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Palladium-catalyzed annulation of internal alkynes

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Palladium-catalyzed annulation of internal alkynes

by

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Signature was redacted for privacy.

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For the Graduate College

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Ames, Iowa

1995

To my parents, my wife, and

the twinkle(s) in my eye.....

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GENERAL INTRODUCTION

Transition metal-catalyzed processes have been proven to be extremely useful for the synthesis of a wide variety of hetero- and carboannulated ring systems. Palladium-based methodologies are especially convenient, since the metal complexes accommodate a number of different functional groups, are not generally moisture or oxygen sensitive, and catalyze some very novel transformations in good yield.

Recent work in the Larock group has shown that the palladium-catalyzed annulation of internal alkynes with appropriately substituted aryl iodides provides a simply route to indoles, benzofurans, benzopyrans, isoquinolines, isocoumarins, and indenes. This dissertation serves to expand and improve the synthetic scope of this methodology and is organized into five different papers that are suitable for publication. The author of this manuscript was the primary investigator and author for each paper.

Dissertation Organization

Chapter 1 concerns the synthesis of indenones from *o*-iodo- or *o*-bromobenzaldehydes via the palladium-catalyzed annulation of internal alkynes. The reaction provides easy entry to the indenone nucleus, possibly though a Pd(IV) intermediate, but the regiochemistry of the product must be controlled sterically and isomerization is a problem with certain indenones.

Chapter 2 describes the synthesis of isocoumarins and α-pyrones from appropriately substituted esters via the palladium-catalyzed annulation of internal alkynes. The reaction regiochemistry must again be controlled sterically and the reaction is thought to proceed though a seven-membered palladacyclic salt. The α-pyrone synthesis represents the first example of annulation onto internal alkynes by vinylic halides or triflates.

Chapter 3 is a publication describing the extension of this methodology to a variety of different aromatic heterocycles. The significant contributions made by the author include the regioselective synthesis and desilylation of more hindered silylated benzofurans and the synthesis of isochromenes from *o*-iodobenzyl alcohols.

Chapter 4 examines the synthesis of phenanthrenes from *o*-iodobiphenyl by the palladium-catalyzed annulation of internal alkynes. The reaction represents a new, efficient route to the phenanthrene substructure and could possibly be extended to other polycyclic aromatic hydrocarbons. The mechanism of the reaction is believed to involve either electrophilic palladation onto an aromatic ring or oxidative insertion into an aryl C-H bond by a vinylic palladium intermediate.

Chapter 5 involves the synthesis of other miscellaneous hetero- and carbocycles from vinylic halides, an expansion of the α-pyrone chemistry mentioned in Chapter 2. Although the chemistry provides a simple route to a number of useful organic substructures, it currently requires the use of cyclic vinylic halides to obtain annulated products in good yield.

The general conclusion will discuss the current scope and limitations of the methodology by examining the common threads that tie all the chapters together.

Finally, a compilation of pertinent ^{1}H and ^{13}C NMR spectra are contained in appendices A-E of this manuscript. These same supplementary spectra are also available through the American Chemical Society as described at the end of each chapter.

CHAPTER 1: SYNTHESIS OF INDENONES VIA PALLADIUM-CATALYZED ANNULATION OF INTERNAL ALKYNES

A paper submitted to the *Journal of Organic Chemistry*

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Abstract

A number of 2,3-disubstituted-1-indenones have been prepared in fair to good yields by treating *o*-iodo- or *o*-bromobenzaldehyde with various internal alkynes in the presence of a palladium catalyst. Synthetically, the methodology provides an especially convenient route to stable hindered indenones containing aryl, silyl, and *tert*-alkyl groups. The reaction is believed to proceed through a palladium(IV) intermediate, and the regiochemistry of the reaction is controlled sterically.

Introduction

Indenones are useful intermediates in the synthesis of a variety of molecules, including the *C*-nor-*D*-homosteroid ring system,[1] photochromic indenone oxides,[2] 2,4- and 3,4-

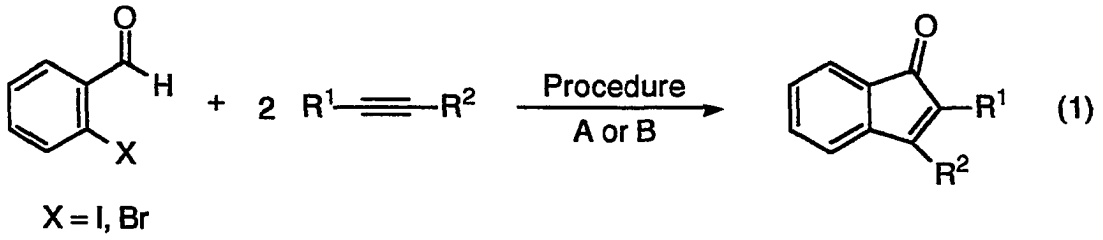
disubstituted-1-naphthols,[3] gibberellins,[4] indanones,[5] and indenes.[6] Indenones themselves have also been used as alcoholic fermentation activators,[7] fungicides,[8] and potential estrogen binding receptors.[9] Among the most recent synthetic targets have been the hindered fungicidally active 2-cyano-3-alkyl-1-indenones[8] and various 2,3-diaryl-1-indenones.[3,9-11]

Although traditional indenone syntheses have largely relied upon Friedel-Crafts-type cyclizations and the addition of Grignard reagents to 2-substituted indanediones, a number of organometallic approaches utilizing alkynes have been reported over the last few years. These approaches tend to be stoichiometric in the metal and/or use carbon monoxide to form the carbonyl group of the indenone. Many different metal complexes have been employed, including nickel,[12] rhodium,[13] iron,[14] manganese,[15] and palladium.[10-12]

Heck first reported the palladium-catalyzed formation of 2,3-diphenyl-1-indenone from *o*-iodobenzaldehyde and diphenylacetylene as a single example in 1989.[10] A stoichiometric approach to 2,3-disubstituted-1-indenones from (*o*-formylaryl)mercury and -palladium complexes and internal alkynes has also been recently reported.[11] Because of our own current interest in this type of annulation process,[16-19] we have explored the scope and limitations of this chemistry and wish now to report improved reaction conditions for the palladium-catalyzed synthesis of a wide variety of 2,3-disubstituted-1-indenones.

Results and Discussion

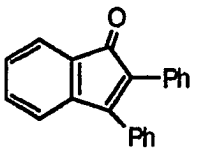
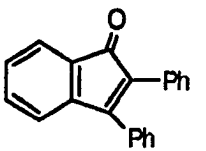
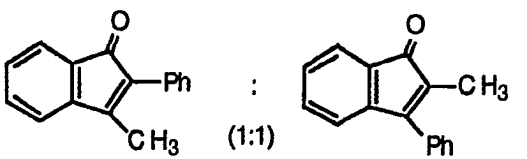
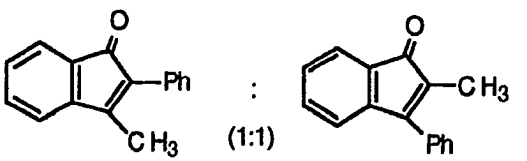
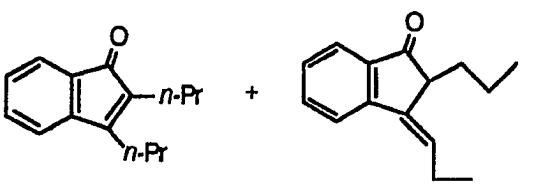
We have developed two general procedures for the annulation of internal alkynes by *o*-iodo- or *o*-bromobenzaldehyde, the use of which depends on the alkyne undergoing annulation: procedure A, 5 mol % $Pd(OAc)_2$, 4 equiv of NaOAc, 1 equiv of *n*-Bu_4NCl, 10 ml of DMF at 100 °C; procedure B, 5 mol % $Pd(OAc)_2$, 1 or 4 equiv of Na_2CO_3, 1 equiv of *n*-Bu_4NCl, 10 ml of *N*,*N*-dimethylacetamide (DMA) at 100 °C (eq. 1). Our results using these procedures are summarized in Table 1. Procedure A works well for diarylalkynes (entries 1,

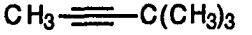
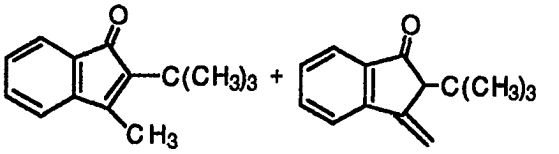
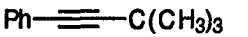
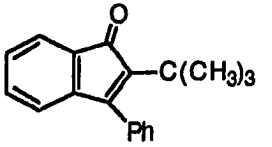
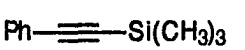
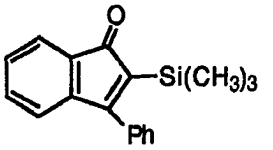
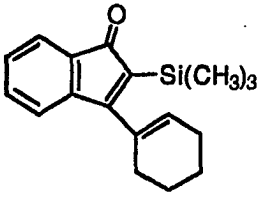
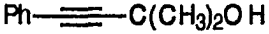
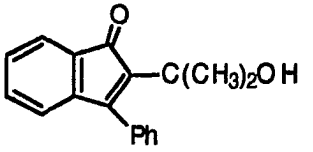


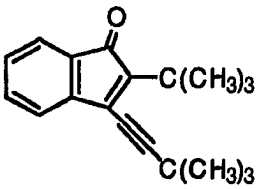
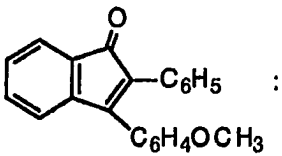
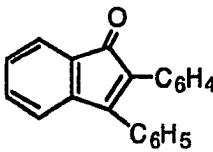
2, and 12) and provides an 84% isolated yield of 2,3-diphenyl-1-indenone, a 26% improvement in yield over the previously reported procedure.[10] Procedure B seems to be a more general procedure for a variety of alkynes containing aryl, silyl, and *tert*-alkyl groups (entries 3-11). Either *o*-iodo- or *o*-bromobenzaldehyde can be employed sucessfully in the annulation process, although the iodide generally provides slightly higher indenone yields and fewer side products. Although the majority of reactions have been run on a 0.5 mmol scale, increasing the scale to 5.0 mmol for the transformation depicted in entry 10 of Table 1 resulted in an almost identical yield (55% versus 58%).

Isomerization of the product is a problem with certain indenones. Isomerization to β,γ-enones is observed with some indenones bearing a primary alkyl group in the 3-position (entries 5 and 6). The β,γ-enones are relatively unstable and this type of isomerization is known to occur under a variety of conditions during the synthesis of indenones.[2,7,9] The ease of isomerization has been attributed to indenone antiaromaticity and a number of different mechanisms have been postulated for the isomerization depending on the reaction conditions. The rate of isomerization was dependent on the indenone being formed. 2-Phenyl-3-methyl-1-indenone isomerized at such a slow rate that the resultant β,γ-enone showed up only after a few days, whereas 2,3-di-*n*-propyl-1-indenone and 2-*tert*-butyl-3-methyl-1-indenone rapidly isomerized to a mixture within minutes. The latter indenone, possessing a bulky group in the 2-position isomerized more extensively, possibly due to a relief in strain (entry 6).

Table 1. Synthesis of Indenones from *o*-Halobenzaldehydes and Internal Alkynes (eq.1)

entry	halide (X)	alkyne	procedure[a]	time (h)	product(s)[b]	yield (%)[c]
1	I	Ph—≡—Ph	A	13		84
2	Br	Ph—≡—Ph	A	36		82
3	I	Ph—≡—CH_3	B	1.5		62
4	Br	Ph—≡—CH_3	B	1		56
5	I	*n*-Pr—≡—*n*-Pr	B	3		52+26[d]

6	I		B	10	 26+26
7	I		B	24	 81
8	I		B	17	 42[e]
9	I		B	30	 49[e,f]
10	I		B	24	 58

11	I	$(CH_3)_3C{-}{\equiv}{-}{\equiv}{-}C(CH_3)_3$	B	24		58
12	I	$p\text{-}CH_3OC_6H_4{-}{\equiv}{-}C_6H_5$	A	24	 (1:1) : 	82

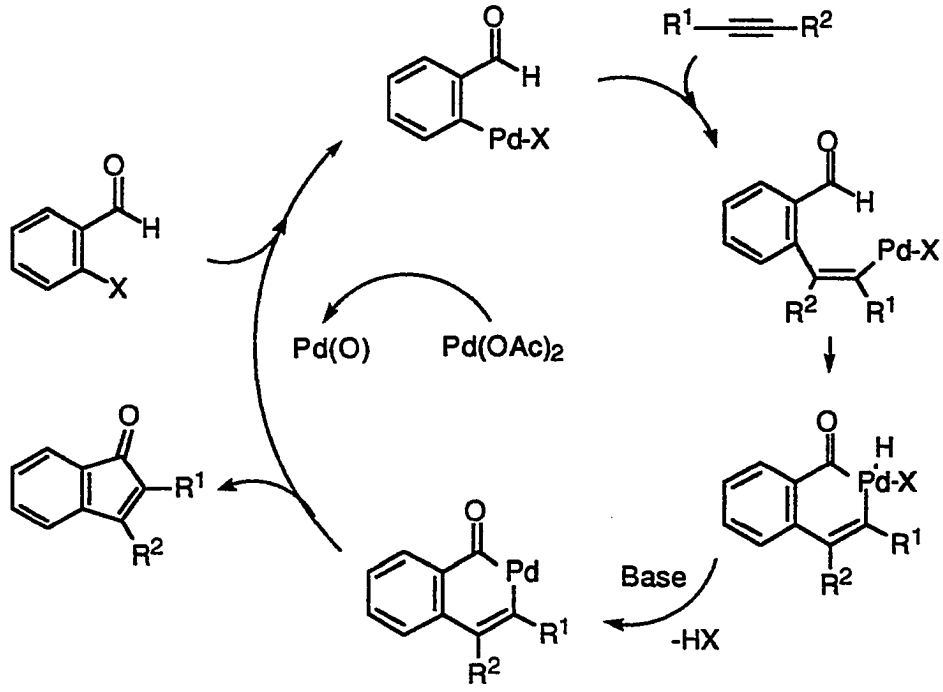
[a] See the text and experimental section for the detailed procedures. [b] A colon (:) indicates that the products were inseparable and a plus (+) indicates that they were separated. [c] Yields refer to isolated compounds purified by chromatography. [d] The second compound is tentatively assigned based on a crude ^1H NMR spectrum and its yield is based on GC measurements. [e] One equiv of base used. [f] Temperature is 80 °C.

This annulation process is highly regioselective for alkynes containing tertiary alkyl, trimethylsilyl, or other hindered groups, with the major isomer having the more sterically demanding group in the 2-position of the indenone (entries 6-11). Less hindered alkynes, such as 1-phenyl-1-propyne, tend to produce a 1:1 mixture of regioisomers (entries 3 and 4). Electronic effects through aromatic rings appear to be minimal (entry 12). The regiochemistry was established for the products of entries 3,[12] 6,[12] and 12[20] by comparsion with known compounds, and was determined by subsequent desilylation for the silyl derivatives (see below). On the basis of these results, the regiochemistry shown was assumed for the products of entries 7, 10, and 11. The reported ^{1}H NMR spectrum for 3-phenyl-1-indenone was inconsistent with the spectrum obtained after desilylation of the product of entry 8.[21] The reported position for the 2-proton was at a chemical shift greater than 7.1 ppm. The proton shift observed for the compound described here was at 6.0 ppm, in agreement with those of other known indenones.[1,12,22]

We believe that this annulation process proceeds as shown in Scheme 1: (1) reduction of $Pd(OAc)_2$ to the actual catalyst Pd(O), (2) oxidative addition of the aryl halide to Pd(O), (3) arylpalladium coordination to the alkyne and then insertion of the alkyne to form a vinylpalladium intermediate, (4) a second oxidative insertion into the aldehyde C-H bond to form a palladium(IV) intermediate, (5) elimination of HX by base, and (6) regeneration of the Pd(O) catalyst by reductive elimination to the indenone. A similiar mechanism involving oxidative addition of an aldehyde to an organopalladium(II) intermediate has been proposed for the palladium-catalyzed reactions of *o*-bromobenzaldehyde with methyl acrylate.[23] Another possible mechanism involves addition of the C-Pd bond of the vinylpalladium intermediate across the C=O bond of the aldehyde to produce a palladium(II) alkoxide, followed by β-hydride elimination. However, there does not appear to be any precedent for either of these steps.

Although the synthetic applications of this process are somewhat limited in scope due to

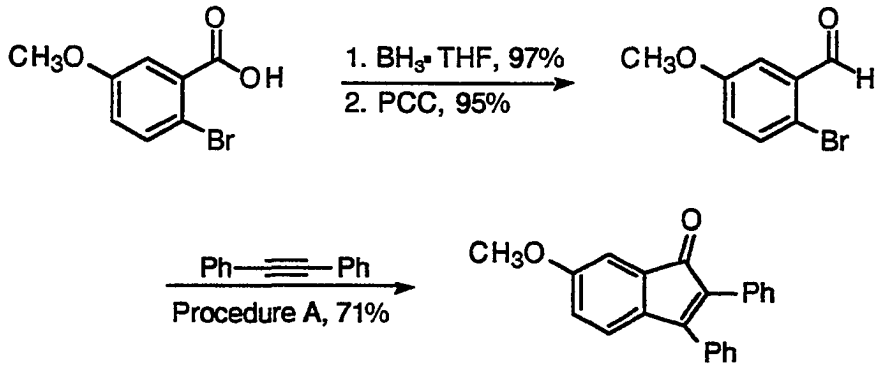
Scheme 1



isomerization and a lack of regiochemical control, this chemistry proves to be very convenient and useful for the synthesis of some indenones that are difficult to obtain by traditional methods.[1] For example, 2,3-diphenyl-6-methoxy-1-indenone was readily prepared regioselectively in 65% overall yield from commercially available 2-bromo-5-methoxybenzoic acid, employing our alkyne annulation as the key step (Scheme 2). This compound has previously been prepared as a potential estrogen binding receptor from 3-methoxybenzoic acid in 23% overall yield as a 16:1 mixture of regioisomers via cyclodehydration.[24]

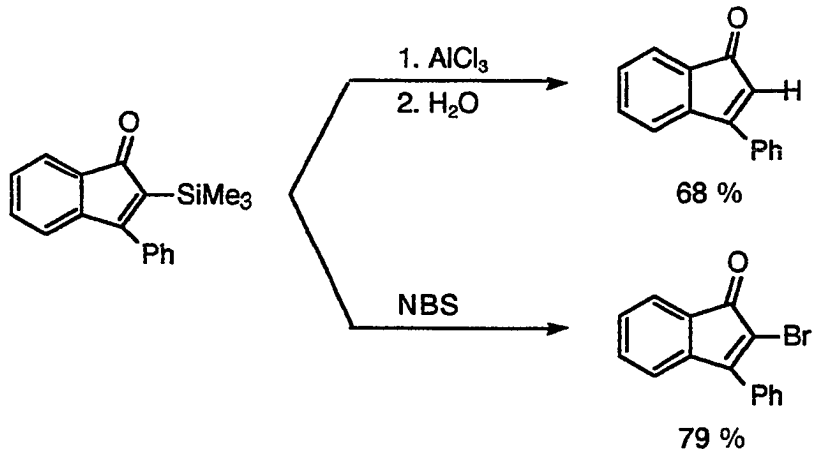
The silyl-substituted indenones are also synthetically useful, as the silyl moiety can be removed or readily converted to other functional groups. For example, 3-phenyl-2-(trimethylsilyl)-1-indenone was easily converted to 3-phenyl-1-indenone in the presence of aluminum chloride, followed by water, or brominated to produce 2-bromo-3-phenyl-1-

Scheme 2



indenone using NBS (Scheme 3).

Scheme 3



In conclusion, a useful synthesis of 2,3-disubstituted-1-indenones has been developed using the palladium-catalyzed annulation of internal alkynes by *o*-iodo- or *o*-bromobenzaldehyde. The procedure utilizes readily available starting materials. The reactions proceed under relatively mild conditions, and give fair to good indenone yields. Although the

reaction is somewhat limited in scope synthetically, it is particularly suited for the synthesis of hindered alkyl, aryl, or silyl 2,3-disubstituted-1-indenones and allows the regiochemistry of the aryl ring of the indenone to be readily controlled, alleviating a problem frequently encountered during traditional Friedel-Crafts type cyclizations and 2-substituted indanedione chemistry.[1,8,9,20]

Experimental Section

General. All ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively. Thin-layer chromatography (TLC) was preformed using commerically prepared 60 mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm), or basic $KMnO_4$ solution [3 g $KMnO_4$ + 20 g K_2CO_3 + 5 ml NaOH (5%) + 300 ml H_20]. All melting points are uncorrected.

Reagents. All reagents were used directly as obtained commerically unless otherwise noted. Anhydrous forms of Na_2CO_3, NaOAc, and $AlCl_3$ were purchased from Fischer-Scientific. All palladium compounds were donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. 2-Bromobenzaldehyde, 2-iodobenzyl alcohol, 4-iodoanisole, phenylacetylene, 1-phenyl-2-(trimethylsilyl)acetylene, 1-(1-cyclohexenyl)-2-(trimethylsilyl)acetylene, 2-chloro-2-methylpropane, borane-THF, CuI, NBS, and PCC were obtained from Aldrich Chemical Co., Inc. 1-Phenyl-1-propyne, 4,4-dimethyl-2-pentyne, and 4-octyne were purchased from Farchan Scientific Co. Diphenylacetylene was purchased from Eastman Kodak Co. 2-Bromo-5-methoxybenzoic acid was purchased from Lancaster Synthesis, Inc. The following starting materials were prepared.

2-Iodobenzaldehyde. 2-Iodobenzyl alcohol (11.5 g, 0.05 mol) and PCC (15.75 g, 0.075 mol) were vigorously stirred in 100 ml of CH_2Cl_2 at rt for 24 h. The reaction mixture was diluted with 400 ml ether and filtered through Florisil. The solvent was evaporated under

reduced pressure and the resulting solid was chromatographed using 15:1 hexane/EtOAc to yield 93% of the desired compound as a white solid with spectral properties identical to those previously reported.[25]

2-Bromo-5-methoxybenzaldehyde. To 2-bromo-5-methoxybenzoic acid (0.5 g, 2.17 mmol) in THF (1 ml) purged with N_2 and cooled to 0 °C was added borane-THF (2.85 mmol) over a period of 10 min. After 5 h, the reaction was quenched with 1.3 ml of a 1:1 THF/H_2O mixture and the aqueous phase was saturated with 0.55 g of K_2CO_3. The mixture was extracted with 3 x 10 ml of ether and dried over $MgSO_4$. The solvent was removed under reduced pressure to yield 0.46 g (97%) of 2-bromo-5-methoxybenzyl alcohol as a clear liquid: ^{1}H NMR ($CDCl_3$) δ 2.03 (s, 1 H, OH), 3.80 (s, 3 H, CH_3), 4.71 (s, 2 H, CH_2), 6.71 (dd, J = 3, 8.7 Hz, 1 H, aryl), 7.06 (d, J = 3 Hz, 1 H, aryl), 7.41 (d, J = 8.7 Hz, 1 H, aryl). This alcohol (0.46 g, 2.13 mmol) and PCC (1.34 g, 6.23 mmol) were stirred at rt for 10 h in 8.5 ml of CH_2Cl_2. The reaction mixture was diluted with 40 ml ether and filtered through Celite. The organic phase was concentrated by evaporation of the solvent at reduced pressure to yield a brown solid. EtOAc was added to the solid and the solution was filtered through silica gel to yield 0.43 g (95%) of the desired compound as a white solid (mp 75-76 °C): ^{1}H NMR ($CDCl_3$) δ 3.76 (s, 3 H, CH_3), 6.95 (dd, J = 3, 8.7 Hz, 1 H, aryl), 7.33 (d, J = 3 Hz, 1 H, aryl), 7.44 (d, J = 8.7 Hz, 1 H, aryl), 10.22 (s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 55.7, 112.6, 117.9, 123.0, 133.8, 134.5, 159.2, 191.8; IR ($CHCl_3$) 1699 (C=O) cm^{-1}; mass spectrum m/z 213.9633 (calcd for $C_8H_7O_2Br$, 213.9630).

***tert*-Butylphenylacetylene.**[26] $AlCl_3$ (0.114 g, 0.086 mmol) was placed in 25 ml of CH_2Cl_2 under N_2 at -78 °C. 1-Phenyl-2-(trimethylsilyl)acetylene (1.5 g, 8.6 mmol) and 2-chloro-2-methylpropane (1.59 g, 17.24 mmol) in 25 ml of CH_2Cl_2 were added dropwise. The reaction was complete in 4.25 h. The reaction mixture was quenched with water, extracted with ether, and filtered through Florisil. The solvent was removed under reduced pressure and

vacuum distillation (104 °C/24 mm Hg) afforded 0.89 g (65%) of a clear liquid whose spectral data were identical with previous reports.[27]

4-Methoxydiphenylacetylene.[28] 4-Iodoanisole (2.34 g, 10 mmol), phenylacetylene (1.02 g, 10 mmol), CuI (17.3 mg, 0.09 mmol), $PdCl_2(PPh_3)_2$ (6.7 mg, 0.0095 mmol), $PdCl_2(CH_3CN)_2$ (11.7 mg, 0.045 mmol), and diethylamine (60 ml) were stirred for 3 d at rt. The reaction solvent was removed under reduced pressure and the residue was diluted with 100 ml ether, extracted with saturated NH_4Cl, and dried over Na_2SO_4. The solvent was evaporated under reduced pressure and the crude product was chromatographed using 15:1 hexane/EtOAc to give 1.45 g of the desired compound with spectral properties identical to those previously reported.[29]

General Procedure for the Palladium-Catalyzed Formation of 2,3-Disubstituted Indenones. $Pd(OAc)_2$ (6 mg, 0.027 mmol), the base (2.0 mmol unless otherwise noted), *n*-Bu_4NCl (150 mg, 0.54 mmol, Lancaster), the aldehyde (0.5 mmol), and the alkyne (1 mmol) were placed in a 4 dram vial which was heated in an oil bath at 100 °C for the necessary period of time. The reaction was monitored by TLC (15:1 hexane/EtOAc) to establish completion. The reaction mixture was cooled, diluted with 30 ml ether, washed with 2 x 45 ml portions of saturated NH_4Cl, dried over anhydrous Na_2SO_4, and filtered. The solvent was evaporated under reduced pressure (may have contained a small amount of solvent) and the product was isolated by chromatography on a silica gel column. The following compounds were prepared by the above procedure.

2,3-Diphenyl-1-indenone (Entries 1 and 2, Table 1). The reaction mixture was chromatographed using 2:1 hexane/CH_2Cl_2 to afford the desired compound with spectral properties identical to those previously reported.[10]

2-Methyl-3-phenyl-1-indenone and 2-Phenyl-3-methyl-1-indenone (Entries 3 and 4, Table 1). The reaction mixture was chromatographed using 15:1

hexane/EtOAc to yield a 1:1 mixture of phenylmethylindenones with spectral properties identical to those previously reported.[12]

2,3-Di-*n*-propyl-1-indenone (Entry 5, Table 1). The reaction mixture was chromatographed using 25:1 hexane/EtOAc to yield a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.93 (t, J = 7.5 Hz, 3 H, CH_3), 1.03 (t, J = 7.5 Hz, 3 H, CH_3), 1.49 (sextet, J = 7.5 Hz, 2 H, CH_2), 1.64 (sextet, J = 7.5 Hz, 2 H, CH_2), 2.23 (t, J = 7.5 Hz, 2 H, CH_2), 2.51 (t, J = 7.5 Hz, 2 H, CH_2), 7.02 (d, J = 7.2 Hz, 1 H, aryl), 7.13 (t, J = 6.9 Hz, 1 H, aryl), 7.2-7.4 (m, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.5, 21.2, 22.5, 24.8, 28.2, 118.9, 121.8, 127.8, 131.1, 133.1, 134.7, 145.8, 157.6, 198.5; IR (neat) 1703 (C=O) cm^{-1}; mass spectrum m/z 214.1356 (calcd for $C_{15}H_{18}O$, 214.1358).

2-*n*-Propyl-3-propylidene-1-indanone (Entry 5, Table 1). The structure of this apparently unstable compound was tentatively assigned based on the ^{1}H NMR spectrum of the crude product mixture. It possesed an R_f slightly lower than that of the indenone and partially decomposed to a red, very low R_f material during chromatography.[9] The isolated compound was contaminated with a small amount of the corresponding indanone and the yield is based on GC measurements.

2-*tert*-Butyl-3-methyl-1-indenone (Entry 6, Table 1). The reaction mixture was chromatographed using 25:1 hexane/EtOAc to yield the desired compound with spectral properties identical to those previously reported.[12]

2-*tert*-Butyl-3-methylidene-1-indanone (Entry 6, Table 1). ^{1}H NMR ($CDCl_3$) δ 1.00 (s, 9 H, CH_3), 2.82 (s, 1 H, CH), 5.28 (s, 1 H, vinyl), 5.87 (d, J = 1.2 Hz, 1 H, vinyl), 7.40 (t, J = 7.8 Hz, 1 H, aryl), 7.60 (t, J = 7.2 Hz, 1 H, aryl), 7.72 (m, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 28.1, 35.2, 61.1, 109.7, 120.5, 122.9, 128.9, 134.6, 137.3, 143.3, 149.9, 205.2; IR ($CHCl_3$) 1710 (C=O) cm^{-1}; mass spectrum m/z 200.1200 (calcd for $C_{14}H_{16}O$, 200.1201).

2-*tert*-Butyl-3-phenyl-1-indenone (Entry 7, Table 1). The reaction mixture was chromatographed using 15:1 hexane/EtOAc to yield a yellow solid (mp 114-116 °C, from *n*-hexane): ^{1}H NMR ($CDCl_3$) δ 1.16 (s, 9 H, CH_3), 6.47 (d, J = 7.2 Hz, 1 H, aryl), 7.0-7.6 (m, 8 H, aryl); ^{13}C NMR ($CDCl_3$) δ 30.6, 33.6, 120.3, 121.7, 127.8, 128.03, 128.08, 128.1, 129.8, 133.3, 135.3, 141.4, 147.6, 153.9, 198.4; IR ($CHCl_3$) 1699 (C=O) cm^{-1}; mass spectrum m/z 262.1362 (calcd for $C_{19}H_{18}O$, 262.1358).

3-Phenyl-2-(trimethylsilyl)-1-indenone (Entry 8, Table 1). The reaction mixture was chromatographed using 15:1 hexane/EtOAc to yield an orange oil: ^{1}H NMR ($CDCl_3$) δ 0.05 (s, 9 H, CH_3), 6.87 (d, J = 6.6 Hz, 1 H, aryl), 7.2-7.6 (m, 8 H, aryl); ^{13}C NMR ($CDCl_3$) δ -0.15, 120.7, 122.1, 127.5, 128.3, 129.00, 129.04, 132.2, 132.9, 134.6, 134.8, 147.1, 170.6, 201.6; IR ($CHCl_3$) 1697 (C=O) cm^{-1}; mass spectrum m/z 278.1126 (calcd for $C_{18}H_{18}OSi$, 278.1127).

3-(1-Cyclohexenyl)-2-(trimethylsilyl)-1-indenone (Entry 9, Table 1). The reaction mixture was chromatographed using 25:1 hexane/EtOAc to yield a yellow oil: ^{1}H NMR ($CDCl_3$) δ 0.23 (s, 9 H, CH_3), 1.75 (m, 4 H, CH_2), 2.2 (m, 4 H, CH_2), 5.78 (m, 1 H, vinyl), 7.02 (d, J = 7.2 Hz, 1 H, aryl), 7.20 (dt, J = 0.9, 6.9 Hz, 1 H, aryl), 7.31 (dt, J = 1.2, 6.6 Hz, 1 H, aryl), 7.40 (d, J = 6.9 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ -0.05, 21.8, 22.3, 24.9, 28.1, 120.2, 121.8, 126.6, 128.7, 132.2, 132.5, 132.8, 133.3, 146.6, 173.7, 202.2; IR (neat) 1697 (C=O) cm^{-1}; mass spectrum m/z 282.1437 (calcd for $C_{18}H_{22}OSi$, 282.1440).

2-(1-Hydroxy-1-methylethyl)-3-phenyl-1-indenone (Entry 10, Table 1). The reaction mixture was chromatographed using 4:1 hexane/EtOAc to yield an orange-yellow solid (mp 103-104 °C, from *n*-hexane): ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 6 H, CH_3), 4.00 (s, 1 H, OH), 6.64 (d, J = 6.9 Hz, 1 H, aryl), 7.1-7.6 (m, 8 H, aryl); ^{13}C NMR ($CDCl_3$) δ 30.5, 71.1, 121.2, 122.4, 127.3, 128.5, 128.5, 128.6, 129.7, 133.5, 133.9, 138.3, 146.7, 153.9,

199.6; IR ($CHCl_3$) 3500 (OH), 1697 (C=O) cm^{-1}; mass spectrum m/z 264.1145 (calcd for $C_{18}H_{16}O_2$, 264.1150). This reaction gave a 55% isolated yield when run on a 5.0 mmol scale.

2-*tert*-Butyl-3-(*tert*-butylethynyl)-1-indenone (Entry 11, Table 1). The reaction mixture was chromatographed using 25:1 hexane/EtOAc to yield an orange solid (mp 95-97 °C, from ethanol): ^1H NMR ($CDCl_3$) δ 1.37 (s, 9 H, CH_3), 1.40 (s, 9 H, CH_3), 7.1-7.4 (m, 4 H, aryl); ^{13}C NMR ($CDCl_3$) δ 29.0, 29.6, 30.4, 33.9, 74.1, 118.2, 119.5, 121.2, 128.3, 130.0, 133.4, 135.9, 144.0, 145.8, 197.9; IR ($CHCl_3$) 1697 (C=O) cm^{-1}; mass spectrum m/z 266.1667 (calcd for $C_{19}H_{22}O$, 266.1671).

2-(*p*-Methoxyphenyl)-3-phenyl-1-indenone and 3-(*p*-Methoxyphenyl)-2-phenyl-1-indenone (Entry 12, Table 1). The reaction mixture was chromatographed using 4:1 hexane/EtOAc to yield a 1:1 mixture of indenones with spectral properties identical to those previously reported.[20]

2,3-Diphenyl-6-methoxy-1-indenone. This compound was isolated in 71% yield after 30 h from the reaction of 2-bromo-5-methoxybenzaldehyde with diphenylacetylene using procedure A. The reaction mixture was chromatographed using 2:1 hexane/CH_2Cl_2 to yield the desired compound with spectral properties identical to those previously reported.[24]

3-Phenyl-1-indenone. 3-Phenyl-2-trimethylsilyl-1-indenone (44 mg, 0.158 mmol) and $AlCl_3$ (23 mg, 0.172 mmol) were stirred in 5 ml of CH_2Cl_2 (dried over 4 A sieves) at 0 °C under N_2 and the temperature was raised to rt after 3.5 h. After 6 h, water was added and the reaction mixture was extracted with ether. The ether solution was dried over $MgSO_4$, and concentrated. The residue was chromatographed using 15:1 hexane/EtOAc to yield 68% of the desired compound as an orange-yellow oil: ^1H NMR ($CDCl_3$) δ 6.01 (s, 1 H, vinyl), 7.26-7.7 (m, 9 H, aryl); ^{13}C NMR ($CDCl_3$) δ 121.5, 122.6, 122.9, 127.3, 128.9, 129.2, 130.4, 132.3, 132.8, 133.0, 143.9, 162.7, 197.0; IR ($CHCl_3$) 1699 (C=O) cm^{-1}; mass spectrum m/z 206.0727 (calcd for $C_{15}H_{10}O$, 206.0732).

2-Bromo-3-phenyl-1-indenone. 3-Phenyl-2-trimethylsilyl-1-indenone (61 mg, 0.219 mmol) and NBS (78 mg, 0.44 mmol) were refluxed in 5.5 ml of CH_2Cl_2 (dried over 4 A sieves) for 52 h. The reaction mixture was concentrated, ether was added to the mixture, and the residual solid was decanted. The solvent was removed under reduced pressure and the residue was chromatographed using 15:1 hexane/EtOAc to yield 48.9 mg (79%) of the desired compound as an orange solid (mp 112-113 °C, from *n*-hexane): ^{1}H NMR ($CDCl_3$) δ 7.1-7.7 (m, 9 H, aryl); ^{13}C NMR ($CDCl_3$) δ 117.9, 121.2, 123.6, 128.1, 128.6, 128.8, 129.8, 130.2, 131.0, 133.7, 144.4, 156.7, 189.7 ; IR ($CHCl_3$) 1717 (C=O) cm^{-1}; mass spectrum m/z 283.9835 (calcd for $C_{15}H_9OBr^{79}$, 283.9837).

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for all new indenones (24 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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CHAPTER 2: SYNTHESIS OF ISOCOUMARINS AND α-PYRONES VIA PALLADIUM-CATALYZED ANNULATION OF INTERNAL ALKYNES

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

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Abstract

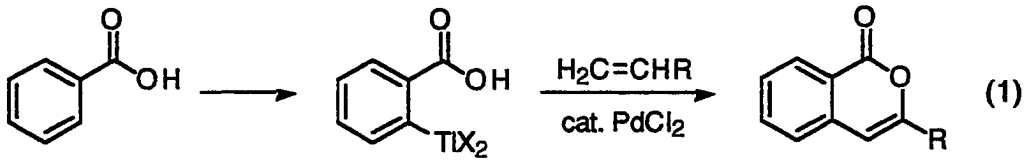
A number of 3,4-disubstituted isocoumarins and α-pyrones have been prepared in good yields by treating halogen- or triflate- containing aromatic and α,β-unsaturated esters respectively, with internal alkynes in the presence of a palladium catalyst. Synthetically, the methodology provides an especially simple and convenient, regioselective route to isocoumarins and α-pyrones containing aryl, silyl, ester, *tert*-alkyl and other hindered groups. The reaction is believed to proceed though a seven-membered palladacyclic salt in which the regiochemistry of the reaction is controlled by steric factors.

Introduction

Isocoumarins[1] and α-pyrones[2] are useful intermediates in the synthesis of a variety of important hetero- and carbocyclic molecules, including isocarbostyrils, isoquinolines, isochromenes, pyridones, and various aromatic compounds. These carbon skeletons also occur

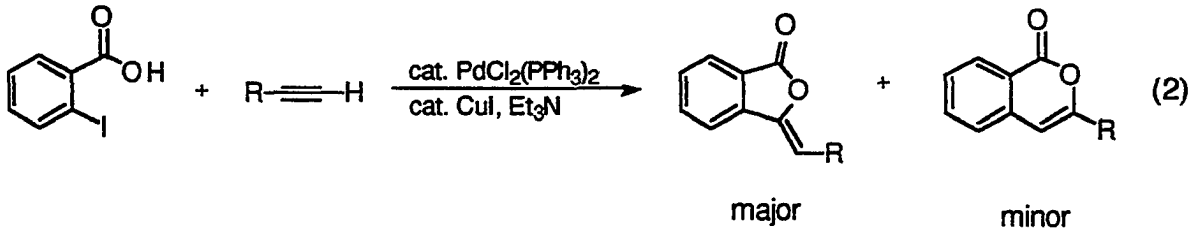
as structural subunits in numerous natural products that exhibit a wide range of biological activity.[3,4]

Although traditional approaches to the synthesis of these ring systems have been diverse,[5,6] a number of organometallic approaches utilizing palladium have been reported over the last few years. Isocoumarins have been prepared by the *ortho*-thallation of benzoic acids and subsequent palladium-catalyzed olefination using simple olefins, allylic halides and vinylic halides or esters (eq. 1).[7] Unsubstituted or 3-substituted isocoumarins have been prepared by



(1)

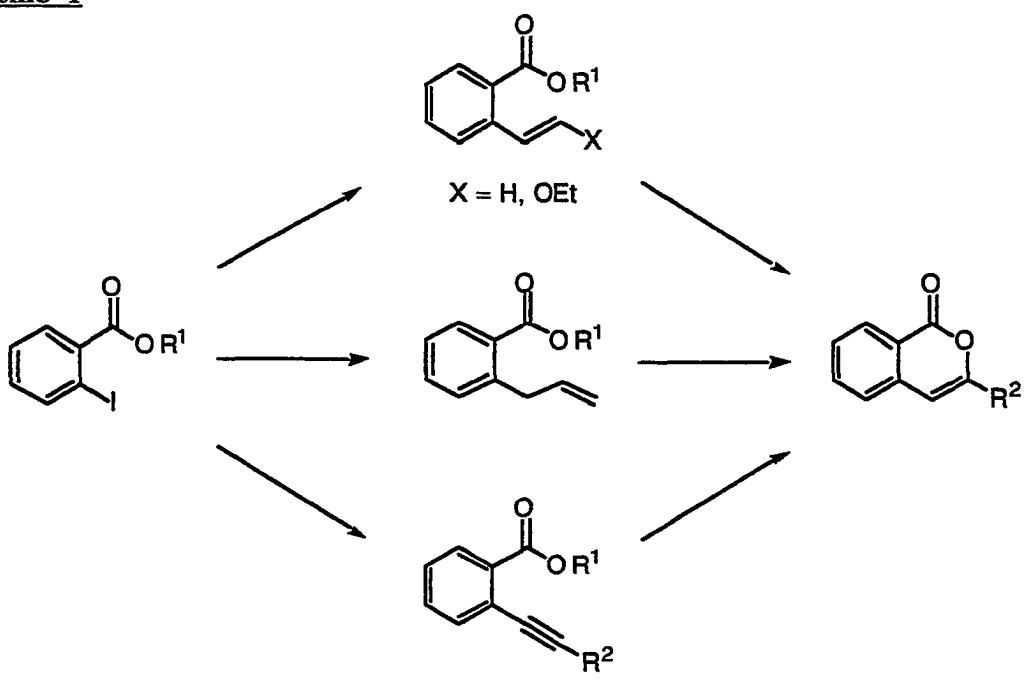
the palladium-catalyzed coupling of 2-halobenzoate esters or 2-halobenzonitriles with alkenes,[8] vinylic stannanes,[9] or terminal alkynes,[10] and subsequent cyclization, or π-allylnickel cross-coupling and palladium-catalyzed cyclization[11] (Scheme 1). Attempts to couple *o*-iodobenzoic acid and terminal alkynes produced unsaturated phthalides as major products and only minor amounts of the 3-substituted isocoumarins (eq. 2).[12]



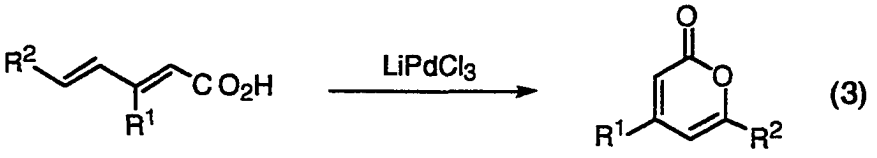
(2)

α-Pyrones have been synthesized by the cyclization of open chain penta-2,4-dienoic

Scheme 1

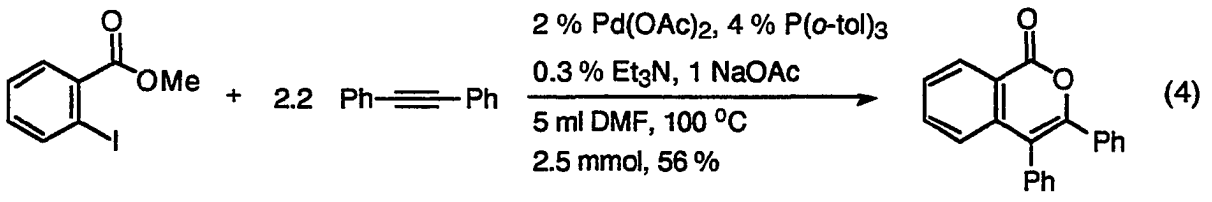


acids using lithium chloropalladite (eq. 3)[13] or formed as unstable multi-insertion products from the reaction of palladium complexes with internal alkynes.[14]



(3)

In 1989 Heck reported the direct formation of 3,4-diphenylisocoumarin in 56% yield from the palladium-catalyzed coupling of methyl 2-iodobenzoate and diphenylacetylene (eq. 4).[15] Di-*p*-anisylacetylene and 1-phenyl-1-hexyne afforded only 38% and 29% yields respectively of the corresponding isocoumarins. Because of our own interest in this type of annulation process,[16] we have explored the scope and limitations of this chemistry and now

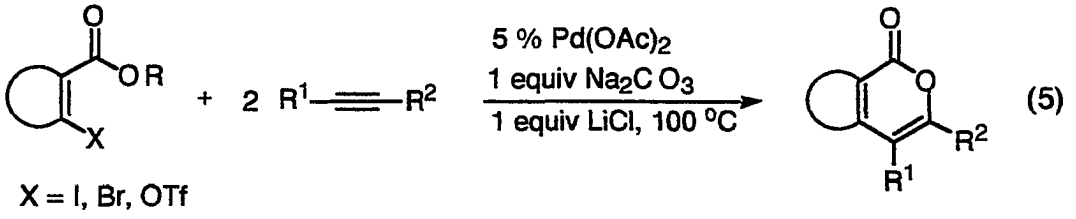


(4)

wish to report reaction conditions for the synthesis of a variety of 3,4-disubstituted isocoumarins and extention of this process to the synthesis of α-pyrones.

Results and Discussion

We have developed a simple procedure for the annulation of internal alkynes by appropriate halogen- or triflate substituted esters as shown below (eq. 5). Our results using this



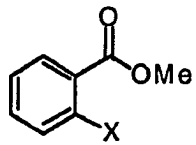
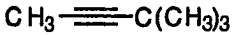
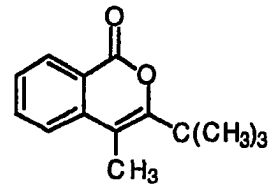
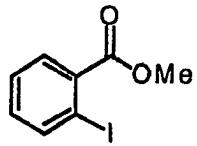
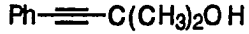
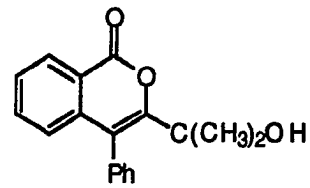
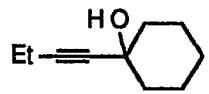
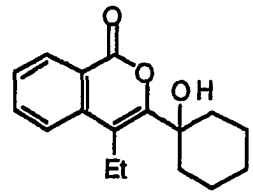
X = I, Br, OTf

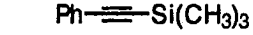
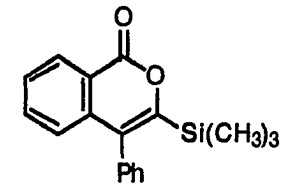
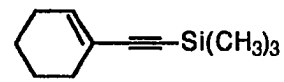
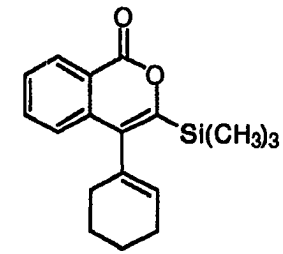
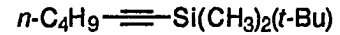
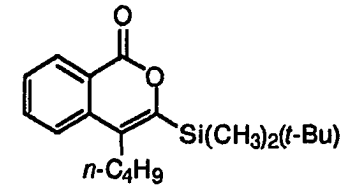
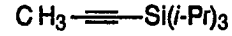
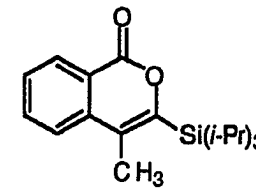
(5)

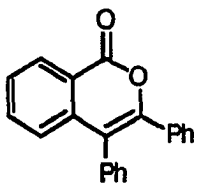
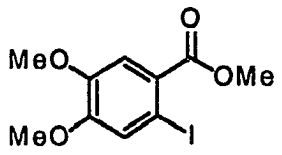
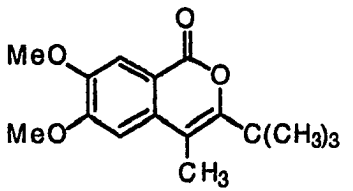
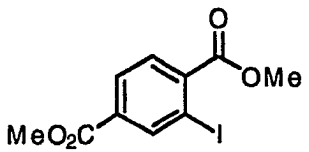
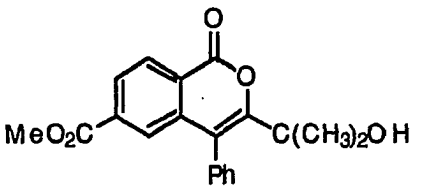
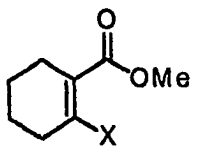
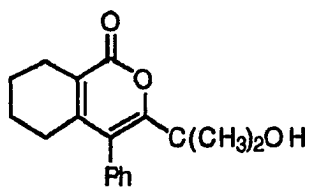
procedure for the synthesis of isocoumarins and α-pyrones are summarized in Table 1.

Isocoumarins can be prepared from either *o*-iodo- or *o*-bromobenzoate esters, although the *o*-iodobenzoate esters generally provide shorter reaction times and higher yields (entries 1 and 2, Table 1). The corresponding aryl triflate was also reacted with similar alkynes under these same conditions, but failed to produce any isocoumarin product, even after 6 days (entry 3, Table 1). Surprisingly, the nature of the R group on the ester had very little effect on the reaction rate or product yield as shown in equation 6. Even the neopentyl, phenyl, and

Table 1. Synthesis of Isocoumarins and α-Pyrones Via Annulation of Internal Alkynes (eq. 5)[a]

entry	ester	alkyne	solvent	time (h)	product(s)	yield (%)[b]
			DMF			
1	X = I			24		72
2	X = Br			96		31
3	X = OTf			144		0
4			DMF	40		77
5			DMF	48		63

6		CH_3CN	84		63
7		CH_3CN	84		51
8		DMF	30		72
9		DMF	24		76

10		Ph—≡—Ph	CH_3CN	216		74
11		CH_3—≡—$C(CH_3)_3$	DMF	20		76
12		Ph—≡—$C(CH_3)_2OH$	DMF	7		70[c]
		Ph—≡—$C(CH_3)_2OH$	DMF			
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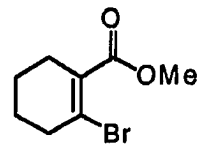
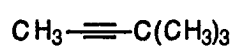
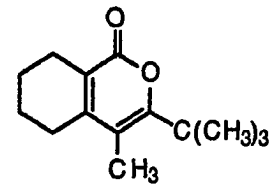
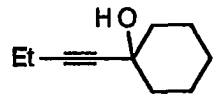
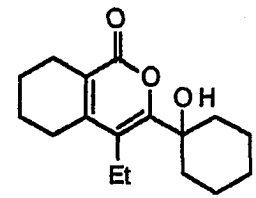
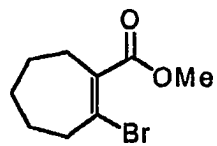
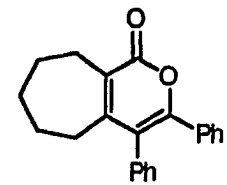
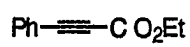
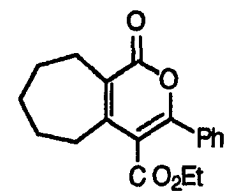
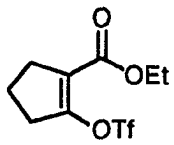
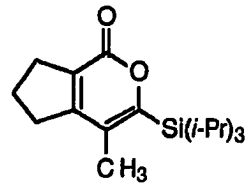
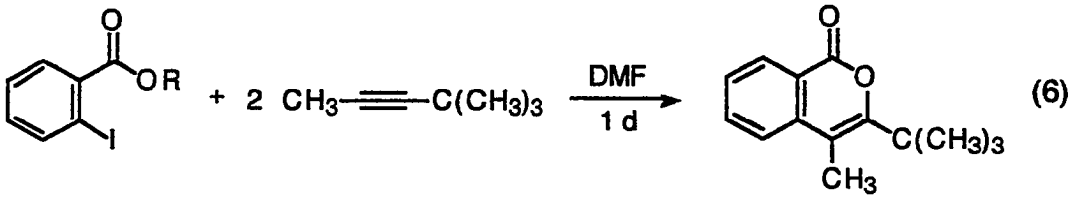
15			DMF	48		65
16			DMF	36		70
17			DMF	8		56
18			DMF	7		77

19		$CH_3-\equiv-Si(i\text{-}Pr)_3$	DMF	21		64

[a] See the text and Experimental Section for the detailed procedures. [b] Yields refer to isolated compounds purified by chromatography. [c] 10 % $Pd(OAc)_2$ was used. [d] Two equivalents of base were used.



(6)

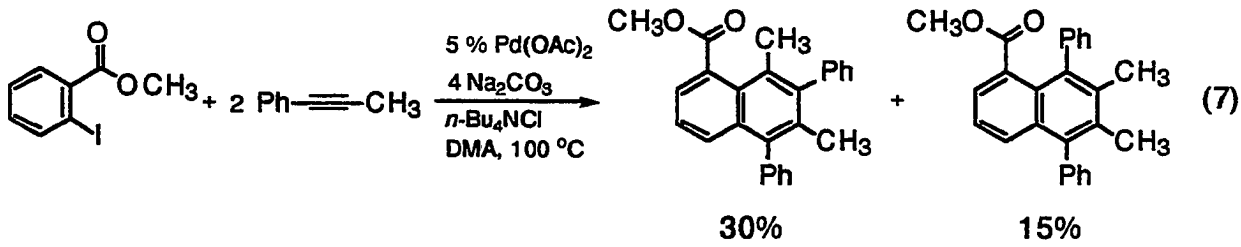
R = Me, 72 %; Et, 68 %; *i*-Pr, 71 %; *t*-Butyl, 82 %; neopentyl, 64 %; phenyl, 75 %

tert-butyl *o*-iodobenzoate esters cyclized in approximately the same time and yield as the corresponding methyl ester. It is necessary to use an ester in the annulation process, as attempted annulation using the parent carboxylic acid, *o*-iodobenzoic acid, resulted in disappearance of the starting material and formation of only a trace amount of the desired product.

In contrast to the isocoumarin chemistry, α-pyrones can be prepared in good yield from either substituted (Z)-2-bromo- or (Z)-2-trifluoromethylsulfonyloxycycloalk-1-ene-1-carboxylate esters (entries 13 and 14, Table 1). The latter are conveniently prepared from the corresponding β-keto esters. Interestingly, the α-pyrone annulation process seems to be limited to cyclic starting materials, since attempted annulation using acyclic vinylic iodides failed to produce any product. It is also unclear why aryl triflates fail to react under these same reaction conditions to produce isocoumarins, whereas α-pyrones are formed readily from vinylic triflates.

Both annulation processes are highly regioselective for alkynes containing tertiary alkyl, trialkylsilyl, or other hindered groups, with the major product isomer having the more sterically demanding group in the position adjacent to the heteroatom; however, high-yielding, clean reactions are generally limited to these types of alkynes. Exceptions to this generality are annulation onto alkynes such as diphenylacetylene (entries 10 and 17, Table 1) and ethyl phenylpropiolate (entry 18, Table 1). Attempted annulation of less substituted alkynes, such as

4-octyne, lead to complex reaction mixtures. Highly substituted naphthalene derivatives were also formed in some cases, such as in the reaction of 1-phenyl-1-propyne and methyl 2-iodobenzoate under slightly different reaction conditions (eq. 7). The regiochemical assignment



(7)

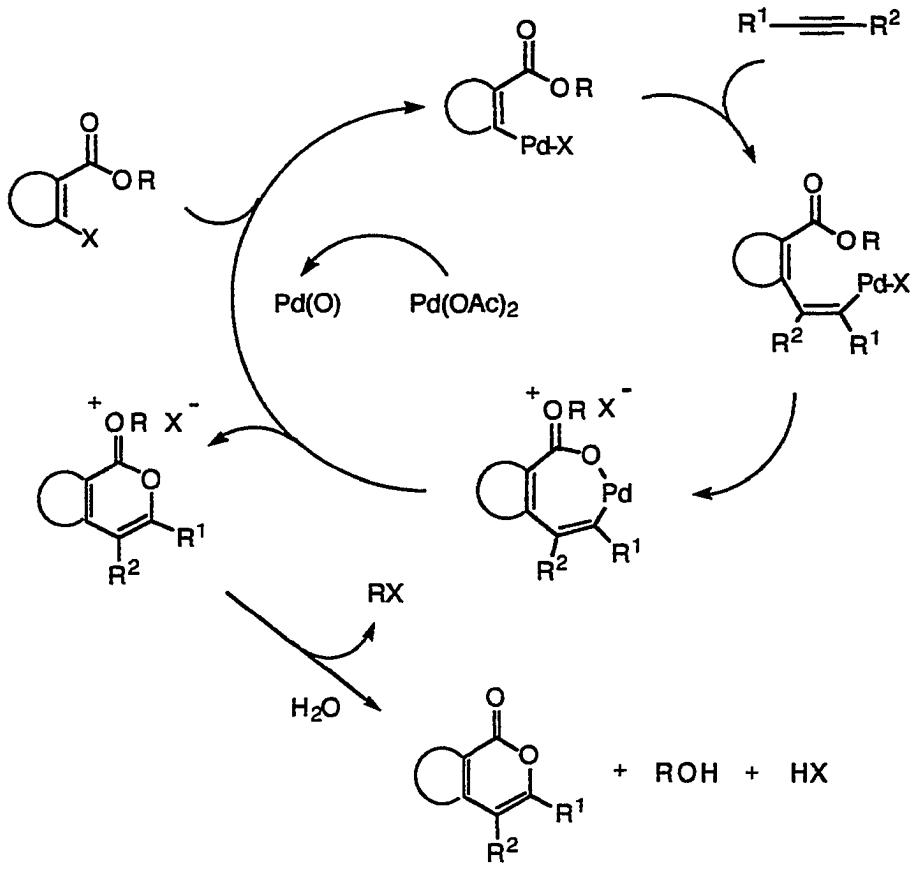
of the naphthalene isomers was based on ^{1}H NMR deshielding of the methyl group by the ester carbonyl group in the major isomer and the assumption that the second alkyne insertion proceeds regioselectively as described in our indole synthesis.[16a]

Alkynes containing a terminal trimethylsilyl group could be annulated in good yield, albeit at a slower rate, by changing the solvent from dimethylformamide to acetonitrile, if the alkyne had a large alkyl group, such as phenyl or 1-cyclohexenyl, on the opposite side of the triple bond (entries 6 and 7, Table 1). Gas chromatographic analysis indicated that acetonitrile prevented desilylation of the alkyne under the reaction conditions. However, for similar alkynes having smaller alkyl groups on the opposite side of the triple bond, such as 1-(trimethylsilyl)propyne, acetonitrile failed to prevent desilylation of the alkyne and hence resulted in low product yields. Therefore, progressively more steric hindrance had to be incorporated into the silyl moiety of these alkynes in order to maintain clean, high-yielding reactions (entries 8 and 9, Table 1). Also, since the majority of reactions have been run on a 0.5 mmol scale, the transformation depicted in entry 9 of Table 1 was increased to 5.0 mmol which resulted in an almost identical yield (72% versus 76%).

The regiochemistry was established for the products of entries 6,[17] 9,[7] and 19[18] of Table 1 by comparison with known compounds following desilylation (see below). Based on these results, the regiochemistry was assumed for all other products containing a tertiary center. The regiochemistry for the ester derivative of entry 18, Table 1 was assigned based on our previous annulation work.[7]

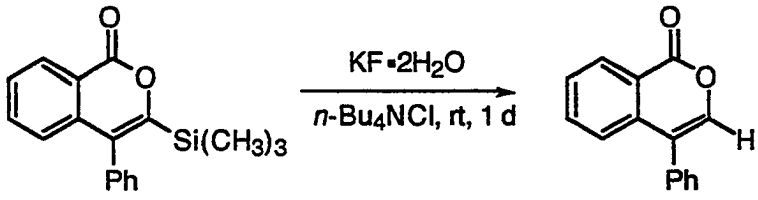
The annulation of 4,4-dimethyl-2-pentyne by β-naphthyl 2-iodobenzoate resulted in a 73 % yield of 3-*tert*-butyl-4-methylisocoumarin and recovery of 53 % of β-naphthol. Based on

Scheme 2



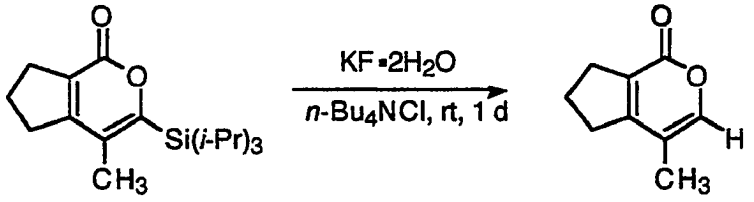
these results, we believe that this annulation process proceeds as shown in Scheme 2 by a sequence involving (1) reduction of $Pd(OAc)_2$ to the actual catalyst Pd(O), (2) oxidative addition of the starting halide or triflate to Pd(O), (3) aryl- or vinylpalladium coordination to the alkyne and then insertion of the alkyne to form a vinylpalladium intermediate, (4) attack of the carbonyl oxygen on the vinylpalladium intermediate to form a seven-membered palladacyclic salt, and (5) regeneration of the Pd(O) catalyst by reductive elimination and formation of the salt. Lost of the R group of the ester is thought to occur during the aqueous workup, since the β-naphthyl ester should preclude the lost of the R group via an S_N1 or S_N2 type process and β-naphthol is actually isolated; however, it is still unclear whether this same mechanism operates throughout the entire range of different R groups where the onium salt can also break down to the observed lactone and the corresponding organic halide by S_N1 or S_N2 processes.

Although the process is limited to the annulation of hindered internal alkynes, the methodology proves to be very convenient and general for the synthesis of 4-substituted isocoumarins or bicyclic α-pyrones via the silylated products, as the silyl moiety can readily be



(8)

90 %



(9)

85 %

cleaved at room temperature in the presence of potassium fluoride dihydrate and tetra-*n*-butylammonium chloride (eqs. 8 and 9).[19]

In conclusion, a useful synthesis of 3,4-disubstituted isocoumarins and bicyclic α-pyrones has been developed using the palladium-catalyzed annulation of internal alkynes via appropriate halogen- and/or triflate- substituted esters. The procedure utilizes readily available starting materials. The reactions proceed under relatively mild conditions, and give good yields. Although the reaction is somewhat limited in scope synthetically, it is particularly suited for the synthesis of the 4-substituted ring systems via the corresponding silyl alkynes.

Experimental Section

General. All ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively. Thin-layer chromatography (TLC) was preformed using commercially prepared 60 mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm), or basic $KMnO_4$ solution [3 g $KMnO_4$ + 20 g K_2CO_3 + 5 ml NaOH (5%) + 300 ml H_2O].

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous Na_2CO_3, LiCl and $KF{\cdot}H_2O$ were purchased from Fisher Scientific. Tetra-*n*-butylammonium chloride was purchased from Lancaster Synthesis, Inc. All palladium compounds were donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. 1-Phenyl-2-(trimethylsilyl)acetylene, 1-(triisopropylsilyl)propyne, and 1-(1-cyclohexenyl)-2-(trimethylsilyl)acetylene were obtained from Aldrich Chemical Co., Inc. Methyl 2-iodobenzoate, ethyl 2-iodobenzoate, 4,4-dimethyl-2-pentyne, 4-phenyl-2-methyl-3-butyn-2-ol, and 1-(1-butynyl)cyclohexanol were purchased from Farchan Scientific Co. Diphenylacetylene and ethyl phenylpropiolate were purchased from Eastman Kodak Co. Dimethyl iodoterephthalate and 4,5-dimethoxybenzoic acid were purchased from Trans World

Chemicals, Inc. The following starting materials were prepared using literature procedures: 1-(*tert*-butyldimethylsilyl)-1-hexyne,[20] methyl (Z)-2-bromocyclohex-1-ene-1-carboxylate,[21] methyl (Z)-2-bromocyclohept-1-ene-1- carboxylate,[21] methyl 2-trifluoromethanesulfonyloxy-1-cyclohexene-1-carboxylate,[22] ethyl 2-trifluoromethanesulfonyloxy-1-cyclopentene-1-carboxylate,[22] and methyl 2-(trifluoromethanesulfonyloxy)benzoate.[23] The following starting materials were prepared.

Isopropyl 2-iodobenzoate. 2-Iodobenzoic acid (5 g, 20 mmol), 20 ml of isopropyl alcohol, and 2 ml of conc. H_2SO_4 were refluxed for 8 h. The reaction was poured into 50 ml of cold water and extracted with ether (3 x 20 ml). The organic phase was washed with water (2 x 20 ml), 5% $NaHCO_3$ (2 x 20 ml), brine (2 x 20 ml), and dried over $MgSO_4$. Removal of the solvent afforded 4.78 g (82%) of the desired product: ^{1}H NMR ($CDCl_3$) δ 1.39 (d, J = 6.6 Hz, 6 H, CH_3), 5.26 (septet, J = 6.6 Hz, 1 H, CH), 7.10 (dt, J = 1.5, 7.8 Hz, 1 H, aryl), 7.37 (dt, J = 0.9, 7.5 Hz, 1 H, aryl), 7.75 (dd, J = 1.5, 7.8 Hz, 1 H, aryl), 7.95 (dd, J = 0.9, 7.8 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 21.7, 69.3, 93.6, 127.6, 130.4, 132.1, 135.7, 140.9, 166.0; IR (neat) 1726 (C=O) cm^{-1}; HRMS m/z 289.9800 (calcd for $C_{10}H_{11}IO_2$, 289.9804).

The hindered 2-iodobenzoate esters and methyl 4,5-dimethoxy-2-iodobenzoate were prepared using the procedure of Neises and Steglich.[24]

***tert*-Butyl 2-iodobenzoate.** Obtained in 65% yield: ^{1}H NMR ($CDCl_3$) δ 1.62 (s, 9 H, CH_3), 7.07 (dt, J = 1.5, 7.5 Hz, 1 H, aryl), 7.34 (dt, J = 0.6, 7.5 Hz, 1 H, aryl), 7.66 (dd, J = 1.5, 7.8 Hz, 1 H, aryl), 7.9 (dd, J = 0.6, 7.8 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 28.0, 82.5, 127.7, 130.3, 131.8, 137.2, 140.8(2), 166.0; IR (neat) 1726 (C=O) cm^{-1}; HRMS m/z 303.9952 (calcd for $C_{11}H_{13}IO_2$, 303.9960).

Neopentyl 2-iodobenzoate. Obtained in 79% yield: ^{1}H NMR ($CDCl_3$) δ 1.04 (s, 9 H, CH_3), 4.04 (s, 2 H, CH_2), 7.10 (dt, J = 1.5, 7.8 Hz, 1 H, aryl), 7.40 (t, J = 7.5 Hz, 1 H, aryl), 7.80 (dd, J = 1.8, 7.5 Hz, 1 H, aryl), 8.0 (d, J = 7.8 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$)

δ 26.5, 31.4, 74.8, 93.9, 127.7, 130.6, 132.3, 135.2, 141.1, 166.3; IR (neat) 1736 (C=O) cm^{-1}; HRMS m/z 318.0118 (calcd for $C_{12}H_{15}IO_2$, 318.0017).

Phenyl 2-iodobenzoate. Obtained in 85% yield: ^1H NMR ($CDCl_3$) δ 7.1-8.2 (m, 9 H, aryl); ^{13}C NMR ($CDCl_3$) δ 94.5, 121.4, 126.0, 127.9, 129.4, 131.3, 133.1, 134.0, 141.3, 150.5, 164.7; IR (neat) 1745 (C=O) cm^{-1}; HRMS for daughter ion $[M\text{-}OPh]^+$ m/z 230.9312 (calcd for $C_{13}H_9IO_2$, 230.9307).

β-Naphthyl 2-iodobenzoate. Obtained in 78% yield: ^1H NMR ($CDCl_3$) δ 7.1-8.5 (m, 11 H, aryl); ^{13}C NMR ($CDCl_3$) δ 94.6, 118.6, 120.9, 125.8, 126.6, 127.7, 127.8, 128.0, 128.1, 129.4, 131.5, 133.2, 133.6, 134.0, 141.6, 148.2, 164.9; IR ($CHCl_3$) 1742 (C=O) cm^{-1}; HRMS m/z 373.9795 (calcd for $C_{17}H_{11}IO_2$, 373.9804).

Methyl 4,5-dimethoxy-2-iodobenzoate. Obtained in 76% yield: ^1H NMR ($CDCl_3$) δ 3.89 (s, 3 H, CH_3), 3.90 (s, 6 H, CH_3), 7.35 (s, 1 H, aryl), 7.41 (s, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 51.8, 55.6, 55.8, 84.3, 113.3, 123.2, 125.4, 148.1, 151.4, 165.2; IR ($CHCl_3$) 1719 (C=O) cm^{-1}; HRMS m/z 321.9703 (calcd for $C_{10}H_{11}IO_4$, 321.9702).

General Procedure for the Palladium-Catalyzed Formation of 3,4-Disubstituted Isocoumarins and α-Pyrones. $Pd(OAc)_2$ (6 mg, 0.027 mmol), the base (0.5 mmol unless otherwise noted), LiCl (22 mg, 0.52 mmol), the ester (0.5 mmol), and the alkyne (1.0 mmol) were placed in a 4 dram vial. The appropriate solvent was added (10 ml) and the vial was heated in an oil bath at 100 °C for the necessary period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with ether, washed with saturated NH_4Cl, dried over anhydrous $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography (*n*-hexane/EtOAc) on a silica gel column. The following compounds were prepared by the above procedure.

3-*tert*-Butyl-4-methylisocoumarin (entries 1-3, Table 1). The reaction mixture was chromatographed using 15:1 *n*-hexane/EtOAc to yield a white solid (mp 94-96 °C, from *n*-hexane): ^{1}H NMR ($CDCl_3$) δ 1.46 (s, 9 H, CH_3), 2.34 (s, 3 H, CH_3), 7.45 (dt, J = 0.9, 7.8 Hz, 1 H, aryl), 7.56 (d, J = 8.1 Hz, 1 H, aryl), 7.73 (dt, J = 1.2, 8.1 Hz, 1 H, aryl), 8.10 (dd, J = 0.9, 7.8 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 12.9, 29.6, 37.2, 107.3, 120.1, 122.4, 127.0, 129.1, 134.3, 139.8, 159.2, 162.5; IR ($CHCl_3$) 1720 (C=O) cm^{-1}; HRMS m/z 216.1150 (calcd for $C_{14}H_{16}O_2$, 216.1150).

3-(1-Hydroxy-1-methylethyl)-4-phenylisocoumarin (entry 4, Table 1). The reaction mixture was chromatographed using 4:1 *n*-hexane/EtOAc to yield a white solid (mp 129-130 °C, from *n*-hexane): ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 6 H, CH_3), 2.08 (s, 1 H, OH), 6.80 (d, J = 8.1 Hz, 1 H, aryl), 7.20-7.60 (m, 7 H, aryl), 8.31 (d, J = 7.8 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 29.8, 73.3, 114.2, 119.8, 125.2, 127.8, 128.2, 128.7, 129.5, 130.6, 134.2, 134.5, 139.5, 156.7, 161.7; IR ($CHCl_3$) 3587 (OH), 1716 (C=O) cm^{-1}; HRMS m/z 280.1097 (calcd for $C_{18}H_{16}O_3$, 280.1099).

4-Ethyl-3-(1-hydroxycyclohexyl)isocoumarin (entry 5, Table 1). The reaction mixture was chromatographed using 8:1 *n*-hexane/EtOAc to yield a white solid (mp 151-153 °C, from *n*-hexane/EtOAc): ^{1}H NMR ($CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3 H, CH_3), 1.60-2.16 (m, 10 H, CH_2), 2.18 (s, 1 H, OH), 3.07 (q, J = 7.2 Hz, 2 H, CH_2), 7.45 (t, J = 7.2 Hz, 1 H, aryl), 7.62 (d, J = 8.1 Hz, 1 H, aryl), 7.73 (t, J = 8.1 Hz, 1 H, aryl), 8.27 (d, J = 8.1 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 15.0, 18.4, 21.4, 25.0, 36.1, 75.0, 115.1, 120.6, 123.1, 127.3, 129.4, 134.4, 138.6, 156.8, 162.2; IR ($CHCl_3$) 3455 (OH), 1711 (C=O) cm^{-1}; HRMS m/z 272.1405 (calcd for $C_{17}H_{20}O_3$, 272.1412).

4-Phenyl-3-(trimethylsilyl)isocoumarin (entry 6, Table 1). The reaction mixture was chromatographed using 38:10:1.5 *n*-hexane/CH_2Cl_2/EtOAc to yield a white solid (mp 159-160 °C, from *n*-hexane/EtOAc): ^{1}H NMR ($CDCl_3$) δ 0.01 (s, 9 H, CH_3), 6.94 (d, J = 7.8 Hz, 1 H, aryl), 7.2-7.7 (m, 7 H, aryl), 8.34 (d, J = 7.5 Hz, 1 H, aryl); ^{13}C NMR

($CDCl_3$) δ -1.4, 121.1, 124.8, 128.4, 128.5 (2), 128.8, 129.1, 131.2, 134.2, 134.4, 137.5, 160.6, 163.3; IR ($CHCl_3$) 1719 (C=O) cm^{-1}; HRMS m/z 294.1079 (calcd for $C_{18}H_{18}O_2Si$, 294.1076).

4-(1-Cyclohexenyl)-3-(trimethylsilyl)isocoumarin (entry 7, Table 1). The reaction mixture was chromatographed using 38:10:1.5 *n*-hexane/CH_2Cl_2/EtOAc to yield a white solid (mp 89-91 °C, from *n*-hexane): ^1H NMR ($CDCl_3$) δ 0.27 (s, 9 H, CH_3), 1.60-2.4 (m, 8 H, CH_2), 5.73 (bs, 1 H, vinyl), 7.30 (d, J = 8.1 Hz, 1 H, aryl), 7.43 (t, J = 7.5 Hz, 1 H, aryl), 7.63 (t, J = 7.5 Hz, 1 H, aryl), 8.24 (d, J = 8.1 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ -0.7, 21.6, 22.5, 25.4, 30.5, 121.6, 124.1, 128.1, 129.2, 130.6, 130.9, 131.9, 134.1, 136.7, 158.9, 163.3; IR ($CHCl_3$) 1723 (C=O) cm^{-1}; HRMS m/z 298.1387 (calcd for $C_{18}H_{22}O_2Si$, 298.1389).

4-*n*-Butyl-3-(*tert*-butyldimethylsilyl)isocoumarin (entry 8, Table 1). The reaction mixture was chromatographed using 15:1 *n*-hexane/EtOAc to yield a clear oil: ^1H NMR ($CDCl_3$) δ 0.39 (s, 6 H, CH_3), 1.0 (s, 12 H, CH_3), 1.53 (m, 4 H, CH_2), 2.65 (t, J = 6.9 Hz, 2 H, CH_2), 7.51 (m, 2 H, aryl), 7.75 (t, J = 7.2 Hz, 1 H, aryl), 8.30 (d, J = 7.8 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ -4.3, 13.9, 17.8, 23.1, 26.7, 27.8, 33.0, 121.8, 122.9, 126.9, 128.1, 129.5, 134.1, 136.4, 158.3, 163.1; IR ($CHCl_3$) 1719 (C=O) cm^{-1}; HRMS m/z 316.1861 (calcd for $C_{19}H_{28}O_2Si$, 316.1859).

4-Methyl-3-(triisopropylsilyl)isocoumarin (entry 9, Table 1). The reaction mixture was chromatographed using 15:1 *n*-hexane/EtOAc to yield a white solid (mp 112-114 °C, from *n*-hexane): ^1H NMR ($CDCl_3$) δ 1.17 (d, J = 7.5 Hz, 18 H, CH_3), 1.51 (septet, J = 7.5 Hz, 3 H, CH), 2.28 (s, 3 H, CH_3), 7.53 (m, 2 H, aryl), 7.76 (t, J = 7.0 Hz, 1 H, aryl), 8.34 (d, J = 7.5 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 12.2, 14.3, 18.6, 121.3, 122.2, 122.7, 128.2, 129.1, 134.2, 137.3, 157.9, 163.4; IR ($CHCl_3$) 1721 (C=O) cm^{-1}; HRMS m/z 316.1860 (calcd for $C_{19}H_{28}O_2Si$, 316.1859).

3,4-Diphenylisocoumarin (entry 10, Table 1). The reaction mixture was chromatographed with 12:6:0.5 *n*-hexane/CH_2Cl_2/EtOAc, followed by 15:1 hexane/EtOAc (mp 169-171 °C, from *n*-hexane; lit[15] mp 168.5-170 °C) to give the desired compound whose spectral properties were identical with those previously reported.[15]

3-*tert*-Butyl-6,7-dimethoxy-4-methylisocoumarin (entry 11, Table 1). The reaction mixture was chromatographed with 2:1 *n*-hexane/EtOAc to yield a solid (mp 127-128 °C, from *n*-hexane): ^{1}H NMR ($CDCl_3$) δ 1.35 (s, 9 H, CH_3), 2.23 (s, 3 H, CH_3), 3.87 (s, 3 H, CH_3), 3.91 (s, 3 H, CH_3), 6.80 (s, 1 H, aryl), 7.55 (s, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 13.0, 29.5, 36.8, 55.8, 55.9, 103.2, 106.8, 108.8, 113.1, 135.4, 148.5, 154.5, 158.1, 162.1; IR ($CHCl_3$) 1705 (C=O) cm^{-1}; HRMS m/z 276.1362 (calcd for $C_{16}H_{20}O_4$, 276.1362).

Methyl 3-(1-hydroxy-1-methylethyl)-4-phenyl-6-isocoumarin carboxylate (entry 12, Table 1). The reaction mixture was chromatographed with 2:1 *n*-hexane/EtOAc to yield a solid (mp 159-160 °C, from *n*-hexane): ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 6 H, CH_3), 2.25 (s, 1 H, OH), 3.84 (s, 3 H, CH_3), 7.31 (m, 2 H, aryl), 7.49 (m, 4 H, aryl), 8.05 (dd, J = 1.2, 8.4 Hz, 1 H, aryl), 8.35 (d, J = 8.4 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 29.6, 52.4, 73.1, 114.0, 122.5, 126.4, 127.9, 128.3, 128.7, 129.1, 130.3, 133.3, 135.2, 139.4, 157.5, 160.6, 165.4; IR ($CHCl_3$) 3490 (OH), 1728 (C=O), 1721 (C=O) cm^{-1}; HRMS m/z 338.1146 (calcd for $C_{20}H_{18}O_5$, 338.1154).

3-(1-Hydroxy-1-methylethyl)-4-phenyl-5,6,7,8-tetrahydroisocoumarin (entries 13 and 14, Table 1). The reaction mixture was chromatographed using 1:1 *n*-hexane/EtOAc to yield a white solid (mp 134-135 °C, from n-hexane): ^{1}H NMR ($CDCl_3$) δ 1.38 (s, 6 H, CH_3), 1.5-1.8 (m, 4 H, CH_2), 1.92 (bt, J = 5.7 Hz, 2 H, CH_2), 2.11 (s, 1 H, OH), 2.50 (bt, J = 5.7 Hz, 2 H, CH_2), 7.1-7.3 (m, 2 H, aryl), 7.35-7.5 (m, 3 H, aryl); ^{13}C NMR ($CDCl_3$) δ 21.1, 21.4, 23.4, 28.2, 29.5, 73.0, 116.9, 120.7, 127.8, 128.3, 130.0,

134.4, 152.2, 159.5, 161.9; IR ($CHCl_3$) 3486 (OH), 1712 (C=O) cm^{-1}; HRMS m/z 284.1408 (calcd for $C_{18}H_{20}O_3$, 284.1421).

3-*tert*-Butyl-4-methyl-5,6,7,8-tetrahydroisocoumarin (entry 15, Table 1). The reaction mixture was chromatographed using 4:1 *n*-hexane/EtOAc to yield a clear oil: ^1H NMR ($CDCl_3$) δ 1.37 (s, 9 H, CH_3), 1.6-1.8 (m, 4 H, CH_2), 2.03 (s, 3 H, CH_3), 2.2-2.5 (m, 4 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 12.9, 21.1, 21.8, 23.4, 27.2, 29.1, 37.0, 110.9, 119.9, 153.2, 161.9, 163.1; IR ($CHCl_3$) 1714 (C=O) cm^{-1}; HRMS m/z 220.1464 (calcd for $C_{14}H_{20}O_2$, 220.1463).

4-Ethyl-3-(1-hydroxycyclohexyl)-5,6,7,8-tetrahydroisocoumarin (entry 16, Table 1). The reaction mixture was chromatographed using 4:1 *n*-hexane/EtOAc to yield a white solid (mp 169-170 °C, from *n*-hexane/EtOAc): ^1H NMR ($CDCl_3$) δ 1.11 (t, J = 7.5 Hz, 3 H, CH_3), 1.29 (m, 2 H, CH_2), 1.5-1.9 (m, 10 H, CH_2), 2.0 (dt, J = 4.5, 13.8 Hz, 2 H, CH_2), 2.4 (t, J = 5.7 Hz, 2 H, CH_2), 2.5 (t, J = 5.7 Hz, 2 H, CH_2), 2.6 (s, 1 H, OH), 2.7 (q, J = 7.5 Hz, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 15.7, 18.2, 21.3, 21.8, 23.6, 24.9, 25.9, 35.8, 35.9, 74.8, 118.3, 121.0, 153.2, 159.7, 162.6; IR ($CHCl_3$) 3457 (OH), 1711 (C=O) cm^{-1}; HRMS m/z 276.1733 (calcd for $C_{17}H_{24}O_3$, 276.1725).

3,4-Diphenyl-6,7,8,9-tetrahydrocyclohepta[c]pyran-1(5*H*)-one (entry 17, Table 1). The reaction mixture was chromatographed using 8:1 *n*-hexane/EtOAc to yield a white solid (mp 124-126 °C, from *n*-hexane): ^1H NMR ($CDCl_3$) δ 1.50 (quintet, J = 5.4 Hz, 2 H, CH_2), 1.63 (quintet, J = 5.4 Hz, 2 H, CH_2), 1.82 (quintet, J = 5.4 Hz, 2 H, CH_2), 2.4 (m, 2 H, CH_2), 2.89 (m, 2 H, CH_2), 7.0-7.4 (m, 10 H, aryl); ^{13}C NMR ($CDCl_3$) δ 25.3, 25.8, 26.6, 31.1, 32.1, 119.8, 126.5, 127.62, 127.69, 128.7, 128.8, 130.6, 132.7, 135.4, 149.3, 154.4, 157.9, 163.0; IR ($CHCl_3$) 1711 (C=O) cm^{-1}; HRMS m/z 316.1463 (calcd for $C_{22}H_{20}O_2$, 316.1463).

Ethyl 4-phenyl-6,7,8,9-tetrahydrocyclohepta[c]pyran-1-(5*H*)-one-3-carboxylate (entry 18, Table 1). The reaction mixture was chromatographed using 8:1 *n*-hexane/EtOAc to yield a white-yellow solid (mp 69-71 °C, from *n*-hexane): ^{1}H NMR ($CDCl_3$) δ 1.08 (t, J = 7.2 Hz, 3 H, CH_3), 1.64 (m, 4 H, CH_2), 1.88 (m, 2 H, CH_2), 2.62 (m, 2 H, CH_2), 2.84 (m, 2 H, CH_2), 4.15 (q, J = 7.2 Hz, 3 H, CH_2), 7.3-7.5 (m, 3 H, aryl), 7.5-7.7 (m, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.0, 25.4, 25.8, 26.3, 31.4, 31.9, 61.7, 114.5, 126.8, 127.5, 128.2, 130.3, 131.8, 154.2, 156.6, 161.9, 166.6; IR ($CHCl_3$) 1701 (C=O), 1731 (C=O) cm^{-1}; HRMS m/z 312.1354 (calcd for $C_{19}H_{20}O_4$, 312.1362).

6,7-Dihydro-4-methyl-3-(triisopropylsilyl)cyclopenta[c]pyran-1-(5H)-one (entry 19, Table 1). The reaction mixture was chromatographed using 8:1 *n*-hexane/EtOAc to yield a white solid (mp 80-82 °C, from *n*-hexane): ^{1}H NMR ($CDCl_3$) δ 1.12 (d, J = 7.5 Hz, 18 H, CH_3), 1.47 (septet, J = 7.5 Hz, 3 H, CH), 2.03 (s, 3 H, CH_3), 2.06 (quintet, J = 7.5 Hz, 2 H, CH_2), 2.8 (m, 4 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 11.8, 14.5, 18.5, 21.9, 30.0, 33.2, 123.7, 126.5, 158.9, 163.2, 164.4; IR ($CHCl_3$) 1714 (C=O) cm^{-1}; HRMS m/z 306.2010 (calcd for $C_{18}H_{30}O_2Si$, 306.2015).

4-Phenylisocoumarin. 4-Phenyl-3-(trimethylsilyl)isocoumarin (70 mg, 0.24 mmol), KF·2H_2O (68.7 mg, 0.73 mmol), tetra-*n*-butylammonium chloride (212 mg, 0.76 mmol), and 1.5 ml acetonitrile were stirred for 24 h at rt. The reaction mixture was added to 15 ml of water, extracted with CH_2Cl_2 (2 x 15 ml), and dried over Na_2SO_4. Removal of the solvent and chromatography (4:1 *n*-hexane/EtOAc) afforded a 90 % yield of the desired compound as a white solid (mp 94-95 °C, lit[17] mp 96-97 °C): ^{1}H NMR ($CDCl_3$) δ 7.3-7.7 (m, 9 H, aryl), 8.39 (d, J = 8.1 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 120.5, 121.2, 124.5, 128.2, 128.4, 128.8, 129.7, 129.9, 132.9, 134.6, 136.6, 142.1, 161.9; IR ($CHCl_3$) 1727 (C=O) cm^{-1}; HRMS m/z 222.0687 (calcd for $C_{15}H_{10}O_2$, 222.0681).

6,7-Dihydro-4-methylcyclopenta[c]pyran-1-(5H)-one. 6,7-Dihydro-4-methyl-3-(triisopropylsilyl)cyclopenta[c]pyran-1-(5H)-one (68 mg, 0.22 mmol), KF·2H_2O

(62 mg, 0.66 mmol), tetra-*n*-butylammonium chloride (233 mg, 0.84 mmol), and 1.5 ml of acetonitrile were stirred for 24 h at rt. Removal of the solvent and chromatography (4:1 hexane/EtOAc) afforded an 85 % yield of the desired compound as a white solid (mp 90-91 °C): ^{1}H NMR ($CDCl_3$) δ 1.94 (d, J = 1.2 Hz, 3 H, CH_3), 2.09 (quintet, J = 7.8 Hz, 2 H, CH_2), 2.79 (m, 4 H, CH_2), 7.19 (bs, 1 H, vinyl); ^{13}C NMR ($CDCl_3$) δ 12.9, 22.2, 29.9, 32.8, 114.1, 126.4, 146.2, 160.0, 161.5; IR ($CHCl_3$) 1710 (C=O) cm^{-1}; HRMS m/z 150.0683 (calcd for $C_9H_{10}O_2$, 150.0681).

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Supplementary Material Available: ^{1}H and ^{13}C NMR spectra for all new isocoumarins and α-pyrones. This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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CHAPTER 3: SYNTHESIS OF AROMATIC HETEROCYCLES VIA PALLADIUM-CATALYZED ANNULATION OF INTERNAL ALKYNES

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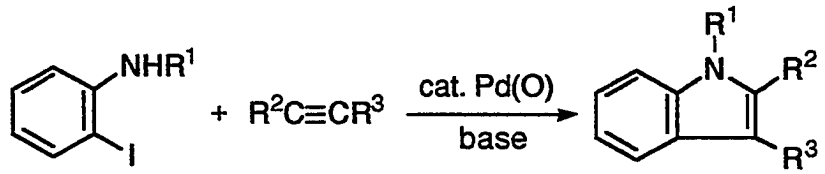
The transition-metal mediated cycloaddition reactions of alkynes are of great current interest.[1] While palladium is among the most widely studied metals for such processes,[2] multiple alkyne insertions, or insertion and subsequent cyclization back on to a preexisting aromatic ring usually predominates. Recent success in the synthesis of indoles by the regioselective, palladium-catalyzed heteroannulation of internal alkynes (eq 1)[3] encouraged us to apply this methodology to the synthesis

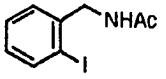
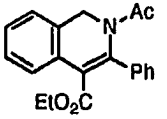
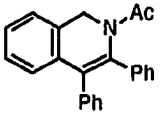
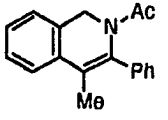
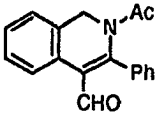
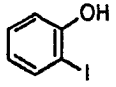
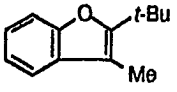
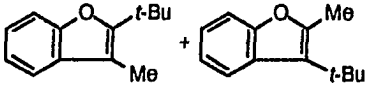


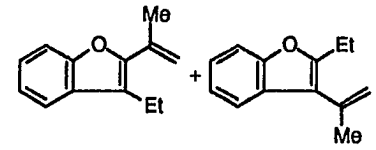
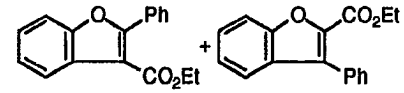
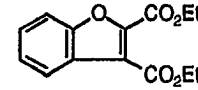
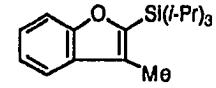
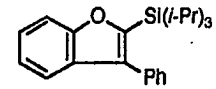
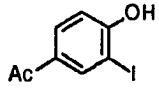
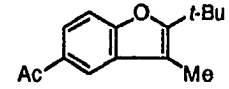
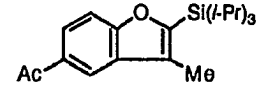
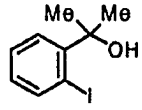
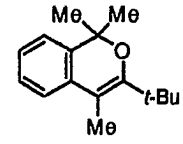
(1)

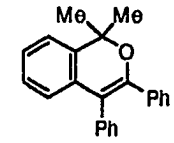
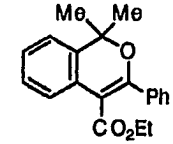
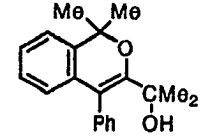
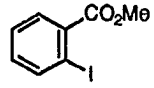
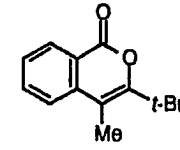
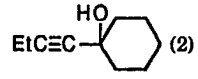
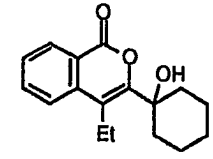
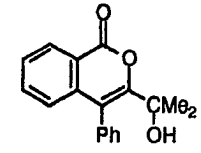
of other heterocycles. We now report that this chemistry provides a valuable new route to a wide variety of heterocycles, including 1,2-dihydroisoquinolines, benzofurans, benzopyrans, and isocoumarins. Our preliminary results are summarized in Table I.

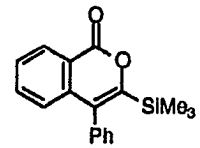
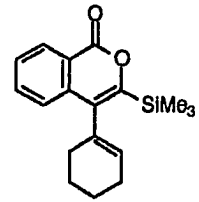
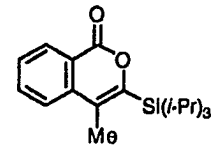
In general, we have employed reaction conditions very similar to those reported earlier by us for the annulation of alkynes,[3a] vinylic cyclopropanes and cyclobutanes,[4] allenes[5] and 1,3-dienes.[6] 5 Mol % $Pd(OAc)_2$, plus sodium or potassium acetate or carbonate, in the presence of

Table I. Palladium-Catalyzed Heteroannulation of Alkynes.[a]

entry	annulating agent	(equiv)	alkyne (equiv)	chloride source	base (equiv)	PPh$_3$	temp (°C), time (h)	product(s)	% isolated yield
1		(1)	PhC≡CCO$_2$Et (2)	LiCl	NaOAc (2)	–	100, 24		80
2		(1)		LiCl	KOAc (2)	–	100, 24		80
3		(1)	PhC≡CPh (2)	*n*-Bu$_4$NCl	KOAc (2)	–	120, 24		83
4		(1)	PhC≡CMe (2)	*n*-Bu$_4$NCl	KOAc (2)	–	100, 48		58
5		(1)		*n*-Bu$_4$NCl	Na$_2$CO$_3$ (2)	+	100, 48		62
6		(1)	PhC≡CCHO (2)	LiCl	NaOAc (2)	–	100, 24		56
7		(1)	*t*-BuC≡CMe (5)	*n*-Bu$_4$NCl	Na$_2$CO$_3$ (5)	+	100, 24		66
8		(1)	(1.1)	LiCl	K$_2$CO$_3$ (5)	+	135, 24	 9:1	93[b]

9		(1)	$H_2C{=}\overset{\overset{Me}{|}}{C}C{\equiv}CEt$ (1.1)	LiCl	K_2CO_3 (5)	+	135, 24	 9:1	69 [b]
10		(1)	$PhC{\equiv}CCO_2Et$ (1.1)	LiCl	K_2CO_3 (5)	+	135, 24	 3:2	69 [b]
11		(1)	$EtO_2CC{\equiv}CCO_2Et$ (1.1)	LiCl	K_2CO_3 (5)	+	135, 24		48 [b]
12		(1.5)	$MeC{\equiv}CSi(i\text{-}Pr)_3$ (1)	LiCl	Na_2CO_3 (1)	-	100, 72		90
13		(2.8)	$PhC{\equiv}CSi(i\text{-}Pr)_3$ (1)	LiCl	Na_2CO_3 (1)	-	100, 504		70
14		(1)	t-BuC≡CMe (5)	n-Bu_4NCl	KOAc (5)	+	100, 24		75
15		(1)	$MeC{\equiv}CSi(i\text{-}Pr)_3$ (2)	LiCl	Na_2CO_3 (1)	-	100, 24		62
16		(1)	t-BuC≡CMe (2)	LiCl	Na_2CO_3 (2)	–	100, 20		52

17		(1)	PhC≡CPh (2)	LiCl	Na_2CO_3(2)	–	100, 24		52
18		(1)	PhC≡CCO_2Et (2)	LiCl	Na_2CO_3(2)	–	80, 8		61
19		(1)	PhC≡CCMe_2 (2) (OH)	LiCl	Na_2CO_3(2)	–	100, 15		57
20		(1)	*t*-BuC≡CMe (2)	LiCl	Na_2CO_3 (1)	–	100, 24		72
21		(1)	 (2)	LiCl	Na_2CO_3 (1)	–	100, 48		63
22		(1)	PhC≡CCMe_2 (2) (OH)	LiCl	Na_2CO_3 (1)	–	100, 40		77

23	(1)	PhC≡CSiMe$_3$ (2)	LiCl	Na_2CO_3 (1)	–	100, 84			63 [c]
24	(1)		LiCl	Na_2CO_3 (1)	–	100, 84			51 [c]
25	(1)	MeC≡CSi(*i*-Pr)$_3$ (2)	LiCl	Na_2CO_3 (1)	–	100, 24			76

[a] Entries 1-7 were run on a 0.25 mmol scale and entries 8-25 on a 0.50 mmol scale. A representative procedure for the 0.5 mmol scale follows: 5 mol % $Pd(OAc)_2$, aryl iodide (0.5 mmol), *n*-Bu_4NCl or LiCl (0.5 mmol), base (0.5, 1.0 or 2.5 mmol), DMF (10 ml), and where necessary 5 mol % PPh_3, were placed in a 4 dram vial and heated at the appropriate temperature for the indicated time.

[b] Dimethylacetamide (20 ml) was used as the solvent.

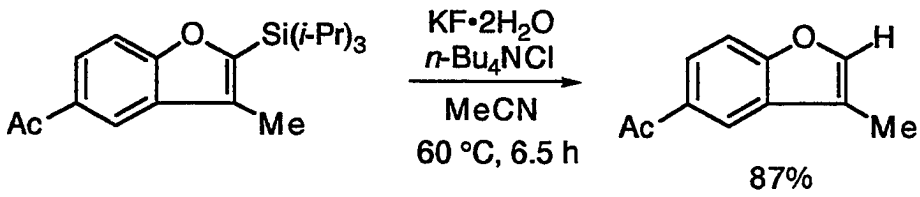
[c] Acetonitrile (10 ml) was used as the solvent.

LiCl or *n*-Bu_4NCl, and occasionally 5 mol % PPh_3, in DMF as solvent generally gives the best results. Temperatures of 80-140 °C are necessary to effect annulation in reasonable reaction times.

We initiated our studies using *o*-iodobenzylamine, but annulation with this substrate proved sluggish and even at elevated temperatures only low yields of 1,2-dihydroisoquinolines could be obtained. By employing the corresponding acetamide, instead of the free amine, we were able to obtain vastly improved results (entries 1-6).[7] Alkynes containing aryl or carbonyl-containing groups gave the best results, and proved highly regioselective.

We next turned to oxygen nucleophiles. Heteroannulation using *o*-iodophenol proved more difficult than analogous reactions of *o*-iodoaniline (entries 7-13). Generally, higher temperatures are required and the process appears limited to hindered alkyl acetylenes or acetylenes bearing vinylic, aryl, carbonyl or silyl groups. At the higher temperatures required, reduced regioselectivity is sometimes observed. While the heteroannulation of 4,4-dimethyl-2-pentyne by *o*-iodoaniline[3] and *o*-iodophenol (entry 7) at 100 °C gave exclusively 2-*t*-butyl-3-methylindole and 2-*t*-butyl-3-methylbenzofuran respectively, the analogous, higher-yielding reaction of *o*-iodophenol run at 135 °C gave a 9:1 mixture of regioisomers (entry 8). The annulation of 2-methyl-1-hexen-3-yne (entry 9) and ethyl phenylpropiolate (entry 10) at 135 °C also afforded mixtures of regioisomers. Hindered silylalkynes give high yields of the corresponding 2-silylbenzofurans (entries 12 and 13). This process nicely complements the palladium-catalyzed coupling of *o*-iodophenol and terminal alkynes, which affords 2-substituted benzofurans,[8,9] because the silyl-substituted benzofurans are readily desilylated to 3-substituted benzofurans by fluoride salts (eq. 2).

Although alcohols are not particularly good nucleophiles in palladium-based methodology, *o*-iodobenzylic alcohols have proven effective for the synthesis of benzopyrans (entries 16-19), best results again being obtained using hindered alkyl, aryl or carbonyl-containing alkynes.



(2)

We have also examined the annulation of internal alkynes by *o*-iodobenzoic acid and derivatives. The acid itself gives only low yields of isocoumarins and many side products. Heck et al. have shown previously that diphenylacetylene could be annulated by methyl *o*-iodobenzoate, although the analogous reaction of 3-hexyne gave very poor results.[10,11] Under our conditions, we have been able to achieve good yields of isocoumarins from methyl *o*-iodobenzoate and hindered alkyl-, silyl- or aryl-substituted internal alkynes (entries 20-25). With certain silylalkynes, cleaner reactions could be obtained using acetonitrile as the solvent (entries 23 and 24), although longer reaction times were required.

Although the regiochemistry of every product has not been rigorously established, it appears that these reactions follow the pattern established in our indole synthesis[3] and prior alkyne addition chemistry[2] of adding the aryl group to the less hindered end of the alkyne and the palladium moiety to the more hindered end. Regioselectivity is often high, but successful annulation often requires the presence of a hindered alkyl, silyl or an aryl group on the C–C triple bond.

Acknowledgment. We gratefully acknowledge the National Institutes of Health for their generous financial support; Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for the palladium acetate; and NATO for a Collaborative Research Grant allowing valuable discussions with Professor Sandro Cacchi at the University of Rome, La Sapienza, Rome, Italy.

Experimental Section

General. All ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively. Thin-layer chromatography (TLC) was preformed using commerically prepared 60 mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm), or basic $KMnO_4$ solution [3 g $KMnO_4$ + 20 g K_2CO_3 + 5 ml NaOH (5%) + 300 ml H_20].

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous KOAc, K_2CO_3, NaOAc, Na_2CO_3, LiCl and $KF{\cdot}H_2O$, as well as DMA, DMF, and Et_2NH were purchased from Fisher Scientific. Tetra-*n*-butylammonium chloride was purchased from Lancaster Synthesis, Inc. All palladium compounds were donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. Diethyl acetylenedicarboxylate, 1-phenyl-2-(trimethylsilyl)acetylene, 1-(triisopropylsilyl)propyne, 1-(1-cyclohexenyl)-2-(trimethylsilyl)acetylene, 2-iodophenol, iodobenzene, triisopropylsilylacetylene, CuI, and triphenylphosphine were obtained from Aldrich Chemical Co., Inc. Methyl 2-iodobenzoate, 1-phenyl-1-propyne, 4,4-dimethyl-2-pentyne, 4-phenyl-2-methyl-3-butyn-2-ol, 2-methyl-1-hexene-3-yne, and 1-(1-butynyl)cyclohexanol were purchased from Farchan Scientific Co. Diphenylacetylene and ethyl phenylpropiolate were purchased from Eastman Kodak Co. The following starting materials were prepared using literature procedures: 4-hydroxy-3-iodoacetophenone,[12] *N*-acetyl-2-iodobenzylamine,[13] and 3-phenyl-2-propynal.[13] The following starting materials were also prepared.

2-(2-Iodophenyl)-2-propanol. Magnesium (1.15 g, 47.4 mmol) was placed in 20 ml of dry ether. Methyl iodide (2.62 ml, 41.8 mmol) was added slowly to the flask to form the Grignard reagent. The flask was heated for an additional 15 minutes after formation and methyl 2-iodobenzoate (5 g, 19.08 mmol) in 10 ml ether was added. The mixture was heated at reflux

for an additional hour. The mixture was quenched with saturated NH_4Cl and 5% HCl, extracted with ether, and dried over K_2CO_3. The crude product was chromatographed with 8:1 hexane/EtOAc to yield 53% of the carbinol: ^1H NMR ($CDCl_3$) δ 1.76 (s, 6 H, CH_3), 2.51 (s, 1 H, OH), 6.89 (t, J = 7.8 Hz, 1 H, aryl), 7.32 (t, J = 7.8 Hz, 1 H, aryl), 7.62 (d, J = 7.8 Hz, 1 H, aryl), 7.95 (d, J = 7.8 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 28.7, 73.5, 93.1, 126.6, 128.0, 128.5, 142.6, 148.4; IR ($CHCl_3$) 3375 (OH) cm^{-1}; HRMS Calcd for $C_9H_{11}IO$: 261.9855. Found: 261.9930.

1-Phenyl-2-(triisopropylsilyl)acetylene. Iodobenzene (2.5 mmol), triisopropylsilylacetylene (2.5 mmol), CuI (0.25 mmol), and $PdCl_2(PPh_3)_2$ (0.0125 mmol) were placed in 15 ml of Et_2NH at rt for 4 d. The solvent was removed under reduced pressure and the crude mixture was filtered through silica gel with CH_2Cl_2. The solvent was removed and the resultant oil was distilled to yield 58% of the desired alkyne: ^1H NMR ($CDCl_3$) δ 1.13 (m, 21 H, CH and CH_3), 7.2-7.4 (m, 3 H, aryl), 7.4 (m, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 11.3, 18.6, 90.3, 107.2, 123.5, 128.0, 128.2, 132.0; IR (neat) 2953, 2155 cm^{-1}; HRMS Calcd for $C_{17}H_{26}Si$: 258.1804. Found: 258.1798.

General procedure for the palladium-catalyzed heteroannulation of alkynes. Palladium acetate (0.025 mmol), LiCl (0.50 mmol) or *n*-Bu_4NCl (Lancaster, 0.50 mmol), the appropriate base (0.5-2.50 mmol), the aryl iodide (0.50-1.5 mmol), the alkyne (0.5-2.5 mmol), the solvent (10 or 20 ml) and, where indicated, PPh_3 (0.025 mmol) were added to a 2 or 4 dram vial equipped with a stirring bar and heated at the appropriate temperature for the necessary period of time. The reaction mixture was diluted with ether, washed successively with saturated NH_4Cl and water, dried over anhydrous $MgSO_4$, and concentrated. The products were purified by flash column chromatography. The following compounds were prepared using this general procedure.

Ethyl 2-Acetyl-1,2-dihydro-3-phenylisoquinoline-4-carboxylate (entry 1): ^1H NMR ($CDCl_3$) δ 0.92 (t, J = 7.2 Hz, 3 H, CH_3), 1.54 (s, 3 H, CH_3), 4.04 (q, J = 7.2 Hz,

2 H, CH_2), 5.05 (s, 2 H, CH_2), 7.26-7.60 (m, 8 H, aryl), 7.76 (d, J = 6.3 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 18.5, 24.5, 40.2, 61.1, 122.2, 123.4, 125.9, 127.7, 128.1, 128.5, 128.7, 129.3, 129.5, 131.9, 138.9, 140.7, 167.4, 171.2; IR ($CDCl_3$) 1717 (C=O) cm^{-1}; HRMS Calcd for $C_{20}H_{19}NO_3$: 321.1365. Found: 321.1364.

2-Acetyl-1,2-dihydro-3,4-diphenylisoquinoline (entry 2): ^1H NMR ($CDCl_3$) δ 1.56 (s, 3 H, CH_3), 5.17 (s, 2 H, CH_2), 7.09-7.37 (m, 14 H, aryl); ^{13}C NMR ($CDCl_3$) δ 24.0, 46.0, 118.1, 125.0, 125.2, 126.9, 127.2, 127.5, 127.7, 128.1, 129.6, 129.9, 130.7, 132.8, 133.6, 136.3, 136.5, 137.2, 170.1; IR ($CDCl_3$) 1659 (C=O) cm^{-1}; HRMS Calcd for $C_{23}H_{19}NO$: 325.1467. Found: 325.1458.

2-Acetyl-1,2-dihydro-4-methyl-3-phenylisoquinoline (entry 3): ^1H NMR ($CDCl_3$) δ 1.47 (s, 3 H, CH_3), 2.24 (s, 3 H, CH_3), 5.00 (s, 2 H, CH_2), 7.2-7.45 (m, 9 H, aryl); ^{13}C NMR ($CDCl_3$) δ 15.6, 24.1, 45.7, 122.6, 123.6, 123.7, 124.8, 127.3, 127.9, 128.2, 129.9, 133.7, 136.1, 137.6, 137.8, 171.0; IR ($CDCl_3$) 1732 (C=O) cm^{-1}; HRMS Calcd for $C_{18}H_{17}NO$: 263.1311. Found: 263.1310.

2-Acetyl-1,2-dihydro-4-formyl-3-phenylisoquinoline (entry 4): ^1H NMR ($CDCl_3$) δ 1.84 (s, 3 H, CH_3), 5.12 (s, 2 H, CH_2), 7.45 (m, 4 H, aryl), 7.85 (m, 4 H, aryl), 8.51 (d, J = 7.8 Hz, 1 H, aryl), 9.75 (s, 1 H, CHO); ^{13}C NMR ($CDCl_3$) δ 24.9, 48.9, 123.4, 124.9, 125.8, 127.7, 128.0, 128.1, 128.9, 131.3, 131.7, 134.0, 140.1, 155.9, 171.1, 190.8; IR ($CDCl_3$) 1736 (C=O) cm^{-1}; HRMS Calcd for $C_{18}H_{15}NO_2$: 277.1103. Found: 277.1101.

2-*t*-Butyl-3-methylbenzofuran (entry 7): ^1H NMR ($CDCl_3$) δ 1.49 (s, 9 H, CH_3), 2.35 (s, 3 H, CH_3), 7.25 (m, 2 H, aryl), 7.40 (m, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 9.0, 29.5, 34.3, 107.3, 110.3, 118.4, 121.7, 123.0, 131.5, 152.8, 159.7; IR (neat) 2961, 1477 cm^{-1}; HRMS Calcd for $C_{13}H_{16}O$: 188.1204. Found: 188.1201.

3-Ethyl-2-isopropenylbenzofuran and 2-ethyl-3-isopropenylbenzofuran (9:1 mixture) (entry 9): ^1H NMR ($CDCl_3$) δ 1.21 (t, J = 7.5 Hz, 3 H, CH_3), 2.14 (s, 3 H,

CH_3), 2.77 (q, J= 7.5 Hz, 2 H, CH_2), 5.15 (s, 1 H, vinyl), 5.44 (s, 1 H, vinyl), 7.15 (m, 2 H, aryl), 7.33 (d, J= 8.1 Hz, 1 H, aryl), 7.43 (d, J= 8.1 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.6, 17.6, 21.0, 110.8, 115.0, 118.0, 119.3, 122.0, 124.2, 130.0, 134.6, 151.4, 153.4; IR (neat) 2964, 1287 cm^{-1}; HRMS Calcd for $C_{13}H_{14}O$: 186.1045. Found: 186.1044.

Ethyl 2-phenylbenzofuran-3-carboxylate and ethyl 3-phenylbenzofuran-2-carboxylate (3:2 mixture) (entry 10): ^1H NMR ($CDCl_3$) δ 1.34 (t, J= 7.5 Hz, 6 H, CH_3), 4.34 (q, J= 7.5 Hz, 4 H, CH_2), 7.28 (m, 4 H, aryl), 7.42 (m, 10 H, aryl), 7.98 (m, 4 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 14.3, 21.0, 60.3, 60.6, 111.0, 122.6, 123.9, 125.1, 127.1, 128.0, 129.5, 129.6, 130.1, 153.7, 160.8, 163.9, 171.1; IR (neat) 1716 (C=O) cm^{-1}; HRMS Calcd for $C_{17}H_{14}O_3$: 266.0943. Found: 266.0944.

Diethyl benzofuran-2,3-dicarboxylate (entry 11): ^1H NMR ($CDCl_3$) δ 1.45 (t, J = 7.2 Hz, 6 H, CH_3), 4.48 (q, J= 7.2 Hz, 4 H, CH_2), 7.38 (t, J= 7.8 Hz, 1 H, aryl), 7.49 (t, J= 7.2 Hz, 1 H, aryl), 7.59 (d, J= 7.8 Hz, 1 H, aryl), 7.92 (d, J= 7.8 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 14.2, 14.3, 61.6, 62.2, 112.2, 118.2, 122.7, 124.6, 125.4, 127.9, 145.6, 154.0, 158.8, 162.5; IR (neat) 1726 (C=O) cm^{-1}; HRMS Calcd for $C_{14}H_{14}O_5$: 262.0841. Found: 262.0843.

3-Methyl-2-(triisopropylsilyl)benzofuran (entry 12): ^1H NMR ($CDCl_3$) δ 1.13 (d, J= 7.5 Hz, 18 H, CH_3), 1.50 (septet, J= 7.5 Hz, 3 H, CH), 2.33 (s, 3 H, CH_3), 7.15-7.30 (m, 2 H, aryl), 7.44 (d, J= 7.8 Hz, 1 H, aryl), 7.51 (d, J= 6.9 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 8.4, 11.6, 18.6, 111.0, 119.0, 121.5, 123.3, 126.3, 129.9, 155.1, 157.6; IR ($CHCl_3$) 2944, 1461 cm^{-1}; HRMS Calcd for $C_{18}H_{28}OSi$: 288.1909. Found: 288.1908.

3-Phenyl-2-(triisopropylsilyl)benzofuran (entry 13): ^1H NMR ($CDCl_3$) δ 1.02 (d, J= 7.5 Hz, 18 H, CH_3), 1.29 (septet, J= 7.5 Hz, 3 H, CH), 7.10-7.60 (m, 9 H, aryl); ^{13}C NMR ($CDCl_3$) δ 11.7, 18.7, 111.1, 120.0, 122.1, 124.3, 127.6, 128.0, 129.5, 130.0, 133.3, 133.7, 156.1, 157.6; IR ($CHCl_3$) 2945, 1463 cm^{-1}; HRMS Calcd for $C_{23}H_{30}OSi$: 350.2066. Found: 350.2093.

5-Acetyl-2-*t*-butyl-3-methylbenzofuran (entry 14): ^{1}H NMR ($CDCl_3$) δ 1.37 (s, 9 H, CH_3), 2.27 (s, 3 H, CH_3), 2.59 (s, 3 H, CH_3), 7.31 (d, J = 8.4 Hz, 1 H, aryl), 7.79 (dd, J = 1.8, 8.4 Hz, 1 H, aryl), 7.99 (d, J = 1.8 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 8.9, 26.7, 29.4, 34.4, 108.1, 110.2, 119.7, 124.2, 131.7, 131.8, 155.6, 161.5, 197.9; IR (neat) 1688 (C=O) cm^{-1}; HRMS Calcd for $C_{15}H_{18}O_2$: 230.1307. Found: 230.1302.

5-Acetyl-3-methyl-2-(triisopropylsilyl)benzofuran (entry 15): ^{1}H NMR ($CDCl_3$) δ 1.13 (d, J = 7.5 Hz, 18 H, CH_3), 1.51 (septet, J = 7.5 Hz, 3 H, CH), 2.37 (s, 3 H, CH_3), 2.67 (s, 3 H, CH_3), 7.45 (d, J = 8.7 Hz, 1 H, aryl), 7.93 (dd, J = 1.8, 8.7 Hz, 1 H, aryl), 8.17 (d, J = 1.8 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 9.3, 11.5, 18.5, 26.7, 110.8, 120.5, 124.8, 127.0, 130.2, 131.7, 157.5, 160.3, 197.7; IR ($CHCl_3$) 1675 (C=O) cm^{-1}; HRMS Calcd for $C_{20}H_{30}O_2Si$: 330.2051. Found: 330.2012.

3-*t*-Butyl-1,1-dimethyl-4-methylisochromene (entry 16): ^{1}H NMR ($CDCl_3$) δ 1.27 (s, 9 H, CH_3), 1.52 (s, 6 H, CH_3), 2.12 (s, 3 H, CH_3), 7.0 -7.3 (m, 4 H, aryl); ^{13}C NMR ($CDCl_3$) δ 13.7, 26.1, 29.0, 36.3, 75.5, 104.0, 120.8, 121.5, 125.6, 127.0, 134.2, 136.8, 155.7; IR ($CHCl_3$) 2921, 1621 cm^{-1}; HRMS Calcd for $C_{16}H_{22}O$: 230.1671. Found: 230.1674.

1,1-Dimethyl-3,4-diphenylisochromene (entry 17): ^{1}H NMR ($CDCl_3$) δ 1.79 (s, 6 H, CH_3), 6.88 (d, J = 7.5 Hz, 1 H, aryl), 7.0-7.4 (m, 13 H, aryl); ^{13}C NMR ($CDCl_3$) δ 27.1, 77.6, 115.6, 122.1, 123.5, 126.8, 127.1, 127.4, 127.5, 127.7, 128.5, 128.7, 131.6, 131.9, 135.9, 136.3, 137.0, 148.1; IR ($CHCl_3$) 2918, 1616 cm^{-1}; HRMS Calcd for $C_{23}H_{20}O$: 312.1514. Found: 312.1523.

Ethyl 1,1-dimethyl-3-phenylisochromene-4-carboxylate (entry 18): ^{1}H NMR ($CDCl_3$) δ 0.89 (t, J = 7.2 Hz, 3 H, CH_3), 1.74 (s, 6 H, CH_3), 4.00 (q, J = 7.2 Hz, 2 H, CH_2), 7.1-7.6 (m, 8 H, aryl), 7.9 (dd, J = 1.2, 7.5 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 13.5, 27.0, 60.4, 79.5, 108.2, 122.2, 122.8, 127.1, 127.5, 127.7, 127.9, 128.4, 129.6,

134.9, 135.6, 157.4, 168.0; IR ($CHCl_3$) 2928, 1708 cm^{-1}; HRMS Calcd for $C_{20}H_{20}O_3$: 308.1412. Found: 308.1419.

1,1-Dimethyl-3-(1-hydroxy-1-methylethyl)-4-phenylisochromene (entry 19): ^1H NMR ($CDCl_3$) δ 1.28 (s, 6 H, CH_3). 1.70 (s, 6 H, CH_3), 2.22 (s, 1 H, OH), 6.50 (d, J = 7.5 Hz, 1 H, aryl), 7.0-7.6 (m, 8 H, aryl); ^{13}C NMR ($CDCl_3$) δ 26.9, 29.3, 72.9, 112.3, 121.8, 123.6, 126.7, 127.1, 127.3, 128.5, 131.3, 132.4, 135.7, 136.9, 153.1; IR ($CHCl_3$) 3500, 2920 cm^{-1}; HRMS Calcd for $C_{20}H_{22}O_2$: 294.1620. Found: 294.1625.

3-*t*-Butyl-4-methylisocoumarin (entry 20): ^1H NMR ($CDCl_3$) δ 1.46 (s, 9 H, CH_3), 2.34 (s, 3 H, CH_3), 7.45 (dt, J = 0.6, 7.8 Hz, 1 H, aryl), 7.56 (d, J = 8.1 Hz, 1 H, aryl), 7.73 (dt, J = 1.2, 8.1 Hz, 1 H, aryl), 8.1 (dd, J = 0.9, 7.8 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 12.9, 26.6, 37.1, 107.3, 120.1, 122.4, 127.0, 129.1, 134.3, 139.8, 159.2, 162.4; IR ($CHCl_3$) 1720 (C=O) cm^{-1}; HRMS Calcd for $C_{14}H_{16}O_2$: 216.1150. Found: 216.1150.

4-Ethyl-3-(1-hydroxycyclohexyl)isocoumarin (entry 21): ^1H NMR ($CDCl_3$) δ 1.23 (t, J = 7.2 Hz, 3 H, CH_3), 1.60-2.16 (m, 10 H, CH_2), 2.18 (s, 1 H, OH), 3.07 (q, J = 7.2, 2 H, CH_2), 7.45 (t, J = 7.2 Hz, 1 H, aryl), 7.62 (d, J = 8.1 Hz, 1 H, aryl), 7.73 (t, J = 8.1 Hz, 1 H, aryl), 8.27 (d, J = 8.1 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 15.0, 18.4, 21.4, 25.0, 36.0, 75.0, 115.0, 120.6, 123.0, 127.3, 129.4, 134.4, 138.7, 156.8, 162.1; IR ($CHCl_3$) 1711 (C=O) cm^{-1}; HRMS Calcd for $C_{17}H_{20}O_3$: 272.1412. Found: 272.1405.

3-(1-Hydroxy-1-methylethyl)-4-phenylisocoumarin (entry 22): ^1H NMR ($CDCl_3$) δ 1.47 (s, 6 H, CH_3), 2.08 (s, 1 H, OH), 6.80 (d, J = 8.1 Hz, 1 H, aryl), 7.2-7.6 (m, 7 H, aryl), 8.31 (d, J = 7.8 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 29.8, 73.3, 114.2, 119.8, 125.3, 127.8, 128.2, 128.7, 129.3, 130.5, 134.2, 134.5, 139.5, 156.7, 161.5; IR ($CHCl_3$) 1716 (C=O) cm^{-1}; HRMS Calcd for $C_{18}H_{16}O_3$: 280.1099. Found: 280.1097.

4-Phenyl-3-(trimethylsilyl)isocoumarin (entry 23): ^1H NMR ($CDCl_3$) δ 0.01 (s, 9 H, CH_3), 6.94 (d, J = 7.8 Hz, 1 H, aryl), 7.1-7.7 (m, 7 H, aryl), 8.34 (d, J = 7.5 Hz, 1

H, aryl); ^{13}C NMR ($CDCl_3$) δ -1.4, 121.1, 124.8, 128.4, 128.5 (2), 128.8, 129.1, 131.2, 134.1, 134.4, 137.5, 160.6, 163.2; IR ($CHCl_3$) 1719 (C=O) cm^{-1}; HRMS Calcd for $C_{18}H_{18}O_2$: 294.1076. Found: 294.1079.

4-(1-Cyclohexenyl)-3-(trimethylsilyl)isocoumarin (entry 24): ^1H NMR ($CDCl_3$) δ 0.27 (s, 9 H, CH_3), 1.6-2.4 (m, 8 H, CH_2), 5.73 (s, 1 H, vinyl), 7.30 (d, J = 8.1 Hz, 1 H, aryl), 7.43 (t, J = 7.5 Hz, 1 H, aryl), 7.63 (t, J = 7.5 Hz, 1 H, aryl), 8.24 (d, J = 8.1 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ -0.7, 21.6, 22.5, 25.3, 30.4, 121.5, 124.1, 128.1, 129.2, 130.6, 130.9, 131.9, 134.1, 136.7, 158.9, 163.3; IR ($CHCl_3$) 1713 (C=O) cm^{-1}; HRMS Calcd for $C_{18}H_{22}O_2Si$: 298.1389. Found: 298.1387.

4-Methyl-3-(triisopropylsilyl)isocoumarin (entry 25): ^1H NMR ($CDCl_3$) δ 1.17 (d, J = 7.5 Hz, 18 H, CH_3), 1.51 (septet, J = 7.5 Hz, 3 H, CH), 2.28 (s, 3 H, CH_3), 7.53 (m, 2 H, aryl), 7.76 (t, J = 7.5 Hz, 1 H, aryl), 8.34 (d, J = 7.5 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 12.2, 14.3, 18.6, 121.3, 122.2, 122.7, 128.2, 129.1, 134.2, 137.3, 157.9, 163.4; IR ($CHCl_3$) 1721 (C=O) cm^{-1}; HRMS for $C_{19}H_{28}O_2Si$: 316.1859. Found 316.1860.

5-Acetyl-3-methylbenzofuran. 5-Acetyl-3-methyl-2-(triisopropylsilyl)benzofuran (69.5 mg, 21 mmol), $KF \cdot 2H_20$ (62 mg, 0.66 mmol), tetra-*n*-butylammonium chloride (220 mg, 0.79 mmol), and 1.5 ml CH_3CN were heated at 60 °C for 6.5 h. The mixture was diluted with ether, washed with water, and dried over $MgSO_4$. The solvent was removed under reduced pressure and the residue was chromatographed using 4:1 hexane/EtOAc to yield 87% of the desired product: ^1H NMR ($CDCl_3$) δ 2.27 (s, 3 H, CH_3), 2.67 (s, 3 H, CH_3), 7.45 (m, 2 H, aryl and vinyl), 7.90 (dd, J = 1.2, 8.7 Hz, 1 H, aryl), 8.16 (s, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 7.8, 26.7, 111.1, 116.3, 120.6, 124.8, 129.0, 132.0, 142.6, 157.7, 197.6; IR ($CHCl_3$) 1675 (C=O) cm^{-1}; HRMS Calcd for $C_{11}H_{10}O_2$: 174.0680. Found: 174.0685.

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CHAPTER 4: SYNTHESIS OF PHENANTHRENES VIA PALLADIUM-CATALYZED ANNULATION OF INTERNAL ALKYNES

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

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Abstract

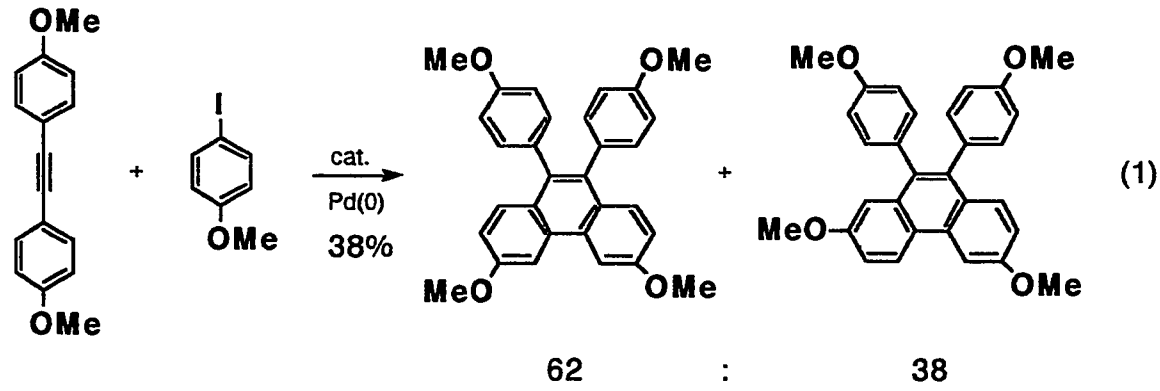
A number of 9,10-disubstituted phenanthrenes have been prepared in good yields by treating 2-iodobiphenyl with various internal alkynes in the presence of a palladium catalyst. Synthetically, the methodology provides an especially efficient and convenient route to hindered phenanthrenes containing aryl, silyl, ester, ketal, and hydroxyl groups. The mechanism of intramolecular ring closure could either involve electrophilic palladation onto an aromatic ring or oxidative insertion into an aryl C-H bond via a vinylpalladium intermediate.

Introduction

The transition-metal mediated annulation reactions of alkynes are of great current interest and have been proven useful for the synthesis of a variety of hetero- and carbocyclic ring systems.[1] A palladium-based methodology is especially convenient, since the metal complexes are readily available, accomodate a number of different functional groups, and are

not generally oxygen or moisture sensitive.[2] Nevertheless, the development of such a methodology towards the synthesis of polycyclic aromatic hydrocarbons has only recently been demonstrated.

Erker has shown that acenaphthylene derivatives can be synthesized from alkenes and alkynes under palladium-catalysis from 1,8-diiodonapthalene.[3] An even more interesting reaction by the same group is the synthesis of 9,10-disubstituted phenanthrenes[4] in fair to good yield from aryl iodides and diarylacetylenes via a palladium-catalyzed domino coupling process.[5] Although extremely efficient, a drawback to the latter reaction is the formation of phenanthrene regioisomers in substituted systems (eq. 1).

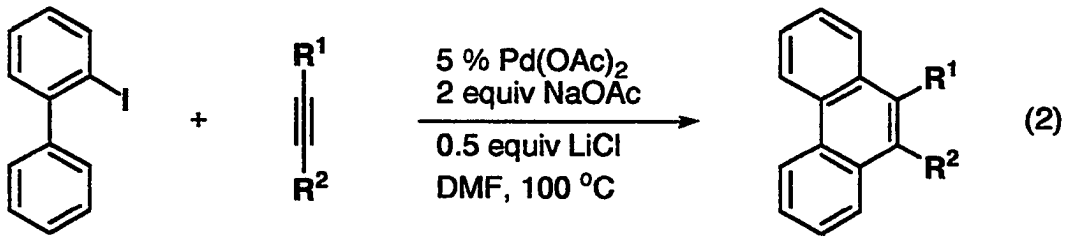


62 : 38 (1)

Another efficient route to such systems was envisioned by Heck in 1989, when it was reported that 9,10-diphenylphenanthrene was formed as a 1:1 adduct from the palladium-catalyzed coupling of 2-iodobiphenyl and diphenylacetylene.[6] Unfortunately, the yield of the reaction under their reported conditions was only 14%. Because of our own interest in similiar annulation processes,[7] we now wish to report substantially improved reaction conditions that effectively accomplish this transformation in good yield with a variety of internal alkynes.

Results and Discussion

We have developed a simple procedure for the annulation of internal alkynes by 2-iodobiphenyl as shown below (eq. 2). Our results using this procedure for the synthesis of



(2)

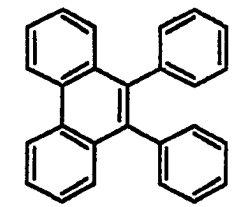
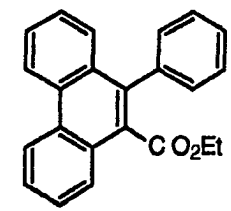
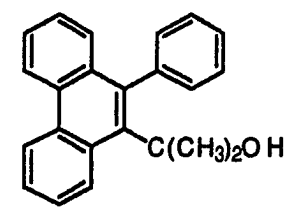
9,10-disubstituted phenanthrenes are summarized in Table 1.

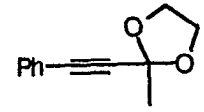
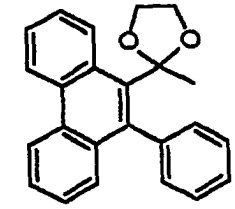
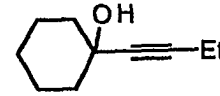
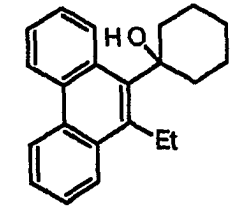
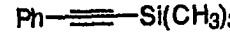
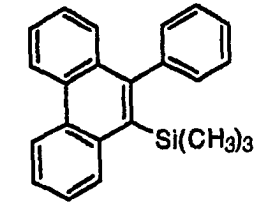
As with our previous work, the annulation process works best for alkynes containing hindered alkyl, trialkylsilyl, or other similar groups (entries 3-6, Table 1). Notable exceptions to this generality include annulation onto diaryl alkynes (entries 1 and 7, Table 1) and ethyl phenylpropiolate (entry 2, Table 1). Reacting diphenylacetylene with 2-iodobiphenyl under these conditions generated an 89 % yield of 9,10-diphenylphenanthrene, a 75 % improvement in yield over the previously reported procedure.

Since desilylation of trimethylsilylalkynes to terminal acetylenes competed with the annulation process, both the desired phenanthrene product and Sonogashira-type coupling products[8] were produced in these reactions (entry 6, Table 1). Recent research[9] and previous results[10] with similar chemistry have shown that this problem can be somewhat remedied by increasing the size of the silyl group, where the best choice of the silyl group is determined by the type of R group on the opposite side of the triple bond.

This reaction may proceed by either of two possible paths involving (1) reduction of $Pd(OAc)_2$ to the actual catalyst Pd(O), (2) oxidative addition of the starting halide to Pd(O),

Table 1. Synthesis of Phenanthrenes from 2-Iodobiphenyl and Internal Alkynes (eq. 2)[a]

entry	2-iodobiphenyl (equiv)	alkyne (equiv)	time (h)	product(s)	yield (%)[b]
1	(1)	Ph—≡—Ph (1)	20		89
2	(1.1)	Ph—≡—CO_2Et (1)	24		76
3	(1.1)	Ph—≡—$C(CH_3)_2OH$ (1)	22		82

4	(1.1)	 (1)	24		71
5	(1.1)	 (1)	14		65
6	(1)	 (2)	24		32[c]

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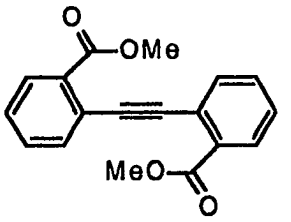
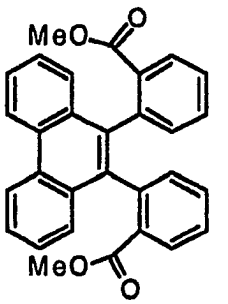
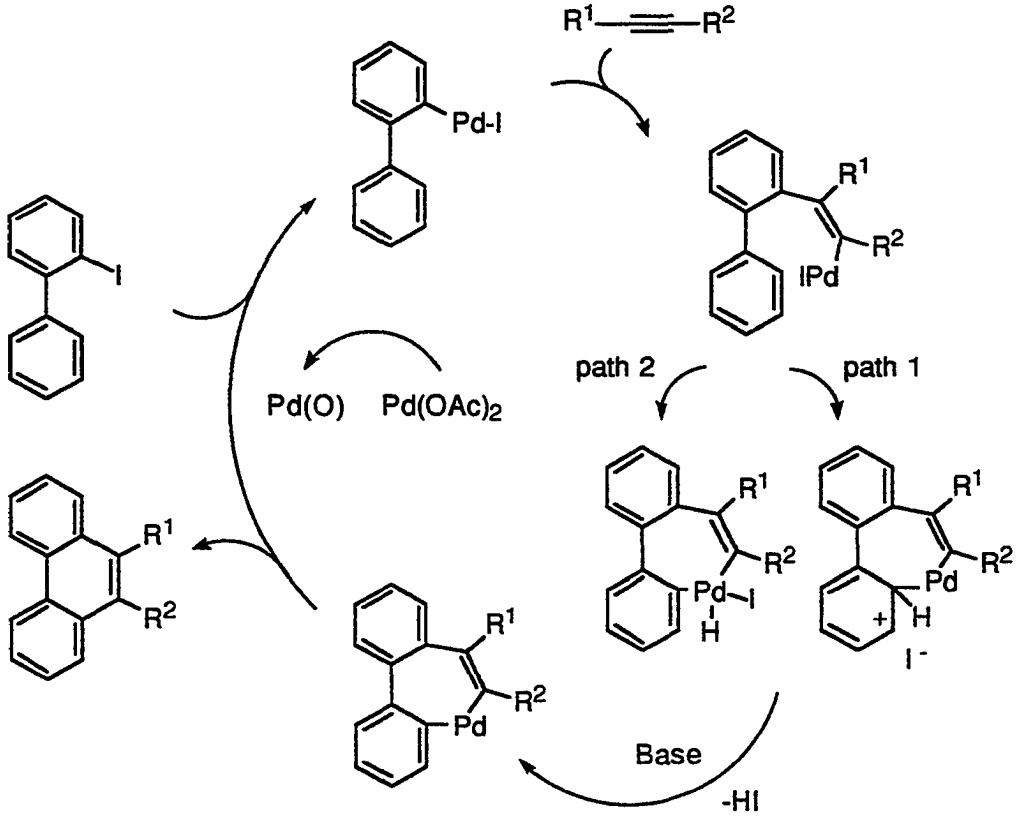
7	(1.2)		(1)	55	 62

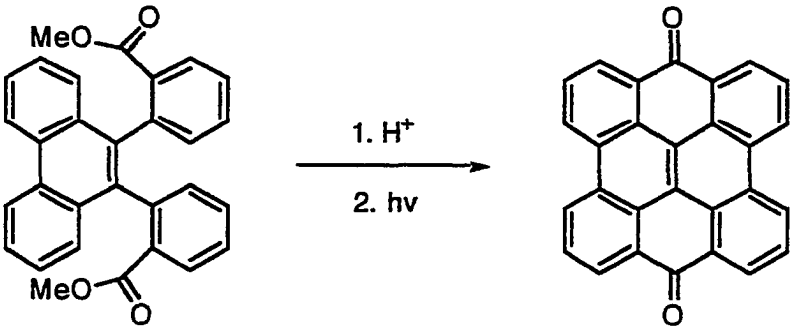
[a] See the text and experimental section for the detailed procedure. [b] Yields refer to isolated compounds purified by chromatography. [c](2-Phenylphenyl)phenylacetylene was also isolated as a separate side product in 32 % yield.

(3) arylpalladium coordination of the alkyne and then insertion of the alkyne to form a vinylpalladium intermediate, (4) either electrophilic palladation of the vinylpalladium onto the adjacent aromatic ring (path 1) or oxidative addition of the neighboring aryl C-H bond to the vinylpalladium intermediate to form a palladium(IV) intermediate (path 2), (5) elimination of HI by base, and (6) regeneration of Pd(O) catalyst by reductive elimination to form the phenanthrene (Scheme 1).

Scheme 1



Synthetic applications of this chemistry are currently under investigation with regard to functionalization of the silyl-substituted phenanthrenes, the synthesis of phenanthrenes substituted in the 1-8 positions, and the synthesis of mesonaphthodianthrone derivatives from the acid-catalyzed closure of 9,10-di(2-carbomethoxyphenyl)phenanthrene precursors (eq. 3).



(3)

Experimental Section

General. All ^{1}H and ^{13}C NMR spectra were recorded at 300 and 75.5 MHz respectively. Thin-layer chromatography (TLC) was performed using commerically prepared 60 mesh silica gel plates (Whatman K6F), and visualization was effected with short wavelength UV light (254 nm), or basic $KMnO_4$ solution [3 g $KMnO_4$ + 20 g K_2CO_3 + 5 ml NaOH (5%) + 300 ml H_20]. All melting points are uncorrected.

Reagents. All reagents were used directly as obtained commerically unless otherwise noted. Anhydrous forms of NaOAc and LiCl, as well as DMF, THF, ethylene glycol, diethylamine, and benzene, were purchased from Fisher Scientific. All palladium compounds were donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. 1-Phenyl-2-(trimethylsilyl)acetylene, 4-phenyl-3-butyn-2-one, pyridinium *p*-toluenesulfonate, and CuI

were obtained from Aldrich Chemical Co., Inc. Methyl 2-iodobenzoate, 4-phenyl-2-methyl-3-butyn-2-ol and 1-(1-butynyl)cyclohexanol were purchased from Farchan Scientific Co. Diphenylacetylene and ethyl phenylpropiolate were purchased from Eastman Kodak Co. The following starting materials were prepared.

2-(2-Phenyl-1-ethynyl)-2-methyl-1,3-dioxolane. 4-Phenyl-3-butyn-2-one (1 g, 6.9 mmol), ethylene glycol (2.15 g, 34.7 mmol), and pyridinium *p*-toluenesulfonate (0.35 g, 1.38 mmol) were placed in 42 ml of benzene. Using a Dean-Stark apparatus, water was removed at reflux over a period of 24 h. The flask was cooled, diluted with 50 ml of ether, and washed with 2 x 50 ml of water. The aqueous phase was extracted with another 25 ml of ether, the ether fractions were combined and dried (Na_2SO_4). Removal of the solvent and column chromatography (8:1 hexane/EtOAc) afforded 1.24 g (96%) of the desired product: ^{1}H NMR ($CDCl_3$) δ 1.79 (s, 3 H, CH_3), 4.01 (m, 2 H, CH_2), 4.13 (m, 2 H, CH_2), 7.29 (m, 3 H, aryl), 7.41 (m, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 26.4, 64.6, 82.7, 87.2, 101.1, 121.9, 128.1, 128.5, 131.7; IR ($CHCl_3$) 2229 (C≡C) cm^{-1}; HRMS m/z 188.0838 (calcd for $C_{12}H_{12}O_2$, 188.0837).

Di(2-carbomethoxyphenyl)acetylene. Methyl 2-iodobenzoate (2.62 g, 10 mmol), CuI (9.5 mg, 0.05 mmol), $PdCl_2(Ph_3P)_2$ (70.1 mg, 0.1 mmol), and Et_2NH (60 ml) were placed in a 500 ml flask purged with N_2 for 5 min (important!). An acetylene balloon was placed over the flask for 24 h. After completion, the solvent was removed under reduced pressure. Ether was added to the flask and the organic layer was separated, washed with water, and dried ($MgSO_4$). Removal of the solvent and column chromatography (8:1 hexane/EtOAc) afforded a 54% yield of the desired alkyne: ^{1}H NMR ($CDCl_3$) δ 3.96 (s, 6 H, CH_3), 7.39 (dt, J = 1.5, 7.5 Hz, 2 H, aryl), 7.51 (dt, J = 1.5, 7.5 Hz, 2 H, aryl), 7.71 (dd, J = 1.5, 7.5 Hz, 2 H, aryl), 7.97 (dd, J = 1.5, 7.5 Hz, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 52.1, 93.0, 123.8, 128.0, 130.4, 131.7 (2), 134.3, 166.5; IR ($CHCl_3$) 1716 (C=O) cm^{-1}; HRMS m/z 294.0895 (calcd for $C_{18}H_{14}O_4$, 294.0892).

General Procedure for the Palladium-Catalyzed Formation of 9,10-Disubstituted Phenanthrenes. $Pd(OAc)_2$ (6 mg, 0.027 mmol), NaOAc (164 mg, 2.0 mmol), LiCl (10.6 mg, 0.25 mmol), 2-iodobiphenyl (0.5-0.6 mmol), and the alkyne (0.5-0.55 mmol) were placed in a 4 dram vial which was heated in an oil bath at 100 °C for the necessary period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with either ether, THF, or methylene chloride, washed with saturated NH_4Cl, dried over anhydrous $MgSO_4$, and filtered. The solvent was evaporated under reduced pressure and the product was isolated by chromatography on a silica gel column The following compounds were prepared by the above procedure.

9,10-Diphenylphenanthrene. The reaction mixture was chromatographed using 4:1 hexane/EtOAc (the product was placed on the column with CH_2Cl_2) to afford the desired compound with spectral properties identical to those previously reported.[6]

Ethyl 10-phenylphenanthrene-9-carboxylate. The reaction mixture was chromatographed using 15:1 hexane/EtOAc to yield a white solid (mp 128-130 °C, from 5:1 ethanol/H_2O): ^1H NMR ($CDCl_3$) δ 0.94 (t, J = 7.5 Hz, 3 H, CH_3), 4.10 (q, J = 6.9 Hz, 2 H, CH_2), 7.43 (m, 6 H, aryl), 7.63 (m, 4 H, aryl), 7.9 (m, 1 H, aryl), 8.71 (m, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 13.7, 61.0, 122.5, 122.6, 122.7, 122.8, 125.8, 126.7, 126.9, 127.3, 127.7, 127.8, 128.0, 129.8, 130.2, 130.5, 130.6, 130.7, 136.3, 138.0, 169.1; IR ($CHCl_3$) 1717 (C=O) cm^{-1}; HRMS m/z 326.1311 (calcd for $C_{23}H_{18}O_2$, 326.1307).

9-(1-Hydroxy-1-methylethyl)-10-phenylphenanthrene. The reaction mixture was chromatographed using 4:1 hexane/EtOAc to yield a solid (mp 152-153 °C, from *n*-hexane): ^1H NMR (D_6-acetone) δ 1.53 (s, 6 H, CH_3), 3.98 (s, 1 H, OH), 7.15 (dd, J = 0.9, 7.5 Hz, 1 H, aryl), 7.25-7.7 (m, 9 H, aryl), 8.77 (d, J = 8.1 Hz, 1 H, aryl), 8.83 (dd, J = 1.5, 8.1 Hz, 1 H, aryl), 9.3 (dd, J = 1.5, 8.4 Hz, 1 H, aryl); ^{13}C NMR (D_6-acetone) δ 34.4, 75.7, 122.7, 123.3, 123.4, 125.6, 126.4, 126.8, 127.0, 127.8, 128.5, 130.6, 131.6, 131.8,

131.9, 132.1, 133.6, 135.8, 141.0, 143.1; IR ($CHCl_3$) 3371 (OH) cm^{-1}; HRMS m/z 312.1508 (calcd for $C_{23}H_{20}O$, 312.1514).

9-Ethyl-10-(1-hydroxycyclohexyl)phenanthrene. The reaction mixture was chromatographed using 4:1 hexane/EtOAc to yield a solid (mp 146-148 °C, from *n*-hexane): ^1H NMR ($CDCl_3$) δ 1.36 (t, J = 7.5 Hz, 3 H, CH_3), 1.43 (s, 1 H, OH), 1.47-2.1 (m, 8 H, CH_2), 2.7 (dt, J = 4.8, 14.4 Hz, 2 H, CH_2), 3.58 (br s, 2 H, CH_2), 7.4-7.7 (m, 4 H, aryl), 8.13 (m, 1 H, aryl), 8.5-8.7 (m, 3 H, aryl); ^{13}C NMR ($CDCl_3$) δ 16.7, 22.2, 24.5, 25.1, 37.8, 77.1, 122.5, 122.9, 124.1, 124.6, 124.8, 125.7, 126.4, 127.4, 130.2, 130.3, 130.6, 132.2, 137.1, 140.0; IR ($CHCl_3$) 3354 (OH) cm^{-1}; HRMS m/z 304.1827 (calcd for $C_{22}H_{24}O$, 304.1828).

9-(2-Methyl-2-(1,3-dioxolanyl))-10-phenylphenanthrene. The reaction mixture was chromatographed using CH_2Cl_2, followed by 15:1 hexane/EtOAc, to yield a white solid (mp 128-130 °C): ^1H NMR ($CDCl_3$) δ 2.02 (s, 3 H, CH_3), 3.52 (m, 2 H, CH_2), 3.71 (m, 2 H, CH_2), 7.2-7.7 (m, 10 H, aryl), 8.6-8.8 (m, 2 H, aryl), 8.9 (m, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 29.4, 63.4, 110.4, 122.0, 122.5, 126.0, 126.32, 126.35, 127.5, 128.2, 128.3 (2), 128.7, 129.8, 130.2, 131.0, 132.5, 134.4, 136.3, 142.5; IR (Nujol) 1189 (C-O) cm^{-1}; HRMS m/z 340.1463 (calcd for $C_{24}H_{20}O_2$, 340.1469).

9-Phenyl-10-trimethylsilylphenanthrene. The reaction mixture was chromatographed using hexane: ^1H NMR ($CDCl_3$) δ 0.12 (s, 9 H, CH_3), 7.2-7.8 (m, 10 H, aryl), 8.35 (d, J = 1.8 Hz, 1 H, aryl), 8.73 (d, J = 8.4 Hz, 1 H, aryl), 8.79 (d, J = 1.8 Hz, 1 H, aryl); ^{13}C NMR ($CDCl_3$) δ 2.8, 122.1, 123.0, 125.6, 125.7, 126.2, 126.8, 127.4, 127.7, 127.8, 129.5, 128.8, 130.7, 131.4, 131.7, 134.5, 134.7, 142.3, 146.8; IR ($CHCl_3$) 2896, 1485 cm^{-1}; HRMS m/z 327.1566 (calcd for $C_{23}H_{23}Si$, 327.1569).

9,10-Di(2-carbomethoxyphenyl)phenanthrene. The reaction mixture was chromatographed using methylene chloride and the product was rinsed with cold methanol to yield a white solid in 62 % yield. Due to the insolubility of the product, it was identified with a

melting point (263-264 °C) and mass spectrum (m/z 446.1513, calcd for $C_{30}H_{22}O_4$, 446.1518). Reactions with substituted biaryls that give similar soluble phenanthrenes have yielded appropriate spectral data.[9]

Acknowledgment. We gratefully acknowledge the National Institutes of Health, the Iowa State University College of Liberal Arts and Sciences, and Proctor and Gamble for their generous financial support; Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. for the palladium compounds; and NATO for a Collaborative Research Grant allowing valuable discussions with Professor Sandro Cacchi of the University of Rome, La Sapienza, Rome, Italy.

Supplementary Material Available: ^1H and ^{13}C NMR spectra for all new phenanthrenes. This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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CHAPTER 5: SYNTHESIS OF VINYLIC HETERO- AND CARBOCYCLES VIA PALLADIUM-CATALYZED ANNULATION OF INTERNAL ALKYNES

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

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Abstract

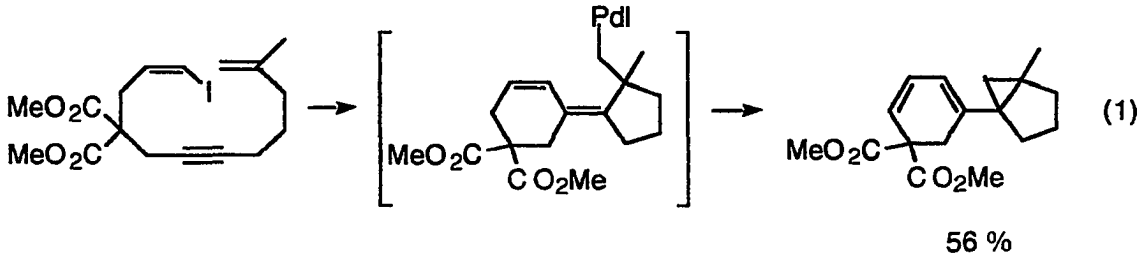
A number of vinylic hetero- and carbocycles have been synthesized in good yield by treating appropriate functionally-substituted vinylic halides with internal alkynes in the presence of a palladium catalyst. Synthetically, the methodology provides a convenient, regioselective route to a variety of vinylic hetero- and carbocyclic ring systems containing aryl, silyl, ester, acetal, and *tert*-alkyl groups.

Introduction

The transition-metal mediated annulation reactions of alkynes are of great current interest.[1] Palladium-based methodology is especially convenient, since the metal complexes are readily available, accommodate a wide range of functionality, and are not generally oxygen or moisture sensitive. Consequently, a considerable number of aromatic heterocyclic ring

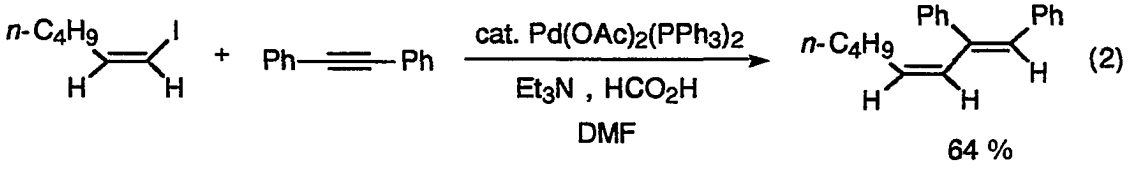
systems have been synthesized from aromatic halides or triflates using palladium chemistry.[2,3]

However, relatively little is known about the annulation reactions of alkynes with analogous vinylic substrates. A few recent examples have demonstrated that intramolecular cascade reactions can be used to annulate vinylic halides onto internal alkynes. These processes are useful for the synthesis of polycyclic ring systems and involve internal propagation of a vinylpalladium intermediate along an alkene and/or alkyne chain, and eventually trapping of the intermediate with either carbon monoxide, terminal alkynes, organometallic reagents, or internal alkenes (eq. 1).[4]



56 % (1)

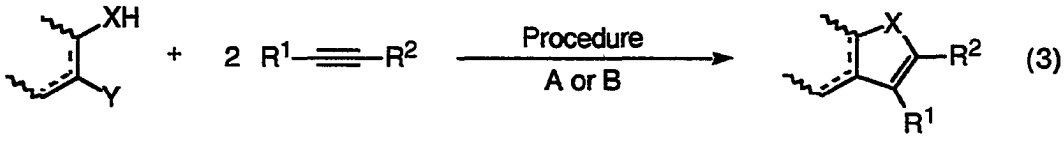
Another reported annulation process is the palladium-catalyzed hydrovinylation of internal alkynes to form 1,3-dienes.[5] In this case, the vinylpalladium intermediate formed by mono-insertion of the alkyne is reduced by triethylammonium formate (eq. 2).



64 % (2)

In conjunction with our studies directed towards the synthesis of aromatic heterocycles via the palladium-catalyzed annulation of internal alkynes,[3a,6] we were interested in extending

this chemistry to vinylic halides, since no examples of this type of chemistry are currently known (eq. 3).[7] We now wish to report that under suitable reaction conditions, a number of



(3)

XH = OH, NHTs, $CH(CO_2Me)_2$, $C(CH_3)_2OH$
Y = I, Br

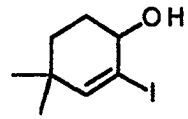
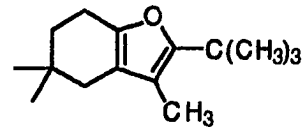
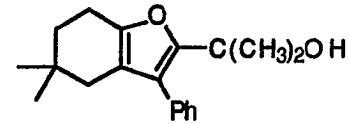
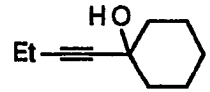
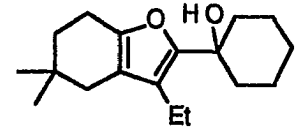
interesting vinylic hetero- and carbocycles can be easily prepared in good yield using this methodology.

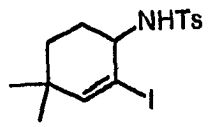
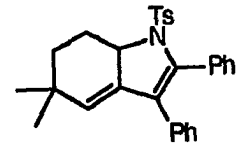
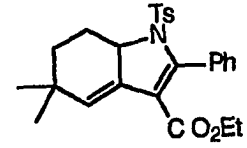
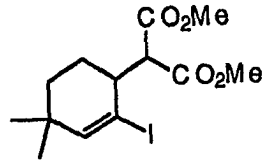
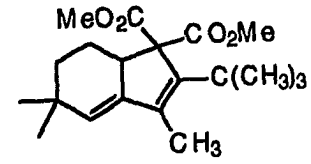
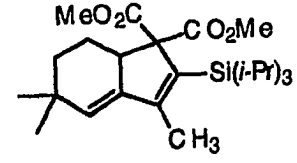
Results

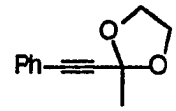
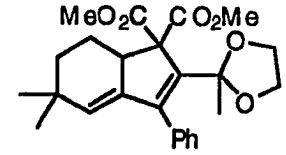
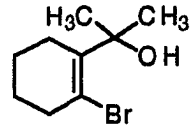
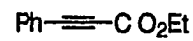
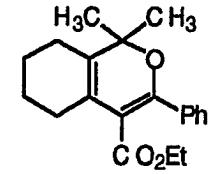
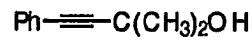
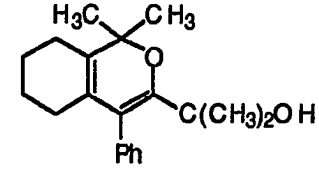
In general, we have employed two sets of reaction conditions very similar to those reported by us for the annulation of alkynes,[3a,6] vinylic cyclopropanes and cyclobutanes,[8] allenes,[9] and 1,3-dienes[10]: procedure A - 5 mol % $Pd(OAc)_2$, 2-4 equiv of NaOAc, 1 equiv of LiCl, in DMF at 100 °C; procedure B - 5 mol % $Pd(OAc)_2$, 1-2 equiv of Na_2CO_3, 1 equiv of LiCl, in DMF at 100 °C. Our preliminary results using these procedures are shown in Table 1.

Furans. In order to probe the feasibility of the annulation process, we initiated our study using 2-iodo-2-cyclohexen-1-ol as the starting halide. We felt that this compound was an ideal candidate for the annulation process since similar carboxylic acid-containing, cyclic vinylic halides had previously worked well in our α-pyrone chemistry.[7] This substrate was also easily prepared by alpha iodination[11] and subsequent 1,2-reduction[12] of the corresponding enone (eq. 4).

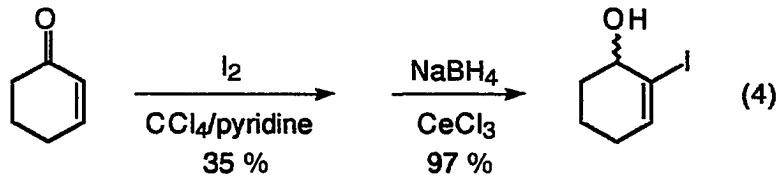
Table 1. Synthesis of Vinylic Heterocycles Via Annulation of Internal Alkynes (eq 3)[a]

entry	starting halide	alkyne	base (equiv)	temp (°C), time (h)	product(s)	yield (%)[b]
1		$CH_3-\equiv-C(CH_3)_3$	NaOAc (2)	100, 24		69
2		$Ph-\equiv-C(CH_3)_2OH$	NaOAc (4)	100, 52		73
3			NaOAc (4)	100, 24		51

4		Ph—≡—Ph	Na_2CO_3 (2)	100, 7		78
5		Ph—≡—CO_2Et	Na_2CO_3 (2)	100, 5		64
6		CH_3—≡—$C(CH_3)_3$	Na_2CO_3 (2)	100, 23		86
7		CH_3—≡—Si(*i*-Pr)$_3$	Na_2CO_3 (2)	100, 67		73

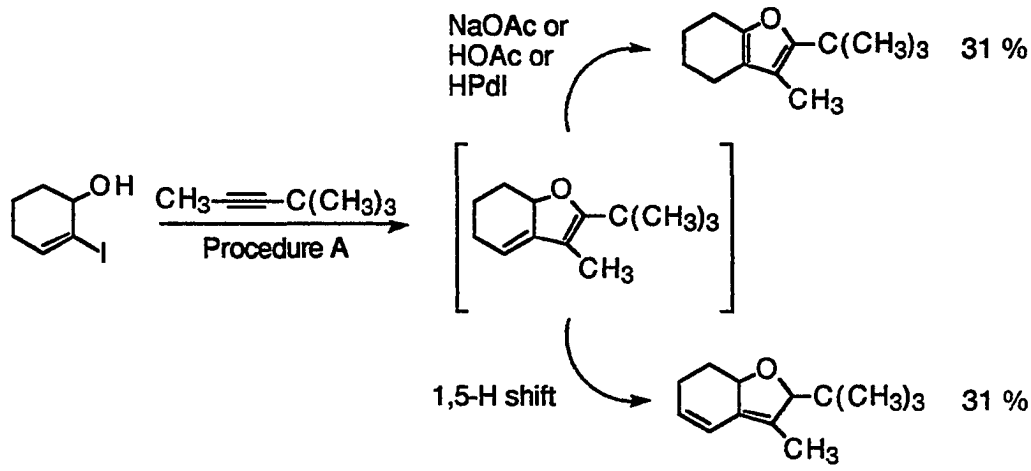
8			Na_2CO_3 (2)	100, 24		53
9			Na_2CO_3 (1)	100, 84		61
10			Na_2CO_3 (1)	100, 168		48

[a] See the text and Experimental Section for the detailed procedures. [b] Yields refer to isolated compounds purified by chromatography.



(4)

From our experiments, we discovered that the products formed from the reaction of 2-iodo-2-cyclohexen-1-ol with internal alkynes depended on the starting vinylic halide, the reaction conditions, and the internal alkyne undergoing annulation. For example, the reaction of 2-iodo-2-cyclohexen-1-ol with 4,4-dimethyl-2-pentyne using procedure A unexpectedly gave a 62 % overall yield of the two isomerized products shown in equation 5. The initially

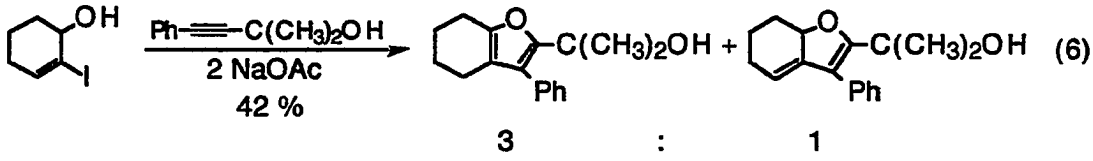


(5)

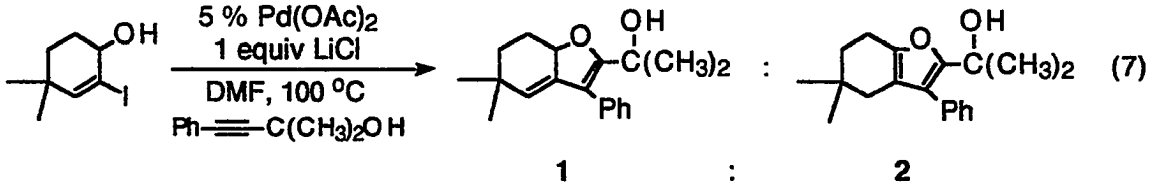
formed heterocyclic intermediate presumably isomerizes to the furan by either base-catalyzed rearrangement by NaOAc[13] or an addition-elimination sequence involving acetic acid or a palladium hydride. The other product is presumably formed by a thermally allowed 1,5-hydrogen shift. The product from the reaction of 4,4-dimethyl-2-butyne and 4,4-dimethyl-2-iodo-2-cyclohexen-1-ol was cleanly the furan which could be isolated in 69 % yield (entry 1,

Table 1). The presence of the two methyl groups now prevents the 1,5-hydrogen shift from occurring.

On the other hand, the reaction of 4-phenyl-2-methyl-3-butyn-2-ol and 2-iodo-2-cyclohexen-1-ol under the same reaction conditions resulted in only a 42 % yield of an inseparable 3:1 mixture of the corresponding furan and the unisomerized product (eq. 6). It is



unclear why no product resulting from a 1,5-hydrogen shift was observed. Using 4,4-dimethyl-2-iodo-2-cyclohexen-1-ol as the starting vinylic halide and chosing the proper base and reaction time, the inseparable mixture of furan and unisomerized product can be avoided and completely converted to the furan (eq. 7; entry 2, Table 1 and entry 4, Table 2). Procedure



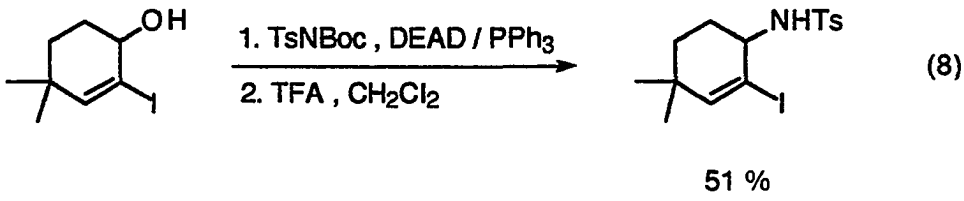
B using Na_2CO_3 was intriguing, as it actually inhibited the isomerization process and reversed the product ratio (entry 5, Table 2). The reaction of this same alcohol with 1-(1-butynyl)cyclohexanol also gave the furan, but only in a 51 % yield (entry 3, Table 1).

Nitrogen Heterocycles. The synthesis of nitrogen heterocycles was next examined. First, 1-iodo-3,3-dimethyl-6-(tosylamino)cyclohexene was prepared in two steps

Table 2. Reaction of 4,4-Dimethyl-2-iodocyclohexen-ol with 4-Phenyl-2-methyl-3-butyn-2-ol (eq 7).

entry	base (equiv)	time (h)	1:2 ratio	% isolated yield
1	NaOAc (2)	10	45 : 55	64
2	NaOAc (2)	24	17 : 83	72
3	NaOAc (4)	24	15 : 85	71
4	NaOAc (4)	52	0 : 100	73
5	Na_2CO_3 (2)	24	87 : 13	73

from the corresponding alcohol via the Mitsunobu reaction (eq. 8).[14] We had envisioned that

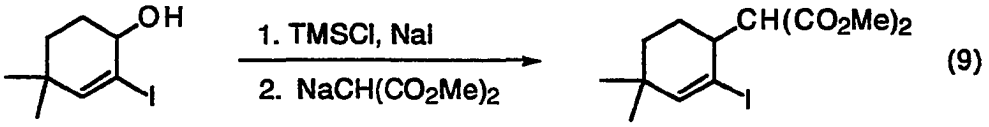


(8)

this substrate would react with internal alkynes using procedure A to form pyrroles, in analogy with the furan chemistry. However, reacting the starting sulfonamide with diphenylacetylene under these conditions gave a 55 % yield of a complex mixture, consisting mainly of unisomerized product and no pyrrole. Fortunately, since the nitrogen heterocycle was more difficult to isomerize and procedure B appeared to inhibit isomerization (entry 5, Table 2), we

were able to cleanly obtain a 78 % yield of the unisomerized product using that procedure (entry 4, Table 1). The regioselective reaction of this same sulfonamide with ethyl phenylpropiolate gave similar results (entry 5, Table 1).

Carbocycles. We were also able to successfully synthesize carbocycles using this methodology. The starting material, dimethyl (2-iodo-4,4-dimethyl-2-cyclohexenyl)malonate, was synthesized in 71 % yield from the alcohol by malonate displacement of the corresponding iodide (eq. 9). Treatment of this substrate with 4,4-dimethyl-2-pentyne, 1-(triisopropylsilyl)propyne, and 2-(phenylethynyl)-2-methyl-1,3-



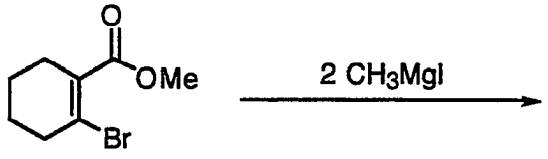
(9)

71 %

dioxolane using procedure B gave good to excellent yields of the pure, unisomerized carbocycles (entries 6-8, Table 1). It is interesting to note that using the sterically-hindered ketal reverses the regiochemistry normally seen with similar unprotected ketone-containing alkynes.[2,3a]

Pyrans. Pyrans were also accessible in fair to good yields from the reaction of internal alkynes with 2-(2-bromo-1-cyclohexenyl)-2-propanol (entries 9 and 10, Table 1). Having the bromide as a leaving group significantly decreased the reaction rate and also gave slightly lower yields. The starting bromo carbinol was prepared by Grignard addition to methyl 2-bromocyclohex-1-ene-1-carboxylate (eq. 10).

As with our previous chemistry, the annulation process is highly regioselective for alkynes containing hindered alkyl, trialkylsilyl, or other similar groups with a tertiary center



(10)

90 %

(entries 1-3, 6-8, and 10, Table 1); however, high-yielding, clean reactions are again generally limited to these types of alkynes. An exception to this generality is the regioselective annulation of various substrates onto ethyl phenylpropiolate (entries 5 and 9, Table 1). The regiochemistry for the products is assumed to have the more sterically-demanding group in the 2-position of these ring systems in accordance with the pattern established in our previous alkyne addition reactions.

The foregoing studies demonstrate that a useful synthesis of vinylic hetero- and carbocycles has been developed using the palladium-catalyzed annulation of sterically-hindered internal alkynes. The procedure utilizes easily synthesized starting materials. The reaction proceeds under relatively mild conditions and gives good yields. Unfortunately, a number of these reactions have also been run with comparable acyclic vinylic halides and have produced either complex mixtures or no identifiable products at all. Thus, we are currently trying to overcome this limitation and continue to expand the scope of this process.

Experimental Section

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

wavelength UV light (254 nm), or basic $KMnO_4$ solution [3 g $KMnO_4$ + 20 g K_2CO_3 + 5 ml NaOH (5%) + 300 ml H_20]. All melting points are uncorrected.

Reagents. All reagents were used directly as obtained commercially unless otherwise noted. Anhydrous forms of NaOAc, Na_2CO_3, LiCl, and sodium borohydride were purchased from Fisher Scientific. DMF, THF, pyridine, trifluoroacetic acid, methylene chloride, methanol, acetonitrile, and CCl_4 were purchased from Fisher Scientific. All palladium compounds were donated by Johnson Matthey, Inc. and Kawaken Fine Chemicals Co., Ltd. 2-Cyclohexen-1-one, 4,4-dimethyl-2-cyclohexen-1-one, cerium(III) chloride heptahydrate, diethyl azodicarboxylate, 1-(triisopropylsilyl)propyne, triphenylphosphine, trimethylsilyl chloride, dimethyl malonate, methyl iodide, magnesium, and I_2 were obtained from Aldrich Chemical Co., Inc. 4,4-Dimethyl-2-butyne, 4-phenyl-2-methyl-3-butyn-2-ol and 1-(1-butynyl)cyclohexanol were purchased from Farchan Scientific Co. Diphenylacetylene and ethyl phenylpropiolate were purchased from Eastman Kodak Co. The following starting materials were prepared according to literature procedures: 2-(2-phenyl-1-ethynyl)-2-methyl-1,3-dioxolane,[15] methyl-2-bromocyclohex-1-ene-1-carboxylate,[16] and *N*-Boc *p*-toluenesulfonamide.[14] The following starting materials were prepared as indicated.

2-Iodo-2-cyclohexen-1-ol. I_2 (13.16 g, 104 mmol) dissolved in 130 ml of 1:1 CCl_4/pyridine was added under N_2 to a solution of 2-cyclohexen-1-one dissolved in 100 ml of 1:1 CCl_4/pyridine at 0-5 °C. The mixture was stirred for 1 h as the temperature was raised from 0 °C to rt. The mixture was diluted with 500 ml of ether, washed with water (2 x 125 ml), 1 N HCl (2 x 200 ml), water (100 ml), 20 % $Na_2S_2O_3$ (2 x 100 ml), and dried ($MgSO_4$). After filtration and concentration, the solid was chromatographed using 2:1 hexane/EtOAc and recrystallized from hexane/ether to yield 4.0 g of 2-iodo-2-cyclohexen-1-one (35 %). This compound (1.09 g, 4.9 mmol) and cerium(III) chloride heptahydrate (1.86 g, 5.0 mmol) were dissolved in 13 ml of MeOH. Sodium borohydride (193 mg, 5.07 mmol) was added in one

portion (careful !) with stirring under N_2. After 10 min, the gas evolution ceased and the reaction was quenched with saturated NH_4Cl, followed by 5 % HCl. The product was extracted with ether, dried over Na_2SO_4, and chromatographed using 4:1 hexane/EtOAc to yield 1.06 g (97%) of the product as a clear oil with spectral properties identical to those previously reported.[17]

2-Iodo-4,4-dimethyl-2-cyclohexen-1-o1. 4,4-Dimethyl-2-cyclohexen-1-one (3.24 g) was placed in 100 ml of 1:1 CCl_4/pyridine and I_2 (13.16 g, 104.2 mmol) in 130 ml of 1:1 CCl_4/pyridine was added over 10 min at rt. The mixture was stirred in the dark for 72 h. The mixture was diluted with 300 ml of ether, washed with 20 % $Na_2S_2O_3$ (2 x 100 ml), water (100 ml), 1 N HCl (4 x 100 ml), and dried ($MgSO_4$). The solvent was removed to yield 86 % of the desired iodoenone: ^{1}H NMR ($CDCl_3$) δ 1.20 (s, 6 H, CH_3), 1.93 (t, J = 6.3 Hz, 2 H, CH_2), 2.68 (t, J = 6.3 Hz, 2 H, CH_2), 7.46 (s, 1 H, vinyl). This compound (2.50 g, 10 mmol) and cerium(III) chloride heptahydrate (3.72 g, 10 mmol) were dissolved in 25 ml of MeOH. Sodium borohydride (380 mg, 10 mmol) was added in one portion (careful !) with stirring under N_2. After 10 min, the gas evolution ceased and the reaction was quenched with saturated NH_4Cl, followed by 5 % HCl. The product was extracted with ether, dried over $MgSO_4$, and chromatographed using 4:1 hexane/EtOAc to yield 2.34 g (97 %) of the product as a clear oil: ^{1}H NMR ($CDCl_3$) δ 0.99 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 1.52 (m, 1 H, CH), 1.63 (m, 1 H, CH), 1.89 (m, 1 H, CH), 2.04 (m, 1 H, CH), 2.12 (br s, 1 H, OH), 4.12 (q, J = 5.1 Hz, 1 H, CH), 6.23 (s, 1 H, vinyl); ^{13}C NMR ($CDCl_3$) δ 27.9, 28.8, 28.9, 32.3, 37.3, 71.4, 102.5, 150.0; IR ($CHCl_3$) 3421 (OH), 1618 (C=C) cm^{-1}; HRMS m/z 252.0013 (calcd for $C_8H_{13}IO$, 252.0011).

1-Iodo-3,3-dimethyl-6-(tosylamino)cyclohexene. Triphenylphosphine (4.67 g, 17.9 mmol) and *N*-Boc *p*-toluenesulfonamide (2.43 g, 8.91 mmol) were dissolved in 80 ml of dry THF. 2-Iodo-4,4-dimethyl-2-cyclohexen-1-o1 (1.65 g, 6.5 mmol) was added, followed by diethyl azodicarboxylate (2.29 ml, 14.6 mmol). The mixture was stirred for 4 h,

concentrated, and the product was purified by chromatography using 8:1 hexanes/EtOAc to yield the crude 6-(*N*-Boc-*N*-tosylamino)-1-iodo-3,3-dimethylcyclohexene: ^{1}H NMR ($CDCl_3$) δ 1.03 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 1.42 (s, 9 H, CH_3), 1.67 (m, 2 H, CH_2), 2.09 (m, 2 H, CH_2), 2.43 (s, 3 H, CH_3), 2.51 (m, 1 H, CH), 4.97 (br s, 1 H, NH), 6.22 (d, J = 0.9 Hz, 1 H, vinyl), 7.29 (d, J = 8.1 Hz, 2 H, aryl), 7.91 (d, J = 8.1 Hz, 2 H, aryl). All of this compound was placed in 70 ml of CH_2Cl_2 containing 2.18 ml of trifluoroacetic acid and stirred for 30 h at rt. After completion, the solvent was removed and the product was purified by chromatography using 8:1 hexanes/EtOAc to afford the desired tosylamide in 51 % overall yield: ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 3 H, CH_3), 0.99 (s, 3 H, CH_3), 1.52 (m, 2 H, CH_2), 1.95 (m, 2 H, CH_2), 2.42 (s, 3 H, CH_3), 3.75 (m, 1 H, CH), 4.58 (br s, 1 H, NH), 6.24 (s, 1 H, vinyl), 7.32 (d, J = 8.1 Hz, 2 H, aryl), 7.81 (d, J = 8.1 Hz, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 21.4, 27.2, 28.5, 29.4, 31.1, 37.2, 57.6, 94.7, 127.6, 129.4, 137.5, 143.3, 153.1; IR ($CHCl_3$) 3247 (NH) cm^{-1}; HRMS m/z (M^+ - I) 278.1213 (calcd for $C_{15}H_{20}NO_2S$, 278.1215).

Dimethyl (2-iodo-4,4-dimethyl-2-cyclohexenyl)malonate. One g (3.96 mmol) of 2-iodo-4,4-dimethyl-2-cyclohexen-1-o1 and 0.88 g (5.94 mmol) of NaI were placed in 10 ml of CH_3CN under N_2. Trimethylsilyl chloride (0.75 ml, 5.94 mmol) was added at rt all at once and the reaction was stirred for 24 h in the dark. The reaction was quenched with water. Ether was added. The organic layer was separated and washed with 10 ml of 10 % $Na_2S_2O_3$, 20 ml of water, and 20 ml of brine, and then dried ($MgSO_4$). The product was purified by chromatography using hexane to yield 1.08 g (76 %) of 1,6-diiodo-3,3-dimethylcyclohexene: ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 3 H, CH_3), 1.05 (s, 3 H, CH_3), 1.22 (d, J = 0.9 Hz, 1 H, CH), 1.80 (m, 1 H, CH), 2.02 (m, 2 H, CH_2), 5.00 (d, J = 2.1 Hz, 1 H, CH), 6.08 (s, 1 H, vinyl). Dimethyl malonate (0.83 g, 6.26 mmol) in 1 ml of 2:1 DMF/THF was added to NaH (150 mg, 6.26 mmol) in 8 ml of 1:1 DMF/THF and stirred for 15 min. 1,6-Diiodo-3,3-dimethylcyclohexene (1.14 g, 3.13 mmol) in 4 ml of 1:1 DMF/THF was added

all at once and stirred for 13 h. The reaction was quenched with saturated NH_4Cl and extracted with ether. The ether layer was separated and dried ($MgSO_4$). The product was isolated by chromatography using 8:1 hexane/EtOAc to yield 1.06 g (93 %) of dimethyl (2-iodo-4,4-dimethyl-2-cyclohexenyl)malonate: ^1H NMR ($CDCl_3$) δ 1.00 (s, 3 H, CH_3), 1.02 (s, 3 H, CH_3), 1.48 (m, 2 H, CH_2), 1.89 (m, 1 H, CH), 2.16 (m, 1 H, CH), 2.97 (m, 1 H, CH), 3.74 (s, 3 H, CH_3), 3.76 (s, 3 H, CH_3), 4.07 (d, J = 4.8 Hz, 1 H, CH), 6.31 (br s, 1 H, vinyl); ^{13}C NMR ($CDCl_3$) δ 22.4, 27.4, 28.2, 34.2, 36.7, 43.4, 51.6, 52.1, 55.4, 99.0, 150.7, 167.5, 168.3; IR (neat) 1755 (C=O), 1732 (C=O), 1618 (C=C) cm^{-1}; HRMS m/z (M^+ - I) 239.1290 (calcd for $C_{12}H_{19}O_4$, 239.1283).

2-(2-Bromo-1-cyclohexenyl)-2-propanol. Magnesium (0.27 g, 11.29 mmol) was placed in 5 ml of dry ether. Methyl iodide (0.66 ml, 10.52 mmol) was added slowly to the flask to form the Grignard reagent. The flask was heated an additional 15 minutes and methyl (Z)-2-bromocyclohex-1-ene-1-carboxylate (1.00 g, 4.56 mmol) in 3 ml of dry ether was added. The mixture was heated at reflux for 1 h and the mixture was quenched with saturated NH_4Cl. The product was extracted with ether, washed with water and brine, and dried over $MgSO_4$. The crude product was chromatographed using 8:1 hexane/EtOAc to yield 0.9 g (90 %) of the carbinol: ^1H NMR ($CDCl_3$) δ 1.43 (s, 6 H, CH_3), 1.63 (m, 4 H, CH_2), 2.22 (m, 2 H, CH_2), 2.56 (m, 2 H, CH_2), 3.34 (s, 1 H, OH); ^{13}C NMR ($CDCl_3$) δ 22.4, 24.3, 27.8, 28.3, 38.9, 73.8, 117.3, 140.5; IR (neat) 3453 (OH), 1630 (C=C) cm^{-1}; HRMS m/z 218.0306 (calcd for $C_9H_{15}BrO$, 218.0304).

General Procedure for the Palladium-Catalyzed Formation of Vinylic Heterocycles. $Pd(OAc)_2$ (3 mg, 0.0135 mmol), the base (2.0 mmol), LiCl (10.6 mg, 0.25 mmol), the starting vinylic halide (0.25 mmol), and the alkyne (0.50 mmol) were placed in a 2 dram vial which was heated in an oil bath at 100 °C under N_2 for the necessary period of time. The reaction was monitored by TLC to establish completion. The reaction mixture was cooled, diluted with ether, washed with saturated NH_4Cl, dried over anhydrous $MgSO_4$, and filtered.

The solvent was evaporated under reduced pressure and the product was isolated by flash column chromatography on a silica gel column. The following compounds were prepared by the above procedure.

2-*t*-Butyl-4,5,6,7-tetrahydro-3,5,5-trimethylbenzofuran (entry 1, Table 1). The reaction mixture was chromatographed using hexane to yield a clear oil: ^{1}H NMR ($CDCl_3$) δ 0.97 (s, 6 H, CH_3), 1.30 (s, 9 H, CH_3), 1.52 (t, J = 6.3 Hz, 2 H, CH_2), 1.93 (s, 3 H, CH_3), 2.05 (s, 2 H, CH_2), 2.48 (t, J = 6.3 Hz, 2 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 9.3, 20.5, 28.2, 28.7, 30.2, 33.7, 34.6, 36.2, 111.4, 118.0, 145.1, 154.8; IR ($CHCl_3$) 1646 (C=C), 1456 (C=C) cm^{-1}; HRMS m/z 220.1832 (calcd for $C_{15}H_{24}O$, 220.1827).

4,5,6,7-Tetrahydro-2-(1-hydroxy-1-methylethyl)-5,5-dimethyl-3-phenylbenzofuran (entry 2, Table 1). The reaction mixture was chromatographed using 8:1 hexane/EtOAc: ^{1}H NMR ($CDCl_3$) δ 0.95 (s, 6 H, CH_3), 1.45 (s, 6 H, CH_3), 1.58 (t, J = 6.6 Hz, 2 H, CH_2), 1.98 (s, 2 H, CH_2), 2.08 (s, 1 H, OH), 2.58 (t, J = 6.6 Hz, 2 H, CH_2), 7.2-7.4 (m, 5 H, aryl); ^{13}C NMR ($CDCl_3$) δ 20.6, 27.9, 29.9, 30.2, 34.8, 36.0, 70.5, 118.1, 120.9, 126.8, 127.9, 129.9, 134.3, 146.6, 152.3; IR ($CHCl_3$) 3460 (OH), 1683 (C=C), 1605 (C=C), 1494 (C=C) cm^{-1}; HRMS m/z 284.1773 (calcd for $C_{19}H_{24}O_2$, 284.1776).

3-Ethyl-4,5,6,7-tetrahydro-2-(1-hydroxycyclohexyl)-5,5-dimethylbenzofuran (entry 3, Table 1). The reaction mixture was chromatographed using 8:1 hexane/EtOAc: ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 6 H, CH_3), 1.07 (t, J = 7.5 Hz, 3 H, CH_3), 1.30-2.05 (m, 13 H, CH_2), 2.11 (t, J = 1.5 Hz, 2 H, CH_2), 2.40-2.60 (m, 4 H, CH_2); ^{13}C NMR ($CDCl_3$) δ 15.6, 17.2, 20.6, 22.0, 25.5, 28.0, 30.2, 34.7, 35.9, 37.2, 72.0, 117.8, 120.9, 146.5, 151.8; IR ($CHCl_3$) 3457 (OH), 1647 (C=C), 1575 (C=C), 1453 (C=C) cm^{-1}; HRMS m/z 276.2086 (calcd for $C_{18}H_{28}O_2$, 276.2089).

***N*-Tosyl-6,7-dihydro-5,5-dimethyl-2,3-diphenyl-7a*H*-indole (entry 4, Table 1).** The reaction mixture was chromatographed using 15:1 hexane/EtOAc: ^{1}H NMR ($CDCl_3$) δ 0.92 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 1.5-2.0 (m, 3 H, CH_2), 2.39 (s, 3 H,

CH_3), 2.65 (m, 1 H, CH), 4.36 (m, 1 H, CH), 4.91 (d, J = 2.7 Hz, 1 H, vinyl), 6.8-7.4 (m, 14 H, aryl); ^{13}C NMR ($CDCl_3$) δ 21.5, 28.0, 28.1, 30.2, 33.0, 36.1, 64.5, 124.3, 126.7, 127.0, 127.1, 127.7, 128.2, 128.3, 129.2, 129.7, 130.5, 131.2, 132.4, 133.6, 138.4, 142.5, 143.6; IR ($CHCl_3$) 1603 (C=C), 1540 (C=C) cm^{-1}; HRMS m/z 455.1919 (calcd for $C_{29}H_{29}NO_2S$, 455.1919).

***N*-Tosyl-3-carboethoxy-6,7-dihydro-2-phenyl-5,5-dimethyl-7a*H*-indole (entry 5, Table 1).** The reaction mixture was chromatographed using 15:1 hexane/EtOAc: ^1H NMR ($CDCl_3$) δ 0.85 (t, J = 7.2 Hz, 3 H, CH_3), 1.04 (s, 3 H, CH_3), 1.09 (s, 3 H, CH_3), 1.5-2.0 (m, 3 H, CH_2), 2.39 (s, 3 H, CH_2), 2.66 (m, 1 H, CH_2), 3.90 (m, 2 H, CH_2), 4.50 (m, 1 H, CH), 5.62 (d, J = 3.0 Hz, 1 H, vinyl), 7.1-7.4 (m, 9 H, aryl); ^{13}C NMR ($CDCl_3$) δ 13.5, 21.5, 28.0, 30.2, 31.0, 33.1, 35.7, 60.0, 65.6, 116.3, 126.6, 126.7, 127.9, 129.0, 129.3, 129.8, 130.7, 133.1, 134.5, 144.2, 153.6, 163.7; IR ($CHCl_3$) 1713 (C=O), 1597 (C=C), 1537 (C=C) cm^{-1}; HRMS m/z 451.1823 (calcd for $C_{26}H_{29}NO_4S$, 451.1817).

2-*t*-Butyl-1,1-dicarbomethoxy-6,7-dihydro-3,5,5-trimethyl-7a*H*-indene (entry 6, Table 1). The reaction mixture was chromatographed using 8:1 hexane/EtOAc: ^1H NMR ($CDCl_3$) δ 0.94 (s, 3 H, CH_3), 1.03 (s, 3 H, CH_3), 1.17 (s, 9 H, CH_3), 1.25 (m, 1 H, CH), 1.40 (m, 1 H, CH), 1.65 (m, 1 H, CH), 1.85 (m, 1 H, CH), 1.95 (s, 3 H, CH_3), 2.82 (m, 1 H, CH), 3.70 (s, 3 H, CH_3), 3.75 (s, 3 H, CH_3), 5.17 (s, 1 H, vinyl); ^{13}C NMR ($CDCl_3$) δ 13.1, 22.4, 29.9, 31.3, 31.7, 32.2, 34.2, 37.7, 50.6, 51.4, 52.0, 68.9, 123.3, 137.7, 144.4, 147.7, 169.7, 172.3; IR ($CHCl_3$) 1761 (C=O), 1737 (C=O) cm^{-1}; HRMS m/z 334.2144 (calcd for $C_{20}H_{30}O_4$, 334.2144).

1,1-Dicarbomethoxy-6,7-dihydro-2-triisopropylsilyl-3,5,5-trimethyl-7a*H*-indene (entry 7, Table 1). The reaction mixture was chromatographed using 15:1 hexane/EtOAc: ^1H NMR ($CDCl_3$) δ 0.95 (s, 3 H, CH_3), 1.00-1.12 (m, 24 H, CH_3), 1.35 (m, 2 H, CH_2), 1.60 (m, 1 H, CH), 1.90 (m, 1 H, CH), 1.94 (s, 3 H, CH_3), 2.95 (m, 1 H, CH), 3.62 (s, 3 H, CH_3), 3.73 (s, 3 H, CH_3), 5.24 (s, 1 H, vinyl); ^{13}C NMR ($CDCl_3$) δ 13.5,

14.9, 19.6, 19.7, 22.5, 29.7, 31.0, 32.3, 37.6, 50.8, 51.2, 52.1, 71.9, 125.5, 138.2, 144.9, 154.2, 169.9, 172.2; IR ($CHCl_3$) 1721 (C=O) cm^{-1}; HRMS m/z (M^+ - $CH(CH_3)_2$) 391.2300 (calcd for $C_{22}H_{35}O_4Si$, 391.2304).

1,1-Dicarbomethoxy-6,7-dihydro-2-(2-methyl-2-(1,3-dioxolanyl))-5,5-dimethyl-3-phenyl-7a*H*-indene (entry 8, Table 1). The reaction mixture was chromatographed using 15:1 hexane/EtOAc: ^1H NMR ($CDCl_3$) δ 0.98 (s, 3 H, CH_3), 1.08 (s, 3 H, CH_3), 1.13 (m, 2 H, CH_2), 1.57 (m, 2 H, CH_2), 1.63 (s, 3 H, CH_3), 1.86 (m, 1 H, CH), 3.28 (s, 3 H, CH_3), 3.59 (s, 2 H, CH_2), 3.73 (s, 2 H, CH_2), 3.74 (s, 3 H, CH_3), 5.94 (m, 1 H, vinyl), 7.07 (m, 2 H, aryl), 7.23 (m, 3 H, aryl); ^{13}C NMR ($CDCl_3$) δ 22.9, 25.9, 29.5, 30.1, 31.0, 32.4, 37.1, 47.5, 51.9, 63.5, 63.7, 72.7, 108.9, 126.9, 127.1, 127.6, 131.3, 137.3, 137.6, 141.8, 144.1, 169.5, 169.9; IR ($CHCl_3$) 1724 (C=O) cm^{-1}; HRMS m/z 426.2047 (calcd for $C_{25}H_{30}O_6$, 426.2042).

Ethyl 5,6,7,8-tetrahydro-1,1-dimethyl-3-phenylisochromene-4-carboxylate (entry 9, Table 1). The reaction mixture was chromatographed using 83:1 hexane/EtOAc: ^1H NMR ($CDCl_3$) δ 0.83 (t, J = 6.9 Hz, 3 H, CH_3), 1.34 (s, 6 H, CH_3), 1.56 (m, 4 H, CH_2), 1.94 (m, 2 H, CH_2), 2.23 (m, 2 H, CH_2), 3.86 (q, J = 6.9 Hz, 2 H, CH_2), 7.24 (m, 3 H, aryl), 7.35 (m, 2 H, aryl); ^{13}C NMR ($CDCl_3$) δ 13.7, 22.2, 22.4, 24.3, 24.5, 25.5, 60.2, 79.3, 110.3, 122.9, 127.3, 127.6, 128.1, 128.9, 135.4, 153.4, 153.7, 168.3; IR ($CHCl_3$) 1713 (C=O), 1646 (C=C), 1586 (C=C) cm^{-1}; HRMS m/z 312.1732 (calcd for $C_{20}H_{24}O_3$, 312.1725).

5,6,7,8-Tetrahydro-3-(1-hydroxy-1-methylethyl)-1,1-dimethyl-4-phenylisochromene (entry 10, Table 1). The reaction mixture was chromatographed using 15:1 hexane/EtOAc: ^1H NMR ($CDCl_3$) δ 1.18 (s, 6 H, CH_3), 1.36 (s, 6 H, CH_3), 1.49 (m, 2 H, CH_2), 1.54 (m, 4 H, CH_2), 1.97 (m, 2 H, CH_2), 2.25 (s, 1 H, OH), 7.10 (m, 2 H, aryl), 7.25 (m, 3 H, aryl); ^{13}C NMR ($CDCl_3$) δ 22.3, 22.5, 24.2, 24.3, 26.1, 29.0, 72.3,

114.1, 125.8, 126.7, 127.6 (2), 127.8, 130.9, 137.4, 149.9; IR ($CHCl_3$) 3500 (OH), 1656 (C=C), 1605 (C=C) cm^{-1}; HRMS m/z 298.1934 (calcd for $C_{20}H_{26}O_2$, 298.1933).

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Supplementary Material Available: ^1H and ^{13}C NMR spectra for all new vinylic hetero- and carbocycles. This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

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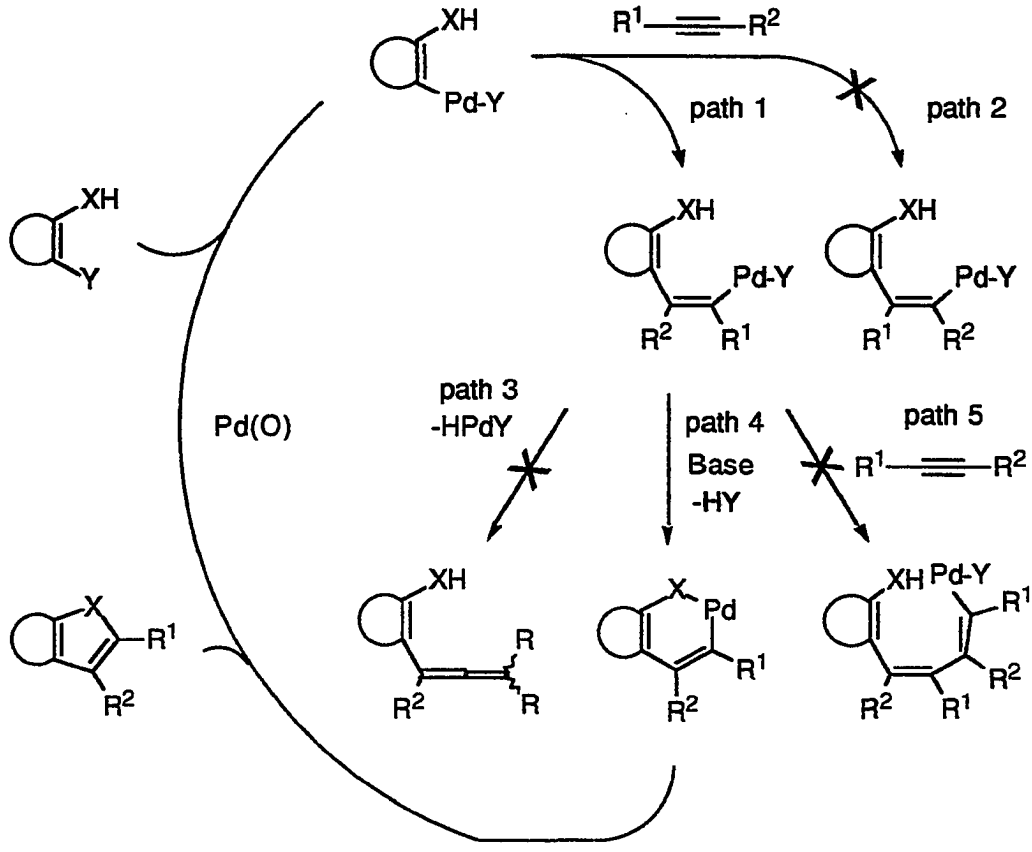
GENERAL CONCLUSION

In this dissertation, it has been demonstrated that the palladium-catalyzed annulation of internal alkynes with a variety of aryl and vinylic halides and triflates provides an efficient route to a number of hetero- and carbocyclic ring systems, including indenones, isocoumarins, benzofurans, isochromenes, phenanthrenes, furans, and other miscellaneous aromatic and vinylic ring systems.

The common thread that ties chapters 1-5 together is that the methodology generally requires hindered or symmetrical alkynes containing tertiary centers to obtain high-yielding, usable, clean reactions. This restriction can perhaps best be explained by examining how a hindered tertiary alkyne limits the available reaction pathways for the annulation process as shown in Scheme 1. Following oxidative addition of the aryl or vinyl halide or triflate to Pd(O), there are two possible paths (paths 1 and 2) by which alkyne insertion can take place. Since the addition of aryl- or vinylpalladium species to unsymmetrical hindered alkynes containing tertiary centers is regioselective and leads to vinylpalladium intermediates in which the sterically more hindered group is located at the carbon atom σ-bonded to the palladium, path 2 is eliminated and only one vinylpalladium intermediate is formed. The resultant vinylpalladium intermediate could then either β-hydride eliminate to form an allene (path 3), close to form a palladacycle (path 4), or insert another alkyne (path 5). The tertiary center prevents the β-hydride elimination (path 3). It also shields the vinylpalladium intermediate, thus simultaneously discouraging insertion of another alkyne (path 5) and allowing more time for the annulation products to form (path 4). Path 4 should also be favored by using better nucleophiles.

Cyclic vinylic halides or triflates are also currently necessary in order to obtain good yields with those systems. It is unclear why these reactions proceed well, whereas similar reactions with acyclic systems give complex mixtures or no discernible products. Perhaps the

Scheme 1



cyclic systems are more stable under the reaction conditions and/or are unable to β-hydride eliminate following insertion into Pd(O). More work needs to be done to elucidate these and other factors governing these reactions.

In summary, a useful and convenient synthesis of hetero- or carbocycles has been developed using the palladium-catalyzed annulation of internal alkynes from aromatic or cyclic vinylic halides or triflates. The reactions proceed under relatively mild conditions and use

easily accessible starting materials. The process works best with hindered alkynes containing tertiary centers and usually gives yields ranging from 50 - 80 %.

ACKNOWLEDGMENTS

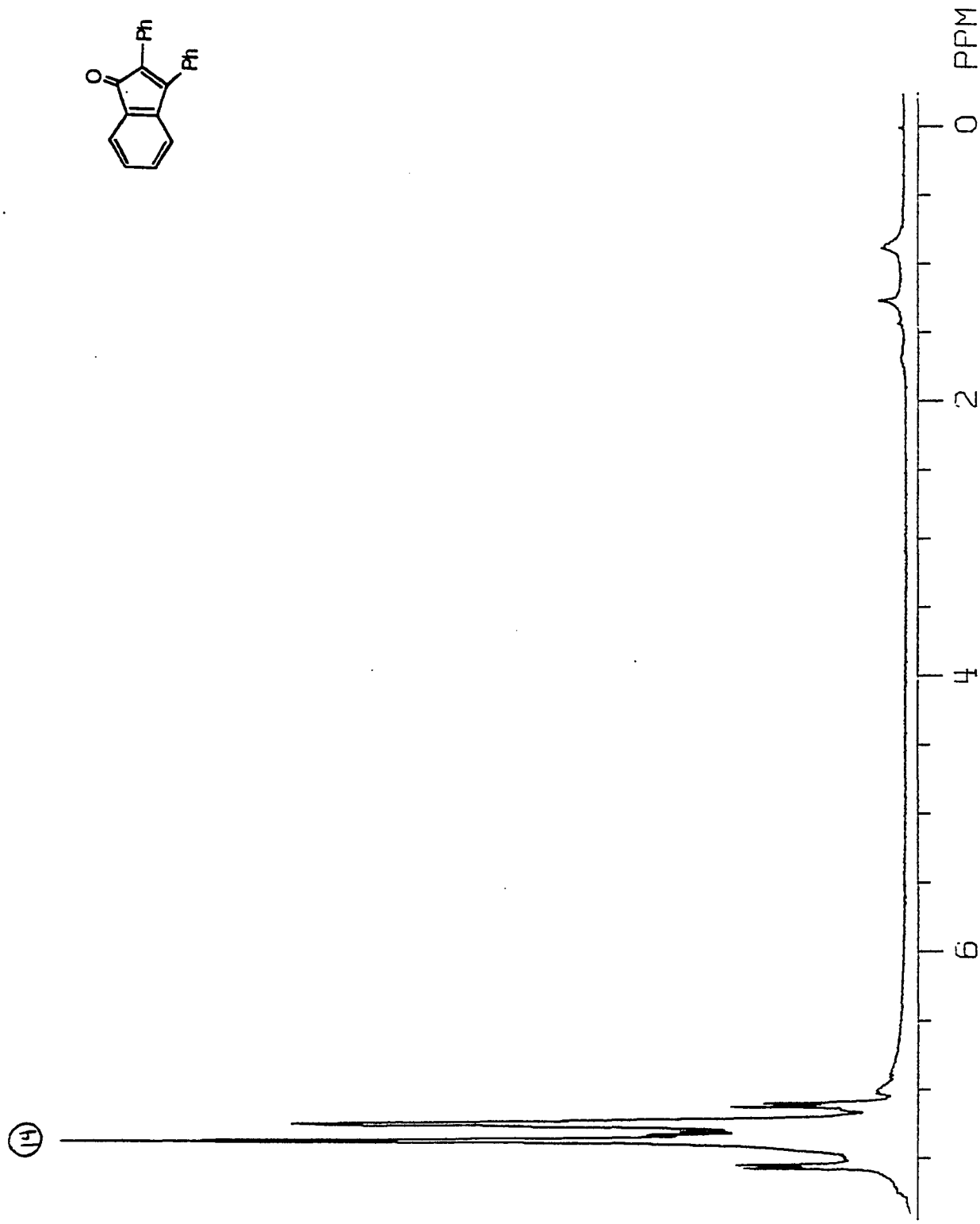
I would like to thank my major professor, Richard C. Larock, for his guidance, kindness, understanding, patience, and financial support during the course of this work. It's been a pleasure to work for such a fantastic person!

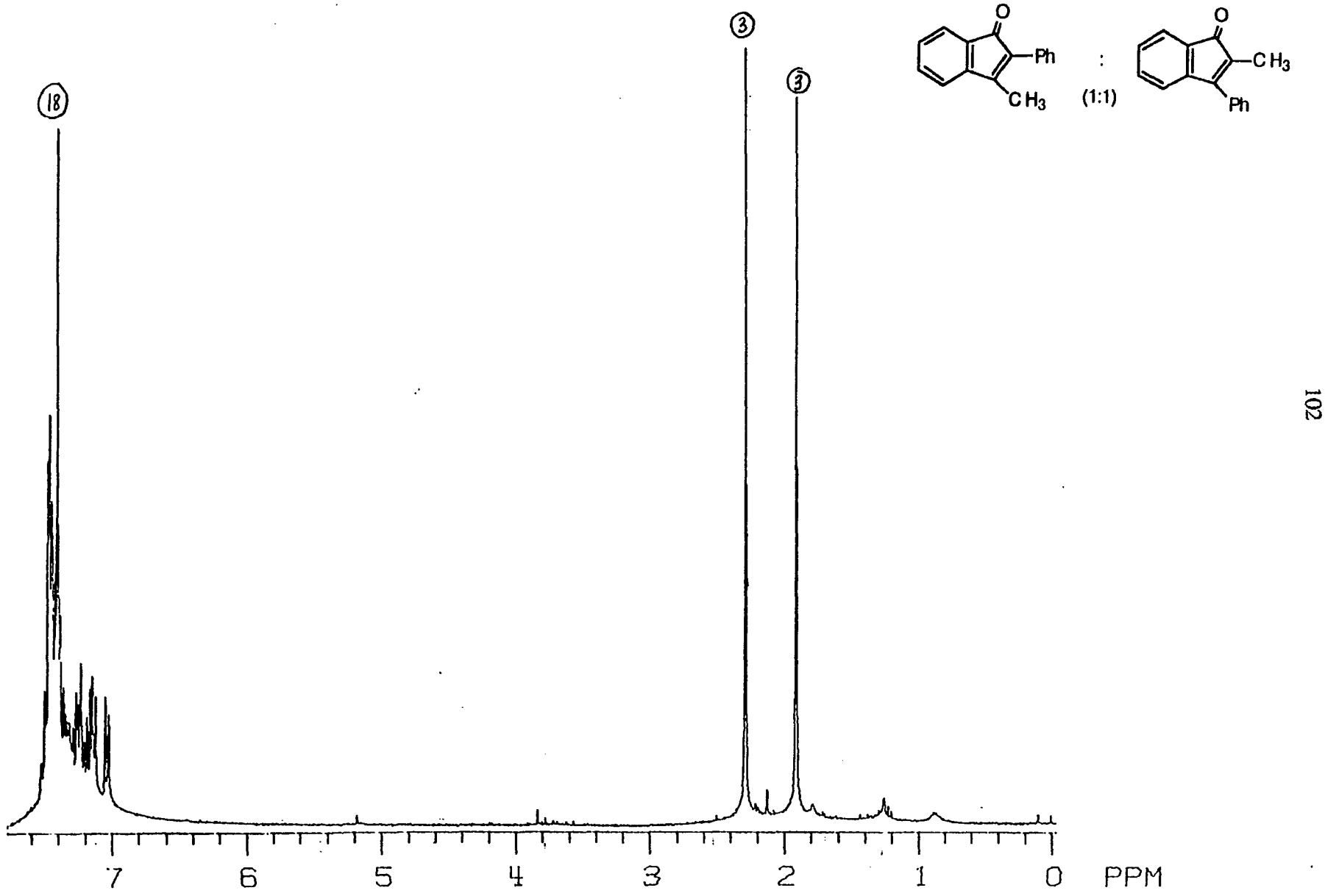
I would to thank all the members in the Larock group, especially Suleka de Silva, for the innumerable conversations that were quite interesting, helpful, and often funny.

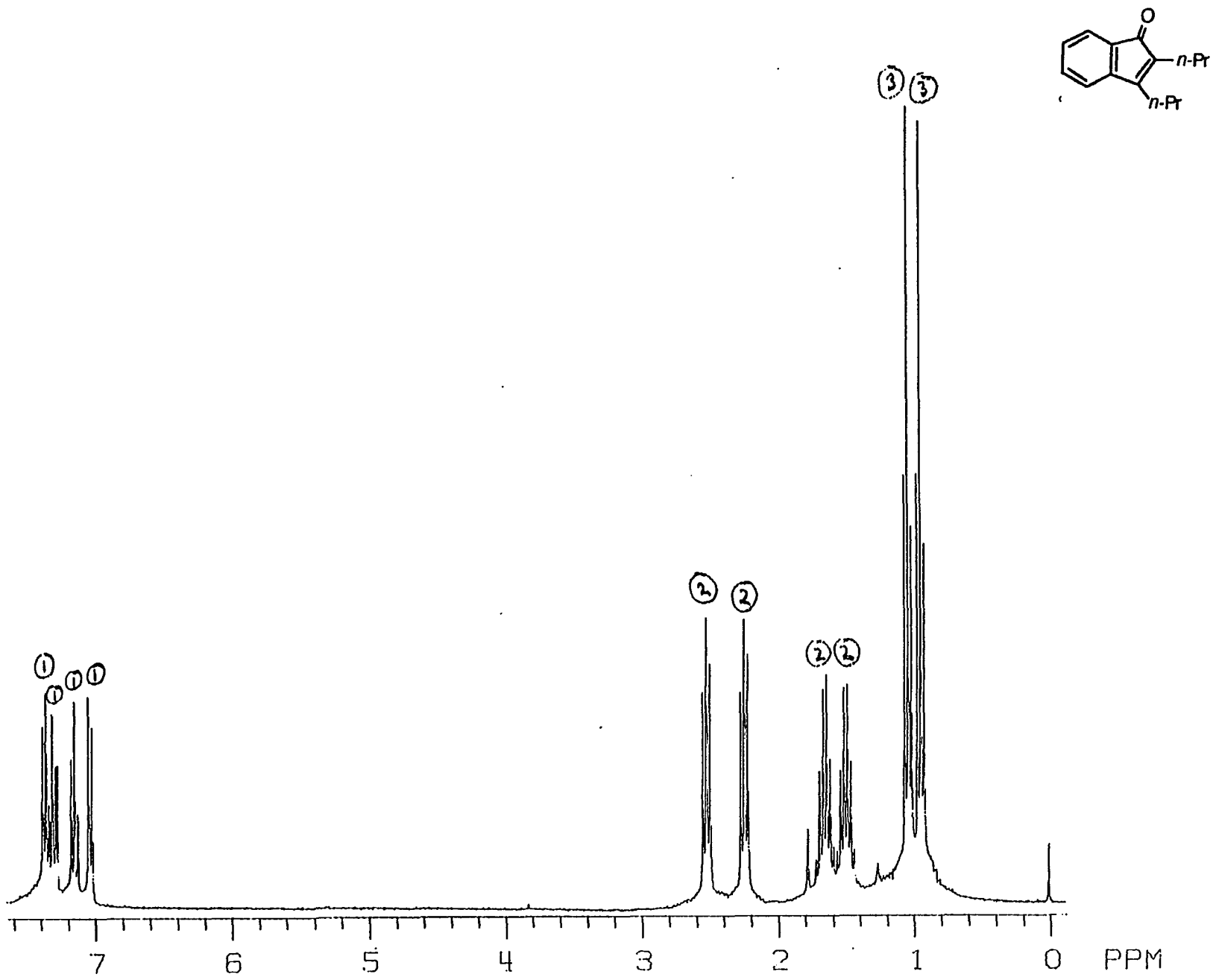
I would like to thank my parents, Joe and Jackie, for their encouragement, support, and understanding. I was lucky to be born into such a great family.

Most of all, I would like to thank my wife, Susan, for her love, her patience, and making me laugh during the last five years.

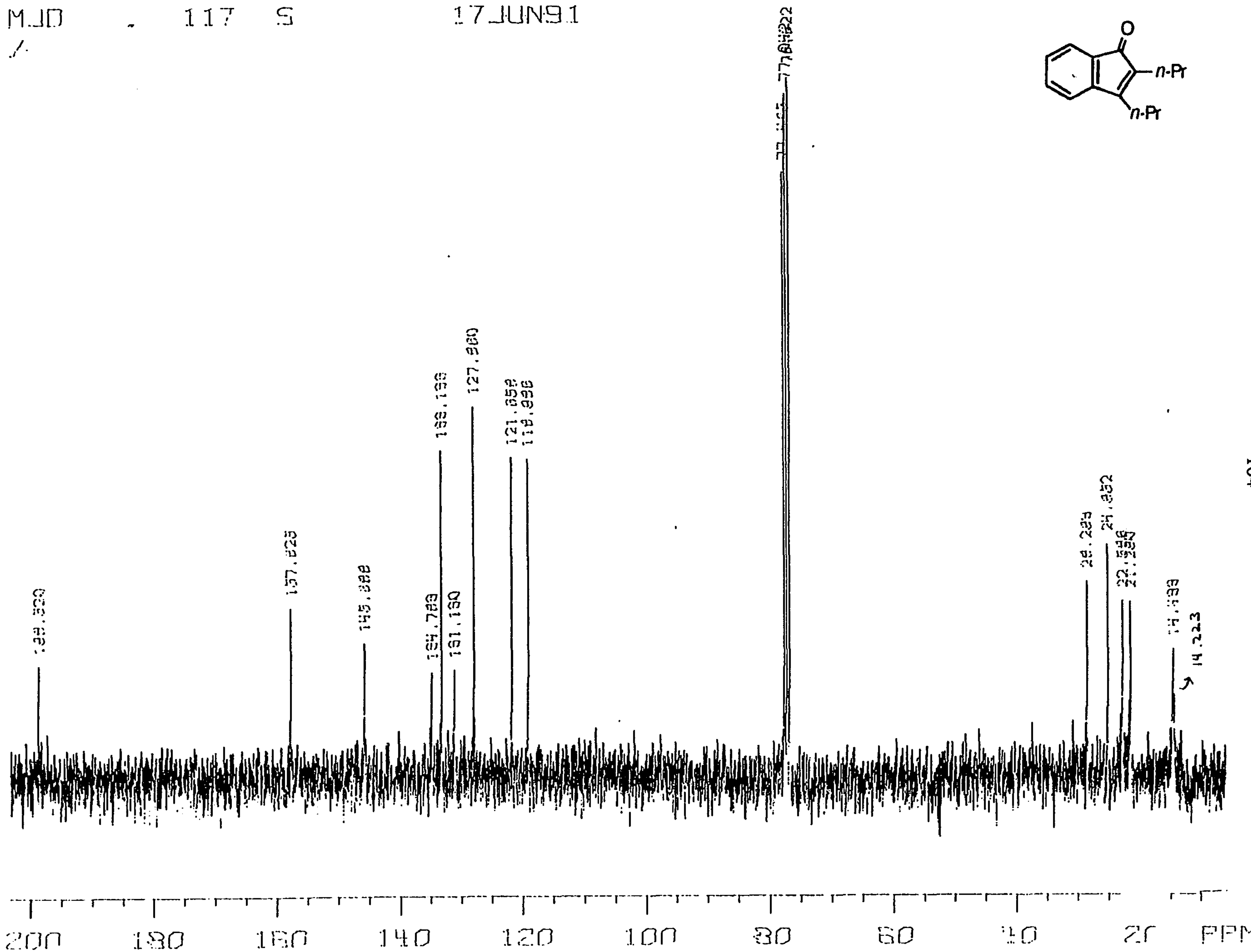
APPENDIX A: CHAPTER 1 ^{1}H AND ^{13}C NMR INDENONE SPECTRA


Ph
Ph
O
PPM
0
2
4
6
(4)

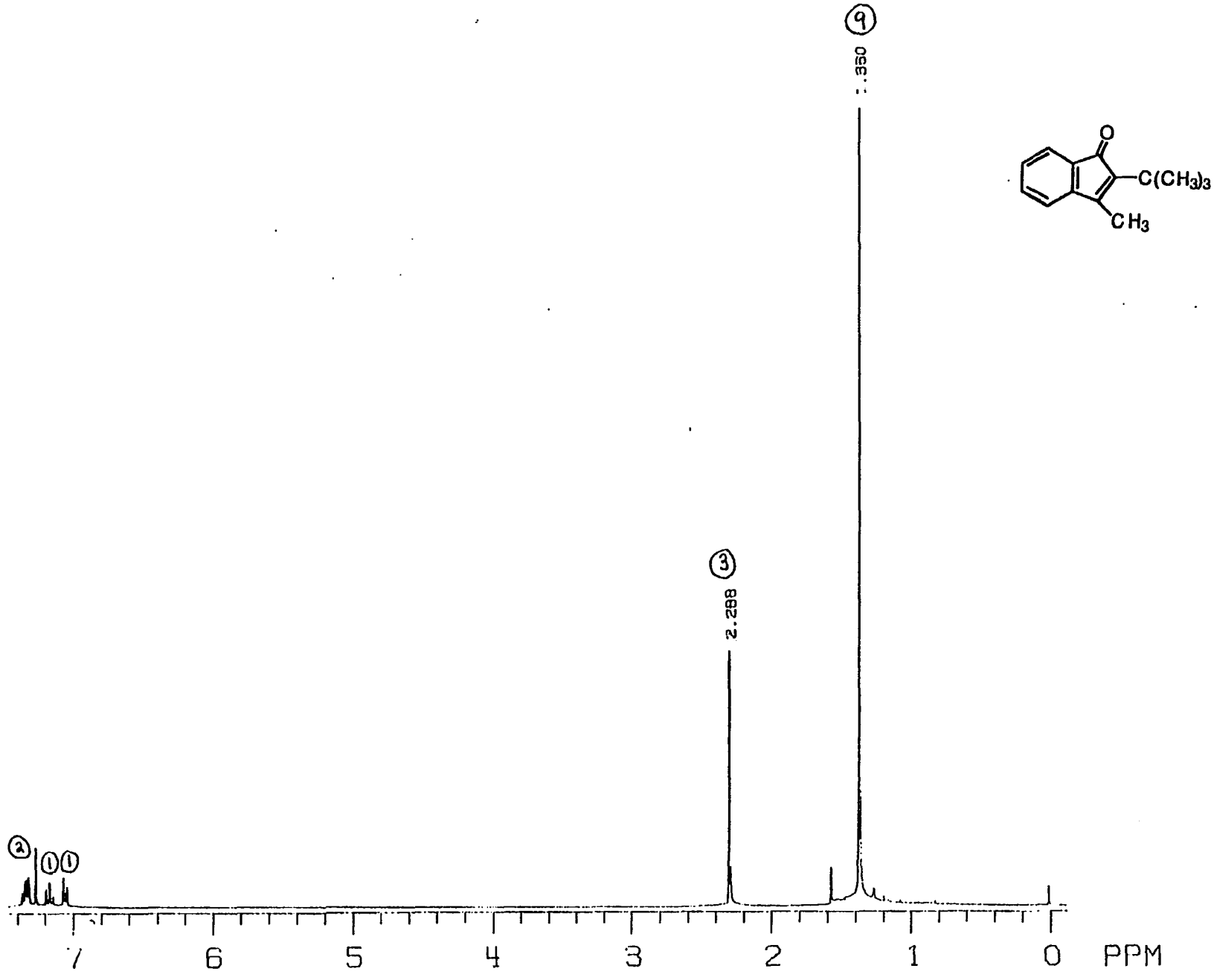

18
3
3
O
Ph
CH3
:
(1:1)
O
CH3
Ph
7
6
5
4
3
2
1
0
PPM

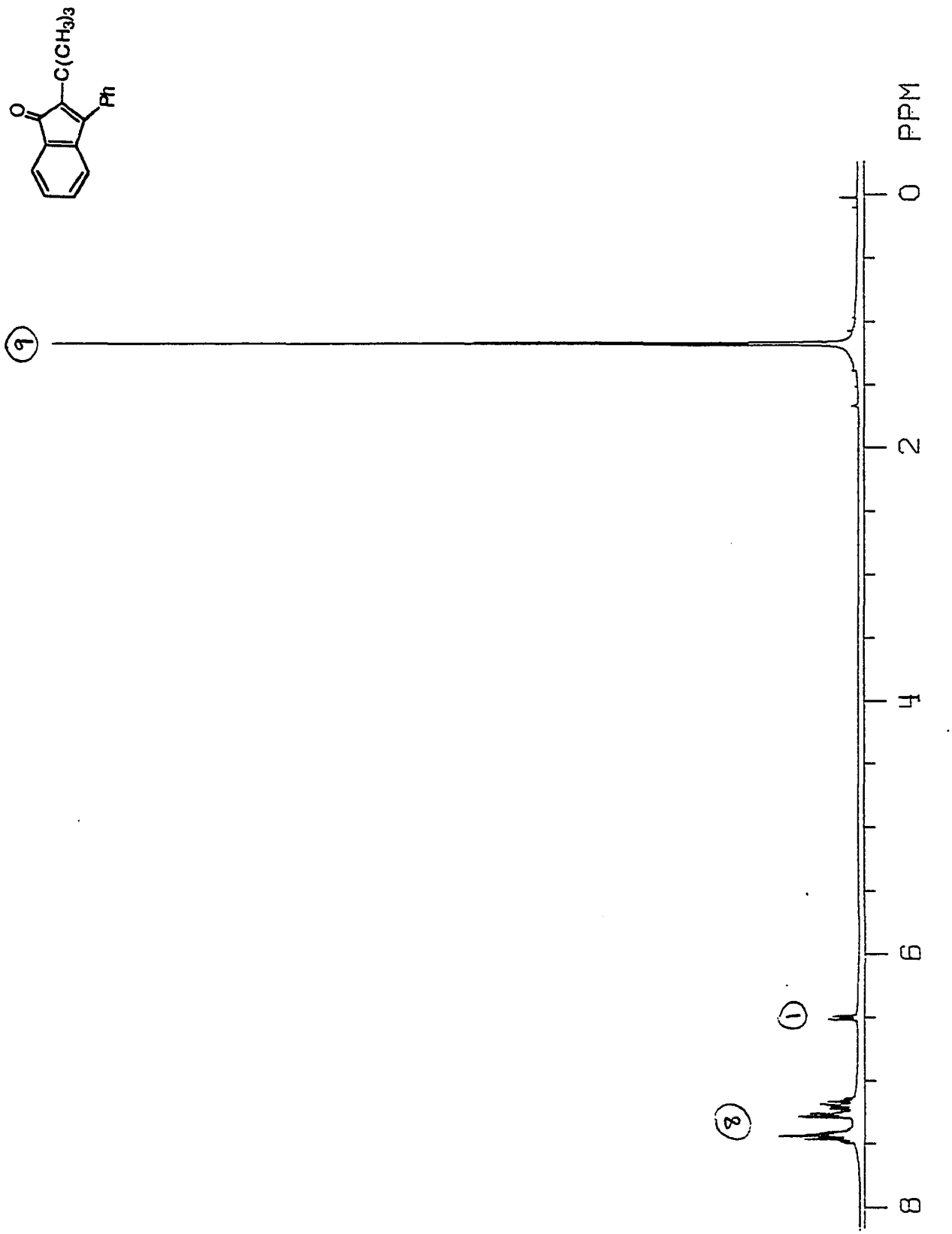

O
n-Pr
n-Pr
3
3
2
2
2
2
1
1
1
1
7
6
5
4
3
2
1
0
PPM

MJD 117 S 17JUN91

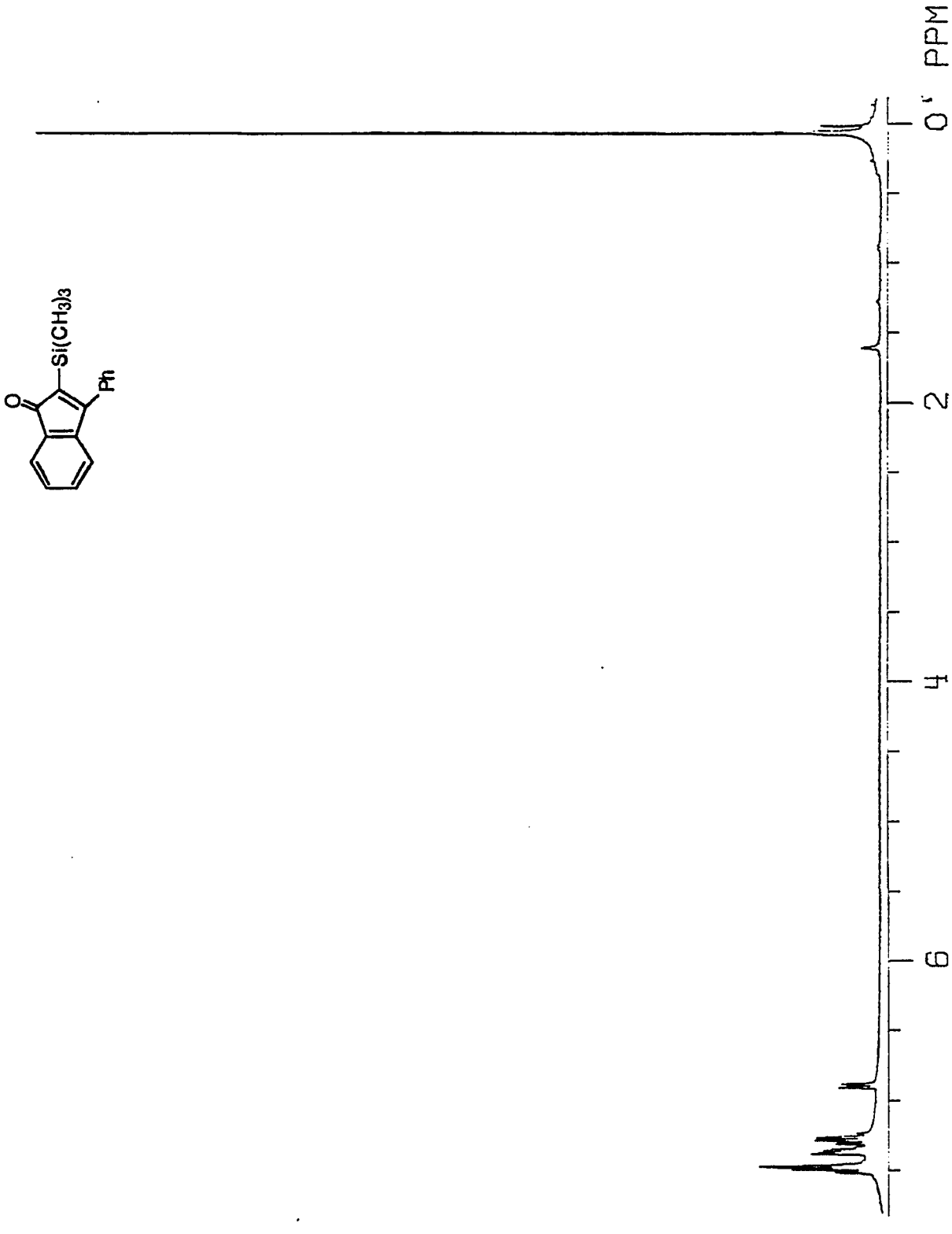


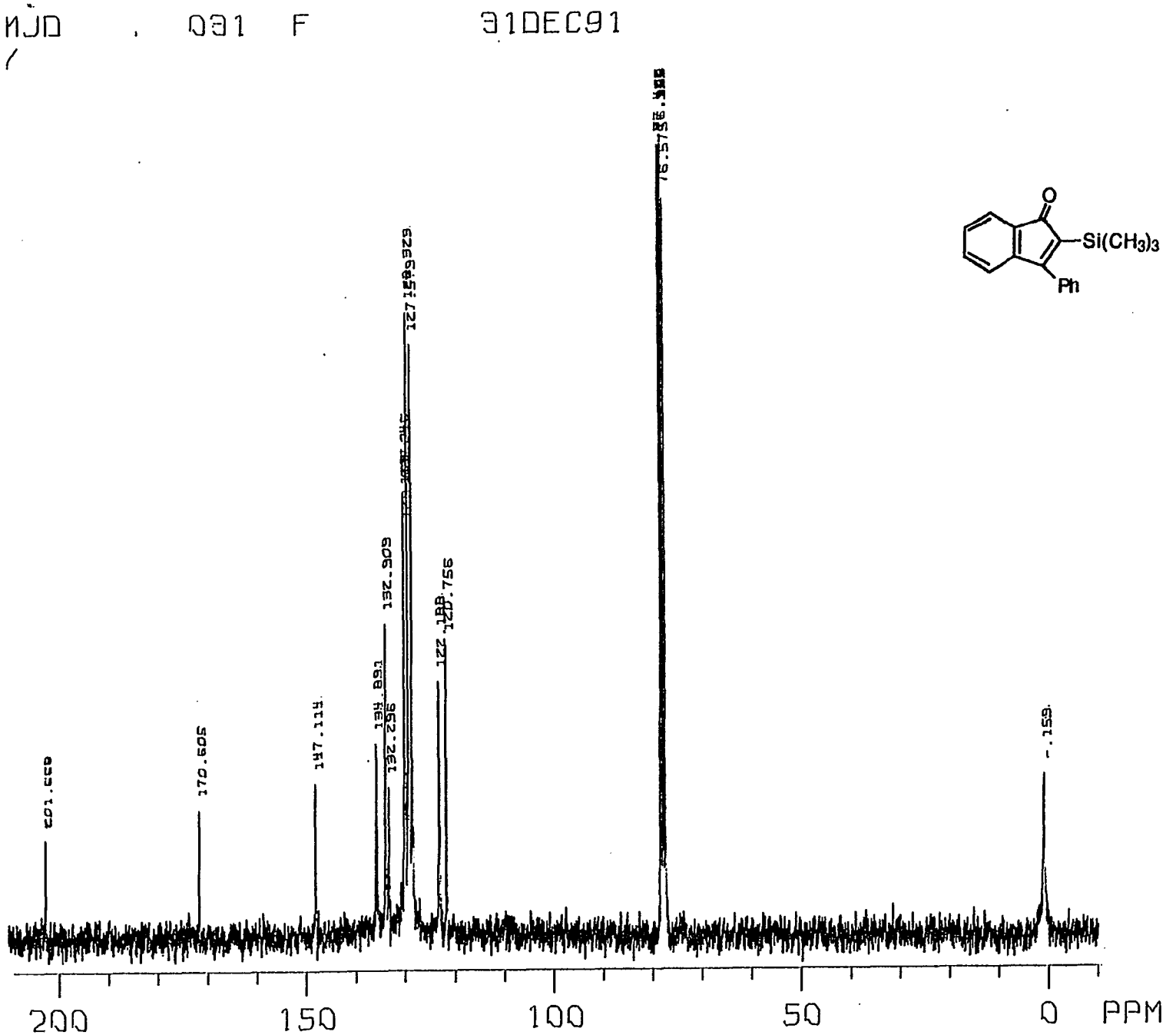
104

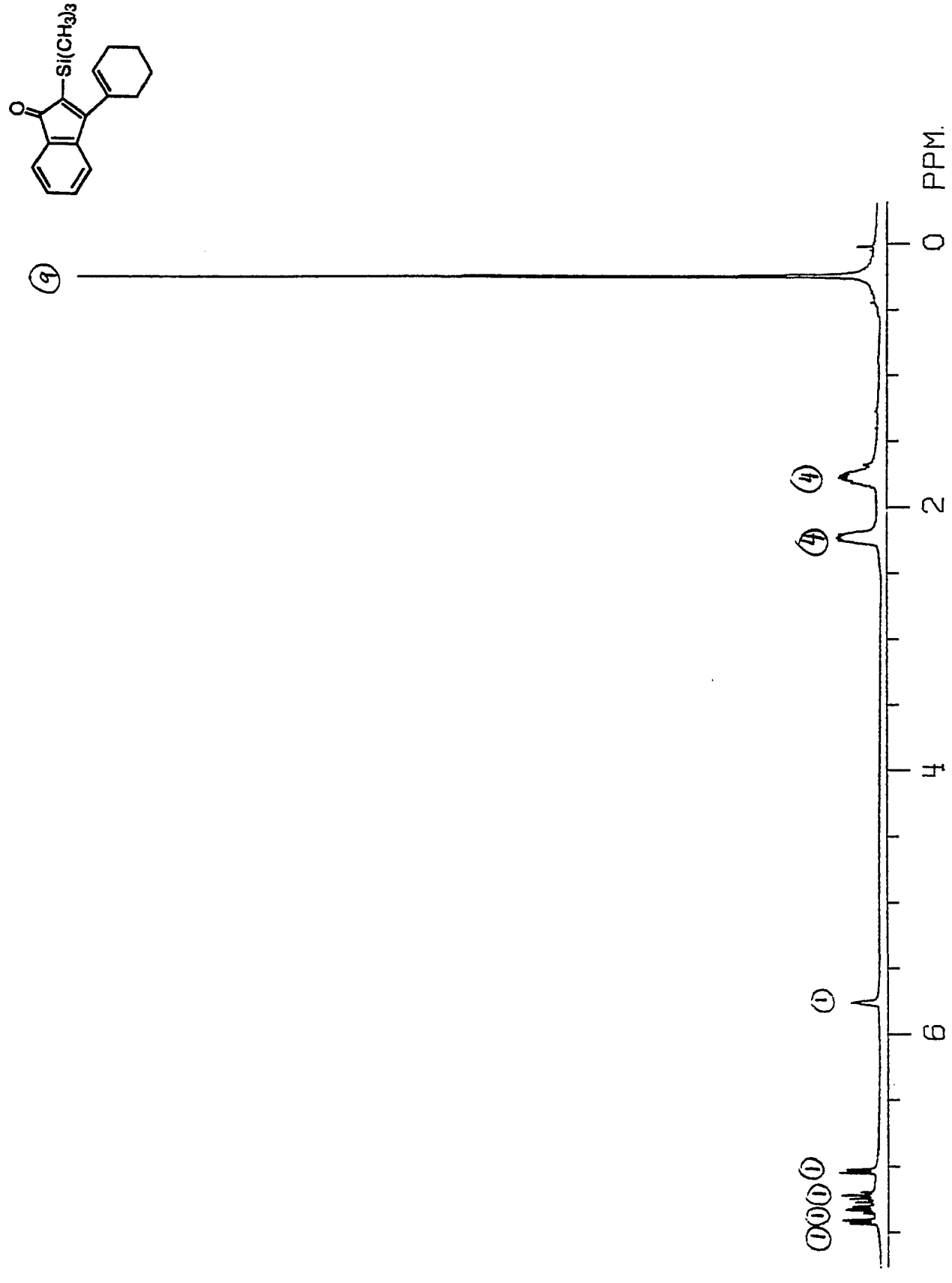

9
1.350
3
2.288
2
1
1
7
6
5
4
3
2
1
0
PPM
O
C(CH3)3
CH3

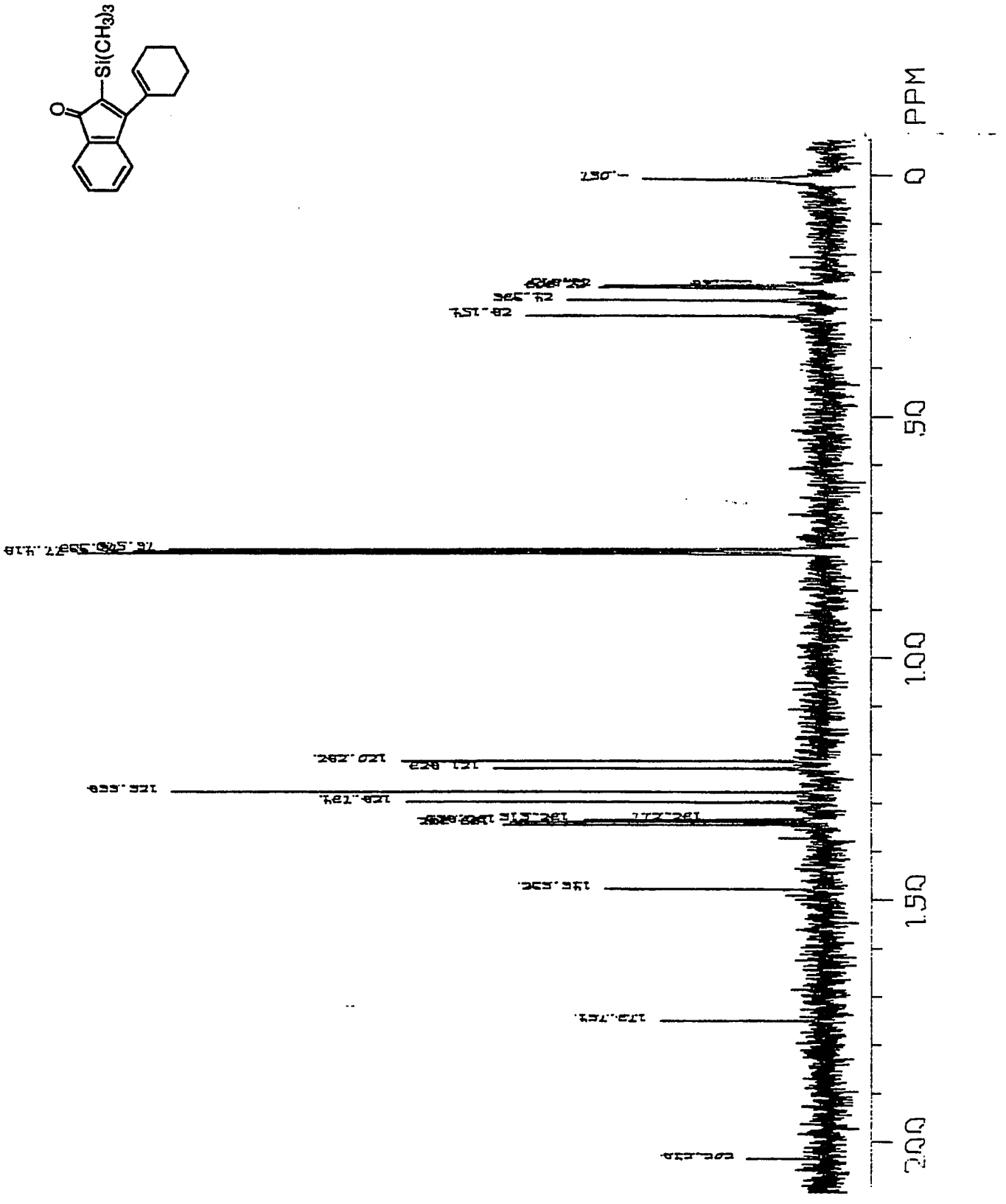

C(CH3)3
Ph
O
9
1
8
0
2
4
6
8
PPM

198.128
153.976
147.689
135.338
133.332
129.867
121.758
120.368
30.686
33.682
200
180
160
140
120
100
80
60
40
20
PPM
C(CH3)3
Ph
O

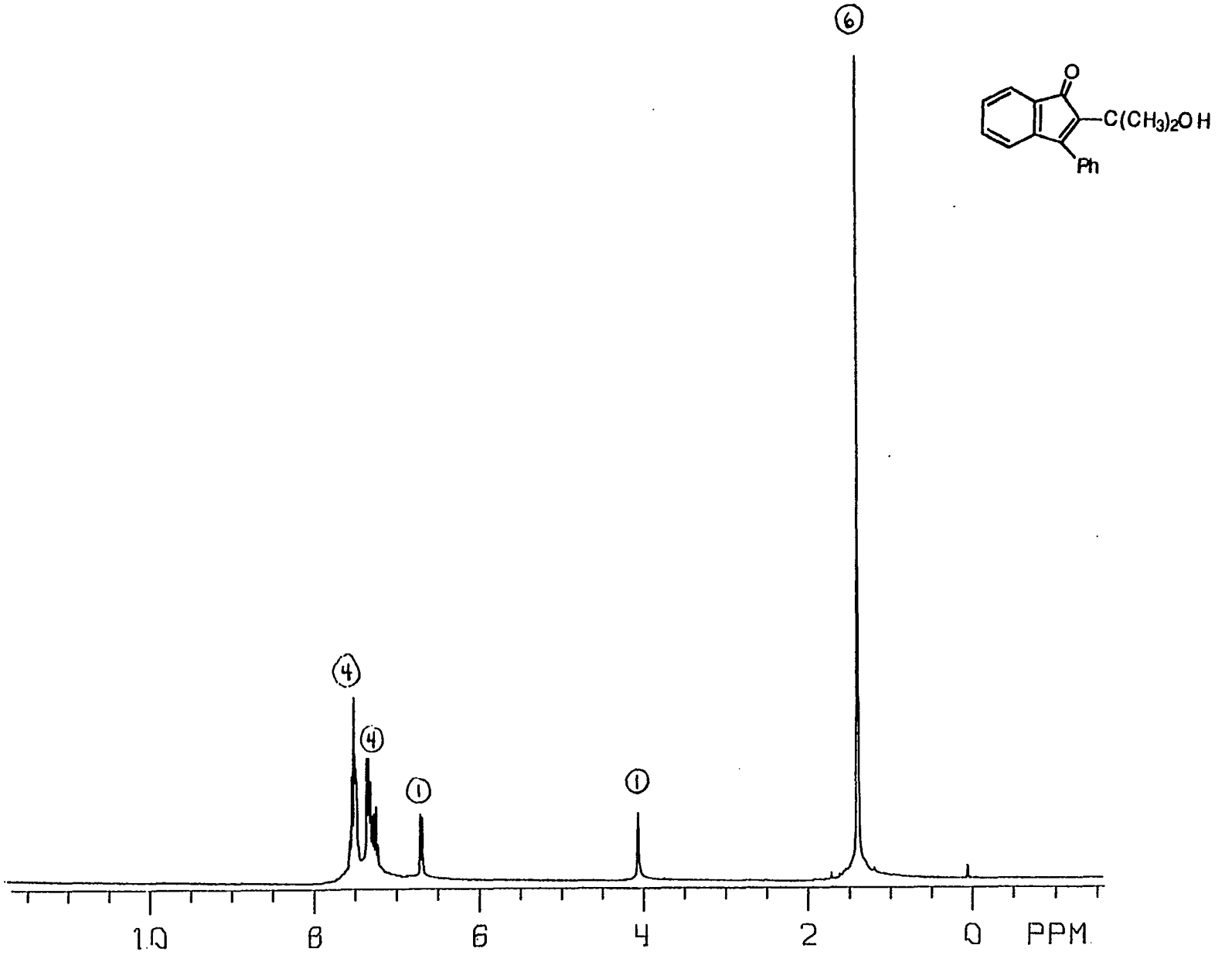

Si(CH3)3
Ph
O
0
PPM
2
4
6

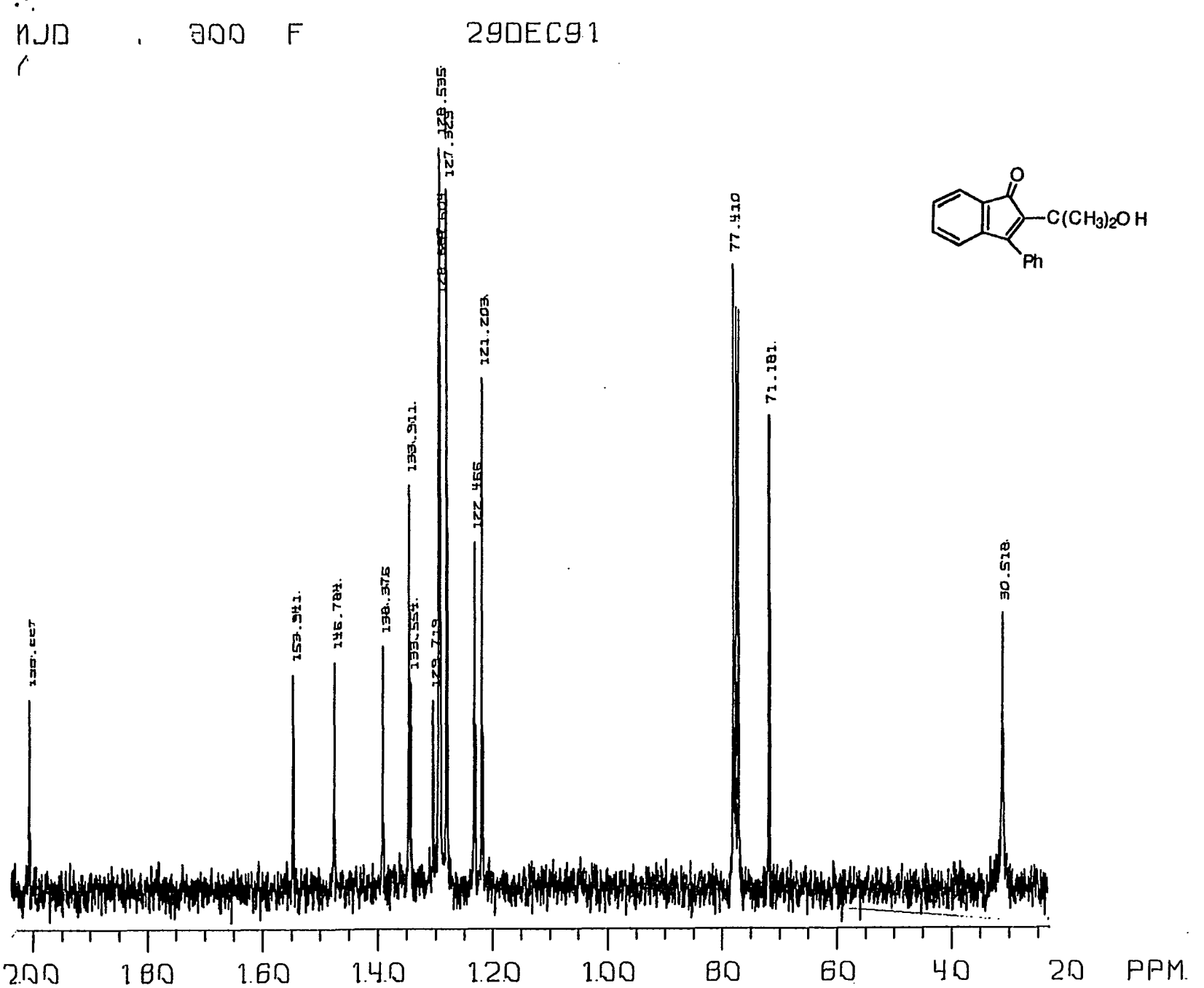

MJD . 091 F 31DEC91
201.659
170.605
147.114
132.296
132.309
127.893
120.756
76.579
-.159
O
Si(CH3)3
Ph
200
150
100
50
0
PPM

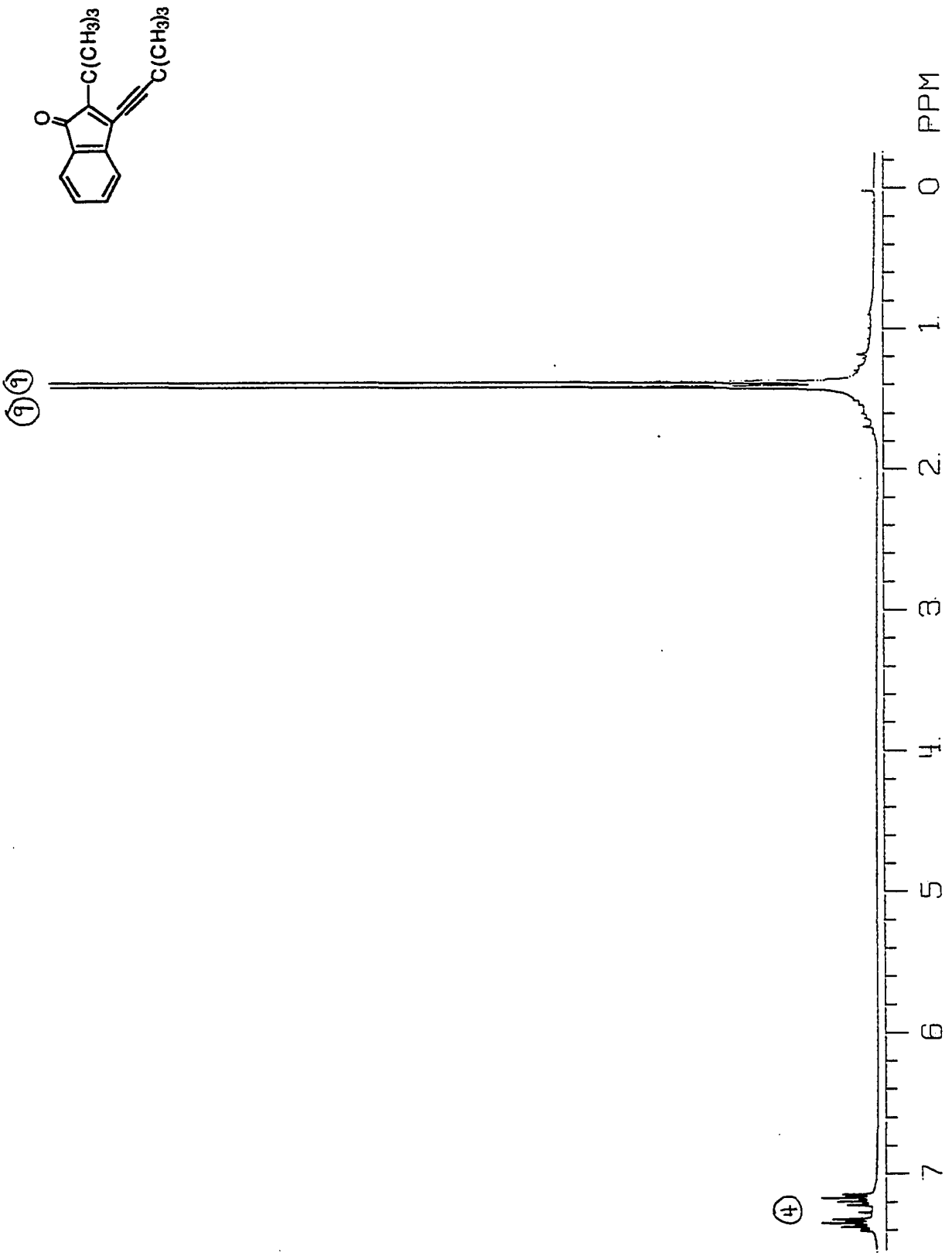

Si(CH3)3
O
9
4
4
1
1
1
1
6
4
2
0
PPM.


Si(CH3)3
O
200
150
100
50
0
PPM

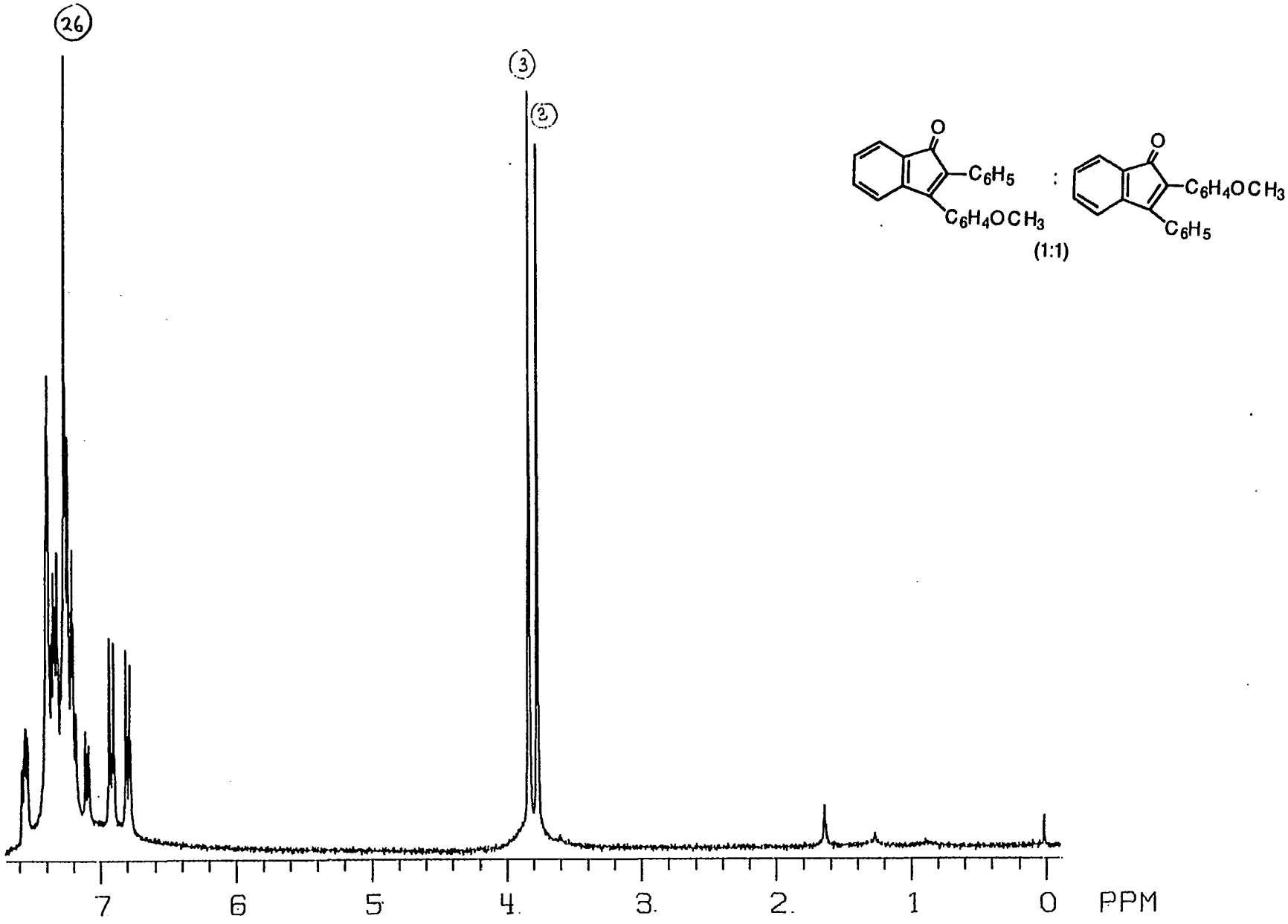
MJD . 130A F. 29DEC91



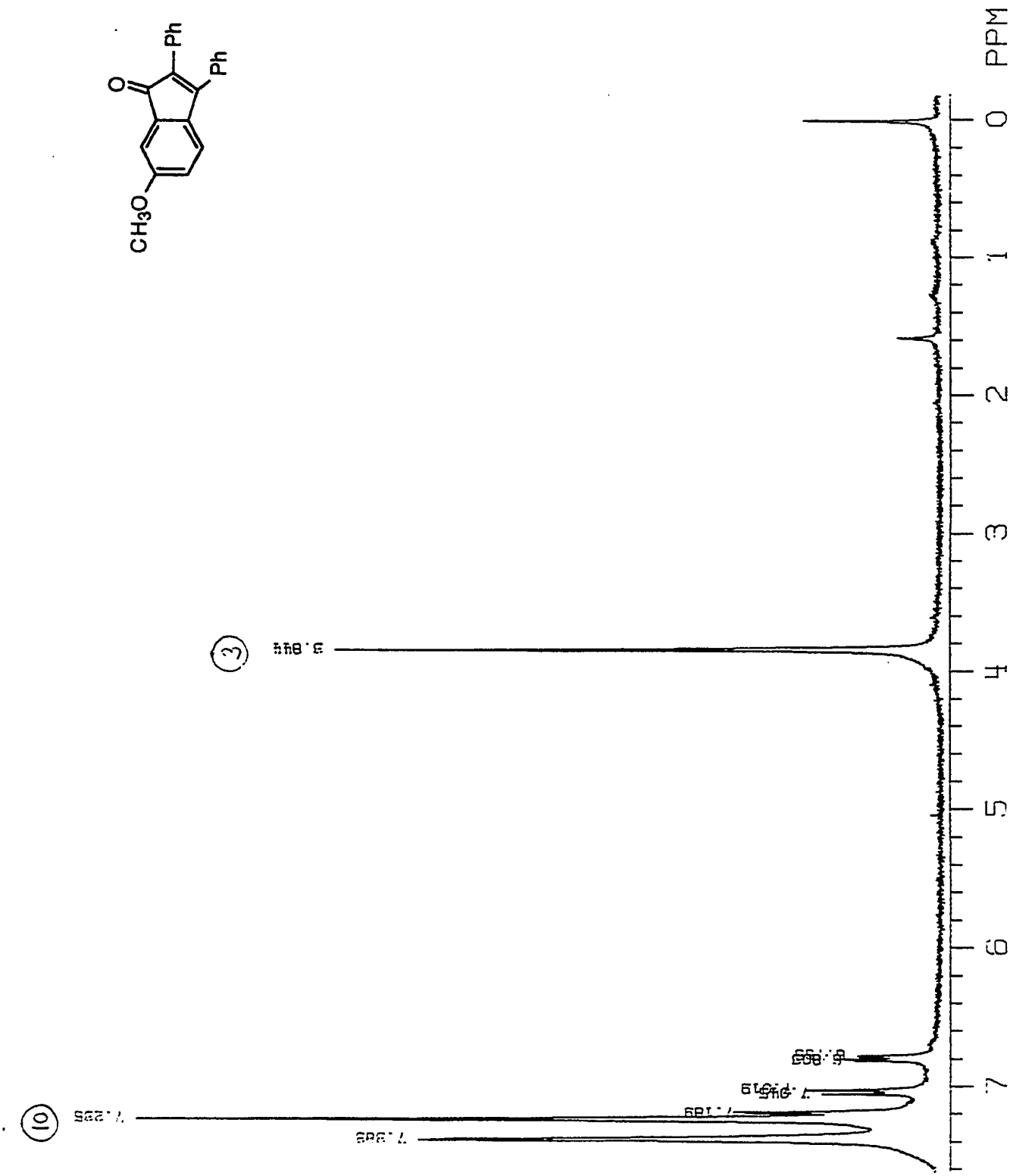

29DEC91
O
C(CH3)2OH
Ph
77.410
71.181
30.518
121.203
133.911
146.784
153.941
200
180
160
140
120
100
80
60
40
20
PPM

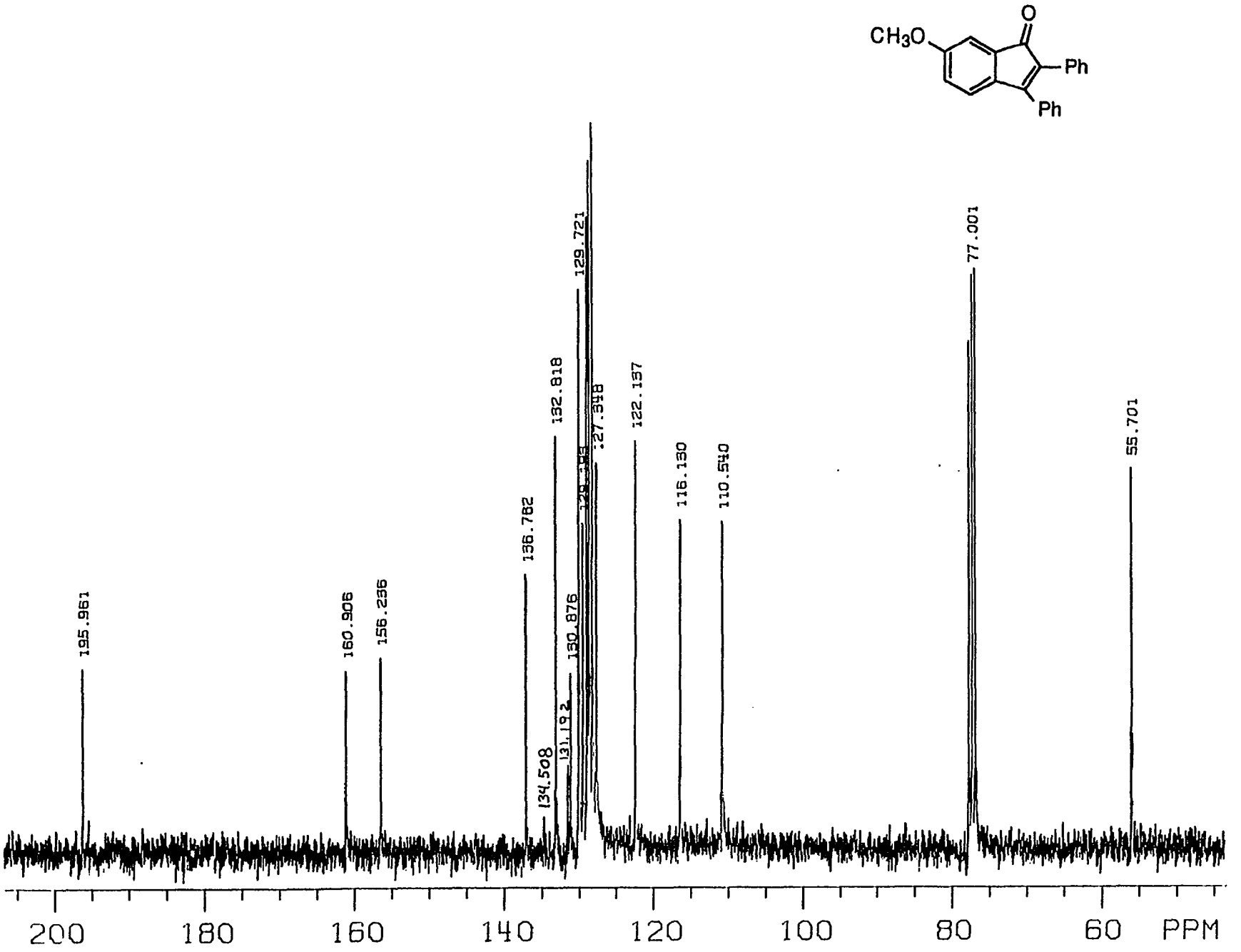

C(CH3)3
C(CH3)3
O
9
1
4
7
6
5
4
3
2
1
0
PPM

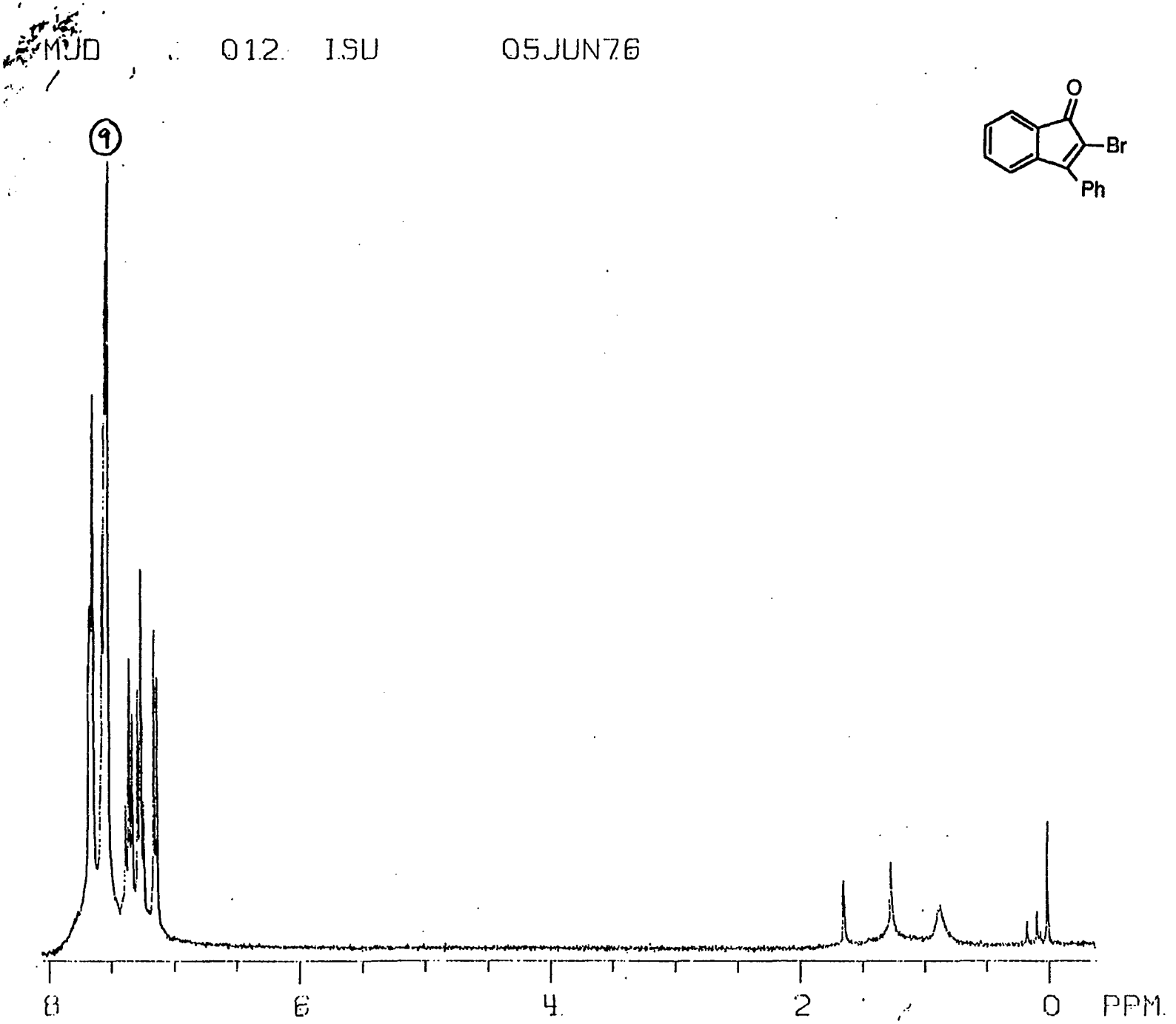
197.930
145.916
144.050
135.915
133.452
130.061
128.374
121.282
119.585
118.298
77.
74.152
38.961
29.031
200
180
160
140
120
100
80
60
40
20
PPM
O
C(CH3)3
C(CH3)3

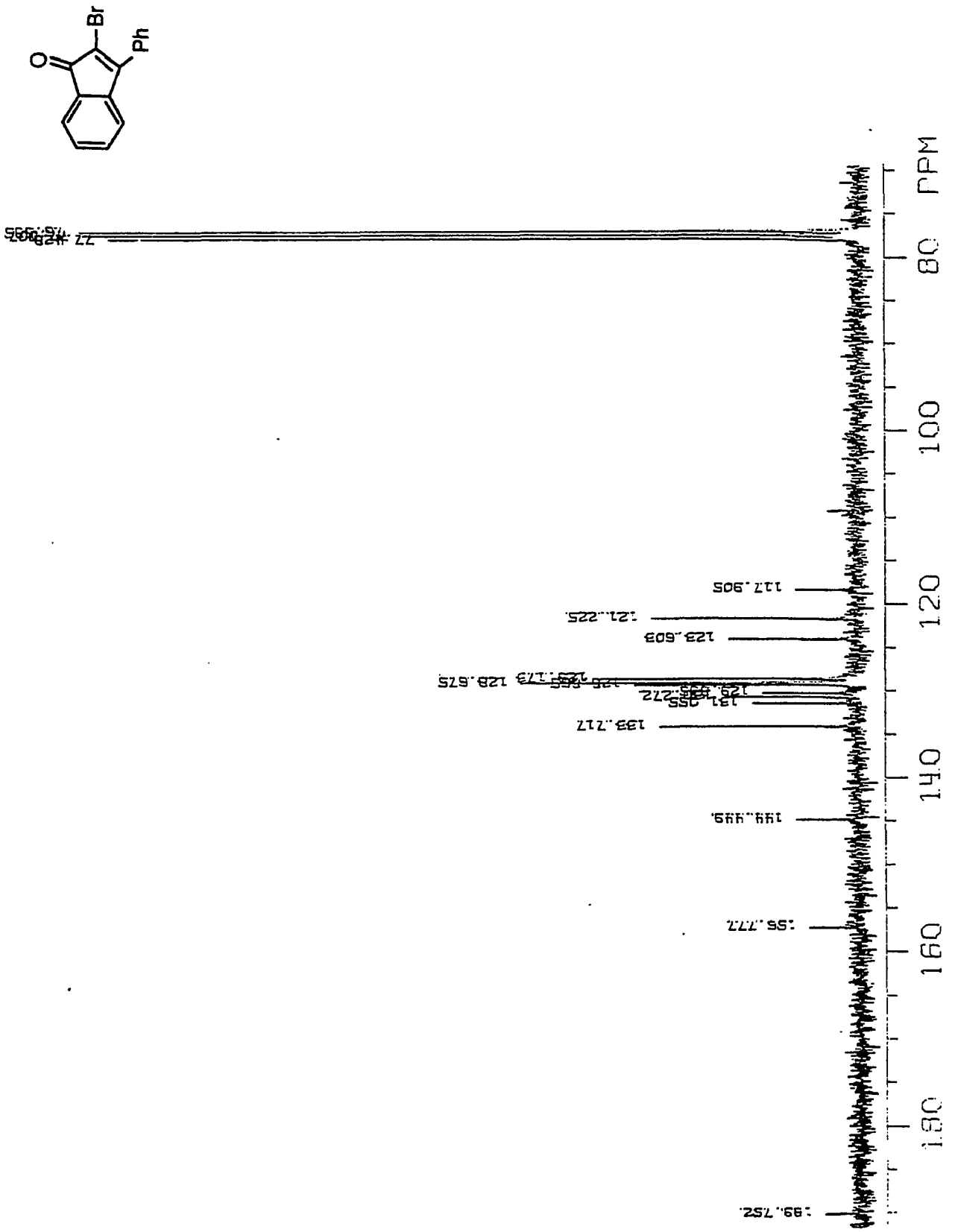


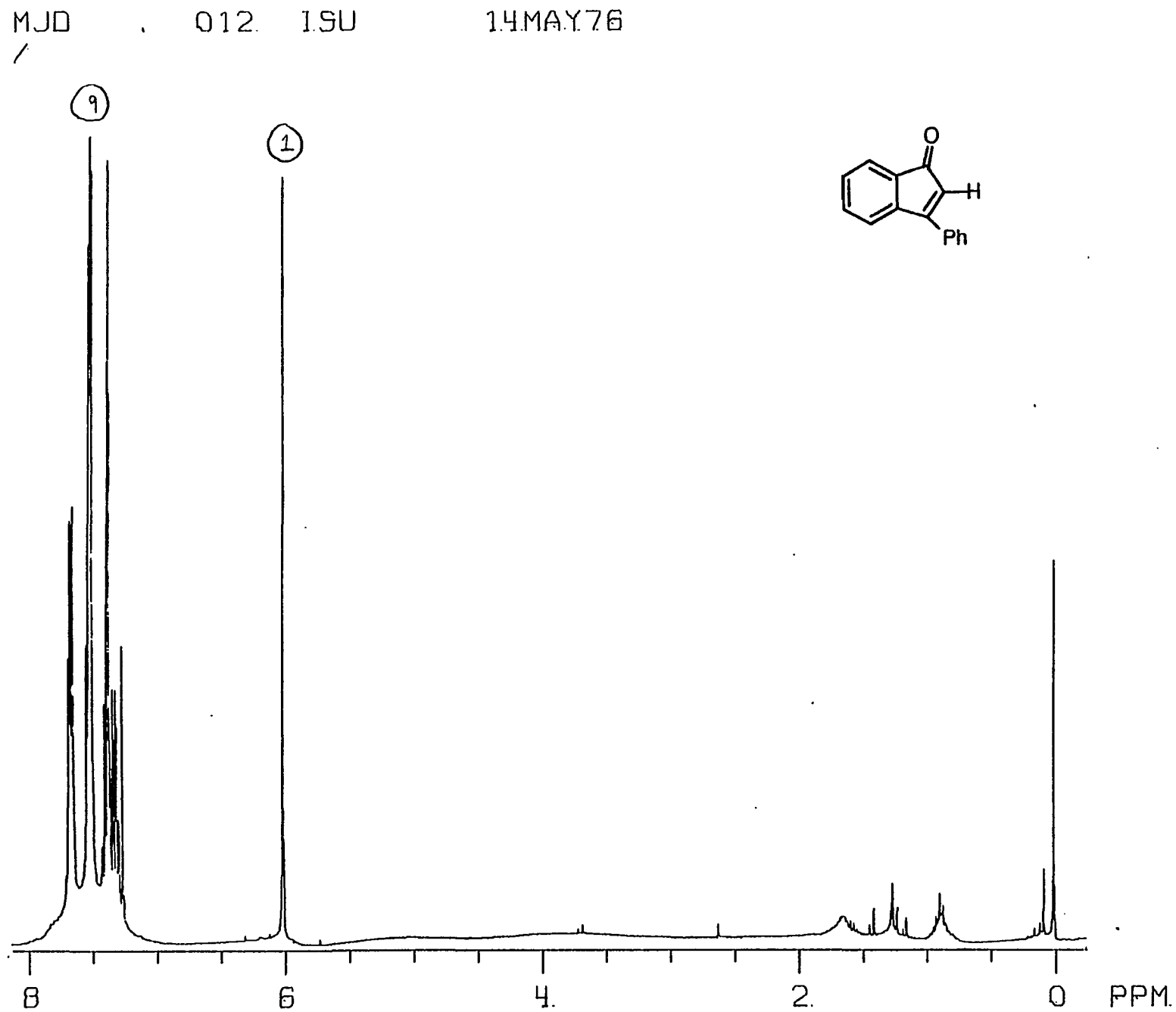
(1:1)

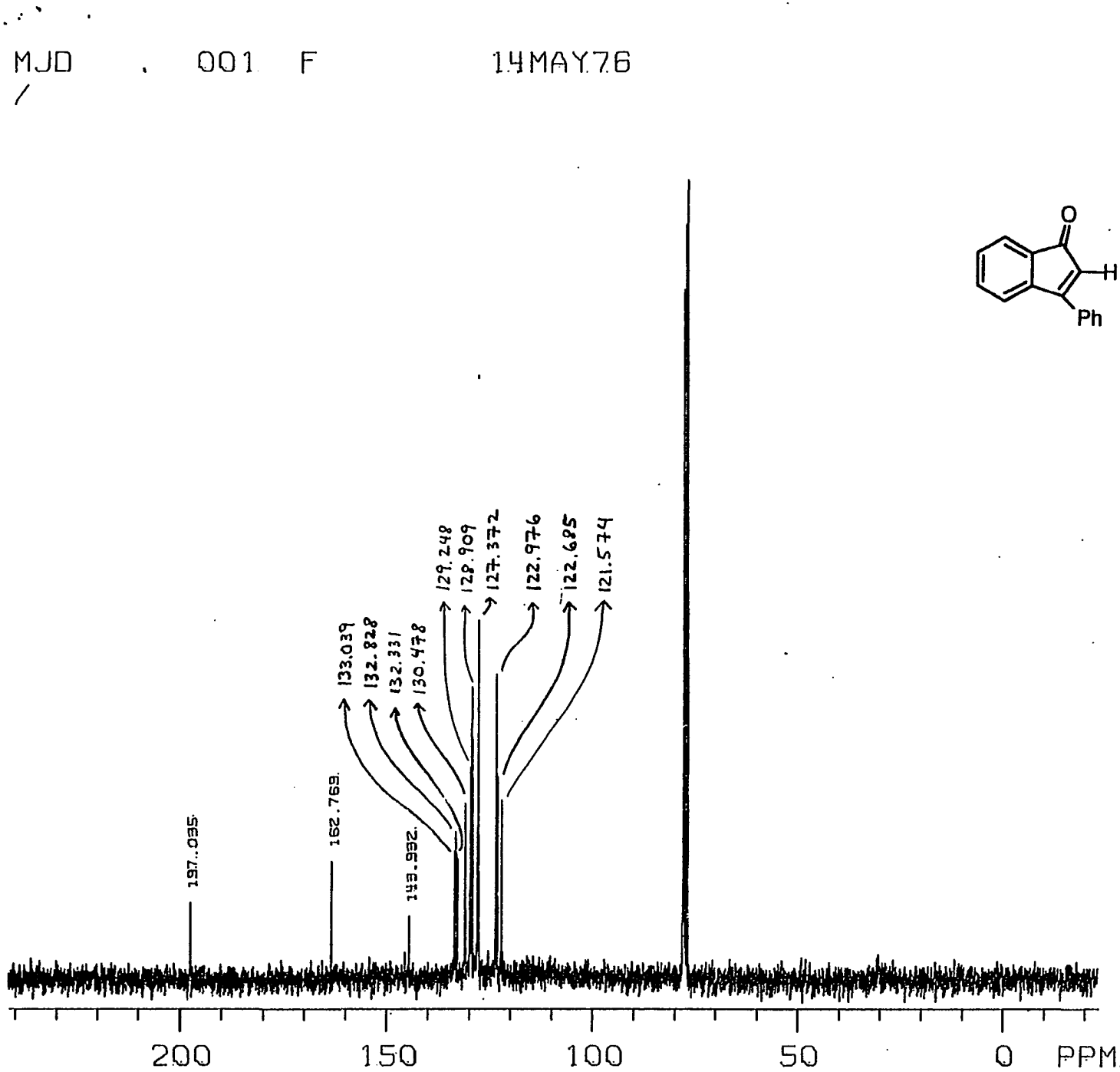

Ph
Ph
O
CH_3O
PPM
0
1
2
3
4
5
6
7
3.884
10


CH3O
O
Ph
Ph
195.961
160.906
156.236
136.782
134.508
132.818
131.192
130.876
129.721
127.548
122.137
116.130
110.540
77.001
55.701
200
180
160
140
120
100
80
60
PPM

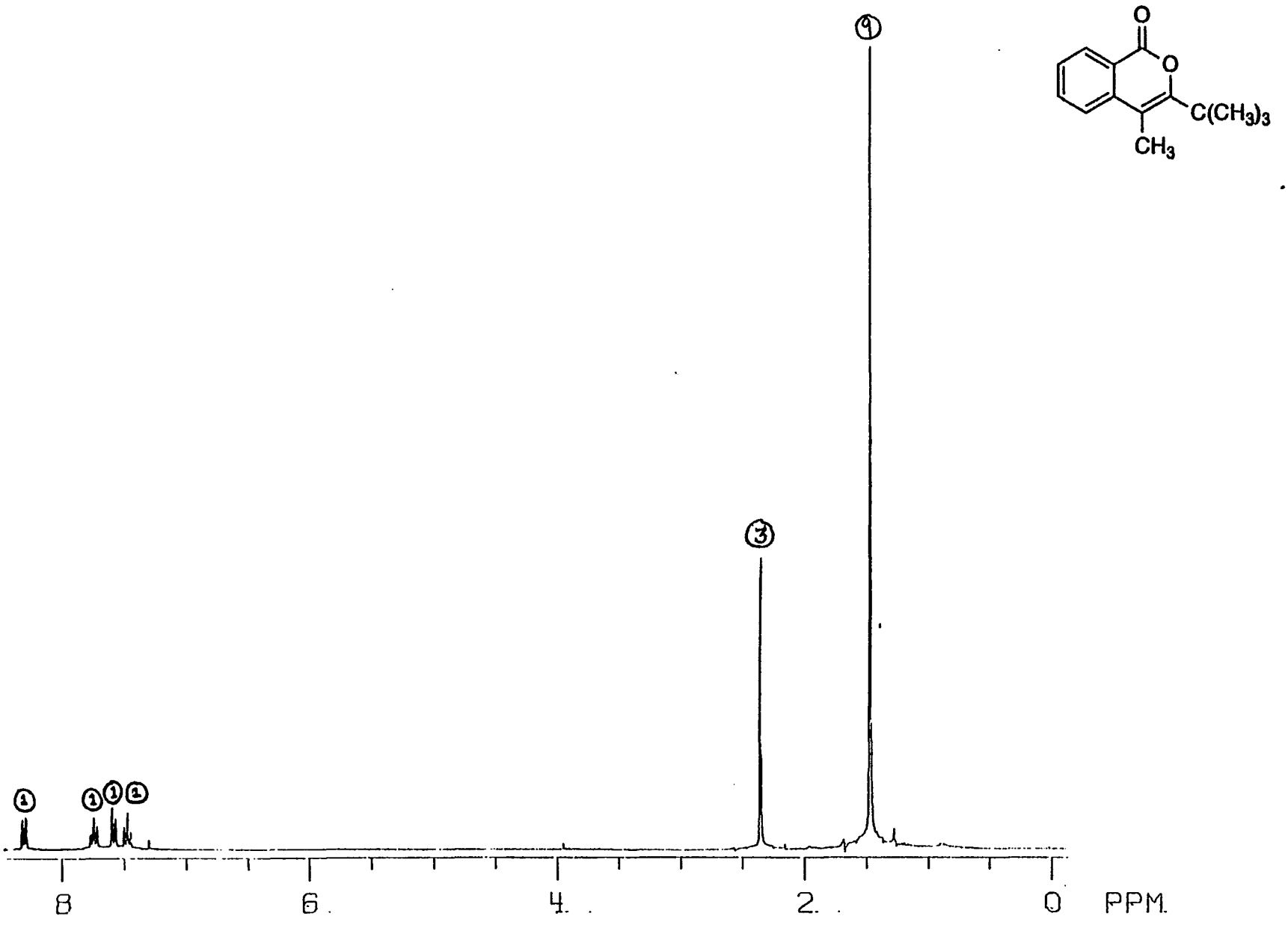

MJD 012 1.SU 05JUN76
9
O
Br
Ph
8
6
4
2
0
PPM


Br
Ph
O
PPM
180
160
140
120
100
80
77.425
77.935
117.905
121.225
123.603
128.673
128.773
129.272
131.055
133.717
144.449
155.777
189.752

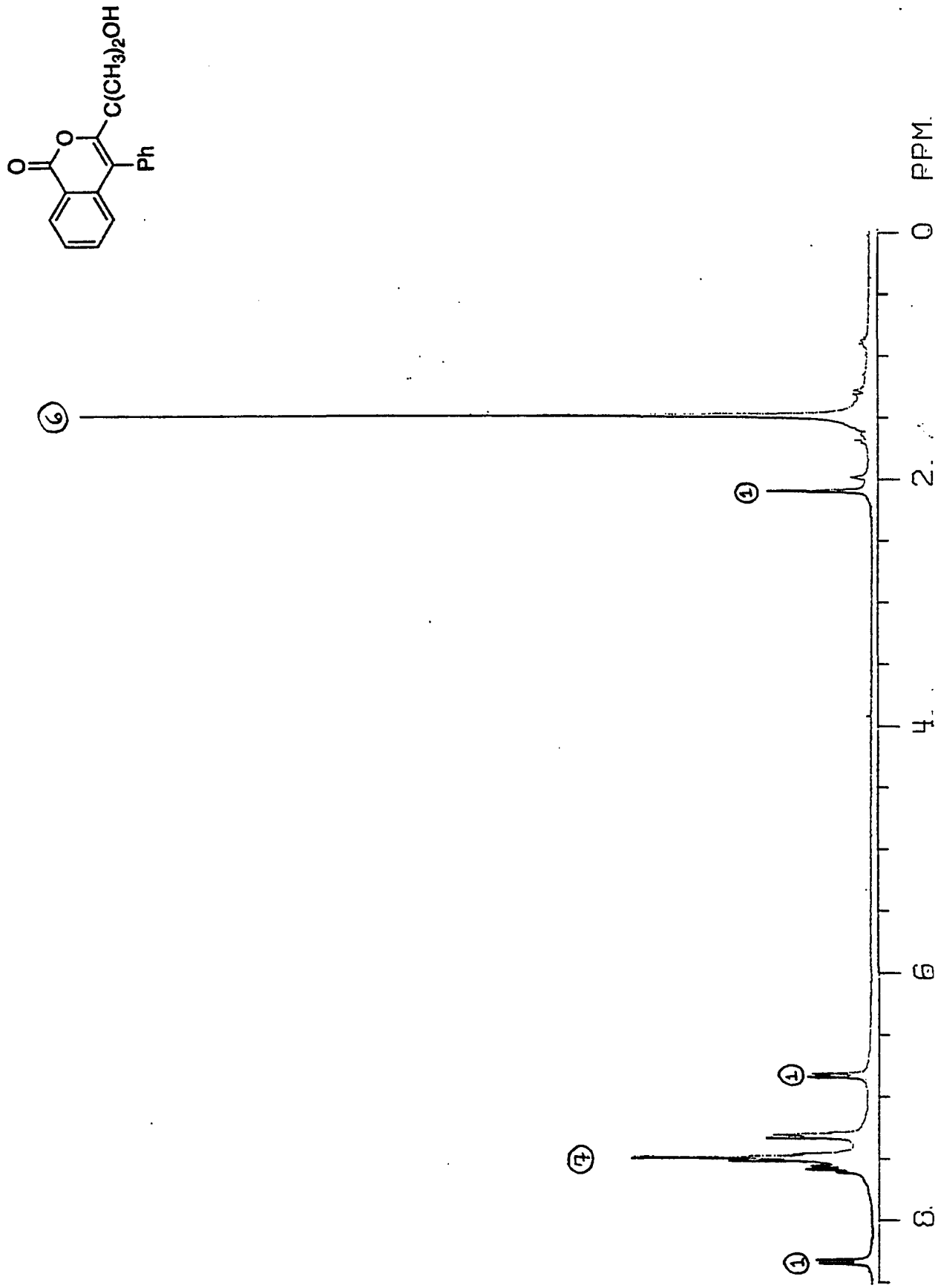

MJD . 012. 1SU 14MAY76
9
1
O
H
Ph
8
6
4.
2.
0
PPM.

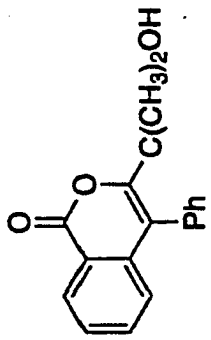

MJD . 001 F 14MAY76
O
H
Ph
197.095
162.769
143.992
133.039
132.828
132.331
130.478
129.248
128.909
127.372
122.976
122.685
121.574
200
150
100
50
0
PPM

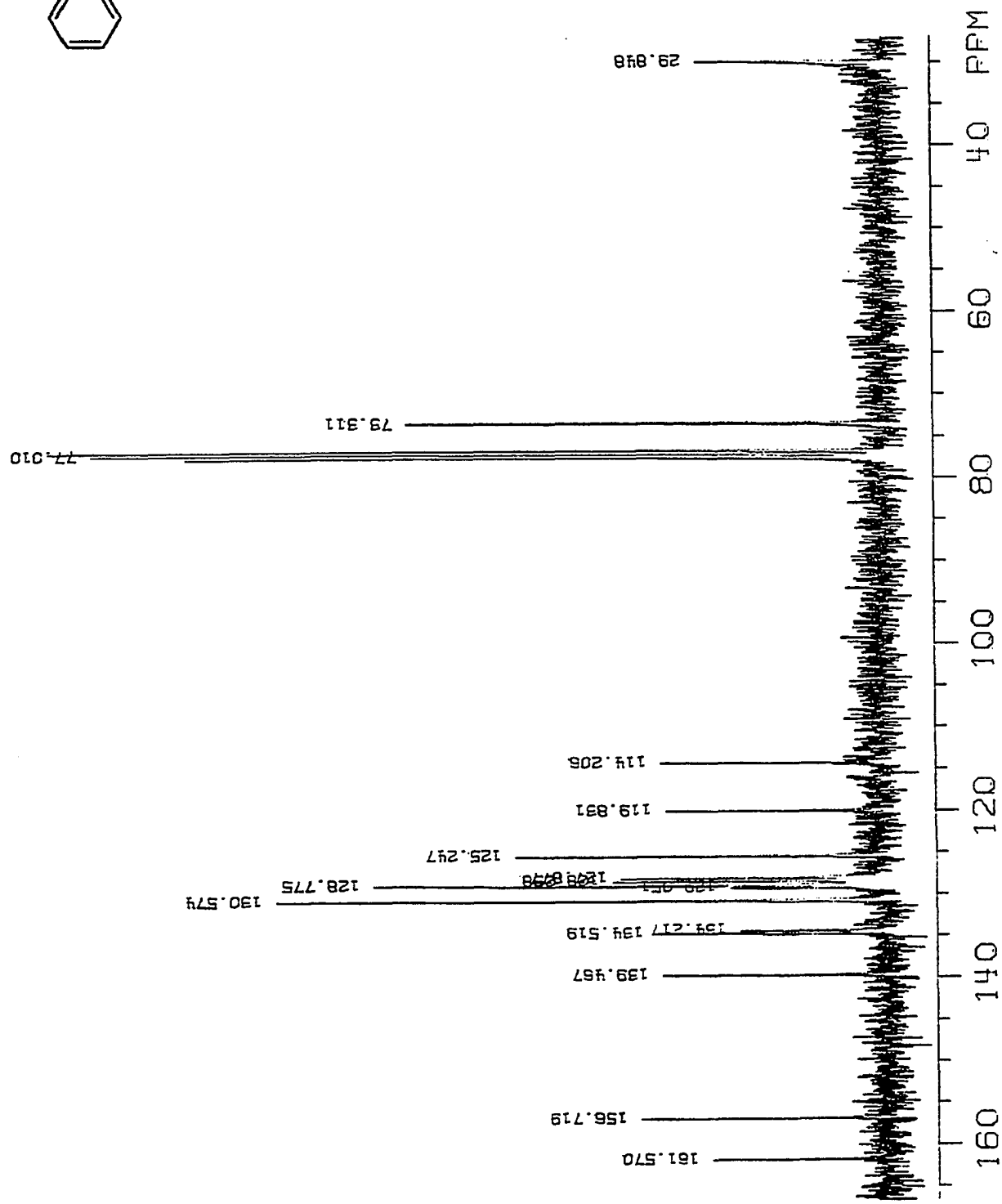
APPENDIX B: CHAPTER 2 ^{1}H AND ^{13}C NMR ISOCOUMARIN AND α-PYRONE SPECTRA

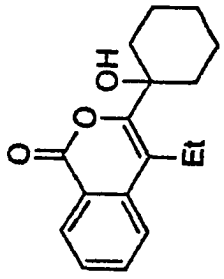

O
O
C(CH3)3
CH3
9
3
1
1
1
2
8
6
4
2
0
PPM

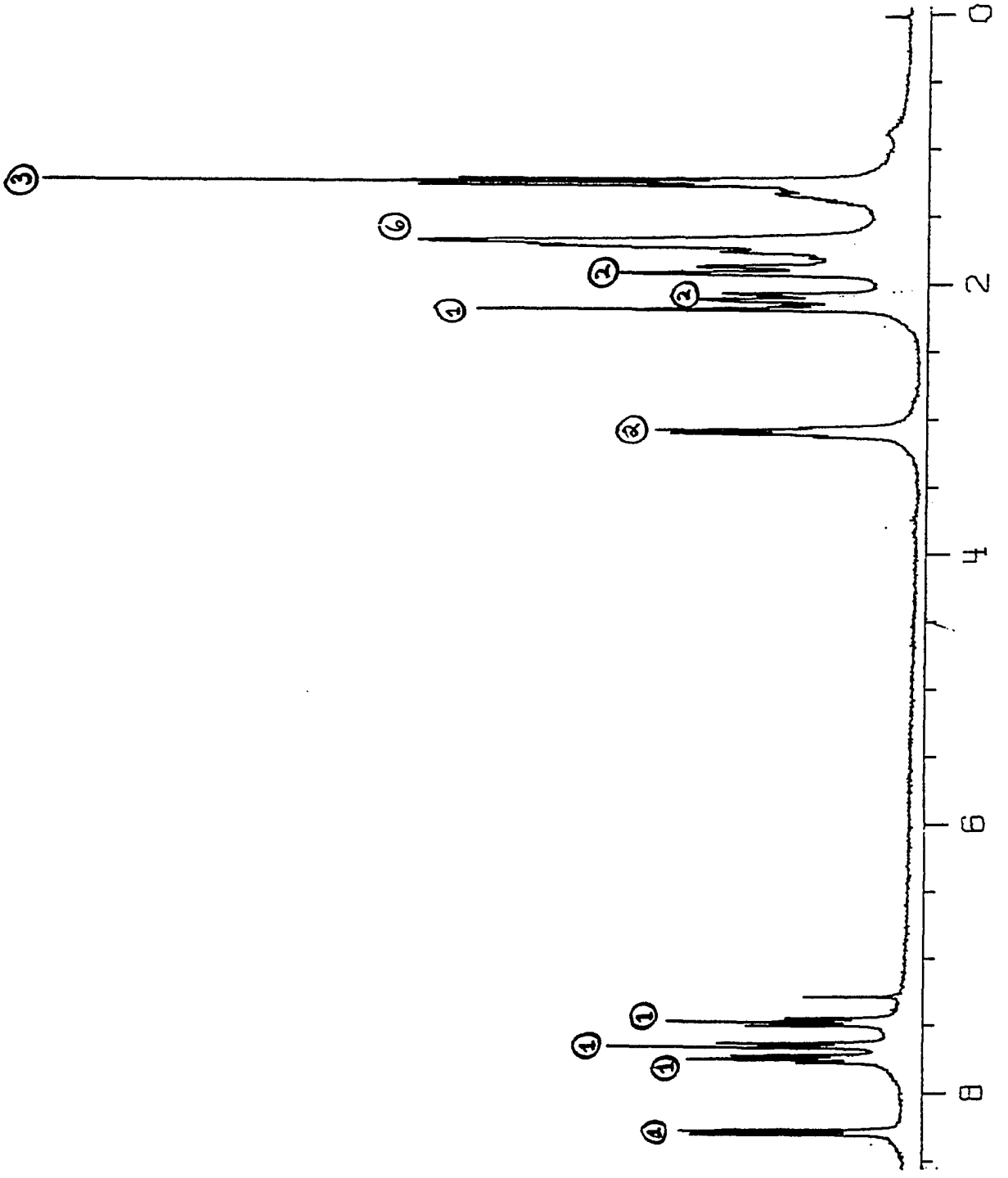
CH3
C(CH3)3
O
O
12.989
29.613
37.172
77.000
107.519
120.152
122.439
127.007
129.129
139.830
159.210
182.445
160
140
120
100
80
60
40
20
PPM


C(CH3)2OH
O
O
Ph
6
1
1
4
1
8
6
4
2
0
PPM

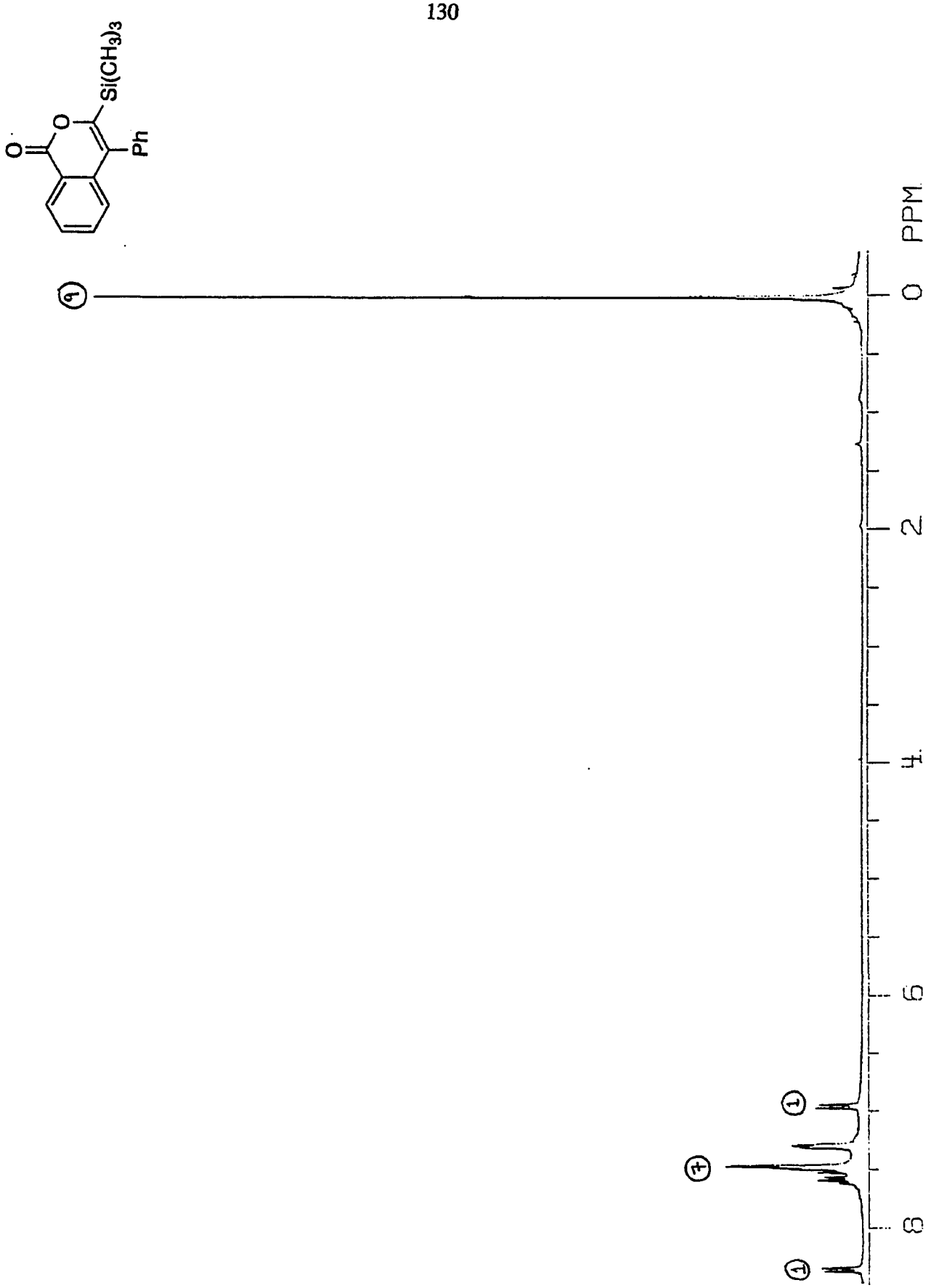

C(CH3)2OH
O
O
Ph

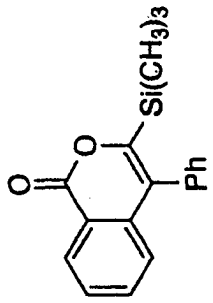

29.898
79.311
77.010
119.831
125.297
128.775
130.574
139.967
161.570
156.719
PPM
40
60
80
100
120
140
160

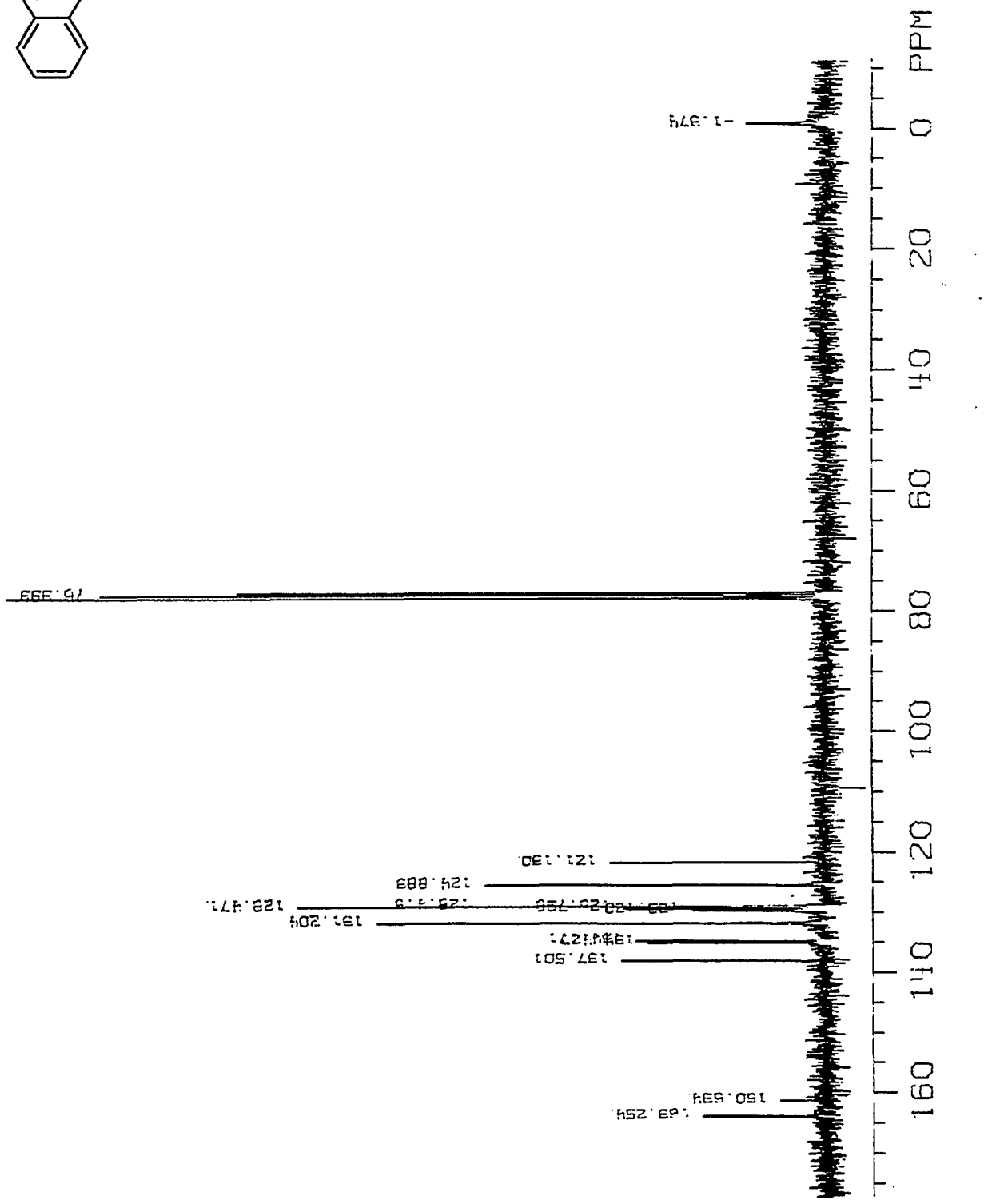

OH
O
O
Et

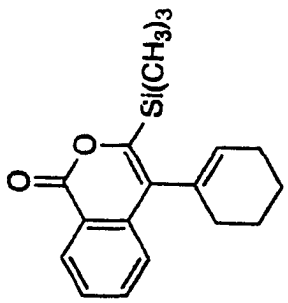

0
2
4
6
8
PPM
3
6
2
2
1
5
1
1
1
4

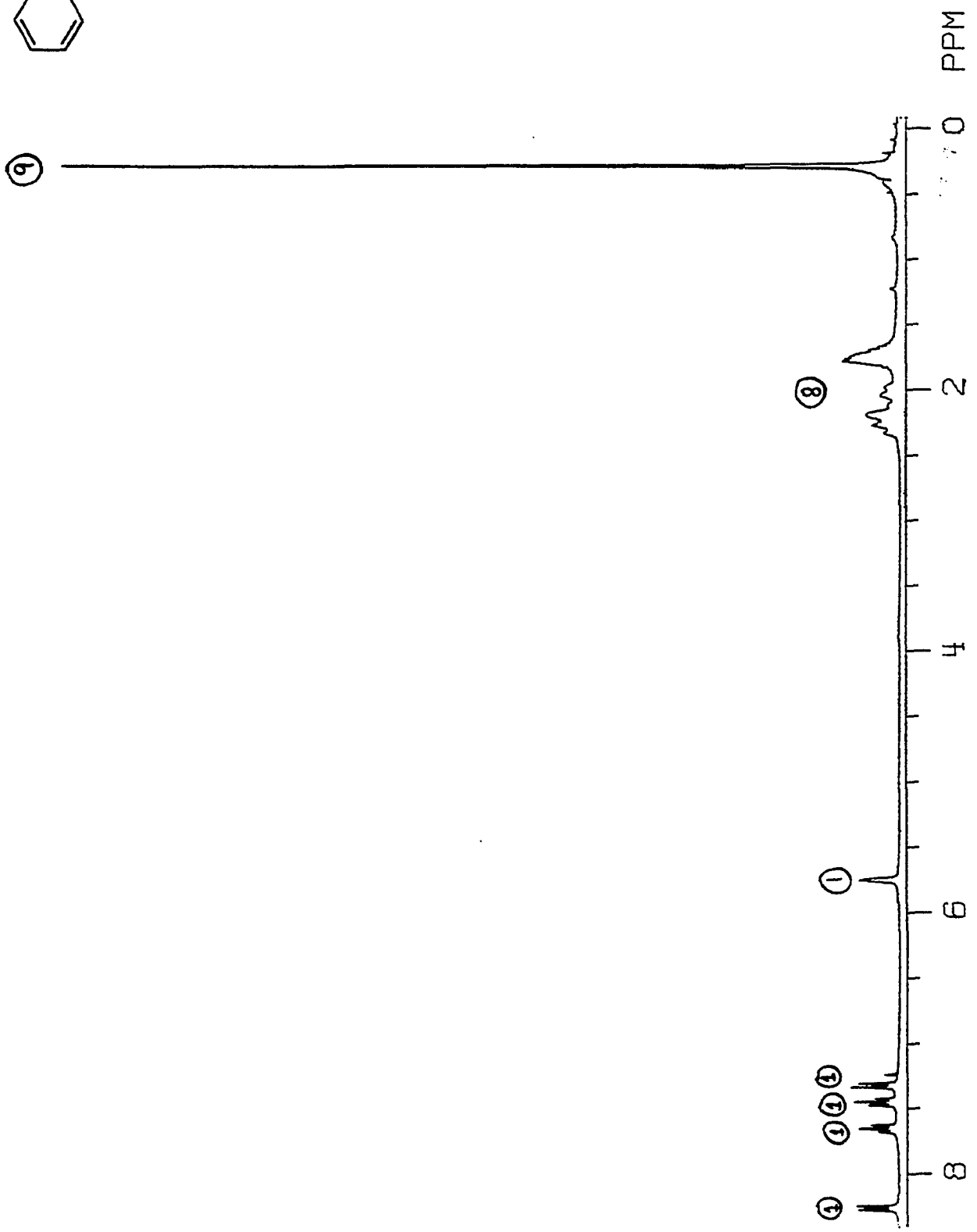
O
O
OH
Et
162.154
156.806
138.675
134.455
129.459
127.940
125.065
120.645
115.088
77.307
75.022
36.097
25.077
21.449
18.415
15.076
160
140
120
100
80
60
40
20
PPM


Si(CH3)3
O
O
Ph
9
1
7
1
0 PPM
2
4
6
8

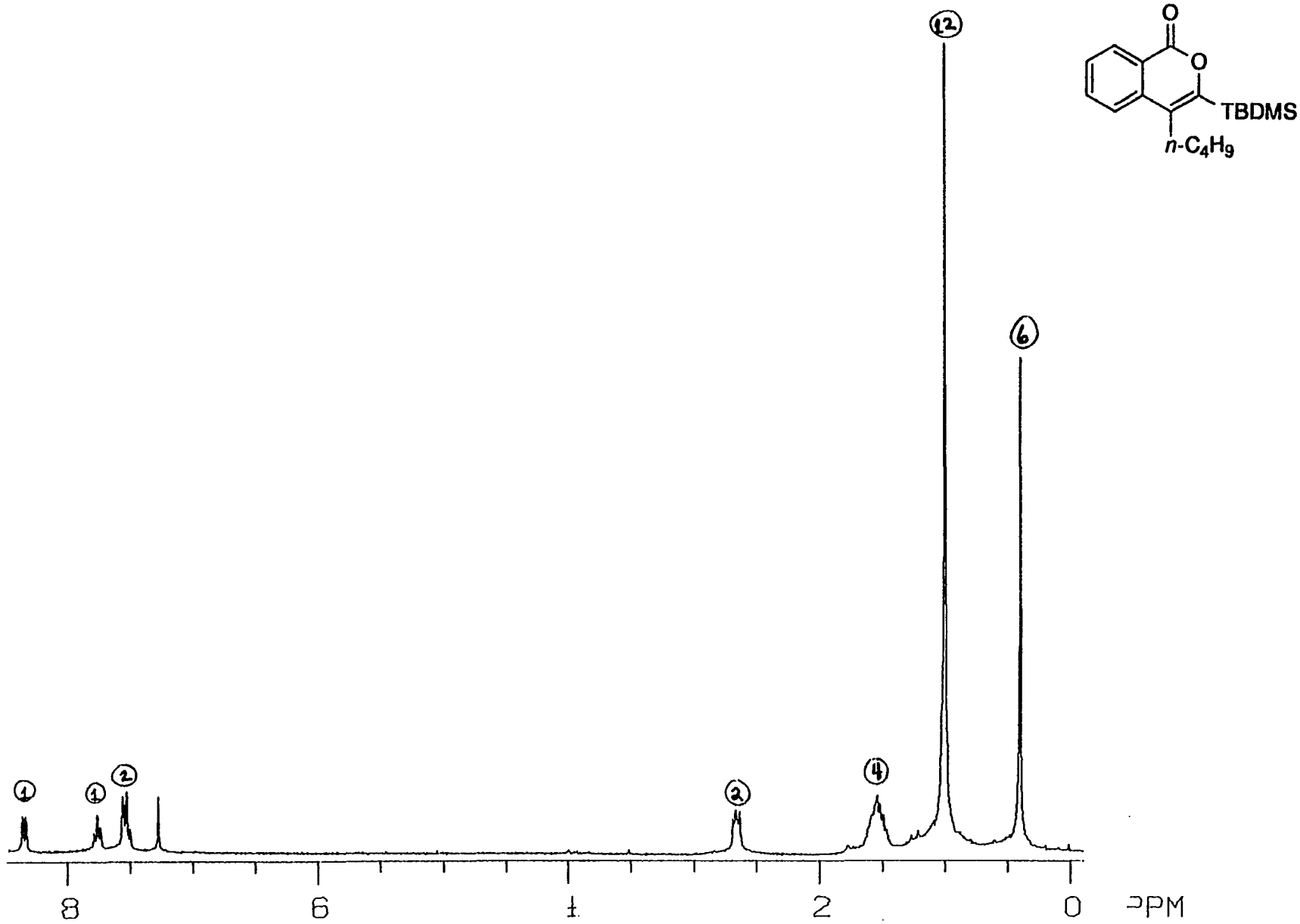

Si(CH3)3
O
O
Ph


PPM
0
20
40
60
80
100
120
140
160
-1.374
76.999
121.130
124.882
128.471
131.204
137.501
150.634
163.254

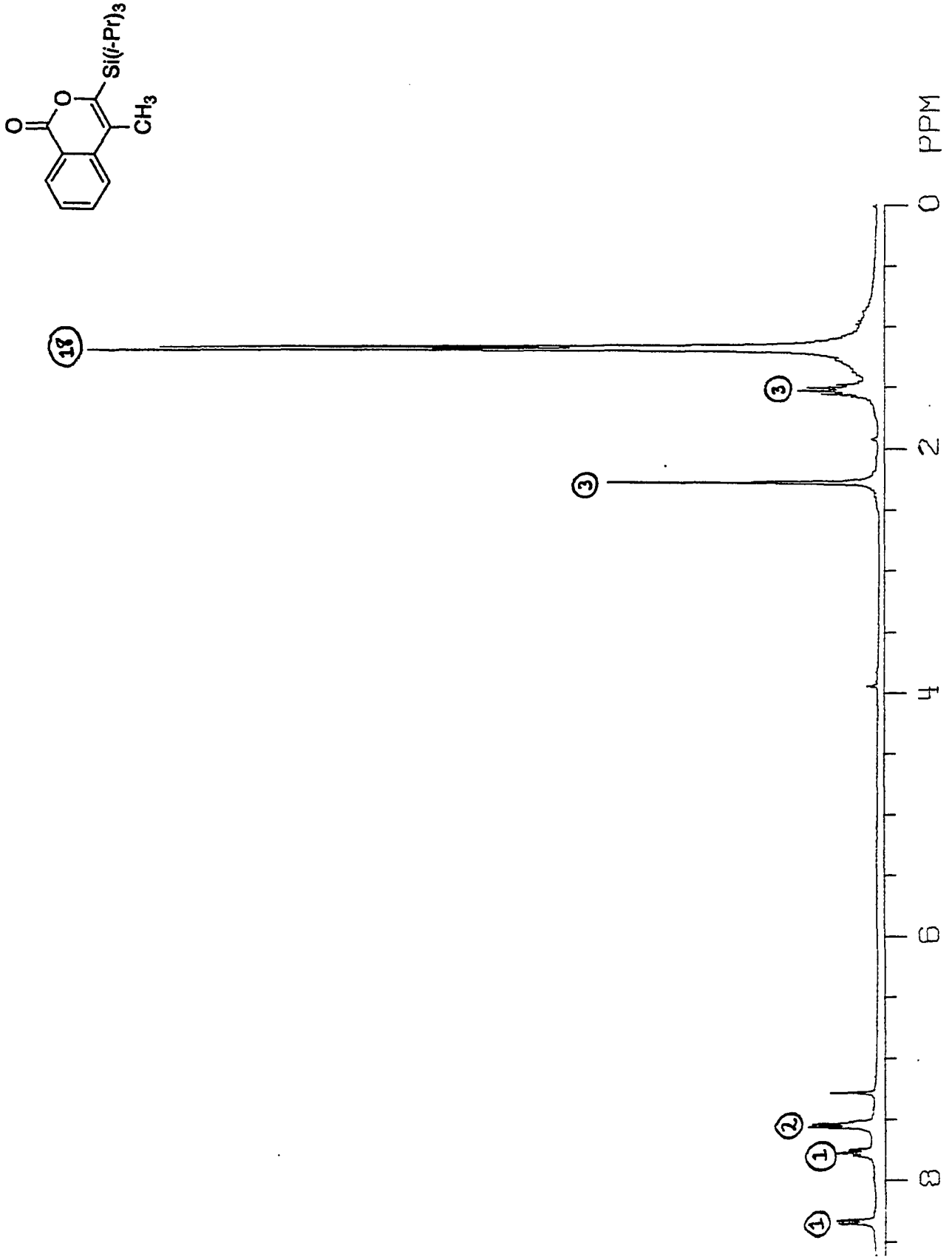

Si(CH3)3
O
O

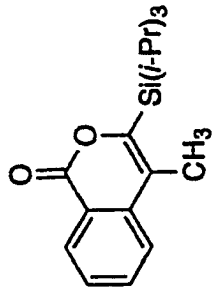

9
8
1
4
PPM
0
2
4
6
8

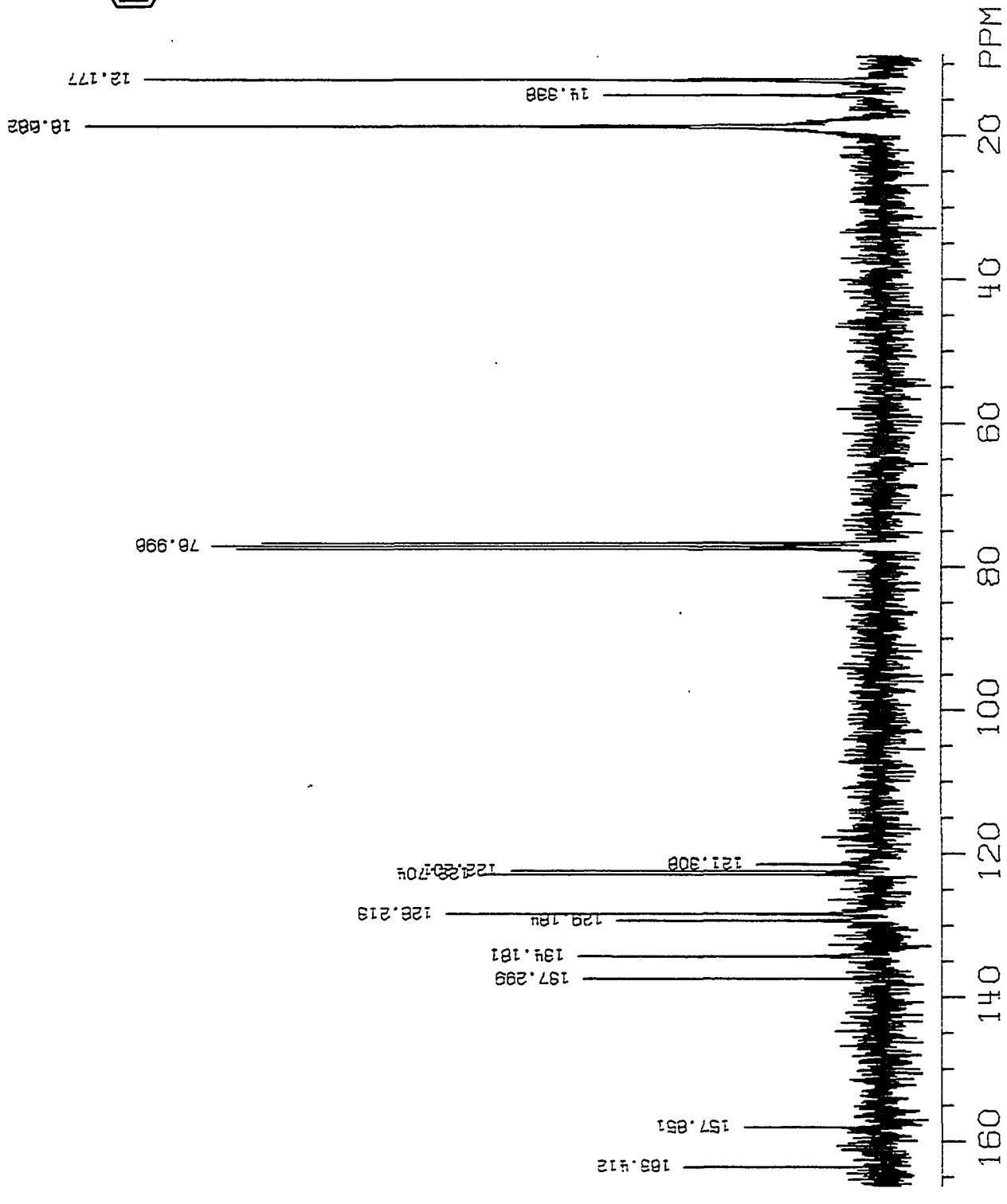
O
O
Si(CH3)3
163.378
158.993
136.727
134.107
130.972
128.185
124.122
121.554
77.008
30.477
25.363
22.671
-.696
160
140
120
100
80
60
40
20
0
PPM

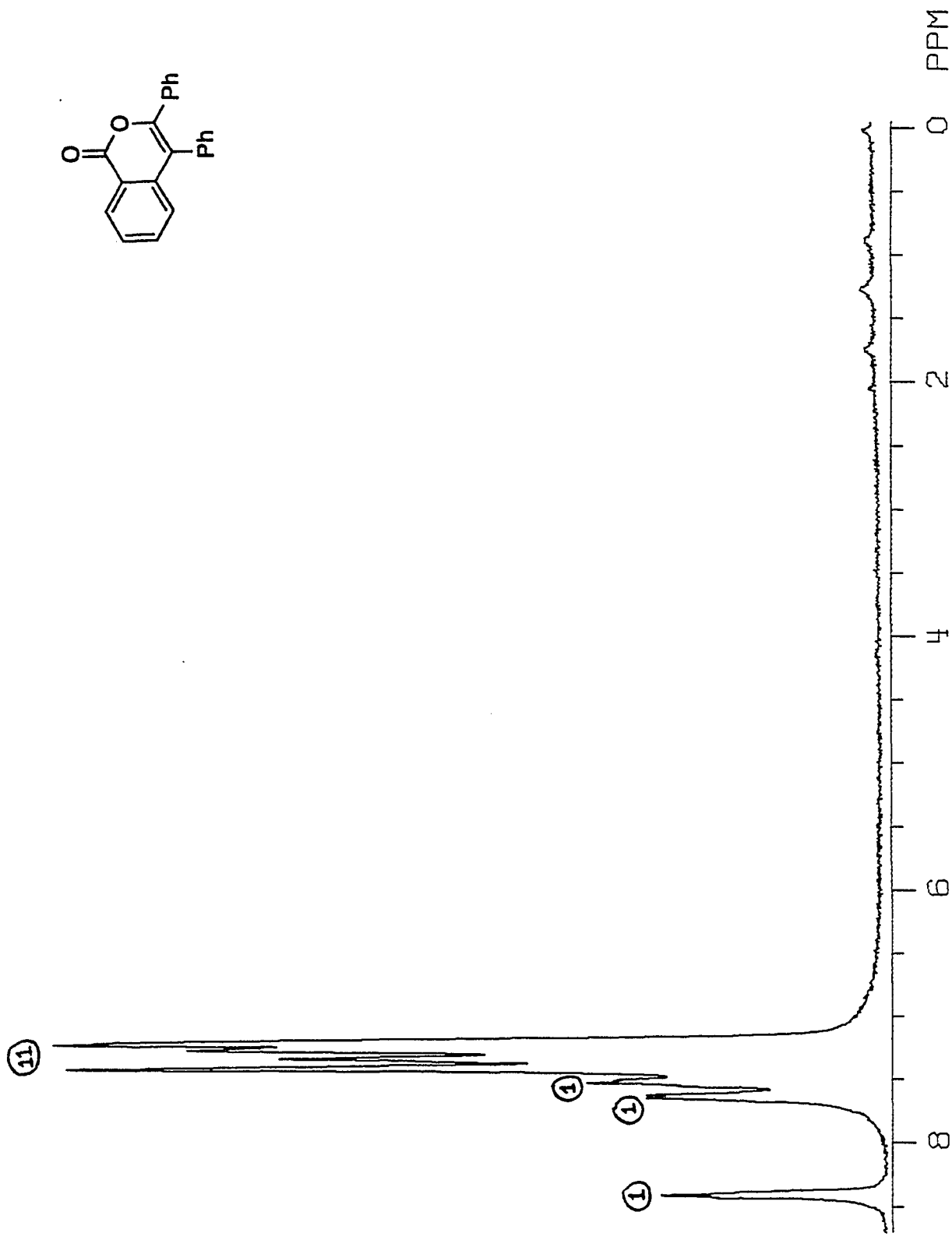

12
6
1
1
2
2
4
TBDMS
n-C4H9
8
6
4
2
0
PPM

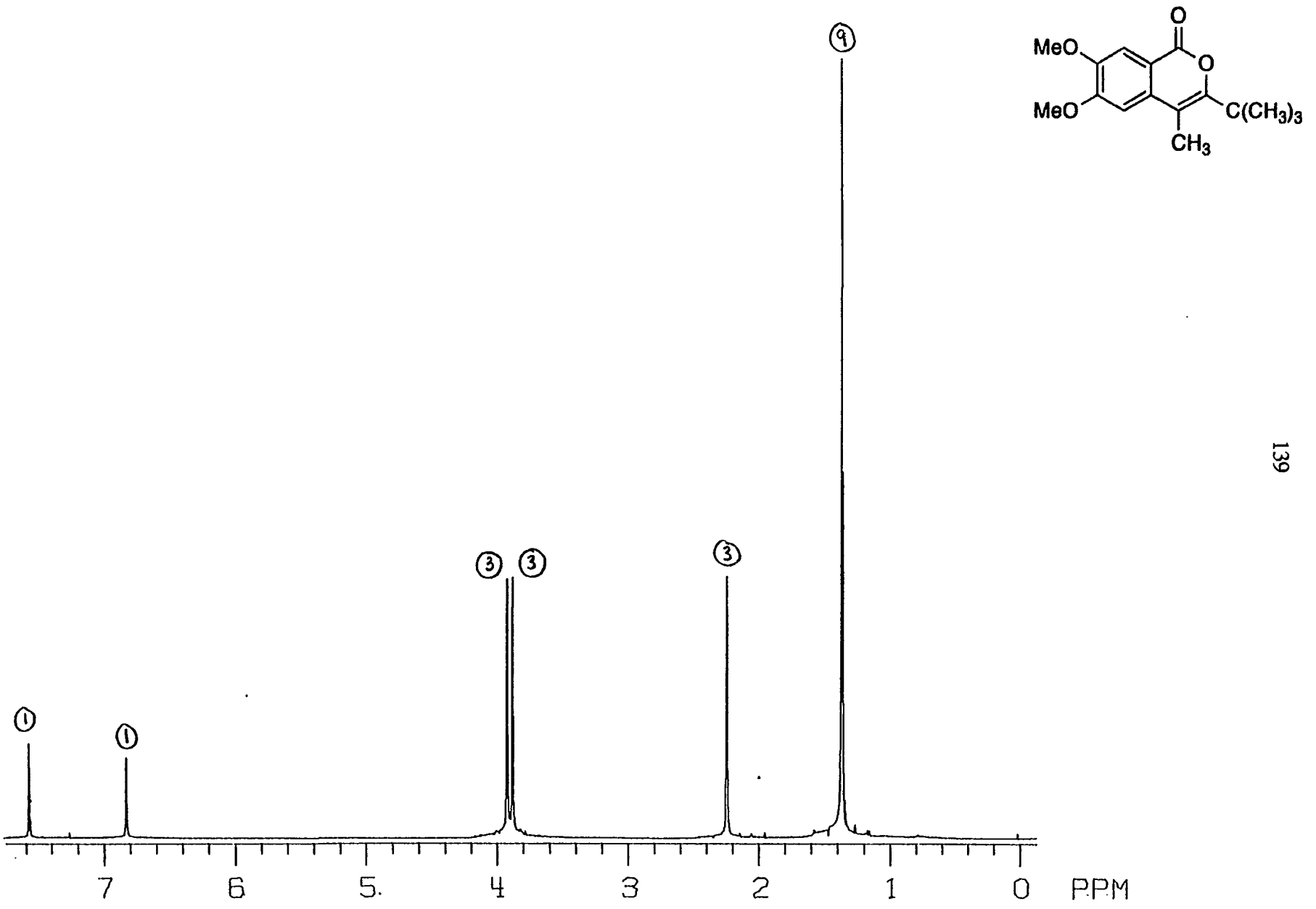
TBDMS
n-C4H9
O
O
-4.304
13.915
17.801
23.131
25.798
27.894
33.070
77.001
121.894
122.934
126.974
128.140
129.529
134.110
136.433
158.362
183.190
160
140
120
100
80
60
40
20
0
PPM

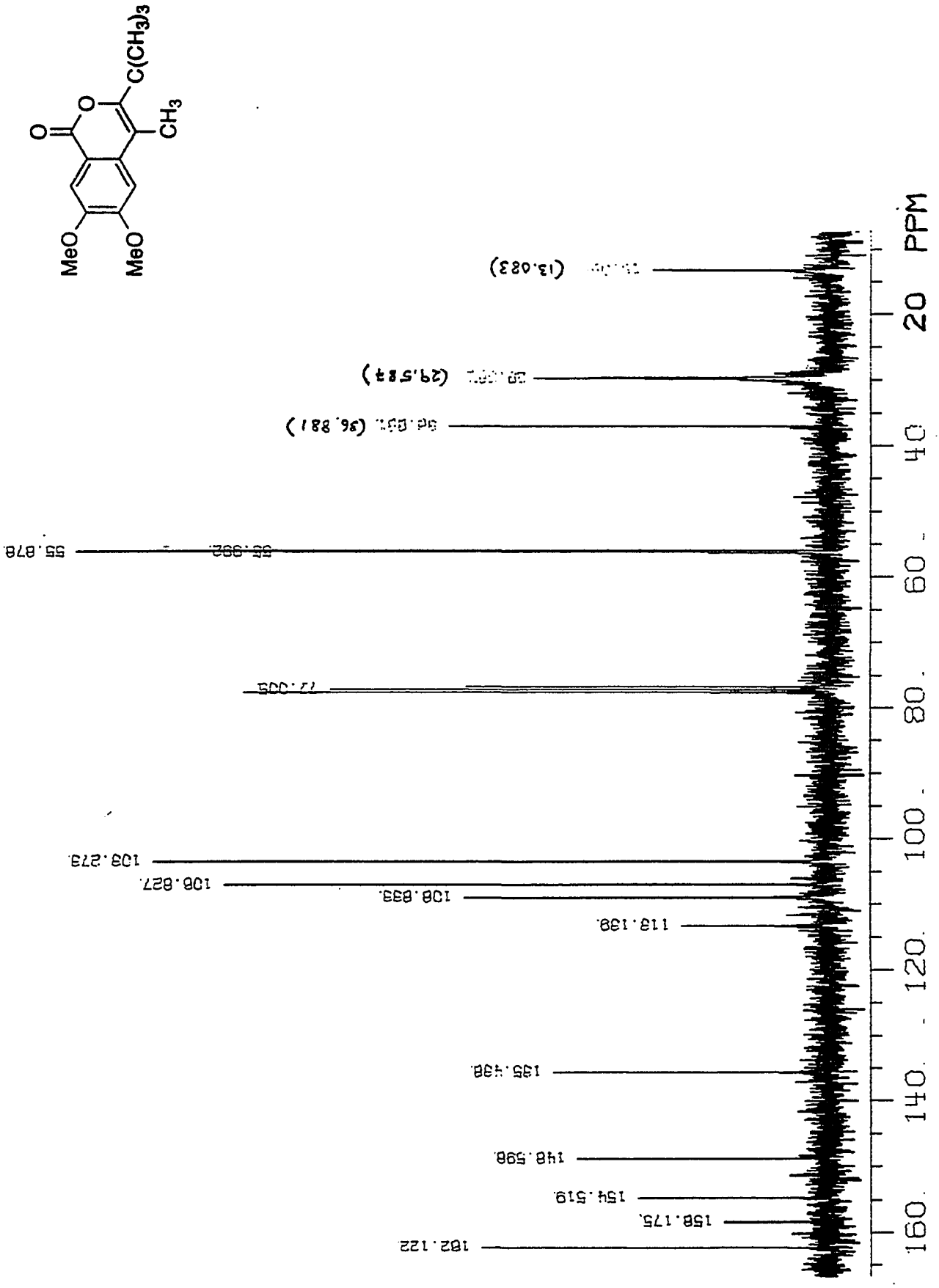

Si(i-Pr)3
CH3
O
O
18
3
3
1
2
1
8
6
4
2
0 PPM

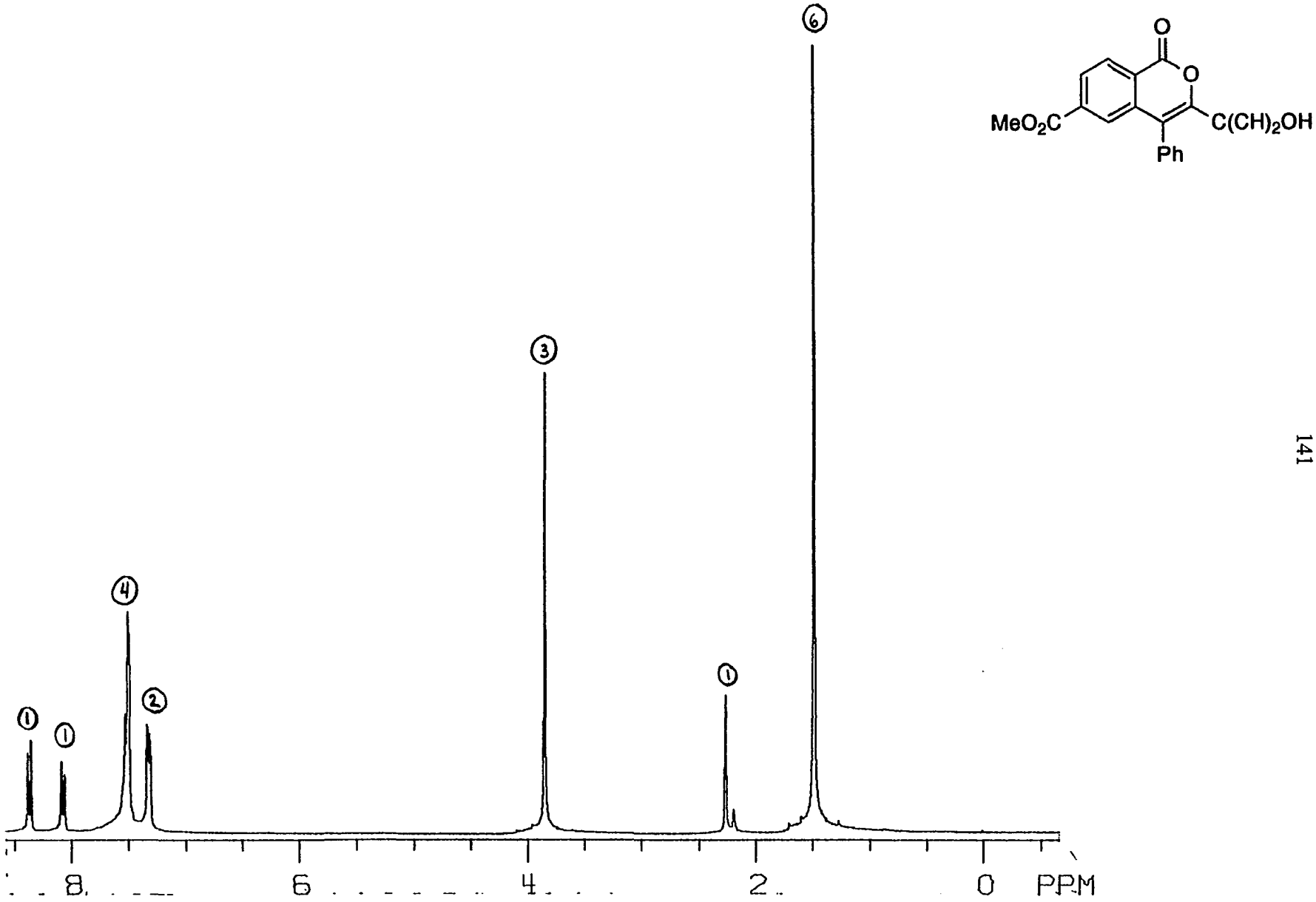

Si(i-Pr)3
O
O
CH3


12.177
14.338
18.682
76.990
121.308
128.218
129.184
137.299
138.181
157.851
163.412
PPM
20
40
60
80
100
120
140
160

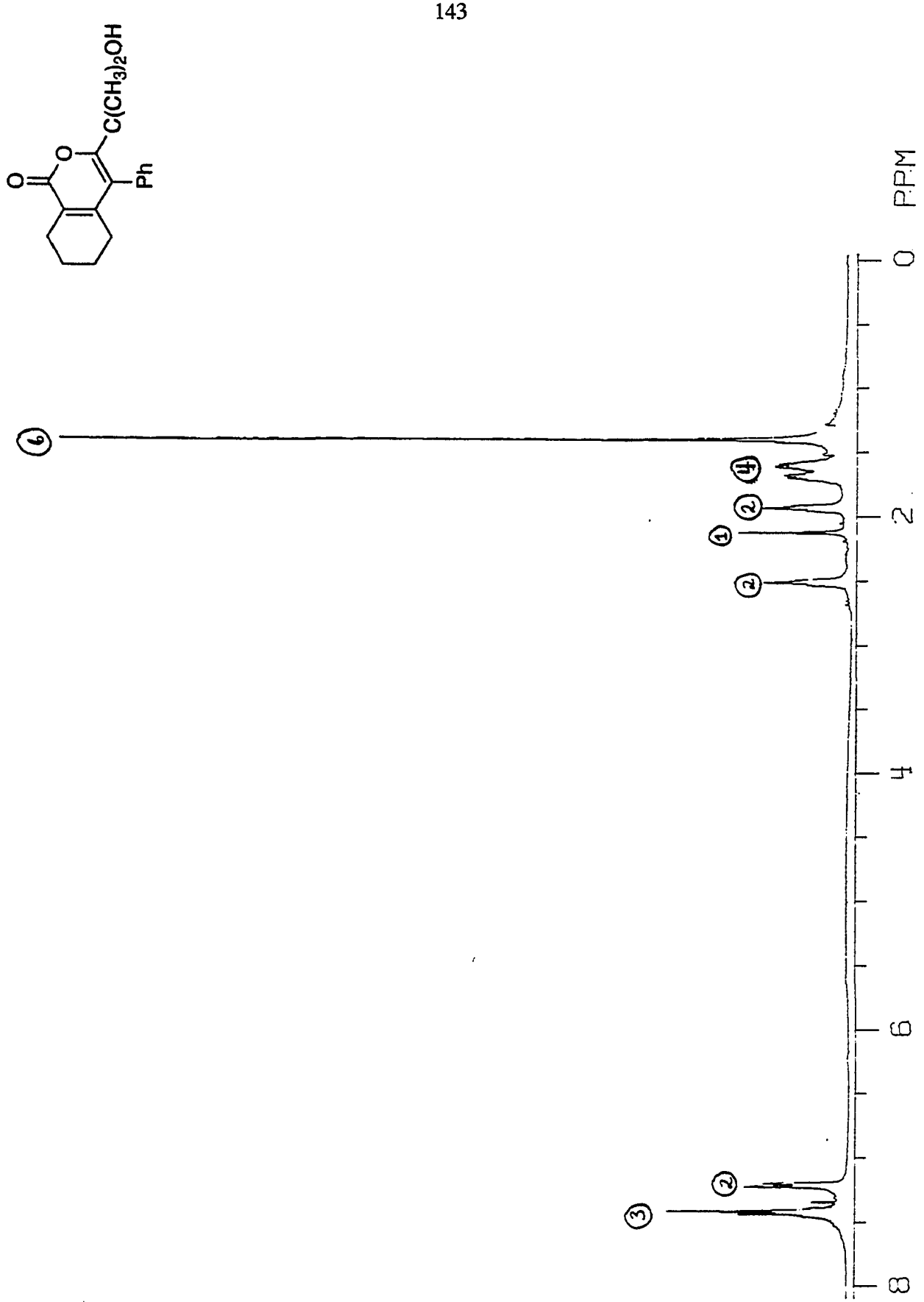

Ph
O
O
Ph
PPM
0
2
4
6
8
11
1
1
1

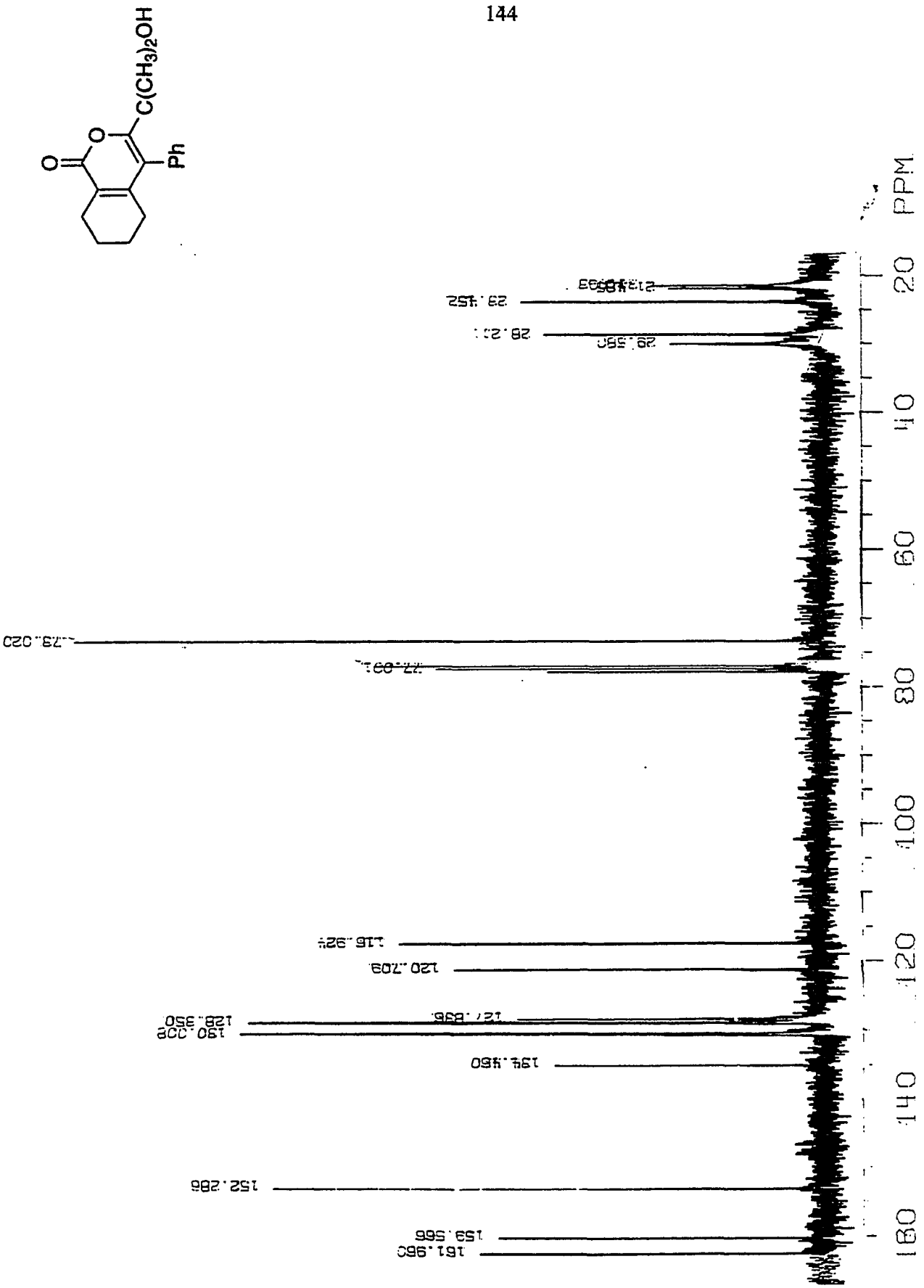

MeO
MeO
O
O
C(CH3)3
CH3
9
3
3
3
1
1
7
6
5.
4
3
2
1
0
PPM

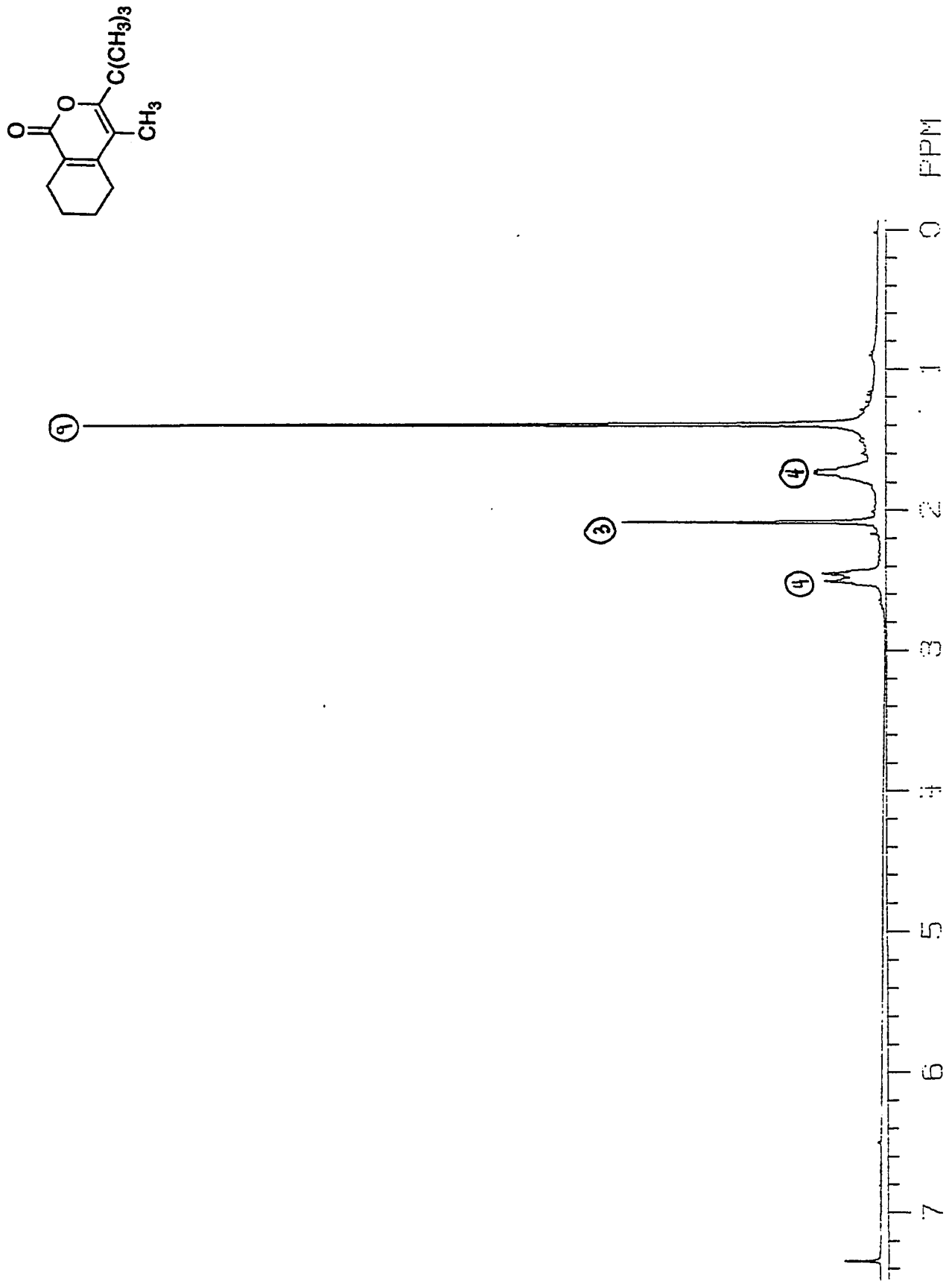

C(CH3)3
CH3
O
O
MeO
MeO
160
140
120
100
80
60
40
20
PPM
182.122
158.175
154.519
148.598
135.438
113.139
108.833
108.827
103.273
77.203
55.878
(13.083)
(29.582)
(56.881)


6
3
4
1
1
2
1
8
6
4
2
0
PPM
O
O
MeO2C
C(CH)2OH
Ph

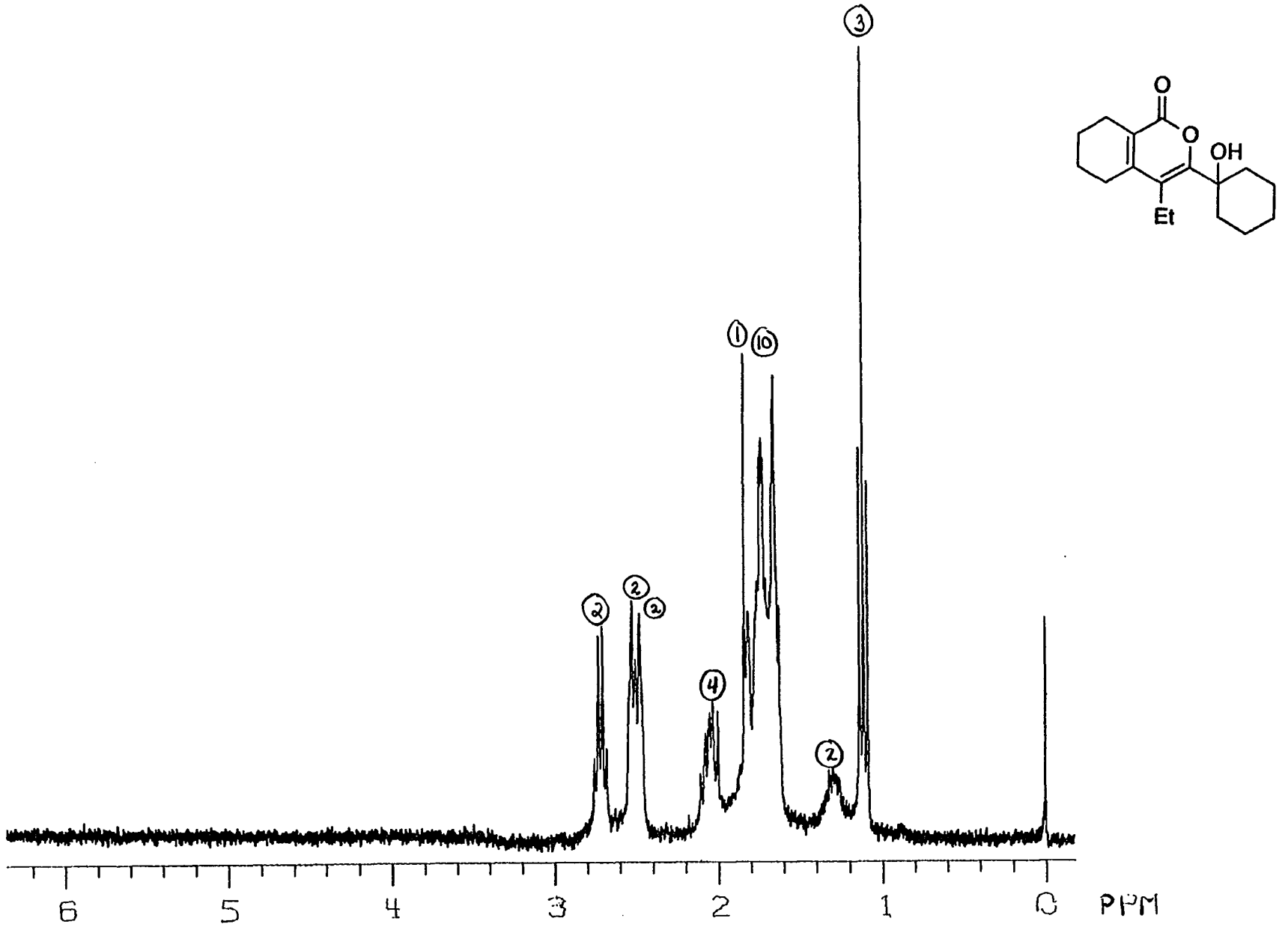
O
O
MeO2C
C(CH)2OH
Ph
165.491.
157.528
138.410.
135.234.
133.360.
130.358
128.780.
122.521.
114.044.
73.151.
52.425.
29.830.
160.
140.
120.
100.
80.
60.
40.
20.
PPM


C(CH3)2OH
O
O
Ph
6
4
2
1
2
2
3
0
2
4
6
8
PPM

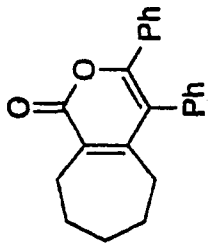

C(CH3)2OH
O
O
Ph
PPM
180
160
140
120
100
80
60
40
20
161.960
159.566
152.286
134.450
130.208
128.350
127.836
120.709
116.927
77.091
73.020
29.580
28.211
23.452

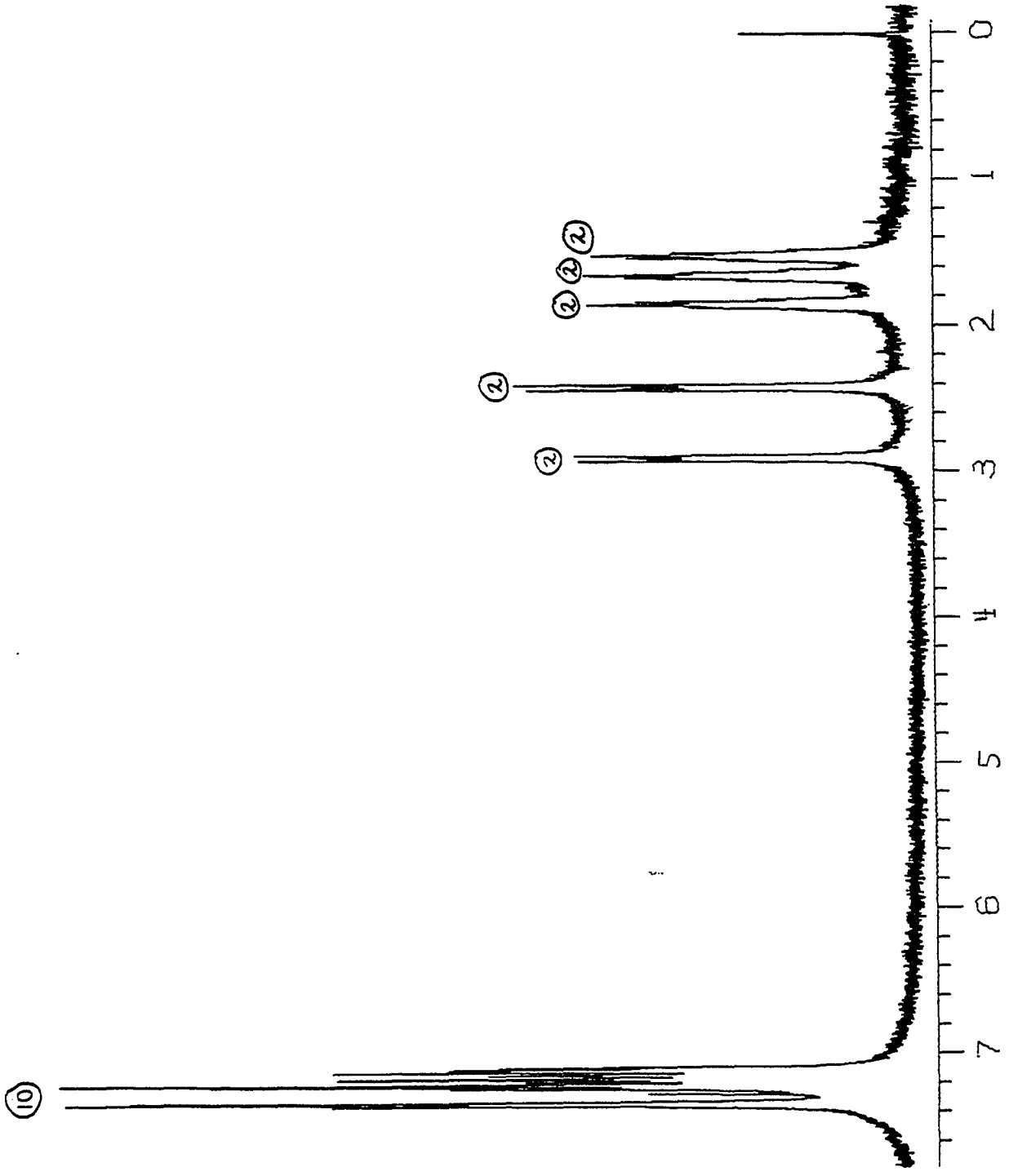

C(CH3)3
O
O
CH3
9
4
3
4
0
1
2
3
4
5
6
7
PPM

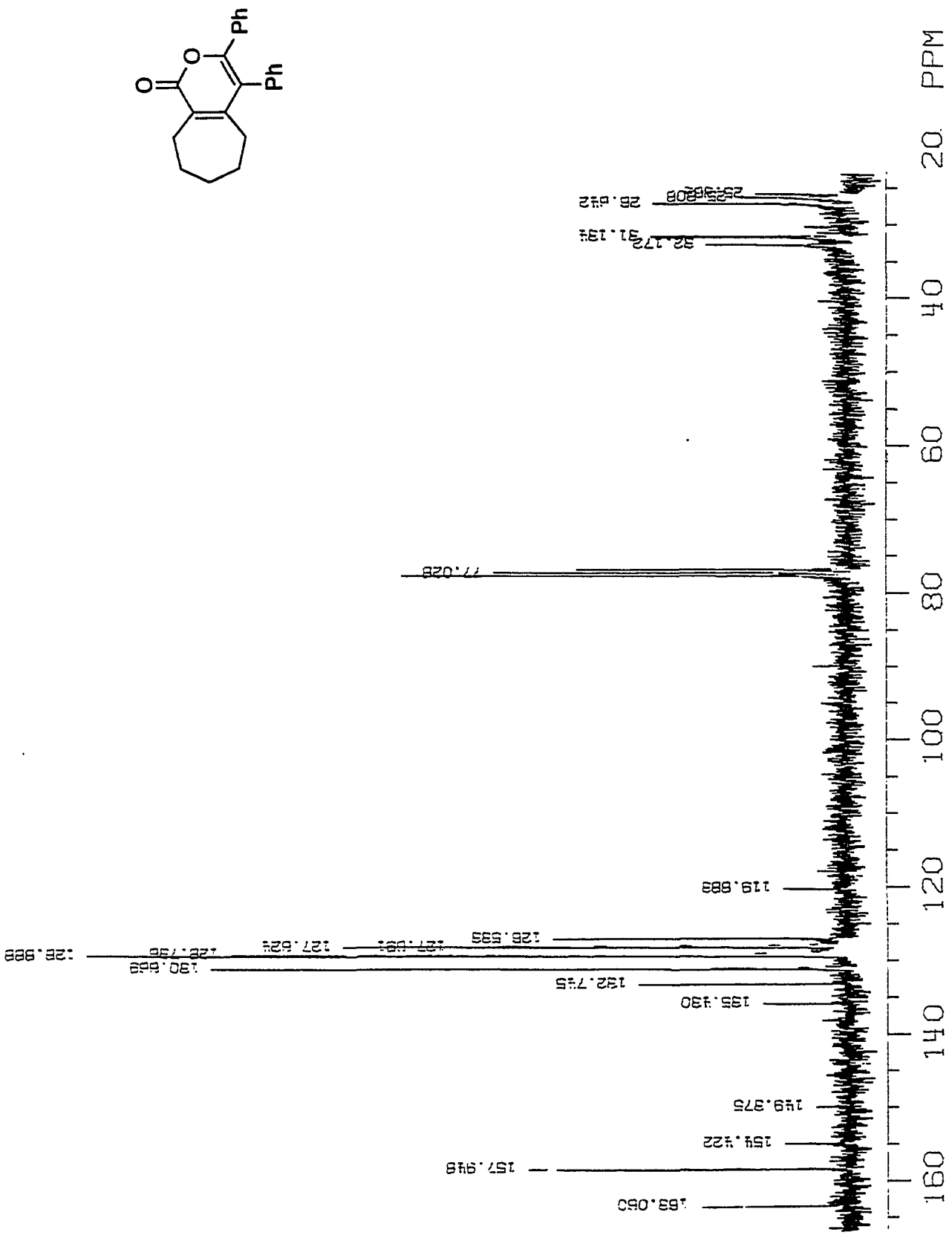
160
140
120
100
80
60
40
20
PPM
12.918
21.886
29.481
29.146
27.208
37.044
110.970
119.962
159.284
181.527
181.158
O
O
O
C(CH3)3
CH3

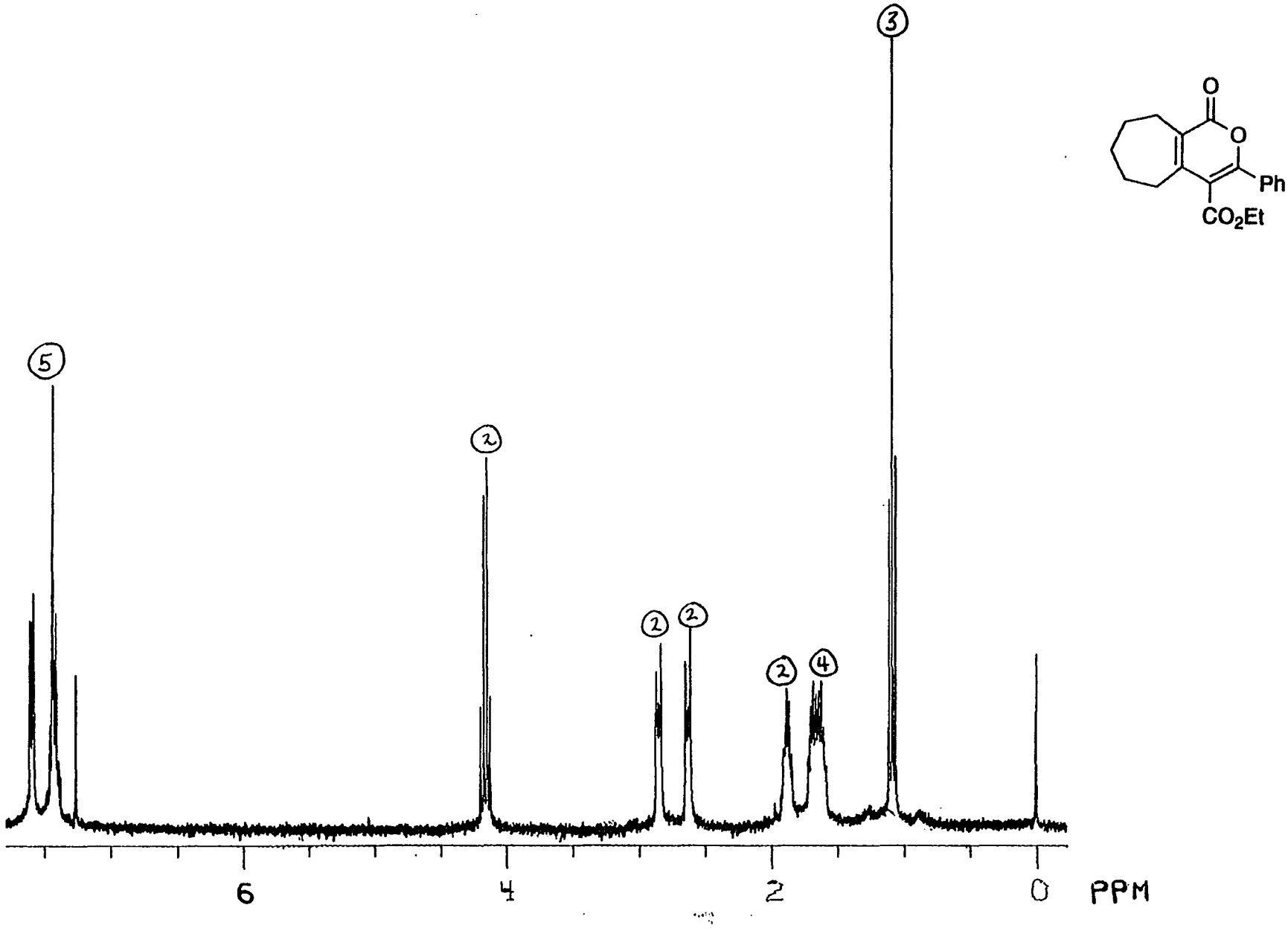

3
O
O
OH
Et
1
10
2
2
2
4
2
6
5
4
3
2
1
0
PPM

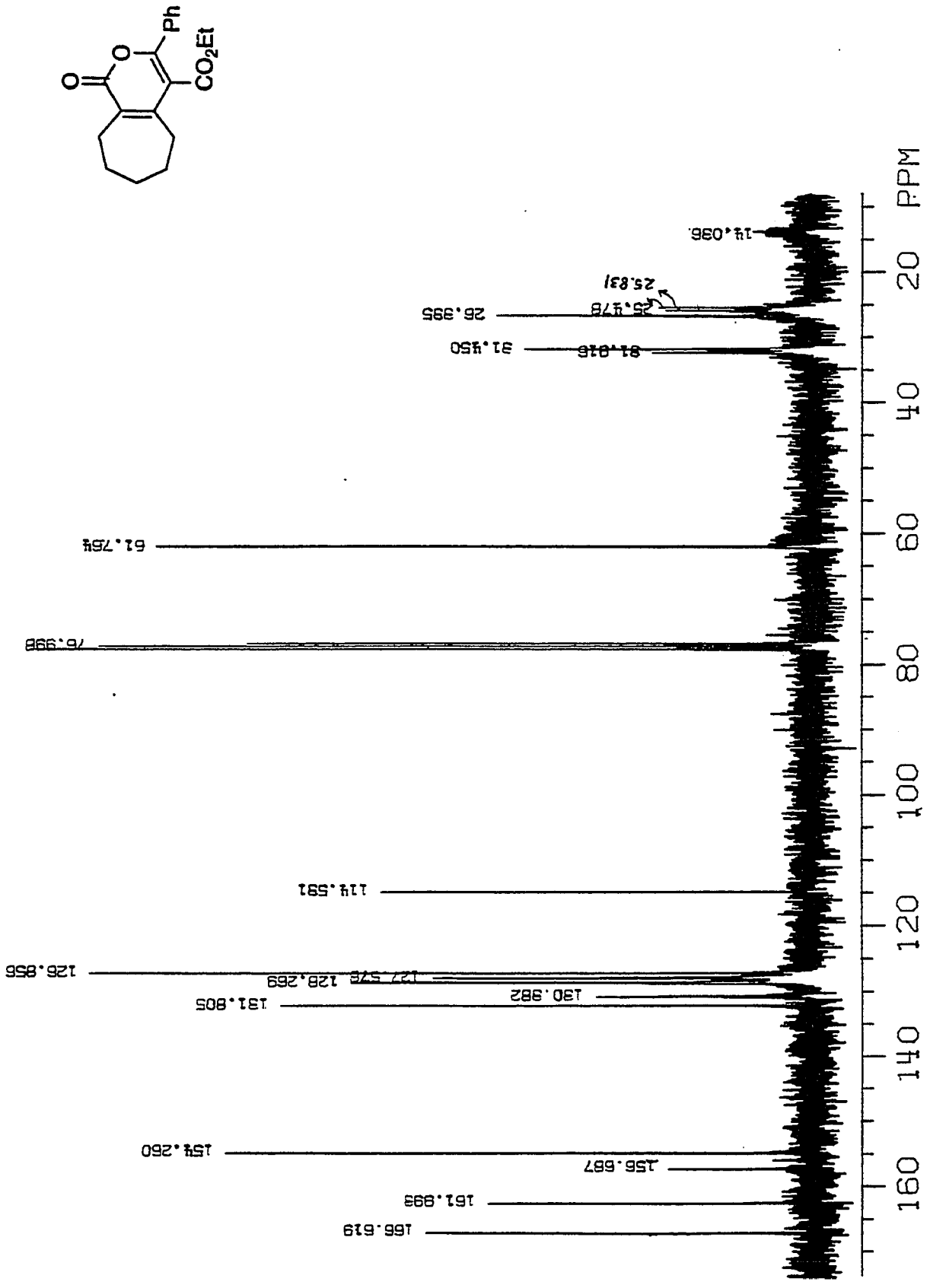
162.611
159.760
153.225
121.033
118.250
76.994
74.879
35.996
25.977
23.678
21.338
18.288
15.709
160
140
120
100
80
60
40
20
PPM
O
O
OH
Et

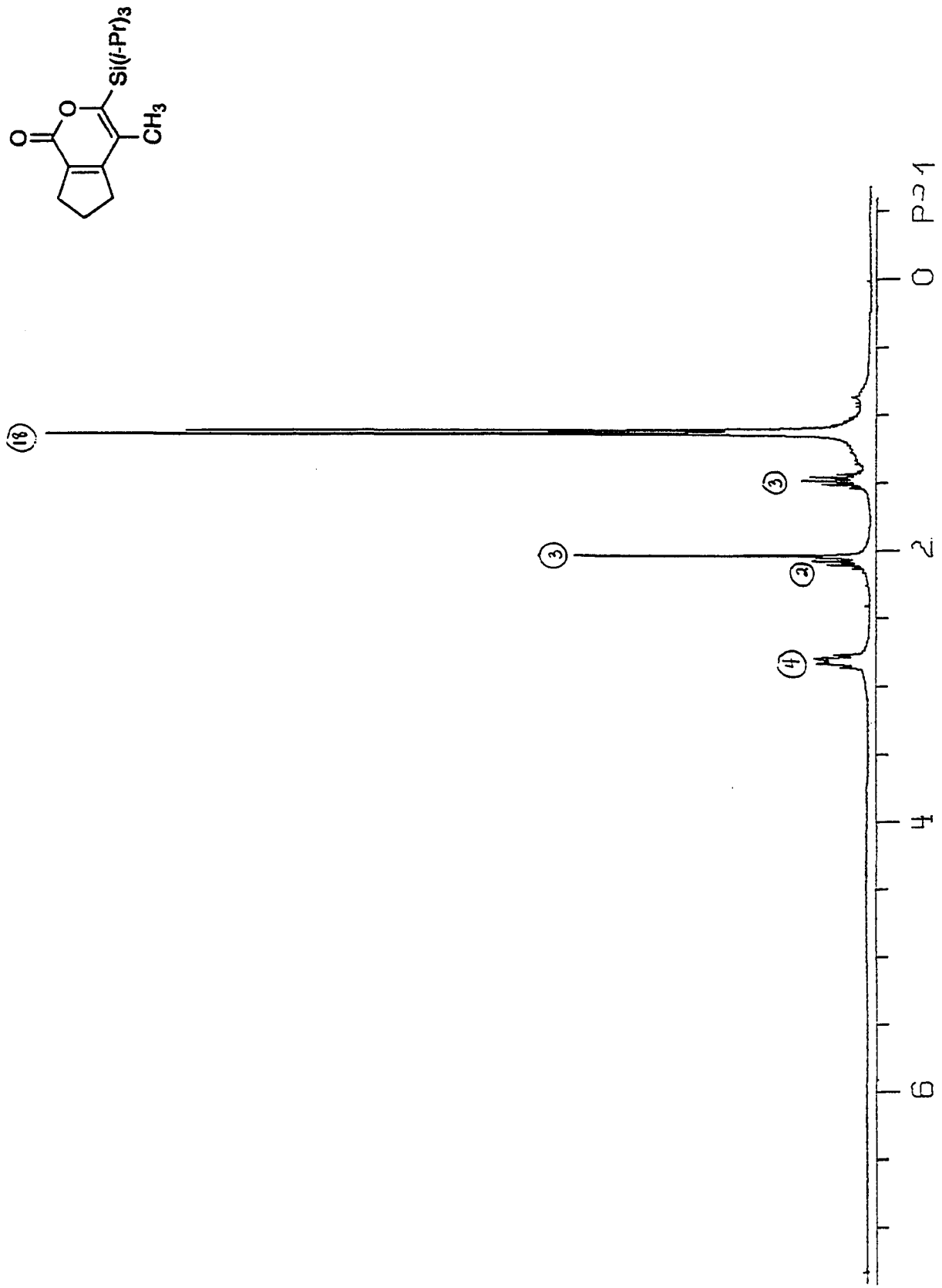

Ph
O
O
Ph


PPM
0
1
2
3
4
5
6
7
10
2
2
2
2
2

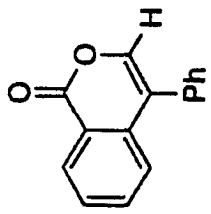

Ph
O
O
Ph
PPM
20
40
60
80
100
120
140
160
163.060
157.948
154.422
149.375
135.430
132.745
130.658
128.888
128.736
127.621
127.081
128.583
119.888
77.028
32.172
31.134
25.408
28.442

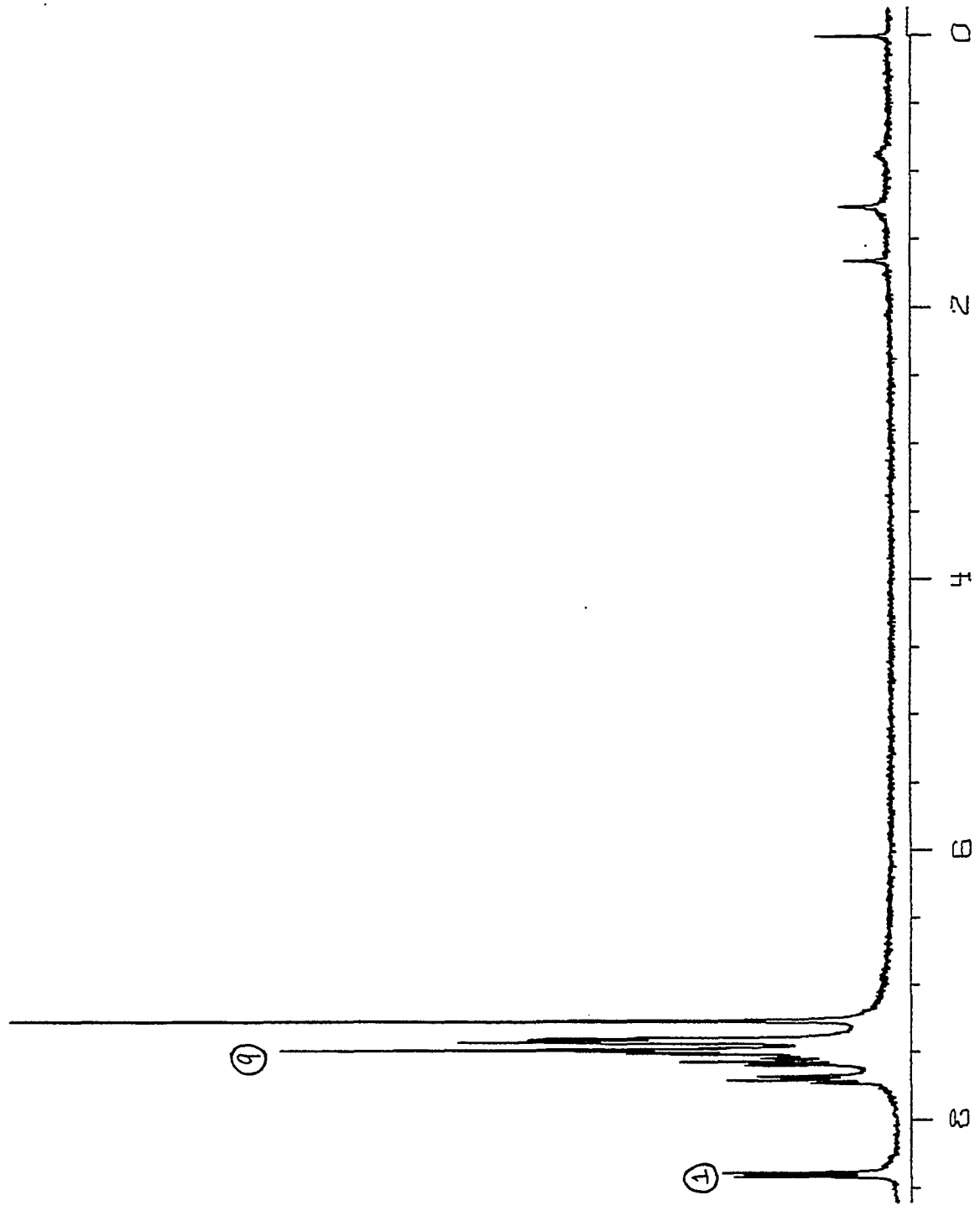

3
5
2
2
2
2
4
6
4
2
0
PPM
O
O
Ph
CO2Et

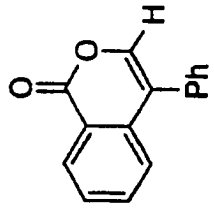

Ph
O
O
CO_2Et
14.036
25.831
25.478
26.395
31.450
61.758
76.998
114.591
126.856
127.578
128.269
130.982
131.805
154.687
161.898
166.619
PPM
20
40
60
80
100
120
140
160

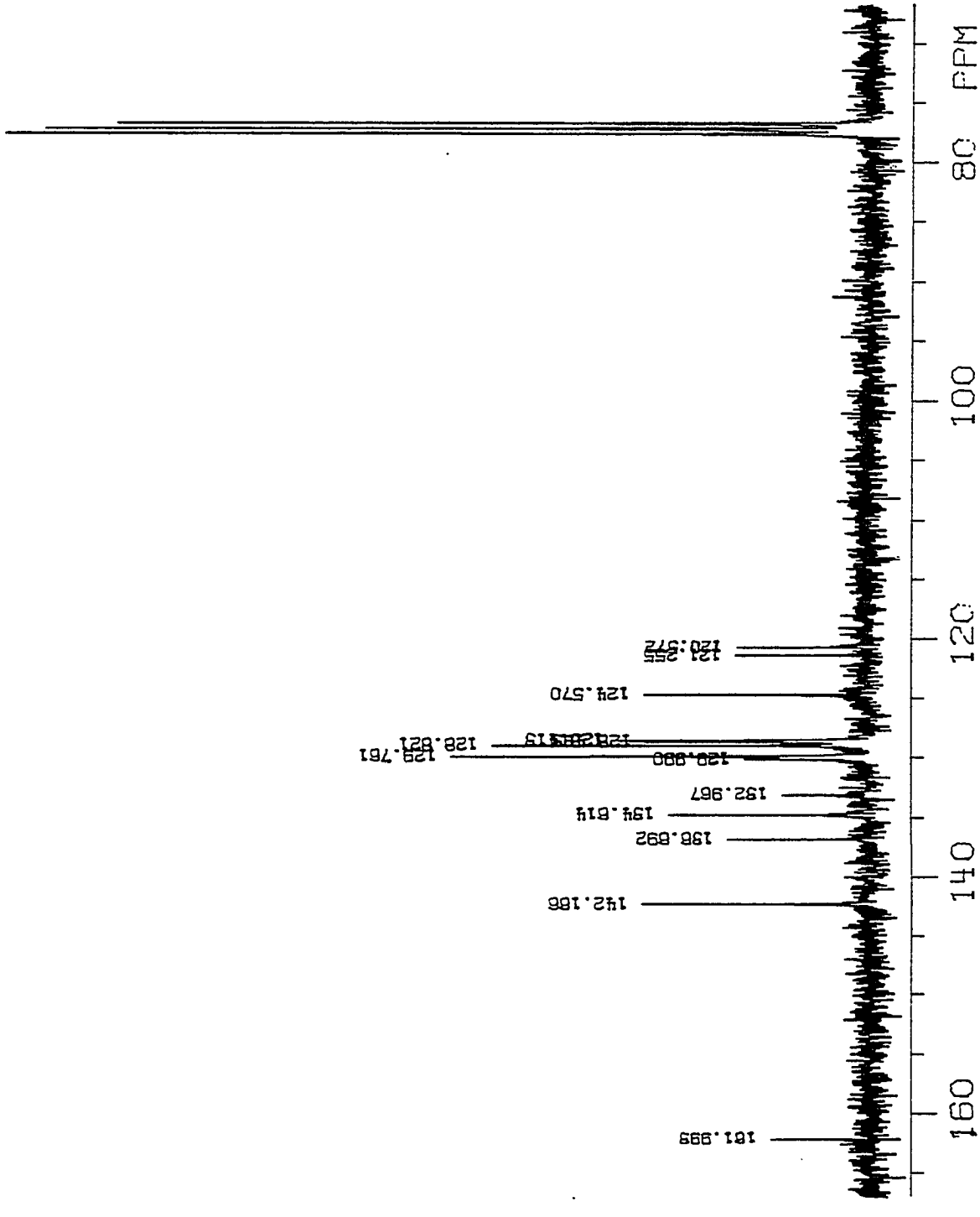

Si(i-Pr)3
CH3
O
O
(18)
(3)
(3)
(2)
(4)
0
2
4
6
PPM

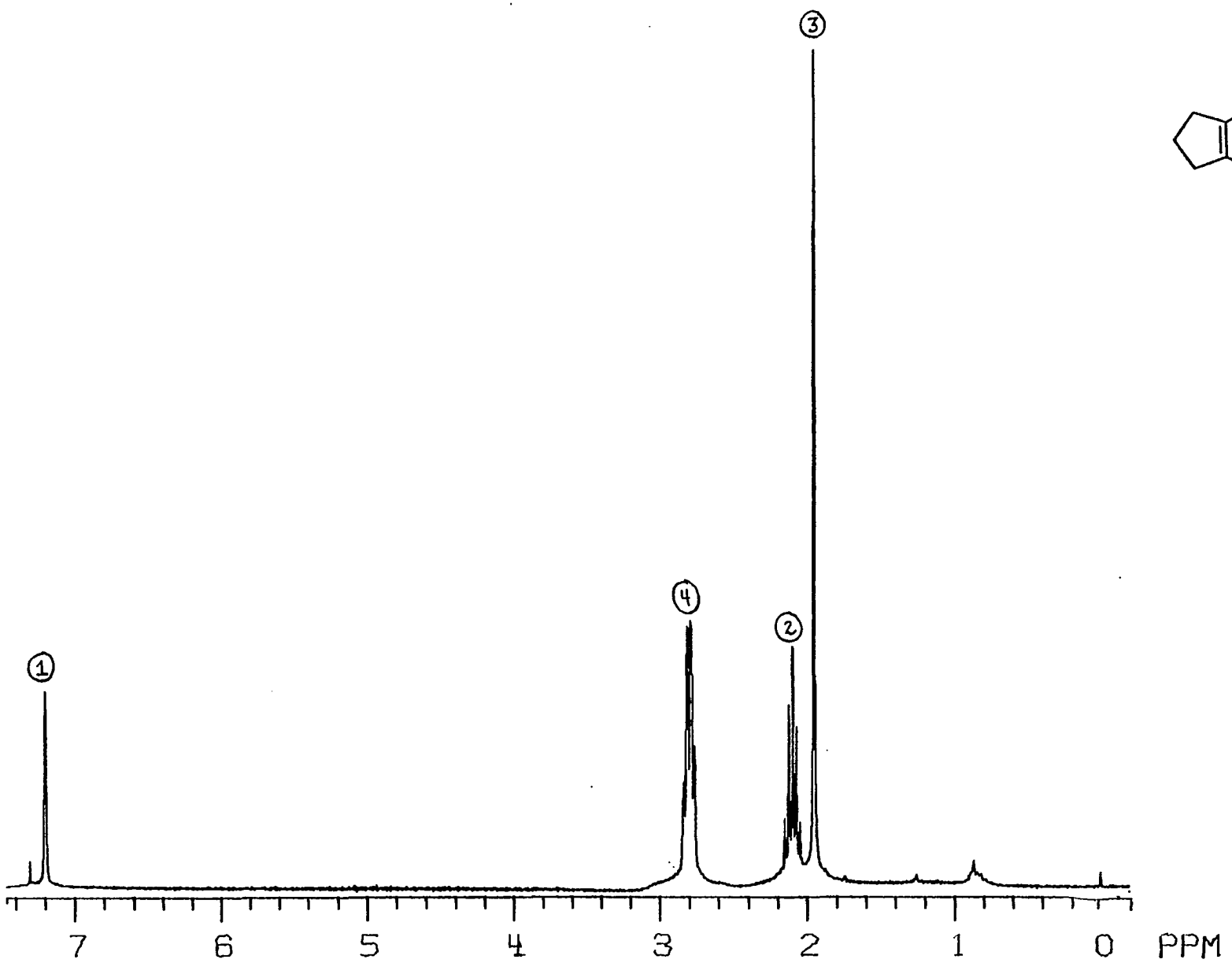
Si(i-Pr)3
CH3
O
O
11.892
18.508
21.987
11.575
33.281
90.057
128.712
126.510
158.810
163.287
PPM
20
40
60
80
100
120
140
160


H
O
O
Ph


PPM
0
2
4
6
8
9
1


H
O
O
Ph

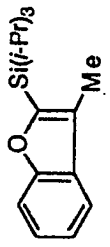

161.999
142.186
138.692
134.814
132.967
129.990
128.821
128.761
124.570
121.255
120.372
160
140
120
100
80
PPM

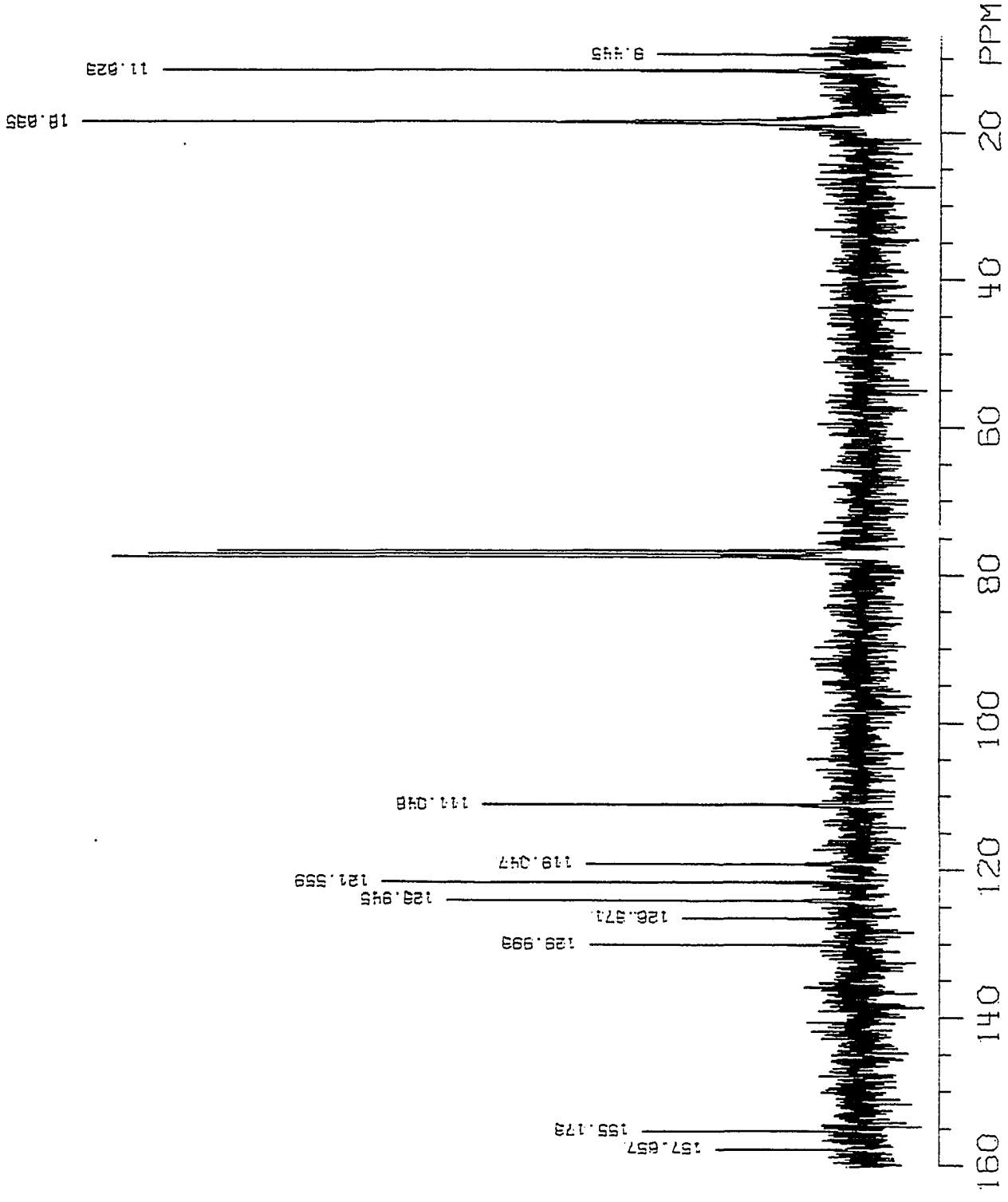

③
④
②
①
7
6
5
4
3
2
1
0
PPM
O
O
H
CH3

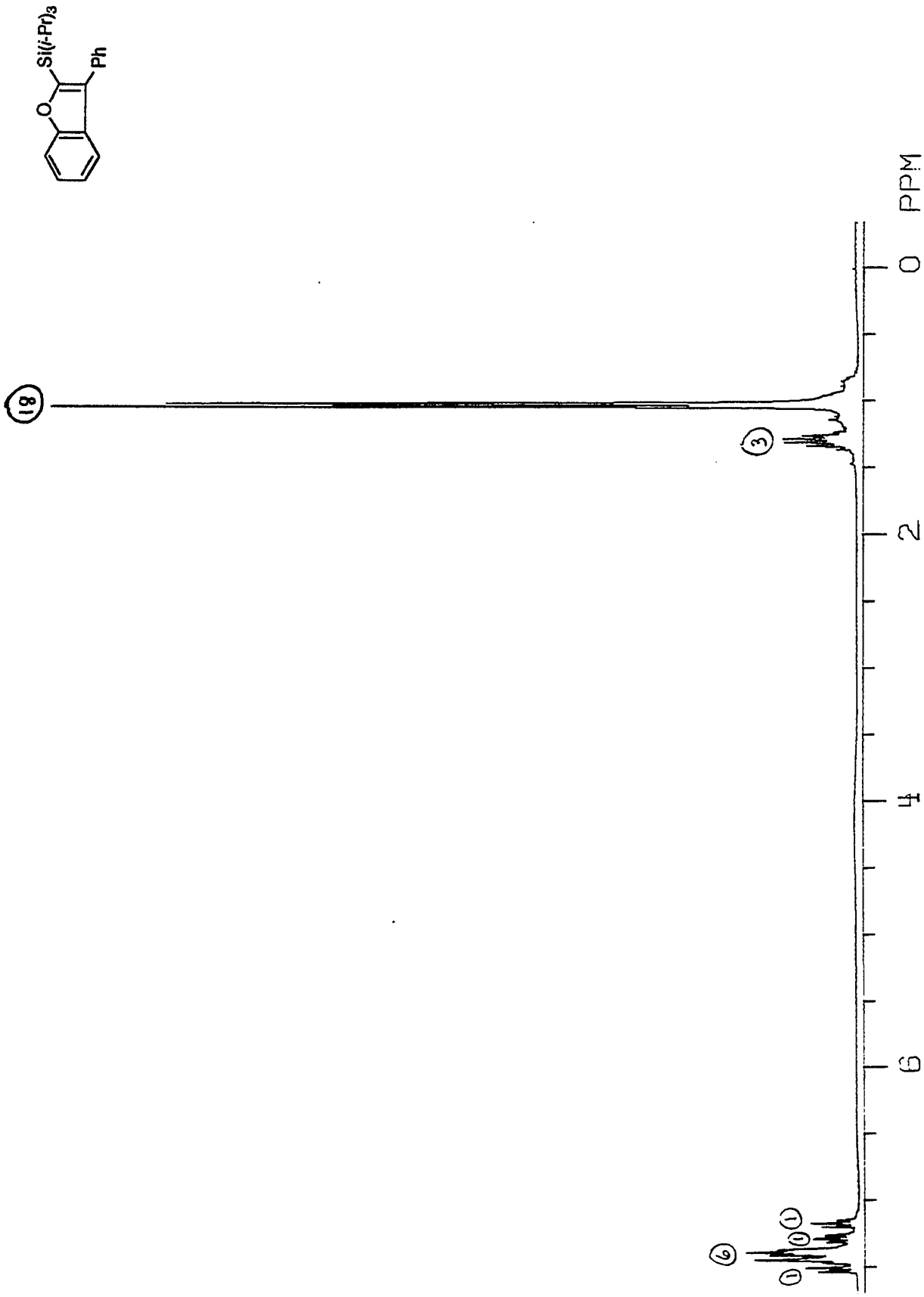
O
O
H
CH3
161.507
160.084
146.212
126.404
114.100
77.226
32.872
29.927
22.228
12.988
100
140
120
100
80
60
40
20
PPM

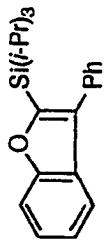
APPENDIX C: CHAPTER 3 ^{1}H AND ^{13}C NMR BENZOFURAN AND ISOCHROMENE SPECTRA

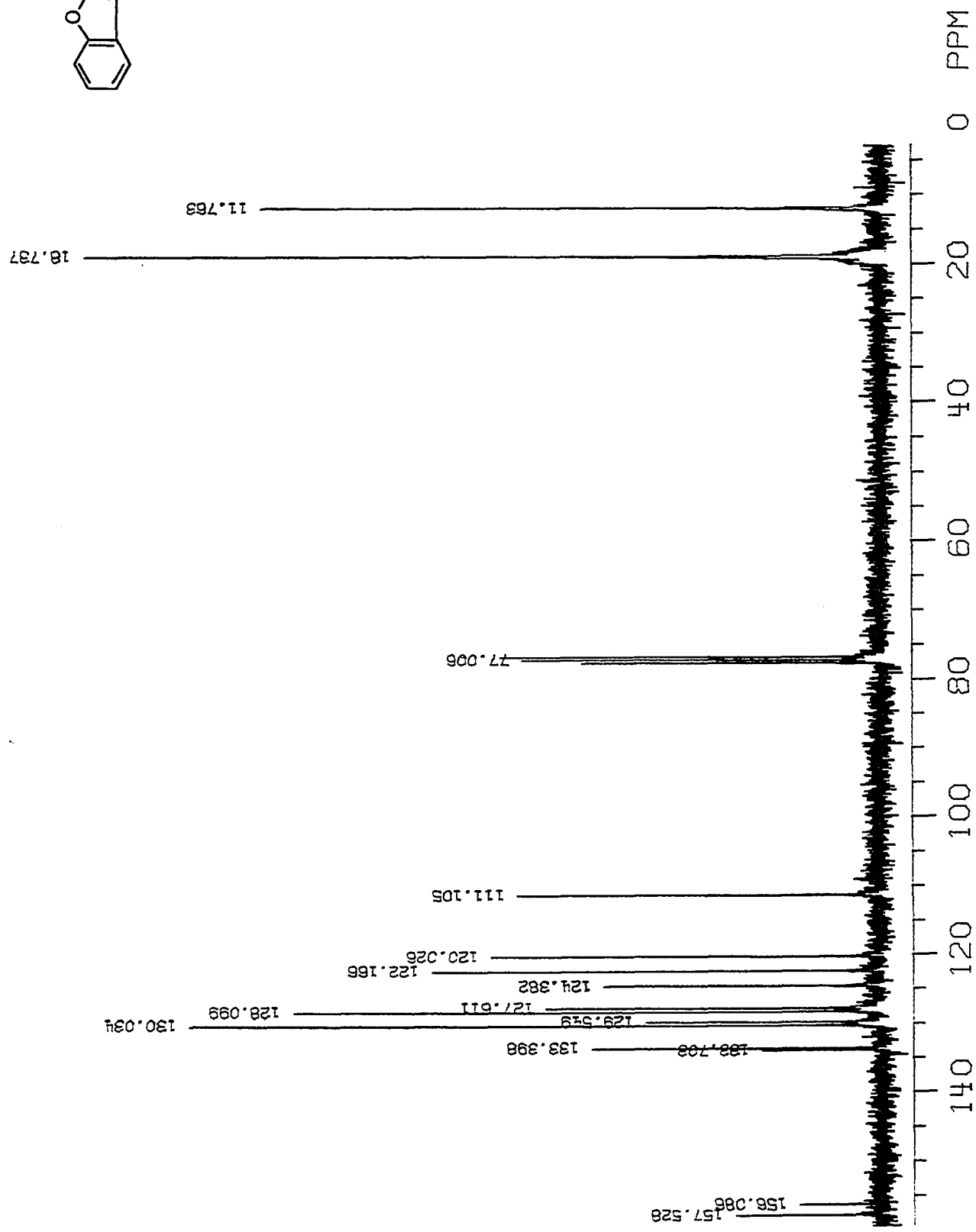
PPM
0
1
2
3
4
5
6
7
1
1
1
3
3
18
O
Si(i-Pr)3
Me

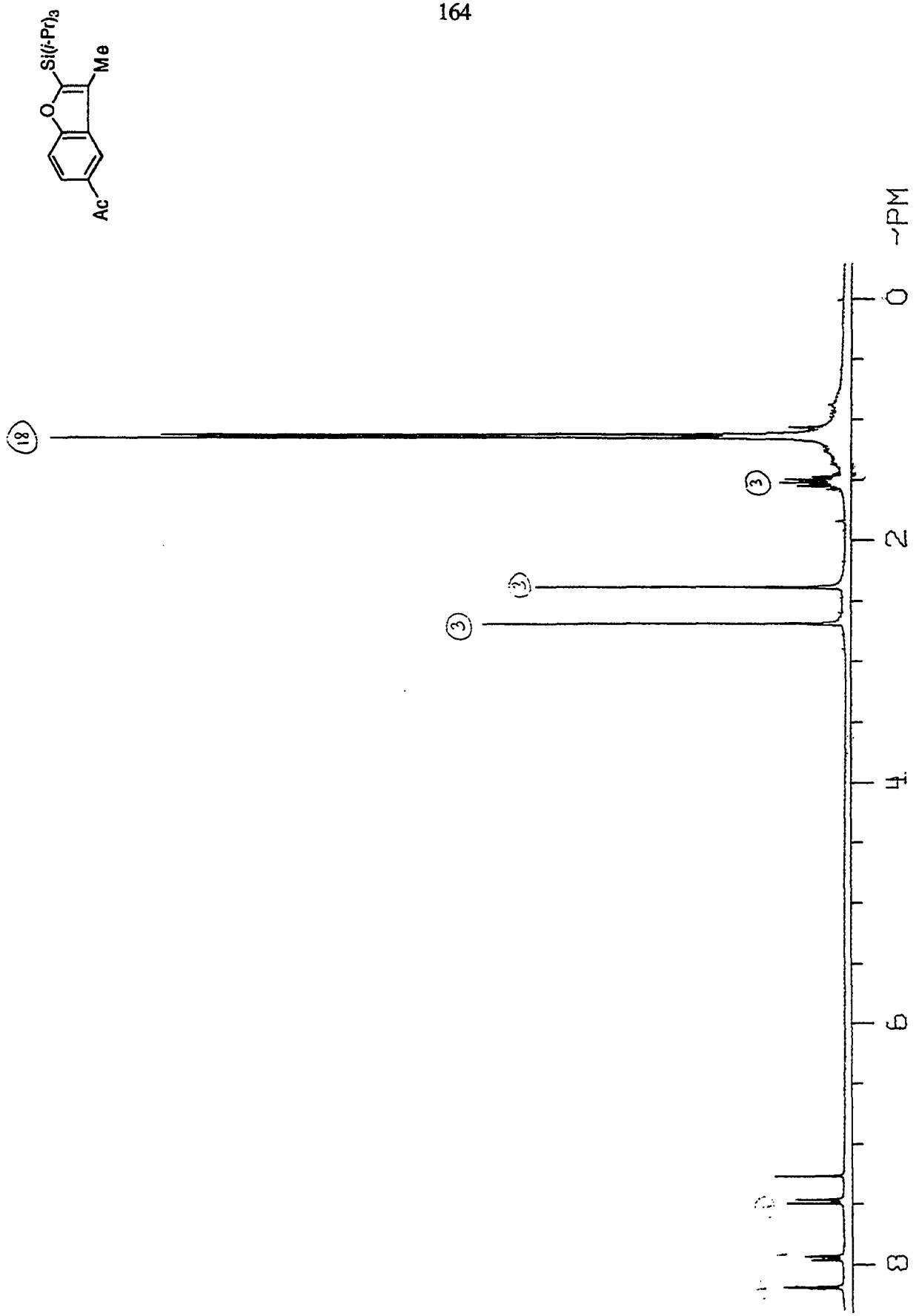

Si(i-Pr)3
Me
O

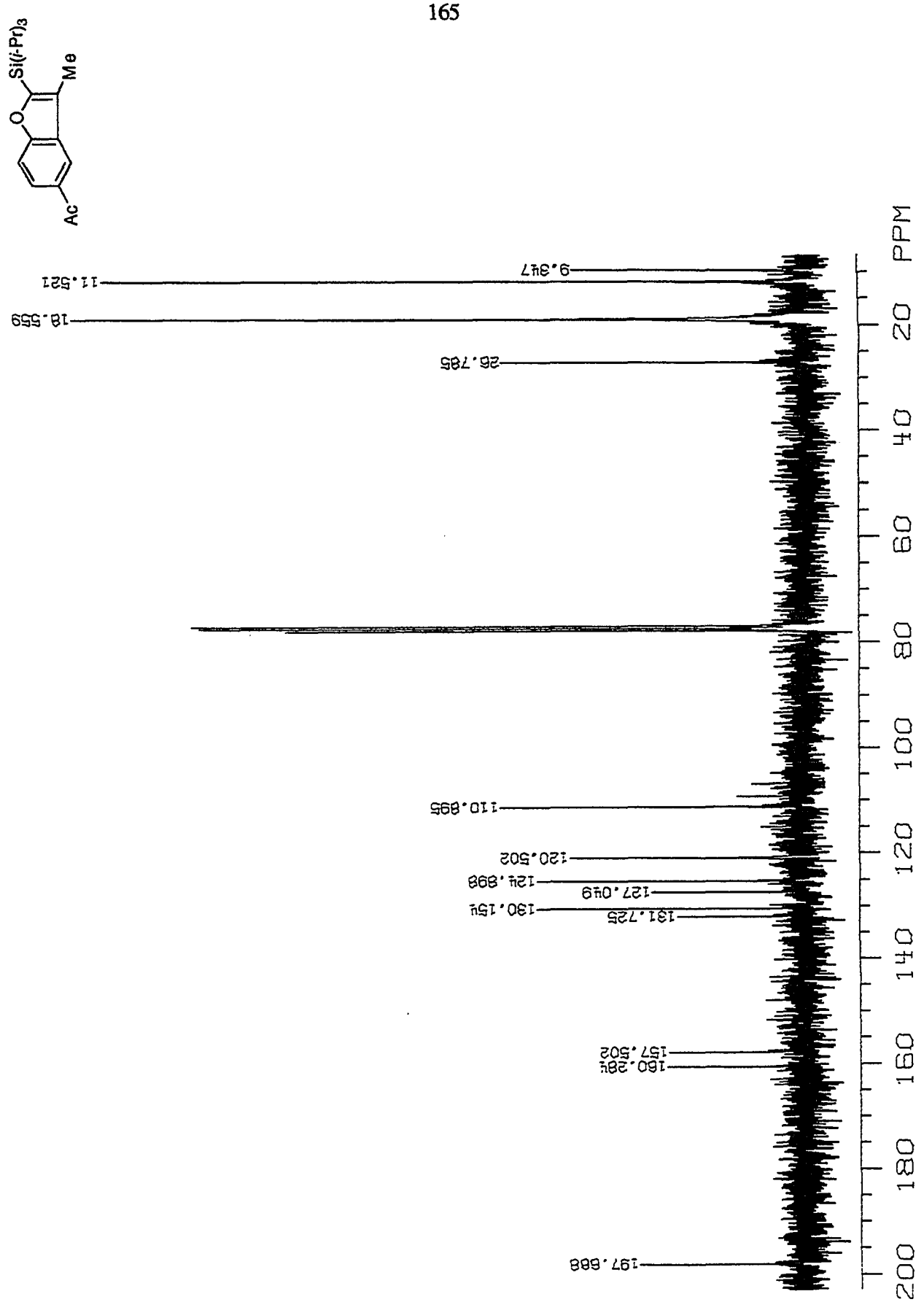

9.445
11.823
18.835
111.048
119.047
121.559
128.945
128.998
126.371
155.178
157.657
160
140
120
100
80
60
40
20
PPM

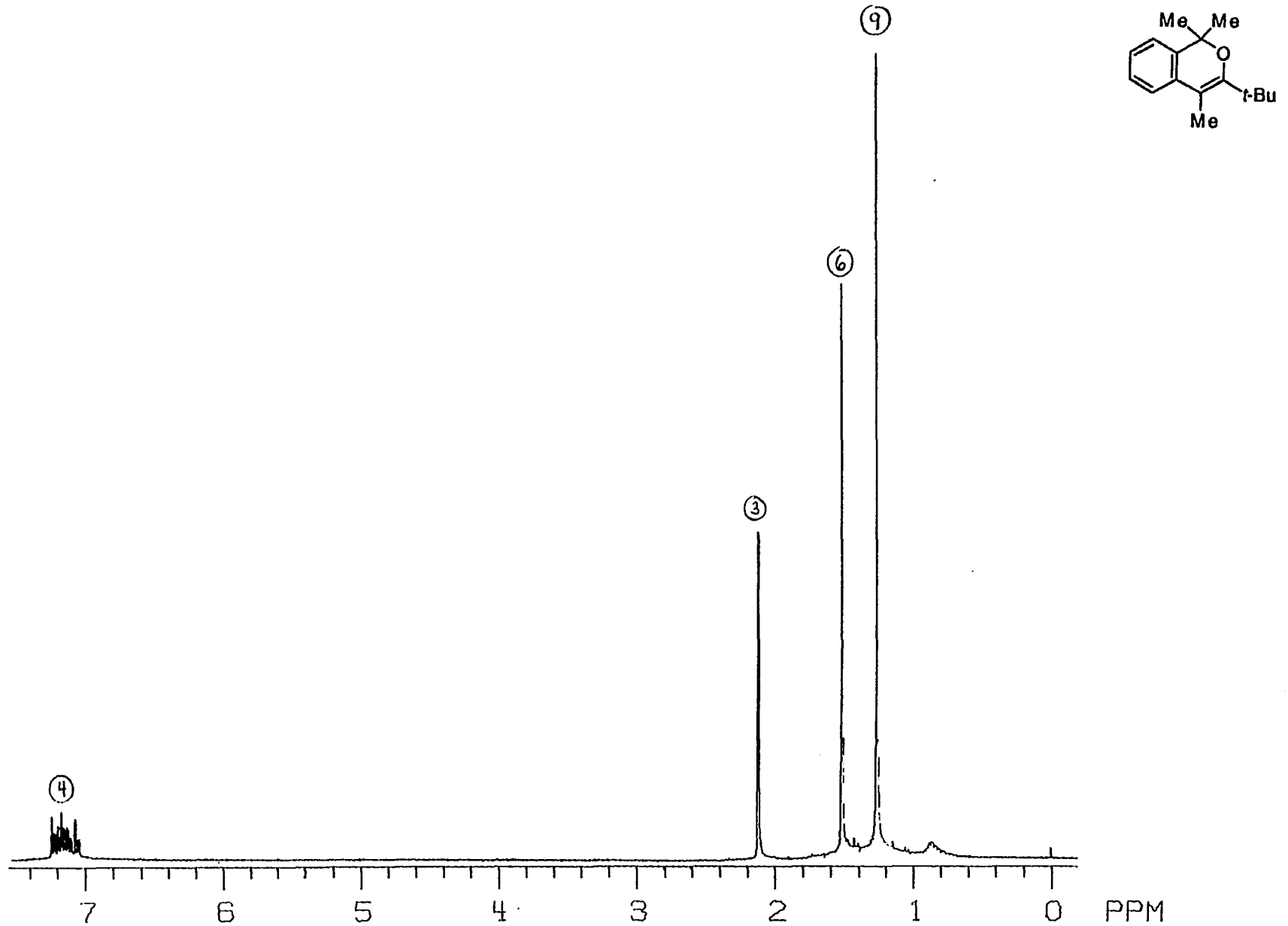

Si(i-Pr)3
Ph
O
18
3
2
1
1
2
6
4
2
0 PPM

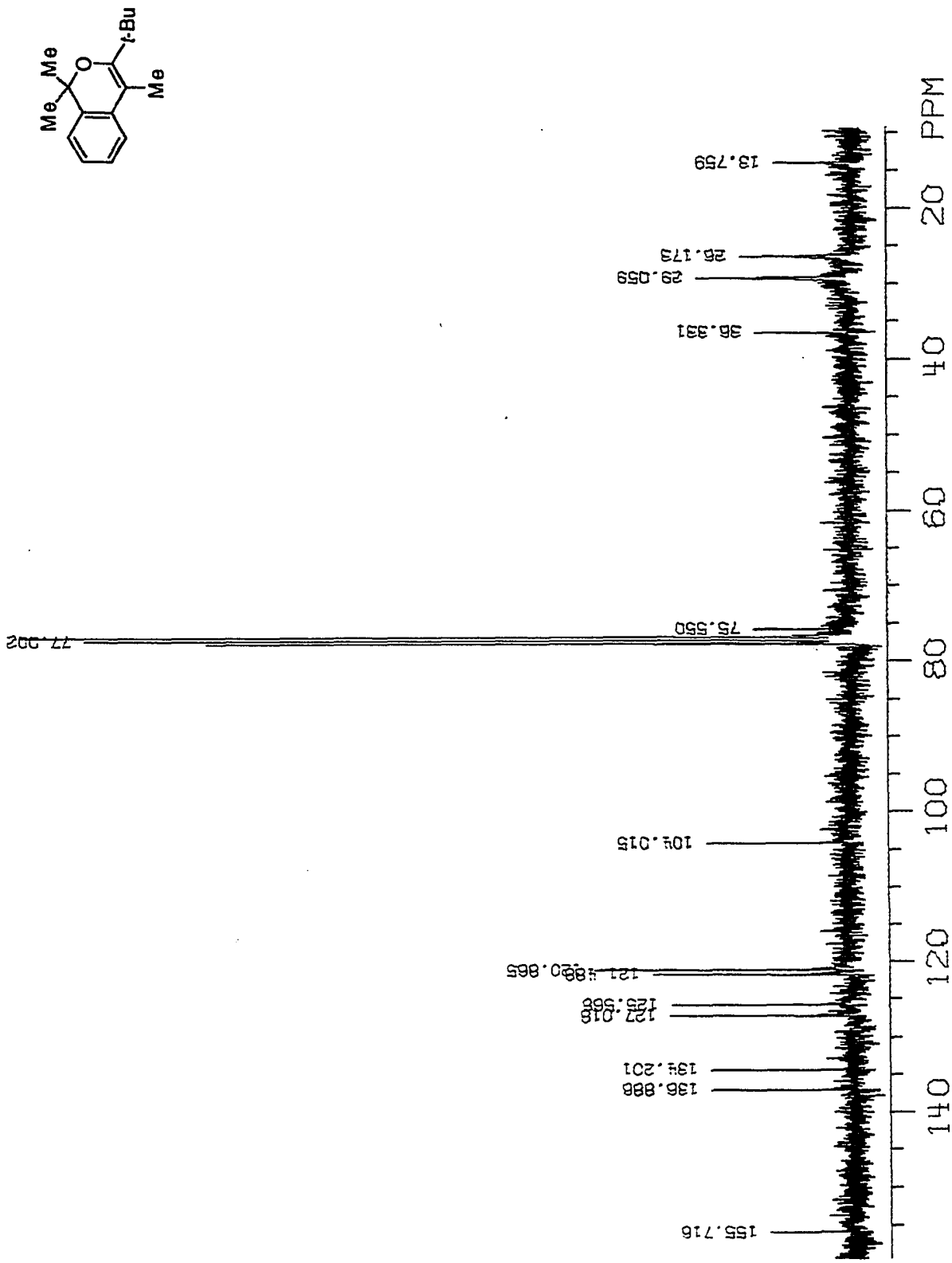

Si(i-Pr)3
Ph
O


PPM
0
20
40
60
80
100
120
140
11.763
18.737
77.006
111.105
120.026
122.166
124.382
127.611
128.099
129.549
130.034
133.398
156.088
157.528


Si(i-Pr)3
Me
O
Ac
18
3
3
3
0
2
4
6
8
PPM

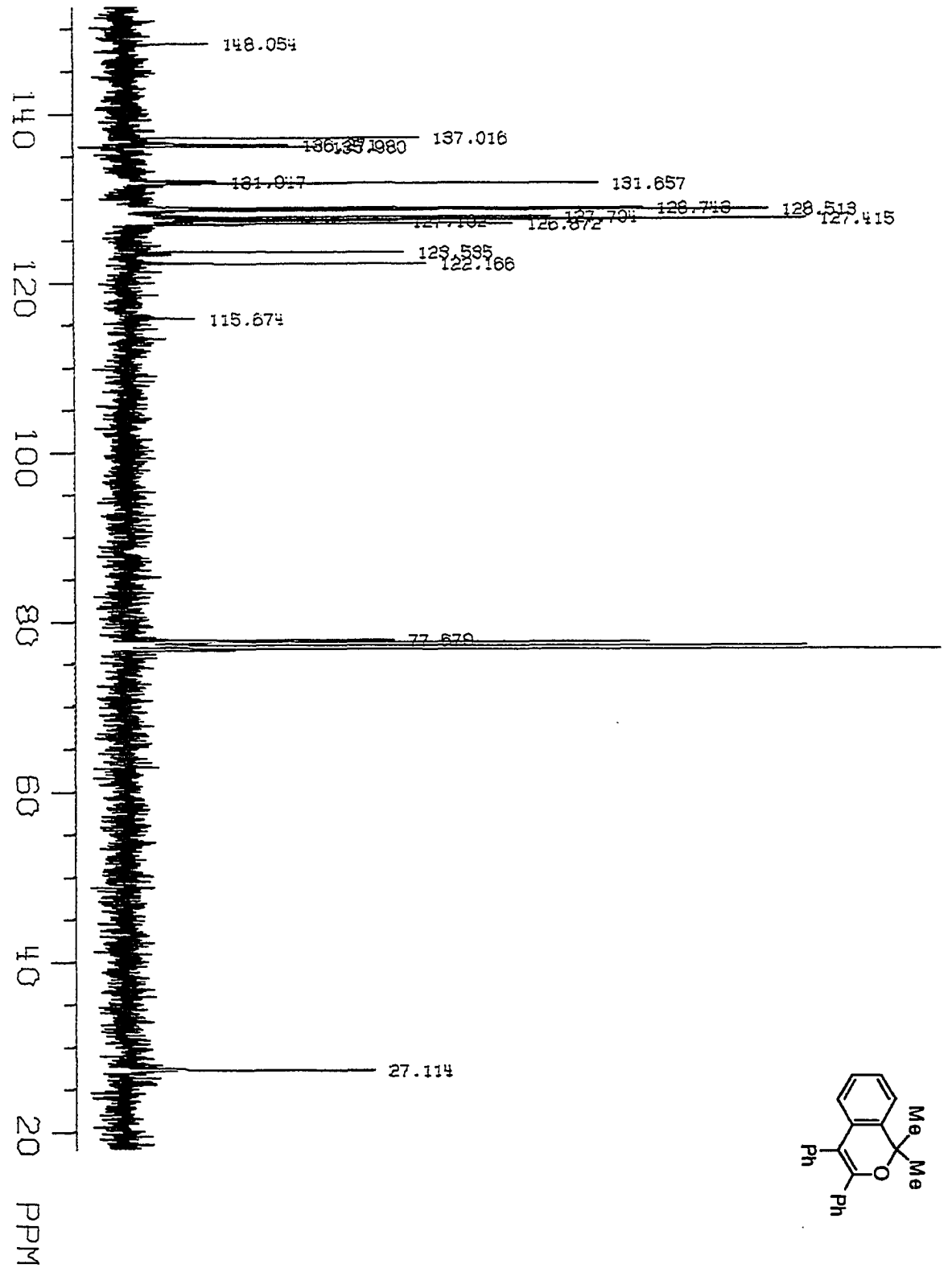

Si(i-Pr)3
Me
O
Ac
9.347
11.521
18.559
26.785
110.895
120.502
124.898
127.049
130.154
131.725
157.502
160.284
197.688
200
180
160
140
120
100
80
60
40
20
PPM

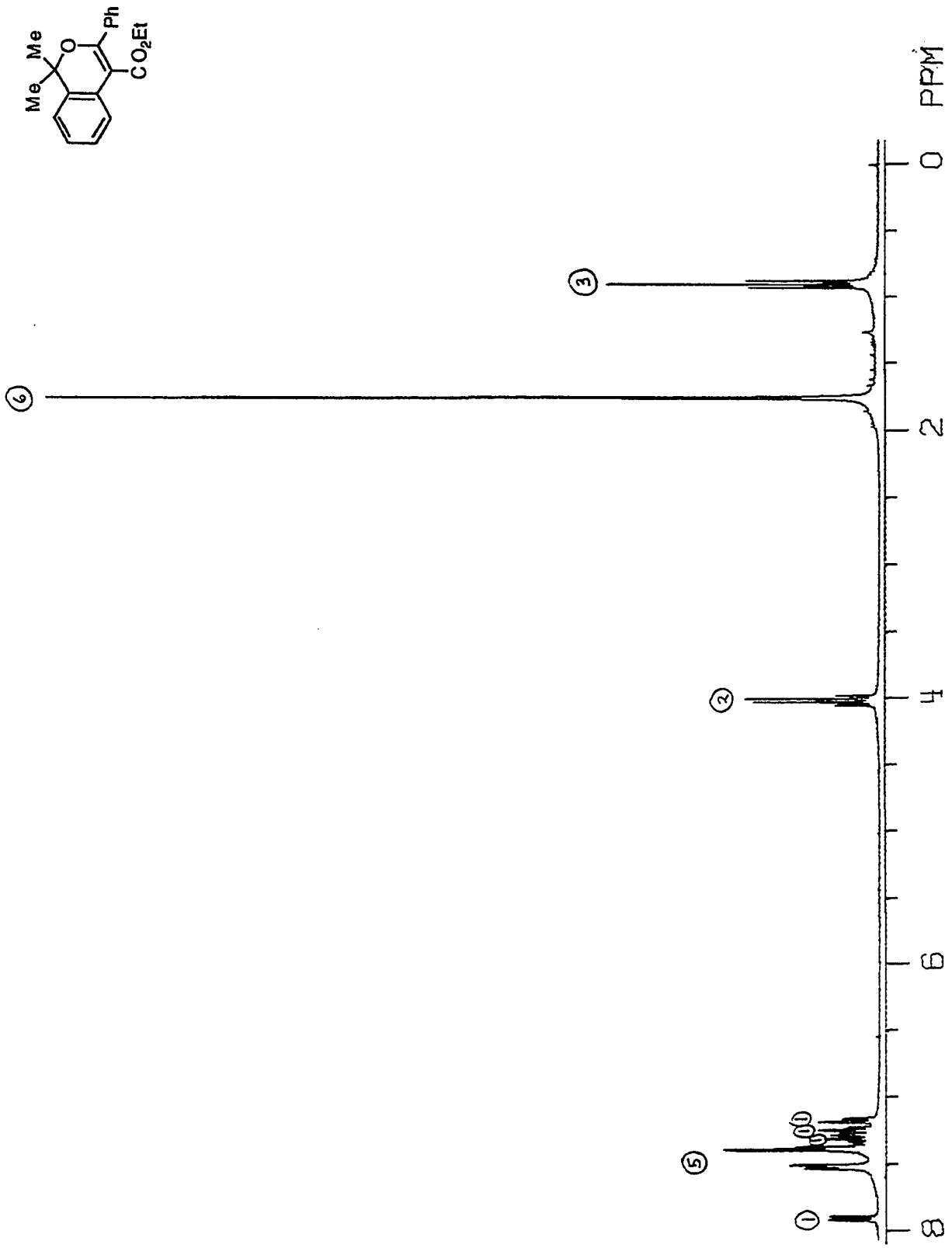

Me
Me
O
t-Bu
Me
9
6
3
4
7
6
5
4
3
2
1
0
PPM


Me
Me
O
t-Bu
Me
155.716
136.886
134.201
127.018
125.366
121.865
104.015
75.550
77.002
36.331
29.059
26.173
13.759
140
120
100
80
60
40
20
PPM

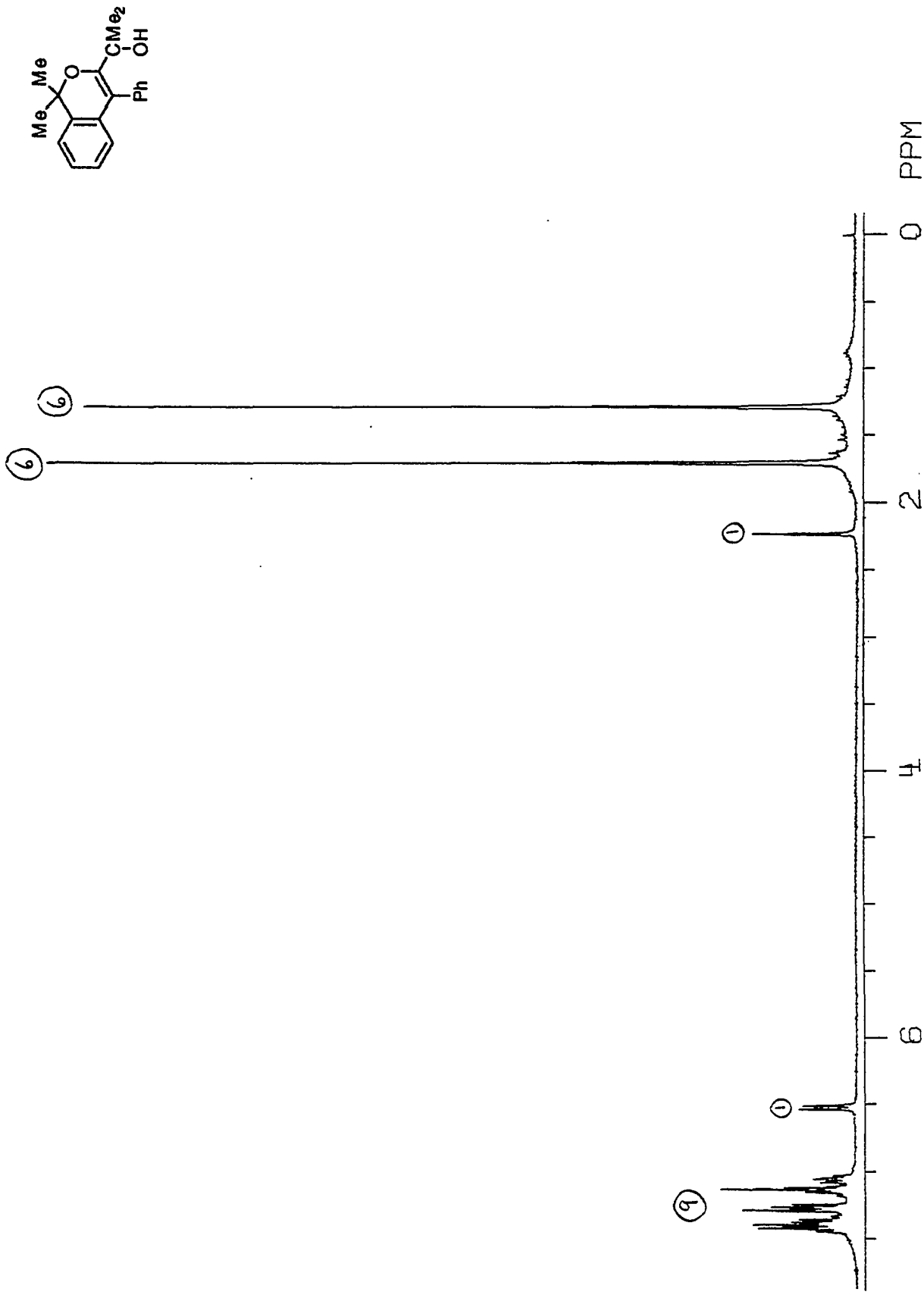
PPM
0
1.
2
3.
4
5.
6.
7.
14
6

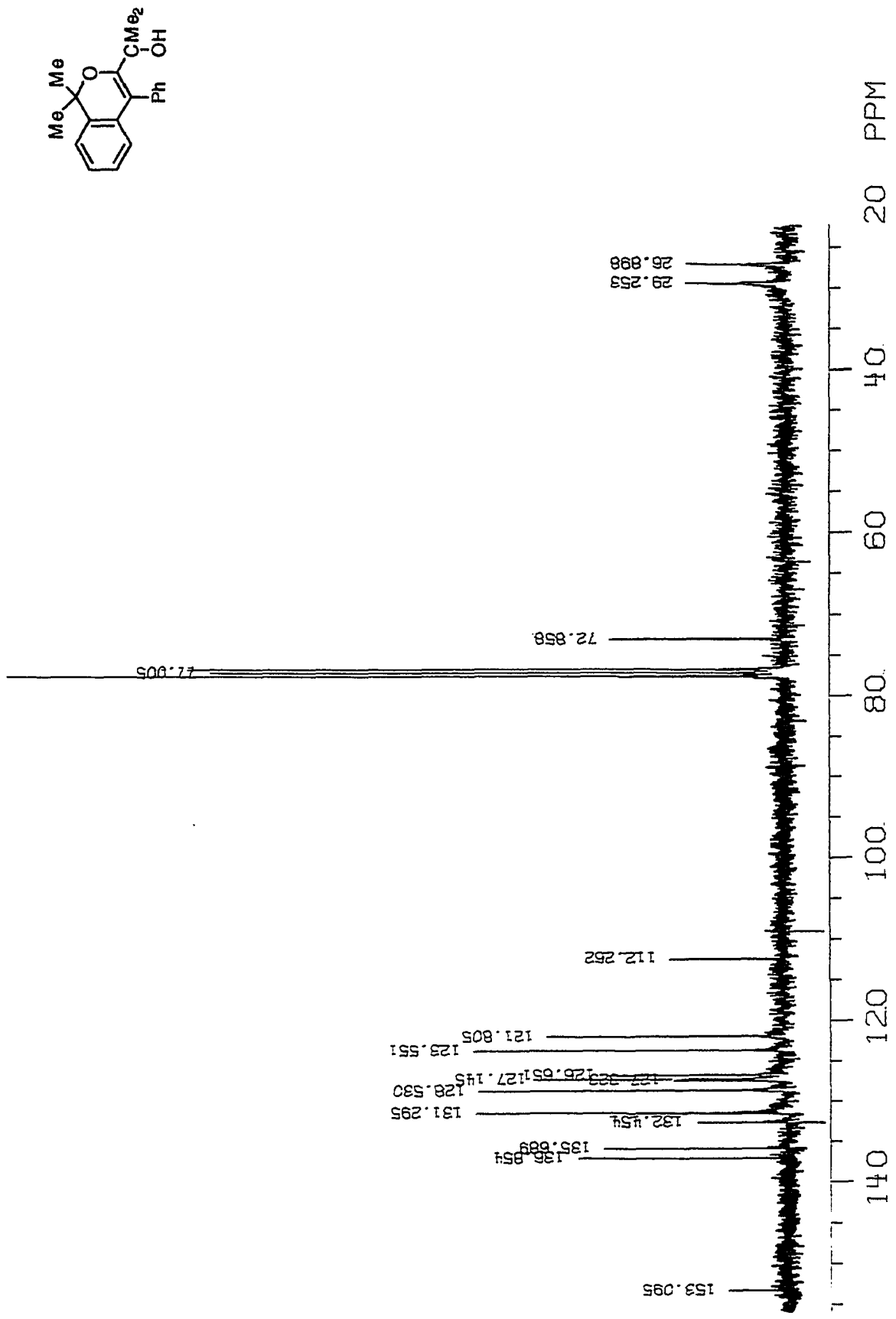
Me
Me
Ph
O
Ph


148.054
137.016
131.657
128.513
127.415
123.595
122.166
115.674
77.679
27.114
140
120
100
80
60
40
20
PPM
Me
Me
Ph
Ph
O

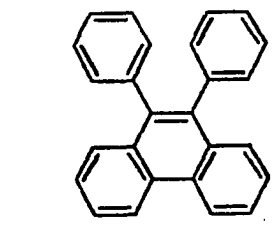

Me
Me
O
Ph
CO2Et
PPM
0
2
4
6
8
1
2
3
5
6

168.077
157.463
135.592
129.627
122.241
108.156
79.492
77.013
60.471
26.985
13.575
160
140
120
100
80
60
40
20
PPM
Me
Me
O
Ph
CO2Et

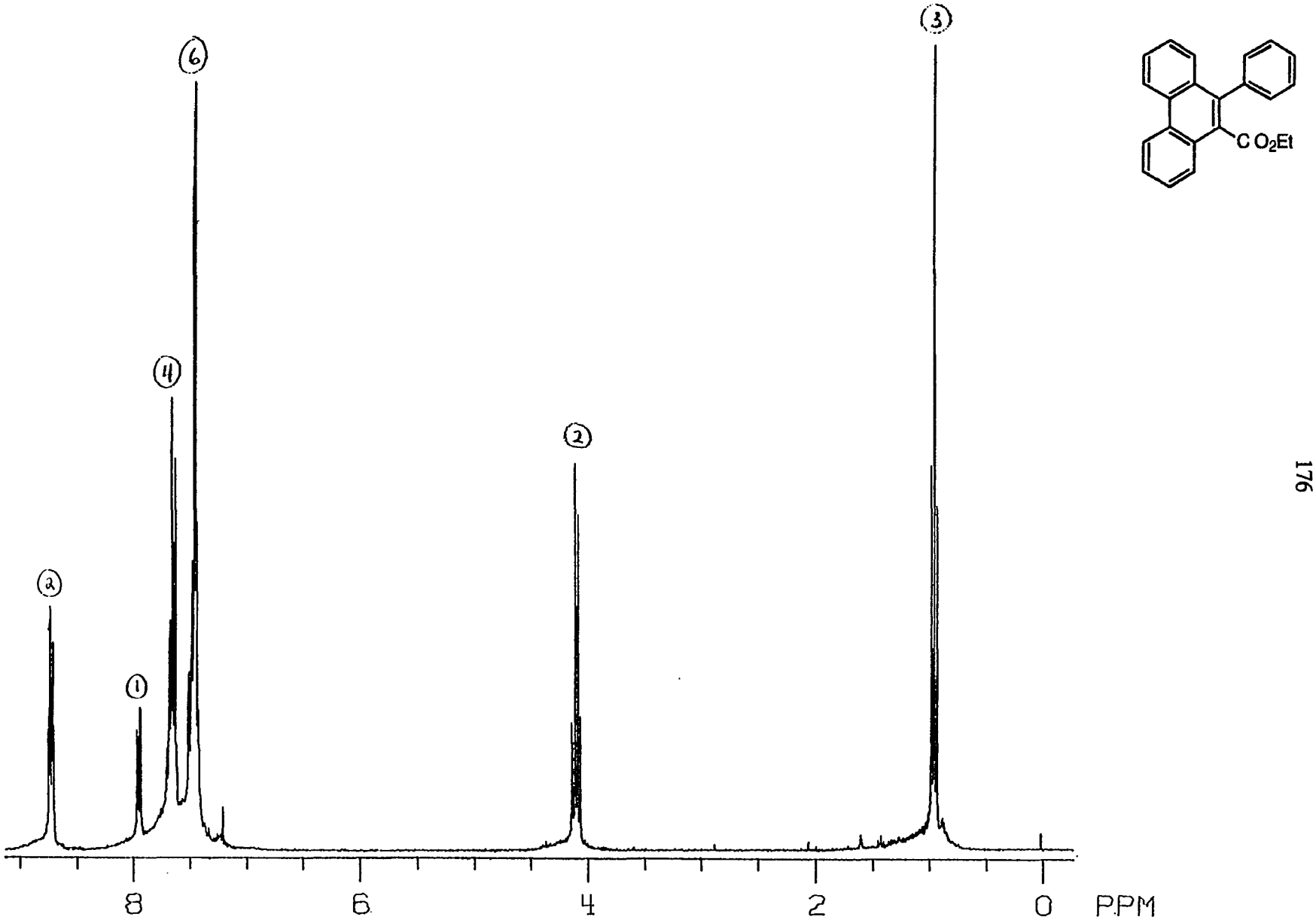

Me
Me
O
CMe2
OH
Ph
6
1
1
9
0
2
4
6
PPM

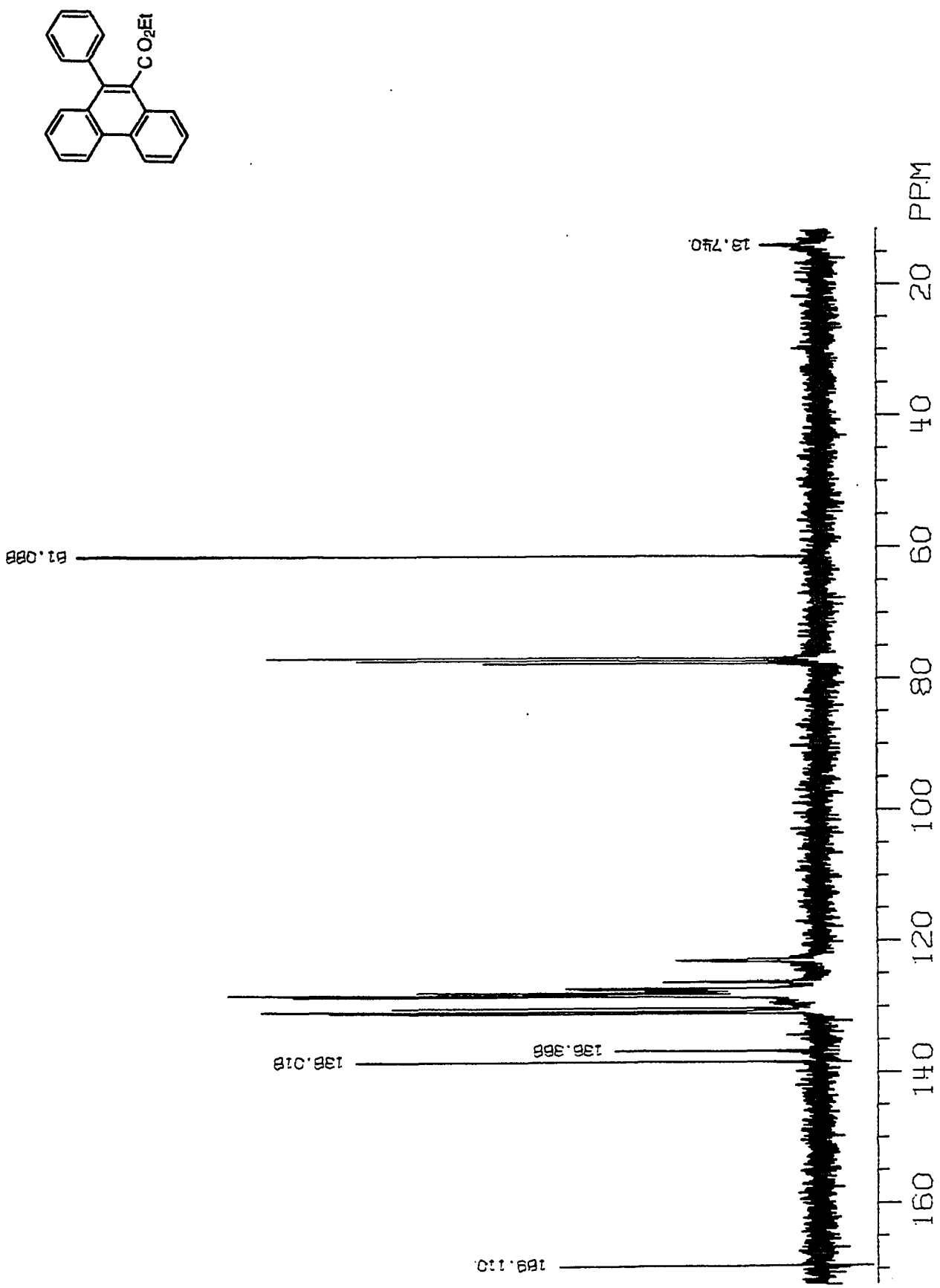

Me
Me
O
CMe2
OH
Ph
PPM
20
40
60
80
100
120
140
153.095
135.689
132.454
131.295
128.530
123.551
121.805
112.252
72.858
42.005
29.253
26.898

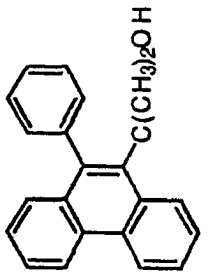
APPENDIX D: CHAPTER 4 ^{1}H AND ^{13}C NMR PHENANTHRENE SPECTRA

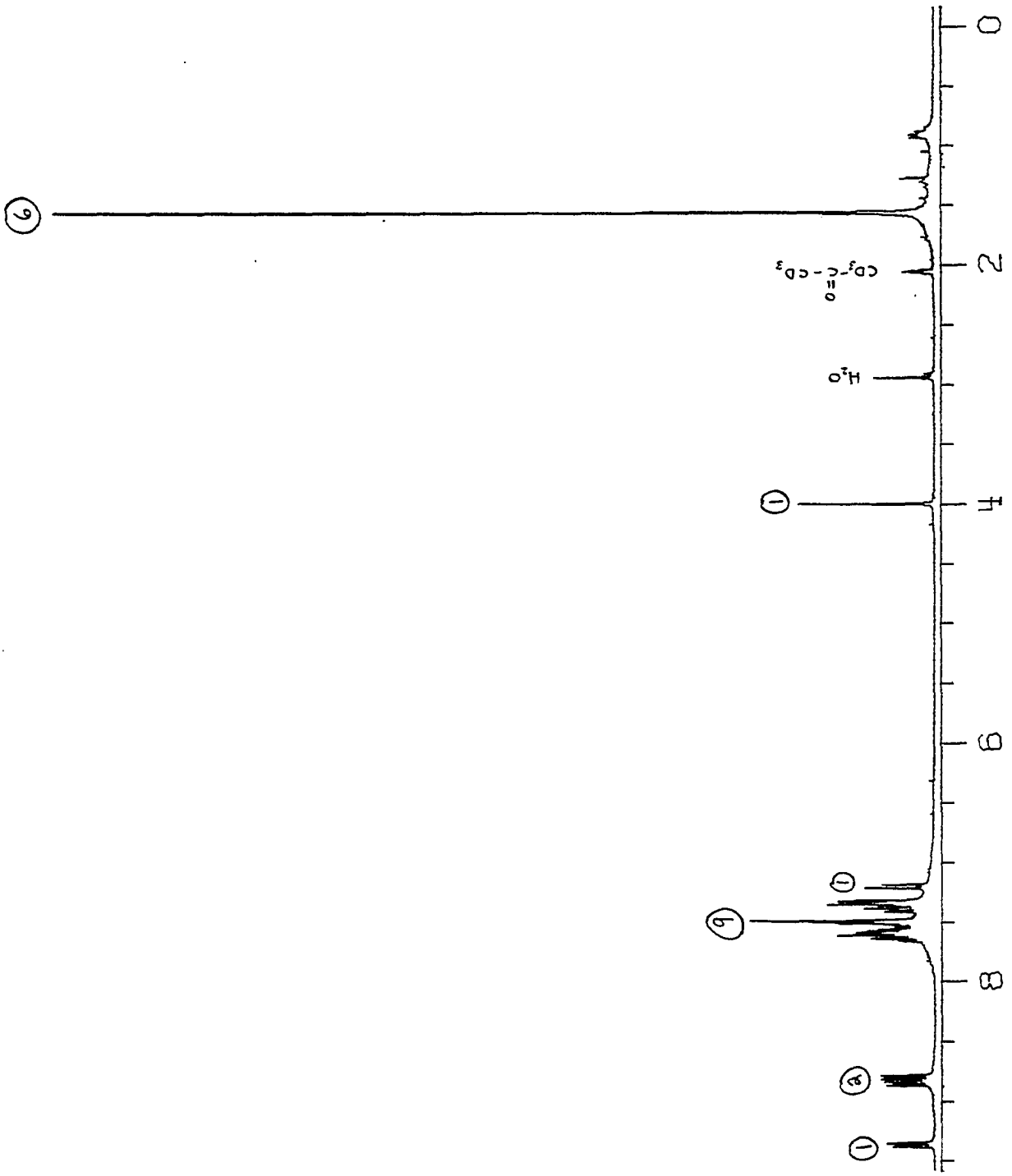


PPM
0
2
4
6
8
10
2
2
2
2

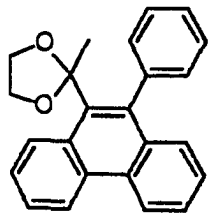

6
3
4
2
5
1
8
6
4
2
0
PPM
CO2Et

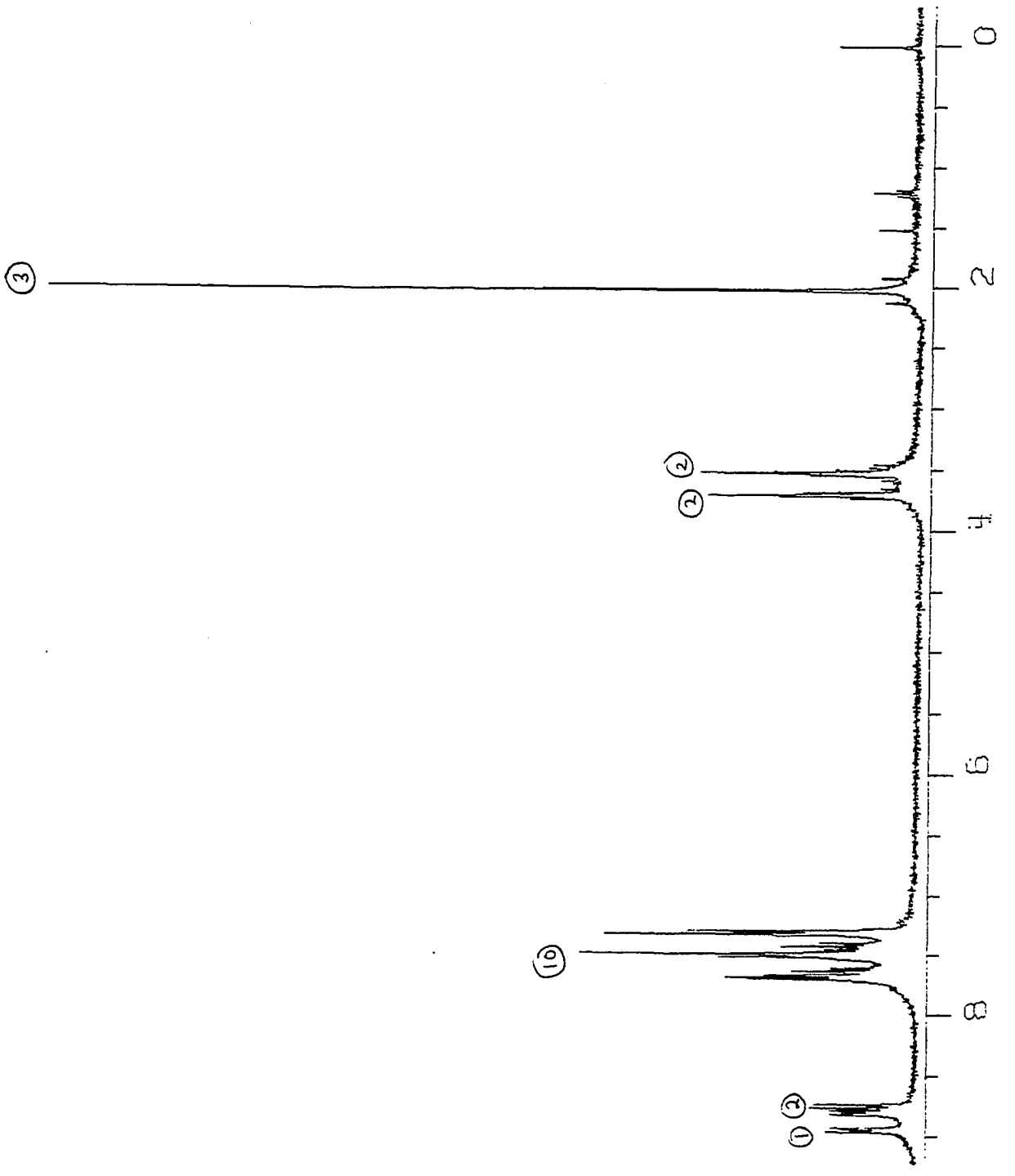

CO2Et
13.740
61.088
136.018
136.368
169.110
PPM
20
40
60
80
100
120
140
160

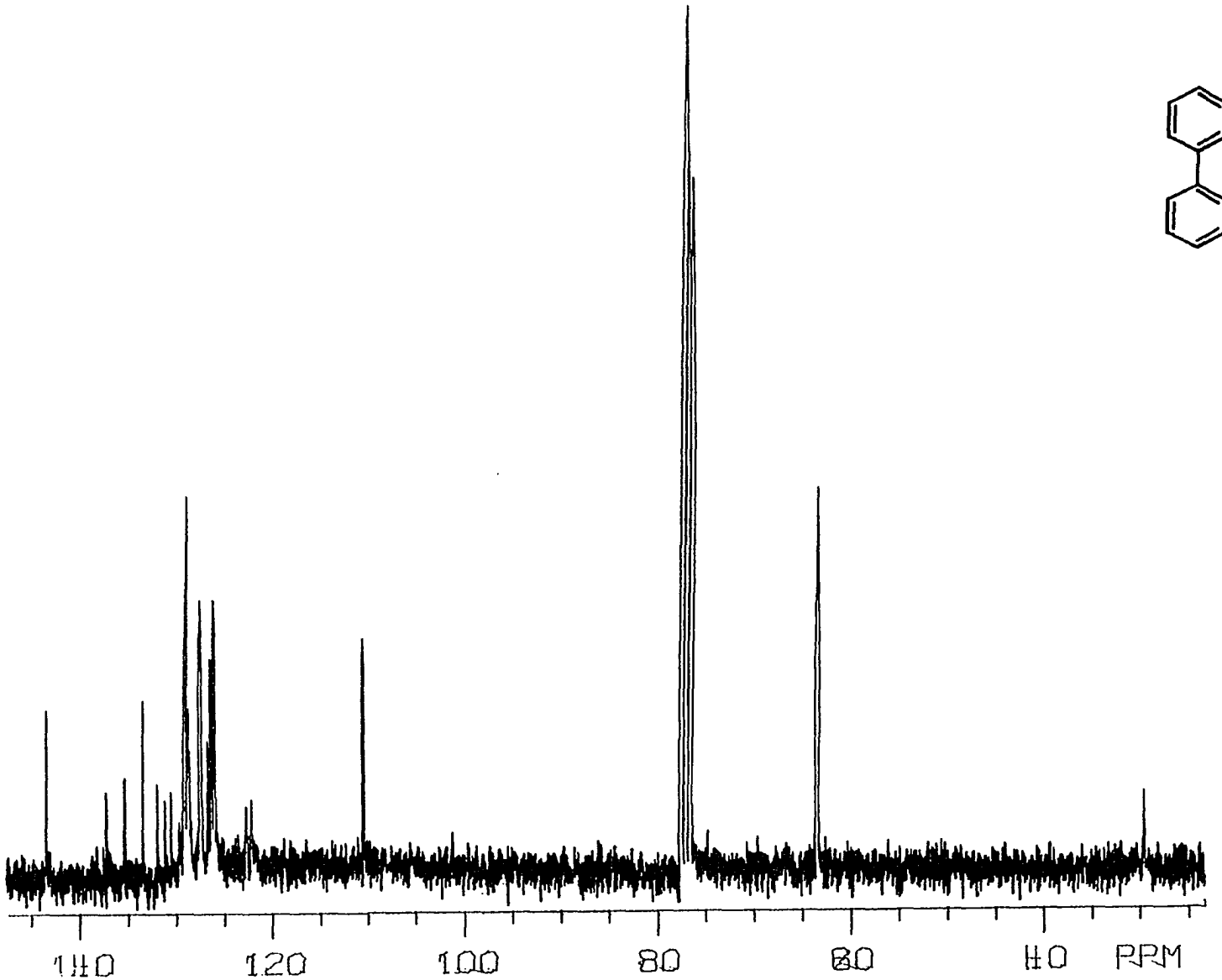

C(CH3)2OH

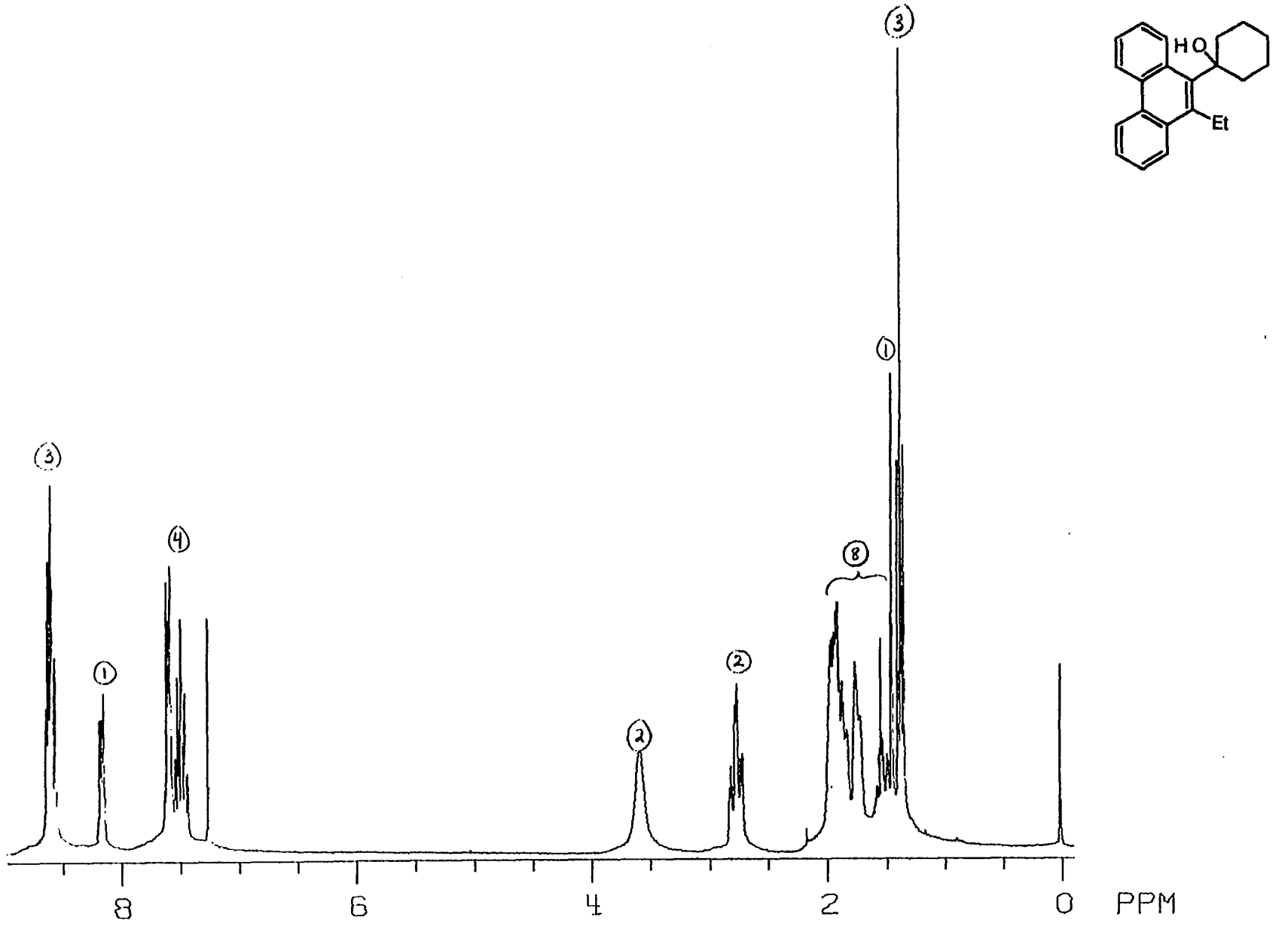

PPM
0
2
4
6
8
H2O
CD3-C=O-CD3

143.102
141.086
135.061
131.823
130.613
128.518
127.867
125.666
75.771
31.458
140
120
100
80
60
40
PPM
C(CH3)2OH

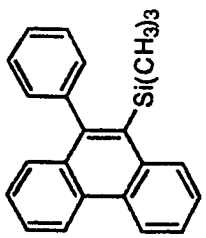


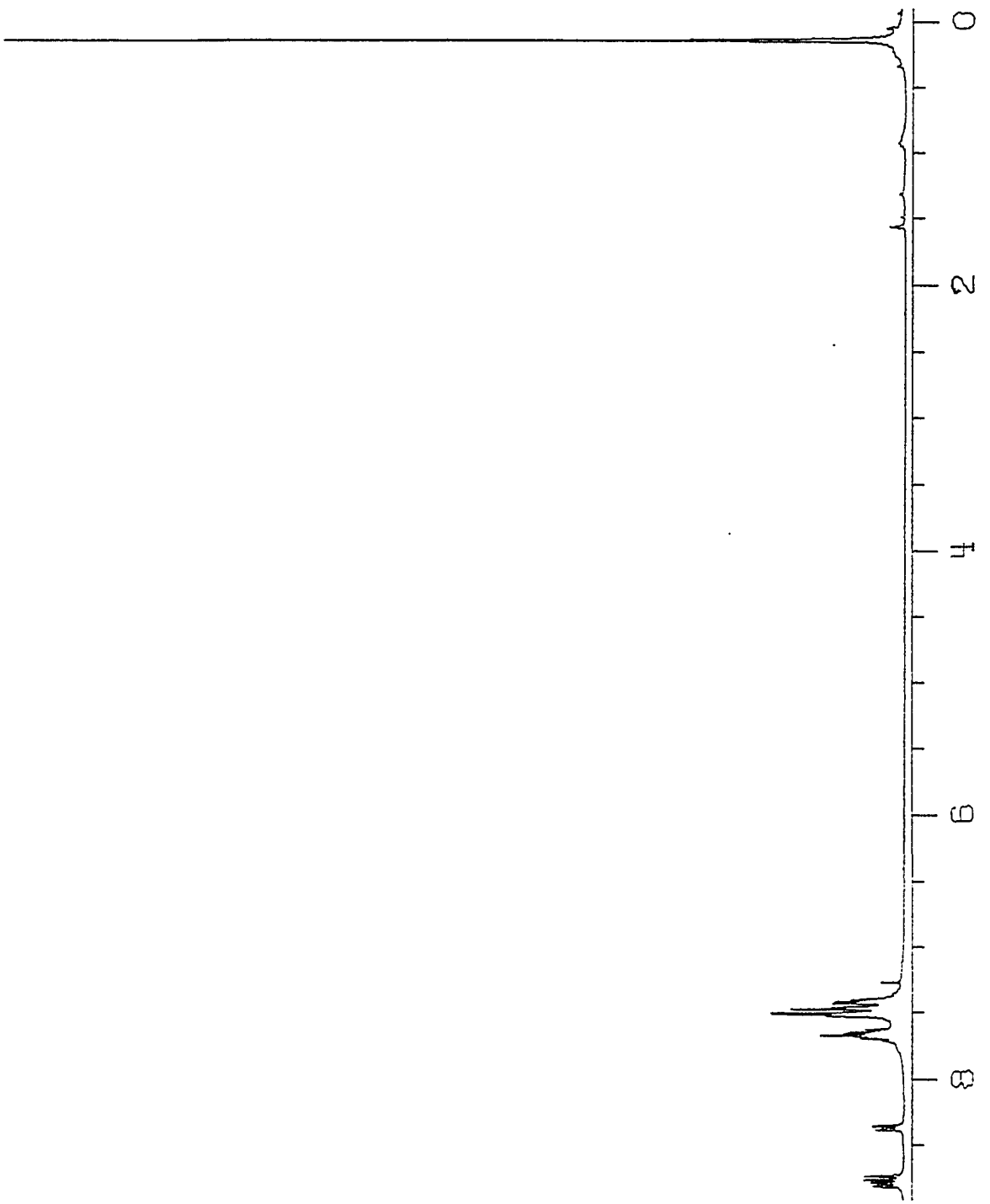

PPM
0
2
4
6
8
3
2
2
10
3
1

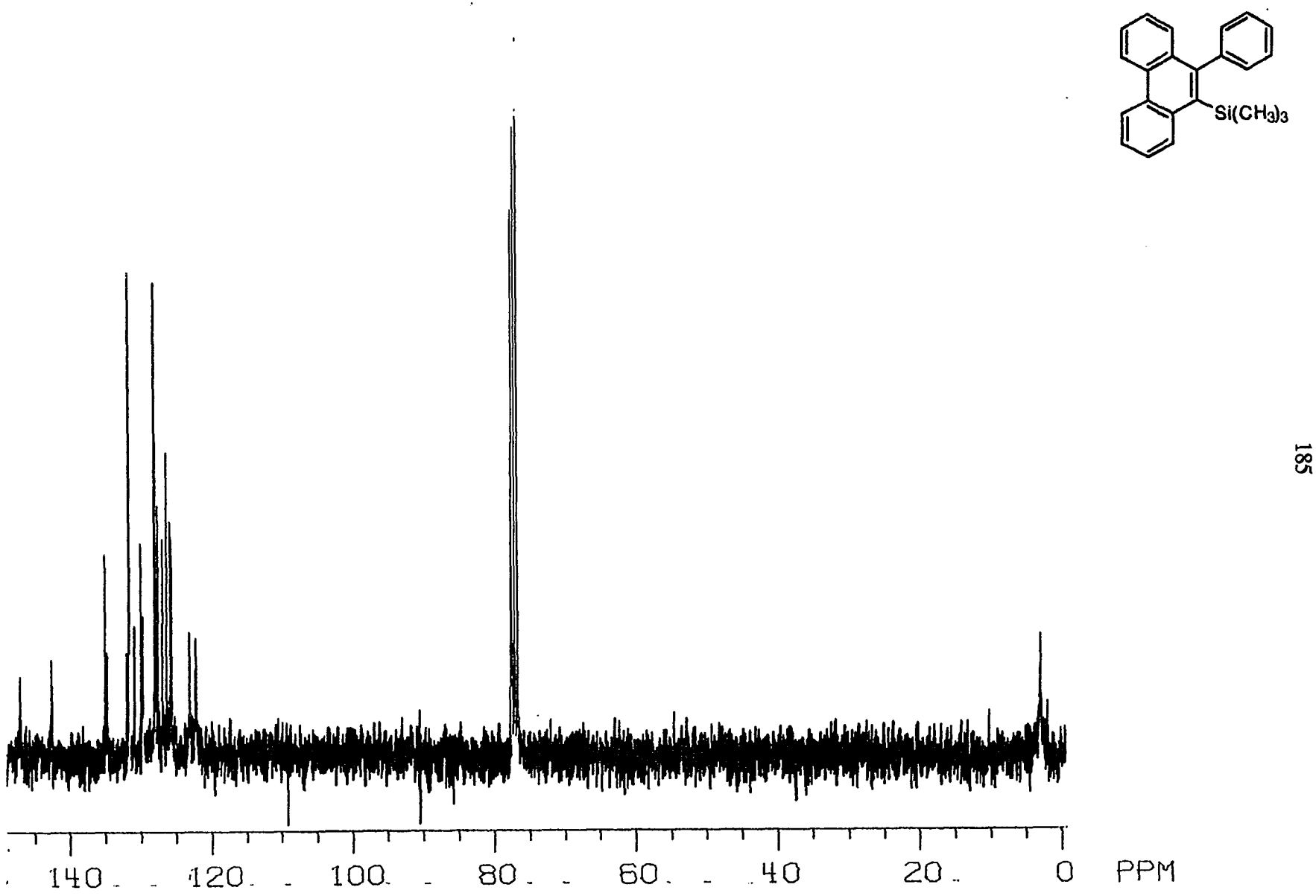

140
120
100
80
60
40
PPM


HO
Et
3
1
4
8
2
2
3
1
8
6
4
2
0
PPM

140.088
137.177
132.227
130.200
127.408
125.702
124.141
37.617
25.134
22.201
10.692
140
120
100
80
60
40
20
PPM
HO
Et

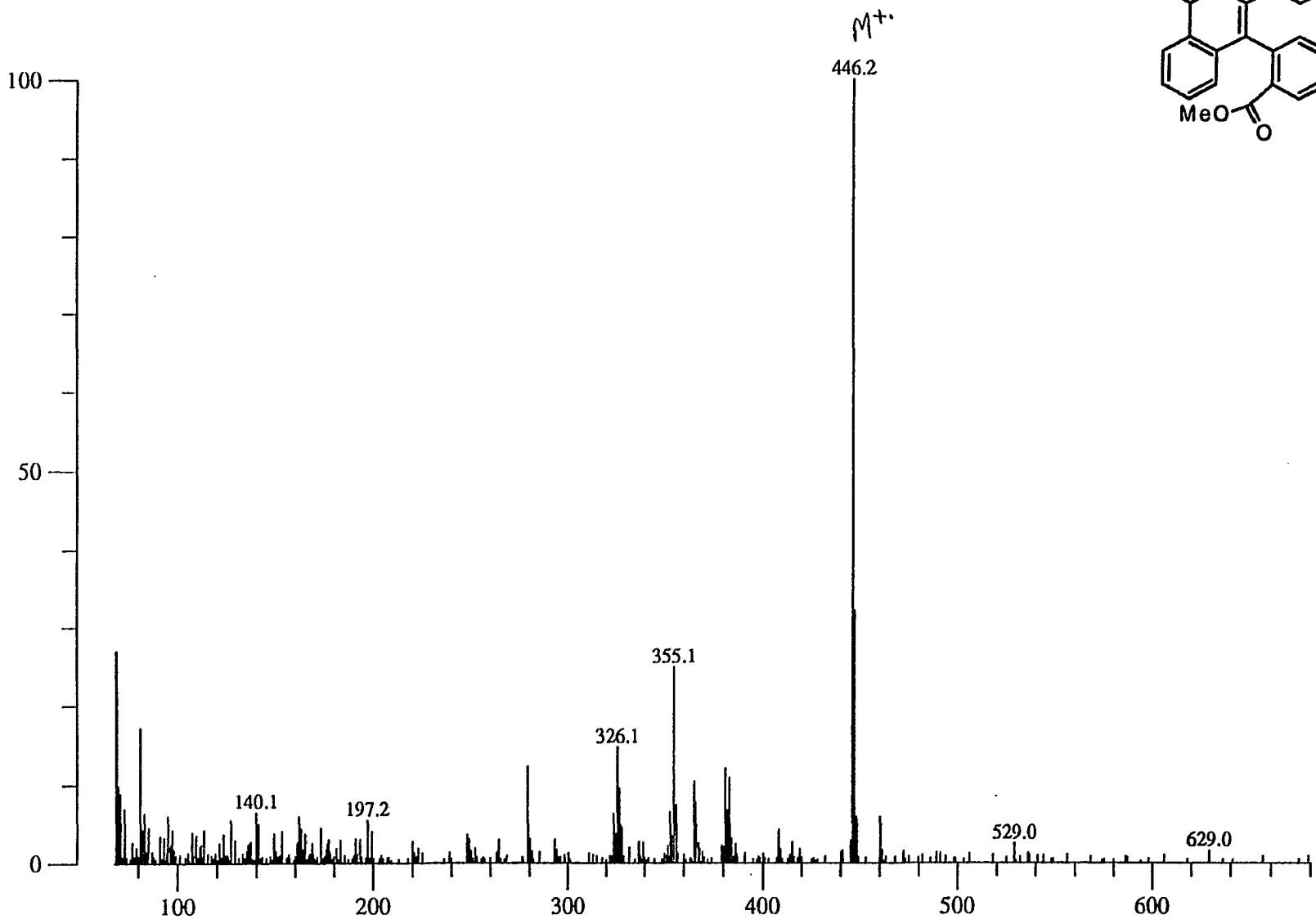

Si(CH3)3


PPM
0
2
4
6
8

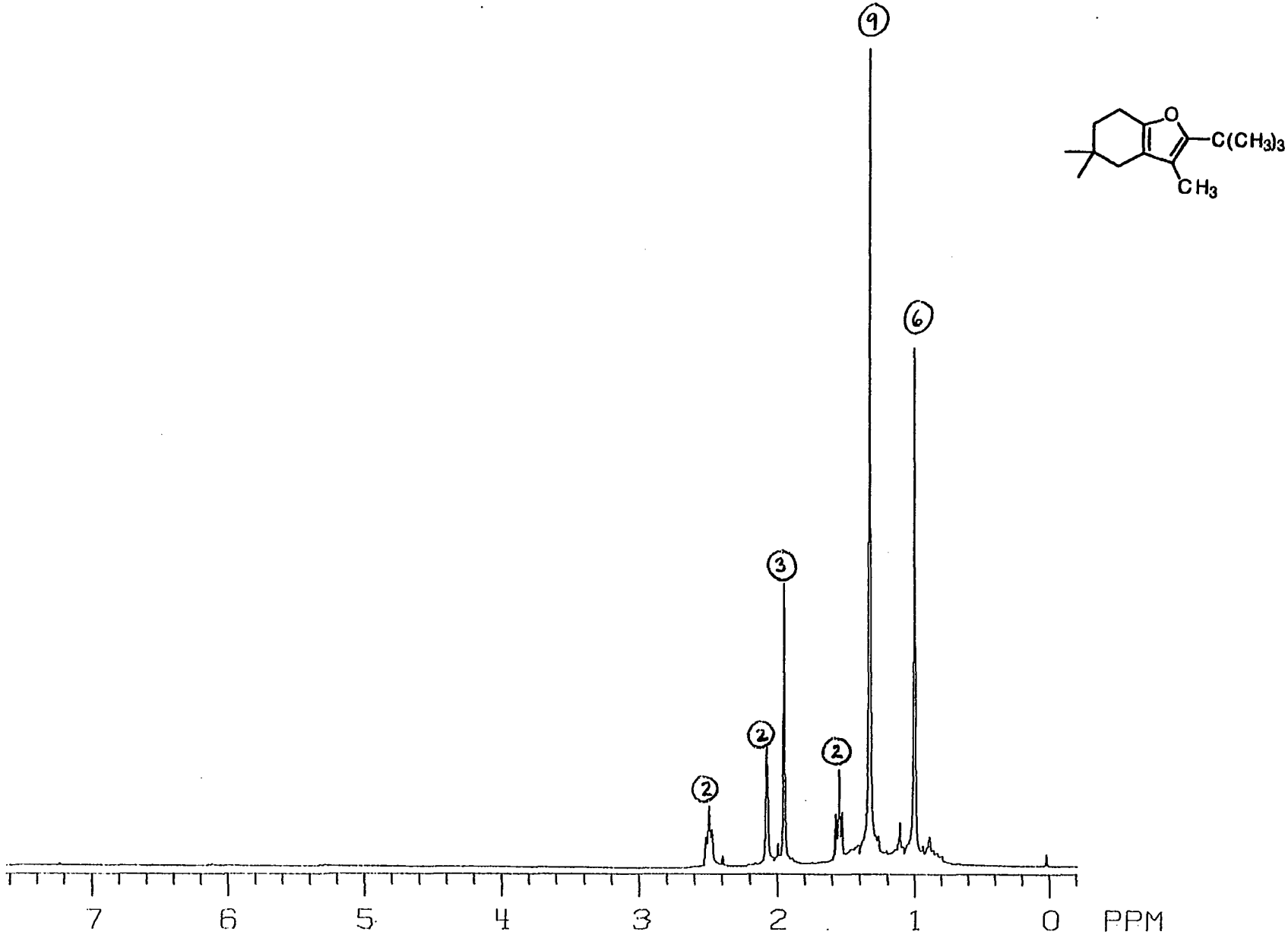

Si(CH3)3
140
120
100
80
60
40
20
0
PPM

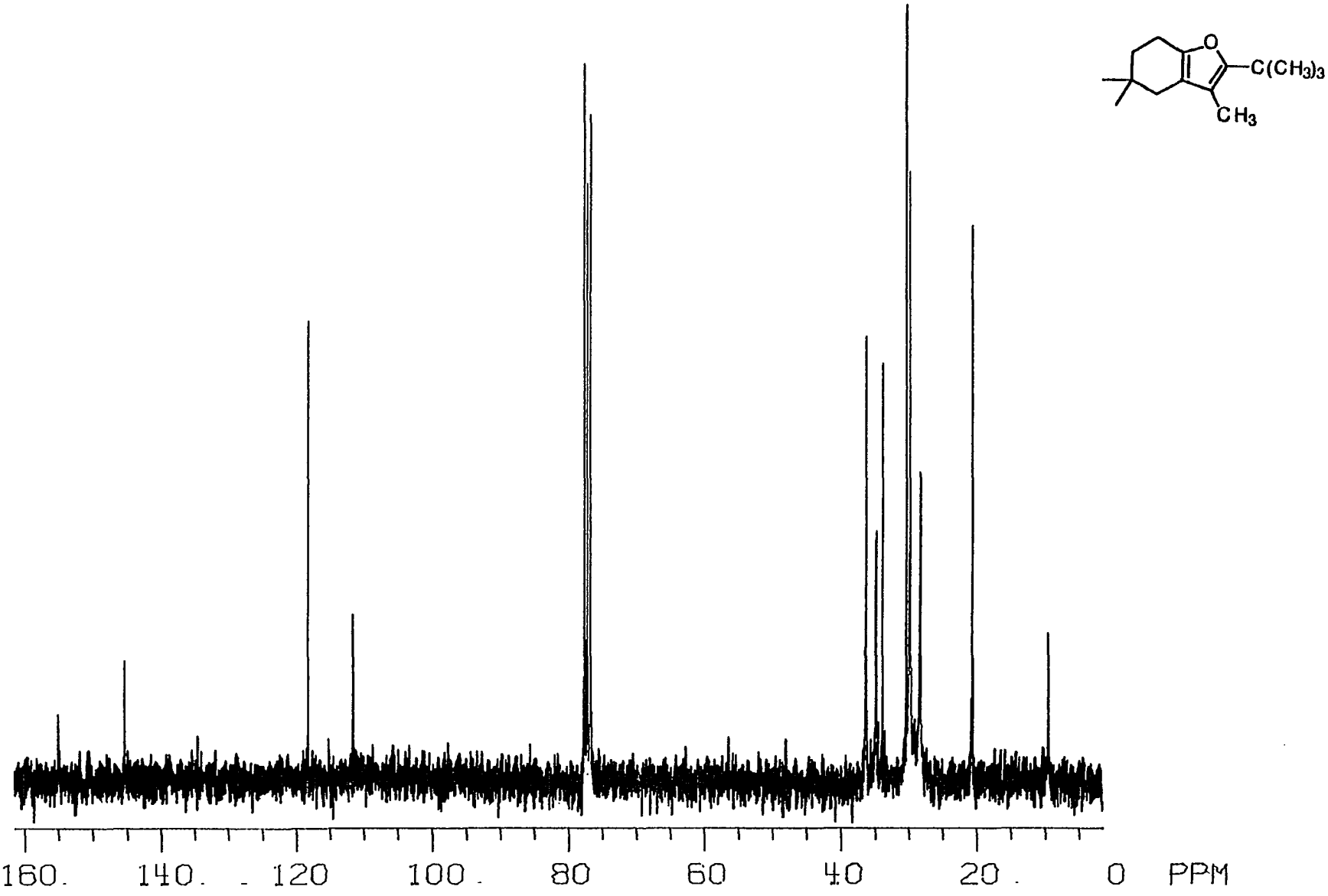
Calculated m/z 446.15181 } dev = −1.24 ppm
measured m/z 446.15126

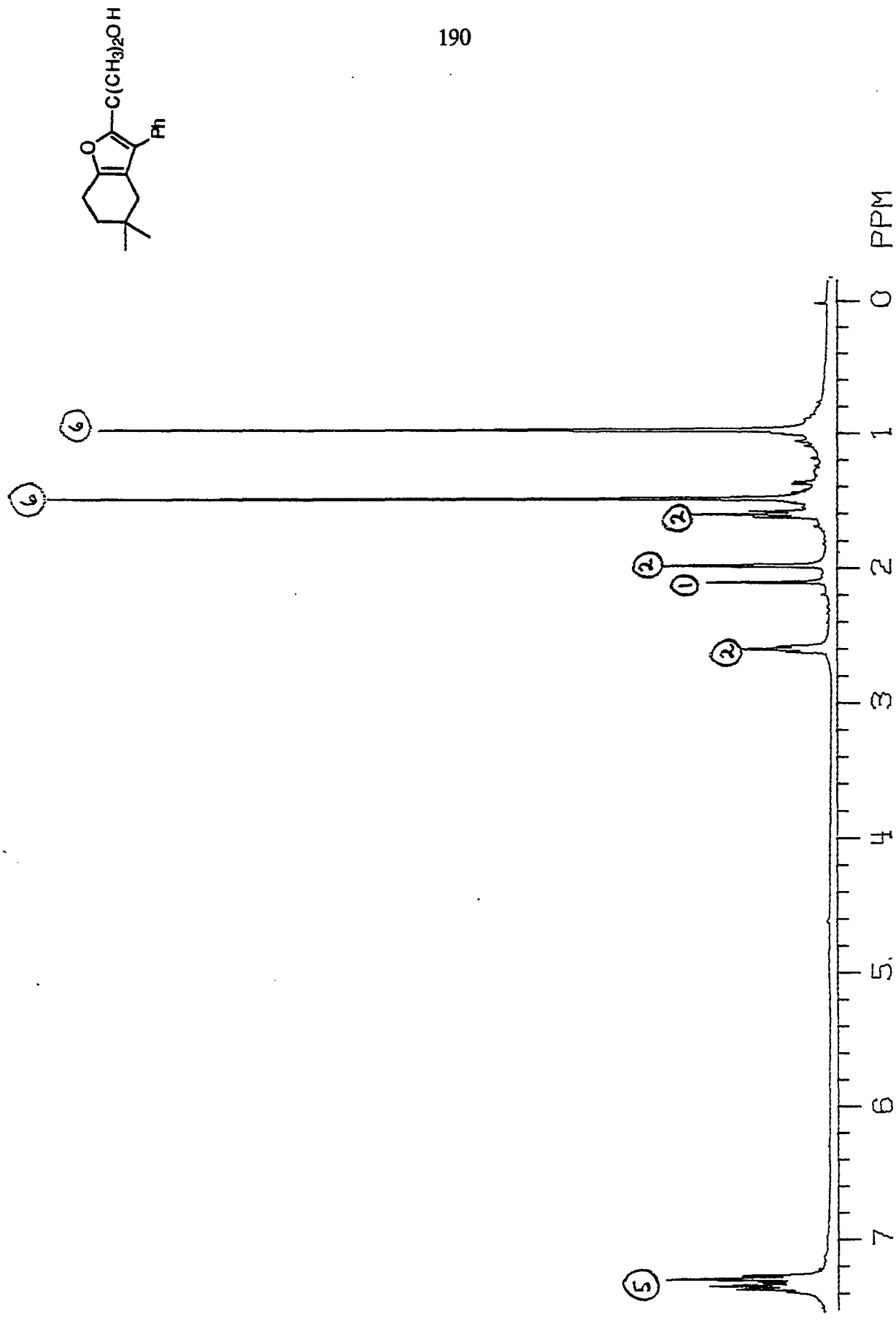
MS54360001 Scan 1 (Av 40-50 Acq) 100%=10000 mv 8 Apr 94 15:40
HRP mjD-VI-3c



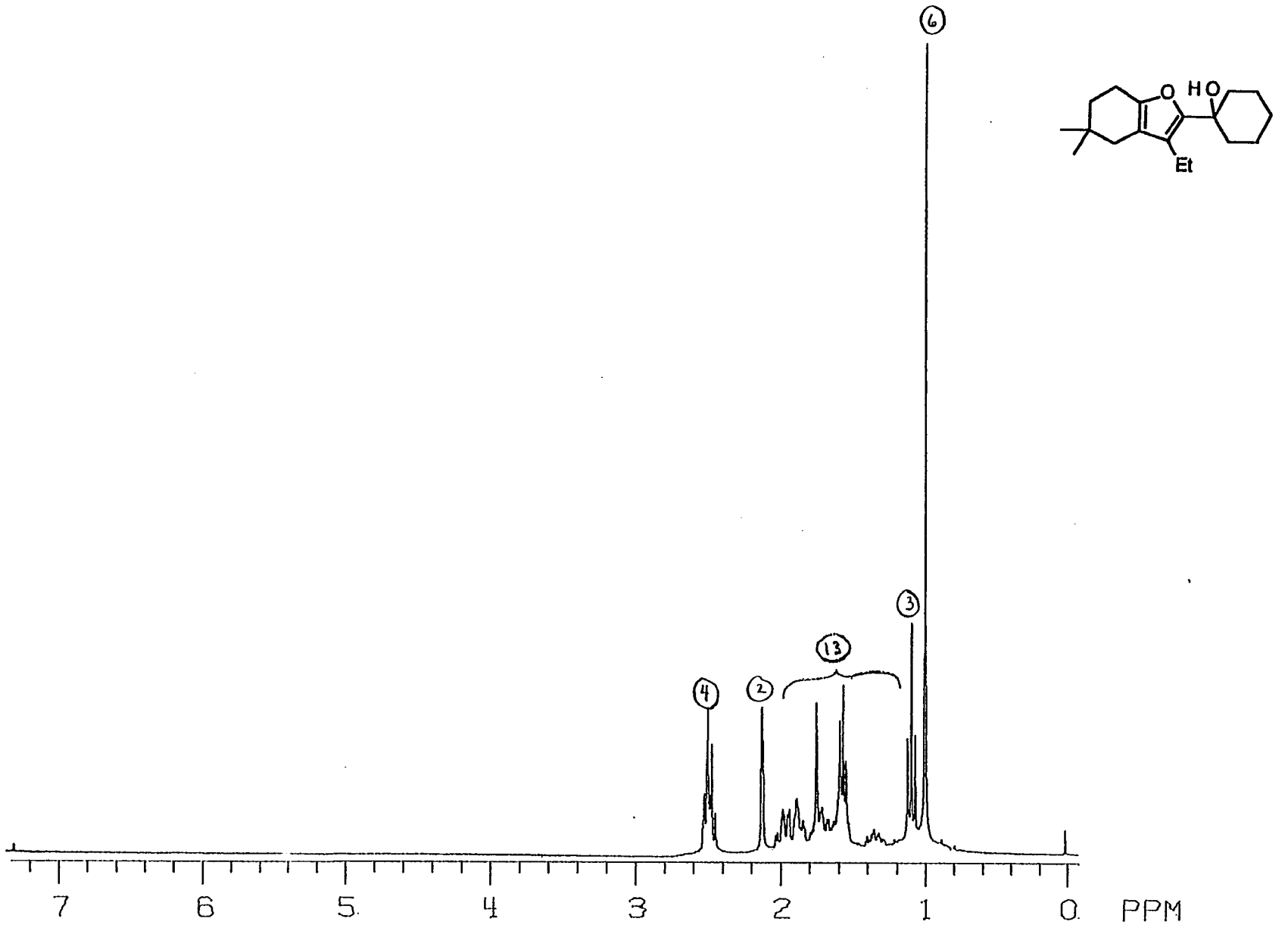
APPENDIX E: CHAPTER 5 ^{1}H AND ^{13}C NMR VINYLIC HETERO- AND CARBOCYCLE SPECTRA


9
6
3
2
2
2
C(CH3)3
CH3
7
6
5
4
3
2
1
0
PPM

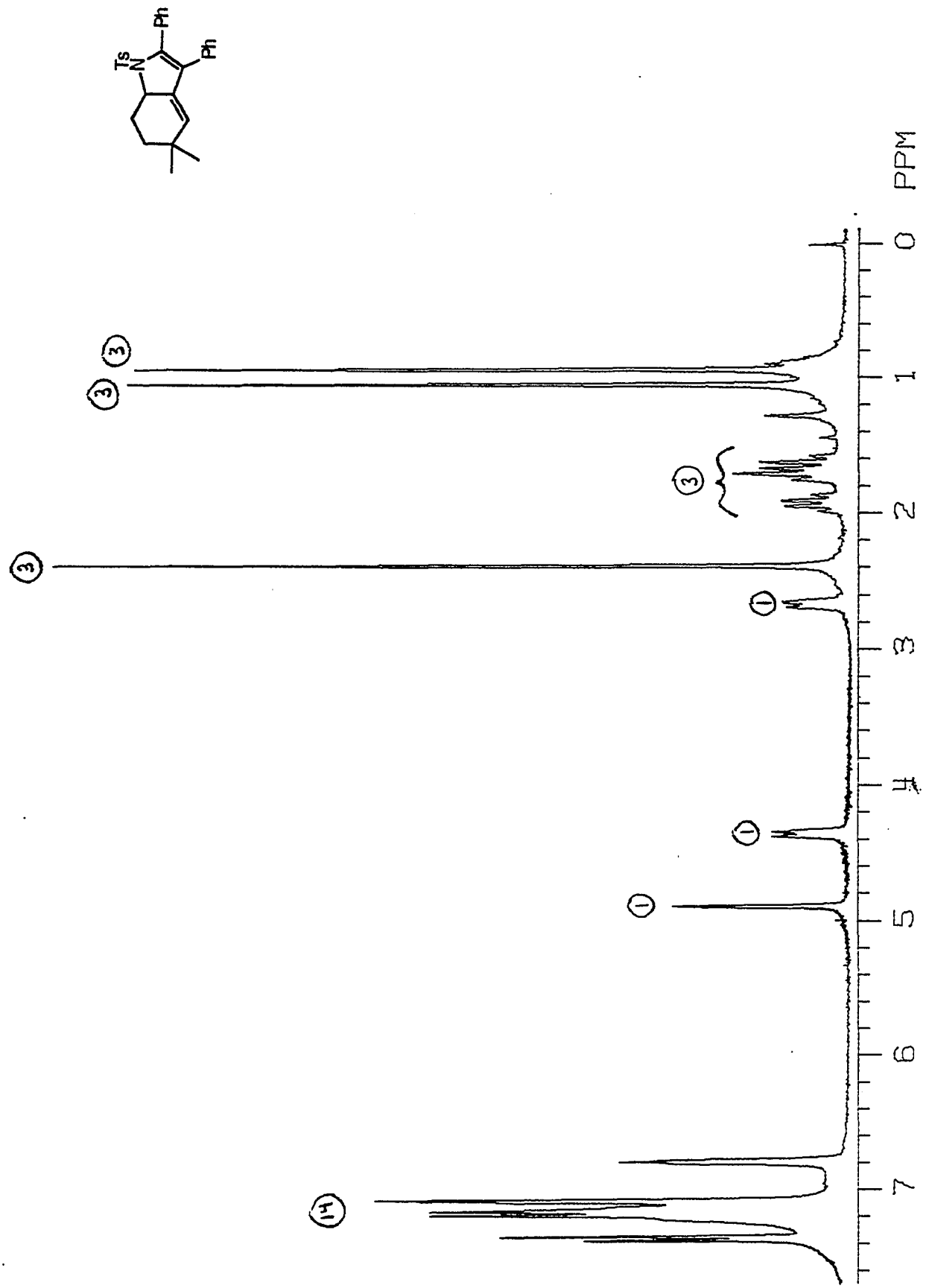

O
C(CH3)3
CH3
160.
140.
120
100.
80
60
40
20.
0
PPM

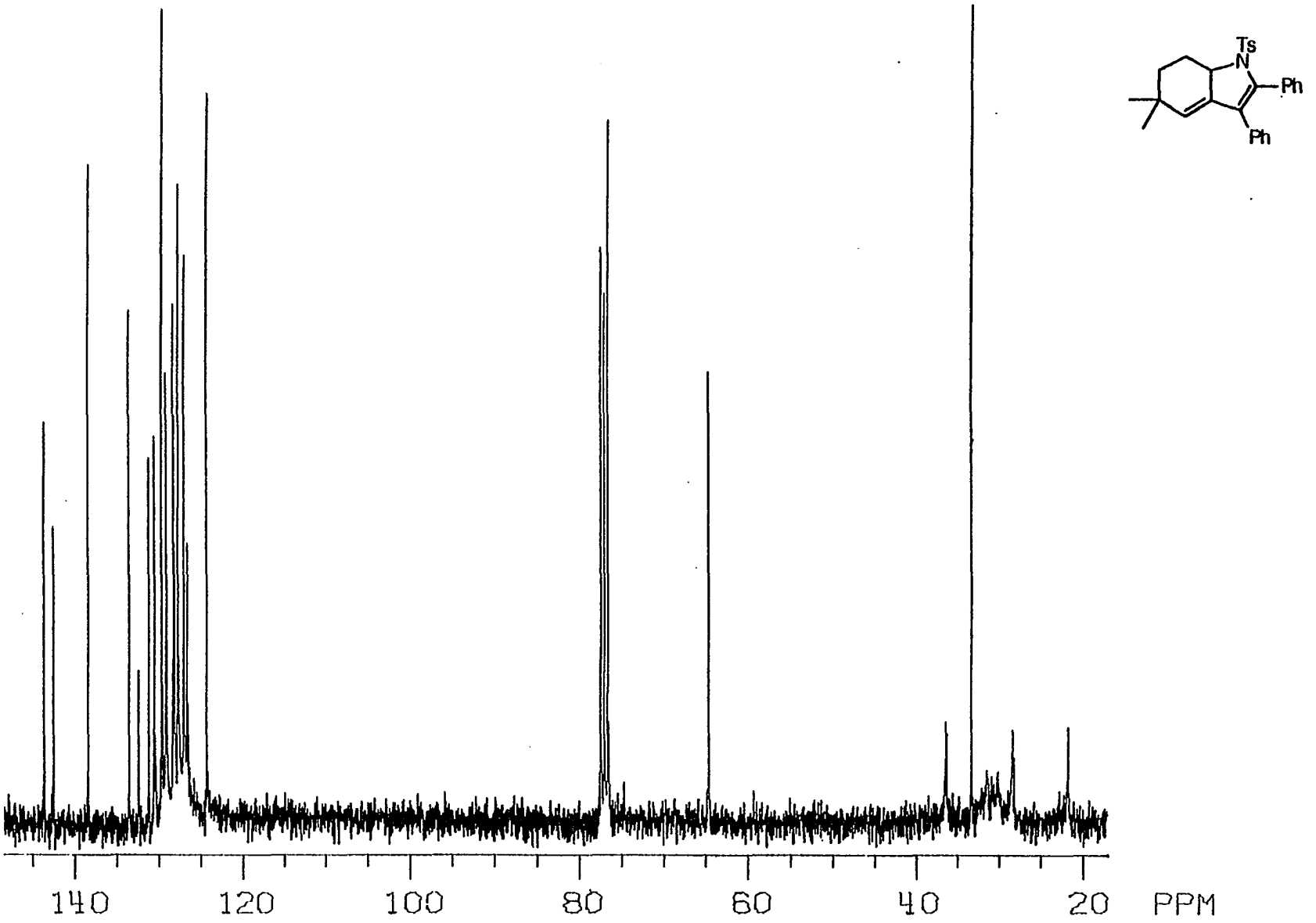

C(CH3)2OH
Ph
O
PPM
0
1
2
3
4
5
6
7
6
3
2
2
1
2
5

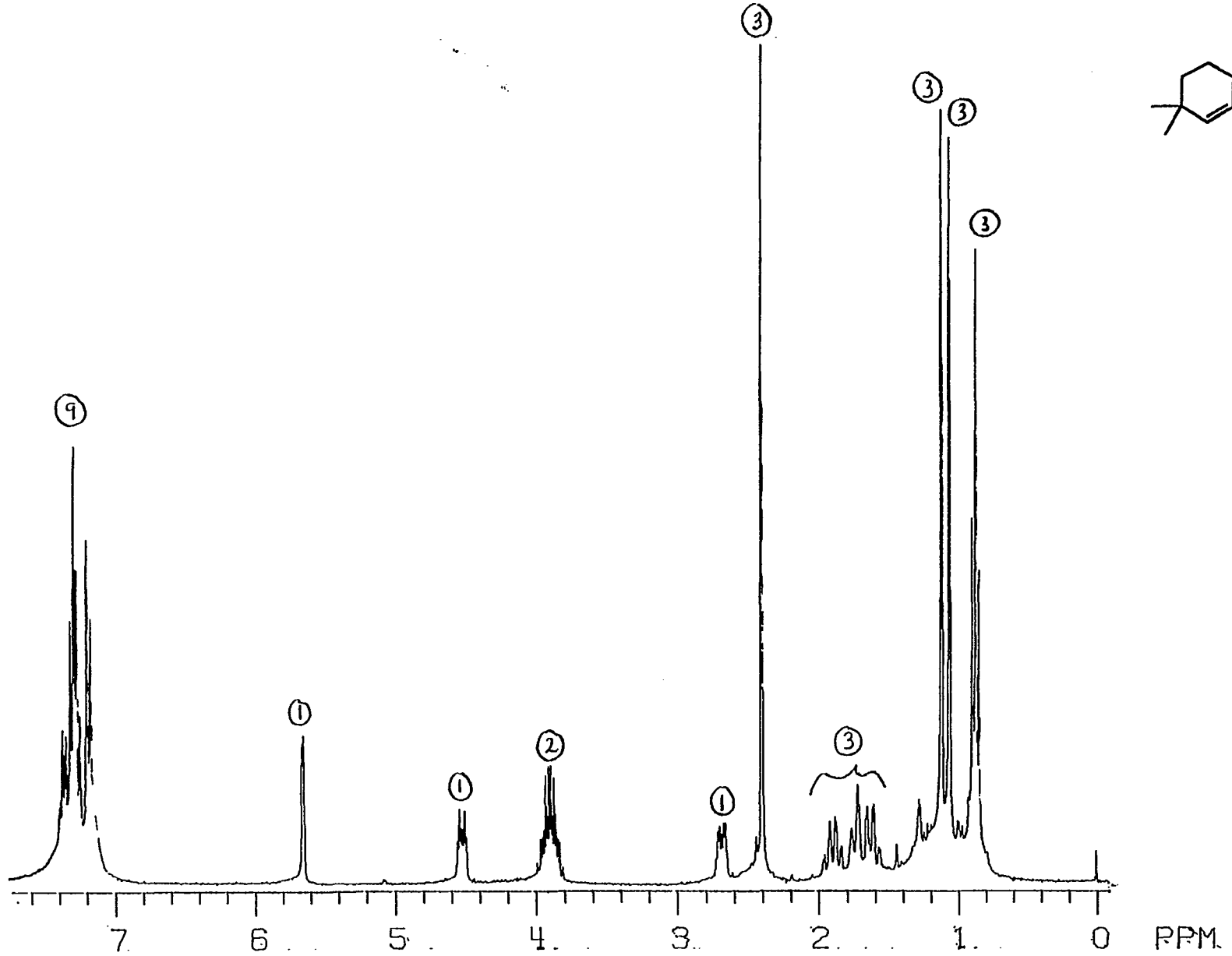
152.982
148.657
134.990
129.971
127.953
126.850
120.906
110.188
70.592
30.215
20.583
38.095
37.883
25.871
27.938
140
120
100
80
60
40
20
PPM
O
C(CH3)2OH
Ph

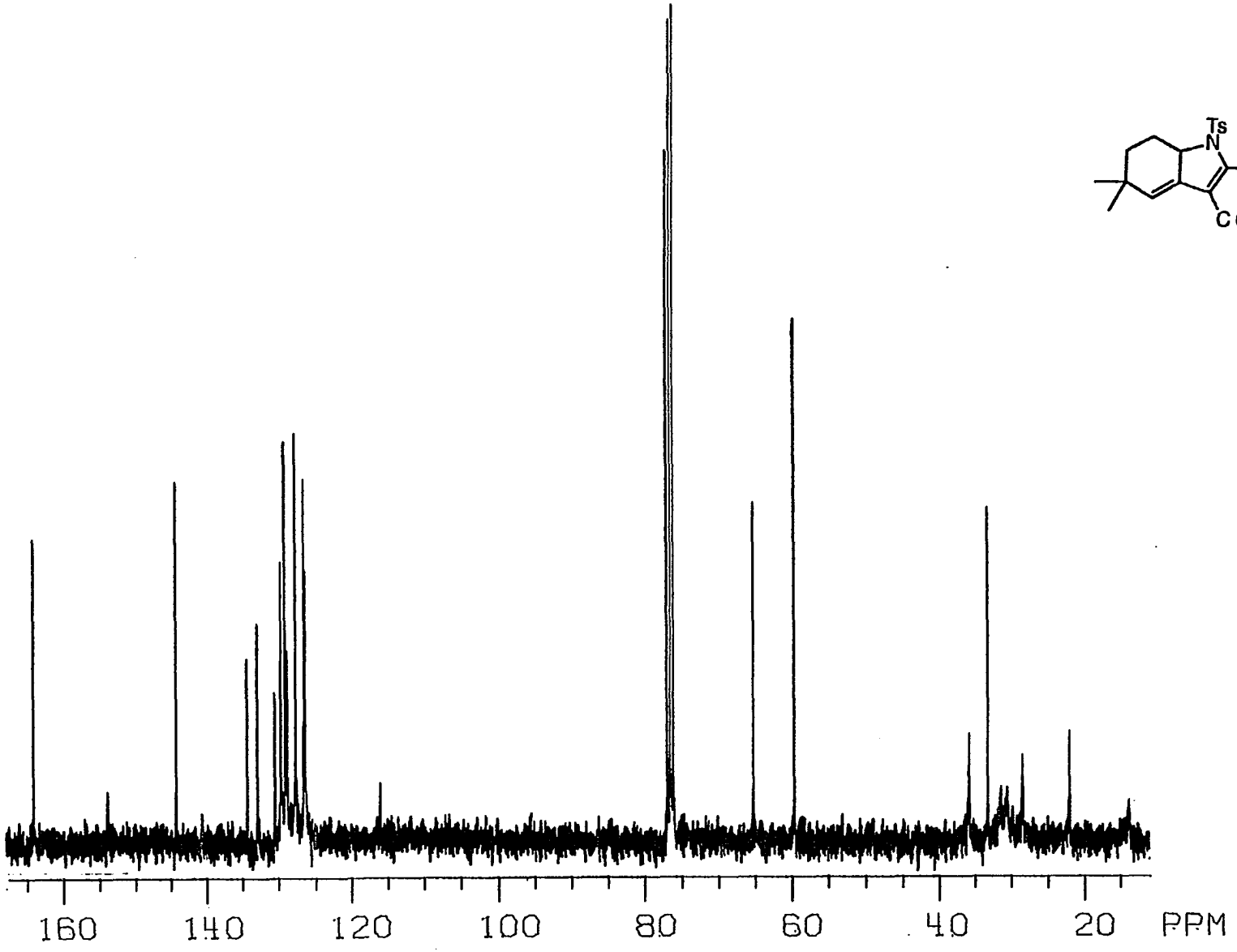

6
HO
O
Et
3
13
4
2
7
6
5
4
3
2
1
0
PPM

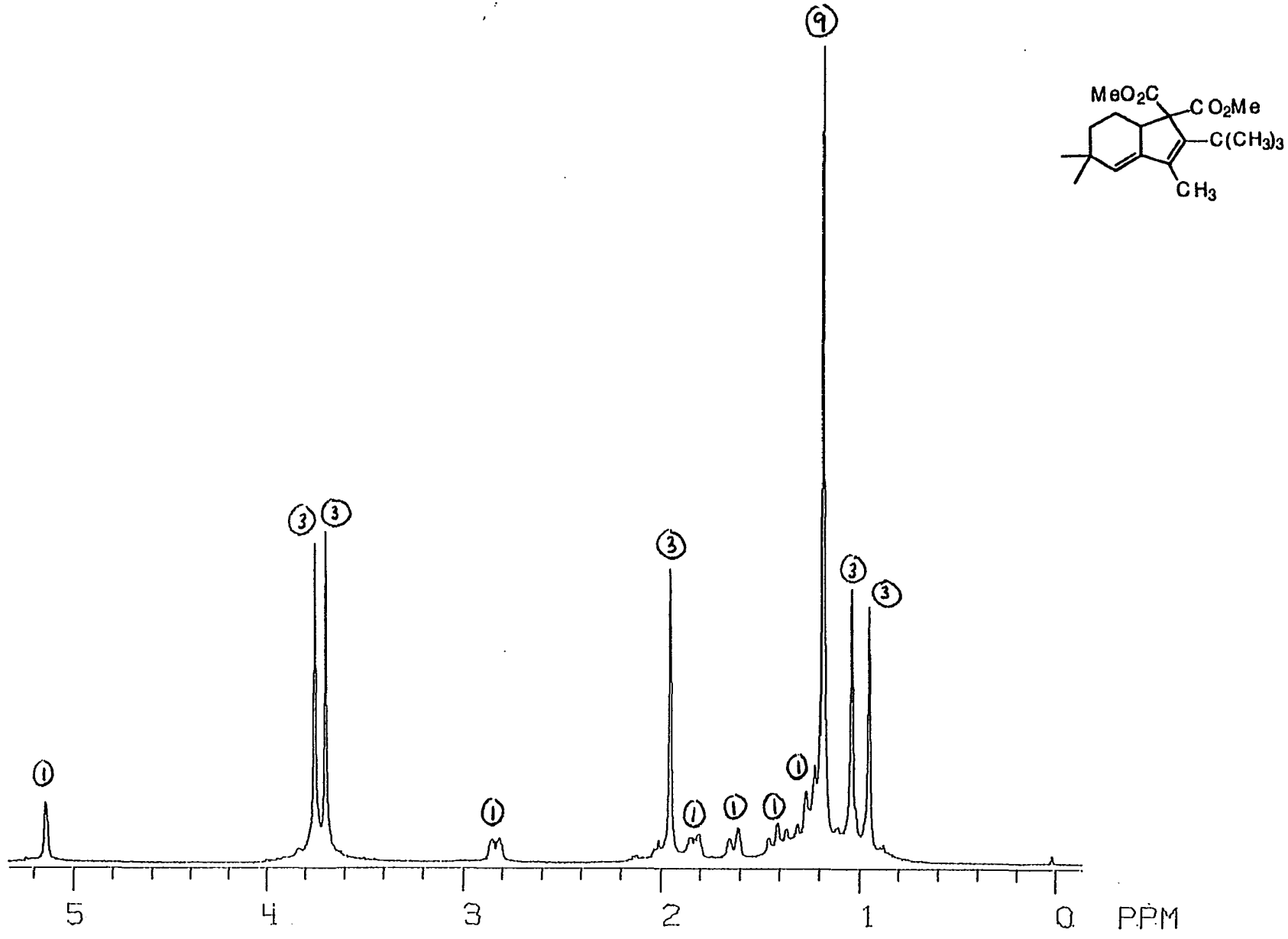
151.801.
146.527.
120.996.
117.030.
72.010.
97.277.
94.710.
35.978.
30.216.
25.549.
22.095.
20.550.
20.077.
17.288.
15.570.
140
120
100
80
60
40
20
PPM
OH
O

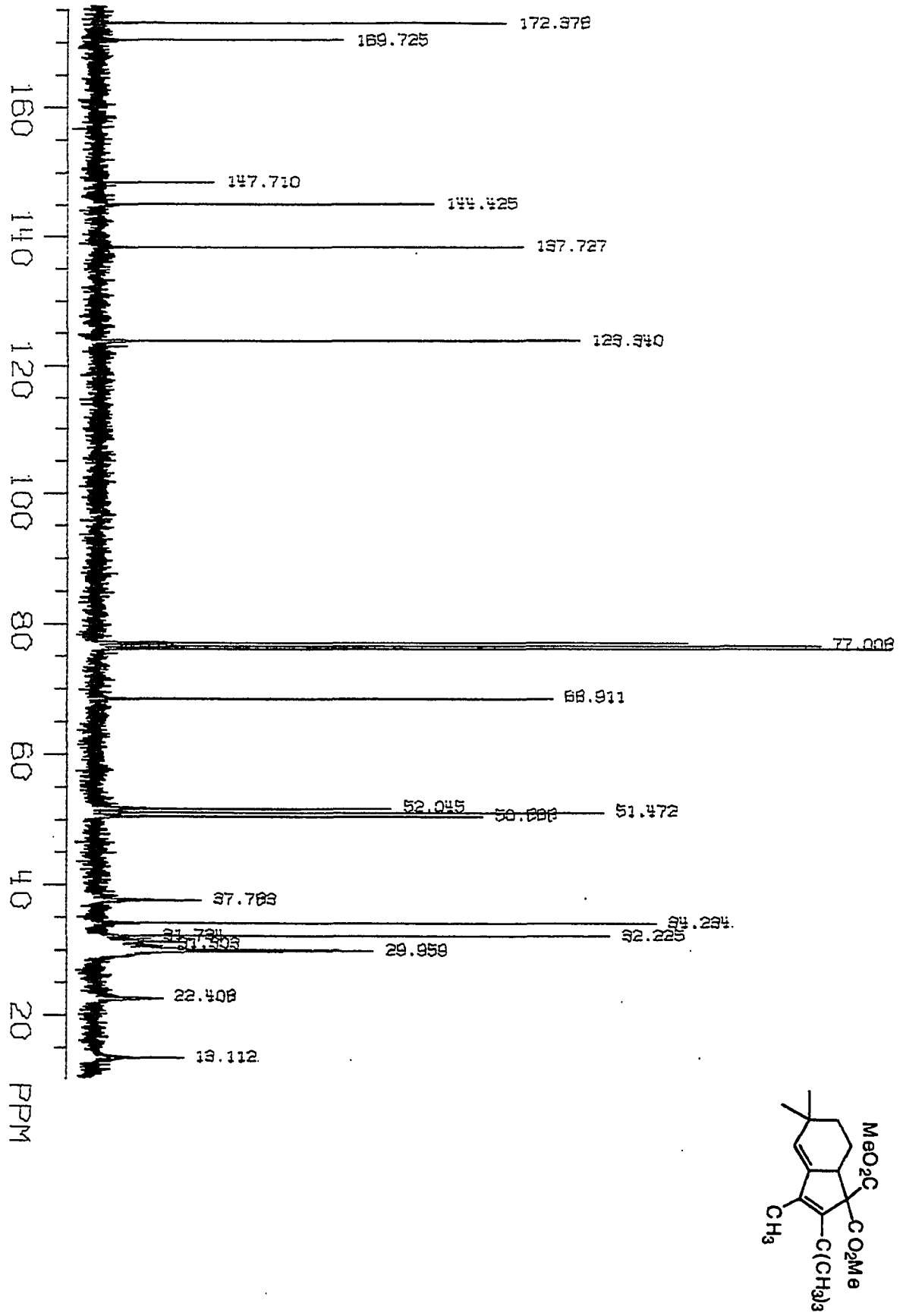

Ts
N
Ph
Ph
PPM
0
1
2
3
4
5
6
7
3
3
3
3
1
1
1
11

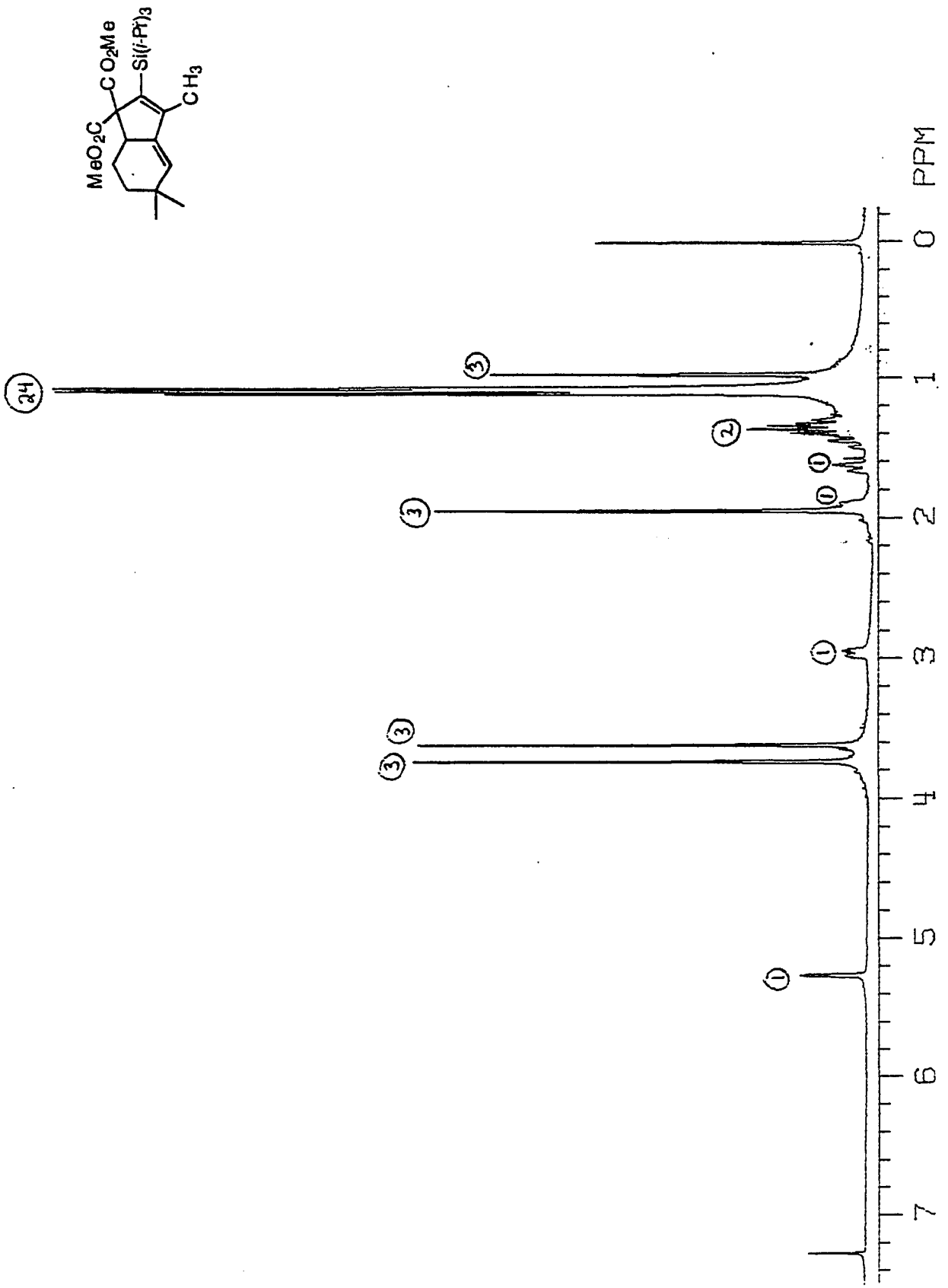

Ts
N
Ph
Ph
140
120
100
80
60
40
20
PPM


Ts
N
Ph
C O2Et
9
1
1
2
1
3
3
3
3
7
6
5
4
3
2
1
0
PPM

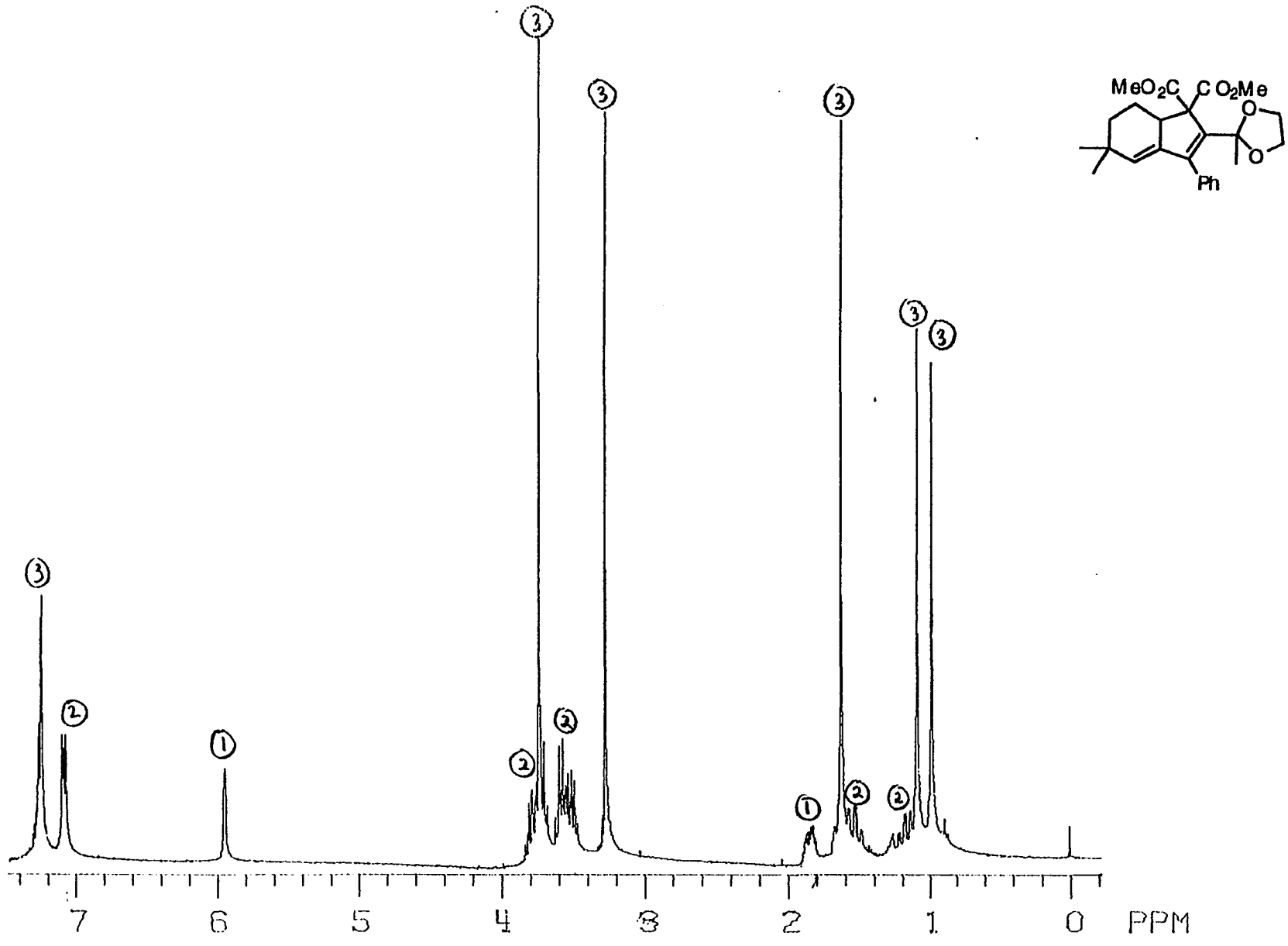

Ts
N
Ph
CO2Et
160
140
120
100
80
60
40
20
PPM


MeO2C
CO2Me
C(CH3)3
CH3
9
3
3
3
3
3
1
1
1
1
1
1
5
4
3
2
1
0
PPM

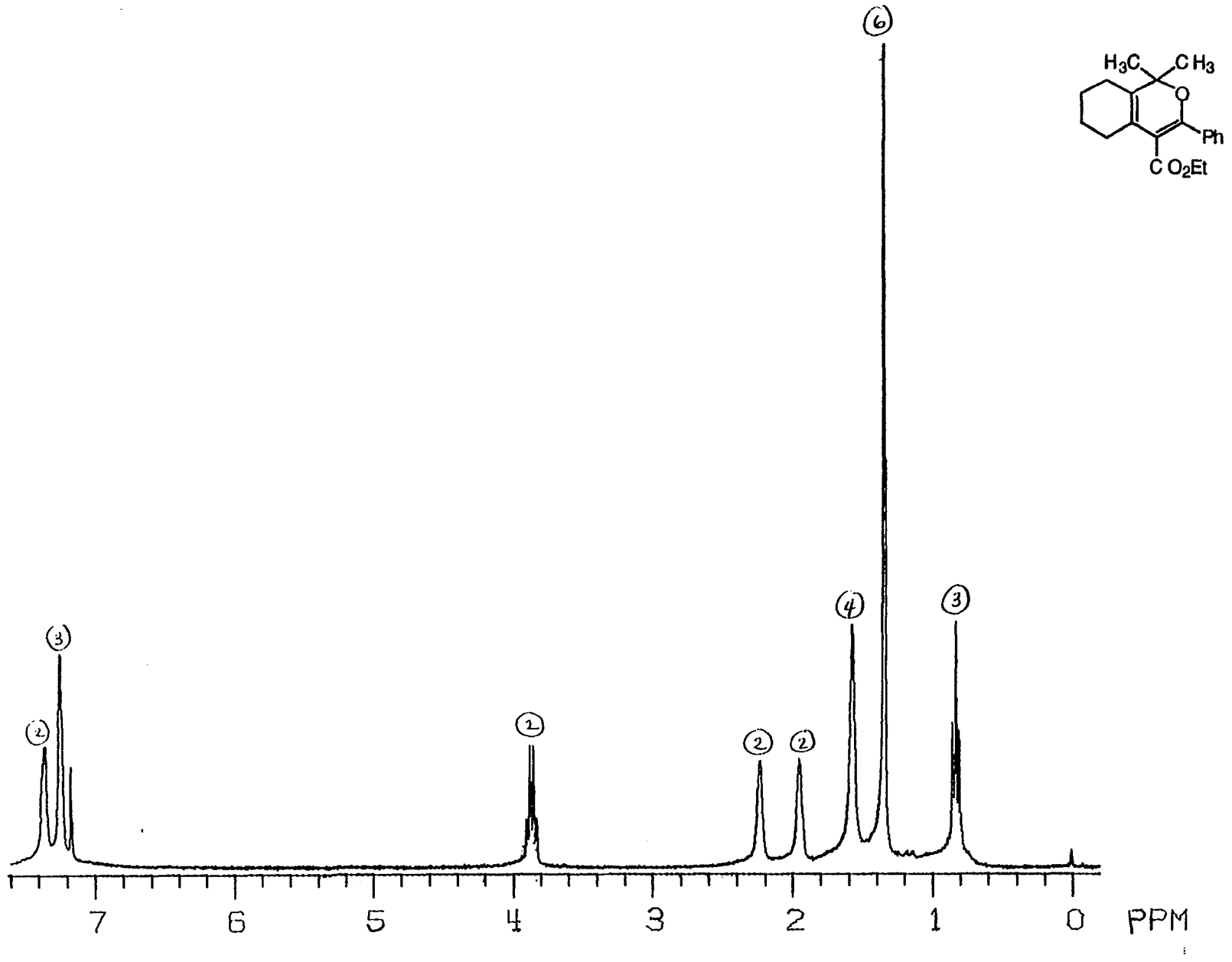

172.378
169.725
147.710
144.425
137.727
129.340
77.008
68.911
52.045
51.472
37.703
32.225
29.959
22.408
13.112
160
140
120
100
80
60
40
20
PPM
MeO2C
CO2Me
C(CH3)3
CH3

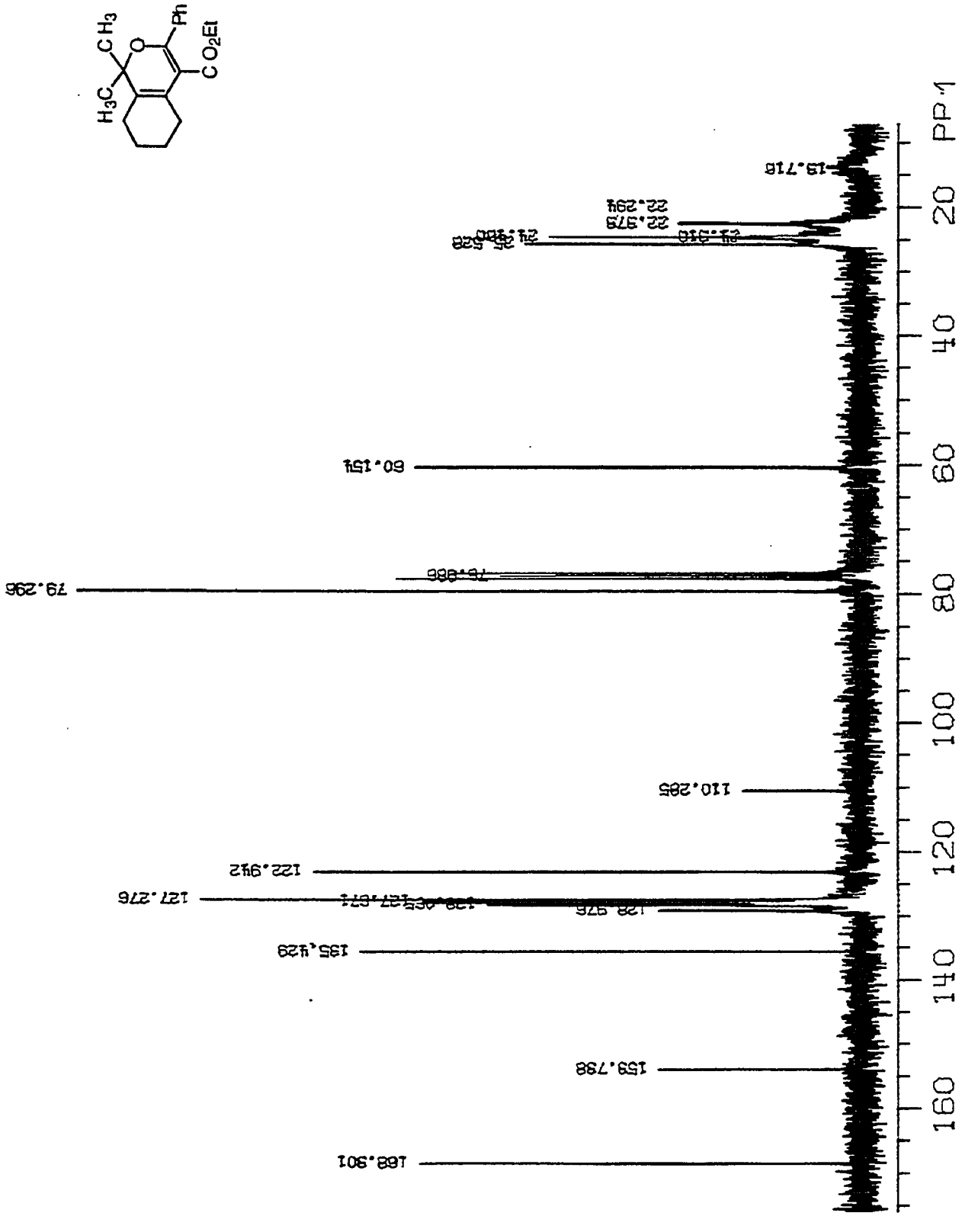

MeO2C
CO2Me
Si(i-Pr)3
CH3
24
3
2
1
1
3
1
3
3
1
0
1
2
3
4
5
6
7
PPM

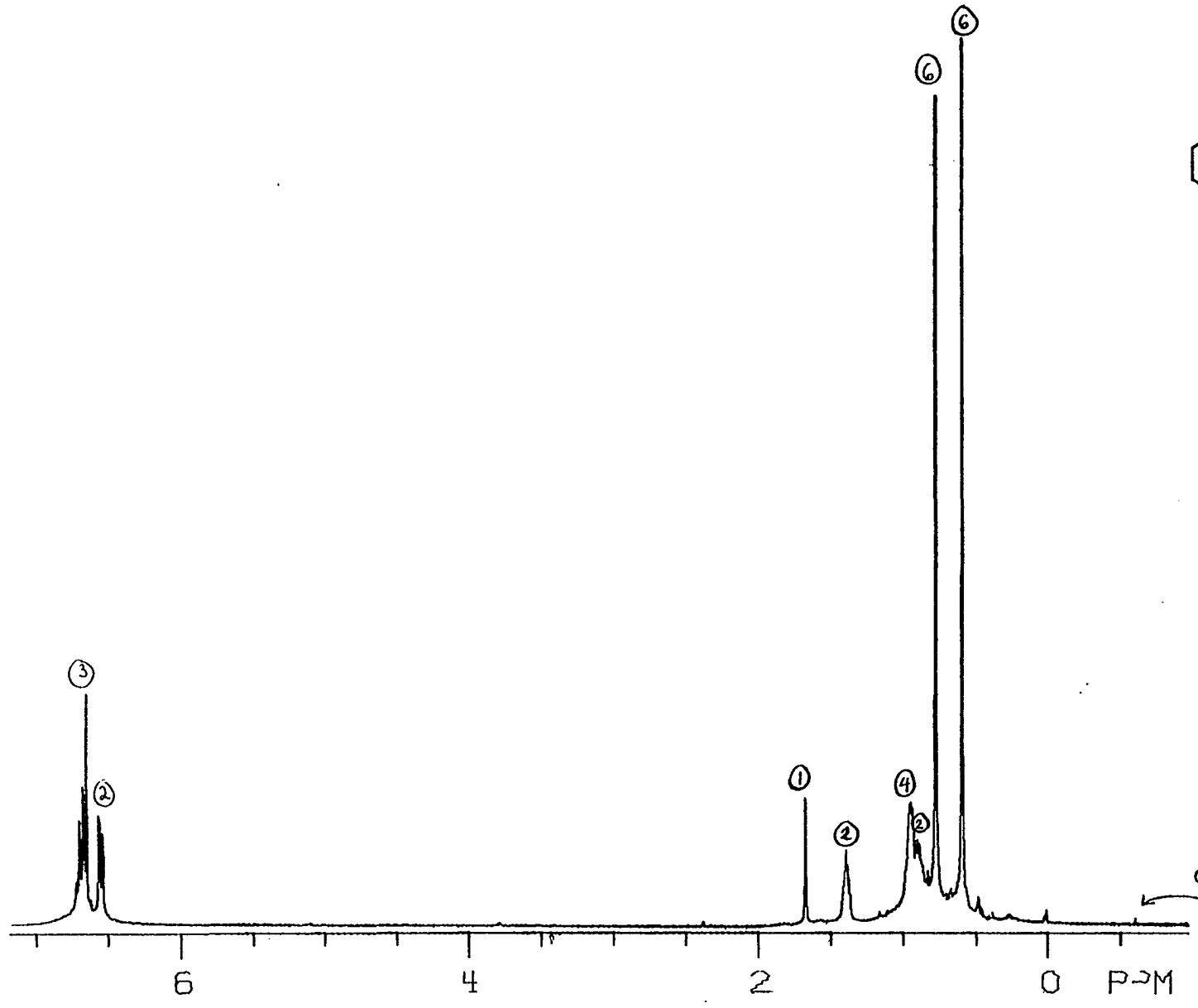
MeO2C
CO2Me
Si(i-Pr)3
CH3
172.299
169.914
154.240
144.910
136.214
125.538
71.859
52.114
51.287
37.628
32.319
22.528
19.790
19.619
13.533
14.892
160
140
120
100
80
60
40
20
PPM

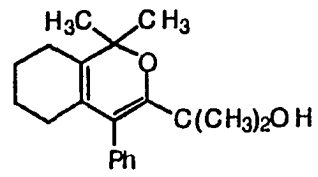

MeO2C
CO2Me
O
O
Ph
7
6
5
4
3
2
1
0
PPM

MeO2C
CO2Me
O
O
Ph
109.510
109.984
144.109
141.803
137.095
137.332
131.284
127.110
127.688
108.906
72.728
63.579
51.953
47.584
37.131
32.410
31.023
25.815
22.927
160.
140
120
100
80
60
40
20
PPM


6
H3C
CH3
O
Ph
CO2Et
3
2
2
2
2
4
3
7
6
5
4
3
2
1
0
PPM


H3C
CH3
O
Ph
CO2Et
PPM
20
40
60
80
100
120
140
160
19.716
22.379
22.294
60.154
79.296
110.285
122.942
127.276
128.976
135.429
159.798
168.301





All peaks need 0.5937 added to scale.

H3C
CH3
O
C(CH3)2OH
Ph

207

ppm
20
40
60
80
100
120
140
149.918
137.468
130.936
127.803
114.109
77.001
72.362
29.098
26.115