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Chen, Chung-Pin

PART I: STERIC AND INDUCTIVE EFFECTS ON THE HYDROLYSIS OF QUINONE BISKETALS. PART II: A CONVENIENT ROUTE TO ORTHO-ALKYLATED PHENOLS AND QUINONE MONOKETALS. PART III: A GENERAL APPROACH TO QUINONE KETALS. PART IV: PREPARATION AND CHEMISTRY OF QUINONE IMIDE KETALS

The Ohio State University PH.D. 1986

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PART I: STERIC AND INDUCTIVE EFFECTS ON THE HYDROLYSIS OF QUINONE BISKETALS

PART II: A CONVENIENT ROUTE TO *ortho*-ALKYLATED PHENOLS AND QUINONE MONOKETALS

PART III: A GENERAL APPROACH TO QUINONE KETALS

PART IV: PREPARATION AND CHEMISTRY OF QUINONE IMIDE KETALS

By

Chung-Pin Chen

****

The Ohio State University

1986

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Approved By

John S. Swenton

Advisor

Department of Chemistry

to

My Parents and Shwu-Huey

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Publications and Presentations

"Substituent Effect in the Monohydrolysis of Quinone Bisketals"
Chung-Pin Chen and John S. Swenton
J. Org. Chem. *50* 4569 (1985)

"A Convenient Route to *ortho*-Alkylated Phenols
and Quinone Monoketals"
Chung-Pin Chen and John S. Swenton
J. Chem. Soc., Chem. Commun., 1291 (1985)

"A General Approach to Quinone Imine Ketals. Interesting
Intermediates for Preparation of 5-Oxygenated
Indoles and Quinone Imines"
Chung-Pin Chen, Chuan Shih, and John S. Swenton
Tetrahedron Lett. *27*, 1891 (1986)

Chung-Pin Chen and John S. Swenton
17th Central Regional Meeting of
The American Chemical Society, Akron, Ohio
June 5, 1985

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PART I

STERIC AND INDUCTIVE EFFECTS ON THE MONOHYDROLYSIS OF QUINONE BISKETALS

J. Org. Chem. **1985**, *50*, 4569–4576

Steric and Inductive Effects on the Hydrolysis of Quinone Bisketals

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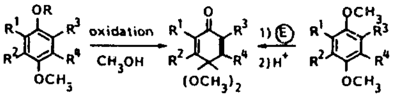
Received April 29, 1985

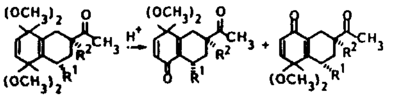
The effects of allylic substituents on the regiochemistry of monohydrolysis of tetralin-type quinone bisketals **12** have been studied. The requisite bisketals were prepared by anodic oxidation of the corresponding 1-substituted 5,8-dimethoxytetralin. Product studies establish that hydroxyl and ether functions at the allylic position preferentially afford quinone monoketals of type **13** wherein the ketal function nearest to the allylic substituent is hydrolyzed. The fluoro system also preferentially forms the monoketal **13** (R = F). A series of alkyl substituents were also studied, and increasing the size of the group led to increasing regioselectivity in favor of **13**. Only the $\Delta^{1,2}$-unsaturated systems **12j,k** preferentially gave monoketals in which the more distant ketal function had hydrolyzed. Kinetic studies established at least two major factors in the regiochemistry of the bisketal hydrolysis. While both the oxygenated and alkylated substituents gave monoketals **13** in which hydrolysis had selectively occurred at the nearer ketal function, the origins of the observed regioselectivity are different. Oxygenated systems gave the observed regiochemistry due to a rate retardation of the hydrolysis of the more distant ketal by what is proposed to be an inductive effect. However, alkyl substituents exerted their effect by increasing the rate of hydrolysis of the nearer ketal function due to a relief of strain energy.

Quinone monoketals serve as valuable regiospecific quinone equivalents in organic synthesis.[1] In addition to the regiochemical control possible in Michael[1–4] type reactions with quinone monoketals, reactions of nucleophiles with monoketals may take a different course than the same reaction with a quinone. A recent review[1] has summarized the reactions of quinone monoketals, and the most recent applications have employed these moieties in the synthesis of anthracyclinones,[3] indoles,[4] and isoindoles.[5]

The most generally useful routes to the quinone monoketal are the chemical[6] [thallium(III) salts[7] or 2,3-dichloro-5,6-dicyano-1,4-benzoquinone[8]] or electrochemical oxidation of *p*-methoxyphenols,[9a] the electrochemical oxidation of trimethylsilyl ethers of *p*-methoxyphenols,[9b] and the anodic oxidation of methoxylated aromatics followed by mild acid hydrolysis.[10] All of these routes are subject to regiochemical constraints since the former two require the appropriate *p*-methoxyphenol and the latter route is dependent on the regiochemistry of hydrolysis of the quinone bisketal. In fact, quinone bisketals unsymmetrically substituted adjacent to the ketal linkage often selectively produce one quinone monoketal[10b] upon hydrolysis. However, bisketals such as **4a** show virtually no regioselectivity in their monohydrolysis.



1, R = H or $(CH_3)_3Si$ **2** **3**



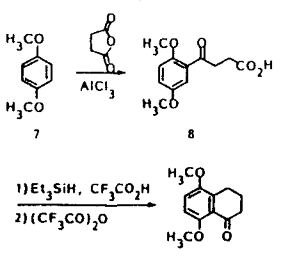
4a, $R^1 = R^2 = H$ **5a** 1 : 1 **6a**

b, $R^1 = OCH_3$, $R^2 = OSi(t\text{-}Bu)(CH_3)_2$ **5b** ∼90 : 10 **6b**

An interesting mechanistic problem was presented by the discovery that an allylic oxygen functionality[3a,c,d] afforded regiochemical control in the hydrolysis of the bisketal **4b**. This was a key feature of our regioselective synthesis of anthracyclinones,[3a] and an understanding of the factors responsible for the regiochemical control would be of general interest. Studies reported herein establish the effect of a variety of allylic substituents on the regiochemistry of bisketal hydrolysis in a tetralin-type system and provide a reasonable, mechanistic rationale for the effect. The results of these studies should be valuable in designing regioselective routes to other quinone monoketals.

Synthesis of the Model Systems for Study

The 1,4-dimethoxytetralin ring system was selected to study the effect of allylic substituents on the regiochemistry of bisketal hydrolysis. The ketone **9** was readily available via the reaction sequence outlined in eq 1. The



7 **8** **9** (78%) (1)

---

[1] Swenton, J. S. *Acc. Chem. Res.* **1983**, *16*, 74. Fugita, S. *Yuki Gosei Kagaku Kyokaishi* **1981**, 307.

[2] Parker, K. A.; Kang, S. *J. Org. Chem.* **1980**, *45*, 1218.

[3] (a) Swenton, J. S.; Freskos, J. N.; Morrow, G. W.; Sercel, A. W. *Tetrahedron* **1984**, *40*, 4625. (b) Chenard, B. L.; Anderson, D. K.; Swenton, J. S. *J. Chem. Soc., Chem. Commun.* **1980**, 932. (c) Dolson, M. G.; Chenard, B. L.; Swenton, J. S. *J. Am. Chem. Soc.* **1981**, *103*, 5263. (d) Chenard, B. L.; Dolson, M. G.; Sercel, A. D.; Swenton, J. S. *J. Org. Chem.* **1984**, *49*, 318. (e) Keay, B. A.; Rodrigo, R. *Tetrahedron* **1984**, *40*, 4597. (f) Russell, R. A.; Warrener, R. N. *J. Chem. Soc., Chem. Commun.* **1980**, 932.

[4] Coates, R. M.; MacManus, P. A. *J. Org. Chem.* **1982**, *47*, 4823.

[5] Parker, K. A.; Cohen, I. D. *Tetrahedron Lett.* **1984**, *25*, 4917.

[6] For complete referencing on the chemical oxidation of aromatics to quinone monoketals, see ref 1 and 10.

[7] McKillop, A.; Perry, D. H.; Edwards, D. H.; Antus, S.; Darkas, L.; Nogradi, M.; Taylor, E. C. *J. Org. Chem.* **1976**, *41*, 282.

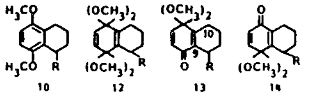
[8] Büchi, G.; Chu, P.; Hoppmann, A.; Mak, C.; Pearce, A. *J. Org. Chem.* **1978**, *43*, 3983.

[9] (a) Nilsson, A.; Rontan, A.; Parker, V. *Tetrahedron Lett.* **1975**, 1107. Foster, C. H.; Payne, D. A. *J. Am. Chem. Soc.* **1978**, *100*, 2834. (b) Steward, R. F.; Miller, L. L. *J. Am. Chem. Soc.* **1980**, *102*, 4999.

[10] (a) Henton, D. R.; McCreery, R. L.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 369. (b) Henton, D. R.; Anderson, D. K.; Manning, M. J.; Swenton, J. S. *J. Org. Chem.* **1980**, *45*, 3422.

0022-3263/85/1950-4569$01.50/0

Table I. Anodic Oxidation/Hydrolysis Studies of 10a–k

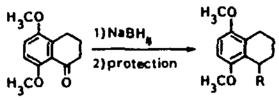


10 12 13 14

entry	R	yield of 12,[a] %	yield of 13/14[a] %	ratio[b] of 13/14 -20 °C	ratio[b] of 13/14 +22 °C
1	a, OH	97	92	8.4:1	8:1
2	b, OCH_3	98	93	6.2:1	6:1
3	c, OSi(*t*-Bu)$(CH_3)_2$	92	90	3.3:1	2.9:1
4	d, OCH_2OCH_3	98	91	3.5:1	
5	e, CH_3	95	98	1.5:1	1.5:1
6	f, CH_2CH_3	90	96	3:1	
7	g, *i*-Pr	99		6.5:1	
8	h, *t*-Bu	97	98	10.5:1	7:1
9	i, F	76	92	10.5:1	11:1
10	j, see text	88	88	1:5	1:5
11	k, see text	96	91	1:10	1:8

[a] Yield of crude product(s) showing no major impurities by ^1H NMR. [b] Ratio determined by ^1H NMR spectroscopy.

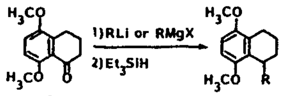
direct conversion of 8 to 9 was especially convenient since the crude product from the triethylsilane reduction[11] was directly cyclized to the tetralone 9.[12] Reduction of 9 with sodium borohydride and functionalization afforded the oxygenated derivatives 10a–d used in the anodic oxidation/hydrolysis studies.



9 10

a, R = OH[$OSi(CH_3)_3$]; b, R = OCH_3;
c, R = OSi(*t*-Bu)$(CH_3)_2$; d, R = OCH_2OCH_3

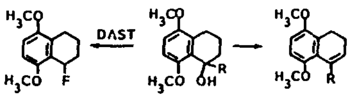
A second series of compounds employed in the study were designed to assess the importance of steric effects on the bisketal hydrolysis. These systems were prepared by addition of organolithium reagents or Grignard reagents to the ketone 9 followed by triethylsilane reduction. Not surprisingly, enolization was a major complication in the reaction of 9 with isopropyl and *tert*-butyl organometallic derivatives. This synthetic work was completed before the report that cerium(III) chloride promoted the addition reaction of organometallics to carbonyl groups subject to enolization;[13] however, it was of interest to investigate this point in the reaction of *tert*-butyllithium with 9. Indeed, the overall yields of 10h from the reaction of 9 and *tert*-butyllithium in the absence and presence of cerium(III) chloride were 13% and 42%, respectively. Any future work involving addition of organometallic reagents to 9 could markedly benefit from the use of cerium(III) chloride.



9 10

e, R = CH_3; f, R = C_2H_5; g, R = *i*-C_3H_7;
h, R = *t*-Bu

The final compounds employed in the studies were the fluoro system 10i and the unsaturated systems 10j,k prepared as shown in eq 2. The benzylic fluoro system 10i was especially labile, and the anodic oxidation chemistry of 10i (vide infra) was performed immediately after its preparation.



(2)

10i

10a, R = H
10ℓ, R = CH_3

10j, R = H
10k, R = CH_3

Anodic Oxidation/Hydrolysis Studies

The results from the anodic oxidation and subsequent hydrolyses of the resulting bisketals from the tetralins 10a–k are given in Table I. All anodic oxidations were conducted in 2% methanolic potassium hydroxide in a single cell (except 10j,k, for which a divided cell was employed) at constant current. Standard workup afforded the crude bisketals which were used directly for the hydrolysis studies. The specific details and spectroscopic data for the bisketals are given in the Experimental Section and supplementary material, and only pertinent points are noted here. As stated earlier, the benzylic fluoride 10i was extremely labile and was not purified prior to anodic oxidation, so bisketal 12i was recrystallized prior to hydrolysis. For 10a (R = OH) the unprotected hydroxyl group complicated the product mixture in the anodic oxidation: thus, the oxidation was conducted on the trimethylsilyl derivative, with the protecting group being removed during the workup of the reaction mixture, to afford 12a.

The preparative hydrolyses were conducted in acetone/5% aqueous acetic acid (4:1) at -20 °C for 24–48 h, and the reaction mixtures were neutralized with saturated sodium bicarbonate. As is apparent from the temperature-dependence data listed in Table II, the regioselectivity of the monohydrolysis is only slightly improved at -20 °C relative to 22 °C. For the systems having oxygenated substituents (entries 1–4), the major monoketals 13a–c and

---

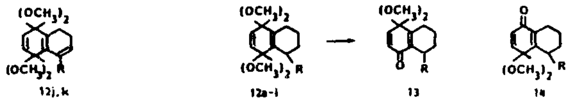
(11) West, C. T.; Donnelly, S. J.; Kooistra, D. A.; Doyle, M. P. *J. Org. Chem.* 1973, *38*, 2673. Swenton, J. S.; Reynolds, P. W. *J. Am. Chem. Soc.* 1978, *100*, 4188.

(12) The keto acid 8 was previously converted to 9 by Wolff–Kishner reduction or hydrogenation followed by polyphosphoric acid cyclization in about 45–50% overall yield.[13] The yield from 7 to 9 in this work was 78%.

(13) Moore, J. A.; Rahm, R. *J. Org. Chem.* 1961, *26*, 1109. Shimizu, T.; Horaguchi, T.; Watanabe, A. *Bull. Chem. Soc. Jpn.* 1979, *46*, 1772.

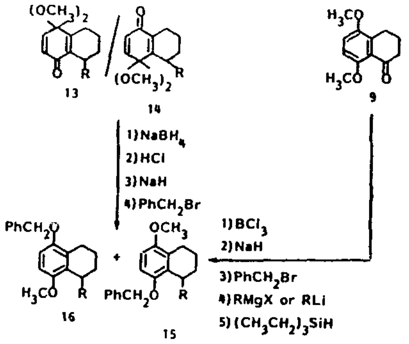
(14) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* 1984, *49*, 3904.

Table II. Kinetics of Bisketal Hydrolysis at 22 °C



entry	compd	R	10^4k, s^{-1}	10^4k, s^{-1}	10^4k, s^{-1}
1	**11**	H	5.8	2.9	2.9
2	**12a**	OH	2.2	2.0	0.2
3	**12b**	OCH_3	3.5	3.0	0.5
4	**12c**	$OSi(t\text{-}Bu)(CH_3)_2$	2.7	2.0	0.8
5	**12e**	CH_3	7.5	4.5	3.0
6	**12h**	*t*-Bu	15.1	13.0	1.9
7	**12i**	F	0.75	0.68	0.06
8	**12j**	H	3.8	0.63	3.2
9	**12k**	CH_3	2.2	0.24	1.8

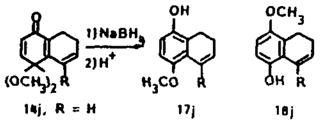
Scheme I. General Procedure for Assignment of Structure for Monoketals



the minor monoketals **14a,d** were isolated pure.[15] Systems that yielded difficult-to-separate mixtures were first reduced to the respective phenols, which were separated either directly or as derivatives. The structures for the phenols or phenol derivatives were established by spectroscopic analysis or by comparison with authentic samples prepared via conventional synthetic methods. A detailed discussion is given in the supplementary material. The ratios of the monoketals from hydrolysis of **12a–d** were readily determined by integration of the tertiary allylic hydrogen in the ^{1}H NMR spectrum: for monoketals of structure **13**, the position for this proton was about δ 0.1 lower than for this proton in **14**.

For entries 5–8, the regioisomeric monoketals were much more difficult to separate chromatographically, and only the major monoketals **13g,h** were obtained pure. For the remaining compounds, the mixtures of monoketals were reduced with sodium borohydride to afford the corresponding phenols. The phenols were separated chromatographically and benzylated. Comparison of major benzylated aromatic compound **15** with an authentic sample prepared by standard chemical methods established the regiochemistry of the major monoketal. The general scheme for the structure proofs is given in Scheme I, and the details are supplied in the supplementary material. The ratios of monoketals were obtained by integration of the appropriate resonances in the ^{1}H NMR spectra.

The final compounds studied were the fluoro system **12c** and the triene compounds **12j,k**. The major monoketal from hydrolysis of **12i** was assigned as **13i** by virtue of the magnitude of the ^{19}F coupling to the carbons in the ^{13}C NMR spectrum. For this monoketal, the ^{19}F coupling constant at C-10 (δ 157.5) was 6 Hz while that at C-9 (δ 133.0) was 16 Hz. This assignment is fully supported by data given in the supplementary material. The ratio of the two monoketals **13i** and **14i** was determined by integration of the resonances in the ^{19}F NMR spectra. For the vinyl systems, **14j** and **14k** were isolated pure and reduced to **17j,k**. Phenols **17j,k** showed similar, but different,

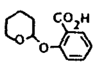


14j, R = H **17j** **18j**
k, R = CH_3 **17k** **18k**

spectroscopic properties (IR, NMR) than phenols **18j,k** which were independently prepared. The ratio of monoketals in this latter case was determined by integration of the methoxyl region of the ^{1}H NMR spectrum of the hydrolysis mixture.

Discussion

The mechanism of acetal/ketal hydrolysis has been extensively studied, and it is generally accepted that the rate-determining step involves formation of a carbonium ion with either specific hydronium ion or general acid catalysis.[16] Several possibilities were considered for the regiocontrol exerted by allylic substituents on the hydrolysis of the quinone bisketals discussed above.[17] Intramolecular general acid catalysis of an acetal or ketal linkage can result in rate accelerations as high as 10^4–10^6 in selected systems,[18] **19** and **20**. A rate change of only



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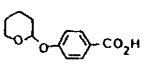


20

a fraction of the above value could account for the observed regiochemistry if the allylic oxygen function were facilitating the hydrolysis of the adjacent bisketal. Such a possibility would involve protonation of the more basic

---

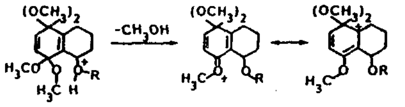
[15] While the *tert*-butyldimethylsiloxyl group does not afford the highest regioselectivity in the monohydrolysis of a quinone bisketal, it was employed in our anthracyclicone synthesis[2a] because it gave the most reproducible yields in subsequent synthetic steps.

[16] (a) Cordes, E. H.; Bull, H. G. *Chem. Rev.* 1974, *74*, 581. (b) Fife, T. H. *Acc. Chem. Res.* 1972, *5*, 264.

[17] For a thorough discussion of stereoelectronic effects in the hydrolysis of bisketals, see ref 10b.

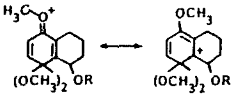
[18] Fife, T. H.; Anderson, E. *J. Am. Chem. Soc.* 1971, *93*, 6610.

ether oxygen (p$K_a \sim -4$) vs. the ketal oxygen (p$K_a \sim -5$), followed by intramolecular proton transfer and loss of methanol to afford 22.



21 22

Second, the inductive effect of the allylic substituent could retard the rate of ionization to form cation 23 relative to cation 22. This type of rationale is essentially that used in explaining the predominant meta substitution in the electrophilic reactions of protonated or trialkylated anilines.[19] Furthermore, the slower rate of hydrolysis ($\sim$10)[20]



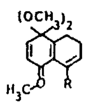
23

of benzoquinone bisketal relative to 2,2-dimethoxypropane could be ascribed to a rate-retarding inductive effect of the second ketal function on the hydrolysis of the first ketal.

Finally, a rate acceleration from relief of steric interactions could account for selective hydrolysis of the ketal moiety adjacent to the allylic substituent. Both rate accelerations[21] and retardations[22] have been attributed to steric effects in acetal/ketal hydrolysis. Such an explanation would be especially attractive in understanding the high regioselectivity observed in the *tert*-butyl system **12h**.

Simple kinetic studies of the bisketal hydrolyses would rule out some of the above-mentioned possibilities. Intramolecular catalysis by a hydroxyl group or steric acceleration would lead to an overall rate enhancement, while an inductive effect would result in a rate retardation. The rates for hydrolysis of bisketals **11** and **12a–c,e,h–k** were measured at 22 °C in a mixture of tetrahydrofuran, water, and acetic acid. The data showed excellent linearity through three to four half-lives when treated as a pseudo-first-order reaction. The results of these determinations are collected in Table II. Since the ratio of monoketals is time invariant, the individual rate constants for hydrolysis of each ketal of the bisketal can be determined from the overall rate and the product ratio. While these numbers are subject to more error than the measured rates since the ratios of the isomeric monoketals are probably not better than ±10%, the numbers are useful for this discussion.

The data of Table II establish that the regioselectivity observed in the hydrolysis of the oxygenated and fluoro systems (entries 2–4, 7) is not due to an acceleration in the rate of **13** formation but to a retardation in the rate of **14** formation. This effect is greatest for the most electronegative substituent fluorine, which slows down the rates for formation of **13i** and **14i** by factors of $\sim$3 and $\sim$50, respectively. Thus, the effect of an allylic electronegative substituent on the regiochemistry of the bisketal hydrolysis is reasonably attributed to the inductive effect discussed above. In contrast to the above systems, the rates for formation of **13e,h** are accelerated by factors of $\sim$2 and $\sim$4.5, respectively. Such a result is reasonably interpreted as a steric acceleration of the bisketal ionization. The results from bisketals **12j,k** are interesting since the regiochemical outcome is a reversal of the previous compounds. This change in regiochemistry is primarily due to the slower rate of formation of monoketals **13j,k** vs. that of **14j,k**. Furthermore, methyl substitution has a small retarding effect on the rates of hydrolysis of both ketal functions in **12k**. An attractive idea for explaining the slower rates for formation of **13j,k** is that steric interaction of the allylic substituent with the *p*-methoxyl group raises the transition-state energy of the reaction.



24

Conclusions[23]

Electron-withdrawing substituents change the regiochemistry of the hydrolysis of quinone bisketals primarily by retarding the rate of hydrolysis of the more distant ketal. This result can be rationalized by assuming that the electron-withdrawing group deactivates the hydrolysis of the more distant ketal by inductively destabilizing the dispersal of positive charge in the allylic cation system. Such an inductive destabilization in the transition state for the other ketal center is less effective. In the case of alkyl groups, hydrolysis is accelerated for the ketal nearer to the alkyl group, and the selectivity of the hydrolysis increases with the size of the alkyl group. Rate studies establish that the alkyl groups result in a rate acceleration for hydrolysis of the nearer ketal. This would reasonably be attributed to some relief of steric strain in the transition state for ionization. Finally, while conjugation of a double bond with the quinone bisketal leads to good regioselectivity, the exact nature of the effect remains to be established.

Experimental Section[24]

5,8-Dimethoxytetralone (9). To a vigorously stirred 25 °C solution of 8 (11.2 g, 0.047 mmol) in CF_3CO_2H (25 mL) was added

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(19) See, for example: Hine, J. "Physical Organic Chemistry", 2nd ed.; McGraw-Hill: New York, 1962; pp 374–376.

(20) Chaturvedi, R. K.; Adams, J.; Cordes, E. H. *J. Org. Chem.* 1968, *33*, 1652.

(21) Anderson, E.; Fife, T. H. *J. Am. Chem. Soc.* 1971, *93*, 1701. Kreevoy, M. M.; Morgan, C. R.; Taft, R. W. *J. Am. Chem. Soc.* 1960, *82*, 3064.

(22) Fife, T. H.; Hagopian, L. *J. Org. Chem.* 1966, *31*, 1722.

(23) The free-energy differences between the hydrolysis of the two ketal functions in all of the systems studied are small. However, an 80:15 vs. a 50:50 mixture of isomeric monoketals can have important synthetic consequences.

(24) The following abbreviations have been used throughout the text: PE (low boiling petroleum ether); THF (tetrahydrofuran). All anodic oxidations were essentially conducted as described in ref 10a. All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Measurements with standard samples indicate that the reported melting points are probably 1–2 °C lower than the correct value. IR spectra were taken on a Perkin-Elmer Model 282B grating spectrometer in the indicated phase: only strong absorptions are reported. ^1H NMR and ^{13}C NMR spectra were recorded at 60 and 20.1 MHz, respectively, in $CDCl_3$ as solvent. The reported chemical shifts for the AB quartets are calculated. Apparent multiplicities are reported, and in some cases, signals reported as triplets are in fact closely spaced doublet of doublets. Mass spectra and exact mass measurements were obtained by C. Weisenberger on a Kratos MS-30 mass spectrometer connected to a DS-55 data system. The kinetic measurements were made on a Beckman DU-7 equipped with the kinetics package. Tetrahydrofuran was freshly distilled from benzophenone/sodium prior to use. All other anhydrous solvents used for reactions were freshly dried and distilled. All reactions were performed under a nitrogen atmosphere. Combustion analyses were performed by Scandinavian Microanalytical Laboratory, Herlev, Denmark. Aluminum and silica gel were from E. Merck and Co., and flash silica gel was obtained from EM reagents (230–400 mesh). "Workup as usual" consisted of extraction of the product (CH_2Cl_2 or Et_2O), drying over $CaSO_4$ or Na_2SO_4, and concentration in vacuo, followed by drying under oil pump vacuum.

dropwise triethylsilane (20.5 mL, 0.13 mol). After being stirred for 10 min, the reaction mixture was concentrated in vacuo, and the dark brown oil was taken up in 10% KOH (50 mL) and Et_2O (50 mL). The phases were separated, the aqueous phase was acidified (concentrated HCl), and the acid was extracted with CH_2Cl_2 (3 × 40 mL) and worked up as usual to afford 10.3 g (98%) of the acid as an oil suitable for use in the next step. Recrystallization of a portion of this material from Et_2O gave a light yellow solid, mp 66–67 °C (lit.[13] mp 64–65 °C).

To the acid from above in CF_3CO_2H (30 mL) was added $(CF_3CO_2)_2O$ (30 mL, 0.21 mol), and after 5 min the reaction mixture was concentrated in vacuo. The reaction mixture was partitioned in a mixture of CH_2Cl_2 (50 mL) and 10% KOH, and the product was extracted with additional CH_2Cl_2 to afford after workup a dark brown oil. Flash chromatography on silica gel (5:1 CH_2Cl_2/Et_2O as eluant) afforded **9** (7.6 g, 78% overall), mp 60–62 °C (lit.[13] mp 58–62 °C).

10a (R = Trimethylsiloxy). The reaction of **10a** (R = OH, 614.7 mg, 2.96 mmol), chlorotrimethylsilane (1.69 mL, 13.3 mmol), and $[(CH_3)_3Si]_2NH$ (2.8 mL, 13.2 mmol) in pyridine (7.7 mL) was allowed to proceed at 50 °C for 24 h. The reaction was quenched with saturated sodium bicarbonate solution (20 mL) and worked up as usual to yield a light brown oil. Flash chromatography (1:1 hexane/CH_2Cl_2) yielded **10a** (R = trimethylsiloxy) as a colorless oil (762.7 mg, 92%): IR (neat) 2940, 1480, 1465, 1440, 1360, 1350, 1100, 1080, 1030, 1010, 960, 890, 840 cm^{-1}; ^1H NMR δ 6.66 (br s, 2 H), 5.17–5.03 (m, 1 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 2.80–1.40 (m, 6 H), 0.16 (s, 9 H); ^{13}C NMR δ 152.0 (s), 151.6 (s), 128.3 (s), 127.9 (s), 109.0 (d), 107.2 (d), 62.0 (q), 55.7 (q), 55.1 (q), 31.7 (t), 23.2 (t), 15.9 (t), 0.56 (3 C, q); mass spectrum, exact mass calcd for $C_{15}H_{24}O_3Si$ *m/e* 280.1495, obsd *m/e* 280.1548.

10b. To a slurry of 60% sodium hydride mineral oil dispersion (30 mg, 1.1 mmol, washed with hexane) in THF (15 mL) was added **10a** (R = OH, 100 mg, 0.481 mmol). The mixture was heated to reflux for 2 h and cooled to 40 °C, methyl iodide (0.15 mL, 1.17 mmol) was added, and the mixture was allowed to stir at 40 °C for 6 h and then at room temperature overnight. The reaction mixture was diluted with water (10 mL), concentrated in vacuo, and then extracted with EtOAc (2 × 50 mL). Workup and flash chromatography (CH_2Cl_2) yielded **10b** as a light yellow oil (86.4 mg, 81%): IR (neat) 2920, 2830, 1480, 1460 (sh), 1440 (sh), 1350, 1080 cm^{-1}; ^1H NMR δ 6.67 (s, 2 H), 4.69–4.47 (m, 1 H), 3.80 (s, 3 H), 3.74 (s, 3 H), 3.43 (s, 3 H), 3.1–1.44 (m, 6 H); mass spectrum, exact mass calcd for $C_{13}H_{18}O_3$ *m/e* 222.1256, obsd *m/e* 222.1267.

10c. The reaction of **10a** (R = OH, 0.1 g, 0.48 mmol) and dimethyl *tert*-butylsilyl chloride (128 mg, 4.81 mmol) in DMF (10 mL), with imidazole (128 mg) as base at 50 °C, was allowed to proceed for 6 h. The reaction was quenched with saturated sodium bicarbonate (10 mL), and the mixture was extracted with CH_2Cl_2 (3 × 30 mL). The combined organic phase was washed with water (4 × 100 mL), dried, and concentrated in vacuo to yield **10c** as a brown oil. Flash chromatography (1:1 hexane/CH_2Cl_2) gave a white crystalline solid (148 mg, 0.460 mmol, 95%): mp 61.2–62 °C; IR (KBr) 2940, 2860, 1560, 1530 (sh), 1430, 1260, 1250, 1100, 1080, 1030, 1010, 960, 880, 830, 770, 710 cm^{-1}; ^1H NMR δ 6.65 (br s, 2 H), 5.10–4.95 (m, 1 H), 3.77 (s, 6 H), 2.8–1.0 (m, 6 H), 0.86 (s, 9 H), 0.15 (s, 3 H); mass spectrum, exact mass calcd for $C_{18}H_{30}O_3$ *m/e* 322.1964, obsd *m/e* 322.1988.

10d. A solution of **10a** (R = OH, 100 mg, 0.48 mmol), CH_2Cl_2 (10 mL), diisopropyl ethyl amine (2 mL, 5.21 mmol, 10.7 equiv per OH), and chloromethyl methyl ether (0.4 mL, 4.81 mmol, 10 equiv per OH) was heated to reflux (orange color developed) for 10 h. The mixture was cooled to room temperature, 5% aqueous sodium bicarbonate solution (10 mL) was added, and the mixture was worked up as usual to afford **10d** as a light orange oil. Flash chromatography (CH_2Cl_2) yielded a colorless oil (110.9 mg, 91%): IR (neat) 2930, 1475, 1460 (sh), 1440, 1250, 1140, 1090, 1030, 705 cm^{-1}; ^1H NMR δ 6.66 (s, 2H), 4.95 (AB q, J = 6.4 Hz, 1 H), 4.92 (br s, 1 H), 4.70 (AB q, J = 6.4 Hz, 1 H), 3.77 (s, 3 H), 3.73 (s, 3 H), 3.41 (s, 3 H), 2.92–1.25 (m, 6 H); mass spectrum, exact mass calcd for $C_{14}H_{20}O_4$ *m/e* 252.1362, obsd *m/e* 252.1373.

10e. To **9** (835.8 mg, 4.058 mmol) dissolved in THF (15 mL) and cooled to −70 °C was added 1.5 M CH_3Li in Et_2O (2.9 mL), and the reaction mixture was stirred for 0.5 h. The reaction was quenched with water (2 mL), and the mixture was concentrated in vacuo and then extracted with CH_2Cl_2 (3 × 30 mL). Workup as usual afforded a yellow oil. Flash chromatography (CH_2Cl_2 as eluant) gave the pure alcohol (855.5 mg, 93%). Recrystallization from PE/CH_2Cl_2 gave colorless crystals: mp 58.2–59.5 °C (lit.[25] mp 71 °C); IR (KBr) 3530 (br), 2970, 1480–1430, 1360, 1330, 1270, 1250, 1075, 1050 cm^{-1}; ^1H NMR δ 6.67 (s, 2 H), 4.63 (s, 1 H), 3.86 (s, 3 H), 3.75 (s, 3 H), 2.7–2.0 (m, 2 H), 2.0–1.5 (m, 4 H), 1.58 (s, 3 H); ^{13}C NMR δ 151.3 (2 C), 132.0, 126.8, 108.1, 107.7, 71.1, 55.2 (2 C), 38.3, 28.9, 23.7, 19.6; mass spectrum, exact mass calcd for $C_{13}H_{18}O_3$ *m/e* 222.1256, obsd *m/e* 222.1284.

To a mixture of the above alcohol (761.1 mg, 3.36 mmol) and Et_3SiH (2.5 mL, 15.7 mmol) was added CF_3CO_2H (5 mL), and the light yellow reaction mixture was then concentrated in vacuo to give a light yellow oil. Flash chromatography (15:2 and then 3:1 PE/CH_2Cl_2) gave **10e** (617.3 mg, 89%) as a colorless oil:[26] IR (film) 2920, 1470, 1430 (sh), 1245, 1090, 1070 cm^{-1}; ^1H NMR δ 6.61 (s, 2 H), 3.78 (s, 3 H), 3.76 (s, 3 H), 3.3–2.0 (m, 3 H), 2.0–1.5 (m, 4 H), 1.19 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 151.4 (2 C), 132.3, 126.5, 106.8, 106.4, 55.1 (2 C), 29.4, 26.7, 23.3, 20.6, 17.0; mass spectrum, exact mass calcd for $C_{13}H_{18}O_2$ *m/e* 206.1387, obsd *m/e* 206.1335.

10f. To a solution of **9** (0.698 g, 3.39 mmol) in dry THF at −70 °C was added EtMgBr (1.2 mL, 2 M THF solution, 1.05 equiv), and the solution was stirred for 1 h. After addition of water (2 mL), the reaction mixture was concentrated in vacuo, and the organic material was extracted with CH_2Cl_2 (3 × 30 mL) and worked up as usual to afford a light yellow oil. Flash chromatography (CH_2Cl_2) gave the alcohol [452.1 mg, 57% (84% based on uncovered starting material)] and recovered starting material (227.1 mg). The pure liquid showed the following IR (film) 3600–3500, 2980, 1480, 1465 (sh), 1440, 1390, 1335, 1250, 1090, 1065, 980, 950 cm^{-1}; ^1H NMR δ 6.66 (s, 2 H), 4.31 (s, 1 H), 3.83 (s, 3 H), 3.75 (s, 3 H), 2.8–1.2 (m, 8 H), 0.89 (t, J = 6.4 Hz, 3 H); ^{13}C NMR δ 151.4, 151.3, 132.5, 127.3, 108.1, 107.7, 73.4, 55.2 (2 C), 32.9, 32.1, 23.8, 18.9, 7.5; mass spectrum, exact mass calcd for $C_{14}H_{20}O_3$ *m/e* 236.1413, obsd *m/e* 236.1391.

A mixture of the above alcohol (446.3 mg, 1.80 mmol) and Et_3SiH (2 mL, 12.6 mmol) was reacted with CF_3CO_2H (3 mL) as for **10e**. Workup followed by flash chromatography (15:1 and then 3:1 PE/CH_2Cl_2) gave **10f** (401.4 mg, 96%) as a colorless liquid: IR (film) 2940, 1480, 1465 (sh), 1400, 1250, 1100, 1080 cm^{-1}; ^1H NMR δ 6.61 (s, 2 H), 3.77 (s, 6 H), 3.00–1.00 (m, 9 H), 0.95 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 151.4 (2 C), 132.4, 126.7, 106.9, 106.5, 55.3, 33.6, 26.7, 24.3, 23.2, 17.0, 12.4; mass spectrum, exact mass calcd for $C_{14}H_{20}O_2$ *m/e* 220.1463, obsd *m/e* 220.1429.

10g. Reaction of **9** (847.5 mg, 4.11 mmol) in THF (15 mL) at −70 °C with a solution of 2 M *i*-PrMgCl (2.16 mL, 1.05 equiv) in THF followed by workup and flash chromatography (1:1 PE/CH_2Cl_2) gave starting **10a** (244.1 mg) and the product alcohol (137.6 mg, 42% yield): IR (film) 3600–3360, 2940, 1470, 1435, 1390, 1335, 1250, 1185, 1160 cm^{-1}; ^1H NMR δ 6.66 (s, 2 H), 3.98 (s, 1 H), 3.81 (s, 3 H), 3.75 (s, 3 H), 3.1–1.32 (m, 7 H), 1.00 (d, J = 6.9 Hz, 3 H), 0.53 (d, J = 6.9 Hz, 3 H); mass spectrum, exact mass calcd for $C_{15}H_{22}O_3$ *m/e* 250.1569, obsd *m/e* 250.1549.

Reduction of the above alcohol (244.1 mg, 0.97 mmol) with Et_3SiH (1.15 mL, 7.2 mmol) in CF_3CO_2H (2.5 mL) gave after workup and flash chromatography (15:1 and then 3:1 PE/CH_2Cl_2) **10g** (197.4 mg, 86%) as an oil: IR (neat) 2940, 1475, 1460 (sh), 1440, 1250, 1090 cm^{-1}; ^1H NMR δ 6.62 (s, 2 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 3.15–1.40 (m, 8 H), 0.86 (d, J = 6 Hz, 6 H); mass spectrum, exact mass calcd for $C_{15}H_{22}O_2$ *m/e* 234.1619, obsd *m/e* 234.1610.

10h. A reaction flask containing cerium chloride heptahydrate (2.48 g, 6.7 mmol) was heated at 140 °C (0.03 mm) for 2 h and then cooled under a nitrogen atmosphere to −78 °C. THF (10 mL) was added to the flask followed by *tert*-butyllithium (4.75 mL of a 1.2 M hexane solution). Then **9** (1.38 g, 6.7 mmol) in THF (10 mL) was added, and the solution was stirred for 40 min at −78 °C. Addition of saturated NH_4Cl and standard workup followed by flash chromatography on silica gel (CH_2Cl_2 as eluant) gave **10h** (0.7 g, 42%). Additional product was present in overlapping fractions, which could be obtained pure by further chromatography. Recrystallization from PE/CH_2Cl_2 gave the

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[25] Coillard, J.; Mentzer, C. *Bull. Soc. Chim.* **1953**, *20*, 168.

[26] Middleton, W. J. *J. Org. Chem.* **1975**, *40*, 574.

analytical sample: mp 120–121 °C; IR (KBr) 3485, 2950, 1475, 1460 (sh), 1455, 1440, 1375, 1335, 1250, 1097, 1055, 950, 805 cm^{-1}; ^{1}H NMR δ 6.68 (s, 2 H), 5.38 (br s, 1 H), 3.77 (s, 6 H), 2.9–1.3 (m, 6 H), 0.88 (s, 9 H); ^{13}C NMR δ 152.4, 151.4, 131.0, 129.4, 108.5, 108.3, 78.9, 55.8, 55.3, 41.6, 35.8, 26.4 (3 C), 23.4, 20.1. Anal. Calcd for $C_{16}H_{24}O_3$: C, 72.69; H, 9.15. Found: C, 72.65; H, 9.17.

Reduction of the alcohol (157.2 mg, 0.595 mmol) with Et_3SiH (0.35 mL, 2.2 mmol) in CF_3CO_2H (5 mL) followed by flash chromatography on silica gel (first with hexane and then with 1:1 hexane/CH_2Cl_2) gave **10h** (139.2 mg, 94%): IR (neat) 2940, 1475, 1440, 1250, 1092, 1070 cm^{-1}; ^{1}H NMR δ 6.61 (s, 2 H), 3.25 (s, 3 H), 3.20 (s, 3 H), 3.3–1.0 (m, 7 H), 0.86 (s, 9 H); ^{13}C NMR δ 152.1, 151.1, 130.3 (2 C), 107.4, 107.0, 55.8, 55.1, 39.2, 36.9, 29.0 (3 C), 24.2, 21.6, 20.2; mass spectrum, exact mass calcd for $C_{16}H_{24}O_2$ *m/e* 248.1777, obsd *m/e* 248.1790.

10k. A solution of CH_3Li (2.5 mL of a 1.2 M solution in Et_2O, 1.2 equiv) in THF (20 mL) was cooled to −78 °C. Then a solution of **9** [0.521 g, 2.53 mmol in THF (10 mL)] was added over a period of 10 min. The mixture was stirred for 0.5 h, the reaction was quenched by adding 20% HCl (10 mL), and the mixture was concentrated in vacuo. Extraction of the residue with CH_2Cl_2 (3 × 30 mL) and workup as usual afforded a light yellow oil. Flash column chromatography (1:1 CH_2Cl_2/PE as eluant) gave colorless oil **10k** (465 mg, 90%): IR (film) 2930, 2830, 1480, 1465, 1435, 1225, 1135, 1090, 1055 cm^{-1}; ^{1}H NMR δ 6.72 (s, 2 H), 6.5–6.2 (m, 1 H), 3.78 (s, 3 H), 3.75 (s, 3 H), 2.68–2.45 (m, 2 H), 2.40–1.76 (m, 5 H); mass spectrum, exact mass calcd for $C_{12}H_{16}O_2$ *m/e* 204.1150, obsd *m/e* 204.1139.

13a and 14a. Anodic oxidation (45 min, 0.8 A) of **10a** (206.3 mg, 0.74 mmol) in 2% CH_3OH/KOH (75 mL) at −20 °C followed by workup gave **12a** as a crude light yellow oil (194.8 mg, 97%), which was used directly in the next step: IR (neat) 3600–3200 (br), 2940, 2830, 1460, 1440, 1400, 1295, 1205, 1170, 1145 (br), 980, 960 cm^{-1}; ^{1}H NMR δ 6.21 (AB q, J = 8 Hz, 1 H), 6.13 (AB q, J = 8 Hz, 1 H), 4.62–4.36 (m, 1 H), 3.46 (br s, 1 H), 3.37 (s, 3 H), 3.16 (s, 3 H), 3.13 (s, 3 H), 3.10 (s, 3 H), 2.5–1.2 (m, 6 H).

To the crude **12a** (194.8 mg, 0.721 mmol) in $(CH_3)_2CO$ (15 mL) at −20 °C was added 5% HOAc (5 mL), and the solution was stored for 48 h. Workup gave a mixture of **13a** and **14a** as a light brown oil (150.1 mg, 0.67 mmol, 92%). Flash chromatography (2:1 hexane/CH_2Cl_2) yielded **13a** (129 mg, 80%): IR (neat) 3650–3200 (br), 2940, 2830, 1675, 1645, 1610, 1405, 1295, 1100–1060 (br) cm^{-1}; ^{1}H NMR (CCl_4) δ 6.78 (AB q, J = 10 Hz, 1 H), 6.41 (AB q, J = 10 Hz, 1 H), 4.81–4.58 (m, 1 H), 3.21 (s, 3 H), 3.20 (br s, 1 H), 2.45–1.20 (m, 6 H); ^{13}C NMR δ 185.9 (s), 154.6 (s), 144.1 (d), 137.3 (s), 132.0 (d), 83.9 (s), 62.4 (d), 50.9 (q), 50.8 (q), 29.7 (t), 23.5 (t), 17.4 (t); mass spectrum, exact mass calcd for $C_{12}H_{16}O_4$ *m/e* 224.1048, obsd *m/e* 224.1080.

The second monoketal **14a** (15.3 mg, 9%) showed the following: IR (neat) 3600–3200 (br), 2940, 2820, 1675, 1650, 1625, 1290, 1160 (br), 990, 960 cm^{-1}; ^{1}H NMR δ 6.78 (AB, q, J = 10 Hz, 1 H), 6.38 (AB q, J = 10 Hz, 1 H), 4.68–4.52 (m, 1 H), 3.43–3.17 (br, 1 H), 3.40 (s, 3 H), 3.17 (s, 3 H), 2.76–1.32 (m, 6 H); ^{13}C NMR δ 194.4 (s), 147.0 (s), 141.4 (s), 137.8 (s), 131.7 (d), 97.2 (s), 62.3 (d), 51.1 (q), 51.0 (q), 29.5 (t), 22.4 (t), 16.3 (t); mass spectrum, exact mass calcd for $C_{12}H_{16}O_4$ *m/e* 224.1048, obsd *m/e* 224.1077.

13b and 14b. Anodic oxidation (0.7 h, 0.8 A) of **10b** (201 mg, 0.901 mmol) in 2% CH_3OH/KOH (75 mL) at −5 °C followed by workup gave the bisketal **12b** (0.252 g, 0.88 mmol) as a crude brown oil (0.25 g, 98%): IR (neat) 2940, 2830, 1410, 1395, 1290, 1205, 1190, 1175, 1140, 1075 (br), 1010, 940 cm^{-1}; ^{1}H NMR δ 6.12 (s, 2 H), 4.02–3.78 (m, 1 H), 3.36 (s, 3 H), 3.24, 3.22, 3.18 (s, 12 H), 3.15, 2.5–1.0 (m, 6 H).

This material was dissolved in $(CH_3)_2CO$ (15 mL) and cooled to −20 °C, 5% HOAc (5 mL) was added, and the solution was stored for 48 h. Workup gave a mixture of two monoketals in the ratio 6.2:1 as determined by integration of the methine signals at δ 4.27–4.23 and 4.04–3.98 in the ^{1}H NMR spectrum. Flash chromatography (CH_2Cl_2) gave pure **13b** (142.9 mg, 65%): IR (neat) 2950, 2820, 1670, 1640, 1620, 1450, 1400, 1350, 1290, 1205, 1190, 1085, 1055, 1010, 960, 840 cm^{-1}; ^{1}H NMR δ 6.72 (AB q, J = 10 Hz, 1 H), 6.42 (AB q, J = 10 Hz, 1 H), 4.37–4.17 (m, 1 H), 3.41 (s, 3 H), 3.19 (s, 6 H), 2.50–1.10 (m, 6 H); ^{13}C NMR δ 183.7 (s), 154.3 (s), 142.9 (d), 136.0 (s), 132.5 (d), 95.0 (s), 68.3 (d), 51.3 (q), 50.9 (q), 50.7 (q), 25.7 (t), 23.1 (t), 15.7 (t); mass spectrum, exact mass calcd for $C_{13}H_{18}O_4$ *m/e* 238.1205, obsd *m/e* 238.1166.

The minor isomer was not obtained pure.

13c and 14c. Anodic oxidation (1.5 h, 1 A) of **10c** (206.5 mg, 0.641 mmol) in 2% CH_3OH/KOH (75 mL) at −5 °C followed by workup as usual gave crude **12c** as a light brown oil (228.67 mg, 0.65 mmol, 92%), which was used directly in the next step: IR (neat) 2930, 2850, 2825, 1460, 1250, 1205, 1175, 1140, 1075 (br), 1020, 1000, 950, 870, 830, 770 cm^{-1}; crude ^{1}H NMR δ 6.10 (br s, 2 H), 5.63–5.41 (m, 1 H), 3.21 (s, 3 H), 3.16 (s, 3 H), 3.13 (s, 6 H), 2.5–1.0 (m, 6 H), 0.88 (s, 9 H), 0.10 (s, 6 H).

To the crude **12c** (220.4 mg, 0.573 mmol) in acetone (15 mL) at −20 °C was added 5% HOAc (5 mL), and the hydrolysis was allowed to proceed for 60 h. Workup gave the monoketals **13c** and **14c** as a crude brown oil (174.6 mg, 0.51 mmol). Integration of the methine hydrogens in the ^{1}H NMR spectrum at δ 4.82–4.75 and 4.66–4.60 showed the **13c**/**14c** ratio to be 3.3:1. This mixture of monoketals was reduced, and the reduction products were characterized as described in the supplementary material.

13d and 14d. Anodic oxidation (40 min, 1 A) of **10d** (203.9 mg, 0.804 mmol) in 2% CH_3OH/KOH (75 mL) at −5 °C followed by workup gave **12d** as a light brown oil (0.252 g, 98%), which was used directly in the next step: IR (neat) 2940, 2820, 1460, 1440, 1390, 1380, 1305, 1250, 1240, 1050 (br), 960 cm^{-1}; ^{1}H NMR δ 6.12 (s, 2 H), 4.89 (AB q, J = 7 Hz, 1 H), 4.59 (AB q, J = 7 Hz, 1 H), 4.38–4.18 (m, 1 H), 3.38 (s, 3 H), 3.18 (s, 3 H), 3.17 (s, 3 H), 3.15 (s, 3 H), 3.14 (s, 3 H), 2.35–1.00 (m, 6 H).

To the crude product **12d** (154.1 mg, 0.491 mmol) in acetone (15 mL) at −20 °C was added a 5% solution of HOAc (5 mL), and hydrolysis was allowed to proceed for 48 h. Standard workup gave the mixture of monoketals **13d** and **14d** as a brown oil (120 mg, 0.44 mmol, 91%). Integration of the methine hydrogen signals at δ 4.68–4.58 and 4.48–4.43 showed the ratio of monoketals **13d**/**14d** to be 3.5:1.0. Flash chromatography (2:1 PE/CH_2Cl_2) yielded a pure sample of the two monoketals in addition to overlapping fractions. The major isomer **13d** (41.0 mg, 31%) showed the following: IR (neat) 2940, 1680, 1650, 1625, 1295, 1210, 1150, 1100, 1060, 1035, 965 cm^{-1}; ^{1}H NMR δ 6.71 (AB q, J = 10 Hz, 1 H), 6.41 (AB q, J = 10 Hz, 1 H), 4.90 (AB q, J = 6 Hz, 1 H), 4.61 (partially obscured, 1 H), 4.60 (AB q, J = 6 Hz, 1 H), 3.43 (s, 3 H), 3.24 (s, 3 H), 3.20 (s, 3 H), 2.60–1.60 (m, 6 H); mass spectrum, exact mass calcd for $C_{14}H_{20}O_5$ *m/e* 268.1311, obsd *m/e* 268.1296.

The minor monoketal, **14d**, showed the following: mp 68–69 °C; IR (KBr) 2940, 1680, 1650, 1290, 1150, 1100, 1080, 1065, 1037 cm^{-1}; ^{1}H NMR δ 6.71 (AB q, J_{AB} = 10 Hz, 1 H), 6.40 (AB q, J_{AB} = 10 Hz, 1 H), 4.92 (AB q, J_{AB} = 7 Hz, 1 H), 4.64 (AB q, J_{AB} = 7 Hz, 1 H), 4.58–4.30 (m, 1 H), 3.42 (s, 3 H), 3.24 (s, 3 H), 3.20 (s, 3 H), 2.06–1.06 (m, 6 H); exact mass calcd for $C_{14}H_{20}O_5$ *m/e* 268.1311, obsd *m/e* 268.1296.

13e and 14e. Anodic oxidation (40 min, 0.8 A) of **10e** (604.1 mg, 2.93 mmol) in 2% CH_3OH/KOH (75 mL) at 0 °C was continued until no starting material could be detected by TLC. The resulting solution was concentrated in vacuo and extracted with CH_2Cl_2 (3 × 30 mL). Workup as usual gave **12e** (760.5 mg, 95%) as a clear oil: IR (film) 2930, 1450, 1280, 1200, 1060 (br), 1040, 940 cm^{-1}; ^{1}H NMR δ 6.11 (s, 2 H), 3.19, 3.17, 3.13 (3 s, 12 H), 2.80–1.35 (m, 7 H), 1.19 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 139.6, 136.4, 132.4, 131.2, 95.9, 94.9, 49.9 (q, 4 C), 30.3 (t), 26.0 (d), 21.4 (t), 19.9 (q), 16.3 (t).

A solution of **12e** (415.8 mg, 1.55 mmol) in $(CH_3)_2CO$ (20 mL) was cooled to −20 °C, and cold 5% HOAc (5 mL) was added. After 48 h at −20 °C the reaction was quenched with saturated $NaHCO_3$ (20 mL), and the reaction was worked up as usual to give a light yellow oil. The crude ^{1}H NMR spectrum showed **13e** and **14e** in the ratio 1.5:1 [integration of the methyl resonances at δ 1.24 (d, J = 6.74 Hz, 3 H) and 1.08 (d, J = 7.2 Hz, 3 H)]. The chemical transformations and separations of the products from this mixture are described in the supplementary material.

13f and 14f. Anodic oxidation (40 min, 0.8 A) of **10f** (383.5 mg, 1.74 mmol) in 2% CH_3OH/KOH (75 mL) at 0 °C was continued until the absorption for starting material (λ_{max} 289 nm) decreased to within 5% of its initial value. Concentration in vacuo and workup as usual afforded the crude bisketal **12f** as a light yellow oil (441.3, 90%), which was used directly in the next step: IR (film) 2940, 2830, 1300, 1150, 1070 (br), 955 cm^{-1}; ^{1}H NMR 6.11 (s, 2 H), 3.19 (s, 3 H), 3.17 (s, 3 H), 3.14 (s, 3 H), 3.11 (s, 3 H), 2.80–1.10 (m, 9 H), 0.87 (t, J = 7 Hz, 3 H); ^{13}C NMR δ 140.0, 136.5, 132.6, 131.4, 96.2, 95.3, 50.4, 50.2, 50.1 (2 C), 33.0, 24.2, 21.2, 16.0, 11.9.

A solution of **12f** (441.3 mg, 1.56 mmol) in $(CH_3)_2CO$ (20 mL) was cooled to −20 °C, and cold 5% HOAc (5 mL) was added. After 2 days at −20 °C, saturated $NaHCO_3$ (30 mL) was added, and the mixture was worked up to afford a yellow oil (392 mg, 96%). Integration of the olefinic region of the ^{1}H NMR spectrum gave a 3:1 mixture of regioisomeric monoketals. This was in qualitative agreement with the ratio of peak heights in the ^{13}C NMR spectrum. The supplementary material describes the chemical transformations and separation of the pure products from this mixture of monoketals.

13g and 14g. The anodic oxidation (40 min, 0.25 A) of **10g** (191.9 mg, 082 mmol) in 2% CH_3OH/KOH (75 mL) at 0 °C gave **12g** (280.2 mg, 99%), which was used directly in the next step: IR (film) 2940, 2830, 1465, 1390, 1305, 1245, 1230, 1070 (br), 960 cm^{-1}; ^{1}H NMR δ 6.20 (AB q, J = 10 Hz, 1 H), 6.04 (AB q, J = 10 Hz, 1 H), 3.24 (s, 3 H), 3.15 (s, 3 H), 3.11 (s, 3 H), 3.09 (s, 3 H), 2.80–1.25 (m, 8 H), 0.93 (d, J = 7 Hz, 3 H), 0.82 (d, J = 7 Hz, 3 H).

The monohydrolysis with $(CH_3)_2CO$ (20 mL) and 5% HOAc (5 mL)) of **12g** (240.2 mg, 0.81 mmol) at −20 °C was allowed to proceed for 48 h. Workup gave a light yellow oil (141 mg, 66%). The ^{1}H NMR spectrum of the crude reaction mixture showed **13g** and **14g** in the ratio 6.5:1 from intergration of the olefinic region. Flash chromatography (1:1 PE/CH_2Cl_2) yielded **13g** and **14g** in addition to overlapping fractions and quinone. Spectroscopic data for **13g** showed the following: IR (film) 2930, 1670, 1640, 1620, 1460, 1370, 1290, 1210, 1100, 1060, 960, 840 cm^{-1}; ^{1}H NMR δ 6.62 (AB q, J = 10 Hz, 1 H), 6.36 (AB q, J = 10 Hz, 1 H), 3.17 (s, 3 H), 3.11 (s, 3 H), 3.00–1.30 (m, 8 H), 0.84 (d, J = 6.8 Hz, 3 H), 0.76 (d, J = 7 Hz, 3 H); ^{13}C NMR δ 184.8, 162.1, 142.8, 140.6, 132.9, 95.5, 50.9, 50.8, 36.6, 30.0, 23.0 (2 C), 21.1, 18.9, 18.7; mass spectrum, exact mass calcd for $C_{15}H_{22}O_3$ m/e 250.1497, obsd m/e 250.1526.

The minor isomer was not obtained pure.

13h and 14h. Electrolysis (0.5 h, 0.7 A) of **10h** (234.3 mg, 0.95 mmol) in 2% CH_3OH/KOH (70 mL) at 0 °C was followed by UV until disappearance of λ_{max} 291-nm absorption. Workup gave **12h** (289.9 mg, 97% crude) as a light yellow oil suitable for use in the next step: IR (neat) 2940, 2820, 1460, 1390, 1200, 1090, 1070 (br), 960 cm^{-1}; ^{1}H NMR δ 6.33 (AB q, J = 10 Hz, 1 H), 5.99 (AB q, J = 10 Hz, 1 H), 3.34 (s, 3 H), 3.15 (s, 3 H), 3.12 (s, 3 H), 3.02 (s, 3 H), 2.5–1.0 (m, 7 H), 1.04 (s, 9 H); ^{13}C NMR δ 142.4, 137.7, 133.1, 130.8, 96.4, 95.0, 50.8, 50.7, 50.3, 49.0, 40.3, 34.7, 31.2 (3 C), 27.2, 20.0, 17.3.

To the crude **12h** (289.9 mg, 0.93 mmol) in $(CH_3)_2CO$ (15 mL) at −20 °C was added 5% aqueous HOAc (5 mL), and the solution was stored for 48 h. The crude ^{1}H NMR spectrum showed a 10.5:1 mixture of monoketals (250 mg, 96%) as determined by integration of the *tert*-butyl resonances at δ 1.05 and 1.37. Flash chromatography (1:1 PE/CH_2Cl_2) gave **13h** (147.6 mg, 57%): IR (neat) 2950, 1675, 1640, 1365, 1290, 1280, 1150, 1100, 1070 (br), 965, 840 cm^{-1}; ^{1}H NMR δ 6.65 (AB q, J = 10 Hz, 1 H), 6.43 (AB q, J = 10 Hz, 1 H), 3.26 (s, 3 H), 3.11 (3 H), 2.5–1.0 (m, 6 H), 0.87 (s, 9 H); ^{13}C NMR δ 185.2, 153.6, 142.3, 140.1, 132.7, 95.5, 51.0, 50.7, 38.1, 36.0, 29.3 (3 C), 23.6, 21.9, 19.8; mass spectrum, exact mass calcd for $C_{16}H_{24}O_5$ m/e 264.1725, obsd m/e 264.1718.

The minor isomer could not be obtained pure, but its reduction product was characterized as described in the supplementary material.

10i, 13i, and 14i. A solution of **10a** (R = OH, 0.665 g, 3.20 mmol) in CH_2Cl_2 (10 mL) was added slowly to a −78 °C solution of diethylaminosulfur trifluoride (0.7 mL, 5.7 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was warmed to room temperature, and water was added. The product was extremely labile, affording the elimination product and hydrogen fluoride on standing. Workup in the usual manner gave a yellow oil, which showed the following: IR (neat) 2930, 2830, 1600, 1480, 1460 (sh), 1440, 1340, 1310, 1300, 1090, 1060 cm^{-1}; ^{1}H NMR δ 6.68–6.80 (m, 2 H), 5.4 (br d, J_{HF} = 49 Hz, 1 H), 3.84 (s, 3 H), 3.78 (s, 3 H), 3.20–1.05 (m, 6 H); ^{13}C NMR δ 129.0, 128.8, 110.8 (J_{HF} = 4 Hz), 109.9, 107.9 (J_{HF} = 2 Hz), 106.4, 86.4 (J_{HF} = 164 Hz), 56.0, 55.6, 28.9 (J_{HF} = 22 Hz), 22.9, 16.2.

This product was immediately dissolved in 2% KOH/CH_3OH (50 mL) and electrolyzed at 0 °C (0.5 A, 45 min) to afford **12i** after workup as a light yellow oil, which was crystallized from PE/CH_2Cl_2 [76%; first crop (547.6 mg), second crop (93.4 mg), third crop (18.7 mg)]: mp 52–54.5 °C; IR (KBr) 2940, 2830, 1205, 1180, 1070 (br), 960 cm^{-1}; ^{1}H NMR δ 6.24 (br s, 2 H), 5.30 (br d, J_{HF} = 46 Hz, 1 H), 3.22 (s, 3 H), 3.20 (s, 6 H), 3.16 (s, 3 H), 2.45–1.20 (m, 6 H); ^{13}C NMR δ 144.2, 143.9 (J_{HF} = 10 Hz), 132.7, 131.7 128.2 (J_{HF} = 22 Hz), 95.0, 81.1 (J_{HF} = 164 Hz), 51.3, 50.7 (2 C), 50.5 (2 C), 28.8 (J_{HF} = 20 Hz), 21.9 (J_{HF} = 4 Hz), 15.6; mass spectrum, exact mass calcd for $C_{14}H_{23}O_4F$ m/e 272.1423, obsd m/e 272.1457.

To a solution of **12i** (547.6 mg, 2.0 mmol) in $(CH_3)_2C{=}O$ (15 mL) at −20 °C was added 5% HOAc (5 mL), and the reaction mixture was stored for 48 h. Workup gave a mixture of two monoketals as a light yellow oil. Flash chromatography (neutral aluminum oxide, Activity III, CH_2Cl_2) did not afford a separation but yielded from integration of the ^{19}F NMR signals [two triplets with extensive additional coupling, $J \sim 40$ Hz at δ −158.4 (**13j**) and −151.2 (**14j**)] a 10.5:1 mixture of **13i** and **14i** as a clear oil (393.7 mg, 1.75 mmol, 88%). The spectroscopic data for **13i** were obtained from the above mixture: IR (film, neat) 2940, 1680, 1650, 1635, 1405, 1290, 1210, 1100, 1040, 960, 905 cm^{-1}; ^{1}H NMR δ 6.77 (AB q, J = 10 Hz, 1 H), 6.46 (AB q, J = 10 Hz, 1 H), 5.65 (d of m, J_{HF} = 46 Hz, 1 H), 3.21 (s, 6 H), 2.73–1.05 (m, 6 H); ^{13}C NMR δ 183.0, 157.50 (J_{CF} = 6 Hz), 143.1, 133.1 (J_{CF} = 16 Hz), 132.1, 94.8, 79.9 (J_{CF} = 166 Hz), 51.0, 50.9, 28.1 (J_{CF} = 22 Hz), 23.1 (J_{CF} = 2 Hz), 15.7; mass spectrum, exact mass calcd for $C_{12}H_{15}O_3F$ m/e 226.1005, obsd m/e 226.1015.

13j and 14j. Anodic oxidation (40 min, 0.2 A) of **10j** (0.198 g, 1.04 mmol) in 75 mL of 1% KOH/CH_3OH at 0 °C was continued until TLC showed no remaining starting material. Workup as usual afforded the bisketal **12j** as a light brown oil (0.21 g, 80%), which was used directly in the next step: IR (film, neat) 2940, 2820, 1460, 1390, 1300, 1285, 1205, 1150, 1070 (br), 960 cm^{-1}; ^{1}H NMR δ 6.3–5.8 (m, 4 H), 3.20 (s, 12 H), 2.23 (br s, 4 H).

To a solution of **12j** (210 mg, 0.83 mmol) in $(CH_3)_2C{=}O$ (20 mL) at −20 °C was added 5% HOAc (0.5 mL), and the reaction mixture was stored for 48 h. Workup gave a mixture of two monoketals as a brown oil. Integration of the methoxy region (δ 3.20 and 3.25) showed the **14j**/**13j** ratio to be 5:1. Flash chromatography (3:1 CH_2Cl_2/PE) gave pure **14j**: IR (film, neat) 2940, 2830, 1670, 1640, 1630, 1460, 1440, 1390, 1300, 1280, 1210, 1150, 1070 (br), 950 cm^{-1}; ^{1}H NMR δ 6.61 (J_{AB} = 10 Hz, 1 H), 6.35 (J_{AB} = 10 Hz overlapping with a broad singlet at δ 6.28, total area 3 H), 3.20 (s, 6 H), 2.8–2.0 (br m, 4 H); ^{13}C NMR δ 184.6 (s), 145.2 (s), 141.8 (d), 135.7 (d), 132.3 (d), 131.3 (s), 122.2 (d), 94.7 (s), 51.0 (2 C, q), 22.4 (t), 17.7 (t); mass spectrum, exact mass calcd for $C_{12}H_{14}O_3$ m/e 206.0943, obsd m/e 206.0948.

The minor monoketal was not obtained pure.

13k and 14k. The anodic oxidation (2 h, 0.15 A) of **10k** (425 mg, 2.08 mmol) in 2% CH_3OH/KOH (75 mL) at 0 °C (divided cell) gave **12k** (590 mg, 96%), which was used directly in the next step: IR (film) 2940, 2860, 1205, 1100, 1065 (br), 950 cm^{-1}; ^{1}H NMR δ 6.08 (s, 2 H), 5.8–5.65 (m, 1 H), 3.23 (s, 3 H), 3.20 (s, 3 H), 2.4–1.7 (m, 7 H).

The monohydrolysis [$(CH_3)_2CO$ (20 mL) and 5% HOAc (5 mL)] of **12k** (590 mg, 1.99 mmol) at −20 °C was allowed to proceed for 48 h. Workup gave the mixture of monoketals as a light yellow oil (400 mg, 91%). The ^{1}H NMR spectrum of the crude reaction mixture showed **13k** and **14k** in the ratio 1:8.5 from integration of the methoxy region. Flash column chromatography (CH_2Cl_2 as eluant) gave **14k** (220 mg, 50%) and a mixture of **13k** and **14k** (170 mg, 39%). Spectroscopic data for **14k** showed the following: IR (film) 2940, 1670, 1630, 1300, 1100, 1060 (br) cm^{-1}; ^{1}H NMR δ 6.55 (AB q, J = 10 Hz, 1 H), 6.39 (AB q, J = 10 Hz, 1 H), 6.2–5.9 (m, 1 H), 3.20 (s, 6 H), 2.6–1.7 (m, 7 H); ^{13}C NMR δ 184.9, 145.6, 143.3, 133.9, 133.1, 132.5, 131.2, 96.4, 50.7 (2 C), 22.4, 20.1, 18.9; mass spectrum, exact mass calcd for $C_{13}H_{16}O_3$ m/e 220.1093, obsd m/e 220.1096.

General Procedure for Kinetics of Bisketal Hydrolysis. To a 22 °C solution of 0.25 mL of 1.71 M aqueous acetic acid (pH 2.2) in a UV cell in the thermostated chamber of a Beckman DU-7 ultraviolet spectrometer was added 1.5 mL of a 22 °C solution of the bisketal in THF, giving a resulting solution of pH 4.2. The final concentration of bisketal was (3.8–17.1) × 10^{-4} M, and the rate constants were within experimental error when the initial concentration of bisketal was changed by a factor of 3 (compound **12b**). The rates were monitored by observing the increase in optical density at the appropriate wavelengths, usually 315 and 295 nm. The rate constants were determined from the slope of a plot of log A/A_0 vs. time by using the infinity optical density for the value of A_0. The plots showed excellent linearity up to three to four half-lives. Representative data are given in the supplementary material. The rate constants were readily reproducible within ±5% and should be accurate within ±10%.

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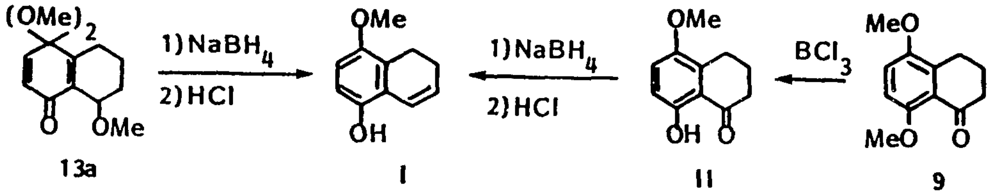
Supplementary Material Available: Experimental details of the structure proofs for compounds **13b,c,e–k** and **14b,c,e–h** and representative kinetic plots of the data (14 pages). Ordering information is given on any current masthead page.

EXPERIMENTAL

Note: Arabic numbers are used for structures that also appear in the text. Roman numerals are used for structures which appear only in the Experimental Section.

Structure Proof for 13b and 14b



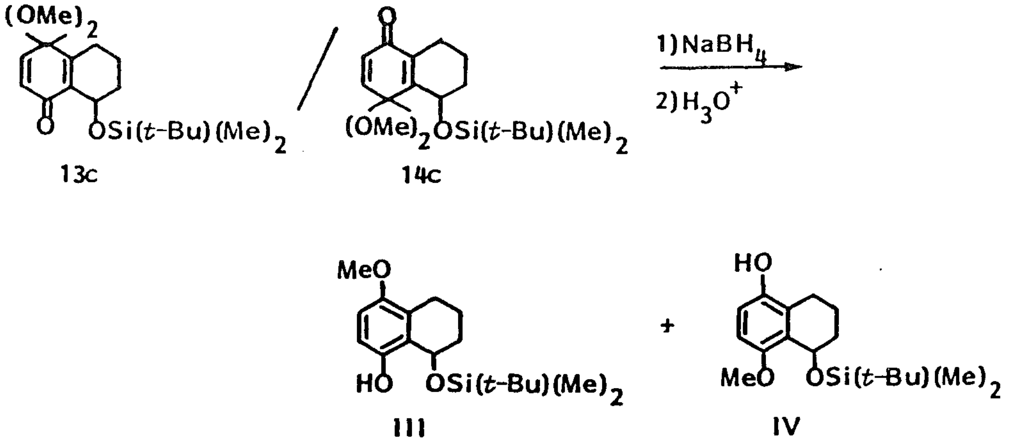
I. The reduction of **13a** (21.5 mg, 0.112 mmol) in EtOH (20 mL) with NaBH$_4$ (0.25 g, excess) was followed by quenching the reaction with 5% HCl to afford after workup and flash chromatography [PE/CH$_2$Cl$_2$ (1:1)] **I** (17.2 mg, 88%): mp 65-66 °C IR (KBr) 3500-3100, 1470, 1460, 1440, 1340, 1250, 1230, 1228 (sh), 1090, 790, 780, 730, 690 cm^{-1}; ^{1}H NMR (CDCl$_3$) δ 6.69 (d of t, *J* = 10, 2 Hz, 1 H) overlapping 6.59 (s, 2 H), 6.06 (structured m, 1 H), 4.42 (s, 1 H), 2.76 (s, 3 H), 2.9-2.5 (structured m, 2 H), 2.5-2.0 (m, 2 H); mass spectrum, exact mass calcd for $C_{11}H_{12}O_2$ m/e 176.0838, obsd 176.0833.

II. A solution of **9** (0.59 g, 2.87 mmol) in CH_2Cl_2 (25 mL) was cooled to -70 °C, and 1 M BCl_3 (17.2 mL, 8.23 mmol) in CH_2Cl_2 was added. The reaction mixture was stirred for 15 min, CH_3OH (10 mL) was added, and the mixture was worked up as usual to afford a light yellow solid. Flash chromatography (CH_2Cl_2) gave II (0.504 g, 91%). Recrystallization (CH_2Cl_2/PE) gave light yellow crystals: mp 91-92.2 °C; IR (KBr) 1640, 1460, 1435, 1330, 1300, 1270, 1210, 1185, 1175 cm^{-1}; ^1H NMR ($CDCl_3$) δ 11.79 (s, 1 H), 7.05 (AB q, J = 9 Hz, 1 H), 6.76 (AB q, J = 9 Hz, 1 H), 3.78 (s, 3 H), 2.87 (t, J = 6 Hz, 2 H), 2.66 (t, J = 6 Hz, 2 H), 2.1-1.7 (5-line m, 2 H); ^{13}C NMR ($CDCl_3$) δ 205.1, 156.4, 148.5, 132.7, 120.1, 117.0, 114.7, 56.3, 38.6, 22.8, 22.0; mass spectrum, exact mass calcd for $C_{11}H_{12}O_3$ m/e 192.0786, obsd 192.0783.

Authentic Synthesis of I. A mixture of **II** (21.5 mg, 0.112 mmol) in EtOH (20 mL) was reduced with $NaBH_4$ (0.25 g, excess) in a manner similar to that for **13a** noted above to give after workup and flash chromatography (1:1 PE/CH_2Cl_2) II (17.2 mg, 88%) identical to the product obtained from the electrolysis route.

Structure Proof for 13c and 14c

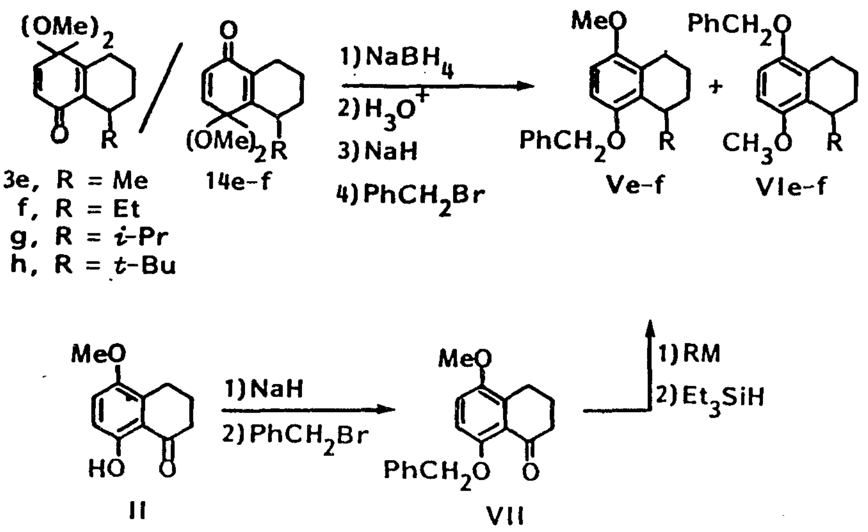
The monoketals **13c** and **14c** could not be readily separated by chromatography, but their reduction products **III** and **IV** were separated by chromatography. The assignment of the major regiosisomer as **13c** from the hydrolysis rests on the downfield shift of the hydroxyl group in III (δ = 7.68, sharp singlet) vs. that same signal for a non-intramolecular hydrogen-bonded hydroxyl group in IV (δ 4.38, broad singlet).



Structure Proof for 13c and 14c. The mixture of monoketals 13c and 13b in EtOH (10 mL) was reduced with $NaBH_4$ (0.25 g, excess) and worked up to yield a light yellow oil. Flash chromatography [PE/CH_2Cl_2 (3:1)] gave **III** (121.8 mg, 73%) and **IV** (23.7 mg, 14%). Spectroscopic data for III showed: IR (film) 3600-3100, 2940, 2860, 1480, 1465 (sh), 1440, 1250 (br), 1100, 1075, 1040, 875, 830, 800, 780, 730 cm^{-1}; ^1H NMR δ 7.68 (s, 1 H), 6.67 (s, 2 H), 5.30-5.00 (br t, 1 H), 3.74 (s, 3 H), 2.8-1.5 (m, 6 H), 0.93 (s, 9 H), 0.24 (s, 3 H). 0.18 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 150.3 (2C), 127.0, 125.0, 113.2, 110.3, 71.0, 55.8, 32.7, 25.8, 23.4, 19.9, 18.0, -3.0, -4.5; mass spectrum, exact mass calcd for $C_{17}H_{28}O_3Si$ m/e 308.1807, obsd 308.1762.

Spectroscopic data for IV showed: IR (film) 3600-3100, 2940, 2860, 1475, 1460, 1440, 1260, 1250, 1095, 1083, 1030, 965, 830, 800, 770, 730 cm^{-1}; ^1H NMR ($CDCl_3$) δ 6.64 (AB q, J = 8 Hz, 1 H), 6.57 (AB q, J = 8 Hz, 1 H), 5.21-5.00 (m, 1 H), 4.38 (br s, 1 H), 3.75 (s, 3 H), 1.72-1.42 (m, 6 H), 0.86 (s, 9 H), 0.16 (s, 3 H), 0.04 (s, 3 H); ^{13}C NMR δ 151.8, 147.0, 128.5, 125.1, 113.4, 107.4, 61.6, 54.8, 31.4, 25.9 (3C), 23.0, 18.2, 15.6, -4.5, -5.1.

Structure Proof for 13e and 14e



Conversion of 13e to Ve and 14e to VIe. To a mixture of 13e and 14e (330.8 mg, 1.72 mmol) in EtOH (10 mL) was added $NaBH_4$ (0.5 g, excess), and the reaction was allowed to proceed for 30 min. The reaction was then quenched with 5% HCl (3 mL) and worked up as usual to afford a mixture of two phenols. The ^{1}H NMR spectrum of the mixture showed methyl resonances at δ 1.23 and 1.18 ($\underline{J}$ = 7 Hz), representing the two isomers in the ratio 1.5:1. Flash chromatography (CH_2Cl_2) afforded the major isomer: mp 88-87 ^oC; IR (film) 3600-3100. 2920, 2860, 1480, 1460, 1440, 1320, 1265, 1250, 1120, 1090, 1050, 1000, 795, 720 cm^{-1}; ^{1}H NMR δ 6.55 (s, 2 H), 4.50 (s, 1 H), 3.75 (s, 3 H), 3.4-1.5 (m, 7 H), 1.25 (d, $\underline{J}$ = 7.0 Hz, 3 H); mass spectrum, exact mass calcd for $C_{12}H_{16}O_2$ $\underline{m/e}$ 192.1150, obsd 192.1174.

The minor isomer was obtained as a 90:10 mixture with the major isomer, and the spectroscopic data are reported from this mixture, neglecting peaks arising from the major isomer: IR (KBr) 3600-3100, 2920, 2860, 1480, 1450, 1440, 1370, 1350, 1330, 1310, 1270, 1240, 1080, 1025, 940, 795, 720 cm^{-1}; ^{1}H NMR δ 6.57 (s, 2 H), 4.27 (s, 1 H), 3.76 (s, 3 H), 3.3-1.5 (m, 7 H), 1.18 (d, $\underline{J}$ = 7 Hz, 3 H); mass spectrum, exact mass calcd for $C_{12}H_{16}O_2$ $\underline{m/e}$ 192.1150, obsd 192.1163.

The major phenol from above (17.7 mg, 0.077 mmol) and sodium hydride (3.4 mg, 1.1 eq) in THF (10 mL) were stirred until hydrogen evolution ceased, then benzyl bromide (13.7 mg, 0,08 mmol) was added, and the solution was heated to reflux for 2 h. Quenching the reaction with H_2O and workup as usual gave a yellow oil which furnished on flash chromatography (3:1, PE/CH_2Cl_2) **Ve** (20.8 mg, 96%) identical with an authentic sample.

The minor phenol (25.0 mg, 0.13 mmol) from above (a 90:10 mixture) and NaH (5.8 mg, 1.1 equiv) in dry THF (15 mL) were reacted as above with benzyl bromide (23.3 mg, 1.05 equiv), and the solution was heated to reflux for 12 h. The reaction was quenched with water (2.0 mL), and the mixture was concentrated in vacuo and extracted with CH_2Cl_2 (3 x 30 mL) to afford, after the usual workup, a yellow oil. Flash chromatography [CH_2Cl_2/PE (1:3)] gave a ca 90:10 mixture of **Ve** and VIe (21.0 mg, 57%). This established that the spectroscopic properties of the minor isomer could be readily differentiated from the major isomer. The ca. 90:10 mixture showed: IR (film) 2920, 2870, 1600, 1500, 1460 (br), 1340, 1320, 1250, 1100, 1065, 1040, 790, 730, 695 cm^{-1}; ^1H NMR ($CDCl_3$) δ 7.6-7.24 (m, 5 H), 6.64 (br s, 2 H), 5.00 (s, 2 H), 3.78 (s, 3 H), 3.5-1.2 (m, 7 H), 1.20 (d, *J* = 7 Hz, 3 H); mass spectrum, exact mass calcd for $C_{19}H_{22}O_2$ *m/e* 282.1620, obsd 282.1646.

VII. A mixture of **II** (384 mg, 2 mmol), 60% NaH (85 mg, 1.1 equiv), THF (20 mL), and benzyl bromide (341 mg, 1.05 equiv) was reacted as above for 12 h. Workup and flash chromatography [CH_2Cl_2/PE (1:3)] gave **VII** (519.0 mg, 92%): IR (film) 2940, 1685, 1590, 1470, 1440, 1270, 1250, 1090, 1030, 785, 695; ^1H NMR ($CDCl_3$) δ 7.7-7.24 (m, 5 H), 6.92 (AB q, *J* = 9 Hz, 1 H), 6.83 (AB q, *J* = 9 Hz, 1 H), 5.11 (s, 2 H), 3.80 (s, 3 H), 2.88 (t, *J* = 6 Hz, 1 H), 2.64 (t, *J* = 6 Hz, 2 H), 2.06 (struc m, 2 H); mass spectrum, exact mass calcd for $C_{18}H_{18}O_3$ *m/e* 282.1256, obsd 282.1262.

Ve from VII. A solution of **VII** (44.2 mg, 0.157 mmol) in dry THF (15 mL) was cooled to -70 °C, and 1.5 M CH_3Li (0.12 mL) was added. After stirring for 10 min the reaction was quenched by addition of water (2 mL). Workup as usual gave a yellow oil which was flash chromatographed (CH_2Cl_2) to give the alcohol (45.2 mg, 97%) as a colorless oil: IR (film) 3600-3400, 2930, 1470 (br), 1245, 1060 cm^{-1}; ^1H NMR δ 7.5-7.4 (m, 5 H), 6.76 (AB q, $\underline{J}$ = 8 Hz, 1 H), 6.64 (AB q, $\underline{J}$ = 9 Hz, 1 H), 5.10 (s, 2 H), 4.66 (s, 1 H), 3.76 (s, 3 H), 3.0-1.5 (m, 6 H), 1.62 (s, 3 H); mass spectrum, exact mass calcd for $C_{19}H_{22}O_3$ $\underline{m/e}$ 298.1569, obsd 298.1612.

To a mixture of the above alcohol (43.1 mg, 0.145 mmol) and Et_3SiH (1.5 mL, excess) was added CF_3CO_2H (3 mL). After stirring for 10 min the reaction mixture was concentrated, and the crude product was filtered through silica gel [PE/CH_2Cl_2 (15:1) and then PE/CH_2Cl_2 (3:1)] to give **Ve** (35.2 mg, 87%), showing identical spectroscopic properties to the major benzyl ether from the electrolysis route: IR (film) 2920, 2850 (sh), 1470 (br), 1460, 1250, 1090, 1060, 1040, 790, 725 cm^{-1}; ^1H NMR δ 7.64-7.24 (m, 5 H), 6.67 (AB q, $\underline{J}$ = 8 Hz, 1 H), 6.61 (AB q, $\underline{J}$ = 8 Hz, 1 H), 5.05 (s, 2 H), 3.78 (s, 3 H), 3.5-1.5 (m, 7 H), 1.28 (d, $\underline{J}$ = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.7. 150.6, 144.8, 138.1, 133.0, 128.5 (2C), 127.6, 127.0 (2C), 108.3, 106.7, 70.2, 55.5, 29.5, 26.9, 23.5, 20.9, 17.0; mass spectrum, exact mass calcd for $C_{19}H_{22}O_2$ $\underline{m/e}$ 282.1619, obsd 282.1638.

Structure Proof for 13f and 14f

Conversion of 13f to Vf and 14f to VIf. A mixture of the crude monoketals from above (347.8 mg, 1.59 mmol) in EtOH (10 mL) was treated with $NaBH_4$ (0.35 g) to give after workup a light yellow oil. Flash chromatography [PE/CH_2Cl_2 (3:2) and then CH_2Cl_2] afforded pure samples of both phenols.

The major phenol showed: IR (KBr) 3600-3100, 2960, 2930, 2870, 1481, 1460, 1440, 1425, 1280, 1260, 1250, 1080, 965, 800, 795, 720 cm^{-1}; ^{1}H NMR δ 6.54 (s, 2 H), 4.27 (s, 1 H), 3.74 (s, 3 H), 3.00-1.40 (m, 9 H), 0.99 (t, *J* = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.4, 147.1, 130.2, 126.9, 111.7, 107.5, 55.6, 33.9, 26.4, 24.3, 23.2, 16.8, 12.3; mass spectrum, exact mass calcd for $C_{13}H_{18}O_2$ *m/e* 206.1307, obsd 206.1310.

The minor phenol showed: IR (film) 3600-3100, 2930, 2860, 1460 (br), 1250, 1090, 1050, 795, 720 cm^{-1}; ^{1}H NMR δ 6.57 (s, 2 H), 4.36 (s, 1 H), 3.75 (3 H), 3.1-1.2 (m, 9 H), 0.95 (t, *J* = 7 Hz, 3 H); ^{13}C NMR δ 151.5, 147.2, 132.5, 124.2, 111.3, 107.9, 55.7, 33.6, 26.6, 24.2, 23.1, 16.8, 12.5; mass spectrum, exact mass calcd for $C_{13}H_{18}O_2$ *m/e* 206.1307, obsd 206.1260.

The major phenol from above (57.1 mg, 0.277 mmol) in THF (15 mL) was benzylated, using sodium hydride (0.31 mmol) and benzyl bromide (50.4 mg, 1.05 equiv) as above. Workup gave a light yellow oil which was purified by flash chromatography [PE/CH_2Cl_2 (5:1 and 1:1)] to give **Vf** (53.7 mg, 66%): IR (film) 2930, 2860, 1475, 1460, 1440, 1250, 1095, 1020, 790, 730, 690 cm^{-1}; ^{1}H NMR δ 7.50-7.24 (m, 5 H), 6.70 (AB q, *J* = 9 Hz, 1 H), 6.60 (AB q, *J* = 9 Hz, 1 H), 5.04 (s, 2 H), 3.78 (s, 3 H), 3.15-1.15 (m, 9 H), 0.96 (t, *J* = 7 Hz, 3 H); ^{13}C NMR ($CDCl_3$) δ 151.6, 150.5, 138.0, 132.9, 128.4 (2C), 127.5, 126.9 (2C), 108.3, 106.5, 70.1, 55.5, 33.8, 26.8, 24.2, 23.3, 17.0, 12.5 (one carbon missing); mass spectrum, exact mass calcd for $C_{20}H_{24}O_2$ *m/e* 296.1776, obsd 296.1788.

The minor phenol from above, (3.83 mg, 0.186 mmol), 60% NaH (8.3 mg, 1.1 equiv), THF (15 mL), and benzyl bromide (33 mg, 1.05 equiv) were reacted as above. Flash chromatography [PE/CH_2Cl_2 (5:1 and then

1:1)] gave **VIf** (39.8 mg, 72%): IR (film) 2930, 2860, 1475, 1460, 1440, 1250, 1095, 1070, 790, 730, 690 cm^{-1}; ^1H NMR δ 7.60-7.24 (m, 5 H), 6.64 (br s, 2 H), 5.00 (s, 2 H), 3.77 (s, 3 H), 3.20-1.2 (m, 9 H), 0.97 (t, $\underline{J}$ = 7, 3 H); ^{13}C NMR δ 151.7, 150.6, 138.0, 132.6, 128.5 (2C), 127.6, 127.4, 127.2 (2C), 108.2, 107.0, 70.2, 55.6, 33.7, 26.7, 24.3, 23.5, 17.0, 12.5; mass spectrum, exact mass calcd for $C_{20}H_{24}O_2$ $\underline{m/e}$ 296.1777, obsd 296.1735.

Vf from VII. To a -77 °C solution of **VII** (122.7 mg, 0.435 mmol) in THF (15 mL) was added ethyl magnesium bromide (0.23 mL of 3M solution in THF). The reaction was stirred for 1h and then worked up as usual to yield a light yellow oil. Flash chromatography (CH_2Cl_2) gave the alcohol (74.2 mg, 32%). Recrystallization gave colorless crystals: mp 92.5-94 °C; IR (film) 3600-3460, 2940, 2800, 1480, 1465, 1440, 1398, 1340, 1250, 1090, 1065, 1055 (sh), 730, 700 cm^{-1}: ^1H NMR δ 7.38 (s, 5 H), 6.74 (AB q, $\underline{J}$ = 9 Hz, 1 H), 6.63 (AB q, $\underline{J}$ = 9 Hz, 1 H), 5.08 (s, 2 H), 4.33 (br s, 1 H), 3.75 (s, 3 H), 2.8-1.0 (m, 8 H), 0.85 (t, $\underline{J}$ = 7 Hz, 3 H); mass spectrum, exact mass calcd for $C_{20}H_{24}O_3$ $\underline{m/e}$ 312.1726, obsd 312.1690.

Reduction of the above alcohol (72.4 mg, 0.23 mmol) with triethylsilane in trifluoroacetic acid gave after workup and flash chromatography **Vf** (53.1 mg, 78%) which showed identical spectroscopic properties to **Vf** obtained form the electrolysis route.

Structure Proof for 13g and 14g

Vg. In a manner similar to above, a 4.5:1 mixture of **13g** and **14g** (40.0 mg, 0.16 mmol) in EtOH (20 mL) was reduced with $NaBH_4$ (0.25 g). Flash chromatography [PE/CH_2Cl_2 (3:1)] gave an easily separated mixture of the major phenol (15.2 mg, 43%) and the minor phenol (4.6 mg, 13%).

The major phenol showed: IR (film) 3600-3150, 2960, 2940, 2880, 1485, 1460, 1440, 1250, 1095, 800, 735 cm^{-1}; ^1H NMR δ 6.54 (s, 2 H), 4.34 (s, 1 H), 3.75 (s, 3 H), 3.0-1.3 (m, 8 H), 0.93 (d, *J* = 7 Hz, 3 H), 0.85 (d, *J* = 7 Hz, 3 H); mass spectrum, mass calcd for $C_{14}H_{20}O_2$ *m/e* 220.1464; 220.1466.

The minor phenol showed: IR (film) 3600-3150, 2920, 2870, 1460, 1440, 1250, 1090, 1070, 800, 720 cm^{-1}; ^1H NMR δ 6.56 (s, 2 H), 4.26 (s, 1 H), 3.72 (s, 3 H), 3.1-1.5 (m, 8 H), 0.83 (d, *J* = 7 Hz, 6 H); mass spectrum, mass calcd for $C_{14}H_{20}O_2$ *m/e* 220.1463; obsd 220.1468.

Reaction of the major phenol (68.8 mg, 0.31 mmol) with NaH (60% mineral oil dispersion, 13.9 mg, 1.1 equiv) in THF (15 mL) and then benzyl bromide (50 mg, 1.05 equiv) gave, after workup and flash chromatography [PE/CH_2Cl_2 (3:1)], **Vg** (96.7 mg, 99%): IR (neat) 2930, 1600, 1460 (br), 1250, 1090, 1060, 790, 730, 695 cm^{-1}; ^1H NMR δ 7.6-7.1 (m, 5 H), 6.70 (AB q, *J* = 9 Hz, 1 H), 6.61 (AB q, *J* = 9 Hz, 1 H), 5.00 (s, 2 H), 3.78 (s, 3 H), 3.30-1.30 (m, 8 H), 0.91 (d, *J* = 7 Hz, 3 H), 0.83 (d, *J* = 7 Hz, 3 H); ^{13}C NMR δ 151.6, 150.9, 138.1, 132.2, 128.4 (2C), 128.2, 127.5, 127.1 (2C), 108.5, 106.9, 70.4, 55.6, 37.5, 31.2, 23.7, 22.3, 21.2, 19.8, 18.7; mass spectrum, exact mass calcd for $C_{21}H_{26}O_2$ *m/e* 310.1933; obsd 310.1884.

Vg from VII. Reaction of **VII** (0.259 mg, 0.918 mmol) in THF (15 mL) with 2 M i-Pr·MgCl (0.49 mL, 1.05 equiv) at -70 °C gave after flash chromatography the expected alcohol (48.2 mg, 16%, 32% based on consumation of starting material) and recovered **VII** (0.128 g): IR (film) 3600-3300, 2930, 2860 (sh), 1600, 1460 (br), 1390, 1290, 1250, 1080, 1050, 730, 695 cm^{-1}; ^1H NMR δ 7.37 (s, 5 H), 6.73 (AB q, J = 10 Hz, 1 H), 6.64 (AB q, J = 10 Hz, 1 H), 5.07 (s, 2 H), 4.05 (s, 1 H), 3.76 (s, 3 H), 3.00-2.3 (m, 7 H), 0.97 (d, J = 7 Hz, 3 H), 0.57 (d, J = 7 Hz, 3 H); mass spectrum, exact mass calcd for $C_{21}H_{26}O_3$ m/e 326.1882, obsd m/e 326.1838.

Reduction of the above alcohol (41.2 mg, 0.126 mmol) with Et_3SiH (1.5 mL, excess), in CF_3CO_2H (2.5 mL) and flash chromatography [PE/CH_2Cl_2 (15:1)] gave **Vg** (30.2 mg, 76%), showing identical spectroscopic properties to **Vg** obtained from the electrolysis route.

Structure Proof for 13h and 14h

Vh. A mixture of **13h** and **14h** (10.5:1, 87.2 mg, 0.33 mmol) in CH_3OH (15 mL) was reacted with $NaBH_4$ (45 mg, excess) in a manner similar to **13e** and **14e** to afford after flash chromatography (3:1 CH_2Cl_2/PE as eluant) the major phenol (63.2 mg, 82%) as a colorless oil: IR (film) 3600-3100, 2940, 1480 (br), 1360, 1250, 1220 (sh), 1080, 790, 730 cm^{-1}; ^1H NMR δ 6.58 (s, 2 H), 4.35 (s, 1 H), 3.75 (s, 3 H), 3.0-1.5 (m, 7 H), 0.93 (s, 9 H); ^{13}C NMR δ 151.1, 147.7, 130.0, 127.9, 112.0, 108.4, 56.0, 40.4, 37.2, 29.1 (3 C), 24.3, 21.5, 19.9; mass spectrum, exact mass calcd for $C_{15}H_{22}O_2$ m/e 234.1619, obsd 234.1636.

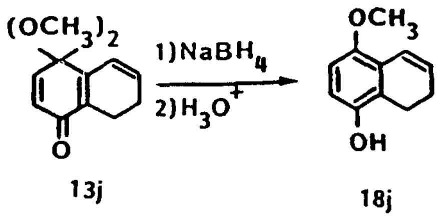
Continued elution gave the minor phenol (3.2 mg, 5%) which showed: IR (film) 3600-3100, 2940, 2860, 1480 (br), 1250, 1080 cm^{-1}; ^{1}H NMR δ 6.58 (s, 2 H), 4.25 (s, 1 H), 3.69 (s, 3 H), 3.25-1.1 (m, 7 H), 0.86 (s, 9 H); **mass** spectrum, exact mass calcd for $C_{15}H_{22}O_2$ m/e 234.1619, obsd 234.1628.

Reaction of the major phenol (63.2 mg, 0.27 mmol) with 60% NaH (11.9 mg) in dry THF (25 mL) was followed by addition of benzyl bromide (22.4 mg, 1.05 equiv), and the solution was heated to reflux for 12 h. Workup and flash chromatography [PE/CH_2Cl_2 (3:1)] gave **Vh** (74.2 mg, 85%): IR (film) 2940, 1475, 1460, 1440, 1250, 1230 (sh), 1090, 1060, 730, 690 cm^{-1}; ^{1}H NMR δ 7.5-7.24 (m, 5 H), 6.72 (AB q, J = 9 Hz, 1 H), 6.66 (AB q, J = 9 Hz, 1 H), 4.97 (s, 2 H), 3.79 (s, 3 H), 3.5-1.2 (m, 7 H), 0.90 (s, 9 H); ^{13}C NMR δ 151.3 (2 C), 138.0, 130.8, 130.1, 128.4 (2C), 127.5, 127.3 (2C), 108.7, 107.3, 70.6, 55.7, 39.3, 36.9, 29.2 (3 C), 24.1, 21.5, 20.0; mass spectrum, exact mass calcd for $C_{22}H_{28}O_2$ m/e 324.2090, obsd 324.2086.

Vh from VII. To a solution of **VII** (0.45 g, 1.76 mmol) in dry THF (25 mL) at -70 °C was added a 1.8 M solution of t-C_4H_9Li (1.05 mL, 1.05 equiv). Workup and flash chromatography [CH_2Cl_2/PE (1:1)] of the reaction mixture gave first the alcohol from Grignard addition (211.7 mg, 37%, 67% based on recovery of starting material) and then recovered starting material. Recrystallization (PE/CH_2Cl_2) gave colorless crystals: mp 105-106 °C; IR (KBr) 3500 (br s), 2940, 1460, 1390, 1250, 1230, 1050, 1030, 780, 690 cm^{-1}; ^{1}H NMR δ 7.39 (s, 5 H), 6.77 (AB q, J = 8 Hz, 1 H), 6.66 (AB q, J = 8 Hz, 1 H), 5.38 (s, 1 H), 5.00 (s, 2 H), 3.71 (s, 3 H), 3.23-1.30 (m, 6 H), 0.84 (s, 9 H); ^{13}C NMR δ 151.8, 151.5, 136.3, 130.9, 130.7, 129.7, 128.7 (2C), 128.2, 127.8 (2C), 109.6, 108.2, 78.9, 71.3, 55.7, 41.7, 35.7, 26.5 (3 C), 23.3, 19.9. Anal. calcd for $C_{22}H_{28}O_3$: C, 77.6; H, 8.3. Found: C, 77.7; H, 8.4.

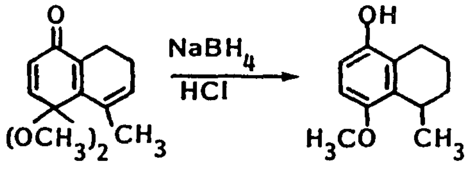
Reduction of the alcohol from above (50.8 mg, 0.15 mmol) with Et_3SiH (1.5 mL, excess) and CF_3CO_2H (3 mL) followed by workup and flash chromatography [PE/CH_2Cl_2 (15:1), then PE/CH_2Cl_2 (3:1)] gave **Vh** (36.1 mg, 76%) which showed spectroscopic properties identical with the product from the electrolysis route.

Structure Proof for 13j



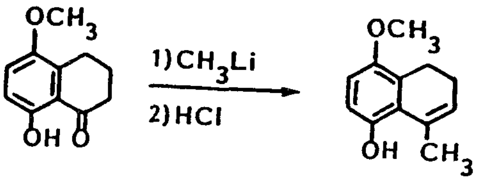
VII The monoketal **13j** in ethanol (10 mL) was treated with $NaBH_4$ (0.2 g, excess), and the reaction mixture was stirred for 1 h at room temperature. Addition of 5% HCl followed by extractive workup (CH_2Cl_2, 3 x 30 mL) yielded a brown oil which was purified by flash chromatography (1:1 CH_2Cl_2/PE as eluant) to afford 0.83 mg (45%) of **18j** as white crystals. Recrystallization from CH_2Cl_2/PE gave the analytical sample: mp 91-92.5 °C; IR (KBr) cm^{-1} 3600-3100, 2960, 2940, 2840, 1480, 1460, 1440, 1390, 1340, 1280, 1250, 1090, 1020, 795, 785, 725, 690; ^{1}H NMR δ 6.81 (d of t, $\underline{J}$ = 10, 2 Hz, 1H), 6.59 (s, 2H), 6.02 (d of t, $\underline{J}$ = 10, 6 Hz, 1H), 4.47 (s, 1H), 3.76 (s,3H), 2.85-2.0 (m, 4H). Mass spectrum exact mass calcd for $C_{11}H_{12}O_2$ $\underline{m/e}$ 176.0838, obsd 176.0802. This material was different than **I** establishing the structure of the monoketal as **13j**.

Structure Proof for 13k



13k **17k**

The reduction of **14k** (179 mg, 0.814 mmol) in EtOH (15 mL) with $NaBH_4$ (0.5 g excess) was followed by quenching the reaction with 5% HCl to afford after workup and flash column chromatography (PE/CH_2Cl_2 1:4 as eluant) **17k** (120 mg, 78%): mp 82-85 °C; IR 3600-3100, 2930, 2890, 2830, 1490, 1460, 1440, 1330, 1270, 1250, 1080, 1070, 790 cm^{-1}; ^{1}H NMR δ 6.65 (s, 2 H), 6.0-5.75 (m, 1 H), 4.65-4.4 (br s, 1 H), 3.74 (s, 3 H), 2.9-1.8 (m, 7 H); ^{13}C NMR δ 151.6, 146.2, 132.9, 126.6, 125.2 (2C), 114.5, 111.7, 56.6, 23.0, 22.3, 21.6; mass spectrum, exact mass calcd for $C_{12}H_{14}O_2$ $\underline{m/e}$ 190.0994, obsd 190.0990.



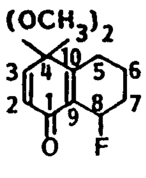
18k

A solution of 1.9 M CH_3Li (0.25 mL, 2.2 equiv) and THF (20 mL) was cooled to -78 °C, and a solution of **11** [45 mg, 0.234 mmol in THF (5 mL)] was added to the solution. After stirring for 30 min, the reaction was quenched by adding 20% HCl (10 mL), and the mixture was extracted with CH_2Cl_2 (3 x 30 mL). Workup as usual yielded a light brown oil. Flash column chromatography (PE/CH_2Cl_2 1:1 as eluant) gave **VIII** (40 mg, 90%). This material showed similar but non-identical spectroscopic properties to that of **17k**: IR (film) 3600-3100, 2930, 2830, 1470 (br), 1435, 1245, 1055, 1010, 800, 730 cm^{-1}; ^1H NMR δ 6.65 (ABq, $\underline{J}$ = 9 Hz, 1 H), 6.55 (ABq, $\underline{J}$ = 9 Hz, 1 H), 6.0-5.75 (m, 1 H), 4.56 (s, 1 H), 3.76 (s, 3 H), 2.9-1.8 (m, 7 H); mass spectrum, exact mass calcd for $C_{12}H_{14}O_2$ $\underline{m/e}$ 190.0993, obds 190.0996.

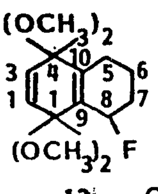
Structure Proof for 13i

The structural assignment for monoketal **13i** is strongly supported by the ^{13}C NMR results collected below. In all monoketals we have studied, the resonance of the &-carbon occurs at lower field than the S-carbon. For the case of **13i** the C-9 shows a coupling constant of 16 Hz while that for C-10 is 6 Hz. One would reasonably expect the

C_9 δ 157.5, $J_{C-9,F}$ = 6 Hz
C_{10} δ 133.0, $J_{C-10,F}$ = 16 Hz
C_8 δ 79.9, $J_{C-8,F}$ = 166 Hz
C_7 δ 28.1, $J_{C-7,F}$ = 22 Hz



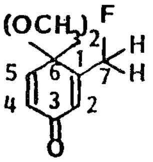
13j



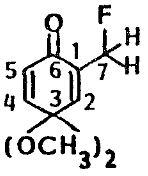
12j

C_1 δ 51.2, $J_{C-1,F}$ = 2.0 Hz
C_8 δ 81.1, $J_{C-8,F}$ = 164 Hz
C_7 δ 28.8, $J_{C-7,F}$ = 20 Hz
C_9 δ 128.2, $J_{C-9,F}$ = 22 Hz
C_{10} δ 143.9, $J_{C-10,F}$ = 10 Hz

C_1 δ 152.9, $J_{C-1,F}$ = 14 Hz
C_2 δ 125.4, $J_{C-2,F}$ = 10.8 Hz
C_6 δ 94.4, $J_{C-6,F}$ = 5.4 Hz
C_7 δ 78.8, $J_{C-7,F}$ = 172.7 Hz



IX



X

C_1 δ 134.8, J = 16.2 Hz
C_2 δ 138.2, J = 9.7 Hz
C_6 δ 183.6, J = 4.4 Hz
C_7 δ 78.8, J = 172.7 Hz

smaller coupling constant to be associated with the more distant C-10 position.

Additional support for this derives from comparison of the ^{13}C NMR data for the monoketals **IX** and **X**. Here the regioisomers can be assigned from the ^{1}H NMR spectra since isomer **X** has two downfield vinyl protons while isomer **IX** has only one downfield vinyl proton. In both cases the two bond coupling constant is larger in the ^{13}C NMR spectrum than the three bond coupling.

NMR SPECTRA

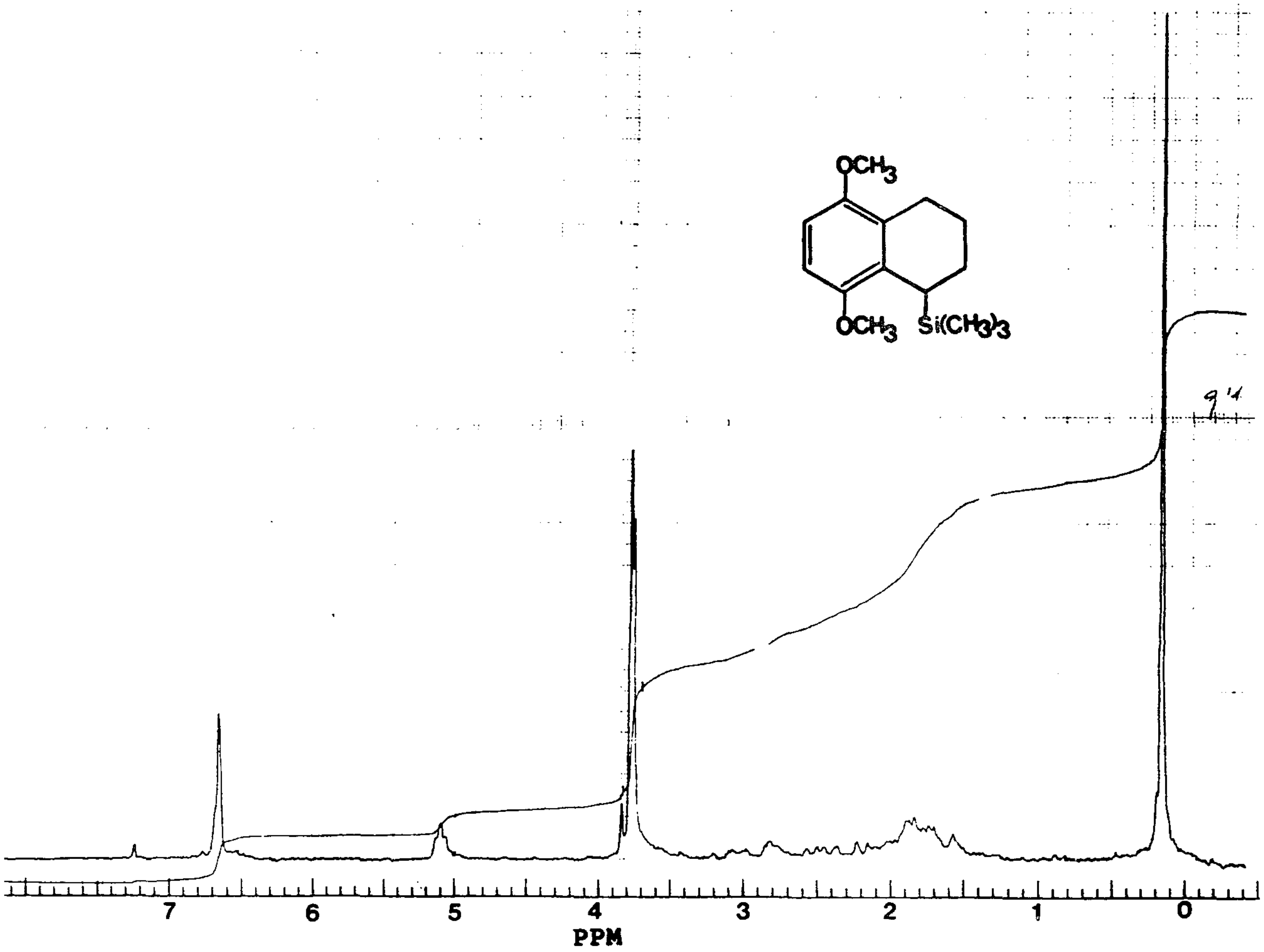


Figure 1. 80 MHz ^{1}H NMR Spectrum of 10a

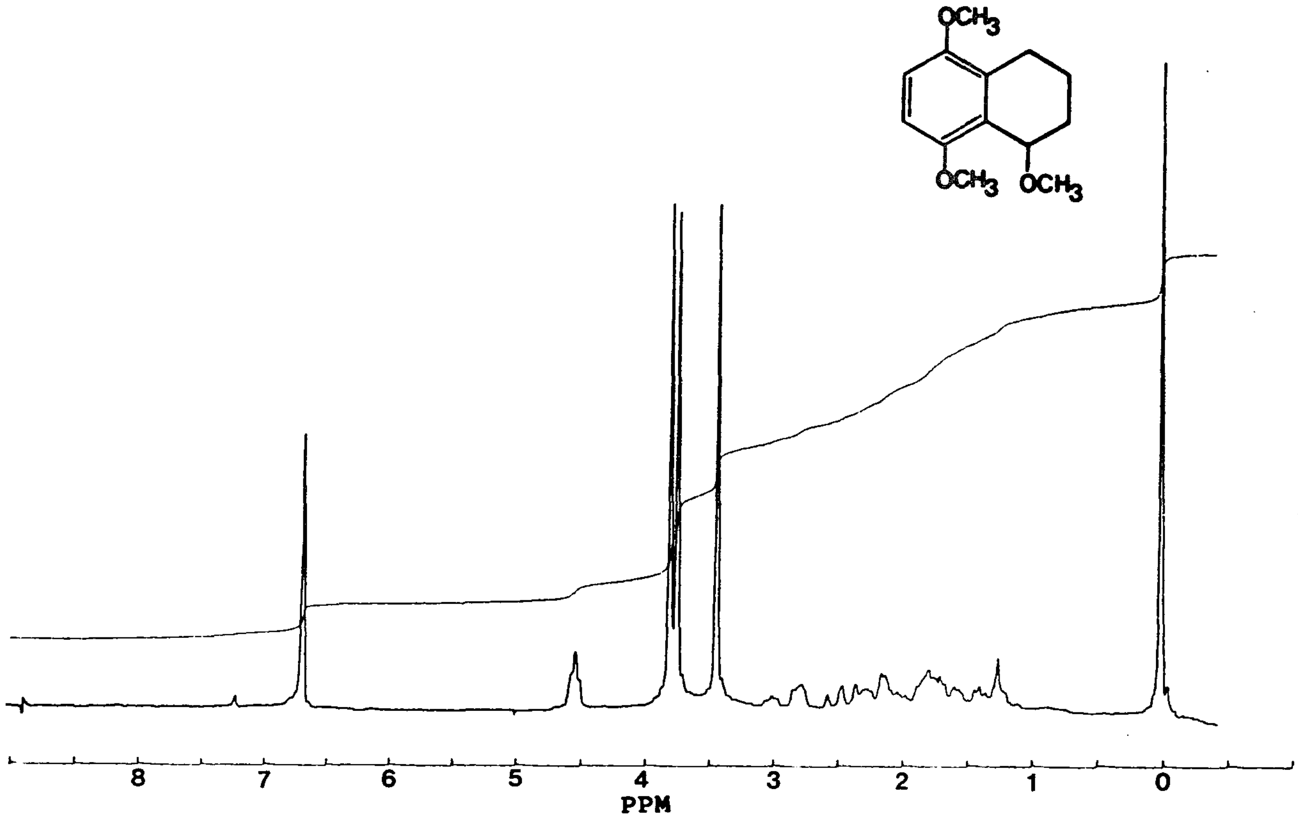


Figure 2. 80 MHz ^{1}H NMR Spectrum of 10b

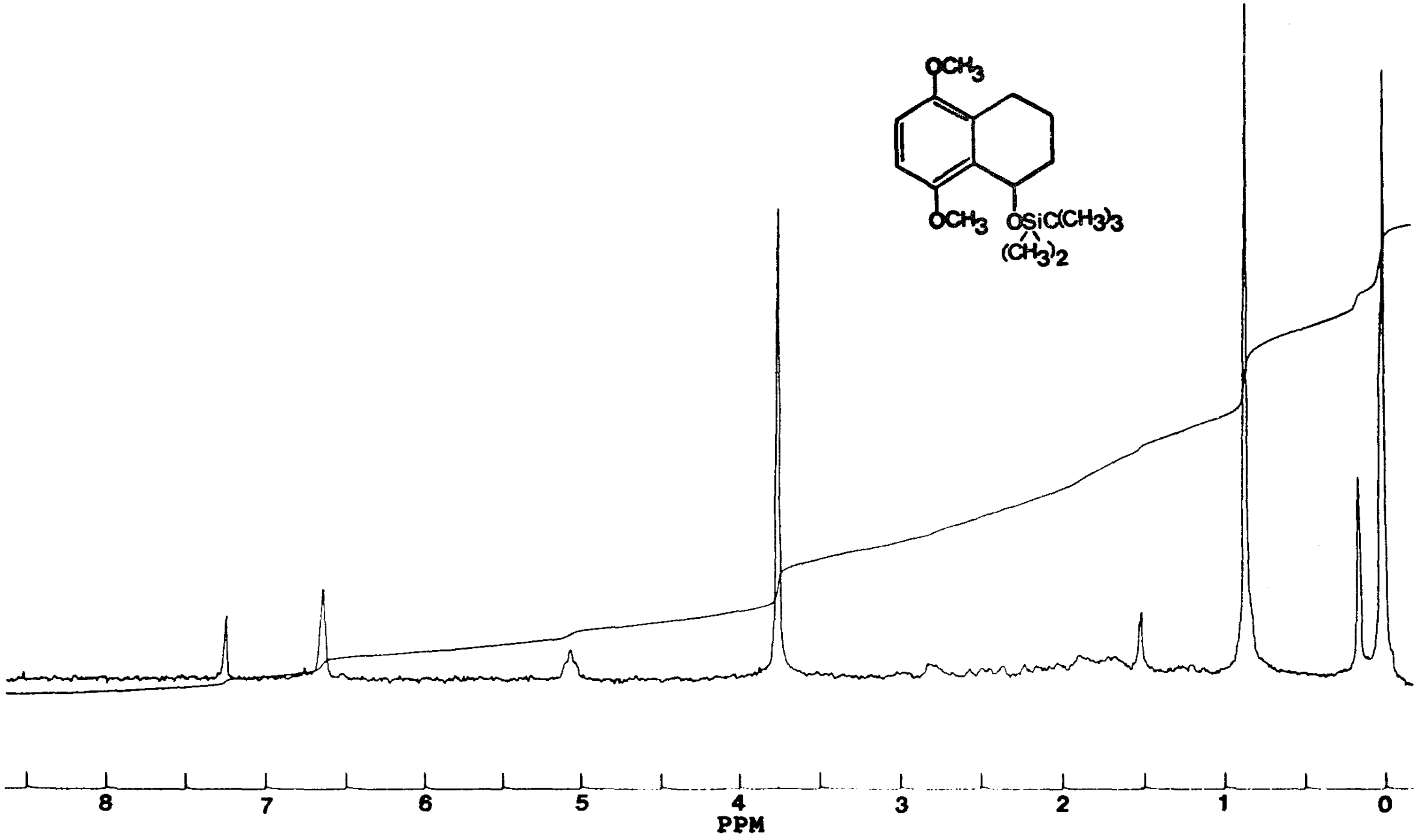


Figure 3. 80 MHz ^{1}H NMR Spectrum of 10c

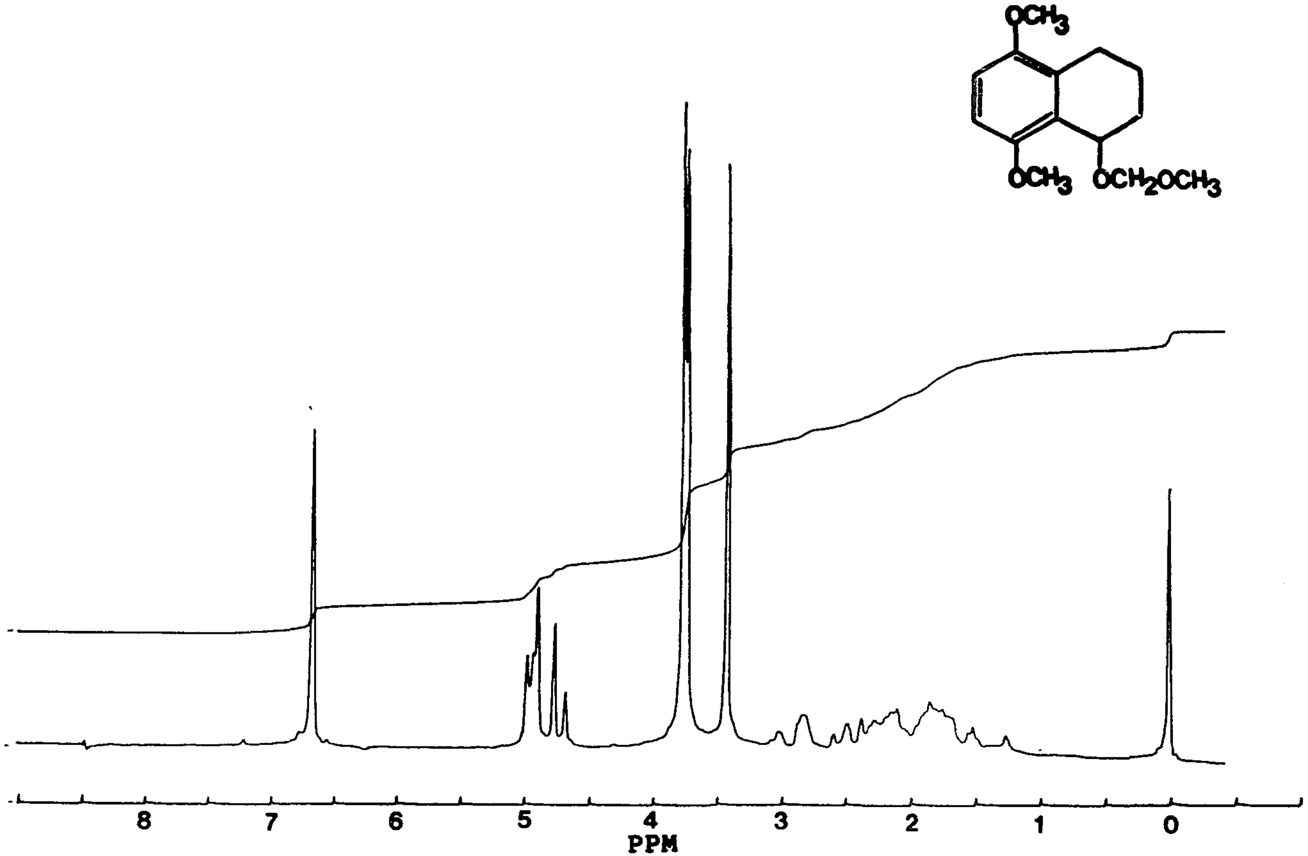


Figure 4. 80 MHz ^{1}H NMR Spectrum of 10d

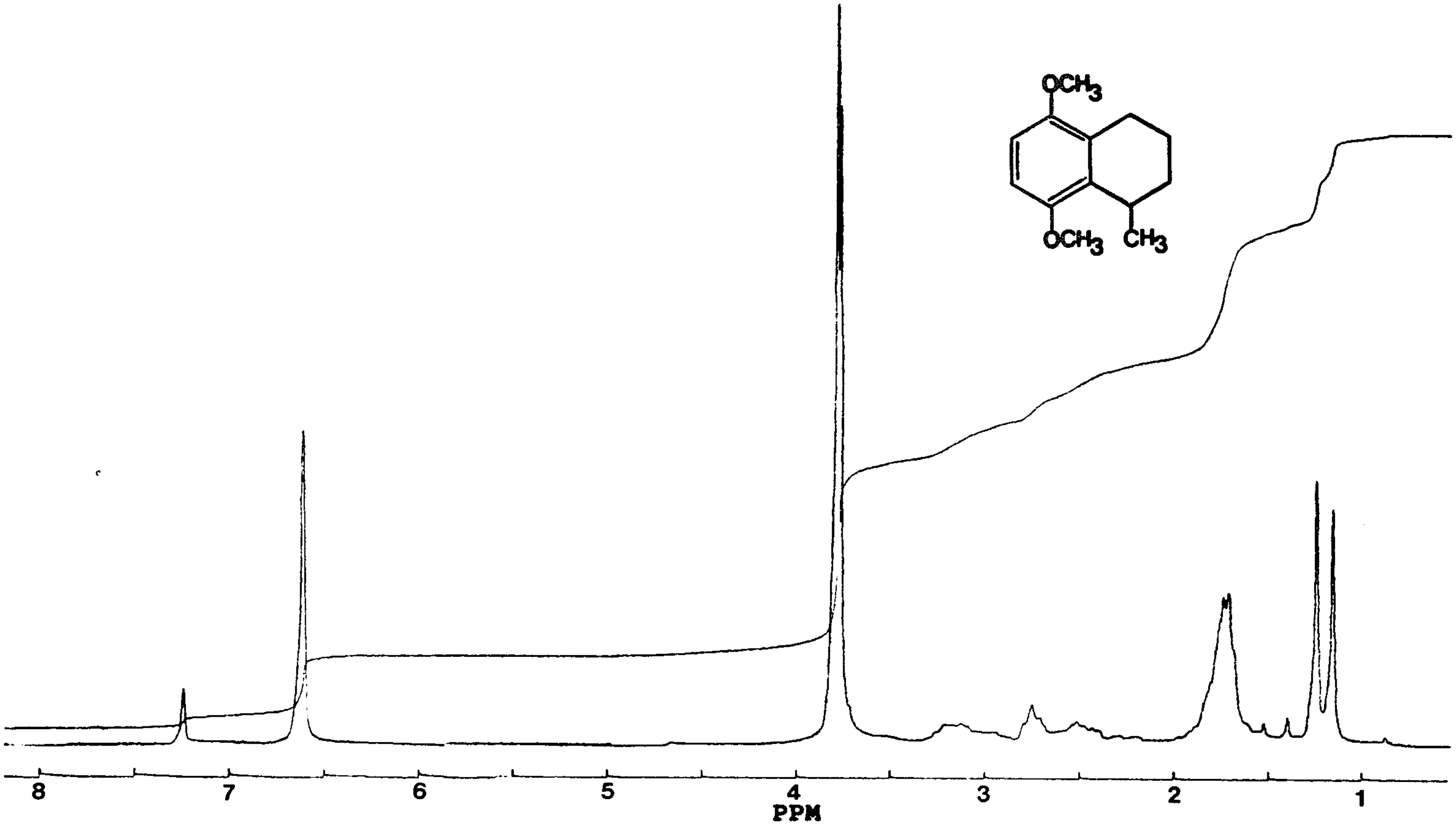


Figure 5. 80 MHz ^{1}H NMR Spectrum of 10e

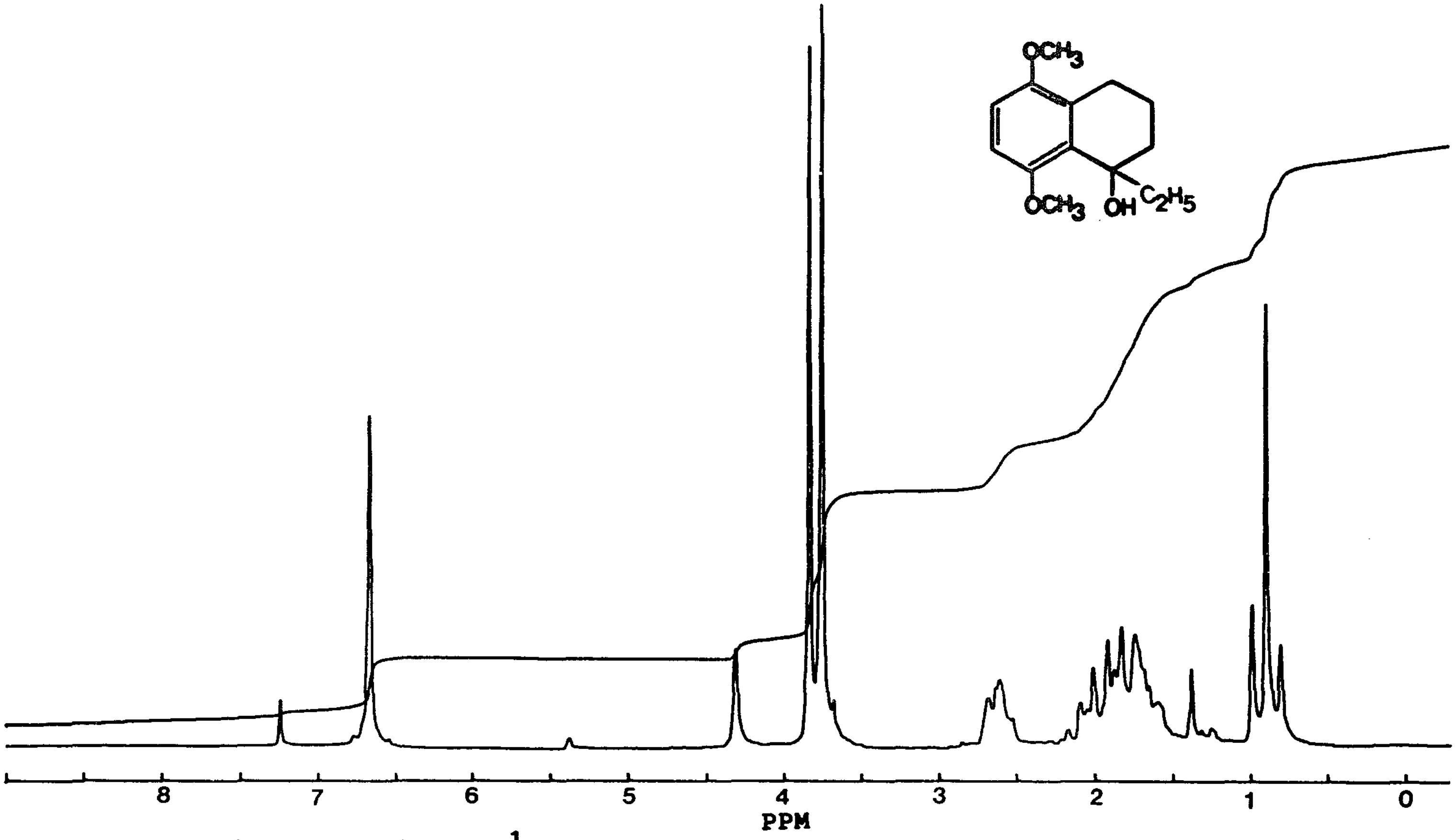


Figure 6. 80 MHz ^{1}H NMR Spectrum of Ethyl Grignard Addition to 9

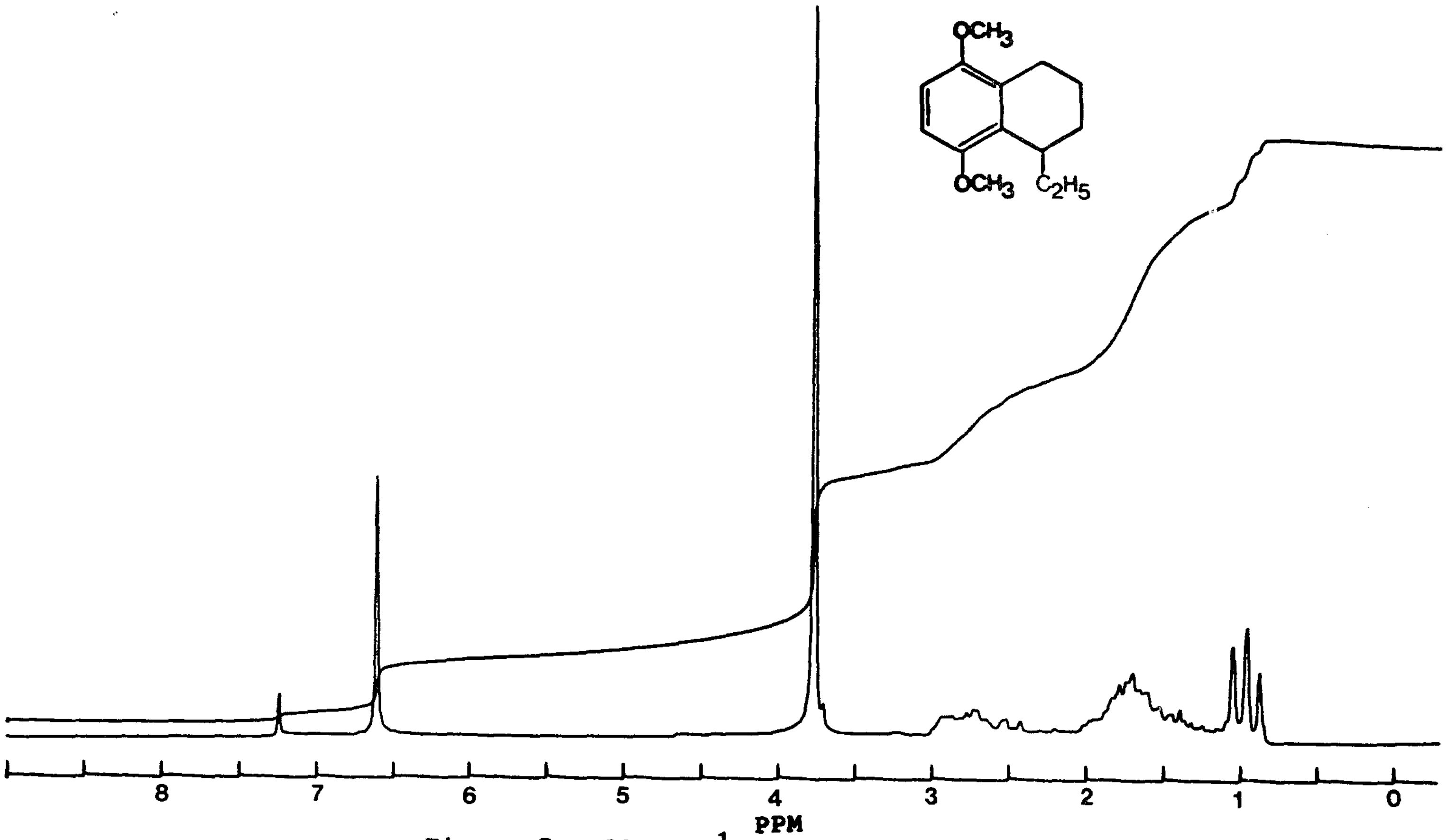


Figure 7. 80 MHz ^{1}H NMR Spectrum of 10f

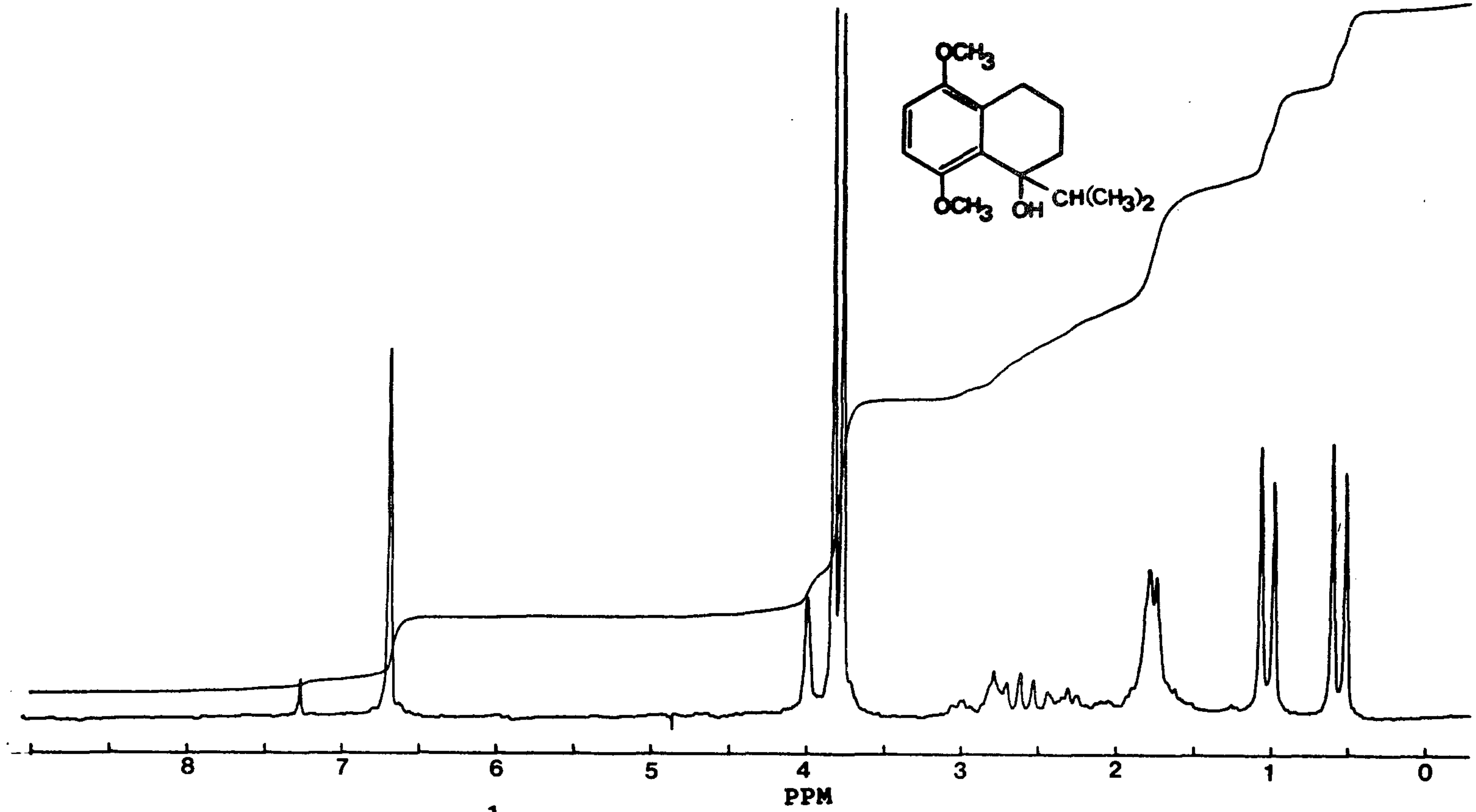


Figure 8. 80 MHz ^{1}H NMR Spectrum of Isopropyl Grignard Addition to 9

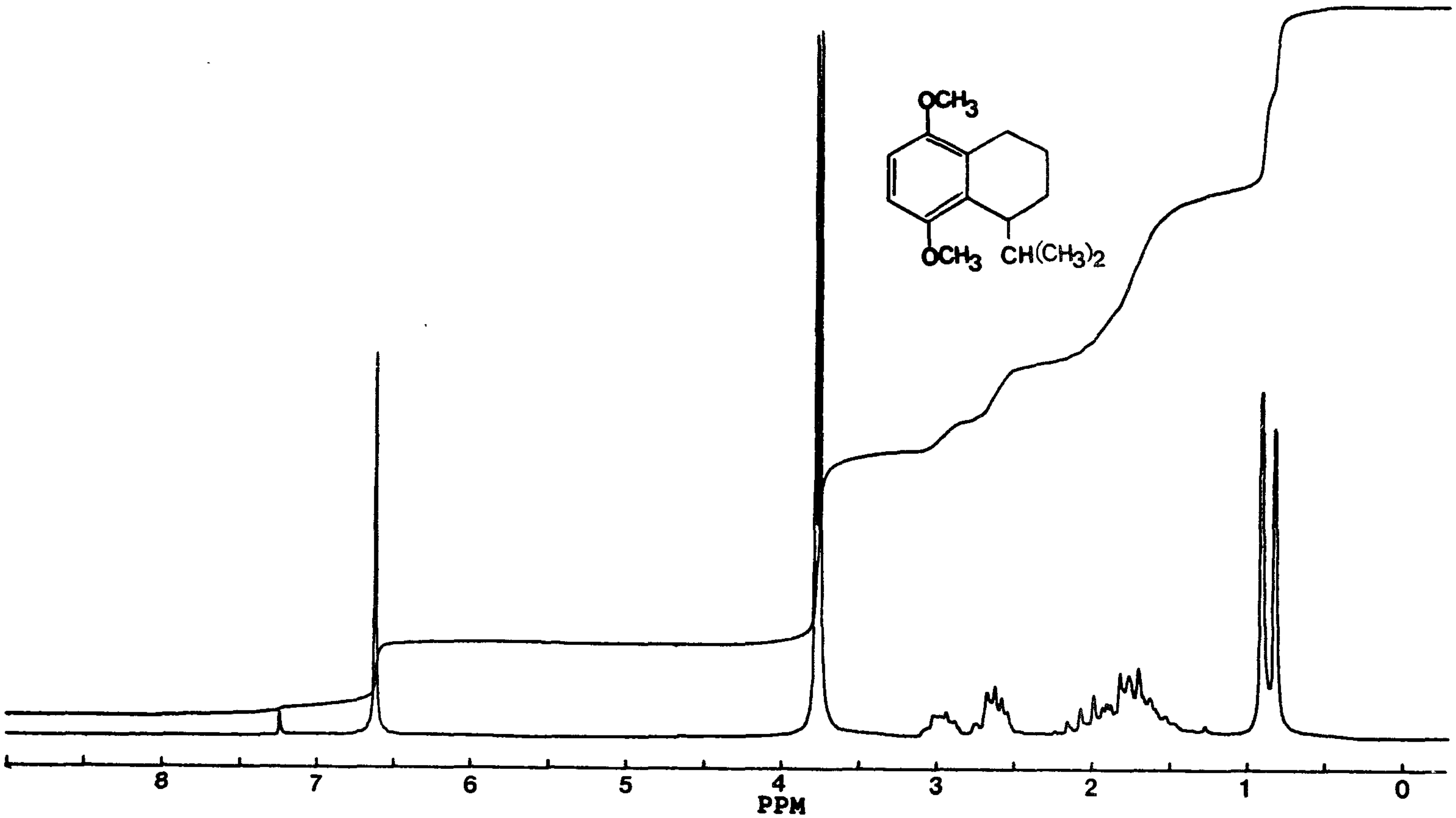


Figure 9. 80 MHz ^{1}H NMR Spectrum of 10g

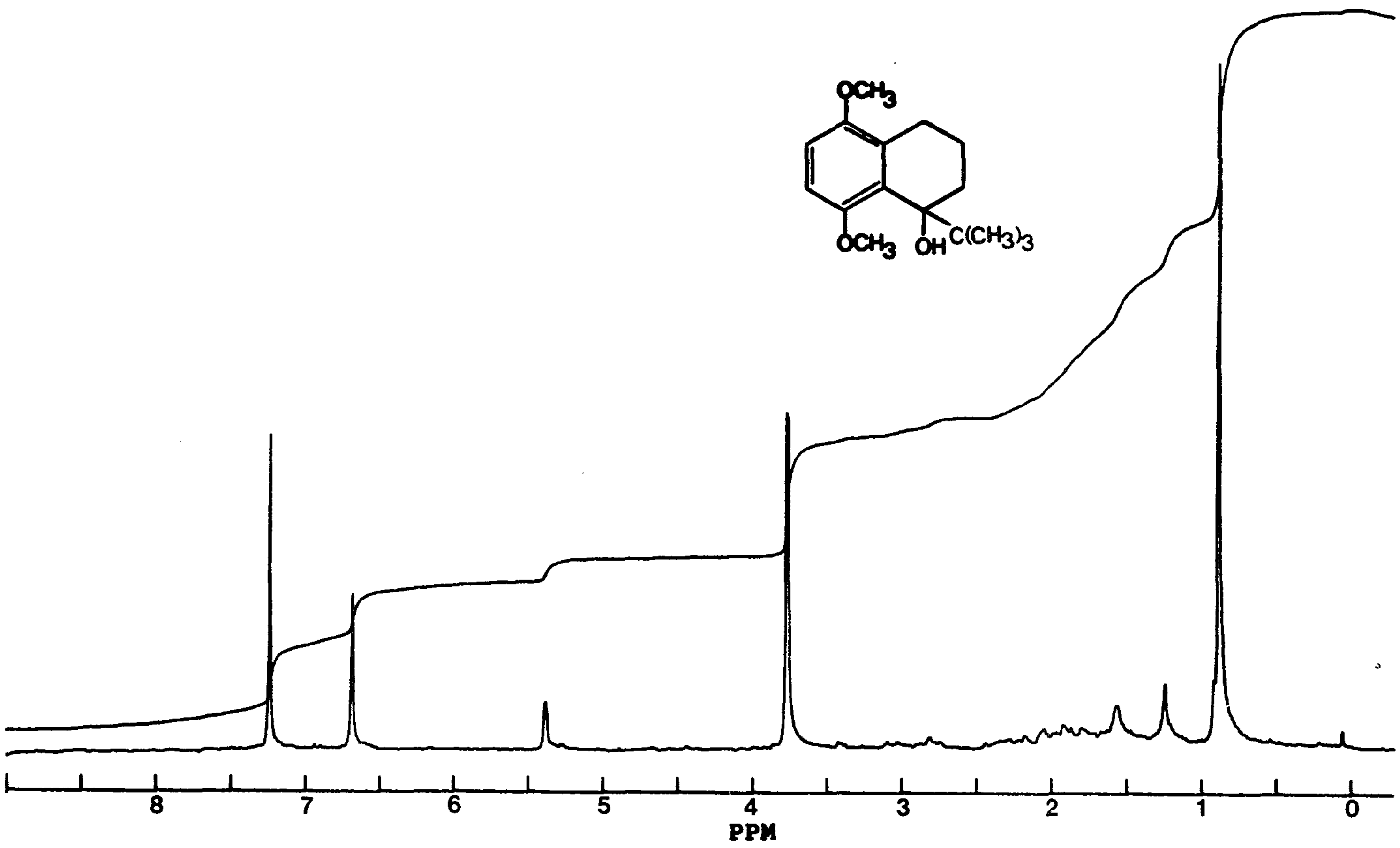


Figure 10. 80 MHz ^{1}H NMR Spectrum of t-BuLi Addition to 9

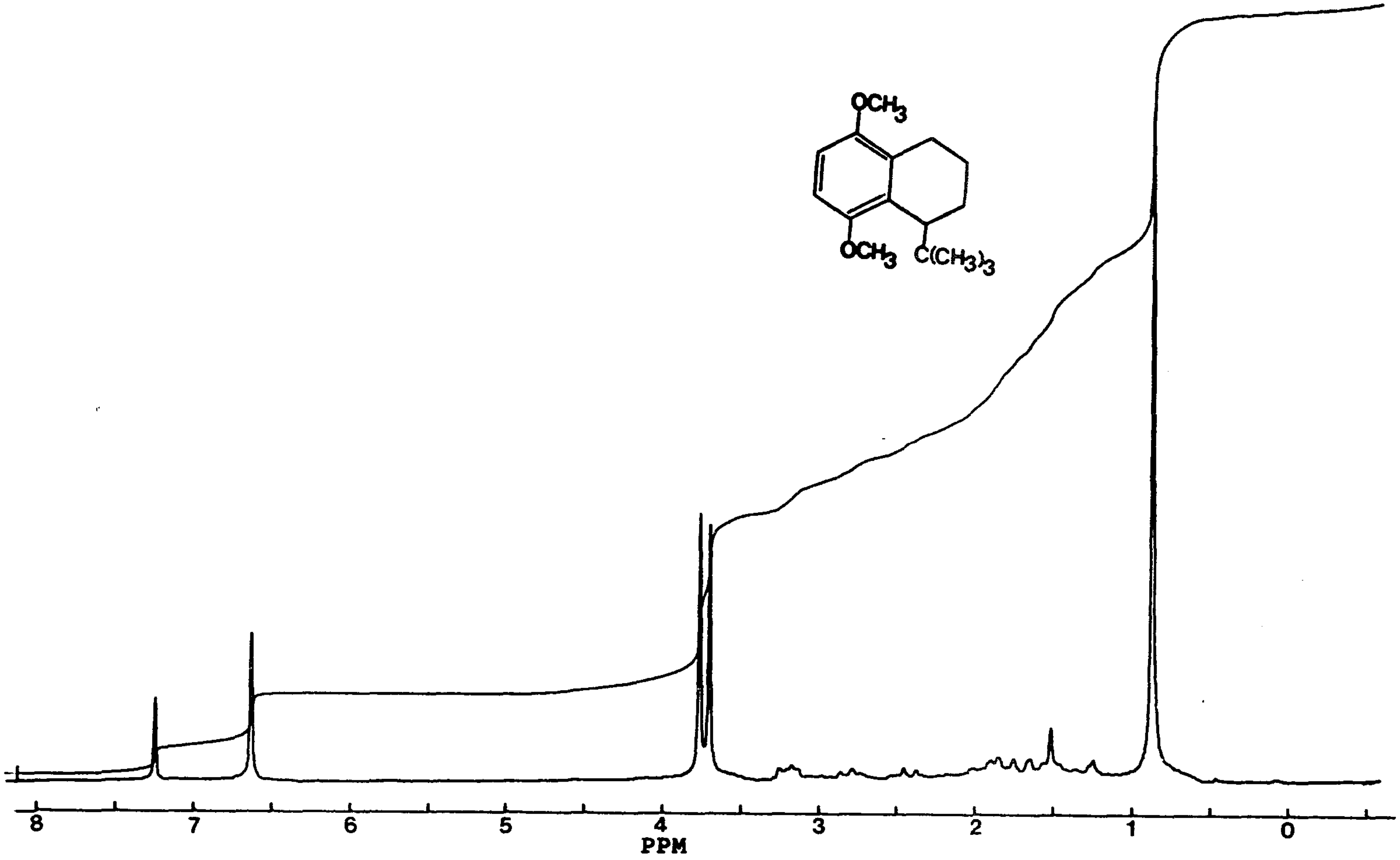


Figure 11. 80 MHz ^{1}H NMR Spectrum of 10h

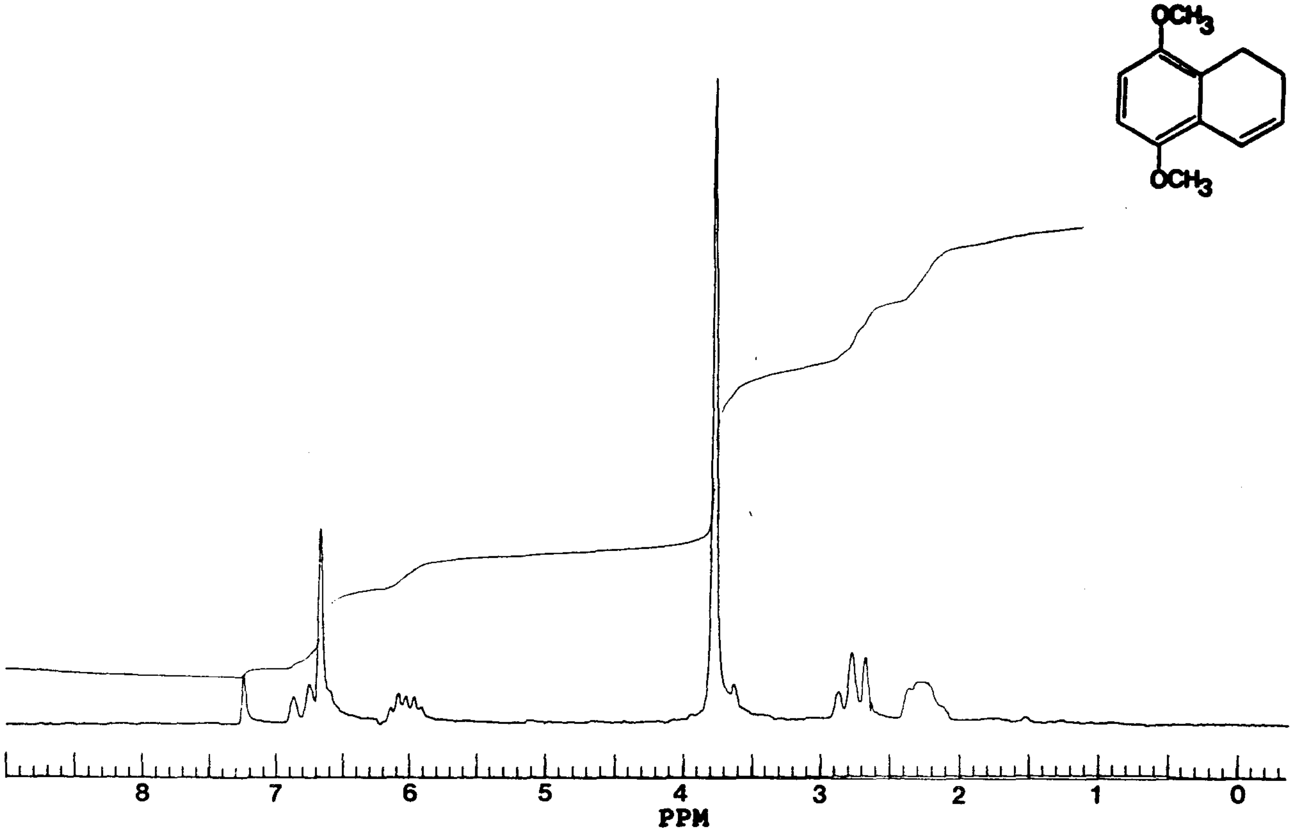


Figure 12. 80 MHz ^{1}H NMR Spectrum of 10k

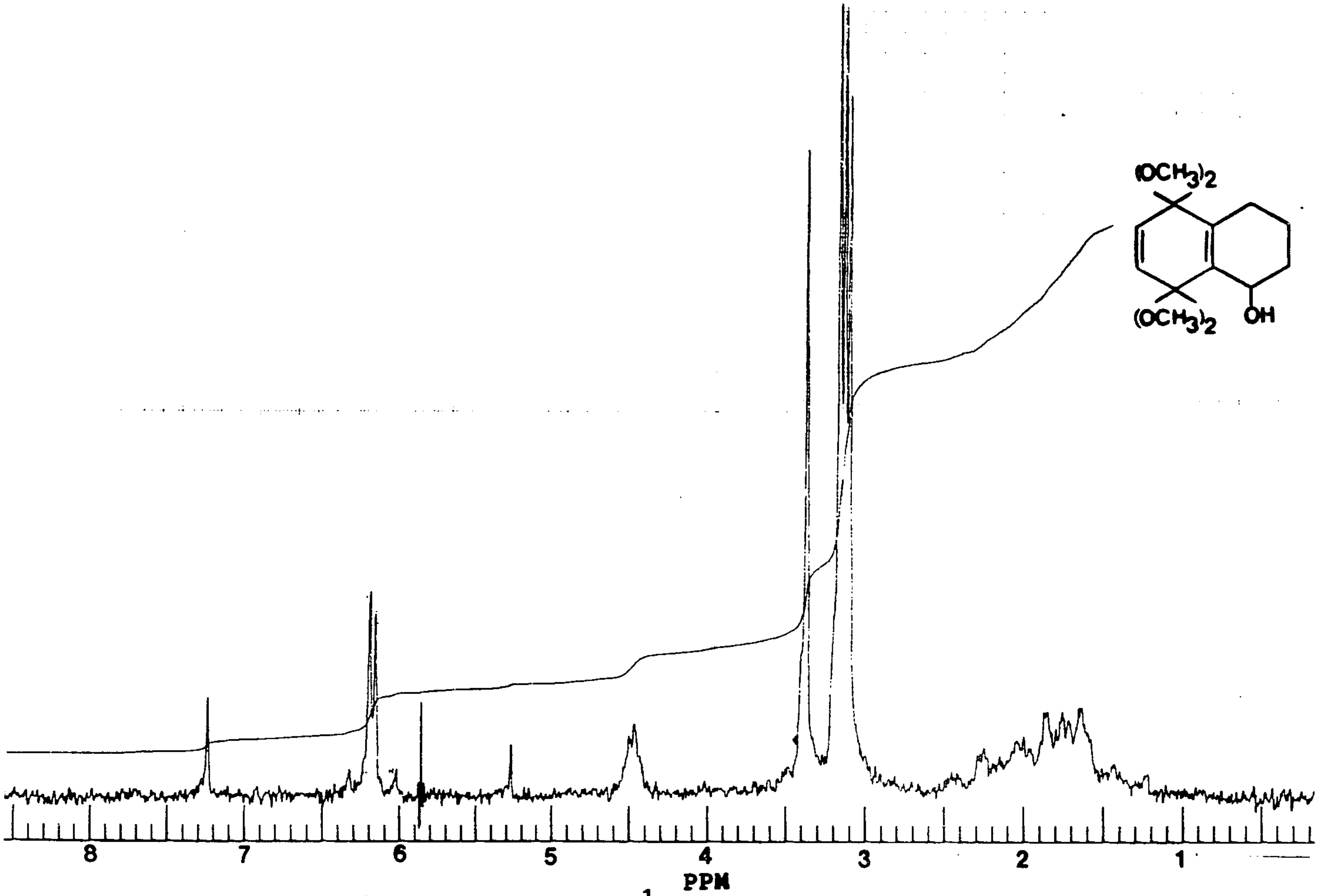


Figure 13. 80 MHz ^{1}H NMR Spectrum of 12a

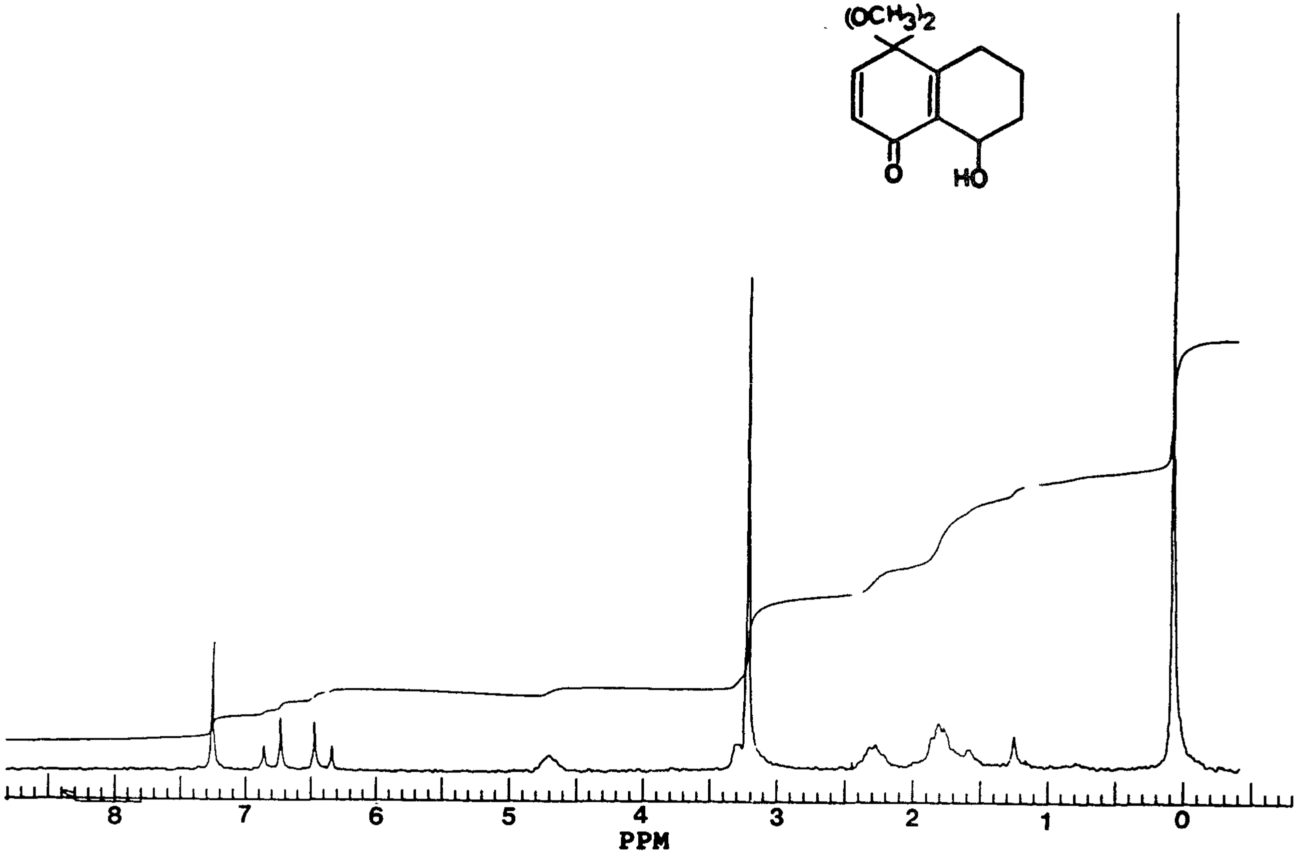


Figure 14. 80 MHz ^{1}H NMR Spectrum of 13a

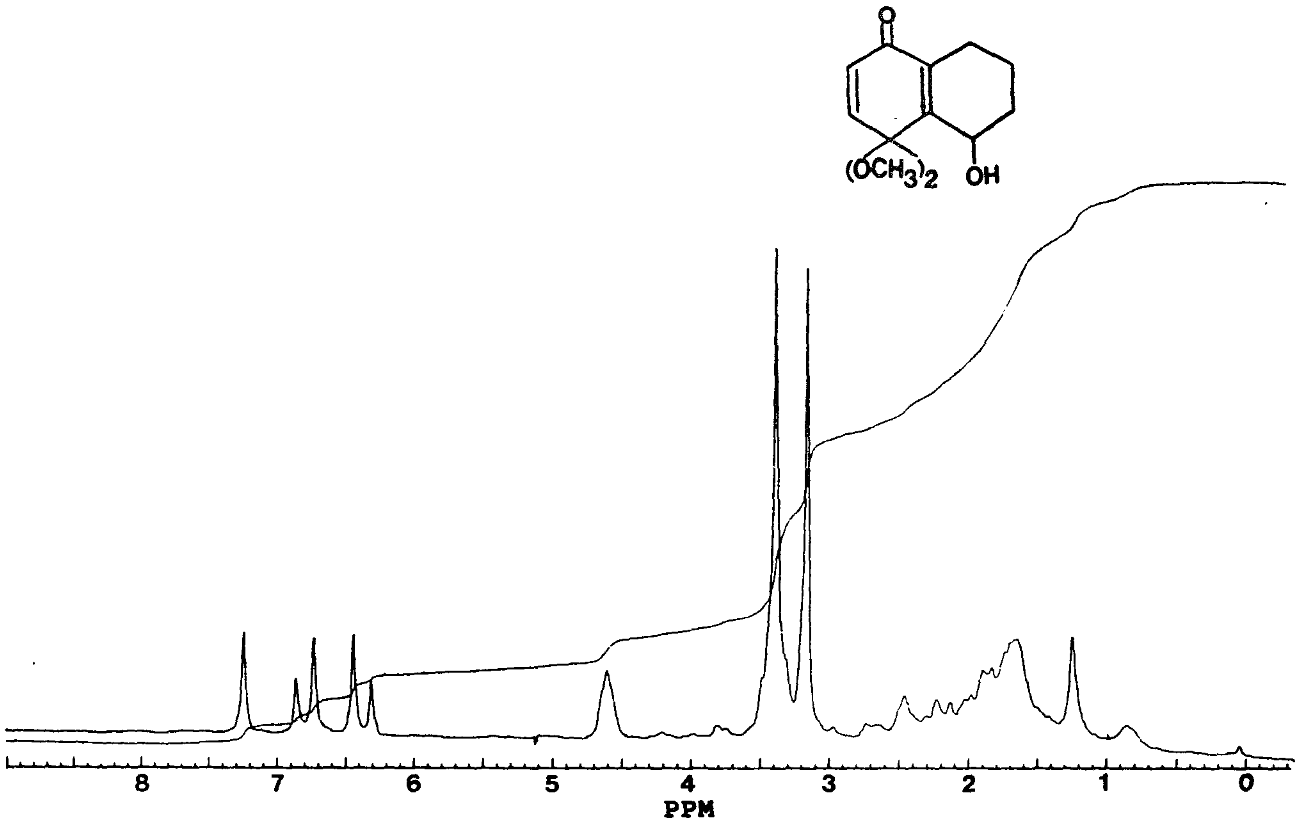


Figure 15. 80 MHz ^1H NMR Spectrum of 14a

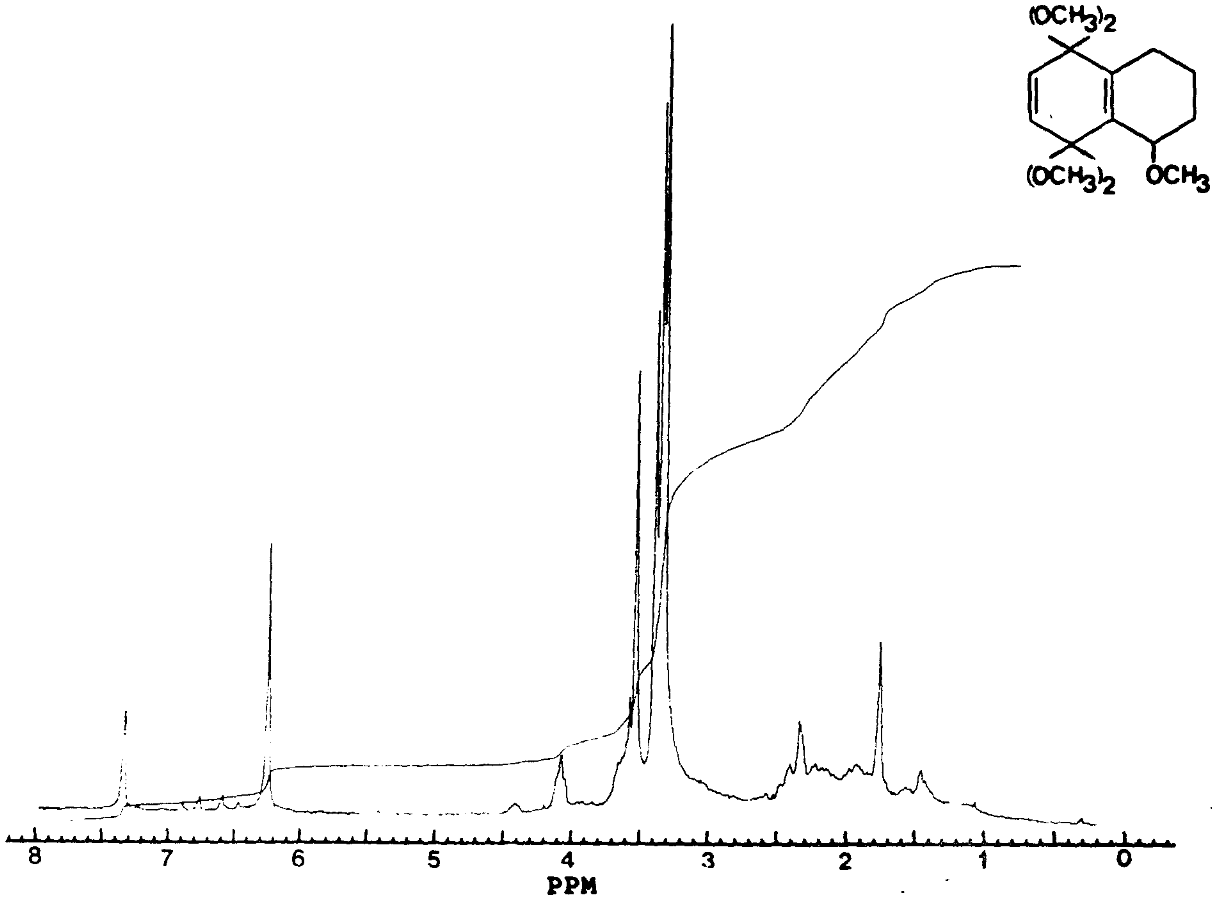


Figure 16. 80 MHz ^{1}H NMR Spectrum of 12b

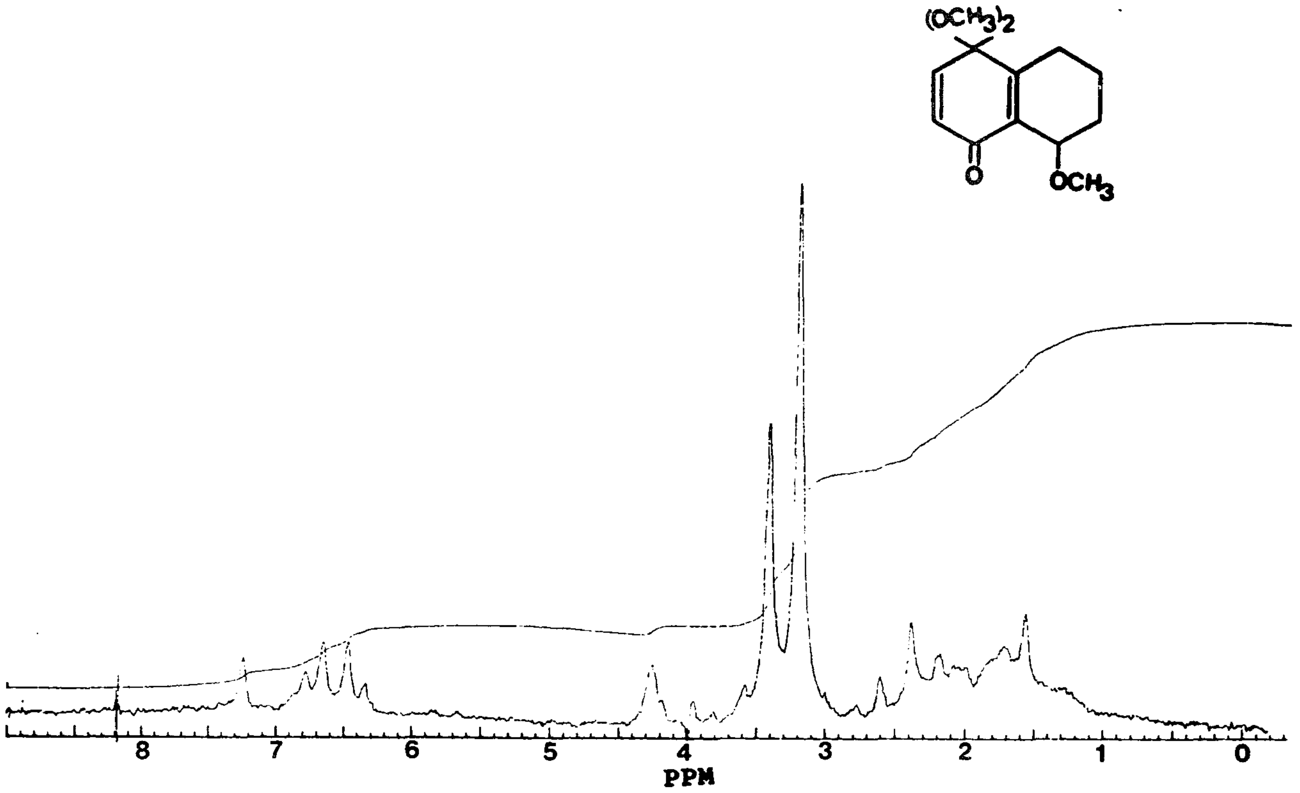


Figure 17. 80 MHz ^{1}H NMR Spectrum of 13b

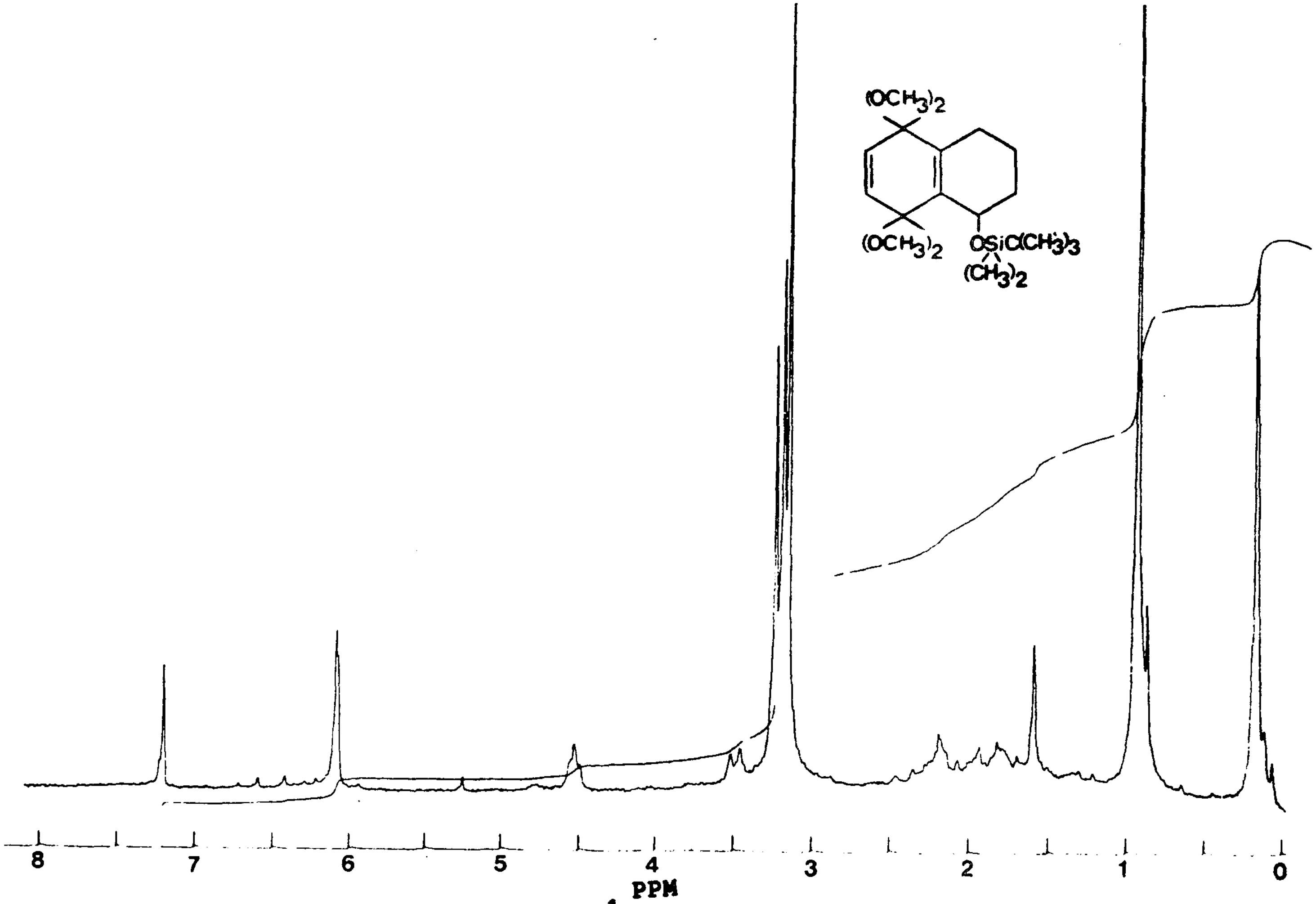


Figure 18. 80 MHz ^{1}H NMR Spectrum of 12c

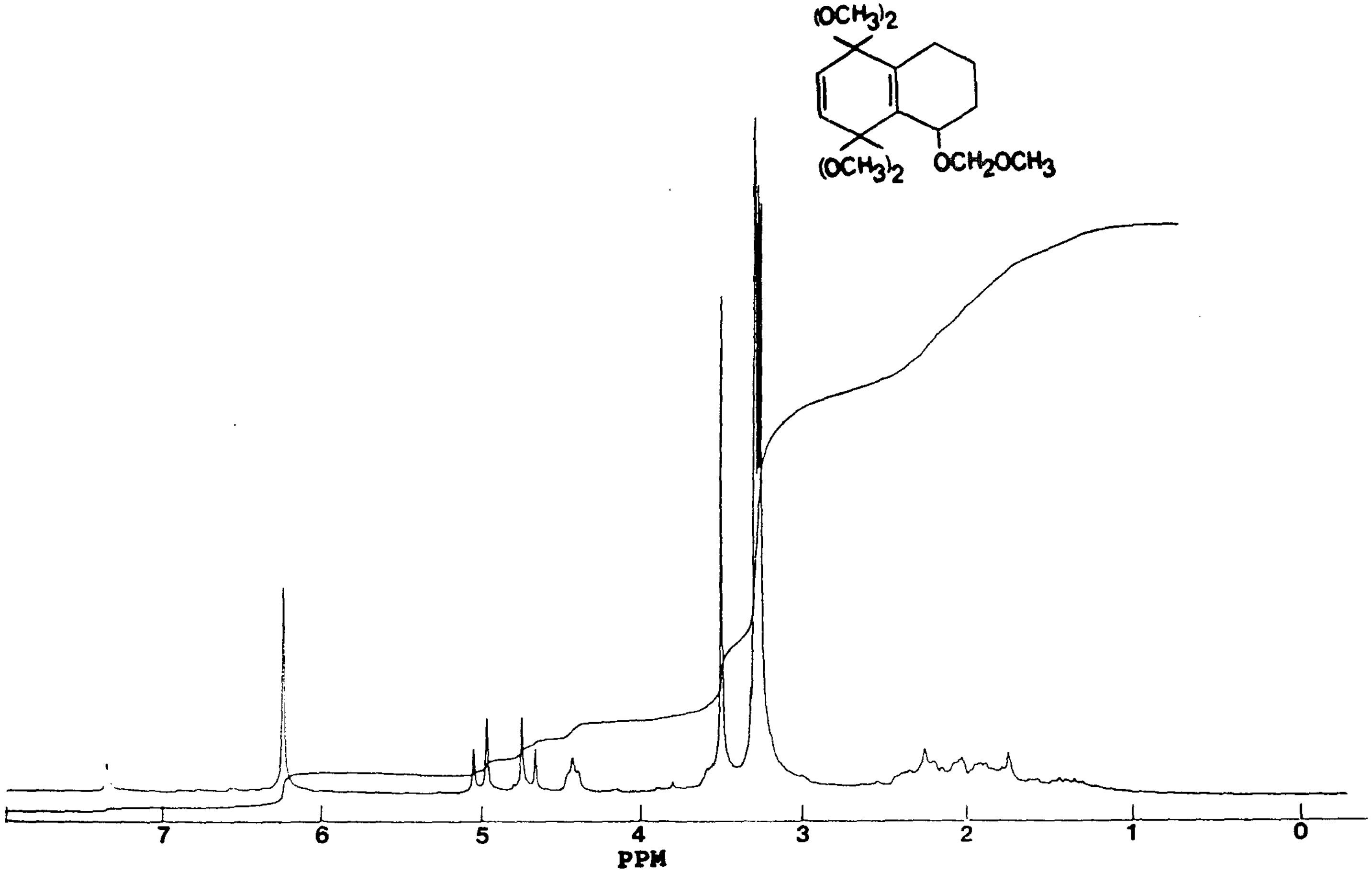


Figure 19. 80 MHz ^{1}H NMR Spectrum of 12d

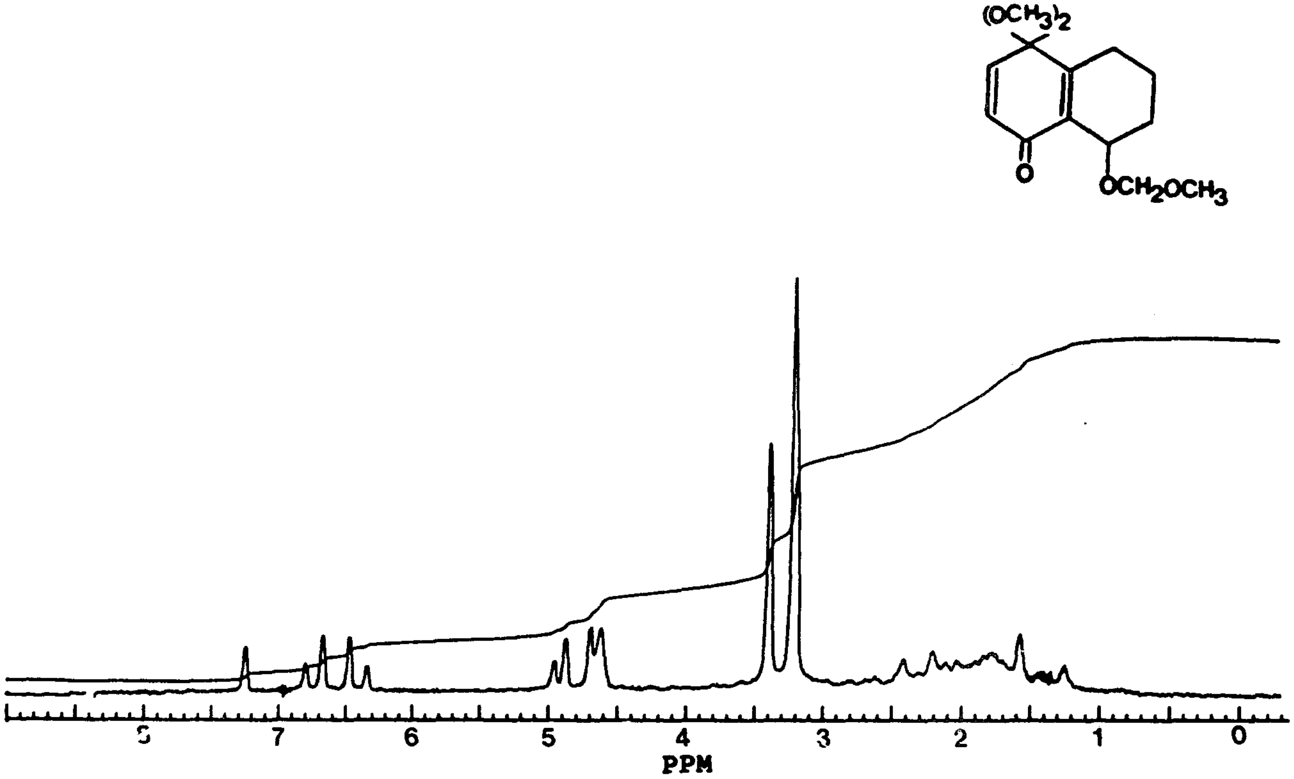


Figure 20. 80 MHz ^{1}H NMR Spectrum of 13d

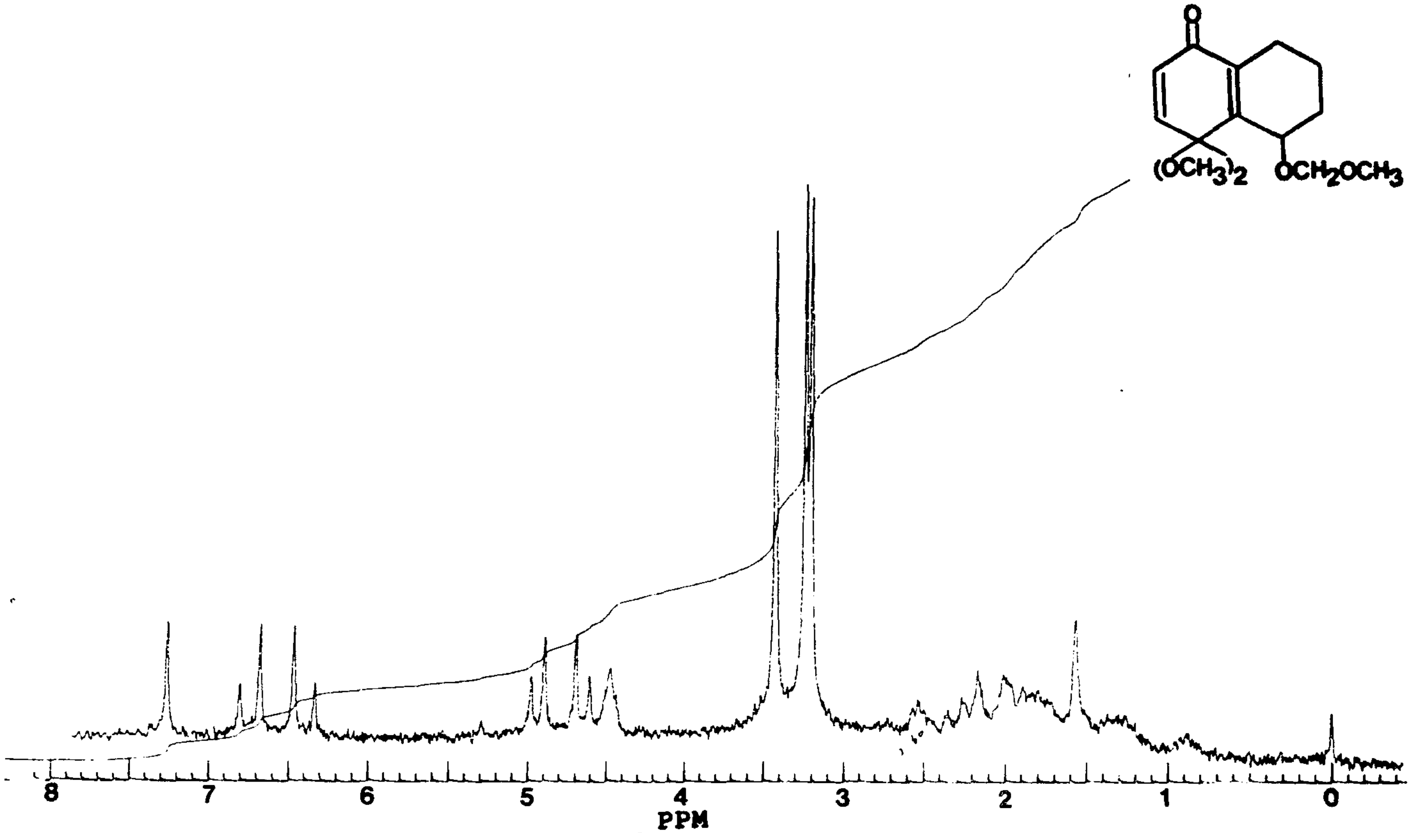


Figure 21. 80 MHz ^{1}H NMR Spectrum of 14d

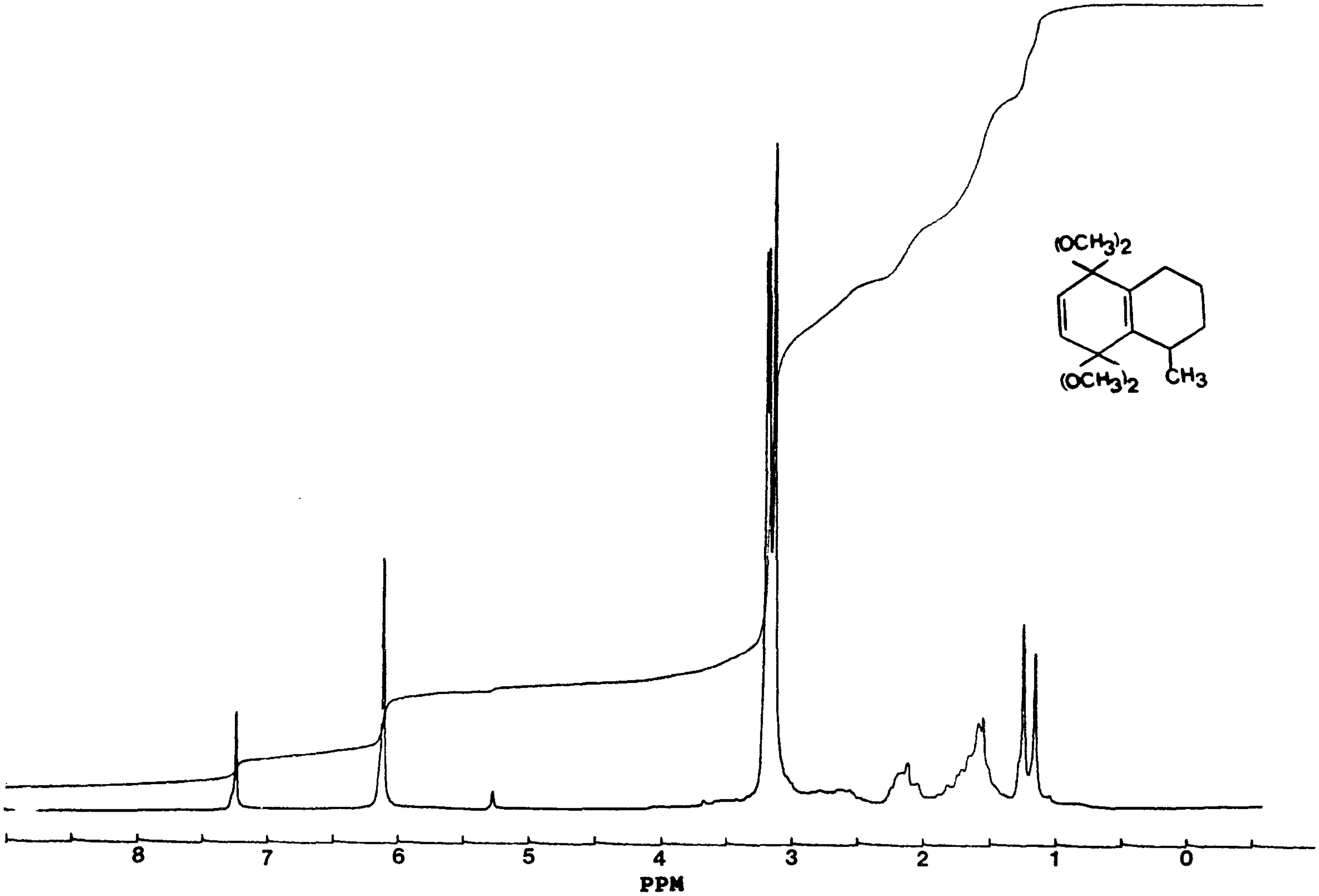


Figure 22. 80 MHz ^{1}H NMR Spectrum of 12e

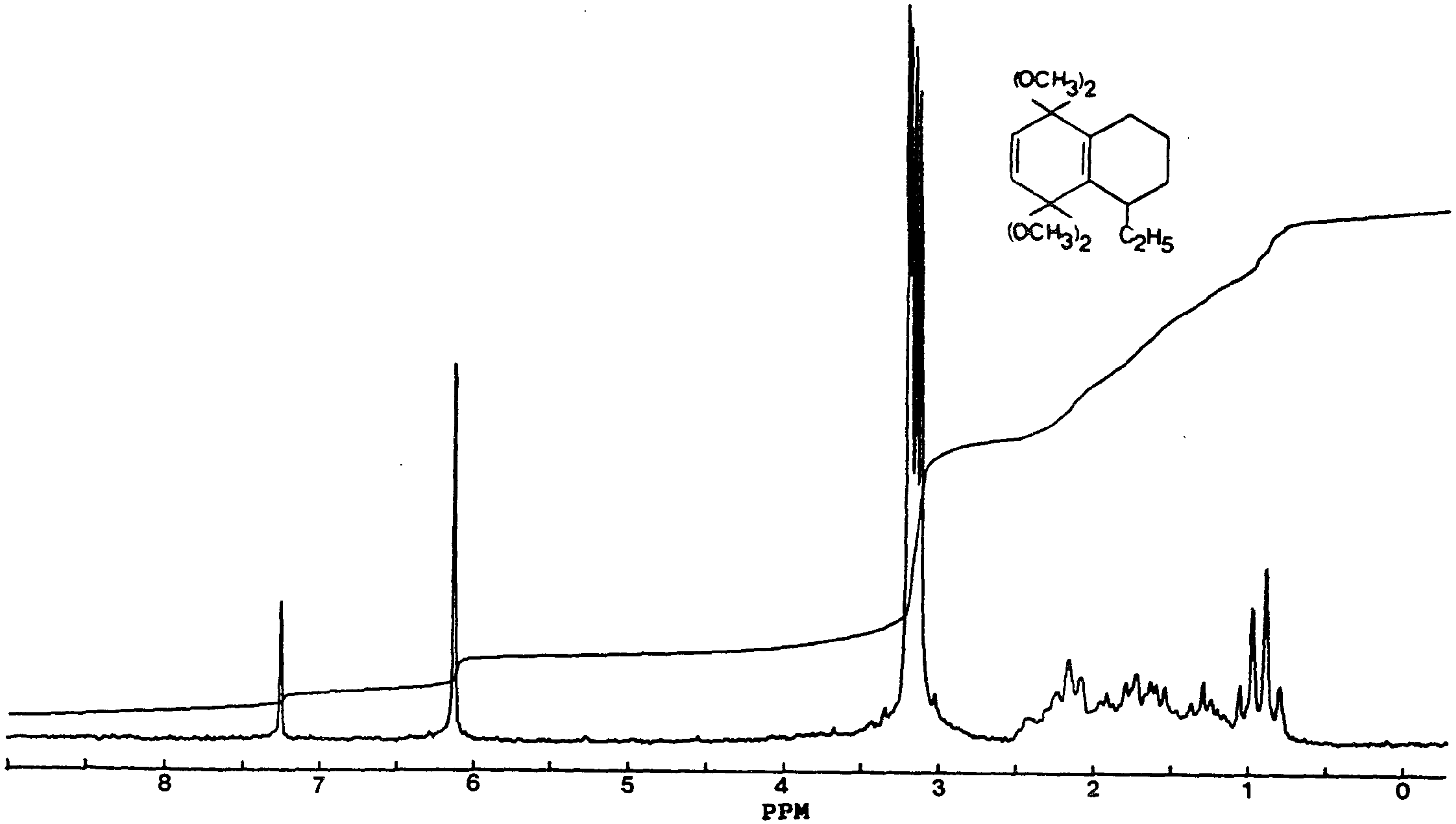


Figure 23. 80 MHz ^{1}H NMR Spectrum of 12f

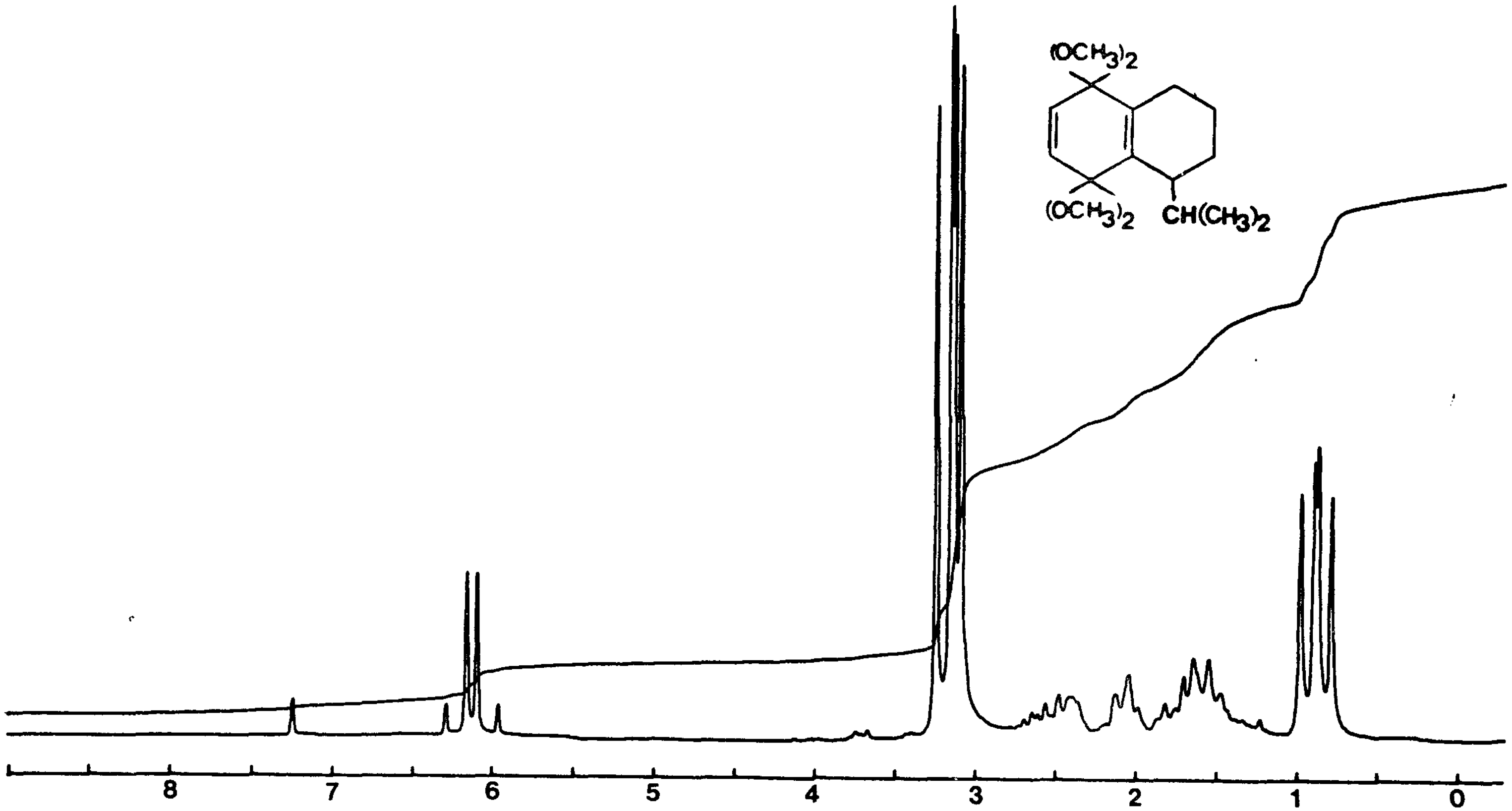


Figure 24. 80 MHz ^{1}H NMR Spectrum of 12g

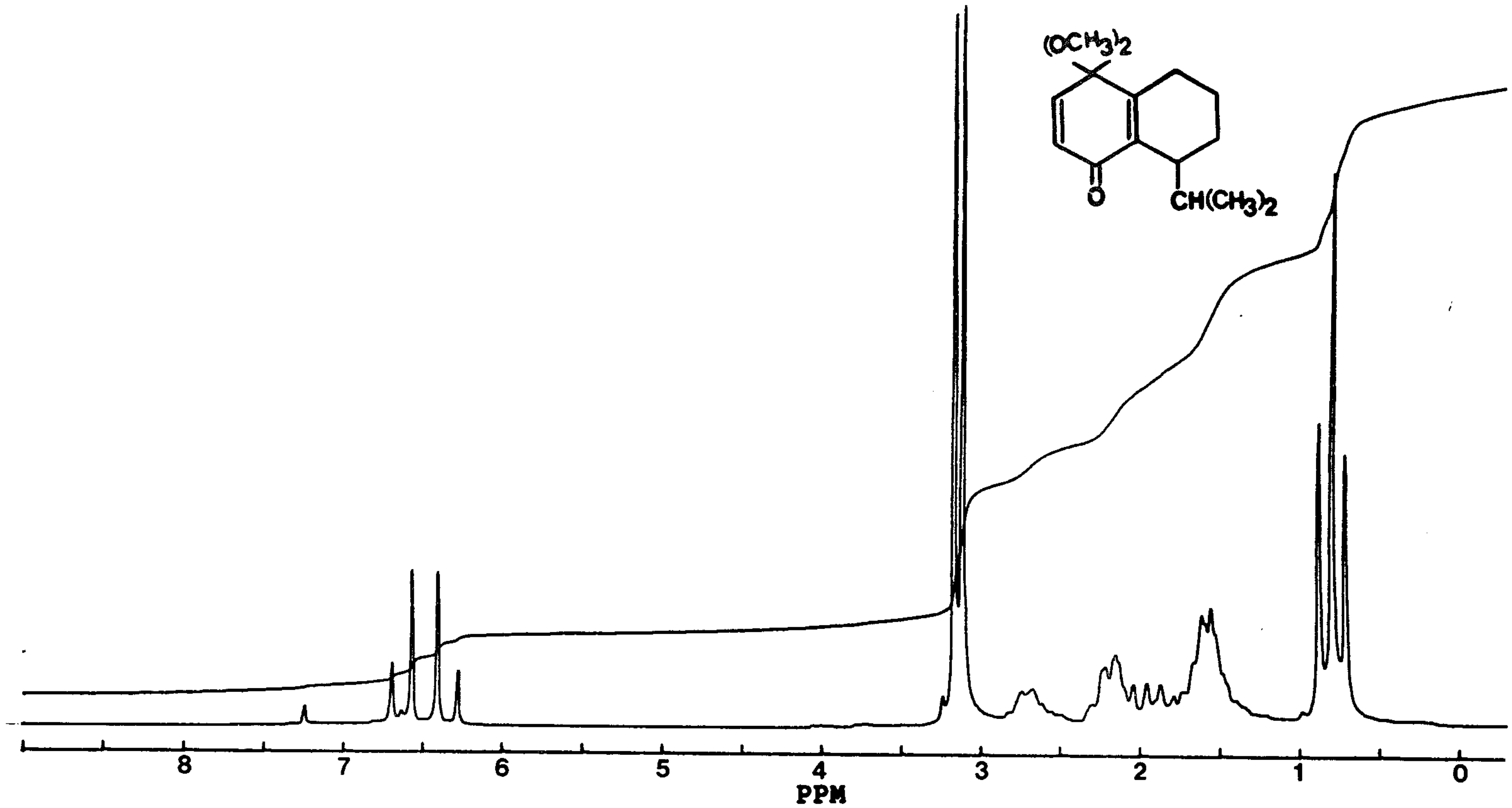


Figure 25. 80 MHz ^{1}H NMR Spectrum of 13g

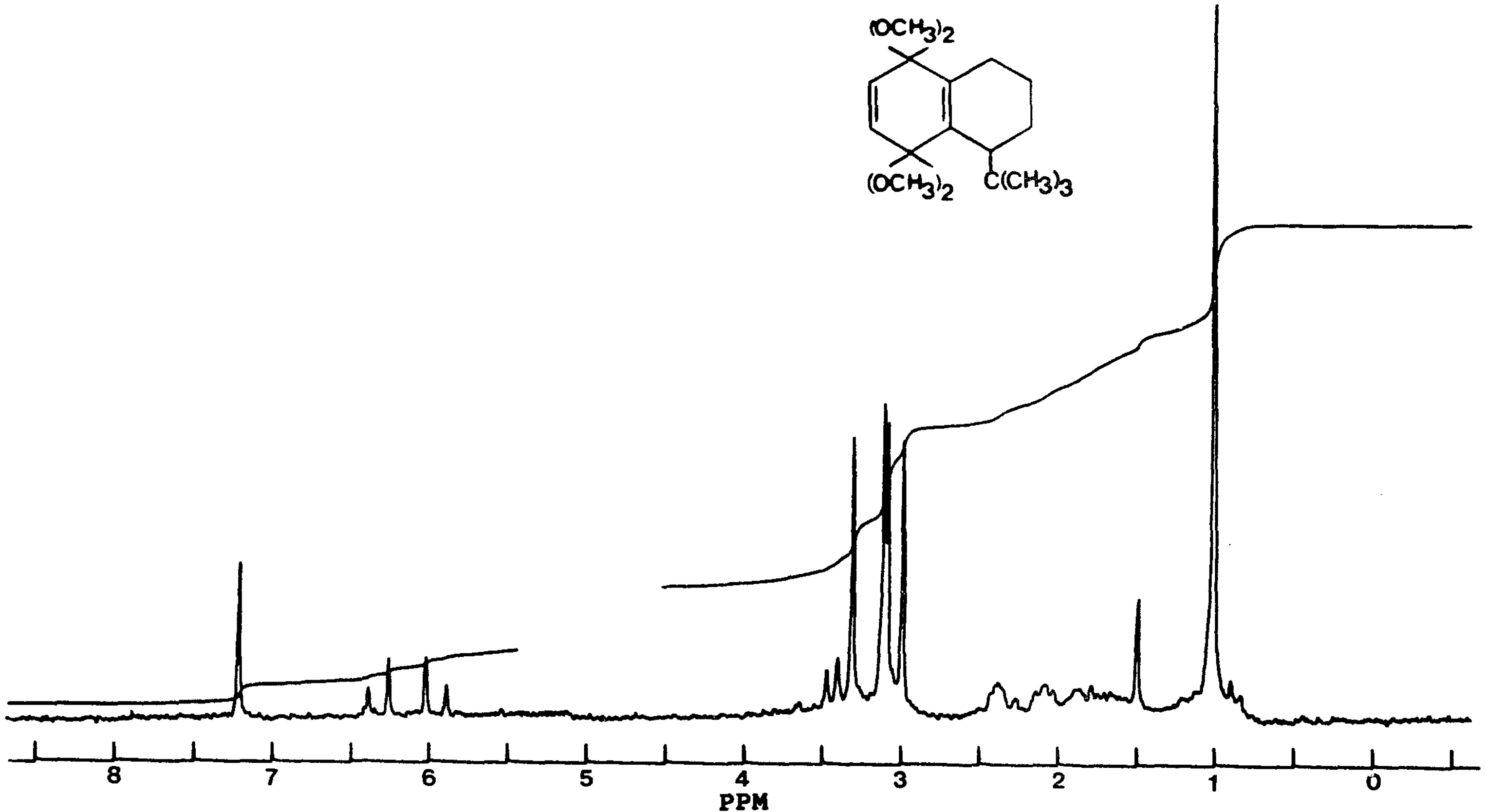


Figure 26. 80 MHz ^{1}H NMR Spectrum of 12h

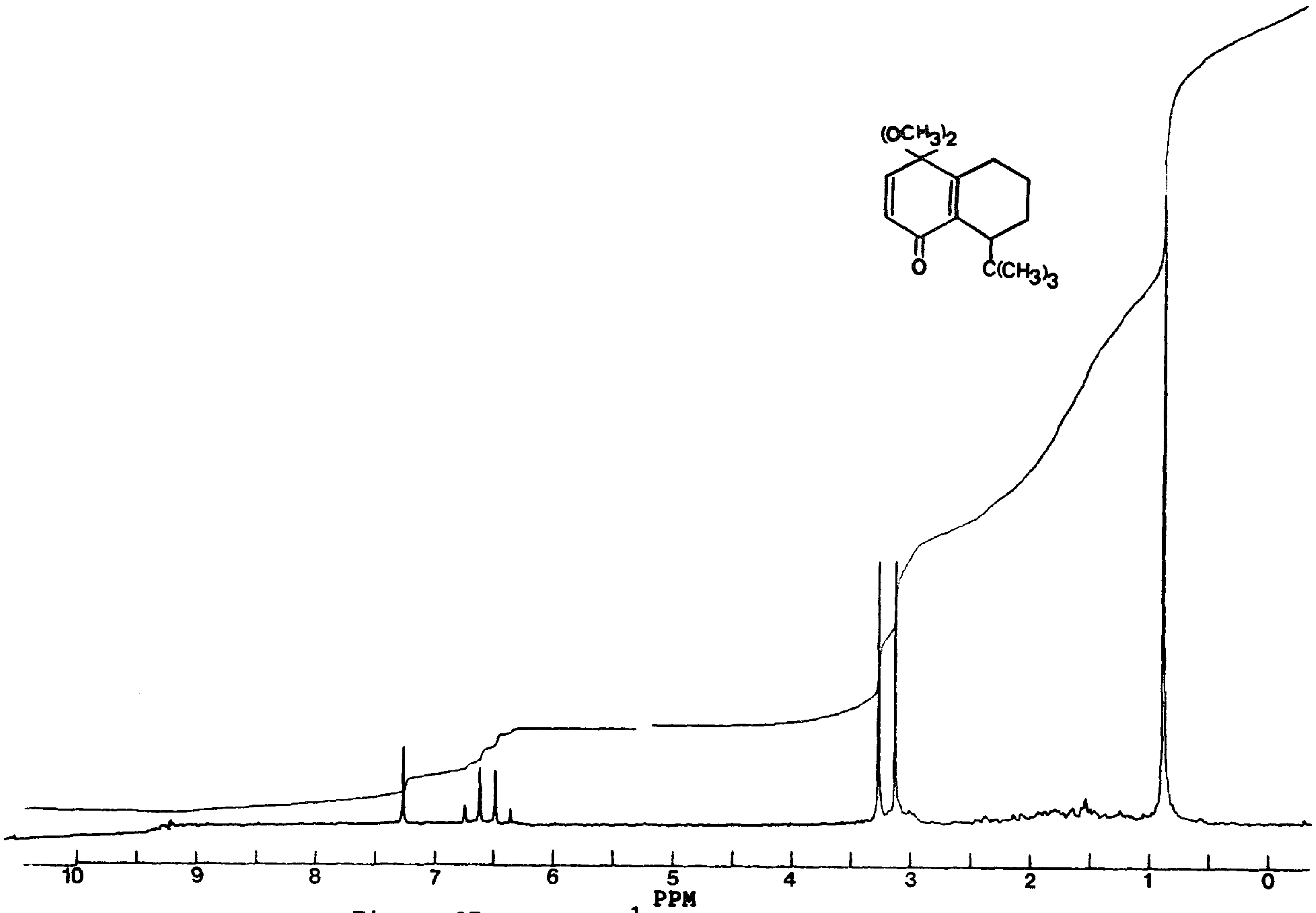


Figure 27. 80 MHz ^{1}H NMR Spectrum of 13h

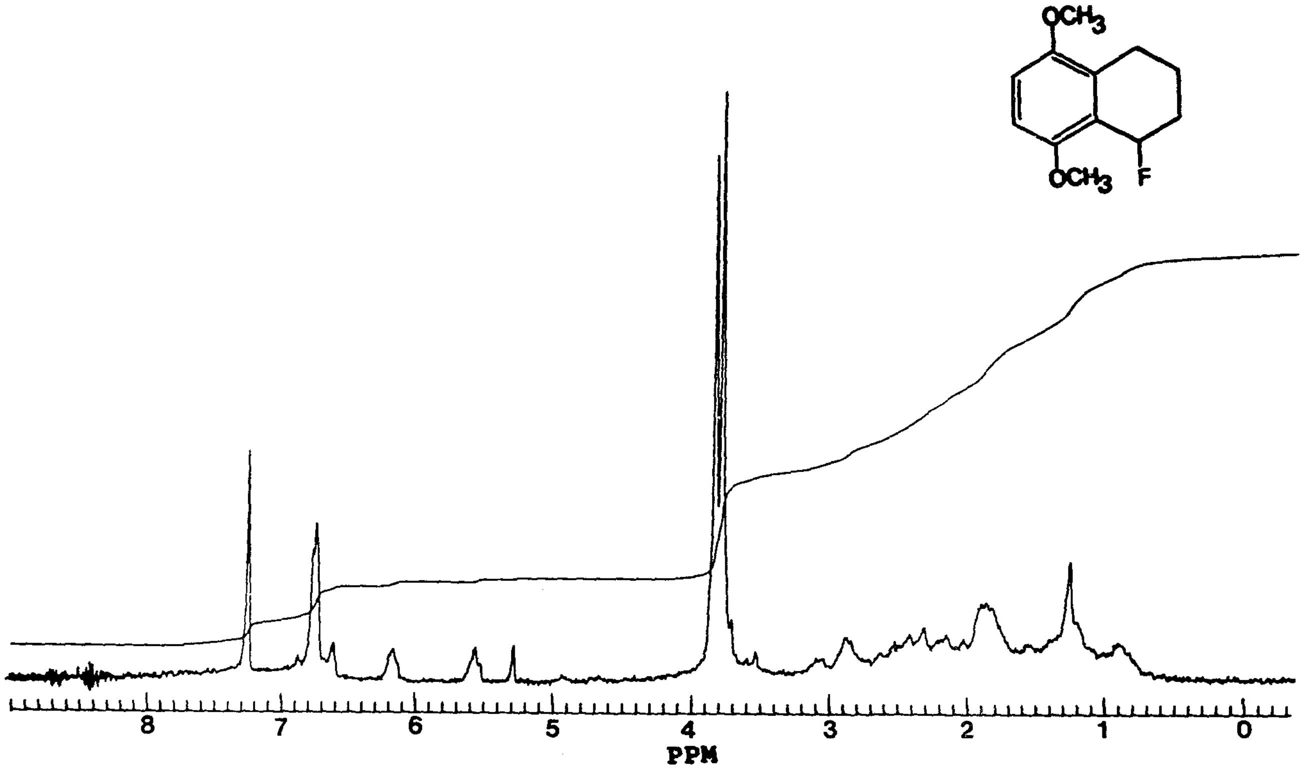


Figure 28. 80 MHz ^{1}H NMR Spectrum of 10i

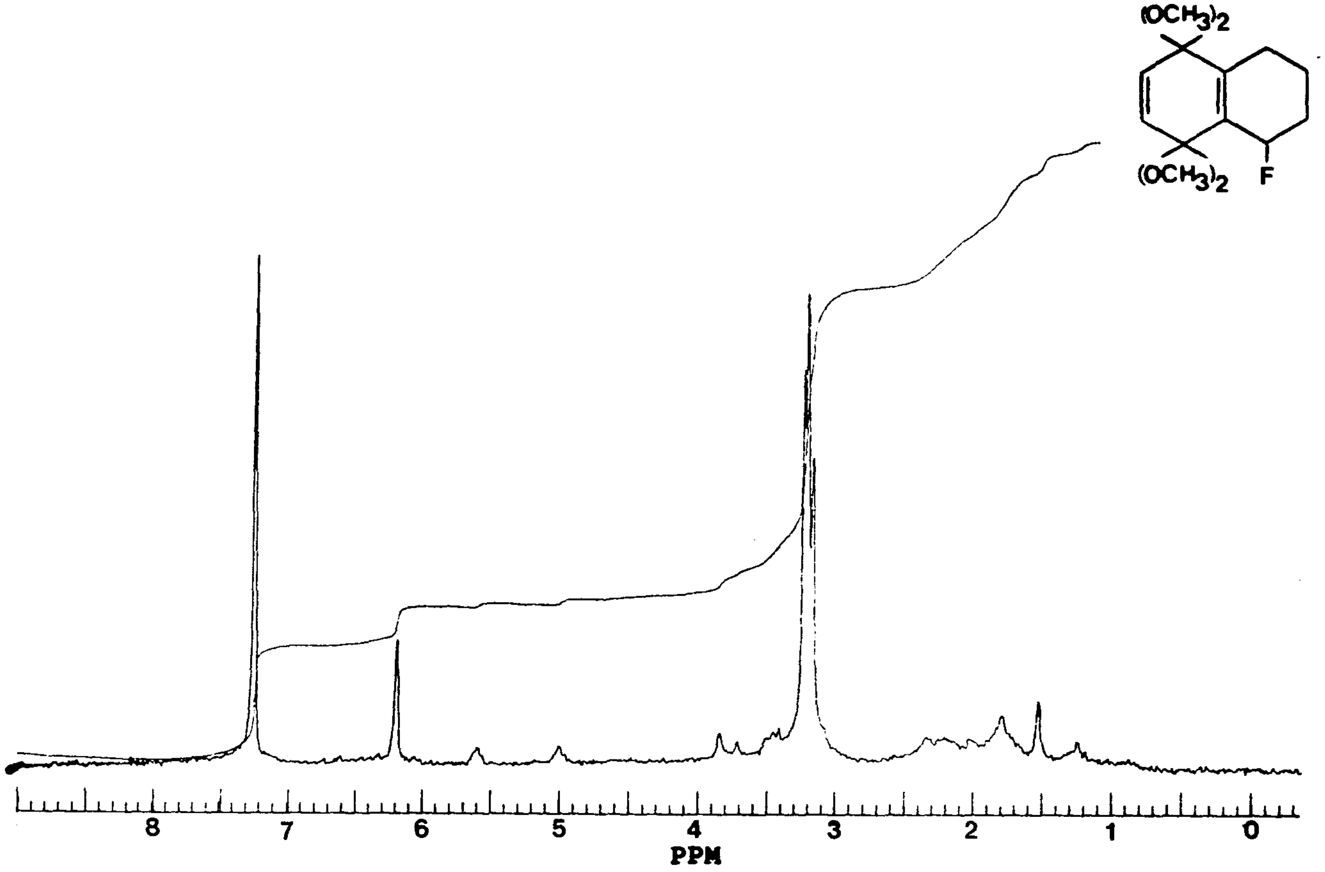


Figure 29. 80 MHz ^{1}H NMR Spectrum of 12i

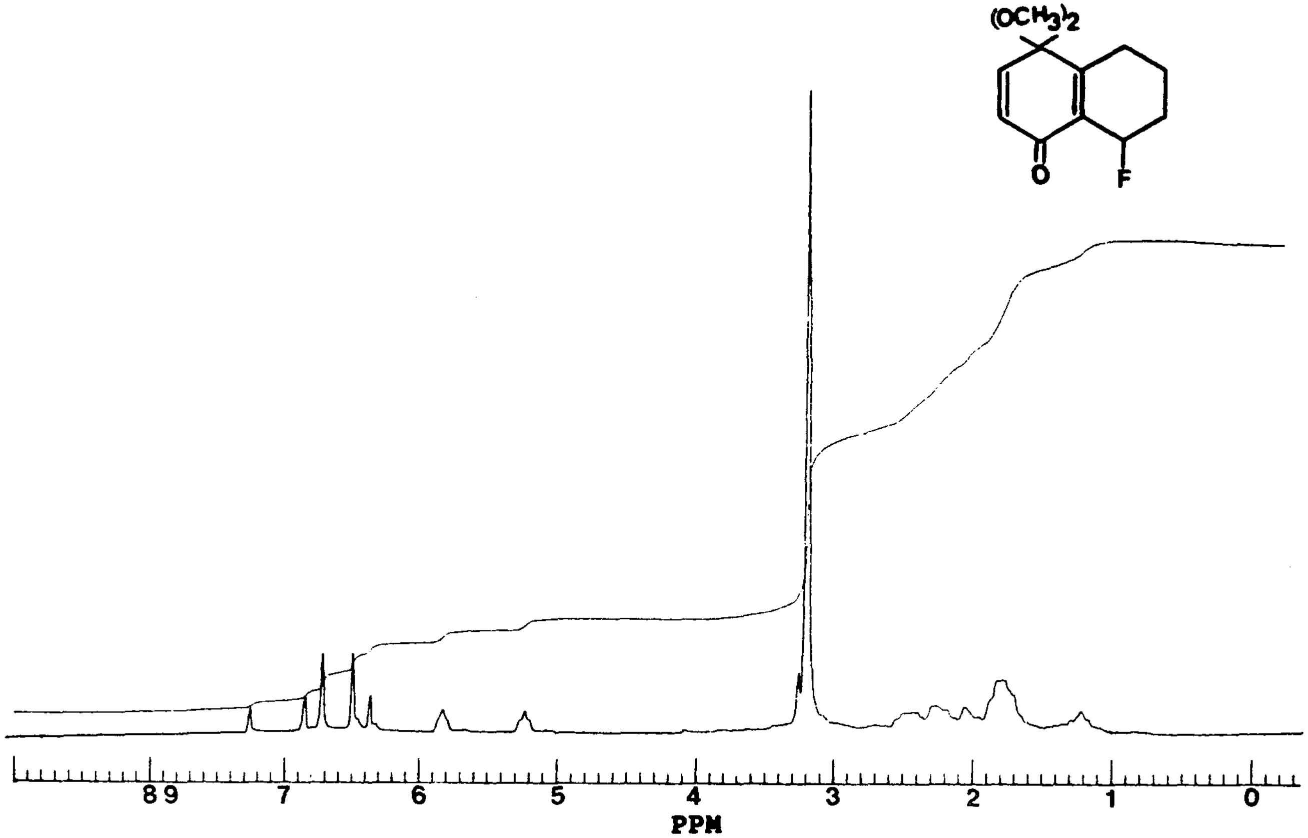


Figure 30. 80 MHz ^{1}H NMR Spectrum of 13i

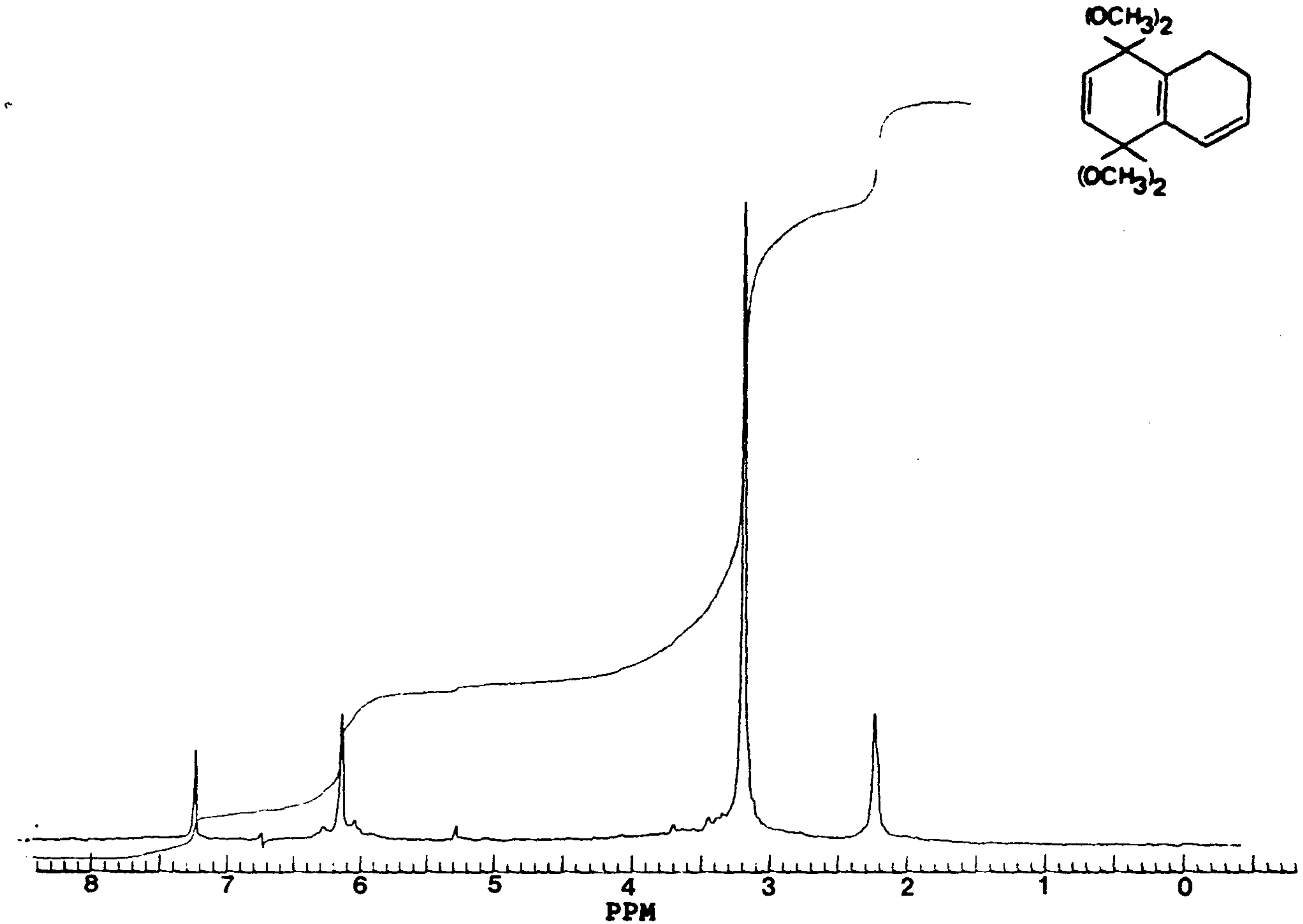


Figure 31. 80 MHz ^{1}H NMR Spectrum of 12j

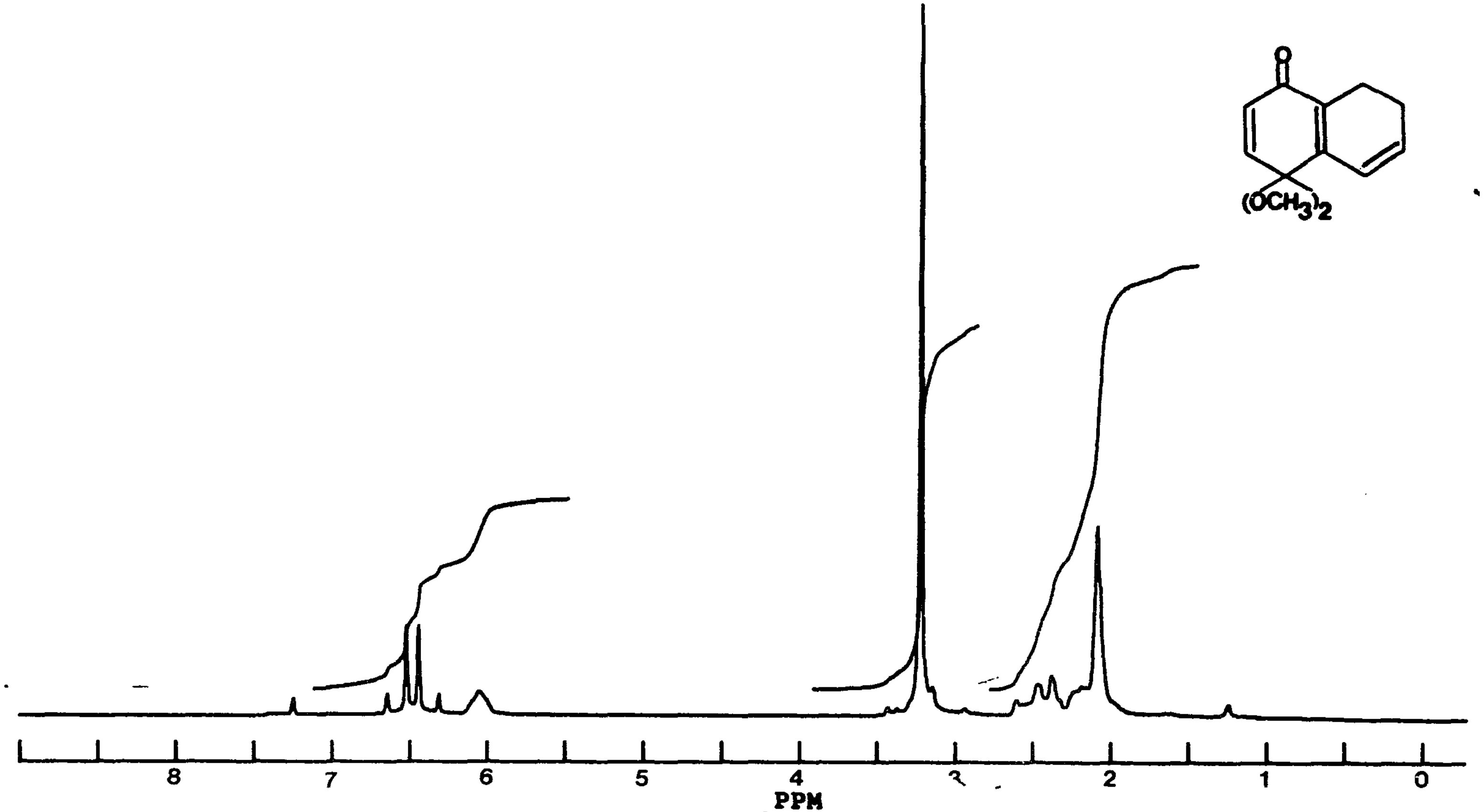


Figure 32. 80 MHz ^{1}H NMR Spectrum of 14j

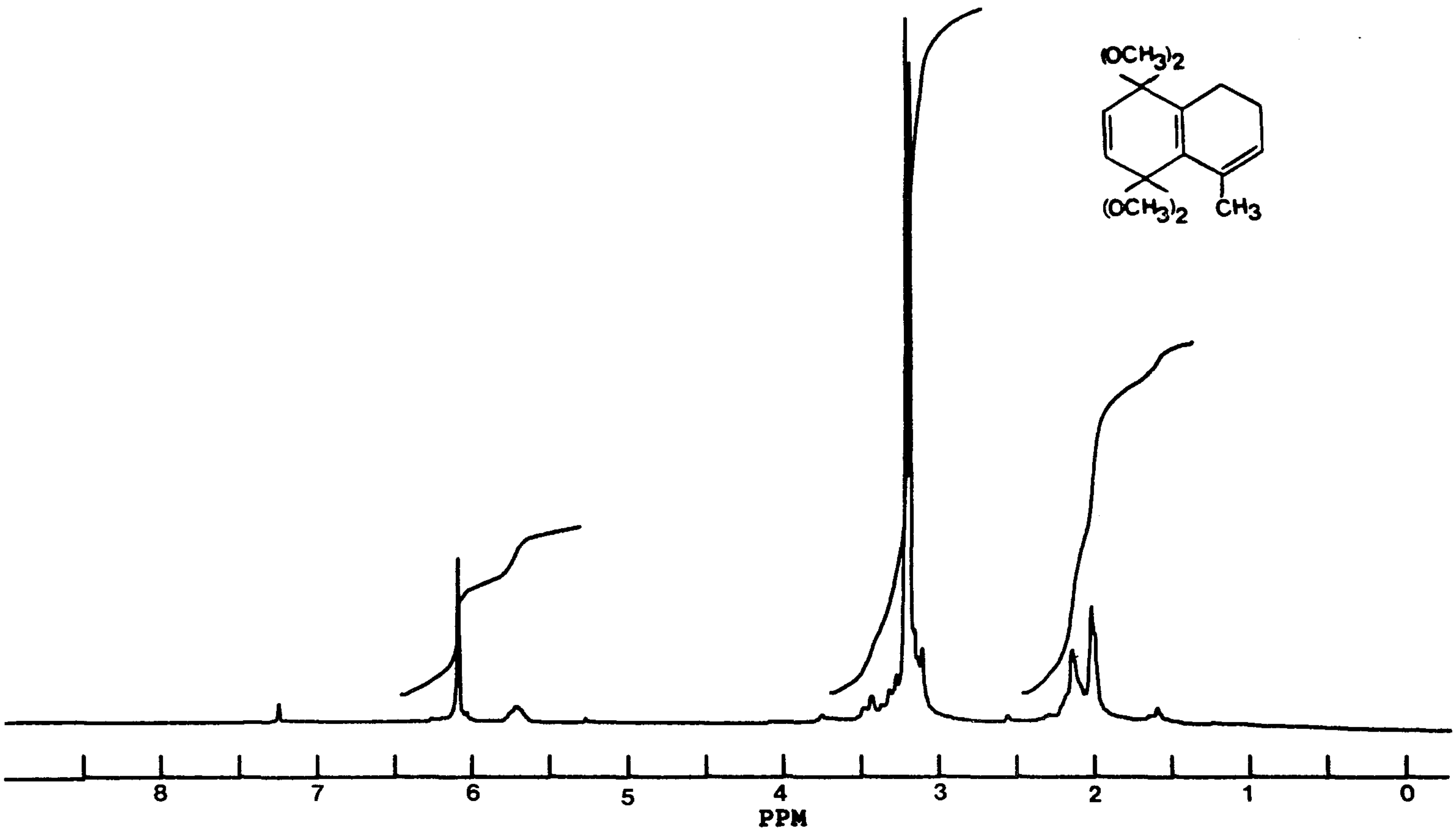


Figure 33. 80 MHz ^{1}H NMR Spectrum of 12k

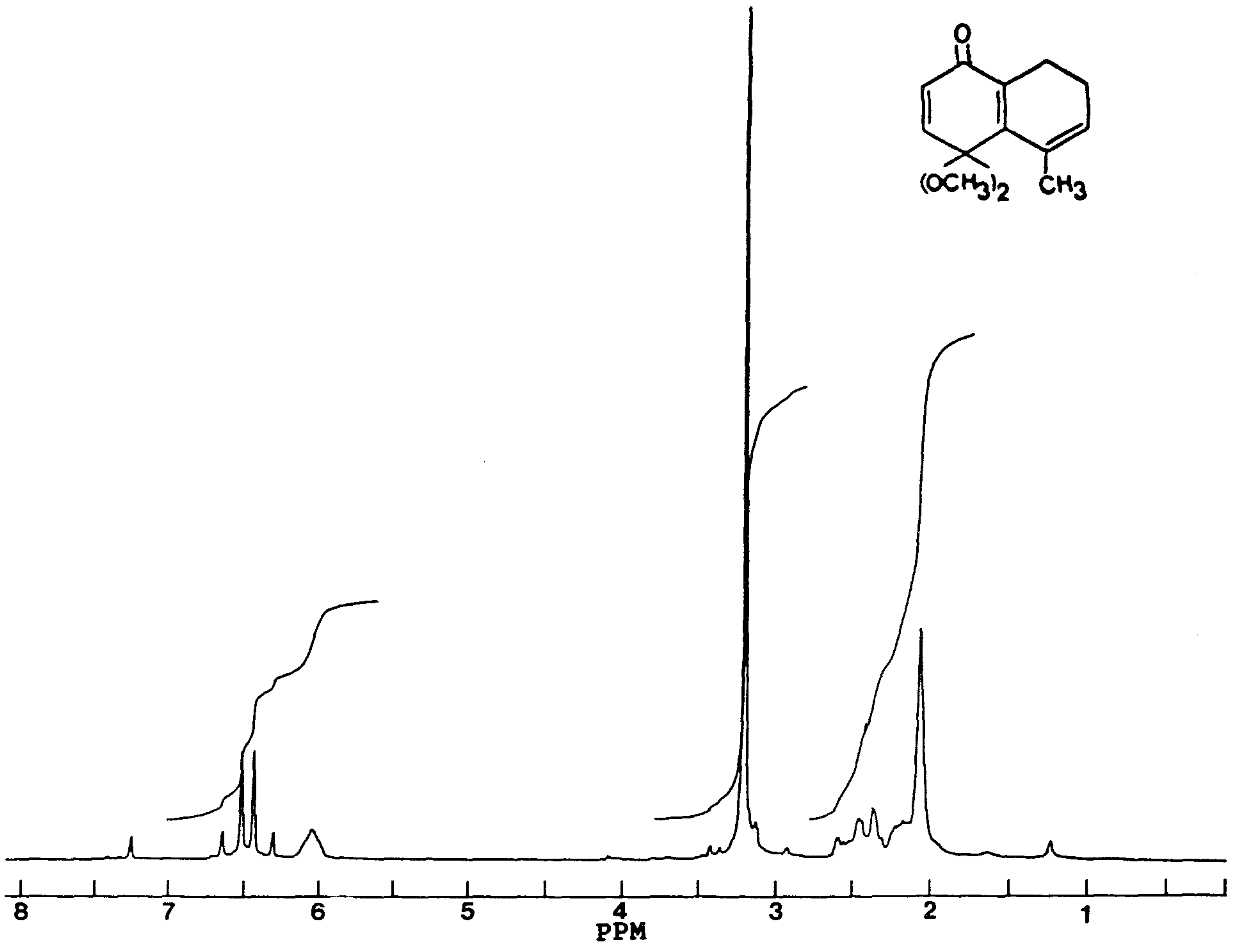


Figure 34. 80 MHz ^{1}H NMR Spectrum of 14k

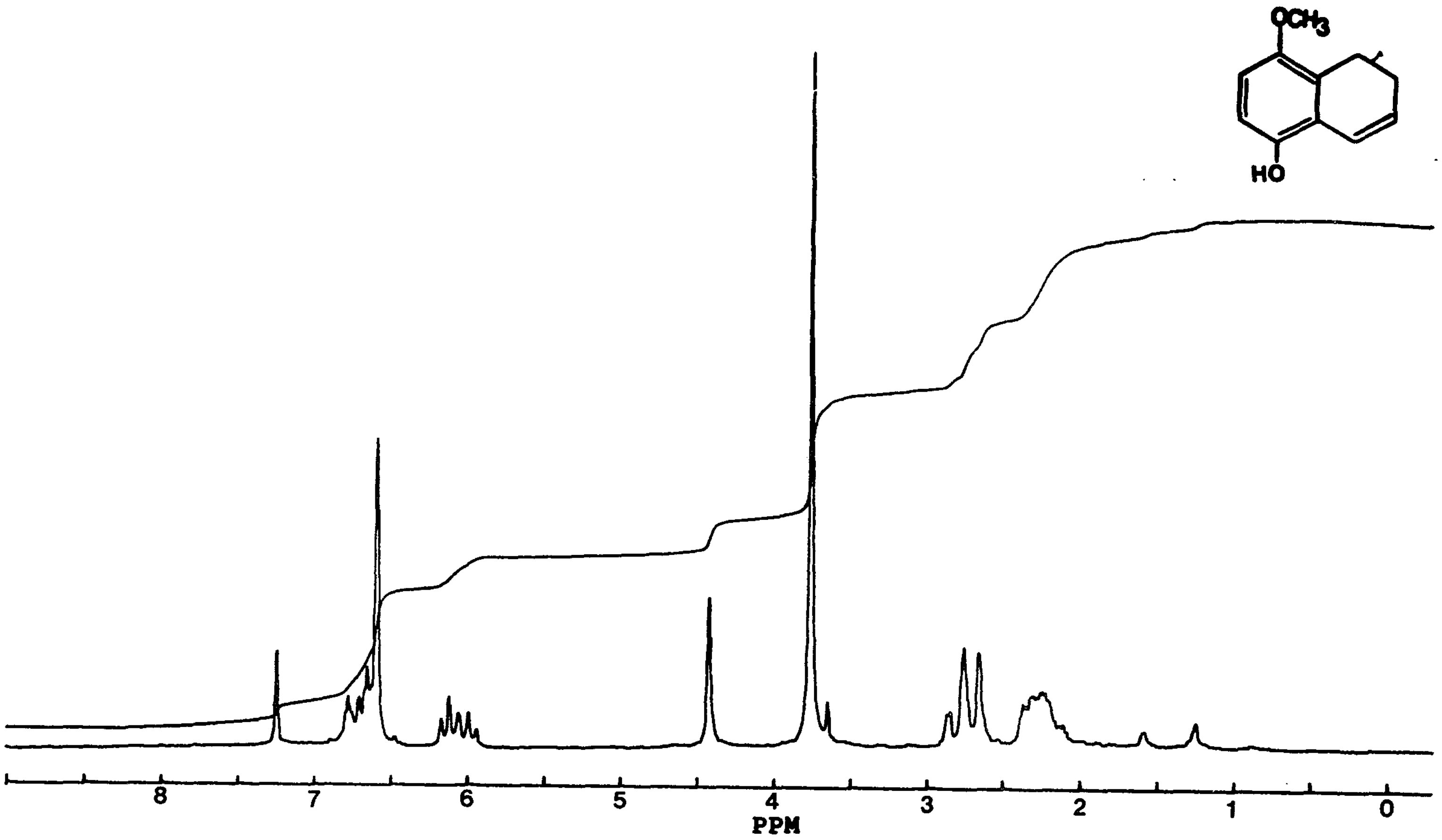


Figure 35. 80 MHz ^{1}H NMR Spectrum of I

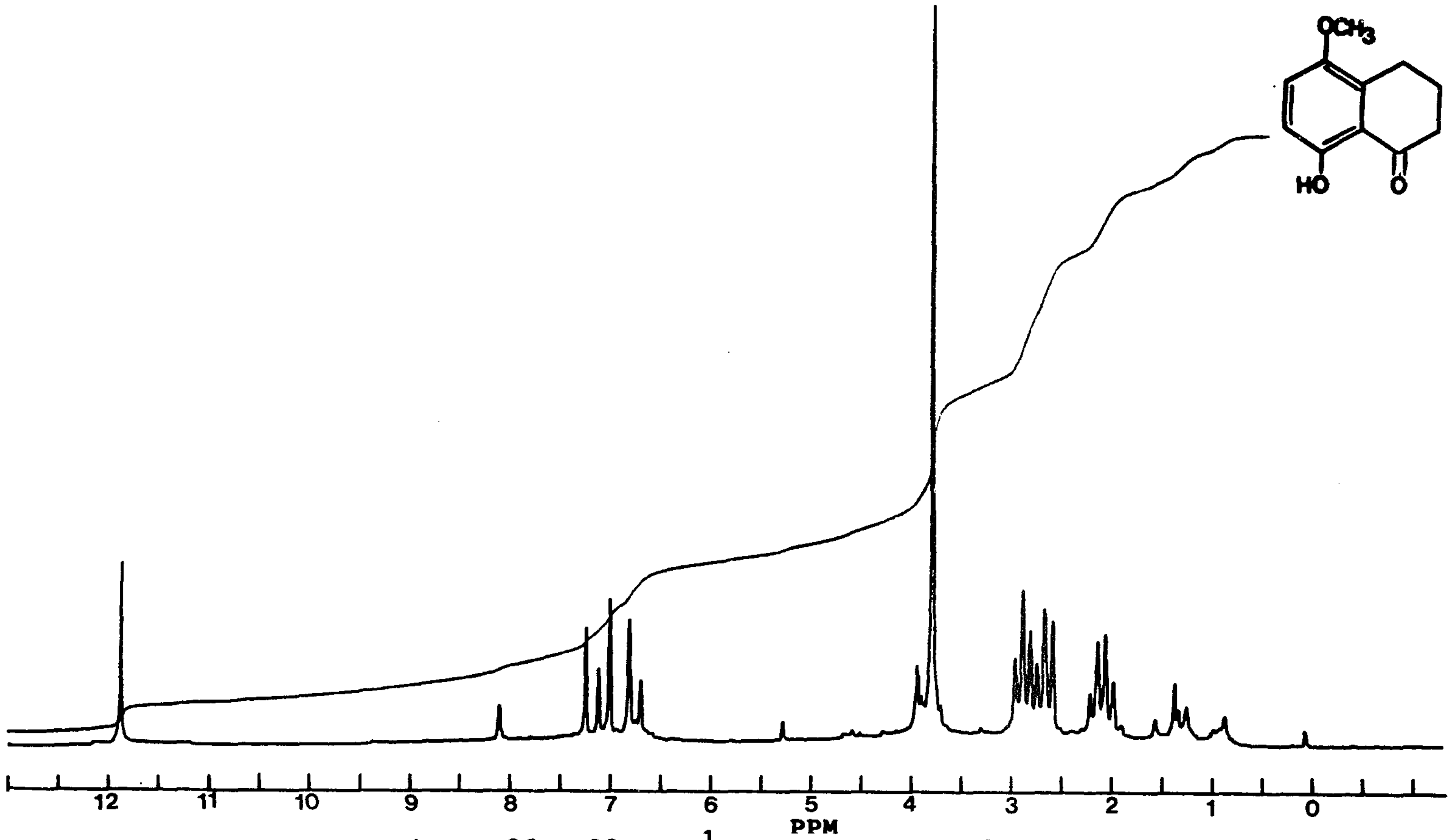


Figure 36. 80 MHz ^{1}H NMR Spectrum of II

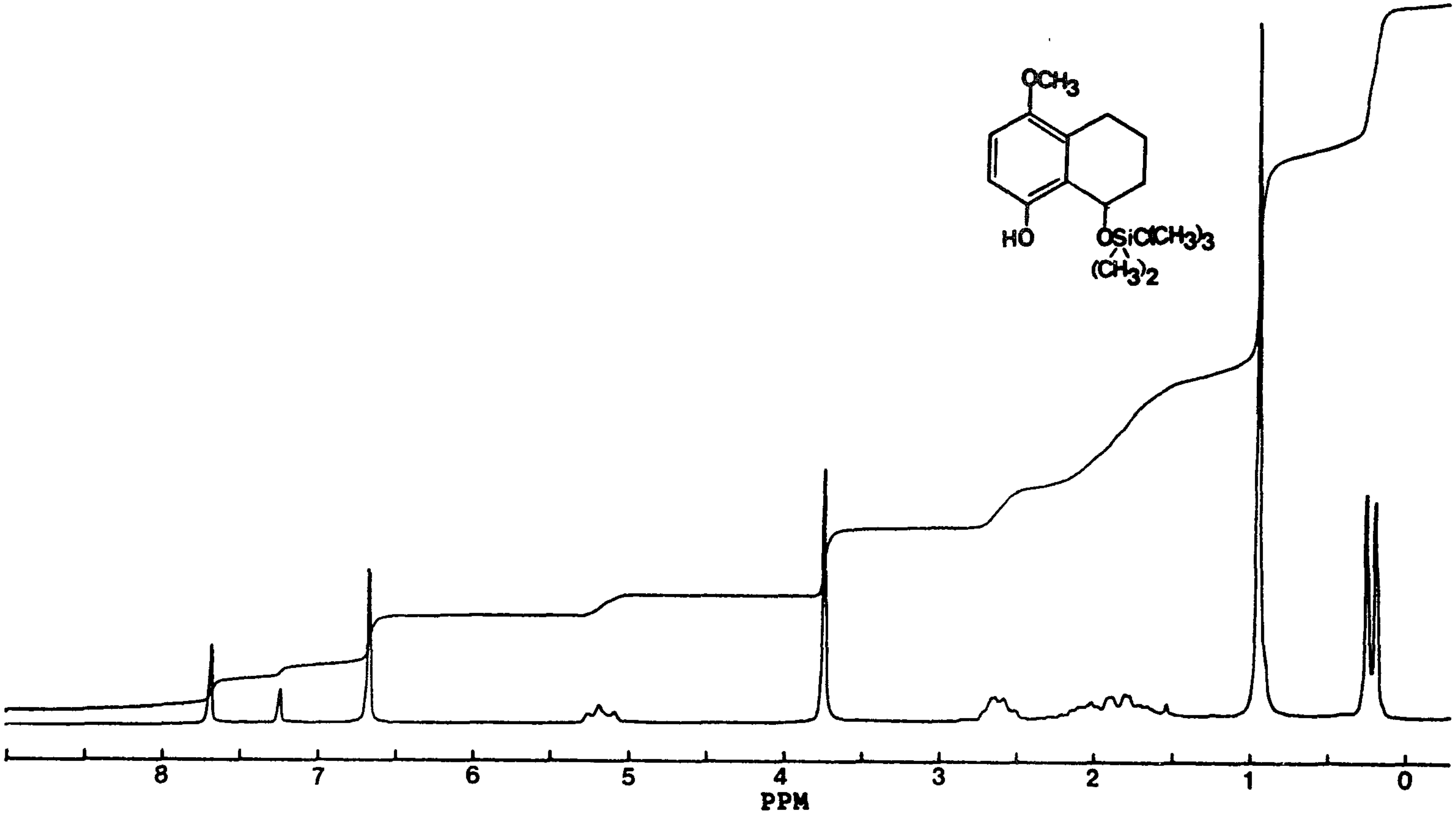


Figure 37. 80 MHz ^{1}H NMR Spectrum of III

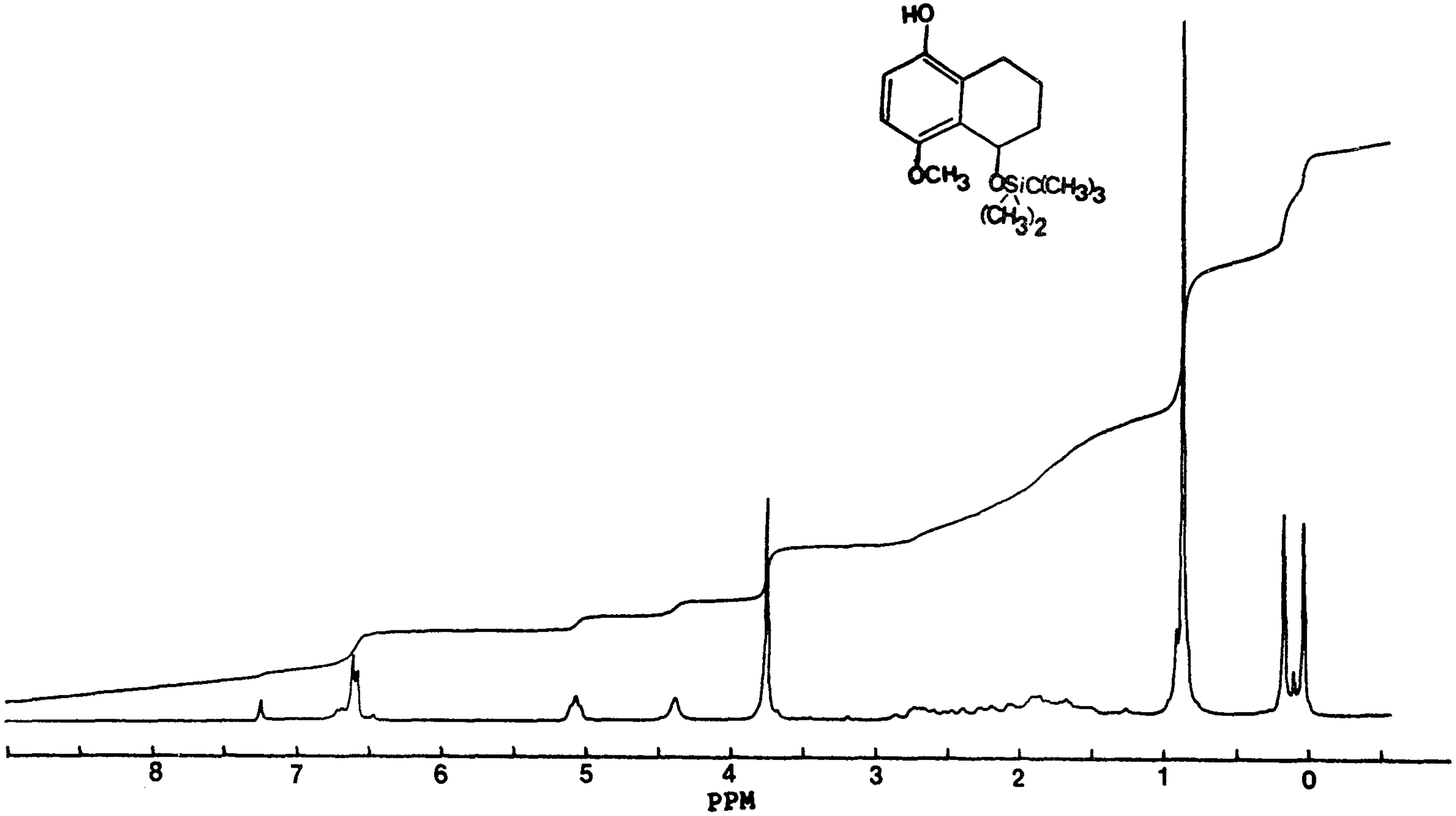


Figure 38. 80 MHz ^{1}H NMR Spectrum of IV

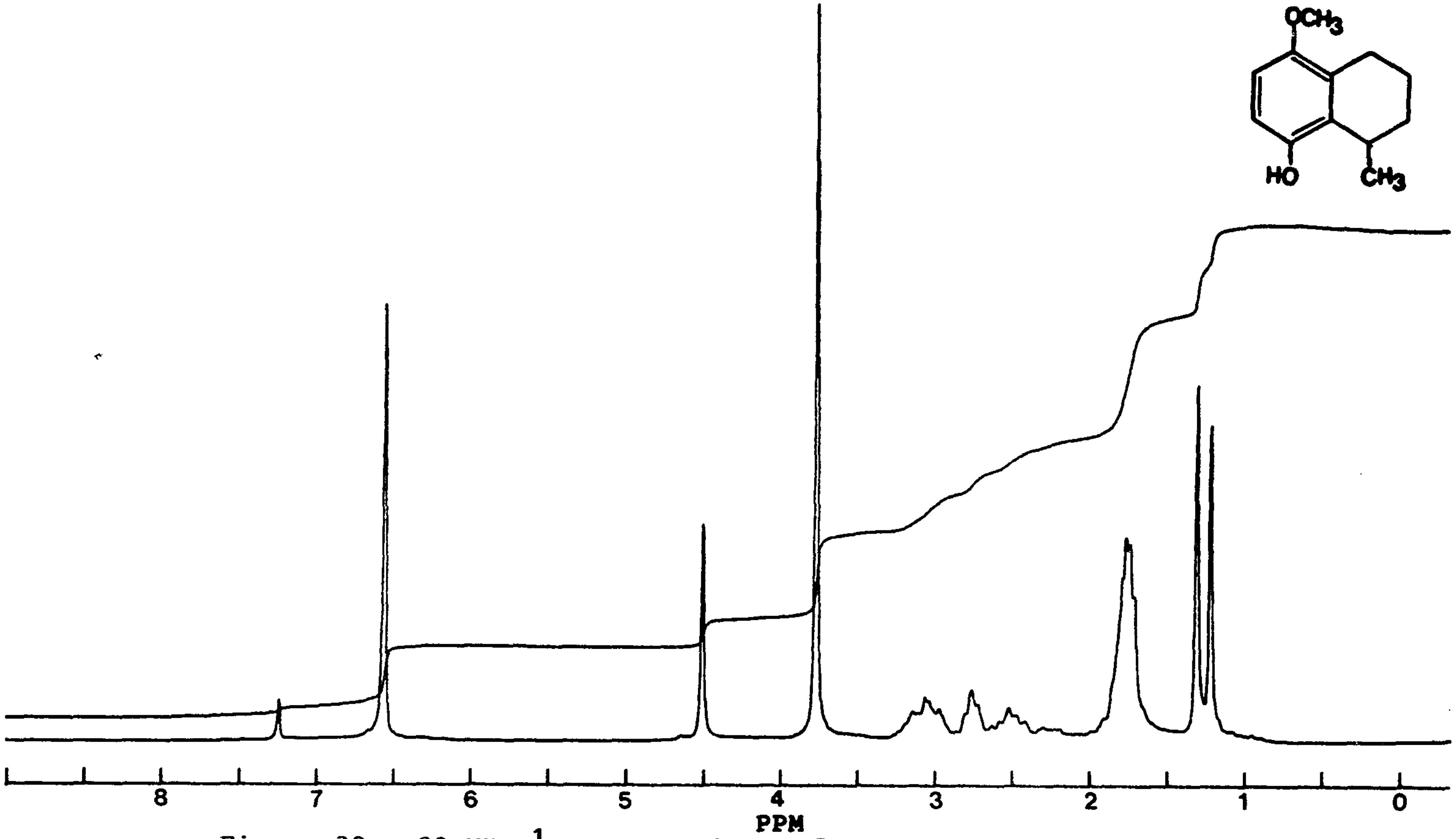


Figure 39. 80 MHz ^{1}H NMR Spectrum of $NaBH_4$ Reduction of 13e and 14e

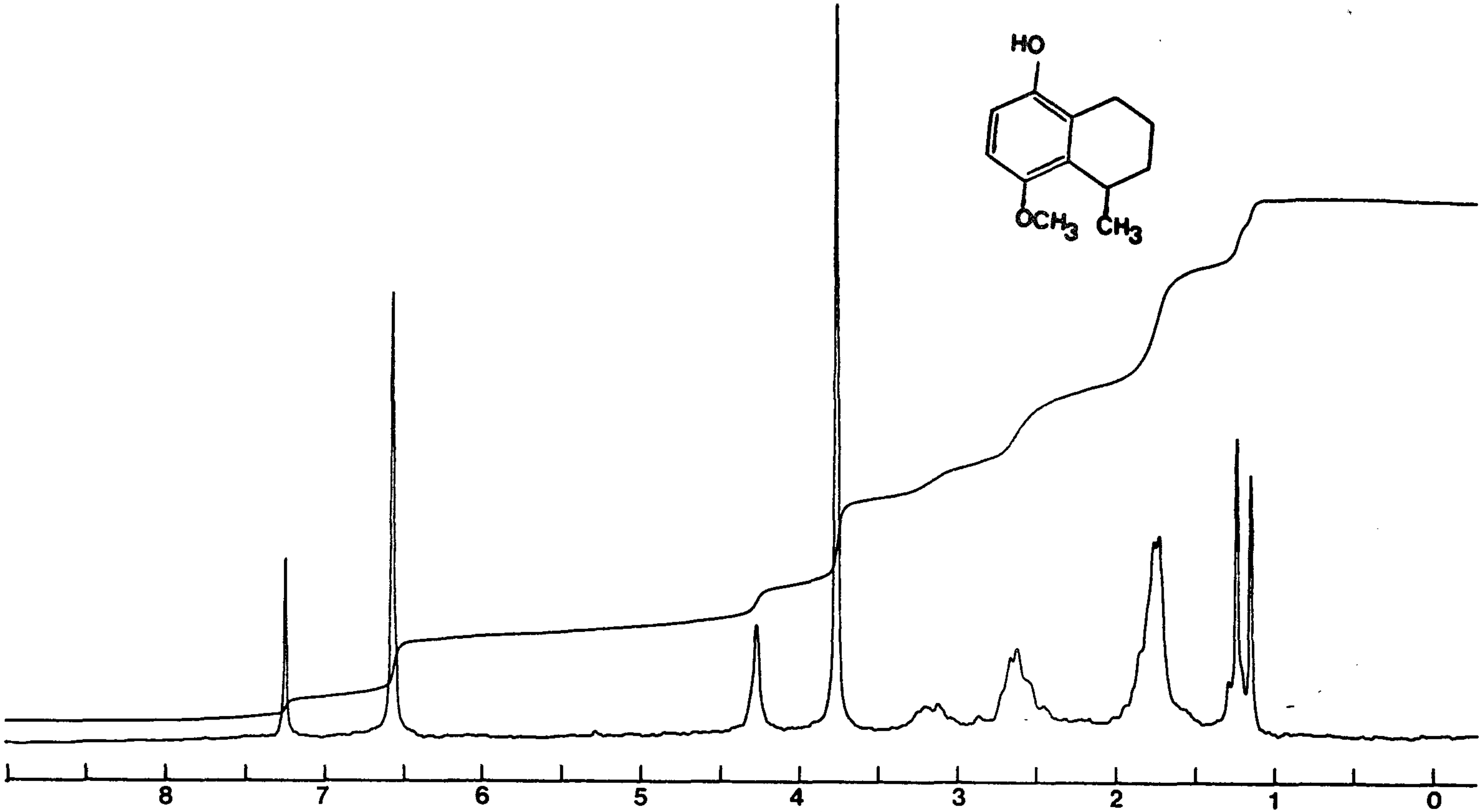


Figure 40. 80 MHz ^1H NMR Spectrum of $NaBH_4$ Reduction of 13e and 14e

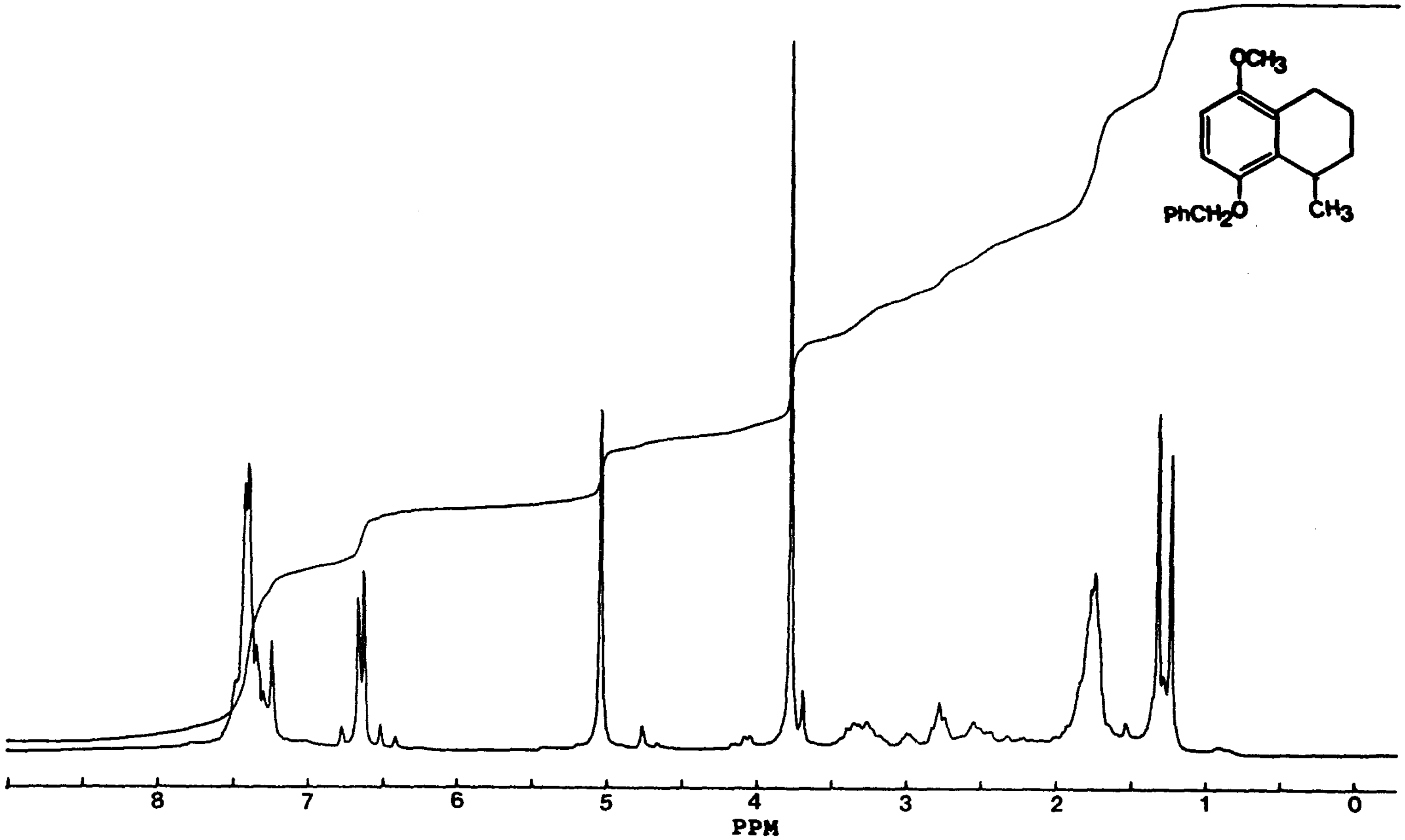


Figure 41. 80 MHz ^{1}H NMR Spectrum of Ve

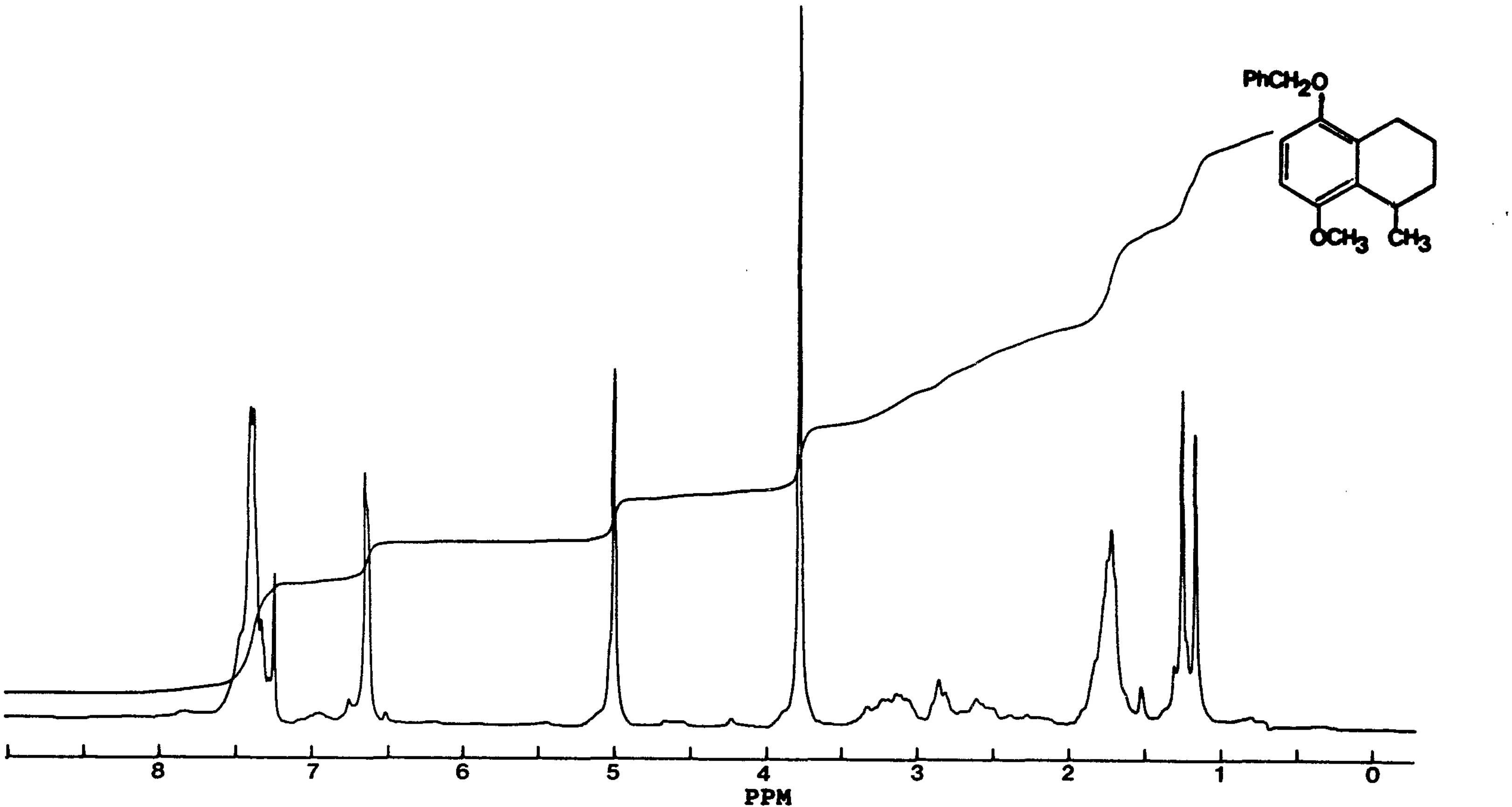


Figure 42. 80 MHz ^{1}H NMR Spectrum of VIe

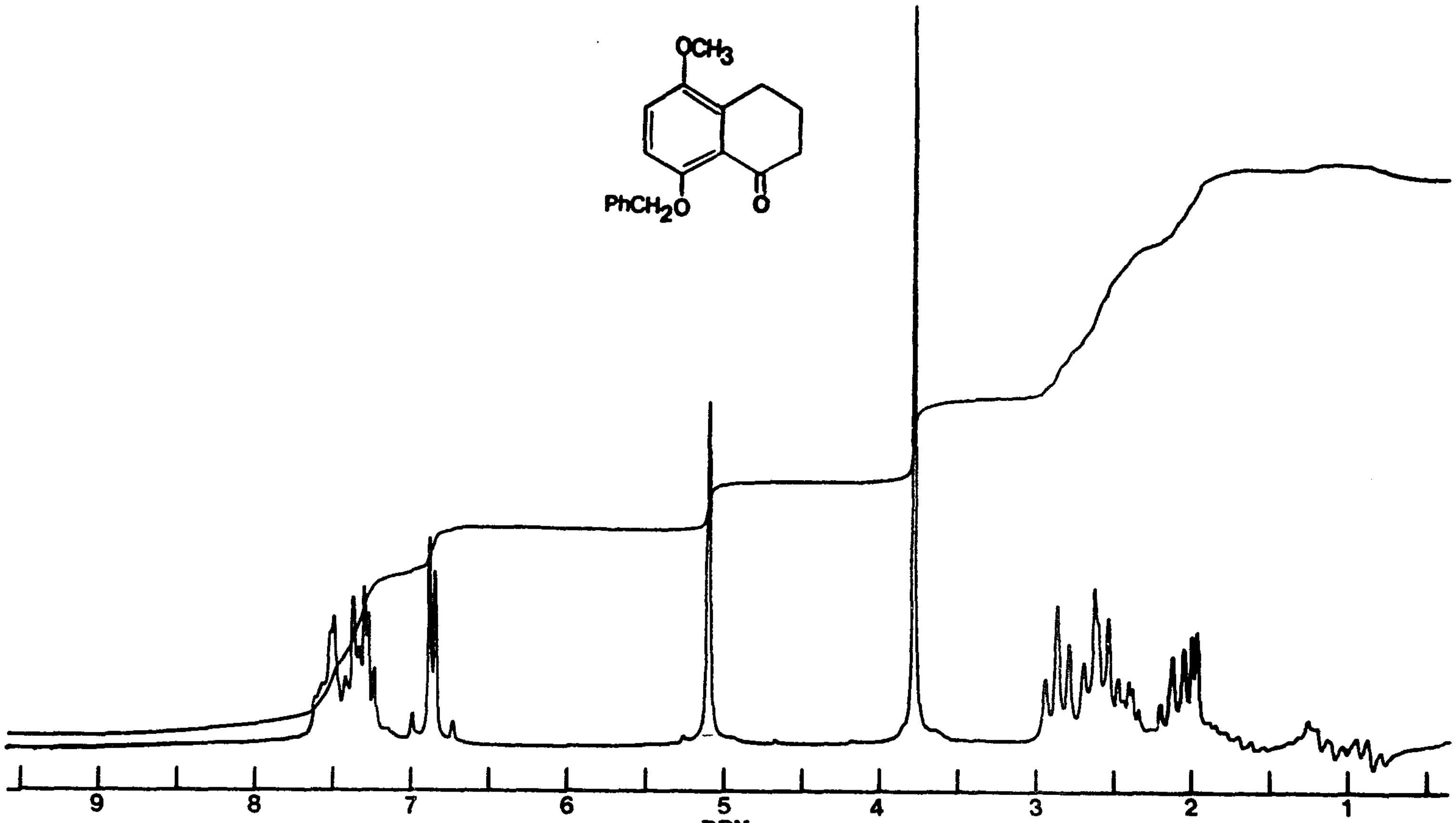


Figure 43. 80 MHz ^{1}H NMR Spectrum of VII

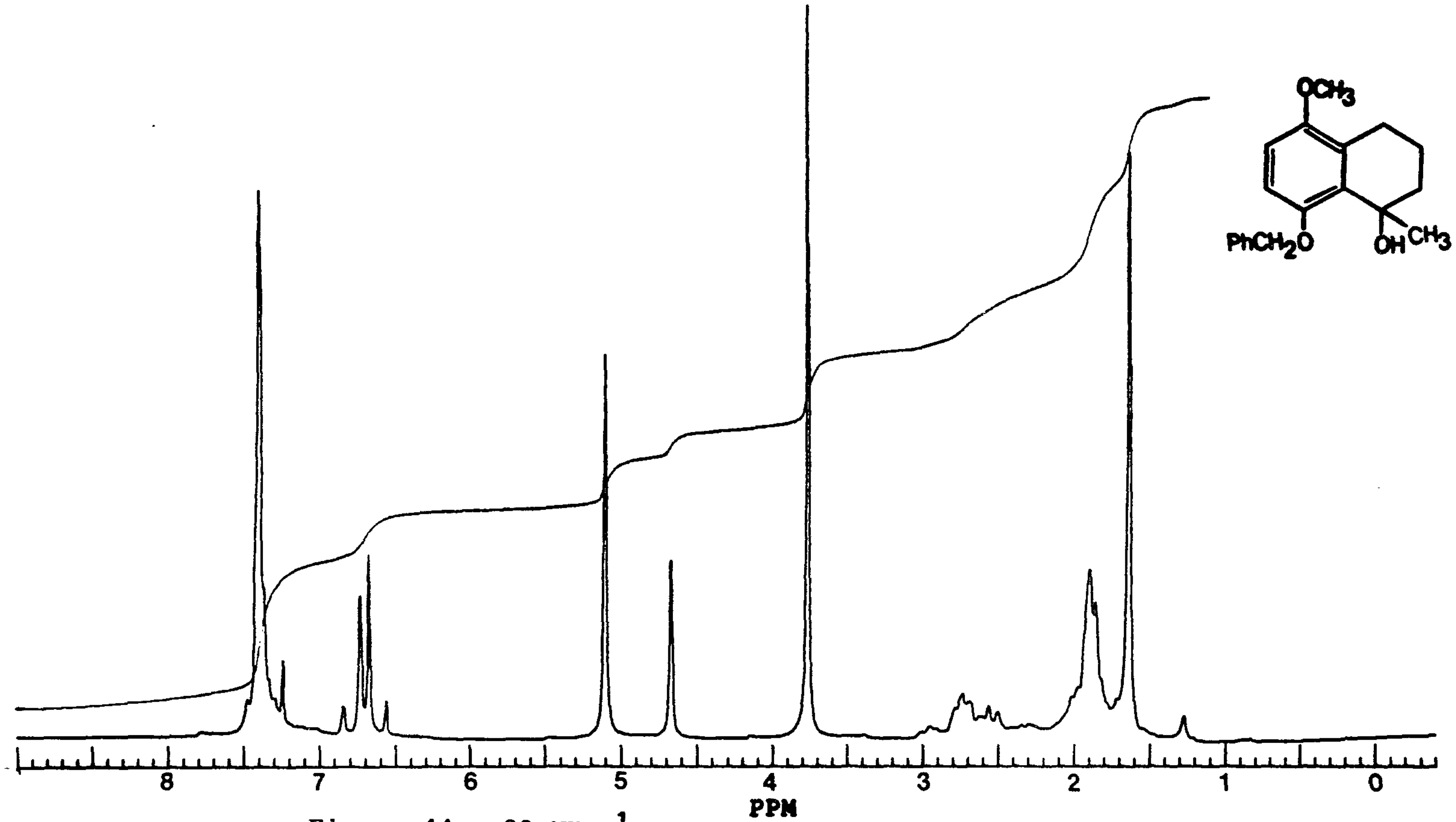


Figure 44. 80 MHz ^{1}H NMR Spectrum of CH_3Li Addition to VII

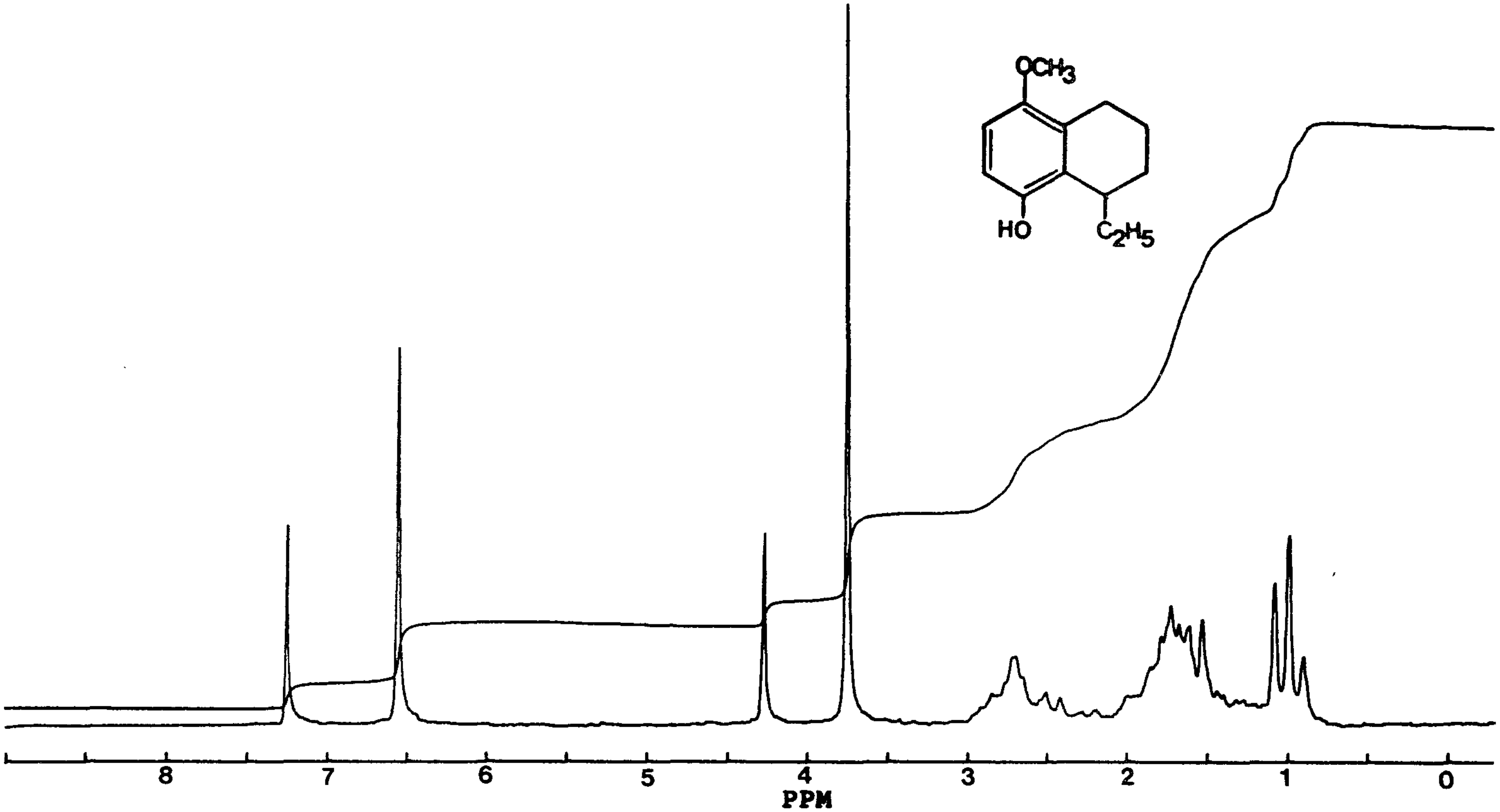


Figure 45. 80 MHz ^{1}H NMR Spectrum of NaBH$_4$ Reduction of 13f and 14f

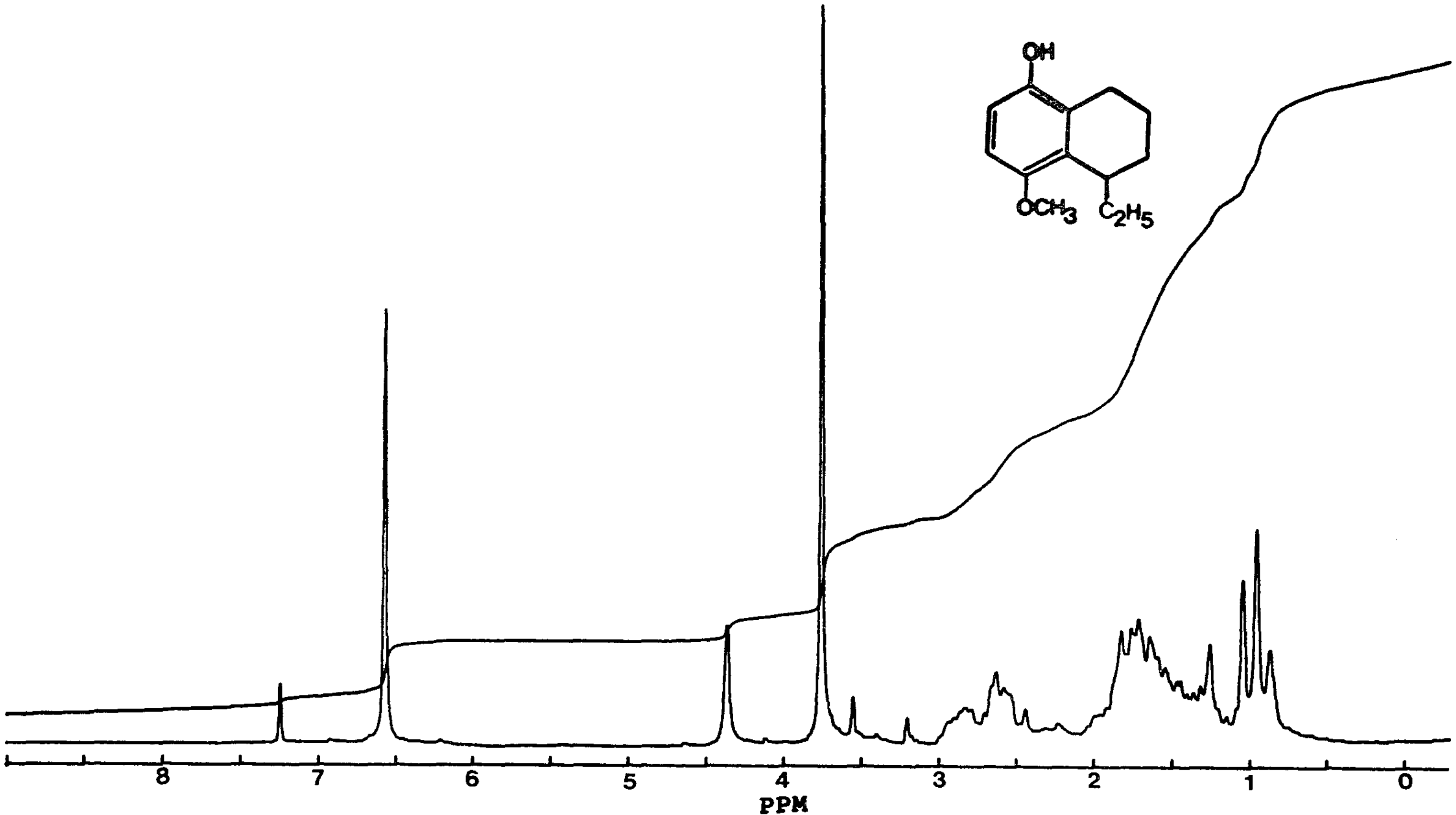


Figure 46. 80 MHz ^{1}H NMR Spectrum of NaBH$_4$ Reduction of 13f and 14f

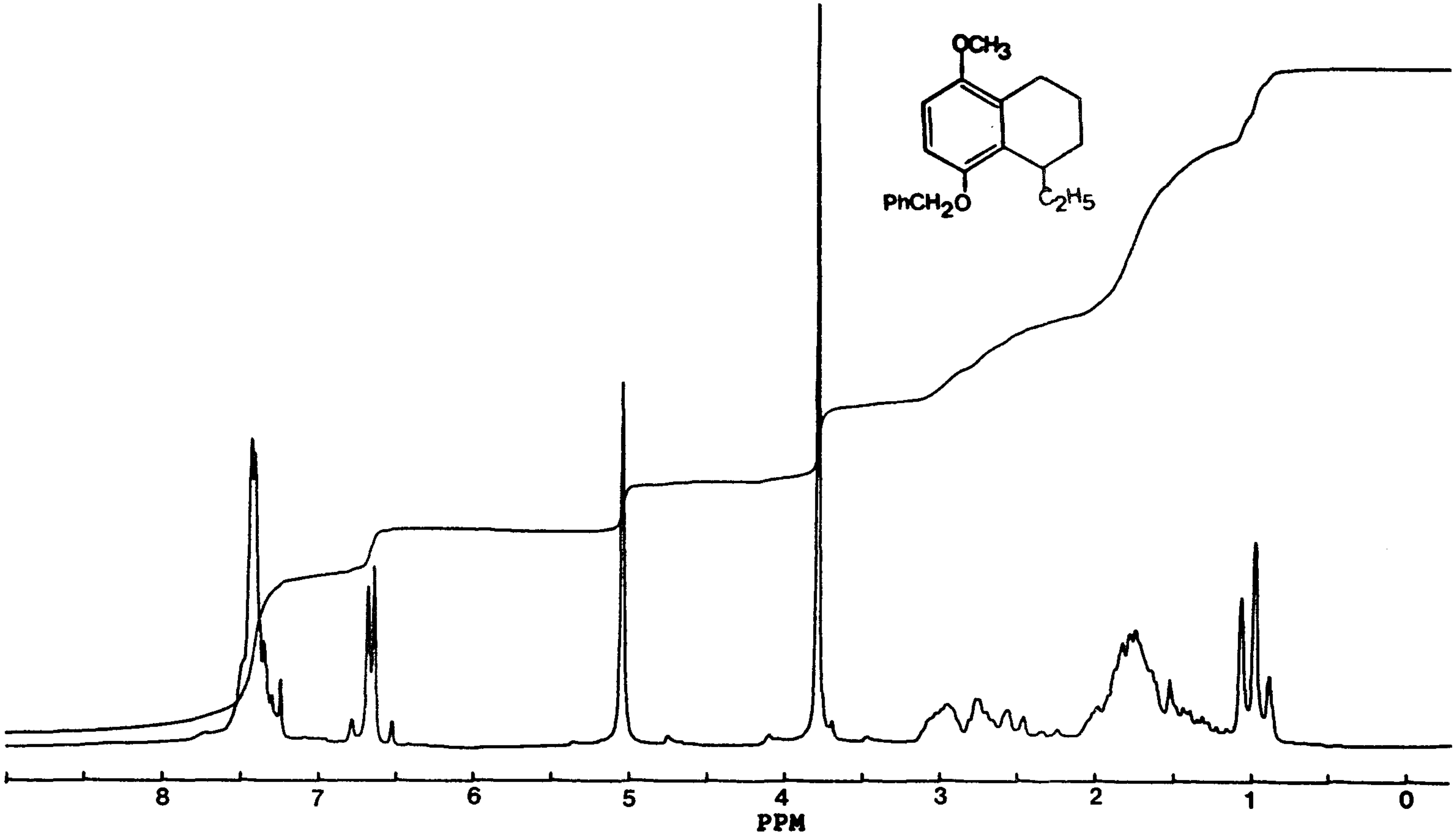


Figure 47. 80 MHz ^1H NMR Spectrum of Vf

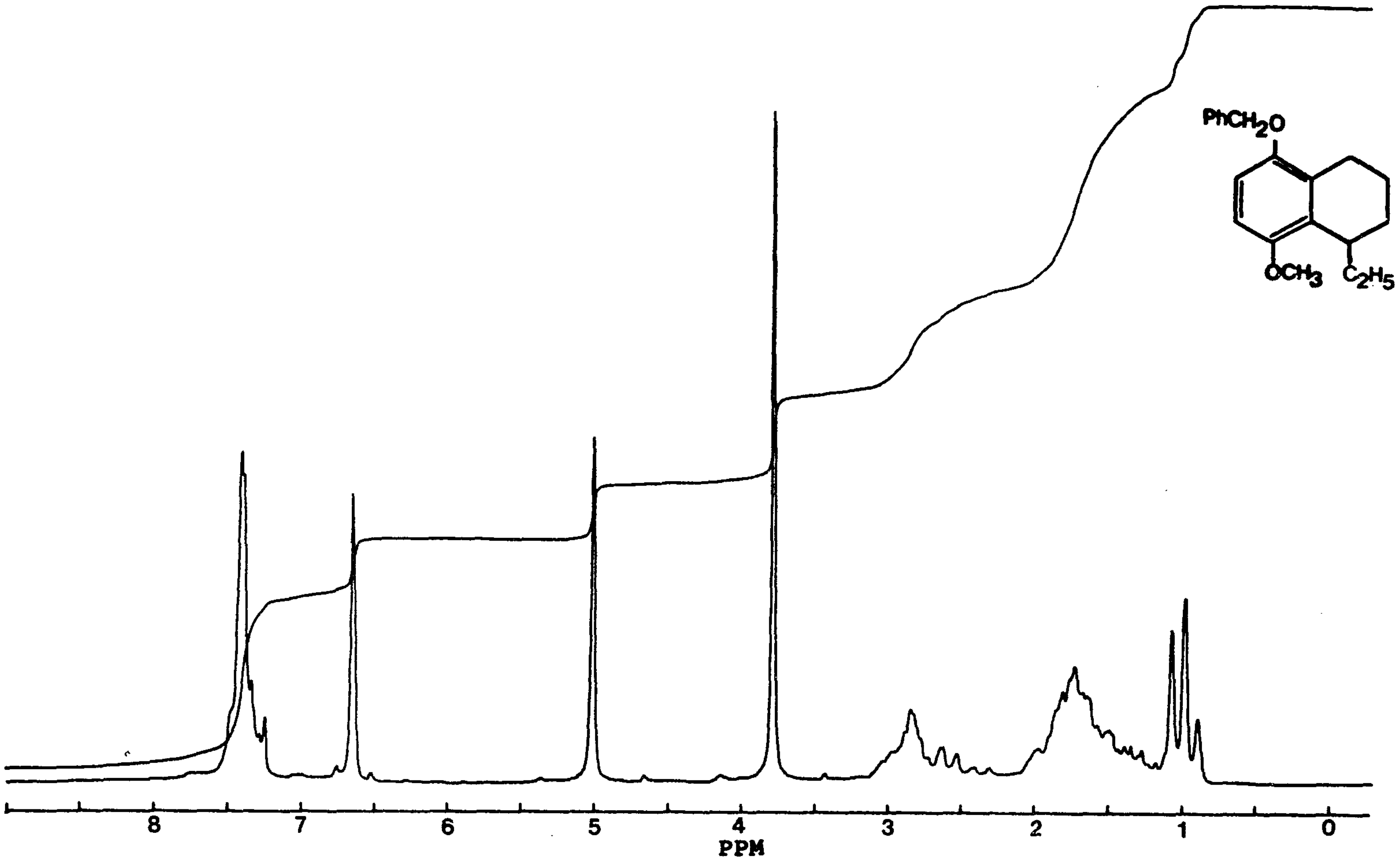


Figure 48. 80 MHz ^{1}H NMR Spectrum of VIf

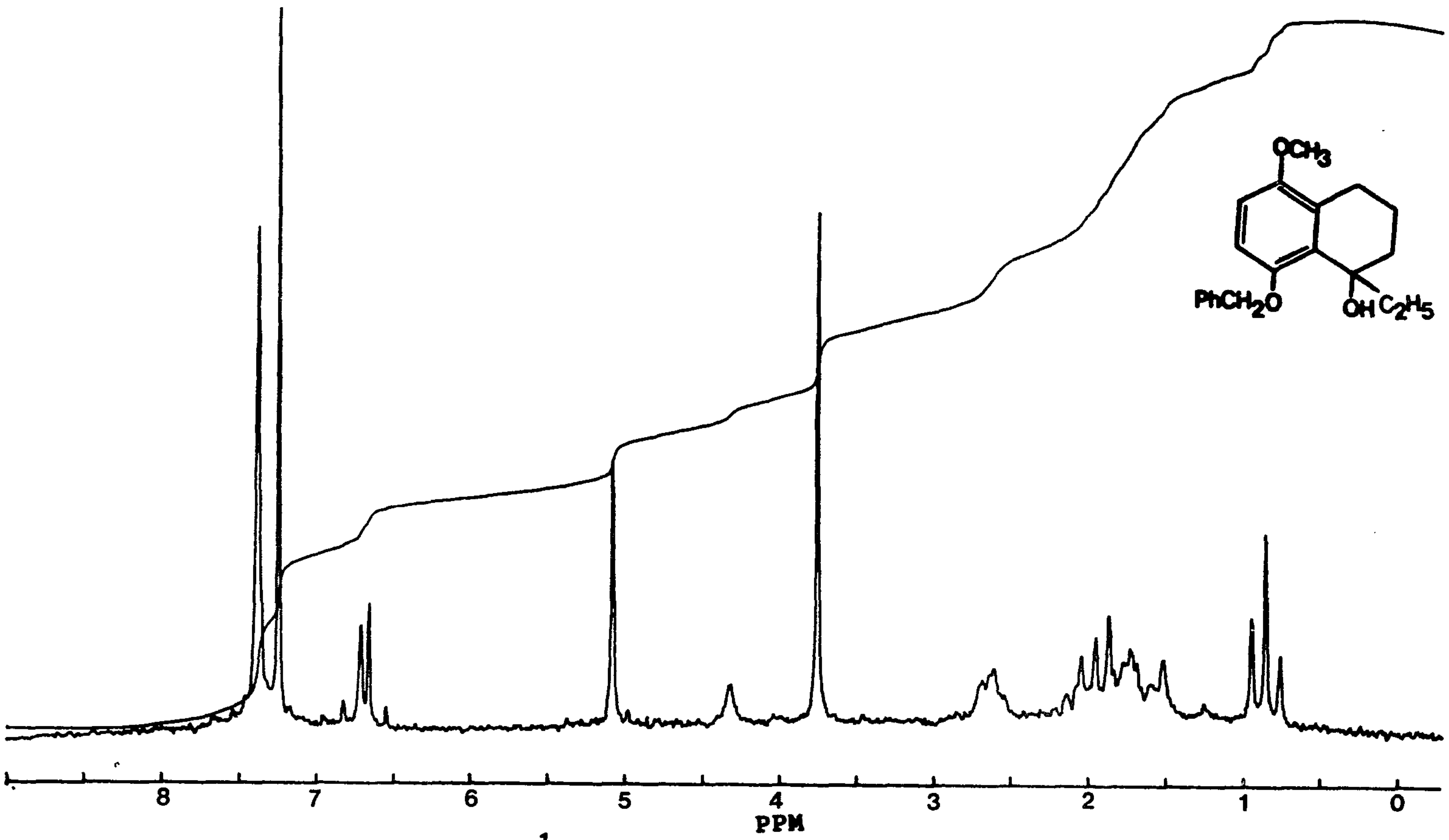


Figure 49. 80 MHz ^{1}H NMR Spectrum of Ethyl Grignard Addition of VII

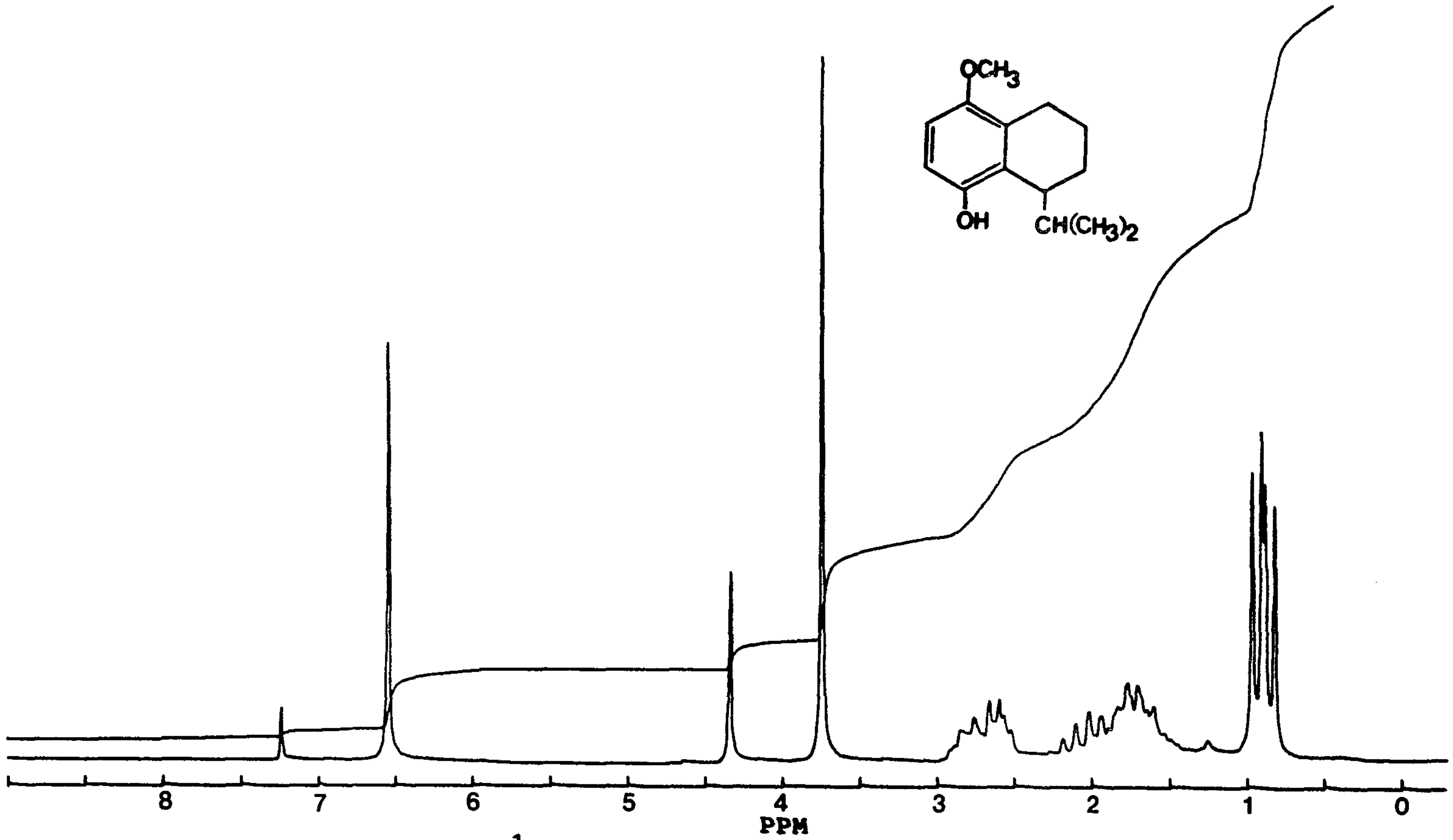


Figure 50. 80 MHz ^{1}H NMR Spectrum of $NaBH_4$ Reduction of 13g and 14g

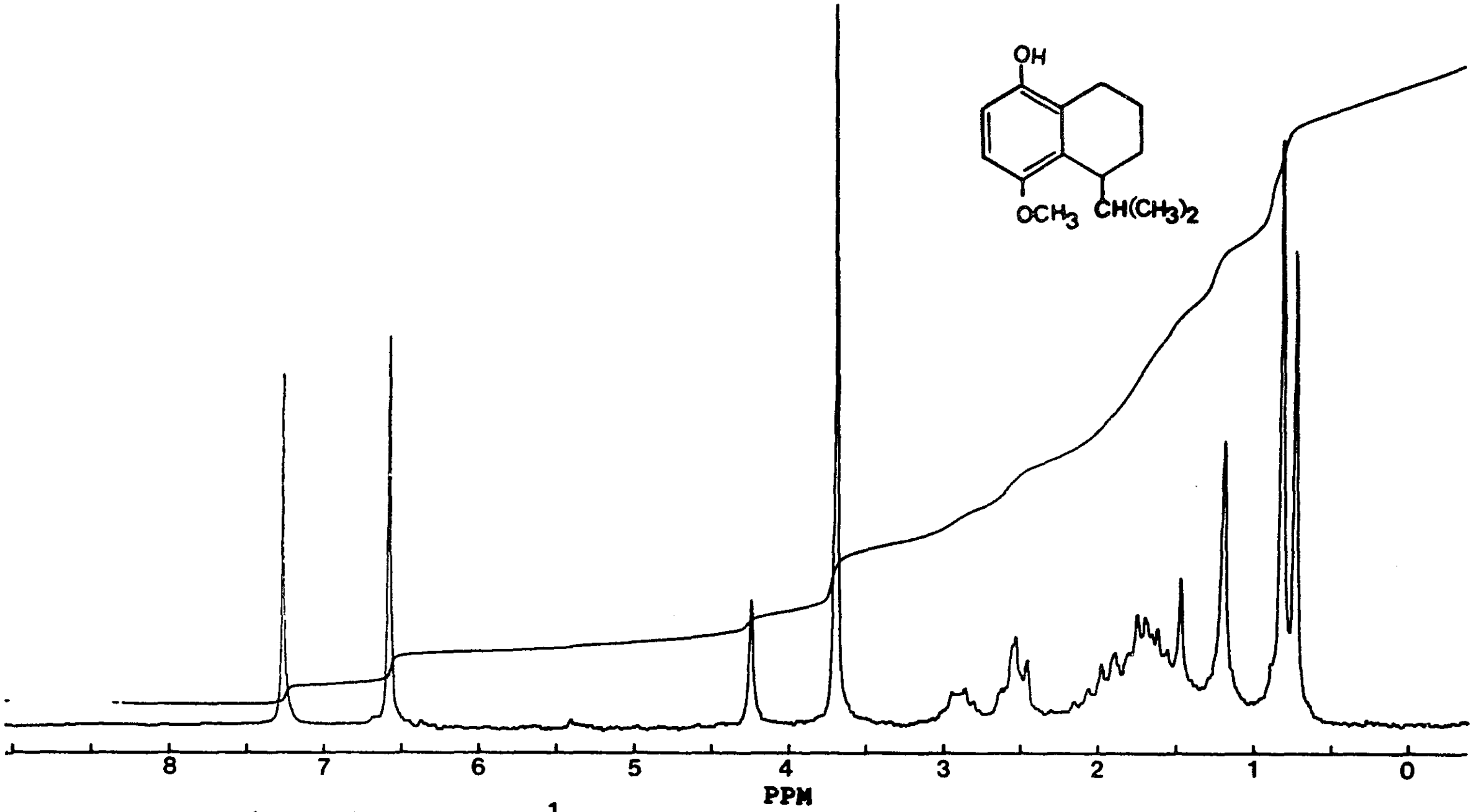


Figure 51. 80 MHz ^{1}H NMR Spectrum of $NaBH_4$ Reduction of 13g and 14g

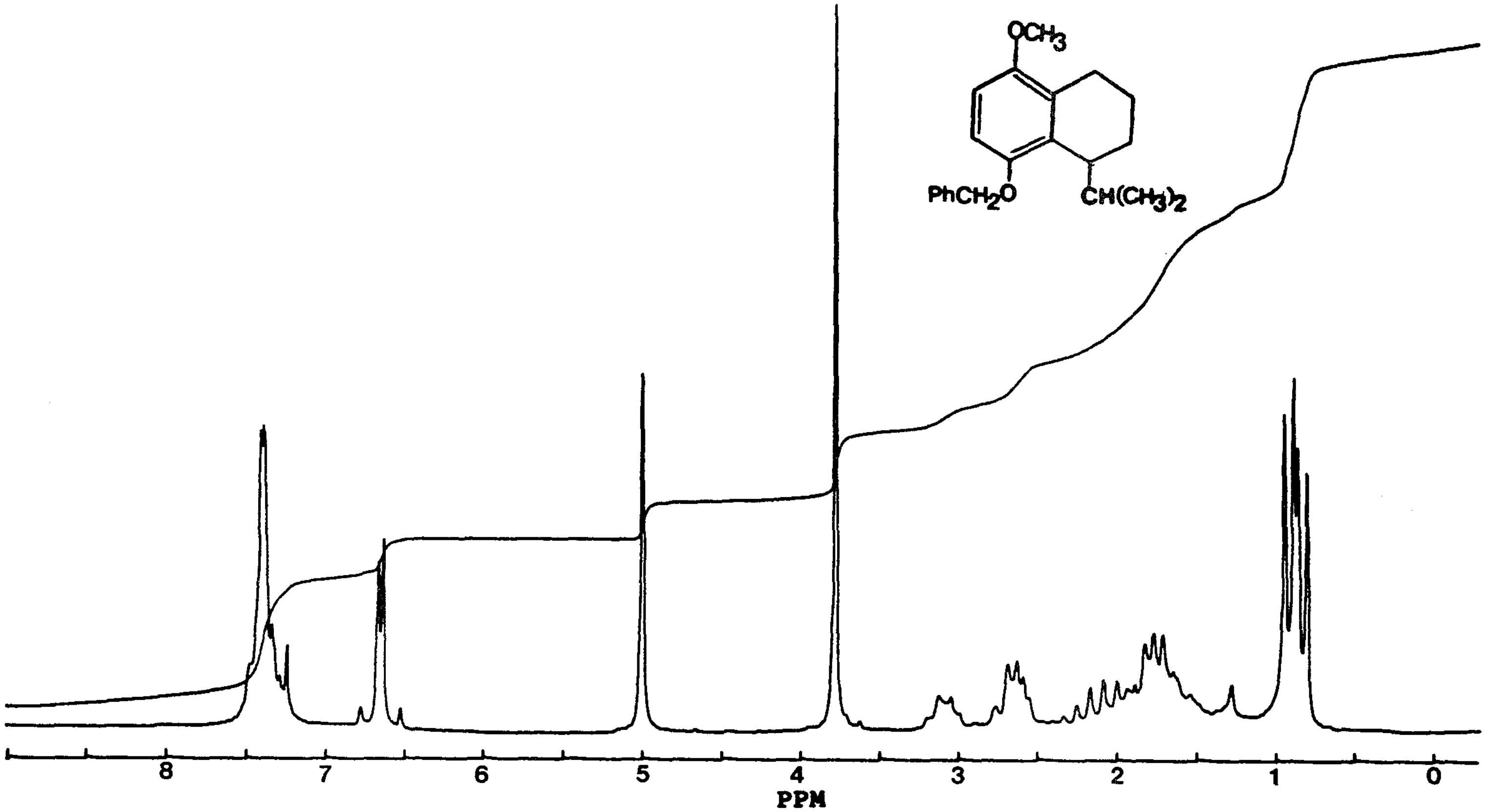


Figure 52. 80 MHz ^{1}H NMR Spectrum of Vg

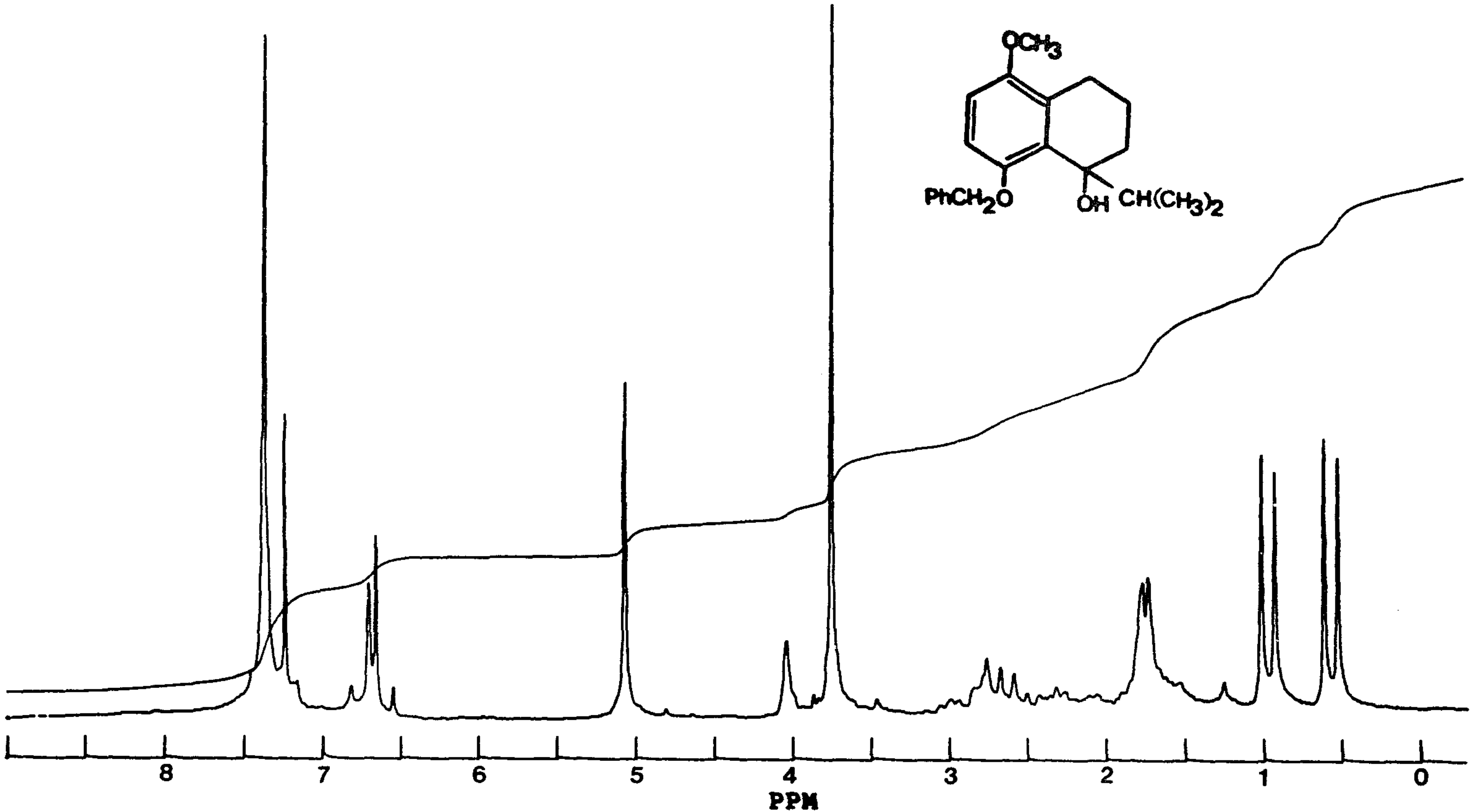


Figure53. 80 MHz ^{1}H NMR Spectrum of Isopropryl Grignard Added to VII

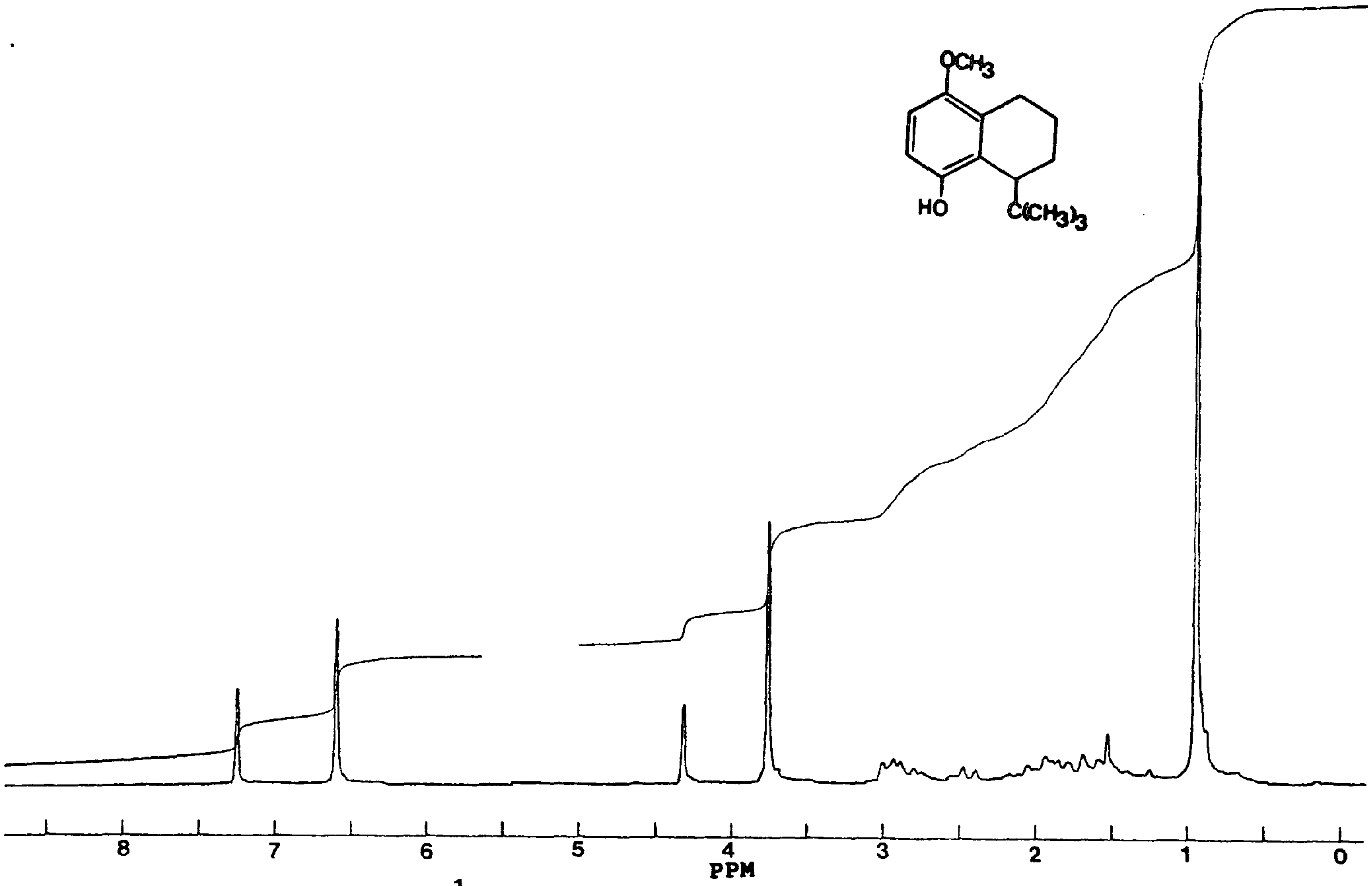


Figure 54. 80 MHz ^{1}H NMR Spectrum of NaBh$_4$ Addition to 13h and 14h

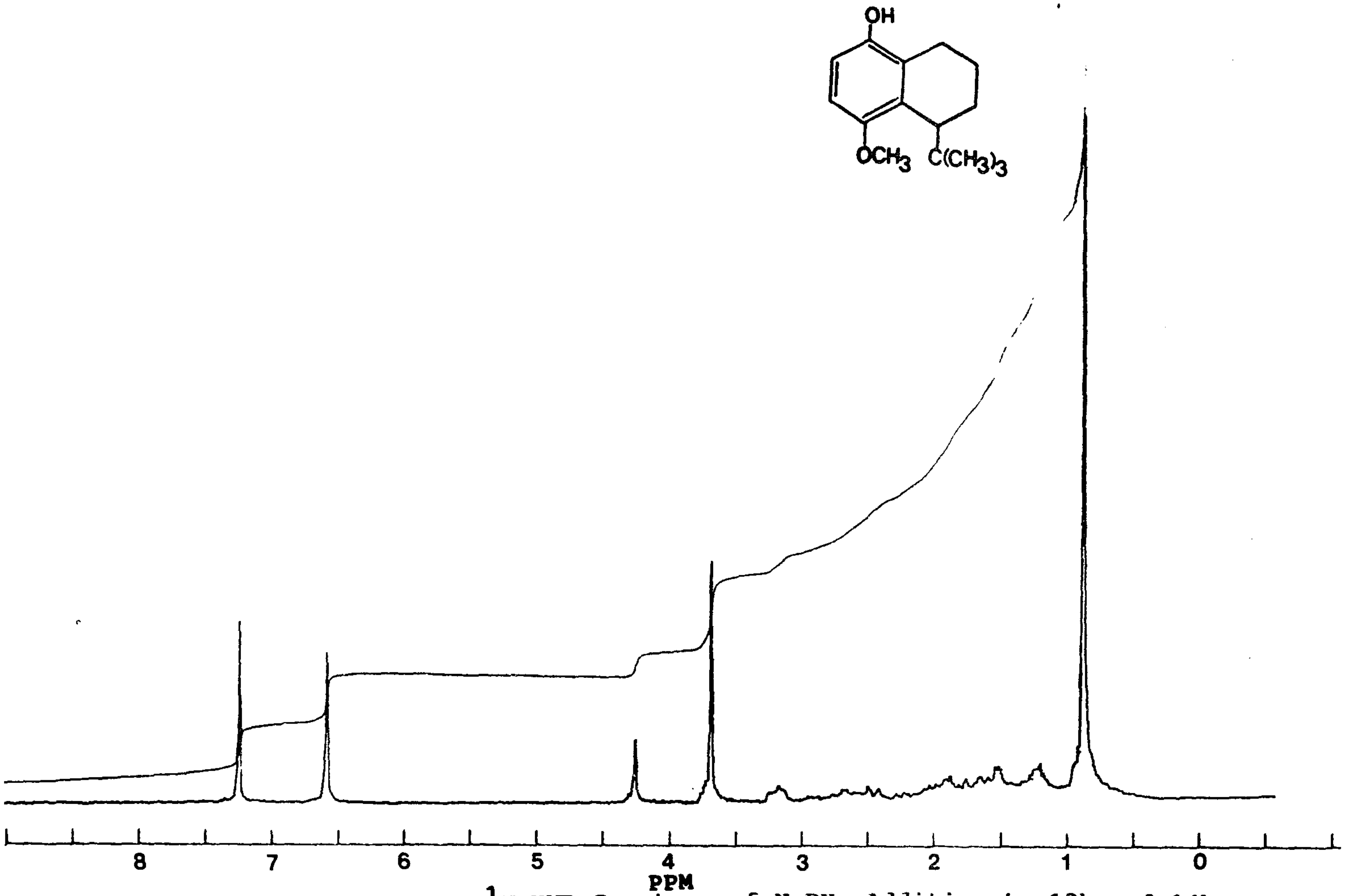


Figure 55. 80 MHz ^{1}H NMR Spectrum of NaBH$_4$ Addition to 13h and 14h

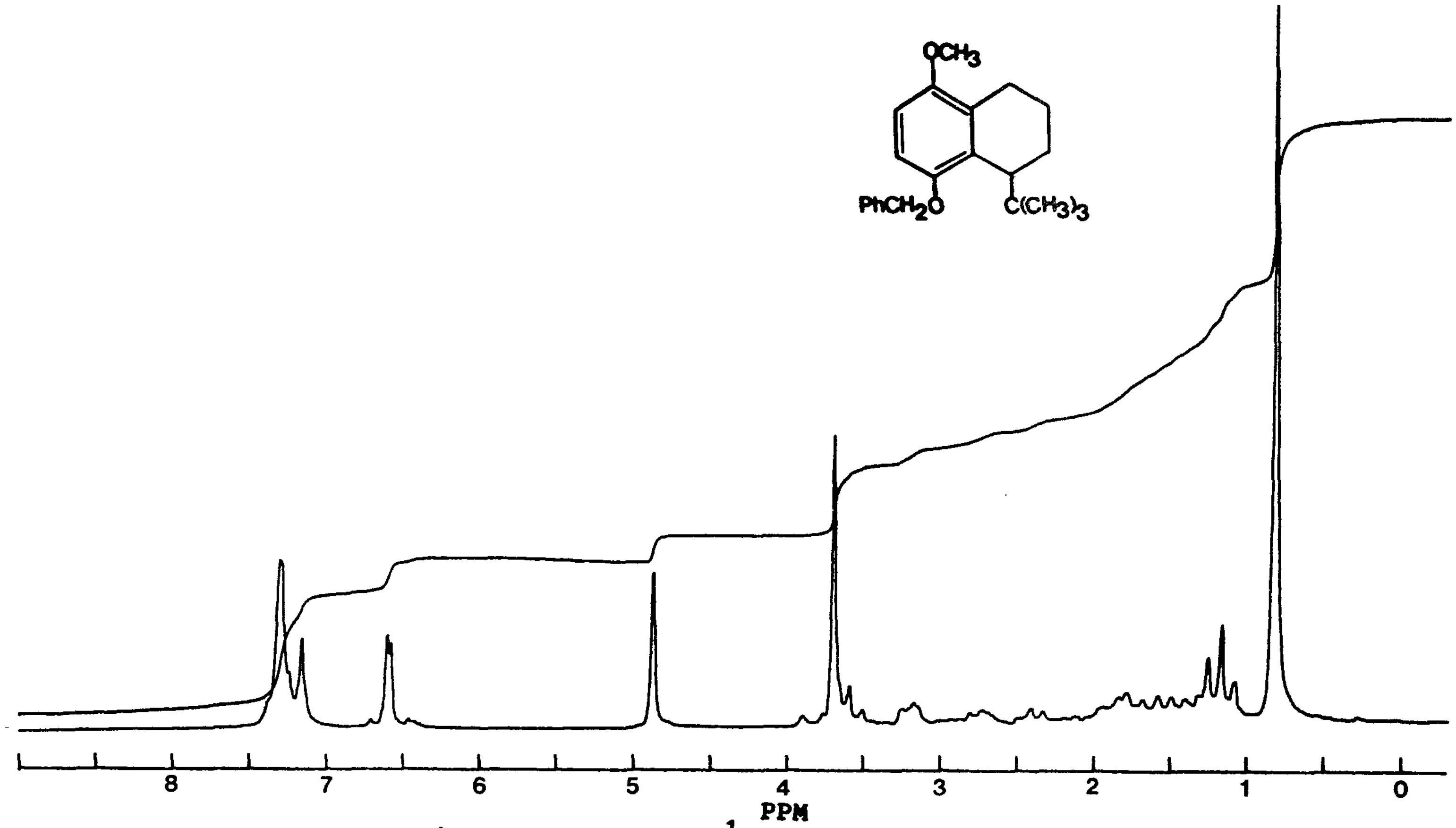


Figure 56. 80 MHz ^{1}H NMR Spectrum of Vh

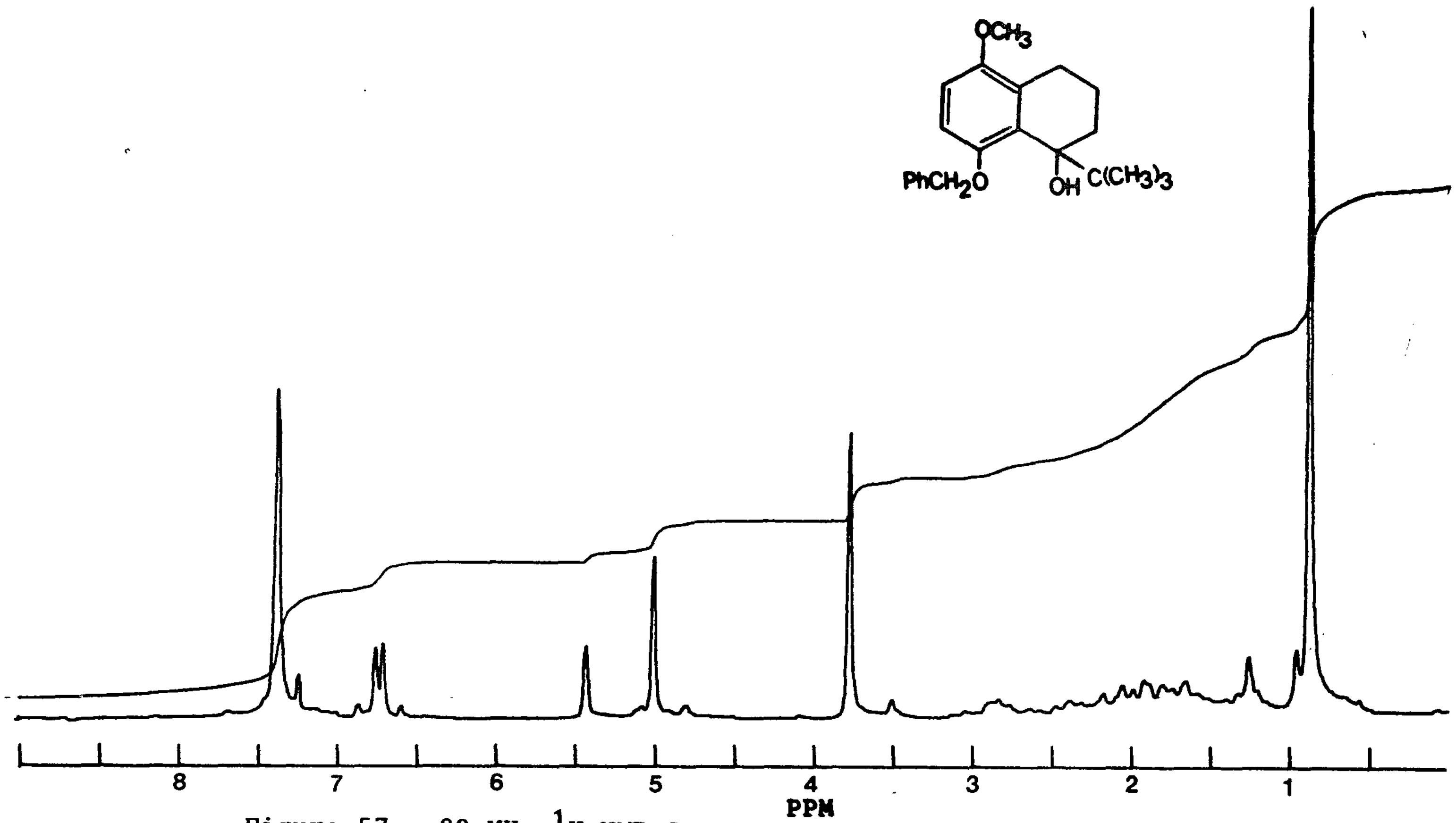


Figure 57. 80 MHz ^{1}H NMR Spectrum of t-BuLi Addition to VII

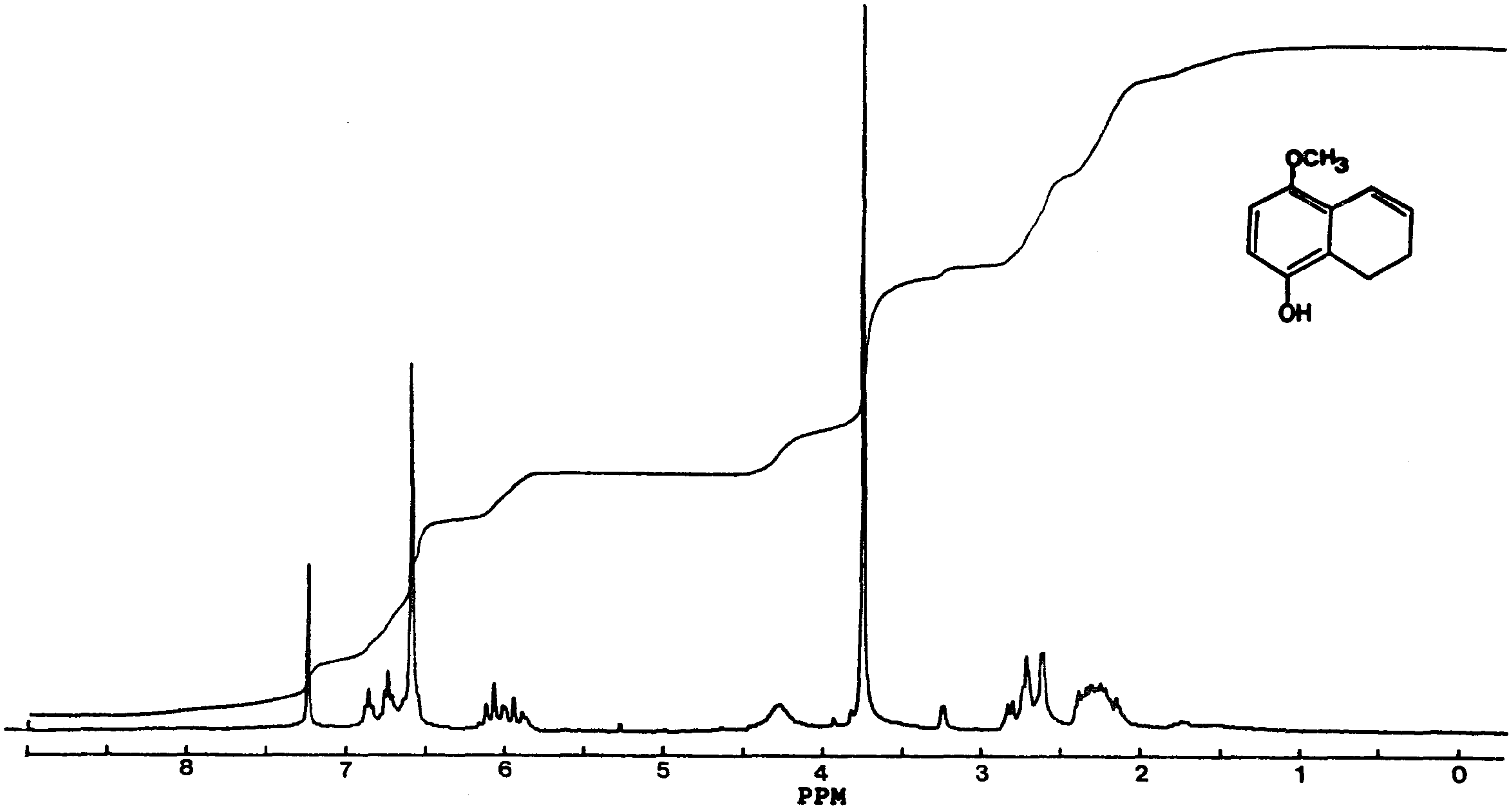


Figure 58. 80 MHz ^{1}H NMR Spectrum of 18j

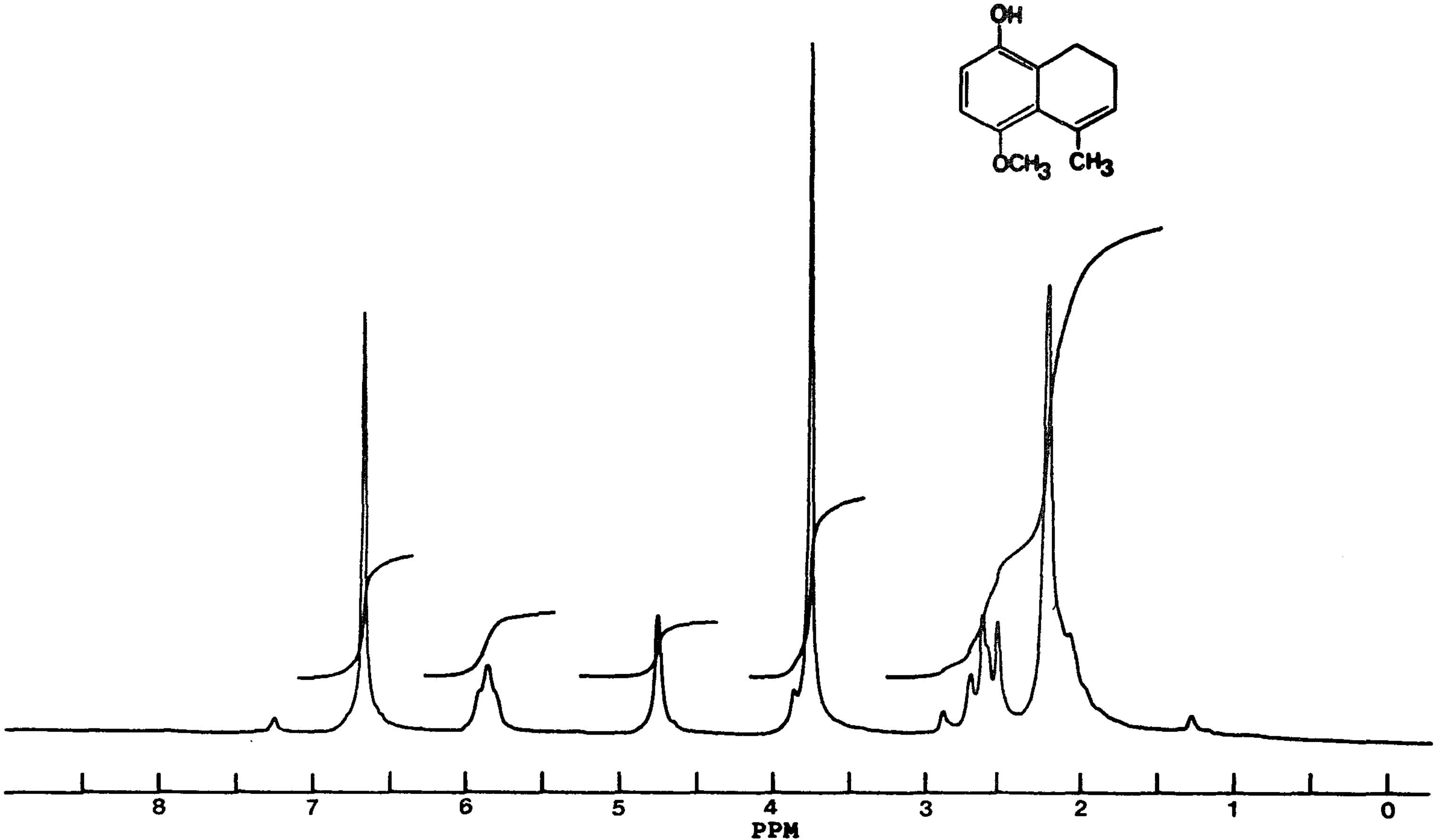
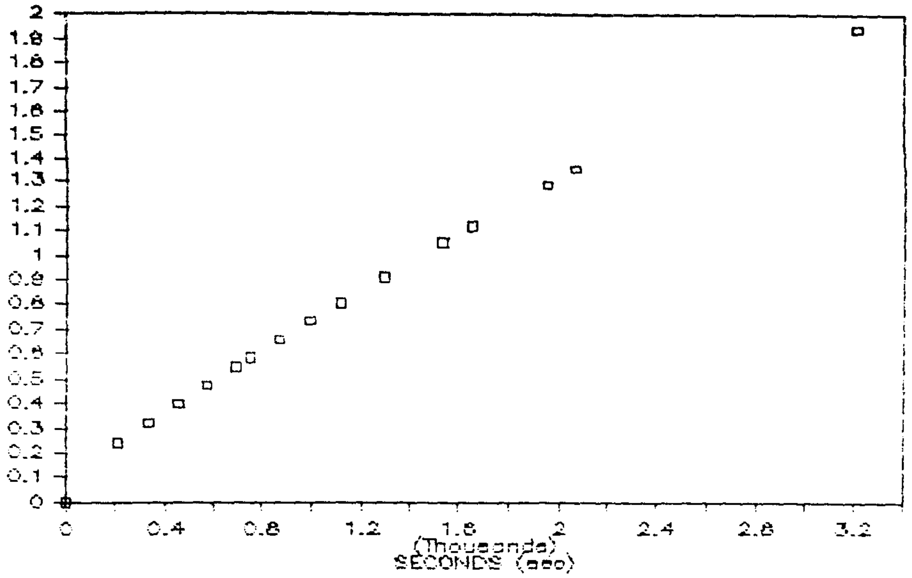


Figure 59. 80 MHz ^{1}H NMR Spectrum of 17k

KINETIC DATA



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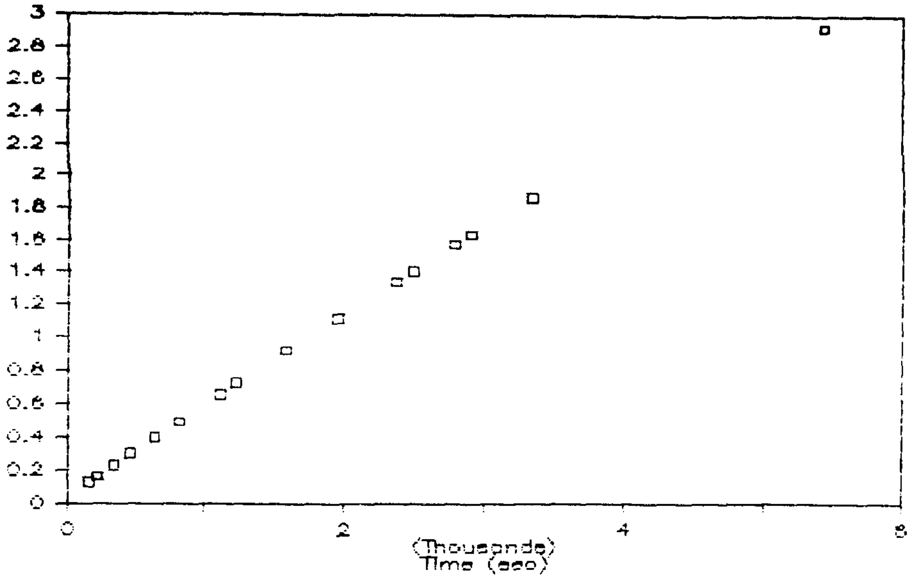
330	0.045			0.3216	0.000568	0.1617
450	0.053			0.3974	0.000564	0.1689
570	0.061			0.4735	0.000560	0.1763
690	0.068			0.5463	0.000557	0.1836
750	0.072			0.5853	0.000553	0.1915
870	0.078			0.6574	0.000549	0.2011
990	0.084			0.7314	0.000544	0.2125
1110	0.090			0.8057	0.000538	0.2255
1290	0.097			0.9101	0.000532	0.2405
1530	0.106			1.0546	0.000525	0.2589
1650	0.109			1.1185	0.000521	0.2681
1950	0.118			1.2884	0.000514	0.2893
2070	0.121			1.3553	0.000511	0.2976
3210	0.139			1.9379	ERR	ERR

Figure 60. Kinetic Data for Structure **11**

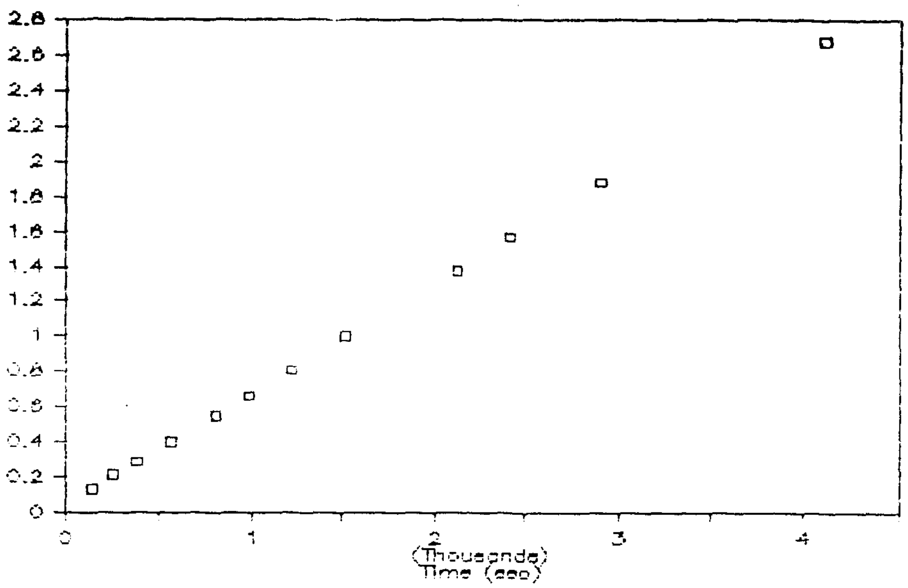
Concentration 6.12 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
150	0.147	1767	1.258	0.1239	0.000534	0.0650
210	0.187			0.1612	0.000533	0.0688
330	0.259			0.2308	0.000531	0.0728
450	0.325			0.2989	0.000530	0.0770
630	0.413			0.3975	0.000529	0.0817
810	0.492			0.4966	0.000527	0.0874
1110	0.609			0.6613	0.000525	0.0945
1230	0.650			0.7277	0.000523	0.1017
1590	0.758			0.9234	0.000520	0.1120
1950	0.847			1.1186	0.000517	0.1226
2370	0.930			1.3454	0.000515	0.1324
2490	0.951			1.4104	0.000513	0.1380
2790	0.996			1.5704	0.000512	0.1448
2910	1.012			1.6331	0.000511	0.1488
3330	1.061			1.8545	0.000509	0.1593
5430	1.190			2.9236	ERR	ERR

Figure 61. Kinetic Data for Structure **11**

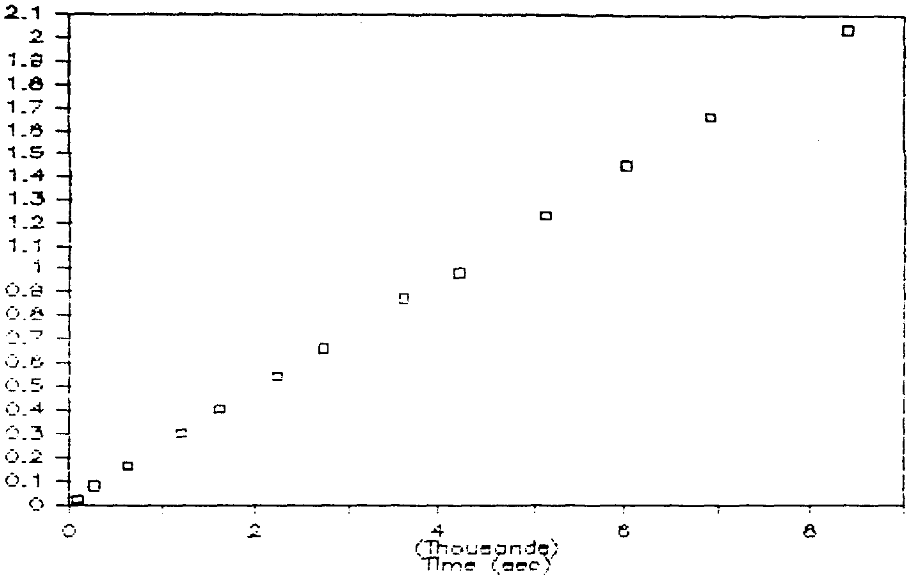
Concentration 7.12 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
142	0.149	1727	1.231	0.1289	0.000639	0.0357
262	0.234			0.2112	0.000640	0.0351
382	0.307			0.2871	0.000641	0.0326
562	0.406			0.3998	0.000642	0.0290
802	0.521			0.5508	0.000644	0.0244
982	0.596			0.6624	0.000646	0.0186
1222	0.684			0.8116	0.000648	0.0109
1522	0.779			1.0012	0.000651	0.0009
2122	0.922			1.3819	0.000657	-0.016
2422	0.976			1.5727	0.000660	-0.029
2902	1.044			1.8823	0.000665	-0.046
4102	1.147			2.6800	ERR	ERR

Figure 62. Kinetic Data for Structure **11**

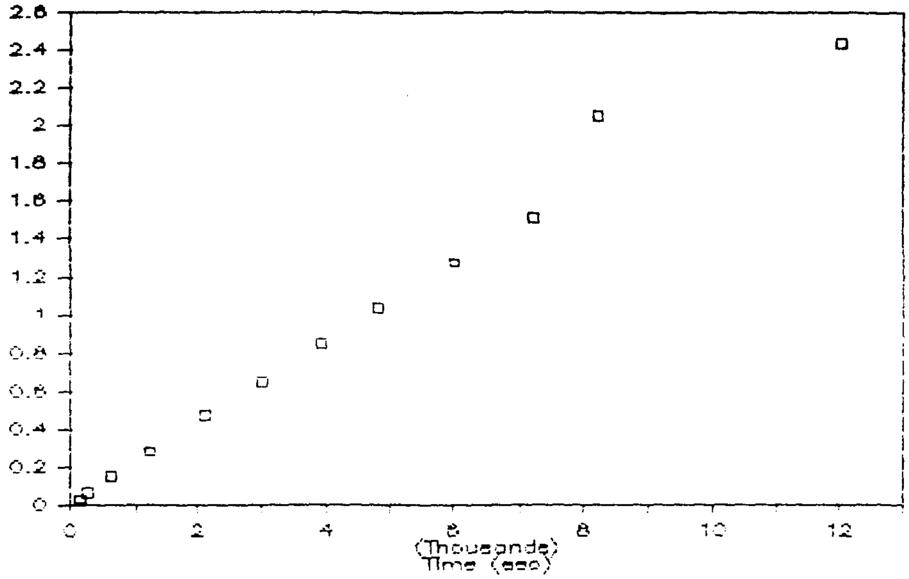
Concentration 7.09 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
80	0.015	924	0.61	0.0254	0.000239	0.0089
260	0.045			0.0764	0.000239	0.0096
620	0.093			0.1646	0.000240	0.0081
1220	0.161			0.3062	0.000240	0.0050
1640	0.204			0.4068	0.000241	0.0010
2240	0.257			0.5481	0.000242	-0.005
2720	0.295			0.6605	0.000243	-0.015
3620	0.355			0.8733	0.000246	-0.033
4220	0.382			0.9836	0.000250	-0.060
5120	0.432			1.2316	0.000246	-0.029
6020	0.467			1.4485	0.000248	-0.047
6920	0.495			1.6650	0.000252	-0.077
8420	0.531			2.0427	ERR	ERR

Figure 63. Kinetic Data for Structure **12a**

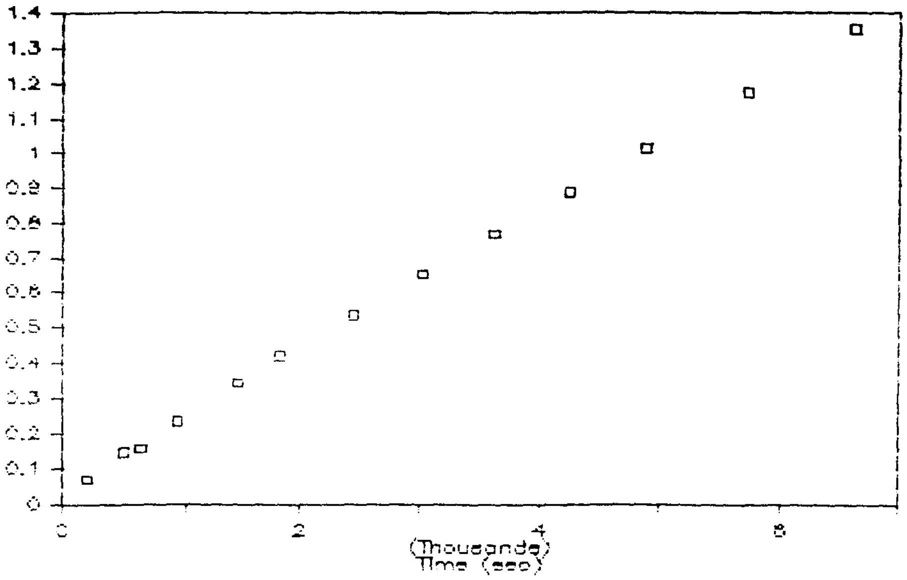
Concentration 6.60 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
140	0.019	949	0.62	0.0311	0.000213	0.0177
260	0.037			0.0622	0.000213	0.0216
620	0.084			0.1450	0.000212	0.0261
1220	0.149			0.2757	0.000212	0.0310
2120	0.232			0.4694	0.000211	0.0379
3020	0.294			0.6440	0.000210	0.0477
3920	0.354			0.8465	0.000206	0.0784
4820	0.399			1.0329	0.000201	0.1238
6020	0.447			1.2787	0.000190	0.2281
7220	0.484			1.5200	0.000167	0.4764
8240	0.541			2.0564	0.000101	1.2228
12020	0.566			2.4388	ERR	ERR

Figure 64. Kinetic Data for Structure **12a**

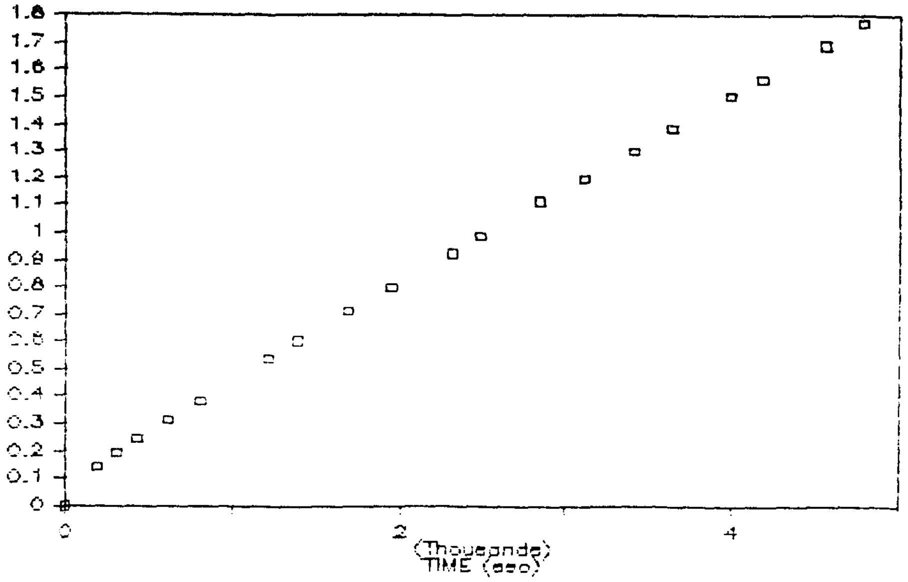
Concentration 6.53 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
210	0.041	930	0.62	0.0682	0.000198	0.0452
510	0.085			0.1482	0.000197	0.0501
630	0.090			0.1566	0.000197	0.0509
930	0.130			0.2344	0.000195	0.0585
1470	0.181			0.3452	0.000195	0.0616
1830	0.213			0.4216	0.000194	0.0634
2430	0.257			0.5344	0.000195	0.0609
3030	0.297			0.6529	0.000195	0.0609
3630	0.332			0.7681	0.000195	0.0576
4230	0.364			0.8841	0.000196	0.0545
4890	0.395			1.0131	0.000197	0.0508
5730	0.429			1.1753	0.000200	0.0305
6630	0.460			1.3551	ERR	ERR

Figure 65. Kinetic Data for Structure **12a**

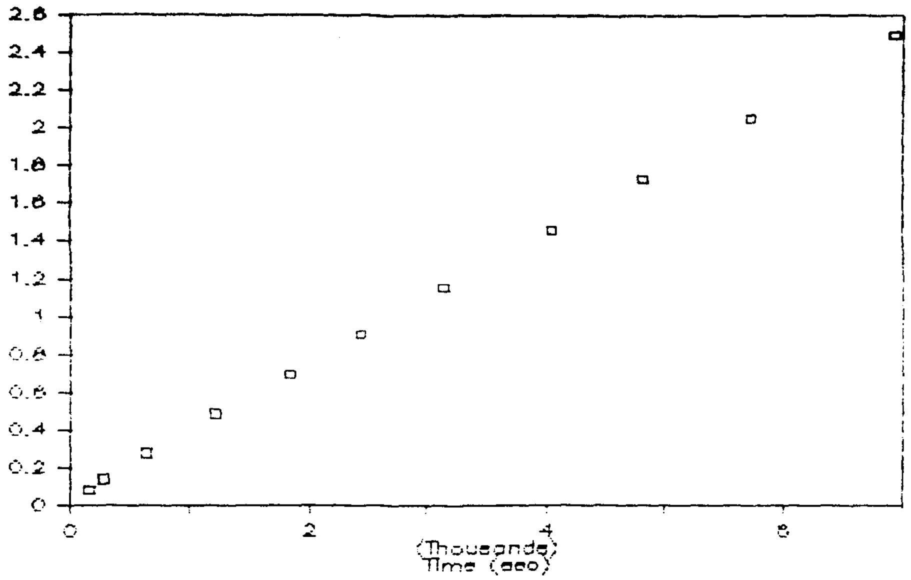
Concentration 6.09 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
210	0.0749	826	0.573	0.1398	0.000355	0.0915
330	0.101			0.1944	0.000354	0.0970
450	0.125			0.2448	0.000352	0.1016
630	0.155			0.3146	0.000351	0.1060
810	0.183			0.3840	0.000350	0.1104
1230	0.239			0.5375	0.000348	0.1145
1410	0.260			0.6025	0.000348	0.1173
1710	0.291			0.7089	0.000347	0.1203
1950	0.315			0.7946	0.000346	0.1237
2310	0.346			0.9220	0.000345	0.1273
2490	0.360			0.9858	0.000344	0.1301
2850	0.385			1.1115	0.000344	0.1332
3090	0.400			1.1943	0.000343	0.1354
3390	0.417			1.2979	0.000342	0.1396
3630	0.430			1.3831	0.000341	0.1467
3990	0.446			1.5049	0.000341	0.1443
4170	0.454			1.5664	0.000340	0.1479

Figure 66. Kinetic Data for Structure **12b**

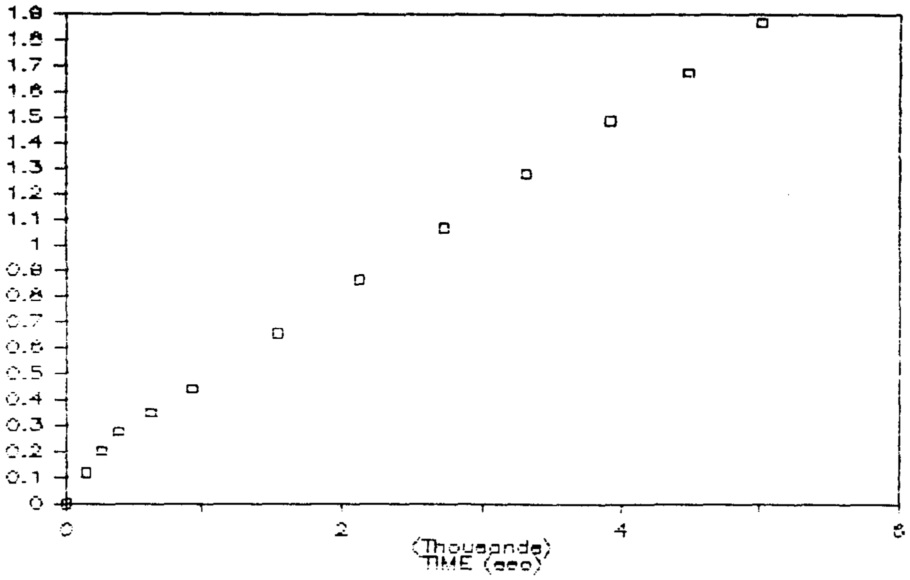
Concentration 6.95 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
150	0.067	882	0.85	0.0824	0.000353	0.0416
270	0.108			0.1353	0.000352	0.0453
630	0.204			0.2750	0.000351	0.0474
1230	0.327			0.4848	0.000352	0.0439
1830	0.425			0.6922	0.000353	0.0381
2430	0.504			0.8990	0.000355	0.0303
3150	0.581			1.1494	0.000357	0.0195
4050	0.653			1.4620	0.000360	0.0014
4830	0.700			1.7372	0.000363	-0.016
5730	0.741			2.0575	0.000367	-0.046
6930	0.780			2.4981	ERR	ERR

Figure 67. Kinetic Data for Structure **12b**

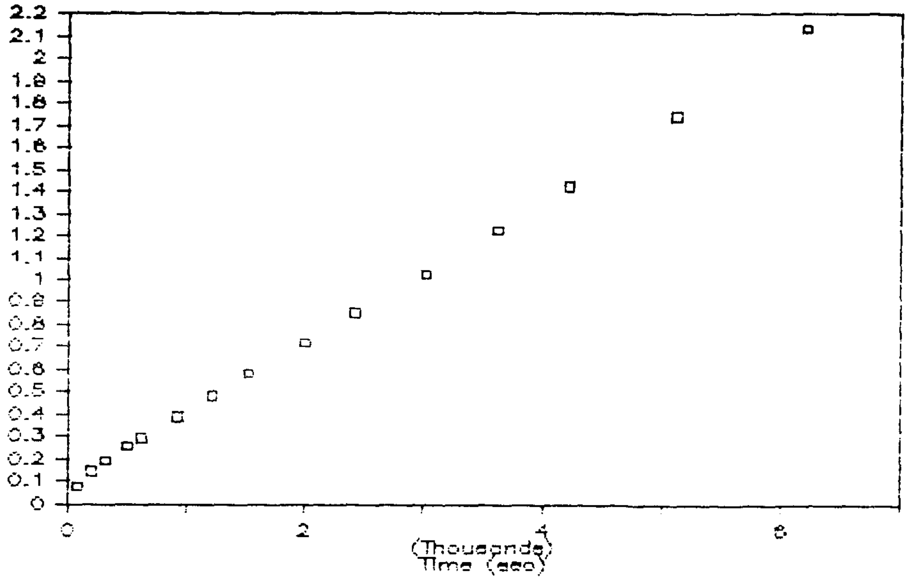
Concentration 1.71×10^{-3} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
145	0.103	941	0.929	0.1179	0.000351	0.1142
265	0.172			0.2040	0.000348	0.1266
385	0.225			0.2765	0.000346	0.1315
625	0.276			0.3516	0.000348	0.1263
925	0.332			0.4412	0.000349	0.1215
1525	0.447			0.6546	0.000348	0.1247
2125	0.539			0.8661	0.000348	0.1265
2725	0.612			1.0750	0.000348	0.1257
3325	0.672			1.2830	0.000349	0.1224
3925	0.720			1.4910	0.000350	0.1149
4470	0.756			1.6798	0.000355	0.0948
5010	0.787			1.8713	ERR	ERR

Figure 68. Kinetic Data for Structure **12b**

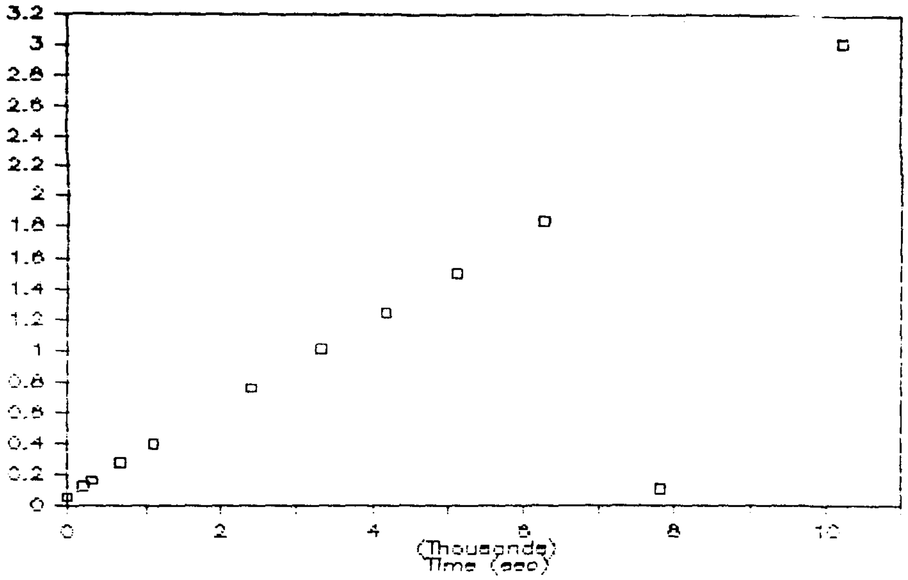
Concentration 1.71 X 10^{-3} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
80	0.049	972	0.65	0.0782	0.000325	0.0768
200	0.087			0.1435	0.000324	0.0812
320	0.114			0.1919	0.000324	0.0817
500	0.146			0.2549	0.000324	0.0800
620	0.166			0.2940	0.000325	0.0763
920	0.209			0.3883	0.000326	0.0704
1220	0.249			0.4830	0.000328	0.0625
1520	0.287			0.5833	0.000331	0.0509
2000	0.334			0.7212	0.000336	0.0275
2420	0.372			0.8504	0.000341	0.0040
3020	0.417			1.0272	0.000348	-0.032
3620	0.460			1.2273	0.000352	-0.054
4220	0.494			1.4239	0.000358	-0.090
5120	0.536			1.7398	0.000364	-0.124
6200	0.573			2.1331	ERR	ERR

Figure 69. Kinetic Data for Structure **12c**

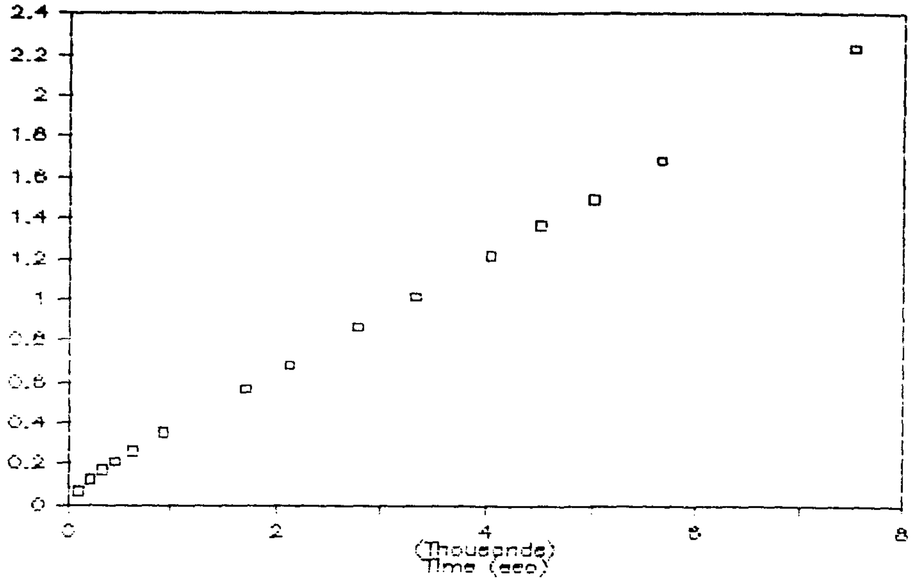
Concentration 6.95 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
78	0.036	967	0.674	0.0545	0.000209	0.1499
198	0.074			0.1166	0.000205	0.1710
318	0.101			0.1626	0.000201	0.1968
678	0.163			0.2760	0.000196	0.2317
1098	0.221			0.3971	0.000190	0.2743
2418	0.358			0.7587	0.000181	0.3356
3318	0.428			1.0074	0.000179	0.3487
4158	0.479			1.2392	0.000189	0.2726
5118	0.524			1.5019	0.000228	-0.064
6258	0.567			1.8366	0.000377	-1.398
7818	0.066			0.1028	0.001217	-9.408
10218	0.641			3.0228	ERR	ERR

Figure 70. Kinetic Data for Structure **12c**

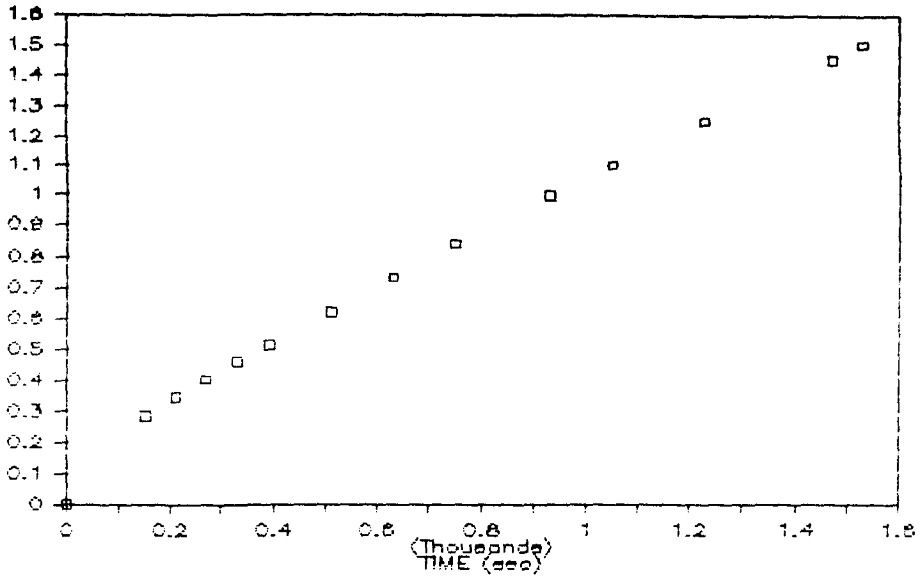
Concentration 6.99 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
85	0.043	950	0.675	0.0651	0.000286	0.0717
205	0.079			0.1243	0.000285	0.0774
325	0.105			0.1696	0.000284	0.0798
445	0.128			0.2095	0.000284	0.0805
625	0.156			0.2622	0.000284	0.0797
925	0.200			0.3513	0.000285	0.0776
1705	0.293			0.5695	0.000286	0.0715
2125	0.335			0.6854	0.000287	0.0643
2785	0.392			0.8678	0.000289	0.0541
3325	0.431			1.0159	0.000291	0.0438
4045	0.475			1.2158	0.000292	0.0354
4525	0.503			1.3689	0.000292	0.0388
5005	0.523			1.4928	0.000296	0.0076
5665	0.550			1.6832	0.000298	-0.006
7525	0.603			2.2380	ERR	ERR

Figure 71. Kinetic Data for Structure **12c**

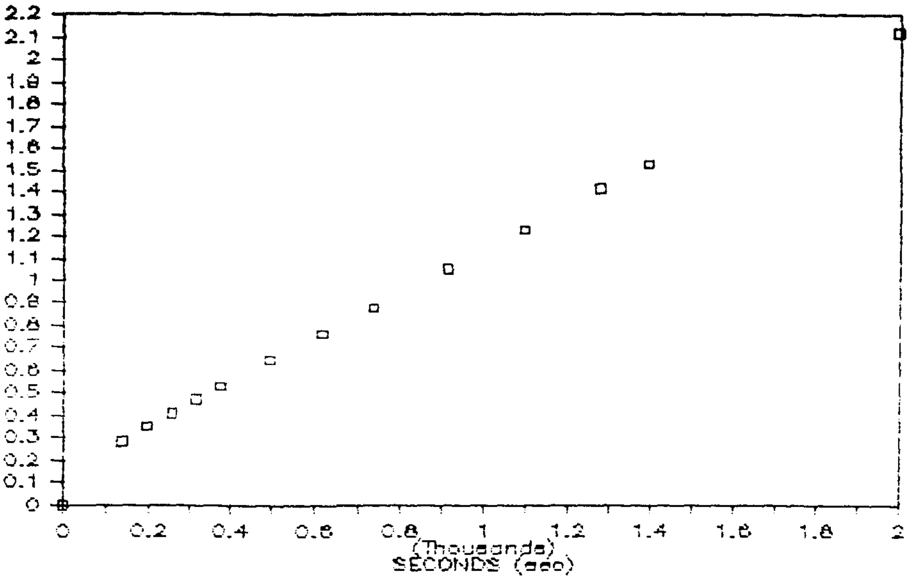
Concentration 7.11 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
150	0.040	195	0.163	0.2840	0.000882	0.1665
210	0.048			0.3443	0.000878	0.1707
270	0.054			0.4021	0.000875	0.1744
330	0.060			0.4585	0.000872	0.1781
390	0.066			0.5132	0.000868	0.1820
510	0.076			0.6222	0.000864	0.1876
630	0.085			0.7305	0.000859	0.1937
750	0.093			0.8377	0.000854	0.2001
930	0.103			0.9952	0.000849	0.2075
1050	0.109			1.0998	0.000844	0.2134
1230	0.117			1.2524	0.000842	0.2168
1470	0.125			1.4559	0.000807	0.2702
1530	0.127			1.5043	ERR	ERR

Figure 72. Kinetic Data for Structure **12e**

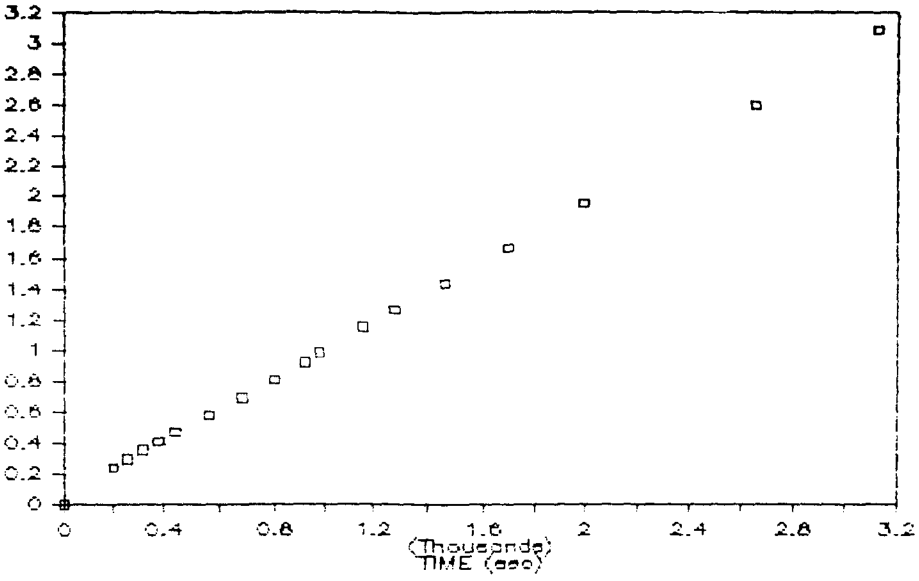
Concentration 8.40 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
135	0.305	1450	1.242	0.2811	0.000981	0.1584
195	0.366			0.3492	0.000979	0.1608
255	0.419			0.4115	0.000978	0.1615
315	0.467			0.4716	0.000979	0.1613
375	0.513			0.5324	0.000979	0.1604
495	0.592			0.6474	0.000981	0.1577
615	0.663			0.7627	0.000983	0.1548
735	0.726			0.8781	0.000985	0.1518
915	0.809			1.0519	0.000987	0.1487
1095	0.879			1.2287	0.000987	0.1489
1275	0.940			1.4113	0.000985	0.1518
1395	0.972			1.5229	0.000992	0.1384
1995	1.093			2.1184	ERR	ERR

Figure 73. Kinetic Data for Structure **12e**

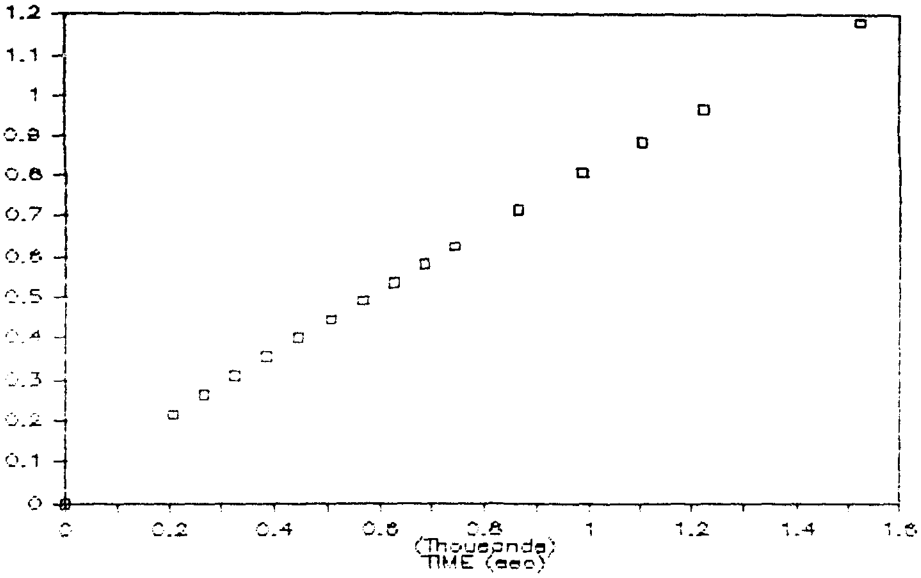
Concentration 8.34 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
198	0.255	1480	1.233	0.2316	0.000966	0.0345
258	0.310			0.2900	0.000967	0.0335
318	0.363			0.3485	0.000967	0.0322
378	0.412			0.4061	0.000968	0.0303
438	0.457			0.4626	0.000970	0.0279
558	0.540			0.5760	0.000971	0.0250
678	0.614			0.6897	0.000972	0.0220
798	0.681			0.8042	0.000974	0.0189
918	0.741			0.9179	0.000975	0.0153
978	0.768			0.9753	0.000977	0.0116
1158	0.842			1.1492	0.000979	0.0059
1278	0.884			1.2629	0.000982	-0.001
1458	0.939			1.4336	0.000987	-0.013
1698	0.999			1.6631	0.000993	-0.030
1998	1.058			1.9507	0.001003	-0.059
2658	1.141			2.5943	0.001047	-0.189
3128	1.177			3.0865	ERR	ERR

Figure 74. Kinetic Data for Structure **12e**

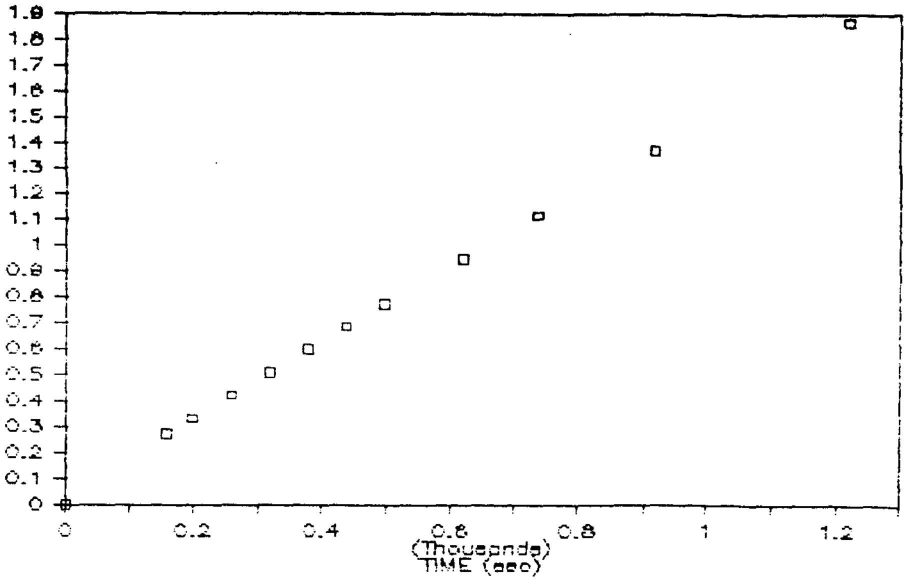
Concentration 8.86 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
205	0.238	1472	1.23	0.2147	0.000733	0.0735
265	0.284			0.2629	0.000730	0.0761
325	0.329			0.3108	0.000728	0.0783
385	0.368			0.3551	0.000727	0.0798
445	0.407			0.4013	0.000725	0.0818
505	0.441			0.4441	0.000723	0.0833
565	0.477			0.4903	0.000721	0.0861
625	0.509			0.5339	0.000719	0.0884
685	0.541			0.5793	0.000716	0.0919
745	0.571			0.6241	0.000713	0.0958
865	0.626			0.7118	0.000709	0.1014
985	0.679			0.8035	0.000703	0.1086
1105	0.722			0.8848	0.000711	0.0983
1225	0.762			0.9669	0.000719	0.0866
1525	0.853			1.1825	ERR	ERR

Figure 75. Kinetic Data for Structure **12e**

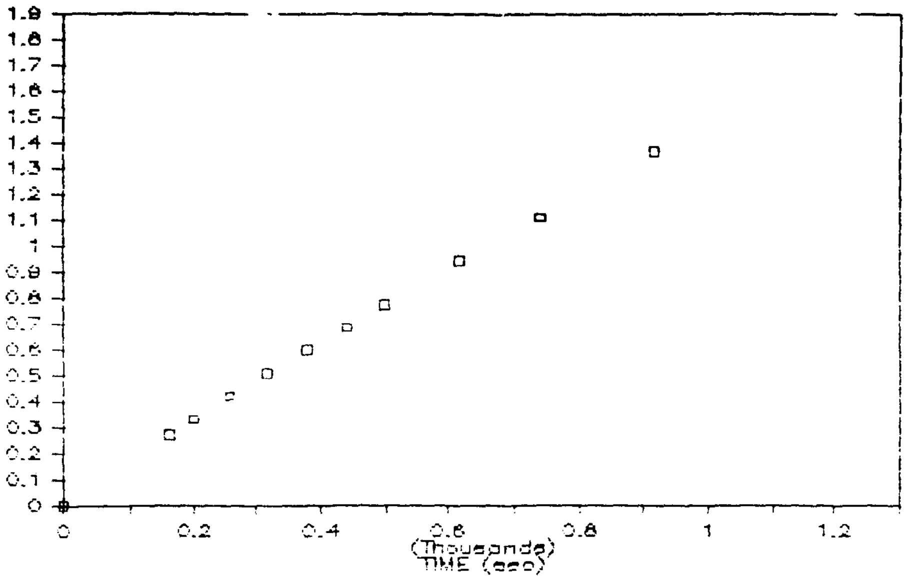
Concentration 8.36 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
158	0.296	1780	1.25	0.2698	0.001488	0.0330
198	0.353			0.3319	0.001488	0.0325
258	0.430			0.4214	0.001491	0.0305
318	0.500			0.5102	0.001495	0.0274
378	0.563			0.5990	0.001500	0.0227
438	0.621			0.6866	0.001508	0.0153
498	0.673			0.7732	0.001520	0.0033
618	0.765			0.9461	0.001544	-0.020
738	0.841			1.1169	0.001580	-0.060
918	0.934			1.3738	0.001658	-0.148
1218	1.058			1.8713	ERR	ERR

Figure 76. Kinetic Data for Structure **12h**

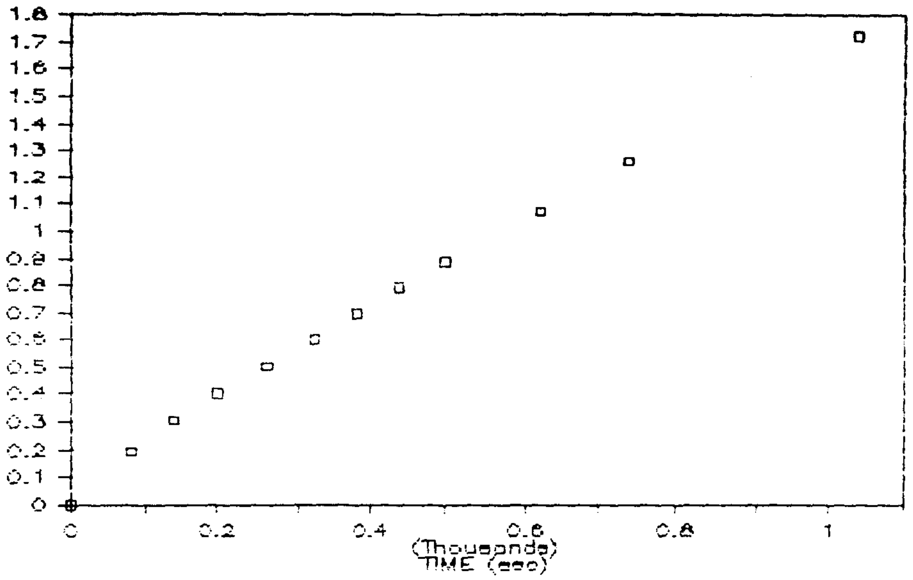
Concentration 6.94 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
158	0.296	1780	1.25	0.2698	0.001488	0.0330
198	0.353			0.3319	0.001488	0.0325
258	0.430			0.4214	0.001491	0.0305
318	0.500			0.5102	0.001495	0.0274
378	0.563			0.5990	0.001500	0.0227
438	0.621			0.6866	0.001508	0.0153
498	0.673			0.7732	0.001520	0.0033
618	0.765			0.9461	0.001544	-0.020
738	0.841			1.1169	0.001580	-0.060
918	0.934			1.3738	0.001658	-0.148
1218	1.058			1.8713	ERR	ERR

Figure 77. Kinetic Data for Structure **12h**

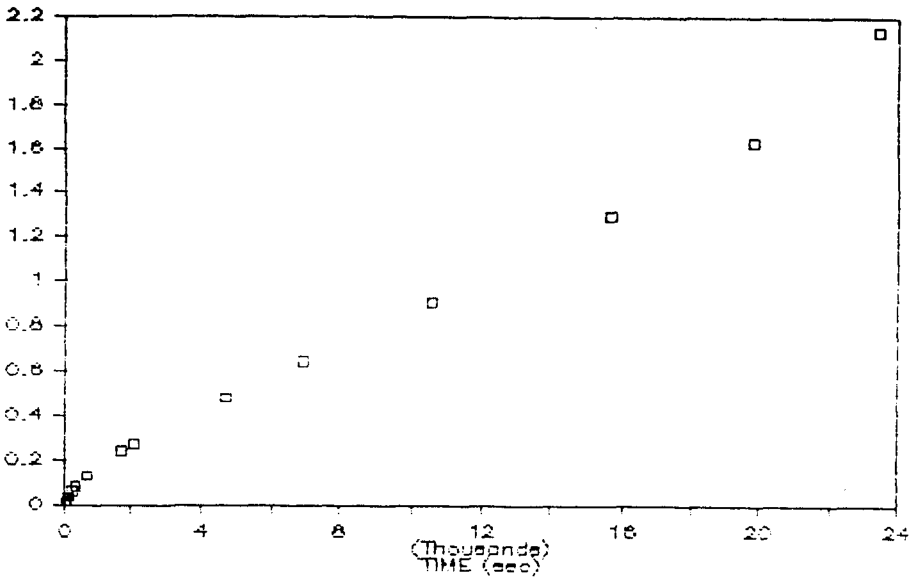
Concentration 7.06 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
81	0.222	1780	1.27	0.1920	0.001589	0.0844
141	0.333			0.3044	0.001577	0.0921
201	0.423			0.4054	0.001570	0.0965
261	0.503			0.5046	0.001566	0.1000
321	0.574			0.6018	0.001562	0.1025
381	0.638			0.6974	0.001560	0.1042
441	0.695			0.7924	0.001559	0.1054
501	0.746			0.8854	0.001558	0.1060
621	0.836			1.0728	0.001555	0.1090
741	0.911			1.2631	0.001545	0.1183
1041	1.044			1.7266	ERR	ERR

Figure 78. Kinetic Data for Structure **12h**

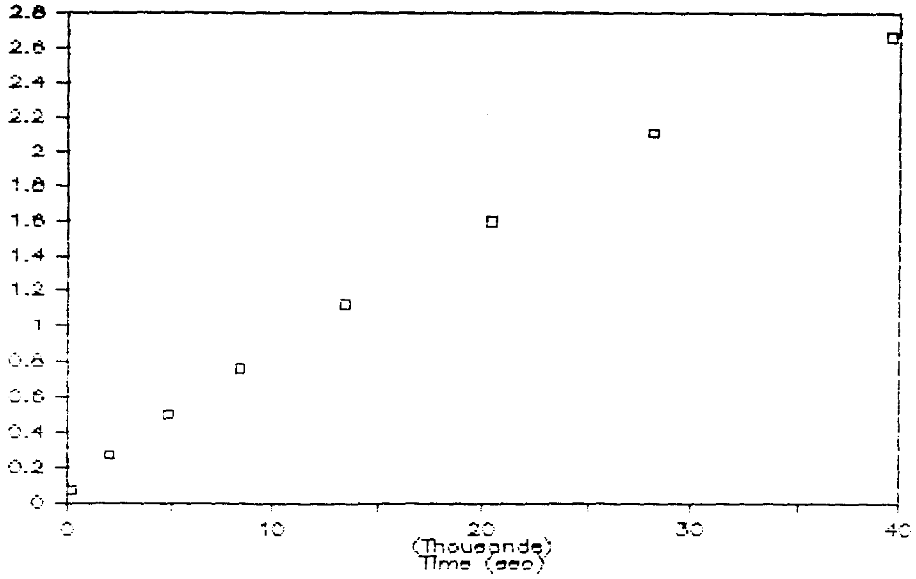
Concentration 7.07 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
35	0.003	441	0.24	0.0133	0.000084	0.0528
95	0.008			0.0339	0.000084	0.0592
215	0.014			0.0605	0.000083	0.0651
335	0.019			0.0811	0.000083	0.0699
675	0.030			0.1312	0.000083	0.0744
1715	0.051			0.2399	0.000083	0.0740
2075	0.057			0.2716	0.000083	0.0630
4655	0.091			0.4773	0.000085	0.0368
6935	0.114			0.6427	0.000088	-0.013
10535	0.143			0.9059	0.000093	-0.122
15635	0.174			1.2940	0.000107	-0.420
19835	0.193			1.6347	0.000140	-1.136
23435	0.212			2.1377	ERR	ERR

Figure 79. Kinetic Data for Structure **12i**

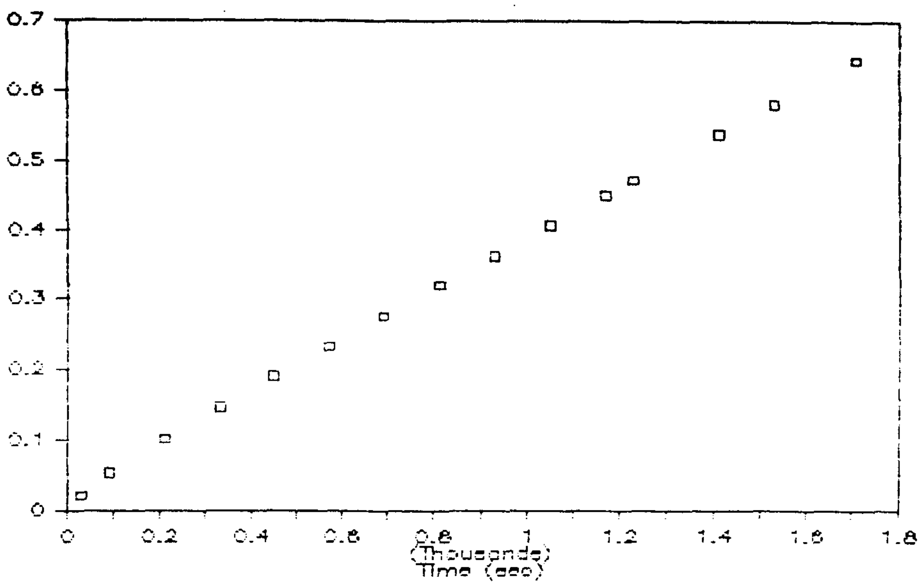
Concentration 5.44×10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
200	0.016	441	0.24	0.0689	0.000066	0.1689
2000	0.057			0.2706	0.000065	0.2132
4820	0.095			0.5032	0.000063	0.2527
8420	0.128			0.7648	0.000062	0.2969
13460	0.162			1.1226	0.000059	0.3676
20480	0.191			1.5970	0.000056	0.4907
28220	0.211			2.1133	0.000049	0.7323
39620	0.223			2.6712	ERR	ERR

Figure 80. Kinetic Data for Structure **12i**

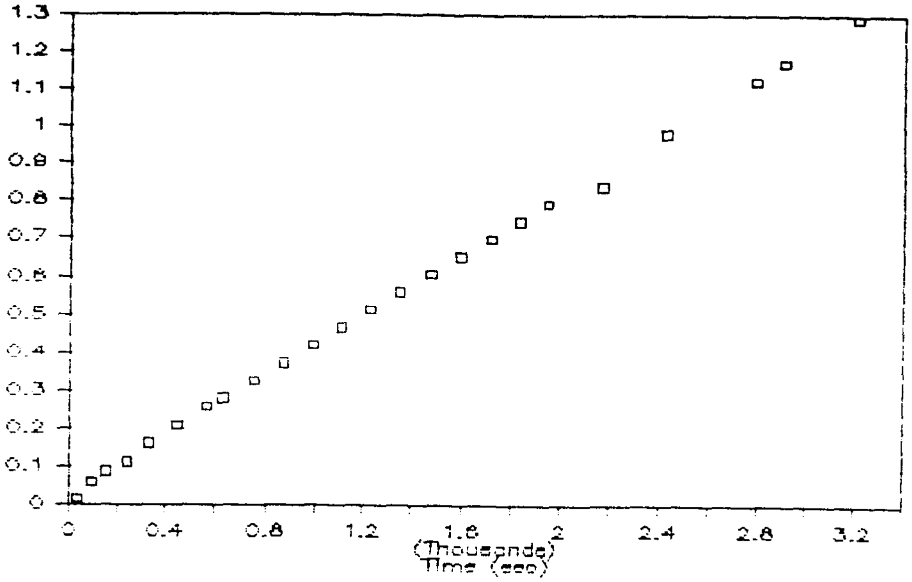
Concentration 4.89 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
30	0.029	3420	1.329	0.0217	0.000366	0.0215
90	0.068			0.0528	0.000363	0.0246
210	0.128			0.1012	0.000362	0.0263
330	0.182			0.1471	0.000361	0.0268
450	0.230			0.1901	0.000362	0.0263
570	0.277			0.2332	0.000362	0.0256
690	0.321			0.2758	0.000363	0.0246
810	0.363			0.3191	0.000364	0.0237
930	0.404			0.3621	0.000365	0.0225
1050	0.443			0.4050	0.000365	0.0212
1170	0.481			0.4485	0.000366	0.0207
1230	0.499			0.4705	0.000365	0.0211
1410	0.552			0.5368	0.000365	0.0222
1530	0.585			0.5798	0.000369	0.0158
1710	0.633			0.6462	ERR	ERR

Figure 81. Kinetic Data for Structure **12j**

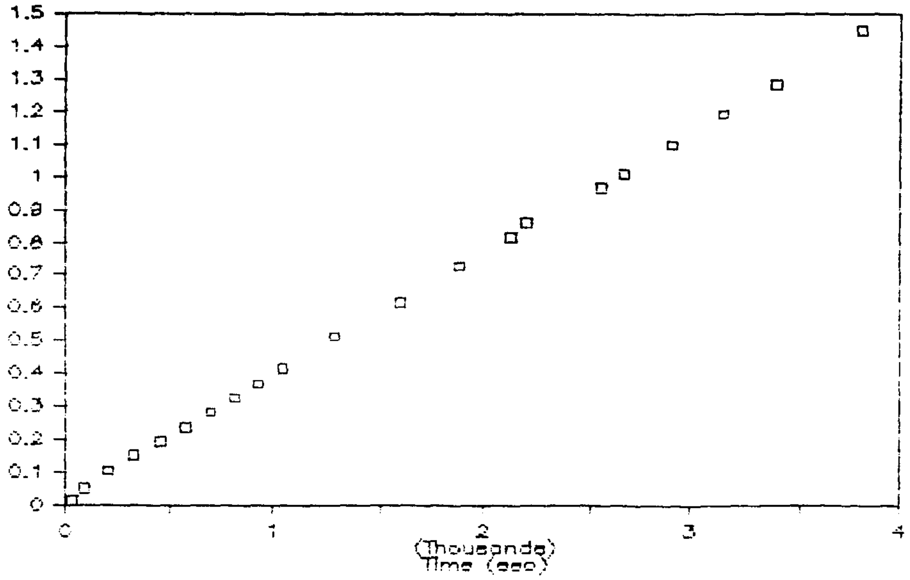
Concentration 3.82 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
30	0.020	3390	1.296	0.0154	0.000393	0.0261
90	0.073			0.0582	0.000392	0.0292
150	0.109			0.0875	0.000391	0.0302
240	0.138			0.1126	0.000391	0.0304
330	0.193			0.1615	0.000390	0.0326
450	0.244			0.2086	0.000390	0.0326
570	0.293			0.2559	0.000390	0.0325
630	0.316			0.2794	0.000390	0.0322
750	0.362			0.3272	0.000390	0.0318
870	0.404			0.3734	0.000391	0.0309
990	0.444			0.4199	0.000391	0.0300
1110	0.483			0.4659	0.000392	0.0289
1230	0.520			0.5132	0.000392	0.0277
1350	0.557			0.5611	0.000393	0.0259
1470	0.590			0.6079	0.000394	0.0227
1590	0.623			0.6546	0.000396	0.0179
1710	0.653			0.7010	0.000399	0.0106
1830	0.682			0.7475	0.000403	-0.000

Figure 82. Kinetic Data for Structure **12j**

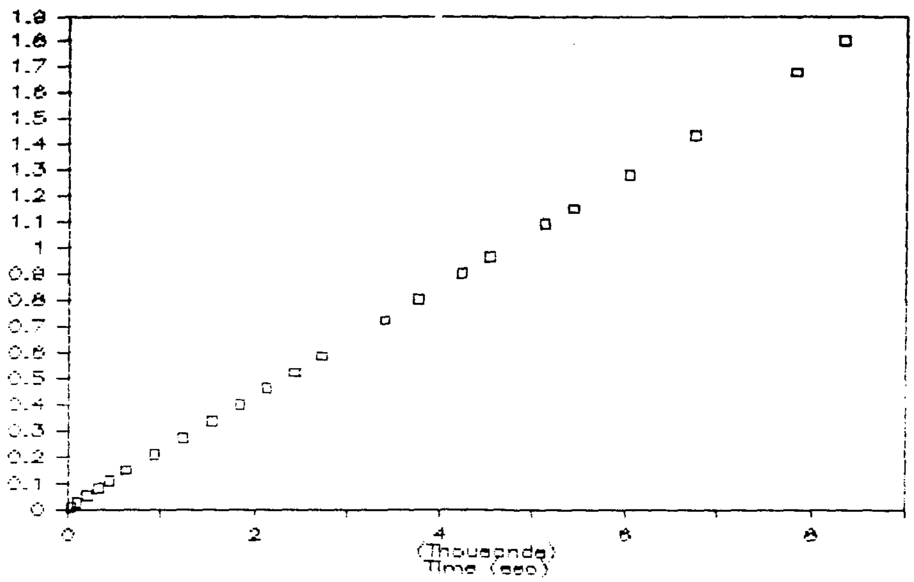
Concentration 3.78 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
30	0.016	3349	1.265	0.0127	0.000374	0.0210
90	0.063			0.0507	0.000373	0.0240
210 0	0.123			0.1025	0.000373	0.0252
330	0.174			0.1482	0.000372	0.0254
450	0.223			0.1936	0.000372	0.0254
570	0.267			0.2374	0.000372	0.0253
690	0.311			0.2817	0.000372	0.0254
810	0.352			0.3262	0.000372	0.0256
930	0.391			0.3702	0.000372	0.0260
1050	0.430			0.4149	0.000372	0.0271
1290	0.508			0.5130	0.000371	0.0289
1590	0.582			0.6158	0.000373	0.0242
1890	0.654			0.7270	0.000372	0.0255
2130	0.707			0.8182	0.000371	0.0284
2200	0.730			0.8613	0.000371	0.0305
2550	0.786			0.9702	0.000383	-0.008
2670	0.806			1.0137	0.000385	-0.016
2910	0.845			1.1023	0.000388	-0.027

Figure 83. Kinetic Data for Structure **12j**

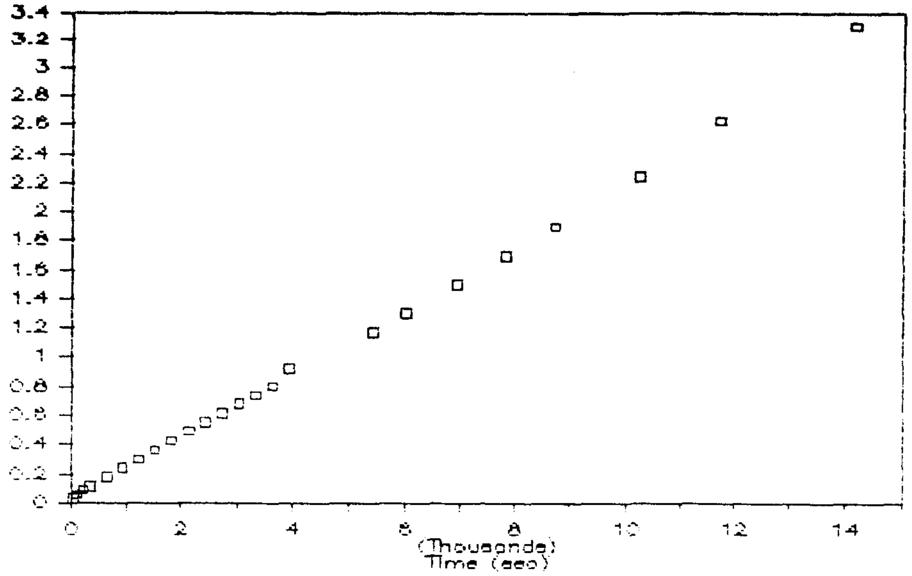
Concentration 3.89 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
30	0.0070	3500	1.17	0.0060	0.0002129	0.0055
90	0.0303			0.0262	0.0002128	0.0060
210	0.0637			0.0559	0.0002128	0.0059
330	0.0924			0.0822	0.0002129	0.0054
450	0.1197			0.1079	0.0002130	0.0046
630	0.1601			0.1471	0.0002132	0.0038
930	0.2214			0.2097	0.0002134	0.0026
1230	0.2787			0.2720	0.0002135	0.0015
1530	0.3333			0.3352	0.0002137	0.0005
1830	0.3840			0.3978	0.0002139	-0.000
2130	0.4319			0.4606	0.0002140	-0.001
2430	0.4764			0.5228	0.0002141	-0.002
2730	0.5190			0.5862	0.0002142	-0.003
3390	0.6029			0.7242	0.0002143	-0.003
3750	0.6439			0.7992	0.0002143	-0.003
4230	0.6943			0.8999	0.0002143	-0.003
4530	0.7233			0.9628	0.0002143	-0.003
5130	0.7764			1.0894	0.0002143	-0.002
5430	0.8007			1.1531	0.0002144	-0.002
6030	0.8450			1.2809	0.0002145	-0.001

Figure 84. Kinetic Data for Structure **12k**

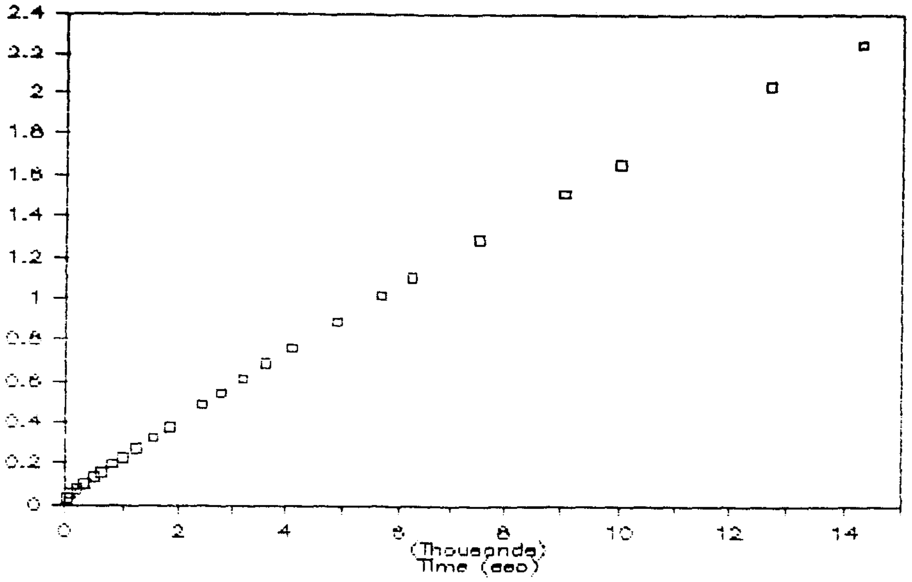
Concentration 8.60 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
30	0.0139	538	0.461	0.0305	0.0002229	0.0105
90	0.0244			0.0543	0.0002230	0.0094
210	0.0379			0.0857	0.0002233	0.0072
330	0.0491			0.1125	0.0002237	0.0042
630	0.0750			0.1774	0.0002241	0.0007
930	0.0986			0.2404	0.0002245	-0.003
1230	0.1204			0.3024	0.0002250	-0.006
1530	0.1407			0.3638	0.0002254	-0.010
1830	0.1603			0.4269	0.0002258	-0.014
2130	0.1793			0.4921	0.0002262	-0.018
2430	0.1961			0.5535	0.0002266	-0.022
2730	0.2119			0.6149	0.0002270	-0.026
3030	0.2270			0.6774	0.0002273	-0.029
3330	0.2401			0.7349	0.0002276	-0.032
3630	0.2543			0.8013	0.0002277	-0.034
3930	0.2784			0.9251	0.0002279	-0.036
5430	0.3187			1.1740	0.0002290	-0.051
6030	0.3357			1.3009	0.0002288	-0.047
6930	0.3579			1.4954	0.0002286	-0.041
7830	0.3767			1.6961	0.0002284	-0.033

Figure 85. Kinetic Data for Structure **12k**

Concentration 8.60 X 10^{-4} M



TIME (sec)	ABSORB	EXTIN COEFF	INFIN ABSORB	y-axis C(0)/ C(0)-P	SLOPE	y INTERCT
30	0.0311	3570	1.02	0.0309	0.0001585	0.0695
90	0.0540			0.0543	0.0001581	0.0727
210	0.0749			0.0762	0.0001578	0.0753
330	0.1001			0.1032	0.0001574	0.0781
510	0.1316			0.1381	0.0001571	0.0806
630	0.1516			0.1609	0.0001569	0.0828
810	0.1817			0.1961	0.0001566	0.0851
990	0.2090			0.2292	0.0001564	0.0869
1230	0.2429			0.2719	0.0001562	0.0884
1530	0.2837			0.3259	0.0001561	0.0896
1830	0.3217			0.3789	0.0001561	0.0900
2430	0.3920			0.4850	0.0001561	0.0895
2790	0.4290			0.5457	0.0001564	0.0870
3210	0.4671			0.6123	0.0001567	0.0831
3630	0.5080			0.6892	0.0001571	0.0784
4110	0.5454			0.7650	0.0001577	0.0707

Figure 86. Kinetic Data for Structure **12k**

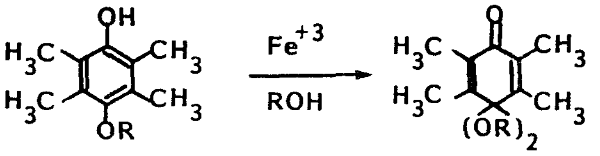
Concentration 4.30 X 10^{-4} M

PART II

A CONVENIENT ROUTE TO *ortho*-ALKYLATED PHENOLS AND QUINONE MONOKETALS

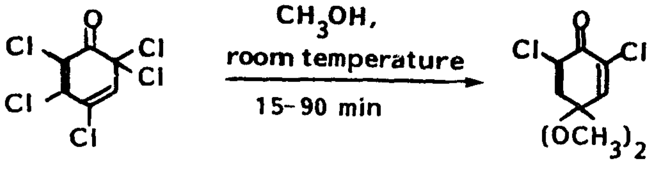
INTRODUCTION

The past few years have seen a renewed interest in the synthesis of naturally occurring quinone and quinone derived products.[1-8] An important class of reagents which has greatly expanded the methods in quinone chemistry is monoprotected quinones. In such compounds, one carbonyl of the quinone has been selectively blocked in some fashion to prevent nucleophilic attack at that site. In order to obtain certain monoprotected quinones, several methods have been used in the literature. The first mention of a quinone monoketal in the literature was in 1957 when Marttius and Eilingsfeld[9] reported the synthesis of the monoketals **1** and **2** by oxidation of the appropriate phenol ether with ferric chloride or potassium hexacyanoferrate(III). No yields for these reactions were given.

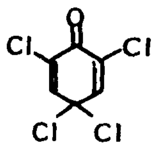


1, R = CH_3
2, R = C_2H_5

At about the same time, a Japanese group[10] reported the solvolysis of an ortho geminal dichloroquinone **3** to the monoketal **4**. This method was lacking in generality for a number of reasons, including the fact that the dichloro compoUnd 5 will not undergo solvolysis.

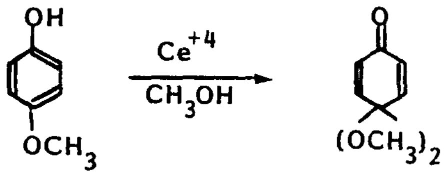


3 4



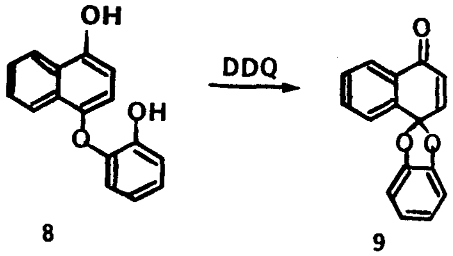
5

Further work on the oxidation of monoethers and esters of hydroquinone was conducted by Duckheimer and Cohen[11,12] in 1964 in connection with their studies of the oxidation of tocopherol. They showed that ceric ammonium nitrate, tetrachloroorthoquinone, and N-bromosuccinimide could be used in specific instances to prepare quinone monoketals (e.g., **6** from **7**).

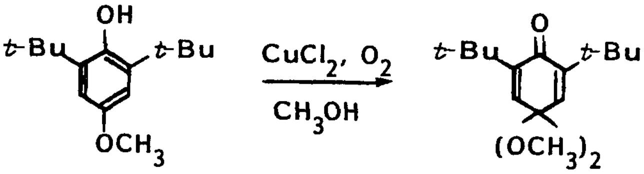


6 7

A number of oxidations of phenolic substrates with manganese dioxide, dichlorodicyanobenzoquinone (DDQ), and silver oxide have been reported by Schofield et al.[14] to give intramolecular trapping of the intermediate phenoxylium ion, affording good to poor yields of spirocyclic compounds such as **9**.



In 1971, Hewitt[14] prepared several quinone monoketals **11** from hindered phenols **10**, utilizing a copper(II) pyridine complex and oxygen in methanol. A variety of oxidizing agents have been used in subsequent years.

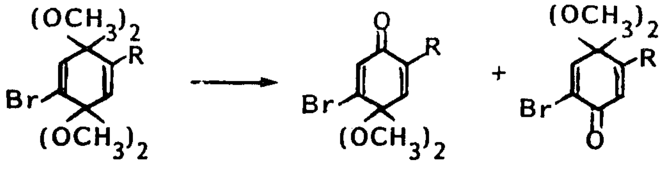


Andersson[15-17] prepared a variety of quinols and monoketals of <u>ortho</u>- and <u>para</u>-quinones (usually in low yield) via periodic acid oxidation of substituted phenols. In the same year, Taylor[18] published his notable study of the preparation of quinone monoketals using thallium(III) nitrate to oxidize a large number of substituted <u>p</u>-methoxyphenols. Where the appropriate phenol is available (and this is often a major problem), thallium(III) nitrate seems to be the most generally applicable oxidizing agent for conversion to the monoketal. In addition to the requirement of having the appropriate phenolic substrate, the major drawbacks are its expense and toxicity.

Buchi and coworkers[19] followed up the Taylor study by doing a comparison of the efficacy of ferric chloride, dichlorodicyanoqunone, and thallium(III) nitrate in oxidizing a variety of substituted *p*-methoxy- and methylenedioxy-phenol to monoketals. In general, the oxidizing agents nicely complemented one another, no one oxidant always working for a particular compound.

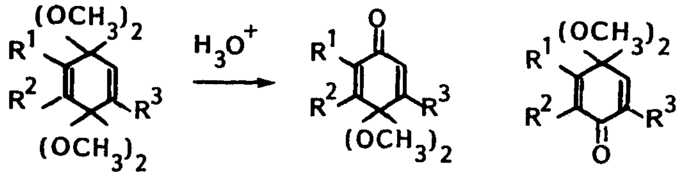
Another method used to oxidize phenols to monoketals is electrochemical oxidation.[20,21] In 1975, Ronlan[22] published an electrochemical oxidation of **6** to the benzoquinone monoketal 7. This procedure was later used by Foster and Payne[23] in their studies of the reaction of **6** with various nucleophiles. Two later studies were performed by Ronlan,[24,25] with substituted phenols. Usually a low yield of quinone monoketal was obtained. Dimerization or over methoxylation occurred during the anodic oxidation process. The second study was primarily mechanistic, although it accompanied product analysis. The monoketals they encountered were limited to two examples. However, little use has been made of this chemistry by other research groups.

The final route to quinone monoketals is via the hydrolysis of quinone bisketals, as illustrated below:



12 **13** **14**

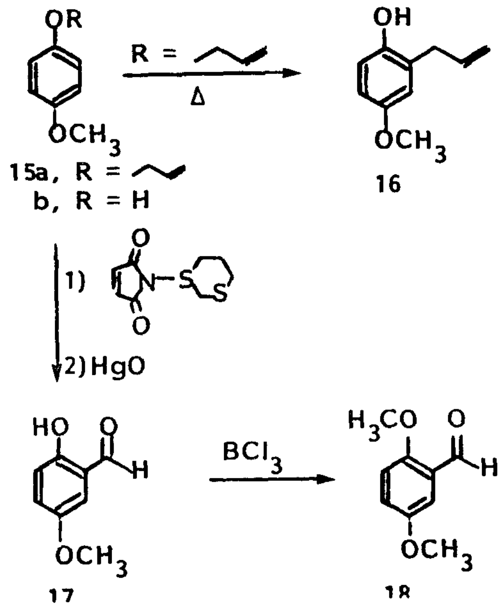
In 1966 Winberg reported[26a] that hydrolysis of the bis-dimethylketal of benzoquinone gave a 65% yield of the monoketal 7; however, difficulty was experienced in duplication of the work.[26b] Swenton and Henton[27] studied the scope and the limitation of the electrochemical oxidation of 1,4-dimethoxy aromatics to bisketals and established the utility of the monohydrolysis of such compounds to monoketals. To obtain high regioselectivity in this monohydrolysis reaction (see Table I),



R^1	R^2	R^3	Yield (%)	Yield (%)
H	H	Br	88	--
H	H	CH_3	64	11
H	H	$Si(CH_3)_3$	29	38
H	H	$CH(CH_3)(OCH_3)$	58	19
H	H	$NHC(O)CH_3$	79	--
Br	H	H	10	82

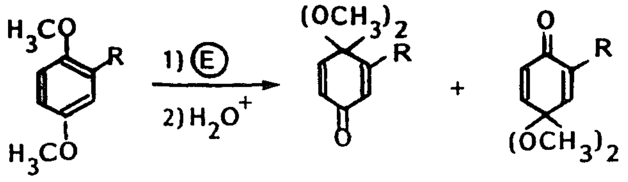
certain substituents have to be attached on aromatics rings. This is the major limitation of this route to quinone monoketals.

The purpose of the work to be described in this part of this manuscript is to explore the electrochemical oxidation of substituted 4-methoxylated phenols. These compounds are available by a variety of methods. Claisen rearrangement of *p*-methoxy allyl ethers,[19] the *ortho*-formylation[28] of *p*-methoxyphenols, and the selective demethylation of 1-acyl 2,5-dimethyl aromatic derivatives serve as routes to functionalized *p*-methoxy phenols. The overall objective was to use this electrochemical oxidation procedure to prepare quinone monoketals as a key step in the preparation of quinone imine ketals. This latter work will be presented in the next section.



RESULTS AND DISCUSSION

Quinone monoketals are valuable quinone equivalents. A major advantage of these molecules relative to quinones is the unambiguous regiochemical outcome of additions to either the carbonyl group or the &-carbon. Thus, it is important to have regiospecific routes to quinone monoketals in order to fully utilize the advantages of their chemistry. In Part I of the thesis, the effect of allylic substitutents on the regiochemistry of quinone bisketal hydrolysis was studied. It was established that for the most favorable case--a tetralin system with an allylic hydroxyl group--the regiochemistry of the hydrolysis was quite synthetically useful. However, in simple monosubstituted benzenoid systems, only a modest regiochemistry was observed in the hydrolysis of the bisketal. For example, anodic oxidation of **19a**, **19b** and monohydrolysis of the resulting quinone bisketal

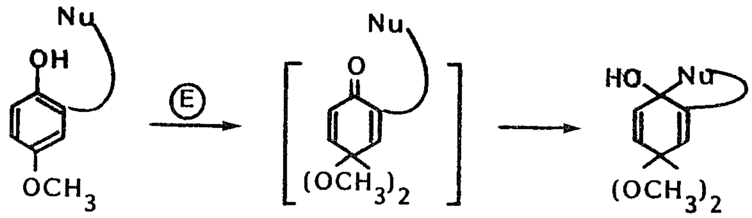


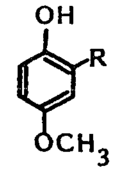
19a, R = CH_2F 1.5 : 1

b, R = *t*-Bu 2.5 : 1

gave no selectivity even with substituents such as an electron-withdrawing fluoromethyl group or a t-butyl group.

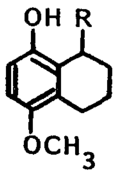
One long-range goal of this research was to investigate intramolecular cyclization reactions of quinone monoketals (Scheme I). Since quinone monoketals formed from monosubstituted quinone bisketals via hydrolysis not only gave a mixture of products but also gave as the major product the monoketal incapable of intramolecular cyclization, an alternative method for preparing these compounds was required. The chemical or electrochemical oxidation of an appropriate p-methoxyphenol would solve this regiochemical problem. Two major considerations were the high-yield preparation of the required substituted p-methoxyphenol and the compatability of the nucleophilic side chain to the anodic oxidation conditions. Conditions for the regiospecific preparation of quinone monoketals were examined. In Part III, these results were applied to the preparation of quinone imine ketals.





20a, R = C_2H_5

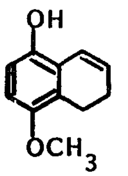
b, R = CH_2-*t*-Bu



21a, R = CH_3

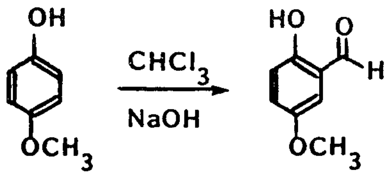
b, R = Et

c, R = *t*-Bu



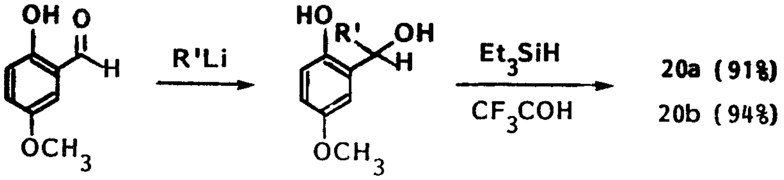
22

The study began with the preparation of the substituted p-methoxy phenols **20a-b**,**21a-c** and **22** as listed above. Many o-hydroxyl benzadehydes and 1-acyl-2,5 dimethoxy aromatic derivatives[29,30] are readily available. For example, the required starting material 2-hydroxyl-5-methoxy-benzadehyde **6** can be prepared by the Reimer-Tieman reaction on commercially available p-methoxy phenol as shown below. Furthermore, the benzyl protected derivative of this system could also be prepared (if difficulties were enconted in perfoming the organometalic addition to the uprotected o-hydroxylbenzadehyde).



6

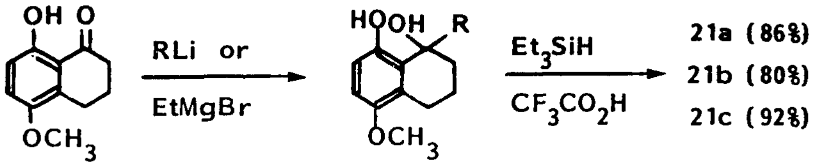
The required phenols **20a,b** were obtained by treating **17a** at -78 °C with two equivalents of alkyllithium reagents to give good yields of **23a,b**. The structures assigned to **23a,b** were supported by spectroscopic and analytical data. The disappearance of carbonyl absorption in the IR spectrum and aldehyde resonance in the ^{1}H NMR spectrum indicated reaction that occurred at the aldehyde carbonyl group. The product showed a strong hydroxyl stretching in the IR spectrum. Reduction of **23a,b** with triethylsilane in trifluroacetic acid at room tempreture gave phenols **20a,b** in excellent yields. The structures of **20a,b** were supported by spectroscopic and analytical data. The IR spectrum showed an absorption peak around 3600-3400 cm^{-1} assigned as the phenolic hydoxyl linkage, and the ^{1}H NMR spectrum showed ethyl resonance (**20a**) at δ = 2.60, 2.12 with $\underline{J}$ = 7 Hz or a t-butyl group at δ = 0.87 (**20b**).



17

23a, R' = CH_3 (94%)
b, R' = *t*-Bu (70%)

Phenol derivatives **21a-c** were prepared in a similar manner. Reaction of alkyllithiums or alkyl Grignard reagents with **24** at -78 °C gave the alcohols **25a-c**. These alcohols were then reduced with triethylsilane at room temperature using trifluroacetic acid as solvent to give the known compounds **21a-c**.



24

25a, R = CH_3 (86%)
b, R = Et (80%)
c, R = *t*-Bu (57%)

Phenol **22** was prepared by treating **24** with $NaBH_4$ followed by acidic workup.

Anodic Oxidation Studies

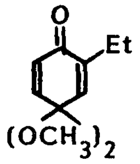
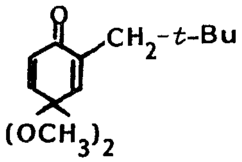
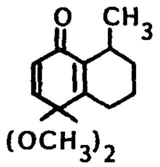
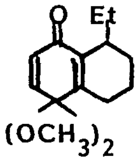
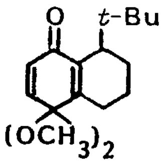
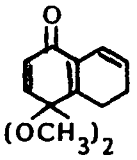
The anodic oxidation of phenols was conducted at 0 °C using 2% $LiClO_4/CH_3OH$ as solvent and electrolyte. The oxidation potential of p-methoxyphenol is very low. By using low applied voltage (<4 V) and low current (<1 A) one can obtain high yields of quinone monoketal at about 100% current efficiency. Table II gave the results and yields of quinone monoketal from the oxidation of substituted p-methoxyphenols.

The structures of the resulting quinone monoketals were easily confirmed by spectroscopic data. The quinone monoketals showed strong absorptions around 1670, 1630 cm^{-1}, assigned to stretching of the conjugated carbonyl group. In addition, the ^1H NMR spectrum showed the expected AB quartets around δ = 7.0-6.0 with coupling constant equal to 10 Hz.

From the above results, functionalized quinone monoketal can be easily prepared via anodic oxidation of p-methoxy phenol derivatives. Because the oxidation potential of p-methoxy phenol is very low and the electrolysis condition is mild (0 °C at near neutral pH), the reaction condition should be compatible with a variety of substituents on the phenol. For example, **17**, containing a conjugated double bond gives the respective quinone monoketal in good yields. Other groups such as ketal groups and secondary alcohols can also be used as substituents in this phenol oxidation. This work demonstrates the general nature of the electrochemical oxidation of p-methoxy phenols for preparation of quinone monoketals.

Table II

Anodic Oxidation of Substituted *p*-methoxy Phenols

Substrate	Product	Yield (%)
20a	 26a	82
20b	 26b	83
21a	 26c	82
21b	 26d	85
21c	 26e	82
22	 26f	77

Summary

An efficient, regiospecific, convergent route to o-alkylated phenols and thence to quinone monoacetals involves reaction of the corresponding 2-hydroxy carbonyl derivative with alkyllithium reagents, followed by triethylsilane reduction and electrochemical oxidation.

EXPERIMENTAL

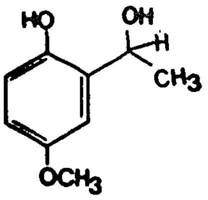
General Procedures

Melting points were taken in capillaries in a Thomas-Hoover "Uni-melt" apparatus and are uncorrected. Infrared spectra were on a Perkin-Elmer Model 283B spectrometer. ^1H and ^{13}C nuclear magnetic resonace spectra (NMR) were recorded on IBM NR 80 Model spectrometer. All NMR spectra were recorded in $CDCl_3$ and are reported in ppm relative to $CHCl_3$ (δ = 7.24) unless otherwise noted. Mass spectral and exact mass mesurements were obtained from Mr. Richard Weisenberger on a Kratos MS-30 spectrometer. Alumina and silica gel were obtained from E. Merck Co. Tetrahydrofuran was purified by distillation from benzophenone ketyl. Dichoromethane, benzene, and toluene were distilled from calcium hydride. Anhydrous diisopropylamine and triethyl amine were distilled from potassium hydroxide. Anhydrous dimethyl formamide was distilled from barium oxide (79 ^{0}C, 35 mm). All of these purified solvents were stored over 4A molecular sieves. Solutions of alkyl lithiums or alkyl magnesium bromides were from Aldrich Chemical Co.

Throughout the experimental, the following abbreviation are used: petroleum ether, bp 35-60 ^oC (PE), tetrahydrofuran (THF), ethyl ether (Et_2O), n-butyllithium (n-BuLi), and diethylaminosulfur trifluoride (DAST).

All preparative anodic oxidations were preformed in a single-cell or in H-type divided-cell apparatus in methanol using a circular platinum gauze anode (33 mm diameter x 28 mm high) and platium sheet cathode (8 x 8 mm) unless otherwise stated.

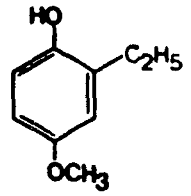
Preparation of 23a from 17



To a magnetically stirred solution of THF (20 mL) and 1.7 M CH_3Li (64.7 mL, 2.2 equiv) at -77 °C under N_2 was added **17** [7.6 g, 0.05 mmol in THF (20 mL)] slowly. The mixture was stirred for 30 min and then warmed to room temperature over 2h. The reaction was quenched by addition of saturated NH_4Cl (40 mL), concentrated in vacuo, extracted with CH_2Cl_2 (350 mL), and washed with brine (50 mL). Drying (Na_2SO_4) and concentration in vacuo gave a light yellow solid. Recrystallization (CH_2Cl_2/PE) gave **23a** (7.9 g, 94%): mp 76-78.5 °C; IR (KBr) 3600-3100 (br), 2970, 1500, 1460 (sh), 1450, 1440, 1270, 1240, 1200, 1110, 1070, 1040; ^1H NMR 7.50 (bs, 1 H), 6.9-6.45 (m, 3 H), 5.15-4.80 (m, 1 H), 3.71 (s, 3 H), 2.82 (bs, 1 H), 1.54 (d, *J* - 6.6 Hz, 3 H); ^{13}C NMR 152.9, 148.7, 129.9, 117.2, 113.6, 112.4, 70.4, 55.7, 23.1; mass spectrum, exact mass calcd for $C_9H_{12}O_3$ *m/e* 168.0787, obsd *m/e* 168.0754.

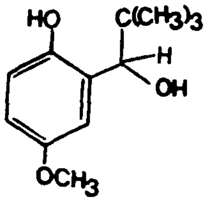
Preparation of 20a from 23a

A magnetically stirred solution of CH_2Cl_2 (20 mL), **23a** (5.8 g, 0.0345 mol), and Et_3SiH (14 mL, ∞ 2.5 equiv) was cooled to 0 °C. After adding CF_3CO_2H (30 mL), the mixture was stirred for 30 min and concentrated in vacuo. Molecular distillation at 80 °C/0.25 torr gave **20a** (4.8g, 91%): IR (film, cm^{-1}) 3600-3100 (br), 2960, 2940, 1510, 1450, 1430, 1250, 1200, 1180, 1150, 1030, 800; ^1H NMR 6.8-6.4 (m, 3 H), 5.1-4.0 (br, 1 H), 3.75 (s, 3 H), 2.60 (q, J = 7.4 Hz, 2 H), 1.21 (t, J = 7.4 Hz, 3 H); ^{13}C NMR 153.3, 147.5, 131.8, 115.9, 111.5, 55.6, 22.9, 13.6; mass spectrum, exact mass calcd for $C_9H_{12}O_2$ m/e 152.0837, obsd m/e 152.0191.



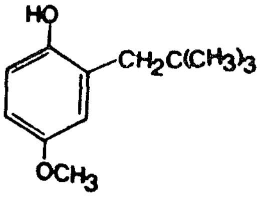
Preparation of 23b from 17

To a solution of THF (20 mL) and 1.7 M t-BuLi (10.5 mL, 2.2 equiv) at -77 °C **17** [1.23 g, 8.11 mmol in THF (10 mL)] was addedslowly. The reaction mixture was stirred for 30 min at -70 °C and then at room temperature for 3 h. The reaction was quenched by addition of saturated NH_4Cl (30 mL), and the mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 30 mL), and washed with brine (30 mL). Drying (Na_2SO_4) and concentration in vacuo yielded a light-yellow oil. Flash column chromatography gave **23b** (1.19 g, 70%): mp 77-79.5 °C; IR (KBr cm^{-1}) 3430, 3600-3100 (br), 2960, 1510, 1465, 1430, 1350, 1270, 1200 (br), 1150, 1085, 1050, 810; ^1H NMR δ 7.79 (s, 1 H), 6.75 (br s, 2 H), 6.45 (br s, 1 H), 4.48 (d, J = 3 Hz, 1 H), 3.72 (s, 3 H), 2.56 (d, J = 3 H, 1 H), 0.98 (s, 9 H); ^{13}C



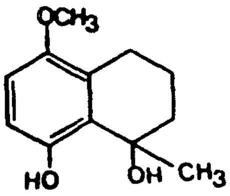
NMR 152.0, 150.1, 125.1, 117.5, 115.5, 113.8, 84.3, 55.8, 37.1, 26.1 (3 C); mass spectrum, exact mass calcd for $C_{10}H_{14}O_3$ m/e 210.1256, obsd m/e 210.1240.

Preparation of 20b from 23b



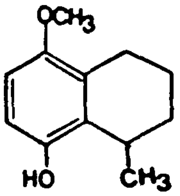
To a magnetically stirred solution of CH_2Cl_2 (3 mL), **23b** (0.782 g, 3.72 mmol) and Et_3SiH (2.5 mL, ∞ 5 equiv, excess) at room temperature was added added CF_3CO_2H (3.3 mL). The mixture was stirred for 5 min and then concentrated in vacuo to yield a yellow oil. Flash column chromatography gave 25a (0.683 g, 94%): mp 66-67.5; IR (KBr, cm^{-1}) 3600-3200 (br), 2940, 2850, 1500, 1430, 1205, 1180, 1150, 1030; ^1H NMR δ 6.67 (s,3 H), 5.24 (br, 1 H), 3.78 (s, 3 H), 2.52 (s, 2 H), 0.99 (s, 9 H); ^{13}C NMR 152.9, 148.3, 127.1, 118.4, 116.0, 112.3, 55.7, 43.3, 32.6, 29.4 (3 C); mass spectrum, exact mass calcd for $C_{12}H_{18}O_2$ m/e 192.1150, obsd m/e 192.1163.

Preparation of 25a from 24



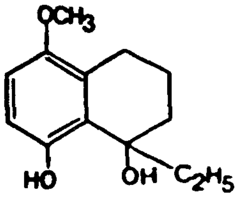
To a -77 ^{0}C magnetically stirred solution of THF (10 mL) and 1.7 M CH_3Li (0.95 mL, 2.2 equiv) at -77 °C was added 24 [289 mg, 1.5 mmol in THF (5 mL)] slowly. After stirring for 15 min at -77 °C and 30 min at room temperature, the reaction was quenched by the addition of saturated NH_4Cl (15 mL). The resulting solution was concentrated in vacuo, extracted with CH_3Cl_2 (2 x 30 mL), and brine (20 mL). Drying (Na_2SO_4) and concentration in vacuo yielded crude **25a** (291 mg, 93%). Flash column chromatography (CH_2Cl_2 as eluant) gave **25a** (276 mg, 88%): IR (neat, cm^{-1}) 3600-3100 (b), 2940, 1470 (b), 1440, 1250 (b), 1060; ^1H NMR δ 8.12 (s, 1 H), 6.65 (s, 2 H), 3.73 (s, 3 H), 1.5-3.0 (m, 7 H), 1.59 (s, 3 H); ^{13}C NMR δ 150.3 (s), 149.5 (s), 128.2 (s), 125.9 (s), 113.9 (d), 110.2 (d), 74.2 (s), 55.8 (q), 39.8 (t), 27.2 (q), 23.2 (t), 20.4 (t); mass spectrum, exact mass calcd for $C_{12}H_{16}O_3$ m/e 208.1009, obsd m/e 208.1151.

Preparation of 21a from 25a



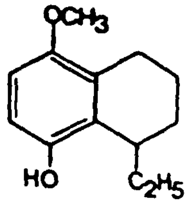
To a solution of CH_2Cl_2 (15 mL), 262 mg (1.26 mmol), and Et_3SiH (7.3 equiv, 1.5 mL) was added CF_3CO_2H (1.5 mL) slowly. After 5 min the reaction mixture was concentrated in vacuo. Flash column chromatography (1:1 PE/CH_2Cl_2) of the residure yielded **25a** (209 mg, 86%). (known compound, see Part I).

Preparation of 25b from 24



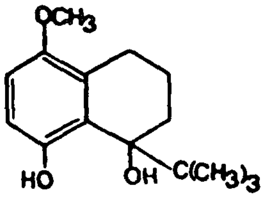
To a -77 ^0C stirred solution of THF (10 mL) and 1.9 M EtMgBr (2.45 mL, 2.2 equiv) was added **24** [406 mg, 2.11 mmol in THF (5 mL)] slowly. The mixture was stirred for 50 min at -78^{0}C, and then for 2 h at room temperature. The reaction was quenched by the addition of saturated NH_4Cl (15 mL), concentrated in vacuo, extracted with CH_2Cl_2 (2 x 30 mL), and washed with brine (20 mL). Drying (Na_2SO_4) and concentration in vacuo yielded a crude yellow oil. Flash column chromatography (CH_2Cl_2) gave **25b** (81%): IR (neat, cm^{-1}) 3600-3100 (br), 2930, 1470 (br), 1435, 1250 (br), 1170, 1050; ^1H NMR δ 6.64 (s, 2 H), 3.73 (s, 3 H), 3.0-1.4 (m, 9 H), 0.94 (t, *J* = 7 Hz, 3 H); mass spectrum, exact mass calcd for $C_{13}H_{18}O_3$ *m/e* 222.1256, obsd *m/e* 222.1261.

Preparation of 21b from 25b



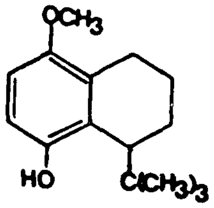
To a magnetically stirred solution of **24** (382 mg, 17.2 mmol), CH_2Cl_2 (2 mL), and Et_3SiH (1.5 mL, excess) was added CF_3CO_2H (1.5 mL). The reaction mixture was stirred for 5 min and concentrated in vacuo to yield crude crystalline **25c**. Recrystallization (CH_2Cl_2/PE) gave **21b** (283 mg, 80%). (known compound, see Part I)

Preparation of 25c from 24c



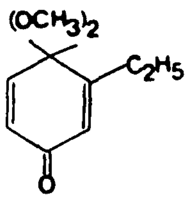
To a magnetically stirred mixture of THF (15 mL) and 1.7 M *t*-BuLi (9.98 mL, 2.2 equiv) under nitrogen at -77 °C was added **24** [1.49 g, 7.7 mmol in THF (10 mL)] slowly. The reaction mixture was stirred for 30 min at -77°C and then at room temperature for 1 h. The reaction was quenched by the addition of saturated NH_4Cl (15 mL), and the mixture was concentrated in vacuo, extracted with CH_2Cl (3 x 30 mL), and washed with brine (20 mL). Drying (Na_2SO_4) and concentration in vacuo gave a yellow oil. Flash column chromatography gave 5 M **25c** (0.82 g) and **25c** (492 mg, 26%, 57% based on unrecovered starting material): IR (film, cm^{-1}) 3600-3100, 2950, 1470, 1440, 1400, 1370, 1250 (br), 1040, 990, 800, 730; ^1H NMR δ 9.91 (s, 1 H), 6.63 (s, 2 H), 3.74 (s, 3 H), 3.0-1.0 (m, 6 H), 0.98 (s, 9 H), 0.87 (s, 1 H); mass spectrum, exact mass calcd for $C_{15}H_{22}O_3$ m/e 250.1569, obsd m/e 250.1606.

Preparation of 21c from 25c



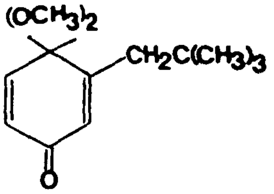
To a sirred solution of CH_2Cl_2 (2 mL), **25c** (270 mg, 1.08 mmol), and Et_3SiH (2 mL, excess) was added CF_3CO_2H (2.5 mL). The mixture was stirred for 5 min and concentrated in vacuo to give crude **21c**. Flash column chromatography gave **21c** (232.1 mg, 92%). Recrystallization (CH_2Cl_2/PE) gave **21c** (202.9 mg, 80%): mp 91.5-93.5 °C (known compound, see Part I).

Anodic Oxidation of 20a



In an electrolysis cell equipped with a magnetic stirrer was dissolved **20a** (4.1 g, 0.029 mmol) and 2% $LiCO_4/CH_3OH$ (170 mL). The solution was electrolyzed at 0 °C (2.95 V, 0.08 A) for 18 h after which time TLC (CH_2Cl_2 as eluant) showed no statting material remaining. The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 60 mL)/H_2O (40 mL), and washed with brine (30 mL), and concentrated in vacuo to give a yellow oil. Molecular distillation (50 °C) gave **26a** (3.87 g, 78%): IR (film, cm^{-1}) 2960, 2940, 1675, 1650, 1460, 1120, 1090 (br), 1050 (br), 960; ^{1}H NMR 6.66 (d of AB q, *J* = 10, 3 Hz, 1 H), 6.55-6.43 (m, 1 H), 6.24 (AB q, *J* = 10 Hz, 1 H), 3.30 (s, 6 H), 2.27 (q, *J* = 7 Hz, 2 H), 1.02 (t, *J* = 7 Hz, 3 H); mass spectrum, exact mass calcd for $C_{10}H_{14}O_3$ *m/e* 182.0943, obsd *m/e* 182.0948.

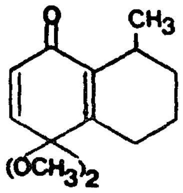
Anodic Oxidation of 20b



In an electrolysis cell equipped with a magnetic stirrer was dissolved **20b** (188 mg, 0.97 mmol) and 2% $LiClO_4/CH_3OH$. The solution was electrolyzed at 0 °C (2.0 V, 0.04 A) for 1.3 h after which timi TLC (CH_2Cl_2 showed no remaining strating material. The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (2 x 30 mL)/H_2O (20 mL), and washed with brine (20 mL). Drying (Na_2SO_4) and concentration in vacuo gave fairly pure **26b** (205 mg, 94%). Flash column chromatography (CH_2Cl_2) gave **26b** (181 mg, 83%): IR (film, cm^{-1}) 2950, 2680, 2650, 1120, 1080, 1060 (sh), 1040, 960; ^{1}H NMR δ 6.75 (d of AB q, *J* = 10, 3 Hz, 1 H), 6.51 (d, *J* = 3 H, 1 H), 6.24 (AB, *J* = 10 Hz, 1 H), 3.35 (s, 3 H), 2.25 (s, 2 H), 0.87 (s, 9 H); ^{13}C NMR 185.3, 142.3, 140.9, 138.5, 130.3, 93.1, 50.2 (2

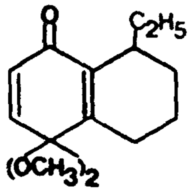
C), 40.9, 31.4, 29.3 (3 C); mass spectrum, mass spectrum, exact mass calcd for $C_{13}H_{20}O_3$ m/e 224.1412, obsd m/e 224.1425.

Anodic Oxidation of 21a



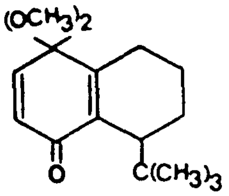
In a single electrolysis cell was placed **21a** (20 mg, 1.09 mmol) and 2% $LiClO_4/CH_3OH$ (70 mL). The solution was electrolyzed at 0°C for 1 h (2.5 V, 0.035 A) with the reaction being monitored by TLC. The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 30 mL)/H_2O (50 mL), and washed with brine (30 mL). Drying (Na_2SO_4) and concentration in vacuo yielded a light yellow oil. Flash column chromatography gave **26c** (198.2 mg, 82%): IR (neat, cm^{-1}) 2960, 1670, 1640, 1620, 1290, 1280 (sh), 1170, 1090, 1060 (br), 1040; ^1H NMR δ 6.65 (ABq, J = 10 Hz, 1 H), 6.36 (ABq, J = 10 Hz, 1 H), 3.17 (s, 3 H), 3.0-1.1 (m, 7 H), 1.06 (d, J = 7 Hz, 3 H); ^{13}C NMR 184, 151.0, 142.9, 141.1, 132.8, 95.5, 50.8, 29.3, 26.0, 23.3, 20.6, 16.9; mass spectrum, exact mass calcd for $C_{13}H_{18}O_3$ m/e 222.1256, obsd m/e 222.1266.

Anodic Oxidation of 21b



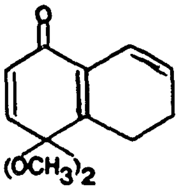
In a single electrolysis cell was placed **21b** (226 mg, 1.09 mmol) and 2% $LiClO_4/CH_3OH$ (70 mL). The solution was electrolyzed (1.2 h) at 0 °C (2.7 V, 0.04 A) until TLC showed disappearance of starting material. The resulting solution was concentrated in vacuo, extracted with CH_2Cl (3 x 30 mL)/H_2O (30 mL), and washed with brine. Drying (Na_2SO_4) and concentration in vacuo yielded a yellow oil. Flash column chromatography (CH_2Cl_2) gave **26d** (209 mg, 85%): IR (film) 2930, 1670, 1640, 1620, 1460, 1290, 1110, 1100, 1060 (br), 960, 840, 730; ^1H NMR δ 6.63 (AB q, $\underline{J}$ = 10 Hz, 1 H), 6.35 (AB q, $\underline{J}$ = 10 Hz, 1 H), 3.15, 3.14 (s, 6 H), 2.9-1.0 (m, 9 H), 0.99 (t, $\underline{J}$ = 7 Hz, 3 H); ^{13}C NMR δ 184.4, 151.0, 142.8, 141.0, 132.8, 95.4, 50.7 (2 C), 32.5, 26.4, 24.6, 23.2, 17.0, 12.0; mass spectrum, exact mass calcd for $C_{14}H_{20}O_3$ $\underline{m/e}$ 236.1413, obsd m/e 236.1319.

Anodic Oxidation of 21c



In an electrolysis cell equipped with a magnetic stirrer was placed **21b** (233 mg, 1 mmol) and 2% $LiCO_4/CH_3OH$ (70 mL). The solution was electrolyzed at 0 °C (2.1 V, 0.034 A) for 1.4 h after which time TLC showed no material remain until disappearance of starting material. The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2/H_2O (3 x 30 mL/30 mL), and washed with brine. Drying (Na_2SO_4) and concentration in vacuo gave **26e** as a light yellow oil (255.1 mg, 97%). Flash column chromatography (CH_2Cl_2) gave **26e** (216.4 mg, 82%, known compound).

Anodic Oxidation of 22



In an electrolysis cell equipped with a magnetic stirrer was placed **22** (234 mg, 1.33 mmol) and 2% $LiClO_4/CH_3OH$ (70 mL). The solution was electrolyzed at 0 °C (2 V, 0.041 A) for 1.5 h, after which time TLC showed no starting material remaining. The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 30 mL)/H_2O (30 mL), and washed with brine (30 mL). Drying (Na_2SO_4) and concentration in vacuo yielded crude **26f** (241 mg, 88%). Flash column chromatography gave **26f** (212 mg, 77%): IR (film, cm^{-1}) 2930, 2820, 1670, 1640, 1620, 1300, 1100, 1060 (br), 950; ^1H NMR 6.23 (AB q, J = 10 Hz, 1 H), 6.39 (AB q, J = 10 Hz, 1 H), 6.85-5.85 (m, 2 H), 3.21 (m, 6 H), 2.48-2.2 (m, 4 H); ^{13}C NMR 182.4, 147.6, 143.4, 133.4, 132.1, 129.1, 119.1, 95.4, 51.0 (2 C), 21.5, 20.6; mass spectrum, exact mass calcd for $C_{12}H_{14}O_2$ m/e 190.0994, obsd m/e190.0990.

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NMR SPECTRA

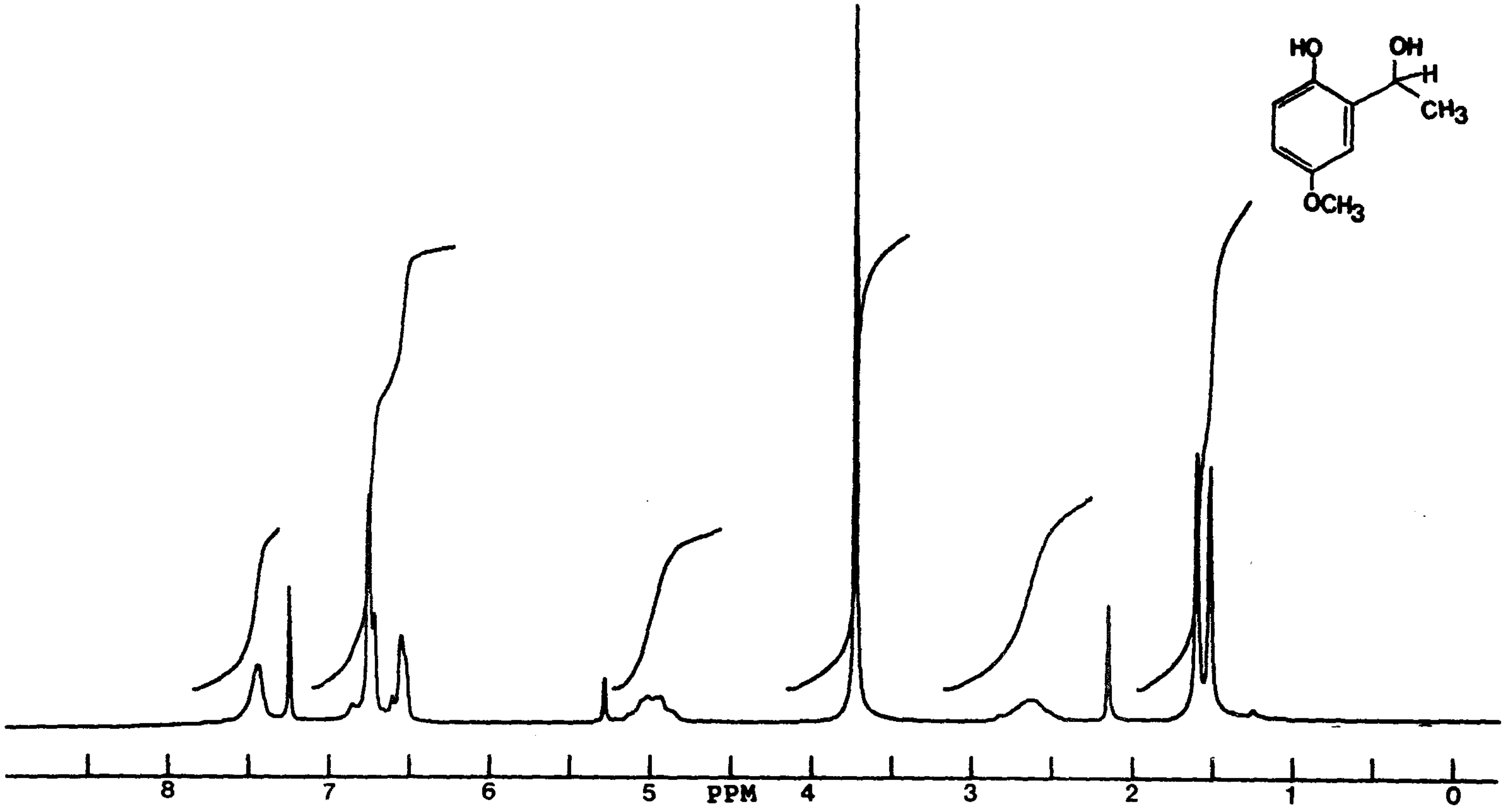


Figure 1. 80 MHz ^{1}H NMR Spectrum of 23a

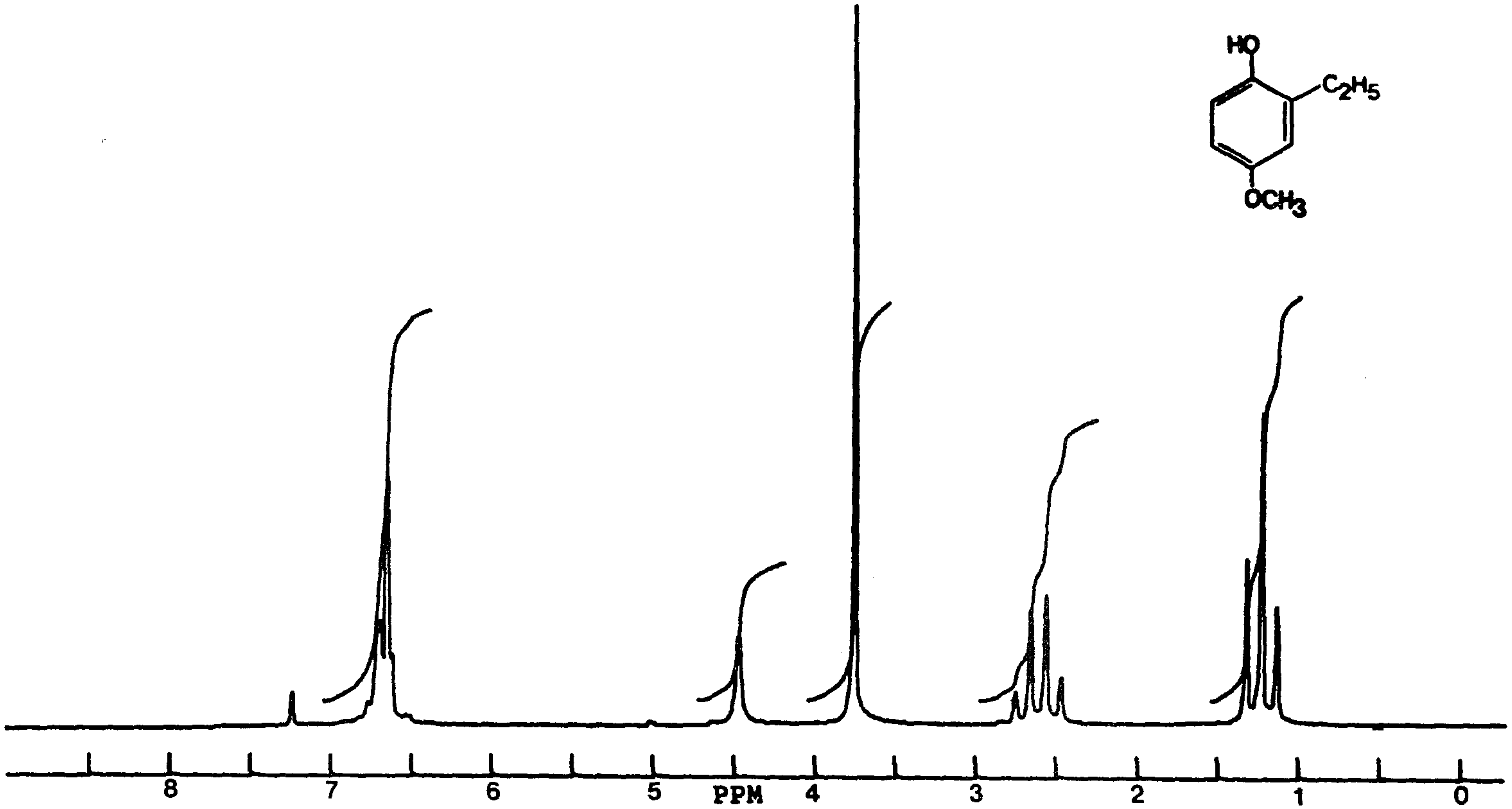


Figure 2. 80 MHz ^{1}H NMR Spectrum of 20a

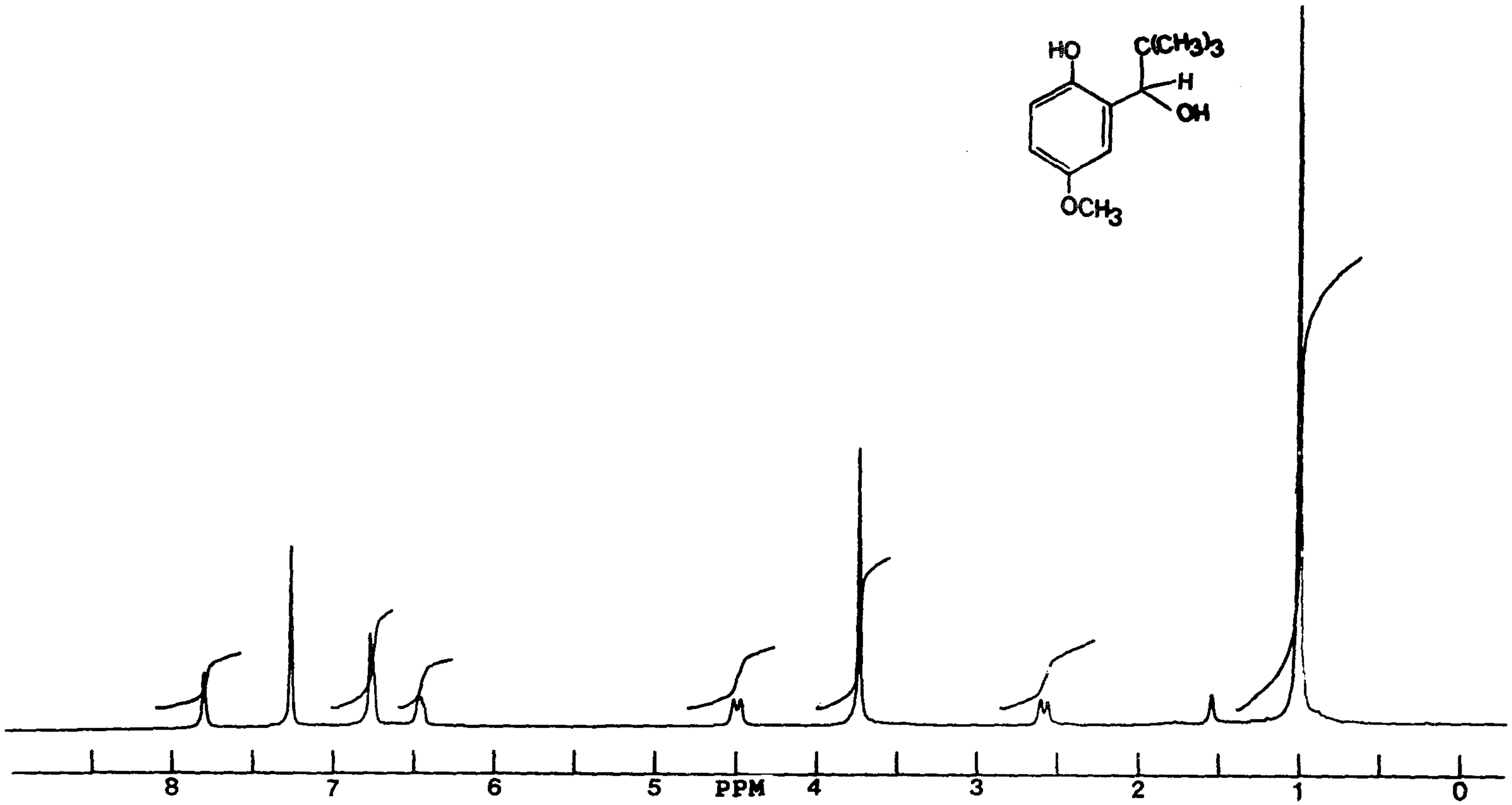


Figure 3. 80 MHz ^{1}H NMR Spectrum of 23b

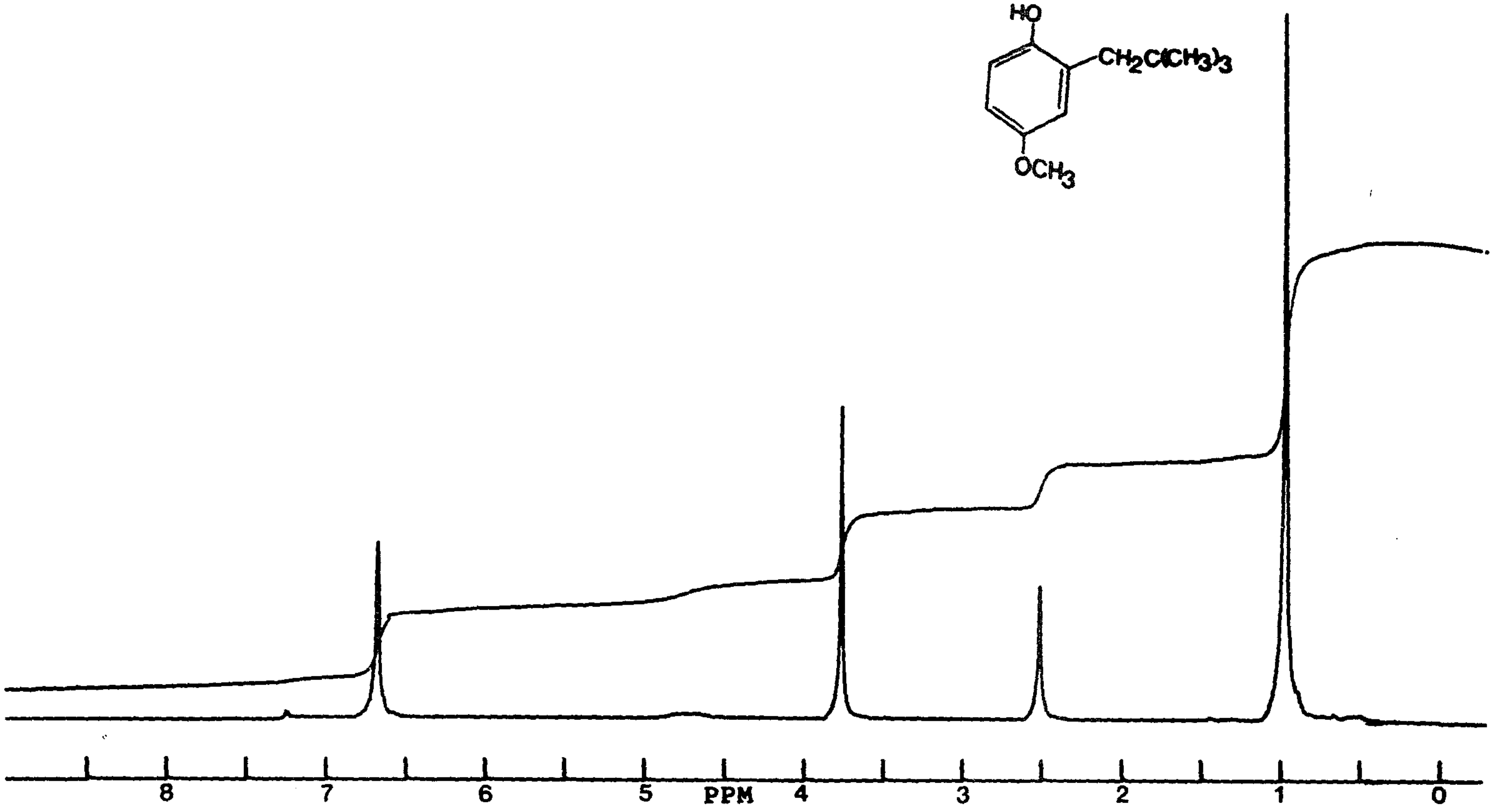


Figure 4. 80 MHz ^{1}H NMR Spectrum of 20b

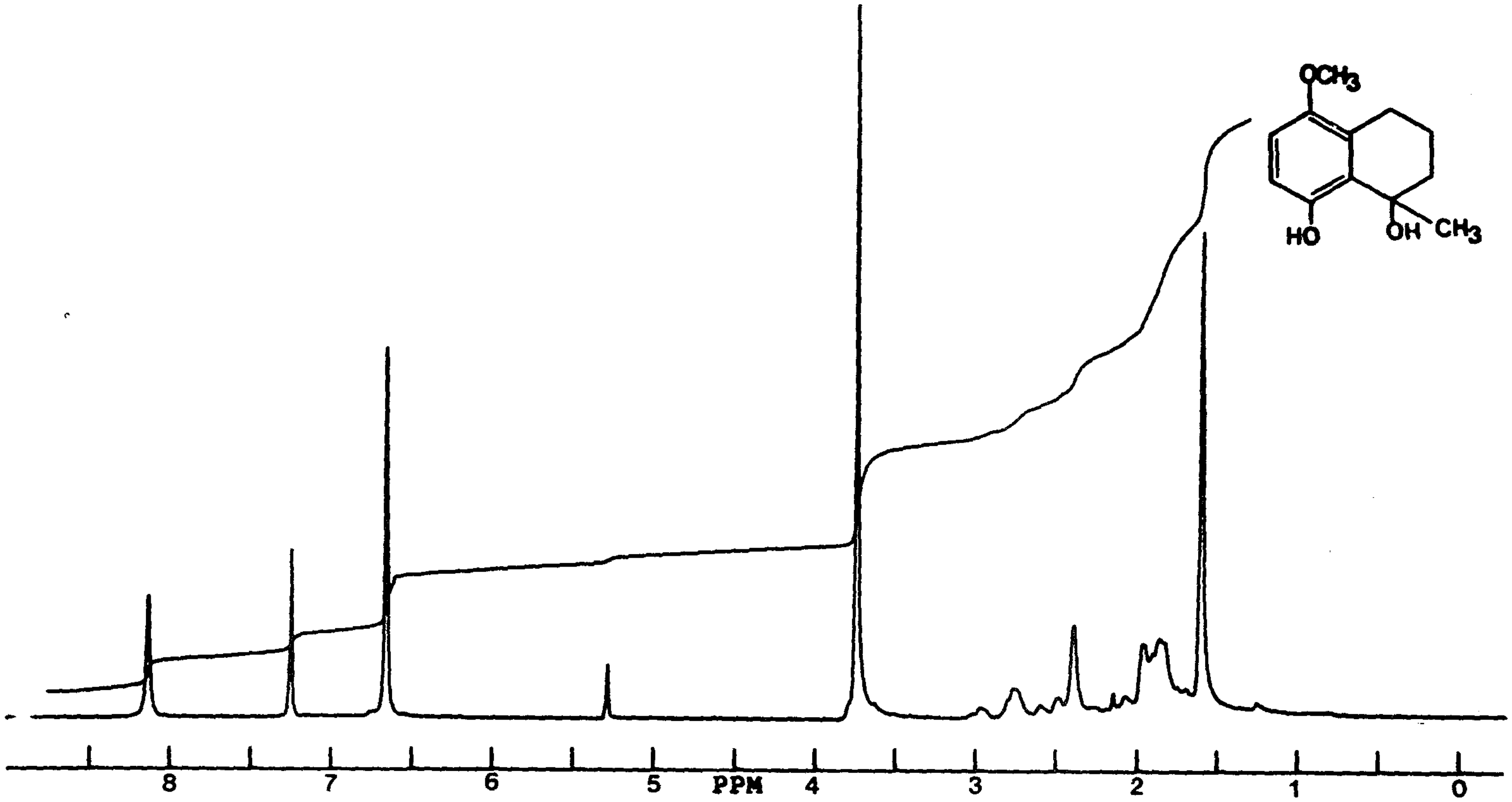


Figure 5. 80 MHz ^{1}H NMR Spectrum of 25a

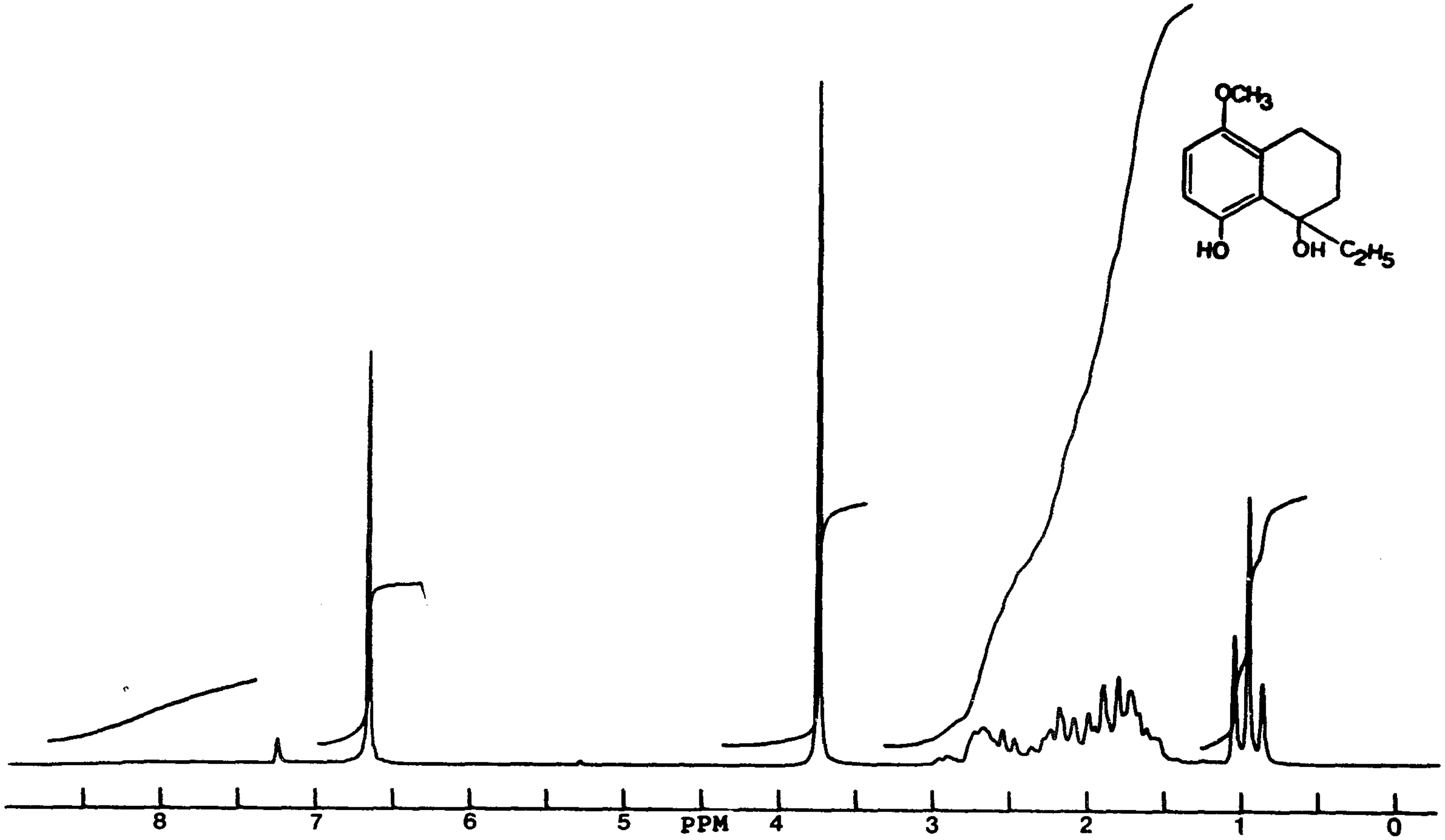


Figure 6. 80 MHz ^{1}H NMR Spectrum of 25b

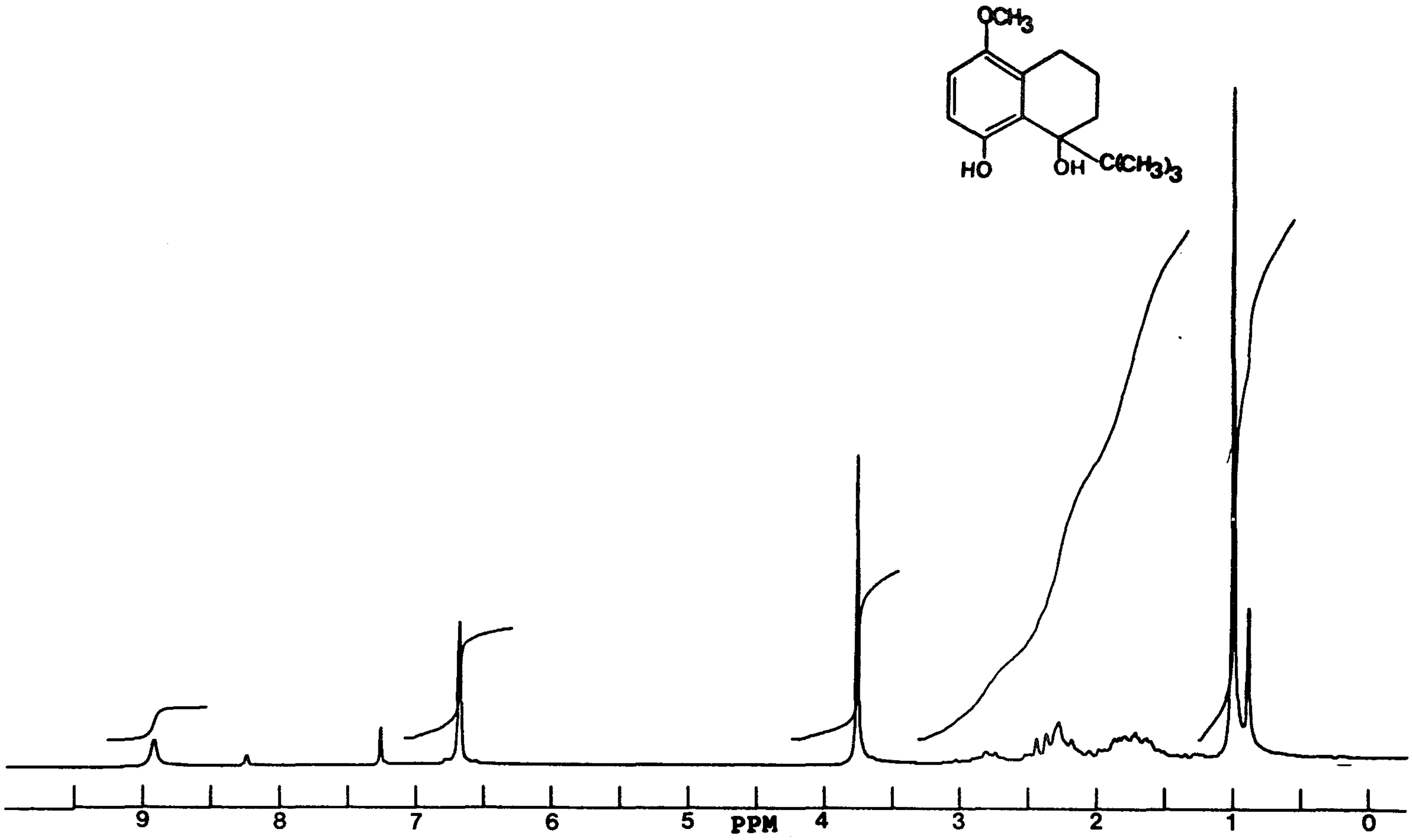


Figure 7. 80 MHz ^{1}H NMR Spectrum of 25c

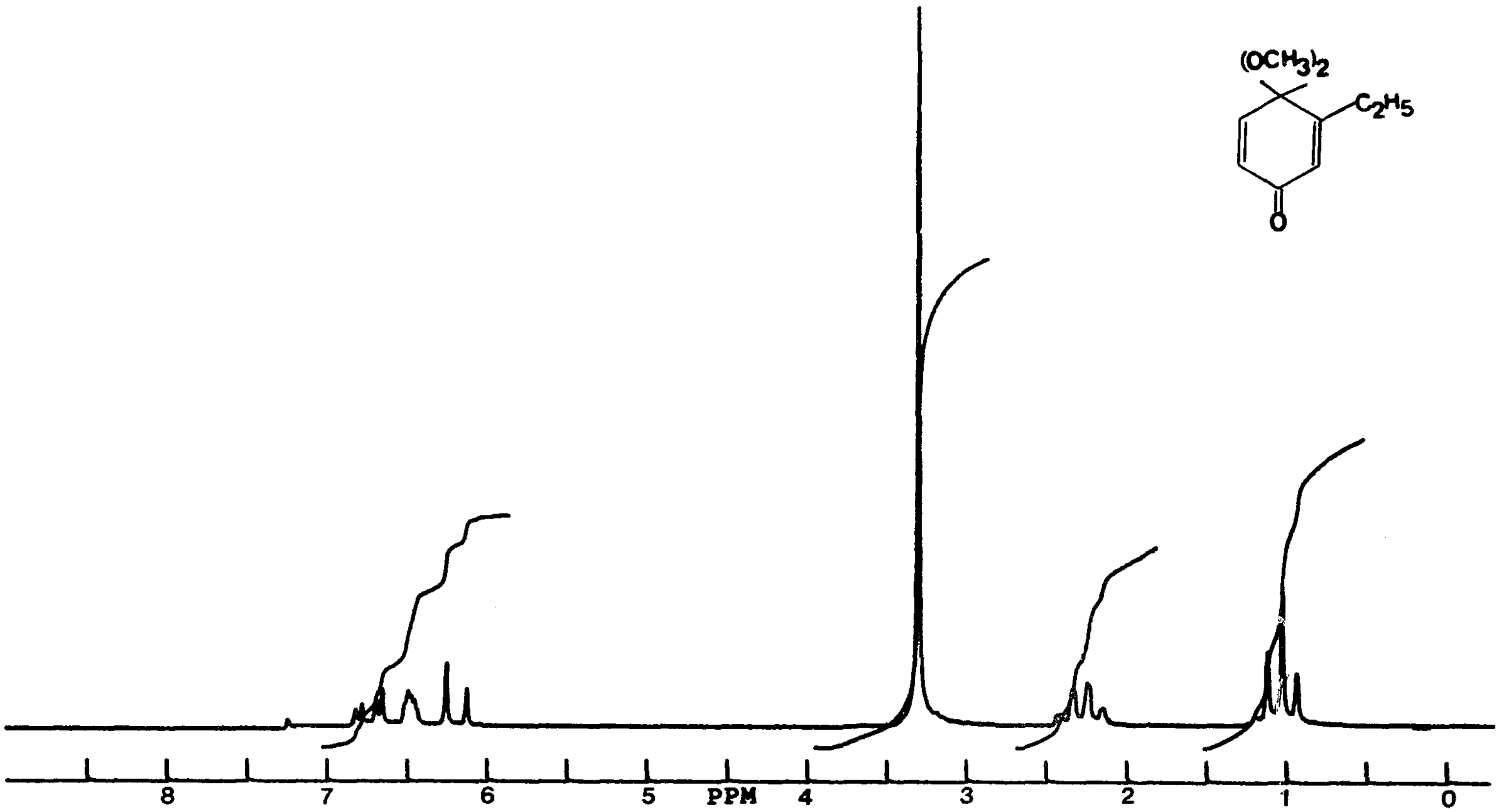


Figure 8. 80 MHz ^{1}H NMR Spectrum of 26a

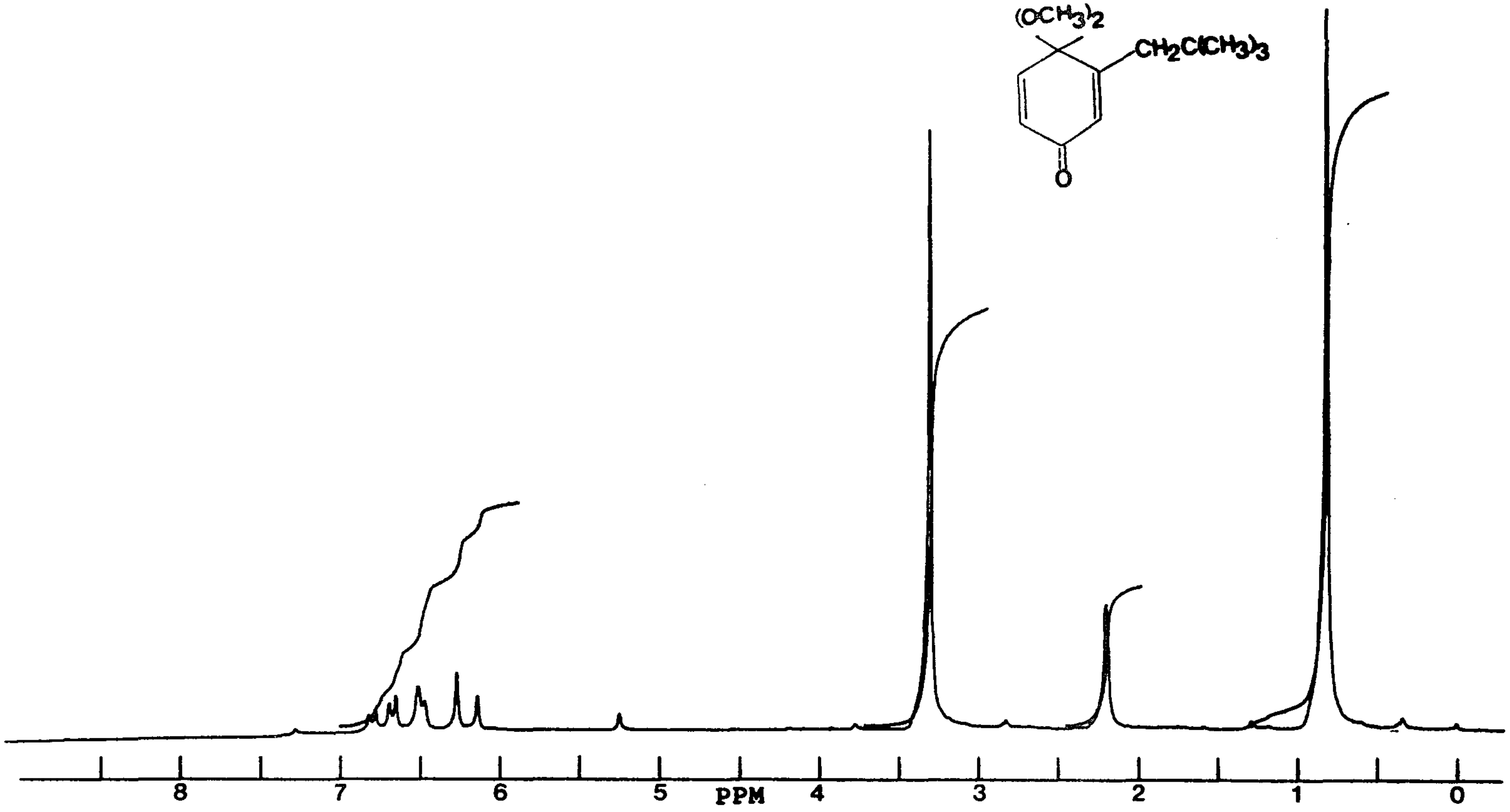


Figure 9. 80 MHz ^{1}H NMR Spectrum of 26b

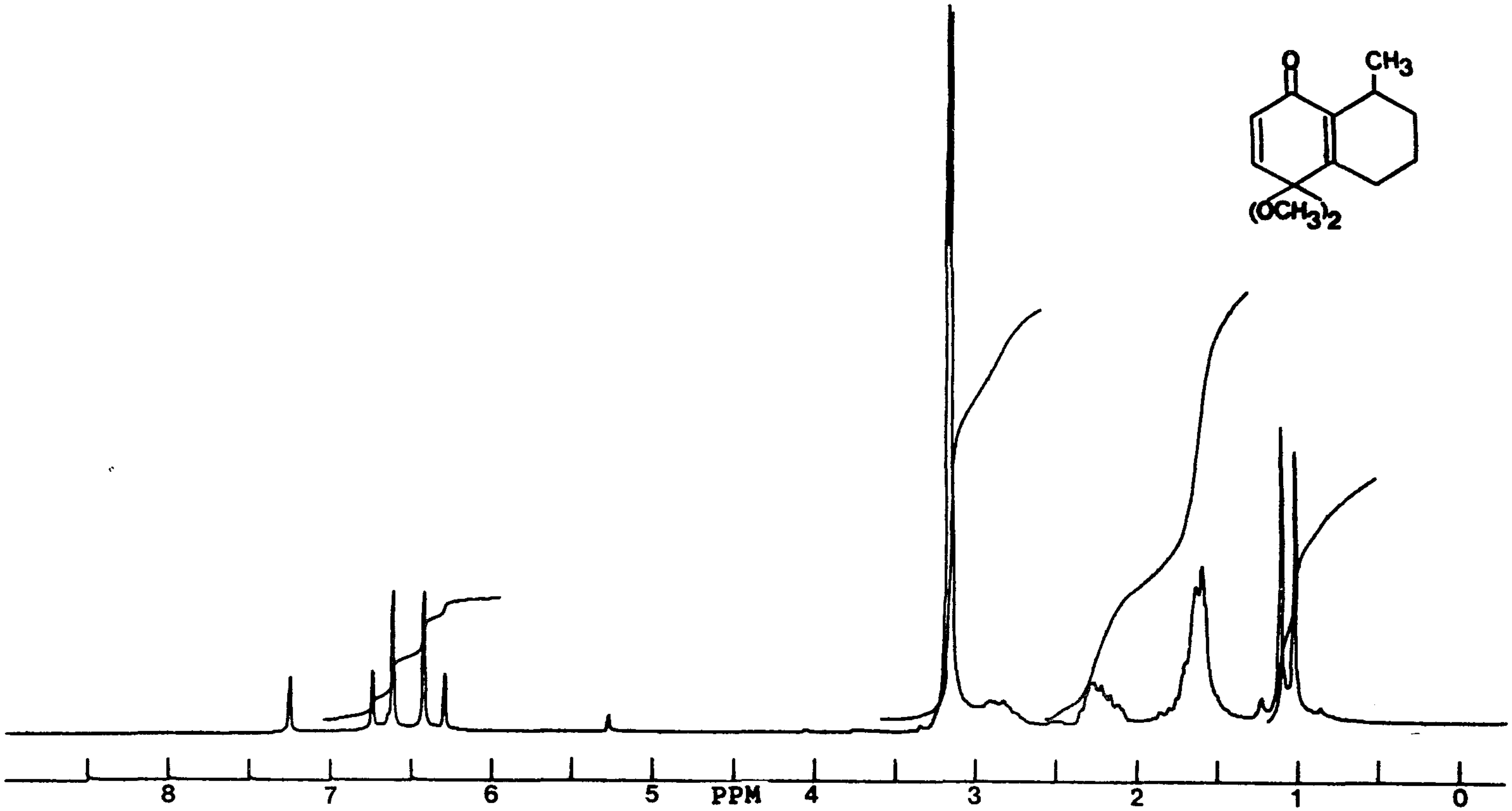


Figure 10. 80 MHz ^{1}H NMR Spectrum of 27a

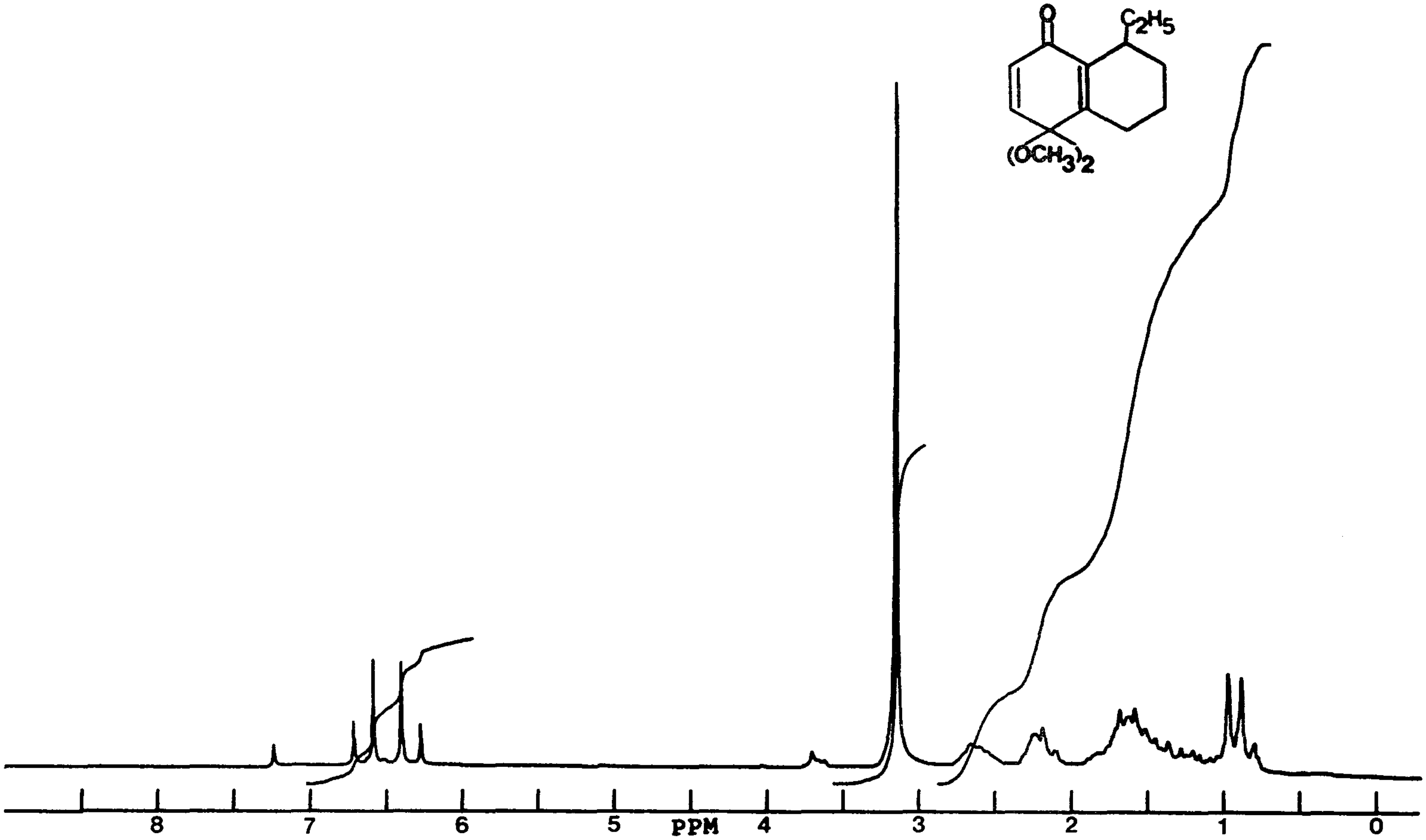


Figure 11. 80 MHz ^{1}H NMR Spectrum of 27b

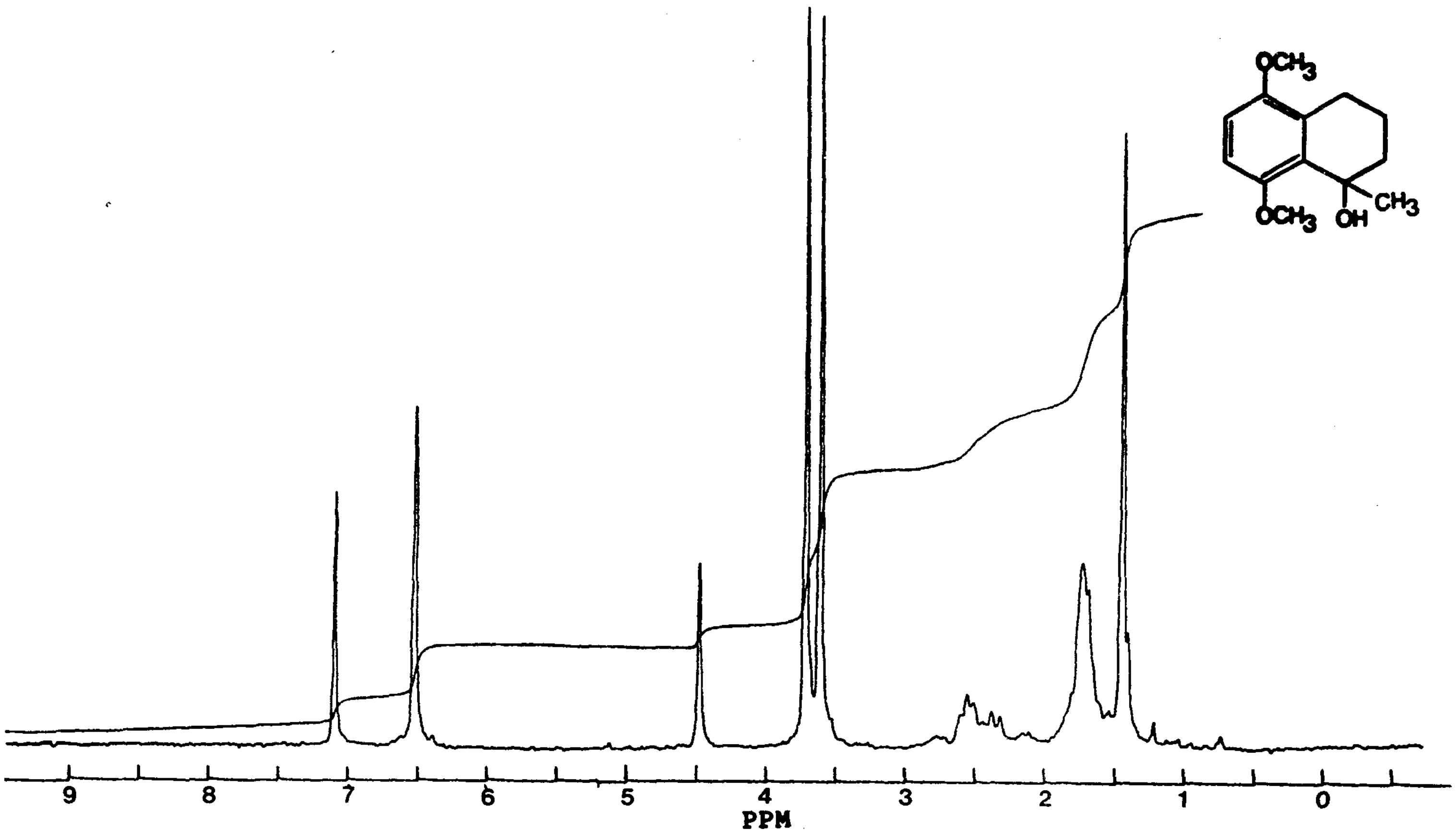


Figure 12. 80 MHz ^{1}H NMR Spectrum of 28

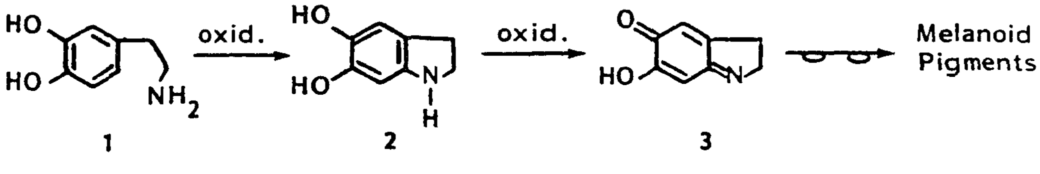
PART III

A GENERAL APPROACH TO QUINONE IMINE KETALS

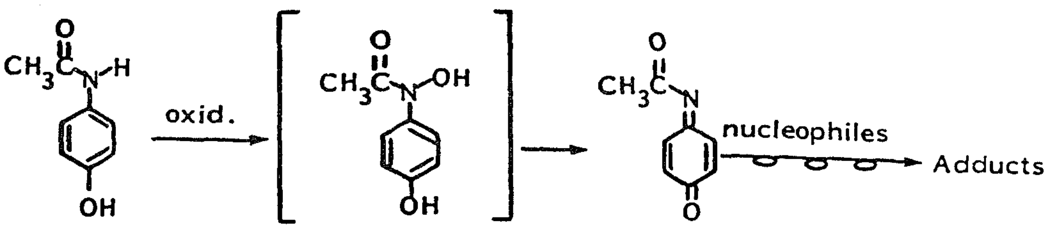
INTRODUCTION

Quinone imines and quinone diimines have been of long-standing interest in chemistry,[1-3] and the former moieties have been proposed as intermediates in a number of biological processes. The simple quinone imine moiety is extremely unstable[1-3] under conditions used for its generation, and it is subject to rapid hydrolysis, condensation reactions with starting material, and nucleophile-induced polymerization. Investigators have generated this intermediate from electrochemical oxidation of o-aminophenols[4] and p-aminophenols,[5] and much of the information on the rates of reaction of quinone imines derives from cyclic voltammetry[4,5] and fast flow kinetic studies of materials generated in situ.

Three areas of current interest illustrate the pivotal role of the quinone imine in biological systems. Thus, the oxidation of dopamine and a number of its derivatives has been studied electrochemically since the quinone imine is a reasonable intermediate for the formation of melanoid pigments, as illustrated in the abbreviated scheme below.

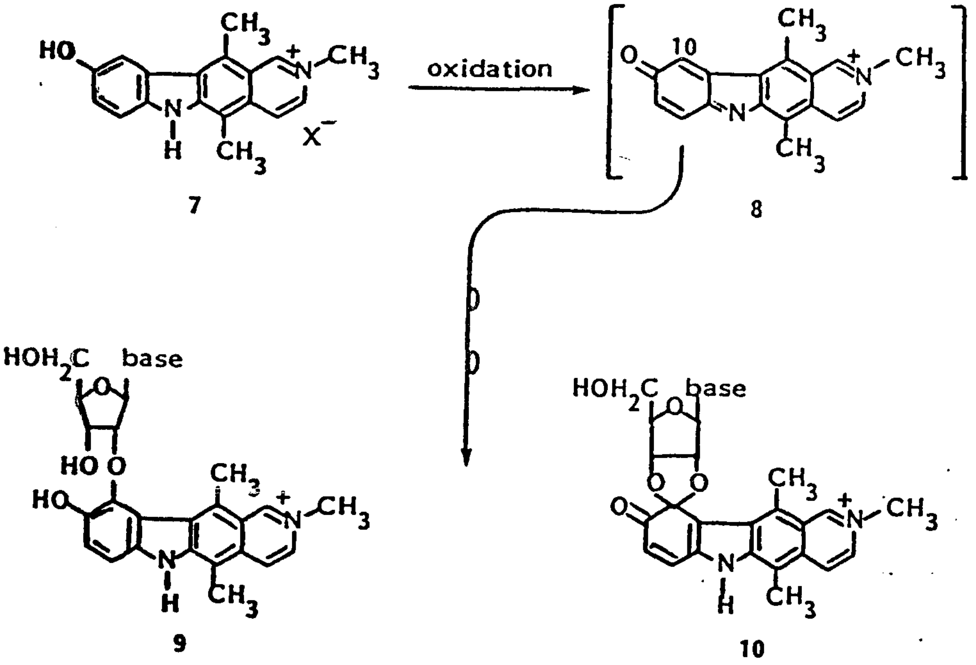


Recent studies of the analgesic paracetamol,[6] **4**, attribute its toxicity to a metabolically formed quinone imine which binds cell macromolecules, presumably via a Michael-type addition.



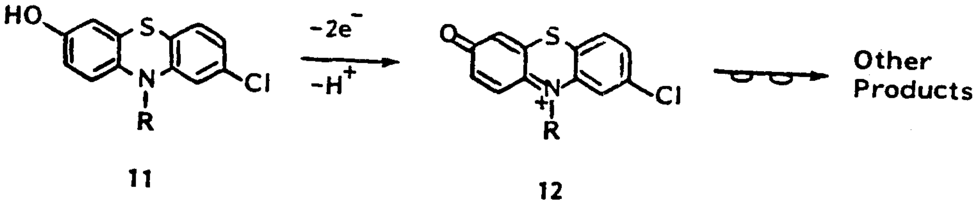
4 **5** **6**

Finally, reaction of N-methyl-9-hydroxyellipticinium acetate, **7**, with horseradish peroxidase in biological systems has led to the isolation of adducts with adenosine[7-10] and guanosine[11] as well as more standard nucleophiles. These products reasonably arise from attack at C-10 of the quinone imine **8** intermediate shown below. Interestingly, only products from nucleophilic attack at C-10 were isolated. While this was ascribed to a regiospecific functionalization reaction, the isolated yields of product were in the 30-40% range so that it is difficult to rule out other positions of attack of the nucleophile on the quinone imine. Furthermore, in at least one case, the initial product was misassigned, and the actual product was the result of a second oxidation of the initially formed adduct.[10]



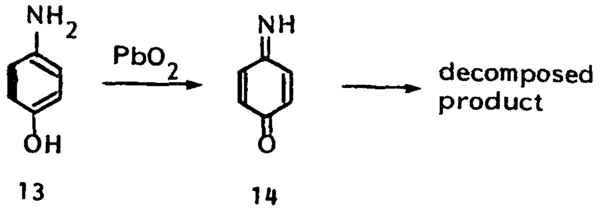
In addition, the chemistry of N-alkylated quinone imine intermediates offers possible explanations for some side effects of long-term chloropromazine therapy.[12]

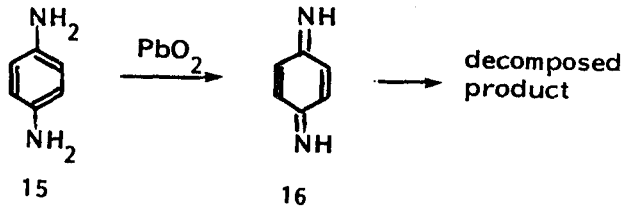
As is evident from the short discussion above, the quinone imine unit is an important entity in biological systems. Conventional methods of generating quinone imines involve oxidation[1] (potassium dichromate, ferricyanide, permanganate, silver oxide, lead dioxide, N-3,5-dinitrobenzoyl-N-t-butyl nitroxyl,[5e] electrochemical) of p-aminophenols. The presence of the unreduced form during the oxidation can lead to condensation and polymerization products. Even biological oxidation (horseradish peroxidase) requires that other species present be stable to the oxidation conditions. As noted above in the ellipticene studies,[10] in situ generation of quinone imines via oxidation can lead to further oxidation of the initially formed products. This could not only complicate interpretation of the chemistry but could also give products derived from reaction of the substrate with other oxidized species. Furthermore, oxidations performed in buffered aqueous solution--typical of many of the mechanistic and biological studies--virtually ensure competing reaction of the quinone imine with water.



Chemical Generation of Quinone Imine

As mentioned before, quinone imines are usually quite unstable under conditions used for their generation. For example, a Japanese group[13] prepared quinone imines and quinone diimines by using PbO_2 and $K_3Fe(CN)_6$ as oxidation agents to oxidize **13** to **14** and **15** to **16** as shown below.

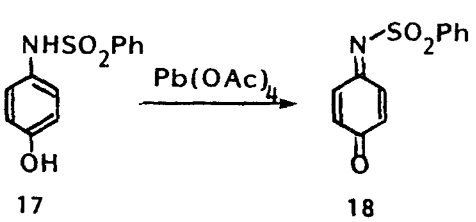




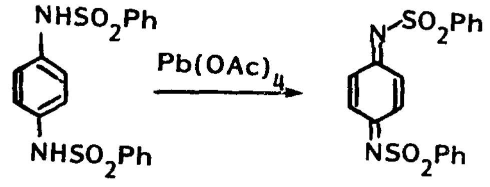
15 16

The yellow compounds **14** and **16** could not be isolated because of their instability. These compounds were identified only by UV absorption spectra (e.g., **14** and **16** could exist only in dilute solution). This instability has prevented their isolation and a more detailed study of their chemistry, spectroscopy, and biology under well defined conditions.

Stable quinone imine derivatives are known; however, the nitrogen substituents are removed only under harsh reaction condition. In the 1950's Adams and his co-workers[14] successfully used lead tetraacetate to oxidized N-protected p-aminophenol **17** to quinone monosulfonimides **18** and N-protected p-phenylenediamine **19** to p-quinone disulfoninides **20** as shown below.



17 18



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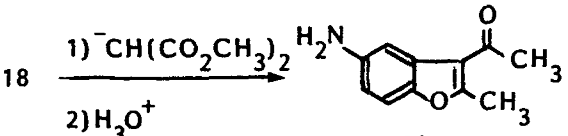
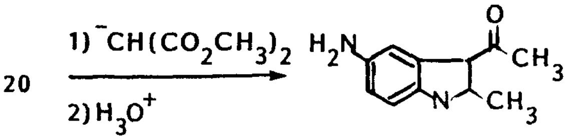
20

These quinone imides and diimides are stable enough to be isolated and can be reacted with acetylacetone anion to afford Michael addition products. However, attempted removal of the phenylsulfonyl group requires heating in concentrated acid and results in cyclization to the furan and indole derivatives **21** and 22. The strongly acidic



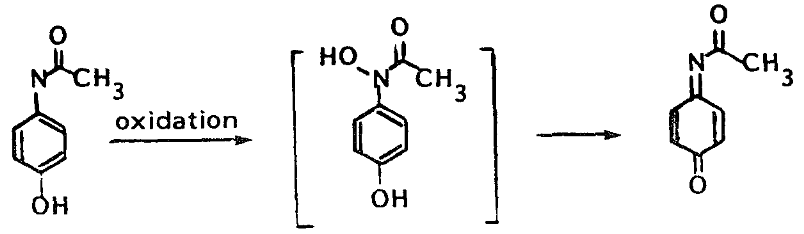
21



22

conditions required for deblocking of the phenylsulfonyl group severely limit the synthetic use of this protecting group for preparing the extremely sensitive unprotected quinone imine linkage.

Alewood and his co-worker[15] studied the oxidation mechanism of analgesic paracetamol (N-acetylated p-aminophenol) 23 to N-acetyl-1,4 benzoquinone imine 24 via N-hydroxyl intermediate 25; however, no yield was reported.



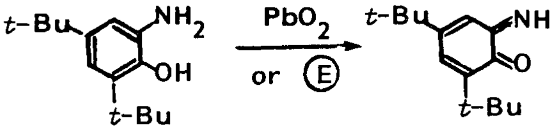
23 25 24

A more readily removable group on quinone imine would be a carboxylic acid amide linkage. Like quinonesulfonimide the quinone imide 24 can be isolated via silica gel chromatography, but some decomposition results and the compound apparently cannot obtained pure.

Electrochemical Generation of Quinone Imines

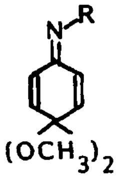
More recently electrochemical oxidation of aminophenol 1 was studied by Young.[16] By using a carbon-paste electrode, oxidation of 1 in 1M $HClO_4$ and McIlvaine buffers gave quinoneimine 3 which polymerized to melanoid pigments. These workers were primarily concerned with kinetic investigations of the electrogenerated quinone imines by cyclic voltammetry. No preparative reactions of the quinone imines generated in this study were reported.

Another electrochemical and spectroscopic study of quinone imines has been descovered by Sawyer and his co-worker.[17] In this work either chemical (lead dioxide) or electrochemical oxidation of 3,5-di-t-butyl-



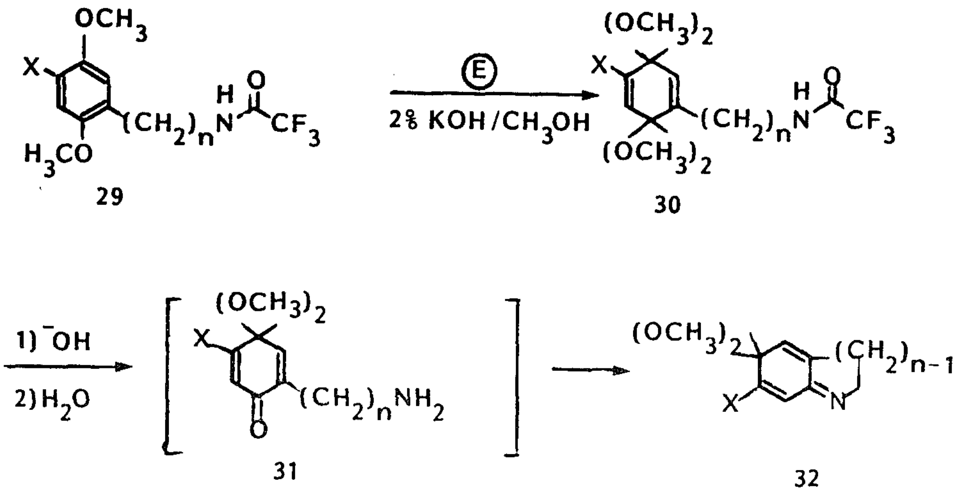
26 **27**

2-aminophenol **26** generated the o-quinone imine 27. However, again a kinetic study of the in situ generated o-quinone imine was the major goal of the study. While the lead dioxide oxidation was reported to give **27** in high yield, even this highly hindered compound reacted with starting **28** to give unreported products.



28

Finally, another way can be used to protect quinone imines, and this would be to prepare quinone imine ketal such as 28. Chuan Shih in this laboratory[18] developed a route to the quinone imine ketals as shown in Scheme I. Anodic oxidation the trifluoroacetamide affords the quinone imine ketals **32a-d** in the yield shown. The trifluoroacetamide group not only blocked oxidation at the amino group but also allowed deprotection to the amine by hydrolysis under mild basic conditions. The cyclization process can be conducted in water at pH 6.5-7.0 for 16 h.



a, X = OCH_3, n = 1 (68%)
b, X = OCH_3, n = 2 (45%)
c, X = Br, n = 1 (46%)
d, X = Br, n = 2 (57%)

While the above approach gives acceptable yields, considering four chemical steps are involved, it is severely limited by requiring a group which directs the monohydrolysis of the ketal function adjacent to the side chain containing the amino group. For the above system, the methoxyl and bromo substituents direct hydrolysis in this manner, but all attempts to prepare unsubstituted quinone imine ketals via this strategy afforded difficult-to-separate mixtures. This is the main limitation of this route.

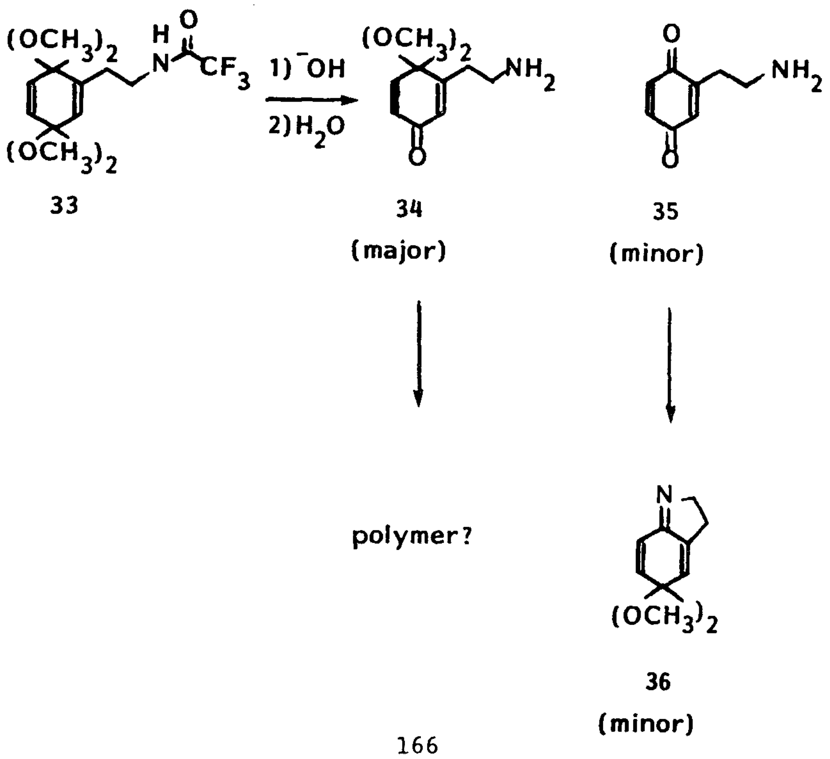
The above discussion was not intented to give a comprehensive review of quinone imine chemistry. This topic is presented in detail in Patai's chapter.[19] However, the chosen examples illustrate the interest and methods used to generate the highly reactive quinone imine linkage.

Objective

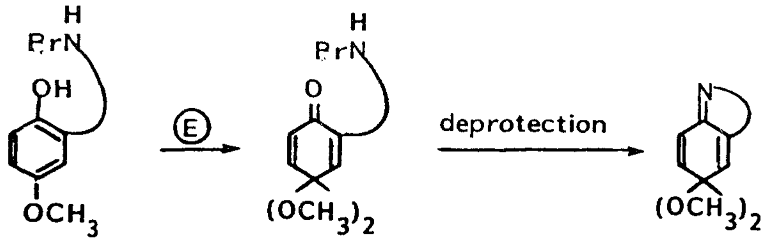
The overall objectives of this research problem were to develop a general route to quinone imine ketals using the oxidation of p-methoxy phenols which were discussed in Part II of this dissertation.

RESULTS AND DISCUSSION

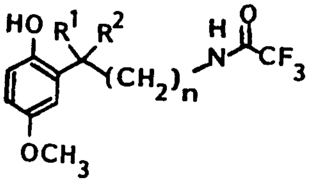
As noted in the introduction, the intramolecular reaction of quinone monoketals with side chains containing amino groups to form quinone imine ketals is not general. The limitation in this approach is the regiochemistry of the bisketal monohydrolysis. If a strong directing group is not present to direct hydrolysis then very poor yields of the quinone imine ketal result. If there is no directing group presented, for example, as in 33, base deprotection and monohydrolysis of 34 gave no isolable quinone imine ketal 35.



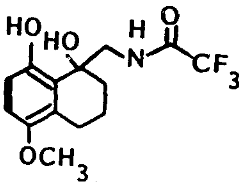
As mentioned in Part II of this thesis, substituted p-methoxy phenols can be electrochemically oxidized to substituted quinone monoketals. The goal was a general route to quinone imine ketals as outlined in Scheme II. This route would avoid the problem inherent with routes requiring regioselectivity in the hydrolysis of quinone bisketals.



The starting phenols 37a-f were prepared as shown below (4

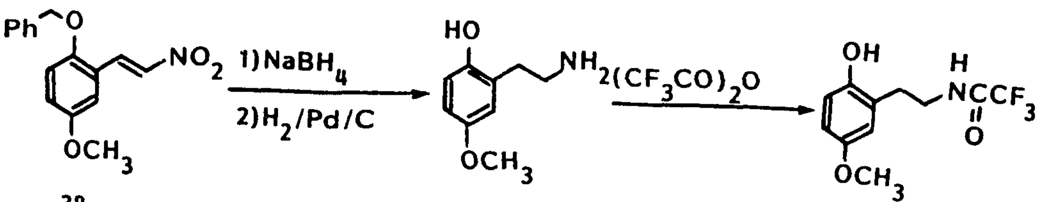


37a, $R^1 = R^2 = H$, n = 1
b, $R^1 = H$, $R^2 = OH$, n = 1
c, $R^1 = CH_3$, $R^2 = OH$, n = 1
d, $R^1 = H$, $R^2 = OH$, n = 2
e, $R^1 = CH_3$, $R^2 = OH$, n = 2



37f

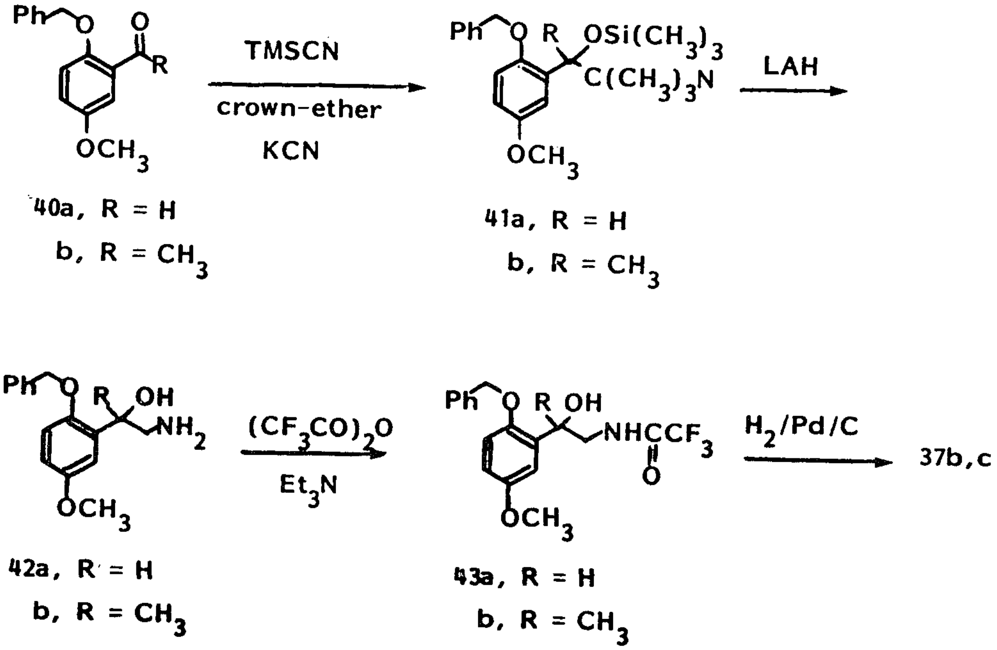
Series I (R^1 - R^2 - H, n - 1):



38 39 37a

Sodium borohydride reduction of **38**, followed by hydrogenation of the nitro group and deprotection of the phenol gave the known compound **39**. Then protection of the amine side chain by reaction of **39** with one equivalent trifluoroacetic anhydride and using triethyl amine as a base to neutralize trifluroacetic acid gave **37a** in good yield. The structure of **37a** was supported by spectroscopic data. Most informative was the strong IR absorption at 1710 cm^{-1} assigned as trifluoroamide linkage.

Series II (R^1 = H, R^2 = OH or R^1 = CH_3, R^2 = OH, n = 1)



40a, R = H
b, R = CH_3

41a, R = H
b, R = CH_3

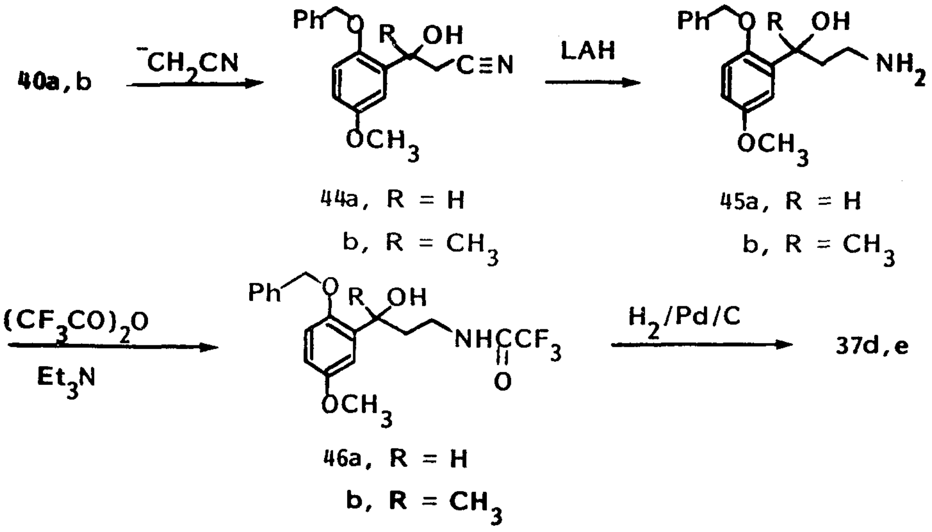
42a, R = H
b, R = CH_3

43a, R = H
b, R = CH_3

The preparation of the second series of compounds involved preparation of the cyanohydrin of **40a,b**. Thus, reaction of one equivalent trimethylsilyl cyanide, a catalytical amount of crown ether (18-crown-6), and potassium cyanide under reflux conditions (150 °C) for 2-3 hours gave **41a,b** in very good yields. The structures of **41a,b** were supported by spectroscopic data. A weak IR absorption at 2220 cm^{-1} was assigned as cyanide linkage. The ^1H NMR showed trimethyl silyl protons at δ 0.1. Lithium aluminum hydride reduction of **41a,b** in dry THF overnight at room temperature gave in high yields products **42a,b**. The structures of **42a,b** were supported by spectroscopic data: a broad IR peak around 3600-3100 cm^{-1} indicating the NH_2 linkage, and the ^1H NMR showed two NH_2 protons as broad peaks at δ 2.1. Like Series I, trifluoroacetyl amide formation of **42a,b** with trifluoroacetic anhydride gave **43a,b**. Finally, hydrogenation of **43a,b** with palladium on carbon as catalyst gave **37b,c** in good yields.

Series III (R^1 = H, R^2 = OH or R^1 = CH_3, R^2 = OH, n = 2):

The next series of compounds was prepared using acetonitrile as the source of the carbon and nitrogen of the side chain. The anion from acetonitrile (which was prepared by addition of acetonitrile/THF solution to a solution of lithium diisopropyl amine) was reacted with **40a,b**. Workup followed by flash column chromatography gave **44a,b** in good yields. The structures of **44a,b** were supported by spectroscopic data. A weak IR absorption around 2210 cm^{-1} is assigned to the cyanide linkage. The ^1H NMR spectrum showed an extra methylene peak at δ 2.97. Lithium aluminum hydride reduction of **44a,b** yielded **45a,b**. Again,



44a, R = H
b, R = CH_3

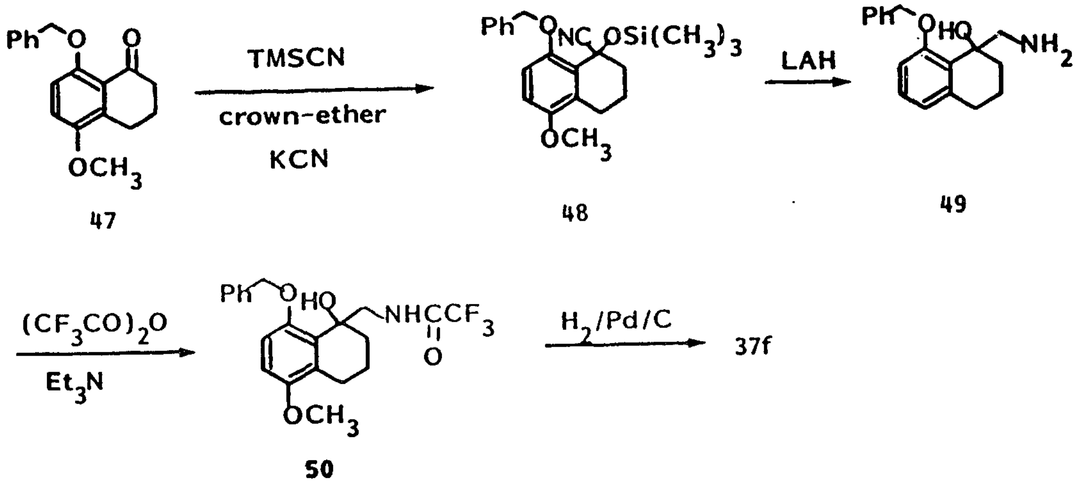
45a, R = H
b, R = CH_3

46a, R = H
b, R = CH_3

trifluoroacetyl group was used to protect the amine, giving **46a,b**. Hydrogenolysis of **46a,b** gave the required phenol **37d,e** in good yields.

Series IV:

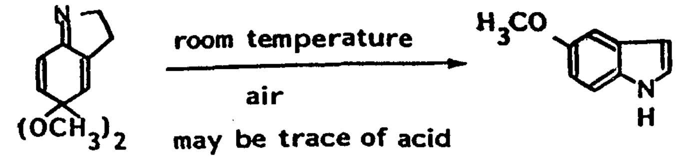
The final series of compounds chosen for study was prepared by adding trimethylsilylcyanide to **47** to afford a good yield of **48**. Lithium aluminum hydride reduction of **48** gave **49** in excellent yield. Trifluoroacetyl protection of **49** gave **50** in 80% yield. Hydrogenation of the benzyl ether **50** gave phenol **37f** in good yield. Benzyl protection of the phenols was necessary in this case since the direct reaction of trimethylsilyl chloride with **51** gave recovered material.



Anodic Oxidation Studies

The anodic oxidation of **50a-f** was conducted at 0°C in a 2% $LiClO_4/CH_3OH$ solution using Pt as both anode and cathode. All anodic oxidations were monitored by ultraviolet spectrometer, and two isosbestic points were observed indicating a clean oxidation. In each case, the resulting quinone monoketals **68a-f** were immediately dissolved in tetrahydrofuran and hydrolyzed by adding about 1-1.5 equivalents 5% aqueous potassium hydoxide. Workup as usual gave crude quinone imine ketals 52a-f as listed in Table I.

The crude quinone imine monoketals are stable when stored in base-washed apparatus. The compounds can be further purified by chromatography on neutral alumina. Some quinone imine monoketals are not stable at room temperature and must be stored at -20 °C. For example, **52a** ($R^1 = R^2 = H$) is converted to indole 53 at room temperature in about



52a

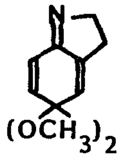
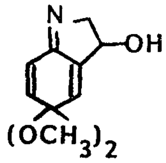
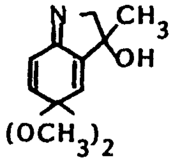
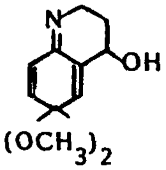
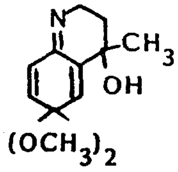
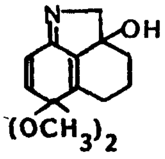
53 (70%)

70% yield (along with some oxidized inpurities). The structure of all quinone imine ketals were supported by spectroscopic data. The strong IR absorption around 1600 cm^{-1} is assigned to imine linkage, and the ^{13}C NMR spectrum showed the carbon of imine linkage at δ 163 (five-membered ring imine), or δ 155 (six-membered ring imine).

Summary

From the above results, the anodic oxidation/hydrolysis/cyclization affords a general convenient route to quinone imine ketals. They are to be transformed to indole and quinoline derivatives or further functionalized at the 2-position as will be described later.

Table I. Anodic Oxidation and Quinone Immine Formation

Substrate	Product	Yield (%)
37a	 52a	82
37b	 52b	91
37c	 52c	81
37d	 52d	91
37e	 52e	89
37f	 52f	89

EXPERIMENTAL

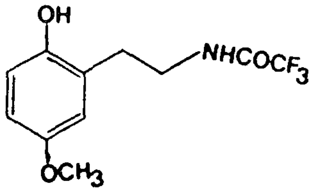
General Procedures

Melting points were taken in capillaries in a Thomas-Hoover "Unimelt" apparatus and are uncorrected. Infrared spectra were on a Perkin-Elmer Model 283B spectrometer. ^{1}H and ^{13}C nuclear magnetic resonace spectra (NMR) were recorded on Bruker NR 80 Model spectrometer. All NMR spectra were recorded in $CDCl_3$ and are reported in ppm relative to $CHCl_3$ (δ = 7.24) unless otherwise noted. Mass spectral and exact mass mesurements were obtained from Mr. Richard Weisenberger on a Kratos MS-30 spectrometer. Alumina and silica gel were obtained from E. Merck Co. Tetrahydrofuran was purified by distillation from benzophenone ketyl. Dichoromethane, benzene, and toluene were distilled from calcium hydride. Anhydrous diisopropylamine and triethyl amine were distilled from potassium hydroxide. Anhydrous dimethyl formamide was distilled from barium oxide (79 ^{0}C, 35 mm). All of these purified solvents were stored over 4A molecular sieves. Solutions of alkyl lithiums or alkyl magnesium bromides were from Aldrich Chemical Co.

Throughout the experimental, the following abbreviation are used: petroleum ether, bp 35-60 ^{o}C (PE), tetrahydrofuran (THF), ethyl ether (Et_2O), n-butyllithium (n-BuLi), and diethylaminosulfur trifluoride (DAST).

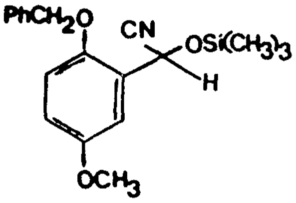
All preparative anodic oxidations were preformed in a single-cell or in H-type divided-cell apparatus in methanol using a circular platinum gauze anode (33 mm diameter x 28 mm high) and platium sheet cathode (8 x 8 mm) unless otherwise stated.

Preparation of 37a from 39



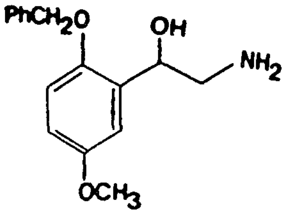
To a round-bottomed flask equipped with a magnetic stirrer and N_2 inlet were mixed **39** (0.183 g, 1.09 mmol) in dry THF (15 mL) and Et_3N (0.3 mL). At 0 °C $(CF_3CO)_2O$ (0.162 mL, 1.05 equiv) was syringed into the flask. After stirring at room temperature for 30 min, the resulting mixture was concentrated in vacuo and extracted with CH_2Cl_2 (3 x 30 mL)/H_2O (30 mL). The combined solution was washed with saturated NH_4Cl (30 mL) and brine (30 mL), Drying (Na_2SO_4), and concentration in vacuo to yield a light brown oil. Flash column chromatography (10:1 CH_2Cl_2/EtOAc) gave **37a** (238.5 mg, 82%): IR (film, cm^{-1}) 3600-3200 (br), 1710, 1560, 1510, 1465, 1450, 1430, 1370-1130 (br); ^1H NMR δ 1.75-1.7 (br, 1 H), 6.8-6.5 (m, 3 H), 3.73 (s, 3 H), 3.56 (q, *J* = 6.5 Hz, 2 H), 2.86 (t, *J* = 7 Hz, 2 H); ^{13}C NMR δ 157.8 (q, *J* = 36 Hz), 153.7, 147.9, 125.8, 116.5, 116.2, 113.4, 55.8, 41.3, 29.4; mass spectrum, exact mass calcd for $C_{11}H_{12}O_3NF_3$ *m/e* 263.0769, obsd *m/e* 263.0768.

Preparation of 41a from 40a



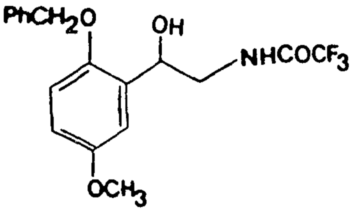
To a round-bottomed flask equipped with a magnetic stirrer and N_2 inlet were mixed **40a** (2.411 g, 9.96 mmol), 18-crown-6 (150 mg), KCN (200 mg), and TMSCN (2 mL, 1.5 equiv). The reaction mixture was heated to reflux (oil bath, 150 ^{o}C) for 1 h, then concentrated in vacuo, and flash chromatographed (1:1 CH_2Cl_2/PE) to give pure 41a (3.1 g, 91%) as a colorless oil: IR (film, cm^{-1}) 1500, 1270 (sh), 1250, 1210, 1080, 1040, 8970, 840; ^{1}H NMR δ 7.5-7.1 (m, 6 H), 6.87 (br s, 2 H), 5.81 (s, 1 H), 5.10 (s, 2 H), 3.79 (s, 3 H), 0.21 (s, 9 H); ^{13}C NMR δ 154.0, 148.8, 136.5, 128.4 (2 C), 127.8, 127.2 (2 C), 125.9, 119.0, 114.9, 113.2, 113.0, 70.8, 58.1, 55.3, -7.0 (3 C); mass spectrum, exact mass calcd for CH m/e ______, obsd m/e ______.

Preparation of 42a from 41a



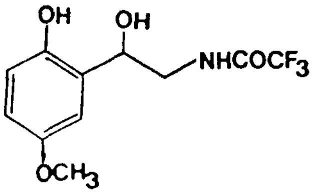
To a round-bottomed flask equipped with a magnetic stirrer and N_2 inlet was dissolved **41a** (2.39 g, 7 mmol) in dry THF (100 mL). After addition of LAH (0.9 g), the reaction mixture was stirred overnight. The reaction was quenched by addition of H_2O (5 mL), and the mixture was concentrated in vacuo, and extracted with CH_2Cl_2 (5 x 50 mL). Drying (Na_2SO_4) and concentration in vacuo yielded **42a** (1.82 g, 95%) as a light yellow oil which was used in the next step without further purification: IR (film, cm^{-1}) 3600-3000 (br), 2930 (br), 1495, 1460, 1450, 1430, 1270, 1205, 1040, 730, 690; ^1H NMR δ 7.35 (s, 5 H), 7.1-6.6 (m, 3 H), 5.01 (s, 2 H), 5.01-4.8 (m, 1 H), 3.85-3.6 (m, 1 H), 3.75 (s, 3 H), 3.2-2.7 (m, 2 H), 2.11 (br s, 2 H); ^{13}C NMR δ 153.6, 148.8, 136.9, 132.5, 128.0 (2 C), 127.3, 126.7 (2 C), 112.4 (2 C), 112.1, 70.1, 68.8, 54.9, 47.4; mass spectrum, exact mass calcd for $C_{16}H_{19}O_3N$ m/e 237.1365, obsd m/e 237.1380.

Preparation of 43a from 42a



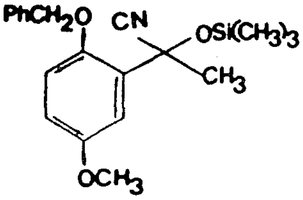
To a round-bottomed flask equipped with a magnetic stirrer and N_2 inlet were mixed **42a** (1.80 g, 6.6 mmol), Et_3N (1 mL), and dry THF (50 mL). After slow addition of $(CF_3CO_2)O$ (0.98 mL, 1.05 equiv) into the flask at 0 °C, the mixture was stirred at room temperature for 20 min. The resulting mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 50 mL)/saturated NH_4Cl (50 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave a light yellow oil. Flash column chromatography (5:1 CH_2Cl_2/EtOAc) gave **43a** as a light yellow oil (2.07 g, 85%). Recrystallization (CH_2Cl_2/PE) gave white crystals (1.83 g, 75%): mp 117-118 °C; IR (KBr) 3440, 3200, 1720, 1555, 1500, 1420, 1335, 1270, 1180 (br); ^{1}H NMR δ 7.35 (s, 5 H), 7.05-6.6 (m, 4 H), 5.01 (s, 2 H), 5.25-4.9 (m, 1 H), 3.73 (s, 3 H), 4.0-3.0 (m, 3 H); ^{13}C NMR δ 205.4, 157.4, (q, $\underline{J}_{C-F}$ = 37 Hz), 153.8, 149.1, 136.7, 130.2, 128.3 (2 C), 127.7, 127.0 (2 C), 113.3, 133.0, 112.6, 70.5, 67.5, 55.2, 45.2; mass spectrum, exact mass calcd for $C_{28}H_{18}O_4NF_3$ *m/e* ______, obsd *m/e* ______.

Preparation of 37b from 43a



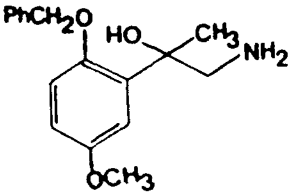
In a hydrogenation bottle were mixed **43a** (154 g, 4.17 mmol), EtOAc (30 mL), and 5% Pd/C (0.2 g), and the mixture was hydrogenated for 6 h. The resulting mixture was filtered through Celite and concentrated in vacuo to give a colorless oil. Filtration through a silica gel column (5:1 CH_2Cl_2/EtOAc as eluant) gave **37a** (1.09 g, 94%) as a solorless oil. Recrystallization (CH_2Cl_2/CH_3OH) gave pure **37a** (0.89 g, 77%): mp 115-117 °C; IR (KBr) 3450, 3280, 1720, 1510, 1430, 1215, 1190, 1165, 1150 (sh); ^{1}H NMR δ 7.4-7.1 (m, 1 H), 6.9-6.5 (m, 3 H), 5.05-4.8 (m, 1 H), 4.4-3.4 (m, 4 H), 3.69 (s, 3 H); mass spectrum, exact mass calcd for $C_{11}H_{12}O_4NF_3$ m/e 279.0718, obsd m/e 279.0716.

Preparation of 41b from 40b



In a round-bottomed flask equipped with a magnetic stirrer and N_2 inlet were mixed **40b** (1.56 g, 6.09 mmol), 18-crown-6 (100 mg), KCN (50 mg), and TMSCN (1.2 mL, 1.5 equiv). After refluxing for 30 min (oil bath, 145 °C), the reaction mixture was concentrated in vacuo to yield a dark brown oil. Flash column chromatography (1:1 CH_2Cl_2/PE) gave **41b** (1.9 g, 95%): IR (film, cm^{-1}) 1490, 1270, 1250, 1215, 1200, 1175, 1110, 1040, 995, 855 (sh), 840; ^1H NMR δ 7.6-7.2 (m, 6 H), 7.0-6.8 (m, 2 H), 5.16 (AB q, J = 12 Hz, 1 H), 5.11 (AB q, J = 12 Hz, 1 H), 3.78 (s, 3 H), 7.00 (s, 3 H), 0.43 (s, 9 H); ^{13}C NMR δ 153.5, 148.5, 136.6, 130.8, 128.2 (2 C), 127.5, 127.0 (21 C), 121.3, 113.7, 113.4, 112.2, 70.7, 68.2, 55.1, 29.6, 0.9 (3 C); mass spectrum, exact mass calcd for $C_{20}H_{25}O3N$ m/e 355.1604, obsd m/e 355.1571.

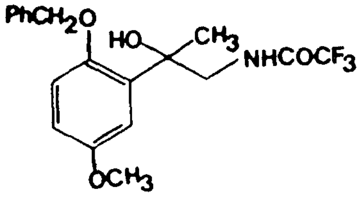
Preparation of 42b from 41b



In a round-bottomed flask equipped with a magnetic stirrer and N_2 inlet was dissolved **41b** (2.335 g, 7.16 mmol) in dry THF (100 mL). After addition of LAH (0.8 g, slight excess), the reaction mixture was stirred overnight. The reaction was quenched by addition of H_2O (4 mL), and the mixture was concentrated in vacuo, and extracted with CH_2Cl_2 (6 x 50 mL)/H_2O (30 mL). Drying (Na_2SO_4) and concentration in vacuo yielded **42b** as a white solid. Recrystallization (EtOAc/CH_2Cl_2) gave **42b** (1.80 g, 88%): mp 147-148 ^{o}C; IR (KBr) 3340 (m), 3500-3000 (br), 2960, 1490, 1465, 1445, 1310, 1285 (sh), 1040, 1015, 975, 740; ^1H NMR δ 7.37 (s, 5 H), 7.14 (d, $\underline{J}$ = 3 Hz, 1 H), 6.87 (AB q, $\underline{J}$ = 9 Hz, 1 H), 6.72 (d of AB q, $\underline{J}$ = 9, 3 Hz, 1 H), 5.04 (s, 2 H), 3.77 (s, 3 H), 3.32 (AB q, $\underline{J}$ = 13 Hz, 1 H), 2.76 (AB q, $\underline{J}$ = 13 Hz, 1 H), 2.5-1.6 (m, 3 H), 1.53 (s, 3 H); mass spectrum, exact mass calcd for CH $\underline{m}/\underline{e}$ ______, obsd $\underline{m}/\underline{e}$ ______.

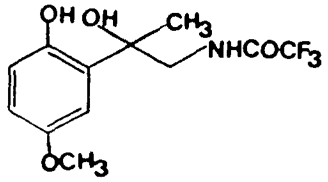
Preparation of 43b from 42b

In a round-bottomed flask equipped with a magnetic stirrer and N_2 inlet were mixed **42b** (1.119 g, 3.90 mmol) and Et_3N (0.8 mL) in dry THF (50 mL). After addition of $(CF_3CO)_2O$ (0.58 mL) at 0 ^{o}C, the reaction mixture was stirred at room temperature for 20 min. The reaction was quenched by addition of H_2O (0.5 mL), and the mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL)/saturated NH_4Cl (140 mL), washed with brine. Drying (Na_2SO_4) and concentration in vacuo gave a light yellow oil. Flash column chromatography (10:1 CH_2Cl_2/EtOAc) gave **43b** (1.231 g, 82%). Recrystallization (CH_2Cl_2/PE) gave white crystals (1.10 g, 73%): mp 98-99 ^{o}C; IR (KBr) 3500-3300 (br), 3420, 1700, 1485, 1420, 1270, 1210,



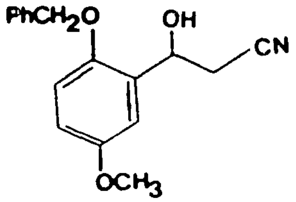
1180 (br), 1040; ^{1}H NMR δ 7.39 (s, 5 H), 7.1-6.6 (m, 1 H), 6.94 (AB q, *J* = 9 Hz, 1 H), 6.92 (d, *J* = 3 Hz, 1 H), 6.78 (d of AB q, *J* = 9, 3 Hz, 1 H), 5.09 (s, 2 H), 4.37 (s, 1 H), 4.2-3.45 (m, 2 H), 3.74 (s, 3 H), 1.56 (s, 3 H); ^{13}C NMR δ 157.4 (q, J_{C-F} = 37 Hz), 154.0, 149.7, 136.2, 132.6, 128.8 (2 C), 128.3, 127.6 (2 C), 113.6, 113.1 (2 C), 74.1, 71.0, 55.5, 48.2, 25.7; mass spectrum, exact mass calcd for $C_{19}H_{20}O_4NF_3$ *m/e* 383.1345, obsd *m/e* 383.1330.

Preparation of 37c from 43b



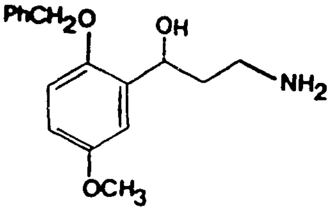
In a hydrogenation bottle were dissolved **43b** (0.188 g, 0.491 mmol) in EtOAc (20 mL) and 5% Pd/C (70 mg). After hydrogenation for 6 h at 70 lb pressure), the reaction mixture was filtered through Celite and concentrated in vacuo to yield a colorless oil. Flash column chromatography (1:1 CH_2Cl_2/EtOAc) to filter the minor impurities gave **37c** (0.142 g, 99%): IR (film, cm^{-1}) 3600-3100 (br), 1710, 1490, 1420, 1230-1140 (br), 1030; ^{1}H NMR δ 8.3 (br s, 1 H), 7.1-6.8 (br s, 1 H), 6.8-6.5 (m, 3 H), 4.6-4.2 (br, 1 H), 3.71 (s, 3 h), 3.65 (s, 2 H), 1.60 (s, 3 H); ^{13}C NMR δ 158.3 (q, *J* = 37 Hz), 153.1, 148.7, 128.2, 117.8, 114.3, 112.4, 76.4, 55.7, 49.1, 25.4; mass spectrum, exact mass calcd for $C_{12}H_{14}O_4NF_3$ *m/e* 293.0875, obsd *m/e* 293.0850.

Preparation of 44a from 40a



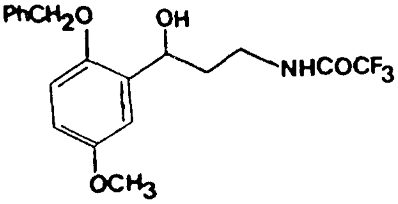
To a round-bottomed flask equipped with a magnetic stirrer and N_2 inlet was dissolved diisopropylamine (0.48 mL, 1.2 equiv) in dry THF (30 mL). At 0 °C 1.7 M BuLi (1.85 mL, 1.1 equiv) was added to the flask, and the mixture was stirred for 30 min. Another portion of dry CH_3CN (0.15 mL, 1.0 equiv) was added into the flask at 0 °C, and the mixture was allowed to stand for 30 min. The resulting mixture was then cooled to -70 °C, and **40a** (0.685 g, 2.83 mmol) in THF (5 mL) was transferred into the flask via syringe. After stirring at -70 °C for 30 min and at room temperature for 1 h, the reaction was quenched by addition of H_2O (1 mL), and the mixture was concentrated in vacuo, extracted with CH_2Cl_2 (4 x 30 mL)/saturated NH_4Cl (40 mL), and washed with brine. Drying (Na_2SO_4) and concentration in vacuo yielded a light yellow oil. Flash column chromatography (100:1 CH_2Cl_2/EtOAc) gave a white solid. Recrystallization (CH_2Cl_2/PE) gave **44a** (0.576 g, 72%): mp 85-90 °C; IR (KBr) 3600-3100 (br), 1500, 1280, 1210, 1020, 990; ^1H NMR δ 7.37 (s, 5 H), 7.1-6.7 (m, 3 H), 5.4-5.0 (m, 1 H), 5.05 (s, 2 H), 3.76 (s, 3 H), 3.0-2.6 (m, 2 H), 2.81 (s, 1 H); ^{13}C NMR δ 154.0, 149.0, 136.5, 130.4, 128.7 (2 C), 128.1, 127.3 (2C), 117.6, 113.9, 113.1, 112.5, 70.7, 65.9, 55.6, 26.0; mass spectrum, exact mass calcd for $C_{17}H_{17}O_3N$ $\underline{m/e}$ 283.1108, obsd $\underline{m/e}$ 283.1179.

Preparation of 45a from 44a



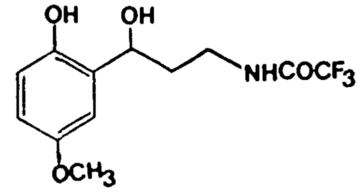
In a round-bottomed flask equipped with a magnetic stirrer and N_2 inlet was dissolved **44a** (0.477 g, 1.69 mmol) in dry THF (50 mL). After LAH (0.5 g, excess) was added, the mixture was stirred overnight, the reaction was quenched by addition of H_2O (2 mL), and the mixture was concentrated in vacuo, and extracted with CH_2Cl_2 (6 x 50 mL)/H_2O (40 mL). Drying (Na_2SO_2) and concentration in vacuo yielded crude **45b** (0.459 g, 95%). The crude product was used directly in the next synthesis without further purification: IR (film, cm^{-1}) 3600-3100(br) 2920, 1490, 1460, 1270, 1210, 1040, 730 cm^{-1}; ^1H NMR δ 7.36 (s, 5 H), 7.24-7.0 (m, 1 H), 6.81 (AB q, $\underline{J}$ = 9 Hz, 1 H), 6.70 (d of AB q, $\underline{J}$ = 9, 2 Hz, 1 H), 5.5-5.1 (m, 1 H), 5.02 (s, 2 H), 3.77 (s, 3 H), 3.4-3.0 (m, 2 H), 1.1-1.6 (m, 2 H); ^{13}C NMR δ 154.0, 149.0, 137.3, 135.1 128.3 (2 C), 127.6, 126.9 (2 C), 112.7, 112.3, 112.1, 70.5, 69.0, 55.4, 39.9, 38.7; mass spectrum, exact mass calcd for $C_{17}H_{21}NO_3$ $\underline{m/e}$ 287.1571, obsd $\underline{m/e}$ 287.1563.

Preparation of 46a from 45a



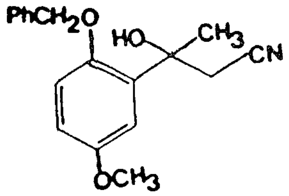
In a round-bottomed flask equipped with a magnetic stirrer and Ninlet were mixed **45a** (0.528 g, 1.98 mmol), dry THF (30 mL), and dry Et_3N (0.8 mL). After addition of $(CF_3CO)_2O$ (0.28 mL, 1.05 equiv) at 0 °C, the reaction mixture was stirred for 30 min. The reaction was quenched by addition of H_2O (0.5 mL), and the mixture was concentrated in vacuo, extracted with CH_2Cl_2(3 x 30 mL)/saturated NH_4Cl (40 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo yielded a light yellow oil. Flash column chromatography (5:1 CH_2Cl_2/EtOAc) gave a light yellow oil **46a** (0.564 g, 75%). Recrystallization (CH_2Cl_2/PE) gave **46a** (0.5 g, 66%): mp 93-94.5 °C; IR (KBr) 3480, 3290, 1695, 1500, 1270, 1210, 1180, 1075; ^1H NMR δ 7.39 (s, 5 H), 7.0-6.55 (m, 4 H), 5.25-4.9 (m, 1 H), 5.03 (s, 2 H), 3.76 (s, 3 H), 3.75-3.1 (m, 2 H), 2.65 (d, *J* = 4 Hz, 1 H), 1.98 (q, *J* = 6 Hz, 2 H); ^{13}C NMR δ 157.1 (q, J_{C-F} = 38 Hz), 154.2, 149.1, 136.7, 133.1, 128.6 (2 C), 128.1, 127.3 (2 C), 113.3, 113.0, 112.4, 70.9, 69.0, 55.5, 37.8, 34.9; mass spectrum, exact mass calcd for $C_{19}H_{20}O_4NF_3$ *m/e* 383.1355, obsd *m/e* 383.1325.

Preparation of 37d from 46a



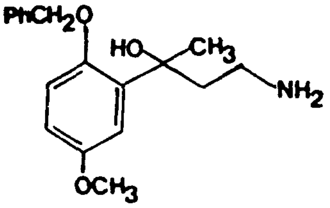
In a hydrogenation bottle were mixed **46a** (0.5 g, 1.31 mmol), 5% Pd/C (100 mg), and EtOAc (80 mL). After hydrogenation for 8 h, the resulting mixture was filtered through Celite and concentrated in vacuo to give a colorless oil. Flash column chromatography (1:2 EtOAc/CH_2Cl_2) filtered out pure **37d** (0.37 g, 96%): IR (film, cm^{-1}) 3600-3100 (br), 1710, 1500, 1465, 1450, 1430, 1270 (sh), 1180 (br), 1030, 730; ^1H NMR δ 7.6-7.0 (m, 1 H), 7.0-6.5 (m, 3 H), 4.89 (t, *J* = 7 Hz, 1 H), 4.1-3.0 (m, 4 H), 3.70 (s, 3 H), 2.3-1.7 (m, 2 H); ^{13}C NMR δ 157.8 (q, *J* = 38 Hz), 153.4, 148.1, 128.6, 117.3, 114.0, 112.4, 71.9, 55.8, 37.5, 35.5; mass spectrum, exact mass calcd for $C_{12}H_{14}O_4NF_3$ m/e 293.0875, obsd m/e 293.0851.

Preparation of 44b from 40b



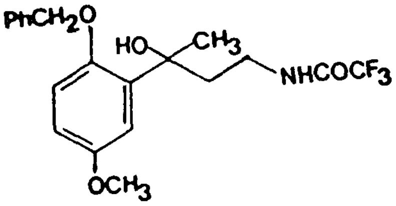
In a round-bottomed flask equipped with a magnetic stirrer and N_2 inlet was dissolved (*i*-Pr)$_2$NH (1.9 mL, 1.3 equiv) in THF (100 mL). After addition of 1.6 M CH_3Li (6.56 mL, 1.05 equiv) and stirring for 0.5 h at 0 °C, CH_3CN (0.55 mL, 1.05 equiv) was added to the reaction mixture. The mixture was cooled to -78 °C, **40b** (2.56 g, 10 mmol) in dry THF (5 mL) was added dropwise, and the mixture was stirred for 1 h at -78 °C and then for 1 h at room temperature. The reaction was quenched by addition of H_2O (2 mL), and the reaction mixture was concentrated in vacuo, extracted with CH_2Cl_2 (4 x 50 mL)/saturated NH_4Cl (50 mL), and washed with brine (50 mL). Drying (Na_2SO_4) and concentration in vacuo yielded a light yellow oil. Flash column chromatography (CH_2Cl_2) gave **44b** (2.67 g, 90%) as a liquid: IR (film, cm^{-1}) 3600-3200 (br), 1490, 1465, 1455, 1415, 1280, 1210, 1040, 1010 (sh); ^1H NMR δ 7.38 (s, 5 H), 7.05 (d, *J* = 2 Hz, 1 H), 6.93 (AB q, *J* = 9 Hz, 1 H), 6.78 (d of AB q, *J* = 9, 2 Hz, 1 H), 5.08 (s, 2 H), 4.11 (s, 1 H), 3.76 (s, 3 H), 2.97 (s, 2 H), 1.73 (s, 3 H); ^{13}C BNR δ 153.8, 149.1, 136.0, 133.03, 128.7 (2 C), 128.2, 127.3 (2 C), 117.6, 113.3 (2 C), 113.0, 72.1, 70.9, 55.5, 31.0, 26.9; mass spectrum, exact mass calcd for $C_{18}H_{29}NO_3$ m/e 297.1365, obsd m/e 297.1393.

Preparation of 45b from 44b



In a round-bottomed flask equipped with a magnetic stirrer and N_2 inlet was dissolved **44b** (2.1 g, 7.07 mmol) in dry THF (80 mL). After addition of LAH (1.0 g, excess), the reaction mixture was stirred overnight. The reaction was quenched with H_2O (5 mL), and the mixture was concentrated in vacuo, and extracted with CH_2Cl_2 (4 x 50 mL)/saturated NH_4Cl (50 mL). Drying (Na_2SO_4) and concentration in vacuo gave a light brown oil **45b** (1.91 g, 90%) which was used for the next reaction without further purification: IR (film, cm^{-1}) 3600-3100, 1490, 1465, 1450, 1420, 1275, 1210, 1195 (sh), 1040, 730, 690; ^1H NMR δ 7.5-7.1 (m, 6 H), 7.0-6.6 (m, 2 H), 5. 94 (br s, 3 H), 4.99 (s, 2 H), 3.70 (s, 3 H), 3.1-1.5 (m, 4 H), 1.58 (s, 3 H); ^{13}C NMR δ 153.2, 148.4, 136.5, 127.9 (2 C), 127.2, 126.7 (2 C), 113.4, 112.7, 111.5, 74.5, 70.1, 67.1, 54.9, 28.1, 24.9; mass spectrum, exact mass calcd for $C_{18}H_{23}NO_3$ m/e 301.1678, obsd m/e 301.1685.

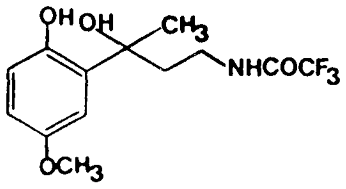
Preparation of 46b from 45b



In a round-bottomed flask equipped with a magnetic stirrer and N_2 inlet were mixed **45b** (1.9 g, 6.31 mmol), THF (30 mL), and Et_3N (3 mL). After addition of $(CF_3CO)_2O$ (0.93 mL, 10.5 equiv) at 0 °C, the reaction mixture was stirred at room temperature for 0.5 h. The resulting mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL)/saturated NH_4Cl (50 mL), and washed with brine. Drying (Na_2SO_4) and concentration in vacuo yielded a light yellow oil. Flash column chromatography (10:1 CH_2Cl_2/EtOAc) gave **46b** (2.2 g, 88%) as a colorless oil: IR (film, cm^{-1}) 3600-3100 (br), 1710, 1485, 1460, 1450, 1270, 200, 1160 (br), 935, 730, 690; ^1H NMR δ 7.75-7.5 (m, 1 H), 7.39 (s, 5 H), 7.1-6.6 (m, 3 H), 5.06 (s, 3 H), 4.11 (s, 1 H), 3.75 (s, 3 H), 3.6-3.3 (m, 2 H), 2.5-1.7 (m, 2 H), 1.60 (s, 3 H); ^{13}C NMR δ (156.9 (q, $\underline{J}_{CF}$ = 37 Hz), 154.0, 149.6, 136.3, 134.9, 128.7 (2 C), 128.3, 127.5 (2 C), 113.6, 113.3, 112.1, 71.1, 55.5, 38.2, 36.6, 28.7; mass spectrum, exact mass calcd for $C_{20}H_{22}NO_4F_3$ m/e 397.1501, obsd m/e 397.1535.

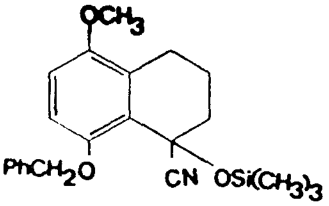
Preparation of 37e from 46b

In a hydrogenation bottle were mixed **46b** (0.92 g, 2.32 mmol), EtOAc (30 mL), and 5% Pd/C (0.1 g). After hydrogenation overnight at 70 lb, the resulting mixture was filtered through Celite and concentrated in vacuo to yield a colorless oil. The oil was purified by filtration through a silica gel column (5:1 CH_2Cl_2/EtOAc) to yield a colorless oil **37e** (0.68 g, 95%): IR (film, cm^{-1}) 3600-3100 (br), 1710, 1490, 1210, 1180 (br); ^1H NMR δ 8.27 (s, 1 H), 7.24-6.5 (m, 1 H), 6.8-6.5 (m, 3 H), 3.72 (s, 3 H), 3.64 (br s, 1 H), 3.44 (q, $\underline{J}$ = 6 Hz, 2 H), 2.4-1.7 (m, 2 H), 1.67 (s, 3 H); ^{13}C NMR δ 157.5 (q, $\underline{J}_{CF}$ = 37 H\), 153.0, 148.8, 130.1, 117.8,



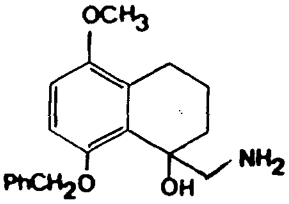
113.6, 112.4, 771., 55.7, 40.2, 36.3, 28.7; mass spectrum, exact mass calcd for $C_{13}H_{16}NO_4F_3$ m/e 307.1031, obsd m/e 307.1020

Preparation of 48 from 47



In a round-bottomed flask equipped with a magnetic stirrer and N_2 inlet were mixed **47** (1.49 g, 1.28 mmol), 18-crown-6 (0.3 g), KCN (0.1 g), and ≡SiCN (1.5 mL, 11.2 mmol). The reaction mixture was heated to reflux (oil bath, 150 °C) for 30 min. The resulting brown oil was concentrated in vacuo, and flash column chromatography (2:1 PE/CH_2Cl_2) gave pure **48** (1.79 g, 90%): mp 120-121.5 °C; IR (KBr) 1480, 1470, 1450, 1280, 1265, 1255 (sh), 1110 (sh), 1100, 1065, 1040 (sh), 1030, 1005, 900, 840, 795, 750; ^{1}H NMR δ 7.7-7.2 (m, 5 H), 6.73 (s, 2 H), 5.27 (AB q, J = 13 Hz, 1 H), 5.16 (AB q, J = 13 Hz, 1 H), 3.75 (s, 3 H), 3.0-1.5 (m, 6 H), 0.16 (s, 9 H); ^{13}C NMR δ 151.2 (2 C), 137.4, 128.4 (2 C), 127.6, 127.3 (2 C), 125.1, 122.9, 110.6 (2 C), 70.9, 65.8, 55.7, 39.8, 23.4, 17.0, 1.2; mass spectrum, exact mass calcd for $C_{22}H_{27}O_3NSi$ m/e 381.1760, obsd m/e 381.1738.

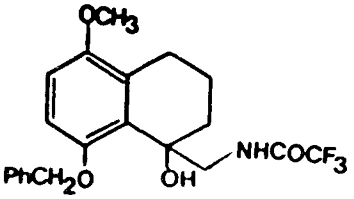
Preparation of 49 from 48



In a round-bottomed flask equipped with a magnetic stirrer and N_2 inlet was dissolved **48** (1.39 g, 3.65 mmol) in dry THF (100 mL). After LAH (0.6 g) was transferred into the solution, the reaction mixture was stirred overnight. After quenching the reaction by addition of H_2O (2 mL), the mixture was concentrated in vacuo, and extracted with CH_2Cl_2 (4 x 50 mL)/saturated NH_4Cl (50 mL). Drying (Na_2SO_4) and concentration in vacuo yielded **49** (0.93 g, 82%): IR (film, cm^{-1}) 3520, 3600-3100 (br), 2940, 1480, 1465, 1455 (sh), 1255, 1050, 1030, 730; ^1H NMR δ 7.6-7.0 (m, 5 H), 6.9-6.5 (m, 2 H), 5.2-4.9 (br, 1 H), 5.07 (s, 2 H), 455 (br s, 2 H), 3.76 (s, 3 H), 3.27 (AB q, *J* = 14 Hz, 1 H), 3.01 (AB q, *J* = 14 Hz, 1 H), 3.0-1.4 (m, 6 H); ^{13}C NMR δ 151.2, 150.1, 136.0, 129.0, 128.3 (2 C), 127.9, 127.6, 126.9 (2 C), 109.4, 108.3, 72.7, 70.1, 54.9, 47.0, 31.4, 23.4, 18.4; mass spectrum, exact mass calcd for $C_{19}H_{23}O_3N$ *m/e* M-CN peak.

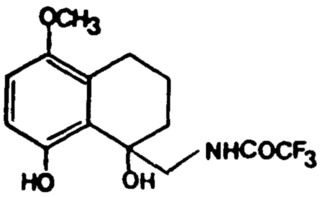
Preparation of 50 from 49

In a round-bottomed flask equipped with a magnetic stirrer and N_2 inlet were dissolved **49** (0.96 g, 3.06 mmol) and dry Et_3N (1 mL) in dry THF (30 mL). At 0 °C $(CF_3CO_2)O$ (0.46 mL, 1.05 equiv) was added, and the mixture was stirred for 0.5 h. The reaction was quenched by addition of H_2O (0.5 mL), and the mixture was concentrated in vacuo, extracted with CH_2Cl_2 (4 x 30 mL)/saturated NH_4Cl (aqueous, 40 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo yielded a light yellow oil. Flash column chromatography (10:1 CH_2Cl_2/EtOAc) gave a light yellow oil **50** (1.152 g, 92%).



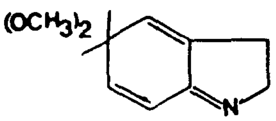
Recrystallization (CH_2Cl_2/PE) gave **50** (1.01 g, 80%): mp 137-138.5 °C; IR (KBr) 3470, 3240, 1710, 1546, 1480, 1465, 1410, 1340, 1260, 1240 (sh), 1215, 1180, 1140, 1115, 1065, 1050 (sh), 1030; ^{1}H NMR δ 7.38 (s, 5 H), 6.8-6.5 (br, 1 H), 6.81 (AB q, J = 9 Hz, 1 H), 6.71 (AB q, J = 9 Hz, 1 H), 5.10 (s, 2 H), 4.87 (br s, 1 H), 4.2-3.4 (m, 2 H), 3.77 (s, 3 H), 3.1-1.5 (m, 6 H); ^{13}C NMR δ 157.3 (q, J_{C-F} = 38), 152.1, 150.3, 135.8, 128.6 (2 C), 128.4, 128.2, 127.8, 127.3 (2 C), 109.7, 109.1, 72.8 70.7, 55.2, 45.6, 31.9, 23.5, 18.7; mass spectrum, exact mass calcd for $C_{21}H_{22}O_4NF_3$ *m/e* __________, obsd *m/e* __________.

Preparation of 37f from 50



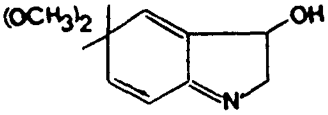
A mixture of **50** (0.989 g, 2.42 mmol), EtOAc (100 mL), and 5% Pd/C (100 mg) was put into a hydrogenation bottle under H_2 atmosphere (70 lb) for 6 h. The resulting solution was filtered through Celite and concentrated in vacuo to yield a clear oil. Flash column chromatography removed trace impurities to yield **37f** (600 mg, 95%): IR (film, cm^{-1}) 3600-3100, 2950, 1715, 1470, 1250, 1210, 1185 (br), 1045; ^{1}H NMR δ 7.85 (s 1 H), 7.3-6.9 (m, 1 H), 6.63 (s, 2 H), 4.2-3.4 (m, 3 H), 3.72 (s, 3 H), 3.0-1.5 (m, 6 H); mass spectrum, exact mass calcd for $C_{14}H_{16}O_4NF_3$ *m/e* 319.1031, obsd *m/e* 319.1002.

Anodic Oxidation of 37a and Quinone Imine Ketal Formation of 52a



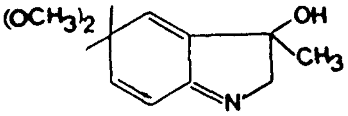
A solution of **37a** (0.140g, 0.531 mmol) in 2% $LiClO_4$ (120 mL) was electrolyzed (3 V, 0.06 A) for 45 min until complete disappearance of starting material as ascertained by UV spectroscopy. The resulting solution was concentrated in vacuo, and extracted with CH_2Cl_2 (3 x 30 mL). Drying (Na_2SO_4) and concentration in vacuo yielded a very light oil. The resulting oil was dissolved in THF (100 mL) and hydrolyzed with 5% KOH (5 mL) for 2 h. The resulting mixture was concentrated in vacuo and extracted with CH_2Cl_2 (3 x 30 mL). The aqueous layer was neutralized by addition of saturated NH_4Cl (30 mL) and extracted with CH_2Cl_2 (2 x 30 mL). The combined organic layer was washed with brine (30 mL), Drying (Na_2SO_4), and concentrated in vacuo to yield a crude, light yellow oil **52a** (90.1 mg, 82%): IR (film, cm^{-1}) 2930, 1220, 1180, 1135, 1070, 1030, 945; ^1H NMR δ 6.70 (AB q, $\underline{J}$ = 10 Hz, 1 H), 6.33 (d of AB q, $\underline{J}$ = 10, 1.6 Hz, 1 H), 5.90 (d, $\underline{J}$ = 1.6 Hz, 1 H), 4.70-4.45 (m, 2 H), 3.24 (s, 6 H), 2.72-2.5 (m, 2 H); ^{13}C NMR δ 164.3, 143.4, 137.5, 125.0, 121.0, 96.7, 60.0, 49.8, 27.1; mass spectrum, exact mass calcd for $C_{10}H_{13}NO_2$ $\underline{m/e}$ 179.0946, obsd $\underline{m/e}$ 179.0953.

Anodic Oxidation of 37b and Quinone Imine Ketal Formation of 52b



A solution of **37b** (0.51 g, 1.83 mmol) in 2% $LiClO_4/CH_3OH$ was electrolyzed at 0 °C (3.1 V, 0.06 A) for 2 h. The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (4 x 50 mL), Drying (Na_2SO_4), and concentration in vacuo to yield a light yellow oil. The resulting oil was dissolved in THF (100 mL) and mixed with 5% KOH (10 mL). After stirring for 2 h, the resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (5 x 30 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave **52b** (0.32 g, 91%) as a light yellow oil: IR (film, cm^{-1}) 3600-3100, 2940, 1560, 1370, 1140, 1080, 1050, 1035 (sh), 950; ^1H NMR δ 6.8-6.2 (m, 3 H), 4.85-4.7 (m, 1 H), 4.45-3.70 (m, 3 H), 3.26 (s, 6 H); mass spectrum, exact mass calcd for $C_{10}H_{13}NO_3$ m/e 195.0896, obsd m/e 195.0840.

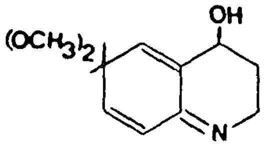
Anodic Oxidation of 37c and Quinone Imine Ketal Formation of 52c



A solution of **37b** (0.51 g, 1.83 mmol) in 2% $LiClO_4/CH_3OH$ was electrolyzed at 0 °C (3.1 V, 0.06 A) for 2 h. The resulting solution was concentrated in vacuo, and extracted with CH_2Cl_2 (4 x 50 mL). Drying (Na_2SO_4) and

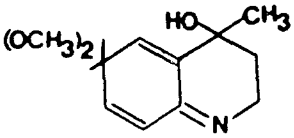
concentration in vacuo yielded a light yellow oil. The resulting oil was disolved in THF (1200 mL), followed by treatment with 5% KOH (15 mL). After stirring for 3 h, the resulting mixture was concentrated in vacuo, extracted with CH_2Cl_2 (5 x 40 mL), and washed with brine (30 mL). Drying (Na_2SO_4) and concentration in vacuo yielded crude **52c** (0.375 g, 89%): IR (film, cm^{-1}) 3600-3000 (br), 2960, 2930, 1580, 1365, 1205, 1120 (sh), 1100, 1060, 1030, 950, 720; ^1H NMR δ 6.67 (AB q, J = 10 Hz, 1 H), 6.38 (d of AB q, J = 10, 2 Hz, 1 H), 6.28 (d, J = 2 Hz, 2 H), 4.06 (s,2 H), 3.29 (s, 3 H), 3.27 (s, 3 H), 3.15-2.70 (br s, 1 H), 1.43 (s, 3 H); ^{13}C NMR δ 163.3, 148.3, 137.7, 124.7, 123.4, 96.1, 75.7, 74.4, 49.8, 49.7, 26.3; mass spectrum, exact mass calcd for $C_{11}H_{15}O_3N$ _______
m/e 178 (M^+-OCH_3).

Anodic Oxidation of 37d and Quinone Imine Ketal Formation of 52d



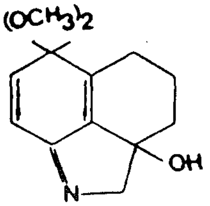
In an electrolysis cell was dissolved **37d** (0.442 g, 1.51 mmol) in 1% $LiClO_4/CH_3OH$, and the mixture was cooled to 0 °C and electrolyzed (3.3 V, 0.06 A) for 1.6 h. The resulting solution was concentrated in vacuo, and extracted with CH_2Cl_2(3 x 30 mL)/H_2O (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave a light yellow oil. The resulting oil was dissolved in THF (100 mL), mixed with 5% KOH (6 mL), and stirred for 3 h. The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (4 x 30 mL), and washed with brine. Drying (Na_2SO_4) and concentration in vacuo gave **52d** (0.283 g, 91%): IR (film, cm^{-1}) 3600-3100, 2930, 1580, 1090, 1060, 1030, 950; ^1H NMR δ 6.63-6.20 (m, 3 H), 4.5-3.4 (m, 3 H), 3.29 (s, 6 H), 2.5-1.4 (m, 3 H); mass spectrum, exact mass calcd for $C_{11}H_{15}NO_3$ m/e 209.1052, obsd m/e 209.1063.

Anodic Oxidation of 37e and Quinone Imine Ketal Formation of 52e



To an electrolysis cell was dissolved **37e** (0.56 g, 1.82 mmol) in 1% $LiClO_4/CH_3OH$. The solution was electrolyzed (3 V, 0.06 A) at 0 °C for 2 h until disappearance of starting material as determined by UV spectroscopy. The resulting mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo yielded a colorless oil. The oil was dissolved in THF (100 mL), 5% KOH (5 mL) was added, and the mixture was stirred for 2 h. The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (4 x 30 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo yielded light yellow oil **52e** (0.36 g, 89%): IR (film, cm^{-1}) 3600-3100 (br), 2940, 1695, 1120, 1105, 1060, 1040, 950; ^1H NMR δ 6.6-6.15 (m, 3 H), 5.26 (s, 1 H), 4.3-3.5 (m, 2 H), 3.27 (s, 6 H), 1.77 (t, J = 5 Hz, 2 H), 1.33 (s, 3 H); ^{13}C NMR δ 156.0, 137.7, 132.6, 131.4, 126.5, 94.6, 67.1, 49.5 (2 C), 48.3, 36.7, 27.2; mass spectrum, exact mass calcd for $C_{12}H_{17}NO_3$ m/e 223.1208, obsd m/e 223.1200.

Anodic Oxidation of 37f and Quinone Imine Ketal Formation of 52f



A solution of **37f** (0.65 g, 2.49 mmol) was dissolved in 1% $LiClO_4/CH_3OH$, and the mixture was electrolyzed at 0 °C (3 V, 0.06 A) for 2.8 h. The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (5 x 40 mL), and washed with brine. Drying (Na_2SO_4) and concentration in vacuo yielded a clear oil. The resulting oil was dissolved in THF (100 mL), mixed with 5% KOH (10 mL), and stirred for 5 h. The mixture was concentrated in vacuo, extracted with CH_2Cl_2 (5 x 40 mL), washed with brine. Drying (Na_2SO_4), and concentration in vacuo to yield a light yellow oil. Recrystallization (CH_2Cl_2/PE) gave **52f** (0.53 g, 89%): mp 129-131 °C; IR (KBr) 3600-3100, 2940, 2830, 1540, 1205, 1100, 1060, 930, 910; ^1H NMR δ 6.81 (AB q, *J* = 10 Hz, 1 H), 6.63 (AB q, *J* = 10 Hz, 1 H), 4.23 (AB q, *J* = 17 Hz, 1 H), 3.73 (AB q, *J* = 17 Hz, 1 H), 3.38 (s, 1 H), 3.20 (s, 3 H), 3.04 (s, 3 H), 2.4-1.2 (m, 6 H); ^{13}C NMR δ 162.9, 143.3, 138.9, 136.7, 126.9, 97.8, 74.8, 71.3, 51.1, 50.6, 31.7, 20.0, 17.6; mass spectrum, exact mass calcd for $C_{13}H_{17}O_3N$ *m/e* 235.1209, obsd *m/e* 235.1220.

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NMR SPECTRA

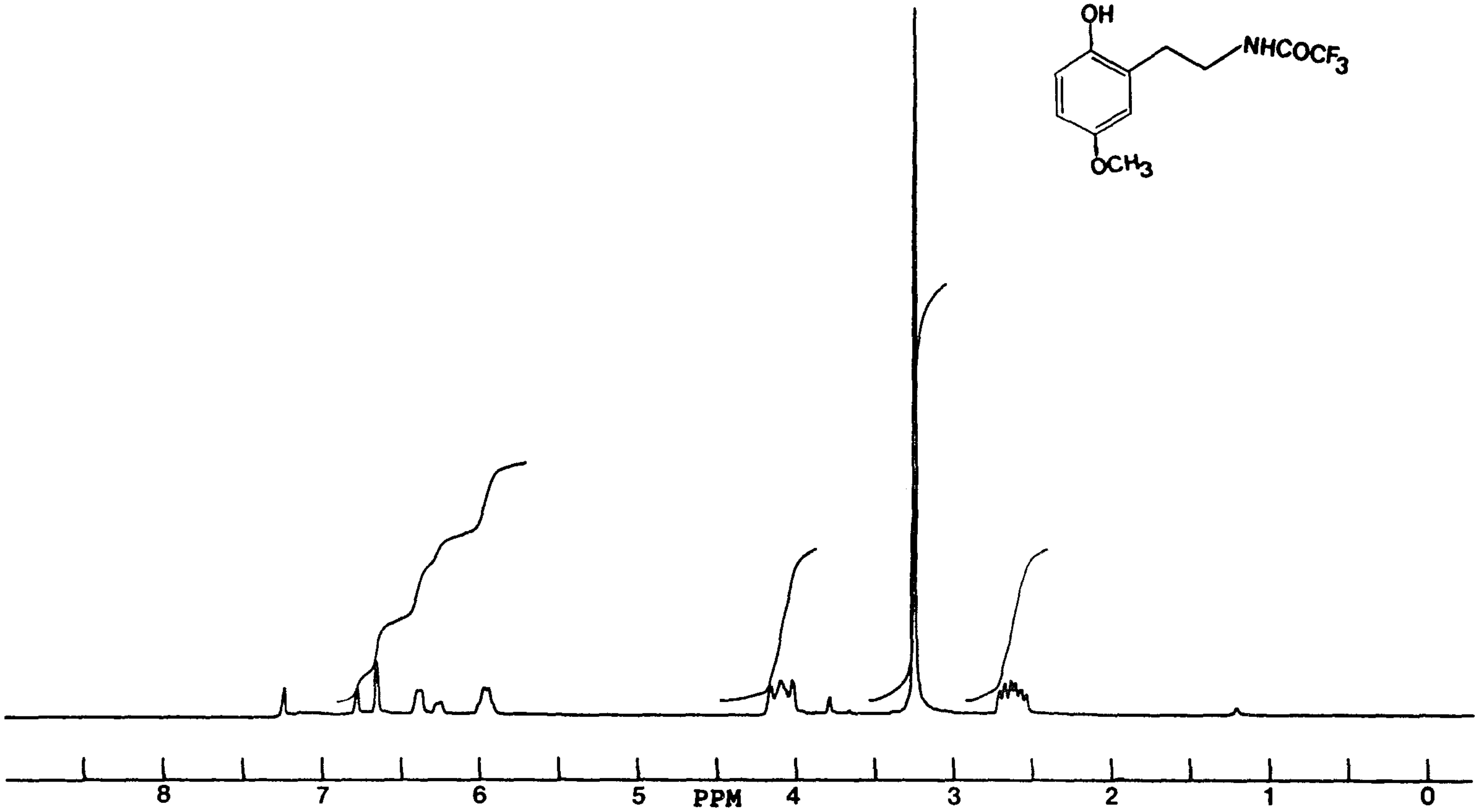


Figure 1. 80 MHz ^{1}H NMR Spectrum of 37a

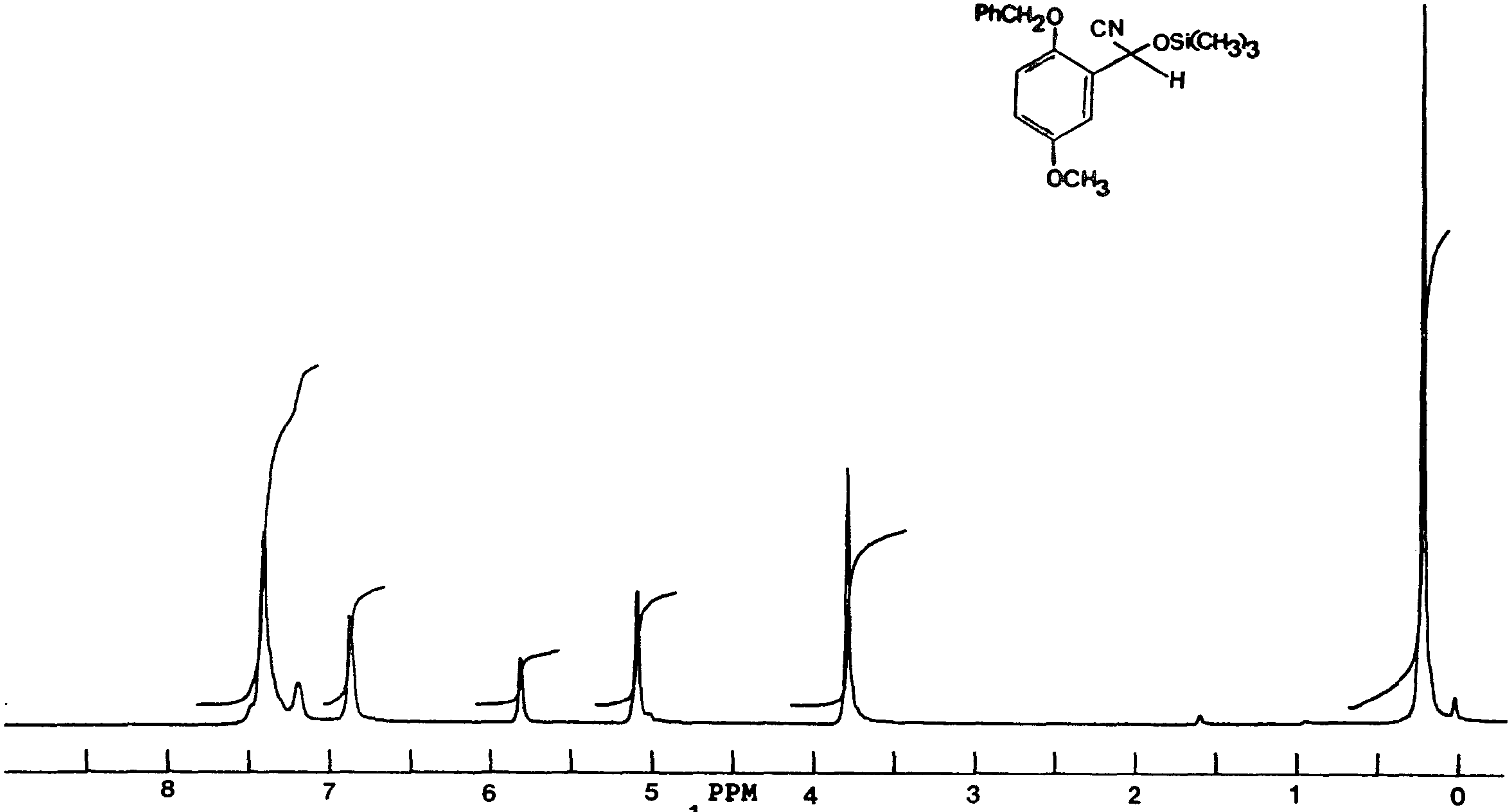


Figure 2. 80 MHz ^{1}H NMR Spectrum of 41a

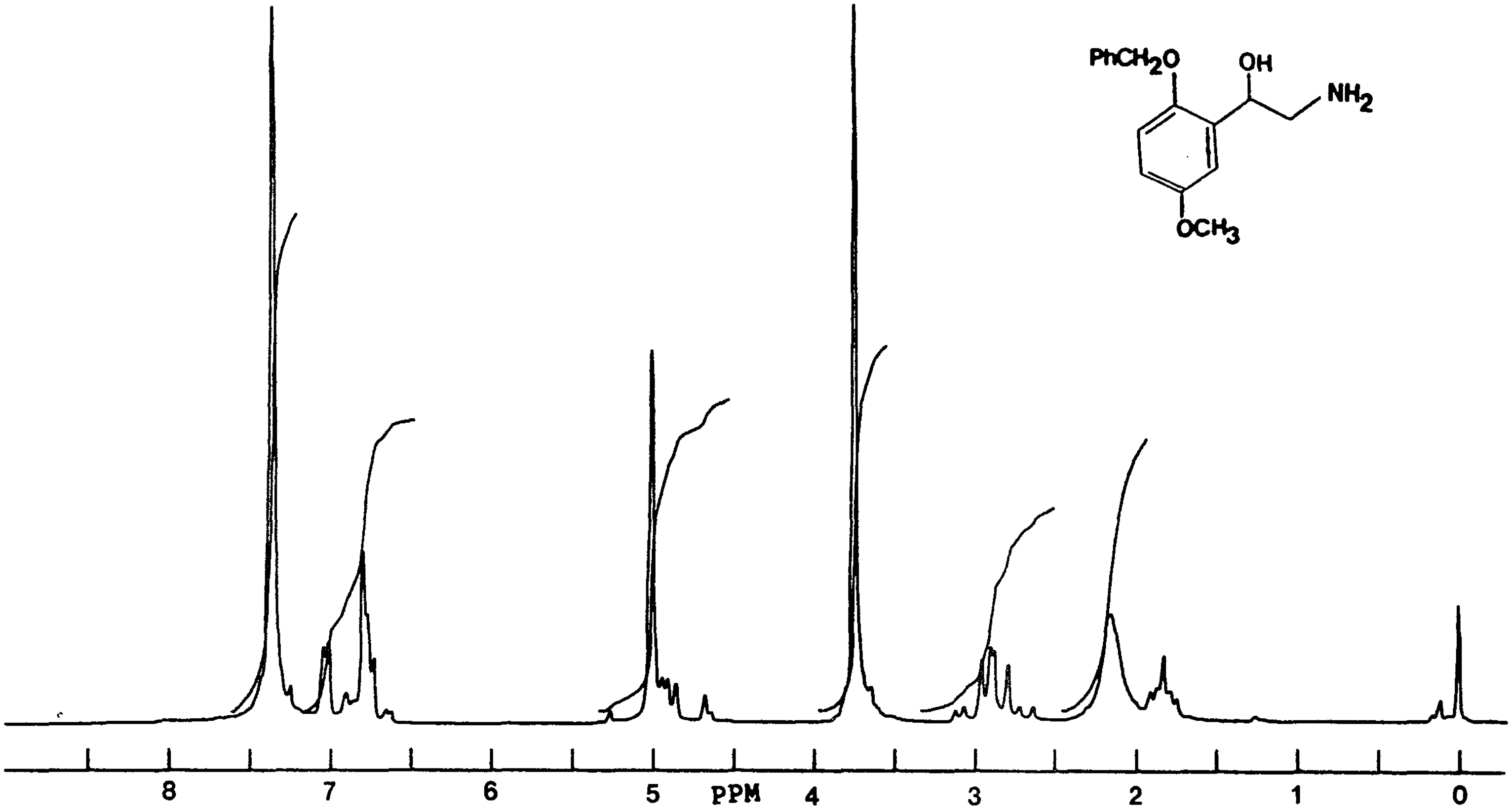


Figure 3. 80 MHz ^{1}H NMR Spectrum of 42a

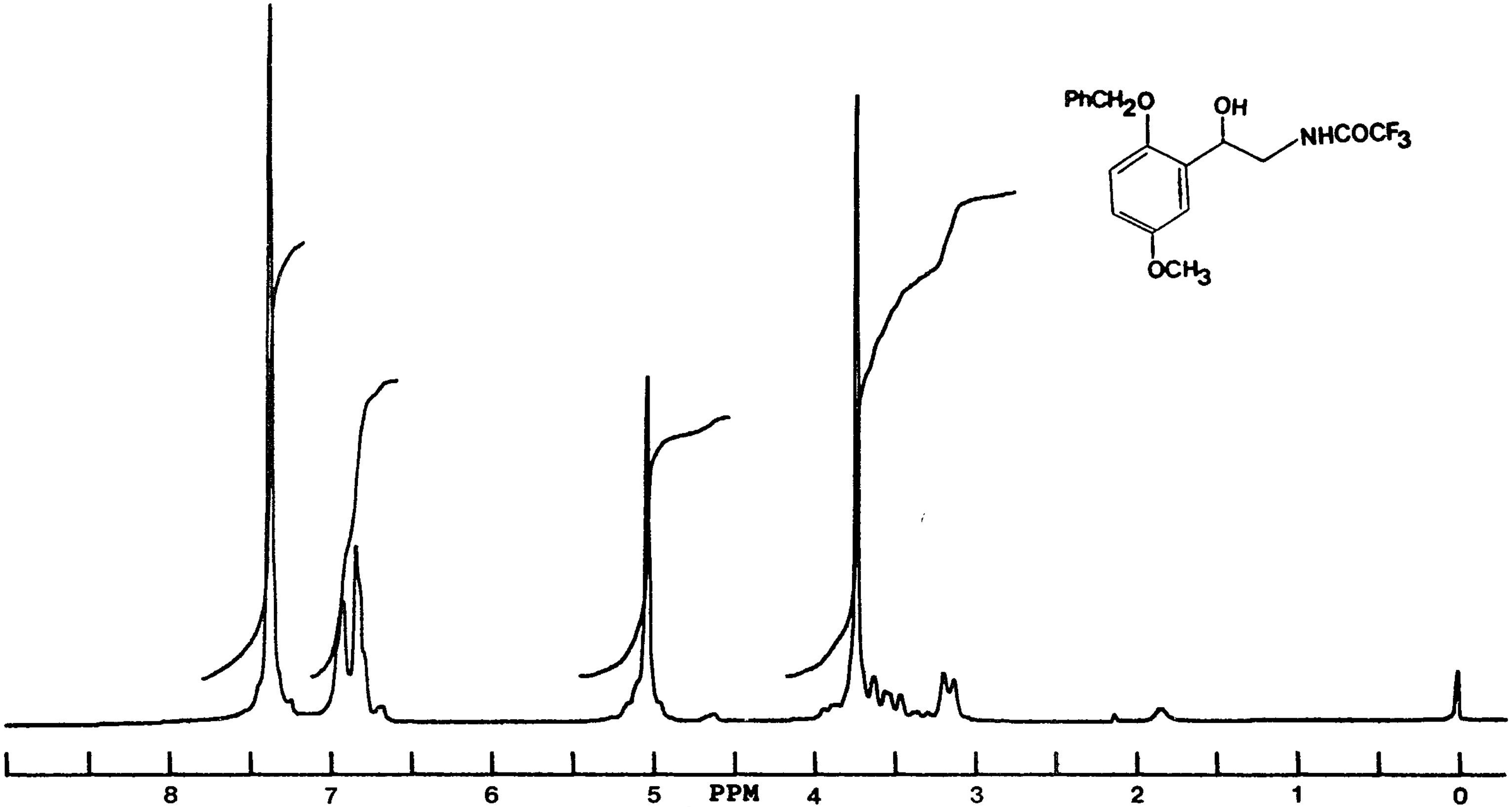


Figure 4. 80 MHz ^{1}H NMR Spectrum of 43a

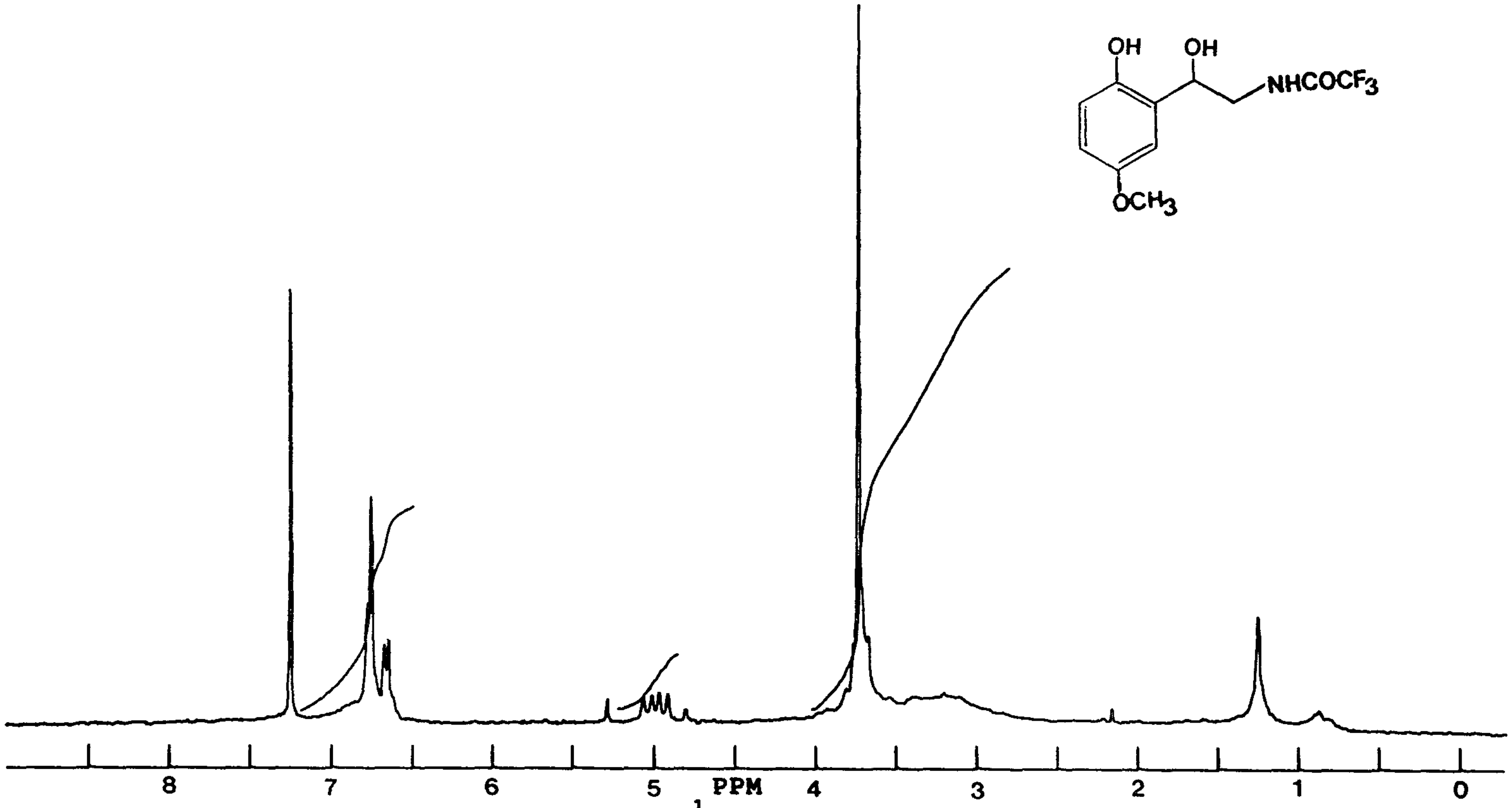


Figure 5. 80 MHz ^{1}H NMR Spectrum of 37b

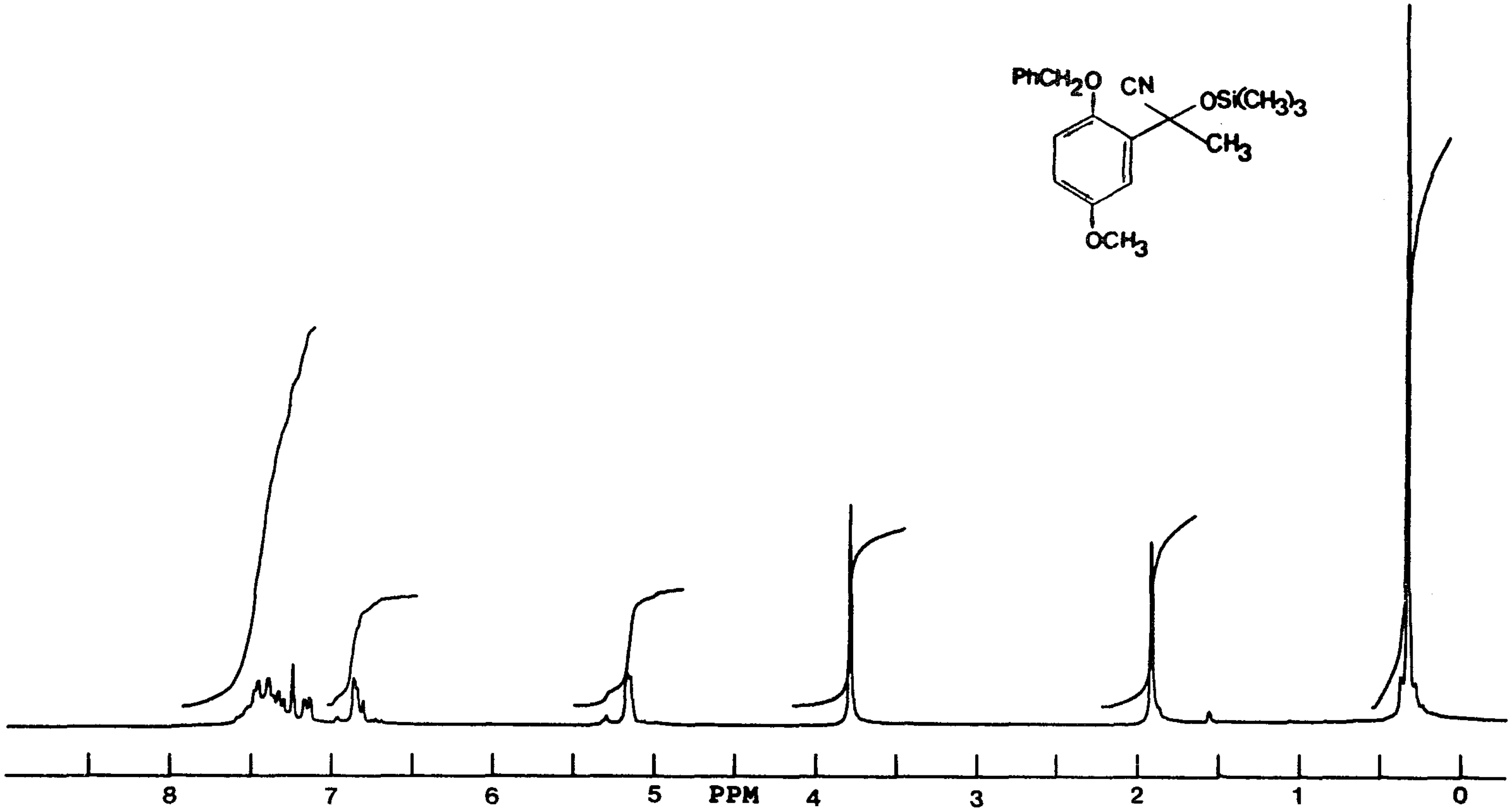


Figure 6. 80 MHz ^{1}H NMR Spectrum of 41b

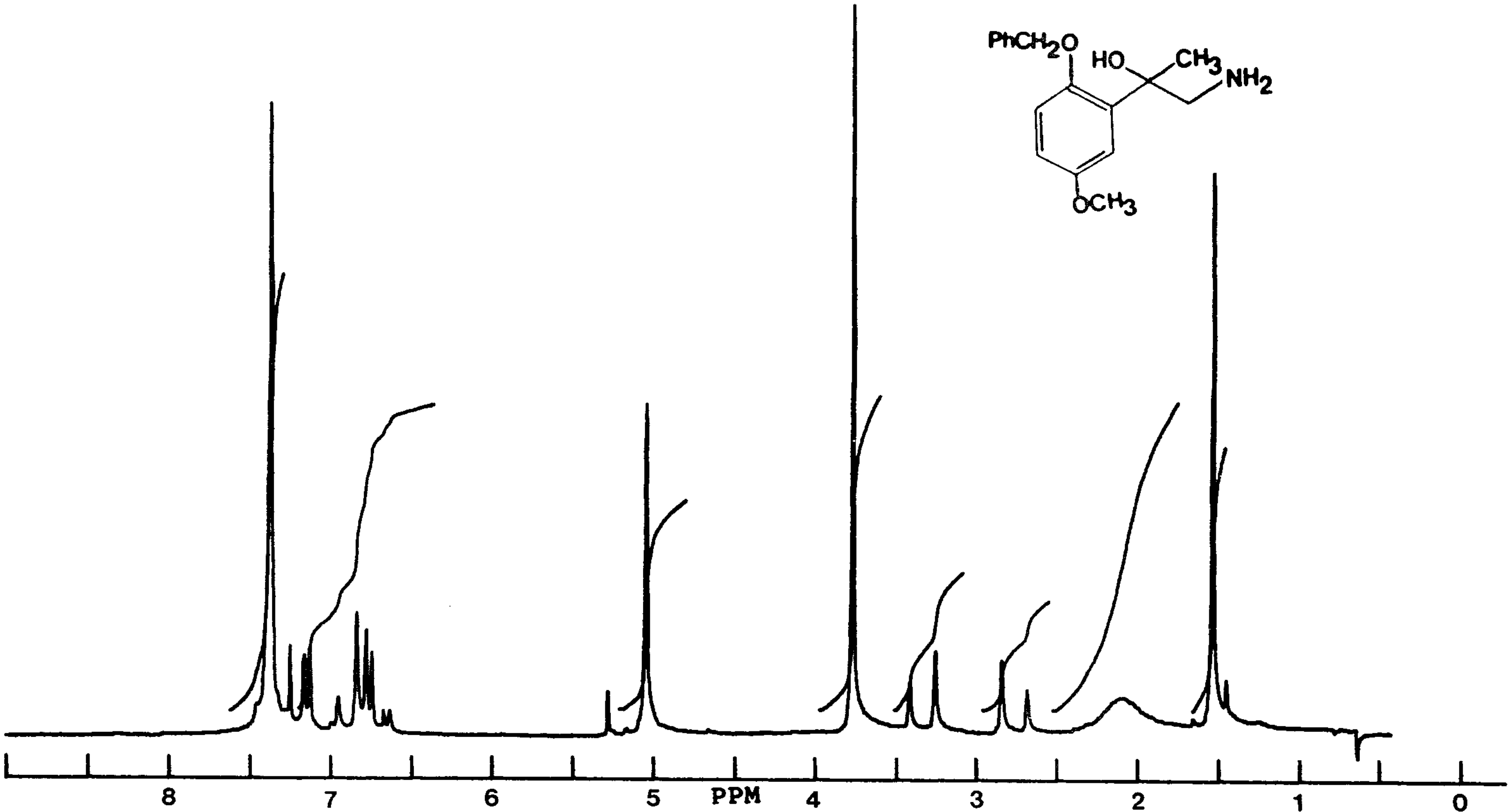


Figure 7. 80 MHz ^{1}H NMR Spectrum of 42b

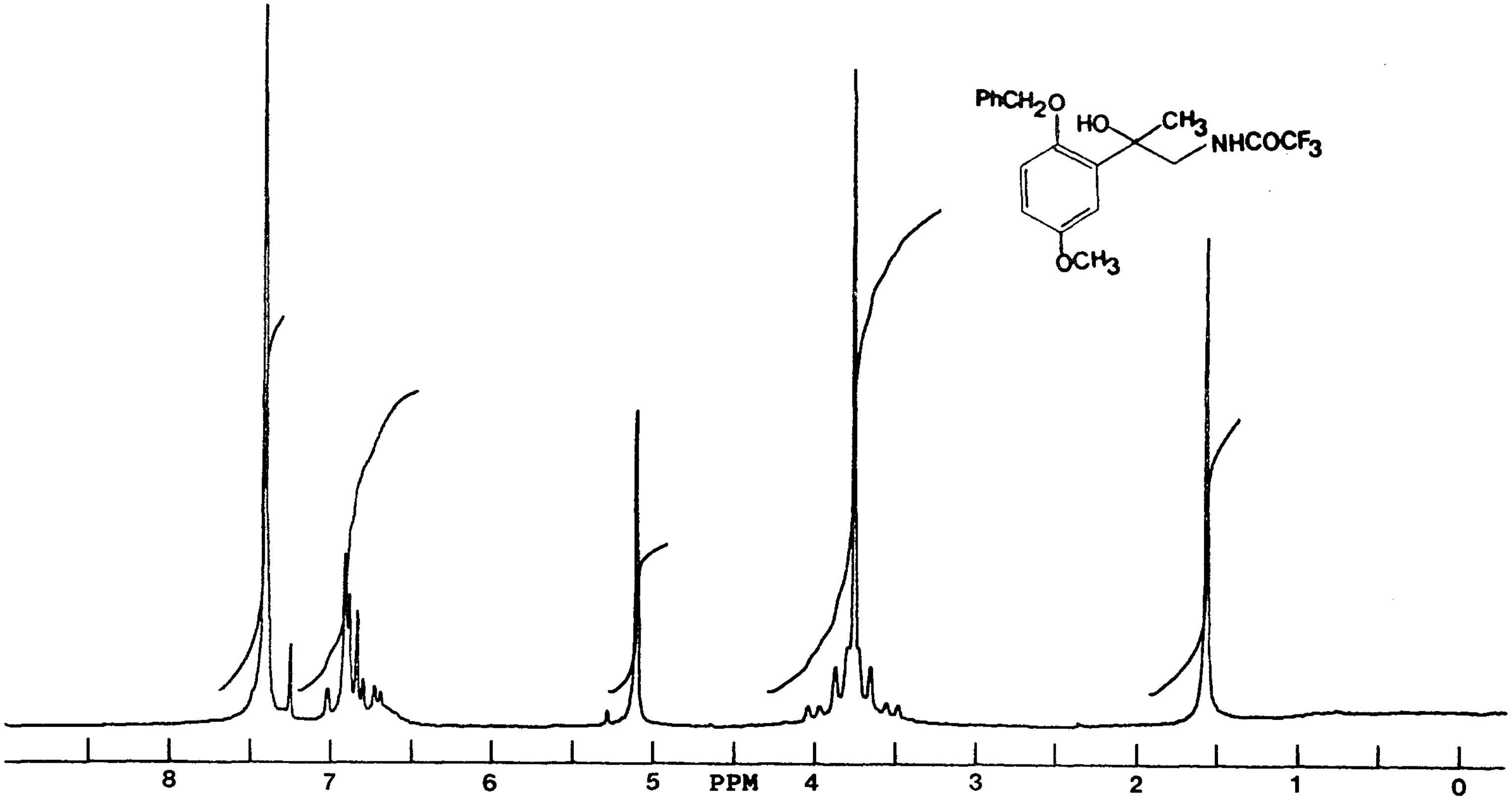


Figure 8. 80 MHz ^{1}H NMR Spectrum of 43b

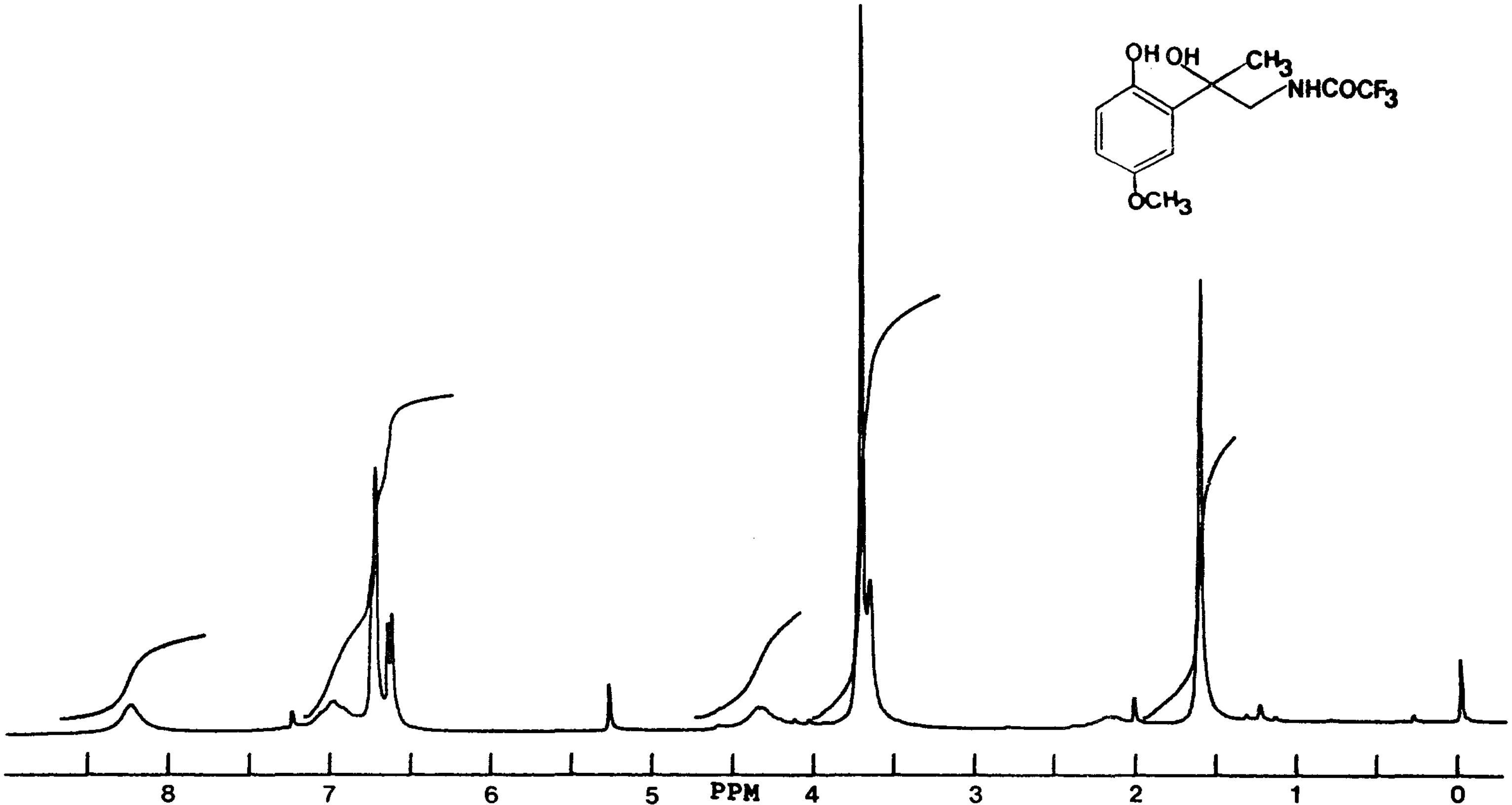


Figure 9. 80 MHz ^{1}H NMR Spectrum of 37c

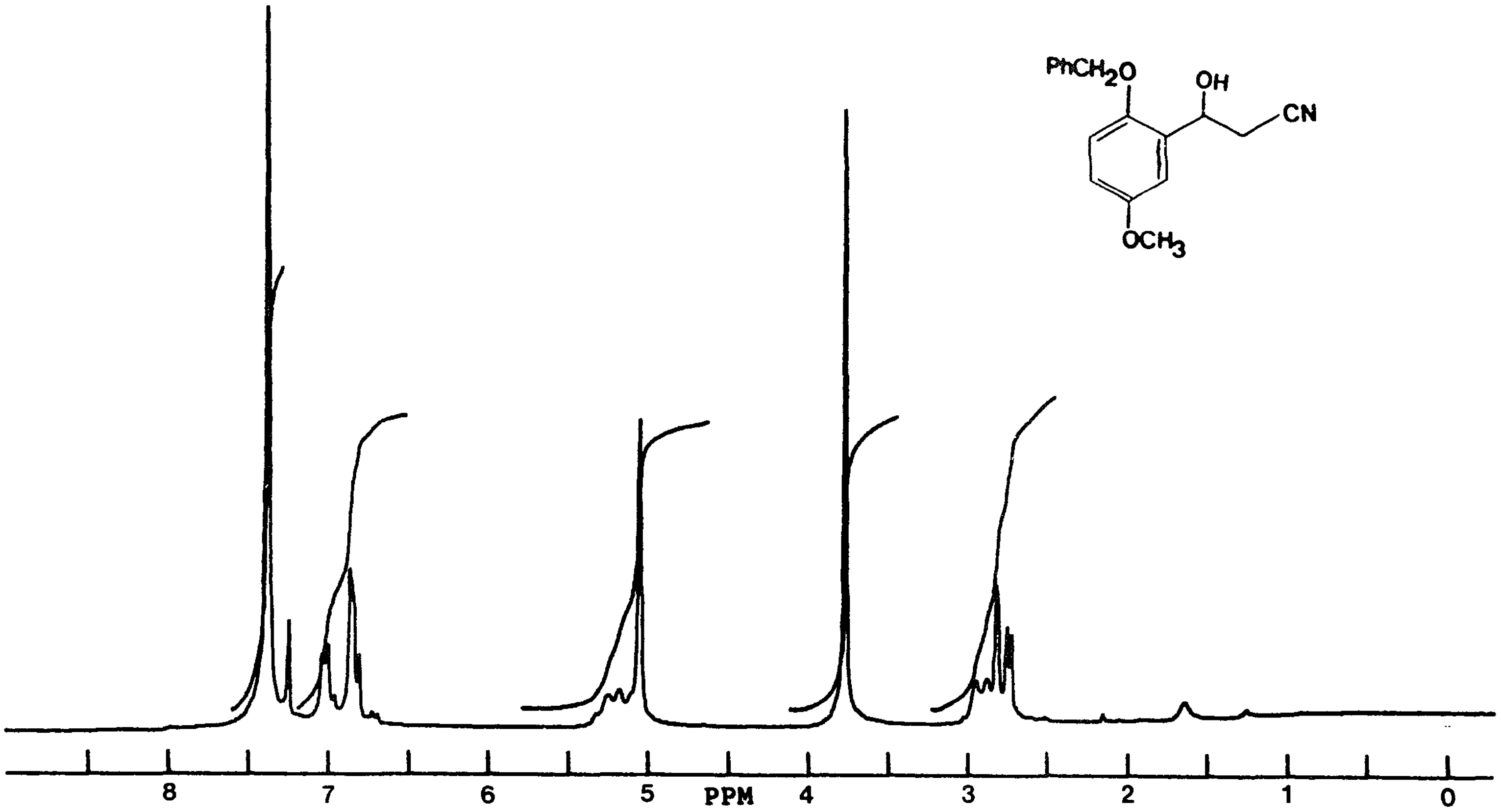


Figure 10. 80 MHz ^{1}H NMR Spectrum of 44a

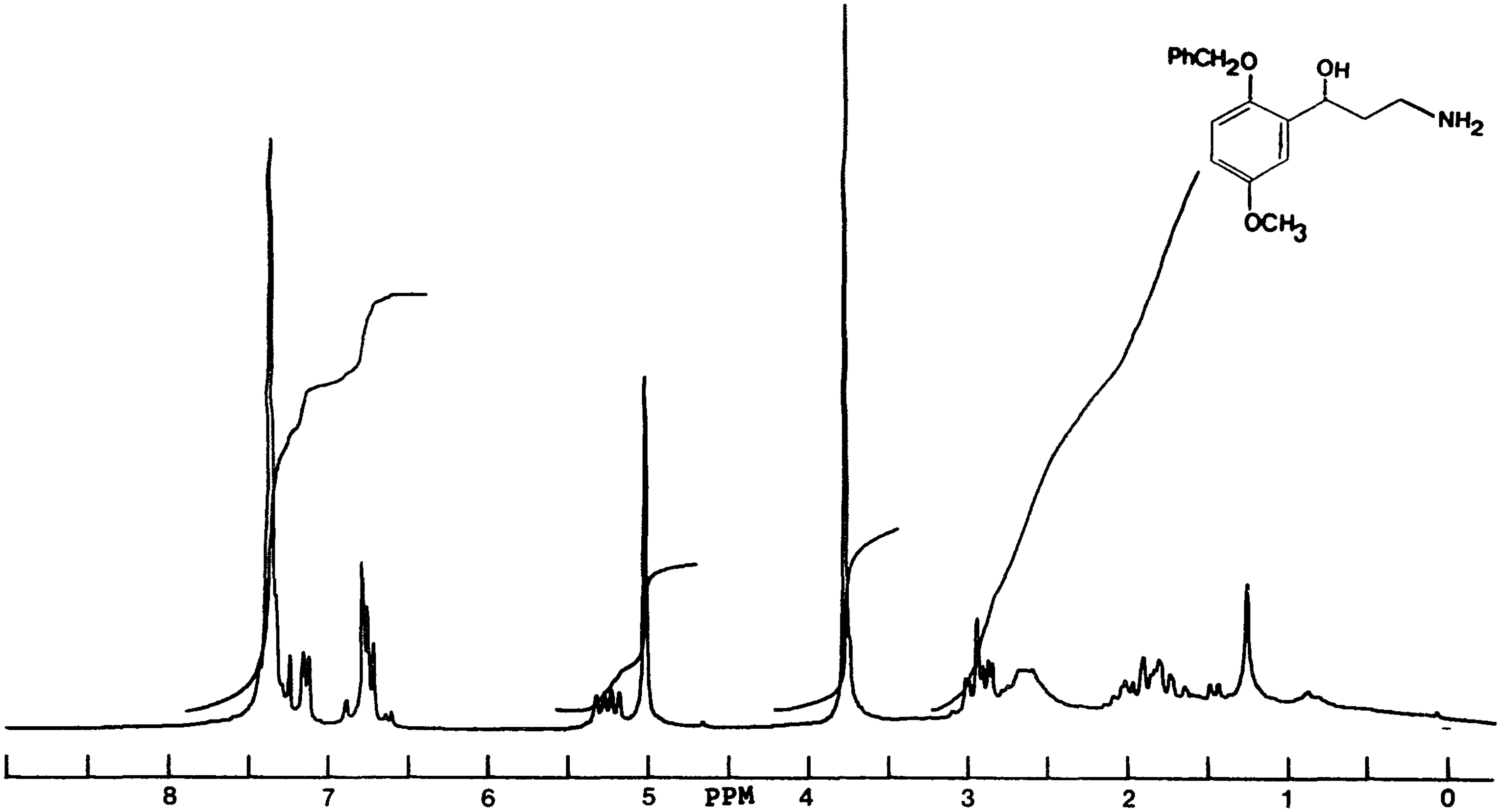


Figure 11. 80 MHz ^{1}H NMR Spectrum of 45a

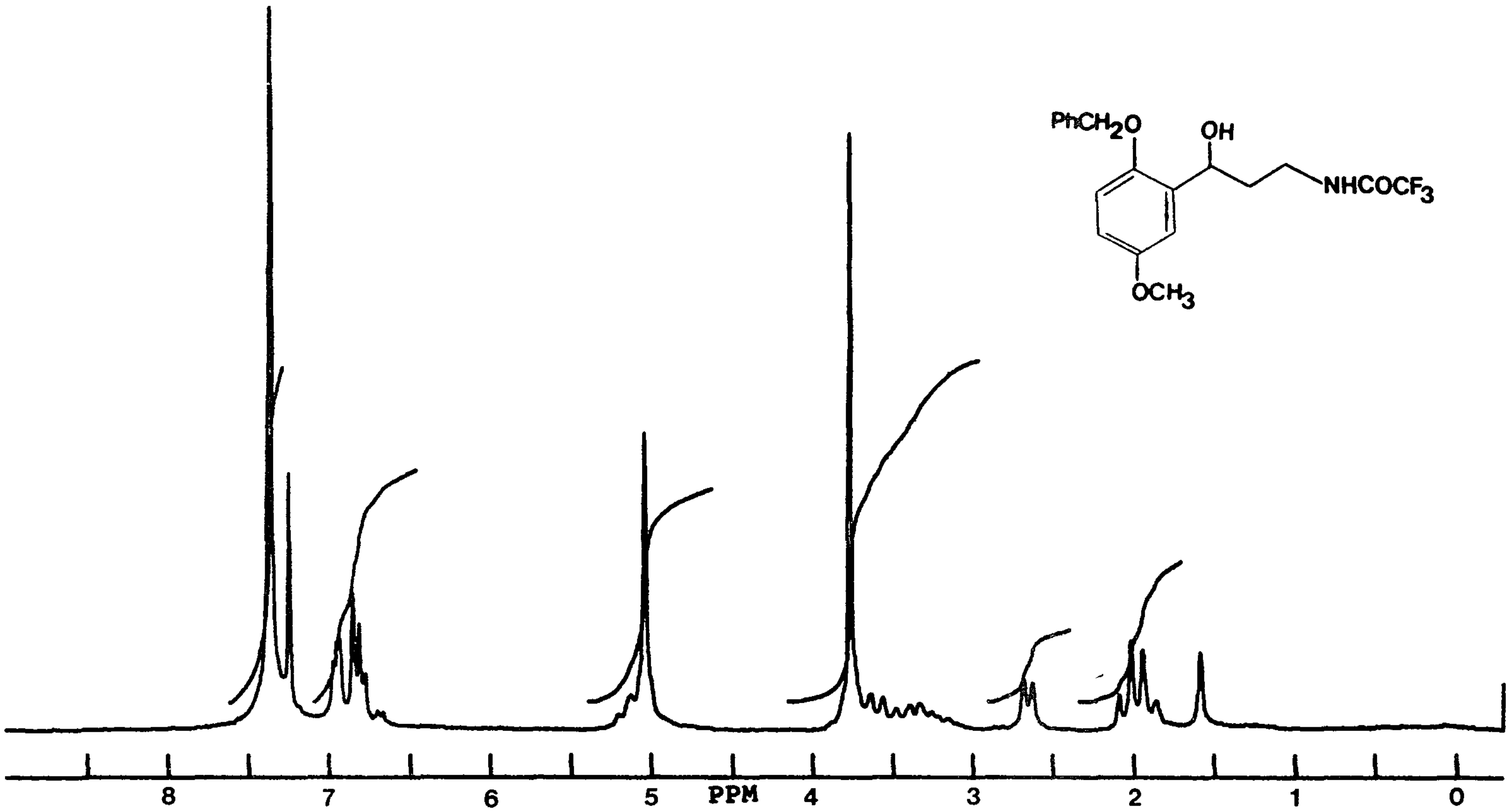


Figure 12. 80 MHz ^{1}H NMR Spectrum of 46a

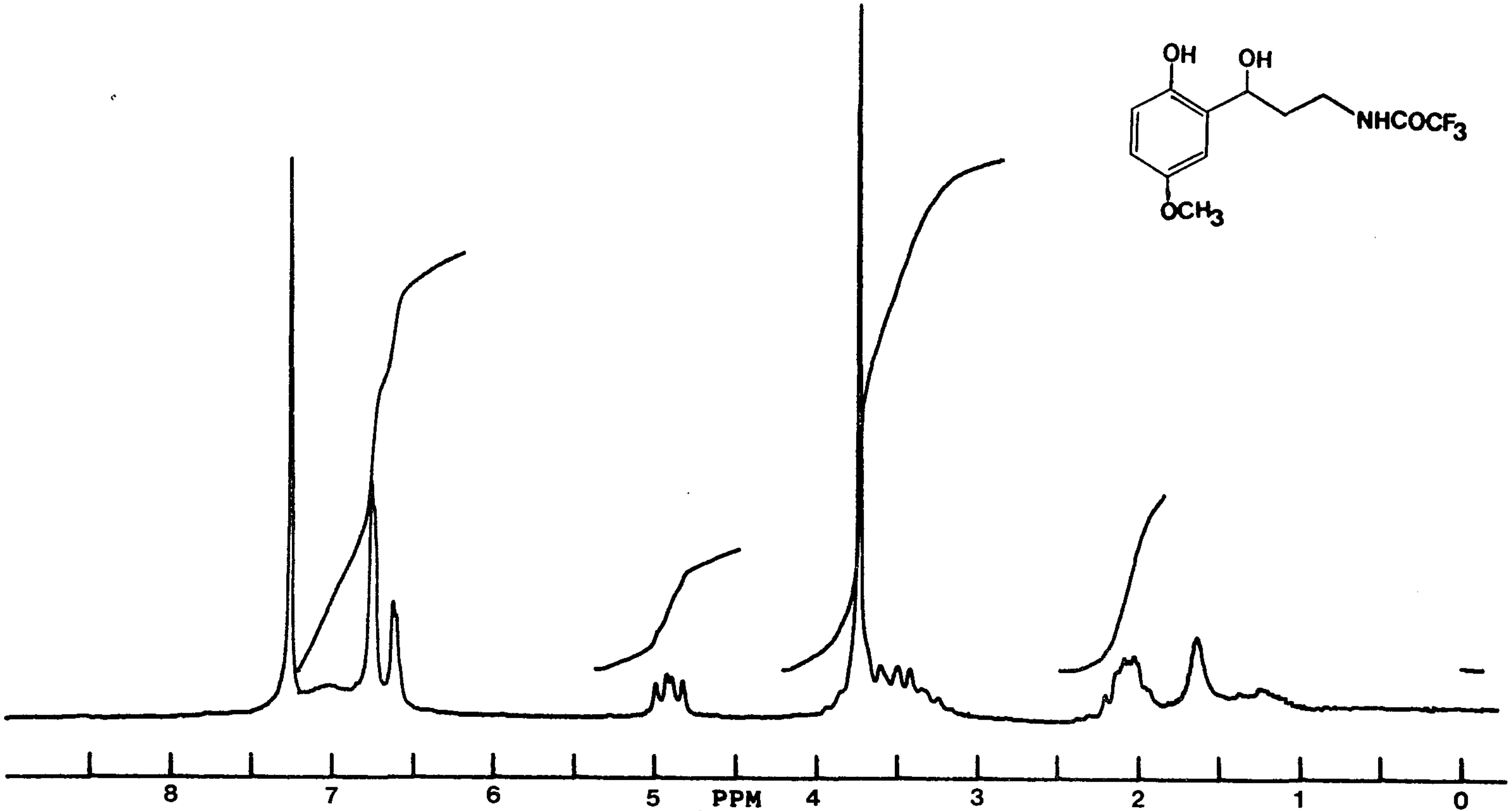


Figure 13. 80 MHz ^{1}H NMR Spectrum of 37d

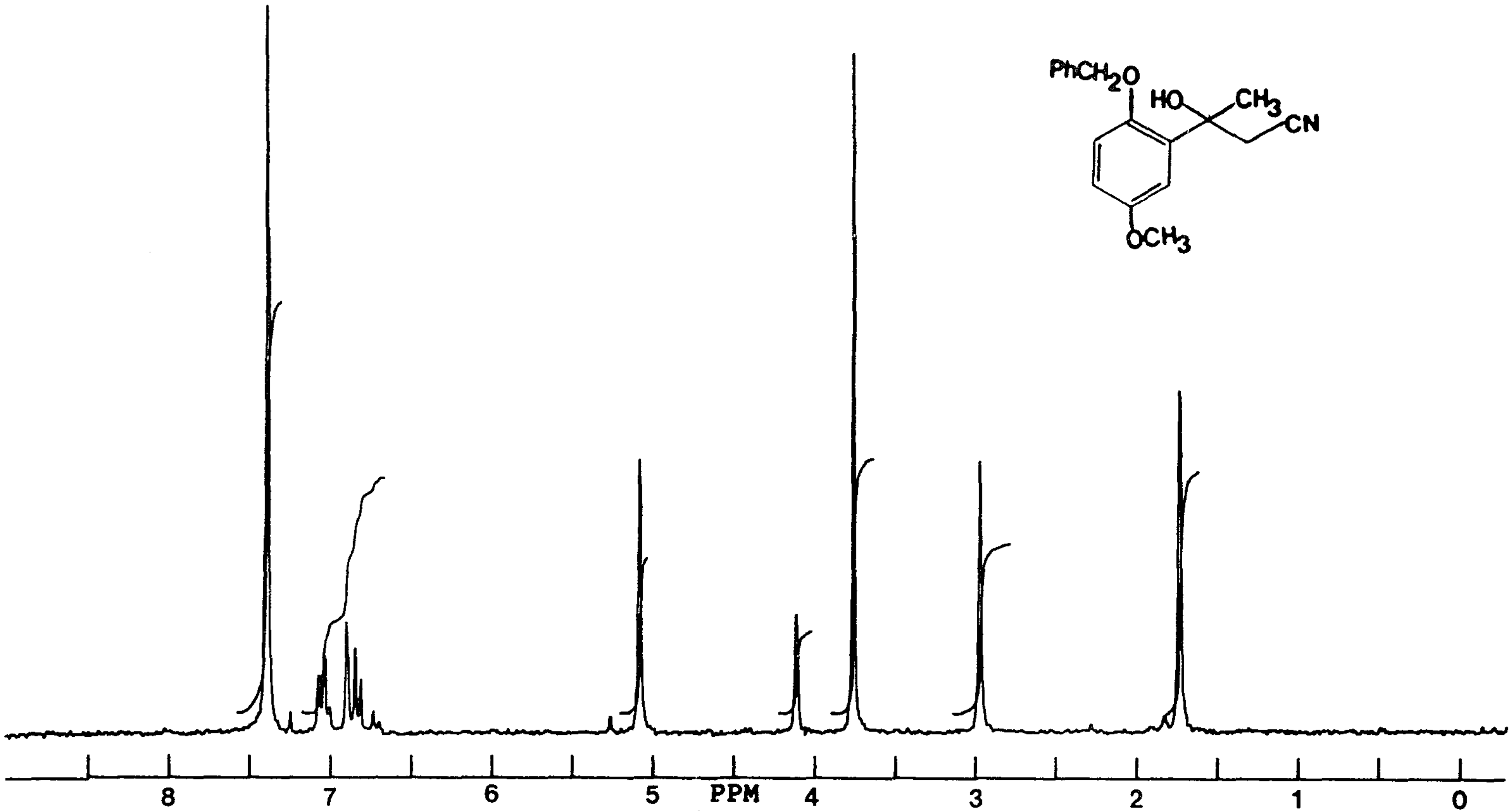


Figure 14. 80 MHz ^{1}H NMR Spectrum of 44b

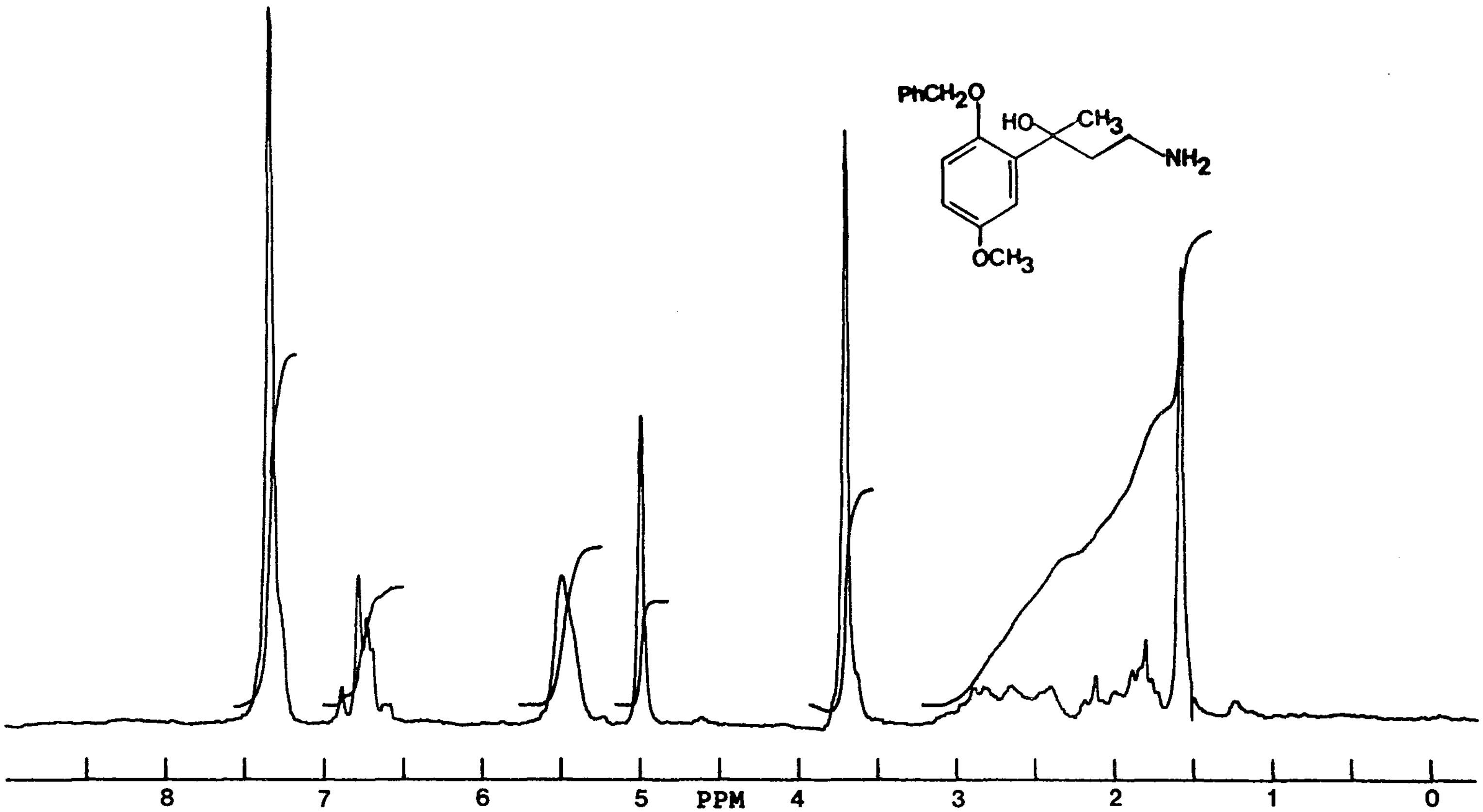


Figure 15. 80 MHz ^{1}H NMR Spectrum of 45b

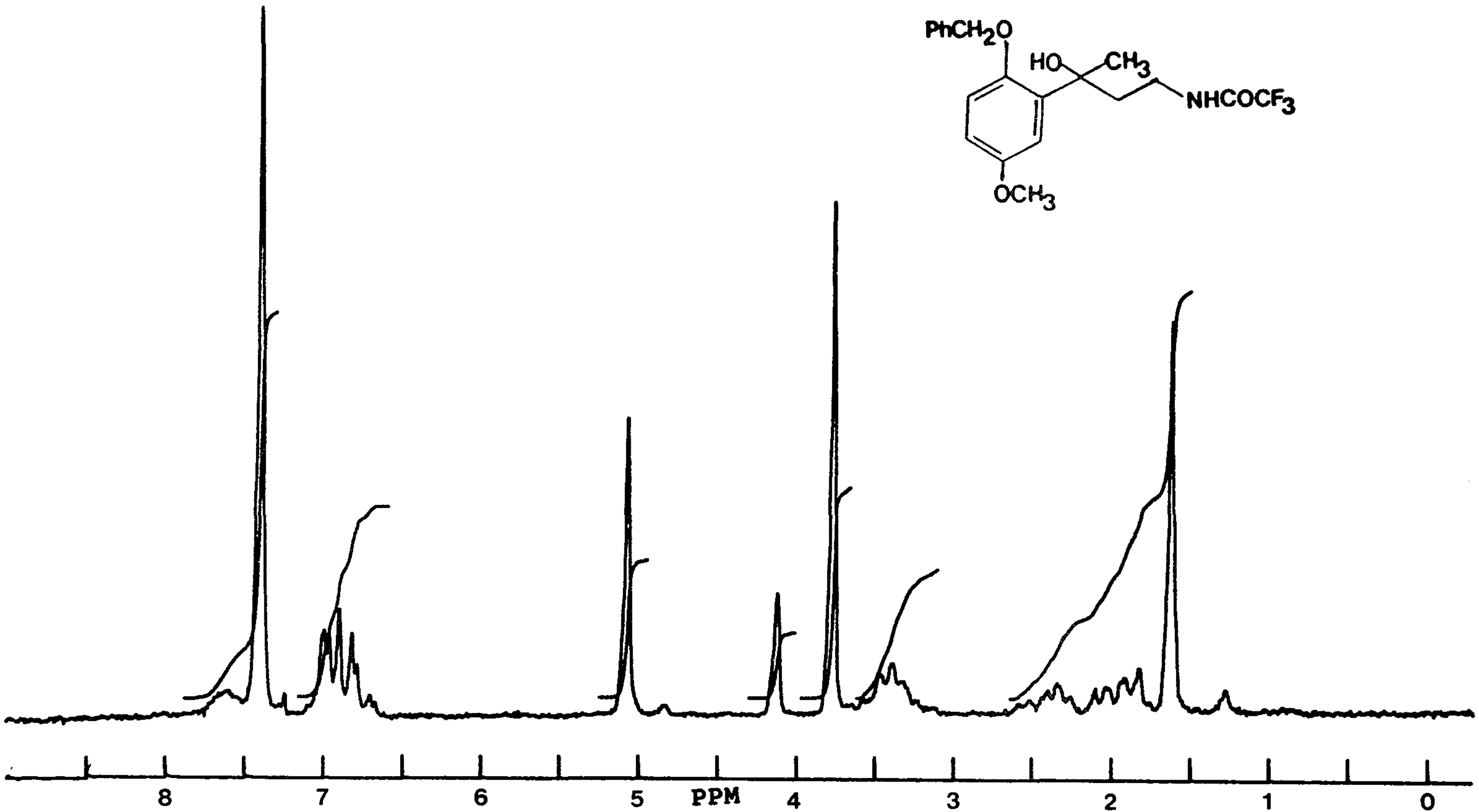


Figure 16. 80 MHz ^{1}H NMR Spectrum of 46b

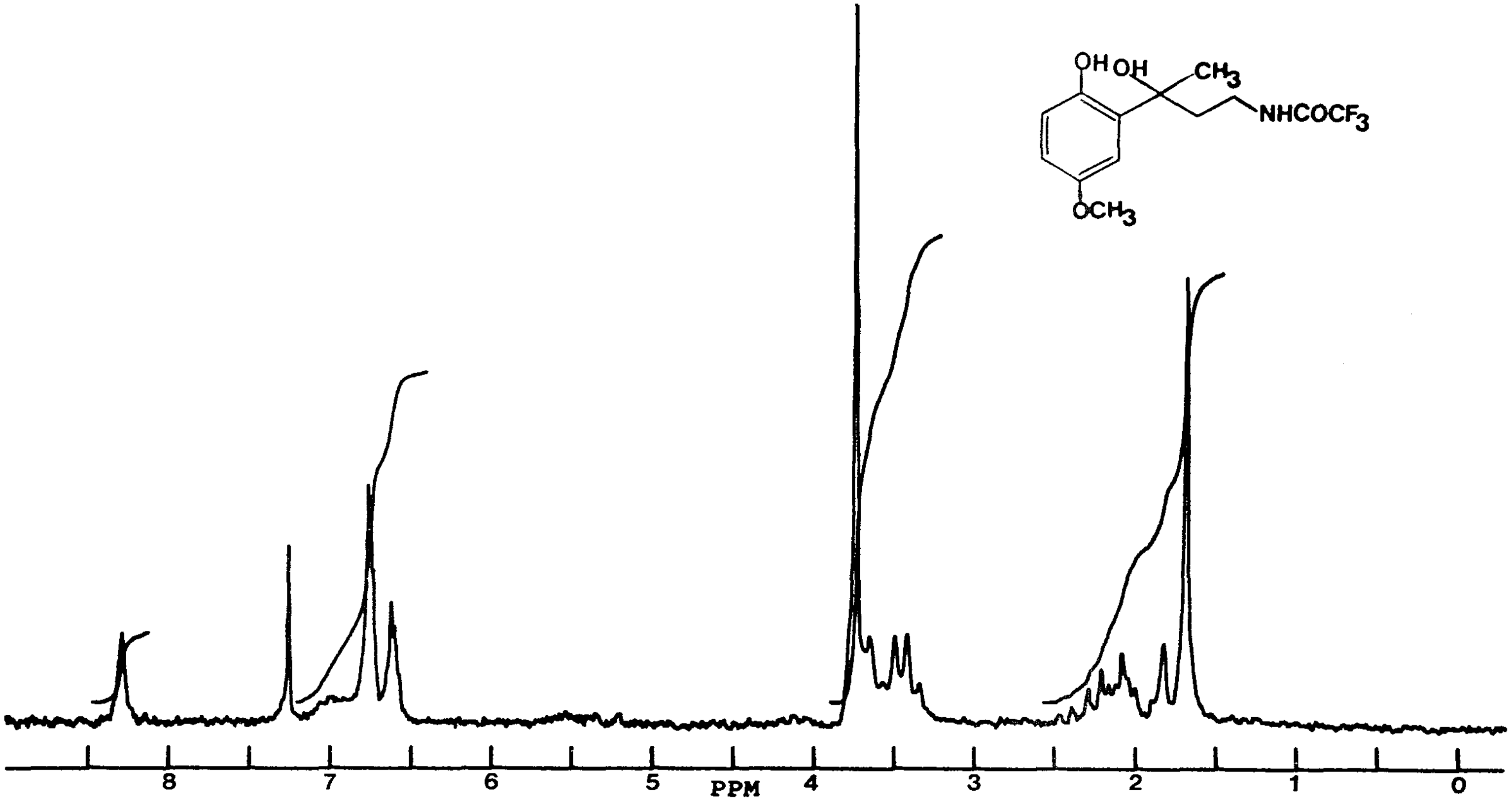


Figure 17. 80 MHz ^{1}H NMR Spectrum of 37e

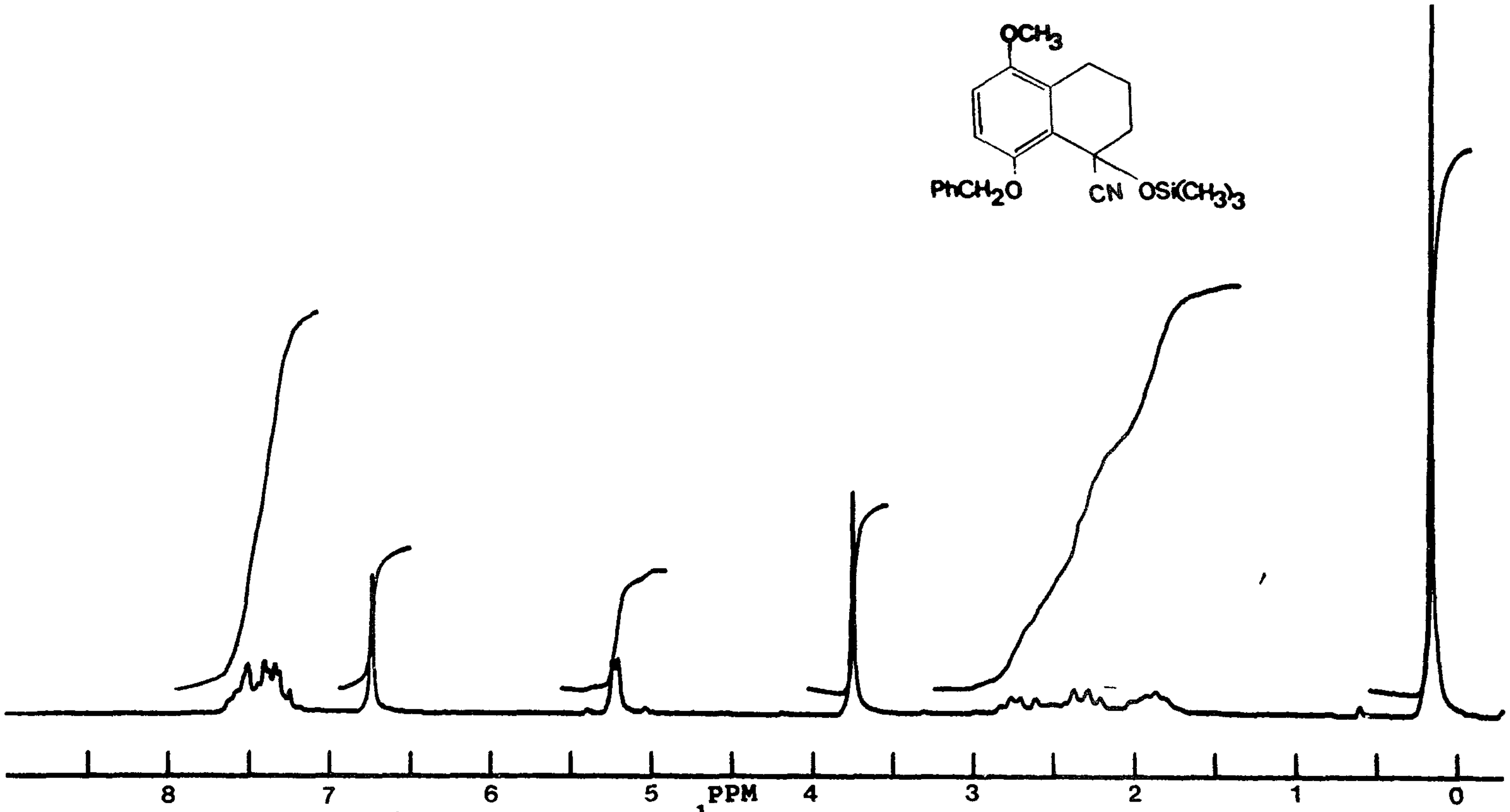


Figure 18. 80 MHz ^{1}H NMR Spectrum of 48

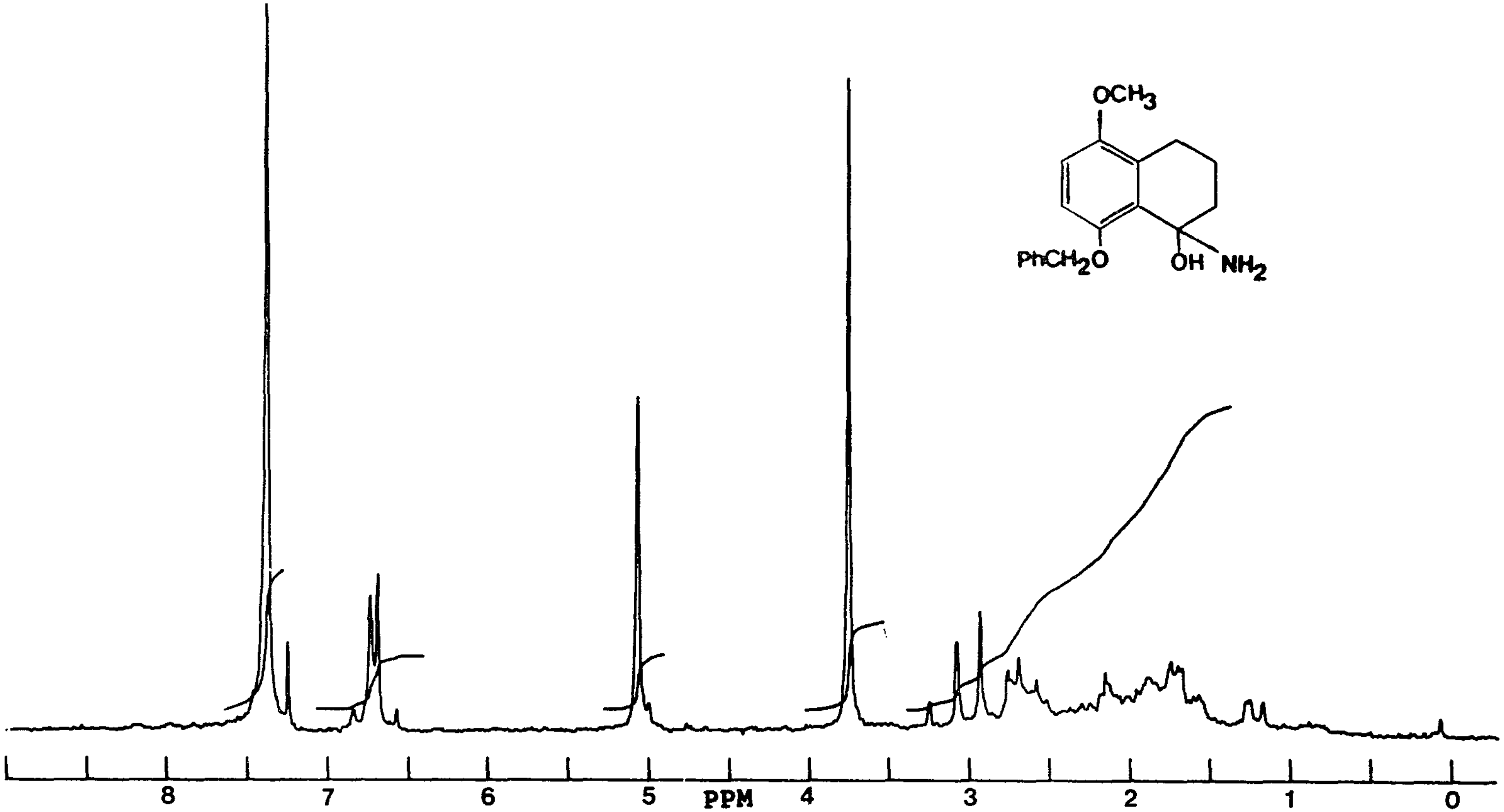


Figure 19. 80 MHz ^{1}H NMR Spectrum of 49

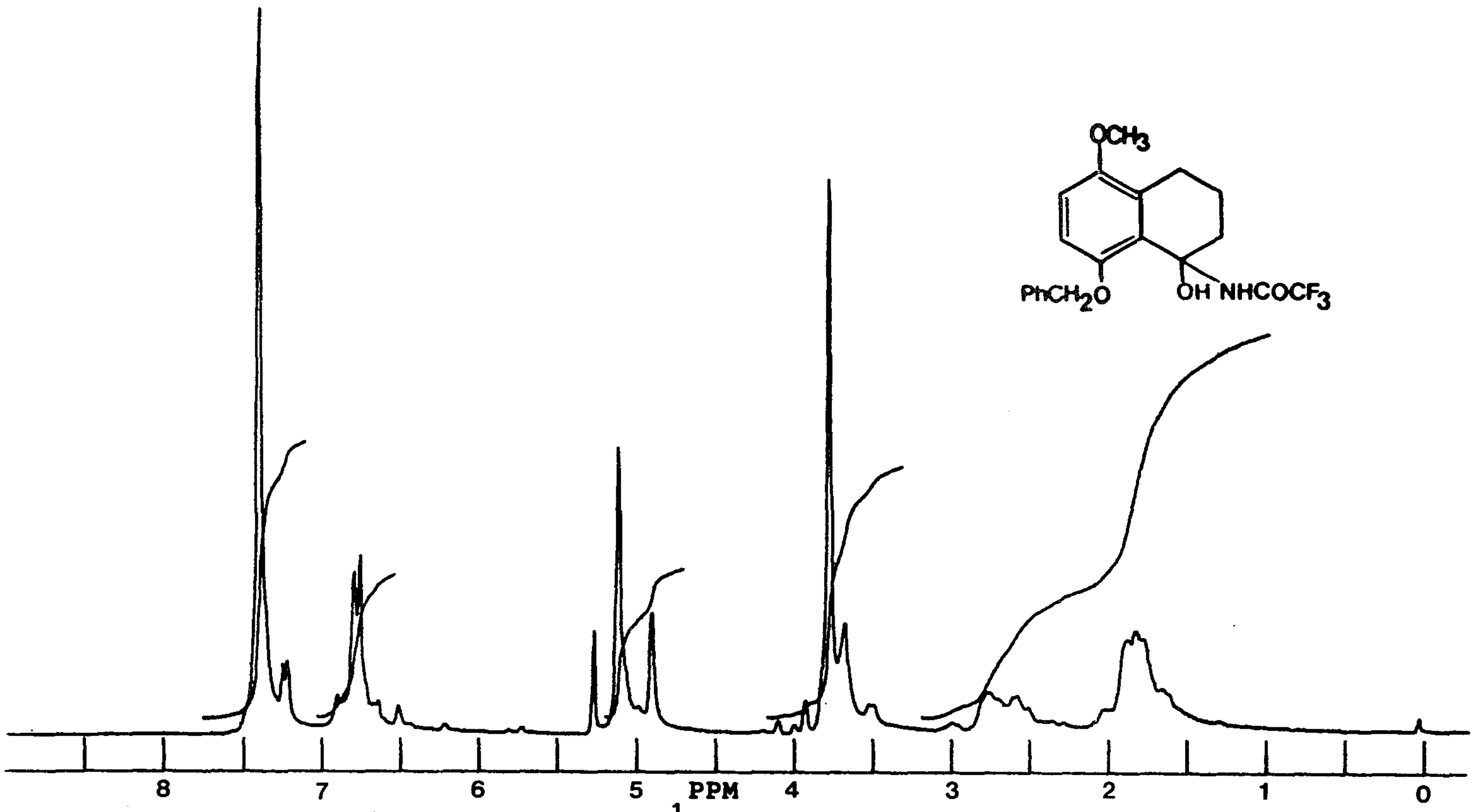


Figure 20. 80 MHz ^{1}H NMR Spectrum of 50

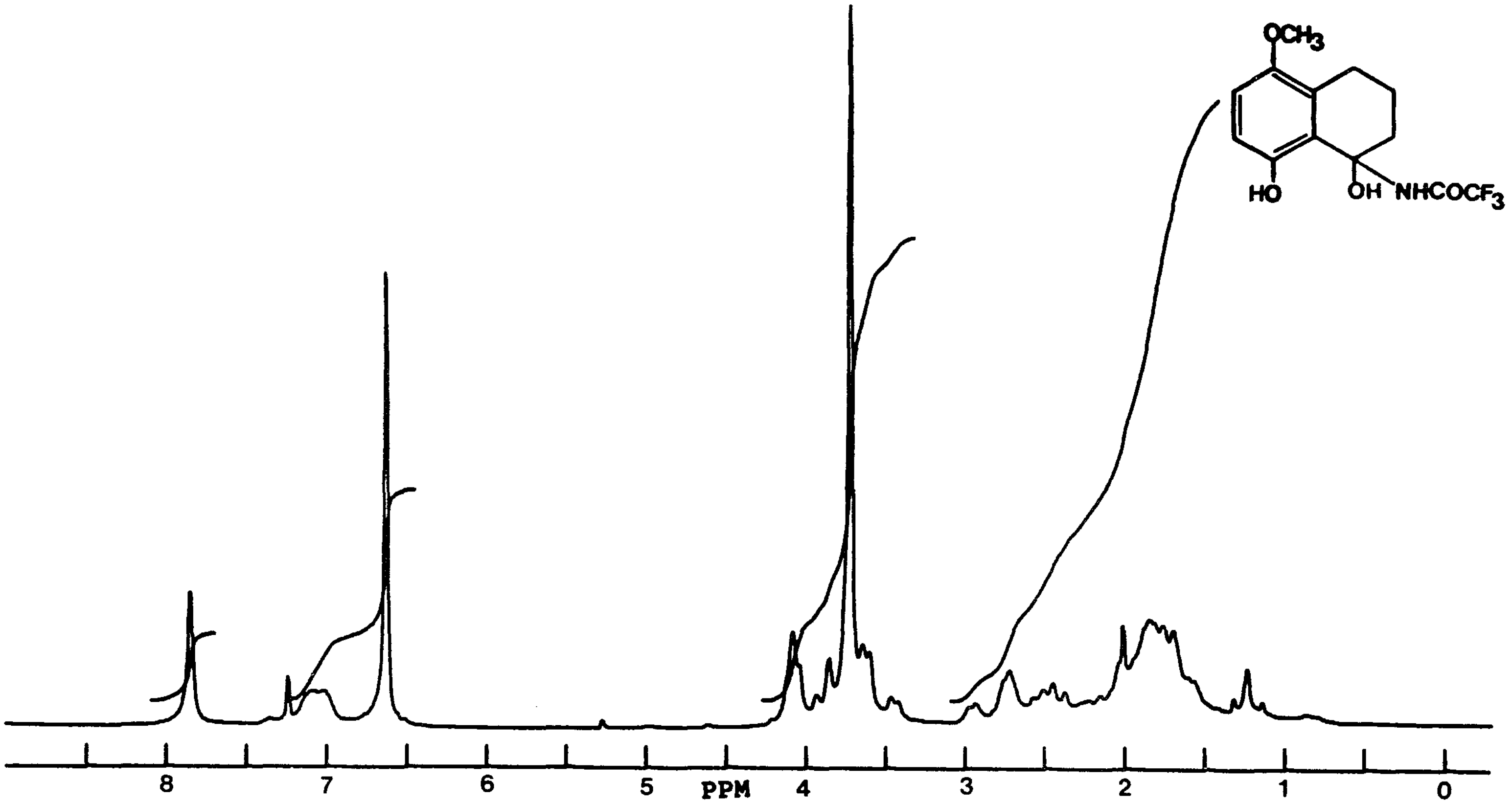


Figure 21. 80 MHz ^{1}H NMR Spectrum of 37f

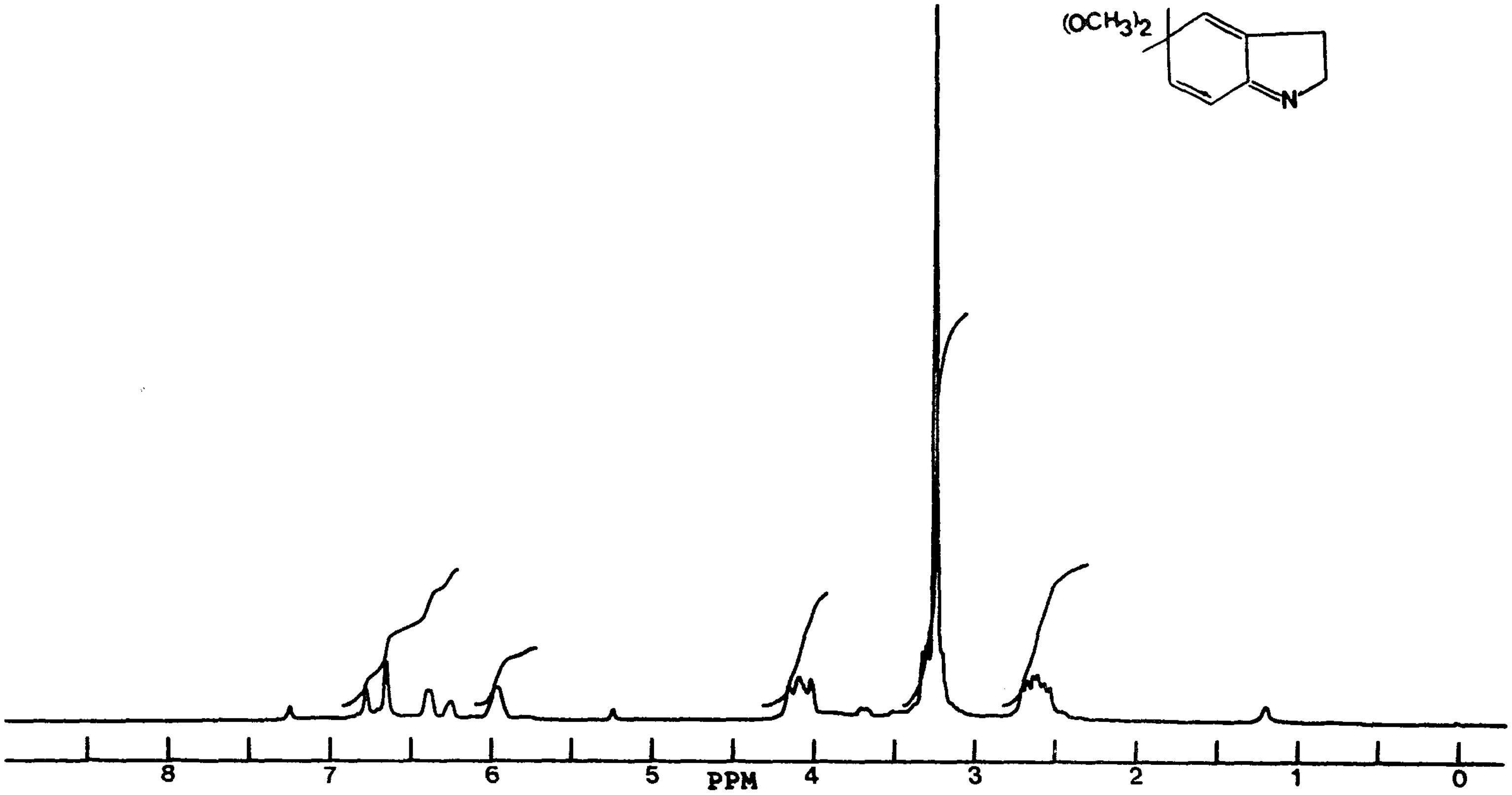


Figure 22. 80 MHz ^{1}H NMR Spectrum of 52a

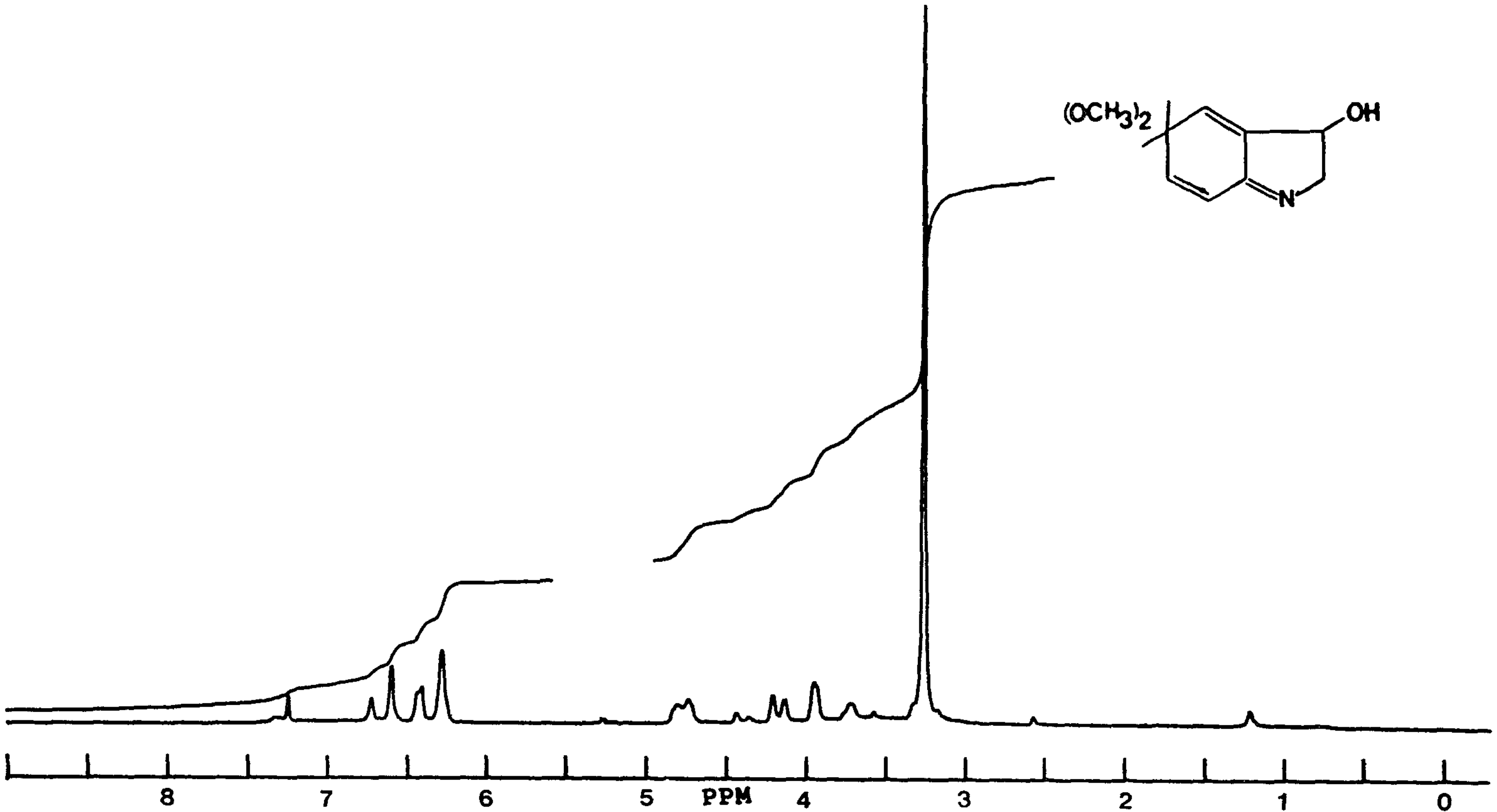


Figure 23. 80 MHz ^{1}H NMR Spectrum of 52b

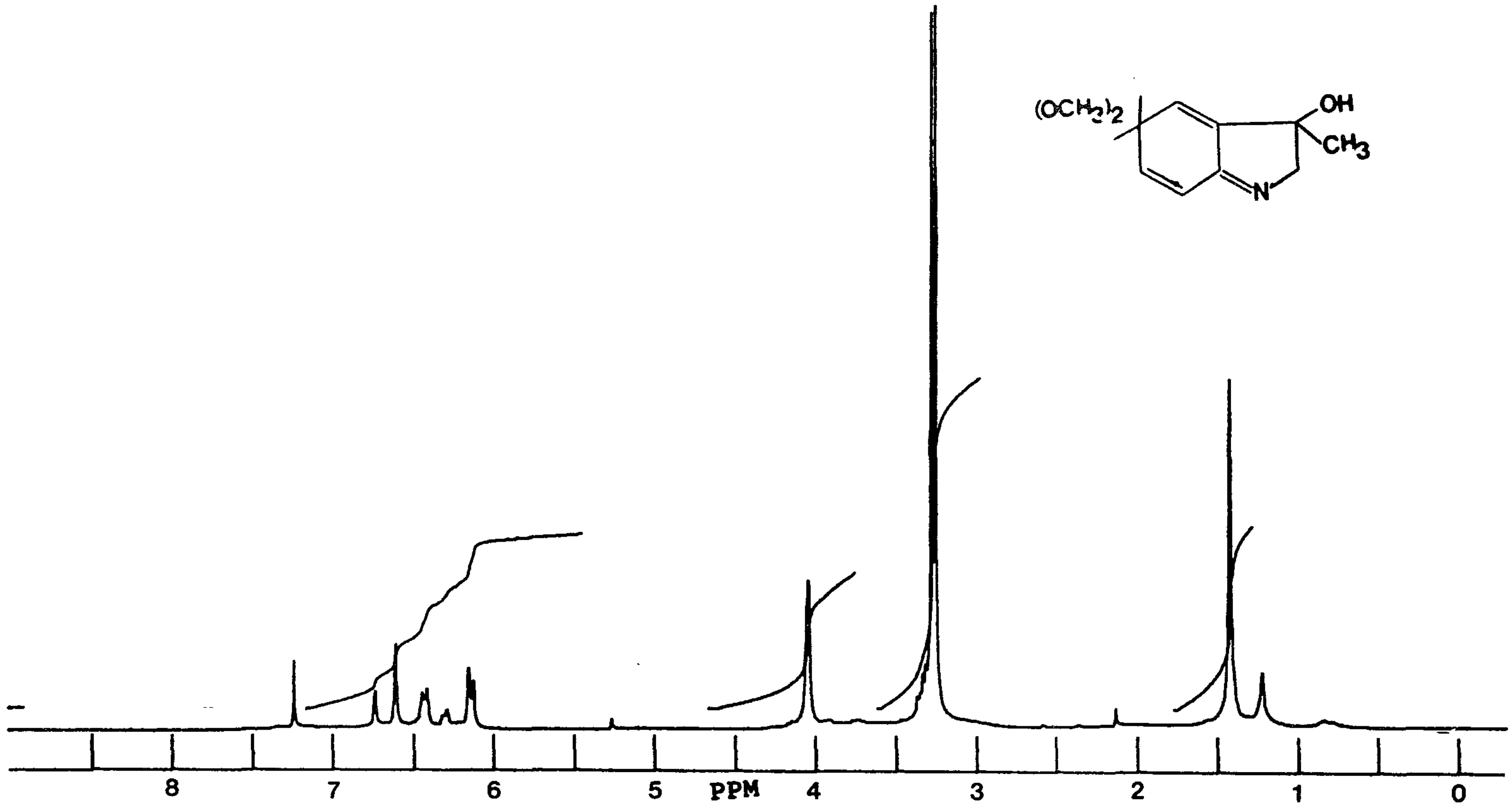


Figure 24. 80 MHz ^{1}H NMR Spectrum of 52c

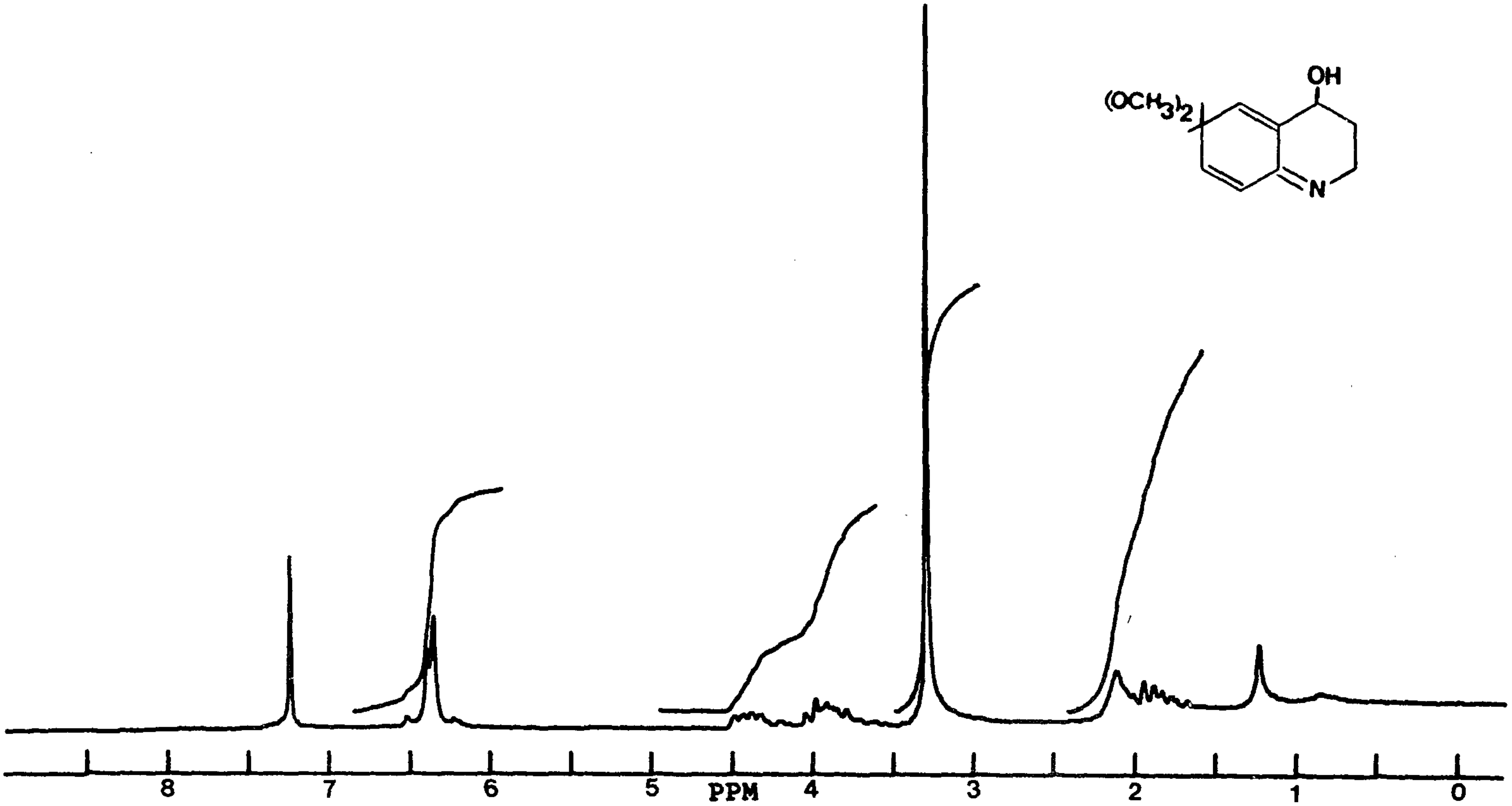


Figure 25. 80 MHz ^{1}H NMR Spectrum of 52d

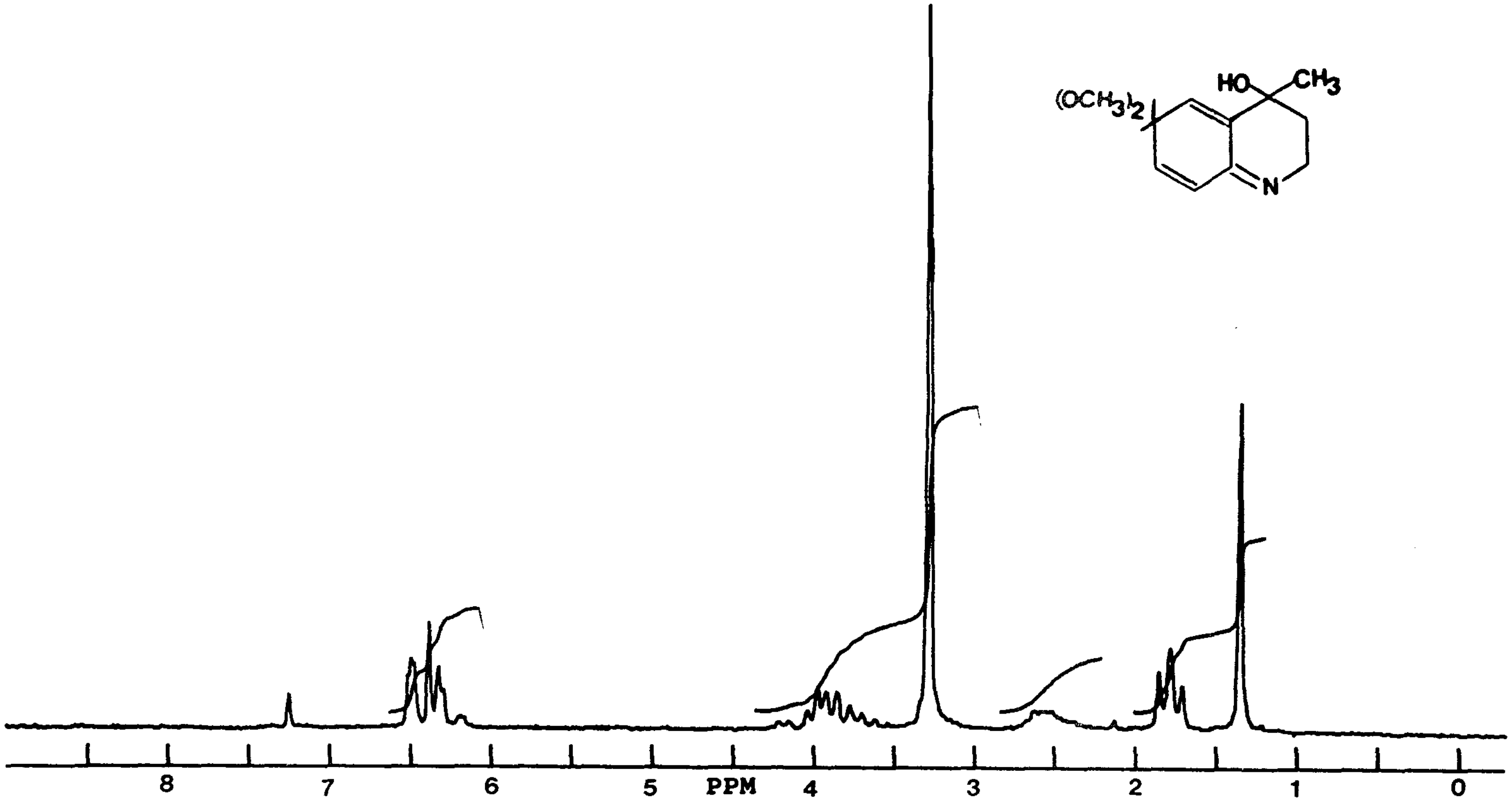


Figure 26. 80 MHz ^{1}H NMR Spectrum of 52e

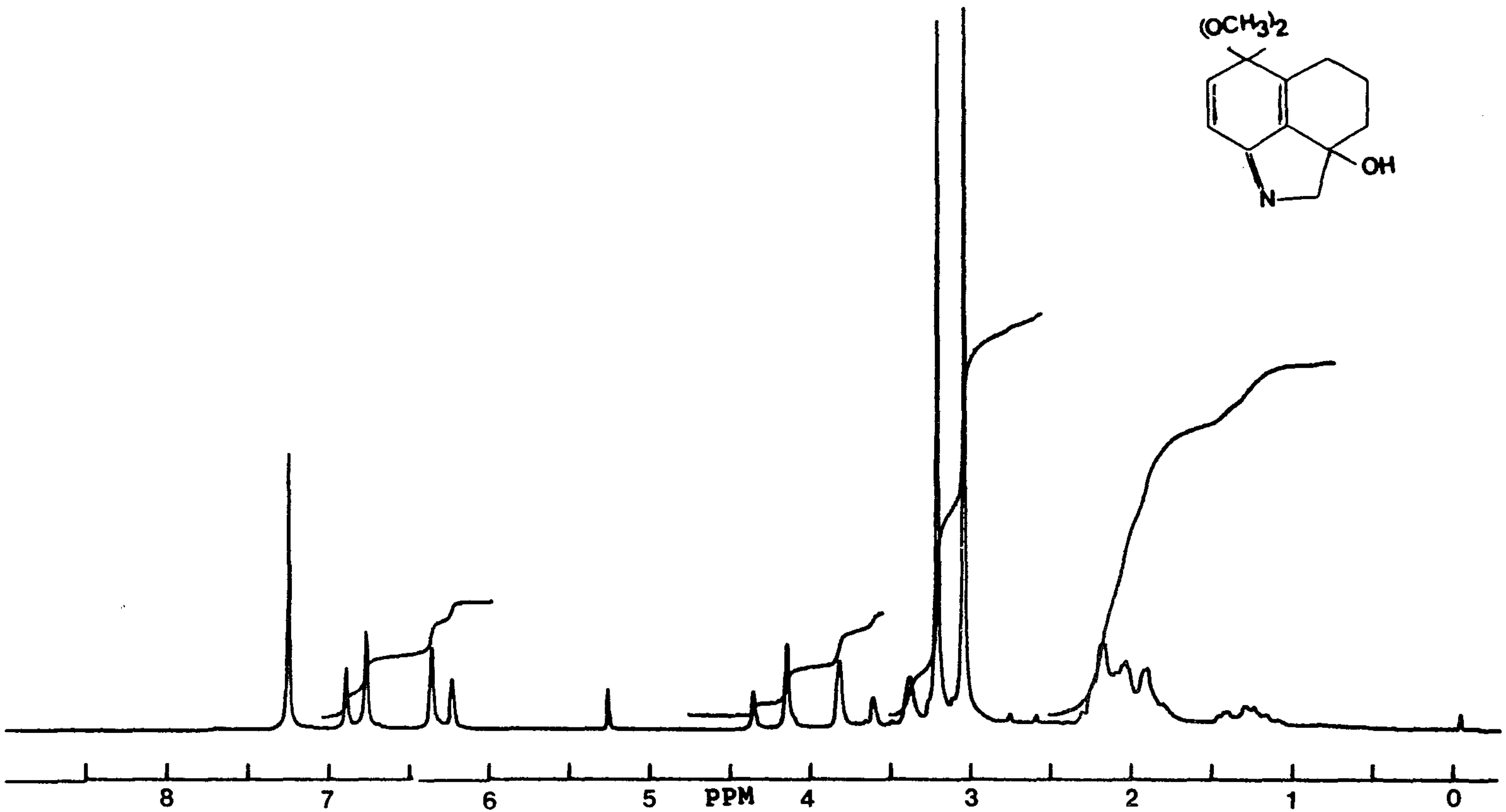


Figure 27. 80 MHz ^{1}H NMR Spectrum of 52f

PART IV

PREPARATION AND CHEMISTRY OF QUINONE IMIDE KETALS

ANODIC OXIDATION OF N-PROTECTED AROMATIC AMINES

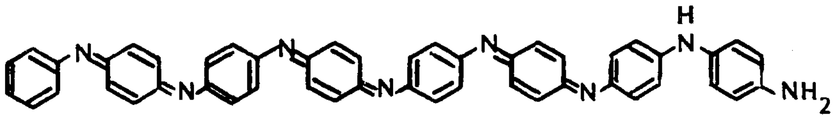
The aromatic amines, because of their ease of oxidation and high solubility in aqueous solution, have been substrates for numerous anodic studies.[1] Systems such as the aminophenols have served as testing grounds for many of the methods and theories of modern electroanalytical chemistry. Wawzonek and McIntyre[2] measured the oxidation half-wave potential of some para-substituted anilines by using a rotating platinum electrode in acetonitrile as shown in Table I.

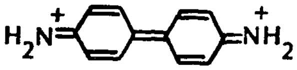
Table I. Oxidation Potentials in Aqueous Solution and in Acetonitrile and Ionization Potentials for Para-Substituted Anilines

Para-Substituent	pK_a	$E_{1/2}$ vs. SCE in H_2O (V)	$E_{1/2}$ vs. $Ag|Ag^+$ (0.1 N) in CH_3CN (V)	Ionization Potential (eV)
Methoxy	5.3	0.44	0.26	7.82
Phenyl	5.3	0.46	----	----
Hydrogen	4.6	0.72	0.54	8.32
Chloro	4.0	0.73	0.60	----
Carboxy	2.4	0.84	----	----
Cyano	1.8	1.03	----	----
Nitro	1.0	1.07	1.03	8.85

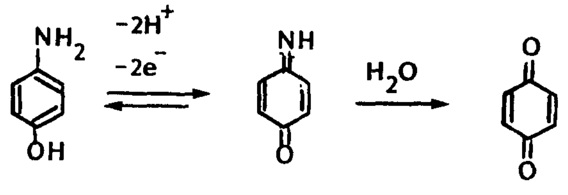
The primary aromatic amines were electrochemically oxidized on a preparative scale in aqueous acid or base as early as 1875 and 1876,[3] but voltametric data were not obtained until 1954,[4] and the major study was done by Adams and co-workers.[5-10] These investigations were not designed to develop new synthetic methods but were mechanism studies.

In the oxidation of aniline the anodically formed cation radical is not observed with ESR or detected by electrochemical techniques. It was presumed to undergo coupling and condensation to dimeric and polymeric species. When oxidized in 3.7 M sulfuric acid, a green precipitate was obtained on the anode, and this was thought to be emeradine **1**,[8] probably formed via p-aminodiphenylamine, which is oxidized at lower anodic potential than aniline, its precussor. At pH 0 to 6.5, p-aminodiphenylamine is the major product formed from aniline oxidation, further oxidation resulted in the formation of 2.



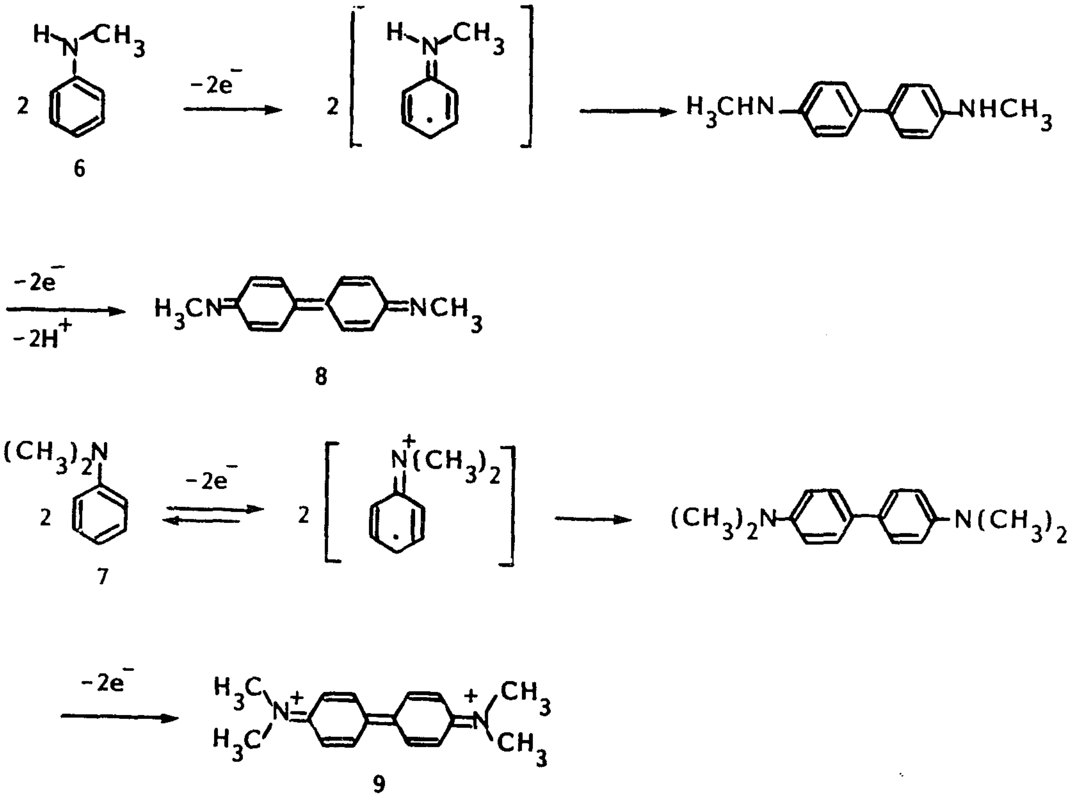


Anodic oxidation of p-aminophenol **3** afforded benzoquinone **4** which was proposed to occur via hydrolysis of the quinone imine 5.



3 5 4

The anodic oxidation of secondary and tertiary aromatic amines in aqueous solution was studied in a wide range of pH.[11] The products **8**,**9** of the reaction were suggested to be oxidized dimethylbenzidene **6** and tetramethylbenzidene **7** on the basis of voltammetric identification. The reaction was complicated by further reaction between product and starting material which is shown as follows:



6 8 7 9

From the above results, the direct anodic oxidation of aromatic amines often resulted in complicated products and can only be used as mechanistic studies, no synthetic applications were used at this stage.

For this reason, N-protected amines were used to investigate the anodic oxidation reactions. In the literature, there is no mention of the anodic oxidation studies of p-methoxy benzamide or p-hydroxyl benzamide. Several chemical oxidation methods were described in the introduction of Part III of this dissertation, but these methods are not suitable for synthetic purposes.

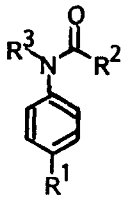
Objective

The objective of this work was to explore the anodic oxidation of N-protected amines and the synthetic application of the resulting products.

RESULTS AND DISCUSSION

Anodic Oxidation Studies

The anodic oxidation of p-substituted aromatic amides apparently have not been previously investigated. Thus, for initial exploratory studies the amides from commercially available p-anisidine and p-toluidine were chosen for study. These compounds were prepared by standard acylation of the corresponding aniline, and the compounds showed the expected spectroscopic properties. The anodic oxidations were performed under three sets of experimental conditions. These will be referenced in the text as Procedures I, II, and III.



10a-g

	R^1	R^2	R^3
a,	OCH_3	Ph	H
b,	OH	Ph	H
c,	OCH_3	CH_3	H
d,	OH	CH_3	H
e,	OCH_3	O-*t*-Bu	H
f,	CH_3	Ph	H
g,	OH	Ph	CH_3

I. These reaction conditions involved a single electrolysis cell with 2% lithium perchlorate/methanol as solvent and electrolyte.

II. These reaction conditions also involved a 2% lithium perchlorate/methanol as solvent and electrolyte. However, this differed from I in that finely ground sodium bicarbonate was employed as a heterogeneous base, and vigorous stirring was used.

III. These conditions involved a divided cell with 2% lithium perchlorate/methanol as solvent and electrolyte. Finely ground sodium bicarbonate was employed as a heterogeneous base, and vigorous stirring was used.

All anodic oxidation studies were conducted at 0 °C and were monitored by UV spectroscopy or TLC. Three types of amides were employed (benzoyl, acetyl, t-BOC) in the studies, and the results are shown in Table II.

The 1,4-addition products (entries 1,4) were obtained as either light yellow liquid or colorless solid from conventional workup of the anodic oxidation mixture. The compounds could not be purified by silica gel chromatography since decomposition of the corresponding quinone imide occurred. However, the spectroscopic data obtained from the crude product indicated the compounds were formed in good yield and high purity. The ^{1}H NMR spectrum of the crude reaction mixture from anodic oxidation of **10** is representative of the products obtained. The ^{13}C NMR spectrum of the crude reaction mixture from the anodic oxidation of **10b** give two tertiary peaks at δ 92.0 and 78.9 and give the

Table II. Anodic Oxidation of 10a-g

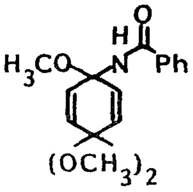
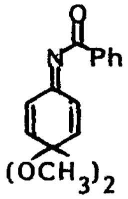
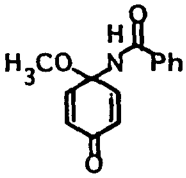
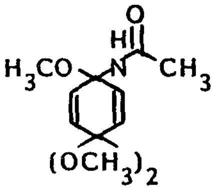
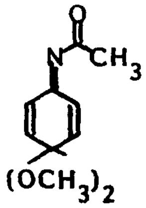
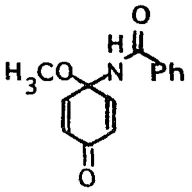
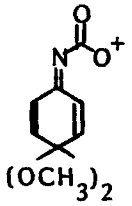
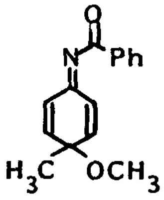
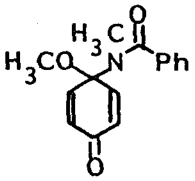
Entry	Substrate	Condition	Product		Yield (%)
1	10a	I		11	80
2	10a	II		12	86
3	10b	I		13	80
4	10c	I		14	89
5	10c	II		15	89

Table II. (continued)

Entry	Substrate	Condition	Product		Yield (%)
6	10d	I		16	89
7	10e	II		17	93
8	10f	III		18	75
9	10g	I		19	82

The anodic oxidation voltage was set around 4 V and 0.1-0.3 A. See details in Experimental sections.

All oxidation products were kept in -20 °C, or slow decomposition occurred at room temperature.

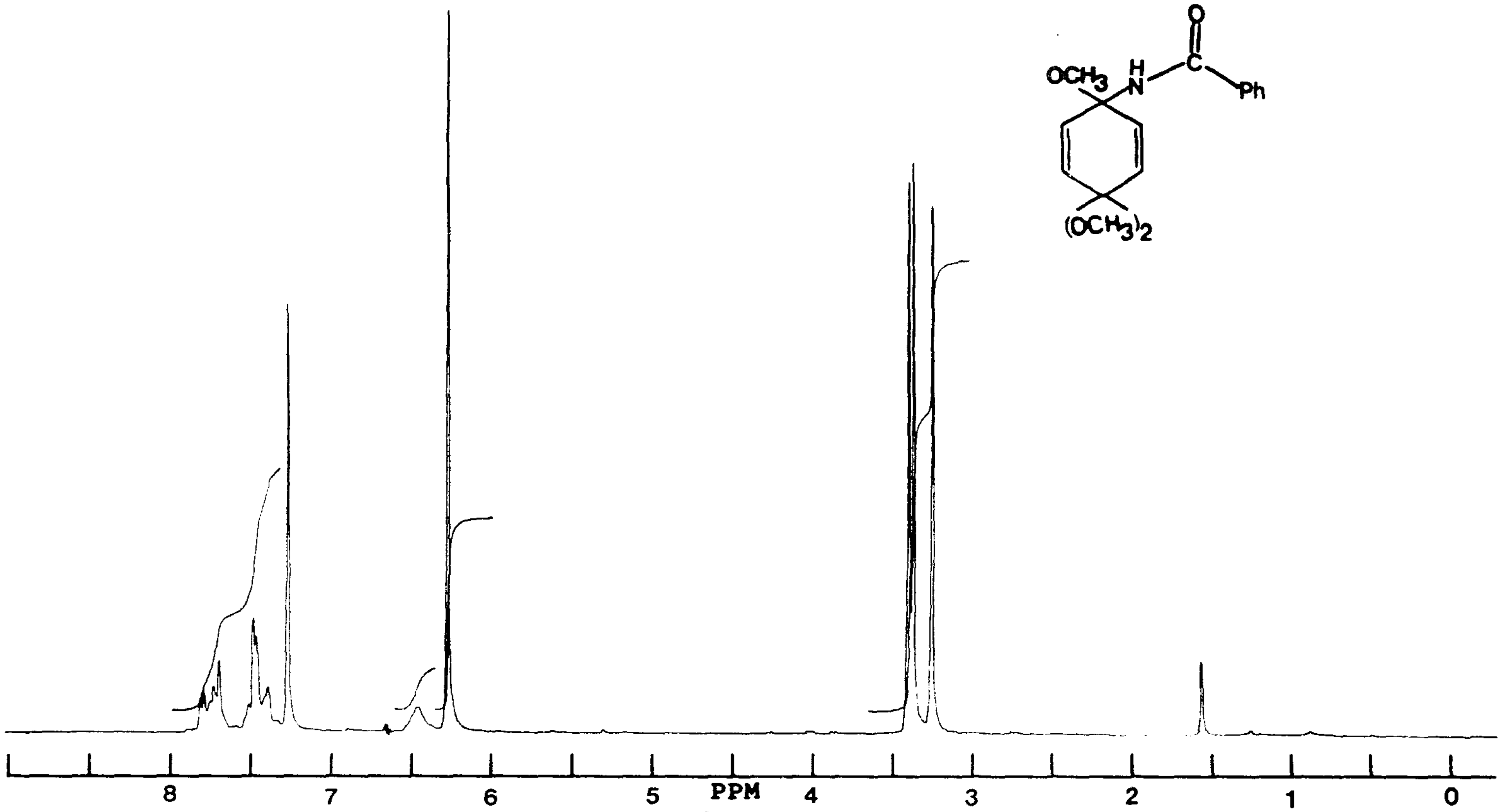


Figure 1. 80 MHz ^{1}H NMR Spectrum of 11

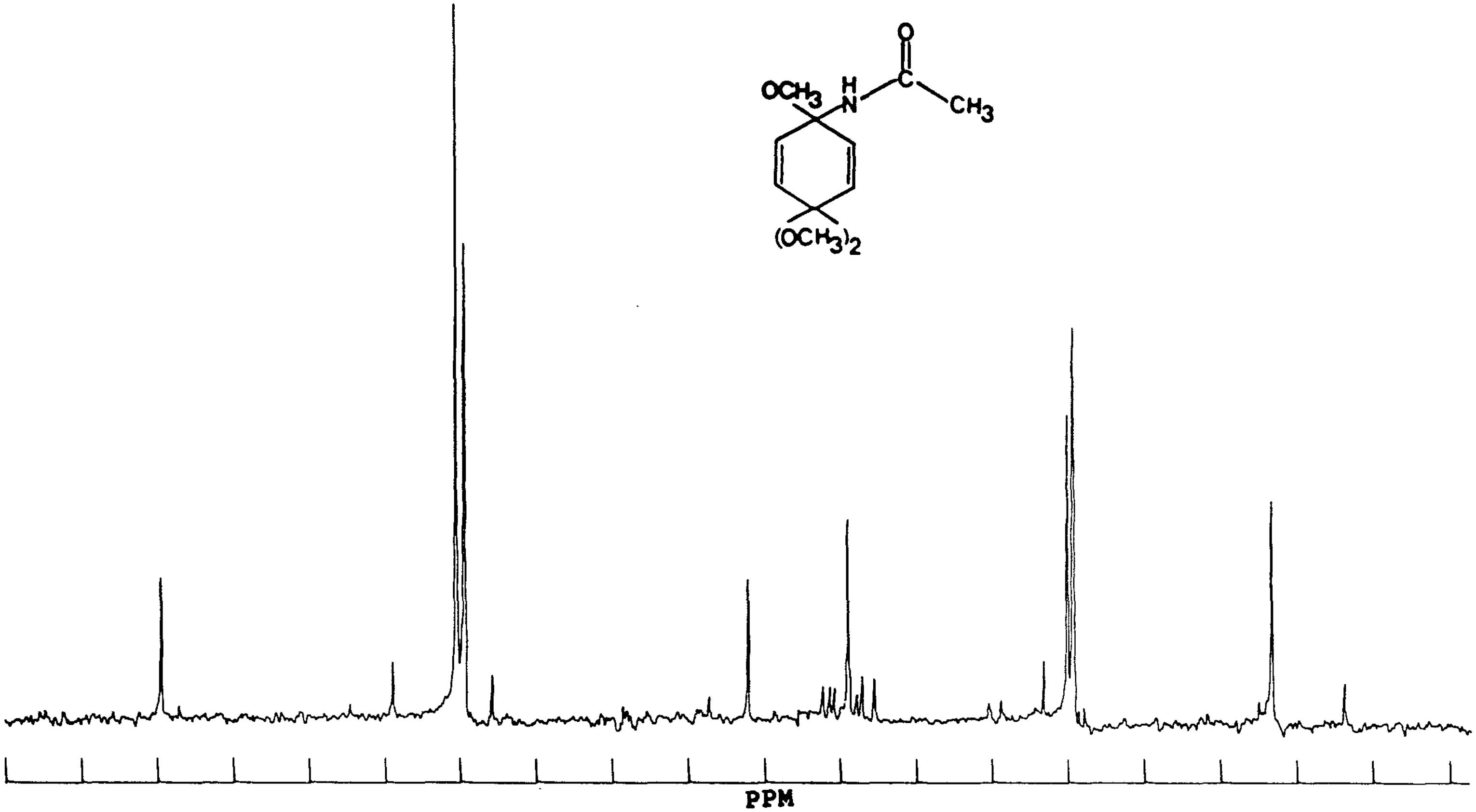


Figure 1a. 20 MHz ^{13}C NMR Spectrum of 14

evidence for the 1,4 addition of anodic oxidation. Infrared spectroscopy is not especially useful in product determination.

Quinone imide ketals (entries 2,5,7) were obtained as light yellow oil from conventional workup of the anodic oxidation mixture. The crude compounds can be purified via silica gel chromatography. All tended to decompose slowly at room temperature; storage at -20 °C is recommended. Representative ^{1}H and ^{13}C NMR spectra of quinone imide ketals **12** produced from the anodic oxidation of aromatic amide in the presence of base showed two methoxy peaks and a carbon-nitrogen double bond at δ . The most convenient method to determine the quinone imide ketal formation is IR spectroscopy. A strong absorption around 1600 cm^{-1} is assigned to the C=N bond stretching vibration.

The anodic oxidation of p-aminophenol derivatives (entries 3,6,9) proceeded in good yield to generate dienenone **13,16,19**. The structure of the compounds were supported by spectroscopic data. Each dienone showed two characteristic carbonyl absorption peaks around 1670 and 1630 cm^{-1} assigned to the conjugated carbonyl linkage, and the ^{1}H NMR spectrum showed a set of AB quartets around δ 7.0-6.0 with coupling constant equal to 10 Hertz.

As illustrated in Table II, anodic oxidation of N-protected amines in lithium perchlorate methanol usually give good yields of the 1,4-addition products. However, when these reactions were performed in the presence of $NaHCO_3$ powder, the quinone imide ketals were virtually the exclusive products. It is important to note that the reaction mixture must be rapidly stirred in order to keep the $NaHCO_3$ powder suspended. Slow stirring leads to a mixture of **11** and **12** from **10a**.

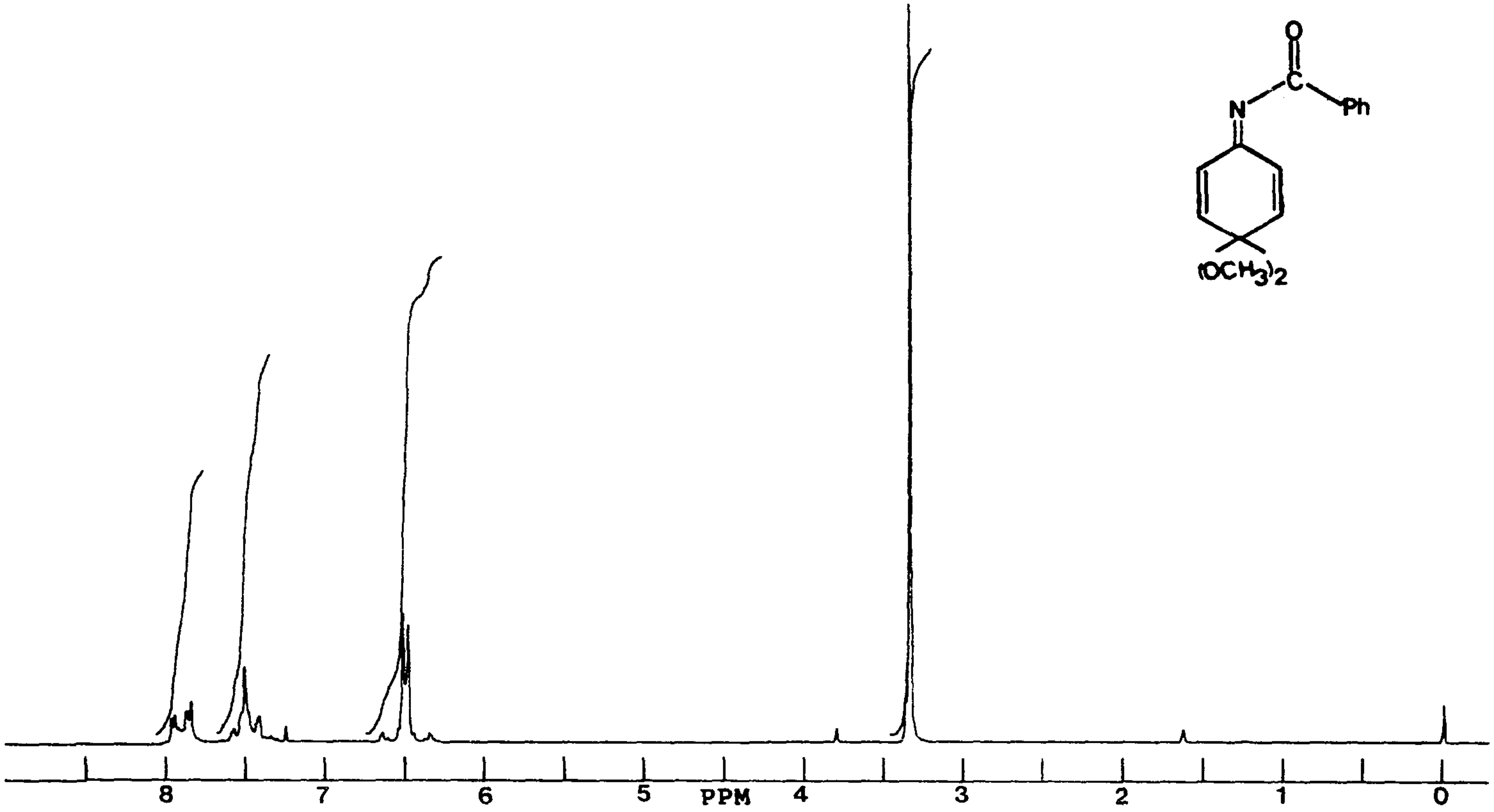


Figure 2. 80 MHz ^{1}H NMR Spectrum of 12

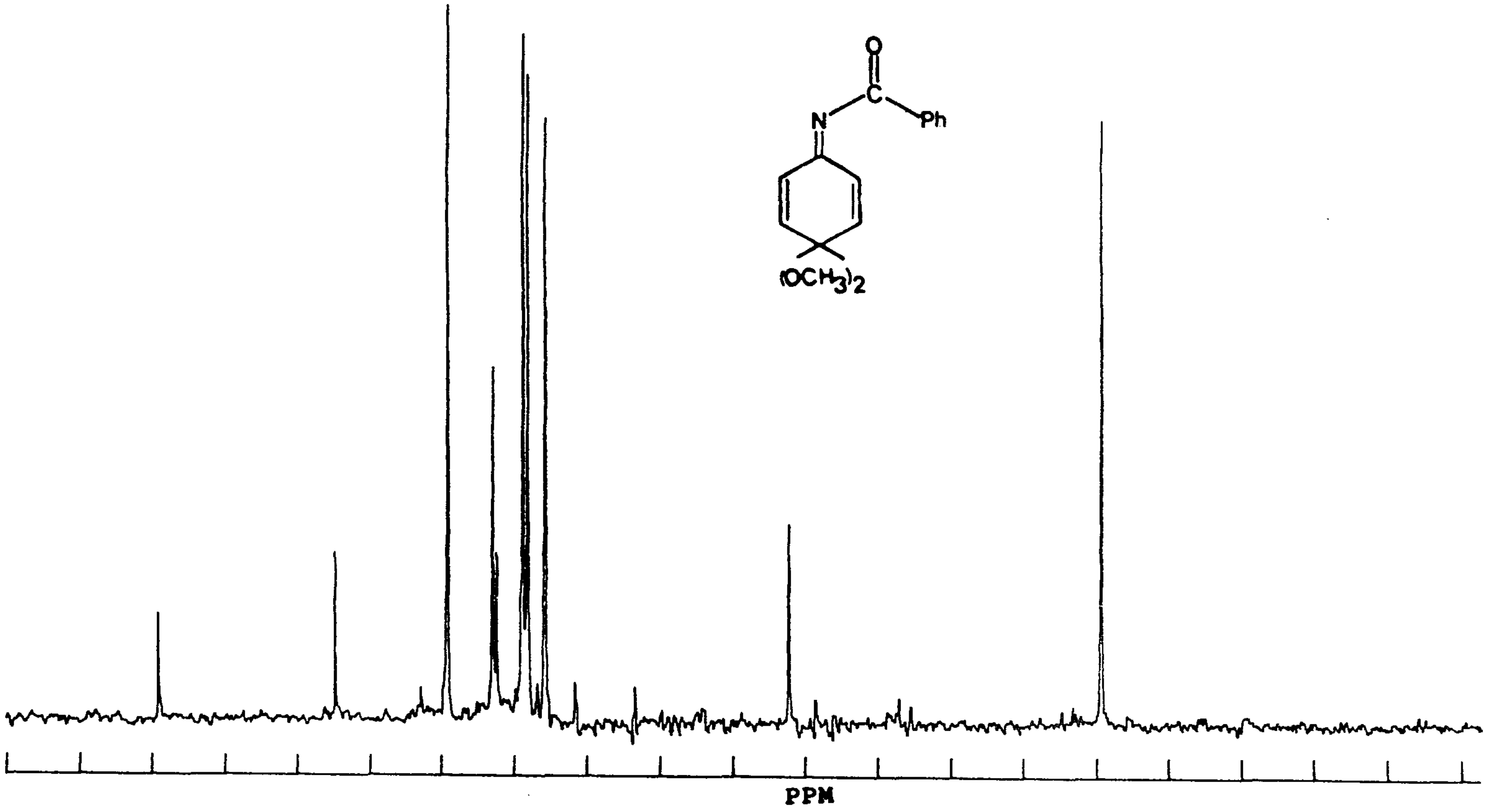
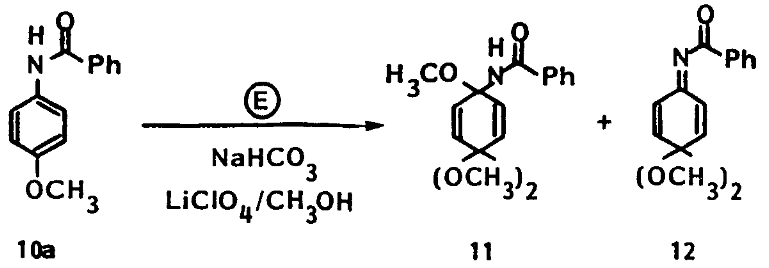
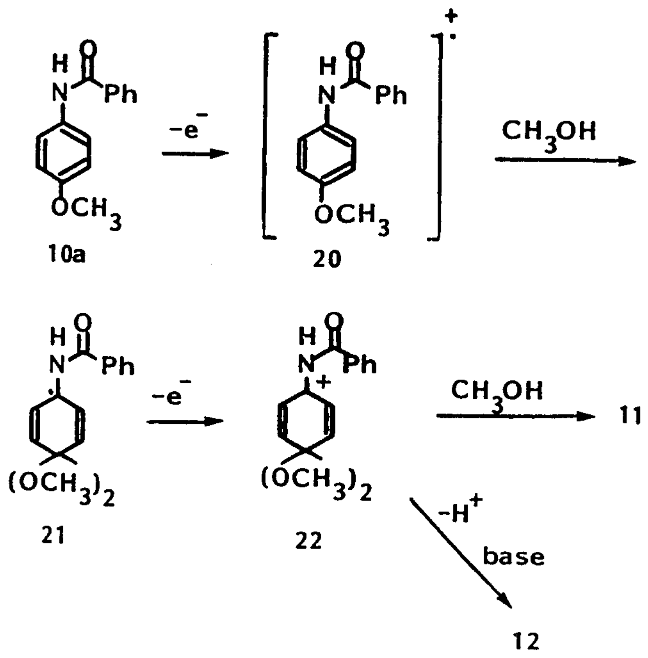


Figure 2a. 20 MHz ^{13}C NMR Spectrum of 12



A possible explanations for the effect of sodium bicarbonate on the product mixture is given in Scheme I.



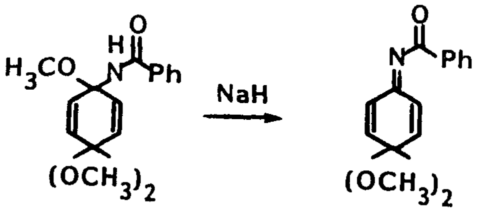
Removal of one electron from **10a** gave a cation radical **20** which underwent addition of methanol to give intermediate **21**. Further removal of one electron from **21** gave a cation intermediate **22**. Reaction of methanol with **22** gave the 1,4-addition product **11**, or base abstraction of a proton from **22** gave the quinone imide ketal **12**. This mechanism rationalizes why it is necessary to have the base like sodium bicarbonate suspended throughout the solution. Experimentally it was observed that low electrolysis current and a large anode surface favors formation of the quinone imide ketal vs. the 1,4-addition product.

The anodic oxidation also proceeded smoothly for p-alkyl substituted aromatic amides (entry 9). For example, anodic oxidation of **10f** in a divided cell in the presence of sodium bicarbonate gave quinone imide ketal type product **18** (70% yield). Its structure was supported by its strong absorption at 1600 cm^{-1} C=N bond as well as its ^1H NMR and ^{13}C NMR spectra. If the same substrate was anodically oxidized in a single electrolysis cell, a low yield of **18** was obtained.

Synthetic Application Studies

1,2-Addition Studies of Quinone Imide Ketals

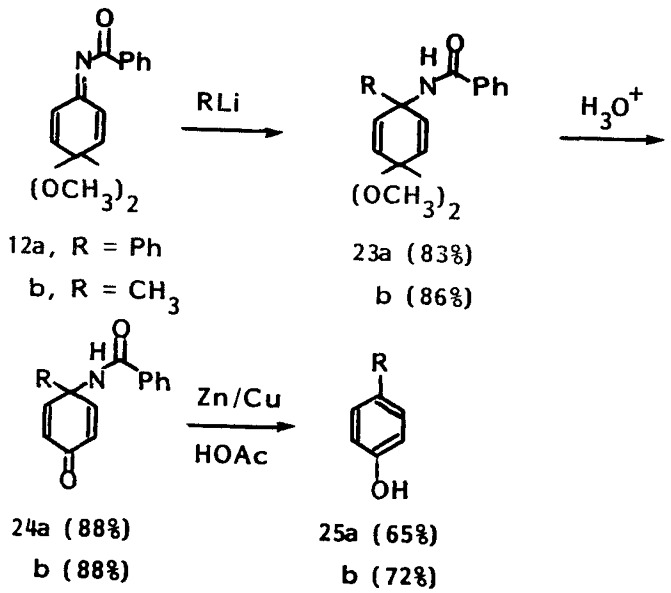
Quinone imide ketals are very synthetically useful intermediates in functionizing positions on the original aromatic amides (or amines). Besides the electrochemical route to quinone imide, a quinone bisketal **11** can be converted to quinone imide **12** (70%) by adding sodium hydride (one equivalent).



11

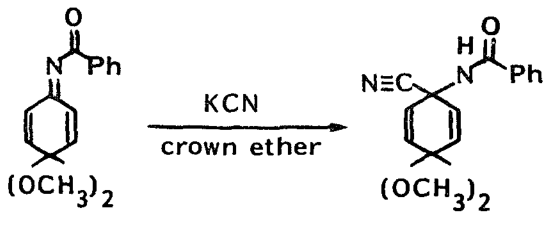
12 (70%)

Quinone imide ketal **12** reacted with phenyllithium or methyllithium at -70 °C to give good yields of **23a** (83%) or **23b** (86%) as light yellow



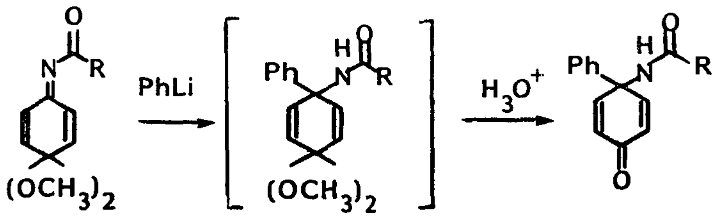
solids. The structures of **23 a,b** were supported by spectroscopic data. The IR absorption at 3390 (**23a**), 3330 (**23b**) cm^{-1} are assigned to the N-H stretch, and the ^{1}H NMR spectra showed aromatic hydrogens at δ 7.6-7.2 (**23a**) or a methyl peak at δ 1.65 (**23b**). These compounds are readily converted to the corresponding dienones and thus are difficult to store at room temperature. This is not a problem since the dienones are the desired final products. The crude **23a,b** were hydrolyzed in mild acidic conditions to produce **24a,b** in 88% yield. The structure of the compounds were supported by spectroscopic data: strong IR absorptions at 1690, 1640 cm^{-1} (**24a**) and 1660, 1615 cm^{-1} (**24b**) assigned for conjugated carbonyl linkage. The ^{1}H NMR spectra also showed dienone AB quartets at δ 7.16, 6.28 (**24a**) or 6.95, 6.30 (**24b**). Furthermore, **24a** and **24b** can be reduced to p-substituted phenols **25a,b** via zinc/copper couple in acetic acid. Both **25a,b** are known compounds.

Quinone imide ketal **12** can also be reacted with potassium cyanide in the presence of crown ether to give adduct **26** in 88% yield. The structure of **26** was supported by spectroscopic data. The IR spectrunmof **26** showed an absorption at 2235 cm^{-1}, and a signal at δ 116.4, indicating incorporation of the cyanide group. The NMR signal at δ 116.4 was assigned to the cyanide group.



12 **26 (88%)**

Other quinone imide ketals also reacted with organolithium compounds via 1,2-addition. For example, quinone imide ketals **15,17** reacted with phenyllithium at -70 °C produced unstable 1,2-adducts **27a,b** Without further purification, the crude adducts were treated with

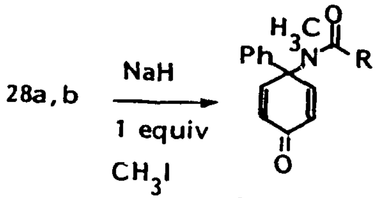


15, R = CH_3 **27a**, R = CH_3 **28a**, R = CH_3 (80%)

17, R = O-*t*-Bu **b**, R = O-*t*-Bu **b**, R = O-*t*-Bu (70%)

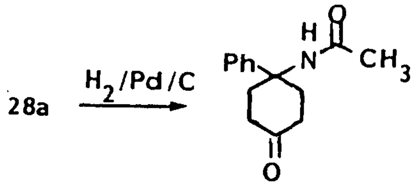
acid to give dienone **28a** (88%) and **28b** (78%). The structure of the compounds were supported by spectroscopic data. The strong IR absorption at 1660, 1630 cm^{-1} (**28a**) and 1670, 1630 cm^{-1} (**28b**) were assigned to the conjugated carbonyl linkage. The AB patterns at δ 6.94, 6.07 (**28a**) and at δ 7.0, 6.29 (**28b**) in the ^{1}H NMR spectra, and the signal at δ 185.3 (**28a**) in the ^{13}C NMR spectrum (conjugated carbonyl group) supported the structure assignment.

Furthermore, the dienones **28a,b** can be methylated by reaction with one equivalent of sodium hydride and methyliodide to produce **29a** (71%) and **29b** (70%). The structure assignment is supported by the appearance of a methyl group resonance peak at δ 2.98 (**29a**) and δ 2.93 (**29b**) in the ^{1}H NMR.



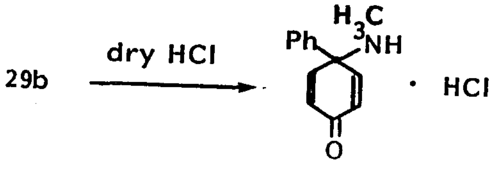
29a, R = CH_3 (71%)
b, R = O-*t*-Bu (70%)

Hydrogenation of **28a** with palladium on carbon as catalyst gave **30** (90% yield). The structure of **30** can be easily identified by IR absorption at 1720 cm^{-1} assigned as a simple ketone instead of a



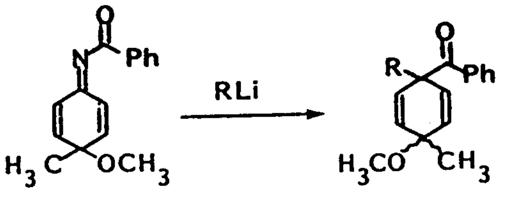
30 (90%)

dienone carbonyl group. Deblocking of **29b** by dry hydrochloric acid in absolute ether produced an ammonium salt **31** (40%).



31 (40%)

Finally, 1,2-addition of phenyllithium and methyllithium to **18** in -70 °C gave a moderate yield of **32a** (79% cis+trans isomers) and **32b**

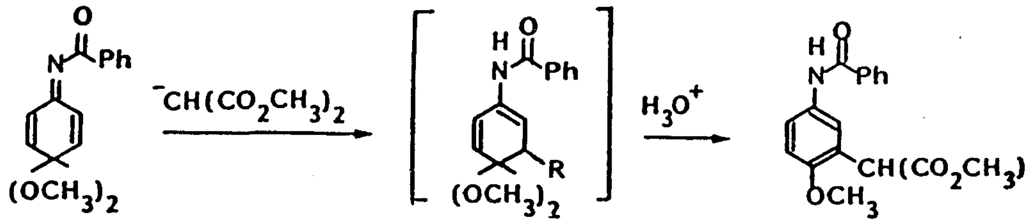


32a, R = Ph (79%)
b, R = CH_3 (89%)

(89% cis+trans isomers). As observed in the ^1H NMR spectrum, the phenyllithium adduct 32a was a 3:1 mixture of cis-trans isomers, and the methyllithium adduct **32b** gave a 1:1 mixture of cis-trans isomers by integration of methoxy peaks at δ 3.20, 3.07.

1,4-Addition Studies of Quinone Imide Ketals

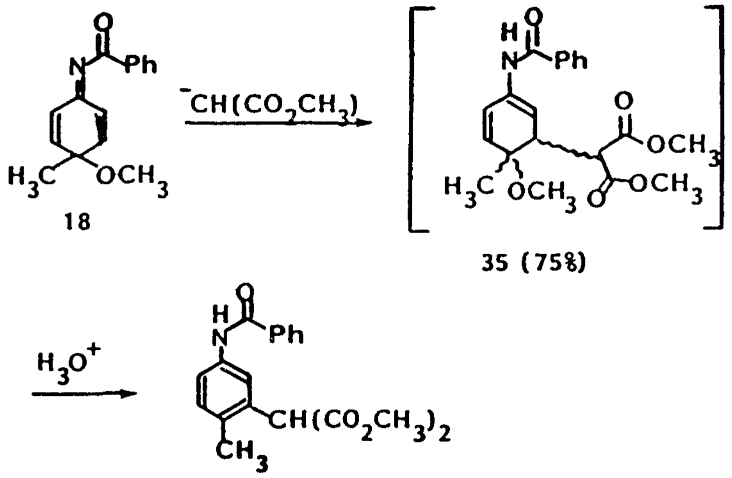
Quinone imide ketals underwent not only 1,2-addition but also 1,4-addition with certain neucleophiles. In general, hard nucleophiles such



12 33 34 (91%)

as organolithium reagents added in 1,2 fashion. Soft nucleophiles such as malonate anion added in 1,4 fashion.

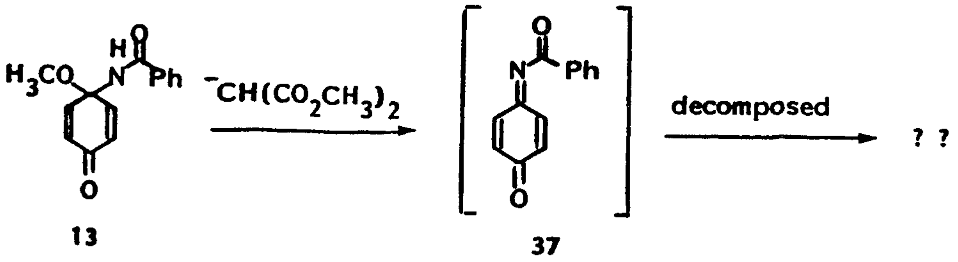
Thus, 1,4-addition of dimethyl malonate anion to quinone imide ketal **12** gave intermediate **33** which could be aromatized to **34** with a trace of acid. This comprises a method for functionalization of this position of the starting material. The structure of the meta-substituted aromatic amide was supported by spectroscopic data: strong IR absorption at 1760, 1740 cm^{-1} assigned to the ester groups and ^1H NMR singlet at δ 3.75 and 3.72 assigned as aromatic methoxyl protons and dimethyl ester protons.



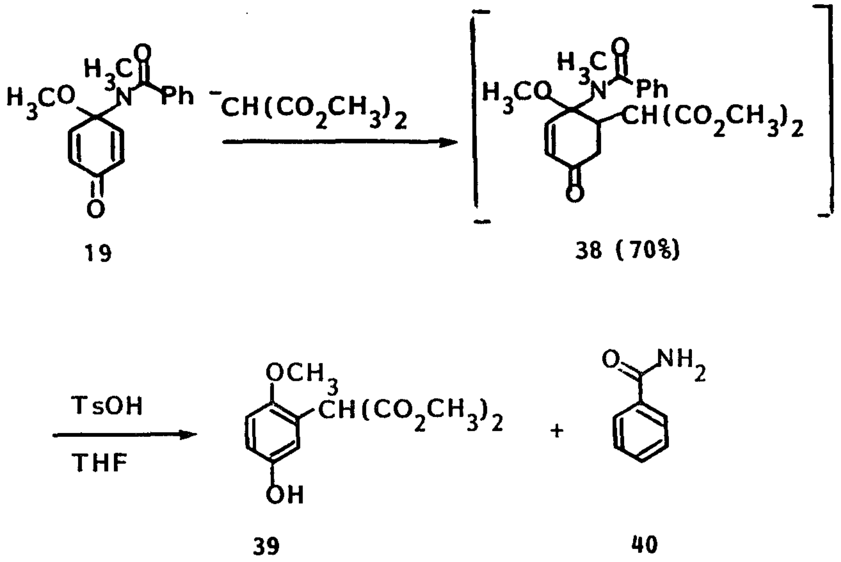
18 35 (75%) 36 (91%)

Imide **18** also reacted in a 1,4 fashion with dimethyl malonate anion to produce **35** (1:1 cis-trans isomers) in 75% yield. After acid treatment of intermediate **35**, a m-substituted aromatic amide **36** was formed in 91% yield. The structure of **36** was supported by spectroscopic data. Most informative were the strong IR absorption peaks at 1750, 1745 cm^{-1} and the three proton singlets at δ 2.28 and at δ 3.73 in the ^1H NMR spectrum.

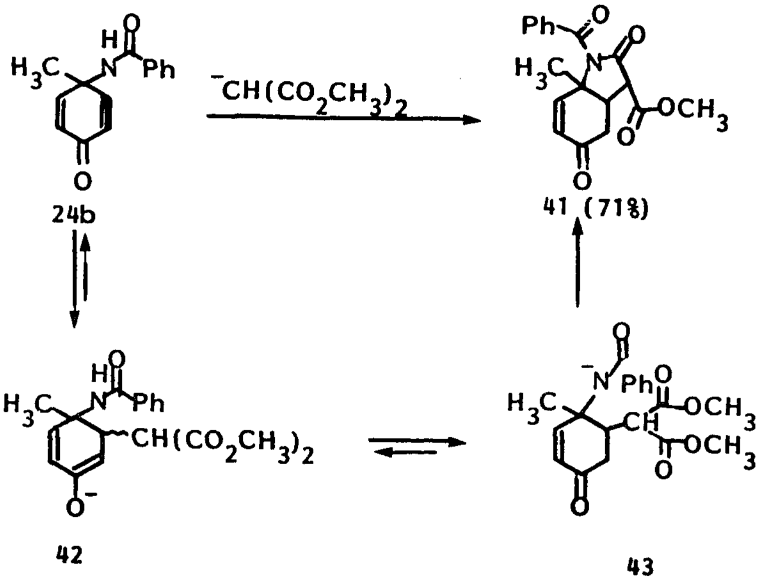
All attempts to functionalize the position ortho to the original amide group by using dienone derivatives such as **13,16,19** were unsuccessful. For example, dienone **13** reacted with one equivalent of dimethyl malonate anion to give a decomposed polymer-like black product. It is believed that the malonate anion eliminated a molecule of methanol to produce intermediate **37** which was subject to decomposition.



Dienone **19** also reacted with dimethyl malonate anion to give 1,4-adduct **38** (cis-trans isomers) in 70% yield. The structure of **38** was supported by its easter carbonyl absorption in the IR spectrum at 1690, 1640 cm^{-1} and the appearance of two vinyl protons at δ 7.20, 6.07 in the ^1H NMR spectrum. Aromatization of **38** with p-toluenesulfonic acid gave a mixture of compounds **39** and **40**.



An interesting reaction was observed in the reaction of dimethyl malonate anion with **24b** compound **41** was obtained in 71% yield. This interesting result can be rationalized by the 1,4-addition of dimethyl malonate anion to produce intermediate 42. Equlibration of 42 to form



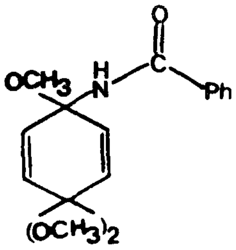
43 followed by ring formation gives the final product **41**. The structure of **41** was supported by the ^1H NMR spectrum which showed only one methoxy peak at δ 3.80 and in the ^{13}C NMR spectrum which showed only one methoxy peak at δ 52.8.

Conclusion

Anodic oxidation of aromatic amides leads to 1,4-addition products or quinone imide ketals. These now readily available intermediates offer interesting synthetic possibilities which have been only briefly explored in this dissertation.

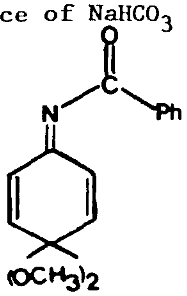
EXPERIMENTAL

Anodic Oxidation of 10a



A magnetically stirred soltuion of 10a (300 mg, 1.32 mmol) in 2% $LiClO_4/CH_3OH$ solution (120 mL) was electrolyzed (3 V, 0.1 A) at 0 °C for 60 min (71% current efficiency). The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL)/H_2O (40 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave a white solid. Recrystallization (PE/CH_2Cl_2) gave **11** (80%) in two crops (272 mg and 26 mg): mp 113-114 °C; IR (KBr, cm^{-1}) 3290, 1650, 1530, 1110, 1080, 1045, 960; ^1H NMR ($CDCl_3$) δ 7.8-7.65 (m, 2 H), 7.5-7.25 (m, 3 H), 6.55-6.8 (br s, 1 H), 6.24 (s, 4 H), 3.37 (s, 3 H), 3.34 (s, 3 H), 3.22 (s, 3H); mass spectrum, only M-CH_3 (15) peak present.

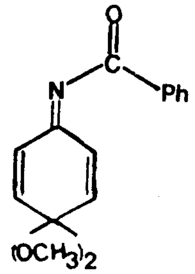
Anodic Oxidation of 10a in the Presence of $NaHCO_3$



A magnetically stirred mixture of 10a (1 g, 4.65 mmol) and finely ground $NaHCO_3$ (2 g) in 2% $LiClO_4/CH_3OH$ (120 mL) was electrolyzed at 0 °C 250 (3.8 V, 0.3

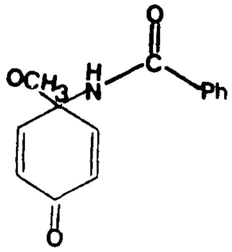
A) for 1.5 h (60% current efficiency). The resulting mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 50 mL)/H_2O (50 mL), and washed with brine (50 mL). Drying (Na_2SO_4) and concentration in vacuo to gave a red oil. Flash column chromatography (20:1 CH_2Cl_2/acetone) gave **12** (1.10 g, 92%): IR (film, cm^{-1}) 1680, 1665, 1605, 1250, 1110, 1075, 1060, 1040, 1005, 710; ^1H NMR ($CDCl_3$) δ 8.0-7.8 (m, 2 H), 7.6-7.26 (m, 3 H), 6.53 (AB q, $\underline{J}_{AB}$ = 11 Hz, 2 H), 6.44 (AB q, $\underline{J}_{AB}$ = 11 Hz, 2 H), 3.32 (s, 6 H); ^{13}C NMR ($CDCl_3$) δ 179.0,. 154.6, 139.0 (2 C), 132.8, 132.2, 128.6 (2 C), 128.0 (2 C), 125.6 (2 C), 92.1, 49.1 (2 C); mass spectrum had no molecular ion, only M-105 ($\overset{O}{C}$-Ph) was observed. The quinone imide ketal is not stable at room temperature and decomposed slowly to a polymeric material.

Preparation of 12 from 11



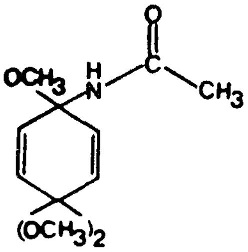
To a magnetically stirred solution of **11** (187 mg, 0.65 mmol) in THF (20 mL) at room temperature under nitrogen was added NaH (31.2 mg, 60% oil dispersion, 1.2 equv). After stirring for 2 h, the reaction was quenched by the addition of $NaHCO_3$ (2 mL), and the mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 30 mL)/H_2O (30 mL), and washed with brine (30 mL). Drying (Na_2SO_4) and concentration in vacuo gave a light brown oil. Flash column chromatography (CH_2Cl_2) gave **12** (140 mg, 86%) as a light yellow oil (decomposed slowly to a polymeric material.

Anodic Oxidation of 10b



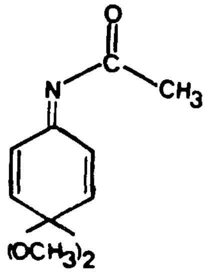
A magnetically stirred solution of **10b** (1 g, 4.69 mmol) in 2% $LiClO_4/CH_3OH$ (120 mL) was electrolyzed at 0 °C (3.4 V, 0.2 A) for about 2 h (63% current efficiency). The resulting solution was concentrated in vacuo, extracted with EtOAc (3 x 50 mL)/H_2O (80 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo yielded a light brown solid. Recrystallization (CH_2Cl_2/EtOAc) gave **13** as a light brown solid (0.91 g, 80%): mp 119-121.5 °C; IR (KBr, cm^{-1}) 3350, 1690, 1680 (sh), 1665, 1640, 1520, 1055, 710; ^1H NMR ($CDCl_3$) δ 8.0-7.3 (m, 5 H), 6.83 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 6.60 (br s, 1 H), 6.42 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 3.28 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 184.9, 166.2, 144.5 (2 C), 130.7, 128.5 (2 C), 127.0 (2 C), 79.9, 50.9; mass spectrum, exact mass calcd for $C_{14}H_{13}NO_3$ $\underline{m/e}$ 243.0895, obsd $\underline{m/e}$ 243.0905.

Anodic Oxidation of 10c



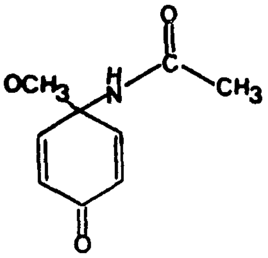
A magnetically stirred solution of **10c** (1.5 g, 9.1 mmol) in 2% $LiClO_4/CH_3OH$ (150 mL) at 0 °C was electrolyzed (3.9 V, 0.15 A) for 4.9 h (67% current efficiency). The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL)/H_2O (40 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave **14** (1.84 g, 89%) as a very light yellow oil. The crude NMR spectrum showed that the material was pure enough for the next reaction: IR (neat, cm^{-1}) 3550-3300 (br), 1665 (br), 1535 (br), 1460, 1405, 1370, 1270, 1100, 1050, 1035 (sh), 955; ^1H NMR ($CDCl_3$) δ 6.14 (s, 4 H), 6.1-5.8 (br s, 1 H), 3.29 (s, 3 H), 3.25 (s, 3 H), 3.12 (s, 3 H), 1.9 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 169.6, 130.4 (2 C), 129.3 (2 C), 92.1, 78.9, 49.9, 49.2 (2C), 23.1; mass spectrum, exact mass calcd for $C_{11}H_{17}NO_4$ m/e 227.1012, obsd m/e 227.1076.

Anodic Oxidation of 10c in the Presence of $NaHCO_3$



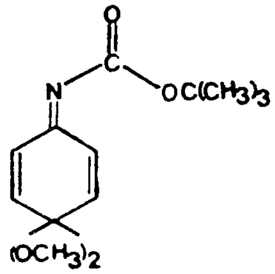
A magnetically stirred mixture of **10c** (0.34 g, 2.06 mmol) and suspended $NaHCO_3$ powder (1 g) in 2% $LiClO_4/CH_3OH$ (1 mL) was electrolyzed at 0 °C (3.5 V, 0.2 A) for about 1 h. The resulting mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 30 mL)/H_2O (30 mL), and washed with brine (30 mL). Drying (Na_2SO_4) and concentration in vacuo gave crude **15**. Flash column chromatography (20:1 CH_2Cl_2/acetone) gave **15** (0.358 mg, 89%) with a little decomposed impurities: IR (film, cm^{-1}) 1695, 1670, 1605, 1220, 1110, 1080, 1060, 1035, 955; ^1H NMR ($CDCl_3$) δ 6.54 (AB q, J_{AB} = 11 Hz, 2 H), 6.35 (AB q, J_{AB} = 11 Hz, 2 H), 3.33 (s, 6 H), 2.23 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 185.3, 151.1, 138.8 (2 C), 125.7 (2 C), 92.3. 49.4 (2 C), 24.8; mass spectrum, exact mass calcd for $C_{10}H_{13}NO_3$ m/e 195.0895, obsd m/e 195.0907.

Anodic Oxidation of 10d



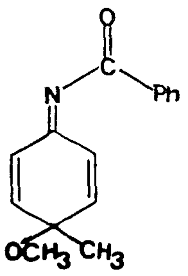
A magnetically stirred solution of **10d** (1 g, 6.62 mmol) in 2% $LiClO_4/CH_3OH$ (100 mL) was electrolyzed at 0 °C (3.3 V, 0.2 A) for 2.5 h (current efficiency 70%). The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL)/H_2O (40 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave a light brown solid. Recrystallization (CH_2Cl_2) gave **16** (1.01 g, 85%): mp 143-145 °C; IR (KBr, cm^{-1}) 3200, 1675, 1650, 1630, 1545, 1290, 1070, 910; ^1H NMR ($CDCl_3$) δ 6.79 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 6.34 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 6.3-5.95 (br s, 1 H), 3.21 (s, 3 H), 1.96 (s, 3 H); mass spectrum, exact mass calcd for $C_9H_{11}NO_3$ m/e 181.0739, obsd m/e 181.0725.

Anodic Oxidation of 10e



A magnetically stirred mixture of **10e** (1.1 g, 4.93 mmol) and $NaHCO_3$ powder (2 g) in 2% $LiClO_4/CH_3OH$ was electrolyzed at 0 °C (3.8 V, 0.2 A) for 2 h (66% current efficiency). The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 50 mL)/H_2O (50 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave **17** as a very light yellow oil which was used in the next step without further purification: IR (neat, cm^{-1}) 1720, 1605, 1370, 1270, 1250, 1160, 1110, 960; ^{1}H NMR ($CDCl_3$) δ 6.47 (AB q, J_{AB} = 11 Hz, 2 H), 6.37 (AB q, J_{AB} = 11 Hz, 2 H), 3.28 (s, 3 H), 1.50 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 160.8, 155.9, 138.9 (4 C), 92.5, 82.2, 49.6 (2 C), 27.5 (3 C); mass spectrum, exact mass calcd for $C_{13}H_{19}NO_4$ m/e 253.1108, obsd m/e 253.1256.

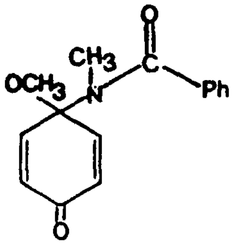
Anodic Oxidation of 10f



A magnetically stirred mixture of **10f** (0.5 g, 2.37 mmol) and $NaHCO_3$ (2 g) in 2% $LiClO_4/CH_3OH$ (80 mL) in a divided electrolysis cell was electrolyzed at 0 °C (11 V, 0.12 A) for 1.8 h (59% current efficiency). The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 30 mL)/H_2O (30 mL), and washed with brine (30 mL). Drying (Na_2SO_4) and concentration in vacuo gave a brown oil. Flash column chromatography (CH_2Cl_2) gave **18** (440 mg, 75%) with a trace of inseparable impurities which could not be seen by NMR spectroscopy: IR (neat, cm^{-1}) 1650 (br), 1600, 1580, 1245, 1090, 1060, 710; ^{1}H NMR ($CDCl_3$) δ 8.07.8 (m, 2 H), 7.6-7.3 (m, 3 H), 6.43 (s, 4 H), 3.13 (s, 3 H), 1.37 (s, 3 H); ^{13}C NMR ($CDCl_3$, MHz) δ 180.1, 165.7, 147.1 (2 C), 133.2, 129.3 (2 C), 128.5 (2 C), 127.0, 126.5 (2 C), 72.1, 52.8, 26.6; mass spectrum, exact mass calcd for $C_{15}H_{15}NO_2$ m/e 251.1103, obsd m/e 241.1060.

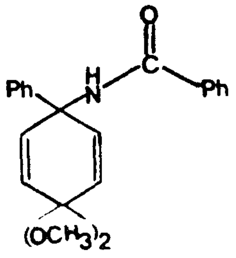
Anodic Oxidation of 10g

A magnetically stirred solution of **10g** (0.71 g, 3.13 mmol) in 2% $LiClO_4/CH_3OH$ (10 mL) was electrolyzed at 0 °C (3.4 V, 0.1 A) for 2.5 h



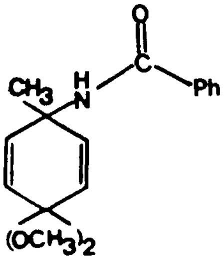
(70% current efficiency). The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL)/H_2O (40 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave a light brown solid. Recrystallization (CH_2Cl_2/PE) gave **19** (0.67 g, 80%) as a light brown solid: mp 178-180 °C; IR (KBr, cm^{-1}) 1690, 1670, 1645, 1385, 1370, 1210, 1080, 1040, 1020, 960; ^1H NMR ($CDCl_3$) δ 7.39 (s, 5 H), 6.74 (AB q, J_{AB} = 10 Hz, 2 H), 6.32 (AB q, J_{AB} = 10 Hz, 2 H),3.25 (s, 3 H), 3.01 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 184.6, 171.5, 143.1 (2 C), 135.7, 130.0, 128.8 (2 C), 127.8 (2 C), 126.9 (2 C), 82.2, 50.3, 32.7; mass spectrum, exact mass calcd for $C_{15}H_{15}NO_3$ m/e 257.1052, obsd m/e 257.1072.

Preparation of 23a from 12



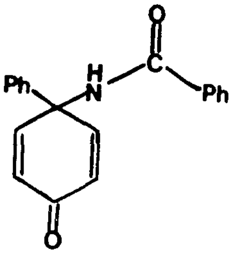
To a -70 °C solution of **12** (750 mg, 2.9 mmol) in THF (30 mL) under nitrogen was added 1.7 M PhLi (1.86 mL, 1.1 equiv). The resulting solution was stirred at for 2 h -70 °C and then for 20 min at room temperature. The reaction was quenched by the addition of H_2O (2 mL), and the mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL)/H_2O (40 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave a light brown solid (82 mg, 92%). A crude NMR spectrum showed product to be pure enough for the next reaction. The light brown solid was recrystallized (CH_2Cl_2) to give **23a** (805 mg, 83%) in two crops (710 mg and 95 mg): mp 151-154 °C; IR (KBr, cm^{-1}) 3390, 1640, 1535, 1110, 1075, 930, 795; ^1H NMR ($CDCl_3$) δ 7.9-7.6 (m, 2 H), 7.6-7.2 (m, 8 H), 6.52 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 6.47 (br s, buried inside AB q), 6.08 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 3.36 (s, 3 H), 3.31 (s, 3 H); mass spectrum, exact mass calcd for $C_{21}H_{21}NO_3$ could not be observed; only M-CH_3 was observed.

Preparation of 23b from 12



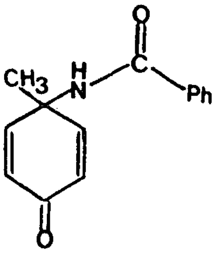
To a -70 °C solution of **12** (205 mg, 0.80 mmol) in THF (40 mL) under nitrogen was added 1.4 M CH_3Li (0.63 mL, 1.1 equiv). After stirring at -70 °C for 1 h and at room temperature for 5 min, the reaction mixture was worked up by adding saturated $NaHCO_3$ (5 mL), concentrating in vacuo, extracting with CH_2Cl_2 (3 x 30 mL)/H_2O (30 mL), and washing with brine (30 mL). Drying (Na_2SO_4) and concentration in vacuo gave a light brown solid (185.9 mg, 86%). Recrystallization (CH_2Cl_2/PE) gave **23b** (168 mg, 77%) as white crystals: mp 89-90.5 °C; IR (KBr, cm^{-1}) 3300, 1650, 1540, 1410, 1315, 1105, 1040, 950; ^1H NMR ($CDCl_3$) δ 7.8-7.5 (m, 2 H), 7.5-7.24 (m, 3 H), 6.37 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 5.94 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 3.35 (s, 3 H), 3.31 (s, 3 H), 1.65 (s, 3 H); mass spectrum, exact mass calcd for $C_{16}H_{19}NO_3$ $\underline{m/e}$ 173.1341, obsd $\underline{m/e}$ 273.1352.

Preparation of 24a from 23a



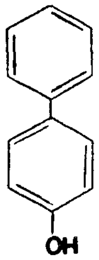
A magnetically stirred solution of **23a** (180 mg, 0.54 mmol), saturated NH_4Cl (10 mL), and THF (20 mL) was stirred at room temperature overnight. The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 30 mL)/H_2O (30 mL), and washed with brine (30 mL). Drying (Na_2SO_4) and concentration in vacuo gave a light brown oil. Flash column chromatography (CH_2Cl_2) gave **24a** (145 mg, 88%) as a white solid. Recrystallization (CH_2Cl_2) gave **24a** (96 mg, 78%) om two crops (96 mg and 32 mg): mp 180.5-182 °C; IR (KBr, cm^{-1}) 3300, 1670, 1640, 1580, 1520, 1490, 1305, 1225, 855, 700; ^1H NMR ($CDCl_3$) δ 7.85-7.65 (m, 2 H), 7.5-6.95 (m, 8 H), 7.16 (d, $\underline{J}$ = 10 Hz, 2 H), 6.7-6.55 (br s, 1 H), 6.28 (d, $\underline{J}$ = 10 Hz, 2 H); mass spectrum, exact mass calcd for $C_{19}H_{15}NO_2$ $\underline{m/e}$ 289.1103, obsd $\underline{m/e}$ 289.1074.

Preparation of 24b from 23b



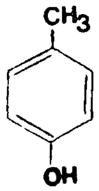
Chromatography of **23b** (172 mg, 0.63 mmol) using 15:1 CH_2Cl_2/acetone gave hydrolyzed product **24b** (125.8 mg, 88%) as a white crystal: mp 178.5-180 °C; IR (KBr, cm^{-1}) 3320, 1660, 1615, 1600 (sh), 1530, 1490, 1390, 1305, 1290, 1190, 885, 710; ^1H NMR ($CDCl_3$) δ 7.8-7.5 (m, 2 H), 7.5-7.24 (m, 3 H), 6.95 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 6.4 (br s, 1 H), 6.30 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 1.63 (s, 3 H); mass spectrum, exact mass calcd for $C_{14}H_{13}NO_2$ m/e 227.0946, obsd m/e 227.0960.

Preparation of 25a from 24a



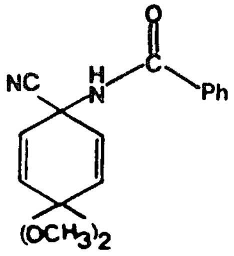
To a magnetically stirred solution of **24a** (0.61 g, 2.11 mmol) and Zn/Cu powder (2.7 g, excess) in THF (20 mL) was added HOAc (2 mL) at room temperature. After stirring for 2 h, the reaction mixture was filtered through Celite, neutralized with saturated $NHCO_3$ (50 mL), and concentrated in vacuo. The resulting solution was extracted with CH_2Cl_2 (3 x 40 mL) and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave a colorless oil/solid. Flash column chromatography (CH_2Cl_2) gave pure **25a** (233 mg, 65%) as a known compound, mp 164-167 °C (lit. mp 165-167 °C, Aldrich catalog).

Preparation of 25b from 24b



To a magnetically stirred solution of **24b** (0.61 g, 2.69 mmol), THF (15 mL), and Zn/Cu (2 g, excess) was added HOAc (2 mL) at room temperature. After stirring for 2 h, the resulting mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL)/H_2O (2 x 40 mL), neutralized with saturated $NaHCO_3$ (40 ml), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave a colorless oil. Flash column chromatography (CH_2Cl_2) gave **25b** (0.209 g, 72%) as a colorless oil (known compound, Aldrich catalog).

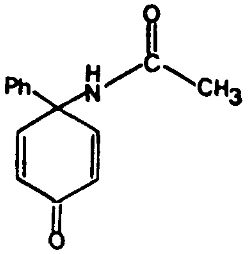
Preparation of 26 from 12



A magnetically stirred solution of **12** (0.72 g, 2.80 mmol), THF (20 mL), KCN (1.7 g, excess), and crown ether (1 g) was allowed to react for 16 h under nitrogen. The reaction mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL)/H_2O (3 x 20 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave a colorless solid. Recrystallization (CH_2Cl_2/PE) gave **26** (0.701 g, 88%) as colorless crystals: mp 138-141 °C; IR (KBr, cm^{-1}) 1655, 1510, 1480, 1110, 1070, 1040, 960, 710; ^1H NMR ($CDCl_3$) δ 7.8-7.5 (m, 2 H), 7.5-7.2 (m, 3 H), 6.9 (br s, 1 H), 6.49 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 6.19 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 3.29 (s, 3 H), 3.27 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.1, 132.4 (2 C), 130.4 (2 C), 128.6 (2 C), 127.3 (2 C), 126.6 (2 C), 116.4, 92.1, 50.0, 49.7, 46.9; mass spectrum, exact mass calcd for $C_{16}H_{16}N_2O_3$ M^+-15(CH_3) was found.

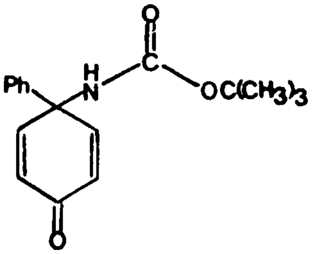
Preparation of 28a from 15

To a -70 °C solution of 15 (0.621 g, 3.18 mmol) in THF (25 mL) under nitrogen was added 1.7 M PhLi (1.97 mL). The reaction mixture was stirred at -70 °C for 0.5 h and then at room temperature for 10



min. The reaction was quenched with saturated NH_4Cl (40 mL), and the mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL)/H_2O (40 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave crude 27a as a light brown solid which was then dissolved in THF (50 mL), and 5% HCl (5 mL) was added. After stirring for 2 min, the reaction was quenched by addition of $NaHCO_3$ (20 mL). The mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 50 mL)/H_2O (40 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave a brown solid. Recrystallization (CH_2Cl_2) gave 28a (0.576 g, 80%) as a light yellow solid: mp 155-157 °C; IR (KBr, cm^{-1}) 3295, 1670, 1660, 1630, 1535, 1370, 1300, 1220, 1230, 855; ^1H NMR ($CDCl_3$) δ 7.84 (s, 1 H), 7.24 (s, 5 H), 6.94 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 6.07 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 1.79 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 185.3, 170.2, 149.4 (2 C), 137.8, 128.7 (2 C), 127.9, 126.7 (2 C), 125.1 (2 C), 57.9, 22.8; mass spectrum, exact mass calcd for $C_{14}H_{13}NO_2$ $\underline{m/e}$ 227.0946, obsd $\underline{m/e}$ 227.0950.

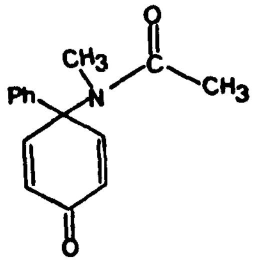
Preparation of 28b from 17



To a magnetically stirred -70 °C solution of 17 (0.7 g, 2.35 mmol) in THF (30 mL) under nitrogen was added 1.7 M PhLi (1.52 mL, 1.1 equiv). After stirring for 1 h at -70 °C and for 20 min at room temperature, the reaction was quenched by the addition of saturated NH_4Cl (3 mL), and the mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL)/H_2O (40 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave **27b** (0.332 g, 85%) as a light yellow oil which was used in the next step without further purification: IR (cm^{-1}) 1710 (s, br), 1490, 1365, 1250, 1160, 1100, 1070, 1035, 950; ^1H NMR ($CDCl_3$) δ 7.6-7.2 (m, 5 H), 6.32 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 5.97 (AB q, $\underline{J}_{AB}$ = 10 Hz,k 2 H), 5.09 (br s, 1 H), 3.31 (s, 3 H), 3.27 (s, 3 H), 1.32 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 153.9, 142.2, 134.5 (2 C), 128.0 (2 C), 126.6, 124.9 (4 C), 92.7, 79.2, 56.1, 49.2, 49.0, 26.7 (3 C); mass spectrum not available for unstable crude product.

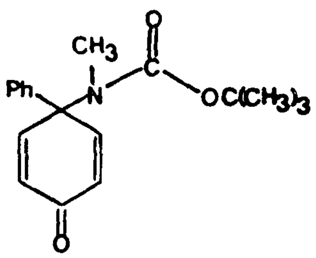
Crude **27b** (0.77 g, 2 mmol) was dissolved in THF (50 mL), 5% HCl (0.5 mL) was added, and the mixture was stirred for 1 min. The resulting solution was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL)/H_2O (40 mL), washed with saturated $NaHCO_3$ (30 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave crude **28b**. Column chromatography (20:1 CH_2Cl_2/acetone) gave pure **28b** (0.483 g, 89%) as a light yellow oil: IR (neat, cm^{-1}) 1710 (br s), 1670, 1630, 1490, 1395, 1370, 1255, 1160, 1230, 1105; ^1H NMR ($CDCl_3$) δ 7.5-7.2 (m, 5 H), 7.0 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 6.29 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 5.3 (br s, 1 H), 1.39 (s, 9 H); mass spectrum not available; only M-57 (t-Bu) group was found.

Preparation of 29a from 28a



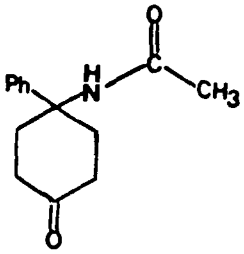
To a solution of **28a** (0.55 g, 2.42 mmol) and CH_3I (1.0 mL, excess) in THF (30 mL) was added NaH (0.105 g, 1.1 equiv of a 60% oil dispersion). The reaction mixture was stirred for 4 h, the reaction was quenched by addition of a saturated NH_4Cl solution (1 mL), and the mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL)/H_2O (40 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave a brown semisolid. Flash column chromatography (20:1 CH_2Cl_2/acetone) gave **29a** (0.414 g, 71%) as light yellow crystals: mp 141-143 °C; IR (KBr, cm^{-1}) 1665 (br), 1640, 1625, 1600, 1490, 1450, 1380 (br), 1345, 1240, 1140, 1060, 1030, 860, 750, 730, 700; ^1H NMR ($CDCl_3$) δ 7.30 (s, 5 H), 7.19 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 6.34 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 2.98 (s, 3 H), 2.14 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 184.6, 171.2, 147.8 (2 C), 138.8, 128.5 (2 C), 127.3, 126.2 (2 C), 124.6 (2 C), 63.5, 34.1, 23.2; mass spectrum, exact mass calcd for $C_{15}H_{15}NO_2$ $\underline{m/e}$ 241.1103, obsd $\underline{m/e}$ 241.1108.

Preparation of 29b from 28b



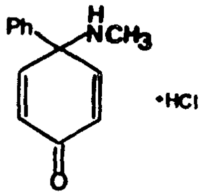
To a solution of **28b** (0.701 g, 2.46 mmol) and CH_3I (2 mL) in THF (20 mL) was added NaH (0.108 g, 1.1 equiv of a 60% oil suspension), and the mixture was stirred for 5 h. The reaction was quenched by addition of H_2O (2 mL), and the mixture was concentrated in vacuo, extracted with CH_2Cl_2 (4 x 40 mL)/H_2O (40 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave crude **29b** as a light brown oil. Flash column chromatography gave a light yellow solid which was recrystallized (CH_2Cl_2/PE) to give **29b** (0.515 g, 70%) as a light yellow solid: mp 146-148.5 °C; IR (KBr, cm^{-1} 1695, 1665, 1625, 1350, 1160; ^1H NMR ($CDCl_3$) δ 7.5-7.2 (m, 5 H), 7.20 (d, *J* = 10 Hz, 2 H), 6.26 (d, *J* = 10 Hz, 2 H), 2.93 (s, 3 H), 1.17 (s, 9 H); ^{13}C NMR ($CDCl_3$) δ 185.1, 155.2, 148.5 (2 C), 140.9, 128.8 (2 C), 127.7, 127.4 (2 C), 124.9 (2 C), 80.9, 63.2, 33.3, 27.8 (3 C); mass spectrum, exact mass calcd for $C_{18}H_{21}NO_3$ *m/e* 299.1601, obsd *m/e* 299.1616.

Preparation of 30 from 29a



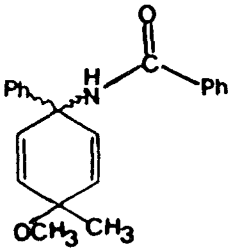
A solution of **29a** (0.72 g, 3.17 mmol) in EtOAc (50 mL) was hydrogenated at 60 lb of pressure overnight. The resulting solution was filtered through Celite and concentrated in vacuo to give a white solid. Recrystallization (CH_2Cl_2/PE) gave **30** (0.66 g, 90%): mp 135.5-138.0 °C; IR (KBr, cm^{-1}) 3310, 1720, 1650, 1545, 755, 695; ^1H NMR ($CDCl_3$) δ 7.5-7.2 (m, 5 H), 5.95 (br s, 1 H), 3.0-2.1 (m, 8 H), 2.03 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 210.4, 170.7, 144.7, 128.0 (2 C), 126.5, 124.5 (2 C), 56.7, 36.9 (2 C), 35.2 (2 C), 23.2; mass spectrum, exact mass calcd for C

Preparation of 31 from 29b



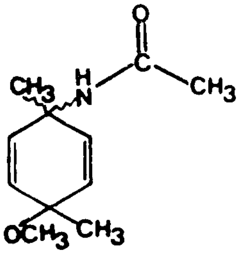
Compound **29b** (0.32 g) was dissolved in dry Et_2O (150 mL) which had been previously saturated with dry HCl. (Dry HCl was generated by adding H_2SO_4 into NaCl which was bubbled into dry Et_2O.) After stirring overnight, saturated light yellow hydrochloride 31 had precipitated out. Filtration and washing with dry Et_2O (20 mL) gave 31 (0.101 g, 40%) as a light yellow solid: IR could not be obtained; ^1H NMR (D_2O) δ 7.13 (s, 5 H), 6.89 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 6.28 (AB q, $\underline{J}_{AB}$ = 10 Hz, 2 H), 2.34 (s, 3 H), NH could not be detected in D_2O; ^{13}C NMR (D_2O) δ 188.2, 146.1 (2 C), 134.9, 134.3 (2 C), 132.5, 132.1 (2 C), 128.0 (2 C), 63.9, 30.6; mass spectrum, mass could not be detected by EI machine.

Preparation of 32a from 18



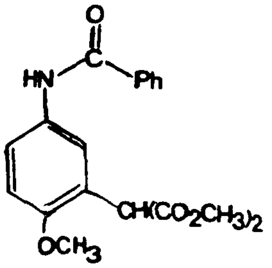
To a -70 °C solution of **18** (600 mg, 2.49 mmol) in THF (40 mL) under nitrogen was added 1.7 M PhLi (1.75 mL, 1.1 equiv). The reaction mixture was stirred at -70 °C for 2 h and at room temperature for 10 min. The reaction was quenched by the addition of $NaHCO_3$ (5 mL), and the reaction mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 30 mL)/H_2O (30 mL), and washed with brine (30 mL). Drying (Na_2SO_4) and concentration in vacuo gave a light brown solid which was recrystallized (CH_2Cl_2) to yield **32a** (379 mg). Flash column chromatography gave **32a** (0.290 g, combined yield 79%): IR (KBr, cm^{-1} 3260, 1640, 1530, 1490, 1315, 1090, 690; ^1H NMR ($CDCl_3$) δ for methoxy group at 3.25, 3.11 at 3:1 ratio methyl group at 1.42, 1.30 at 1:3 ratio; mass spectrum, exact mass calcd for $C_{21}H_{21}NO_2$ m/e 319.1570, obsd m/e 319.1722.

Preparation of 32b from 18



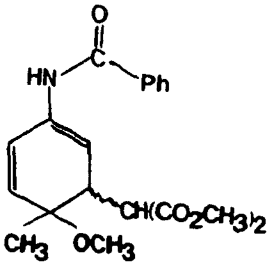
To a -70 °C solution of **18** (260 mg, 1.08 mmol) in THF (40 mL) under nitrogen was added 1.4 M CH_3Li (0.92 mL, 1.2 equiv). After stirring the solution for 1 h at -70 °C and for 5 min at room temperature, the reaction was quenched by the addition of a saturated $NaHCO_3$ solution (5 mL). The mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 30 mL) /H_2O (30 mL), and washed with brine (30 mL). Drying (Na_2SO_4) and concentration in vacuo yielded a light yellow semisolid compound. Flash column chromatography (15:1 CH_2Cl_2/acetone) gave a 1:1 mixture of stereoisomer **32b** (546 g, 89%) as a semisolid: IR (KBr, cm^{-1}) 3300, 1655 (sh), 1640, 1603, 1580, 1540, 1490, 1310, 1090, 1080; ^1H NMR ($CDCl_3$) δ 7.7-7.05 (m, 5 H), 6.75-6.45 (m, 3 H), 6.25-5.95 (m, 5 H), 3.20, 3.07 (s, 3 H), 1.55, 1.50, 1.36, 1.256 (s, 6 H); mass spectrum, exact mass calcd for $C_{16}H_{19}NO_2$, only M-CH_3(15) found.

Preparation of 34 from 12



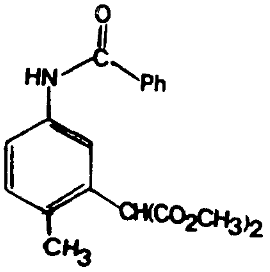
To a solution of dimethylmalonate (0.132 mL, 1.05 equiv) in THF (15 mL) under nitrogen was added NaH (46.2 mg, 1.05 equiv of mineral oil dispersion), and the mixture was stirred for 15 min. To the resulting solution was added **12** (0.27 g, 1.05 mmol) in THF (5 ML), and the mixture was stirred overnight. The resulting mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 30 mL)/H_2O (30 mL), and washed with brine (30 mL). Drying (Na_2SO_4) and concentration in vacuo gave a light yellow oil. Flash column chromatography gave **34** (344 g, 91%) as a colorless oil: IR (solution cell, cm^{-1}) 3420, 2950, 1760, 1740, 1675, 1530, 1505, 1440, 1320, 1295, 1240, 1200, 1185, 1160, 1030; ^1H NMR ($CDCl_3$) δ 8.15-7.9 (br s, 1 H), 7.9-7.7 (m, 3 H), 7.55-7.30 (m, 4 H), 6.83 (d, *J* = 9 Hz, 1 H), 5.13 (s, 1 H), 3.75 (s, 3 H), 3.72 (s, 6 H); mass spectrum, exact mass calcd for $C_{19}H_{19}NO_6$ *m/e* 357.1213, obsd *m/e* 357.1259.

Preparation of 35 from 18



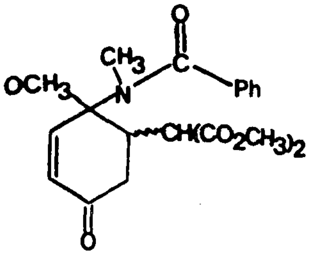
To a solution of dimethyl malonate (0.56 mL, 2.2 equiv) in THF (80 mL) under nitrogen was added 60% NaH (196 mg, 2.2 equiv of 60% mineral oil dispersion). After the solution had stopped bubbling, **18** (540 mg, 2.24 mmol) in THF (25 mL) was transferred into the anion solution, and the mixture was stirred overnight. The reaction was quenched by the addition of saturated $NaHCO_3$ (5 mL), and the mixture was extracted with CH_2Cl_2 (3 x 50 mL)/H_2O (50 mL), and washed with brine (50 mL). Drying (Na_2SO_4) and concentration in vacuo gave crude **35** (785 mg, 94%). Flash column chromatography (25:1 CH_2Cl_2/acetone) gave a 1:1 mixture as trans isomer (0.689 g, 82%) which was used in the next step without further isolation.

Preparation of 36 from 35



To a solution of **35** (84.2 mg, 0.22 mmol) in THF (20 mL) was added 10% HCl (20 drops). The mixture was stirred at room temperature for 40 min, and then the reaction was quenched by the addition of $NaHCO_3$ (5 mL). The mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 30 mL)/H_2O (30 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave crude **36**. Flash column chromatography (CH_2Cl_2) gave pure **36** (68.5 mg, 89%): IR (solution cell, cm^{-1}) 1750 (sh), 1740, 1680, 1520, 1510, 1315, 1280, 1230, 1220, 1195, 1150; ^1H NMR ($CDCl_3$) δ 8.05 (br s, 1 H), 7.95-7.7 (m, 3 H), 7.6-7.0 (m, 5 H), 4.88 (s, 1 H), 3.73 (s, 6 H), 2.26 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 168.4 (2 C), 165.7, 136.5, 134.6, 131.9, 131.3, 131.1, 130.6, 128.0 (2 C), 126.7 (2 C), 120.5, 120.2, 53.8, 52.8 (2 C), 18.5; mass spectrum, exact mass calcd for $C_{19}H_{19}NO_5$ m/e 341.1263, obsd m/e 341.1247.

Preparation of 38 from 19

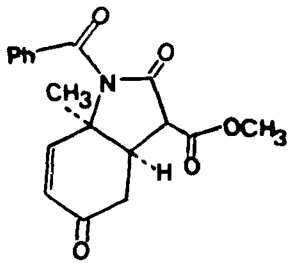


To a solution of dimethyl malonate (0.25 mL, 1.1 equiv) in THF (30 mL) under nitrogen was slowly added NaH (88 mg, 1.1 equiv of a 60% mineral oil dispersion). After the solution had stopped bubbling, **19** (0.51 g, 2 mmol) was added, and the mixture was stirred overnight. The reaction was quenched by the addition of H_2O (1 mL), and the mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL)/H_2O (40 mL), and washed with brine (40 mL). Drying (Na_sSO_4) and concentration in vacuo gave crude **38** as a brown oil. Flash column chromatography (20:1 CH_2Cl_2/acetone) gave **38** (0.54 g, 70%) as a light yellow oil: IR (film, cm^{-1}) 1760, 1740, 1690, 1640, 1375, 1050; ^1H NMR ($CDCl_3$) δ 7.40 (s, 5 H), 7.27 (dd, J = 2, 10 Hz, 1 H), 6.07 (d, J = 10 Hz, 1 H), 4.47 (d,. J = 9 Hz, 1 H), 3.67 (s, 6 H), 3.6-2.8 (m, 3 H), 3.38 (s, 3 H), 2.82 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 196.4 (2 C), 172.9, 168.0, 148.5, 136.1, 130.0, 128.2 (2 C), 126.6, 126.2 (2 C), 87.9, 52.3, 52.0 (2 C), 50.4, 41.3, 36.9, 33.6; mass spectrum, exact mass calcd for $C_{20}H_{23}NO_{17}$ m/e 389.1474, obsd m/e 389.1468.

Preparation of 39 and 40 from 38

A solution of **38** (0.38 g, 1 mmol) and TsOH (20 mg) in THF (50 mL) under nitrogen was heated to reflux overnight. The reaction mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL)/H_2O (40 mL), washed with a saturated $NaHCO_3$ solution (40 mL), and washed with brine (40 mL). Drying (Na_2SO_4) and concentration in vacuo gave a light brown oil. Flash column chromatography (20:1 CH_2Cl_2/acetone) gave **39** (0.228 g, 89%) and **40** (110 mg, 91%) as known compounds (Aldrich catalog).

Preparation of 41 from 24b



To a solution of dimethyl malonate (0.304 mL, 1.1 equiv) in THF (20 mL) under nigrogen was slowly added NaH (0.10 g,   equiv of a 60% mineral oil dispersion). After the bubbling had ceased (10 min), **24b** (0.51 g, 2.42 mmol) was added, and the mixture was stirred overnight. The reaction was quenched by the addition of H_2O (1 mL), and the mixture was concentrated in vacuo, extracted with CH_2Cl_2 (3 x 40 mL)/H_2O (40 mL), and washed with brine (40 mL). Drying (Na_sSO_4) and concentration in vacuo gave a brown oil. Flash column chromatography gave **41** (0.546 g, 69%) as colorless crystals: mp 117-179 °C; IR (KBr, cm^{-1}) 1750, 1740, 1720, 1690, 1680, 1315, 1305, 1280, 1270, 1105, 1190, 1170, 1100, 720; ^1H NMR ($CDCl_3$) δ 7.8-7.2 (m, 6 H), 6.08 (d, $\underline{J}$ = 10 Hz, 1 H), 3.80 (s, 3 H), 3.5-3.2 (m, 2 H), 3.0-2.6 (m, 2 H), 1.81 (s, 3 H), ^{13}C NMR ($CDCl_3$) δ 193.9, 171.0, 168.3, 167.9, 147.3, 133.9, 132.8, 128.9 (2 C), 128.3, 128.0 (2 C), 61.7, 52.8, 51.9, 42.8, 35.3, 22.0; mass spectrum, exact mass calcd for $C_{18}H_{17}NO_5$ $\underline{m/e}$ 327.1107, obsd $\underline{m/e}$ 327.1121.

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NMR SPECTRA

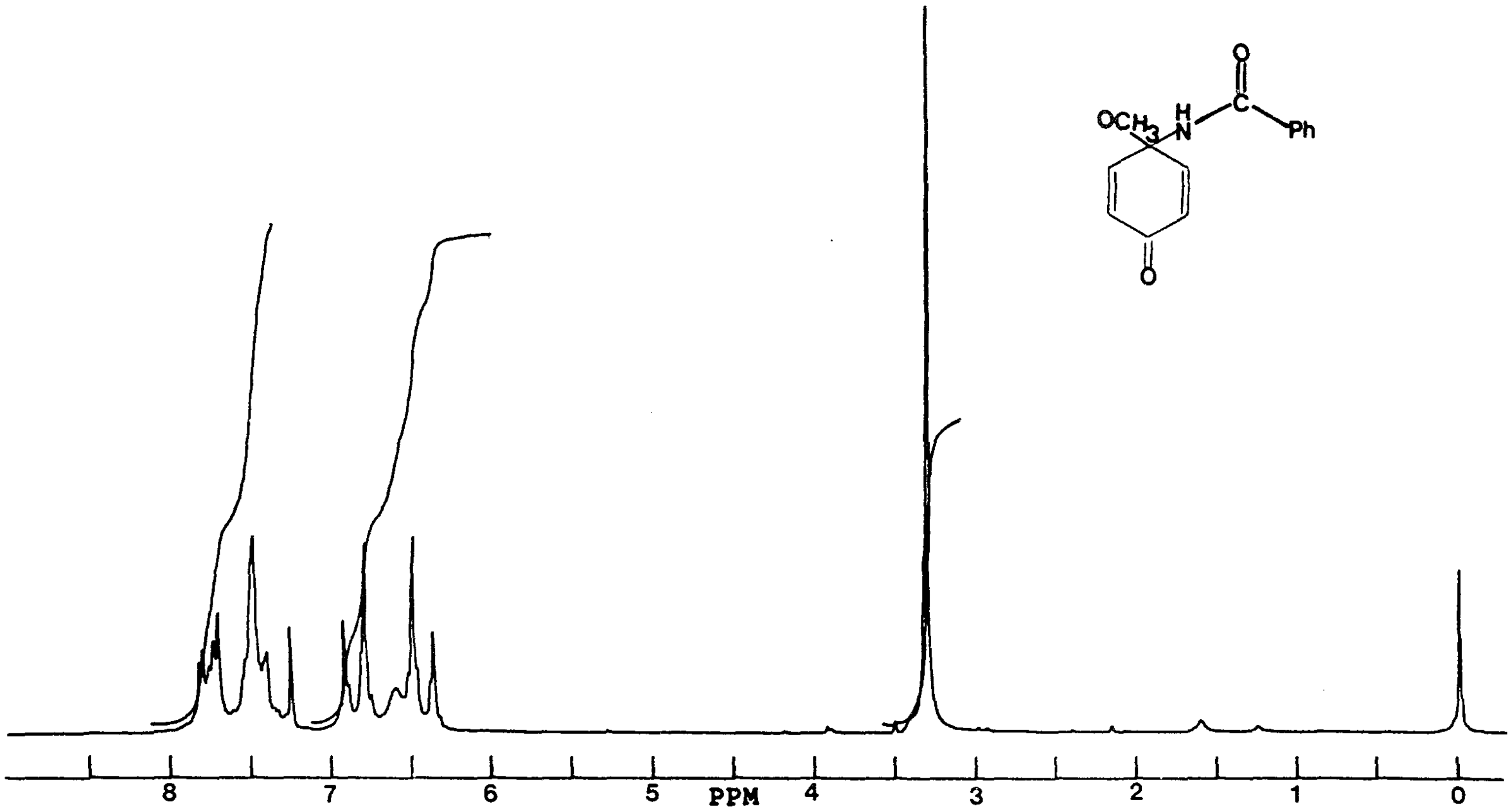

Figure 3. 80 MHz ^{1}H NMR Spectrum of 13

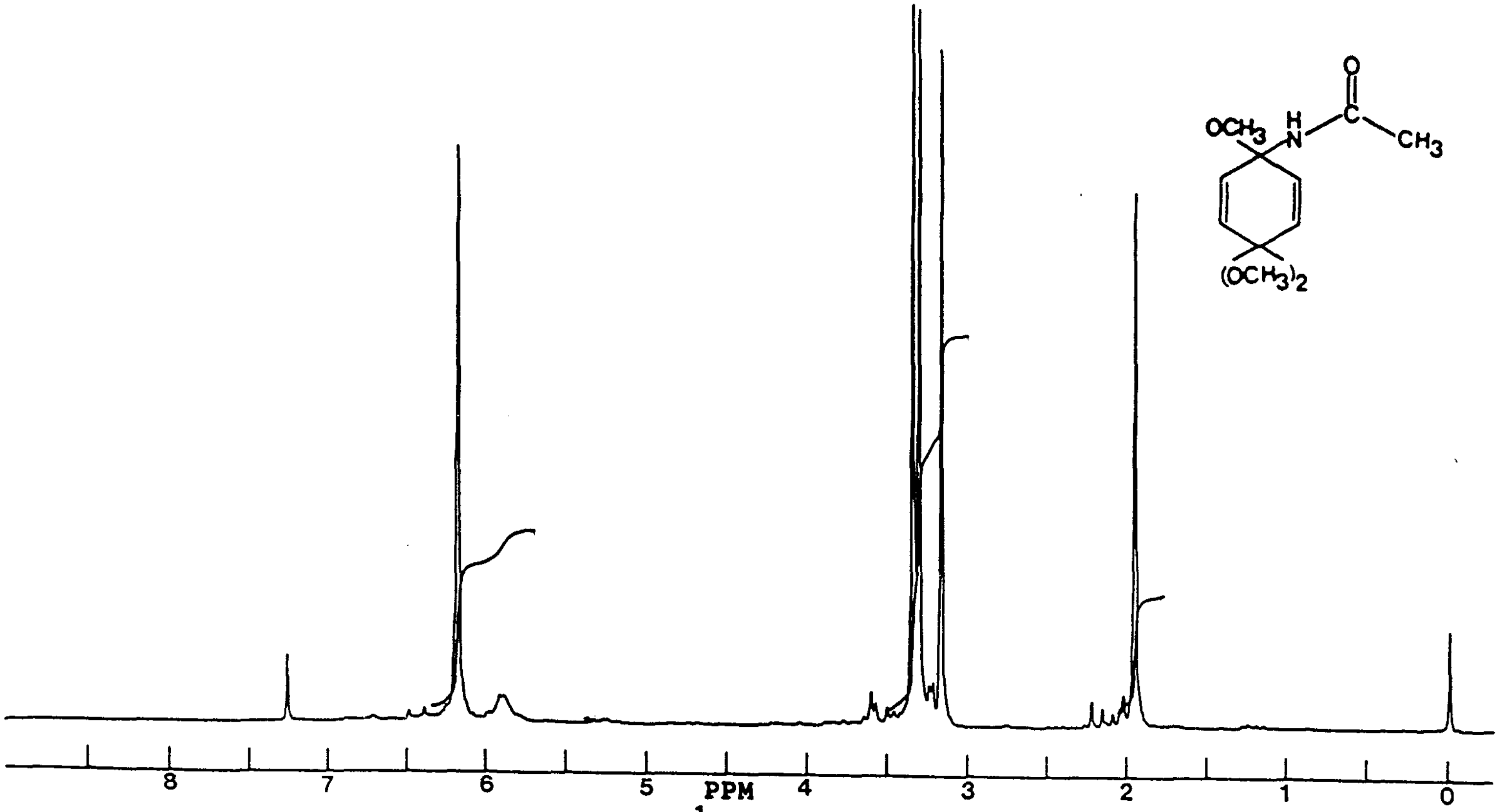

Figure 4. 80 MHz ^{1}H NMR Spectrum of 14

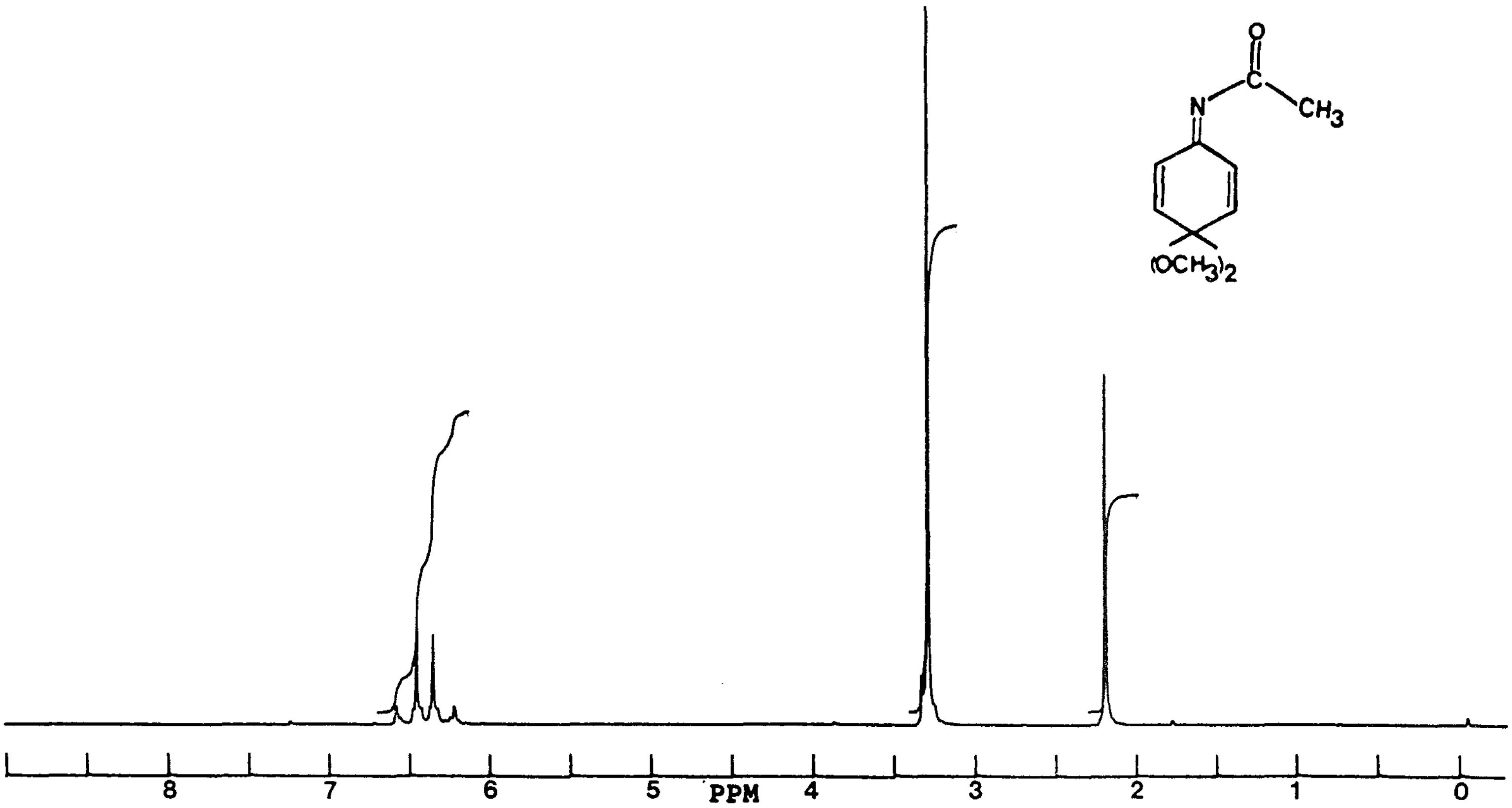

Figure 5. 80 MHz ^{1}H NMR Spectrum of 15

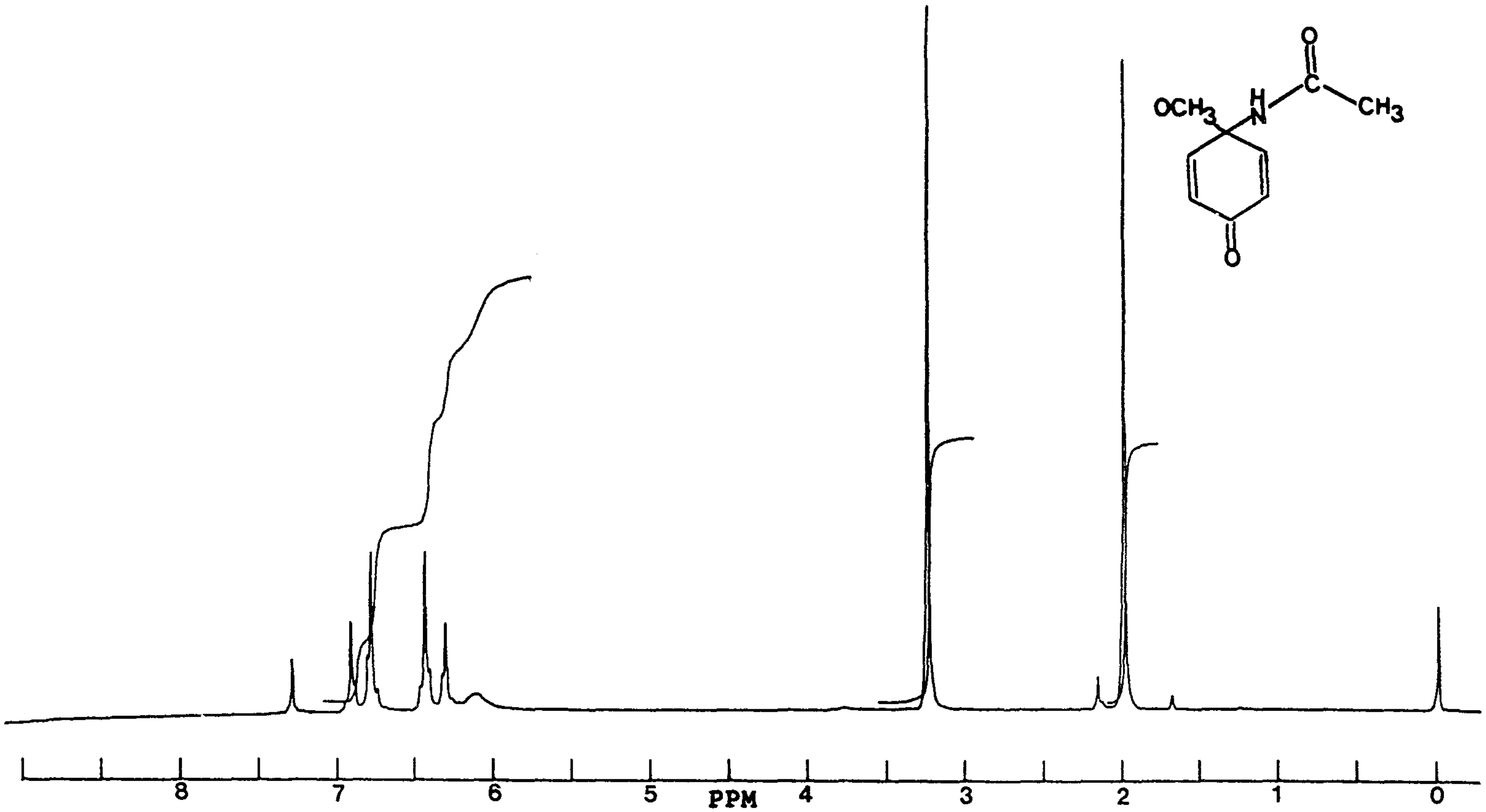

Figure 6. 80 MHz ^{1}H NMR Spectrum of 16

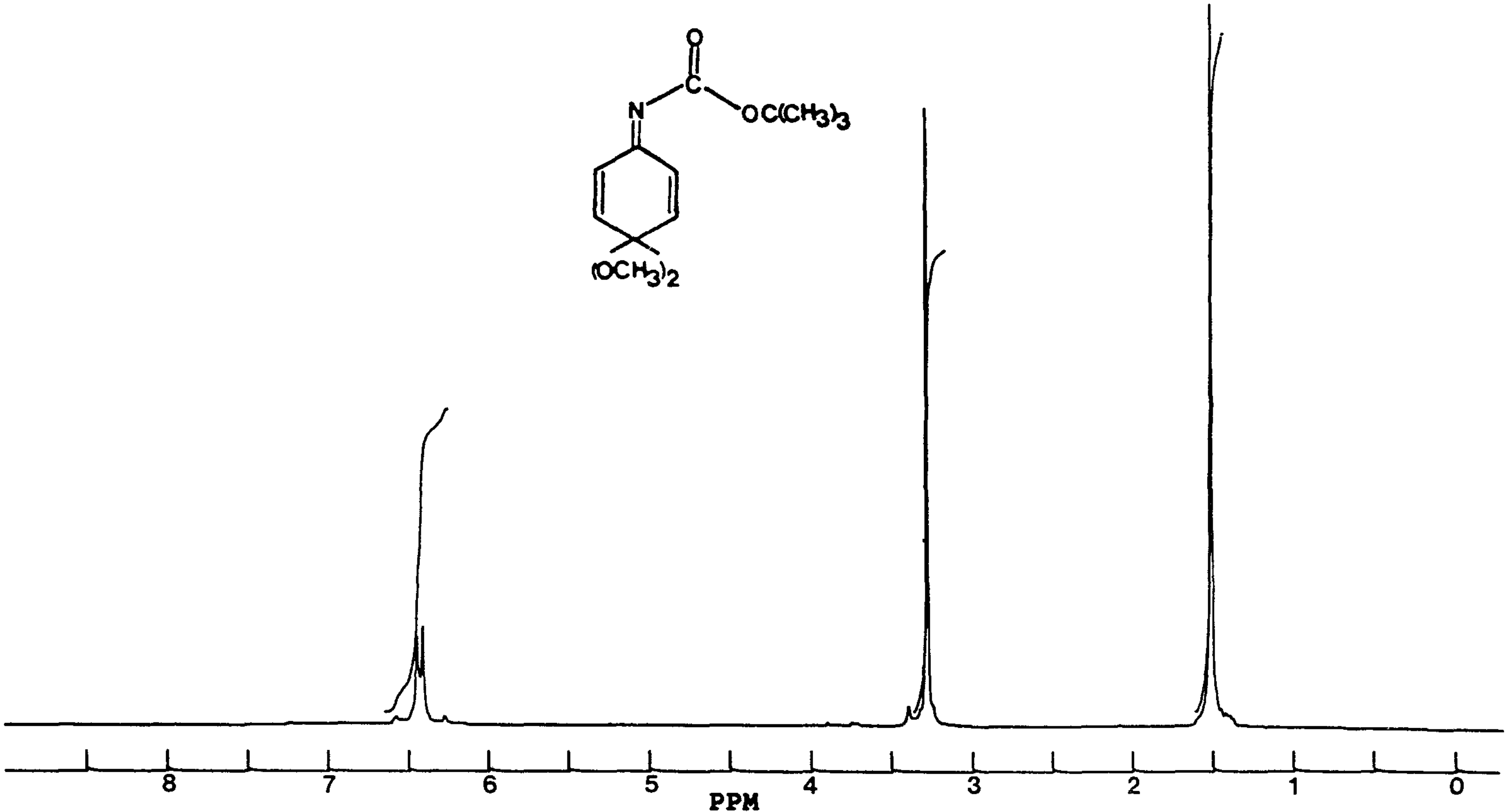

Figure 7. 80 MHz ^{1}H NMR Spectrum of 17

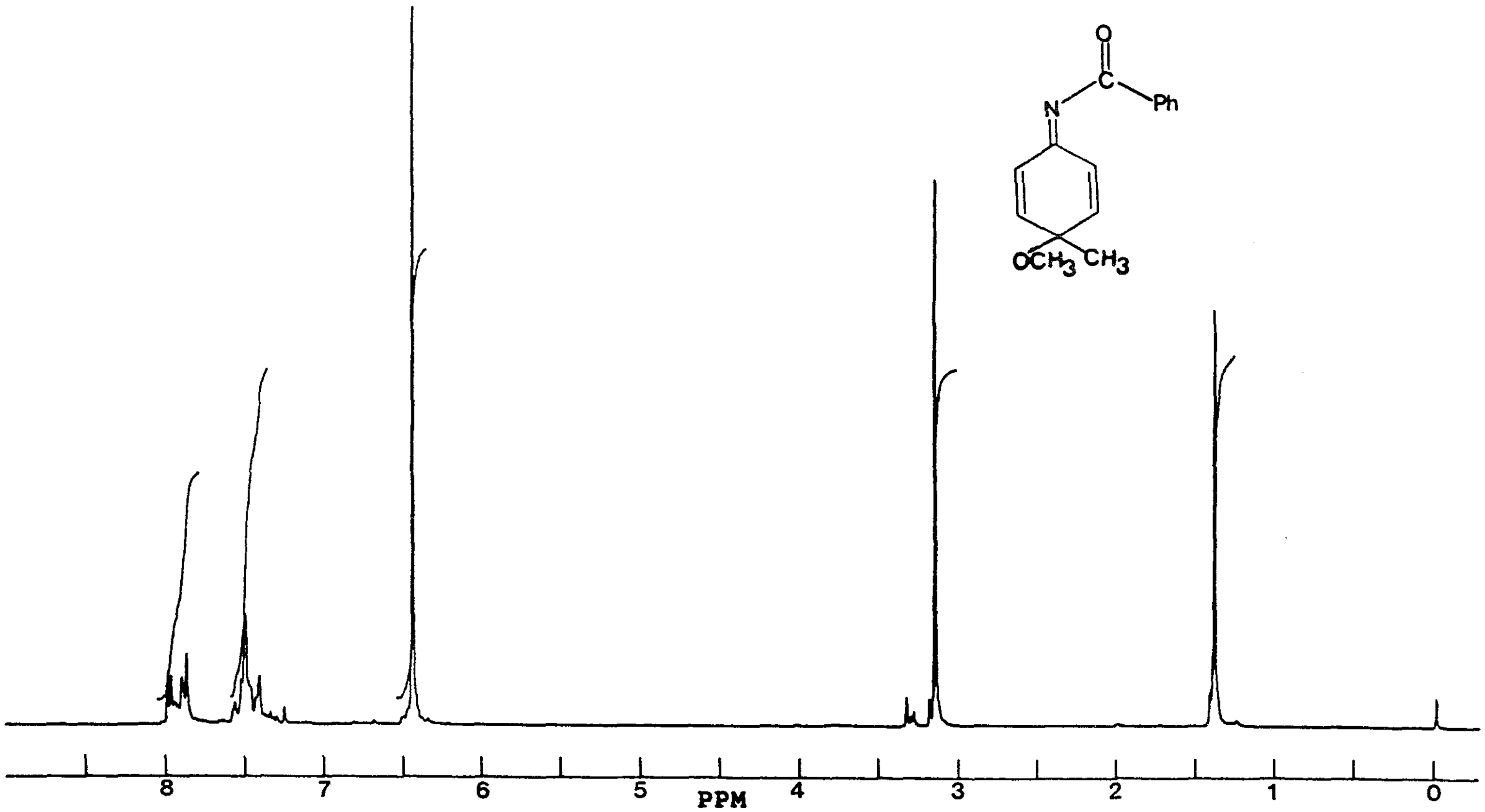

Figure 8. 80 MHz ^{1}H NMR Spectrum of 18

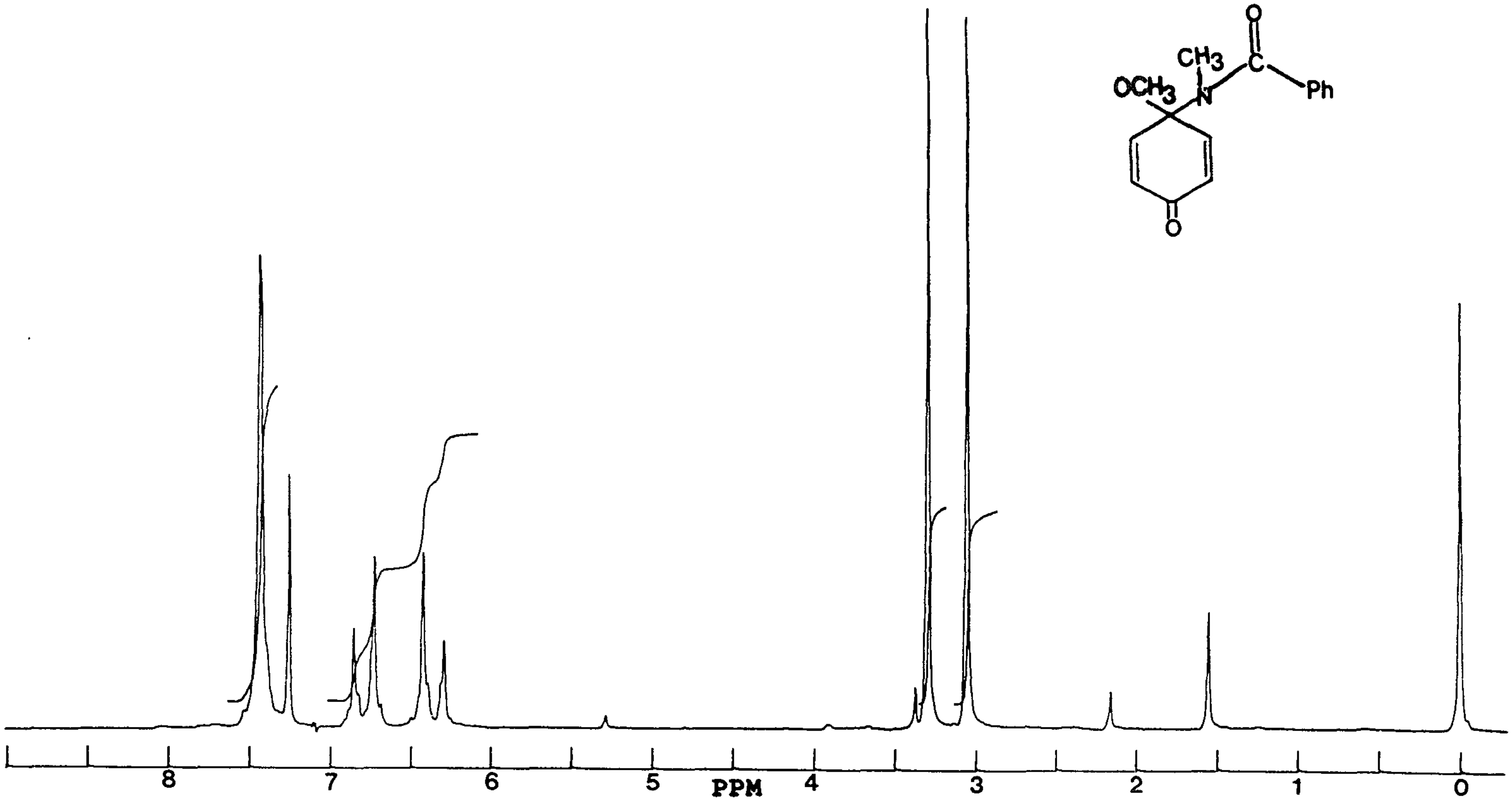

Figure 9. 80 MHz ^{1}H NMR Spectrum of 19

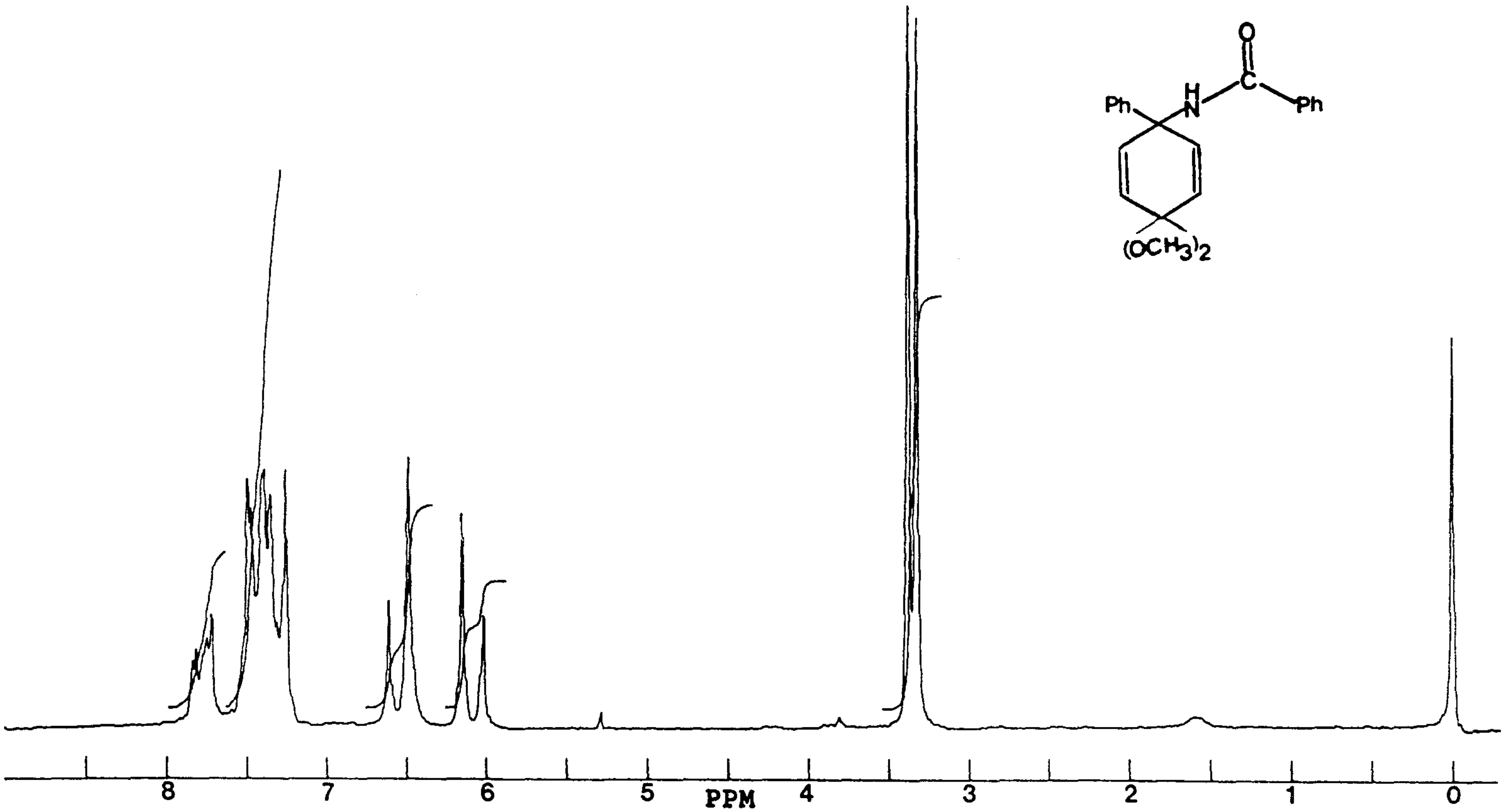

Figure 10. 80 MHz ^{1}H NMR Spectrum of 23a

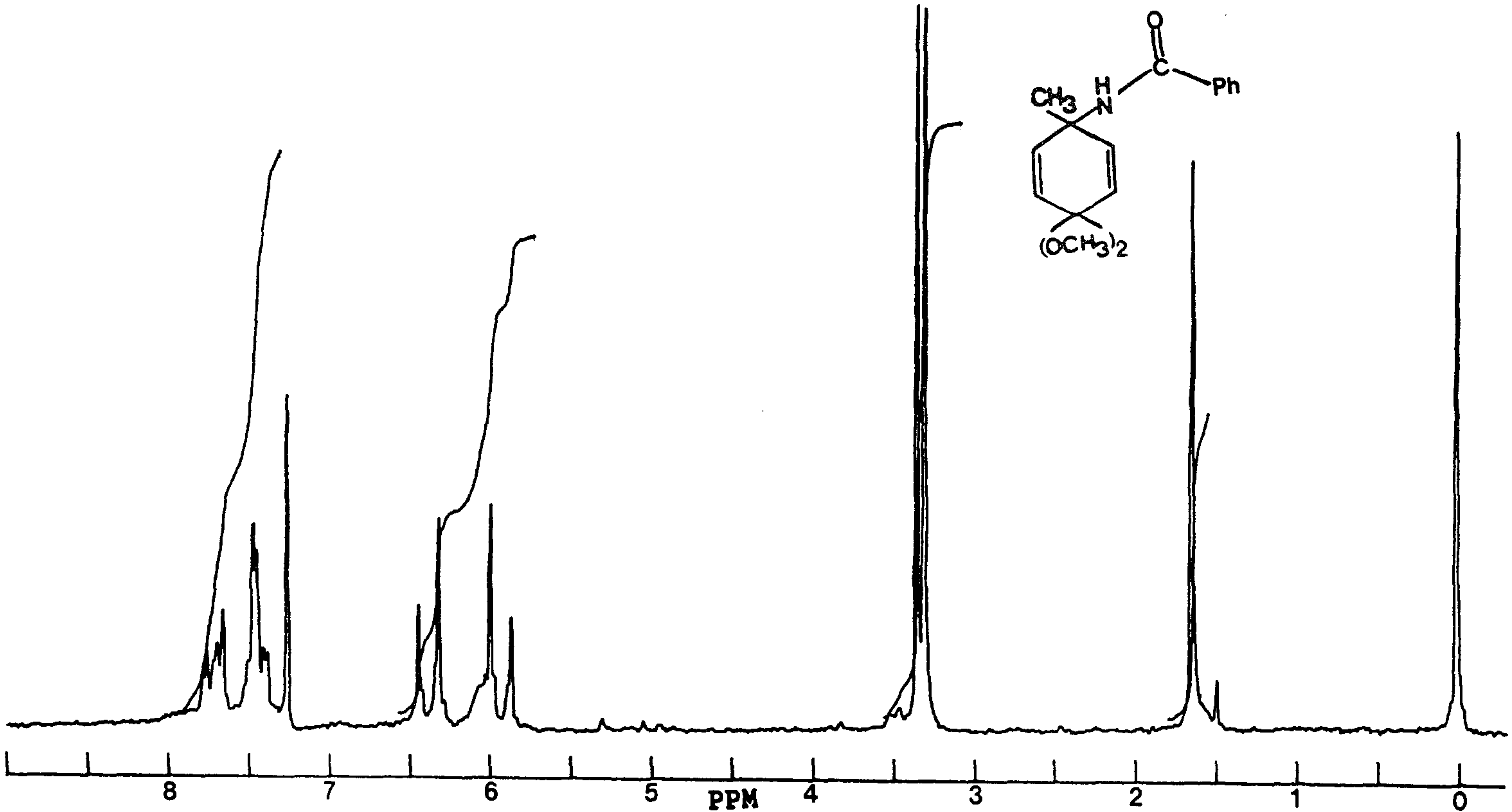

Figure 11. 80 MHz ^{1}H NMR Spectrum of 23b

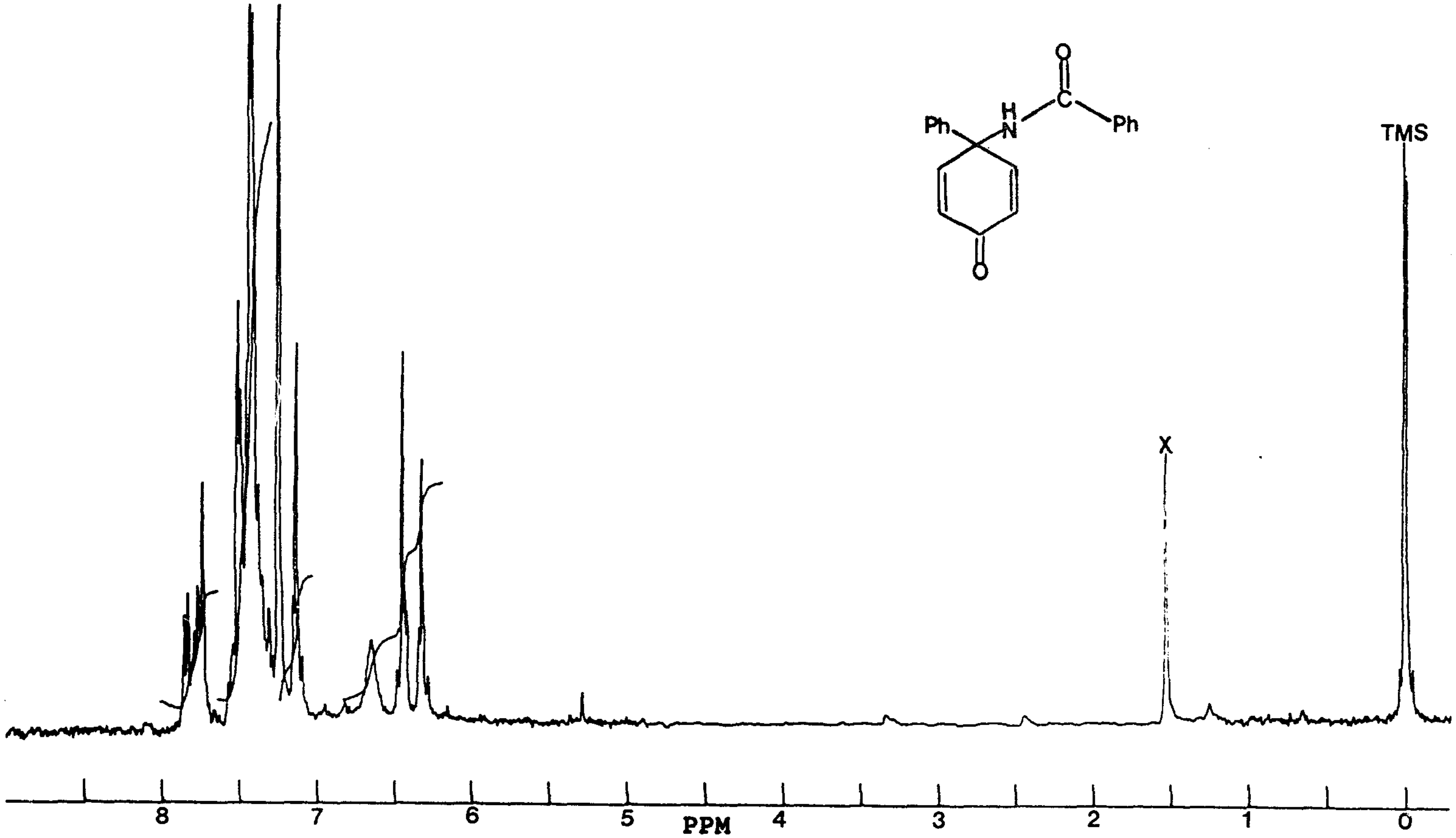

Figure 12. 80 MHz ^{1}H NMR Spectrum of 24a

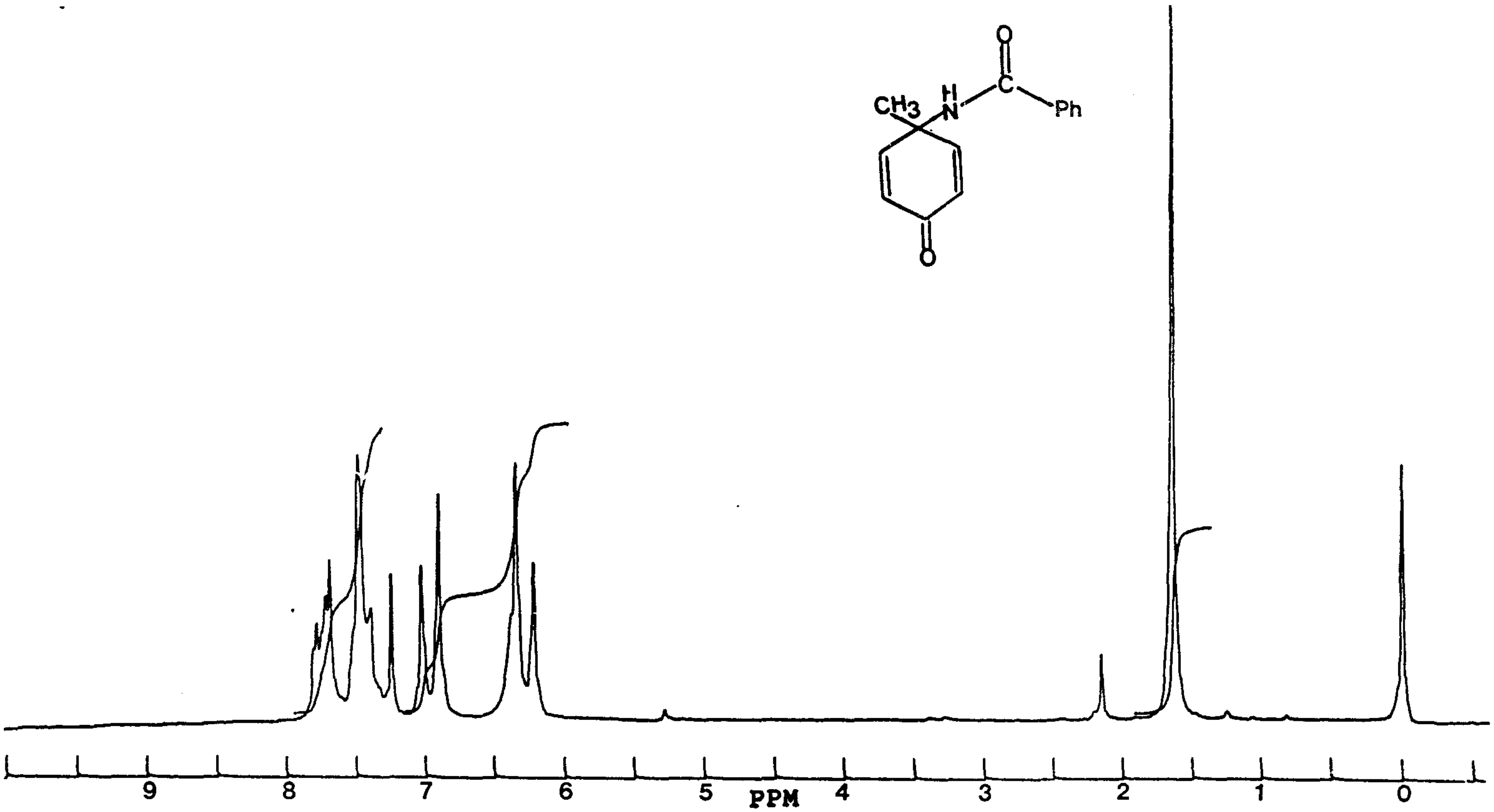

Figure 13. 80 MHz ^{1}H NMR Spectrum of 24b

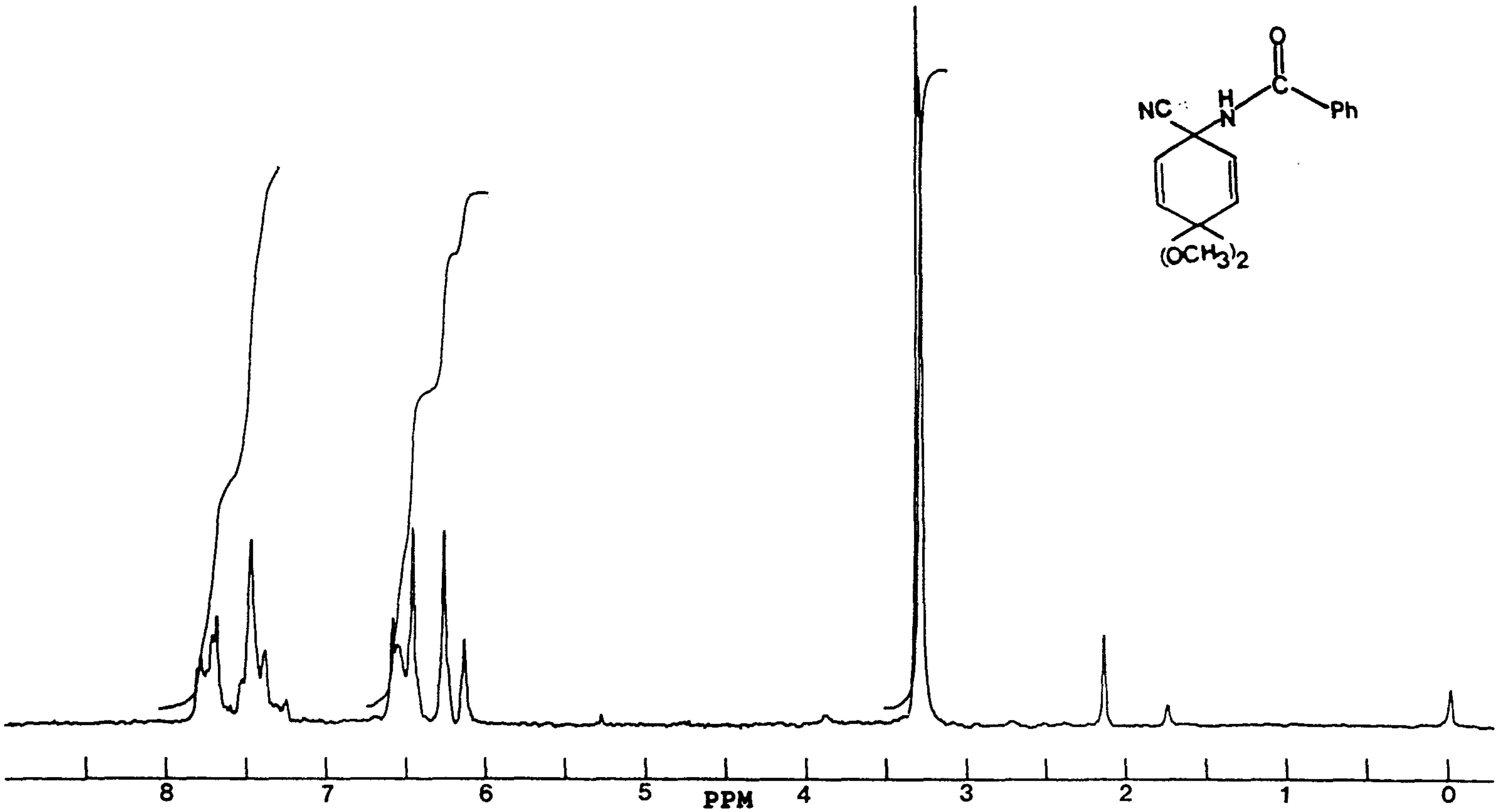

Figure 14. 80 MHz ^{1}H NMR Spectrum of 26

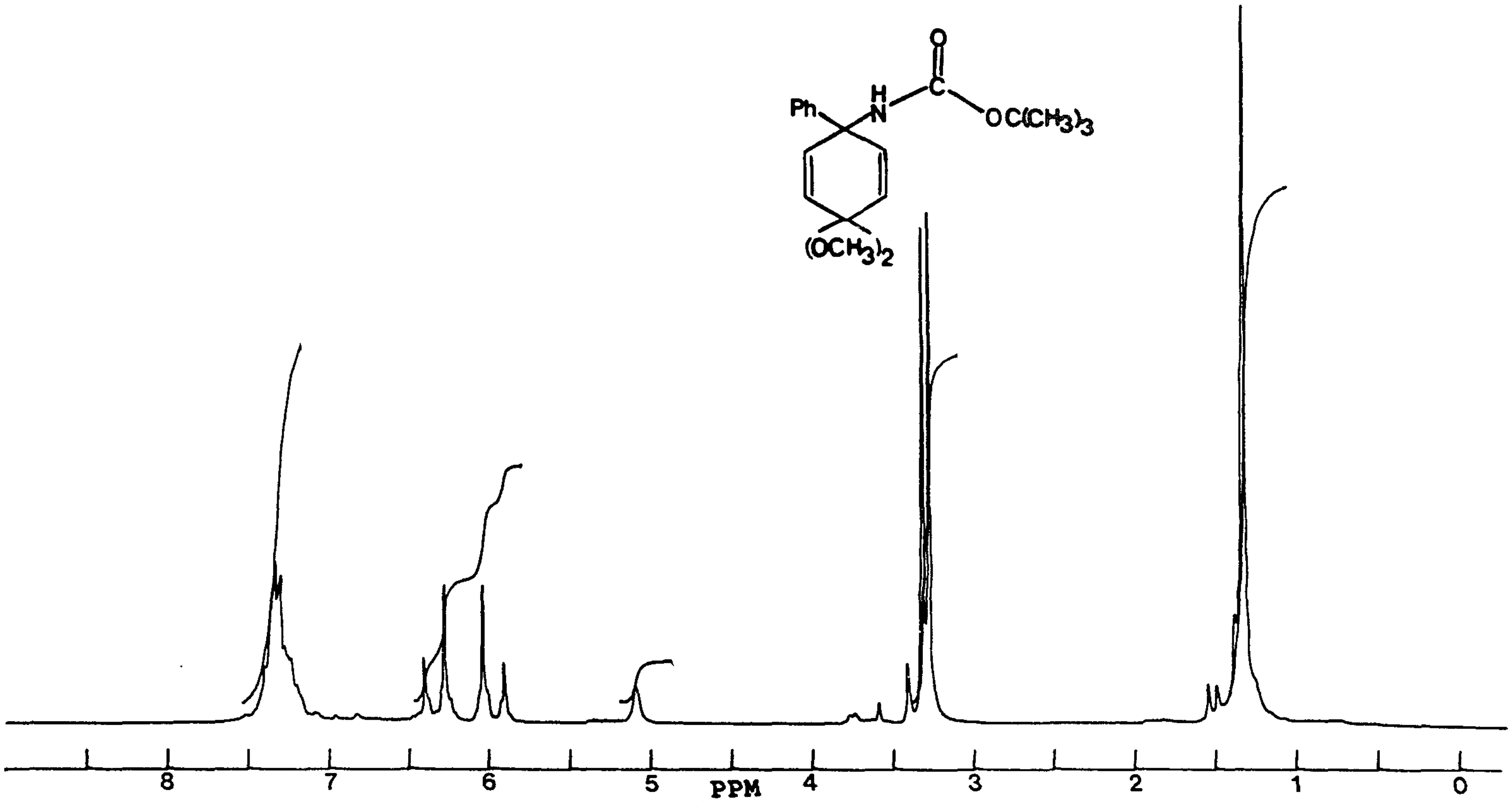

Figure 15. 80 MHz ^{1}H NMR Spectrum of 27b

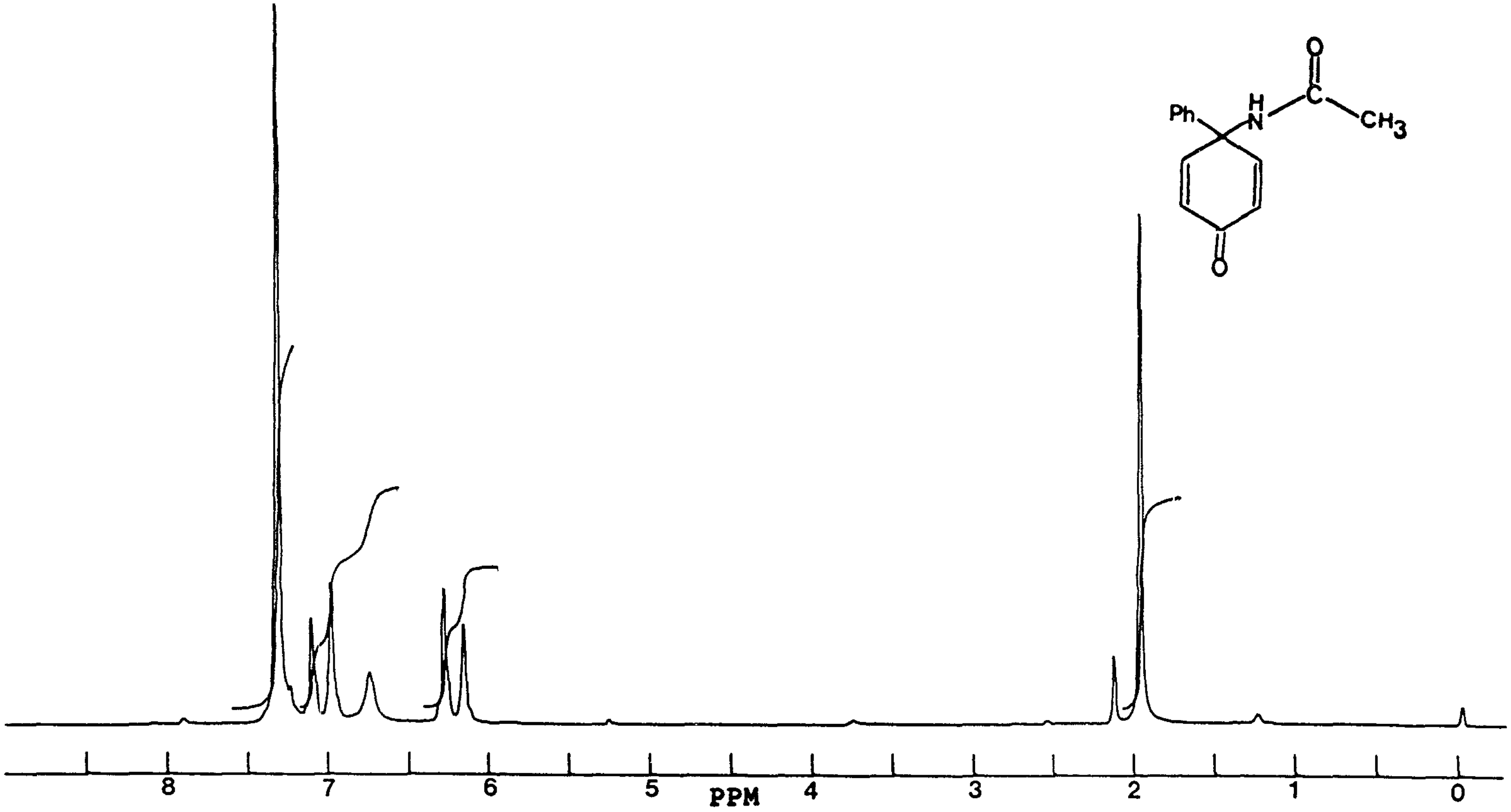

Figure 16. 80 MHz ^{1}H NMR Spectrum of 28a

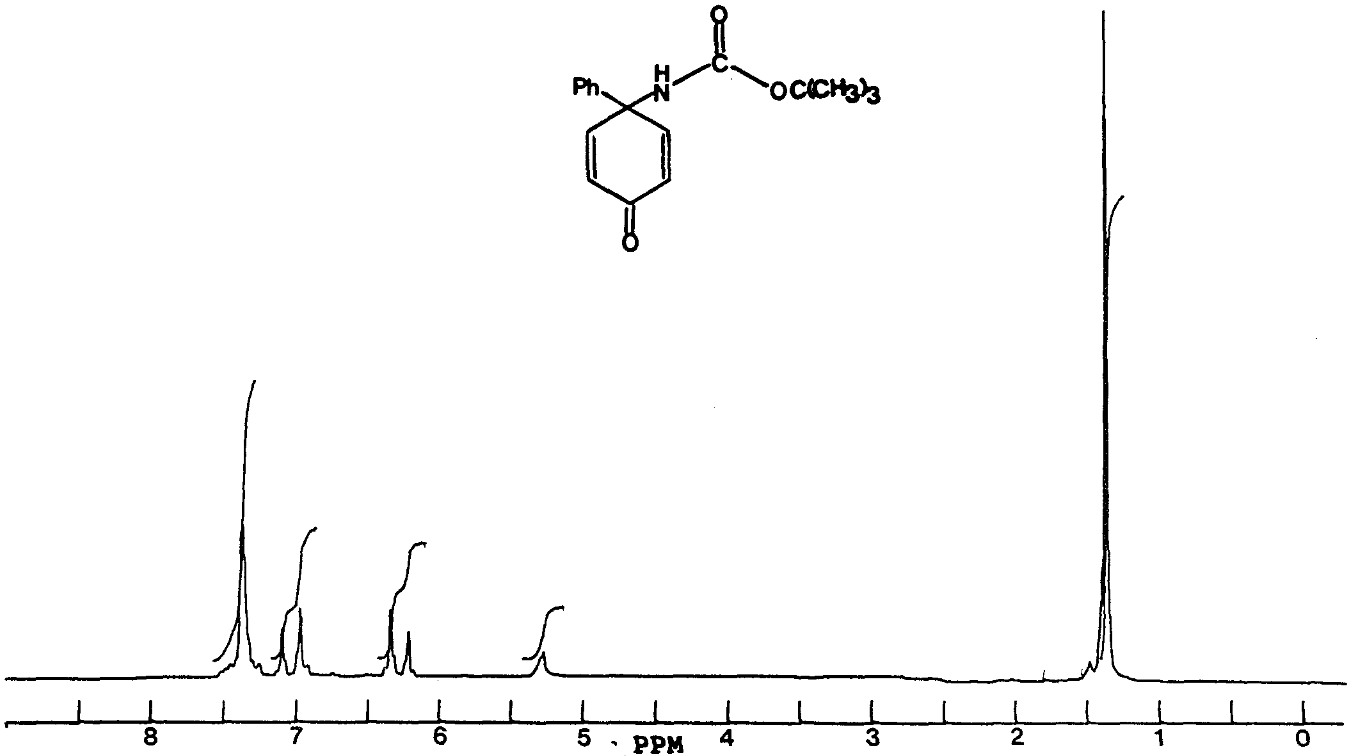

Figure 17. 80 MHz ^{1}H NMR Spectrum of 28b

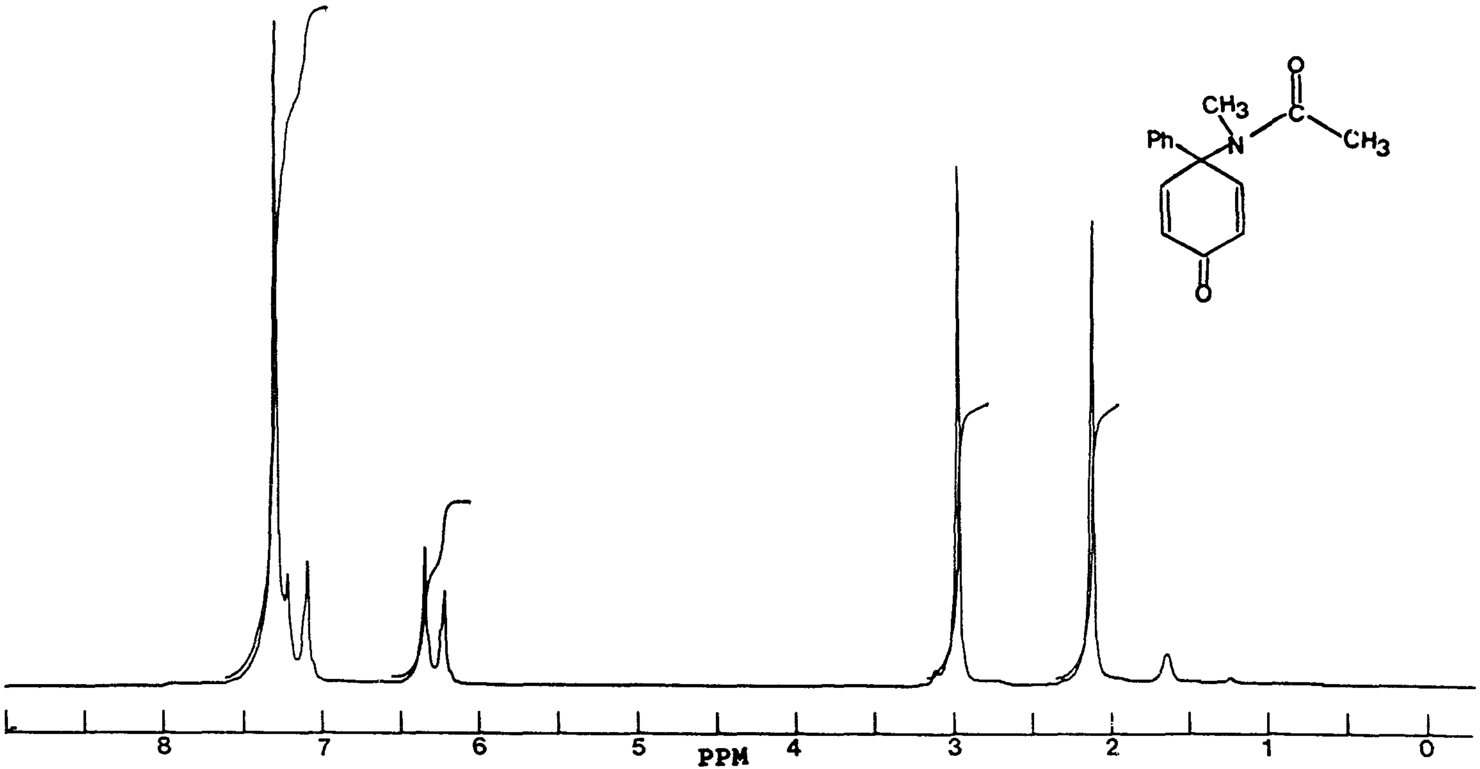

Figure 18. 80 MHz ^{1}H NMR Spectrum of 29a

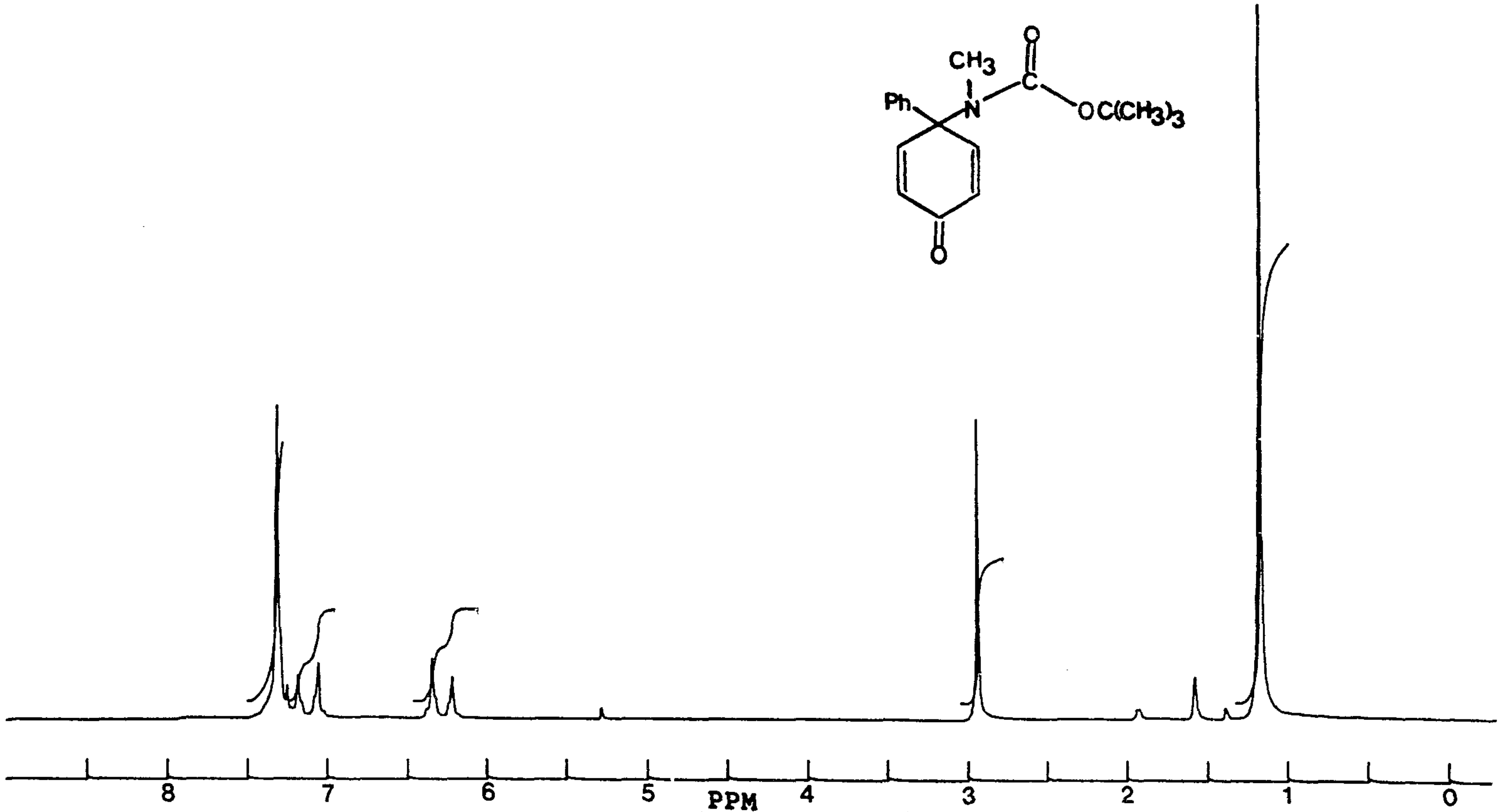

Figure 19. 80 MHz ^{1}H NMR Spectrum of 29b

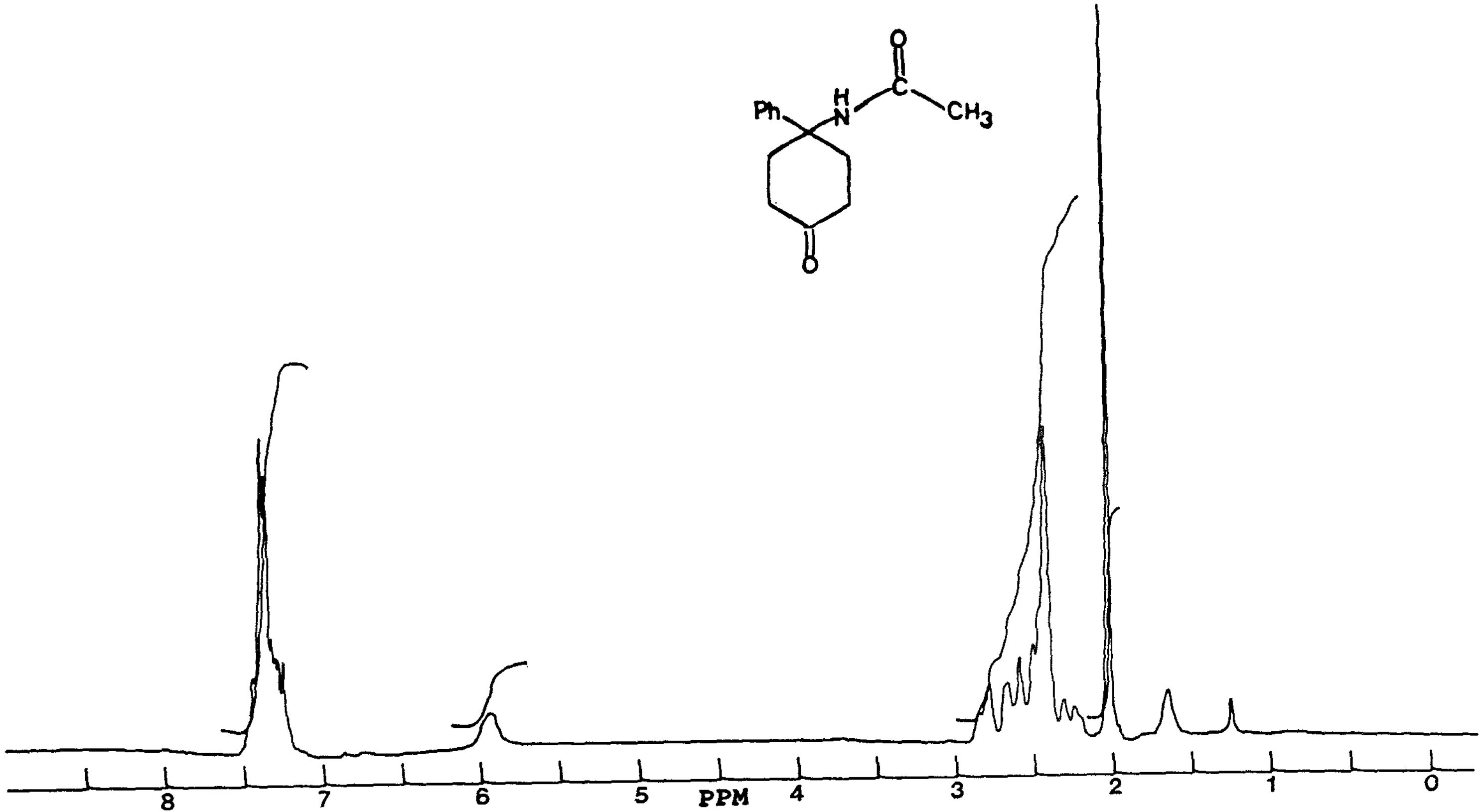

Figure 20. 80 MHz ^{1}H NMR Spectrum of 30

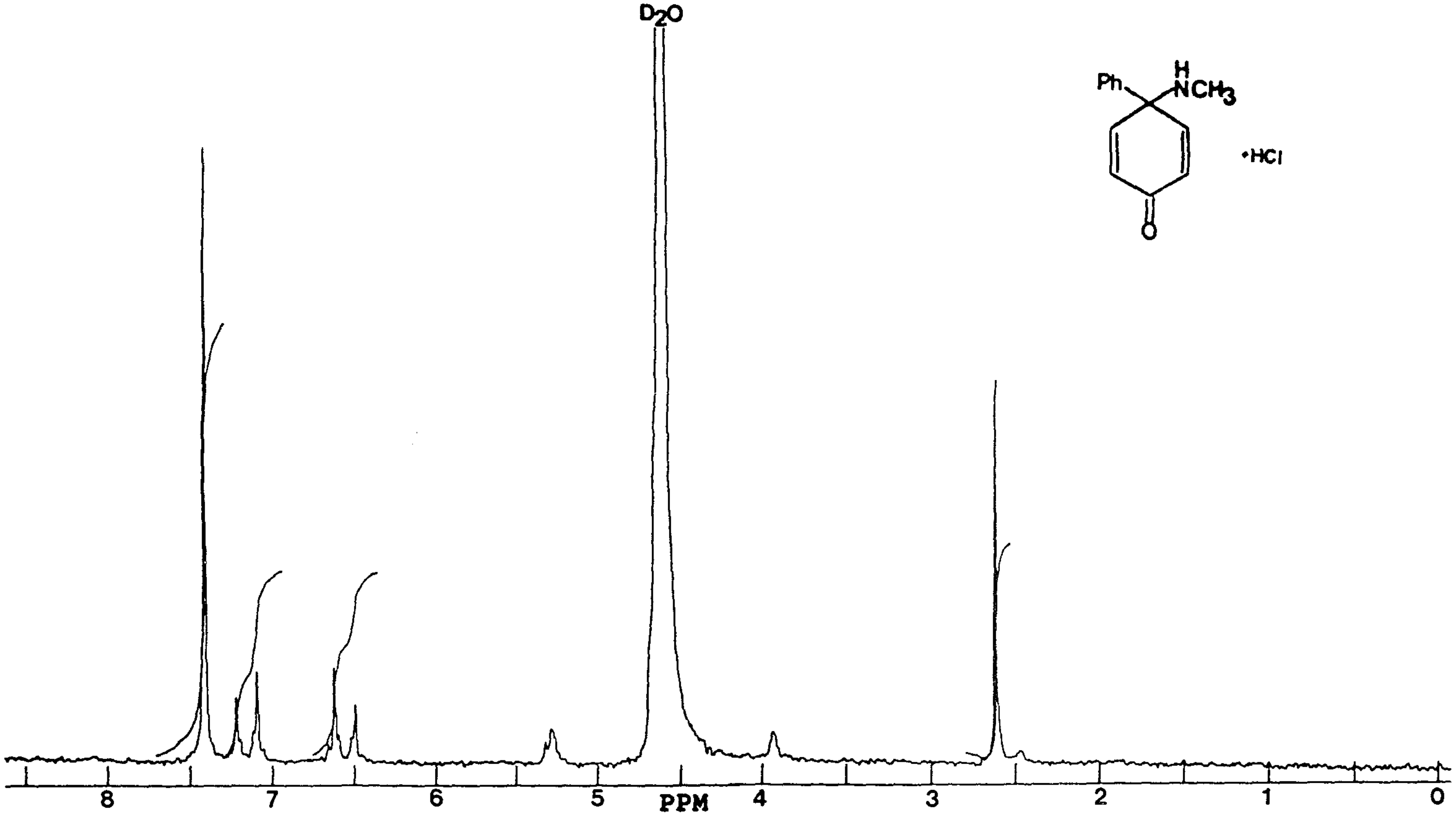

Figure 21. 80 MHz ^{1}H NMR Spectrum of 31

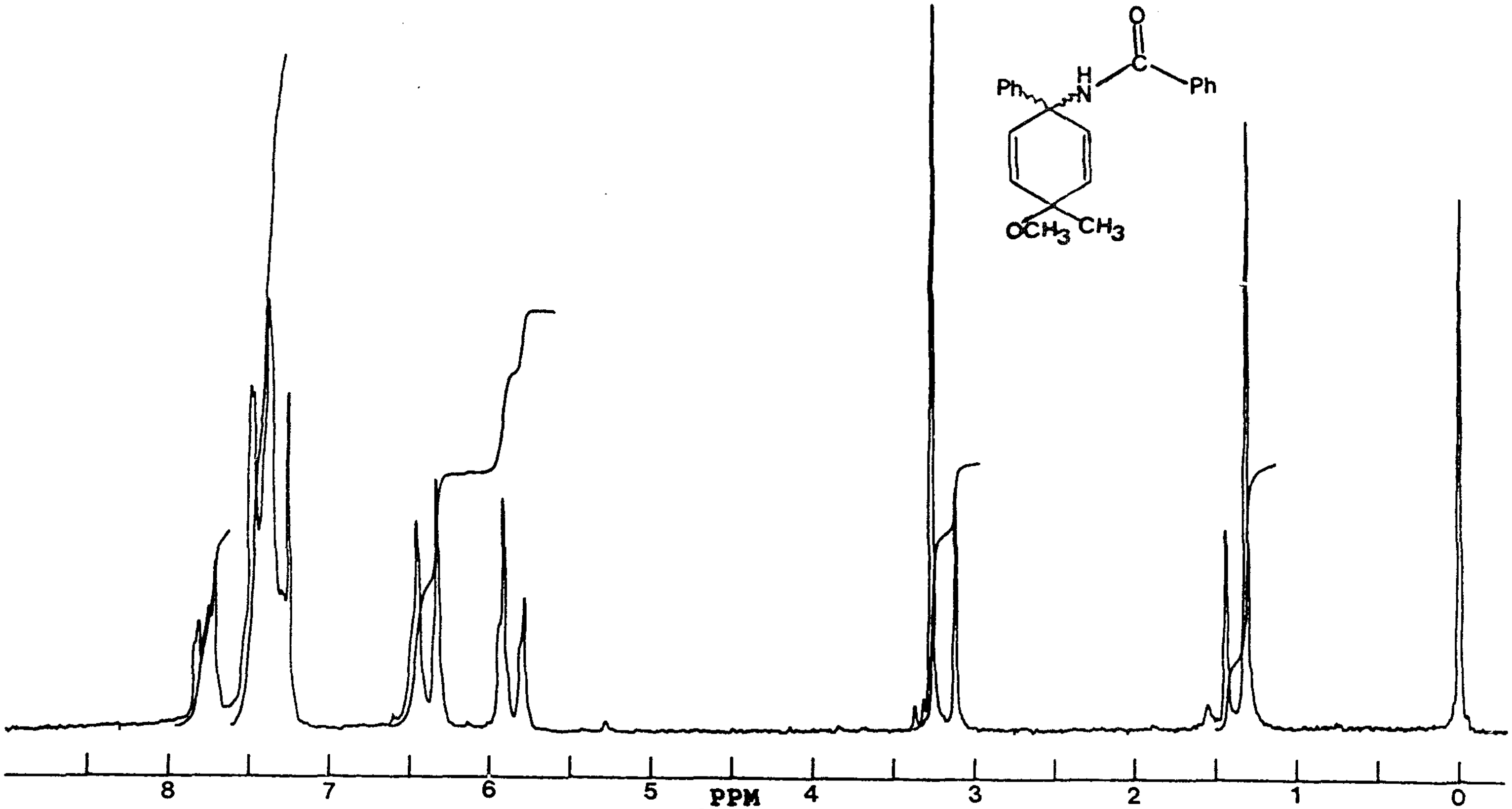

Figure 22. 80 MHz ^{1}H NMR Spectrum of 32a

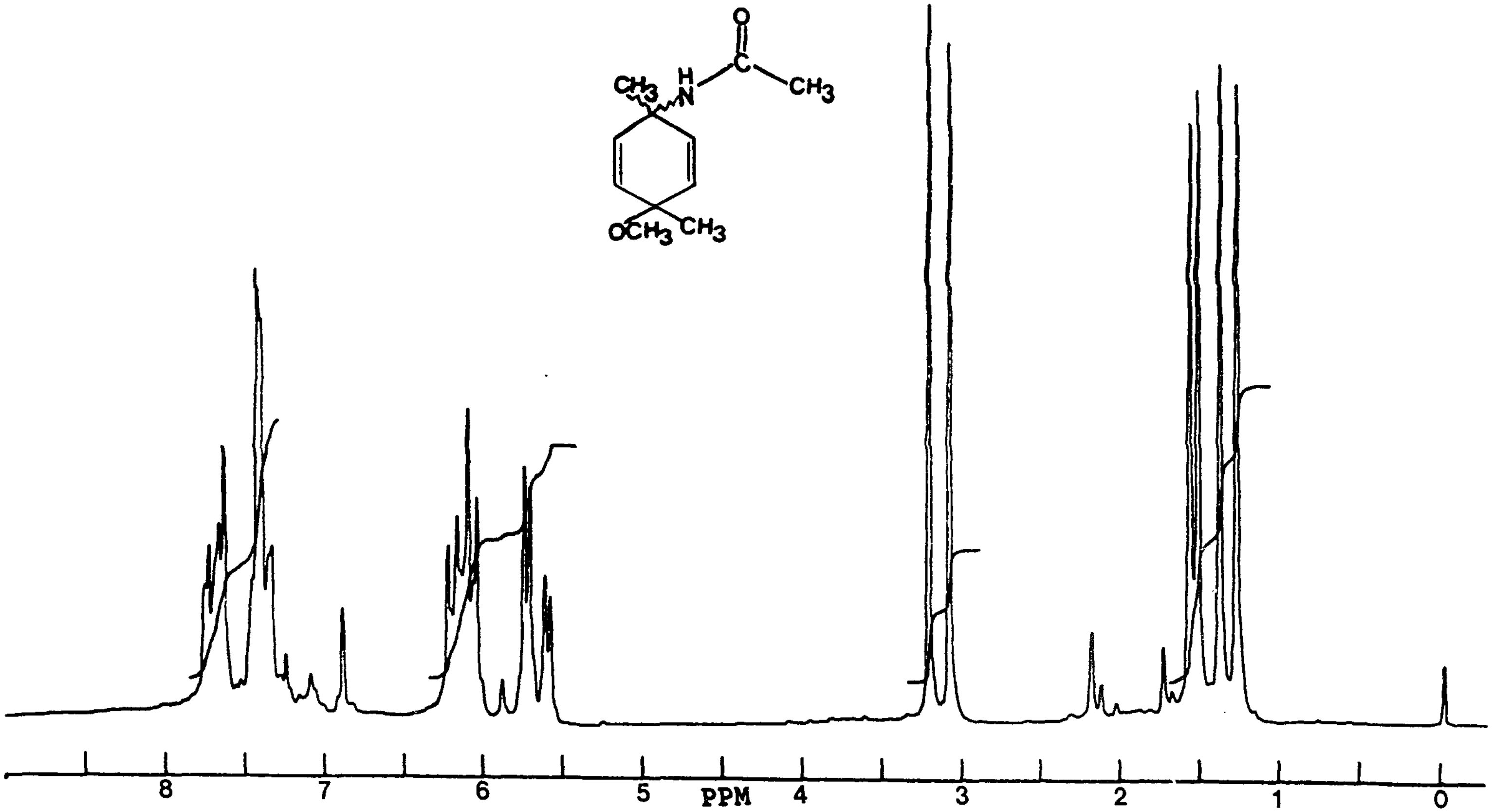

Figure 23. 80 MHz ^{1}H NMR Spectrum of 32b

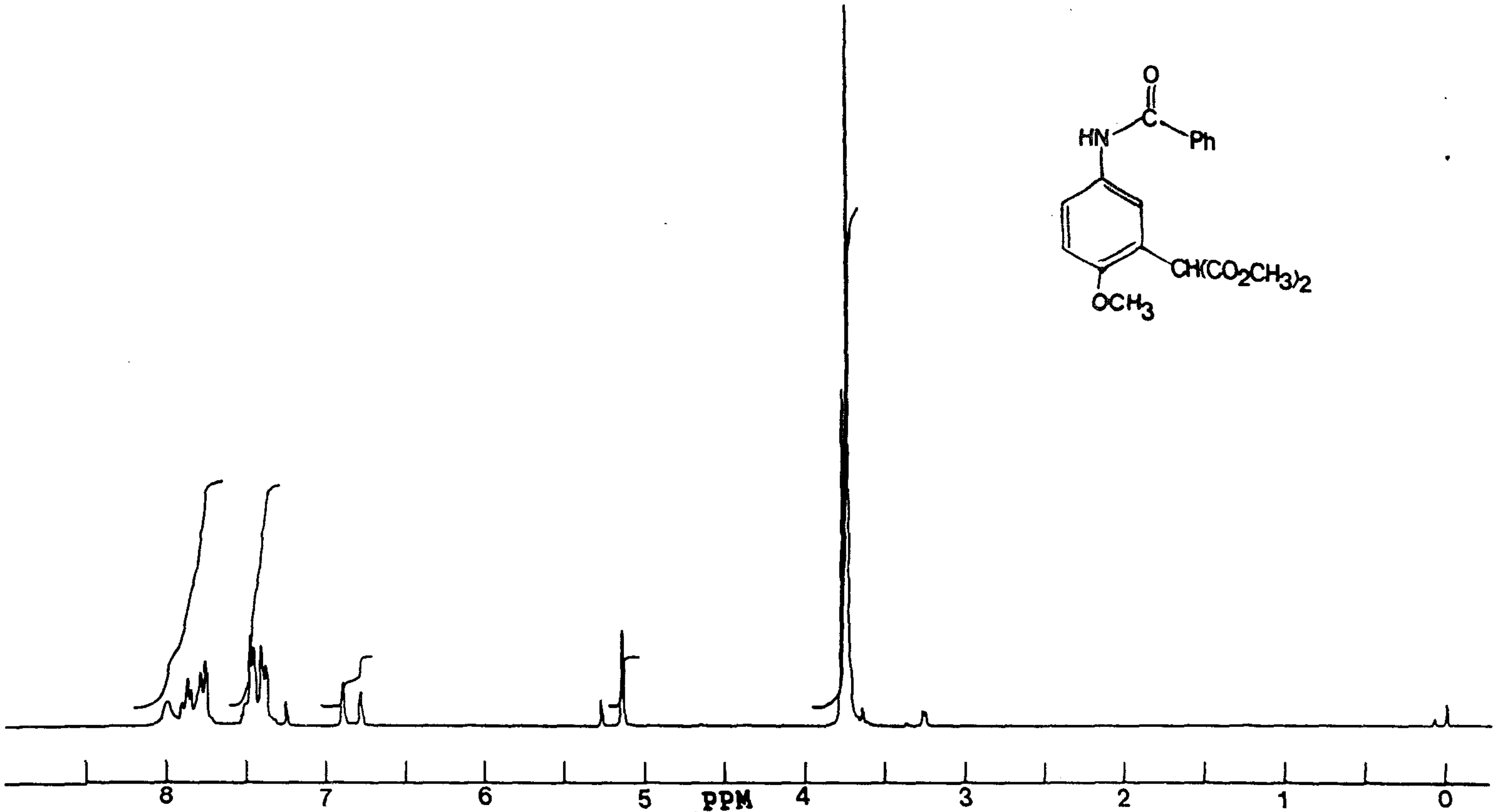

Figure 24. 80 MHz ^{1}H NMR Spectrum of 34

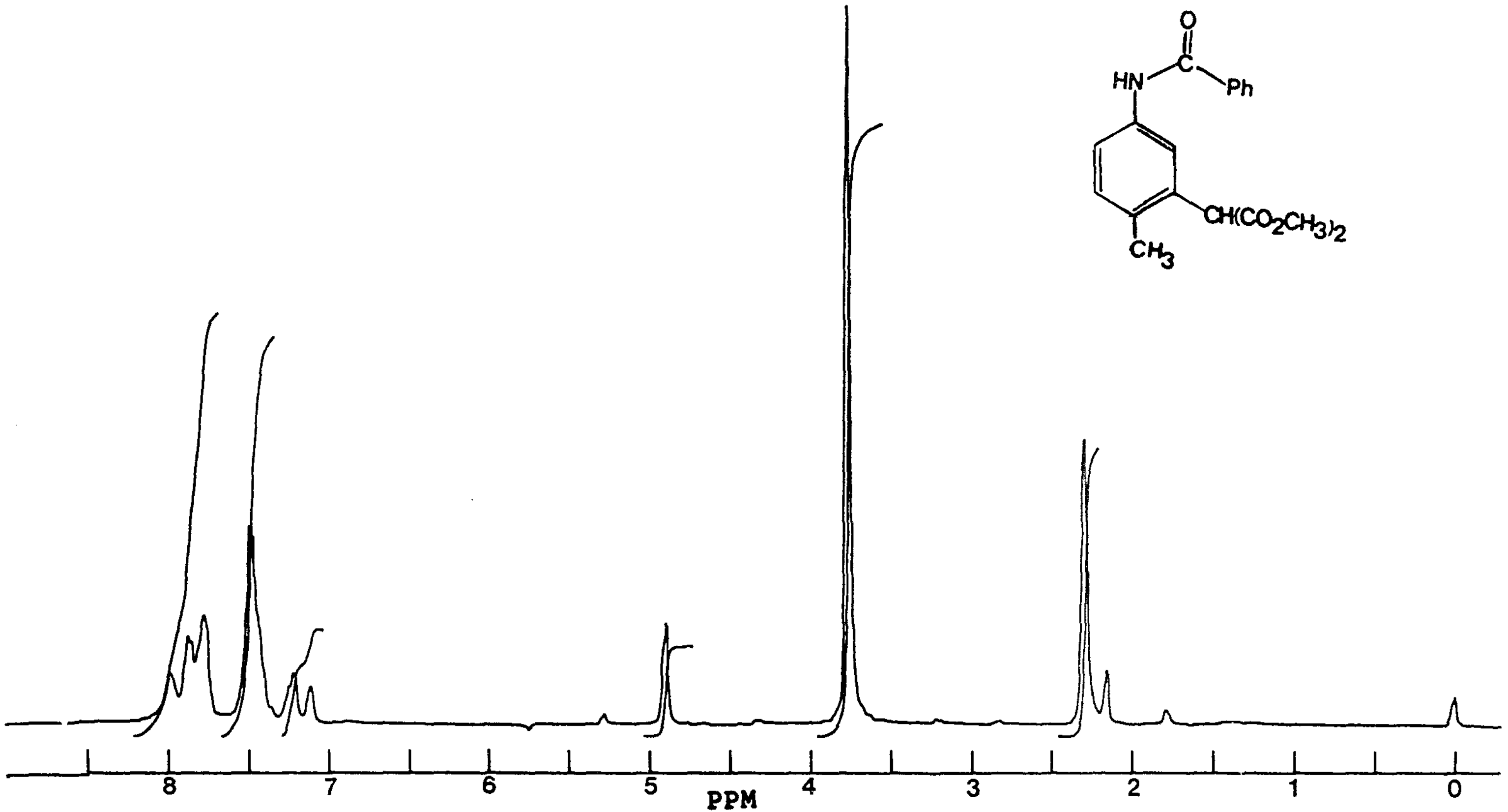

Figure 25. 80 MHz ^{1}H NMR Spectrum of 36

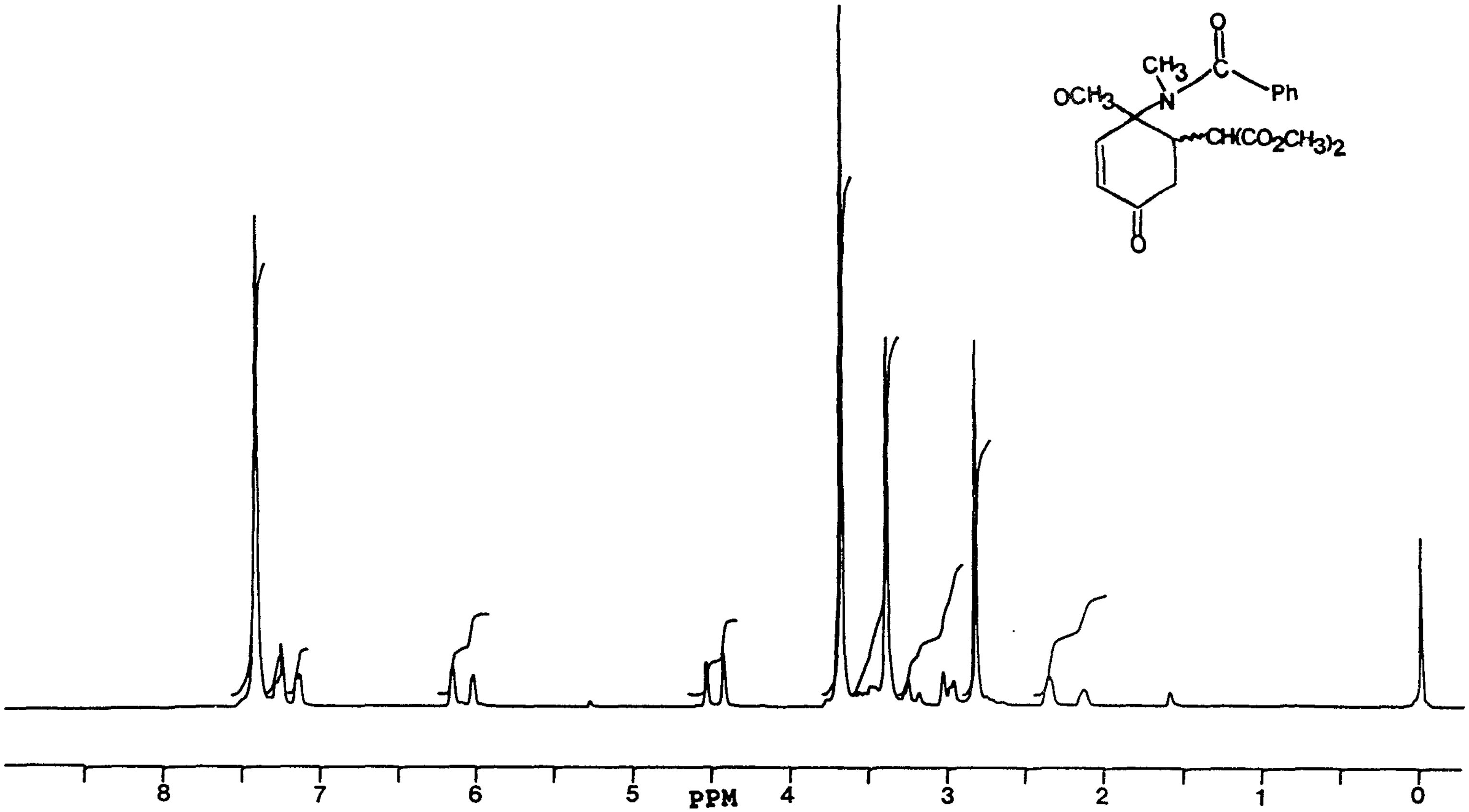

Figure 26. 80 MHz ^{1}H NMR Spectrum of 38