] Traditional routes to cyclopentenones include the Dieckmann condensation of 1,4-diketones,[27] the Nazarov cyclization,[25c,28] the Pauson-Khand reaction[29] and other variations of carbonylative cycloaddition processes.[26b,30] Many of these methods, however, suffer from the use of strongly acidic or basic conditions or sensitive organometallic reagents, often in stoichiometric amounts.



(5)

For our studies, we synthesized a variety of substituted 5-iodopent-4-enenitriles **11** as shown in Scheme 9. Copper-catalyzed addition of Grignard reagents to the appropriate propargylic alcohols, followed by quenching with iodine and conversion of the resulting allylic alcohols, provided allylic bromides that were used in the alkylation of isobutyronitrile to afford 4-substituted vinylic substrates **11a-d**. Compounds **11e** and **11f** were made via a similar route starting with reduction of the corresponding propargylic alcohols with Red-Al.

**Scheme 9**

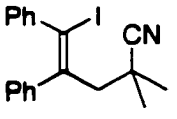
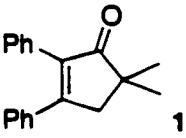
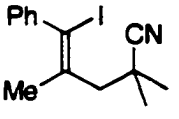
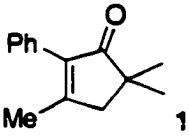
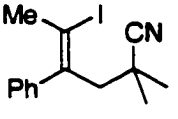
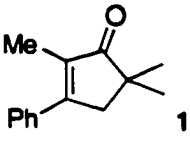
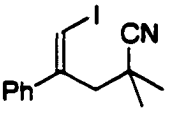
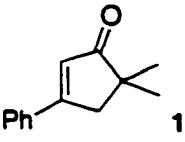
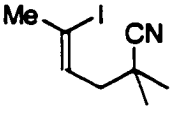
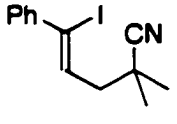
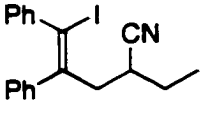
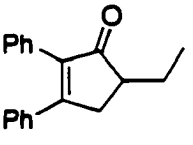



(a) PhMgBr or $CH_3MgBr$, cat. CuI, THF, 0 °C; then $I_2$, -78 °C to r.t.; (b) $CBr_4$, $PPh_3$, $CH_2Cl_2$, 0 °C; (c) alkylation of isobutyronitrile; (d) $CH_3ONa$, methanol, reflux; (e) Red-Al, THF, 0 °C; then $I_2$, -78 °C to r.t.

Cyclization of the 4,5-disubstituted 5-iodo-2,2-dimethylpent-4-enenitriles **11a-c** proved successful as highly substituted cyclopentenones **12a-c** were obtained in very good yields (Table 5, entries 1-3). In contrast with the benzocyclic ketone synthesis (eq 2), none of the reduction byproduct was detected in the reaction mixtures. 5,5-Dimethyl-3-phenyl-cyclopentenone (**12d**) was prepared from **11d** in a 67% yield (entry 4). Substrates **11e** and **11f** failed to give rise to their expected cyclization products (entries 5 and 6). The major product of the attempted cyclization of **11f** was identified from GC-MS analysis as 2,2-dimethyl-5-phenylpent-4-ynenitrile, which probably arose from **11f** by base-promoted dehydroiodination.[19b]

Since reduction of the carbon-iodine bond of the vinylic substrates **11** was not observed, we prepared the secondary nitrile **13** and subjected it to our standard cyclization conditions. The 5-monosubstituted cyclopentenone **14** was obtained in a 63% isolated yield (entry 7). Even though the reduction byproduct corresponding to **II** in eq 2 was formed in about 5% yield (as determined by analysis of the GC-MS data obtained from the reaction mixture), this problem does not appear to present any significant limitations for the synthesis of 5-monosubstituted cyclopentenones.

**Table 5. Synthesis of Cyclopentenones by the Pd-Catalyzed Cyclization of 5-Iodopent-4-enenitriles (eq 5)**[a]

| entry | nitrile | time (h) | cyclopentenone | % yield[b] |
|---|---|---|---|---|
| 1 |  **11a** | 12 |  **12a** | 94 |
| 2 |  **11b** | 12 |  **12b** | 72 |
| 3 |  **11c** | 12 |  **12c** | 82 |
| 4 |  **11d** | 12 |  **12d** | 67[c] |
| 5 |  **11e** | 12 | - | 0 |
| 6 |  **11f** | 12 | - | 0 |
| 7 |  **13** | 12 |  **14** | 63[d] |

[a] See the Experimental Section for the reaction conditions. [b] Isolated yield unless specified otherwise. [c] Yield determined by $^1$H NMR spectral analysis. [d] Accompanied by 5% of the reduced starting material.

## Conclusions

We have developed a general and efficient method for the synthesis of 2,2-disubstituted benzocyclic ketones from ω-(2-iodoaryl)alkanenitriles. The procedure affords indanones and

tetralones in good to excellent yields and is compatible with a wide variety of functional groups. The suitability of this methodology for the preparation of various cyclopentenones has also been demonstrated.

## Experimental Section

**General.** $^{1}H$ and $^{13}C$ NMR spectra were recorded at 300 and 75 MHz or 400 and 100 MHz, respectively. Thin-layer chromatography was performed using commercially prepared 60-mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm) 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. High resolution mass spectra were recorded on a Kratos MS50TC double focusing magnetic sector mass spectrometer using EI at 70 eV. IR spectra were measured on a Bomem Michelson MB-102 FT-IR spectrometer. All reagents were used directly as obtained commercially unless otherwise noted. $Pd(OAc)_2$ was donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. $PPh_3$ was also donated by Kawaken Fine Chemicals Co., Ltd.

**Reagents.** *o*-Iodobenzyl bromide was obtained from Lancaster Synthesis Ltd. Isobutyronitrile, cyclohexanecarbonitrile, cyclopropanecarbonitrile, cyclobutanecarbonitrile, butyronitrile, diphenylacetonitrile, 4,5-dimethoxybenzyl alcohol, *o*-iodobenzoic acid, 5-bromo-2-iodobenzoic acid, methyl *o*-iodobenzoate, 2,2'-diiodobiphenyl, *n*-butyllithium, diisopropylamine and triethylamine were obtained from Aldrich Chemical Co., Inc. (*Z*)-3-Bromo-1-iodo-1,2-diphenylpropene, (*Z*)-3-bromo-1-iodo-2-methyl-1-phenylpropene, (*Z*)-1-bromo-3-iodo-2-butene, (*Z*)-3-bromo-1-iodo-1-phenylpropene, (*Z*)-3-bromo-1-iodo-2-phenylpropene, (*Z*)-1-bromo-3-iodo-2-phenyl-2-butene,[31] as well as 2-iodophenethyl mesylate and 2-iodophenethyl iodide,[32] were prepared as previously described.

**Synthesis of ω-(2-Iodoaryl)alkanenitriles and related starting materials.**

**General procedure for the α-alkylation of aliphatic nitriles.** Compounds **1a-e**, **1g**, **1h**, **1o**, **1q**, **7a**, **7c**, **8**, **11a-f** and **13** were prepared by a procedure reported by Taber *et al.*[33] A hexane solution of 3.62 mmol of *n*-BuLi was added to a solution of 3.45 mmol of *i*-$Pr_2NH$ in 10 mL of THF at –78 °C under an Ar atmosphere. After 5 min, 3 mmol (9 mmol if not

tertiary) of the nitrile was added (dissolved in THF if the nitrile is a solid). The reaction mixture was stirred at –78 °C for 1 h, after which a solution of 3.6 mmol of *o*-iodobenzyl bromide in 4 mL of THF was added at once and the reaction mixture was stirred with warming to room temperature for about 1.5 h, then diluted with water and extracted with ether. The ethereal extracts were dried with $Na_2SO_4$, the solvent was evaporated, and the residue was separated by column chromatography on silica gel with a proper eluant. The following compounds were prepared using the above procedure:

**3-(2-Iodophenyl)-2,2-dimethylpropanenitrile (1a).** Obtained in a 94% yield from the alkylation of isobutyronitrile with *o*-iodobenzyl bromide after column chromatography using 10:1 hexanes/ethyl acetate: white solid, mp 59-61 °C (hexanes); $^1$H NMR ($CDCl_3$) δ 1.43 (s, 6H), 3.08 (s, 2H), 6.96 (td, *J* = 7.5, 1.2 Hz, 1H), 7.35 (td, *J* = 7.5, 1.2 Hz, 1H), 7.51 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.87 (dd, *J* = 7.5, 1.5 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 26.6, 34.3, 48.7, 102.6, 124.6, 128.4, 129.0, 130.7, 139.0, 139.9; IR (neat) 3072, 2995, 2928, 2232 cm$^{-1}$; HRMS *m/z* 285.00180 (calcd for $C_{11}H_{12}IN$, 285.00145).

**1-(2-Iodobenzyl)cyclohexanecarbonitrile (1b).** Obtained in a 96% yield from the alkylation of cyclohexanecarbonitrile with *o*-iodobenzyl bromide after column chromatography using 10:1 hexanes/ethyl acetate: white solid, mp 58-60 °C (hexanes); $^1$H NMR ($CDCl_3$) δ 1.19-1.22 (m, 1H), 1.45-1.76 (m, 7H), 1.92 (d, *J* = 11.4 Hz, 2H), 3.08 (s, 2H), 6.94 (td, *J* = 7.5, 1.5 Hz, 1H), 7.33 (td, *J* = 7.5, 1.5 Hz, 1H), 7.51 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.85 (dd, *J* =7.5, 1.5 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 16.3, 22.9, 25.1, 35.4, 41.0, 48.8, 102.8, 122.9, 128.3, 128.9, 130.9, 138.6, 139.8; IR (neat) 3062, 2935, 2860, 2228 cm$^{-1}$; HRMS *m/z* 325.03330 (calcd for $C_{14}H_{16}IN$, 325.03275).

**1-(2-Iodobenzyl)cyclobutanecarbonitrile (1c).** Obtained in a 74% yield from the alkylation of cyclobutanecarbonitrile with *o*-iodobenzyl bromide after column chromatography using 10:1 hexanes/ethyl acetate: white solid, mp 29-30 °C (hexanes/ethyl acetate); $^1$H NMR ($CDCl_3$) δ 2.07-2.20 (m, 2H), 2.25-2.32 (m, 2H), 2.47-2.54 (m, 2H), 3.23 (s, 2H), 6.96 (td, *J* = 7.6, 1.6 Hz, 1H), 7.31-7.35 (m, 1H), 7.38-7.41 (m, 1H), 7.86 (dd, *J* = 8.0, 1.6 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 17.1, 31.7, 36.4, 45.9, 102.1, 124.4, 128.4, 128.8, 129.7, 139.0, 139.8; IR (neat) 3059, 2991, 2946, 2229 cm$^{-1}$; HRMS *m/z* 297.00187 (calcd for $C_{12}H_{12}IN$, 297.00145).

**1-(2-Iodobenzyl)cyclopropanecarbonitrile (1d).** Obtained as a colorless oil in a 93% yield from the alkylation of cyclopropanecarbonitrile with *o*-iodobenzyl bromide after column chromatography using 10:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.00-1.03 (m, 2H), 1.29-1.32 (m, 2H), 3.01 (s, 2H), 6.96 (td, $J$ = 8.0, 1.6 Hz, 1H), 7.35 (td, $J$ = 7.6, 1.2 Hz, 1H), 7.45 (dd, $J$ = 7.6, 1.6 Hz, 1H), 7.84 (dd, $J$ = 8.0, 1.2 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 9.4, 13.6, 43.5, 101.2, 123.1, 128.5, 128.8, 129.5, 139.3, 139.6; IR (neat) 3062, 3010, 2928, 2232 cm$^{-1}$; HRMS *m/z* 282.98628 (calcd for $C_{11}H_{10}IN$, 292.98580).

**3-(2-Iodophenyl)-2-methyl-2-phenylpropanenitrile (1e).** Obtained as a colorless oil in a 78% yield from the alkylation of 2-phenylpropanenitrile with *o*-iodobenzyl bromide after column chromatography using 10:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.79 (s, 3H), 3.32-3.46 (m, 2H), 6.91-6.97 (m, 1H), 7.24-7.27 (m, 2H), 7.33-7.42 (m, 3H), 7.46-7.49 (m, 2H), 7.84 (dt, $J$ = 8.4, 0.6 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 25.5, 43.5, 50.7, 103.1, 123.1, 125.9, 128.0, 128.2, 128.9, 129.1, 130.8, 138.3, 139.7, 139.8; IR (neat) 3067, 3031, 2985, 2928, 2238 cm$^{-1}$; HRMS *m/z* 347.01747 (calcd for $C_{16}H_{14}IN$, 347.01710).

**2-(2-Iodobenzyl)butanenitrile (1g).** Obtained as a colorless oil in an 87% yield from the alkylation of butyronitrile with *o*-iodobenzyl bromide after column chromatography using 10:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.16 (t, $J$ = 7.5 Hz, 3H), 1.71-1.77 (m, 2H), 2.85-2.98 (m, 1H), 3.01 (d, $J$ = 0.9 Hz, 2H), 6.94-7.00 (m, 1H), 7.33 (dd, $J$ = 5.1, 0.9 Hz, 2H), 7.84 (d, $J$ = 7.8 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 11.5, 25.4, 33.9, 42.7, 100.2, 115.3, 121.1, 128.6, 129.1, 130.7, 139.7; IR (neat) 3062, 2969, 2933, 2876, 2238 cm$^{-1}$; HRMS *m/z* 285.00180 (calcd for $C_{11}H_{12}IN$, 285.00145).

**Methyl 2-cyano-3-(2-iodophenyl)-2-methylpropanoate (1h).** Obtained in a 40% yield from the alkylation of methyl 2-cyanopropanoate with *o*-iodobenzyl bromide after column chromatography using 4:1 hexanes/ethyl acetate: white solid, mp 37-39 °C (hexanes/ethyl acetate); $^1$H NMR ($CDCl_3$) δ 1.68 (s, 3H), 3.36-3.46 (m, 2H), 3.82 (s, 3H), 6.98 (td, $J$ = 8.0, 2.0 Hz, 1H), 7.34 (td, $J$ = 7.6, 1.6 Hz, 1H), 7.39 (dd, $J$ = 7.6, 1.6 Hz, 1H), 7.88 (dd, $J$ = 8.0, 1.2 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 22.9, 44.6, 45.9, 53.7, 102.2, 119.3, 128.5, 129.4, 130.2, 137.3, 140.0, 169.1; IR (neat) 3057, 3008, 2955, 2848, 2250, 1745 cm$^{-1}$; HRMS *m/z* 328.99176 (calcd for $C_{12}H_{12}INO_2$, 328.99128).

**3-(2-Iodo-4,5-dimethoxyphenyl)-2,2-dimethylpropanenitrile (1o).** Obtained in a 100% yield from the alkylation of isobutyronitrile with 2-iodo-4,5-dimethoxybenzyl bromide (prepared in two steps from 4,5-dimethoxybenzyl alcohol)[34] after column chromatography using 2:1 hexanes/ethyl acetate: white solid, mp 67-68 °C (hexanes/ethyl acetate); $^1$H NMR ($CDCl_3$) δ 1.43 (s, 6H), 3.00 (s, 2H), 3.87 (s, 3H), 3.90 (s, 3H), 7.10 (s, 1H), 7.24 (s, 1H); $^{13}$C NMR ($CDCl_3$) δ 26.3, 34.4, 48.5, 55.8, 55.9, 90.0, 112.8, 121.5, 124.9, 131.4, 148.4, 149.0; IR (neat) 2974, 2933, 2840, 2233 cm$^{-1}$; HRMS *m/z* 345.02315 (calcd for $C_{13}H_{16}INO_2$, 345.02258).

**3-(5-Bromo-2-iodophenyl)-2,2-dimethylpropanenitrile (1q).** Obtained in a 48% yield from the alkylation of isobutyronitrile with 5-bromo-2-iodobenzyl bromide (prepared in two steps from 5-bromo-2-iodobenzoic acid)[32,31b] after column chromatography using 4:1 hexanes/ethyl acetate: white solid, mp 61-63 °C (hexanes/ethyl acetate); $^1$H NMR ($CDCl_3$) δ 1.45 (s, 6H), 3.04 (s, 2H), 7.12 (dd, $J$ = 8.4, 2.4 Hz, 1H), 7.62 (d, $J$ = 2.4 Hz, 1H), 7.72 (d, $J$ = 8.4 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 26.6, 34.1, 48.5, 100.5, 122.7, 124.2, 132.2, 133.5, 141.1 (1 sp$^2$ carbon missing due to overlap); IR (neat) 3072, 2985, 2238 cm$^{-1}$; HRMS *m/z* 362.91250 (calcd for $C_{11}H_{11}INBr$, 362.91196).

**4-(2-Iodophenyl)-2,2-dimethylbutanenitrile (7a).** Obtained as a colorless oil in a 38% yield from the alkylation of isobutyronitrile with 2-iodophenethyl mesylate after column chromatography using 10:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.45 (s, 6H), 1.78 (m, 2H), 2.91 (m, 2H), 6.88-6.94 (m, 1H), 7.24-7.30 (m, 2H), 7.80 (dd, $J$ = 8.1, 1.2 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 26.5, 32.1, 36.8, 41.3, 100.1, 124.7, 128.1, 128.6, 129.5, 139.5, 143.3; IR (neat) 3057, 2985, 2933, 2866, 2233 cm$^{-1}$; HRMS *m/z* 299.01767 (calcd for $C_{12}H_{14}IN$, 299.01710).

**1-(2-Iodophenethyl)cyclohexanecarbonitrile (7c).** Obtained as a colorless oil in a 31% yield from the alkylation of cyclohexanecarbonitrile with *o*-iodophenethyl iodide after column chromatography using 10:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.17-1.39 (m, 2H), 1.60-1.79 (m, 8H), 2.05-2.10 (m, 2H), 2.90-2.95 (m, 2H), 6.87-6.93 (m, 1H), 7.22-7.29 (m, 2H), 7.80 (dd, $J$ = 7.8, 0.9 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 23.1, 25.4, 35.5, 36.0, 38.8, 40.8, 100.1, 123.3, 128.1, 128.6, 129.5, 139.5, 143.6; IR (neat) 3056, 2938, 2856, 2228 cm$^{-1}$; HRMS *m/z* 339.04893 (calcd for $C_{15}H_{18}IN$, 339.04840).

**5-(2-Iodophenyl)-2,2-dimethylpentanenitrile (8).** To a solution of 2-iodophenethyl mesylate (0.736 g, 2.26 mmol) in 5 mL of MeCN were added KCN (0.9 g, 13.85 mmol) and a catalytic amount of 18-crown-6. The reaction mixture was refluxed with stirring for 24 h, the amount of solvent was reduced on a rotary evaporator, and the mixture was diluted with water and extracted with $CH_2Cl_2$. The extracts were dried ($Na_2SO_4$), evaporated and chromatographed using 4:1 hexanes/ethyl acetate to afford a 70% yield of 3-(2-iodophenyl)propanenitrile, which was dissolved in 2 mL of MeOH and added to 1M aq KOH solution (15 mL). The mixture was refluxed overnight, cooled, acidified with aq HCl, and extracted with ether. Upon evaporation, 3-(2-iodophenyl)propanoic acid was obtained in a 100% yield. The acid was converted to 1-iodo-3-(2-iodophenyl)propane (85% yield),[32] and the latter was used for the alkylation of isobutyronitrile to afford **8** as a colorless oil in a 72% yield after column chromatography using 10:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.35 (s, 6H), 1.60-1.64 (m, 2H), 1.76-1.82 (m, 2H), 2.73-2.77 (m, 2H), 6.90 (td, $J$ = 7.6, 1.6 Hz, 1H), 7.20-7.26 (m, 1H), 7.27-7.31 (m, 1H), 7.82 (dd, $J$ = 8.0, 1.2 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 25.8, 26.5, 26.6, 32.2, 40.4, 100.4, 124.9, 127.8, 128.3, 129.2, 139.4, 143.9; IR (neat) 3057, 2985, 2939, 2233 cm$^{-1}$; HRMS *m/z* 313.03332 (calcd for $C_{13}H_{16}IN$, 313.03275).

***(E)*-5-Iodo-2,2-dimethyl-4,5-diphenyl-4-pentenenitrile (11a).** Obtained in a 61% yield from the alkylation of isobutyronitrile with (*E*)-3-bromo-1-iodo-1,2-diphenylpropene after column chromatography using 10:1 hexanes/ethyl acetate: light yellow solid, mp 90-92 °C; $^1$H NMR ($CDCl_3$) δ 1.36 (s, 6H), 3.24 (s, 2H), 7.03-7.11 (m, 10H); $^{13}$C NMR ($CDCl_3$) δ 27.3, 32.4, 53.6, 105.2, 123.8, 127.3, 127.4, 127.6, 128.1, 129.4, 129.6, 138.2, 144.1, 144.4; IR (neat) 3060, 2976, 2933, 2234 cm$^{-1}$; HRMS *m/z* 387.04910 (calcd for $C_{19}H_{18}IN$, 387.04840).

***(Z)*-5-Iodo-2,2,4-trimethyl-5-phenyl-4-pentenenitrile (11b).** Obtained as a colorless oil in a 17% yield from the alkylation of isobutyronitrile with (*Z*)-3-bromo-1-iodo-2-methyl-1-phenylpropene after column chromatography using 10:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.55 (s, 6H), 1.91 (s, 3H), 2.83 (s, 2H), 7.19-7.26 (m, 3H), 7.31-7.37 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ 19.9, 27.2, 31.8, 53.2, 100.9, 125.5, 127.8, 128.2, 128.4, 138.9, 144.7; IR (neat) 3063, 2982, 2925, 2232, 1444 cm$^{-1}$; HRMS *m/z* 325.03330 (calcd for $C_{14}H_{16}IN$, 325.03275).

***(E)*-5-Iodo-2,2-dimethyl-4-phenyl-4-hexenenitrile (11c).** Obtained as a colorless oil in a 21% yield from the alkylation of isobutyronitrile with (*Z*)-1-bromo-3-iodo-2-phenyl-2-butene after column chromatography using 10:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.30 (s, 6H), 2.50 (t, $J$ = 0.8 Hz, 3H), 3.01 (q, $J$ = 0.8 Hz, 2H), 7.19-7.22 (m, 2H), 7.32-7.37 (m, 3H); $^{13}$C NMR ($CDCl_3$) δ 27.2, 32.1, 32.4, 53.9, 103.8, 123.9, 127.9, 128.5, 128.7, 137.8, 141.5; IR (neat) 3057, 2980, 2918, 2233, 1439 cm$^{-1}$; HRMS *m/z* 325.03330 (calcd for $C_{14}H_{16}IN$, 325.03275).

***(E)*-5-Iodo-2,2-dimethyl-4-phenyl-4-pentenenitrile (11d).** Obtained as a yellow oil in a 36% yield from the alkylation of isobutyronitrile with (*Z*)-3-bromo-1-iodo-2-phenylpropene after column chromatography using 10:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.32 (s, 6H), 3.05 (s, 2H), 6.64 (s, 1H), 7.32-7.36 (m, 5H); $^{13}$C NMR ($CDCl_3$) δ 27.2, 32.3, 46.3, 84.4, 124.1, 126.9, 128.6, 128.7, 140.6, 147.9; IR (neat) 3057, 2980, 2928, 2232, 1444 cm$^{-1}$; HRMS *m/z* 311.01772 (calcd for $C_{13}H_{14}IN$, 311.01710).

***(Z)*-5-Iodo-2,2-dimethyl-4-hexenenitrile (11e).** Obtained as a light yellow oil in a 66% yield from the alkylation of isobutyronitrile with (*Z*)-1-bromo-3-iodo-2-butene after column chromatography using 10:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.37 (s, 6H), 2.37-2.39 (m, 2H), 2.58 (dd, $J$ = 2.4, 1.2 Hz, 3H), 5.55-5.60 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ 26.3, 32.1, 33.9, 47.4, 105.4, 124.6, 129.5; IR (neat) 2980, 2918, 2238, 1650, 1264 cm$^{-1}$; HRMS *m/z* 249.00175 (calcd for $C_8H_{12}IN$, 249.00145).

***(Z)*-5-Iodo-2,2-dimethyl-5-phenyl-4-pentenenitrile (11f).** Obtained as a yellow oil in a 36% yield from the alkylation of isobutyronitrile with (*Z*)-3-bromo-1-iodo-1-phenylpropene after column chromatography using 10:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.45 (s, 6H), 2.61 (d, $J$ = 6.8 Hz, 2H), 6.02 (t, $J$ = 6.8 Hz, 1H), 7.29-7.33 (m, 3H), 7.45-7.48 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ 26.5, 32.4, 48.4, 109.4, 124.6, 128.3, 128.6, 128.7, 132.6, 142.7; IR (neat) 3062, 2980, 2933, 2233, 1444 cm$^{-1}$; HRMS *m/z* 311.01772 (calcd for $C_{13}H_{14}IN$, 311.01710).

***(E)*-2-Ethyl-5-iodo-4,5-diphenyl-4-pentenenitrile (13).** Obtained as a yellow oil in a 74% yield from the alkylation of butyronitrile with (*E*)-3-bromo-1-iodo-1,2-diphenylpropene after column chromatography using 10:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.07 (t, $J$

= 7.2 Hz, 3H), 1.69 (quintet, $J$ = 7.2 Hz, 2H), 2.48-2.56 (m, $J$ = 7.2 Hz, 1H), 3.05-3.10 (m, 1H), 3.26-3.31 (m, 1H), 6.98-7.14 (m, 10H); $^{13}$C NMR ($CDCl_3$) δ 11.6, 24.9, 31.5, 46.3, 103.5, 120.9, 127.31, 127.33, 127.6, 128.2, 128.9, 129.5, 137.9, 144.0, 144.2; IR (neat) 3052, 3021, 2969, 2933, 2238, 1440 cm$^{-1}$; HRMS *m/z* 387.04880 (calcd for $C_{19}H_{18}IN$, 387.04840).

**3-(2-Iodophenyl)-2,2-diphenylpropanenitrile (1f)** was prepared according to the procedure of Parham.[35] A solution of diphenylacetonitrile (0.97 g, 5.0 mmol) in 2 mL of DMF was added to a mixture of NaH (0.144 g, 6.0 mmol), 2 mL of DMF and 1 mL of benzene at 0 °C. The reaction mixture was stirred at 0 °C for 30 min, then a solution of *o*-iodobenzyl bromide (1.78 g, 6.0 mmol) in 1 mL of DMF was added. The resulting mixture was allowed to warm up to room temperature, poured into water and extracted with $CH_2Cl_2$, dried over $Na_2SO_4$, evaporated, and recrystallized from ethyl acetate to afford 1.96 g (96%) of the desired compound **1f**: white solid, mp 122-123 °C; $^1$H NMR ($CDCl_3$) δ 3.89 (s, 2H), 6.91 (td, $J$ = 5.7, 1.2 Hz, 1H), 6.98 (dd, $J$ = 5.7, 1.2 Hz, 1H), 7.15 (td, $J$ = 5.7, 1.2 Hz, 1H), 7.32-7.37 (m, 10H), 7.80 (dd, $J$ = 5.7, 1.2 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 48.4, 52.0, 103.3, 121.8, 127.6, 127.8, 128.1, 128.7, 129.0, 130.8, 137.6, 139.5, 139.7; IR (neat) 3067, 3046, 3031, 2964, 2938, 2238 cm$^{-1}$; HRMS *m/z* 409.03323 (calcd for $C_{21}H_{16}IN$, 409.03275).

**3-(2-Iodo-4,5-dimethoxyphenyl)-2,2-diphenylpropanenitrile (1p)** was prepared according to the procedure for **1f** from diphenylacetonitrile and 2-iodo-4,5-dimethoxybenzyl bromide (prepared in two steps from 4,5-dimethoxybenzyl alcohol)[34,31b] in an 81% yield after recrystallization from ethyl acetate: white solid, mp 155-156 °C; $^1$H NMR ($CDCl_3$) δ 3.47 (s, 3H), 3.81 (s, 3H), 3.84 (s, 2H), 6.24 (s, 1H), 7.19 (s, 1H), 7.31-7.40 (m, 10H); $^{13}$C NMR ($CDCl_3$) δ 28.0, 52.2, 55.3, 55.9, 91.0, 113.1, 121.4, 121.6, 127.6, 128.0, 128.7, 129.6, 139.6 (2 $sp^2$ carbons missing due to overlap); IR (neat) 3093, 3062, 3005, 2943, 2912, 2840, 2248 cm$^{-1}$; HRMS *m/z* 469.05450 (calcd for $C_{23}H_{20}INO_2$, 469.05388).

**4-(2-Iodophenyl)-2,2-diphenylbutanenitrile (7b)** was prepared in a 90% yield according to the procedure for **1f** from diphenylacetonitrile and 2-iodophenethyl iodide: white solid, mp 98-99 °C (hexanes/ethyl acetate); $^1$H NMR ($CDCl_3$) δ 2.57-2.63 (m, 2H), 2.79-2.85 (m, 2H), 6.80-6.88 (m, 1H), 7.15-7.37 (m, 8H), 7.42-7.46 (m, 4H), 7.73-7.76 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ 37.0, 39.9, 51.4, 99.9, 122.0, 126.8, 126.9, 127.9, 128.2, 128.5,

128.8, 128.9, 129.7, 129.9, 132.3, 139.5, 139.6, 143.3; IR (neat) 3062, 3036, 2964, 2933, 2238 $cm^{-1}$; HRMS *m/z* 423.04889 (calcd for $C_{22}H_{18}IN$, 423.04840).

**2-Cyano-3-(2-iodophenyl)-2-methylpropanenitrile (1i)** was prepared according to a procedure by Diez-Barra.[36] A neat mixture of malononitrile (0.66 g, 10.0 mmol), MeI (0.31 mL, 5.0 mmol), and *n*-$Bu_4NBr$ (0.064 g, 0.2 mmol) was stirred for 30 min at room temperature and cooled to 0 °C. Upon addition of dry $K_2CO_3$ (0.69 g, 5.0 mmol), the reaction mixture was stirred at 0 °C for 15 min, extracted with $CH_2Cl_2$, and the organic layer was dried with $Na_2SO_4$. 2-Methylpropanedinitrile (0.22 g, 2.75 mmol, 55%) was isolated after column chromatography using $CH_2Cl_2$. The nitrile (0.22 g, 2.75 mmol) was mixed with *o*-iodobenzyl bromide (0.90 g, 3.03 mmol), *n*-$Bu_4NBr$ (0.035 g, 0.11 mmol) and benzene (0.5 mL), stirred for 30 min at room temperature, dry $K_2CO_3$ (0.42 g, 3.03 mmol) was added, and stirring was continued for 5 h. The reaction mixture was extracted with $CH_2Cl_2$, the extract was dried ($Na_2SO_4$), the solvent was evaporated and the mixture was separated by column chromatography using 2:1 hexanes/ethyl acetate to afford 0.506 g (34%) of **1i**: white solid, mp 51-52 °C (hexanes/ethyl acetate); $^1H$ NMR ($CDCl_3$) δ 1.89 (s, 3H), 3.50 (s, 2H), 7.07 (td, *J* = 7.6, 1.6 Hz, 1H), 7.41 (td, *J* = 7.2, 1.2 Hz, 1H), 7.54 (dd, *J* = 7.2, 1.6 Hz, 1H), 7.93 (dd, *J* = 8.0, 1.2 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 24.4, 32.6, 46.7, 102.3, 115.7, 128.9, 130.4, 130.6, 135.2, 140.4; IR (neat) 3062, 3005, 2938, 2248 $cm^{-1}$; HRMS *m/z* 295.98160 (calcd for $C_{11}H_9IN_2$, 295.98105).

**3-(2-Iodo-4-nitrophenyl)-2,2-dimethylpropanenitrile (1r)** and **3-(2-iodo-5-nitrophenyl)-2,2-dimethylpropanenitrile (1s).** To a solution of **1a** (0.88 g, 3.09 mmol) in 3 ml of acetic anhydride at 0 °C was added 1.5 ml of white fuming nitric acid. The reaction mixture was allowed to warm up to room temperature and stirred overnight, poured into ice-water, and extracted with ether. The combined ethereal extracts were washed successively with aq $NaHCO_3$ and water, and dried over $Na_2SO_4$. The solvent was removed and the residue chromatographed using 4:1 hexanes/ethyl acetate to afford 0.415 g (41%, $R_f$ = 0.40) of **1r** and 0.165 g (16%, $R_f$ = 0.26) of **1s**. Nitrile **1r**: light yellow solid, mp 115-117 °C (4:1 hexanes/ethyl acetate); $^1H$ NMR ($CDCl_3$) δ 1.50 (s, 6H), 3.19 (s, 2H), 7.83 (dd, *J* = 8.7, 2.7 Hz, 1H), 8.11 (d, *J* = 8.7 Hz, 1H), 8.30 (d, *J* = 2.7 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 26.8, 34.1, 48.8, 110.6, 123.3, 123.7, 124.8, 141.1, 148.1 (1 $sp^2$ carbon missing due to overlap); IR

(neat) 3068, 2984, 2934, 2226, 1524, 1343 $cm^{-1}$; HRMS *m/z* 329.98693 (calcd for $C_{11}H_{11}IN_2O_2$, 329.98653). Nitrile **1s**: light yellow solid, mp 59-60 °C (4:1 hexanes/ethyl acetate); $^1H$ NMR ($CDCl_3$) δ 1.49 (s, 6H), 3.27 (s, 2H), 7.48-7.55 (m, 2H), 7.71-7.75 (m, 1H); $^{13}C$ NMR ($CDCl_3$) δ 26.7, 34.4, 49.3, 93.8, 123.3, 124.1, 129.1, 133.0, 142.7 (1 $sp^2$ carbon missing due to overlap); IR (neat) 3072, 2983, 2235, 1528, 1350 $cm^{-1}$; HRMS *m/z* 329.98693 (calcd for $C_{11}H_{11}IN_2O_2$, 329.98653).

**3-(4-Cyano-2-iodophenyl)-2,2-dimethylpropanenitrile (1t).** A solution of $SnCl_2$ (1.05 g, 5.5 mmol) in 5 mL of a 5:4:1 DME-EtOH-AcOH solvent mixture was added dropwise, with stirring, to a solution of **1r** (0.23 g, 0.7 mmol) in 3 mL of the same solvent mixture under Ar at room temperature. The reaction mixture was stirred at room temperature for 5 min, and then heated at 60 °C until the starting material was consumed (about 1.5 h). The reaction mixture was then poured into aq $NaHCO_3$ and extracted with ether. The extracts were dried ($Na_2SO_4$), evaporated, and chromatographed using 1:1 hexanes/ethyl acetate to afford 0.21 g (100%) of 3-(4-amino-2-iodophenyl)-2,2-dimethylpropanenitrile, which was immediately converted to **1t** according to a procedure by Rapaport.[37] A solution of $NaNO_2$ (0.046 g, 0.67 mmol) in 0.3 mL of water was added, with stirring, to a cold (0 °C) solution of 3-(4-amino-2-iodophenyl)-2,2-dimethylpropanenitrile (0.2 g, 0.67 mmol) in 2 ml of concentrated HCl and 1 mL of ice-water. The mixture was stirred at 0 °C for 30 min, and the cold solution of the resulting diazonium salt was neutralized by addition of solid $Na_2CO_3$ and added slowly, with stirring, to a suspension of CuCN (0.064 g, 0.71 mmol) and NaCN (0.069 g, 1.41 mmol) in 0.5 mL of $H_2O$ at 0 °C. The reaction mixture was stirred for 1 h at room temperature, the precipitate was dissolved in $CH_2Cl_2$, the aqueous layer was discarded, and the organic layer was washed with water, dried over $Na_2SO_4$ and evaporated to afford 0.108 g (52%) of **1t**: yellow solid, mp 135-136 °C (hexanes/ethyl acetate); $^1H$ NMR ($CDCl_3$) δ 1.47 (s, 6H), 3.12 (s, 2H), 7.23-7.28 (m, 1H), 7.32 (d, $J$ = 1.8 Hz, 1H), 8.04 (d, $J$ = 7.5 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 26.6, 34.0, 48.5, 108.6, 112.6, 117.7, 123.8, 131.6, 133.2, 140.8, 141.0; IR (neat) 3055, 2985, 2924, 2228 $cm^{-1}$; HRMS *m/z* 309.99725 (calcd for $C_{12}H_{11}IN_2$, 309.99670).

**3-(2-Iodophenyl)-2,2-dimethyl-3-trimethylsilyloxypropanenitrile (1j)** was prepared according to the procedure of Silverman.[38] To a solution of the lithium salt of

isobutyronitrile prepared from 0.77 mL (8.5 mmol) of the nitrile according to the procedure of Taber *et al.*[33] in 10 mL of THF at –78 °C under Ar was added a solution of *o*-iodobenzaldehyde (2.0 g, 8.62 mmol) in 3 mL of THF. The reaction mixture was stirred for 45 min at –78 °C, then $Me_3SiCl$ (1.72 mL, 13.6 mmol) was added, followed by MeOH (2 mL) 10 min later. The reaction mixture was allowed to warm up to room temperature, the solvent was evaporated, the residue was taken up into ethyl acetate, washed with water, and dried over $Na_2SO_4$. The solvent was removed and the residue was chromatographed using 10:1 hexanes/ethyl acetate to afford a 69% yield of **1j**: white solid, mp 65-66 °C; $^1$H NMR ($CDCl_3$) δ 0.02 (s, 9H), 1.26 (s, 3H), 1.52 (s, 3H), 4.83 (s, 1H), 7.00-7.04 (td, $J$ = 7.6, 1.2 Hz, 1H), 7.38-7.42 (td, $J$ = 7.6, 1.2 Hz, 1H), 7.74-7.76 (dd, $J$ = 8.0, 1.6 Hz, 1H), 7.80-7.83 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ -0.0, 22.8, 25.2, 41.1, 81.2, 99.9, 123.5, 128.5, 129.5, 130.1, 139.2, 142.1; IR (neat) 3067, 2949, 2235 cm$^{-1}$; HRMS *m/z* 373.03653 (calcd for $C_{14}H_{20}INOSi$, 373.03589).

**3-Hydroxy-3-(2-iodophenyl)-2,2-dimethylpropanenitrile (1k).** Compound **1j** (1.84 g, 4.93 mmol) was dissolved in 40 mL of THF containing 6 mL of a 1M solution of *n*-$Bu_4NF$. The reaction mixture was stirred for 5 h at room temperature, concentrated, diluted with brine, and extracted with $CH_2Cl_2$. The organic extracts were washed with brine, dried ($Na_2SO_4$), evaporated, and the residue was chromatographed with 4:1 hexanes/ethyl acetate to afford 1.37 g (93 %) of **1k** as a very viscous bright yellow oil: $^1$H NMR ($CDCl_3$) δ 1.27 (s, 3H), 1.61 (s, 3H), 2.60 (d, $J$ = 4.0 Hz, 1H), 4.94 (d, $J$ = 4.0 Hz, 1H), 7.03-7.07 (m, 1H), 7.44 (td, $J$ = 8.0, 1.6 Hz, 1H), 7.79 (dd, $J$ = 8.0, 1.6 Hz, 1H), 7.85 (dd, $J$ = 8.0, 1.2 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 23.0, 25.3, 40.3, 100.2, 123.2, 128.4, 128.9, 130.5, 139.6, 141.6; IR (neat) 3448, 3067, 2986, 2940, 2242 cm$^{-1}$; HRMS *m/z* 300.99726 (calcd for $C_{11}H_{12}INO$, 300.99637).

**3-(2-Iodophenyl)-3-methoxy-2,2-dimethylpropanenitrile (1l).** Compound **1k** was methylated according to a procedure by Melder.[39] To a stirred suspension of NaH (0.025 g, 1.05 mmol) in 2 mL of THF at 0 °C under Ar was added a solution of **1k** (0.301 g, 1.0 mmol) in 3 mL of THF. After stirring for 45 min at room temperature, MeI (0.125 mL, 2.0 mmol) was added and stirring was continued overnight at room temperature. The reaction mixture was then quenched with satd aq $NH_4Cl$, diluted with water and extracted with ether. The

extracts were dried ($Na_2SO_4$), evaporated, and the residue was chromatographed using 4:1 hexanes/ethyl acetate to afford 0.262 g (83%) of **1l**: colorless oil; $^1$H NMR ($CDCl_3$) δ 1.25 (s, 3H), 1.59 (s, 3H), 3.22 (s, 3H), 4.47 (s, 1H), 7.04-7.10 (m, 1H), 7.42-7.48 (m, 1H), 7.67-7.70 (dd, $J$ = 7.8, 1.8 Hz, 1H), 7.85-7.88 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ 23.0, 25.4, 39.5, 57.1, 89.0, 101.7, 123.1, 128.5, 128.8, 130.4, 138.9, 139.5; IR (neat) 3061, 2986, 2938, 2821, 2234 cm$^{-1}$; HRMS *m/z* 315.01242 (calcd for $C_{12}H_{14}INO$, 315.01202).

**3-Acetoxy-3-(2-iodophenyl)-2,2-dimethylpropanenitrile (1m)** was prepared according to a published procedure.[40] Compound **1k** (0.452 g, 1.5 mmol), DMAP (0.046 g, 0.375 mmol) and $Ac_2O$ (0.21 mL, 2.25 mmol) were dissolved in 0.3 mL of $Et_3N$, and the reaction mixture was stirred overnight at room temperature. Methanol was added to remove excess acetic anhydride, then the mixture was concentrated on a rotary evaporator, the residue was dissolved in ether, washed with water, dilute aq HCl, dilute aq $NaHCO_3$, and brine, and dried over $Na_2SO_4$. The solvent was evaporated and the residue was recrystallized from 4:1 hexanes/ethyl acetate to afford 0.398 g (77%) of **1m**: beige solid, mp 127-128 °C; $^1$H NMR ($CDCl_3$) δ 1.34 (s, 3H), 1.58 (s, 3H), 2.14 (s, 3H), 5.93 (s, 1H), 7.03-7.09 (m, 1H), 7.39-7.45 (m, 1H), 7.68 (dd, $J$ = 7.8, 1.5 Hz, 1H), 7.86 (dd, $J$ =7.8, 1.2 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 20.8, 23.3, 25.4, 38.9, 81.0, 100.7, 122.3, 128.2, 128.8, 130.6, 138.6, 139.7, 169.3; IR (neat) 3071, 2999, 2989, 2236, 1745 cm$^{-1}$; HRMS *m/z* 343.00693 (calcd for $C_{13}H_{14}INO_2$, 343.00736).

**3-(2-Iodophenyl)-2,2-dimethyl-3-oxopropanenitrile (1n)** was prepared according to the general procedure for the alkylation of aliphatic nitriles using isobutyronitrile (0.18 mL, 2.0 mmol) and methyl *o*-iodobenzoate (0.55 g, 2.1 mmol) instead of *o*-iodobenzyl bromide. The residue was chromatographed using 4:1 hexanes/ethyl acetate to afford 0.431 g (72 %) of **1n** as a yellow oil: $^1$H NMR ($CDCl_3$) δ 1.73 (s, 6H), 7.16-7.22 (m, 1H), 7.41-7.49 (m, 2H), 7.92 (dd, $J$ = 7.2, 0.9 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 24.9, 43.7, 90.9, 121.2, 126.4, 127.7, 131.6, 139.8, 143.1, 199.6; IR (neat) 3060, 2938, 2238, 1714 cm$^{-1}$; HRMS *m/z* 298.98164 (calcd for $C_{11}H_{10}INO$, 298.98072).

**3-(4-{3-Bromopyridyl})-3-hydroxy-2,2-dimethylpropanenitrile (3)** was prepared according to the general procedure for the alkylation of aliphatic nitriles using isobutyronitrile (0.181 mL, 2.0 mmol) and 3-bromopyridine-4-carbaldehyde (0.378 g, 2.03

mmol) instead of *o*-iodobenzyl bromide. The residue was chromatographed using 2:1 hexanes/ethyl acetate to afford 0.203 g (40%) of **3**: white solid, mp 125-127 °C; $^1$H NMR ($CDCl_3$) δ 1.27 (s, 3H), 1.59 (s, 3H), 4.73 (br s, 1H), 5.03 (s, 1H), 7.76 (d, $J$ = 4.8 Hz, 1H), 8.45 (d, $J$ = 4.8 Hz, 1H), 8.56 (s, 1H); $^{13}$C NMR ($CDCl_3$) δ 22.6, 24.8, 39.8, 74.5, 121.9, 122.6, 124.1, 148.2, 148.4, 151.4; IR (neat) 3407, 3087, 2938, 2238 cm$^{-1}$; HRMS *m/z* 254.00592 (calcd for $C_{10}H_{11}BrN_2O$, 254.00547).

**2-Cyano-2'-iodobiphenyl (4)** was prepared by modifying the procedure of Grinham.[41] A mixture of 2,2'-diiodobiphenyl (0.406 g, 1 mmol), CuCN (0.09 g, 1 mmol) and pyridine (2 mL) was heated at 150 °C for 6 h, cooled to room temperature, dissolved in benzene and washed with a 1:1 $NH_4OH$ (aq., 30%)/water mixture. The benzene extract was dried ($Na_2SO_4$), evaporated, and chromatographed using 4:1 hexanes/ethyl acetate to afford 0.092 g (30 %) of the target biaryl **4** as a white solid: mp 71-72 °C (lit.[41] mp 73-74 °C), along with unreacted starting material (25%) and 2,2'-dicyanobiphenyl (29%); $^1$H NMR ($CDCl_3$) δ 7.13 (td, $J$ = 7.8, 1.5 Hz, 1H), 7.30-7.53 (m, 4H), 7.63-7.70 (m, 1H), 7.74-7.77 (m, 1H), 7.97 (dd, $J$ = 8.1, 1.5 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 98.3, 112.8, 117.6, 128.2, 128.3, 129.8, 130.2, 130.6, 132.3, 132.7, 139.4, 143.0, 143.7; IR (neat) 3059, 2225 cm$^{-1}$.

**General Procedure for the Pd-Catalyzed Cyclization of ω-(2-Iodoaryl)-alkanenitriles.** All reactions were performed under an Ar atmosphere. 0.25 Mmol of the ω-(2-iodoaryl)alkanenitrile, 0.025 mmol (10 mol %) of $Pd(OAc)_2$, and 0.05 mmol (20 mol %) of $Ph_3P$ were dissolved in 4.5 mL of DMF and 0.5 mL of water, and 0.3 mmol (1.2 equiv) of $Et_3N$ were added to the solution. The reaction mixture was stirred at 130 °C for the appropriate amount of time. Then, the reaction mixture was allowed to cool to room temperature and poured into 25 mL of diethyl ether. The ether solution was washed with aq $NH_4Cl$ and dried over $Na_2SO_4$. The identity of all known products was established by GC-mass spectrometry and $^1$H NMR spectroscopy of the reaction mixtures. The yields of known products were determined by $^1$H NMR spectroscopy by integration of the appropriate outstanding signals using 1,4-dimethoxybenzene as an internal standard. New products were isolated by column chromatography on a silica gel column. The following known compounds were prepared using the above procedure: 2,2-dimethyl-1-indanone (**2a**),[42] spiro[cyclohexane-1,2'-indan]-1'-one (**2b**),[43] 2-methyl-2-phenyl-1-indanone (**2e**),[44] 2,2-

diphenyl-1-indanone (**2f**),[45] 2-ethyl-1-indanone (**2g**),[46] 3-hydroxy-2,2-dimethyl-1-indanone (**2k**),[47] 3-methoxy-2,2-dimethyl-1-indanone (**2l**),[48] 2,2-dimethyl-1,3-indandione (**2n**),[49] 2,2-dimethyl-6-nitro-1-indanone (**2r**),[50] 9-fluorenone (**5**),[51] 2,2-dimethyl-1-tetralone (**9a**),[52] 3',4'-dihydrospiro[cyclohexane-1,2'(1'H)-naphthalen]-1'-one (**9c**),[53] 6,6-dimethyl-6,7,8,9-tetrahydrobenzocyclohepten-5-one (**10**),[54] 3,5,5-trimethyl-2-phenylcyclopent-2-en-1-one (**12b**),[55] and 5,5-dimethyl-3-phenylcyclopent-2-en-1-one (**12d**).[56]

**Spiro[cyclobutane-1,2'-indan]-1'-one (2c)** was obtained as a colorless oil in an 83% isolated yield from **1c** according to the general procedure after column chromatography using 10:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 2.00-2.20 (m, 4H), 2.47-2.54 (m, 2H), 3.30 (s, 2H), 7.33-7.43 (m, 2H), 7.57 (td, $J$ = 7.5, 1.2 Hz, 1H), 7.76 (dd, $J$ = 7.5, 1.6 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 16.1, 31.6, 42.2, 50.7, 124.0, 126.2, 127.3, 134.6, 135.9, 152.3, 209.3; IR (neat) 3077, 2933, 2845, 1702, 1604 cm$^{-1}$; HRMS *m/z* 172.08900 (calcd for $C_{12}H_{12}O$, 172.08882).

**Methyl 2-methyl-1-indanone-2-carboxylate (2h)**, a known compound, was obtained as a white solid, mp 57-58 (lit.[57] mp 57-58 °C), in a 73% isolated yield from **1h** according to the general procedure after column chromatography using 4:1 hexanes/ethyl acetate. The 78% yield determined by $^1$H NMR spectroscopy was obtained straight from the reaction mixture. The spectral properties were identical to those previously reported.[57]

**2-Cyano-2-methyl-1-indanone (2i)** was obtained as a light yellow oil in an 89% isolated yield from **1i** according to the general procedure after column chromatography using 4:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.67 (s, 3H), 3.24 (d, $J$ = 13.2 Hz, 1H), 3.76 (d, $J$ = 13.2 Hz, 1H), 7.47-7.52 (m, 2H), 7.70-7.74 (m, 1H), 7.83-7.86 (m, 1H); $^{13}$C NMR ($CDCl_3$) δ 23.7, 40.5, 43.2, 120.6, 125.9, 126.9, 129.0, 133.0, 136.7, 150.5, 198.5; IR (neat) 3058, 2982, 2934, 2241, 1724 cm$^{-1}$; HRMS *m/z* 171.06867 (calcd for $C_{11}H_9NO$, 171.06841).

**3-Acetoxy-2,2-dimethyl-1-indanone (2m)** was obtained as a colorless oil in an 80% isolated yield from **1m** according to the general procedure (reaction time 40 h) after column chromatography using 4:1 hexanes/ethyl acetate: $^1$H NMR ($CDCl_3$) δ 1.14 (s, 3H), 1.33 (s, 3H), 2.18 (s, 3H), 6.09 (s, 1H), 7.53 (td, $J$ = 7.6, 0.4 Hz, 1H), 7.59 (dd, $J$ = 7.6, 0.4 Hz, 1H), 7.69 (td, $J$ = 7.6, 1.2 Hz, 1H), 7.79 (d, $J$ = 7.6 Hz, 1H); $^{13}$C NMR ($CDCl_3$) δ 19.6, 20.8, 24.0,

49.7, 78.5, 123.9, 126.6, 129.9, 135.0, 135.3, 149.3, 170.9, 207.5; IR (neat) 3078, 2969, 2933, 2872, 1728, 1604 $cm^{-1}$; HRMS *m/z* 218.09456 (calcd for $C_{13}H_{14}O_3$, 218.09429).

**5,6-Dimethoxy-2,2-dimethyl-1-indanone (2o)** was obtained in a 75% isolated yield from **1o** according to the general procedure after column chromatography using 2:1 hexanes/ethyl acetate: white solid, mp 97-98 °C; $^1H$ NMR ($CDCl_3$) δ 1.23 (s, 6H), 2.92 (s, 2H), 3.92 (s, 3H), 3.97 (s, 3H), 6.85 (s, 1H), 7.19 (s, 1H); $^{13}C$ NMR ($CDCl_3$) δ 25.4, 42.6, 45.7, 56.0, 56.1, 104.8, 107.4, 127.8, 147.3, 149.4, 155.5, 210.1; IR (neat) 3066, 2984, 2867, 2832, 1684 $cm^{-1}$; HRMS *m/z* 220.11016 (calcd for $C_{13}H_{16}O_3$, 220.10994).

**5,6-Dimethoxy-2,2-diphenyl-1-indanone (2p)** was obtained in an 84% isolated yield from **1p** according to the general procedure after recrystallization from ethyl acetate: off-white solid, mp 172-174 °C; $^1H$ NMR ($CDCl_3$) δ 3.83 (s, 2H), 3.91 (s, 3H), 4.00 (s, 3H), 6.94 (s, 1H), 7.18-7.32 (m, 11H); $^{13}C$ NMR ($CDCl_3$) δ 44.8, 56.1, 56.3, 62.9, 105.3, 106.7, 126.6, 128.0, 128.1, 128.2, 128.3, 143.7, 147.3, 149.7, 155.9, 203.9; IR (neat) 3080, 3066, 2984, 2834, 1699 $cm^{-1}$; HRMS *m/z* 344.14185 (calcd for $C_{23}H_{20}O_3$, 344.14124).

**5-Bromo-2,2-dimethyl-1-indanone (2q)** was obtained as a colorless oil in a 64% isolated yield from **1q** according to the general procedure after column chromatography using 4:1 hexanes/ethyl acetate: $^1H$ NMR ($CDCl_3$) δ 1.24 (s, 6H), 2.99 (s, 2H), 7.50-7.53 (m, 1H), 7.61-7.63 (m, 2H); $^{13}C$ NMR ($CDCl_3$) δ 25.2, 42.5, 45.7, 125.7, 129.9, 130.1, 131.1, 134.2, 153.8, 210.0; IR (neat) 3063, 2965, 2927, 2867, 1716, 1591 $cm^{-1}$; HRMS *m/z* 237.99971 (calcd for $C_{11}H_{11}BrO$, 237.99933).

**6-Cyano-2,2-dimethyl-1-indanone (2t)** was obtained in a 43% yield from **1t** according to the general procedure. This product could not be separated from the reduced starting material by column chromatography; its yield was determined by $^1H$ NMR spectroscopy performed on the crude compound by integrating the methylene signal at 3.06 ppm (2H) and the dimethyl signal at 1.26 ppm (6H).

**2,2-Diphenyl-1-tetralone (9b)** was obtained in a 55% isolated yield from **7b** according to the general procedure after column chromatography using 10:1 hexanes/ethyl acetate: white solid, mp 99-101 °C (hexanes/ethyl acetate); $^1H$ NMR ($CDCl_3$) δ 2.85-2.95 (m, 4H), 7.12-7.15 (m, 5H), 7.22-7.33 (m, 7H), 7.40-7.46 (m, 1H), 8.19 (dd, $J$ = 7.8, 1.5 Hz, 1H); $^{13}C$ NMR ($CDCl_3$) δ 26.4, 35.1, 59.9, 126.7, 126.9, 128.1, 128.4, 128.6, 133.0, 133.2, 142.0,

143.3, 198.8 (1 $sp^2$ carbon missing due to overlap); IR (neat) 3061, 3026, 2934, 1685 $cm^{-1}$; HRMS *m/z* 298.13629 (calcd for $C_{22}H_{18}O$, 298.13577).

**5,5-Dimethyl-2,3-diphenylcyclopent-2-en-1-one (12a)** was obtained as a yellow oil in a 94% isolated yield from **11a** according to the general procedure after column chromatography using 4:1 hexanes/ethyl acetate: $^1H$ NMR ($CDCl_3$) δ 1.29 (s, 6H), 2.93 (s, 2H), 7.21-7.34 (m, 10H); $^{13}C$ NMR ($CDCl_3$) δ 25.5, 43.4, 46.6, 127.7, 128.1, 128.3, 129.5, 129.7, 132.5, 135.7, 137.0, 164.5, 211.7 (1 $sp^2$ carbon missing due to overlap); IR (neat) 3055, 3023, 2961, 2926, 1694 $cm^{-1}$; HRMS *m/z* 262.13617 (calcd for $C_{19}H_{18}O$, 262.13577).

**3,5,5-Trimethyl-2-phenylcyclopent-2-en-1-one (12b)**, a known compound, was obtained as a light yellow oil in a 72% isolated yield from **11b** according to the general procedure after column chromatography using 10:1 hexanes/ethyl acetate: $^{13}C$ NMR ($CDCl_3$) δ 18.2, 25.2, 43.3, 48.9, 127.4, 128.1, 129.1, 132.1, 137.4, 168.2, 211.6; HRMS *m/z* 200.12051 (calcd for $C_{14}H_{16}O$, 200.12012). Other spectral properties were identical to those previously reported.[55]

**2,5,5-Trimethyl-3-phenylcyclopent-2-en-1-one (12c)** was obtained as a colorless oil in an 82% isolated yield from **11c** according to the general procedure after column chromatography using 10:1 hexanes/ethyl acetate: $^1H$ NMR ($CDCl_3$) δ 1.20 (s, 6H), 1.99 (t, *J* = 2.0 Hz, 3H), 2.79 (q, *J* = 2.0 Hz, 2H), 7.40-7.48 (m, 3H), 7.52-7.55 (m, 2H); $^{13}C$ NMR ($CDCl_3$) δ 10.3, 25.4, 42.6, 46.3, 127.6, 128.5, 129.4, 133.6, 136.3, 163.1, 214.0; IR (neat) 3057, 2959, 2923, 2866, 1697 $cm^{-1}$; HRMS *m/z* 200.12051 (calcd for $C_{14}H_{16}O$, 200.12012).

**5-Ethyl-2,3-diphenylcyclopent-2-en-1-one (14)** was obtained as an amber oil in a 63% isolated yield from **13** according to the general procedure after column chromatography using 10:1 hexanes/ethyl acetate: $^1H$ NMR ($CDCl_3$) δ 1.06 (t, *J* = 7.2 Hz, 3H), 1.52-1.65 (m, 1H), 1.95-2.05 (m, 1H), 2.60-2.65 (m, 1H), 2.72 (dd, *J* = 18.0, 2.8 Hz, 1H), 3.22 (dd, *J* = 18.0, 6.8 Hz, 1H), 7.19-7.32 (m, 10H); $^{13}C$ NMR ($CDCl_3$) δ 11.5, 24.9, 36.1, 46.9, 127.7, 128.1, 128.4, 129.4, 129.5, 129.7, 132.4, 135.7, 139.2, 166.5, 209.4; IR (neat) 3088, 3052, 2959, 2933, 1697, 1346 $cm^{-1}$; HRMS *m/z* 262.13617 (calcd for $C_{19}H_{18}O$, 262.13577).

**2-Cyano-3,4-dihydronapthalene (6)** was obtained in a 58% isolated yield from **1d** according to the general procedure after column chromatography using 4:1 hexanes/ethyl acetate. The 64% yield determined by $^1H$ NMR spectroscopy was obtained straight from the

reaction mixture. Compound **6**: white solid, mp 58-59 °C (lit.[58] 58-59 °C); $^1$H NMR ($CDCl_3$) δ 2.51 (td, $J$ = 8.0, 1.6 Hz, 2H), 2.88 (t, $J$ = 8.0 Hz, 2H), 7.11-7.20 (m, 3H), 7.22-7.29 (m, 2H); $^{13}$C NMR ($CDCl_3$) δ 24.7, 26.7, 109.7, 119.7, 127.1, 127.9, 128.0, 130.2, 131.2, 135.4, 141.7; IR (neat) 3067, 3019, 2944, 2894, 2206, 1622, 1452 cm$^{-1}$; HRMS *m/z* 155.073718 (calcd for $C_{11}H_9N$, 155.07350).

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# GENERAL CONCLUSION

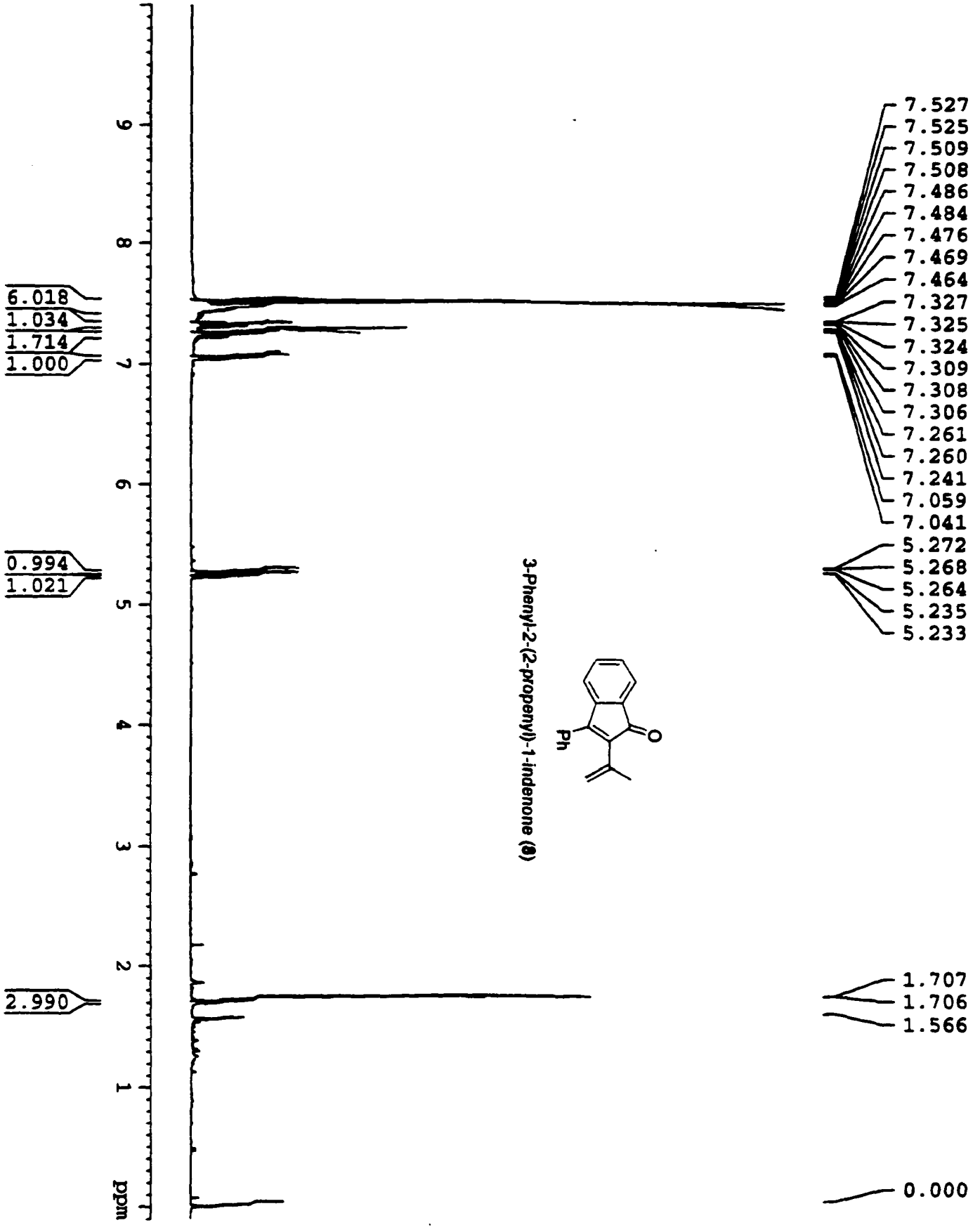
The cyano group has long been considered unreactive towards organopalladium reagents. We have investigated the intramolecular carbopalladation of nitriles and have found that not only can it proceed with high efficiency, but also can be developed into useful synthetic methodology for the construction of carbocyclic molecules.

2,3-Diarylindenones and polycyclic aromatic ketones are synthesized in very good yields by a convenient procedure for the palladium-catalyzed annulation of internal alkynes and bicyclic olefins by 2-iodobenzonitrile. This reaction tolerates a variety of functional groups and can be extended to substituted 2-iodoarenenitriles and related heterocyclic compounds. Mechanistically, the annulation proceeds via a nucleophilic intramolecular addition of the vinyl- or alkylpalladium species across the carbon-nitrogen triple bond of the neighboring cyano group.

The palladium-catalyzed annulation of alkynes with (2-iodophenyl)acetonitrile results in the synthesis of 3,4-disubstituted 2-aminonaphthalenes in good yields. In many cases, the regioselectivity of this reaction is excellent. The scope and limitations of this process, which proceeds via a mechanism similar to the reaction between 2-iodoarenenitriles and alkynes, have been studied. Annulation of hindered propargylic alcohols has been found to afford 1,3-benzoxazine derivatives. The involvement of trialkylamine bases in the formation of these heterocyclic compounds has been established and a mechanism for this transformation has been proposed.

The nitrile carbopalladation has also been employed in developing useful methodology for the synthesis of 2,2-disubstituted indanones by the palladium-catalyzed cyclization of 3-(2-iodoaryl)propanenitriles. A variety of indanones have been prepared in high yields from readily available starting materials containing various functional groups that are compatible with the reaction conditions. The reaction is not limited to the synthesis of indanones as other benzocyclic ketones, as well as a number of substituted cyclopentenones, have been synthesized by this methodology.

# APPENDIX A. CHAPTER 1 $^{1}H$ AND $^{13}C$ NMR SPECTRA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7.308
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7.260
7.241
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7.041
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5.268
5.264
5.235
5.233
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1.706
1.566
0.000
6.018
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0.994
1.021
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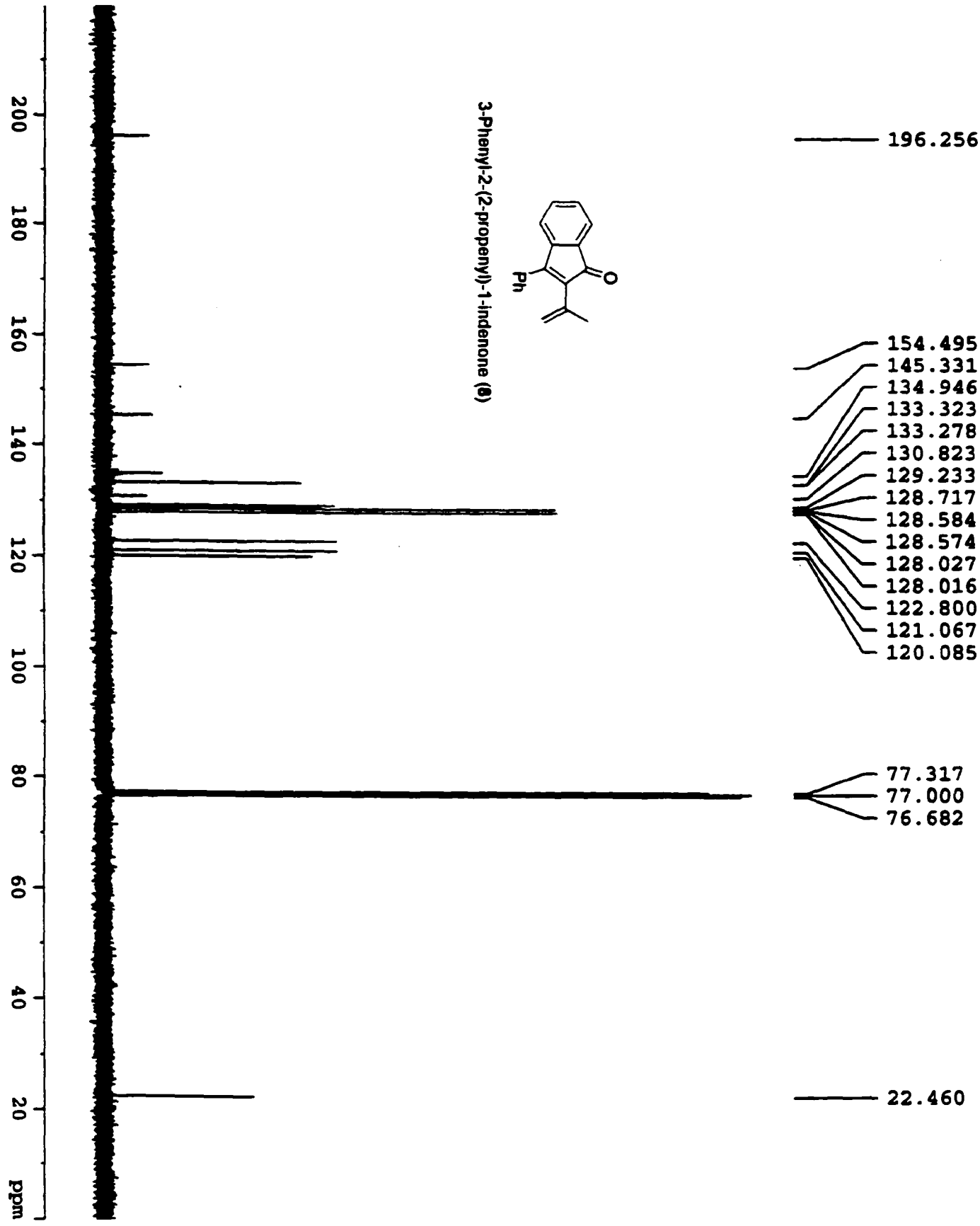
Ph
O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40
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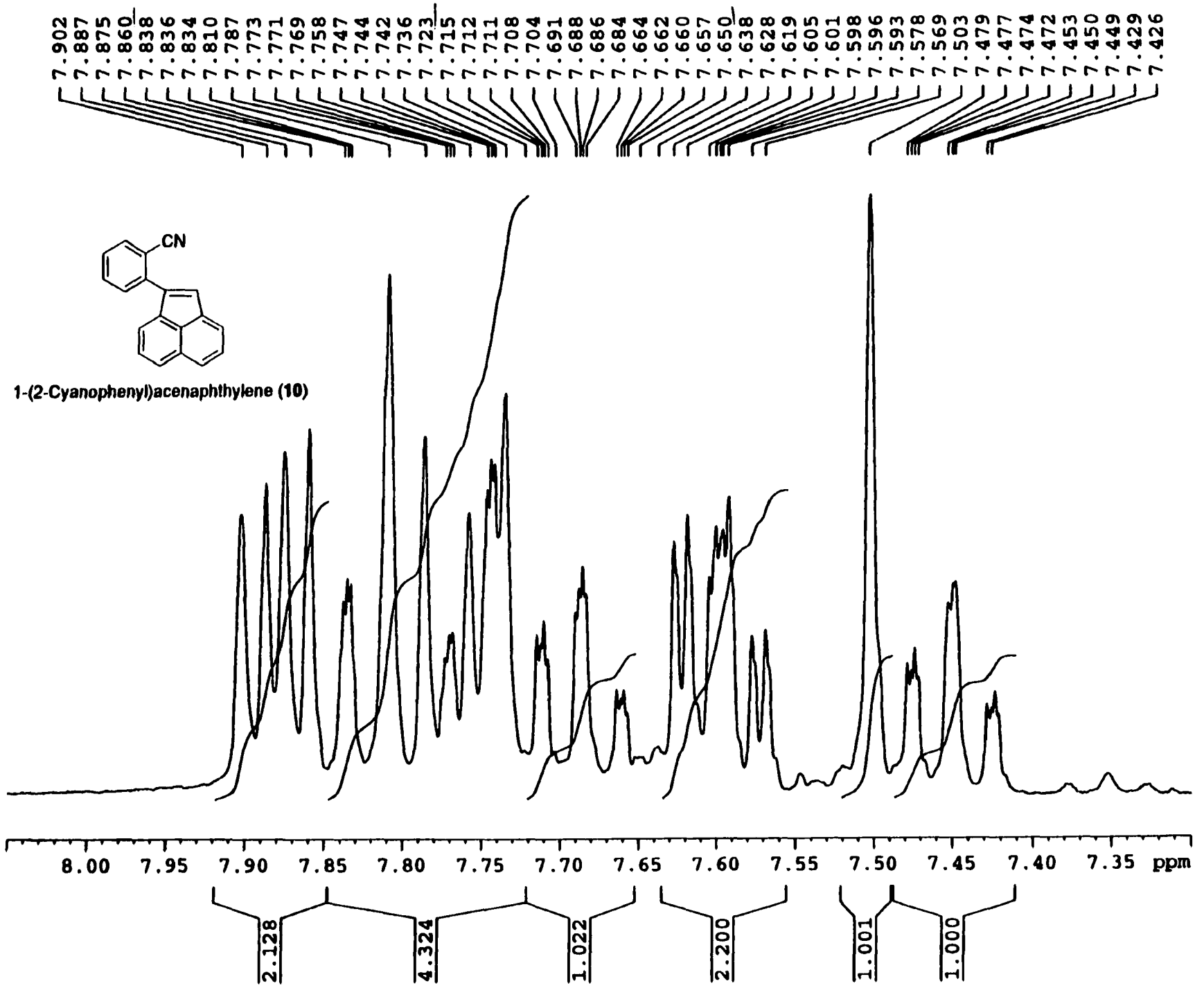
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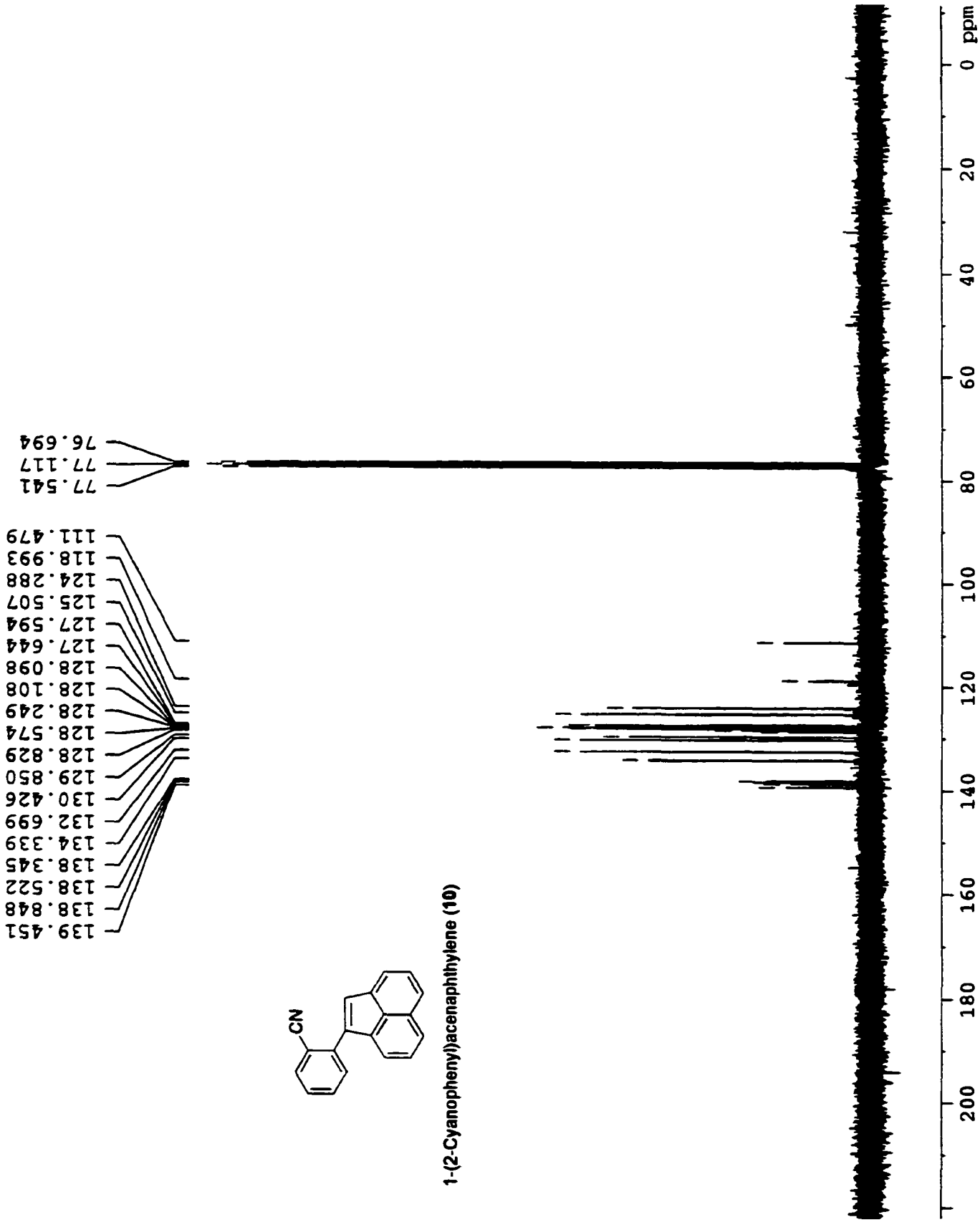
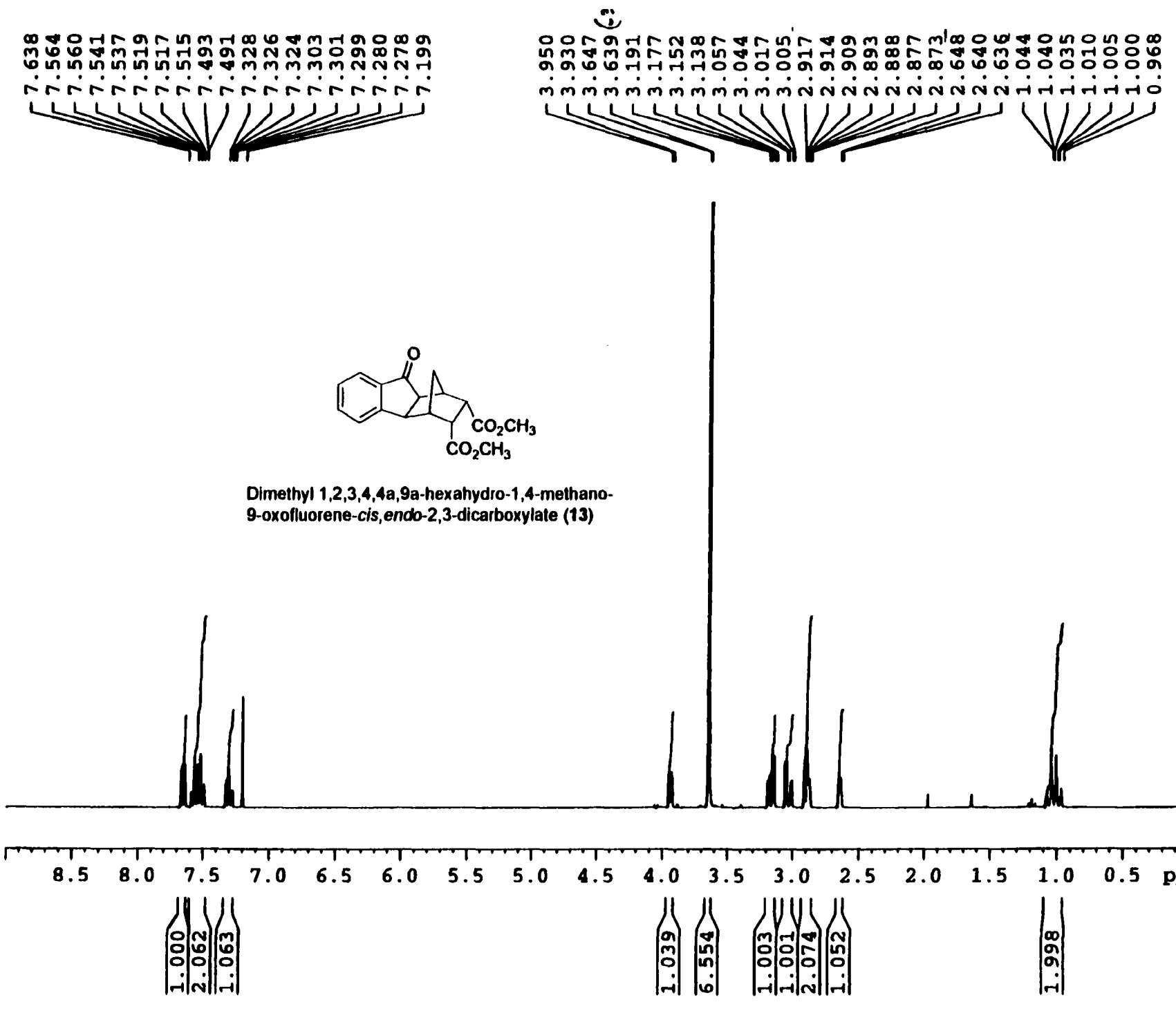
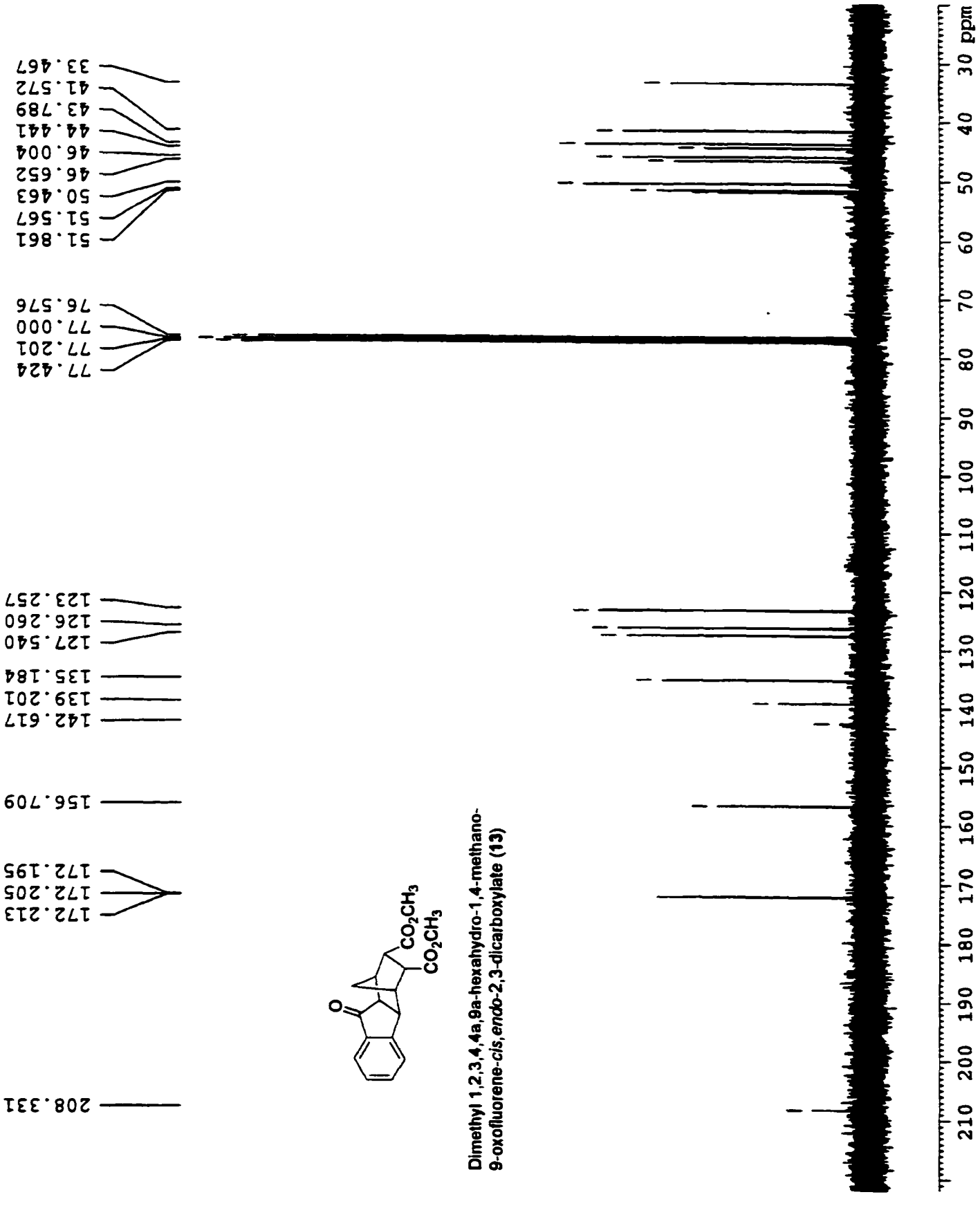
1.001
1.000

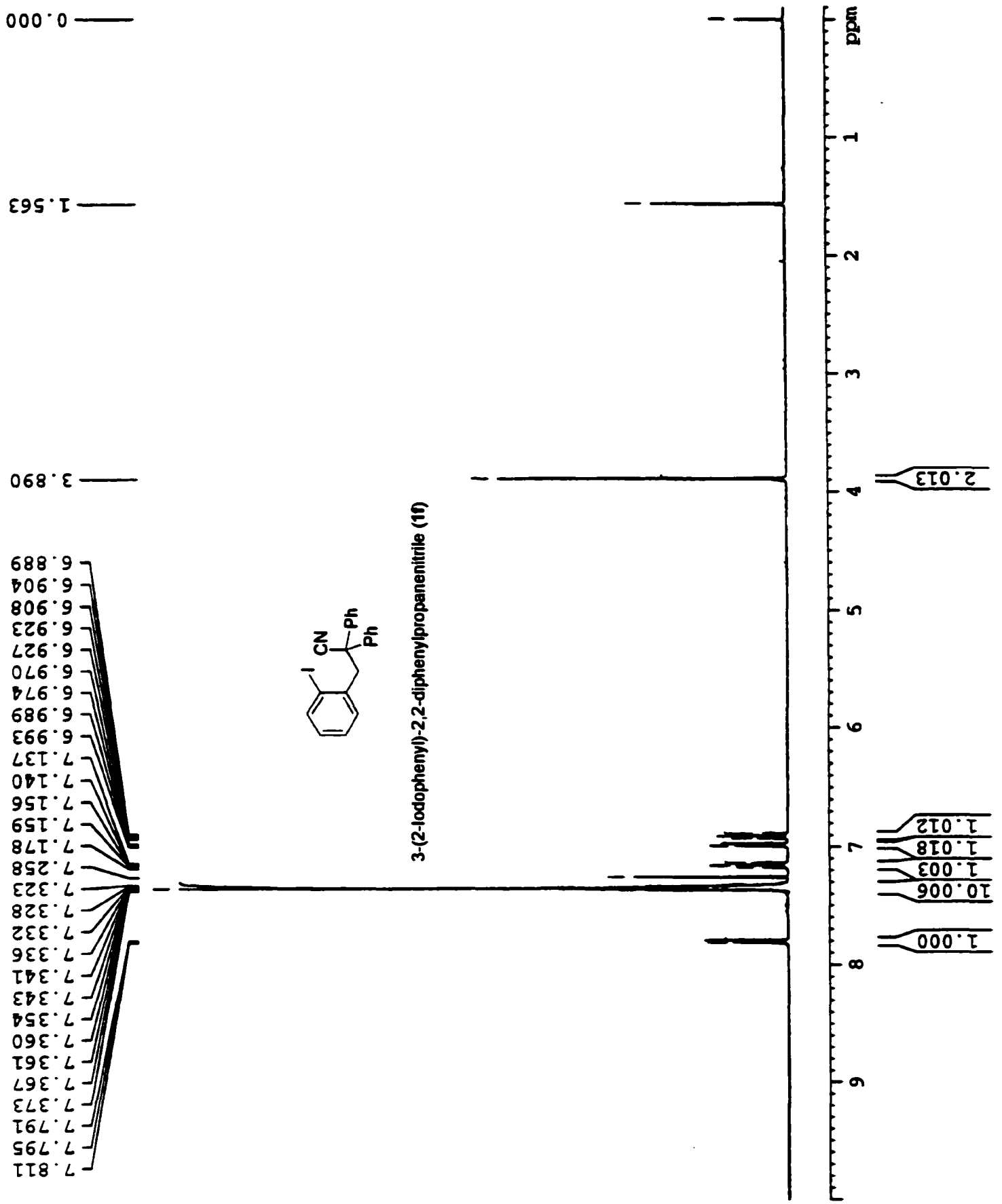

77.541
77.117
76.694
111.479
118.993
124.288
125.507
127.594
127.644
128.098
128.108
128.249
128.574
128.829
129.850
130.426
132.699
134.339
138.345
138.522
138.848
139.451
CN
1-(2-Cyanophenyl)acenaphthylene (10)
200
180
160
140
120
100
80
60
40
20
0 ppm



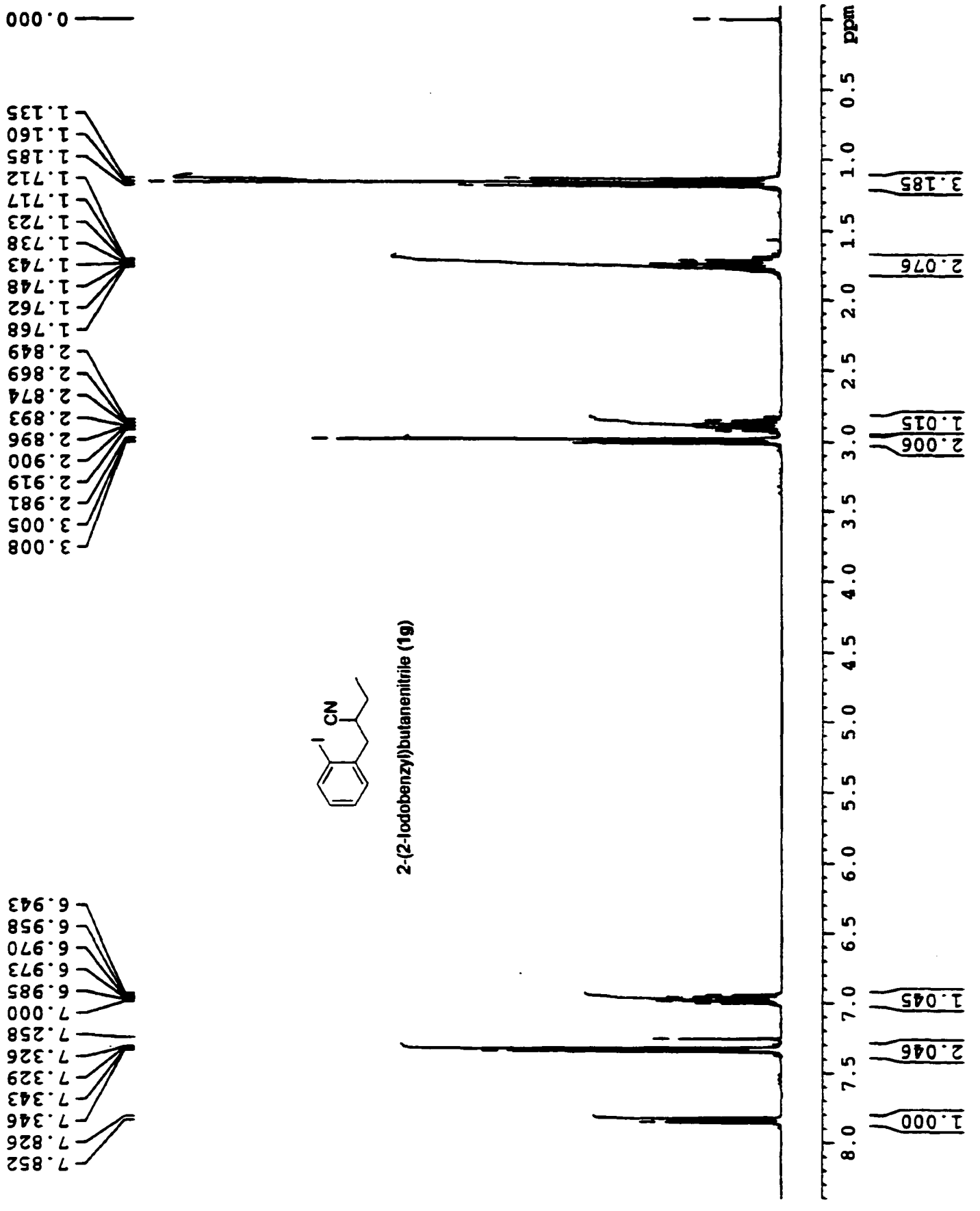

Dimethyl 1,2,3,4,4a,9a-hexahydro-1,4-methano-9-oxofluorene-*cis*,*endo*-2,3-dicarboxylate (**13**)



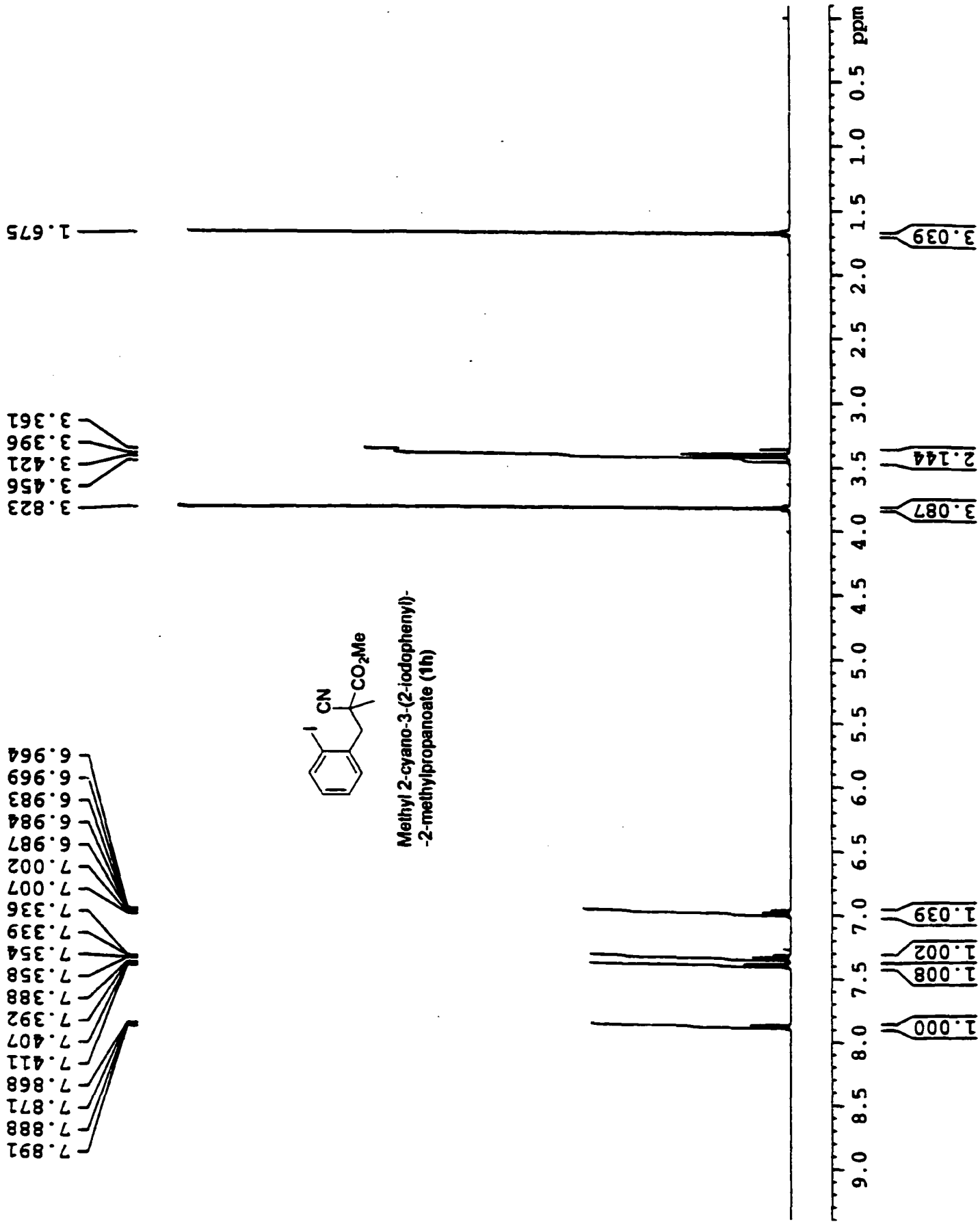

Dimethyl 1,2,3,4,4a,9a-hexahydro-1,4-methano-9-oxofluorene-*cis*,*endo*-2,3-dicarboxylate (13)


3-(2-Iodophenyl)-2,2-diphenylpropanenitrile (1f)
I
CN
Ph
Ph
ppm
0.000
1.563
3.890
6.889
6.904
6.908
6.923
6.927
6.970
6.974
6.989
6.993
7.137
7.140
7.156
7.159
7.178
7.258
7.323
7.328
7.332
7.336
7.341
7.343
7.354
7.360
7.361
7.367
7.373
7.791
7.795
7.811
2.013
1.012
1.018
1.003
10.006
1.000

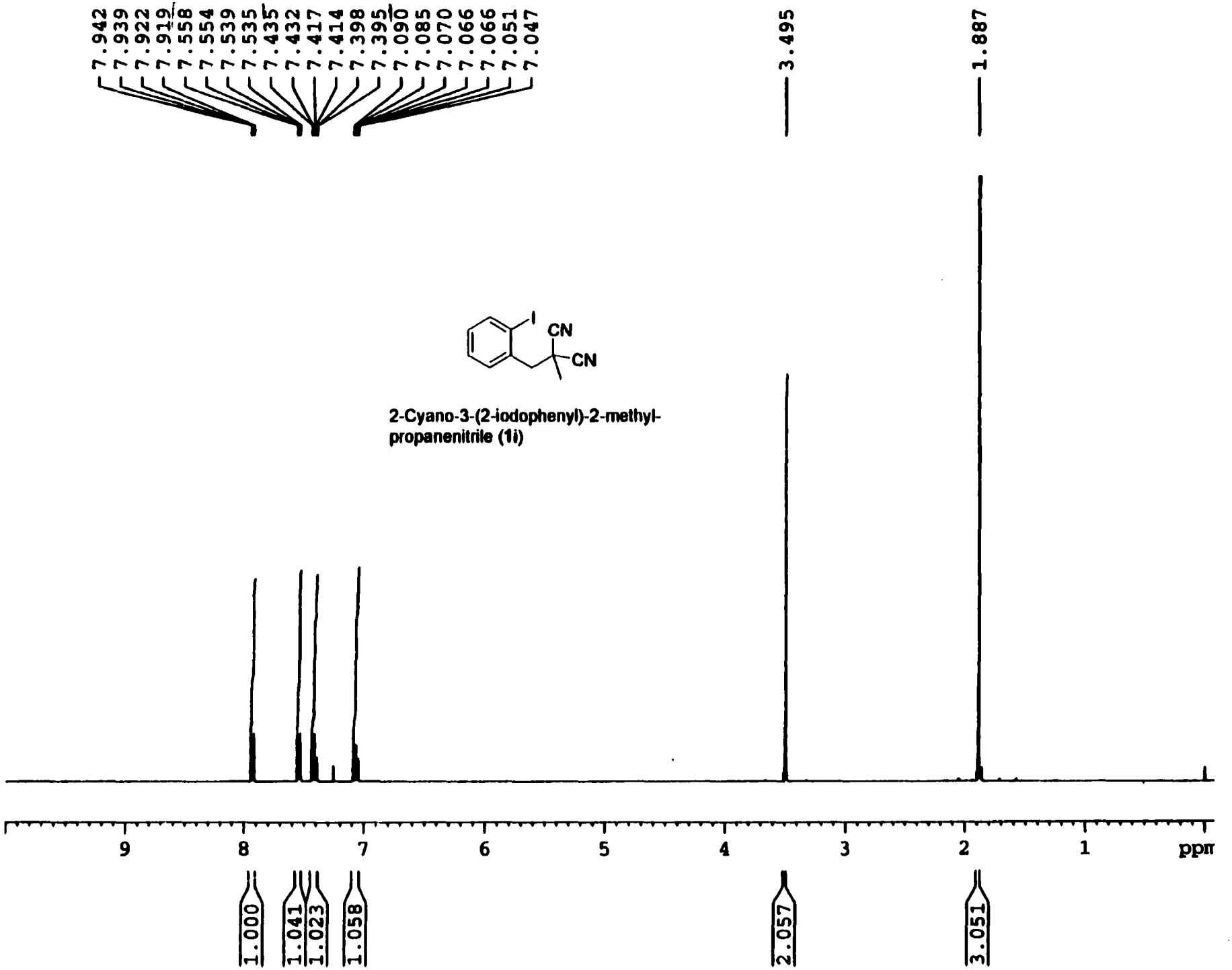
3-(2-Iodophenyl)-2,2-diphenylpropanenitrile (1f)
CN
Ph
Ph
I
139.753
139.452
137.562
130.754
128.949
128.745
128.093
127.796
127.646
121.831
103.298
77.318
77.001
76.683
51.996
48.411
200
180
160
140
120
100
80
60
40
20
ppm


2-(2-Iodobenzyl)butanenitrile (1g)
CN
I
ppm
0.000
1.135
1.160
1.185
1.712
1.717
1.723
1.738
1.743
1.748
1.762
1.768
2.849
2.869
2.874
2.893
2.896
2.900
2.919
2.981
3.005
3.008
6.943
6.958
6.970
6.973
6.985
7.000
7.258
7.326
7.329
7.343
7.346
7.826
7.852
3.185
2.076
1.015
2.006
1.045
2.046
1.000

2-(2-Iodobenzyl)butanenitrile (1g)
CN
I
139.672
130.655
129.062
128.614
121.136
115.249
100.241
77.316
77.000
76.682
42.745
33.918
33.908
25.418
11.541
200
180
160
140
120
100
80
60
40
20
ppm

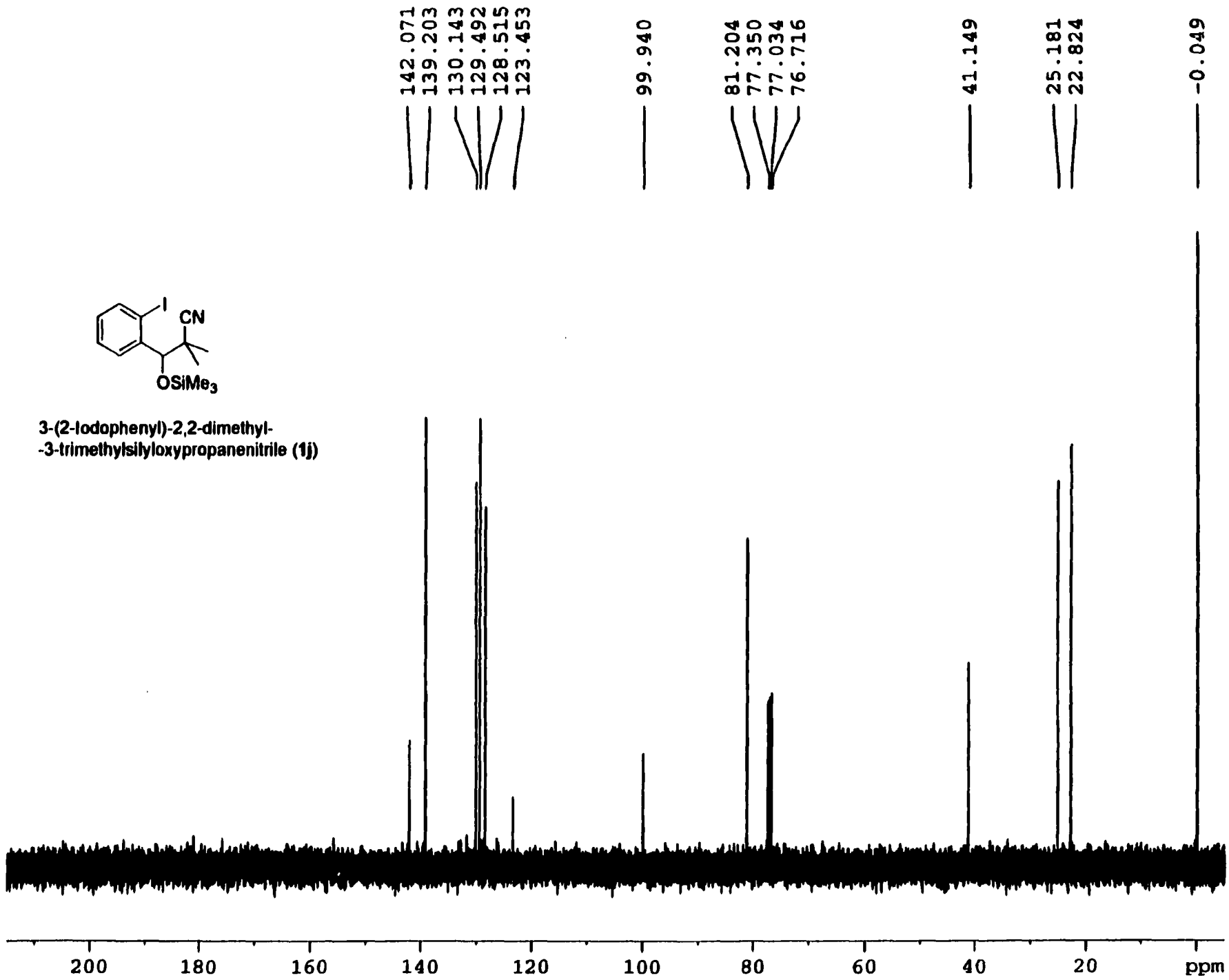

Methyl 2-cyano-3-(2-iodophenyl)-
-2-methylpropanoate (1h)
CN
CO2Me
I
7.891
7.888
7.871
7.868
7.411
7.407
7.392
7.388
7.358
7.354
7.339
7.336
7.007
7.002
6.987
6.984
6.983
6.969
6.964
3.823
3.456
3.421
3.396
3.361
1.675
1.000
1.008
1.002
1.039
3.087
2.144
3.039
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

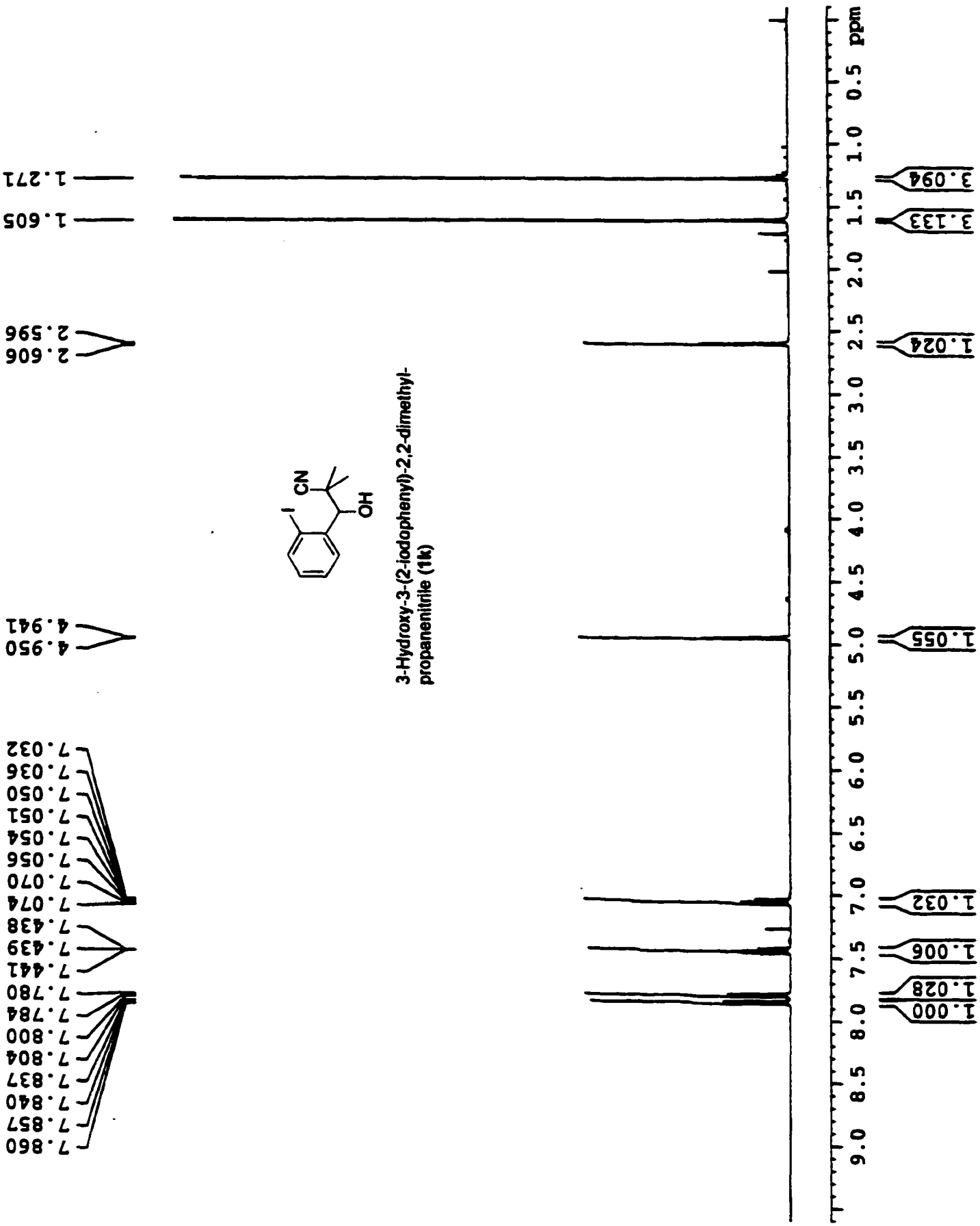
Methyl 2-cyano-3-(2-iodophenyl)-
-2-methylpropanoate (1h)
CN
CO2Me
169.056
140.023
137.302
130.170
129.427
128.452
119.285
102.208
77.316
76.998
76.680
53.694
45.933
44.599
22.861
ppm


7.942
7.939
7.922
7.919
7.558
7.554
7.539
7.535
7.435
7.432
7.417
7.414
7.398
7.395
7.090
7.085
7.070
7.066
7.066
7.051
7.047
3.495
1.887
I
CN
CN
2-Cyano-3-(2-iodophenyl)-2-methyl-propanenitrile (1i)
9
8
7
6
5
4
3
2
1
ppm
1.000
1.041
1.023
1.058
2.057
3.051

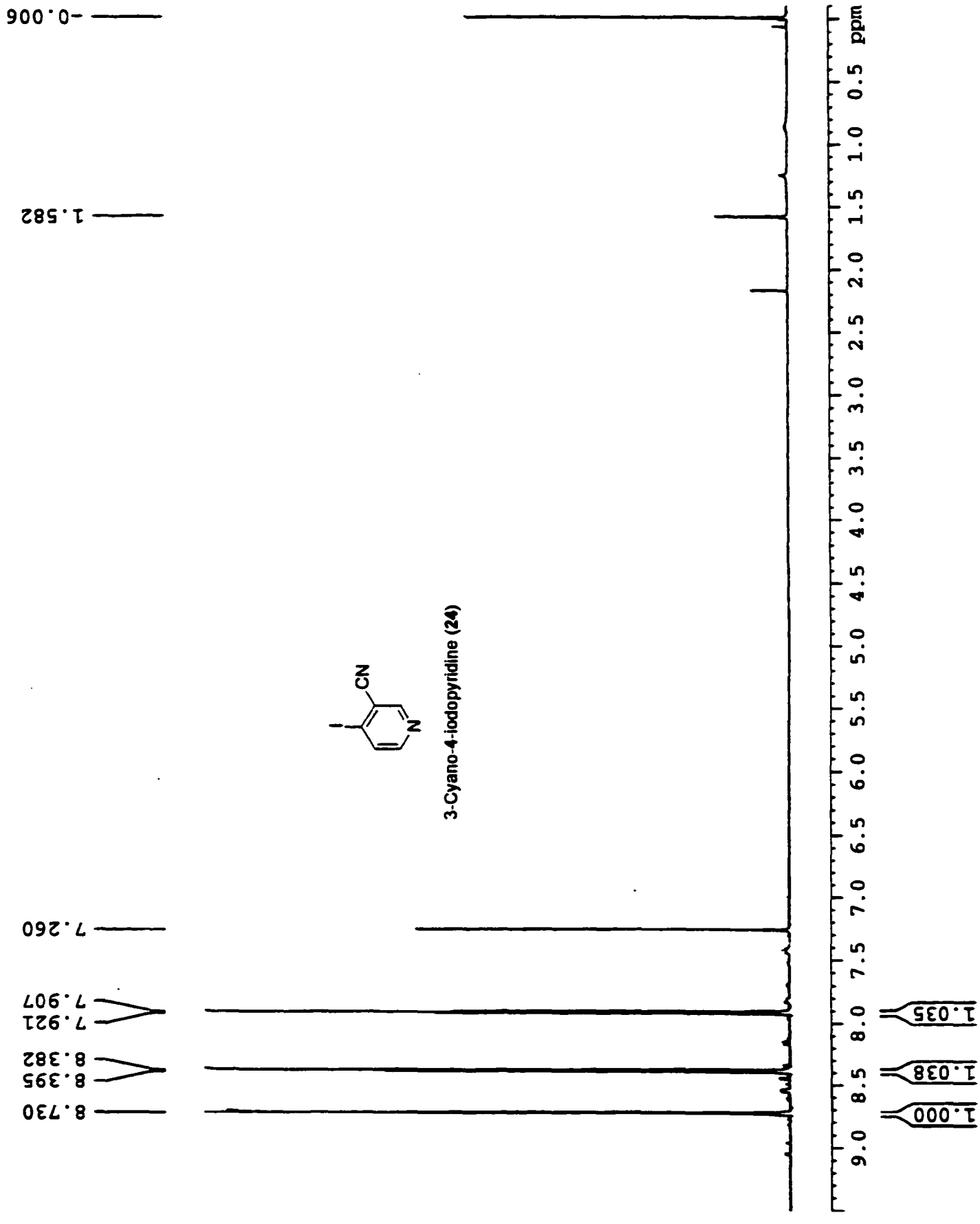
2-Cyano-3-(2-iodophenyl)-2-methyl-propanenitrile (1l)
CN
CN
I
140.390
135.206
130.630
130.382
128.929
115.677
102.258
77.318
77.002
76.683
46.715
32.649
24.408
200
180
160
140
120
100
80
60
40
20
ppm

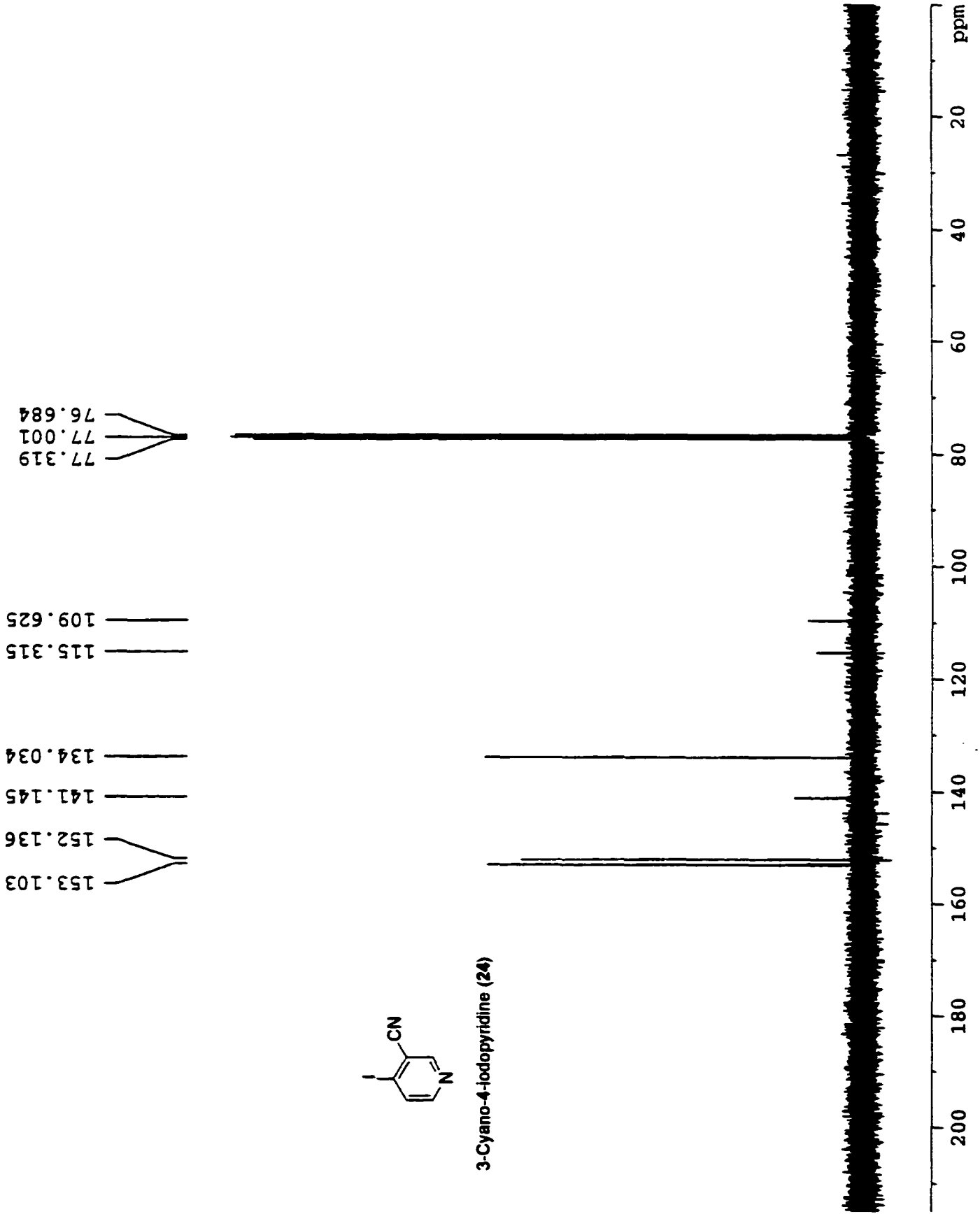
3-(2-Iodophenyl)-2,2-dimethyl-
-3-trimethylsilyloxypropanenitrile (1j)
CN
OSiMe3
7.825
7.822
7.819
7.805
7.802
7.799
7.759
7.755
7.739
7.735
7.420
7.401
7.385
7.383
7.042
7.038
7.022
7.019
7.003
7.000
4.830
1.517
1.257
0.029
0.020
0.017
1.000
0.996
1.016
1.023
0.994
3.006
3.014
8.978
ppm

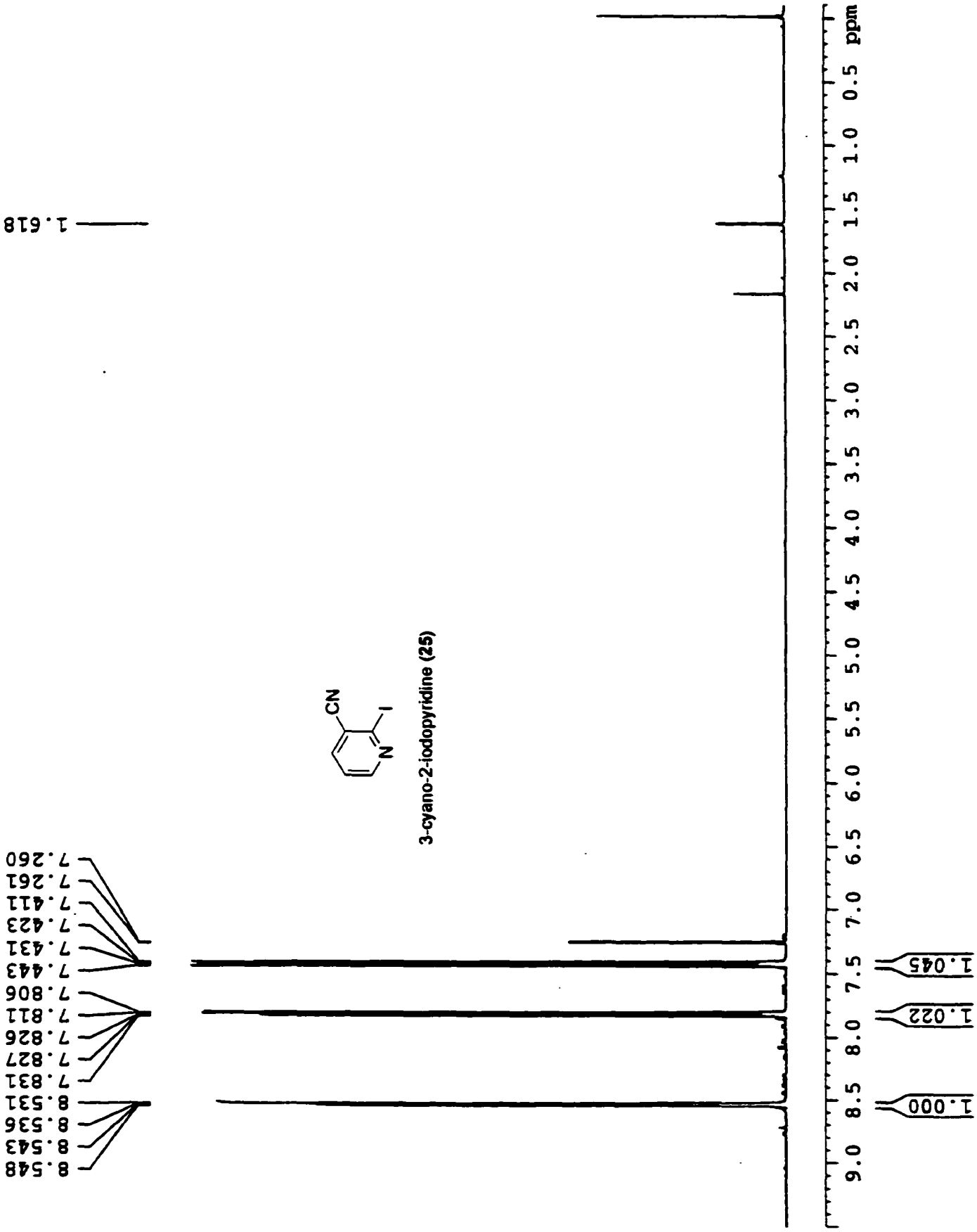

142.071
139.203
130.143
129.492
128.515
123.453
99.940
81.204
77.350
77.034
76.716
41.149
25.181
22.824
-0.049
I
CN
OSiMe3
3-(2-Iodophenyl)-2,2-dimethyl-
-3-trimethylsilyloxypropanenitrile (1j)
200
180
160
140
120
100
80
60
40
20
ppm

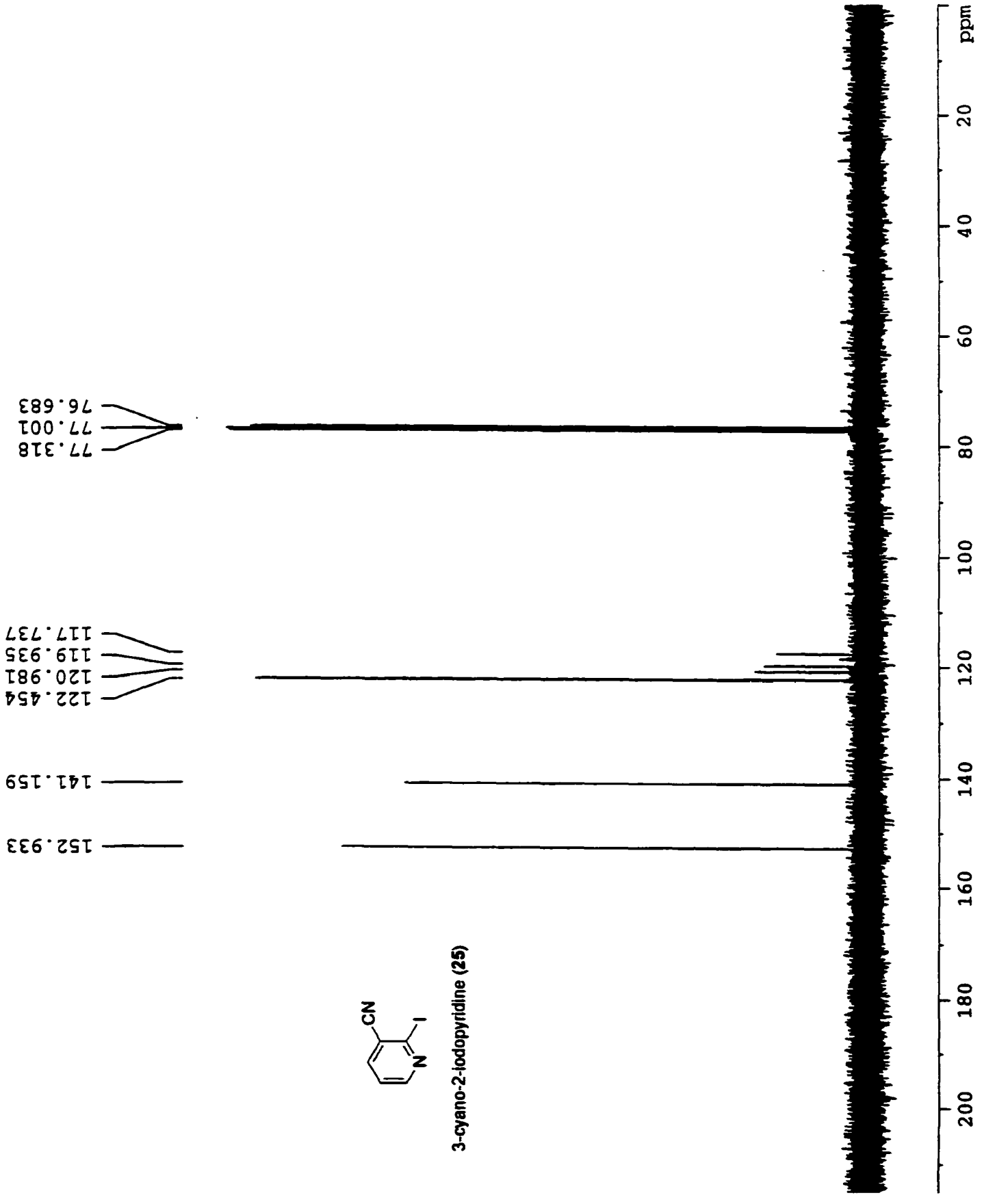

3-Hydroxy-3-(2-iodophenyl)-2,2-dimethyl-propanenitrile (1k)
CN
OH
I
1.271
1.605
2.606
2.596
4.950
4.941
7.860
7.857
7.840
7.837
7.804
7.800
7.784
7.780
7.441
7.439
7.438
7.074
7.070
7.056
7.054
7.051
7.050
7.036
7.032
3.094
3.133
1.024
1.055
1.032
1.006
1.028
1.000
ppm

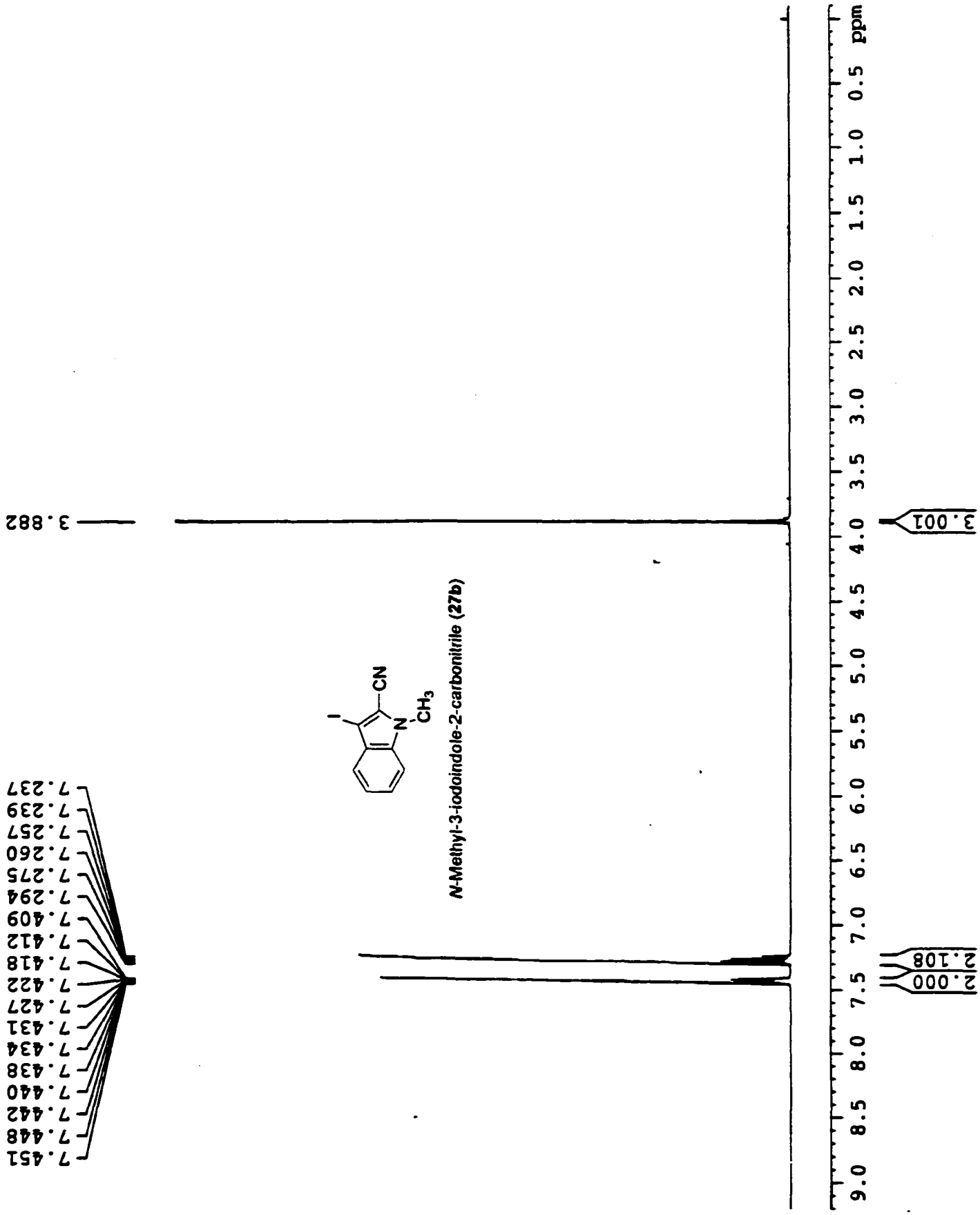
2,3-Dicyano-1,4-diiodobenzene (23)
I
CN
CN
I
143.513
143.504
143.496
125.477
115.832
98.610
77.319
77.002
76.684
200
180
160
140
120
100
80
60
40
20
ppm

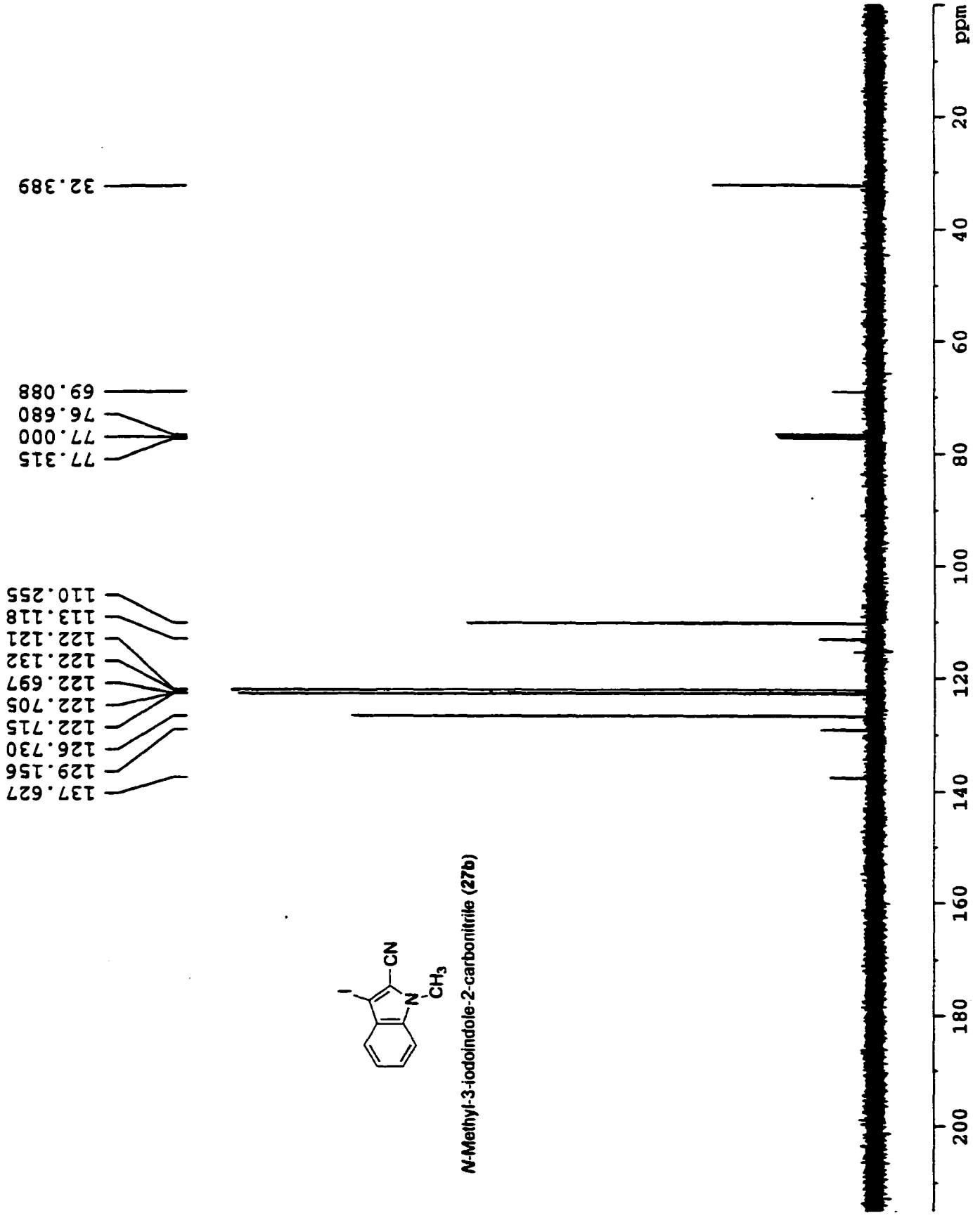

3-Cyano-4-iodopyridine (24)
CN
N
8.730
8.395
8.382
7.921
7.907
7.260
1.582
-0.006
1.000
1.038
1.035
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


153.103
152.136
141.145
134.034
115.315
109.625
77.319
77.001
76.684
ppm
20
40
60
80
100
120
140
160
180
200
CN
N
3-Cyano-4-iodopyridine (24)

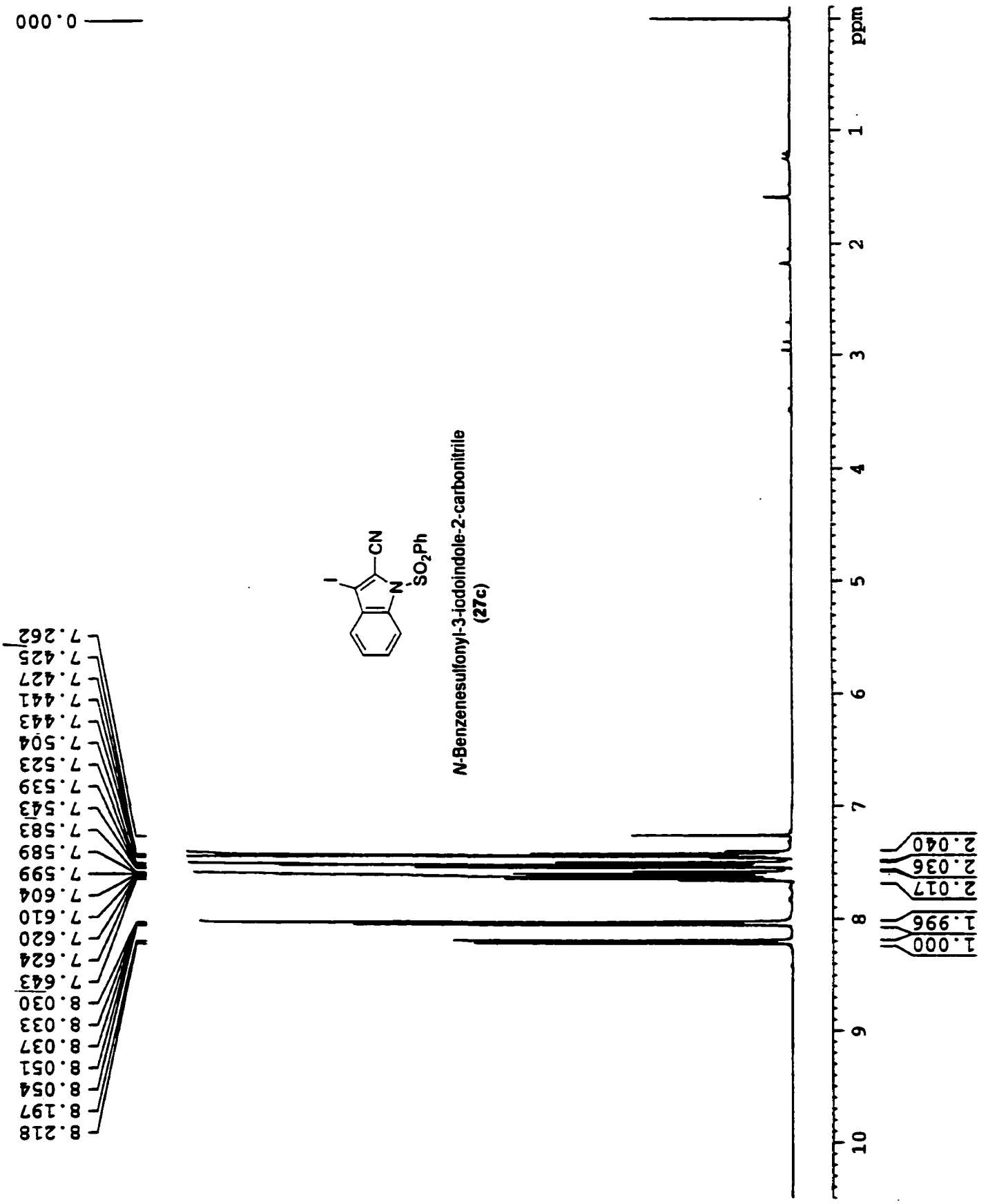

3-cyano-2-iodopyridine (25)
CN
I
N
1.618
8.548
8.543
8.536
8.531
7.831
7.827
7.826
7.811
7.806
7.443
7.431
7.423
7.411
7.261
7.260
1.000
1.022
1.045
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

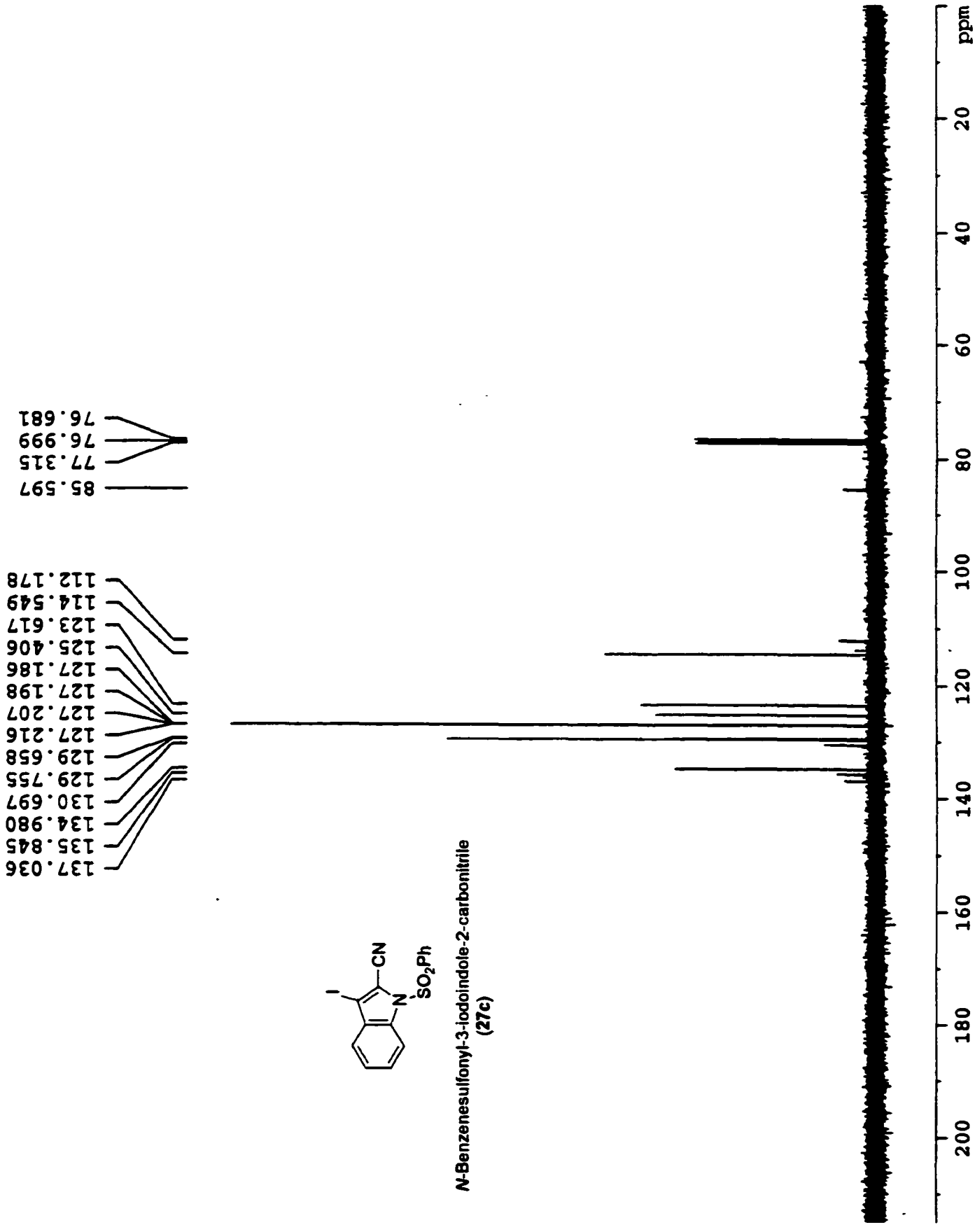

152.933
141.159
122.454
120.981
119.935
117.737
77.318
77.001
76.683
CN
I
N
3-cyano-2-iodopyridine (25)
ppm
200
180
160
140
120
100
80
60
40
20

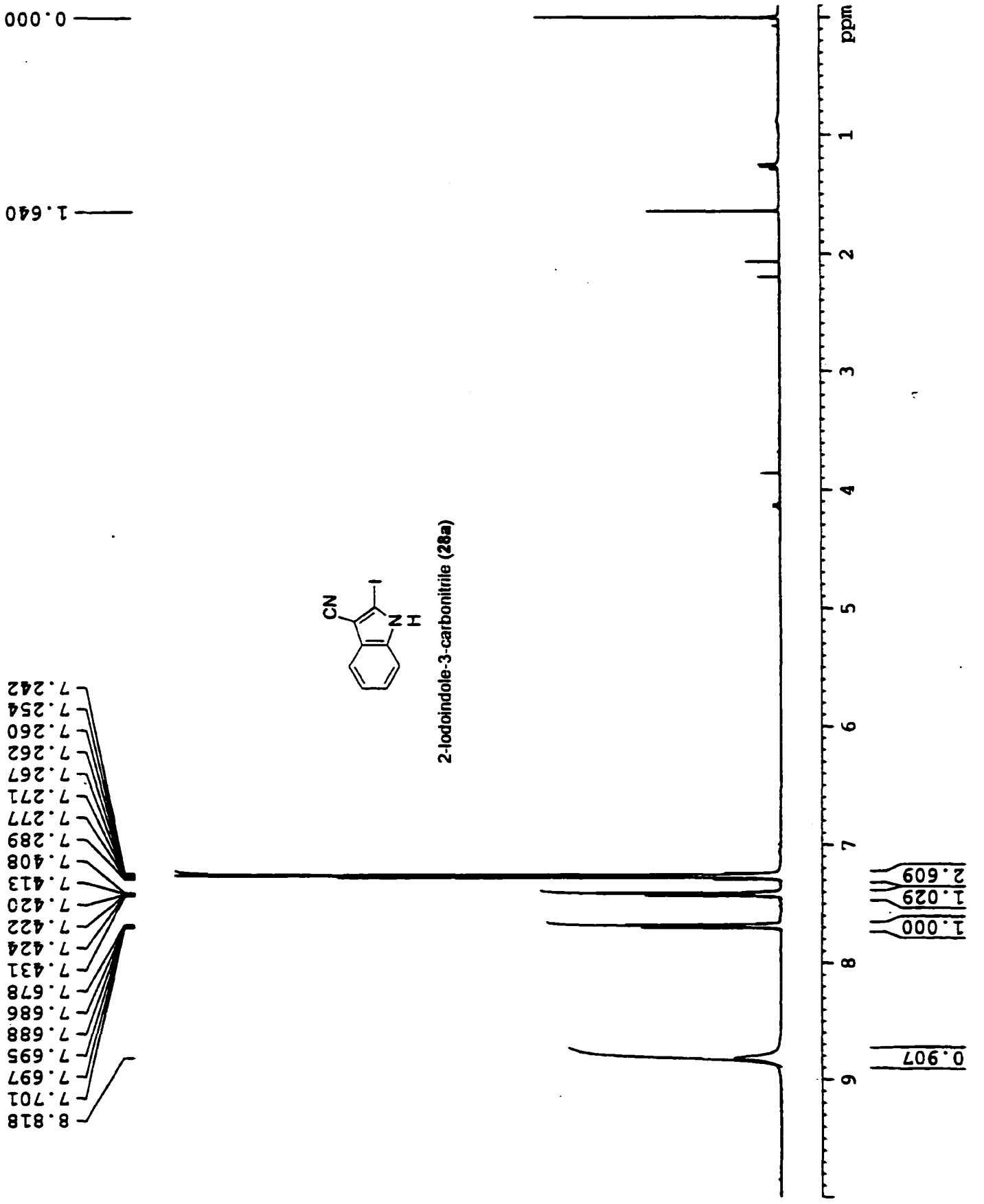

3.882
7.237
7.239
7.257
7.260
7.275
7.294
7.409
7.412
7.418
7.422
7.427
7.431
7.434
7.438
7.440
7.442
7.448
7.451
N-Methyl-3-iodoindole-2-carbonitrile (27b)
CN
I
N
CH3
3.001
2.000
2.108
ppm



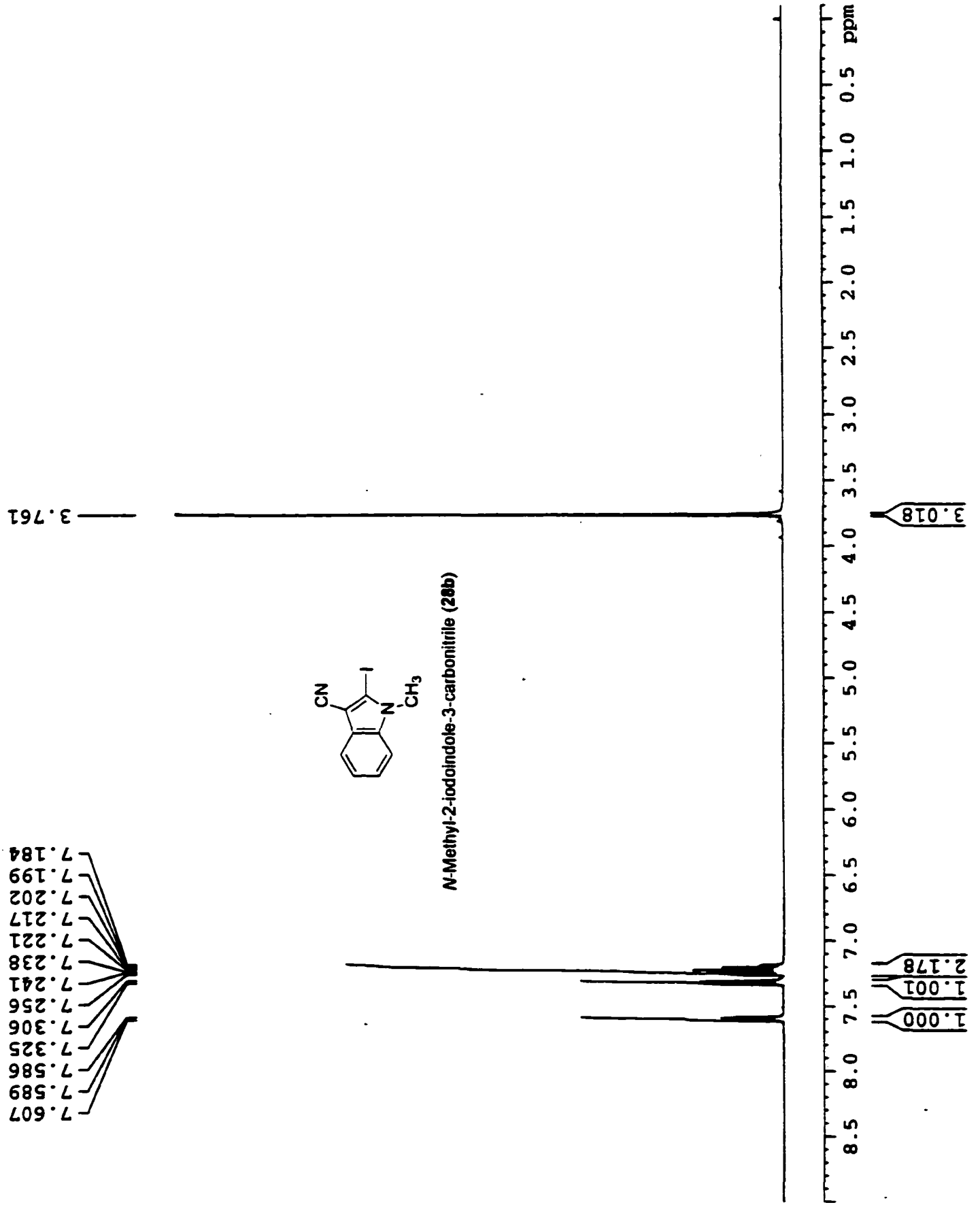

*N*-Methyl-3-iodoindole-2-carbonitrile (27b)

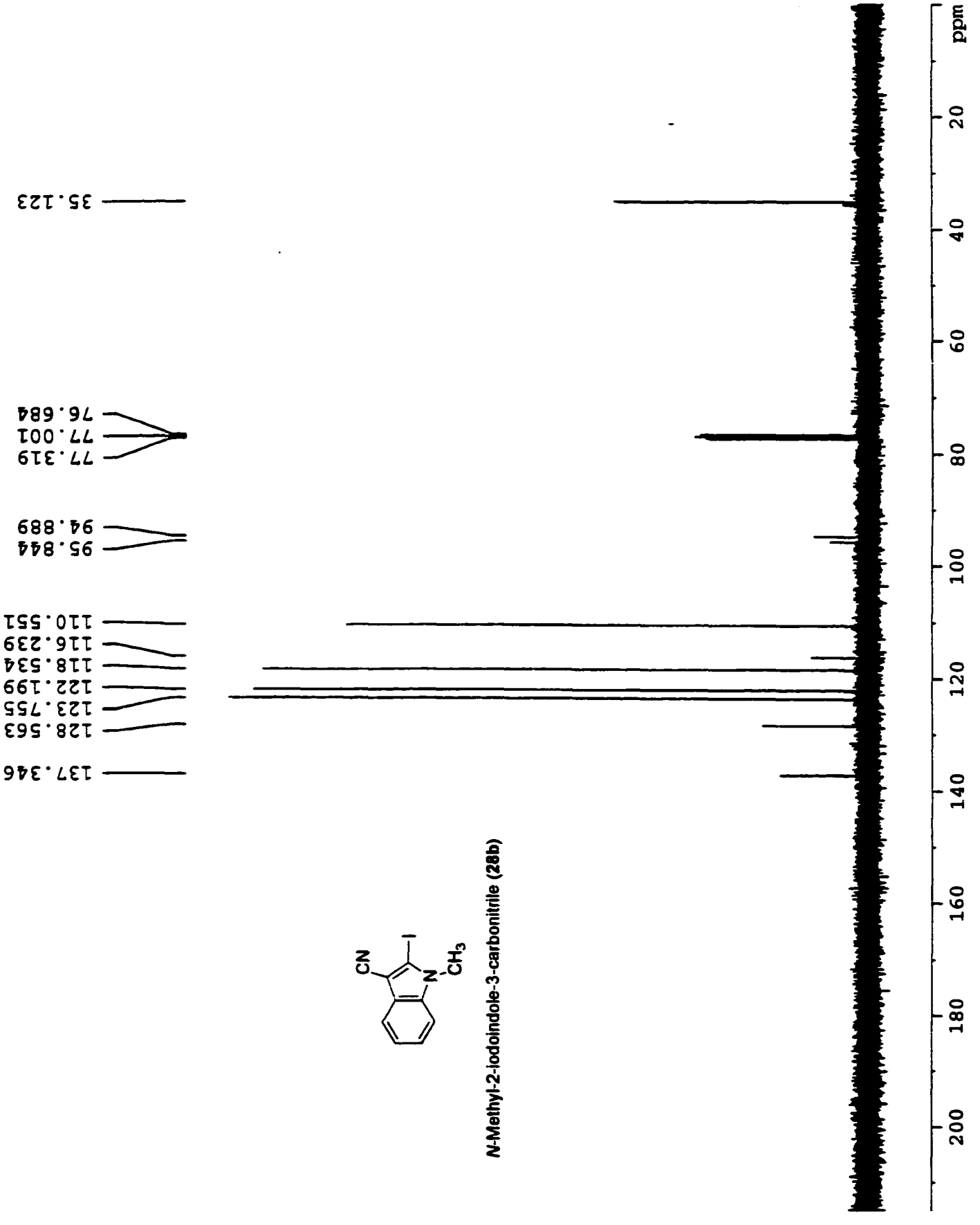

0.000
8.218
8.197
8.054
8.051
8.037
8.033
8.030
7.643
7.624
7.620
7.610
7.604
7.599
7.589
7.583
7.543
7.539
7.523
7.504
7.443
7.441
7.427
7.425
7.262
CN
I
N
SO2Ph
N-Benzenesulfonyl-3-iodoindole-2-carbonitrile
(27c)
ppm
1
2
3
4
5
6
7
8
9
10
1.000
1.996
2.017
2.036
2.040


137.036
135.845
134.980
130.697
129.755
129.658
127.216
127.207
127.198
127.186
125.406
123.617
114.549
112.178
85.597
77.315
76.999
76.681
CN
SO2Ph
N-Benzenesulfonyl-3-iodoindole-2-carbonitrile
(27c)
ppm
200
180
160
140
120
100
80
60
40
20

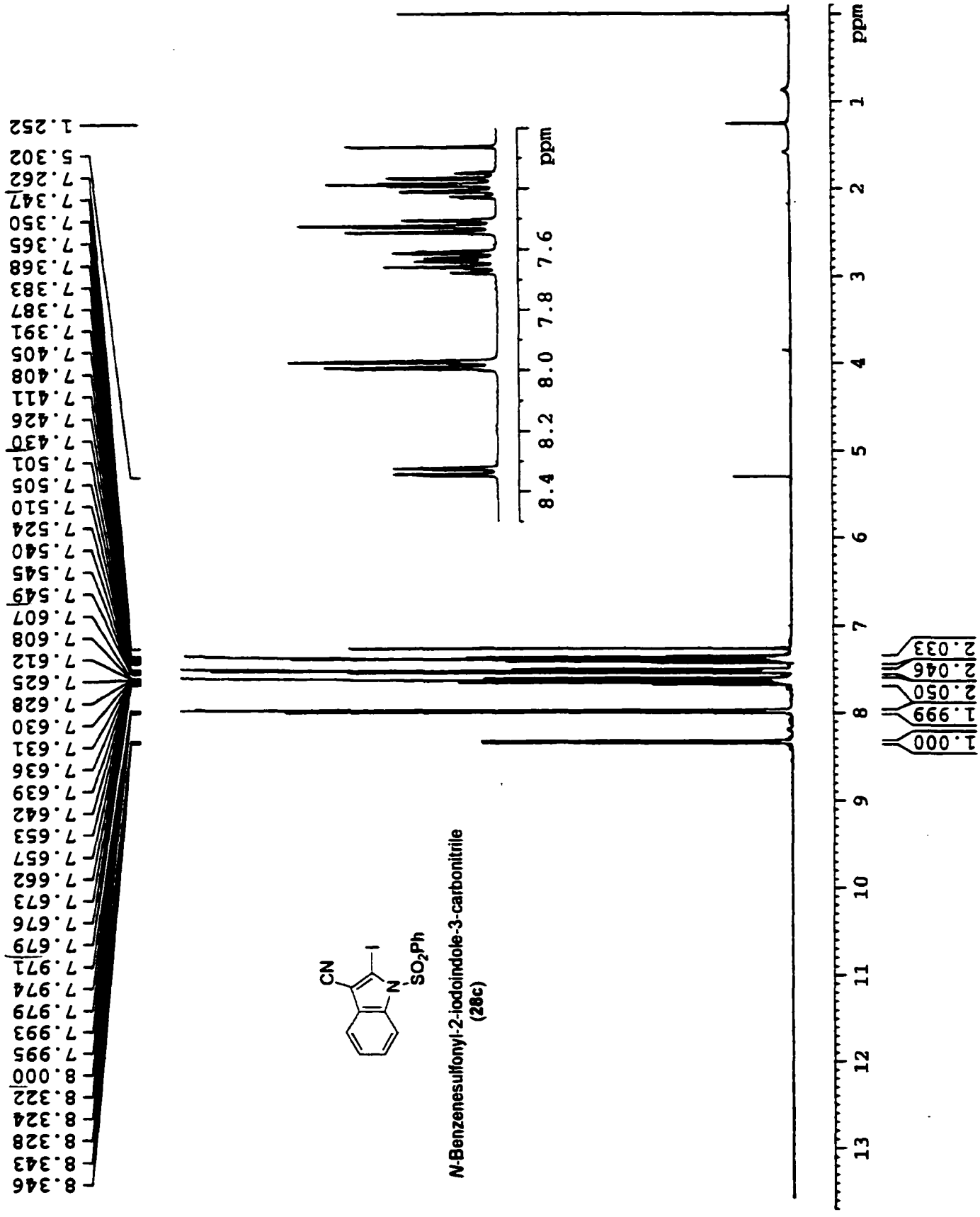

0.000
1.640
ppm
1
2
3
4
5
6
7
8
9
7.242
7.254
7.260
7.262
7.267
7.271
7.277
7.289
7.408
7.413
7.420
7.422
7.424
7.431
7.678
7.686
7.688
7.695
7.697
7.701
8.818
2.609
1.029
1.000
0.907
CN
N
H
I
2-Iodoindole-3-carbonitrile (28a)

2-Iodoindole-3-carbonitrile (28a)
CN
N
H
I
ppm
200
180
160
140
120
100
80
60
40
20
138.045
128.207
123.457
121.971
117.488
116.545
112.010
93.971
92.455
40.135
39.926
39.718
39.511
39.302
39.092
38.883

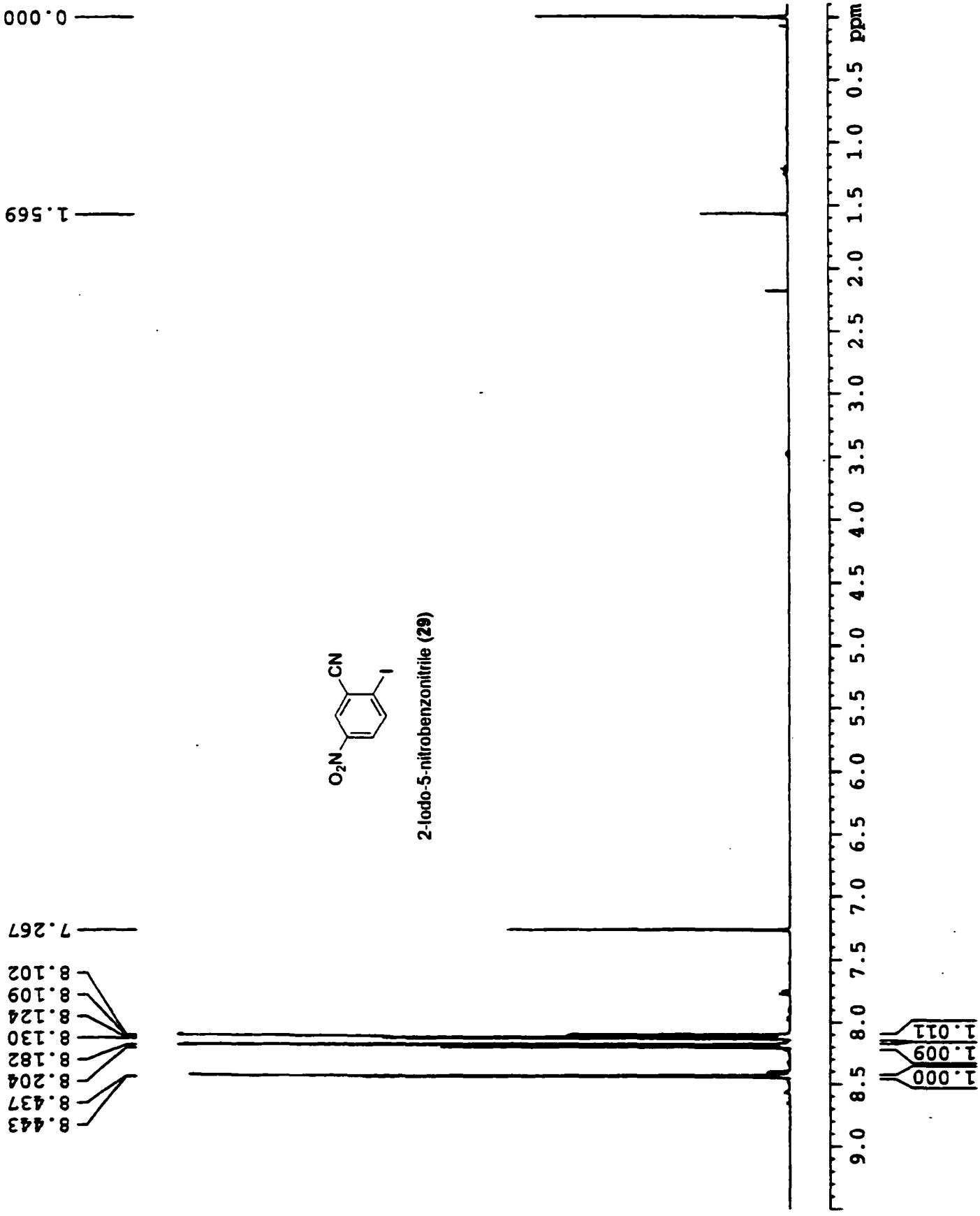

3.761
7.184
7.199
7.202
7.217
7.221
7.238
7.241
7.256
7.306
7.325
7.586
7.589
7.607
N-Methyl-2-iodoindole-3-carbonitrile (28b)
CN
I
N
CH3
3.018
2.178
1.001
1.000
ppm
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

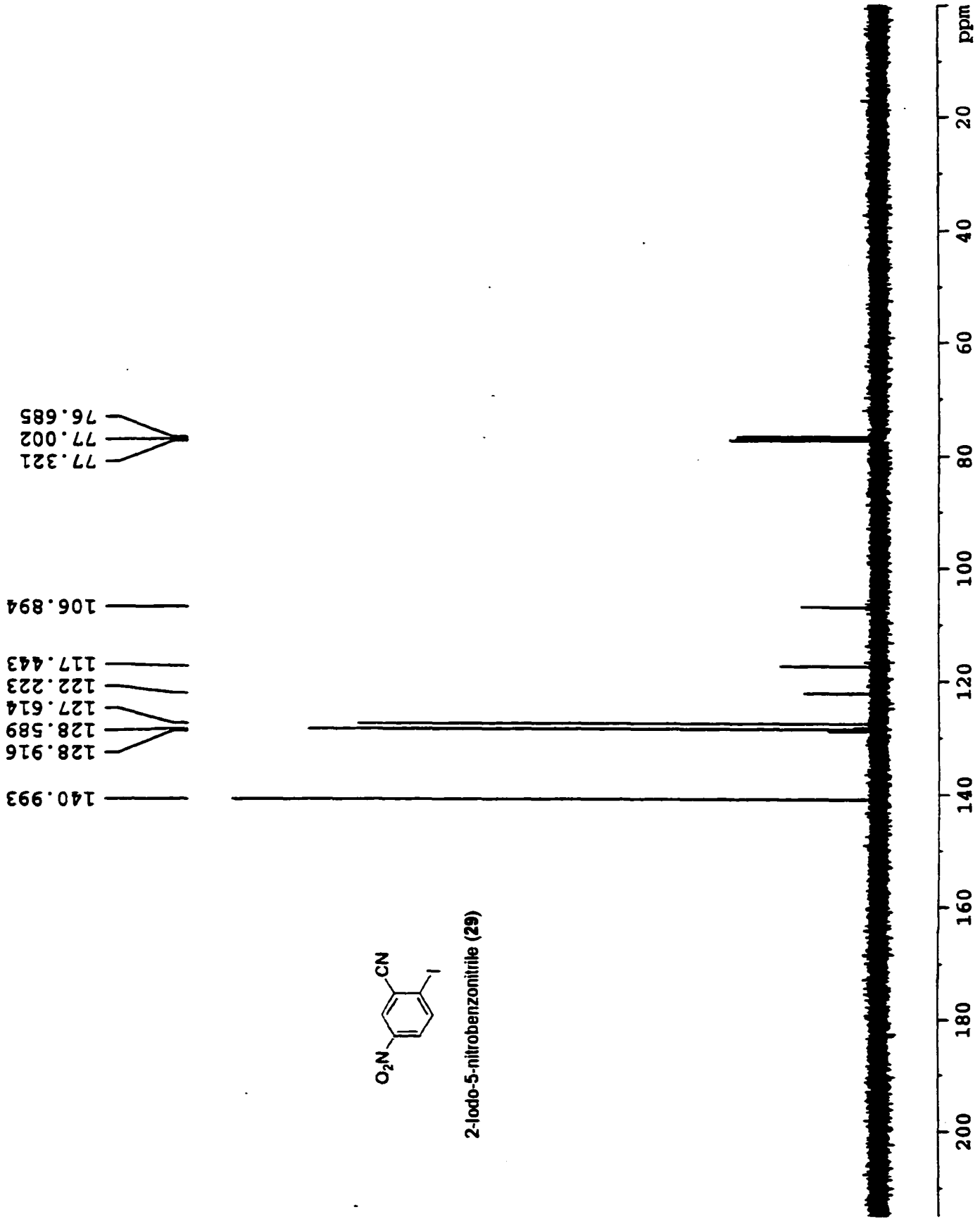


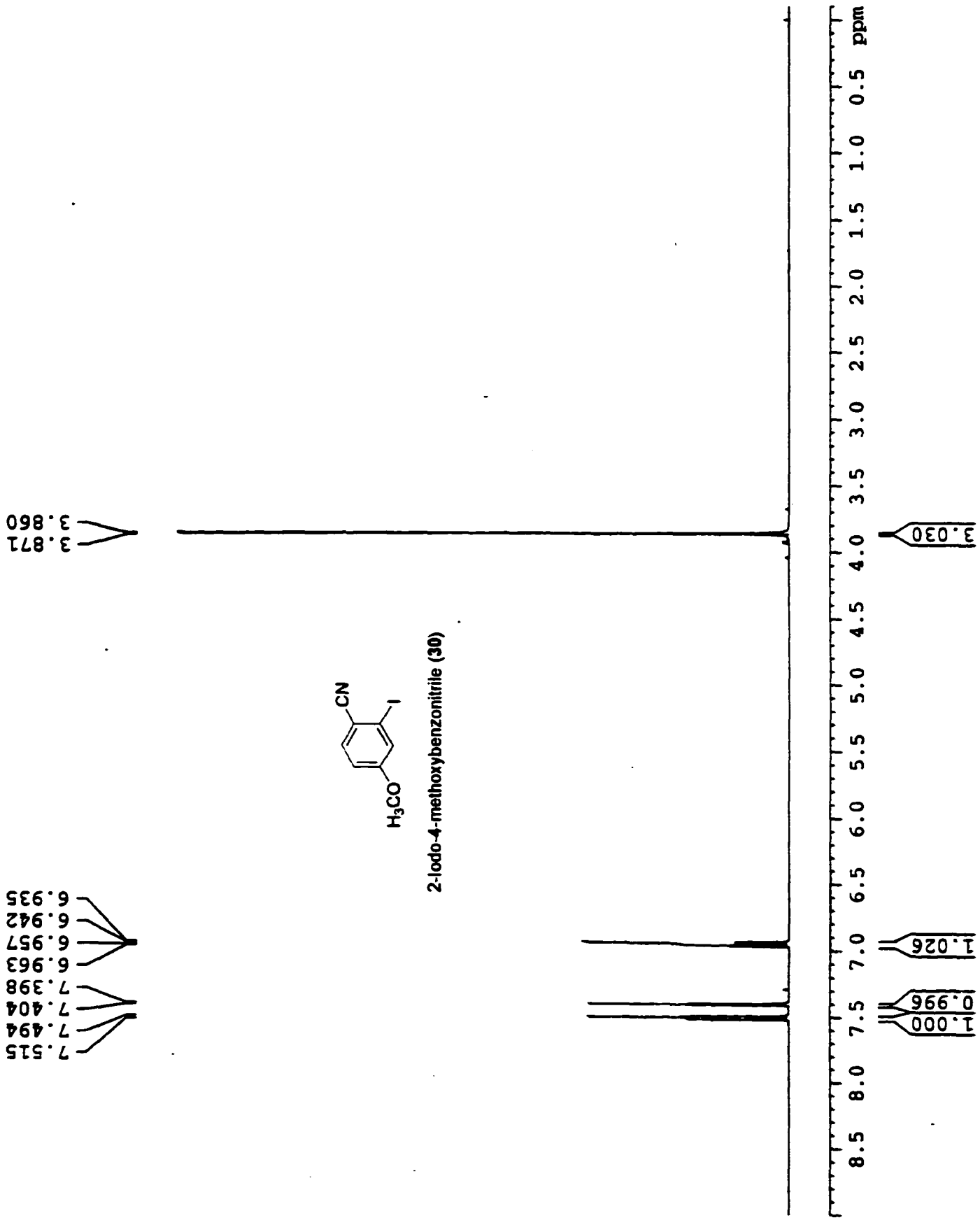

*N*-Methyl-2-iodoindole-3-carbonitrile (28b)


1.252
5.302
7.262
7.347
7.350
7.365
7.368
7.383
7.387
7.391
7.405
7.408
7.411
7.426
7.430
7.501
7.505
7.510
7.524
7.540
7.545
7.549
7.607
7.608
7.612
7.625
7.628
7.630
7.631
7.636
7.639
7.642
7.653
7.657
7.662
7.673
7.676
7.679
7.971
7.974
7.979
7.993
7.995
8.000
8.322
8.324
8.328
8.343
8.346
ppm
8.4
8.2
8.0
7.8
7.6
ppm
1.000
1.999
2.050
2.046
2.033
CN
I
N
SO2Ph
N-Benzenesulfonyl-2-iodoindole-3-carbonitrile
(28c)

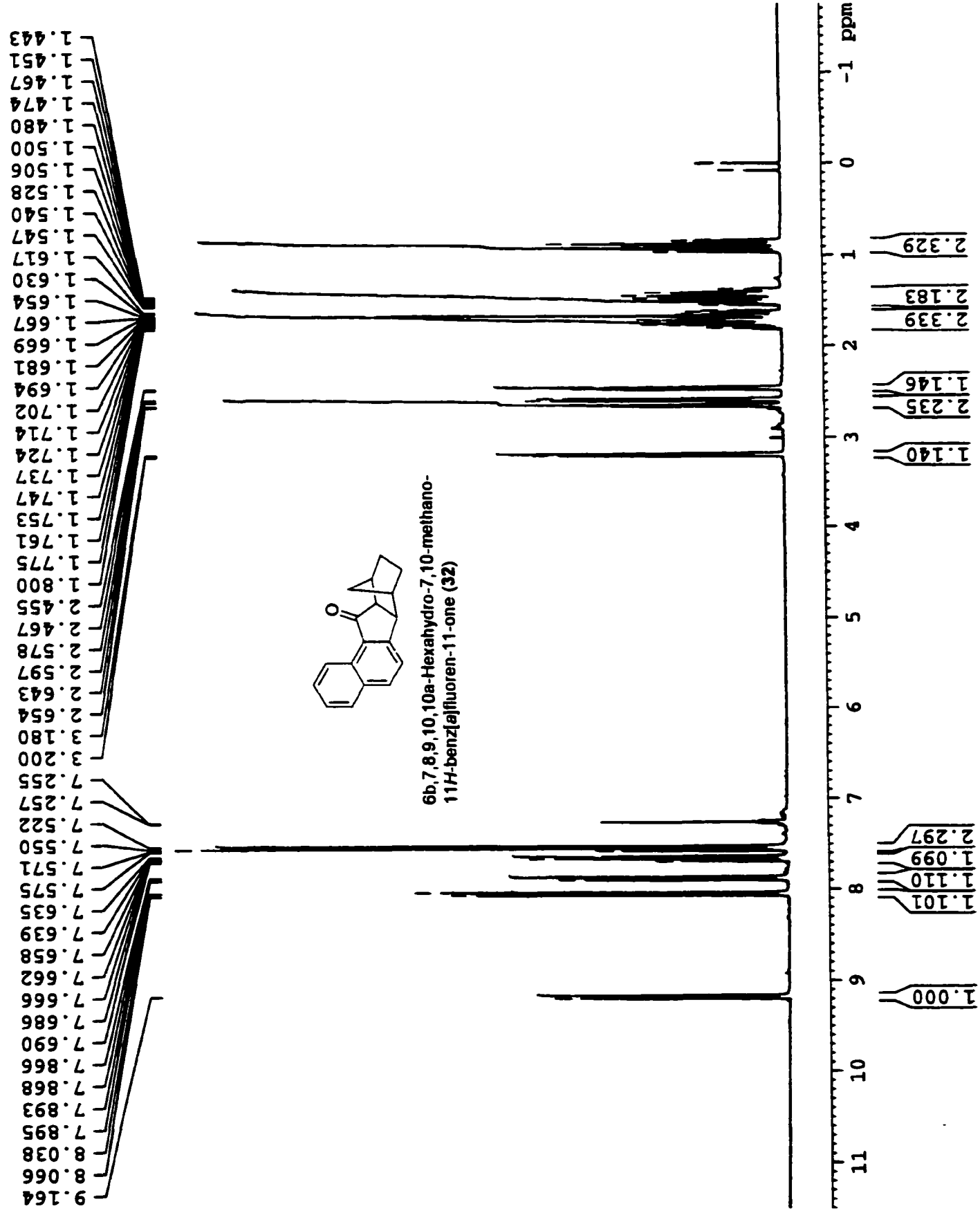
N-Benzenesulfonyl-2-iodoindole-3-carbonitrile
(28c)
SO2Ph
N
CN
I
137.570
135.043
130.087
129.598
129.259
127.432
127.421
126.599
125.103
119.089
115.545
114.535
86.976
77.317
77.000
76.682
200
180
160
140
120
100
80
60
40
20
ppm

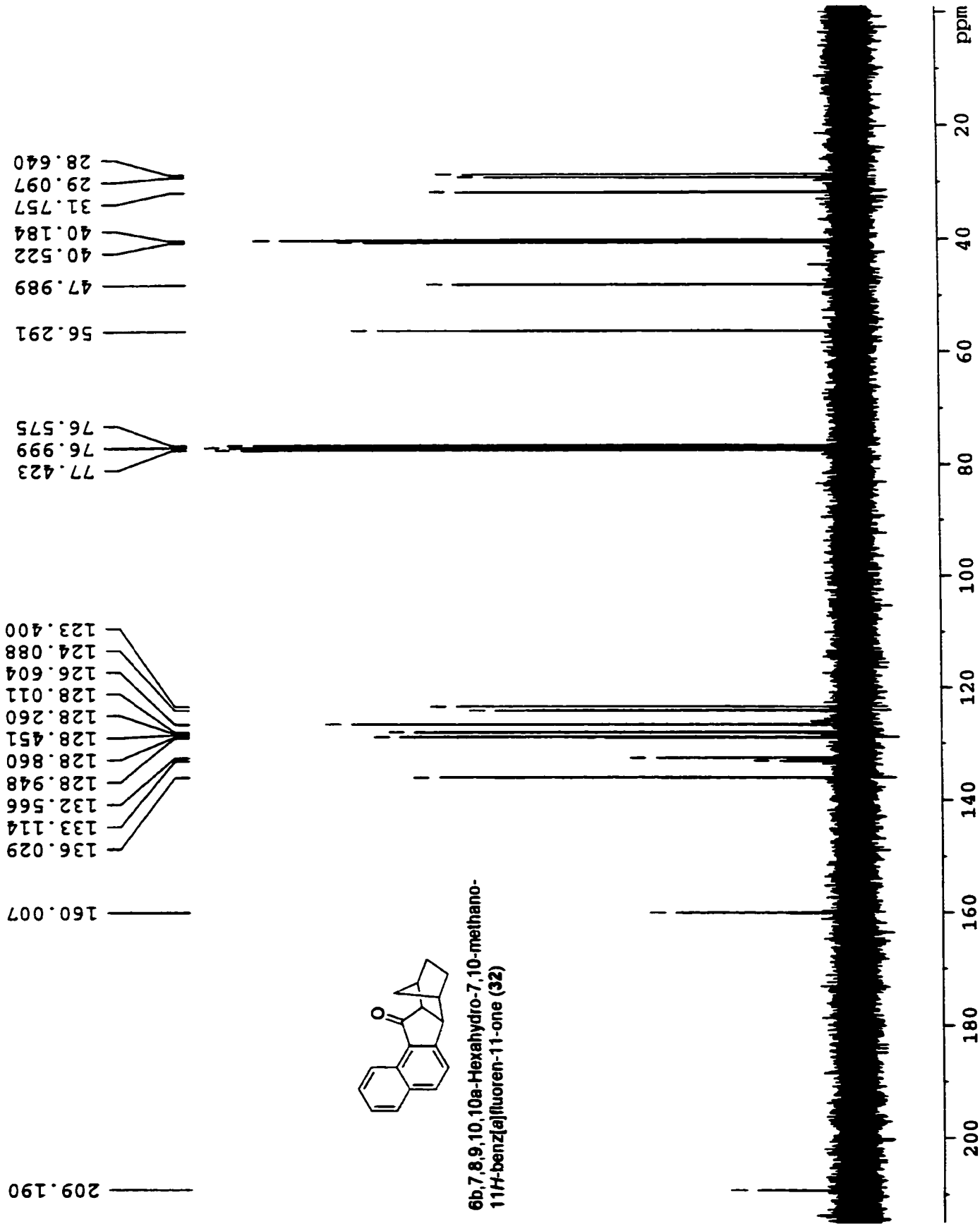

0.000
1.569
7.267
8.102
8.109
8.124
8.130
8.182
8.204
8.437
8.443
1.000
1.009
1.011
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
CN
I
O2N
2-Iodo-5-nitrobenzonitrile (29)

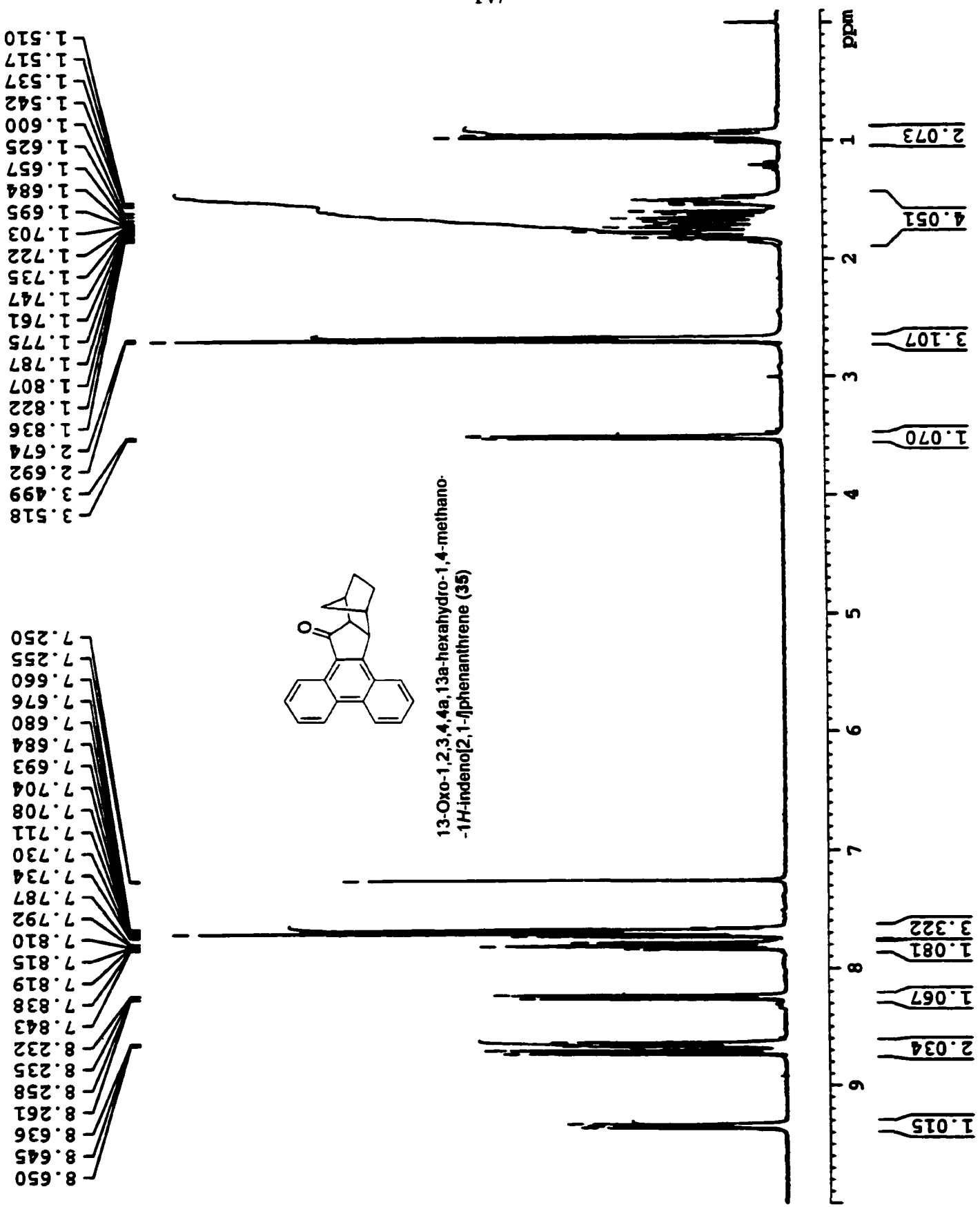

140.993
128.916
128.589
127.614
122.223
117.443
106.894
77.321
77.002
76.685
2-Iodo-5-nitrobenzonitrile (29)
CN
I
O2N
ppm
20
40
60
80
100
120
140
160
180
200

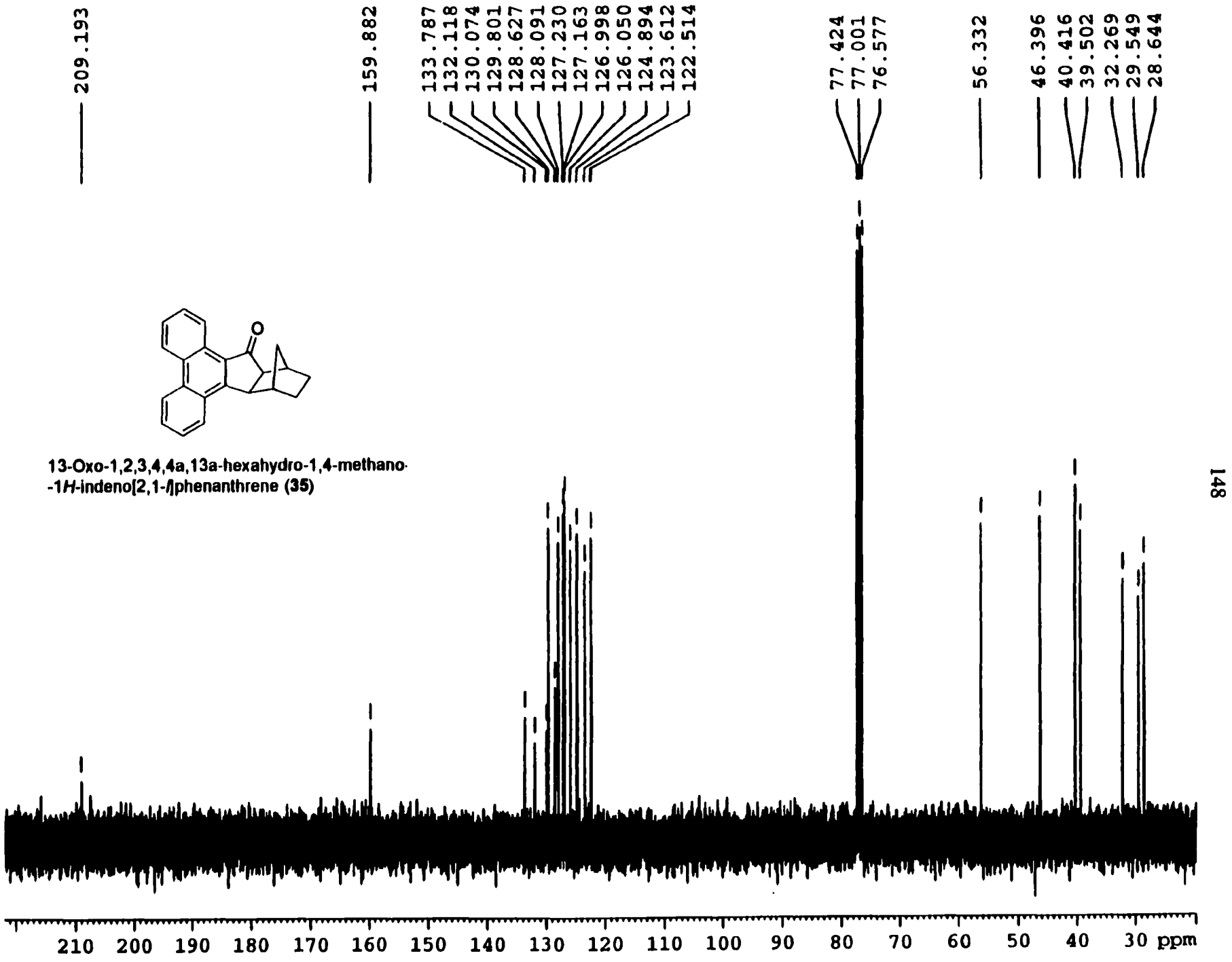

3.871
3.860
7.515
7.494
7.404
7.398
6.963
6.957
6.942
6.935
CN
I
H3CO
2-Iodo-4-methoxybenzonitrile (30)
3.030
1.026
0.996
1.000
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

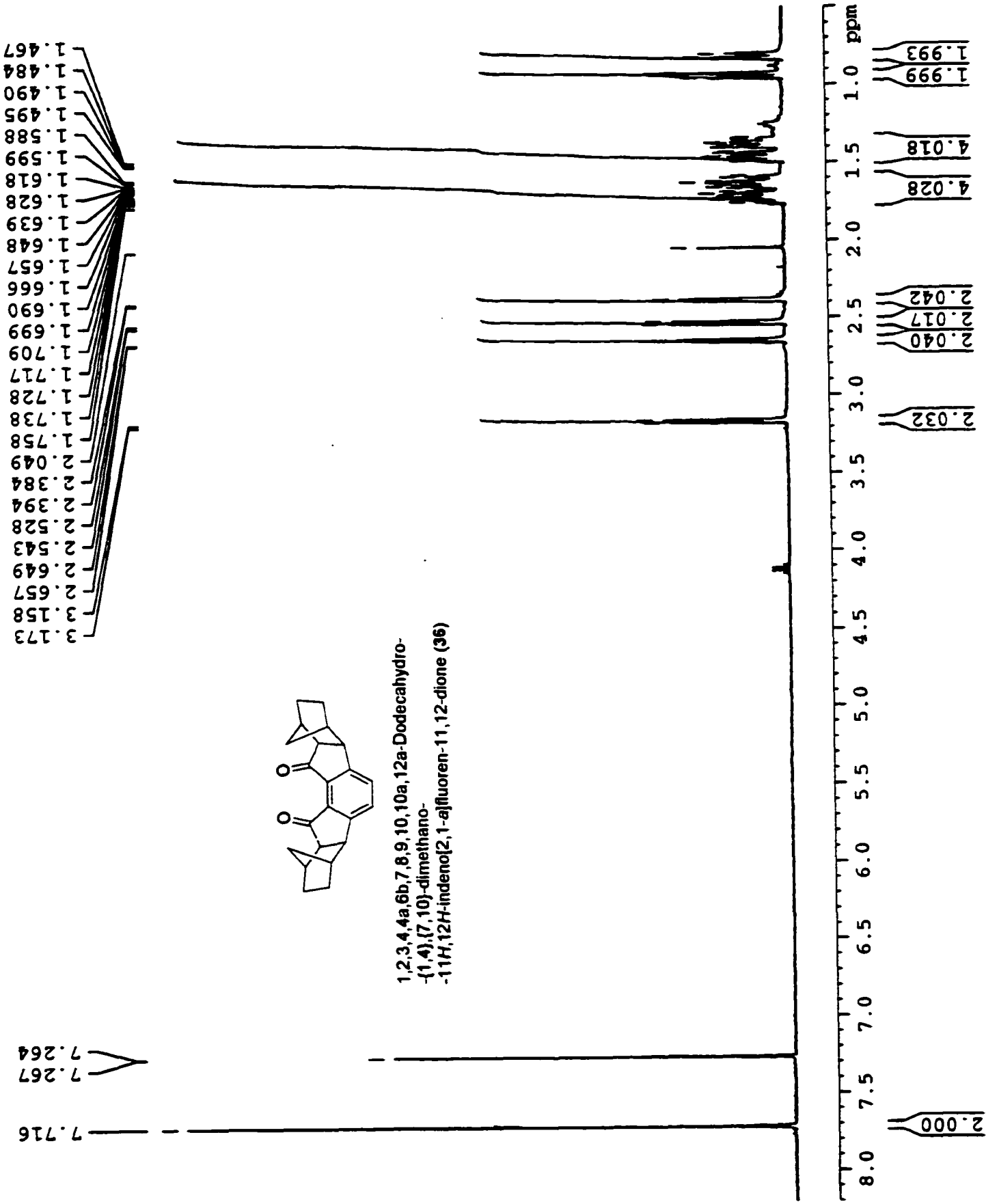
2-Iodo-4-methoxybenzonitrile (30)
H3CO
I
CN
162.422
135.061
124.906
119.589
114.386
112.052
99.213
77.319
77.001
76.684
55.805
200
180
160
140
120
100
80
60
40
20
ppm

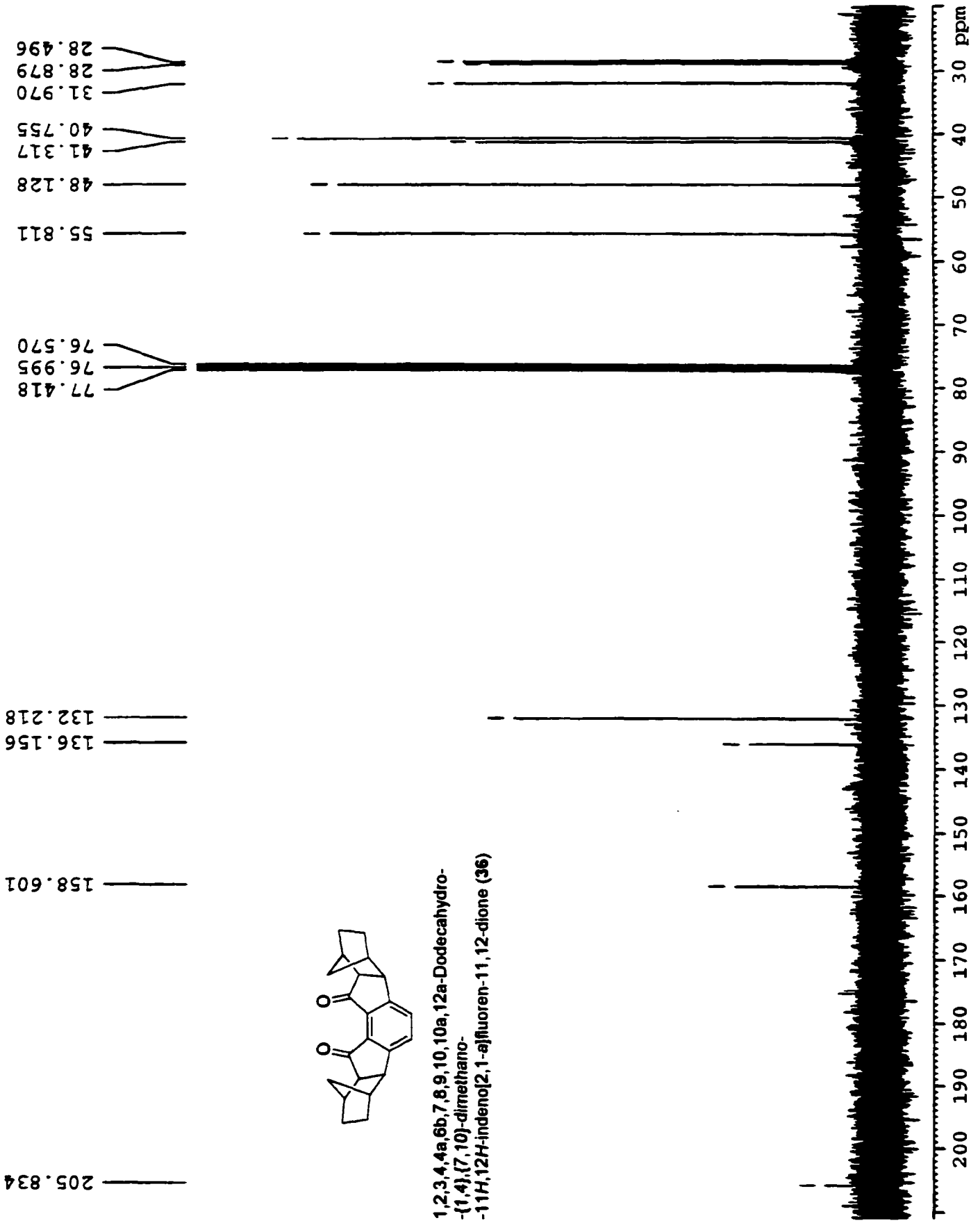

6b,7,8,9,10,10a-Hexahydro-7,10-methano-11H-benz[a]fluoren-11-one (32)
O
ppm
-1
0
1
2
3
4
5
6
7
8
9
10
11
2.329
2.183
2.339
1.146
2.235
1.140
2.297
1.099
1.110
1.101
1.000
9.164
8.066
8.038
7.895
7.893
7.868
7.866
7.690
7.686
7.666
7.662
7.658
7.639
7.635
7.575
7.571
7.550
7.522
7.257
7.255
3.200
3.180
2.654
2.643
2.597
2.578
2.467
2.455
1.800
1.775
1.761
1.753
1.747
1.737
1.724
1.714
1.702
1.694
1.681
1.669
1.667
1.654
1.630
1.617
1.547
1.540
1.528
1.506
1.500
1.480
1.474
1.467
1.451
1.443

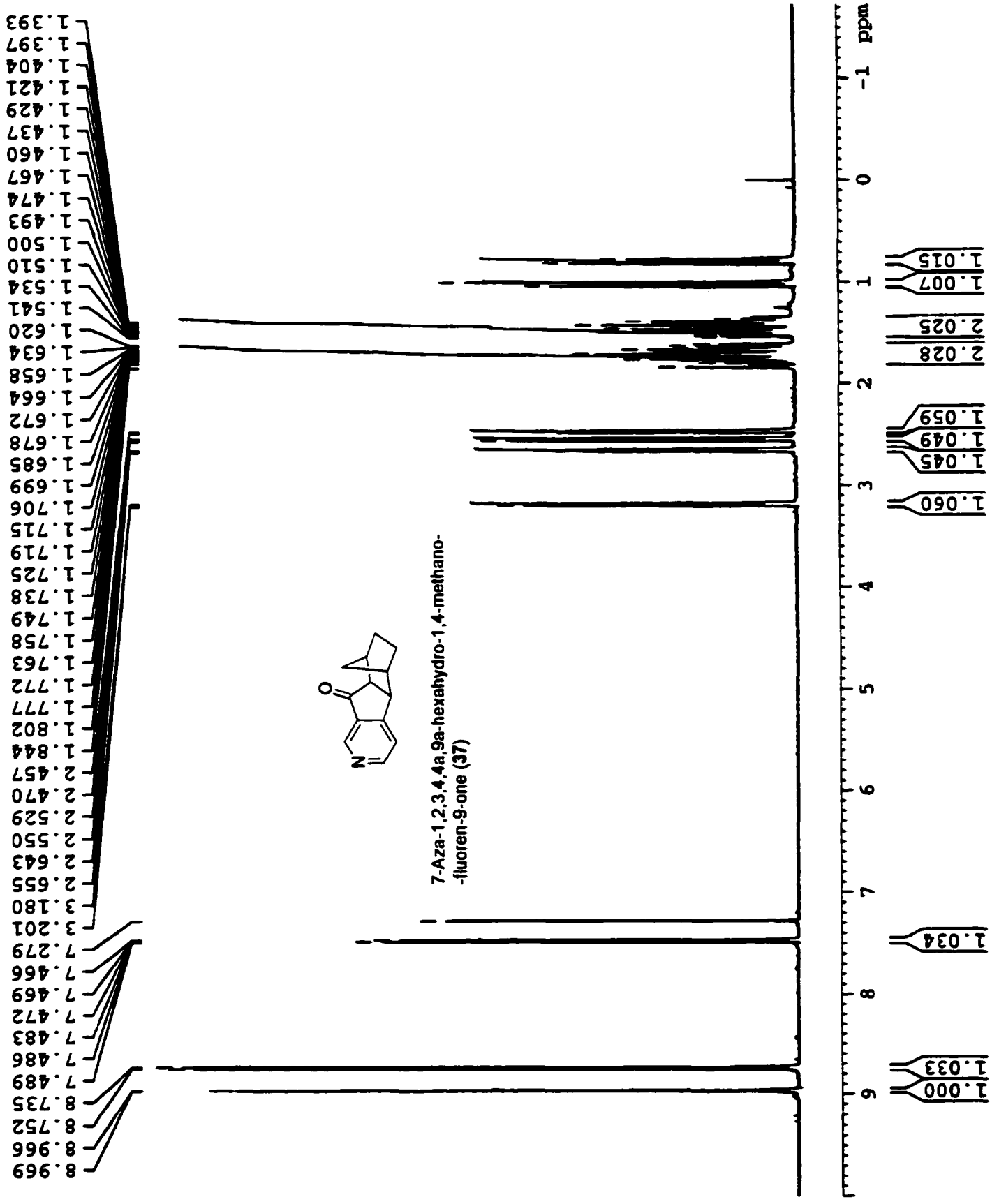

209.190
160.007
136.029
133.114
132.566
128.948
128.860
128.451
128.260
128.011
126.604
124.088
123.400
77.423
76.999
76.575
56.291
47.989
40.522
40.184
31.757
29.097
28.640
O
6b,7,8,9,10,10a-Hexahydro-7,10-methano-11H-benz[a]fluoren-11-one (32)
ppm
20
40
60
80
100
120
140
160
180
200

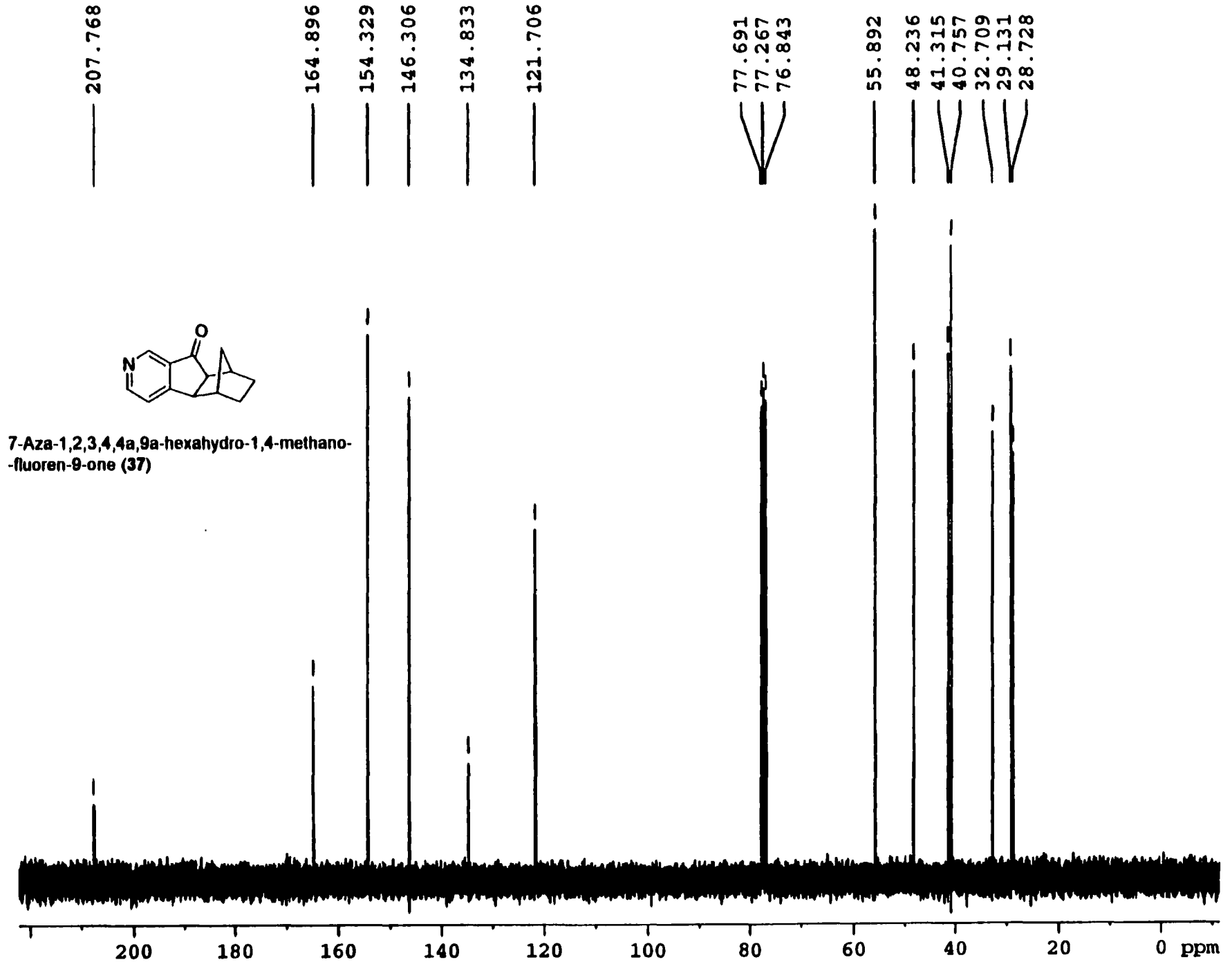

13-Oxo-1,2,3,4,4a,13a-hexahydro-1,4-methano-
-1H-indeno[2,1-l]phenanthrene (35)
O
ppm
1
2
3
4
5
6
7
8
9
2.073
4.051
3.107
1.070
3.322
1.081
1.067
2.034
1.015
1.510
1.517
1.537
1.542
1.600
1.625
1.657
1.684
1.695
1.703
1.722
1.735
1.747
1.761
1.775
1.787
1.807
1.822
1.836
2.674
2.692
3.499
3.518
7.250
7.255
7.660
7.676
7.680
7.684
7.693
7.704
7.708
7.711
7.730
7.734
7.787
7.792
7.810
7.815
7.819
7.838
7.843
8.232
8.235
8.258
8.261
8.636
8.645
8.650

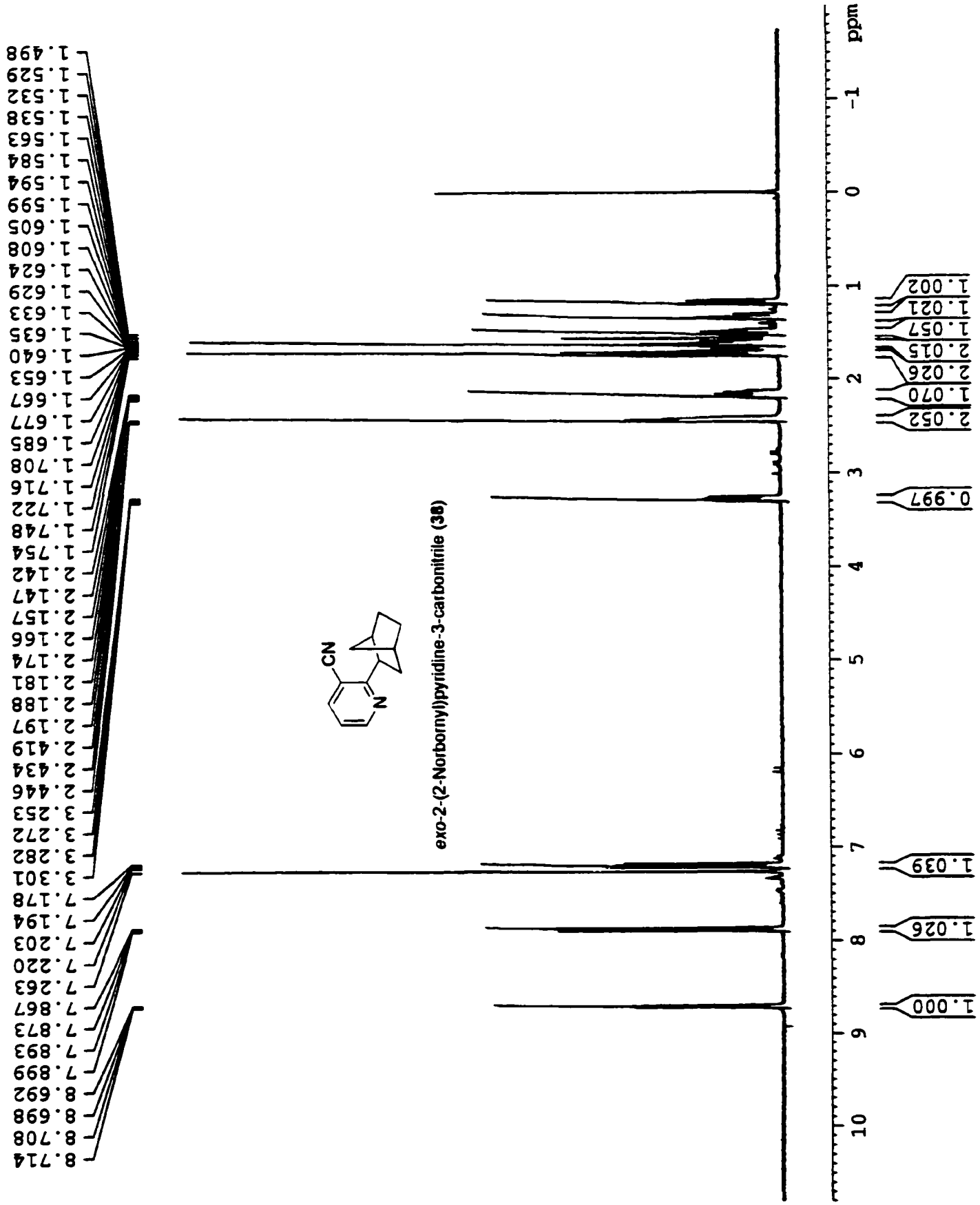

209.193
159.882
133.787
132.118
130.074
129.801
128.627
128.091
127.230
127.163
126.998
126.050
124.894
123.612
122.514
77.424
77.001
76.577
56.332
46.396
40.416
39.502
32.269
29.549
28.644
O
13-Oxo-1,2,3,4,4a,13a-hexahydro-1,4-methano-
-1H-indeno[2,1-l]phenanthrene (35)
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 ppm

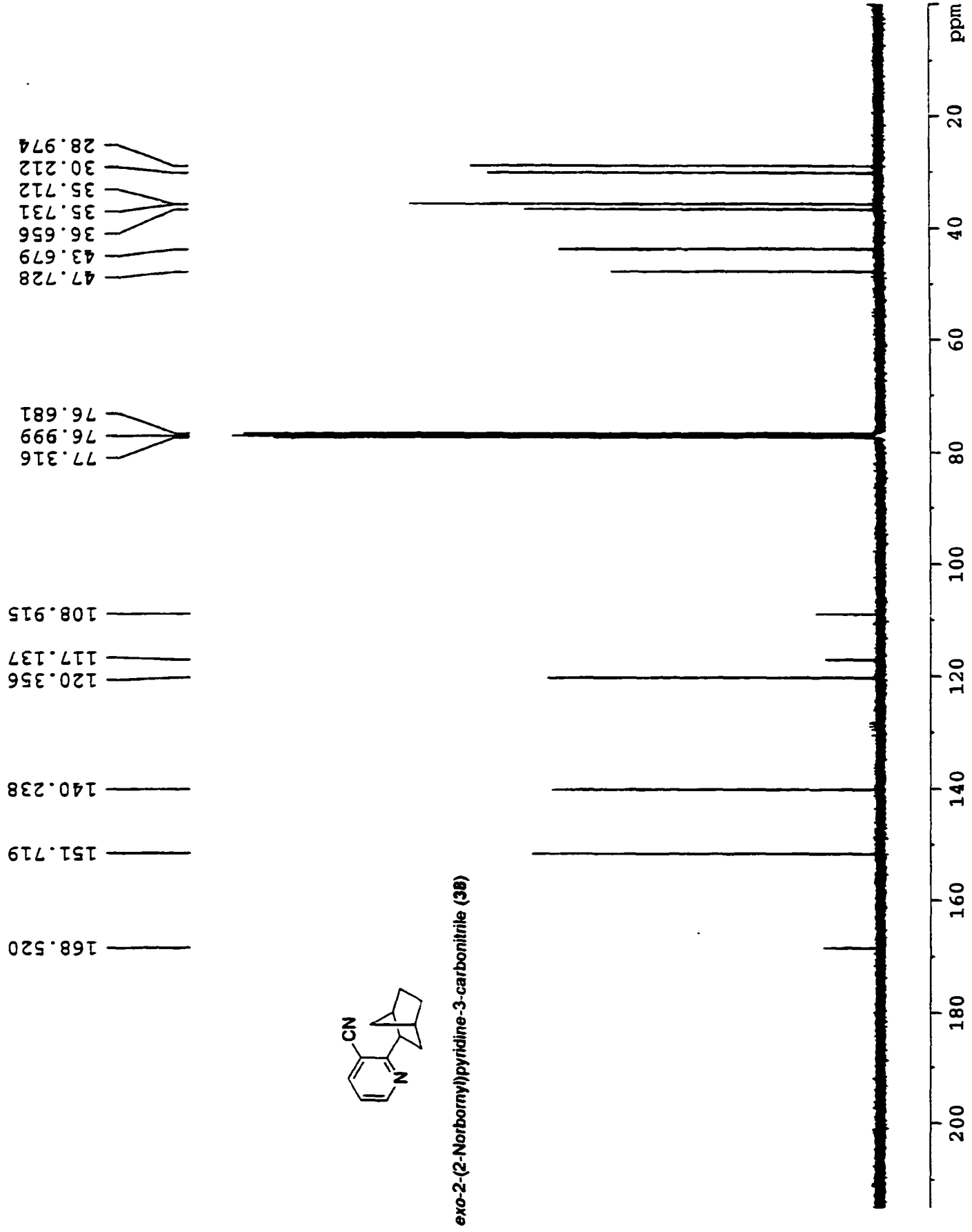

1,2,3,4,4a,6b,7,8,9,10,10a,12a-Dodecahydro-
-[1,4],[7,10]-dimethano-
-11H,12H-indeno[2,1-a]fluoren-11,12-dione (36)
O
O
7.716
7.267
7.264
3.173
3.158
2.657
2.649
2.543
2.528
2.394
2.384
2.049
1.758
1.738
1.728
1.717
1.709
1.699
1.690
1.666
1.657
1.648
1.639
1.628
1.618
1.599
1.588
1.495
1.490
1.484
1.467
2.000
1.032
2.042
2.017
2.040
4.028
4.018
1.999
1.993
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0

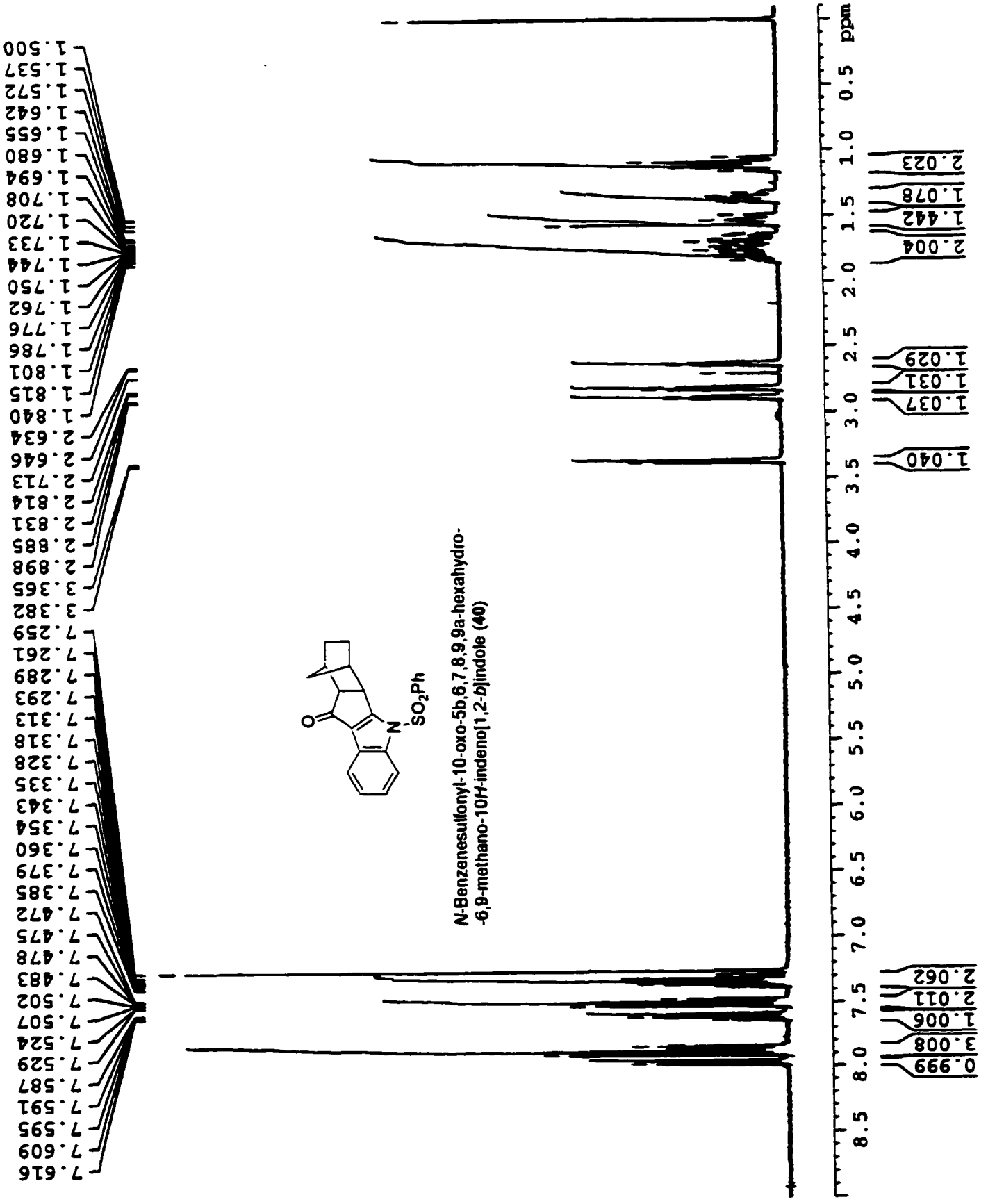

205.834
158.601
136.156
132.218
77.418
76.995
76.570
55.811
48.128
41.317
40.755
31.970
28.879
28.496
ppm
1,2,3,4,4a,6b,7,8,9,10,10a,12a-Dodecahydro-
-(1,4),(7,10)-dimethano-
-11H,12H-indeno[2,1-a]fluoren-11,12-dione (36)

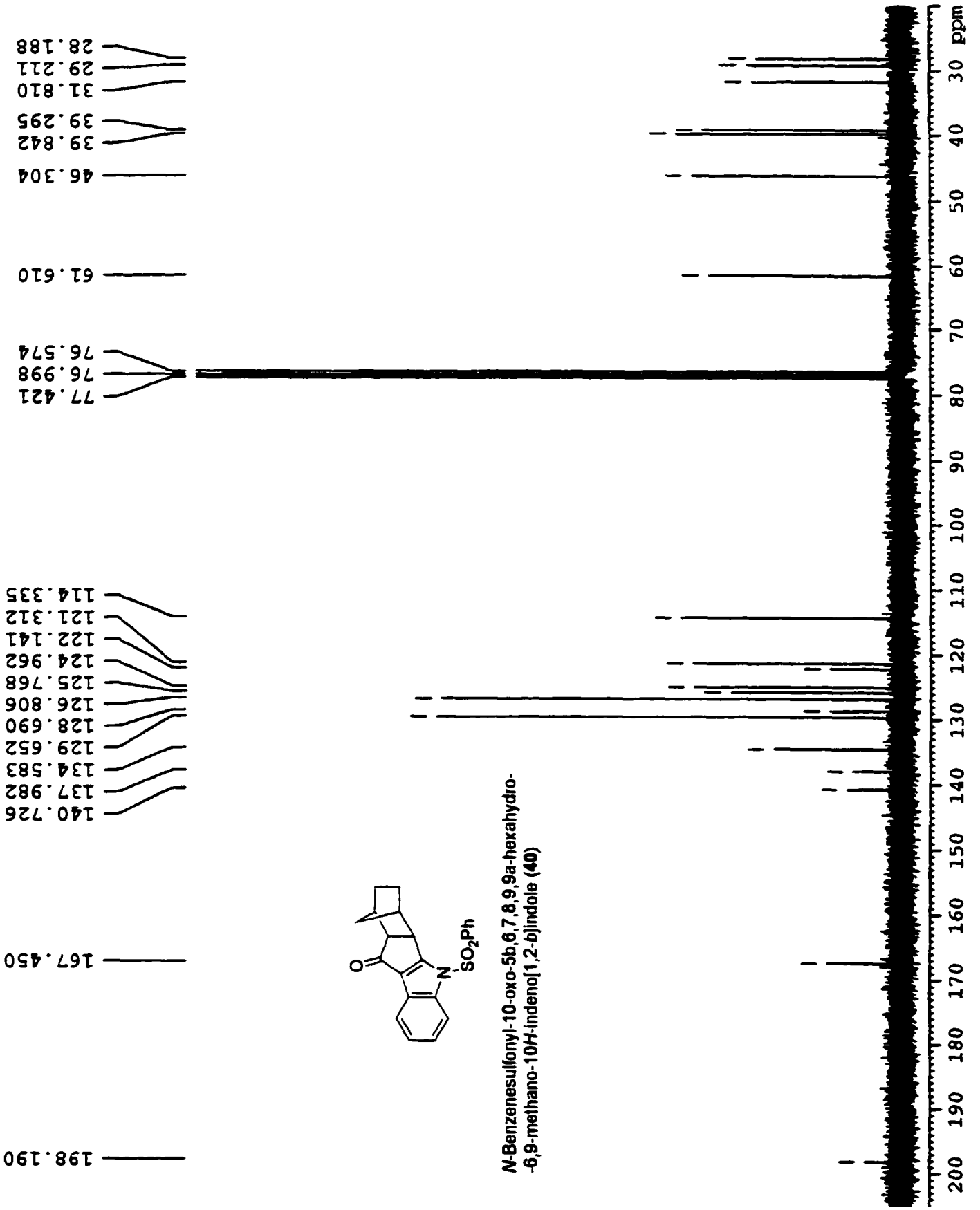

7-Aza-1,2,3,4,4a,9a-hexahydro-1,4-methano-
-fluoren-9-one (37)
O
N
ppm
1.000
1.033
1.034
1.045
1.049
1.059
1.060
2.028
2.025
1.015
1.007

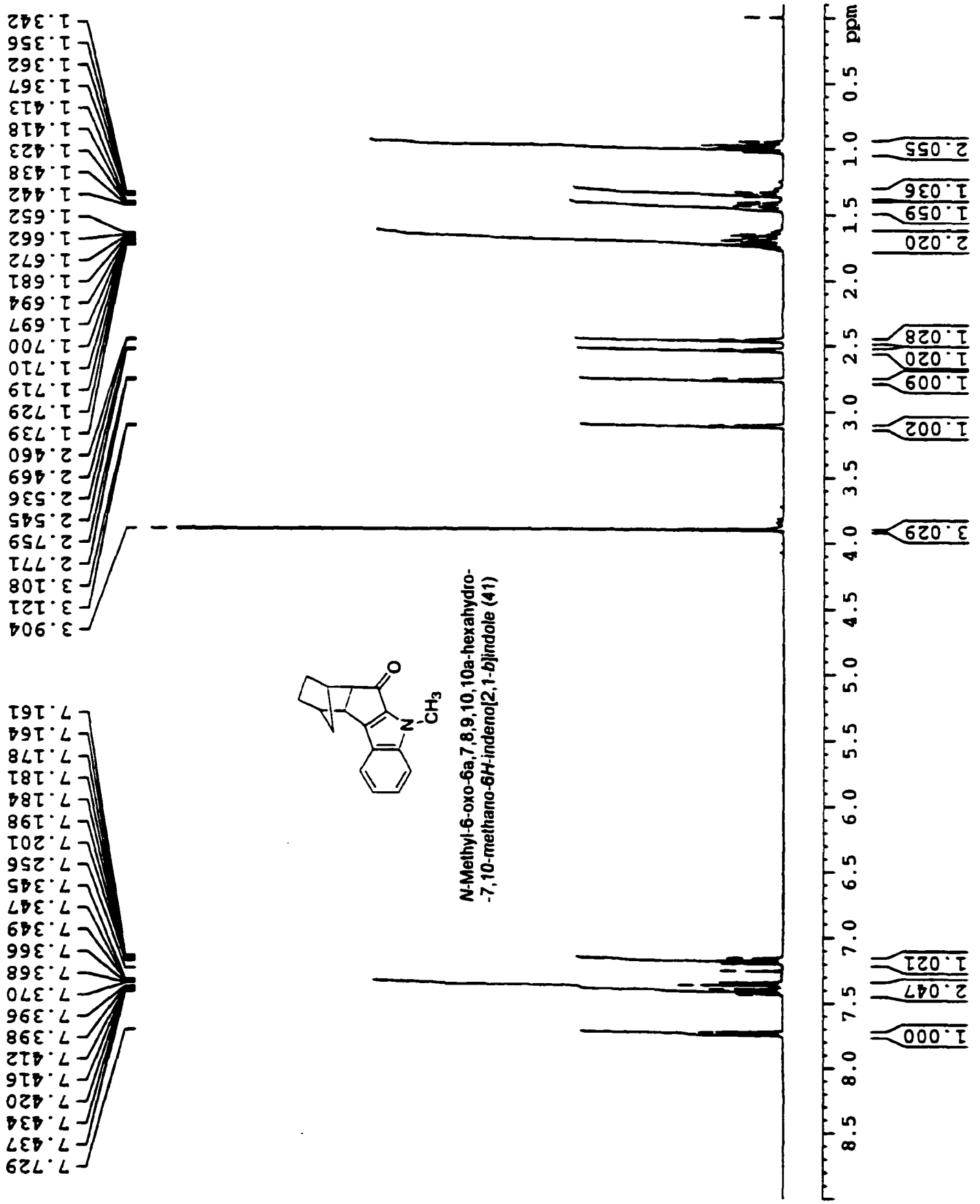

207.768
164.896
154.329
146.306
134.833
121.706
77.691
77.267
76.843
55.892
48.236
41.315
40.757
32.709
29.131
28.728
O
N
7-Aza-1,2,3,4,4a,9a-hexahydro-1,4-methano-
-fluoren-9-one (37)
200
180
160
140
120
100
80
60
40
20
0 ppm

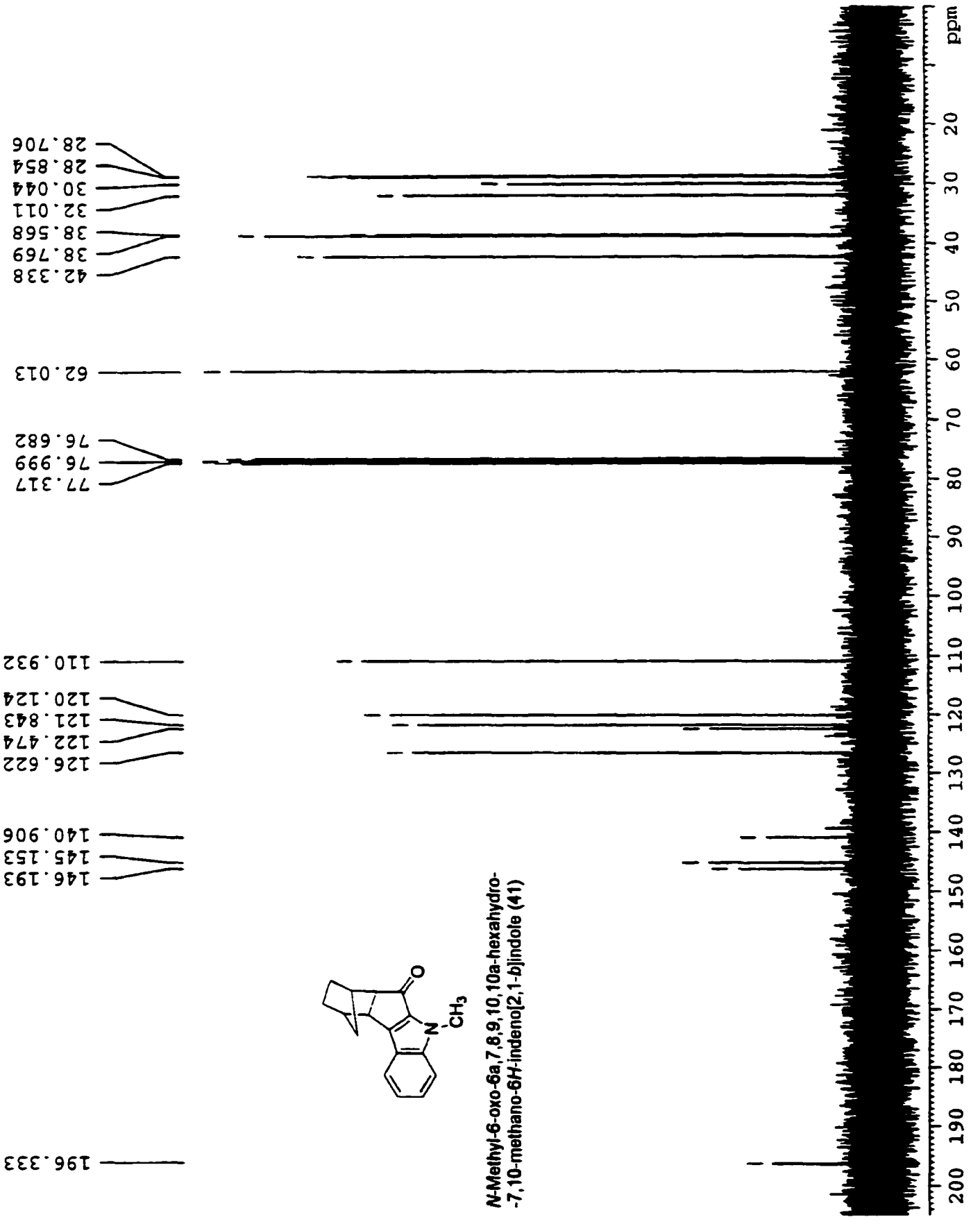

exo-2-(2-Norbornyl)pyridine-3-carbonitrile (38)
CN
N
ppm
10
9
8
7
6
5
4
3
2
1
0
−1
1.000
1.026
1.039
0.997
2.052
1.070
2.026
2.015
1.057
1.021
1.002
8.714
8.708
8.698
8.692
7.899
7.893
7.873
7.867
7.263
7.220
7.203
7.194
7.178
3.301
3.282
3.272
3.253
2.446
2.434
2.419
2.197
2.188
2.181
2.174
2.166
2.157
2.147
2.142
1.754
1.748
1.722
1.716
1.708
1.685
1.677
1.667
1.653
1.640
1.635
1.633
1.629
1.624
1.608
1.605
1.599
1.594
1.584
1.563
1.538
1.532
1.529
1.498

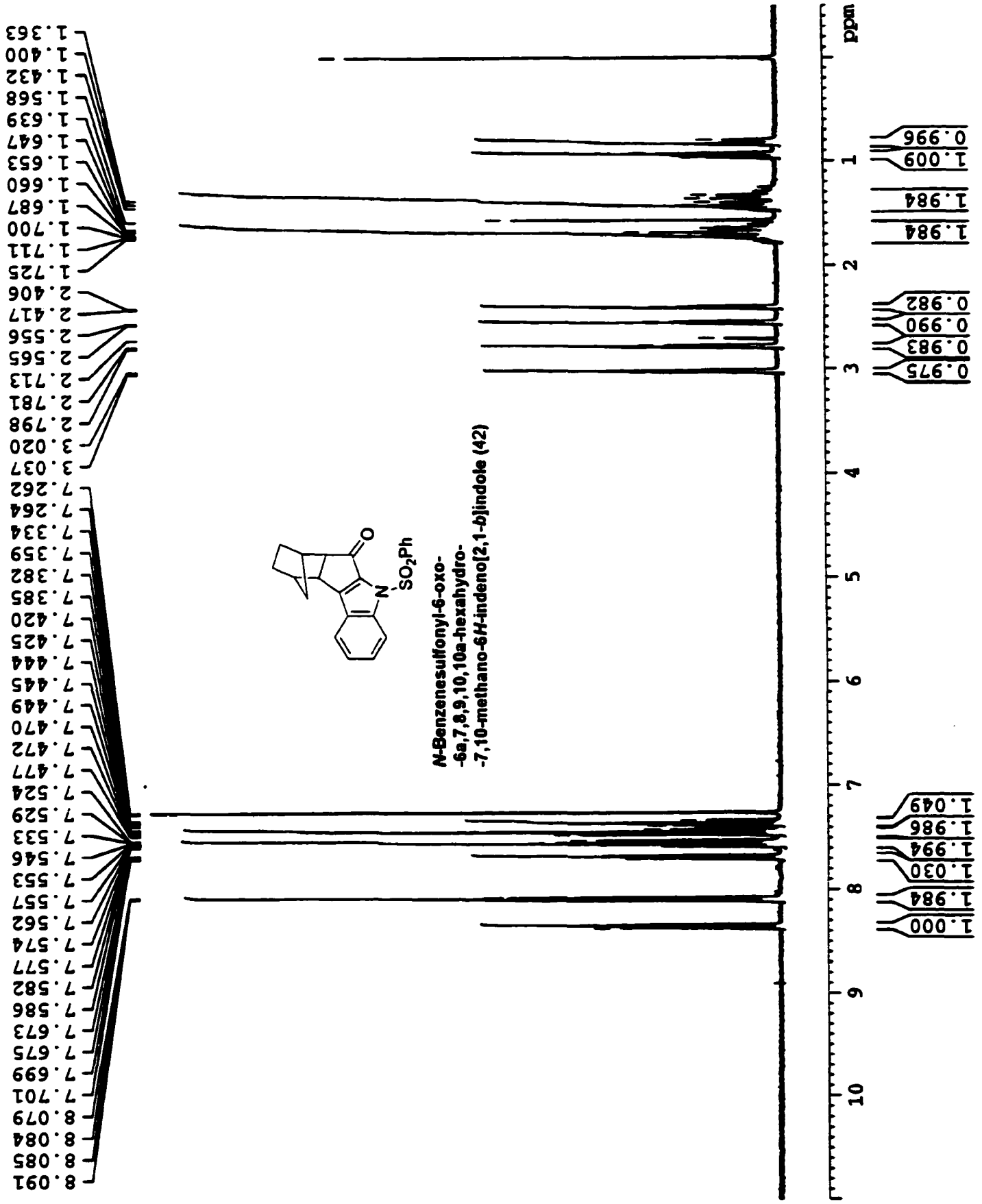

168.520
151.719
140.238
120.356
117.137
108.915
77.316
76.999
76.681
47.728
43.679
36.656
35.731
35.712
30.212
28.974
CN
N
exo-2-(2-Norbornyl)pyridine-3-carbonitrile (38)
ppm
20
40
60
80
100
120
140
160
180
200

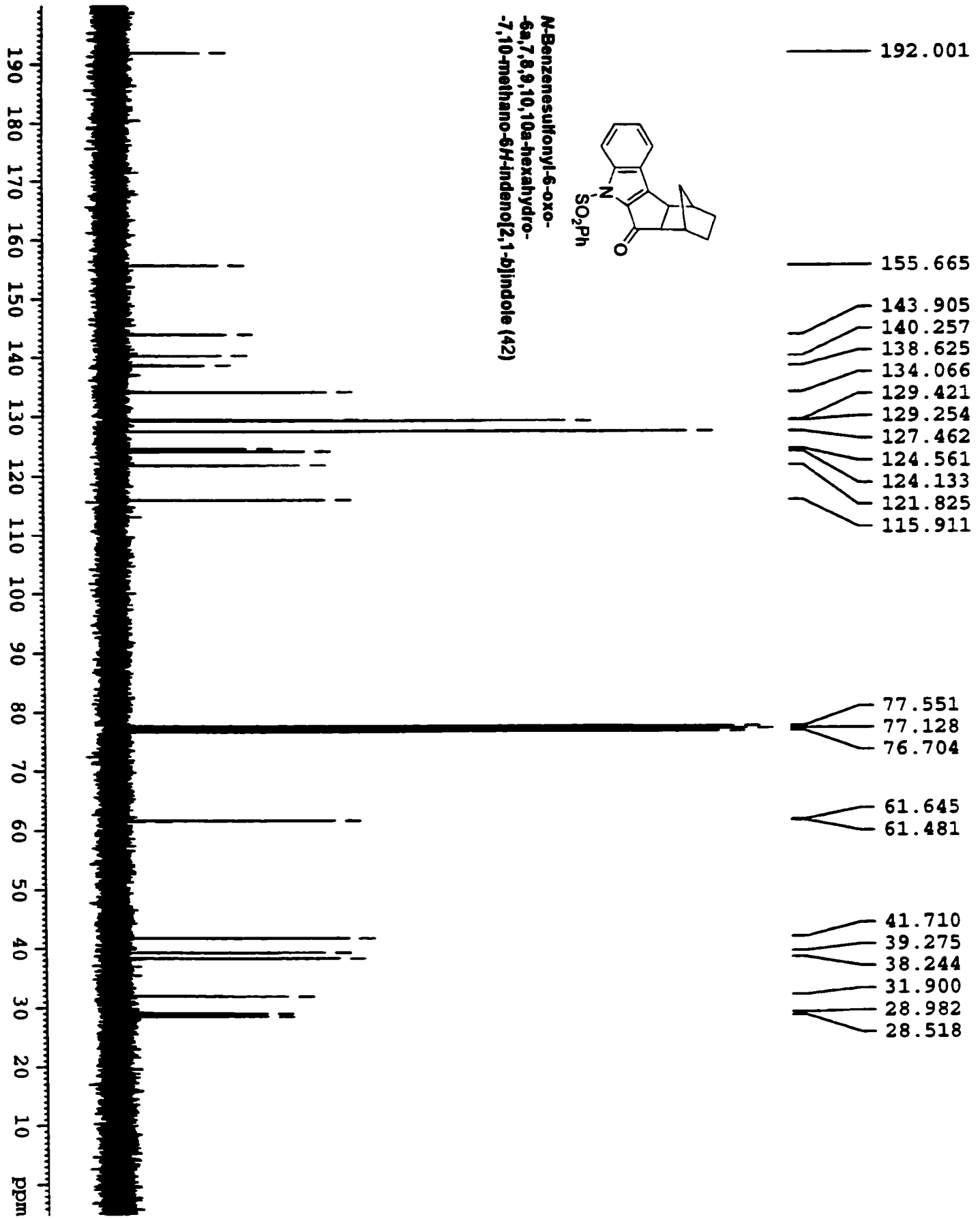

7.616
7.609
7.595
7.591
7.587
7.529
7.524
7.507
7.502
7.483
7.478
7.475
7.472
7.385
7.379
7.360
7.354
7.343
7.335
7.328
7.318
7.313
7.293
7.289
7.261
7.259
3.382
3.365
2.898
2.885
2.831
2.814
2.713
2.646
2.634
1.840
1.815
1.801
1.786
1.776
1.762
1.750
1.744
1.733
1.720
1.708
1.694
1.680
1.655
1.642
1.572
1.537
1.500
O
N
SO2Ph
N-Benzenesulfonyl-10-oxo-5b,6,7,8,9,9a-hexahydro-6,9-methano-10H-indeno[1,2-b]indole (40)
ppm
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.999
3.008
1.006
2.011
2.062
1.040
1.037
1.031
1.029
2.004
1.442
1.078
2.023

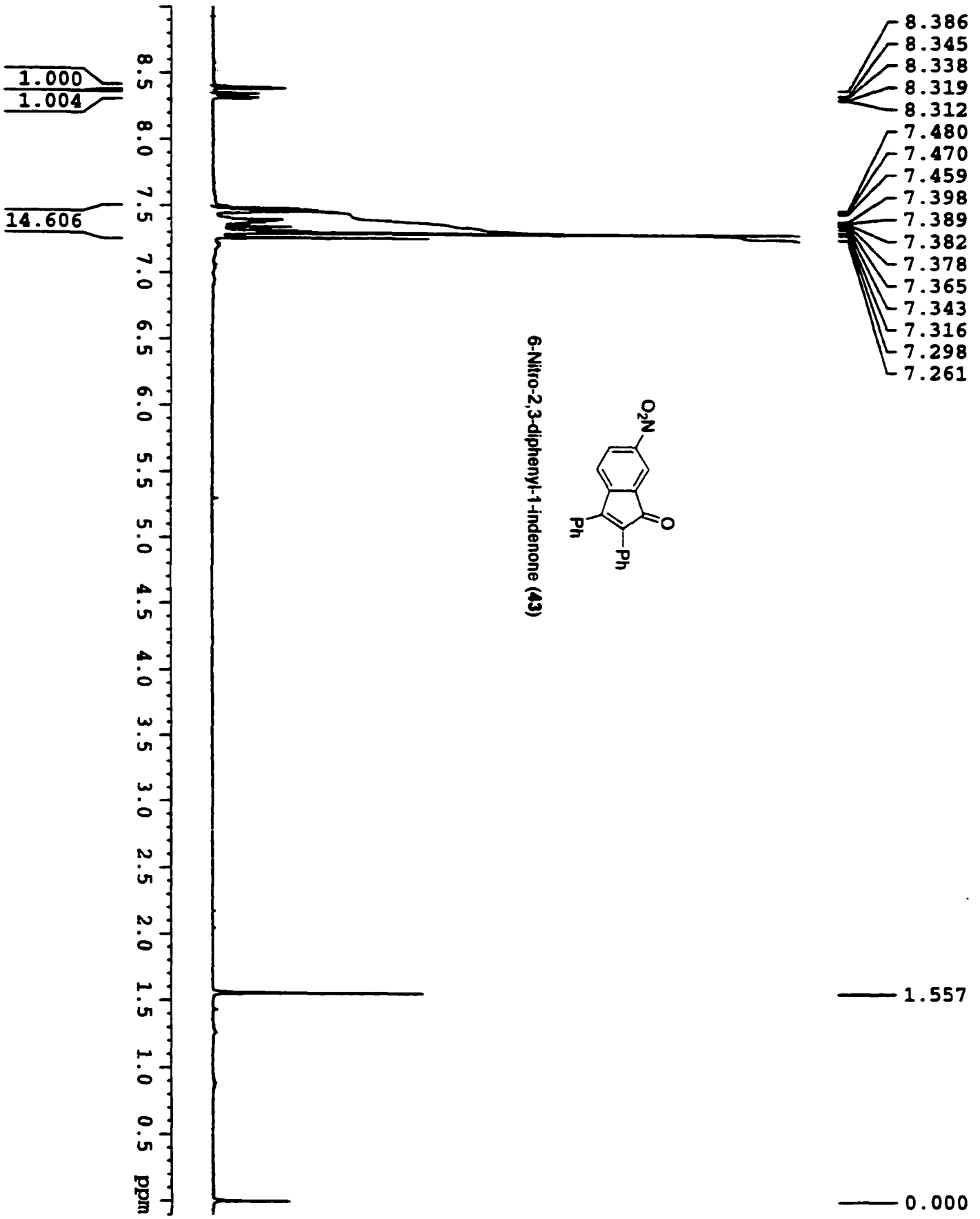

28.188
29.211
31.810
39.295
39.842
46.304
61.610
76.574
76.998
77.421
114.335
121.312
122.141
124.962
125.768
126.806
128.690
129.652
134.583
137.982
140.726
167.450
198.190
O
N
SO2Ph
N-Benzenesulfonyl-10-oxo-5b,6,7,8,9,9a-hexahydro-6,9-methano-10H-indeno[1,2-b]indole (40)
ppm
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200


1.342
1.356
1.362
1.367
1.413
1.418
1.423
1.438
1.442
1.652
1.662
1.672
1.681
1.694
1.697
1.700
1.710
1.719
1.729
1.739
2.460
2.469
2.536
2.545
2.759
2.771
3.108
3.121
3.904
7.161
7.164
7.178
7.181
7.184
7.198
7.201
7.256
7.345
7.347
7.349
7.366
7.368
7.370
7.396
7.398
7.412
7.416
7.420
7.434
7.437
7.729
O
N
CH3
N-Methyl-6-oxo-6a,7,8,9,10,10a-hexahydro-
-7,10-methano-6H-indeno[2,1-b]indole (41)
ppm
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.000
2.047
1.021
3.029
1.002
1.009
1.020
1.028
2.020
1.059
1.036
2.055

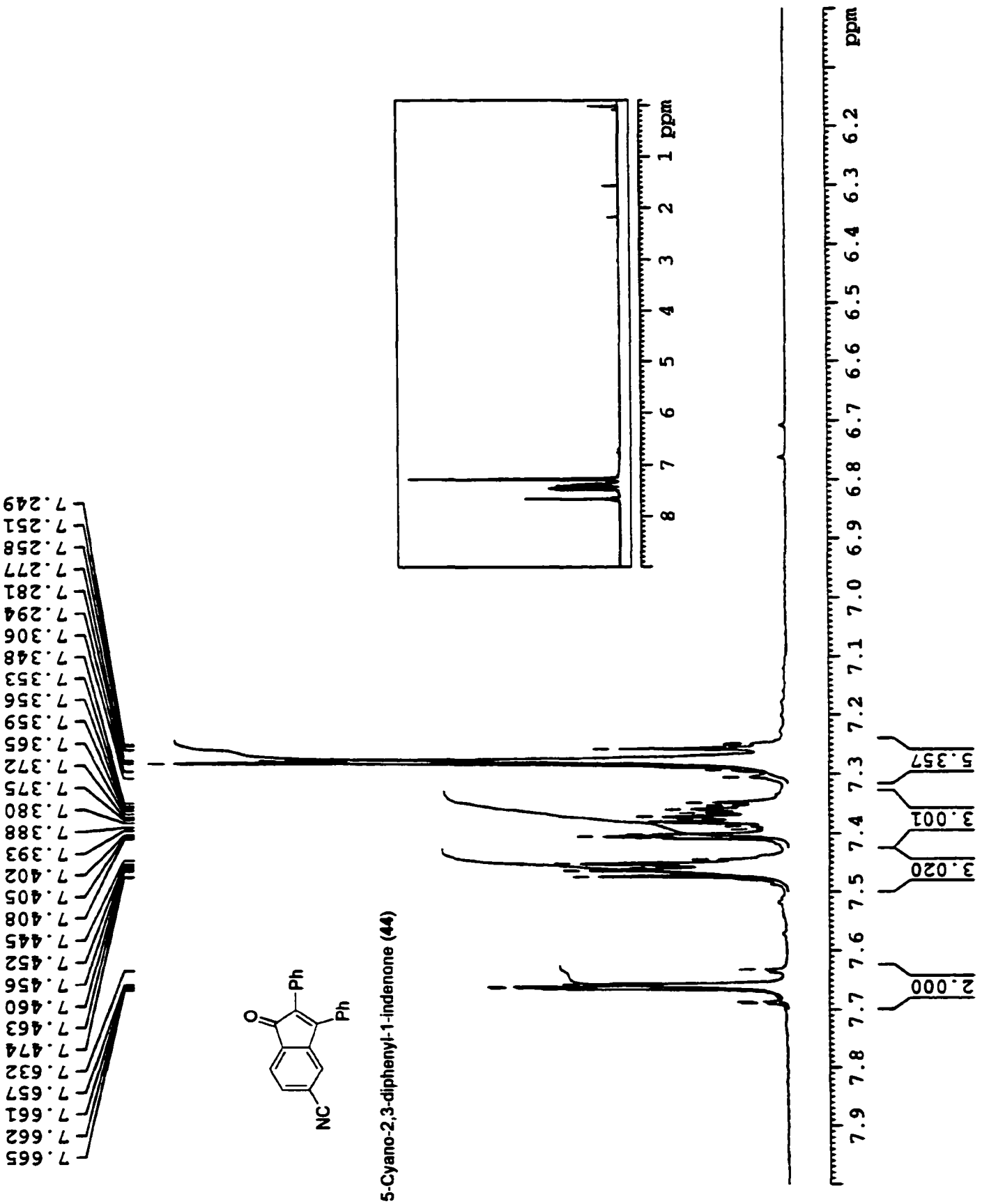

28.706
28.854
30.044
32.011
38.568
38.769
42.338
62.013
76.682
76.999
77.317
110.932
120.124
121.843
122.474
126.622
140.906
145.153
146.193
196.333
O
N
CH3
N-Methyl-6-oxo-6a,7,8,9,10,10a-hexahydro-
-7,10-methano-6H-indeno[2,1-b]indole (41)
ppm
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20


N-Benzenesulfonyl-6-oxo-
-6a,7,8,9,10,10a-hexahydro-
-7,10-methano-6H-indeno[2,1-b]indole (42)
SO2Ph
O
N
ppm
1.363
1.400
1.432
1.568
1.639
1.647
1.653
1.660
1.687
1.700
1.711
1.725
2.406
2.417
2.556
2.565
2.713
2.781
2.798
3.020
3.037
7.262
7.264
7.334
7.359
7.382
7.385
7.420
7.425
7.444
7.445
7.449
7.470
7.472
7.477
7.524
7.529
7.533
7.546
7.553
7.557
7.562
7.574
7.577
7.582
7.586
7.673
7.675
7.699
7.701
8.079
8.084
8.085
8.091
0.996
1.009
1.984
1.984
0.975
0.983
0.990
0.982
1.049
1.986
1.994
1.030
1.984
1.000

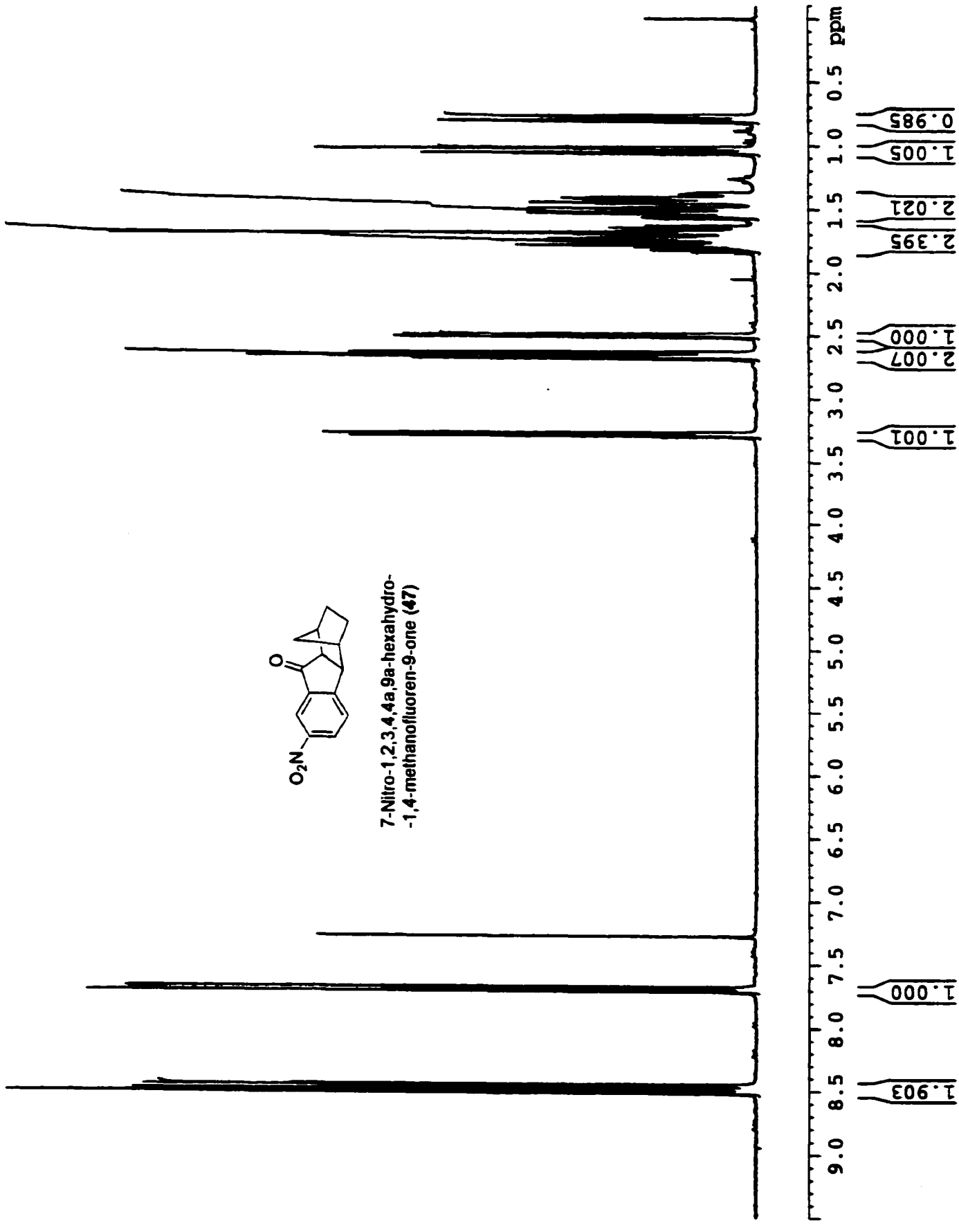

N-Benzenesulfonyl-6-oxo-6a,7,8,9,10,10a-hexahydro-7,10-methano-6H-indeno[2,1-b]indole (42)
SO2Ph
O
192.001
155.665
143.905
140.257
138.625
134.066
129.421
129.254
127.462
124.561
124.133
121.825
115.911
77.551
77.128
76.704
61.645
61.481
41.710
39.275
38.244
31.900
28.982
28.518
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

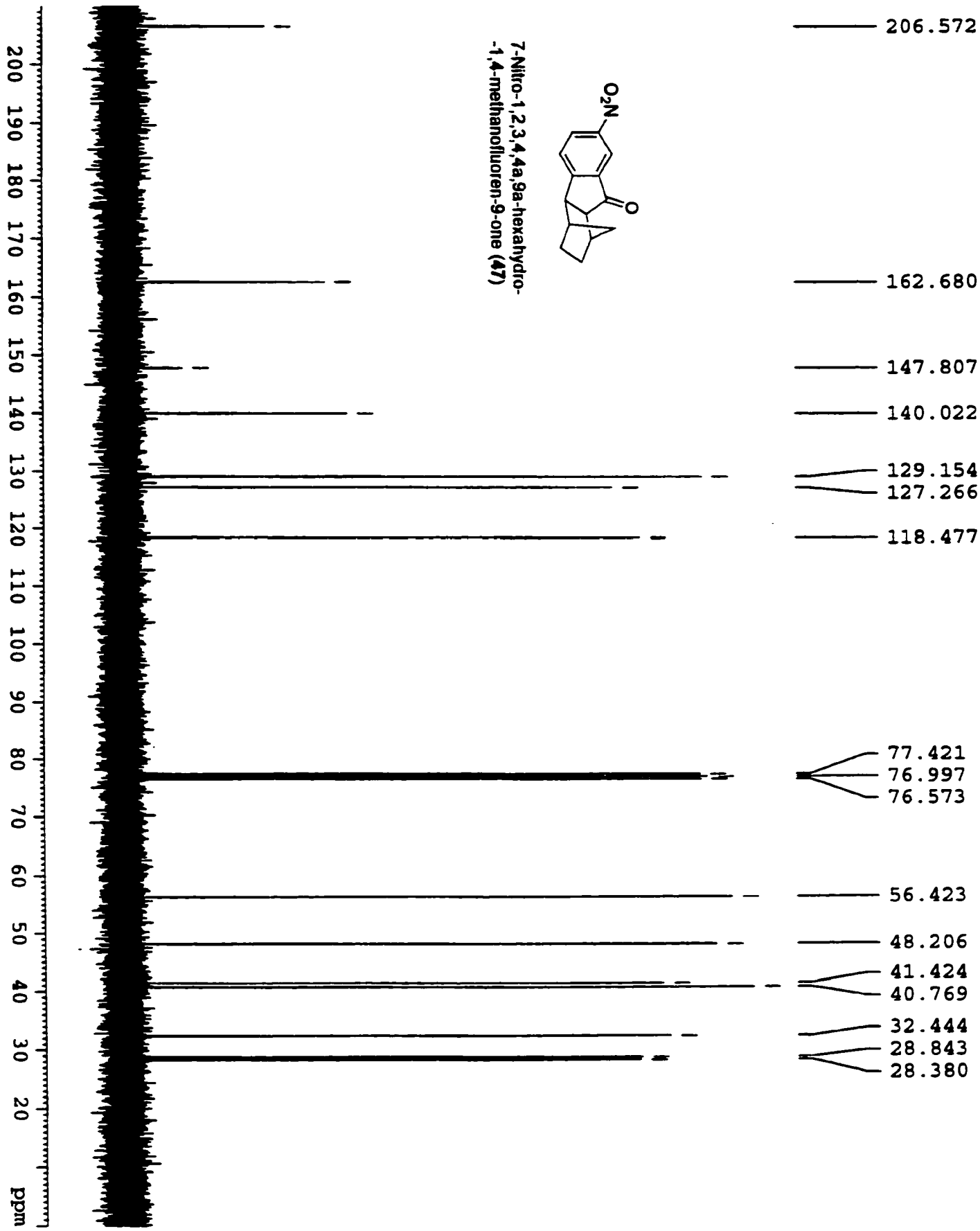

8.386
8.345
8.338
8.319
8.312
7.480
7.470
7.459
7.398
7.389
7.382
7.378
7.365
7.343
7.316
7.298
7.261
1.000
1.004
14.606
1.557
0.000
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
6-Nitro-2,3-diphenyl-1-indenone (43)
O2N
Ph
Ph
O

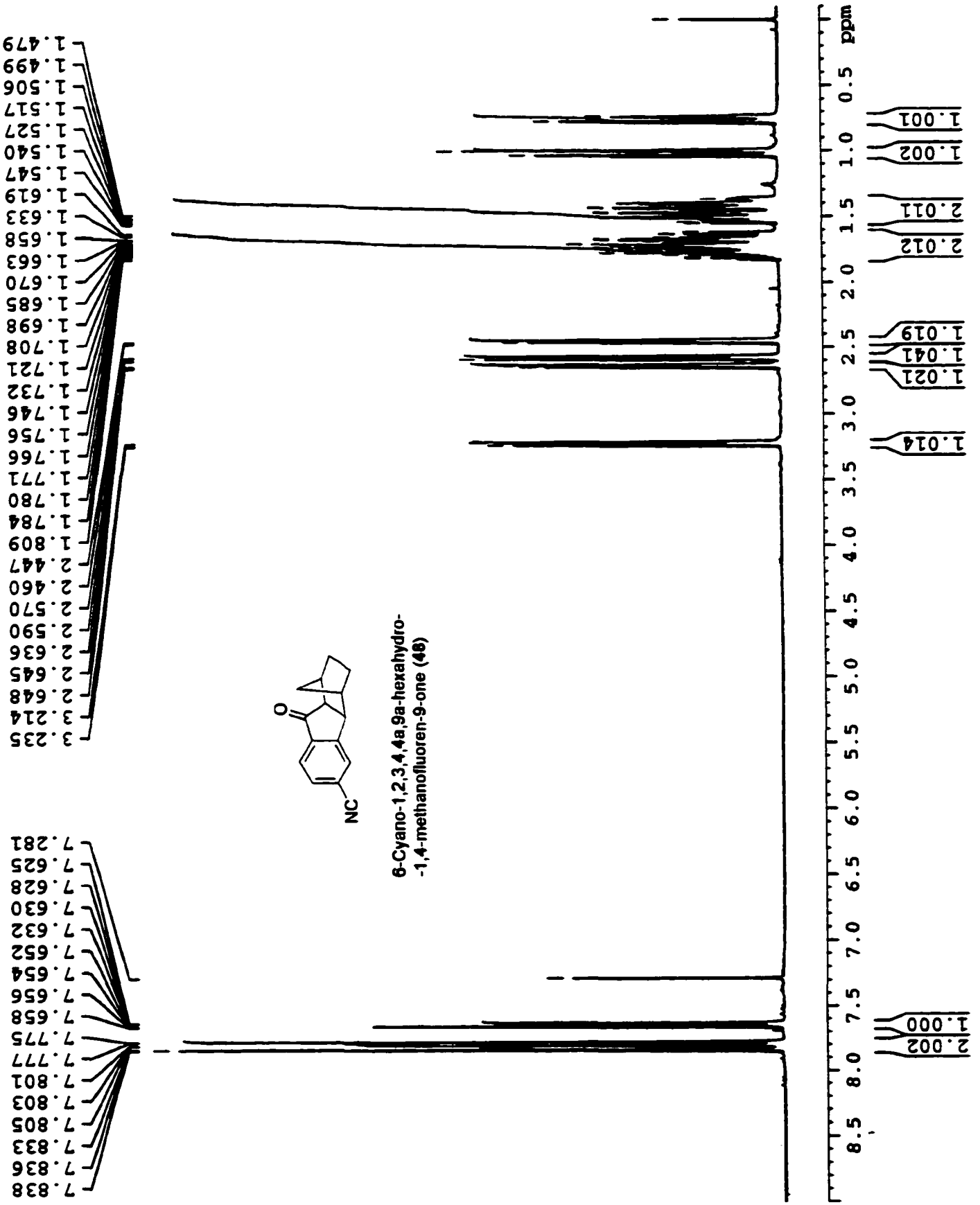
6-Nitro-2,3-diphenyl-1-indenone (43)
O2N
Ph
Ph
O
193.420
153.870
151.137
148.643
136.178
131.685
131.615
129.987
129.647
129.273
129.170
128.709
128.366
128.308
121.279
117.867
77.424
77.204
77.001
76.577
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
ppm

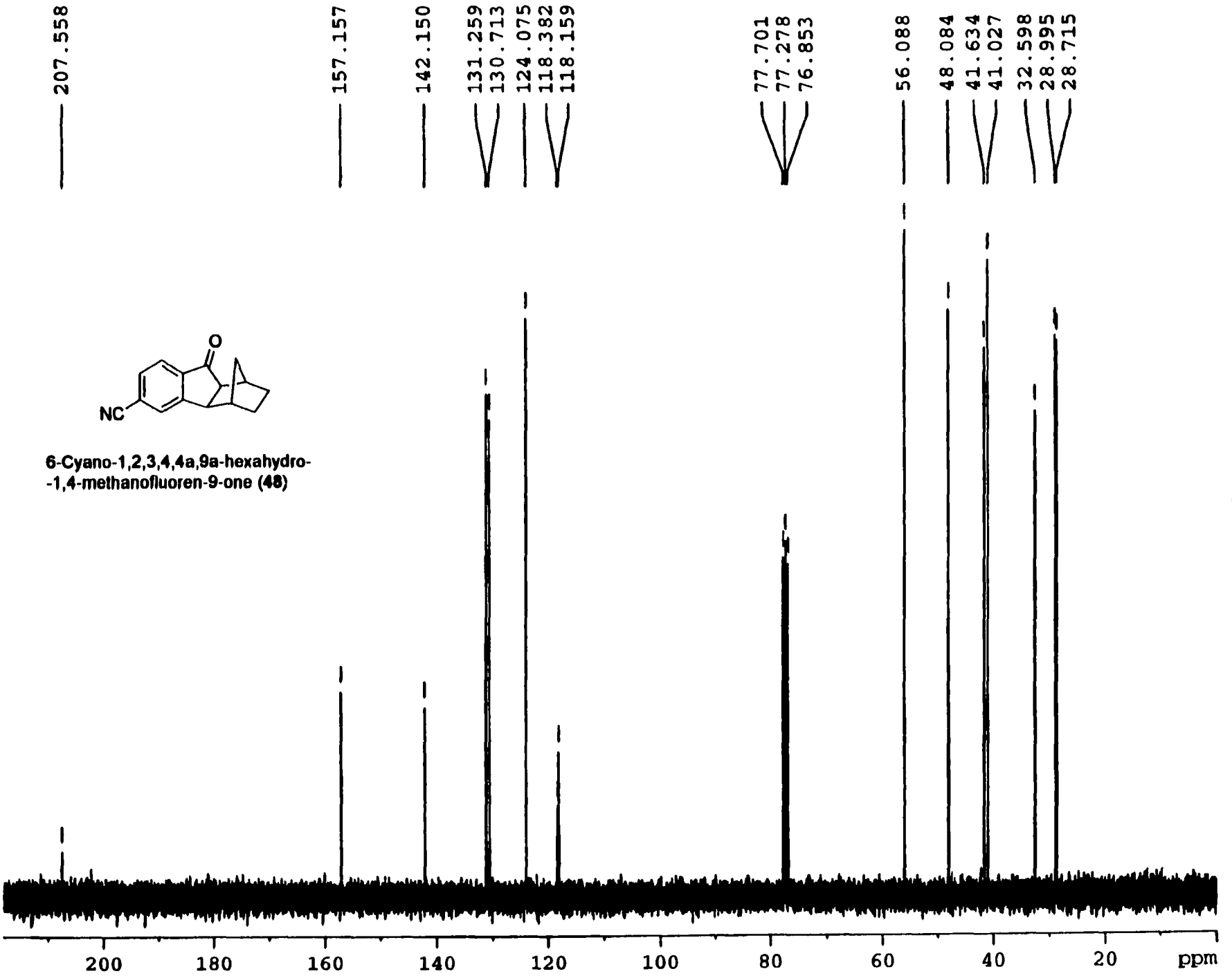

7.665
7.662
7.661
7.657
7.632
7.474
7.463
7.460
7.456
7.452
7.445
7.408
7.405
7.402
7.393
7.388
7.380
7.375
7.372
7.365
7.359
7.356
7.353
7.348
7.306
7.294
7.281
7.277
7.258
7.251
7.249
Ph
Ph
O
NC
5-Cyano-2,3-diphenyl-1-indenone (44)
8 7 6 5 4 3 2 1 ppm
7.9 7.8 7.7 7.6 7.5 7.4 7.3 7.2 7.1 7.0 6.9 6.8 6.7 6.6 6.5 6.4 6.3 6.2 ppm
2.000
3.020
3.001
5.357

5-Cyano-2,3-diphenyl-1-indenone (44)
NC
Ph
Ph
O
194.551
154.419
146.006
133.933
133.841
133.756
131.600
130.021
129.936
129.738
129.168
128.929
128.498
128.424
128.374
128.270
128.256
123.586
122.939
118.151
116.620
77.424
77.000
76.576
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm

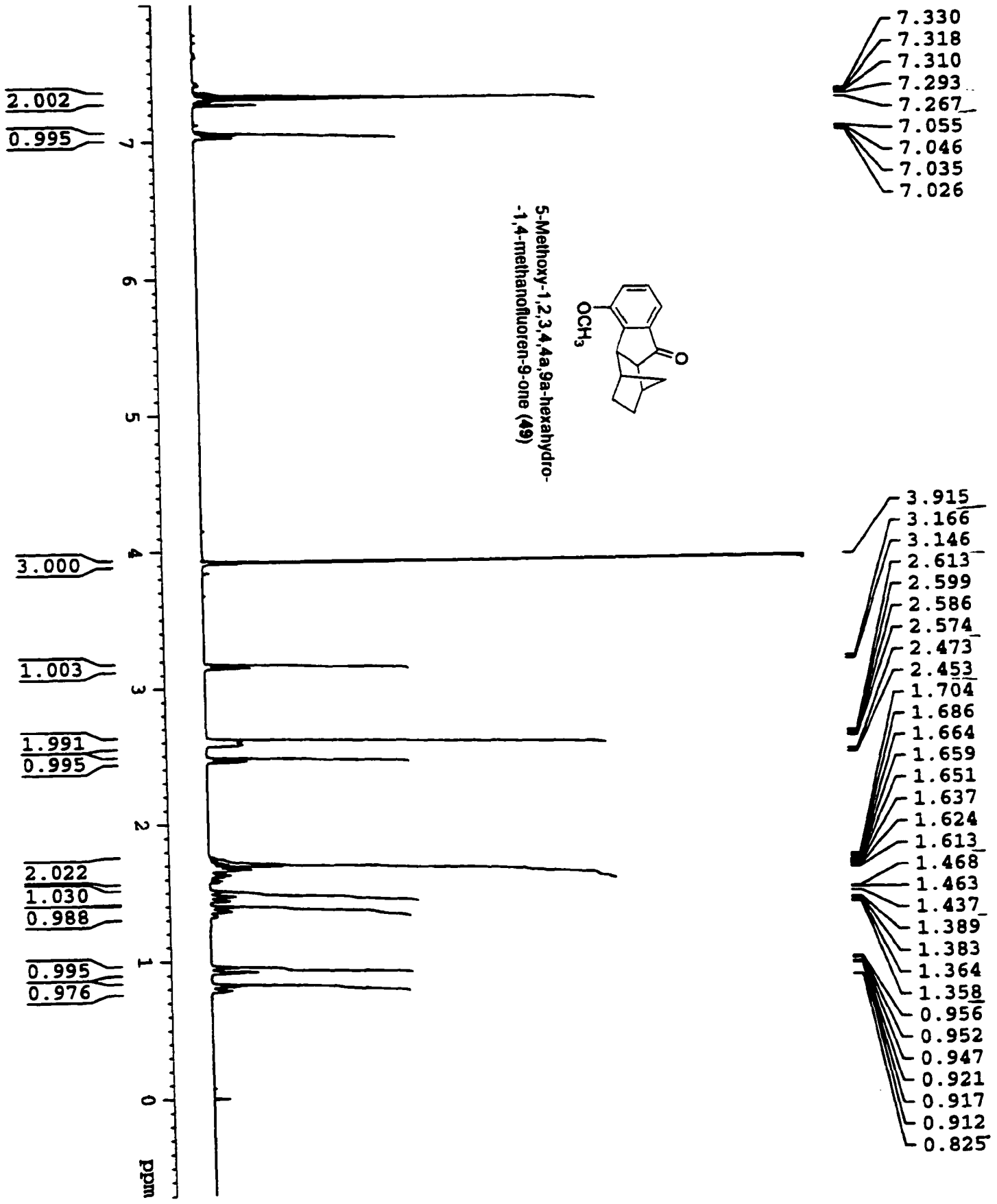

7-Nitro-1,2,3,4,4a,9a-hexahydro-
-1,4-methanofluoren-9-one (47)
O
O2N
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.903
1.000
1.001
2.007
1.000
2.395
2.021
1.005
0.985

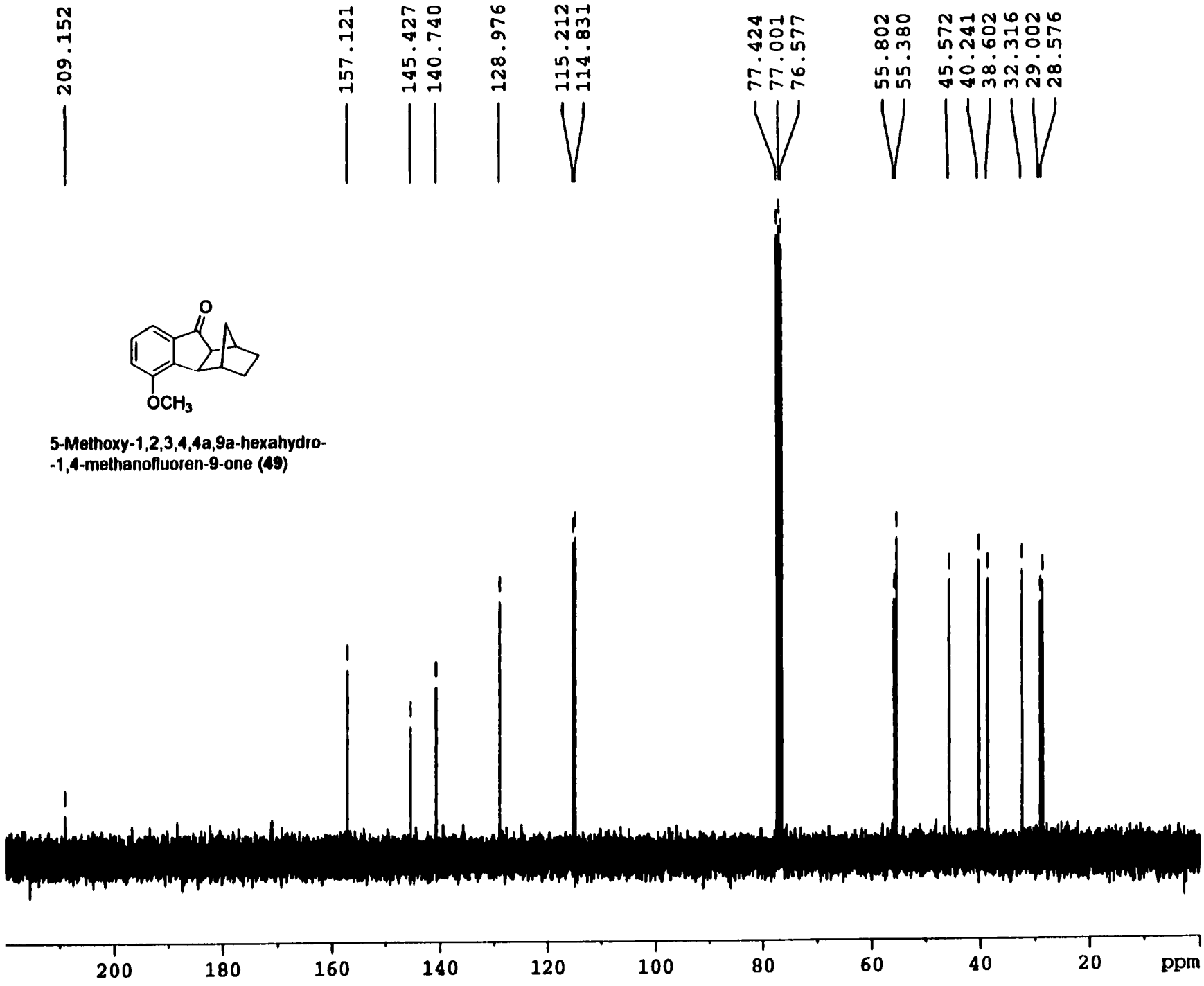

7-Nitro-1,2,3,4,4a,9a-hexahydro-
-1,4-methanofluoren-9-one (47)
O2N
O
206.572
162.680
147.807
140.022
129.154
127.266
118.477
77.421
76.997
76.573
56.423
48.206
41.424
40.769
32.444
28.843
28.380
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


6-Cyano-1,2,3,4,4a,9a-hexahydro-
-1,4-methanofluoren-9-one (48)
NC
O
ppm

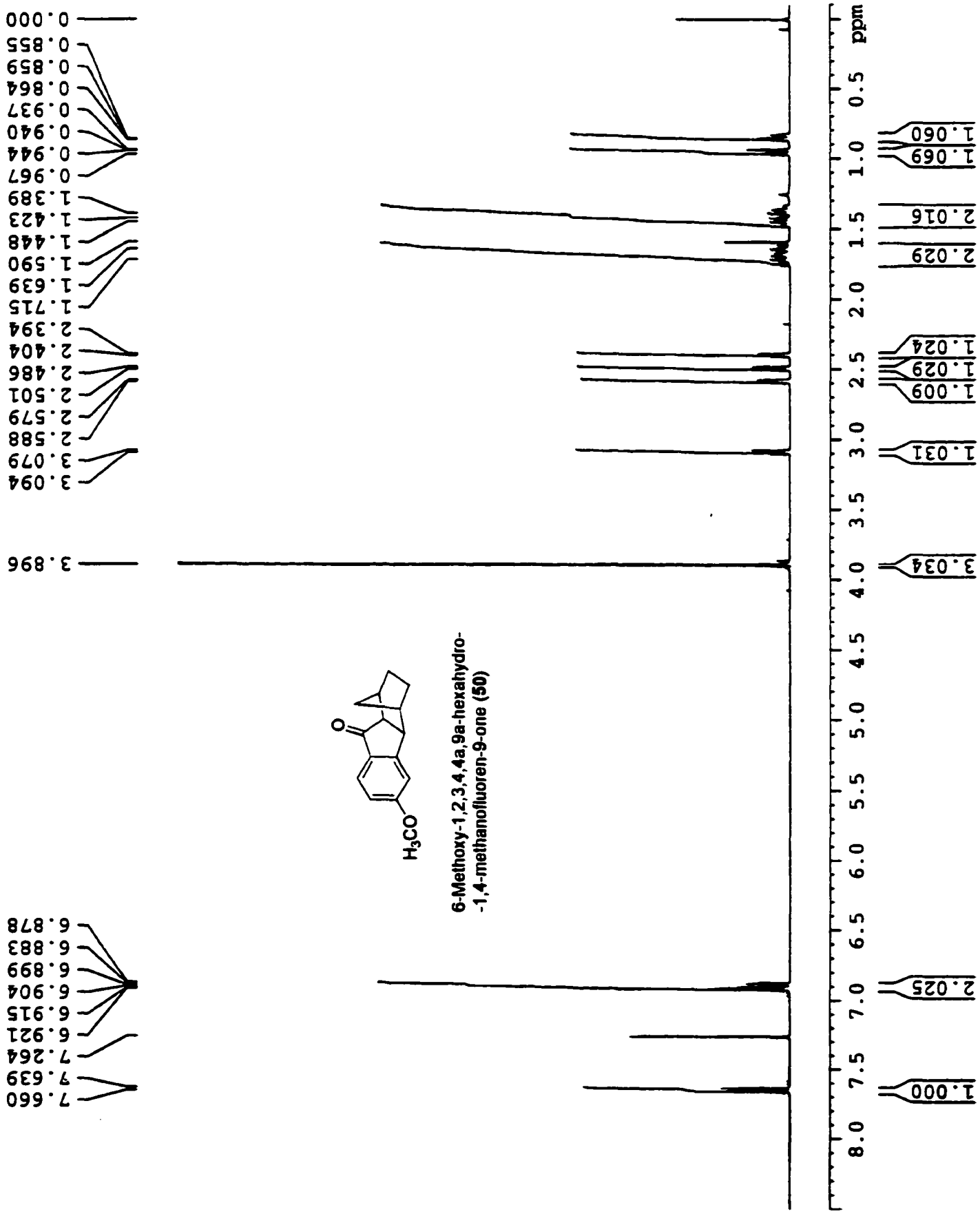


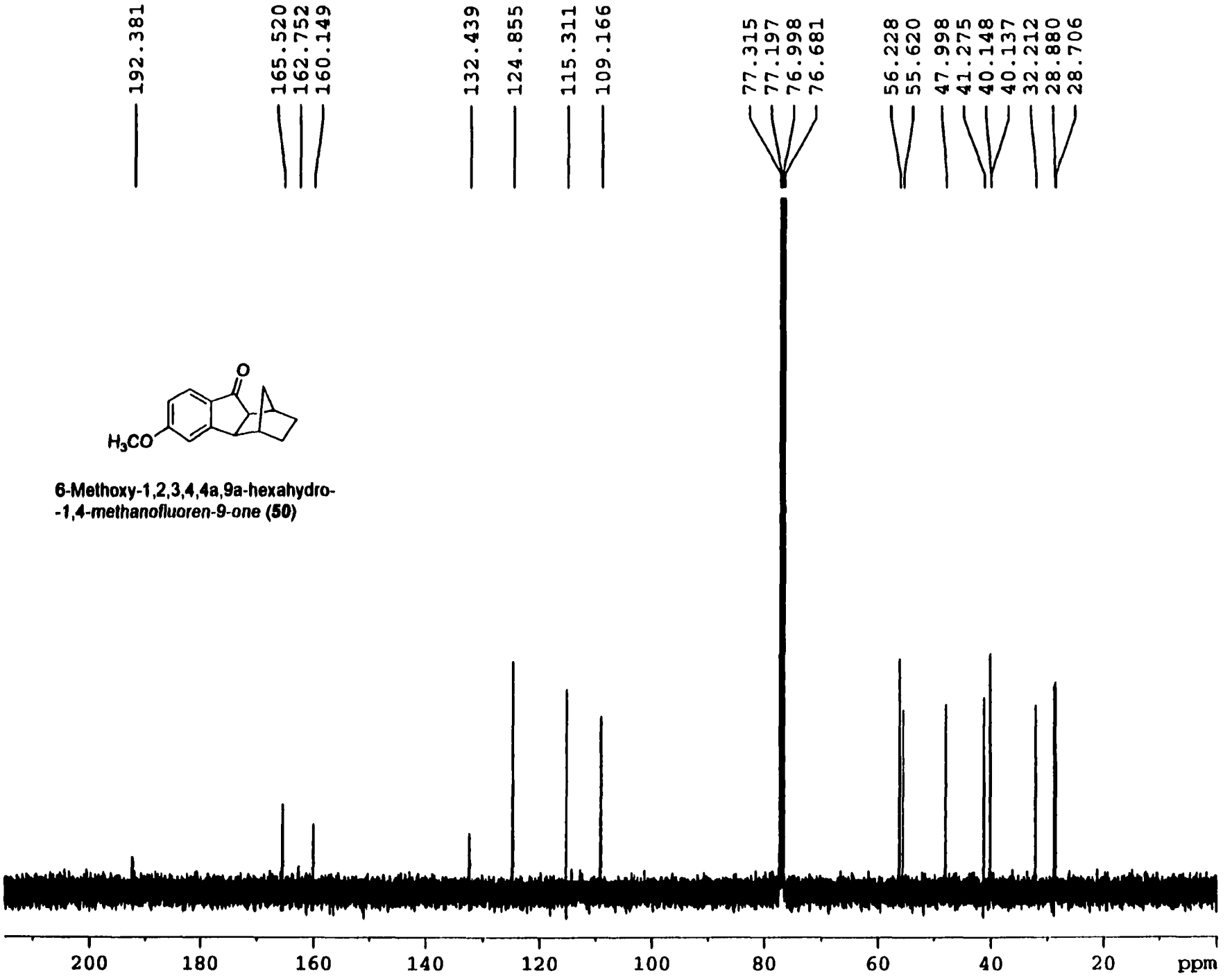

6-Cyano-1,2,3,4,4a,9a-hexahydro-
-1,4-methanofluoren-9-one (**48**)


5-Methoxy-1,2,3,4,4a,9a-hexahydro-
-1,4-methanofluoren-9-one (49)
OCH3
O
ppm
2.002
0.995
3.000
1.003
1.991
0.995
2.022
1.030
0.988
0.995
0.976
7.330
7.318
7.310
7.293
7.267
7.055
7.046
7.035
7.026
3.915
3.166
3.146
2.613
2.599
2.586
2.574
2.473
2.453
1.704
1.686
1.664
1.659
1.651
1.637
1.624
1.613
1.468
1.463
1.437
1.389
1.383
1.364
1.358
0.956
0.952
0.947
0.921
0.917
0.912
0.825




5-Methoxy-1,2,3,4,4a,9a-hexahydro-
-1,4-methanofluoren-9-one (**49**)


6-Methoxy-1,2,3,4,4a,9a-hexahydro-
-1,4-methanofluoren-9-one (50)
H3CO
O
ppm

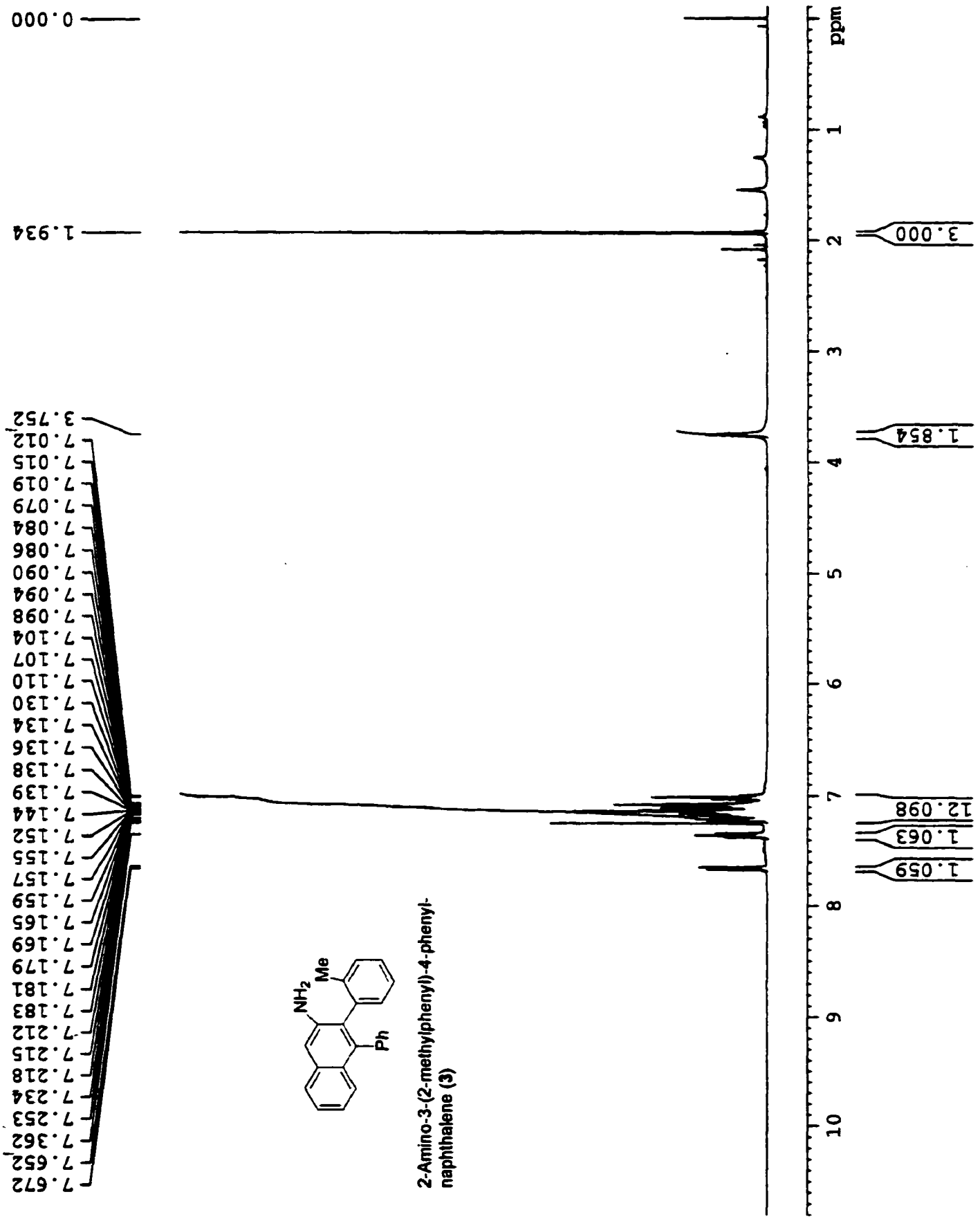



**6-Methoxy-1,2,3,4,4a,9a-hexahydro-**
**-1,4-*methanofluoren*-9-*one* (*50*)**

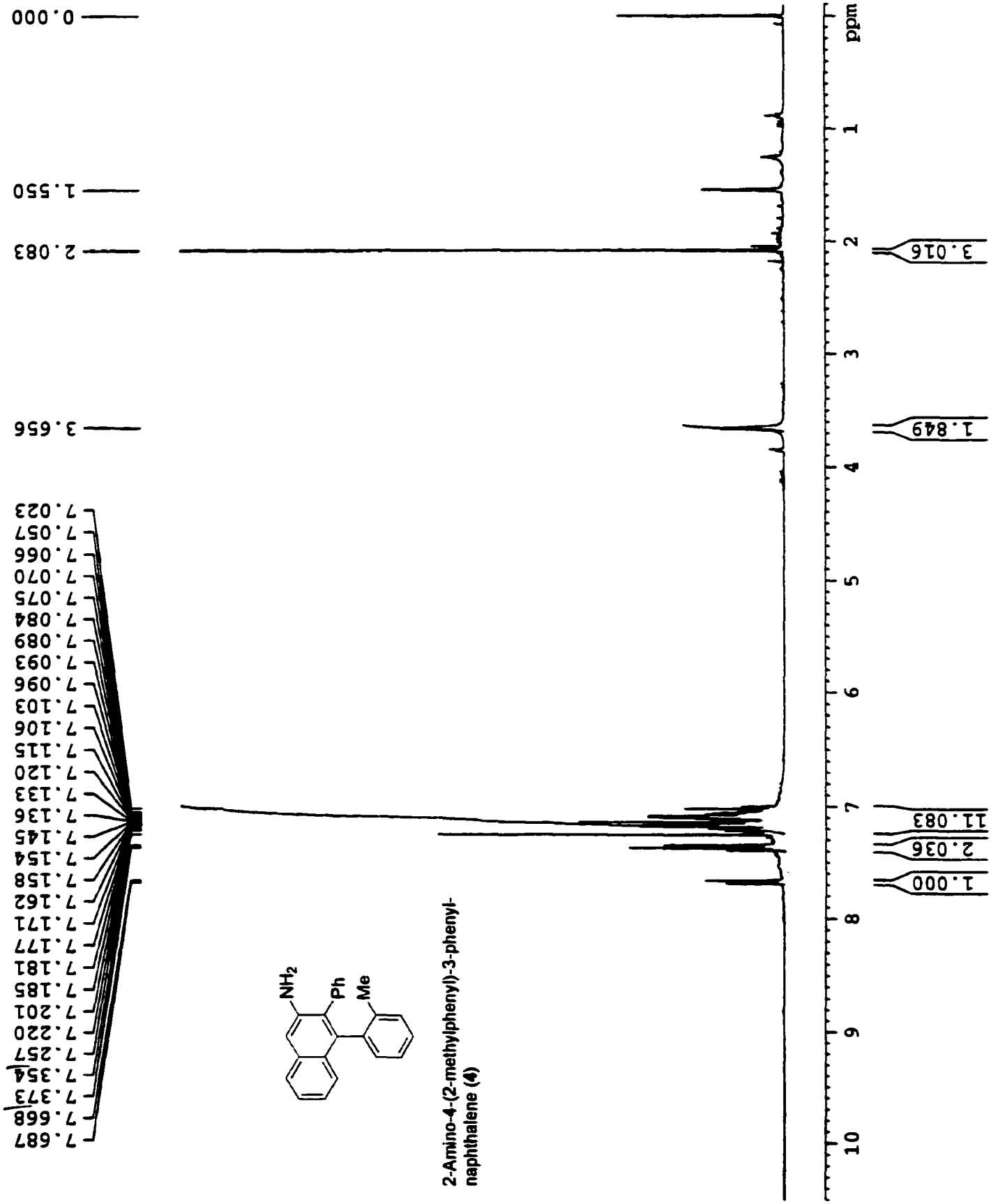
# APPENDIX B. CHAPTER 2 $^{1}H$ AND $^{13}C$ NMR SPECTRA

7.654
7.634
7.404
7.383
7.353
7.258
7.123
7.116
7.105
7.045
7.040
7.025
7.023
7.009
7.003
6.790
6.785
6.774
6.768
6.758
6.753
3.783
3.765
3.758
1.559
0.000
1.000
2.066
2.040
3.995
4.015
7.936
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2-Amino-3,4-di(4-methoxyphenyl)naphthalene (2)
OMe
NH2
OMe

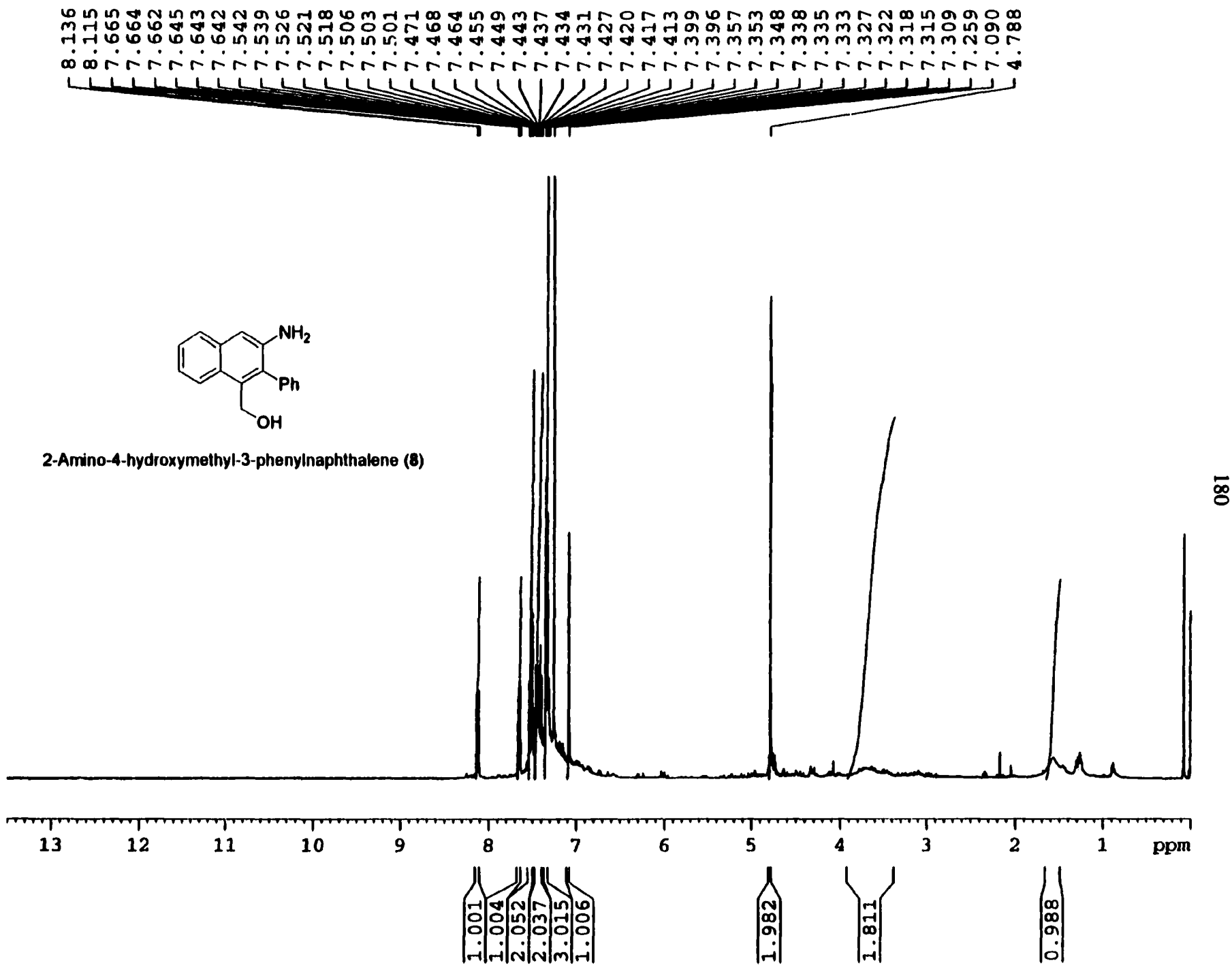
2-Amino-3,4-di(4-methoxyphenyl)naphthalene (2)
OMe
OMe
NH2
158.207
157.898
142.731
139.683
134.310
131.867
131.630
131.553
129.802
127.636
126.941
125.983
125.498
122.257
113.764
112.926
107.983
77.316
76.999
76.681
55.107
200
180
160
140
120
100
80
60
40
20
ppm

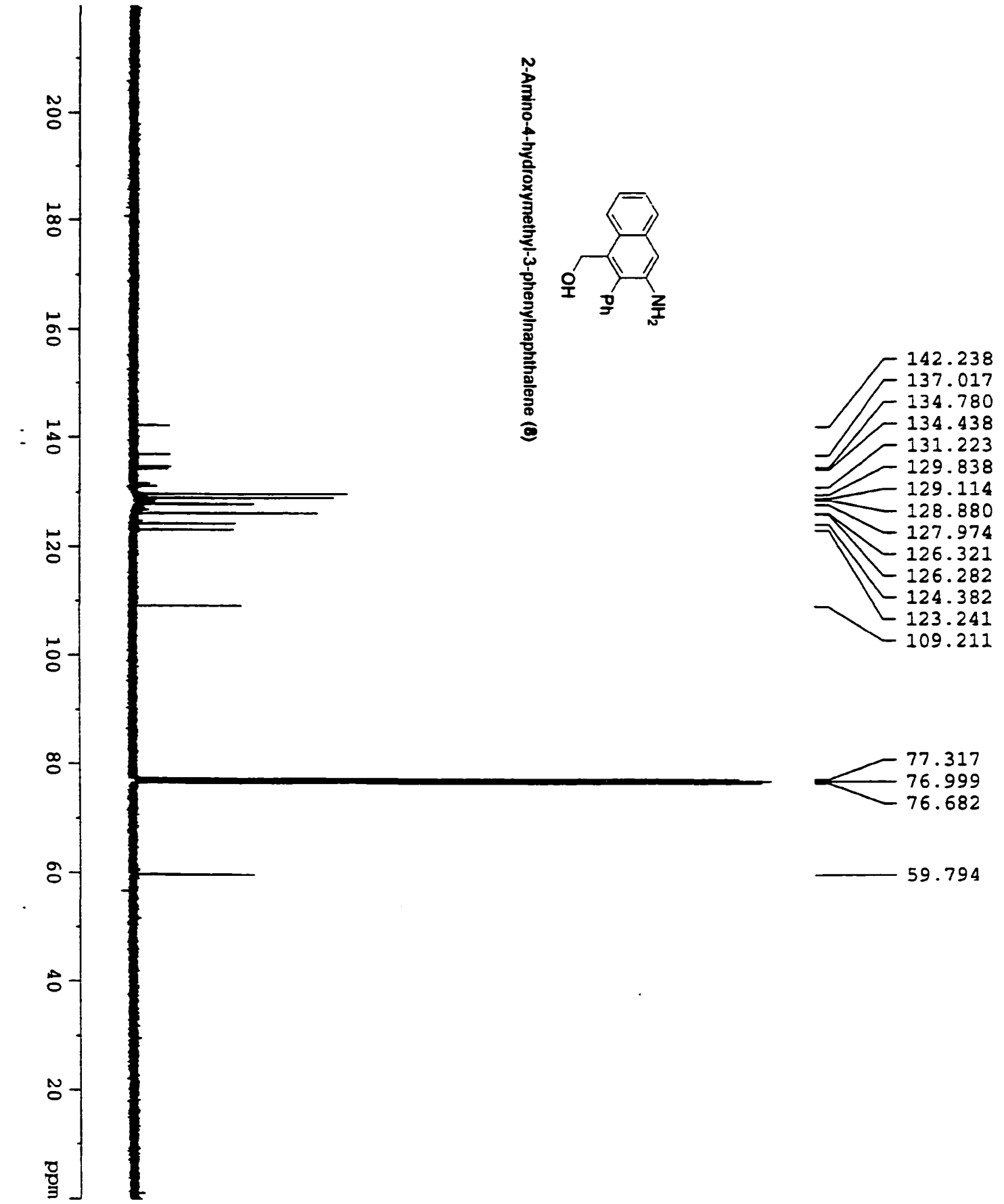

0.000
1.934
3.752
7.012
7.015
7.019
7.079
7.084
7.086
7.090
7.094
7.098
7.104
7.107
7.110
7.130
7.134
7.136
7.138
7.139
7.144
7.152
7.155
7.157
7.159
7.165
7.169
7.179
7.181
7.183
7.212
7.215
7.218
7.234
7.253
7.362
7.652
7.672
ppm
1
2
3
4
5
6
7
8
9
10
3.000
1.854
12.098
1.063
1.059
NH2
Me
Ph
2-Amino-3-(2-methylphenyl)-4-phenyl-naphthalene (3)

2-Amino-3-(2-methylphenyl)-4-phenyl-naphthalene (3)
Ph
NH2
Me
142.399
138.525
136.531
134.284
131.082
130.744
129.637
129.290
128.917
128.274
128.134
127.026
126.931
126.546
126.116
125.605
124.836
122.518
108.214
77.315
76.998
76.680
19.992
200
180
160
140
120
100
80
60
40
20
ppm

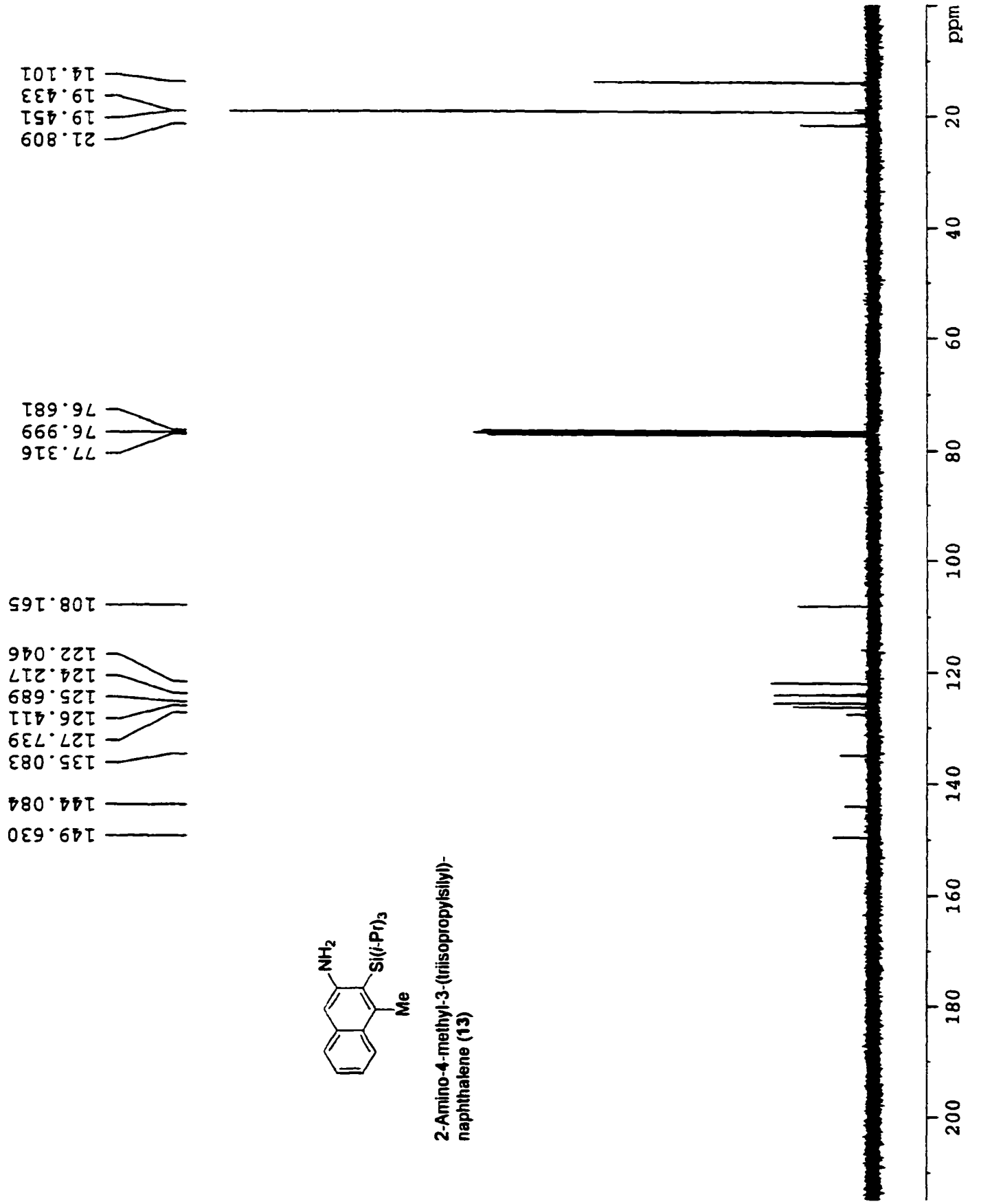

0.000
1.550
2.083
3.656
7.023
7.057
7.066
7.070
7.075
7.084
7.089
7.093
7.096
7.103
7.106
7.115
7.120
7.133
7.136
7.145
7.154
7.158
7.162
7.171
7.177
7.181
7.185
7.201
7.220
7.257
7.354
7.373
7.668
7.687
NH2
Ph
Me
2-Amino-4-(2-methylphenyl)-3-phenyl-naphthalene (4)
ppm
1
2
3
4
5
6
7
8
9
10
3.016
1.849
11.083
2.036
1.000

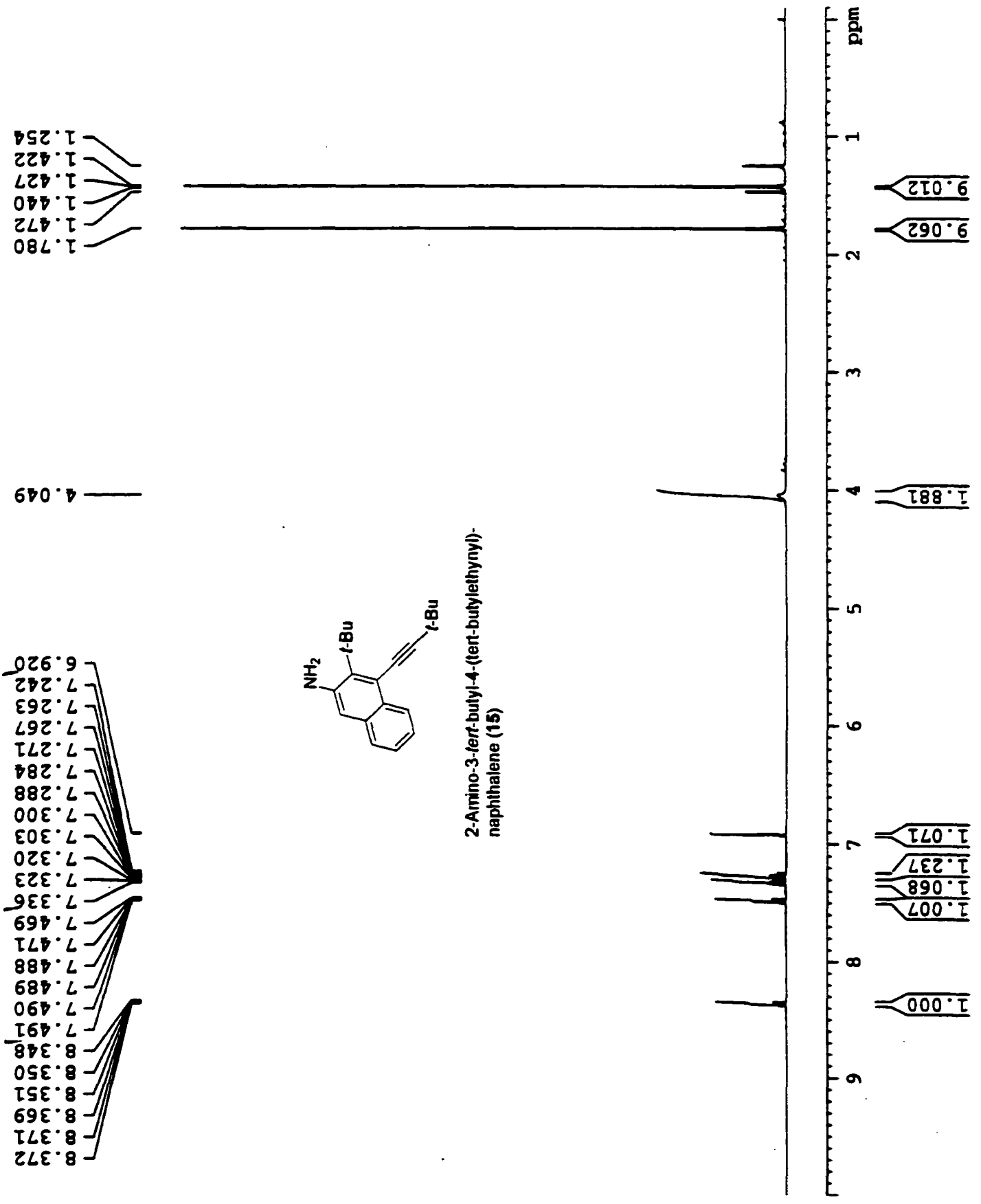
2-Amino-4-(2-methylphenyl)-3-phenyl-naphthalene (4)
Me
Ph
NH2
142.268
139.368
139.054
136.820
134.477
131.054
131.035
129.908
129.299
127.481
127.427
127.302
127.266
126.838
126.511
126.010
125.676
125.567
122.263
107.934
77.319
77.002
76.684
19.763
200
180
160
140
120
100
80
60
40
20
ppm


8.136
8.115
7.665
7.664
7.662
7.645
7.643
7.642
7.542
7.539
7.526
7.521
7.518
7.506
7.503
7.501
7.471
7.468
7.464
7.455
7.449
7.443
7.437
7.434
7.431
7.427
7.420
7.417
7.413
7.399
7.396
7.357
7.353
7.348
7.338
7.335
7.333
7.327
7.322
7.318
7.315
7.309
7.259
7.090
4.788
NH2
Ph
OH
2-Amino-4-hydroxymethyl-3-phenylnaphthalene (8)
180
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.001
1.004
2.052
2.037
3.015
1.006
1.982
1.811
0.988


2-Amino-4-hydroxymethyl-3-phenylnaphthalene (8)
OH
Ph
NH2
142.238
137.017
134.780
134.438
131.223
129.838
129.114
128.880
127.974
126.321
126.282
124.382
123.241
109.211
77.317
76.999
76.682
59.794
200
180
160
140
120
100
80
60
40
20
ppm

2-Amino-4-methyl-3-(triisopropylsilyl)-naphthalene (13)
Me
Si(i-Pr)3
NH2
7.929
7.901
7.532
7.507
7.505
7.371
7.367
7.349
7.345
7.322
7.318
7.247
7.242
7.219
7.214
6.835
3.970
2.787
1.704
1.679
1.654
1.629
1.605
1.181
1.172
1.162
1.157
1.147
1.138
1.118
1.112
1.109
1.101
1.093
1.000
1.001
0.999
1.305
1.009
1.962
3.059
3.021
18.005
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm


14.101
19.433
19.451
21.809
76.681
76.999
77.316
108.165
122.046
124.217
125.689
126.411
127.739
135.083
144.084
149.630
ppm
20
40
60
80
100
120
140
160
180
200
NH2
Si(i-Pr)3
Me
2-Amino-4-methyl-3-(triisopropylsilyl)-naphthalene (13)


ppm
1
2
3
4
5
6
7
8
9
9.012
9.062
1.881
1.071
1.237
1.068
1.007
1.000
4.049
1.780
1.472
1.440
1.427
1.422
1.254
8.372
8.371
8.369
8.351
8.350
8.348
7.491
7.490
7.489
7.488
7.471
7.469
7.336
7.323
7.320
7.303
7.300
7.288
7.284
7.271
7.267
7.263
7.242
6.920
NH2
t-Bu
t-Bu
2-Amino-3-tert-butyl-4-(tert-butylethynyl)-naphthalene (15)

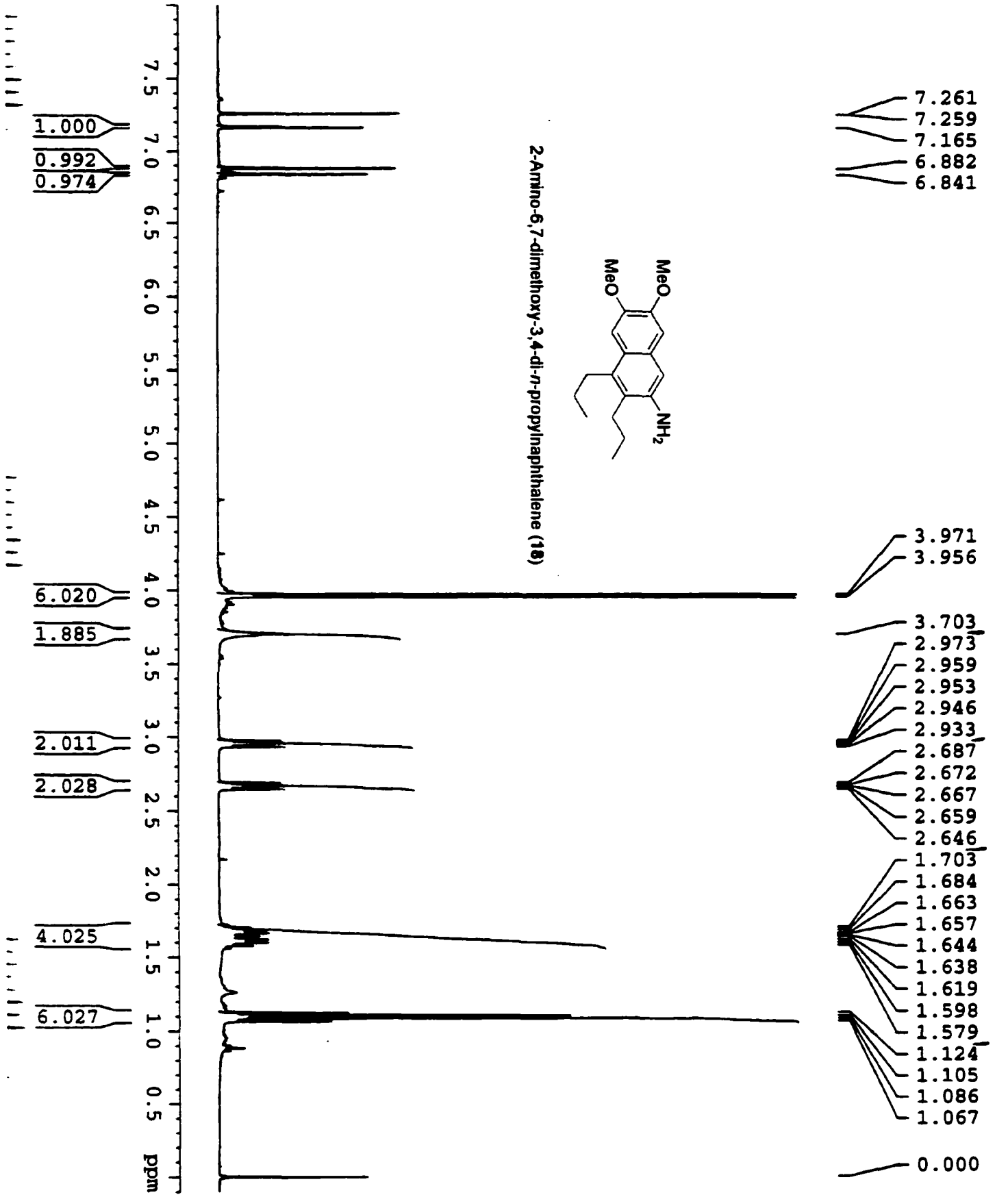
2-Amino-3-*tert*-butyl-4-(tert-butylethynyl)-naphthalene (15)

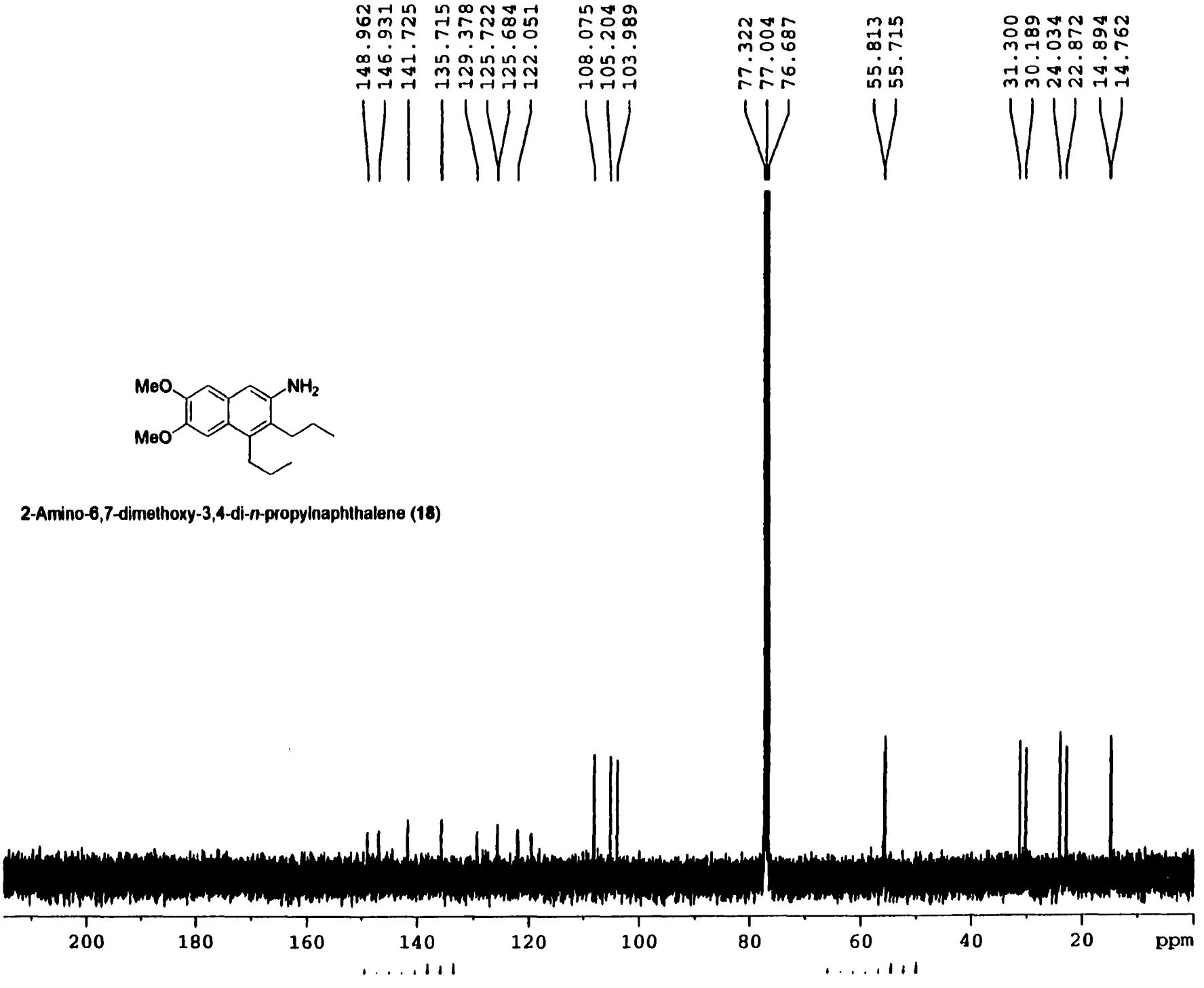
(2-Iodo-4,5-dimethoxyphenyl)acetonitrile (16)
MeO
MeO
I
CN
1.000
1.004
3.048
3.051
2.010
7.295
7.239
6.984
3.895
3.870
3.762
3.686
0.000
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

(2-Iodo-4,5-dimethoxyphenyl)acetonitrile (16)
MeO
MeO
I
CN
149.528
149.050
125.142
121.483
117.419
111.536
86.834
77.315
76.998
76.679
56.111
55.935
29.210
200
180
160
140
120
100
80
60
40
20
ppm

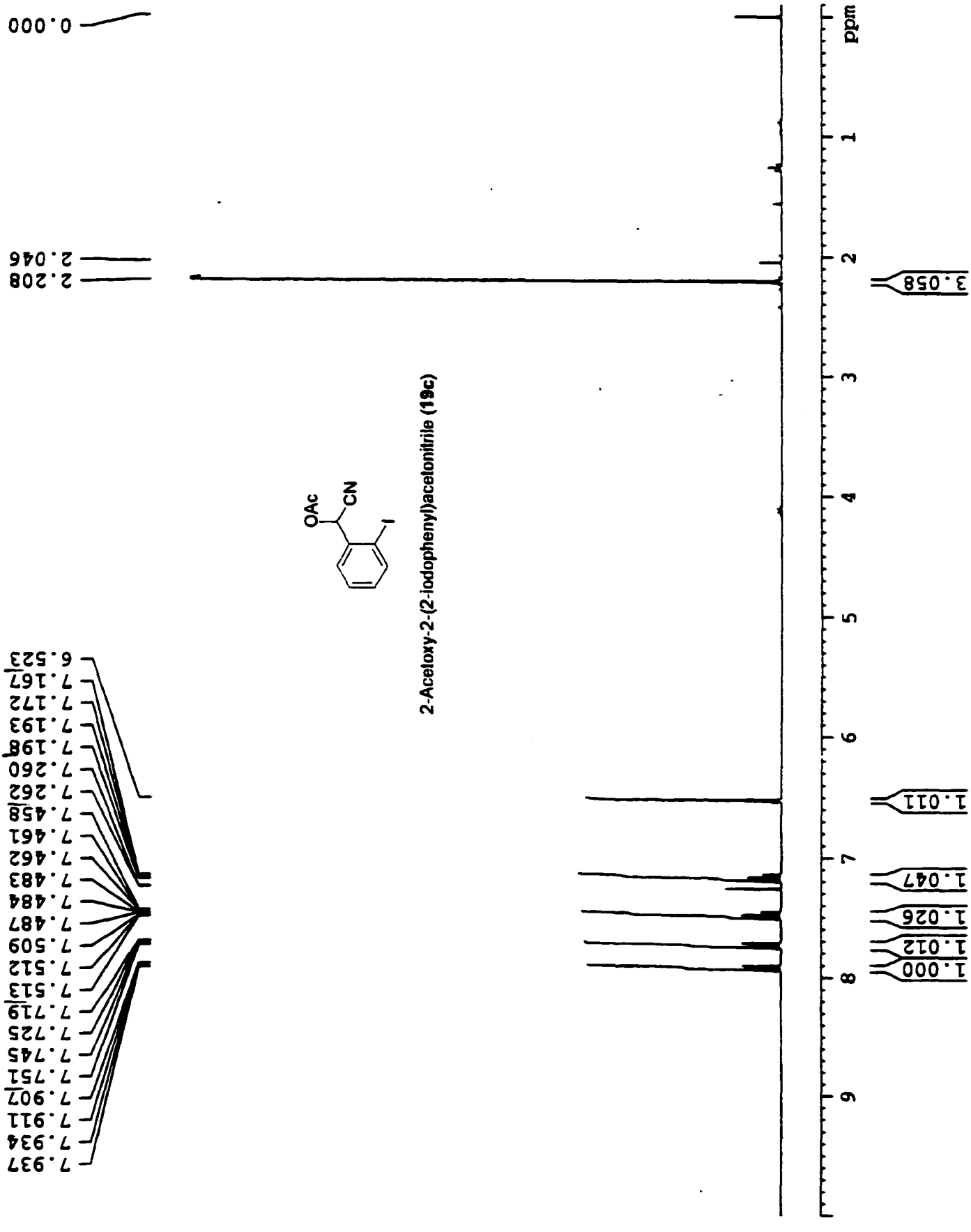
7.258
7.215
7.211
7.204
7.197
7.191
7.179
7.123
7.102
7.097
7.048
6.983
6.702
9.984
1.017
1.018
1.000
3.004
3.034
1.840
3.998
3.664
3.636
2-Amino-6,7-dimethoxy-3,4-diphenyl-naphthalene (17)
MeO
MeO
Ph
Ph
NH2
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
ppm

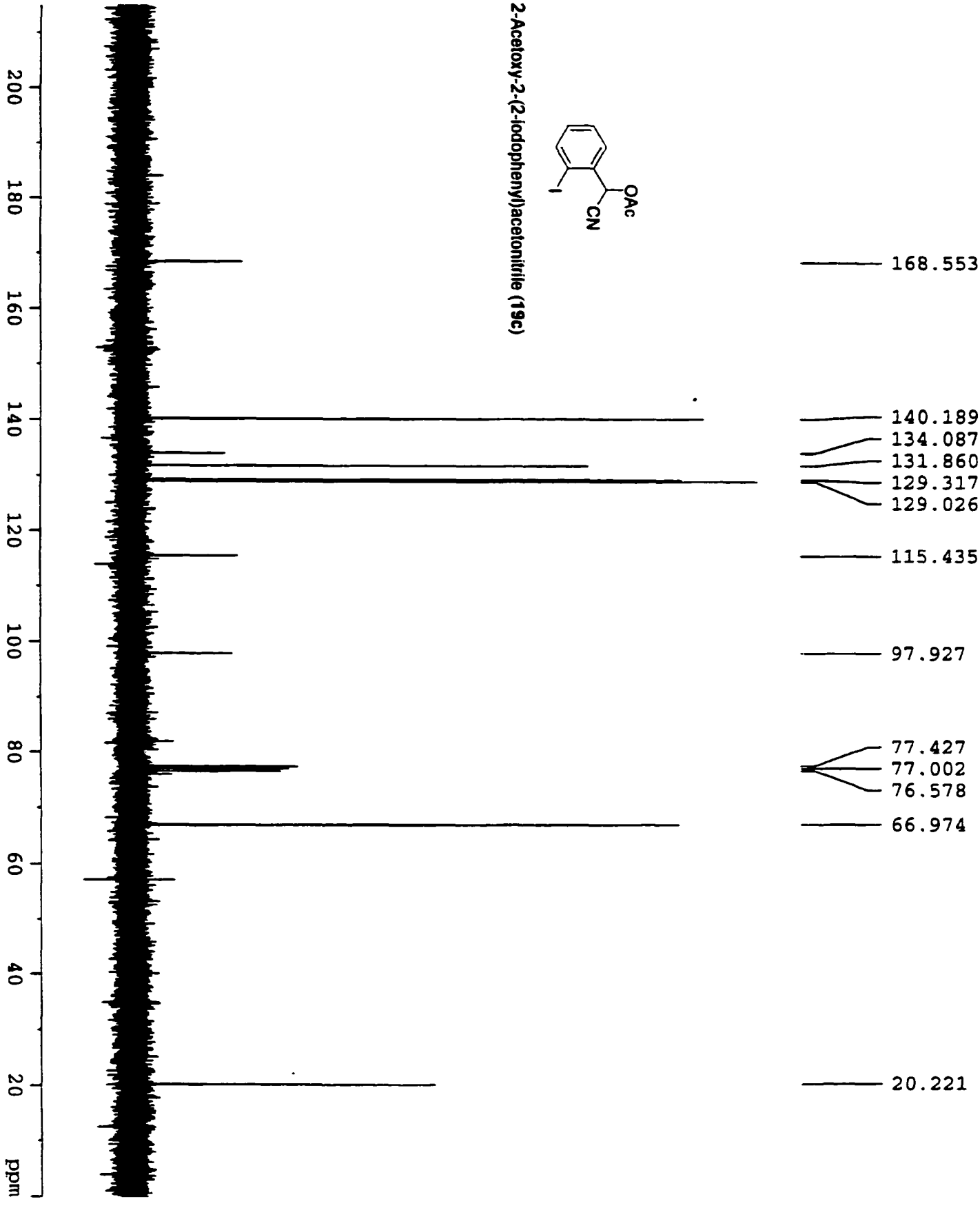
2-Amino-6,7-dimethoxy-3,4-diphenyl-naphthalene (17)
MeO
MeO
Ph
Ph
NH2
149.829
146.877
141.100
139.444
138.423
137.881
130.750
130.728
130.198
128.166
127.486
126.682
126.354
122.255
107.956
106.166
104.446
77.318
77.001
76.684
55.800
55.560
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


2-Amino-6,7-dimethoxy-3,4-di-n-propylnaphthalene (18)
MeO
MeO
NH2
7.261
7.259
7.165
6.882
6.841
3.971
3.956
3.703
2.973
2.959
2.953
2.946
2.933
2.687
2.672
2.667
2.659
2.646
1.703
1.684
1.663
1.657
1.644
1.638
1.619
1.598
1.579
1.124
1.105
1.086
1.067
0.000
1.000
0.992
0.974
6.020
1.885
2.011
2.028
4.025
6.027
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm



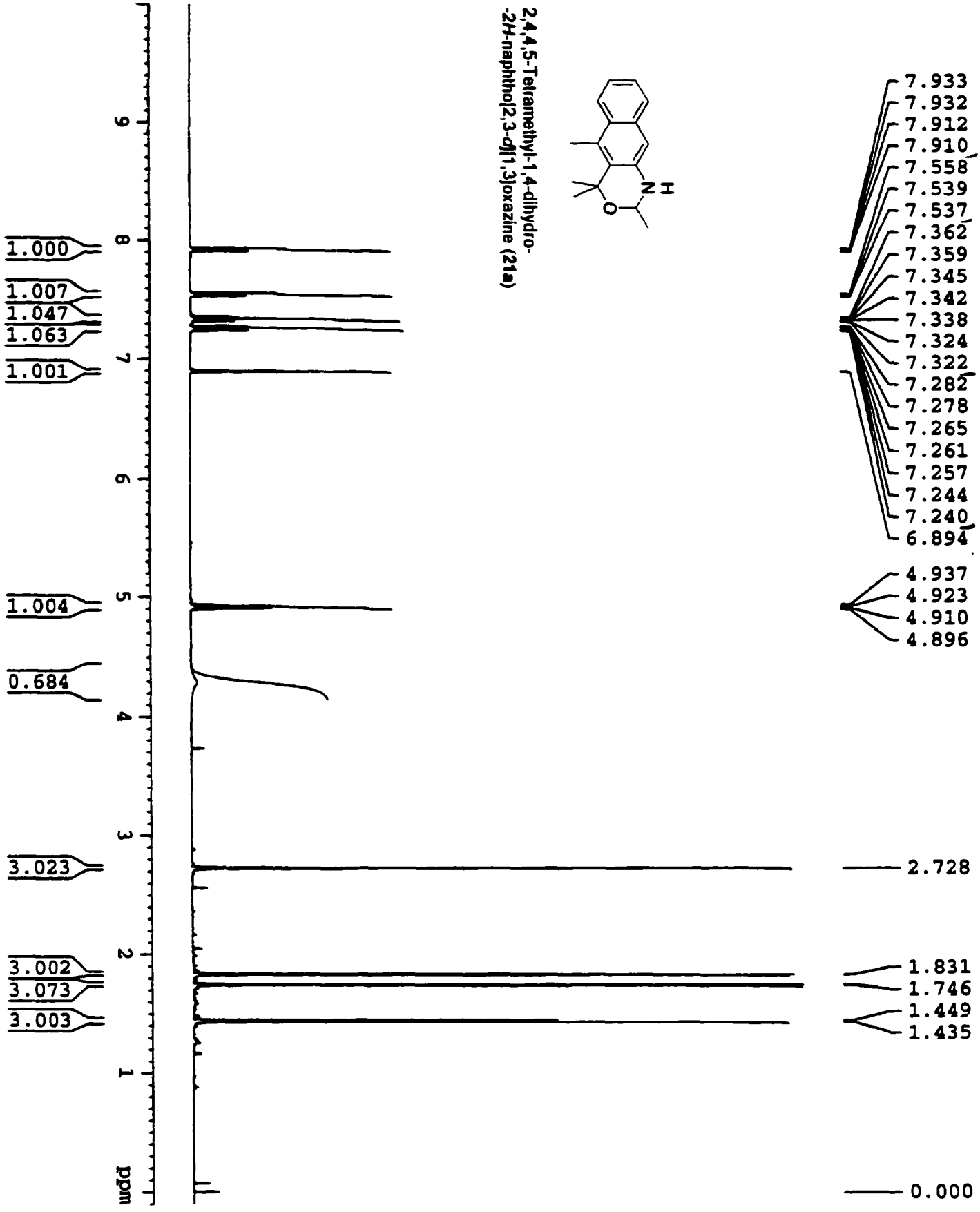

2-Amino-6,7-dimethoxy-3,4-di-*n*-propylnaphthalene (18)


2-Aceloxy-2-(2-iodophenyl)acetonitrile (19c)
OAc
CN
I
ppm
0.000
2.046
2.208
3.058
1.011
1.047
1.026
1.012
1.000
6.523
7.167
7.172
7.193
7.198
7.260
7.262
7.458
7.461
7.462
7.483
7.484
7.487
7.509
7.512
7.513
7.719
7.725
7.745
7.751
7.907
7.911
7.934
7.937

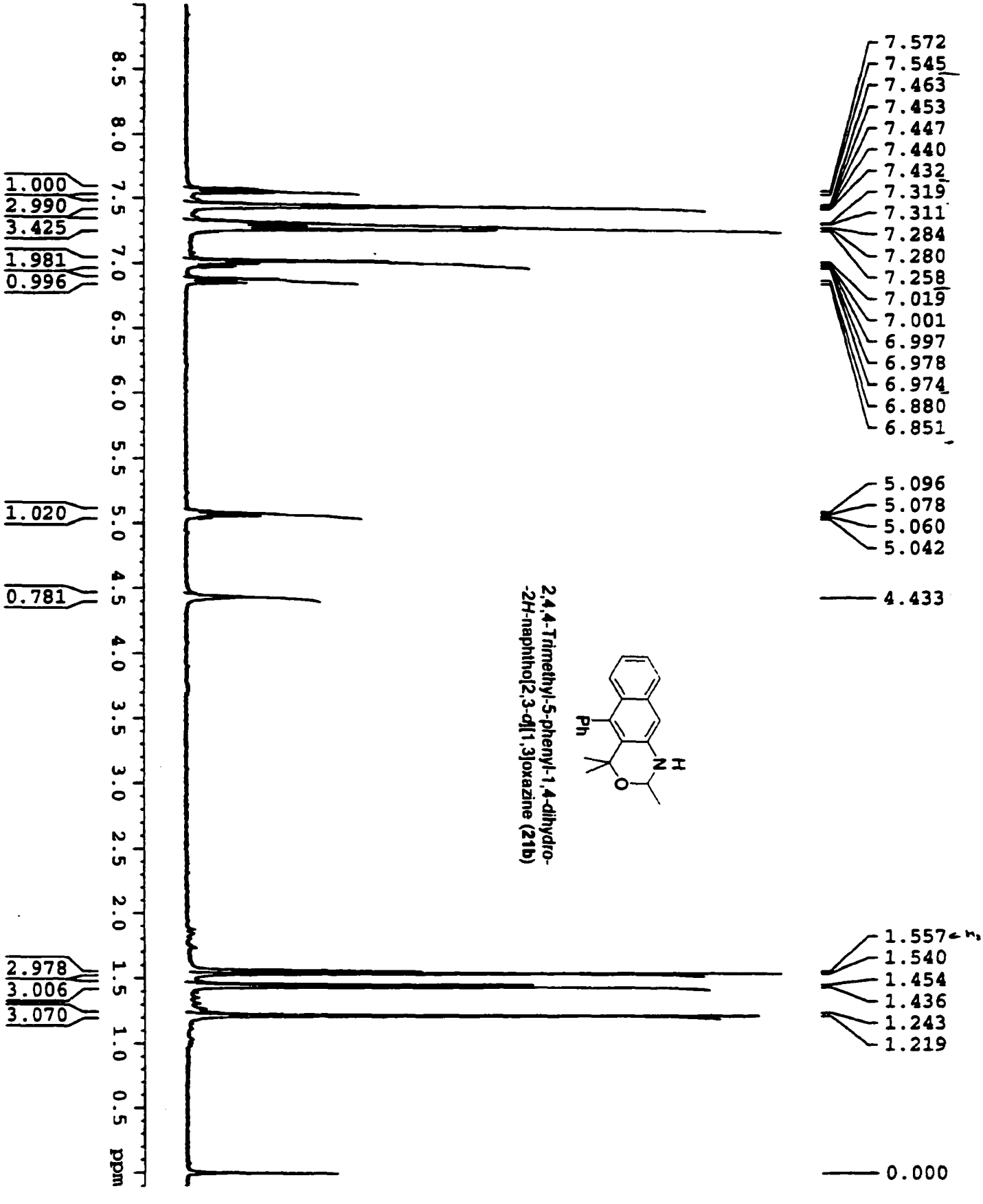

2-Acetoxy-2-(2-iodophenyl)acetonitrile (19c)
OAc
CN
I
168.553
140.189
134.087
131.860
129.317
129.026
115.435
97.927
77.427
77.002
76.578
66.974
20.221
200
180
160
140
120
100
80
60
40
20
ppm

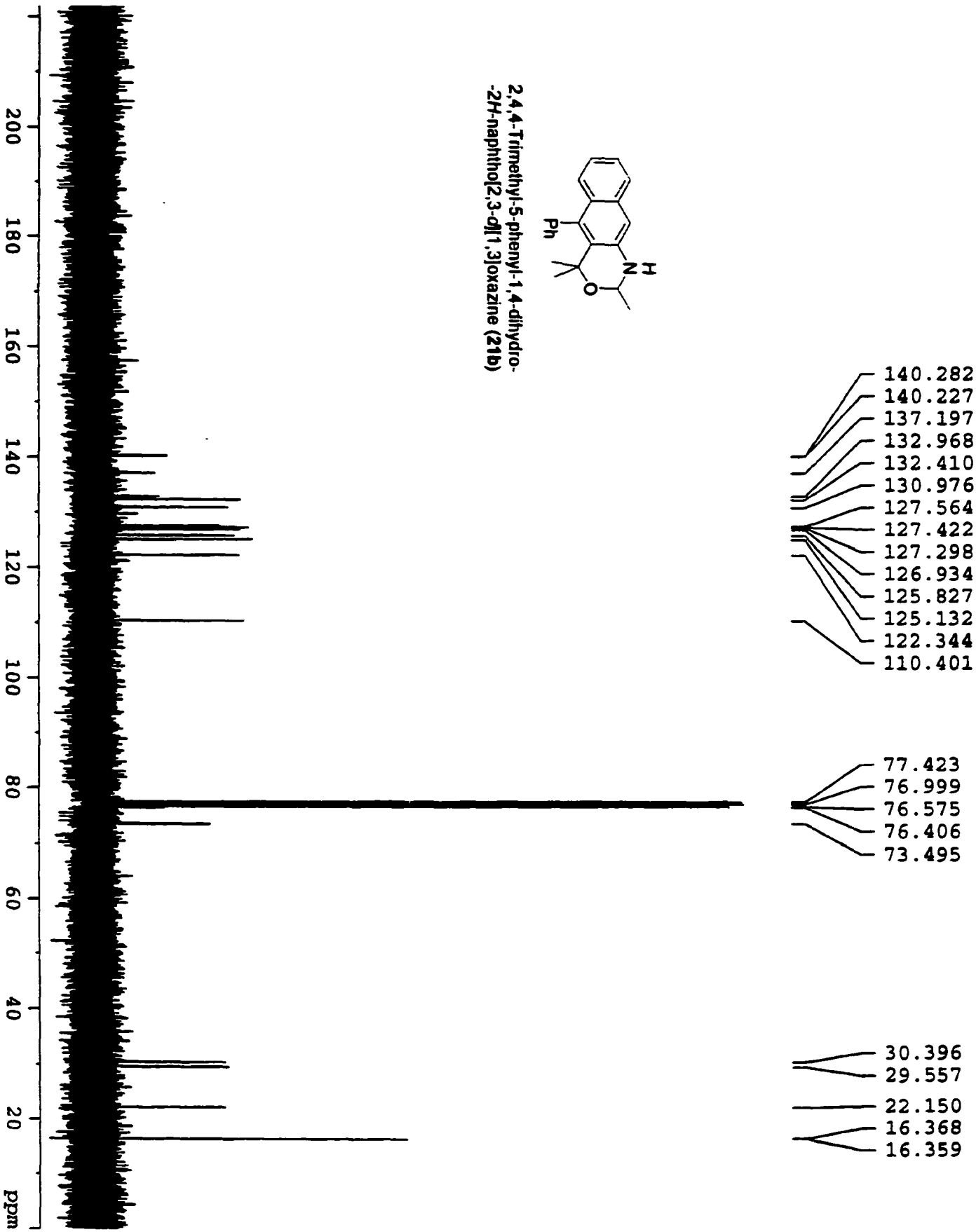
2-Methyl-4,5-diphenyl-naphtho[2,1-d]oxazole (20)
Ph
Ph
O
N
9.565
9.562
8.518
8.517
8.497
8.495
7.538
7.535
7.522
7.518
7.514
7.501
7.498
7.461
7.460
7.440
7.399
7.396
7.382
7.378
7.375
7.358
7.277
7.260
7.258
7.255
7.255
7.246
7.242
7.241
7.233
7.229
7.226
7.225
7.217
7.211
7.205
7.201
7.195
7.183
7.180
7.175
7.164
7.162
7.096
7.092
7.083
7.080
7.076
7.073
7.063
7.060
7.015
2.029
0.993
0.993
1.020
0.990
1.017
5.260
3.042
1.007
3.000
14
13
12
11
10
9
8
7
6
5
4
3
2
1
ppm

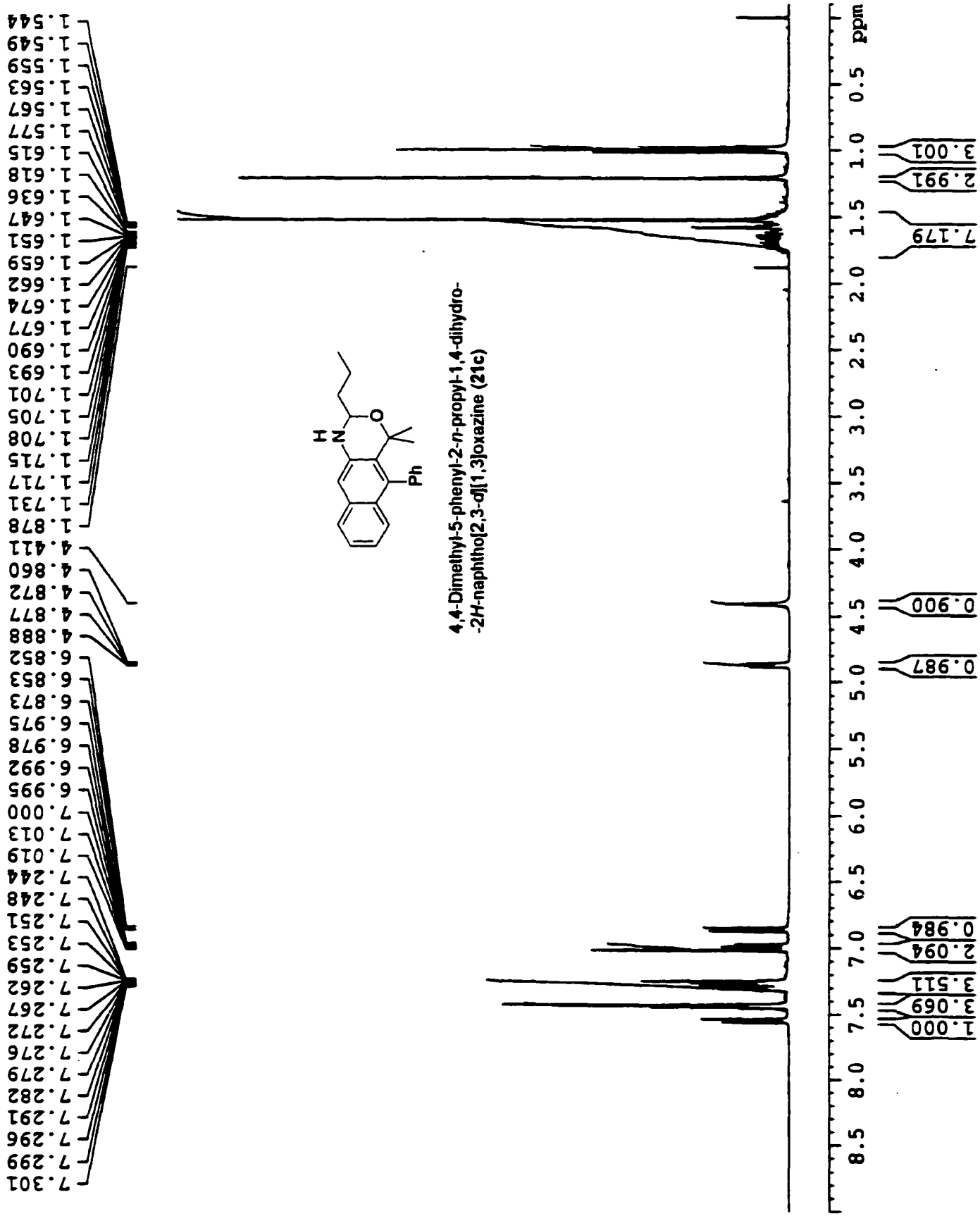
2-Methyl-4,5-diphenyl-naphtho[2,1-d]oxazole (20)
Ph
Ph
O
N
170.320
144.240
138.639
136.796
132.662
131.876
131.639
131.295
130.565
128.454
127.568
127.555
126.871
126.480
126.440
126.332
125.604
123.076
117.874
77.323
77.006
76.688
23.540
200
180
160
140
120
100
80
60
40
20
ppm


2,4,4,5-Tetramethyl-1,4-dihydro-2H-naphtho[2,3-d][1,3]oxazine (21a)
7.933
7.932
7.912
7.910
7.558
7.539
7.537
7.362
7.359
7.345
7.342
7.338
7.324
7.322
7.282
7.278
7.265
7.261
7.257
7.244
7.240
6.894
4.937
4.923
4.910
4.896
2.728
1.831
1.746
1.449
1.435
0.000
1.000
1.007
1.047
1.063
1.001
1.004
0.684
3.023
3.002
3.073
3.003
ppm

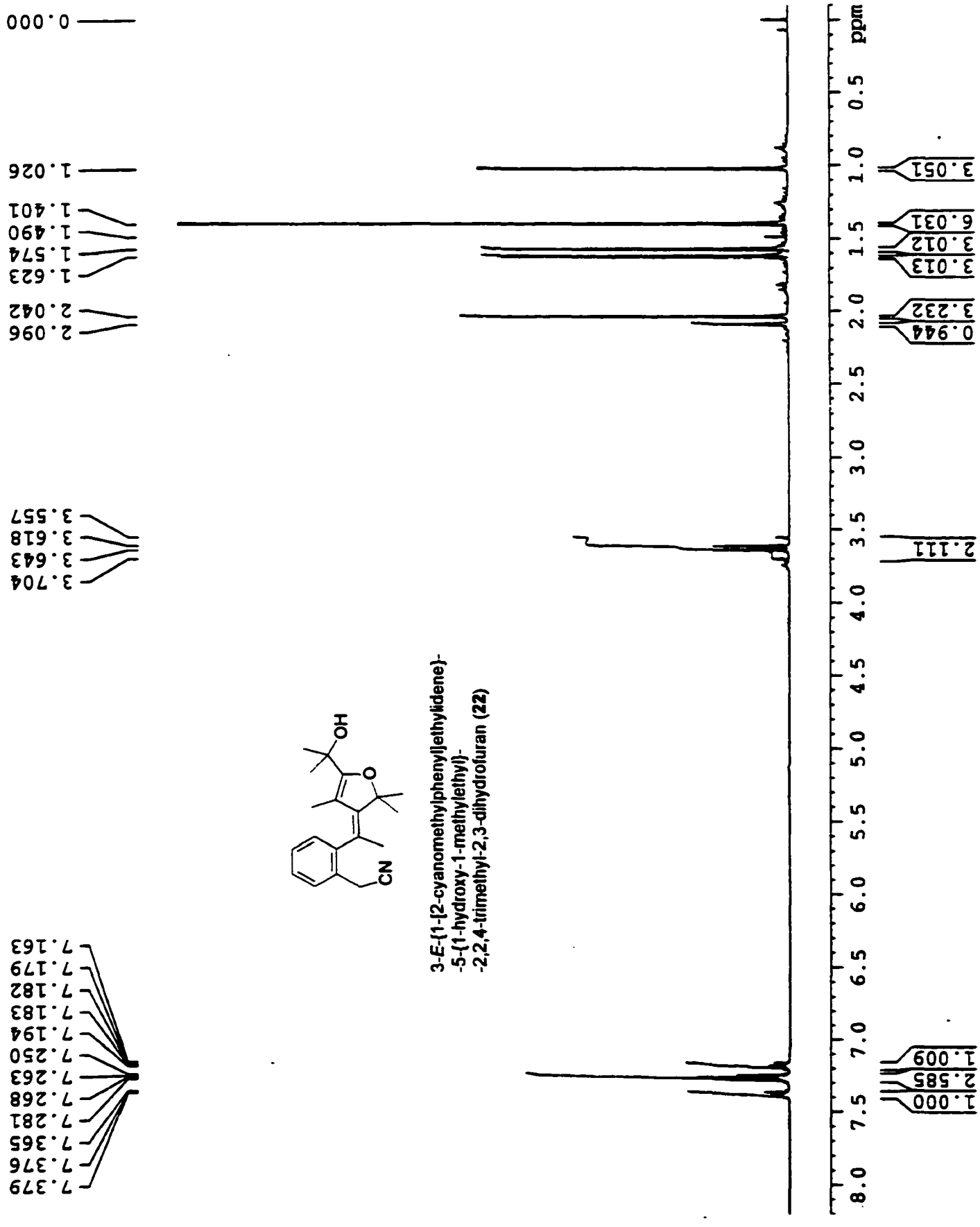
2,4,4,5-Tetramethyl-1,4-dihydro-
-2H-naphtho[2,3-d][1,3]oxazine (21a)
H
N
O
200
180
160
140
120
100
80
60
40
20
ppm
140.663
132.986
130.476
128.558
126.133
125.676
123.901
122.741
109.867
77.316
76.999
76.681
76.248
73.341
30.205
28.387
21.794
17.662


7.572
7.545
7.463
7.453
7.447
7.440
7.432
7.319
7.311
7.284
7.280
7.258
7.019
7.001
6.997
6.978
6.974
6.880
6.851
5.096
5.078
5.060
5.042
4.433
1.557
1.540
1.454
1.436
1.243
1.219
0.000
1.000
2.990
3.425
1.981
0.996
1.020
0.781
2.978
3.006
3.070
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2,4,4-Trimethyl-5-phenyl-1,4-dihydro-2H-naphtho[2,3-d][1,3]oxazine (21b)
Ph
H
N
O


2,4,4-Trimethyl-5-phenyl-1,4-dihydro-
-2H-naphtho[2,3-d][1,3]oxazine (21b)
Ph
H
N
O
140.282
140.227
137.197
132.968
132.410
130.976
127.564
127.422
127.298
126.934
125.827
125.132
122.344
110.401
77.423
76.999
76.575
76.406
73.495
30.396
29.557
22.150
16.368
16.359
200
180
160
140
120
100
80
60
40
20
ppm

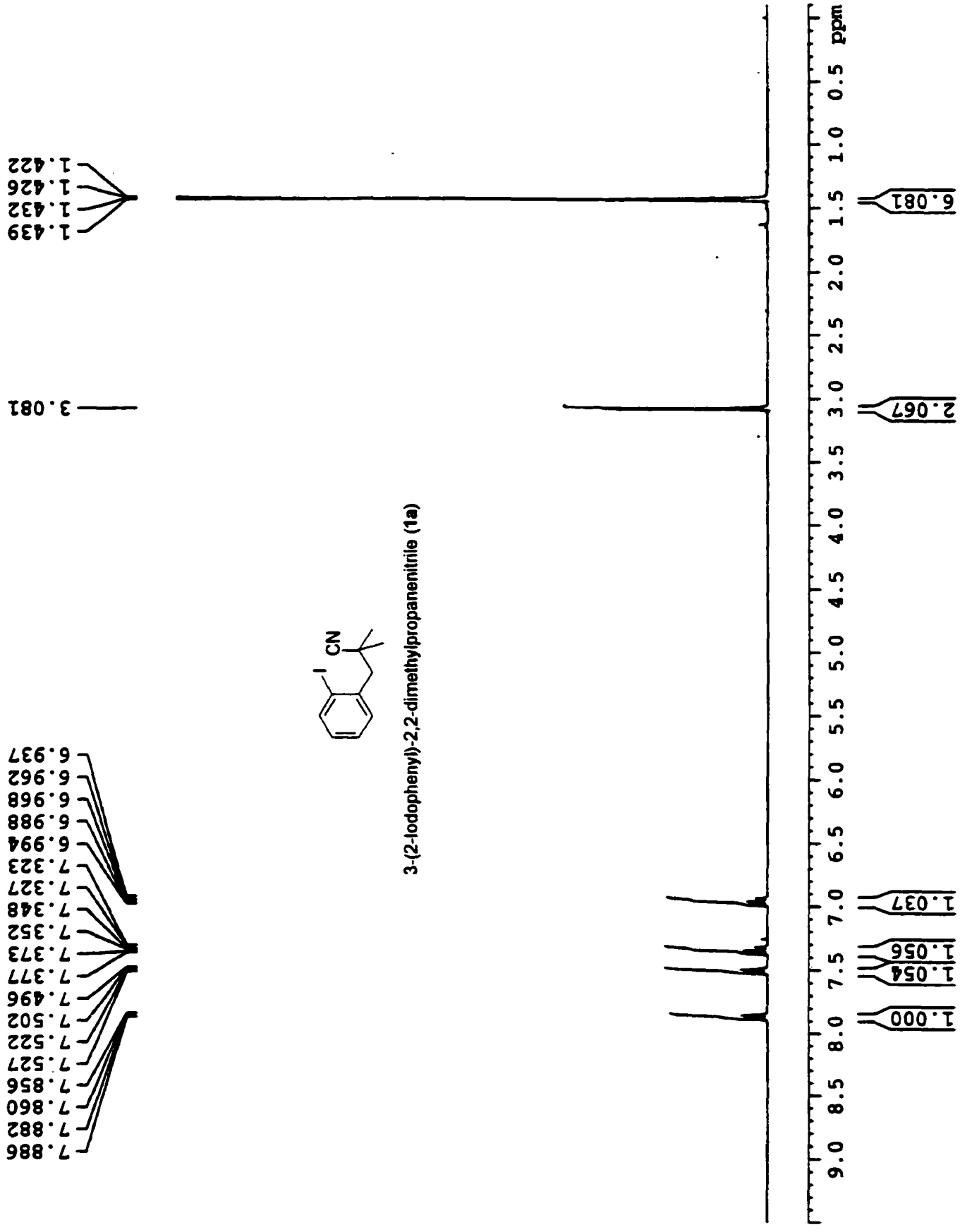

4,4-Dimethyl-5-phenyl-2-n-propyl-1,4-dihydro-2H-naphtho[2,3-d][1,3]oxazine (21c)
H
N
O
Ph
ppm
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.000
3.069
3.511
2.094
0.984
0.900
0.987
7.179
2.991
3.001
7.301
7.299
7.296
7.291
7.282
7.279
7.276
7.272
7.267
7.262
7.259
7.253
7.251
7.248
7.244
7.019
7.013
7.000
6.995
6.992
6.978
6.975
6.873
6.853
6.852
4.888
4.877
4.872
4.860
4.411
1.878
1.731
1.717
1.715
1.708
1.705
1.701
1.693
1.690
1.677
1.674
1.662
1.659
1.651
1.647
1.636
1.618
1.615
1.577
1.567
1.563
1.559
1.549
1.544

4,4-Dimethyl-5-phenyl-2-n-propyl-1,4-dihydro-
-2H-naphtho[2,3-d][1,3]oxazine (21c)
Ph
H
N
O
140.485
140.231
137.156
132.945
132.383
130.969
130.108
128.858
127.531
127.383
127.254
126.895
125.771
125.085
122.254
110.395
77.319
77.001
76.788
76.684
76.214
37.956
30.389
29.518
17.685
14.020
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

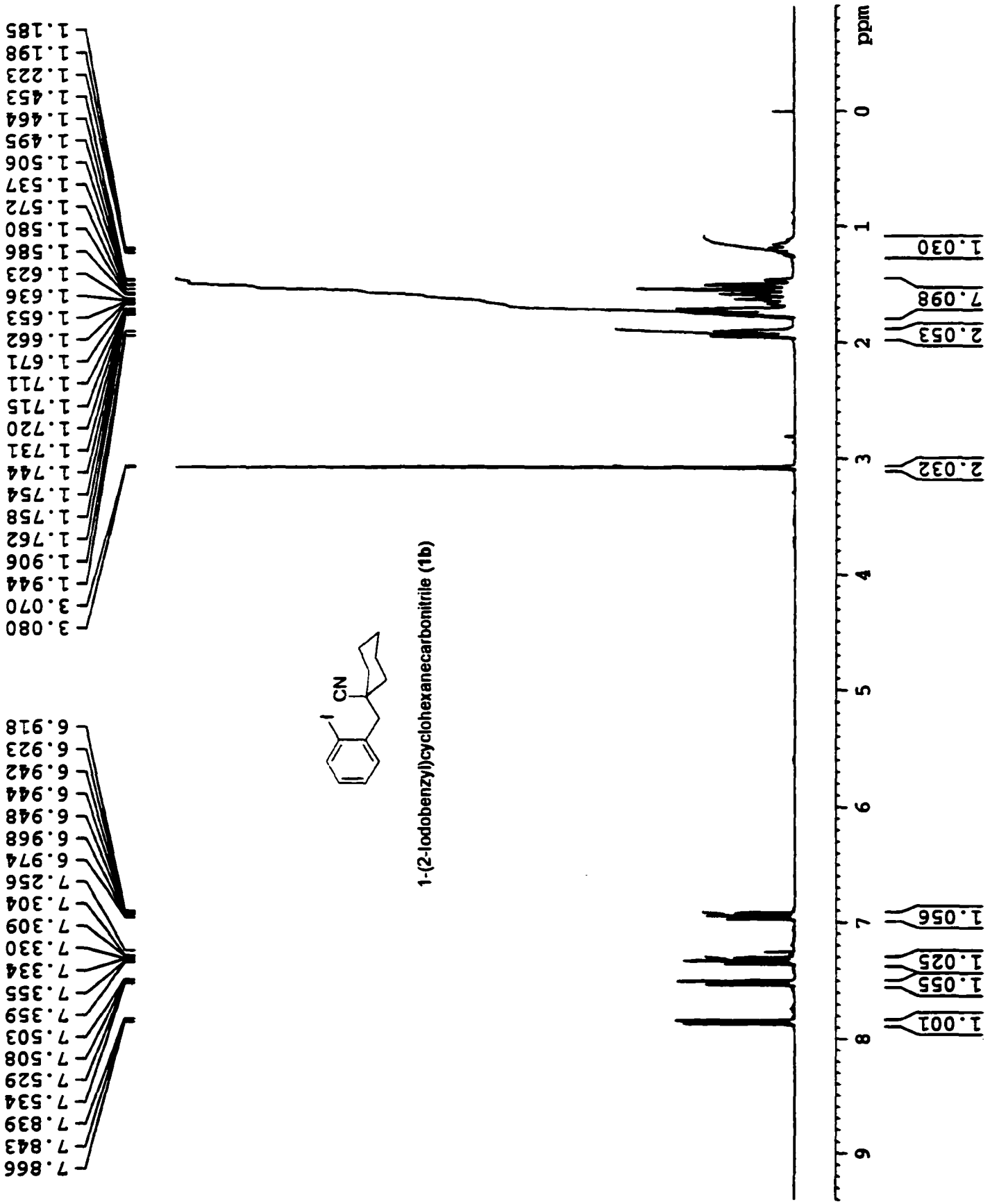

3-E-{1-[2-cyanomethylphenyl]ethylidene}-
-5-(1-hydroxy-1-methylethyl)-
-2,2,4-trimethyl-2,3-dihydrofuran (22)
OH
O
CN
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.000
1.026
1.401
1.490
1.574
1.623
2.042
2.096
3.557
3.618
3.643
3.704
7.163
7.179
7.182
7.183
7.194
7.250
7.263
7.268
7.281
7.365
7.376
7.379
1.000
2.585
1.009
2.111
3.051
6.031
3.012
3.013
3.232
0.944

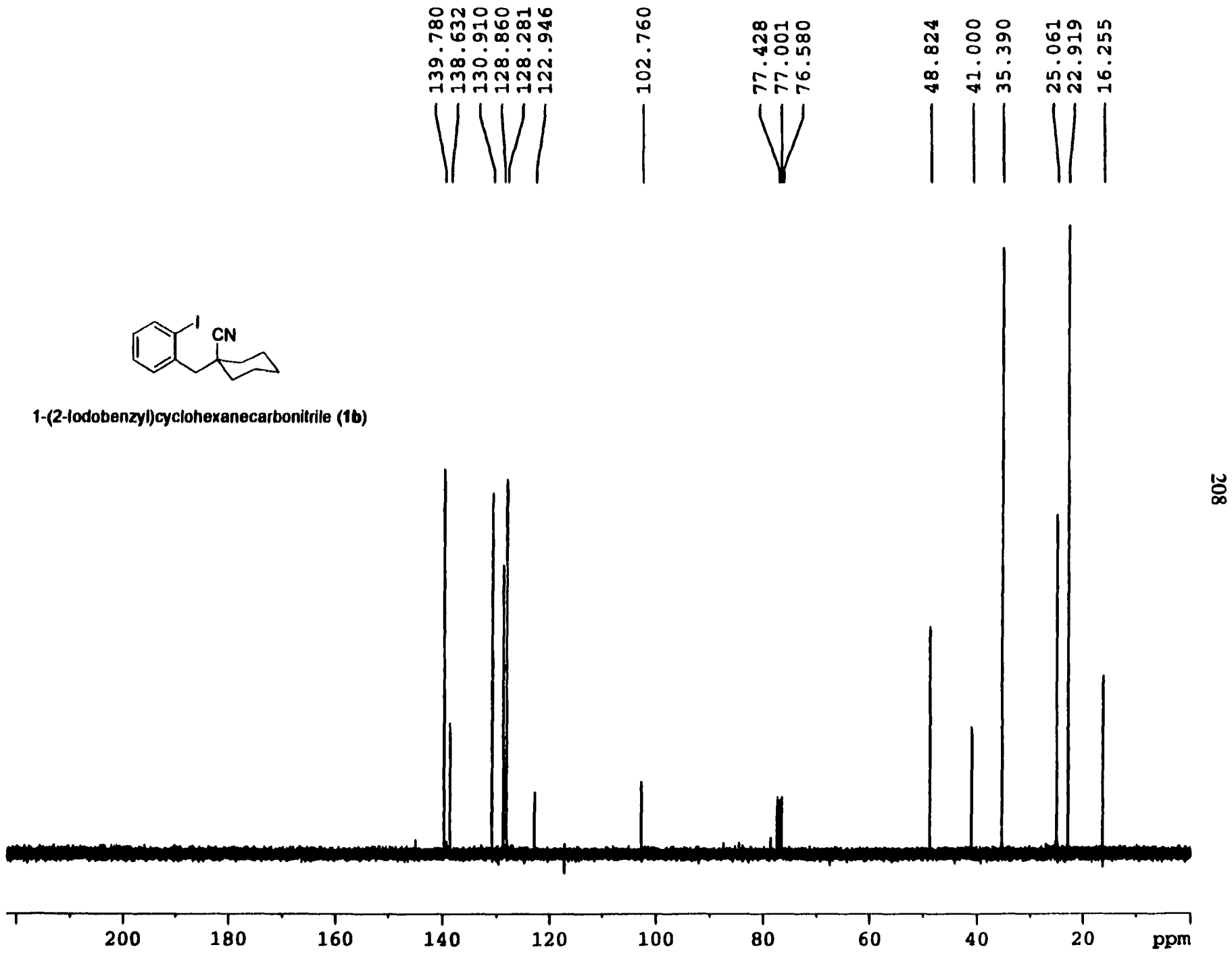
3-E-[1-[2-cyanomethylphenyl]ethylidene]-
-5-[1-hydroxy-1-methylethyl]-
-2,4-trimethyl-2,3-dihydrofuran (22)
CN
OH
O
161.944
144.054
130.110
128.184
128.001
127.768
127.322
118.163
116.504
104.332
85.652
77.317
77.000
76.682
70.853
28.975
28.657
26.173
26.091
22.445
21.314
10.564
200
180
160
140
120
100
80
60
40
20
0
ppm

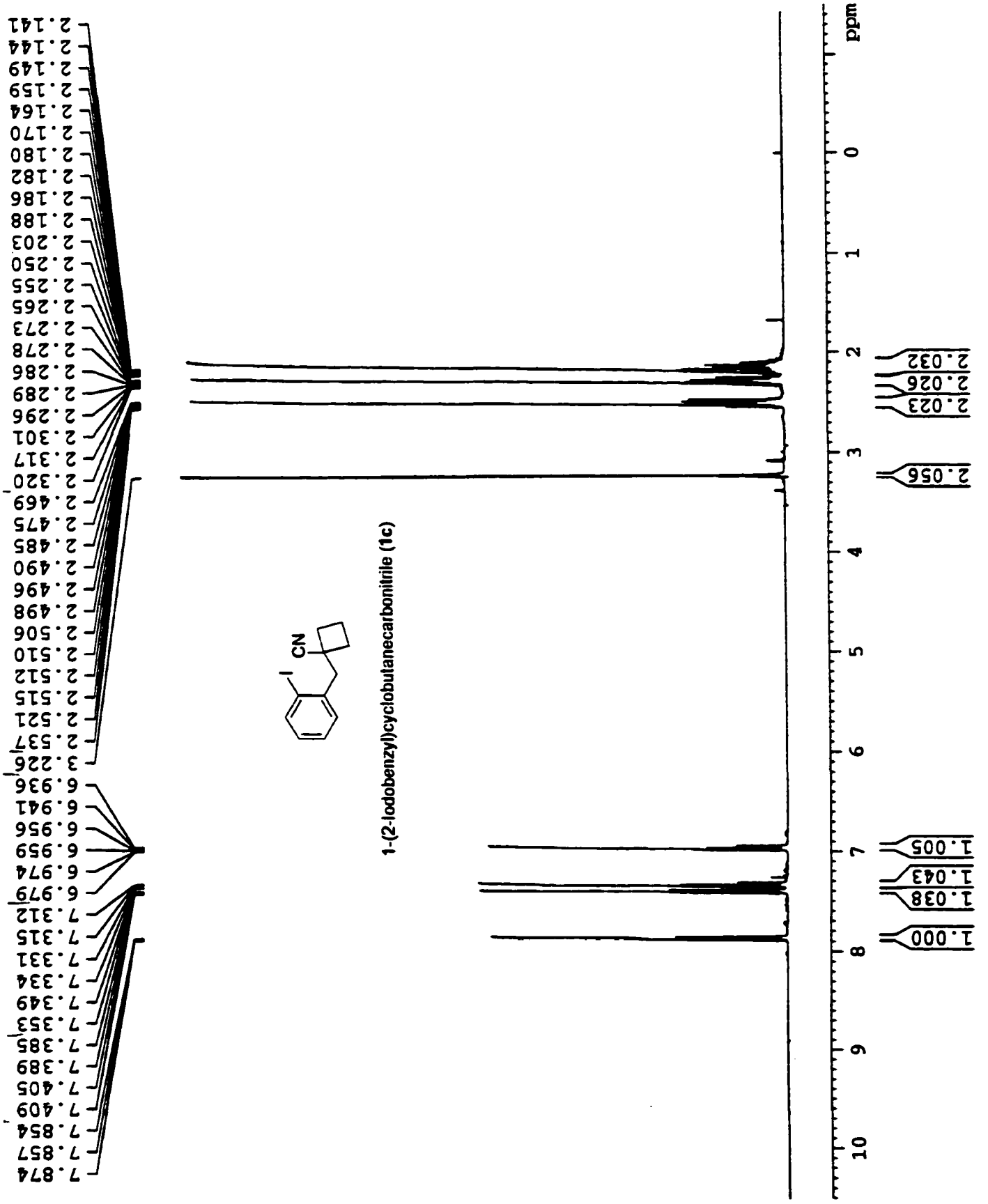
# APPENDIX C. CHAPTER 3 $^{1}H$ AND $^{13}C$ NMR SPECTRA


3-(2-Iodophenyl)-2,2-dimethylpropanenitrile (1a)
CN
I
1.422
1.426
1.432
1.439
3.081
6.937
6.962
6.968
6.988
6.994
7.323
7.327
7.348
7.352
7.373
7.377
7.496
7.502
7.522
7.527
7.856
7.860
7.882
7.886
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
6.081
2.067
1.037
1.056
1.054
1.000

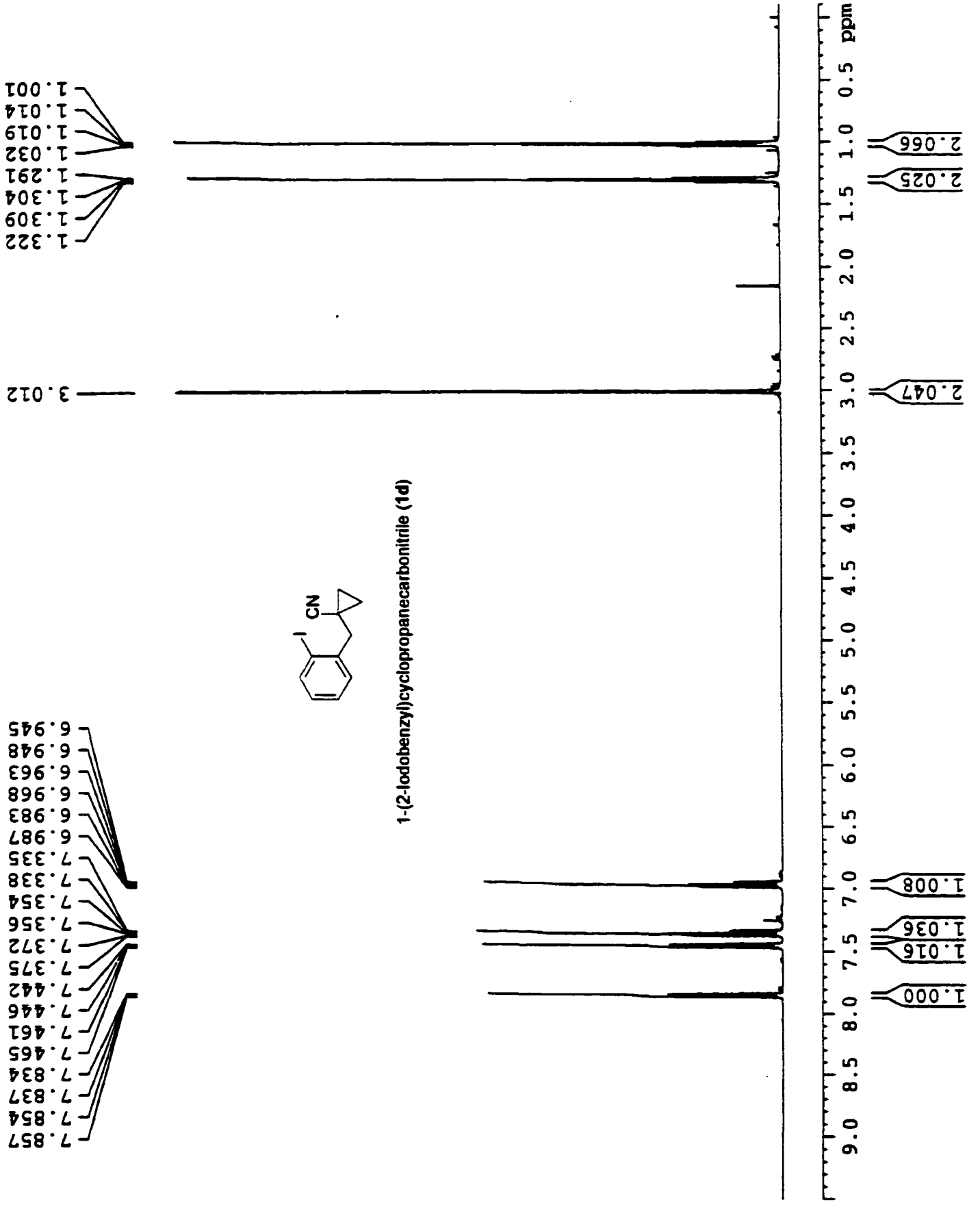
3-(2-Iodophenyl)-2,2-dimethylpropanenitrile (1a)
CN
I
139.898
139.888
138.967
130.659
129.005
128.414
124.627
102.610
77.325
77.009
76.689
48.735
34.280
26.594
26.584
190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 ppm

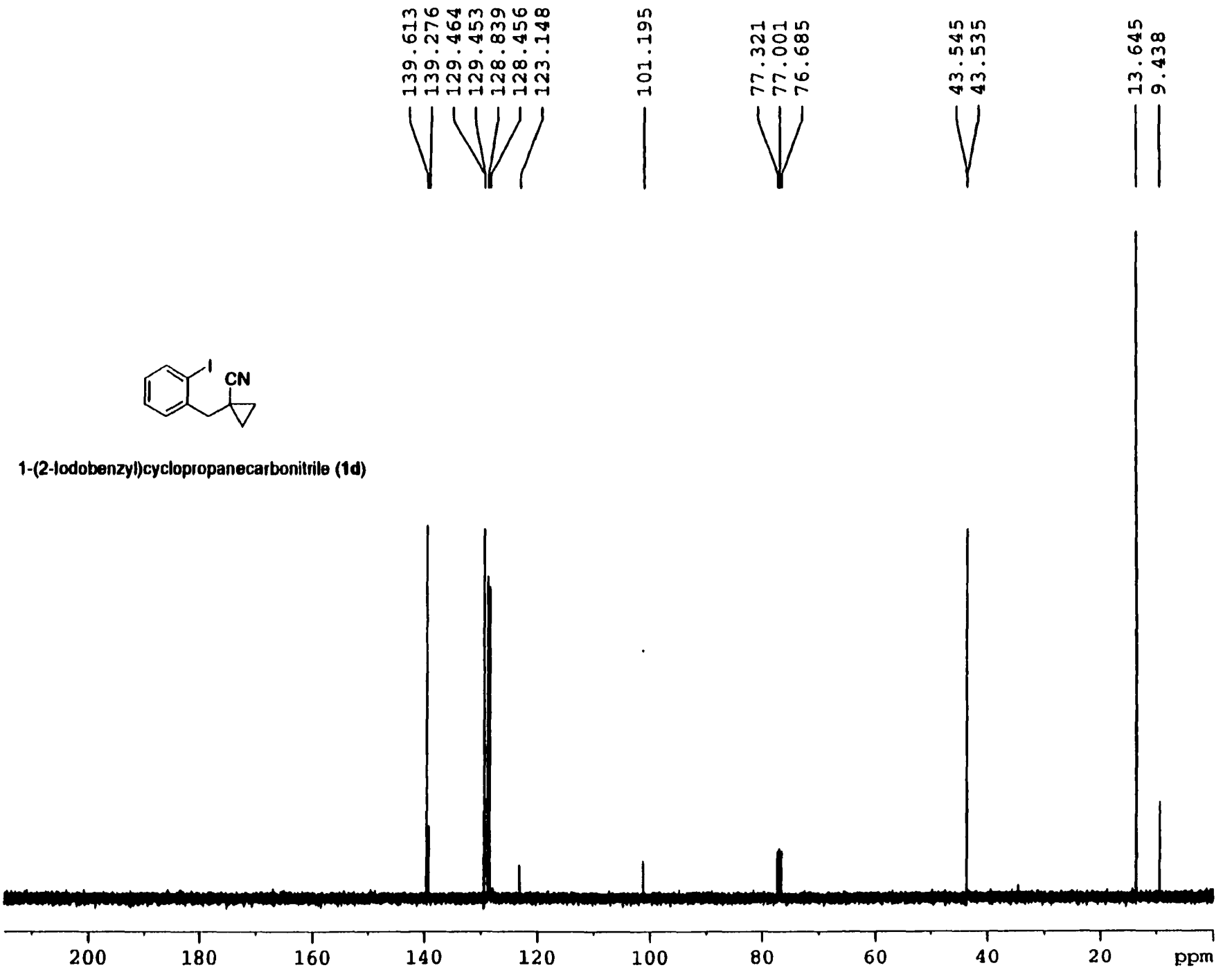

1-(2-Iodobenzyl)cyclohexanecarbonitrile (1b)
CN
I
ppm
0
1
2
3
4
5
6
7
8
9
1.030
7.098
2.053
2.032
1.056
1.025
1.055
1.001
1.185
1.198
1.223
1.453
1.464
1.495
1.506
1.537
1.572
1.580
1.586
1.623
1.636
1.653
1.662
1.671
1.711
1.715
1.720
1.731
1.744
1.754
1.758
1.762
1.906
1.944
3.070
3.080
6.918
6.923
6.942
6.944
6.948
6.968
6.974
7.256
7.304
7.309
7.330
7.334
7.355
7.359
7.503
7.508
7.529
7.534
7.839
7.843
7.866


139.780
138.632
130.910
128.860
128.281
122.946
102.760
77.428
77.001
76.580
48.824
41.000
35.390
25.061
22.919
16.255
I
CN
1-(2-Iodobenzyl)cyclohexanecarbonitrile (1b)
208
200
180
160
140
120
100
80
60
40
20
ppm

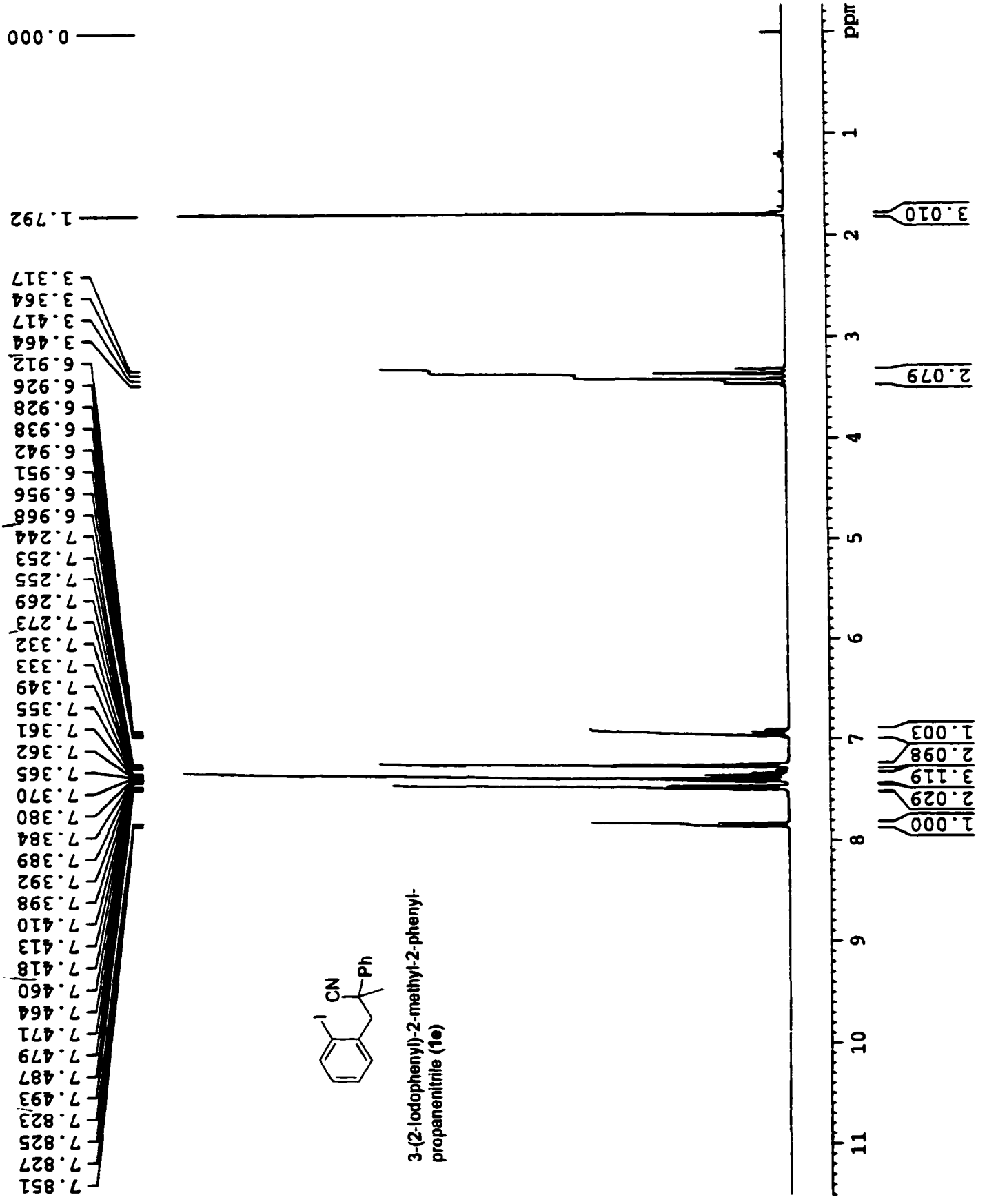

1-(2-Iodobenzyl)cyclobutanecarbonitrile (1c)
CN
I
ppm
10
9
8
7
6
5
4
3
2
1
0
1.000
1.038
1.043
1.005
2.056
2.023
2.026
2.032
7.874
7.857
7.854
7.409
7.405
7.389
7.385
7.353
7.349
7.334
7.331
7.315
7.312
6.979
6.974
6.959
6.956
6.941
6.936
3.226
2.537
2.521
2.515
2.512
2.510
2.506
2.498
2.496
2.490
2.485
2.475
2.469
2.320
2.317
2.301
2.296
2.289
2.286
2.278
2.273
2.265
2.255
2.250
2.203
2.188
2.186
2.182
2.180
2.170
2.164
2.159
2.149
2.144
2.141

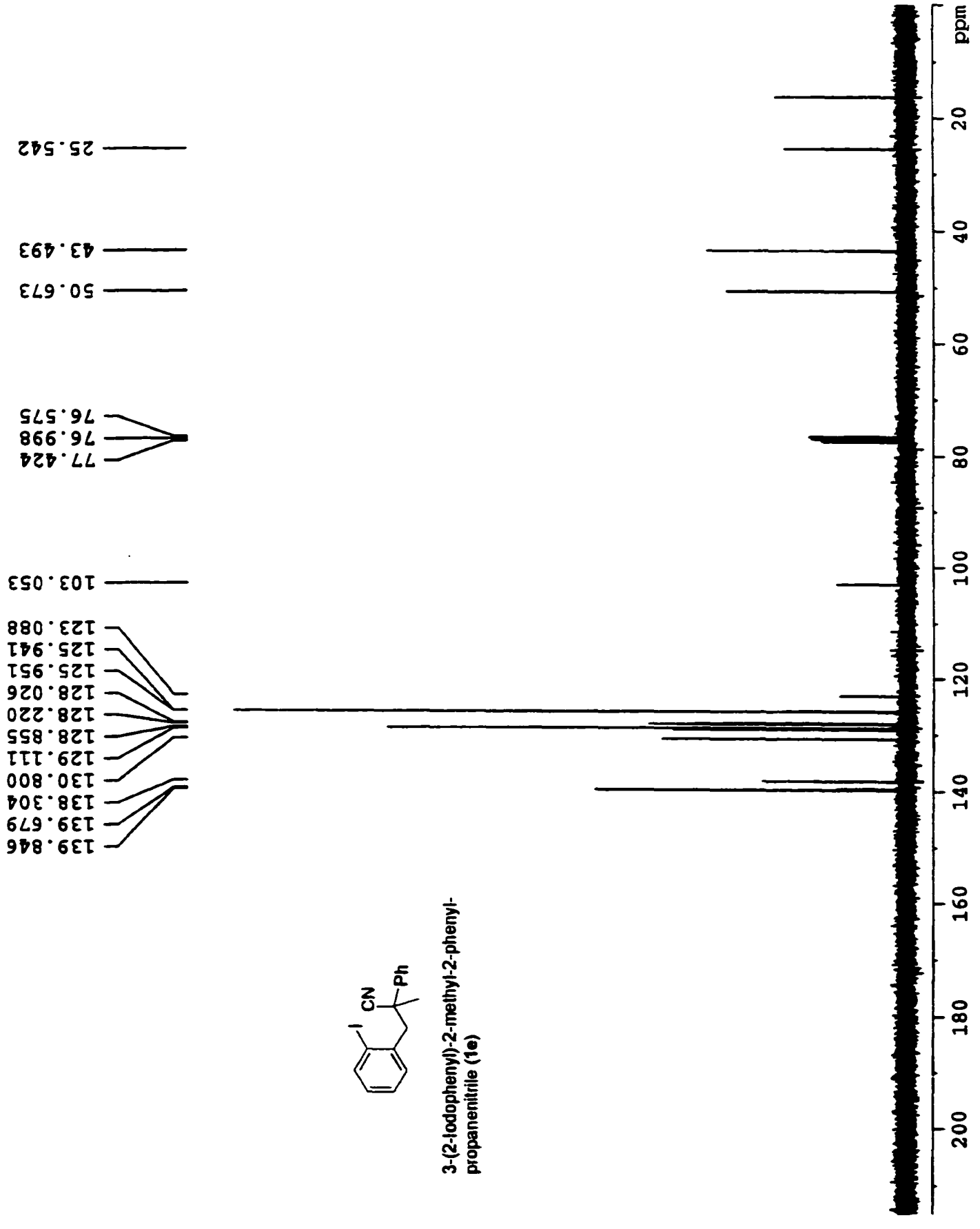
1-(2-Iodobenzyl)cyclobutanecarbonitrile (1c)
CN
I
ppm
200
180
160
140
120
100
80
60
40
20
139.767
138.962
129.712
128.830
128.424
124.385
102.061
77.424
76.998
76.574
45.860
36.410
31.703
17.058

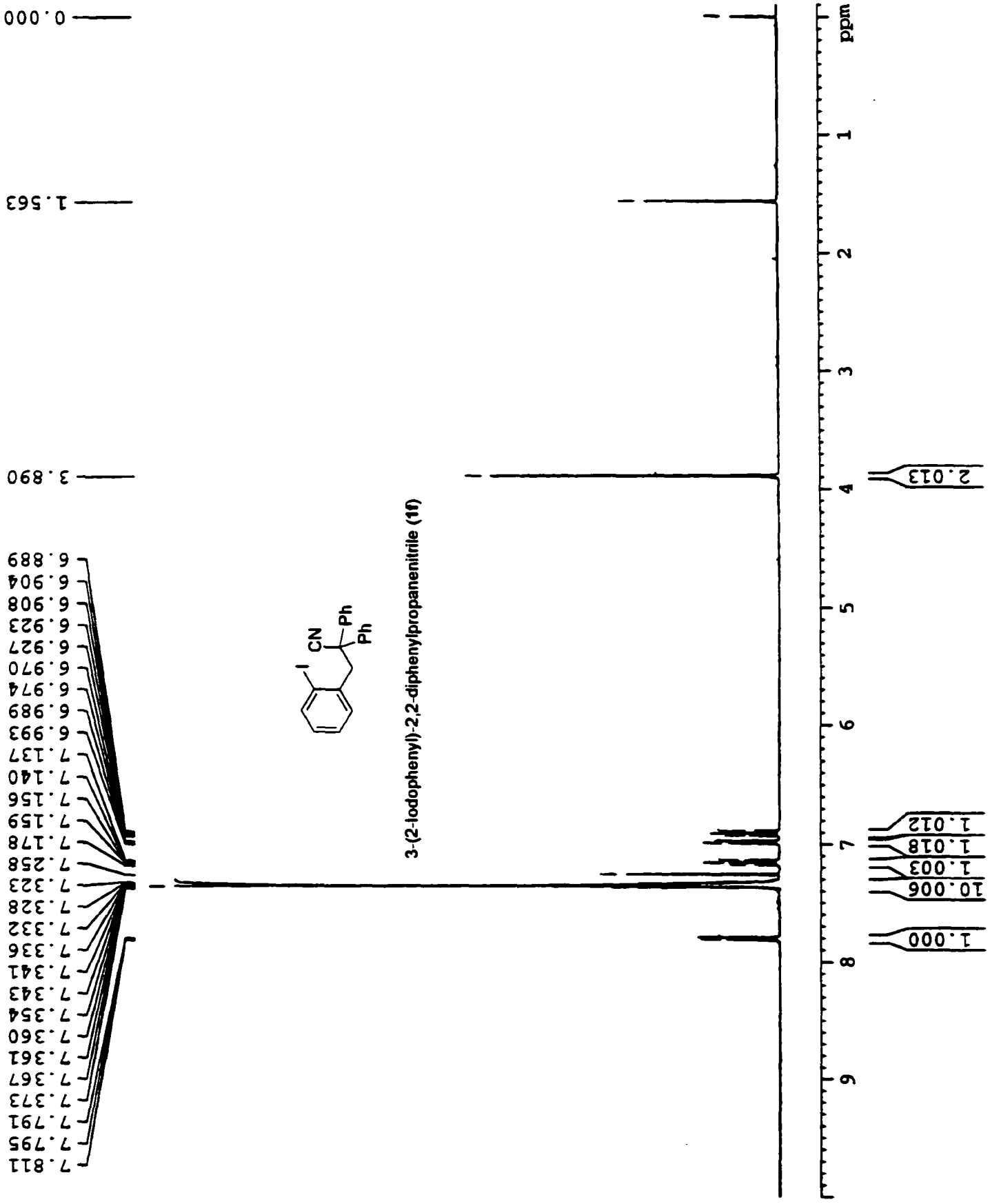

1-(2-Iodobenzyl)cyclopropanecarbonitrile (1d)
CN
I
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.000
1.016
1.036
1.008
2.047
2.025
2.066
3.012
7.857
7.854
7.837
7.834
7.465
7.461
7.446
7.442
7.375
7.372
7.356
7.354
7.338
7.335
6.987
6.983
6.968
6.963
6.948
6.945
1.322
1.309
1.304
1.291
1.032
1.019
1.014
1.001

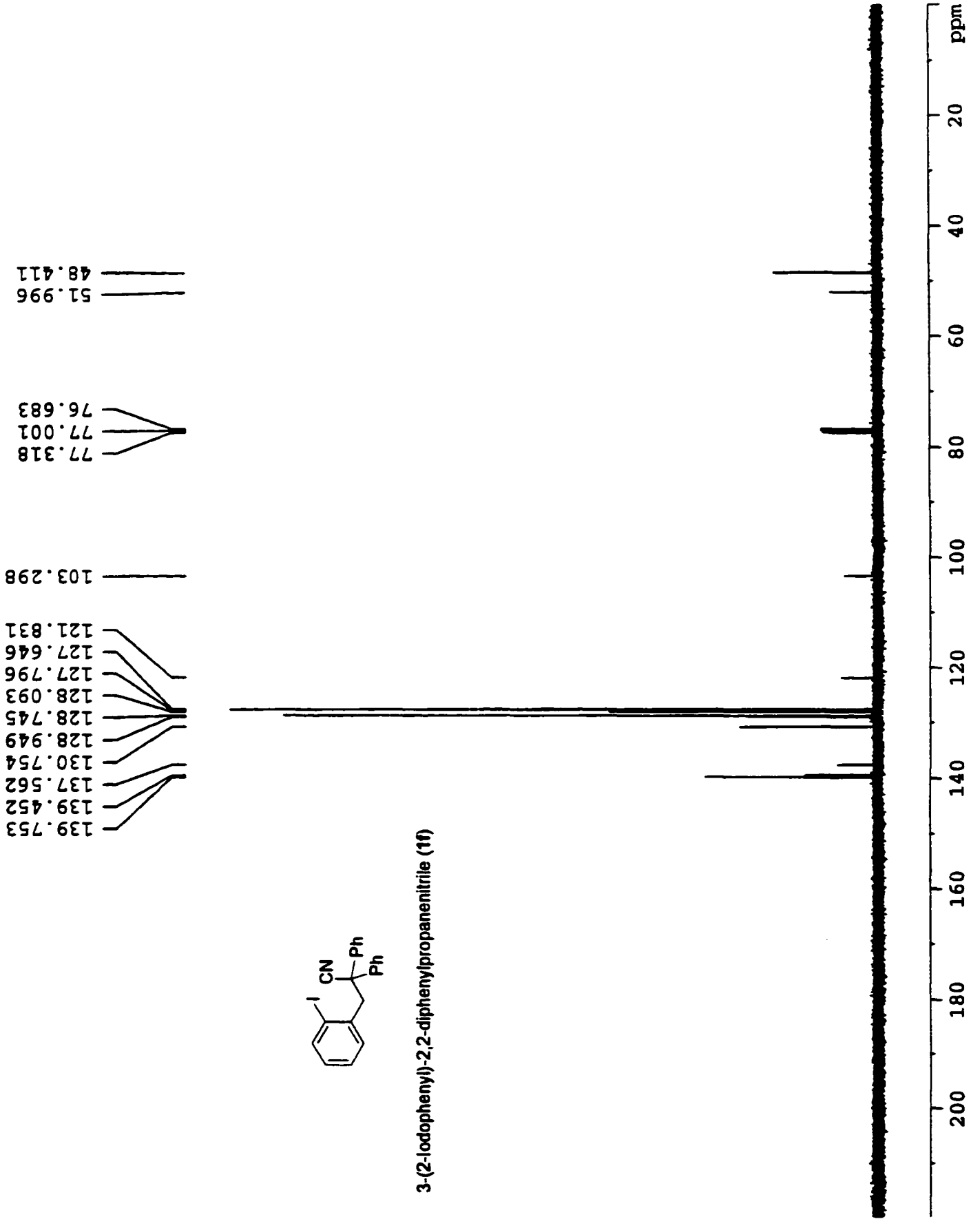


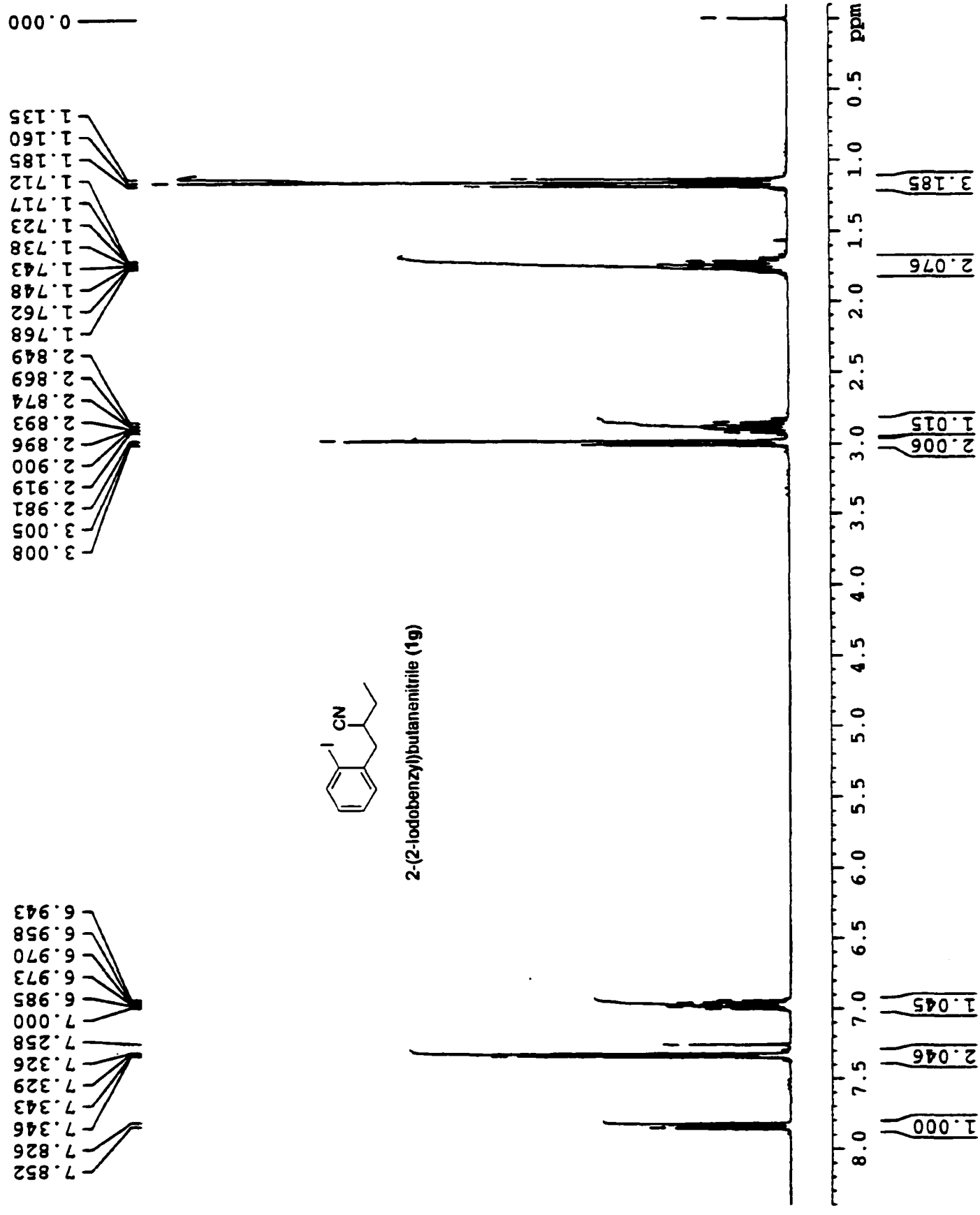

1-(2-Iodobenzyl)cyclopropanecarbonitrile (1d)


0.000
1.792
3.317
3.364
3.417
3.464
6.912
6.926
6.928
6.938
6.942
6.951
6.956
6.968
7.244
7.253
7.255
7.269
7.273
7.332
7.333
7.349
7.355
7.361
7.362
7.365
7.370
7.380
7.384
7.389
7.392
7.398
7.410
7.413
7.418
7.460
7.464
7.471
7.479
7.487
7.493
7.823
7.825
7.827
7.851
ppm
1
2
3
4
5
6
7
8
9
10
11
3.010
2.079
1.000
2.029
3.119
2.098
1.003
CN
Ph
I
3-(2-Iodophenyl)-2-methyl-2-phenyl-propanenitrile (1e)

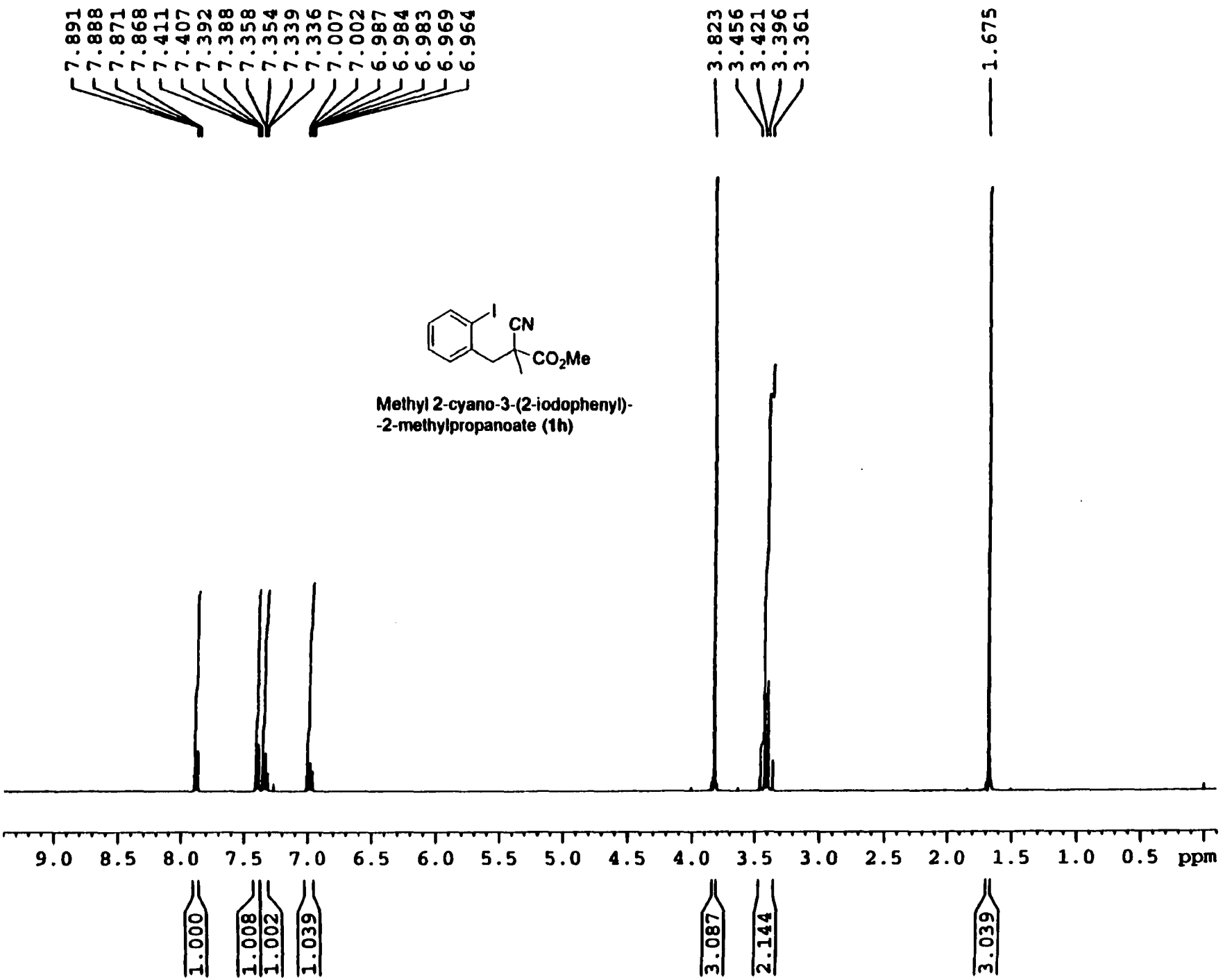

ppm
20
40
60
80
100
120
140
160
180
200
25.542
43.493
50.673
76.575
76.998
77.424
103.053
123.088
125.941
125.951
128.026
128.220
128.855
129.111
130.800
138.304
139.679
139.846
CN
Ph
3-(2-Iodophenyl)-2-methyl-2-phenyl-propanenitrile (1e)

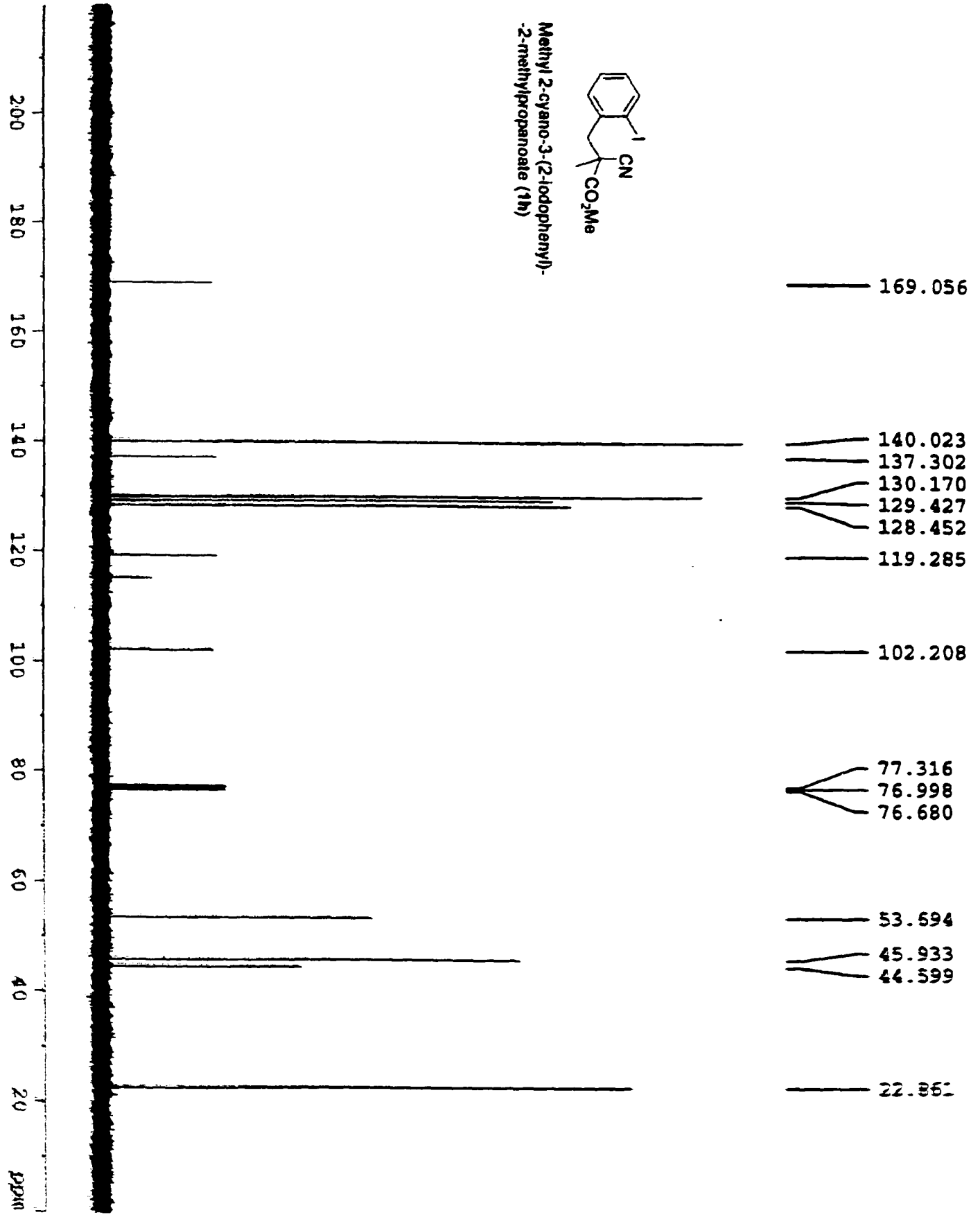

3-(2-Iodophenyl)-2,2-diphenylpropanenitrile (1f)
CN
Ph
Ph
I
ppm
0.000
1.563
3.890
6.889
6.904
6.908
6.923
6.927
6.970
6.974
6.989
6.993
7.137
7.140
7.156
7.159
7.178
7.258
7.323
7.328
7.332
7.336
7.341
7.343
7.354
7.360
7.361
7.367
7.373
7.791
7.795
7.811
2.013
1.012
1.018
1.003
10.006
1.000

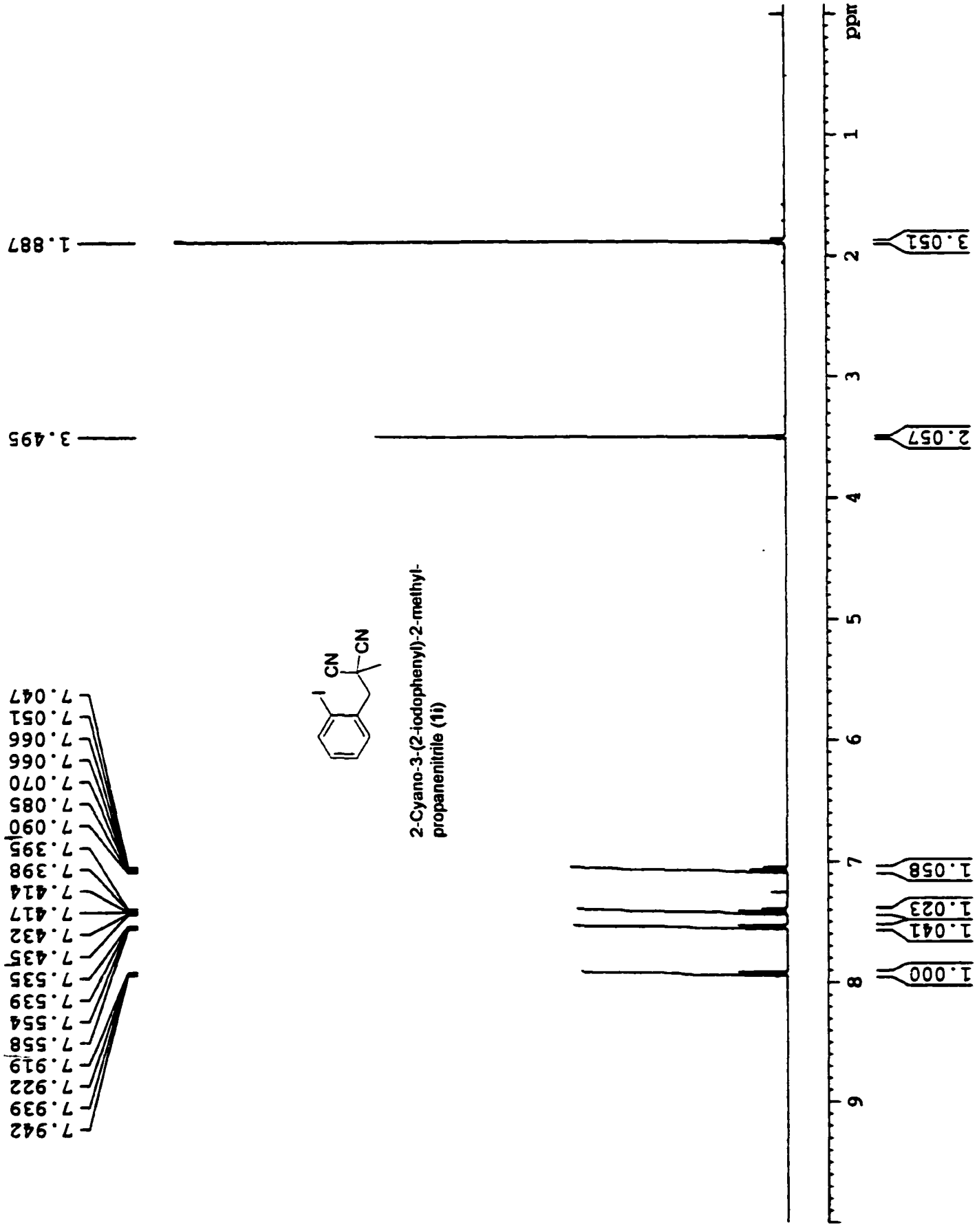

ppm
20
40
60
80
100
120
140
160
180
200
48.411
51.996
76.683
77.001
77.318
103.298
121.831
127.646
127.796
128.093
128.745
128.949
130.754
137.562
139.452
139.753
CN
Ph
Ph
I
3-(2-Iodophenyl)-2,2-diphenylpropanenitrile (1f)

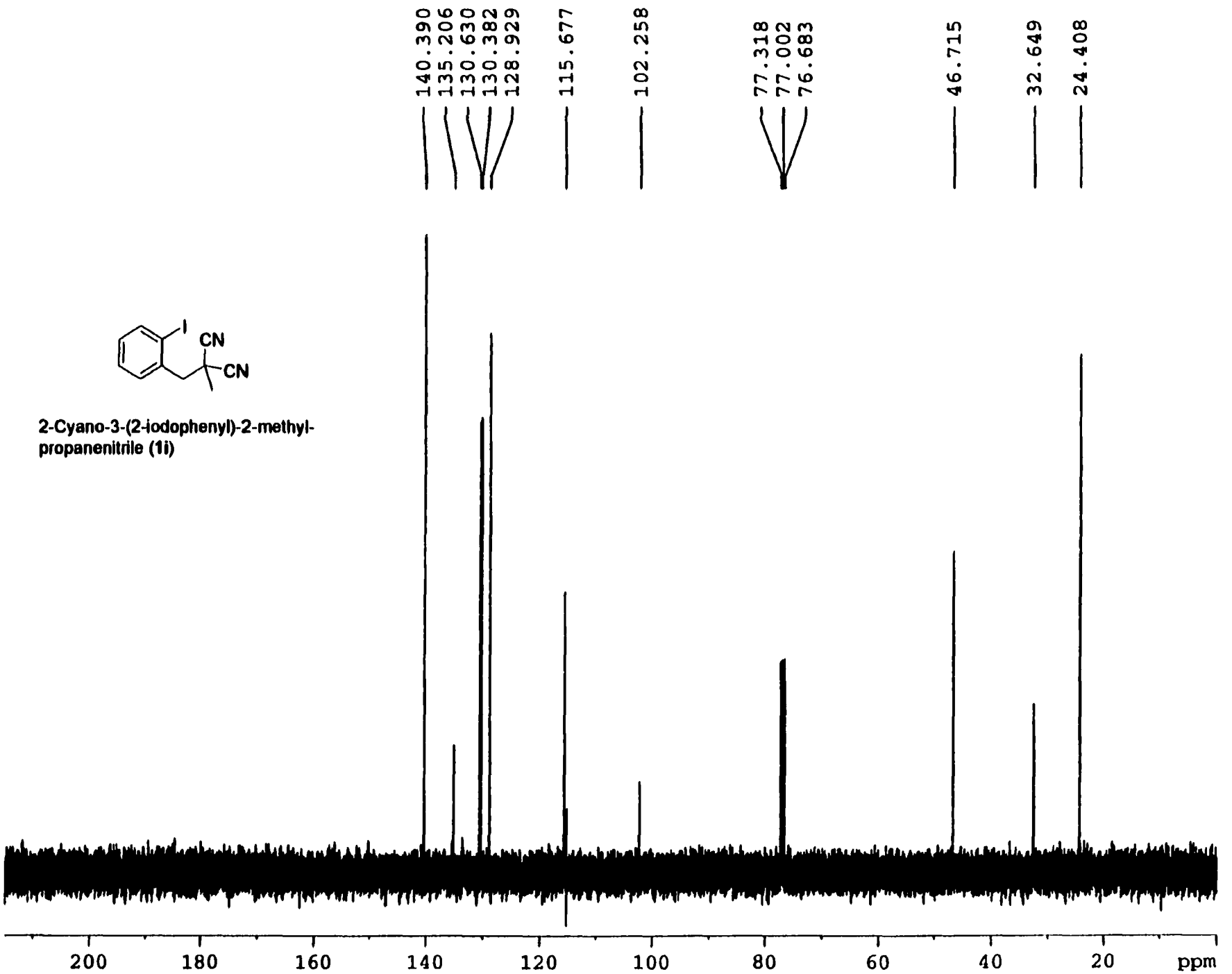

2-(2-Iodobenzyl)butanenitrile (1g)
CN
I
ppm
0.000
1.135
1.160
1.185
1.712
1.717
1.723
1.738
1.743
1.748
1.762
1.768
2.849
2.869
2.874
2.893
2.896
2.900
2.919
2.981
3.005
3.008
6.943
6.958
6.970
6.973
6.985
7.000
7.258
7.326
7.329
7.343
7.346
7.826
7.852
3.185
2.076
1.015
2.006
1.045
2.046
1.000

2-(2-Iodobenzyl)butanenitrile (1g)
CN
I
ppm
200
180
160
140
120
100
80
60
40
20
139.672
130.655
129.062
128.614
121.136
115.249
100.241
77.316
77.000
76.682
42.745
33.918
33.908
25.418
11.541

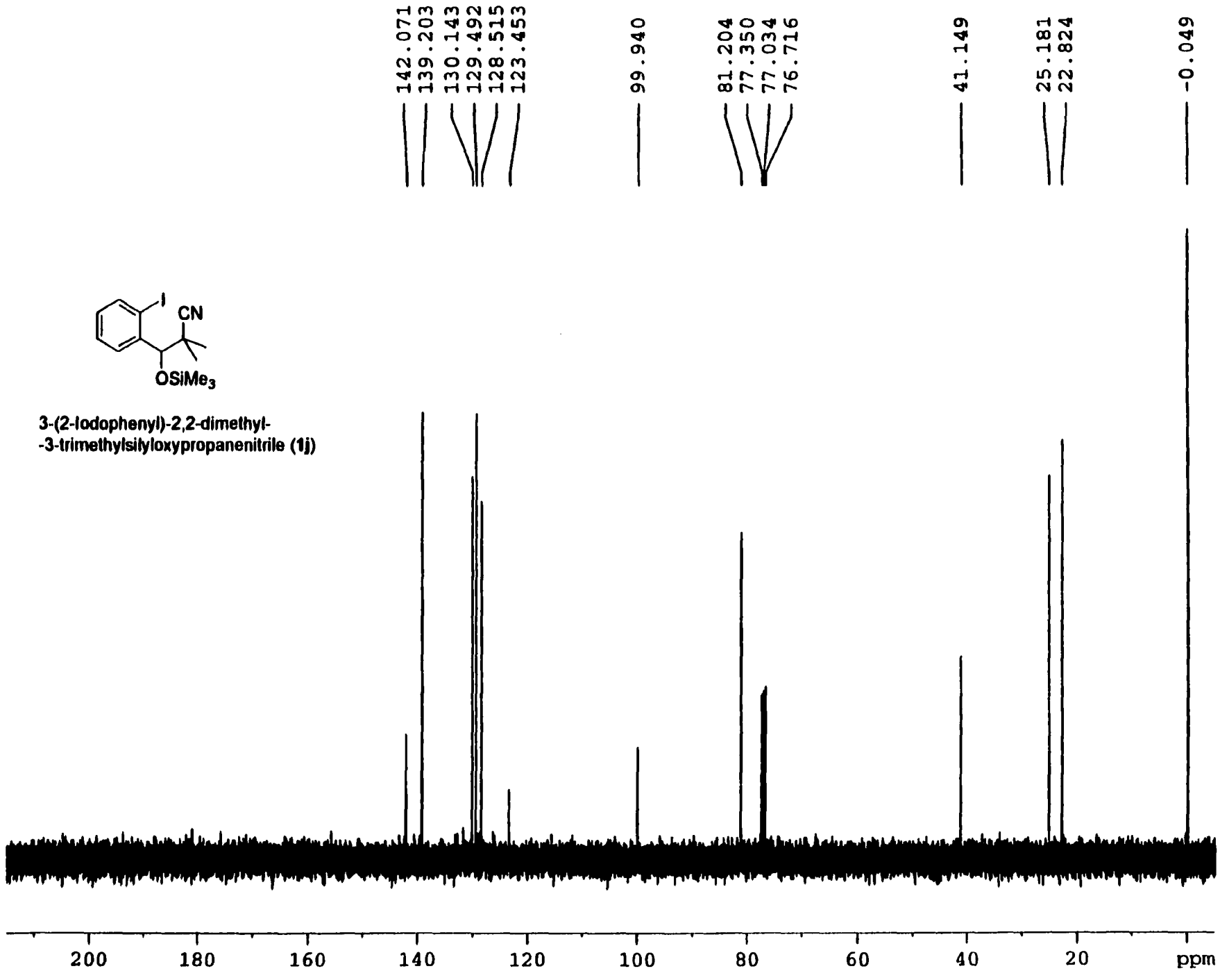

7.891
7.888
7.871
7.868
7.411
7.407
7.392
7.388
7.358
7.354
7.339
7.336
7.007
7.002
6.987
6.984
6.983
6.969
6.964
3.823
3.456
3.421
3.396
3.361
1.675
I
CN
CO2Me
Methyl 2-cyano-3-(2-iodophenyl)-
-2-methylpropanoate (1h)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.000
1.008
1.002
1.039
3.087
2.144
3.039

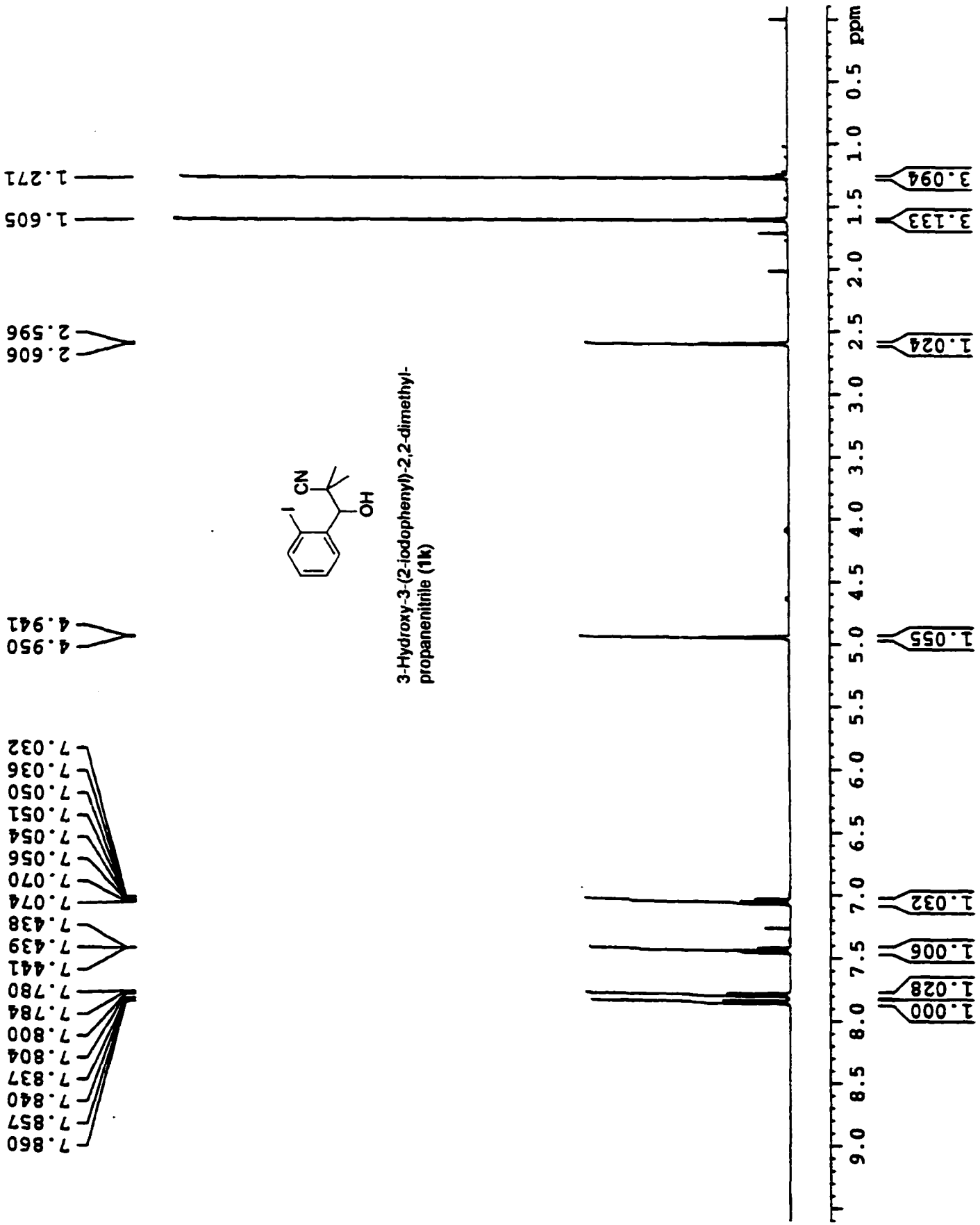

Methyl 2-cyano-3-(2-iodophenyl)-
-2-methylpropanoate (1h)
CN
CO2Me
169.056
140.023
137.302
130.170
129.427
128.452
119.285
102.208
77.316
76.998
76.680
53.694
45.933
44.599
22.861
200
180
160
140
120
100
80
60
40
20
ppm

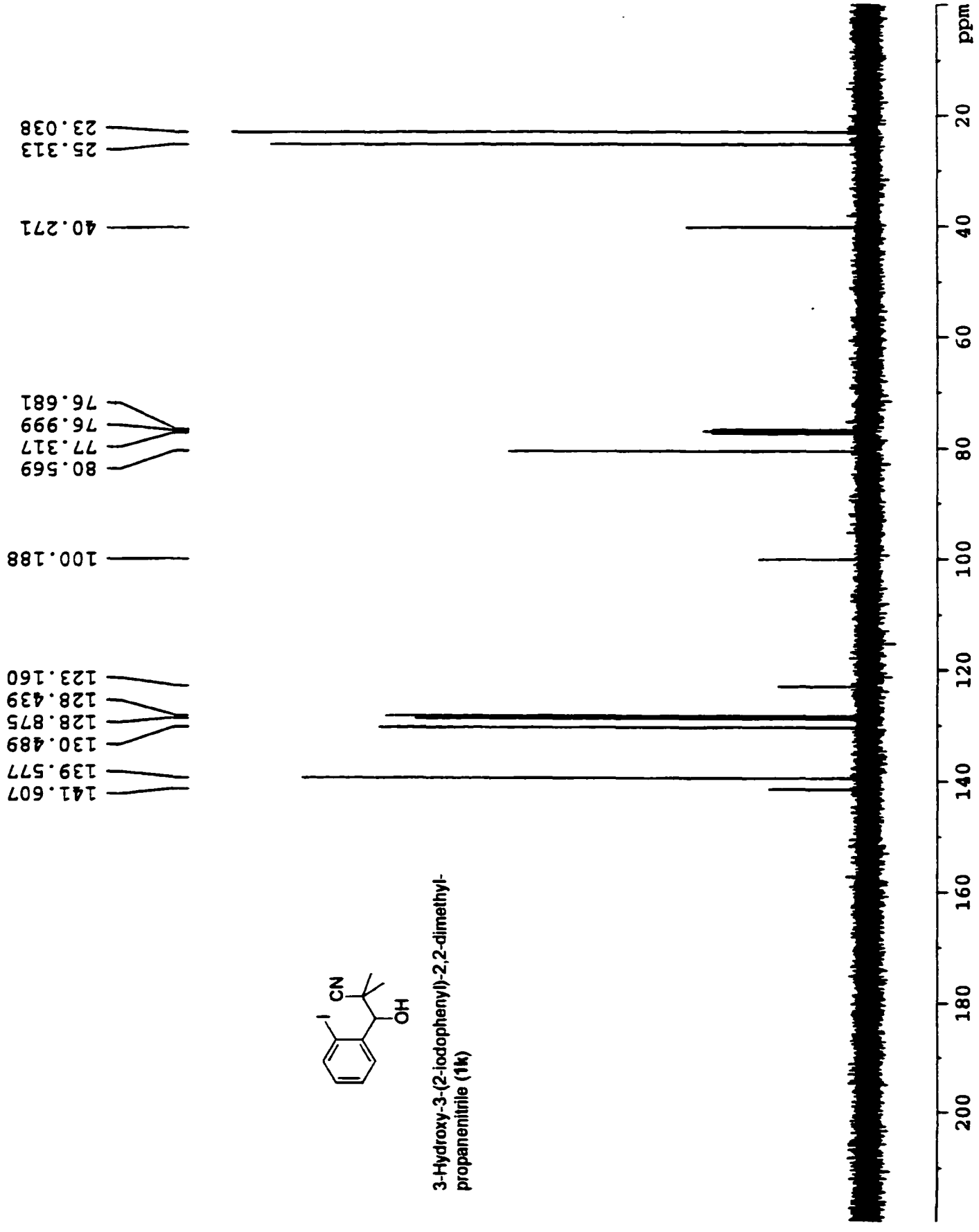

ppm
1
2
3
4
5
6
7
8
9
1.887
3.495
7.042
7.939
7.922
7.919
7.558
7.554
7.539
7.535
7.435
7.432
7.417
7.414
7.398
7.395
7.090
7.085
7.070
7.066
7.066
7.051
7.047
3.051
2.057
1.058
1.041
1.023
1.000
CN
CN
2-Cyano-3-(2-iodophenyl)-2-methyl-propanenitrile (1i)

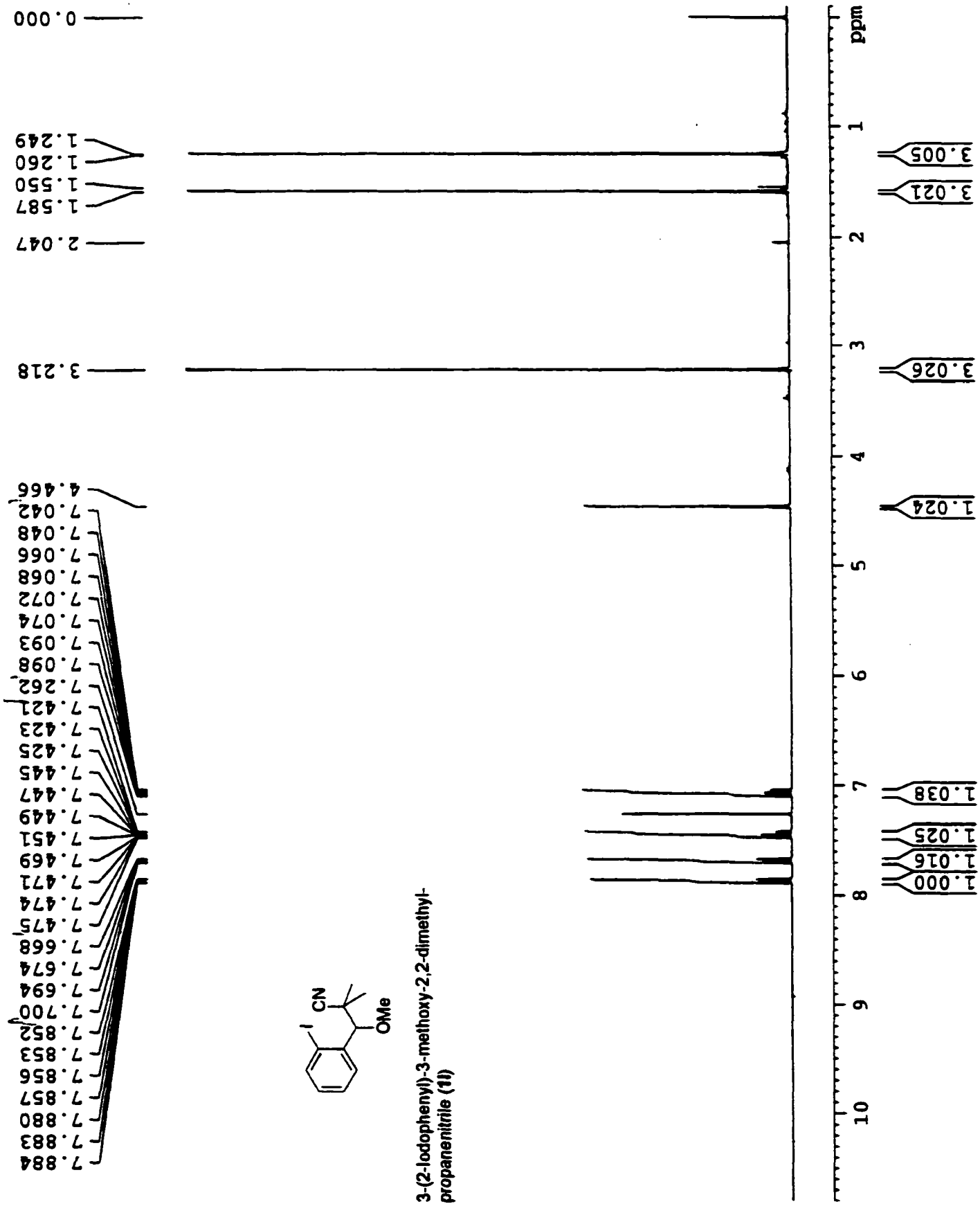

140.390
135.206
130.630
130.382
128.929
115.677
102.258
77.318
77.002
76.683
46.715
32.649
24.408
I
CN
CN
2-Cyano-3-(2-iodophenyl)-2-methyl-propanenitrile (1i)
200
180
160
140
120
100
80
60
40
20
ppm

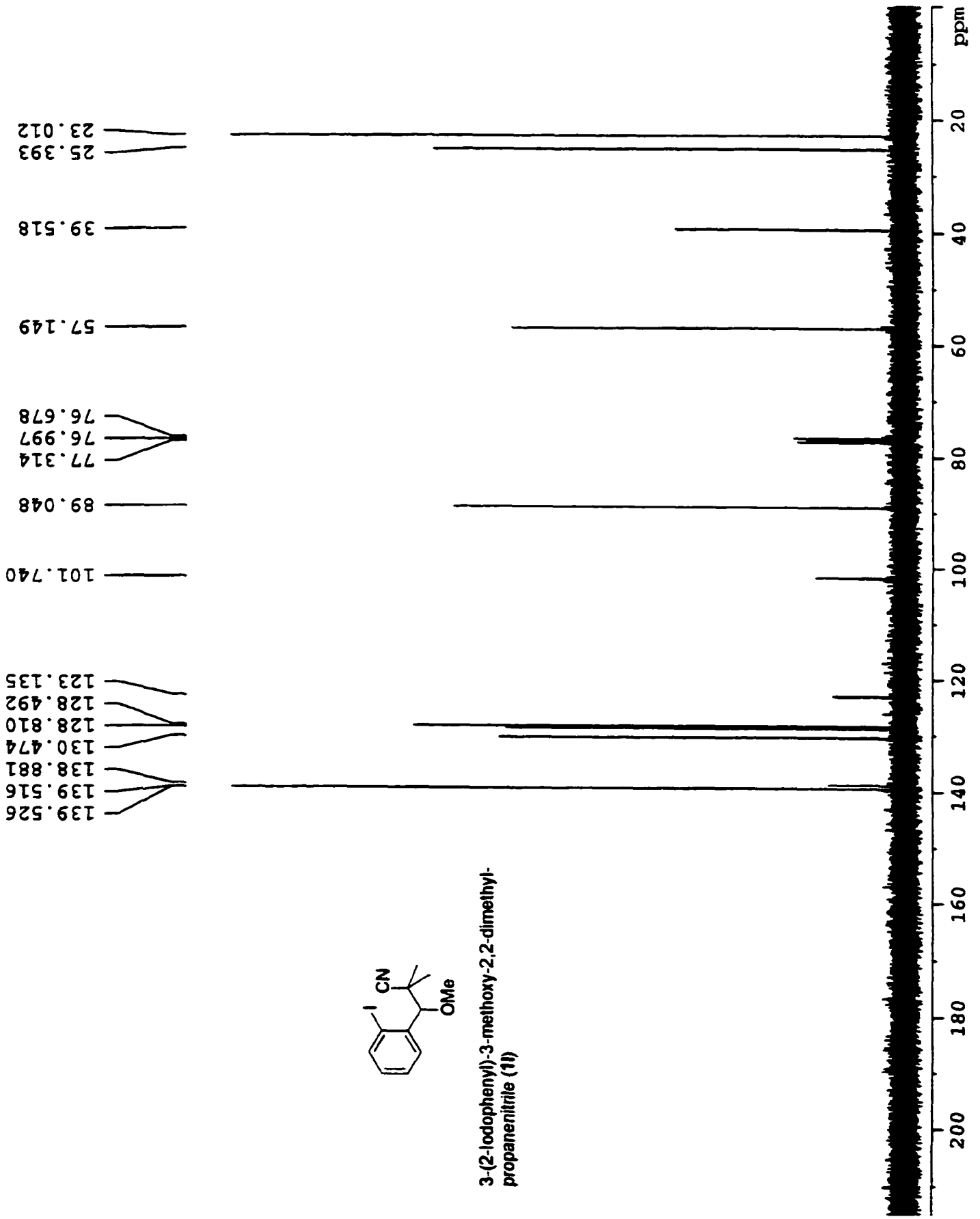
3-(2-Iodophenyl)-2,2-dimethyl-
-3-trimethylsilyloxypropanenitrile (1l)
CN
OSiMe3
7.825
7.822
7.819
7.805
7.802
7.799
7.759
7.755
7.739
7.735
7.420
7.401
7.385
7.383
7.042
7.038
7.022
7.019
7.003
7.000
4.830
1.517
1.257
0.029
0.020
0.017
1.000
0.996
1.016
1.023
0.994
3.006
3.014
8.978
ppm

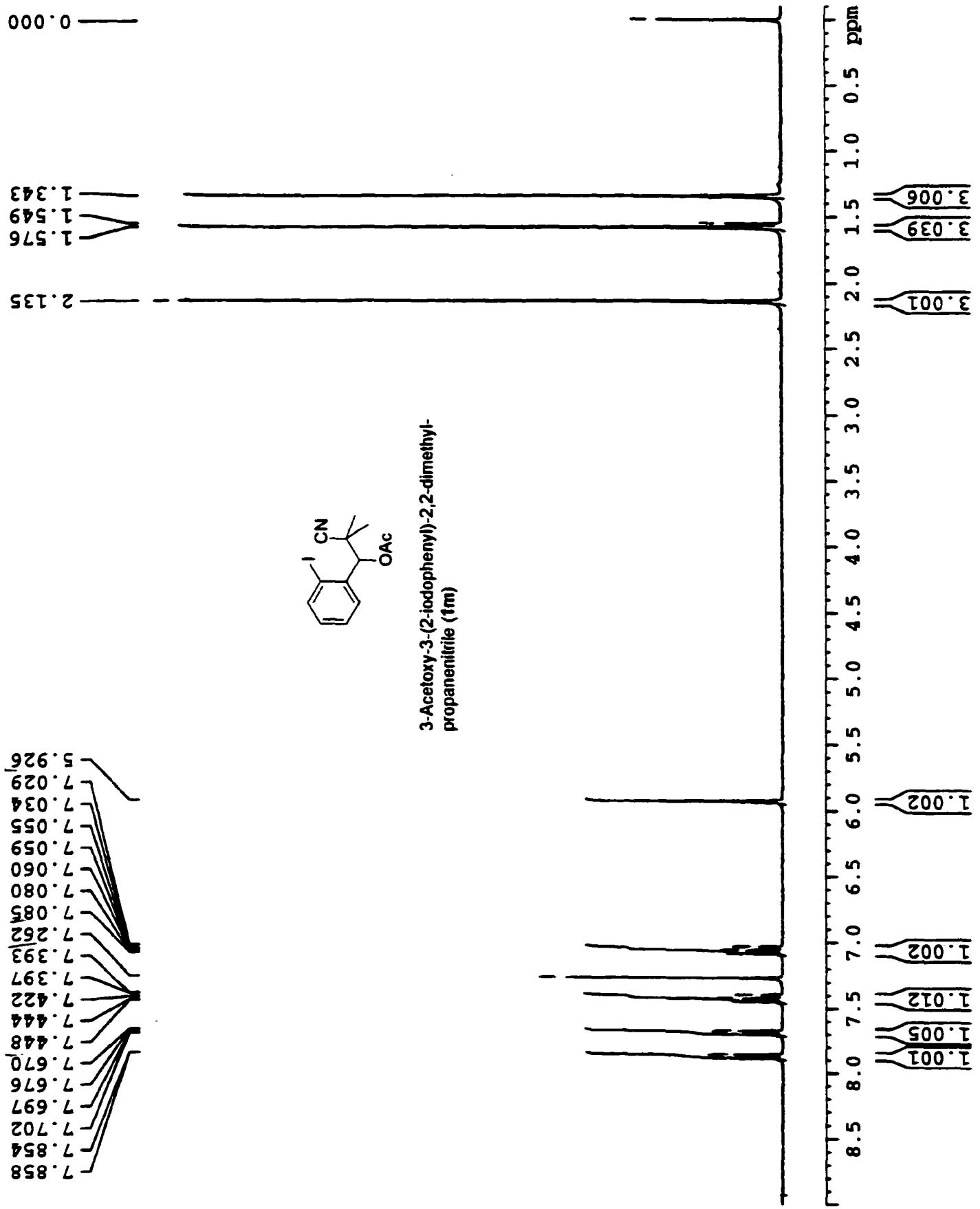

142.071
139.203
130.143
129.492
128.515
123.453
99.940
81.204
77.350
77.034
76.716
41.149
25.181
22.824
-0.049
I
CN
OSiMe3
3-(2-Iodophenyl)-2,2-dimethyl-
-3-trimethylsilyloxypropanenitrile (1j)
200
180
160
140
120
100
80
60
40
20
ppm

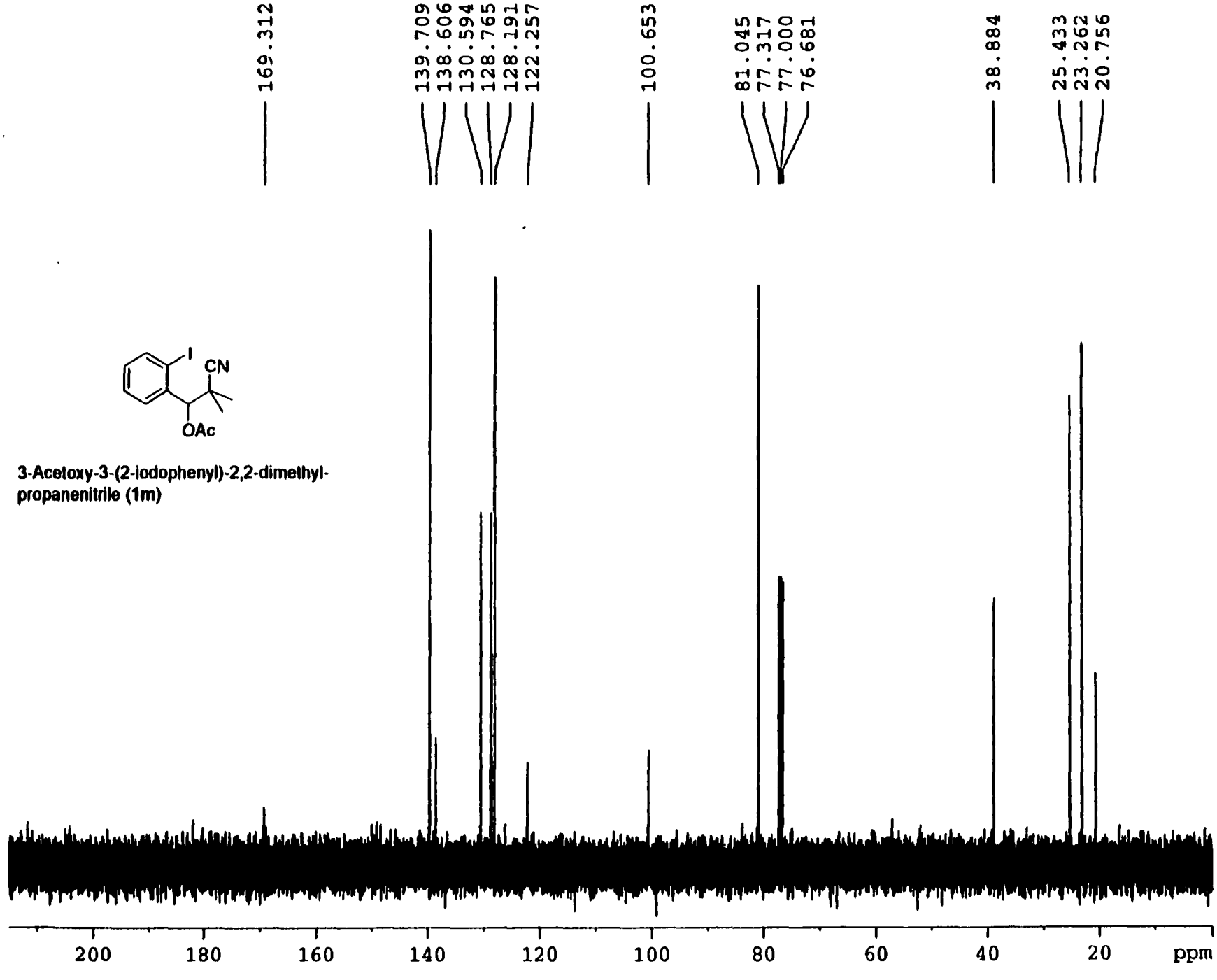

3-Hydroxy-3-(2-iodophenyl)-2,2-dimethyl-propanenitrile (1k)
CN
OH
I
ppm
1.000
1.028
1.006
1.032
1.055
1.024
3.133
3.094
1.271
1.605
2.606
2.596
4.950
4.941
7.860
7.857
7.840
7.837
7.804
7.800
7.784
7.780
7.441
7.439
7.438
7.074
7.070
7.056
7.054
7.051
7.050
7.036
7.032


23.038
25.313
40.271
76.681
76.999
77.317
80.569
100.188
123.160
128.439
128.875
130.489
139.577
141.607
ppm
20
40
60
80
100
120
140
160
180
200
CN
OH
I
3-Hydroxy-3-(2-iodophenyl)-2,2-dimethyl-propanenitrile (1k)

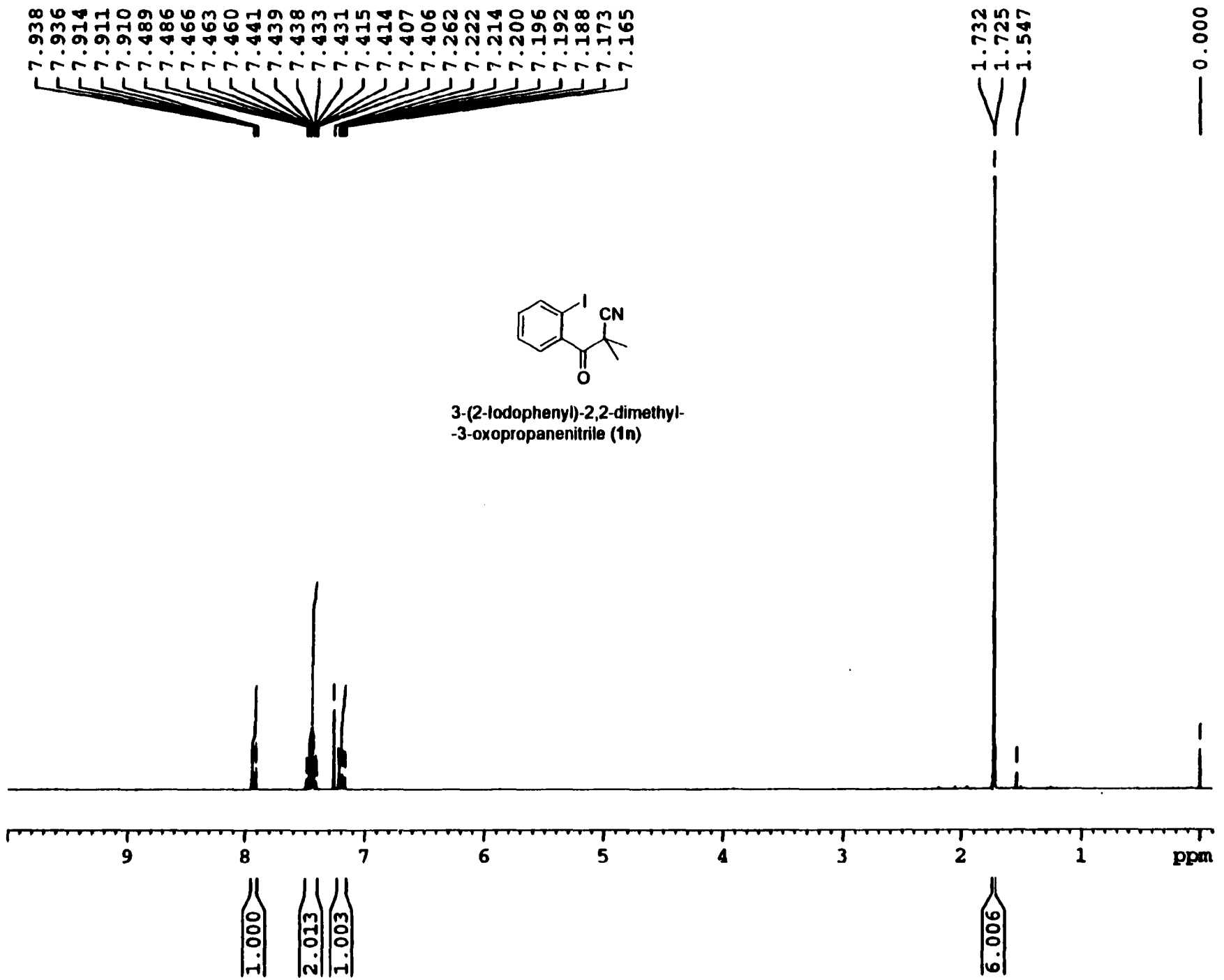

0.000
1.249
1.260
1.550
1.587
2.047
3.218
4.466
7.042
7.048
7.066
7.068
7.072
7.074
7.093
7.098
7.262
7.421
7.423
7.425
7.445
7.447
7.449
7.451
7.469
7.471
7.474
7.475
7.668
7.674
7.694
7.700
7.852
7.853
7.856
7.857
7.880
7.883
7.884
ppm
1
2
3
4
5
6
7
8
9
10
3.005
3.021
3.026
1.024
1.038
1.025
1.016
1.000
CN
OMe
3-(2-Iodophenyl)-3-methoxy-2,2-dimethyl-propanenitrile (1l)

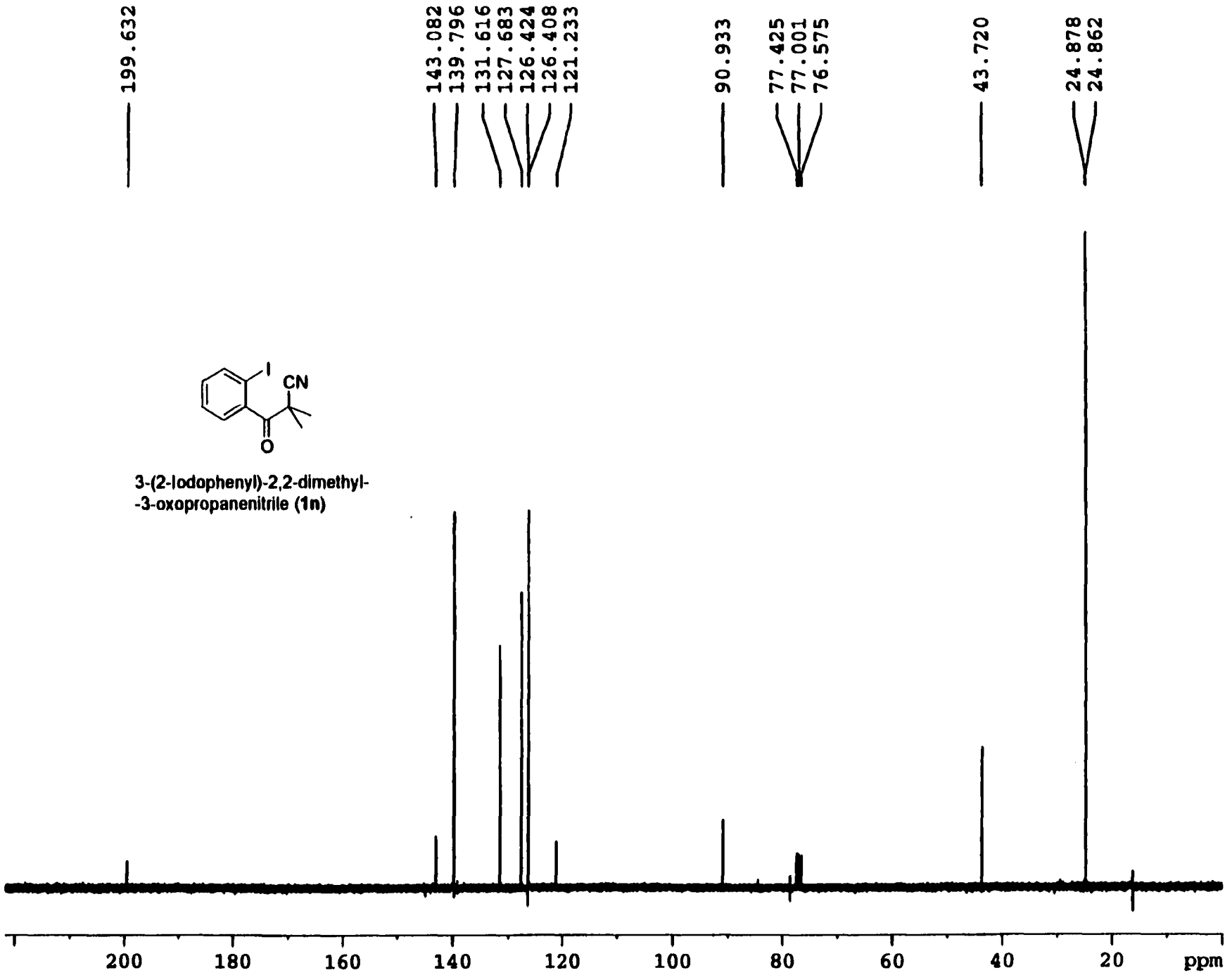

ppm
20
40
60
80
100
120
140
160
180
200
23.012
25.393
39.518
57.149
76.678
76.997
77.314
89.048
101.740
123.135
128.492
128.810
130.474
138.881
139.516
139.526
CN
OMe
3-(2-Iodophenyl)-3-methoxy-2,2-dimethyl-propanenitrile (11)

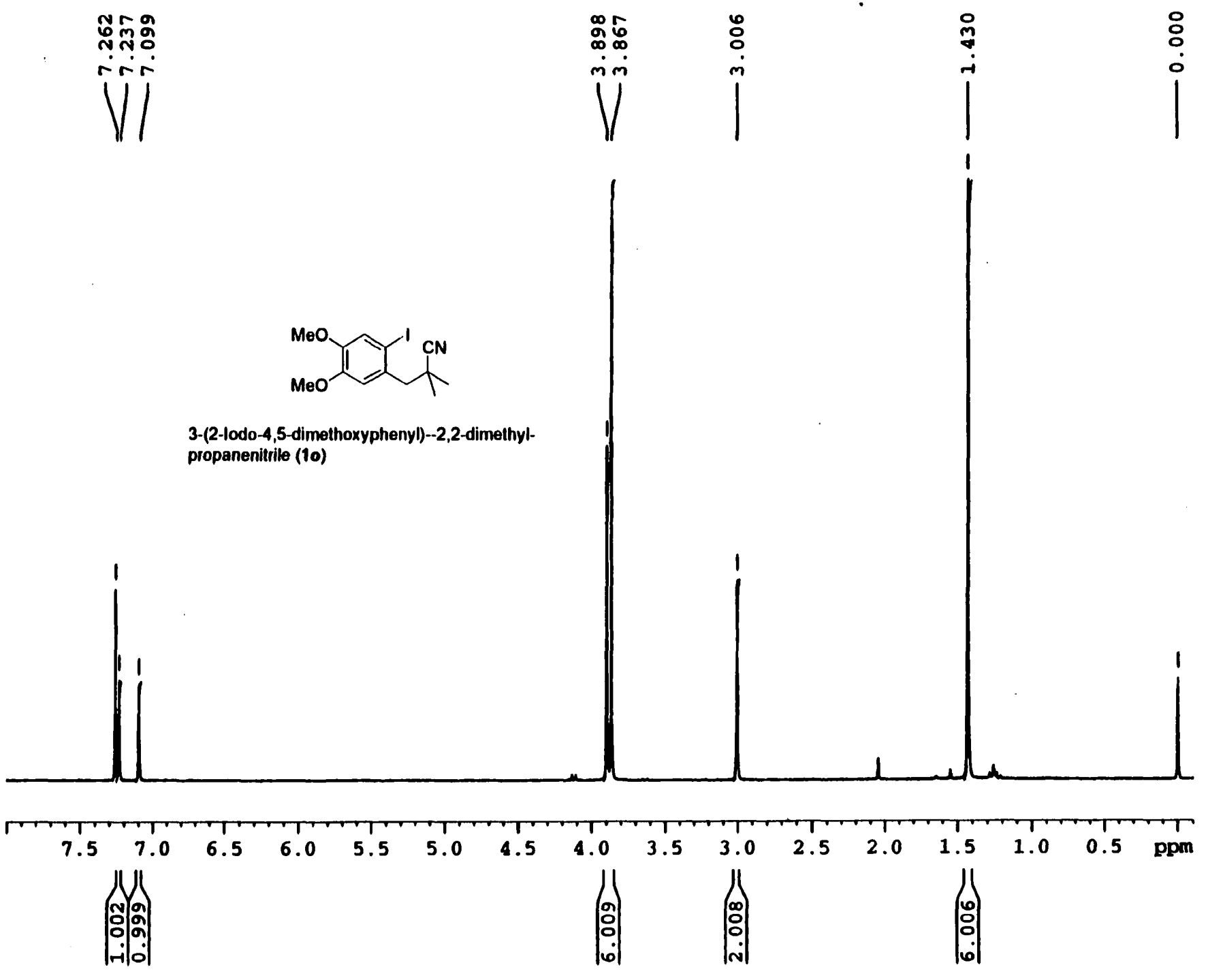

3-Acetoxy-3-(2-iodophenyl)-2,2-dimethyl-propanenitrile (1m)
CN
OAc
I
ppm
0.000
1.343
1.549
1.576
2.135
5.926
7.029
7.034
7.055
7.059
7.060
7.080
7.085
7.262
7.393
7.397
7.422
7.444
7.448
7.670
7.676
7.697
7.702
7.854
7.858
3.006
3.039
3.001
1.002
1.002
1.012
1.005
1.001



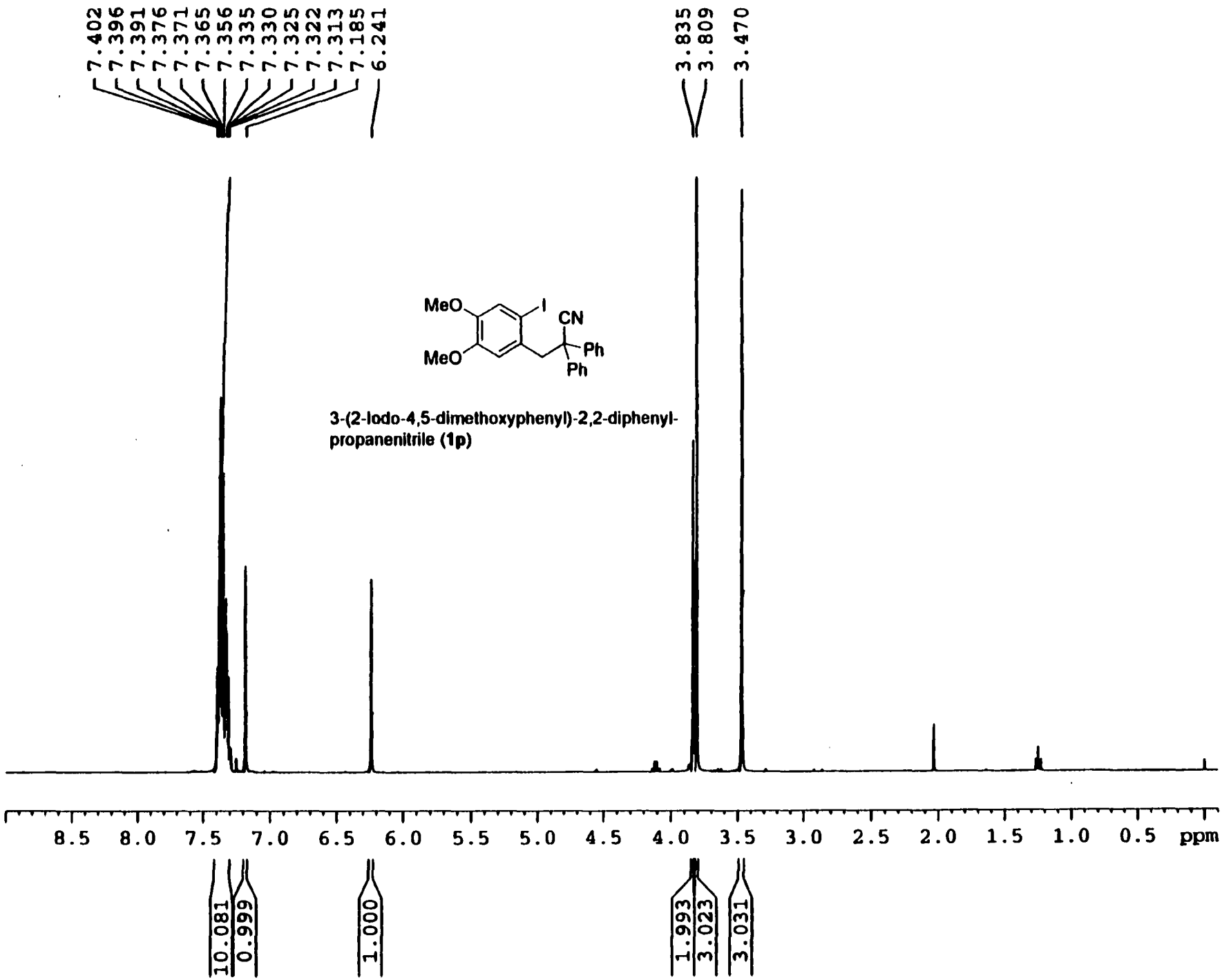

**3-Acetoxy-3-(2-iodophenyl)-2,2-dimethyl-propanenitrile (1m)**


7.938
7.936
7.914
7.911
7.910
7.489
7.486
7.466
7.463
7.460
7.441
7.439
7.438
7.433
7.431
7.415
7.414
7.407
7.406
7.262
7.222
7.214
7.200
7.196
7.192
7.188
7.173
7.165
1.732
1.725
1.547
0.000
I
CN
O
3-(2-Iodophenyl)-2,2-dimethyl-
-3-oxopropanenitrile (1n)
9
8
7
6
5
4
3
2
1
ppm
1.000
2.013
1.003
6.006


199.632
143.082
139.796
131.616
127.683
126.424
126.408
121.233
90.933
77.425
77.001
76.575
43.720
24.878
24.862
I
CN
O
3-(2-Iodophenyl)-2,2-dimethyl-
-3-oxopropanenitrile (1n)
200
180
160
140
120
100
80
60
40
20
ppm


7.262
7.237
7.099
3.898
3.867
3.006
1.430
0.000
MeO
MeO
I
CN
3-(2-Iodo-4,5-dimethoxyphenyl)--2,2-dimethyl-propanenitrile (1o)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.002
0.999
6.009
2.008
6.006

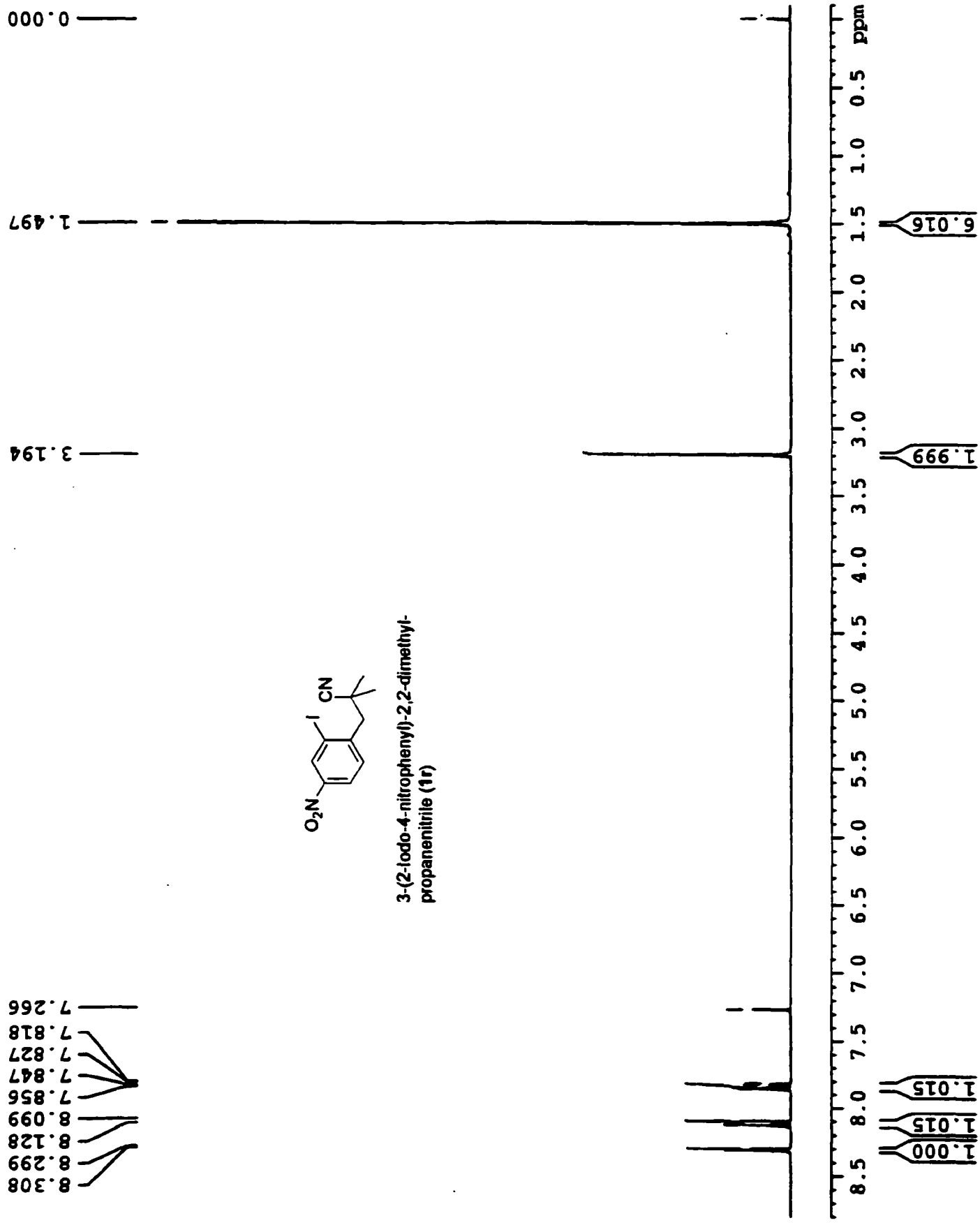
3-(2-Iodo-4,5-dimethoxyphenyl)--2,2-dimethyl-propanenitrile (1o)
MeO
MeO
I
CN
149.037
148.394
131.359
124.923
121.453
112.789
90.026
77.322
77.002
76.683
55.936
55.757
55.747
48.529
34.411
26.344
200
180
160
140
120
100
80
60
40
20
ppm

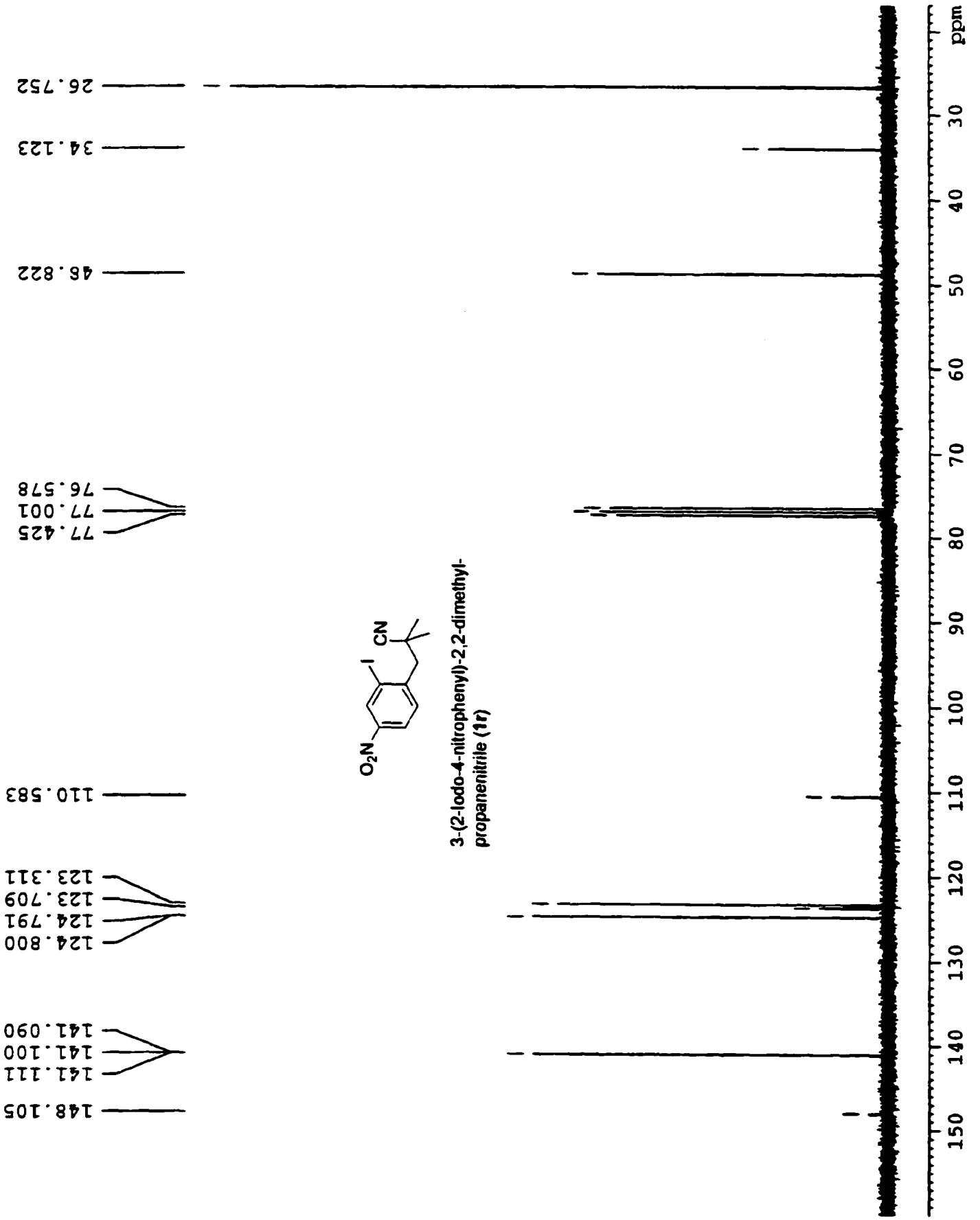

7.402
7.396
7.391
7.376
7.371
7.365
7.356
7.335
7.330
7.325
7.322
7.313
7.185
6.241
3.835
3.809
3.470
MeO
MeO
I
CN
Ph
Ph
3-(2-Iodo-4,5-dimethoxyphenyl)-2,2-diphenyl-propanenitrile (1p)
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
10.081
0.999
1.000
1.993
3.023
3.031

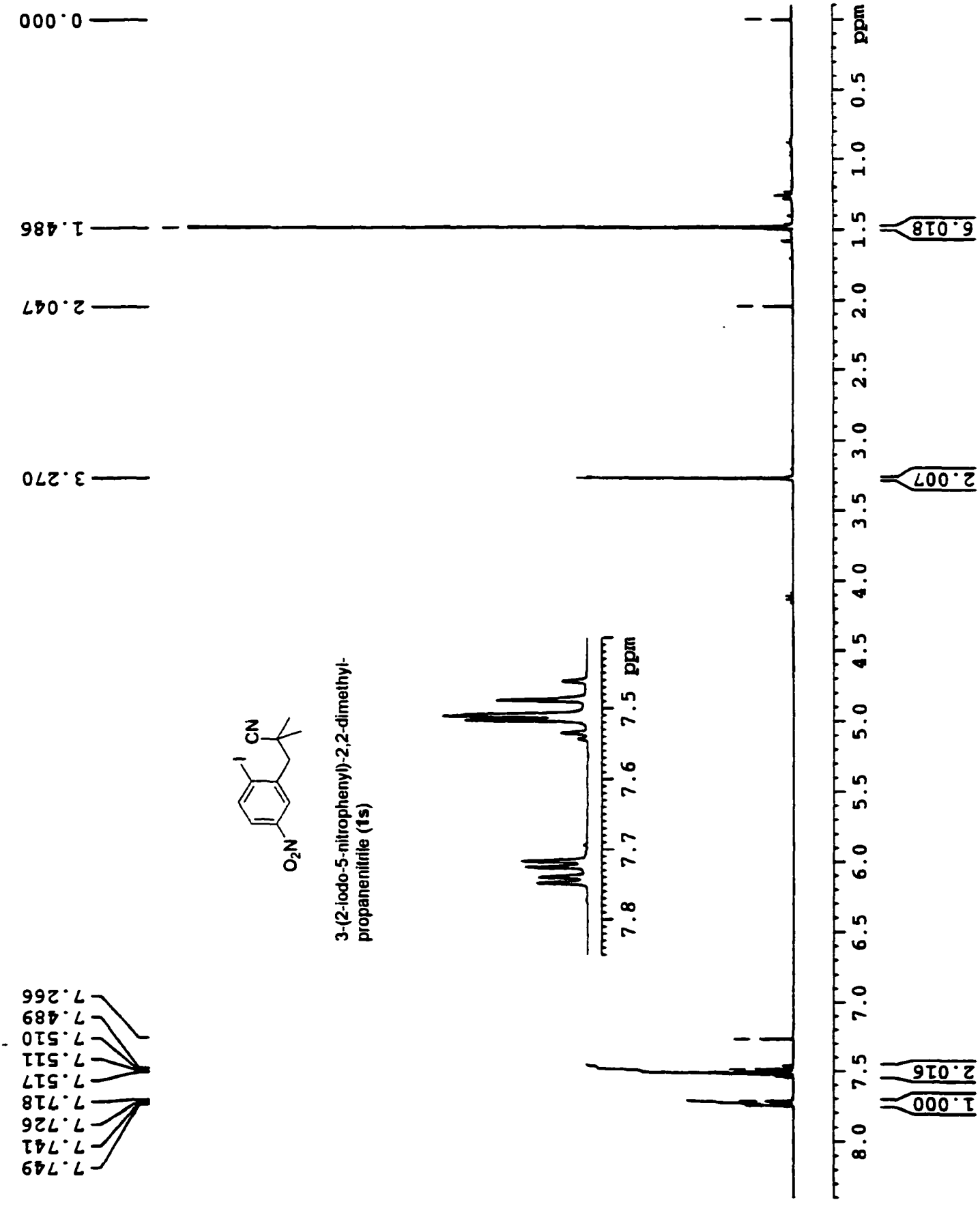
3-(2-Iodo-4,5-dimethoxyphenyl)-2,2-diphenyl-propanenitrile (1p)
MeO
MeO
I
CN
Ph
Ph
139.553
129.649
128.702
127.968
127.597
121.620
121.413
113.062
91.013
77.314
76.997
76.676
55.867
55.254
52.206
47.975
200
180
160
140
120
100
80
60
40
20
ppm

7.738
7.710
7.623
7.615
7.138
7.130
7.110
7.102
3.040
1.449
1.000
0.987
1.008
2.012
6.030
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3-(5-Bromo-2-iodophenyl)-2,2-dimethyl-propanenitrile (1q)
Br
I
CN

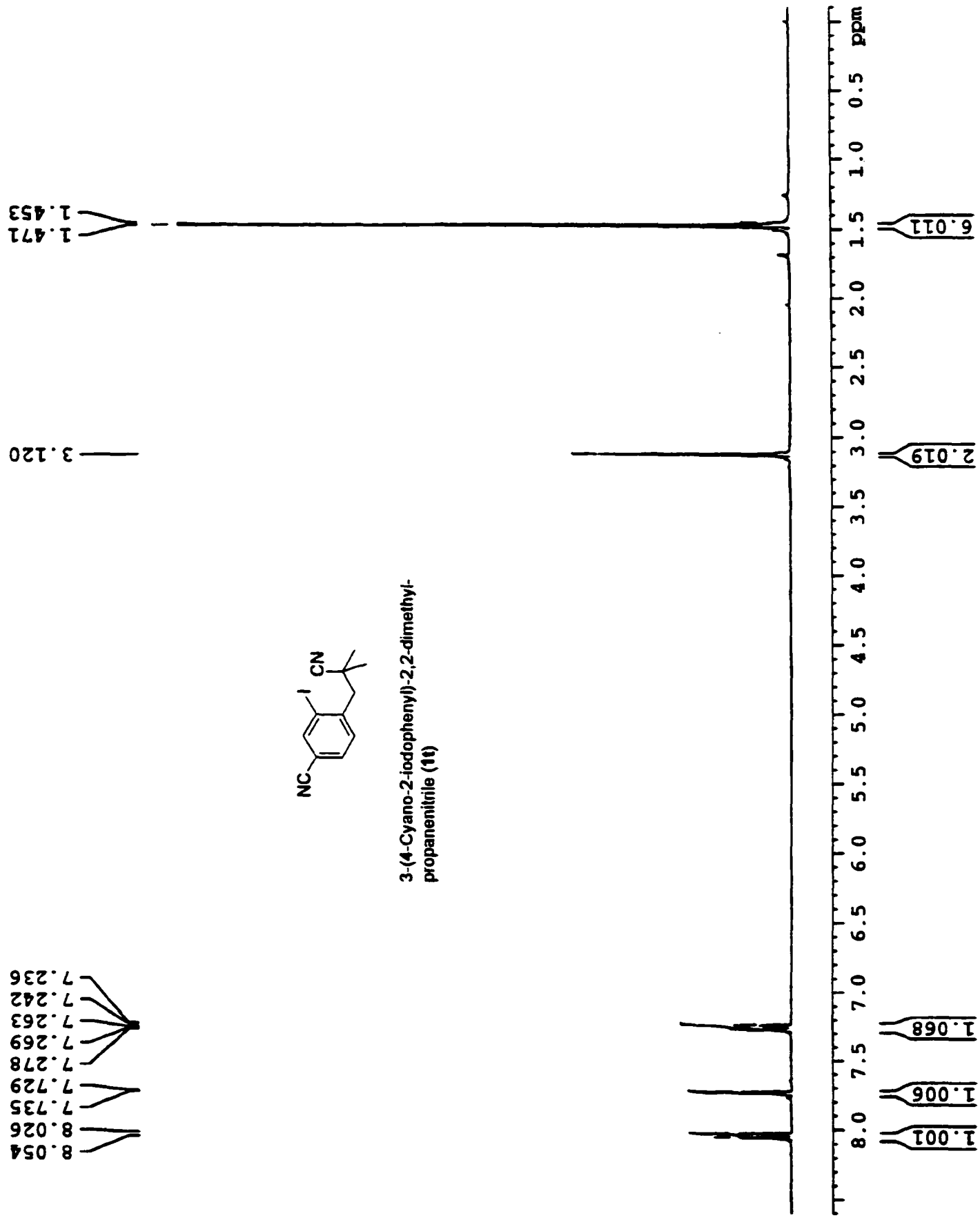
3-(5-Bromo-2-iodophenyl)-2,2-dimethyl-propanenitrile (1q)
Br
I
CN
141.117
141.102
133.457
132.244
124.167
122.682
100.505
77.423
76.999
76.576
48.505
34.121
26.629
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm


0.000
1.497
3.194
7.266
7.818
7.827
7.847
7.856
8.099
8.128
8.299
8.308
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
1.015
1.015
6.016
1.999
I
CN
O2N
3-(2-Iodo-4-nitrophenyl)-2,2-dimethyl-propanenitrile (1r)

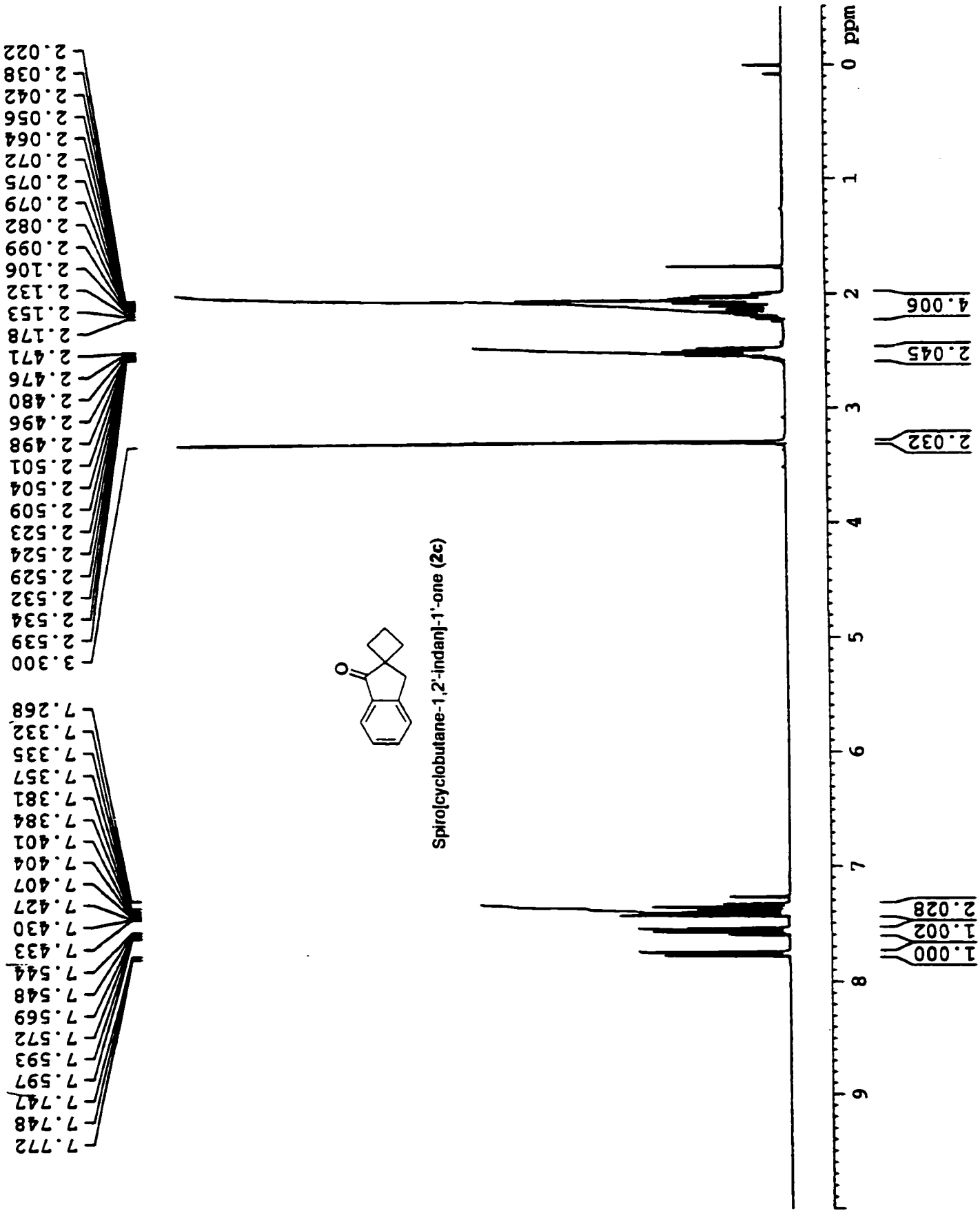

26.752
34.123
46.822
76.578
77.001
77.425
110.583
123.311
123.709
124.791
124.800
141.090
141.100
141.111
148.105
ppm
3-(2-Iodo-4-nitrophenyl)-2,2-dimethyl-propanenitrile (1r)
CN
I
O2N

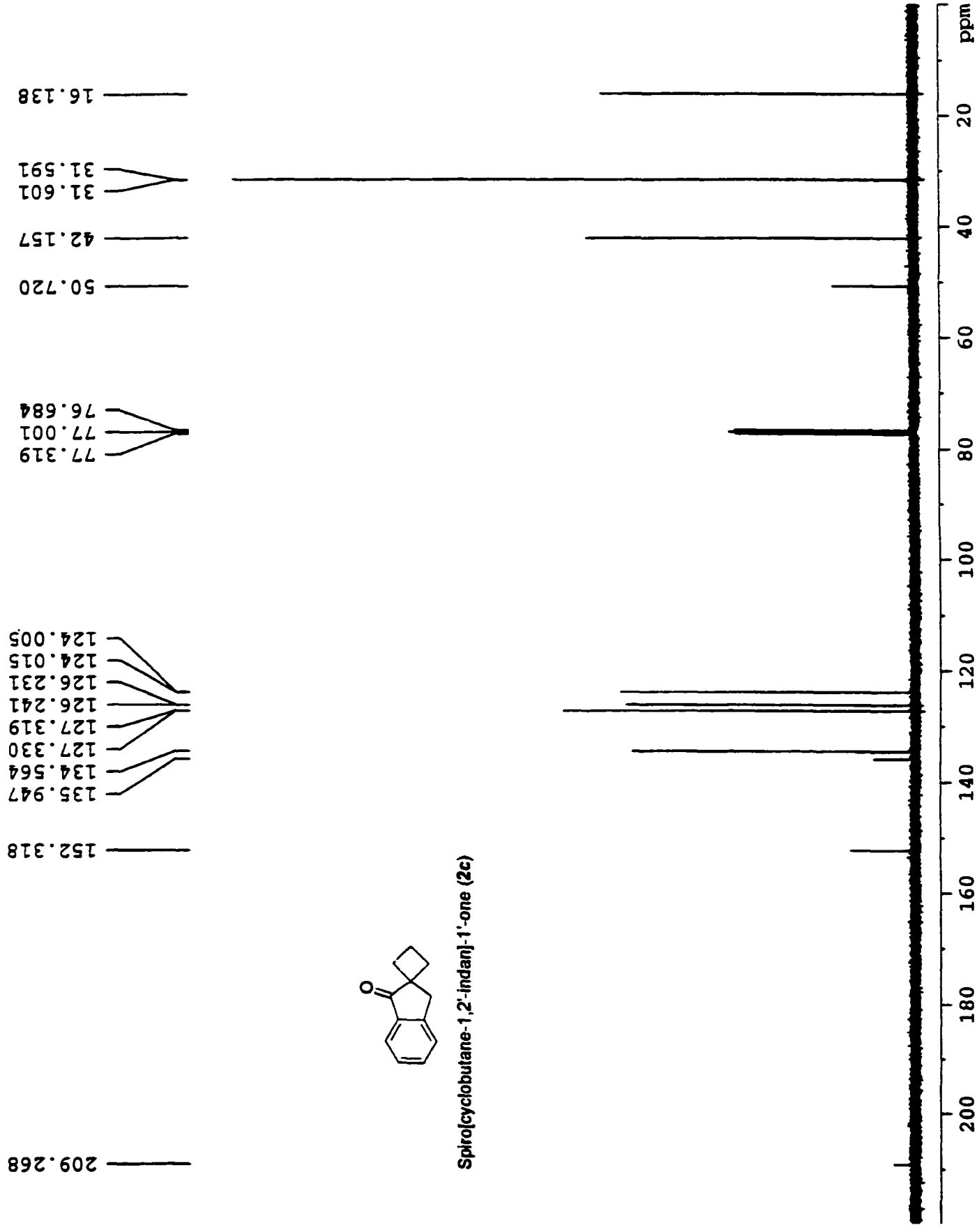

3-(2-iodo-5-nitrophenyl)-2,2-dimethyl-propanenitrile (1s)
CN
I
O2N
7.8
7.7
7.6
7.5 ppm
0.000
1.486
2.047
3.270
7.749
7.741
7.726
7.718
7.517
7.511
7.510
7.489
7.266
1.000
2.016
2.007
6.018
ppm

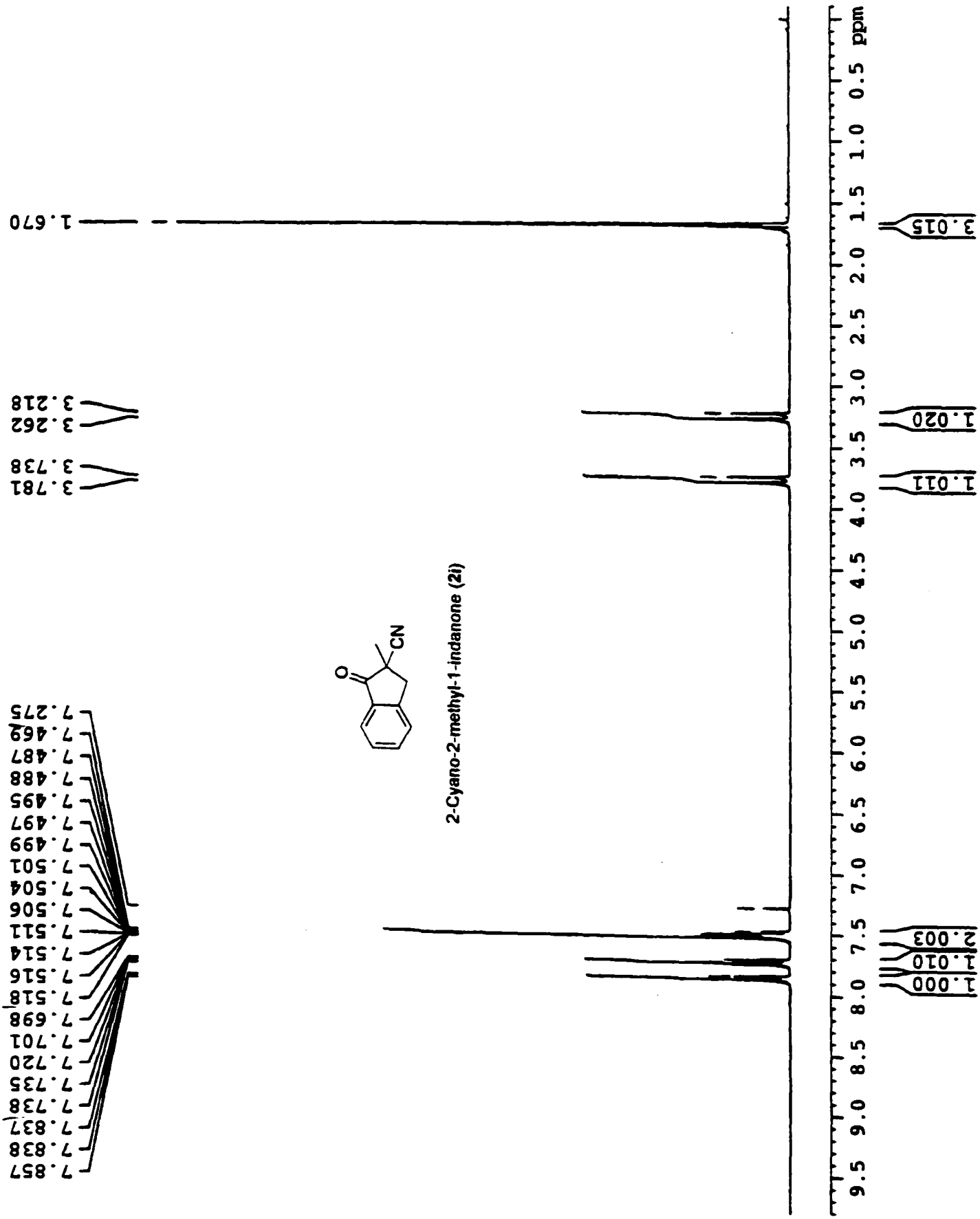
148.105
141.111
141.100
141.090
124.800
124.791
123.709
123.311
110.583
77.425
77.001
76.578
48.822
34.123
26.752
3-(2-Iodo-4-nitrophenyl)-2,2-dimethyl-propanenitrile (1f)
O2N
I
CN
150
140
130
120
110
100
90
80
70
60
50
40
30
ppm


8.054
8.026
7.735
7.729
7.278
7.269
7.263
7.242
7.236
3.120
1.471
1.453
1.001
1.006
1.068
2.019
6.011
ppm
3-(4-Cyano-2-iodophenyl)-2,2-dimethyl-propanenitrile (1t)
NC
I
CN

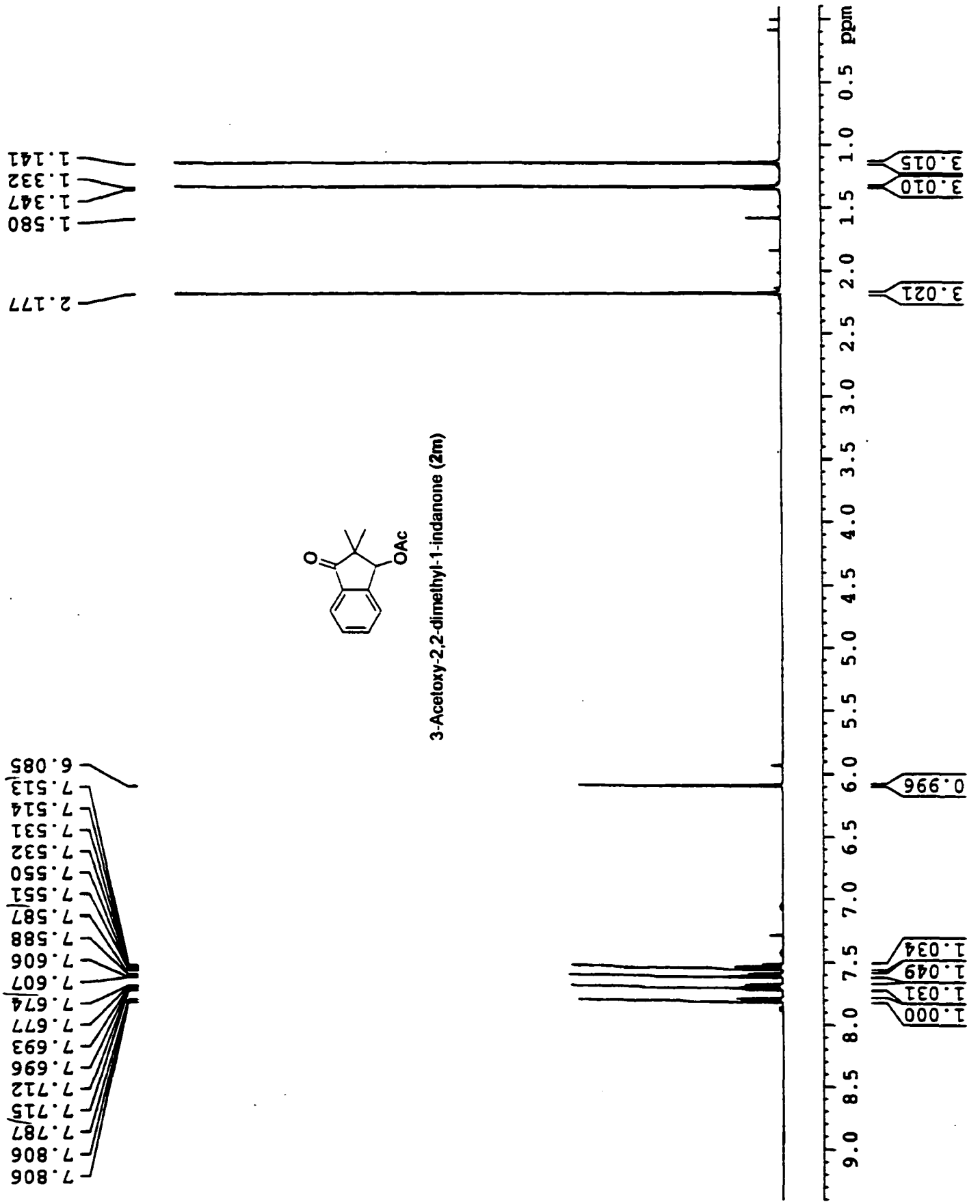
141.026
140.794
133.202
131.625
123.777
117.706
112.626
108.564
77.424
77.001
76.579
48.526
34.025
26.619
3-(4-Cyano-2-iodophenyl)-2,2-dimethyl-propanenitrile (1t)
NC
I
CN
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
ppm

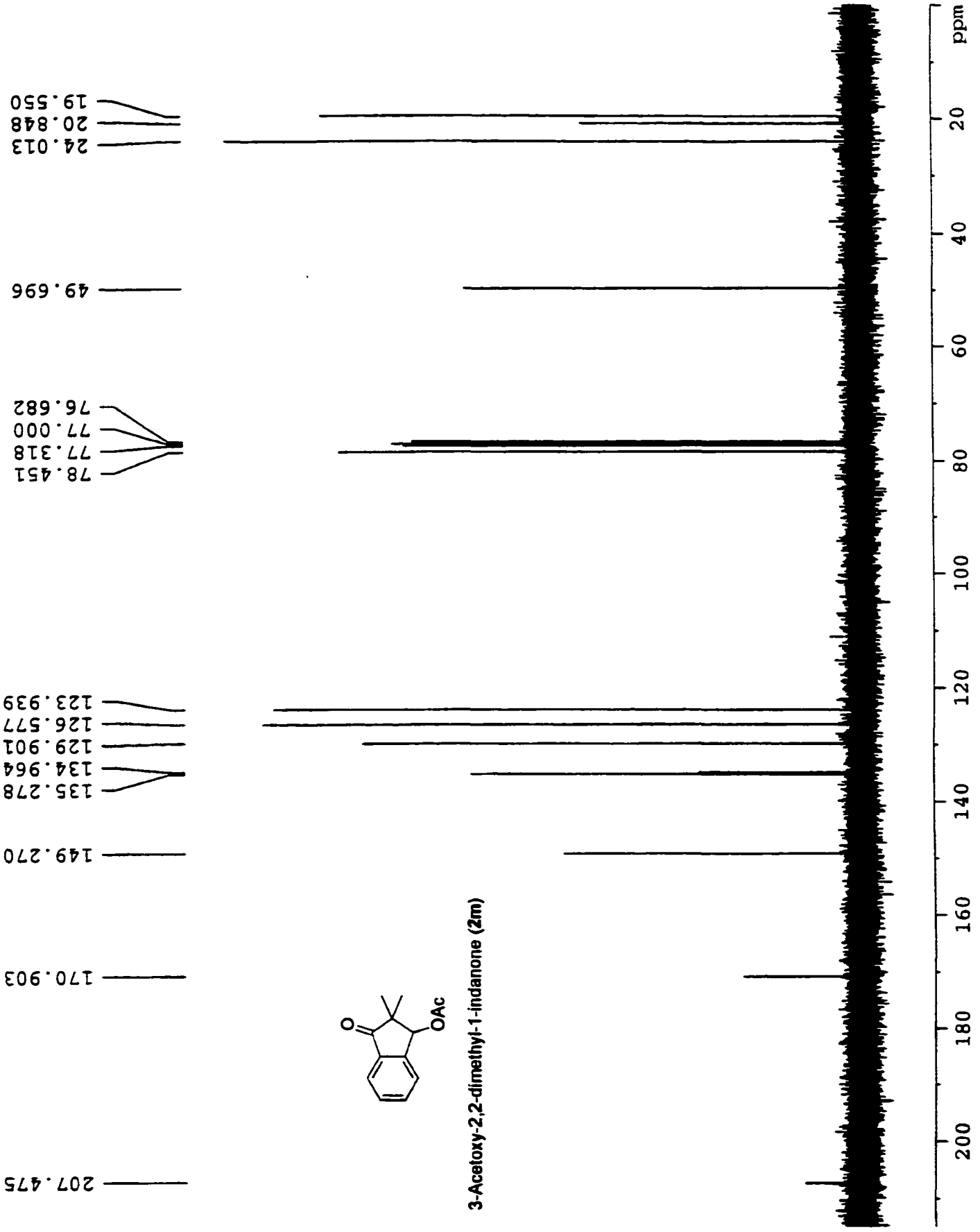

Spiro[cyclobutane-1,2'-indan]-1'-one (2c)
O
ppm
0
1
2
3
4
5
6
7
8
9
4.006
2.045
2.032
1.000
1.002
2.028
2.022
2.038
2.042
2.056
2.064
2.072
2.075
2.079
2.082
2.099
2.106
2.132
2.153
2.178
2.471
2.476
2.480
2.496
2.498
2.501
2.504
2.509
2.523
2.524
2.529
2.532
2.534
2.539
3.300
7.268
7.332
7.335
7.357
7.381
7.384
7.401
7.404
7.407
7.427
7.430
7.433
7.544
7.548
7.569
7.572
7.593
7.597
7.747
7.748
7.772

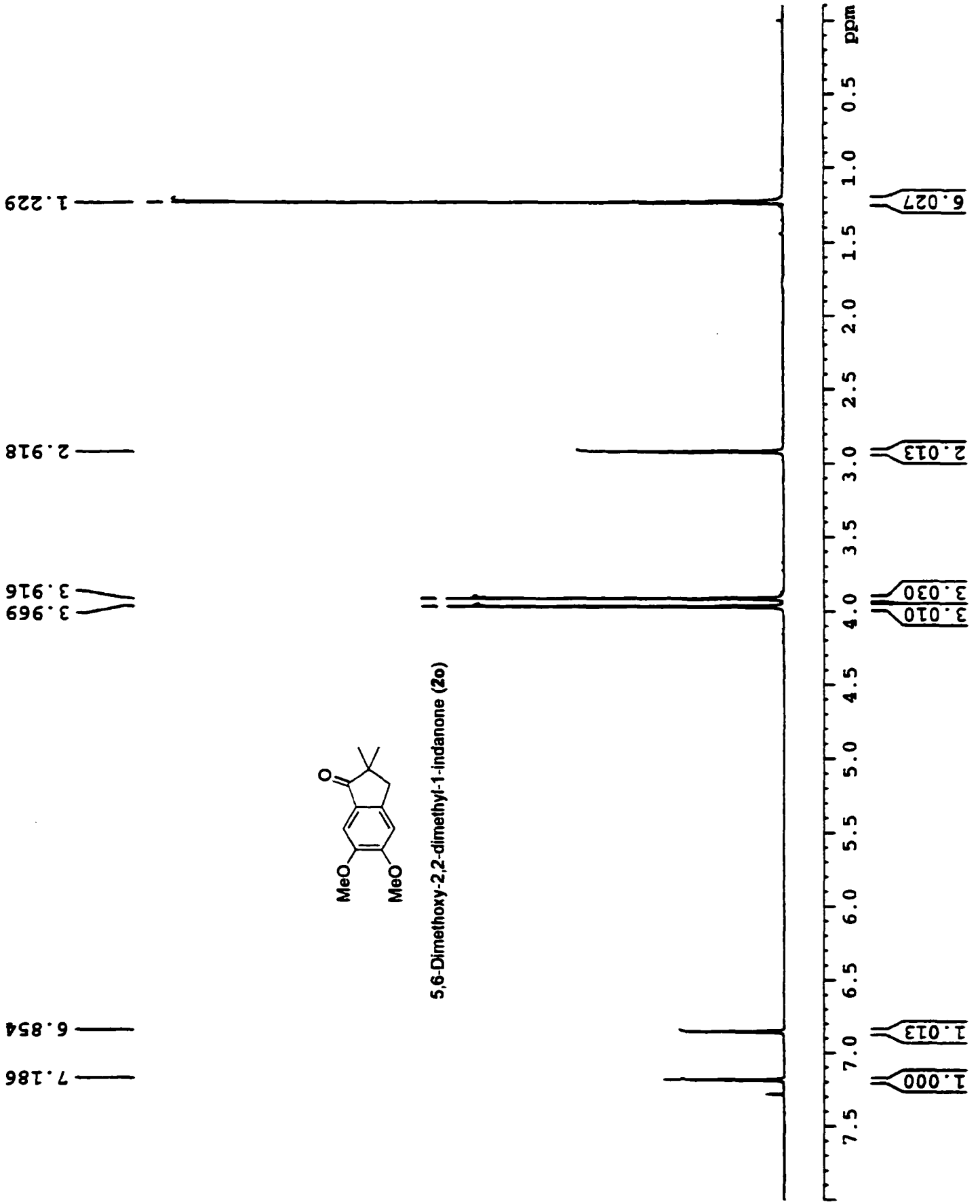

209.268
152.318
135.947
134.564
127.330
127.319
126.241
126.231
124.015
124.005
77.319
77.001
76.684
50.720
42.157
31.601
31.591
16.138
ppm
20
40
60
80
100
120
140
160
180
200
O
Spiro[cyclobutane-1,2'-indan]-1'-one (2c)

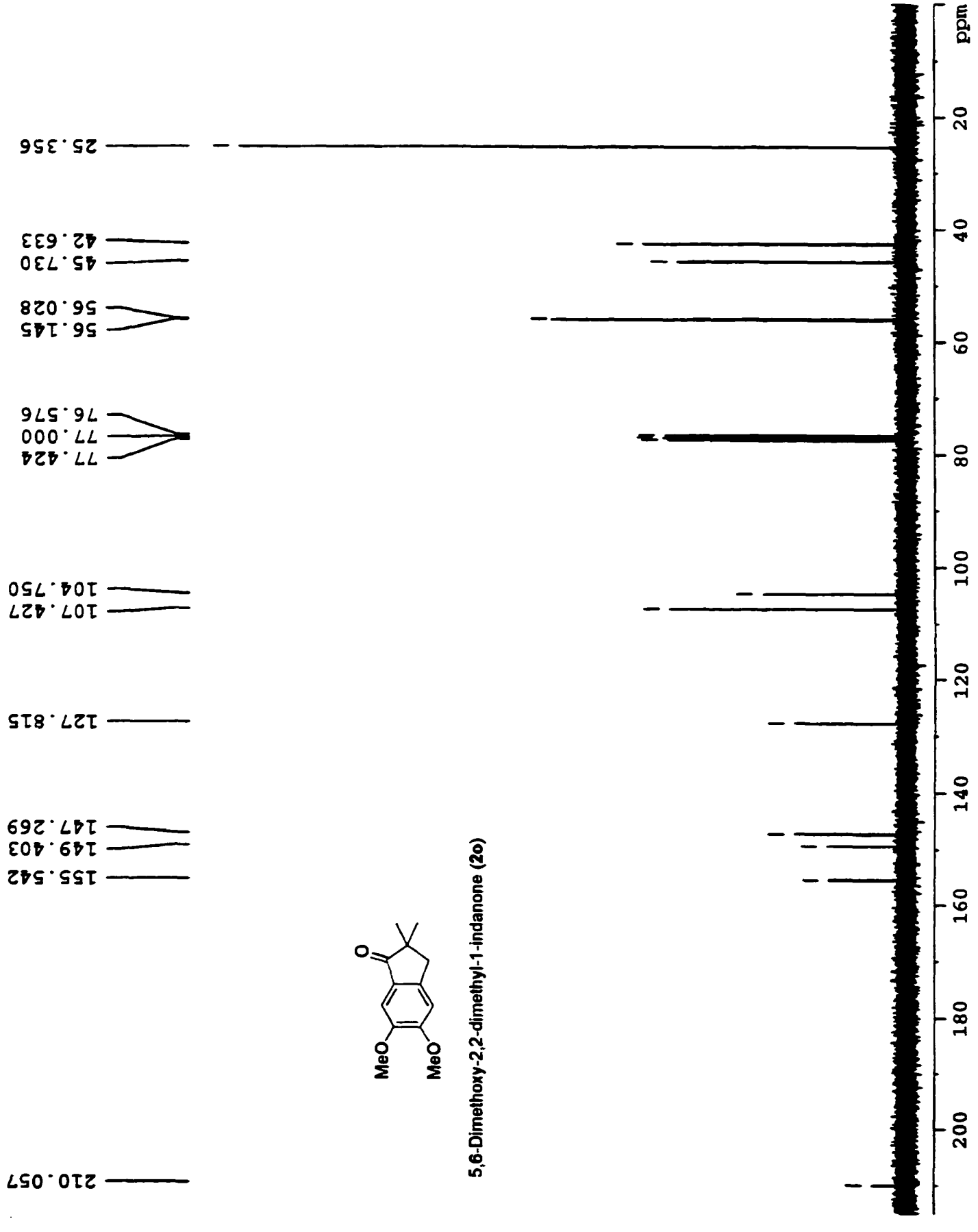

2-Cyano-2-methyl-1-indanone (2i)
O
CN
1.670
3.218
3.262
3.738
3.781
7.275
7.469
7.487
7.488
7.495
7.497
7.499
7.501
7.504
7.506
7.511
7.514
7.516
7.518
7.698
7.701
7.720
7.735
7.738
7.837
7.838
7.857
3.015
1.020
1.011
1.000
1.010
2.003
ppm

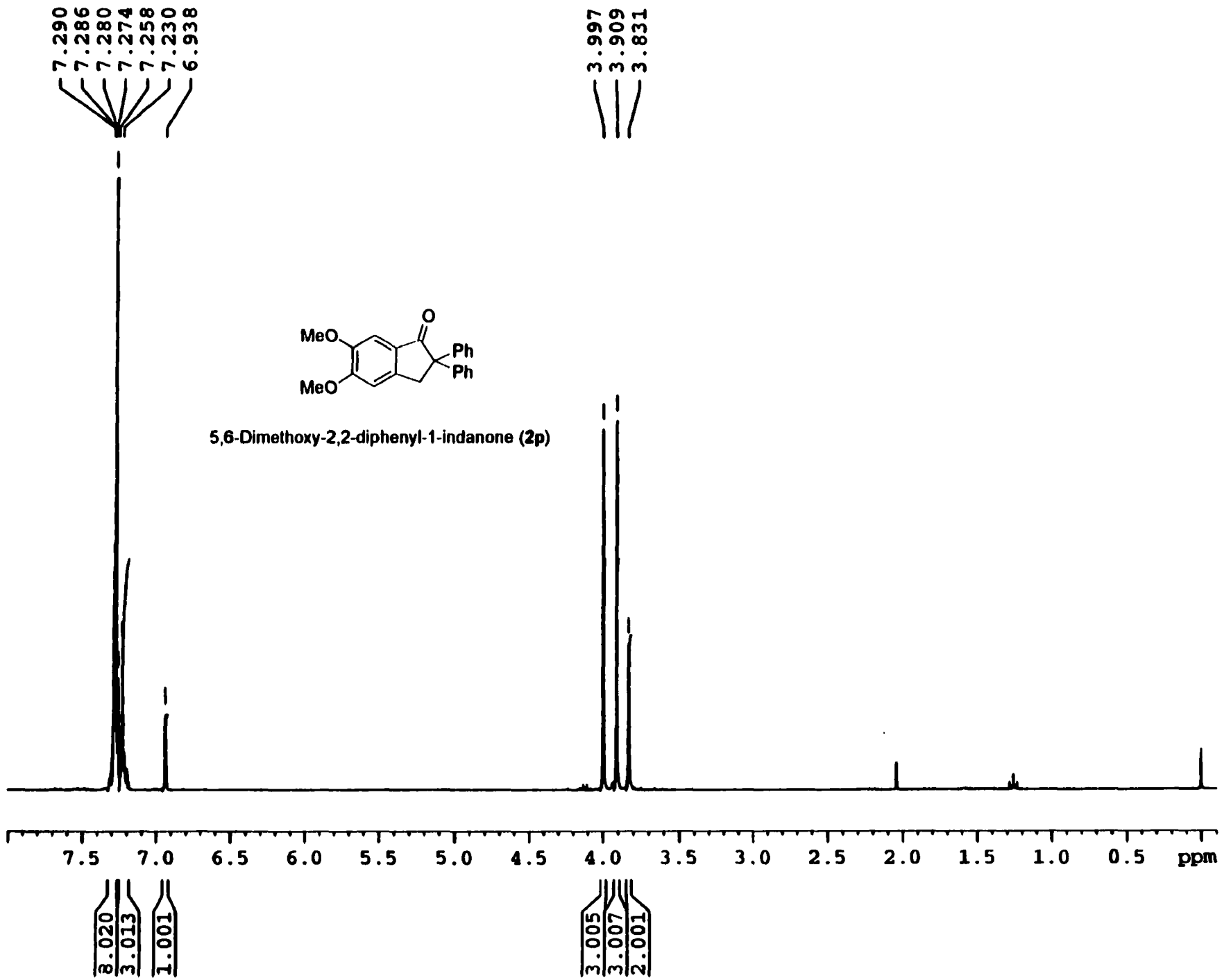
2-Cyano-2-methyl-1-indanone (2i)
O
CN
198.475
150.540
136.715
132.965
128.990
126.931
125.940
125.923
120.574
77.715
77.291
76.867
43.157
40.450
23.711
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20
ppm

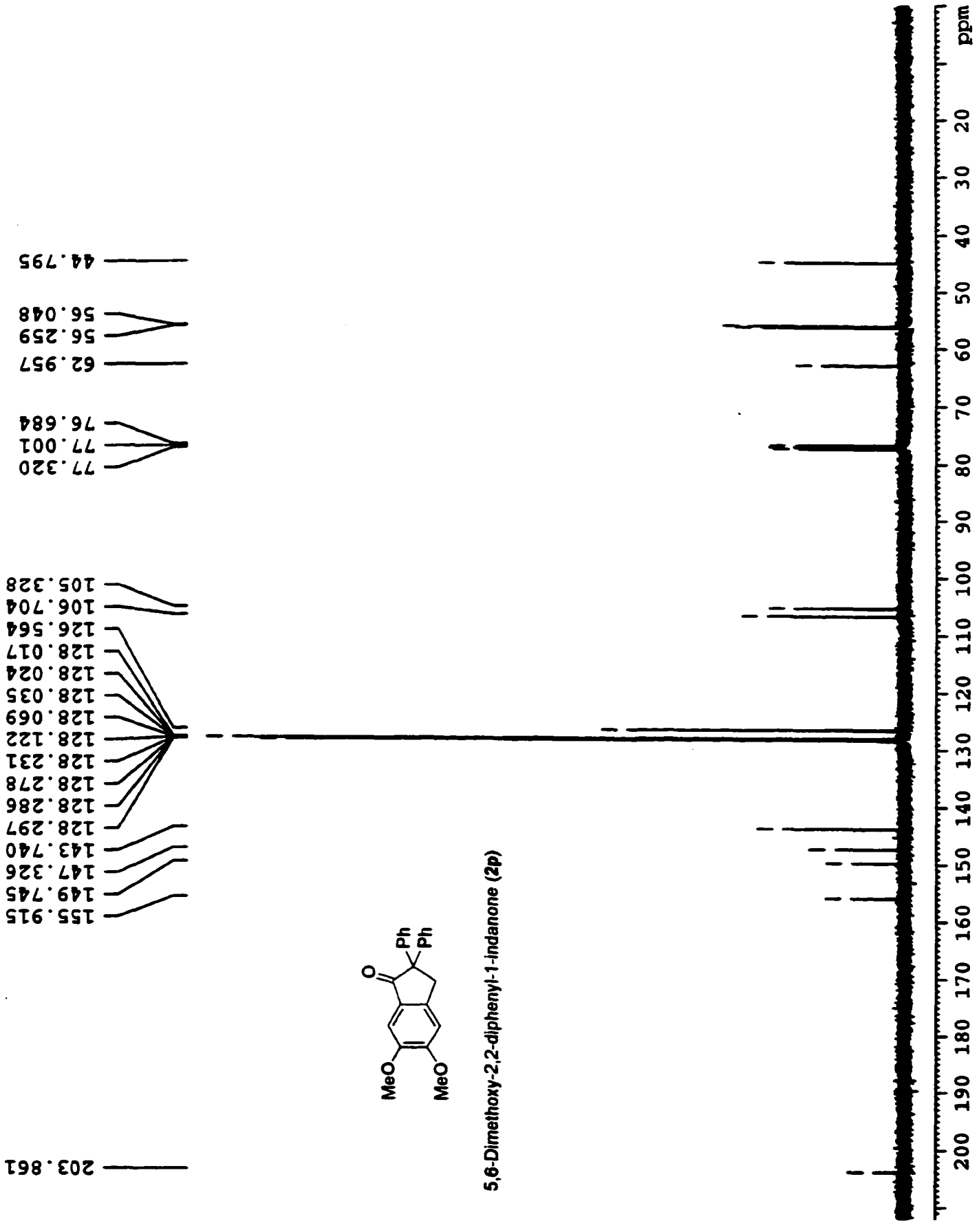

3-Acetoxy-2,2-dimethyl-1-indanone (2m)
O
OAc
ppm
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.000
1.031
1.049
1.034
0.996
3.021
3.010
3.015
2.177
1.580
1.347
1.332
1.141
6.085
7.513
7.514
7.531
7.532
7.550
7.551
7.587
7.588
7.606
7.607
7.674
7.677
7.693
7.696
7.712
7.715
7.787
7.806
7.806


19.550
20.848
24.013
49.696
76.682
77.000
77.318
78.451
123.939
126.577
129.901
134.964
135.278
149.270
170.903
207.475
O
OAc
3-Acetoxy-2,2-dimethyl-1-indanone (2m)
ppm
20
40
60
80
100
120
140
160
180
200


1.229
2.918
3.916
3.969
6.854
7.186
MeO
MeO
O
5,6-Dimethoxy-2,2-dimethyl-1-indanone (2o)
6.027
2.013
3.030
3.010
1.013
1.000
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5

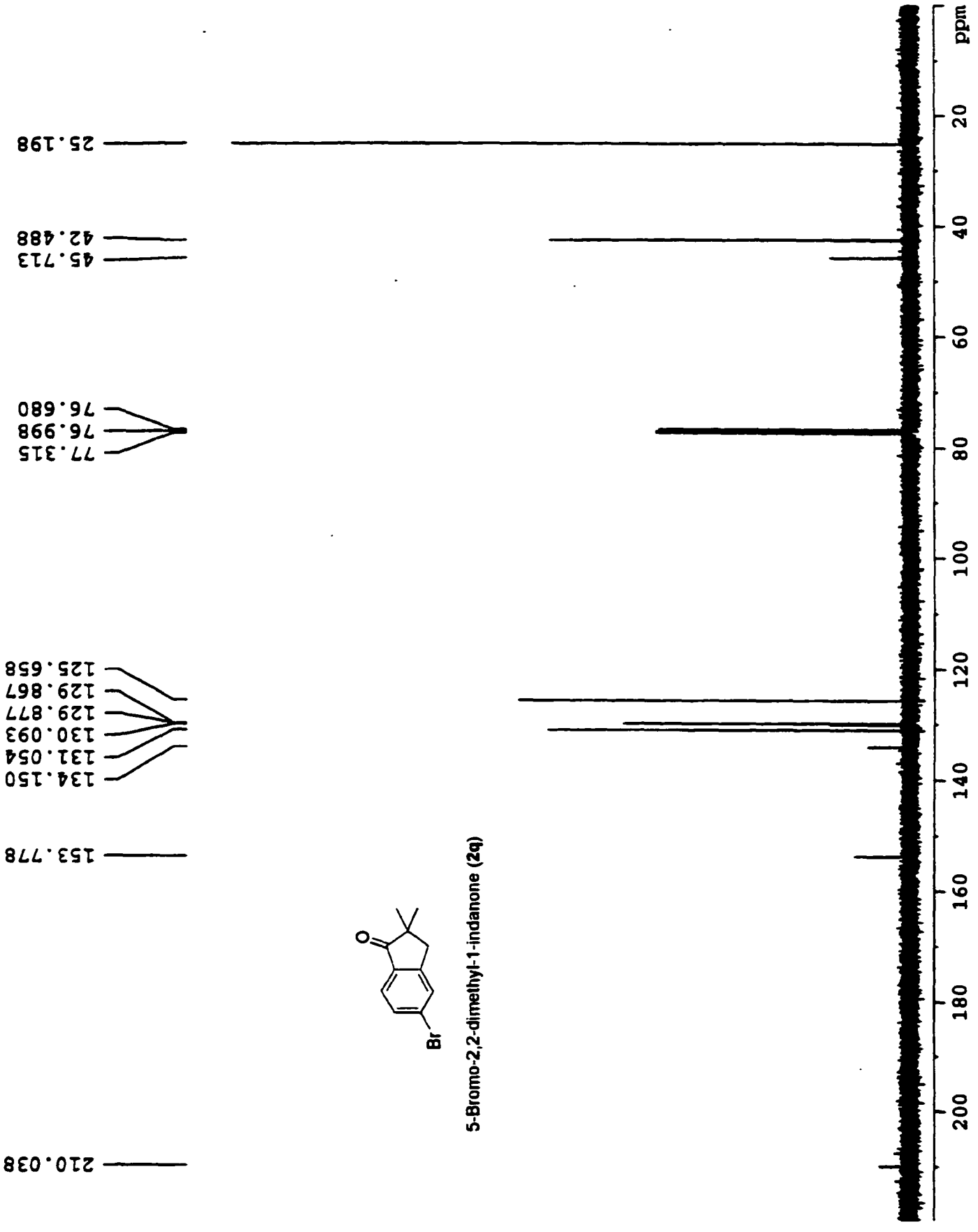

25.356
42.633
45.730
56.028
56.145
76.576
77.000
77.424
104.750
107.427
127.815
147.269
149.403
155.542
210.057
O
MeO
MeO
5,6-Dimethoxy-2,2-dimethyl-1-indanone (2o)
ppm
20
40
60
80
100
120
140
160
180
200

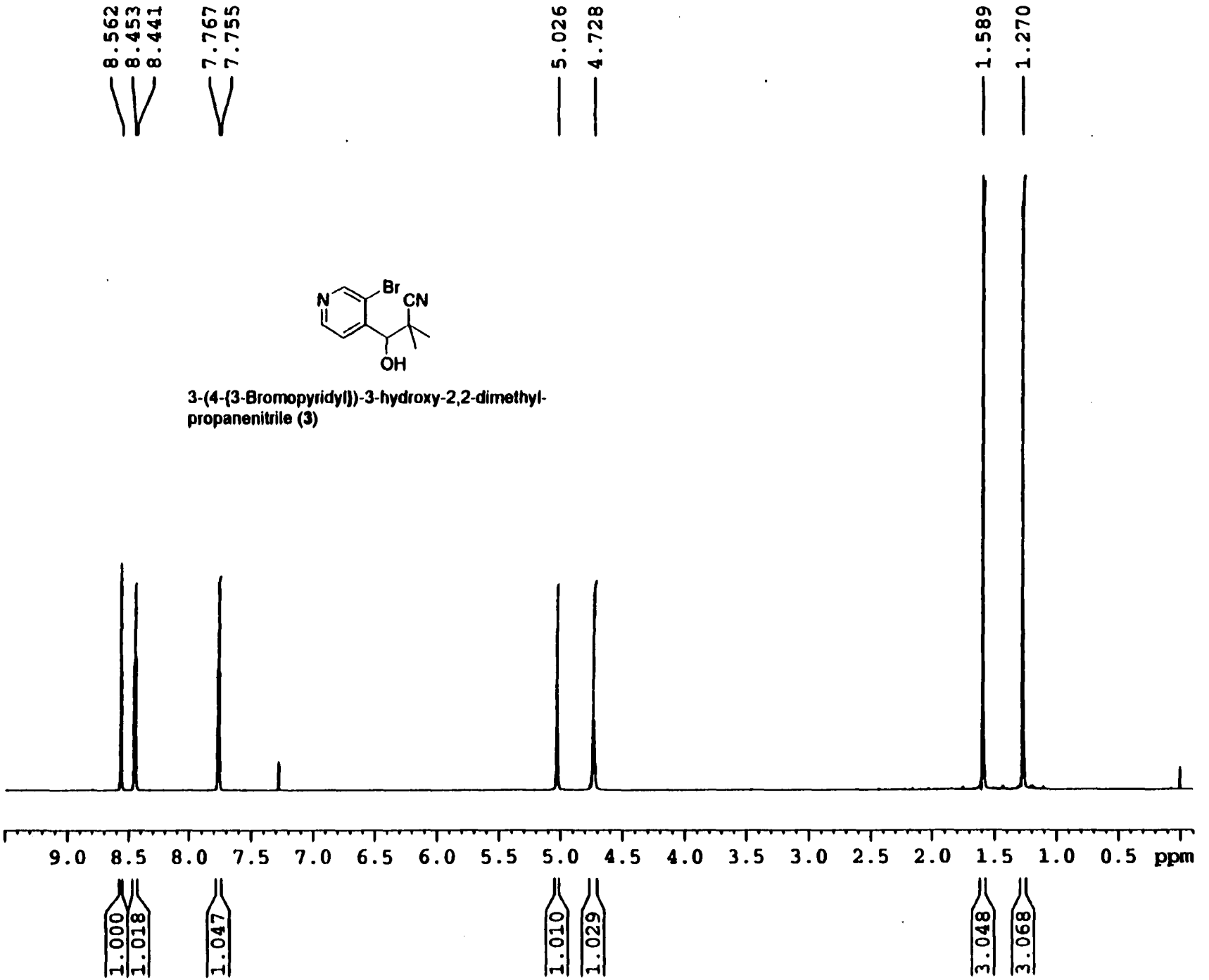

7.290
7.286
7.280
7.274
7.258
7.230
6.938
3.997
3.909
3.831
MeO
MeO
O
Ph
Ph
5,6-Dimethoxy-2,2-diphenyl-1-indanone (2p)
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
8.020
3.013
1.001
3.005
3.007
2.001

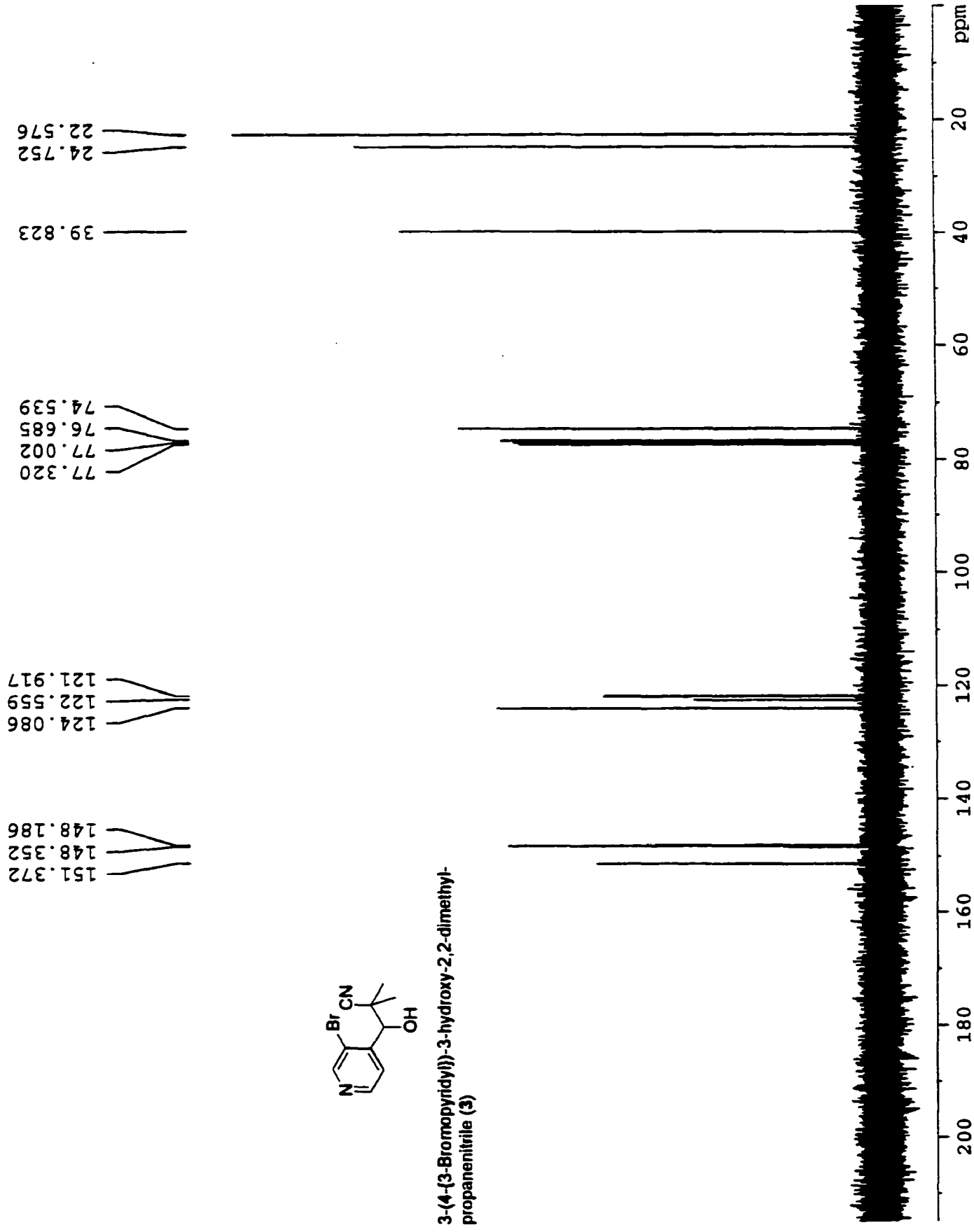


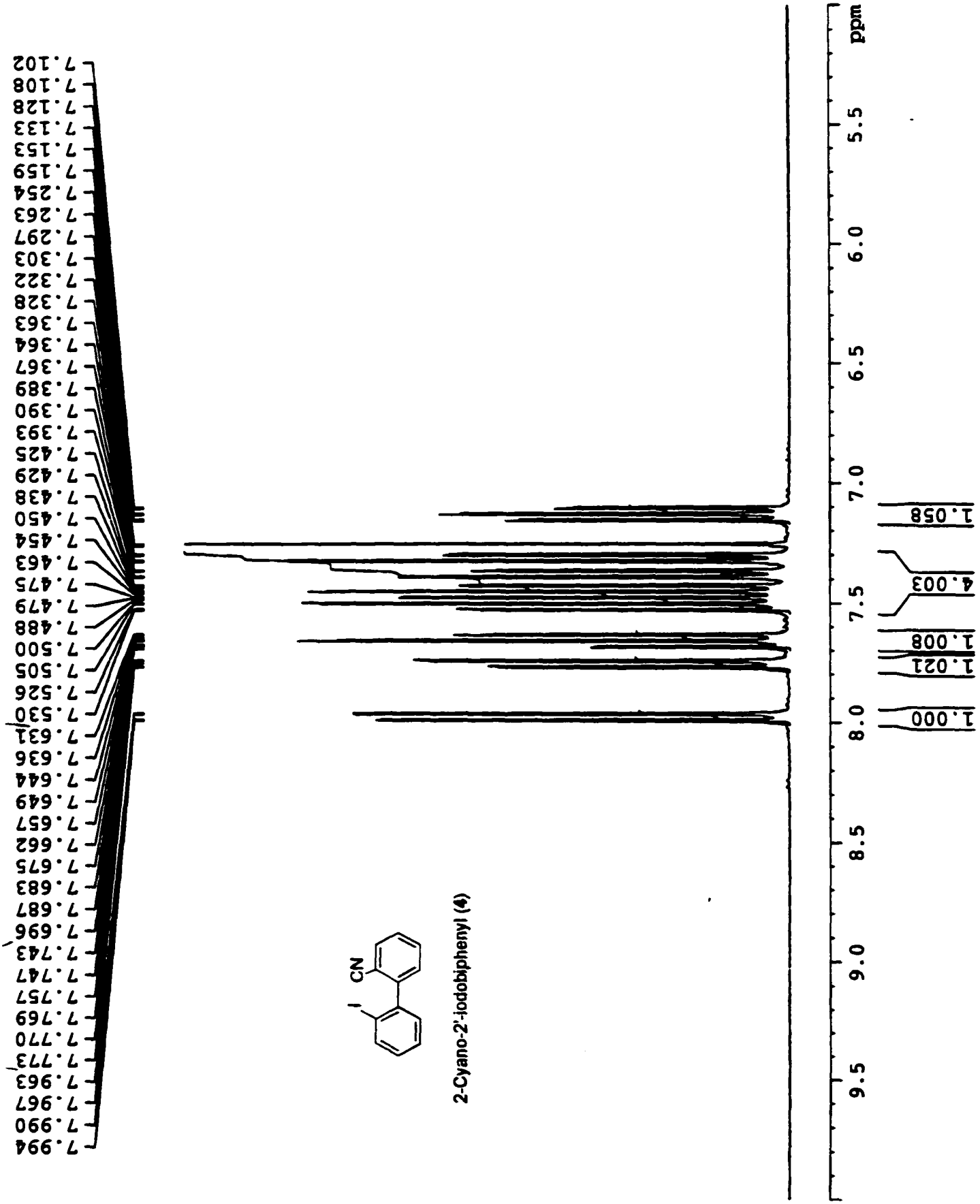

5,6-Dimethoxy-2,2-diphenyl-1-indanone (2p)

7.630
7.611
7.530
7.529
7.510
7.509
7.507
7.505
7.267
7.267
7.265
2.036
1.000
2.023
6.032
2.986
1.624
1.235
0.001
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
Br
O
5-Bromo-2,2-dimethyl-1-indanone (2q)

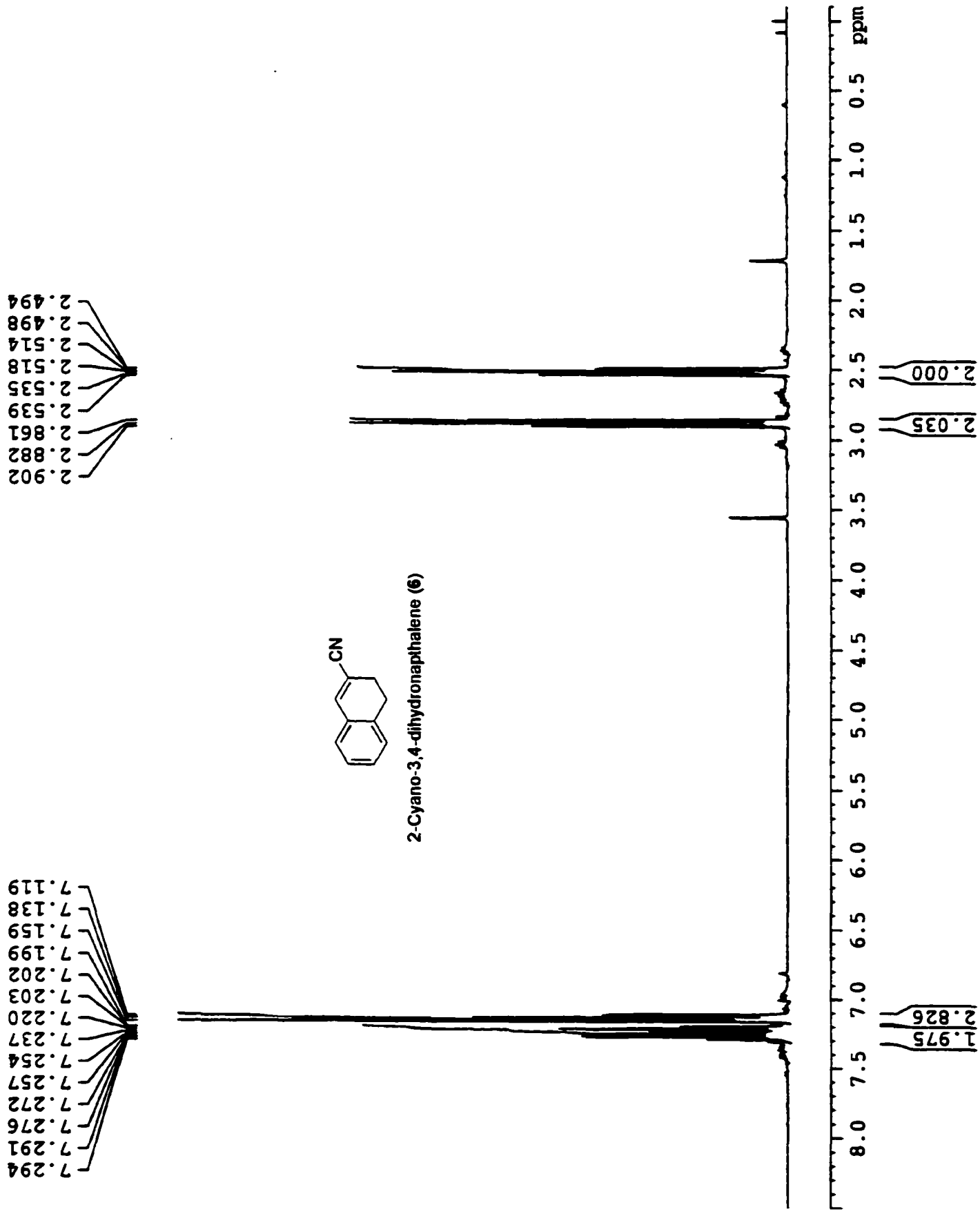

210.038
153.778
134.150
131.054
130.093
129.877
129.867
125.658
77.315
76.998
76.680
45.713
42.488
25.198
ppm
20
40
60
80
100
120
140
160
180
200
O
Br
5-Bromo-2,2-dimethyl-1-indanone (2q)


8.562
8.453
8.441
7.767
7.755
5.026
4.728
1.589
1.270
Br
N
CN
OH
3-(4-(3-Bromopyridyl))-3-hydroxy-2,2-dimethyl-propanenitrile (3)
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
1.000
1.018
1.047
1.010
1.029
3.048
3.068

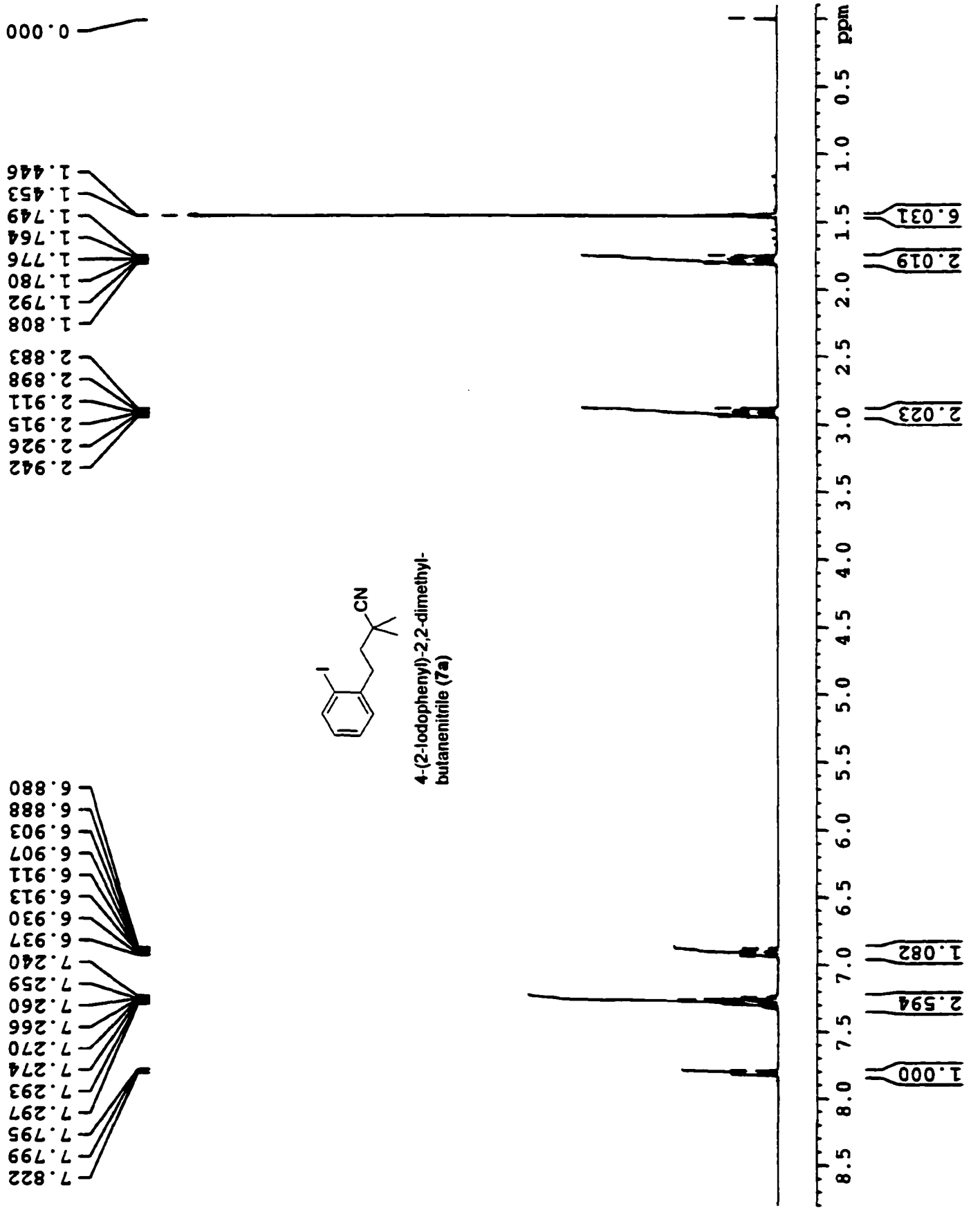

22.576
24.752
39.823
74.539
76.685
77.002
77.320
121.917
122.559
124.086
148.186
148.352
151.372
Br
CN
OH
N
3-(4-(3-Bromopyridyl))-3-hydroxy-2,2-dimethyl-propanenitrile (3)
ppm
20
40
60
80
100
120
140
160
180
200


7.102
7.108
7.128
7.133
7.153
7.159
7.254
7.263
7.297
7.303
7.322
7.328
7.363
7.364
7.367
7.389
7.390
7.393
7.425
7.429
7.438
7.450
7.454
7.463
7.475
7.479
7.488
7.500
7.505
7.526
7.530
7.631
7.636
7.644
7.649
7.657
7.662
7.675
7.683
7.687
7.696
7.743
7.747
7.757
7.769
7.770
7.773
7.963
7.967
7.990
7.994
CN
I
2-Cyano-2'-iodobiphenyl (4)
ppm
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
1.000
1.021
1.008
4.003
1.058

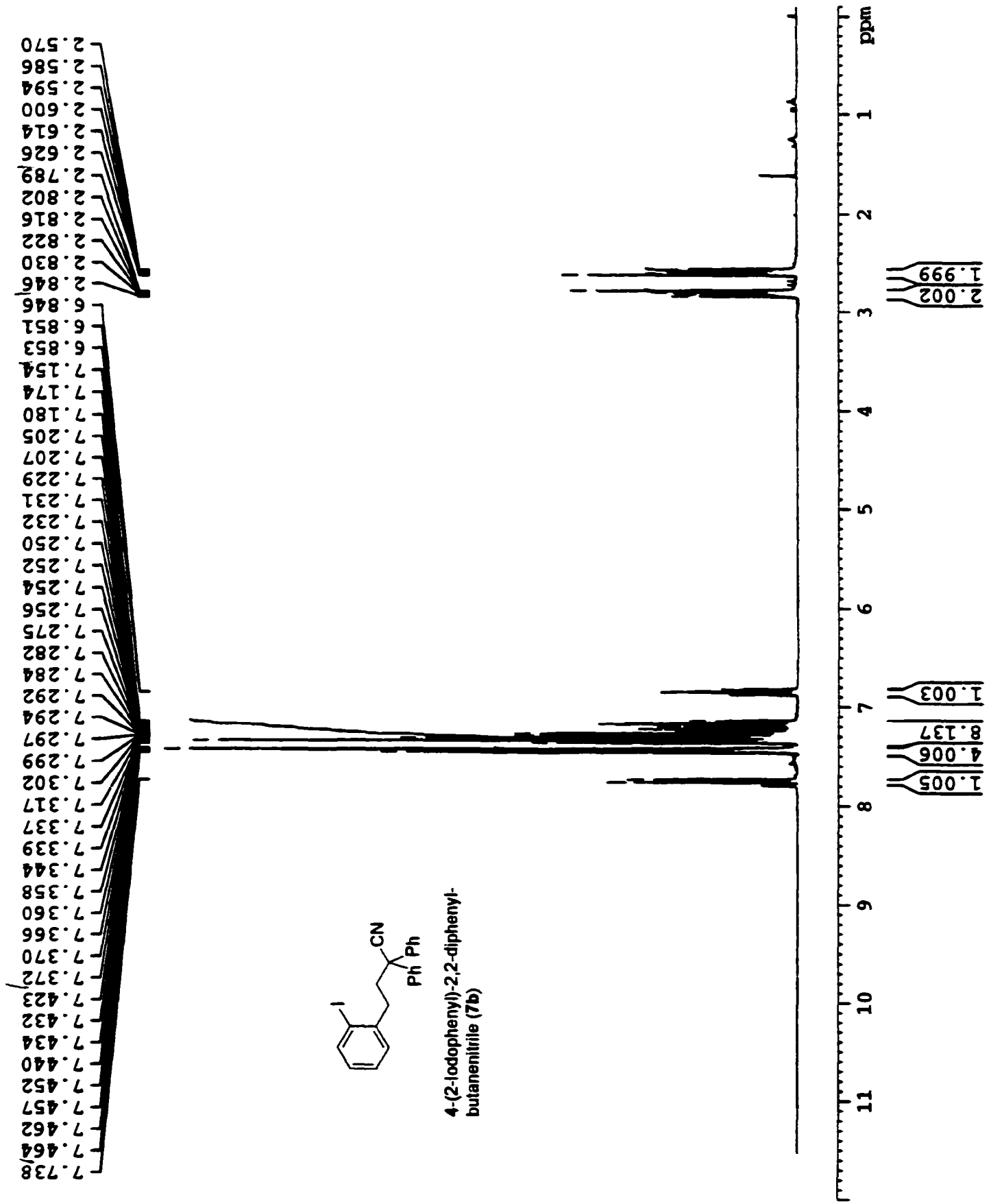
2-Cyano-2'-iodobiphenyl (4)

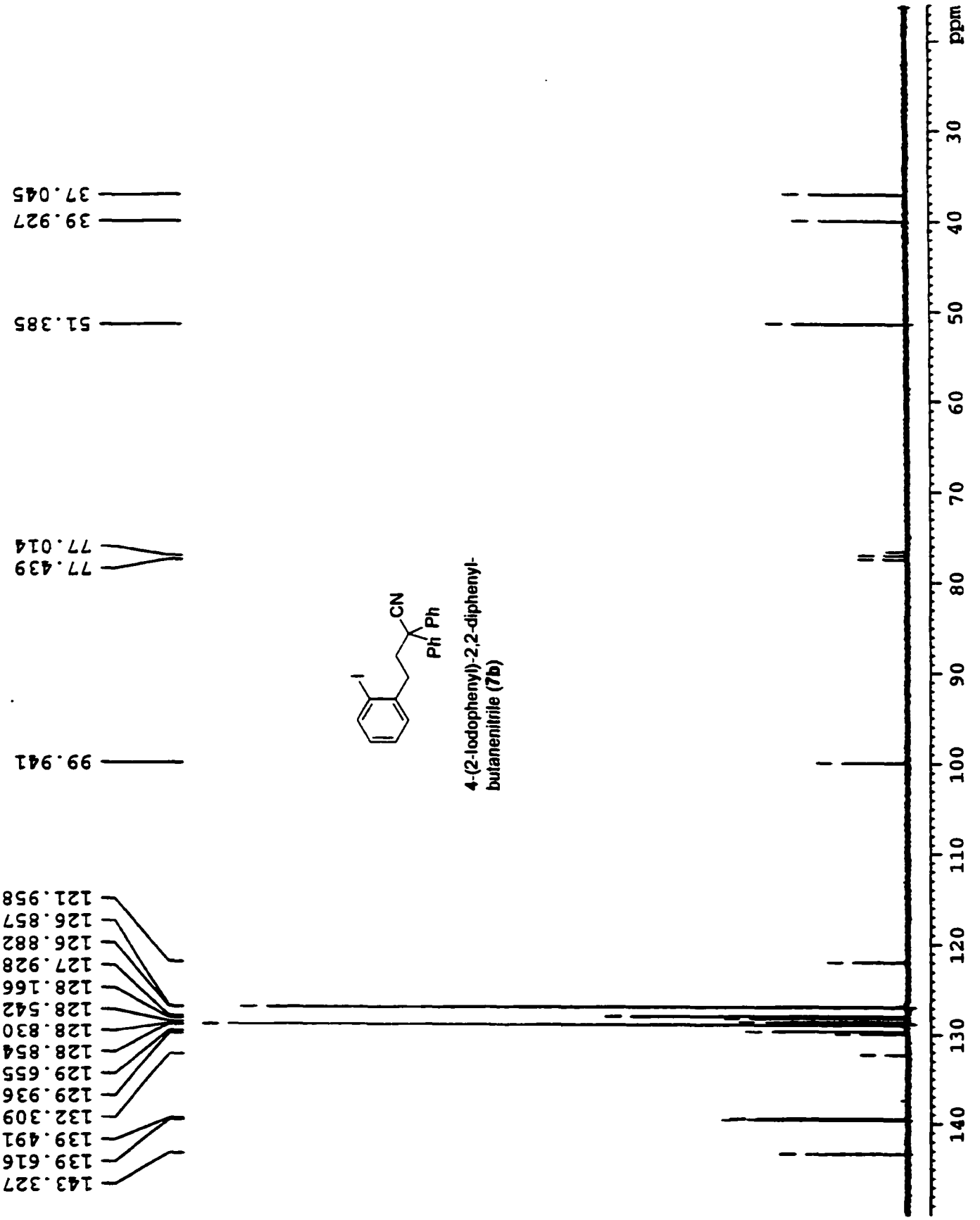

2-Cyano-3,4-dihydronapthalene (6)
CN
ppm
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
1.975
2.826
2.000
2.035
7.294
7.291
7.276
7.272
7.257
7.254
7.237
7.220
7.203
7.202
7.199
7.159
7.138
7.119
2.902
2.882
2.861
2.539
2.535
2.518
2.514
2.498
2.494

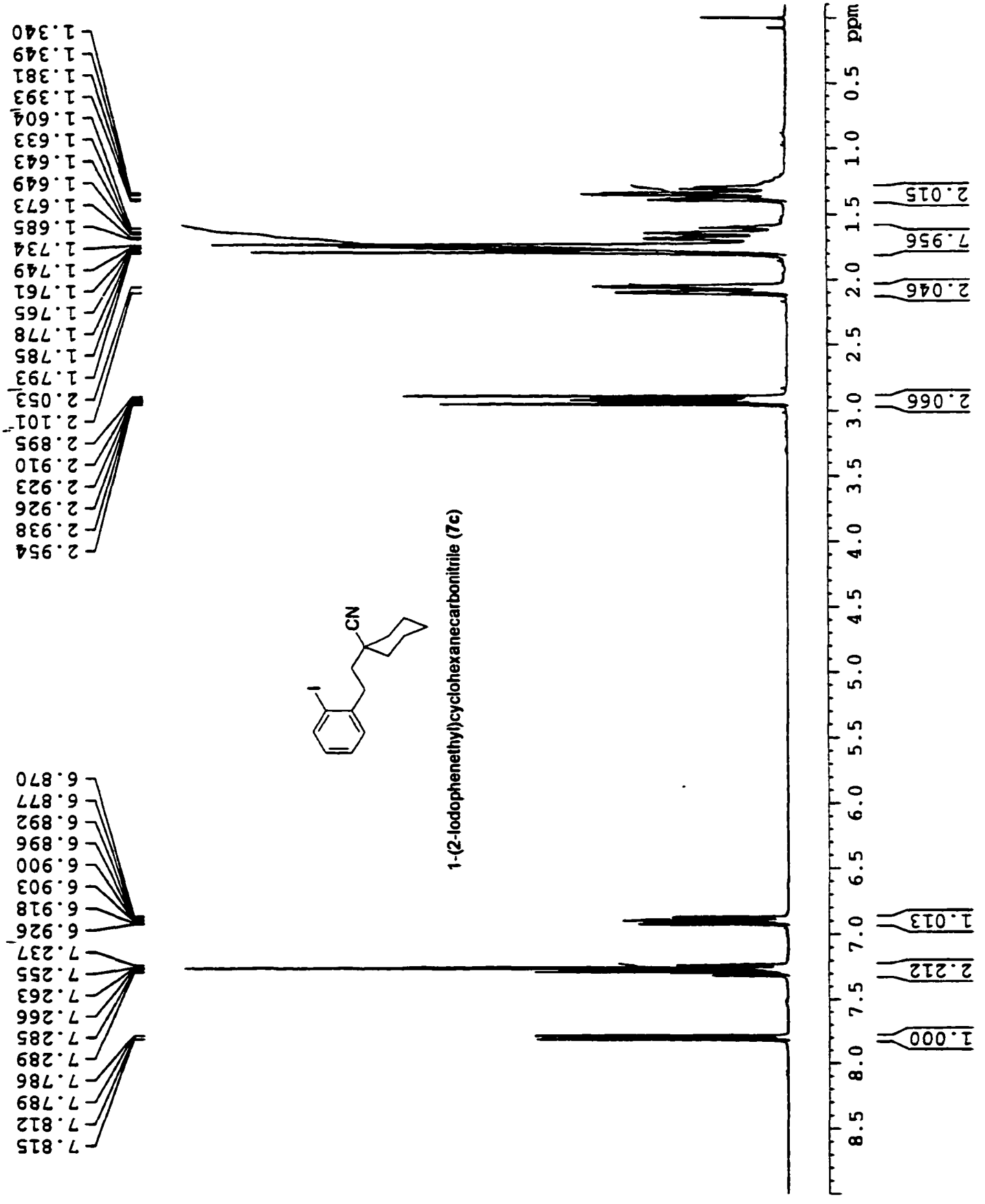
141.668
135.393
131.172
130.249
127.970
127.953
127.120
109.652
77.425
77.206
77.001
76.578
26.678
24.676
2-Cyano-3,4-dihydronapthalene (6)
CN
ppm


0.000
1.446
1.453
1.749
1.764
1.776
1.780
1.792
1.808
2.883
2.898
2.911
2.915
2.926
2.942
6.880
6.888
6.903
6.907
6.911
6.913
6.930
6.937
7.240
7.259
7.260
7.266
7.270
7.274
7.293
7.297
7.795
7.799
7.822
CN
I
4-(2-Iodophenyl)-2,2-dimethyl-butanenitrile (7a)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
1.000
2.594
1.082
2.023
2.019
6.031

4-(2-Iodophenyl)-2,2-dimethyl-butanenitrile (7a)
CN
I
143.257
139.546
129.452
128.621
128.143
124.651
100.063
77.426
77.000
76.577
41.329
36.756
32.219
32.211
26.547
200
180
160
140
120
100
80
60
40
20
ppm


7.738
7.464
7.462
7.457
7.452
7.440
7.434
7.432
7.423
7.372
7.370
7.366
7.360
7.358
7.344
7.339
7.337
7.317
7.302
7.299
7.297
7.294
7.292
7.284
7.282
7.275
7.256
7.254
7.252
7.250
7.232
7.231
7.229
7.207
7.205
7.180
7.174
7.154
6.853
6.851
6.846
2.846
2.830
2.822
2.816
2.802
2.789
2.626
2.614
2.600
2.594
2.586
2.570
CN
Ph Ph
I
4-(2-Iodophenyl)-2,2-diphenyl-butanenitrile (7b)
ppm
1
2
3
4
5
6
7
8
9
10
11
1.005
4.006
8.137
1.003
2.002
1.999


ppm
30
40
50
60
70
80
90
100
110
120
130
140
37.045
39.927
51.385
77.014
77.439
99.941
121.958
126.857
126.882
127.928
128.166
128.542
128.830
128.854
129.655
129.936
132.309
139.491
139.616
143.327
CN
Ph
Ph
I
4-(2-Iodophenyl)-2,2-diphenyl-butanenitrile (7b)


1-(2-Iodophenethyl)cyclohexanecarbonitrile (7c)
CN
I
ppm
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
1.000
2.212
1.013
2.066
2.046
7.956
2.015
7.815 7.812 7.789 7.786 7.289 7.285 7.266 7.263 7.255 7.237 6.926 6.918 6.903 6.900 6.896 6.892 6.877 6.870
2.954 2.938 2.926 2.923 2.910 2.895 2.101 2.053 1.793 1.785 1.778 1.765 1.761 1.749 1.734 1.685 1.673 1.649 1.643 1.633 1.604 1.393 1.381 1.349 1.340

1-(2-Iodophenethyl)cyclohexanecarbonitrile (7c)
CN
I
143.592
139.532
129.487
128.620
128.086
123.343
100.104
77.423
77.000
76.576
40.837
38.819
35.995
35.548
25.355
23.011
200
180
160
140
120
100
80
60
40
20
ppm

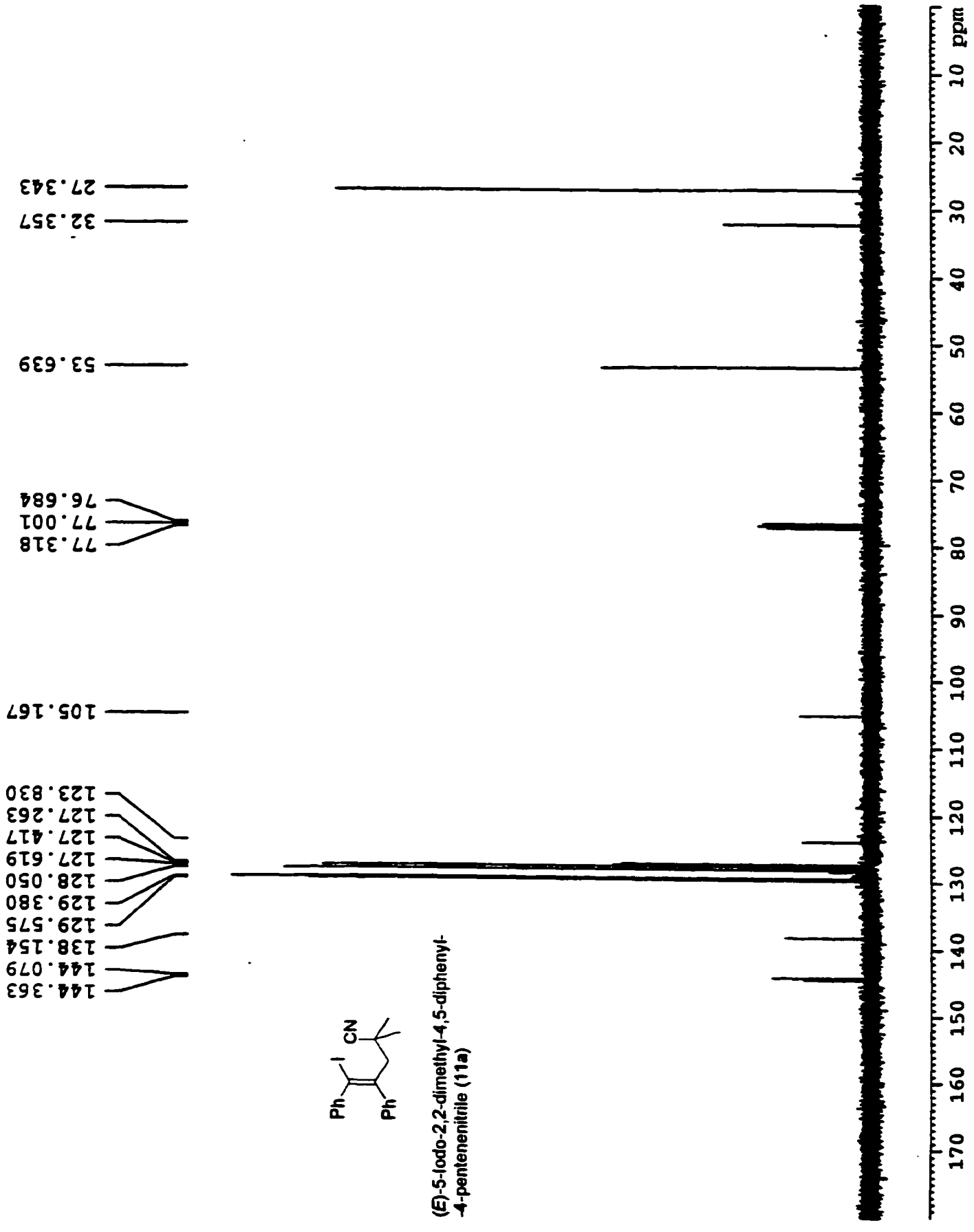
7.830
7.827
7.810
7.807
7.305
7.302
7.286
7.283
7.268
7.265
7.261
7.228
7.223
7.209
7.204
6.920
6.916
6.901
6.897
6.882
6.878
2.772
2.753
2.734
1.820
1.817
1.807
1.800
1.797
1.786
1.782
1.777
1.758
1.640
1.630
1.624
1.620
1.615
1.610
1.597
1.558
1.351
1.000
1.045
1.094
1.045
2.020
2.011
2.016
6.008
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
5-(2-Iodophenyl)-2,2-dimethylpentanenitrile (8)
I
CN

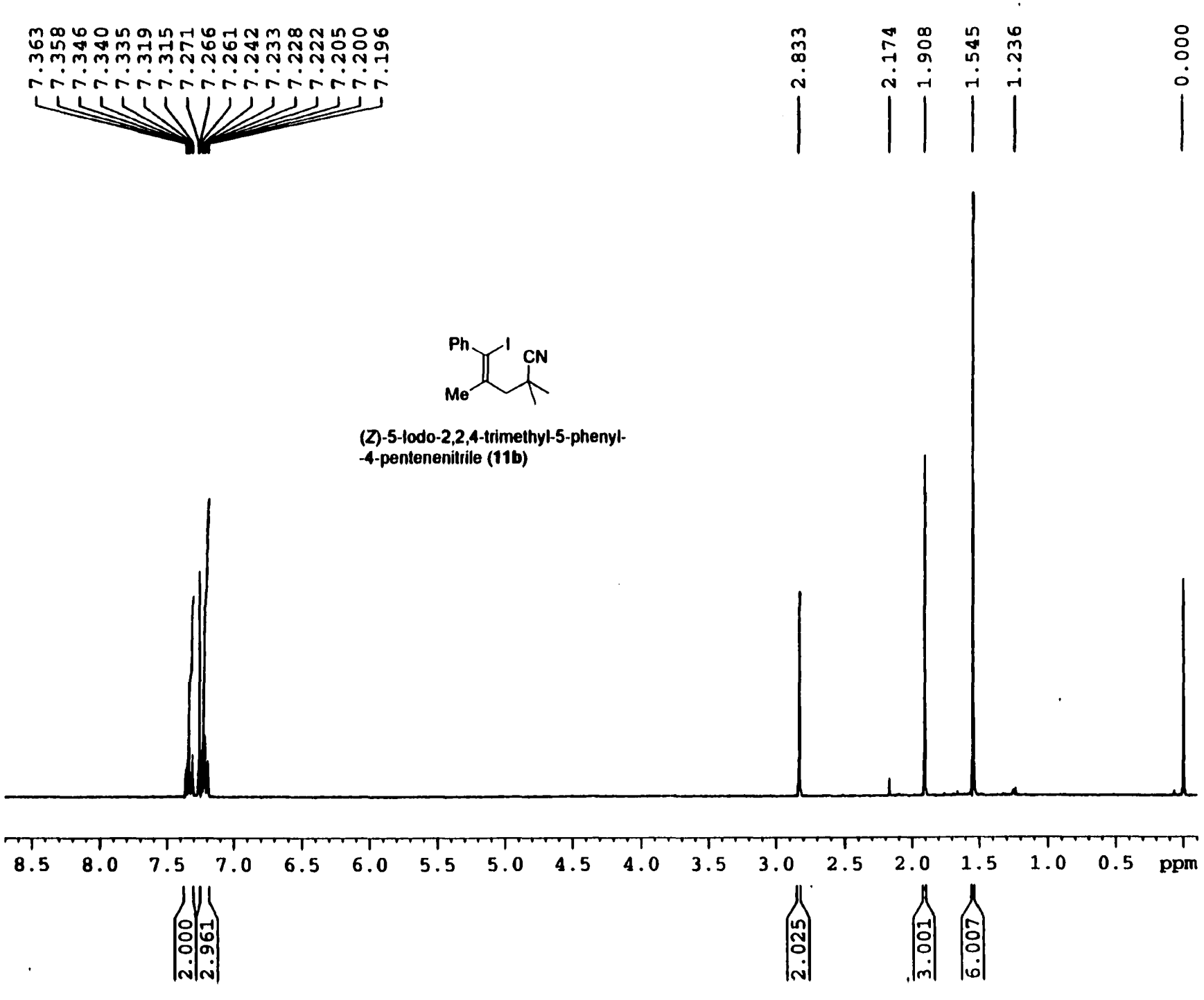
5-(2-Iodophenyl)-2,2-dimethylpentanenitrile (8)
CN
I
143.925
139.414
129.214
128.310
127.837
124.879
100.439
77.324
77.005
76.689
40.363
32.195
26.545
26.535
25.814
200
180
160
140
120
100
80
60
40
20
ppm

8.205
8.200
8.179
8.174
7.433
7.428
7.314
7.306
7.284
7.279
7.276
7.265
7.259
7.250
7.244
7.238
7.229
7.151
7.145
7.138
7.130
7.123
7.119
2.931
2.926
2.915
2.901
2.887
1.553
1.000
1.012
6.999
5.244
4.043
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2,2-Diphenyl-1-tetralone (9b)
O
Ph
Ph

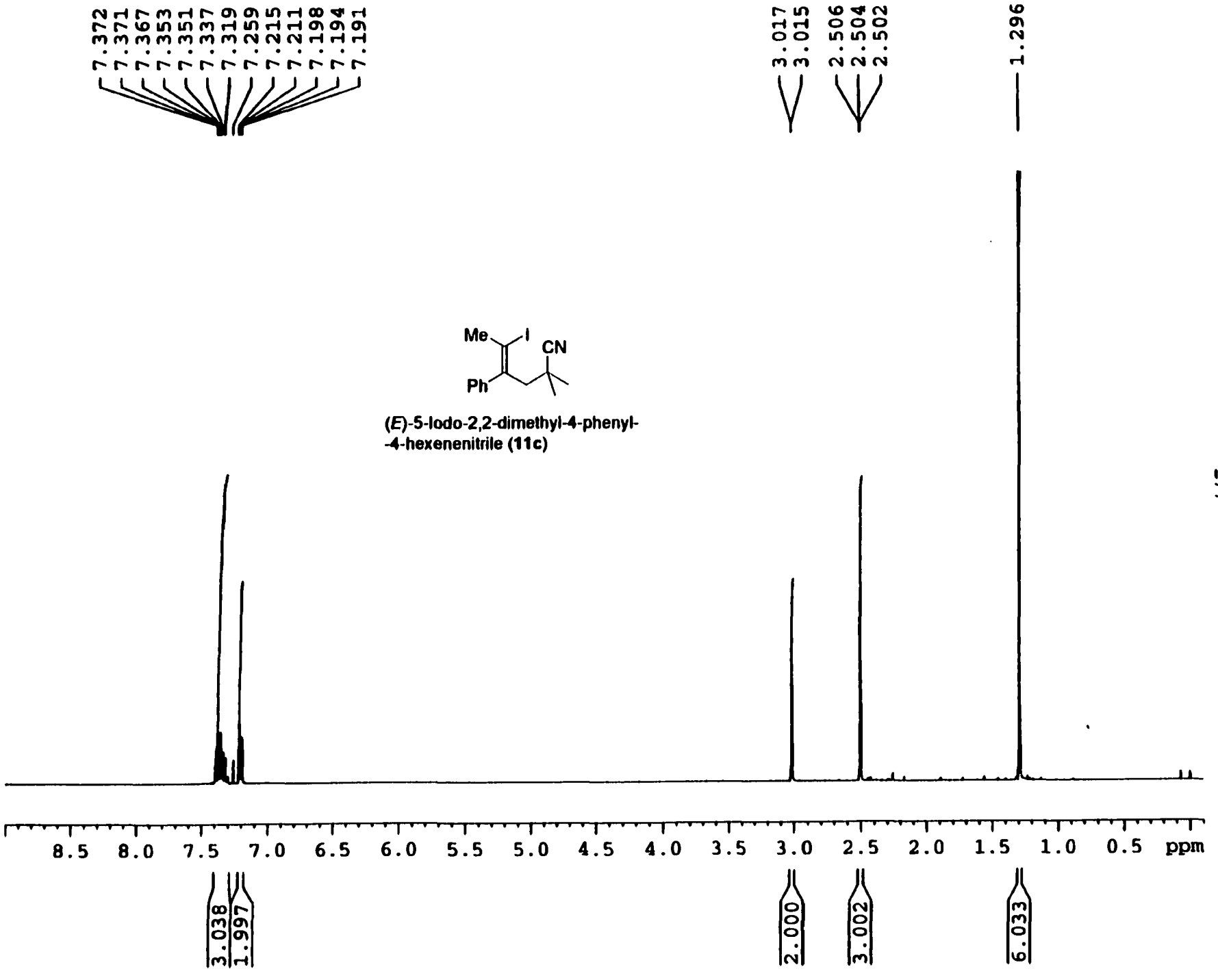
2,2-Diphenyl-1-tetralone (9b)
O
Ph
Ph
198.842
143.298
142.024
133.215
133.035
128.591
128.584
128.369
128.110
128.099
126.846
126.668
77.421
76.998
76.574
59.852
35.107
26.421
ppm
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30

(E)-5-Iodo-2,2-dimethyl-4,5-diphenyl-4-pentenenitrile (11a)

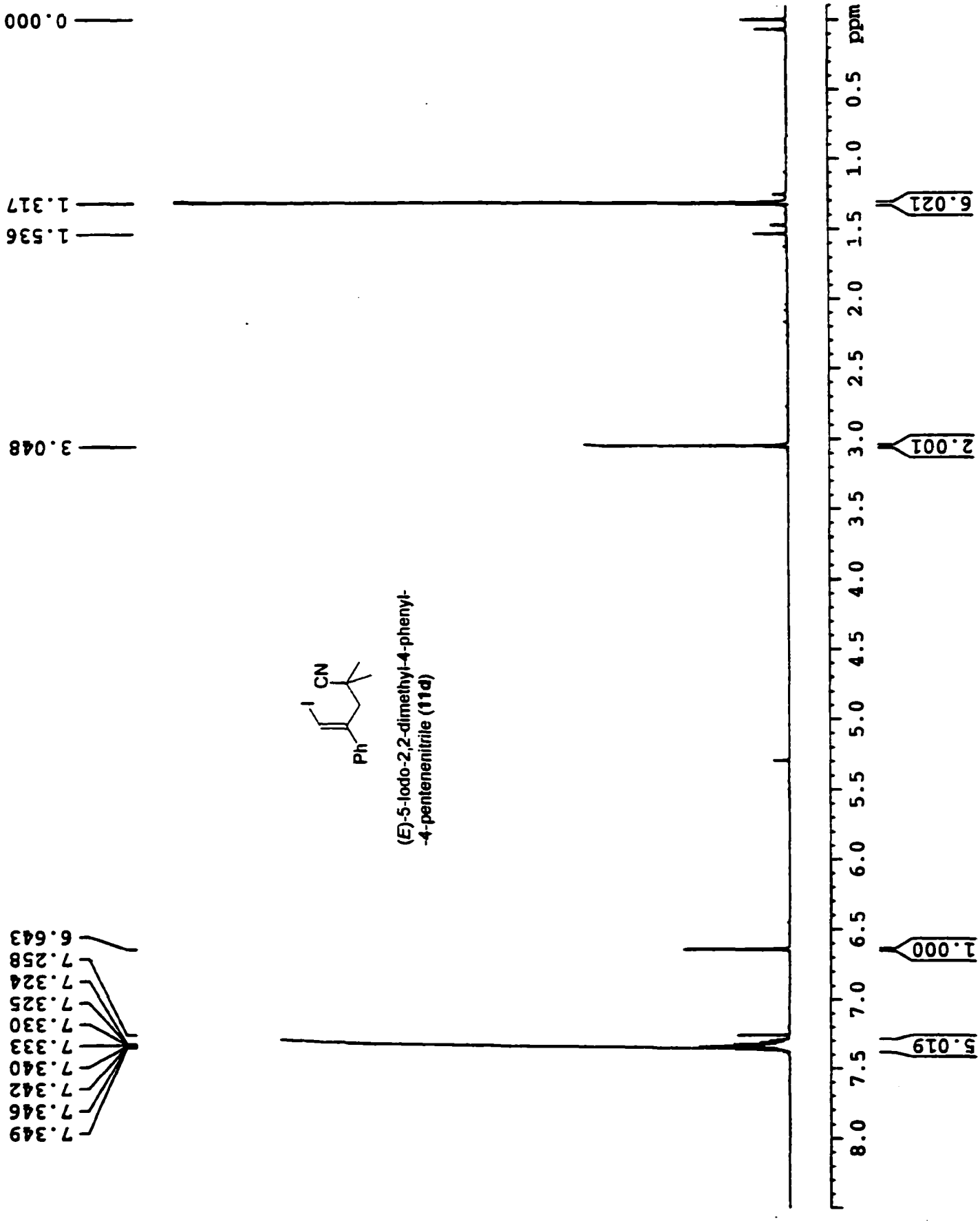

27.343
32.357
53.639
76.684
77.001
77.318
105.167
123.830
127.263
127.417
127.619
128.050
129.380
129.575
138.154
144.079
144.363
Ph
Ph
CN
(E)-5-Iodo-2,2-dimethyl-4,5-diphenyl-4-pentenenitrile (11a)
ppm

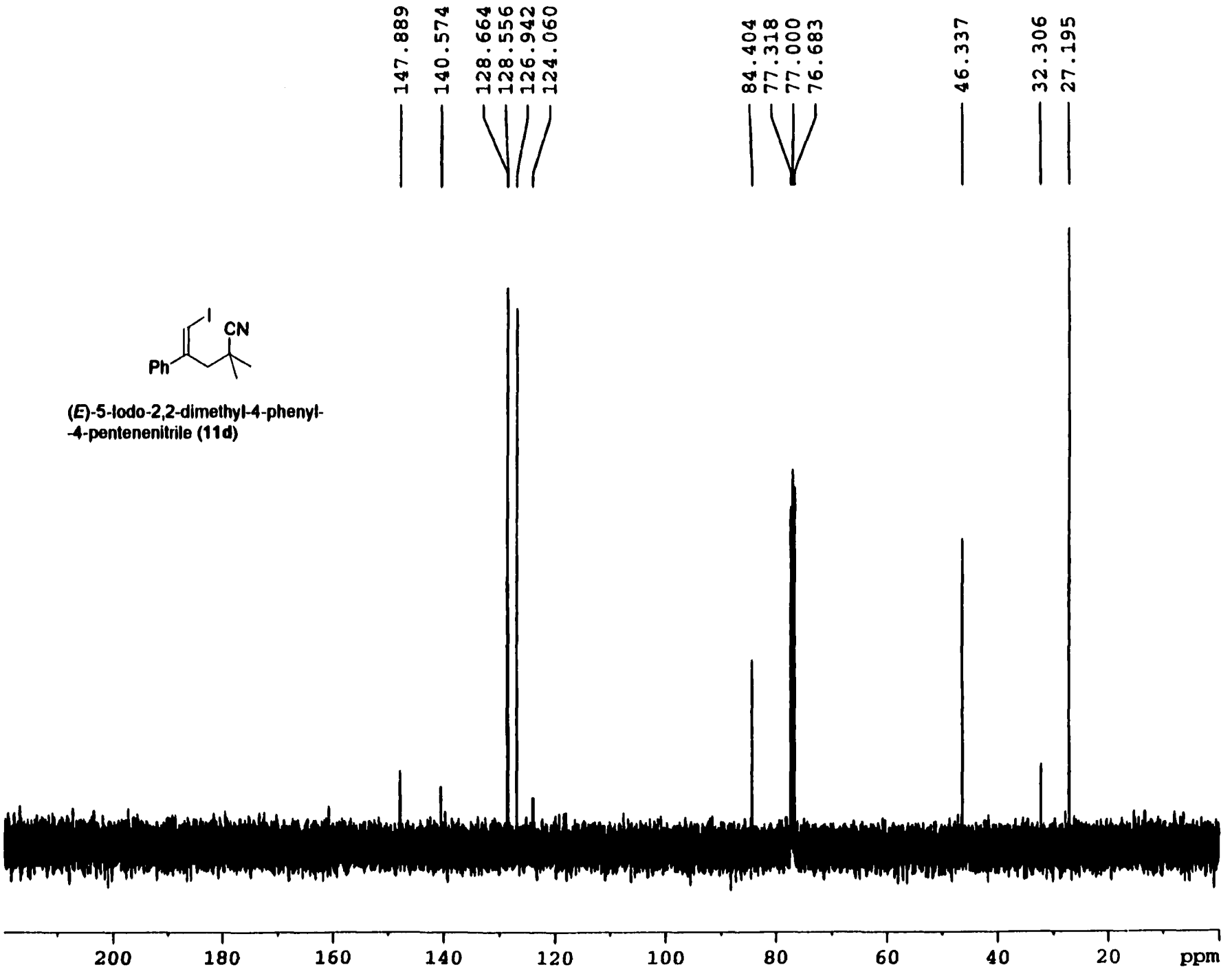

7.363
7.358
7.346
7.340
7.335
7.319
7.315
7.271
7.266
7.261
7.242
7.233
7.228
7.222
7.205
7.200
7.196
2.833
2.174
1.908
1.545
1.236
0.000
Ph
I
CN
Me
(Z)-5-Iodo-2,2,4-trimethyl-5-phenyl-
-4-pentenenitrile (11b)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
2.000
2.961
2.025
3.001
6.007

(Z)-5-Iodo-2,2,4-trimethyl-5-phenyl-4-pentenenitrile (11b)

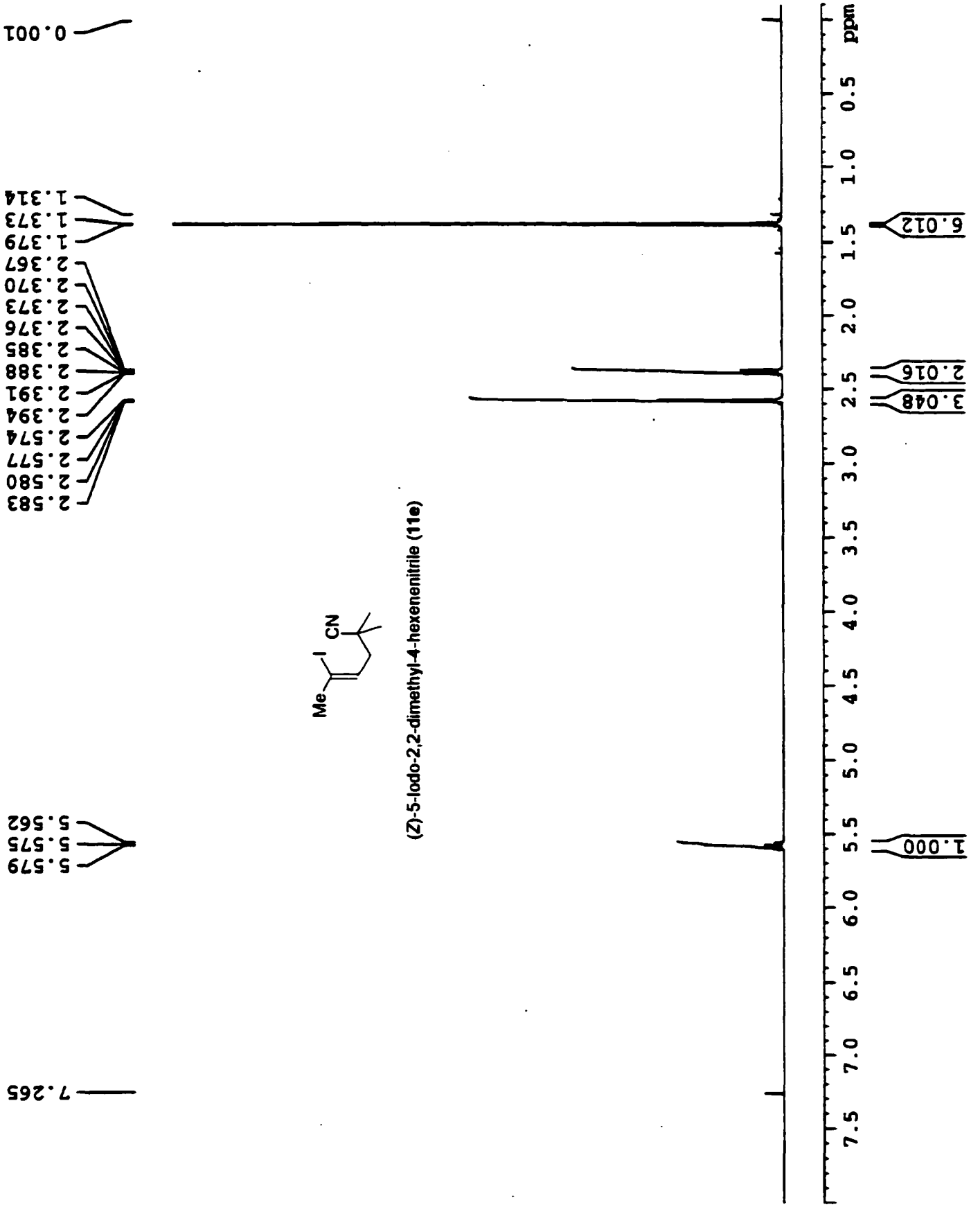

7.372
7.371
7.367
7.353
7.351
7.337
7.319
7.259
7.215
7.211
7.198
7.194
7.191
3.017
3.015
2.506
2.504
2.502
1.296
Me
I
CN
Ph
(E)-5-Iodo-2,2-dimethyl-4-phenyl-
-4-hexenenitrile (11c)
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3.038
1.997
2.000
3.002
6.033

(E)-5-Iodo-2,2-dimethyl-4-phenyl-4-hexenenitrile (11c)
Me
I
Ph
CN
141.508
137.818
128.749
128.529
127.879
123.927
103.756
77.317
76.999
76.681
53.895
32.425
32.106
27.212
200
180
160
140
120
100
80
60
40
20
0
ppm

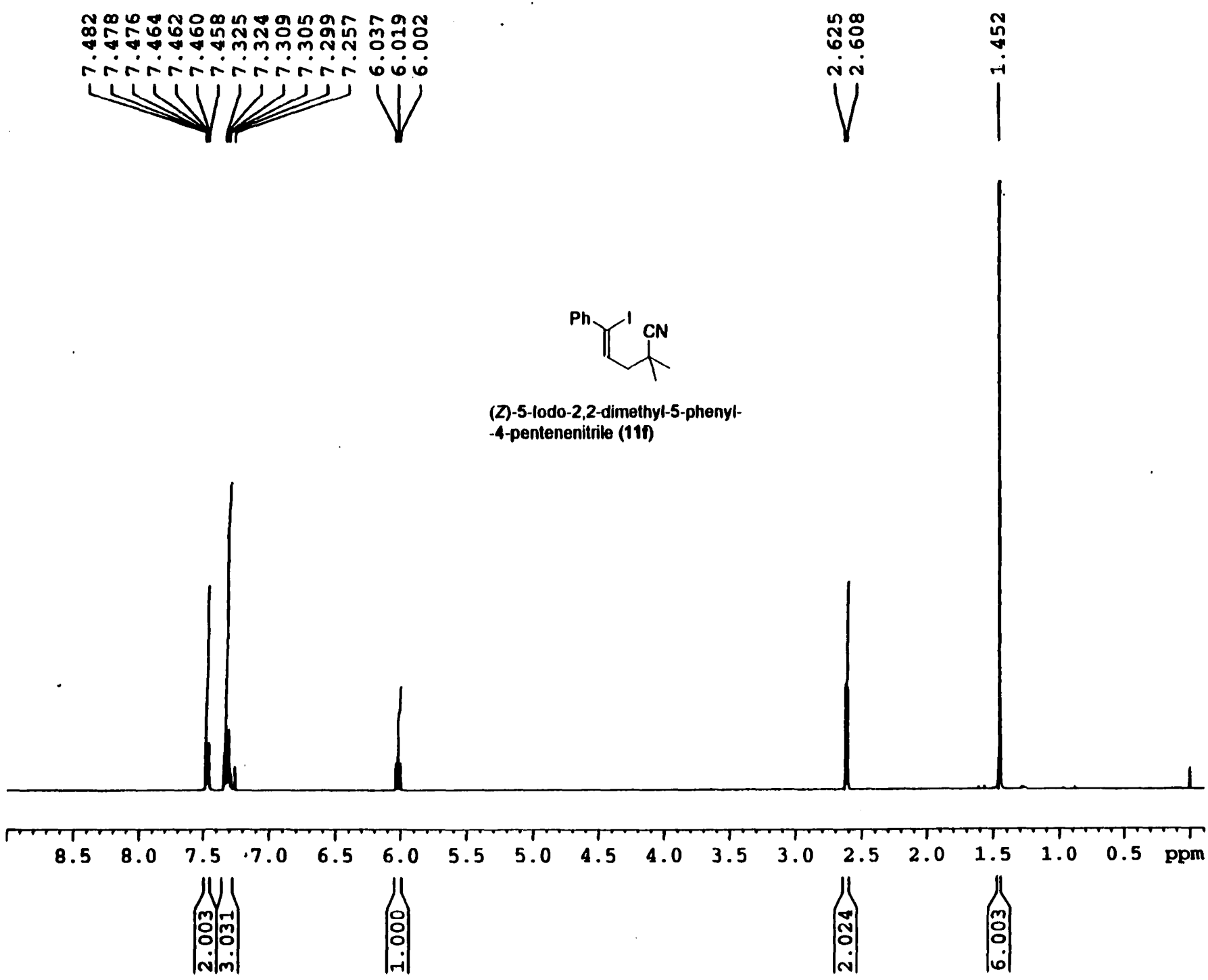

(E)-5-Iodo-2,2-dimethyl-4-phenyl-
-4-pentenenitrile (11d)
I
CN
Ph
ppm
0.000
1.317
1.536
3.048
6.643
7.258
7.324
7.325
7.330
7.333
7.340
7.342
7.346
7.349
6.021
2.001
1.000
5.019



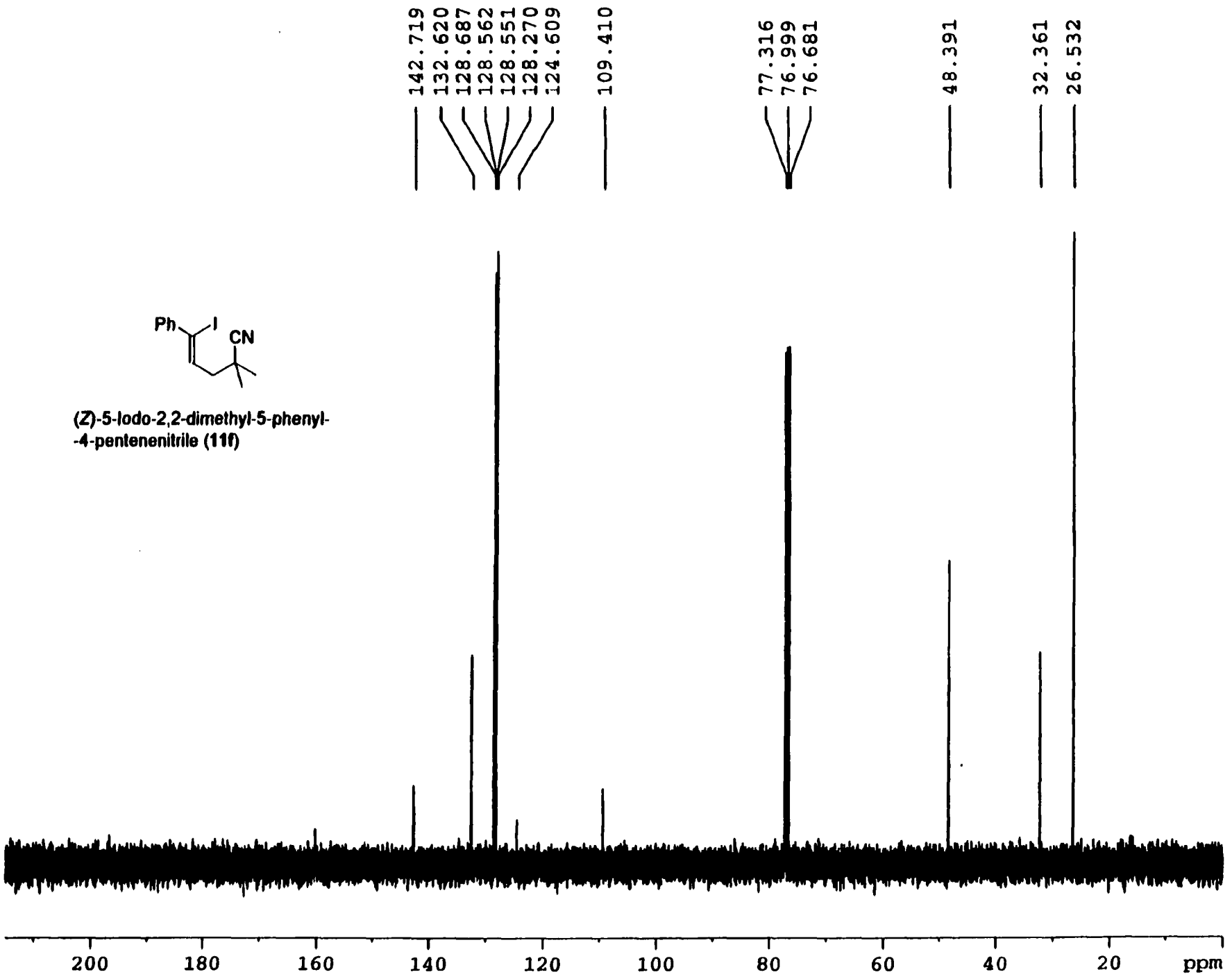

**(*E*)-5-Iodo-2,2-dimethyl-4-phenyl-**
**-4-pentenenitrile (11d)**

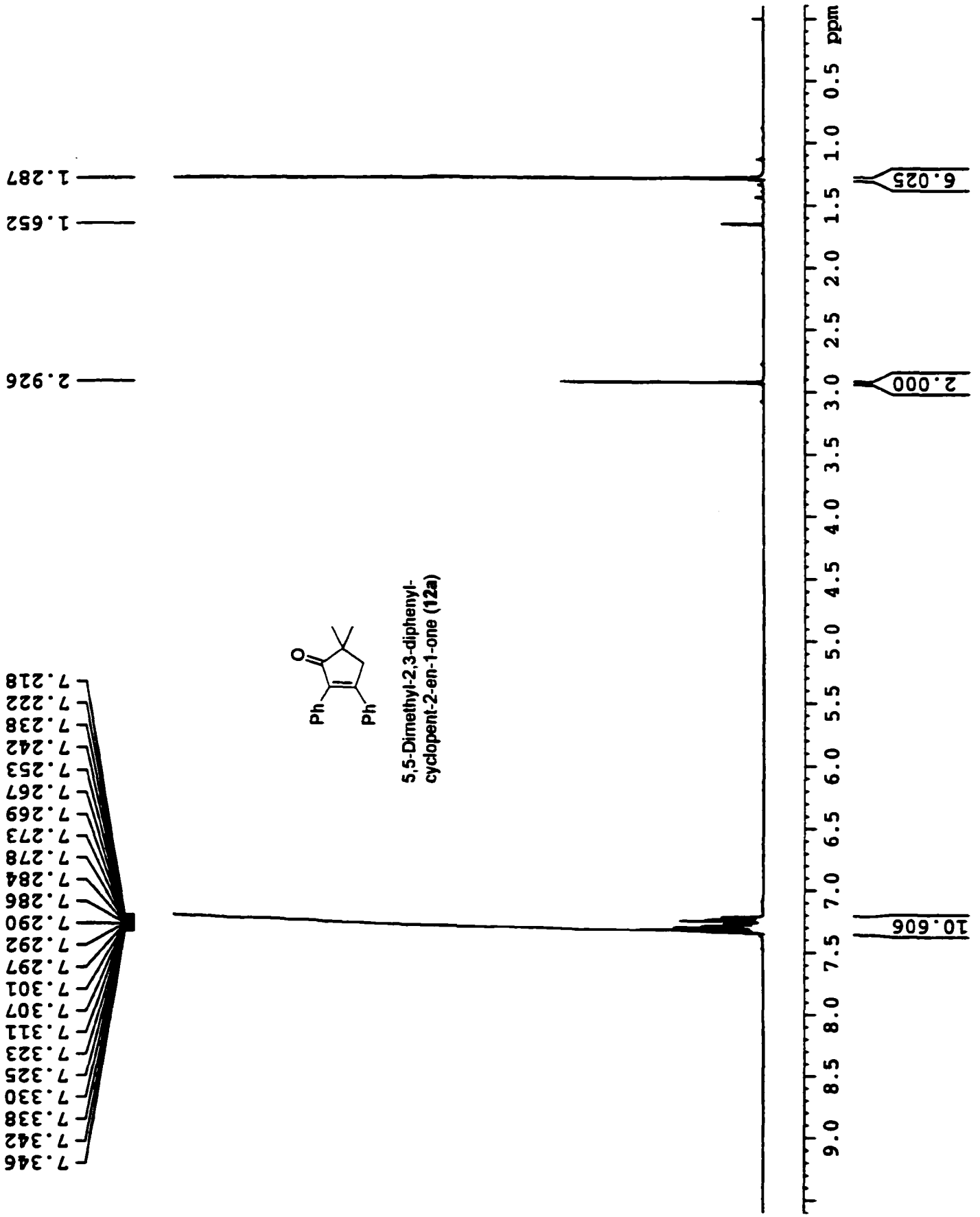

0.001
1.314
1.373
1.379
2.367
2.370
2.373
2.376
2.385
2.388
2.391
2.394
2.574
2.577
2.580
2.583
5.562
5.575
5.579
7.265
6.012
2.016
3.048
1.000
ppm
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
Me
I
CN
(Z)-5-Iodo-2,2-dimethyl-4-hexenenitrile (11e)

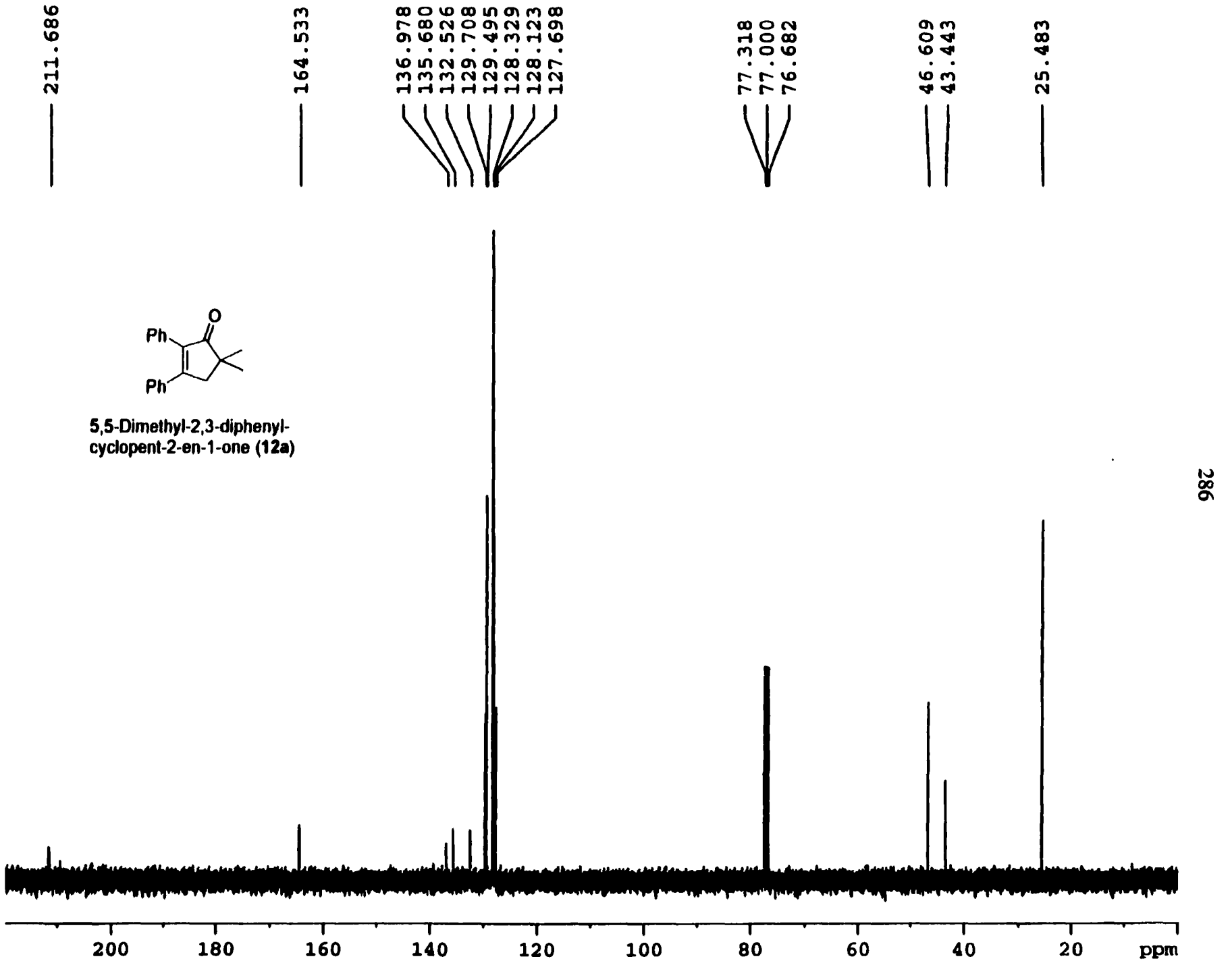
(Z)-5-Iodo-2,2-dimethyl-4-hexenenitrile (11e)



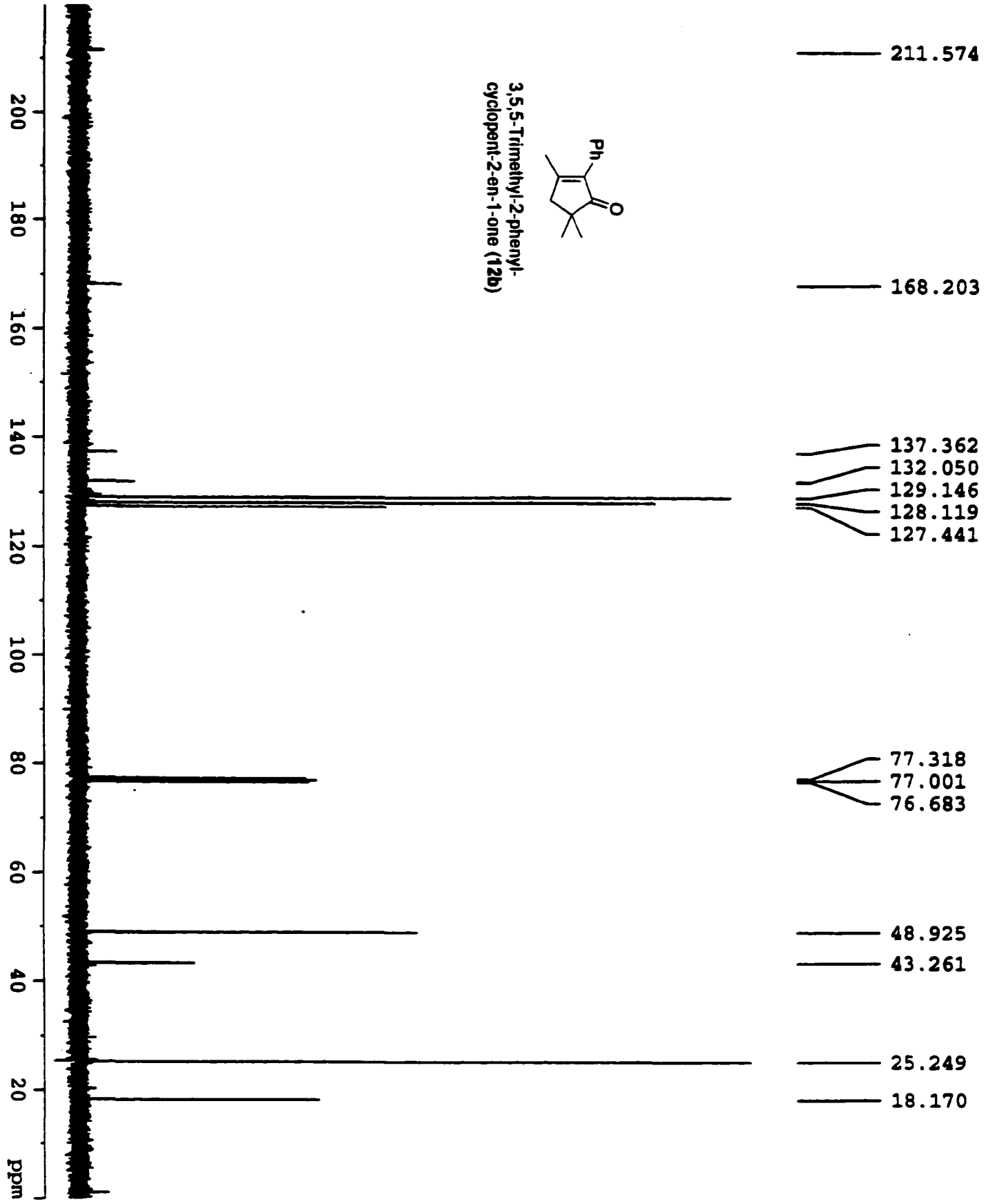

(Z)-5-Iodo-2,2-dimethyl-5-phenyl-
-4-pentenenitrile (11f)

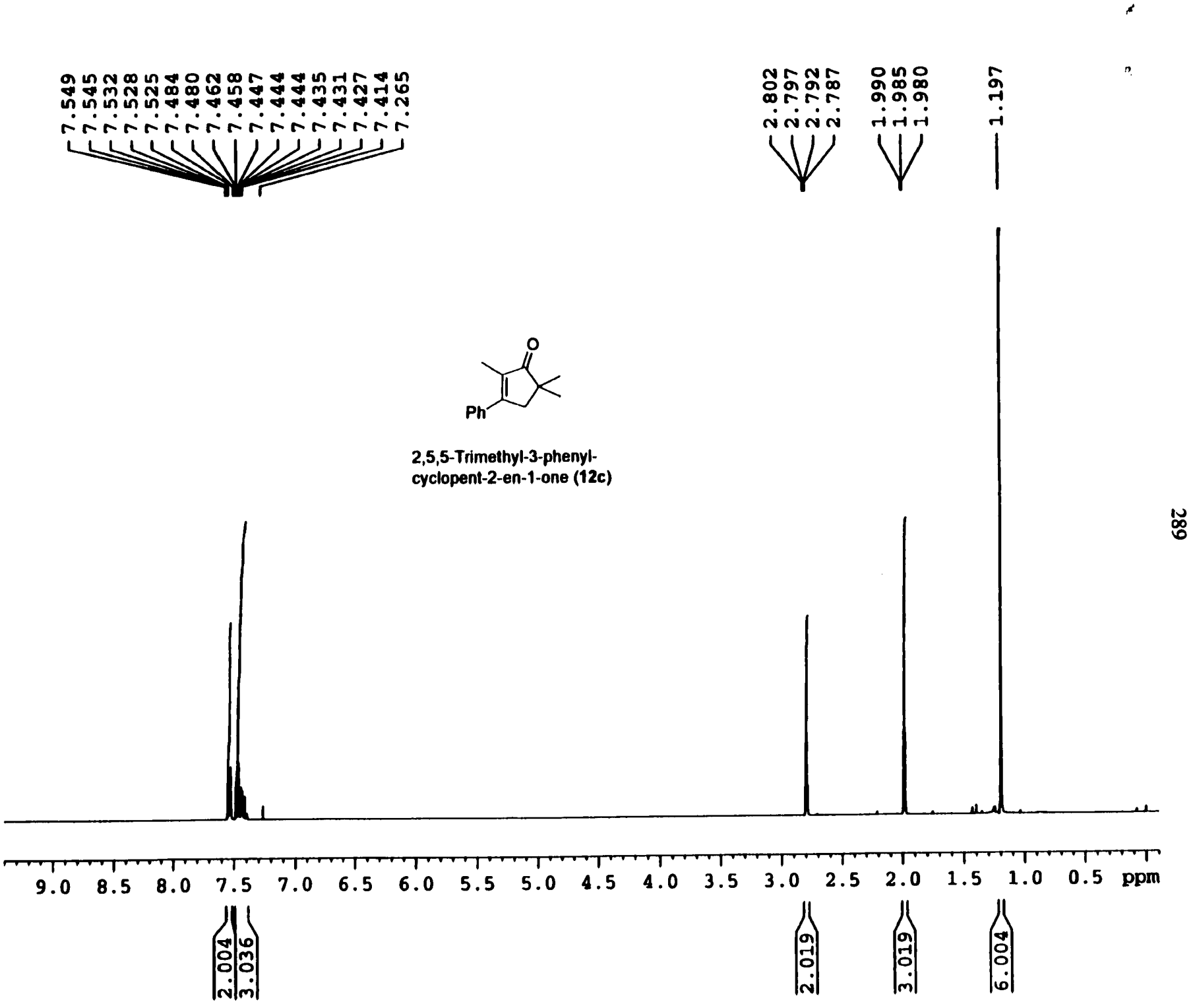

142.719
132.620
128.687
128.562
128.551
128.270
124.609
109.410
77.316
76.999
76.681
48.391
32.361
26.532
Ph
I
CN
(Z)-5-Iodo-2,2-dimethyl-5-phenyl-
-4-pentenenitrile (11f)
200
180
160
140
120
100
80
60
40
20
ppm

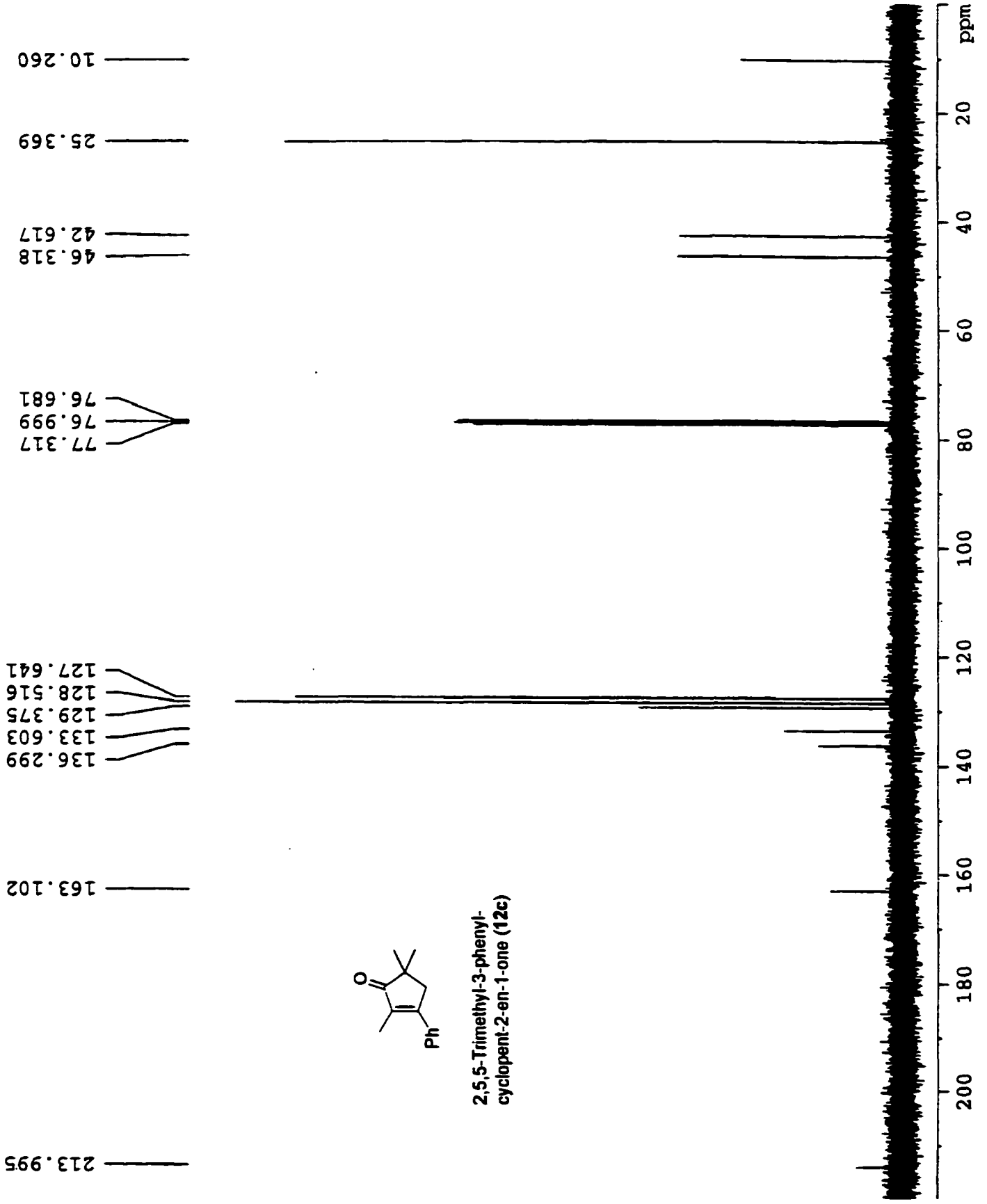

1.287
1.652
2.926
7.218
7.222
7.238
7.242
7.253
7.267
7.269
7.273
7.278
7.284
7.286
7.290
7.292
7.297
7.301
7.307
7.311
7.323
7.325
7.330
7.338
7.342
7.346
O
Ph
Ph
5,5-Dimethyl-2,3-diphenyl-cyclopent-2-en-1-one (12a)
6.025
2.000
10.606
ppm


211.686
164.533
136.978
135.680
132.526
129.708
129.495
128.329
128.123
127.698
77.318
77.000
76.682
46.609
43.443
25.483
O
Ph
Ph
5,5-Dimethyl-2,3-diphenyl-
cyclopent-2-en-1-one (12a)
200
180
160
140
120
100
80
60
40
20
ppm

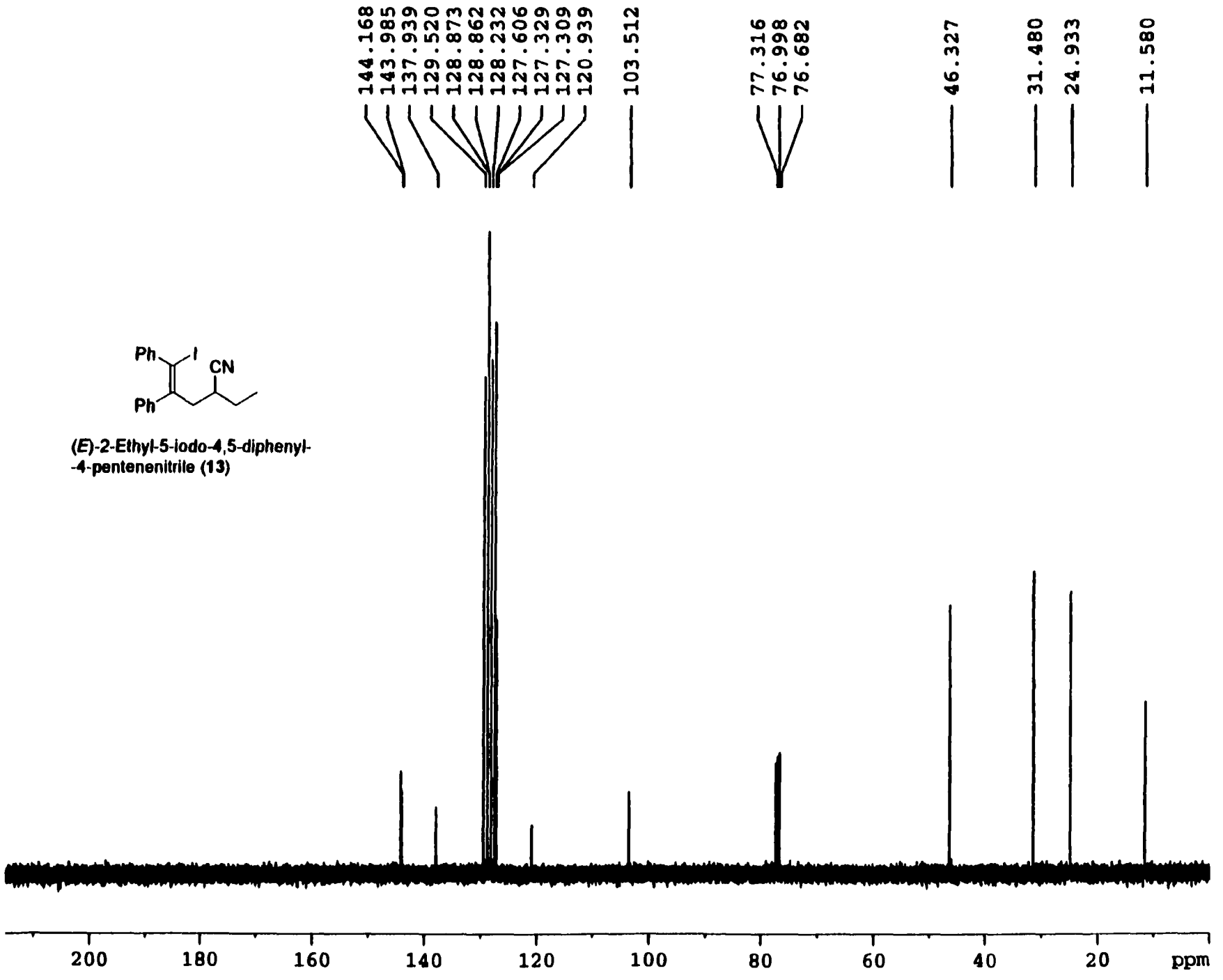
7.420
7.401
7.383
7.322
7.314
7.308
7.303
1.987
2.902
2.065
3.055
6.067
2.534
2.168
1.188
0.073
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm
3,5,5-Trimethyl-2-phenyl-cyclopent-2-en-1-one (12b)
Ph
O


3,5,5-Trimethyl-2-phenyl-cyclopent-2-en-1-one (12b)
Ph
O
211.574
168.203
137.362
132.050
129.146
128.119
127.441
77.318
77.001
76.683
48.925
43.261
25.249
18.170
200
180
160
140
120
100
80
60
40
20
ppm

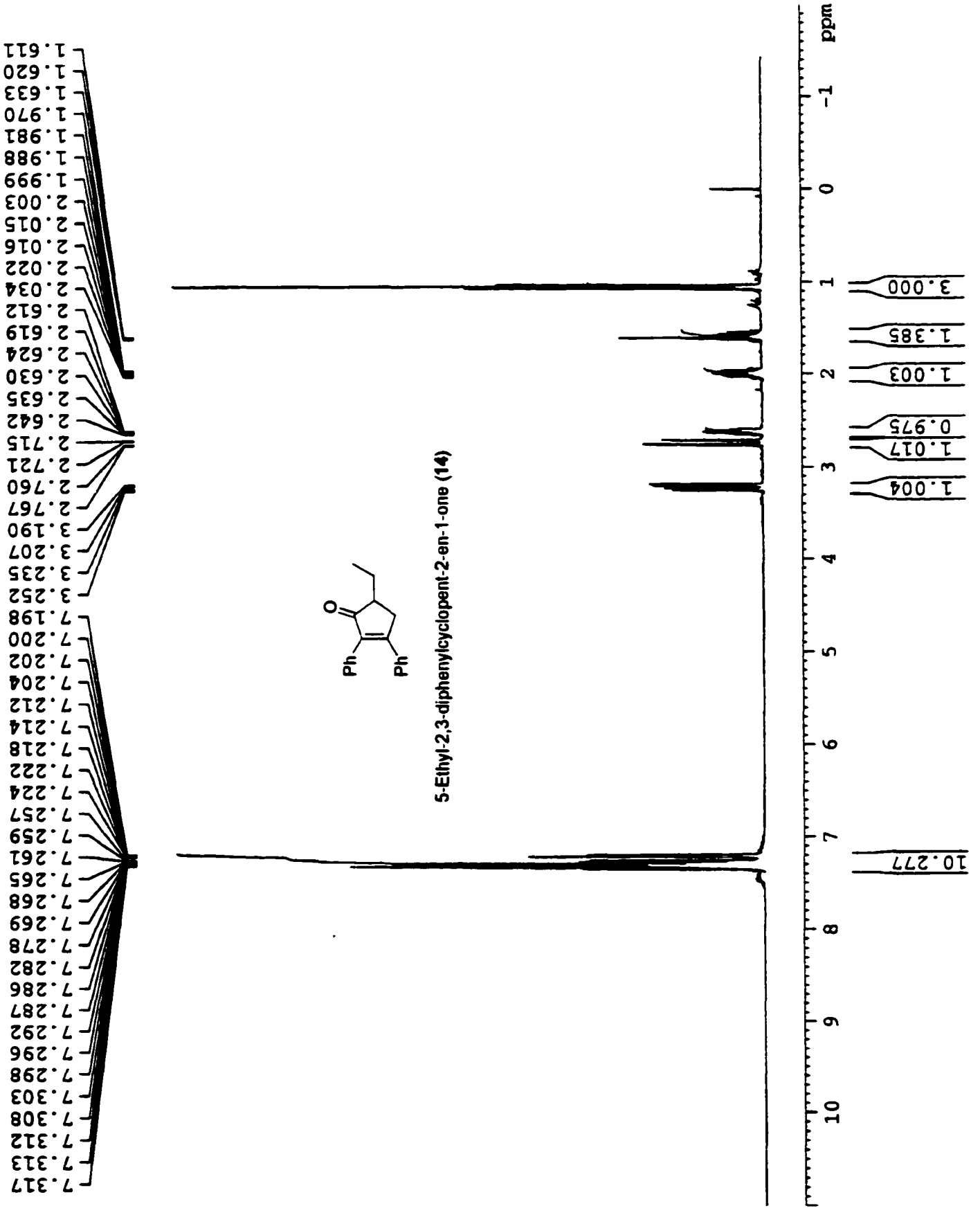

7.549
7.545
7.532
7.528
7.525
7.484
7.480
7.462
7.458
7.447
7.444
7.444
7.435
7.431
7.427
7.414
7.265
2.802
2.797
2.792
2.787
1.990
1.985
1.980
1.197
O
Ph
2,5,5-Trimethyl-3-phenyl-
cyclopent-2-en-1-one (12c)
289
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
2.004
3.036
2.019
3.019
6.004

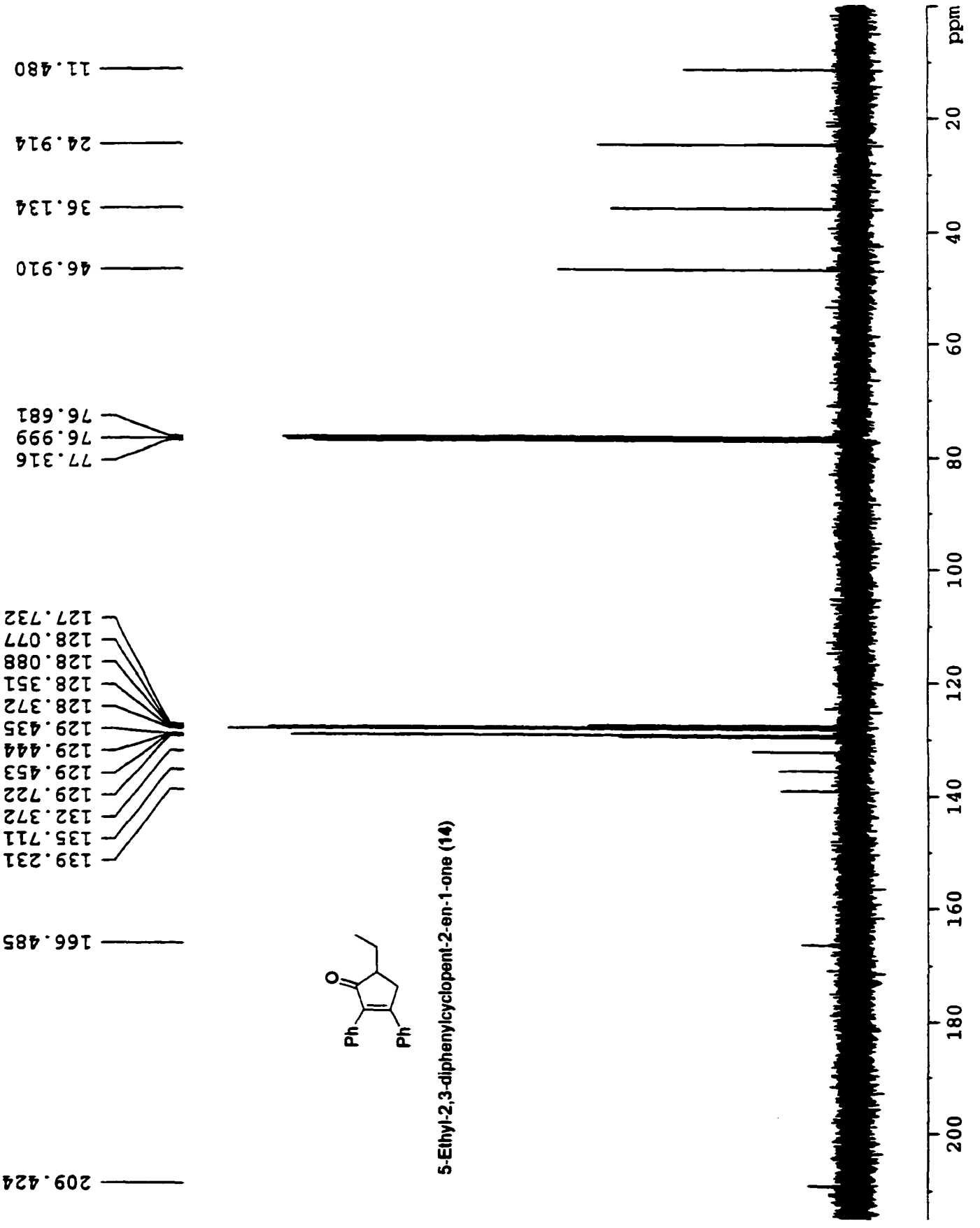

213.995
163.102
136.299
133.603
129.375
128.516
127.641
77.317
76.999
76.681
46.318
42.617
25.369
10.260
ppm
20
40
60
80
100
120
140
160
180
200
O
Ph
2,5,5-Trimethyl-3-phenyl-
cyclopent-2-en-1-one (12c)

7.137
7.129
7.124
7.120
7.114
7.110
7.102
7.097
7.089
7.081
7.076
7.072
7.067
7.065
7.060
7.051
7.047
7.046
7.038
7.032
7.025
7.019
7.016
7.014
7.004
6.997
6.993
6.989
6.984
6.980
3.313
3.292
3.279
3.257
3.102
3.084
3.067
3.049
2.557
2.539
2.522
2.518
2.504
2.500
2.483
1.727
1.709
1.691
1.672
1.654
1.090
1.072
1.053
0.000
10.043
1.017
1.025
1.012
2.031
3.000
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 ppm
(E)-2-Ethyl-5-iodo-4,5-diphenyl-4-pentenenitrile (13)
Ph
Ph
I
CN




**(*E*)-2-Ethyl-5-iodo-4,5-diphenyl-**
**-4-pentenenitrile (13)**


5-Ethyl-2,3-diphenylcyclopent-2-en-1-one (14)
O
Ph
Ph
ppm
10 9 8 7 6 5 4 3 2 1 0 −1
10.277
1.004
1.017
0.975
1.003
1.385
3.000
7.317 7.313 7.312 7.308 7.303 7.298 7.296 7.292 7.287 7.286 7.282 7.278 7.269 7.268 7.265 7.261 7.259 7.257 7.224 7.222 7.218 7.214 7.212 7.204 7.202 7.200 7.198
3.252 3.235 3.207 3.190 2.767 2.760 2.721 2.715 2.642 2.635 2.630 2.624 2.619 2.612 2.034 2.022 2.016 2.015 2.003 1.999 1.988 1.981 1.970 1.633 1.620 1.611


209.424
166.485
139.231
135.711
132.372
129.722
129.453
129.444
129.435
128.372
128.351
128.088
128.077
127.732
77.316
76.999
76.681
46.910
36.134
24.914
11.480
ppm
20
40
60
80
100
120
140
160
180
200
O
Ph
Ph
5-Ethyl-2,3-diphenylcyclopent-2-en-1-one (14)

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