HETEROAROTINOIDS WITH A FIVE-MEMBERED A-RING

By

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A-RING

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CHAPTER I

HISTORICAL

Introduction

The term "retinoids" refers to a broad spectrum of compounds, natural and synthetic, which structurally or spatially resemble the parent, retinol (**1**), and which may or may not exhibit any of the many biological effects elicited by vitamin A (retinol, **1**), vitamin A aldehyde (retinal, **2**), or vitamin A acid (retinoic acid, **3**) (see Figure 1). The biochemist

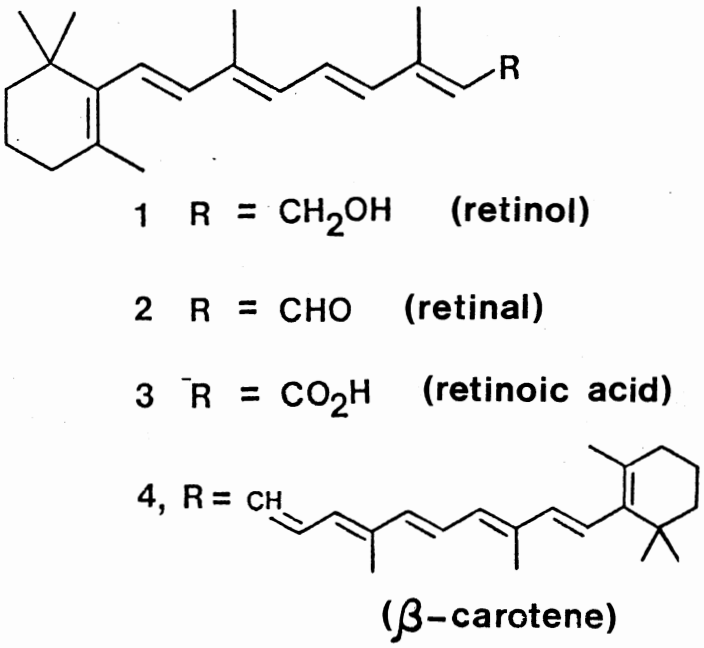


Figure 1. The Vitamin A Family.

M. B. Sporn proposed the following definition: "a retinoid is a substance that can elicit specific biological responses by binding to and activating a specific receptor or set of receptors".[95] The organic chemist, on the other hand, may prepare compounds which resemble retinol (**1**) but which feature important structural modifications, and, in collaboration with the biologist, he may report a preliminary biological evaluation. Such compounds have been called "retinoids" long before a complete biological profile was available.[26,62,94]

Several reviews, books, symposia and theses have discussed in detail the following aspects of the vitamin A family: (a) the history of the discovery, isolation, characterization, and synthesis of retinol (**1**), retinal (**2**), and retinoic acid (**3**);[4,33,35,79,96,97] (b) the nutritional aspects of vitamin A;[106] (c) the relationship between vitamin A deficiency and biological disorders including cancer;[4,35,79,106] (d) the visual cycle involving all-*trans*-retinal (**2**) and 11-*cis*-retinal;[109] (e) the role retinol plays in reproduction;[106] (f) the regulation of cell differentiation and cell proliferation by retinol and retinoic acid;[79,90,91] and (g) the history of retinoids as therapeutic agents including recent advances in the use of retinoids in the treatment of several forms of psoriasis and acne and preliminary clinical tests in the treatment of several types of cancer.[19,61,77,79,80,88,106] The scope of the background material in this work focuses on the metabolism of retinoids (part of the synthetic thrust of this work involves the preparation of potential metabolites of heteroarotinoids), mechanism of action (the recent discovery of the DNA binding/retinoic acid receptors deserves special attention),[12,42,81] a history of the new generation of heteroarotinoids and their arotinoid roots, recent toxicity studies which confirm the overt toxicity of arotinoids and which reveal the greatly diminished toxicity of heteroarotinoids, and a summary of two assays which were used in this work to assess the carcinostatic activity of a series of new heteroarotinoids.

Natural Retinoids and Metabolites

The metabolism of the natural retinoids begins with β-carotene (**4**), the major natural dietary source of retinol in man.[35] In the liver, oxidative cleavage gives retinal (**2**) which can be either reduced reversibly to retinol (**1**) or oxidized (irreversibly) to all-*trans*-retinoic acid (**3**).[35] From retinol, several oxidative and non-oxidative pathways are involved.

Several oxidative pathways have been suggested from many *in vitro* and *in vivo* studies by different research groups (see Figure 2 and references cited). From Figure 2 several sites of metabolic degradation are: (a) oxidation at C(4), (b) epoxidation of the double bond in the cyclohexyl ring, (c) oxidation of one of the methyl carbons of the *gem*-dimethyl pair, (d) oxidation of the methyl group at C(5) and (e) shortening of the polyene chain with partial reduction of the conjugated system. Thus, oxidation may occur at a double bond (to give **5**, **7**, **8**), at a carbon atom one bond removed from a double bond [allylic oxidation or benzylic oxidation (as will be shown for the metabolism of an aromatic retinoid) produced: **5**, **6**, **8-11**, **13-15**], or at a carbon atom two bonds removed from a double bond (such as **6**, **8**, **10**). Non-oxidative metabolism of either retinol or retinoic acid may involve isomerization (such as **12**, **14**, **15**) or the formation of carboxylic or phosphate esters (see Figure 3 and references cited therein for **16-20**).

Few of the metabolites characterized have also been studied with regard to their biological activity. 13-*cis*-Retinoic acid, believed to be a metabolite of all-*trans*-retinoic acid, has been shown to be equally active as the all-*trans* isomer both in *in vivo* and *in vitro* studies.[13,25,70,117] Although the isomerization of all-*trans*-retinal (**2**) is important in the visual cycle, it is not certain whether the isomerization of all-*trans*-retinoic acid (**3**) to 13-*cis*-retinoic acid (**12**) is necessary in the control of epithelial differentiation.[35] The 5,6-epoxy derivative **7** (Figure 2) has given varying results with respect to its biological activity in specific assays. One research group reported that **7** was 157%[50] (and later adjusted to 80%)[63] more active than all-*trans*-retinoic acid (**3**) in supporting growth in

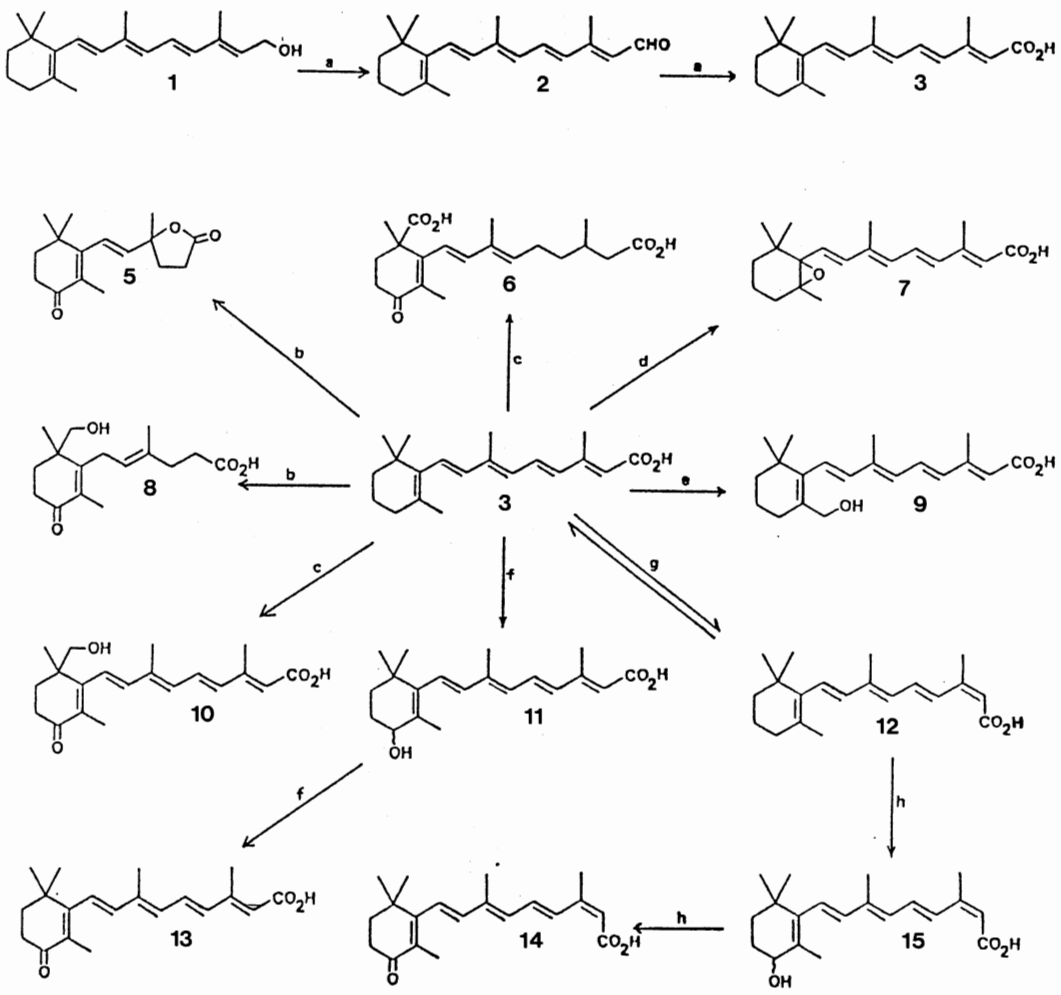


Figure 2. Some Oxidative Pathways of Retinol (**1**), Retinoic Acid (**3**) and 13-*cis*-Retinoic Acid (**12**). (a) Reference 35; (b) Reference 45; (c) Reference 83; (d) Reference 65; (e) Reference 44; (f) References 34, 36; (g) References 30, 37, 116; (h) References 34, 37.

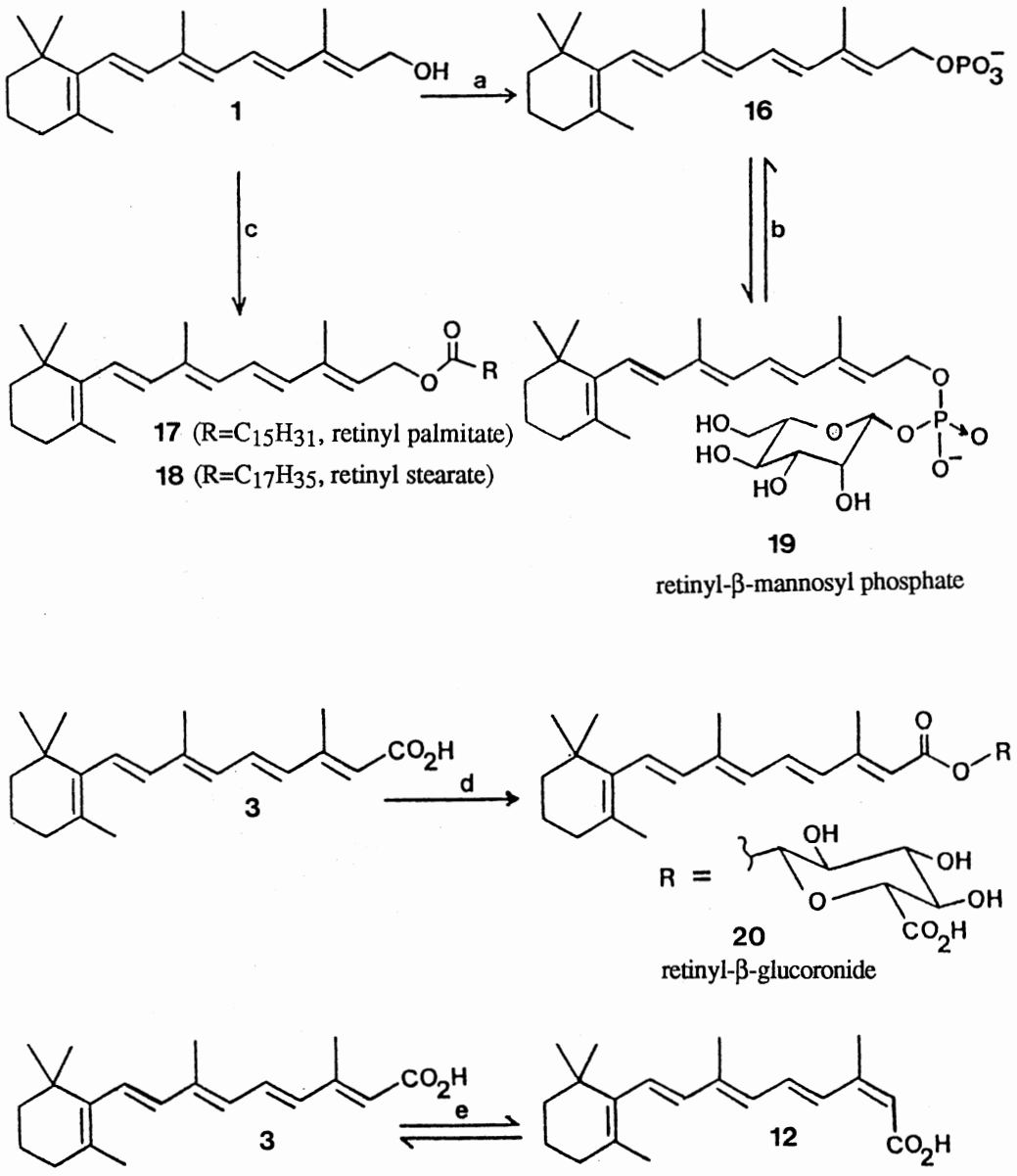


Figure 3. Some Non-oxidative Pathways of Retinol (**1**) and Retinoic Acid (**3**). (a) References 1, 27; (b) Reference 27; (c) Reference 41; (d) Reference 29; (e) References 30, 37, 116.

rats. In the hamster tracheal organ culture and vaginal smear assays, however, this metabolite was found to be much less active than retinoic acid (**3**).[70,93] Much work remains to determine whether any other metabolites of either vitamin A or of a synthetic retinoid may have activity equivalent to or better than that of vitamin A [particularly all-*trans*- (**3**) and 13-*cis*-retinoic acid (**12**)], especially in terms of carcinostatic and antitumor activity.

As observed in the metabolism of the natural retinoids, the metabolism of the synthetic aromatic retinoid Etretinate (**21**, used in the treatment of psoriasis)[19,80] also occurred via shortening of the polyene side chain[46] or by oxidation at a carbon atom one bond removed from a double bond (benzylic oxidation in this case, see Figure 4).[46] It is interesting to note that allylic oxidation of the methyl groups bonded to the polyene side chain has not as yet been reported for either vitamin A or Etretinate. Etretinate, which contains an aromatic methyl ether linkage, was also metabolized by the cleavage of the ether linkage.[46]

This collection of metabolic data is important in the consideration of potential oxidation sites of heteroarotinoids[35] (see Aromatic Retinoids and Heteroarotinoids) which also contain loci vulnerable to oxidation of carbon atoms one and two bonds removed from a double bond, for epoxidation, and for the cleavage of an ether linkage. For a more complete discussion of the metabolic studies of retinoids to date, see References 1, 27, 29, 30, 34-37, 41, 44-46, 50, 63, 65, 70, 83, 93, 116, 117.

Mechanism of Action

The biological effects of retinoids are numerous and include the regulation of (a) enzyme biosynthesis (i.e. the synthesis of ornithine decarboxylase),[60,107,108] (b) the synthesis and distribution of membrane glycoproteins and other molecules important in membrane function,[60,85] (c) the effects of growth factors (i.e. the epidermal growth factor),[60,85] (d) gene expression,[60,85] and (e) the immune system.[60] The mechanisms

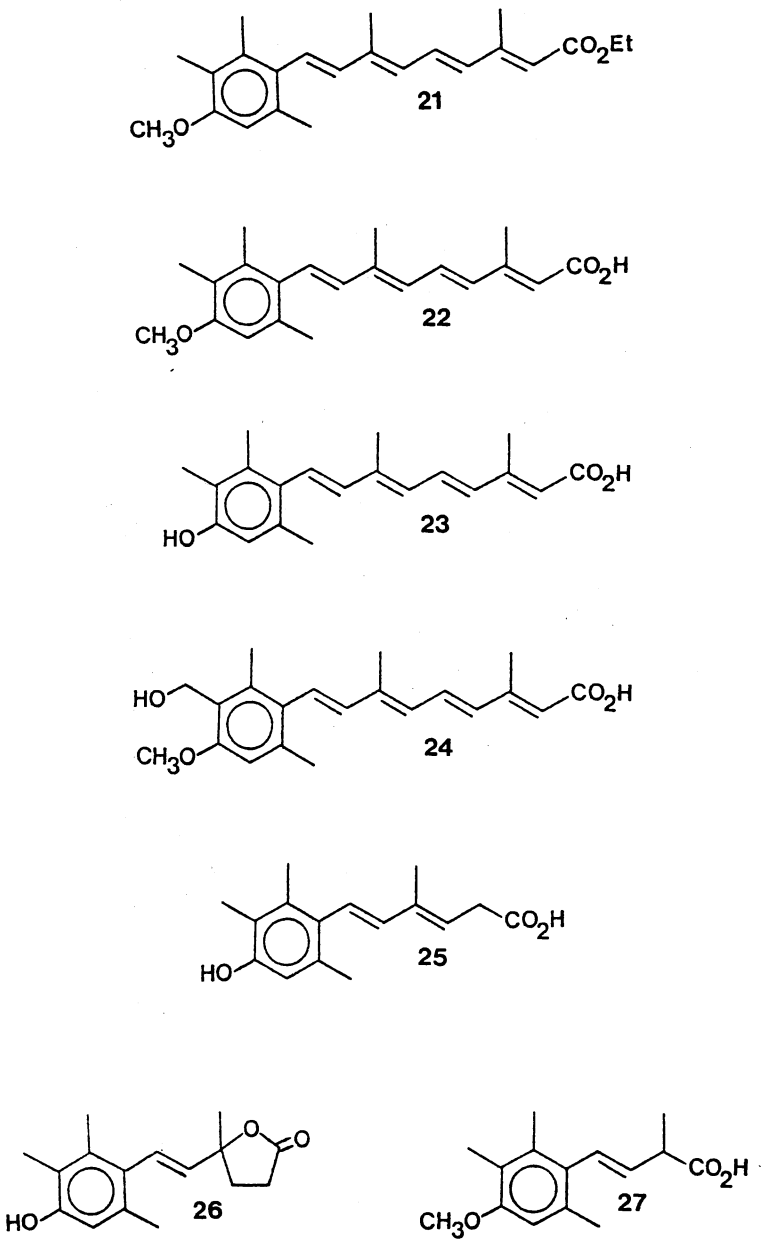


Figure 4. Etretinate (**21**) and Some Metabolites Found in Either the Bile of Rats (**22-24**, see Reference 46) or Urine of Humans (**25-27**, Reference 46) Administered Etretinate.

of action that have been evoked, therefore, are numerous. Several books and reviews have discussed in detail many of the biological effects of retinoids and probable mechanisms of action to which the reader is alerted.[4,28,60,61,72,79,88,90,91,96]

The mechanism that agrees best with the largest range of *in vitro* and *in vivo* data is that retinoids affect gene expression.[60,85] Green and co-workers[38] showed that retinoids suppress the synthesis of a 67-kDa keratin (keratins are fibrous proteins that form the chemical basis of horny epidermal tissue)[115] at the level of mRNA synthesis. Wang and co-workers[110] discovered nucleotide sequences in DNA in F9 cells (a type of murine cancer cell), the transcription of which was regulated by retinoic acid.

It was postulated early that gene expression could be regulated by a complex of the retinoid with a protein receptor.[17,85,91] A cellular retinol binding protein (cRBP) and a cellular retinoic acid binding protein (cRABP) were isolated and characterized.[5,67,74-76] Experimental evidence suggests that the retinol-cRBP complex penetrates the nuclear membrane into the nucleoplasm and delivers retinol to the chromatin[57] (polymerized nucleic acid/protein complex present in chromosomes).[115] There is no evidence, however, for the retinol-cRBP complex remaining bound to the chromatin.[57] Likewise, the retinoic acid-cRAPB complex has been found in nuclear fractions,[66,67,87,104,112] and evidence suggests that this complex mediates the binding of retinoic acid to transcriptionally active chromatin in F9 embryonal cancer cells,[66] but the nature of the binding is not certain (whether the suggested binding is to DNA, RNA or the protein components of the chromatin).[91] Thus, although cRBP and cRABP may be involved in the overall role by which retinol and retinoic acid exert their numerous effects (i.e. cell differentiation), it is yet not certain whether the roles involve direct regulation of gene expression by binding to DNA.[60,91]

An important discovery was very recently made by Chambon and co-workers[81] and by Evans and co-workers.[42] A protein receptor was identified which contains a DNA-binding domain as well as a ligand binding site. Of several possible ligands,

retinoic acid was found to be the ligand to which the polypeptide receptor bound specifically and with high affinity. Because this very recent discovery is not discussed in any of the recent (but older) books and reviews concerning retinoids, a brief description of some of the experiments involved in this finding will be given.

Evans and co-workers[42] isolated and characterized a cloned full-length cDNA (which they called λhK1R) which encodes for a 462 amino acid polypeptide. The polypeptide (molecular mass 50,772), called hRR (human retinoic acid receptor), contained DNA-binding and ligand-binding domains which were similar to those present in steroid and thyroid hormone receptors. The DNA-binding domain consists of a sequence of 66 amino acids which closely resembles the DNA-binding domain of hGR (the human glucocorticoid receptor). In order to determine the identity of the ligand for the ligand-binding site of this new receptor, the following was done: the DNA-binding domain of the polypeptide receptor was replaced by the DNA binding domain of hGR. This was done by inserting the gene for this hybrid receptor into CV-1 cells (derived from the kidney of a male adult African green monkey)[46a], thus providing a means for the biosynthesis of the hybrid receptor. A reporter gene, MMTV-CAT, was also inserted. This gene is so called because the changes in the activity of CAT (chloramphenicol acetyltransferase enzyme) can be monitored upon induction by hGR (or a mimic peptide containing the hGR DNA-binding domain). A large number of natural and synthetic ligands (i.e., testosterone, oestrogen, cortisol, and others) were tested. Retinoic acid and retinol were also tested due to their hormone-like activities. Surprisingly, retinoic acid caused a dramatic increase in CAT activity. The ED_{50} (effective dose which causes one half of the population in the system of an assay to respond positively to a test agent) for CAT activity using retinoic acid was 6×10^{-10} M which is consistent with ED_{50} values observed for retinoic acid in several biological assays (i.e. TOC, S91, F9 and HL-60 assays).[98] The ED_{50} for retinol was greater than 1×10^{-7} which corresponds approximately to a more than 160-fold reduction in affinity (for the receptor) relative to

that measured for retinoic acid. Furthermore, the affinity of retinyl acetate and retinyl palmitate (**17**) for the receptor was even lower. None of the other ligands induced any CAT activity. To confirm the affinity of the non-hybrid receptor for retinoic acid, COS-1 cells (fibroblast-like cells derived from CV-1 Simian cells) were injected with λhK1R (the gene encoding for the receptor) and, as expected, the capacity for ^{3}H labelled retinoic acid increased in the COS-1 cells. Thus a gene sequence was discovered, the polypeptide product of which contains a DNA-binding domain and which also binds specifically and with high-affinity to retinoic acid (**3**). Both Evans[42] and Chambon[81] and their respective co-workers predicted the potential future discovery of one or more other human retinoic acid nuclear receptors. Shortly after the initial discovery of a retinoic acid receptor, Chambon and co-workers[12] discovered a second human retinoic acid receptor (now called hRAR-β) which was found to bind to retinoic acid with even better affinity than that observed for the first nuclear receptor (now called hRAR-α).[12]

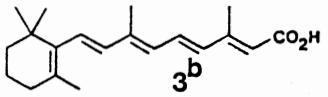
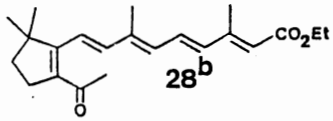
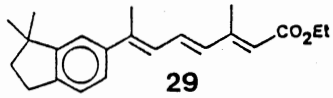
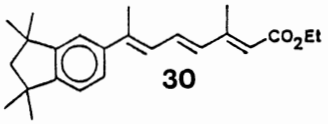
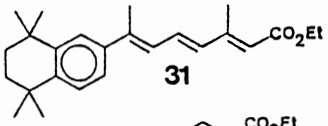
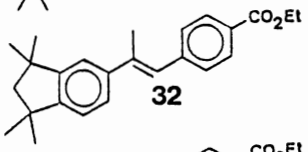
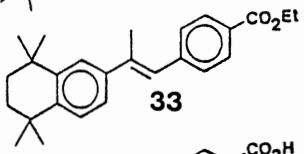
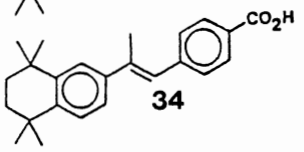
From the above discoveries, it appears quite possible that many of the biological effects of retinoids (including cancer chemoprevention) are the result of the direct regulation of gene expression (i.e. oncogene expression in cancer chemoprevention) by the complex of retinoids with specific DNA-binding receptors like those identified by Evans and co-workers[42] and Chambon and co-workers.[12,81]

Arotinoids and Heteroarotinoids

In the late 1970's Bollag and co-workers[62,64] at Hoffmann-La Roche found that incorporation of an aromatic ring in the retinoic acid skeleton could improve the therapeutic ratio relative to retinoic acid by a factor as great as ten. This therapeutic ratio was determined from the dose (mg/kg) which caused 50% regression of papillomas in Swiss albino mice relative to that dose (mg/kg) which produced the hypervitaminosis A syndrome. Etretinate (**21**) was such a compound. Because of the promising activity of the cyclopentenyl analogue **28**[11,62] (see Table I), investigators at Hoffmann-La Roche

TABLE I

THE THERAPEUTIC PROFILE OF AROTINOIDS BASED ON THE MOUSE PAPILLOMA ASSAY AND THE OBSERVATION OF SYMPTOMS ASSOCIATED WITH HYPERVITAMINOSIS A[a]

Arotinoid	Antipapilloma Activity ED_{50} (mg/kg/day)	Hypervitaminosis A (mg/kg/day)	Therapeutic Ratio
 3[b]	400	80	5
 28[b]	200	25	8
 29	12.5	12.5	1
 30	3	3	1
 31	1.5	0.75	2
 32	< 0.2	0.2	< 1
 33	0.05	0.1	0.5
 34	> 0.8[c]	0.1	> 8

[a]Reference 62 (see also Reference 79).

[b]Not an arotinoid but included for comparison.

[c]At 0.8 mg/kg only 38% regression of papillomas was observed. A higher dose was not tried (or not reported).

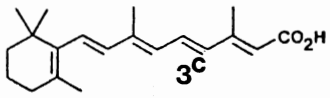
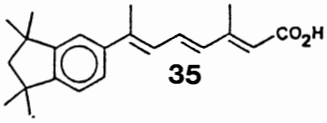
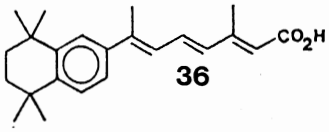
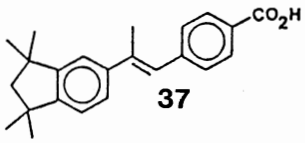
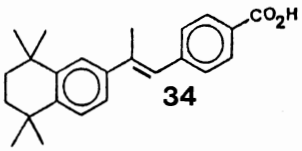
proceeded to prepare the aromatic retinoid **29** containing a five-membered ring. This successful modification (see Table I) spurred further research including the synthesis of analogues **30** and **31** (containing a six-membered ring).[62] The modification which resulted in a series of aromatic retinoids with very high antipapilloma activity (ability to cause regression of this type of skin tumor) involved the incorporation of a second aromatic ring in the polyene side chain (i.e. **32-34**).[62] The most notable of these arotinoids (in this text this term will also include all retinoids containing an aromatic ring) is the tetrahydronaphthalene derivative **33** which had a therapeutic ratio ten times greater than retinoic acid (see Table I). Although the carboxylic acid **34** showed less activity than the corresponding ester **33** in the papilloma assay (see Table I), more tests have been reported for the carboxylic acid (see Table II), presumably due to the commonly held belief that the carboxylic acid forms of the retinoids are the active forms *in vivo* because of their ability to bind to cRABP.[48]

Other arotinoids were prepared by Dawson (see Table III) and co-workers, some of which displayed good activity.[21-26] One of these, naphthalene derivative **39**, showed good activity in the ornithine decarboxylase (ODC) assay and showed better activity than retinoic acid in the tracheal organ culture (TOC) assay.[26] The main problem, as will be discussed later (see Toxicology), is that both of the potent tetrahydronaphthalene derivatives **34** and **39** were found to be extremely toxic.[26,59]

With the intent of maintaining the basic skeleton for the potent arotinoids **33** and **34** and hopefully reducing the toxicity (relative to arotinoids **33** and **34** and to retinoic acid), it was one goal of Berlin and co-workers[111] and Dawson and co-workers[26] to prepare arotinoids containing a heteroatom [see Figure 5a (X = O, S, S(O)] in the place of the $C(CH_3)_2$ group *para* to the central double bond (thus still blocking the potential oxidation site at C(4) of the basic retinoid structure). These heteroarotinoids showed great activity in the ODC and TOC assays (see section entitled Pharmacological Activity of Heteroarotinoids)[26,111] and some have been shown to be much less toxic than the

TABLE II

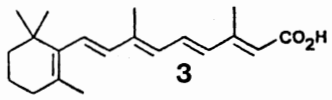
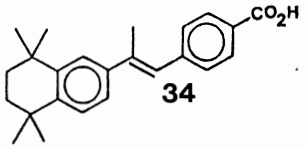
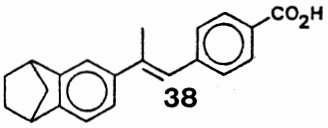
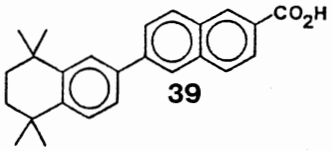
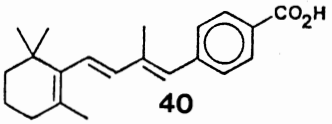
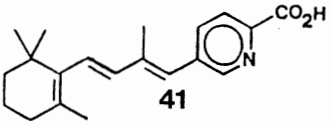
THE ABILITY OF AROTINOIDS TO INDUCE DIFFERENTIATION IN THE HUMAN PREMYELOCYTIC LEUKEMIA CELL LINE (HL-60) AND TO COMPLETELY INHIBIT SCALE FORMATION IN THE SKIN OF CHICK EMBRYO FOOT[a]

Arotinoid	Induction of differentiation HL-60 assay[b] ED_{50}	Complete inhibition of scale formation, M
 3[c]	1×10^{-7} (1×10^{-8})[e]	10^{-5}
 35	8×10^{-8}	10^{-7}
 36	8×10^{-9}	10^{-8}
 37	[d]	10^{-7}
 34	7×10^{-8}	10^{-8}

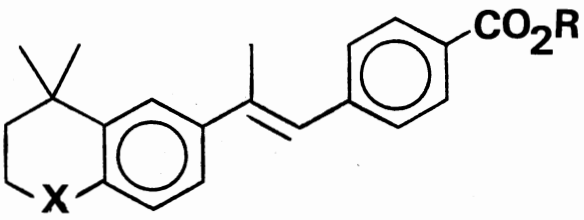
[a]Reference 10.
[b]See Assays of Activity.
[c]Not an arotinoid but included for comparison.
[d]HL-60 activity not reported.
[e]Reference 13.

TABLE III

ACTIVITY OF SELECTED AROTINOIDS IN THE TOC AND ODC ASSAYS[a]

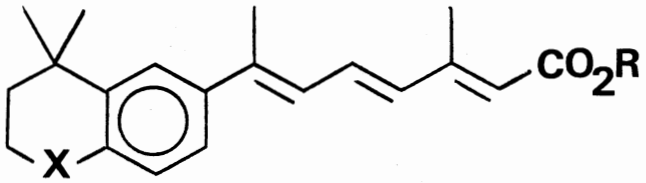
Arotinoid	TOC Assay ED_{50}, M (mg/kg/day)	ODC dose, nmol	ODC % inhibition of control
 3	1 x 10^{-11}	1.7	88
 34	1 x 10^{-12}	17 1.7	91 89
 38	6 x 10^{-10}	17 1.7	69 33
 39	3 x 10^{-12}	17 1.7	80 56
 40	3 x 10^{-10}	17 1.7	77 34
 41	>1 x 10^{-10}	17 1.7	68[b] 29[b]

[a]Reference 26.
[b]Reference 21.



X = O, S, S(O), SO_2,
NH, NMe, NAc

Figure 5a. Diaryl Heteroarotinoids.



42 (X = O, R = H)
43 (X = S, R = H)
44 (X = S, R = Et)

Figure 5b. Monoaryl Heteroarotinoids.

hydrocarbon counterpart **34**.[26,59] Indeed, Hoffmann-La Roche secured a German patent for several of these heteroarotinoids (Figure 5a, X = O, S, S(O), SO_2, NH, NMe, NAc).[54]

As can be seen in Tables I and II, the monoaryl retinoids with a triene side chain also showed therapeutic ratios comparable with that of arotinoids **33** and **34** (TTNPB).[62] In fact, in the HL-60 assay the arotinoid **36** possessing the octatrienoic acid side chain gave an ED_{50} nearly 10 times better than that of **34** (TTNPB).[10] Heteroarotinoid analogues of **36** (Figure 5b, X = 0, S) were prepared by Berlin and co-workers[100] and these showed good activity. In fact, heteroarotinoid **44** showed better activity than the standard, 13-*cis*-retinoic acid (**12**), with complete inhibition of ODC activity.[100]

It is evident that incorporation of a heteroatom in the retinoid skeleton does not reduce high activity. More importantly, as will be discussed in the next section, the heteroarotinoids (those tested to date) are much less toxic than the potent arotinoid **34** (TTNPB) by several orders of magnitude and are even less toxic than the standard, all-*trans*-retinoic acid (**3**).[26,59] New heteroarotinoids will be presented whose preparation and biological activity are the central focus of this work.

Toxicology

The toxic effects of retinol, all-*trans*-retinoic acid (**3**) and 13-*cis*-retinoic acid (**12**) are well documented[52,61,106] and will only be discussed briefly. A particular emphasis will be given to the toxicology of synthetic retinoids, some of which have been recently prepared and which exhibit better toxicity profiles relative to the above parent compounds while maintaining promising carcinostatic activity as assessed in several experiments.

The toxic effects of vitamin A in humans have been known for more than 100 years (before vitamin A was known to exist)[52,61] and the symptoms associated with large doses of this vitamin are collectively called the "Hypervitaminosis A Syndrome". The toxic side effects of retinol (**1**) include cheilitis, severe headaches, conjunctival inflammation,

nausea, vomiting, bulging fontanelles in infants, dryness and scaling, tenderness of bones, and others.[61] Side effects from the topical treatment of all-*trans*-retinoic acid (**3**, Tretinoin, Retin-A) include skin irritation (redness/scaling) and reversible hypopigmentation.[61] Oral treatment of all-*trans*-retinoic acid (**3**) may cause headache, dizziness, cheilitis, xerosis, anorexia and others.[61] Side effects from the oral treatment of 13-*cis*-retinoic acid (**12**, Isotretinoin, Accutane) include abdominal pain, cheilitis, conjunctivitis, excessive thirst, xerosis and others.[61] Serious teratogenic properties of 13-*cis*-retinoic acid (**12**) have been reported in animals and more recently in humans.[61] Etretinate (**21**), just recently approved by the FDA, gives some of the same symptoms as the natural retinoids but also poses two additional problems: (1) there are increasing reports of abnormalities in liver function in patients administered this drug and (2) marked teratogenic properties due to the long half-life of this drug after chronic therapy.[61]

Early reports of improved therapeutic ratios (improved activity relative to toxicity) for a series of aromatic retinoids (i.e. **29-33**, see Table I) relative to retinoic acid (**3**) appeared promising.[62] These therapeutic ratios were based on the data from only one activity assay (the regression of papillomas) and from a limited means of measuring toxicity. For example, the ethyl ester arotinoid **33** (see Table I) appeared 8000 times more active than the standard (retinoic acid, **3**) in the regression of papillomas but was 800 times more toxic than the standard **3**. Thus, an apparent 10-fold enhancement in the relative therapeutic index exists. Different therapeutic ratios, however, may be obtained if other assays are used to measure activity. For example, the carboxylic acid counterpart **34** (which has been tested in several different assays)[98] is 300 times more active than the standard (**3**, retinoic acid) in the inhibition of scale formation in the chick embryo (see Table II),[10] but gave ED_{50} values 20 and 10 times better than the standard **3** in the F9 and TOC assays,[98] respectively, and showed essentially the same activity as the standard in the ODC[26] and HL-60 assays.[10] While the activity of **34** varies relative to retinoic acid (**3**), depending on the assay, the toxicity of **34** has consistently shown to be much more

toxic than the standard by several orders of magnitude.[26,59,62] The method of determining the relative toxicity based on the hypervitaminosis syndrome showed arotinoid **34** to be 800 times more toxic than retinoic acid (**3**, see Table I),[62] and based on the 30-day maximally tolerated dose in male B6D2F1 mice (from another more thorough toxicity study) the arotinoid **34** was approximately 1000 times more toxic than the standard (**3**).[59] Thus the therapeutic ratios of such arotinoids with high hydrocarbon character may not be as good as originally thought. The hypothesis that the incorporation of a heteroatom at C(4) in the basic retinoid structure may reduce toxicity (presumably by increasing hydrophilicity and/or altering the metabolic pathway) relative to the hydrocarbon counterparts, while still maintaining high activity, appears to have been proven true.

Two preliminary toxicity evaluations in which heteroarotinoids were tested simultaneously with TTNPB (**34**) have been completed.[26,59] There are important similarities among the two reports. In the first report (see Table IV and Reference 2) toxicity was determined by measuring the mortality rates of female Swiss mice for several arotinoids at different dose levels.[26] Although exact ratios of the relative toxicities of the retinoids cannot be determined from this study, some important observations can be made. At a dose of only 30 μmol/kg day, none of the mice treated with arotinoid **34** survived by the end of day 8 (see day of death, in Table IV) whereas at a similar dose [33 μmol/kg-day] of retinoic acid (**3**) no deaths were observed even by day 15. A very different picture is seen for the heteroarotinoids. At a dose of 600 μmol/kg-day the survival rate with retinoic acid (**3**, 95%) at day 8 was only slightly higher than that observed for oxygen analogue **45** (70%), while no deaths were reported by day 8 for sulfur analogue **46** at the same dose. Moreover, at 300 μmol/kg-day the survival rates of the mice treated with heteroarotinoids **45** and **46** at day 15 were 50% and 80%, respectively, while no survivors were observed for the mice treated similarly with retinoic acid (**3**).

TABLE IV

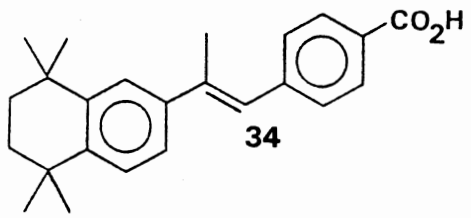
TOXICITY OF SELECTED RETINOIDS IN FEMALE SWISS MICE[a,b]

Retinoid	Dose, μmol/kg-day	% Survivors day 8	% Survivors day 15	Days of death	Total animals
Control	0	100	100	—	30
Retinoic acid (**3**)	600	95	0	7-13	20
	300	100	0	10-14	20
	200	100	63	14-15	30
	100	100	100		30
	67	100	100		20
	33	100	100		10
TTNPB (**34**)	30	50	0	6-8	20
	10	87	0	7-10	30
	3.3	97	0	7-11	30
	1.0	100	30	10-15	30
Arotinoid **39**	100	100	0	8	10
	30	100	0	9-12	10
	10	100	68	10-15	30
	3.3	100	100		10
Heteroarotinoid **45**	600	70	0	7-10	10
(Fig. 5a, X = 0, R = H)	300	100	50	12-15	10
	200	100	90	14	10
	100	100	100		10
	30	100	100		10
Heteroarotinoid **46**	600	100	0	9-10	10
(Fig. 5a, X = S, R = H)	300	100	80	14-15	10
	100	100	100		10
	30	100	100		10

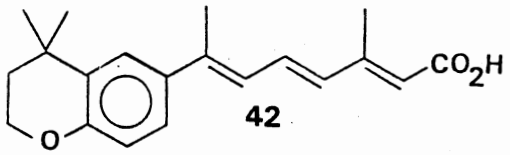
[a]From Reference 26.
[b]Retinoid administered by ip injection on weekdays over a period of 2 weeks.

That heteroarotinoids exhibit markedly diminished toxic effects relative to arotinoid **34** (TTNPB) and even relative to retinoic acid (**3**, although to a lesser extent) is further confirmed by a second toxicity evaluation. The latter study was more thorough in that several factors (effects on organ weights, fracture incidence, hair loss, skin scaling, hemoglobin levels, blood cell counts, triglyceride levels and others), in addition to mortality, were considered. Three heteroarotinoids (**42**, **43** and **45**) plus TTNPB (**34**) were tested (see Figure 6) over a period of 65 days. There were 4 different dose groups (beginning at 0.1, 0.2, 0.4 and 0.8 mg/kg day, respectively) per arotinoid with 16 male B6D2F1 mice per dose group. The control also consisted of 16 mice. Due to the lack of toxicity for the heteroarotinoids, the dose levels in each of the 4 respective dose groups were raised three times (two times for heteroarotinoid **45**) during the 65 day study (beginning at day 15) such that the dose levels during the last 14 days were as high as 64 mg/kg day for the octatrienoic acid analogues **42** and **43** and 32 mg/kg for **45** in the corresponding high dose groups. In contrast, because of the great toxicity of arotinoid **34** at the starting dose levels, two new dose groups (0.01 and 0.05 mg/kg day, 8 animals each) were introduced for treatment with **34** and a second control group. Even within 25 days (the experiment was cut short for the set of animals treated with **34**) significant toxicity was observed at these low levels of hydrocarbon analogue **34**. The following is a summary and evaluation of the data obtained from this toxicity study.[59] Emphasis is placed on the portions of the data which help in comparing the relative toxicities of the arotinoids one to another and Table V contains most (but not all, i.e. effects on blood cell counts and some changes in the weights of some other organs like thymus and testes are not given) of the gross observations from the study.[59]

First, a comparison of the data for arotinoid **34** and oxygen counterpart **45** will be made (see Table V). At a daily dose of 0.2 mg/kg-day, all 16 mice of the group treated with **34** died by day 19, whereas all mice treated with heteroarotinoid **45** (initially at 0.2 mg/kg day but raised to 8 mg/kg-day by day 29) survived throughout the 65-day study. A



34



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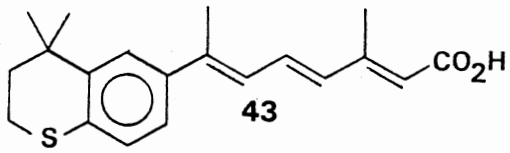

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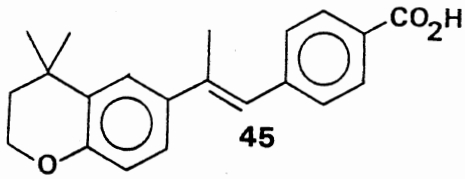


45

Figure 6. Arotinoids Studied in the Preliminary Toxicity Study by Lindamood and Co-workers.[59]

TABLE V

SUMMARY OF SOME OF THE TOXICOLOGICAL PARAMETERS IN THE TOXICITY STUDY OF HETEROAROTINOIDS **42**, **43**, AND **45** WITH AROTINOID **34** (TTNPB) IN MALE B6D2F1 MICE[a,b]

Dose group[c]	Mortalities (days of death)	Fracture incidence at end of study	Skin scaling[b] (—)[d]	Hair loss[e] (—)[d]	Enlarged spleen[f]	Enlarged[f,g] Lymph nodes	30-Day[h] Maximally tolerated dose
Control 1	0	0/8	0.16	0/16	0/16	0/16	—
Arotinoid **34**							
0.1 mg/kg-day	7 (12-24)	5/7[i]	14/16 (8)	10/16 (8)	4/16[i]	16/16[i]	d
0.2 "	6 (8-19)	3/8[i]	14/16 (6)	10/16 (8)	0/16[i]	16/16[i]	d
0.4 "	14 (8-19)	3/12[i]	15/16 (6)	8/16 (6)	0/16[i]	12/16[i]	d
0.8 "	16 (7-8)	0/16[i]	12/16 (6)	3/16 (6)	0/16[i]	8/16[i]	d
Heteroarotinoid **42**							
Low-dose	0	0/8	0/16	0/16	0/16	1/16	> 6.9
Mid-dose 1	0	0/8	0/16	2/16 (38)	1/16	2/16	> 13.8
Mid-dose 2	0	4/8	0/16	3/16 (41)	0/16[j]	1/16	24.4
High-dose	0	3/8	2/16 (57)	4/16 (36)	0/16[j]	1/16	31.8
Heteroarotinoid **43**							
Low-dose	0	0/8	0/16	1/16 (38)	0/16	1/16	> 6.9
Mid-dose 1	1 (57)	0/8	1/16 (41)	1/16 (10)	0/16	0/16	> 13.8
Mid-dose 2	0	0/8	0/16	1/16 (19)	0/16	2/16	> 27.6
High-dose	0	2/8	0/16	1/16 (45)	0/16[j]	1/16	33.9
Heteroarotinoid **45**							
Low-dose	0	2/8	7/16 (61)	6/16 (26)	3/16	6/16	> 4.9
Mid-dose 1	0	5/9	6/16 (57)	6/16 (43)	5/16	6/16	6.3
Mid-dose 2	4 (57-63)	6/7	7/16 (38)	7/16 (45)	6/16	8/16	7.4
High-dose	8 (43-62)	4/7	6/16 (36)	4/16 (41)	4/16	8/16	9.4

TABLE V (Continued)

Dose group[c]	Mortalities (days of death)	Fracture incidence at end of study	Skin scaling[b] (—)[d]	Hair loss[e] (—)[d]	Enlarged spleen[f]	Enlarged[f,g] Lymph nodes	30-Day[h] Maximally tolerated dose
Control 2	0	0/8					
Arotinoid **34**							
0.01 mg/kg-day	0[k]	1/7	4/8 (14)	6/8 (16)	5/8	6/8	> 0.008
0.05 "	3 (14-22)[k]	7/8	8/8 (9)	8/8 (7)	5/8	8/8	0.01

[a]Unpublished results. Lindamood III, C.; Hill, D. L.; Kettering-Meyer Laboratories, Southern Research Institute, P. O. Box 55305, Birmingham, Alabama. Spruce, L. W.; Berlin, K.D. Oklahoma State University, Stillwater, OK, 1987.

[b]Sites of skin scaling were ears, mouth, nose, eyelids, feet, tail and/or ventral body.

[c]Retinoids or corn oil (in the control) were administered in gavage (10 mL/kg).

[d]Day of first observation.

[e]Sites of hair loss were face, ventral body, and/or forelimbs.

[f]Number of animals in gorup with gross observations/total number of animals in group.

[g]Mesenteric, mandibular, inguinal, iliac, renal, and/or axillary.

[h]Total dose to 10% weight loss divided by 30 days.

[i]These reductions of signs of toxicity probably indicate that death from overt toxicity precluded (at least in part) development of fractures and enlarged spleen and lymph nodes.

[j]The small enlargements of spleen (relative to those observed for heteroarotinoid **45**) were, however, significant ($p < 0.05$ relative to control group) by the students' t-test.

[k]Toxicity study on these mice was ended at day 25.

relative toxicity ratio of arotinoid **34** versus heteroarotinoid **45** (see Figure 6, X = O) was determined by a comparison of the 30-day maximally tolerated dose (total dose to 10% body weight divided by 30 days) of the two arotinoids: 6.3-9.4 mg/kg for heteroarotinoid **45** and 0.01 mg/kg for arotinoid **34**. By this standard, the heteroarotinoid **45** is 630 to 940 times less toxic than the hydrocarbon counterpart **34**. Symptoms of hypervitaminosis A were prevalent in the mice treated with arotinoid **34** (0.05 mg/kg-day) as evidenced by hair loss and skin scaling in 100% of the mice (8/8) and by enlarged spleen and lymph nodes in 63% of the mice (5/8). By comparison, much higher doses of heteroarotinoid **45** over longer periods of time were required to produce noticeable signs of hypervitaminosis A.

The data for the three heteroarotinoids (**42, 43, 45**) reveal an interesting pattern (see Table V). The 30-day maximally tolerated doses for oxygen analogue **45** and the two triene side chain-containing heteroarotinoids **42** (X = O) and **43** (X = S) were 6-9 mg/kg, 24-32 mg/kg and 34 mg/kg, respectively. That the polyene side chain containing heteroarotinoids **42** and **43** are less toxic than the diaryl heteroarotinoid **45** is further confirmed by the signs associated with hypervitaminosis A (skin scaling, hair loss, enlarged spleen and lymph nodes). For the octatrienoic acid analogues **42** and **43**, less than 4% of the mice (2/64 and 1/64 for **42** and **43**, respectively) developed skin scaling, whereas 26 of the 64 mice (4 x 16) treated with heteroarotinoid **45** (X = O) developed such. Likewise, hair loss was observed in 0-25%, 6% and 25-41% of the mice treated with heteroarotinoids **42, 43** and **45**, respectively, depending on the dose group. Enlargements of spleen were not great among the heteroarotinoids except for diaryl analogue **45**. The incidence of enlarged lymph nodes and fractures was also greater for the diaryl heteroarotinoid **45**. Furthermore, while deaths were observed in the two highest dose groups (4/8 and 8/8) administered heteroarotinoid **45** (X = O), none were observed in the groups administered polyene heteroarotinoid **42**, and only one death was observed (day 57) for heteroarotinoid **43** (X = S).

From this study a comparison can be made regarding the effects resulting from the replacement of an oxygen atom in heteroarotinoid **42** with a sulfur atom (heteroarotinoid **43**) (see Table IV). Fractures were not observed in any of the mice administered the triene side chain-containing heteroarotinoids in the two lowest dose groups, but the fracture incidence was greater in the mice administered oxygen analogue **42** than in the mice administered sulfur analogue **43** in the corresponding higher dose groups. Skin scaling was almost non-existent for the two triene side chain-containing heteroarotinoids. None of the mice treated with heteroarotinoid **43** (X = S) avoided putting pressure on their limbs (a clinical sign of fractured limbs), whereas 25% of the mice treated with oxygen analogue **42** avoided putting pressure on limbs in the high dose group. Finally, according to the 30-day maximally tolerated dose criteria, heteroarotinoid **43** (X = S) was found to be slightly less toxic than heteroarotinoid **42** (X = O).

Some tentative structure-toxicity relationships can be made from the above toxicity data (and to a smaller extent from the hypervitaminosis assay used by Bollag and co-workers[62]). First and foremost, the replacement of the $C(CH_3)_2$ group *para* to the central double bond in arotinoid **34** with a heteroatom results in a reduction of toxicity as great as 3400-fold.[26,59] Second, comparison of the effects of the two oxygen heteroarotinoids **42** and **45**, reveals that replacement of the 1-propenyl benzoic acid moiety by an octatrienoic acid side chain can result in a 3- to 5-fold reduction in toxicity (according to the 30-day minimally tolerated dose but confirmed by the other effects described above).[59] Third, both preliminary toxicity reports of the heteroarotinoids reveal that replacement of an oxygen atom (position 4 in the basic retinoid structure) with a sulfur atom in the heteroarotinoid skeleton also reduces toxicity.[26,59] Fourthly (although further toxicity work in addition to that reported by Bollag and co-workers[62] may be necessary to confirm this), reduction in the ring size of the partially saturated ring can result in the reduction of the signs associated with the hypervitaminosis A syndrome (compare **30** with **31**, and, **32** with **33** in Table I). Finally, a progression from most toxic to least toxic (based on the

30-day minimally tolerated dose) can be made for the following retinoids (including retinoic acid): Arotinoid **34** (0.01 mg/kg) >>> heteroarotinoid **45** (6-9 mg/kg) ≈ retinoic acid (10 mg/kg)[58] > heteroarotinoid **42** (24-32 mg/kg) > heteroarotinoid **43** (34 mg/kg). The above structure-toxicity relationships together with structure activity relationships discussed elsewhere[71] should be considered in drug design.

In conclusion, heteroarotinoids show great promise due to the high activity [comparable in several instances to that of TTNPB and retinoic acid (**3**); see also the pharmacological activity of the new heteroarotinoids presented in this work] and greatly diminished toxicity relative to arotinoid **34** (and most likely relative to the other members of the hydrocarbon arotinoids) and to a lesser extent relative to all-*trans*-retinoic acid (**3**).

Assays of Retinoids

Several assays have been developed to determine the carcinostatic or antitumor activity of a test retinoid. For an overview of these methods see The Retinoids (Volume I).[96] Two popular assays will be discussed which were used to evaluate the activity of some of the new heteroarotinoids presented in this work: an *in vivo* method [the ornithine decarboxylase (ODC) assay][107,108] and an *in vitro* method [the human promyelocytic leukemia cell line (HL-60) assay].[14,15]

The ability of a test substance (i.e. a retinoid) to inhibit the biosynthesis of the enzyme ornithine decarboxylase can be readily measured and reflects the extent to which the substance can inhibit skin tumor promotion.[107,108] The decarboxylation of ornithine to putrescine is an important step in the biosynthesis of some of the polyamines believed to play a role (along with the enzymes by which they were prepared) in malignant transformation.[107] 12-O-Tetradecanoylphorbol-13-acetate (TPA) is a potent inducer of ornithine decarboxylase activity. The ability of a retinoid to inhibit the synthesis of ODC, therefore, appears as a measure of its ability to inhibit skin tumor promotion.[107,108] Indeed, studies reveal a good correlation between the ability of retinoids to inhibit the

synthesis of ornithine decarboxylase and their ability to inhibit the formation of skin tumors.[108] The method[107,108] requires the backs of mice to be shaven 3 to 4 days prior to TPA treatment. One hour before this TPA treatment (8-17 nmol in acetone) the mice are pretreated with the retinoid (commonly 17 or 34 nmol in acetone). In the controls, only TPA (in acetone) is applied. After 4.5-5 h from the TPA treatment (this corresponds approximately to the greatest ODC activity in the control) the mice are sacrificed. The epidermis is separated, homogenized, and the resulting mixtures are centrifuged. The ODC activity is then determined form the soluble extracts by measurement of the release of $^{14}CO_2$ from ^{14}C-labelled ornithine. Percent inhibition of the synthesis of ODC is determined from the difference in the ODC activity in the mice treated with retinoid and the ODC activity of the control: [100 x ODC activity (retinoid) – ODC activity (control)] / ODC activity (control). The experiment is always run side by side with mice treated similarly with a standard, either all-*trans*-retinoic acid (**3**) or 13-*cis*-retinoic acid (**12**), both of which exhibit high activity in this assay.[13]

One method used to assess the potential of a test substance to induce differentiation in cells is referred to as the HL-60 assay involving a cell line from a patient with acute promyelocytic leukemia.[14,15,98] HL-60 cells do not produce superoxide anions upon stimulation by agents like TPA. Differentiated HL-60 cells, however, do produce these anions (upon similar stimulation), the presence of which is detectable due to their ability to reduce the yellow dye nitroblue tetrazolium to the water insoluble blue-black formazan.[15] Thus, under a light microscope the number of cells containing this dark precipitate can be counted. This allows the percentage of differentiated cells to be determined (a direct indication of the ability of a test retinoid to induce differentiation and a convenient way to determine ED_{50} values).[10,15,101]

It must be noted that the positive or negative results from one particular assay do not eliminate or establish the potential carcinostatic activity of a test retinoid *in vivo* in humans. Several tests are necessary for a nearly complete biological profile. Furthermore, the

effects of retinoic acid (**3**) on different cell types or tissues are numerous and varied and it should not be surprising that the effects of a test retinoid on the cell type in one assay may not correlate with that elicited in a different cell type. For example, Etretinate (**21**) is a potent antitumor agent[62] and used effectively in the treatment of psoriasis;[19,80] yet both Etretinate (**21**) and the free acid (Etretin, **22**; see Figure 4) are totally ineffective in inducing differentiation in the HL-60 and U-937 cell systems, allowing a tentative and possibly premature conclusion that neither of these compounds should be used *in vivo* in the treatment of acute myelocytic leukemia patients.[16]

Sites for Heteroatoms in Retinoids

Several investigators have prepared retinoids containing heteroatoms (N, O or S) within the carbon skeleton of the basic retinoid structure.[21,26,33,47,53-55,82,99,100,111] These heteroatoms have generally been incorporated (see numbering of carbons in retinoids in Figure 1) at either C(4) (**49**, **54** and the general heteroarotinoid structures **Ha** and **Hb** in Figure 7)[26,33,47,54,82,99,100,111] or in heteroaromatic rings placed within the conjugated system (**47**, **48** and **51-56**).[21,33,53,55,82] Other locations for heteroatom placement are illustrated by structure **50**.[33] It is apparent that among the heteroarotinoids containing a saturated six-membered heterocyclic ring, incorporation of the heteroatom has been only at C(4) in the basic retinoid structure.[26,33,47,54,82,100,111] In the saturated five-membered ring systems, the heteroatom has been placed beta to the double bond of the ring (**50**)[33] and (as will be discussed later in Synthesis of New Heteroarotinoids) more recently *para* to the central double bond in the basic heteroarotinoid structure.

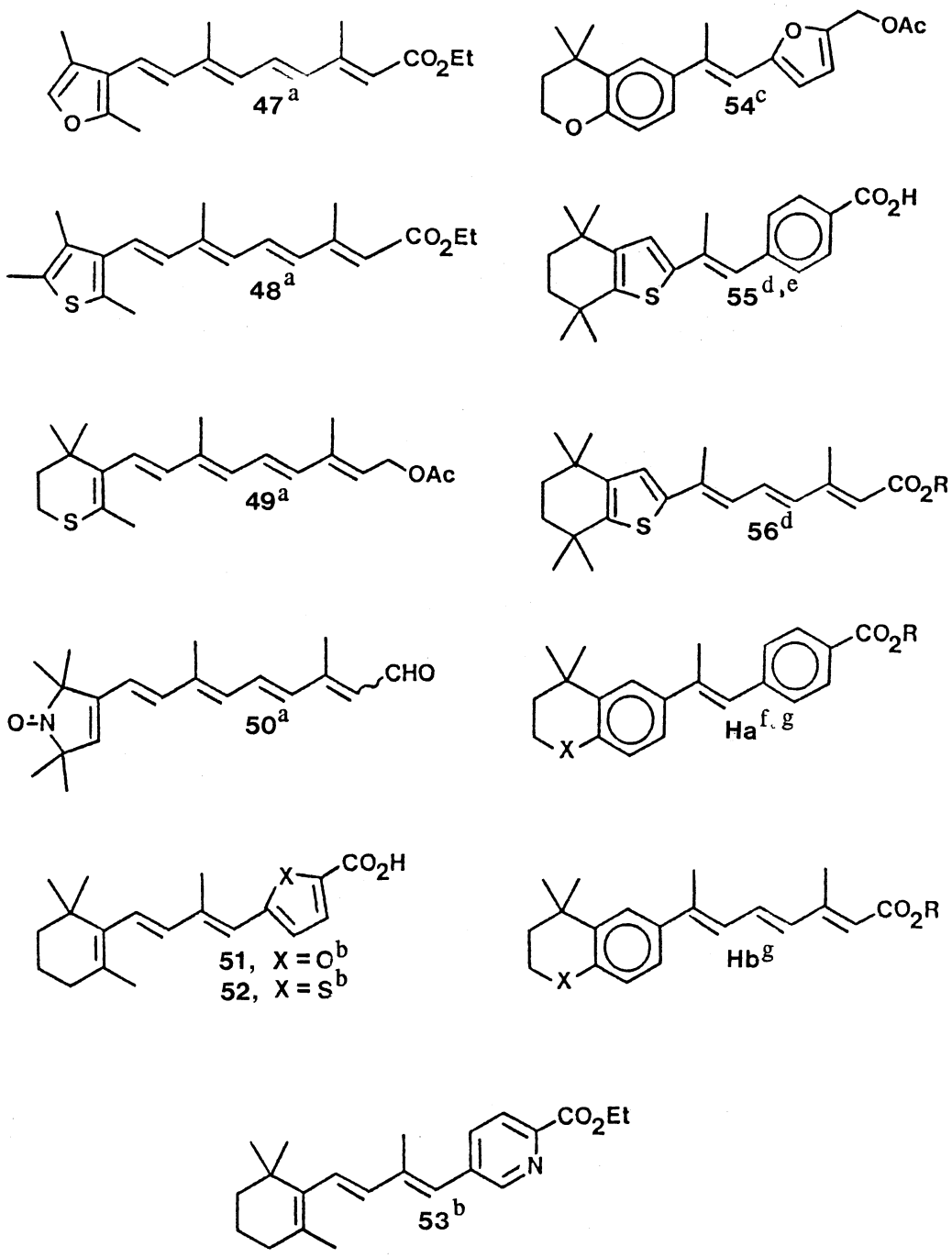


Figure 7. Retinoids Containing Heteroatoms Within the Carbon Skeleton of the Basic Retinoid Structure. (a) Reference 33, (b) Reference 21, (c) Reference 82;, (d) Reference 55, (e) Reference 53, (f) References 26, 47, 54, 111, (g) References 99, 100.

CHAPTER II

RESULTS AND DISCUSSION

Fourteen new heteroarotinoids have been prepared (see Figures 8 and 9) and may be categorized into two groups: (1) those heteroarotinoids which possess the stilbene (1,2-diarylethene) moiety {**58-66**}, and (2) those which bear an octatrienoic acid skeleton fused to a benzoheterocyclic system {**67-71**}. The most studied of the stilbene retinoids, **34** (abbreviated TTNPB), spatially resembles all-*trans*-retinoic acid as determined by X-ray crystallography[33] and binds well with the cellular retinoic acid binding protein (cRABP).[68] This spatial resemblance to retinoic acid, together with the potential carcinostatic activity exhibited by several stilbene-like arotinoids and heteroarotinoids (as revealed in several assays),[26,62,100,111] provides convincing reasons for the synthesis of new arotinoids bearing a stilbene skeleton. Moreover, the diminished toxicity of a few heteroarotinoids relative to TTNPB (and even relative to all-*trans*-retinoic acid) as determined by two preliminary toxicity studies (see section on Toxicology), gives further impetus to the search for heteroarotinoids with improved therapeutic efficacy. Heteroarotinoids bearing a five-membered heterocyclic ring {**58, 60, 62, 63**} were prepared in the hope of maintaining high activity with a further diminishment in overall toxicity relative to TTNPB (and relative to retinoic acid) and with the awareness of a potential altered metabolic pathway which may enhance their relative therapeutic efficacy. Assuming that certain metabolites of retinoids *may* possibly be as active as the parent (but with presumed less toxicity), heteroarotinoids **64-66** were synthesized (it was hoped that the *trans*-aryl isomer of **66** would have been the predominant isomer). Heteroarotinoids **64** ad **65** contain a hydroxyl group attached to one of the *gem*-dimethyls, which, as

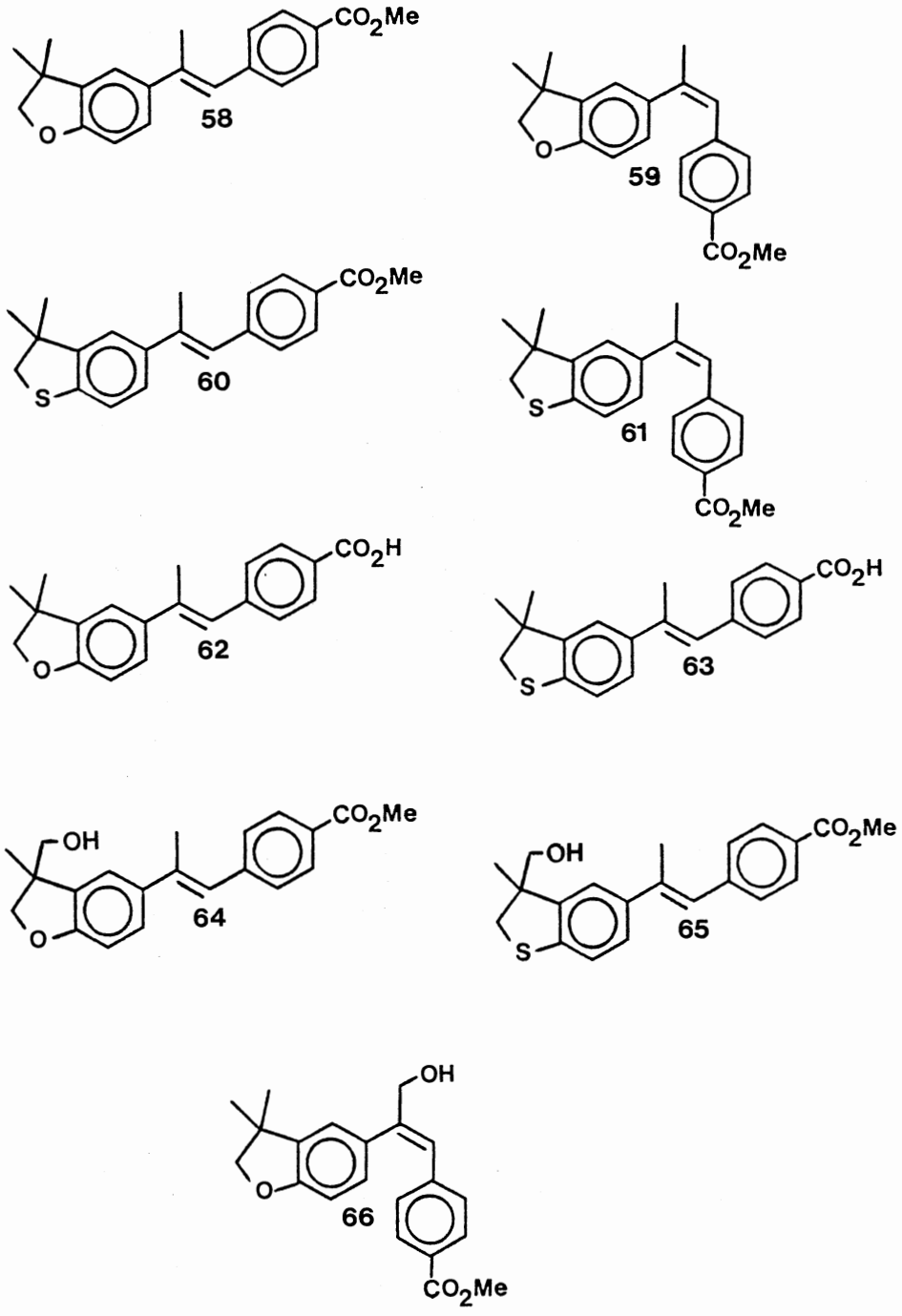
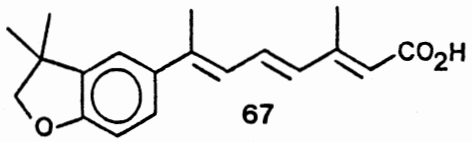


Figure 8. Structures of New Heteroarotinoids **58-66**.



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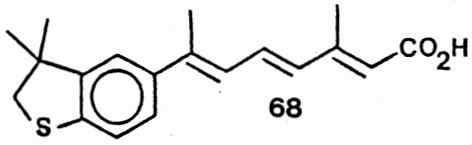

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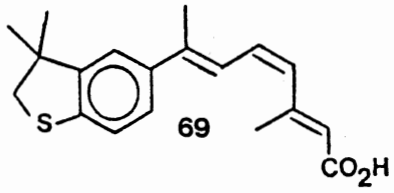

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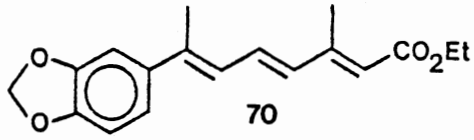

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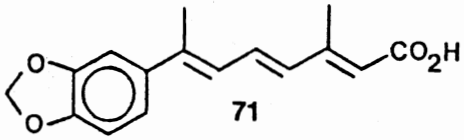

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Figure 9. Structures of New Heteroarotinoids **67-71**.

discussed earlier, was one of the sites of metabolic oxidation of retinoic acid. Heteroarotinoid **66** was also synthesized since it too is a potential metabolite of **58**. On the other hand, heteroarotinoids with a triene side chain have also shown good activity. In one particular assay (HL-60), the heteroarotinoids with the octatrienoic carboxyl side chain have shown better activity than the stilbene-like heteroarotinoids.[100] Furthermore, arotinoids with an octatrienoic acid side chain and bearing a five-membered ring exhibited better therapeutic ratios than the six-membered-ring counterpart (see Table I), and one (only one reported)[10] showed activity slightly higher than retinoic acid in the HL-60 assay (see Table II). Thus, in the light of their potential activity and reduced toxicity, five-membered-ring octatrienoic acid analogues **67-71** were prepared.

Synthesis of New Heteroarotinoids

To prepare heteroarotinoid **58**, the benzofuran **75** was a logical target intermediate (see Figure 10). Alcohol **74** was a reasonable synthon and was prepared in two steps: (1) esterification of phenoxyacetic acid (**72**) in CH_3OH with the removal of water from the condensate by molecular sieve 3A (yield of 80%), followed by (2) the reaction of CH_3MgI (prepared *in situ*) with ester **73** and by an acidic work-up (yield of crude **74**, 96%). The reaction of crude alcohol **74** with H_3PO_4 and P_2O_5 in boiling benzene, however, gave a complex mixture. The NMR spectra of the crude mixture, moreover, did not provide convincing evidence for the presence of benzofuran **75** but rather for **76**. Although **75** may have been present in small quantities, a more productive synthetic approach to the preparation of **75** (or a similar dihydrobenzofuran) was sought. Ultimately, the key intermediate found was bromosubstituted benzofuran **80** (readily prepared in two steps from ether **77**). Thus, heteroarotinoid **58** was prepared by a 5-step (6-steps via methyl ketone **81**) reaction pathway starting with 4-bromoanisole (**77**) (see Figure 11). An acid-catalyzed (H_2SO_4) alkylation of **77** with β-methallyl chloride (**78**) (neat) gave methyl ether **79** as a white crystalline solid in average yields of better than

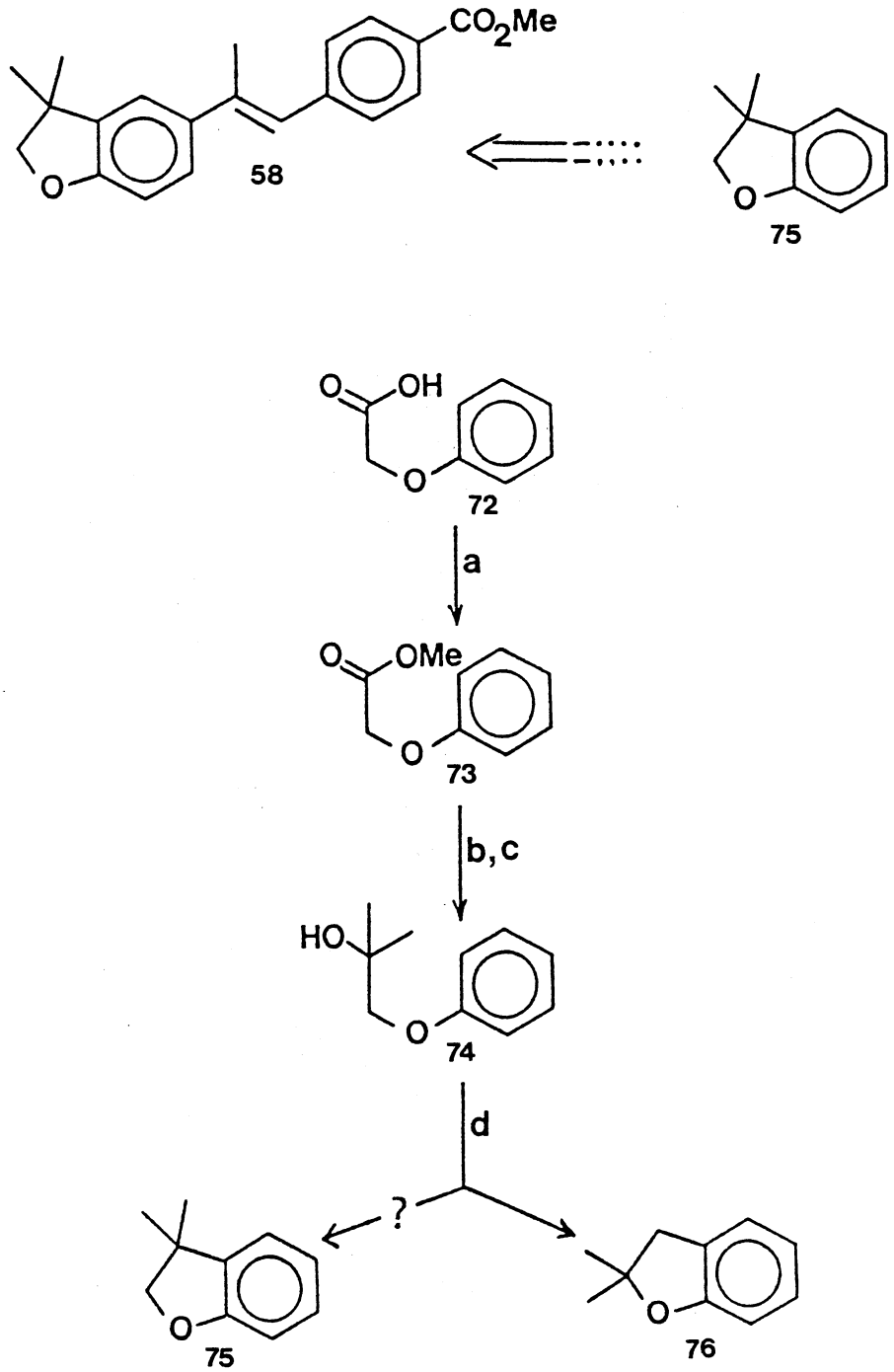


Figure 10. Attempted Preparation of the Intermediate **75**. (a) CH_3OH, H_2SO_4, $-H_2O$; (b) CH_3MgI, ether; (c) H_3O^+; (d) H_3PO_4, P_2O_5, benzene, Δ.

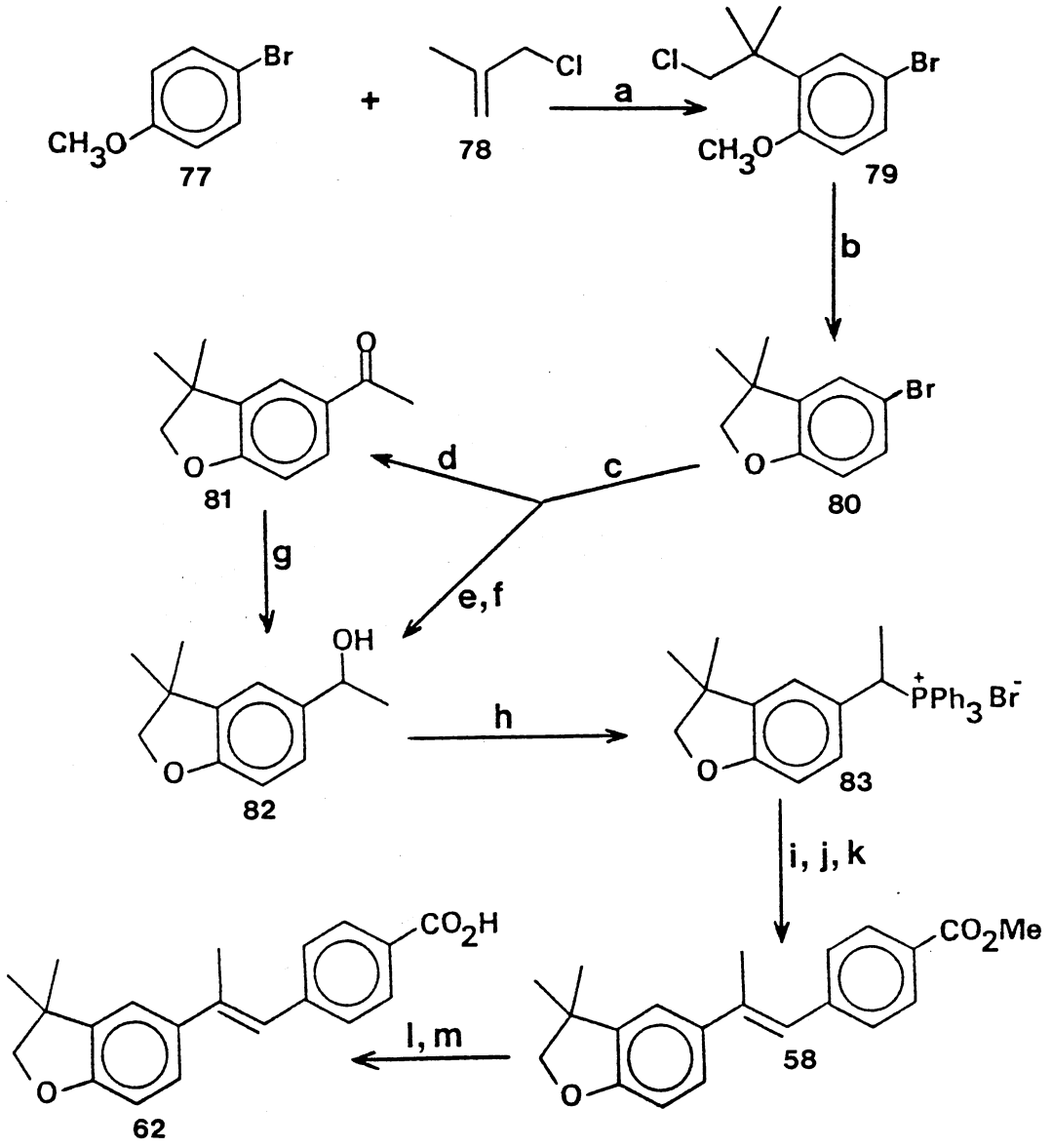


Figure 11. Preparation of Heteroarotinoids **58** and **62**. (a) H_2SO_4; (b) Pyridine•HCl, Quinoline, reflux; (c) Mg, THF; (d) AcCl, -40°C; (e) CH_3CHO, -5° to -10°C; (f) H_3O^+; (g) LAH, ether; (h) MeOH, Ph_3P•HBr; (i) *n*-BuLi; (j) -78°C; (k) *p*-$CHOC_6H_4CO_2CH_3$; (l) NaOH, EtOH, H_2O, reflux; (m) H_3O^+.

60%. The next reaction involved cleavage of the methyl ether followed by an internal Williamson ether synthesis in one step via heating ether **79** in quinoline and pyridine hydrochloride between 164° and 170°C. Yields of 75-82% for benzofuran **80** were common. The latter two reactions involved conditions similar to those described by Gates and co-workers[40] but with a few critical modifications (better yields were obtained in our lab). Alcohol **82** was obtained in one of two ways: (1) by the reaction of a large excess of freshly distilled acetaldehyde with the Grignard reagent from **80** at -5° to -10°C followed by an acidic work-up or (2) by a two step sequence involving the reaction of acetyl chloride with the Grignard reagent from **80** at -39° to -43°C followed by slow warming to room temperature over a period of 3.5 h. After an aqueous work-up, methyl ketone **81** was obtained as low melting crystals (mp 39.0-39.9°C, from hexanes) in a yield of 49%. Reduction with $LiAlH_4$ gave alcohol **82** after quenching with EtOAc and 5% HCl. Of the two methods for preparing alcohol **82**, the two-step sequence via the methyl ketone **81** is preferred. The work-up of the Grignard reaction with acetyl chloride resulted in an easier purification process than did the reaction with acetaldehyde which produced large amounts of apparent condensation products. Furthermore, the reduction of ketone **81** was straightforward and provided alcohol **82** as an oil which could be crystallized (mp 38.2-39.2°C).

Phosphonium salt **83** was prepared by condensation of alcohol **82** with $Ph_3P{\bullet}HBr$ in methanol. Recrystallization in 4:1 EtOAc:H_2CCl_2 (ether vapor from an ether bath diffused into the crystallization mixture to complete the crystal formation process) gave salt **83** (mp 212-213°C) in a yield of 81%. This crystallization method for **83** was better than recrystallization in CH_3OH/ether which gave crystals of **83** (mp 184.5-185.8°C), the ^1H NMR spectra of which indicated the presence of CH_3OH trapped apparently within the crystalline lattice. The Wittig reagent, formed by treatment of **83** in THF with an equivalent of *n*-butyllithium, was allowed to react at -78°C with a slight excess of methyl 4-formylbenzoate to give **58**-(*E*) as white flakes (yield of 36%) and **59**-(*Z*) as white

needles (0.8%). The yields (after one or two recrystallizations) of **58**-(*E*) and **59**-(*Z*), using THF as the reaction medium, generally were 30-40% for **58**-(*E*) and between 1 and 3% for **59**-(*Z*). Saponification of **58**-(*E*) with NaOH in boiling H_2O:ethanol (5:2) gave the high melting (mp 190.7-191.8°C) carboxylic acid **62** in a yield of 73%.

Heteroarotinoid **60** was prepared by a 7-step reaction pathway starting with (phenylthio)acetic acid (**84**) (see Figures 12 and 13). Esterification in methanol (H_2SO_4 as acid catalyst) with the removal of water from the condensate by molecular sieve 3A gave (after vacuum distillation) **85** as a colorless oil in a yield of 92%. Reaction of CH_3MgI with **85** followed by an aqueous work-up gave tertiary alcohol **86** containing ca. 10% of an impurity, tentatively assigned 1-phenylthio-2-propanone. Although this impurity could be removed by chromatography on silica gel (9:1 hexanes:EtOAc), a purification method more suitable for large scale reactions was developed which involved the conversion of the impurity (a methyl ketone) to a carboxylic acid (carboxylic acids generally have very high boiling points and low R_f values on silica gel and so are readily separable) in an iodoform reaction. The yield of the purified alcohol **86** from a large scale reaction (10-40 g of starting ester **85**) employing this method was 56-61%. Cyclization of **86** was effected with 3.5 equivalents of $AlCl_3$ in boiling CS_2 to give (after a cautious aqueous work-up) the purified thiophene **87** in yields of 73-89%. Acylation of **87** was also effected using $AlCl_3$ in CS_2 (but at RT) to give methyl ketone **88a** (89%). Reduction with $LiAlH_4$, followed by quenching with EtOAc and 5% HCl and recrystallization in hexanes, gave alcohol **89** as colorless crystals (mp 60.5-61.5°C). Conversion of **89** to phosphonium salt **90** was effected in the usual manner by treatment of benzyl alcohol **89** with Ph_3P•HBr in methanol. The salt **90** (a non-recrystallized powder, yield of 70%) was used without further purification when treated in THF with 1.06 equivalents of *n*-butyllithium. Condensation of the Wittig reagent (formed *in situ*) with methyl 4-formylbenzoate gave, after two recrystallizations, **60**-(*E*) as white flakes in a yield of 51%. From the mother liquors was isolated the (*Z*)-isomer (**61**) in a yield of 1%.

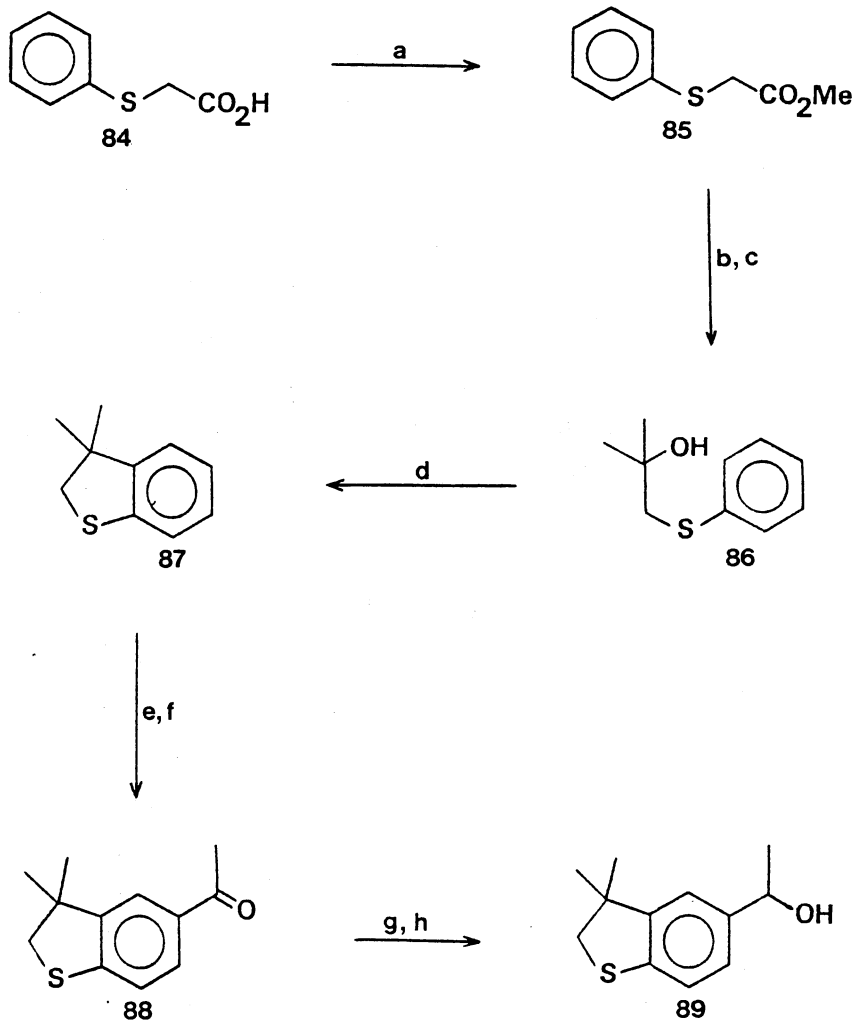


Figure 12. Preparation of Intermediate **89**. (a) CH_3OH, H_2SO_4, $-H_2O$; (b) CH_3MgI, ether; (c) H_3O^+; (d) CS_2, $AlCl_3$, reflux; (e) $AlCl_3$, CS_2, AcCl; (f) H_3O^+; (g) LAH, ether; (h) H_3O^+.

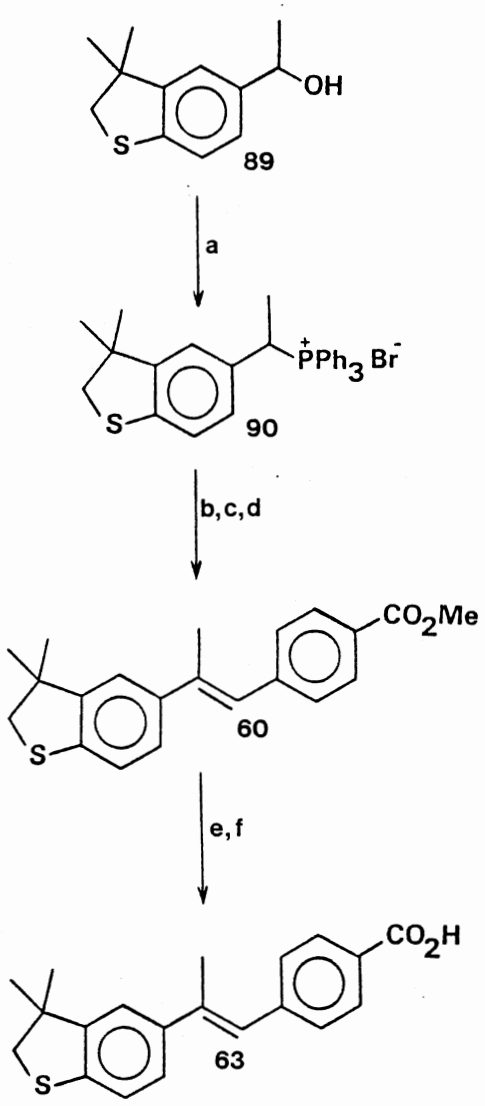


Figure 13. Preparation of **60**, **61** and **63**. (a) CH_3OH, $Ph_3P{\bullet}HBr$; (b) *n*-BuLi; (c) -78°C; (d) *p*-$CHOC_6H_4CO_2Me$; (e) KOH, EtOH, H_2O, reflux; (f) H_3O^{+}.

Saponification of **60**-(*E*) was effected using KOH in 3:1 ethanol:H_2O to give the *E*-carboxylic acid (**63**) as white fluffy needles (yield of 61.5%).

To prepare heteroarotinoids **64** and **65**, the hydroxymethyl substituted dihydrobenzofurans **107** and **121**, respectively, were logical intermediates (Figure 14). It was reasoned that ketones **93** and **94** could be converted to the alcohols **107** and **121**, respectively, by the series of reactions shown. While ketones **93** and **94** were successfully prepared from the carboxylic acids **72** and **84**, respectively, vinyl ethers **95** and **96** could not be isolated from the reaction of the ketones **93** and **94** with the ylide from $Ph_3PCH_2OCH_3Cl^-$. This route was therefore set aside. Ultimately, heteroarotinoids **64** and **65** were prepared by a completely different synthetic route which is now described.

The synthesis of heteroarotinoid **64**-(*E*) begins with *o*-nitrophenol in a ten-step reaction sequence (see Figures 15, 18). The sodium salt of *o*-nitrophenol (prepared *in situ* with aqueous NaOH) was treated with β-methallyl chloride (see Reference 32) in a boiling 1,2-dichloroethane bath (84°C) to give allyl ether **100** in a yield of 56%. Reduction of **100** with $SnCl_2$ and HCl in ethanol at RT gave arylamine **101** (60%) as a colorless oil. The fluoroborate diazonium salt **102** was obtained as a light tan powder (see Reference 6) after treatment of **101** with 21% HBF_4 and aqueous $NaNO_2$ at 0°C followed by precipitation at -20°C and recrystallization in acetone/ether (RT). Because **103** was easily prepared by the reaction of diazonium salt **102** with NaI in acetone (yield of 72% with **104** as an impurity, ratio of **103**:**104** ≈ 10:1, see Reference 8 in which only **103** was isolated), the preparation of **107** from **103** by hydrolysis was attempted. A solution of the iodo compound **103** in ether was allowed to react with $AgNO_3$ in aqueous acetone (a two-phase reaction). While essentially all of **104** (the impurity present with **103**) was recovered, evaporation of the major eluting band from the polar fractions by centrifugal thin-layer chromatography (Chromatotron) on silica gel gave a compound whose ^1H and ^{13}C spectra suggest the tentatively assigned structure **105** rather than **107**. A cationic

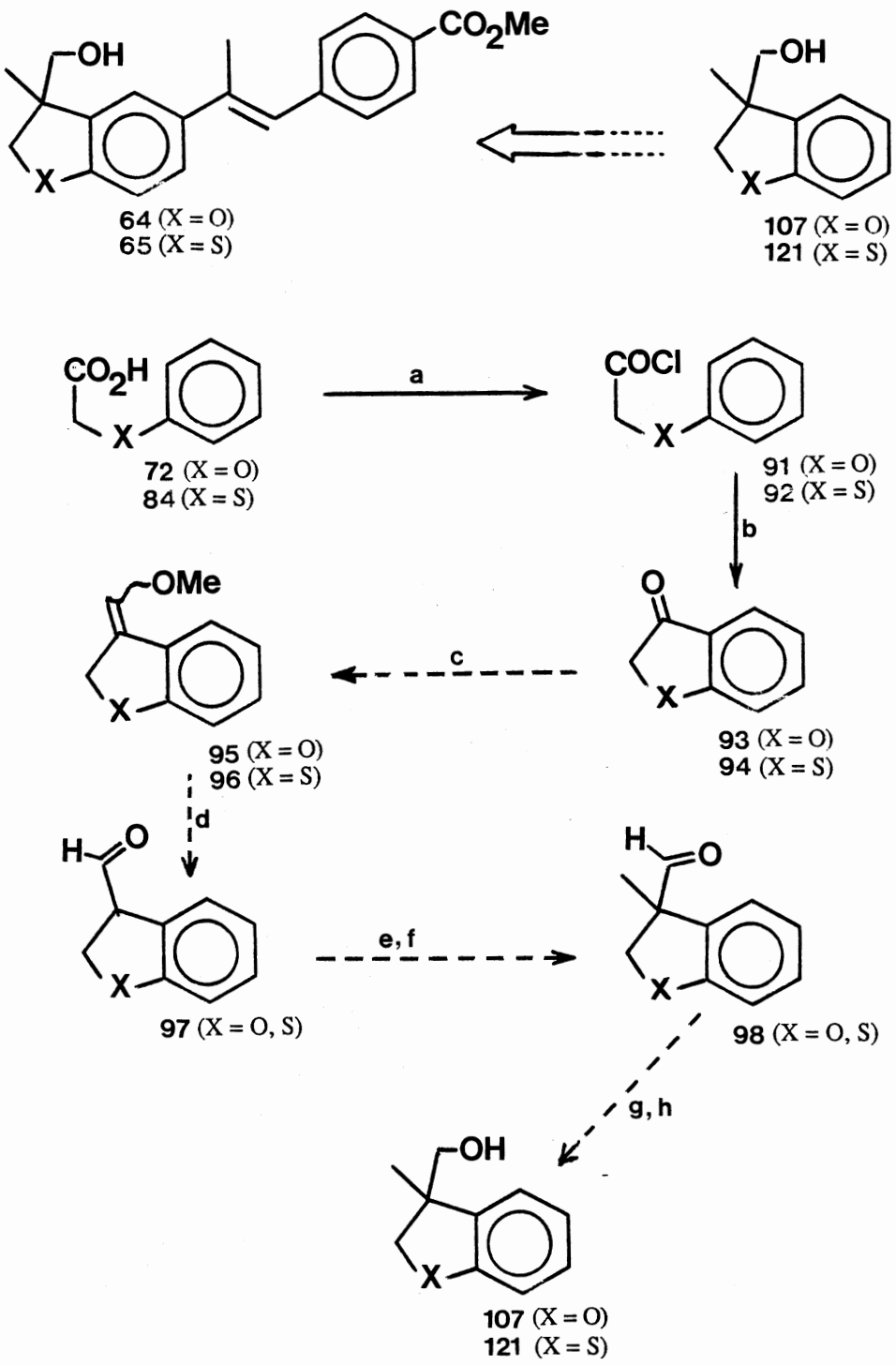


Figure 14. Conceivable Preparation of Alcohols **107** and **121** from Carboxylic Acids **72** and **84** Via Ketones **93** and **94**. (a) $SOCl_2$; (b) $AlCl_3$, H_2CCl_2; (c) $Ph_3P{=}CHOCH_3$; (d) $HClO_4$; (e) KH; (f) CH_3I; (g) LAH; (h) H_3O^+.

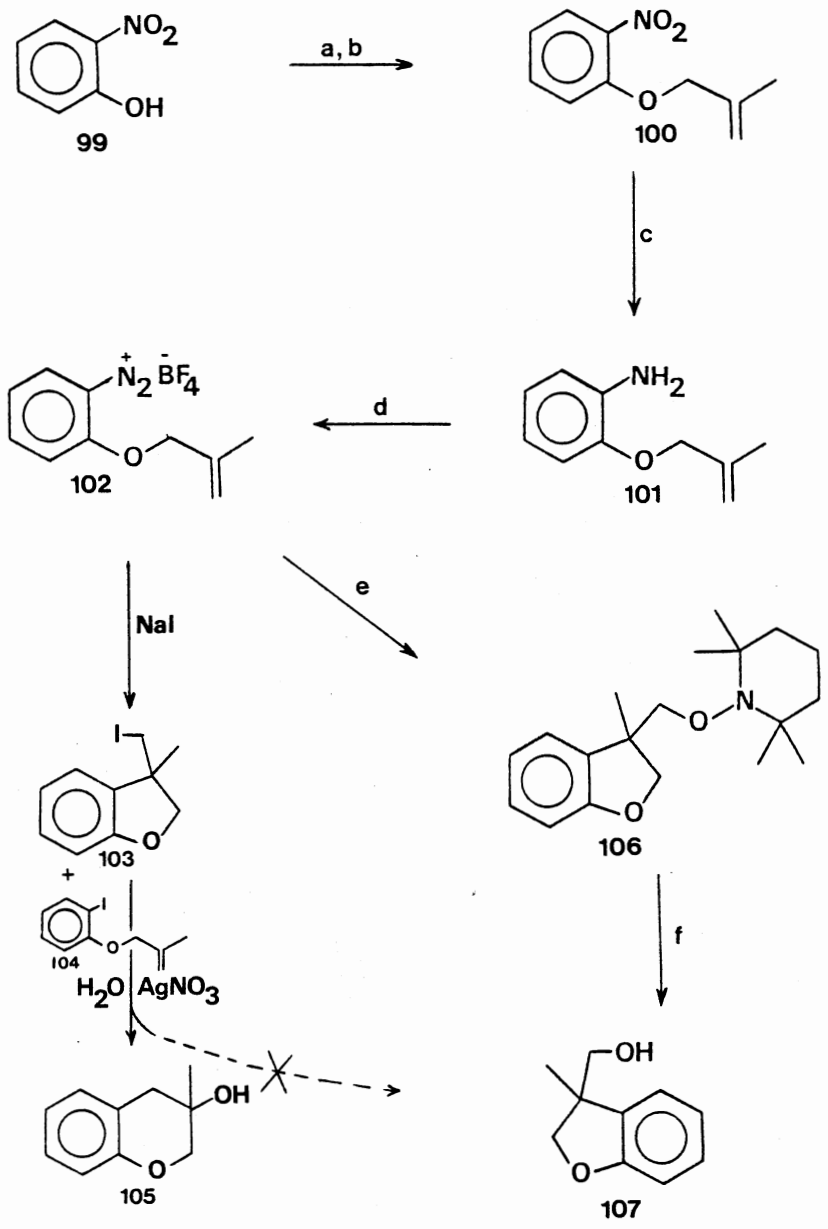


Figure 15. Preparation of Intermediate **107**. (a) NaOH, H_2O; (b) $ClCH_2C(CH_3)=CH_2$, reflux; (c) $SnCl_2$, EtOH, HCl; (d) HBF_4, $NaNO_2$, H_2O, 0°C; (e) acetone, TEMPO (see Figure 16), reflux; (f) Zn, AcOH, H_2O, 70°C.

rearrangement involving aryl migration presumably occurred. Alcohol **107** was successfully prepared instead from salt **102** via heterocycle **106**. The cyclization of **102** to **106** has been described by Beckwith and co-workers[9] (minimal experimental detail was given) and is believed to occur by a free-radical mechanism requiring two equivalents of the stable free radical TEMPO (see Figure 15 and 16).[9]

A solution of the stable free radical TEMPO in dry acetone and a solution of salt **102** in acetone were mixed and heated at reflux for 1.5 h. The concentrations used were such that the final concentration of **102** [and ultimately the concentration of radical A (X = O), see Figure 16] was relatively dilute in order to maximize *intramolecular* cyclization of radical A (to form radical B, X = O) versus *intermolecular* coupling of radical A (X = O, see Figure 16) with the free radical TEMPO. Chromatography on silica gel gave the 5-membered-ring heterocycle **106** in a yield of 63%. Neither our laboratory nor that of Beckwith and co-workers[9] report the presence of product obtained from radical C (X = O, see Figure 16) although a more careful search for such a product may reveal small amounts of the 6-membered-ring heterocycle. Reductive cleavage of the N–O bond in **106** with zinc in acetic acid at 70°C (see reference 9) gave racemic alcohol **107** in a yield of 67%. Benzyl ether **110** was prepared using xylyl bromide (prepared from *p*-xylene with NBS in boiling CCl_4 with a small amount of benzoyl peroxide in a yield of 66%) in order to protect the hydroxyl group in the ensuing Friedel-Crafts acylation to obtain ketone **111** (see Figure 17). Inspection of the complex ^1H NMR spectra of the crude product, after the attempted acylation, indicated cleavage of the benzyl ether with acylation of an acetate intermediate to give a crude material containing **113**. The apparent stability of **113** to Friedel-Crafts acetylation conditions provided a new target compound. Consequently, acetate **112** (Figure 18) was prepared in a high yield (86%) from **107** using acetyl chloride and pyridine in dry ether:THF (2:1 after all reagents were mixed). Acylation of **112** with acetyl chloride (large excess) in CS_2 in the presence of $AlCl_3$ at 0°C gave **113** in a yield of 88%. Reduction of **113** with LAH was essentially quantitative and gave diol

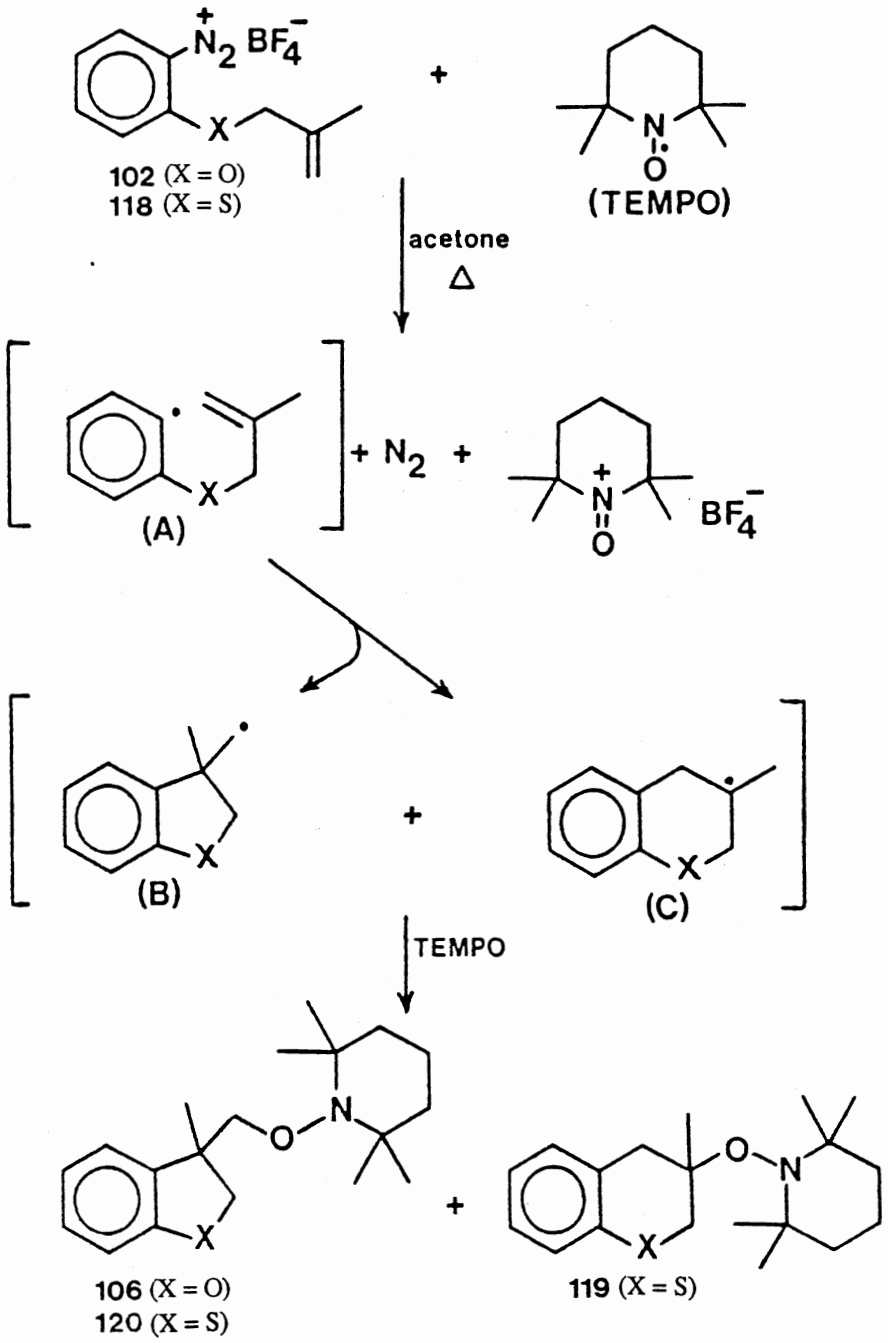


Figure 16. Suggested Mechanism of Cyclization of **102** to **106** and of **118** to **119** and **120**.

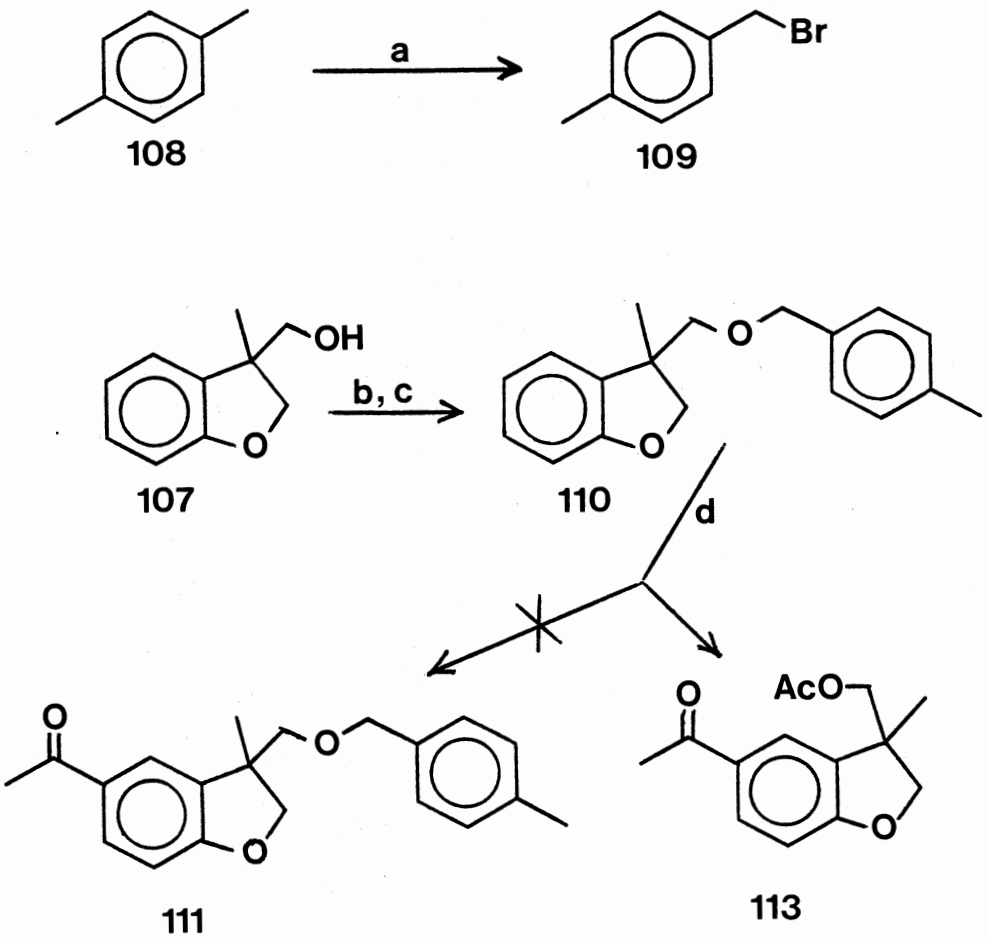


Figure 17. Attempted Preparation of **111**. (a) NBS, CCl_4, $(PhCO_2)_2$; (b) NaH, 15-crown-5, THF; (c) **109** in THF, Δ; (d) CS_2, AlC_3, AcCl.

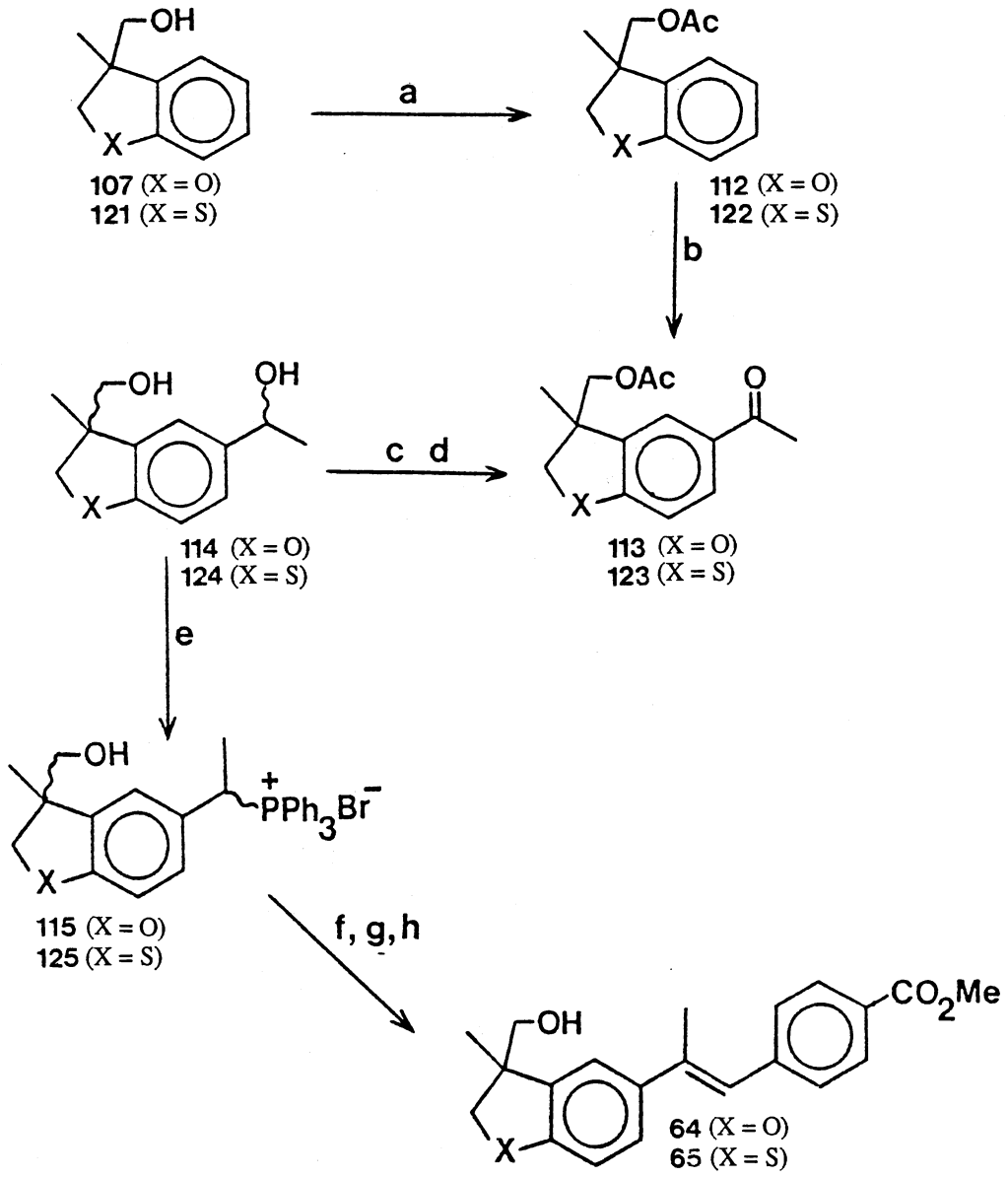


Figure 18. Preparation of Heteroarotinoids **64** and **65**. (a) Pyridine, AcCl, ether/THF; (b) $AlCl_3$, CS_2, AcCl; (c) LAH, ether; (d) H_3O^+; (e) CH_3OH, $Ph_3P{\bullet}HBr$; (f) *n*-BuLi; (g) -78°C; (h) *p*-$CHOC_6H_4CO_2CH_3$.

114 (diastereomeric mixture, 1:1). Treatment of **114** with an equivalent of Ph_3P•HBr in CH_3OH gave phosphonium salt **115** as a diastereomeric mixture (1:1) in a yield of 96%. It appears that reaction of Ph_3P•HBr with the benzylic hydroxyl group (presumably by an S_Nl mechanism) is much faster than reaction with the hindered primary hydroxyl group (which would likely occur via an S_N2 mechanism). The Wittig reagent from **115** was prepared *in situ* with *n*-BuLi (1.4 equivalents), cooled in a liquid N_2/EtOAc bath (-84°C), and allowed to react with *p*-$CHOC_6H_4CO_2CH_3$ in dry THF (-84°C to RT, 12 h). After repeated chromatographic separations and crystallizations, heteroarotinoid **64**-(*E*) was isolated as fine white crystals (mp 106-108°C) in a yield of 6%. The other isomer, **64**-(*Z*), was not isolated in pure form but as an oil containing a small amount of **64**-(*E*) [**64**-(*Z*):**64**-(*E*) ≈ 82:18] and a significant amount of an impurity the ^1H NMR of which suggested a tentative assignment as *p*-carboxymethyl benzyl alcohol.

Heteroarotinoid **65**-(*E*) was prepared via a 9-step reaction sequence beginning with *o*-aminothiophenol (see Figures 18 and 19). Nucleophilic displacement of chloride from β-methallyl chloride (see Reference 56) at 100°C gave **117** in a yield of 83%. Diazotization of **117** with 21% HBF_4 and $NaNO_2$ at 0°C gave **118** as bright yellow crystals (76%). Decomposition of **118** in boiling dry acetone (concentration of **118** kept dilute) in the presence of an excess (2.4 equivalents) of the free radical TEMPO gave (after chromatographic separation with 40:1 hexanes:ether) both the 6-membered-ring heterocycle **119** (16%) and the 5-membered-ring heterocycle **120** (19%). It is important to note that in the references of Beckwith and co-workers,[8,9,69] no report was made of the isolation of 6-membered-ring heterocycles from diazonium salts of type D (see Figure 20). On the other hand, Oae and co-workers[73] only isolated the 6-membered-ring heterocycles (low yields) from diazonium salts of type E (see Figure 20) and made no mention of the isolation of 5-membered-ring heterocycles. Here we report the isolation of both (**119** and **120**). As stated previously, oxygen analogue **102**, however, apparently gave only the 5-membered-ring analogue **106**, and the six-membered-ring analogue (X = O) was not

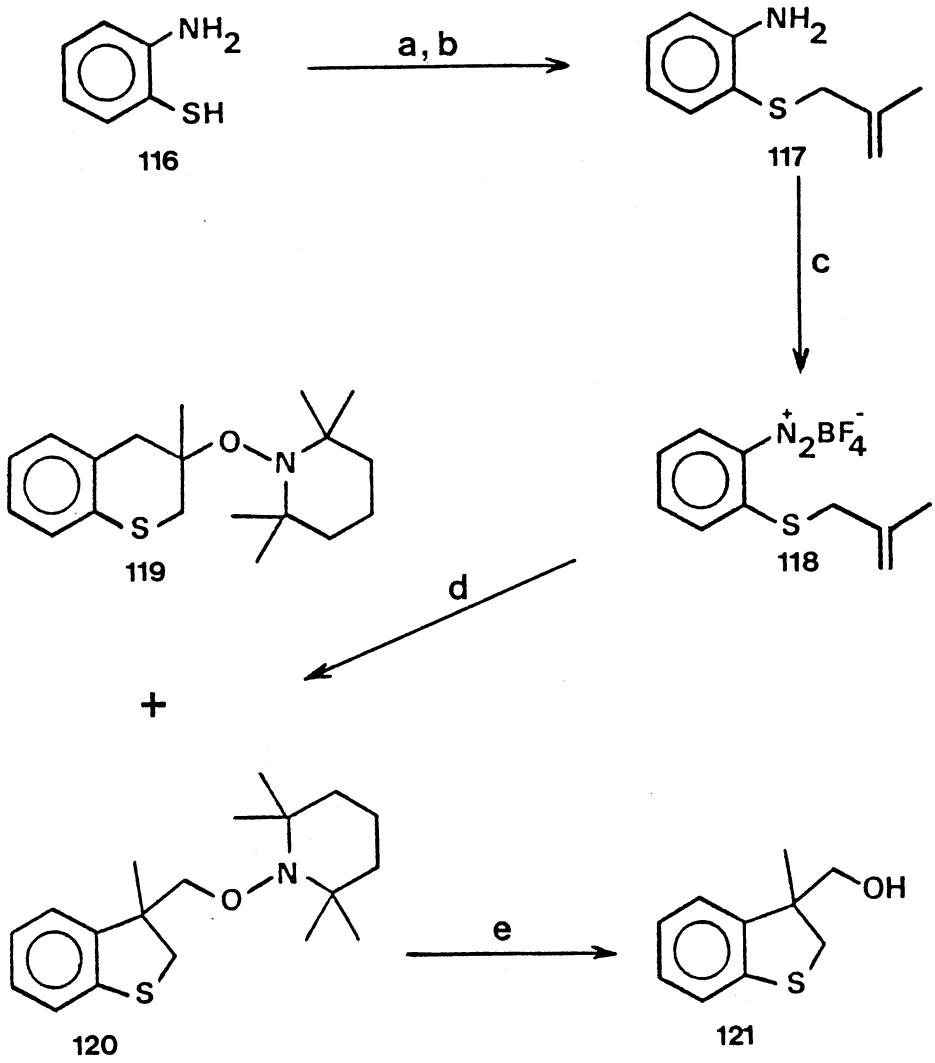
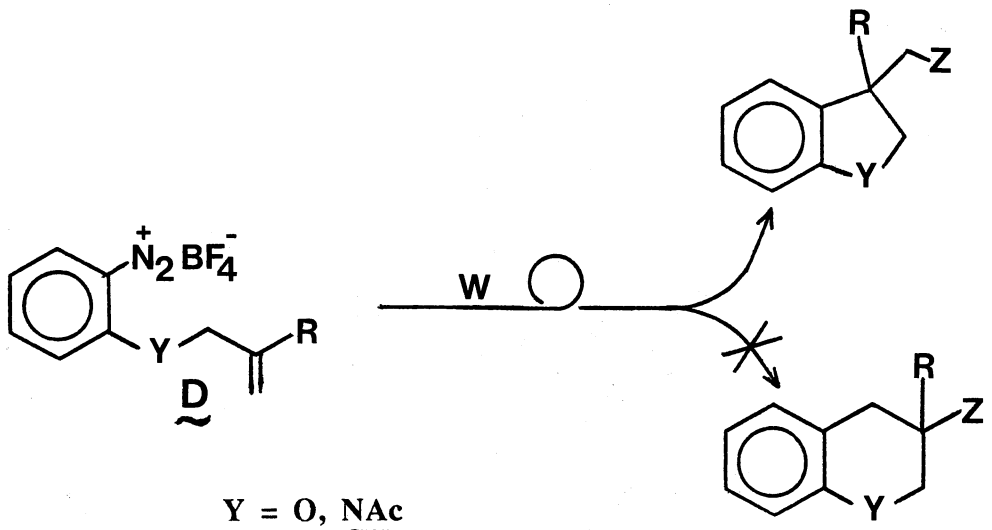


Figure 19. Preparation of Intermediate **121**. (a) NaOH, H_2O; (b) $ClCH_2(CH_3)=CH_2$, reflux; (c) HBF_4, $NaNO_2$, H_2O, 0°C; (d) acetone, TEMPO (see Figure 16), reflux; (e) Zn, AcOH, H_2O, 70°C.



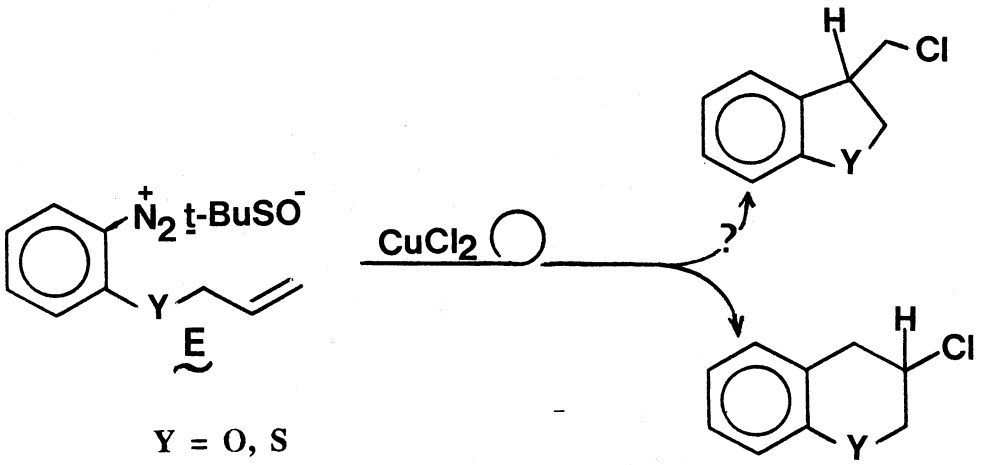
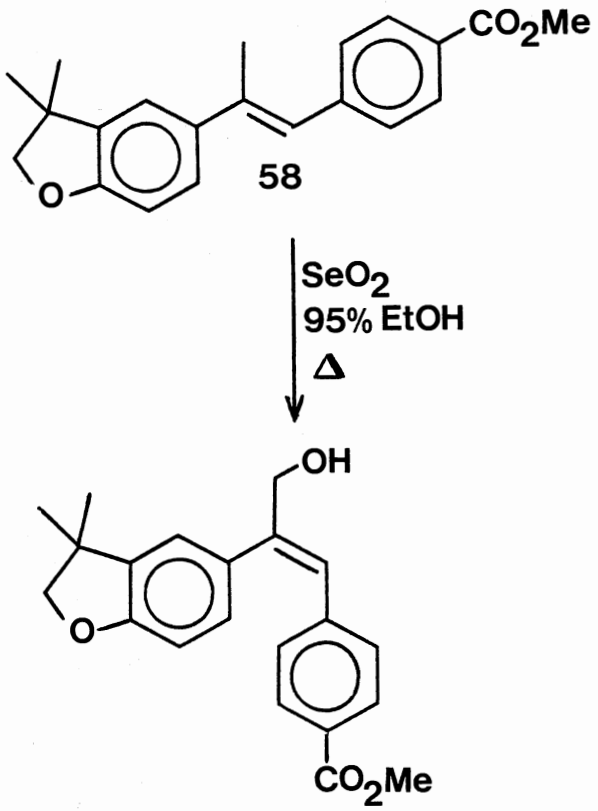


Figure 20. Cyclizations of Propenylheterodiazonium Salts as Reported by Beckwith[8,9,69] and Oae[73] and Their Respective Co-workers.

identified, which is consistent with findings of Beckwith and co-workers.[9] Reductive cleavage of the N–O bond in **120** with Zn/AcOH at 70°C gave **121** in a yield of 60%. O-Acetylation of **121** with AcCl and pyridine in ether/THF (1.5:1) gave acetate **122** in good yield (92%). Acylation of **122** was effected using acetyl chloride (large excess) in CS_2 in the presence of $AlCl_3$ at 0°C-RT to give **123** in a yield of 86%. Reduction of keto acetate **123** with LAH (excess) in dry ether gave diol **124** (90%), which was converted to salt **125** (crude yield of 100%, 1:1 diastereomeric ratio) using $Ph_3P{\bullet}HBr$ in CH_3OH. The Wittig reagent from salt **125** was prepared *in situ* from *n*-BuLi (1.4 equivalents), cooled at -84°C (liquid N_2/EtOAc slurry), and allowed to react with *p*-$CHOC_6H_4CO_2CH_3$ at -84°C-RT (11 h). After repeated chromatographic separations and recrystallizations, heteroarotinoid **65**-(*E*) was obtained as white crystalline flakes (mp 115.1-116.1°C) in a yield of 6%. The other isomer, **65**-(*Z*), was isolated as an oil (10%) containing small amounts of **65**-(*E*) [**65**-(*Z*):**65**-(*E*) ≈ 93:7].

An attempt was made to prepare **66**-(*Z*) [in this case, the *trans*-aryl isomer] (see Figure 21), a potential metabolite of **58**, by allylic oxidation of **58** using SeO_2. While much of the starting ester **58** was recovered (70%), the chromatographed product (20%) contained a mixture of isomers (*cis*-aryl:*trans*-aryl ≈ 10:1) from which the *cis*-aryl isomer, **66**-(*E*), was crystallized (mp 125.1-125.7°C) in a yield of 12%.

Heteroarotinoids **67-71** containing an octatrienoic acid side chain were all prepared in a similar fashion (see Figures 22 and 23). The methyl aryl ketones (**81**, **88a**, or **128**) were allowed to react (separately) with CH_2=CHMgBr (prepared *in situ* in dry THF by standard conditions) to give (after an aqueous workup at 0°C) tertiary and allylic alcohols **129-131**, respectively, in yields of 99-100%. Without further purification, the allyl alcohols were allowed to react with $Ph_3P{\bullet}HBr$ in CH_3OH to give salts **132-134**. Phosphonium salt **132** was recrystallized from CH_3OH/ether [ether was allowed to diffuse into a methanolic solution of crude salt **132**] and obtained in a yield of 61%; salt **133** was recrystallized from CH_3OH/ether (yield of 75%); salt **134** was recrystallized



66-(*E*)

Figure 21. Preparation of Heteroarotinoid **66**-(*E*).

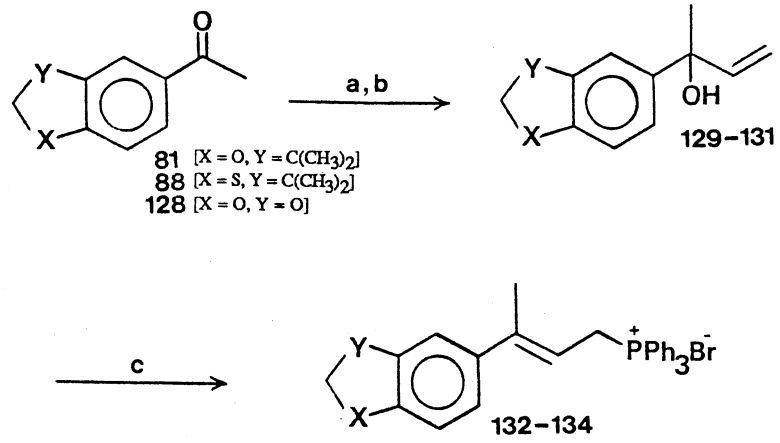


Figure 22. Preparation of Butenylphosphonium Salts. (a) CH_2=CHMgBr, THF; (b) H_2O; (c) CH_3OH, Ph_3P•HBr.

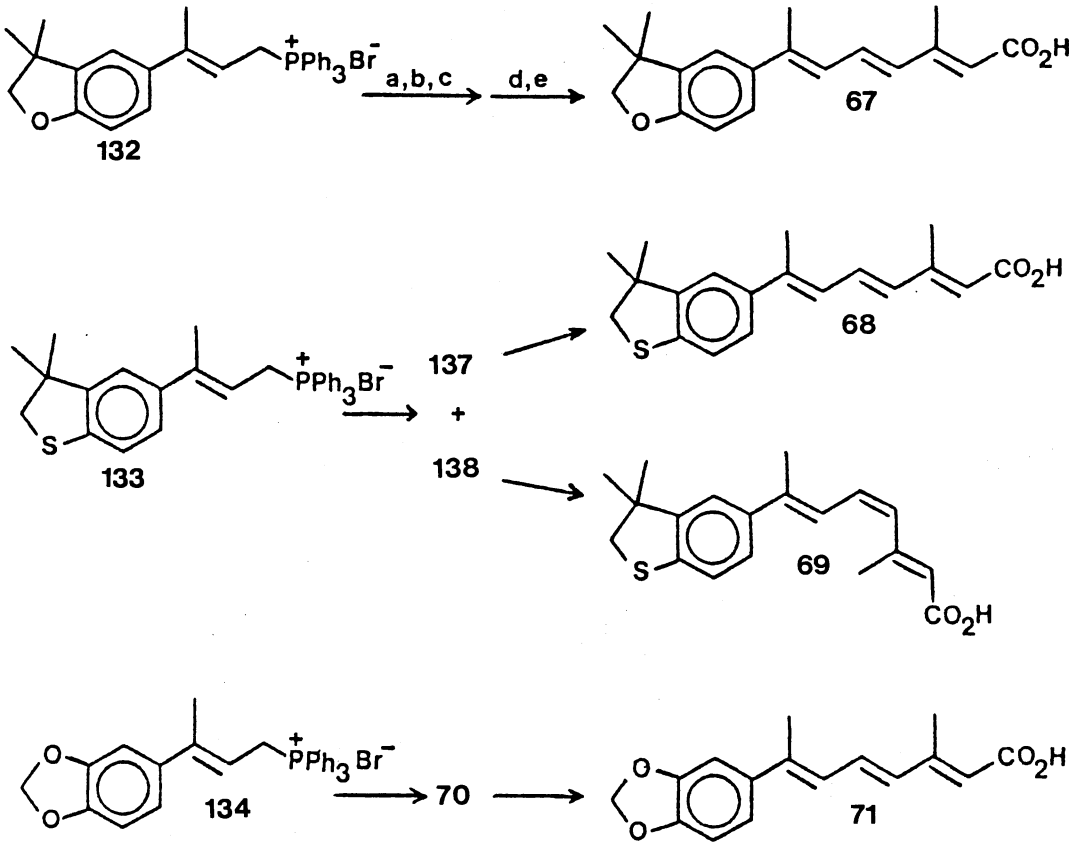


Figure 23. Preparation of Octatrienoic Acid Heteroarotinoids **67-69, 71**. (a) *n*-BuLi; (b) -78°C; (c) *trans*-OHC-C(CH_3)=$CHCO_2Et$; (d) KOH, EtOH, H_2O, reflux; (e) CH_3CO_2H, H_2O.

from $CHCl_3$/ether (yield of 82%). Each of the phosphonium salts **132-134** was converted *in situ* to their respective Wittig reagents using *n*-BuLi in dry ether. After cooling to -78°C (dry ice-acetone bath), the Wittig reagents were allowed to react with ethyl β-formyl-crotonate at -78°C to RT. The (2*E*,4*E*,6*E*)- and (2*E*,4*Z*,6*E*)-isomers of the resulting conjugated esters from **132** had identical R_f values (using 10:1 hexanes:ether) and so were not separated. Saponification (KOH in aqueous EtOH) of this mixture of isomers gave a solid from which only the all-*trans*-isomer (**67**) crystallized out as golden yellow plates (mp 204-205°C) using boiling absolute ethanol (yield of 23% from the phosphonium salt). The (2*E*,4*E*,6*E*)- and (2*E*,4*Z*,6*E*)-isomers of the conjugated esters (**137** and **138**, respectively, see Figure 24 for structure), were separated by chromatography on silica gel (using 20:1 hexanes/ether) and obtained as oils in yields of 36% and 11%, respectively. Saponification (KOH in aqueous EtOH) of **137** and **138** gave the free acids **68** (all-*trans*-isomer, golden yellow plates, mp 211-212°C) and **69** [the (2*E*,4*Z*,6*E*)-isomer; a yellow powder, mp 140-141°C) in yields of 70% and 21%, respectively (yields calculated from the starting esters). Ester **70** (from salt **134**) crystallized on standing after the reaction mixture was concentrated. Recrystallization in hexanes afforded the all-*trans*-ester **70** as yellow needles (mp 70-70.5°C) in a yield of 14%. Saponification of **70** gave the free acid **71** as a yellow powder, mp 199.5-200°C (68%).

Structural Elucidation of New Heteroarotinoids Via NMR and UV Spectroscopy and X-ray Crystallography

^1H and ^{13}C NMR analyses provide a rapid and convenient tool for the determination of the structures of organic compounds. In the preparation of heteroarotinoids it is particularly important to assess the configurations at the alkene linkage present in the carbon skeleton since evidence suggests that the biological activity of retinoids is

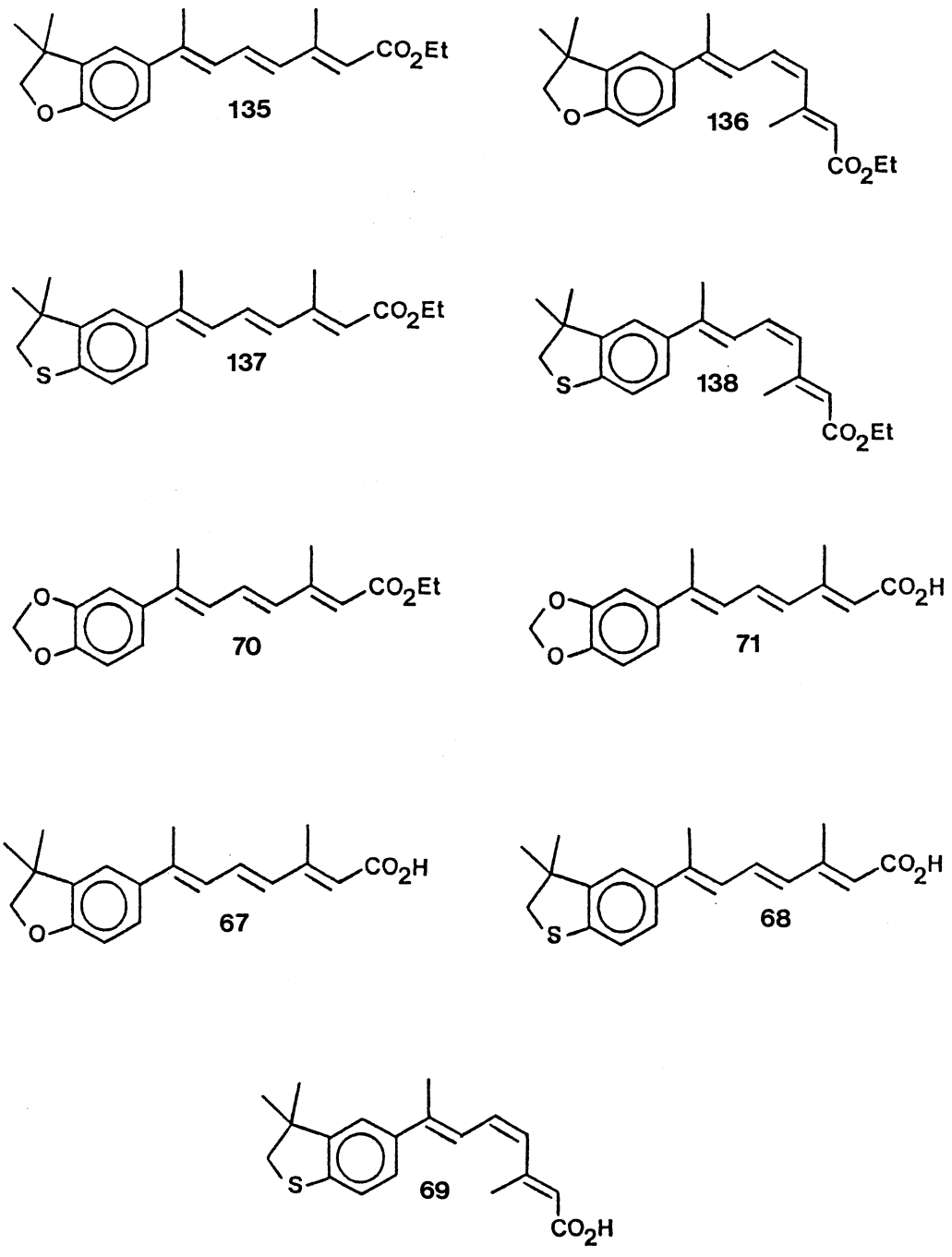


Figure 24. New Triene Heteroarotinoids {**67-71**} and the Isomers of the Precursor Esters Detected by ^{1}H NMR {**135-138**}.

dependent (at least in part) upon the stereochemical nature about the double bonds.[25,70] Although the chemical shifts observed in ^{1}H and ^{13}C NMR spectra are useful in determining such configurations, the ^{1}H-^{1}H coupling constants are often more diagnostic, particularly when vicinal hydrogen atoms are present about or between double bonds. Such is the case for the new heteroarotinoids **67-71** and related esters (see Figure 24). The stilbene-like heteroarotinoids **58-66** and isomers **64**-(*Z*), 65-(*Z*), **66**-(*Z*) (see Figure 25), however, contain only one double bond with only one vinylic hydrogen atom and so the use of such ^{1}H-^{1}H coupling constants is negated. However, the proximity of the two aryl rings (particularly in the *cis*-aryl isomers) induces changes in the chemical shifts of all the hydrogen nuclei with particularly large chemical shift differences (δ_{trans}-δ_{cis}) for those protons at the vinyl and aromatic positions. Only two stereoisomers are possible in these diaryl heteroarotinoids. Furthermore, the degree to which the conjugation is conserved should differ among the two possible isomers and thus it would be expected that the differences in the UV spectral properties should also be useful in determining the configuration about the double bond. Indeed, large differences in the UV spectra for the *cis*- and *trans*-aryl isomers were observed. The absolute configuration about the double bond in solid **58**, **60** and **61** was established by X-ray crystallography.

A comparison of the proton chemical shifts and shift differences for the (*E*)- and (*Z*)-isomers **58** and **59**, and, **60** and **61** is shown in Table VI. These differences are designated $\Delta\delta$ and are *all positive,* indicating that the chemical shifts of the hydrogen nuclei in the (*Z*)-isomers are all *upfield* relative to those observed in the (*E*)-isomers. While some of the chemical shifts of the corresponding protons of the sulfur and oxygen analogues are different, the corresponding $\Delta\delta$ values are very similar. Particularly noteworthy are the large chemical shift differences ($\Delta\delta$ values) for the aromatic and vinyl protons. Among the aromatic protons, the largest $\Delta\delta$ values were observed for the four protons *ortho* to the central double bond. The data suggest that the two aryl rings (rings B and C, see Table VI) in these systems are turned in the *cis*-aryl isomers such that the

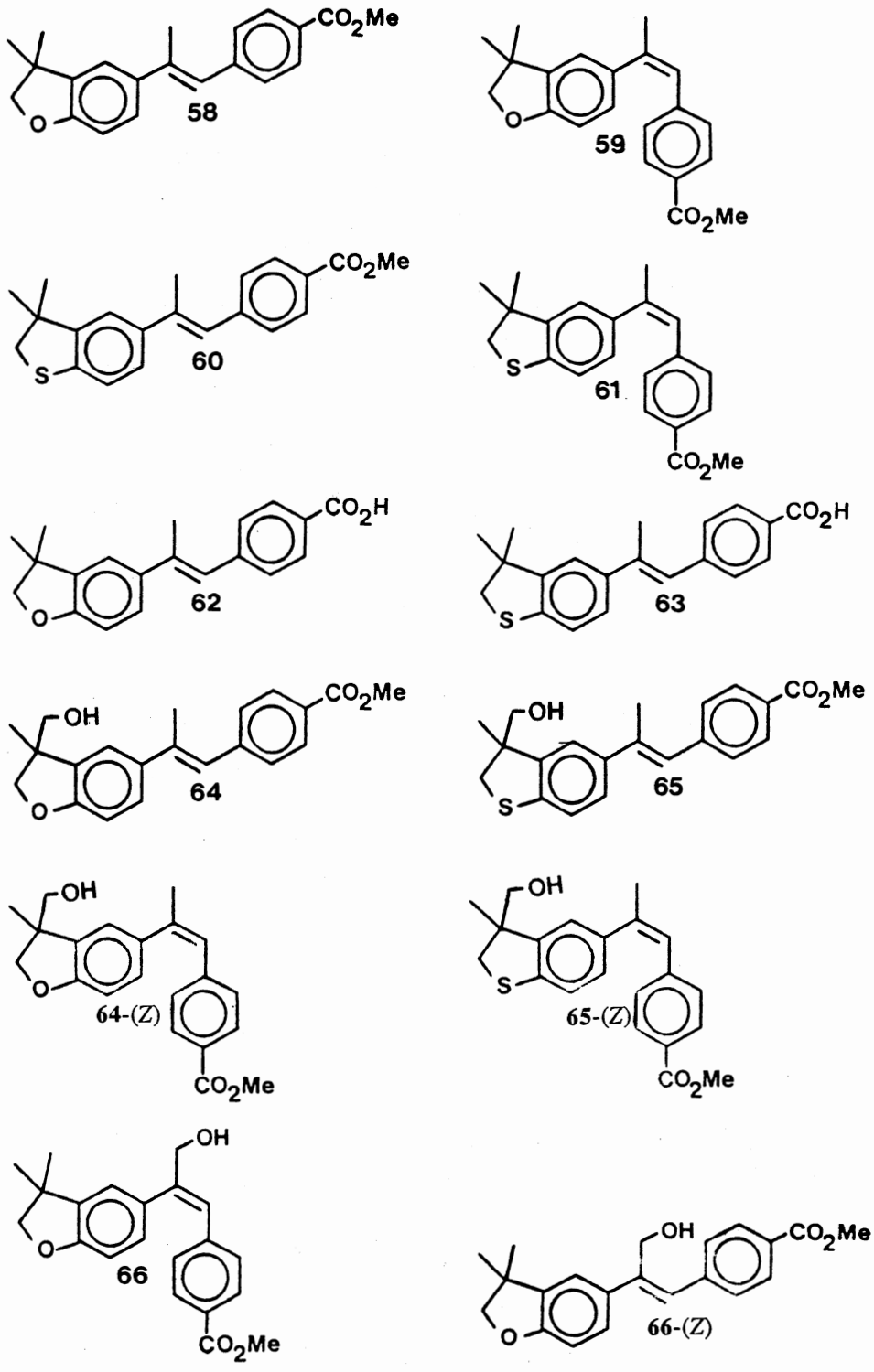
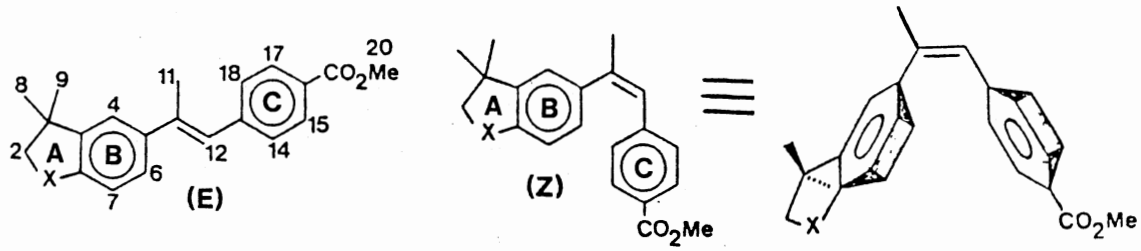


Figure 25. New Triene Heteroarotinoids {**58-66**} and Other Isomers Detected by ^{1}H NMR {**64**-(Z), **65**-(Z), **66**-(Z)}.

TABLE VI

COMPARISON OF THE ^1H NMR CHEMICAL SHIFTS (δ) AND SHIFT DIFFERENCES (Δδ) OF THE (*E*)- AND (*Z*)-ISOMERS OF TWO DIARYL HETEROAROTINOIDS

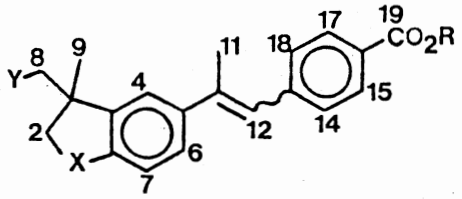


Heteroarotinoids **58**-(*E*) and **59**-(*Z*), (X = 0)				Heteroarotinoids **60**-(*E*) and **61**-(*Z*), (X=S)			
H(#)	δ(E)	δ(Z)	$\Delta\delta=\delta_{trans}-\delta_{cis}$	H(#)	δ(E)	δ(Z)	$\Delta\delta=\delta_{trans}-\delta_{cis}$
2	4.31	4.24	0.07	2	3.21	3.15	0.06
4	7.31	6.86	0.45	4	7.20	6.78	0.42
6	7.34	6.98	0.36	6	7.30	6.97	0.33
7	6.83	6.73	0.10	7	7.19	7.12	0.07
8,9	1.39	1.21	0.18	8,9	1.42	1.22	0.20
11	2.31	2.23	0.08	11	2.28	2.21	0.07
12	6.81	6.45	0.36	12	6.80	6.46	0.34
14,18	7.45	7.04	0.41	14,18	7.42	7.02	0.40
15,17	8.07	7.79	0.28	15,17	8.04	7.78	0.26
20	3.95	3.87	0.08	20	3.93	3.86	0.07

protons in aryl-ring B (plus those hydrogen atoms within or adjacent to the fused heterocyclic ring) are shielded by aryl-ring C and, conversely, the protons of aryl-ring C (plus the CO_2CH_3 protons near it) are shielded by aryl-ring B. The reason for the largest $\Delta\delta$ values being observed for the *ortho* aromatic protons can be explained by their proximity to the center of the shielding cones of the corresponding opposite aryl-rings. The degree to which these aryl rings are turned in solution cannot be established, however, from these data. Nevertheless, two pieces of data suggest that in solution (in $DCCl_3$) ring B in the *cis*-aryl isomers may be turned (on the average) such that H(4) is closer to the center of the shielding cone of ring C than is H(6): first, $\Delta\delta$ for H(4) is significantly greater than $\Delta\delta$ for H(6) and second, $\Delta\delta$ for H(7) [*meta*-H on the *opposite* side (relative to H(4)) of the same aryl-ring] is much less than would be expected [see $\Delta\delta$ for *meta*-H(15,17)]. The ^{13}C NMR data for heteroarotinoids **58**-**65**, and **65**-(*Z*) are given in Table VII. No large differences can be seen in the ^{13}C NMR chemical shifts of the two isomers **58** and **59** (and **60** and **61**) except for those observed for the allylic carbon atom C(11) which appears *downfield* (by more than 9 ppm) in the (*Z*)-isomer relative to the (*E*)-isomer, an anomaly which apparently cannot, as yet, be explained by the above shielding-deshielding arguments. The ^{13}C NMR assignments for proton-bearing aromatic carbon atoms of the (*E*)-isomers **58** and **60** were assigned by inspection of 2-D HETCOR (heteronuclear correlation) plots (see Figures 26 and 27). The carbon assignments for the (*Z*)-isomer **59** were made by comparison with the pattern observed in the ^{13}C NMR spectra of the (*Z*)-isomer of a previously prepared pyran analogue.[82] The above ^1H NMR data for **58**-**61** provided a basis for the assignment of the configurations for the other diaryl heteroarotinoids **62**-**66** and isomers **64**-(*Z*), **65**-(*Z*) and **66**-(*Z*) in which only one of the isomers of each pair (namely, **62**-**66**) was isolated in pure crystalline form (see Table VIII). The above ^1H NMR data conforms with that previously described for other heteroarotinoids and arotinoids.[24,26,62,100,111] In short, it appears that signals at δ 8.0-8.2 (d, protons *ortho* to the carboxyl group), δ 6.7-6.9 (br s, vinyl

TABLE VII

^{13}C NMR SIGNALS FOR HETEROAROTINOIDS **58-66**, **65**-(*Z*)



Carbon	**58**-(*E*)	**59**-(*Z*)	**60**-(*E*)	**61**-(*Z*)	**62**-(*E*)	**63**-(*E*)	**64**-(*E*)	**65**-(*E*)	**65**-(*Z*)	**66**-(*E*) (*cis*-aryl)
2	84.9	84.7	47.3	47.3	84.9	47.5	80.6	42.1	41.7	84.8
3	41.9	41.8	47.5	47.1	41.9	47.3	47.7	52.7	52.5	41.8
4	120.0	122.6	120.3	122.4	120.0	120.3	120.7	121.3	122.5	123.2
6	126.1	127.7	125.4	127.0	126.1	125.4	127.0	126.1[a]	127.3	128.1
7	109.3	109.6	122.2	123.0	109.4	122.2	109.6	122.4	123.9	110.0
7a	159.0	158.6	[b]	[b]	159.1	[b]	161.1	[b]	[b]	159.1
8	27.6	27.4	27.4	27.3	27.6	27.4	69.0	67.8	67.2	27.5
9	27.6	27.4	27.4	27.3	27.6	27.4	21.9	22.5	22.1	27.5
11	17.9	27.1	17.8	26.9	18.0	17.9	17.9	17.8	26.6	68.1
12	125.1	125.1	125.9	125.6	125.1	125.8	125.4	126.1[a]	125.6	124.8
14,18	129.0	128.8	129.1	128.8[a]	129.1	129.2	129.0	129.0	128.8	129.1[a]
15,17	129.4	129.1	129.5	129.2[a]	130.1	130.2	129.5	129.5	129.1	129.2[a]
19	167.0	167.0	167.0	167.0	171.7	171.8	167.0	167.0	166.9	166.9
20	52.0	51.9	52.1	51.9	–	–	52.1	52.1	51.9	52.0
Other Quaternary Carbons	127.6	127.3	127.8	127.4	126.7	126.9	127.7	127.9	127.6	128.0
	136.4	133.6	139.5	137.5	136.4	139.9	132.1	139.2	137.2	129.8[a]
	136.8	136.8	140.2	139.7	136.8	140.1	136.5	140.1	140.9	137.4
	139.6	141.6	143.1	141.2	140.0	140.3	139.3	141.6	141.2	141.8
	143.4	142.9	148.2	142.7	144.3	144.1	143.3	143.0	142.6	144.2
			[a]	148.2		148.2		143.7	143.8	

[a]Two signals must be overlapping nearly perfectly.

[b]Could not be asigned (one of the quaternary carbons below).

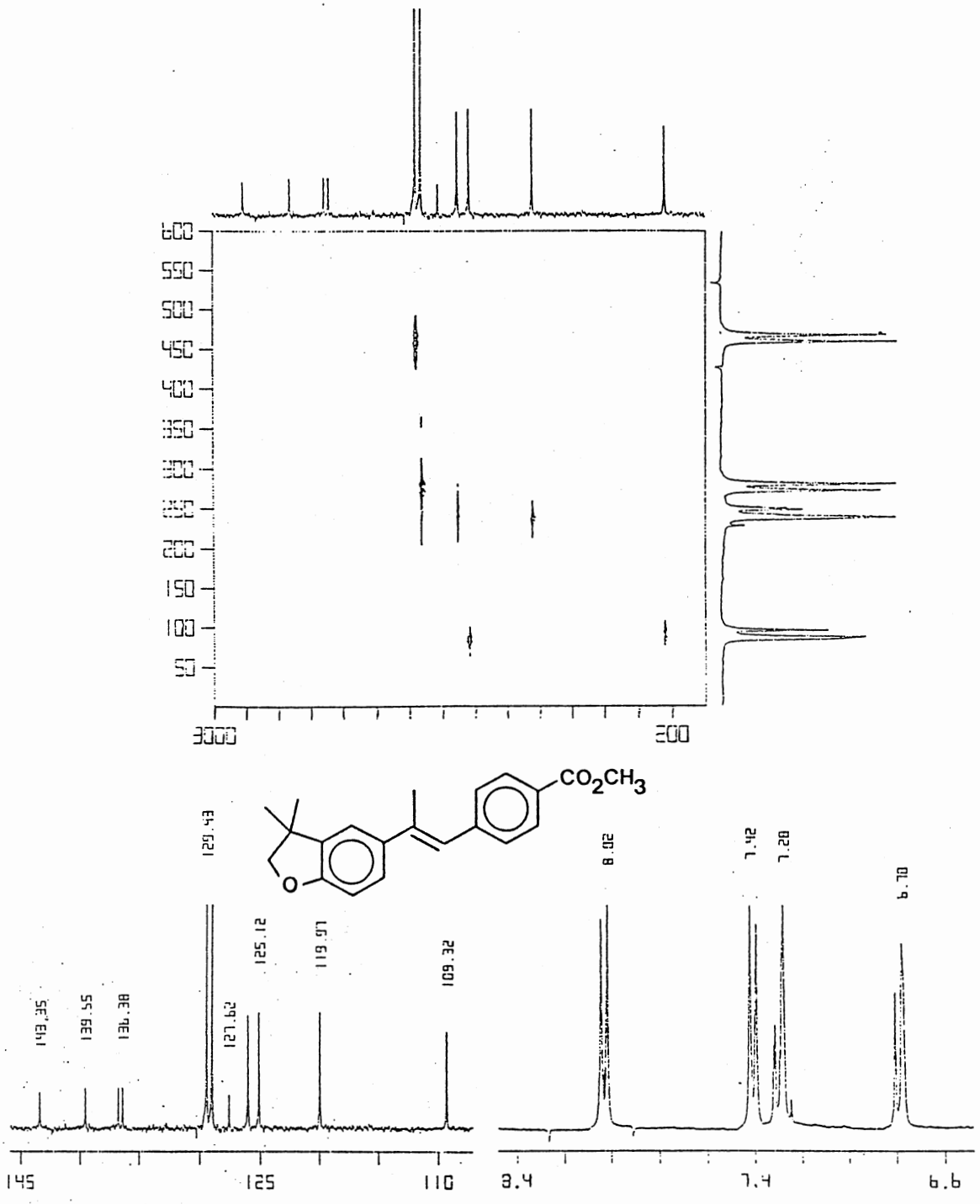


Figure 26. 2-D HETCOR Plot of Aromatic Region of **58**.

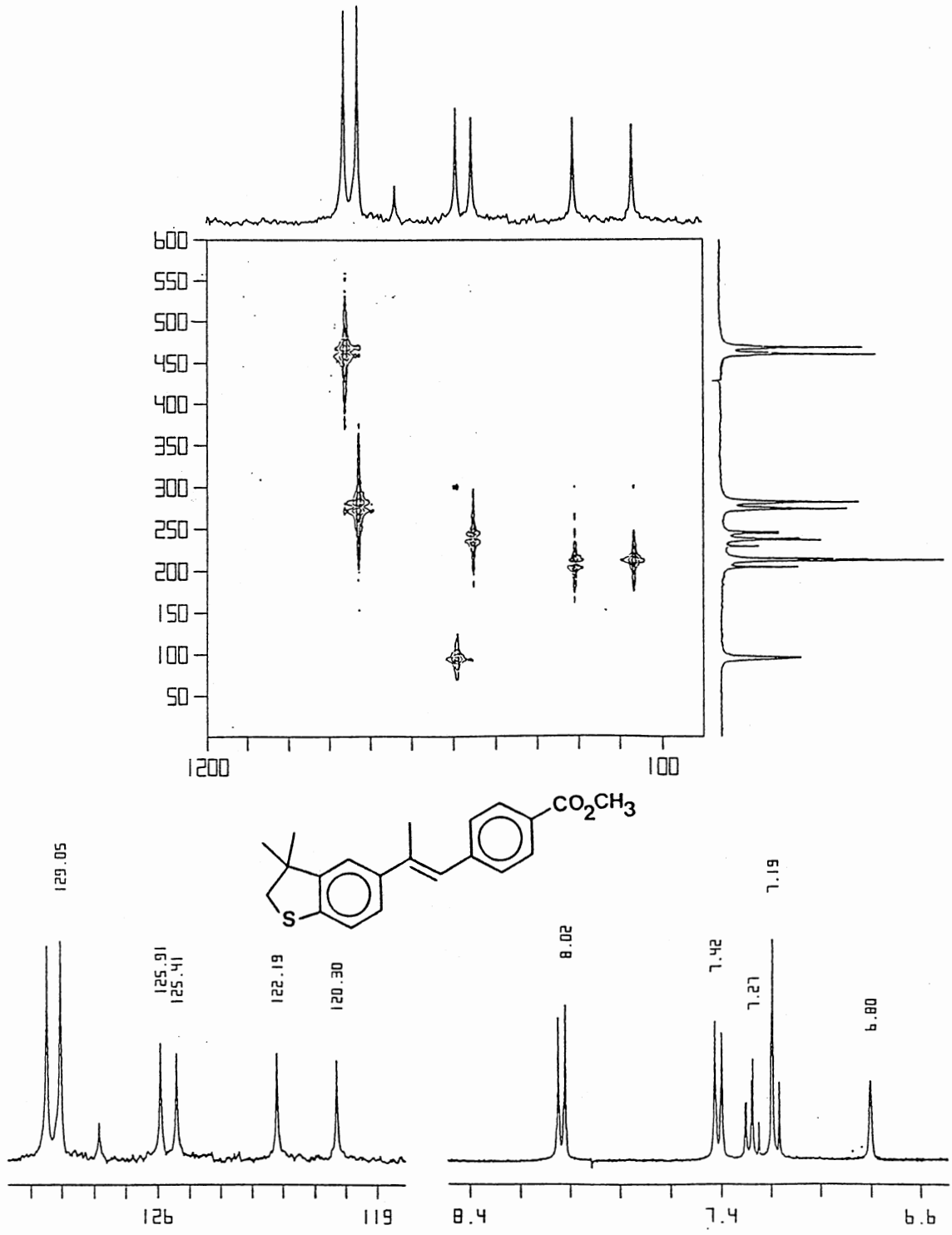
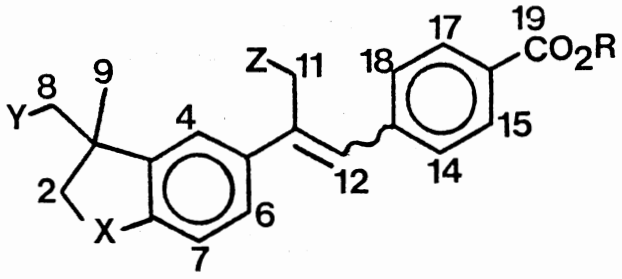


Figure 27. 2-D HETCOR Plot of Aromatic Region of **60**.

TABLE VIII

^{1}H NMR CHEMICAL SHIFTS (δ) FOR DIARYL HETEROAROTINOIDS **62-66**, **64**-(*Z*), **65**-(*Z*)



Proton	**62**-(*E*)	**63**-(*E*)	**64**-(*E*)	**64**-(*Z*) (***cis*-aryl**)	**65**-(*E*)	**65**-(*Z*)[b] (***cis*-aryl**)	**66**-(*E*) (***cis*-aryl**)
2	4.28	3.23	4.24[d]	4.16[d]	3.21[d]	3.09[d]	4.25
	4.28	3.23	4.62[d]	4.54[d]	3.49[d]	3.35[d]	4.25
4	7.29	[a]	7.29	6.79	7.21	6.74	6.89
6	7.32	7.32	7.35	7.02	7.34	7.02	6.99
7	6.81	[a]	6.82	6.73	7.22	7.13	6.76
8	1.39	1.42	3.63[d]	3.41[d]	3.64[d]	3.43[d]	1.23
	1.39	1 42	3.72[d]	3.49[d]	3.77[d]	3.54[d]	1.23
9	1.39	1.42	1.42	1.20	1.45	1.21	1.20
11	2.31	2.31	2.28	2.20	2.28	2.20	4.49
12	6.79	6.84	6.77	6.43	6.80	6.46	6.68
14,18	7.46	7.48	7.41	6.98	7.42	7.00	7.07
15,17	8.12	8.14	8.03	7.76	8.04	7.77	7.79
20	–	–	3.93	3.84	3.93	3.84	3.87

[a]H(4) and H(7) overlap at δ 7.18-7.24.

[b]From a mixture containing 93% *Z*- and 7% *E*-isomer.

[c]From a small portion purified by HPLC.

[d]The two values of these respective positions correspond to the protons which are non-equivalent due to the presence of the adjacent chiral center.

proton) and ~ δ 1.4 (s, *gem*-dimethyl H's) are indicative of heteroarotinoids with the *trans*-aryl configuration and containing a carboxyl/carboxyalkyl group *para* to the central double bond. Signals at δ 7.7-8.0 (d), δ 6.9-7.2 (d), δ 6.4-6.5 (br s) and δ 1.1–1.2 (s) are indicative of the corresponding heteroarotinoids but with the *cis*-aryl configuration. An important exception results from the replacement of the vinyl methyl group with a trifluoromethyl group or a hydroxymethyl group. The vinyl proton, which appears to interact with the fluorine atoms of the trifluoromethyl group in the *cis*-aryl isomers (as revealed by X-ray crystallography),[49,86] appears downfield (near δ 7.0)[99] from its normal position (at δ 6.4-6.5 in the *cis*-aryl isomers) and a similar interaction may exist between the vinyl proton and the hydroxyl proton in **66** since the vinyl proton (δ 6.68) is also downfield from normal for *cis*-aryl arotinoids.

A convenient and possibly more definitive method for determining the configuration of the aryl rings about the central double bond utilizes UV spectroscopy. Readily recognizable and predictable differences were observed in the UV-spectra of the (*E*)- and (*Z*)-isomers of stilbene and derivatives.[84,103] Heteroarotinoids contain the stilbene skeleton and the UV spectra of their respective isomers also follow the same pattern observed in the UV spectra of stilbene derivatives. Two maxima are generally seen, one at 280-350 nm and the other at 210-270 nm. These two bands may contain fine structure but the most intense of the peaks within these two bands fall within the above regions. The band at 280-350 nm in stilbene derivatives has been called the "conjugation band"[103] apparently because of its dependence upon changes in conjugation. One striking observation that can be seen in the collection of UV spectra of *cis*- and *trans*-stilbene derivatives by Riezebos and co-workers[84] is that the "conjugation band" in the spectra of the *trans*-aryl isomers was always much more intense than the lower wavelength band, whereas the opposite was true for the spectra of the *cis*-isomers [Riezebos and co-workers[84] did not report the observed UV_{max} (and corresponding ε values) for some of the stilbene derivatives and so these were determined by us from the recorded spectra and

given in Table IX). Two of the factors which induce significant changes in the location of the absorption maxima of the "conjugation band", relative to that for *trans*-stilbene, were found to be the incorporation of a methyl group at the central double bond (**141**) or the presence of a syn-aryl arrangement (**140** in Table IX). Both of these changes result in *hypsochromic* shifts (from 295 nm to 272 nm and 280 nm, respectively, in ethanol, see Table IX) with concomitant reductions in intensities (extinction coefficients reduced from 27,850 to 21,000 and 10,450, respectively) indicating reductions in the overall conjugation of the systems relative to that in *trans*-stilbene. Incorporation of a heteroatom (oxygen) *para* to the middle double bond in the stilbene **143** resulted in a *bathochromic* shift from 294 nm to about 303 nm. Incorporation of electron withdrawing groups (e.g. nitro group in **145**) resulted in *bathochromic* shifts of the "conjugation band" relative to that found in *trans*-stilbene (see Table IX). Heteroarotinoids [those previously prepared (see Table IX) and **58-66** (Table X)] presented here contain a methyl group at the central double bond, a heteroatom *para* to the middle double bond and an electron withdrawing group (carboxyl group) *para* to the double bond; in some cases, both isomers were isolated. As can be seen in Table X, hypsochromic shifts of the "conjugation band" (at 270-350 nm) were observed for the *cis*-aryl heteroarotinoids relative to the corresponding *trans*-aryl isomers. Also, it is important to note the large *bathochromic* shift of the lower-wavelength band from 244 nm for sulfur analogue **60** to 269 nm in the *cis*-aryl counterpart **61**. Significant but smaller *bathochromic* shifts of the corresponding "conjugation bands" and the band at 210-270 nm were also observed as a result of changing the heteroatom from oxygen (**58**) to sulfur (**60**). Most important, the relative intensities of the "conjugation band" and the lower wavelength band (maxima at 210-270 nm) provide a diagnostic tool in assessing which isomer is present. *trans*-Aryl-substituted heteroarotinoids give UV spectra containing an intense "conjugation band" relative to that of the lower wavelength band, whereas, *cis*-aryl-substituted heteroarotinoids provide

TABLE IX

UV DATA OF SELECTED STILBENE DERIVATIVES (INCLUDING SOME HETEROAROTINOIDS)

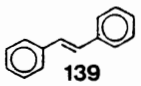
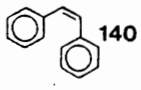
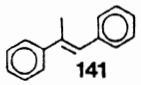
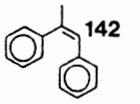
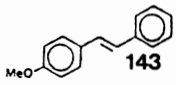
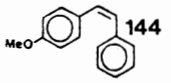
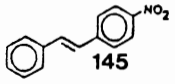
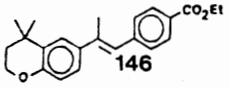
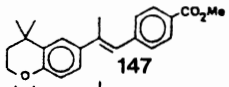
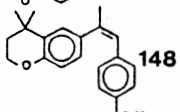
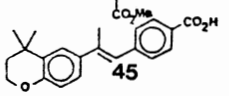
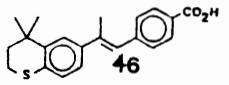
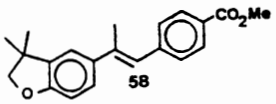
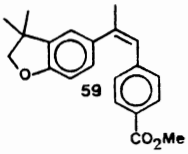
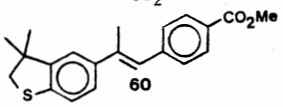
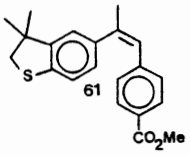
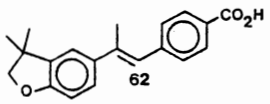
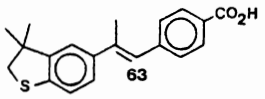
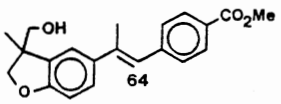
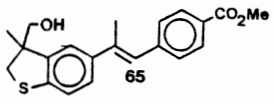
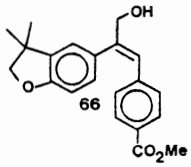
Compound	"conjugation band" λ_{max}, nm (ε, x 10^4)	lower-wavelength band λ_{max}, nm (ε, x 10^4)	Solvent	Reference
 139	294.5 (2.78) 294.0 (2.81) 294.1 (2.80)	228.8 (1.64) 228.3 (1.65) 228.5 (1.62)	EtOH (95%) MeOH *n*-heptane	103 84 103
 140	280 (1.04) 276 (1.0)	224 (2.44) 224 (2.3)	EtOH MeOH	103 84
 141	273.5 (2.11) 272 (2.1)	217 (1.25) —	*n*-heptane EtOH	103 103
 142	267 (0.93)	—	EtOH	103
 MeO 143	302.7 (2.90) 305 (2.95)	230.0 (1.36) 228 (1.37)	*n*-heptane MeOH	103 84
 MeO 144	286 (1.3)	228 (2.0)	MeOH	84
 NO_2 145	345.0 (2.38)	233.7 (1.18) 240.0 (1.18)	*n*-heptane	103
 CO_2Et 146	316 (2.4)	236 (1.4)	EtOH	26
 CO_2Me 147	318 (2.5)	237 (1.5)	EtOH	82
 148	310 (1.6)	245 (2.2)	EtOH	82
 CO_2Me CO_2H 45	307 (2.5)	231 (1.3)	EtOH	26
 CO_2H S 46	319 (2.5)	233 (1.1)	EtOH	26

TABLE X

UV DATA OF NEW HETEROAROTINOIDS **58-66**

Heteroarotinoid	"conjugation band" λ_{max}, nm (ε, x 10^4)	lower-wavelength band λ_{max}, nm (ε, x 10^4)	Solvent	Concentration
 58	319 (2.2)	237 (1.2)	EtOH	5.6 x 10^{-5}
 59	310 (1.7)	242 (2.1)	EtOH	2.5 x 10^{-5}
 60	326 (2.4)	244 (1.2)	EtOH	5.0 x 10^{-5}
 61	317 (1.2)	269 (2.0)	EtOH	5.0 x 10^{-5}
 62	311 (2.2)	230 (1.2)	EtOH	5.8 x 10^{-5}
 63	309 (1.77) 316 (1.78)	238 (1.3)	EtOH	8.0 x 10^{-5} M
 64	308 (1.52) 315 (1.53	240 (1.2)	EtOH	8.9 x 10^{-5} M
 65	308 (1.23) 317 (1.29)	245 (1.1)	EtOH	1.1 x 10^{-4} M
 66	287 (1.3)	242 (1.5)	EtOH	8.9 x 10^{-5} M

spectra containing a "conjugation band" that is less intense than that of the respective lower wavelength band.

Heteroarotinoids **58**, **60** and **61** were submitted to Dr. van der Helm at OU for X-ray analysis to establish the configurations and potential conformations of the aryl rings about the central double-bond (see Tables XI-XV and Figures 28-30). The results of such experiments could provide information useful in determining the spatial arrangement of retinoid binding sites. From a theoretical viewpoint, it is also interesting to investigate the potential conformations in the sterically crowded *cis*-aryl systems. The X-ray plot of **58** and **60** established the *trans*-aryl configuration. It is important to differentiate between the numbering system for heteroarotinoids in Table VIII and that used by the crystallographer (see Figures 28-30). Unless otherwise indicated, the latter numbering will be used in the context of the X-ray data. Both aryl rings were twisted out of plane with the central double as indicated by the torsional angles C(6)-C(7)-C(9)-C(11) [-34.3°] and C(9)-C(11)-C(12)-C(17) [-46.2°] in **60**-(*E*) [similar angles were observed for the X-ray plot of **61**-(*E*) (see Table XIII)]. These two angles sum to about -80° indicating that the planes of the two aryl rings are nearly perpendicular to one another as was shown in the X-ray of the benzothiopyran counterpart.[111] The X-ray data for **58**-(*E*) and **60**-(*E*) were energy-refined using the MMP2 program.[2] This program predicts the most energetically stable conformation. It does not take into account intermolecular crystal formation forces which are absent in solution. Nevertheless, it must be kept in mind that the nature of the solvent is critical and different solvents may stabilize different conformations. The energy-refined structure of **60** indicates that the disubstituted aryl ring is almost completely co-planar with the central double bond (see Table XIII) and with the carbonyl of the ester group [torsional angle C(9)-C(11)-C(12)-C(13) = 179.4°]. The heterosubstituted aryl ring still remains twisted out of planarity with the central double bond in this refined structure [torsional angle C(6)-C(7)-C(9)-C(11) = -43.6°]. Similar torsional angles were observed in the X-ray and energy-refined data for **58**. Of particular interest are the conformations of *cis*-aryl

TABLE XI

DATA COLLECTION PARAMETERS AND CRYSTAL DATA

	Molecule		
	58-(*E*)	**60**-(*E*)	**61**-(*Z*)
Scan width	(0.95+0.20tanT)	(0.80+0.20tanT)	(0.90+0.15tanT)
Aperature	(2.00+0.86tanT)	(3.00+0.86tanT)	(2.00+0.86tanT)
Reflections measured	3477	3574	3472
Reflections observed[a]	3185	2966	3449
Mr	322.17	338.15	338.15
mu	5.77	16.06	15.61
F(000)	680	720	360
Temperature (K)	150	135	150
Space group	P21/n	P21/a	P1-bar
a(A)	10.034(1)	10.039(1)	10.577(3)
b(A)	26.600(7)	26.378(8)	12.254(8)
c(A)	6.788(1)	7.029(2)	7.680(2)
α (degree)	90	90	97.66(4)
β (degree)	108.81(1)	109.94(2)	107.45(2)
γ (degree)	90	90	103.96(2)
V(A')	1715.0	1749.8	898.5
Z	4	4	2
Dc	1.248	1.284	1.250
R	0.043	0.036	0.046
Rw	0.063	0.044	0.077
S	4.77	1.54	6.67

[a] I = > 2sigma(I)

TABLE XII

BOND LENGTHS AND STANDARD DEVIATIONS (ANGSTROMS)

	Bond		
	58-(*E*)	**60**-(*E*)	**61**-(*Z*)
S(1)-C(1)[a]	1.456(2)	1.830(2)	1.833(2)
S(1)-C(4)[a]	1.370(2)	1.761(2)	1.754(2)
C(1)-C(2)	1.538(2)	1.538(3)	1.540(3)
C(2)-C(3)	1.518(2)	1.522(2)	1.523(1)
C(2)-C(20)	1.529(2)	1.524(2)	1.527(2)
C(2)-C(21)	1.533(2)	1.537(3)	1.534(2)
C(3)-C(4)	1.384(2)	1.397(3)	1.399(3)
C(3)-C(8)	1.380(2)	1.386(2)	1.379(2)
C(4)-C(5)	1.385(2)	1.390(2)	1.401(2)
C(5)-C(6)	1.392(2)	1.392(2)	1.383(3)
C(6)-C(7)	1.405(2)	1.403(2)	1.400(3)
C(7)-C(8)	1.408(2)	1.406(2)	1.408(1)
C(7)-C(9)	1.489(2)	1.490(2)	1.482(2)
C(9)-C(10)	1.510(2)	1.508(2)	1.504(2)
C(9)-C(11)	1.343(2)	1.348(2)	1.345(2)
C(11)-C(12)	1.477(2)	1.475(2)	1.477(2)
C(12)-C(13)	1.397(1)	1.406(3)	1.404(1)
C(12)-C(17)	1.404(2)	1.403(2)	1.400(2)
C(13)-C(14)	1.386(2)	1.386(2)	1.379(2)
C(14)-C(15)	1.396(2)	1.402(2)	1.400(2)
C(15)-C(16)	1.392(2)	1.396(2)	1.394(2)
C(16)-C(17)	1.384(2)	1.383(3)	1.384(3)
C(15)-C(18)	1.487(2)	1.486(2)	1.477(2)
C(18)-O(2)[a]	1.204(2)	1.207(2)	1.211(2)
C(18)-O(1)[a]	1.336(2)	1.377(2)	1.346(1)
O(1)-C(19)[a]	1.444(2)	1.446(3)	1.446(2)

[a]For **58**-(*E*), S(1) becomes O(1), and O(1) and O(2) become O(2) and O(3), respectively.

TABLE XIII

SELECTED TORSION ANGLES (DEGREES) FOR **58, 60, 61** FROM CRYSTAL DATA AND FROM MMP2 PROGRAM ENERGY REFINEMENTS

Angle	**58**-(*E*)	**60**-(*E*)	**61**-(*Z*)
C(7)-C(9)-C(11)-C(12)	179.5 [177.9][b]	177.9 [178.9][b]	10.8 [11.7][b]
C(10)-C(9)-C(11)-C(12)[a]	-1.3(2)	-4.0(2)	-172.2(1)
C(6)-C(7)-C(9)-C(10)[a]	147.8(1)	147.5(1)	-130.7(1)
C(6)-C(7)-C(9)-C(11)	-33.9 [-45.2][b]	-34.3 [-43.6][b]	46.9 [46.9][b]
C(8)-C(7)-C(9)-C(10)[a]	-32.2(1)	-31.2(2)	44.0(2)
C(8)-C(7)-C(9)-C(11)[a]	146.1(1)	147.1(2)	-138.5(1)
C(9)-C(11)-C(12)-C(13)	132.1 [179.0][b]	134.1 [179.4][b]	37.7 [16.7][b]
C(9)-C(11)-C(12)-C(17)[a]	-48.4(2)	-46.2(2)	-147.0(1)

[a]These angles in the crystal were determined before the refinement of the X-ray data was complete. The energy-refined data from the MMP2 program was not determined for these angles.

[b]Energy-refined data from the MMP2 program.

TABLE XIV

CRYSTAL BOND ANGLES ABOUT THE CENTRAL DOUBLE BOND IN **58**, **60**, AND **61**[a]

Angle	**58**-(*E*)	**60**-(*E*)	**61**-(*Z*)
C(7)-C(9)-C(10)	116.2(1)	116.4(1)	116.7(1)
C(7)-C(9)-C(11)	120.4(1)	120.1(1)	122.0(1)
C(10)-C(9)-C(11)	123.4(1)	123.5(1)	121.4(1)
C(9)-C(11)-C(12)	127.1(1)	126.5(1)	128.6(1)

[a]These angles were determined before the refinement of the X-ray data was complete. The energy-refined data form the MMP2 program was not determined for these angles.

TABLE XV

SELECTED THRU-SPACE INTERATOMIC DISTANCES (ANGSTROMS) BETWEEN ATOMS IN THE ARYL RINGS IN **61** CRYSTAL DATA[a]

Angle	**58**-(*E*)	**60**-(*E*)	**61**-(*Z*)
C(3)-C(12)	6.220(2)	6.241(3)	5.279(2)
C(4)-C(12)	6.545(2)	6.570(3)	5.336(2)
C(5)-C(12)	5.792(2)	5.789(3)	4.459(2)
C(6)-C(12)	4.408(2)	4.408(3)	3.242(2)
C(8)-C(12)	4.990(2)	4.995(3)	4.323(2)
C(13)-C(7)	4.844(2)	4.879(3)	3.246(2)
C(14)-C(7)	6.146(2)	6.172(3)	4.557(2)
(C16)-C(7)	5.962(2)	5.935(3)	5.432(2)
C(17)-C(7)	4.606(2)	4.577(3)	4.399(2)

[a]These interatomic distances were determined before the refinement of the X-ray data was complete. The energy-refined data from the MMP2 program was not determined for these interatomic distances.

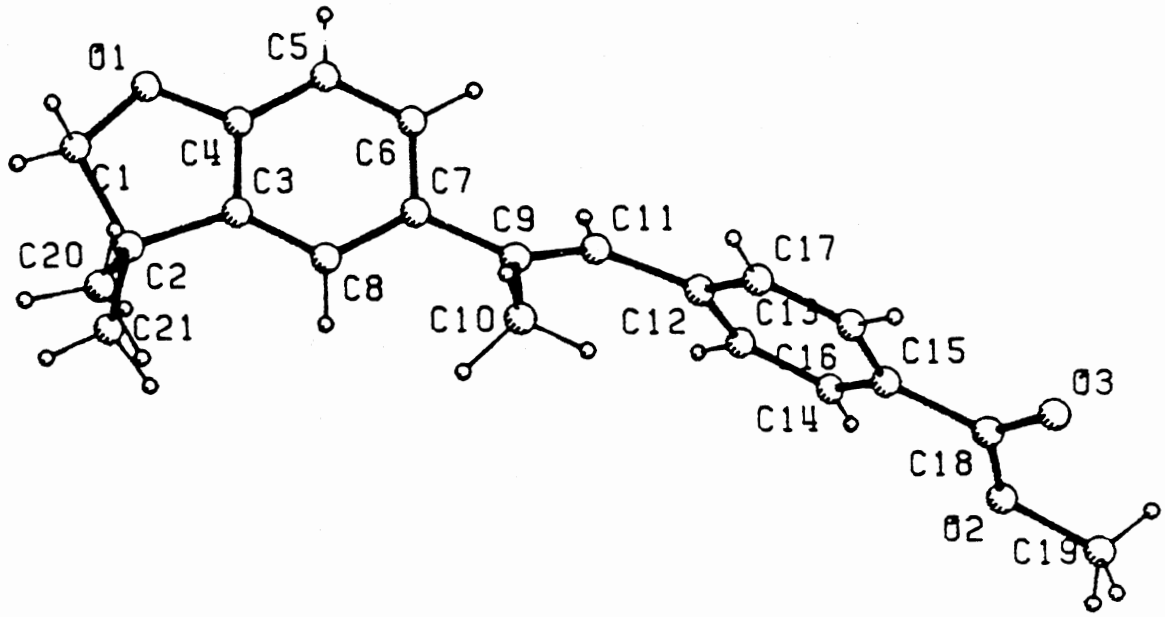


Figure 28. X-Ray Plot of **58**-(*E*).

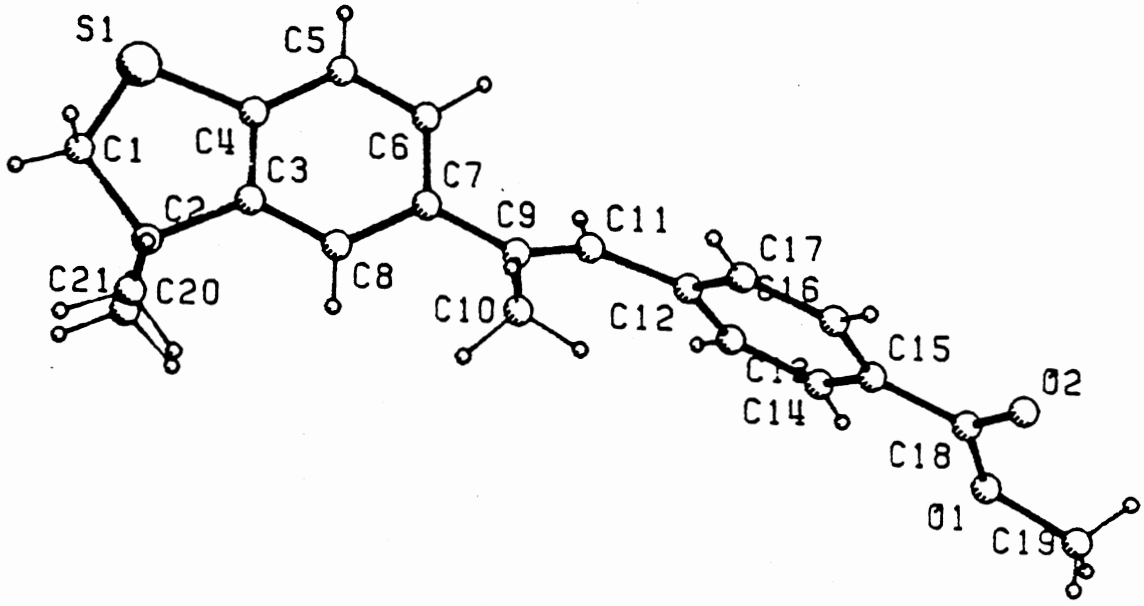


Figure 29. X-Ray Plot of **60**-(*E*).

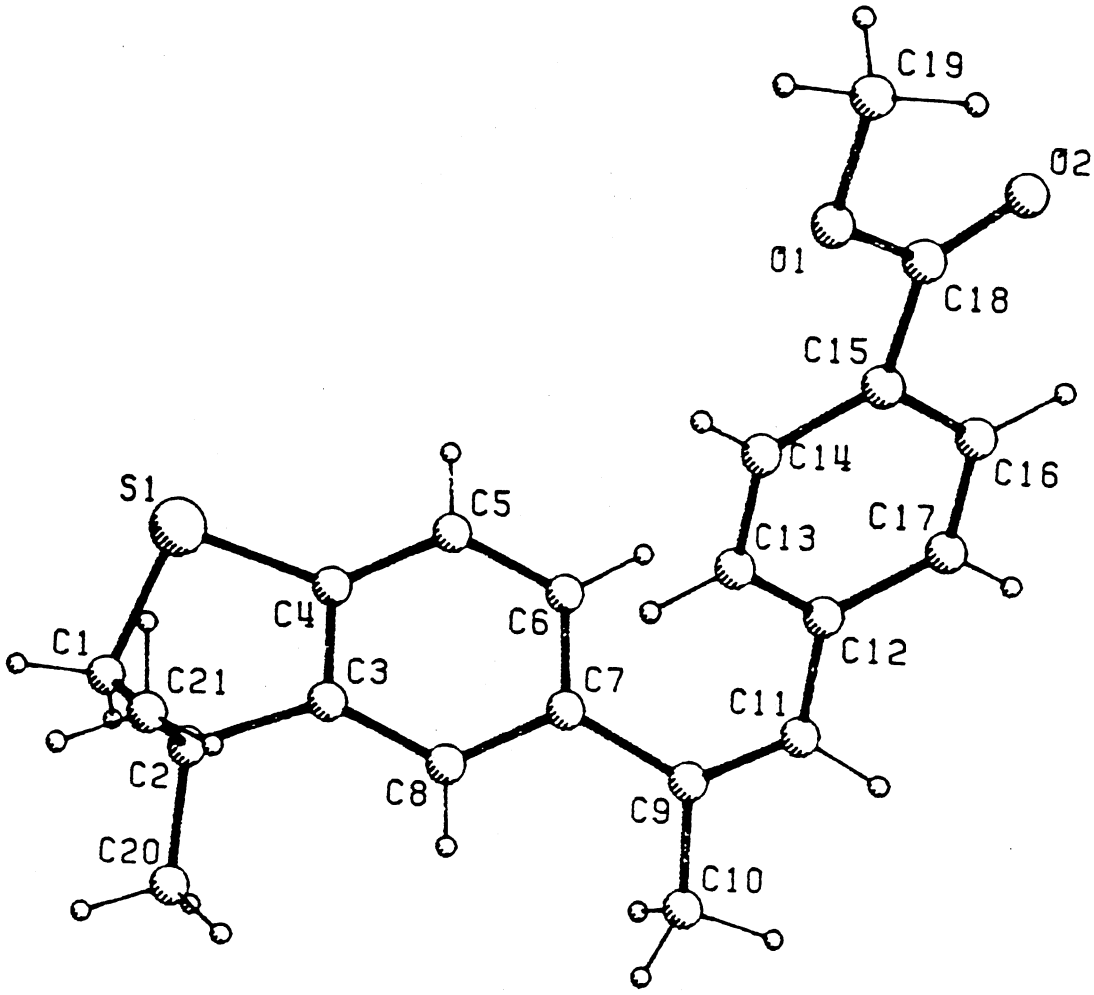


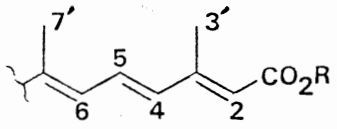
Figure 30. X-Ray Plot of **61**-(*Z*).

61-(Z) in the crystalline state and in the energy-refined structure. Both aryl rings are turned in **61**-(Z) to minimize steric repulsion of the bulky aromatic rings. Even in the energy-refined structure this is so, indicating that the energy gained by complete conjugation is not possible. The steric repulsion of the two aryl rings in **61** appears to be relieved in part by three other conformational changes in the crystal (see Tables XIII, XIV): (a) angles C(9)-C(11)-C(12) and C(7)-C(9)-C(11) are greater in **61** than in **60** suggesting that the aryl-rings have moved apart in **61**; (b) torsional angle (C7)-C(9)-C(11)-C(12) deviates from normal bond angles by about 10° to further separate the two aryl rings in **61** whereas the double in **60** is nearly planar, and (c) it appears that the two aryl-rings in **61** are slightly bent back with respect to bonds C(7)-C(9) and C(11)-C(12), respectively $\{|\angle$ C(6)-C(7)-C(9)-C(11)$| + |\angle$ C(8)-C(7)-C(9)-C(11)$| > 180° < |\angle$ C(9)-C(11)-C(12)-C(13)$| + |\angle$ C(9)-C(11)-C(12)-C(17)$|\}$. While ^{1}H NMR, X-ray crystallography and the energy-refined structure all agree that the two aryl rings are turned, one difference exists between the conformation predicted by ^{1}H NMR (using $DCCl_3$ as solvent) and the conformation present in the crystalline lattice and predicted by the energy-refined structure. As described earlier, the ^{1}H NMR spectra of **61** suggests that the heterosubstituted aryl ring is turned such that C(4) [C(8) in the X-ray plot] is closer to the shielding cone of the opposite aryl ring than is C(6) [also C(6) in the X-ray plot]. This is <u>not</u> the case in the X-ray plot and the energy-refined structure of **61** where C(6) is closer to the opposite ring than is C(4) [C(8) in the X-ray plot, C(6)-C(12) = 3.242 Å, C(8)-C(12) = 4.323 Å] (see Table XV). It is important to note that solvation effects are not taken into account in either the X-ray or energy-refined data. Furthermore, the shielding-deshielding effects described previously may be more complicated than assumed.

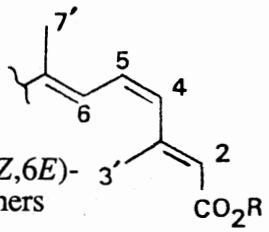
The all-*trans* configurations of **67**, **68**, **70**, **71**, **135**, **137** (see Figure 24) were confirmed by comparison with the ^{1}H-^{1}H coupling constants (and to a lesser extent the chemical shifts) of all-*trans*-Etretinate (**21**, page 7), and heteroarotinoid **44**[100] (see Table XVI). The (2*E*, 4*Z*, 6*E*)-configurations of **69**, **136** and **138** (see Figure 24) were

TABLE XVI

^{1}H NMR CHEMICAL SHIFTS (δ) AND COUPLING CONSTANTS (*J*) OF THE TRIENE PORTION OF ALL-*TRANS*-HETEROAROTINOIDS **67, 68, 70, 71, 137** AND THE (2*E*, 4*Z*, 6*E*)-ISOMERS **69, 138**. ETRETINATE (**21**) AND ITS (2*E*, 4*Z*, 6*E*)-ISOMER INCLUDED FOR COMPARISON[a]



all-*trans*-Retinoids



(2*E*,4*Z*,6*E*)-isomers

all-*trans*-Retinoids	H(2)	H(3')	H(4)	H(5)	J_{H4-H5}	H(6)	J_{H5-H6}	H(7')
	δ	δ	δ	δ	Hz	δ	Hz	δ
all-*trans*-Etretinate (**21**)	5.79	2.369	6.32	7.02	15.1	6.20	11.4	2.107
67	5.83	2.40	6.40	7.08	14.9	6.54	11.3	2.25
68	5.86	2.39	6.44	7.10	15	6.59	12	2.24
70	5.80	2.37	6.35	6.99	15.1	6.49	11.1	2.20
71	5.83		6.39	7.05	15.0	6.51	11.1	
137	5.80	2.38	6.38	7.02	15.1	6.55	~12	2.23
(2*E*, 4*Z*, 6*E*)-isomers	H(2) δ (Δδ)[b]	H(3') δ (Δδ)[b]	H(4) δ (Δδ)[b]	H(5) δ (Δδ)[b]	J_{H4-H5} Hz	H(6) δ (Δδ)[b]	J_{H5-H6} Hz	H(7') δ (Δδ)[b]
(4*Z*)-Etretinate	5.85 (+0.07)	2.34 (-0.03)	5.94 (-0.38)	6.62 (-0.40)	~12	6.54 (+0.34)	~12	2.07 (-0.04)
69	5.90 (+0.08)	2.38 (-0.01)	5.98 (-0.48)	6.61 (-0.45)	11.7	6.92 (+0.35)	11.8	2.20 (-0.04)
138	5.89 (+0.09)	2.37 (-0.01)	5.96 (-0.42)	6.56 (-0.46)	~12	6.92 (+0.37)	~12	2.19 (-0.04)

[a]Reference 31.

[b]$\Delta\delta=\delta_{cis} - \delta_{trans}$. Thus negative Δδ indicate upfield shifts of *cis*-isomers relative to the *trans* isomers.

[c]Numbering system of triene skeleton based on carboxyl receiving position number 1.

confirmed by comparison of their chemical shift differences (relative to those in the all-*trans* isomers) and ^1H-^1H coupling constants with those of the corresponding isomer of Etretinate[31] (see Table XVI). Isomers **135** and **136** were not separated (overlapping R_f values) and the crude (contained a ratio of **135** to **136** of about 2.5:1, respectively, as indicated by ^1H NMR) was converted to an isomeric mixture of carboxylic acids which fractionally crystallized out of absolute ethanol to give all-*trans* **67**. The isomeric esters **137** and **138** were isolated by chromatography in a ratio of about 3:1, respectively. These were individually converted to carboxylic acids **68** and **69** by saponification. All-*trans* ester **70** fractionally crystallized out of hexanes and was similarly converted to acid **71**.

The methyl groups along the side chain of ester **70** gave similar chemical shifts and were assigned by a two-dimensional proton "COSY" (COrrelated SpectroscopY) pulse sequence (see Figure 31). This experiment correlates protons which are coupled to one another. Thus the fine doublet ($^4J_{HH}$ = 1.3 Hz) for the methyl group at δ 2.20 was found to be coupled to the multiplet for vinyl H(10) at δ 6.49, and, the fine doublet ($^4J_{HH}$ = 1.3 Hz) at δ 2.37 was found to be coupled to the broad singlet for vinyl H(15) at δ 5.80. The ^1H assignments for these methyl groups were further confirmed by radiation at δ 5.80 and δ 6.49 which caused the corresponding fine doublets to collapse to tall singlets (see Figure 32). By establishing the ^1H assignments for these methyl groups, it was possible to assign the corresponding ^{13}C NMR signals by a 2-D HETCOR experiment (see Figure 33). Thus the ^{13}C signals at 13.8 and 16.6 ppm correspond to the methyl groups at positions 14 and 9, respectively (in Figure 33). In addition to providing a basis for the ^{13}C assignments of the methyl groups, the 2-D HETCOR plot (see Figure 33) provides the basis for the ^{13}C NMR assignments of all the other carbon atoms of ester **70** (Figure 9). Heteroarotinoid **70** then served as a model for making the ^{13}C NMR assignments of the all-*trans* heteroarotinoids **67**, **68**, **71** (Figure 9) bearing a triene side chain (see Table XVII).

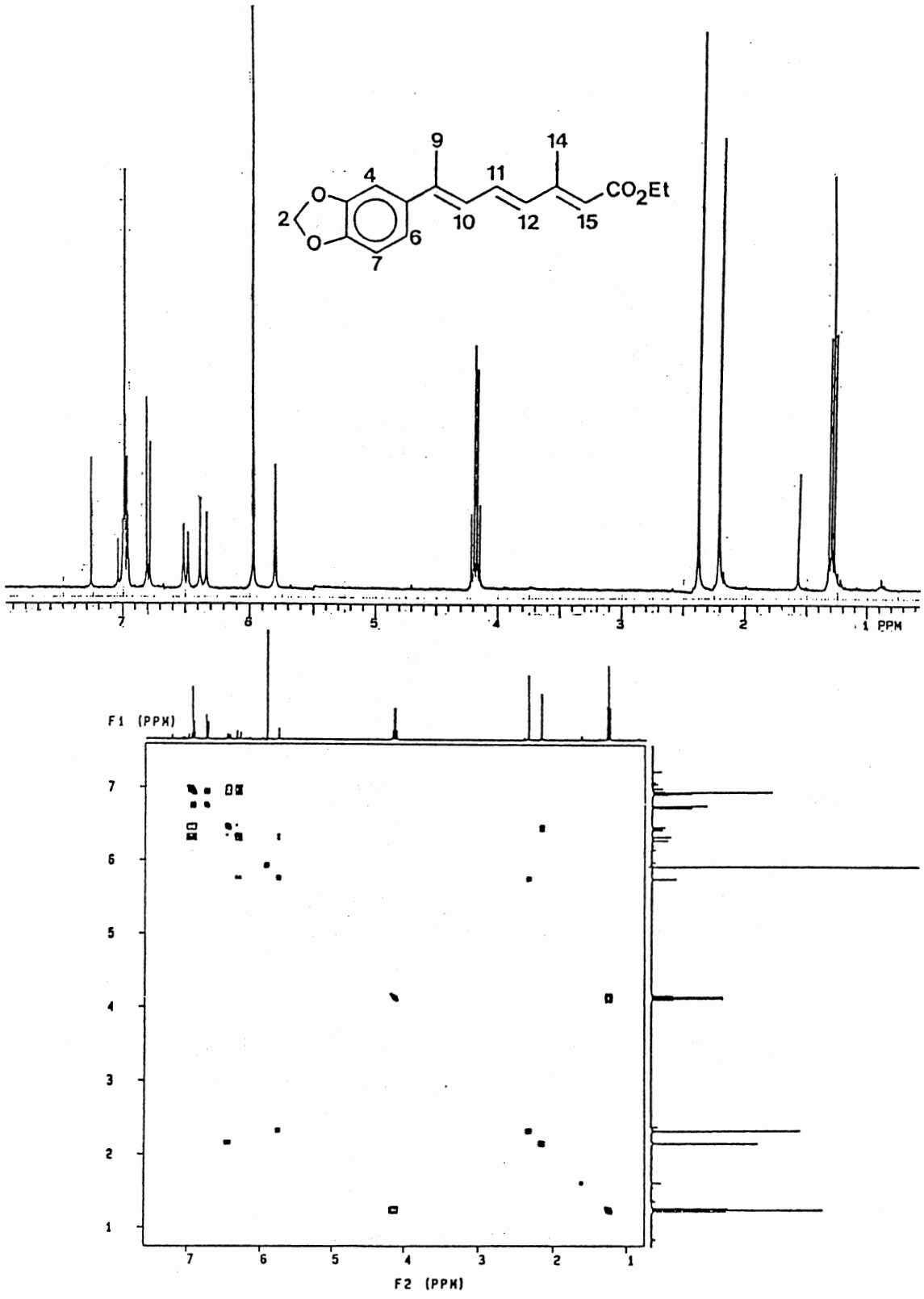


Figure 31. 2-D COSY Pulse Sequence of Heteroarotinoid **70**.

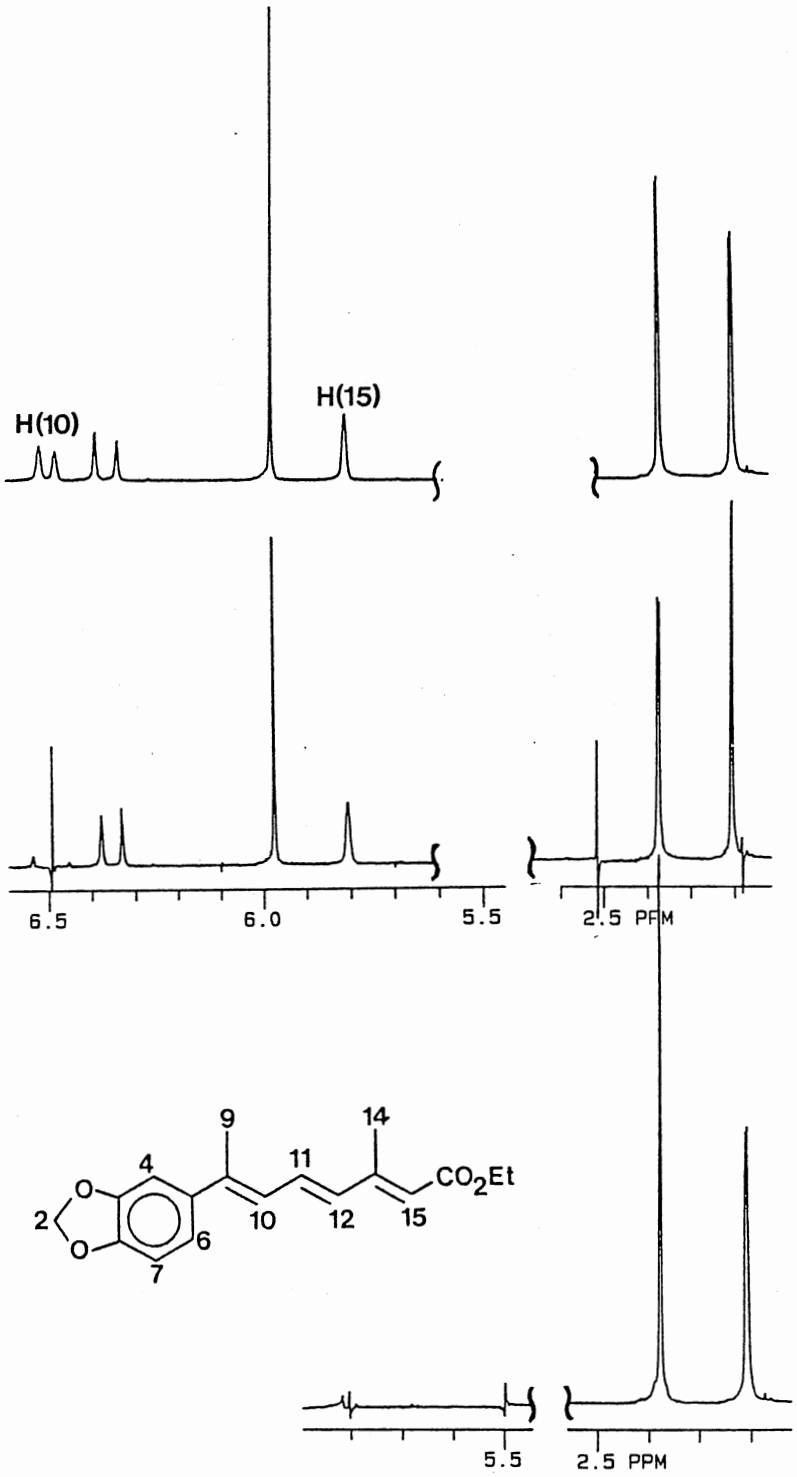


Figure 32. Radiation of the H(10) and H(15) in **70** at δ 6.49 and δ 5.80, Respectively with Resulting NOE Enhancement of Doublets ($^4J_{HH} \approx 1$ Hz) at δ 2.20 and δ 2.37 into Tall Singlets. Thus H(9) and H(14) correspond to the signals at δ 2.20 and δ 2.37, respectively.

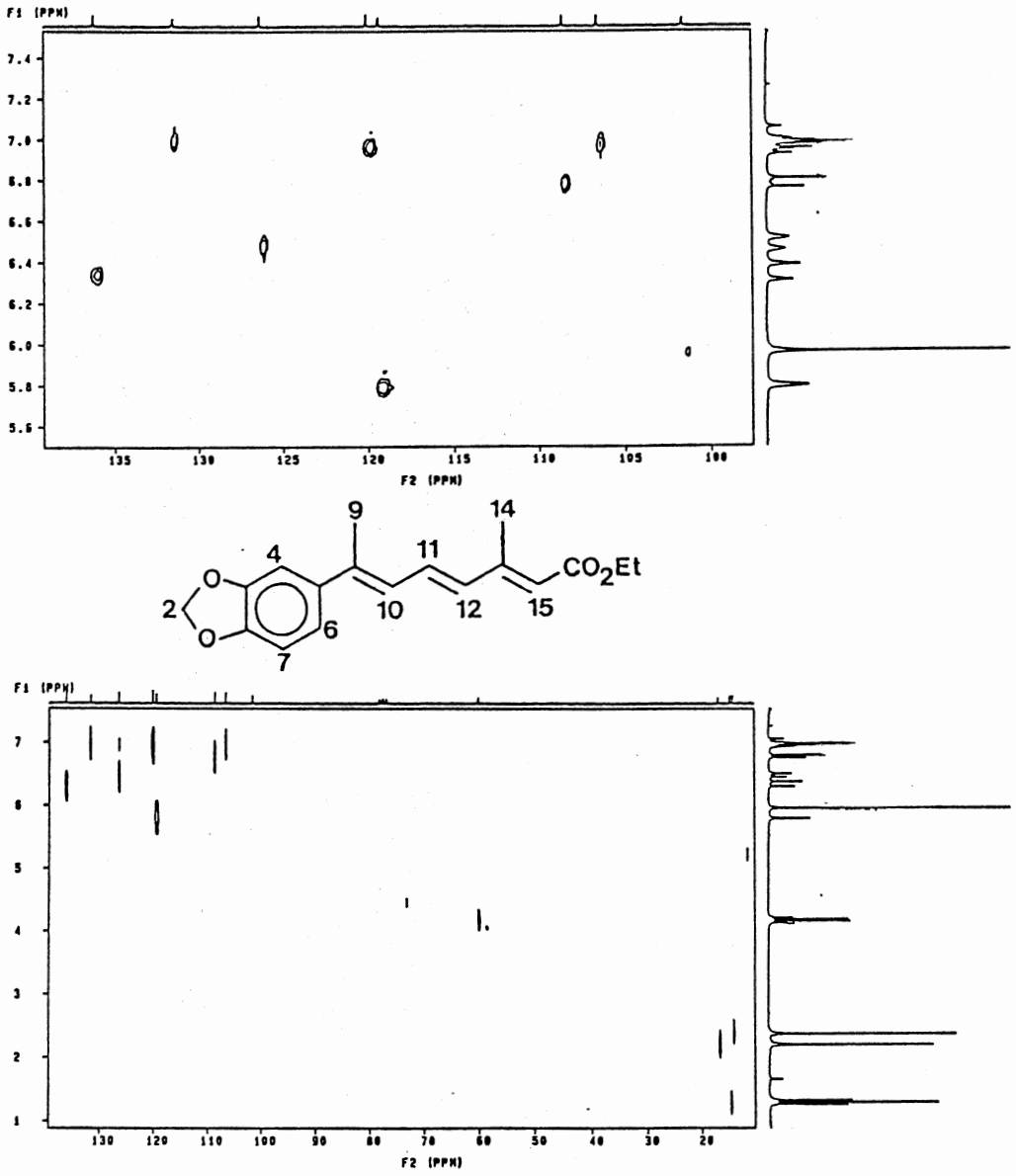
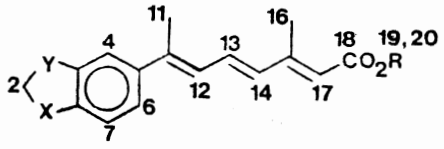
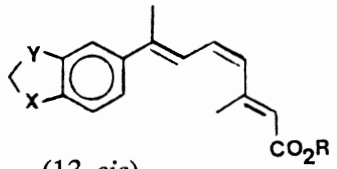


Figure 33. 2-D HETCOR Plot of Heteroarotinoid **70**.

TABLE XVII

^{13}C NMR SIGNALS FOR HETEROAROTINOIDS **67-71**





(13-*cis*)

Carbon	**67**	**68**	**69** (13-*cis*)	**70**[a]	**71**
2	84.9	47.5	47.5	101.2	101.2
3	41.9	47.2	47.2	–	–
3a	134.8[e]	148.2	148.2	147.8[e]	147.9[e]
4	119.7	119.9	120.1	106.1	106.1
5	136.9[e]	1139.0	139.5[f]	136.9	136.8
6	126.0	125.2[e]	125.3	119.6	119.7
7	109.4	122.2	122.2[e]	108.1	108.1
7a	159.3	132.1	131.5	147.3[e]	147.4[e]
8,9[b]	27.6	27.4	27.4	–	–
10	140.9	140.7	140.9[f]	139.4	140.3
11	16.6	16.5	16.1	16.6	16.6
12	124.9	125.6[e]	122.3[e,c]	125.8	125.7
13	132.3	132.1	140.5[f,c]	131.0	132.0
14	135.3	135.4	130.0[c]	135.7	135.4
15	155.4	155.2	156.1	152.6	155.2
16	14.1	14.1	19.6[c]	13.8	14.1
17	117.5	117.5	118.5	118.8	117.5
18	172.1	171.2	171.4	167.2	170.7
19[d]	–	–	–	59.7	–
20[d]	–	–	–	14.4	–

[a]All non-quaternary carbon atoms of **70** were assigned by inspection of the 2D-HETCOR plot (see Figure 33).

[b]Carbon atoms 8,9 correspond to C(CH_3)$_2$ in **67-69**.

[c]The chemical shift differences observed for these carbons in **69** relative to **68** are consistent with those observed for these carbons of the 11-*cis* and 11-*trans* isomers of retinol except for that at C(13). See the proton chemical shift differences of **68** and **69** in Table XVI.

[d]Carbon atoms 19,20 correspond to the CH_2 and CH_3 portions of the ethyl group of **70**.

[e]These signals could be interchanged.

[f]These signals could be interchanged.

CHAPTER III

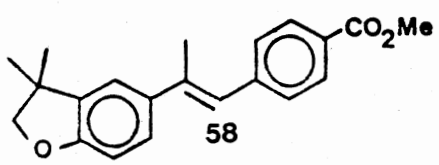
PHARMACOLOGICAL ACTIVITY OF NEW HETEROAROTINOIDS

One objective of this project was to prepare heteroarotinoids **58-71** containing a five-membered heterocyclic ring. To date, the biological activities of heteroarotinoids **58**, **60**, **62**, and **63** have been assessed in terms of ornithine decarboxylase activity [by Dr. A. K. Verma at the Department of Human Oncology, University of Wisconsin] and in terms of their ability to induce differentiation in HL-60 cells [by Dr. T. R. Breitman at the National Cancer Institute].

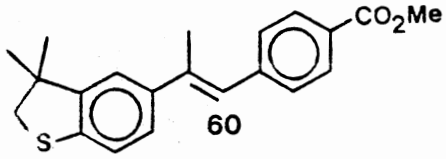
The results of the ODC assay correlate well with the ability of a test substance to inhibit tumor formation in mice.[108] The general procedure followed in the ODC assay is described in the section entitled Assays of Retinoids and will be described here briefly only for completeness. One hour prior to the application of the tumor promoter TPA (see Table XVIII) the retinoids were applied to the shaved backs of the mice. After 4.5-5 h from TPA treatment, the mice were killed and the epidermis were separated, homogenized and centrifuged. The release of $^{14}CO_2$ from labelled ornithine by the soluble extracts of the centrifuged mixture was measured. The presence of large amounts of $^{14}CO_2$ (i.e. in the control, see Table XVIII) indicates a large production of the enzyme ornithine decarboxylase, an expression typical of tumor cells.[107,108] The degree to which the retinoid can inhibit the production of this enzyme (as indicated by the amounts of $^{14}CO_2$ released relative to that measured for the control) is presented as percent inhibition, where 0% inhibition is assigned to the control. Thus, the new heteroarotinoids **60** and **63** containing a sulfur atom exhibited very high activity [i.e. better than the standard, all-

TABLE XVIII

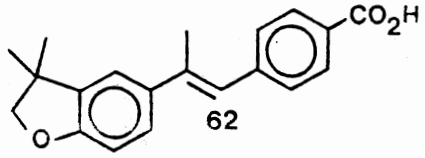
ODC ACTIVITY OF HETEROAROTINOIDS **58**, **60**, **62** AND **63**



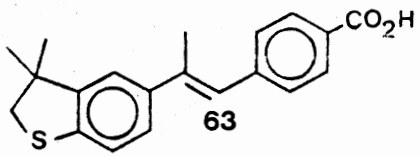
58



60



62



63

Test system	Retinoid dose, nmol	ODC activity	Percent inhibition[a]
Acetone + TPA	0	5.3 ± 0.7[b]	0 (control)
3 + TPA	34	1.0 ± 0.1[b]	81
58 + TPA	34	1.5 ± 0.4[b]	72
Acetone + TPA	0	1.02[c]	0 (control)
3 + TPA	34	0.13[c]	87
60 + TPA	34	0.062[c]	94
62 + TPA	34	0.283[c]	72
63 + TPA	34	0.09[c]	91

[a]Percent Inhibition = $\frac{\text{ODC activity (control)} - \text{ODC activity (retinoid + TPA)}}{\text{ODC activity (control)}}$

[b]nmol CO_2/60 min/mg protein.

[c]nmol CO_2/30 min/mg protein

trans-retinoic acid (3)] exerting almost complete inhibition of ODC activity at the dose tested. The heteroarotinoids **58** and **62** containing an oxygen atom showed good activity but less than the standard. These data are consistent with that previously described for other heteroarotinoids in which an increase in activity (as assessed in the ODC assay) was observed by replacement of an oxygen atom with a sulfur atom.[26,100] Similar increases in the activity of sulfur containing heteroarotinoids relative to their oxygen containing counterparts have also been observed in the tracheal organ culture and HL-60 assays.[26,100,111] It is interesting to note that the replacement of a carboxylic acid group with a methyl ester functionality did not alter the activity significantly.

Heteroarotinoids **58**, **60**, **62**, and **63** were also tested in the HL-60 assay. The procedure is described in the section entitled Assays of Retinoids. This *in vitro* assay determines the ability of a test substance to induce differentiation in HL-60 cells, a cell line derived from a patient with acute promyelocytic leukemia.[14,15,98] Heteroarotinoids **58**, **60**, **62**, and **63** exhibited poor activity in this assay. At 3 μM of **58** or **62**, the percent of induced differentiation (3-5%) was the same as that observed in the control. Similar results were observed for the sulfur analogues **60** and **63**: only a small percentage of the cells were made to differentiate by these two heteroarotinoids. It is important to note that the six-membered-ring analogue of **62** (**45**, structure shown in Figure 5a. X = O, R = H), which has shown good activity in the TOC and ODC assays and in the ability to reduce the number of papillomas in mice,[26] also showed greatly reduced activity in the HL-60 assay relative to that observed for all-*trans*-retinoic acid (**3**).[82,100] That a potent retinoid may exhibit high activity in certain assays and yet display very poor activity in one particular assay is further demonstrated by the report that both Etretinate (**21**, a potent retinoid approved by FDA) and its free acid (**22**, see Figure 4) were totally ineffective in inducing differentiation in HL-60 and U-937 cells.[35]

Although further testing is required to establish the cancer chemotherapeutic capabilities of these new heteroarotinoids, the very high activities of **60** and **63** in the

ODC assay (and to a lesser extent **58** and **62**) justify the need for a further and more complete pharmacological assessment of these heteroarotinoids. The observations that several heteroarotinoids were less toxic than all-*trans*-retinoic acid (see section entitled Toxicology) and that five-membered-ring arotinoids showed reduced signs of hypervitaminosis A relative to their six-membered-ring counterparts (see Table I), provide further justification to warrant a more complete biological evaluation of these new heteroarotinoids. The other heteroarotinoids of this project [**59**, **61**, **64-71**], some of which are to be tested soon, may also show great promise. It is conceivable that the all-*trans*-octatrienoic acid derivatives **67**, **68** and **71** may display high activity in assays including the HL-60 assay, since other octatrienoic acid heteroarotinoids have shown good activity in both the ODC and HL-60 assays[100] (particularly the potent sulfur containing analogue **43**,[100] structure shown in Figure 5b).

CHAPTER IV

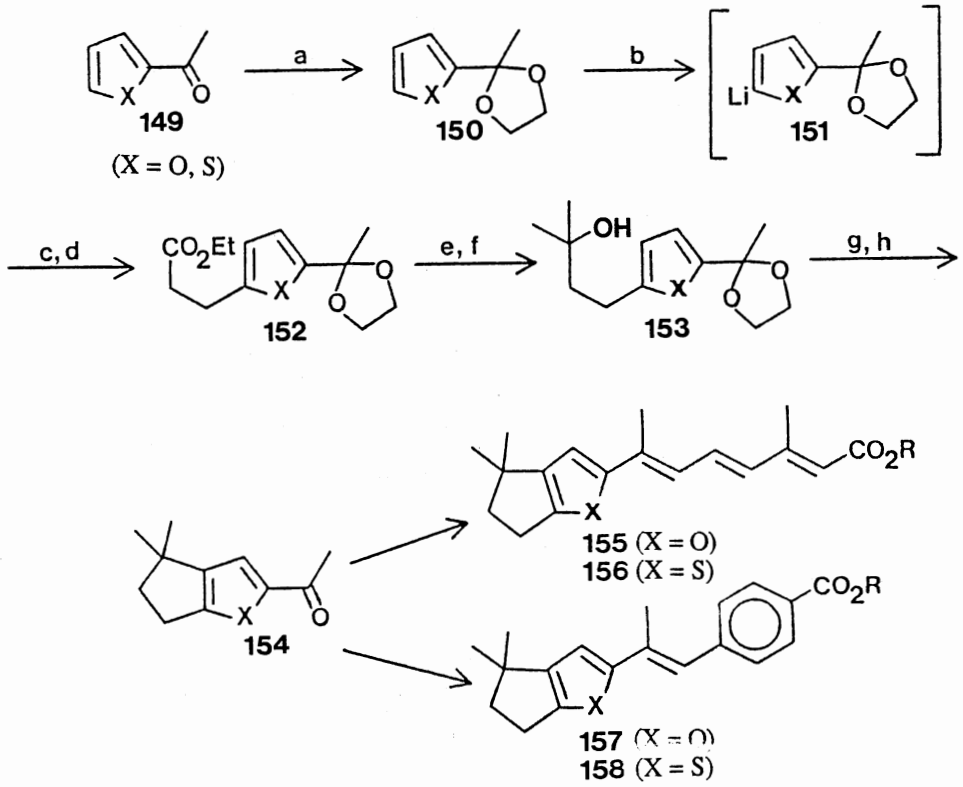
SUGGESTIONS FOR FUTURE WORK

In the last several years several potent retinoids have been prepared although few of these retinoids whose relative toxicities have been determined have toxicities significantly reduced from all-*trans*-retinoic acid (**3**).[26,59,62,78,79] The recent reports of the preparation and biological evaluation of some of the heteroarotinoids may prompt more investigators to explore these and related systems.[26,100,111] The synthesis and biological activity of the new five-membered ring heteroarotinoids described in the previous chapter revealed that these systems also retain good activity, and, in the case of the sulfur analogues **60** and **63** exhibited activity greater than the standard **3** as assessed by the ODC assay. Furthermore, these five-membered ring systems may be less toxic than the six-membered analogues (assuming that the trend seen in the hydrocarbon analogues holds true in the heteroarotinoids, see Table I). Thus, retinoids containing 5-membered rings also hold promise.

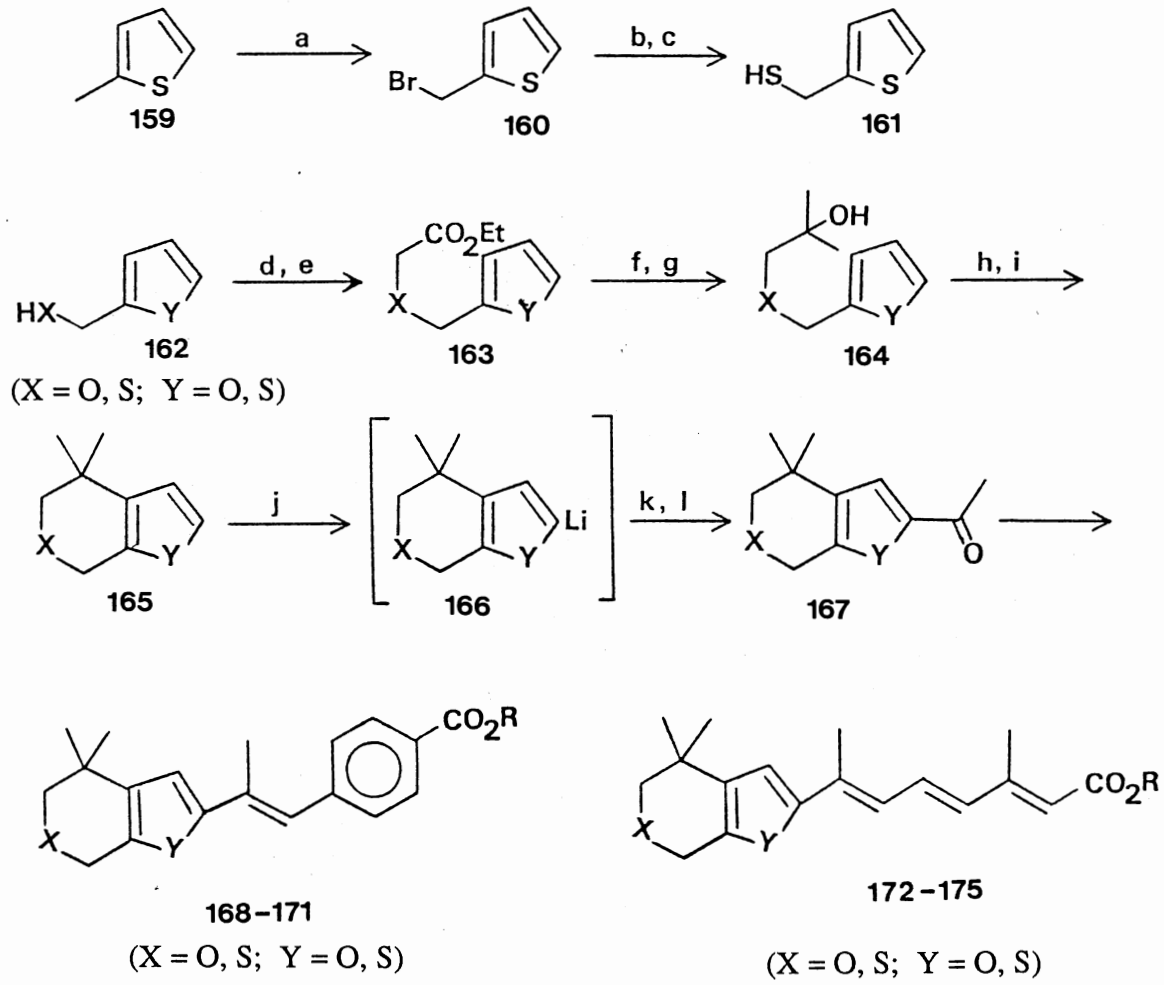
The incorporation of a thiophene ring in the retinoid skeleton may result in reduced toxicity relative to retinoic acid (i.e. **48** in Figure 7, Reference 79), but some retinoids containing a thiophene ring (i.e. **55** and **56** in Figure 7) appear to be more toxic than desired.[55] A structural modification of the retinoid skeleton that could prove useful and which may result in reduced toxicity relative to retinoic acid is shown below and involves the preparation of bicyclic retinoids **155** -**158** (containing two five-membered rings) from either 2-acetylfuran or 2-acetylthiophene. Lithiation at C(2) in **149** and formation of the corresponding lithium cuprate reagent followed by a Michael addition on ethyl acrylate should give **152**. Cyclization of **153**, followed by deprotection of the ketone during

acidic work-up, should give ketone **154** which can readily be converted to the retinoids **155-158** using the techniques described in the previous chapter and also in reference 100.

Retinoids containing more than one heteroatom in the retinoid skeleton are not common. Such retinoids may prove less toxic due to increased hydrophilicity and may also prove useful in the treatment of cancer and/or other disorders involving uncontrolled cell proliferation or cell differentiation (or the lack of the latter). Potential target retinoids **168-175** contain a five-membered heteroaromatic ring fused to a pyran or thiopyran ring. The heteroatom is placed at C(3) [relative to $C(CH_3)_2$] because placement at either C(2) or C(4) may result in compounds particularly vulnerable to hydrolysis. Retinoids **168-175** may be prepared from **162** (all of these alcohols and thiols are available commercially except **161** which may be prepared as shown) as shown on the next page.



(a) $HOCH_2CH_2OH$, $BF_3 \cdot Et_2O$, $-H_2O$; (b) *n*-BuLi; (c) CuI; (d) $CH_2{=}CHCO_2Et$; (e) $2CH_3MgI$; (f) H_2O; (g) $AlCl_3$; (h) H_3O^+



(a) NBS; (b) Na_2S; (c) H_3O^+; (d) NaH; (e) $BrCH_2\ CO_2Et$; (f) $2CH_3MgI$; (g) H_3O^+; (h) $AlCl_3$; (i) H_3O^+; (j) *n*-BuLi; (k) CuI; (k) CuI; (l) Ch_3COCl.

CHAPTER V

EXPERIMENTAL

General Information

All reactions were carried out under a nitrogen atmosphere using a magnetic stirrer unless otherwise specified. During work-up, solvents were removed by a rotary evaporator unless otherwise stated. NMR spectral data were obtained using Varian XL-100 (equipped with a Nicolet TT-100 PFT accessory, ^{13}C spectra recorded at 25.2 MHz), Varian XL-300 (^{1}H and ^{13}C spectra recorded at 299.94 MHz and 75.43 MHz, respectively) or Varian XL-400 (^{1}H and ^{13}C spectra recorded at 399.95 MHz and 100.6 MHz, respectively) NMR spectrometers except for two special experiments, 2D-HETCOR and a "COSY" pulse sequence, which were performed with heteroarotinoid **70** using VARIAN XL-GEM 200 (2D-HETCOR recorded at 50.289 MHz) and VARIAN XL-GEMA 300("COSY" recorded at 300.075 MHz) NMR spectrometers. All NMR data were reported in ppm or δ values downfield from TMS using $DCCl_3$. IR spectra were taken on the Perkin-Elmer 681 IR spectrophotometer. All IR spectra were recorded as films unless otherwise specified. UV spectra were taken on the Perkin-Elmer Lambda Array 3840 UV-VIS spectrophotometer with a 7300 Professional Computer PR 210 Printer. Solutions for recording UV spectra were prepared by dissolving 0.4-2.0 mg (weighed on a standard balance to 0.1 mg) of the heteroarotinoid crystals in 50-100 mL of absolute ethanol (volumetric flasks). Melting points were determined using a Thomas Hoover melting point apparatus (unless otherwise specified, in which case a Fisher-Johns apparatus was used) and were uncorrected. The Chromatotron (Model 7924T) is available

from Harrison Research, 340 Moana Court, Palo Alto, CA 94306. Compounds **75**,[40] **79**,[40] **80**,[40] **94**,[102] **100**,[32] **102**,[6] **103**,[8] **106**,[9] **109**,[51] and **117**[56] were prepared by modifications of reported procedures (some of which contained very little experimental detail).

2-(2-Methoxy-5-bromophenyl)-2-methyl-1-chloropropane (79)

Concentrated H_2SO_4 (7.6 g, 4 mL, 77 mmol) was added dropwise (ca. 1 min) to stirred 4-bromoanisole (**77**, 44.0 g, 0.235 mol) in a 200-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer, addition funnel (N_2 inlet in the top of the funnel), and a Y-adapter to which was attached a second addition funnel (for the H_2SO_4) and a N_2 outlet (a drying tube, $CaSO_4/MgSO_4$). After warming the mixture (35-37°C water bath, 15 min), freshly distilled β-methallyl chloride (20.0 g, 21.5 mL, 0.221 mol) was added dropwise in four equal portions over a period of 1.6 h (4 x 0.4 h). During the addition of the β-methallyl chloride, the temperature of the purple mixture was maintained at 35-44°C (warm water bath). After the addition was complete, the mixture (now a wet solid) was allowed to stand [1 h over water bath (29-32°C), 2 h at RT]. The wet solid was partitioned between H_2CCl_2 (500 mL) and H_2O (175 mL). The organic layer was separated, washed [5% $NaHCO_3$ (175 mL) and H_2O (175 mL); 5 mL of brine followed to destroy an emulsion which formed], dried ($MgSO_4$, 36 h), filtered (Celite, suction), and evaporated (rotovap) to a moist brown solid. The solid residue was melted and vacuum distilled to remove a lower boiling liquid (bp 42°C/0.04 mm-95°C/0.015 mm, mostly 4-bromoanisole). A solution of the remaining solid residue (brown-black) in H_2CCl_2 (300 mL) was treated (twice) with decolorizing charcoal (Norit A). Evaporation of the H_2CCl_2 gave a tan solid. Two recrystallizations (*n*-heptane, 45 mL, then 30 mL) gave crystals which were washed (chilled *n*-heptane) and dried [P_2O_5, ≤ 0.5 mm, RT, 5.5 h] to give ether **79** as a white crystalline solid (37.7 g, 61.5%); mp 87.8-89.1°C (Fisher-

Johns) (lit[40] 82-84°C). Another 3.4 g (5.5 %, mp 87.7-89.4°C) could be obtained by the following procedure: the mother liquors were evaporated (rotovap), and the solid residue was dissolved in H_2CCl_2 (120 mL) and treated (twice) with decolorizing charcoal followed by evaporation and recrystallization (*n*-heptane); total yield of **79** was 41.4 g (67%). IR (KBr) 1246 cm^{-1} (C-O); ^1H NMR ($DCCl_3$) δ 1.43 [s, 6 H, $C(CH_3)_2$], 3.84 [s, 3 H, OCH_3], 3.96 [s, 2 H, CH_2Cl], 6.78 [d, 1 H, Ar-*H*], 7.32-7.41 [m, 2 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 25.8 [q, $C(CH_3)_2$], 40.4 [s, $C(CH_3)_2$], 53.3 [t, CH_2Cl], 55.4 [q, OCH_3]; Ar-C [113.1 (s and d), 130.6 (d), 131.2 (d), 135.4 (s), 157.2 (s)]. The above procedure for the preparation of ether **79** is similar to that described in U.S. Patent 4,333,749.[40]

5-Bromo-2,3-dihydro-3,3-dimethylbenzofuran (80)

A 200-ml, jacketed flask [equipped internally with two stacked condensers, magnetic stir bar, thermometer (with adapter), N_2 inlet and a N_2 outlet ($CaCl_2$ drying tube); the jacket of this jacketed flask contained isobutylbenzene and was also equipped with condensers] was charged with ether **79** (12.60 g, 45.4 mmol), pyridine•HCl (23.7 g, 0.205 mol), and quinoline (22.9 g, 0.177 mol). After the mixture was heated to 164°C (ca. 0.6 h, boiling isobutylbenzene bath), the mixture was maintained at reflux (164-167°C) for 3 h. After cooling (ca. 50°C), the mixture was partitioned between ice-cold 6 N HCl (225 mL) and ether (200 mL). The organic layer was separated and the aqueous layer was extracted (ether, 200 mL). The combined organic layers were dried ($MgSO_4$, overnight), filtered (suction) and evaporated to an oil. Vacuum distillation gave ether **80** as a colorless liquid (8.49 g, 82%): bp 58.9-60.0°C/0.01 mm (major fraction) (lit[40] 62-64°C/0.01 mm); IR (neat) 1197 cm^{-1} (C-O); ^1H NMR ($DCCl_3$) δ 1.31 [s, 6 H, $C(CH_3)_2$], 4.24 [s, 2 H, OCH_2], 6.67 [d, 1 H, Ar-H], 7.18-7.25 [m, 2 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 27.3 [$C(CH_3)_2$], 42.1 [$C(CH_3)_2$], 84.7 [OCH_2]; Ar-*C* [111.3, 112.3,

125.5, 130.6, 139.0, 158.3]. The above procedure is similar to that described in U.S. Patent 4,333,759.[40]

1-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)-ethanol (82). Method I

In a 100-mL, three-necked, round-bottomed flask [equipped with a mechanical stirrer, dry ice condenser, a N_2 outlet (drying tube, $CaSO_4$, in top of condenser) and a Y-adapter to which was attached an addition funnel and a N_2 inlet; all glass items were dried overnight in an oven (ca. 140°C) and assembled hot], a mixture of ether **80** (0.21 g, 0.9 mmol), Mg turnings (1.0 g, 0.041 g at) and dry THF (3 mL) was heated under N_2 until the mixture turned cloudy (ca. 15 min). Dry THF (15 mL) was added to the mixture which was then heated at reflux (15 min). A solution of ether **80** (2.92 g, 12.9 mmol) in dry THF (25 mL) was added dropwise to the vigorously stirred mixture over a period of 0.75 h. After vigorous stirring at reflux for 2.75 h, another 0.25 g (0.010 g at) of Mg turnings were added. The new mixture was stirred at reflux for 0.75 h and with no external heat for 0.5 h. Upon cooling the mixture (-5 to -10°C, ice-salt bath), a solution of freshly distilled acetaldehyde (2.0 g, 0.045 mol) in dry THF (20 mL) was added dropwise to the vigorously stirred mixture over a period of 0.7 h. This reaction mixture was stirred in an ice-salt bath (-5 to -10°C) for 1.5 h, after which time a solution of acetaldehyde (0.9 g, 0.020 mol) in dry THF (5 mL) was added dropwise (over a period of about 0.2 h), and the new mixture was stirred 0.3 h. With continued cooling (-5 to -10°C), saturated aqueous NH_4Cl (3 mL) was added, and the excess Mg turnings were removed from the mixture by filtration. Saturated aqueous NH_4Cl (10 mL) and ether rinses (from glassware and Mg turnings, 50 mL) were added to the filtrate. After separating the organic layer, the aqueous phase (pH > 8) was acidified (pH 6.5 to 7) with saturated aqueous NH_4Cl (15 mL) and 4% H_2SO_4 (4 mL). The aqueous solution was extracted with ether (5 x 40 mL), and ether (90 mL) was added to the combined organics. The organic solution was washed

with saturated aqueous $NaHCO_3$ (75 mL) and brine (50 mL). After drying ($MgSO_4$) the solution, the solvent was removed, and the residual oil was chromatographed through a circular silica gel plate (4 mm) spun by a Chromatotron. Half of the product was eluted with petroleum ether (bp 50-110°C):ether [20:1, 8:1, then 4:1], and then the same solvent system was used to elute the other half. In both separations, the 4:1 ratio was required to elute the title compound. Concentration of the eluent in the desired fractions gave 1.18 g (44%) of alcohol **82** as a light yellow, viscous oil. TLC analysis [4:1 petroleum ether:ether] indicated the compound was essentially pure and was used without further purification. IR (neat) 3150-3650 cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.31 [s, 3 H, $C(CH_3)CH_3$], 1.32 [s, 3 H, $CCH_3(CH_3)$], 1.45 [d, 3 H, $CH(CH_3)$], 2.36 (bs, 1 H, O-*H*), 4.81 [q, 1 H, $CH(CH_3)$], 6.71 [d, J = 8 Hz, 1 H, H(7)], 7.08 [dd, J = 8 Hz, J = 1.9 Hz, 1 H, H(6)], 7.13 [d, J = 1.9 Hz, 1 H, H(4)]; ^{13}C NMR ($DCCl_3$) ppm 25.1 [$CH(CH_3)$], 27.5 [$C(CH_3)_2$], 41.9 [$C(CH_3)_2$], 84.7 [OCH_2]; Ar-*C* [109.3, 119.5, 125.4, 136.8, 138.3, 158.6].

1-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)-ethanone (81)

A freshly prepared solution of the Grignard reagent from aryl bromide **80** [5.20 g (22.9 mmol) of aryl bromide **80** and 1.7 g (70 mmol) of Mg turnings, in dry THF (30 mL); prepared as described previously in the preparation of alcohol **82** (Method I)] was transferred (under N_2) from the round-bottomed flask in which the Grignard reagent was formed to an addition funnel [a bent (ca. 90°) U-tube was made to connect the top of the addition funnel with the flask used to form the Grignard reagent] attached to a 100-mL, two-necked, round-bottomed flask equipped with a rubber septum, magnetic stir bar, and a N_2 inlet [as soon as the transfer of Grignard reagent was complete, the U-tube at the top of the addition funnel was replaced with a N_2 inlet (positive pressure from an oil bubbler)]. During the transfer of the Grignard reagent, care was taken to insure that a

rapid N_2 stream passed through the system whenever the N_2 seal was broken (e.g., when the U-tube was replaced by a N_2 inlet after Grignard reagent transfer). The 100-mL flask was charged with dry THF (20 mL), cooled in a dry ice-CH_3CN bath (-40° to -45°C), and charged (syringe) with $CH_3C(O)Cl$ (16 mL, 17 g, 0.22 mol). After stirring the $CH_3C(O)Cl$/THF solution at -40° to -45°C for 5 min, the Grignard reagent was added dropwise and slowly (0.80 h) to the $CH_3C(O)Cl$/THF solution (continued cooling in the dry ice-CH_3CN bath, -39° to -43°C). After the addition was complete, the temperature of the bath was allowed to rise slowly (20 min) to ca. -23°C (dry ice added to the bath when necessary to slow the warming process), at which time the dry ice-CH_3CN bath was replaced with a dry ice-CCl_4 bath (ca. -20° to -25°C). The reaction mixture was kept at -20° to -25°C for 2 h and then allowed to rise to 0°C (ca. 40 min). After the bath was removed, the mixture was stirred at ambient temperature (ca. 30 min), quenched carefully with water (40 mL) and extracted with ether (5 x 50 mL, then 30 mL). The combined ether extracts were washed with alkali (4 x 50 mL; 1 N NaOH) and then with saturated brine (2 x 30 mL) and finally dried ($MgSO_4$, overnight). The organic solution was filtered and evaporated on an oil, which was vacuum distilled to remove a lower boiling liquid (bp 36-38°C/0.12 mm). The residue (dissolved in a minimal amount of hexanes, 3 mL) was divided in 3 portions each of which was eluted on a silica gel plate (4 mm, Chromatotron) with hexanes:ether [9:1 (130-150 mL), 3:1 (140-160 mL)]. The principal band of each of the 3 separations was collected and evaporated to an oil which crystallized upon cooling (dry ice). The combined solids (2.6 g) were dissolved in hexanes (20 mL). Careful crystallization of ketone **81** was accomplished using the method described for the crystallization of methyl ketone **88a**. After washing the resulting crystals with chilled (-78°C) hexanes (10 mL), the crystals were dried (P_2O_5, ≤ 0.5 mm, RT) to yield ketone **81** as a light tan crystalline solid (2.25 g, 51.6%), mp 36.8-37.9°C. Higher melting crystals (1.61 g, 37%, mp 39.0-39.9°C) were obtained by recrystallization in hexanes at -10° to -15°C (ice/water/salt bath) with seeding. Another 0.53 g (12%) of higher melting

crystals (mp 38.5°-40°C) were obtained by concentrating (rotovap) the combined mother liquors of the two prior crystallizations, followed by repeated chromatographic separations (Chromatotron) on silica gel [2 mm, 9:1 hexanes:ether in one separation, 4:1 hexanes:ether in a later separation] and by repeated crystallizations in cold hexanes (0° to -20°C); total yield of ketone **81** was 2.14 g (49.1%); mp 39.2-39.7°C; IR (KBr) 1679 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) 1.36 [s, 6 H, $C(CH)_3)_2$], 2.55 [s, 3 H, $C(O)CH_3$], 4.33 [s, 2 H, OCH_2], 6.81 [d, 1 H, Ar-*H*], 7.77-7.86 [m, 2 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 26.4 [$C(O)CH_3$], 27.6 [$C(CH_3)_2$], 41.4 [$C(CH_3)_2$], 85.4 [OCH_2], 109.2 [C(7)], 163.6 [C(7a)]; other Ar-*C* [122.9, 130.5, 131.0, 137.4], 196.6 [*C*=O]. Anal. Calcd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42. Found: C, 75.72; H, 7.23. Mass spectral data for $C_{12}H_{14}O_2$: m/e (M^+) 190.0994; Found: 190.0998.

1-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)ethanol (82). Method II

A solution of methyl ketone **81** (2.50 g, 13.1 mmol) in dry ether (15 mL) was added dropwise (ca. 25 min) to a stirred suspension of $LiAlH_4$ (0.82 g, 21.6 mmol) in dry ether (50 mL) in a 350-mL, three-necked, round-bottomed flask equipped with an addition funnel, a glass stopper, condenser, magnetic stirring bar and N_2 inlet in the top of the condenser (positive pressure from an oil bubbler). The resulting mixture was stirred at very gentle reflux for 18 h. The mixture was diluted with ether (40 mL) and then quenched with the careful addition of EtOAc (15 mL). After cooling in an ice-water bath (0°C), the mixture was diluted further with ether (50 mL) and acidified (pH ~ 4) with 5% HCl (60 mL). Two layers separated and the aqueous layer was extracted (ether, 4 x 30 mL). The combined organic layers were washed [5% $NaHCO_3$ (2 x 35 mL), saturated brine (2 x 35 mL)], dried (Na_2SO_4, 36 h) and evaporated [rotovap followed by high vacuum (≤ 0.5 mm, RT, ca. 5 min)]. This gave alcohol **82** as a pale yellow oil (2.44 g, 97%): R_f = 0.24 (silica gel, 9:1 hexanes:ether), R_f = 0.83 (trace impurity) (9:1

hexanes:ether). Exactly 1.29 g (51%) of the alcohol was obtained in crystalline form using the following procedure: A solution of the oil (2.44 g) in 6:1 hexanes:ether (20 mL) in a stoppered flask was placed in a dry ice-acetone bath. As the temperature of the bath rose without perturbation (slow release of CO_2 from the dry ice), crystals began to form. The bath was maintained at -20° to -30°C (small amounts of dry ice added to the acetone) for 2 h to complete crystallization. The supernatant fluid was decanted, the crystals were washed (chilled hexanes, 2 x 20 mL), and the residual solvent was removed (high vacuum, ≤ 0.5 mm). This gave crystals that melted low, 30.3-31.7°C. Another 0.53 g (21%) of crystalline alcohol **82**, suitable for quantitative analysis (mp 38.2-39.2°C), was obtained by evaporation of the mother liquors of the previous crystallization, followed by purification on silica gel (2 mm, Chromatotron) using petroleum ether (bp 50-110°C):ether [9:1 (100 mL), 2:1 (120 mL), 1:1 (80 mL), and 1:2 (75 mL)]. The fractions containing pure alcohol **82** were combined and evaporated to an oil which did not crystallize effectively in 3:1 hexanes:ether at -65°C. Crystallization was successful when the oil was dissolved in 9:1 hexanes:ether and slowly cooled to ca. -40°C over a period of 100 min. These crystals were washed with hexanes (10 mL, not chilled) and traces of hexanes were removed (high vacuum, ca. ≤ 0.5 mm, RT) to give sharp melting crystals, mp 38.2-39.2°C (Fisher-Johns). The IR (KBr) of the crystals had unique differences from that of the oil **82** obtained by Method I. However, if the IR beam was allowed to melt the sample in the KBr pellet, the resulting IR spectra was essentially identical to that of the oil **82** prepared by Method I (see Method I for NMR data). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.84; H. 8.26. Mass spectral data for $C_{12}H_{16}O_2$: m/e (M^+) 192.1150; Found: 192.1151. Crystals melting as low as 31°C appeared to be pure (TLC, 5:1 hexanes:EtOAc) and were used without further purification.

[1-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)-ethyl]triphenylphosphonium Bromide (83)

A solution of alcohol **82** (1.00 g, 5.20 mmol) in CH_3OH (5 mL) was added dropwise (3 min) to a stirred mixture of $Ph_3P{\bullet}HBr$ (1.75 g, 5.10 mmol) and CH_3OH (5 mL) in a 25-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar, addition funnel and a N_2 inlet in the top of the addition funnel (positive pressure from an oil bubbler). A rinse (2 mL of CH_3OH) of the funnel was added to the mixture, which became a solution within 2 min of stirring. After stirring for 18 h (RT), the solution was concentrated to a white foam, which solidified during evaporation [rotovap, warm water bath (55-65°C)]. The solid was changed to a powder by stirring (magnetically) in dry ether (20 mL) under N_2 (2 h). The powder was filtered, washed (ether, 3 x 10 mL) and dried (P_2O_5, ≤ 0.5 mm, 100°C, 1 h). The resulting white powder was recrystallized in the following manner: ethyl acetate (40 mL) was added to a solution of the powder in H_2CCl_2 (10 mL) in a beaker. The new solution (initially cloudy but clear after stirring) was heated gently over a hot plate (2 min) with stirring (glass rod). When crystals began to appear, the beaker was placed in an ether bath (overnight) in a closed screw-top jar at RT and then in a freezer (ca. -8°C, 2 h). Crystals formed and were filtered (after jar had warmed to RT), washed (ether, 20 mL), and dried (P_2O_5, ≤ 0.5 mm, 100°C, 1 H) to give salt **83** as white crystals (2.24 g, 81%): mp 212.4-213.0°C; IR (KBr) 1367, 1389 cm^{-1} (*gem*-dimethyl C-H bend); ^1H NMR ($DCCl_3$) δ 1.13 [s, 3 H, $C(CH_3)CH_3$], 1.16 [s, 3 H, $C(CH_3)CH_3$], 1.77 [dd, J_{HH} = 7.2 Hz, J_{HP} = 19.0 Hz, CH_3CHP], 4.19 [s, 2 H, OCH_2], 6.34 [dq merged into a hextet, J_{HH} = 7.2 Hz, J_{HP} = 13.7 Hz, 1 H, CH_3CHP], 6.57 [d, J = 8.3 Hz, 1 H, H(7)], 6.74 [dd merged into a t, J_{HH} = 2 Hz, J_{HP} = 2 Hz, 1 H, H(4)], 6.94 [ddd merged into a dt, $^3J_{HH}$ = 8.3 Hz, $^4J_{HH}$ = 2 Hz, J_{HP} = 2 Hz, 1 H, H(6)], 7.62-7.85 [m, 15 H, $P(C_6H_5)_3$]; ^{13}C NMR ($DCCl_3$) ppm 27.3 [$C(CH_3)CH_3$], 27.6 [$C(CH_3)CH_3$], 35.1 [d, $^1J_{CP}$ = 40.8 H, CH_3CHP], 41.7 [$C(CH_3)_2$], 84.8 [OCH_2], 109.8 [C(7)], 117.7 [d, $^1J_{CP}$ = 82.1 Hz, *orthogonal*-C's of $P(C_6H_5)_3$], 124.6 [d, $^3J_{CP}$ =

5.7 Hz, C(4)], 130.2 [d, $^3J_{CP}$ = 12.0 Hz, *meta*-C's of P(C_6H_5)$_3$], 130.4 [d, $^3J_{CP}$ = 6.0 Hz, C(6)], 134.6 [d, $^2J_{CP}$ = 8.9 Hz, *ortho*-C's of P(C_6H_5)$_3$], 134.8 [d, $^4J_{CP}$ = 3.0 Hz, *para*-C's of P(C_6H_5)$_3$], 137.2 [C(3a) or C(5)], 137.3 [C(3a) or C(5)]. Anal. Calcd for $C_{30}H_{30}BrOP$: P, 5.99. Found: P, 6.39.

Methyl (E)-4-[2-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)-1-propenyl]benzoate (58)

A solution of *n*-butyllithium (1.6 M, 3.0 mL, 4.8 mmol) in hexane was added (syringe, ca. 2 min) to a mixture of salt **83** (2.50 g, 4.83 mmol) in dry THF (15 mL) in a 100-mL, three-necked, round-bottomed flask equipped with an addition funnel, rubber septum, condenser and a N_2 inlet at the top of the condenser (positive pressure from an oil bubbler) [all glassware were dried in an oven (100°C, 0.5 h) and assembled hot]. After stirring at RT for 15 min, the black-red Wittig reagent was cooled (dry ice-acetone bath, -78°C, 5 min), followed by the addition (continued cooling at -78°C) of a solution of methyl 4-formylbenzoate (0.80 g, 4.9 mmol) in dry THF (10 mL) over a period of about 2 min. The cold bath (-78°C) was removed and the mixture was stirred (RT) for 12 h. Dry ether (40 mL) was added which caused greater amounts of a white precipitate (presumably Ph_3P=O) to form. After filtering the mixture, the precipitate (now on the filter paper) was washed (20 mL of dry ether); the wash was collected as a filtrate. The combined filtrates were concentrated (rotovap) to about 5 mL, and this concentrate was applied to a column (2 x 20 cm) of silica gel (20 g) packed in hexanes. Elution was effected using hexanes:EtOAc (9:1, 200 mL). A large fraction [ca. 80 mL, principal component R_f 0.80 (9:1 hexanes:EtOAc)] was collected and evaporated to a thick oil which crystallized upon standing (crystallization was initiated by cooling flask over dry ice). Two recrystallizations (boiling 95% ethanol) followed by drying (P_2O_5, ≤ 0.5 mm, 77°C, 30 min) gave **58** as white flakes (0.51 g, 33%). Another 61 mg (3.9%) of **58** was obtained by concentrating the mother liquors from the first recrystallization, adjusting the volume to

about 8 mL by adding 95% ethanol, boiling the resulting solution, and allowing time for crystallization. After filtrating and washing the crystals (5 mL of chilled 95% ethanol), the crystals were recrystallized two more times (95% ethanol); the total yield of **58** was 0.57 g (36%): mp 96.8-97.8°C; IR (KBr) 1717 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.38 [s, 6 H, H(8,9)], 2.29 [d, J = 1.2 Hz, 3 H, H(11)], 3.93 [s, 3 H, H(20)], 4.28 [s, 2 H, H(2)], 6.77 [br s, 1 H, H(12)], 6.80 [d, J = 8.3 Hz, 1 H, H(7)], 7.28 [d, J = 2 Hz, 1 H, H(4)], 7.31 [dd, J = 8.3 Hz, J = 2 Hz, 1 H, H(6)], 7.41 [d, 2 H, H(14,18)], 8.03 [d, 2 H, H(15,17)]; ^{13}C NMR ($DCCl_3$) ppm 17.9 [q, C(11)], 27.6 [q, C(8,9)], 41.9 [s, C(3)], 52.0 [q, C(20)], 109.3 [d, C(7)], 120.0 [d, C(4)], 125.1 [d, C(12)], 126.1 [d, C(6)], 129.0 [d, C(14,18)], 129.5 [d, C(15,17)], 159.0 [s, C(7a)], 167.0 [s, C(19)]; other non-protonated carbons [127.6, 136.4, 136.8, 139.6, 143.4]. Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 77.88; H, 6.98. Mass spectral data for $C_{21}H_{22}O_3$: m/e (M^+) 322.1569; Found: 322.1572.

Slow evaporation of the mother liquors from the recrystallization mixture over a period of 4.5 full days [which was reduced to 8 mL (see above)] gave a mixture of flakes and needles. The needles were isolated manually, recrystallized (minimum amount of boiling, 95% ethanol), rinsed with chilled 95% ethanol, and dried (P_2O_5, ≤ 0.5 mm, RT, 30 min) to give the *Z*-isomer (**59**) as white needles (12 mg, 0.8%): mp 100.0-101.0°C; IR (KBr) 1718 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.22 [s, 6 H, H(8,9)], 2.22 [d, J = 1.4 Hz, 3 H, H(11)], 3.87 [s, 3 H, H(20)], 4.24 [s, 2 H, H(2)], 6.43 [br s, 1 H, H(12)], 6.71 [d, J = 8.1 Hz, 1 H, H(7)], 6.84 [d, J = 2 Hz, 1 H, H(4)], 6.96 [dd, J = 8.1 Hz, J = 2 Hz, 1 H, H(6)], 7.01 [d, J = 8 Hz, 2 H, H(14,18)], 7.78 [d, J = 8 Hz, 2 H, H(15,17)]; ^{13}C NMR ($DCCl_3$) ppm 27.1 [C(11)], 27.5 [C(8,9)], 41.8 [C(3)], 51.9 [C(20)], 84.7 [C(2)], 109.6 [C(7)], 128.8 and 129.1 [C(14,18) and C(15,17)], 158.6 [C(7a)], 167.0 [C(19)]; other non-protonated carbons [122.6, 125.1, 127.3, 127.7, 133.6, 136.8, 141.6, 142.9]. Anal. Calcd for $C_{21}H_{22}O_3$: C, 78.23; H, 6.88. Found: C, 78.28, H, 6.84.

4-[2-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)-1-propenyl]benzoic Acid (62)

A mixture of ester **58** (0.200 g, 0.62 mmol), NaOH (one pellet, 0.1 g, 2.5 mmol), 95% ethanol (2 mL) and H_2O (5 mL) was heated to a boil (ca. 10 min) in a 25-mL, single-necked, round-bottomed flask equipped with a Y-adapter to which was attached a N_2 inlet, condenser and a N_2 outlet ($CaSO_4$ tube at top of condenser). Another 1 mL of 95% ethanol was added and the mixture became a solution after another 10 min of boiling. The resulting solution was maintained at reflux for 4.5 h during which time the sodium salt precipitated. After adding 95% ethanol (2 mL) and water (1 mL) and heating the contents to achieve solution, the mixture was quenched with 6 N HCl (0.6 mL) until precipitation of the carboxylic acid ceased (pH ~ 3). The mixture was filtered (suction) and the solid was washed (chilled absolute ethanol, 3 mL) and recrystallized in absolute ethanol (2 mL). The crystals were washed [absolute ethanol (3 mL), then chilled hexanes (15 mL)], dried [P_2O_5, ≤ 0.5 mm, RT (18 h), 56°C (1 h)] to yield carboxylic acid **62** as nearly colorless and flattened needles (139 mg, 72.7%): mp 190.7-191.8°C; IR (KBr) 1678 cm^{-1} (broad C=O frequency); ^1H NMR ($DCCl_3$) δ 1.39 [s, 6 H, H(8,9)], 2.31 [d, J = 1 Hz, 3 H, H(11)], 4.28 [s, 2 H, H(2)], 6.79 and 6.81 [overlapping s and d (J = 8.2 Hz), 2 H, H(11) and H(7), respectively], 7.29 [d, J = 2 Hz, 1 H], 7.32 [dd, J = 8.2 Hz, J = 2 Hz, 1 H, H(6)], 7.46 [d, J = 8.3 Hz, 2 H, H(14,18)], 8.12 [d, J = 8.3 Hz, 2 H, H(15,17)]; ^{13}C NMR ($DCCl_3$) ppm 18.0 [C(11)], 27.6 [C(8,9)], 41.9 [C(3)], 84.9 [C(2)], 109.4 [C(7)], 120.0 [C(4)], 125.1 [C(12)], 126.1 [C(6)], 129.1 [C(14,18)], 130.1 [C(15,17)], 159.1 [C(7a)], 171.7 [C(19)], other non-protonated carbons [126.7, 136.4, 136.8, 140.0, 144.3]. Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.90; H, 6.54. Found: C, 78.03; H, 6.47.

Methyl 2-(Phenylthio)acetate (85)

A solution of (phenylthio)acetic acid (**84**, 40.0 g, 0.238 mol), dry CH_3OH (600 mL), and H_2SO_4 (2.0 mL, 3.7 g, 38 mmol) in a two-necked, round-bottomed flask [1000 mL, equipped with a Soxhlet extractor containing molecular sieve 3A (125 g) to which was attached a water condenser and an N_2 inlet in the top of the condenser] was stirred (magnetic stir bar) at reflux for 74 h. Upon cooling at room temperature for 20 min, the mixture was neutralized (pH 7) with a solution of Na_2CO_3 (4.00 g, 37.7 mmol) in H_2O (16 mL). After concentrating the mixture (rotary evaporation) to approximately 50 mL, water (200 mL) and CH_2Cl_2 (200 mL) were added and two layers separated. The aqueous layer was then extracted with CH_2Cl_2 (4 x 140 mL) and the combined organic layers were washed with 5% aqueous $NaHCO_3$ (2 x 100 mL), water (100 mL) and saturated brine (100 mL). The organic solution was dried ($MgSO_4$, overnight), filtered and evaporated. Distillation gave **85** as a colorless oil (40.0 g, 92%), the major fraction boiling at 85.9-86.7°C/0.23 mm (lit[113] 93-95°C/0.6 mm); IR (neat) 1742 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 3.62 [2, 2 H, SCH_2], 3.66 [s, 3 H, OCH_3], 7.38 [d, 2 H, Ar-*H*], 7.15-7.30 [m, 3 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 36.3 [*t*, SCH_2], 52.4 [*q*, OCH_3], 126.8 [*d*, Ar-*C*], 129.0 [*d*, Ar-*C*], 129.7 [*d*, Ar-*C*], 135.0 [Ar-*C*], 170.0 [s, CO_2CH_3].

2-Methyl-1-phenylthio-2-propanol (86)

To a cooled (0°C), freshly prepared solution of methylmagnesium iodide [25.0 g (0.176 mol) of CH_3I and 4.0 g (0.165 mol) of magnesium, in 100 mL of dry ether] was added a solution of ester **85** (10.0 g, 54.9 mmol) in dry ether (15 mL followed by a 5 mL rinse of the addition funnel). The system consisted of a 300-mL three-necked, round-bottomed flask equipped with a mechanical stirrer, addition funnel, dry ice condenser, and a N_2 inlet in the top of the condenser. The resulting mixture was stirred at 0-25°C for 1 h and at reflux for 18 h. The mixture was then diluted (75 mL of ether), cooled (0°C), and

quenched (pH ~7) with water (20 mL) , 20% NH_4Cl (40 mL), and finally with 10% H_2SO_4 (77 mL). The layers were separated and the aqueous phase was extracted with ether (5 x 50 mL). The combined organic layers were washed with 5% $NaHCO_3$ (100 mL) and then dried briefly (Na_2SO_4, ca. 10 min). Evaporation of the solvent gave an oil containing variable amounts (≤ 10%) of 1-phenylthio-2-propanone. It was necessary to remove this impurity which otherwise created a difficulty in the ensuing cyclization and acylation reactions. To remove this impurity, a solution of I_2 (2.5 g) and NaI (5.0 g) in water (20 mL) was added dropwise to a stirred solution of about one half of the oil (4.8 g) in 40 mL of 6% KOH in CH_3OH. The resulting mixture was stirred for 10 min (5 min of gentle warming and 5 min at RT). This procedure was repeated for the other half of the oil. The resulting mixtures were each filtered and extracted (Et_2O, 100 mL and 50 mL), and, the extracts were dried (Na_2SO_4, overnight), and evaporated to an oil (no C=O frequency in the IR spectrum). Further purification by vacuum distillation of the combined oils (the major fraction boiled at 80°-85°C/0.12 mm, lit[20] bp 136-137°C/12 mm) and chromatography over silica gel [3 x 34 cm column, 3:1 hexanes ether (800 mL)] gave alcohol **86** as a yellow oil [5.6 g, 56%, pure by TLC (9:1 hexanes:ether)]; $n^{26.8}$=1.5582 (lit[20] n^{23}=1.5609); IR (neat) 3150-3650 cm^{-1} (O-H); ^1H NMR ($DCCl_3$) δ 1.29 [s, 6 H, $C(CH_3)_2$], 2.31 [br s, 1 H, O-*H*], 3.11 [s, 2 H, CH_2], 7.22-7.32 [m 2 H, Ar-*H*], 7.13-7.21 [m, 1 H Ar-*H*], 7.41 [d, 2 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) δ ppm 28.6 [$C(CH_3)_2$], 48.2 [CH_2], 70.6 [$C(CH_3)_2$]; Ar-*C* [125.9, 128.7, 129.2, 136.8].

2,3-Dihydro-3,3-dimethylbenzo[*b*]thiophene (87)

A solution of alcohol **86** (9.60 g, 52.7 mmol) in freshly distilled CS_2 (55 mL) was added dropwise (ca. 35 min) to a stirred suspension of $AlCl_3$ (25.0 g, 0.187 mol) in CS_2 (50 mL) in a 200-mL, three-necked, round-bottomed flask equipped with an addition funnel, dry ice condenser, magnetic stir bar, and an N_2 inlet in the top of the condenser (positive pressure from an oil bubbler). The resulting orange-red mixture was stirred at

reflux for 3 h. After cooling in an ice water bath (0°C) for 10 min, the mixture was *very* cautiously quenched with 5% HCl (90 mL) and diluted with CH_2Cl_2 (40 mL). The layers were separated and the aqueous layer was extracted with CH_2Cl_2 (2 x 75 mL). The combined organic layers were washed with saturated aqueous $NaHCO_3$ (2 x 75 mL), water (75 mL) and saturated brine (75 mL). The organic solution was dried ($MgSO_4$, overnight), filtered, and evaporated to an oil. Vacuum distillation (the major fraction boiled at 56.3-58.2°C/0.37 mm) gave a pale yellow oil (6.97 g, 80.5%) which was essentially pure (silica gel TLC, $R_f = 0.89$ in hexanes). The pure colorless oil (6.30 g, 72.8%) was obtained by chromatography on silica gel [3 x 35 cm column, hexanes (800 mL)]; $n^{25.6}$=1.5757; IR (neat) 1364, 1384 cm^{-1} (*gem*-dimethyl C-H bend); ^1H NMR ($DCCl_3$) δ 1.35 [s 6 H, $C(CH_3)_2$], 3.16 [s, 2 H, SCH_2], 7.02-7.22 [m, 4 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 27.2 [$C(CH_3)_2$], 46.90 [SCH_2], 46.90 [$C(CH_3)_2$]; Ar-*C* [122.0, 122.3, 124.1, 127.0, 140.1, 147.5]. This sulfur heterocycle, although previously isolated from petroleum, was never adequately characterized by conventional methods (i.e., IR, UV, NMR). The derivative of the heterocycle obtained by treatment with HI and trinitrobenzene was, however, characterized by IR and mass spectrometry.[105] In our work, heterocycle **87** gave satisfactory elemental analysis. Anal. Calcd for $C_{10}H_{12}S$: C, 73.12; H, 7.36. Found: C, 73.04; H, 7.36.

1-(2,3-Dihydro-3,3-dimethylbenzo[*b*]thien-5-yl)-ethanone (88a)

A solution of thioether **87** (8.00 g, 48.7 mmol) and freshly distilled $CH_3C(O)Cl$ (4.40 g, 56.1 mmol) in CS_2 (65 mL) was added dropwise (ca. 40 min) to a stirred suspension of $AlCl_3$ (9.8 g, 73 mmol) in CS_2 (70 mL) in a 500-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar, glass stopper, addition funnel, dry ice condenser, and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler). The resulting mixture was stirred vigorously (stir bar) at room temperature for 2

h. The reaction mixture was then cooled (0°C) and cautiously quenched by the dropwise addition of water (170 mL, the first 20 mL being added *very* slowly). Two layers were separated and the aqueous layer was extracted with ether (4 x 75 mL). The combined organic layers were washed with 5% $NaHCO_3$ (2 x 100 mL) and saturated brine (100 mL) and then dried (Na_2SO_4, overnight). Filtration and evaporation (rotovap) of solvent gave an oil which was subjected to chromatography using silica gel (3 x 52 cm) packed in hexanes. Elution was effected with hexanes:ether [4:1 (700 mL), 2:1 (150 mL), 1:1 (150 mL) and 1:2 (150 mL)]. Evaporation of the fractions of the major band (mostly from the 4:1 ratio) gave a yellow oil. A round-bottomed flask (200 mL) containing a solution of the oil in hexanes (110 mL) was flushed with N_2 and stoppered (glass stopper). The system was immersed in a dry ice-acetone bath (-78°C) which caused the ketone to precipitate as a pale yellow solid. The flask was removed from the bath and swirled at RT until most of the solid had dissolved except a small amount of solid (partly crystalline, partly amorphous). In order to decrease the amount of amorphous solid and to increase the amount of crystalline solid, the system was reimmersed (dry ice-acetone bath) and rewarmed (RT) several times until the small amount of solid (seeds for the ensuing completion of the crystallization) was essentially all crystalline and only slightly colored. To complete the crystallization, the flask was immersed intermittently (ca. 0.5 min between immersions) and briefly (ca. 5-10 sec per immersion) in the dry ice-acetone bath (now ca. -60°C) until essentially all the ketone had crystallized. The mother liquors were immediately decanted (quickly), and the crystals were immediately subjected to high vacuum (0.3 mm, ca. 15 min), the flask being kept in an ice-water bath to prevent the crystals from melting (using mildly chilled glass plates on a chilled Fisher-Johns platform, the mp of some sample crystals was determined to be 20.1-21.4°C). At RT, the off-white crystals melted to give **88a** as a pale yellow oil (8.28 g, 82.4%). Concentration of the mother liquors, followed by crystallization in hexanes, afforded another 0.65 g (6.5%) of title product to yield a total weight of 8.93 g (88.9%) for **88a**. Properties of ketone **88a**

were: n^{26}=1.6048; IR (neat) 1683 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.39 [s, $C(CH_3)_2$], 2.57 [s, 3 H, CH_3], 3.24 [s, 2 H, SCH_2], 7.25 [d, 1 H, Ar-*H*], 7.67 [d, 1 H, Ar-*H*], 7.73 [dd, 1 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 26.4 [CH_3], 27.6 [$C(CH_3)_2$], 47.3 [$C(CH_3)_2$], 47.7 [SCH_2]; Ar-*C* [122.7, 122.9, 129.2, 134.9, 149.0, 149.5], 198.3 [*C*=O]. Anal. Calcd for $C_{12}H_{14}OS$: C, 69.86; H, 6.84. Found: C, 69.55; H, 6.89.

From some late fractions in the above chromatographic separation (during elution with 1:2 hexanes:EtOAc), a diacetylated benzothiophene (**88b**) was obtained in a yield of 1% (119 mg) after recrystallization from hexanes:EtOAc (9:1); mp 108.4-109.6°C; IR (KBr) 1681, 1667 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.40 [s, 6 H, $C(CH_3)_2$], 2.64 [s, 3 H, CH_3], 2.68 [s 3 H, CH_3], 3.18 [s, 2 H, SCH_2], 7.75 [d, J = 1.6 Hz, 1 H, Ar-*H*] 8.34 [d, J = 1.6 Hz, 1 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 26.5 [CH_3], 26.8 [CH_3], 27.9 [CH_3], 45.6 [$C(CH_3)_2$], 47.3 [SCH_2], Ar-*C* [125.1, 129.8, 130.6, 133.9, 151.2, 151.4], 196.4 [*C*=O], 197.0 [C=O]. Anal. Calcd for $C_{14}H_{16}O_2S$: C, 67.71; H, 6.49. Found: C, 67.65; H, 6.75.

1-(2,3-dihydro-3,3-dimethylbenzo[*b*]thien-5-yl)-ethanol (89)

A solution of methyl ketone **88** (1.00 g, 4.85 mmol) in dry ether (7 mL) was added dropwise [ca. 20 min] under N_2 to a stirred suspension of $LiAlH_4$ (0.30 g, 7.9 mmol) in dry ether (18 mL) in a 50-mL, three-necked, round-bottomed flask equipped with an addition funnel, glass stopper, magnetic stirring bar, two stacked condensers, and N_2 inlet in the top of the condensers (positive pressure from an oil bubbler). The resulting mixture was stirred at reflux for 24 h and then carefully treated with EtOAc (5 mL), diluted with ether (5 mL), and finally quenched with 5% HCl (15 mL). The mixture was transferred to a separatory funnel containing water (10 mL). The reaction flask was rinsed with 5% HCl (7 mL) and ether (2 x 10 mL) and the rinses were transferred to the funnel. The layers were separated and the aqueous layer was extracted with ether (3 x 40 mL). The

combined organic layers were washed [5% $NaHCO_3$, (2 x 30 mL), followed by saturated brine (2 x 30 mL], dried (Na_2SO_4), filtered, and evaporated to an oil (1.02 g, 100%) which crystallized via scratching with a glass rod under a stream of N_2 over a dry ice bath. Recrystallization in hot hexane (5 mL) using a few tiny seeds gave [after filtration (suction), washing of crystals (2 x 1 mL of cold hexanes), and high vacuum (10 min)] alcohol **89** as a white crystalline solid (0.92 g, 91%); mp 60.5-61.5°C (Fisher-Johns); IR (KBr) 3050-3650 cm^{-1} (O-H); ^1H NMR ($DCCl_3$) δ 1.373 [s, 3 H, CH_3], 1.379 [s, 3 H, CH_3], 1.47 [d, 3 H, $CHCH_3$], 3.17 [s, 2 H, SCH_2], 4.86 [q, 1 H, $CHCH_3$], 7.07-7.16 [m, 3 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 25.2 [$CHCH_3$], 27.5 [$C(CH_3)_2$], 47.5 [$C(CH_3)_2$], 47.6 [SCH_2], 70.6 [$CH(OH)CH_3$]; Ar-*C* [120.6, 122.9, 125.5, 140.3, 143.4, 149.1]; Anal. Calcd. for $C_{12}H_{16}OS$: C, 69.19; H, 7.74; S, 15.39. Found: C, 69.10; H, 7.80; S, 15.68.

1-(2,3-Dihydro-3,3-dimethylbenzo[*b*]thien-5-yl)-ethyl]triphenylphosphonium Bromide (90)

A mixture of alcohol **89** (0.800 g, 3.84 mmol) and Ph_3P•HBr (1.30 g, 3.79 mmol) in dry CH_3OH (30 mL) was stirred at room temperature for 36 h in a 50-mL, single-necked, round-bottomed flask equipped with a magnetic stir bar, condenser, and N_2 inlet in the top of the condenser (positive pressure from an oil bubbler). The mixture was concentrated to an oil which was dissolved in CH_2Cl_2 (150 mL). The organic solution was dried briefly ($MgSO_4$, ca. 30 min), filtered, and evaporated to a foam which solidified during the evaporation. A mixture of the foam in dry ether (50 mL) was partially pulverized with a spatula and then with stirring (magnetic stir bar) under N_2 for 8 h. Filtration and removal of traces of solvent (high vacuum, 0.07-0.025 mm, 15 h) at RT gave salt **90** as a white powder (1.44 g, 70.3%): mp 194.3-197.3°C; IR (KBr) 1468 cm^{-1} (C=C); ^1H NMR ($DCCl_3$) δ 1.12 [s, 3 H, $C(CH_3)CH_3$], 1.19 [s, 3 H, $C(CH_3)CH_3$], 1.80 [dd, 3 H, $CHCH_3$], 3.09 [d, J = 11 Hz, 1 H, $SC(H)H$], 3.13 [d, J =

11 Hz, 1 H, SCH(*H*)], 6.59 [m, 1 H, C*H*CH$_3$], 6.85-7.01 [m, 3 H, Ar-*H*], 7.61-7.88 [m, 15 H, P(C$_6$*H*$_5$)$_3$]; ^{13}C NMR ($DCCl_3$) ppm 17.1 [CH*C*H$_3$], 27.1 and 27.3 [C(8) and C(9), 35.5 [d, J_{CP} = 42.4 Hz, CH$_3$*C*HP], 47.1 and 47.2 [C(2) and C(3)], 117.5 [d, J_{CP} = 82.5 Hz, *orthogonal*-C's of P(*C*$_6$H$_5$)$_3$], 122.4 [d, J_{CP} = 2.2 Hz, Ar-*C*], 124.8 [d, J_{CP} = 5.4 Hz, Ar-*C*], 129.1 [d, J_{CP} = 5.8 Hz, Ar-*C*], 129.5 [d, J_{CP} = 6.5 Hz, Ar-*C*], 130.2 [d, J_{CP} = 12.2 Hz, *meta*-C's of P(*C*$_6$H$_5$)$_3$], 134.6 [d, J_{CP} = 9.4 Hz, *ortho*-C's of P(*C*$_6$H$_5$)$_3$], 134.9 [d, J_{CP} = 2.7 Hz, *para*-C's of P(*C*$_6$H$_5$)$_3$], 141.7 [d, J_{CP} = 3.4 Hz, Ar-*C*], 148.6 [C(3a)]. The salt was used without further purification.

Methyl (*E*)-4-[2-(2,3-Dihydro-3,3-dimethylbenzo-[*b*]thien-5-yl)-1-propenyl]benzoate (60)

To a stirred mixture of salt **90** (5.00 g, 9.37 mmol) in THF (100 mL) in a 200-mL, three-necked, round-bottomed flask equipped with an addition funnel, rubber septum, condenser, magnetic stir bar, and N_2 inlet in the top of the condenser (positive pressure from an oil bubbler) was added (syringe, ca. 2 min) under N_2 a solution of *n*-butyllithium (6.2 mL, 1.6 M, 9.9 mmol) in hexane. The resulting black-brown mixture was stirred at room temperature for 1.5 h. After cooling the Wittig reagent in a dry ice-acetone bath (-78°C) for 10 min, a solution of methyl 4-formylbenzoate (1.55 g, 9.44 mmol) in dry THF (50 mL) was added to the Wittig reagent over a period of 10 min, after which time the color of the mixture had turned to a creamy yellow. The cold bath (-78°C) was removed and the mixture was allowed to stir at ambient temperature for 25 h. To the mixture was added dry ether (150 mL) dropwise. The creamy white precipitate was removed by filtration (the filtrate was set aside) and dissolved in an aqueous acetone solution (5:3 H_2O:acetone, 80 mL). The resulting solution was extracted with hexanes (3 x 50 mL). Evaporation of the combined filtrate and hexanes extracts gave a total weight of 5.19 g of a crude solid which was divided in four portions. Each portion was subjected to centrifugal thin layer chromatography (Chromatotron) using a silica gel plate (4 mm).

Elution of the first portion was effected with hexanes:ether [9:1 (200 mL), 4:1 (50 mL) and 150 mL of ether to strip the plate]. Immediate use of the same plate to separate the components of the other three portions required slightly increased amounts of hexanes [ratio of hexanes:ether was 14:1] due to increased amounts of residual ether in the silica gel plate. Evaporation of the fractions from the principal band gave 3 g of solid. Recrystallization from boiling 95% ethanol (50 mL) gave the heteroarotinoid ester **60** as white crystalline flakes (1.87 g, 59.0%) which was essentially pure (mother liquors set aside, see isolation of Z-isomer below). A second recrystallization (95% EtOH, 50 mL) gave pure **60** (1.62 g, 51.1%) as assessed by TLC (silica gel, 9:1 hexanes:ether):mp 120.9-122.0°C; IR (KBr) 1716 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.42 [s, 6 H, H(8,9)], 2.28 [d, J = 1.4 Hz, 1 H, H(11)], 3.21 [s, 1 H, H(2)], 3.93 [s, 3 H, H(20)], 6.81 [br s, 1 H, H(12)], 7.20 [d, J = 2 Hz, 1 H, H(4)], 7.19 [d, J = 8 Hz, 1 H, H(7)], 7.30 [dd, J = 8 Hz, J = 2 Hz, 1 H, H(6)], 7.42 [d, J = 8.3 Hz, 2 H, H(14, 18)], 8.04 [d, J = 8.3 Hz, 2 H, H(15, 17)]; ^{13}C NMR ($DCCl_3$) ppm 17.8 [C(11)], 27.4 [C(8,9)], 47.3 [C(2)], 47.5 [C(3)], 52.1 [C(20)], 120.3 [C(4)], 122.2 [C(7)], 125.4 [C(6)], 125.9 [C(12)], 127.8, 129.1 [C(14, 18)], 129.5 [C(15, 17)], 139.5, 140.2, 143.1, 148.2, 167.0 [C(19)]. Anal. Calcd for $C_{21}H_{22}O_2S$: C, 74.52; H, 6.55; S, 9.47. Found: C, 74.70; H, 6.70; S, 9.33.

Slow evaporation of the mother liquors from the first recrystallization gave rod-shaped crystals which were recrystallized twice (boiling 95% ethanol) to give the Z-isomer, **61**, as pale yellow crystals (36 mg, 1.1%): mp 84.0-84.5°C; IR (KBr) 1725 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.21 [s, 6 H, H(8, 9)], 2.21 [d, J = 1.4 Hz, 3 H, H(11)], 3.15 [s, 2 H, H(2)], 3.86 [s, 3 H, H(20)], 6.46 [br s, 1 H, H(12)], 6.78 [d, J = 1.6 Hz, 1 H, H(4)], 6.97 [dd, J = 7.9 Hz, J = 1.6 Hz, 1 H, H(6)], 7.02 [d, J = 8.4 Hz, 2 H, H(14, 18)], 7.12 [d, J = 7.9 Hz, 1 H, H(7)], 7.78 [d, J = 8.4 Hz, 2 H, H(15, 17)]; ^{13}C NMR ($DCCl_3$) ppm 26.9 [C(11)], 27.3 [C(8,9)], 47.1 [C(3)], 47.3 [C(2)], 51.9 [C(20)], 122.4 [C(4)], 123.0 [C(7)], 125.6 [C(12)], 127.0 [C(6)], 128.8 and 129.2 [C(14,18) and

C(15,17)], 167.0 [C(19)]; other quaternary carbons [127.4, 137.5, 139.7, 141.2, 142.7, 148.2]. Anal. Calcd for $C_{21}H_{22}O_2S$: C, 74.52; H, 6.55. Found: C, 74.71; H, 6.47.

(*E*)-4-[2-(2,3-Dihydro-3,3-dimethylbenzo[*b*]thien-5-yl)-1-propenyl]benzoic Acid (63)

A mixture of heteroarotinoid ester **60** (1.20 g, 3.55 mmol) in a degassed solution (N_2, 10 min) of dry KOH (0.62 g, 11 mmol) in absolute ethanol (9 mL) and H_2O (3 mL) in a 50-mL, single-necked, round-bottomed flask (equipped with a magnetic stir bar, condenser, and N_2 inlet into the top of the condenser) was heated *to* reflux over a period of 10 min, after which time the mixture became a solution. This solution was heated at reflux for 45 min. After cooling to RT, the solution was quenched with 15% acetic acid (10 mL) and saturated brine (10 mL). Ethyl acetate (100 mL) was added to the mixture and the layers were separated. The aqueous layer was extracted with ethyl acetate (50 mL). The combined organic layers were washed [brine (2 x 25 mL), H_2O (25 mL)], dried (Na_2SO_4, overnight), filtered (suction), and evaporated to a white solid. The solid was recrystallized twice from boiling absolute ethanol (25 mL, then 18 mL) rinsing the crystals each time with cold absolute ethanol (15 mL) and hexanes (20 mL) to give **63** as white fluffy needles (0.65 g, 56.4%); mp 203.7-204.8°C. Another 61 mg (5.3%, mp 204.0-204.7°C) could be obtained by concentration of the mother liquors and two recrystallizations. This gave a total weight of **63** of 0.71 g (61.7%). IR (KBr) 3250-2000 cm^{-1} (CO_2H); ^1H NMR ($DCCl_3$) δ 1.42 [s, 6 H, H(8, 9)], 2.31 [d, 3 H, H(11)], 3.23 [s, 2 H, H(2)], 6.84 [br s, 1 H, H(12)], 7.18-7.24 [m, 2 H, H(4) and H(7)], 7.32 [dd 1 H, H(6)], 7.48 [d, 2 H, H(14, 18)], 8.14 [d, 2 H, H(15, 17)]; ^{13}C NMR ($DCCl_3$) ppm 17.9 [C(11)], 27.4 [C(8,9)], 47.3 [C(3)], 47.5 [C(2)], 120.3 [C(4)], 122.2 [C(7)], 125.4 [C(6)], 125.8 [C(12)], 129.2 and 130.2 [C(14,18) and C(15,17)], 171.8 [C(19)]; other quaternary carbons [126.9, 139.9, 140.1, 140.3, 144.1, 148.2]; mass spectral data

for $C_{20}H_{20}O_2S$: m/e (M^+) 324.1184; Found 324.1184. Anal. Calcd for $C_{20}H_{20}O_2S$: C, 74.04; H, 6.21. Found: C, 74.28; H, 6.17.

2-[(2-Methyl-2-propenyl)oxy]nitrobenzene (100)

To a warmed and dark red solution of 2-nitrophenol (**99**, 30.00 g, 0.216 mol) in aqueous NaOH [8.65 g (0.216 mol) in H_2O (60 mL)] was added (ca. 10 min) freshly distilled β-methallyl chloride (25.5 g, 0.282 mol), the system being heated such that the reaction mixture began to boil towards the end of the addition. The system consisted of a 200-mL, jacketed flask equipped internally with two stacked water condensers, magnetic stir bar, addition funnel and a N_2 inlet in the top of the condensers (positive pressure from an oil bubbler). The jacket of the jacketed flask contained 1,2-dichloroethane (bp 84°C) and was also equipped with condensers. The reaction mixture was heated (boiling dichloroethane bath in surrounding jacket) for 4 h and was then allowed to cool (RT) for 45 min. The reaction mixture was transferred to a separatory funnel; the reaction flask was rinsed (ether, 50 mL), and the rinse was added to the funnel. After the two layers were separated, the aqueous layer was extracted with ether (3 x 50 mL). The combined organic layers were washed with 10% NaOH (2 x 50 mL, the first wash was dark red) and saturated brine (50 mL) and finally dried (Na_2SO_4, ca. 15 min with magnetic stirring). Filtration and then removal of the solvent (rotary evaporation) gave an oil. Vacuum distillation afforded the allyl ether **100** as a yellow oil (23.2 g, 56%):bp 106-111°C/0.18 mm (major fraction) (lit[32] bp 86-107°C/0.1 mm); IR (neat) 1353 cm^{-1} and 1525 cm^{-1} (NO_2); ^1H NMR ($DCCl_3$) δ 1.83 [narrow m, 3 H, CH_3], 4.55 [s, 2 H, OCH_2], 5.01 [narrow m, 1 H, C=C(*H*)H], 5.15 [narrow m, 1 H, C=CH(*H*)], 7.00 [m, 1 H, Ar-*H*], 7.07 [dd, 1 H, Ar-*H*], 7.50 [m, 1 H, Ar-*H*], 7.81 [dd, 1 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 19.2 [CH_3], 72.7 [OCH_2], 113.4, 114.7, 120.4, 125.5, 134.1, 139.5, 139.9, 151.9. The above procedure is a modification of one given (no spectral data) in Chemical Abstracts.[32]

2-[(2-Methyl-2-propenyl)oxy]benzenamine (101)

A chilled (ice water bath) solution of the nitrobenzene derivative **100** (30.0 g, 0.155 mol) in absolute ethanol (75 mL) and chilled concentrated HCl (145 mL) were mixed in a 500-mL, three-necked, round-bottomed flask equipped with a thermometer (with adapter), magnetic stir bar, addition funnel, condenser and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler). A solution of $SnCl_2 \cdot 2H_2O$ (108.0 g, 0.479 mol) in absolute ethanol (145 mL) was added dropwise (ca. 30 min) to the stirred and cooled (0°C, ice-water bath) nitrobenzene derivative **100**/ethanol/HCl mixture. The new mixture was stirred at ambient temperature for 18 h [the temperature of the reaction mixture was maintained below 30°C (ice-water bath) during the first 45 min of the exothermic reaction]. The mixture was then partitioned between H_2O (500 mL) and $HCCl_3$ (300 mL) and the resulting two layers were separated. The organic layer was extracted with water (2 x 100 mL). The combined water extracts and the original water layer were then combined. After adding $HCCl_3$ (300 mL) to the aqueous solution, the resulting two layers were stirred and cooled (0°C) followed by the dropwise addition of ca. 58% NH_4OH (200 mL). An emulsion formed. The layers were separated as best as possible (bottom layer was the $HCCl_3$ layer; the top layer was primarily an aqueous emulsion). The aqueous layer was made alkaline (pH ~7-8) by the addition of more 58% NH_4OH (20 mL). The emulsion was extracted ($HCCl_3$, 2 x 150 mL), saturated brine (50 mL) being added before the first extraction to aid in the slow destruction of the emulsion (agitation at the bottom of the emulsion with a glass rod also helped). The last two $HCCl_3$ extracts were combined with the $HCCl_3$ layer obtained when the aqueous layer was made alkaline. This organic solution was dried (Na_2SO_4, ca. 10 min with magnetic stirring), filtered and evaporated to an oil. Vacuum distillation afforded the aromatic amine **101** as a pale yellow oil (15.27 g, 60.4%): bp 80.7-90.1°C/0.17 mm (lit[39] bp 105-110°C/0.5 mm); IR (neat) 3376 cm^{-1} 3468 cm^{-1} (N-H); ^1H NMR ($DCCl_3$) δ 1.81 [narrow m, 3 H, CH_3], 3.75 [br s, 2 H,

NH_2], 4.41 [s, 2 H, OCH_2], 4.96 [narrow m, 1 H, C=C(H)H], 5.07 [s, 1 H, C=CH(H)], 6.63-6.80 [m, 4 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 19.4 [CH_3], 71.9 [OCH_2]; aromatic carbons [111.9, 112.5, 115.1, 118.3, 121.3, 136.4, 141.0, 146.3].

2-[(2-Methyl-2-propenyl)oxy]benzenediazonium Fluoroborate (102)

Amine **101** (8.45 g, 51.8 mmol) and a solution of HBF_4 (21%, 47 mL) were both chilled (ice bath) and then mixed in a 150 mL beaker. To the resulting chilled (0°C) and stirred solution was added dropwise (pipette) a cold solution of $NaNO_2$ (3.58 g, 51.9 mmol) in water (7.6 mL) over a period of 5 min. The resulting mixture containing precipitated diazonium salt was cooled in a dry ice-CCl_4 bath (ca. -20°C, 2 min) and then filtered through a chilled sintered glass funnel (suction). The solid was washed with cold 5% HBF_4 (30 mL, 20 mL) and finally with cold distilled water (2 x 25 mL). The resulting moist, brownish-grey solid was briefly dried over filter paper (ca. 5 min) and was more thoroughly dried under high vacuum (RT, 0.15-1 mm, 5 h). The dry solid was dissolved in acetone (42 mL) and the salt was precipitated by the slow addition (ca. 10 min) of dry ether (175 mL). The resulting powder was redissolved in acetone (50 mL), reprecipitated with dry ether (175 mL), and subjected to high vacuum (15 min) to give the fluoroborate salt **102** as a semicrystalline, light tan powder (9.15 g, 67.4%); mp 99.0-100.2°C (sl dec); IR (KBr) 2275 cm^{-1} (C-N); ^{1}H NMR ($DCCl_3$) δ 1.89 [s, 3 H, CH_3], 4.85 [s, 2 H, OCH_2], 5.18 [br s, 2 H, C=CH_2], 7.30 [d, J = 8.8 Hz, 1 H, Ar-H], 7.36 [m, 1 H, Ar-H], 8.05 [ddd, J = 8.8 Hz, J = 7.4 Hz, J = 1.6 Hz, 1 H, Ar-H], 8.64 [dd, J = 8.5 Hz, J = 1.6 Hz, 1 H, Ar-H]. The salt was used without further purification. The above procedure is similar to that described by Beckwith and Gara who only reported some IR maxima.[6]

1-[(2,3-Dihydro-3-methyl-3-benzofuranyl)methoxy]-2,2,6,6-tetramethylpiperidine (106)

To a solution of TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxide, 11.35 g, 72.6 mmol) in dry freshly distilled and degassed (N_2, rapid stream thru liquid, 1 h) acetone (600 mL) in a 1000-mL, three-necked, round-bottomed flask (equipped with a magnetic teflon stir bar, glass stopper, addition funnel, condenser and N_2 inlet) was added (ca. 15 min) a solution of the fluoroborate salt **102** (9.10 g, 34.7 mmol) in degassed acetone (45 mL). The stirred mixture was heated to boiling over a period of 8 min and then maintained at reflux with stirring for 1.5 h. Without cooling, the solvent was evaporated (reduced pressure) to dryness. Dry ether (65 mL) and then hexanes (130 mL) were added to the residue and, after swirling the mixture, the supernatant fluid was filtered. The remaining residue was extracted with hexanes (25 mL x 2), the extracts being filtered. All filtrates were combined and concentrated to a brown oil which was dissolved in hexanes (5 mL) for elution on a column (2.5 x 99 cm) of silica gel (190 g, mesh 60-200) packed in hexanes. Elution was effected with hexanes/ethyl acetate (715 mL 10:1, 60 mL 5:1). Thirteen fractions (10-15 mL each) were collected and evaporated to a pale green oil (6.01 g, 57%). Another 0.60 g (6%) of title product was obtained by concentration of some less pure fractions followed by a second chromatographic separation (Chromatotron) on silica gel (4 mm) using the same solvent ratios. The total yield of this substituted piperdine **106** was 6.61 g (63%): $n^{22.3}$=1.5148; IR (neat) 1362 cm^{-1} and 1376 cm^{-1} (*gem*-dimethyl C-H bend); ^1H NMR ($DCCl_3$) δ 1.0-1.6 [m, 21 H with a singlet at 1.45 for CH_3], 3.81 [s, 2 H, CH_2ON], 4.15 [d, J = 8.7 Hz, 1 H, OCH(*H*)], 4.54 [d, J = 8.7 Hz, 1 H, OC(*H*)H], 6.78 [d, J = 8 Hz, 1 H, Ar-*H*], 6.82-6.89 [m, 1 H, Ar-*H*], 7.08-7.19 [m, 2 H]; ^{13}C NMR ($DCCl_3$) ppm 22.7 [CH_3], 46.4 [CCH_2O], 80.7 [OCH_2], 81.5 [OCH_2]; piperidine ring *C*[17.0, 20.1, 20.2, 32.9, 33.2, 39.7, 60.08, 60.12]; Ar-*C*[109.5, 120.2, 123.6, 128.3, 132.9, 159.7]. A procedure for the preparation of this nitrogen heterocycle was

given by Beckwith and Meijs[9] who did not give amounts of solvent (concentration being critical in free radical cyclizations), nor modes of addition of reagents, nor details of purification. Furthermore, no spectral properties were given. This oil was used without further purification in our work.

2,3-Dihydro-3-methyl-3-benzofuranmethanol (107)

In a 250-mL, jacketed flask (equipped internally with a magnetic stir bar, condenser, and N_2 inlet and equipped externally with two condensers) a stirred mixture of piperidine **106** (6.20 g, 20.4 mmol), acetic acid/water (1:2, 60 mL), and Zn powder (5.65 g, 86.4 mmol) was heated at 68-70°C (boiling hexanes bath) for 12 h. Upon cooling, the reaction mixture was added (pipette) slowly (ca. 15 min) to a cooled, two-phase mixture of ether (100 mL) and aqueous Na_2CO_3 (35 g in 140 mL of water). The two layers were separated and the aqueous phase was extracted with ether (3 x 50 mL). The combined organic layers were washed with 4% HCl (2 x 75 mL), H_2O (75 mL) and 5% Na_2CO_3 (75 mL) and then dried (Na_2SO_4, overnight). Evaporation of solvent (reduced pressure) gave a yellow oil which crystallized upon addition of a few tiny seeds of alcohol **107**. Recrystallization in hexanes (10 mL), followed by two washes [chilled hexanes (20 mL), RT hexanes (10 mL)] and then removal of traces of solvent by high vacuum (15 min), gave alcohol **107** as a creamy white solid (2.25 g, 67.2%): mp 59.6-60.6°C (Lit[114] mp 58°C); IR (KBr) 3000-3600 cm^{-1} (O-H); ^1H NMR ($DCCl_3$) δ 1.36 [s, 3 H, CH_3], 1.62 [br s, 1 H, O*H*], 3.55 [d, J = 10.7 Hz, 1 H, C(*H*)HOH], 3.65 [d, J = 10.7 Hz, 1 H, CH(*H*)OH], 4.17 [d, J = 8.8 Hz, 1 H, OC(*H*)H], 4.56 [d, J = 8.8 H, 1 H, OCH(*H*)], 6.81 [d, J = 7.8 H, 1 H, Ar-*H*], 6.89 [m, 1 H, Ar-*H*], 7.11 [dd, J = 7.3 Hz, J = 1.4 Hz, 1 H, Ar-*H*], 7.16 [m, 1 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 21.9 [CH_3], 47.6 [CCH_3], 69.0 [CH_2OH], 80.1 [OCH_2]; Ar-*C*[109.0, 120.6, 123.1, 128.8, 131.8, 160.2].

3-Acetoxymethyl-2,3-dihydro-3-methylbenzofuran (112)

To a cooled solution (-35°C, dry ice-CCl_4 bath) of acetyl chloride (2.0 mL, 2.2 g, 28 mmol) in dry ether (35 mL) in a three-necked, round-bottomed flask (equipped with a magnetic stir bar, rubber septum, glass stopper, condenser, and N_2 inlet into the top of the condenser) was added (ca. 2 min) dry pyridine (2.6 mL, 2.5 g, 32 mmol). To the resulting white mixture (-30°C) was added (syringe) a bolus of alcohol **107** (2.25 g, 13.7 mmol) in dry freshly distilled THF (15 mL). A rinse (2 mL of THF) of the container and the syringe was added to the mixture and the dry ice-CCl_4 bath was removed. The cloudy white mixture was stirred at ambient temperature for 8 h, then placed in an ice bath and quenched with ether (25 mL) and water (25 mL). Stirring was continued until two clear layers could be seen. After separating the layers, the organic layer was washed with water (3 x 25 mL). The organic solution was then dried (Na_2SO_4), filtered, and concentrated (rotovap) to a yellow oil. A solution of the oil in hexanes (1 mL) was eluted on a column (91 x 2 cm) of silica gel (mesh 60-200) with hexanes/ether 9:1 (450 mL), 6:1 (210 mL), 4:1 (75 mL). Several fractions were collected containing pure acetate and were evaporated (rotary evaporator, high vacuum) to give acetate **112** as a colorless oil (2.43 g, 86%): n^{22}=1.5149; IR (neat) 1749 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.40 [s, 3 H, CH_3], 2.05 [s, 3 H, C(O)CH_3], 4.09 [d, J = 11 Hz, 1 H, C(*H*)HOC(O)], 4.13 [d, J = 11 Hz, 1 H, CH(*H*)OC(O)], 4.17 [d, J = 9 Hz, 1 H, OC(*H*)H], 4.49 [d, J = 9 Hz, 1 H, OCH(*H*)], 6.81 [d, 1 H, Ar-*H*], 6.89 [m, 1 H, Ar-*H*], 7.1-7.2 [m, 2 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 20.8 [C(O)*C*H_3], 22.3 [*C*H_3], 45.6 [CH_2*C*CH_3], 69.4 [*C*H_2OC(O)], 80.2 [O*C*H_2], 109.9 [C(7)], 159.8 [C(7a)], 170.9 [*C*=O]; Ar-*C* [120.7, 123.3, 128.9, 131.4]. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.88; H, 6.84. Found: C, 69.85; H, 6.74.

1-(3-Acetoxymethyl-2,3-dihydro-3-methyl-5-benzofuranyl)ethanone (113)

To a stirred suspension of $AlCl_3$ (2.25 g, 16.9 mmol) in freshly distilled CS_2 (10 mL) in a 100-mL, three-necked, round-bottomed flask [equipped with a rubber septum, addition funnel, magnetic stirring bar, dry ice condenser, and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler)] in an ice-water bath (0°C), was added dropwise (15 min) a solution of acetate **112** (1.30 g, 6.30 mmol) and AcCl (1.1 mL, 1.2 g, 15 mmol) in CS_2 (10 mL) — during the addition, the $AlCl_3$ (which gummed up during the addition) was chopped up (spatula, addition being temporarily discontinued). The resulting mixture was stirred at 0°C for 1 h during which time additional quantities of $AlCl_3$ (0.8 g, 6 mmol at 15 min) and AcCl (0.22 g, 2.8 mmol at both 15 min and 30 min by syringe) were added. The $AlCl_3$ was broken up a couple of times during the hour. After diluting the mixture with ether (40 mL), the mixture was quenched by the slow and careful addition of H_2O (25 mL) at 0°C. Two layers were separated and the aqueous layer was extracted with ether (4 x 25 mL). The combined organic layers were washed [5% $NaHCO_3$, 2 x 50 mL], dried (Na_2SO_4, overnight) and evaporated (rotovap) to an oil (1.51 g). The oil was separated by column (1.8 x 66 cm) chromatography on silica gel [hexanes: ether, 1:0 (10 mL), 4:1 (50 mL), 3:1 (40 mL), 2:1 (30 mL), 3:2 (570 mL)]. Thirteen fractions (ca. 15 mL each) containing product were collected, combined, and evaporated (rotovap, then at ≤ 0.5 mm at 50-60°C for 5 min) to give keto ester **113** as a colorless oil (1.37 g, 88%): IR (neat) 1677 cm^{-1} (C=O), 1745 cm^{-1} (C=O); ^{1} NMR ($DCCL_3$) δ 1.44 [s, 3 H, CH_3], 2.05 [s, 3 H, $CH_3C(O)$], 2.56 [s, 3 H, $CH_3C(O)Ar$], 4.10 [d, J = 11.0 Hz, 1 H, C(*H*)HOC(O)], 4.16 [d, J = 11.0 Hz, 1 H, CH(*H*)OC(O)], 4.28 [d, J = 9.2 Hz, 1 H, ArOC(*H*)H], 4.59 [d, J = 9.2 Hz, 1 H, ArOCH(*H*)], 6.83 [d, J = 8.4 Hz, 1 H, Ar-*H*], 7.81 [d, J = 1.8 Hz, 1 H, Ar-*H*], 7.85 [dd, J = 8.4 Hz, J = 1.8 Hz, 1 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 20.7 [CH_3], 22.4 [CH_3], 26.4 [$CH_3C(O)Ar$],

45.2 [$C(CH_2)CH_3$], 69.2 [$CH_2OC(O)$], 81.3 [OCH_2], 170.8 [$OC(O)$], 196.4 [$CH_3C(O)Ar$]; Ar-*C* [109.5, 124.0, 131.0, 131.3, 132.4, 164.1]. Anal. Calcd for $C_{14}H_{16}O_4$: C, 67.73; H, 6.50. Found: C, 67.63; H, 6.42.

1-(2,3-Dihydro-3-methyl-3-benzofuranmethanol-5-yl)ethanol (114)

To a stirred suspension of $LiAlH_4$ (0.60 g, 16 mmol) in dry ether (20 mL) in a 100-mL, two-necked, round-bottomed flask [equipped with a magnetic stir bar, two stacked condensers, an addition funnel, and a N_2 inlet in the top of the condensers (positive pressure from an oil bubbler)] was added a solution of keto acetate **113** (1.25 g, 5.03 mmol) in dry ether (8 mL) over a period of about five minutes. A dry ether rinse (2 mL) of both the addition funnel and the neck of the flask was added to the mixture, and the addition funnel was replaced by a glass stopper. The mixture was stirred at room temperature for 38 h. The mixture was then diluted with ether (20 mL), cooled in an ice-water bath (0°C) and quenched by the dropwise addition of H_2O (20 mL) and finally 5% HCl (25 mL, pH ~8). After separating the two layers, the aqueous layer was extracted with ether (10 x 25 mL). All the organic layers were combined and the resulting solution was dried (Na_2SO_4, overnight). Filtration and evaporation of the solvent [rotovap followed by high vacuum (≤ 0.3 mm), with warming (50-65°C, ca. 10 min)] gave a diastereomeric mixture (ratio, ca. 1:1 by ^1H NMR) of **114** as a thick and very pale yellow oil [1.08 g, "103%"; ^1H NMR indicated the presence of trapped ether in the oil (ca. 8% ether by weight): adjusted yield, 95%]: IR (neat) 3050-3700 cm^{-1} (O-H); ^1H NMR ($DCCl_3$) δ 1.337 and 1.342 [2 s, 3 H, $C(CH_2)CH_3$], 1.45 and 1.46 [2 d, 2 x J = 9 Hz, 1 H, $CHCH_3$], 2.32 and 2.45 [2 br s, 2 H, O-*H*], 4.16 [d, J = 9 Hz, 1 H, ArOC(*H*)H], 4.52 and 4.53 [2 d, 2 x J = 9 Hz, 1 H, ArOCH(*H*)], 4.78 and 4.80 [2 q, 2 x J = 6 Hz, 1 H, $CHCH_3$], 6.74 and 6.76 [2 d, 1 H, Ar-*H*], 7.05-7.20 [m, 2 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 21.9 [$CHCH_3$], 24.9 and 25.1 [CH_3], 47.6 [CCH_2], 68.77 and 68.81

[CH_2OH], 70.1 and 70.3 [$CHCH_3$], 80.4 [OCH_2]; Ar-*C* [109.3, 109.5, 120.3, 120.8, 126.0, 126.5, 132.2, 132.4, 138.0, 159.7]. The diastereomeric mixture of this diol was used without further purification.

[1-(2,3-Dihydro-3-methyl-3-benzofuranmethanol-5-yl)ethyl]triphenylphosphonium Bromide (115)

In a 50-mL, single-necked, round-bottomed flask [equipped with a magnetic stir bar and an N_2 inlet (positive pressure from an oil bubbler)] a solution of diol **114** (1.03 g, ca. 4.55 mmol assuming 92% purity) and Ph_3P•HBr (4.46 g, 4.46 mmol) in absolute methanol (35 mL) was stirred at room temperature for 15 h. Rotary evaporation with warming (warm water bath at 50-60°C toward the end of the evaporation) gave a foam which solidified. The solid foam was scraped (spatula) from the sides of the flask and pulverized by stirring (stir bar) in dry ether (25 mL) under N_2 for 9 h. The mixture was then filtered (suction), and the white powder was rinsed with dry ether (75 mL). The powder was immediately subjected to high vacuum (≤ 0.1 mm) at room temperature for 12 h and at 77°C (Abderhalden, boiling EtOAc) for 1 h to give a diastereomeric mixture (ratio by ^1H NMR ca. 1:1) of salt **115** as a white powder (2.28 g, 96%): mp 212.2-215.0°C; IR (KBr) 3100-3650 cm^{-1} (O-H); ^1H NMR ($DCCl_3$) δ 1.11 and 1.15 [2 s, 3 H, CH_3], 1.77 and 1.78 [2 dd, 2 x J_{HH} = 7.1 Hz, 2 x J_{HP} = 19 Hz, 3 H, $CHCH_3$], 3.35-3.55 [m, 2 H, CH_2OH], 4.08 and 4.10 [2 d, 2 x J = 8.8 Hz, 1 H, OC(*H*)H], 4.61 and 4.63 [2 d, 2 x J = 9.9 Hz, 1 H, OCH(*H*)], 5.85-6.1 [m, 1 H, $CHCH_3$], 6.51 [d, 1 H, Ar-*H*], 6.7-6.95 [m, 2 H, Ar-*H*], 7.6-7.9 [m, 15 H, $P(C_6H_5)_3$]. The position and breadth of the O-H proton was variable – from a broad singlet (δ 1.9-2.5, 1 H) to that hidden in the baseline (δ 1.9-4.0, integration ca. 1 H). The diastereomeric mixture of the salt was used without further purification.

Methyl (*E*)-4-[2-(2,3-Dihydro-3-methyl-3-benzofuranmethanol)-1-propenyl]benzoate (64)

A solution of *n*-butyllithium in hexane (1.6 M, 3.2 mL, 5.1 mmol) was added (syringe, ca. 2 min) to a stirred suspension of salt **115** (2.25 g, 4.22 mmol) in dry THF (30 mL) in a 50-mL, three-necked, round-bottomed flask [equipped with a magnetic stirring bar, rubber septum, glass stopper, and a N_2 inlet (positive pressure from an oil bubbler)]. The resulting dark red mixture was stirred at RT for 1 h followed by the addition of more *n*-butyllithium in hexane (1.6 M, 0.5 mL, 0.8 mmol) with continued stirring for another 30 min (RT). The dark red Wittig reagent was then cooled (ca. 5 min) in a liquid N_2/EtOAc bath (-84°C) and a solution of *p*-$CHOC_6H_4CO_2CH_3$ (0.71 g, 4.3 mmol) in dry THF (15 mL) was added (syringe, ca. 5 min). The cold bath was removed and the reaction mixture stirred (no external heating/cooling) for 12 h. After diluting with ether (100 mL) and quenching [saturated brine (50 mL) and 5% HCl (2.5 mL)] to a pH of ca. 5, two layers were separated (1 g of salt used to help destroy emulsion). The aqueous layer was extracted with ether (50 mL). The remaining emulsion and aqueous layer were separated and extracted separately with ether (2 x 50 mL each). The combined organic layers were washed (saturated brine, 75 mL), dried (Na_2SO_4, > 24 h), and filtered. After evaporation (rotovap) of the solvent, purification of the crude product was effected by column and centrifugal thin layer chromatography on silica gel [best separation of components obtained using 1:1 hexanes:ether, *E*-isomer (R_f = 0.21), *Z*-isomer (R_f = 0.24)] followed by multiple crystallizations and recrystallizations. Crystallizations were generally effected by dissolving partially crystallized material (obtained from chromatographic fractions after removal of solvent) in a minimal amount of EtOAc followed by the addition of the *n*-pentane (final pentane:EtOAc ratio ≈ 3-4:1) and by allowing the resulting solution to stand in a pentane bath (closed jar). Finally, recrystallization in boiling hexanes (i.e. 4 mL/20 mg) afforded ester **64**-(*E*) as a fine white

crystalline solid (60 mg, 4.2%), mp 106-108°C, which showed as one spot by TLC (on silica gel) using three solvent systems: R_f = 0.24 (1:1 hexanes/ether), R_f = 0.57 (1:1 *n*-pentane/EtOAc), R_f = 0.25 (2:1 $HCCl_3$/benzene). Another 28 mg (mp 105-108°C also pure by TLC by the above three solvent systems) was obtained by crystallization of an oil (from a final chromatographic separation) using *n*-pentane/EtOAc (method described above). All batches gave identical IR spectra. Total yield was 88 mg (6.2%): IR (KBr) 1722 cm^{-1} (C=O), 3050-3650 cm^{-1} (O-H); ^1H NMR ($DCCl_3$) δ 1.42 [s, 3 H, H(9)], 2.28 [d, J = 1 Hz, 3 H, H(11)], 3.63 [d, $^2J_{HH}$ = 10.7 Hz, 1 H, H(8)], 3.72 [d, $^2J_{HH}$ = 10.7 Hz, 1 H, H(8')], 3.93 [s, 3 H, H(20)], 4.24 [d, $^2J_{HH}$ = 8.9 Hz, 1 H, H(2)], 4.62 [d, $^2J_{HH}$ = 8.9 Hz, 1 H, H(2')], 6.77 [br s, 1 H, H(12)], 6.82 [d, J = 8.3 Hz, 1 H, H(7)], 7.29 [d, J = 2 Hz, 1 H, H(4)], 7.35 [dd, J = 8.3 Hz, J = 2 Hz, 1 H, H(6)], 7.41 [d, J = 8.3 Hz, 2 H, H(14,18)], 8.03 [d, J = 8.3 Hz, 2 H, H(15,17)]; ^{13}C NMR ($DCCL_3$) ppm 17.9 [C(11)], 21.9 [C(9)], 47.7 [C(3)], 52.1 [C(20], 69.0 [C(8)], 109.6 [C(7)], 120.7 [C(4)], 125.4 [C(12)], 127.0 [C(6)], 129.0 [C(14,18)], 129.5 [C(15,17)], 161.1 [C(7a)], 167.0 [C(19)]; other quaternary carbons [127.7, 132.1, 136.5, 139.3, 143.3]. Anal. Calcd for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.56; H, 6.66. Evaporation of the mother liquors from the final crystallizations gave an oil (29 mg) which contained mostly a mixture of the two isomers (*Z*:*E* ≈ 55:45) and a small amount of an impurity.

Other fractions from the above chromatographic separations and which contained essentially only one spot [R_f = 0.24 (1:1, hexanes:ether)] were evaporated [rotovap, then ≤ 0.5 mm at RT for ca. 5 min] to an oil (110 mg) which contained the (*Z*)-isomer and significant amounts of an impurity (as judged by ^1H NMR) whose ^1H NMR signals allow the tentative assignment as *p*-carboxymethylbenzyl alcohol. A trace of the (*E*)-isomer was also present. ^1H NMR data was obtained for the (*Z*)-isomer a small portion of which was isolated (1.5 mg, an oil) in nearly pure form by HPLC [Waters Model 6000A pump connected to a Whatman (Clifton, N.J.) 0.46 x 25 cm Partisil 10/25 C-18 column with detection at 254 nm using a Waters Model 440 spectrophotometer. Columns were

protected by Whatman precolumns packed with CoPell ODS. Solvent system was 75:25 MeOH:0.01 M HOAc with a 1.5 mL/min flow rate, R_T = 98 min]: ^{1}H NMR ($DCCl_3$) δ 1.20 [s, 3 H, H(9)], 2.20 [s, 3 H, H(11)], 3.41 [d, 1 H, H(8)], 3.49 [d, 1 H, H(8')], 3.84 [s, 3 H, H(20)], 4.16 [d, 1 H, H(2), 4.54 [d, 1 H, H(2')], 6.43 [br s, 1 H, H(12)], 6.73 [d, 1 H, H(7)], 6.79 [d, 1 H, H(4)], 6.98 [d, 2 H, H(14,18)], 7.02 [dd, 1 H, H(6)], 7.76 [d, 2 H, H(15,17)].

2-[(2-Methyl-2-propenyl)thio]benzenamine (117)

To a warm (ca. 40°C) mixture of 2-aminothiophenol (**116**, 19.00 g, 0.152 mol) and aqueous NaOH [6.33 g (0.158 mol) in H_2O (17 mL)] in a 200-mL, jacketed flask equipped internally with a magnetic stir bar, water condenser, glass stopper and a N_2 inlet in the top of the condenser [(positive pressure from an oil bubbler) - the jacket of the jacketed flask contained water and was also equipped with a condenser] was added dropwise β-methallyl chloride (15.20 g, 0.168 mol). The resulting mixture was heated at 100°C (boiling water bath in surrounding jacket) for 2 h and then cooled (RT) for 15 min. Water (50 mL) and ether (100 mL) were added to the mixture and the two layers separated. After extracting the aqueous layer (ether, 3 x 50 mL), the combined organic layers were washed [9% NaOH (50 mL), saturated brine (50 mL)], dried (Na_2SO_4, two nights), filtered, and evaporated to a brown oil. Vacuum distillation gave aniline derivative **117** as a colorless oil (22.7 g, 83.4%): bp 91-93°C/0.5 mm (major fraction); IR (neat) 3360 cm^{-1}, 3457 cm^{-1} (NH_2); ^{1}H NMR ($DCCl_3$) δ 1.85 [very narrow m, 3 H, C*H*$_3$], 3.33 [d, J = 0.9 Hz, 2 H, SC*H*$_2$], 4.33 [br s, 2 H, N*H*$_2$], 4.62 [narrow m, 1 H, C=C(*H*)H], 4.72 [narrow m, 1 H, C=CH(*H*)], 6.66 [m, 1 H, H(5)], 6.71 [dd, J = 8.0 Hz J = 1.3 Hz, 1 H, H(3)], 7.10 [ddd, J = 8.0 Hz, J = 7.3 Hz, J = 1.6 Hz, 1 H, H(4)], 7.31 [dd, J = 7.6 Hz, J = 1.6 Hz, 1 H, H(6)]; ^{13}C NMR ($DCCl_3$) ppm 21.0 [*C*H$_3$], 42.3 [S*C*H$_2$]; vinyl and Ar-*C* [113.9, 114.8, 117.8, 118.3, 129.7, 136.2, 141.1, 148.2]. A

procedure with very little experimental detail and no physical properties is given in Chemical Abstracts.[56]

2-[(2-Methyl-2-propenyl)thio]benzenediazonium Fluoroborate (118)

To a stirred (magnetic stirring br) and cooled (ice-water bath, 0°C) solution of amine **117** (1.74 g, 9.70 mmol) in 21% HBF_4 [48% HBF_4 (3.1 g) in H_2O (5.3 g)] in a 20-mL beaker was added (ca. 5 min, Pasteur pipette) a chilled (0°C) solution of $NaNO_2$ (0.67 g, 9.7 mmol) in H_2O (1.7 mL). After stirring at 0°C another 5 min, the mixture was cooled in a dry ice-CCl_4 bath (ca. -20°C, 5 min). The mixture was filtered through a chilled (freezer) sintered glass funnel and the yellow solid was washed [chilled 5% HBF_4 (15 mL) and chilled H_2O (2 x 10 mL)], dried [in air on filter paper (no suction, ca. 5 min), and then under high vacuum (≤ 0.5 mm, 2 h)] and recrystallized in the following manner: the dry solid was dissolved in dry acetone (35 mL) followed by the slow addition of dry ether (100 mL). The crystals were filtered (suction), washed (dry ether, 50 mL), recrystallized again in the same manner (except using 75 mL of ether for washing the crystals), and finally dried [high vacuum, ≤ 0.5 mm, 1 h] to yield diazonium salt **118** as yellow crystals (2.05 g, 76%) which were used without further purification: mp 91°C (dec, darkening began without melting at 88.5°C) IR (KBr) 2260 cm^{-1} (C-N); ^1H NMR ($DCCl_3$) δ 1.92 [s, 3 H, CH_3], 3.81 [s with fine splitting, 2 H, SCH_2], 4.96 [narrow m, 1 H, C=C(*H*)H], 5.05 [narrow m, 1 H, C=CH(*H*)], 7.67-7.79 [m, 2 H, Ar-*H*], 7.99-8.06 [m, 1 H, Ar-*H*], 8.83-8.89 [m, 1 H, Ar-*H*].

1-[2,3-Dihydro-3-methylbenzo[*b*]thien-3-yl)methoxy]-2,2,6,6-tetramethylpiperidine (120) and 1-[3,4-Dihydro-3-methylbenzothiopyran-1(2H)-3-yl)oxy]-2,2,6,6-tetramethylpiperidine (119)

To a solution of TEMPO (2,2,6,6-tetramethylpiperidine *N*-oxide, 2.70 g, 17.3 mmol) in dry deoxygenated (rapid N_2 stream through liquid, 1 h) acetone (145 mL) in a 200-mL, three-necked, round-bottomed flask [equipped with a magnetic stir bar, two glass stoppers, two stacked condensers and a N_2 inlet in the top of the condensers (positive pressure from an oil bubbler)] was added a bolus of salt **118** (2.00 g, 7.19 mmol). The resulting brown-red solution was heated to boiling (5 min) and maintained at reflux for 45 min and finally, without cooling, was evaporated (rotovap) to dryness. The dark residue was extracted with hexanes:ether [1:1, 3 x 30 mL; in each extraction the ether (15 mL) was added first, the mixture was swirled, and then the hexanes (15 mL) were added; total volume of each extract was 30 mL] and finally with hexanes:acetone {4:1, 50 mL [i.e., acetone (10 mL) was added, the mixture was swirled, and then hexanes (40 mL) was added; total volume was 50 mL]}. The combined extracts were filtered, concentrated to about 30 mL, diluted (50 mL of hexanes, caused some precipitate to form), filtered and finally evaporated to an oil. Two consecutive chromatographic separations on silica gel (mesh 60-200) were effected using 40:1 hexanes:ether (400-500 mL per separation). The best separation was achieved in the second chromatographic separation in which the silica gel was packed in 40:1 hexanes:ether. Two components (R_f = 0.72, 0.92 in 40:1 hexanes:ether) were separated. The fractions containing pure or nearly pure (traces of other impurities as assessed by TLC, 40:1 hexanes:ether) bands of the two components were collected separately and evaporated to yield the benzothiophene **120** as a yellow oil (0.44 g, 19%) and the benzothiopyran **119** (0.37 g, 16%) as an off-white crystalline solid

(mp 97.7-99°C). The same yields for **120** and **119** were obtained in two other small scale reactions (< 2 g of salt **118**).

The following data is for heterocycle **120**: R_f = 0.72 (40:1 hexanes:ether); IR (neat) 1361 cm^{-1} and 1374 cm^{-1} (*gem*-dimethyl C-H bend); ^1H NMR ($DCCl_3$) δ 1.0-1.6 [m, 21 H, contains singlets at δ 1.51, 1.17, 1.12, 1.10 and 1.06 each of which integrates to ~ 3 H], 3.14 [d, J = 11.1 Hz, 1 H, SC(*H*)H], 3.47 [d, J = 11.1 Hz, 1 H, SCH(*H*)], 3.73 [d, J = 8.2 Hz, 1 H, C(*H*)HON], 3.83 [d, J = 8.2 Hz, 1 H, CH(*H*)ON], 7.0-7.23 (m, 4 H, Ar-*H*); the following ^{13}C NMR assignments are tentative: ^{13}C NMR ($DCCl_3$) ppm 17.0 [*t*, $(CH_2)_2CH_2$], 20.3 [q, *axial*-CH_3's], 22.9 [q, $ArCCH_3$], 32.8 [q, *equatorial*-CH_3], 33.4 [q, other *equatorial*-CH_3], 39.8 [t, $(CH_2)_2CH_2$], 42.4 [t, SCH_2], 51.8 [s, SCH_2C], 59.9 [s, $NC(CH_3)_2$], 60.1 [s, other $NC(CH_3)_2$], 80.0 [t, CH_2ON]; Ar-*C* [122.4, 124.0, 124.1, 127.8, 141.4, 144.3]. This heterocycle was used without further purification.

The following data is for heterocycle **119**: R_f 0.92 (40:1 hexanes:ether); mp 99.7-100.6°C; IR (KBr) 1355 cm^{-1} and 1370 cm^{-1} (*gem*-dimethyl C-H bend); ^1H NMR ($DCCl_3$ δ 1.0-1.6 [m, 21 H, contains singlets at δ 1.44, 1.19, 1.16, 1.11, and 1.02 each of which integrates to ~ 3 H], 2.89 [dd, J = 15.5 Hz, J = 1.7 Hz, 1 H, ArC(*H*)H], 2.96 [dd, J = 12.2 Hz, J = 1.9 Hz, 1 H, SC(*H*)H], 3.10 [d, J = 15.5 Hz, 1 H, ArCH(*H*)], 3.25 [d, J = 12.2 Hz, 1 H, SCH(*H*)], 6.95-7.20 [m, 4 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 17.0 [$(CH_2)_2CH_2$], 20.5 and 20.7 [*axial*-CH_3's], 23.3 [$ArCH_2CCH_3$], 34.9 and 35.0 [*equatorial*-CH_3's], 37.9 [$ArCH_2CCH_3$], 40.8 [$(CH_2)_2CH_2$], 43.4 [SCH_2], 59.5 and 59.6 [both $NC(CH_3)$], 76.7 [CH_2ON], Ar-*C* [124.0, 125.7, 126.2, 130.5, 132.8, 134.5]. Anal. Calcd for $C_{19}H_{29}NOS$: C, 71.43; H, 9.15. Found: C, 71.51; H, 9.49.

The cyclization (presumed to occur via a free-radical mechanism, see References 6-9) was found to proceed with equal or better effectiveness on a large scale [i.e. using 25.0 g (89.9 mmol) of fluoroborate salt **118**, 34.0 g (0.218 mol) of TEMPO, 1850 mL of degassed dry acetone and 6 h at reflux; yields of 19.9% for **120** and 16% for **119** were realized (the yield may be as high as 25% for **120** but some of the material was lost during

chromatography)]. These data were gathered only from one experiment on a *large scale* and the yields of **120** and **119** may be capable of being improved.

2,3-Dihydro-3-methyl-3-benzo[*b*]thienmethanol

(121)

To a jacketed flask (internal volume ca. 200 mL) equipped with a condenser, magnetic stirring bar, and N_2 inlet (positive pressure, from oil bubbler into top of condenser; the outer jacket contained hexanes and was equipped with two stacked condensers) was added nitrogen heterocycle **120** (5.64 g, 17.7 mmol), acetic acid:water (1:2, 52 mL), and zinc powder (4.90 g, 74.9 mmol). The mixture was stirred at 68-70°C (boiling hexanes bath) a total of 18 h. During this time, additional quantities of Zn powder (4.90 g x 2, 74.9 mmol x 2 - one portion at 6 h, the other at 12 h) and 1:2 acetic acid:water (10 mL x 2 - one portion at 6 h, the other at 12 h) were added and the magnetic stir bar was replaced with a mechanical stirring rod to facilitate stirring the zinc. The mixture was allowed to cool and was then transferred (Pasteur pipette, excess Zn remained) to a stirred, two-phase mixture of ether (150 mL) and 20% Na_2CO_3 (150 mL). The reaction vessel was also rinsed with ether, the rinse being added to the mixture. Upon completion of the evolution of gas (loss of CO_2), two layers were separated. The aqueous layer was extracted with ether (3 x 75 mL), and the combined organic layers (including the original organic layer) were washed with saturated brine (50 mL), 2% HCl (2 x 50 mL) and 5% $NaHCO_3$ (2 x 50 mL). After drying (Na_2SO_4), the organic solution was evaporated (reduced pressure and high vacuum -0.2 mm, 2 h) to a viscous oil to which was added hexanes (10 mL). After standing in the freezer overnight, the supernatant liquid was decanted and the resulting crystals were washed with hexanes (20 mL), the wash also being decanted. Evaporation (high vacuum -0.2 mm, RT, 1 h) of residual solvent gave the title alcohol **121**, as pale yellowish white crystals; (1.93 g, 60.5%), mp 63.9-66.0°C (lit[114] mp 62-64.5°C); IR (KBr) 3100-3600 cm^{-1} (O-H); ^1H NMR ($DCCl_3$) δ 1.40 [s, 3

H], 1.58 [m, 1 H, O-*H*], 3.15 [d, J = 11.2 Hz, 1 H, SC(*H*)H], 3.44 [d, J = 11.2 Hz, 1 H, SCH(*H*)], 3.55 [br d, J = 11.2 Hz, 1 H, C(*H*)HOH], 3.72 [br d, J = 11.2 Hz, 1 H, CH(*H*)OH], 7.03-7.25 [m, 4 H]. Irradiation at δ 1.57 (power, 10 db) caused both small broad doublets [δ 3.55, 3.72] to become narrow, tall doublets; ^{13}C NMR ($DCCl_3$) ppm 22.4 [*C*H_3], 41.7 [S*C*H_2], 52.7 [CH_2*C*CH_3], 67.7 [*C*H_2OH]; Ar-*C* [122.6, 123.7, 124.4, 128.1, 142.0, 143.4].

3-Acetoxymethyl-2,3-dihydro-3-methylbenzo[*b*]-thiophene (122)

To a stirred solution of $CH_3C(O)Cl$ [1.60 g, 20.4 mmol] in dry ether (25 mL) in a cooled (dry ice-CCl_4 bath, -40 to -50°C, excess dry ice) 200-mL, three-necked, round-bottomed flask [equipped with condenser, stir bar, rubber septum, addition funnel, and an N_2 inlet in the top of the condenser (positive pressure from an oil bubbler)] was added (syringe, ca. 1 min) pyridine (1.9 mL, ca. 1.9 g, 24 mmol). After stirring at -40 to -50°C for 15 min, a solution of alcohol **121** (1.80 g, 9.99 mmol) in dry THF (15 mL) was added quickly followed by a 2 mL THF rinse of both the addition funnel and the neck (funnel replaced now by a glass stopper). The cold bath was removed and the white mixture was stirred 14 h (room temperature). The reaction flask was cooled (ice-water bath) and the mixture was diluted (ether, 35 mL). After stirring in the 0°C bath for 5 min, water (25 mL) was added slowly (ca. 5 min). Two clear and colorless layers were separated. The aqueous layer was extracted (ether, 4 x 25 mL). The combined organic layers were washed [2% HCl (2 x 50 mL), saturated $NaHCO_3$ (2 x 50 mL)], dried (Na_2SO_4, 8 h), filtered and evaporated (rotovap) to an oil. Purification by column chromatography on silica gel (70 g, 1.8 x 71 cm) packed in hexanes was effected by elution with hexanes:ether [9:1 (110 mL), 8:1 (90 mL), 7:1 (80 mL), 6:1 (200 mL)] using a flow rate of about 5 mL/min. Twenty two fractions (7-13 mL each) containing essentially pure acetate (TLC, 6:1 hexanes:ether, R_f = 0.53) were collected primarily

during the 6:1 ratio and were combined and evaporated [rotovap, then high vacuum (≤ 0.3 mm) at RT for 20 min and at 50°C for 2 min] to afford ester **122** as a nearly colorless oil (2.05 g, 92.3%): IR (neat) 1743 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.42 [s, 3 H, CH_3], 2.07 [s, 3 H, C(O)CH_3], 3.15 [d, J = 11.3 Hz, 1 H, SCH(*H*)], 3.37 [d, J = 11.3 Hz, 1 H, SC(*H*)H], 4.10 [d, J = 11.0 Hz, 1 H, C(*H*)(H)OAc], 4.14 [d, J = 11.0 Hz, 1 H, C(H)(*H*)OAc], 7.05-7.25 [m, 4 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$] ppm 20.9 [C(O)CH_3], 22.5 [CH_3], 42.1 [SCH_2], 50.7 [CH_2CCH_3]68.0 [CH_2OAc]; Ar-*C* [122.6, 123.8, 124.5, 128.3, 141.5, 142.8], 171.0 [*C*=O]. Anal. Calcd for $C_{12}H_{14}O_2S$: C, 64.84; H, 6.35, Found: C, 64.56; H, 6.43.

1-(3-Acetoxymethyl-2,3-dihydro-3-methylbenzo[*b*]-thien-5-yl)ethanone (123)

To a stirred and cooled (ice-water bath, 0°C) suspension of $AlCl_3$ (2.25 g, 16.9 mmol) in distilled CS_2 (10 mL) in a 100-mL, three-necked, round-bottomed flask [equipped with a magnetic stir bar, rubber septum, addition funnel, dry ice condenser, and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler)] was added (ca. 8 min) a solution of acetate **122** (1.40 g, 6.30 mmol) and distilled $CH_3C(O)Cl$ (1.1 mL, 1.2 g, 15 mmol) in CS_2 (9 mL). A rinse (CS_2, 1 mL) of the addition funnel and neck was added to the mixture, and the addition funnel was then replaced by a glass stopper. The mixture was stirred a total of 85 min [at 0-8°C (45 min) and at RT (40 min)] during which time additional quantities of $AlCl_3$ and $CH_3C(O)Cl$ were added: 0.40 mL (0.44 g, 5.6 mmol) of $CH_3C(O)Cl$ was added both after 15 and 35 min; 0.90 mL (0.99 g, ca. 13 mmol) of $CH_3C(O)Cl$ was added at 45, 60 and 75 min; $AlCl_3$ (0.5 g, 4 mmol) was added at 30 min. It was necessary to break up (spatula) the $AlCl_3$ (clumping occurred at the beginning of reaction) several times during the reaction (rapid N_2 stream while system was opened). At the end of 85 min, the reaction appeared to be essentially complete [TLC, hexanes:ether 2:1, R_f (product)=0.45]. The reaction mixture was cooled (ice-water bath,

0°C), diluted with wet ether (25 mL) and quenched carefully (10 min) with 5% HCl (20 mL). After the layers were separated, the aqueous layer was extracted (ether, 4 x 25 mL). The combined organic layers were washed [saturated brine (50 mL), saturated $NaHCO_3$ (2 x 50 mL)], dried (Na_2SO_4, overnight), and evaporated; during evaporation (rotovap), the crude keto acetate was adsorbed onto silica gel (5 g) for purification by column chromatography (1.8 x 68 cm, silica gel packed in hexanes). Elution was effected with hexanes:ether [4:1 (50 mL), 3:1 (40 mL), 2:1 (610 mL)]. Fifteen fractions (10-18 mL each) were collected from the 2:1 ratio and contained essentially pure keto acetate (TLC, 2:1 hexanes:ether). Evaporation [rotovap, then high vacuum (0.3 mm, 50-60°C for 5 min)] of the solvent gave keto acetate **123** as a yellow oil (1.427 g, 85.7%); IR (neat) 1682 cm^{-1}, 1743 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.47 [s, 3 H, C*H*$_3$], 2.06 [s, 3 H, OC(O)C*H*$_3$], 2.56 [s, 3 H, C(O)C*H*$_3$], 3.22 [d, J = 11.4 Hz, 1 H, SC(*H*)H], 3.43 [d, J = 11.4 Hz, 1 H, SCH(*H*)], 4.12 [d, J = 11.1 Hz, 1 H, OC(*H*)H], 4.16 [d, J = 11.1 Hz, 1 H, OCH(*H*)], 7.26 [d, J = 8.1 Hz, 1 H, H(7)], 7.68 [d, J = 1.6 Hz, 1 H, H(4)], 7.77 [dd, J = 8.1 Hz, J = 1.6 Hz, 1 H, H(6)]; ^{13}C NMR ($DCCl_3$) ppm; 20.9 [OC(O)*C*H$_3$], 22.8 [CH$_2$*C*CH$_3$], 26.5 [C(O)*C*H$_3$], 42.4 [S*C*H$_2$], 50.4 [CH$_2$*C*CH$_3$], 67.9 [O*C*H$_2$]; Ar-*C* [122.2, 123.4, 129.2, 134.1, 143.7, 148.9], 170.8 [O*C*(O)CH$_3$], 196.9 [*C*(O)CH$_3$]. Anal. Calcd for $C_{14}H_{16}O_3S$: C, 63.61; H, 6.10. Found: C, 63.46; H, 6.45.

1-(2,3-Dihydro-3-methyl-3-benzo[*b*]thienmethanol-5-yl)ethanol (124)

To a stirred suspension of $LiAlH_4$ (0.09 g, 2.4 mmol) in dry ether (2 mL) in a 15-mL, two-necked, round-bottomed flask [equipped with rubber septum, magnetic stir bar, two stacked condensers and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler)] was added dropwise (ca. 2 min, syringe) a solution of keto acetate **123** (0.21 g, 0.79 mmol) in dry ether (2 mL) followed by the addition of a dry ether rinse (1 mL) of the syringe and the original container. The resulting mixture was stirred at a mild

reflux for 8 h and then cooled in an ice-water bath (0°C). After dilution with wet ether (2 mL), the cooled mixture was quenched with H_2O (2 mL) and finally 5% HCl (4 mL, pH ~4). The mixture was further diluted with ether (8 mL) and the two were layers separated. The aqueous layer was extracted with ether (10 x 10 mL) and the combined organic layers were washed (saturated $NaHCO_3$, 20 mL), dried (Na_2SO_4, 0.5 h with stirring), filtered and evaporated to an oil. To remove as much ether as possible from this diol, the oil was stirred (magnetic stir bar) overnight in pentane (15 mL). After decanting the pentane, the oil was subjected to high vacuum (≤ 0.3 mm) with warming (50-60°C, warm water bath, ca. 10 min) to give a diastereomeric mixture (ratio by ^1H NMR, ca. 1:1) of diol **124** as a pale yellow paste (0.16 g, 90%): IR (neat) 3050-3700 cm^{-1} (O-H); ^1H NMR ($DCCl_3$) δ 1.34 [s, C*H*$_3$], 1.42 and 1.43 [2 d, 2 x J = 6.4 Hz, 3 H, CHC*H*$_3$], 2.6-3.1 [br m, 2 H, CH_2O*H* and CH_3CHO*H*], 3.08 and 3.10 [2 d, 2 x J = 11.2 Hz, 1 H, SC(*H*)H], 3.366 and 3.370 [2 d, 2 x J = 11.2 Hz, 1 H, SCH(*H*)], 3.47 [d, J = 10.9 Hz, 1 H, C(*H*)HOH], 3.60 [d, J = 10.9 Hz, 1 H, CH(*H*)OH], 4.7-4.8 [m, 1 H, C*H*CH_3], 7.0-7.2 [m, 3 H, Ar-*H*]. In a separate sample from another reaction, the two protons of the two hydroxyl groups of this diol product appeared as one broad singlet (δ 2.2-2.6, 2 H); ^{13}C (NMR) ppm 22.40 and 22.44 [*C*H_3], 24.7 and 25.1 [CH*C*H_3], 42.0 [S*C*H_2], 52.61 and 52.59 [CH_2*C*CH_3], 67.3 [*C*H_2OH], 70.0 and 70.1 [CH_3*C*HOH]; Ar-*C* [120.7, 121.6, 122.2, 122.4, 125.2, 125.8, 140.86, 140.89, 141.9, 142.0, 143.8, 144.0]. The diastereomeric mixture of this diol was used without further purification.

[1-(2,3-Dihydro-3-methyl-3-benzo[*b*]thienmethanol-5-yl)ethyl]triphenylphosphonium Bromide (125)

In a 50-mL, single-necked, round-bottomed flask [equipped with a magnetic stir bar and N_2 inlet (positive pressure from an oil bubbler)] a solution of diol **124** (0.59 g, ca. 2.4 mmol assuming 92% purity) and Ph_3P•HBr (0.81 g, 2.4 mmol) in absolute methanol (18 mL) was stirred at room temperature for 15 h. Rotary evaporation with warming

(warm water bath at 50-60°C toward the end of the evaporation) gave a foam which solidified. The solid foam was scraped (spatula) from the sides of the flask and pulverized by stirring (stir bar) in dry ether (18 mL) under N_2 for 8 h. The mixture was then filtered (suction), and the white powder was rinsed with dry ether (50 mL). The powder was immediately subjected to high vacuum (≤ 0.1 mm) at room temperature for 12 h and at 77°C (Abderhalden, boiling EtOAc) for 1 h to give a diastereomeric mixture (ratio by ^1H NMR ca. 50:50) of salt **125** as a creamy white powder (1.31 g, 100%): mp 128-138°C; IR (KBr) 3100-3700 cm^{-1} (O-H); ^1H NMR ($DCCl_3$) δ 1.07 and 1.14 [2 s, 3 H, CH_3], 1.68-1.85 [m, 3 H, $CHCH_3$], 2.92 and 2.98 [2 d, 2 x J = 11 Hz, 1 H, SC(*H*)H], 3.34 and 3.44 [2 d, 2 x J = 11 Hz, 1 H, C(*H*)HOH], 3.53 and 3.59 [2 d, 2 x J = 11 Hz, 1 H, SCH(*H*)], 3.59 and 3.68 [2 d, 2 x J = 11 Hz, 1 H, CH(*H*)OH], 6.0-6.2 [m, 1 H, $CHCH_3$], 6.70 and 6.82 [2 m, 1 H, H(6)], 6.93 and 6.94 [2 d, 1 H, H(7)], 7.00 and 7.09 [2 m, 1 H, H(4)], 7.6-7.9 [m, 15 H, $P(C_6H_5)_3$]. The proton signal for the O-*H* appeared to be buried in the baseline between δ 1.8 and 2.8 (integration, 1 H). The diastereomeric mixture of this salt was used without further purification.

Methyl (*E*)-4-[2-(2,3-Dihydro-3-benzo[*b*]thien-methanol-5-yl)-1-propenyl]benzoate (65)

A solution of *n*-butyllithium in hexane (3.2 mL, 1.6 M, 5.1 mmol) was added (syringe, ca. 2 min) to a stirred mixture of salt **125** (2.30 g, 4.19 mmol) in dry THF (30 mL) in a 100-mL, three-necked, round-bottomed flask [equipped with a magnetic stirring bar, rubber septum, glass stopper and a N_2 inlet (positive pressure from an oil bubbler)]. The resulting dark red mixture was stirred under N_2 at RT for 50 min after which time more *n*-butyllithium in hexane (1.6 M, 0.5 mL, 0.8 mmol) was added (syringe). After stirring another 45 min (RT), the dark red Wittig reagent was cooled (ca. 5 min) in a liquid N_2/EtOAc bath (-84°C) followed by the addition of *p*-$OHCC_6H_4CO_2Me$ (0.72 g, 4.4 mmol) in dry THF (15 mL) over a period of about 5 min. The cold bath was removed and

the mixture was stirred (no external heating or cooling) for 11 h. After diluting with dry ether (20 mL) and quenching with saturated brine (25 mL) and 5% HCl (1.7 mL) to a pH of ca. 5, the mixture was transferred to a separatory funnel containing brine (25 mL). The reaction vessel was rinsed (ether, 80 mL). The combined organic layers were washed (saturated brine, 50 mL), dried (Na_2SO_4, > 24 h), and filtered. The crude product obtained by evaporation (rotovap) of the organic solution was purified by repeated chromatographic separations [column and centrifugal thin layer chromatography; hexanes:ether (1:1) provided the best separation of the components which included the (*E*)- and (*Z*)-isomers (R_f's = 0.23 and 0.29, respectively)] and repeated crystallizations and recrystallizations. The latter were generally effected by dissolving chromatographed material (often partially crystallized) or crystalline material (obtained after prior crystallization) in EtOAc (i.e. 2 mL/0.2 g) followed by the addition of *n*-pentane (i.e. 6 mL/0.2 g) and standing in an *n*-pentane bath (closed jar) with seeding. This method of crystallization was effective in providing crystalline material (i.e. mp 106-108.5°C) free of the (*Z*)-isomer but containing traces of pentane. Finally, recrystallization in hexanes (i.e. ca. 10 mL/0.1 g) followed by washing in slightly chilled hexanes and drying [wax chips, ≤ 0.5 mm, ≥ 1 h] gave ester **65**-(*E*) as white crystalline flakes (88 mg, 6%): mp 115.1-116.1°C; IR (KBr) 3150-3650 cm^{-1} (O-H), 1716 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.45 [s, 3 H, H(9)], 2.28 [d, $^4J_{HH}$ = 1 Hz, 3 H, H(11)], 3.21 [d, $^2J_{HH}$ = 11.2 Hz, 1 H, H(2)], 3.49 [d, $^2J_{HH}$ = 11.2 Hz, 1 H, H(2')], 3.64 [dd, $^2J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 5.6 Hz, 1 H, H(8)], 3.77 [dd, $^2J_{HH}$ = 10.9 Hz, $^3J_{HH}$ = 5.8 Hz, 1 H, H(8')], 3.93 [s, 3 H, H(20)], 6.80 [br s, 1 H, H(12), 7.21 [d, J = 2 Hz, 1 H, H(4)], 7.22 [d, J = 8 Hz, 1 H, H(7)], 7.34 [dd, J = 8 Hz, J = 2 Hz, 1 H, H(6)], 7.42 [d, J = 8.2 Hz, 2 H, H(14,18)], 8.04 [d, J = 8.2 Hz, 2 H, H(15,17)]; ^{13}C NMR ($DCCl_3$) ppm 17.8 [C(11)], 22.5 [C(9)], 42.1 [C(2)], 52.1 [C(20)], 52.7 [C(3)], 67.8 [C(8)], 121.3 [C(4)], 122.4 [C(7)], 126.1 [C(6) and C(12)], 129.0 [C(14,18)], 129.5 [C(15,17)], 167.0 [C(19)]; other quaternary carbons [127.9, 139.2, 140.1, 141.6, 143.0, 143.7]. A similar recrystallization in

hexanes (but with chilling during crystal formation) gave 5 mg of **65**, mp 107.8-108.8°C, the ^{1}H NMR spectral data of which was identical to that above except for the apparent absence of coupling to the hydroxyl proton. Furthermore, the IR spectra were very similar. When a small portion of the higher melting crystals were crushed with the lower melting solid, the resulting melting point (114.8-115.8°C) was higher than that observed for the sharp but lower melting solid. Possibly, two different crystalline forms of **65** exist. Anal. Calcd. for $C_{21}H_{22}O_3S$: C, 71.16; H, 6.26. Found: C, 71.45; H, 6.32. The mother liquors from the final recrystallization evaporated to an oil (8 mg) containing a mixture of the two isomers (*E* :*Z* ≈ 59:41).

The above chromatographic separations provided the (*Z*)-isomer as an oil (154 mg, 10%) containing a small amount of the (*E*)-isomer as an impurity [(*Z*):(*E*) molar ratio, 93:7 by integration of the ^{1}H NMR spectra]. The following spectral data is for the (*Z*)-isomer: ^{1}H NMR ($DCCl_3$) δ 1.21 [s, 3 H, H(9)], 2.20 [s, 3 H, H(11)], 3.09 [d, 1 H, H(2)], 3.35 [d, 1 H, H(2')], 3.43 [d, 1 H, H(8)], 3.54 [d, 1 H, H(8')], 3.84 [s, 3 H, H(20)], 6.46 [br s, 1 H, H(12)], 6.74 [d, 1 H, H(4)], 7.00 [d, 2 H, H(14,18)], 7.02 [dd, 1 H, H(6)], 7.13 [d, 1 H, H(7)], 7.77 [d, 2 H, H(15,17)], ^{13}C NMR ($DCCl_3$) ppm 22.1 [C(9)], 26.6 [C(11)], 41.7 [C(2)], 51.9 [C(20)], 52.5 [C(3)], 67.2 [C(8)], 122.5 {C(4)], 123.9 [C(7)], 125.6 [C(12)], 127.3 [C(6)], 128.8 [C(14,18], 129.1 [C(15,17)], 143.8 [C(7a)], 166.9 [C(19)]; other quaternary carbons [127.6, 137.2, 140.9, 141.2, 142.6].

Methyl (*E*)-4-[2-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)-3-hydroxy-1-propen-1-yl]-benzoate (66)

A mixture of heteroarotinoid **58** (0.200 g, 0.620 mmol), SeO_2 (0.208 g, 1.87 mmol), and 95% ethanol (15 mL) in a 25-mL, two-necked, round-bottomed flask [equipped with a magnetic stirring bar, two stacked condensers, glass stopper, and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler)] was stirred at

reflux 22 h. After allowing 1 h to cool (RT), the mixture was filtered (plug of glass wool) followed by an ether (5 mL) rinse (also filtered) of the reaction vessel. The resulting organic solution (containing the ether rinse) was concentrated (to ca. 0.5 mL) and rediluted with ether (30 mL), refiltered, and concentrated again. The residue was separated by centrifugal thin layer chromatography [Chromatotron on silica gel (1:1 hexanes:ether, 130 mL)]. One early fraction evaporated [1 atm (2-3 days), then ≤ 0.5 mm (RT) for 5 min] to a white crystalline solid [starting material (**58**), 139 mg (70%), mp 92.5-94.5°C (before reaction, pure **58** gave mp 96.8-97.8°C)]. Five fractions (total volume ≈ 30 mL) comprising the polar band [R_f = 0.31-0.35 (1:1 hexanes:ether)] evaporated (rotovap, then ≤ 0.3 mm at 55°C for 5 min) to an oil (43 mg, 20%, *trans*-aryl:*cis*-aryl ≈ 1:10) which partially crystallized on standing but which completely crystallized when hexanes were added. Crystallization of the solid from boiling hexanes gave the (*E*)-isomer **66** (*cis*-aryl) as a pale yellow solid [10 mg (mp 125.1-125.7°C), 15 mg (124.0-124.9°C), total = 25 mg (12%)]; IR (KBr) 3150-3600 cm^{-1} (O-H), 1717 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.23 [s, 6 H, H(8,9)], 1.6 [s, O-*H*], 3.87 [s, 3 H, H(20)], 4.25 [s, 2 H, H(2)], 4.49 [d, 2 H, H(11)], 6.68 [br s, 1 H, H(12)], 6.76 [d, 1 H, H(7)], 6.89 [fine d, 1 H, H(4)], 6.99 [dd, 1 H, H(6)], 7.07 [d, 2 H, H(14,18)], 7.79 [d, 2 H, H(15,17)]; ^{13}C NMR ($DCCl_3$) ppm 27.5 [C(8,9)], 41.8 [C(3)], 52.0 [C(20)], 68.1 [C(11)], 84.8 [C(2)], 110.0 [C(7)], 123.2 [C(4)], 124.8 [C(12)], 128.1 [C(6)], 129.1 and 129.2 [C(14,18) and C(15,17), 159.1 [C(7a)], 166.9 [C(19)]; other quaternary carbons [128.0, 129.8, 137.4, 141.8, 144.2]. Anal. Calcd. for $C_{21}H_{22}O_4$: C, 74.54; H, 6.55. Found: C, 74.58; H, 6.57.

2-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)-3-buten-2-ol (129)

To a freshly prepared solution of CH_2=CHMgBr [1.85 g (17.3 mmol) of CH_2=CHBr and 0.38 g (15.6 mmol) of Mg turnings, in dry THF (10 mL)] in a 50-mL,

three-necked, round-bottomed flask [equipped with a mechanical stirrer, addition funnel, dry ice condenser and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler)] was added (ca. 2 min) a solution of methyl ketone **81** (1.00 g, 5.26 mmol) in dry THF (5 mL). The mixture was heated at reflux (2 h) and at RT (2 h). After cooling (ice-water bath, 0°C, 10 min), the mixture was diluted (ether, 10 mL) and quenched (14 mL of saturated NH_4Cl, pH 6-7). The second dilution (ether, 10 mL) was followed by the separation of the two layers and then by the extraction of the aqueous layer (ether, 4 x 25 mL). The combined organic layers were washed [5% $NaHCO_3$ (2 x 25 mL), saturated brine (25 mL)], dried (Na_2SO_4, 1 h), filtered and evaporated [rotovap followed by high vacuum (≤ 0.5 mm, RT, 10 min)] to give alcohol **129** as a yellow oil (1.14 g, 99%) which was used without further purification: IR (neat) 3150-3650 (O-H); ^1H NMR ($DCCl_3$) δ 1.34 [s, 6 H, $C(CH_3)_2$], 1.64 [s, 3 H, $C(OH)CH_3$], 1.94 [br s, 1 H, O-*H*], 4.23 [s, 2 H, OCH_2], 5.13 [dd, J = 10.7 Hz, J = 1.0 Hz, 1 H, CH=C(*H*)H], 5.30 [dd, J = 17.2 Hz, J = 1.0 Hz, 1 H, CH=CH(*H*)], 6.16 [dd, J = 17.2 Hz, J = 10.7 Hz, 1 H, $CH=CH_2$], 6.73 [d, J = 8.3 Hz, 1 H, H(7)], 7.19 [dd, J = 8.3 Hz, J = 2.0 Hz, 1 H, H(6)], 7.24 [d, J = 2.0 Hz, 1 H, H(4)].

[3-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)-2-buten-1-yl]triphenylphosphonium Bromide (132)

A solution of alcohol **129** (0.80 g, 3.66 mmol) in CH_3OH (5 mL) was added dropwise to a stirred mixture of Ph3P•HBr (1.25 g, 3.64 mmol) and CH_3OH (5 mL) in a 25-ml, single-necked, round-bottomed flask equipped with a magnetic stir bar, an addition funnel and a N_2 inlet in the top of the addition funnel (positive pressure from an oil bubbler). A rinse (2 ml, CH_3OH) of the addition funnel was added to the mixture. The mixture (which became a solution during the addition of the alcohol **129** solution) was stirred at RT for 20 h and then concentrated to a thick oil which was transferred to a 150-mL beaker using 6 mL of CH_3OH to make the transfer complete. The addition of ether

(75 mL) caused the salt to precipitate, which was filtered (suction), washed with dry ether (50 mL) and recrystallized (CH_3OH/ether). The following procedure illustrates the technique used in this recrystallization method: the precipitate was dissolved in CH_3OH (ca. 10 mL) in a 50-mL beaker followed by the slow addition of dry ether (20 mL). The beaker was allowed to stand in an ether bath in a closed screw-top jar (< 0°C, overnight). The resulting crystals (which formed during the slow diffusion of ether vapor into the methanolic solution) were filtered, washed [dry ether (50 mL)] and dried (≤ 0.5 mm, RT, overnight) to afford salt **132** as white crystals (1.06 g, 54%): More salt **132** (0.158 g, mp 249.5-251°C, 7.9%) precipitated from the mother liquors during the above ether wash. The powder was filtered and dried (RT, ≤ 0.5 mm, overnight) which gave a total yield of salt **132** of 61%; mp 251.0-252.5°C. IR (KBr) 3043 cm^{-1} (Ar C-H); ^1H NMR ($DCCl_3$) δ 1.31 [s, 6 H, $C(CH_3)_2$], 1.59 [dd, $^5J_{HP}$ = 4.3 Hz, J_{HH} = 1 Hz, 3 H, $CH{=}CCH_3$], 4.21 [s, 2 H, OCH_2], 4.86 [dd, $^2J_{HP}$ = 15.1 Hz, J_{HH} = 7.8 Hz, 2 H, CH_2P], 5.56 [m, 1 H, $CH{=}CCH_3$], 6.67 [d, J = 8.3 Hz, 1 H, H(7)], 6.91 [dd, J = 8.3 Hz, J = 1.8 Hz, 1 H, H(6)], 6.95 [d, J = 1.8 Hz, 1 H, H(4)], 7.66-7.96 [m, 15 H, $P(C_6H_5)_3$]; ^{13}C NMR ($DCCl_3$) ppm (the following assignments are tentative) 17.2 [d, $^4J_{CP}$ = 2.9 Hz, $CH{=}CCH_3$], 25.6 [d, $^1J_{CP}$ = 49.5 Hz, CH_2P], 27.5 [$C(C_3)_2$], 41.9 [$C(CH_3)_2$], 84.9 [OCH_2], 109.3 [C(7)], 109.5 [d, $^2J_{CP}$ = 10.5 Hz, $C{=}CHCH_2P$], 118.3 [d, $^1J_{CP}$ = 85.2 Hz, *orthogonal*-C's of $(C_6H_5)_3$], 120.0 [d, $^5J_{CP}$ = 2.3 Hz, C(4)], 125.7 [d, $^5J_{CP}$ = 2.5 Hz, C(6)], 130.4 [d, $^3J_{CP}$ = 12.4 Hz, *meta*-C's of $P(C_6H_5)_3$], 134.0 [d, $^2J_{CP}$ = 9.8 Hz, *ortho*-C's of $P(C_6H_5)_3$], 135.0 [d, $^4J_{CP}$ = 2.5 Hz, *para*-C's of $P(C_6H_5)_3$], 135.2 [d, $^4J_{CP}$ = 3.9 Hz, C(5)], 136.9 [C(3a)], 145.6 [d, $^3J_{CP}$ = 13.5 Hz, $C{=}CHCH_2P$]. The salt was used without further purification.

(2*E*,4*E*,6*E*)-7-(2,3-Dihydro-3,3-dimethyl-5-benzofuranyl)-3-methyl-2,4,6-octatrienoic Acid (67)

To a stirred suspension of salt **132** (1.50 g, 2.76 mmol) in dry ether (20 mL) in a 50-mL, three-necked, round-bottomed flask [equipped with an air condenser, magnetic stirring bar, glass stopper, rubber septum, and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler)] was added (1-2 min, syringe) a solution of *n*-butyllithium in hexanes (1.6 M, 1.9 mL, 3.0 mmol) in near darkness (at night). The resulting black-red mixture was stirred at RT (15 min) and then in a dry ice-acetone bath (-78°C, 15 min) followed by the addition of (ca. 2 min) a solution of (*E*)-OHC-$C(CH_3)$=$CHCO_2Et$ (~ 90%, 1.22 g, ~ 7.7 mmol) in dry ether (5 mL) at -78°C. After removing the cold bath, the mixture was allowed to stir (no external heat/cooling) for 46 h. Hexanes:ether (3:1, 25 mL) was added to the mixture and the mixture was stirred for 15 min and then filtered (suction). The remaining pad [presumably mostly $Ph_3P(O)$] was extracted (1:1 hexanes:ether, 30 mL) and the extract was also filtered (suction) followed by a rinse (suction, 5 mL of ether) of the solid. The combined filtrates were evaporated to an oil which was separated [to remove baseline material, i.e. residual $Ph_3P(O)$] by radial thin layer chromatography (Chromatotron) using silica gel (4 mm plate, 20:1 hexanes:ether, 100 mL). The single moving band [no separation of isomers R_f = 0.28 (20:1 hexanes:ether) for both isomeric esters] was collected as a single fraction which was evaporated (rotovap, then ≤ 0.5 mm at ≤ 50°C for 5 min) to an oil (0.46 g, 51%) containing a mixture of two isomeric esters [(2*E*,4*E*,6*E*):(2*E*,4*Z*,6*E*) ≈ 2.5:1]. The mixture of esters and aqueous 35% KOH (1.5 mL) was heated at reflux in absolute EtOH (6 mL) in a 25-mL, single-necked, round-bottomed flask [equipped with a magnetic stirring bar, water condenser, and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler)] for 1 h. After cooling (RT, 30 min), the mixture was diluted with

H_2O (10 mL) and EtOAc (35 mL) and quenched with AcOH/H_2O (1:1, 2 mL). Two layers separated and the aqueous layer was extracted (EtOAc, 25 mL). The combined organic layers were dried (Na_2SO_4, > 24 h), filtered, and evaporated (rotovap, then ≤ 0.5 mm for 10 min) to a yellow solid. Recrystallization in absolute ethanol (5 mL) followed by rinsing [chilled ethanol (~ 5 mL) and RT hexanes (10 mL)] and drying [wax chips, ≤ 0.5 mm, 8 h] gave heteroarotinoid **67** with the (2*E*,4*E*,6*E*)-configuration as bright yellow plates, 186 mg (23% from salt): mp 204.0-205.2°C; IR (KBr) 2300-3250 cm^{-1} (CO_2H), 1674 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.37 [s, 6 H, H(8,9)], 2.25 [d, J = 1 Hz, 3 H, H(11)], 2.40 [d, J = 1 Hz, 3 H, H(16)], 4.27 [s, 2 H, H(2)], 5.83 [br s, 1 H, H(17)], 6.40 [d, J = 14.9 Hz, 1 H, H(14)], 6.54 [d, J = 11 Hz, 1 H, H(12)], 6.77 [d, J = 8.3 Hz, 1 H, H(7)], 7.08 [dd, J = 14.9 Hz, J = 11 Hz, 1 H, H(13)], 7.24 [d, J = 2 Hz, 1 H, H(4)], 7.28 [dd, J = 8.3 Hz, J = 2 Hz, 1 H, H(6)]; ^{13}C NMR ($DCCl_3$) ppm 14.1 [C(16)], 16.6 [C(11)], 27.6 [C(8,9)], 41.9 [C(3)], 84.9 [C(2)], 109.4 [C(7)], 117.5 [C(17)], 119.7 [C(4)], 124.9 [C(12)], 126.0 [C(6)], 132.3 [C(13)], 134.8 [C(3a)], 135.3 [C(14)], 136.9 [C(5)], 140.9 [C(10)], 155.4 [C(15)], 159.3 [C(7a)], 172.1 [C(18)]. Anal. Calcd. for $C_{19}H_{22}O_3$: C, 76.48; H, 7.43. Found: C, 76.07; H, 7.55. Both ^1H NMR and elemental analysis indicate a non-stoichiometric amount of ethanol (trace, ca. 1/20th of an equivalent by ^1H NMR integration).

2-(2,3-Dihydro-3,3-dimethylbenzo[*b*]thien-5-yl)-
3-buten-2-ol (130)

To a freshly prepared solution of CH_2=CHMgBr [3.5 g (33 mmol) of CH_2=CHBr and 0.70 g (29 mmol) of Mg turnings in dry THF (25 mL)] in a 100-mL, three-necked, round-bottomed flask [equipped with a magnetic stir bar, addition funnel, dry ice condenser and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler)] was added a solution of methyl ketone **88a** (2.00 g, 9.69 mmol) in dry THF (20 mL) over a period of 15 min. The resulting mixture was stirred at room temperature for 3

h and at reflux for 1 h. After cooling (water bath, then ice-water bath), the reaction mixture was cautiously quenched (pH 8-8.5) by the dropwise addition of saturated NH_4Cl (50 mL). The two layers were separated, and the aqueous layer was extracted (ether, 4 x 25 mL). The combined organic layers were washed [5% $NaHCO_3$ (50 mL), saturated brine (50 mL)], dried (Na_2SO_4, overnight), filtered (suction) and evaporated [rotovap, then high vacuum (≤ 0.5 mm, RT, ca. 5 min)] to a yellow oil (2.35 g, 103%): R_f = 0.49 (4:1 hexanes:ether); IR (neat) 3150-3600 cm^{-1} (O-H); ^1H NMR ($DCCl_3$) δ 1.35 [s, 6 H, $C(CH_3)_2$], 1.60 [s, 3 H, CH_3], 2.32 [br s, 1 H], 3.15 [s, 2 H, SCH_2], 5.11 [dd, J_{cis} = 10.6 Hz, J_{gem} = 1.1 Hz, 1 H, CH=C(*H*)H], 5.26 [dd, J_{trans} = 17.2, J_{gem} = 1.1 Hz, 1 H, CH=CH(*H*)], 6.12 [dd, J_{trans} = 17.2 Hz, J_{cis} =10.6 Hz, 1 H, $CH=CH_2$], 7.08-7.22 [m, 3 H]; ^{13}C NMR ($DCCl_3$) ppm 27.3 [$C(CH_3)_2$], 29.3 [CH_3], 47.2 [$C(CH_3)_2$], 47.3 [SCH_2], 74.6 [CH_3COH]; aromatic and vinyl carbons [112.2, 119.5, 121.9, 124.6, 139.0, 143.1, 144.8, 147.9]. This allylic alcohol was used without further purification.

[3-(2,3-Dihydro-3,3-dimethylbenzo[*b*]thien-5-yl)
-2-buten-1-yl]triphenylphosphonium
Bromide (133)

A solution of allyl alcohol **130** (2.00 g, 8.53 mmol) in CH_3OH (8 mL) was added dropwise to a stirred and cooled (0-5°C, ice water bath) mixture of Ph_3P•HBr (2.90 g, 8.45 mmol) in CH_3OH (10 mL) in a 100-mL, two-necked, round-bottomed flask equipped with a condenser, magnetic stir bar, additional funnel and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler). The addition funnel was rinsed (CH_3OH, 2 mL), and the rinse was added to the mixture. A light blue-green solution formed which, after stirring 14 h (RT), was bright yellow. The mixture was concentrated to about 7 mL, and transferred to a beaker (a 1 mL CH_3OH rinse was used to aid in the transfer). The addition of dry ether (60 mL) with scratching (glass rod) caused the salt to solidify. The solid was broken up. The addition of more dry ether (40 mL) caused the

supernatant liquid to become more cloudy. The mixture was filtered (suction) and the light yellow powder was washed with dry ether (70 mL). Recrystallization of the salt was achieved in the following manner: the powder was dissolved in CH_3OH (ca. 4 mL) in a 100-mL beaker which was then placed in an ether bath in a closed screw-top jar. After several hours, the slow diffusion of ether vapor caused a crop of crystals to form which were filtered, washed (ether:methanol 9:1), crushed, and then dried (high vacuum, ≤ 0.3 mm, P_2O_5, overnight) to give salt **133** as a white crystalline powder (3.53 g, 74.7%): mp 236-238°C; IR (KBr) 1362, 1381 cm^{-1} (*gem*-dimethyl C-H bend); ^1H NMR ($DCCl_3$) δ 1.32 [s, H, $C(CH_3)_2$], 1.61 [dd, $^5J_{HP}$ = 4.4 Hz, J = 1 Hz, 3 H, $CH_3C{=}CHCH_2P$], 3.14 [s, 2 H, SCH_2], 4.91 [dd, $^3J_{HP}$ = 15.2 Hz, J = 8.0 Hz, 2 H, CH_2P], 5.55-5.65 [m, 1 H, $CH_3C{=}CHCH_2P$], 6.85 [d, J = 1.8 Hz, 1 H, H(4)], 6.90 [dd, J = 8.0 Hz, J = 1.8 Hz, 1 H, H(6)], 7.06 [d, J = 8.0 Hz, 1 H, H(7)], 7.6-8.0 [m, 15 H, $P(C_6H_5)_3$]; ^{13}C NMR ($DCCl_3$) ppm 17.1 [d, J_{CP} = 3.0 Hz, CH_3CHP], 25.5 [d, J_{CP} = 49.3 Hz, CH_2P], 27.3 [C(8,9)], 47.2 and 47.4 [C(2) or C(3)], 110.5 [d, J_{CP} = 11.5 Hz, $CHCH_2P$], 117.7 [d, J_{CP} = 85.2 Hz, *orthogonal*-C's of $P(C_6H_5)_3$], 120.2 [d, J_{CP} = 2.2 Hz, Ar-*C*], 122.1 [Ar-*C*], 125.0 [d, J_{CP} = 2.5 Hz, Ar-*C*], 130.4 [d, J_{CP} = 12.6 Hz, *meta*-C's of $P(C_6H_5)_3$], 134.0 [d, J_{CP} = 9.8 Hz, *ortho*-C's of $P(C_6H_5)_3$], 135.1 [d, J_{CP} = 2.7 Hz, *para*-C's of $P(C_6H_5)_3$, 138.9 [d, J_{CP} = 3.8 Hz, Ar-*C*], 140.8 [Ar-*C*], 145.5 [d, J_{CP} = 13.8 Hz, *C*=CH], 148.3 [C(3a)]. Anal. Calcd for $C_{32}H_{32}SBrP$: C, 68.69; H, 5.76. Found: C, 68.85; H, 5.86.

(2*E*,4*E*,6*E*)-7-(2,3-Dihydro-3,3-dimethylbenzo-[*b*]thien-5-yl)-3-methyl-2,4,6-octatrienoic Acid (68)

A solution of *n*-butyllithium (1.6 M, 3.4 mL, 5.4 mmol) in hexane was added (syringe, ca. 3-4 min) to a stirred suspension of salt **133** (3.00 g, 5.35 mmol) in dry ether (36 mL) in a 100-mL, two-necked, round-bottomed flask equipped with a magnetic

stirring bar, rubber septum, condenser and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler). After stirring (near darkness) at room temperature (15 min), the Wittig reagent (dark brown) was cooled in a dry ice-acetone bath (-78°C, 55 min) and then (continued cooling at -78°C) a solution of ethyl (*E*)–OHC–$C(CH_3)$=$CHCO_2Et$ (~ 90%, 0.76 g, ~ 5.35 mmol) in dry ether (10 mL) was added dropwise (ca. 5 min). The dry ice-acetone bath was removed and the reaction mixture (wrapped in aluminum foil to prevent entrance of light) was stirred at RT for 45 h. After the addition of hexanes (30 mL), the mixture was filtered (suction) and the remaining pad (presumably $Ph_3P\rightarrow O$) was stirred in 1:1 hexanes:ether (40 mL). The solid was filtered followed by an ether rinse (ca. 5 mL). The combined filtrates [TLC on silica gel indicated the presence of two yellow spots (R_f's = 0.34 and 0.42, 20:1 hexanes:ether)] were concentrated (rotovap) to an oil which was purified by column (1.8 x 72 cm) chromatography on silica gel packed in 20:1 hexanes:ether. Separation was effected using 20:1 hexanes:ether (550 mL). Those fractions containing only the (2*E*,4*E*,6*E*)-isomer (**137**, R_f = 0.34) were kept separate from the fractions containing only the (2*E*,4*Z*,6*E*)-isomer (**138**, Rf = 0.42) while the fractions containing mixtures of **137** and **138** were concentrated to an oil the two components of which were separated by preparative TLC on silica gel (20:1 hexanes:ether). All the fractions containing the component of R_f = 0.34 were evaporated (rotovap, then ≤ 0.5 mm at RT for 5 min) which gave ester **137** as a yellow oil (0.667 g, 36.3%), while the fractions containing the component of R_f = 0.42 evaporated to give ester **138** as a yellow oil (0.208 g, 11.3%). Isomer **137**, containing a trace of **138** (ca. 4% by ^1H NMR integration) was used without further purification. A mixture of ester **137** (0.665 g, 1.94 mmol) and 35% aqueous KOH (2.0 mL) in absolute ethanol (8 mL) was stirred at reflux (dark) for 1 h [in a 50-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar, water condenser, and a N_2 inlet (positive pressure from an oil bubbler in top of condenser)] and then allowed to cool (RT, 30 min). The mixture was diluted with EtOAc (110 mL) and H_2O (10 mL) followed by

quenching with 50% aqueous AcOH (2.5 mL). After separating the layers, the aqeous layer was extracted (EtOAc, 25 mL). The combined organic layers were dried (Na_2SO_4, 40 h), filtered, and evaporated (rotovap, then ≤ 0.5 mm at RT for 15 min) to a yellow solid. Recrystallization in boiling absolute ethanol (ca. 30 mL) followed by filtration of the crystals, washing [chilled absolute ethanol (20 mL), hexanes (20 mL)] and drying [wax chips, ≤ 0.5 mm, RT, 18 h] gave free acid **68** as golden yellow flakes (0.395 g, 65% from ester **137**, 23.4% from salt **133**), mp 211-212°C. Another 29 mg (6.1%) of acid **68** (mp 209.5-210.7°C) was obtained by recrystallization (absolute ethanol, 2 mL) of the solid residue from the evaporation of the mother liquors. Total yield of **68**: 70% (from **137**), 25% (from salt **133**); IR (KBr) 1683 cm^{-1} (CO_2H); ^1H NMR ($DCCl_3$) δ 1.40 [s, 6 H, H(8,9)], 2.24 [s, 3 H, H(11)], 2.39 [s, 3 H, H(16)], 3.20 [s, 2 H, H(2)], 5.85 [br s, 1 H, H(17)], 6.41 [d, J = 14.9 Hz, 1 H, H(14)], 6.56 [d, J = 11.3 Hz, 1 H, H(12)], 7.06 [dd, J = 14.9 Hz, J = 11.2 Hz, 1 H, H(13)], 7.13-7.28, [m, 3 H, H(4,6,7)]; ^{13}C NMR ($DCCl_3$) ppm 14.1 [C(16)], 16.5 [C(11)], 27.4 [C(8,9)], 47.2 [C(3)], 47.5 [C(2)], 117.5 [C(17)], 119.9 [C(4)], 122.2 [C(7)], 125.2 [C(6)], 125.6 [C(12)], 132.1 [C(7a)] and C(13)], 135.4 [C(14)], 139.0 [C(5)], 140.7 [C(10)], 148.2 [C(3a)], 155.2 [C(15)], 171.2 [C18)]. Anal. Calcd for $C_{19}H_{22}O_2S$: C, 72.58; H, 7.05. Found: C, 72.22; H, 6.85. The isomeric ester (**138**, an oil) was used without further purification in the saponification to acid **69**.

(2*E*,4*Z*,6*E*)-7-(2,3-Dihydro-3,3-dimethylbenzo[*b*]-thien-5-yl)-3-methyl-2,4,6-octatrienoic Acid (69)

A mixture of ester **138** (0.32 g, 0.93) and aqueous 35% KOH (1 mL) in absolute ethanol was stirred at reflux (1 h) in a 25-mL, single-necked, round-bottomed flask [equipped with a magnetic stirring bar, condenser, and a N_2 inlet (positive pressure from an oil bubbler in the top of the condenser)]. After cooling (RT, ca. 10 min), the slightly warm mixture was quenched [50% AcOH until no more precipitation occurred, pH 5.9]

and diluted with H_2O (10 mL) and EtOAc (20 mL). The layers were separated. The organic layer was then dried (Na_2SO_4, ca. 1 h), evaporated (rotovap, then ≤ 0.5 mm at RT for 15 min) to a yellow solid. Recrystallization in boiling absolute ethanol (ca. 10 mL), followed by filtration, washing of crystals [chilled ethanol (ca. 5 mL), hexanes (ca. 10 mL)] and drying (≤ 0.5 mm, RT, 3 h) gave isomeric free acid **69** [63 mg, 21%], mp 140-141°C; IR (KBr) 1678 cm^{-1} (CO_2H); ^1H NMR ($DCCl_3$) δ 1.39 [s, 6 H, H(8,9)], 2.20 [d, J = 1.1 Hz, 3 H, H(11)], 2.38 [d, J = 1.3 Hz, 3 H, H(16)], 3.19 {s, 2 H, H(2)], 5.93 [br s, 1 H, H(17)], 5.98 [d, J = 11.7 Hz, 1 H, H(14)], 6.61 [dd, J = 11.8 Hz, J = 11.7 Hz, 1 H, H(13)], 6.92 [d, J = 11.8 Hz, 1 H, H(12)], 7.12 [d, J = 1.8 Hz, 1 H, H(4)], 7.16 [d, J = 8.2 Hz, 1 H, H(7)], 7.23 [dd, J = 8.2 Hz, J = 1.8 Hz, 1 H, H(6)]; ^{13}C NMR ($DCCl_3$) ppm 16.1 [C(11)], 19.6 [C(16)], 27.4 [C(8,9)], 47.2 [C(3)], 47.5 [C(2)], 118.5 [C(17)], 120.1 [C(4)], 122.2 and 122.3 [C(7) or C(12)], 125.3 [C(6)], 130.0 [C(14)], 131.5 [C(7a)], 139.5 [C(5)], 140.5 [C(13)], 140.9 [C(10)], 148.2 [C(3a)], 156.1 [C(15)], 171.4 [C(18)]. Anal. Calcd for $C_{19}H_{22}O_2S$: C, 72.58; H, 7.05. Found: C, 72.21, H, 7.19.

2-(1,3-Benzodioxol-5-yl)-3-buten-2-ol (131)

To a cooled (0-5°C, ice water bath) and freshly prepared solution of CH_2=CHMgBr [4.9 g (46 mmol) of CH_2=CHBr and 0.90 g (37 mmol) of magnesium turnings, in dry THF (25 mL) in a 200-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar, glass stopper, addition funnel, dry ice condenser and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler)] was added dropwise (ca. 30 min) a solution of methyl ketone **128** (2.00 g, 12.2 mmol) in dry THF (35 mL). After removing the cold bath, the resulting mixture was stirred at room temperature for 1 h. The mixture was cooled again (0°C, ice water bath), the mixture was cautiously quenched by the slow addition (*very* slow initially) of water (40 mL). The mixture was diluted with ether (100 mL) and two layers separated. The aqueous layer was extracted with ether (2 x 25 mL)

and CH_2Cl_2 (2 x 25 mL) and all the organic layers were combined, dried (Na_2SO_4, overnight), filtered, and evaporated [rotovap followed by high vacuum (≤0.5 mm)] to a yellow oil (2.32 g, 99%): R_f = 0.37 (5:1 hexanes:ether); IR (neat) 3150-3650 cm^{-1} (O-H); ^1H NMR ($DCCl_3$) δ 1.59 [s, 3 H, CH_3], 2.25 [br s, 1 H, O*H*], 5.11 (dd, J_{cis} = 10.5 Hz, J_{gem} = 1 Hz, 1 H, CH=C(*H*)H], 5.27 [dd, J_{trans} = 17.3 Hz, J_{gem} = 1 Hz, 1 H, CH=CH(*H*)], 5.91 [s, 2 H, CH_2O], 6.10 [dd, J_{trans} = 17.3 Hz, J_{cis} = 10.5 Hz, 1 H, $CH=CH_2$], 6.74 [d, J = 8.2 Hz, 1 H, H(7)], 6.91 [dd, J = 8.2 Hz, J = 1.8 Hz, 1 H, H(6)], 6.6 [d, J = 1.8 Hz, 1 H, H(4)]; ^{13}C NMR ($DCCl_3$) ppm 29.3 [CH_3], 74.6 [CH_3COH], 100.9 [OCH_2O]; aromatic and vinyl carbons [106.4, 107.7, 112.2, 118.3, 140.7, 144.8, 146.4, 147.4]. This alcohol was used without further purification.

[3-(1,3-Benzodioxol-5-yl)-2-buten-1-yl]triphenylphosphonium Bromide (134)

A solution of allyl alcohol **131** (2.41 g, 12.5 mmol) and Ph_3P•HBr (4.30 g, 12.5 mmol) in CH_3OH (30 mL) was stirred at room temperature for 11 h. After concentrating (rotovap) the mixture, the resulting oil was transferred to a beaker (500 mL) with the aid of a CH_3OH rinse (10 mL) followed by the addition of dry ether (250 mL). The resulting precipitate was filtered, washed (dry ether, 100 mL) and dried (≤ 0.5 mm, 2 h). The solid was recrystallized in $CHCl_3$ with the diffusion of ether vapor by the method described in the preparation of salt **132**. This gave salt **134** as a light tan solid (5.32 g, 82%): mp 226.5-227.2°C (dec); IR (KBr) 1444, 1501 cm^{-1} (ArC=C); ^1H NMR ($DCCl_3$) δ 1.60 [d, 3 H, CH_3], 4.87 [dd, J_{HP} = 15 Hz, J_{HH} = 8 Hz, 2 H, CH_2P], 5.57 [m, 1 H, C=C*H*], 5.93 [s, 2 H, OCH_2O], 6.6-6.8 [m, 3 H, H(4,6,7)], 7.65-8.0 [m, 15 H, $P(C_6H_5)_3$]; the following ^{13}C NMR assignments are tentative: ^{13}C NMR ($DCCl_3$) ppm 17.1 [d, $^4J_{CP}$ = 2.6 Hz, CH_3], 25.4 [d, $^1J_{CP}$ = 49.9 Hz, CH_2P], 101.2 [OCH_2O], 106.2 [C(4) or C(7)], 108.1 [C(4) or C(7)], 110.3 [d, $^2J_{CP}$ = 10.4 Hz, C=*C*H], 118.1 [d, $^1J_{CP}$ = 85.3 Hz,

orthogonal-C's in $P(C_6H_5)_3$], 119.4 [d, $^5J_{CP}$ = 2.6 Hz, C(6)], 130.4 [d, $^3J_{CP}$ = 12.4 Hz, *meta-C*'s in $P(C_6H_5)_3$], 133.9 [d, $^2J_{CP}$ = 9.7 Hz, ortho-*C*'s in $P(C_6H_5)_3$], 135.2 [*para-C*'s in $P(C_6H_5)_3$], 136.4 [d, $^4J_{CP}$ = 3.8 Hz, C(5)], 145.1 [d, $^3J_{CP}$ = 13.5 Hz, C(8)], 147.7 [C(3a)], 147.4 [C(7a)]. This salt was used without further purification.

Ethyl (2*E*,4*E*,6*E*)-7-(1,3-Benzodioxol-5-yl)-3-methyl-2,4,6-octatrienoate (70)

A solution of *n*-butyllithium (1.6 M, 3.7 mL, 5.9 mmol) in hexane was added slowly (ca. 2 min, syringe) to a stirred suspension of salt **134** (3.00 g, 5.8 mmol) in dry ether (40 mL) in a 100-mL, three-necked, round-bottomed flask equipped with a magnetic stir bar, condenser, glass stopper, rubber septum, and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler). The resulting black-brown mixture was stirred at room temperature for 35 min. After replacing the glass stopper with an addition funnel, the Wittig reagent was cooled (5 min) in a dry ice-acetone bath (-78°C), and a solution of (*E*)-β-formylcrotonate (0.82 g, 5.8 mmol) in dry ether (10 mL) was added dropwise (ca. 5 min). The dry ice-acetone bath was removed, and the mixture was allowed to stir at ambient temperature for 6 h. Hexanes (20 mL) were added dropwise to the stirred mixture. The resulting mixture was filtered and the powder on the filter paper was washed with 1:1 hexanes:ether (10 mL) and finally with hexanes (10 mL). The combined filtrate and washes were filtered again and concentrated (rotovap) to about 10 mL. After standing a few minutes at room temperature, crystals formed in the concentrate. The supernatant liquid was removed (Pasteur pipette) and the crystals were washed with cold hexanes (10 mL). Traces of solvent were removed [high vacuum (≤ 0.3 mm), RT, overnight] which gave *all-trans* ester **70** (0.25 g, 14%) as pale yellow fine needles: mp 70.0-70.5°C; IR (KBr) 1698 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.29 [t, J = 7.1 Hz, 3 H, H(18)], 2.20 [d, J = 1.3 Hz, 3 H, H(9)], 2.37 [d, J = 1.3 Hz, 3 H, H(14)], 4.18 [q, J = 7.1 Hz, 2 H, H(17)], 5.80 [br s, 1 H, H(15)], 5.96 [s, 2 H, H(2)], 6.35 [d, J = 15.1 Hz, 1 H, H(12)],

6.49 [multiplet of a doublet, J = 11.1 Hz, H(10)], 6.79 [m, 1 H, H(7)], 6.94-7.05 [m, 3 H, H(4,6,11)- contained a dd for H(11) (J = 15.1 Hz, J = 11.1 Hz) which was partially masked by H(4) and H(6)], for a more thorough discussion of data obtained by "COSY", 2-D HETCOR, and radiation experiments (see discussion of spectra); ^{13}C NMR ($DCCl_3$) ppm 13.8 [C(14), 14.4 [C(18)], 16.6 [C(9)], 59.7 [C(17)], 101.2 [C(2)], 106.1 [C(4)], 108.1 [C(7)], 118.8 [C(15)], 119.6 [C(6)], 125.8 [C(10)], 131.1 [C(11)], 135.7 [C(12)], 167.2 [C(16)], *quaternary-C* [136.9, 139.5, 147.3, 147.8, 152.6]. Anal. Calcd for $C_{18}H_{20}O_4$: C, 71.98; H, 6.71. Found: C, 72.27; H, 6.71.

(2*E*,4*E*,6*E*)-7-(1,3-Benzodioxol-5-yl)-3-methyl-2,4,6-octatrienoic Acid (71)

A mixture of heteroarotinoid ester **70** (140 mg, 0.466 mmol), absolute ethanol (2 mL) and aqueous 35% KOH (0.5 mL) were stirred at reflux (dark) in a 5-mL, single-necked, round-bottomed flask [equipped with a magnetic stirring bar, water condenser, and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler)] for 1 h. After allowing the mixture to cool (RT, ca. 15 min), H_2O (5 mL) EtOAc (50 mL), and AcOH/H_2O (1:1, 0.8 mL) were added to the mixture. Two clear layers separated. The aqueous layer was extracted with EtOAc (10 mL) and the combined organic layers were dried (Na_2SO_4, two days), filtered, and evaporated (rotovap) to a yellow solid. Recrystallization in absolute ethanol (3 mL) gave a bright yellow powder which was rinsed [chilled absolute EtOH (5 mL), hexanes (5 mL)] and dried [wax chips, ≤ 0.5 mm, RT, 8 h] to give free acid **71** as a bright yellow powder [86 mg, 68%]: mp 199.5-200.0°C; IR (KBr) 2300-3150 cm^{-1} (CO_2H), 1680 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) 2.21 [s, 3 H, H(9)], 2.39 [s, 3 H, H(14)], 5.83 [s, 1 H, H(15)], 6.39 [d, J = 15.0 Hz, 1 H, H(12)], 6.51 [d, J = 11.1 Hz, 1 H, H(10)], 6.80 [m, 1 H, H(7)], 6.95-7.12 [m, 3 H, H(4,6,11) with a dd (J = 15.0 Hz and J = 11.1 Hz) at δ 7.05 for H(11)]; ^{13}C NMR ($DCCl_3$) ppm 14.1 [C(14), 16.6 [C(9)], 101.2 [C(2)], 106.1 [C(4)], 108.1 [C(7)], 117.5

[C(15)], 119.7 [C(6)], 125.7 [C(10)], 132.0 [C(11)], 135.4 [C(12)], 136.8 [C(5)], 140.3 [C(8)], 147.4 [C(3a) or C(7a)], 147.9 [C(3a) or C(7a)], 155.2 [C(13)], 170.7 [C(16)]. Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.57; H, 5.92. Found: C, 70.26; H, 5.81.

Methyl Phenoxyacetate (73)

A solution of concentrated H_2SO_4 (2.0 mL, 3.7 g, 0.037 mol) in dry CH_3OH (100 mL) was added dropwise to a stirred solution of phenoxyacetate acid (**72**, 20.03 g, 0.132 mol) in dry CH_3OH (100 mL) in a 500-mL, three-necked, round-bottomed flask equipped with an addition funnel, magnetic stirring bar, glass stopper, a Soxhlet extractor filled with molecular sieve 3A (containing enough dry CH_3OH so as to just cover the sieves), a N_2 inlet in the top of the funnel, a condenser joined to the top of the extractor and a N_2 outlet ($CaCl_2$ tube) in the top of the condenser. The resulting solution was heated at reflux for 11 h after which time the mixture was allowed to cool and was then neutralaized (Na_2CO_3, powder). The reaction mixture was filtered (suction) and evaporated (rotovap) to a wet solid (probably contained sodium salts) which was partitioned between H_2O (70 mL) and H_2CCl_2 (70 mL). After separating the two layers, the aqueous layer was extracted (H_2CCl_2, 2 x 50 mL), and the combined organic layers were washed [5% $NaHCO_3$ (80 mL), brine (ca. 120 mL)], dried (Na_2SO_4), filtered (celite, suction), and evaporated (rotovap) to an oil (19.9 g). Vacuum distillation gave ester **73** as a colorless oil (17.50 g, 80.0%): bp 107-110°C/3.75 mm (lit[89] bp 140°C/10 mm); $n^{29.0} = 1.5107$; IR (neat) 1746, 1765 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 3.78 [s, 3 H, OC*H*$_3$], 4.64 [s, 2 H, OC*H*$_2$], 6.92 [d, 2 H, Ar-*H*], 7.00 [t, 2 H, Ar-*H*], 7.30 [t, 2 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 52.1 [O*C*H$_3$], 65.1 [O*C*H$_2$], 169.3 [*C*=O]; Ar-*C* [114.5, 121.7, 129.5, 157.7].

2-Methyl-1-phenoxy-2-propanol (74)

To a freshly prepared solution of CH_3MgI [8.0 mL (18 g, 0.13 mol) of CH_3I and 2.63 g (0.108 mol) of Mg turnings, in dry ether (70 mL)] in a 300-mL, three-necked,

round-bottomed flask [equipped with a mechanical stirrer, two stacked condensers, a N_2 inlet and a N_2 outlet (drying tube, $CaCl_2$)] was added (ca. 15 min) a solution of ester **73** (5.99 g, 0.036 mol) in dry ether (40 mL). The resulting grey mixture was stirred at reflux for 20.7 h, cooled (ice-water bath, 0°-6°C) and quenched by the slow addition of saturated NH_4Cl (ca. 6 mL) and then water (20 mL). The resulting mixture was further quenched (no ice-water bath) with water (22 mL) and saturated NH_4Cl (7 mL). The ether layer was decanted, dried ($MgSO_4$, a few days) and evaporated (rotovap) to a nearly colorless oil (1.20 g, 20%). More alcohol **74** was obtained in the following manner: the remaining aqueous layer was further treated with saturated NH_4Cl (13 mL) and H_2O (70 mL), and suspended solid was broken up with a glass rod. The water layer was filtered (Buchner funnel used without filter paper to remove large pieces of solid) and extracted (ether, 3 x 75 mL). The combined ether extracts were washed [5% $NaHCO_3$ (2 x 100 mL), H_2O (2 x 100 mL)], dried ($MgSO_4$, overnight), filtered and evaporated (rotovap) to a dark reddish oil (4.54 g, 76%); total yield of alcohol **74** was 5.74 g (96%). Crude alcohol **74** was used without futher purification: IR (neat) 3120-3700 cm^{-1} (O-H); ^1H NMR ($DCCl_3$) δ 1.34 [s, 6 H, $C(CH_3)_2$], 2.36 [br s, 1 H, O-*H*], 3.81 [s, 2 H, OCH_2], 6.90-7.02 [m, 3 H, Ar-H], 7.31 [t, 2 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 26.1 [$C(CH_3)_2$], 70.0 [OCH_2], 75.8 [*C*OH]; Ar-*C* [114.5, 121.0, 129.4, 158.7].

Attempted Preparation of 2,3-Dihydro-3,3-dimethyl-benzofuran (75) by an Acid-catalyzed (H_3PO_4/P_2O_5) Cyclization of Alcohol 74

To a cooled (ice bath) solution of alcohol **74** (2.02 g, 0.012 mol) in benzene (15 mL) in a 100-mL, three-necked, round-bottomed flask [equipped with two stacked condensers, magnetic stirring bar, glass stopper, a N_2 inlet, and a N_2 outlet (drying tube, $CaCl_2$) in the top of the condenser] was added 85% H_3PO_4 (3 mL) and more benzene (10 mL, used first

to rinse containers of both alcohol **74** and the 85% H_3PO_4). The resulting mixture was stirred vigorously and heated to a boil at which time P_2O_5 (1.0 g) was added in one portion. After about 5 min, more P_2O_5 (1.08 g) was added. The resulting two-phase mixture was stirred vigorously at reflux (20 h) during which time additional quantities of P_2O_5 (2.07 g at 6.3 h, 2.26 g at 14.3 h) were added. After cooling to RT, the organic layer was decanted and the remaining dark brown residue was washed (ether, 3 x 10 mL). The combined ether washes and the original organic layer were washed [5% $NaHCO_3$ (25 mL) and saturated brine (3 x 25 mL)], dried (Na_2SO_4, overnight), filtered (Celite, suction), and evaporated (rotovap) to an oil (1.01 g). Analysis by TLC ($HCCl_3$, silica gel) indicated as many as seven components. ^1H and ^{13}C NMR also indicated a complex mixture. One of the components appeared to be the isomer **76** (2,3-dihydro-2,2-dimethylbenzofuran) as indicated by singlets at δ 3.02 and 1.47 (see NMR data in the preparation of **75** and **76,** next page). Interestingly, Gripenberg and co-workers isolated isomeric benzofuran **76** in a yield of 21% by heating alcohol **74** with $ZnCl_2$ (neat).[43] (Isomer **76** is probably formed by a mechanism involving a Claissen rearrangement of the disubstituted alkene obtained by dehydration of alcohol **74**; see reference 43). The expected singlet at approximately δ 4.2 for the desired benzofuran **75** (see NMR data from the preparation of **75** and **76**, next page) was not observed in the relatively clean baseline between δ 3.8 and 4.7 in the ^1H NMR spectra of the crude oil, although the presence of **75** in small amounts cannot be ruled out.

Treatment of alcohol **74** with $AlCl_3$ in CH_3NO_2 at RT also gave a complex mixture. There was no convincing evidence by ^1H NMR for the presence of either **75** or **76** in the crude product. Signals at 28.2, ~ 43, and ~ 86 ppm (small) in the ^{13}C NMR spectra of the crude product most resembled the pattern observed for **76** (see NMR data for **75** and **76**, next experiment), although the presence of **75** cannot be ruled out.

2,3-Dihydro-3,3-dimethylbenzofuran (75) and
2,3-Dihydro-2,2-dimethylbenzofuran (76)

Benzofuran **75** (containing approximately 30% benzofuran **76**) was prepared by the method of Gates and co-workers[40] in a yield of 22%.

The NMR data for **75** was: ^{1}H NMR ($DCCl_3$) δ 1.32 [s, 6 H, $C(CH_3)_2$], 4.23 [s, 2 H, OCH_2], the signals for the aromatic protons (4 H) overlapped with those for **76** between δ 6.7 and 7.2; ^{13}C NMR ($DCCl_3$) ppm 27.5 [q, $C(CH_3)_2$], 41.8 [s, $C(CH_3)_2$], 84.3 [t, OCH_2], 84.3 [t, OCH_2]; aromatic carbons for both **75** and **76** including 3 impurity peaks [109.5, 109.6, 119.9, 120.5, 122.2, 125.1, 125.3, 126.7, 127.9, 128.2, 129.0, 129.6, 136.5, 158.7, 159.1].

The NMR Data for **76** was: ^{1}H NMR ($DCCl_3$) δ 1.46 [s, 6 H, $C(CH_3)_2$], 3.00 [s, 2 H, $ArCH_2$], see previous paragraph concerning the aromatic proton signals; ^{13}C NMR ($DCCl_3$) ppm 28.2 [q, $C(CH_3)_2$], 42.8 [t, $ArCH_2$], 86.4 [s, $C(CH_3)_2$], see previous paragraph concerning the aromatic carbon signals.

3(2H)-Benzofuranone (93)

Thionyl chloride ($SOCl_2$, 6.9 mL, 11.3 g, 95 mmol) was added in one portion (bolus) to phenoxyacetic acid (**72**, 5.00 g, 32.9 mmol) in a 25-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar, dry ice condenser and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler) (N_2 inlet was removed temporarily during the addition of the $SOCl_2$). The resulting mixture was heated (oil bath) until the temperature of the bath had reached 80°C (ca. 20 min). The mixture was stirred at 80-88°C (oil bath) for 30 min and then allowed to cool to RT. The excess $SOCl_2$ was removed under high vacuum (pressure reduced slowly to prevent bumping), and the residue was vacuum distilled (major fraction, bp 87°C/0.40 mm-87.7°C/0.45 mm) to give acid chloride **91** (2.96 g, 53%) which was used without further purification [IR (neat)

1807 cm^{-1} (C=O)]. A solution of the acid chloride **91** (2.95 g, 17.3 mmol) in dry CH_2Cl_2 (10 mL) was added dropwise (15 min) to a stirred suspension of $AlCl_3$ (2.5 g, 19 mmol) in dry H_2CCl_2 (20 mL) followed by a rinse (1 mL of CH_2Cl_2) from the addition funnel. The mixture was stirred at RT for 15 min during which time a lump of dark black material formed. The mixture was then added in one portion to a mixture of ice (25 g) and concentrated HCl (2 mL). The reaction vessel was rinsed (20 mL of H_2CCl_2 and 20 mL of $HCCl_3$) and the rinses were added to the mixture. After shaking (separatory funnel), two layers separated, the aqueous layer was extracted (H_2CCl_2, 2 x 20 mL), and the combined organic layers were dried ($CaCl_2$, overnight). The organic solution was evaporated (rotovap) to ~ 10 mL; silica gel (5 g) in hexanes (ca. 10 mL) was added, and the new mixture was evaporated to dryness. The adsorbed sample was eluted on a silica gel (ca. 30 g, 60-200 mesh) column (2 x 24 cm, packed in hexanes) using hexanes:ether (4:1, 300 mL). The fractions containing only the principal band (R_f 0.60 in 4:1 hexanes:ether) were evaporated (rotovap) to a yellow crystalline solid (0.48 g). Recrystallization in boiling hexanes (9 mL), followed by a wash (30 mL of hexanes), gave ketone **93** as yellow crystals (0.24 g, 10% from acid chloride): mp 101-102°C (lit[3] mp 100°C); IR (KBr) 1724 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 4.63 [s, 2 H, OCH_2], 7.03-7.28 [m, 2 H, Ar-*H*], 7.57-7.78 [m, 2 H, Ar-*H*]; ^{13}C ($DCCl_3$) ppm 74.6 [CH_2], 113.6 [C(7)], 121.1 [C(3a)], 173.9 [C(7a)]; other Ar-*C* [121.9, 124.0, 137.8], 199.8 [*C*=O].

Benzo[*b*]thien-3(2*H*)-one (94)

Freshly distilled (over triphenyl phosphite) $SOCl_2$ (13.0 mL, 21.2 g, 0.178 mol) was added in one portion (bolus) to (phenylthio)acetic acid (**84** 10.0 g, 59.4 mmol) in a 50-mL, single-necked, round-bottomed flask equipped with a magnetic stirring bar, dry ice condenser and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler) (N_2 inlet was temporarily removed during the addition of $SOCl_2$). The resulting greenish mixture was heated (oil bath) until the temperature of the bath had reached 80°C (ca. 15

min) during which time gas was seen to evolve. The mixture was stirred at 75-85°C (oil bath) and then the oil bath was removed. The excess $SOCl_2$ was removed under high vacuum (≤ 0.5 mm) with warming (40-60°C), and the residue was vacuum distilled to give 9.65 (87%) of the acid chloride **92** as a nearly colorless liquid [bp 100.5°C/0.6 mm-100.9°C/0.65 mm; IR (neat) 1801 cm^{-1} (C=O); $n^{23.3}$ = 1.5810 (lit[102] n_D^{23} = 1.5810)]. A solution of the acid chloride **92** (9.65 g, 51.7 mmol) in dry H_2CCl_2 (40 mL) was added dropwise (45 min) to a stirred suspension of $AlCl_3$ (7.6 g, 57 mmol) in dry H_2CCl_2 (50 mL) in a 300-mL, three-necked, round-bottomed flask equipped with a glass stopper, addition funnel, magnetic stir bar, condenser and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler). The resulting dark brown mixture was stirred at RT for 1 h and then added in one portion to a mixture of ice (75 g) and concentrated HCl (5 mL) in a 500-mL Erlenmeyer flask. The reaction flask was rinsed with H_2CCl_2 (25 mL) and added to the mixture along with $HCCl_3$ (50 mL) and H_2O (50 mL). To complete the quenching process, the mixture was shaken in a separatory funnel and the two layers were separated. After extracting the aqueous layer with $HCCl_3$ (2 x 50 mL), the combined organic layers were washed (H_2O, 100 mL), dried ($CaCl_2$, overnight), filtered and evaporated (rotovap) to an oil which crystallized after briefly chilling in a dry ice-acetone bath. The solid was recrystallized in two portions. The first portion was recrystallized in boiling hexanes/petroleum ether (bp 35-60°C) and the second portion was recrystallized with boiling hexanes. The crystals were washed with hexanes to give the ketone **94** as off-white crystals (2.65 g, 30% from acid) which were used without further purification: mp 66.4-68.0°C (lit[102] 64.5-65.5°C); IR (KBr) 1693, 1701 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 3.78 [s, 2 H, C*H*$_2$], 7.17-7.27 [m, 1 H, Ar-*H*], 7.42 [d, 1 H, Ar-*H*], 7.50-7.60 [m, 1 H, Ar-*H*], 7.73-7.81 [m, 1 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 39.2 [*C*H$_2$]; Ar-*C* [124.5, 124.6, 126.5, 130.9, 135.5, 154.2], 199.9 [*C*=O]. The above procedure was similar to that described by Stridsberg and Allenmark.[102]

Attempted Olefinations of Benzo[*b*]thien-3(2*H*)-one (94) and of 3(2H)-Benzofuranone (93) by Reaction with $Ph_3P{=}CHOCH_3$

A solution of *n*-butyllithium (1.6 M, 2.6 mL, 4.2 mmol) in hexane was added (syringe, ca. 2 min) to a stirred suspension of $Ph_3PCH_2OCH_3$, Cl^- (1.5 g, 4.4 mmol) in dry ether (10 mL) in a 50-mL, three-necked, round-bottomed flask equipped with a magnetic stirring bar, glass stopper, rubber septum, condenser and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler). The resulting orange-red mixture [supernatant, dark red; light colored precipitate (presumably either LiCl and/or unreacted phosphonium salt)] was stirred at RT for 1 h. A solution of benzo[*b*]thien-3(2*H*)-one (**94**, 0.50 g, 3.3 mmol) in dry ether (10 mL) was added dropwise (ca. 15 min, glass stopper quickly replaced by an addition funnel prior to addition) to the dark Wittig reagent (RT). The resulting mixture (which quickly turned to an off-white suspension) was stirred at RT for 25 h [after 45 min TLC (10:1 hexanes:ether) indicated three principal components: R_f = 0.88, 0.16 (starting ketone), 0.0 and a small component of R_f = 0.71 was also seen]. The reaction mixture was filtered (plug of glass wool) and concentrated to about 2 mL. The addition of hexanes (ca. 10 mL) caused a solid to form which was removed by filtration. The filtrate was combined with a rinse (ether, 10 mL, rinse was also filtered) of the reaction flask. The resulting organic solution was evaporated to a dark brown oil. To isolate the high R_f component (assumed to be the desired olefinic product), the soil was dissolved in hexanes:ether (6:1, 3.5 mL) and eluted by flash chromatograph (gentle air pressure) on a column (0.9 x 18 cm) of neutral alumina (Merck, Art. 1077, 70-230 mesh, 90 aktiv) using hexanes (ca. 75 mL). Evaporation (rotovap) of the eluent gave an oil (106 mg) the IR and ^1H NMR spectra of which indicated an aromatic compound the structure of which could not be assigned but which was certainly *not* the expected vinyl methyl ether derivative (which would then have been converted to 2,3-dihydro-3-formylbenzofuran).

Reaction of $Ph_3P{=}CHOCH_3$ with one equivalent of benzo[*b*]thien-3(2*H*)-one (**94**) in dry THF at -78°C caused a white precipitate to form (generally indicative of the formation of $Ph_3P{\rightarrow}O$). Fifteen minutes after the dry ice-acetone bath (-78°C) was removed, the mixture was off-white and TLC analysis (10:1 hexanes:ether) showed the same pattern as in the above Wittig reaction in ether at RT except that a larger amount of starting ketone predominated.

Reaction of $Ph_3P{=}CHOCH_3$ with 0.8 equivalents of 3(2*H*)-benzofuranone (**93**) in dry ether at RT also gave a TLC pattern similar to those described above [principal bands were starting ketone and component with $R_f = 0.88$ (10:1 hexanes:ether)].

It appears that, at best, the desired methyl vinyl ether derivatives (oxygen and sulfur analogues) were only small components of the reaction mixtures and so this synthetic route was abandoned.

2,3-Dihydro-3-iodomethyl-3-methylbenzofuran (103)

To a cooled (8°-13°C water bath) and stirred solution of salt **102** (7.70 g, 29.4 mmol) in acetone (35 mL) in a 10-mL, two-necked, round-bottomed flask [equipped with a thermometer, addition funnel, magnetic stir bar and a N_2 inlet in the top of the addition funnel (positive pressure from an oil bubbler)] was added (ca. 15 min) a solution of NaI (8.80 g, 58.7 mmol) in acetone (40 mL) at a rate such that the temperature of the reaction mixture did not exceed 21°C. During the addition of the NaI solution, the evolution of gas (N_2) was evident and the mixture turned dark brown. After the addition was complete (evolution of gas ceased 3 min prior to completion of the addition), the mixture was transferred to an Erlenmeyer flask with the aid of a rinse (20 mL of acetone) of the reaction flask. The addition of hexanes (200 mL) caused a dark purple solid to precipitate which was filtered (gravity). More solid (brown crystals) formed upon refrigeration (overnight) of the stoppered filtrate. After a second filtration, the filtrate was washed with 5% $Na_2S_2O_3{\cdot}2H_2O$ (50 mL), dried (Na_2SO_4, ca. 5 min), filtered, and evaporated [rotovap

followed by high vacuum (≤ 0.5 mm) at RT] to an oil (6.76 g, 83.9%) which contained the cyclized adduct **103** as the major product with the non-cyclized adduct **104** [*o*-$IC_6H_4OCH_2C(CH_3)=CH_2$] present in a much smaller amount. Vacuum distillation (bp 77°C-83.5°C/0.05 mm, major fraction) did not remove **104** but gave a yellow to orange oil (5.79 g, 72%) containing a mixture of **103** and **104** (ratio 10:1, respectively, as indicated by ^1H NMR for major fraction). This oil was used without further purification in the ensuing reaction with $AgNO_3$. The following spectral data was obtained from a spectra of the mixture of **103** and **104** (ratio ca. 10:1, respectively): IR (neat) 1480 cm^{-1} (ArC=C); ^1H NMR ($DCCl_3$) for **103** δ 1.48 [s, 3 H, CH_3], 3.35 [s, 2 H, CH_2I], 4.15 [d, J = 9.3 Hz, 1 H, OC(*H*)H], 4.47 [d, J = 9.3 Hz, 1 H, OCH(*H*)], 6.78 [d, 1 H, Ar-H], 6.89 [m, 1 H, Ar-*H*], 7.10 [dd, 1 H, Ar-*H*], 7.15 [apparent dt, 1 H, Ar-*H*]. Three small singlets at δ 1.86 [C=CCH_3], 5.01 [C=C(*H*)H], and 5.19 [C=CH(*H*)] were particularly useful in assignment of the structure of the impurity designated **104**. A signal overlapped with the doublet at δ 4.47 in **103** and probably corresponds to the methylene protons alpha to the oxygen atom [OCH_2] in **104**.

The above method was derived from a procedure described by Beckwith and co-workers[8] which gave little experimental detail. They claimed **103** as the sole product. Apparently they must have used much greater dilution.

Attempted Preparation of 2,3-Dihydro-3-methyl-3-benzofuranmethanol (107) by Hydrolysis Using Aqueous $AgNO_3$

To a vigorously stirred (magnetic stir bar) solution of halide **103** (0.30 g, 1.1 mmol; contained up to 10% of the isomer **104**) in ether (25 mL) in a 100-mL Erlenmeyer flask was added rapidly (Pasteur pipette) a solution of $AgNO_3$ (0.60 g, 5.6 mmol) in 50% acetone/H_2O (10 mL). The resulting two-phase mixture was stirred vigorously for 40 min during which time a solid (presumably AgI) formed at the interphase. After adding more

$AgNO_3$ (0.60 g, 5.6 mmol, in 5 mL of H_2O) and acetone (2 mL), the mixture was stirred another 10 min. The layers were separated and the aqueous layer was extracted (ether, ca 15 mL). The combined organic layers were dried briefly (Na_2SO_4, ca. 5 min), and evaporated (rotovap). The residue was dissolved as best as possible in hexanes (ca. 2 mL) and eluted on a silica gel plate (4 mm) spun by the Chromatotron using hexanes:ether [8:1 (90 mL), 4:1 (100 mL), 3:1 (80 mL)]. The principal band (one of the last bands) was collected and evaporated (rotovap) to a colorless thick oil (57 mg, 32%). The following NMR data of the oil is not consistent with any of several alcohols or alkenes expected which might form by cationic rearrangements, eliminations or substitutions except possibly for 2,3-dihydro-3-methyl-4H-benzopyran-3-ol (**105**). The NMR data was: ^{1}H NMR ($DCCL_3$) δ 1.33 [s, 3 H, C*H*$_3$], 2.32 [br s, 1 H, O-*H*], 2.76 [dd, J_{gem} = 16.6 Hz, J ≈ 2 Hz, 1 H, ArC(*H*)H], 2.87 [d, J_{gem} = 16.6 Hz, 1 H, ArCH(*H*)], 3.81 [d, J_{gem} = 10.8 Hz, 1 H, OC(*H*)H], 3.92 [dd, J_{gem} = 10.8 Hz, J = 2.3 Hz, 1 H, OCH(*H*)], 6.84-6.93 [m, 2 H, Ar-*H*], 7.04 [d, 1 H, Ar-*H*], 7.08-7.17 [m, 1 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 24.7 [*C*H$_3$], 39.2 [Ar*C*H$_2$], 65.9 [CH$_3$*C*OH], 73.7 [O*C*H$_2$], 116.6 [C(8)], 153.1 [C(8a)]; other Ar-*C* [120.1, 121.2, 127.6, 130.4].

The other isomer of the starting halide **103** (that is, **104**) was isolated from early fractions (see chromatographic separation above) in a yield of approximately 9% (nearly all that was present in the starting mixture of **103** and **104**). Therefore, the alcohol **105** was obtained by the rearrangement of a cation derived solely from benzofuran **103** and not from **104**.

α-Bromo-*p*-xylene (109)

In a 100-mL, three-necked, round-bottomed flask [equipped with a magnetic stirring bar, two glass stoppers, condenser and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler)] a mixture of *p*-xylene (**108**, 15.00 g, 0.141 mol), *N*-bromosuccinimide (mp 177-181°C, 20.10 g, 0.113 mol), dibenzoyl peroxide (0.45 g, 1.86

mmol) and dry CCl_4 (50 mL) was heated to a gentle boil over a period of 15 min. The resulting mixture was maintained at a gentle reflux for 5 min and then heated at vigorous reflux (exothermic reaction) for ~ 7 min during which time a large amount of a white solid formed and vigorous boiling subsided. After 10 min of cooling (RT), the mixture was filtered (suction), the solid was washed (suction) with ether (50 mL), and the combined filtrate and wash were evaporated to an oil which partially crystallized. Vacuum distillation (30 cm Vigreaux fractionating column) gave one fraction (bp 71-74°C/1.7 mm, lit[51] bp 120°C/15 mm) which crystallized on standing to a colorless solid (13.90 g, 66%): mp 32.2-36.6°C; IR (melt) 1620 cm^{-1} (C=C); ^1H NMR ($DCCl_3$) 2.33 [s, 3 H, CH_3], 4.47 [s, 2 H, CH_2Br], 7.13 [d, 2 H, Ar-*H*], 7.27 [d, 2 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 21.2 [CH_3], 33.7 [CH_2Br]; Ar-*C* [128.9, 129.4, 134.8, 138.3]. This xylyl bromide was used without further purification. The above procedure is similar to that reported by Johnstone and Stevens.[51]

2,3-Dihydro-3-methyl-3-[(*p*-xylyloxy)methyl]-benzofuran (110)

A 50-mL, three-necked, round-bottomed flask [equipped with two glass stoppers, two stacked condensers and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler)] was charged with NaH (0.12 g, 5.0 mmol). A solution of alcohol **107** (0.55 g, 3.3 mmol) and 15-crown-5 (Lancaster Synthesis Ltd., 0.18 g, 0.82 mmol) in dry THF (ca. 8 mL) was added in one portion (bolus) to the NaH. The resulting mixture was stirred at RT for 15 min. After replacing one glass stopper with an addition funnel, a solution of α-bromo-*p*-xylene (**109**, 0.75 g, 4.0 mmol) in dry THF (ca. 7 mL) was added dropwise (ca. 2 min) followed by a rinse (5 mL of dry THF) from the addition funnel. The reaction mixture was then stirred at reflux for 6 h and then cooled to RT (1 h). After diluting with dry ether (25 mL), the reaction mixture was filtered (gravity), the reaction flask was rinsed (25 mL of ether; rinse was also filtered) and the combined filtrate and rinse were evaporated

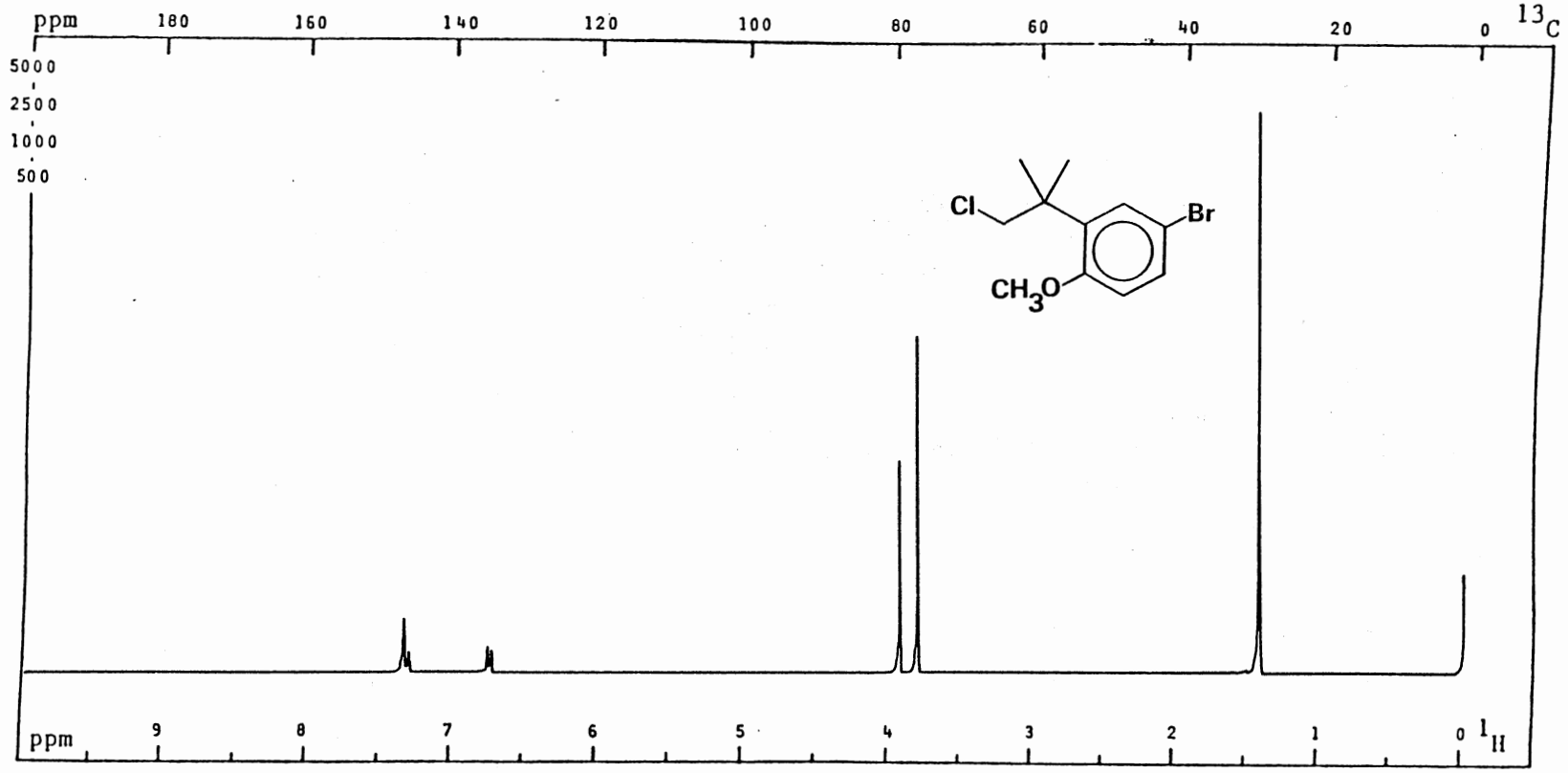
to an oil. After dissolving the oil in 4:1 hexanes:ether (100 mL), the organic solution was washed (H_2O, 3 x 50 mL), dried (Na_2SO_4, ca. 5 min), filtered and evaporated to an oil. The oil was transferred (1 mL hexanes) to a silica gel plate (4 mm, Chromatotron) and eluted with hexanes:ether [20:1 (150 mL), 10:1 (50 mL)]. Evaporation of a single large fraction containing the principal band gave benzyl ether **110** as a nearly colorless oil, 0.52 g (58%); IR (neat) 1099 cm^{-1} (C-O); ^1H NMR ($DCCl_3$) δ 1.40 [s, 3 H, ArCC*H*$_3$], 2.32 [s, 3 H, ArC*H*$_3$], 3.41 [s, 2 H, ArCC*H*$_2$O], 4.13 [d, J = 8.8 Hz, 1 H, ArOC(*H*)H], 4.45 [s, 2 H, ArC*H*$_2$O], 4.54 [d, J = 8.8 Hz, 1 H, ArOCH(*H*)], 6.75-6.87 [m, 2 H, Ar-*H*], 7.05-7.19 [m, 6 H, contained 2 d (J = 8.2 Hz) for the xylyl group]; ^{13}C NMR ($DCCl_3$) ppm 21.1 [*C*H$_3$], 22.6 [*C*H$_3$], 46.5 [Ar*C*CH$_3$], 73.2 [ArCC*H*$_2$O], 76.0 [Ar*C*H$_2$O], 80.7 [ArO*C*H$_2$], 109.6 [C(7)], 127.6 and 129.0 [xylyl group *ortho*-Ar-*C*], 159.8 [C(7a)]; other Ar-*C* [120.3, 123.3, 128.4, 132.8, 135.2, 137.2]. The oil was used without further purification.

Attempted Preparation of 1-[2,3-Dihydro-3-methyl-3-(*p*-xylyloxy)methyl-5-benzofuranyl]ethanone (111)

To a stirred suspension of $AlCl_3$ (0.30 g, 2.25 mmol) in freshly distilled CS_2 (2 mL) in a 25-mL, two-necked, round-bottomed flask [equipped with a magnetic stirring bar, rubber septum, dry ice condenser and a N_2 inlet in the top of the condenser (positive pressure from an oil bubbler)] in an ice-water bath (0°-6°C) was added (syringe, ca. 8 min) a solution of benzyl ether **110** (0.40 g, 1.49 mmol) in CS_2 (2 mL). The new mixture was stirred at 0-6°C for 1 h, diluted with ether (10 mL), and quenched cautiously (0-6°C) with water (10 mL). After separating two layers, the aqueous phase was extracted (ether, 5 x 10 mL). The combined organic layers were dried (Na_2SO_4, overnight), filtered, and evaporated to an oil. The oil was transferred (2:1 hexanes:ether, 2 mL) to a silica gel plate (2 mm, Chromatotron) and eluted with hexanes:ether [6:1 (40 mL), 4:1 (50 mL), 3:1 (80

mL), 2:1 (60 mL), 3:2 (50 mL)]. Two fractions from the 2:1 and 3:2 ratios contained the principal band and were combined and evaporated [rotovap, then high vacuum (RT, ca. 5 min)] to an oil (0.125 mg) which indicated (^{1}H and ^{13}C NMR) the presence (possibly 40-50% of the mixture according to ^{1}H NMR integration) of keto acetate **113**. See ^{1}H and ^{13}C NMR data for keto acetate **113**.

PLATE I



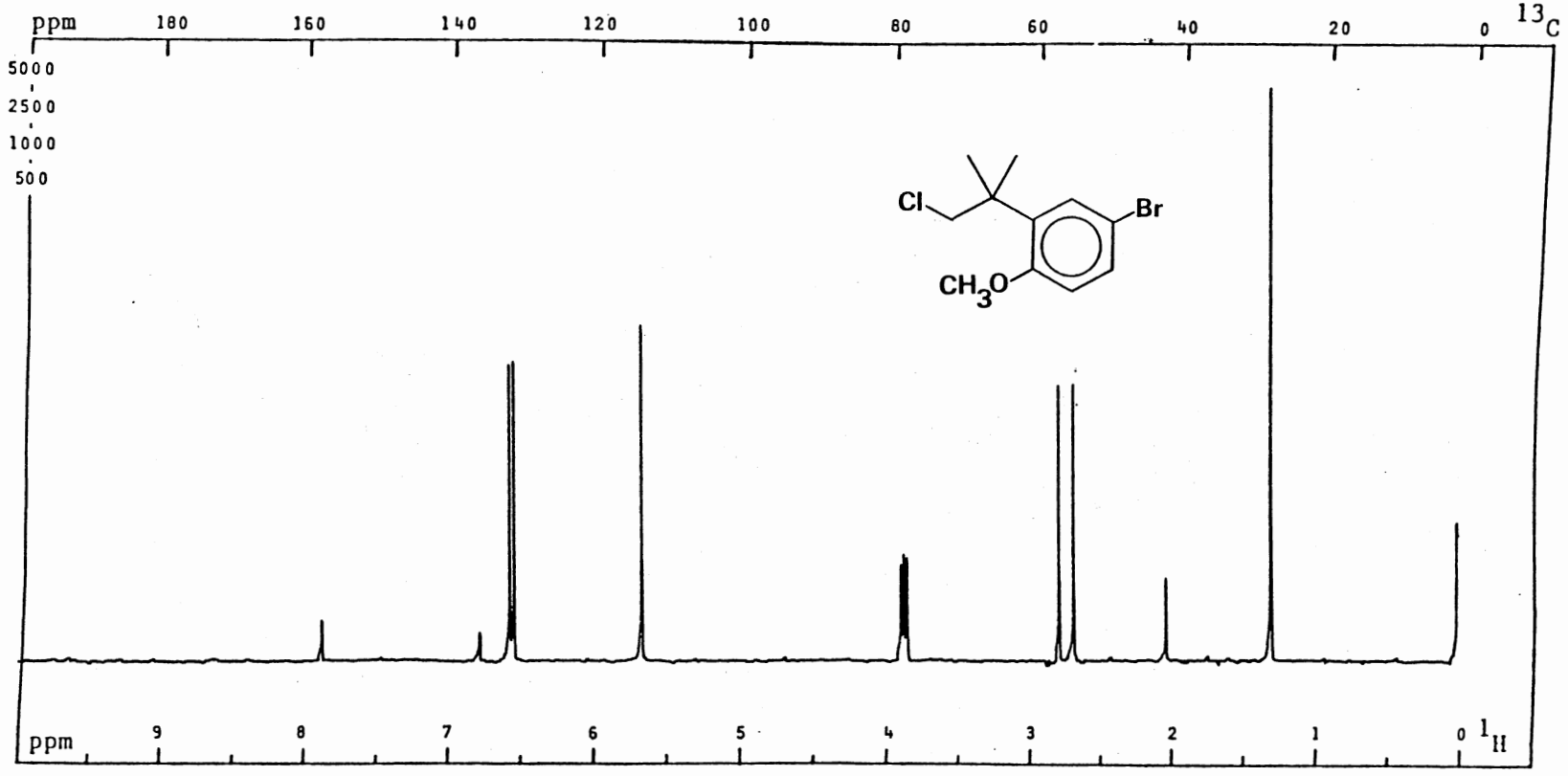
^{1}H NMR Spectrum of **79**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.94 MHz; WC: 2999.4 Hz; T: RT °C; NT: 12 .

Size: 4 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: Hz; Lock: ^{2}H ; D1,D5: 0.5 s.

DC: Y, N ; Gated Off: A or D ; DO: 638.9 Hz; RF(Power): 12 W/dB; NBW: 200 Hz; LB: Hz.

PLATE II



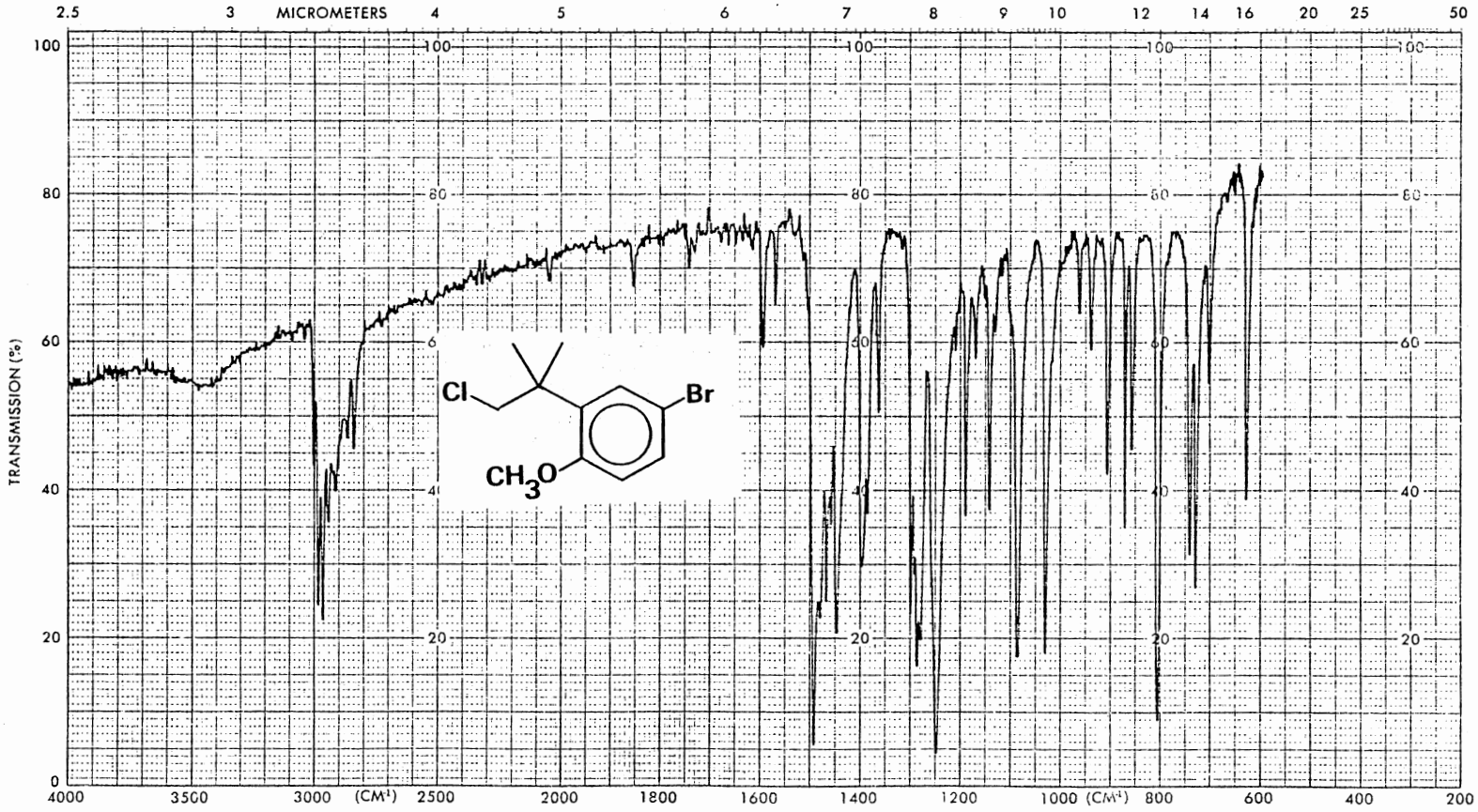
^{13}C NMR Spectrum of **79**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 64

Size: 20 K; PW/RF: 12.5 μs/dB; TO: 1000 Hz; FB: Hz; Lock: ^{2}H ; D1,D5:4.0 s.

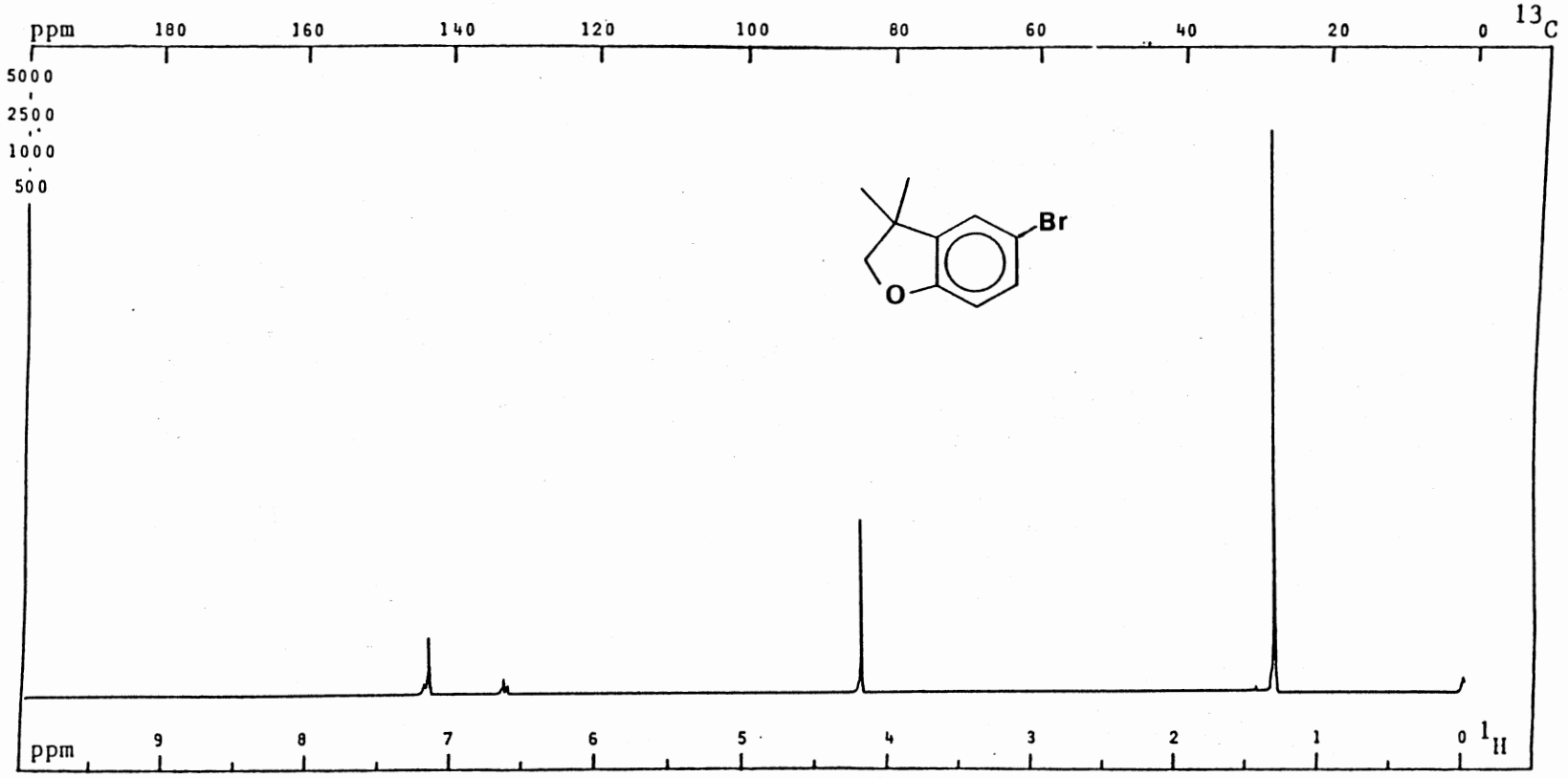
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

PLATE III



IR Spectrum of **79** -KBr

PLATE IV



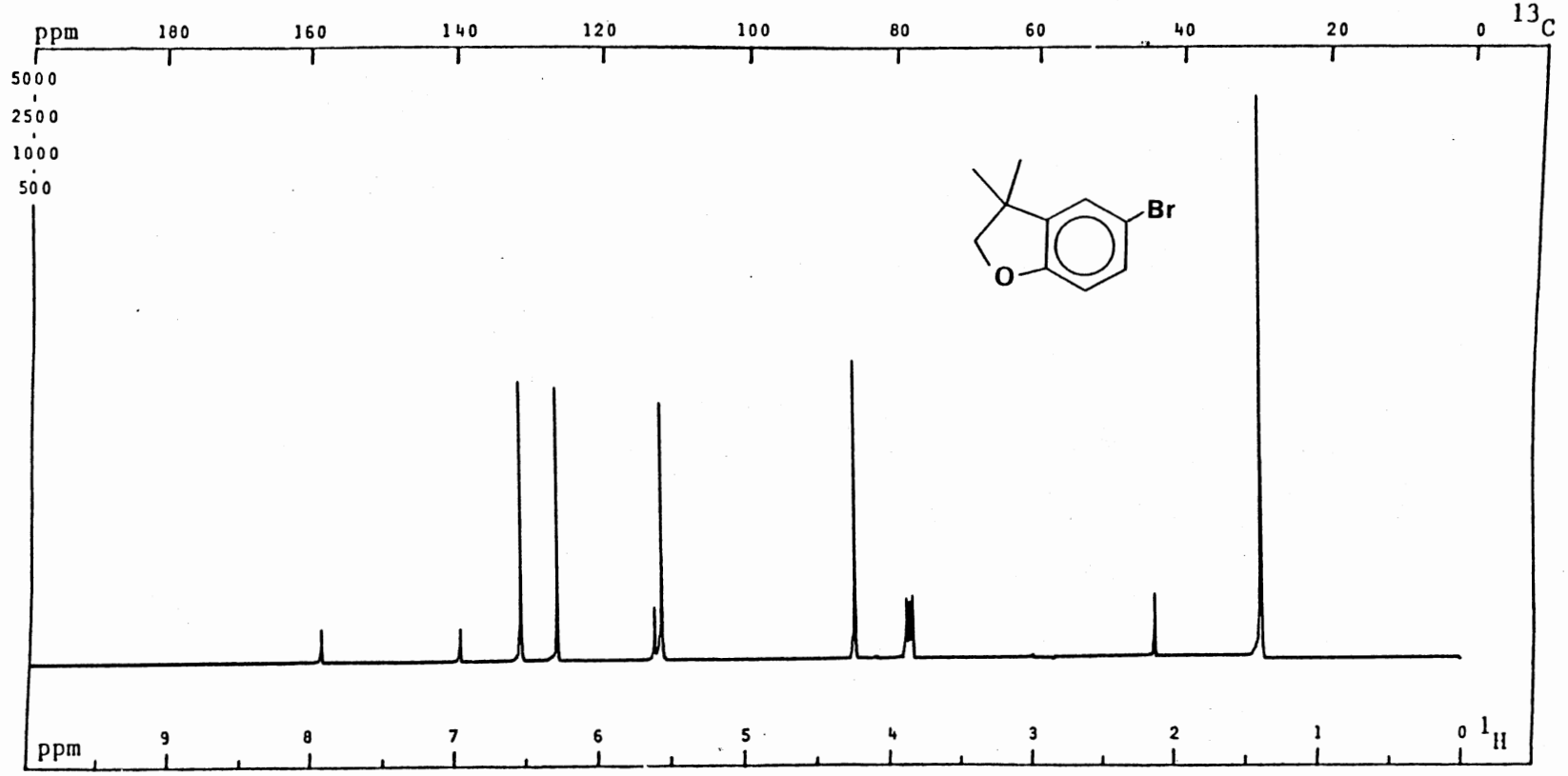
^{1}H NMR Spectrum of **80**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.94 MHz; WC: 2999.4 Hz; T: RT °C; NT: 12

Size: 4 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: Hz; Lock: ^{2}H ; D1,D5: 0.5 s.

DC: Y, N ; Gated Off: A or D ; DO: 638.9 Hz; RF(Power) 12 W/dB; NBW: 200 Hz; LB: Hz.

PLATE V



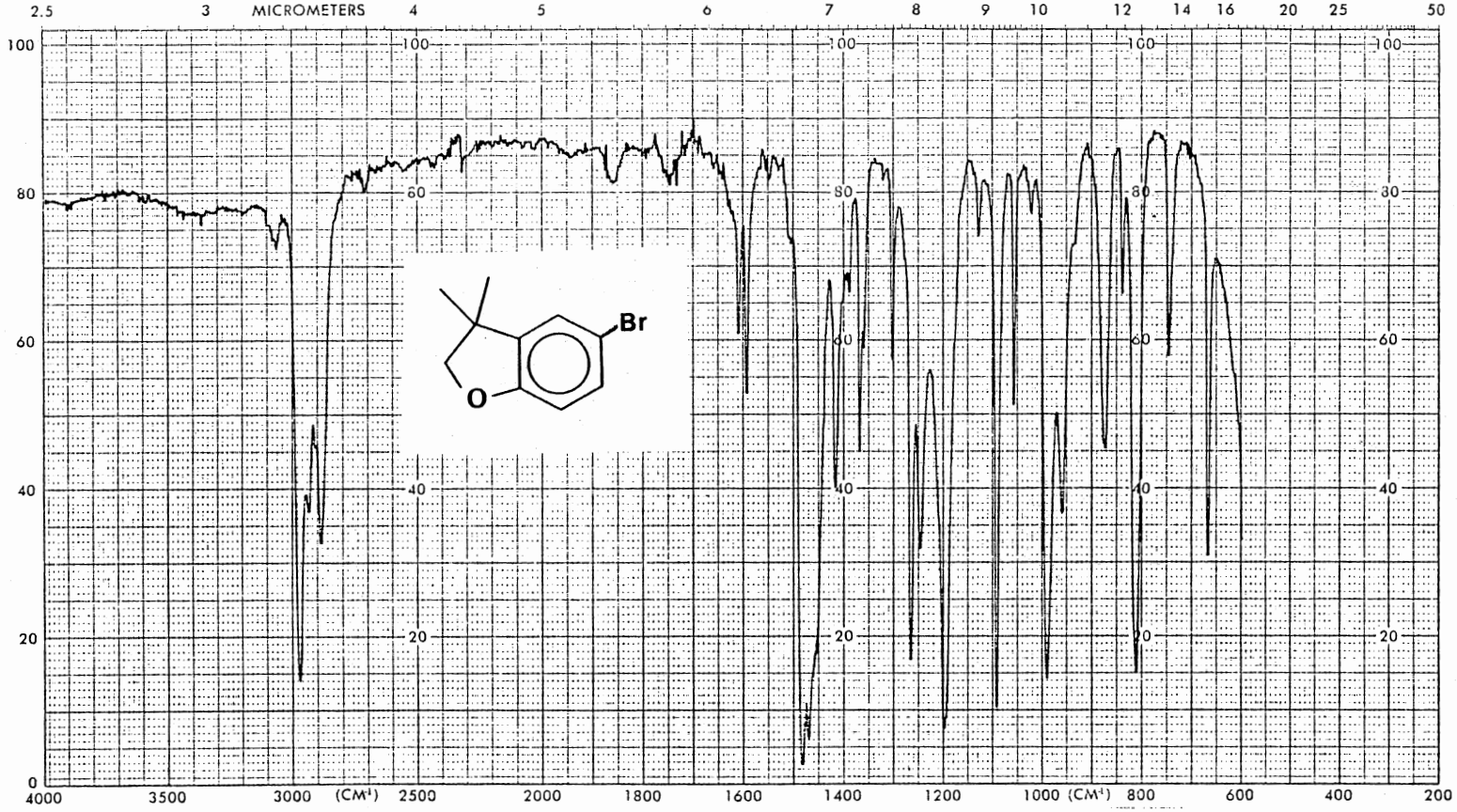
^{13}C NMR Spectrum of **80**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC:15085.9 Hz; T: RT °C; NT:220

Size: 20K K; PW/RF:12.5 µs/dB; TO:1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.0 s.

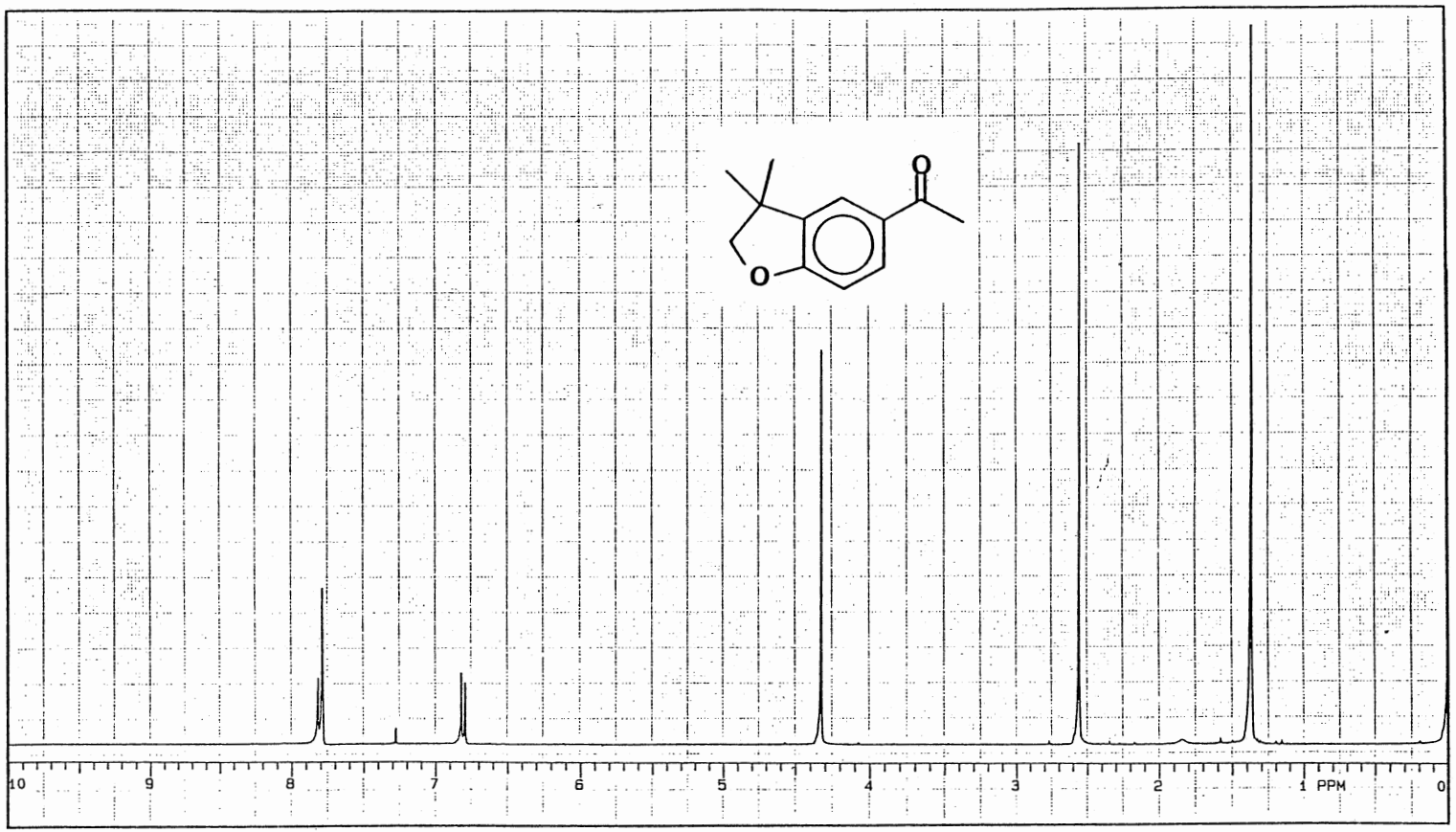
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

PLATE VI



IR Spectrum of **80**

PLATE VII



OBSERVE: Nucleus 1.500 Freq 300 MHz; Spec. Width 4000.0 Hz Offset 100 Hz; Acq. Time 2.000 sec Delay 0 sec; Pulse Width 5.0 μsec Transients 16

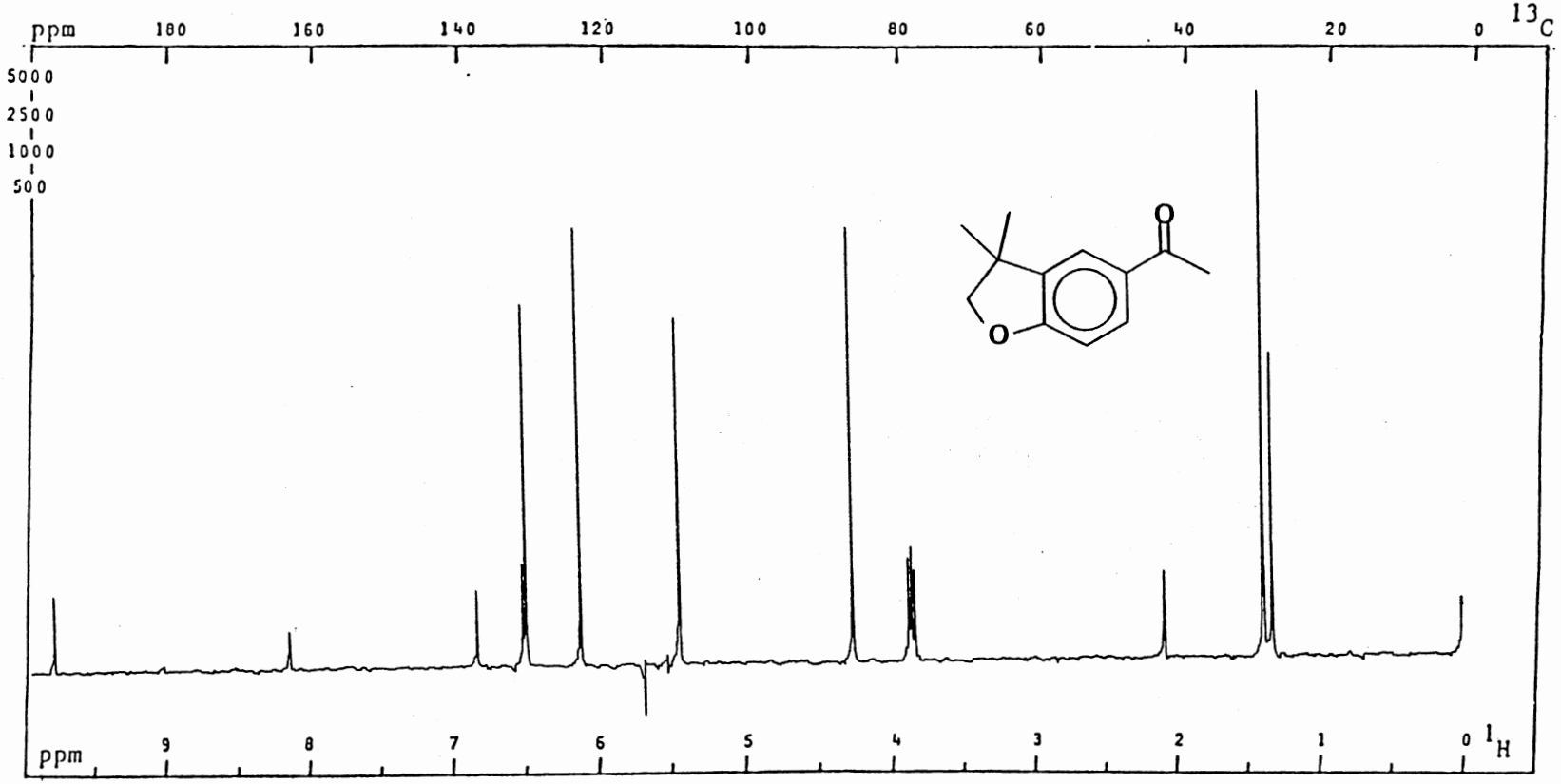
DECOUPLE: Nucleus 1.500 Offset 0 Hz; Mode NNN Power 20 db; Modulation Mode C Freq 200 Hz; Pulse Width μsec Power Mode ---

PLOT/PROCESSING: FN 16 K RE --- sec CD --- sec; LB 0.500 Hz AF --- sec CCD ---; Width 2999.4 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence C13PUL; Tube O.D. mm; Temp °C; Solvent CDCL3

^{1}H NMR Spectrum of **81**

PLATE VIII



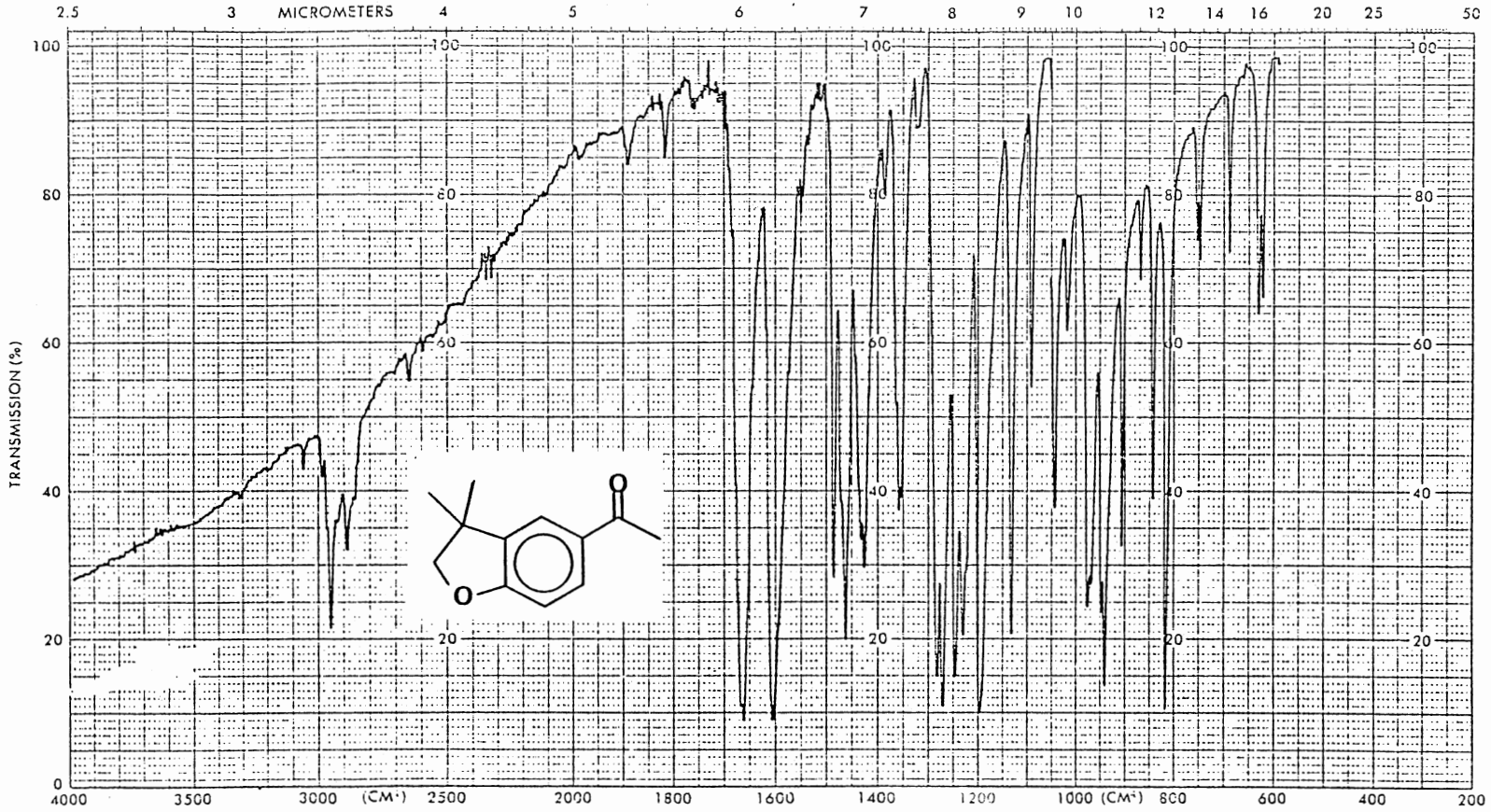
^{13}C NMR Spectrum of **81**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC:15085.9 Hz; T: RT °C; NT: 40

Size: 20 K; PW/RF:14.0 µs/dB; TO: 1000 Hz; FB: Hz; Lock: ^2H ; D1,D5:5.0 s.

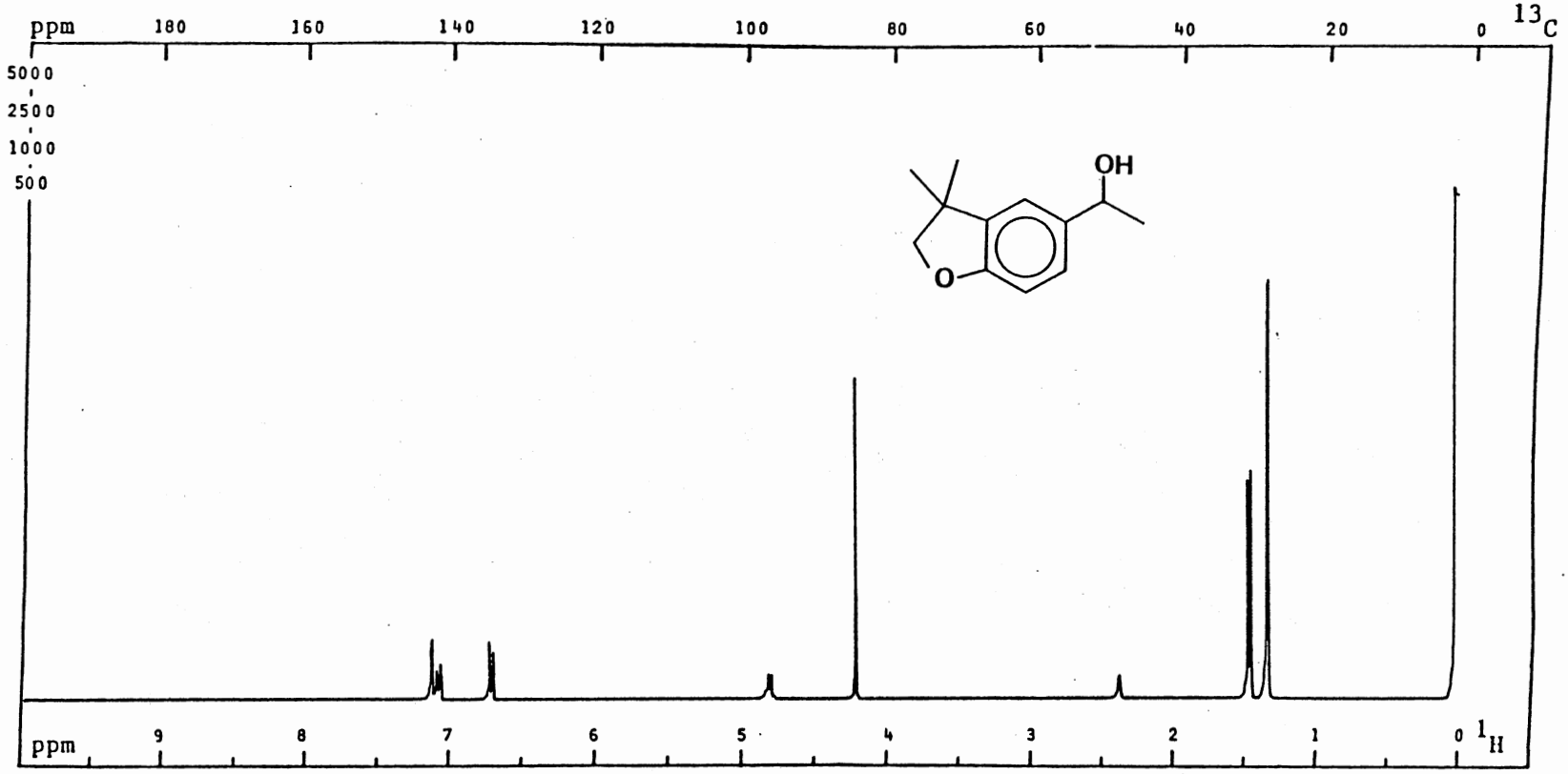
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

PLATE IX



IR Spectrum of **81** -KBr

PLATE X



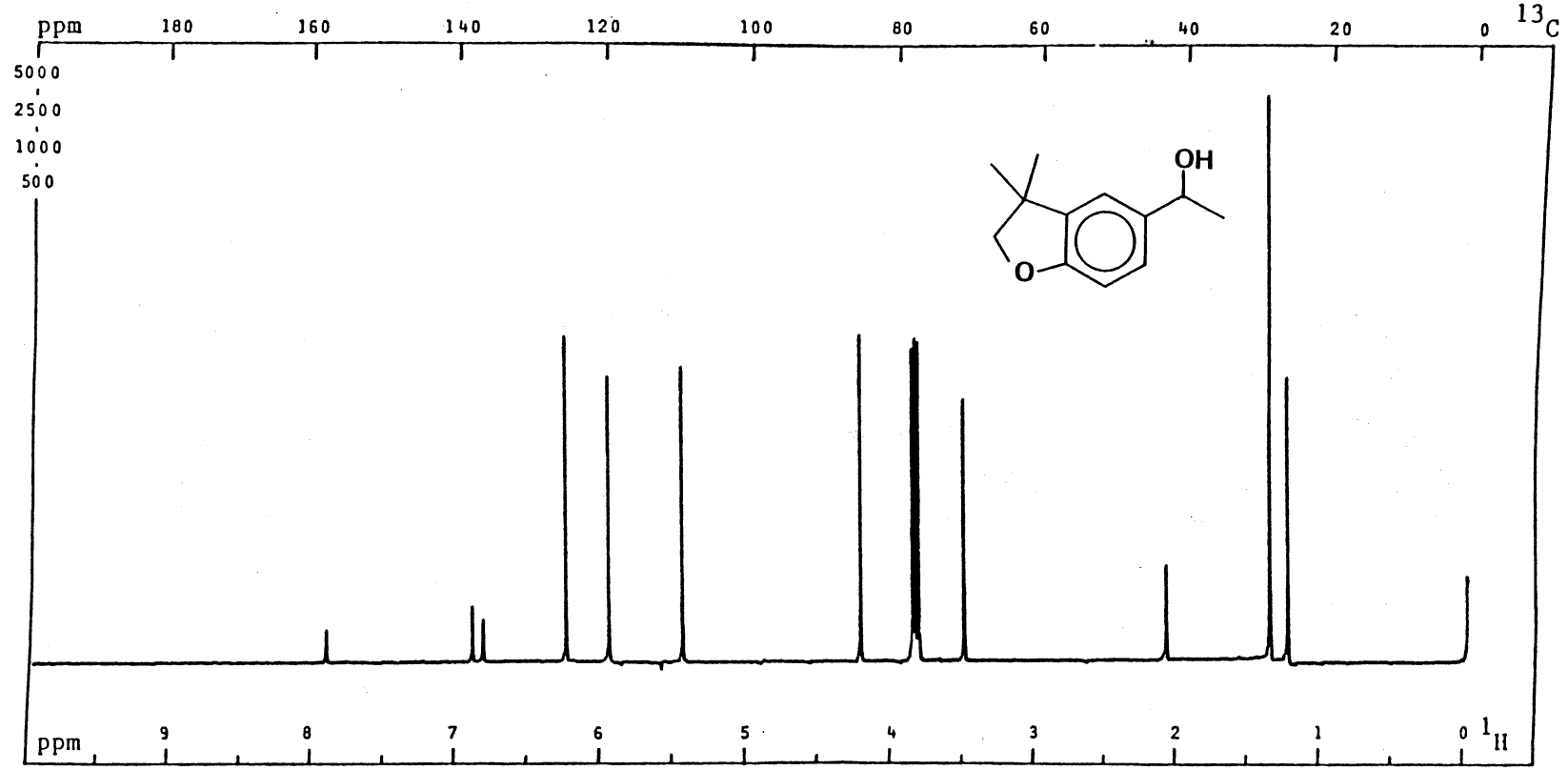
^{1}H NMR Spectrum of **82**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.94 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16

Size: 4 K; PW/RF: 5.0 μs/dB; TO: 0 0 Hz; FB: Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 12 W/dB; NBW: 200 Hz; LB: Hz.

PLATE XI



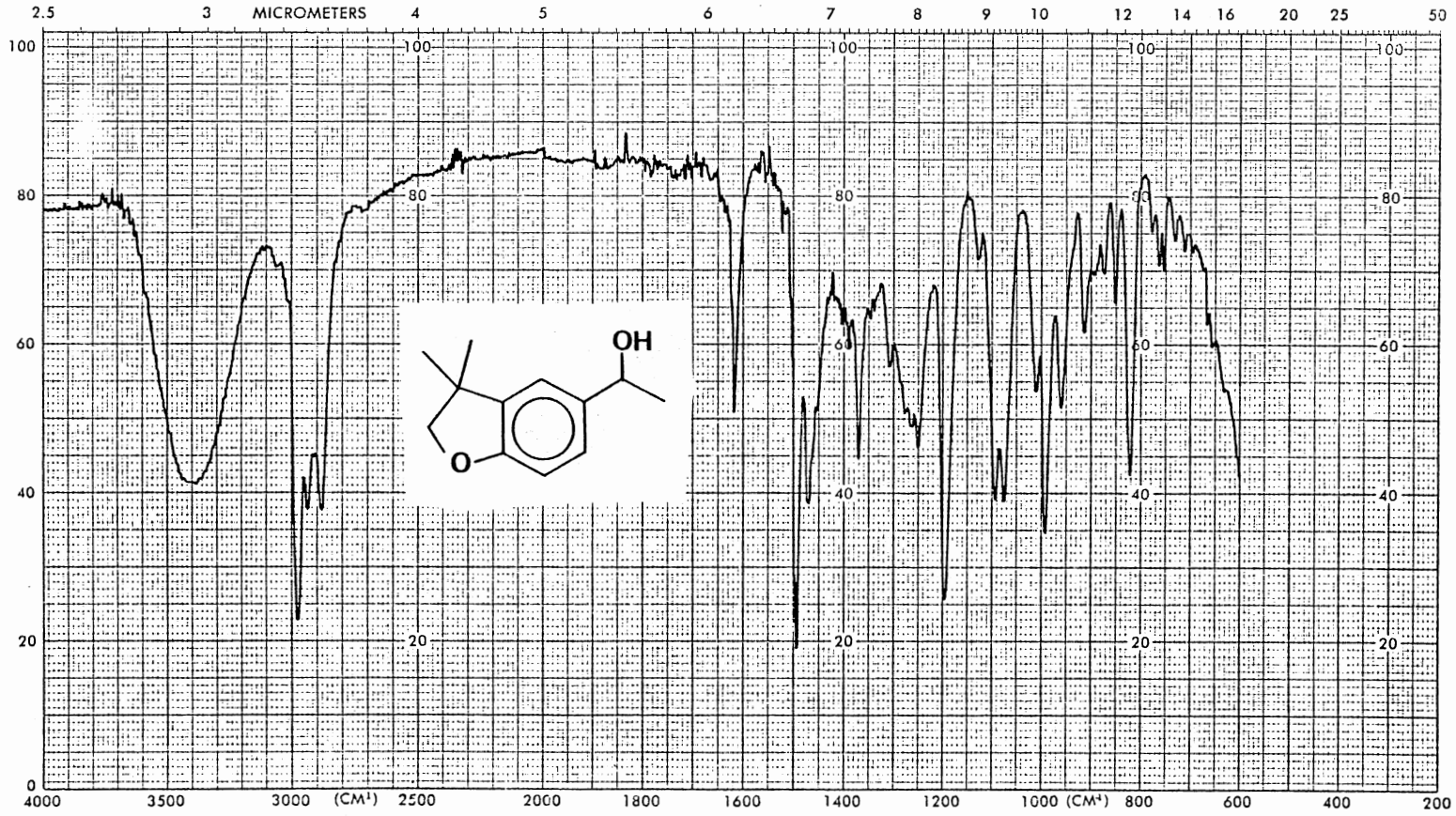
^{13}C NMR Spectrum of **82**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 1040 .

Size: 20 K; PW/RF: 12.5 µs/dB; TO: 1000 Hz; FB: Hz; Lock: ^2H ; D1,D5: 4.0 s.

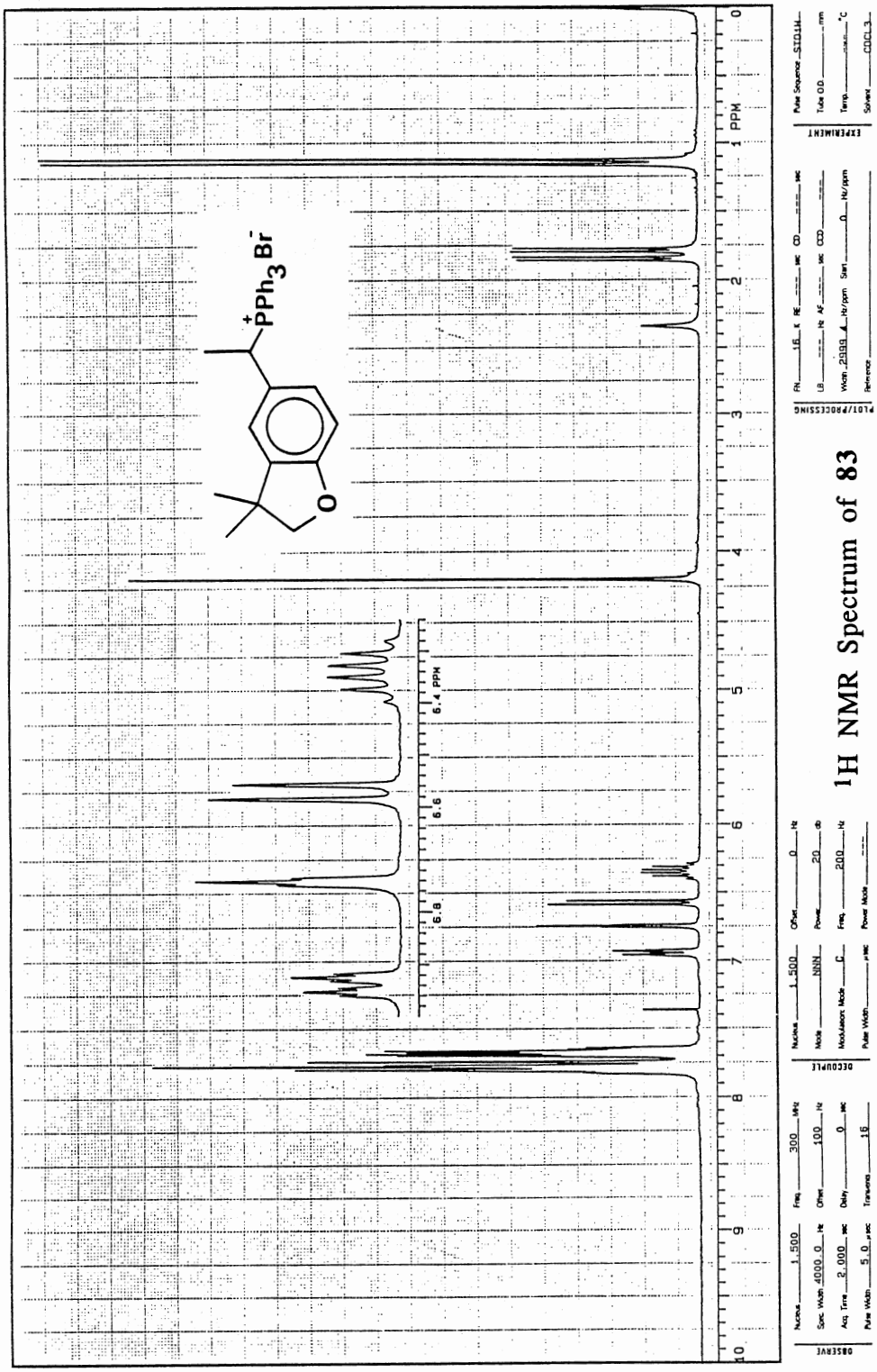
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW 200 Hz; LB: 2.0 Hz.

PLATE XII



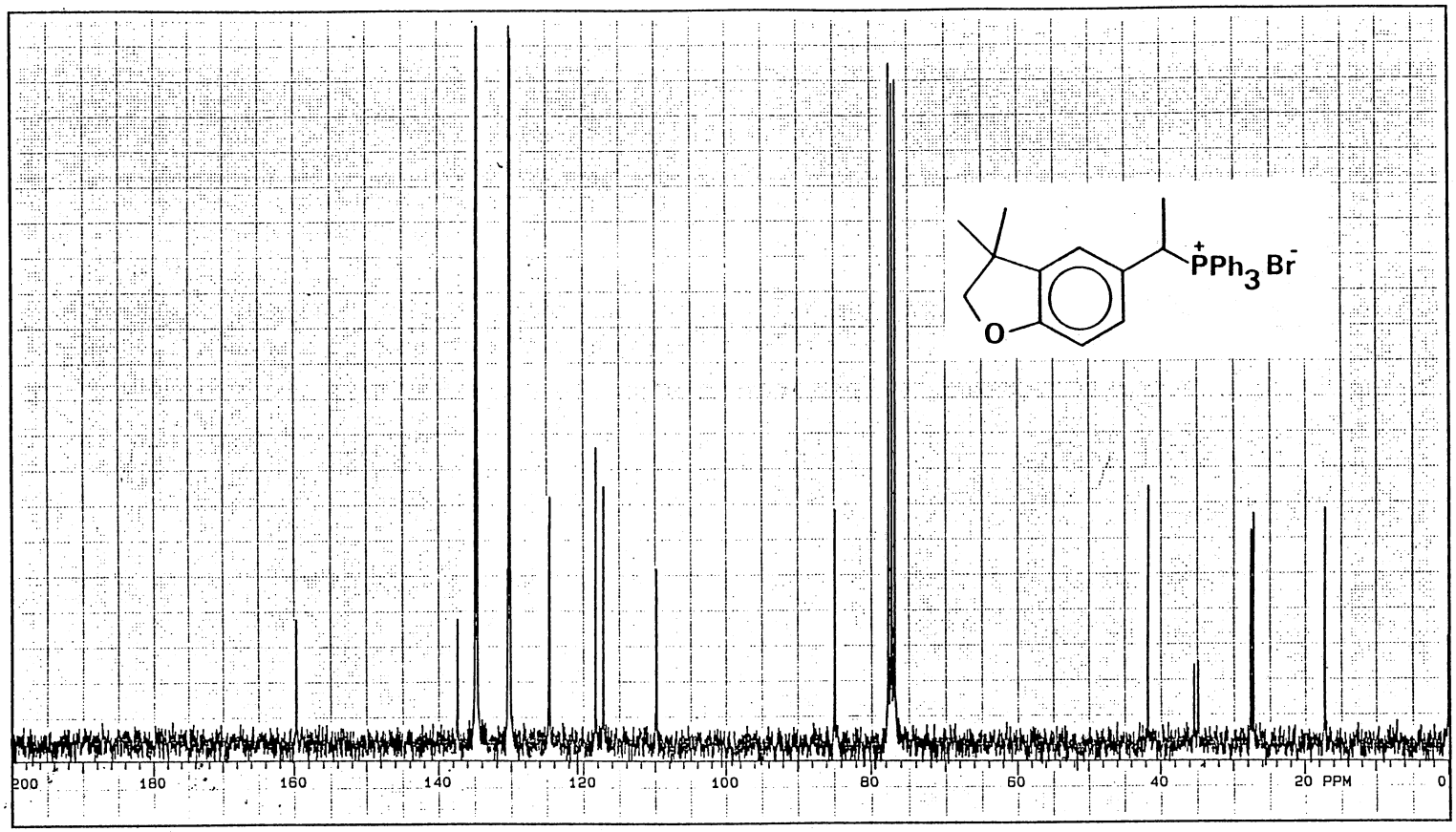
IR Spectrum of **82**

PLATE XIII



^{1}H NMR Spectrum of **83**

PLATE XIV



OBSERVE: Nucleus 13.500 Freq 75 MHz; Spec. Width 20000.0 Hz Offset 1500 Hz; Acq. Time 0.800 sec Delay 3.000 sec; Pulse Width 10.0 µsec Transients 192

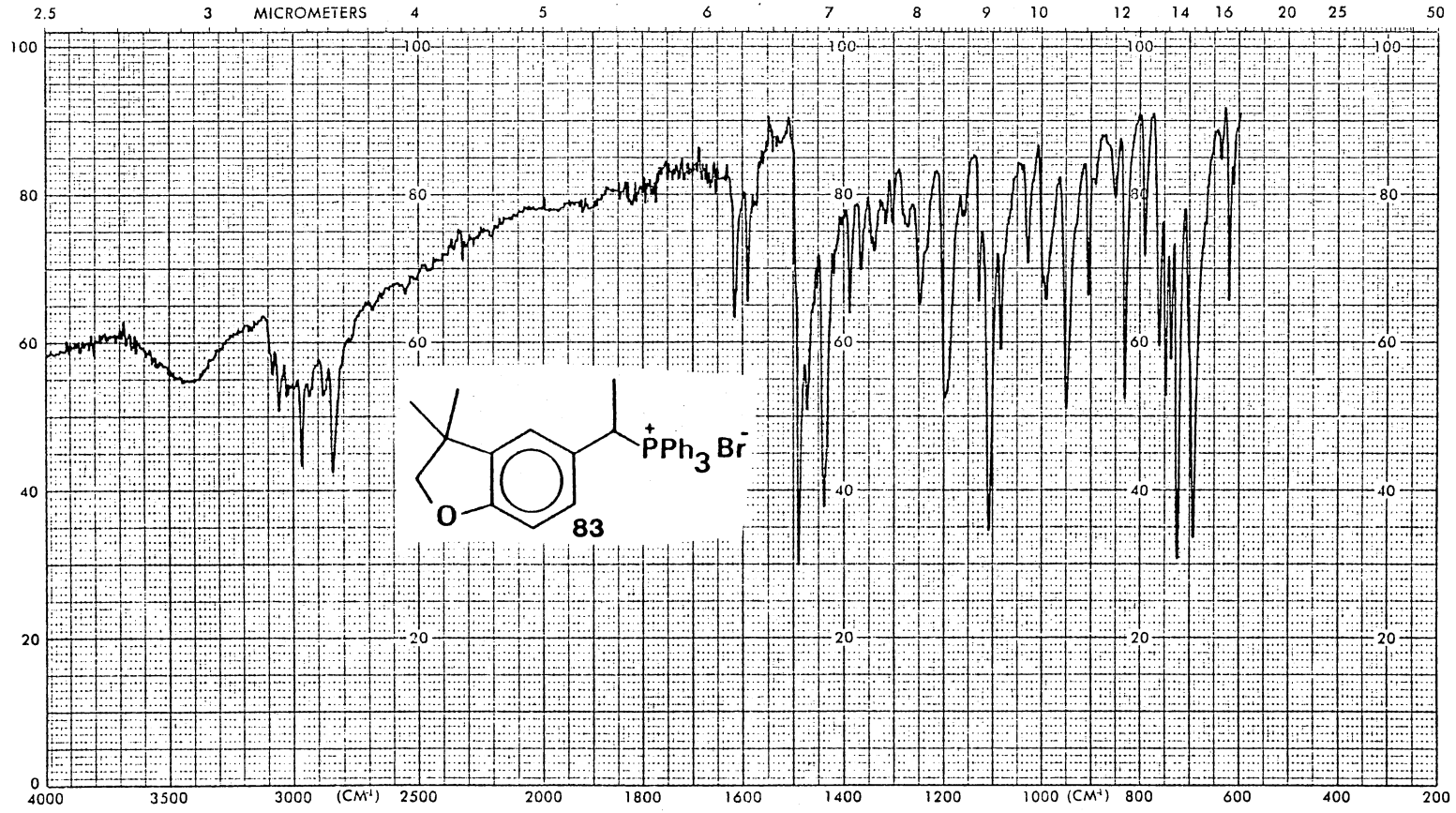
DECOUPLE: Nucleus 1.500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation Mode S Freq 7900 Hz; Pulse Width 17.5 µsec Power Mode ---

^{13}C NMR Spectrum of **83**

PLOT/PROCESSING: FN 32 K RE --- sec CD --- sec; LB 2.000 Hz AF --- sec CCD ---; Width 15085.9 Hz/ppm Start 0 Hz/ppm; Reference

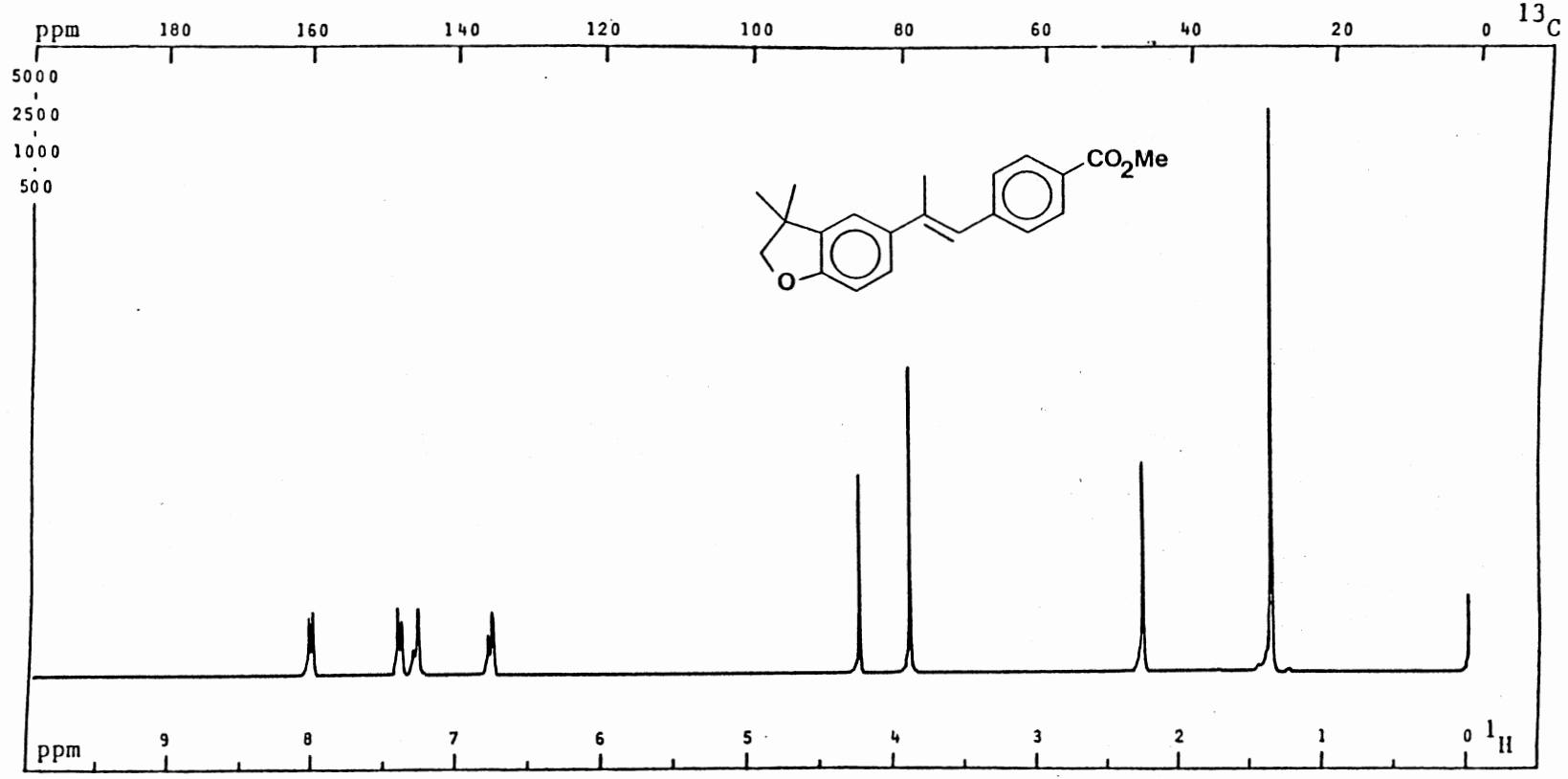
EXPERIMENT: Pulse Sequence SI013C; Tube O.D. mm; Temp. --- °C; Solvent CDCl3

PLATE XV



IR Spectrum of **83**-KBr

PLATE XVI



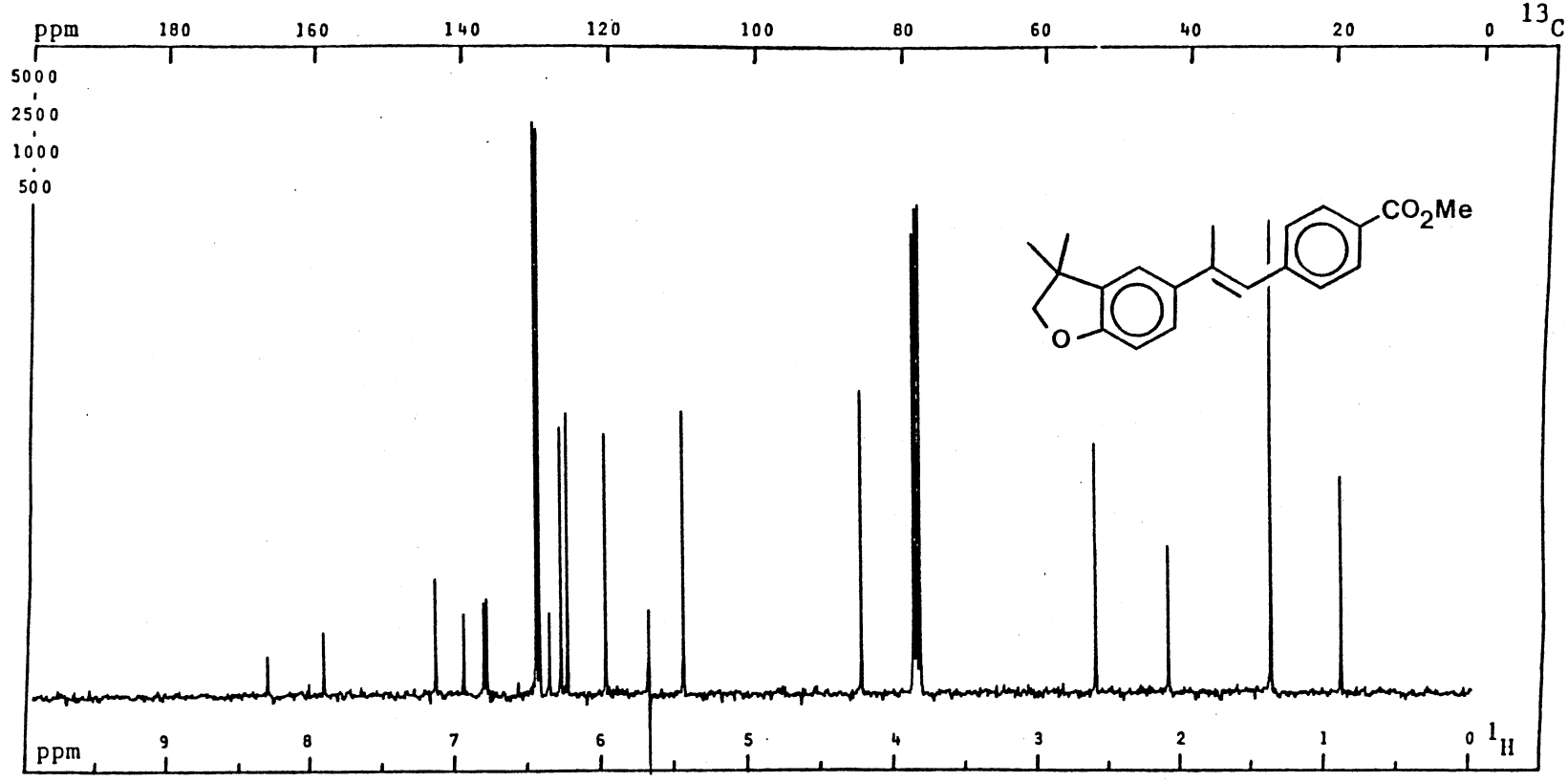
^{1}H NMR Spectrum of **58**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.94 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 4 K; PW/RF: 6.0 µs/dB; TO: 0 Hz; FB: Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 1 W/dB; NBW: Hz; LB: Hz.

PLATE XVII



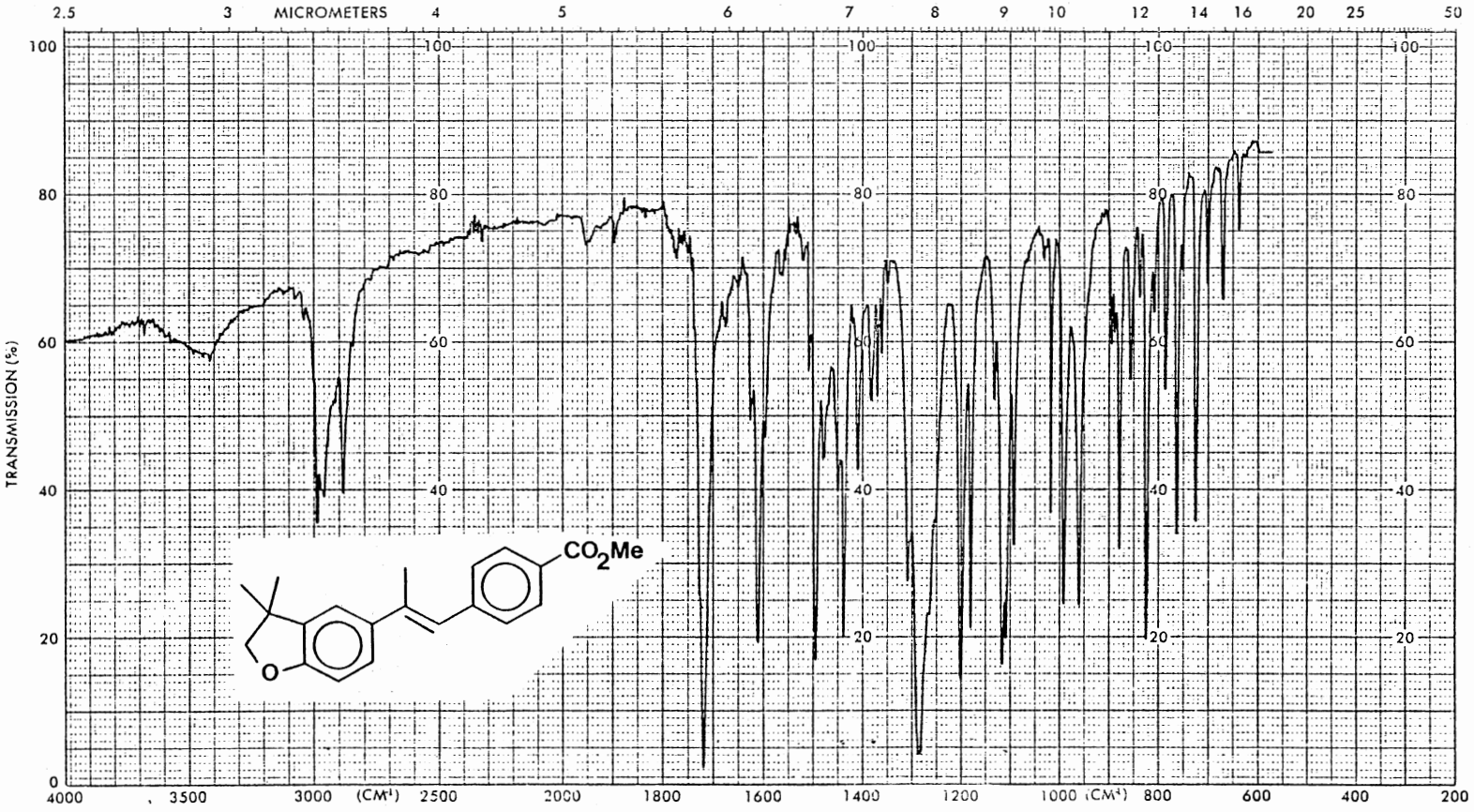
^{13}C NMR Spectrum of **58**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 352 .

Size: 20 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: Hz; Lock: ^{2}H ; D1,D5: 4.0 s.

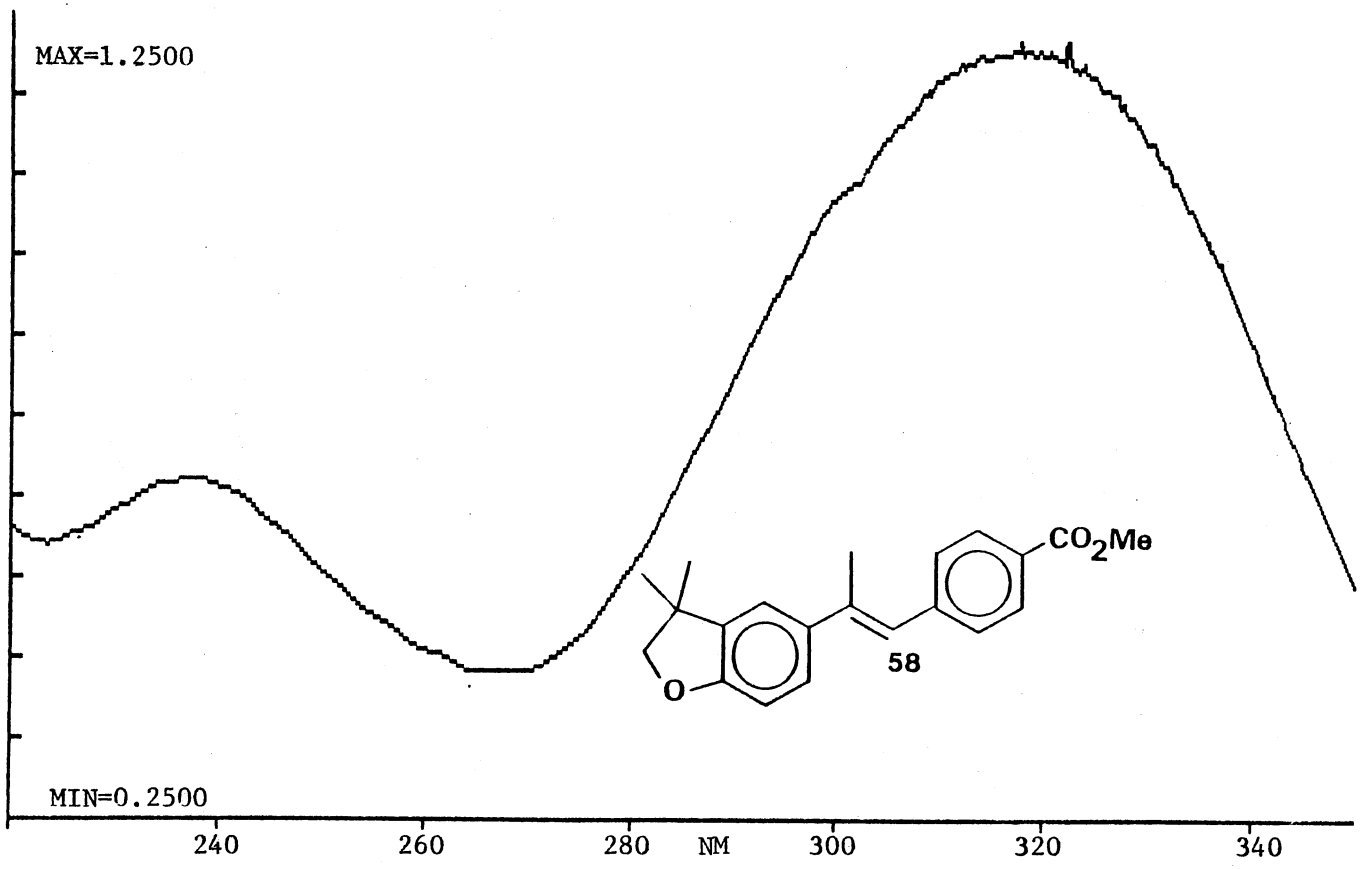
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 1.0 Hz.

PLATE XVIII



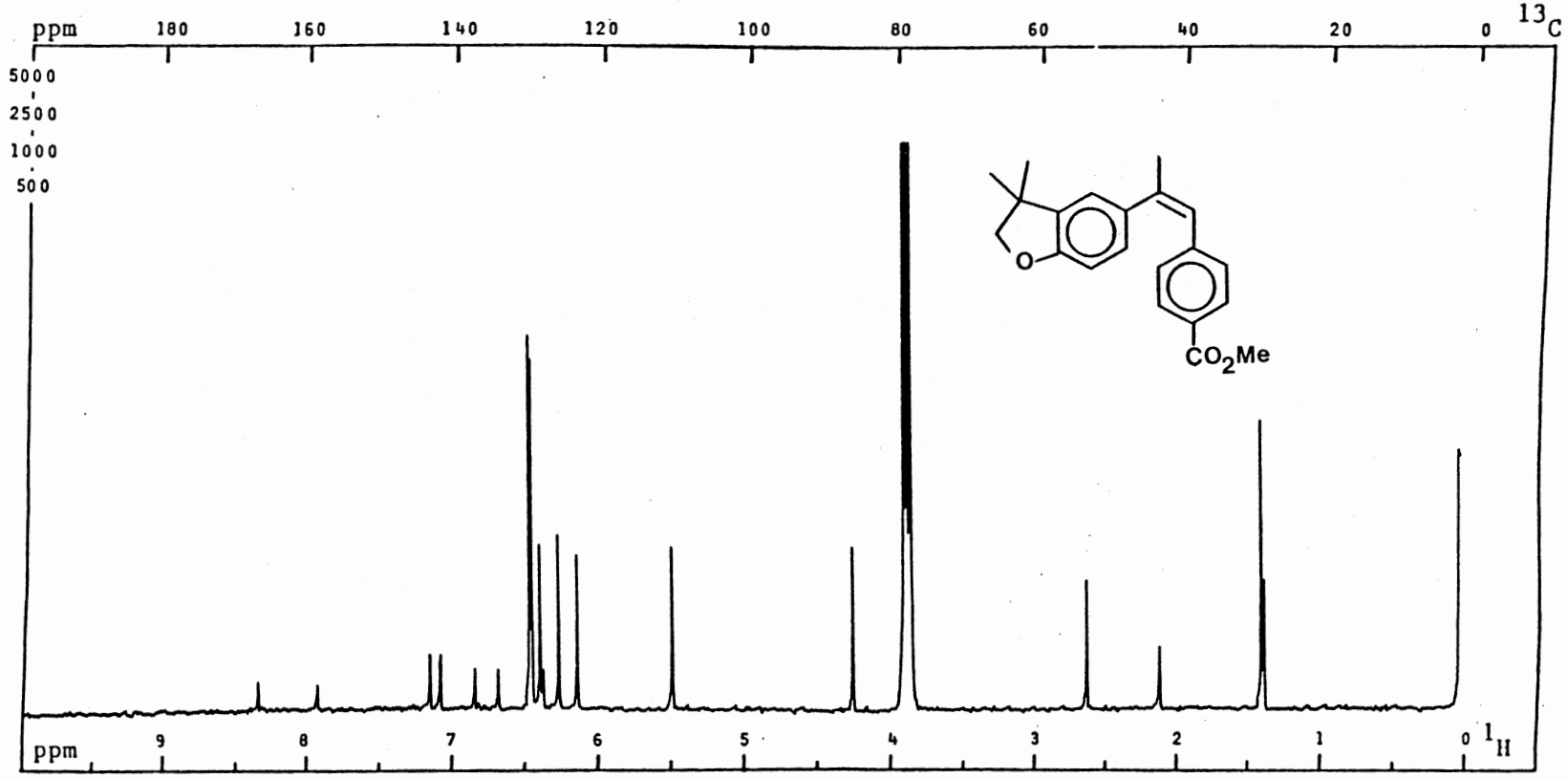
IR Spectrum of **58**-KBr

PLATE XIX



UV Spectrum of **58**

PLATE XX



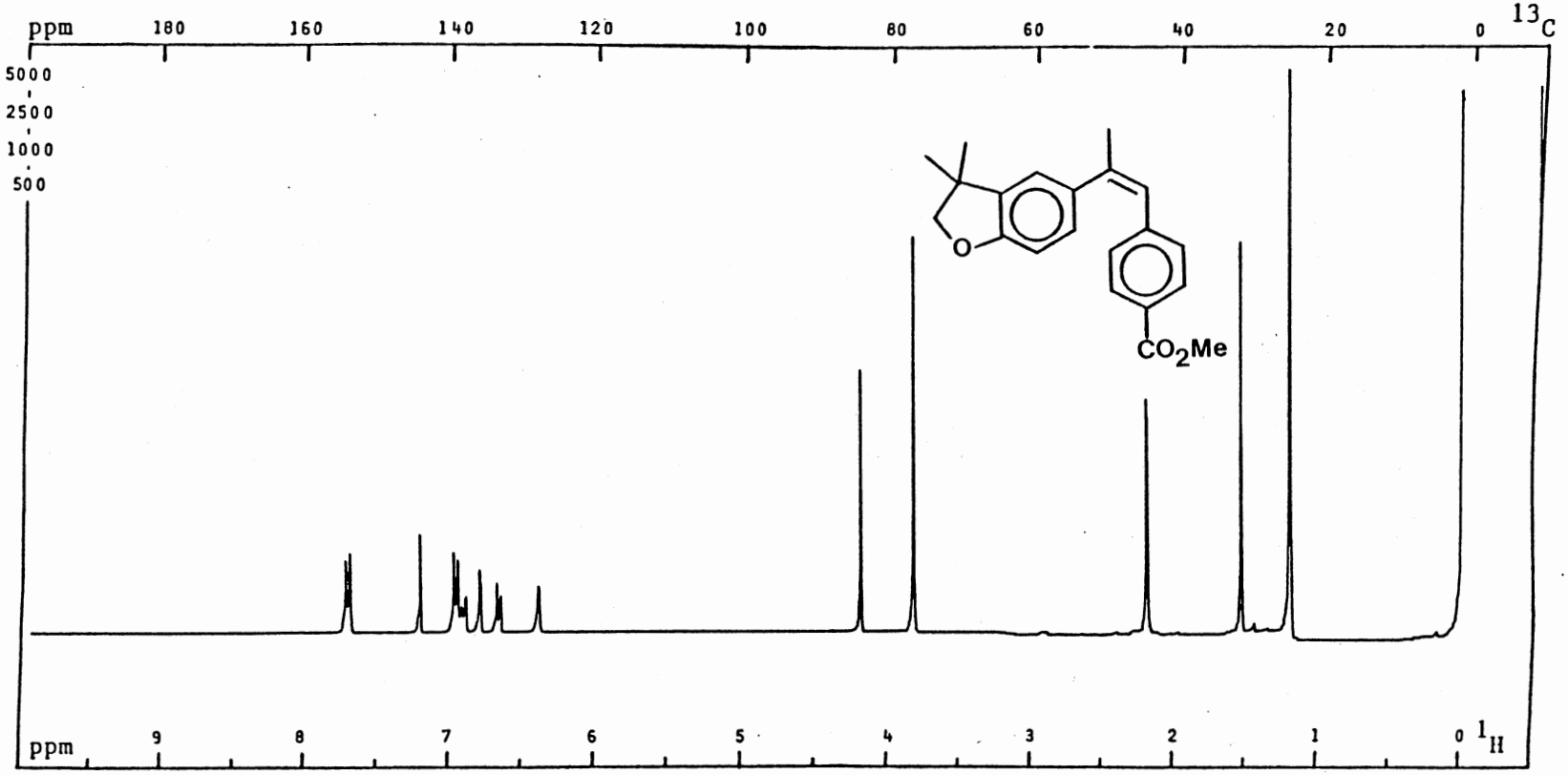
^{13}C NMR Spectrum of **59**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC:15085.9 Hz; T: RT °C; NT: 12000 .

Size: ^{20}K; PW/RF: 12.5 µs/dB; TO: 1000 Hz; FB: Hz; Lock: ^{2}H ; D1,D5: 4.0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.5 Hz.

PLATE XXI



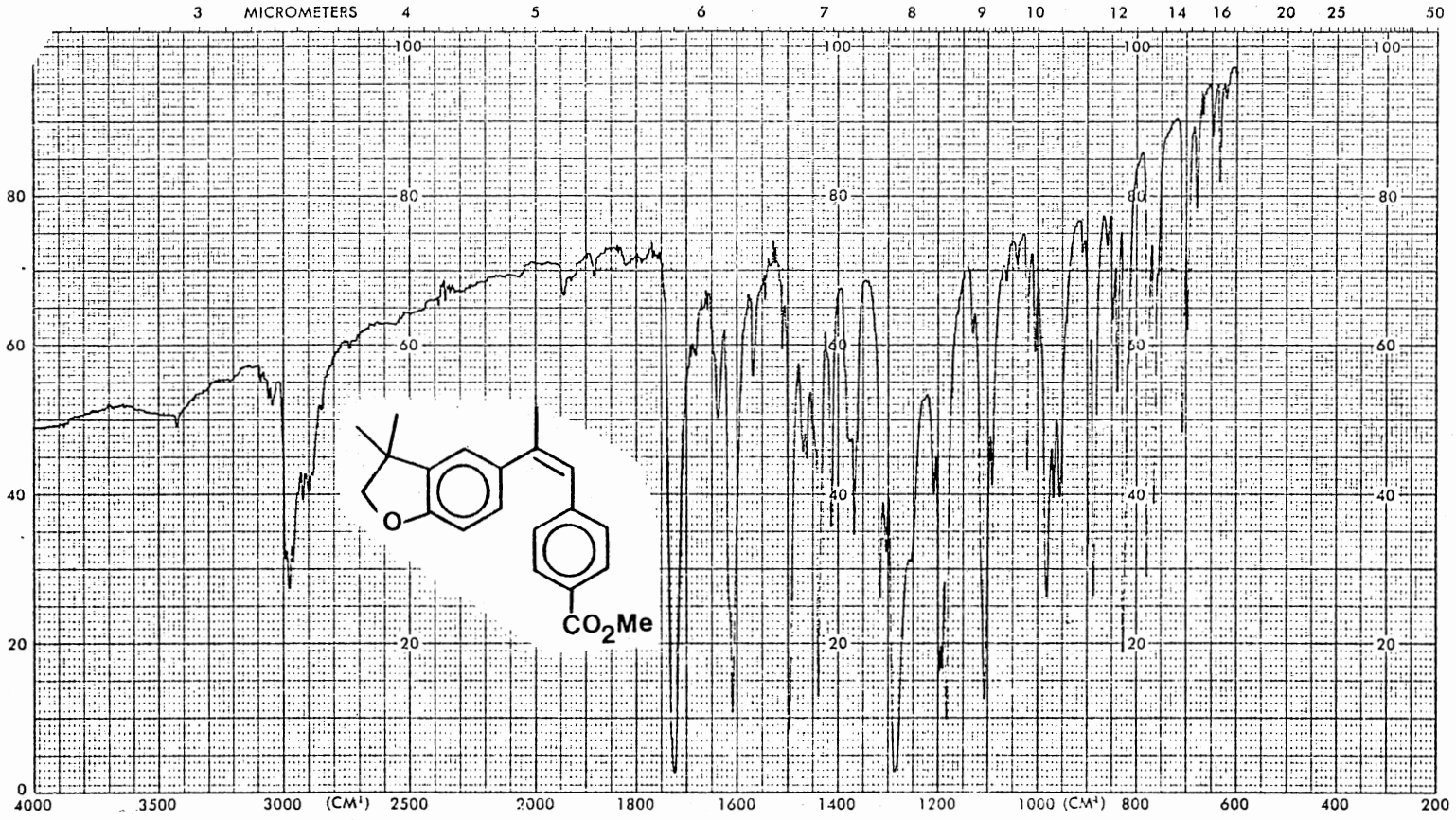
^{1}H NMR Spectrum of **59**

PFT X CW _ ; Solvent: $DCCl_3$; SF:299.94 MHz; WC: 2999.4 Hz; T: RT °C; NT: 100 .

Size: 4 K; PW/RF:5.0 µs/dB; TO: 0 Hz; FB: Hz; Lock: ^{2}H ; D1,D5:0 s.

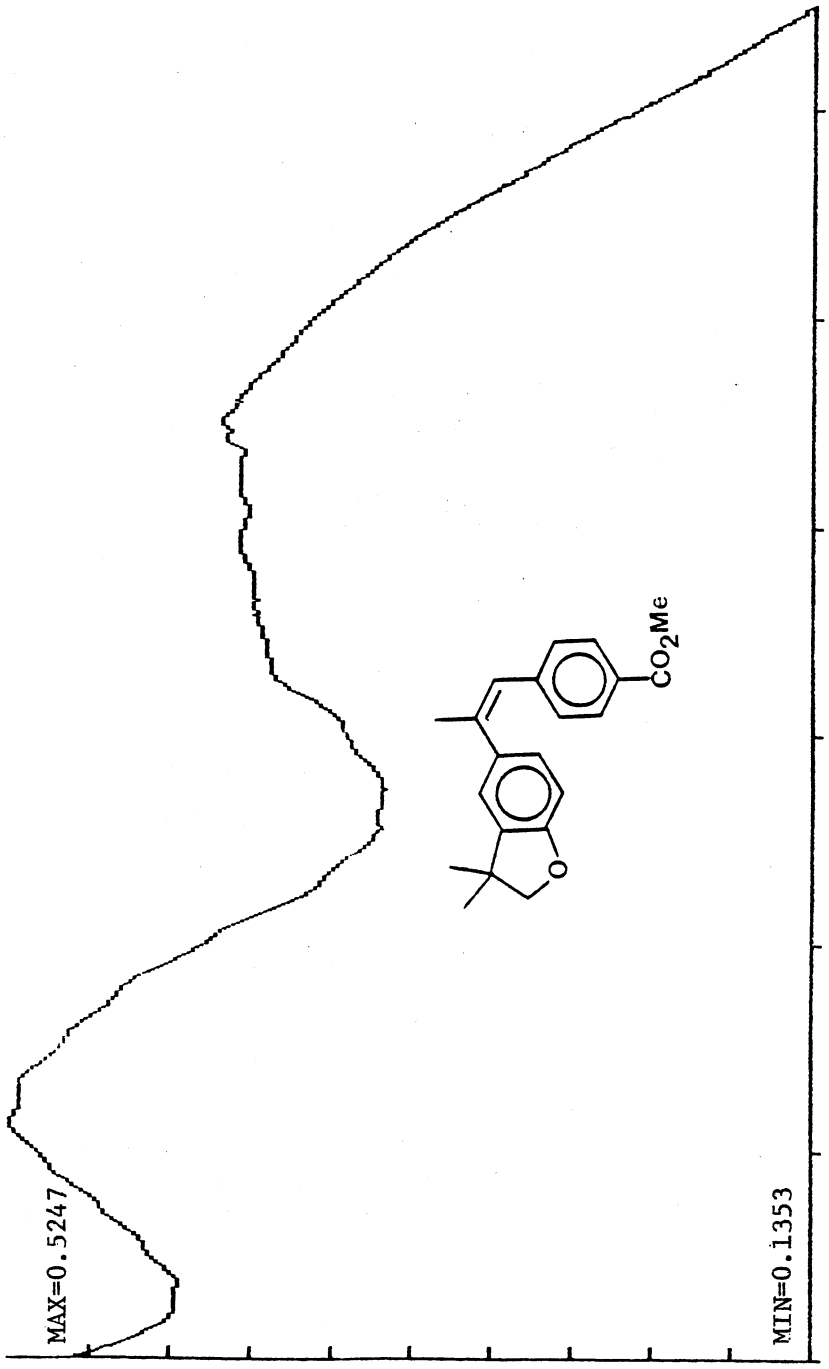
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 12 W/dB; NBW:200 Hz; LB:0.7 Hz.

PLATE XXII



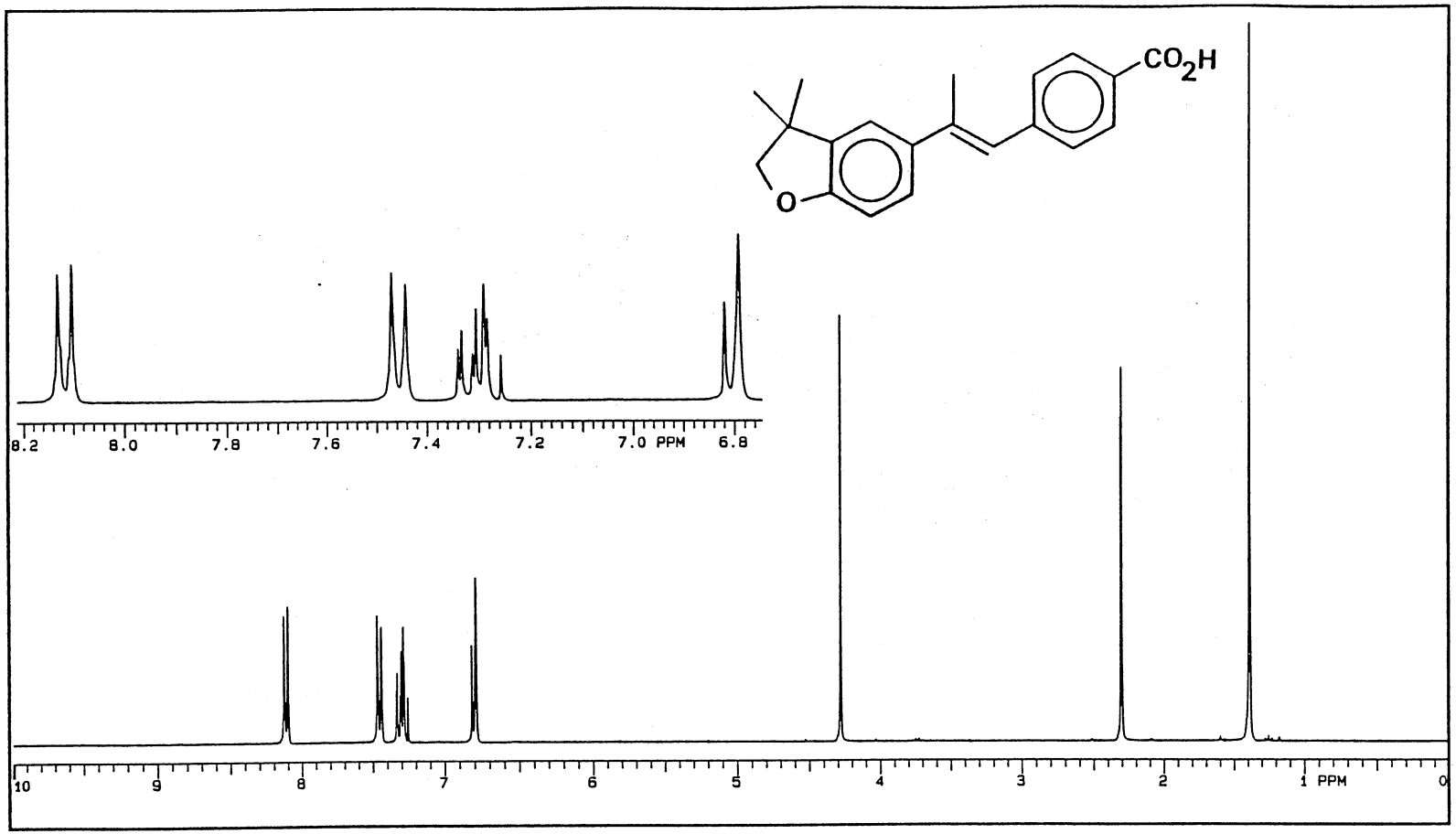
IR Spectrum of **59**-KBr

PLATE XXIII



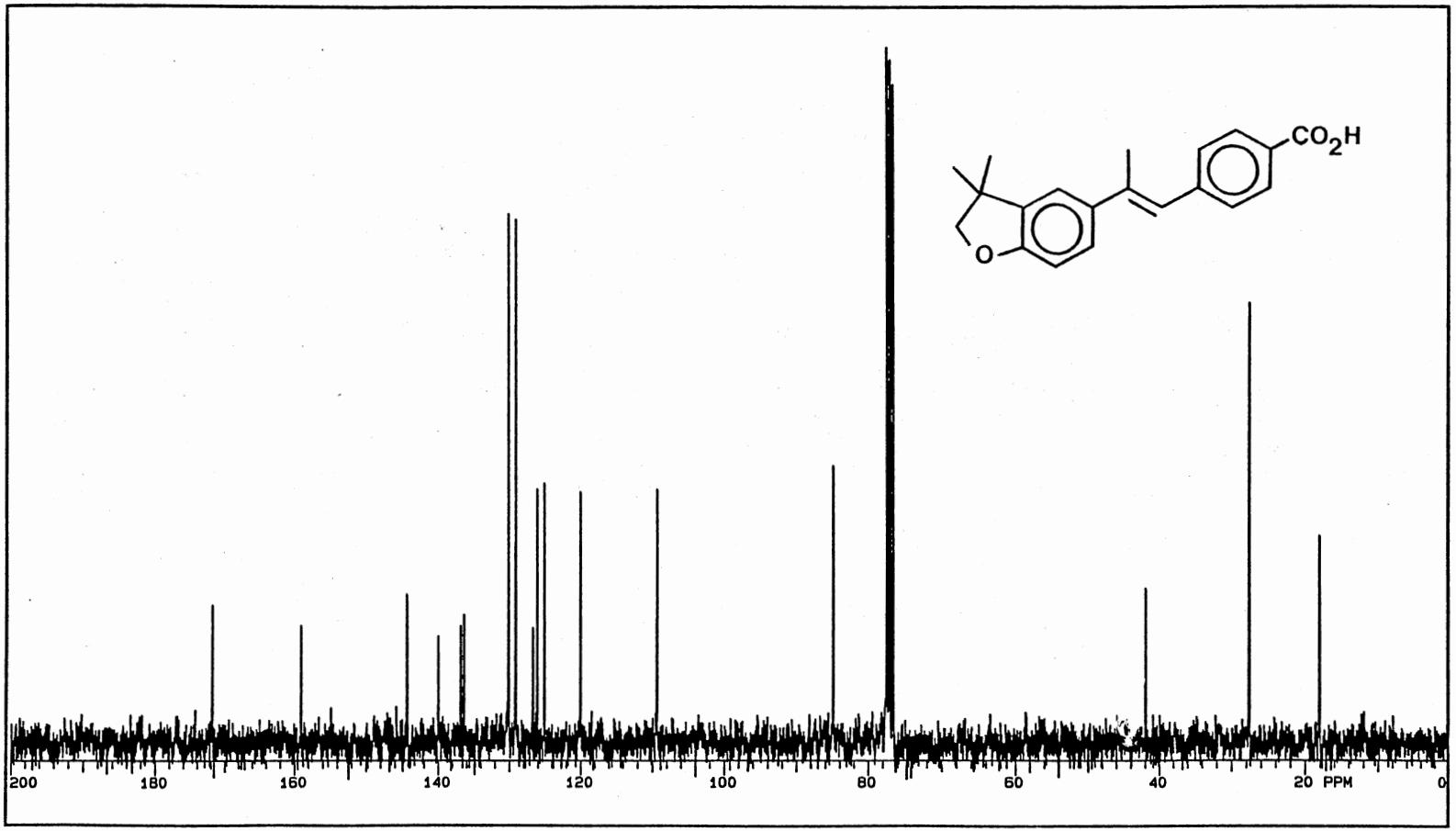
UV Spectrum of **59**

PLATE XXIV



^{1}H NMR Spectrum of **62**

PLATE XXV



OBSERVE: Nucleus 13.500 Freq 75 MHz; Spec. Width 20000.0 Hz Offset 1500 Hz; Acq. Time 1.000 sec Delay 3.000 sec; Pulse Width 12.0 µsec Transients 160

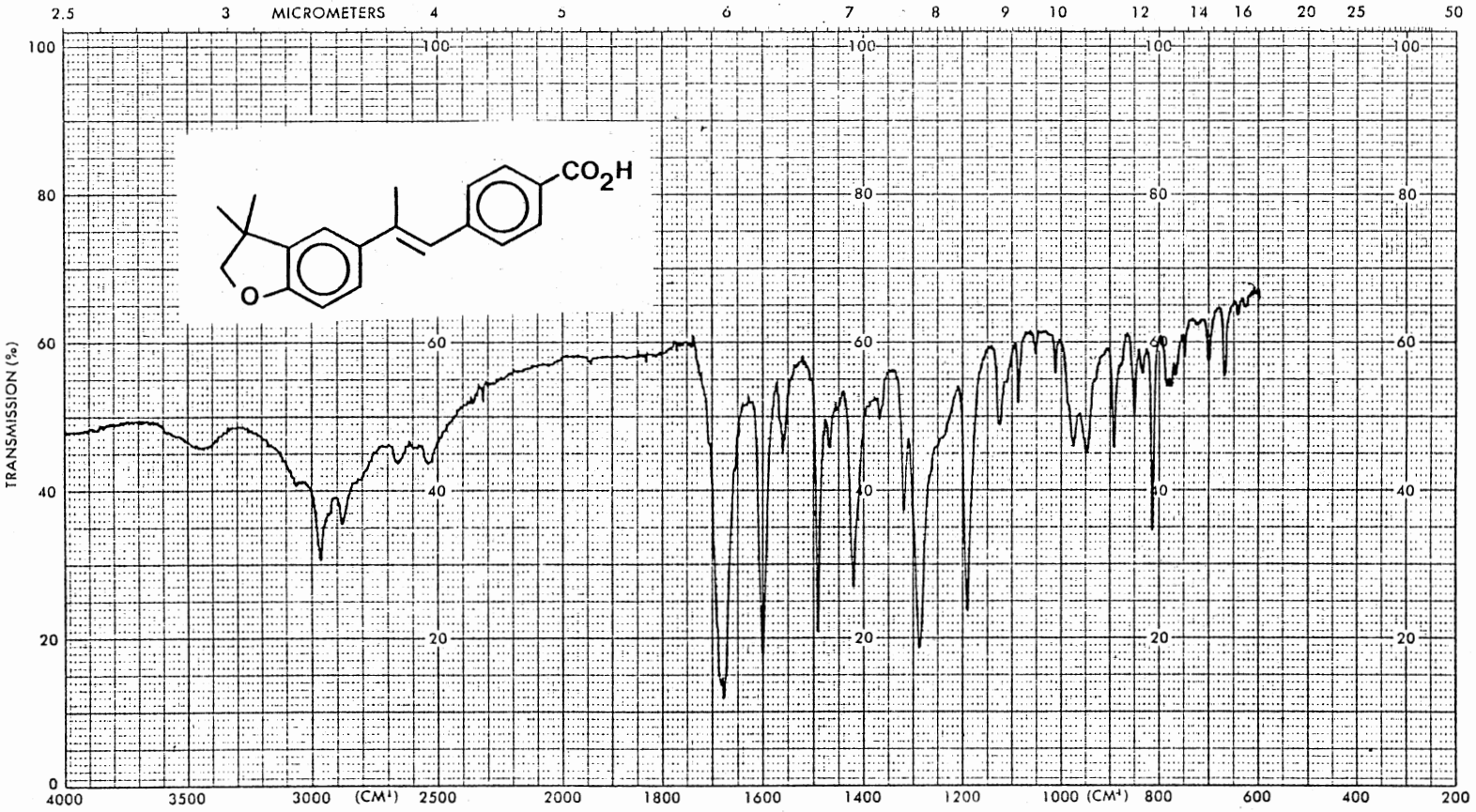
DECOUPLE: Nucleus 1.500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation Mode S Freq 7900 Hz; Pulse Width 17.5 µsec Power Mode ——

^{13}C NMR Spectrum of **62**

PLOT/PROCESSING: FN 64 K RE —— sec CD —— sec; LB 2.000 Hz AF —— sec CCD ——; Width 15085.9 Hz/ppm Start 0 Hz/ppm; Reference ——

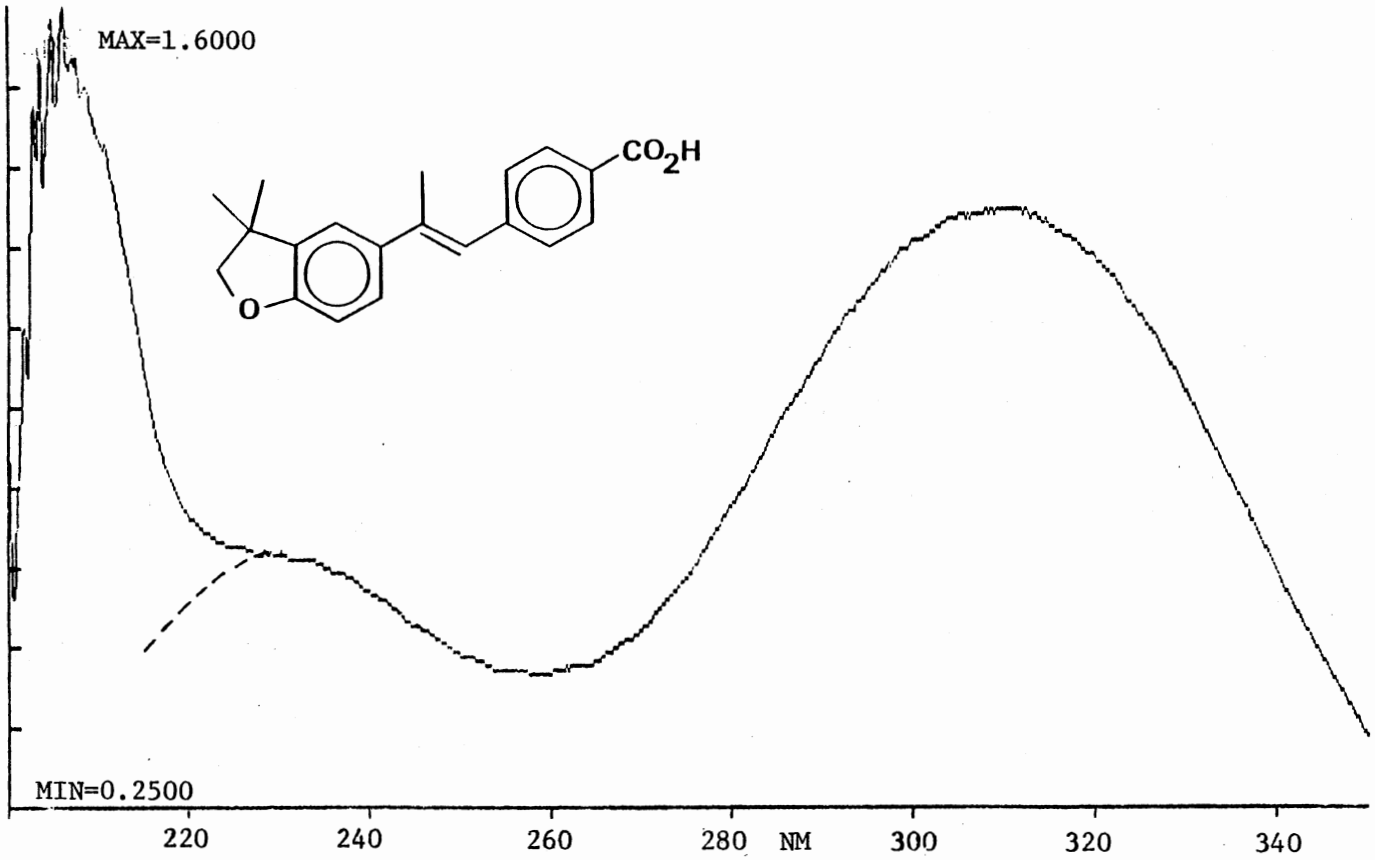
EXPERIMENT: Pulse Sequence STD13C; Tube O.D. —— mm; Temp. —— °C; Solvent CDCL3

PLATE XXVI



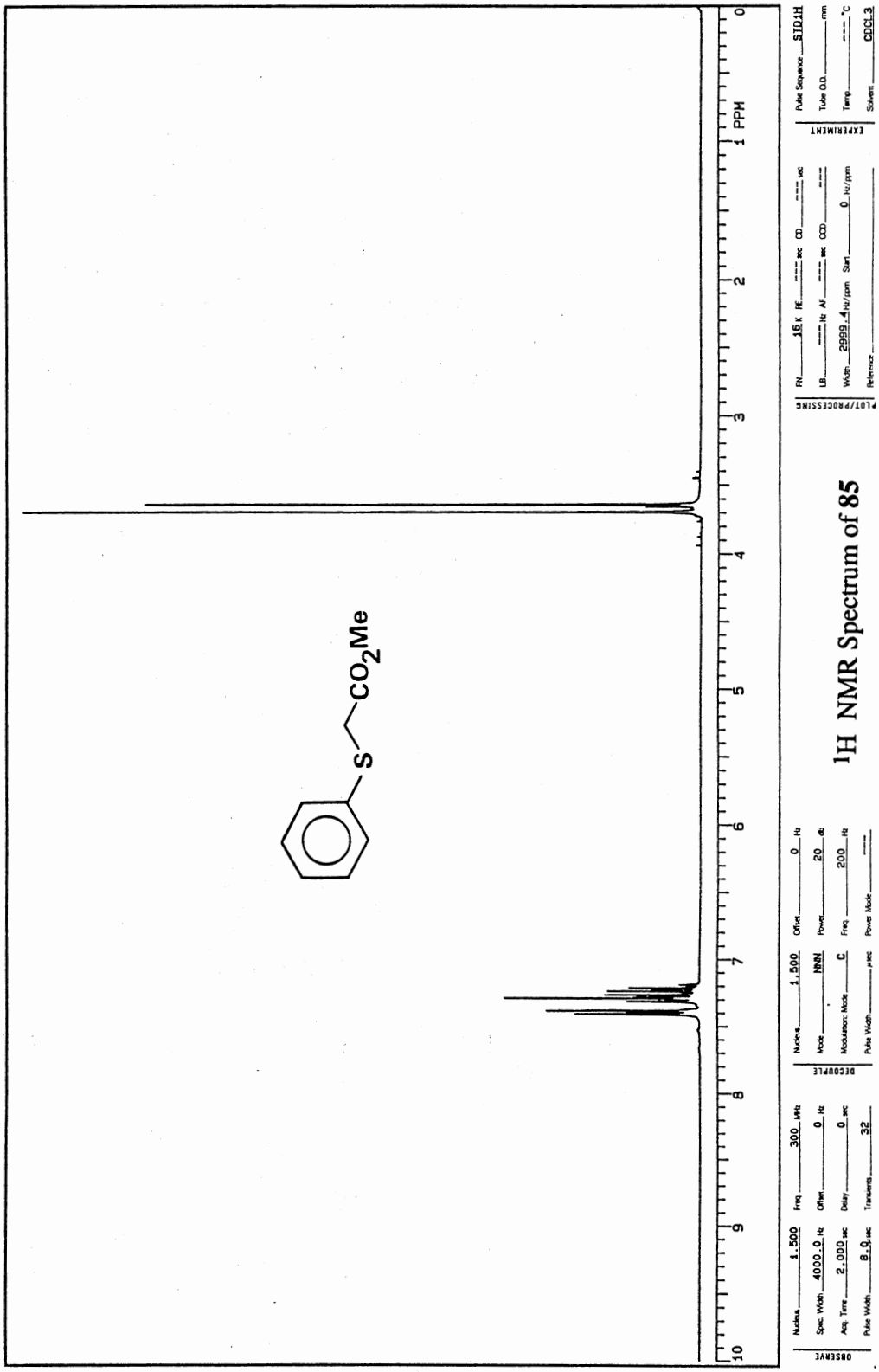
IR Spectrum of **62**-KBr

PLATE XXVII



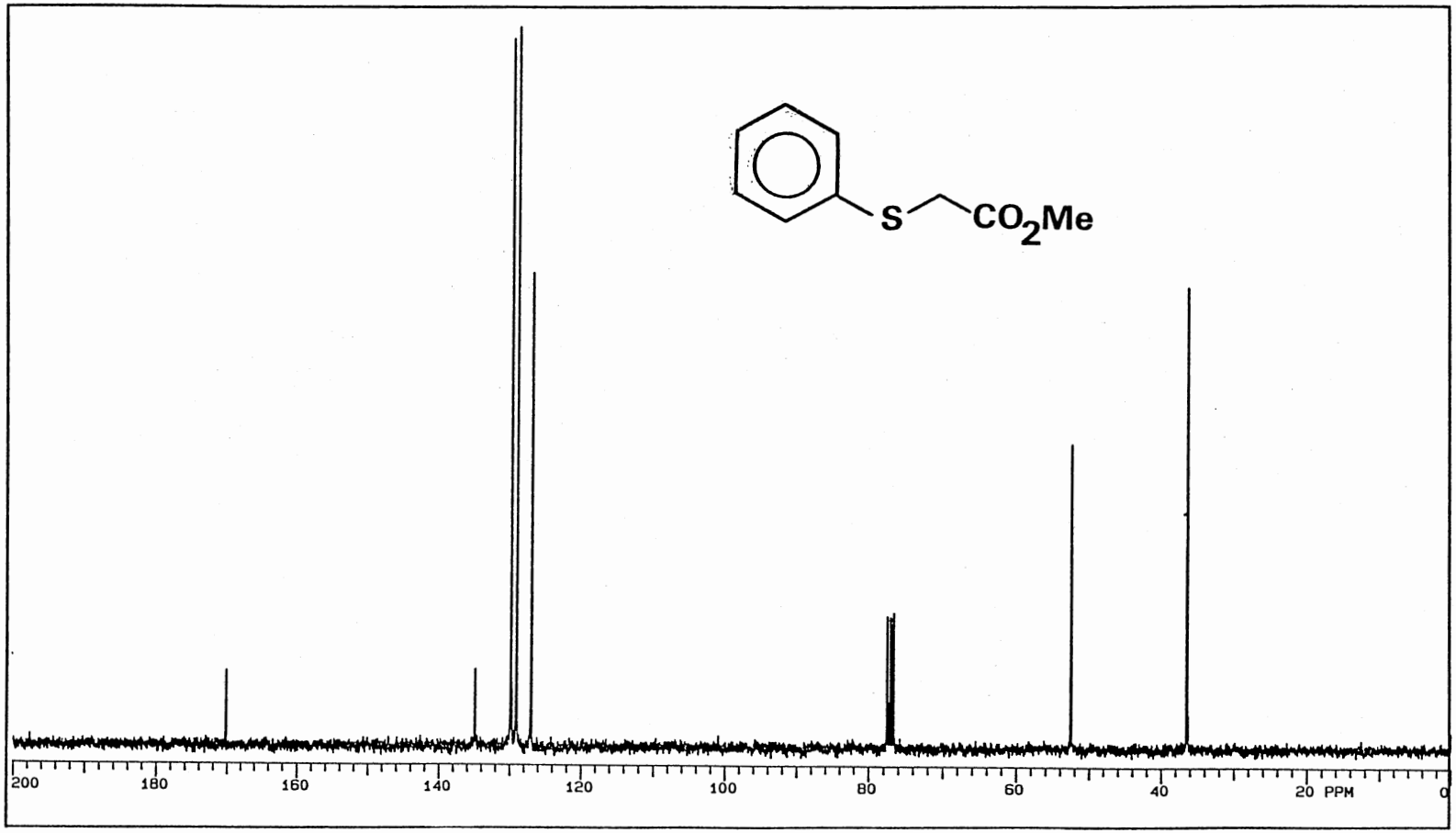
UV Spectrum of **62**

PLATE XXVIII



^{1}H NMR Spectrum of **85**

PLATE XXIX



OBSERVE: Nucleus 13.500 Freq 75 MHz; Spec. Width 20000.0 Hz Offset 1500 Hz; Acq. Time 1.000 sec Delay 3.000 sec; Pulse Width 12.0 µsec Transients 64

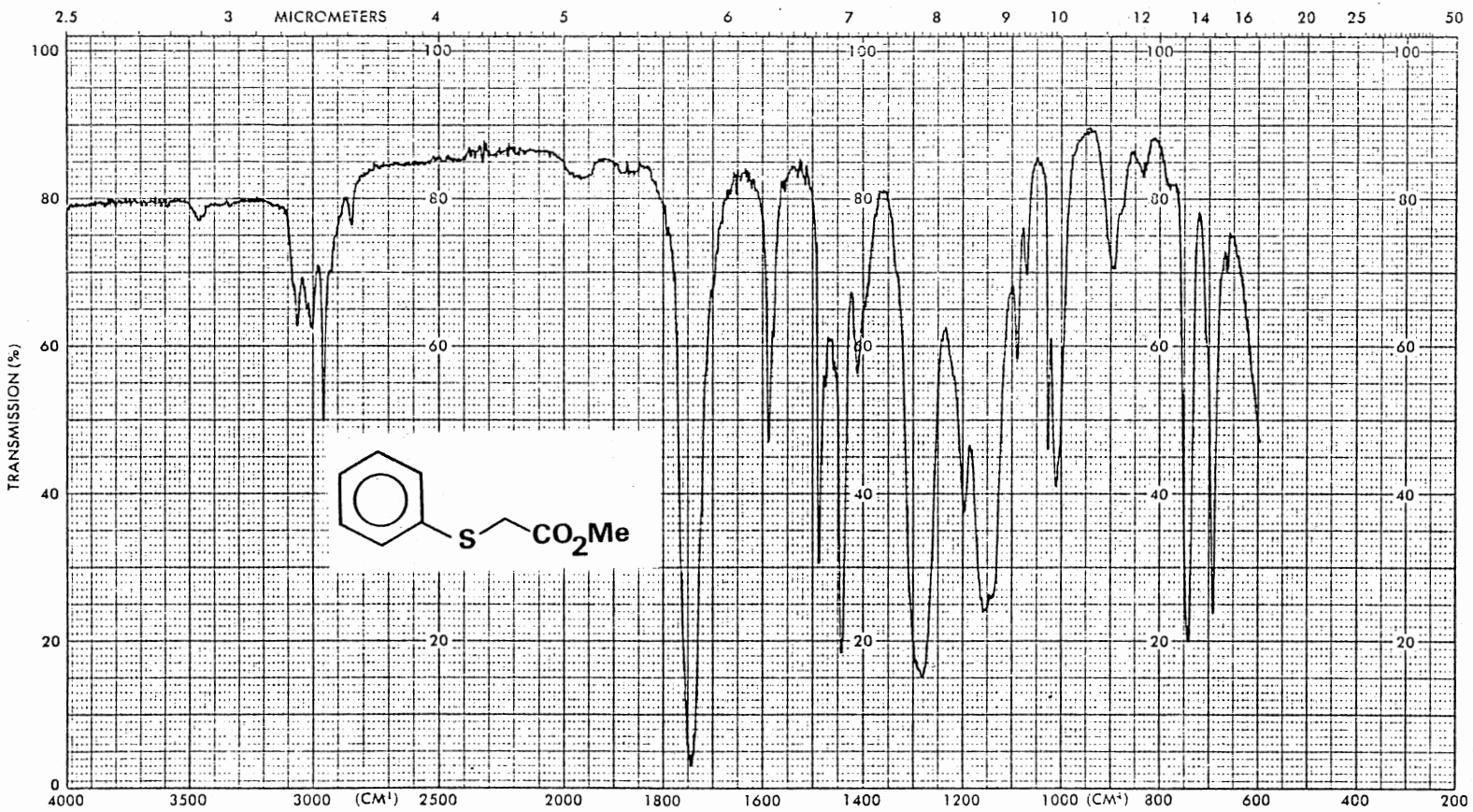
DECOUPLE: Nucleus 1.500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation. Mode S Freq 7900 Hz; Pulse Width 17.5 µsec Power Mode ——

PLOT/PROCESSING: FN 64K RE —— sec CD —— sec; LB 2.000 Hz AF —— sec CCD ——; Width 15085.9Hz/ppm Start 0 Hz/ppm; Reference ——

EXPERIMENT: Pulse Sequence STD13C; Tube O.D. —— mm; Temp. —— °C; Solvent CDCL3

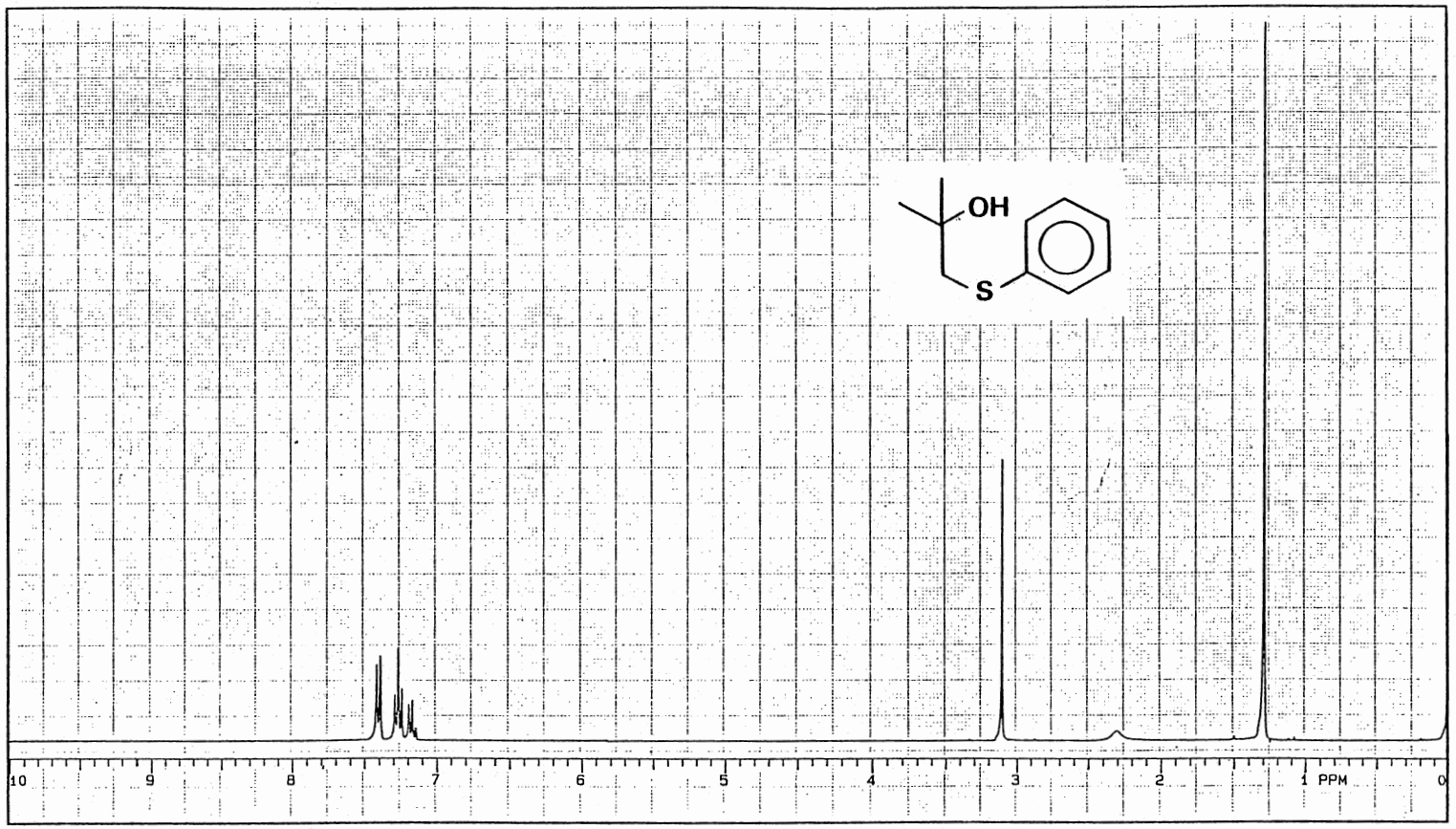
^{13}C NMR Spectrum of **85**

PLATE XXX



IR Spectrum of **85**

PLATE XXXI



OBSERVE: Nucleus 1.500 Freq 300 MHz; Spec. Width 4000.0 Hz Offset 100 Hz; Acq. Time 2.000 sec Delay 0 sec; Pulse Width 5.0 μsec Transients 16

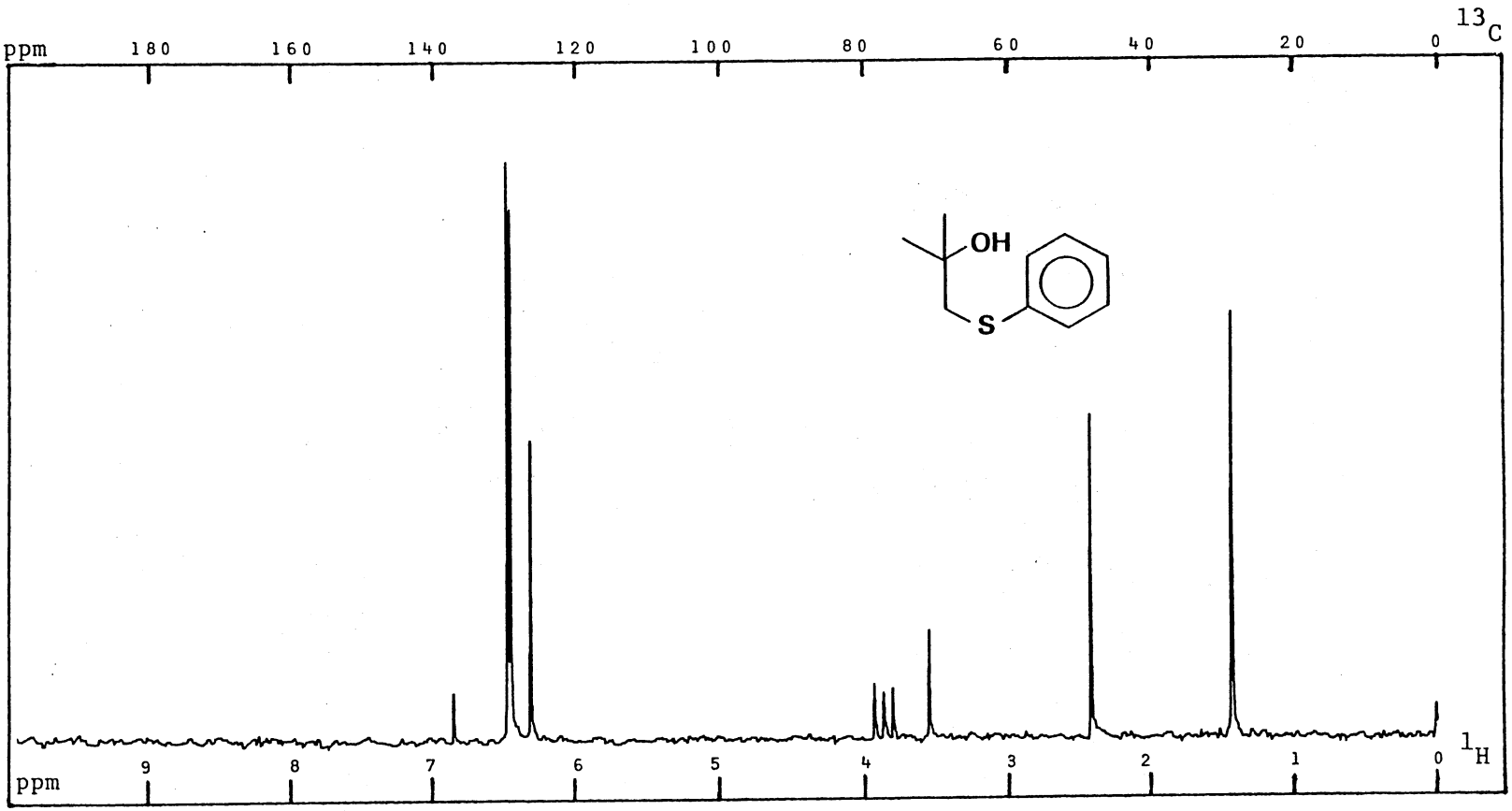
DECOUPLE: Nucleus 1.500 Offset 0 Hz; Mode NNN Power 20 db; Modulation Mode C Freq 200 Hz; Pulse Width μsec Power Mode ---

^{1}H NMR Spectrum of **86**

PLOT/PROCESSING: FN 16 K RE --- sec CD --- sec; LB 0.500 Hz AF --- sec CCD ---; Width 2999.4 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence S2PUL; Tube O.D. mm; Temp --- °C; Solvent CDCL3

PLATE XXXII



^{13}C NMR Spectrum of 86

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: Hz; T: RT °C; NT: 600 .

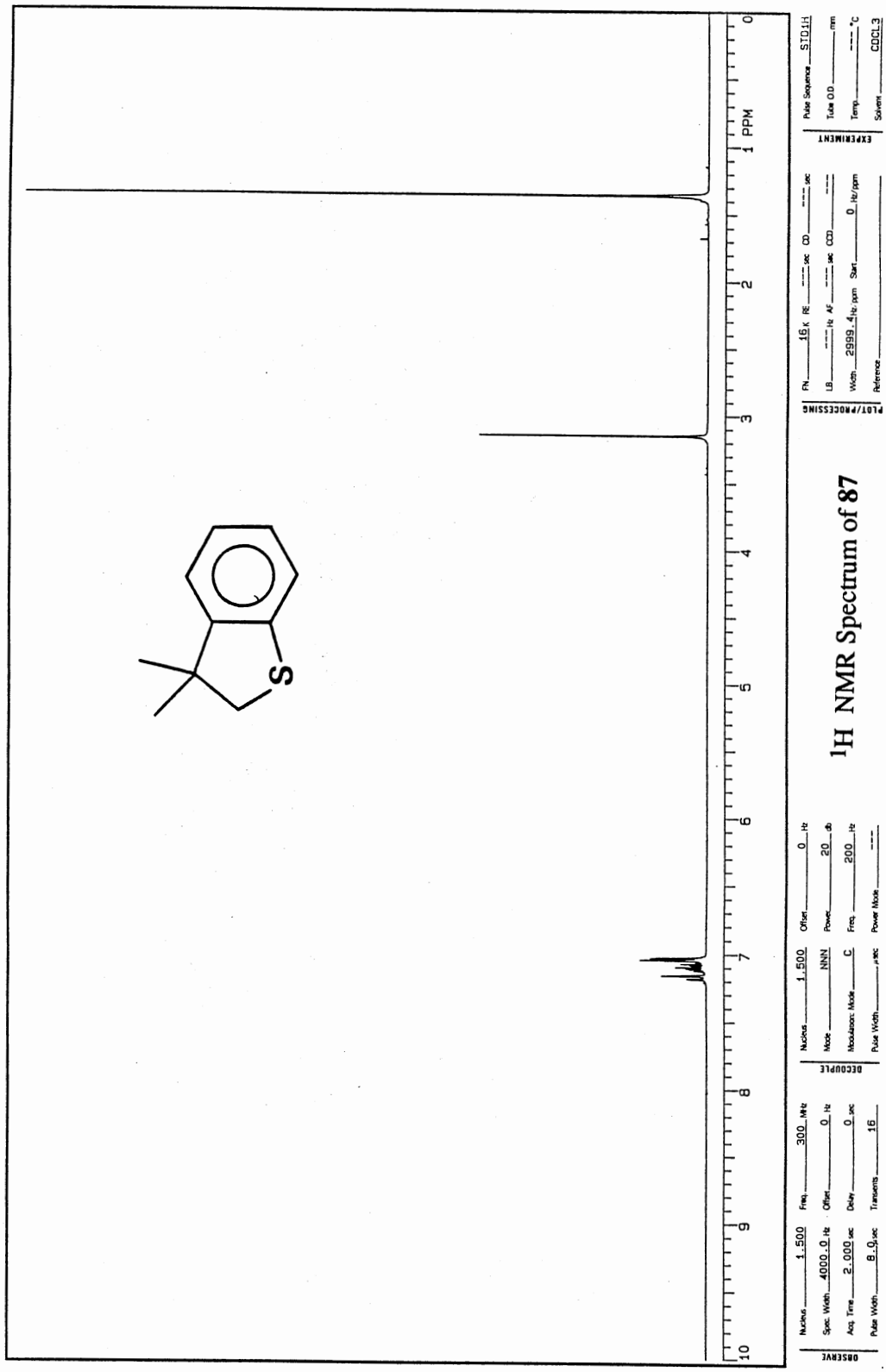
Size: 8 K; PW/RF:22 µs/dB; TO: Hz; FB: Hz; Lock: ^2H ;D1,D5: 4.0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): W/dB; NBW: Hz; LB: Hz.

PLATE XXXIII

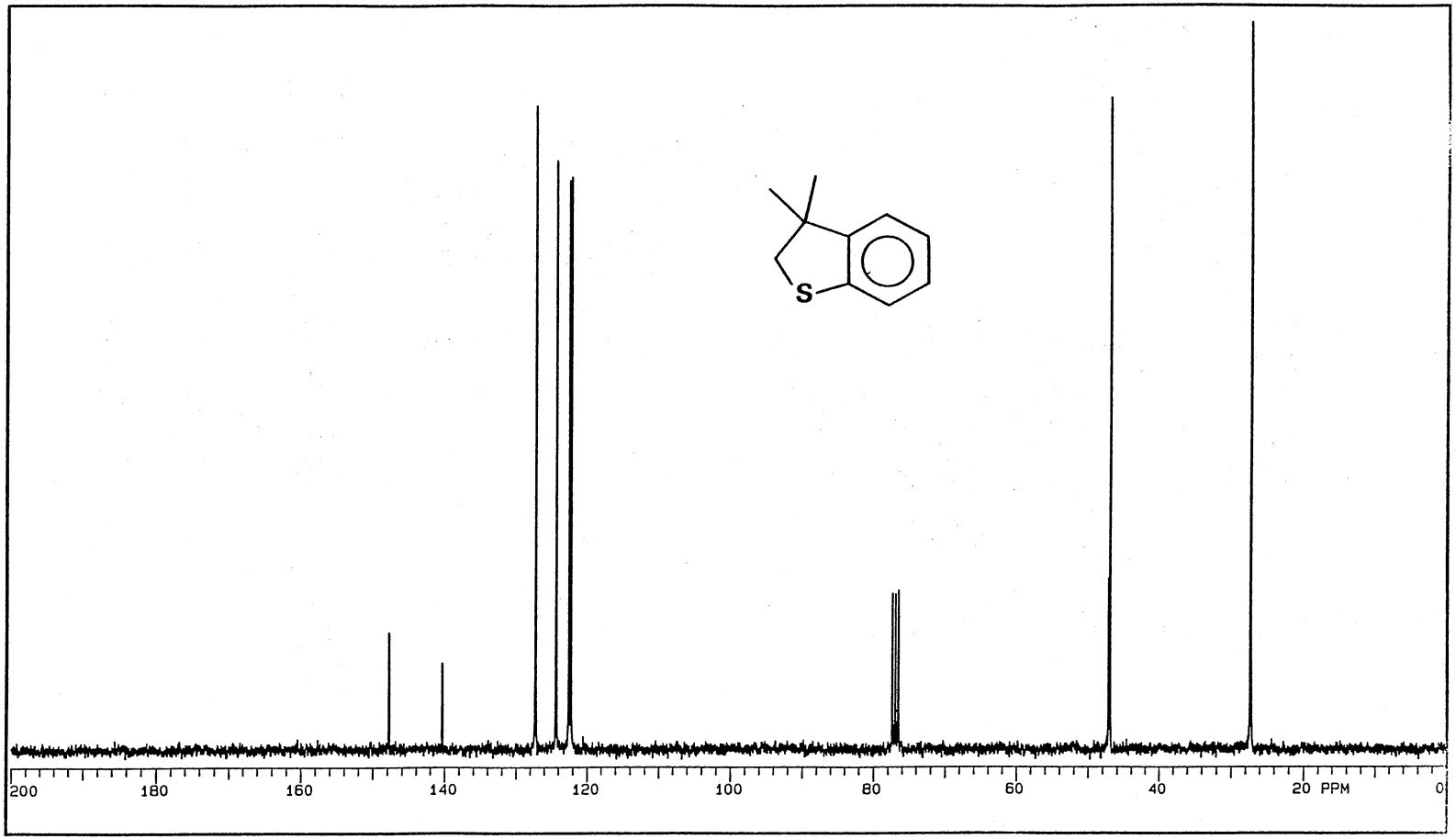
IR Spectrum of **86**

PLATE XXXIV



^{1}H NMR Spectrum of **87**

PLATE XXXV



OBSERVE: Nucleus 13.500 Freq. 75 MHz; Spec. Width 20000.0 Hz Offset 1500 Hz; Acq. Time 1.000 sec Delay 3.000 sec; Pulse Width 12.0 µsec Transients 128

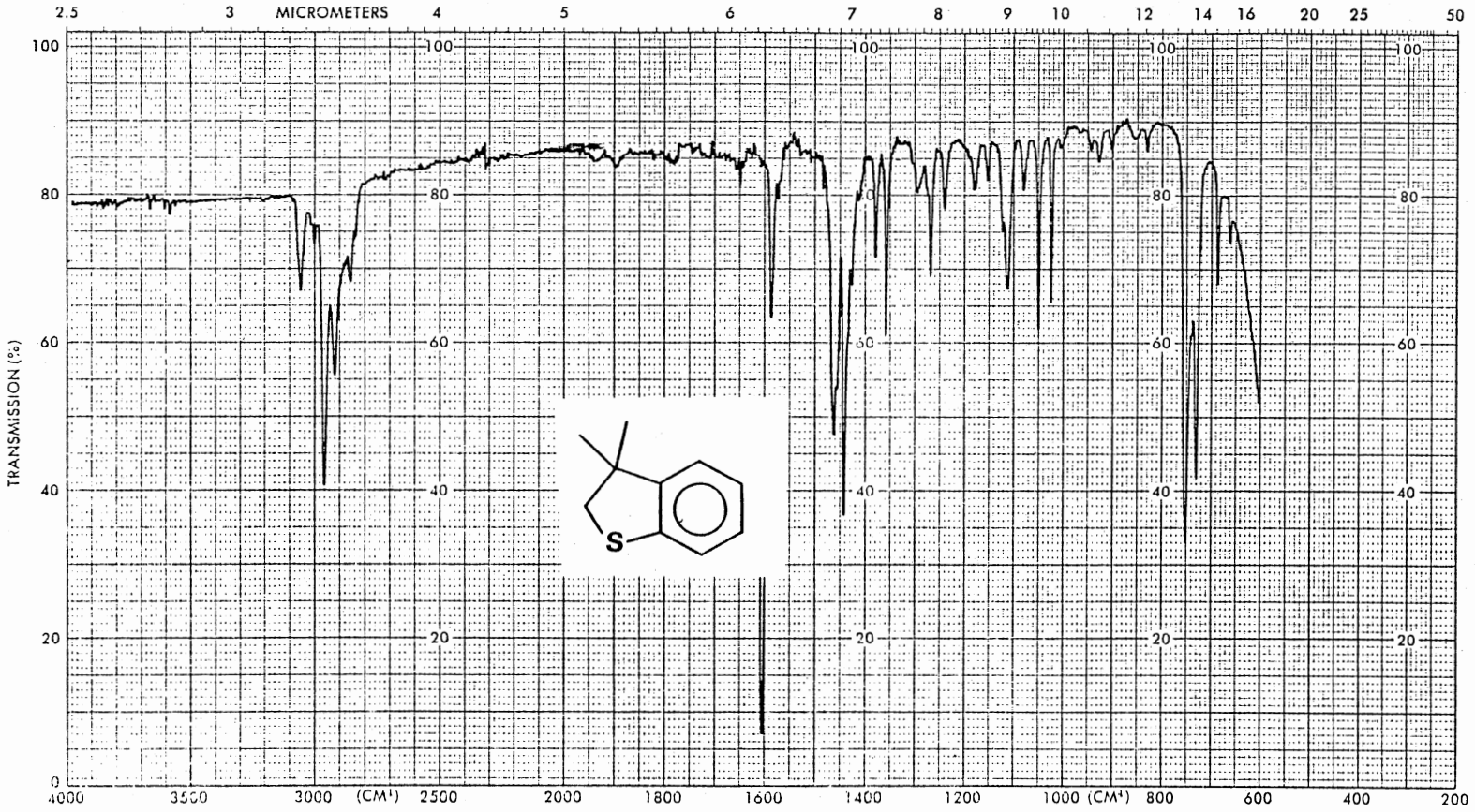
DECOUPLE: Nucleus 1.500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation Mode S Freq. 7900 Hz; Pulse Width 17.5 µsec Power Mode ---

PLOT/PROCESSING: FN 64 K RE --- sec CD --- sec; LB 2.000 Hz AF --- sec CCD ---; Width 15085.9 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence STD13C; Tube O.D. ___ mm; Temp. --- °C; Solvent CDCL3

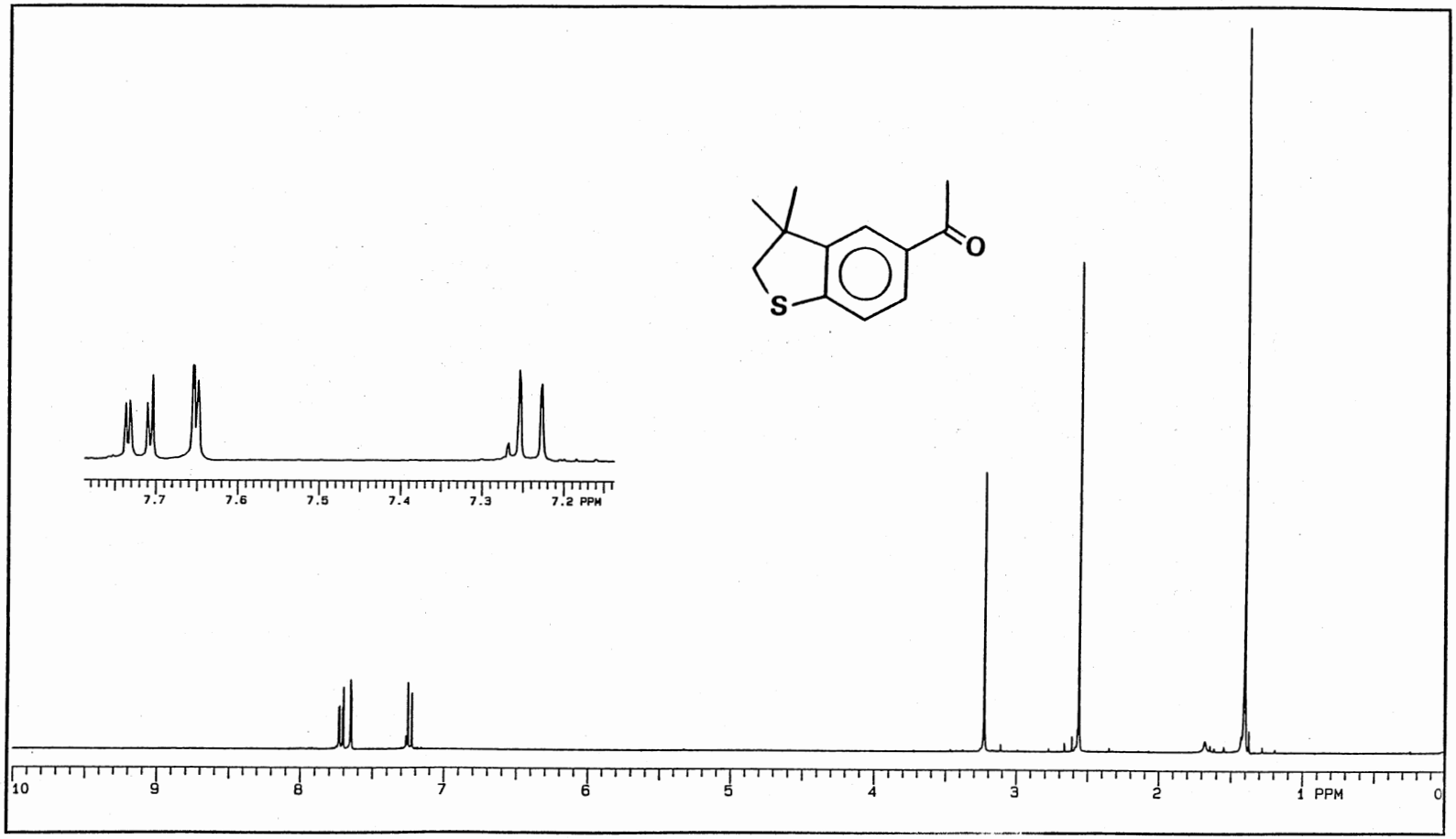
^{13}C NMR Spectrum of **87**

PLATE XXXVI



IR Spectrum of **87**

PLATE XXXVII



OBSERVE Nucleus 1.500 Freq 300 MHz Spec. Width 4000.0 Hz Offset 0 Hz Acq. Time 2.000 sec Delay 0 sec Pulse Width 8.0 sec Transients 32 SU STD 1H

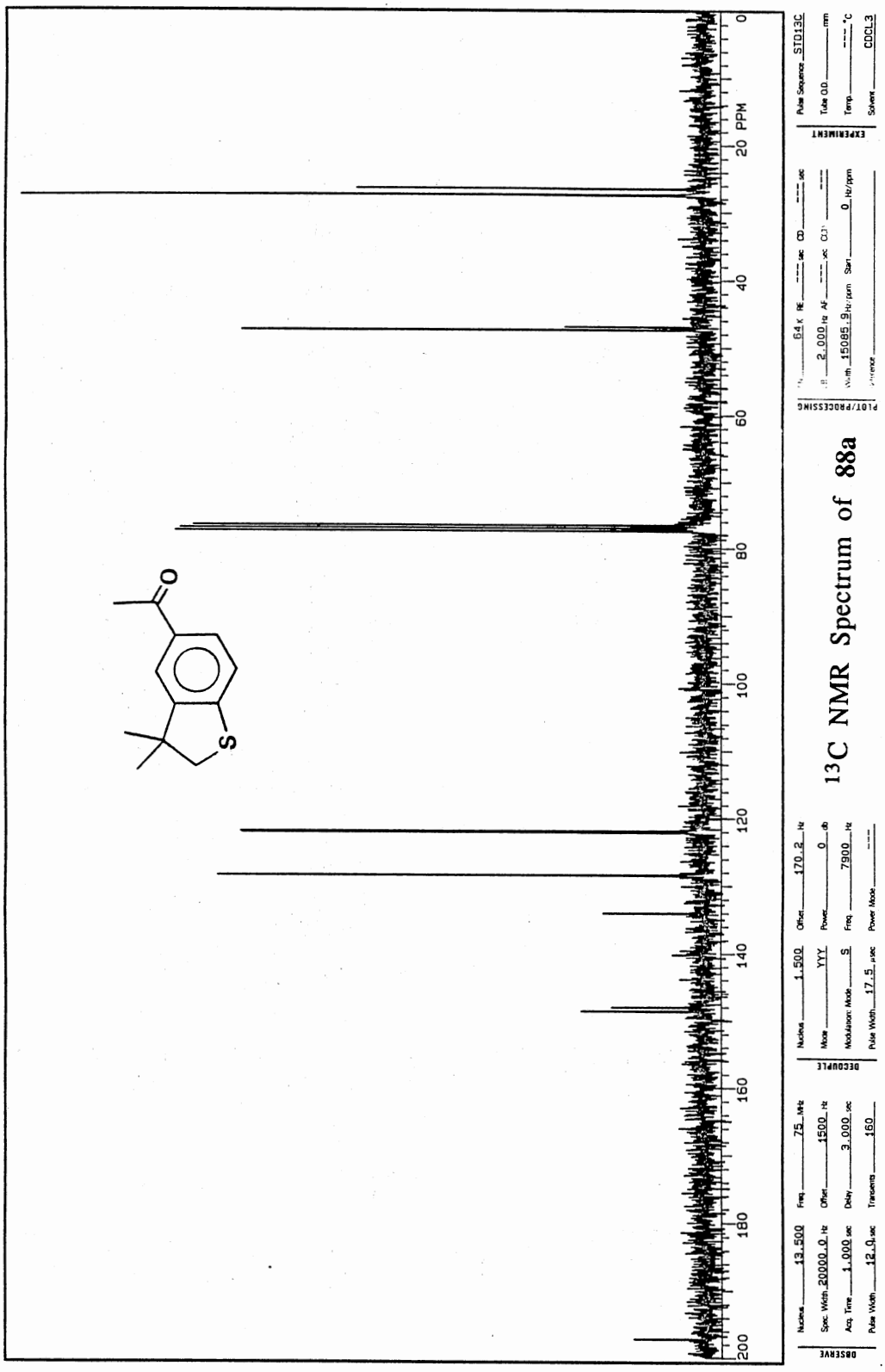
DECOUPLE Nucleus 1.500 Offset 0 Hz Mode NNN Power 20 db Modulation: Mode C Freq 200 Hz Pulse Width µsec Power Mode

PLOT/PROCESSING FN 16 K RE sec CD sec LB Hz AF sec CCD Width 2999.4 Hz/ppm Start 0 Hz/ppm Reference

EXPERIMENT Pulse Sequence STD1H Tube O.D. mm Temp. °C Solvent CDCL3

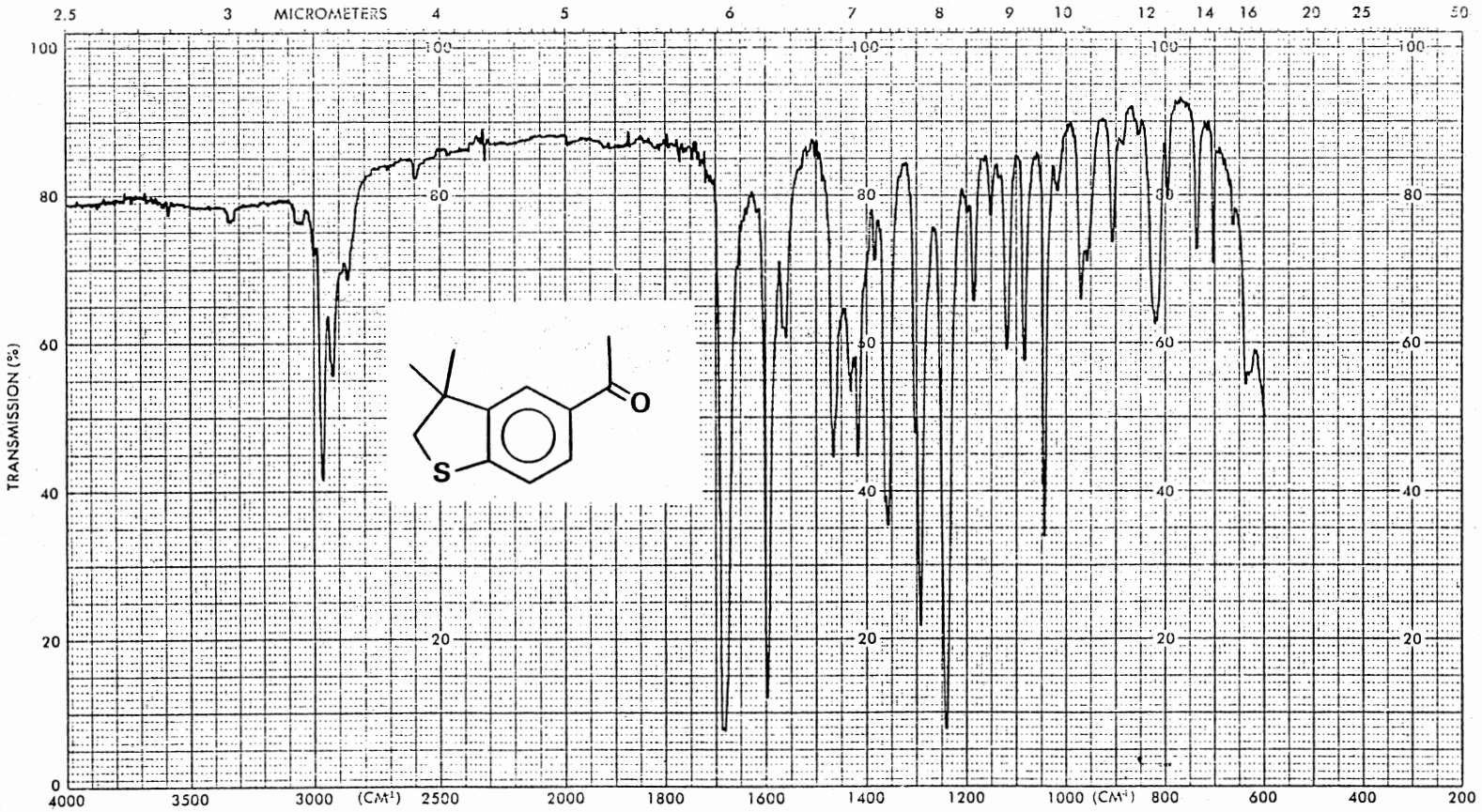
^{1}H NMR Spectrum of **88a**

PLATE XXXVIII



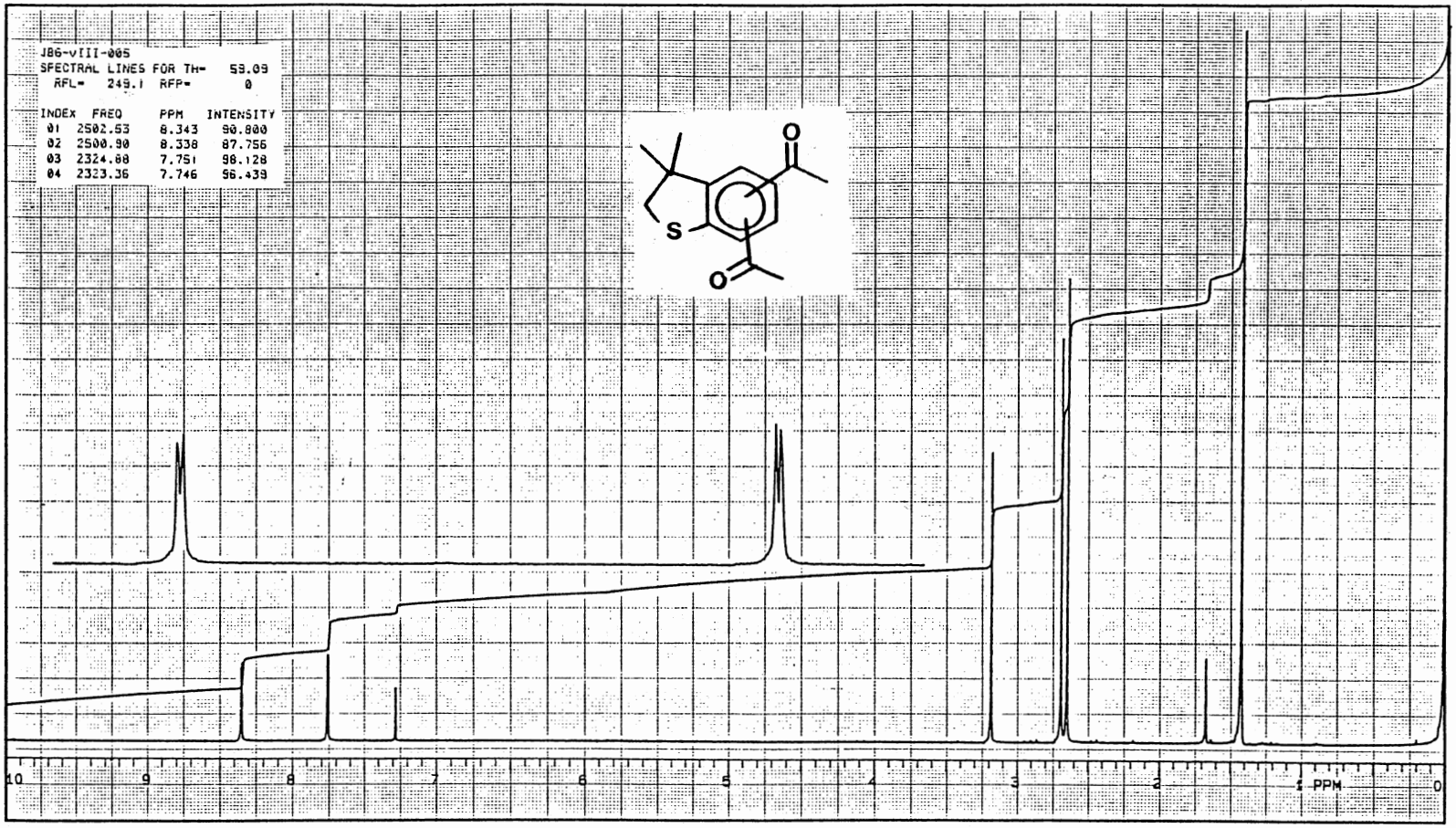
^{13}C NMR Spectrum of 88a

PLATE XXXIX



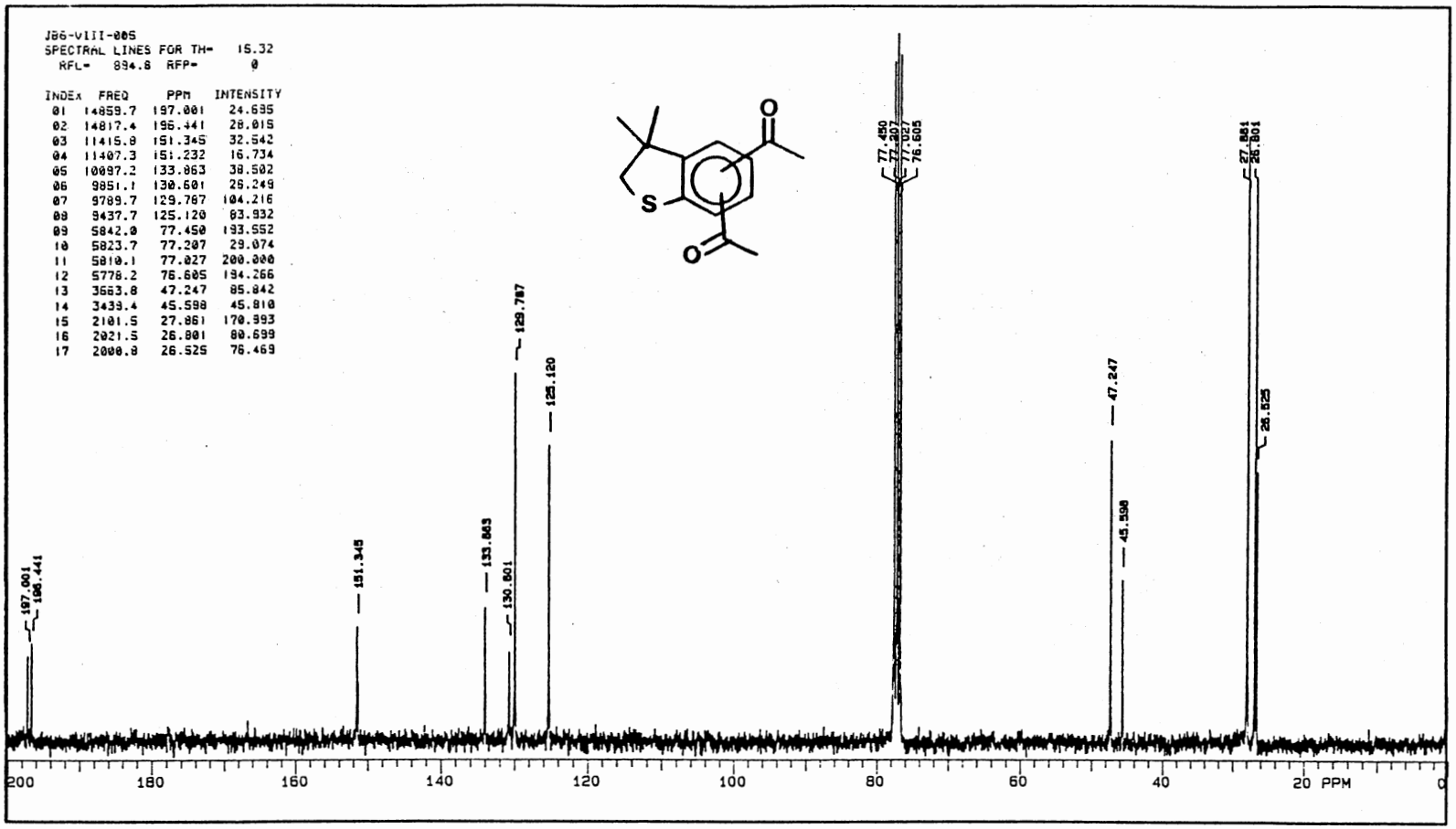
IR Spectrum of **88a**

PLATE XXXX



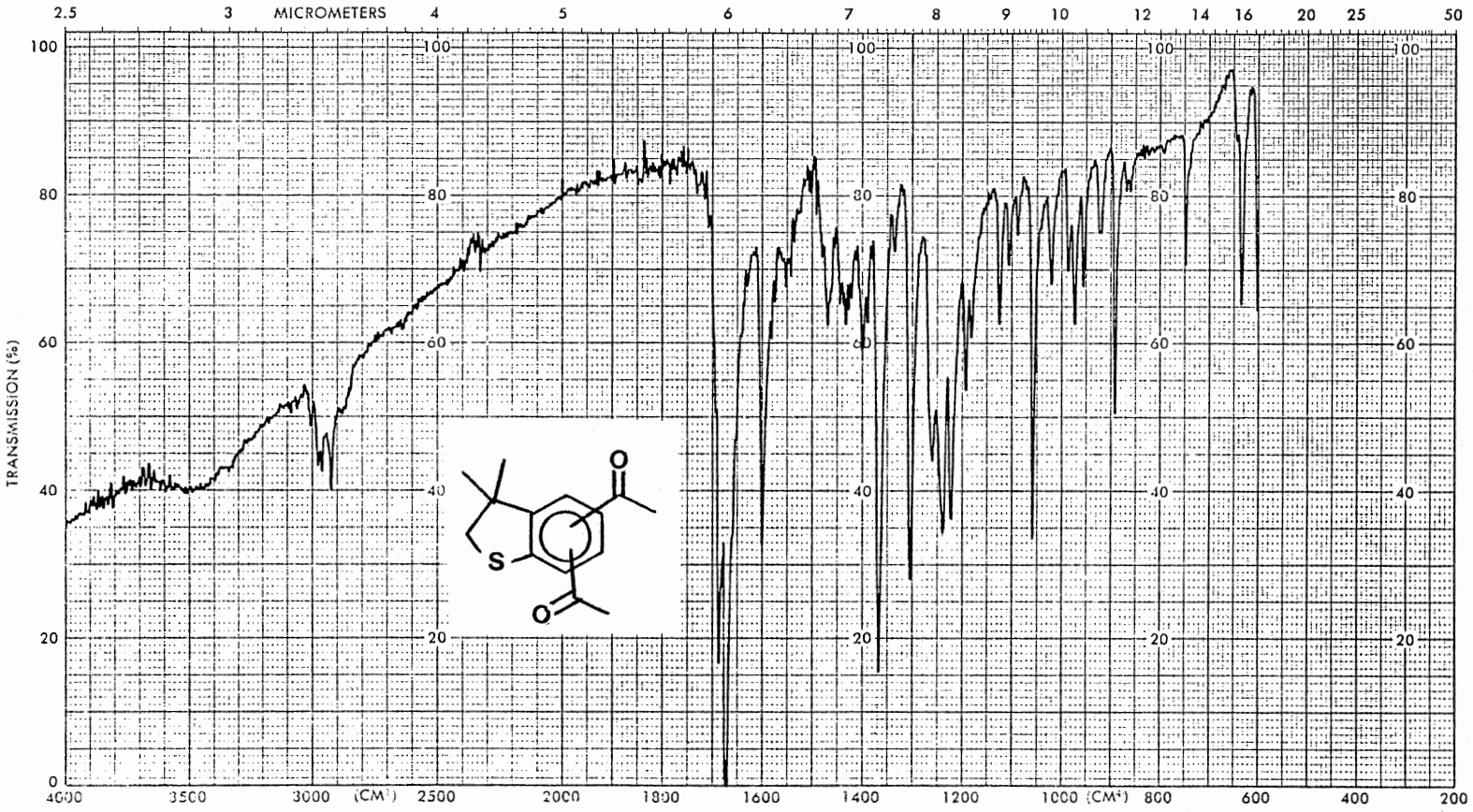
^{1}H NMR Spectrum of **88b**

PLATE XXXXI



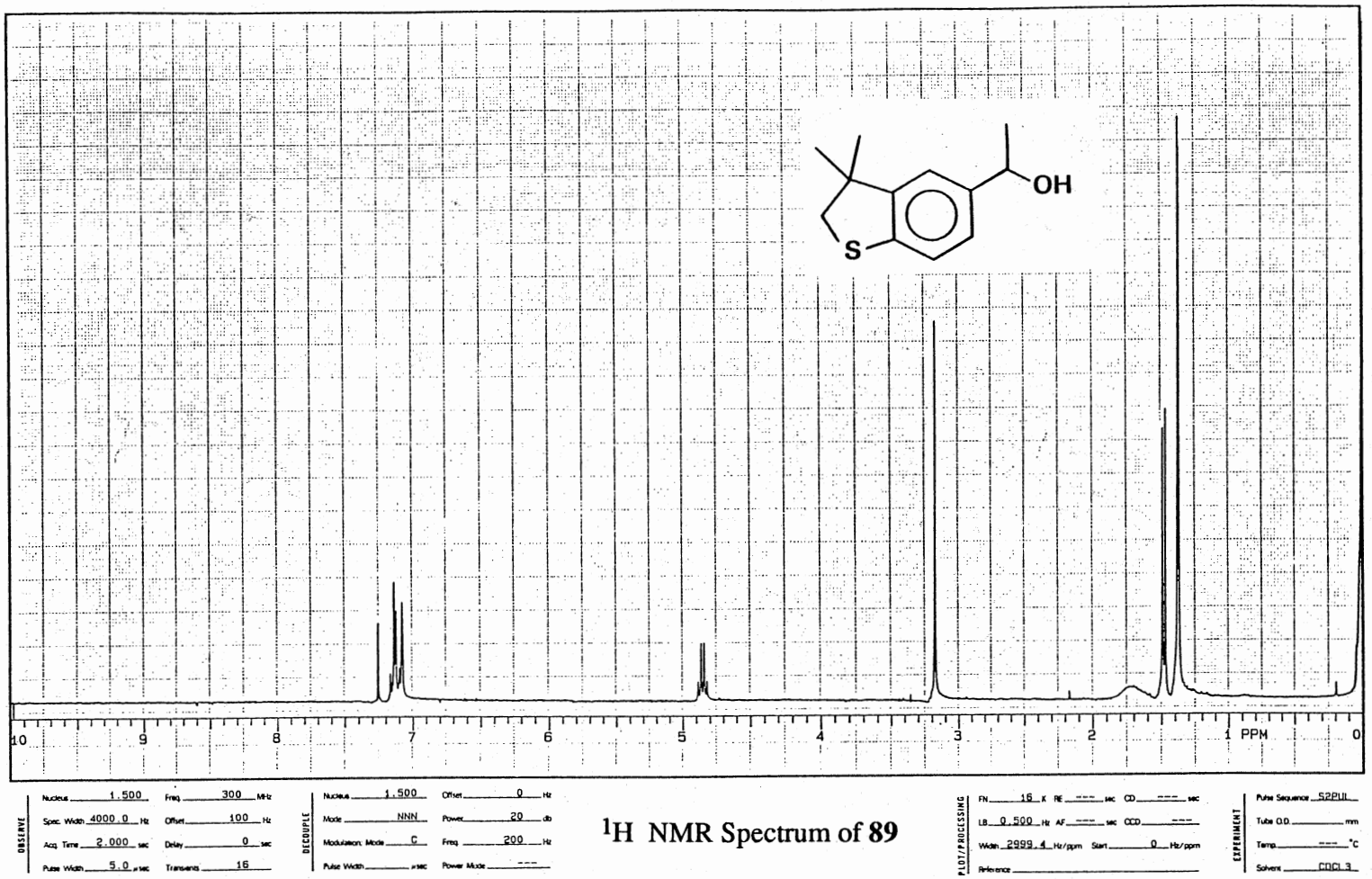
^{13}C NMR Spectrum of **88b**

PLATE XXXXII



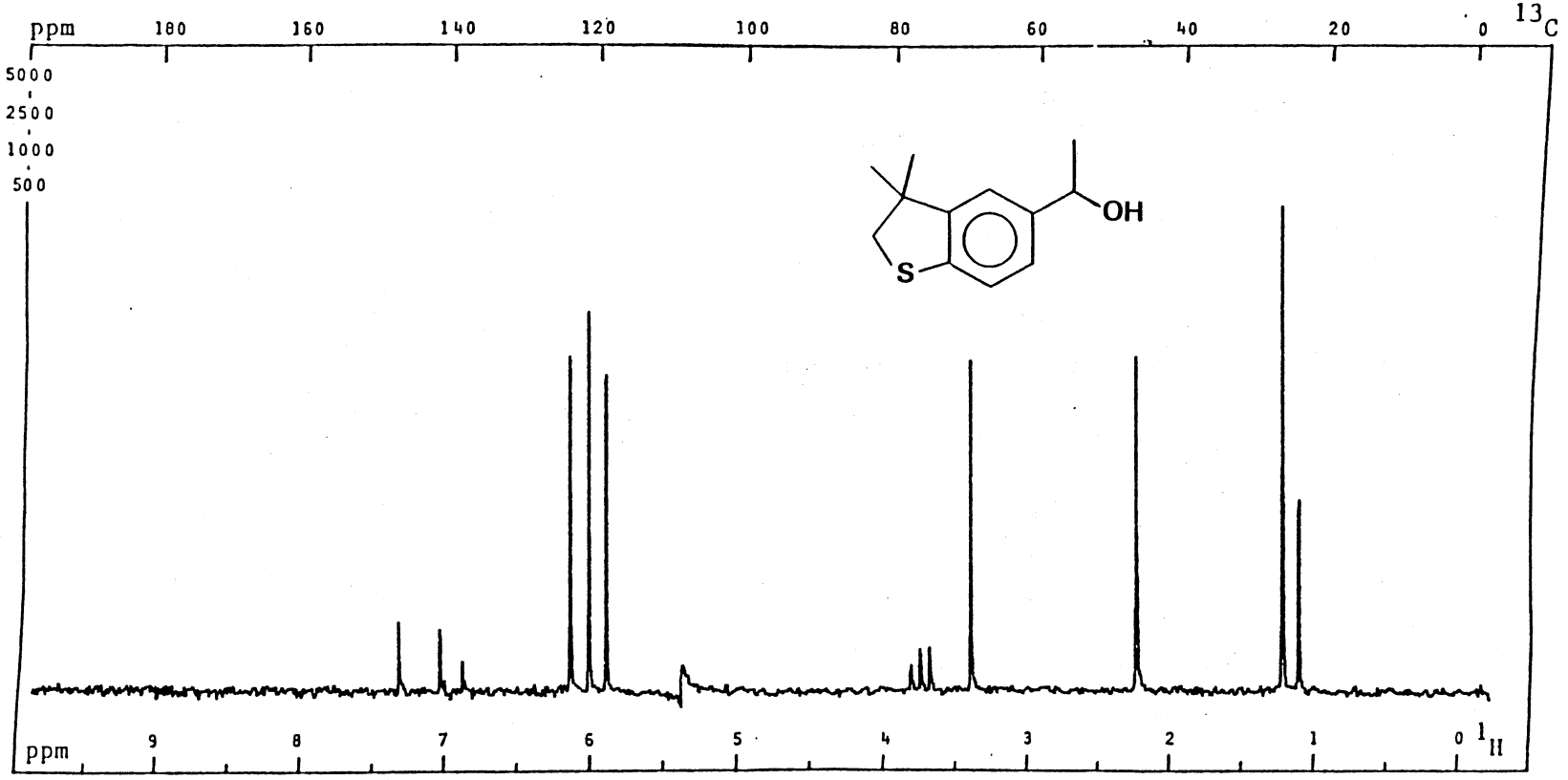
IR Spectrum of **88b** -KBr

PLATE XXXXIII



^{1}H NMR Spectrum of **89**

PLATE XXXXIV



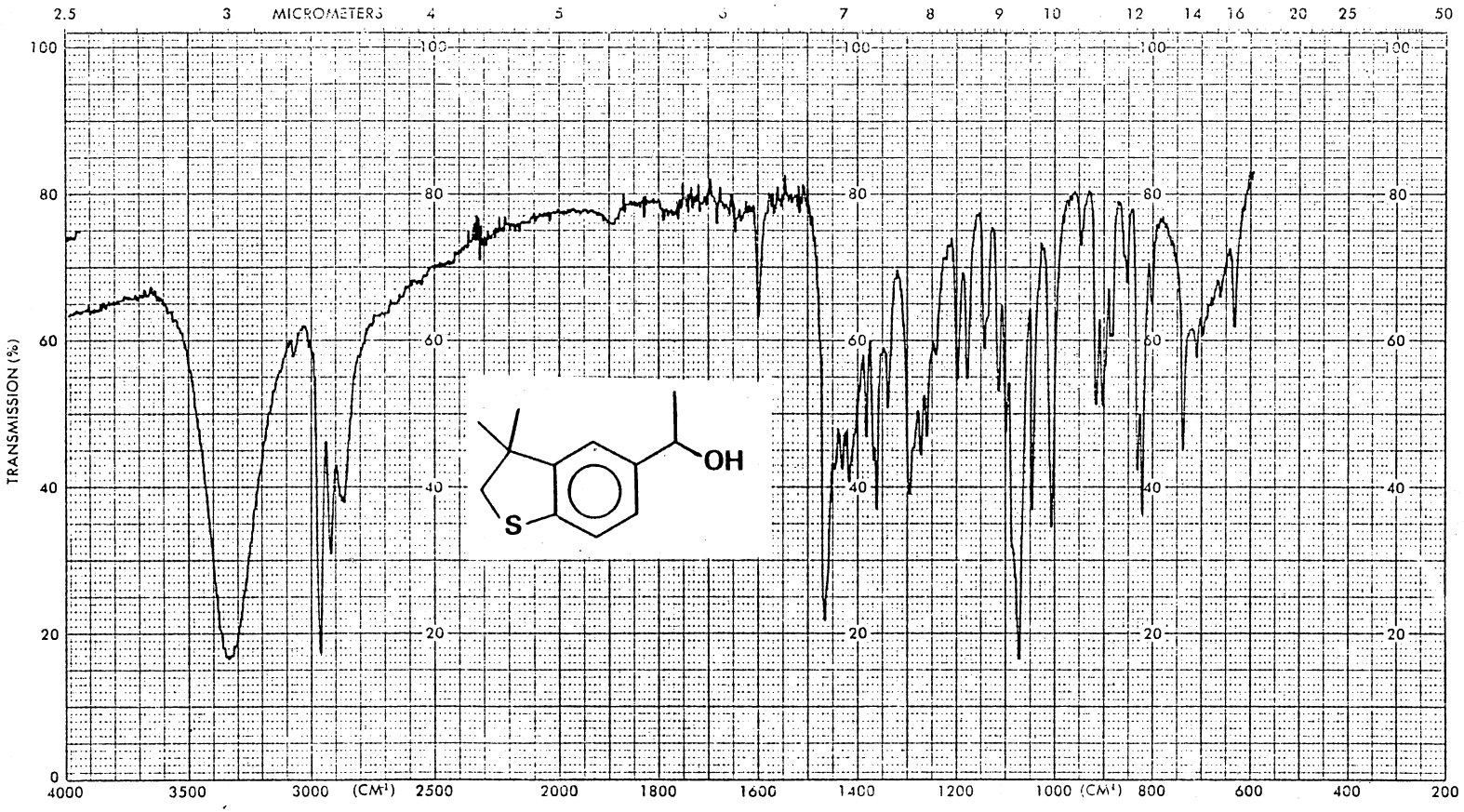
^{13}C NMR Spectrum of **89**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: Hz; T: RT °C; NT: 900

Size: 8 K; PW/RF: 22 μs/dB; TO: Hz; FB: Hz; Lock: ^2H ; D1,D5: 4.0 s.

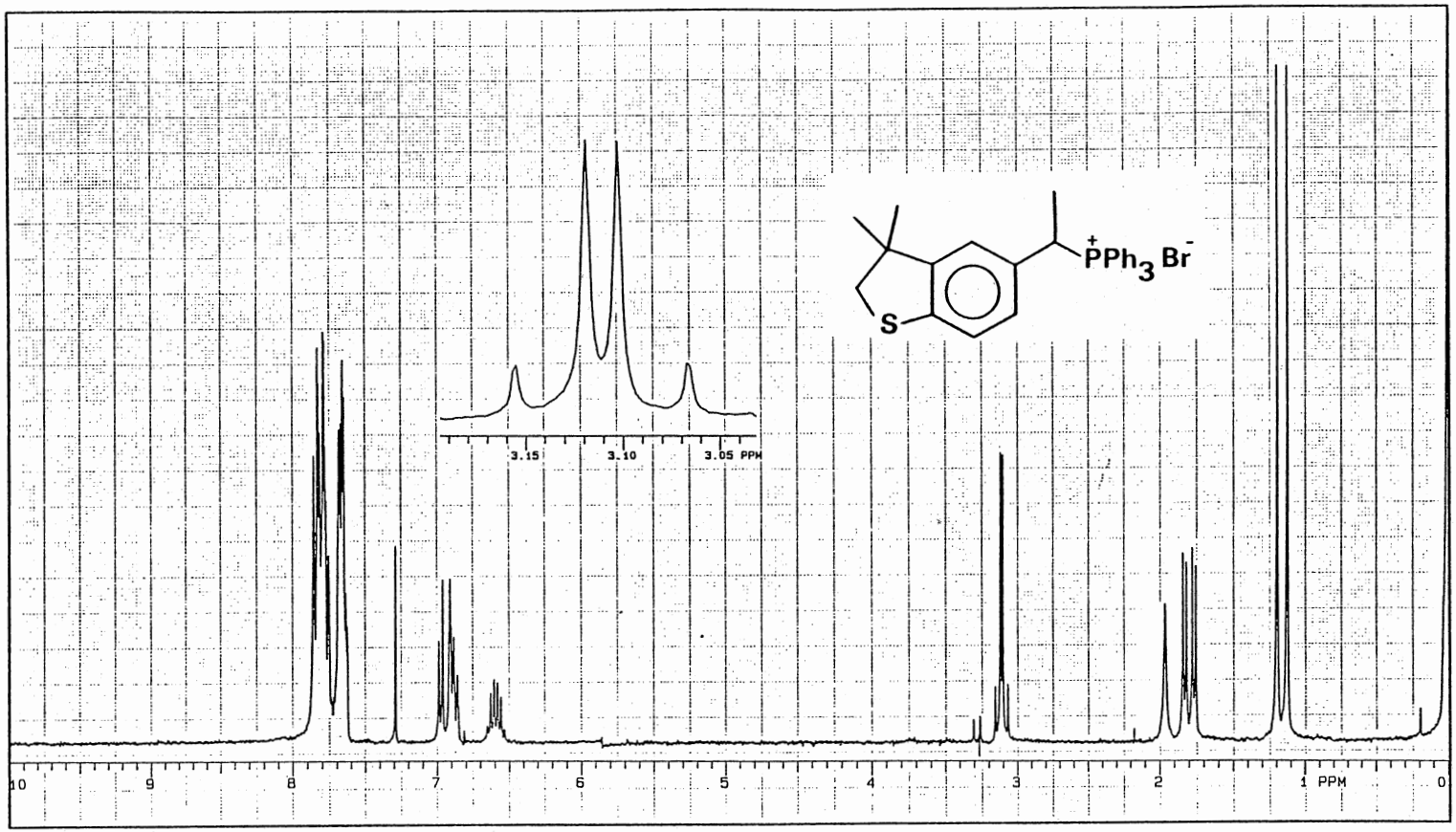
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): W/dB; NBW: Hz; LB: Hz.

PLATE XXXXV



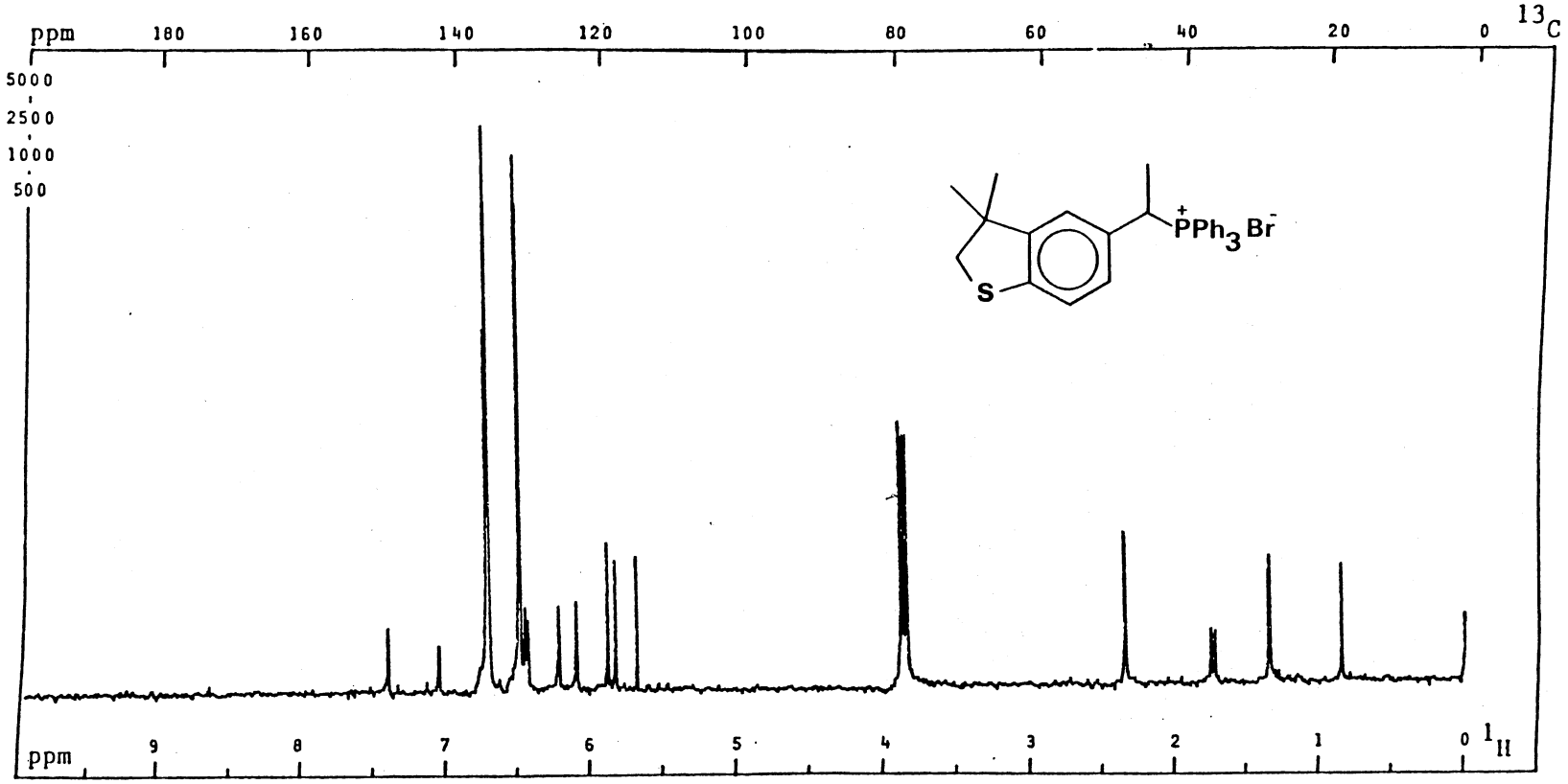
IR Spectrum of **89** -KBr

PLATE XXXXVI



^{1}H NMR Spectrum of **90**

PLATE XXXXVII



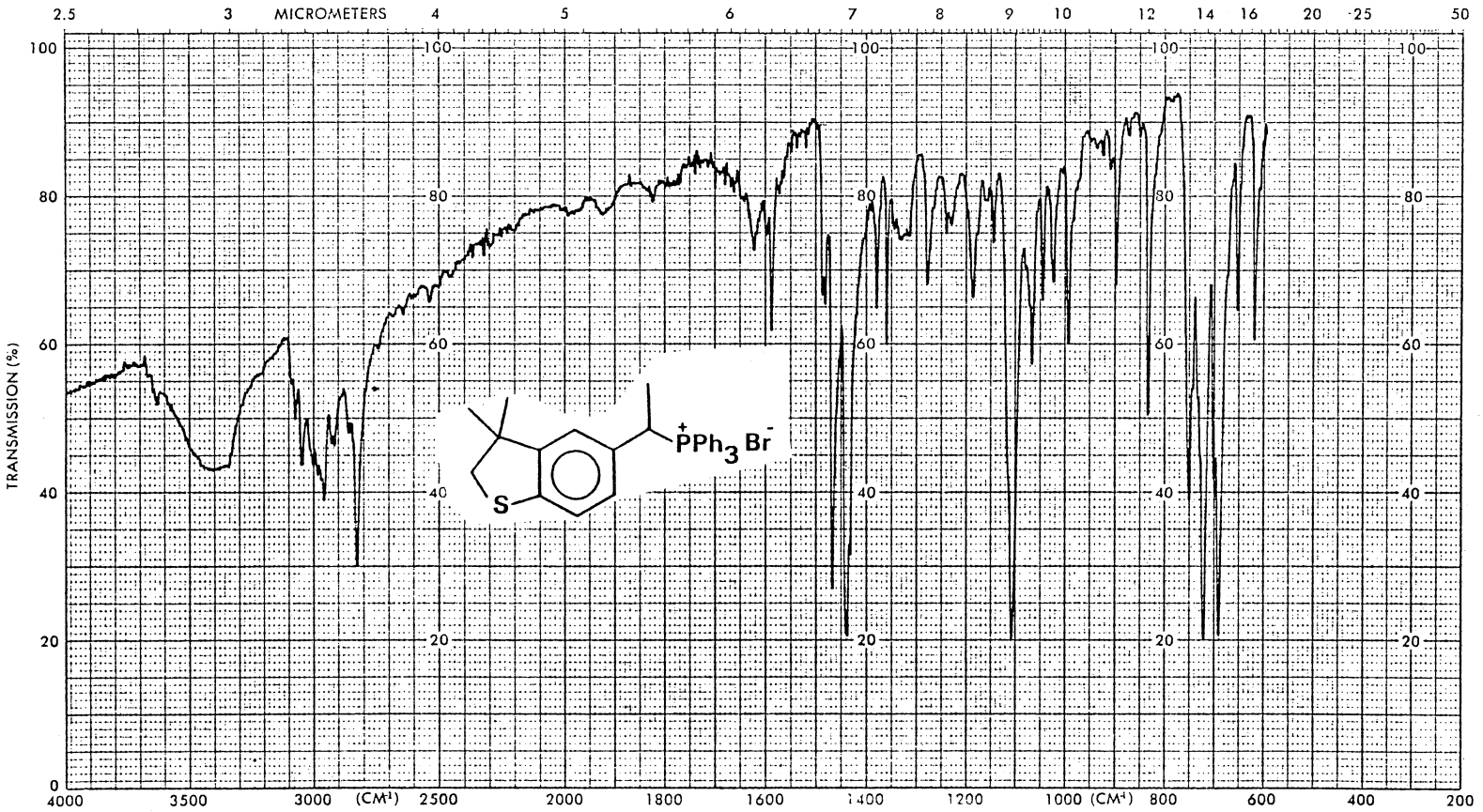
^{13}C NMR Spectrum of **90**

PFT X CW _ ; Solvent: $DCCl_3$; SF:75.429 MHz; WC:15085.9 Hz; T: RT °C; NT: 192

Size: 20 K; PW/RF:12.0 µs/dB; TO: 1000 Hz; FB: Hz; Lock: ^{2}H ;D1,D5:4.0 s.

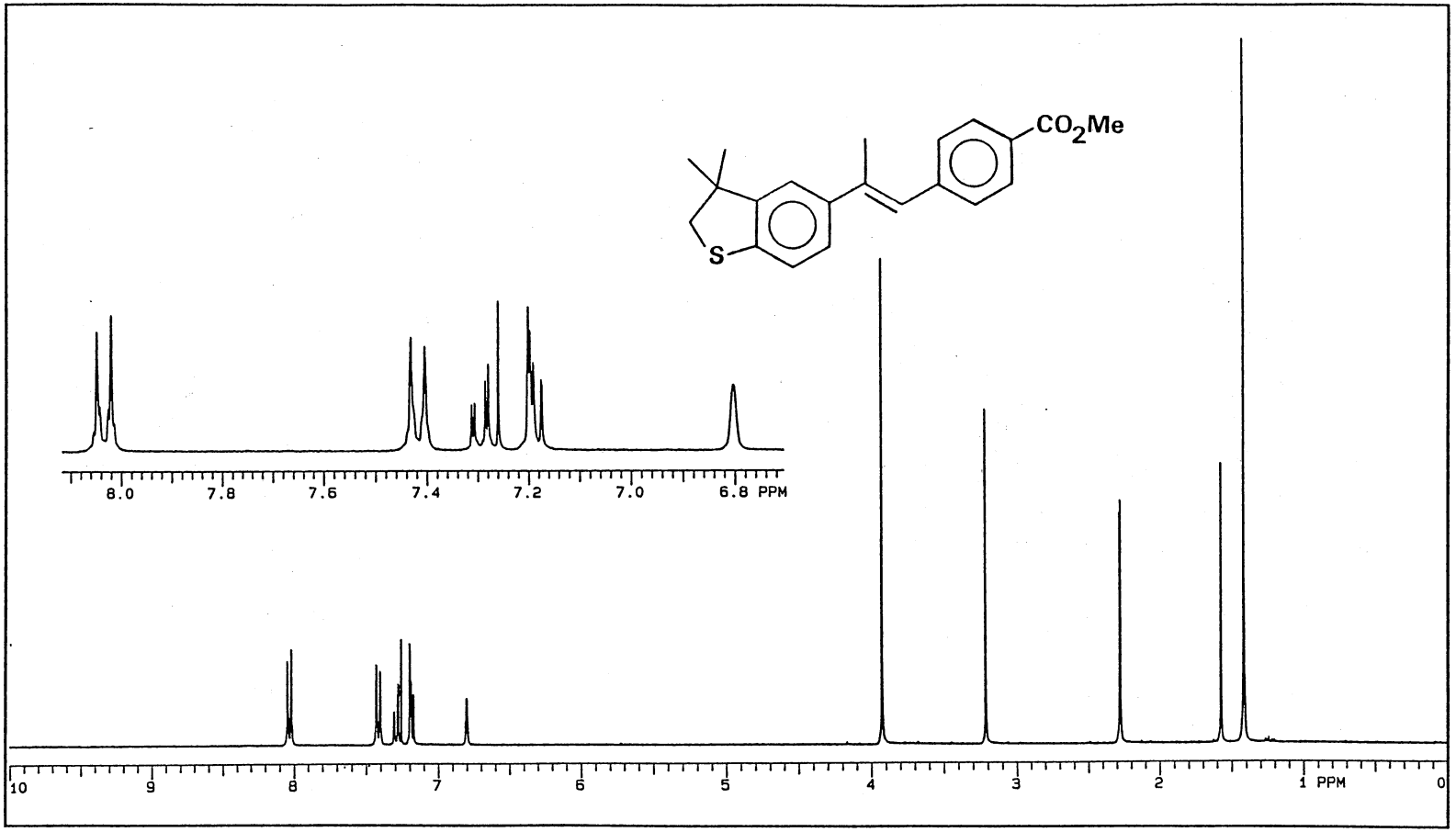
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW:200 Hz; LB:1.0 Hz.

PLATE XXXXVIII



IR Spectrum of **90** -KBr

PLATE IL



OBSERVE Nucleus 1.500 Freq. 300 MHz; Spec. Width 4000.0 Hz Offset 0 Hz; Acq. Time 8.000 sec Delay 0 sec; Pulse Width 8.0 sec Transients 128

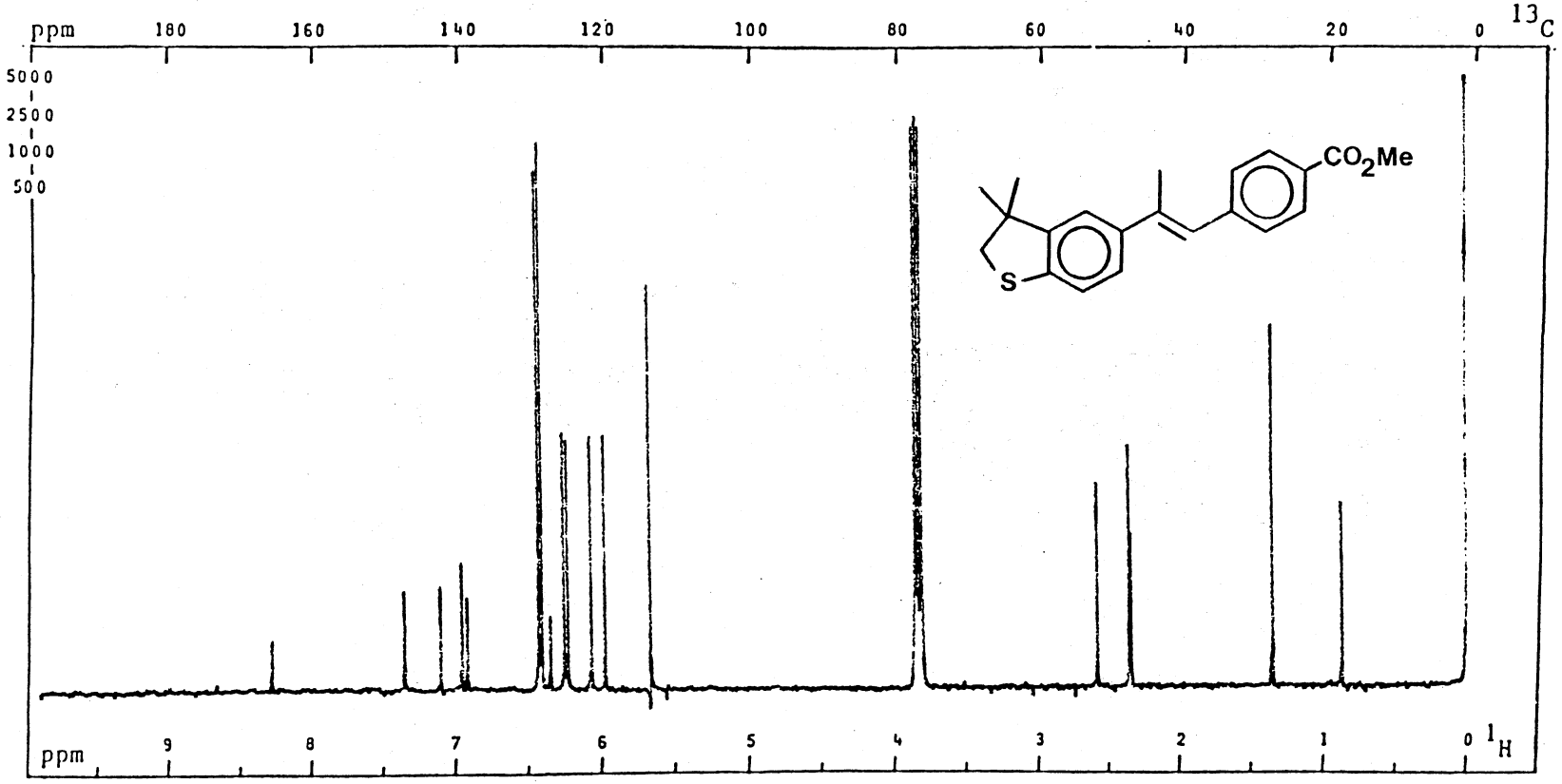
DECOUPLE Nucleus 1.500 Offset 0 Hz; Mode NNN Power 20 db; Modulation Mode C Freq. 200 Hz; Pulse Width µsec Power Mode ---

PLOT/PROCESSING FN 64 K RE --- sec CD --- sec; LB --- Hz AF --- sec CCD ---; Width 2999.4 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT Pulse Sequence STD1H; Tube O.D. mm; Temp. --- °C; Solvent CDCL3

^{1}H NMR Spectrum of **60**

PLATE L



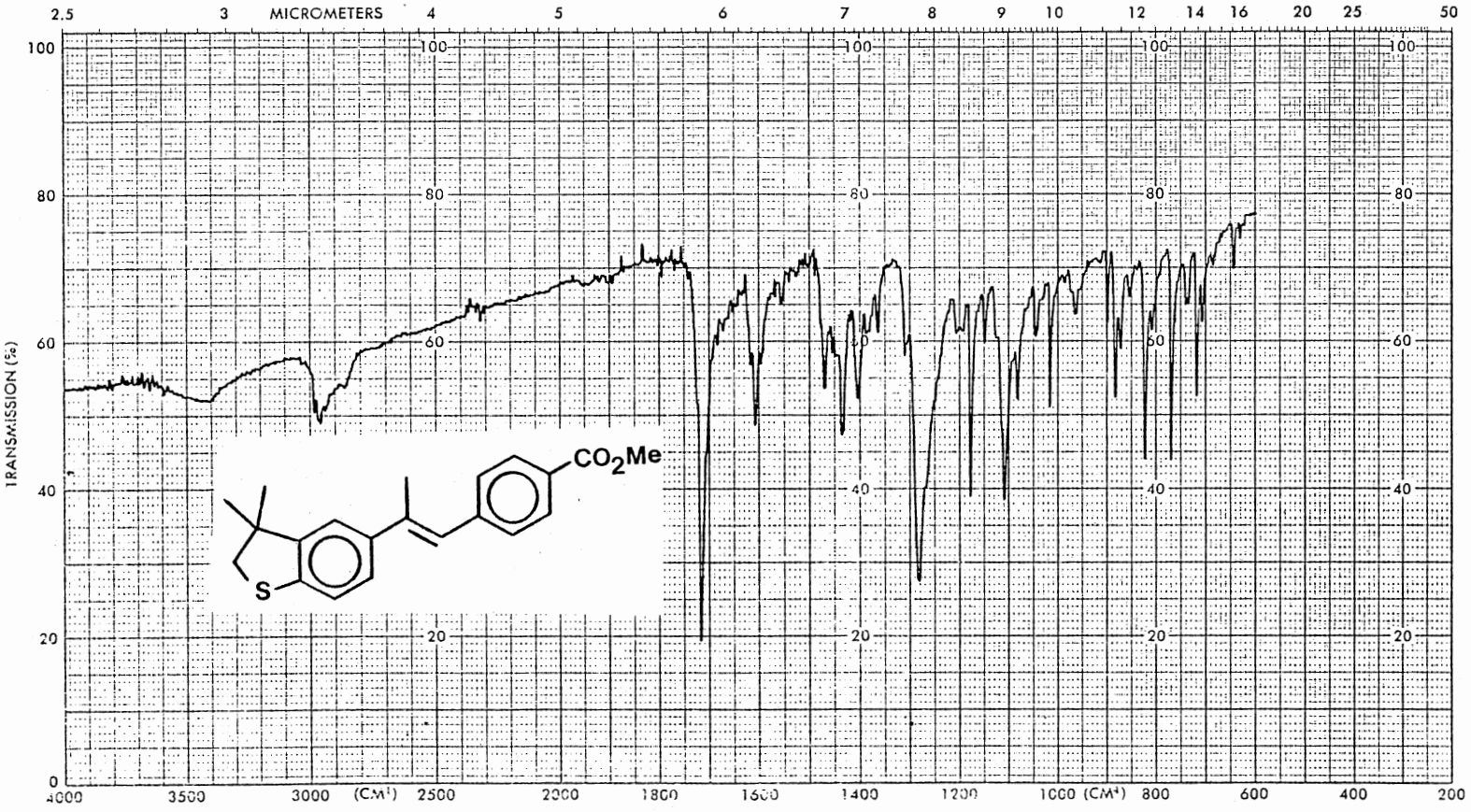
^{13}C NMR Spectrum of **60**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 2620

Size: 20 K; PW/RF: 12.0 μs/dB; TO: 1000 Hz; FB: Hz; Lock: ^2H ; D1,D5: 5.0 s.

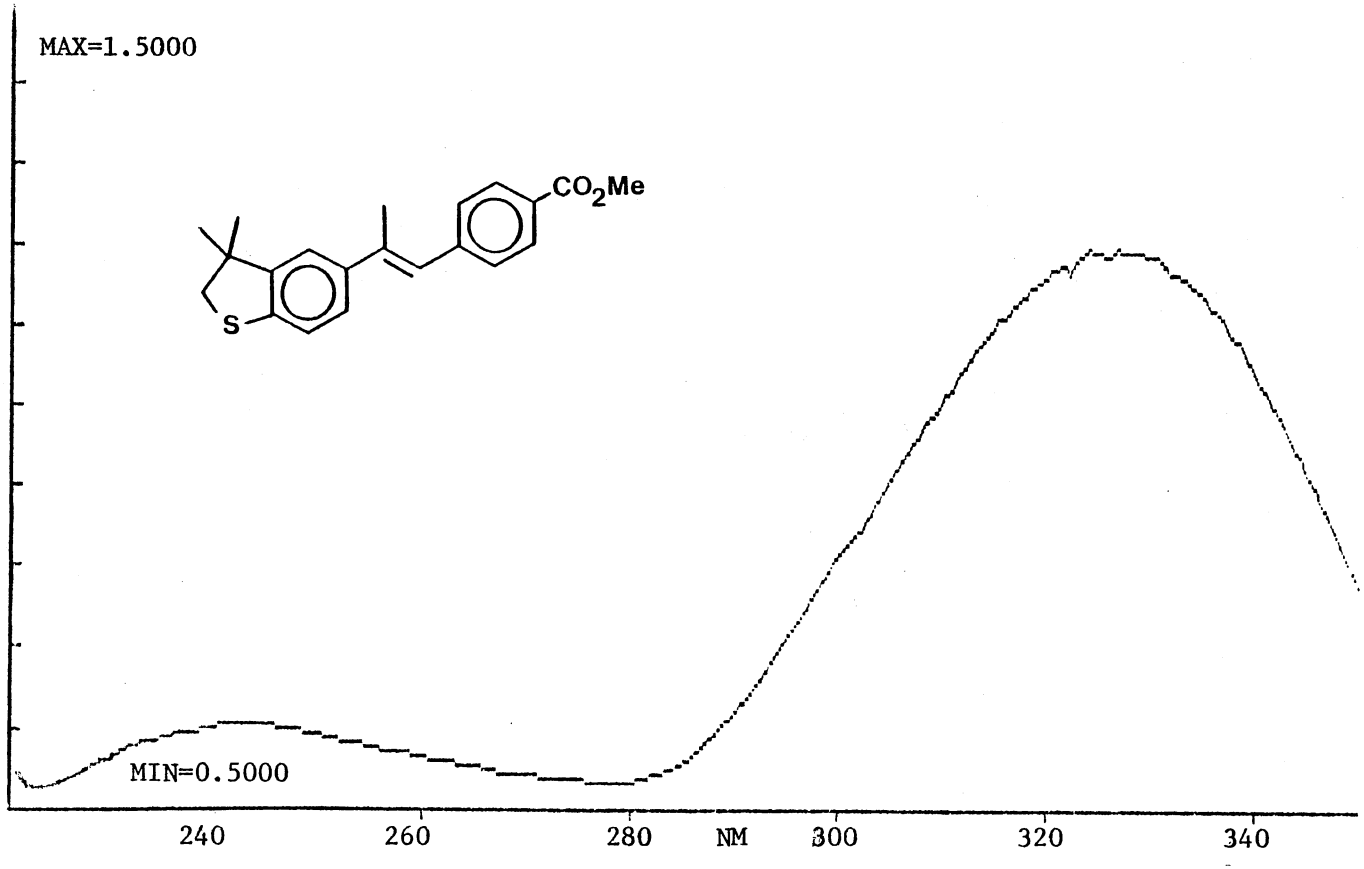
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 1.0 Hz.

PLATE LI



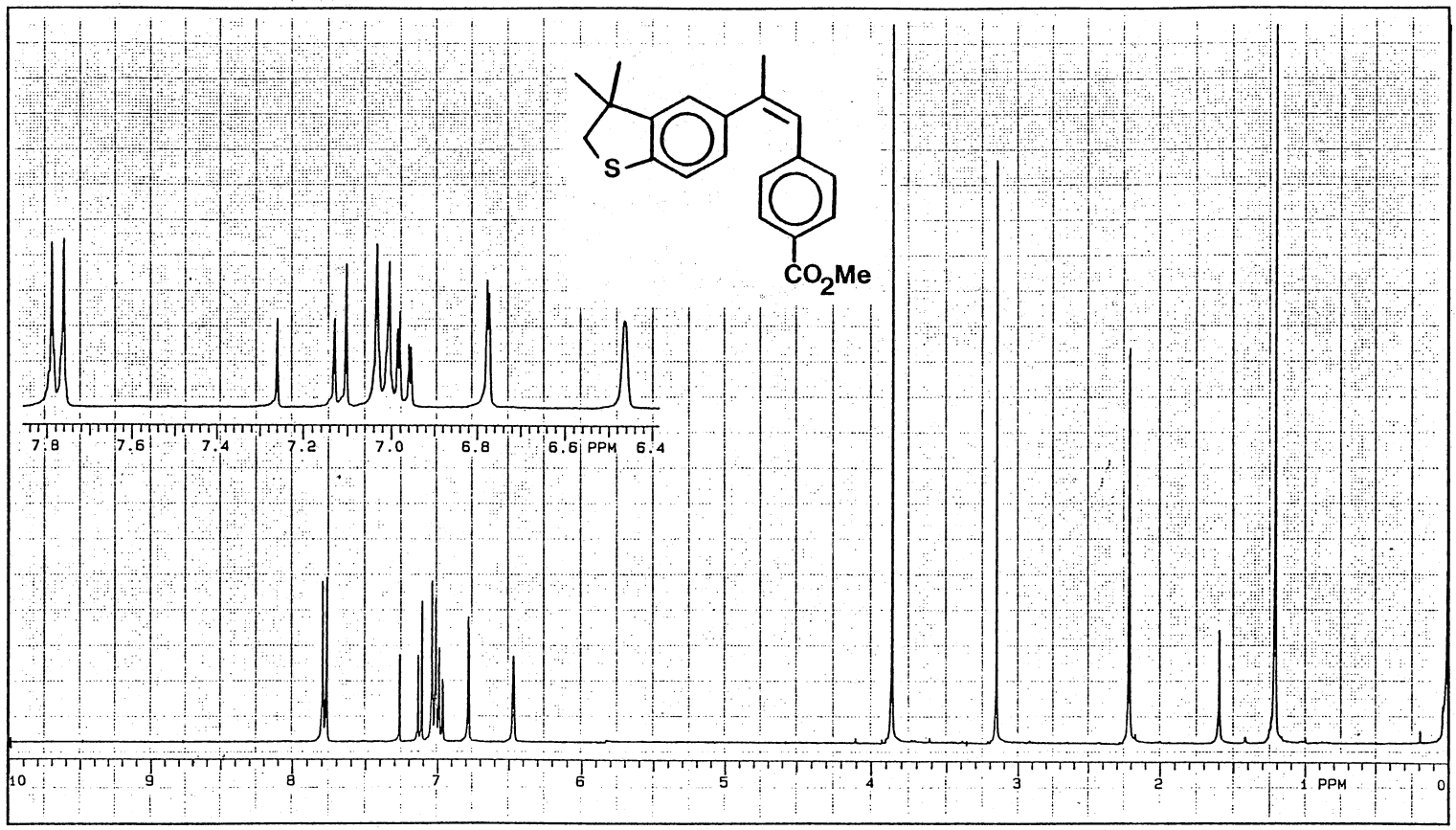
IR Spectrum of **60** -KBr

PLATE LII



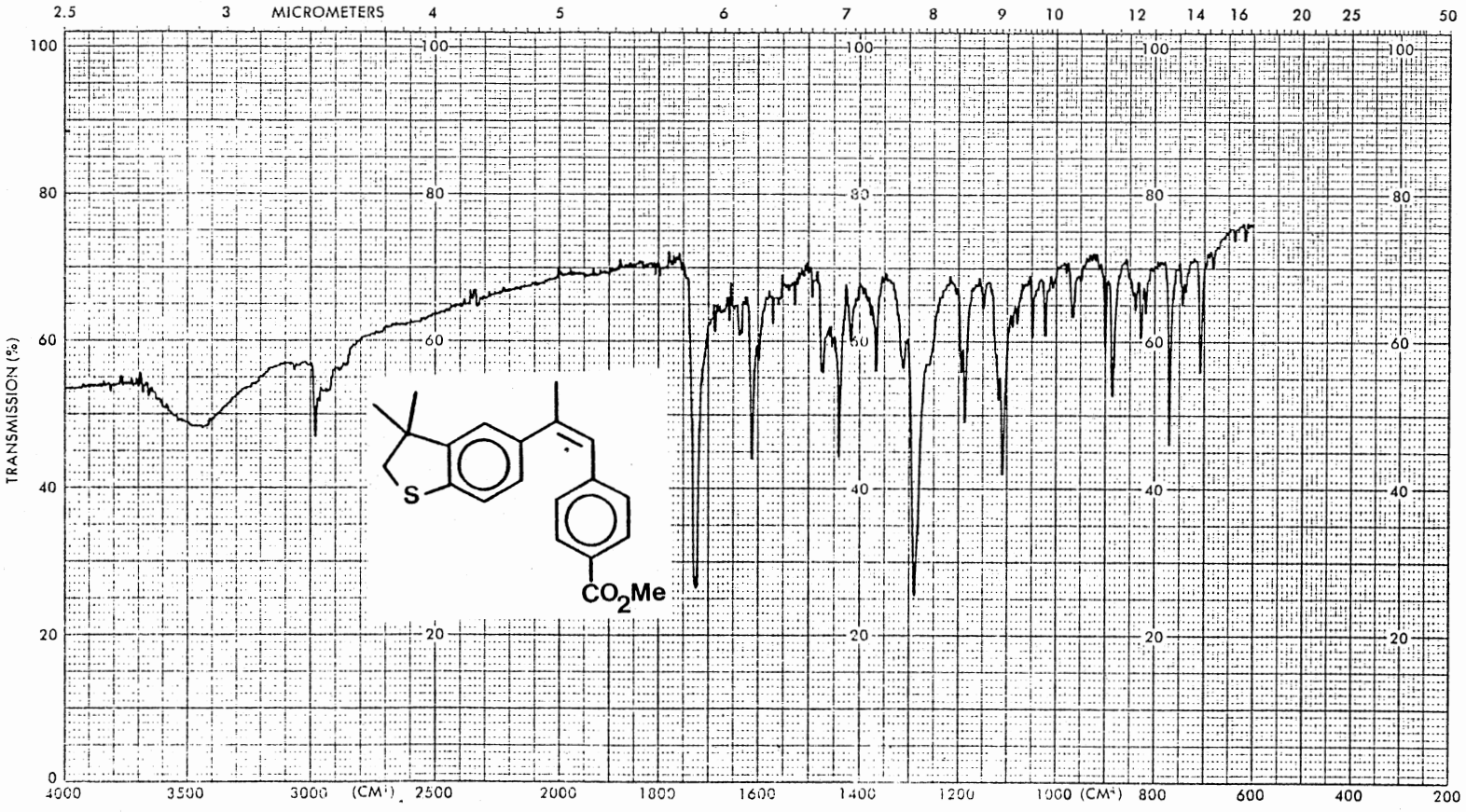
UV Spectrum of **60**

PLATE LIII



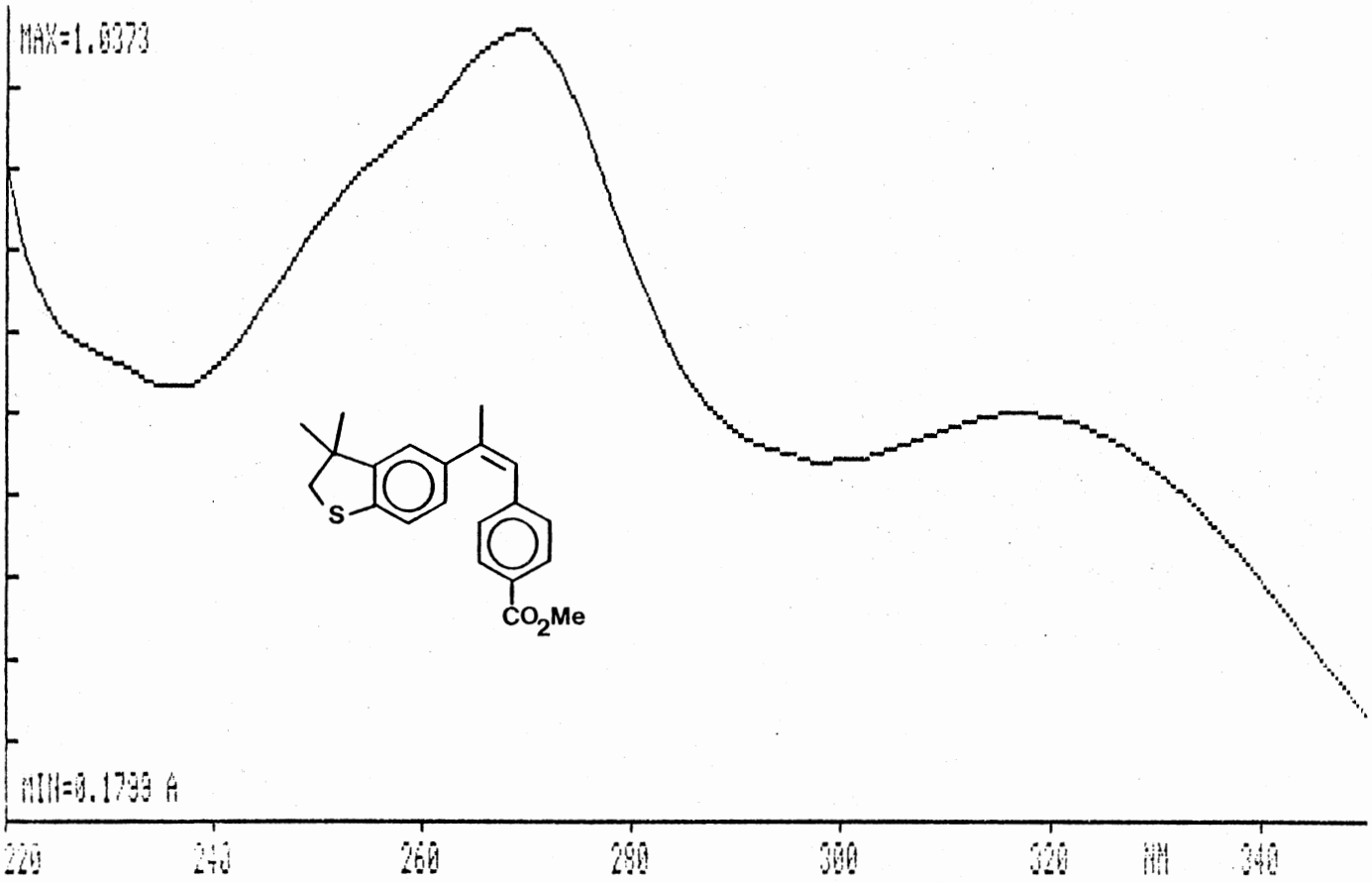
^{1}H NMR Spectrum of **61**

PLATE LIV



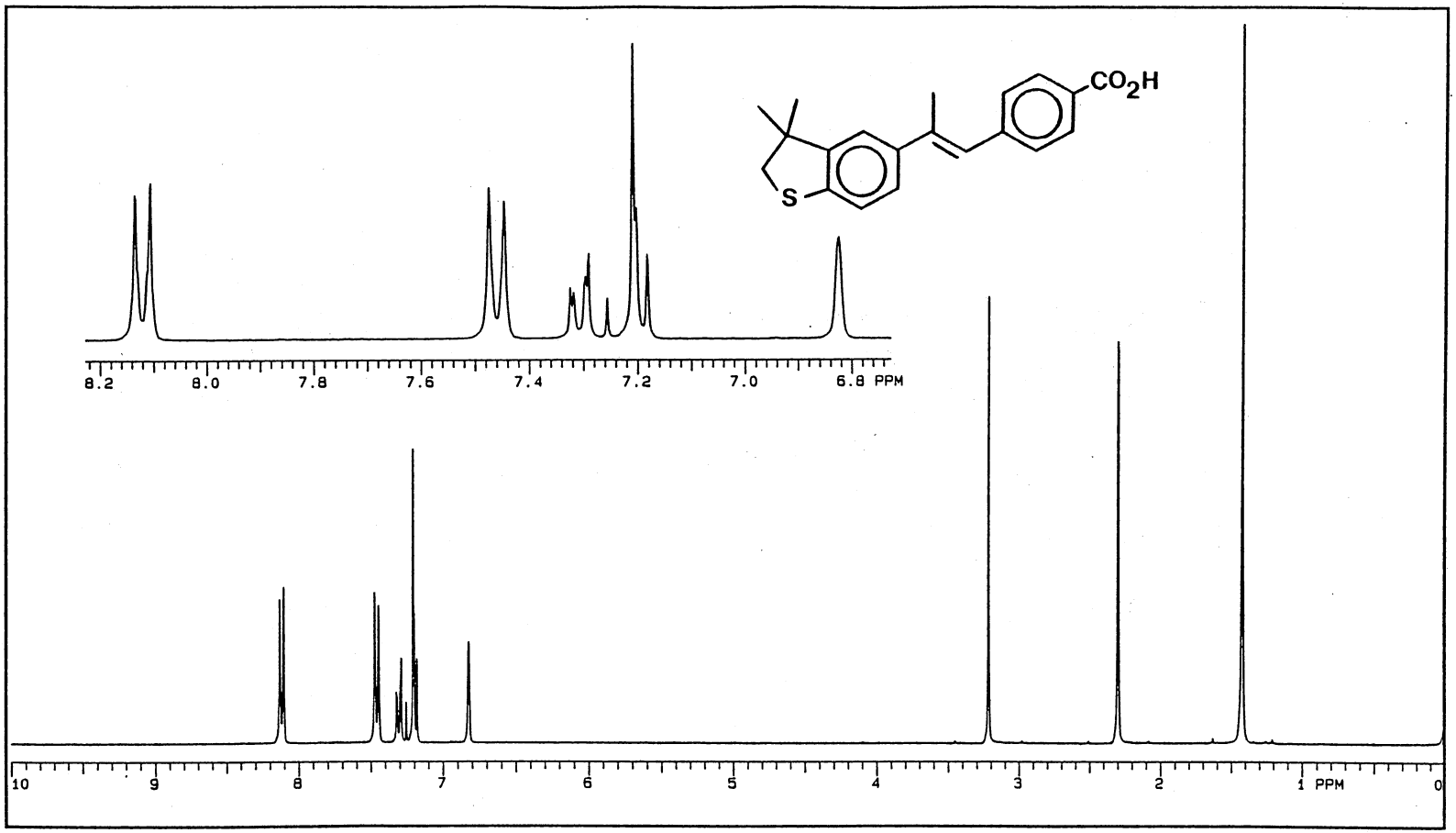
IR Spectrum of **61**-KBr

PLATE LV



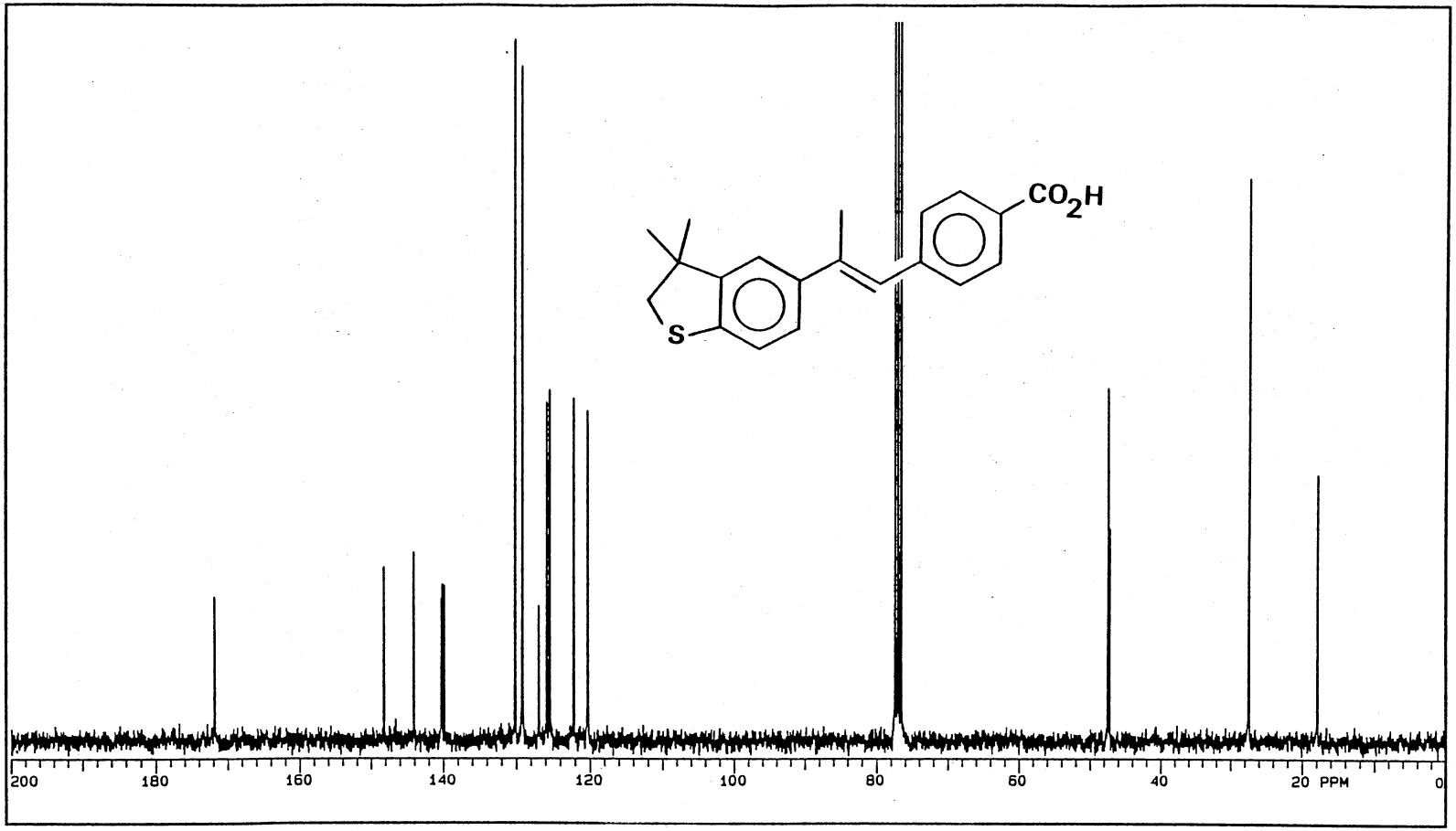
UV Spectrum of **61**

PLATE LVI



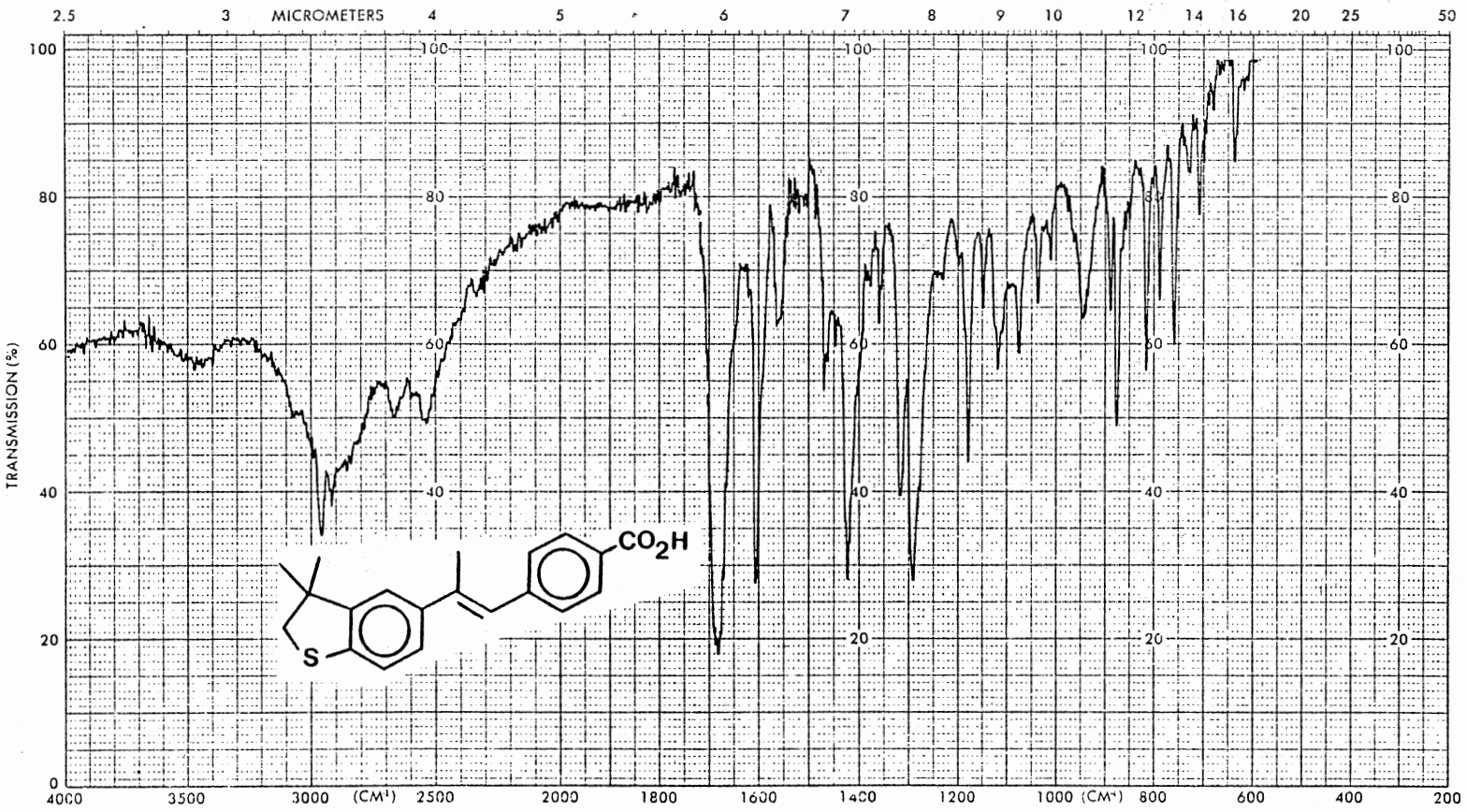
^{1}H NMR Spectrum of **63**

PLATE LVII

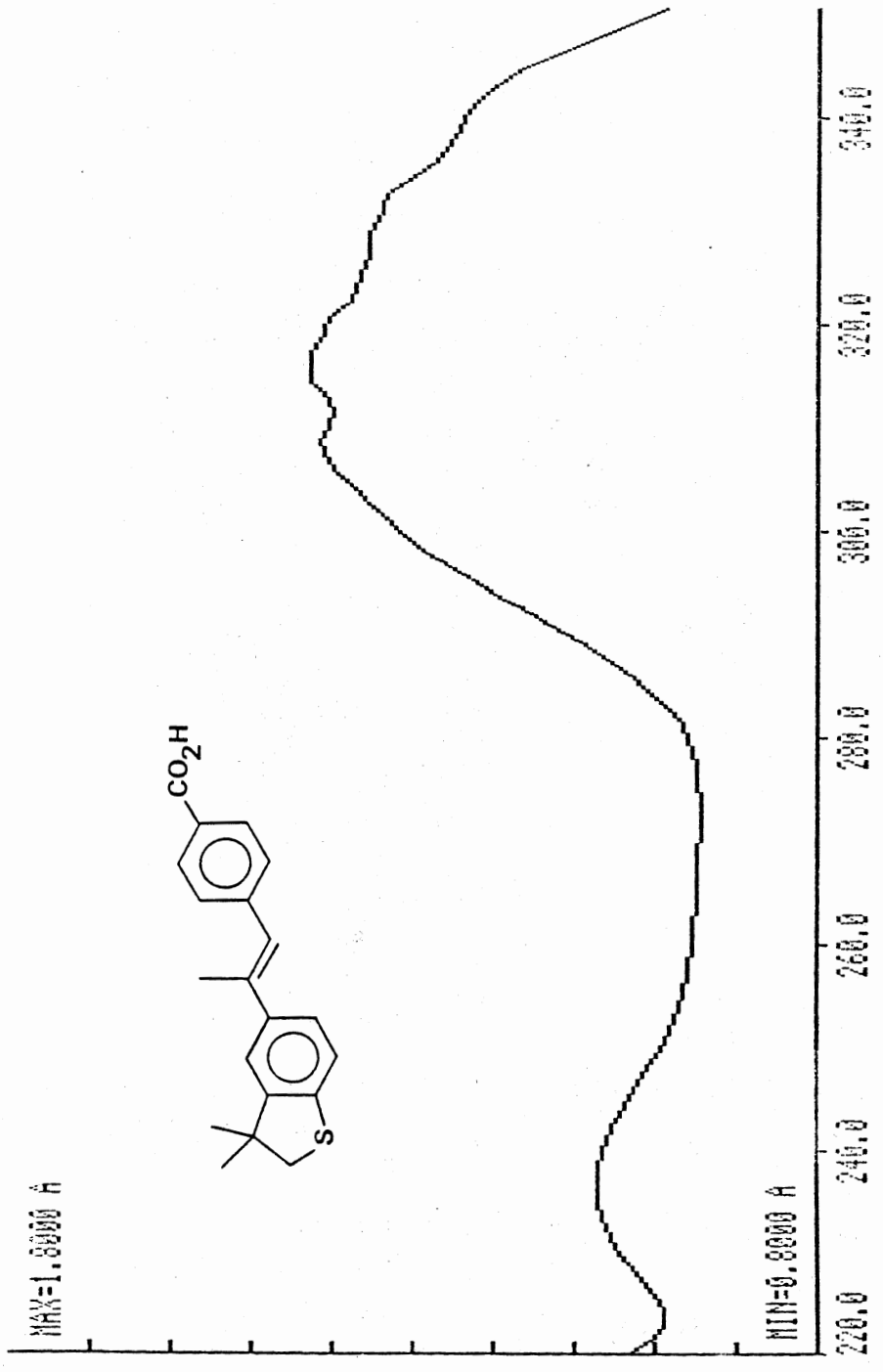


^{13}C NMR Spectrum of **63**

PLATE LVIII

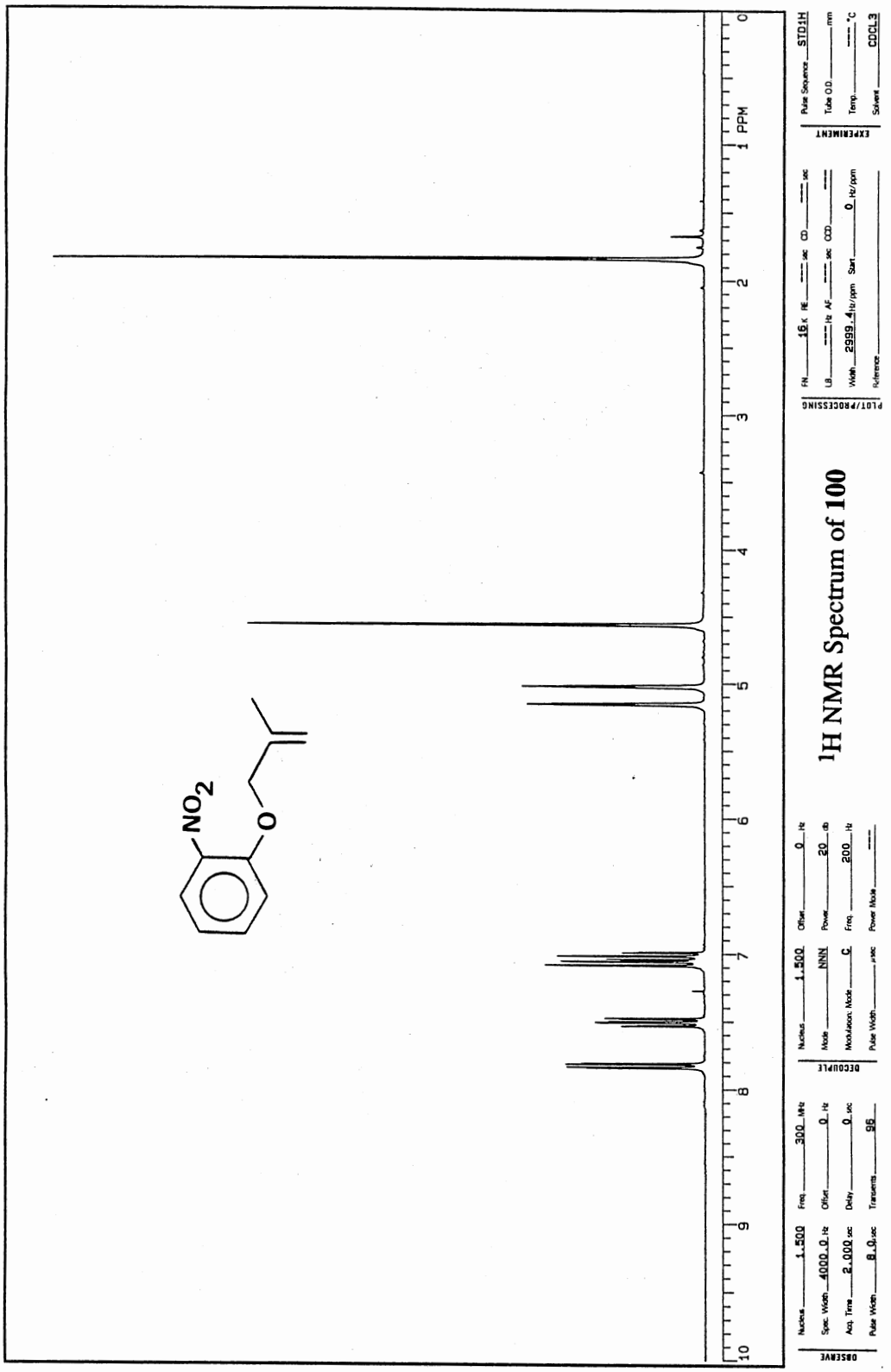


IR Spectrum of 63 -KBr



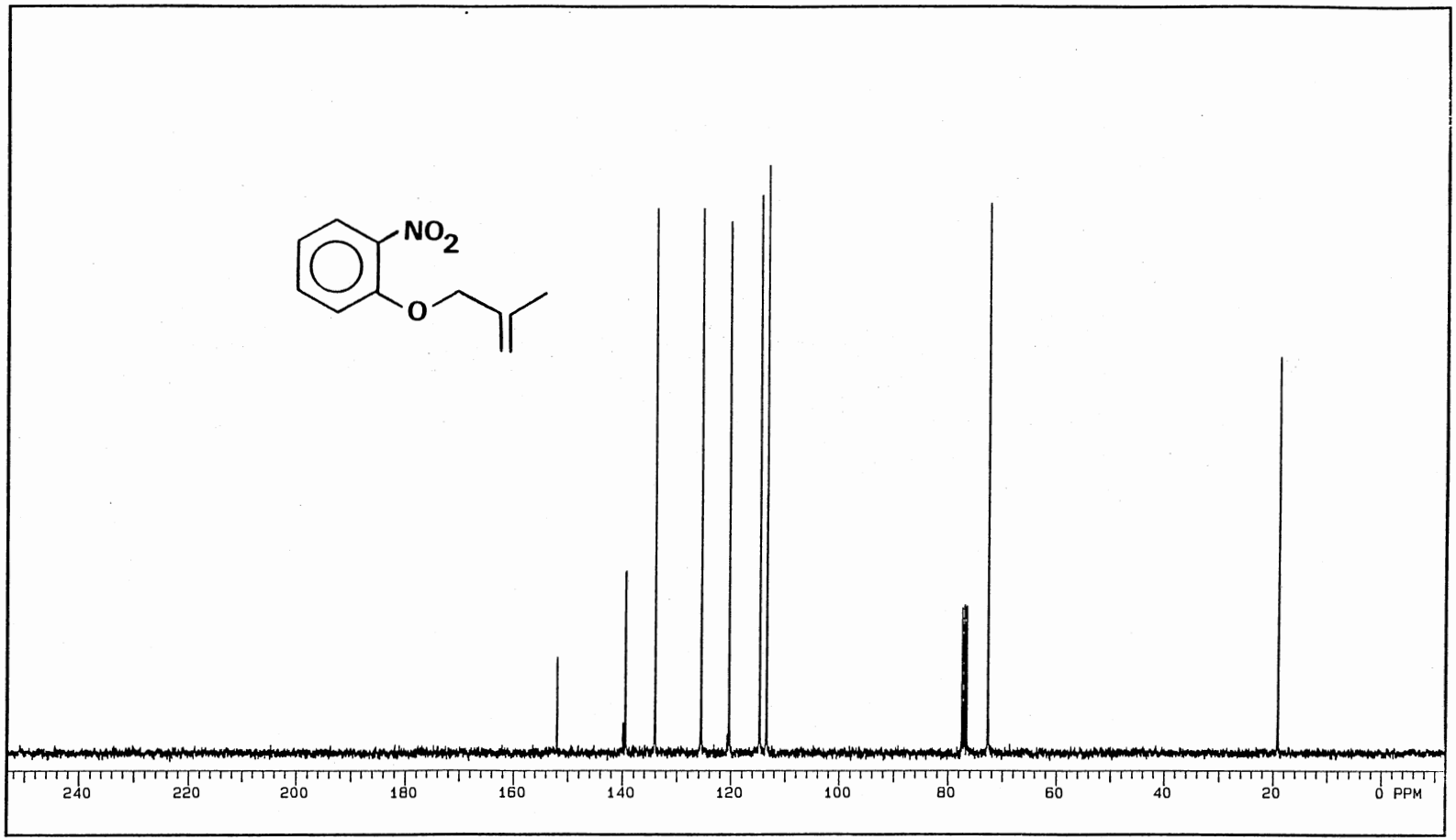
UV Spectrum of 63

PLATE LX



^{1}H NMR Spectrum of **100**

PLATE LXI



OBSERVE: Nucleus 13 500 Freq. 75 MHz; Spec. Width 20000.0 Hz Offset 1500 Hz; Acq. Time 1.000 sec Delay 3.000 sec; Pulse Width 12.0 µsec Transients 128

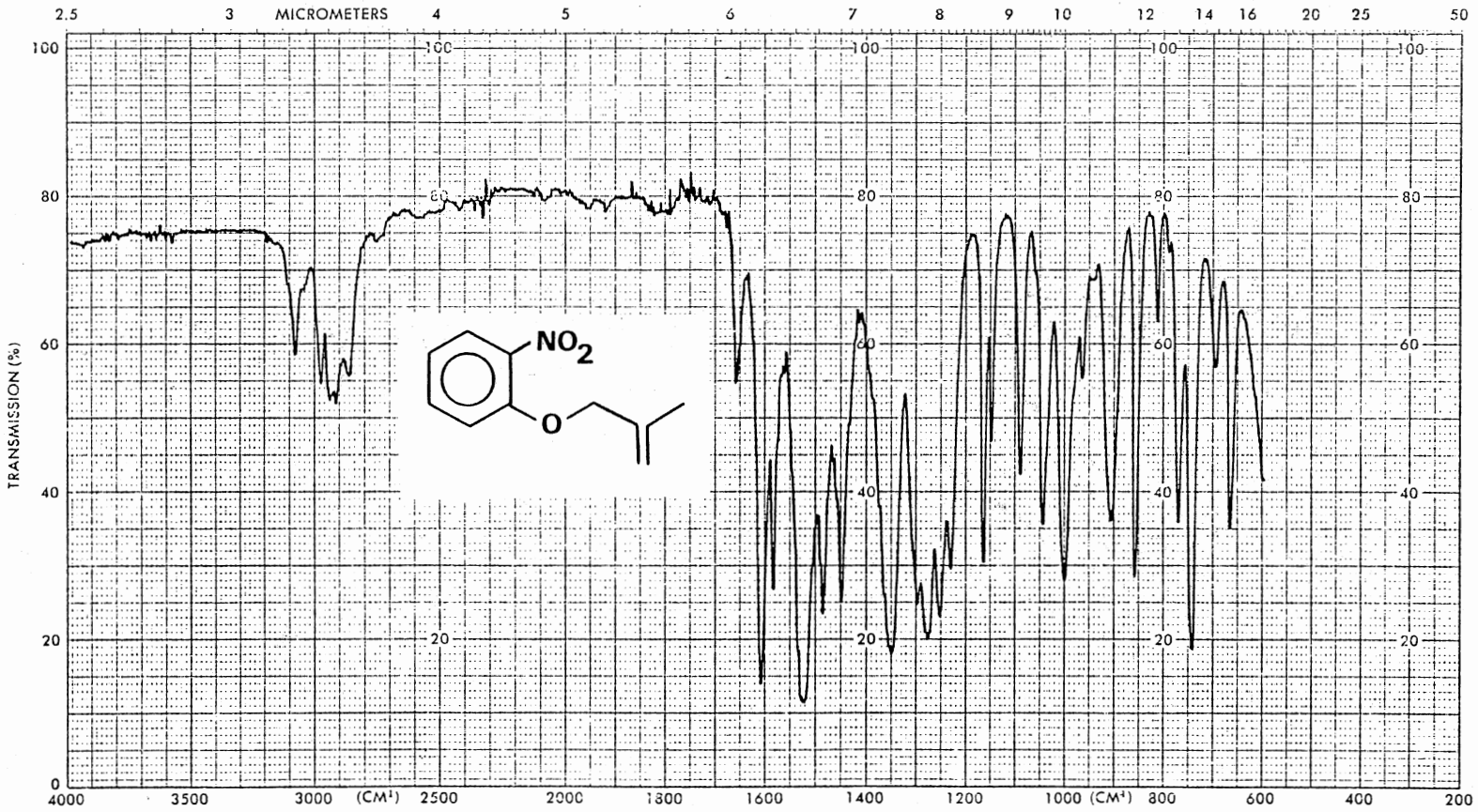
DECOUPLE: Nucleus 1 500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation Mode S Freq. 7900 Hz; Pulse Width 17.5 µsec Power Mode ---

^{13}C NMR Spectrum of **100**

PLOT/PROCESSING: FN 64 K RE --- sec CD --- sec; LB 2.000 Hz AF --- sec CCD ---; Width 20000.0 Hz/ppm Start -903.5 Hz/ppm; Reference

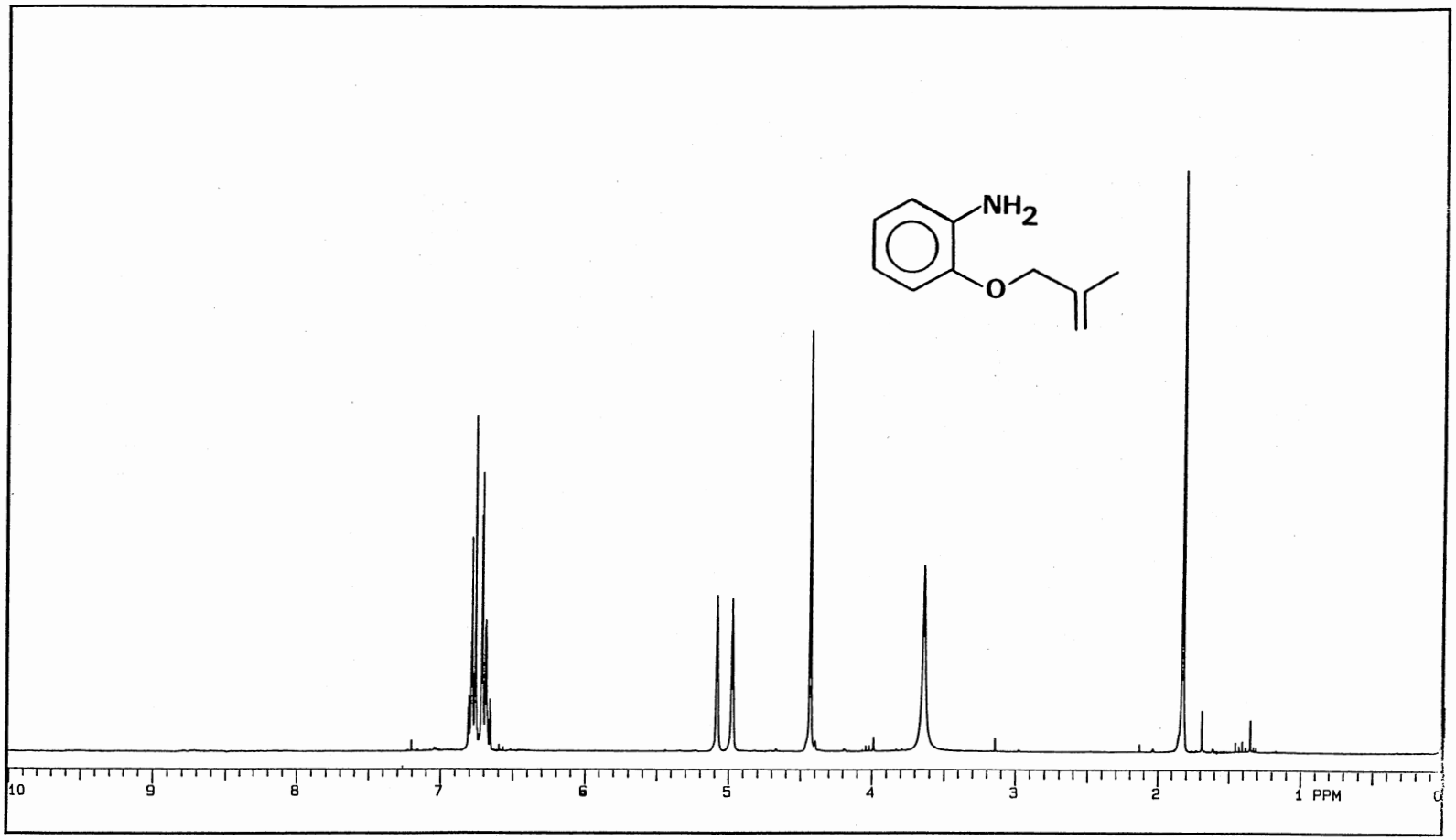
EXPERIMENT: Pulse Sequence STD13C; Tube O.D. --- mm; Temp. --- °C; Solvent CDCl3

PLATE LXII



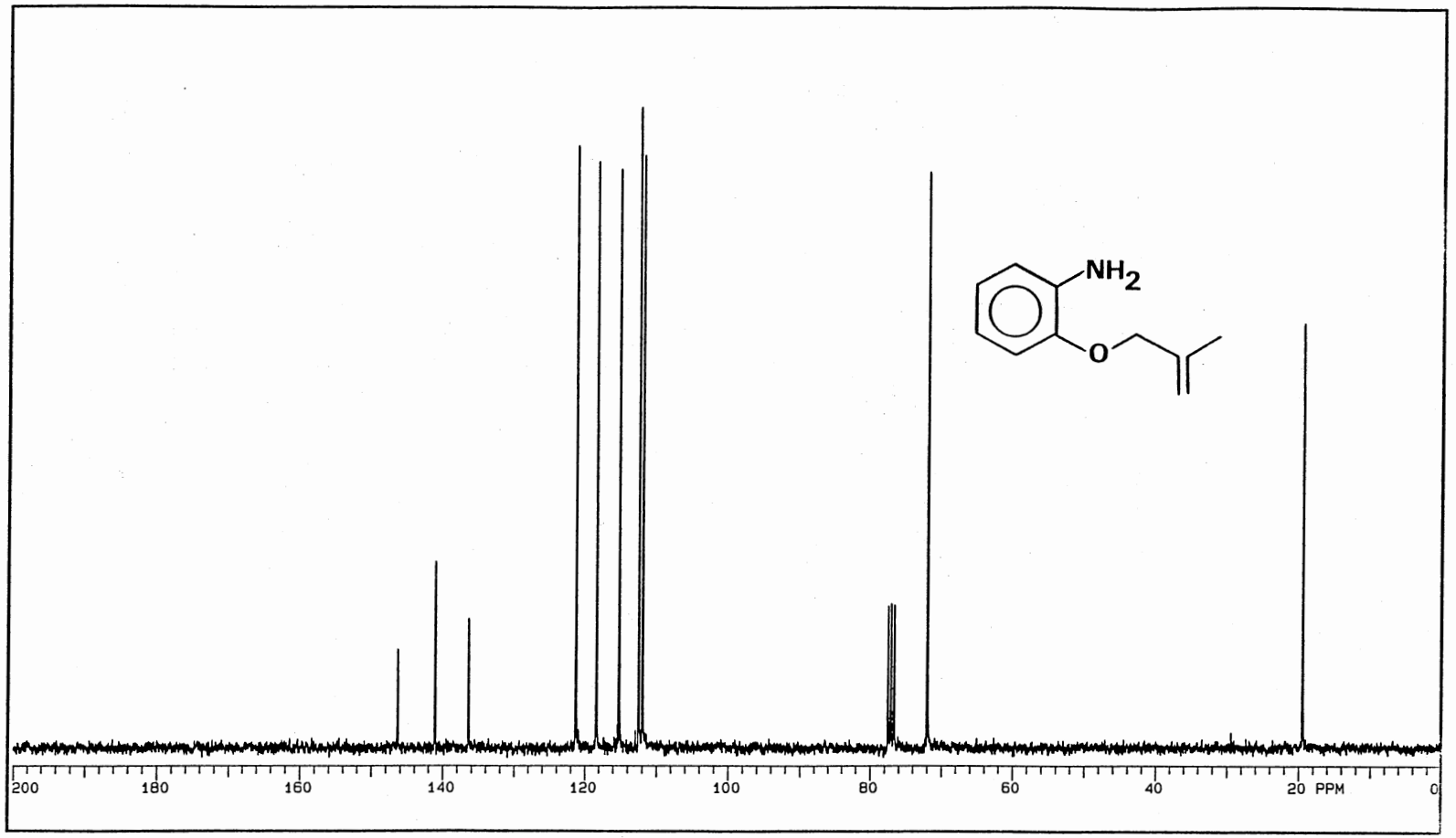
IR Spectrum of **100**

PLATE LXIII



^{1}H NMR Spectrum of **101**

PLATE LXIV



OBSERVE: Nucleus 13.500 Freq 75 MHz; Spec. Width 20000.0 Hz Offset 1500 Hz; Acq. Time 1.000 sec Delay 3.000 sec; Pulse Width 12.0 sec Transients 96

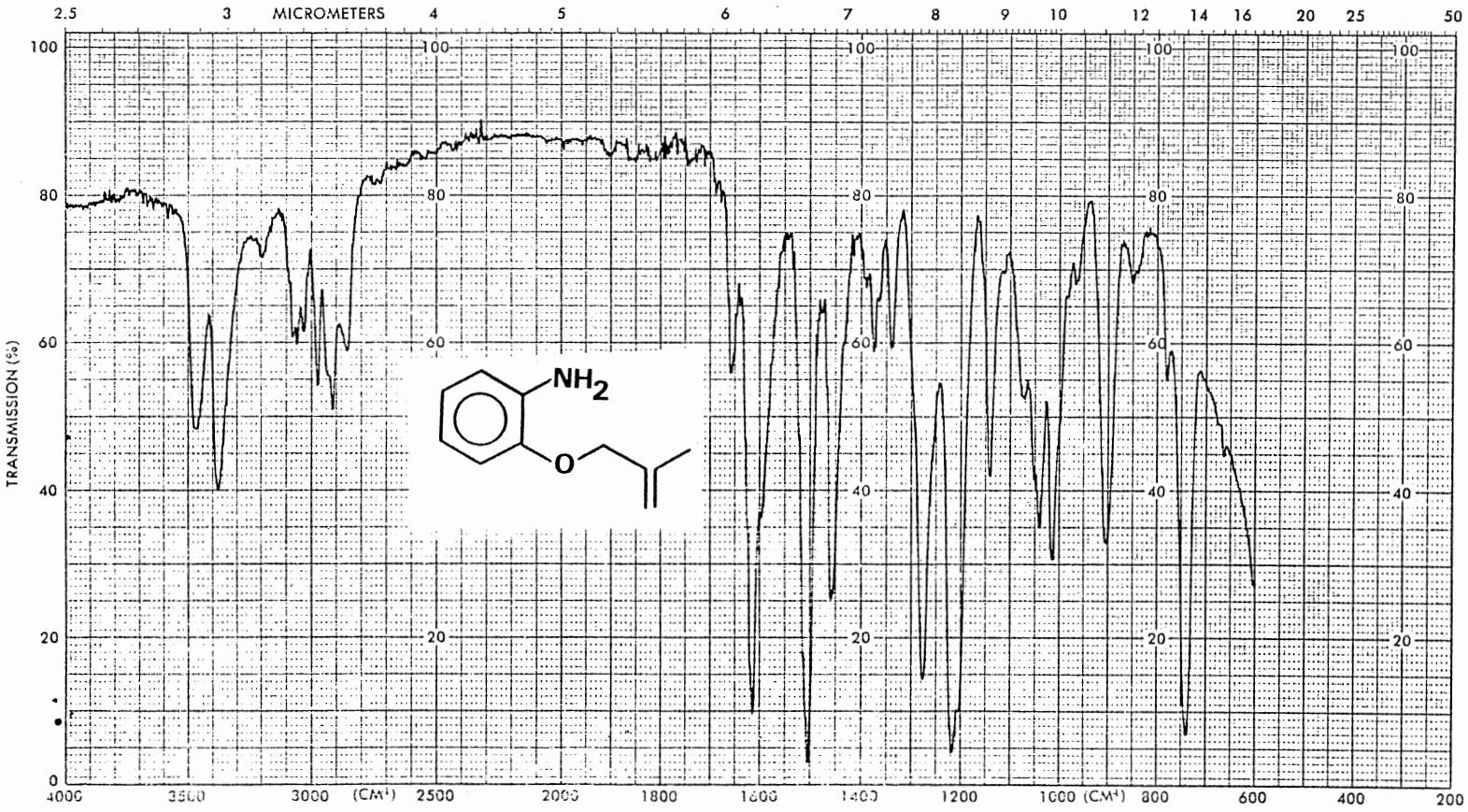
DECOUPLE: Nucleus 1.500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation Mode S Freq 7900 Hz; Pulse Width 17.5 µsec Power Mode ---

^{13}C NMR Spectrum of **102**

PLOT/PROCESSING: FN 64 K RE --- sec CD --- sec; LB 2.000 Hz AF --- sec OCD ---; Width 15085.9 Hz/ppm Start 0 Hz/ppm; Reference

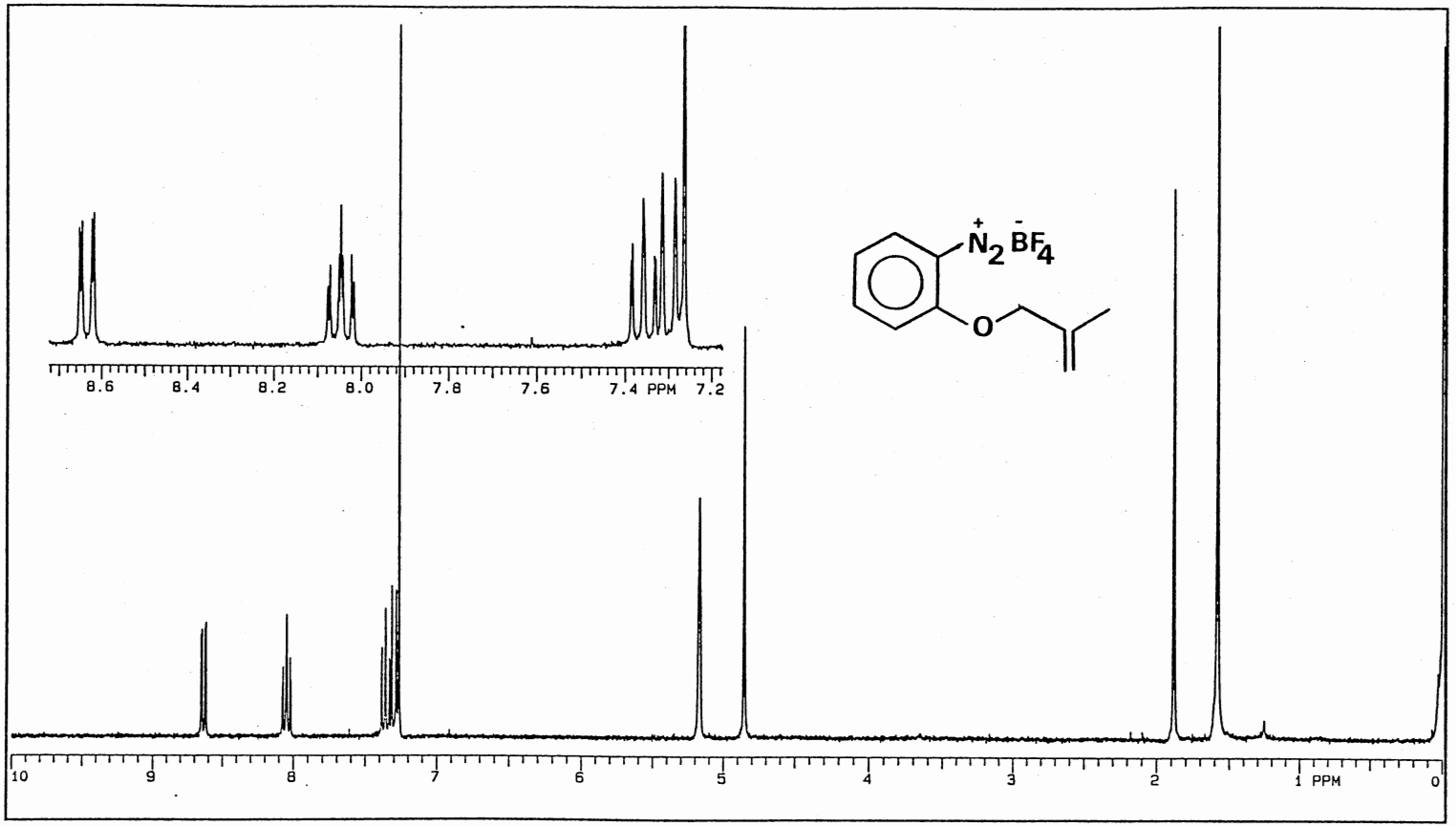
EXPERIMENT: Pulse Sequence STD13C; Tube O.D. --- mm; Temp. --- °C; Solvent CDCL3

PLATE LXV



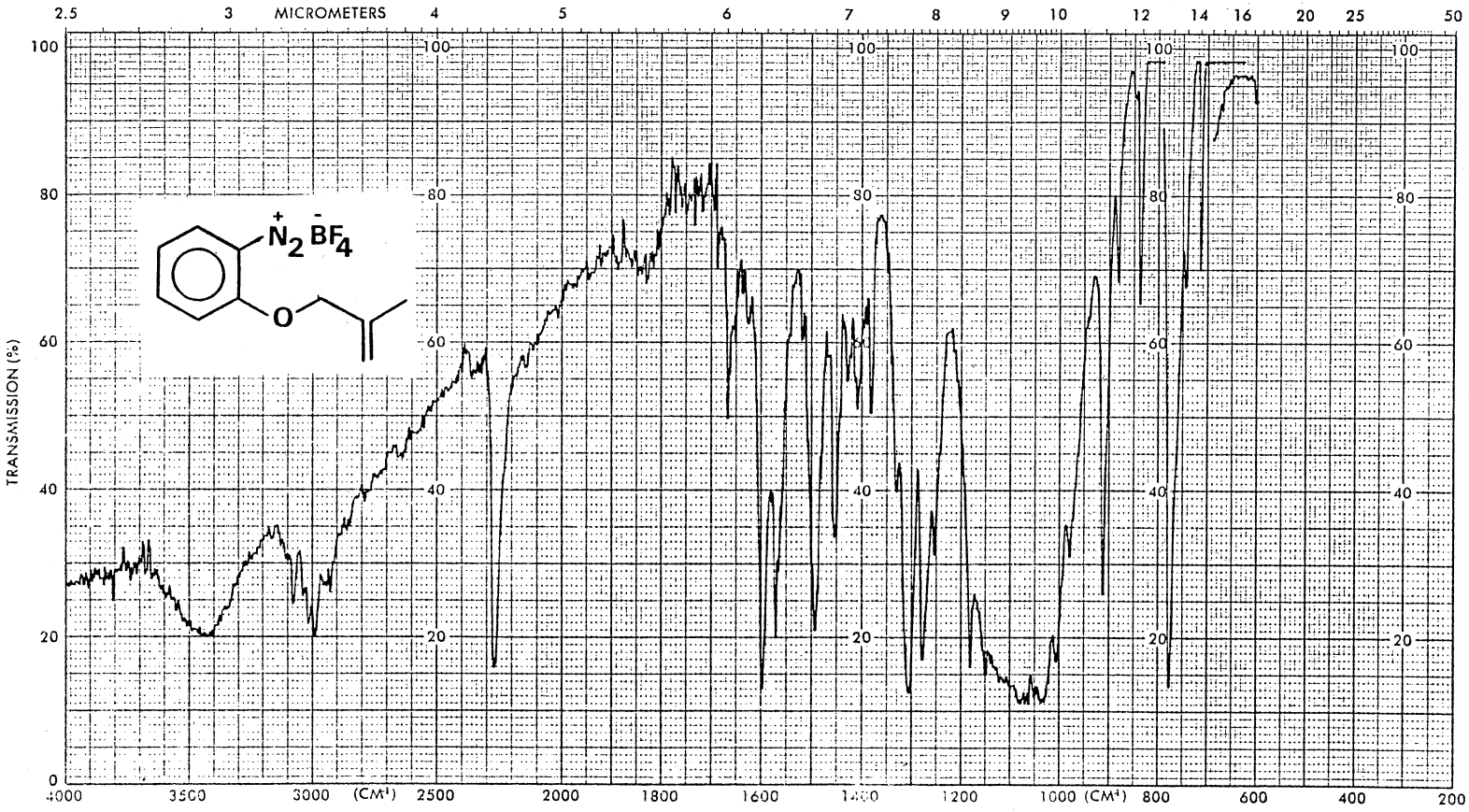
IR Spectrum of **101**

PLATE LXVI



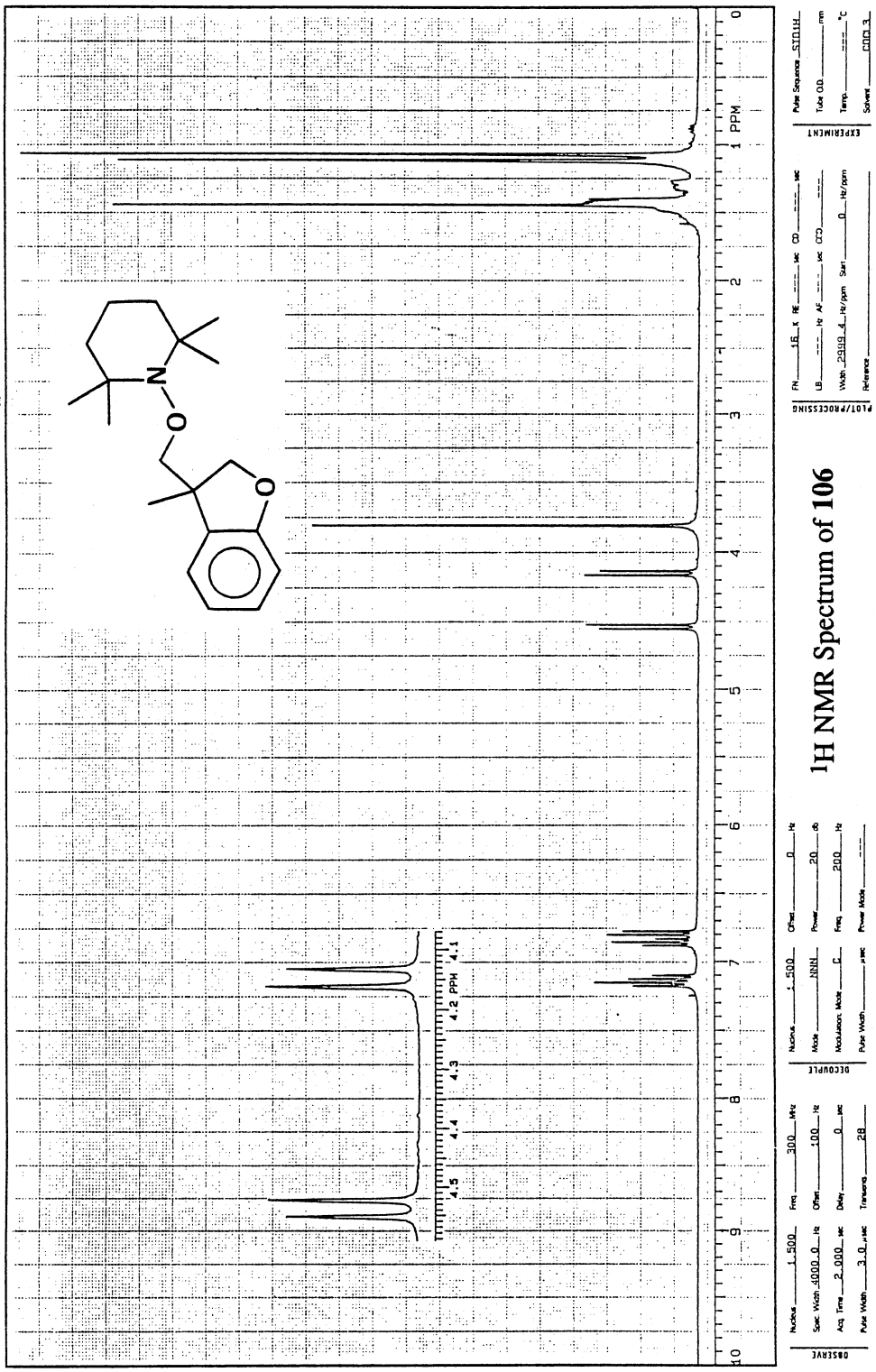
^{1}H NMR Spectrum of **102**

PLATE LXVII



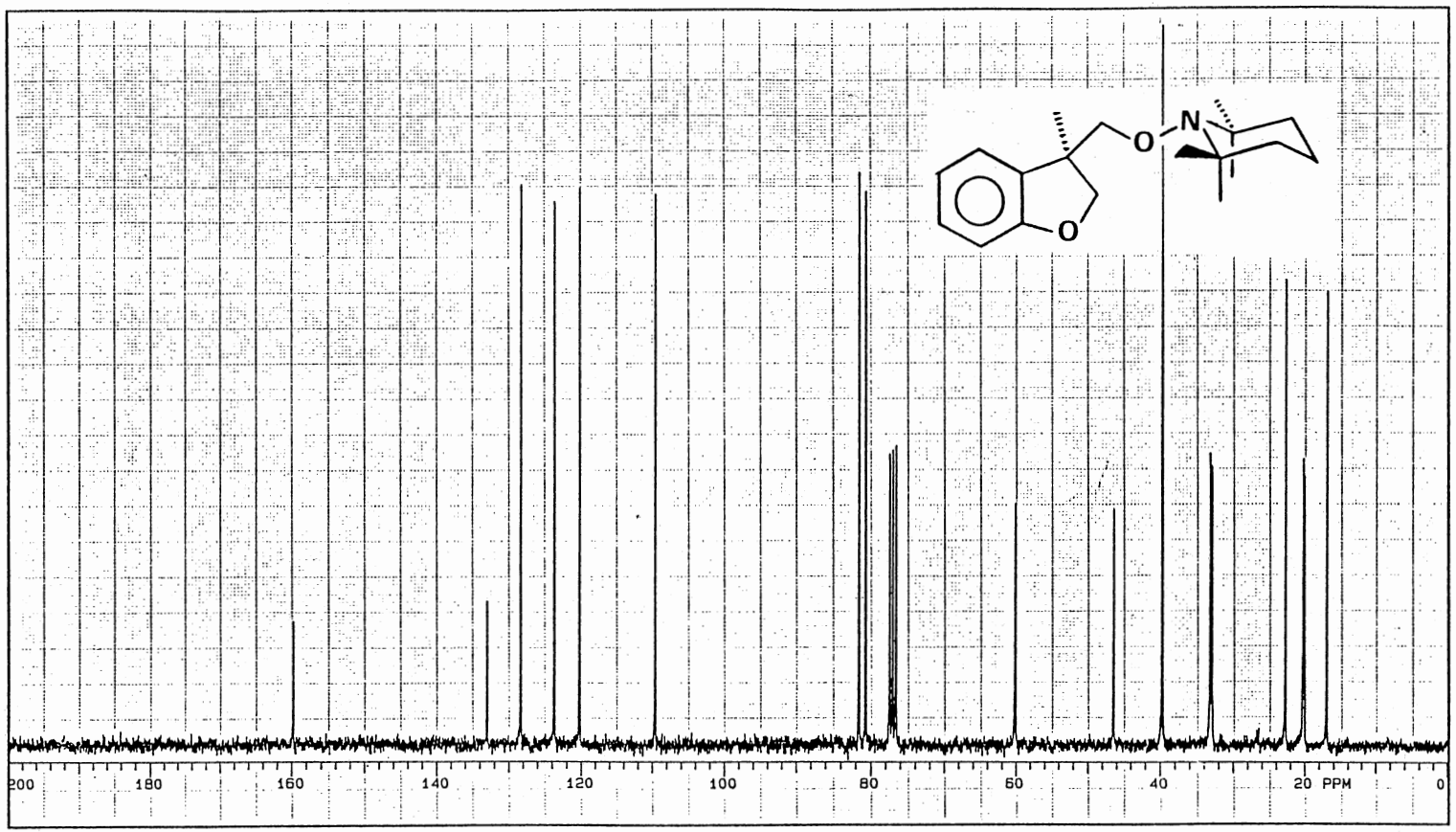
IR Spectrum of 102 -KBr

PLATE LXVIII



^{1}H NMR Spectrum of **106**

PLATE LXIX



OBSERVE: Nucleus 13.500 Freq 75 MHz; Spec Wdth 20000.0 Hz Offset 1500 Hz; Acq Time 1.000 sec Delay 3.000 sec; Pulse Width 10.0 μsec Transients 192

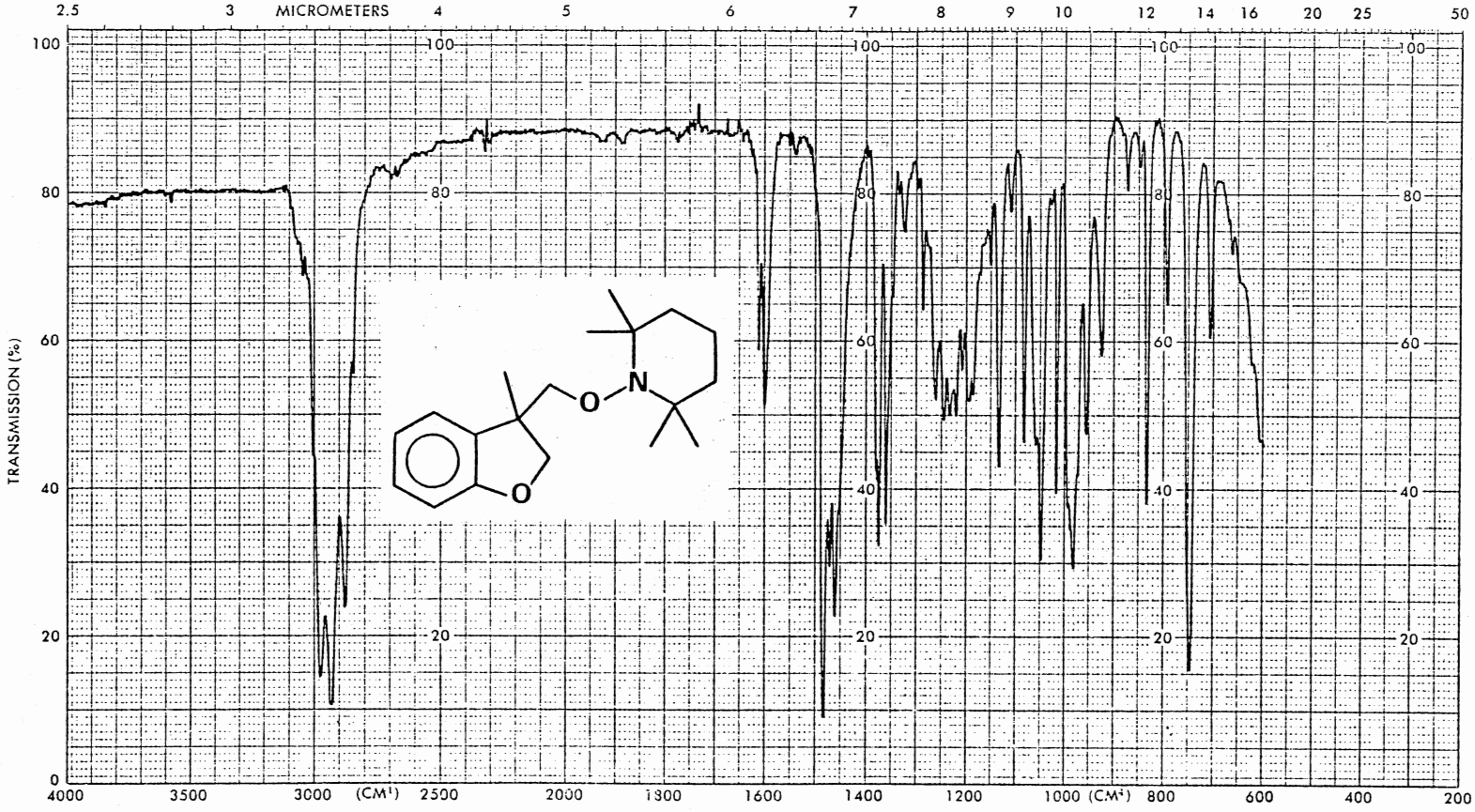
DECOUPLE: Nucleus 1.500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation Mode S Freq 7900 Hz; Pulse Width 17.5 μsec Power Mode ---

^{13}C NMR Spectrum of **106**

PLOT/PROCESSING: FN 64 K RE --- sec CD --- sec; LB 2.000 Hz AF --- sec CCD ---; Wdth 15085.9 Hz/ppm Start 0 Hz/ppm; Reference

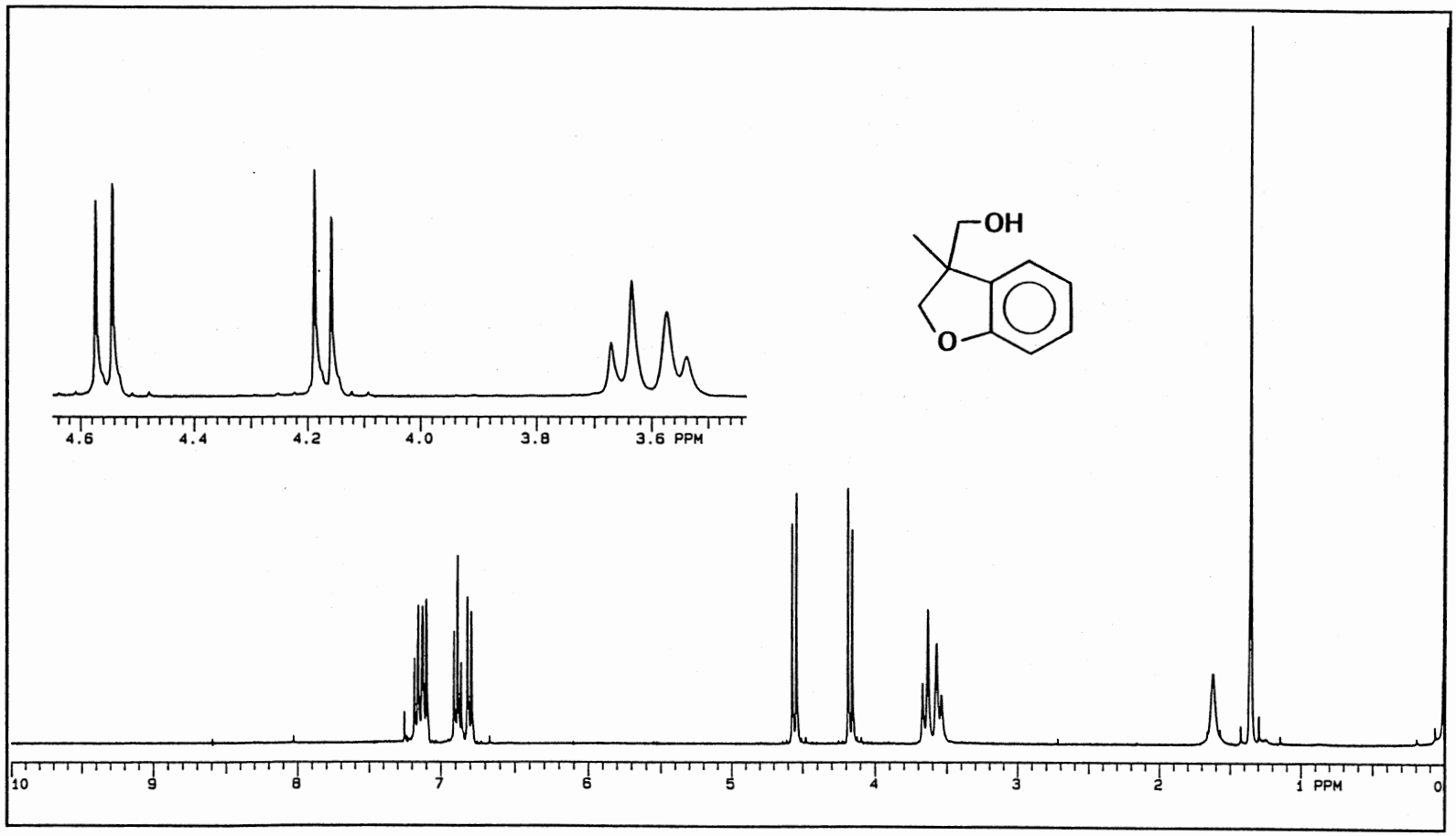
EXPERIMENT: Pulse Sequence STD13C; Tube OD mm; Temp --- °C; Solvent CDCl3

PLATE LXX



IR Spectrum of **106**

PLATE LXXI



OBSERVE Nucleus 1.500 Freq. 300 MHz Spec. Width 4000.0 Hz Offset 100 Hz Acq. Time 2.000 sec Delay 0 sec Pulse Width 7.0 sec Transients 64

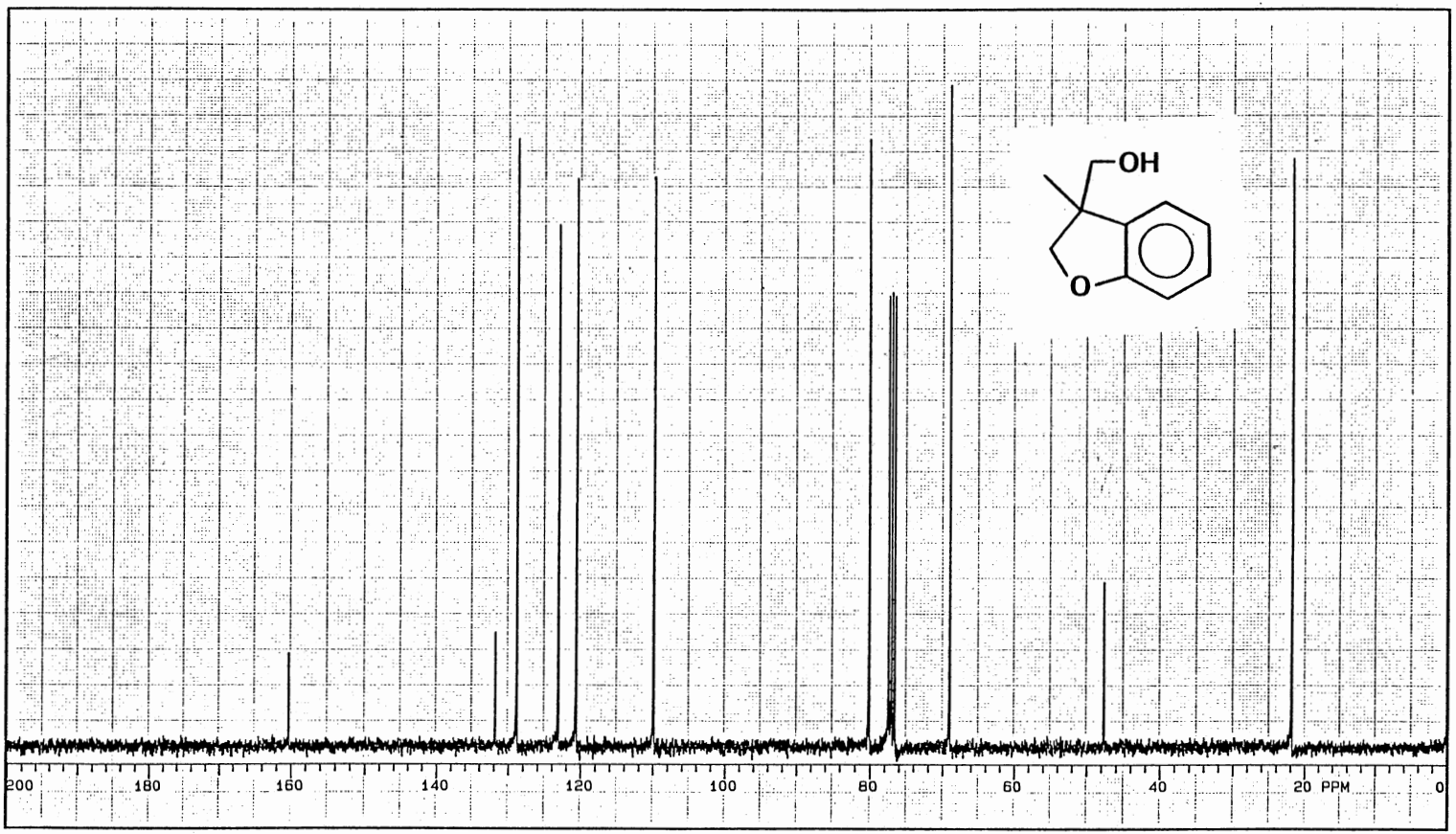
DECOUPLE Nucleus 1.500 Offset 170.2 Hz Mode NNN Power 20 db Modulation Mode C Freq. 200 Hz Pulse Width ___ sec Power Mode ___

^{1}H NMR Spectrum of **107**

PLOT/PROCESSING FN 16 K RE ___ sec CD ___ sec LB ___ Hz AF ___ sec CCD ___ Width 2999.4 Hz/ppm Start 0 Hz/ppm Reference ___

EXPERIMENT Pulse Sequence STD1H Tube O.D. ___ mm Temp. ___ °C Solvent CDCL3

PLATE LXXII



OBSERVE: Nucleus 13.500 Freq 75 MHz; Spec. Width 20000.0 Hz Offset 1500 Hz; Acq. Time 1.000 sec Delay 3.000 sec; Pulse Width 10.0 μsec Transients 624

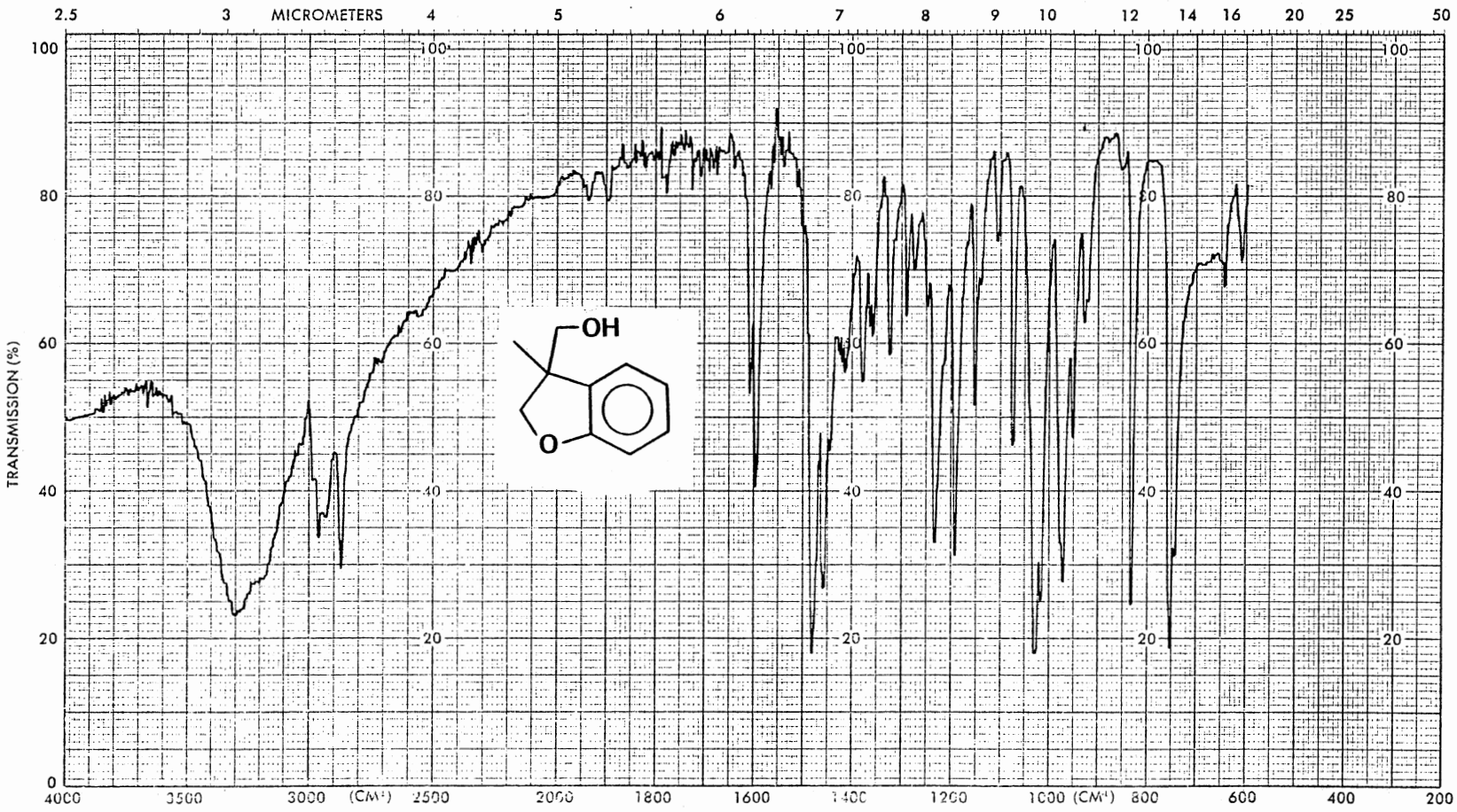
DECOUPLE: Nucleus 1.500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation Mode S Freq. 7900 Hz; Pulse Width 17.5 μsec Power Mode ---

PLOT/PROCESSING: FN 64 K RE --- sec CD --- sec; LB 1.500 Hz AF --- sec OCD ---; Width 15085.9 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence STD13C; Tube O.D. --- mm; Temp --- °C; Solvent CDCL3

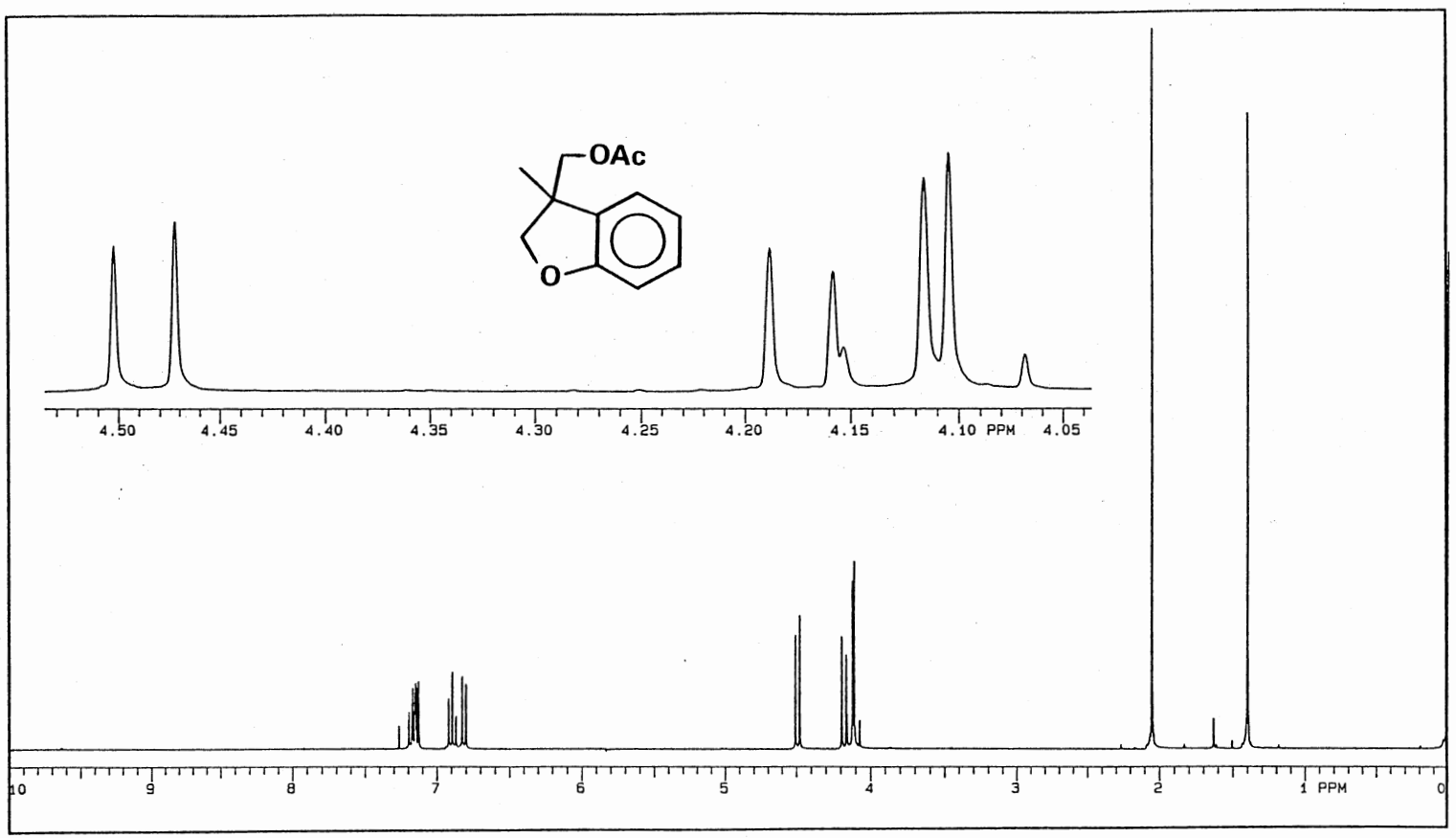
^{13}C NMR Spectrum of **107**

PLATE LXXIII



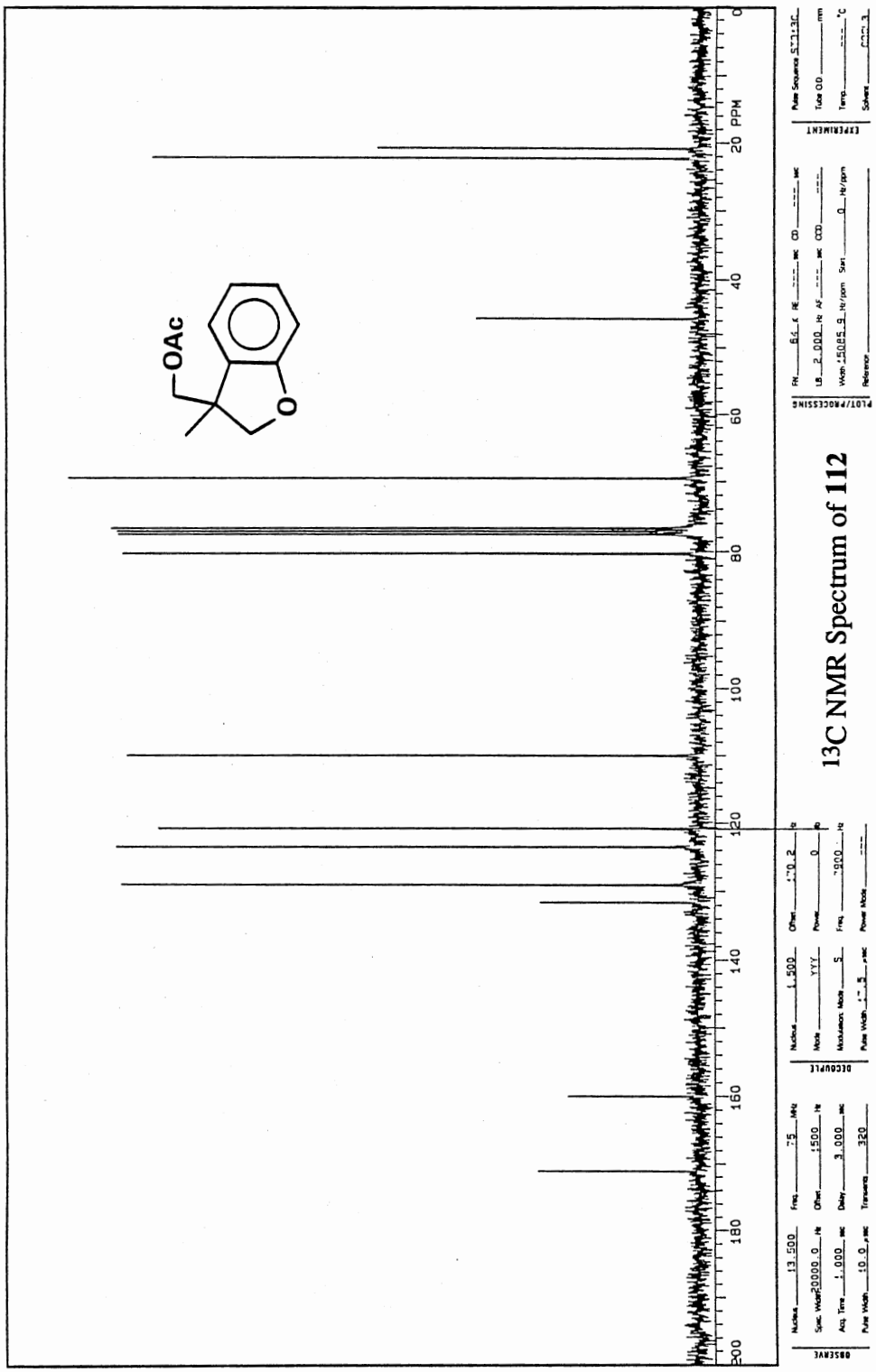
IR Spectrum of **107** -KBr

PLATE LXXIV



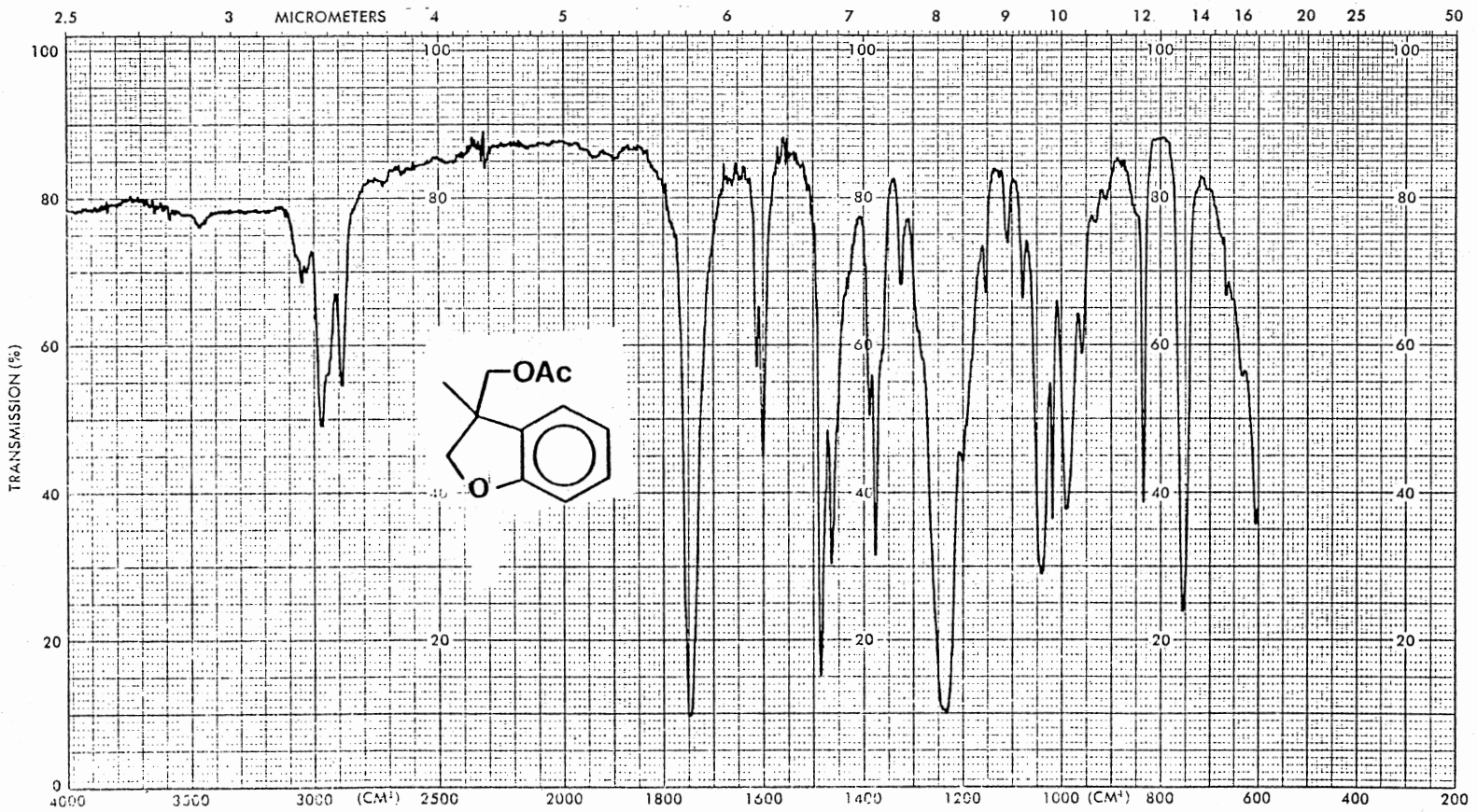
^{1}H NMR Spectrum of **112**

PLATE LXXV



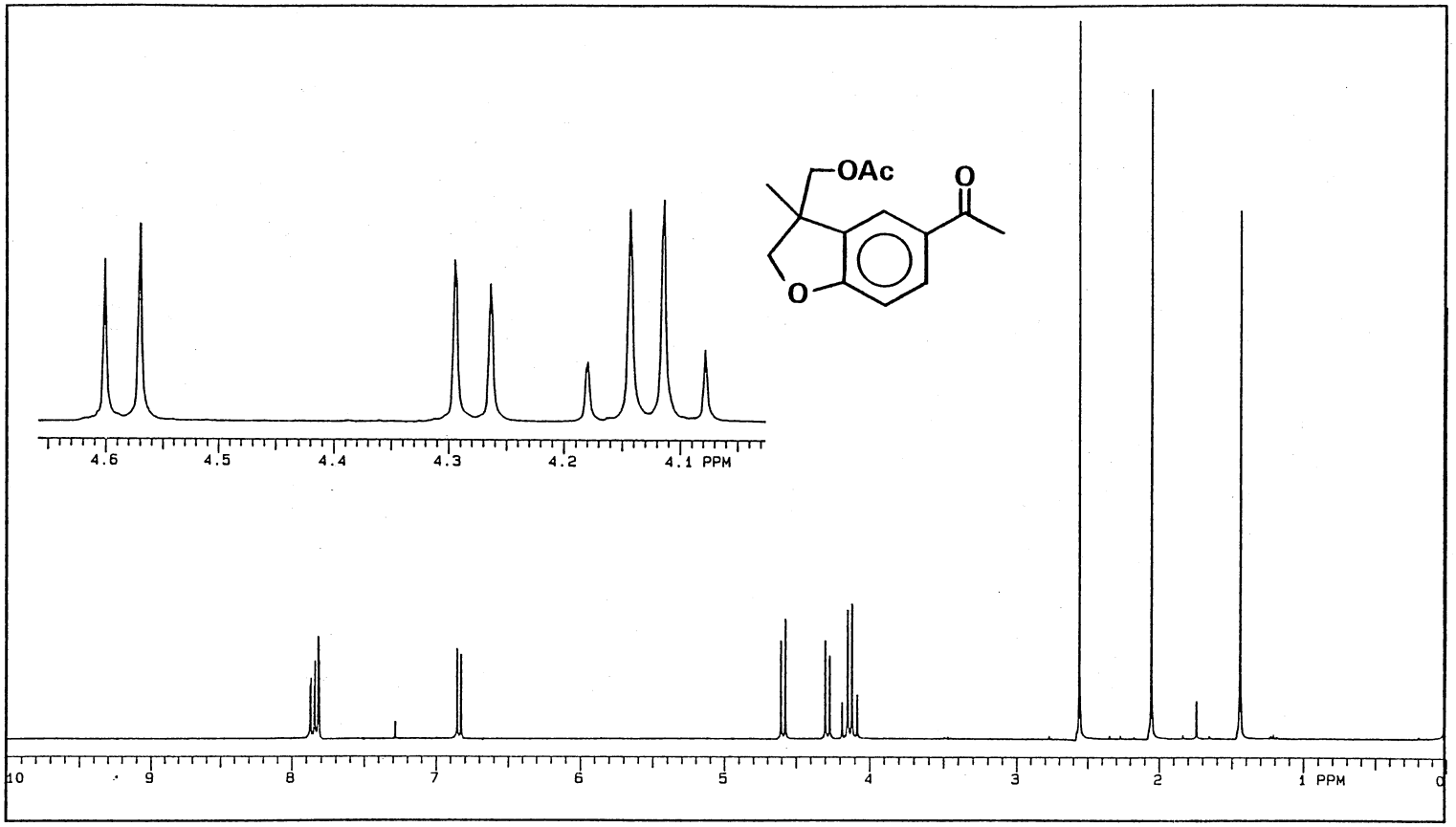
^{13}C NMR Spectrum of **112**

PLATE LXXVI



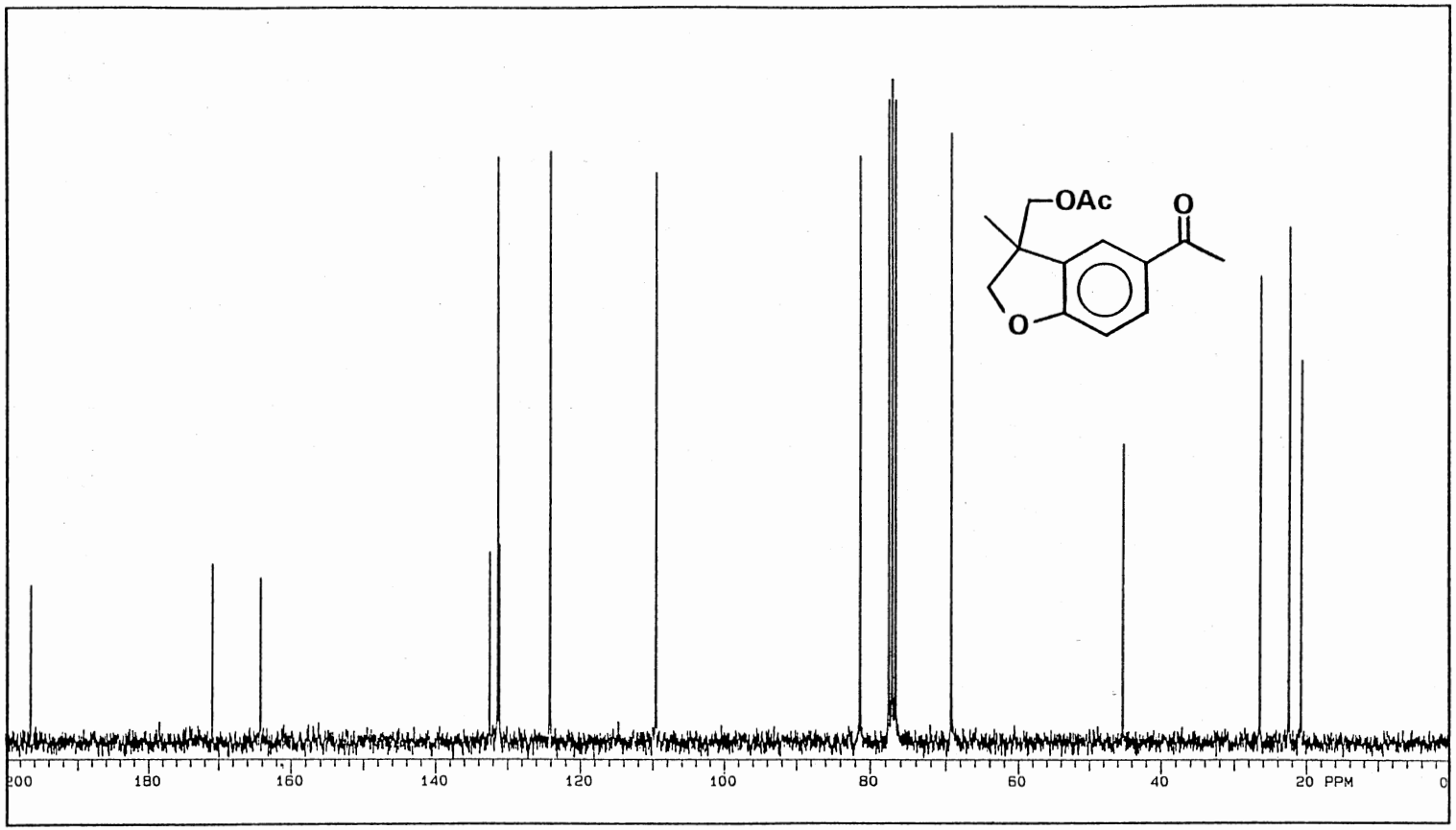
IR Spectrum of 112

PLATE LXXVII



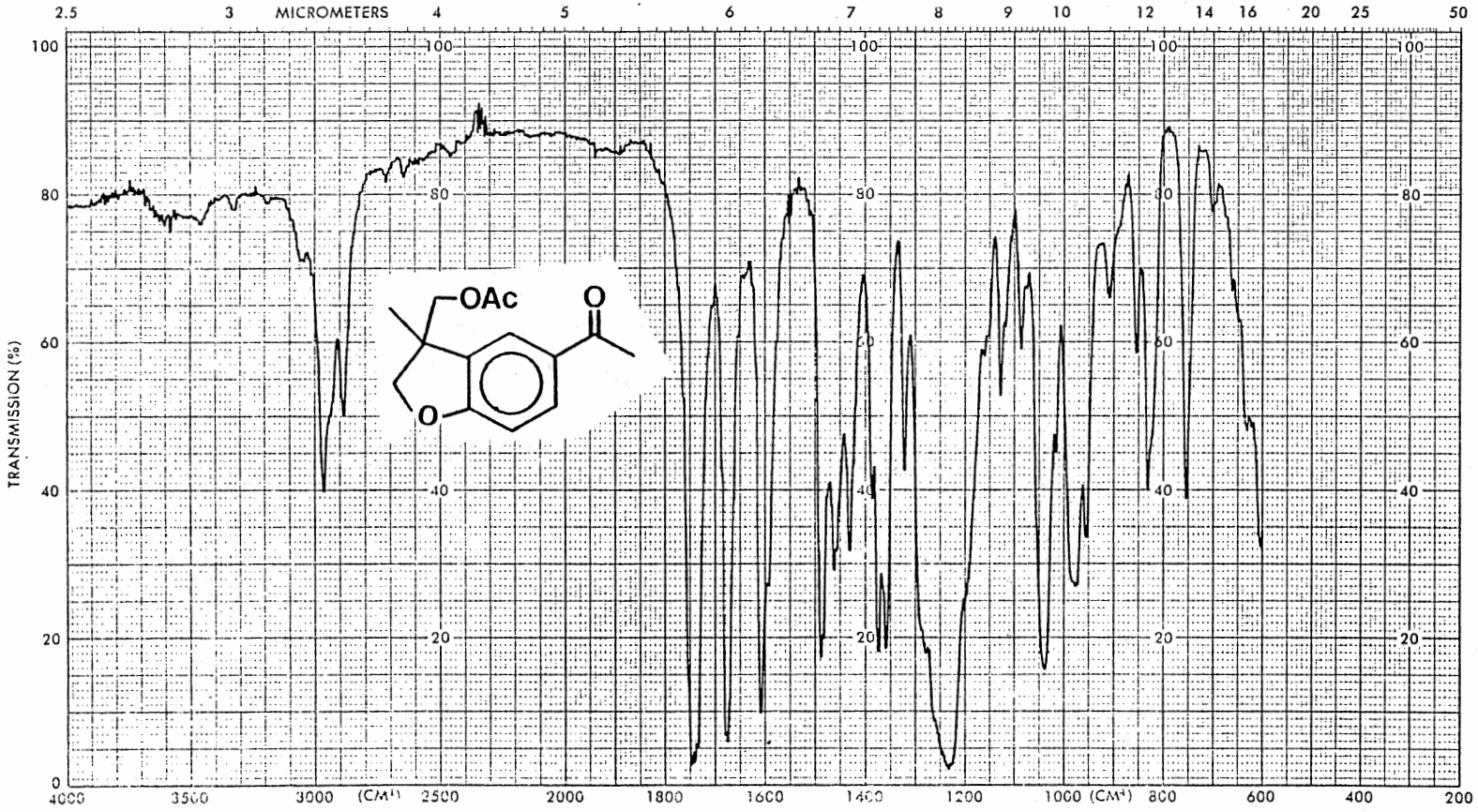
^{1}H NMR Spectrum of **113**

PLATE LXXVIII



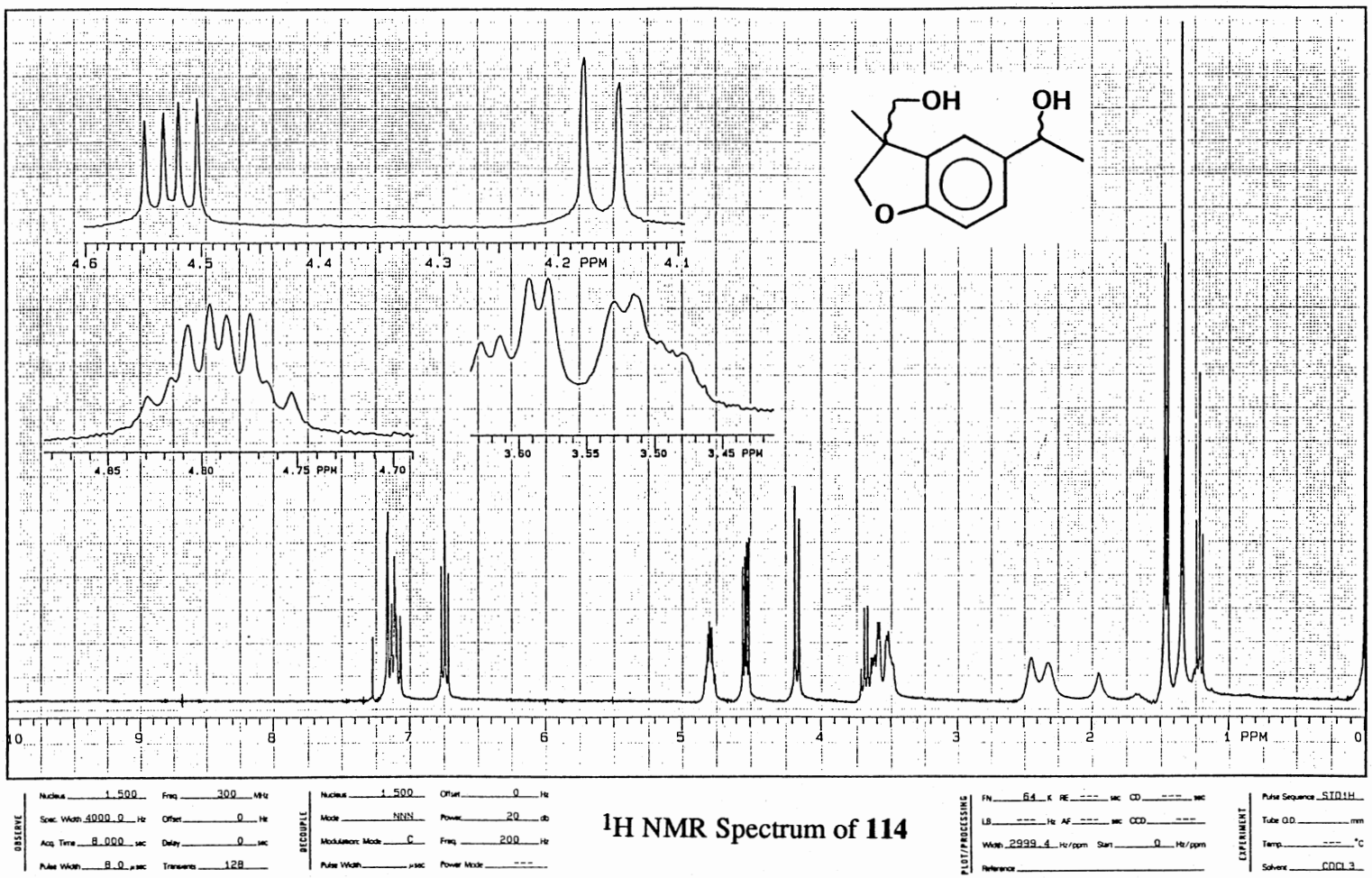
^{13}C NMR Spectrum of **113**

PLATE LXXIX



IR Spectrum of 113

PLATE LXXX



OBSERVE: Nucleus 1 500 Freq 300 MHz; Spec Width 4000 0 Hz Offset 0 Hz; Acq Time 8 000 sec Delay 0 sec; Pulse Width 8 0 µsec Transients 128

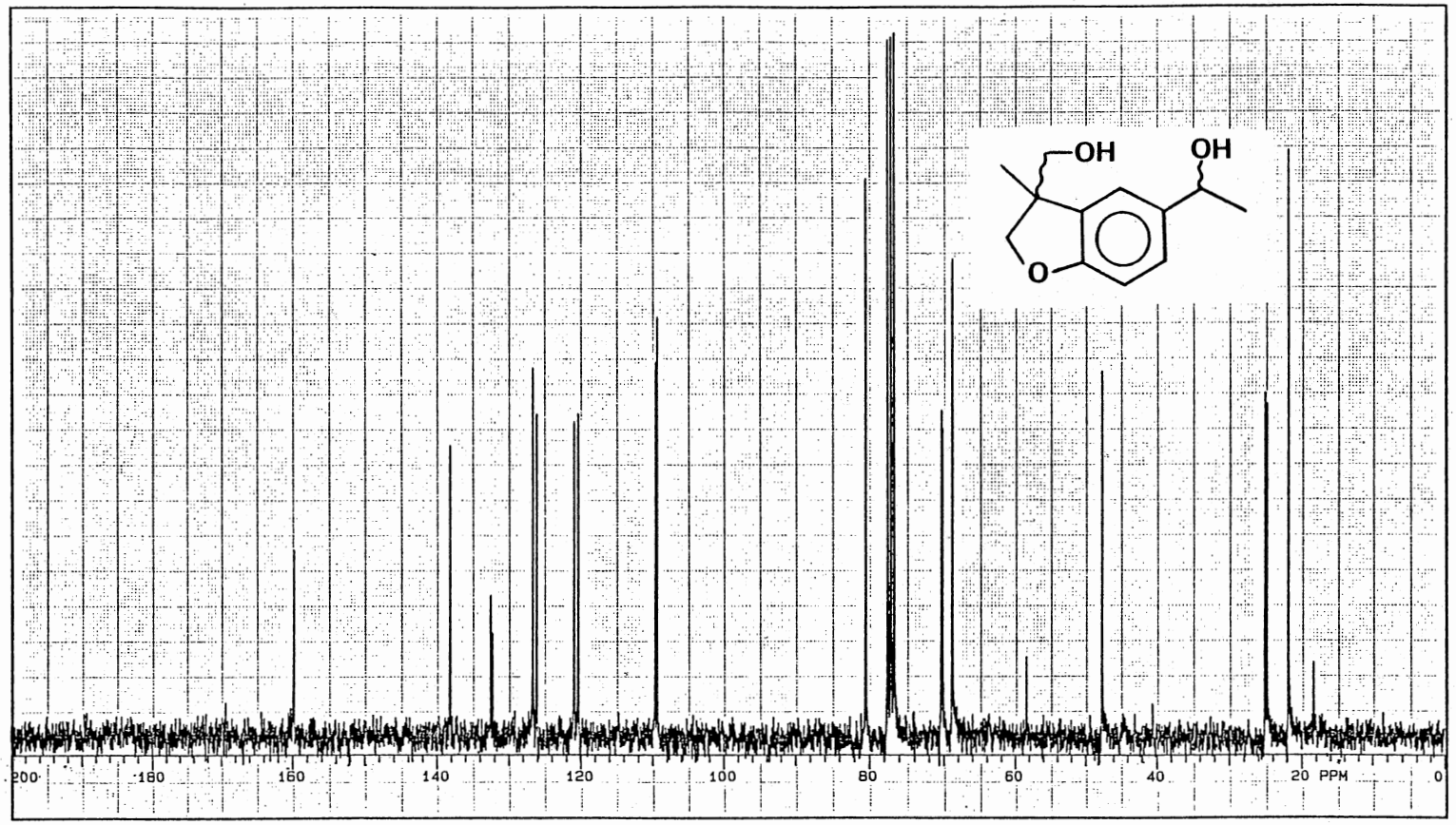
DECOUPLE: Nucleus 1 500 Offset 0 Hz; Mode NNN Power 20 db; Modulation Mode C Freq 200 Hz; Pulse Width µsec Power Mode ---

PLOT/PROCESSING: FN 64 K RE --- sec CD --- sec; LB --- Hz AF --- sec CCD ---; Width 2999 4 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence STD1H; Tube O.D. mm; Temp. --- °C; Solvent CDCl 3

^{1}H NMR Spectrum of **114**

PLATE LXXXI



OBSERVE: Nucleus 13.500 Freq 75 MHz; Spec. Width 20000.0 Hz Offset 1500 Hz; Acq. Time 1.000 sec Delay 3.000 sec; Pulse Width 12.0 μsec Transmtr 400

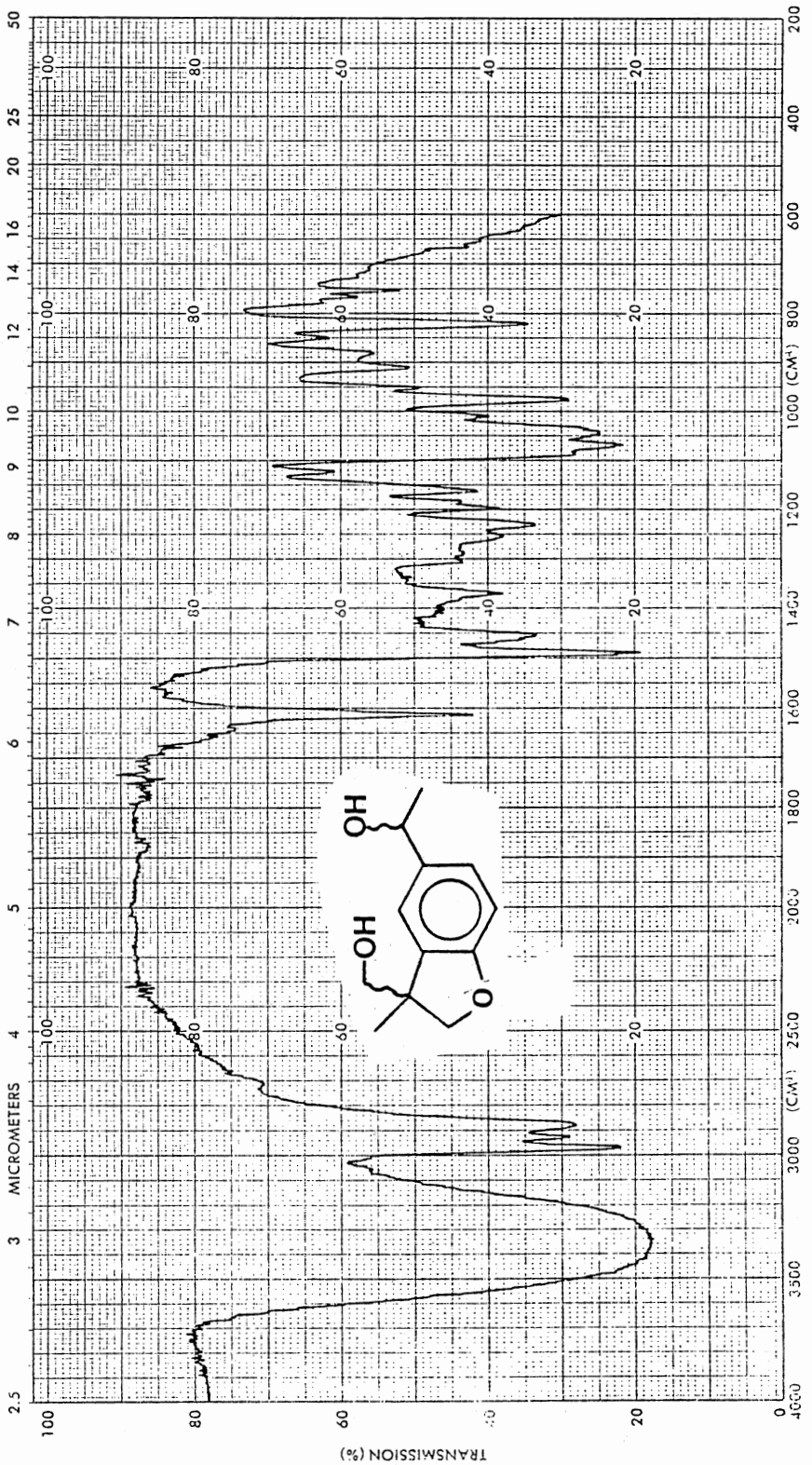
DECOUPLE: Nucleus 1.500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation Mode S Freq 7900 Hz; Pulse Width 17.5 μsec Power Mode ---

PLOT/PROCESSING: FN 64 K RE --- sec CD --- sec; LB 2.000 Hz AF --- sec OCD ---; Width 15085.9 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence STD13C; Tube O.D. ---mm; Temp ---°C; Solvent CDCl3

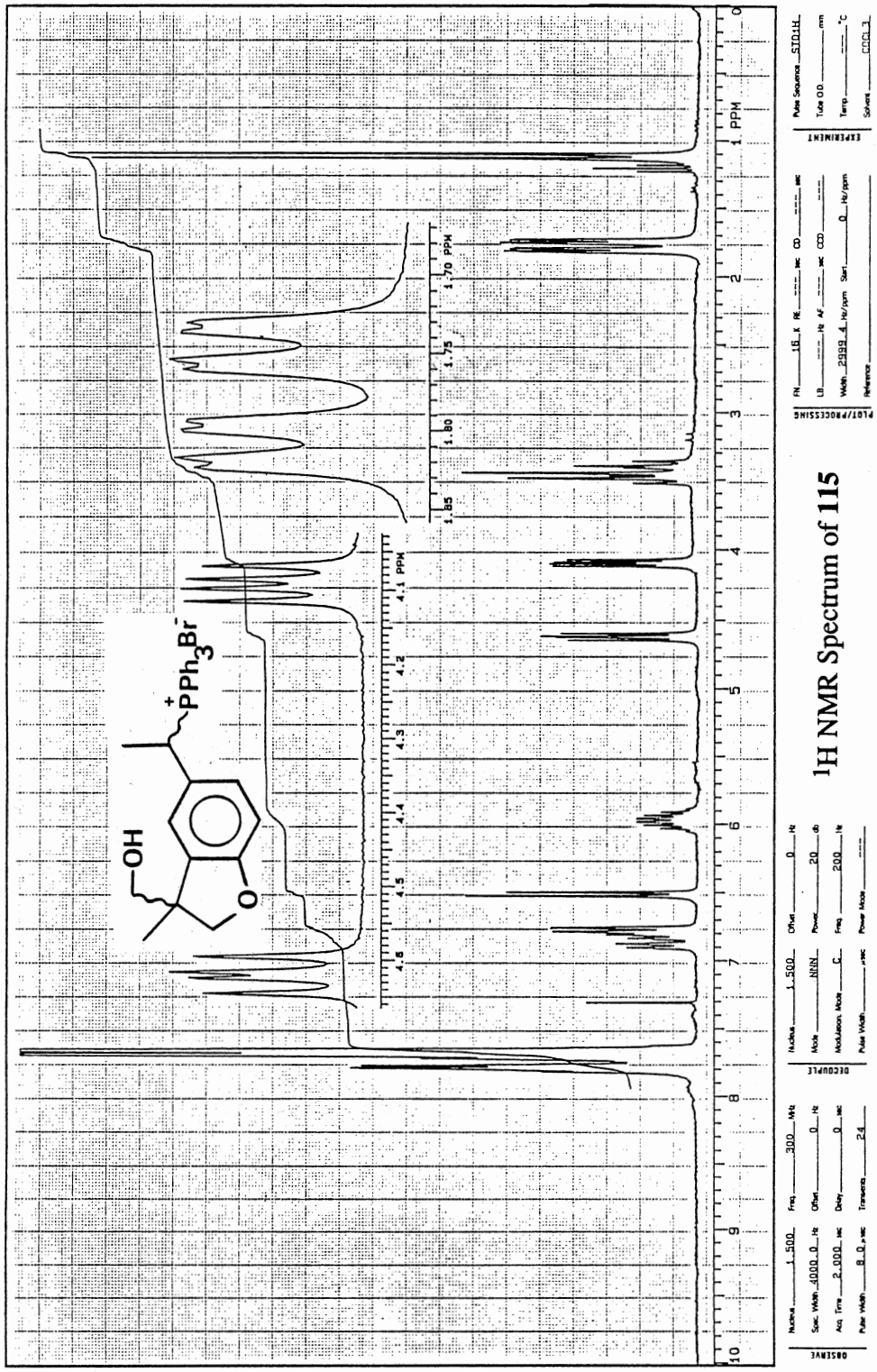
^{13}C NMR Spectrum of **114**

PLATE LXXXII



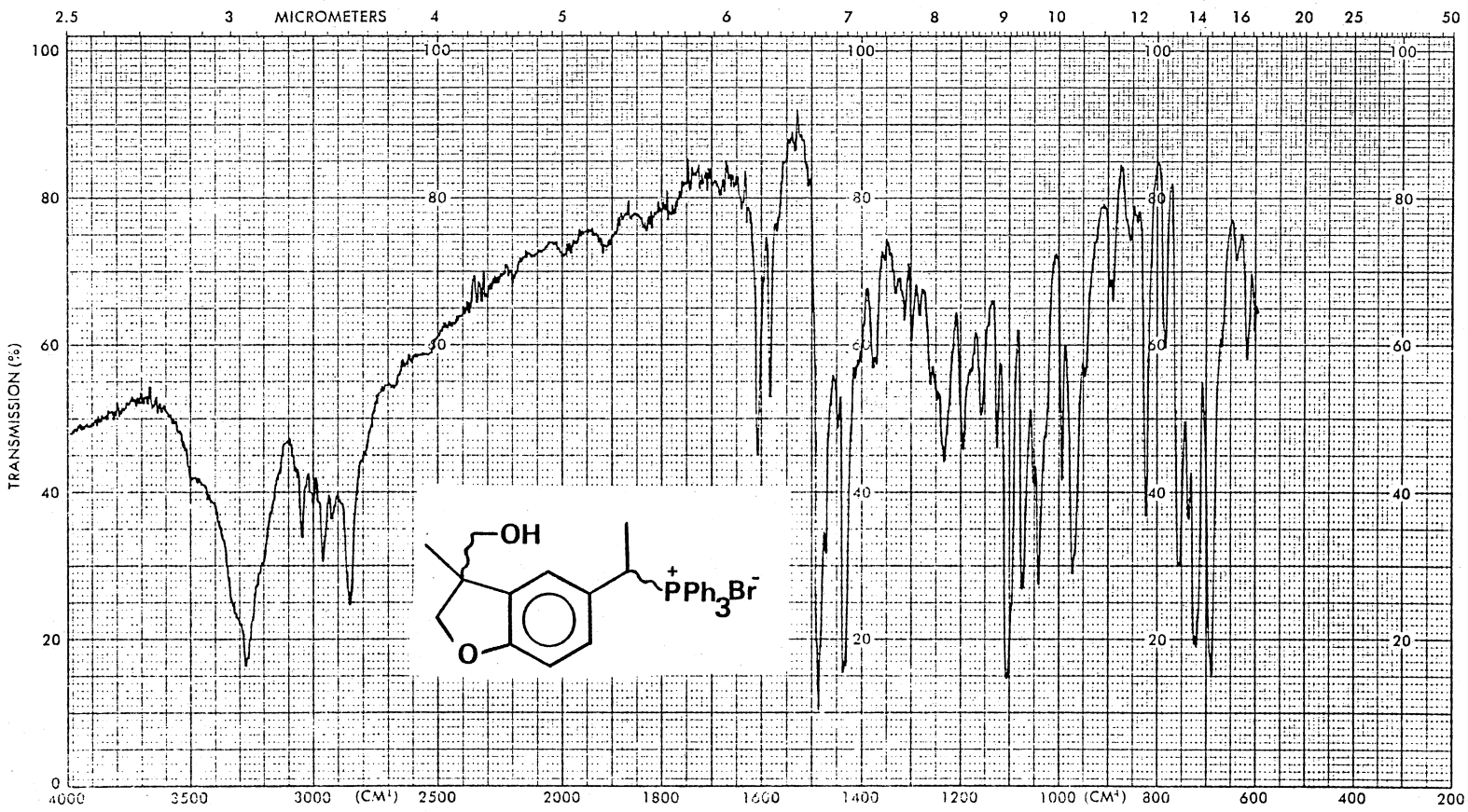
IR Spectrum of **114**

PLATE LXXXIII



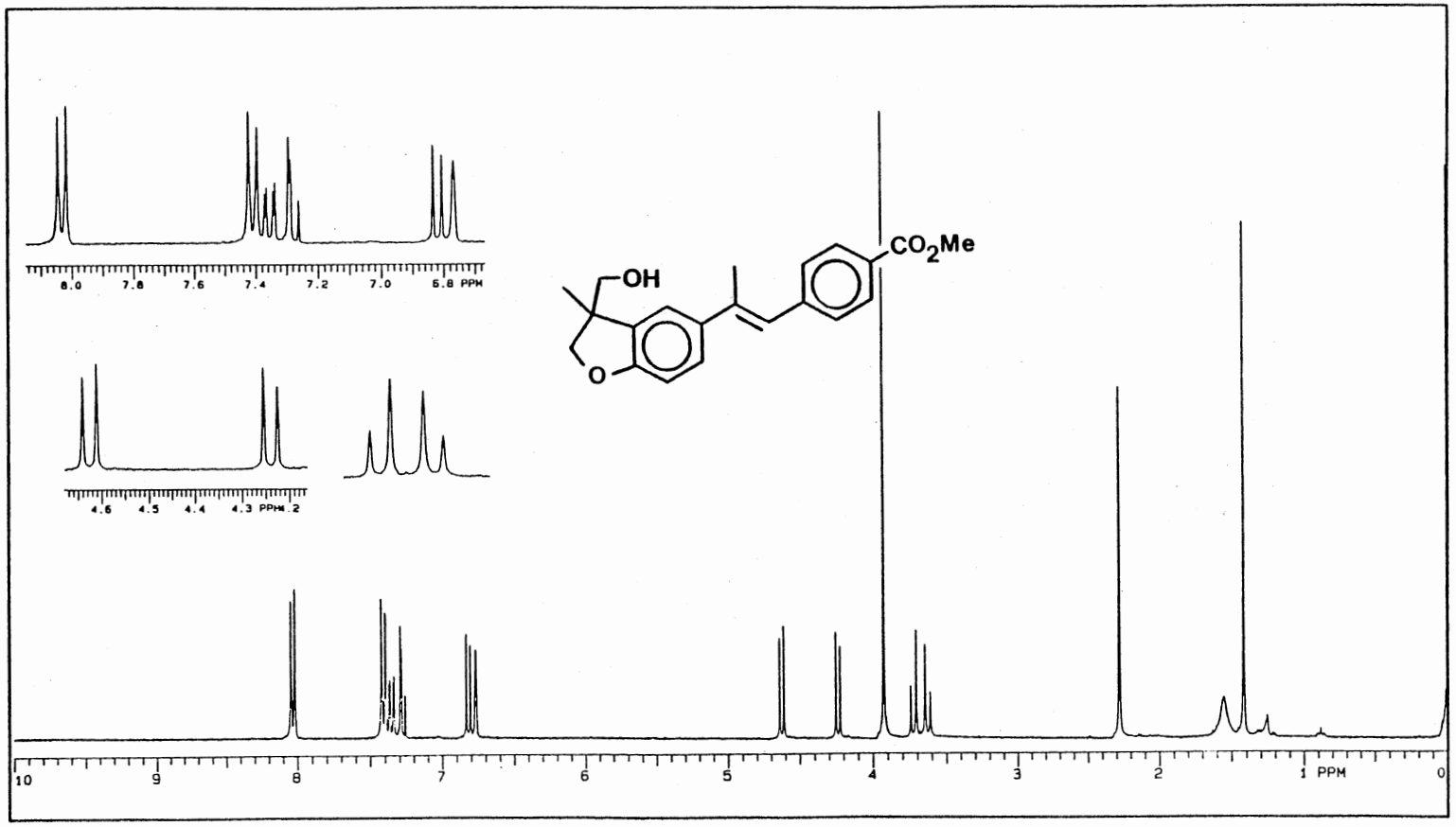
^{1}H NMR Spectrum of **115**

PLATE LXXXIV



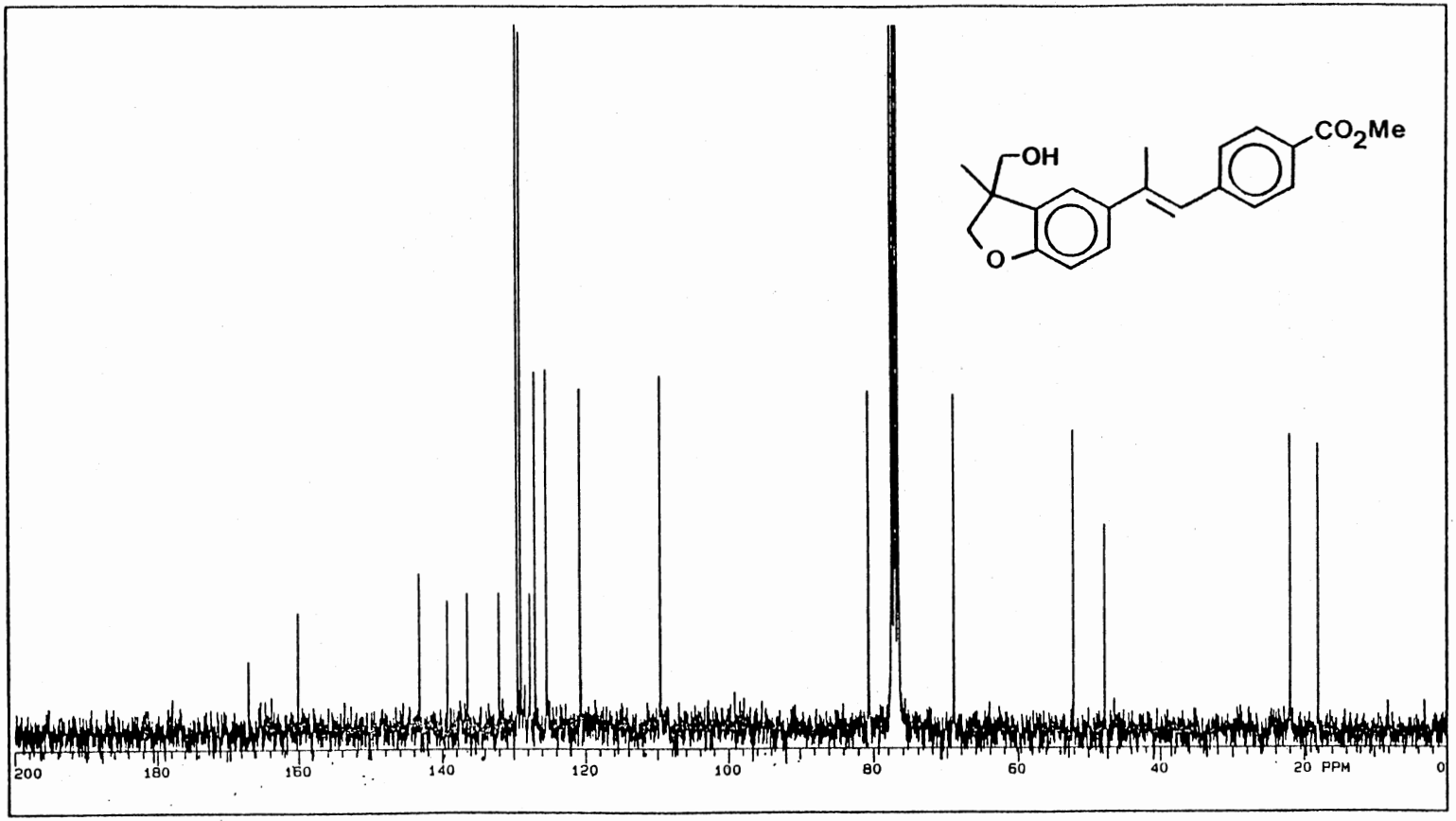
IR Spectrum of **115** -KBr

PLATE LXXXV



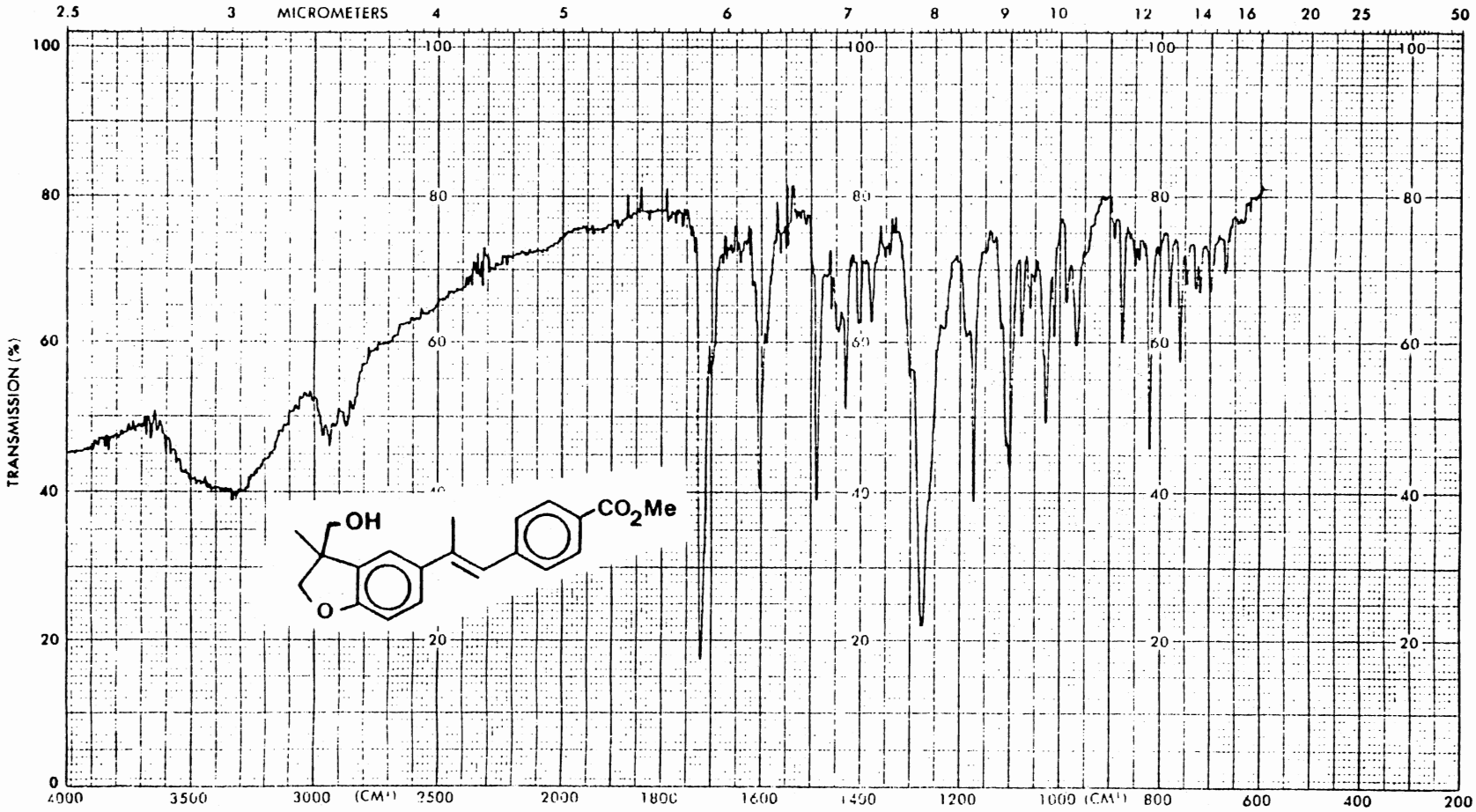
^{1}H NMR Spectrum of **64**

PLATE LXXXVI



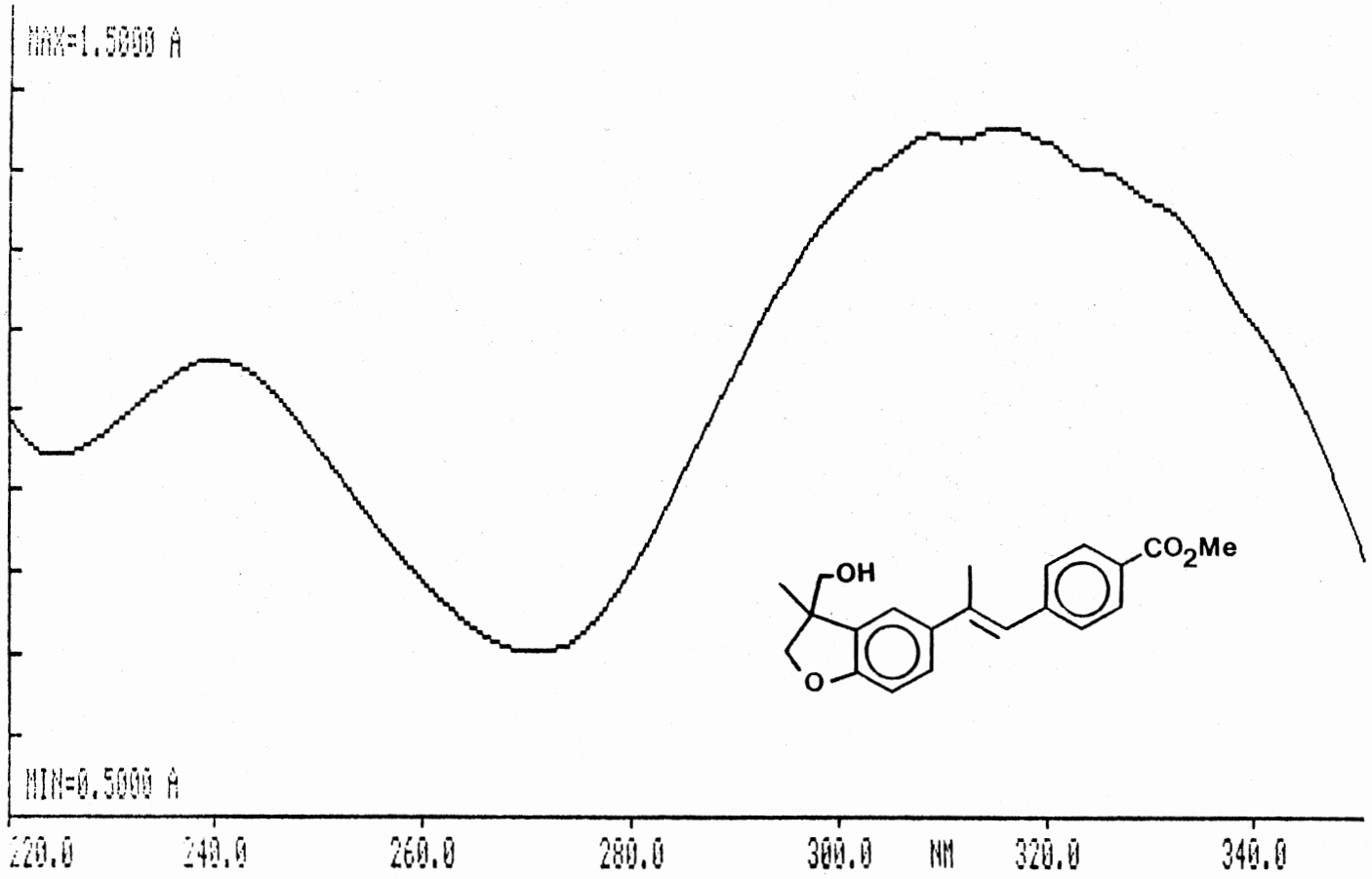
^{13}C NMR Spectrum of **64**

PLATE LXXXVII



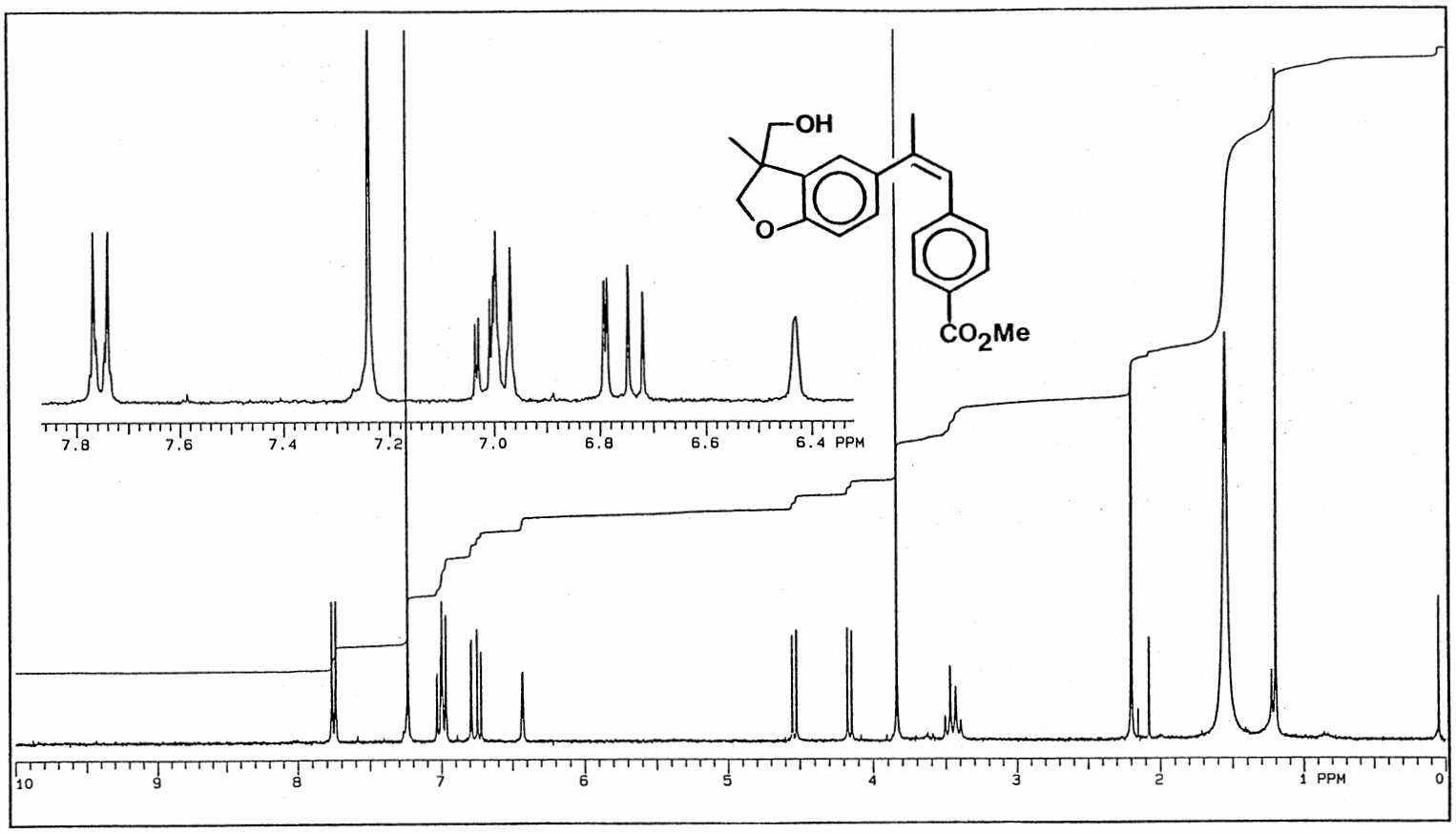
IR Spectrum of **64**-KBr

PLATE LXXXVIII



UV Spectrum of **64**

PLATE LXXXIX



OBSERVE: Nucleus 1.500 Freq 300 MHz; Spec. Width 4000.0 Hz Offset 0 Hz; Acq. Time 2.000 sec Delay 0 sec; Pulse Width 8.0 sec Transients 432

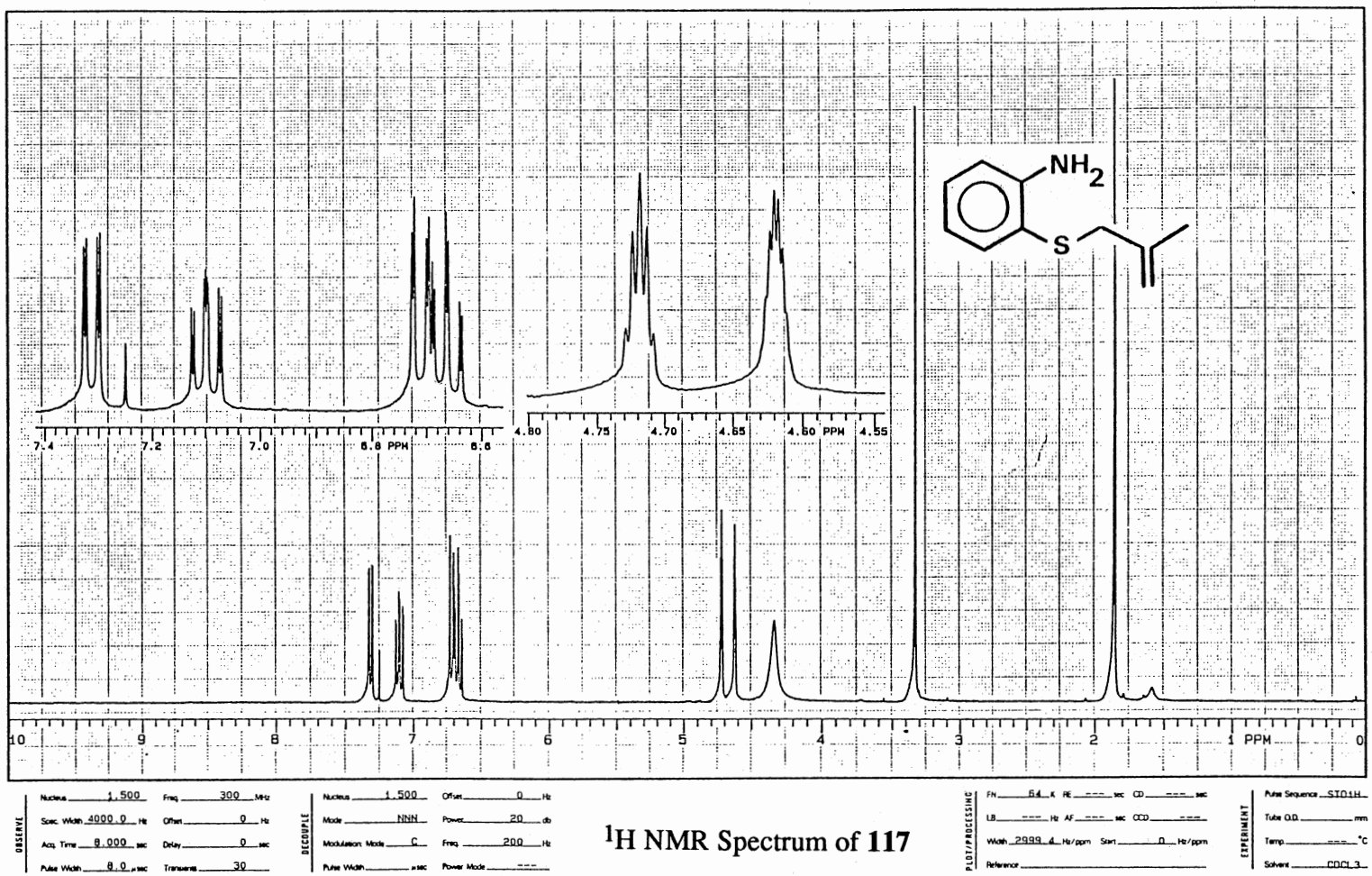
DECOUPLE: Nucleus 1.500 Offset 0 Hz; Mode NNN Power 20 db; Modulation Mode C Freq 200 Hz; Pulse Width ---- μsec Power Mode ---

PLOT/PROCESSING: FN 16 K RE ---- sec CD ---- sec; LB ---- Hz AF ---- sec CCD ---; Width 2999.4 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence STD1H; Tube OD ---- mm; Temp. ---- °C; Solvent CDCL3

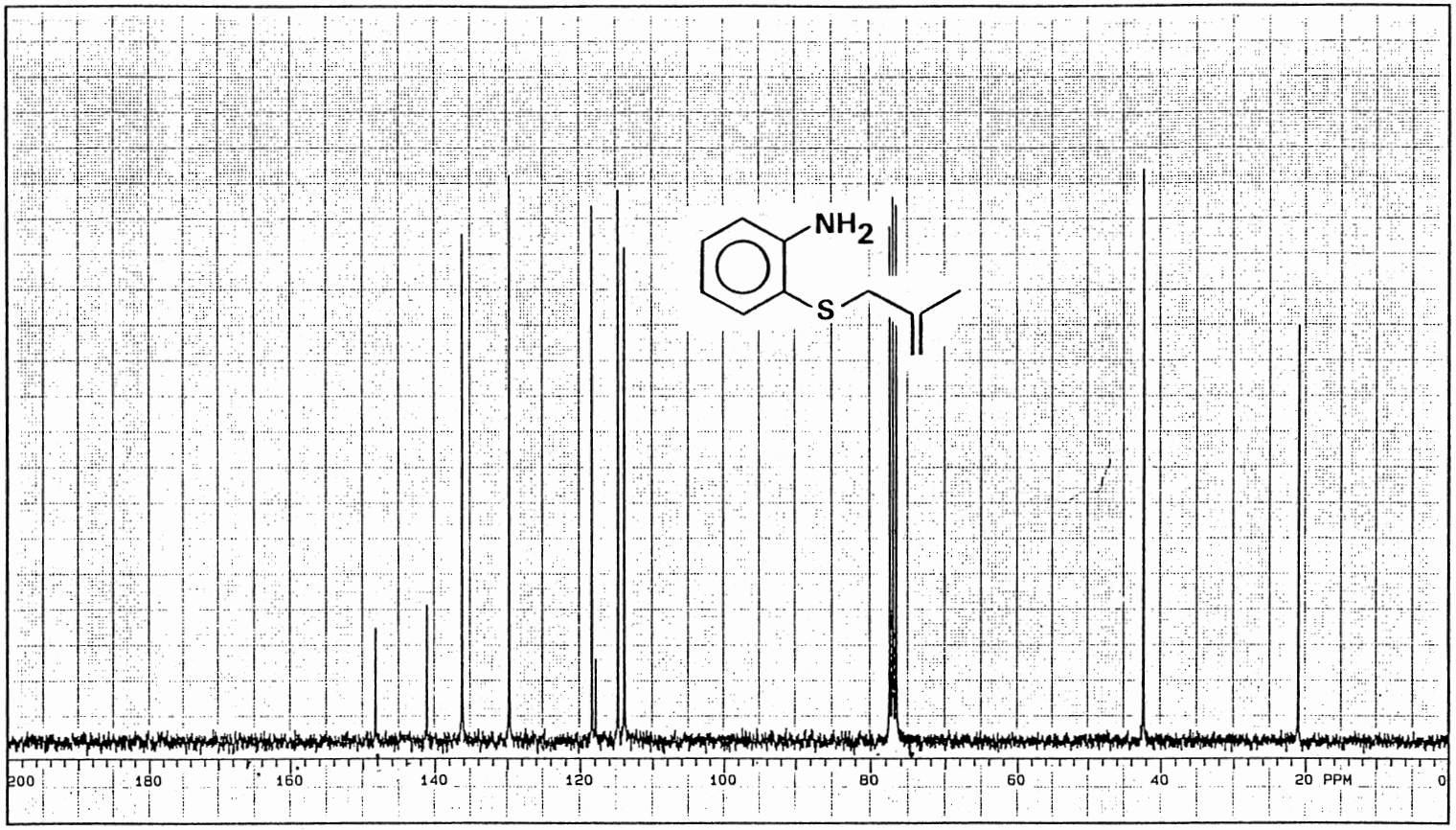
^{1}H NMR Spectrum of **64**-(*Z*)

PLATE LXXXX



^{1}H NMR Spectrum of **117**

PLATE LXXXXI



OBSERVE: Nucleus 13.500 Freq 75 MHz; Spec Width 20000.0 Hz Offset 1500 Hz; Acq Time 1.000 sec Delay 3.000 sec; Pulse Width 12.0 µsec Transients 1024

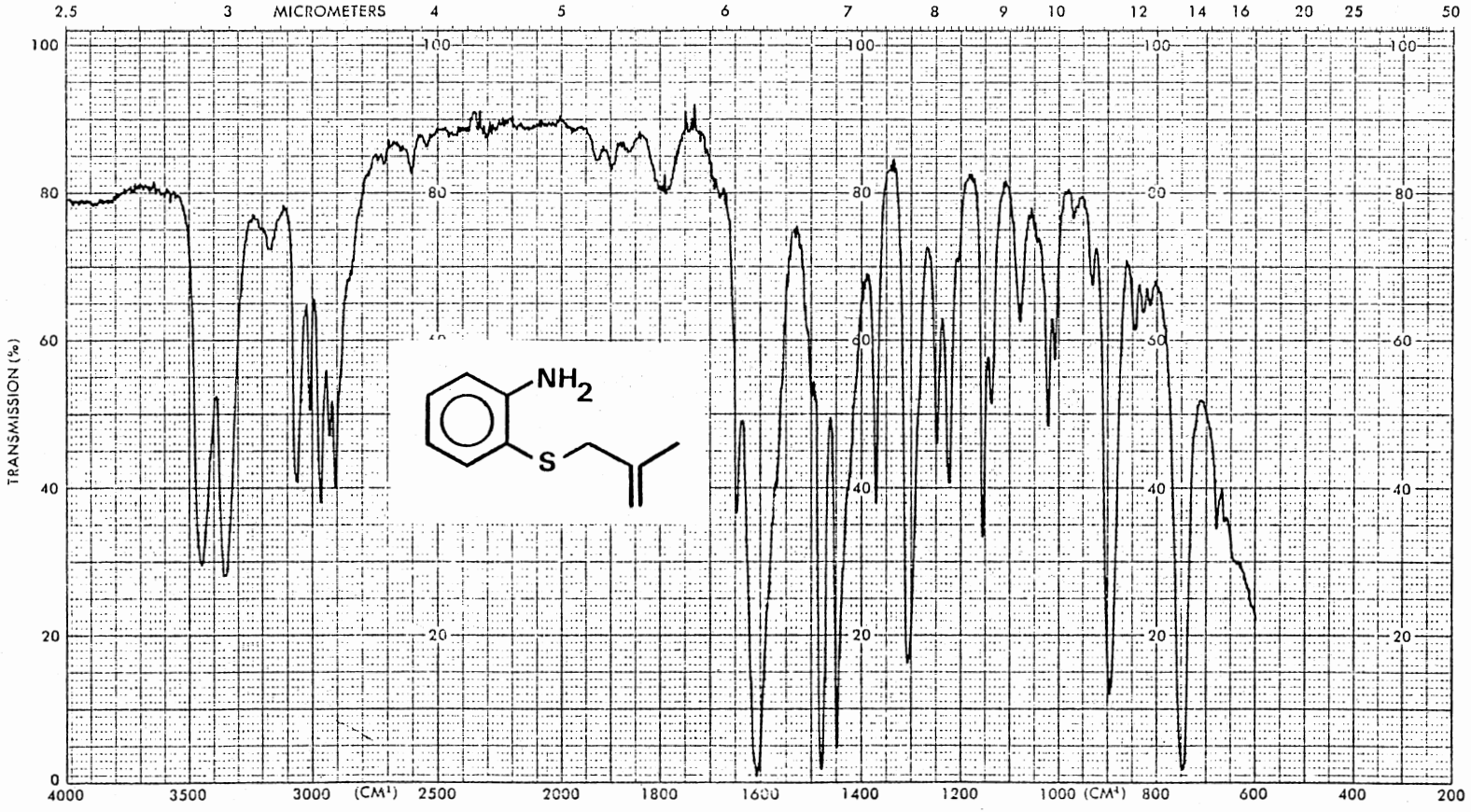
DECOUPLE: Nucleus 1 500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation Mode S Freq 7900 Hz; Pulse Width 17.5 µsec Power Mode ---

PLOT/PROCESSING: FN 64 K RE --- sec CD --- sec; LB 2.000 Hz AF --- sec CCD ---; Width 15085.9 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence STD13C; Tube O.D. --- mm; Temp. --- °C; Solvent CDCL3

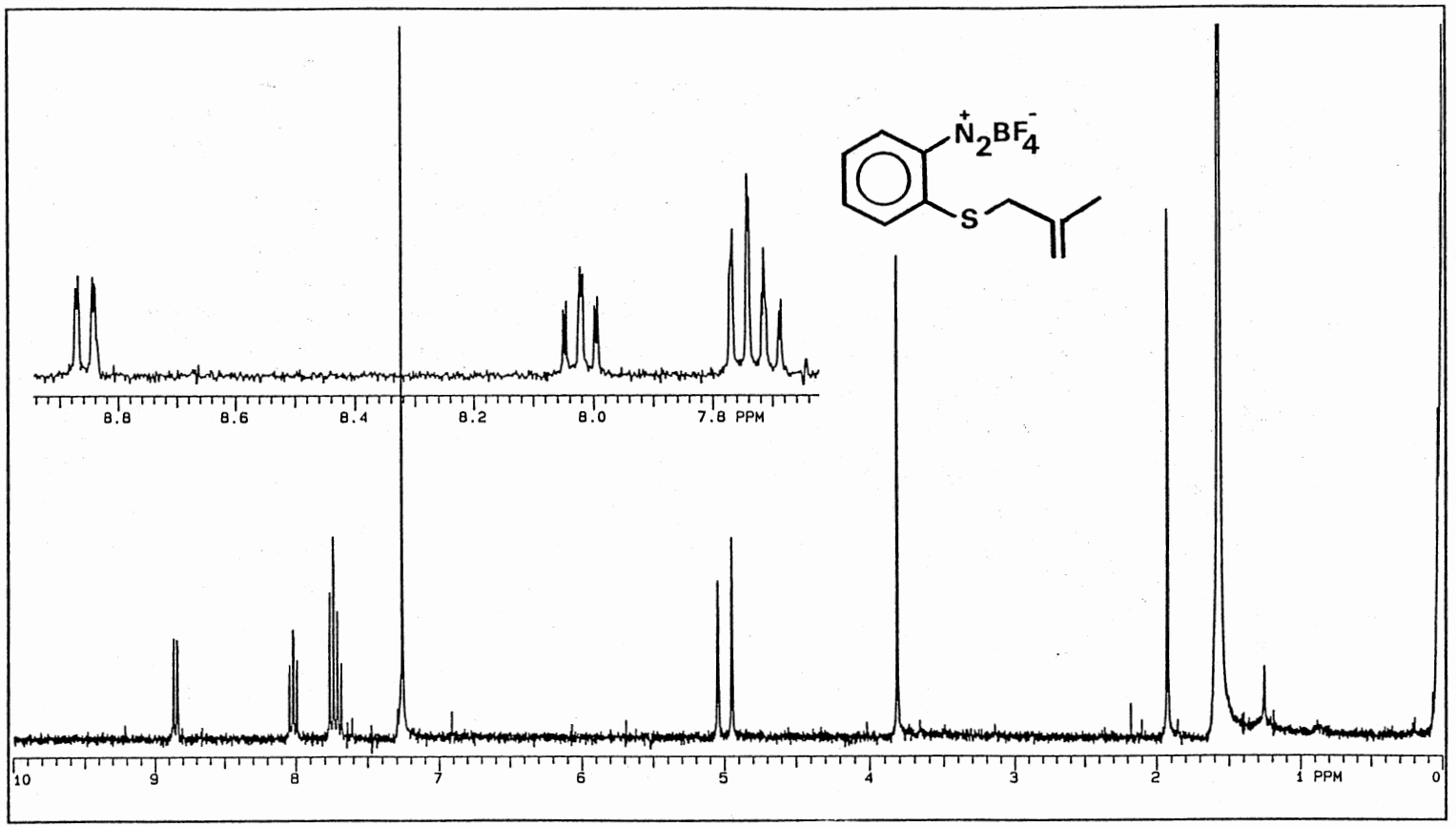
^{13}C NMR Spectrum of **117**

PLATE LXXXXII



IR Spectrum of **117**

PLATE LXXXXIII



OBSERVE: Nucleus 1.500 Freq. 300 MHz; Spec Width 4000.0 Hz Offset 0 Hz; Acq. Time 2.000 sec Delay 0 sec; Pulse Width 8.0 µsec Transients 320

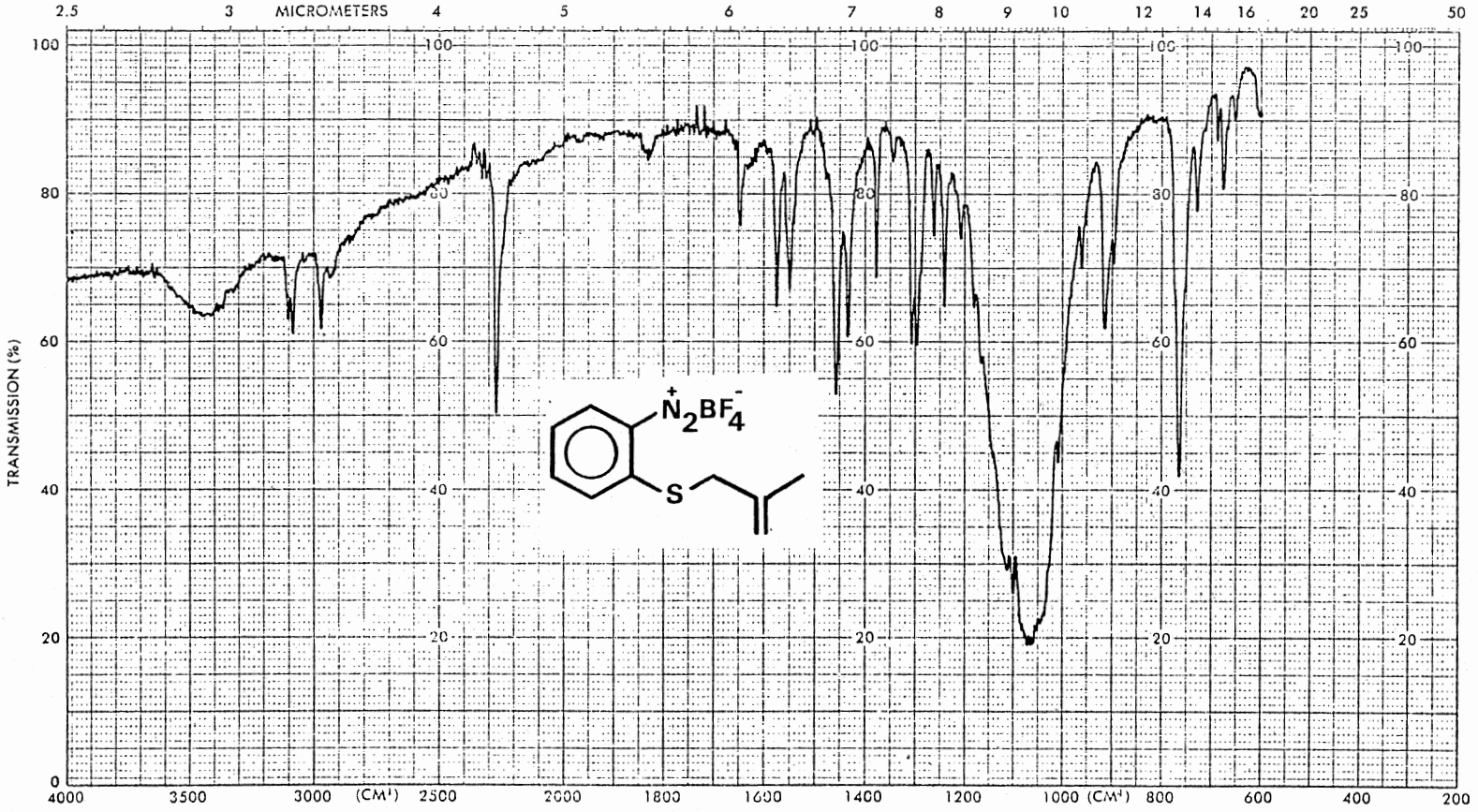
DECOUPLE: Nucleus 1.500 Offset 0 Hz; Mode NNN Power 20 db; Modulation Mode C Freq. 200 Hz; Pulse Width µsec Power Mode ---

^{1}H NMR Spectrum of **118**

PLOT/PROCESSING: Fn 16 K RE sec CD sec; LB Hz AF sec CCD ---; Width 2999.4 Hz/ppm Start 0 Hz/ppm; Reference

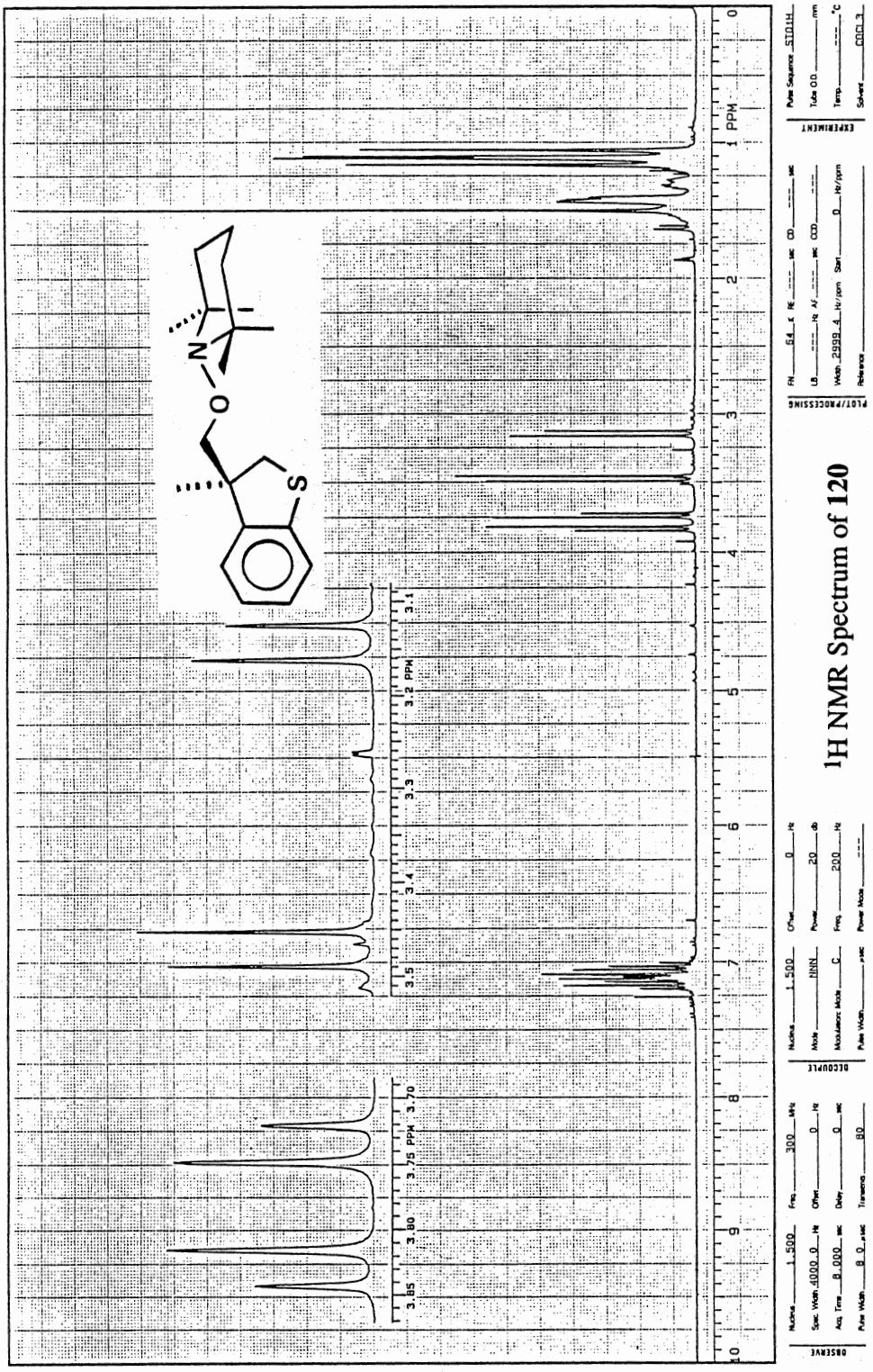
EXPERIMENT: Pulse Sequence STD1H; Tube O.D. mm; Temp. °C; Solvent COCL3

PLATE LXXXXIV



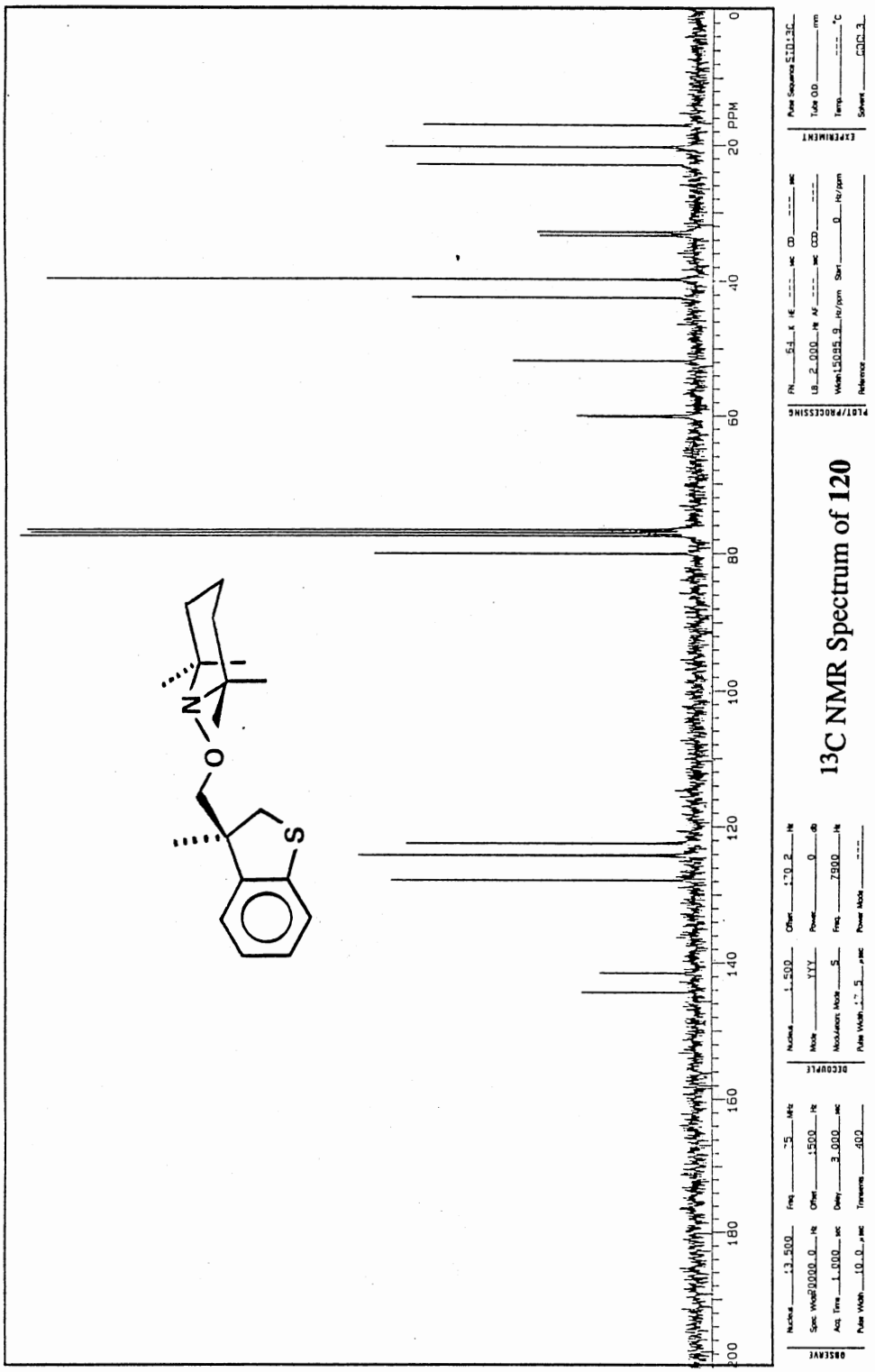
^{13}C NMR Spectrum of **118** -KBr

PLATE LXXXXV



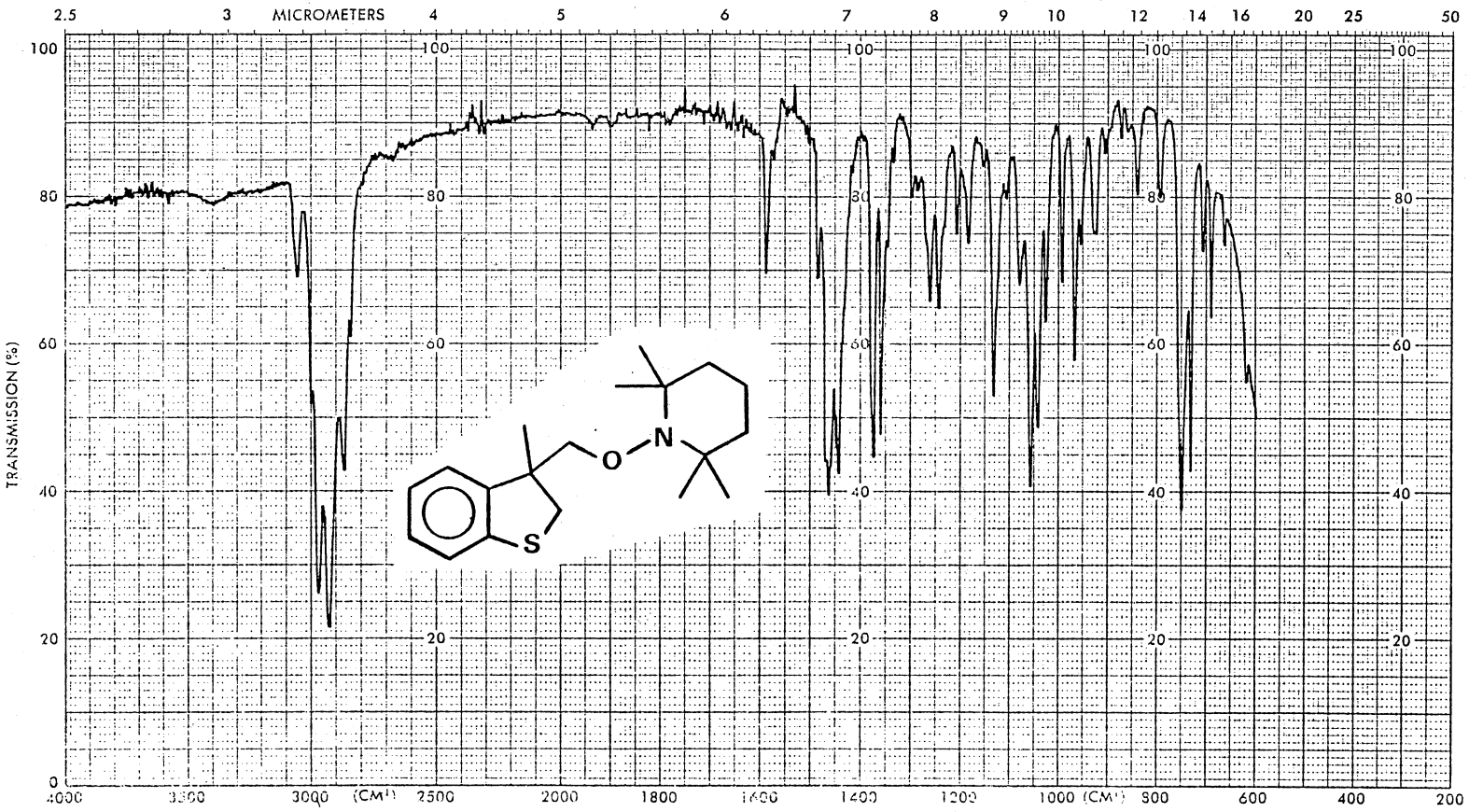
^{1}H NMR Spectrum of **120**

PLATE LXXXXVI



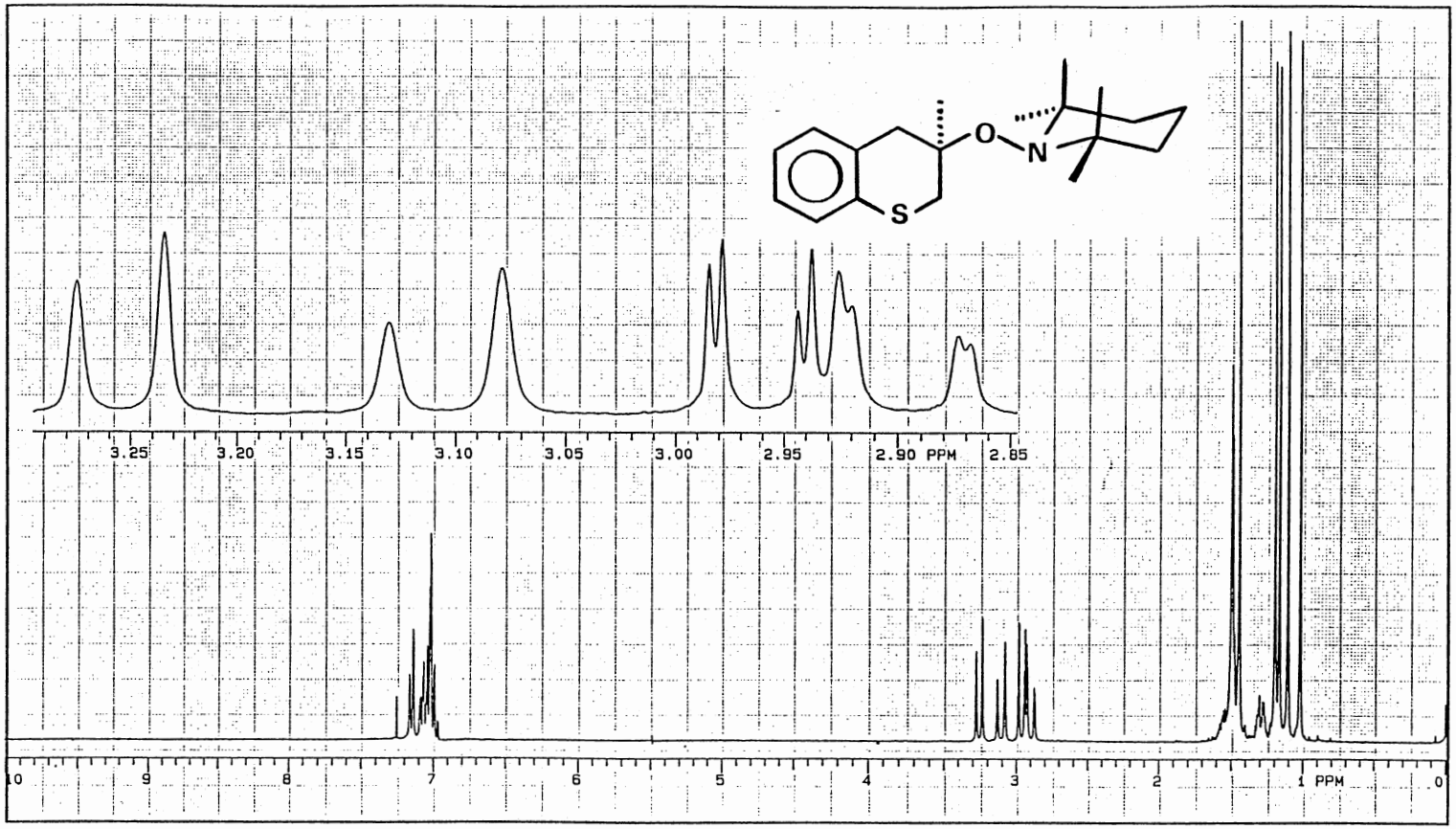
^{13}C NMR Spectrum of **120**

PLATE LXXXXVII



IR Spectrum of **120**

PLATE LXXXXVIII



OBSERVE Nucleus 1.500 Freq 300 MHz; Spec Width 4000.0 Hz Offset 0 Hz; Acq Time 8.000 sec Delay 0 sec; Pulse Width 8.0 µsec Transients 128

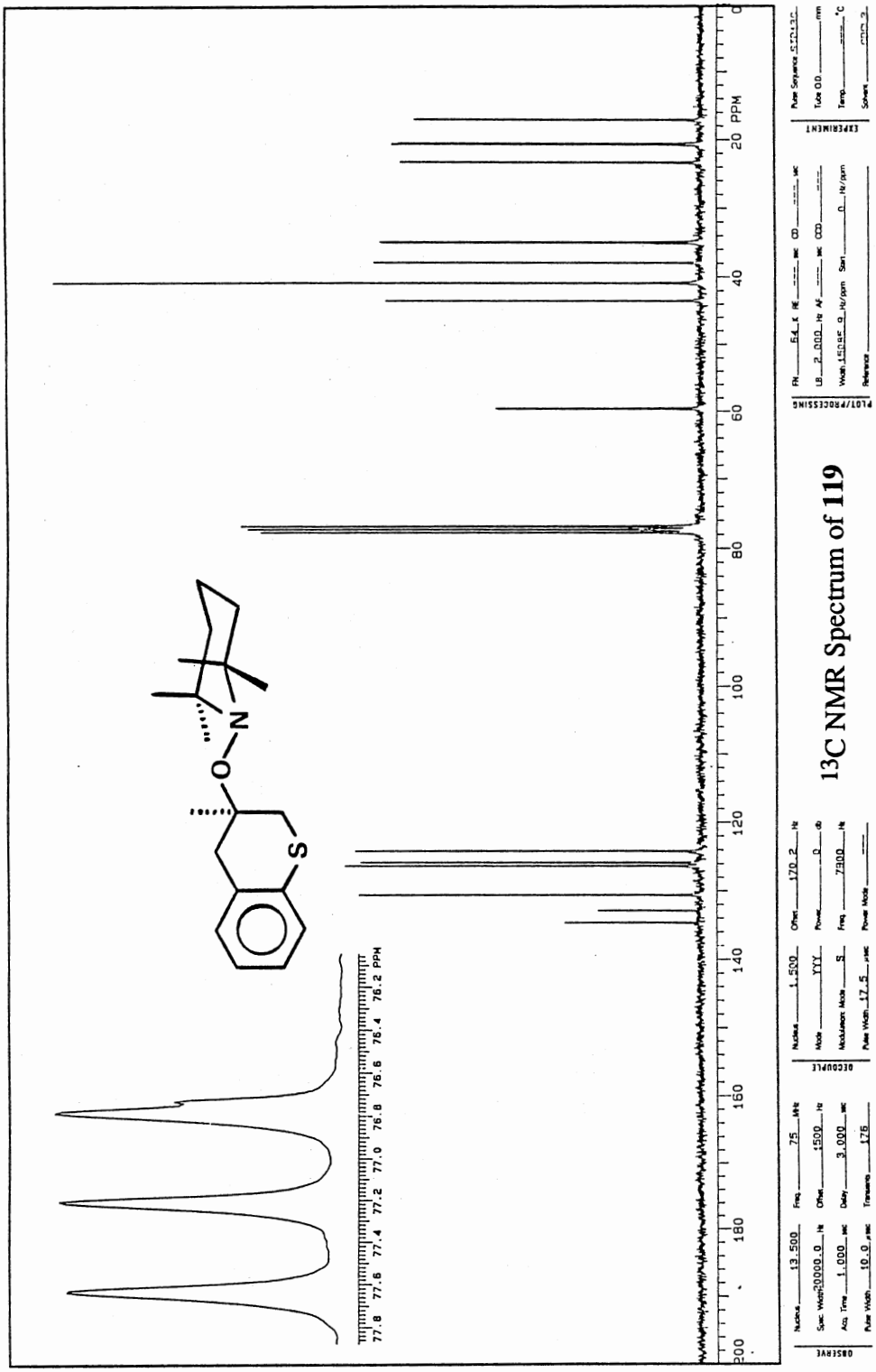
DECOUPLE Nucleus 1.500 Offset 0 Hz; Mode NNN Power 20 db; Modulation Mode C Freq 200 Hz; Pulse Width µsec Power Mode ---

PLOT/PROCESSING FN 64 K RE --- sec CD --- sec; LB --- Hz AF --- sec CCD ---; Width 2999.4 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT Pulse Sequence STD1H; Tube O.D. mm; Temp --- °C; Solvent CDCL3

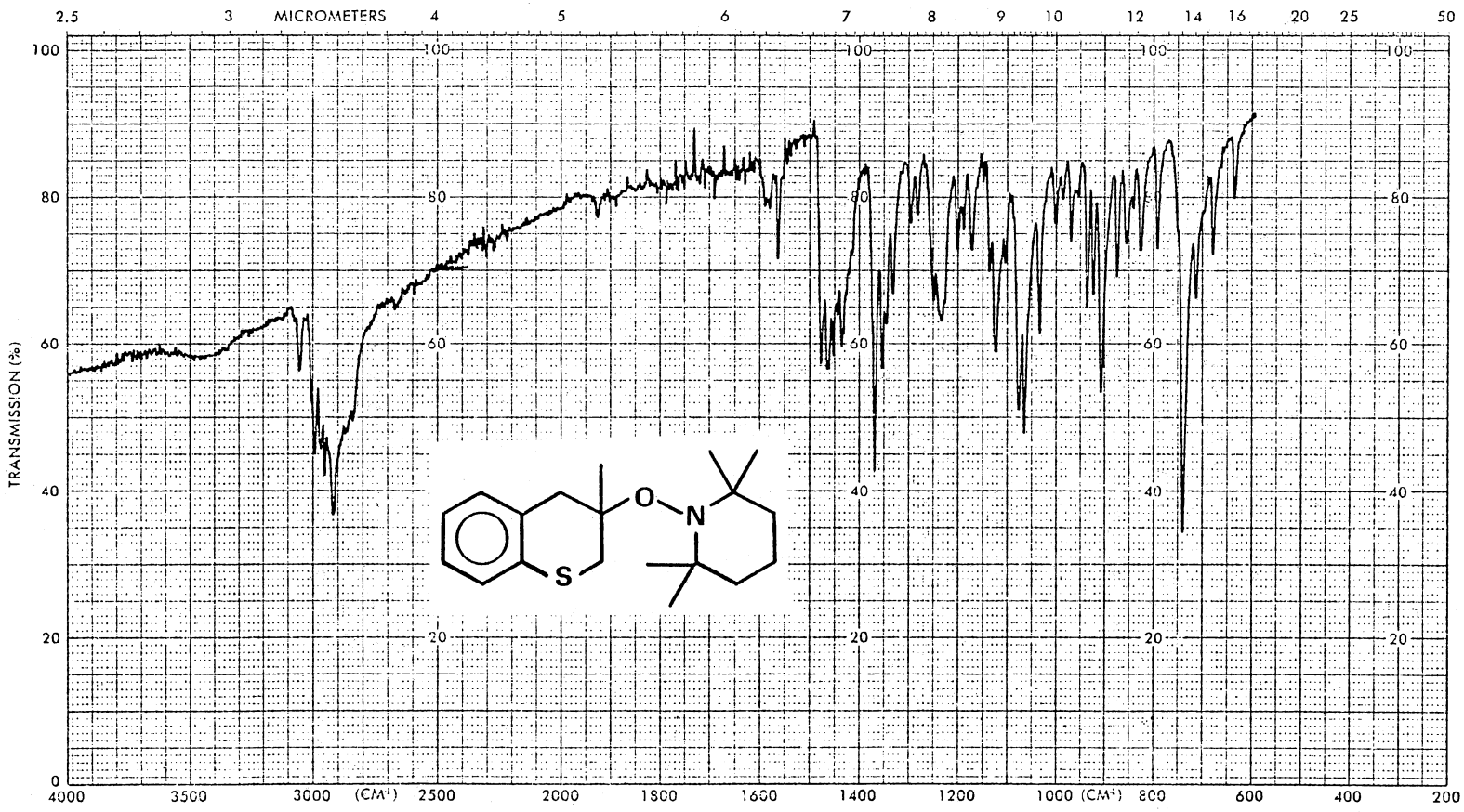
^{1}H NMR Spectrum of **119**

PLATE IC



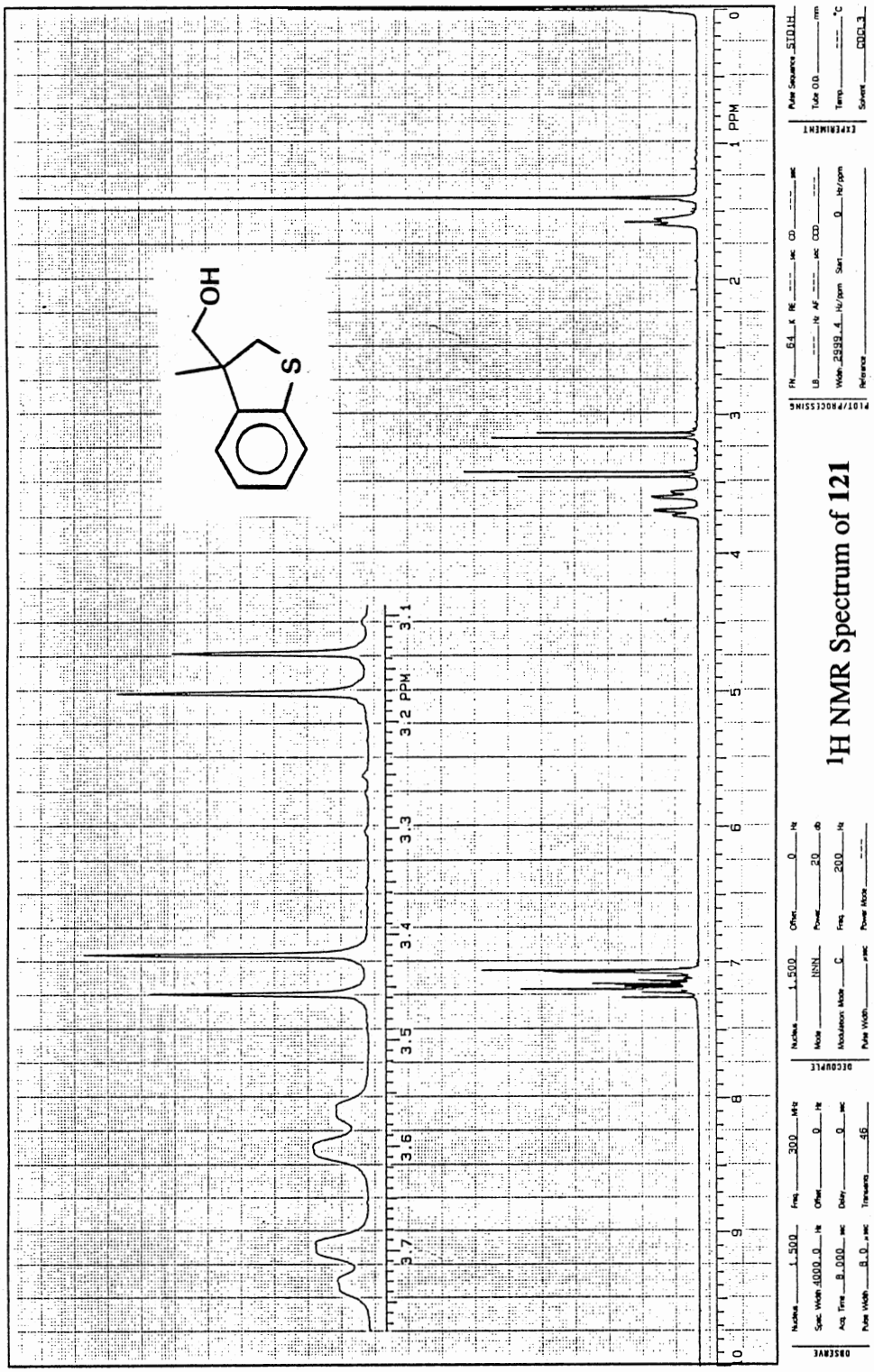
^{13}C NMR Spectrum of **119**

PLATE C



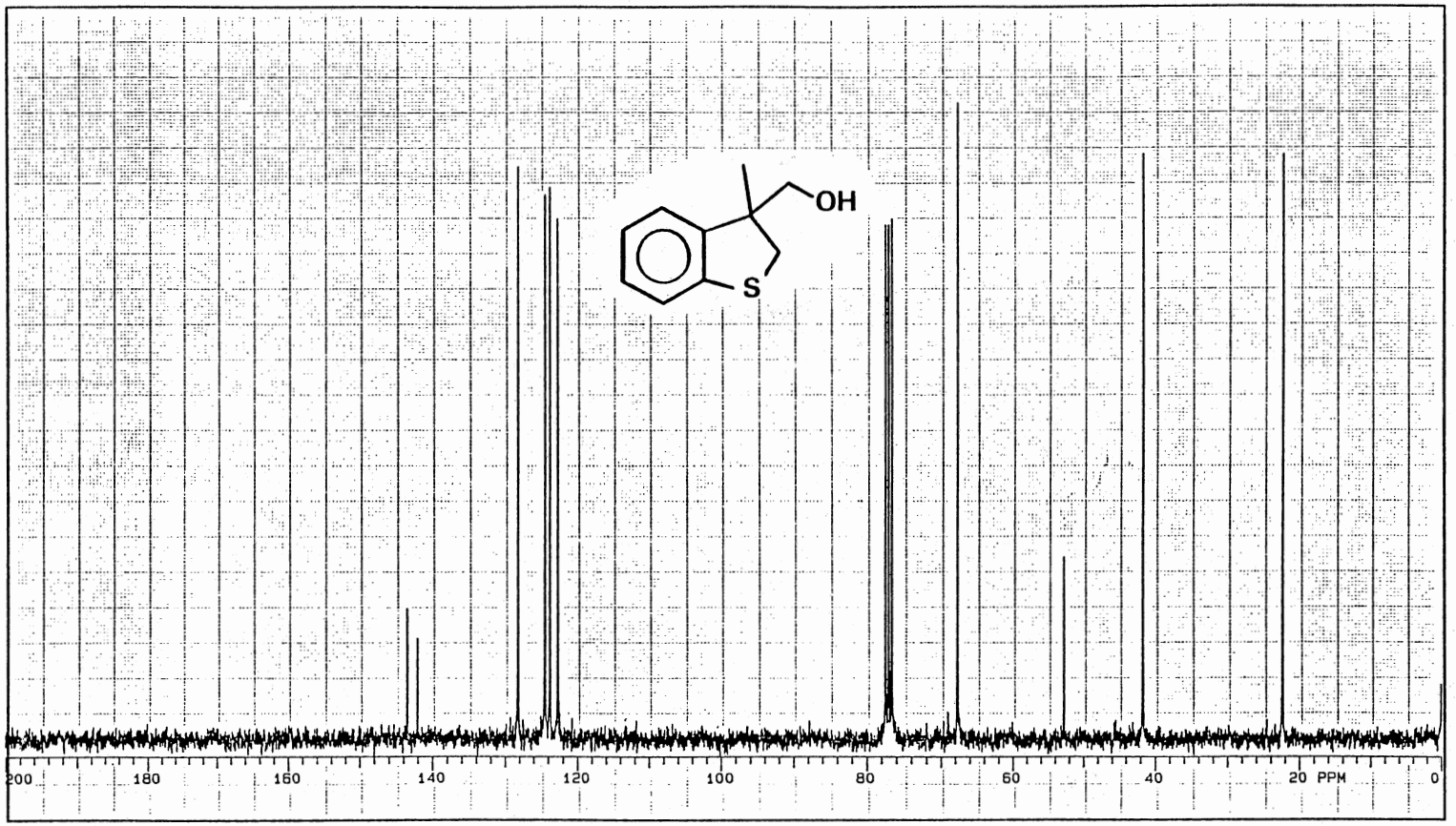
IR Spectrum of **119** -KBr

PLATE CI



^{1}H NMR Spectrum of **121**

PLATE CII



OBSERVE Nucleus 13.500 Frq 75 MHz
Spec Wid 20000.0 Hz Offset 1500 Hz
Acq Time 1.000 sec Delay 3.000 sec
Pulse Width 12.0 µsec Transients 512

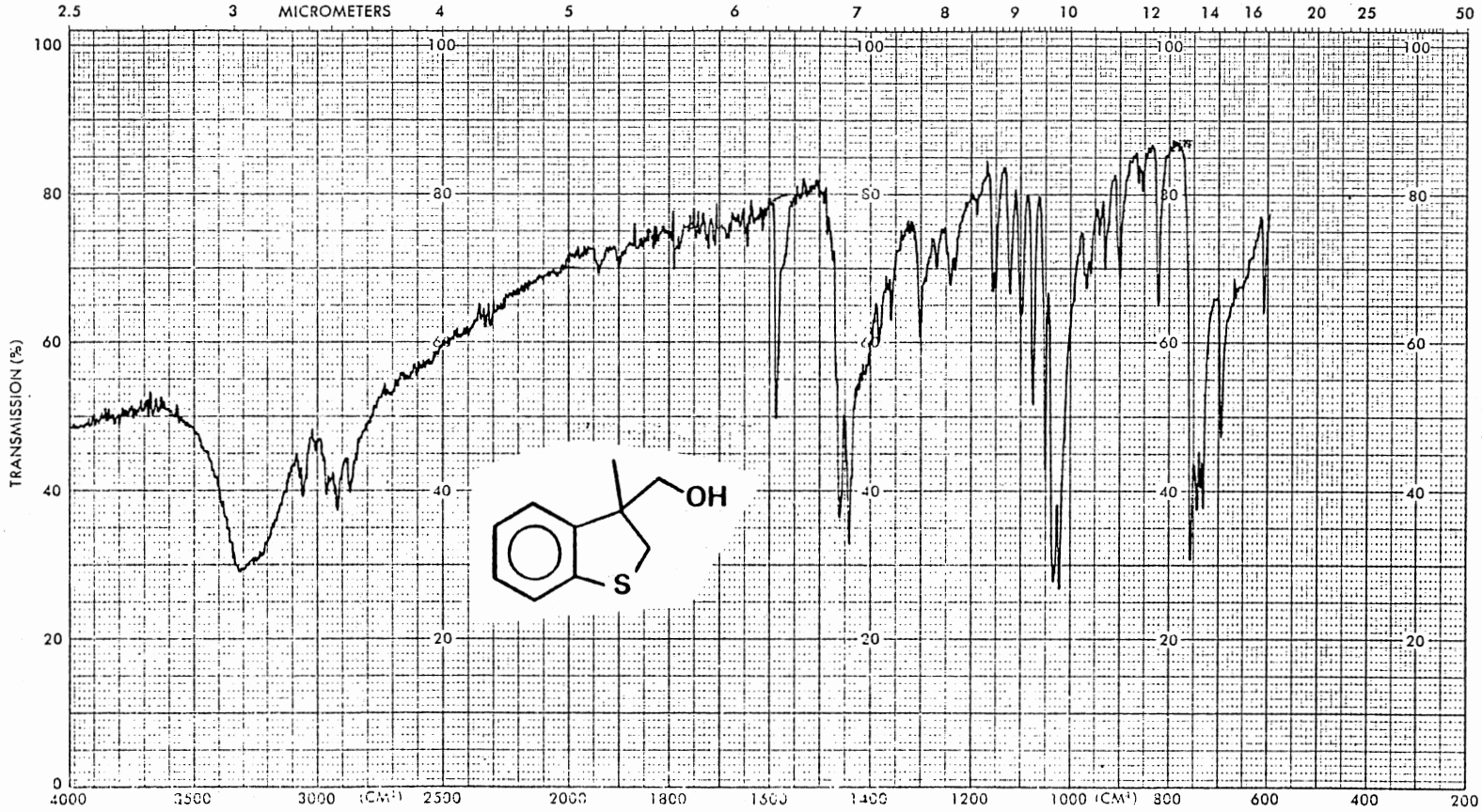
DECOUPLE Nucleus 1.500 Offset 170.2 Hz
Mode YYY Power 0 db
Modulation Mode S Freq 7900 Hz
Pulse Width 17.5 µsec Power Mode ---

PLOT/PROCESSING FN 64 K RE --- sec CD --- sec
LB 2.000 Hz AF --- sec CCD ---
Wids 15085.9 Hz/ppm Start 0 Hz/ppm
Reference

EXPERIMENT Pulse Sequence STD13C
Tune OD nm
Temp --- °C
Solvent CDCl3

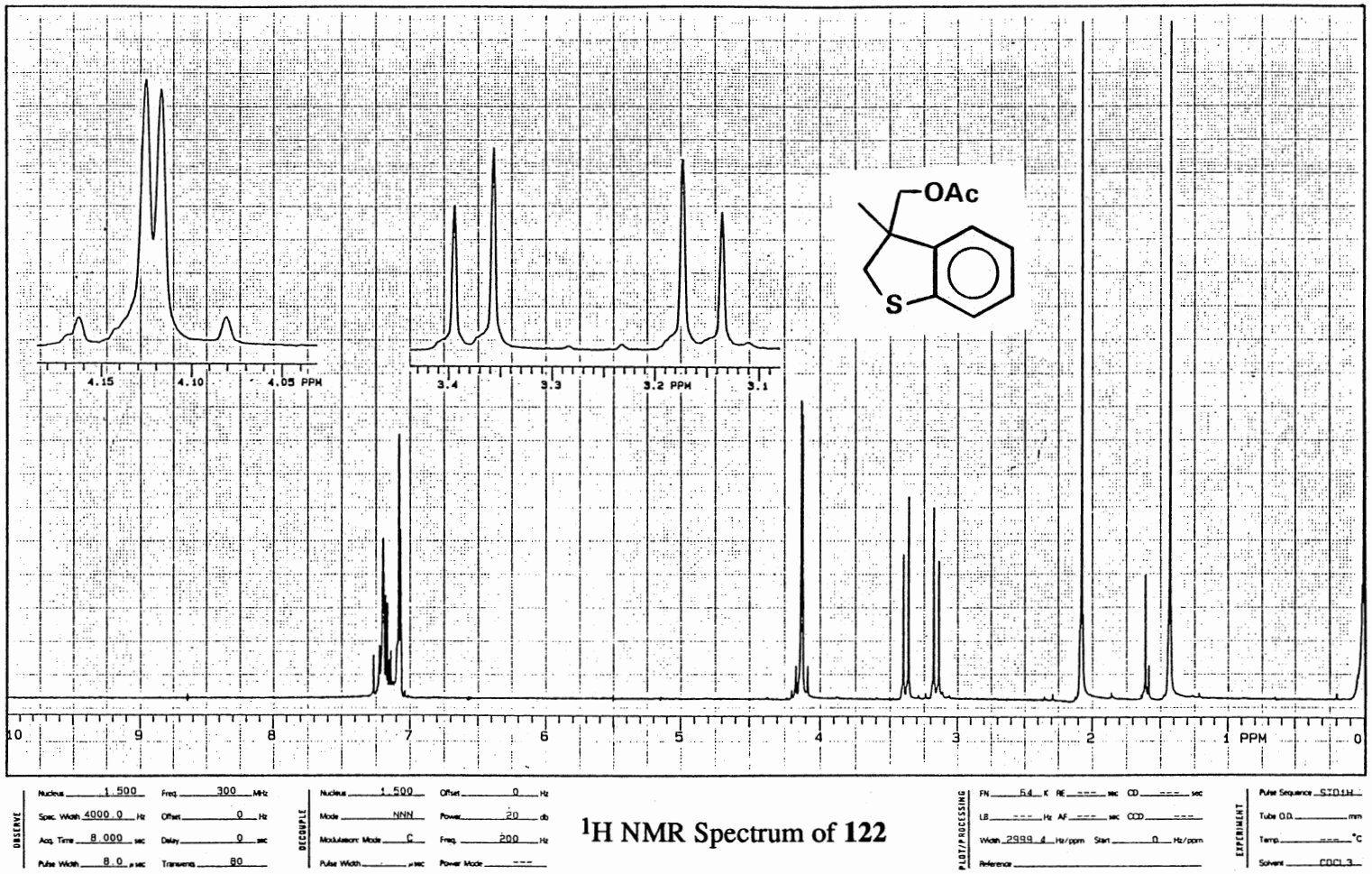
^{13}C NMR Spectrum of **121**

PLATE CIII



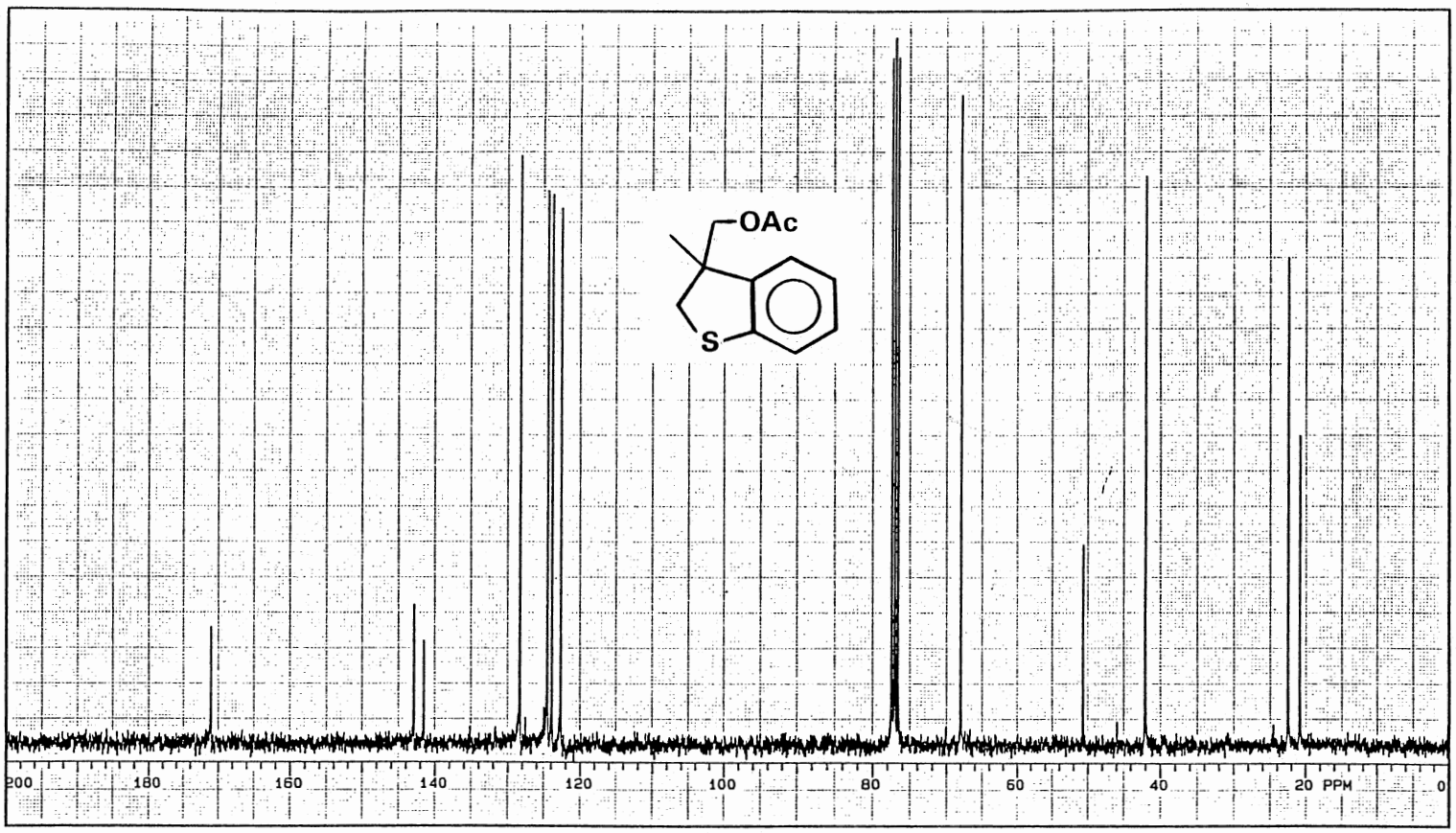
IR Spectrum of **121** -KBr

PLATE CIV



^{1}H NMR Spectrum of **122**

PLATE CV



OBSERVE: Nucleus 13.500 Freq 75 MHz; Spec. Width 20000.0 Hz Offset 1500 Hz; Acq. Time 1.000 sec Delay 3.000 sec; Pulse Width 12.0 μsec Transients 1024

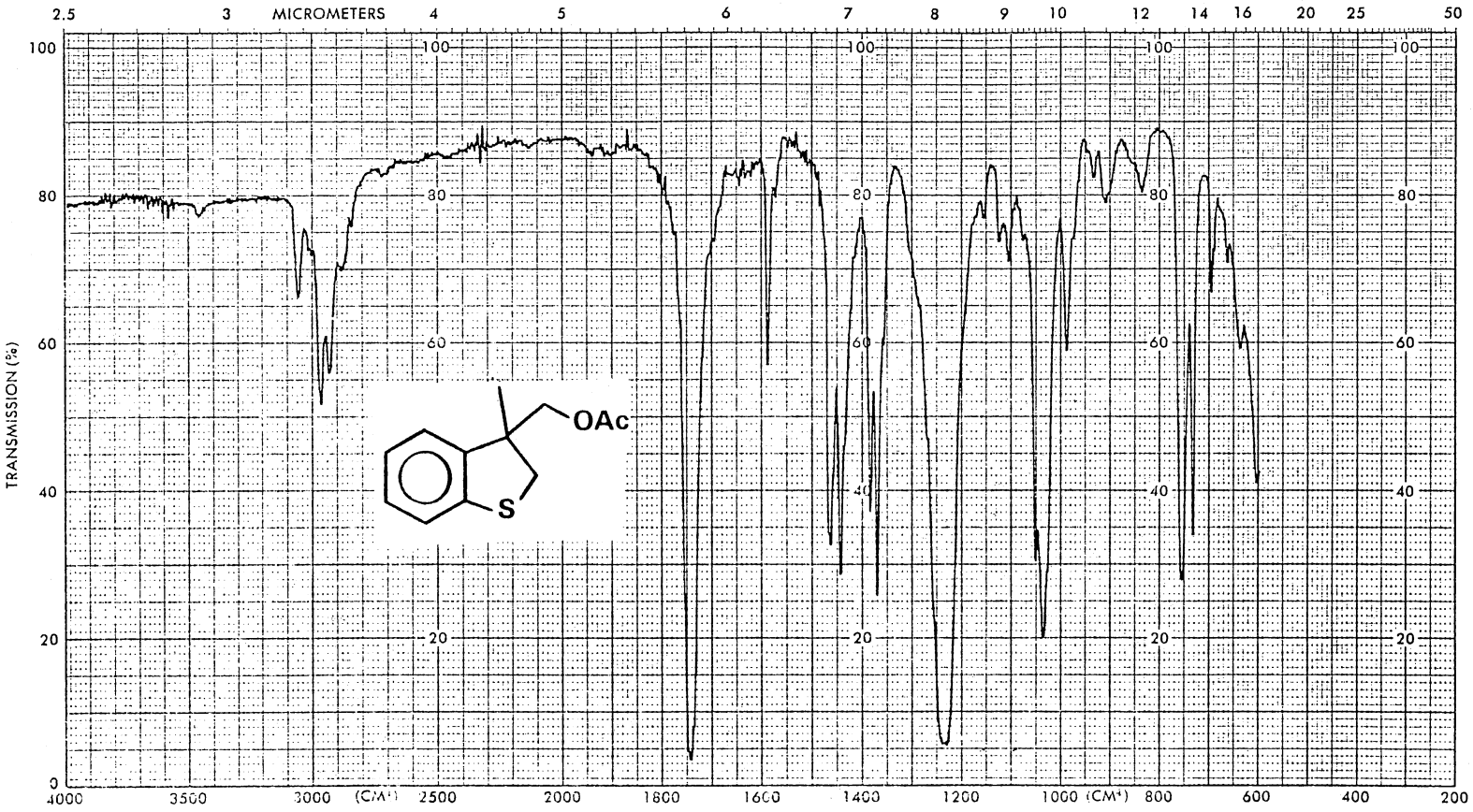
DECOUPLE: Nucleus 1.500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation Mode S Freq. 7900 Hz; Pulse Width 17.5 μsec Power Mode ---

PLOT/PROCESSING: FN 64 K RE --- sec CD --- sec; LB 2.000 Hz AF --- sec CCD ---; Width 15085.9 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence STD13C; Tube O.D. mm; Temp. --- °C; Solvent CDCl 3

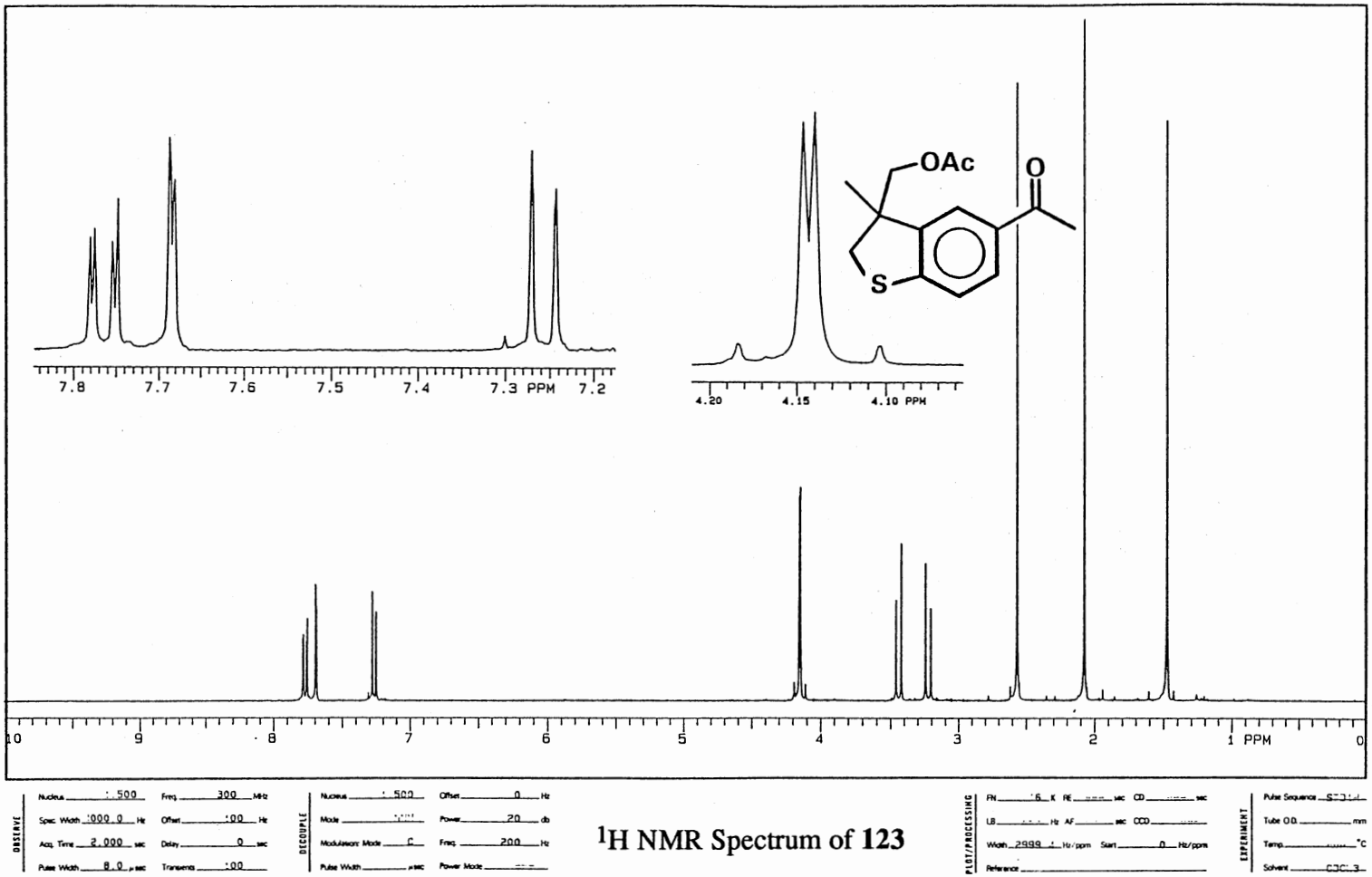
^{13}C NMR Spectrum of **122**

PLATE CVI



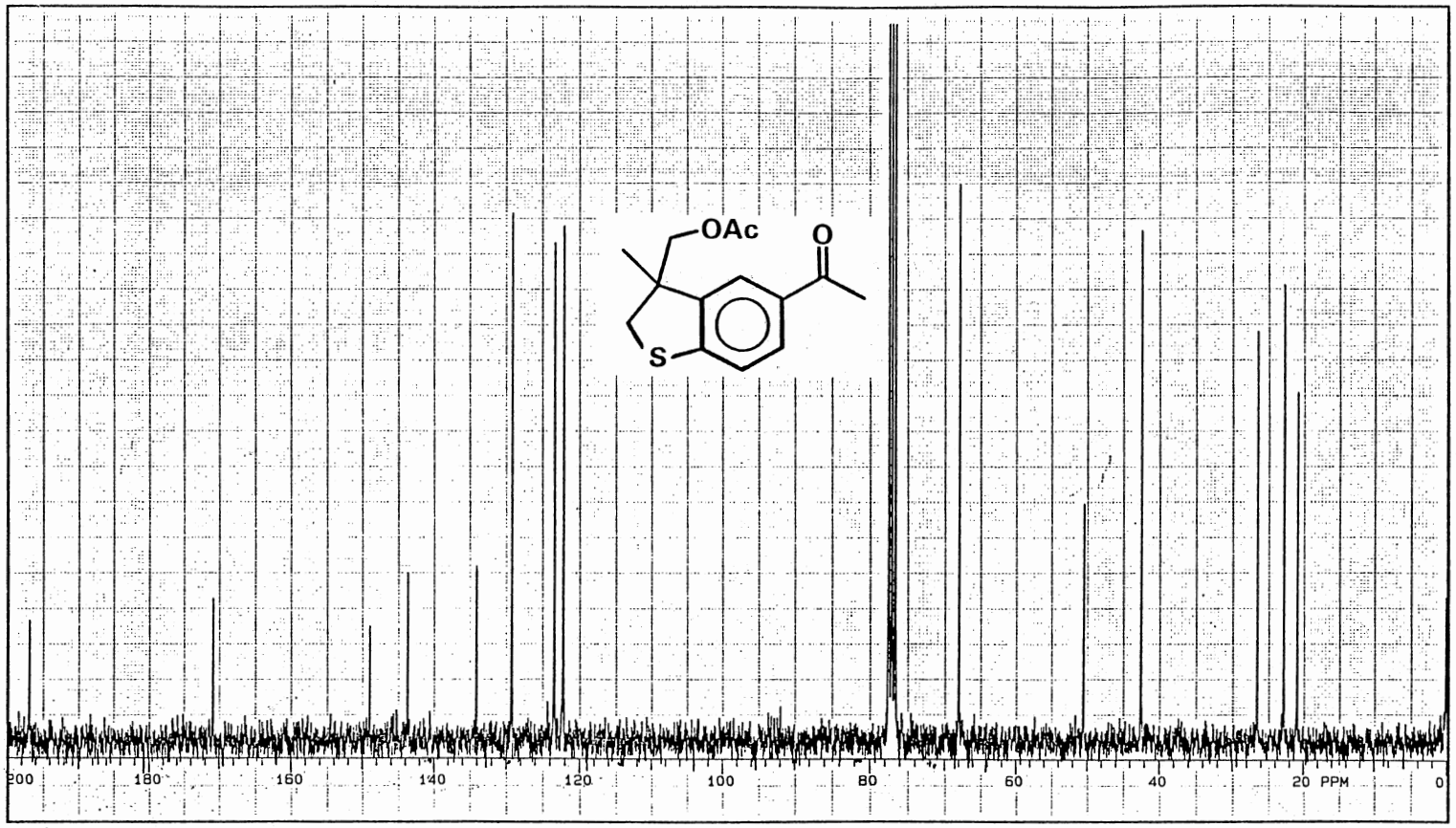
IR Spectrum of **122**

PLATE CVII



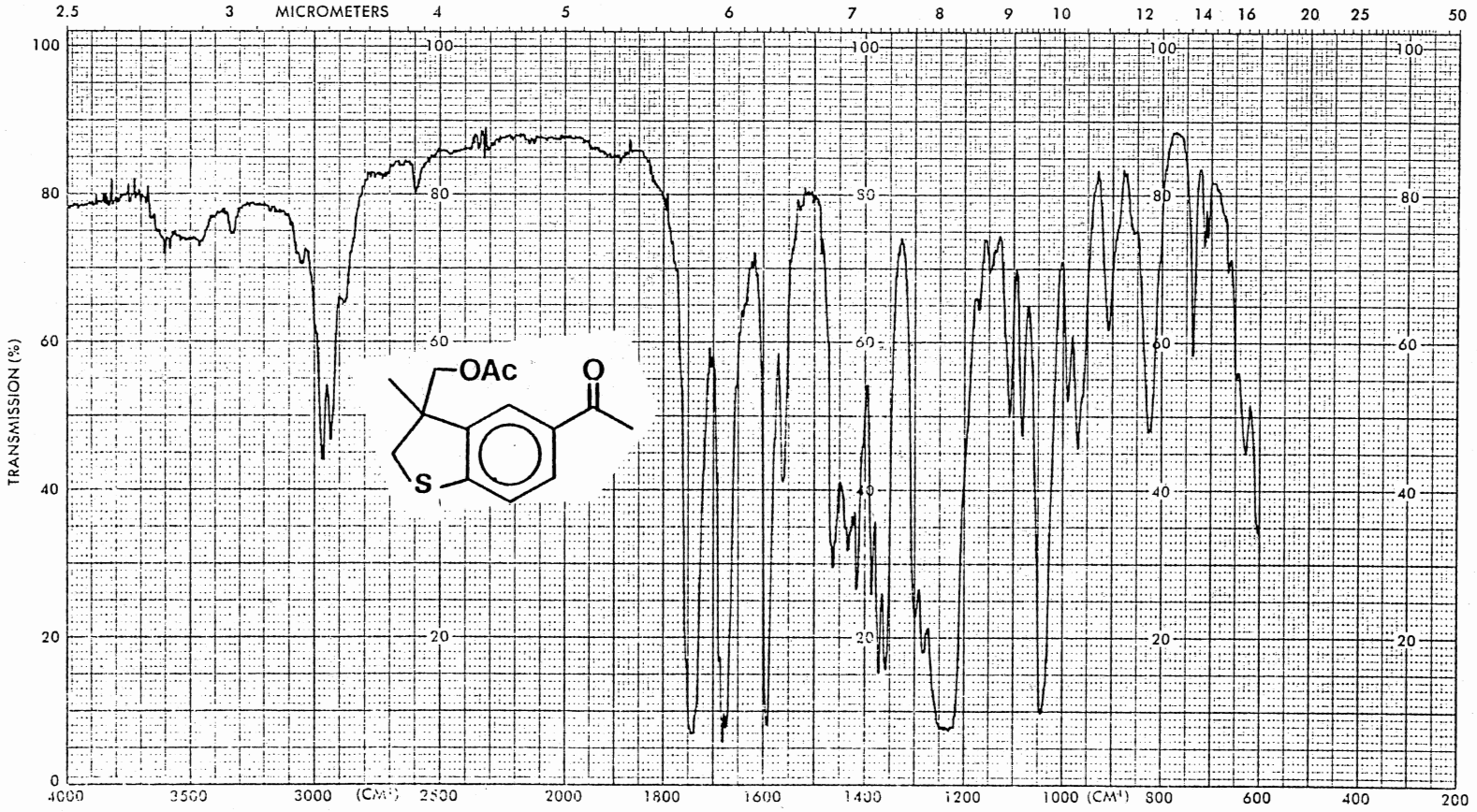
^{1}H NMR Spectrum of **123**

PLATE CVIII



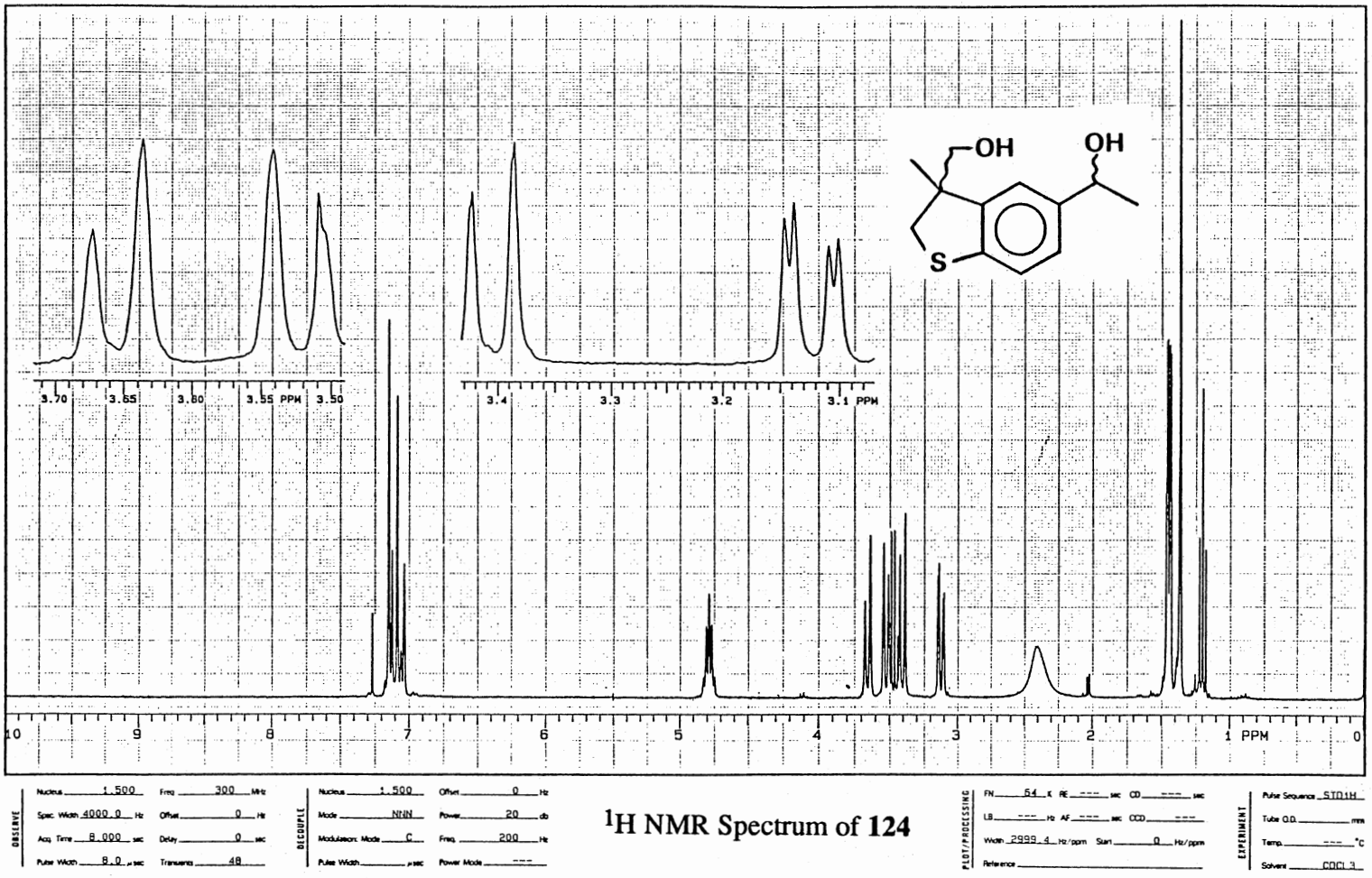
^{13}C NMR Spectrum of **123**

PLATE CIX



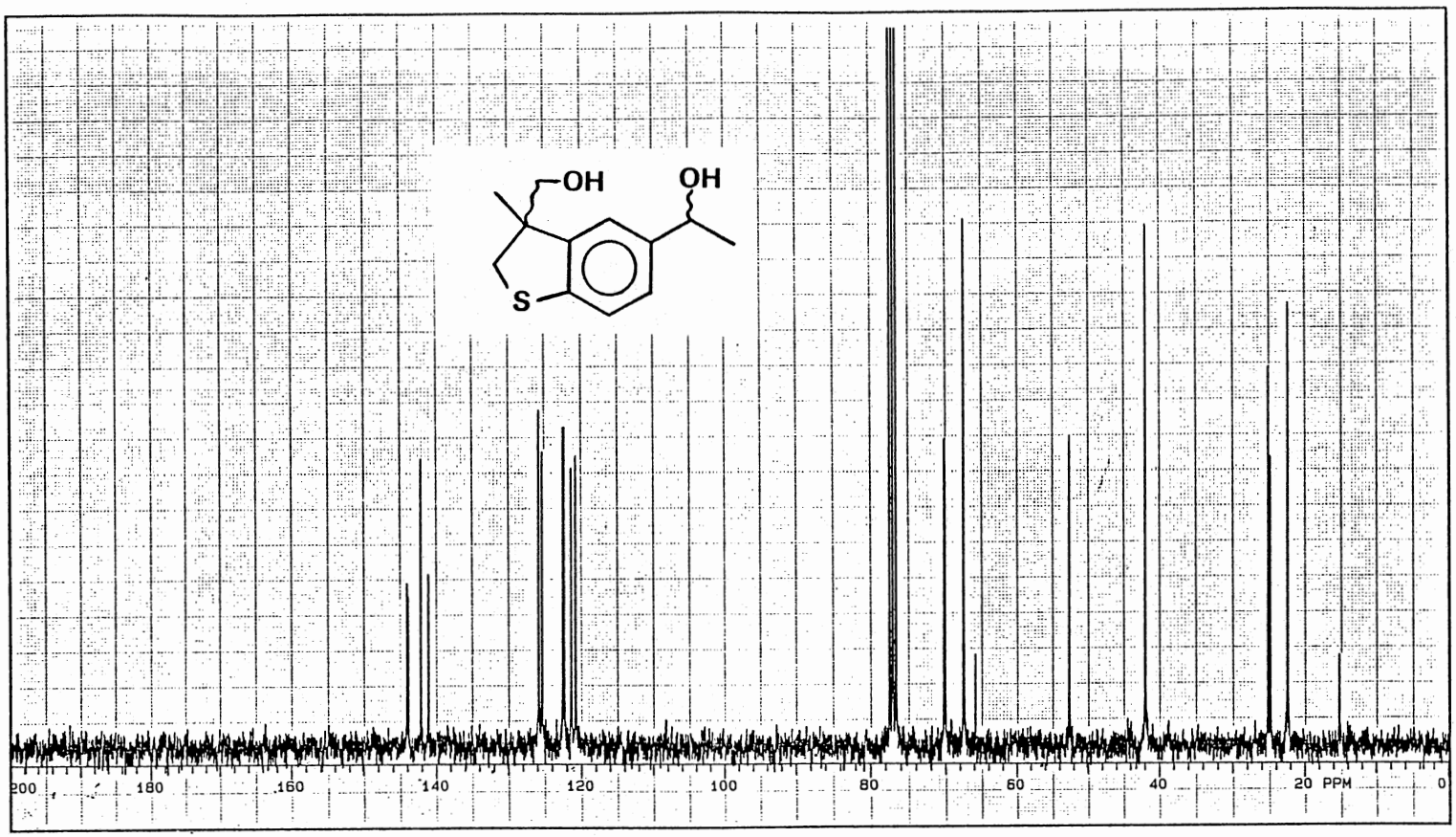
IR Spectrum of **123**

PLATE CX



^{1}H NMR Spectrum of **124**

PLATE CXI



OBSERVE: Nucleus 13.500 Freq 75 MHz; Spec. Width 20000.0 Hz Offset 1500 Hz; Acq Time 1.000 sec Delay 3.000 sec; Pulse Width 12.0 µsec Transients 384

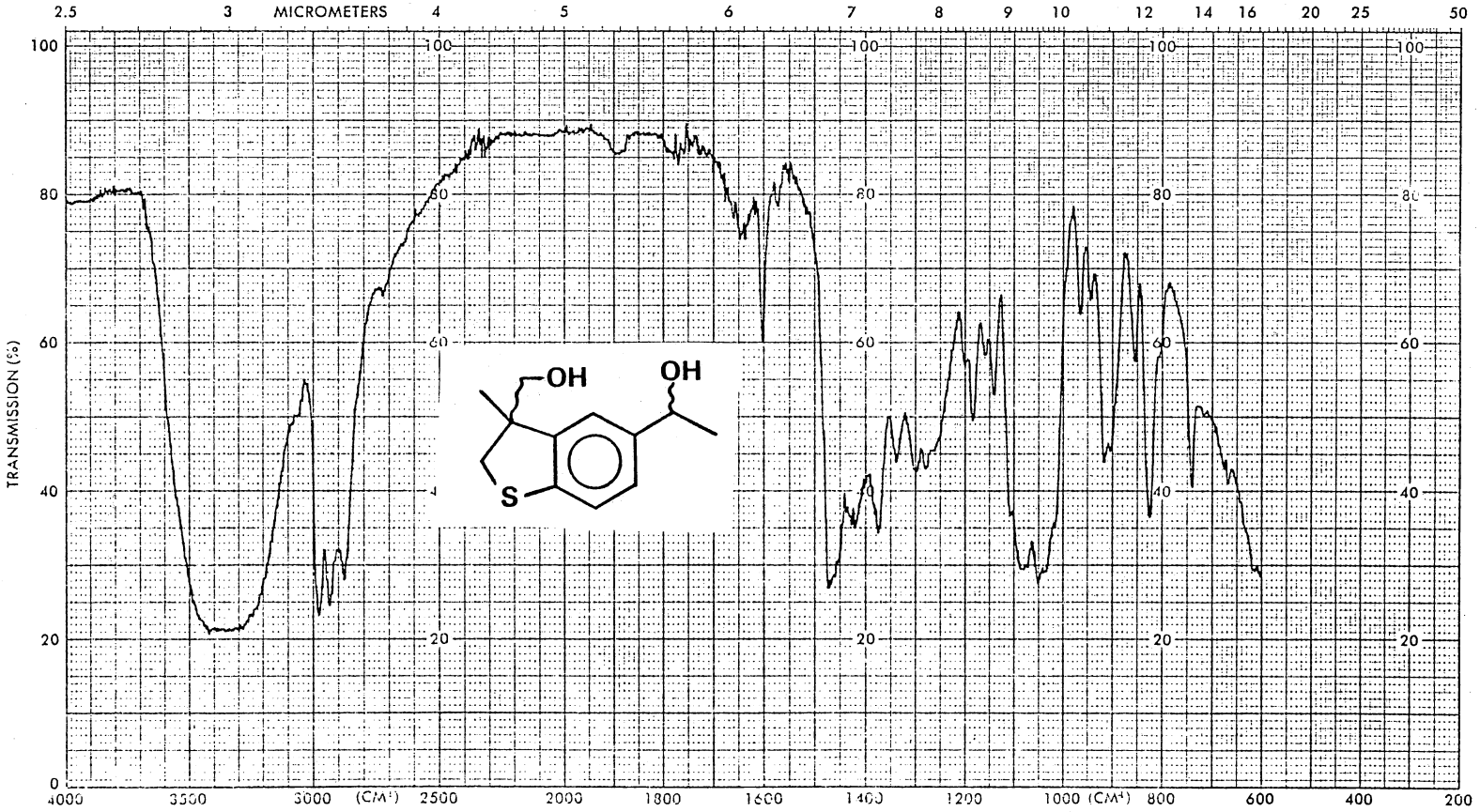
DECOUPLE: Nucleus 1.500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation Mode S Freq 7900 Hz; Pulse Width 17.5 µsec Power Mode ---

^{13}C NMR Spectrum of **124**

PLOT/PROCESSING: FN 64 K RE --- sec CD --- sec; LB 2.000 Hz AF --- sec CCD ---; Width 15085.9 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence STD13C; Tube O.D ___ mm; Temp. --- °C; Solvent CDCl3

PLATE CXII



IR Spectrum of **124**

PLATE CXIII

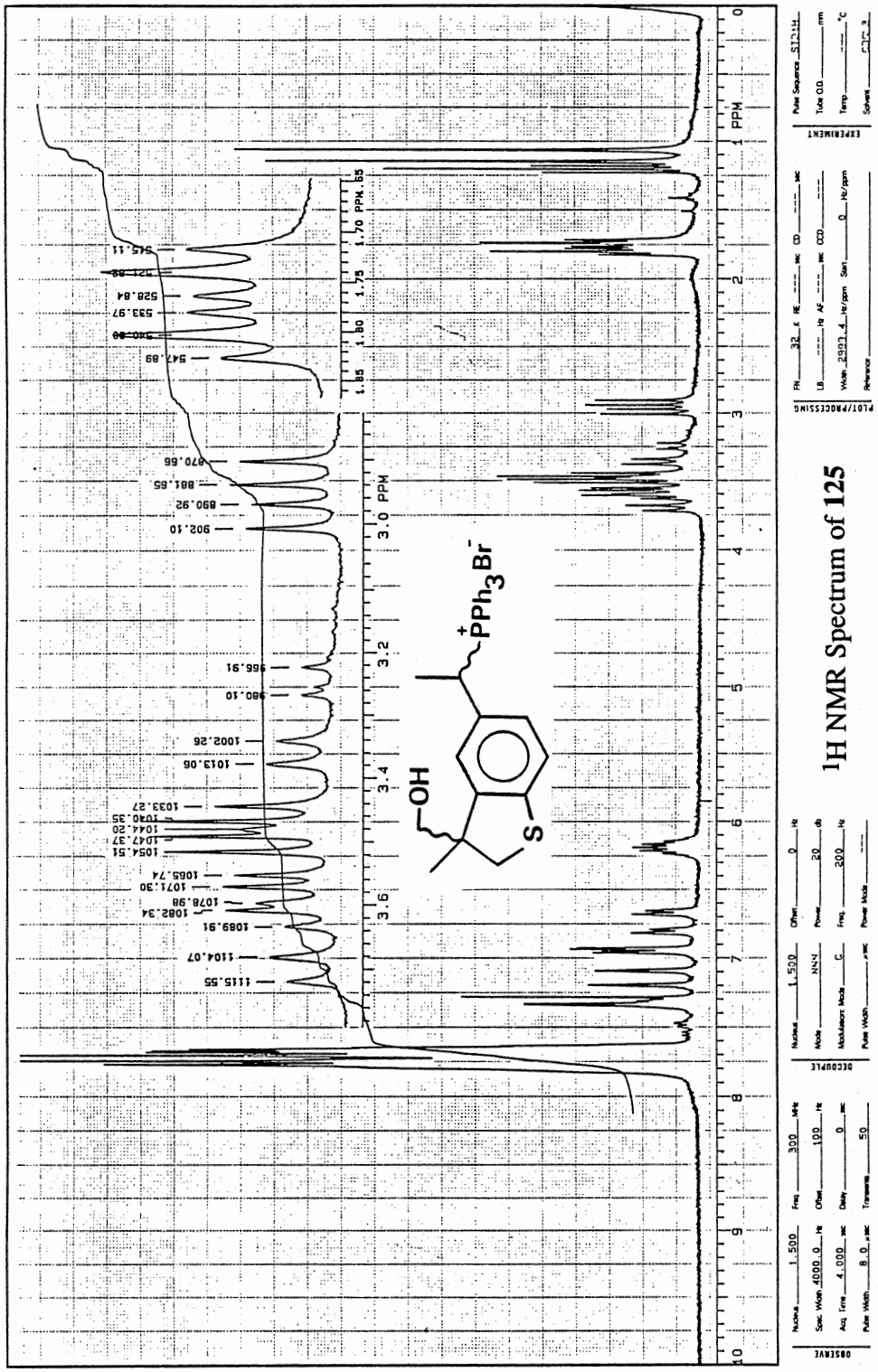
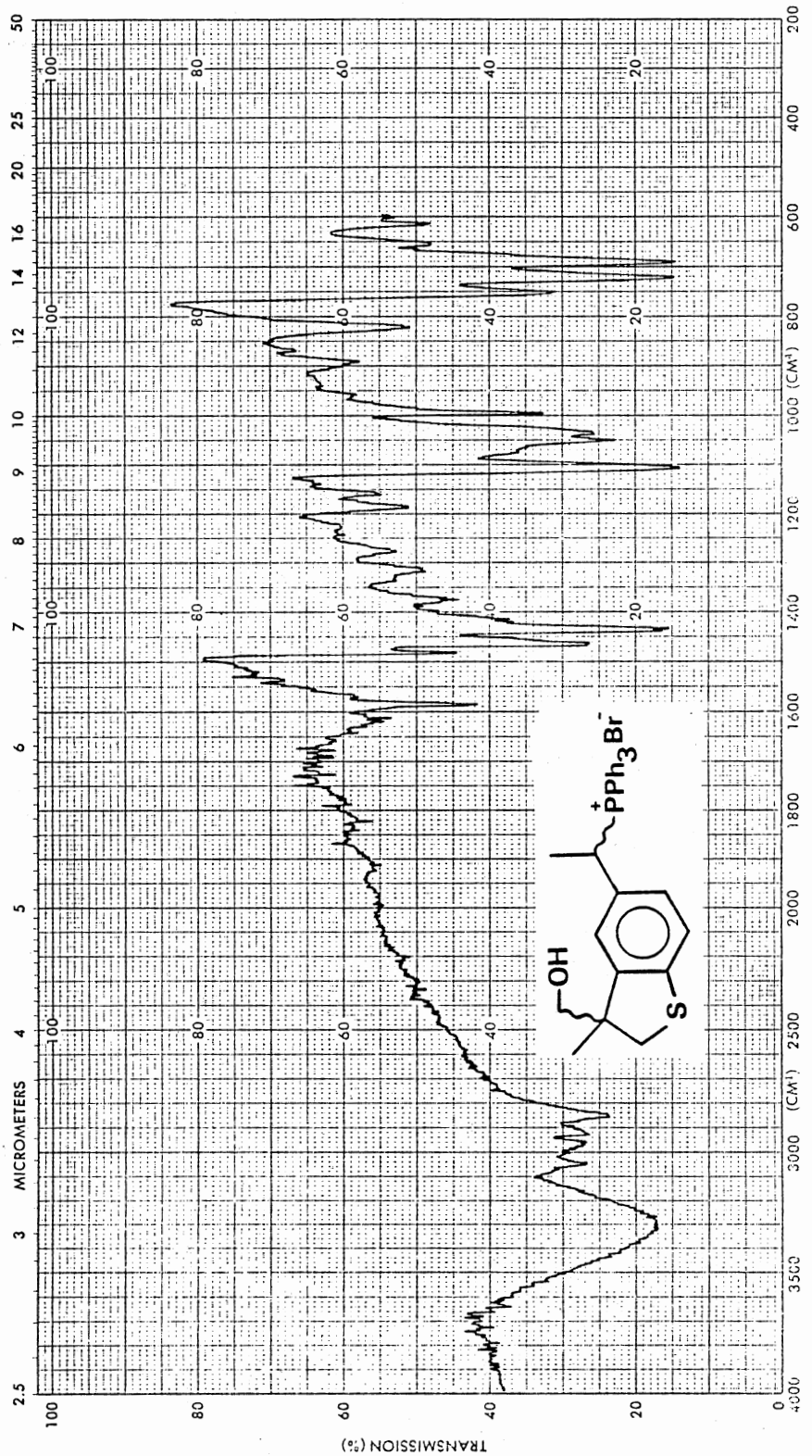
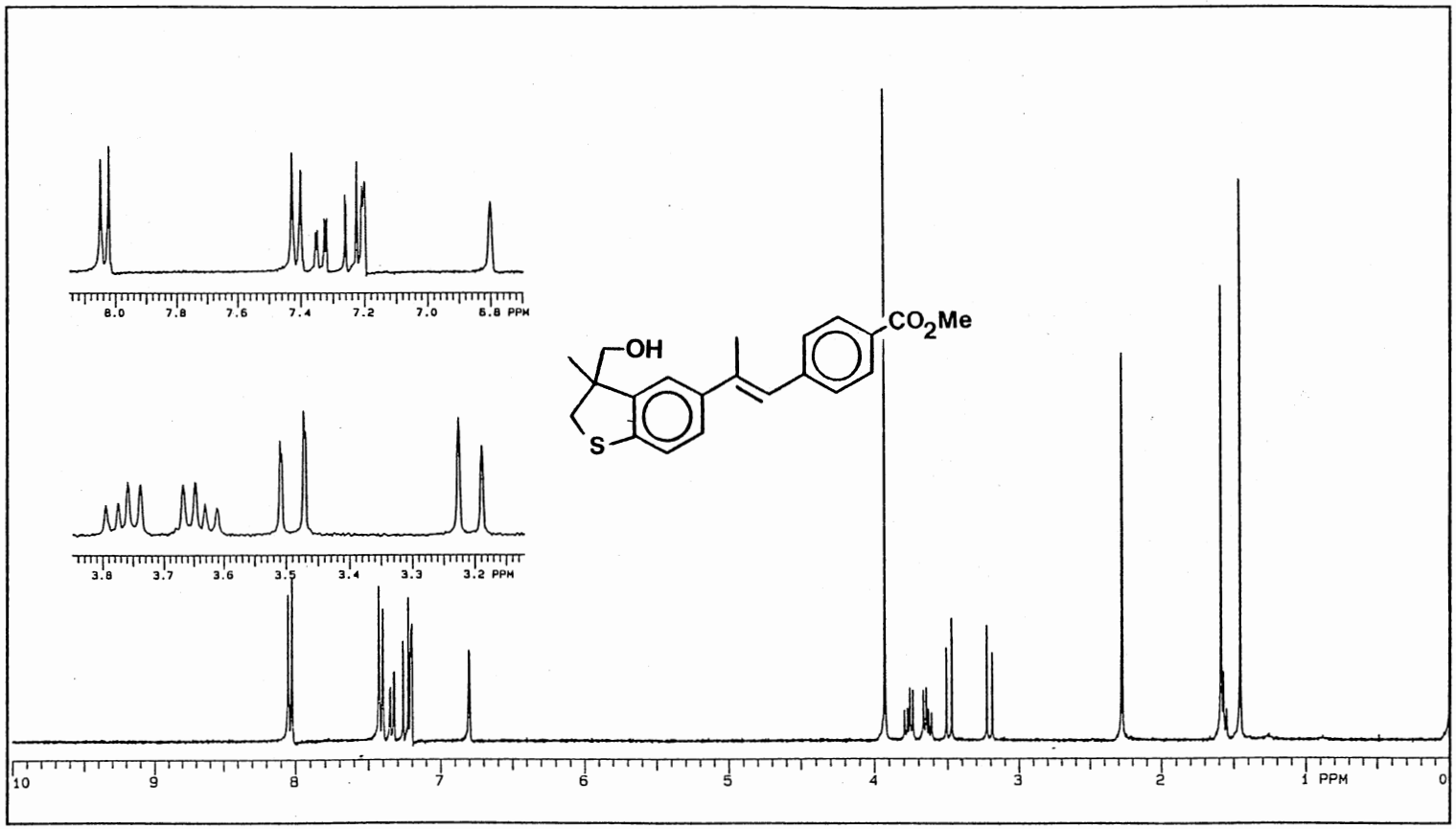


PLATE CXIV



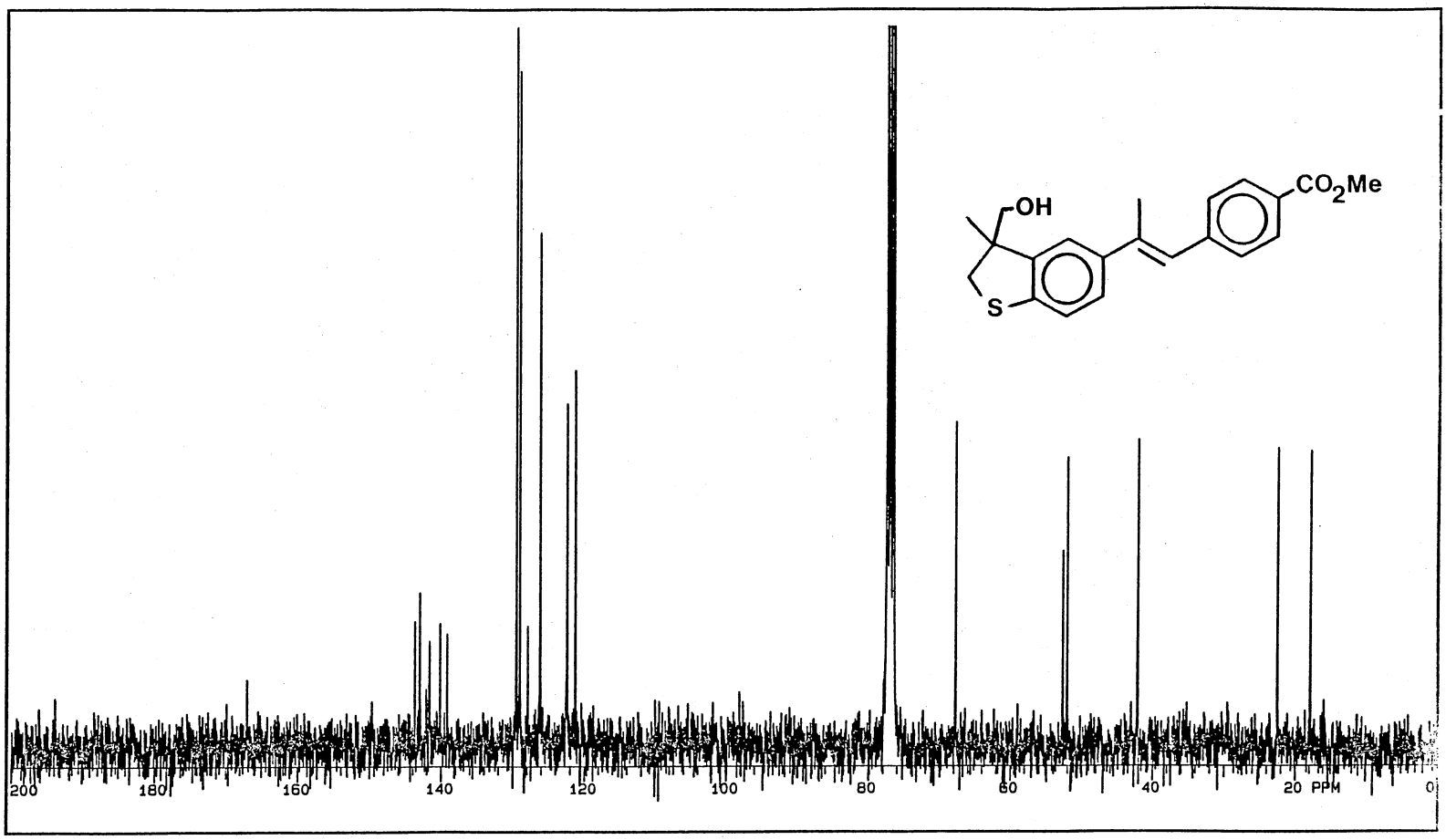
IR Spectrum of **125**-KBr

PLATE CXV



^{1}H NMR Spectrum of **65**

PLATE CXVI



OBSERVE: Nucleus 13.500 Freq 75 MHz; Spec. Width 20000.0 Hz Offset 1500 Hz; Acq. Time 1.000 sec Delay 3.000 sec; Pulse Width 12.0 µsec Transients 6080

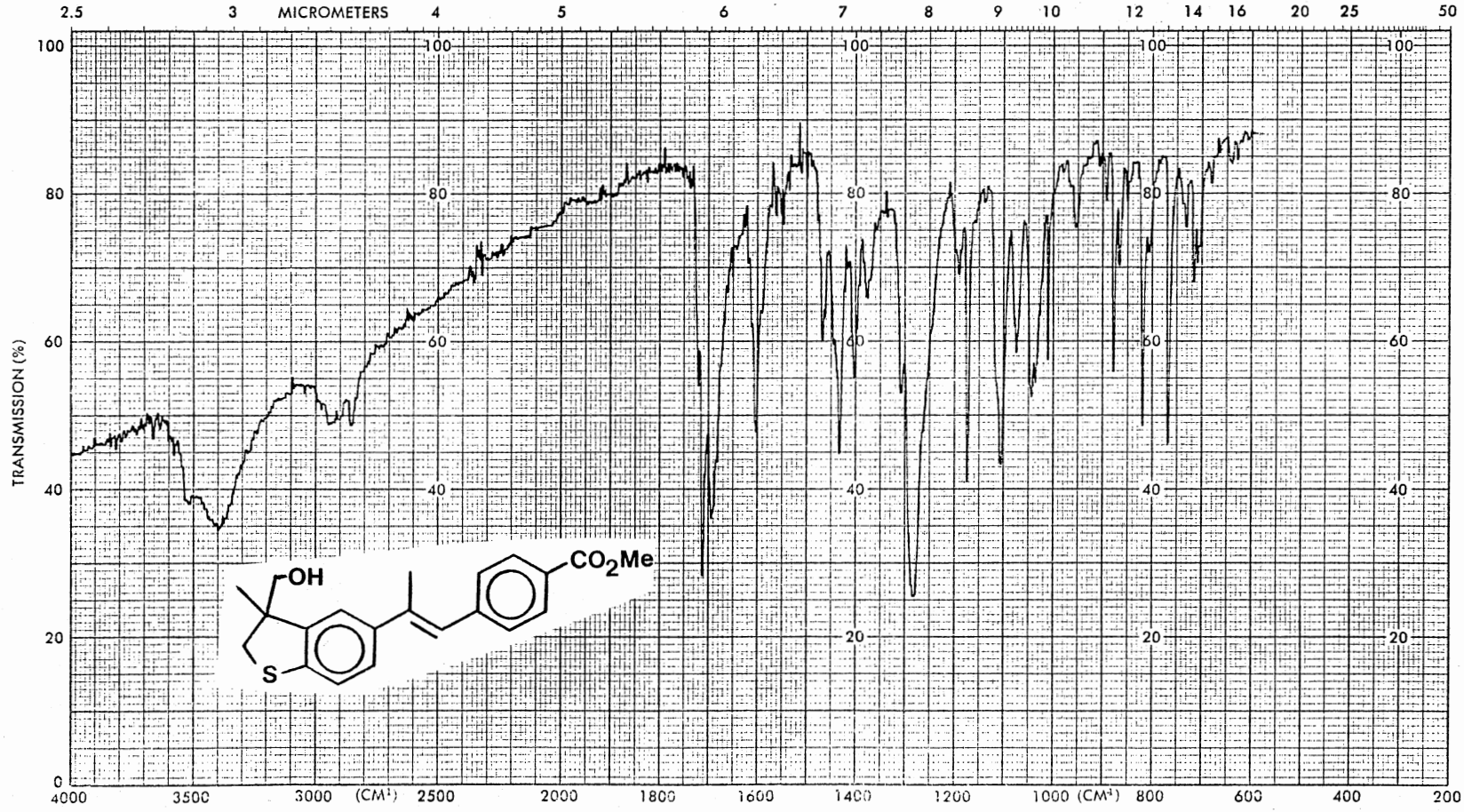
DECOUPLE: Nucleus 1.500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation: Mode S Freq 7900 Hz; Pulse Width 17.5 µsec Power Mode ---

PLOT/PROCESSING: FN 64 K RE --- sec CD --- sec; LB 2.000 Hz AF --- sec CCD ---; Width 15085.9 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence STD13C; Tube O.D. ___ mm; Temp. --- °C; Solvent CDCL3

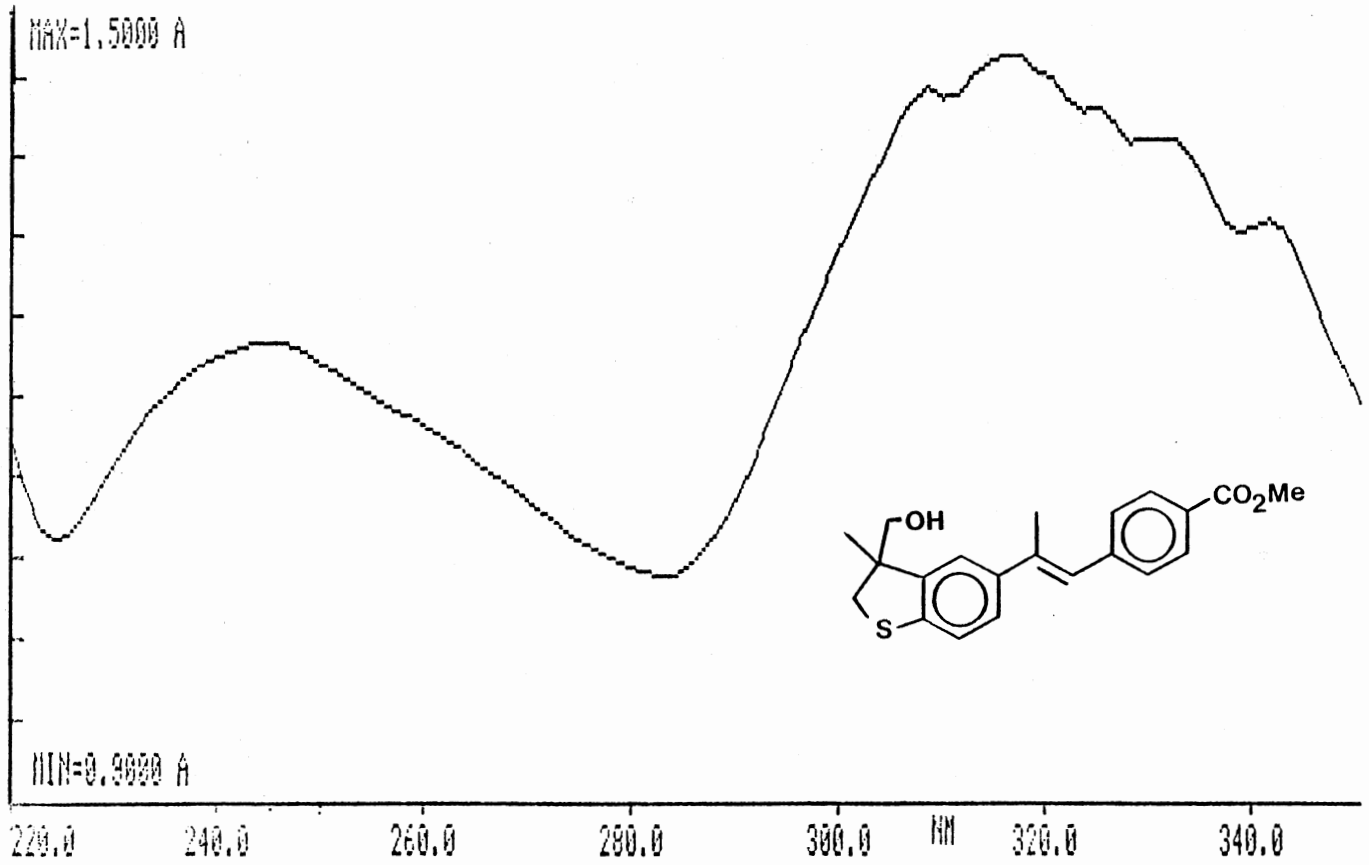
^{13}C NMR Spectrum of **65**

PLATE CXVII



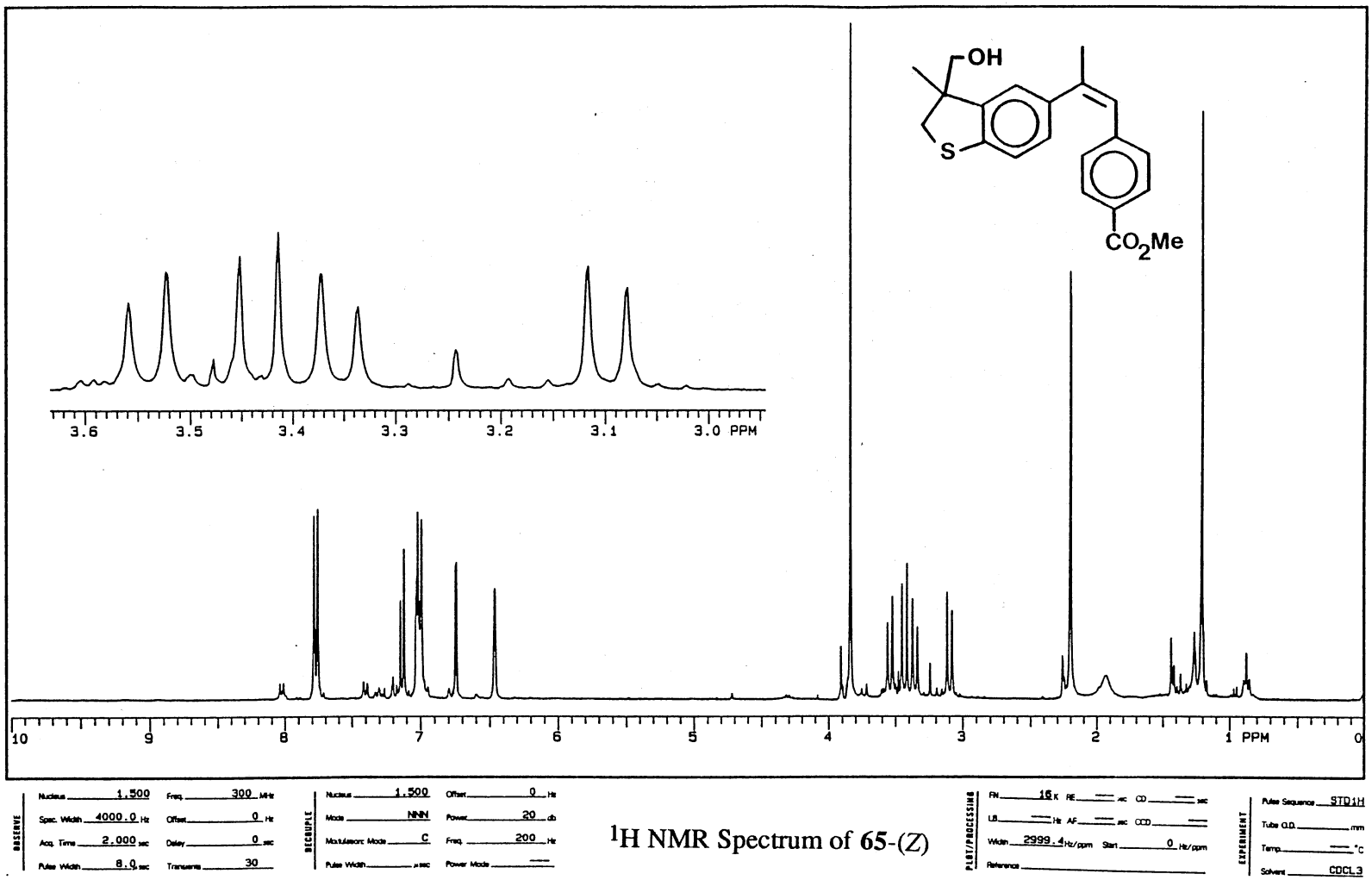
IR Spectrum of **65** -KBr

PLATE CXVIII



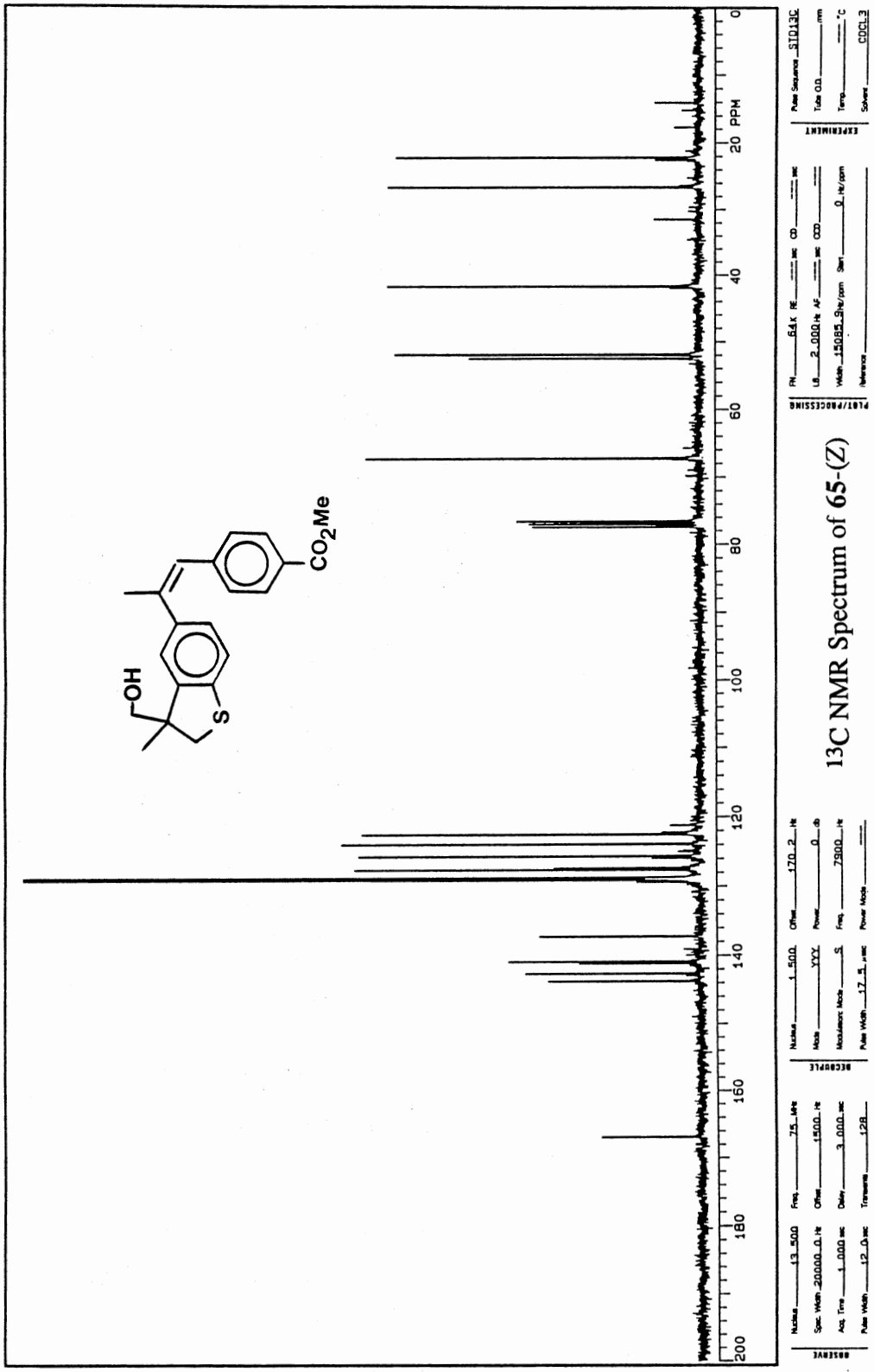
UV Spectrum of **65**

PLATE CXIX



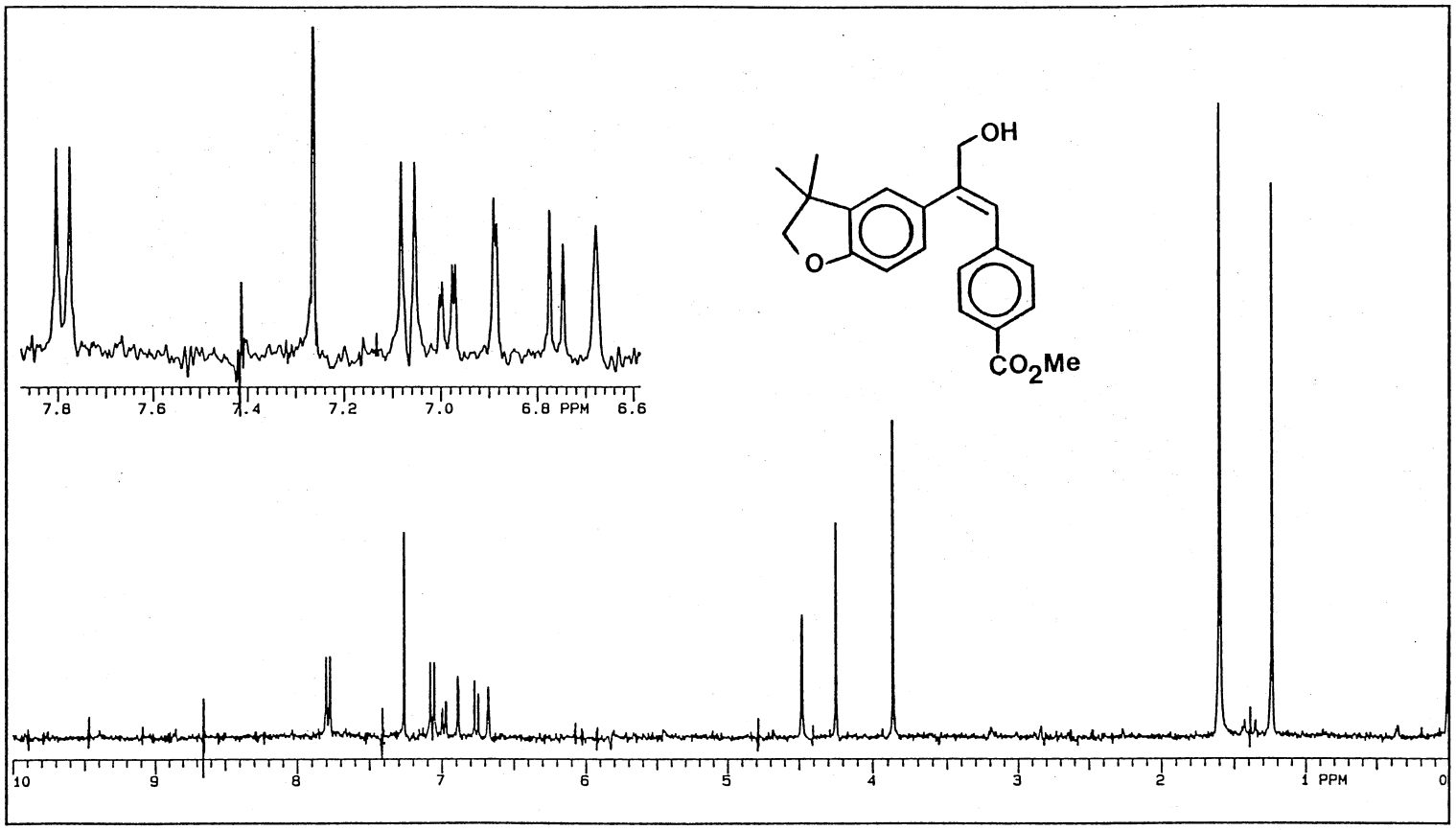
^{1}H NMR Spectrum of **65**-(*Z*)

PLATE CXX



^{13}C NMR Spectrum of **65**-(*Z*)

PLATE CXXI



OBSERVE: Nucleus 1.500, Freq 300 MHz; Spec. Width 4000.0 Hz, Offset 0 Hz; Acq. Time 2.000 sec, Delay 0 sec; Pulse Width 8.0 sec, Transients 832

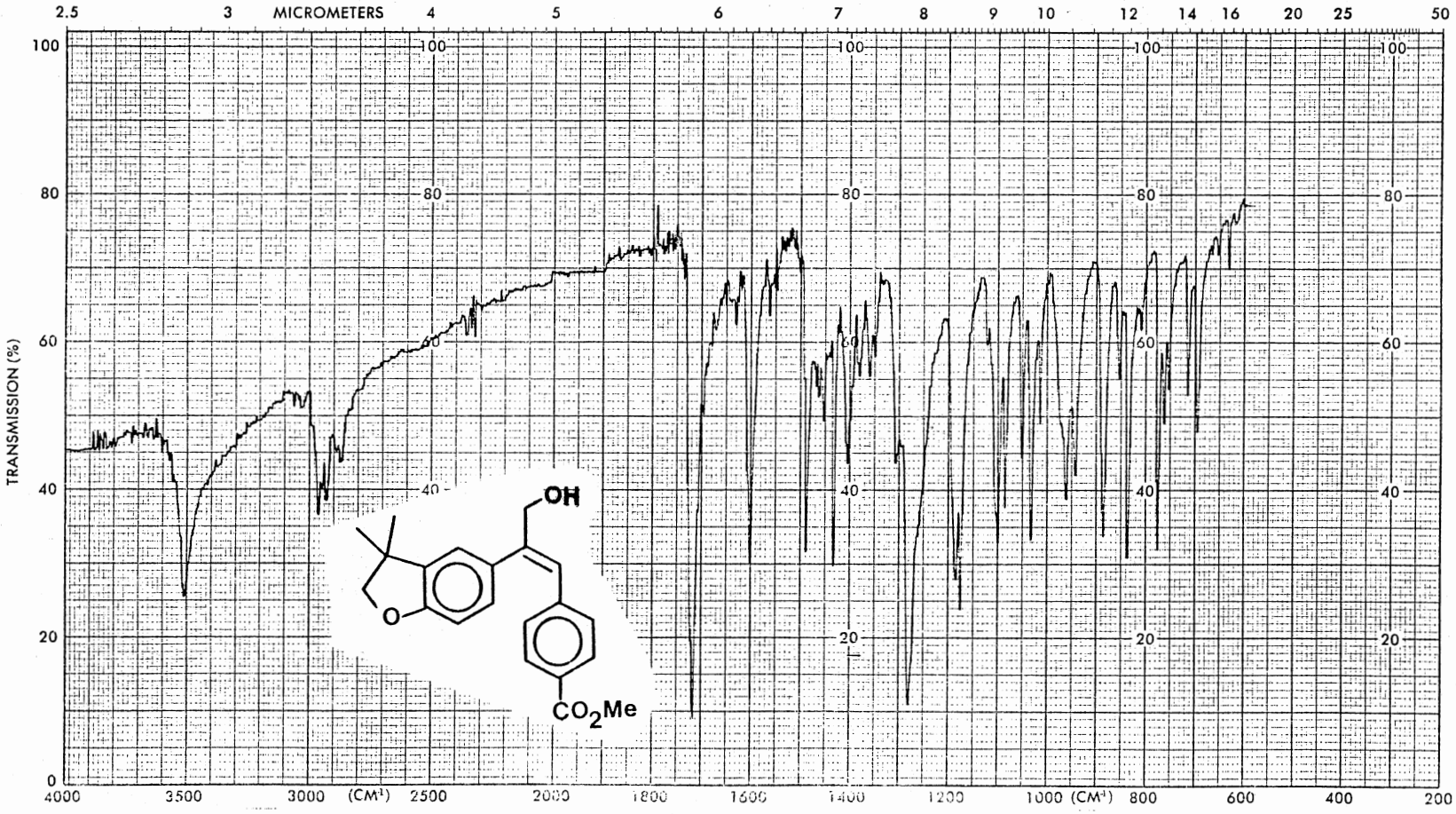
DECOUPLE: Nucleus 1.500, Offset 0 Hz; Mode NNN, Power 20 db; Modulation Mode C, Freq 200 Hz; Pulse Width ---- µsec, Power Mode ----

^{1}H NMR Spectrum of **66**

PLOT/PROCESSING: FN 16K, RE ---- sec, CD ---- sec; LB ---- Hz, AF ---- sec, CCD ----; Width 2999.4 Hz/ppm, Start 0 Hz/ppm; Reference ----

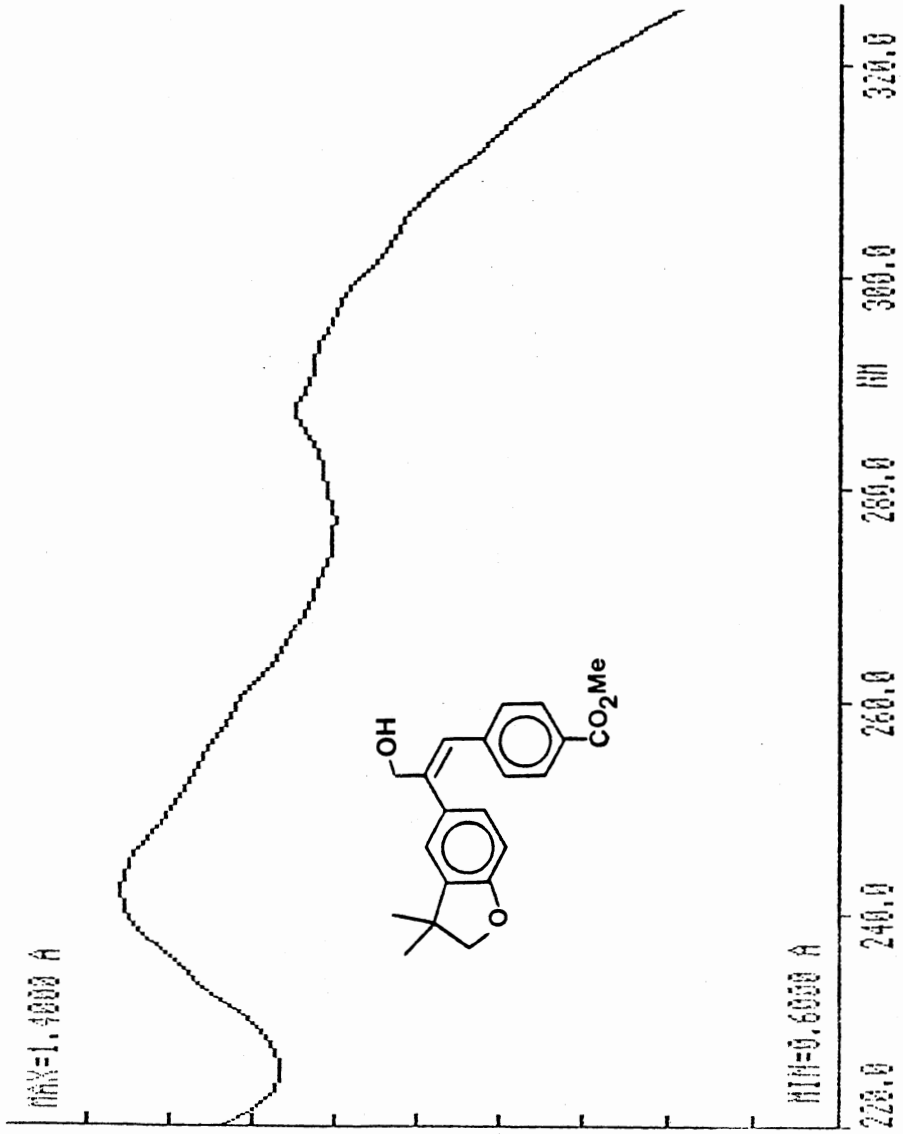
EXPERIMENT: Pulse Sequence STD1H; Tube O.D. ---- mm; Temp. ---- °C; Solvent CDCL3

PLATE CXXII



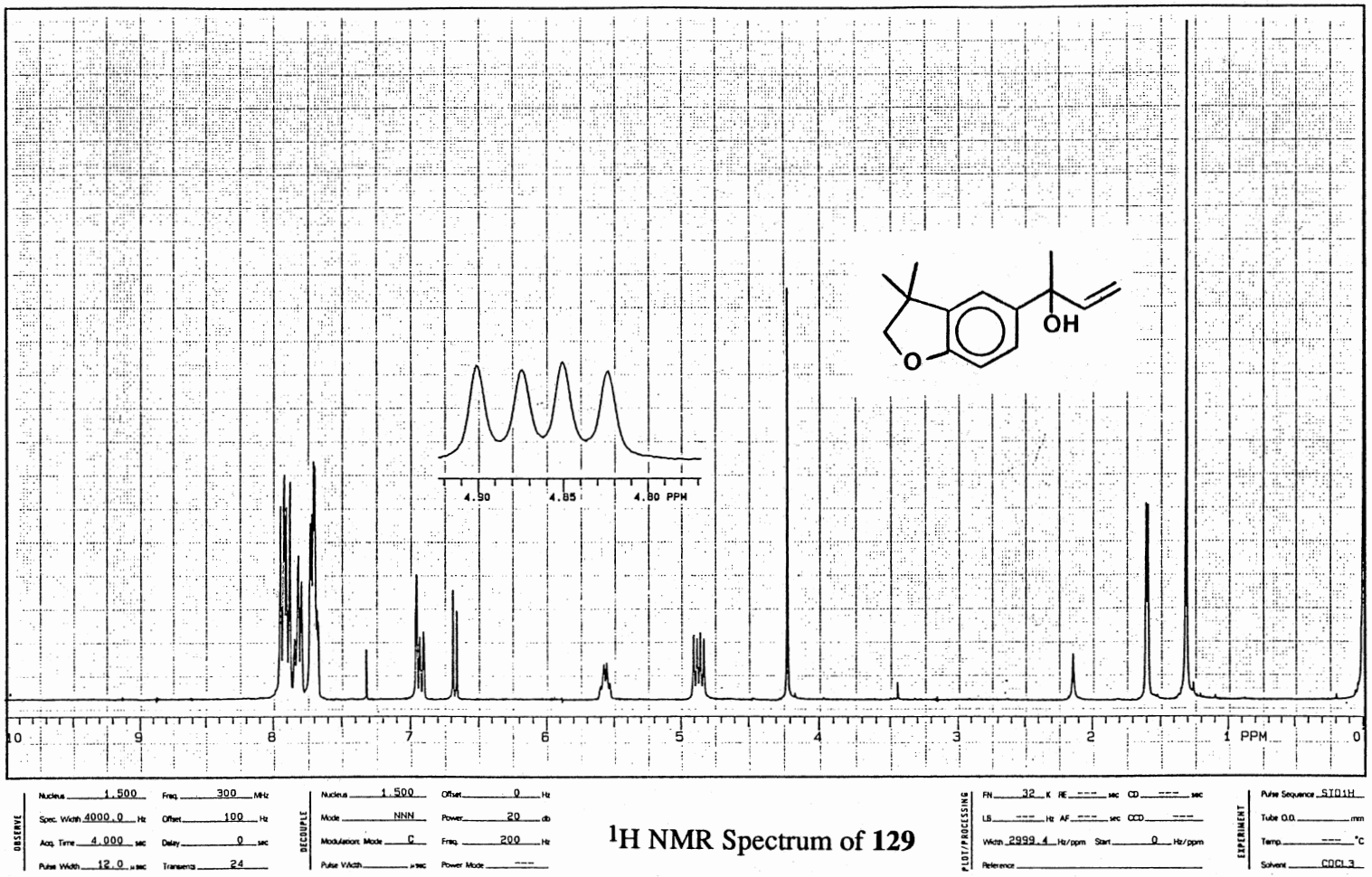
IR Spectrum of **66** -KBr

PLATE CXXIII



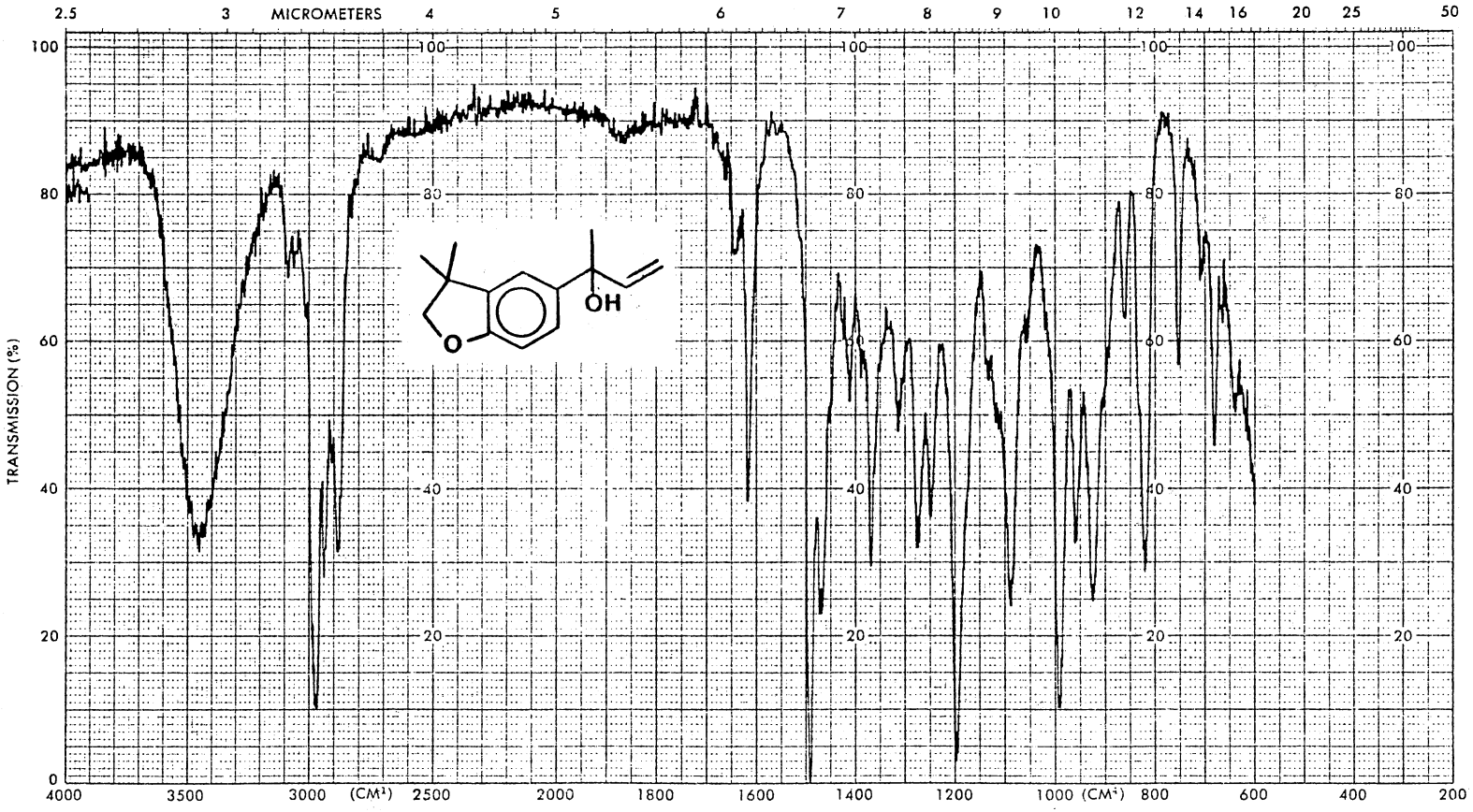
UV Spectrum of **66**

PLATE CXXIV



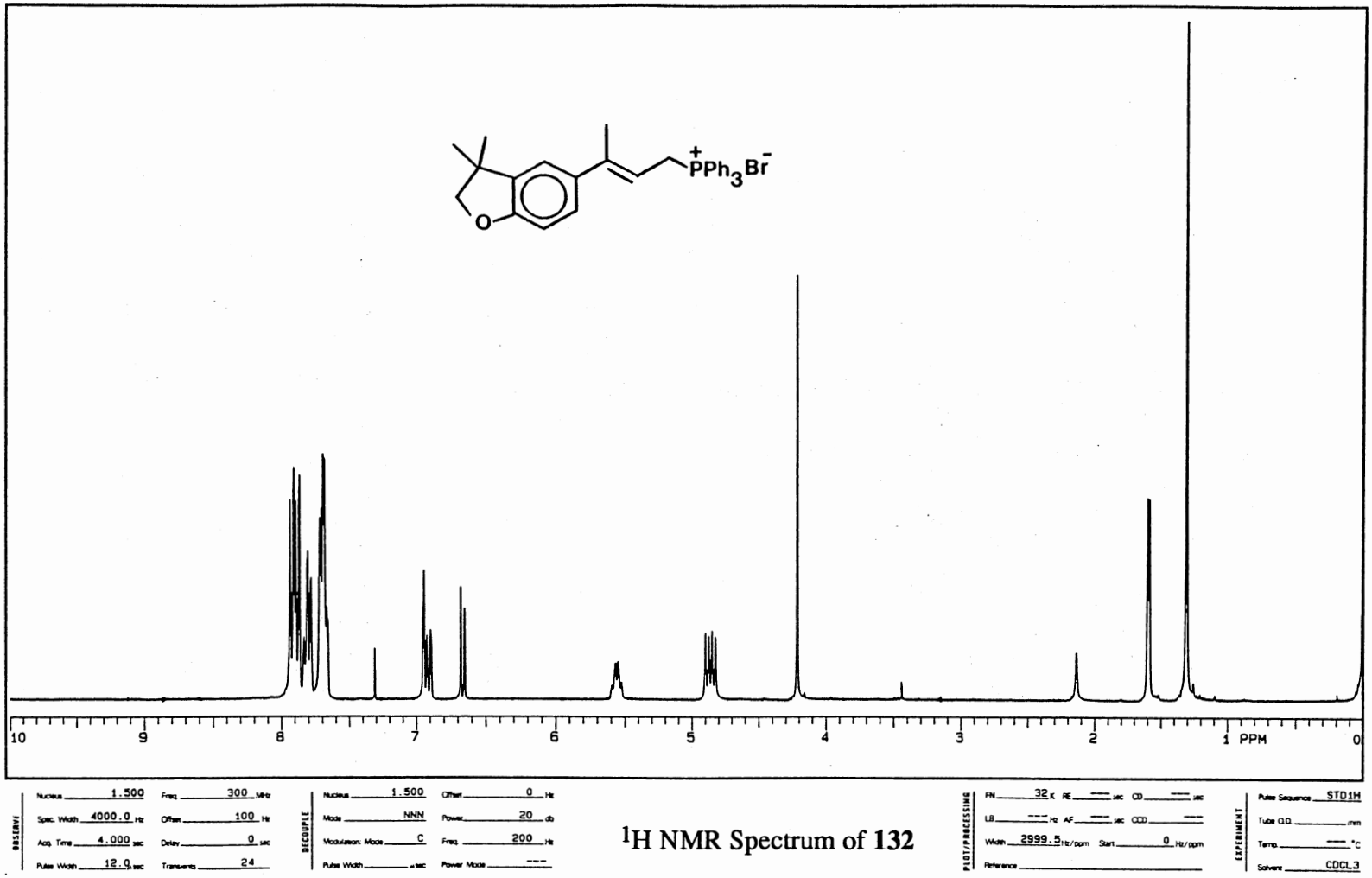
^{1}H NMR Spectrum of **129**

PLATE CXXV



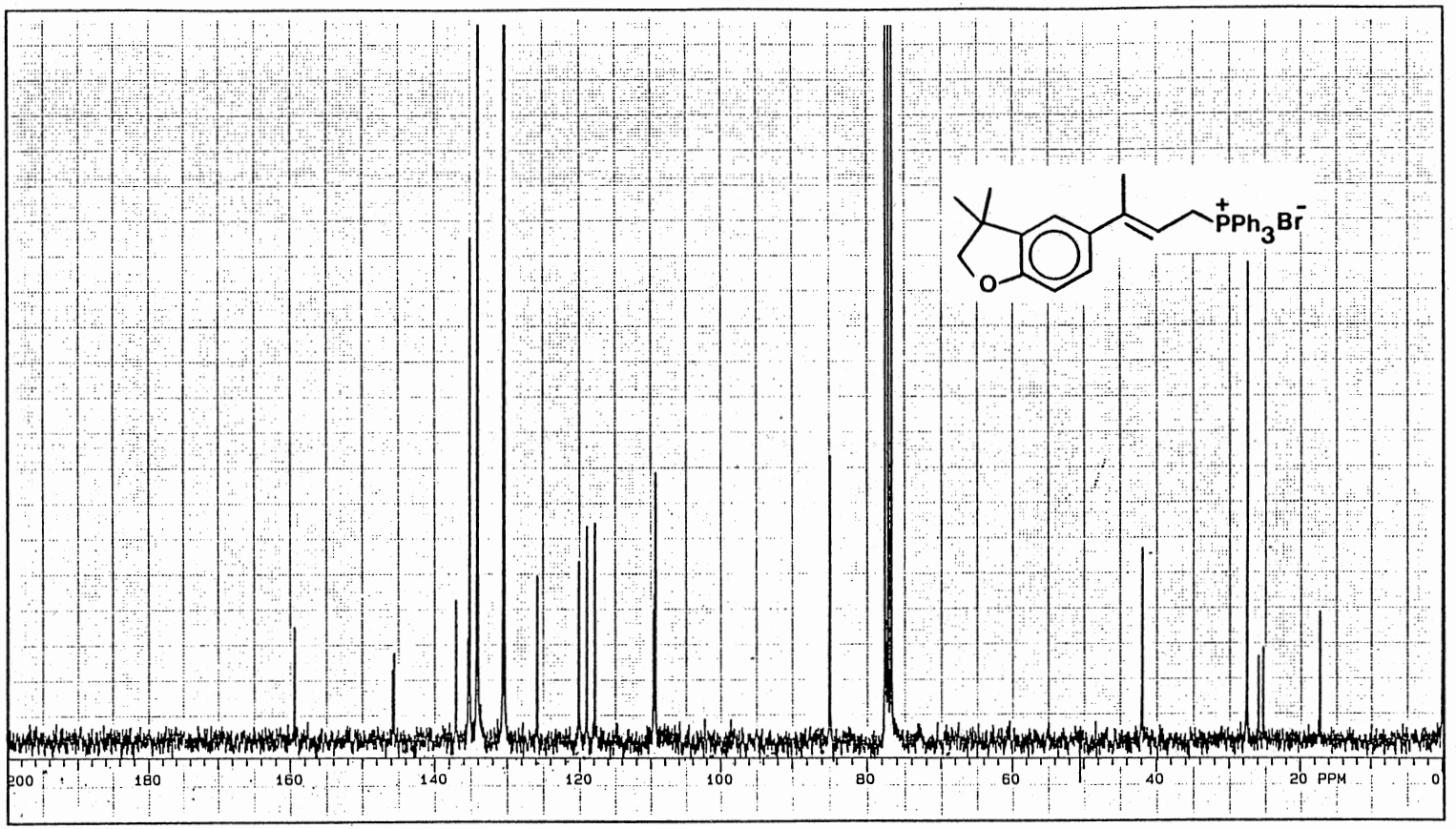
IR Spectrum of **129**

PLATE CXXVI



^{1}H NMR Spectrum of **132**

PLATE CXXVII



OBSERVE: Nucleus 13.500 Freq 75 MHz; Spec. Width 20000.0 Hz Offset 1500 Hz; Acq. Time 1.600 sec Delay 3.000 sec; Pulse Width 10.0 μsec Transients 400

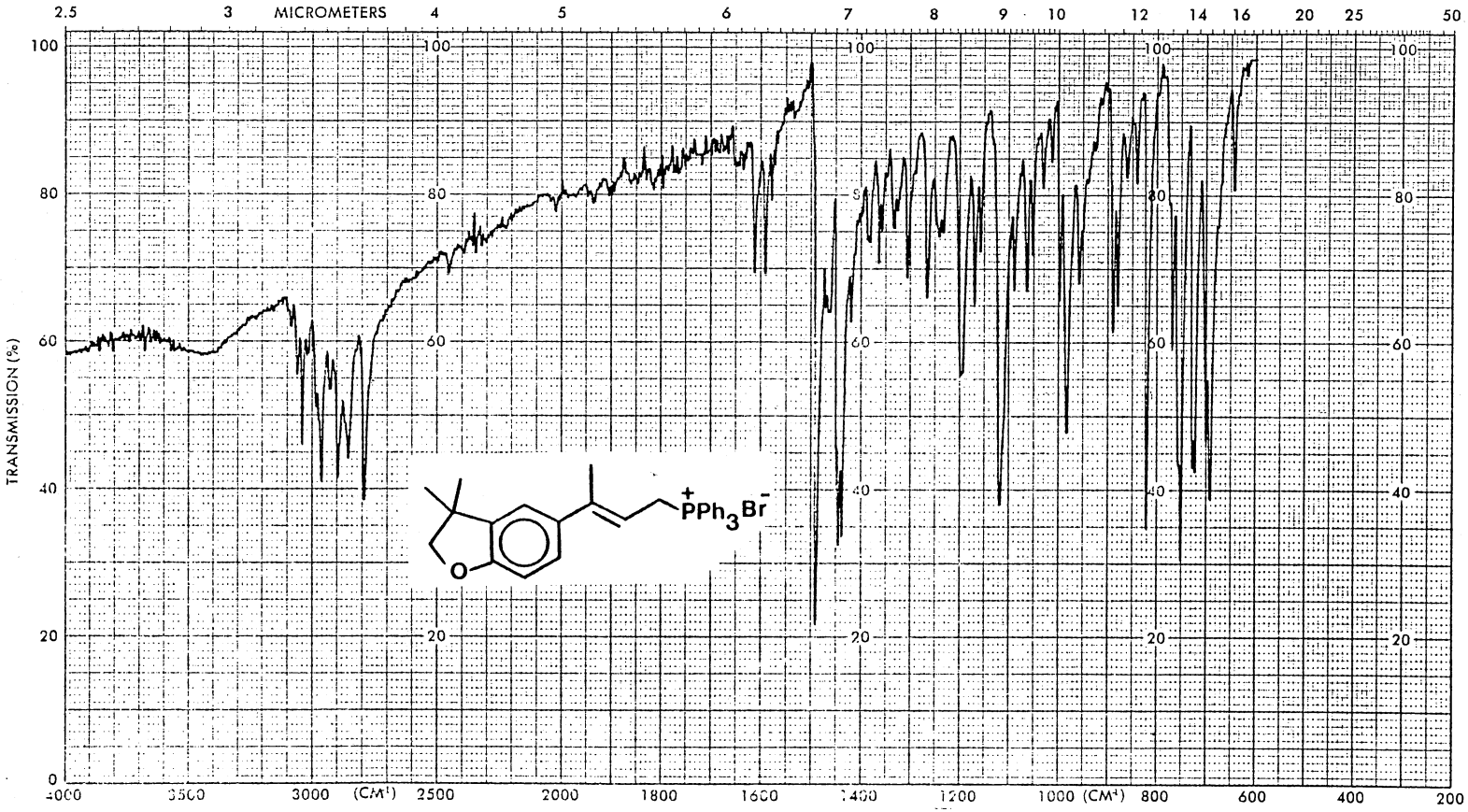
DECOUPLE: Nucleus 1.500 Offset 0 Hz; Mode YYY Power 0 db; Modulation Mode S Freq 7900 Hz; Pulse Width 17.5 μsec Power Mode ---

PLOT/PROCESSING: FN 64 K RE --- sec CD --- sec; LB 2.500 Hz AF --- sec CCD ---; Width 15085.9 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence STD13C; Tube OD ___ mm; Temp --- °C; Solvent CDCl3

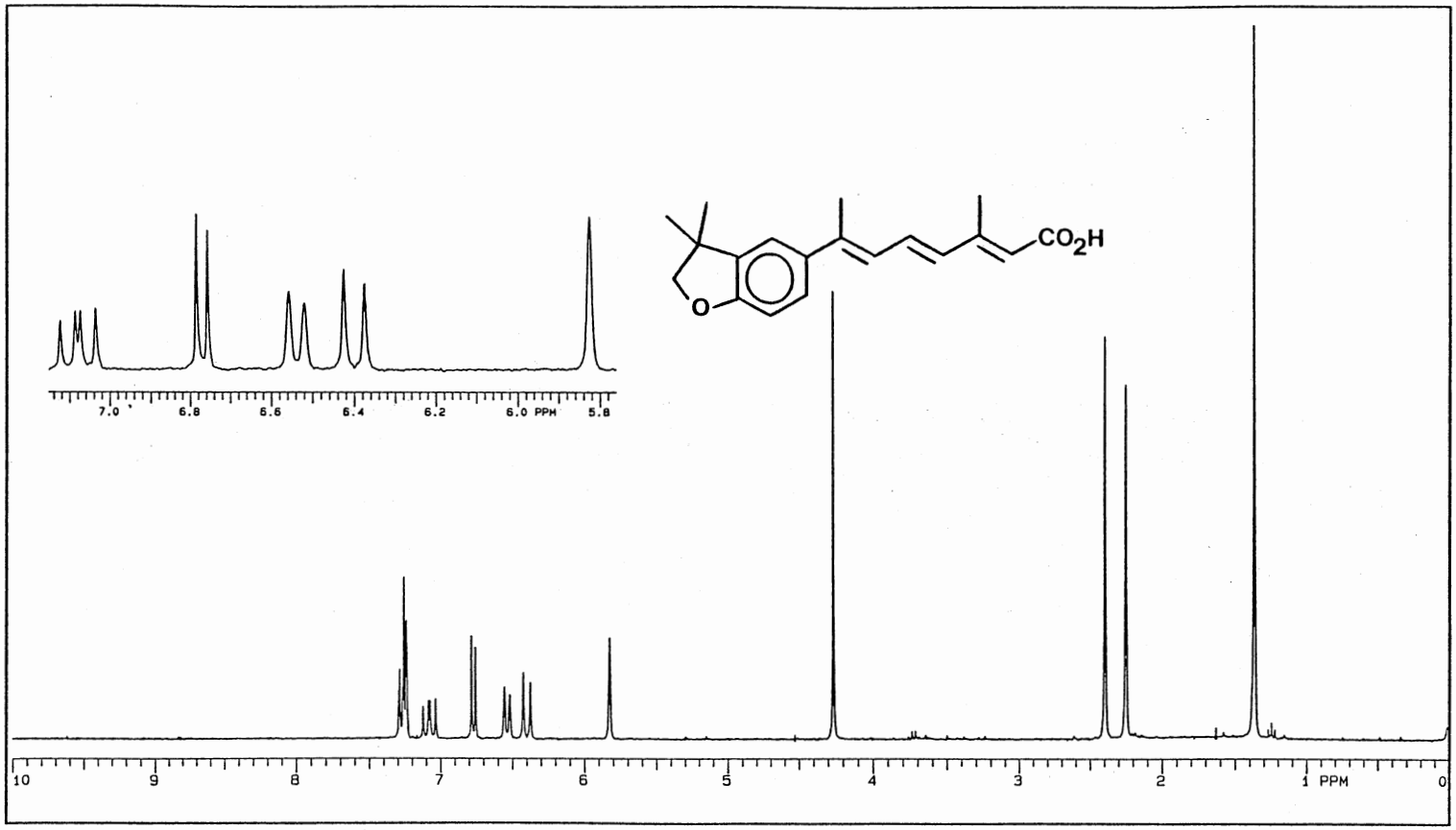
^{13}C NMR Spectrum of **132**

PLATE CXXVIII



IR Spectrum of **132** -KBr

PLATE CXXIX



OBSERVE: Nucleus 1.500 Freq. 300 MHz; Spec. Width 4000.0 Hz Offset 0 Hz; Acq. Time 2.000 sec Delay 0 sec; Pulse Width 8.0 sec Transients 128

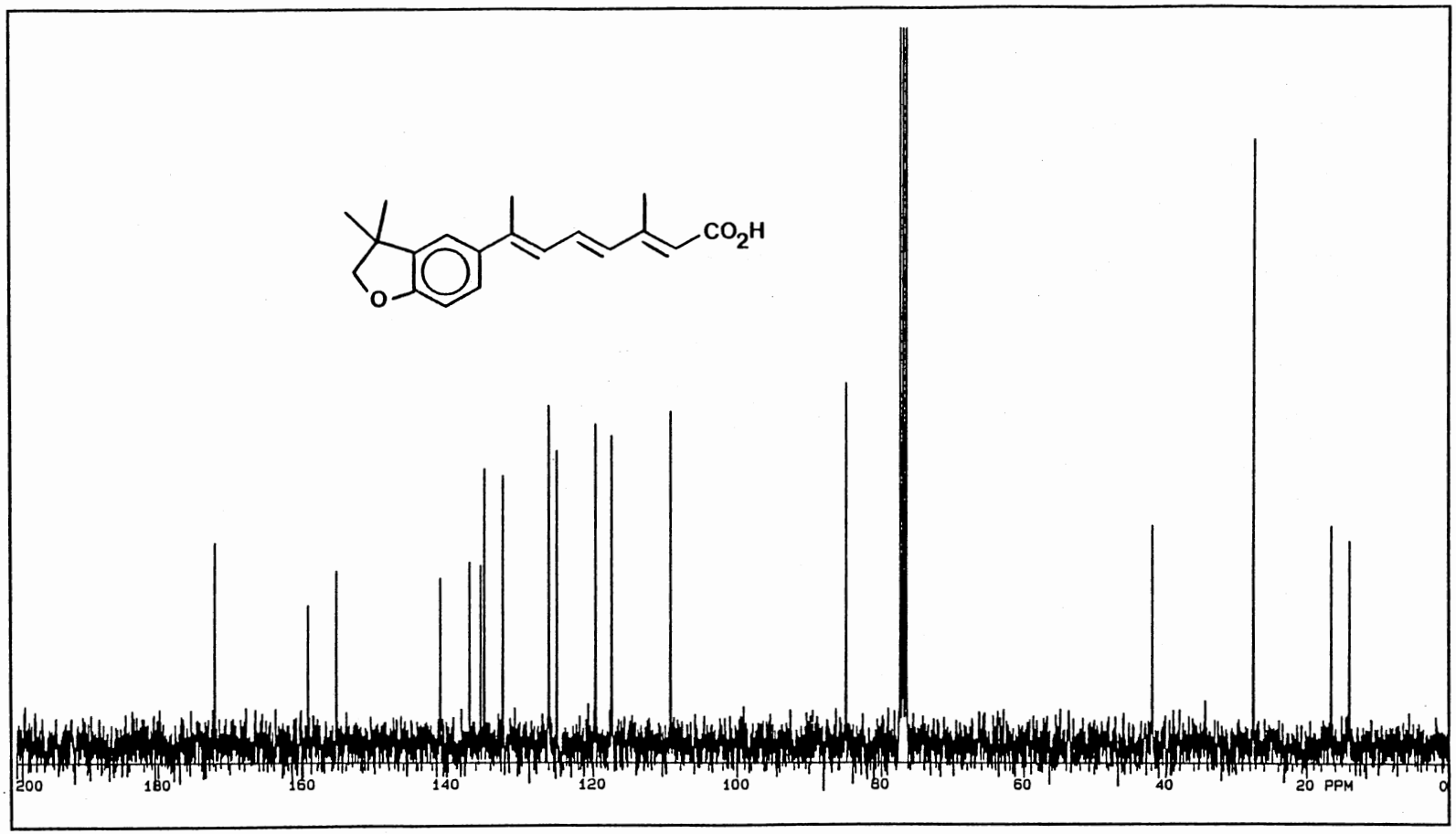
DECOUPLE: Nucleus 1.500 Offset 0 Hz; Mode NNN Power 20 db; Modulation Mode C Freq. 200 Hz; Pulse Width ___ usec Power Mode ---

PLOT/PROCESSING: FN 16 K RE --- sec CD --- sec; LB --- Hz AF --- sec CCD ---; Width 2999.4 Hz/ppm Start 0 Hz/ppm; Reference ___

EXPERIMENT: Pulse Sequence STD1H; Tube O.D. ___ mm; Temp. --- °C; Solvent CDCL3

^{1}H NMR Spectrum of **67**

PLATE CXXX



OBSERVE: Nucleus 13.500 Freq. 75 MHz; Spec. Width 20000.0 Hz Offset 1500 Hz; Acq. Time 1.000 sec Delay 3.000 sec; Pulse Width 12.0 µsec Transients 256

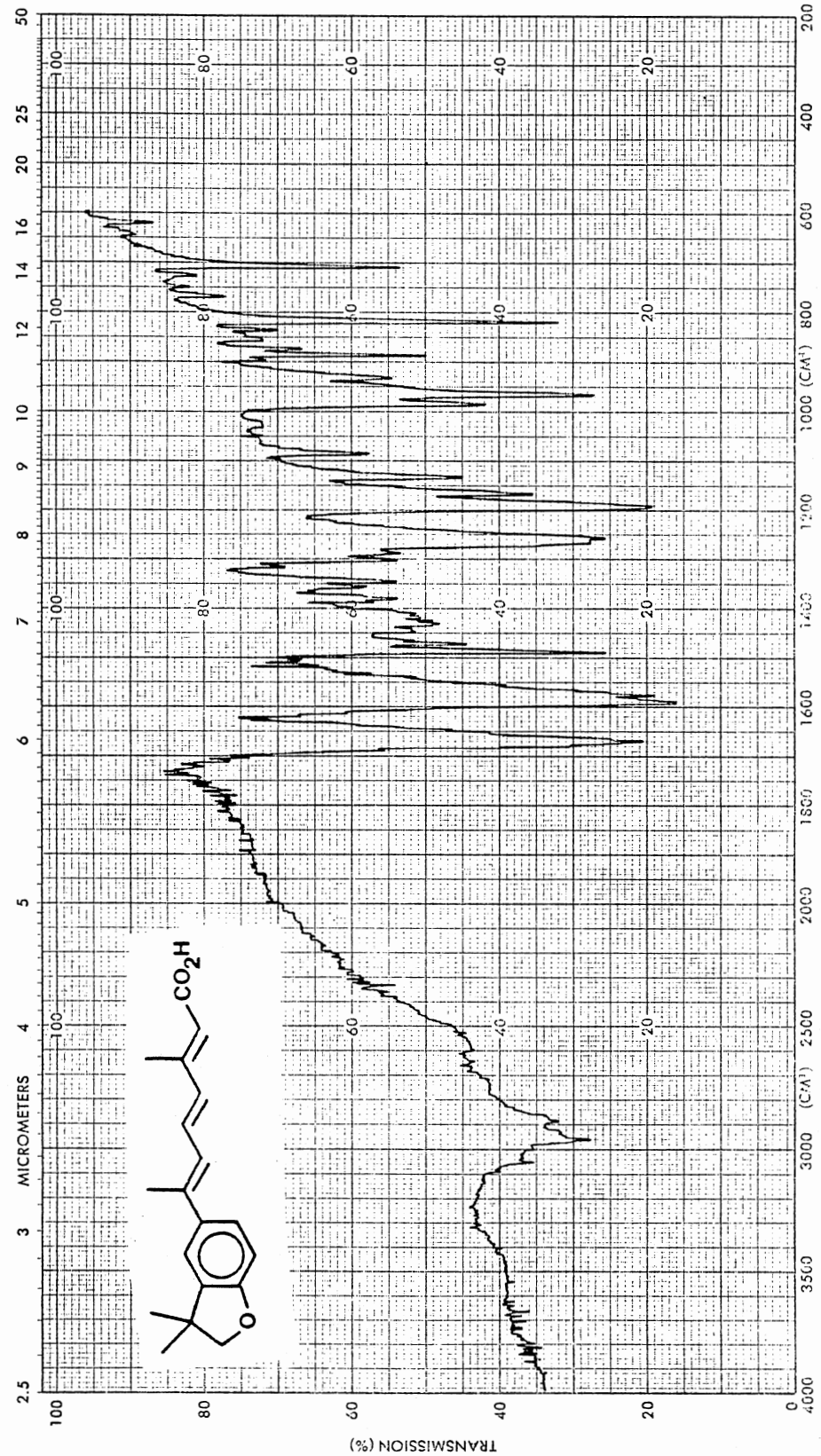
DECOUPLE: Nucleus 1.500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation Mode S Freq. 7900 Hz; Pulse Width 17.5 µsec Power Mode ---

^{13}C NMR Spectrum of **67**

PLOT/PROCESSING: FN 64K RE --- sec CD --- sec; LB 2.000 Hz AF --- sec CCD ---; Width 15085.9 Hz/ppm Start 0 Hz/ppm; Reference

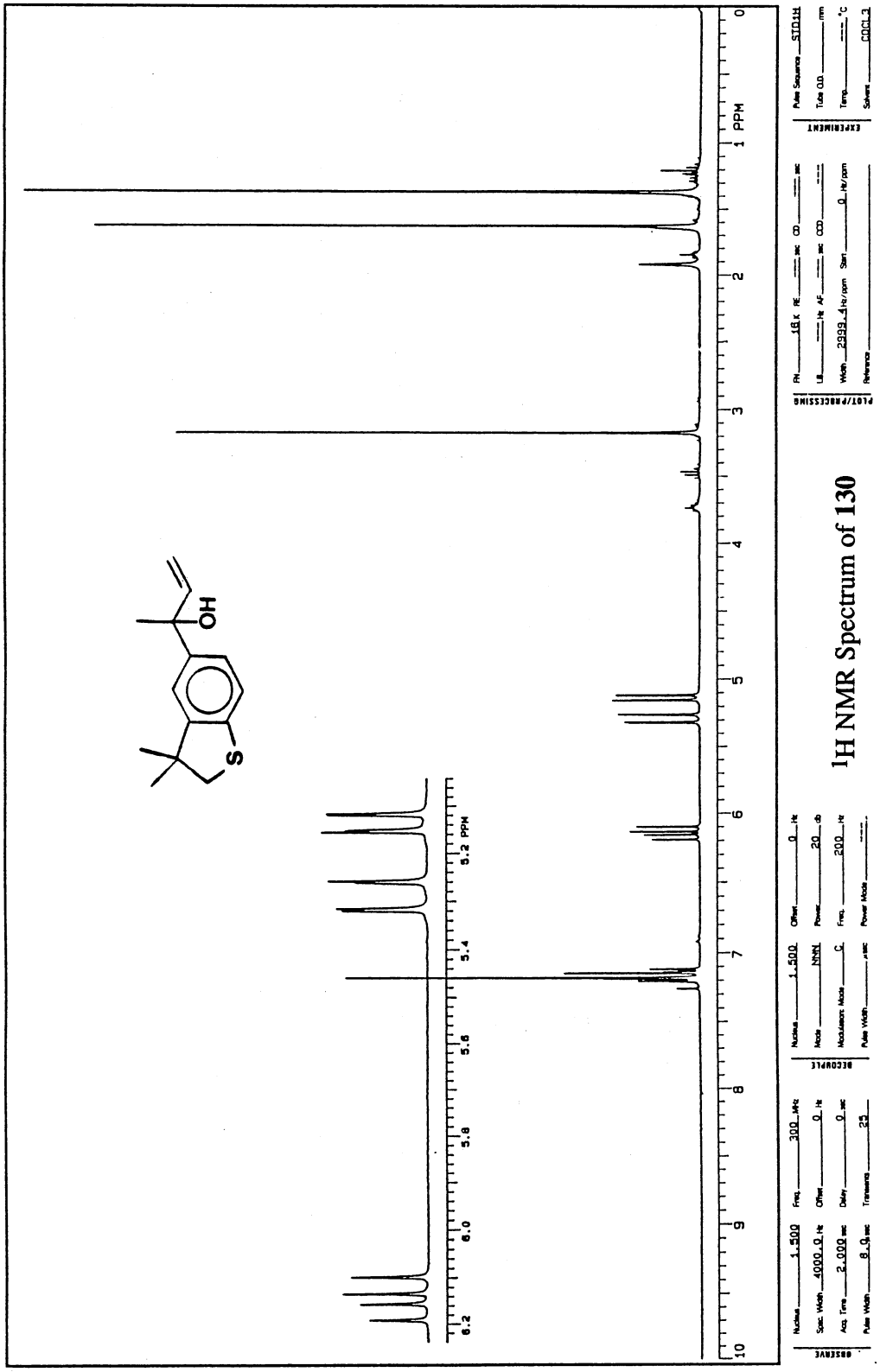
EXPERIMENT: Pulse Sequence STD13C; Tube O.D. --- mm; Temp. --- °C; Solvent CDCl3

PLATE CXXXI



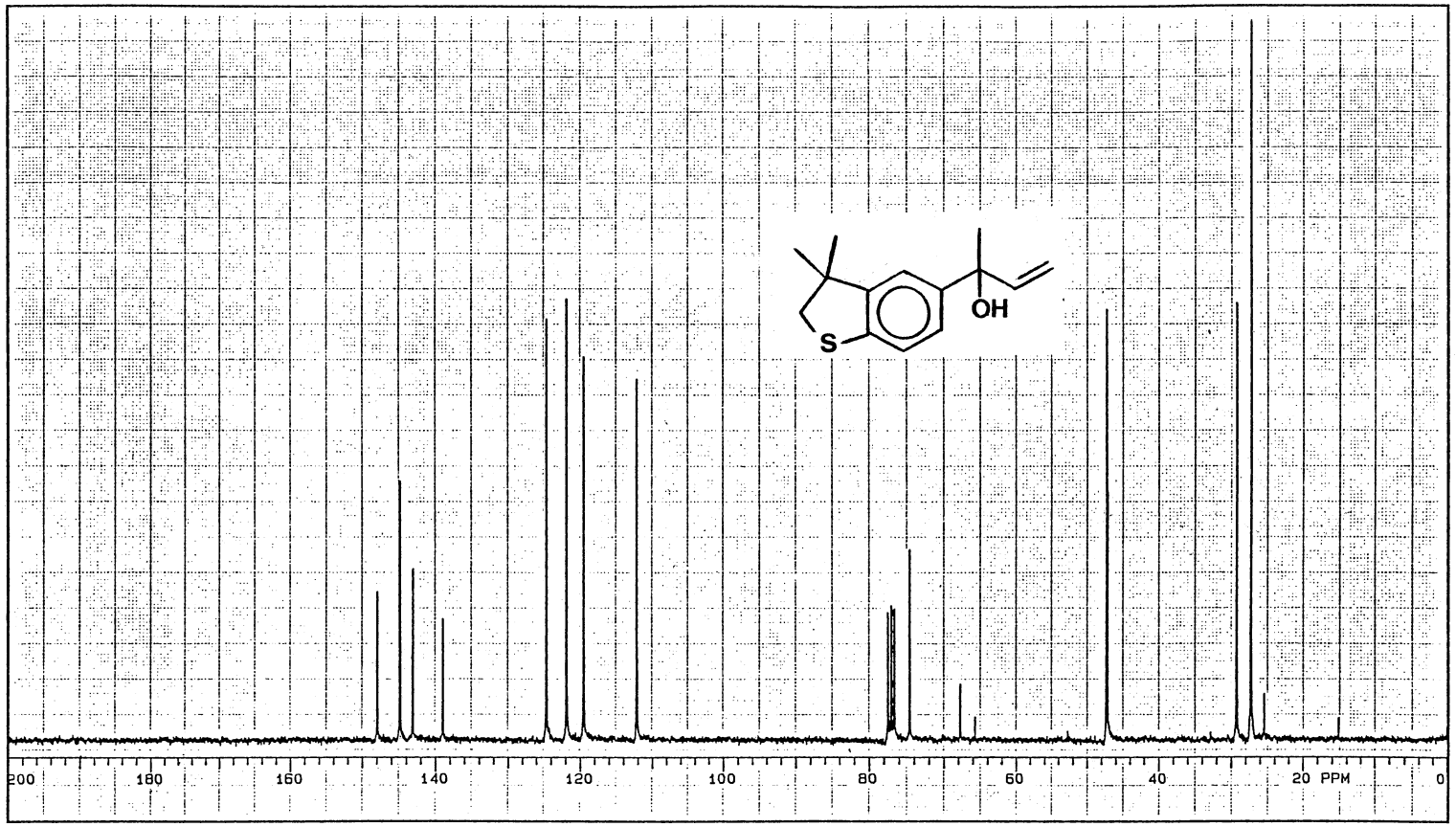
IR Spectrum of **67** -KBr

PLATE CXXXII



^{1}H NMR Spectrum of **130**

PLATE CXXXIII



OBSERVE: Nucleus 13.500 Freq 75 MHz; Spec Width 20000.0 Hz Offset 1500 Hz; Acq Time 1.000 sec Delay 3.000 sec; Pulse Width 10.0 µsec Transmit 160

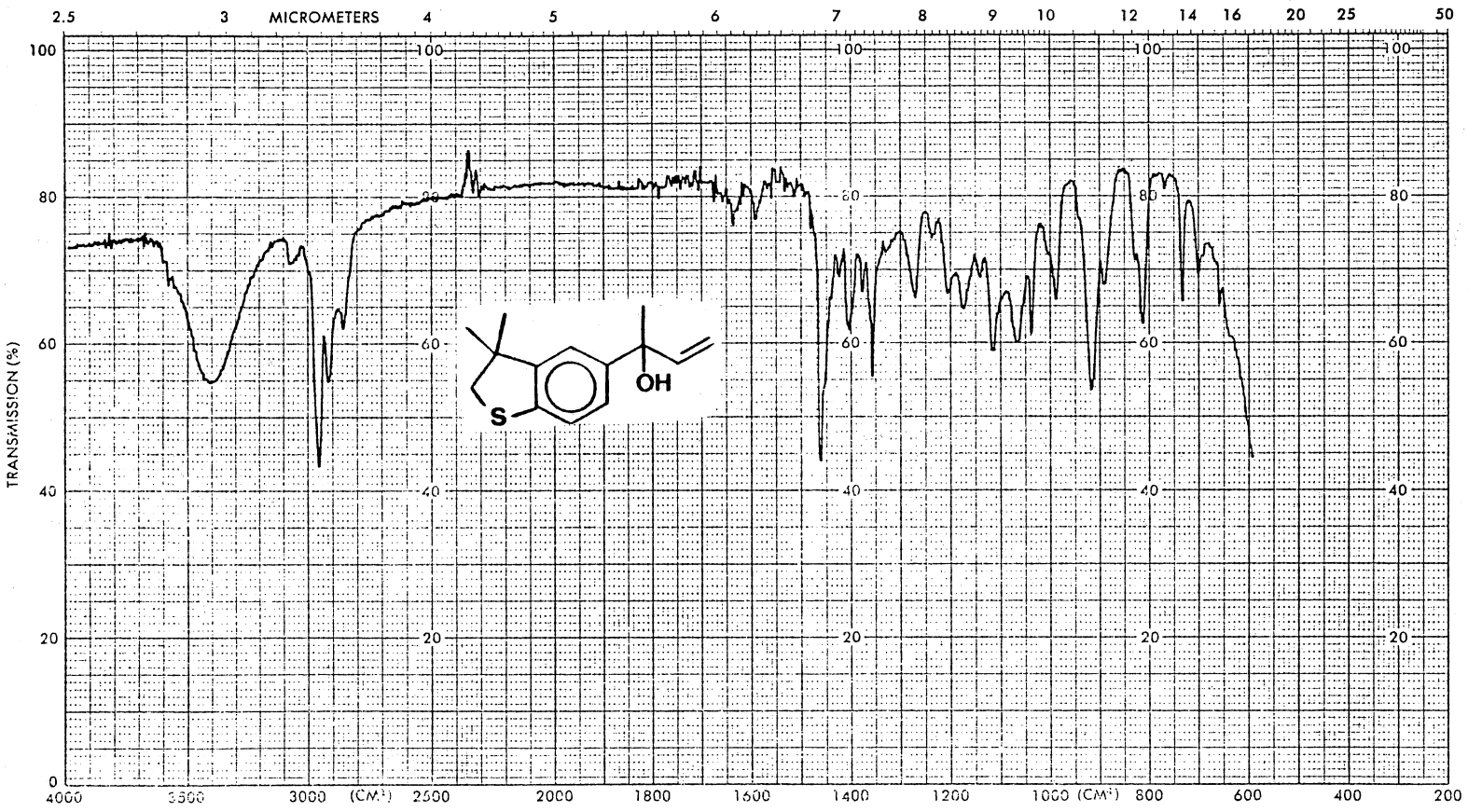
DECOUPLE: Nucleus 1.500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation Mode S Freq 7900 Hz; Pulse Width 17.5 µsec Power Mode ---

^{13}C NMR Spectrum of **130**

PLOT/PROCESSING: FN 64 K RE --- sec CD --- sec; LB 2.000 Hz AF --- sec CCD ---; Width 15085.9 Hz/ppm Start 0 Hz/ppm; Reference

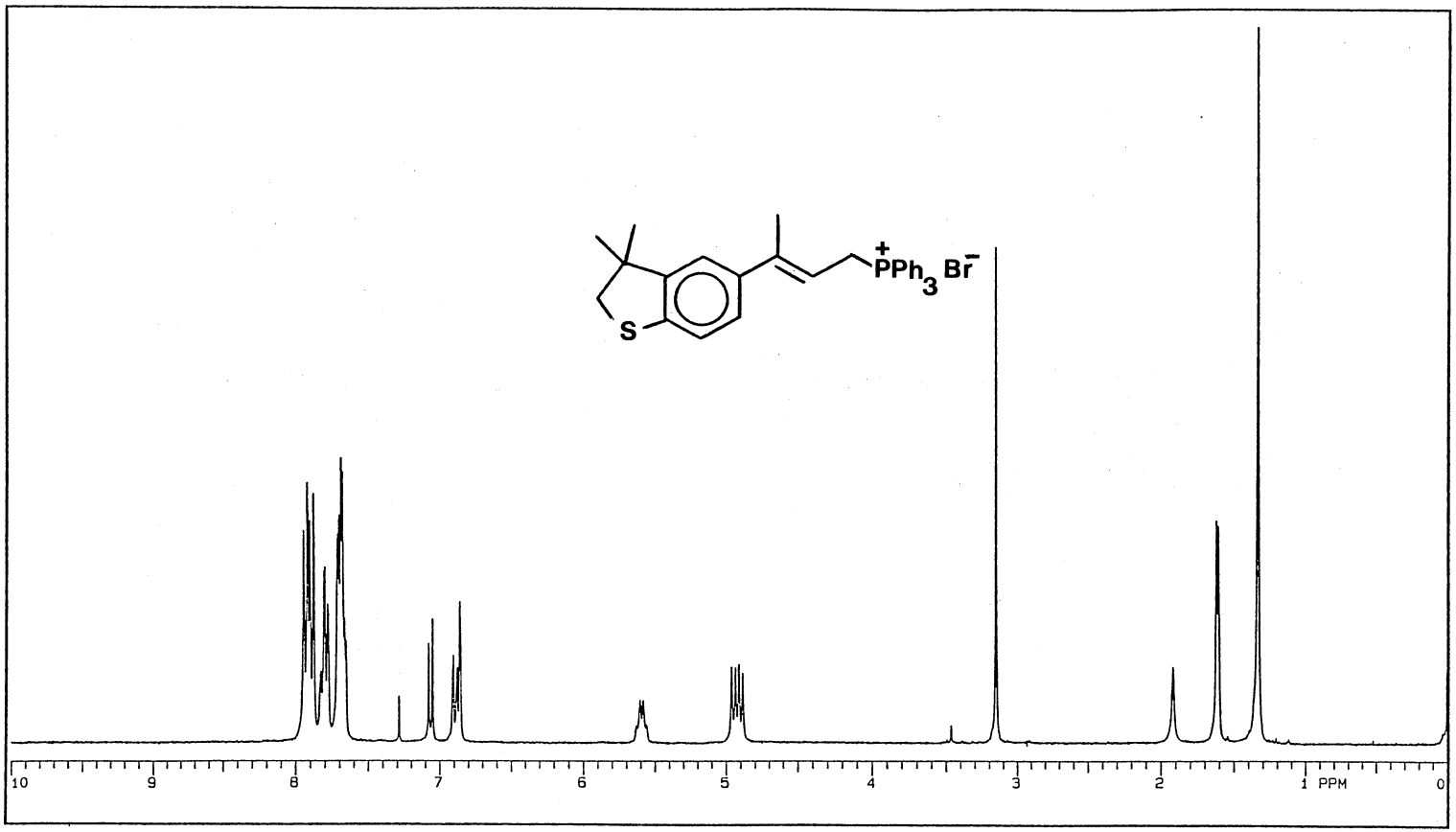
EXPERIMENT: Pulse Sequence STD13C; Tube O.D. --- mm; Temp --- °C; Solvent CDCL3

PLATE CXXXIV



IR Spectrum of **130**

PLATE CXXXV



OBSERVE: Nucleus 1.500 Freq 300 MHz; Spec Width 4000.0 Hz Offset 0 Hz; Acq Time 2.000 sec Delay 0 sec; Pulse Width 8.0 usec Transients 16

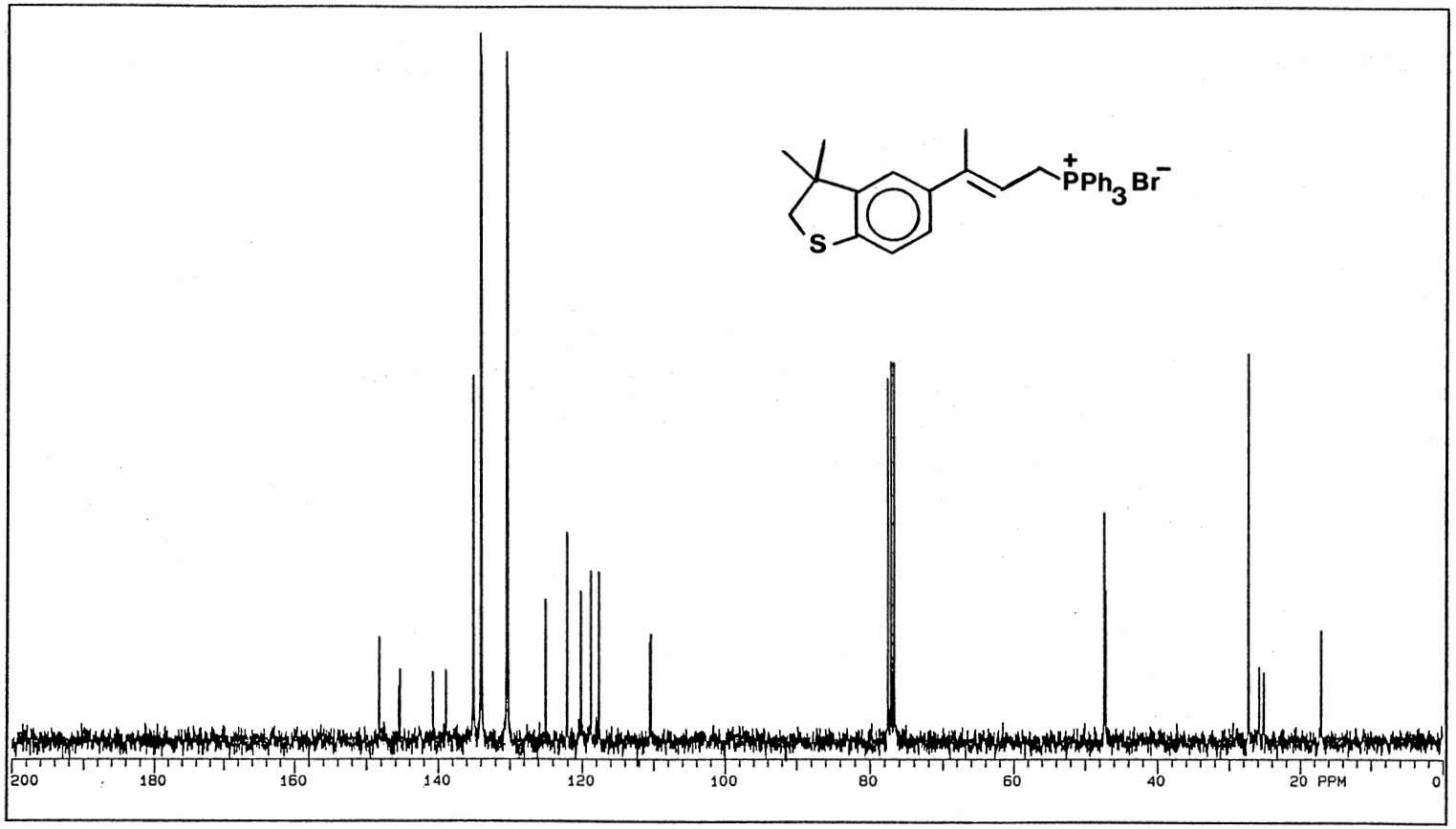
DECOUPLE: Nucleus 1.500 Offset 0 Hz; Mode NNN Power 20 db; Modulation Mode C Freq 200 Hz; Pulse Width usec Power Mode ---

^{1}H NMR Spectrum of **133**

PLOT/PROCESSING: FN 16 K RE --- sec CD --- sec; LB --- Hz AF --- sec CCD ---; Width 2999.4 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence STD1H; Tube OD mm; Temp --- °C; Solvent CDCL3

PLATE CXXXVI



OBSERVE Nucleus 13.500 Freq 75 MHz
Spec Width 20000.0 Hz Offset 1500 Hz
Acq Time 1.000 sec Delay 3.000 sec
Pulse Width 12.0 sec Transients 192

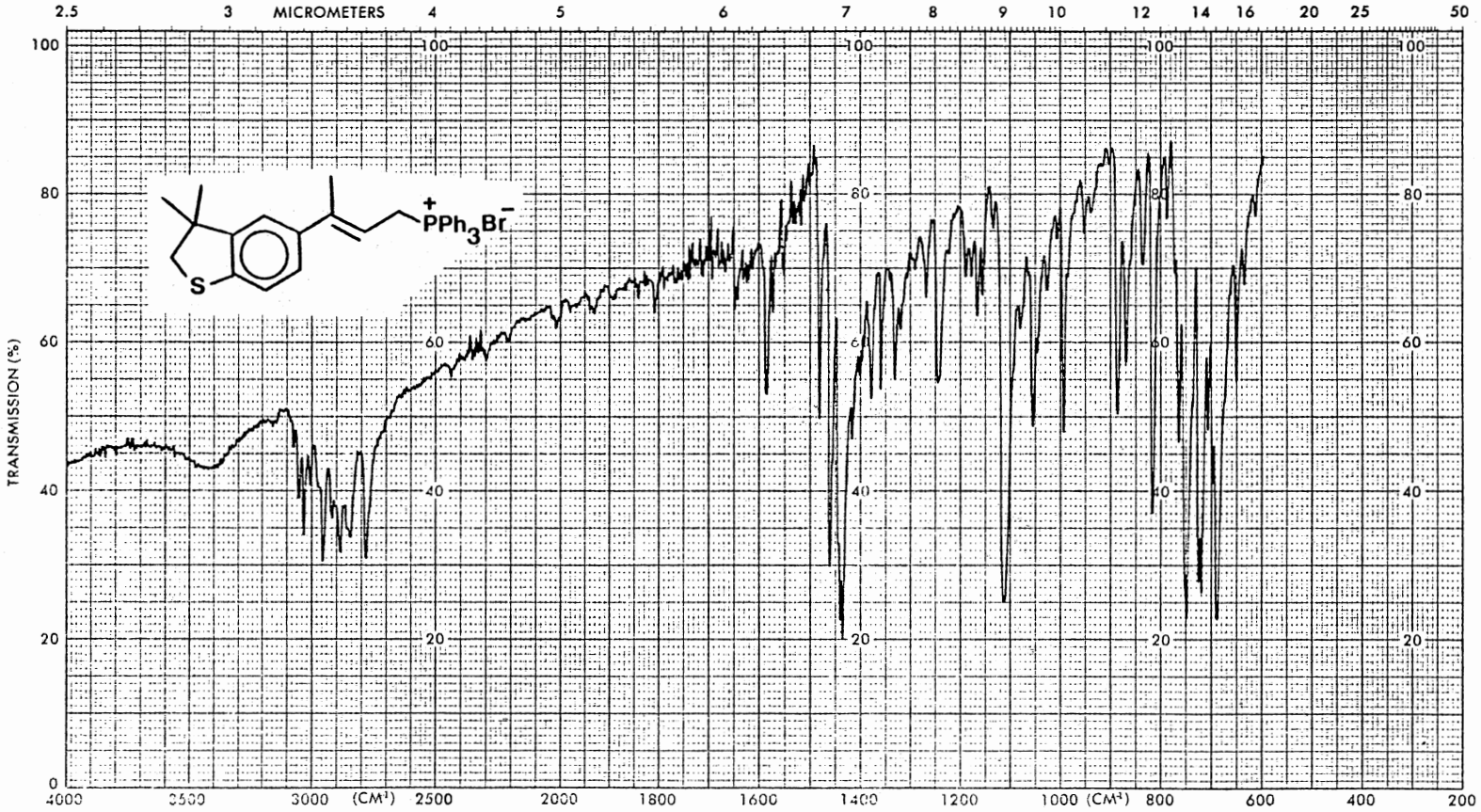
DECOUPLE Nucleus 1.500 Offset 170.2 Hz
Mode YYY Power 0 db
Modulation Mode S Freq 7900 Hz
Pulse Width 17.5 µsec Power Mode ——

^{13}C NMR Spectrum of **133**

PLOT/PROCESSING FN 64 K RE —— sec CD —— sec
LB 2.000 Hz AF —— sec CCD ——
Width 20000.0 Hz/ppm Start −893.6 Hz/ppm
Reference

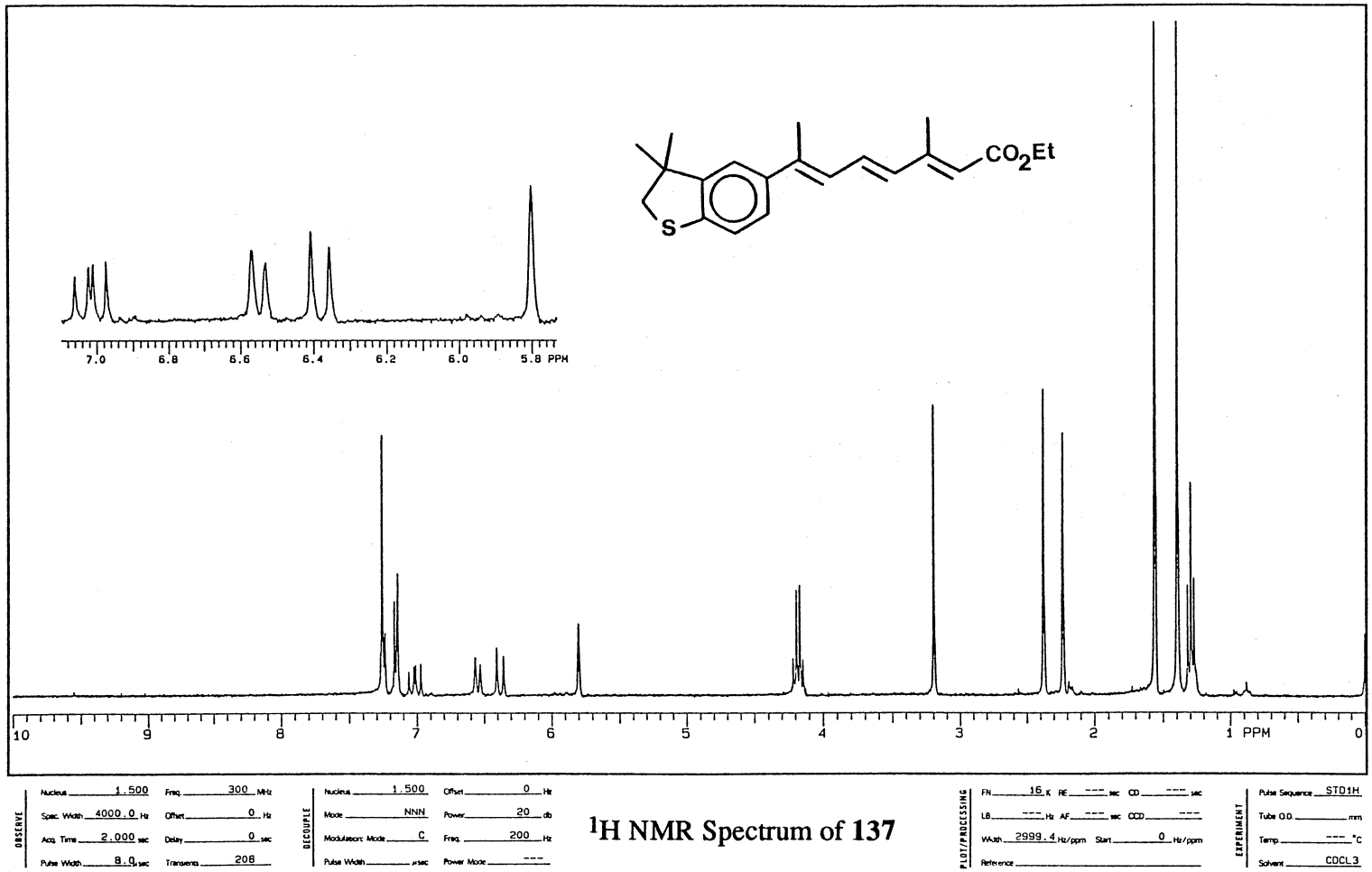
EXPERIMENT Pulse Sequence STD13C
Tube O.D. —— mm
Temp. —— °C
Solvent CDCL3

PLATE CXXXVII



IR Spectrum of **133**-KBr

PLATE CXXXVIII



OBSERVE: Nucleus 1.500, Freq. 300 MHz; Spec. Width 4000.0 Hz, Offset 0 Hz; Acq. Time 2.000 sec, Delay 0 sec; Pulse Width 8.0 µsec, Transients 208

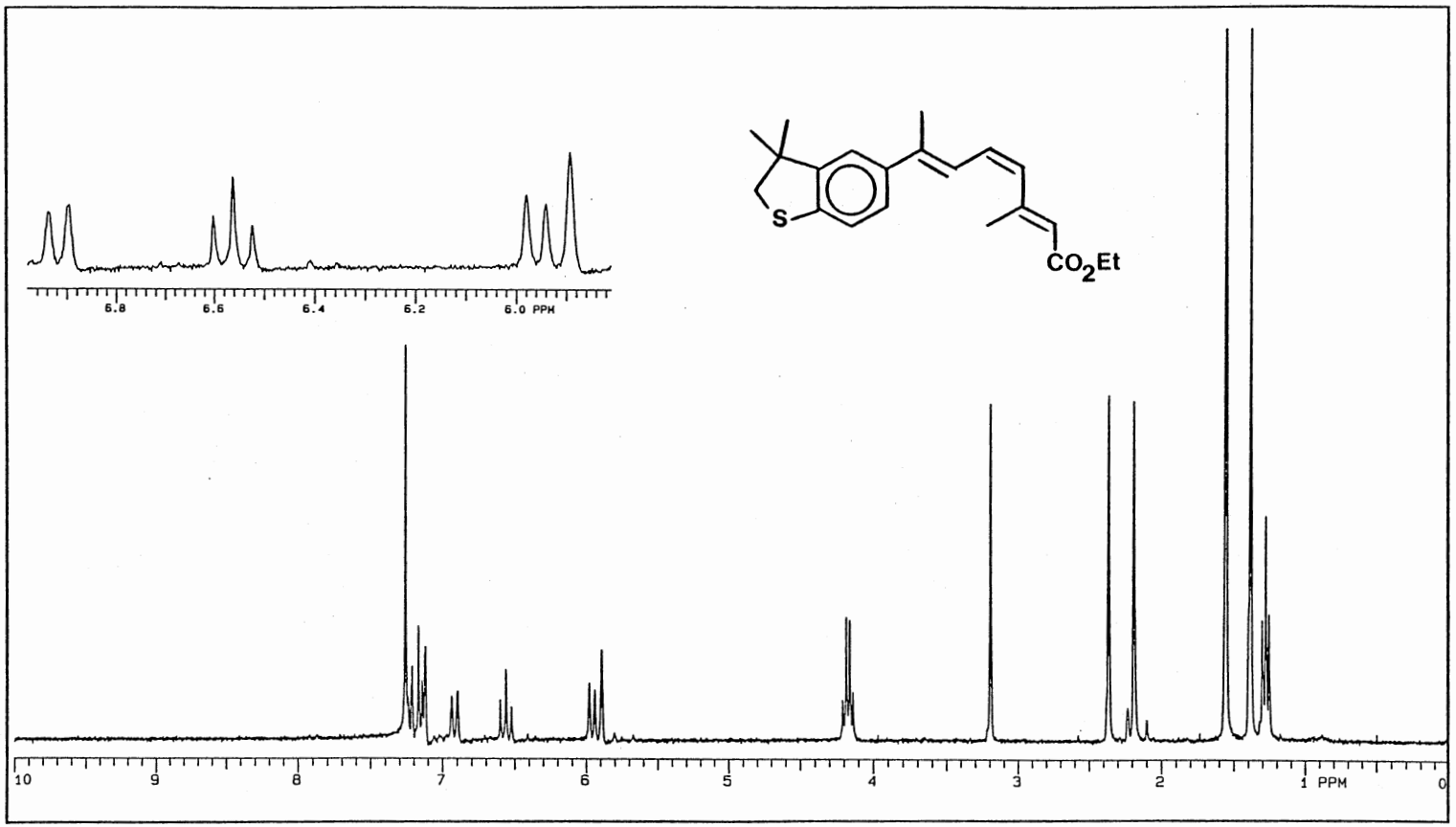
DECOUPLE: Nucleus 1.500, Offset 0 Hz; Mode NNN, Power 20 db; Modulation Mode C, Freq. 200 Hz; Pulse Width µsec, Power Mode ---

PLOT/PROCESSING: FN 16 K, RE --- sec, CD --- sec; LB --- Hz, AF --- sec, CCD ---; Width 2999.4 Hz/ppm, Start 0 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence STD1H; Tube O.D. mm; Temp. --- °C; Solvent CDCL3

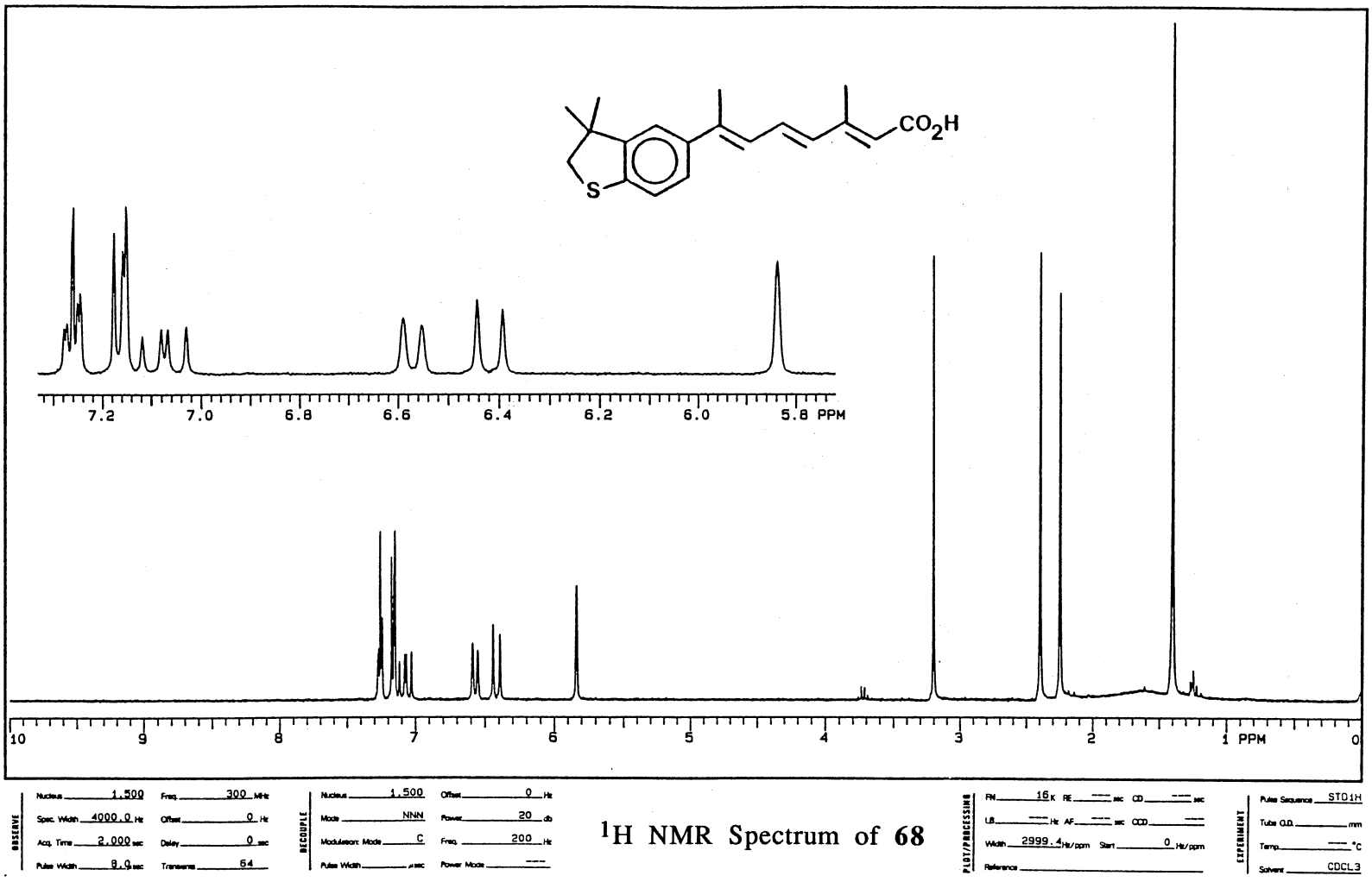
^{1}H NMR Spectrum of **137**

PLATE CXXXIX



^{1}H NMR Spectrum of **138**

PLATE CXXXX



OBSERVE: Nucleus 1.500 Freq 300 MHz; Spec. Width 4000.0 Hz Offset 0 Hz; Acq. Time 2.000 sec Delay 0 sec; Pulse Width 8.9 sec Transients 64

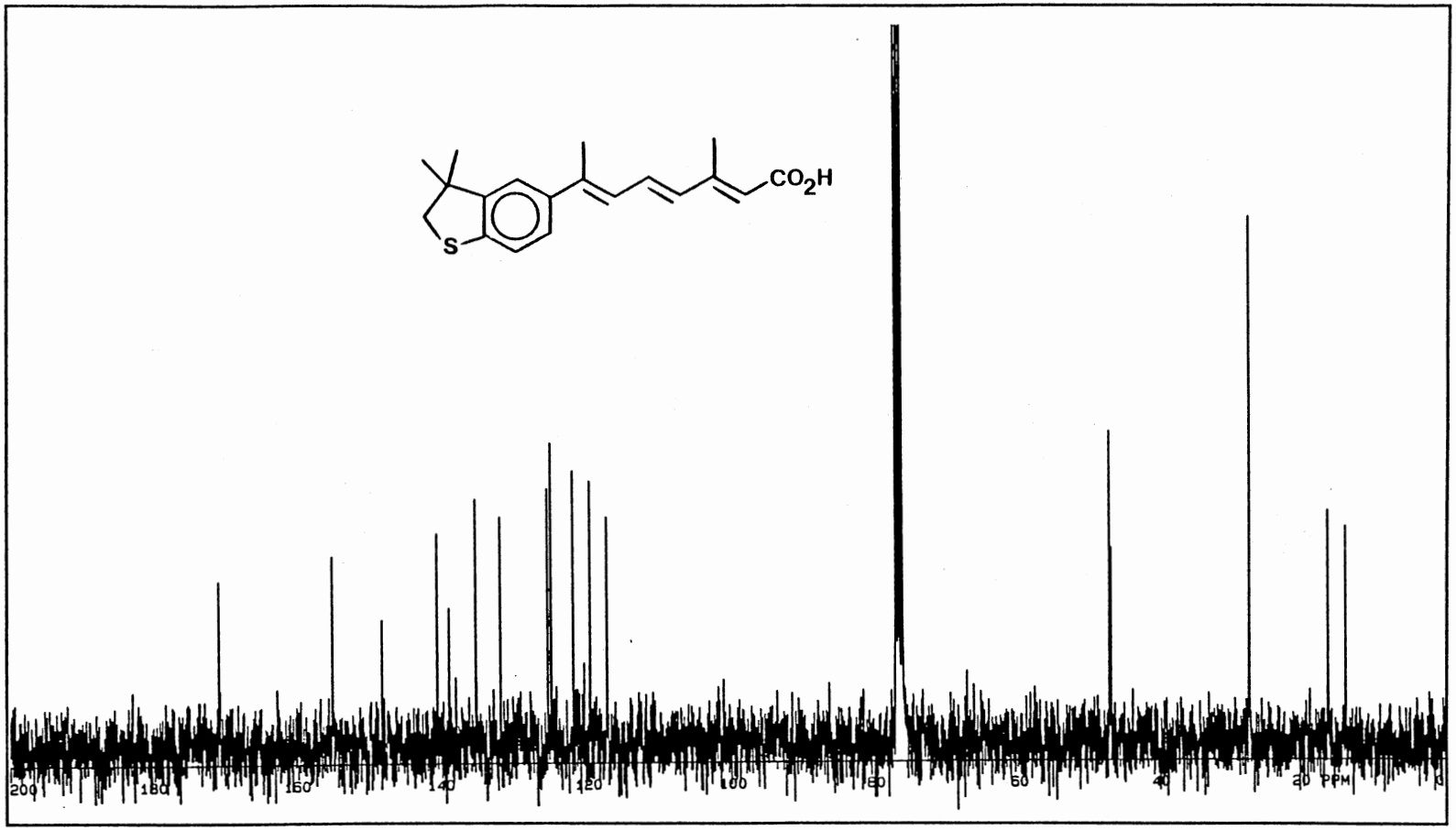
DECOUPLE: Nucleus 1.500 Offset 0 Hz; Mode NNN Power 20 db; Modulation Mode C Freq 200 Hz; Pulse Width ___ μsec Power Mode ---

^{1}H NMR Spectrum of **68**

PLOT/PROCESSING: FN 16K RE ___ sec CD ___ sec; LB ___ Hz AF ___ sec CDD ___; Width 2999.4 Hz/ppm Start 0 Hz/ppm; Reference ___

EXPERIMENT: Pulse Sequence STD1H; Tube O.D. ___ mm; Temp. ___ °C; Solvent CDCL3

PLATE CXXXXI



OBSERVE Nucleus 13.500 Freq. 75 MHz
Spec. Width 20000.0 Hz Offset 1506 Hz
Acq. Time 1.000 sec Delay 3.000 sec
Pulse Width 12.0 sec Transients 1024

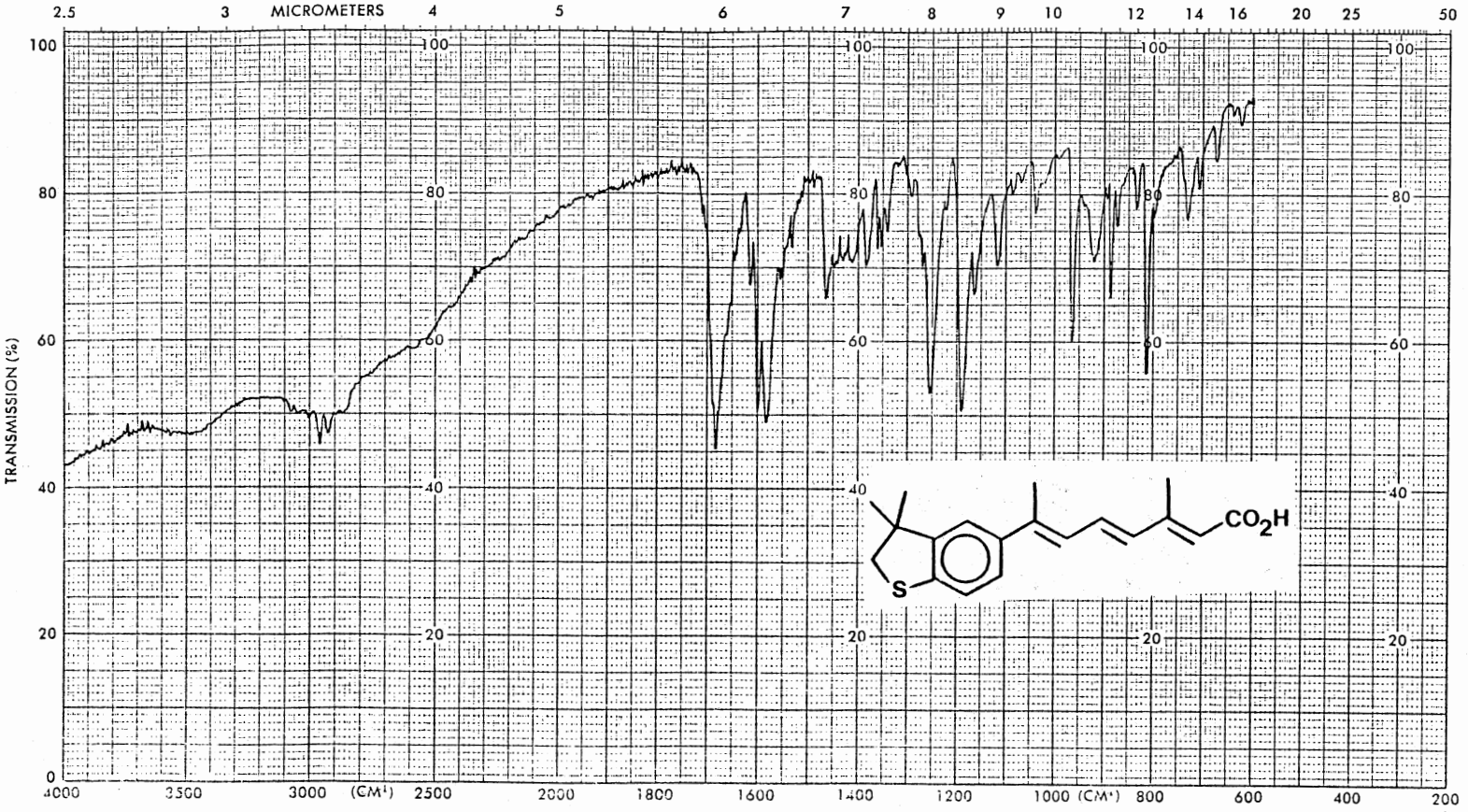
DECOUPLE Nucleus 1.500 Offset 470.3 Hz
Mode YYY Power 0 db
Modulation Mode 0 Freq. 7900 Hz
Pulse Width 17.5 sec Power Mode

^{13}C NMR Spectrum of **68**

PLOT/PROCESSING FN 64 K RE sec CD sec
LB 2.000 Hz AF sec CCD
Width 15085.9 Hz/ppm Start 0 Hz/ppm
Reference

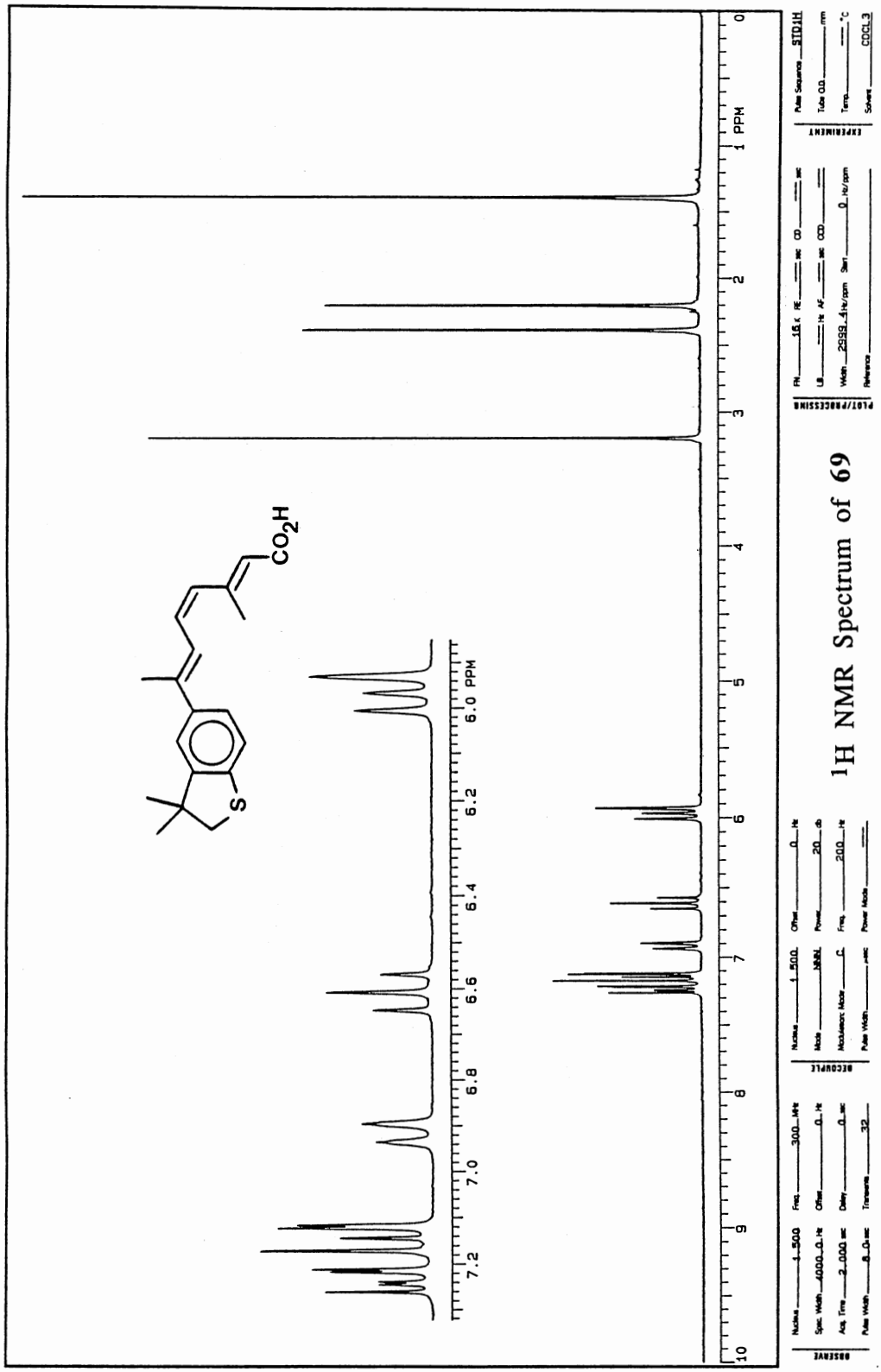
EXPERIMENT Pulse Sequence STD13C
Tube O.D. mm
Temp. °C
Solvent CDCL3

PLATE CXXXXII



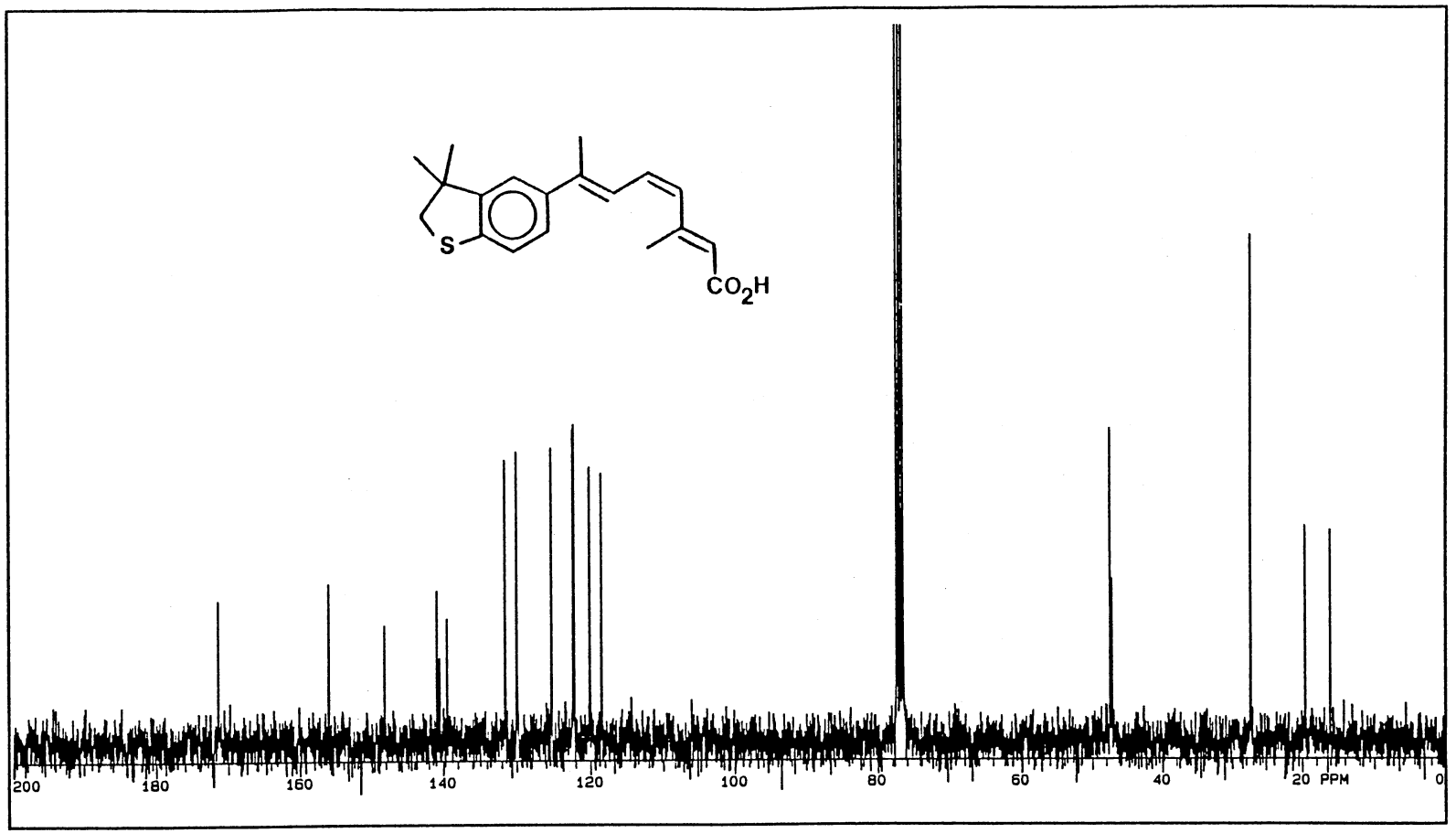
IR Spectrum of **68** -KBr

PLATE CXXXXIII



^{1}H NMR Spectrum of **69**

PLATE CXXXXIV



OBSERVE Nucleus 13.500 Freq. 75 MHz
Spec. Width 20000.0 Hz Offset 1500 Hz
Acq. Time 1.000 sec Delay 3.000 sec
Pulse Width 12.0 µsec Transients 448

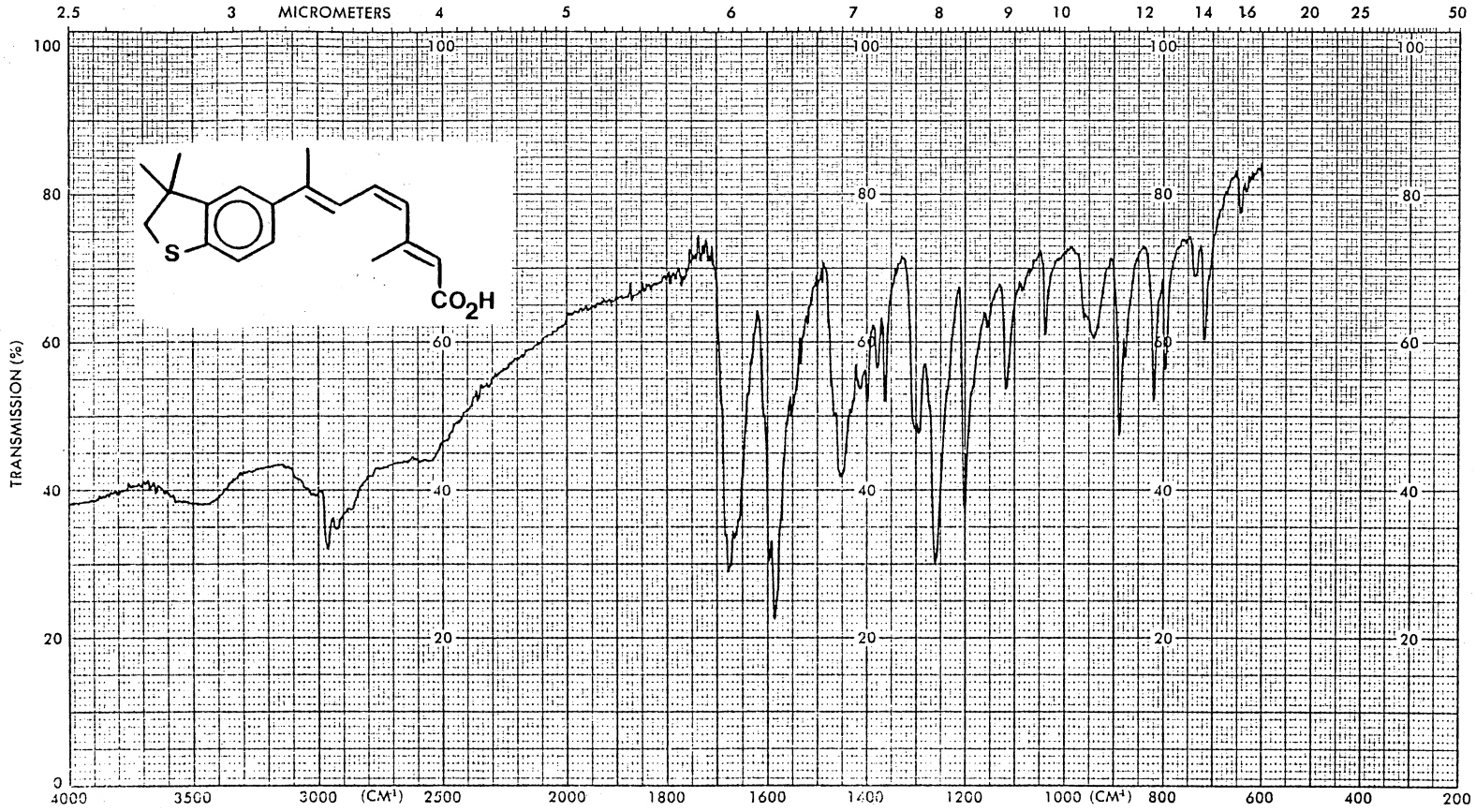
DECOUPLE Nucleus 1.500 Offset 170.2 Hz
Mode YYY Power 0 db
Modulation Mode 9 Freq. 7900 Hz
Pulse Width 17.5 µsec Power Mode —

^{13}C NMR Spectrum of **69**

PLOT/PROCESSING FN 64 K RE — sec CD — sec
LB 2.000 Hz AF — sec CCD —
Width 15085.9 Hz/ppm Start 0 Hz/ppm
Reference

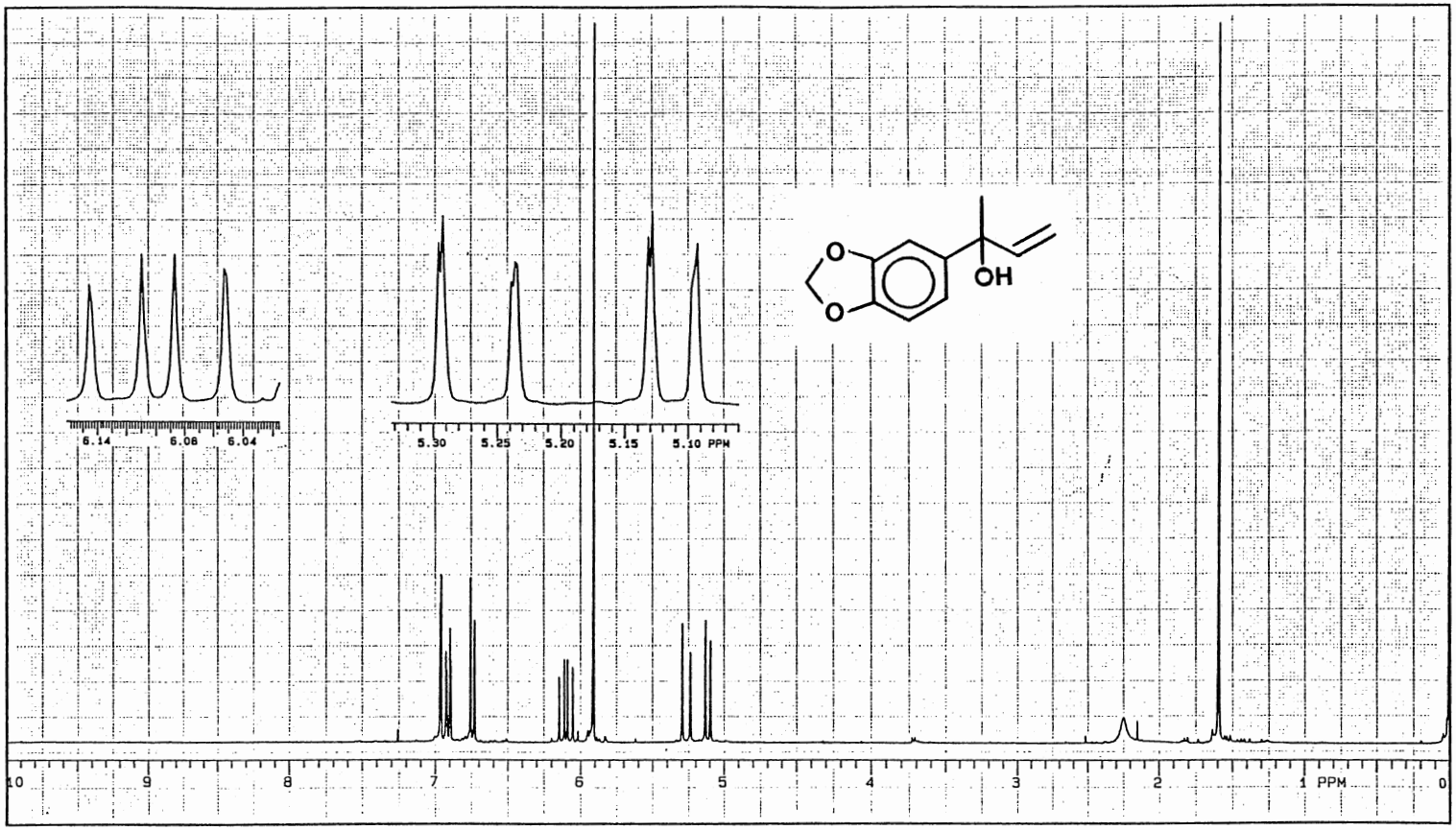
EXPERIMENT Pulse Sequence STD13C
Tube O.D. — mm
Temp. — °C
Solvent CDCL3

PLATE CXXXXV



IR Spectrum of **69** -KBr

PLATE CXXXXVI



OBSERVE: Nucleus 1.500 Freq 300 MHz; Spec. Width 4000.0 Hz Offset 100 Hz; Acq. Time 2.000 sec Delay 0 sec; Pulse Width 5.0 µsec Transients 16

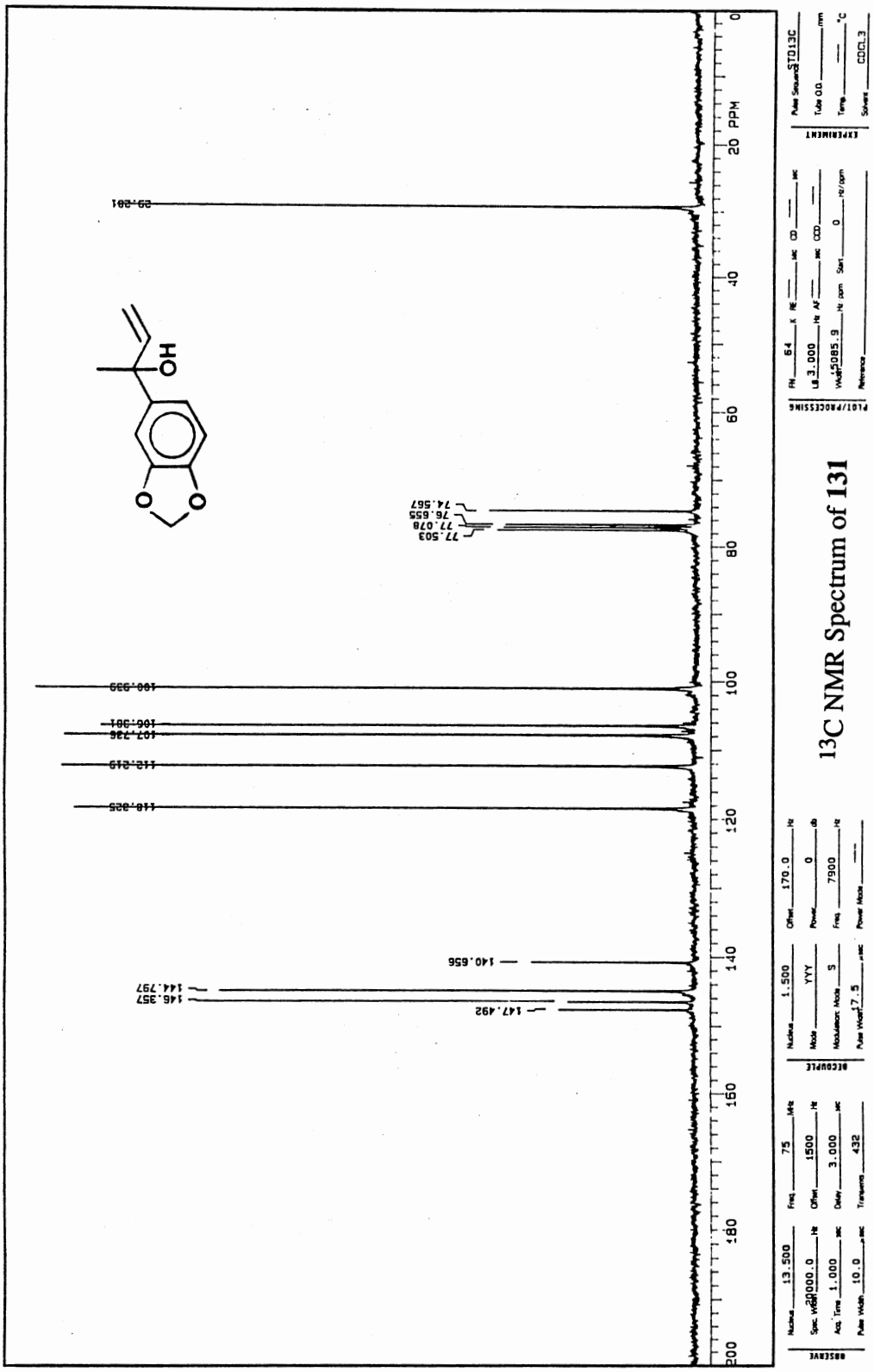
DECOUPLE: Nucleus 1.500 Offset 0 Hz; Mode NNN Power 20 db; Modulation Mode C Freq 200 Hz; Pulse Width µsec Power Mode ---

PLOT/PROCESSING: FN 16 K RE --- sec CD --- sec; LB --- Hz AF --- sec CCD ---; Width 2999.4 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence STD1H; Tube O.D. mm; Temp. --- °C; Solvent CDCl3

^{1}H NMR Spectrum of **131**

PLATE CXXXXVII

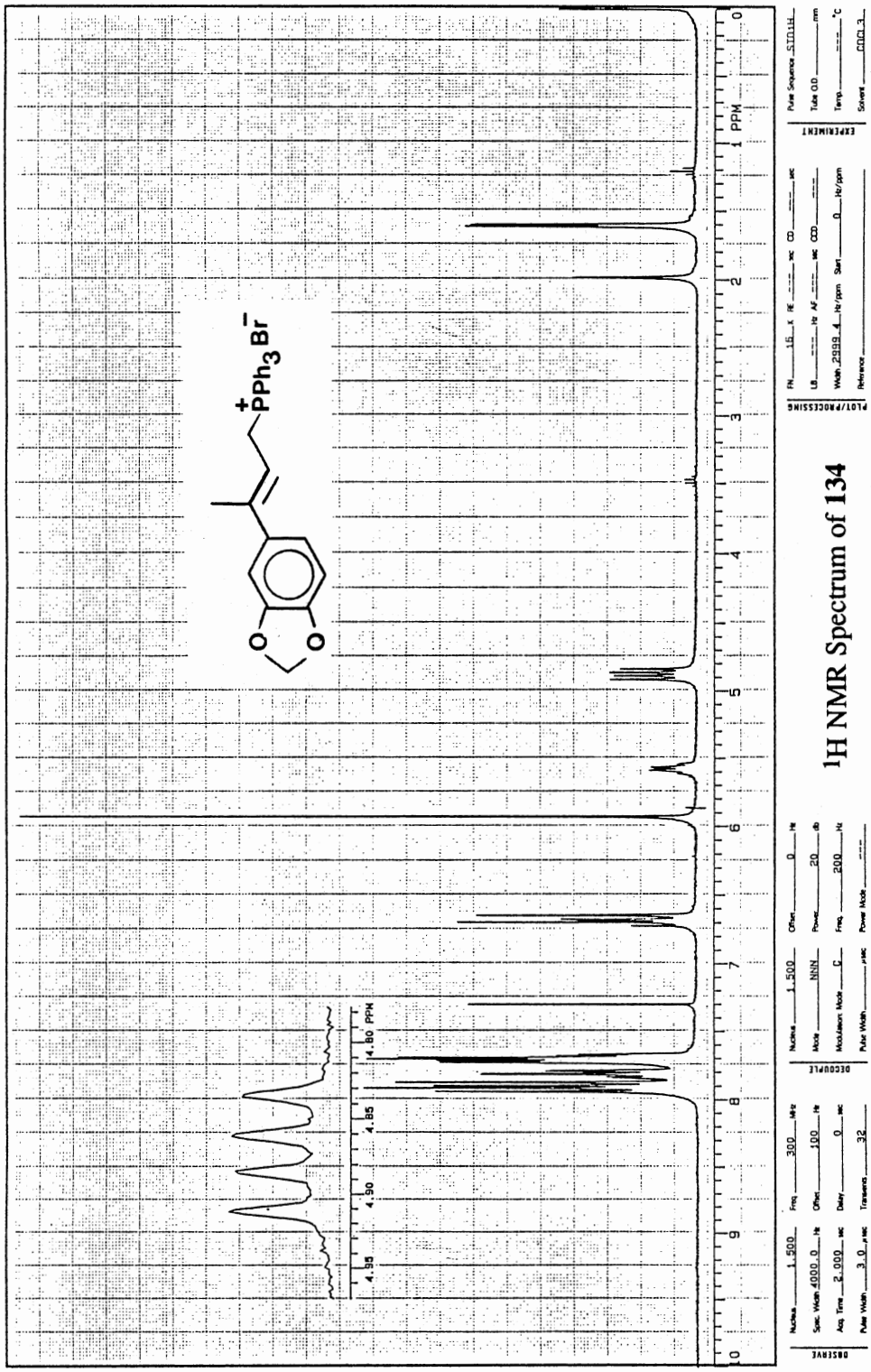


^{13}C NMR Spectrum of **131**

PLATE CXXXXVIII

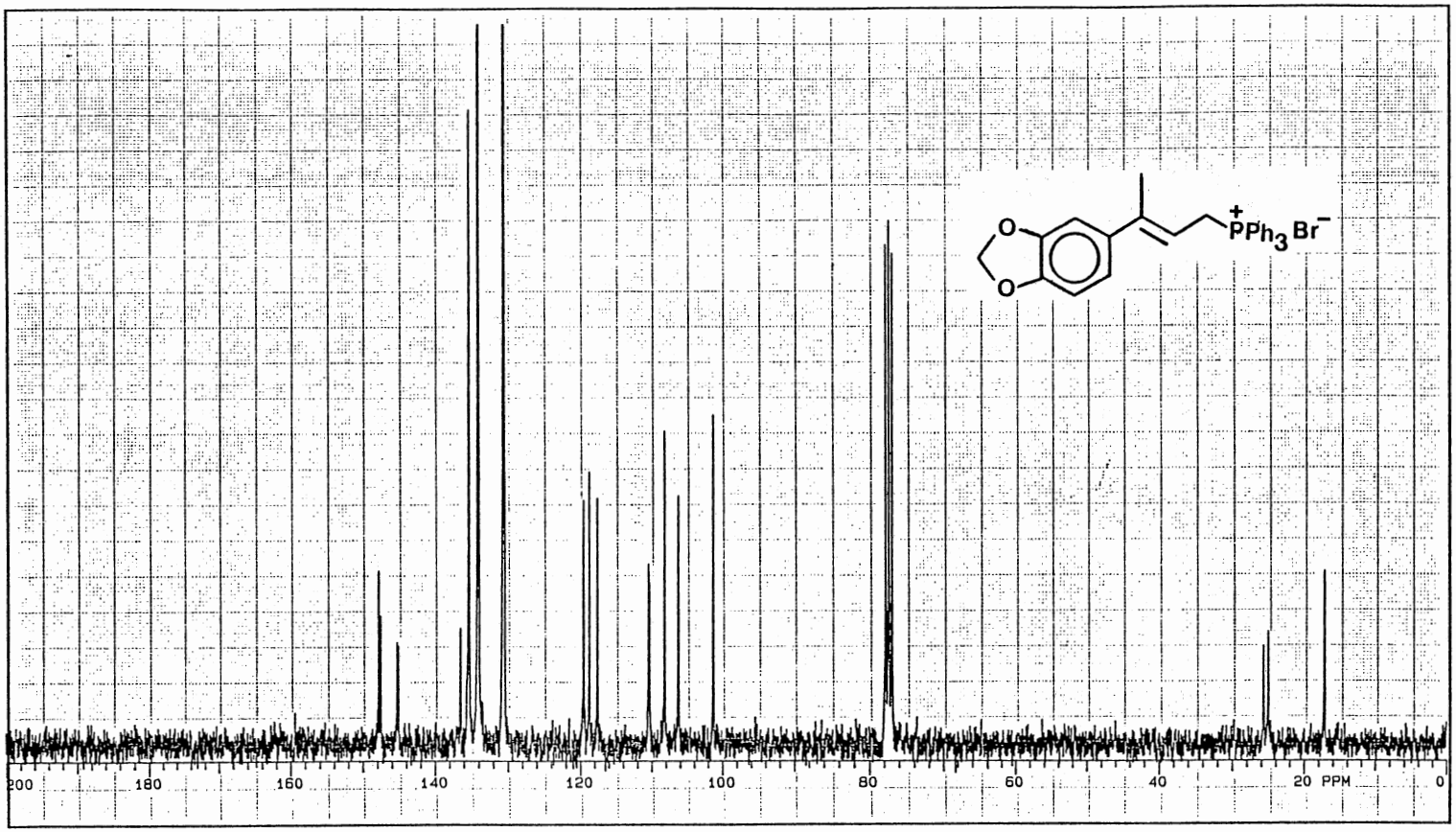
IR Spectrum of **131**

PLATE CIL



^{1}H NMR Spectrum of **134**

PLATE CL



OBSERVE Nucleus 13.500 Freq 75 MHz; Spec. Wid 20000.0 Hz Offset 1500 Hz; Acq. Time 1.000 sec Delay 3.000 sec; Pulse Width 10.0 μsec Transients 208

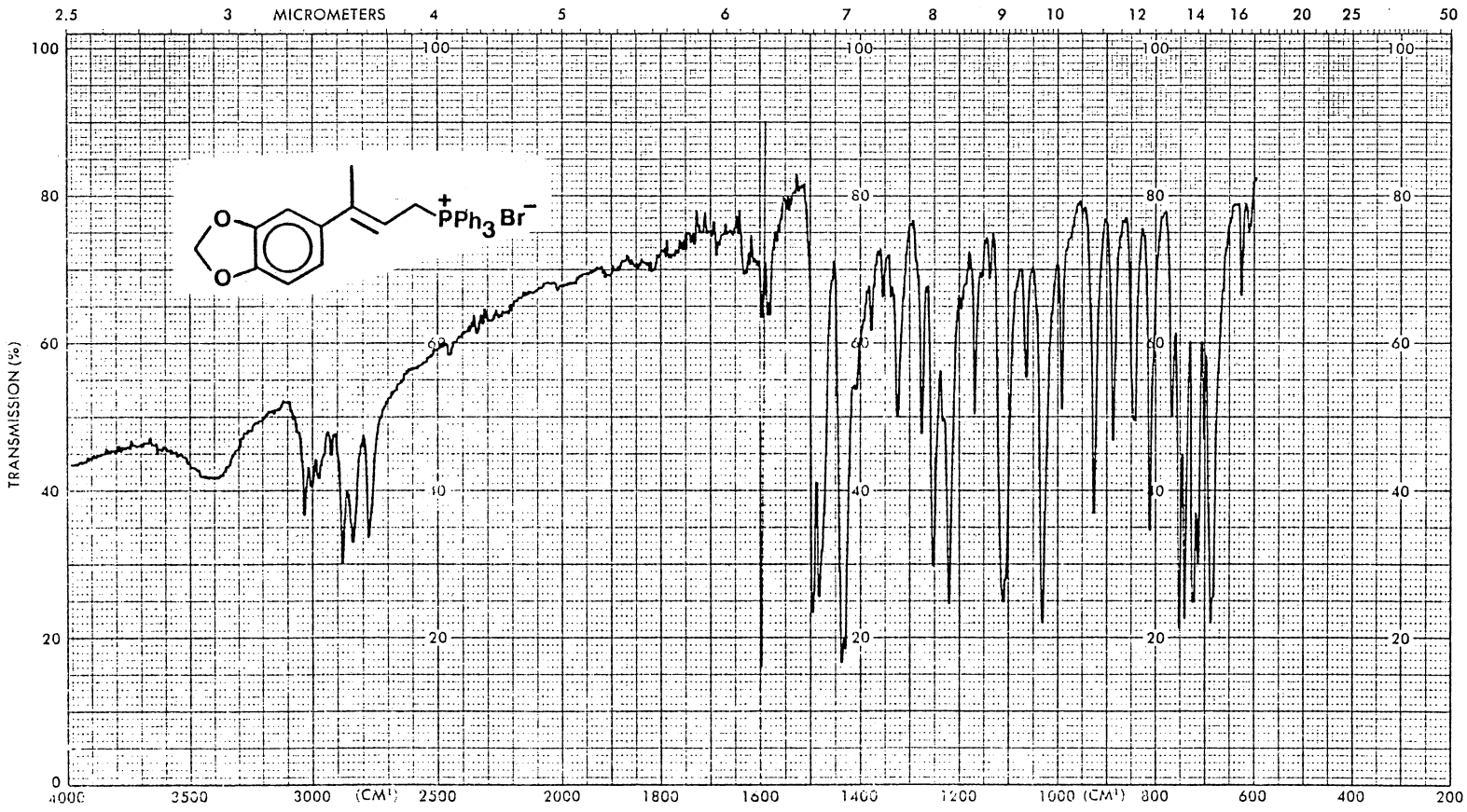
DECOUPLE Nucleus 1.500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation Mode S Freq 7900 Hz; Pulse Width 17.5 μsec Power Mode ---

PLOT/PROCESSING FN 64 K RE --- sec CD --- sec; LB 2.000 Hz AF --- sec CCD ---; Width 15085.9 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT Pulse Sequence ST013C; Tube O.D. mm; Temp --- °C; Solvent CDCL3

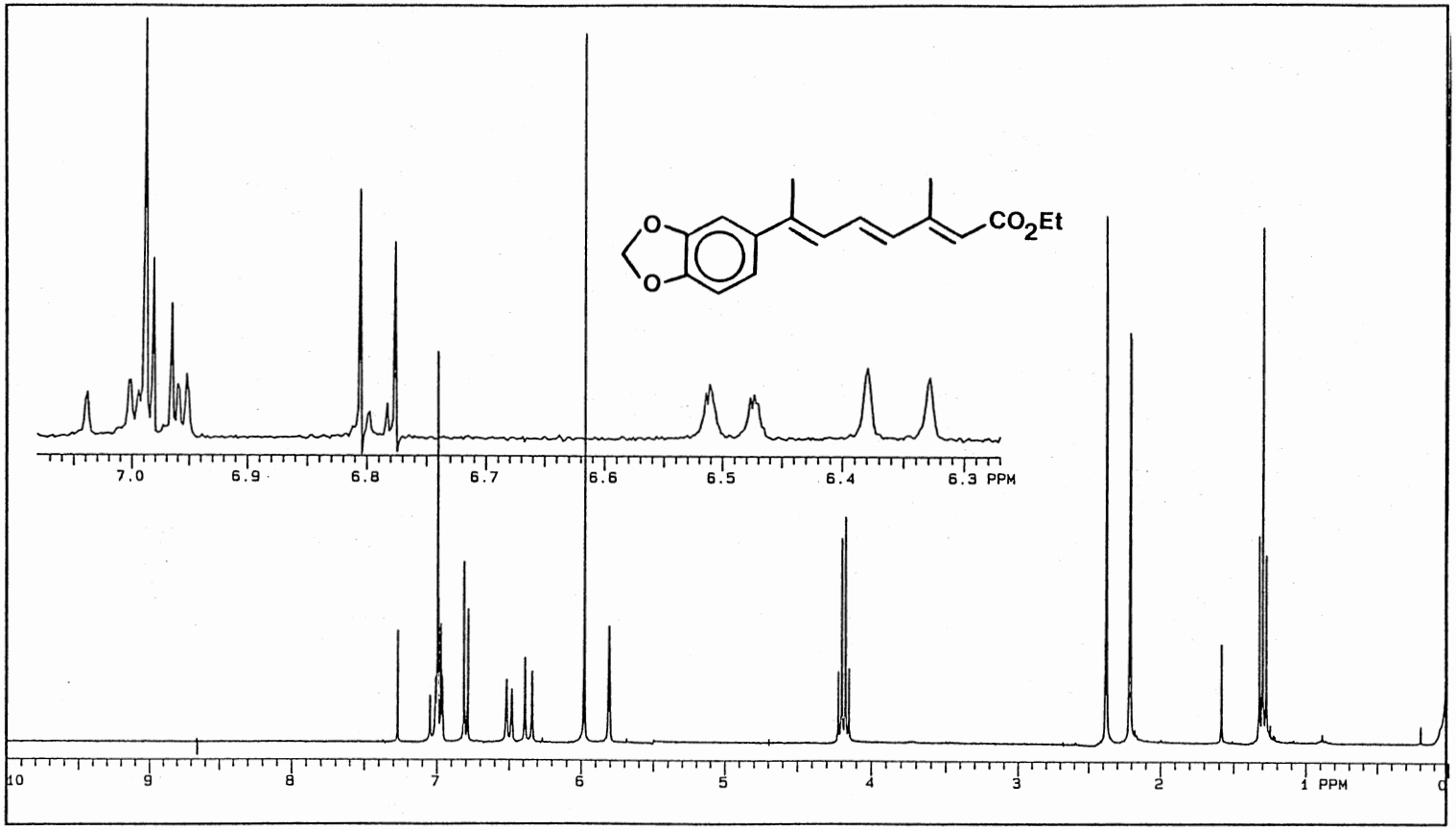
^{13}C NMR Spectrum of **134**

PLATE CLI



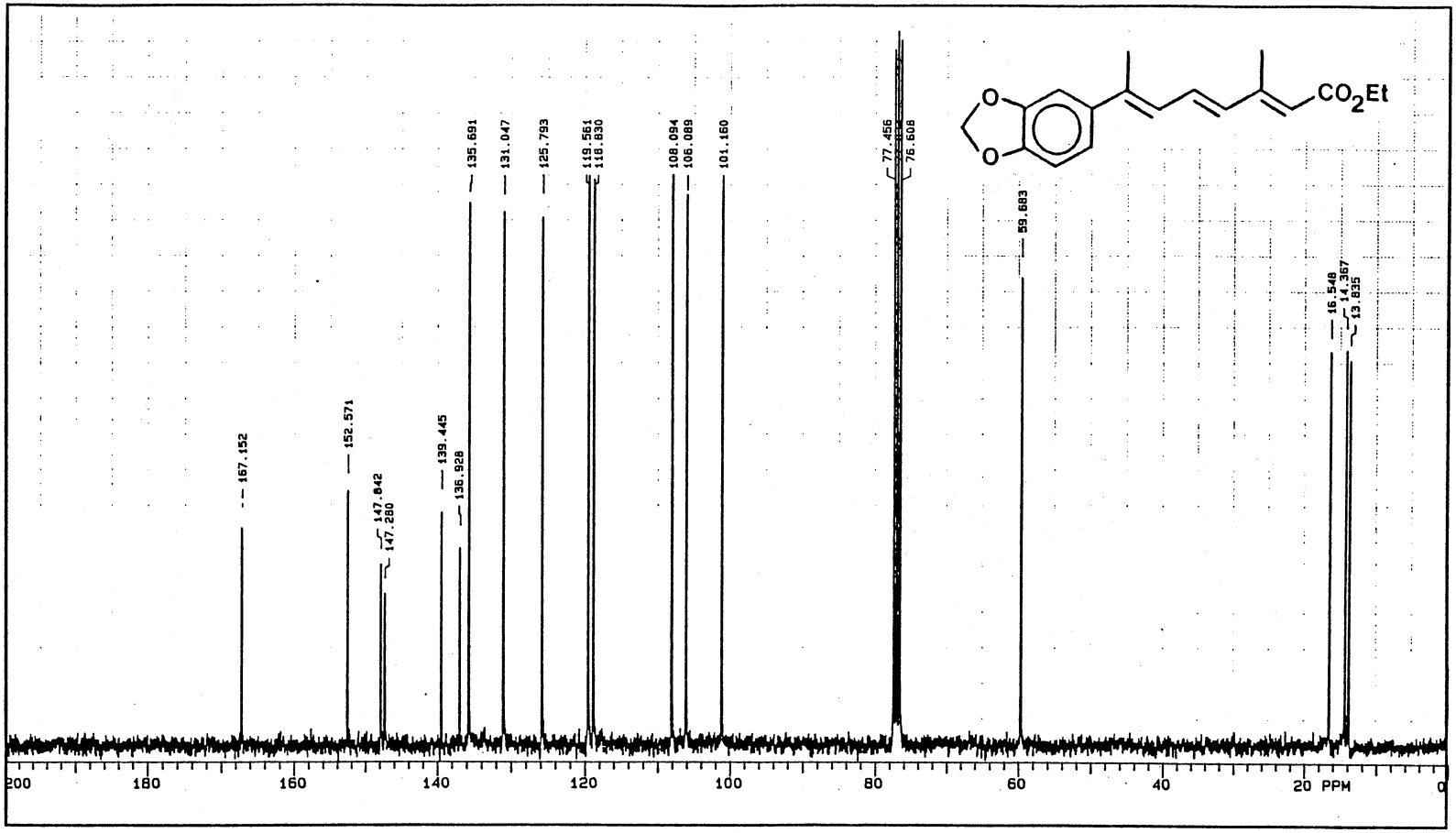
IR Spectrum of **134** -KBr

PLATE CLII



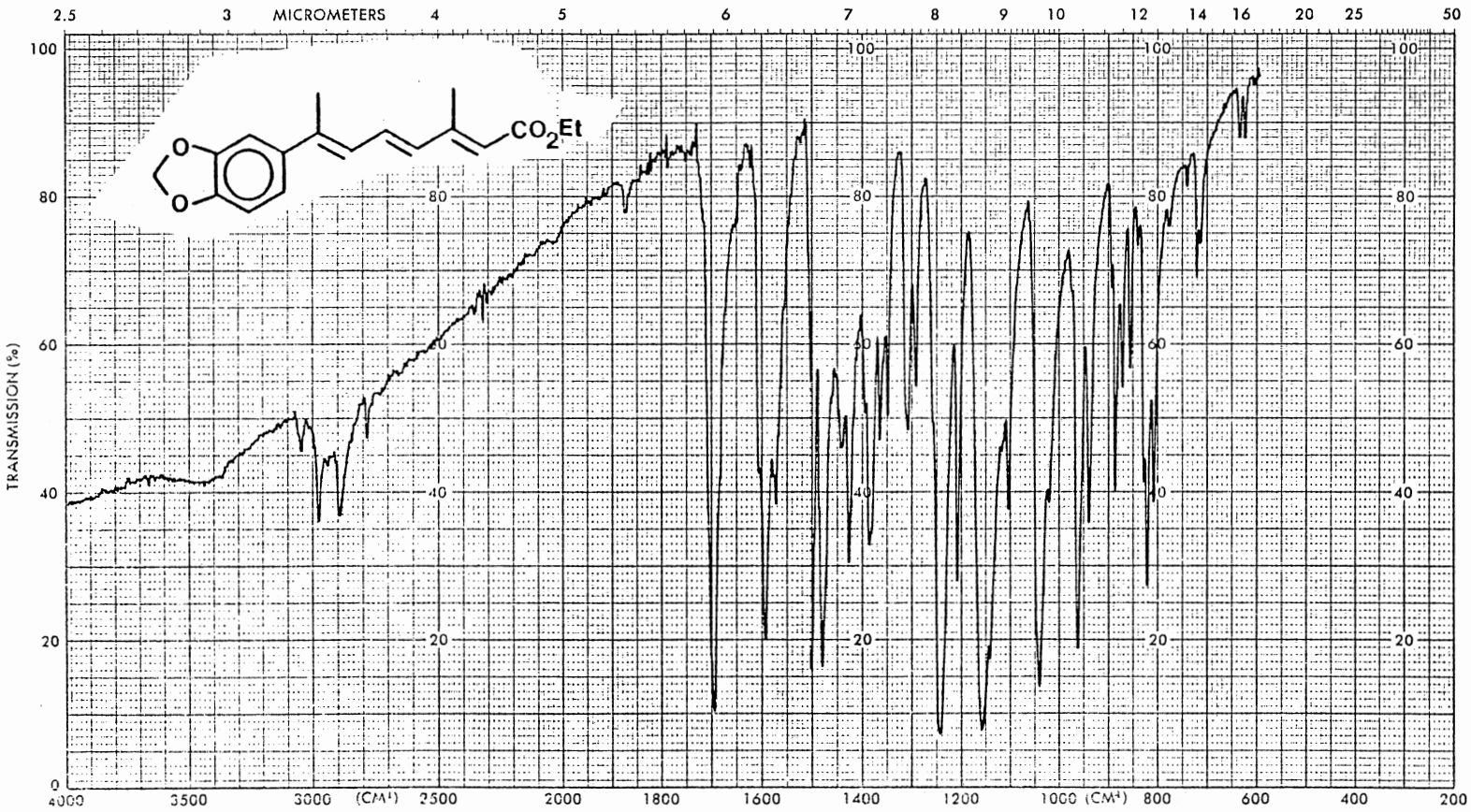
^{1}H NMR Spectrum of **70**

PLATE CLIII



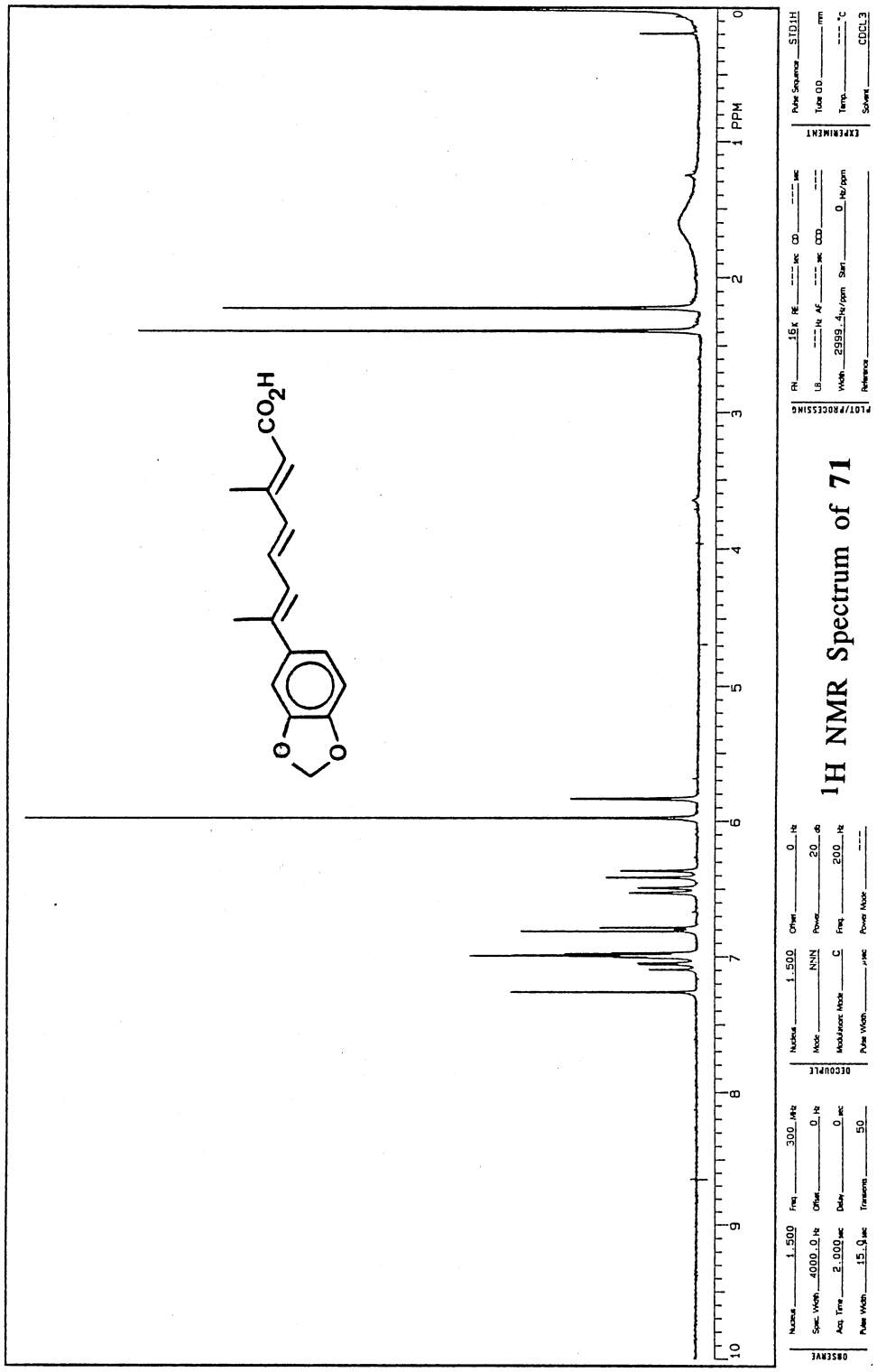
^{13}C NMR Spectrum of **70**

PLATE CLIV



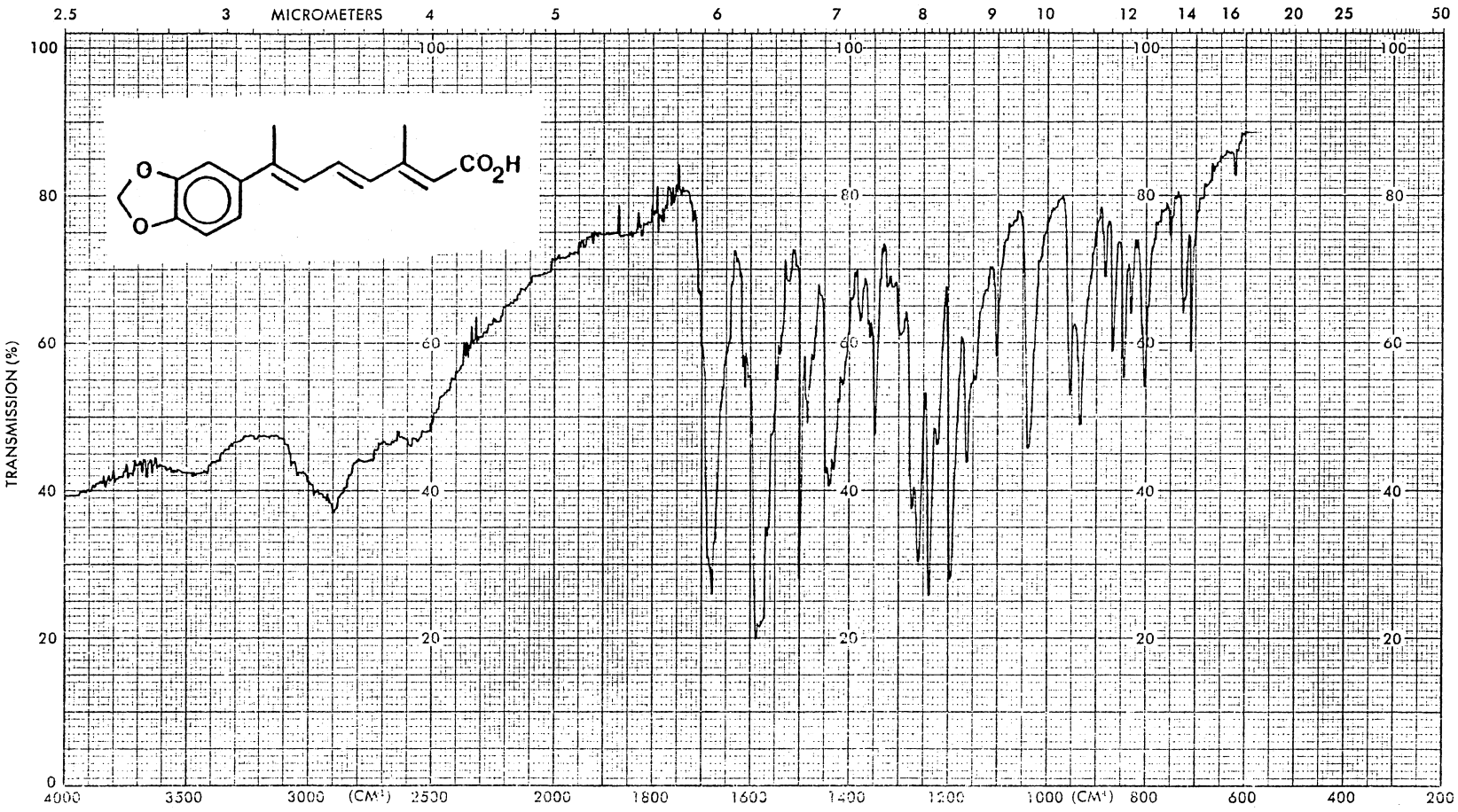
IR Spectrum of 70 -KBr

PLATE CLV



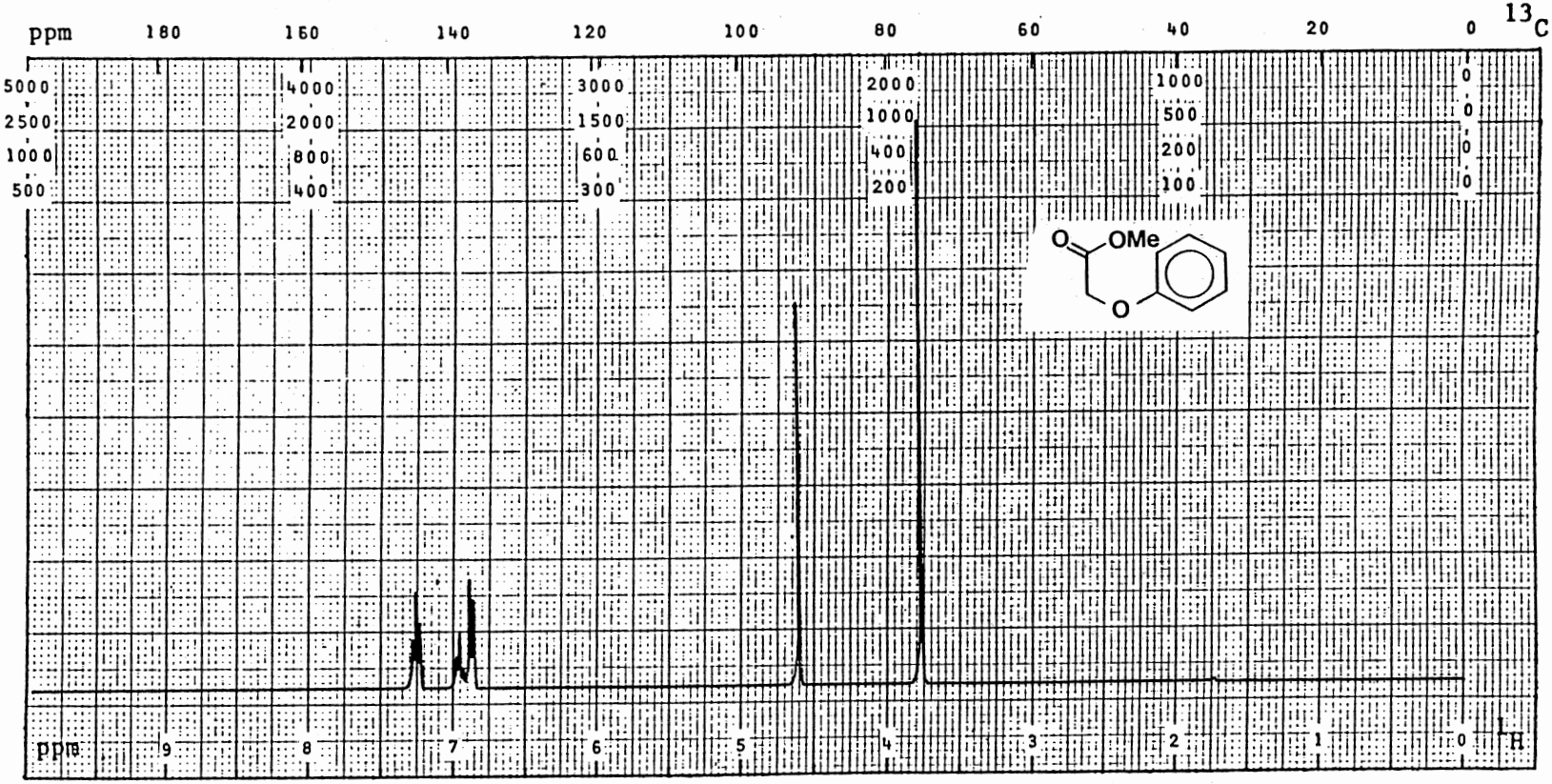
^{1}H NMR Spectrum of **71**

PLATE CLVI



IR Spectrum of **71** -KBr

PLATE CLVII



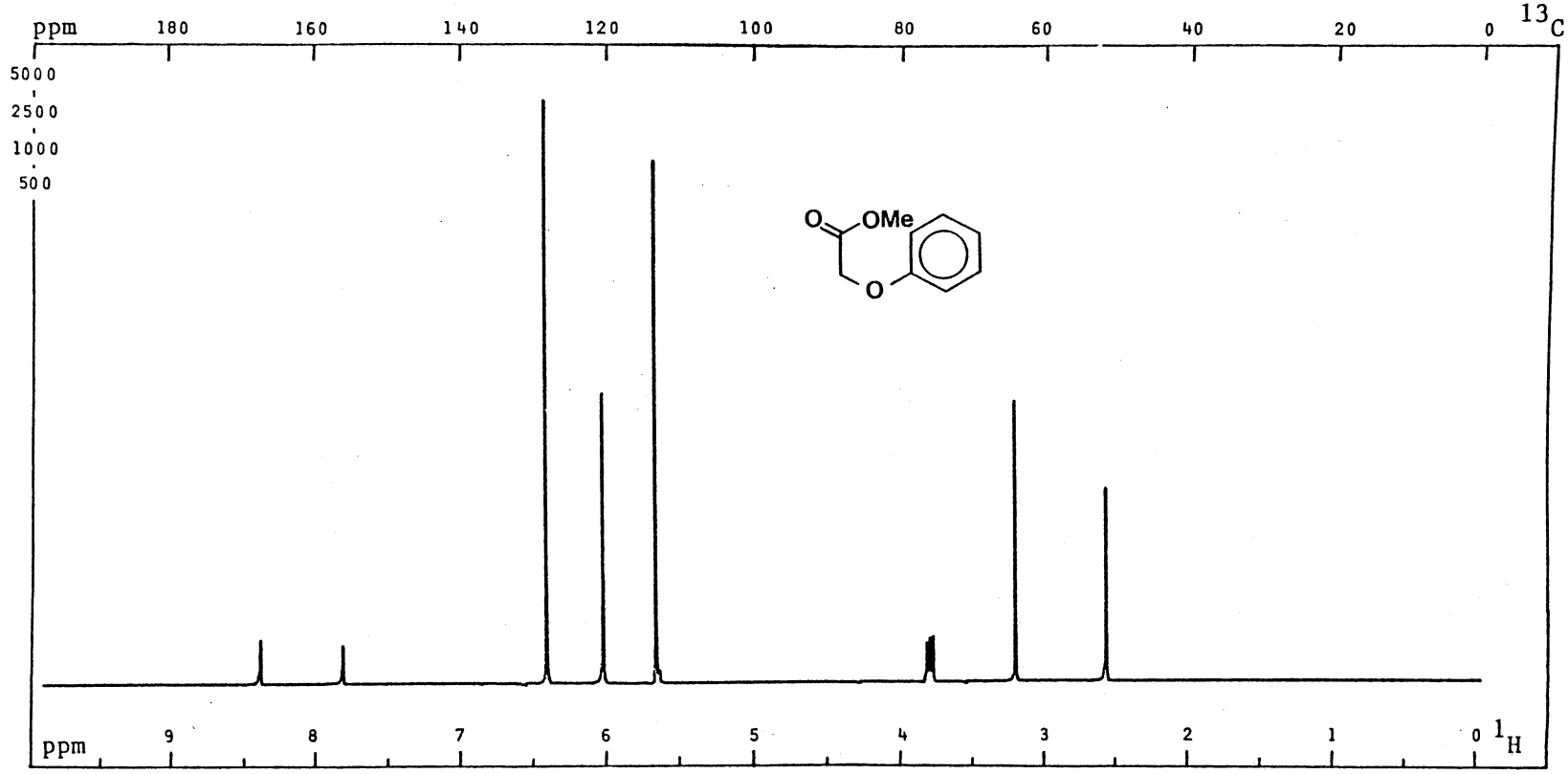
^{1}H NMR Spectrum of 73

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.94 MHz; WC: 2999.4 Hz; T: RT °C; NT: 4

Size: 4 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: Hz; Lock: ^{2}H ; D1,D5 : 0.5 s.

DC: Y, N ; Gated Off: A or D ; DO: 776.9 Hz; RF(Power): 15 W/dB; NBW:200 Hz; LB: Hz.

PLATE CLVIII



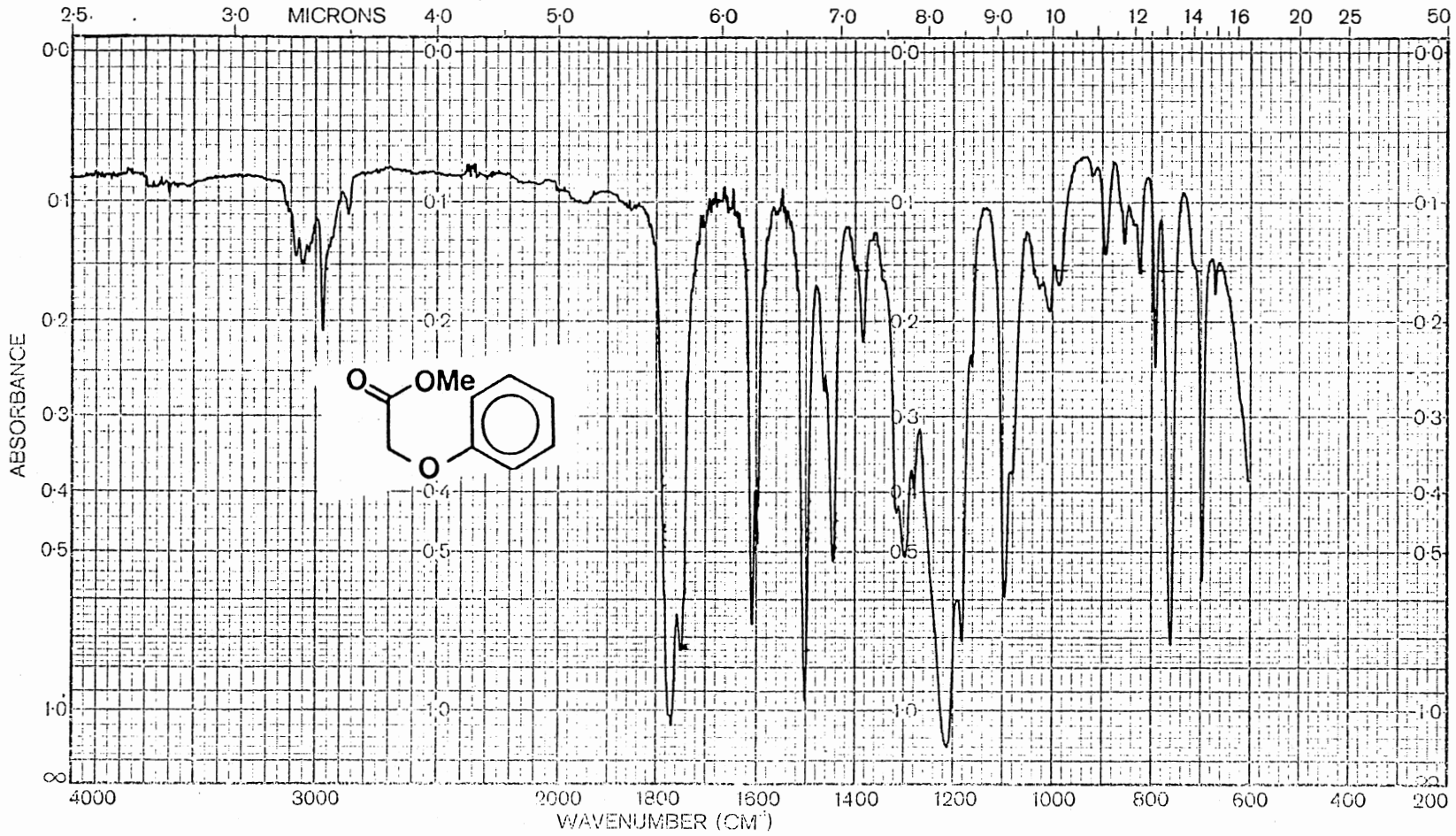
^{13}C NMR Spectrum of 73

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 44

Size: 20 K; PW/RF: 12.0 μs/dB; TO: 1000 Hz; FB: Hz; Lock: ^{2}H ; D1,D5: 4.0 s.

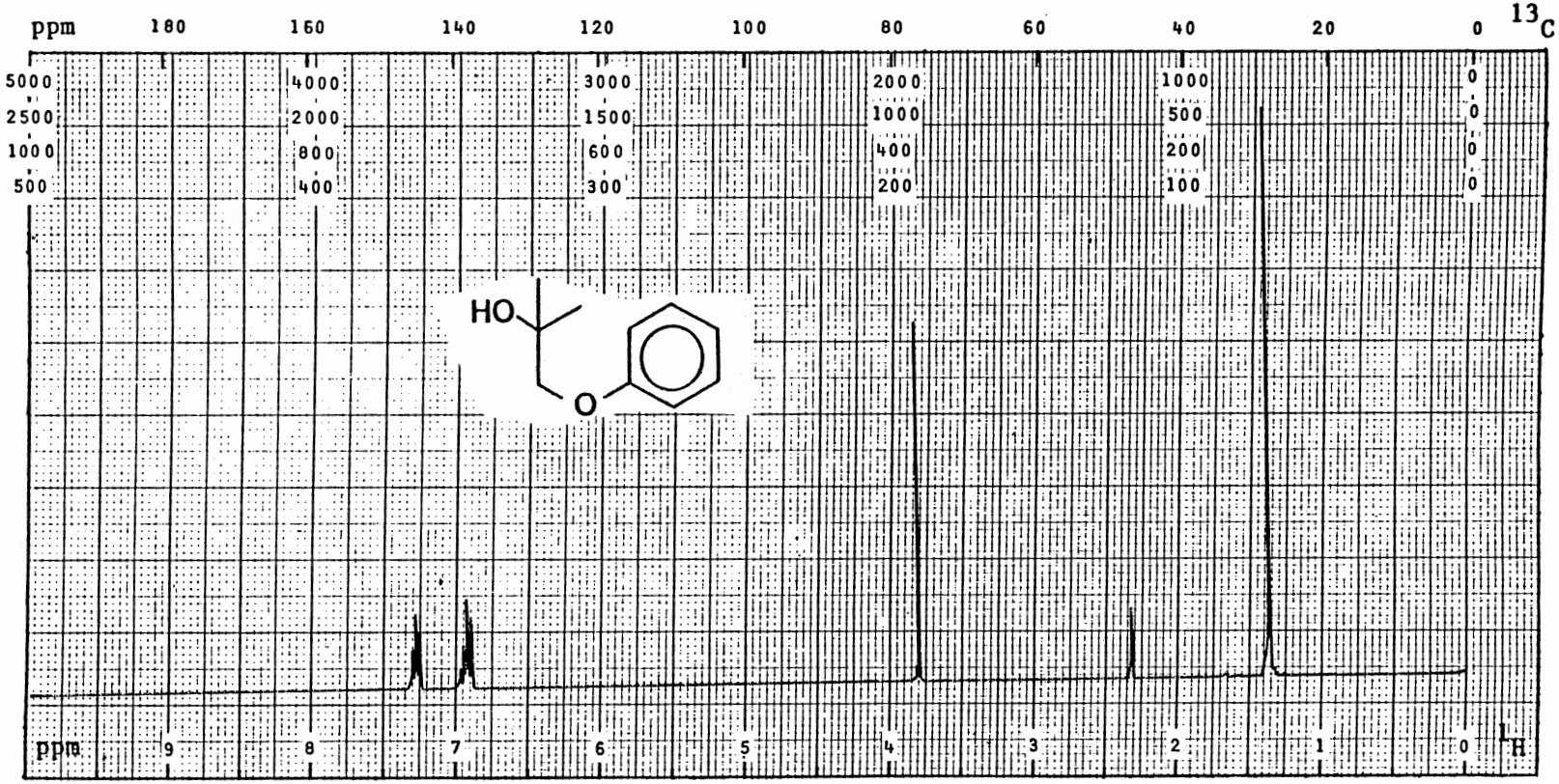
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 25 W/dB; NBW: 200 Hz; LB: 3.0 Hz.

PLATE CLIX



IR Spectrum of 73

PLATE CLX



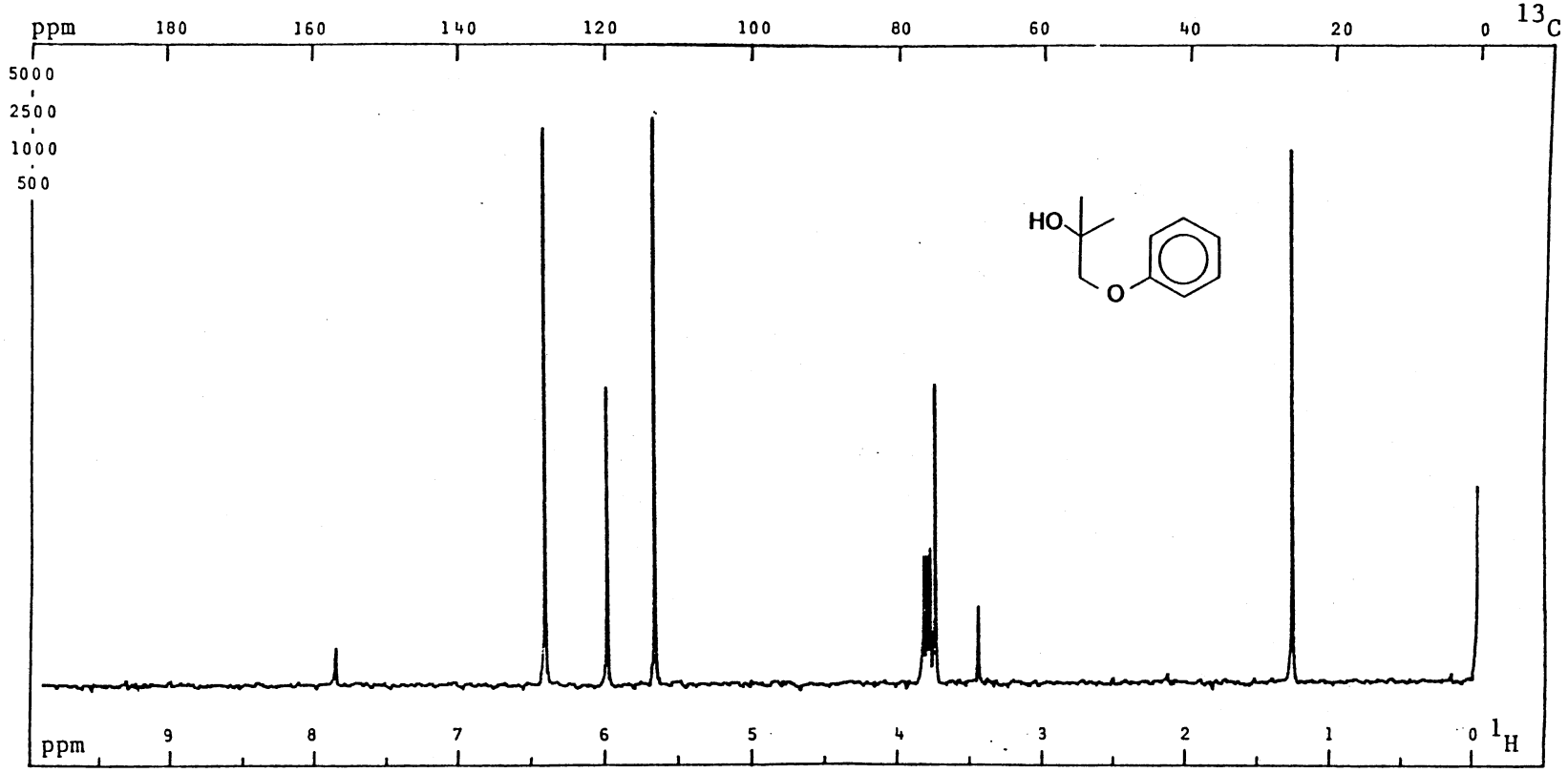
^{1}H NMR Spectrum of **74**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.4 MHz; WC:2999.4 Hz; T: RT °C; NT: 4

Size:4K K; PW/RF:5.0 µs/dB; TO:0 Hz; FB: Hz; Lock: ^{2}H ; D1,D5 : 0.5 s.

DC: Y, N ; Gated Off: A or D ; DO: 776.9 Hz; RF(Power):15 W/dB; NBW:200 Hz; LB: Hz.

PLATE CLXI



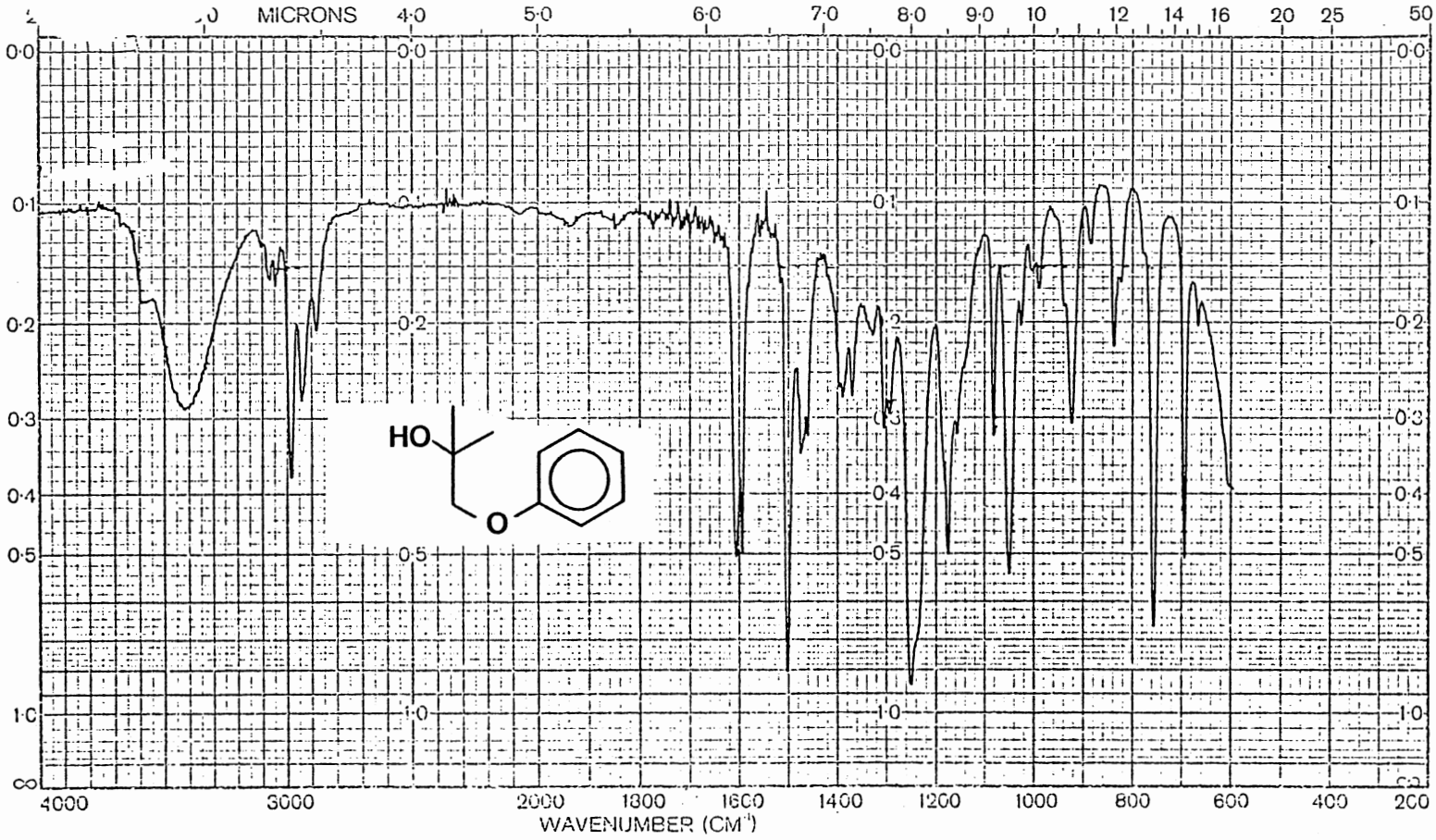
^{13}C NMR Spectrum of **74**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC:15085.9 Hz; T: RT °C; NT: 400

Size: 20K K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: Hz; Lock: ^2H ; D1,D5: 4.0 s.

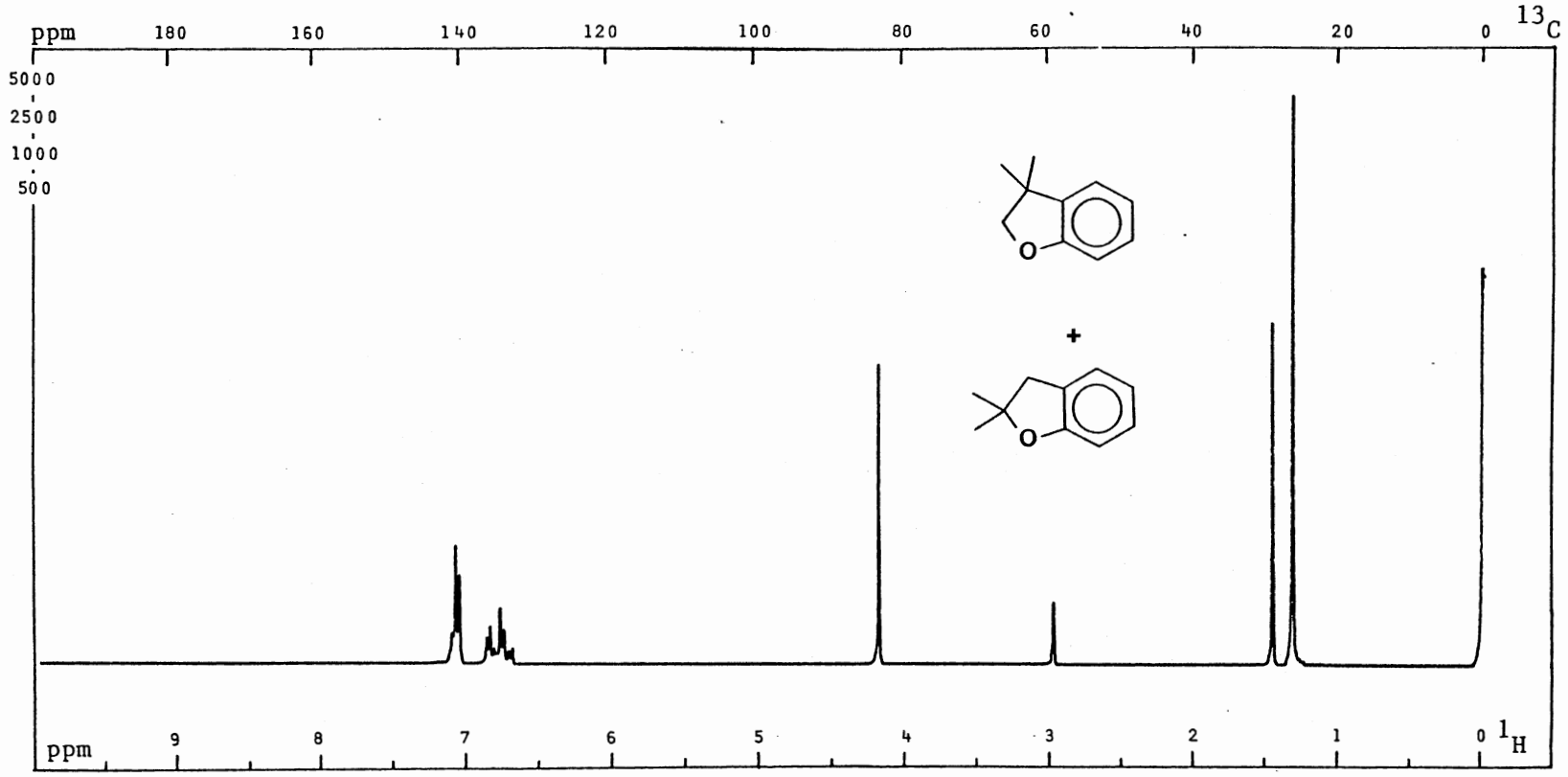
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 25 W/dB; NBW: 200 Hz; LB: 3.0 Hz.

PLATE CLXII



IR Spectrum of **74**

PLATE CLXIII



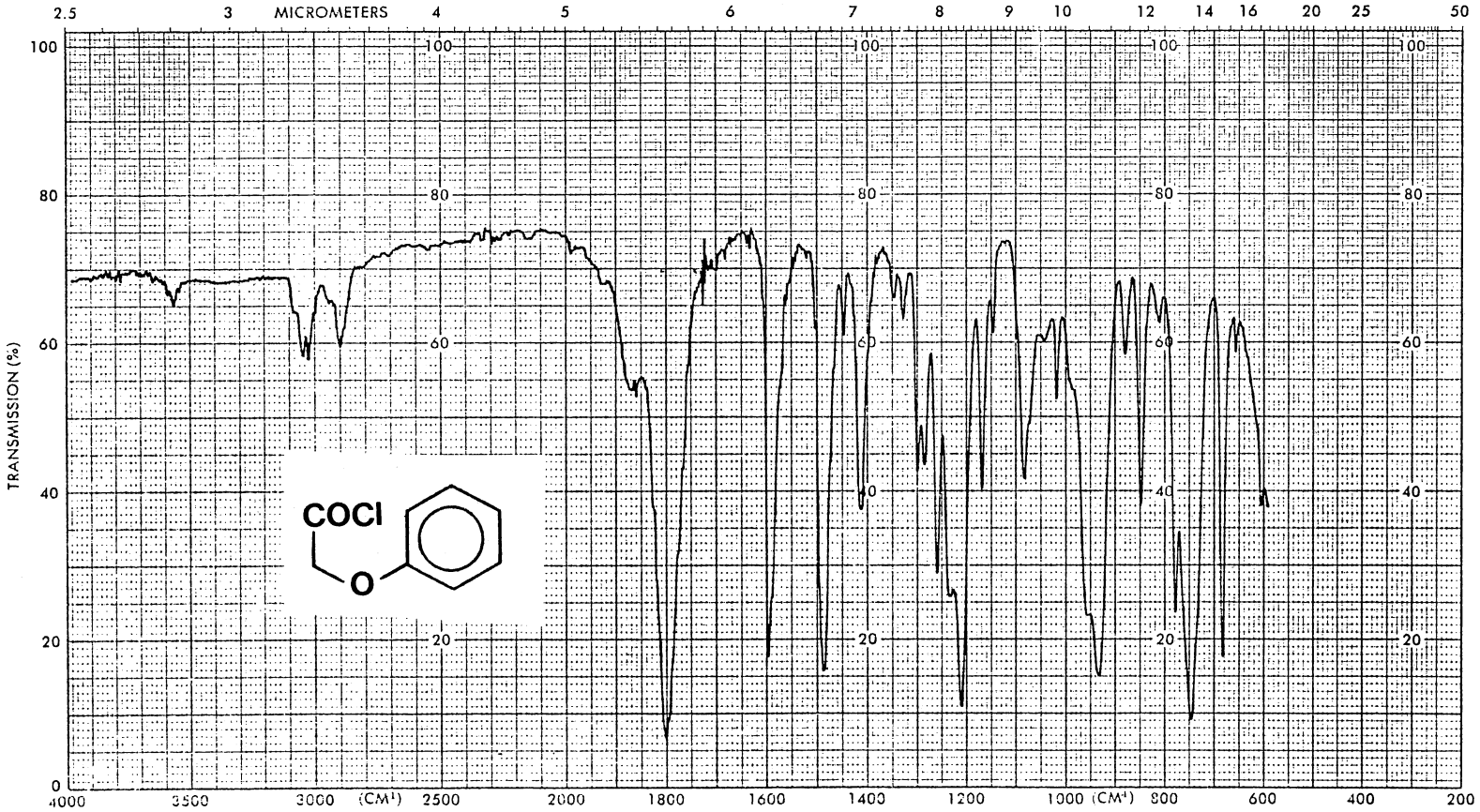
^{1}H NMR Spectrum of 75 Containing 76

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.94 MHz; WC: 2999.4 Hz; T: RT °C; NT: 12 .

Size: 4K K; PW/RF: 5.0 µs/dB; SO: 0 Hz; FB: Hz; Lock: ^{2}H ; Delay: 0.5 s.

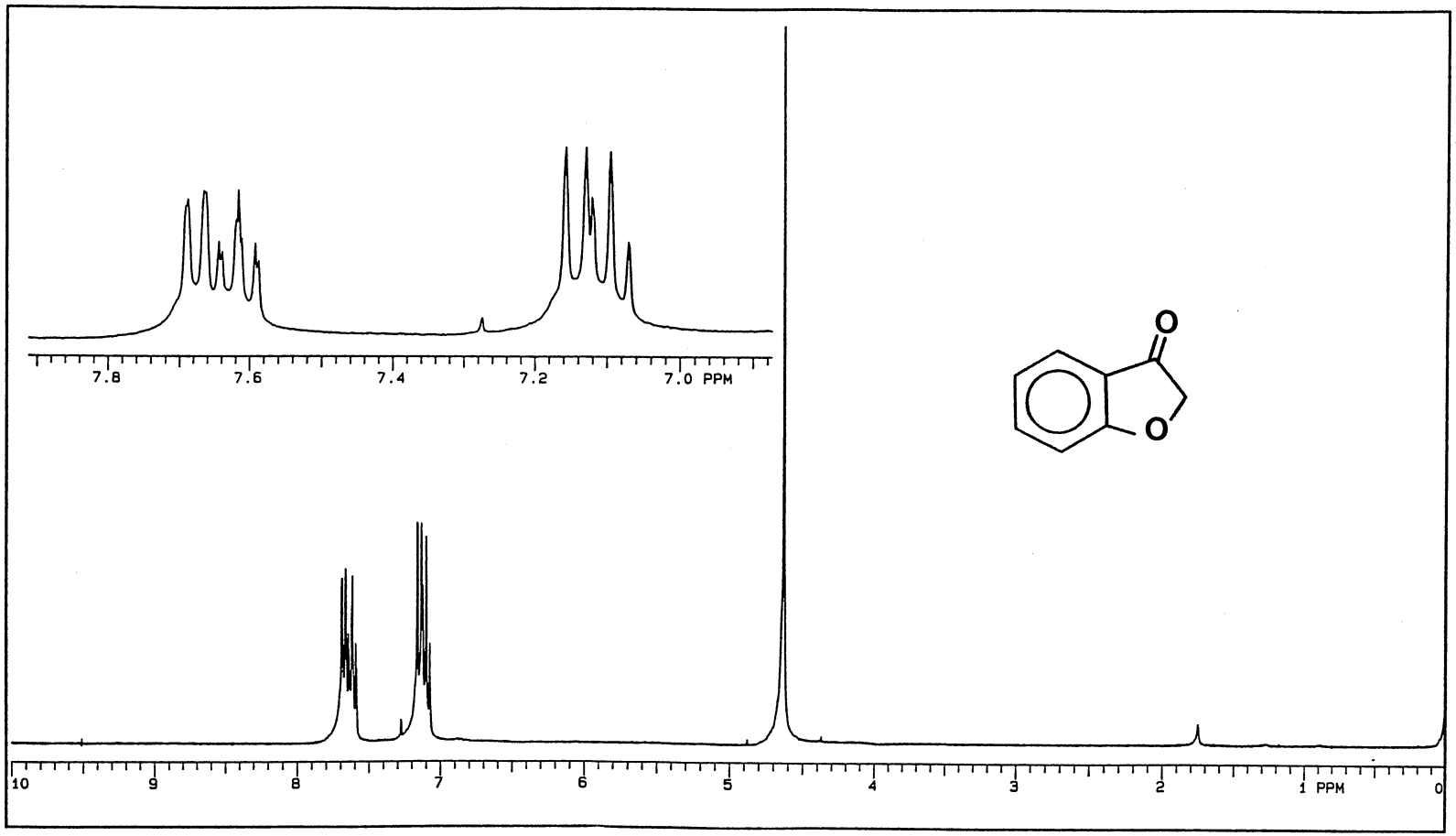
DC: ; Gated Off: ; Offset: Hz; RF: 15 W/dB; NBW:200 Hz; LB: 0 .

PLATE CLXIV



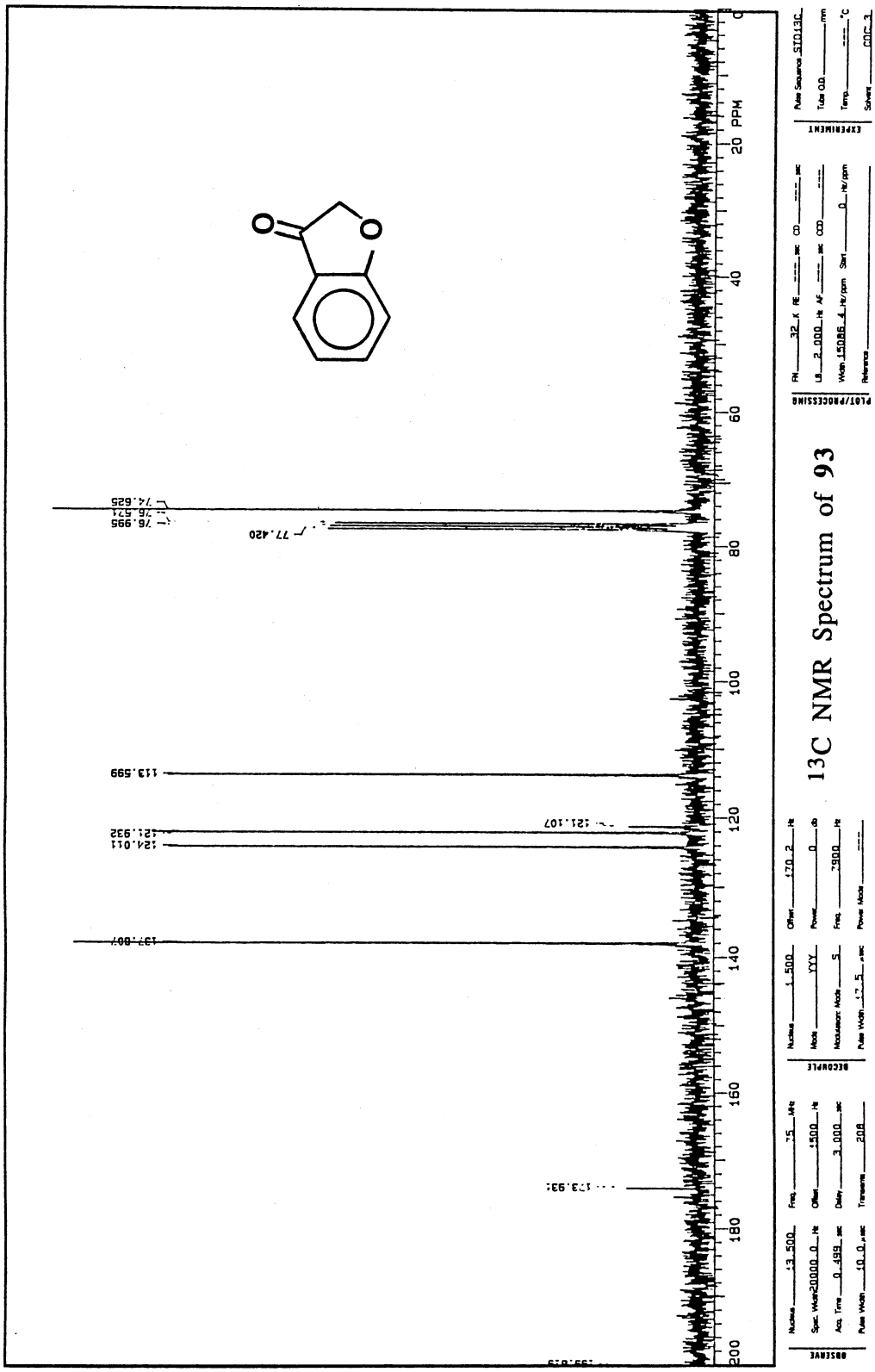
IR Spectrum of **91**

PLATE CLXV



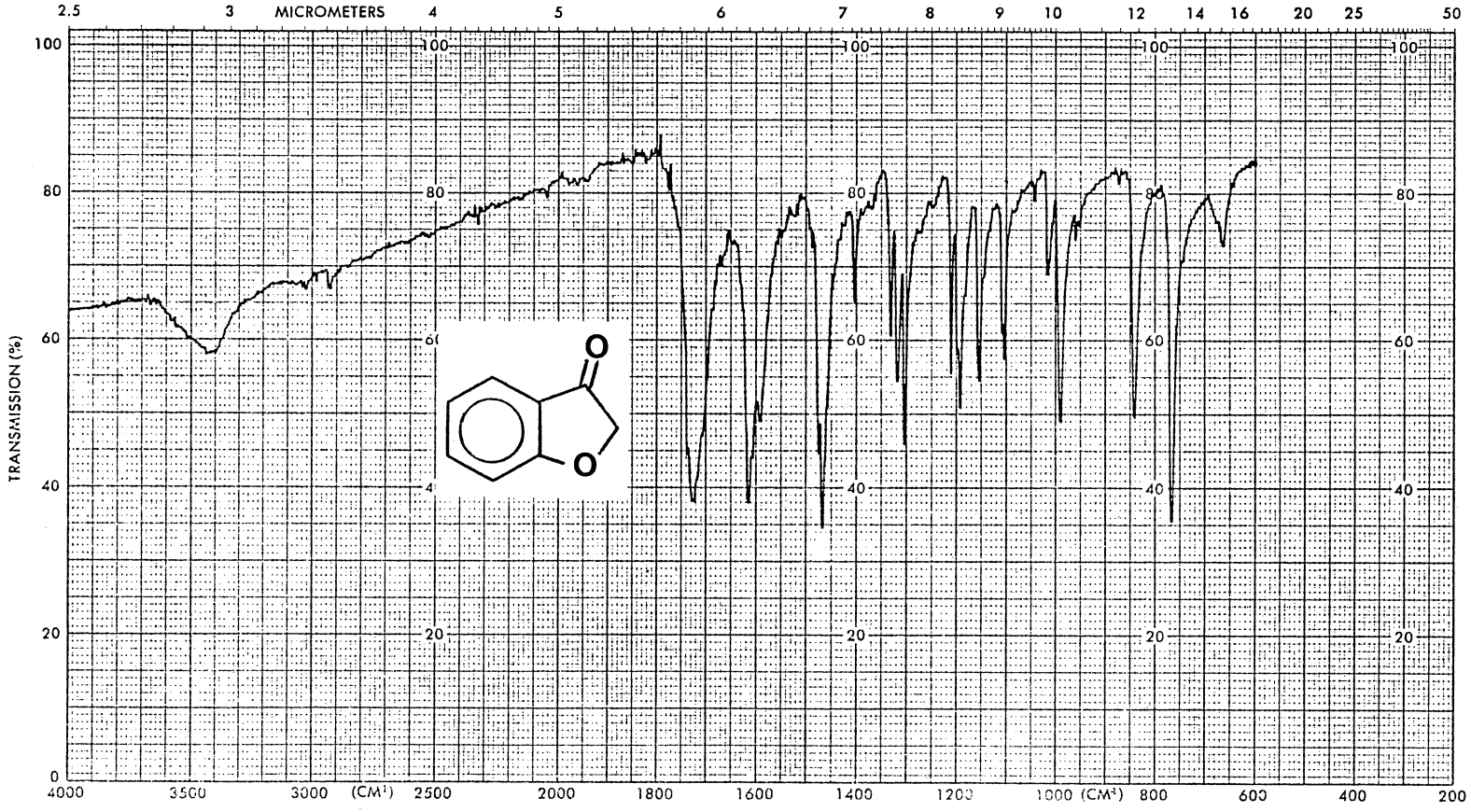
^{1}H NMR Spectrum of **93**

PLATE CLXVI



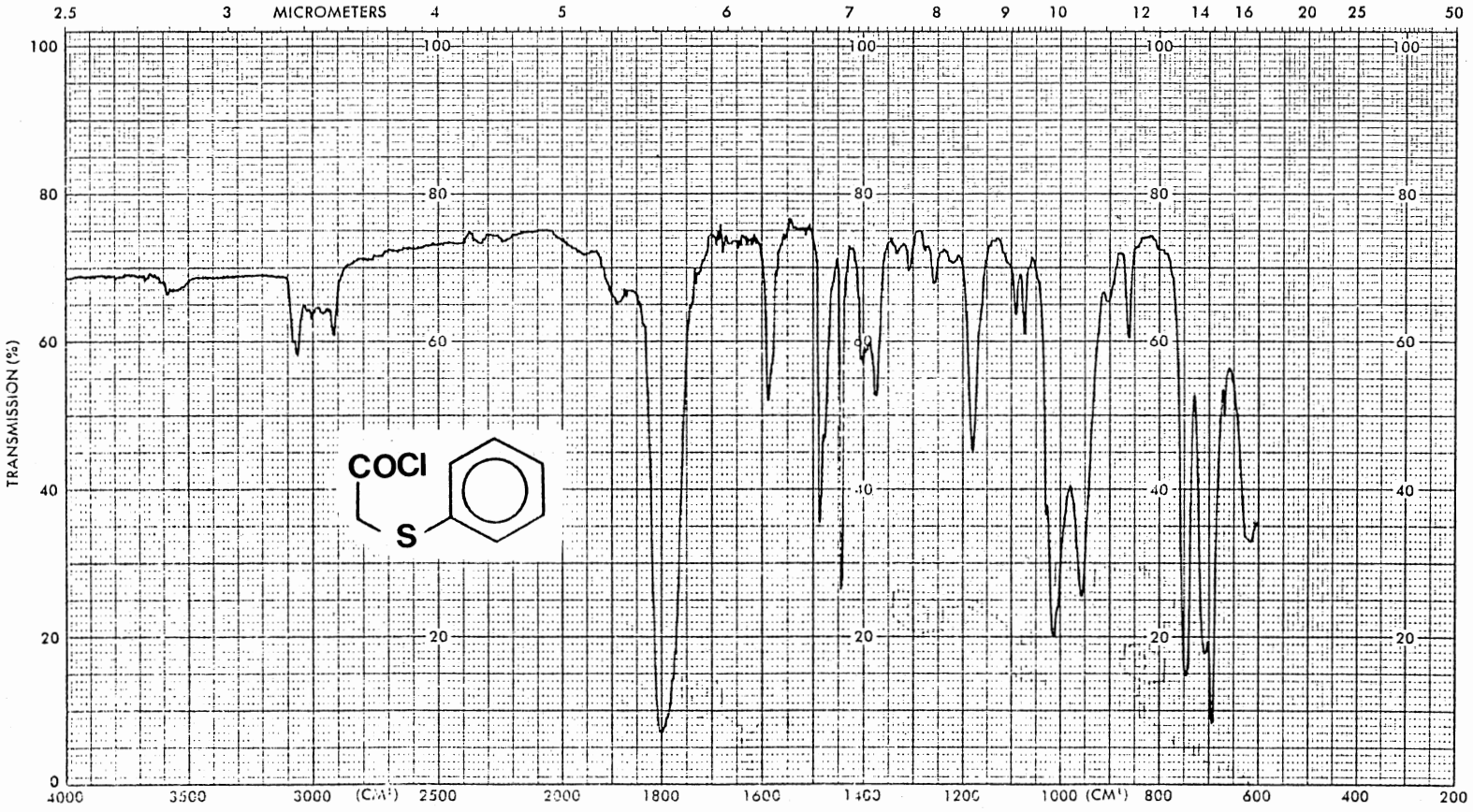
13C NMR Spectrum of **93**

PLATE CLXVII



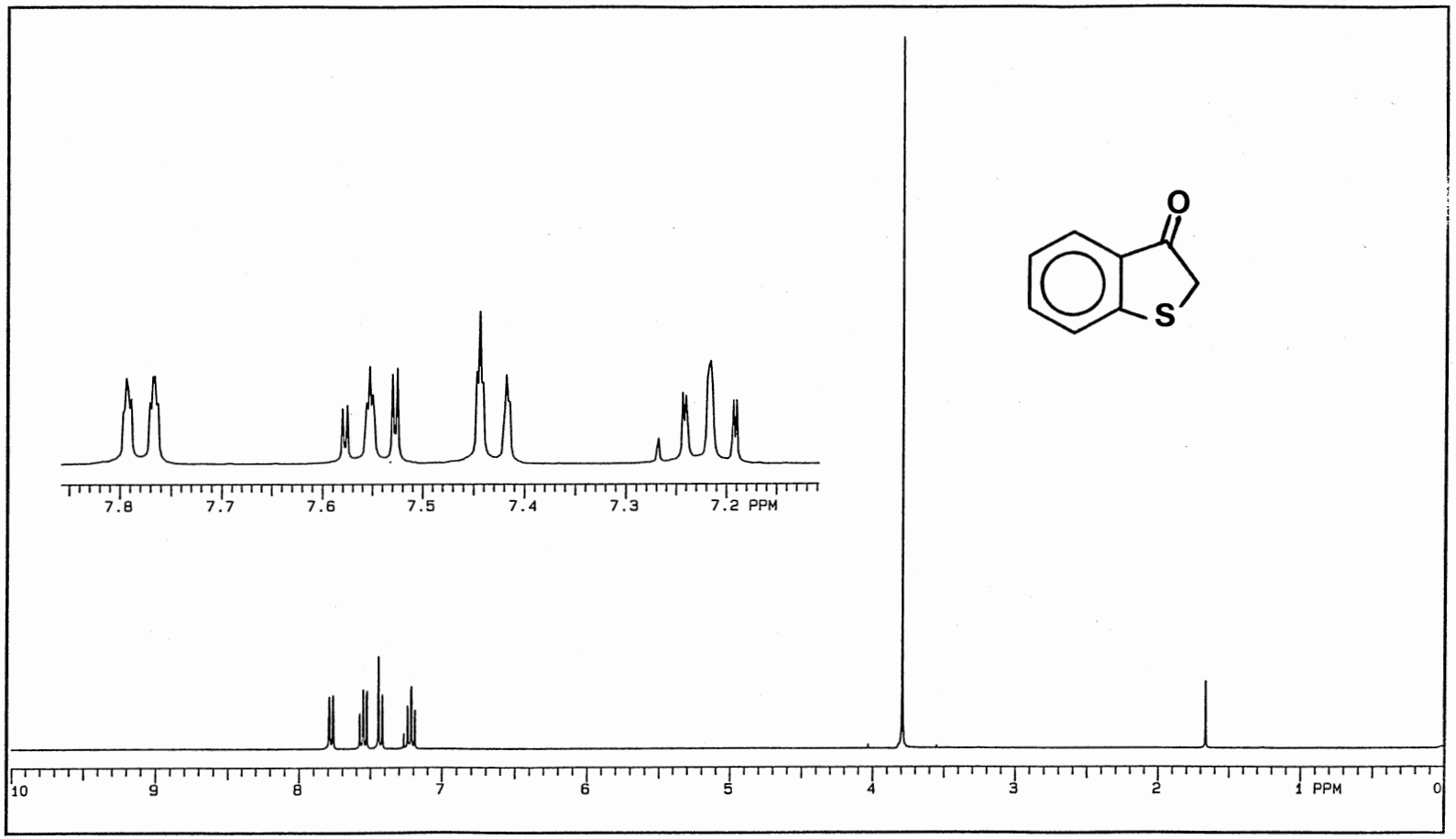
IR Spectrum of 93 - KBr

PLATE CLXVIII



IR Spectrum of **92**

PLATE CLXIX



OBSERVE: Nucleus 1.500 Freq 300 MHz; Spec. Width 4000.0 Hz Offset 0 Hz; Acq. Time 2.000 sec Delay 0 sec; Pulse Width 8.0 µsec Transients 48

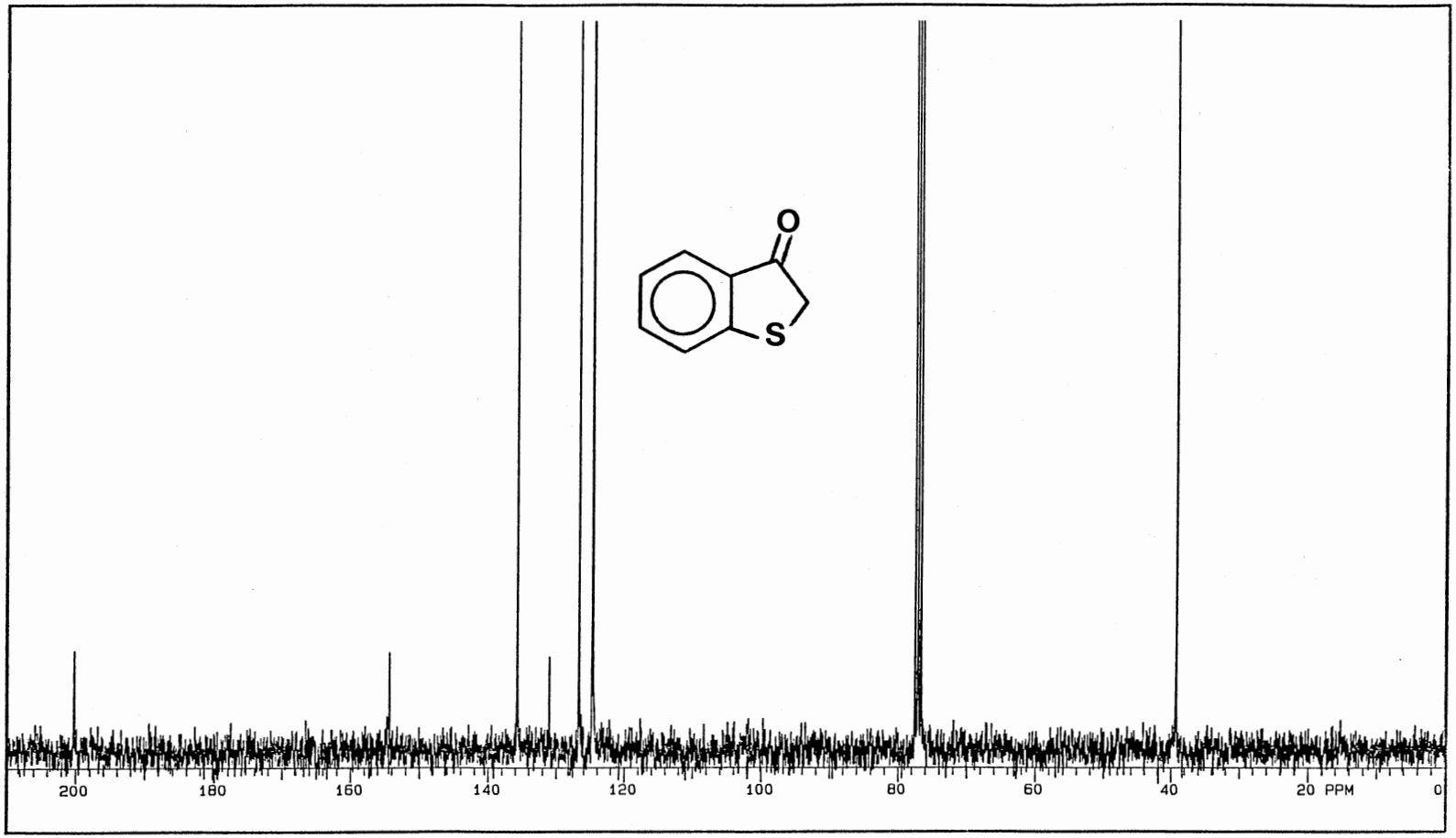
DECOUPLE: Nucleus 1.500 Offset 0 Hz; Mode NNN Power 20 db; Modulation Mode C Freq 200 Hz; Pulse Width µsec Power Mode ---

PLOT/PROCESSING: FN 16 K RE --- sec CD --- sec; LB --- Hz AF --- sec CCD ---; Width 2999.4 Hz/ppm Start 0 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence STD1H; Tube O.D. --- mm; Temp. --- °C; Solvent CDCL3

^{1}H NMR Spectrum of **94**

PLATE CLXX



OBSERVE: Nucleus 13.500 Freq. 75 MHz; Spec. Width 20000.0 Hz Offset 1500 Hz; Acq. Time 1.000 sec Delay 3.000 sec; Pulse Width 12.0 µsec Transients 256

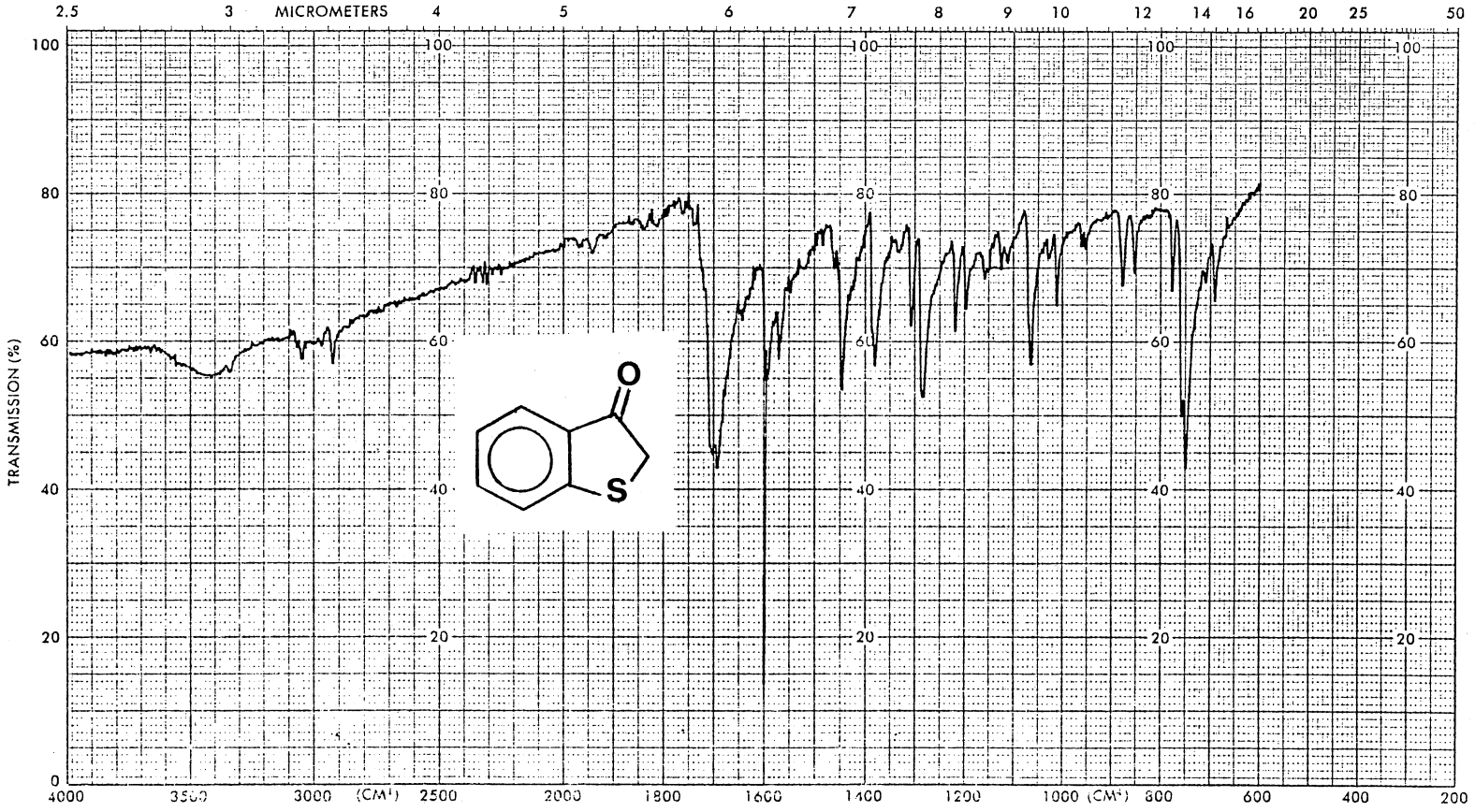
DECOUPLE: Nucleus 1.500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation Mode S Freq. 7900 Hz; Pulse Width 17.5 µsec Power Mode ---

^{13}C NMR Spectrum of **94**

PLOT/PROCESSING: FN 64 K RE --- sec CD --- sec; LB 2.000 Hz AF --- sec CCD ---; Width 15840.3 Hz/ppm Start 0 Hz/ppm; Reference

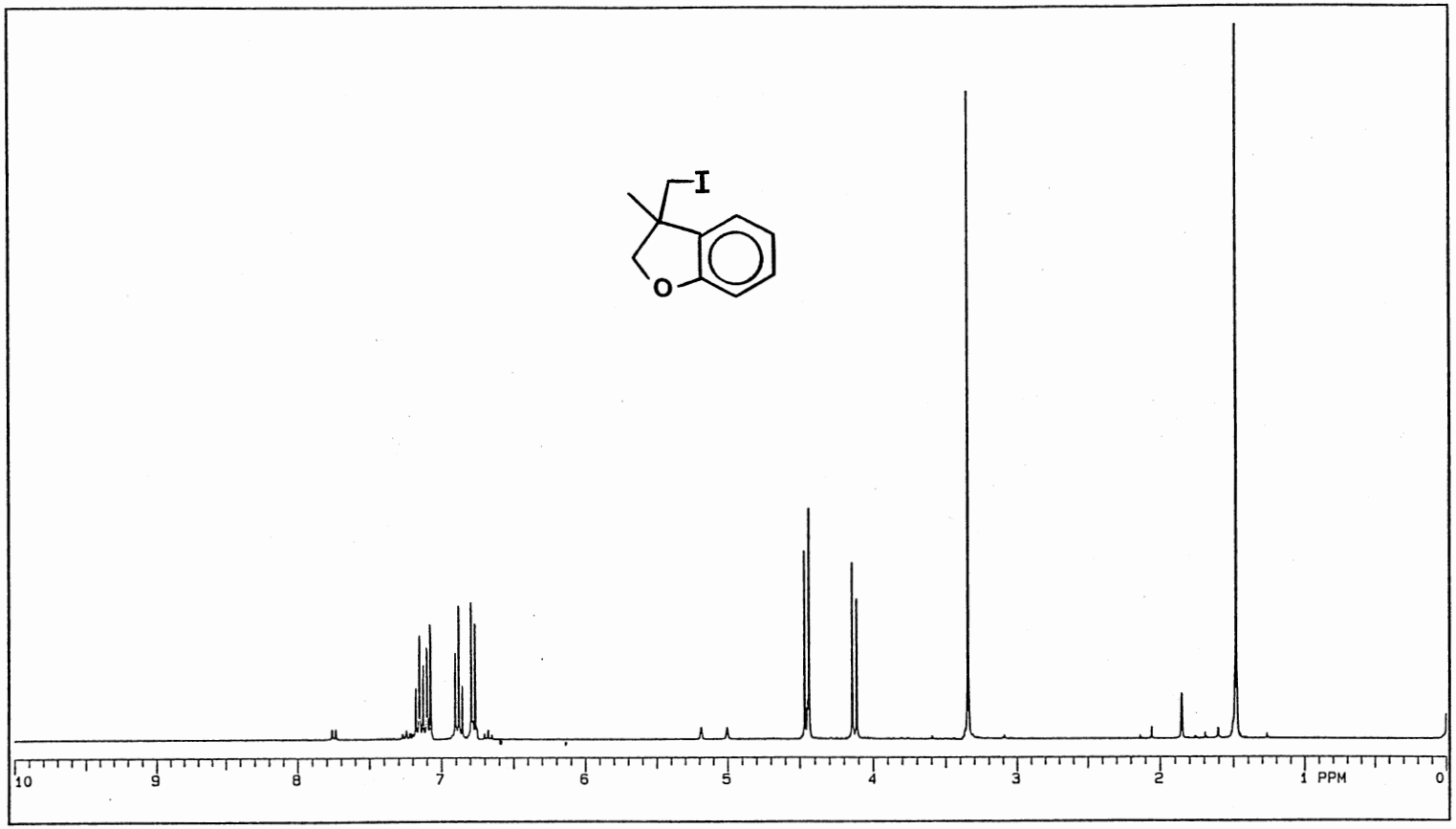
EXPERIMENT: Pulse Sequence STD13C; Tube O.D. mm; Temp. --- °C; Solvent CDCL3

PLATE CLXXI



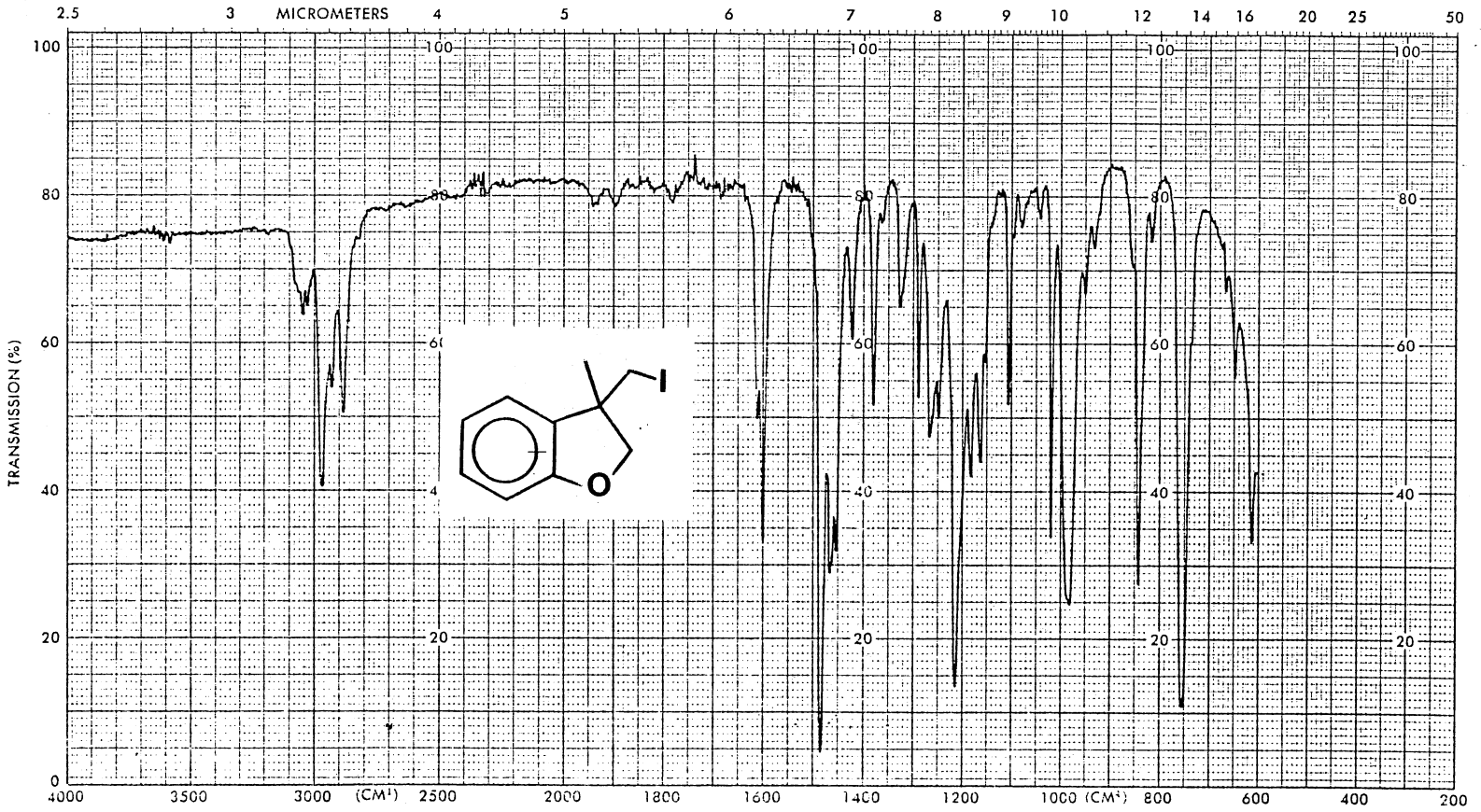
IR Spectrum of **94** - KBr

PLATE CLXXII



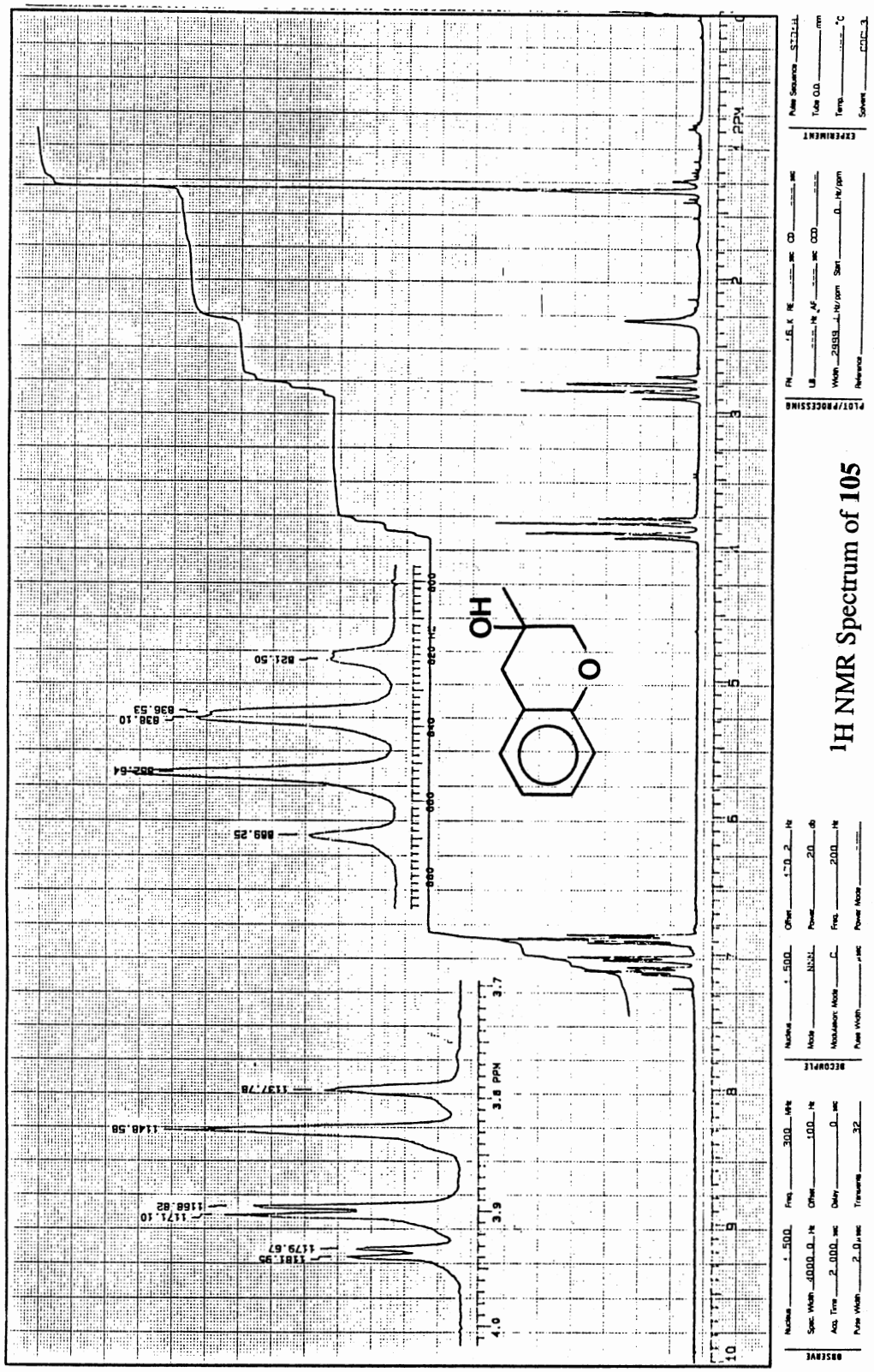
^{1}H NMR Spectrum of **103**

PLATE CLXXIII



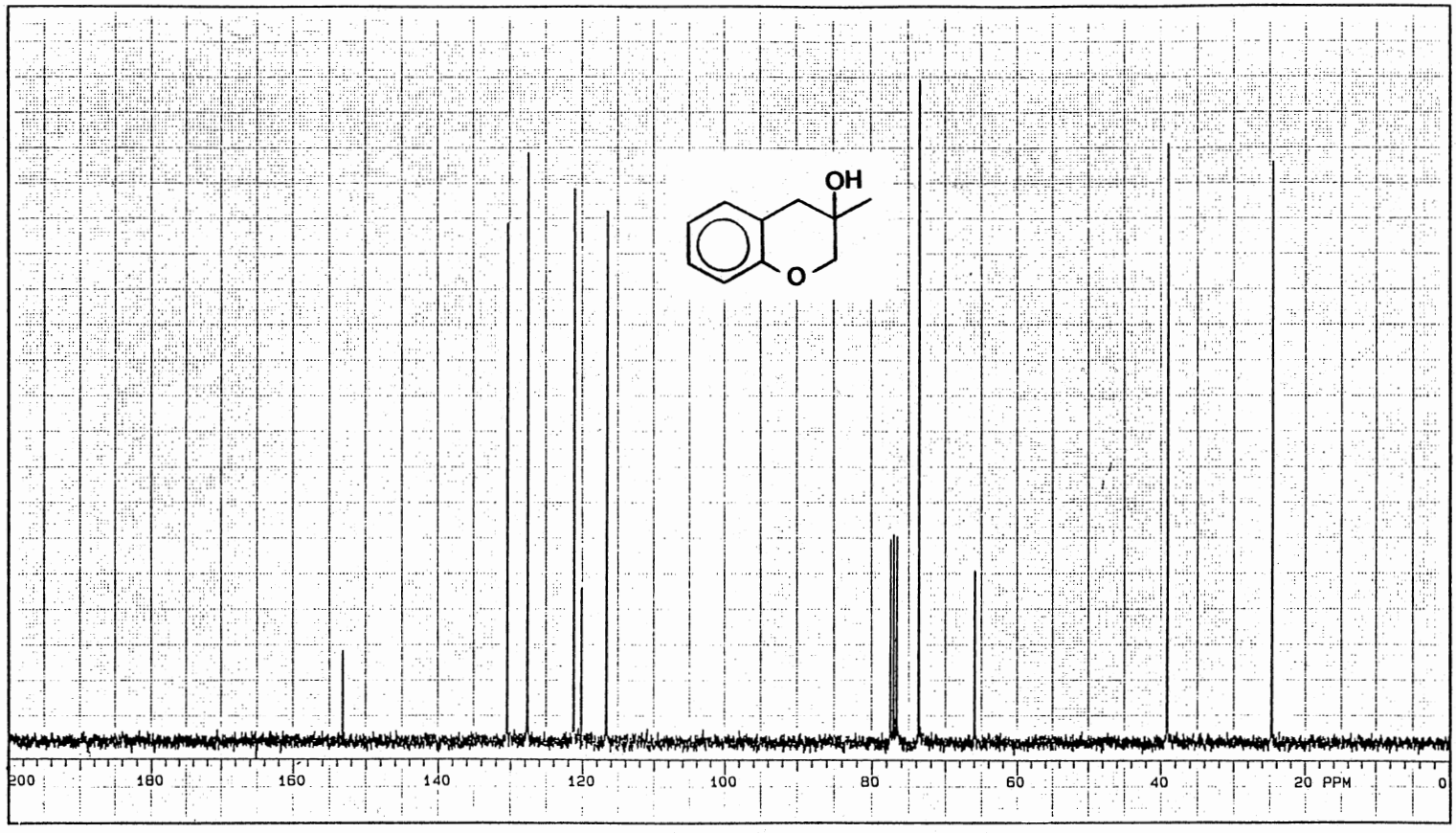
IR Spectrum of **103**

PLATE CLXXIV



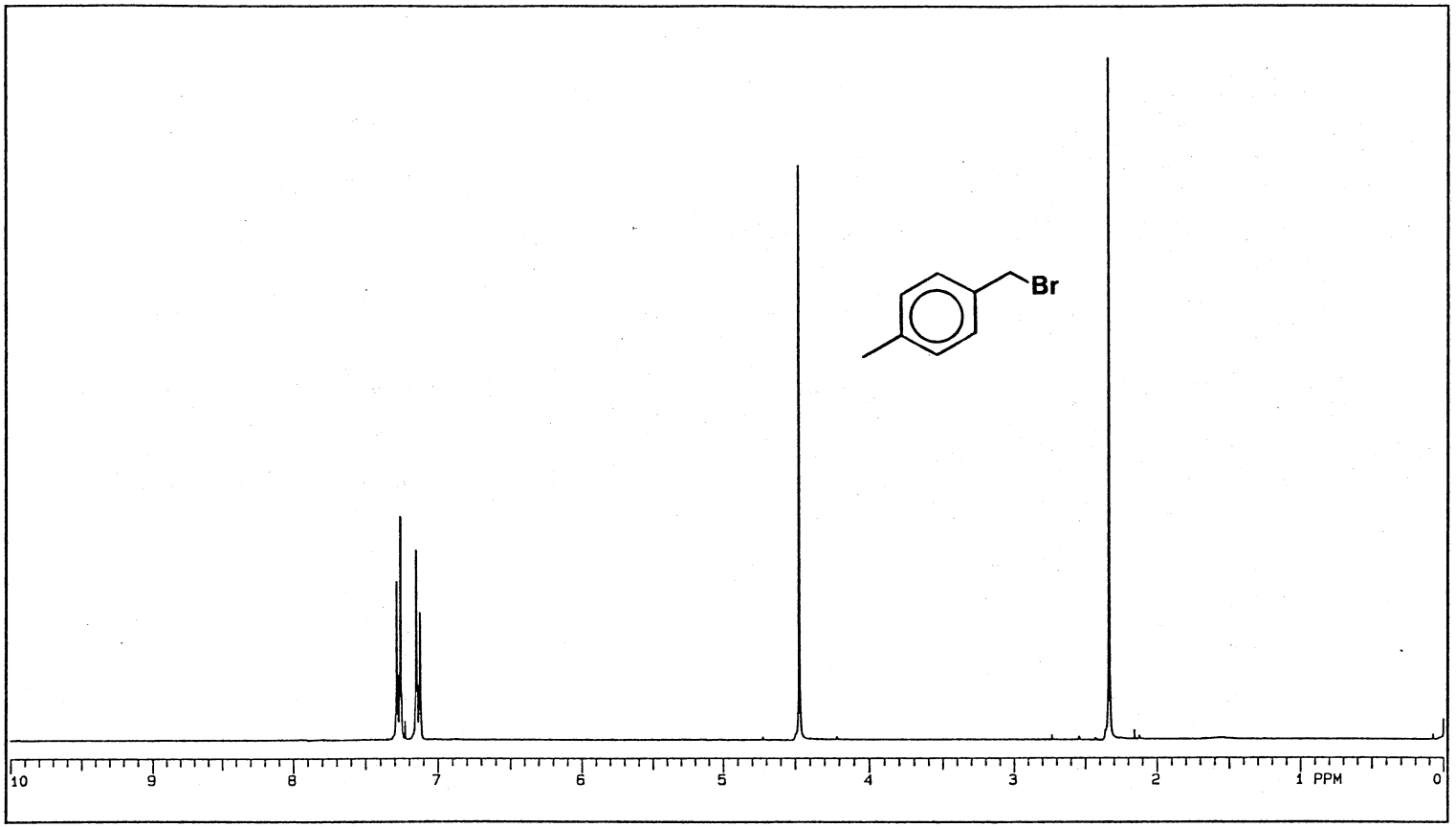
^{1}H NMR Spectrum of **105**

PLATE CLXXV



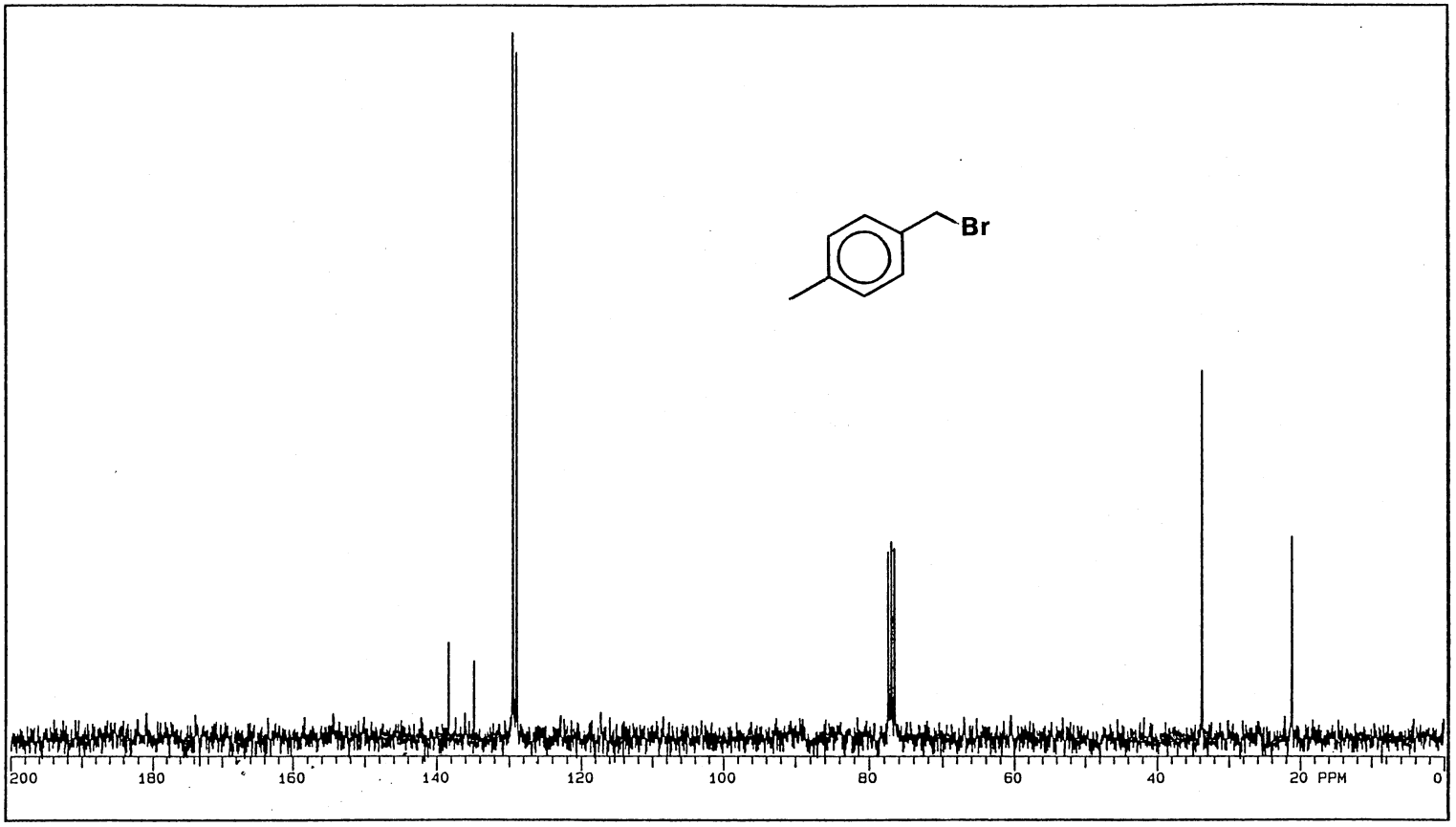
^{13}C NMR Spectrum of **105**

PLATE CLXXVI



^{1}H NMR Spectrum of **109**

PLATE CLXXVII



OBSERVE Nucleus 13.500 Freq 75 MHz; Spec Width 20000.0 Hz Offset 1500 Hz; Acq. Time 1.000 sec Delay 3.000 sec; Pulse Width 12.0 µsec Transients 32

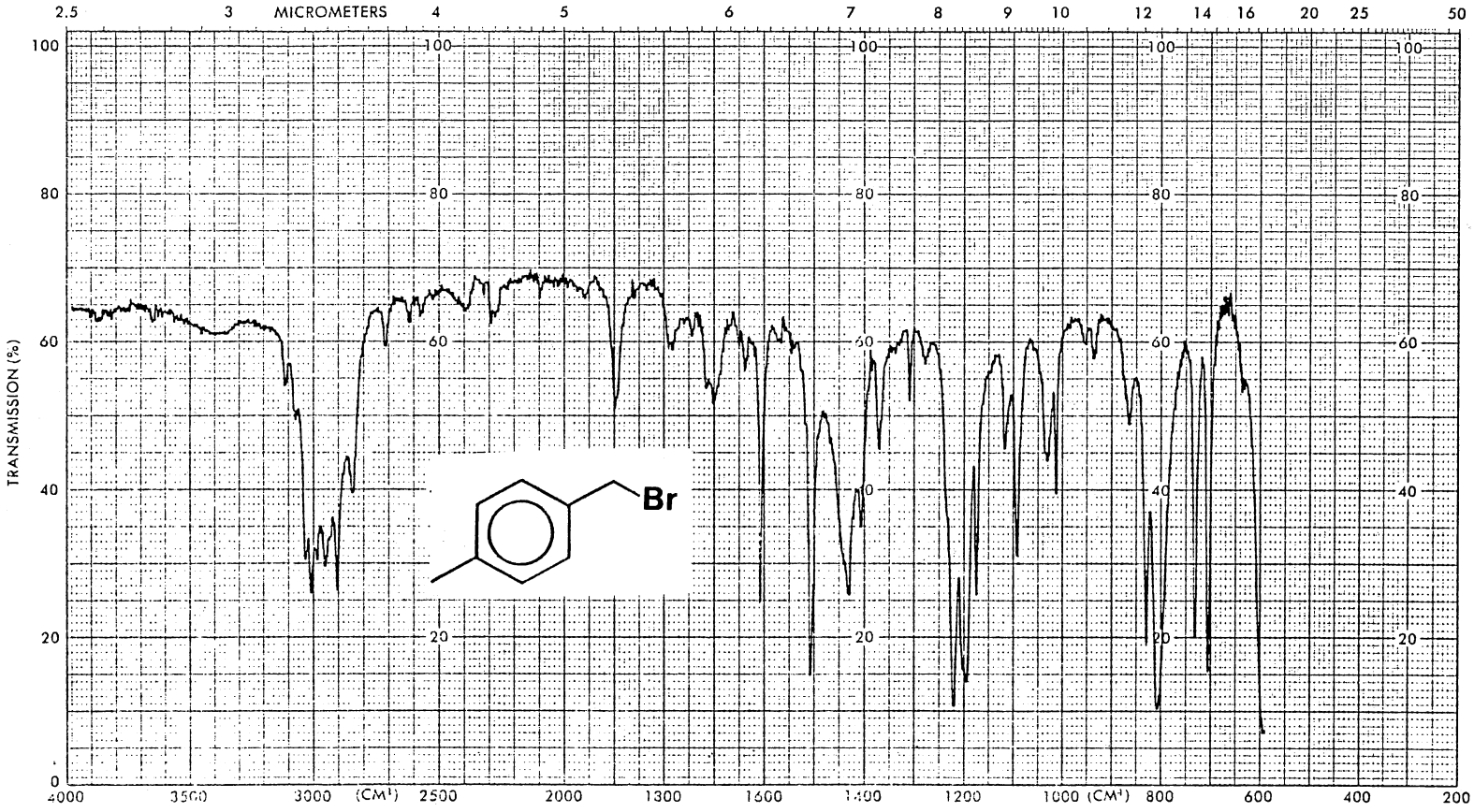
DECOUPLE Nucleus 1.500 Offset 170.2 Hz; Mode YYY Power 0 db; Modulation Mode S Freq 7900 Hz; Pulse Width 17.5 µsec Power Mode ---

^{13}C NMR Spectrum of **109**

PLOT/PROCESSING FN 64 K RE --- sec CD --- sec; LB 3.000 Hz AF --- sec CCD ---; Width 15085.9 Hz/ppm Start 0 Hz/ppm; Reference

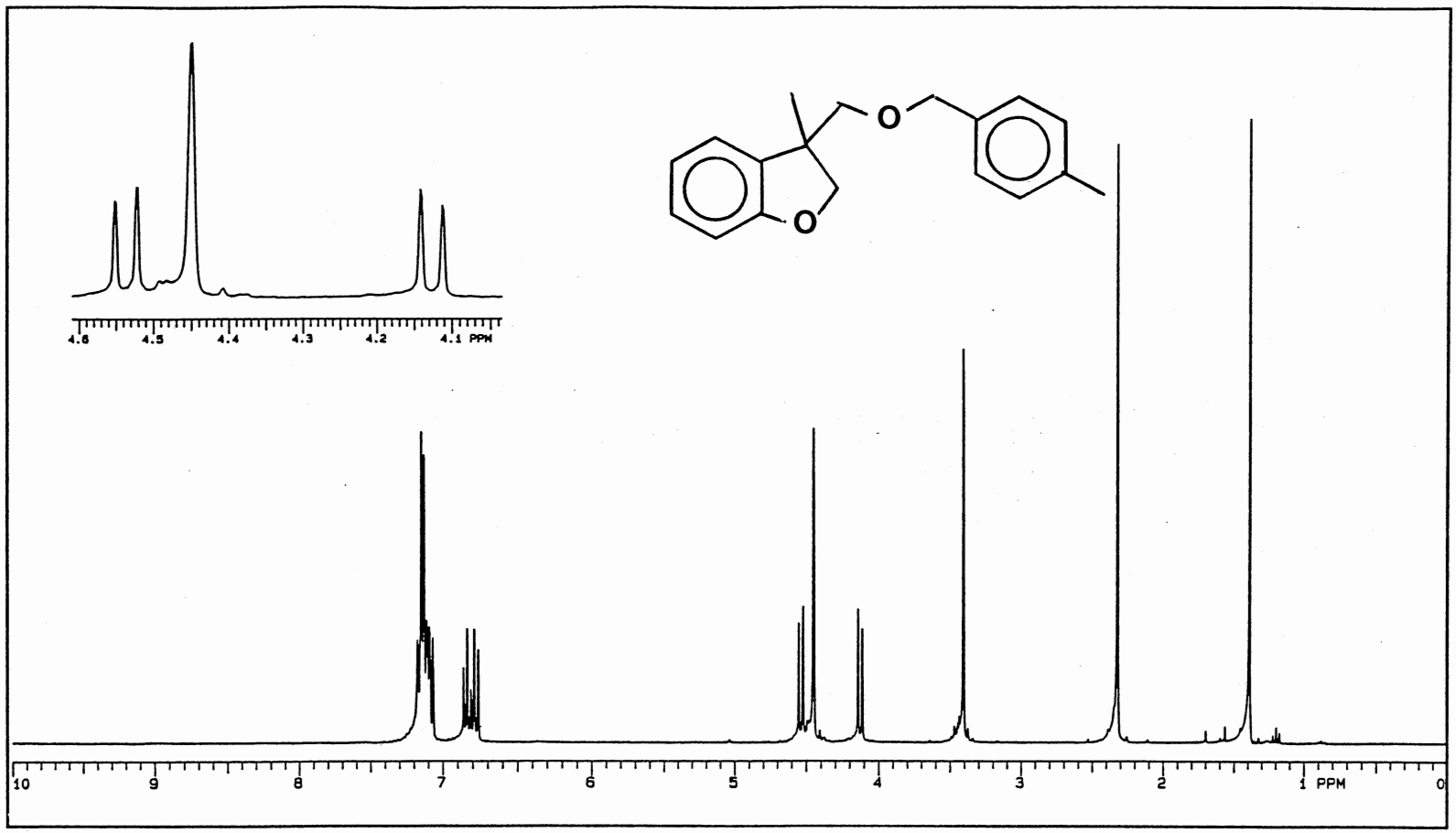
EXPERIMENT Pulse Sequence STD13C; Tube O.D. --- mm; Temp. --- °C; Solvent CDCL3

PLATE CLXXVIII



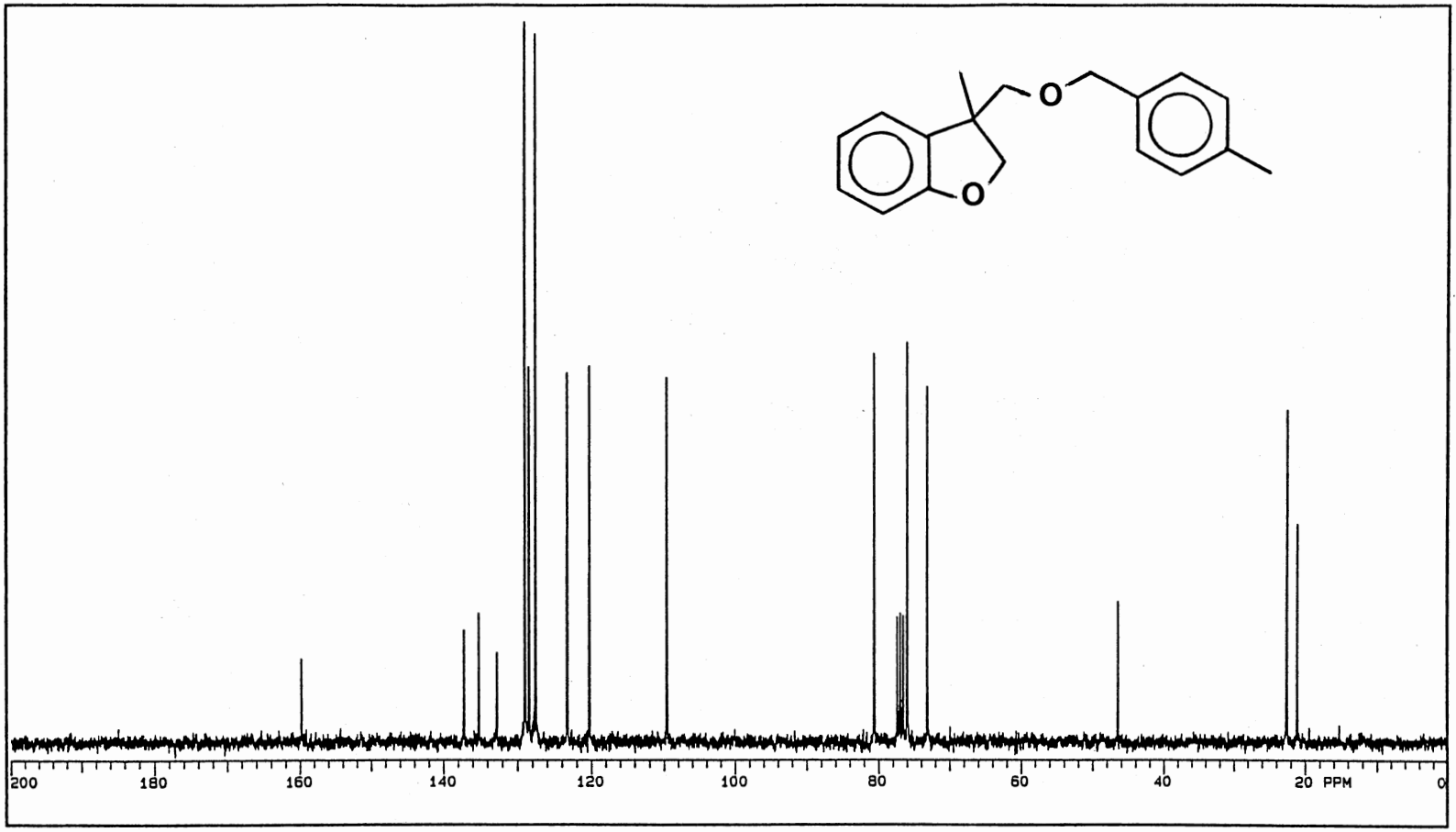
IR Spectrum of **109** -Melt

PLATE CLXXIX



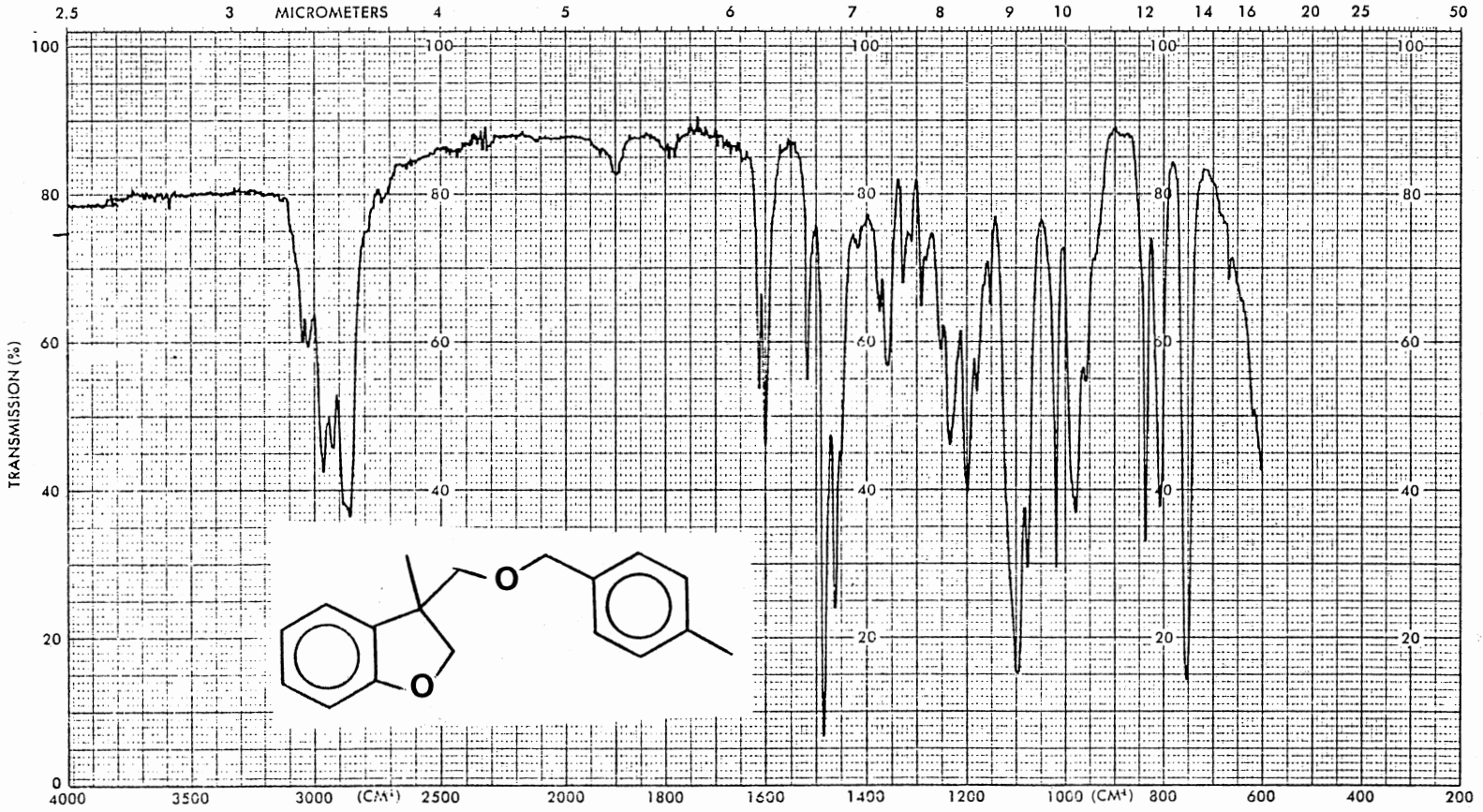
^{1}H NMR Spectrum of **110**

PLATE CLXXX



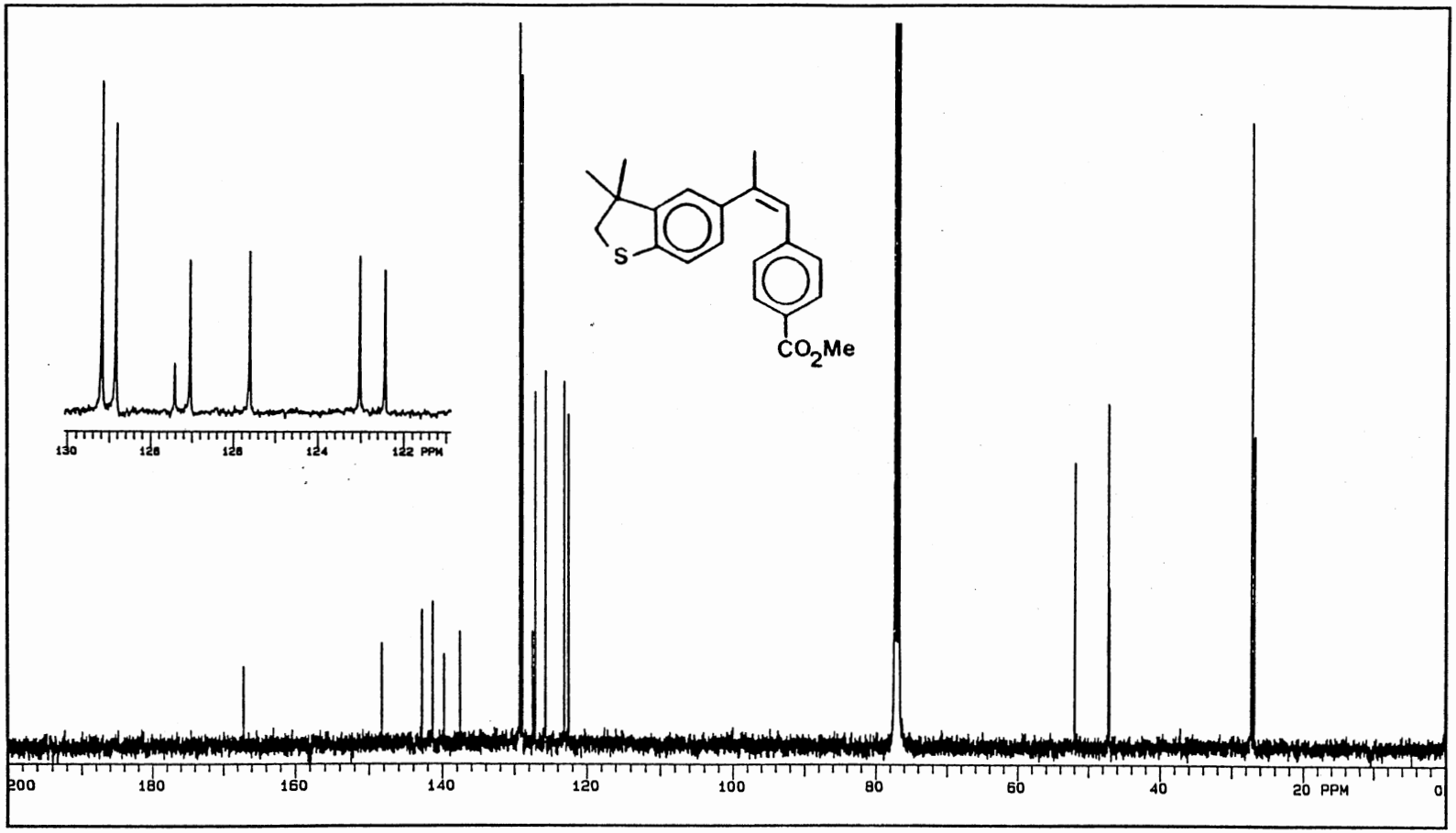
^{13}C NMR Spectrum of **110**

PLATE CLXXXI



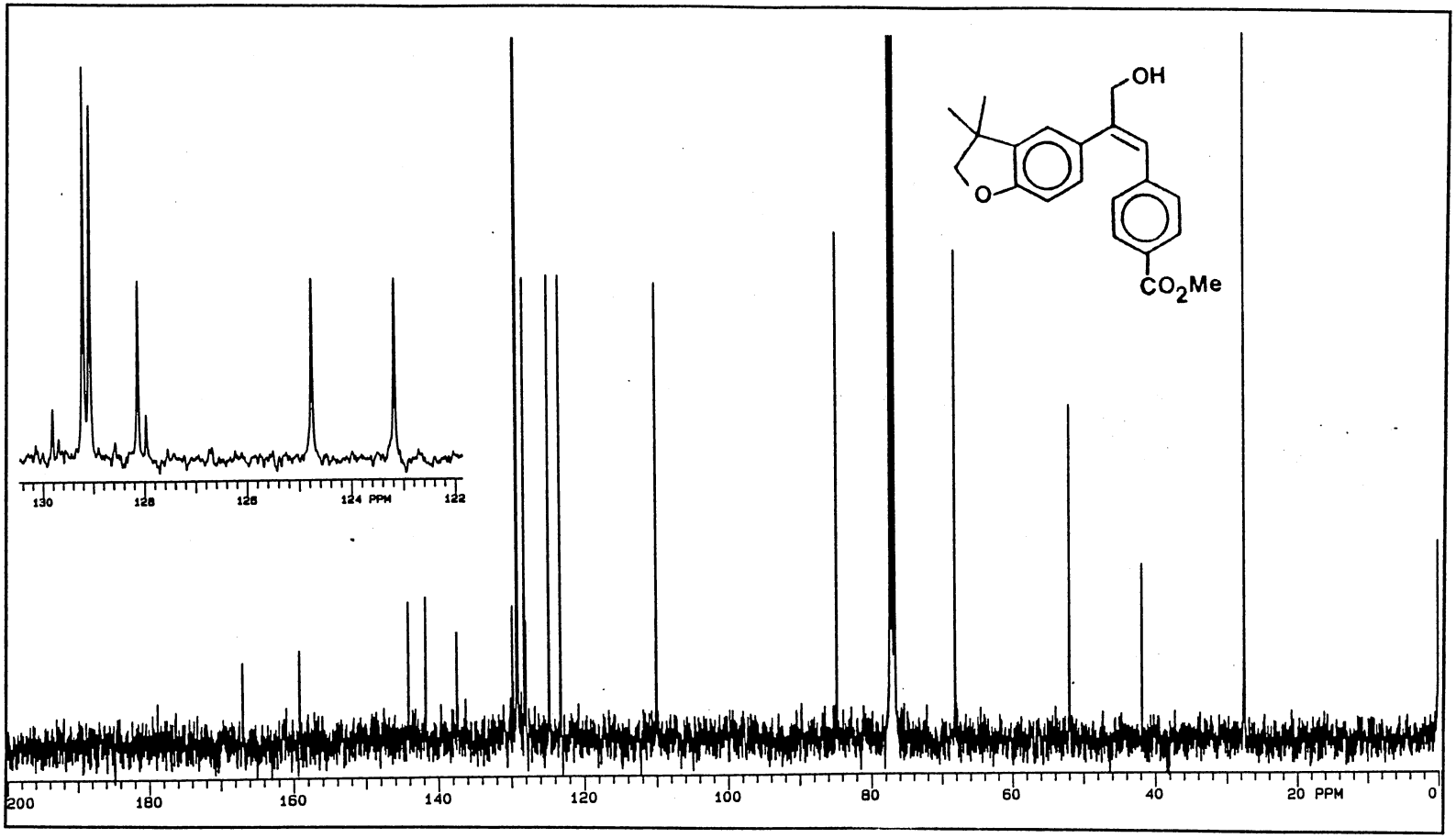
IR Spectrum of 110

PLATE CLXXXII



^{13}C NMR Spectrum of **61**-(*Z*)

PLATE CLXXXIII



OBSERVE Nucleus 13.750 Freq. 101 MHz Spec. Width 23584.9 Hz Offset 1713 Hz Acq. Time 1.018 sec Delay 2.000 sec Pulse Width 12.0 µsec Transmit 2304

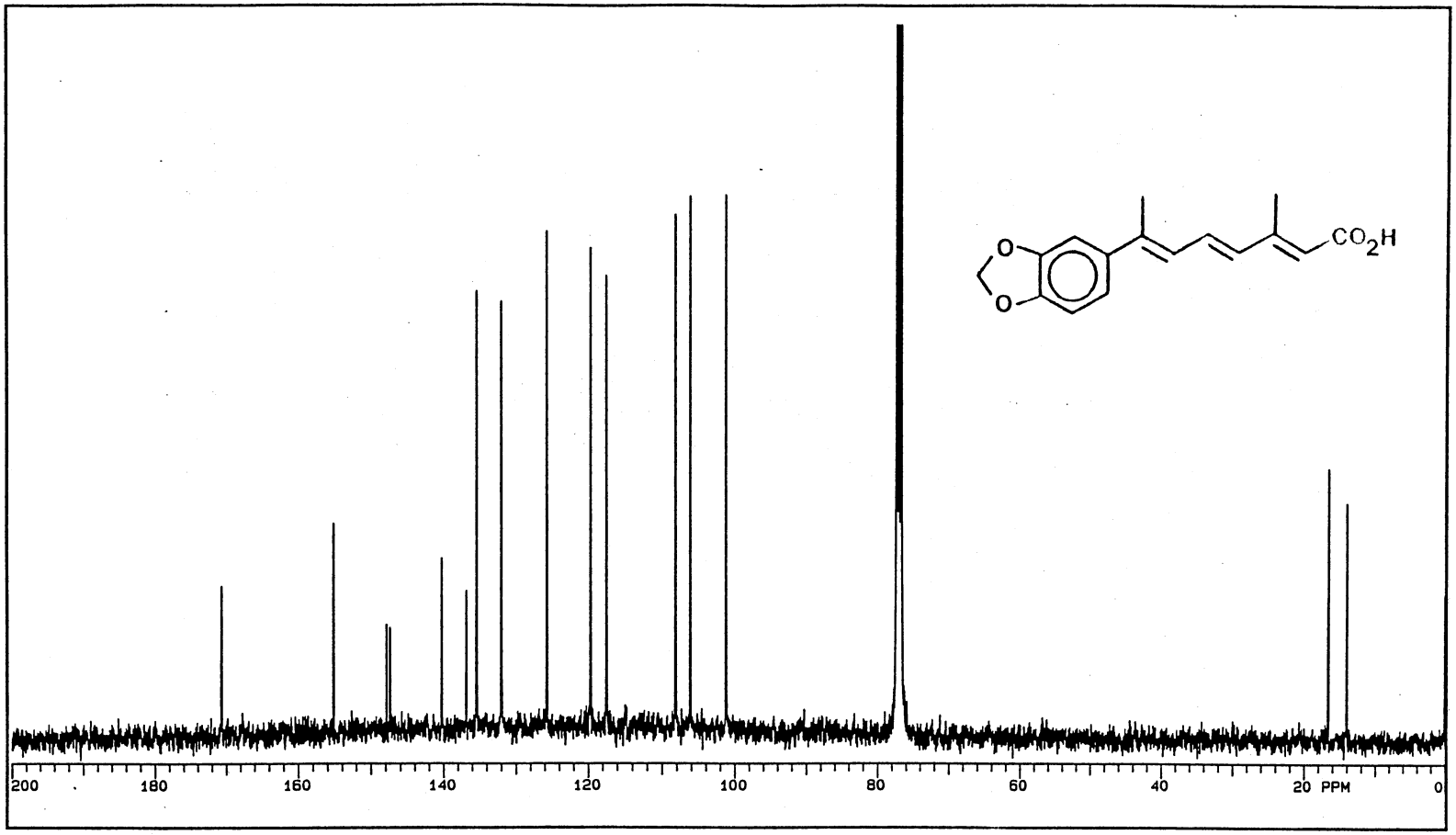
DECOUPLE Nucleus 1.750 Offset 75.0 Hz Mode YYY Power 0 dh Modulation Mode S Freq. 9000 Hz Pulse Width 17.5 µsec Power Mode

^{13}C NMR Spectrum of **66**-(*E*)

PLOT/PROCESSING FN 64 K RE sec CD sec US 3.500 Hz AF sec CCD Width 20115.6 Hz/ppm Start 0 Hz/ppm Reference

EXPERIMENT Pulse Sequence STD13C Tube O.D. mm Temp. °C Solvent CDCL3

PLATE CLXXXIV



OBSERVE Nucleus 13.750 Freq. 101 MHz; Spec. Width 23584.9 Hz Offset 1713 Hz; Acq. Time 0.636 sec Delay 2.000 sec; Pulse Width 12.0 µsec Transients 29696

DECOUPLE Nucleus 1.750 Offset 75.0 Hz; Mode YYY Power 0 db; Modulation Mode S Freq. 9000 Hz; Pulse Width 17.5 µsec Power Mode ——

^{13}C NMR Spectrum of **71**

PLOT/PROCESSING FN 32 K RE —— sec CD —— sec; LB 2.500 Hz AF —— sec CCD ——; Width 20115.4 Hz/ppm Start 0 Hz/ppm; Reference ——

EXPERIMENT Pulse Sequence STD13C; Tube O.D. —— mm; Temp. —— °C; Solvent CDCL3

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