Progress on the Synthesis of 1,2,3,5,9-cyclodecapentaen-7-yne and Supporting Studies

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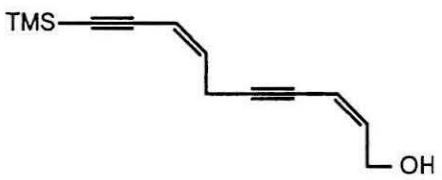
Abstract

Progress on the synthesis of 1,2,3,5,9-cyclodecapentaen-7-yne (**1**), a compound structurally related to both (Z)-1,2,4-heptatrien-6-yne and the activated core of neocarzinostatin chromophore, is reported. The novel compound **1** is of theoretical interest as an example of a monocyclic 10-membered ring that fulfills the aromaticity requirements of Hückel's rule. The alcohol **24**, envisioned to serve as a possible precursor to **1**, has been synthesized.

In related, collaborative studies, 1-bromo-4-trimethylsilylnaphthalene, 1-bromo-5-trimethylsilylnaphthalene, 2-bromo-7-trimethylsilylnaphthalene, 1-chloro-4-trimethylsilylnaphthalene, 1-chloro-5-trimethylsilylnaphthalene, and 2-chloro-7-trimethylsilylnaphthalene have been synthesized. These compounds will be used in gas-phase studies as precursors to the corresponding naphthalene biradicals. These studies will determine the heat of formation of each corresponding naphthalene biradical.

1



24

Table of Abbreviations

Bu	butyl
CSA	camphorsulfonic acid
eq	equivalents
DMSO	dimethylsulfoxide
EtOAc	ethyl acetate
EtOH	ethanol
Et_3N	triethylamine
h	hour(s)
IR	infrared
Me	methyl
MeOH	methanol
min	minute(s)
n	normal
NMR	nuclear magnetic resonance
Ph	phenyl
t	tertiary
Tf_2O	trifluoromethanesulfonic acid anhydride (triflic anhydride)
THF	tetrahydrofuran
THP	tetrahydropyran
TLC	thin layer chromatography
TMS	trimethylsilyl

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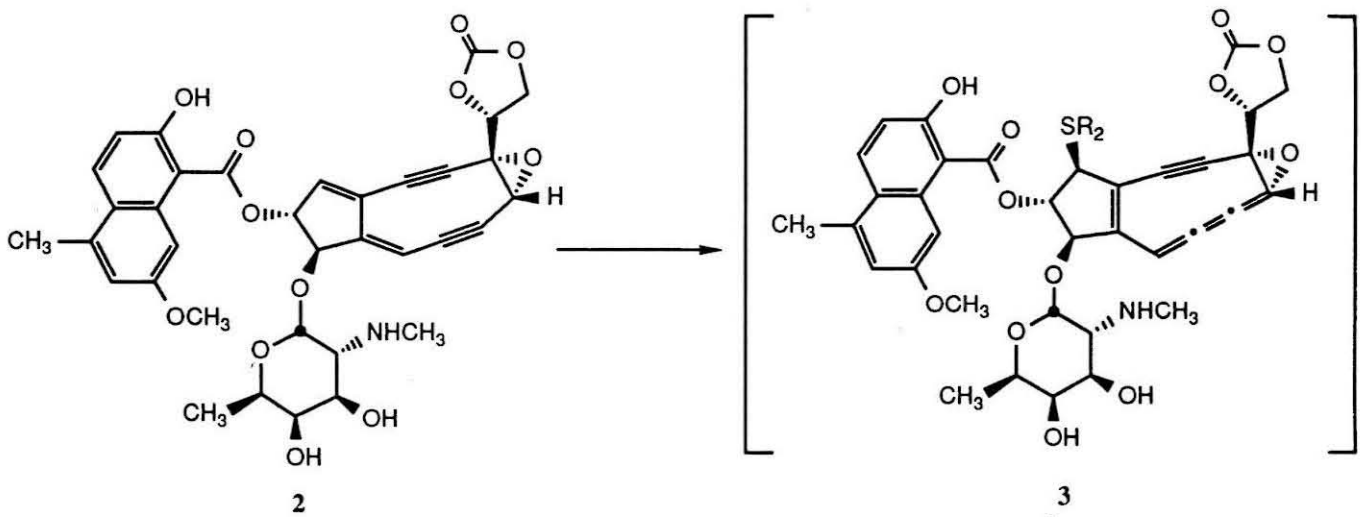
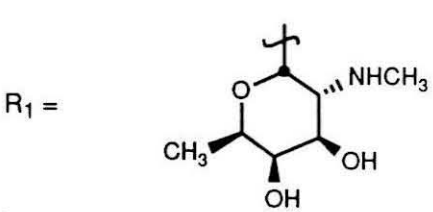
Introduction

Within the last several years a new class of antitumor antibiotics has been defined on the basis of the proposed ability of these compounds to form highly reactive, DNA-bound biradical intermediates. These biradical intermediates have been implicated in the biological activity of these compounds. Examples include calichemicin and esperamicin[1] which are proposed to form a 1,4-dehydrobenzene derivative via a Bergman-like rearrangement.[2] Similarly, studies carried out by the Myers lab on the neocarzinostatin (NCS) chromophore (**2**) indicate the formation of a 3,7-dehydroindene derivative[3] (**4**) via a reactive cumulene intermediate (**3**) (Scheme I):

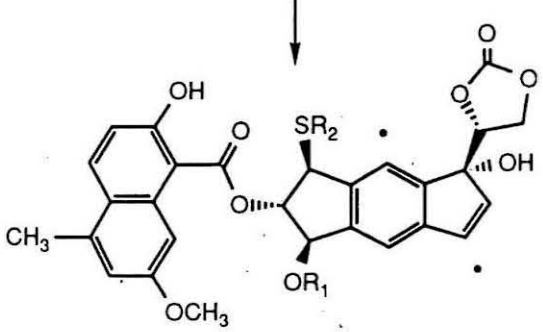
Scheme I



2 **3**



$R_2 = CH_2CO_2CH_3$



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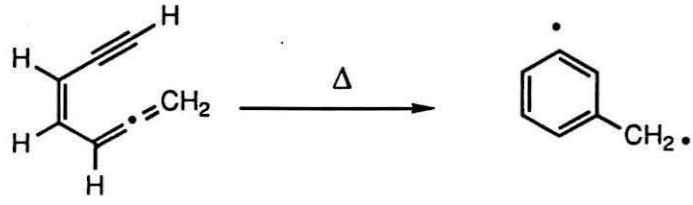
Further studies carried out to elucidate the mechanistic aspects of the NCS biradical formation have included the synthesis and thermal rearrangement of (Z)-1,2,4-heptatrien-6-yne[4] (Scheme II).

Scheme II

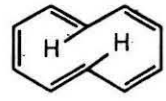


5 **6**

The goal of the research presented here is the synthesis of 1,2,3,5,9-cyclodecapentaen-7-yne (**1**), a monocyclic structure similar to both **3** and **5**. This novel cumulene system contains the essential structural features of reactivity of both **3** and **5**, but is nonetheless quite different in that a symmetric resonance delocalized structure can be drawn for it. The classical Kekulé structure for **1** is unsatisfactory since it does not show the symmetric nature of the molecule.

1

A framework molecular model of **1** shows the compound to be planar and to have very little bond or angle strain. This is significant since the 10 π electron containing compound would then fulfill the requirements for aromaticity under Hückel's rule. This interesting possibility has been the motivation behind various unsuccessful attempts to the synthesize **1** and closely related 10-membered rings.[5,6] The parent [10]-annulene **7** is not aromatic since the strong steric interaction of the hydrogen atoms on the inside of the ring force the molecule out of planarity. This problem is not encountered in compound **1**. On the other hand, the in-plane π electrons of **1** may interact, perhaps facilitating the formation of the biradical intermediate **8** analogous to that of **4** and **6**.



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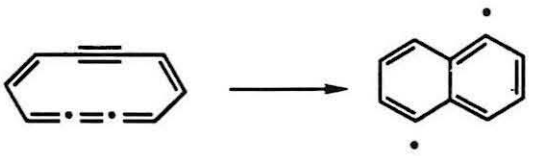
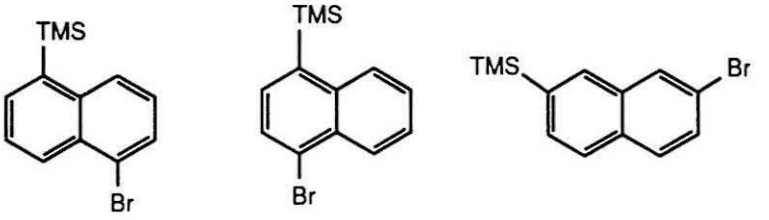


1 8

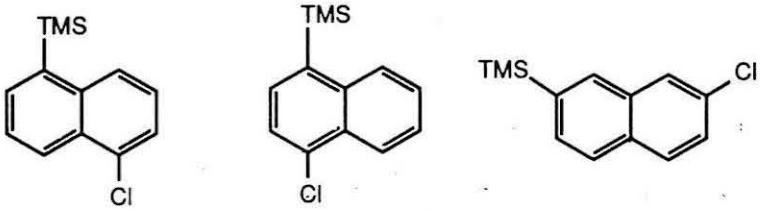
A successful synthesis of **1** would not only solve a synthetic problem that has been in the literature for over 40 years, it would also be of great theoretical interest. A successful synthesis of **1** would allow physical studies of this unusual molecule and perhaps bring new understanding to the current theories of aromaticity. The similarity of compound **1** to **3** and **5** and its hypothetical cyclization to the reactive biradical intermediate **8** would make it an interesting compound for further studies in biradical formation.

In related, collaborative studies with the Squires lab, a series of naphthalene derivatives (Figure 1) were synthesized to be used as gas-phase precursors to the respective naphthalene biradicals.[7] In particular, 1-chloro-5-trimethylsilylnaphthalene was synthesized as a precursor to 1,5-dehydronaphthalene (**8**), a potential product from the thermal cyclization of **1.** These gas-phase studies may provide reliable, and otherwise elusive, thermodynamic data for each respective biradical.

Figure 1



9 10 11

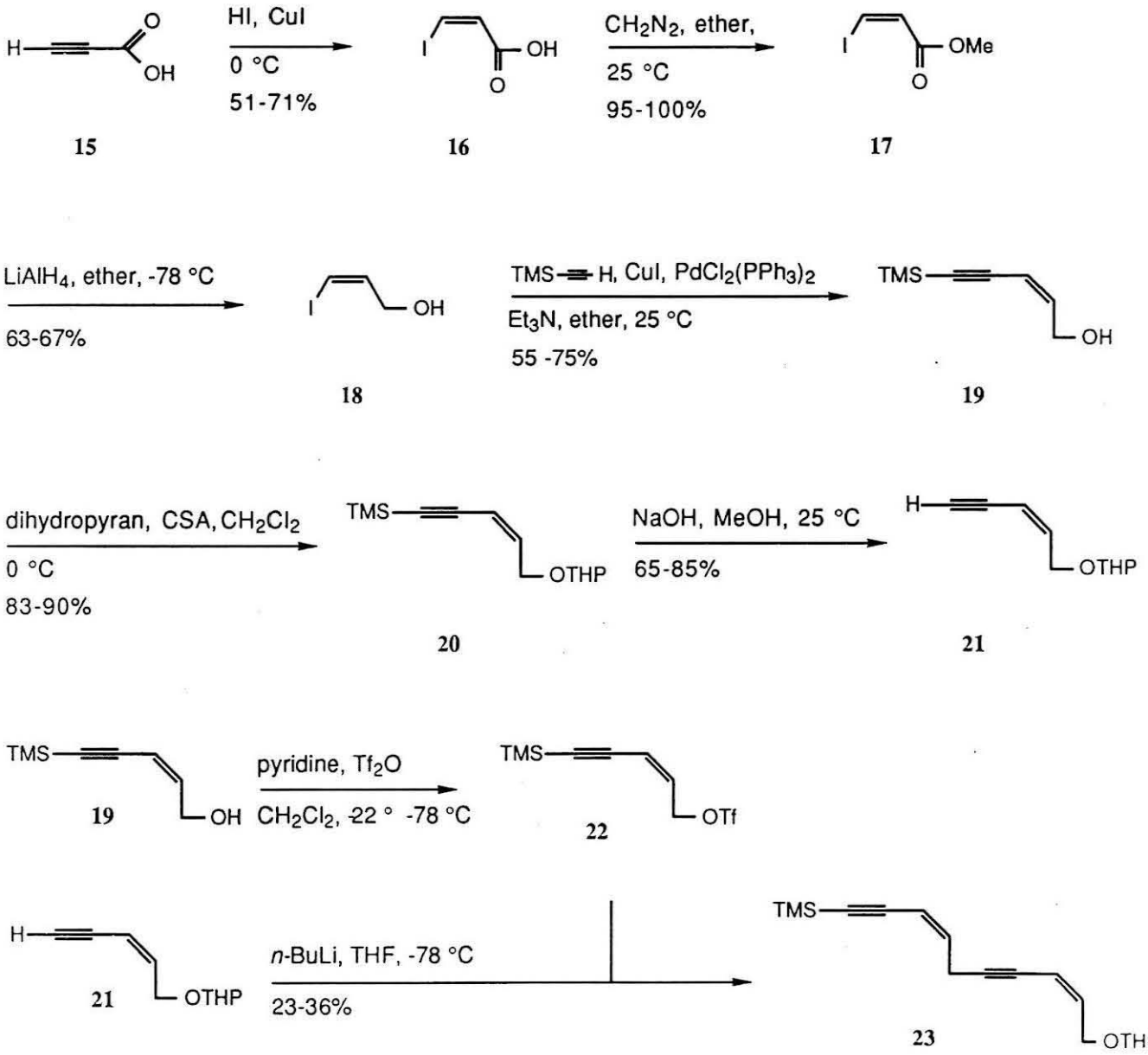


12 13 14

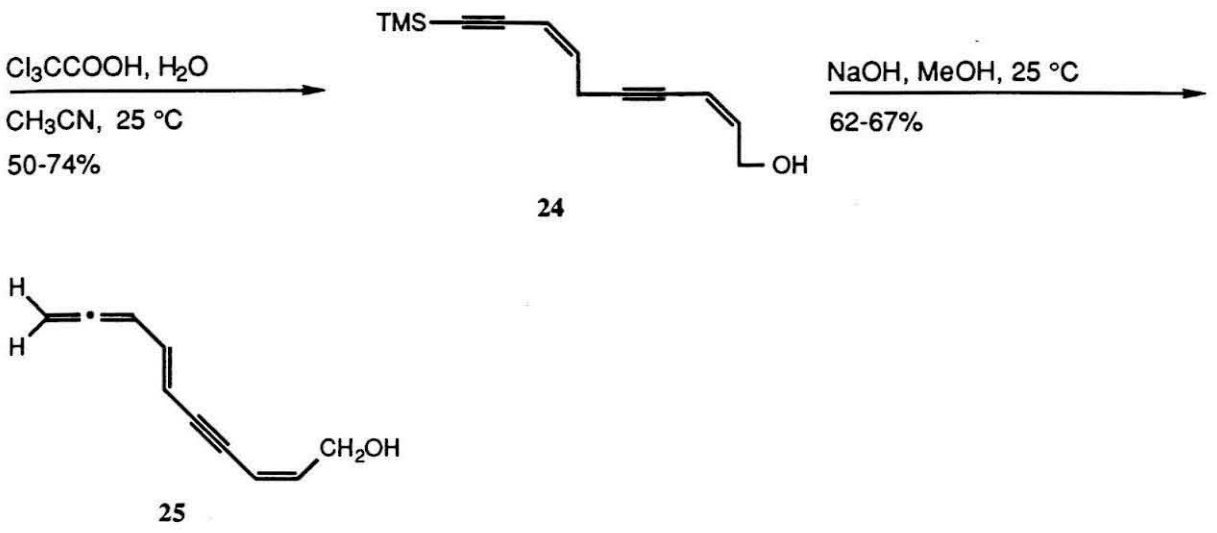
Discussion

The alcohol **24**, envisioned to serve as a synthetic precursor to the hydrocarbon **1**, was synthesized by the convergent multistep route outlined in Scheme IV and discussed in the following pages. This synthesis featured the use of the same starting material, propiolic acid, and a common synthetic route to the two fragments **19** and **21**.

Scheme IV



Scheme IV (cont.)



The alcohol **18** was synthesized from propiolic acid (**15**) by a slight modification of the procedure of Moss et al.[8] Treatment of **15** with CuI and HI formed the acid **16**. A small amount of *trans* product was produced, but it was easily removed by recrystallization. Diazomethane was used for methylation of the acid **16** (Moss et al. used methanol-sulfuric acid). Reduction of the ester **17** with lithium aluminum hydride gave the alcohol **18**. Small amounts of *trans* isomer were produced (less than 5% by NMR) by this procedure, but were not removed until the next step.

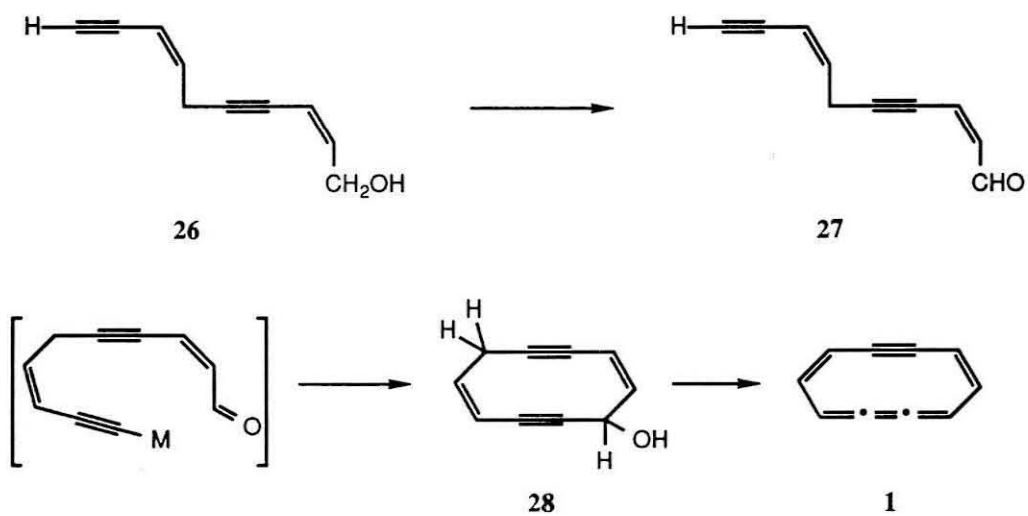
The alcohol **19** was prepared by coupling **18** and (trimethylsilyl)acetylene using CuI, Et_3N, and Pd catalyst. Flash chromatography was used to separate the *cis* and *trans* isomers of **19**. The pure *cis* isomer of **19** was then converted to the tetrahydropyranyl ether **20** by treatment with dihydropyran and catalytic amounts of camphorsulfonic acid. Treatment of **20** with NaOH afforded **21**.

The triflate **22** was prepared by the procedure of Vedejs.[9] The best yields were obtained when **22** was filtered, and stored in crude form at -78 °C under inert atmosphere immediately before the subsequent coupling reaction; no attempt was made to purify **22**. The coupled product **23** was synthesized by a nucleophilic displacement of the triflate **22** by the lithium acetylide derived from **21**. Purification of **23** by chromatography was complicated by the similarity in polarity of the starting material **21** and the desired product **23**. Improved yields were obtained by using the impure **23** for the next step. Deprotection of **23** with trichloroacetic acid gave the alcohol **24**. The deprotection of **24**, which was briefly explored with NaOH, not only removed

the trimethylsilyl group, but unfortunately isomerized the expected terminal acetylene **26** to give the allene **25**. Evidence for the formation of **25** was seen in the IR and NMR spectra (IR absorption of 1930 cm^{-1} corresponding to the C=C=C stretch, and J = 6.6 Hz for the CH_2=C=CH coupling).

This isomerization, rationalized to be caused by deprotonation of the relatively acidic methylene protons under the basic conditions, may be avoided by use of more acidic approaches to remove the trimethylsilyl group. Many alternatives are available, such as treatment with HF•Et_3N or KF, and future studies would have to explore the options for the deprotection of **24** to avoid the presumed deprotonation and subsequent isomerization to the allene **25** that is experienced with NaOH. Once the deprotection is achieved, **26** could be oxidized to the aldehyde **27**, which is expected to allow closure to the 10-membered ring by an intramolecular acetylide-aldehyde addition of **27**. Elimination of water from the resulting alcohol **28** is then projected to form the target compound **1** (Scheme V).

Scheme V



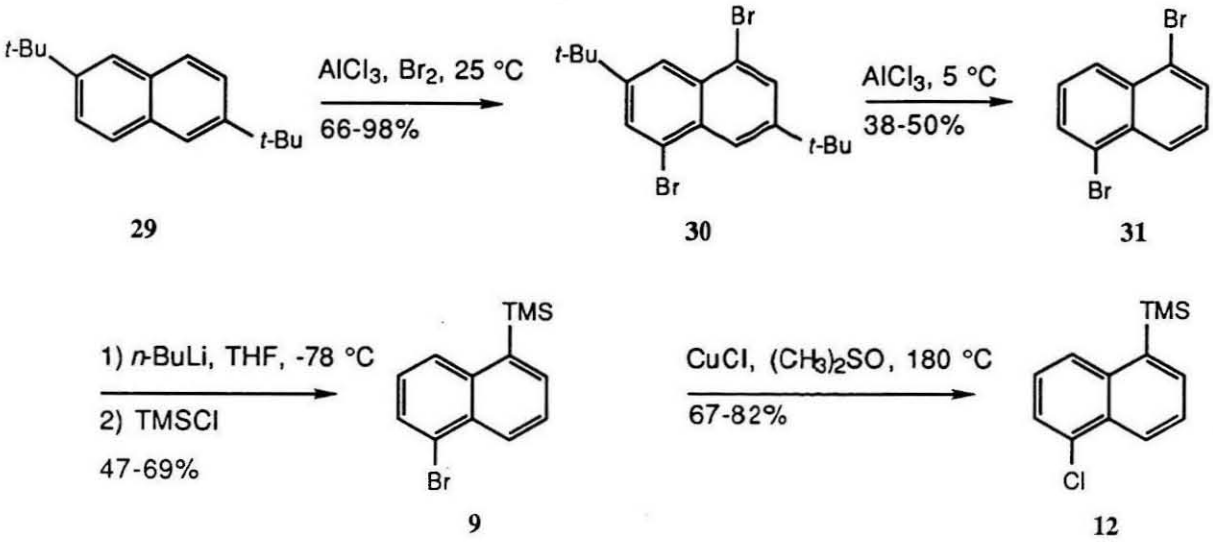
26 **27** **28** **1**

Naphthalene Derivatives

The synthesis of the naphthalene derivatives is outlined in Scheme VI:

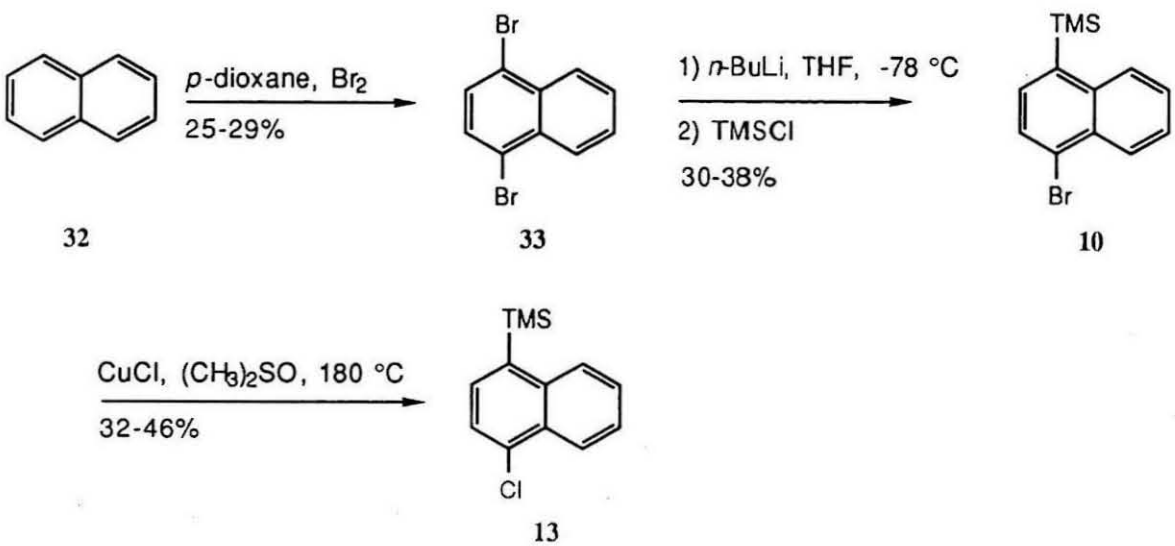
Scheme VI

1,5 series



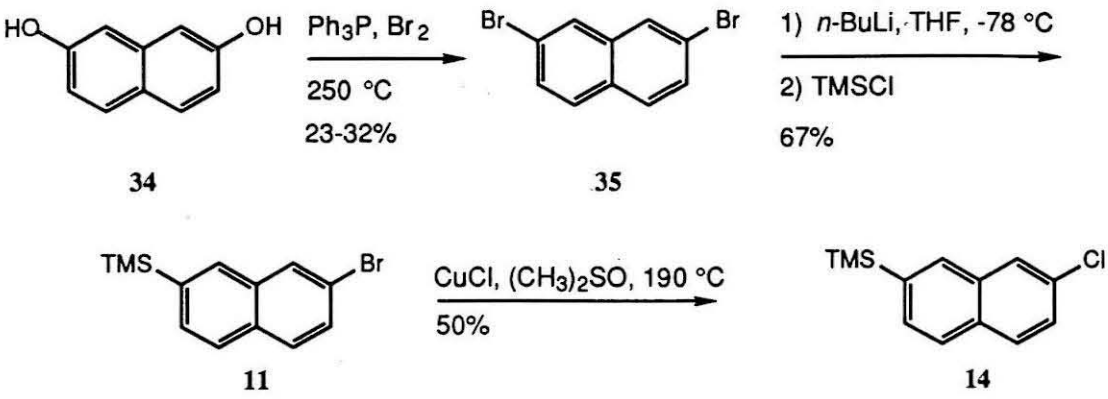
29 30 31 9 12

1,4 series



32 33 10 13

2,7 series



The individual dibromonaphthalene compounds were synthesized as follows: 1,5-dibromonaphthalene was synthesized from 2,6-di-*t*-butyl-naphthalene by a literature procedure;[10] 1,4-dibromonaphthalene was synthesized from naphthalene by treatment with *p*-dioxane and bromine;[11] and 2,7 dibromonaphthalene was synthesized from 2,7-dihydroxynaphthalene by treatment with triphenylphosphine and bromine in analogy to a procedure for the preparation of 2-bromonaphthalene.[12] Each dibromonaphthalene was purified by recrystallization. Flash chromatography (using petroleum ether as eluent) was sometimes used for small scale experiments and found to be much more efficient than recrystallization.

The bromotrimethylsilylnaphthalene derivatives were then obtained from the selective metallation of each dibromide by treatment with *n*-BuLi in THF and subsequent addition of trimethylsilylchloride at -78 °C.[13] The purification of each bromotrimethylsilylnaphthalene derivative was achieved by careful chromatography. Petroleum ether as eluent afforded the best separation. Recrystallization was also required when working with larger amounts of compound (>100 mg). The conversion of the bromide to the chloride was then achieved by refluxing each bromotrimethylsilylnaphthalene derivative with CuCl in DMSO.[14] Purification of the chlorotrimethylsilylnaphthalene derivatives required a combination of chromatography and recrystallization.

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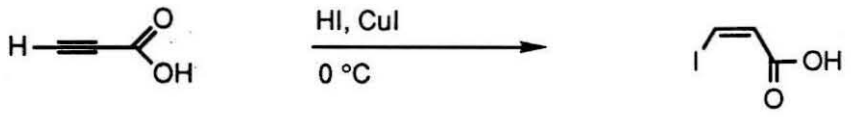
Experimental Section:

NMR spectra were recorded on JEOL JNM-GX400, Bruker AM-500, or GE QE Plus (300 MHz) instruments. Chemical shifts for proton spectra were reported as δ in units of parts per million (ppm) relative to residual chloroform (@ 7.26) or residual benzene (@ 7.15) serving as internal reference. Chemical shifts for carbon-13 spectra were reported as δ in units of parts per million (ppm) relative to deuteriochloroform (77.0) as internal reference. Multiplicities were reported as follows: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet), dd (doublet of doublets), dt (doublet of triplets). FTIR spectra were recorded on a Perkin-Elmer 1600 Series FTIR instrument. Intensity of IR peaks were abbreviated as follows: vw = very weak, w = weak, m = medium, s = strong, vs = very strong, br = broad. Mass spectra (MS) and high-resolution mass spectra were obtained from the UC Riverside mass spectroscopy facility. Spectra were reported in units of mass to charge (m/e). Melting points were determined on a Büchi apparatus and are uncorrected.

Analytical and preparative thin layer chromatography were performed on Merck pre-coated silica gel 60 F-254 plates (25 mm, glass-backed) and Aldrich pre-coated silica gel 60 Å, (250 μm, glassbacked, fluorescent at 254 nm), Merck Silica Gel 60 (230-400 mesh ASTM), and JT Baker Silica Gel 40 μm. Extrations and chromatography employed HPLC grade ethyl acetate and hexanes, used as received.

Tetrahydrofuran and ethyl ether were distilled from sodium and benzophenone. Benzene was distilled from sodium. Dimethylsulfoxide, acetonitrile, trimethylsilylchloride, triethylamine, and methylene chloride were distilled from calcium hydride. Cuprous chloride was purified by recrystallization from 6 M HCl. Triflic anhydride was prepared by distillation of triflic acid from phosphorus pentoxide. (Trimethylsilyl)acetylene (Farchan labs) was stored over molecular sieves (4 Å) prior to use. Diazomethane was distilled as an ethereal solution from Diazald® and potassium hydroxide. Dihydropyran (Aldrich) was stored over molecular sieves (4 Å) prior to use. All other reagents were used as received. All reactions were carried out at room temperature unless otherwise specified.

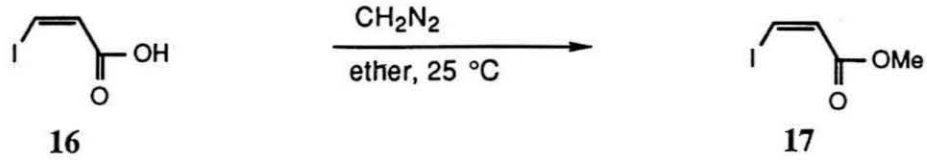


15 **16**

(Z)-3-Iodopropenoic Acid **16**

Cuprous iodide (7.00 g, 0.037 mol, 0.19 eq) and 48% HI (38 mL, 57 g, 0.446 mol, 1.13 eq) were placed in a 250-mL round-bottom flask and stirred. The brownish suspension was cooled to 0 °C and **15** (13.3 g, 0.190 mol, 1 eq.) was added dropwise over twenty minutes. The mixture was stirred for 4.5 h and was then allowed to crystallize at -20 °C overnight. A tan precipitate was collected by filtration, triturated with approximately 200 mL of chloroform, and filtered to remove the copper residue. This was washed with 15-mL portions of water, 1 M sodium thiosulfate, and water. The resulting yellow solution was dried over sodium sulfate and concentrated under vacuum to give a yellow solid. The crude product was recrystallized from hot hexane to yield 26.77 g (71%) of pale yellow crystals.

^{1}H NMR (400 MHz, $CDCl_3$):	11.3 (br s, 1H, OH), 7.69 (d, 1H, J = 8.4 Hz, vinyl), 6.99 (d, 1H, J = 8.4 Hz, vinyl).
FTIR (neat film, cm^{-1}):	3060 (br), 1698 (s), 1599 (s), 730 (m).
MS (EI):	198 (M^+), 181 (M^+-OH), 153 (M^+-COOH), 71 (M^+-I).
Exact Mass:	calcd: 197.9117 found: 197.9172
TLC (100% EtOAc):	R_f = 0.11



16 **17**

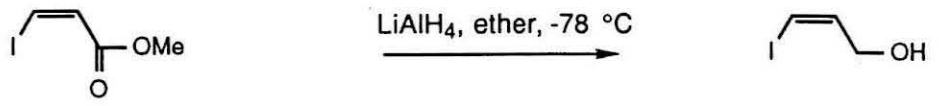
Methyl-(Z)-3-iodopropenoate **17**

The acid **16** (13.85 g, 0.0700 mol, 1 eq) was placed in a 125-mL erlenmeyer flask, dissolved in approximately 40 mL of dry ether, and cooled to 0 °C with stirring. Diazomethane in ether solution (1 M) was added dropwise to the starting material via a fire-polished glass pipette. The addition was continued until gas evolution stopped and TLC monitoring showed that all starting material was consumed. The solution was then concentrated under vacuum to give a yellow oil (14.56 g, 98%). The product was used without further purification in the next experiment.

^{1}H NMR (500 MHz, $CDCl_3$): 7.47 (d, 1H, J = 9.0 Hz, vinyl), 6.91 (d, 1H, J = 9.0 Hz, vinyl), 3.78 (s, 3H, OCH_3).

FTIR (neat film, cm^{-1}): 3062 (m), 2950 (m), 1726 (s), 1598 (s), 1204 (s), 1164 (s).

TLC (30% EtOAc-hexanes): R_f = 0.75

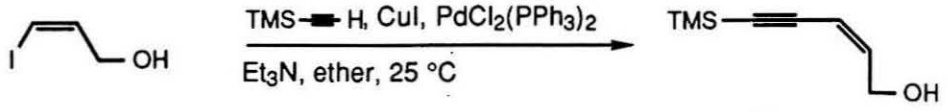


17 **18**

(Z)-3-Iodopropenol **18**

A 100-mL flask was flame-dried under vacuum and then flushed with argon. Dry ether (30 mL) was added and the solution was cooled to -78 °C. Lithium aluminum hydride (0.81 g, 0.021 mol, 0.75 eq) was added portionwise and the suspension was stirred. A solution of **17** (4.70 g, 0.028 mol, 1.0 eq) in 15 mL of dry ether was added dropwise to the supension over 30 minutes with vigorous stirring. The solution was then allowed to warm to room temperature. After 0.75 h the excess lithium aluminum hydride was carefully quenched with water, poured into approximately 30 mL of cold 3 M sulfuric acid, and stirred for five minutes to give a greenish mixture. The layers were separated and the aqueous layer was extracted with five portions of ether. The combined ether extracts were washed with one portion of saturated sodium carbonate, one portion of 1 M sodium thiosulfate, and one portion of saturated sodium chloride solution. The combined organic layers were dried over sodium sulfate and concentrated under vacuum to give 3.78 g of an orange liquid. Purification by flash chromatography on silica gel (10-15% EtOAc-hexane) afforded 3.46 g (67%) of yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$):	6.50 (dt, 1H, J = 7.6, 5.9 Hz, vinyl), 6.40 (dt, 1H, J = 1.5, 7.6 Hz, vinyl), 4.25 (dt, 2H, J = 1.5, 5.9 Hz, allylic), 1.70 (br, 1H, OH).
FTIR (neat film, cm^{-1}):	3316 (br s), 3068 (w), 2870 (w), 1608 (s), 1279 (s).
MS (EI):	184 (M^+), 167 (M^+-OH), 57 (M^+-I).
Exact Mass:	calcd: 183.9385 found: 183.9379
TLC (30% EtOAc-hexanes):	R_f = 0.37



18 **19**

5-Trimethylsilyl-(Z)-2-penten-4-ynol **19**

The starting material **18** (3.46 g, 0.019 mol, 1 eq) was placed in flame-dried flask and dissolved in approximately 50 mL of dry ether. Bis(triphenylphosphine)palladium(II) chloride (1.32 g, 1.9 mmol, 0.1 eq) was added and the mixture was stirred at 0 °C. The reaction vessel was evacuated and flushed with argon several times. Cuprous iodide (36 g, 1.9 mmol, 0.1 eq) and 10 mL of dry ether were placed in another flask. This reaction vessel was evacuated and flushed with argon several times and treated with 20 mL of triethylamine. The vessel was then evacuated and flushed with argon several times again. The suspension was then treated with (trimethylsilyl)acetylene (2.9 mL, 0.021 mol, 1.1 eq) causing a cloudy white suspension to be formed which subsequently became slightly yellow and then slightly green. This suspension was transferred by cannula into the starting material solution which subsequently turned brownish and then dark green within the first five minutes of the reaction. After a few more minutes the color reverted to a pale brown color. After 3.5 h the mixture was poured into a solution of 75 mL of saturated potassium carbonate and 75 mL of saturated ammonium chloride, and was stirred vigorously for one hour. The aqueous phase became deep blue. The layers were separated and the aqueous layer was extracted with five portions of ether. The combined organic layers were then washed with two portions of saturated sodium chloride solution and dried over sodium sulfate. Concentration under vacuum and purification by flash chromatography (10% EtOAc-hexanes) yielded 2.22 g (75%) of yellow oil.

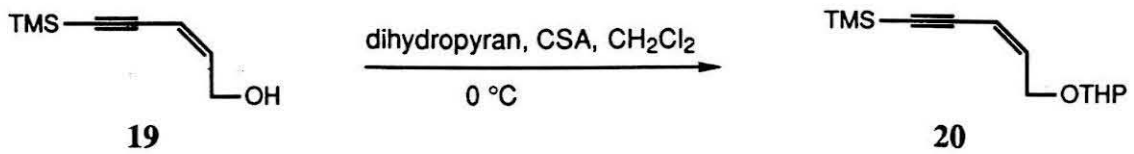
^{1}H NMR (400 MHz, $CDCl_3$): 6.10 (dt, 1H, J = 6.4, 11.0 Hz, H2), 5.61 (d, 1H, J = 11.0 Hz, H3), 4.42 (d, 2H, J = 6.4 Hz, H1), 1.70 (br, 1H, OH), 0.20 (s, 9H, TMS).

FTIR (neat film, cm^{-1}): 3346 (br m), 2922 (s), 2851 (m), 1250 (m), 844 (s).

MS (CI NH_3): 172 ($M+NH_4^+$), 155 (MH^+), 139 (M^+-OH).

Exact Mass: calcd: 155.0892 found: 155.0893

TLC (30% EtOAc-hexanes): $R_f = 0.49$



19 **20**

Tetrahydropyranyl Ether **20**

The starting material **19** (1.745 g, 11.3 mmol, 1 eq) was placed in a flamed-dried flask, dissolved in approximately 10 mL of dry methylene chloride, and cooled to 0 °C. Dihydropyran (1.55 mL, 17 mol, 1.5 eq) and 0.130 g of CSA were added. The solution was stirred for 1.5 h, poured into 50 mL of water, and extracted with three portions of 1:1 EtOAc-hexanes. The combined organic layers were washed with two portions of saturated sodium bicarbonate and one portion of saturated sodium chloride. The solution was dried over sodium sulfate, concentrated under vacuum, and purified by flash chromatography (5-10% EtOAc-hexanes) to give a yellow oil (2.42 g, 90%).

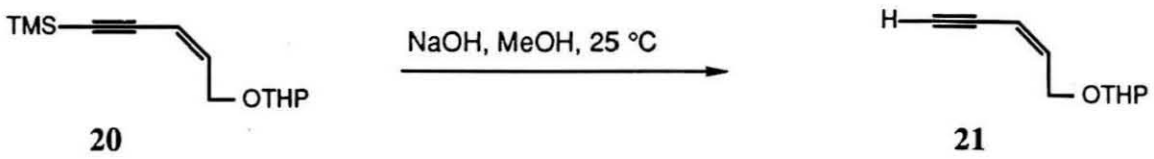
^{1}H NMR (400 MHz, $CDCl_3$): 6.10 (dt, 1H, J = 11.0, 6.8 Hz, H2), 5.63 (d, 1H, J = 11.0 Hz, H3), 4.66 (t, 1H, J = 3.4 Hz, OCH(C)O), 4.46 (q, 1H, J = 6.8, 13.2 Hz, H1), 4.32 (q, 1H, J = 6.8, 13.2 Hz, H1), 3.90 (m, 1H, THP), 3.53 (m, 1H, THP), 1.56-1.82 (m, 6H, THP), 0.19 (s, 9H, TMS).

FTIR (neat film, cm^{-1}): 3032 (w), 2955 (s), 1250 (s), 1201 (s), 1120 (s), 844 (s), 760 (s).

MS (DCI, NH_3): 256 ($M+NH_4^+$), 239 (MH^+).

Exact Mass [$M+NH_4^+$]: calcd: 256.1732 found: 256.1735

TLC (30% EtOAc-hexanes) R_f = 0.8



20 **21**

Tetrahydropyranyl Ether **21**

To a solution of starting material **20** (0.337 g, 1.41 mmol, 1 eq) dissolved in MeOH (approx. 10 mL) was added 6 drops of 50% NaOH. The solution was stirred for 1.5 h and then diluted with water and extracted with three portions of ether. The combined organic layers were then washed with three portions of saturated sodium chloride solution, dried over sodium sulfate and concentrated under vacuum. Purification by flash chromatography (5-10% EtOAc-hexanes) gave a colorless oil (0.197 g, 84%).

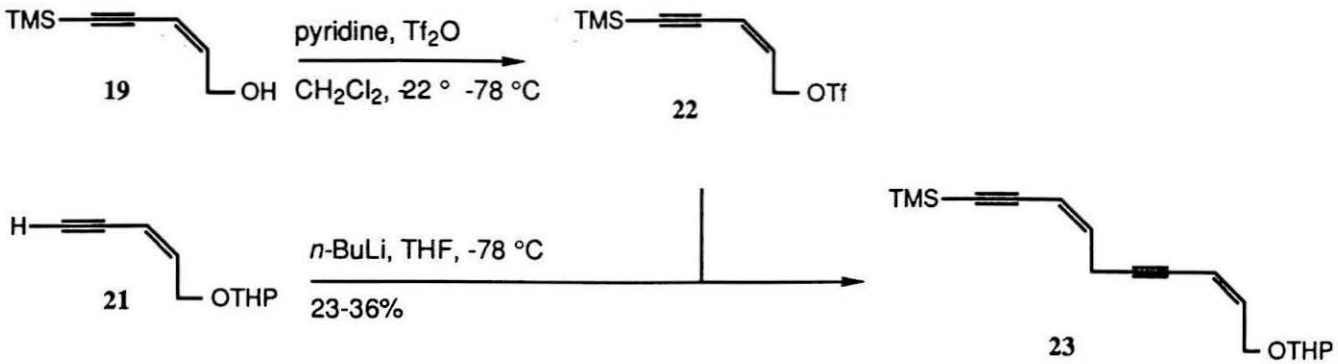
^{1}H NMR (400 MHz, $CDCl_3$): 6.15 (dt, 1H, J = 11.0, 5.8 Hz, H2), 5.58 (dd, 1H, J = 11.0, 2.3 Hz, H3), 4.64 (t, 1H, J = 11.0 Hz, chiral H), 4.42-4.49 (m, 1H, J = 5.8, 12.9Hz, H1), 4.27-4.34 (m, 1H, J = 5.8, 12.9Hz, H1), 3.83-3.91 (m, 1H, THP), 3.48-3.55 (m, 1H, THP), 3.15 (d, 1H, J = 2.3 Hz, H5), 1.49-1.86 (m, 6H, THP).

FTIR (neat film, cm^{-1}): 3289 (m), 2942 (s), 2870 (m), 1441 (w), 1386 (w), 1201 (m), 1120 (s), 1032 (s).

MS (DCI NH_3): 184 ($M+NH_4^+$), 167 (MH^+).

Exact Mass: calcd: 184.1337 found: 184.1345

TLC (30% EtOAc-hexanes): R_f = 0.69



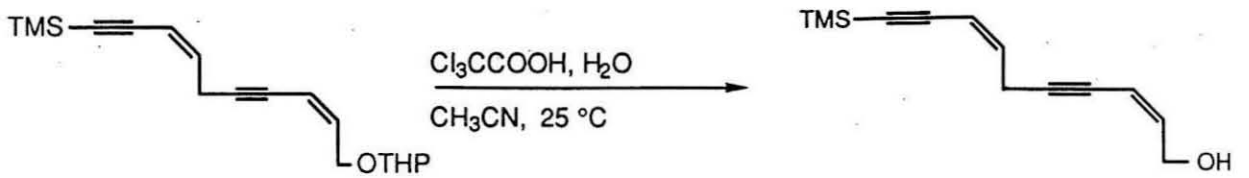
Coupled Acetylenic Product **23**

A reaction flask was flame-dried under vacuum and filled with argon. Dry methylene chloride (3 mL) was added and cooled to -22 °C. Pyridine (0.052 mL, 0.65 mmol, 1.1 eq) and triflic anhydride (0.109 mL, 0.65 mmol, 1.1 eq) were added sequentially. A white precipitate was formed and the solution became slightly colored with a pink hue. The solution was further cooled to -40 °C. Starting material **19** (0.100 mL, 0.59 mmol, 1 eq) and, after 0.5 h, 3 mL of dry hexane was added, causing further precipitation. The solution was cooled to -78 °C and then quickly filtered cold through sintered glass under inert atmosphere. The filtered precipitate became dark purple on standing. The filtrate was slightly brownish in color. This solution was kept at -78 °C until used as described below.

In another flame-dried reaction flask the starting material **21** (0.132 g, 0.79 mmol, 1.3 eq) was added, cooled to -78 °C, and dissolved with 5 mL of dry THF. *n*-BuLi (0.5 mL, 1.6 M in hexanes, 0.79 mmol, 1.3 eq) was slowly added and the solution turned slightly orange in color. After 1 h the triflate **22** solution was introduced by cannula. The color of the solution immediately darkened to an orange color. The mixture was stirred for 0.5 h and then poured into 60 mL of water. The aqueous layer was extracted with three portions of 1:1 EtOAc-hexanes solution. The combined organic layers were washed with one portion of saturated aqueous sodium bicarbonate solution and two portions of saturated sodium chloride solution, dried over sodium sulfate, and concentrated under vacuum. Purification by flash chromatography (8% EtOAc-hexanes) yielded 0.064 g (36%) of desired **23**.

^{1}H NMR (400 MHz, $CDCl_3$): 6.01 (dt, 1H, J = 10.7, 6.4 Hz, H2), 5.93 (dt, 1H, J = 10.7, 6.8 Hz, H7), 5.55-5.60 (2d, 2H, $J \approx$ 11 Hz, H8+H3), 4.65 (d, 1H, OCH(C)O), 4.43 (dd, 1H, J = 6.4, 12.5 Hz, CH_2O), 4.27 (dd, 1H, J = 6.4, 12.5 Hz, CH_2O), 3.89 (m, 1H, THP),

	3.52 (m, 1H, THP), 3.38 (d, 2H, J = 6.8 Hz, H6), 1.54-1.82 (m, 6H, THP), 0.20 (s, 9H, TMS).
FTIR (neat film, cm^{-1}):	2955 (s), 2152 (m), 1250 (s), 1119 (s), 844 (s).
TLC (30% EtOAc-hexanes)	R_f = 0.85



23 **24**

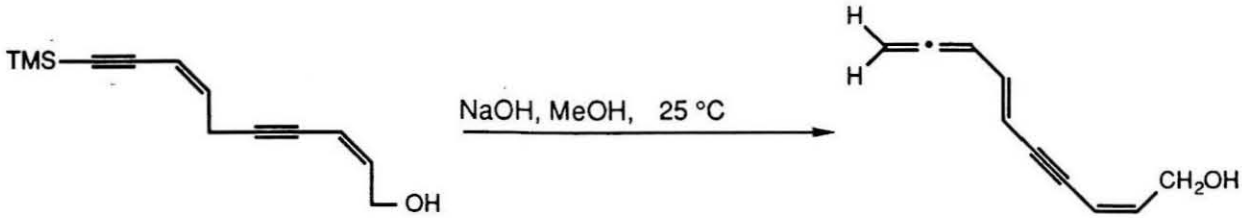
10-Trimethylsilyl-(Z,Z)-2,7-decadien-4,9-diynol **24**

The starting material **23** (36 mg, 0.119 mmol, 1 eq) was dissolved in 6 mL of acetonitrile and was treated with water (approximately 1 mL) and trichloroacetic acid (0.107 g, 0.655 mmol, 5.5 eq). The solution was stirred for 4.5 h and then poured into approximately 50 mL of water. The aqueous layer was extracted with four portions of 1:1 EtOAc-hexanes. The combined organic layers were washed with two portions of saturated sodium bicarbonate and with one portion of saturated sodium chloride solution, and dried over sodium sulfate. Concentration and purification by flash chromatography (10% EtOAc-hexanes) gave a yellow oil (20 mg, 74%).

^{1}H NMR (400 MHz, $CDCl_3$): 6.04 (dt, 1H, J = 6.1, 10.7 Hz, H2), 5.94 (dt, 1H, J = 10.7, 6.8 Hz, H7), 5.57-5.6 (2d, 2H, J = 10.7 Hz, H3+H8), 4.39 (d, 2H, J = 6.1 Hz, H1), 3.38 (d, 2H, J = 6.8 Hz, H6), 0.20 (s, 9H, TMS).

FTIR (neat film, cm^{-1}): 3332 (br), 2959 (m), 2153 (m), 1614 (w), 1250 (m), 842 (s).

TLC (30% EtOAc-hexanes): $R_f = 0.52$



24 **25**

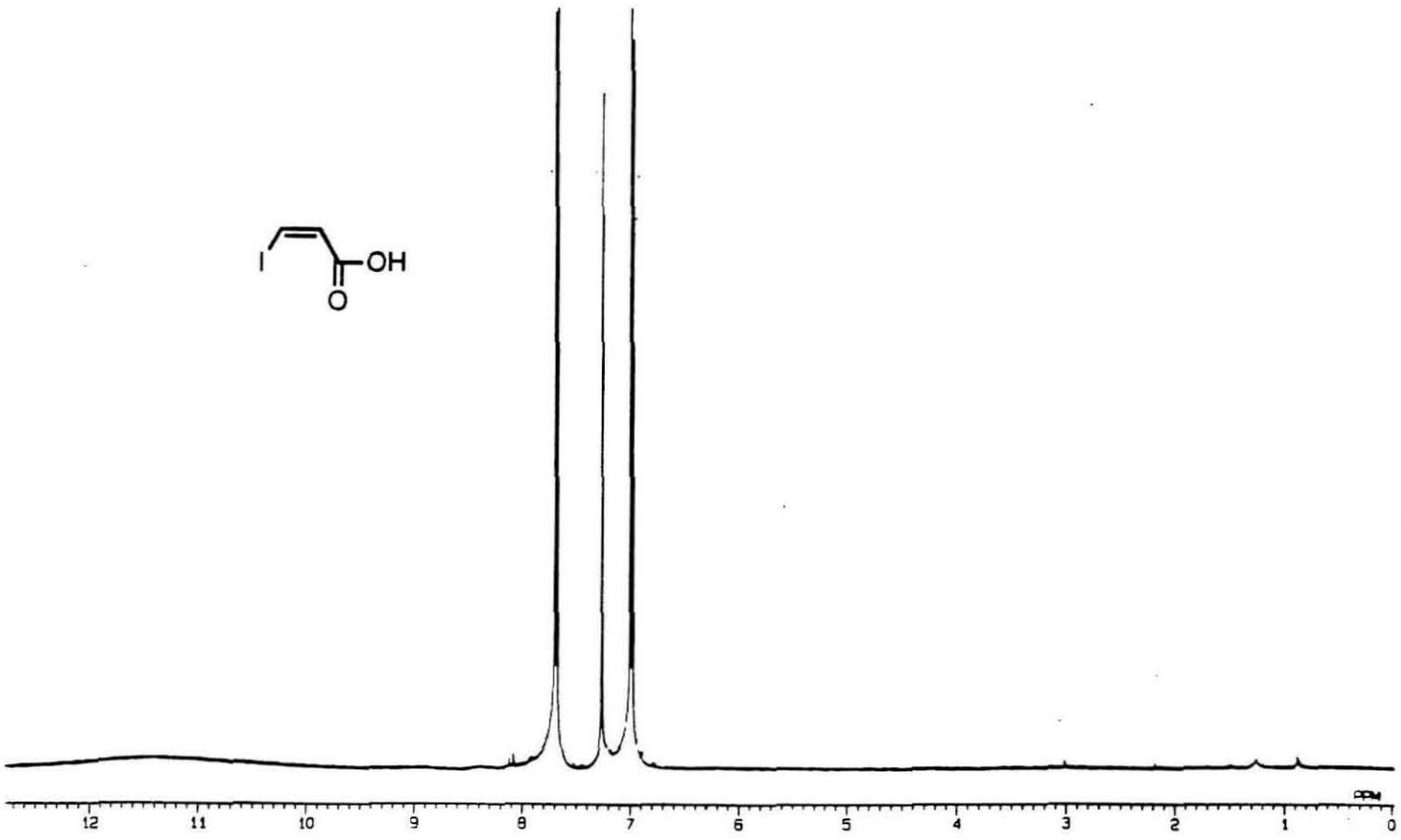
Allene **25**

A solution of starting material **24** (0.019 g, 0.082 mmol, 1 eq) in 10 mL of MeOH was treated with five drops of 10% NaOH. The reaction mixture turned bright yellow-orange within a few seconds. After ten minutes the solution became dark orange. The reaction was stirred for 1 h and then poured into 25 mL water. The solution was extracted with four portions of ether. The combined organic layers were washed with two portions of saturated sodium bicarbonate solution, one portion of saturated sodium chloride solution, dried over sodium sulfate, and concentrated under vacuum. The black tarry residue was purified by flash chromatography (10% EtOAc-hexanes) to yield a yellow oil (8 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$): 6.44 (dd, 1H, J = 10.7, 15.4 Hz, H7), 6.07 (dt, 1H, J = 6.1, 10.7 Hz, H2), 5.90 (dt, 1H, J = 6.6, 10.7 Hz, H7), 5.7 (d, 1H, J = 10.7, H3), 5.7 (d, 1H, J = 15.4, H6), 5.00 (d, 2H, J = 6.6 Hz, C=C=CH_2), 4.41 (d, 2H, J = 6.1 Hz, H1).

FTIR (neat film, cm^{-1}): 3345 (br s), 3029 (m), 2925 (m), 2177 (m), 1930 (s),1225 (m), 849 (s).

TLC (30% EtOAc-hexanes): R_f = 0.44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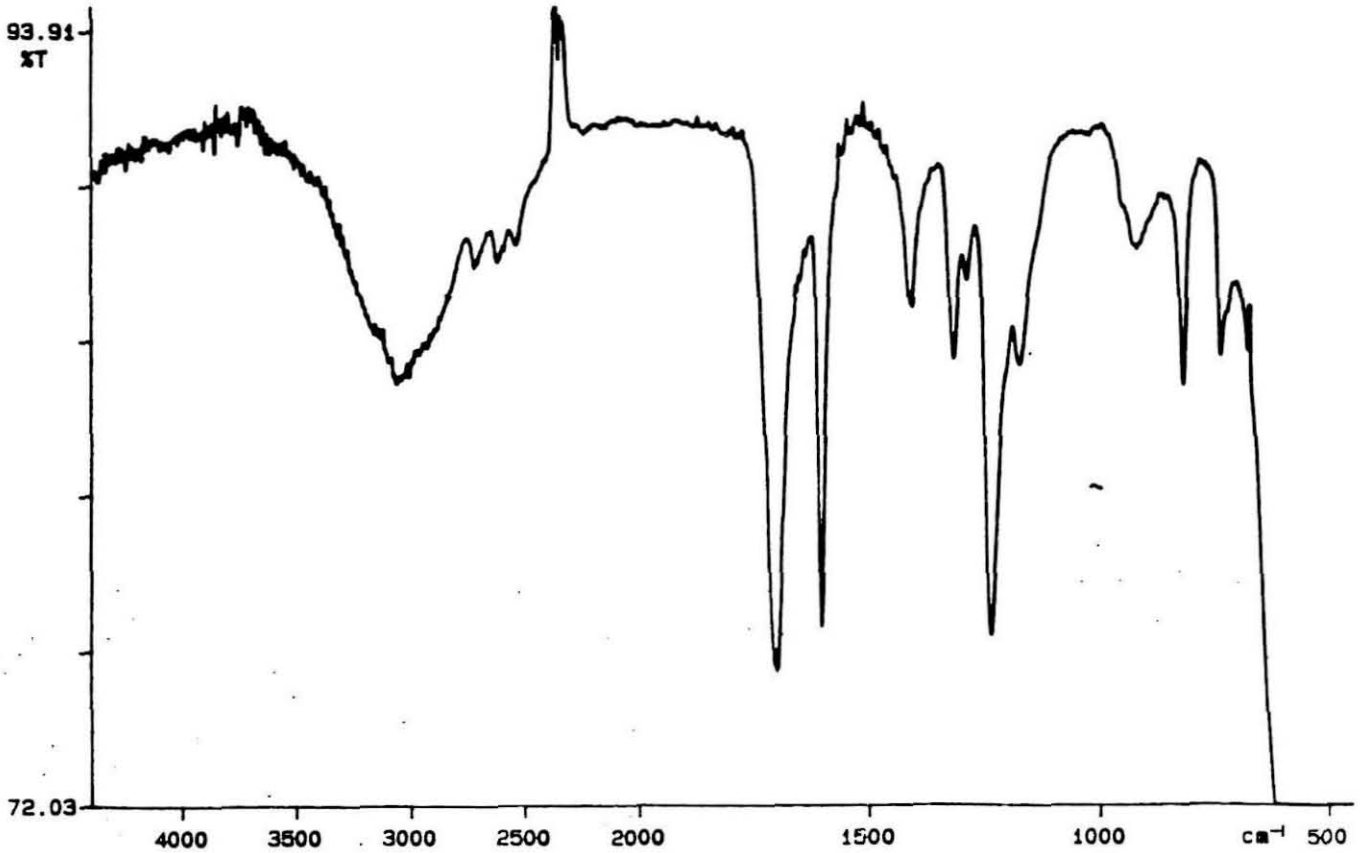
OH
O
12
11
10
9
8
7
6
5
4
3
2
1
0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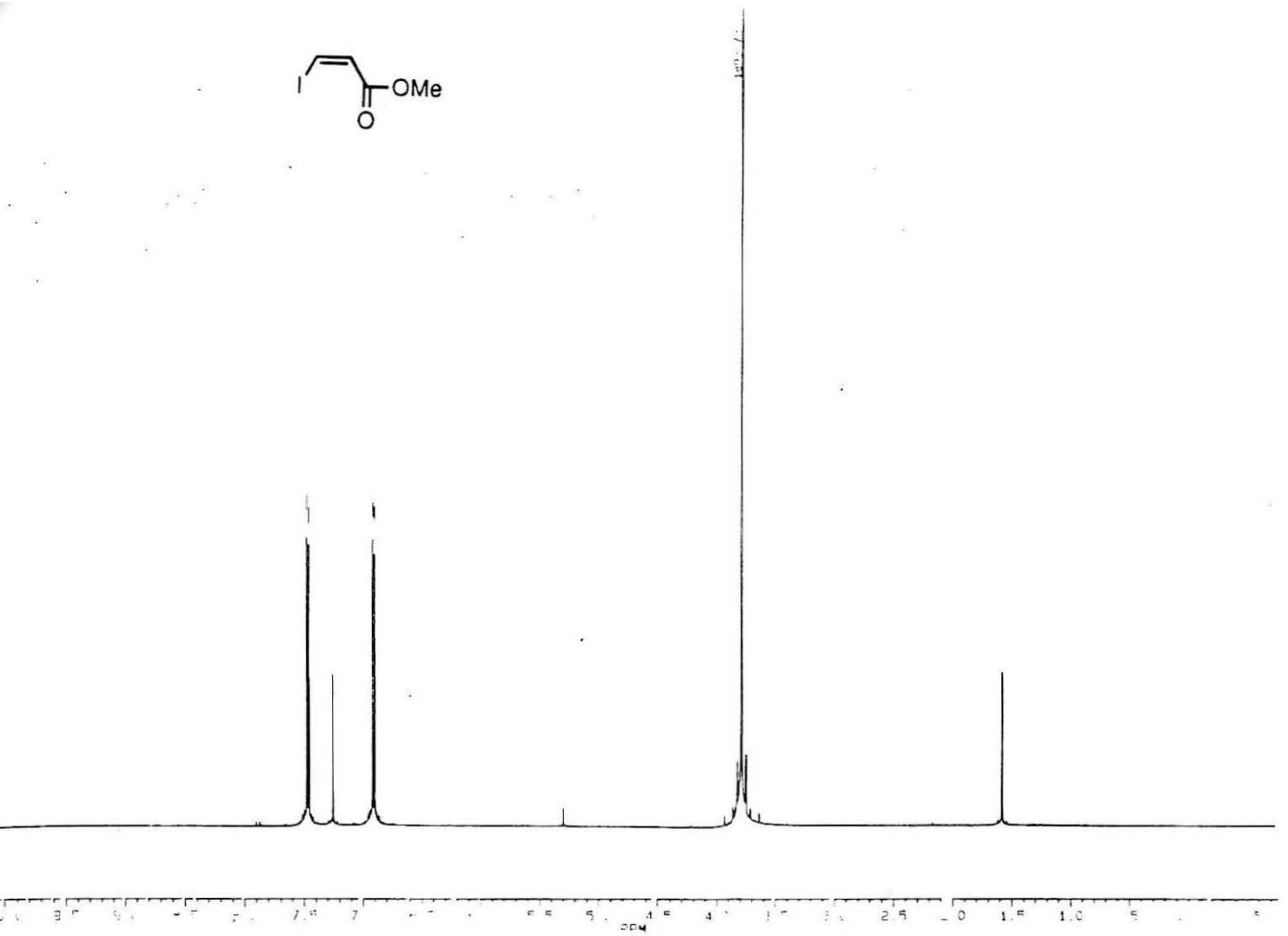
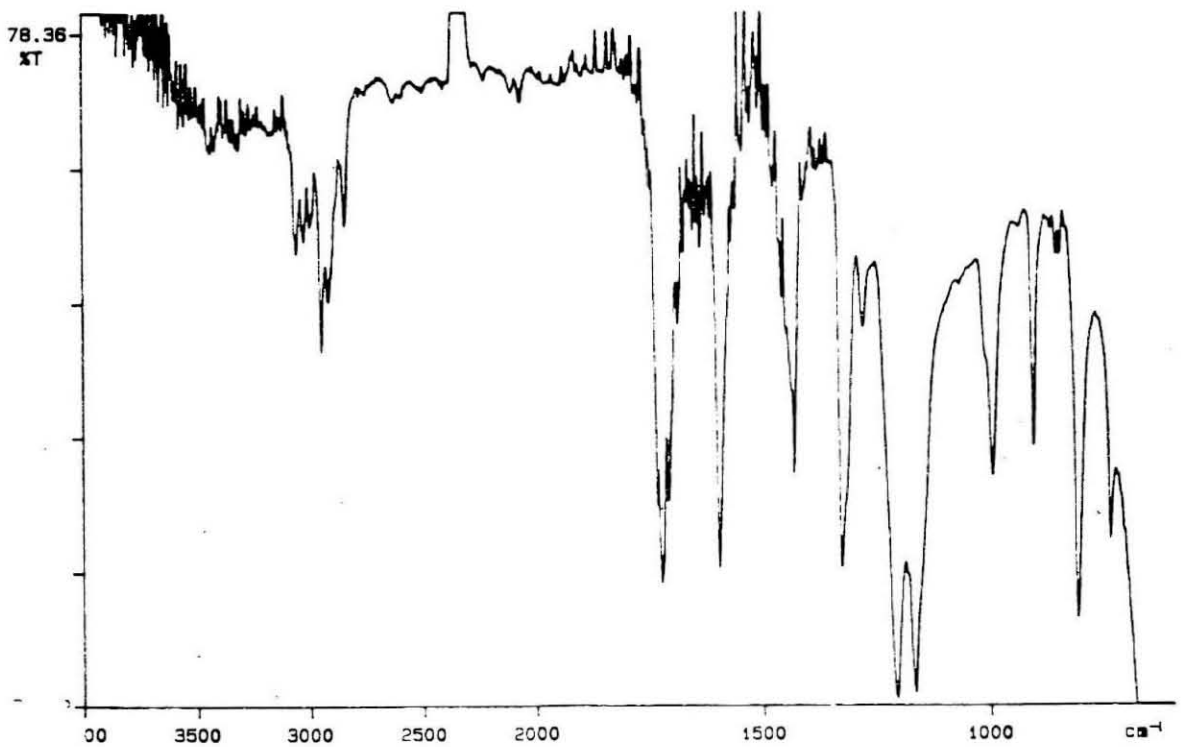
3500
3000
2500
2000
1500
1000
cm⁻¹
500


I
OMe
O
ppm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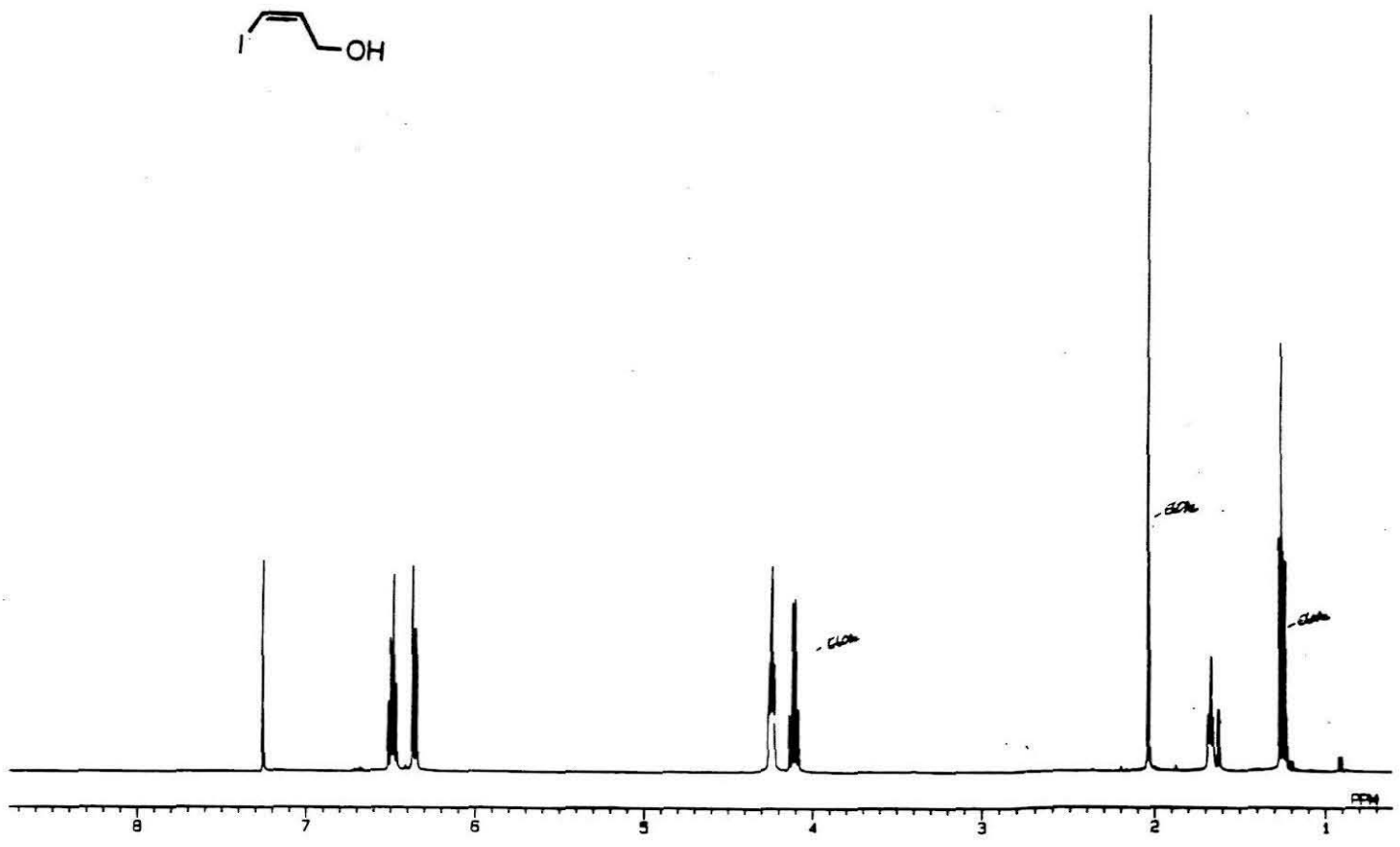
1500
1000
cm⁻¹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OH
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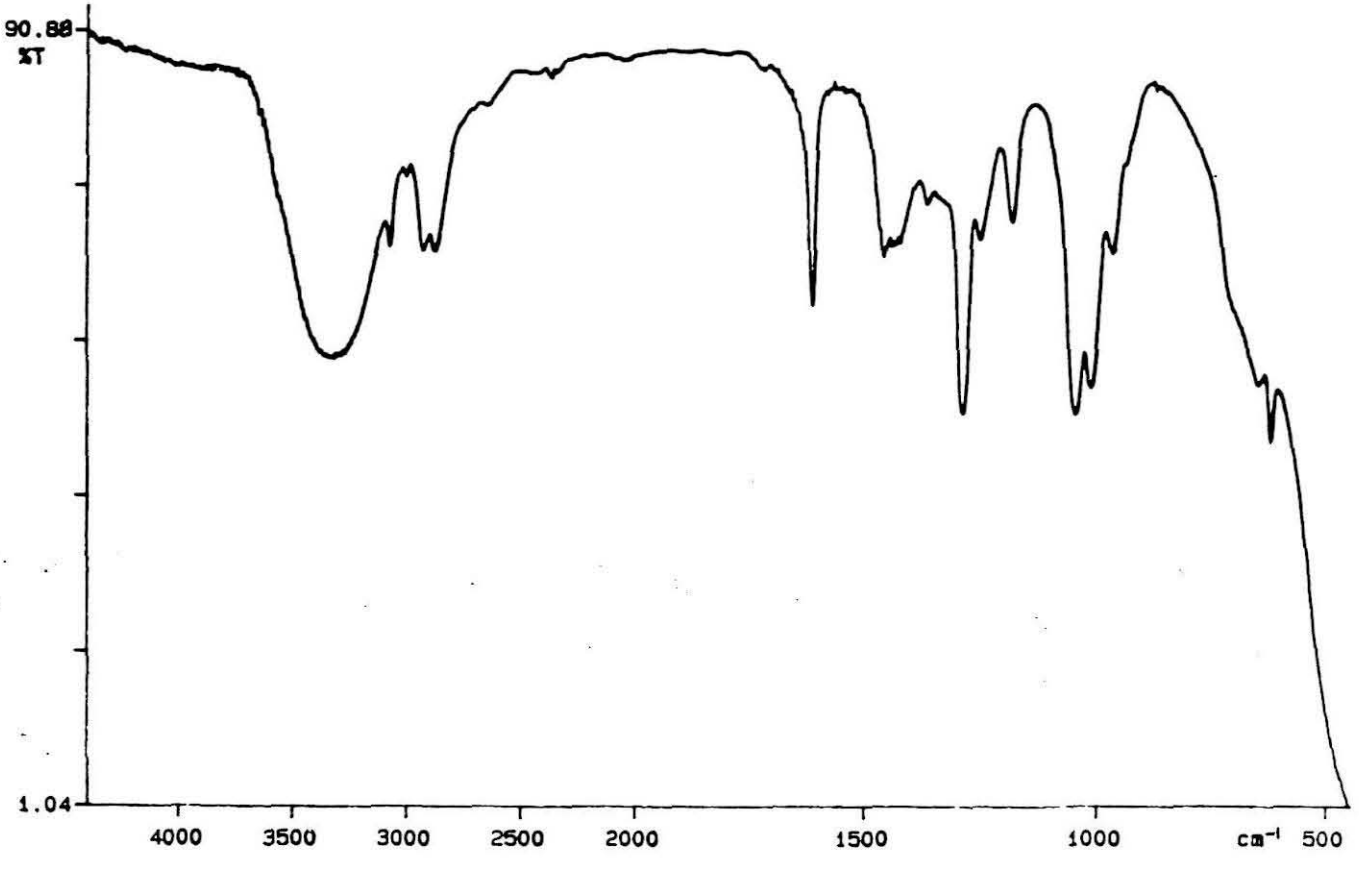
7
6
5
4
3
2
1
PPM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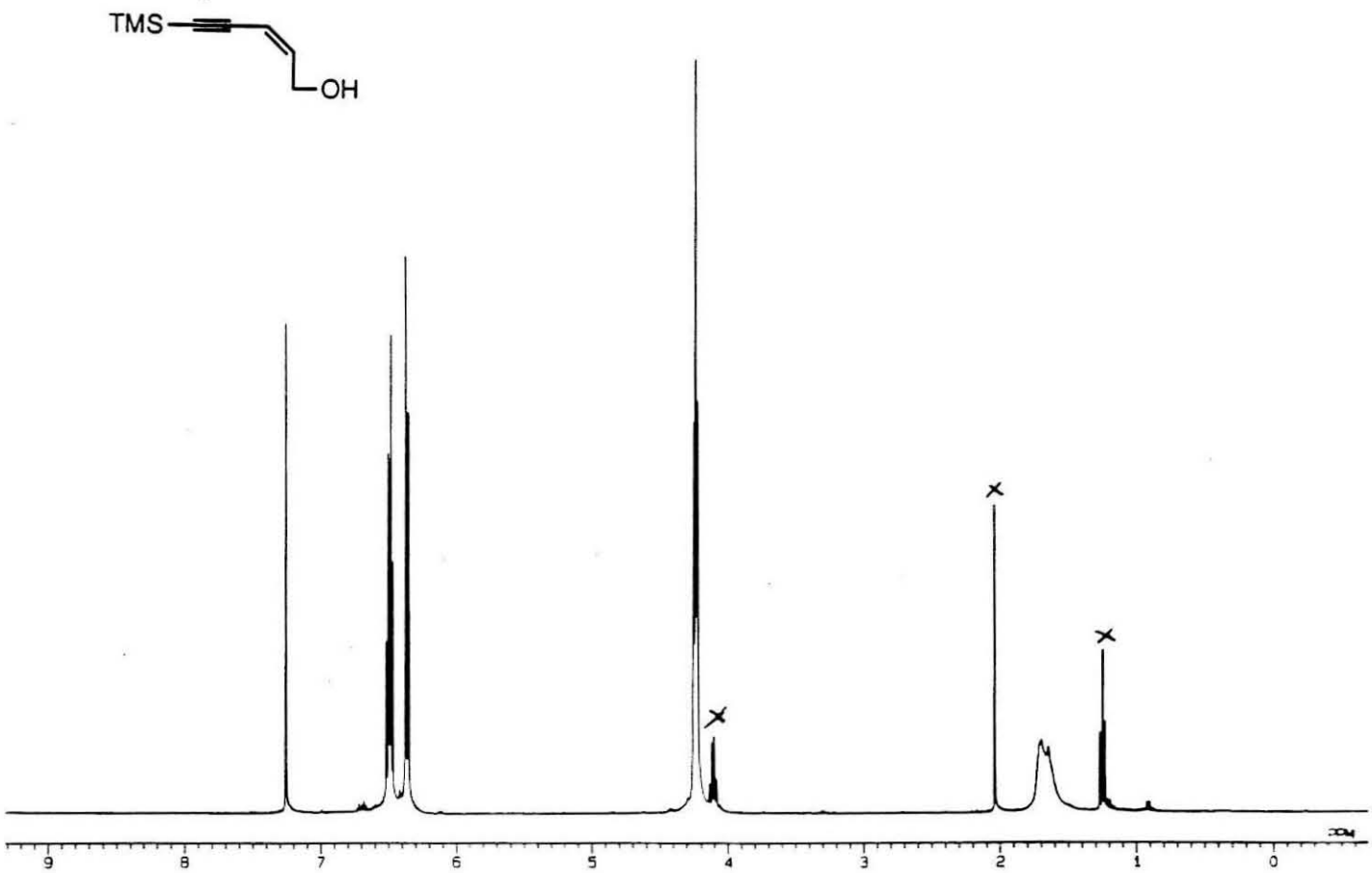
1000
cm⁻¹
500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OH
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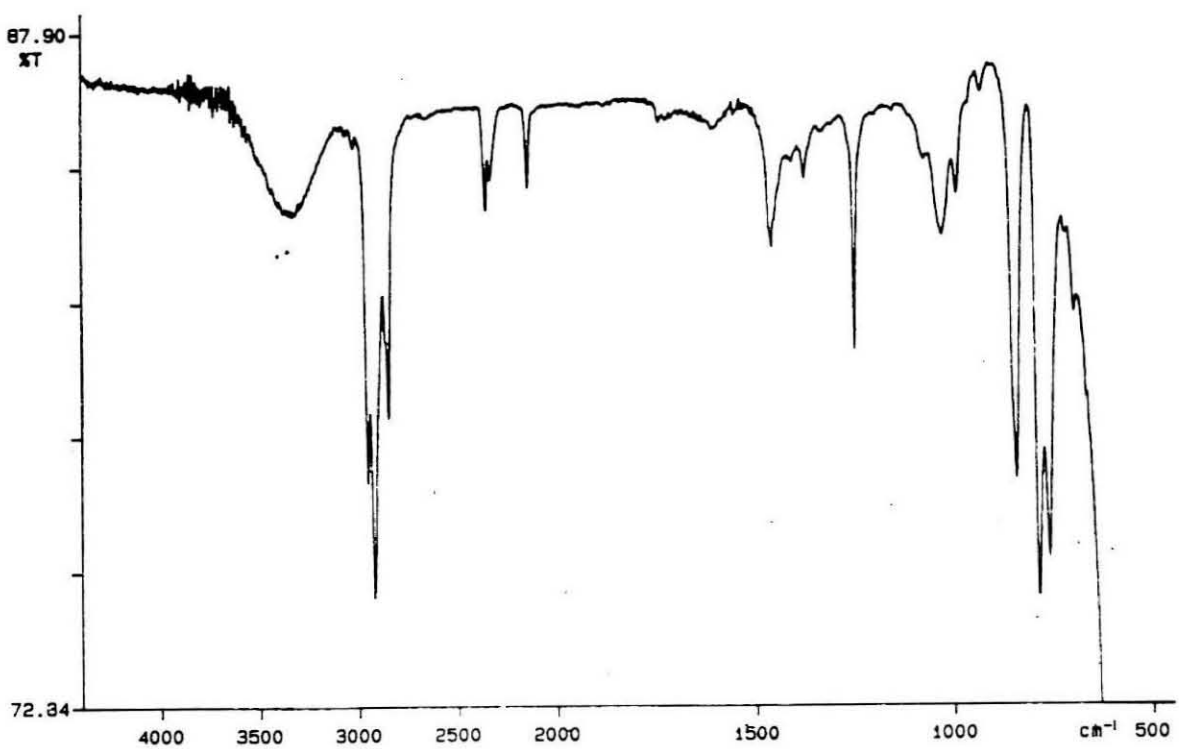
8
7
6
5
4
3
2
1
0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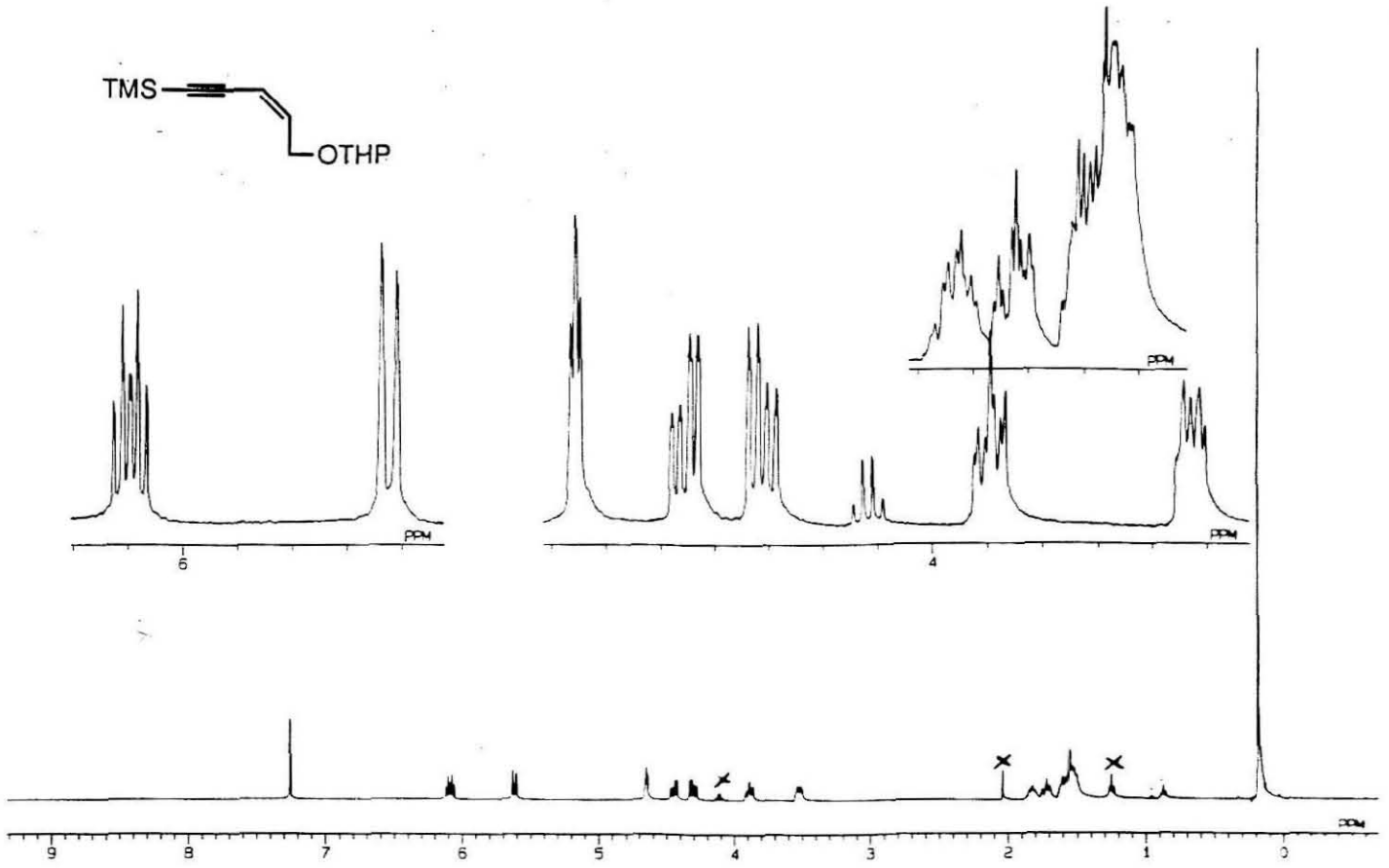
1000
cm⁻¹
500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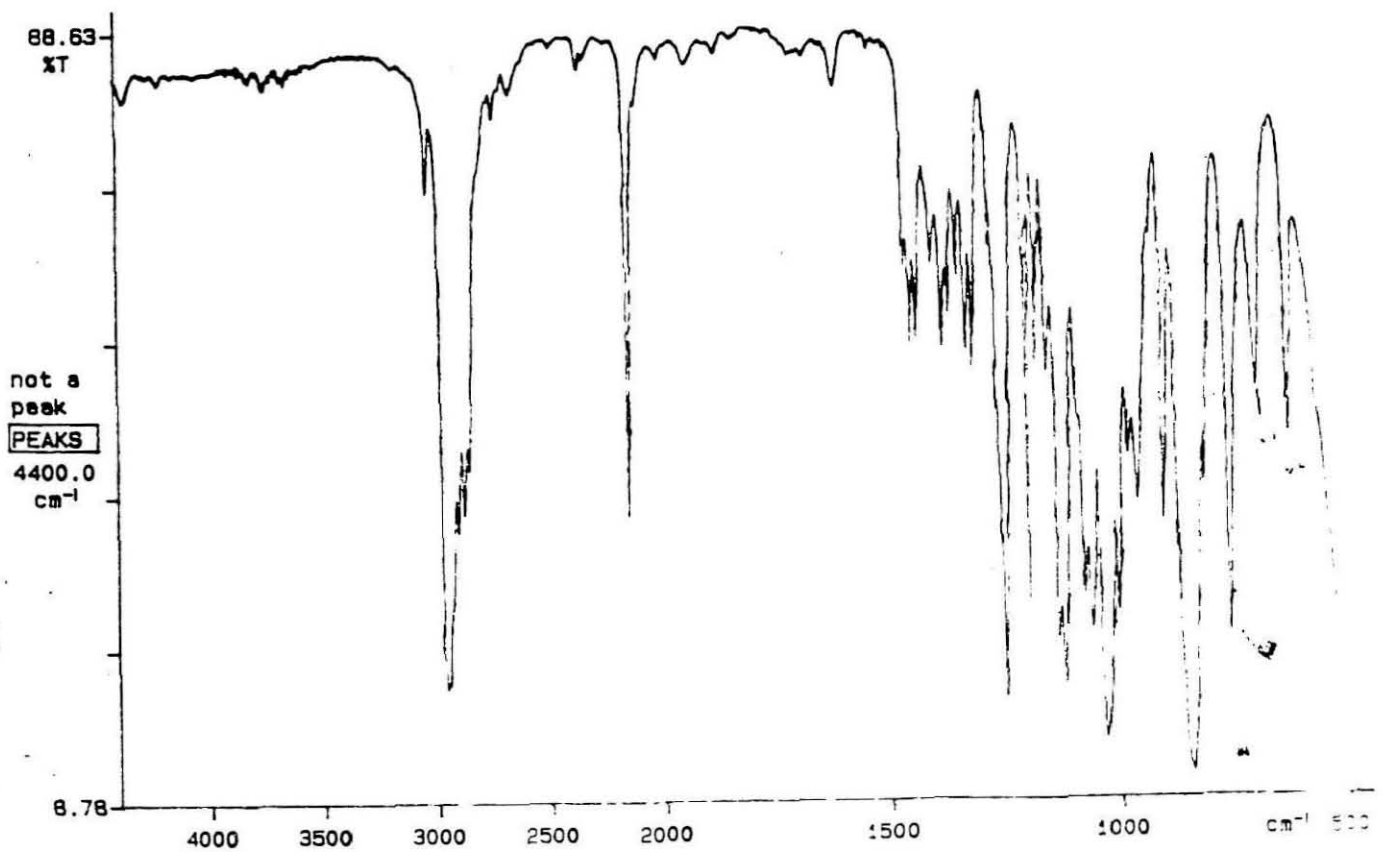
3
2
1
0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cm-1
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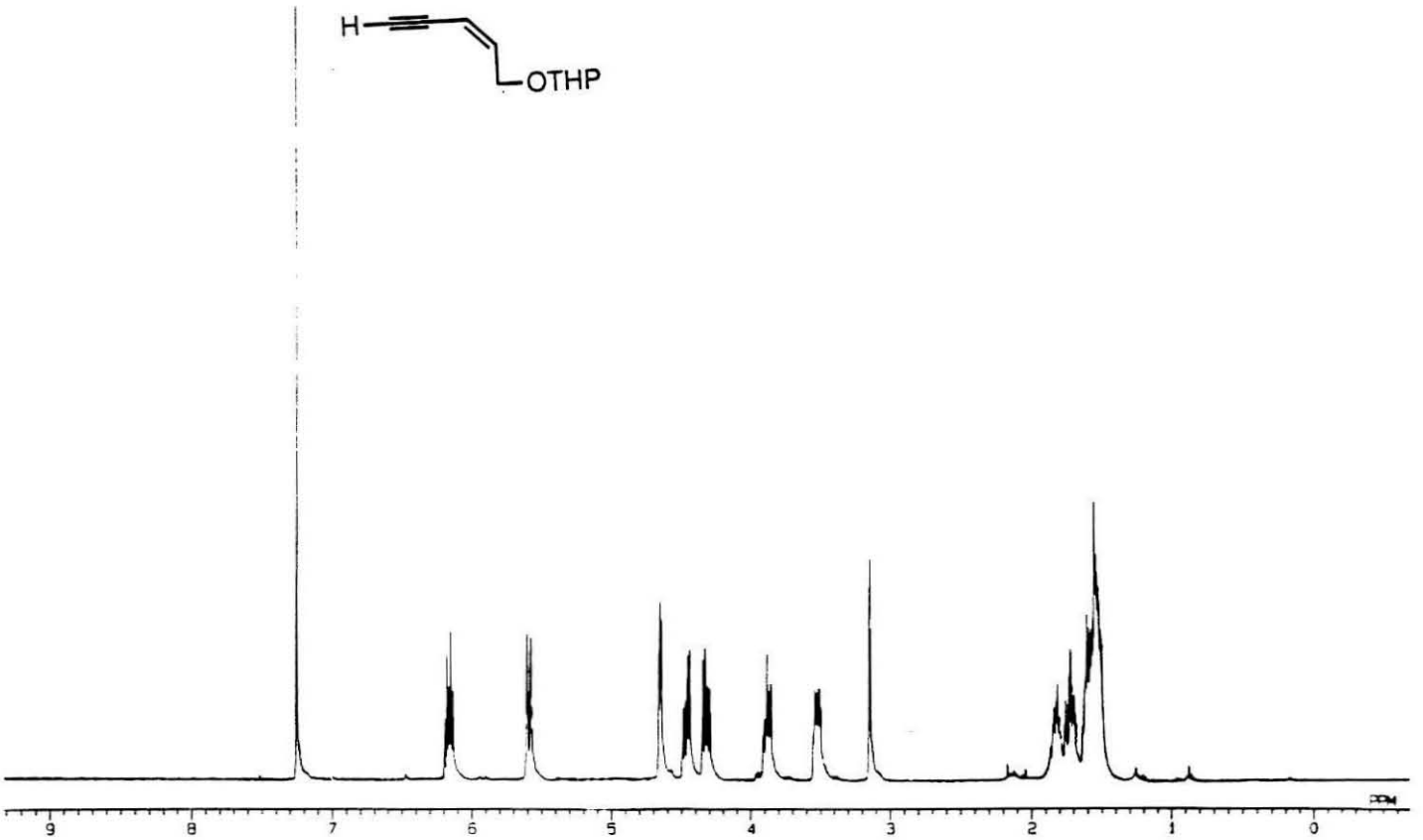
3000
2500
2000
1500
1000
cm-1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7
6
5
4
3
2
1
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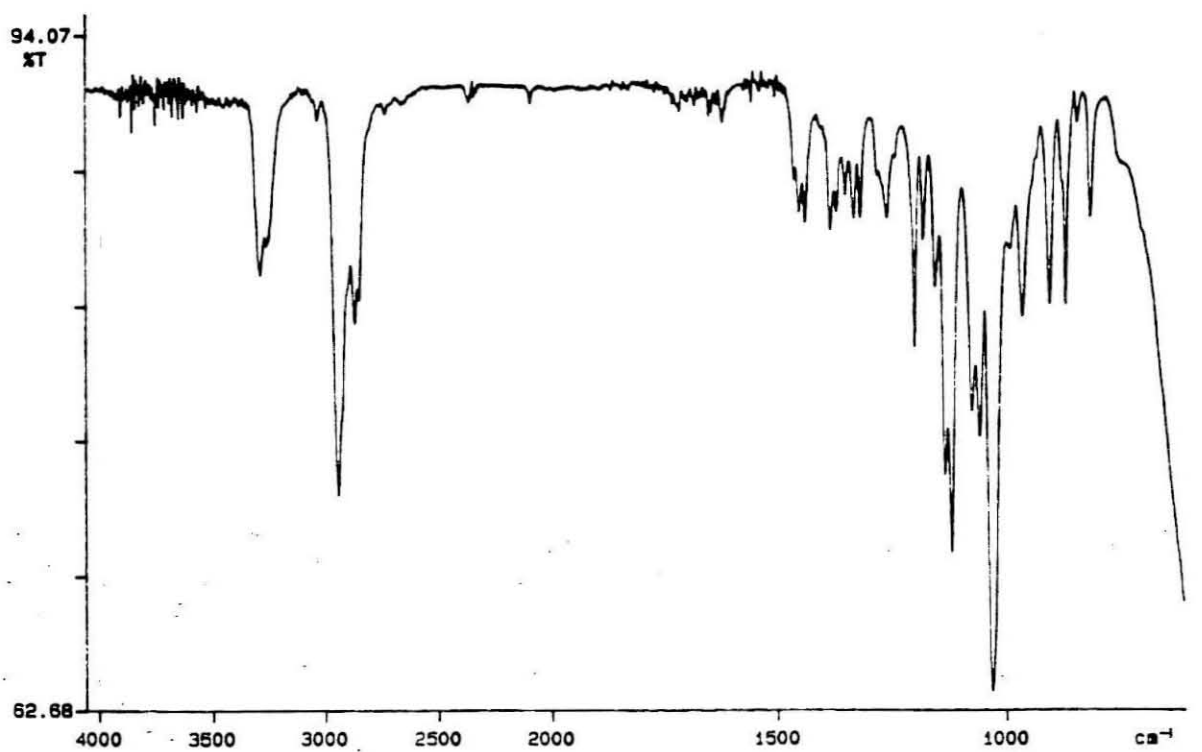
PPM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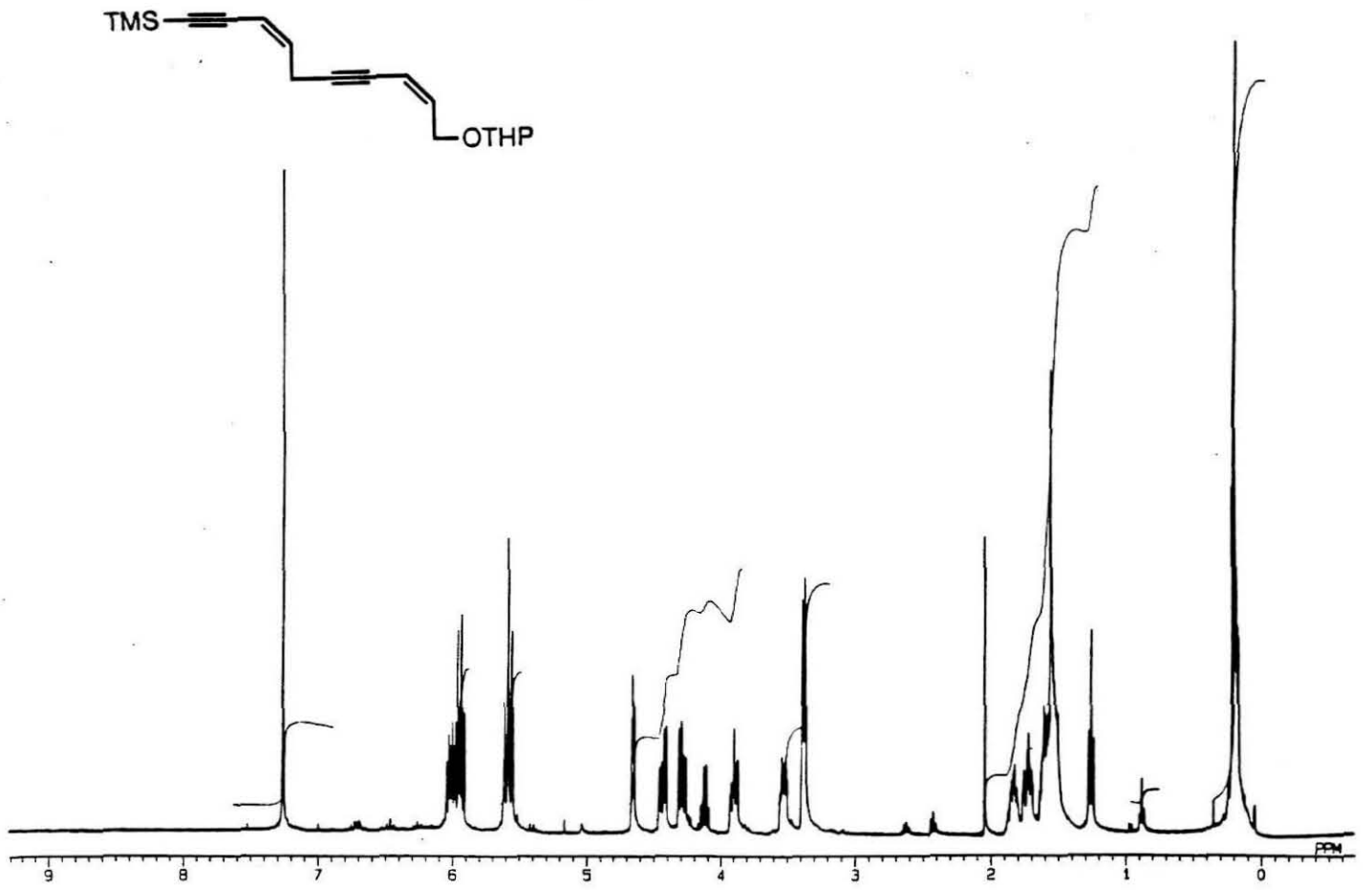
1500
1000
cm-1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5
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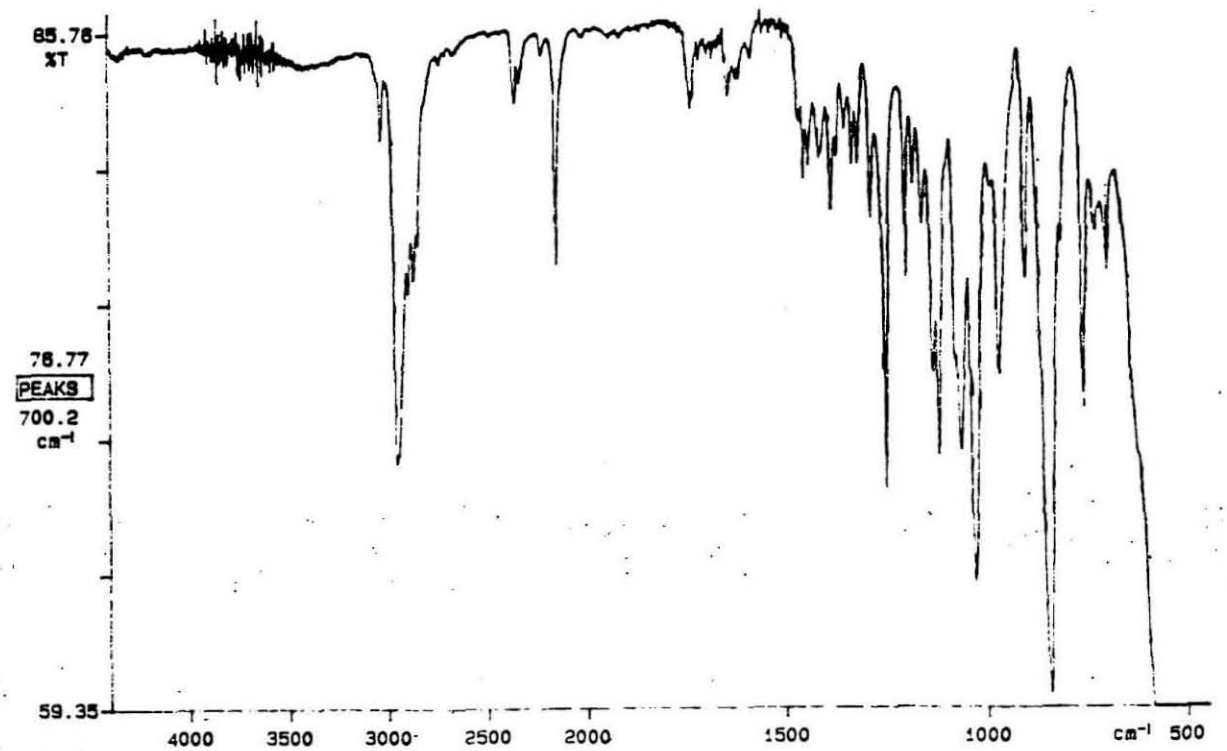
2
1
0
PPM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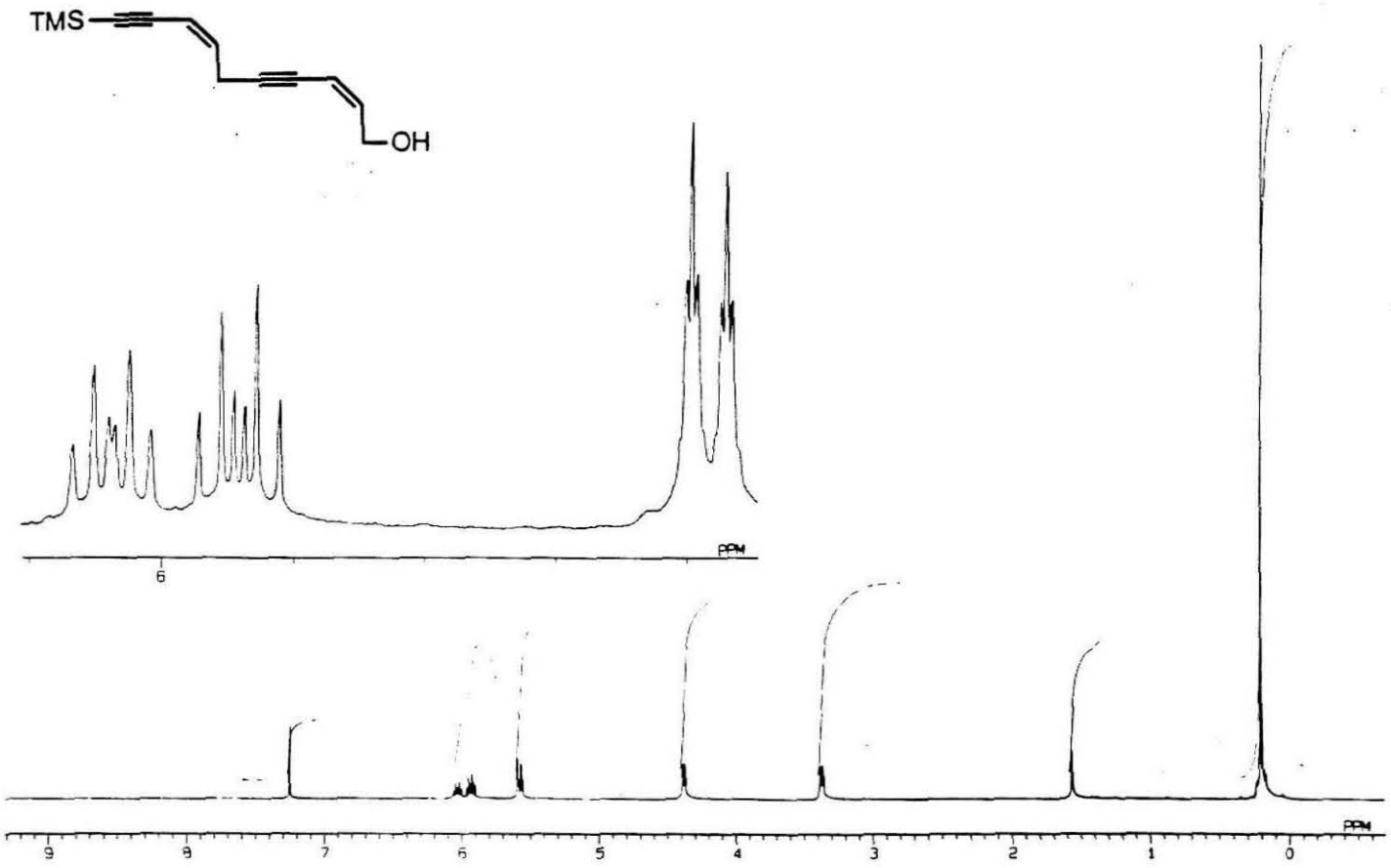
cm-1
500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PPM
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PPM
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8
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4
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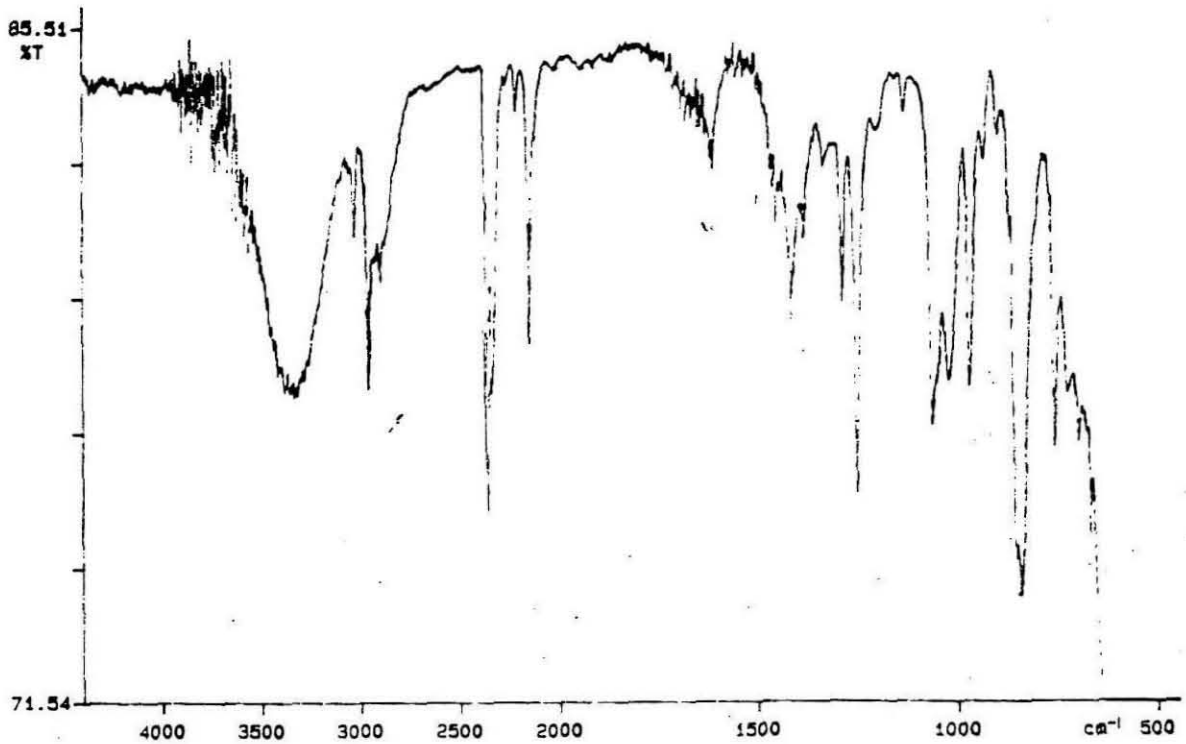
2
1
0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cm-1
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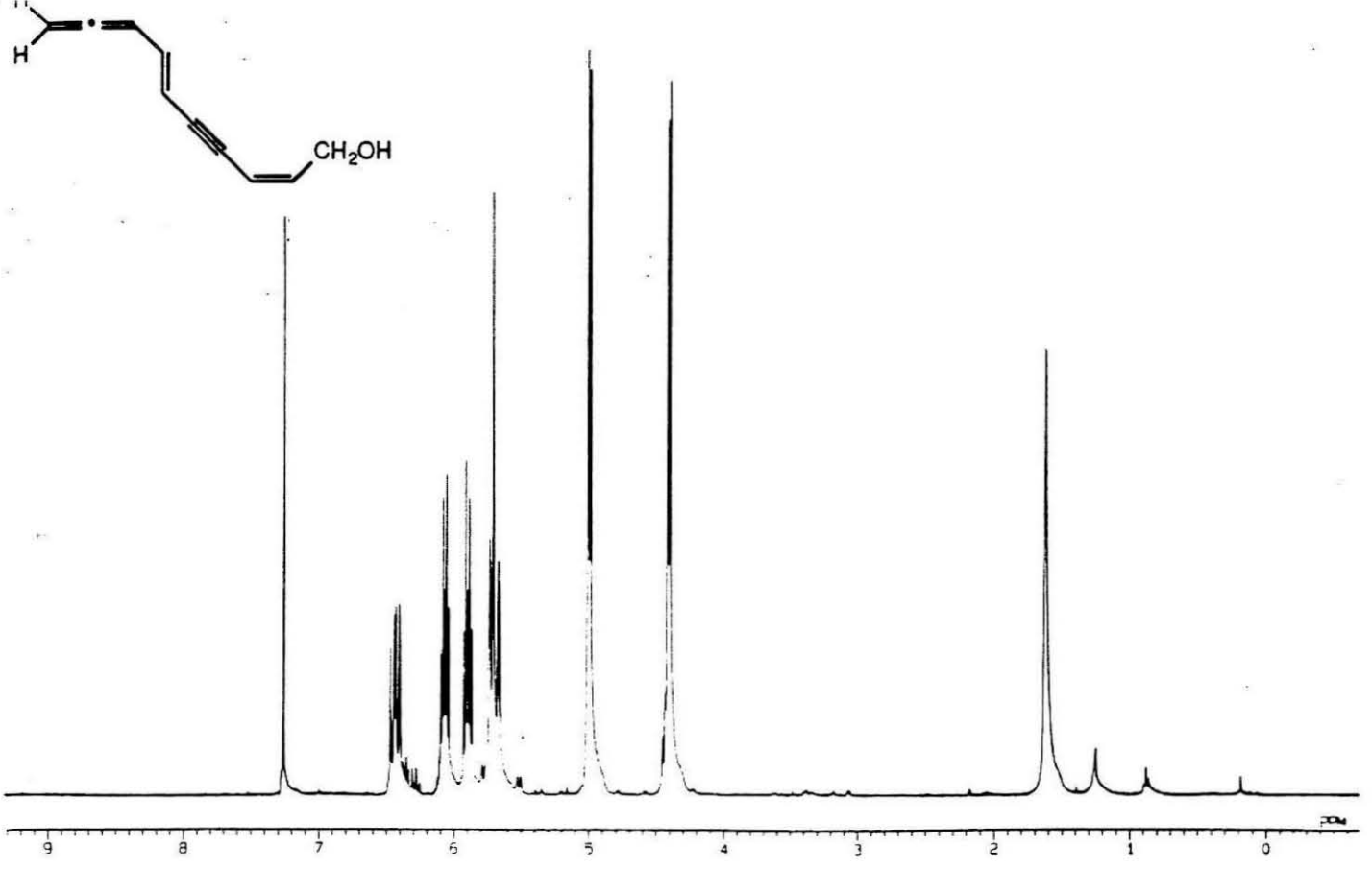
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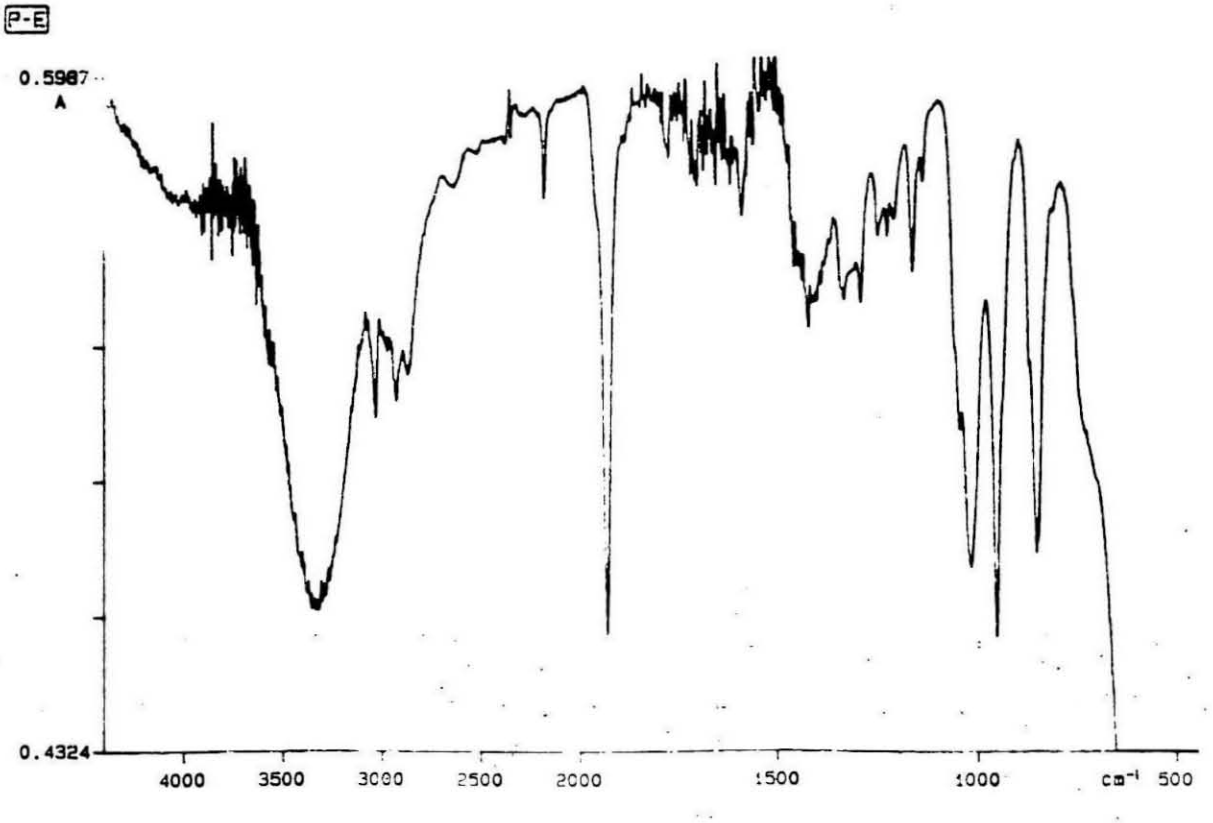
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3000
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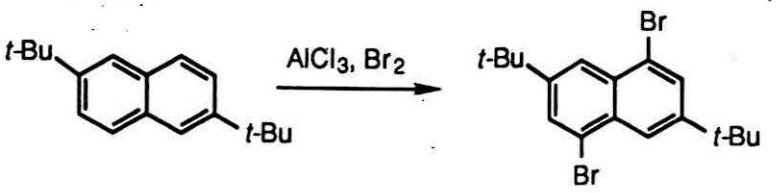
1000
cm-1
500



29 **30**

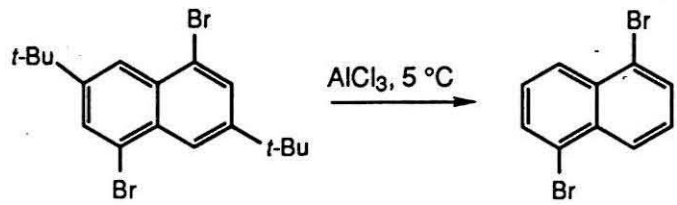
1,5-Dibromo-3,7-di-*tert*-butylnaphthalene **30**

A 500-mL flask was flame-dried under vacuum and filled with argon. The starting material **29** (24.11 g, 0.100 mol, 1 eq) was dissolved in approximately 200 mL of dry methylene chloride and treated with aluminum chloride (60 mg, 0.450 mmol, 0.005 eq). A solution of bromine (12 ml, 0.233 mol, 2.3 eq) in 100 mL of dry methylene chloride was added dropwise via addition funnel over approximately two hours. The mixture was stirred overnight, resulting in a red solution which was washed with two portions of water and two portions of saturated sodium carbonate to give a light green solution. The organic layers were dried over sodium sulfate and concentrated under vacuum to yield a semi-crystalline solid. Recrystallization from benzene-ethanol gave a white crystalline material (26.39 g, 66%).

^{1}H NMR (400 MHz, $CDCl_3$): 8.10 (s, 2H, H4+H8), 7.88 (s, 2H, H2+H6), 1.41 (s, 18H, *t*-butyl).

FTIR (neat film, cm^{-1}): 2963 (s), 1594 (m), 1374 (m), 880 (s).

TLC (hexanes): $R_f = 0.74$



30 **31**

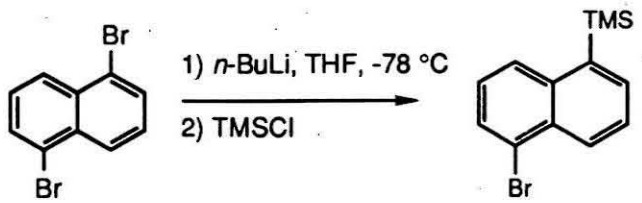
1,5-Dibromonaphthalene **31**

A 200-mL flask was flame-dried under vacuum and filled with argon. The starting material **30** (5.0 g, 12.6 mmol, 1 eq) was added and dissolved in approximately 100 mL of dry benzene. The solution was cooled to 5 °C, aluminum chloride was added (1.68 g, 12.6 mmol, 1 eq), and the solution was stirred for 1 h (close monitoring of the reaction is necessary since over-reaction yields an intractable mixture composed of mostly naphthalene). The reaction mixture was then poured into 50 g of ice and stirred for five minutes and extracted with three portions of 1:1 EtOAc-hexanes. The combined organic layers were washed with two portions of water, dried over sodium sulfate and concentrated. The solid residue was purified by recrystallization from EtOH to give a white solid (1.827 g, 50%). mp = 125-126 °C.

^{1}H NMR (400 MHz, $CDCl_3$): 8.26 (d, 2H, J = 7.6 Hz, H4+H8), 7.83 (d, 2H, J = 7.2 Hz, H2+H6), 7.42 (t, 2H, J = 7.6 Hz, H3+H7).

FTIR (neat film, cm^{-1}): 1192 (m), 1138 (m), 777 (vs).

TLC (hexanes): $R_f = 0.70$

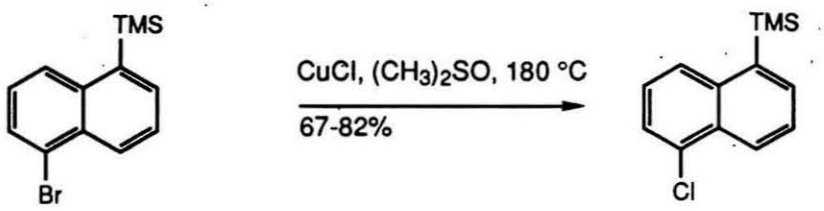


31 **9**

1-Bromo-5-trimethylsilylnaphthalene **9**

A 250-mL flask was flame-dried under vacuum and filled with argon. The starting material **31** (1.67 g, 5.9 mmol, 1 eq) was added, dissolved with 100 mL of dry THF, and cooled to -78 °C. Cooling caused some precipitation. *n*-BuLi (4.0 mL, 6.4 mmol, 1.1 eq) was added over 5 min, which caused the solution to become lime green and the precipitate to dissolve. After allowing the solution to stir for 10 min, trimethylsilylchloride (0.82 mL, 6.46 mmol, 1.1 eq) was added over a couple of minutes and the reaction mixture was allowed to stir for another fifteen minutes. The mixture was poured into water, extracted with three portions of ether, washed with two portions of saturated sodium bicarbonate and one portion of saturated sodium chloride solution, dried over sodium sulfate, and concentrated under vacuum. Purification by flash chromatography (petroleum ether) yielded 0.785 g of clear liquid (48%).

^{1}H NMR (400 MHz, $CDCl_3$):	8.31 (d, 1H, J = 8.6 Hz, H4 or H8), 8.08 (d, 1H, J = 8.6 Hz, H4 or H8), 7.80 (d, 1H, J = 6.8 Hz, H2 or H6), 7.74 (d, 1H, J = 6.8 Hz, H2 or H6), 7.56 (t, 1H, $J \approx$ 8 Hz, H3 or H7), 7.35 (t, 1H, $J \approx$ 8 Hz, H3 or H7), 0.47 (s, 9H, TMS).
FTIR (neat film, cm^{-1}):	3075 (w), 2956 (s), 2897 (w), 1584 (m), 1557 (s), 1251 (vs), 998 (vs), 838 (vs), 756 (s).
^{13}C NMR (400 MHz, $CDCl_3$):	139.2, 138.5, 134.3, 132.3, 129.8, 129.0, 128.3, 126.8, 126.1, 124.2, 1.0.
TLC (hexanes)	R_f = 0.70
MS (EI):	280 (MH^+).

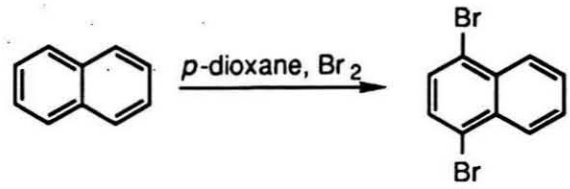


9 **12**

1-Chloro-5-trimethylsilylnaphthalene **12**

A reaction flask was flame-dried under vacuum and filled with argon. Starting material **9** (0.530 g, 1.89 mmol, 1 eq) was added and dissolved in 10 mL of dry dimethylsulfoxide. Cuprous chloride (0.215 g, 2.17 mmol, 1.15 eq) was added and the mixture refluxed for one hour with stirring. The reaction mixture was allowed to cool to room temperature and was then poured into 50 mL of cold 6 N HCl. The mixture was extracted with three portions of ether. The combined organic layers were washed with two portions of water, dried over sodium sulfate, and concentrated under vacuum. Purification by flash chromatography (petroleum ether) gave a clear colorless oil of >90% purity by NMR (0.299 g, 67%). Resubjecting the product mixture to the reaction conditions gave >97% purity.

^{1}H NMR (400 MHz, $CDCl_3$):	8.34 (d, 1H, J = 8.6 Hz, H4 or H8), 8.03 (d, 1H, J = 8.6 Hz, H4 or H8), 7.76 (d, 1H, J = 6.6 Hz, H6), 7.58 (m, 2H, H2+H3), 7.42 (t, 1H, $J \approx 7$ Hz, H7), 0.046 (s, 9H, TMS).
FTIR (neat film, cm^{-1}):	3075 (w), 2957 (m), 2897 (m), 1585 (m), 1560 (m), 1252 (s), 854 (s), 839 (s), 785 (s).
^{13}C NMR (400 MHz, $CDCl_3$):	139.1, 138.3, 134.3, 133.1, 131.1, 127.6, 126.5, 126.2, 126.0, 125.6, 1.0.
MS (EI):	234 (M^+), 219 (M^+-CH_3).
Exact Mass:	calcd: 234.0631 found: 234.0629
TLC (hexanes):	R_f = 0.70



32 **33**

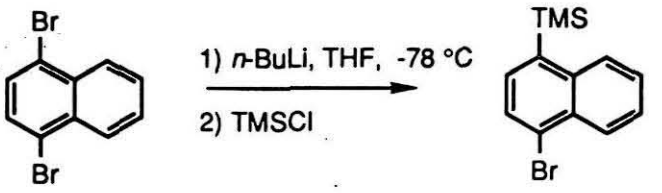
1,4-Dibromonaphthalene **33**

A reaction flask was flame-dried under vacuum and filled with argon. *p*-Dioxane (9.2 mL, 0.11 mol, 2.2 eq), and bromine (5.5 mL, 0.11 mol, 2.2 eq) were added (exothermic) forming a deep red solution with yellow solids. Naphthalene (**32**, 6.4 g, 0.050 mol, 1 eq) was added to this solid complex, which dissolved and began to give off white fumes. The reaction flask was placed in a hot water bath (40 °C) for three hours and then allowed to stand at room temperature overnight. The solid was treated with 10% NaOH at 0 °C until mixture was basic by pH paper. Crystals were formed and collected by filtration. Recrystallization twice from 95% EtOH gave a white needle solid (4.08 g, 31%). mp = 79-80 °C.

^{1}H NMR (400 MHz, $CDCl_3$): 8.24 (q, 2H, J = 3 Hz, H8+H5), 7.65 (q, 2H, J = 3 Hz, H6+H7), 7.64 (s, 2H, H2 +H3).

FTIR (neat film, cm^{-1}): 1183 (m), 1139 (m), 961 (s), 812 (s), 751 (vs).

TLC (hexanes): $R_f = 0.67$



33 **10**

1-Bromo-4-trimethylsilylnaphthalene **10**

A reaction flask was flame-dried under vacuum and filled with argon. The starting material **33** (4.08 g, 0.014 mol, 1 eq) was added and dissolved in approximately 50 mL of dry THF and cooled to -78 °C. *n*-BuLi (11.6 mL, 0.0185 mol, 1.3 eq) was then added over seven minutes giving a yellow solution. After 15 min, trimethylsilylchloride (2.35 mL, 0.0185 mol, 1.3 eq) was added over five minutes. The solution became a light lime green color. The mixture was stirred for 0.5 h and then poured in 50 mL of water and extracted with three portions of ether. The combined organic layers were washed with two portions of saturated sodium chloride solution, dried over sodium sulfate, and concentrated under vacuum. Purification by flash chromatography (hexane) twice yielded a white solid which was then recrystallized twice from EtOH to give 1.16 g of desired **20** (30%). mp = 60.5-62 °C.

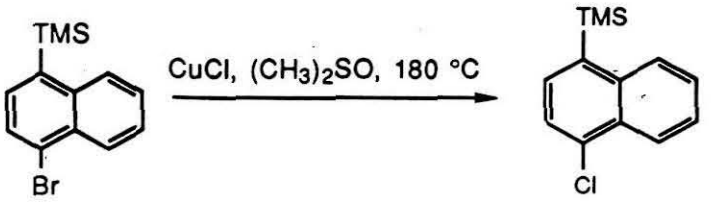
^{1}H NMR (400 MHz, $CDCl_3$): 8.32 (d, 1H, J = 8.2 Hz, H5 or H8), 8.09 (d, 1H, J = 8.2 Hz, H5 or H8), 7.75 (d, 1H, J = 7.3 Hz, H2 or H3), 7.52 -7.61 (m, 2H, H6+H7), 7.49 (d, 1H, J = 7.3 Hz, H2 or H3), 0.48 (s, 9H, TMS).

^{13}C NMR (400 MHz, $CDCl_3$): 138.5, 138.2, 133.3, 131.9, 129.3, 128.6, 128.1, 126.7, 126.4, 125.2, 0.2.

FTIR (neat film, cm^{-1}): 3073 (m), 2956 (m), 2896 (w), 1573 (w), 1557 (m), 1251 (s), 877 (vs), 838 (vs), 765 (vs).

TLC (hexanes): R_f = 0.67

MS (EI): 280 (MH^+).



10 **13**

1-Chloro-4-trimethylsilylnaphthalene **13**

A reaction flask was flame-dried under vacuum and filled with argon. The starting material **10** (1.02 g, 3.65 mmol, 1 eq) was added and dissolved in 20 mL of dry dimethyl sulfoxide. Cuprous chloride (0.397 g, 4.01 mmol, 1.1 eq) was added and the reaction mixture was refluxed for 1.25 h. The mixture was cooled down to room temperature and poured into 50 mL of cold 6 N HCl. The mixture was extracted with three portions of ether. The combined ethereal extracts were washed with three portions of water, dried over sodium sulfate, and concentrated under vacuum. The residue was purified by flash chromatography (pentane) yielding 0.465 g of semi-pure compound which was further purified by recrystallization from EtOH to give 0.400 g of white flaky crystals (46%). mp = 52.5-53.5 °C.

^{1}H NMR (400 MHz, $CDCl_3$): 8.35 (d, 1H, J = 8.2 Hz, H5 or H8), 8.10 (d, 1H J = 8.2 Hz, H5 or H8), 7.53-7.62 (m, 4H, H2+H3+H6+H7) 0.48 (s, 9H, TMS).

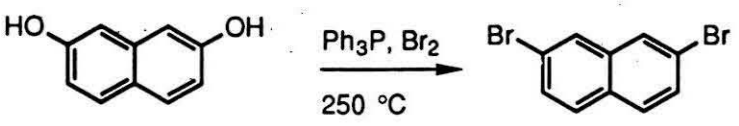
^{13}C NMR (400 MHz, $CDCl_3$): 138.5, 138.3, 134.2, 133.2, 131.0, 128.8, 126.7, 126.7, 125.8, 125.7, 0.0.

FTIR (neat film, cm^{-1}): 2958 (m), 1576 (w), 1250 (s), 898 (vs), 839 (vs), 765 (vs).

MS (EI): 234 (M^+), 219 (M^+-CH_3).

Exact Mass: calcd: 234.0631 found: 234.0637

TLC (hexanes): R_f = 0.67



34 **35**

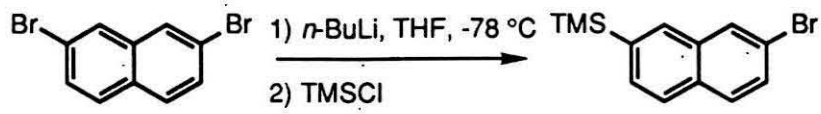
2,7-Dibromonaphthalene **35**

A reaction flask was flame-dried under vacuum and filled with argon. Triphenylphosphine (6.92 g, 26.4 mmol, 2.2 eq) and 15 mL of dry acetonitrile were added, stirred, and cooled to 0 °C (partial solution). Bromine (1.36 mL, 26.4 mmol, 2.2 eq) was added dropwise via pipette, forming a solid orange mixture. The starting material **34** (1.91 g, 0.012 mol, 1 eq) was dissolved in 10 mL of dry acetonitrile and added to reaction mixture. The reaction mixture was refluxed for 50 min and then the acetonitrile was distilled off under water aspirator pressure. The reaction mixture was heated on a sand bath to 230 °C for an additional hour. The black tarry gum formed in the reaction was transferred to a beaker while hot where it solidified upon cooling. The tarry solid was extracted with boiling petroleum ether and boiling hexane until the solid became a grey, almost granular solid. The extracts were washed with 10% NaOH, dried over sodium sulfate, and concentrated under vacuum. The resulting solid was purified by recrystallization from EtOH (95%) to give 1.09 g of slightly pink solid (32%). mp = 137 -138 °C.

^{1}H NMR (400 MHz, $CDCl_3$): 7.91 (d, 2H, J = 1.9 Hz, H1+H8), 7.68 (d, 2H, J = 9.4 Hz, H4+H5), 7.57 (AB q, 2H, J = 9.4, 1.9 Hz, H3+H6).

FTIR (neat film, cm^{-1}) : 3056 (vw), 1567 (m), 906 (s), 870 (s), 838 (vs).

TLC (hexanes): $R_f = 0.59$



35 **11**

2-Bromo-7-trimethylsilylnaphthalene **11**

A reaction flask was flame-dried under vacuum and filled with argon. Starting material **35** (1.05 g, 3.67 mmol, 1 eq) was added, dissolved in 25 mL of dry THF, and cooled to -78 °C. *n*-BuLi (2.52 mL, 4.04 mmol, 1.1 eq) was added over 4 min giving a bright yellow solution. After 10 min, trimethylsilylchloride (0.6 mL, 4.72 mmol, 1.2 eq) was added causing solution to lose color and intensity. The mixture was stirred for 0.5 h, poured into 50 mL of water, and extracted with three portions of ether. The combined organic layers were washed with two portions of saturated sodium chloride solution, dried over sodium sulfate, and concentrated under vacuum. Purification by flash chromatography (petroleum ether) gave a colorless oil (0.683 g, 67%). mp = 42 - 43 °C.

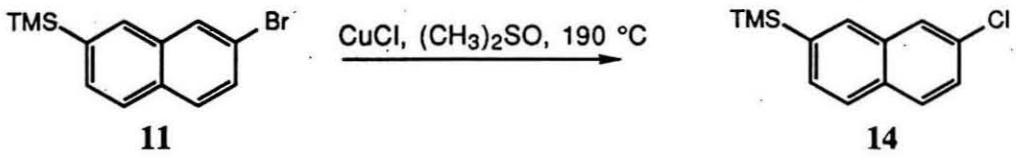
^{1}H NMR (400 MHz, $CDCl_3$): 8.01 (s, 1H, H8), 7.90 (s, 1H, H1), 7.78 (d, 1H, J = 8.2 Hz, H4 or H5), 7.69 (d, 1H, J = 8.2 Hz, H4 or H5), 7.61 (d, 1H, J = 8.2 Hz, H3 or H6), 7.54 (d, 1H, J = 8.2, 1.4 Hz, H3 or H6), 0.35 (s, 9H, TMS).

FTIR (neat film, cm^{-1}): 3048 (w), 2955 (m), 2898 (w), 1583 (m), 1495 (m), 1249 (s), 1090 (s), 1060 (s), 887 (vs), 832 (vs), 750 (s).

^{13}C NMR (400 MHz, $CDCl_3$): 139.7, 134.3, 133.1, 132.3, 130.6, 130.4, 129.9, 129.7, 127.1, 120.0, -0.5.

TLC (hexanes): R_f = 0.59

MS (EI): 278 (M^+-H).

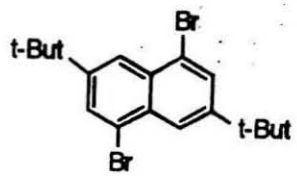


11 **14**

2-Chloro-7-trimethylsilylnaphthalene **14**

A reaction flask was flame-dried under vacuum and filled with argon. The starting material **11** (0.363 g, 1.30 mmol, 1 eq) was placed in a 50-mL flask and dissolved with 20 mL of dry dimethylsulfoxide. Cuprous chloride (0.154 g, 1.56 mmol, 1.2 eq) was added and stirred, forming a cloudy yellow solution. The system was flushed with argon and heated to a temperature of 190 °C for two hours. The solution was allowed to cool to room temperature, poured into 50 mL of ice-cold 6 N HCl, and stirred for five minutes. The solution was extracted with four portions of ether. The combined ethereal extracts were washed with two portions of saturated sodium bicarbonate solution, dried over sodium sulfate, and concentrated under vacuum. Purification by flash chromatography (petroleum ether) followed by recrystallization from EtOH gave 0.15 g of desired (49%).

^{1}H NMR (300 MHz, $CDCl_3$):	7.91 (s, 1H, H8), 7.83 (d, 1H, J = 1.7 Hz, H1), 7.80 (d, 1H, J = 7.8 Hz, H4 or H5), 7.76 (d, 1H, J = 8.7 Hz, H4 or H5), 7.61 (d, 1H, J = 7.8 Hz, H3 or H6), 7.33 (AB q, 1H, J = 1.7, 8.7 Hz, H3 or H6), 0.35 (s, 9H, TMS).
^{13}C NMR (300 MHz, $CDCl_3$):	139.4, 132.8, 131.8, 131.4, 130.1, 129.3, 127.1, 126.8, 126.7, -1.1.
FTIR (neat film, cm^{-1}):	3044 (w), 2956 (s), 1586 (m), 1249 (s), 899 (s), 834 (vs).
MS (EI):	234 (M^+), 219 (M^+-CH_3).
Exact Mass:	calcd: 234.0631 found: 234.0637
TLC (hexanes):	R_f = 0.59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t-But
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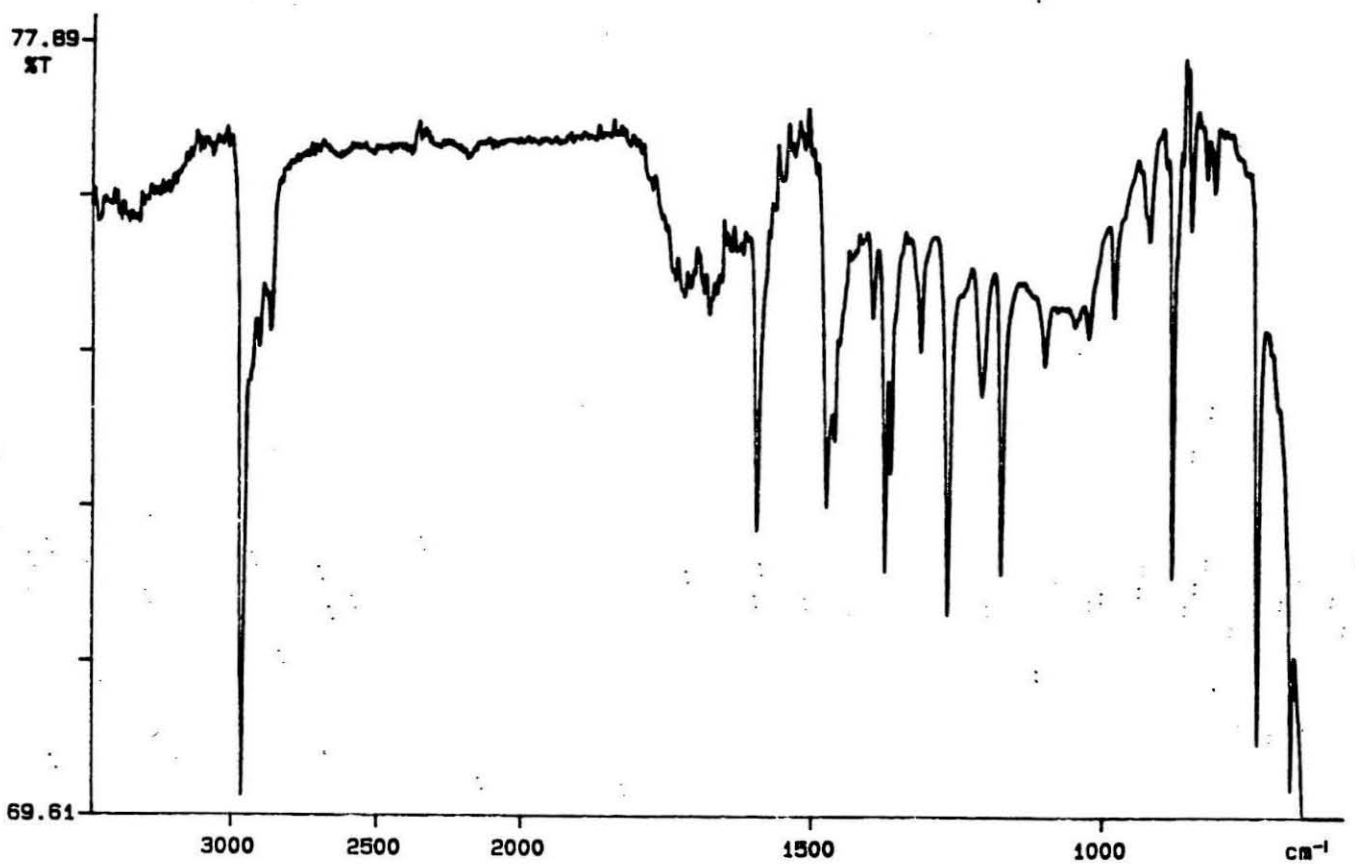
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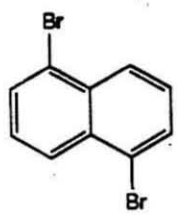
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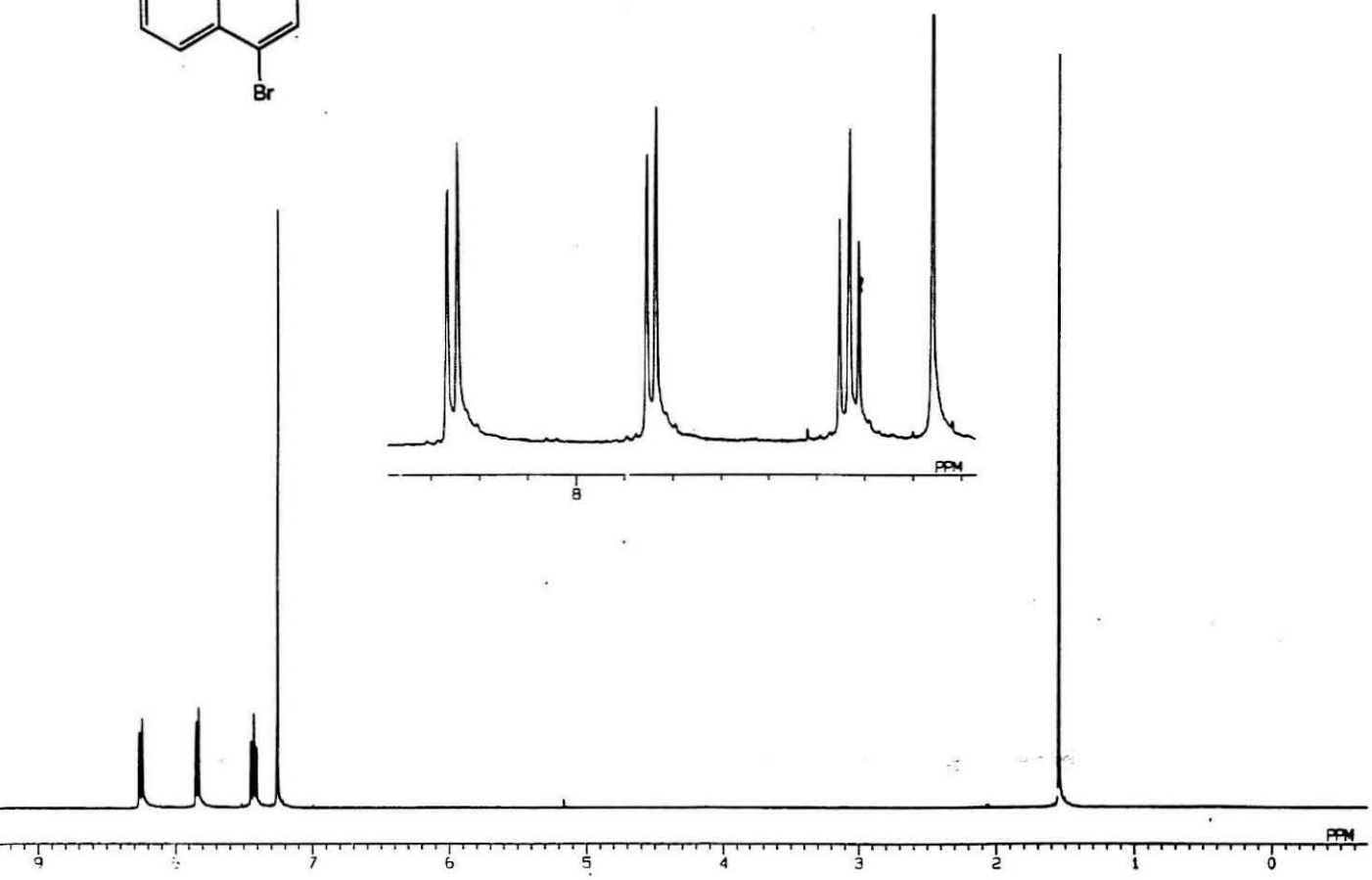
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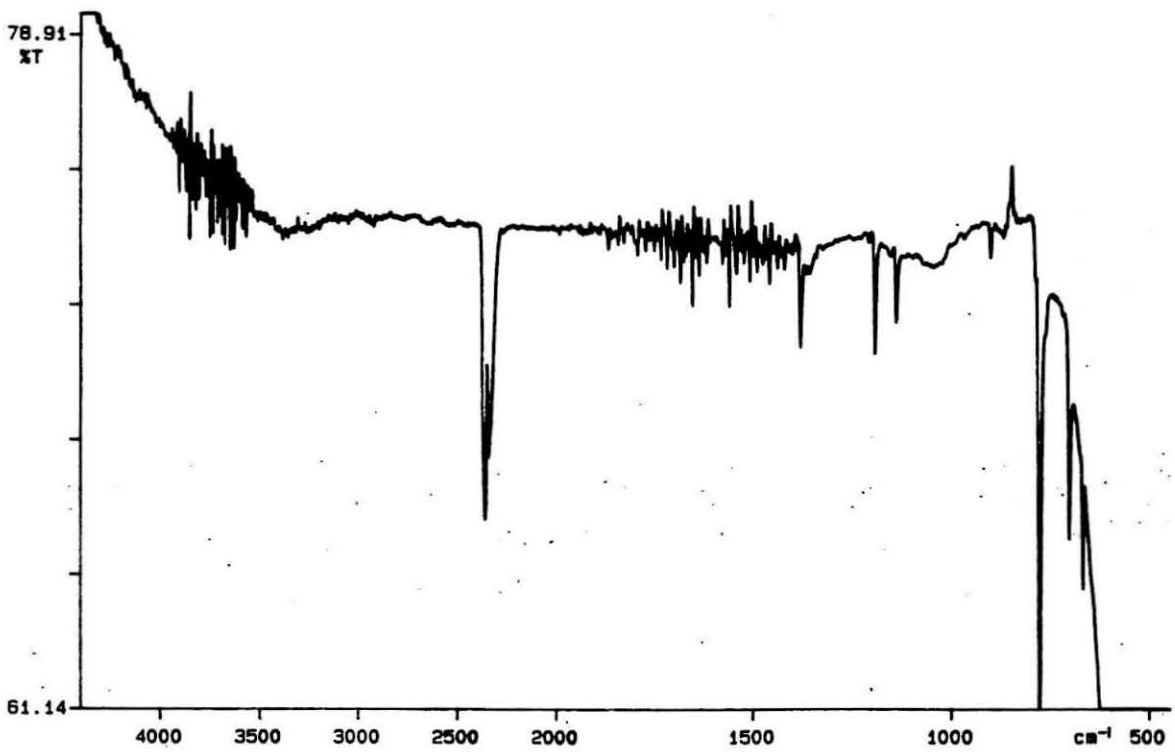
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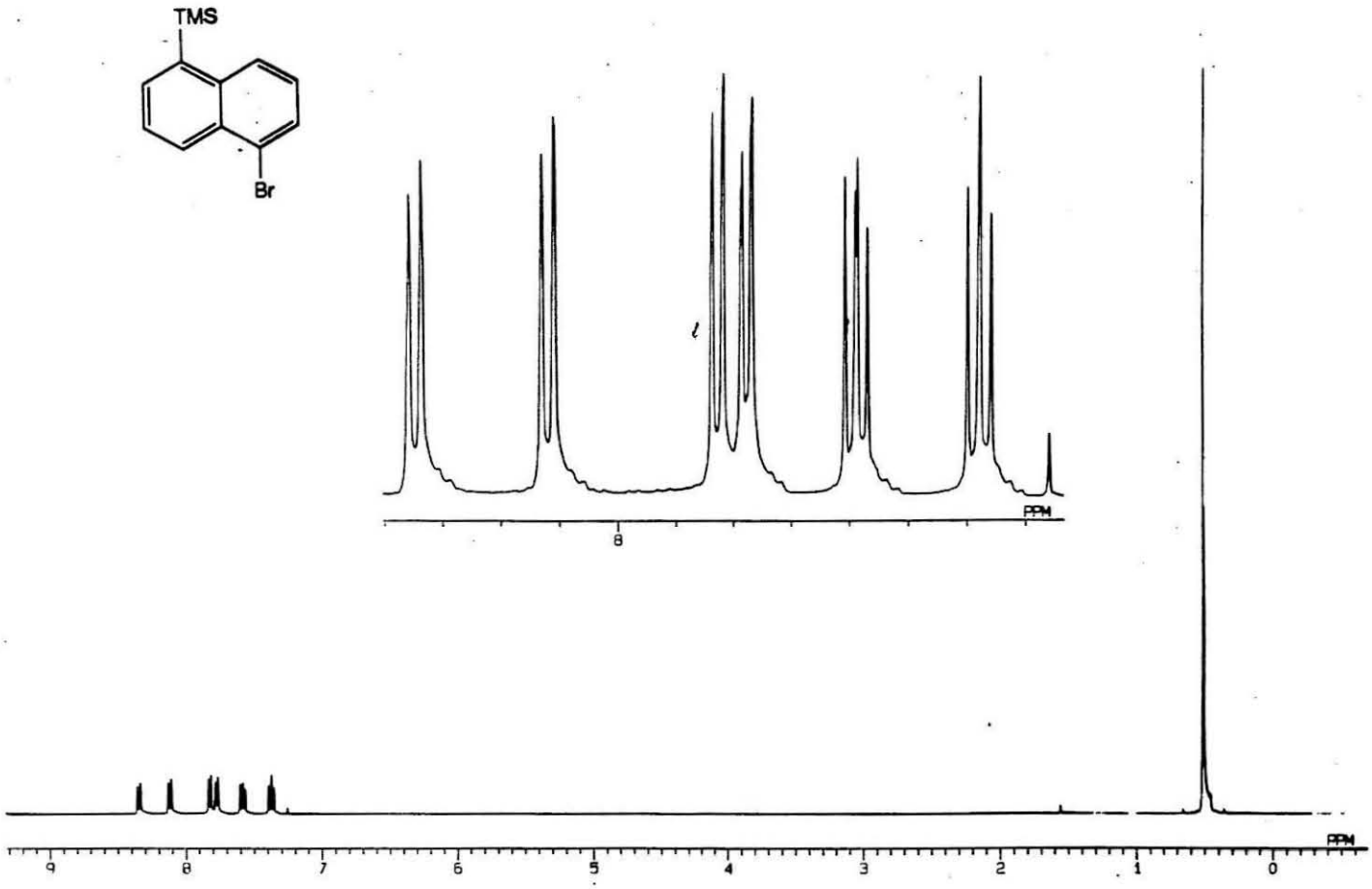
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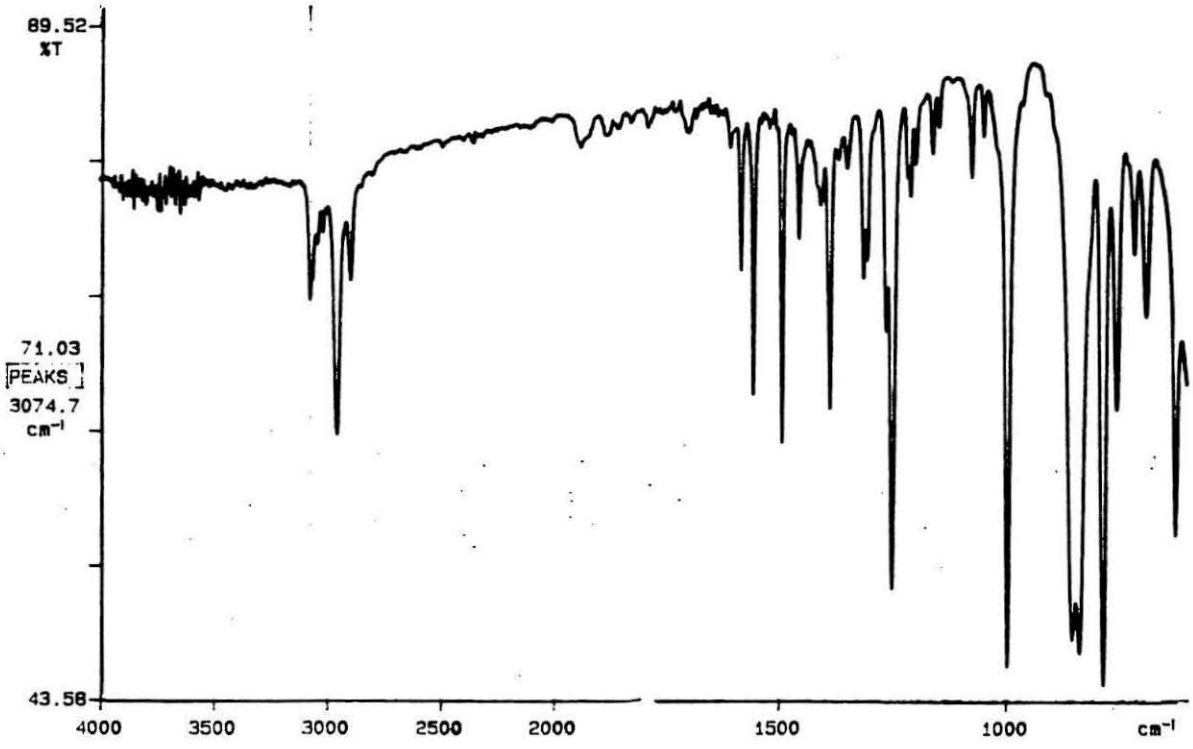
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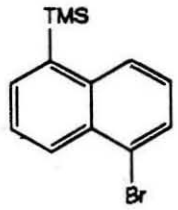
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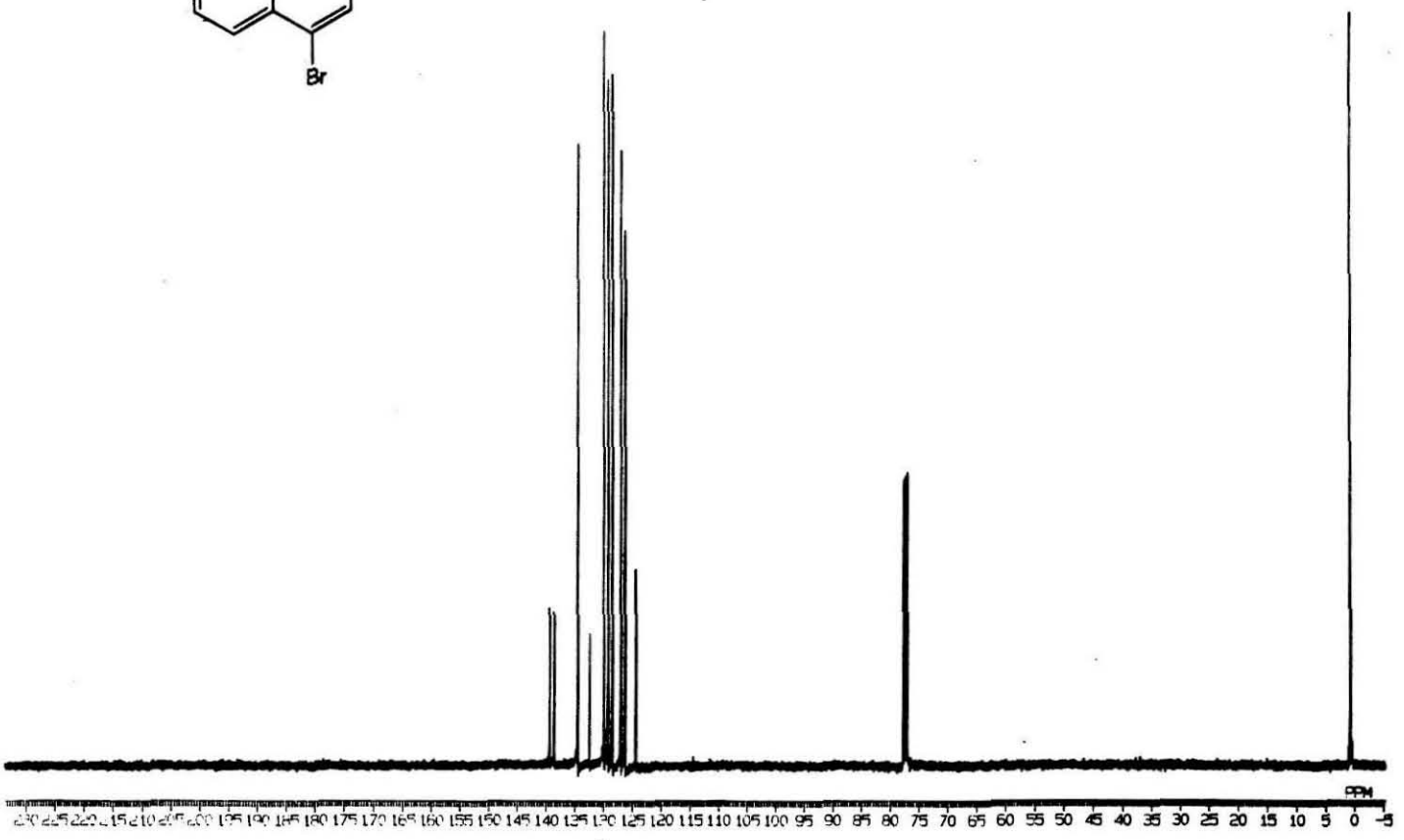
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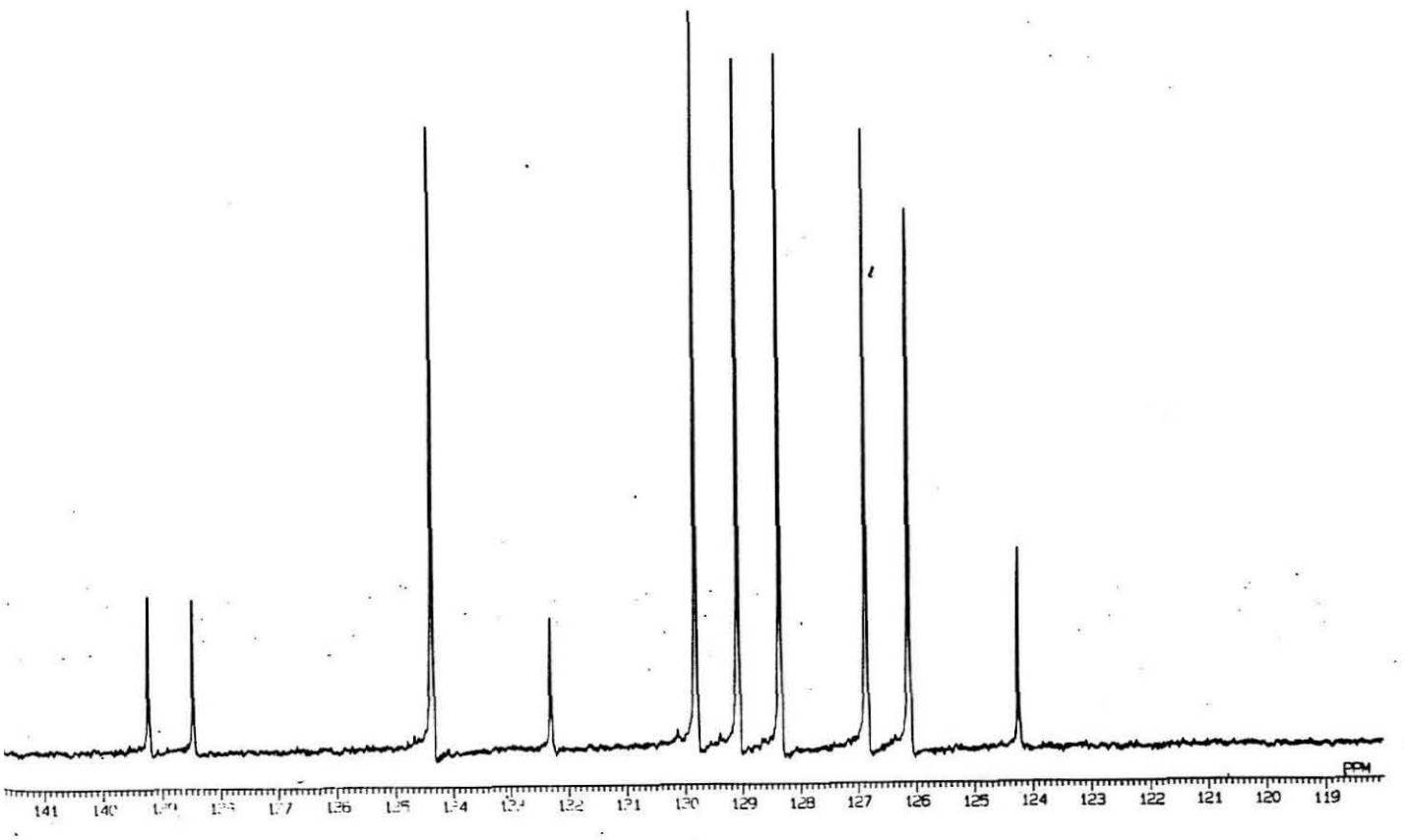
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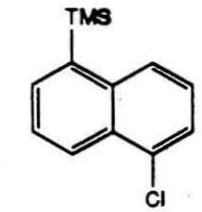
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Cl

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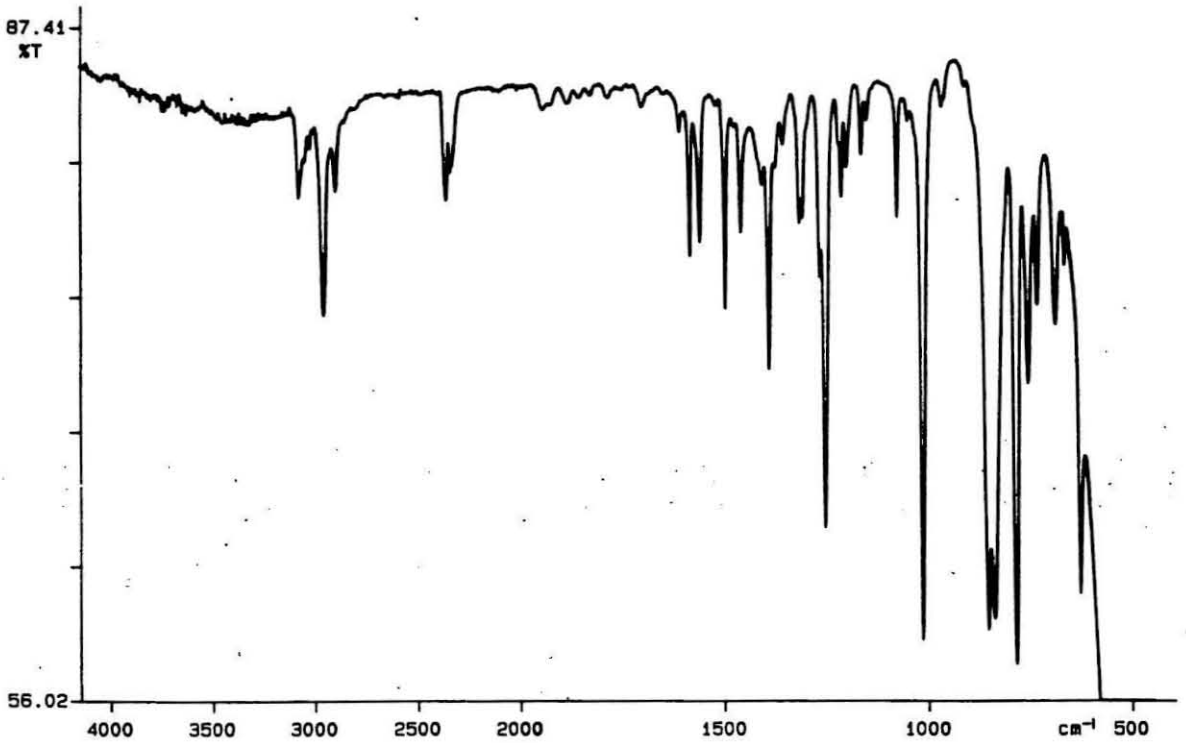
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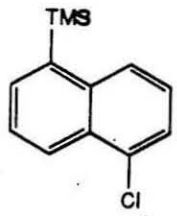
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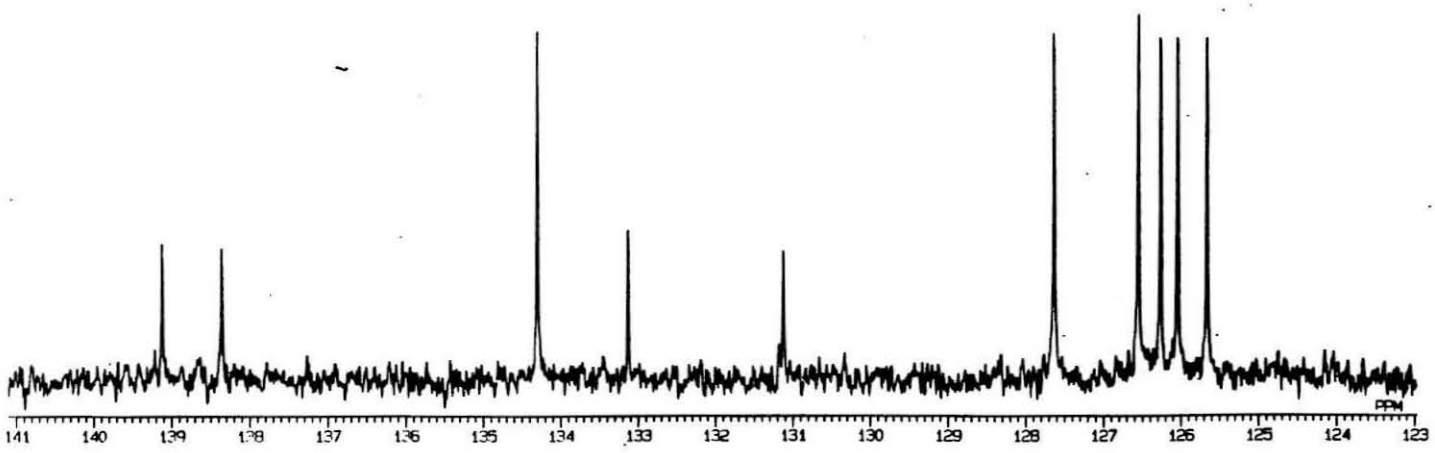
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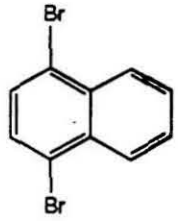
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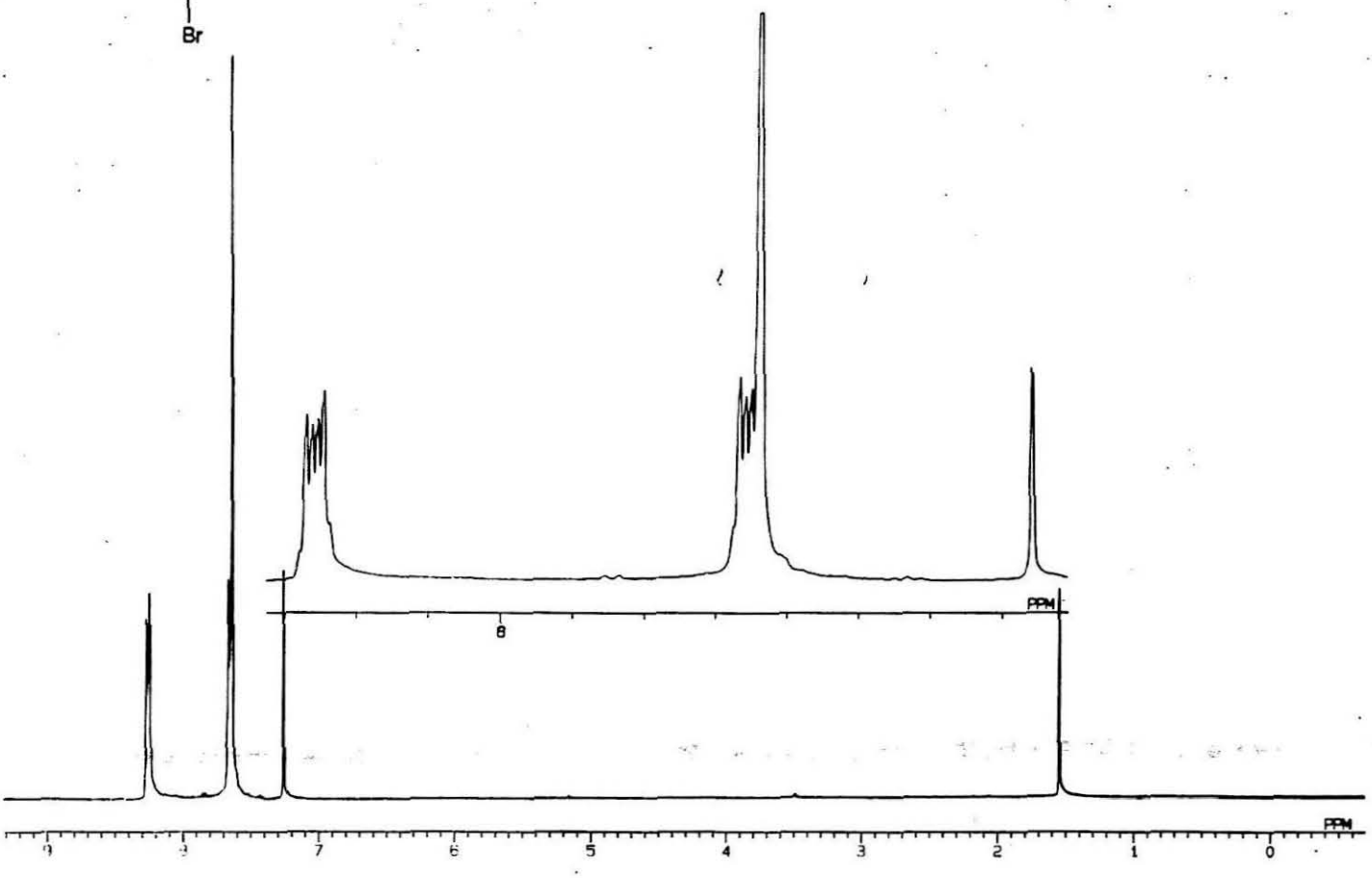
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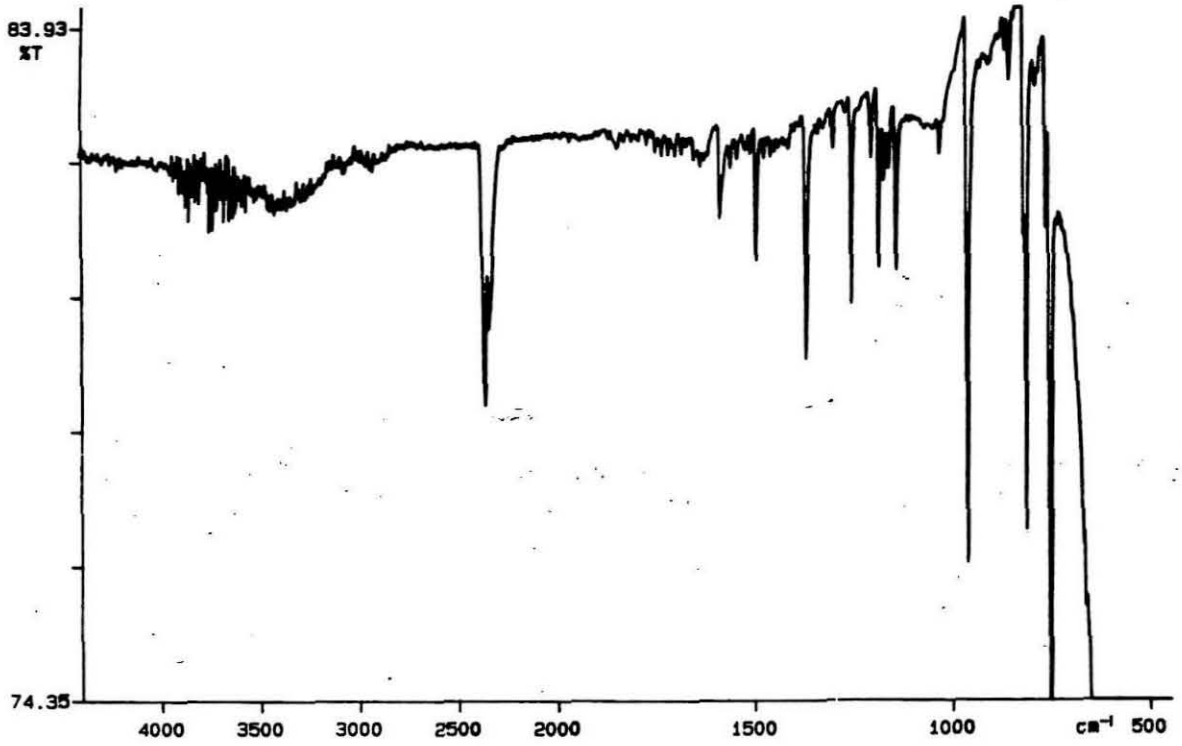
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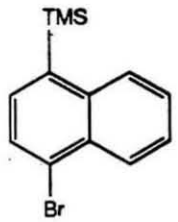
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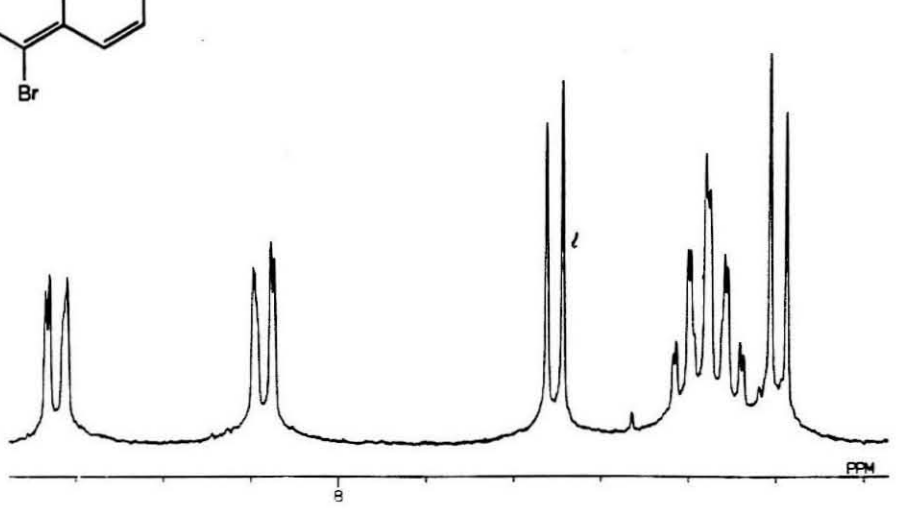
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PPM
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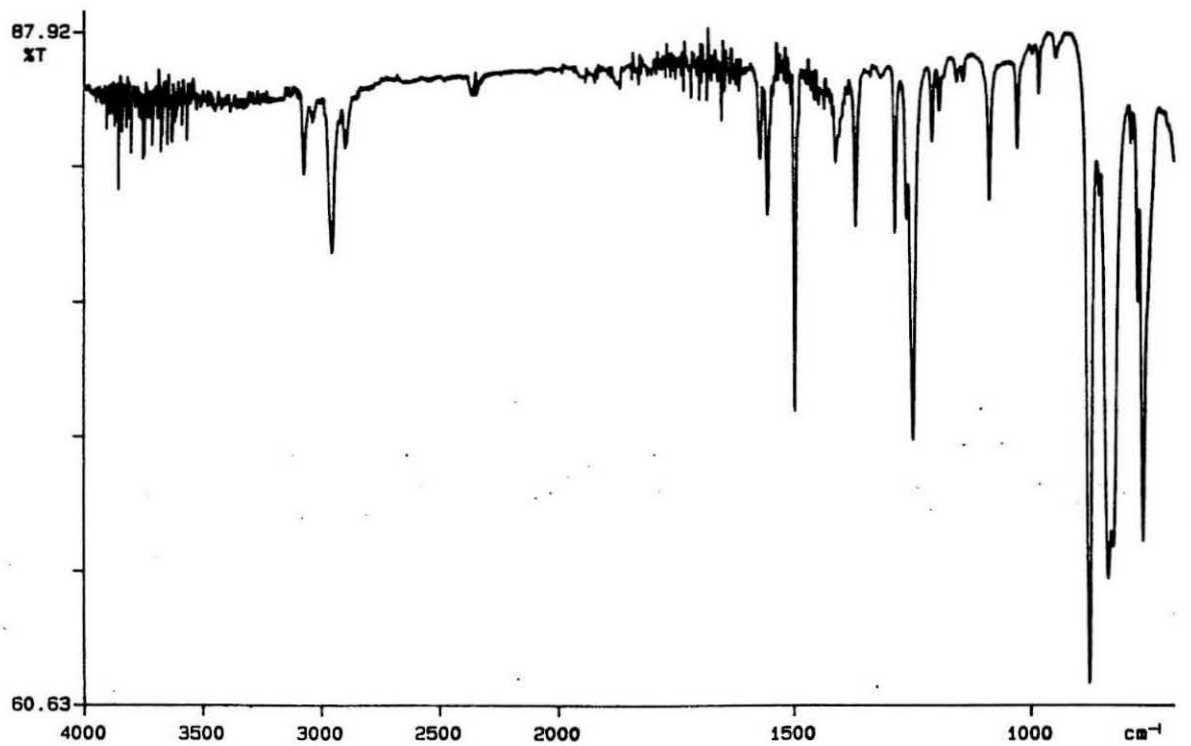
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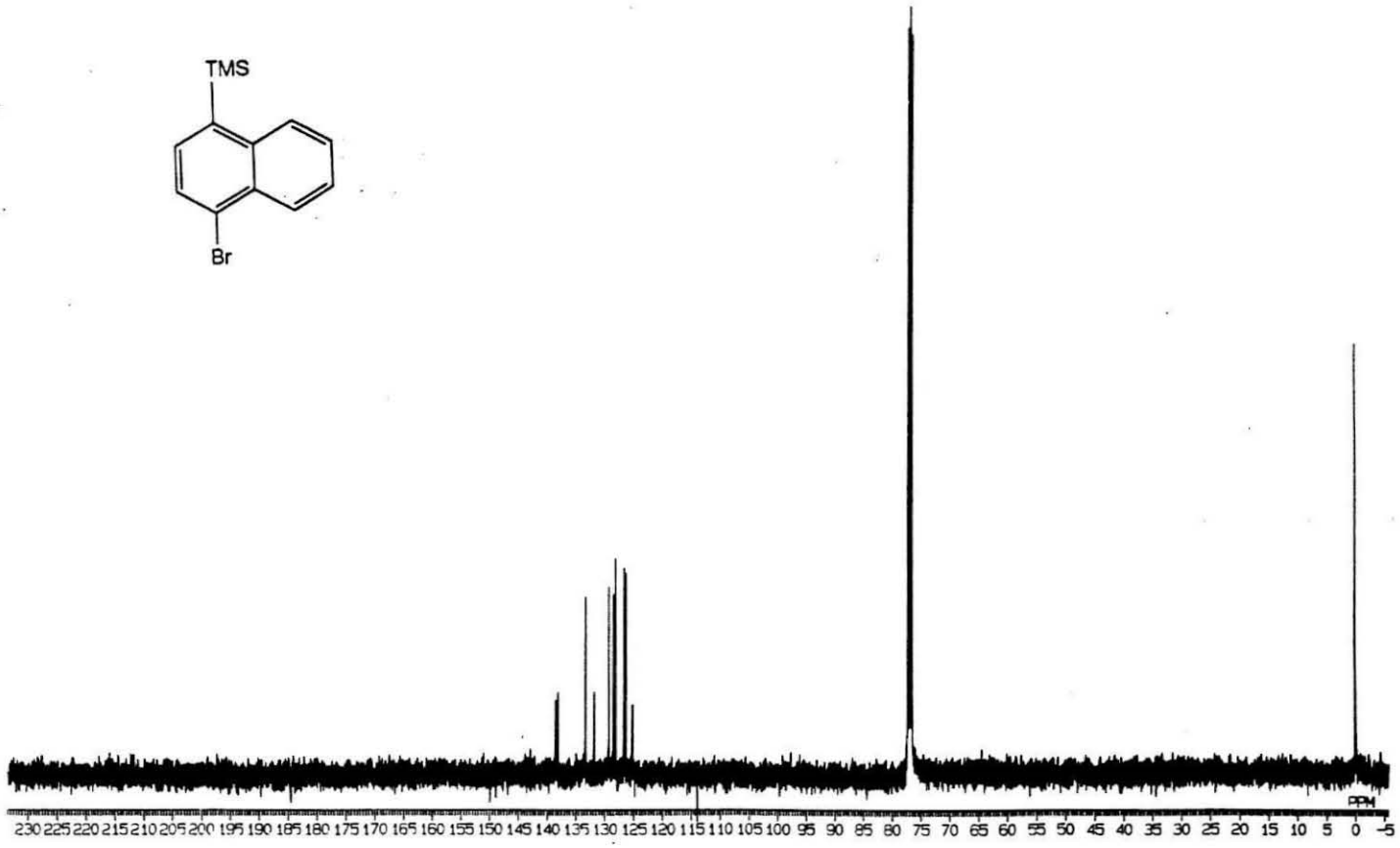
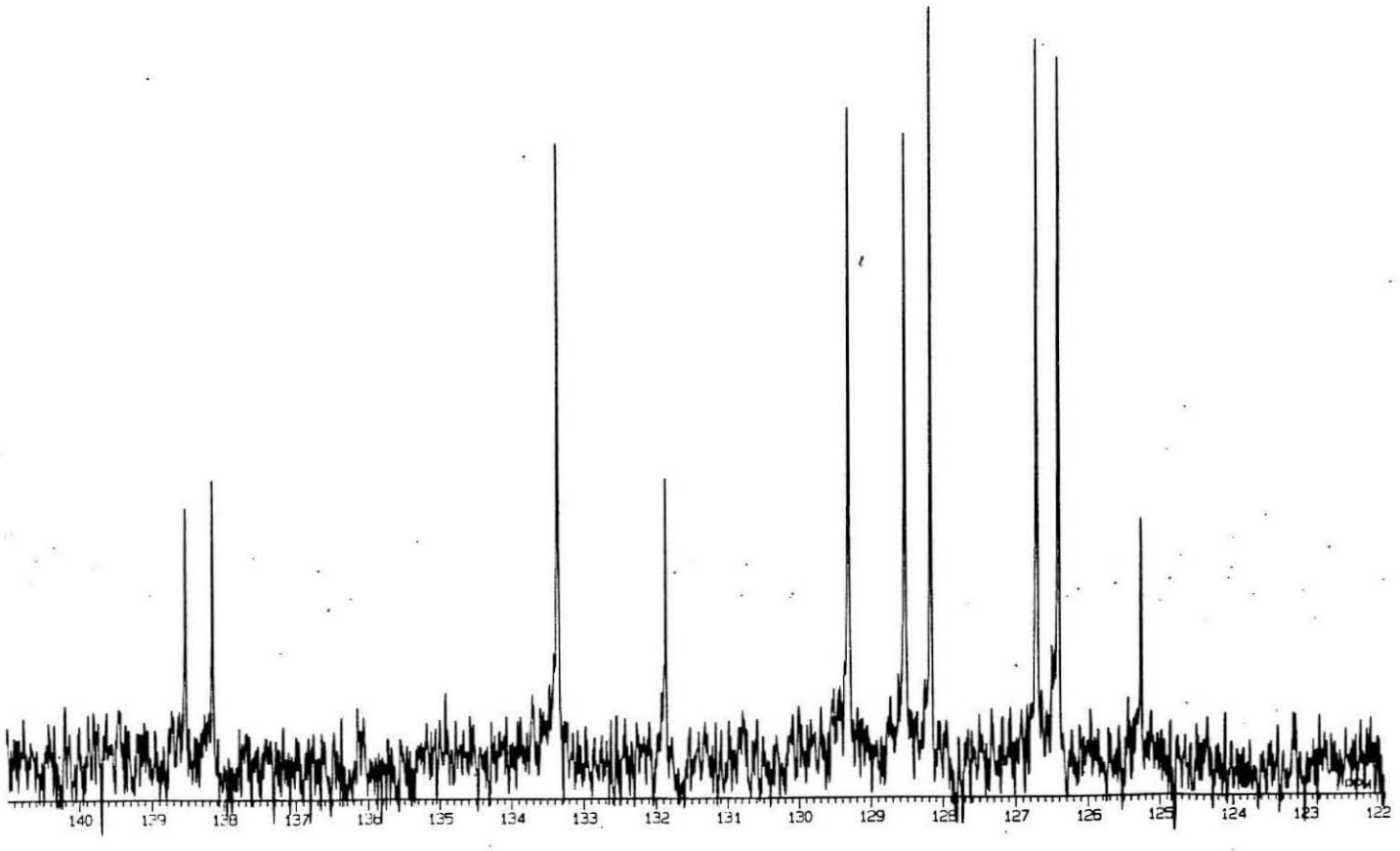
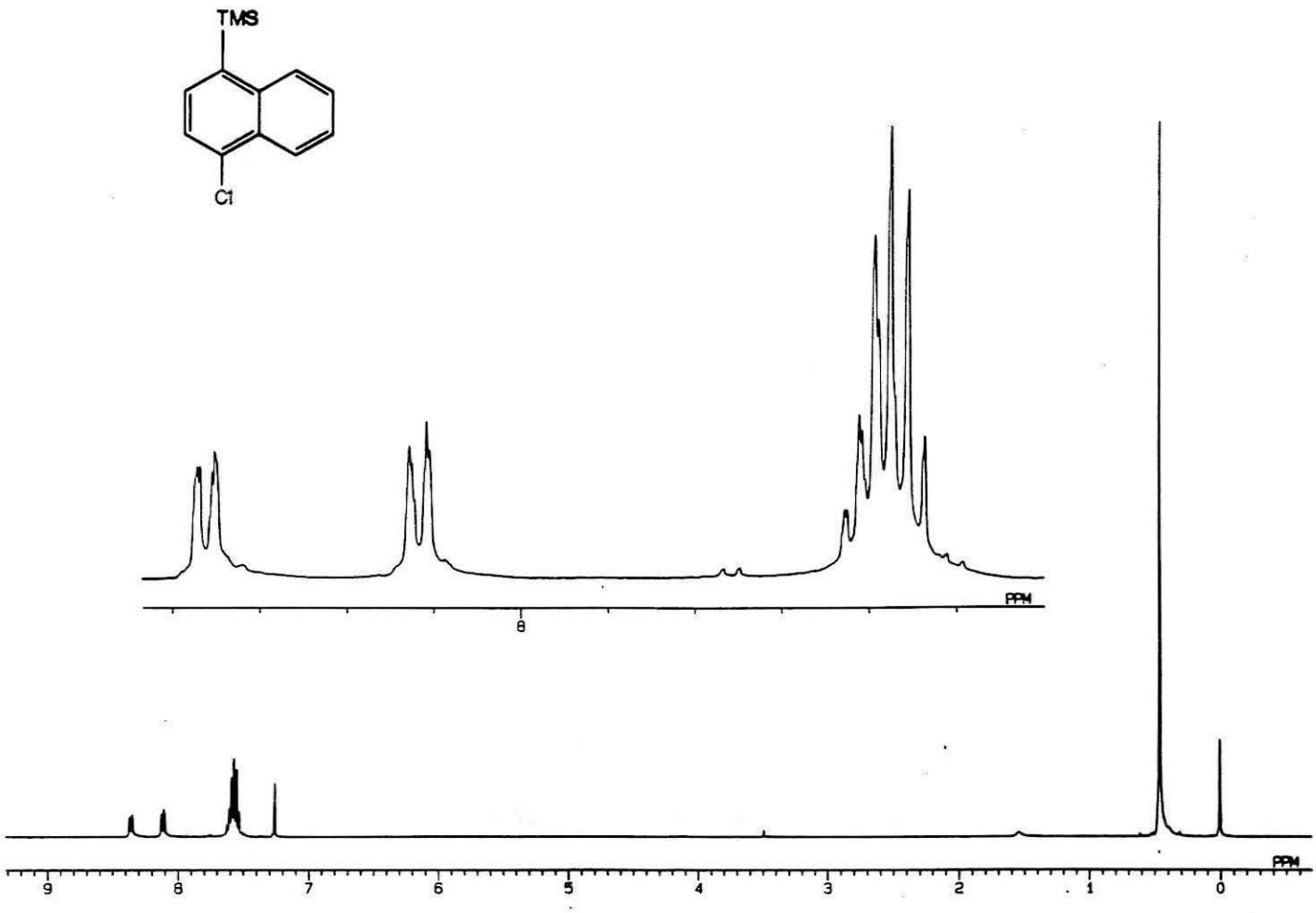
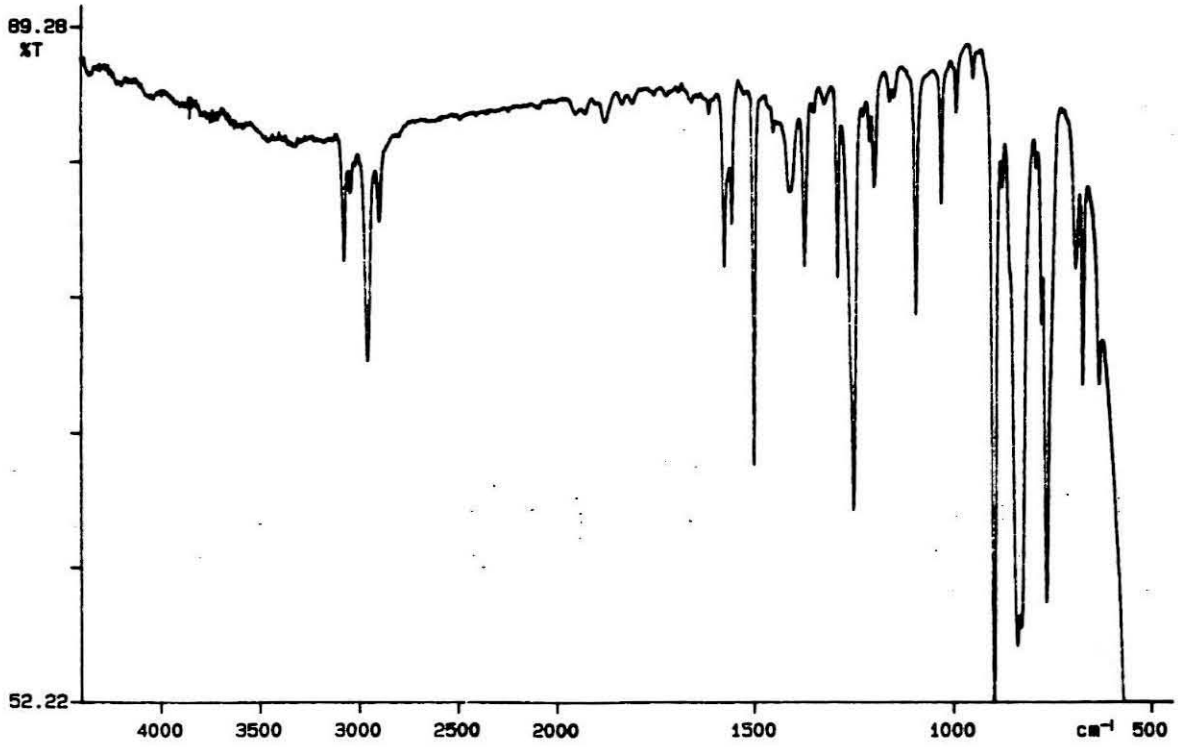
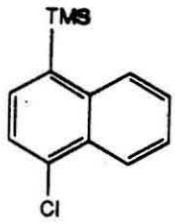
2000
1500
1000
cm⁻¹


TMS
Br
PPM
230 225 220 215 210 205 200 195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5

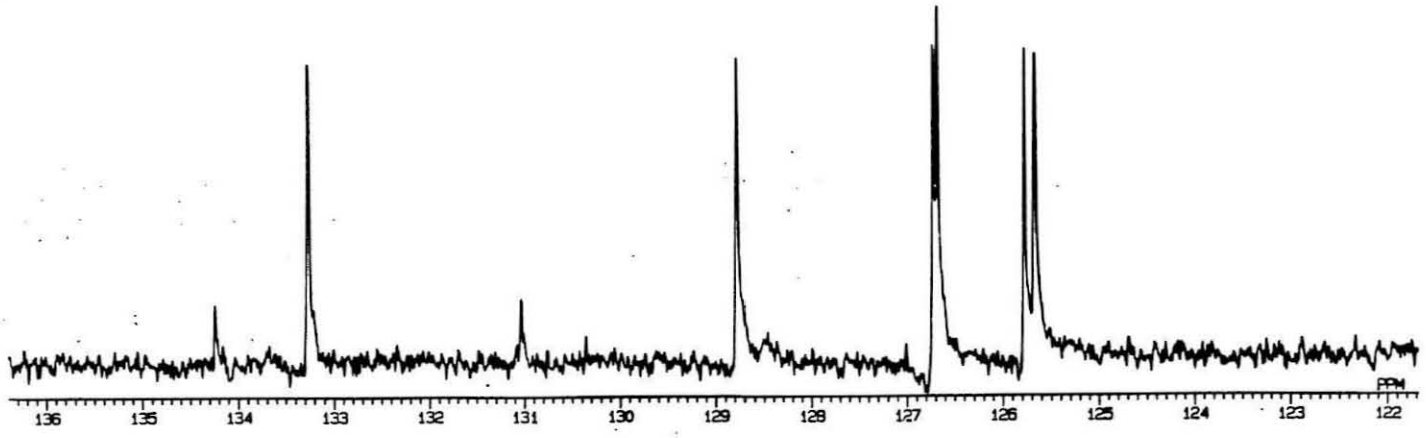

140 139 138 137 136 135 134 133 132 131 130 129 128 127 126 125 124 123 122

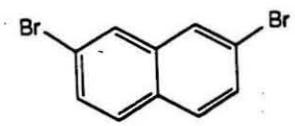

TMS
Cl
PPM
8
9
8
7
6
5
4
3
2
1
0
PPM

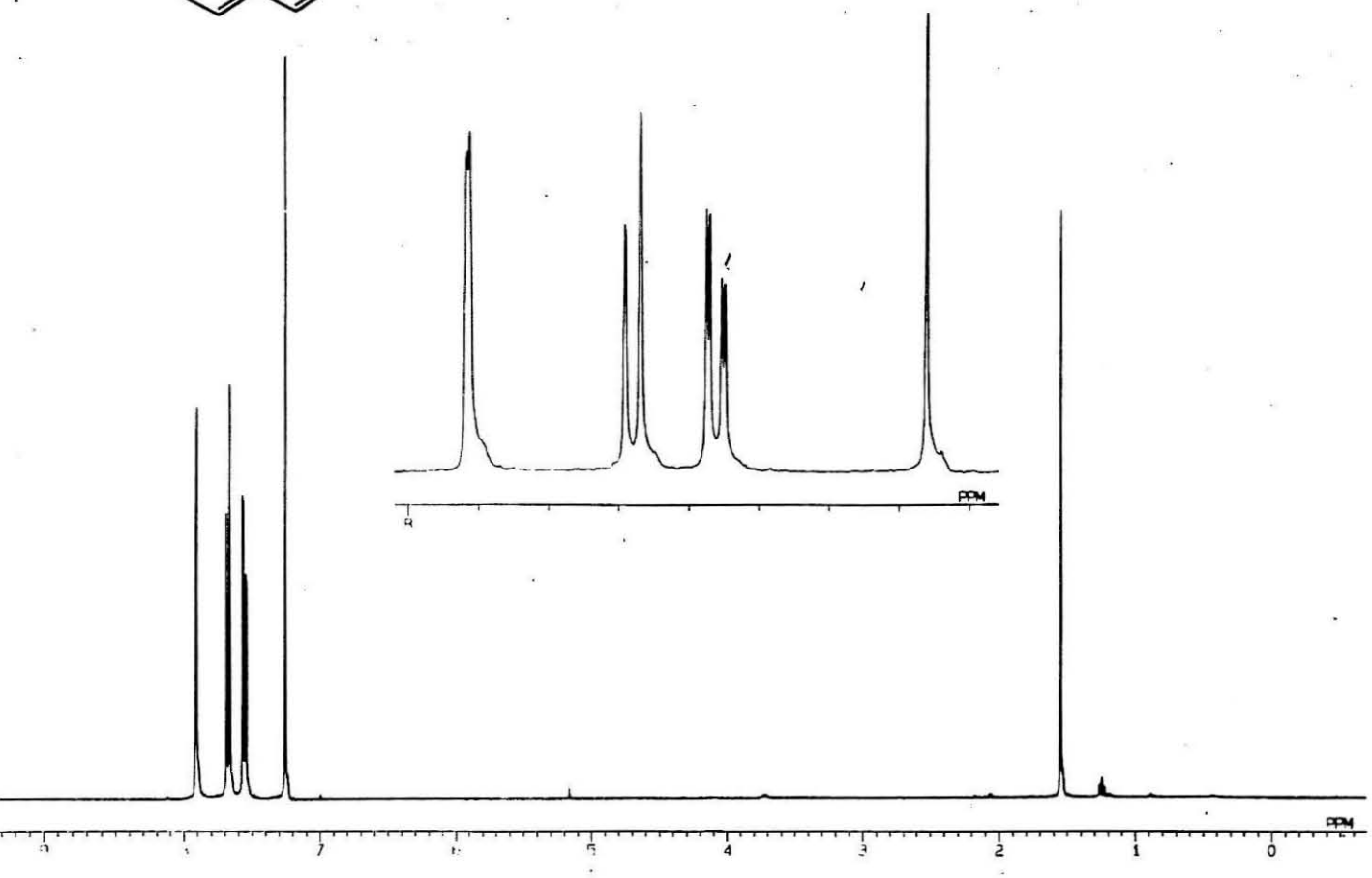

89.28
%T
52.22
4000
3500
3000
2500
2000
1500
1000
cm⁻¹
500

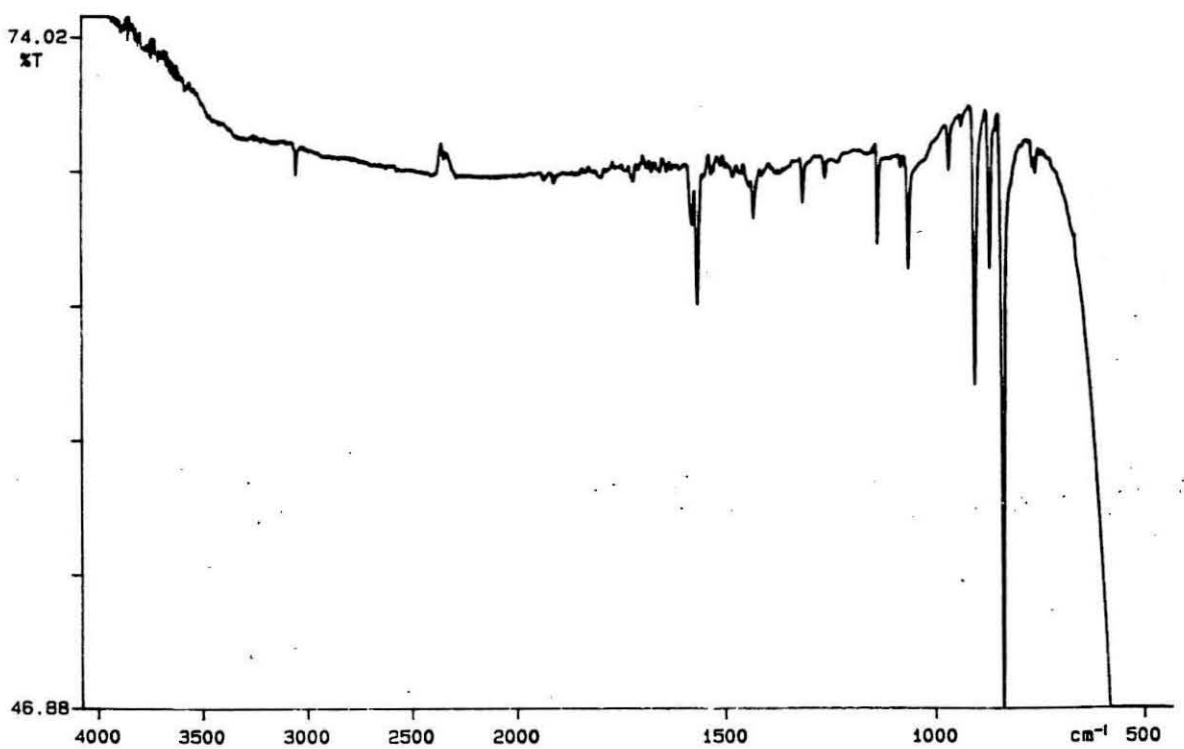

TMS
Cl

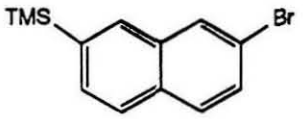
PPM
230 225 220 215 210 205 200 195 190 185 180 175 170 165 160 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0 -5

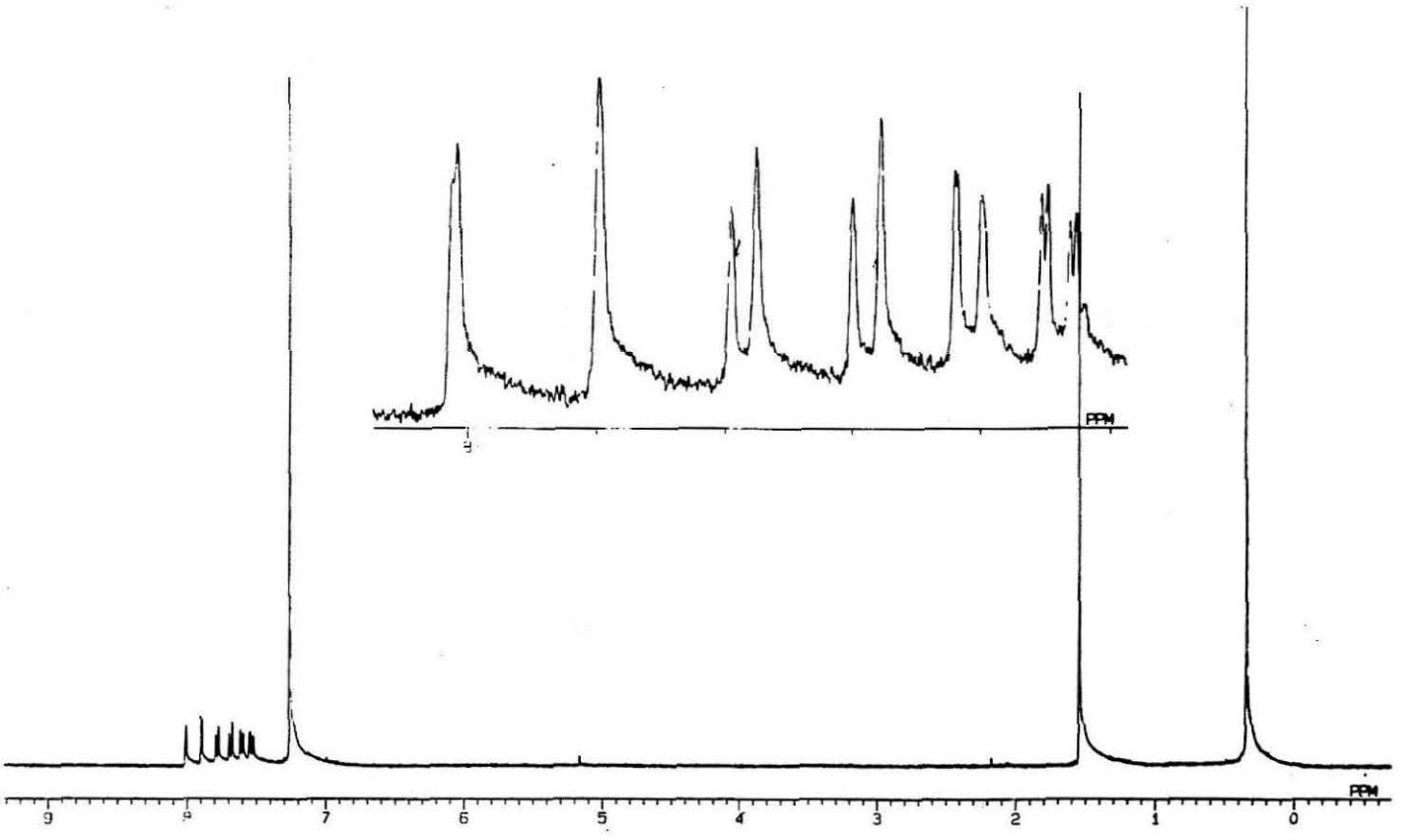

PPM
136 135 134 133 132 131 130 129 128 127 126 125 124 123 122

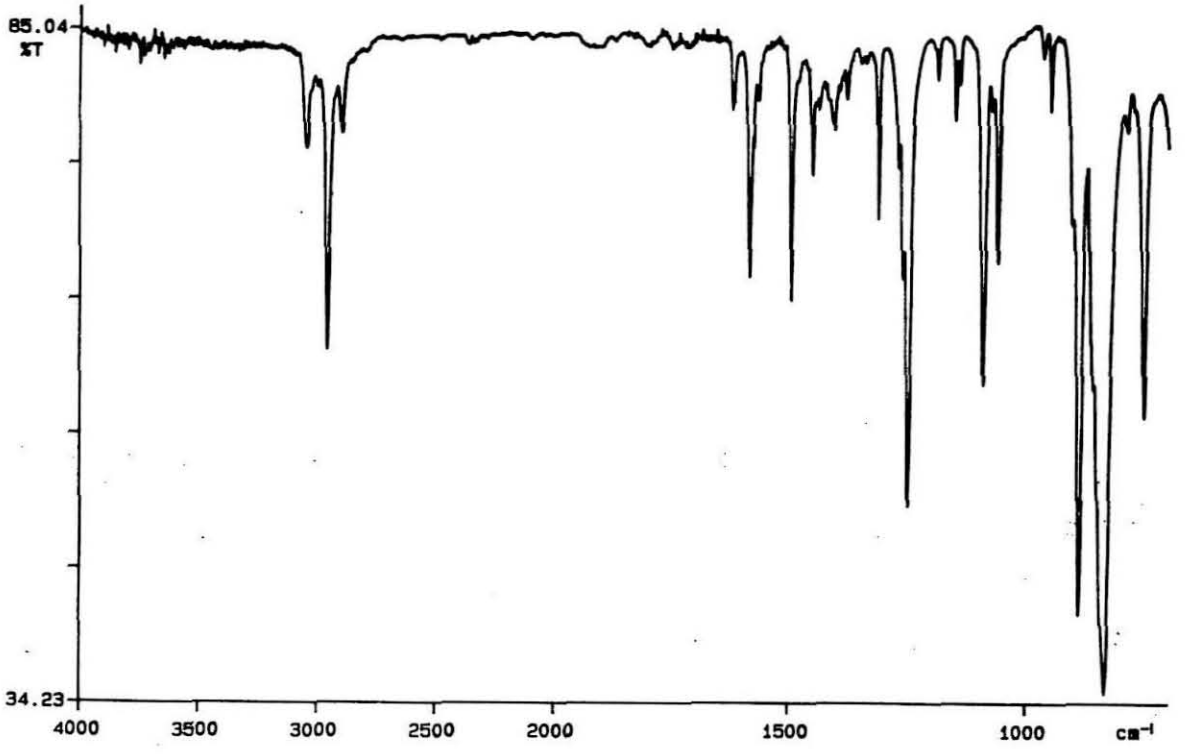

Br
Br

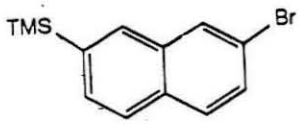

PPM
PPM
0
1
2
3
4
7

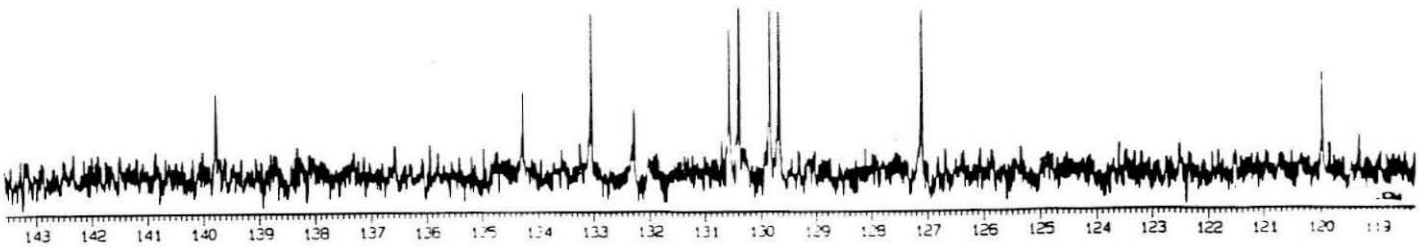

74.02
%T
46.88
4000
3500
3000
2500
2000
1500
1000
cm-1
500

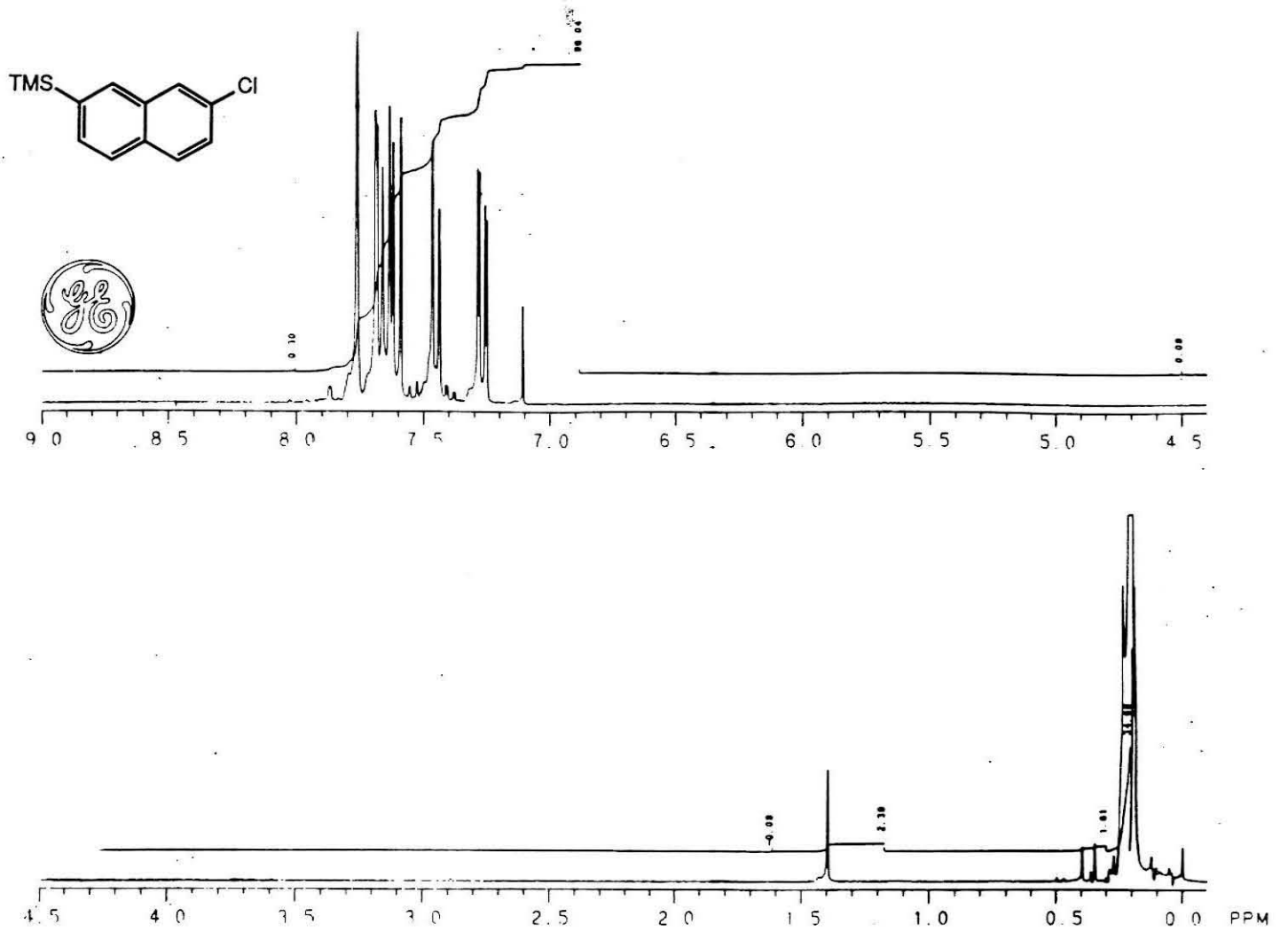

TMS
Br


PPM
9
8
7
6
5
4
3
2
1
0
PPM

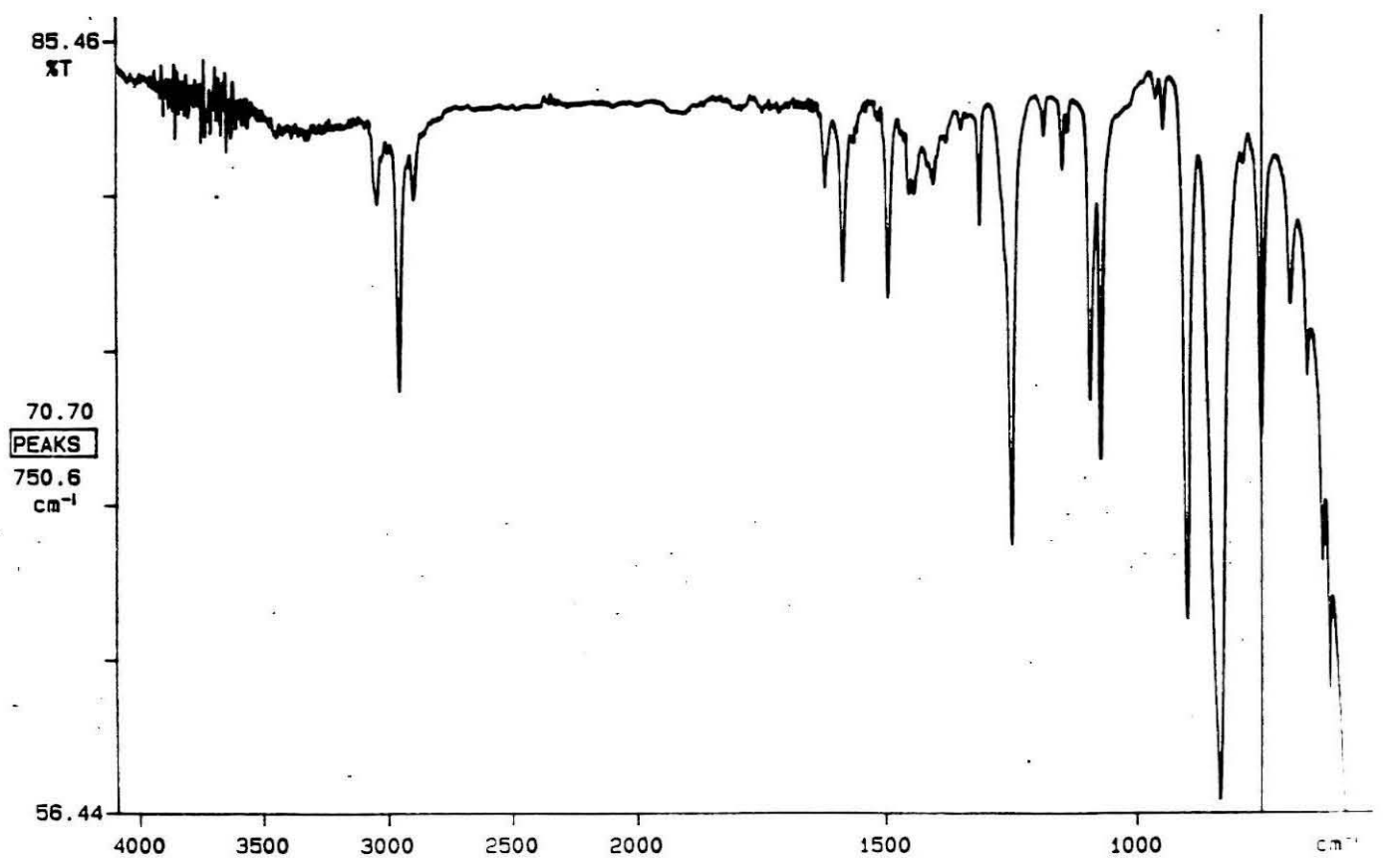

85.04
%T
34.23
4000
3500
3000
2500
2000
1500
1000
cm⁻¹

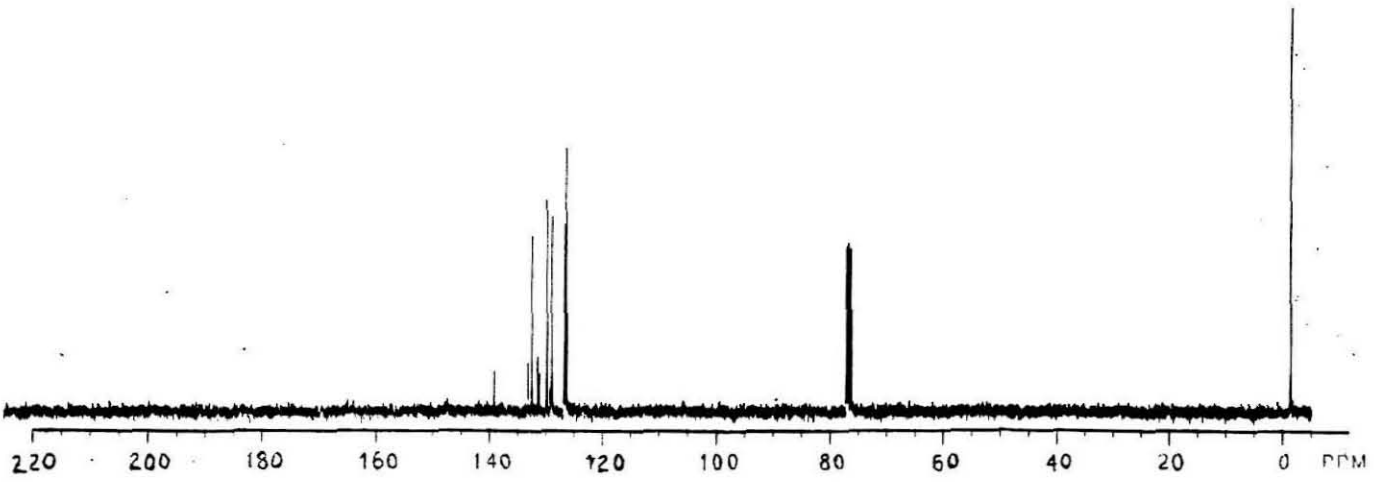

TMS
Br




TMS
Cl
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5

4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
PPM


85.46
%T
70.70
PEAKS
750.6
cm-1
56.44
4000
3500
3000
2500
2000
1500
1000
cm-1


220
200
180
160
140
120
100
80
60
40
20
0
PPM