SYNTHESES OF POTENTIAL METABOLITES OF ETHYL (*E*)-4-[2-(3,4-DIHYDRO-4,4-DIMETHYL-2*H*-1-BENZOPYRAN-6-YL)-1-PROPENYL]BENZOATE, 4-[(ALL-*E*)-2-METHYL-4-(2,6,6-TRIMETHYL-3-THIA-1-CYCLOHEXEN-1-YL)-1,3-BUTADIENYL]-BENZOIC ACID AND CERTAIN DERIVATIVES

BY

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SYNTHESES OF POTENTIAL METABOLITES OF ETHYL (*E*)-4-[2-(3,4-DIHYDRO-4,4-DIMETHYL-2*H*-1-BENZOPYRAN-6-YL)-1-PROPENYL]BENZOATE, 4-[(ALL-*E*)-2-METHYL-4-(2,6,6-TRIMETHYL-3-THIA-1-CYCLOHEXEN-1-YL)-1,3-BUTADIENYL]-BENZOIC ACID AND CERTAIN DERIVATIVES

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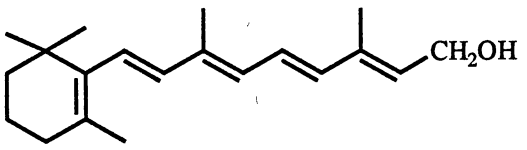
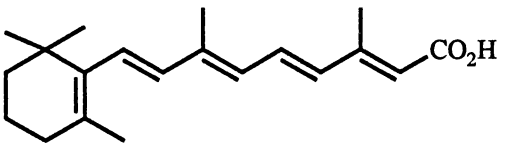
HISTORICAL

Introduction

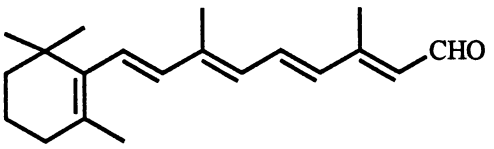
Vitamin A (retinol, **1**) is stored in the liver as retinyl palmitate and is essential for the growth and development of higher life forms and functions in many different ways within an organism.[68] In mammals, vitamin A is essential for vision [converted to retinal (**2**)] reproduction and the regulation of differentiation and proliferation of a very wide range of epithelial tissues.[64] Retinoic acid (**3**) can substitute for retinol in vitamin A deficient animals in growth promotion and cell differentiation.[13]



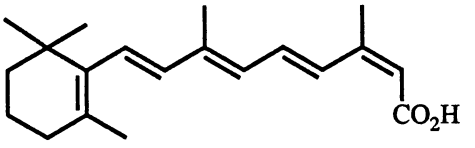
Retinol (**1**)



all-*trans*-Retinoic Acid (**3**)

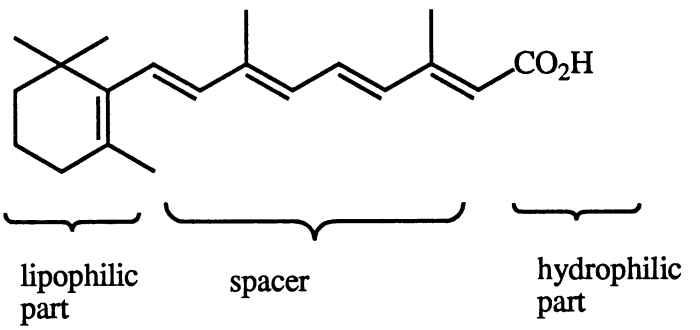


Retinal (**2**)



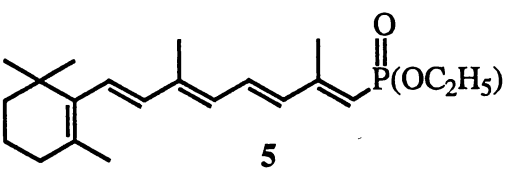
13-*cis*-Retinoic Acid (**4**)

The term "retinoids" is applied to naturally occurring vitamin A derivatives, such as retinol, retinal, and retinoic acid, as well as to synthetic compounds having structural similarities regardless of whether they possess biological activity.[19,67] Since the late 1960's, a number of structurally-modified retinoids (synthetic retinoic acid derivatives) have been made with the focus to improve on the ratio of toxic effects (e.g. hypervitaminosis A) to the therapeutic activity compared to retinoic acid.[53] Retinoic acid (**3**) consists of three main sections: a lipophilic part at one end connected via a polyunsaturated chain as a spacer to a hydrophilic group at the other end as shown below.



all-*trans*-Retinoic Acid (**3**)

Different synthetic retinoids have been prepared by making alterations in one or more parts of the basic retinoic acid skeleton. For example, the hydrophilic CO_2R group has been replaced by a phosphoric ester group as in **5** and sulfonic ester group as in **6**.[40]



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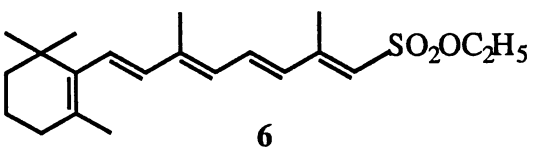
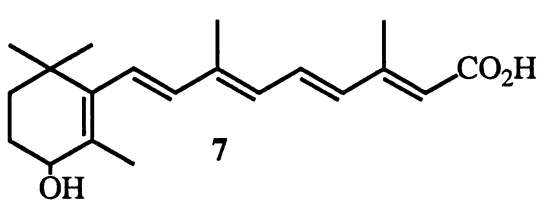


6

The oxygen-containing metabolites from **3**, namely **7-9**, are a group of compounds in which the cyclohexenyl ring (lipophilic part) has been altered.[38,58,59] Keto acid **9** has been shown to be teratogenic.[77]



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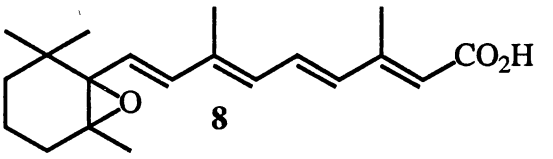

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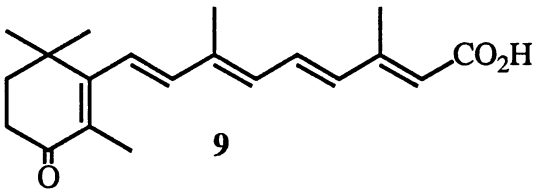

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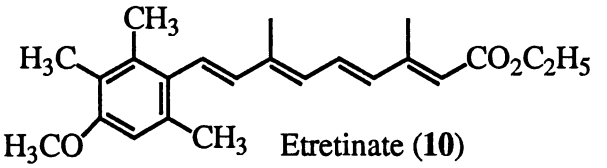
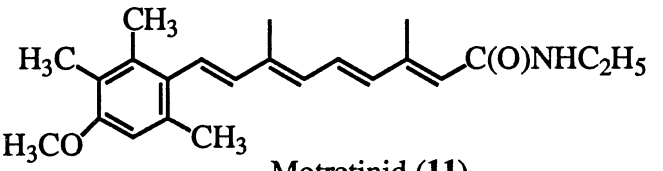


Etretinate (**10**)

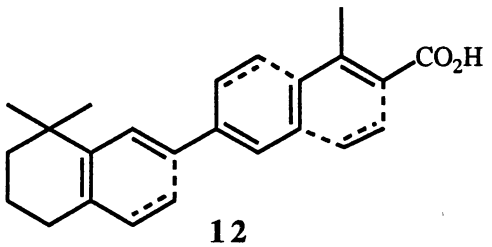


Motretinid (**11**)

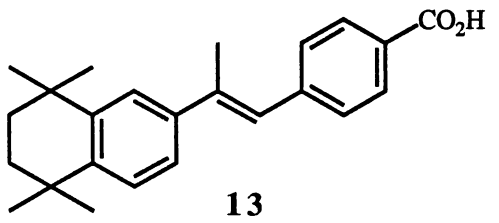
Aromatization of the cyclohexenyl ring leads to compounds like Etretinate (**10**) and Motretinid (**11**).[48] A number of arotinoids (retinoids with an aryl ring as in **13** and **14**)

have been synthesized[12] and have exhibited anticancer activity in several assays but they are toxic.[45]

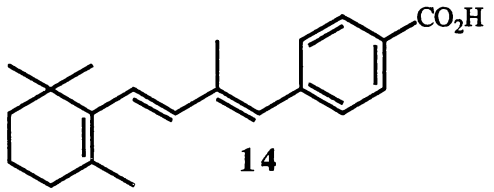
Structure **12** illustrates the closeness of these arotinoids to retinoic acid (**3**). It shows how the polyene side of the retinoic acid is condensed into an aromatic ring structure, thus



12



13



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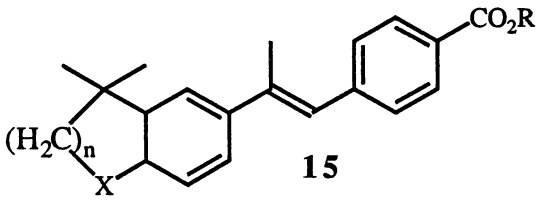
making fixed conformations at these bonds and more planar structures.

Another class of synthetic retinoids are the heteroarotinoids[18,41,70,76] (retinoids consisting of an aryl ring and the heteroatom incorporated in one of the rings as shown below in **15**) which have also shown anticancer activity with reduced toxicity in several assays. This area is in a time of rigorous development. Several members of **15** have exhibited reduced toxicity compared to retinoic acid (**3**).[18,70]



15

X = O, S, N-CH_3
R = H, CH_3, C_2H_5
n = 1, 2

Degradative Biopathways and Metabolism

Many oxidative pathways for retinoic acid (**3**) have been suggested from *in vitro* and *in vivo* studies.[24] The major oxidation sites are: (1) the oxidation of the cyclohexenyl ring at C(4), (2) the oxidation of one of the methyl groups on the ring and on the side chain, and (3) shortening of the side chain as shown below (Figure 1).

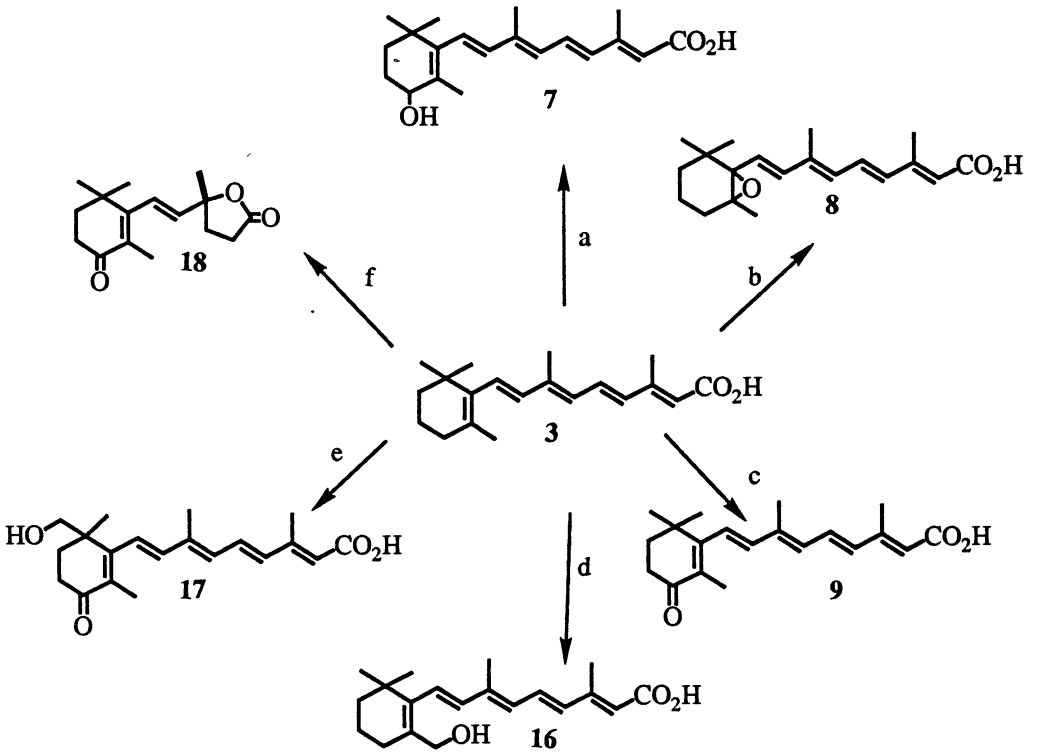


Figure 1. Some Oxidative pathways of all *trans*-retinoic acid (**3**): (a) Reference 25; (b) Reference 49; (c) Reference 33; (d) Reference 31; (e) Reference 56; (f) Reference 32

Among synthetic retinoids, Etretinate (**10**) is the most widely studied. Many oxidative metabolites have been isolated and characterized from the bile of rats and from human urine as shown below.[34,35] The major metabolites in humans are **22-24** (Figure 2).

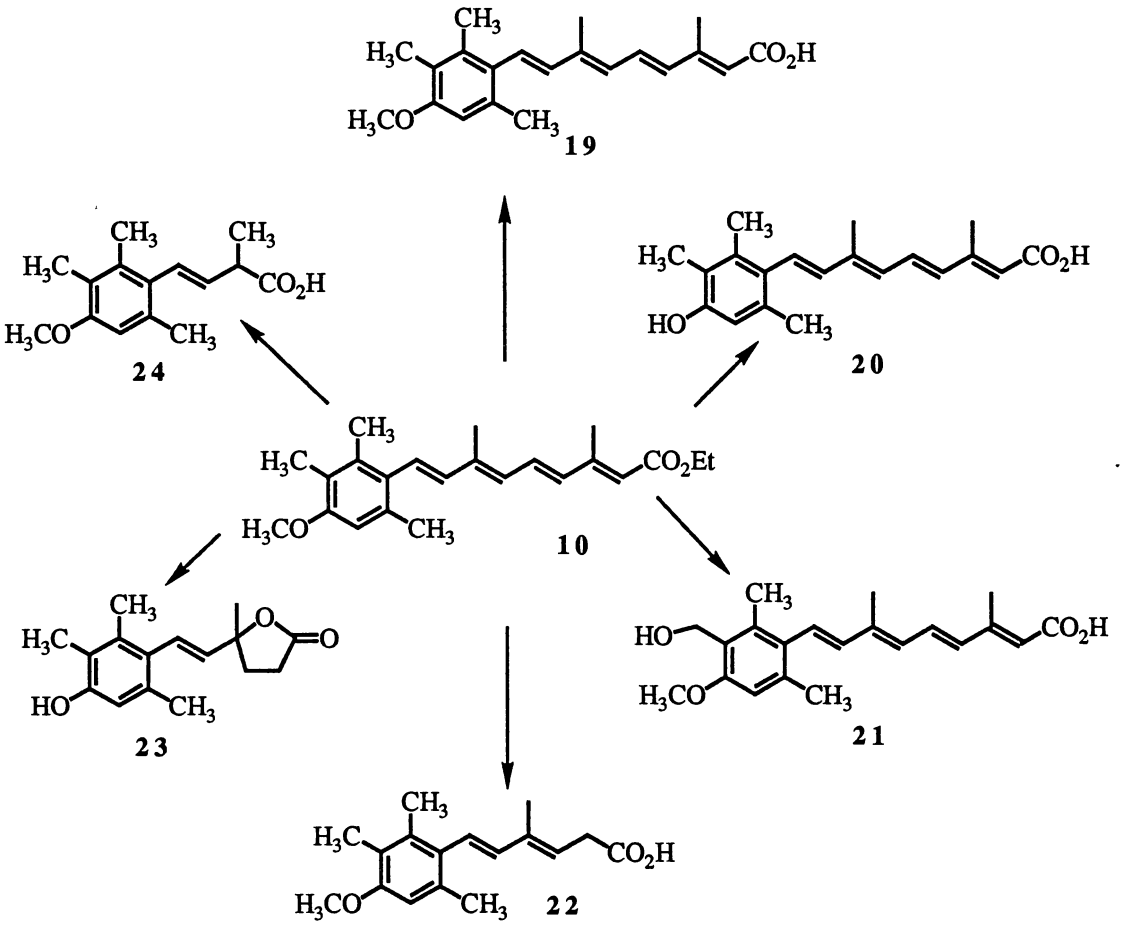


Figure 2. Etretinate (**10**) and Its Metabolites **19-21** Isolated From the Bile of the Rat [33] and **22-24** Isolated From Human Urine[23]

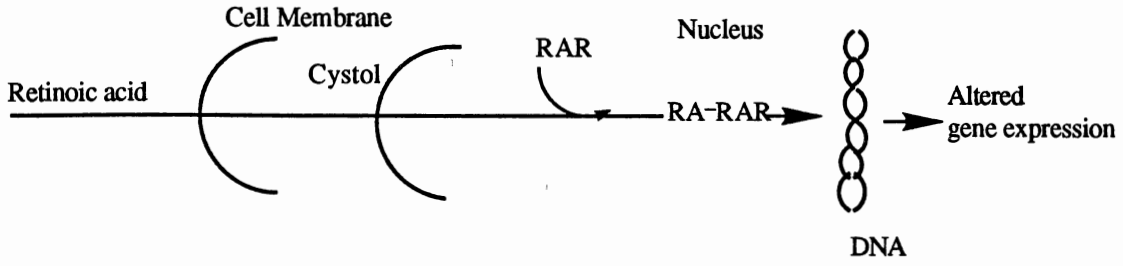
Mode of Action

The important functions of vitamin A (**1**) are exerted in the control of normal differentiation of epithelial tissues, in bone remodeling to maintain growth, and in reproduction.[21,50,78,79] Although the biological and biochemical responses to retinoids have been studied intensively in a variety of different cell systems,[36, 64,68] the mechanism of action is still not fully understood. It is presently clear that retinoids play an important role in the control of cell differentiation and in the inhibition of carcinogenesis.[19, 68]

It is possible that retinoids may exhibit their responses via more than one independent mechanism. There is enough evidence to support the idea that retinoic acid (**3**) influences genomic expression by activating or repressing specific genes.[26] Retinoids are believed to affect the expression of these genes at a transcriptional or post-transcriptional level.[23]

Chytil and Ong[10,11] have proposed that the cellular retinoic acid binding proteins and cellular retinol binding proteins (CRABP and CRBP, respectively) may be involved in the mechanism of action which is reminiscent of that for steroid hormones which act via specific receptors that bind to specific sites in the chromatin thereby altering gene expression. There are conflicting results regarding an exact mechanism of action and the involvement of specific cellular binding proteins. Some studies show that cells which lack CRABP do not respond to retinoids [74] whereas other studies show that cells devoid of any CRABP respond to retinoids.[22,43] Recently, several laboratories[28,54,65] have identified nuclear retinoic acid receptors (RAR's), which belong to a family of receptors that include the receptors for steroids hormones, thyroid hormones and vitamin D_3. It was shown that these receptors have a high affinity for retinoic acid (**3**). These receptors have a molecular weight of approximately 50,000 and are largely associated with nucleus.[51]

Retinoic acid receptors appear to act as ligand responsive transcriptional factors and likely mediate the action of the retinoids on proliferation and differentiation.[37] Three human retinoic acid receptors have been cloned, namely RARα[54] (steroid hormone), RARβ (found in human hepatocellular carcinoma)[5] and RARγ.[42] Recently, another retinoic acid receptor (RXRα) has been cloned[46] which is substantially different from primary sequence from the previously described RAR's. Thus, possibly CRABP transports retinoic acid (**3**) to the nucleus and **3** is then transferred to the nuclear retinoic acid receptor (RAR'S). This pathway represents the retinoic acid-dependent, transacting enhancer factor that interacts with a specific sequence in the DNA (see outline below) thereby inducing changes in the rate of transcription of specific genes.



Pharmacology and Toxicity

It is known that retinoids influence cellular differentiation by modifying gene expression.[66] Depending upon the concentration present in the target tissue, retinoids either induce or adversely affect the normal biochemical expression of differentiation and morphogenesis.[71] Clinically the most important retinoids are, to date, 13-*cis*-retinoic acid (**4**) (Isotretinoin, Accutane, Roaccutan), which has high clinical effectiveness in severe, treatment-resistant modulystic acne,[75] and Etretinate (**10**, Tigason, Tegison) or Acritretin (Neotigeson, Soriatane) which give significant clinical improvement in severe forms of psoriasis, particularly generalized pustular psoriasis.[29] Side effects from the oral treatment of 13-*cis*-retinoic acid (**4**) include abdominal pain, cheilitis, conjunctivitis, xerosis and others.[44] Etretinate (**10**) gives some of the same symptoms as natural retinoids but also poses two additional problems: (1) there are increasing reports of abnormalities in liver function and (2) marked teratogenic properties have been observed, apparently due to the long half-life of this drug after chronic therapy.[44]

It is difficult to test for the effectiveness or the adverse effect of retinoids since the dermatological diseases in which retinoids have shown major effectiveness do not occur in animals. The mouse papilloma system is the useful model, although the skin disorders are not perfectly comparable, but there are a number of features and morphological analogies to skin diseases in human.

A retinoid is considered active when the average diameter of the papillomas per group is reduced by 50%.[4] This is done by measuring papillomas directly. In addition to the effectiveness, a test is performed to determine the dose levels which produce a defined

degree of retinoid side effects (hypervitaminosis A). Since various retinoids are pharmacologically active at different doses and cause side effects at different doses, it is necessary to have a parameter that allows comparision of a large number of retinoids. This parameter is called as therapeutic index (T. I.) and is defined as

$$\text{T.I.} = \frac{\text{Minimal toxic dose causing hypervitaminosis A}}{\text{ED}_{50}\text{ papilloma regression}}$$

The higher the T.I. value, the better the range between these two values and thus the more potent the retinoids (Table I). Table II shows the structures of selected natural and synthetic retinoids (arotinoids and heteroarotinoids) and their activity in the ornithine decarboxylase (ODC) assay. It gives the ID_{50} values (amount of retinoid required to inhibit by 50% the induction of ODC in mouse dorsal epidermis treated with a tumor promoter TPA). The ED_{50} is defined in Table III. All *trans*-retinoic acid (**3**) and 13-*cis*-retinoic acid (**4**) are used as controls. Modification of the ring to give pentamethyl sustituted cyclohexyl ring derivatives showed a good activity (**26** Table II). In the benzoic acid series (**13** and **14**, Table II), both acids demonstrated good activities,[45] but the corresponding esters were found to be less active. When the phenyl ring of compound **14** was replaced by a furan ring (**27**, Table II), ether **27** was found to be completely inactive, probably due to instability of the ester in the epidermus.[16] The heterocyclic derivatives of **13** (**28** and **29**) have a heteroatom at the C(5) position where oxidative metabolism normally occurs.[57] Benzothiopyran derivative **29** was found to be more active than benzopyran derivative **28**.[18,76] The percentage of inhibition as compared to control is calculated as follows:

$$\frac{\text{(ODC with acetone + TPA) - (ODC with retinoid)}}{\text{(ODC with acetone + TPA)}} \times 100$$

TABLE I

THERAPEUTIC INDICES OF VARIOUS RETINOIDS [53]

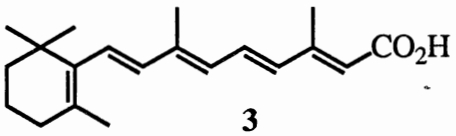
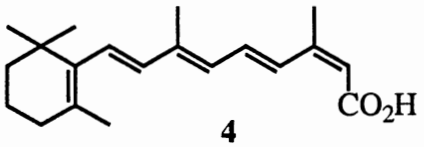
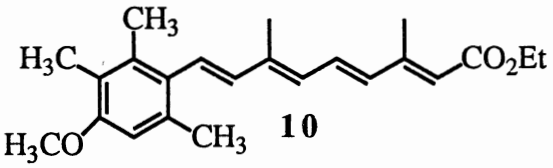
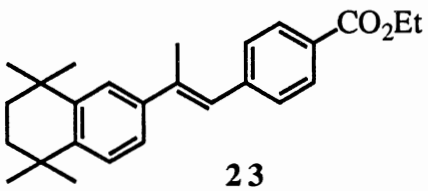
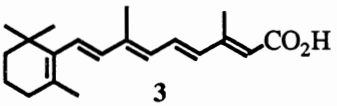
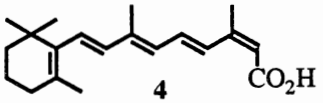
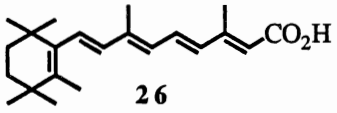
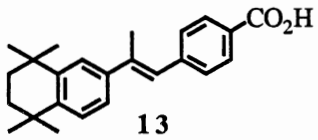
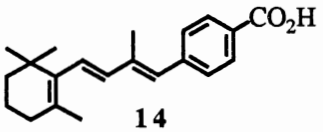
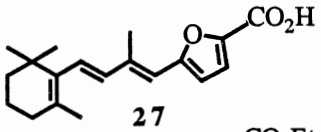
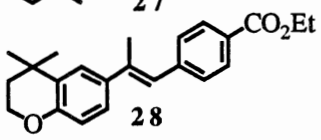
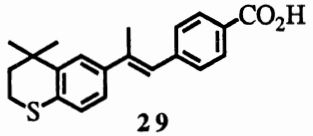
Retinoids	Hypervitaminosis A (mg/kg)	Antipapilloma effect (mg/kg)	T.I
 **3**	80	400	0.2
 **4**	400	800	0.5
 **10**	50	25	2
 **23**	0.1	0.05	2

TABLE II

RETINOID INHIBITION OF MOUSE EPIDERMAL ODC INDUCTION AND TUMOR PROMOTION BY TPA

Retinoid	ODC Assay ID_{50}(nmol)	Antipapilloma Assay ID_{50}(nmol)	Reference
Control			
 **3**	0.04	3.50	17, 45
 **4**	1.40	64.00	17, 45
Ring Modified			
 **26**	0.19	2.50	45
Conformationally Restricted			
 **13**	0.03	0.14	18
 **14**	4.00	---	18
Heteroarotinoids			
 **27**	252.00	---	16
 **28**	0.70	---	18, 76
 **29**	0.50	3.00	18

The hamster tracheal organ culture (TOC) bioassay has been extremely valuable for providing information on retinoid structure-activity relationship.[68] A number of synthetic retinoids have been examined in the TOC bioassay. In this bioassay, an organ culture system is employed that has the capacity for metabolizing the compounds, and thus the activity exhibited by retinoids may be due to the metabolites of that particular retinoid and not the retinoid itself.[77] Introduction of two methyl groups at the C(4) position of the retinoic acid (**3**) (such as **26**, Table III) blocks oxidative metabolism at this position and the activity drops by 50%.[62] Acid **13** exhibited the highest activity of any retinoid screened in the TOC bioassay.[18] Removal of the two methyl groups from the C(5) position of **13** led to acid **32** which showed less activity, thus suggesting the importance of the lipophilic moiety at that end.[62] The benzoic acid derivative **14** (Table III), with the polyene side chain partially replaced by an aryl ring, has only 5% of the activity of retinoic acid (**3**) at 100 fold higher concentration.[52] Ester **30** (Table III) of acid **14** has similar activity. In contrast, shifting the CO_2Et group from the *para* to the *meta* position (**31**, Table III) abolished the activity.[18] The activity increased when the phenyl ring in **14** was replaced by a thiophen ring (**35**, Table III), whereas when it was replaced by a furan ring (**27**, Table III), the activity diminished. In the case of heteroarotinoids, the introduction of benzopyran (**33**, Table III) reduced the ED_{50} by over 1 log unit, compared to that of acid **13**, whereas in the case of the less polar thiobenzopyran (**29**, Table III), the activity was reduced by 60%. The activity increased when the phenyl ring of acids **14** or **32** was replaced by a thiophene ring as in acid **35**.

The main hindrance to clinical utility of presently available retinoids is their toxicity.[35] Thus, prolonged use of retinoids as chemopreventive or therapeutic agents is limited by their toxic side effects. Differences in metabolic degradation, distribution and the *in vivo* storage of various retinoids can lead to differences in toxicity which is one of the important reasons for synthesizing new analogues.[9] The main symptoms of the hyper-

TABLE III

RETINOID ACTIVITY IN TOC ASSAY

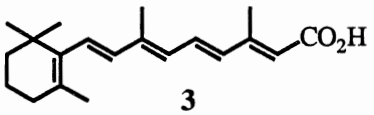
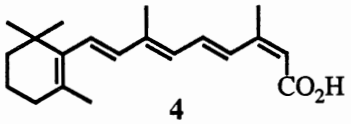
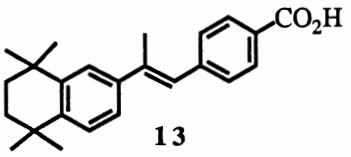
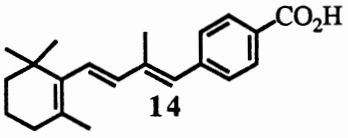
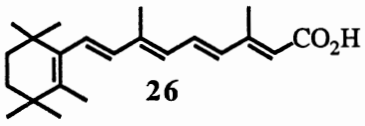
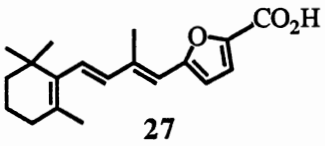
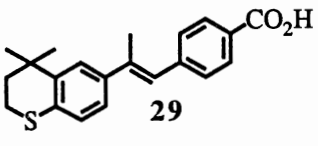
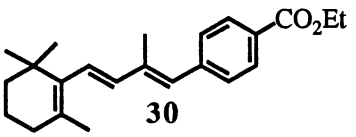
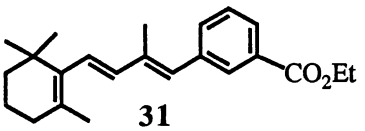
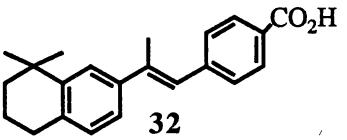
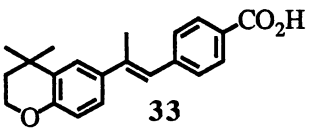
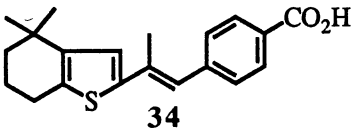
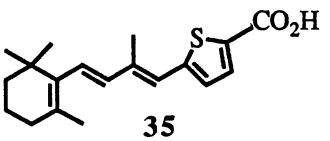
Retinoid Structure	TOC Assay			
	Conc. M	Active Total Culture %	ED_{50}[a],	Reference
 **3**	10^{-10}	86	1×10^{-11}	62
 **4**	10^{-10}	86	2×10^{-11}	62
 **13**	10^{-8}	100	2×10^{-12}	18
 **14**	10^{-8}	100	2×10^{-10}	52
 **26**	10^{-10}	88	2×10^{-11}	62
 **27**	10^{-8}	46	$> 1 \times 10^{-8}$	16
 **29**	10^{-9}	100	5×10^{-11}	18

TABLE III (Continued)

Retinoid Structure	TOC Assay			
	Conc. M	Active Total Culture %	ED_{50}[a],	Reference
 **30**	10^{-8}	100	2×10^{-10}	62
 **31**	10^{-10}	29	$> 1 \times 10^{-8}$	62
 **32**	10^{-8}	100	3×10^{-11}	62
 **33**	10^{-9}	100	2×10^{-10}	62, 76
 **34**	10^{-9}	100	5×10^{-11}	19
 **35**	10^{-8}	100	1×10^{-10}	62

[a]The activities are given as ED_{50}; the estimated dose of retinoid required to reverse keratinization in 50% of the organ culture.

vitaminosis A syndrome in man involve changes in the skin such as cheilitis, desquamation pruntis, pigmentation and hair loss.[9] Other side effects include pain in the bones, joints and muscles as well as hepatic dysfunctions. Teratogenicity has been observed in animals and recently in humans exposed to 13-*cis*-retinoic acid (**4**).[20]

Summary

In conclusion retinoic acid (**3**) plays an important role in cell differentiation and growth promotion.[4,13] Recent studies have indicated that **3** is teratogenic and toxic in high doses.[53] It is evident that incorporation of the heteroatom into the retinoid skeleton does *not* reduce the activity by a wide range. More importantly, the heteroarotinoids are much less toxic than potent arotinoid TTNPB (**13**).[18,70] Studies have also shown that more planar structures with ability to bind to receptors is probably a very important feature for more optimum retinoid activity.[77]

CHAPTER II

RESULTS AND DISCUSSION

We have developed methodologies to synthesize several new heteroarotinoids and potential metabolites of heteroarotinoid **28.** Heteroarotinoid **28** and possible metabolites are shown in Figures 3 and 4.

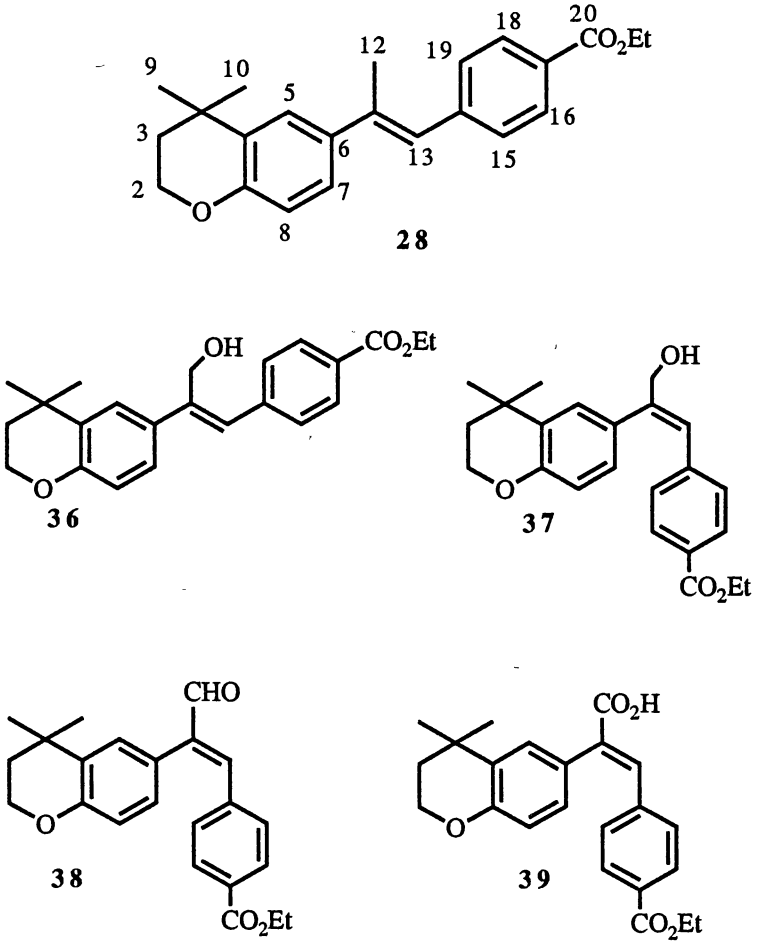


Figure 3. Structures of Heteroarotinoid **28** and Potential Metabolites of Heteroarotinoid **28**

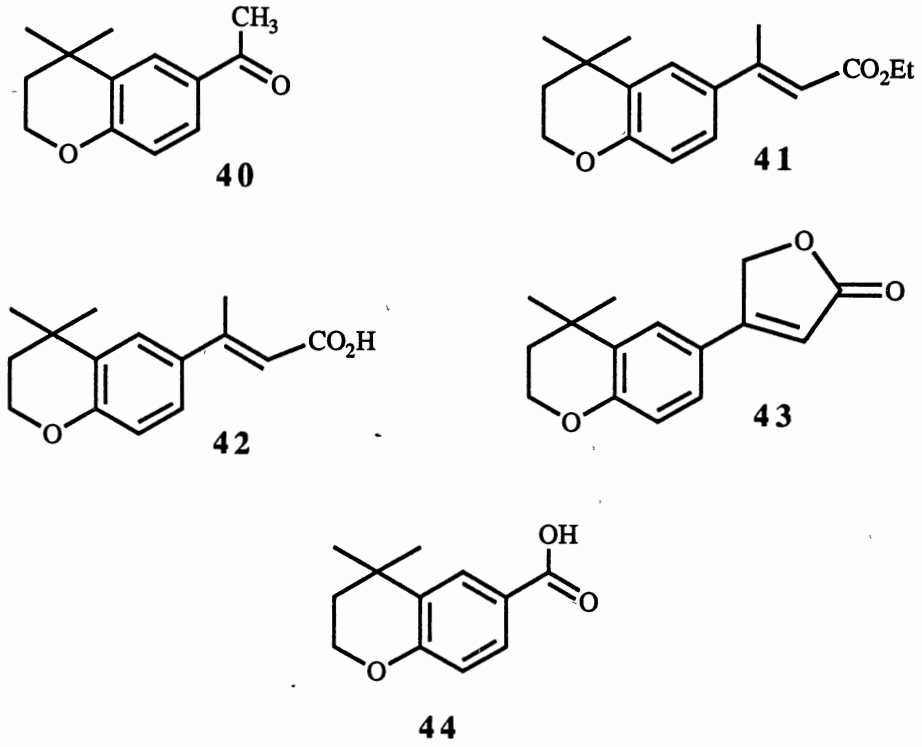


Figure 4. Structures of New Potential Metabolites **40-44** From **28** via Chain Cleavage.

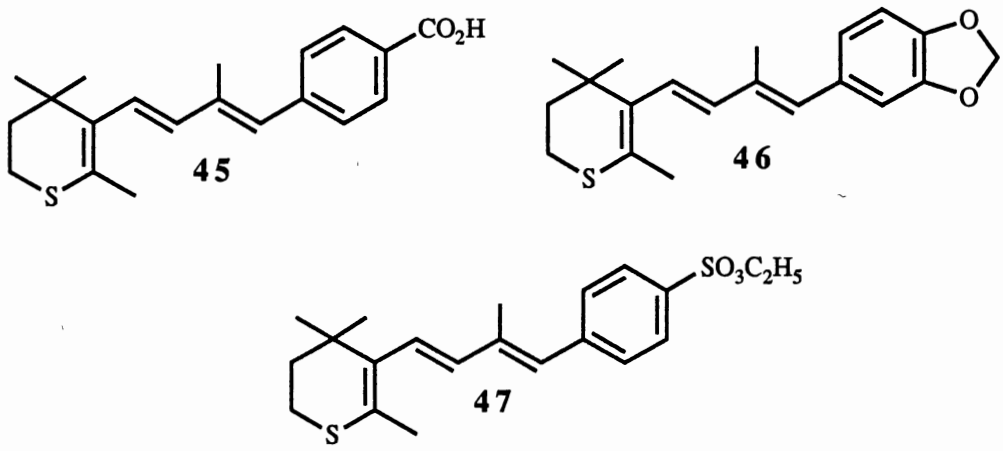
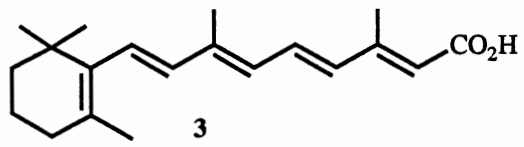


Figure 5. Structures of New Heteroarotinoids **45-47** with a Long Side Chain

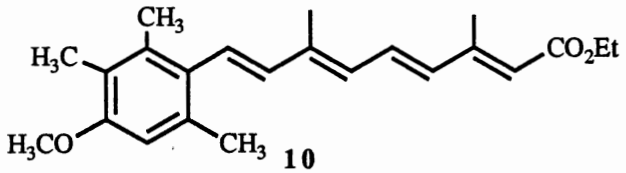
A new group of heteroarotinoids with a long side chain was also prepared (Figure 5).

The compounds **36-44** can be classified as potential oxidative metabolites of ethyl (*E*)-4-[2-(3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-1-propenyl]benzoate (**28**). Hetero-arotinoid **28** had been synthesized in our laboratory and had been shown to possess good activity in several bioassays.[19,76]

The potential metabolites **36-44** can further be classified into two groups, namely that obtainable from the oxidation of the allylic methyl group at C(12), as in compounds **36-39** (Figure 3), and those in which the side chain has undergone oxidative cleavage as in compounds **40-44** (Figure 4). The products prepared as potential metabolites of **28** are, to some degree, reminiscent of those observed from *trans*-retinoic acid (**3**) and from the clinically-approved, synthetic arotinoid Etretinate (**10**) (see pages 5 and 6). It has been documented that retinoic acid (**3**) undergoes oxidative metabolism[32] and some of the *in vivo* metabolites were found to be active whereas some were apparently produced for the purpose of excretion.[53]



3



10

Figure 5 shows the structures of new and novel heteroarotinoids which have a longer polyene side chain (compared to that in **28**) and thus are possibly closer mimics of retinoic acid (**3**). A sulfur atom has been sustituted for C(4) in the cyclohexenyl ring of the retinoic acid (**3**), and a small part of the polyene side chain was condensed into an aromatic ring. These compounds were made by multi-step syntheses starting from commercially available reagents. The intermediates in the syntheses are shown in Figure 6.

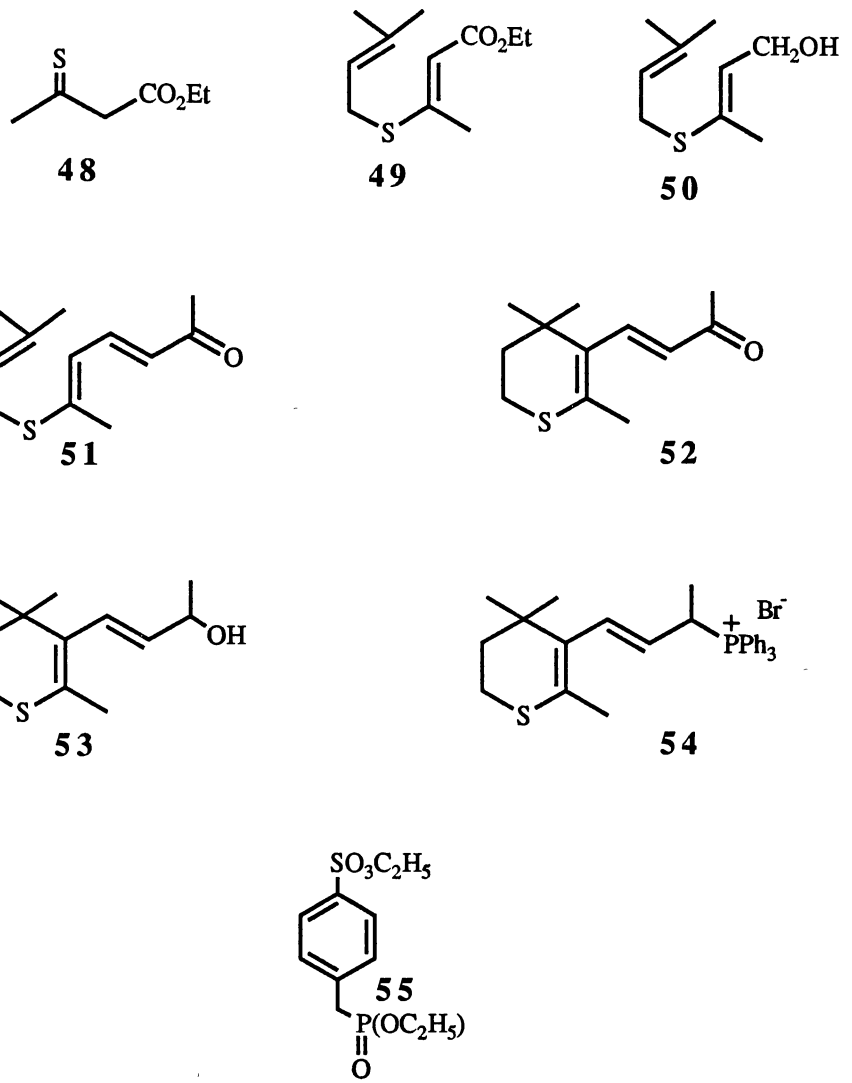
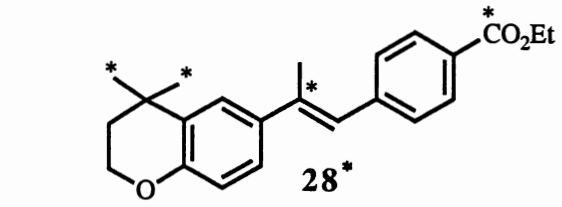
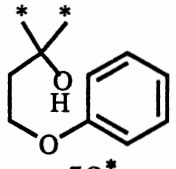


Figure 6. Intermediates in the Syntheses of New Heteroarotinoids **48-55**

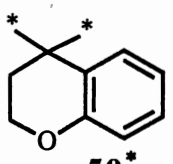
In order to investigate the potential metabolites obtainable from **28**, it was decided to prepare labelled heteroarotinoid **28***. Figure 7 shows labelled compound **28*** and the intermediates for the syntheses (* carbon atoms denote a ^{14}C label introduced into **28***). In collaboration with Dr. Nelson and co-workers in the Biochemistry Department, a current investigation is underway to determine the pharmacokinetics and the major metabolites formed *in vivo* in rats given compound **28***.



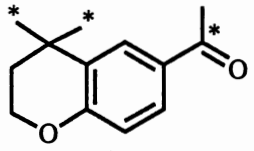
28*



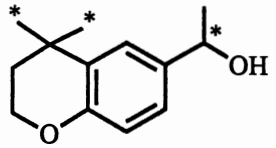
58*



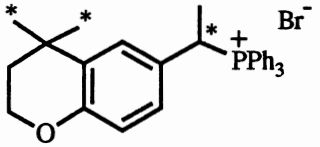
59*



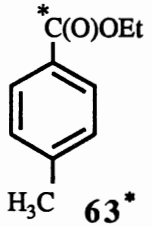
40*



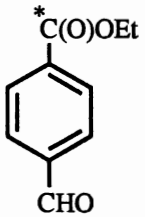
50*



61*



63*



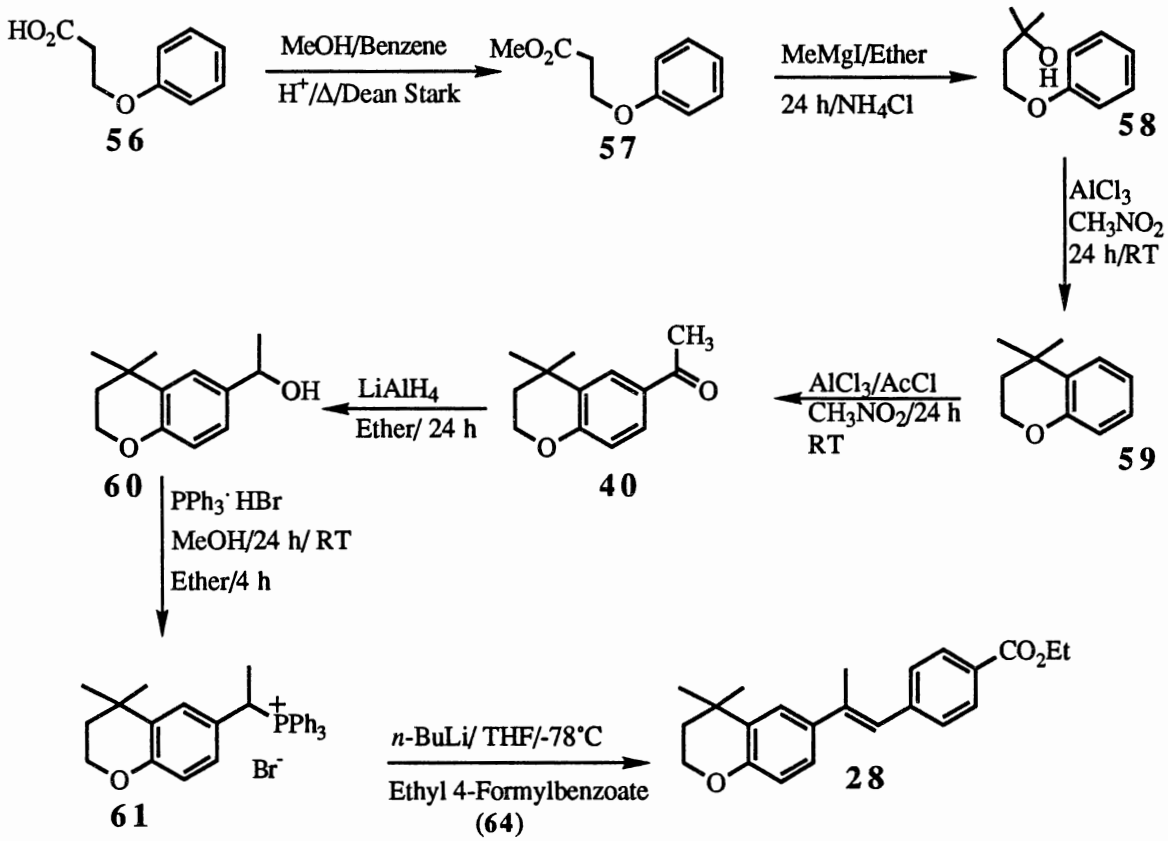
64*

Figure 7. Labelled Heteroarotinoid **28*** and Synthetic Intermediates.

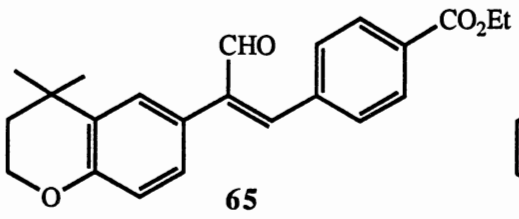
Synthetic Methodology

The ester **28** was synthesized according to Scheme I and as reported in the literature.[76] Pure **28** was obtained as white crystalline solid (95% ethanol), mp 72-73°C (lit[76] mp 72.5-73.5°C).

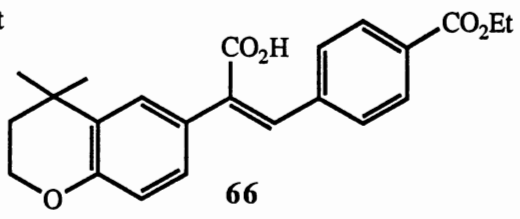
SCHEME I



The approach to obtain potential metabolites **36-39** (page 16) utilized the parent compound **28** as starting material. Compounds **36-39** could be envisioned as accessible via successive oxidation of the allylic methyl at the C(12) first to hydroxymethyl derivatives **36** and **37**, then to aldehyde **38**, and finally to carboxylic acid **39**. Of course, isomeric aldehyde *Z*-**65** and acid *Z*-**66** are conceivable from the procedures but were not



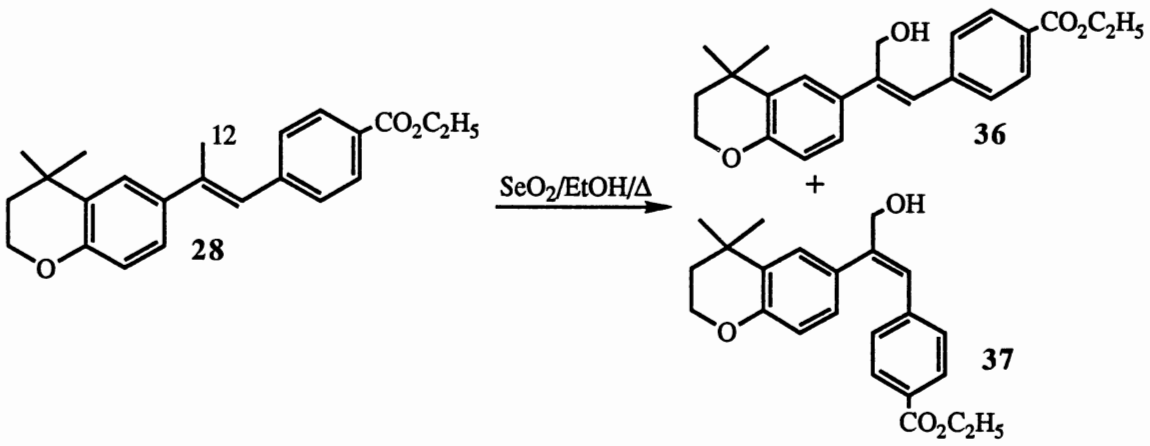
65



66

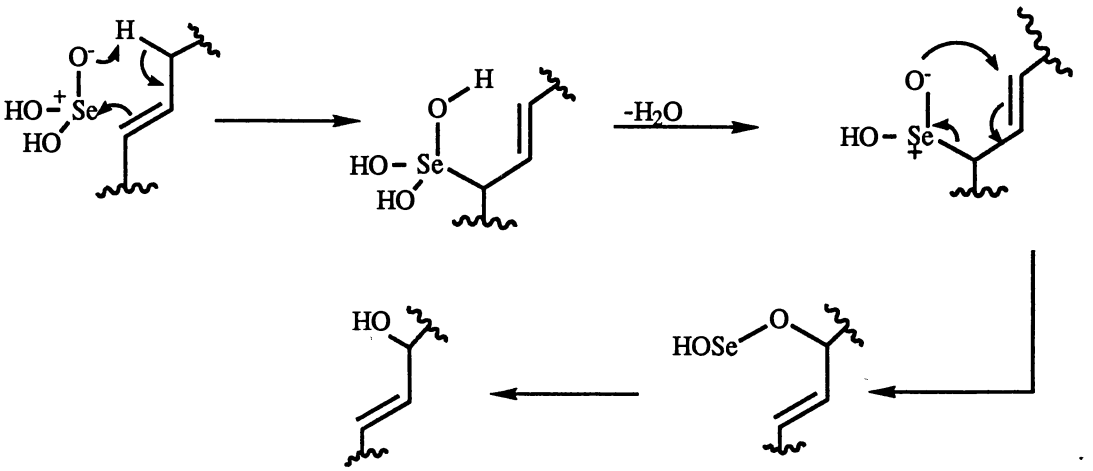
observed.

A literature search and some previous experience in the area of oxidation of this type of heterocyclic system suggested that SeO_2 might be the the reagent of choice for the oxidation of the C(12) methyl group to the corresponding hydroxymethyl group. Indeed, that was the case as illustrated below. Both isomers **36** and **37** formed but, surprisingly, the major product isolated was the *E*-isomer **37** in which the two phenyl rings were *syn* to each other.

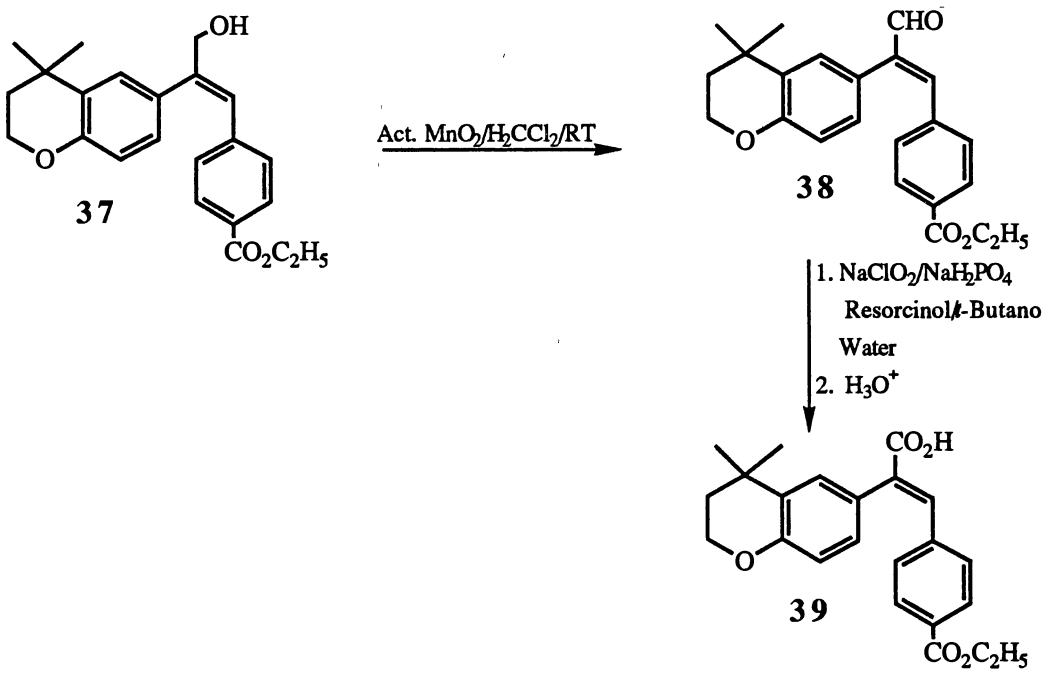


This could be explained on the basis of the mechanism[63] of oxidation with SeO_2 which involves a [2,3]-sigmatropic shift in one of the intermediates as shown below. Small quantities of the allylic alcohol **36** (*Z*-isomer), along with some aldehyde **38,** were also detected. An oxidation experiment was carried out using 3 equivalents of the SeO_2 in boiling 95% ethanol with **28**. Although allylic alcohol **37** was obtained in fair yield (31%), increasing the reaction times or the number of equivalents of SeO_2 did not change

the yield of **37**.



The *E*-isomer **37** was purified on a 4 mm silica gel plate (Chomatotron) using a gradient elution with hexanes:ethyl acetate (8:2; 7:3) as eluents. Ester **37** was obtained as a thick, yellow-colored oil but all measures to convert it to a solid failed. The elemental analysis of the oil showed the presence of trace amounts of water which were retained even after prolonged heating under vacuum (110°C, 10 mm Hg). However ^{1}H, ^{13}C NMR and the mass spectral analyses confirmed the stucture of **37**.



The *E*-isomer **37** was used as starting material for preparation of aldehyde **38**. Treatment of **37** with activated MnO_2[1] in CH_2Cl_2 at room temperature gave the corresponding aldehyde **38** (76%) which was isolated as a yellow-colored solid melting at 157-158°C. Again in this reaction, the major product isolated was isomer **38** in which the two phenyl groups were syn to each other.

Carboxylic acid **39** was obtained by direct oxidation of aldehyde **38** as shown. Various oxidizing reagents were employed in attempts to effect this latter conversion, including the conventional use of moist Ag_2O[47] and NiO_2[7], but the best results were obtained when the unusual reagents shown were employed. Teatment of aldehyde **38** with $NaH_2PO_4/NaClO_2$ in *t*-butanol gave acid **39** in a yield of 82%. Since ClO_2 (the oxidant generated in this reaction) and Cl^- are formed *in situ,* resorcinol was added as a scavenger to limit further oxidation.[2]

Confirmation of all the products was established by UV, mass, ^1H NMR and ^{13}C NMR spectral analyses. A comparison of the UV maxima of stilbene and some of its derivatives, along with some arotinoids and heteroarotinoids, is given in Table IV. As can be seen from the Table, the *E*-isomers have a maxima with higher ε values at long wavelengths whereas the *Z*-isomers have a maxima with higher ε value at shorter wavelengths. Thus, it is implied that the *E*-isomers have greater conjugation and are probably more nearly planar.

Another class of potential metabolites are **40-44** (page 17) in which the side chain of the parent compound **28** has undergone a C-C cleavage concommitant with some oxidation. The approach to these compounds originated from the 4,4-dimethylchroman **40** which had been an intermediate in the synthesis of compound **28**[76] and could itself be a metabolite. Condensation of **40** with triethyl phosphonoacetate (**67**) using NaH/THF yielded the α,β-unsaturated ester **41** isolated as a thick oil. The oil was purified on a silica gel plate (Chromatotron). Saponification of ester **41** with 4.3% alcoholic KOH gave, after

TABLE IV

UV DATA OF SELECTED STILLBENE DERIVATIVES AND SOME HETEROAROTINOIDS

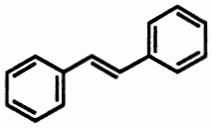
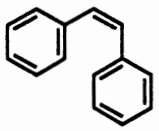
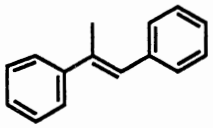
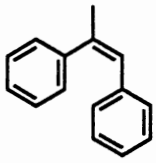
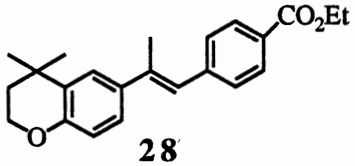
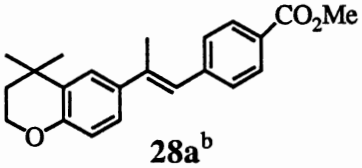
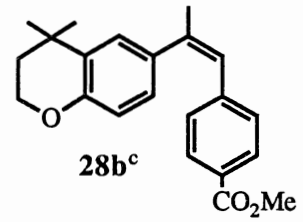
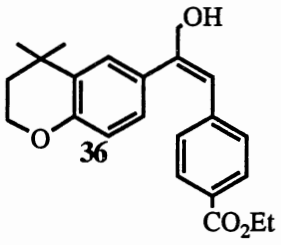
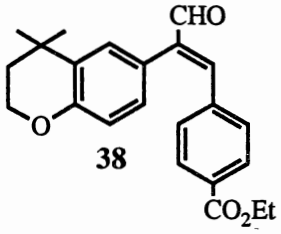
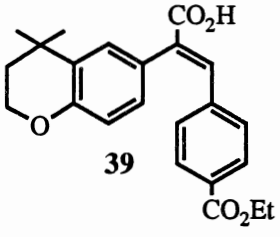
Compound	Conjugation band λ_{max}, nm (ε, x 10^4)	Lower-wavelength band λ_{max}, nm (ε, x 10^4)	Solvent
 *trans*-Stilbene[a]	294.5 (2.78)	228.8 (1.64)	95% EtOH
 *cis*-Stilbene[a]	280.0 (1.04)	224.0 (2.44)	EtOH
 *trans*-1,2-diphenylpropene[a]	272.0 (2.10)	----	EtOH
 *cis*-1,2-diphenylpropene[a]	267.0 (0.93)	---	EtOH
 **28**	316.0 (2.40)	236.0 (1.40)	EtOH
 **28a**[b]	318.0 (2.50)	237.0 (1.50)	EtOH

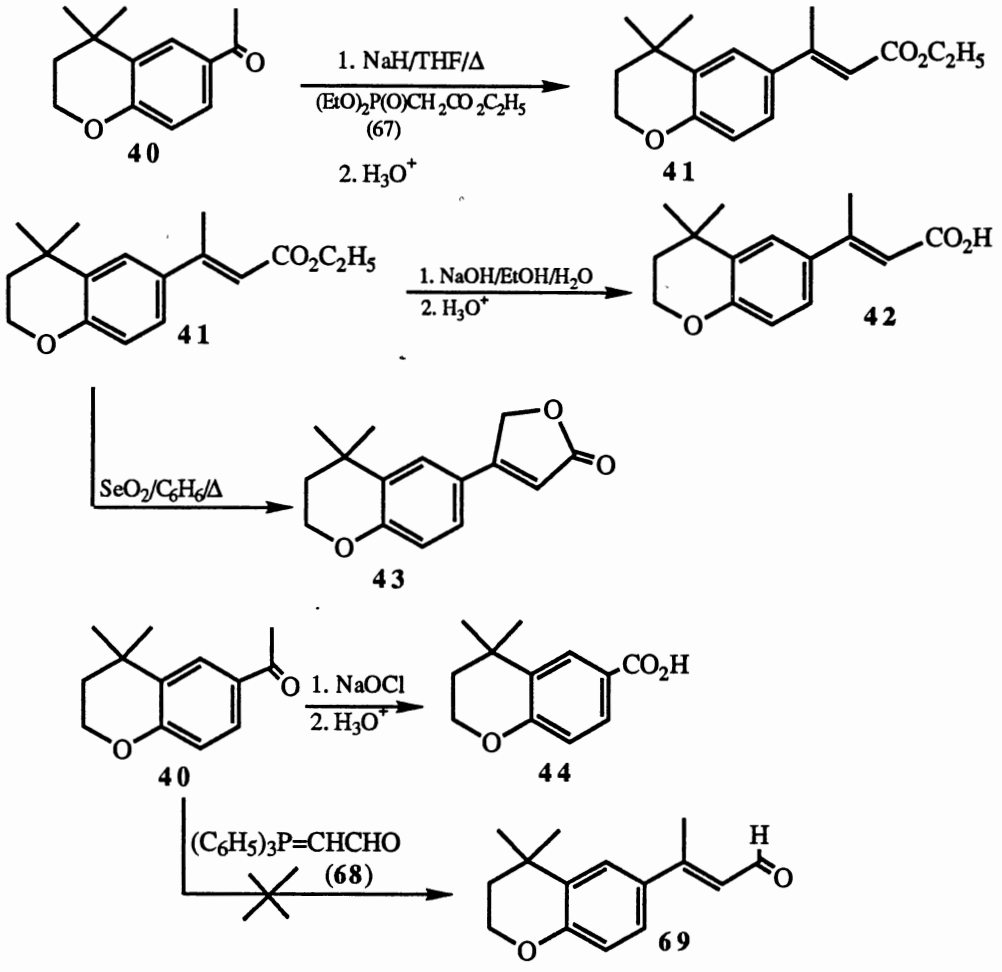
TABLE IV (Continued)

Compound	Conjugation band λ_{max}, nm (ε, x 10^4)	Lower-wavelength band λ_{max}, nm (ε, x 10^4)	Solvent
 **28b**[c]	310.0 (1.60)	245.0 (2.20)	EtOH
 **36**	284.0 (1.16)	240.0 (1.41)	95% EtOH
 **38**	330.0 (0.37)	286. 0 (1.47)	95% EtOH
 **39**	330.0 (0.66)	286.0 (1.28)	95% EtOH

[a]Suzuki, H. *Bull. Chem. Soc. Jpn.* **1960**, *33*, 379-388, 396-405.

[b]Methyl (*E*) 4-[2-(3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl-1-propenyl]benzoate (**28a**) (reference 27).

[c]Methyl (*Z*) 4-[2-(3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl-1-propenyl]benzoate (**28b**) (reference 27)



neutralization, acid **42**. Acid **42** was obtained as a white solid after recrystallization (alcohol:water, 1:1). This acid retained traces of water in the crystals even after drying under vacuum for several hours. The mass spectral analysis, along with ^{1}H NMR and ^{13}C NMR spectra, confirmed the structure of the acid **42** unambiguously.

Another interesting metabolite, which has a structure similar to the metabolites **18** (page 5) and **23** (page 6) obtained from *trans*-retinoic acid (**3**) and Etretinate (**9**), respectively, is that which contains a butyrolactone ring, namely **43**. One method for the synthesis of this general type of system has been described by Corey and co-workers.[12] In our example,

conversion of **40** to the homologated α,β-unsaturated aldehyde was the key initial step. Reaction of ketone **40** with (triphenylphosphoranylidene)acetaldehyde (**68**, Aldrich) did *not* generate the homologated aldehyde **69**. A comprehensive literature search revealed an obscure example in the field of steroid chemistry wherein an unsaturated ester was converted to a lactone using SeO_2.[15] Treatment of α,β-unsaturated ester **41** with SeO_2 in boiling benzene resulted in the formation of lactone **43** in a one-pot reaction. The Δ-butanolide derivative **43** is likely formed via initial oxidation of the allylic methyl group to a hydroxymethyl function which undergoes lactonization with concommitant loss of ethanol. After workup, lactone **43** was obtained as a thick oil which solidified upon trituration. Purification (95% ethanol) of the lactone gave a yellow-colored, crystalline solid melting at 133-134°C, identified by spectral analyses (see Experimental).

Carboxylic acid **44** was obtained as a white solid when methyl ketone **40** was treated with household bleach "Clorox" (5.25% NaOCl) mixed with 95% ethanol. The yield of **44** was 67%. The simplicity of this method is an asset.

In order to study the metabolism of the compound **28** in rats, it was decided to synthesize labeled **28*** incorporating a ^{14}C label at certain positions so as to facilitate a determination of the pattern of cleavage *in vivo*. Stratigically positioned ^{14}C atoms or markers could also help in identification of metabolites via comparison with labelled compounds synthesized as potential metabolites. The synthesis of **28*** with ^{14}C label at four different carbon atoms was achieved as illustrated (Figure 8).

Methyl 3-phenoxypropionate (**57**) was prepared from commercially available 3-phenoxypropionic acid (**56**). Treatment of **57** with two equivalents of $H_3{}^{14}CMg\text{-}I$ [prepared from $H_3{}^{14}CI$ (^{14}C, 2.5 mg, 1 mCi, 56.6 mCi/mmol sp.act., ICN) and Mg] gave the corresponding labelled tertiary alcohol **58***. Cyclialkylation of alcohol **58*** in presence of anhydrous aluminum chloride in nitromethane produced 4,4-dimethylchroman **59*** with the ^{14}C label at the *gem*-dimethyl groups. Acetylation of **59*** was effected with $H_3C{}^{14}C(O)Cl$ (1 mCi, 50 mCi/mmol, sp. act., ICN) and $AlCl_3$ to yield methyl ketone

40*. Reduction of **40*** with $LiAlH_4$ resulted in formation of secondary alcohol **60*** with labels at three carbons. Phosphorylation of the alcohol with triphenylphosphine hydrobromide gave the phosphonium salt **61***.

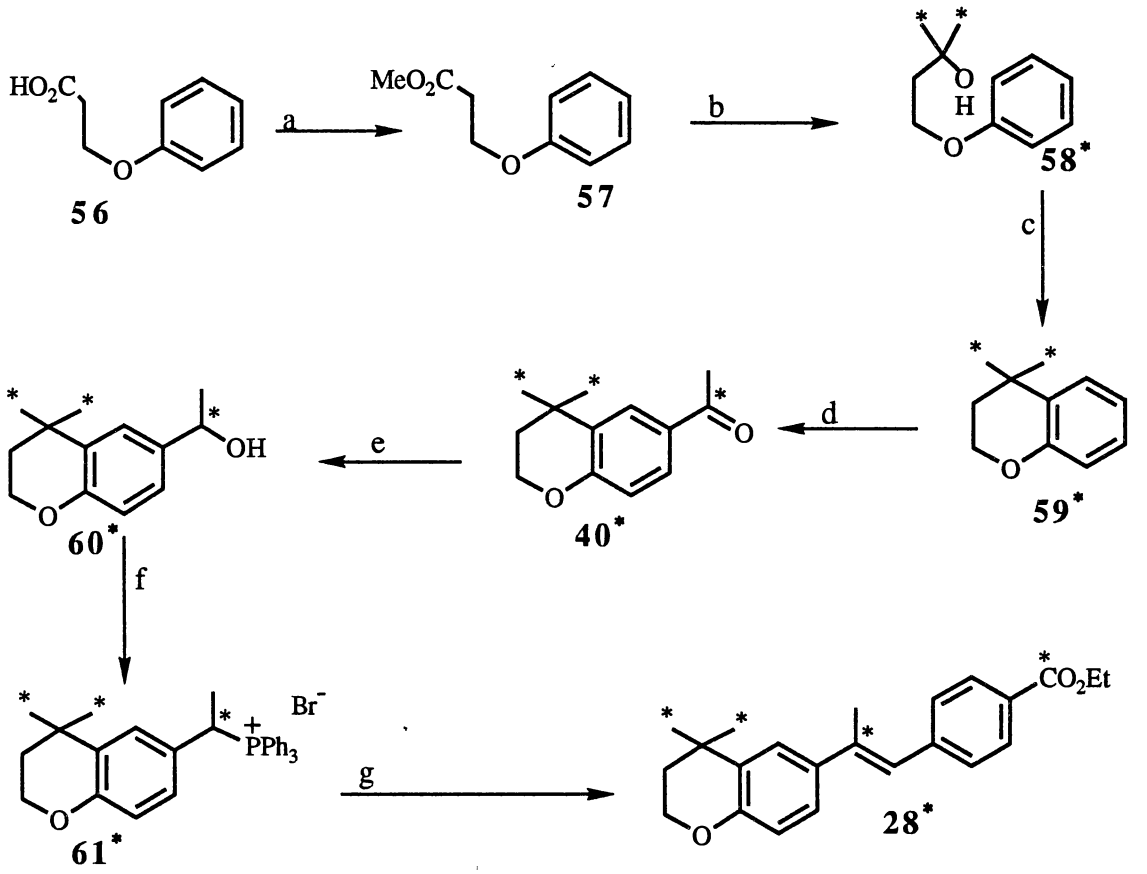
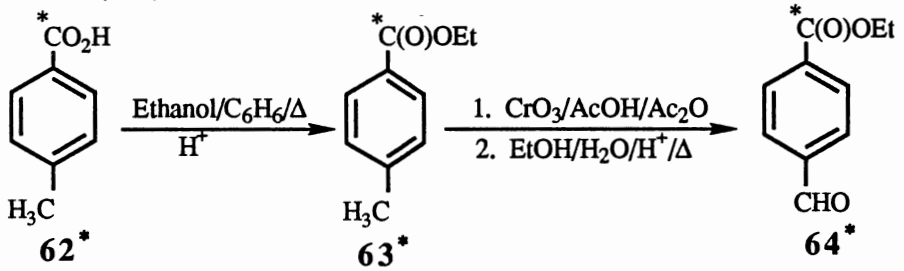


Figure 8. Preparation of Heteroarotinoid **28*** (a) MeOH, H^+, C_6H_6, heat, Dean-Stark; (b) $^{14}CH_3MgI$, Ether; (c) $AlCl_3$, CH_3NO_2; (d) $H_3C^{14}C(O)Cl$, $AlCl_3$, H_3CNO_2; (e) $LiAlH_4$, Ether; (f) $Ph_3P{\cdot}HBr$, MeOH, Ether; (g) *n*-BuLi, Ether, 4-OHC-$C_6H_4{}^{14}CO_2Et$ (**64***)

The ^{14}C-labelled phosphonium salt was then mixed with some cold phosphonium salt, and the mixture was used in the Wittig condensation. In this final step, the anion generated from phosphonium salt **61*** was treated with ethyl 4-formylbenzoate [**64***, $^{14}C(O)OEt$] at -78°C, and then the reaction was allowed to warm and stir for 24 h at room temperature. Purification of a yellow-colored oil obtained was achieved on a Chromatotron (4 mm silica

gel plate) using 200 mL of hexanes:ethyl acetate (9:1) as eluent. The bands with highest R_f values (0.75 and 0.7) were collected, and the solvent was evaporated to give a colorless oil. A solution of this oil in 95% ethanol was refrigerated to give the target labelled heteroarotinoid **28***. The specific activity was determined on a 10μL aliquot of a solution (prepared by dissolving 7.3 mg of **28*** in 4 mL of HPLC grade methanol) via the use of a TRI-CARB liquid scintillation analyzer. The specific activity of **28*** was 0.15 mCi/mg or 4.28×10^{-5} mCi/mmol. An average count of 6043.8 DPM (disintegrations/minute) was obtained. This low activity must result from losses at one of more steps. Some use of **28*** was possible by Dr. Nelson although reliance on UV spectral analysis to detect **28*** was excellent at 10^{-4}M and even lower concentrations.

Aldehyde **64***, used in the last step to prepare **28*** was synthesized from commercially available *p*-toluic acid-^{14}C=O (**62***, 0.5 mCi, 4.5 mCi/mmol sp. act., Sigma). Esterification of **62*** with ethanol in presence of concentrated sulfuric acid, while removing the water as an azeotrope with benzene, gave ethyl *p*-toluate-^{14}C=O (**63***). Oxidation of ester **63*** with CrO_3 in acetic acid/acetic anhydride produced ethyl 4-formy-l benzoate ^{14}C=O (**64***).[78]



We, in collaboration with Dr. Nelson of the Biochemistry Department, were able to identify certain metabolites from the bile of rats injected with **28.** Identification of metabolites from **28** was done by comparing HPLC and the mass spectral profiles, as well as the UV spectra, with those obtained for synthesized potential metabolites. As can be seen from one region of the HPLC profile of bile and the HPLC profile of the standards, (Figure 9), two peaks appear at about the same T_R value (75 and 79 min) which two bands

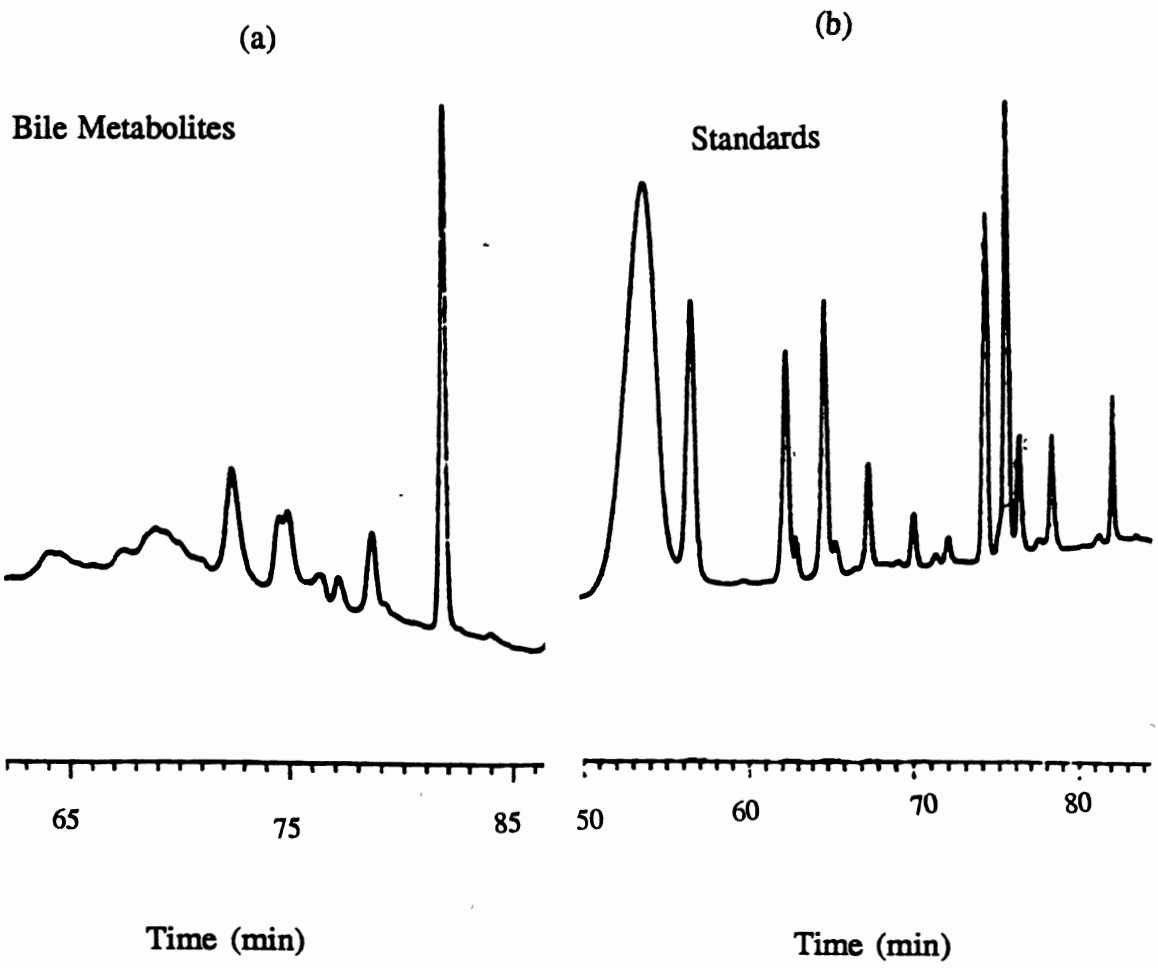


Figure 9. HPLC Profile of (a) Section of Bile and (b) Standard Metabolites [C18 reverse phase (Whatman, ODS-3, 0.47 x 23.5 cm), flow rate 1 mL/min, at 22°C and 1600 psi, with 0.01*M* HOAc:MeOH (7:3)]

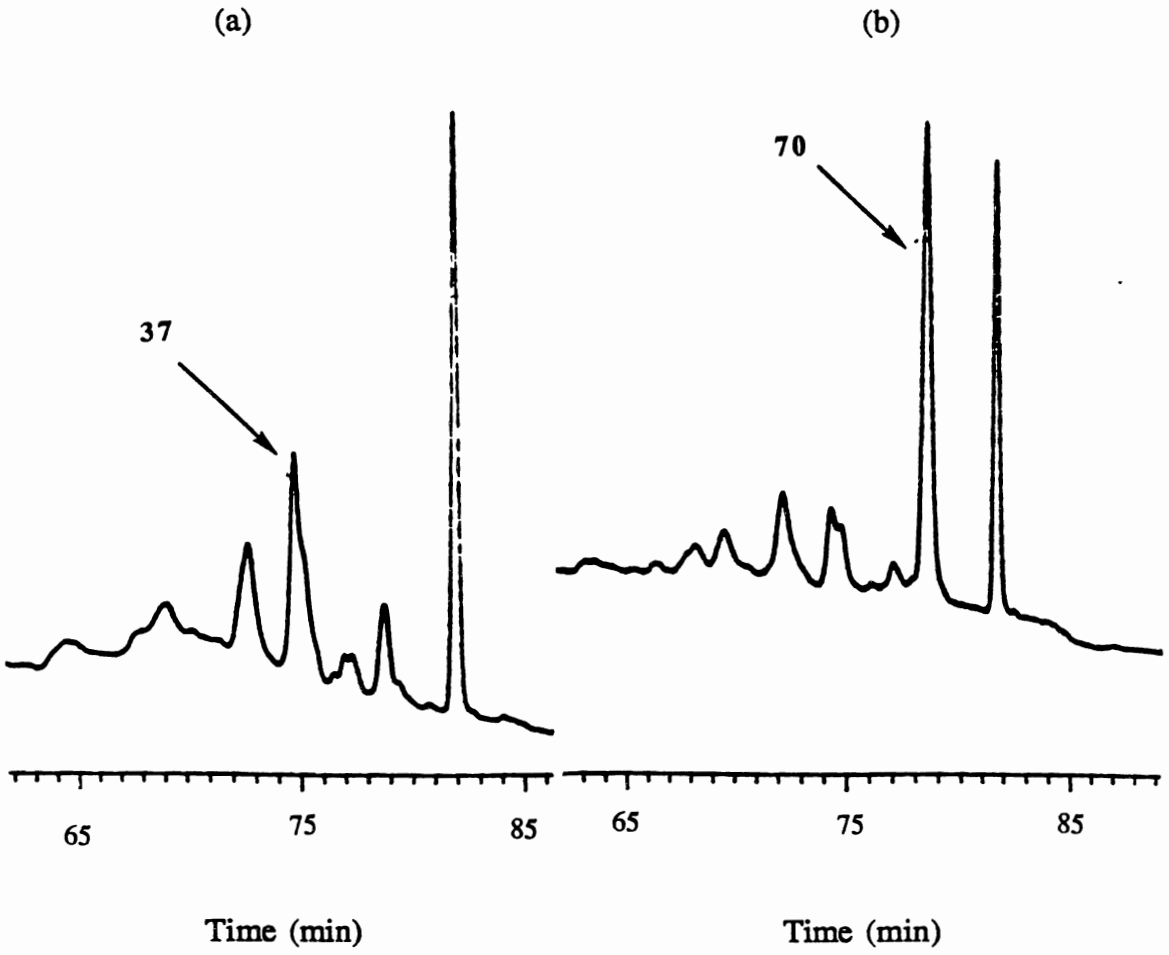


Figure 10. HPLC Profile of Bile Sample Spiked With Standards (a) **37** and (b) **70** [C18 reverse phase (Whatman, ODS-3, 0.47 x 23.5 cm), flow rate 1 mL/min, at 22°C and 1600 psi, with 0.01*M* HOAc:MeOH (7:3)]

correspond to ester **37** and the acid **70**, respectively (Figures 9 and 10). This was furthur confirmed by spiking the HPLC sample of bile with the standard compounds, and, as expected the peak height increased (Figure 10). Additional evidence for the presence of the compounds was obtained by comparison of the molecular ion in the mass spectra. The $MH^{+\bullet}$ peak, in the case of ester **37**, was seen at 367 *m/z*, whereas that in case of acid **70** was seen at 323 *m/z* in both the standards and the fragments obtained from the bile.

Another interesting study undertaken in collaboration with Dr. Nelson was to determine the nutritional value of heteroarotinoid **28** in comparison with that of retinoic acid (**3**). In this study, the gain in weight of rats whose diets were supplemented with or without ester **28** or retinoic acid (**3**) was monitored over a period of 95 days. The rats were maintained initially on a vitamin A deficient diet until their weight plateaued. From this day (day 0), the rats were fed with diets supplemented with retinoic acid (**3**, in the case of control rats) or with compound **28** (in the case of test rats). As can be seen from the graphs (Figure 11), growth with ester **28** paralleled that induced by *trans*-retinoic acid (**3**). Thus **28** could have some nutritional value and should be investigated more extensively.

Syntheses Of New Heteroarotinoids

In recent years the main objective of the researchers in the field of retinoids has been to synthesize compounds which would be close mimics of *trans*-retinoic acid (**3**), would exhibit good activity at low dose levels, and would be less toxic compared to **3**. It has been shown with heteroarotinoids that the incorporation of a sulfur atom to replace C(4) reduces toxicity while maintaining good activity in several assays.[69] We have prepared new heteroarotinoids **45-47** (page 17) which substitutes a sulfur atom for C(4) and may alter metabolism at that position.[24] Part of the side chain has also been condensed into an

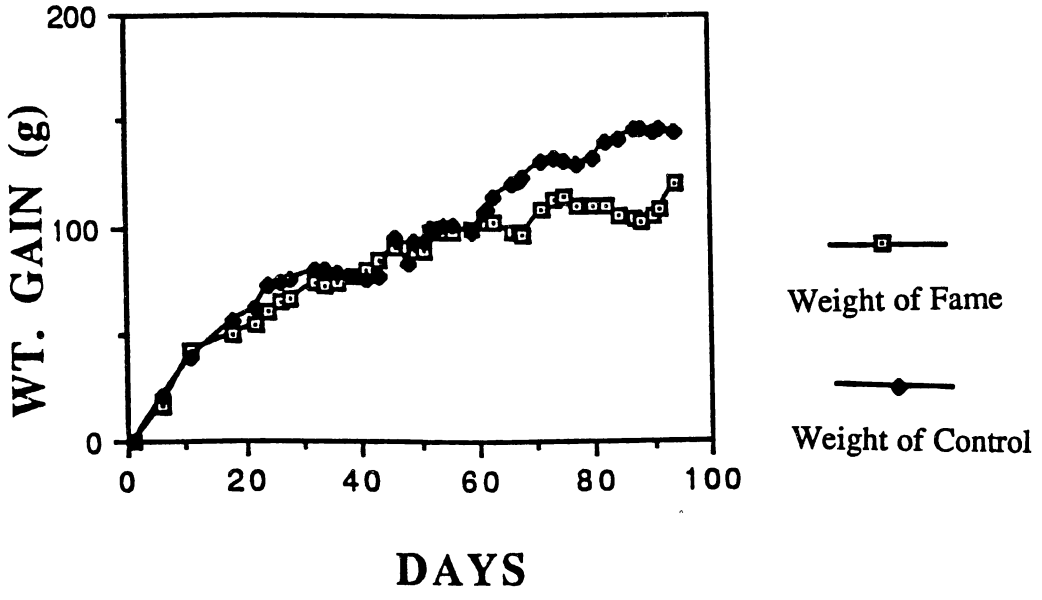
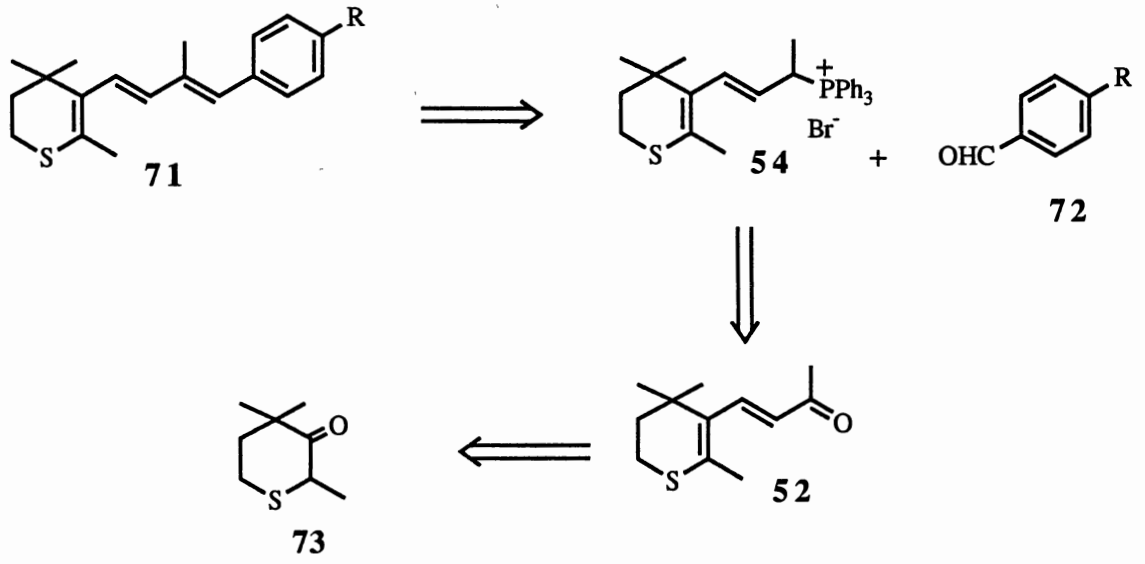
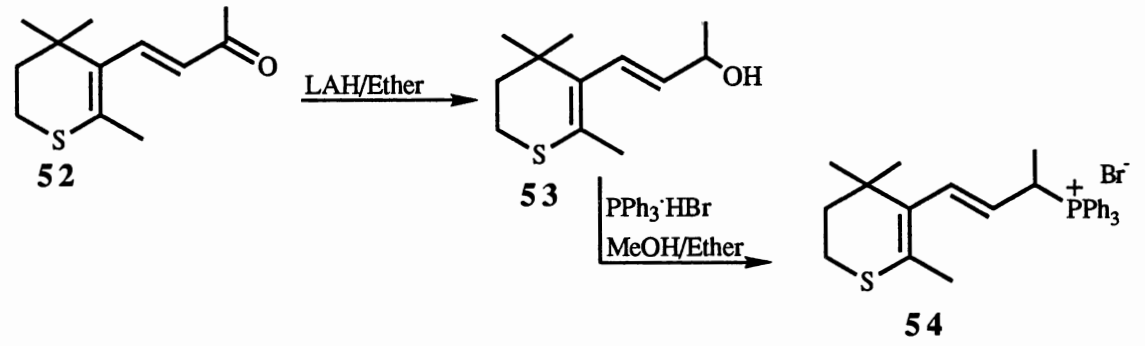


Figure 11. Growth Curve For Retinoic Acid (**3**, Control Rat) and Heteroarotinoid **28** (Test Rat Fame)

aromatic ring thus restricting rotation along those bonds and possibly making the structure more planar. A retro-synthetic approach to the basic skeleton for this compound can be envisioned as follows.

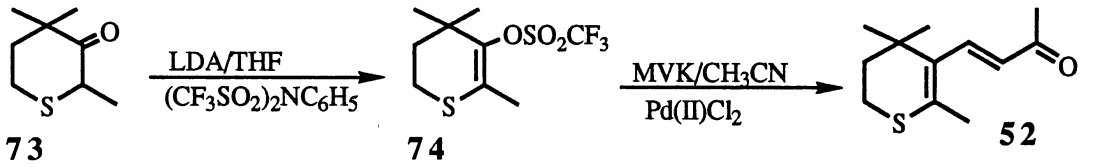


An important intermediate in this multi-step synthesis was the thiaionone **52.** With the thiaionone **52** in hand, conversion was effected to the corresponding alcohol **53**, which, upon phosphorylation, could yield the phosphonium salt **54**. Phosphonium salt **54** could then be condensed with various aldehydes under Wittig reaction conditions to give the target heteroarotinoids **45-47**.

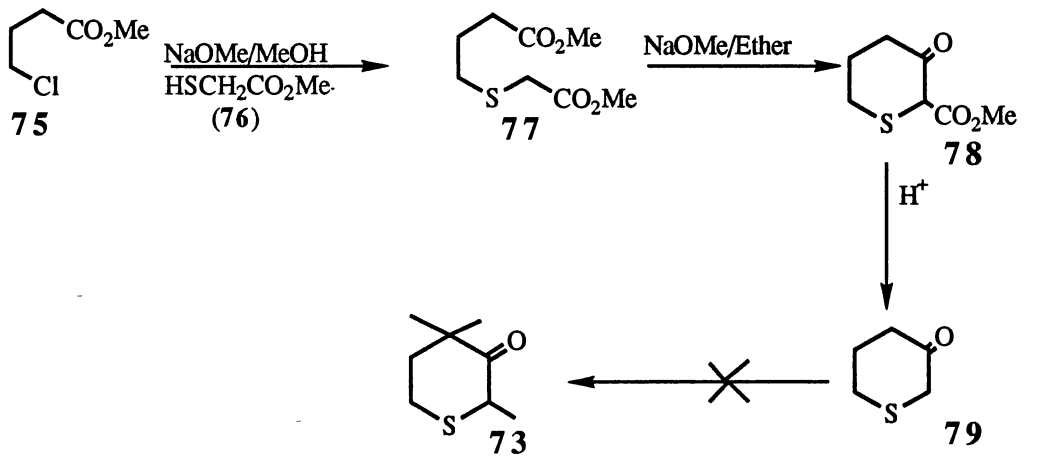


A viable starting material for intermediate ketone **52** was 2,4,4-trimethylthiacyclo-

hexan-3-one (**73**) which could be converted to **74**. One possible route to ketone **52** from **73** is as indicated below. As 2,4,4-trimethylthiacyclohexan-3-one (**73**) was not



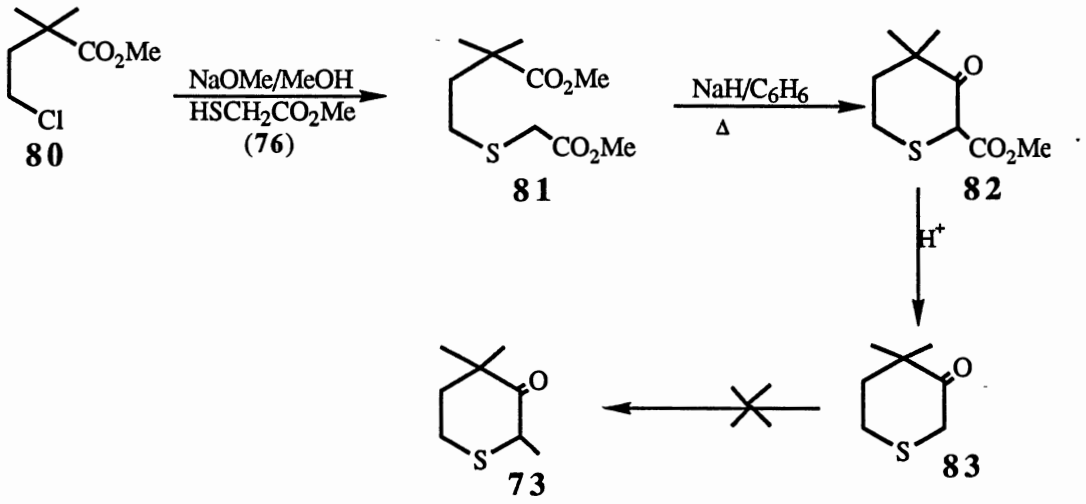
commercially available, a synthesis was developed, an initial approach is shown below as **75** + **76**→**77**→**78**→**79**→**73**.[80]



Condensation of methyl 4-chlorobutyrate (**75**) with methyl thioglycolate (**76**) gave diester **77**. Cyclization of **77** under Dieckmann conditions using NaOMe gave thia β-keto ester **78** which was saponified and decarboxylated to thiacyclohexan-3-one (**79**). However, all attempts to alkylate thiacyclohexan-3-one (**79**) or β-keto ester **78** failed. In all cases either the starting material or a complex mixture was obtained from which no pure product could be isolated.

Another approach to **73** was to condense methyl 2,2-dimethyl-4-chlorobutyrate (**80**) with methyl thioglycolate (**76**) which gave the corresponding diester **81** (68%).

Dieckmann cyclization of **81** with NaH gave β-keto ester **82** (53%). Saponification and decarboxylation of **82** was effected with concentrated sulfuric acid to give 4,4-dimethylthiacyclohexan-3-one (**83**) (80%). Unfortunately, all attempts to generate **73** via monomethylation of **83** failed.



It was decided to follow the multi-step approach of Huisman and co-workers[3] to prepare 4-thiaionone (**52**). The synthetic pathway (Figure 11) illustrates the methodology. Ethyl acetoacetate (**84**), on treatment with dry H_2S gas and dry HCl gas at -50 to -60°C, gave ethyl 3-mercaptoacetoacetate (**48**, 62%). Ethyl 3-mercaptoacetoacetate was obtained as a mixture of *cis*- and *trans*-isomer of the thioketo tautomer as illustrated. Treatment of **48** with freshly prepared NaOEt/EtOH produced the corresponding sodium salt which was condensed with 4-bromo-2-methyl-2-butene (**85**, Aldrich) in benzene to afford 2,6-dimethyl-1-ethoxycarbonyl-3-thiahepta-1,5-diene (**49**, 65%) as a mixture of isomers. This ethyl ester was also obtained as a mixture of isomers which distilled under reduced pressure over a wide temperature range (75-125°C/0.4 mm Hg). This mixture of isomers was used in the next reaction without further separation. Reduction of the mixture of isomers of **49** with $LiAlH_4$ in ether at -30°C gave the corresponding primary alcohol **50.**

Alcohol **50** was used without purification as it appeared to undergo some type of structural rearrangement reactions upon standing. Oppenauer oxidation of **50** with $Al[OCH(CH_3)_2]_3$, followed by *in situ* condensation with acetone, resulted in the formation of pseudo 4-thiaionone (**51**). Cyclization of **51** to 4-thiaionone (**52**) was carried out using concentrated sulfuric acid in nitromethane at -15°C.

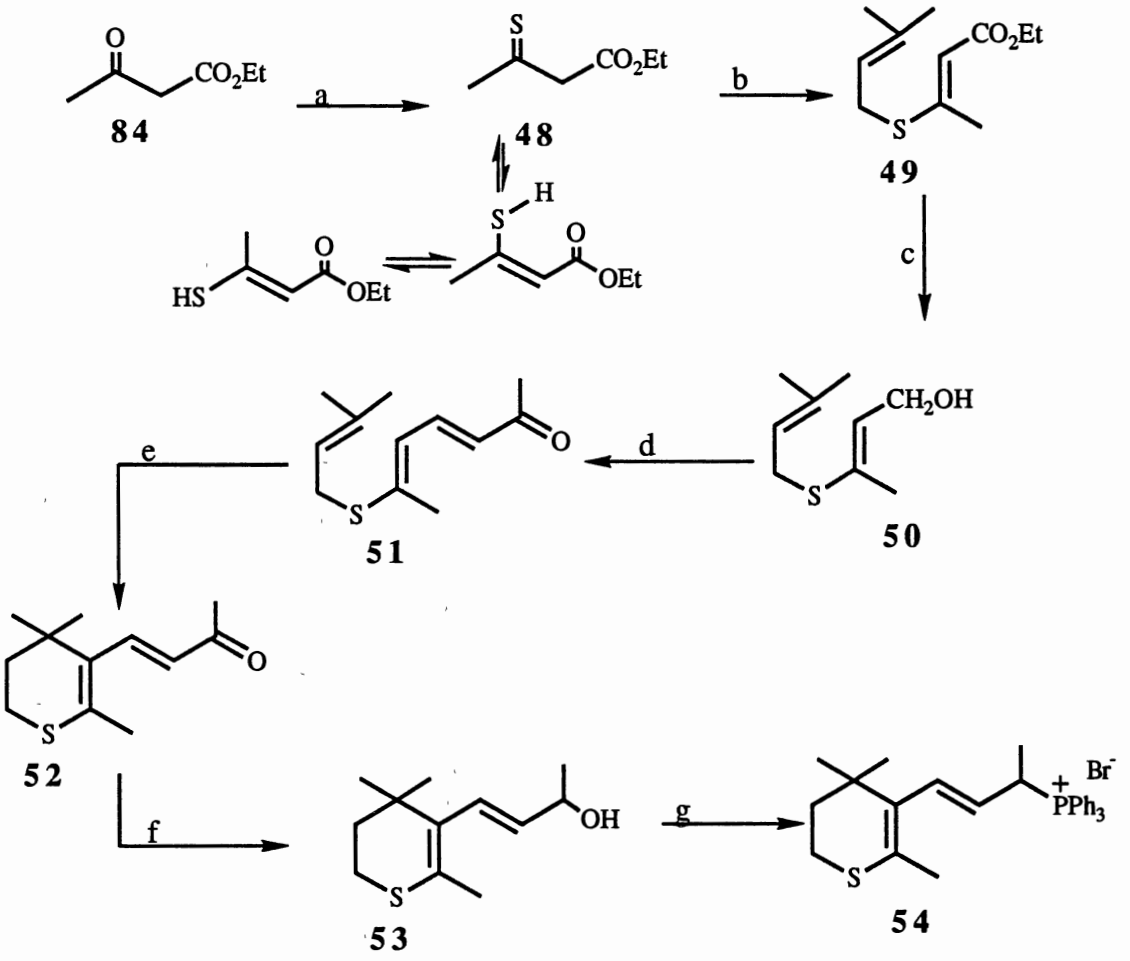
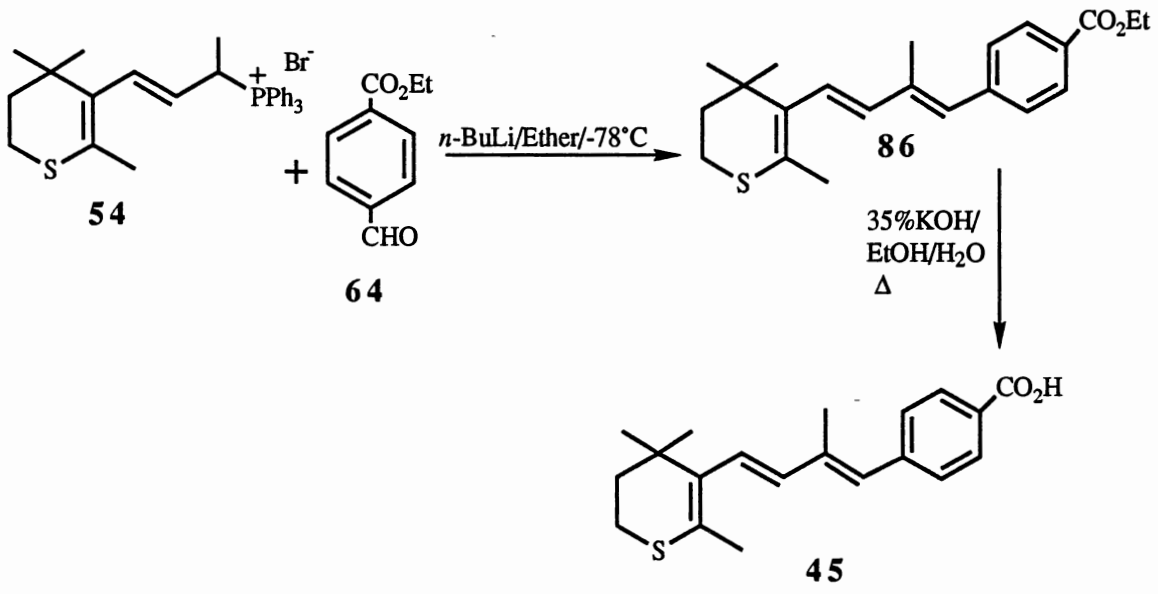


Figure 12. Preparation of Intermediates **48-54.** (a) H_2S/ HCl/-50°C; (b) NaOEt; EtOH/2,2-dimethyl-4-bromo-2-butene, (**85**); (c) LAH/Ether/-15°C; (d) $Al[OCH(CH_3)_2]_3$/acetone/benzene/Δ; (e) H_2SO_4/H_3CNO_2/-15°C; (f) LAH/Ether; (g) PPh_3/ HBr/MeOH/Ether

4-Thiaionone (**52**) was present predominantly in the trans form as shown. Reduction of **52** with $LiAlH_4$ in ether afforded the corresponding secondary alcohol **53**.

Phosphorylation with triphenylphosphine hydrobromide produced phosphonium salt **54** as a thick oil. This oil was then triturated with ether to give a yellow-colored solid. All compounds in this sequence, especially the phosphonium salt, were found to be *extremely* hygroscopic.

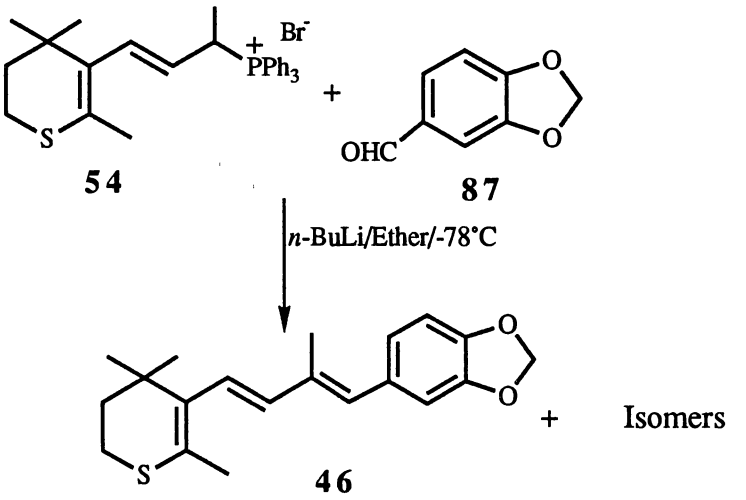
Phosphonium salt **54** was used in a Wittig reaction with different aldehydes. In one reaction, the anion generated with *n*-BuLi from salt **54** was condensed with ethyl 4-formylbenzoate (**64**) at -78°C which, after 24 h of stirring at room temperature and work-up, resulted in the formation of a yellow-colored oil. Chromatography of the oil on a 4 mm silica gel plate (Chromatotron), using hexane:ethyl acetate (9:1) as eluent, gave ethyl ester **86** but as a mixture of isomers. This isomeric mixture of esters was saponified and, after



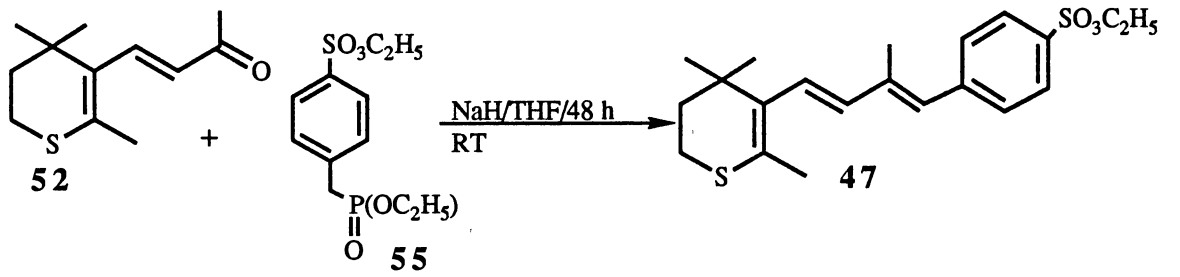
neutralization, gave a yellow-colored solid which was crystallized (95% ethanol) to give carboxylic acid **45** as light yellow solid.

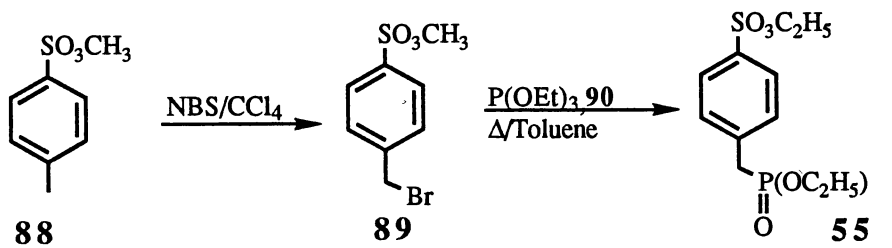
In order to study the effects on activity by different hydrophilic groups at the chain terminus, it was decided to use a highly polarized aldehyde in the Wittig condensation. Commercially available piperonal (**87**) was treated with the anion generated from the

phosphonium salt **54**. After workup, the oil obtained was separated on a 4 mm silica gel plate using hexane:ether (9.5:0.5). Heteroarotinoid **46** was obtained as a mixture of isomers and all efforts to separate these failed.

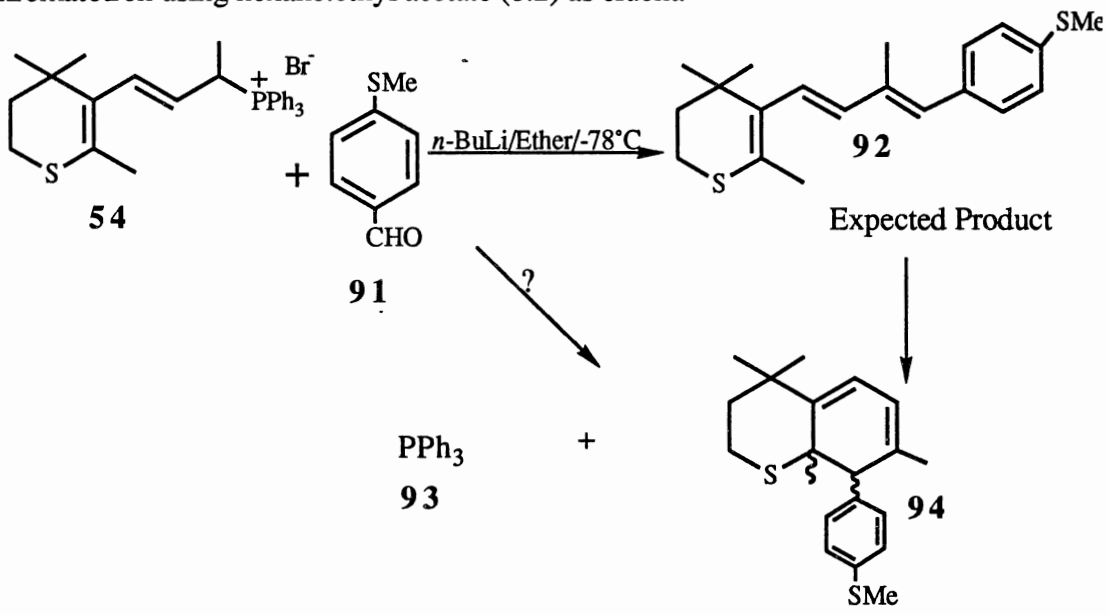


The last target heteroarotinoid **47** was prepared by a Wadsworth-Emmons modification in the condensation step. 4-Thiaionone (**52**) was condensed with the anion of methyl 4-diethylphosphonomethylbenzenesulfonate (**55**) to yield **47** (9%) as a crystalline solid. Sulfonate **47** permits a structure-activity assessment of the influence by SO_3Et versus CO_2Et.

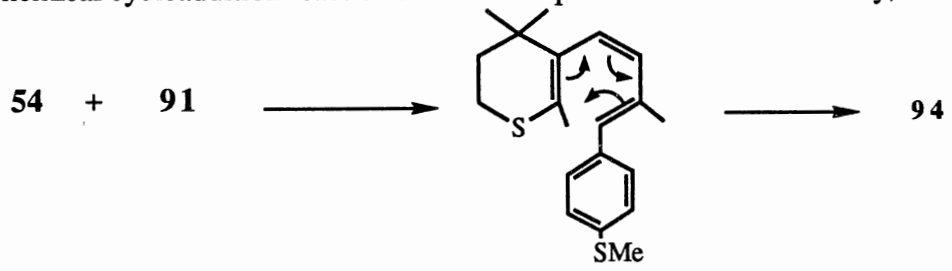




Phosphonate **55** was prepared from methyl 4-methylbenzenesulfonate (**88**) by initial allylic bromination to give methyl 4-bromomethylbenzenesulfonate (**89**) which participated in a Michaelis-Arbuzov reaction involving triethyl phosphite (**90**). In this latter reaction both a rearrangement and a transesterification occurred since the product isolated was the triethyl sulfonate **55**. Sulfonate **55** was a viscous, yellow-colored oil which was purified on the Chromatotron using hexane:ethyl acetate (8:2) as eluent.

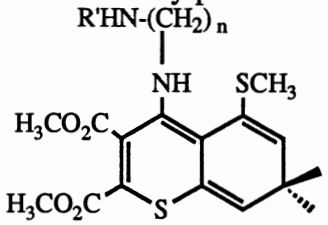


Another Wittig reaction of salt **54** was attempted with 4-methylthiobenzaldehyde (**91**). Rather than the expected thio ether **92**, two major products were isolated. One was triphenylphosphine (**93**) in addition to a crystalline solid tentatively identified as **94**. IR analysis showed the presence of the *para*-sustituted aromatic ring. The ^{1}H NMR spectrum of **94** had signals for five methyl groups at ∂ 0.9, 1.3-1.45, 1.5-1.8 and 2.5, which are not in the exact region expected for **92.** One can envision an intramolecular thermochemical cycloaddition reaction as shown to produce **94**. Theoretically, one might

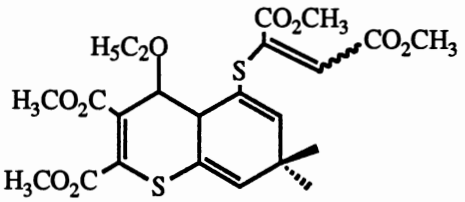


expect a *trans* arrangement of the C-CH_3 (bridgehead) and the C-$C_6H_4SCH_3$ via a disrotatory closure.

Ether **94** may be structurally related to certain natural products. Interesting systems **95** and **96** were recently published[39] and are relatives of **94.**



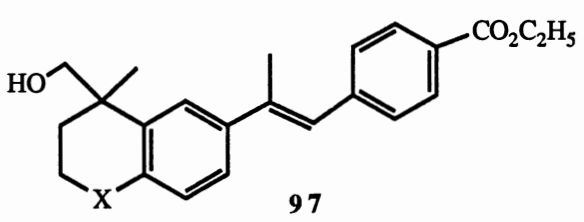
95



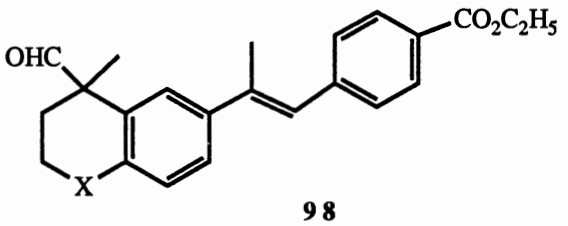
96

Suggestions For Future Work

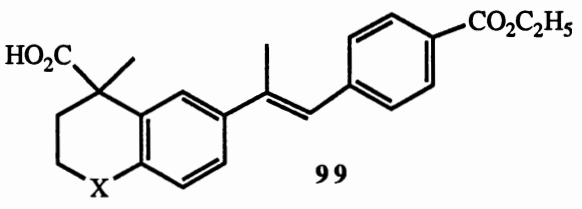
We have prepared possible metabolites of **28** in which the side chain has undergone oxidation. Another site in **28** where oxidation can occur is at the *gem*-dimethyl position in the benzopyran ring. As can be seen from the metabolites obtained from *trans*-retinoic acid (**3**) and Etretinate (**10**), the methyl groups on the ring undergo oxidation to a hydroxymethyl group and a carboxylic acid. Thus, as shown below compounds, **97-99** are likely metabolites from ester **28.**



97



98



99

X = O, S

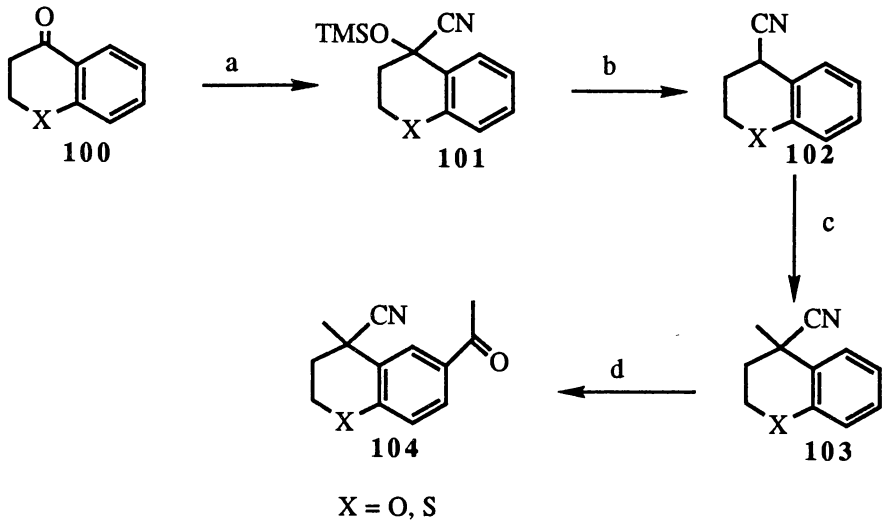


Figure 13. Conversion of **100** to **104**: (a) TMSCN/KCN/18-C-6/CH_2Cl_2; (b) TMSCl/NaI/CH_3CN/Hexane/Water; (c) NaH/THF/CH_3I; (d) $AlCl_3/CH_3C(O)Cl/CH_3NO_2$

A possible route to these compounds is shown (Figure 13). Commercially available chromanone **100**, (X = O), upon treatment with TMSCN in CH_2Cl_2 resulted in formation of cyanohydrin **101**. Treatment of **101** with NaI in the presence of TMSCl and acetonitrile gave 4-cyanobenzopyran (**102**).[61] Methylation of **102** under normal conditions formed **103.** Acetylation of **103** gave **104** (X = O) which, by selective reduction with Dibal-H at low temperature, should yield keto aldehyde **105** (Figure 14). Reduction of **105** with LAH could result in formation of diol **106**, which, upon regioselective phosphorylation, should give phosphonium salt **107.** This latter reaction has also been done in our lab in 5-membered heteroarotinoid family.[27] A Wittig reaction with the anion of **107** and ethyl 4-formylbenzoate (**64**) should yield ester **97.** Oxidation of **97** to aldehyde **98** and then to **99** should follow under mild conditions. To date, we have been able to obtain **104** (X = O) via this reaction sequence.

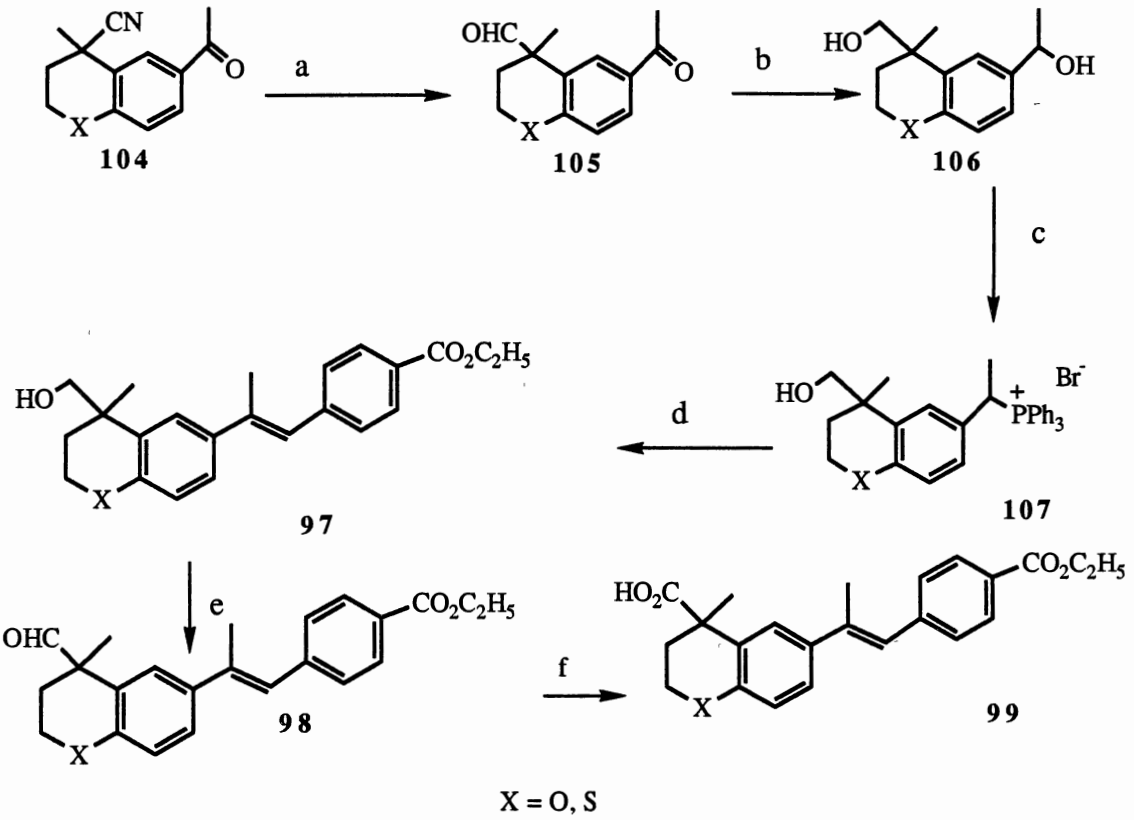


Figure 14. Suggested Syntheses of **97-99**: (a) DIBAL-H, -78°C-RT; (b) LAH, Ether, RT (c) PPh_3·HBr, MeOH; (d) *n*-BuLi, Ether, -78°C, Ethyl 4-Formylbenzoate (**64**); (e) MnO_2, CH_2Cl_2; (f) Ag_2O, EtOH

CHAPTER III

EXPERIMENTAL

General Information. Melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. IR spectra were recorded on a Perkin-Elmer 681 as KBr pellets or as films. All NMR spectra were taken on an Varian XL-300 spectrometer (with ^{1}H and ^{13}C being observed at 299.94 and 75.43 MHz, respectively) and on an XL-400 spectrometer (with ^{1}H and ^{13}C being observed at 399.95 and 100.57 MHz, respectively), on solutions with $DCCl_3$. Data are reported as follows: chemical shift (in δ values or ppm), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, qn = quintet, m = multiplet), coupling constant (in Hz), and assignment. Mass spectral data were recorded on a VG analytical instrument model ZAB-2SE. Elemental analyses were performed by Galbraith Laboratories, Knoxville, TN. Preparative chromatography was performed using Chromatotron (on silica gel PF_{254} containing gypsum, model 7924T, Harrison Research Inc., 840 moana Court, Palo Alto, CA 94306). TLC was performed on silica gel (Kodak chromatogram sheets, 132181 silica gel with fluoroscent indicator).

Syntheses were executed, unless otherwise indicated, under an atmosphere of N_2. The following reagents were obtained commercially and used without further purification: glacial acetic acid (Dupont), *n*-BuLi (Aldrich), *t*-butanol (Fischer), SeO_2 (Alfa), NaH (60%, dispersion in mineral oil, Aldrich), 15-crown-5 ether (Aldrich), triethyl phosphonoacetate (Aldrich), ethyl acetoacetate (Aldrich), H_2S (g) (Aldrich), CH_3I (^{14}C, ICN), $CH_3C(O)Cl$ [$^{14}C(O)$, ICN], *p*-toluic acid [$^{14}C(O)OEt$, Sigma], methyl thioglycolate (Aldrich), methyl 4-chlorobutyrate (Aldrich), 1-bromo-2-chloroethane (Lancaster), methyl

p-toluenesulfonate (Aldrich), piperonal (Aldrich), *N*-bromosuccinimde (Alfa), potassium hydroxide (85%, Baker), and sodium hydroxide (97%, Baker). The following compounds required distillation prior to use: nitromethane (bp 100°C), THF (bp 65°C), and acetic anhydride (bp 138°C).

Ethyl (*E*)-4-[2-(3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6yl)-3-hydroxy-1-propenyl]benzoate (37). A 100-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer and a condenser. To the suspension of 1.29 g (11.6 mmol) of SeO_2[6] in 95% alcohol (30 mL) was added 1.35 g (3.85 mmol) of ethyl (*E*)-4-[2-(3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-1-propenyl]benzoate (**28**).[76] The reaction mixture was boiled for 24 h. The new mixture was then cooled to room temperature, and black elemental Se was separated by gravity filtration. The residue was washed with 95% alcohol (10 mL). Evaporation (rotary evaporator) of the alcohol gave a residue which was dissolved in ether (50 mL). The ether layer was washed with water (1 x 20 mL), saturated $NaHCO_3$ (1 x 20 mL), and finally with brine (1 x 30 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated (rotary evaporator) to a light brown oil. Purification of this oil was accomplished by chromatography using the Chromatotron with a 4 mm silica gel plate. Gradient elution was effected using 100 mL of hexanes:ethyl acetate (95:5), 100 mL of hexanes:ethyl acetate (9.0:1.0), 100 mL of hexanes:ethyl acetate (8.0:2.0), and finally with 250 mL of hexanes:ethyl acetate (75:25). Different fractions (1 to 20) of 20 mL each were collected. Fractions 16, 17 and 18 were combined, and the solvent was evaporated to afford 0.44 g (31.2%) of a very thick brown colored oil of ester **37**. IR (neat) 3650-3120, 1720 (C=O) cm^{-1}; UV (EtOH) λ_{max} 284.2 nm (ε 1.16 x 10^4); ^1H NMR ($DCCl_3$) δ 1.15 [s, 6 H, H(9,10)], 1.35 [t, 3 H, H(22)], 1.61 [s, 1 H, O*H*], 1.80 [m, 2 H, H(3)], 4.18 [m, 2 H, H(2)], 4.30 [q, 2 H, H(21)], 4.47 [s, 2 H, H(12)], 6.67-7.8 [m, 8 H, Ar-*H* and C=C*H*]; ^{13}C NMR ($DCCl_3$) ppm 14.2 [C(22)], 30.4 [C(4)],

30.4 [C(9,10)], 37.3 [C(3)], 60.7 [C(21)], 63.1 [C(2)], 63.1 [C(12)]; Ar-*C* and vinylic-*C*: 117.3, 124.6, 127.9, 128.2, 128.9, 129.1, 129.2, 132.0, 141.7, 143.8, 153.4; 166.4 [C(20)]. Unfortunately compound **37** retained trace amounts of water even after drying under vacuum for several hours. Anal. Calcd for $C_{23}H_{26}O_4$: C, 75.38; H, 7.15; Anal. Calcd. for $C_{23}H_{26}O_4 \cdot 0.25H_2O$: C, 74.49; H, 7.15; Found: C, 74.10; H, 7.29 . Mass spectral data calculated for $C_{23}H_{26}O_4$ *m/z* ($M^{+\cdot}$): 366.1831; Found: 366.1831.

Ethyl *(E)*-4-[2-(3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-2-propenal]benzoate (38). A 50-mL, single-necked, round-bottomed flask was equipped with a magnetic stirrer and a condenser. To 0.04 g (0.11 mmol) of ethyl (*E*)-4-[2-(4,4-dimethyl-3,4-dihydro-2*H*-1-benzopyran-6-yl)-3-hydroxy-1-propenyl]benzoate (**37**) in 15 mL of CH_2Cl_2 was added 0.15 g (2.2 mmol) of activated MnO_2.[1] The reaction mixture was stirred at room temperature for 24 h and was then filtered. The residue was washed with 10 mL of CH_2Cl_2. The combined filtrate and washing were concentrated (rotary evaporator) to yield 0.03 g (76%) of a yellow-colored solid **38**. The solid was crystallized (95% alcohol) to give yellow-colored crystals of ester **38**, mp 157-158°C. IR (KBr) 1725(C=O), 1680 cm^{-1}; UV (EtOH) λ_{max} 286.8 nm (ε 1.48 x 10^4); ^1H NMR ($DCCl_3$) δ 1.15 [s, 6 H, H(9,10)], 1.3 [t, 3 H, H(22)], 1.8 [m, 2 H, H(3)], 4.15 [m, 2 H, H(2)], 4.30 [q, 2,H, H(21)], 6.72-7.85 [m, 8 H, Ar-*H* and -C=C*H* (13)], 9.7 [s, 1 H, H(12)]; ^{13}C NMR ($DCCl_3$) ppm 14.2 [C(23)], 30.5 [C(4)], 30.8 [C(9,10)], 37.3 [C(3)], 61.1 [C(21)], 63.1 [C(2)]; Ar-*C* and vinylic-*C*: 117.4, 124.0, 128.1, 128.4, 129.4, 130.2, 131.0, 132.0, 138.7, 143.0, 154.0; 165.8 [C(20)], 194.0 [C(12)]. Anal. Calcd for $C_{23}H_{24}O_4$: C, 75.80; H, 6.64; Found: C, 75.64; H, 6.72. Mass spectral data calculated for $C_{23}H_{24}O_4$ *m/z* ($M^{+\cdot}$): 364.1668; Found: 364.1662.

Ethyl (*E*)-4-[2-(3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-2-propanoic acid]benzoate (39). A 50-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser, and an addition funnel. To 0.035 g (0.096 mmol) of ethyl (*E*)-4-[2-(3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-2-propenal]benzoate (**38**) and 0.012 g (0.11 mmol) of resorcinol in *t*-butanol (5 mL) was added a solution of 0.079 g (0.87 mmol) of $NaClO_2$ and 0.093 g (0.672 mmol) of NaH_2PO_4 in water (10 mL).[2] The reaction mixture was stirred at room temperature for 24 h. Evaporation (rotary evaporator) of the solvent gave a residue to which was added water (25 mL), and the new solution was cooled (ice bath). This cold solution was acidified with 6 *M* HCl (1 mL) to pH 1 (litmus). The aqueous solution was extracted with ether (3 x 25 mL). The combined extracts were dried (Na_2SO_4) and filtered, and the solvent was evaporated (rotary evaporator) to give 0.03 g (82%) of a yellow-colored oil. Crystallization was induced by scratching to give a solid. Recrystallization (absolute alcohol) of the solid gave yellow crystals of ester **39**, mp 197-198°C. IR (KBr) 3600-2850, 1740 (C=O), 1680 cm^{-1}; UV (EtOH) λ_{max} 286.2 nm (ε 1.28 x 10^4); ^1H NMR ($DCCl_3$) δ 1.18 [s, 2 H, H(9,10)], 1.36 [t, 3 H, H(22)], 1.82 [m, 2 H, H(3)], 4.21 [m, 2 H, H(2)], 4.33 [q, 2 H, H(21)], 6.79-7.89 [m, 8 H, Ar-*H* and C=C*H*(13)]; ^{13}C NMR ($DCCl_3$) ppm 14.2 [C(22)], 30.5 [C(4)], 30.8 [C(9,10)], 37.4 [C(3)], 61.0 [C(21)], 63.1 [C(2)]; Ar-*C* and vinylic-*C*; 117.3, 126.0, 128.5, 128.9, 129.3, 130.3, 130.4, 131.9, 133.8, 139.2, 140.3, 153.7; 166.0 [C(20)], 172.7 [C(12)]. Anal Calcd for $C_{23}H_{24}O_5$: C, 72.61 ; H, 6.36 ; Found: C, 72.36; H, 6.64. Mass spectral data calculated for $C_{23}H_{24}O_5$ *m/z* ($M^{+\cdot}$): 380.1623; Found: 380.1625.

Ethyl 3-[3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl]crotonate (41). A 50-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle and a condenser. To 0.212 g (5.39 mmol) of NaH (60% dispersion in

mineral oil washed with *n*-pentane 25 mL) in dry THF (10 mL) was added dropwise a mixture of 1.0 g (4.9 mmol) of 4,4-dimethylchroman-6-yl methyl ketone (**40**),[76] 1.21 g (5.39 mmol) of triethyl phosphonoacetate (**67**), and 0.10 g (0.454 mmol) of 15-crown-5 in THF (10 mL) over a period of 10 min. The reaction mixture was stirred at room temperature for 24 h. It was then boiled for 2 h and allowed to cool to room temperature over a period of 24 h. This reaction mixture was acidified with glacial acetic acid (1 mL) to pH 6. Then a saturated solution of NaCl (50 mL) was added and the organic layer separated. The aqueous layer was extracted with ether (2 x 30 mL), and the combined extracts and the organic layer were washed with water (3 x 30 mL) and brine (30 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated (rotary evaporator) to give 1.03 g of reddish brown oil. The oil was purified by chromatography on the Chomatotron with a 4 mm silica gel plate using 50 mL of hexanes:ethyl acetate (95:5) and 200 mL of hexanes:ethyl acetate (9.0:1.0). Ester **41** was obtained as a thick oil (0.52 g, 38.7%). IR (neat) 1720 (C=O) cm^{-1}; UV (EtOH) λ_{max} 298.2 nm (ε 1.39 x 10^4); ^1H NMR ($DCCl_3$) δ 1.32 [t, 3 H, H(16)], 1.35 [s, 6 H, $(CH_3)_2C$], 1.84 [m, 2 H, H(3)], 2.55 [s, 3 H, H(12)], 4.19 [q, 2 H, H(15)], 4.20 [m, 2 H, H(2)], 6.08 [s, 1 H, H(13)], 6.76 [d, J = 8.50 Hz, 1 H, H(8)], 7.21 [dd, J = 8.47 Hz, J = 2.38 Hz, 1 H, H(7)], 7.40 [d, J = 2.33 Hz, 1 H, H(5)]; ^{13}C NMR ($DCCl_3$) ppm 14.3 [C(16)], 17.7 [C(12)], 30.6 [C(14)], 30.9 [C(9,10)], 37.4 [C(3)], 59.6 [C(15)], 63.6 [C(2)], 114.9 [C(8)], 116.9 [C(13)], 125.0 [C(5)], 125.3 [C(7)], 131.4 [C(6)], 134.0 [C(4a)], 154.6 [C(11)], 155.4 [C(8a)], 167.0 [C(14)]. Anal. Calcd for $C_{17}H_{22}O_3$: C, 74.43; H, 8.08; Found: C, 74.46; H, 8.00. Mass spectral data calculated for $C_{17}H_{22}O_3$ *m/z* ($M^{+\cdot}$): 274.1569; Found: 274.1566

3-[3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl]crotonic Acid (42). A 50-mL, single-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle and a condenser. To 52 mg (0.19 mmol) of ethyl 3-[3,4-dihydro-4,4-

dimethyl-2*H*-1-benzopyran-6-yl]crotonate (**41**) in 2 mL of absolute ethanol was added 5 mL of H_2O and 1 mL of 35 % (w/v) KOH. The solution was boiled for 5 h and then allowed to cool to the room temperature. It was further cooled in an ice bath (0-5°C) and was then neutralized with 6 M HCl (2 mL). A white solid formed and was filtered and washed with cold water. This solid was recrystallized [absolute alcohol/water (1:1)] to afford 35 mg (74.8%) of acid **42**, mp 126-128°C. IR (KBr) 3500-3010, 1670 (C=O) cm^{-1}; UV (EtOH) λ_{max} 291.6 nm (ε 1.30 x 10^4); ^1H NMR ($DCCl_3$) δ 1.2 [s, 6 H, H(9,10)], 1.7 [m, 2 H, H(3)], 2.4 [s, 3 H, H(12)], 5.9 [s, 1 H, H(13)], 6.6-7.3 [m, 3 H, Ar-*H*]; ^{13}C NMR ($DCCl_3$) ppm 18.1 [C(12)], 30.6.[C(4)], 36.9 [C(9,10)], 37.3 [C(3)], 63.2 [C(2)], 114.1 [C(8)], 117.1 [C(13)], 125.2 [C(5)], 125.5 [C(7)], 131.5 [C(6)], 133.8 [C(4a)], 155.0 [C(11)], 158.4 [C(8a)], 172.3 [C(14)]. Acid **42** retained traces of water even after drying under vacuum for prolonged period. Anal. Calcd for $C_{15}H_{18}O_3$: C, 73.15, H, 7.37; Anal. Calcd. for $C_{15}H_{18}O_3 \cdot 1/8H_2O$: C, 72.51, H, 7.35; Found: C, 72.42; H, 7.43. Mass spectral data calculated for $C_{15}H_{18}O_3$: *m/z* ($M^{+\cdot}$): 246.1256; Found: 246.1260.

4-[3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl]Δ^2-butenolide (43). A 50-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle and a condenser. To 0.2 g (0.75 mmol) of ethyl 3-[3,4-dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl]crotonate (**41**) in dry benzene (25 mL) was added 0.41 g (3.70 mmol) of SeO_2.[15] The reaction mixture was boiled for 20 h. After cooling the mixture to room temperature, the deposited metallic Se was separated by gravity filtration through a cotton plug. Water (25 mL) was added to the filtrate and the organic layer separated. The aqueous layer was extracted with ether (2 x 25 mL), and the combined extracts and organic layer were dried (Na_2SO_4), filtered and concentrated (rotary

evaporator) to a thick yellow oil. Crystallization was induced by scratching to give 0.18 g (98.2%) of a yellowish, orange solid. The solid was recrystallized (95% alcohol) to give yellow crystals of **43**, mp 133-134°C. IR (KBr) 1780, 1740 (C=O) cm^{-1}; UV (EtOH) λ_{max} 308.1 nm (ε 2.52 x 10^4); ^1H NMR ($DCCl_3$) δ 1.36 [s, 6 H, H(9,10)] 1.86 [m, 2 H, H(3)], 4.26 [m, 2 H, H(2)], 5.19 [s, 2 H, H(12)], 6.22 [s,1 H, H(15)], 6.82 [d, J = 8.52 Hz, 1 H, H(8)], 7.22 [dd, J = 8.46 Hz, J = 2.28 Hz, 1 H, H(7)], 7.39 [d, J = 2.28 Hz, 1 H, H(5)]; ^{13}C NMR ($DCCl_3$) ppm 30.5 [C(4)], 30.7 [C(9,10)], 36.9 [C(3)], 63.4 [C(2)], 70.9 [C(12)], 110.1 [C(15)], 118.0 [C(11)]; Ar-*C*: 121.9, 125.3, 125.7, 132.5, 156.8; 164.0 [C(14)]. Anal. Calcd for $C_{15}H_{16}O_3$: C, 73.75; H, 6.60; Found: C, 73.57; H, 6.65. Mass spectral data calculated for $C_{15}H_{16}O_3$ *m/z* ($M^{+\cdot}$): 244.1099; Found: 244.1099.

3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-carboxylic Acid (44). A 50-mL, single-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle and a condenser. To 15 mL of commercially available Clorox solution containing 5.25% NaOCl was added 0.3 g (1.47 mmol) of 4,4-dimethylchroman-6-yl methyl ketone (**40**)[76] in 95% alcohol (5 mL). The reaction mixture was stirred well and boiled for 1.5 h and then cooled to room temperature. This mixture was first neutralized with a 25% solution of sodium metabisulfite (25 mL) and then with concentrated HCl (2 mL). A white solid formed and was filtered and then washed with cold water (50 mL) until the filtrate was free of acid. Recrystallization (95% alcohol) of the product afforded 0.2 g (67%) of white crystalline solid **44**,[8] mp 227-229°C. IR (KBr) 3400-2950, 1680 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.37 [s, 6 H, H(9,10)], 1.85 [m, 2 H, H(3)], 4.27 [m, 2 H, H(2)], 6.83 [d, J = 8.62 Hz, 1 H, H(8)], 7.84 [dd, J = 8.67 Hz, J = 2.85 Hz, 1 H, H(7)] 8.07 [d, J = 2.12 Hz, 1 H, H(5)]; ^{13}C NMR ($DCCl_3$) ppm 30.59 [C(4)], 30.75 [C(9,10)], 36.97 [C(3)], 63.49 [C(2)]; Ar-*C*: 117.1, 121.7, 129.5, 129.9, 131.5, 158.5; 171.8

[C(11)]. Anal. Calcd for $C_{12}H_{14}O_3$: C, 69.87; H, 6.84. Found: C, 69.79, H, 6.67. Mass spectral data calculated for $C_{12}H_{14}O_3$ *m/z* ($M^{+\cdot}$): 206.0943; Found: 206.0943.

4-[(All-*E*)-2-methyl-4-(2,6,6-trimethyl-3-thia-1-cyclohexen-1-yl)-1,3-butadienyl]benzoic Acid (45). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a rubber septum, and a condenser. To a stirred suspension of 0.5 g (0.93 mmol) of phosphonium salt **54** in ether (10 mL) was added dropwise 0.1 mL (1.0 mmol) of 10 M *n*-BuLi solution. The resulting dark red-colored solution was stirred at room temperature for 15 min. This solution was then cooled to -78°C (dry ice/acetone bath) and to this was then added ethyl 4-formylbenzoate (**54**). The solution was stirred at -78°C for 5 min and then allowed to warm to room temperature over a period of 24 h. Precipitated triphenylphosphine was separated and the filtrates were concentrated (rotary evaporator) to a yellow-colored oil. This oil was then transferred to a 50-mL, round-bottomed flask and absolute ethanol (10 mL) was added, followed by 0.2 g of KOH in 10 mL of water. The solution was boiled for 90 min and then cooled to room temperature. It was then neutralized with 5% sulfuric acid (15 mL), and then the aqueous layer was extracted with ether (3 x 10 mL). The combined extracts were washed with brine (3 x 10 mL), then dried (Na_2SO_4), and concentrated (rotary evaporator) to give a yellow-colored solid. This solid was crystallized (95% ethanol) to give 0.8 g (12%) of yellow-colored crystalline solid **47** (mp 186-187°C). IR (KBr) 3500-3250 (OH), 1680 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.1 [s, 6 H, $(CH_3)_2$], 1.85 [m, 2 H, H (3)], 1.9 [s, 3 H, CH_3], 2.1 [s, 3 H, CH_3], 2.85 [m, 2 H, H (2)], 6.45-6.51 [m, 3 H, vinylic-*H*], 7.35 [d, 2 H, Ar-*H*], 8.05 [d, 2 H, Ar-*H*]; 13C ($DCCl_3$) ppm 21.23 [C(9)], 22.02 [C(13)], 23.58 [C(1)], 28.6 [C(7, 8)], 33.23 [C(2)], 38.8 [C(3)], 123.89, 126.81, 129.25, 129.83, 130.08, 130.09, 133, 45, 137.18, 143.44 [Ar-*C* and vinylic-*C*]; 170.80 [C(C=O)]. Anal. Calcd. for $C_{20}H_{24}O_2S$: C, 72.74, H, 7.52; Found: C, 73.13, H, 7.52.

5-[(All-*E*)-2-Methyl-4-(2,6,6-trimethyl-3-thia-1-cyclohexen-1-yl-1,3-butadienyl]-1,3-benzodioxazole (46). A 50-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a rubber septum and a condenser. To a suspension of 1.5 g (2.7 mmol) of phosphonium salt **54** in ether (20 mL) was added dropwise 0.35 mL of a solution of 10 M *n*-BuLi over a period of 10 min. The resulting red-colored solution was stirred at room temperature for 10 min and was then cooled to -78°C (dry ice/acetone bath) for 30 min. To the cold solution was added a solution of 0.41 g (2.7 mmol) of piperonal (**86**) in ether (10 mL). The resulting solution was stirred at -78°C for 10 min and then allowed to warm to room temperature over a period of 24 h. Precipitated triphenylphosphine was separated (vacuum filtration), and the filtrates were collected and concentrated (rotary evaporator) to a light yellow-colored oil. This oil was separated on a 4 mm silica gel plate (Chromatotron) using hexane:ethyl acetate (9:1). The first fraction was collected and concentrated to give 0.6 g of triphenylphosphine. The second fraction 100 mL was collected and concentrated to obtain 0.1 g (9%) of thick, light-colored oil. The proton NMR spectrum of this oil showed the presence of several isomers and all efforts to separate these isomer using different solvent systems on silica gel and alumina TLC plates were unsuccessful. IR (neat) 1600 cm^{-1} (C=C); ^1H NMR ($DCCl_3$) δ 1.1 [s, 3 H, *gem*-CH_3], 1.8 [m, 2 H, H (2)], 1.9 [d, 3 H, CH_3 (12)], 2.8 [m, 2 H, H (3)], 5.9 [s, 2 H, O-CH_2-O], 6.2-7.8 [m, 6 H, Ar-*H* and vinylic-*H*]. Anal. Calcd. for $C_{20}H_{24}O_2S$: C, 73.13, H, 7.37; Found: C, 79.58; H, 5.72. Decomposition may occur readily with this compound in view of the unsatisfactory analysis.

Ethyl 4-[(All-*E*)-2-methyl-4-(2,6,6-trimethyl-3-thia-1-cyclohexen-1-yl)-1,3-butadienyl]benzenesulfonate (47). A 100-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer and a condenser. To a suspension of 0.03 g (0.71 mmol) of NaH (60% dispersion in mineral oil) in THF (15 mL) was added 0.24 g (0.71 mmol) of ethyl 4-triethylphosphonomethylbenzenesulfonate (**91**) and 0.01g

(0.05 mmol) of 15-crown-5. The resulting solution was stirred at room temperature for 10 min. To this stirred solution was then added 0.1 g (0.4 mmol) of 4-thiaionone **52** in THF (10 mL) and the resulting red-colored solution was stirred at room temperature for 48 h. To this was added 1 mL of 6 *M* acetic acid and 10 mL of water. The resulting aqueous layer was extracted with ether (3 x 30 mL), and the combined extracts were washed with brine (50 mL). The aqueous layer was dried (Na_2SO_4), filtered and concentrated (rotary evaporator) to give a dark-colored oil. This oil was separated on a 2 mm silica gel plate using hexane:ethyl acetate (95:5). The first fraction (100 mL) was collected and the solvent was evaporated to give 0.03 g (15%) of yellow-colored oil **47**. IR (neat) 1550 (C=C) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.2 [2 s, 6H, $(CH_3)_2$], 1.4 [t, 3 H, CH_3CH_2], 1.8 [m, 2 H, H (3)] 1.9 [d, 3 H, CH_3], 2.1 [bs, 3 H, CH_3], 4.2 [q, 2 H, CH_2-CH_3]. Anal. Calcd. for $C_{21}H_{28}O_3S_2$: C, 64.25; H, 7.19; Anal. Calcd. for $C_{21}H_{28}O_3S_2 \cdot 1/8H_2O$: C 63.96; H 7.19. Found: C, 63.88, H, 7.15.

Ethyl 3-Mercaptocrotonate (48). A 1000-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser and a gas inlet. A solution of 65 g (0.50 mol) of ethyl acetoacetate (**84**) in 500 mL of dry CH_3CN was cooled from -50°C to -60°C in a dry ice-chloroform bath (0.5 h). Then H_2S gas was bubbled through the solution for 3 h. After addition of the H_2S gas, dry HCl gas was bubbled into the system via a steady stream for 4 h. The temperature of the reaction mixture was maintained between -50°C and -60°C (dry ice/chloroform bath).[32] The color of the reaction mixture turned light orange. The reaction mixture was then poured into a mixture of cold water:petroleum ether (1:1, 1000 mL). The organic layer was separated, and the aqueous layer was extracted (petroleum ether, 6 x 100 mL). The combined organics were dried ($MgSO_4$), filtered, and concentrated (rotary evaporator) to give 50 g of a red-colored liquid **48**. The liquid was distilled under reduced pressure [bp 65-70°C/9 mm (lit[3] bp 77°C/12 mm)] to obtain 45.0 g (62%) of isomers **48** (page 38). IR (neat) 2560-2400 (S-H), 1750-1680 cm^{-1}(C=O)

cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.3 (t, 3 H, CH_3-CH_2-), 2.3 (s, 3 H, CH_3), 3.45 (s, 2 H, CH_2), 4.2 (q, CH_2-CH_3).

2,6-Dimethyl-1-ethoxycarbonyl-3-thia-1,5-heptadiene (49). A 500-mL, single-necked, round-bottomed flask was equipped with a Y-Claisen adapter bearing a condenser in the one arm and an addition funnel in the other. To freshly cut sodium (5.6 g, 0.24 mol) in 100 mL of absolute alcohol was added another 100 mL of absolute alcohol in a steady stream so as to keep the reaction mixture boiling. After stirring for 0.5 h, 22 g (0.15 mol) of ethyl 3-mercaptocrotonate (**48**) was added over a period of 10 min. The reaction mixture turned light yellow at the end of the addition. After being stirred at the room temperature for 0.5 h, the mixture was concentrated (rotary evaporator) to a light yellow semi-solid and benzene (200 mL) was added. To the stirred solution was added 20 g (0.13 mol) of 4-bromo-2-methyl-2-butene (**85**) over a period of 10 min, after which time the reaction mixture became clear. This solution was stirred for 1 h at room temperature and then slowly added to cold water (500 mL). The organic layer was separated, and the aqueous layer was extracted (benzene, 6 x 100 mL). The combined organic layers were washed with water (4 x 100 mL), 6 *M* HCl (4 x 100 mL), saturated $NaHCO_3$ (2 x 100 mL) and finally with brine (100 ml). After the organics were dried ($MgSO_4$) and filtered, the solution was concentrated (rotary evaporator) to give 18.2 g (0.085 mol, 65%) of a yellow colored liquid which was distilled under reduced pressure [bp 75-125°C/0.4 mm (lit[3] bp 75-123°C/0.5mm)] to give a mixture of isomers of **49** . IR (neat) 1740-1720 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$), δ 1.3 (t, 3 H, CH_3-CH_2), 1.7 [d, 6 H, $(CH_3)_2C$], 2.5 (s, 3 H, CH_3), 2.6 (m, 2 H, CH_2-S), 3.5 [m, 1 H, H(5)], 4.25 (q, 2 H, CH_2-CH_3), 5.05 [m, 1 H, H(1)] [lit[3] IR 1700 (C=O) cm^{-1} for corresponding methyl ester].

3,7-Dimethyl-4-thia-octa-2,6-dien-1-ol (50). A 300-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, an addition funnel and a condenser. The suspension of $LiAlH_4$ (5.43 g, 0.143 mol) in ether (70 mL) was cooled in the ice bath (2 h), and then the temperature was brought to 0°C. To this cooled suspension was added 18 g (0.084 mol) of 2,6-dimethyl-1-ethoxycarbonyl-3-thia-1,5-heptadiene (**49**) in 10 mL of ether over a period of 15 min. The reaction mixture was stirred at the same temperature for another 2 h. This reaction mixture was cooled to -30°C (in dry ice/acetonitrile bath, 1 h), and water (50 mL), was added followed by 6 *M* HCl (20 mL). The organic layer was separated, and the aqueous layer was extracted (cold ether, 5 x 50 mL). The combined organics were dried ($MgSO_4$) at -30°C, filtered, and concentrated (rotary evaporator) to give 13 g (89%) of the light yellow colored liquid **50** which was used immediately in the next step. IR (neat) 3550-3200 (O-H) cm^{-1} [lit[3] IR 3390 (O-H) cm^{-1}].

6,7-Dimethyl-7-thia-undeca-3,5,9-triene-2-one (51). A 2-L, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle and a condenser. A mixture of 3,7-dimethyl-4-thia-octa-2,6-diene-1-ol (**50**, 13 g , 0.075 mol), aluminum isopropoxide (25 g, 0.122 mol) in 450 mL of acetone and 900 mL of benzene was brought to reflux and maintained at reflux for 36 h. The mixture changed from colorless to yellow. The new solution was then allowed to cool to the room temperature (1 h) and was washed with water (2000 mL), until the water washings were neutral, and then with 2000 mL of brine. The organics were dried (Na_2SO_4), filtered and concentrated (rotary evaporator) to give 12.2 gm (0.058 mole, 77%) of a light yellow-colored liquid **51**. IR (neat) 1680 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.7 (d, 6 H, $(CH_3)_2C$), 2.15 (d, 3 H, CH_3), 2.29 (bs, 3 H, CH_3-C=O), 3.45 (d, 2 H, CH_2), 5.23 [m, 1 H, H(5)], 5.25 [m, 1 H, H(9)], 5.9-6.0 [m, 1 H, H(4)], 7.4-7.45 [m, 1 H, H(3)] [lit[3] UV (cyclohexane) λ_{max} 328 nm (ε 2.86 x 10^4)].

4-Thia-ß-ionone (52). A 300-mL, two-necked, round-bottomed flask was equipped with a condenser, a magnetic stirrer and an addition funnel. A solution of 30 mL of concentrated sulfuric acid in 40 mL of CH_3NO_2 was cooled in dry ice/CCl_4 bath[30] and the temperature was brought to -15°C (30 min). A solution of 12 g (0.057 mol) of 4-pseudothiaionone (**51**) in 35 mL of CH_3NO_2 was added dropwise over a period of 30 min. The color of the reaction mixture became dark red . This red-colored reaction mixture was stirred at -15°C for an additional 1.5 h and then poured into 100 mL of ice water. The organic layer was separated and the aqueous layer was extracted (petroleum ether, 8 x 100 mL). The combined organics were washed with brine (2 x 100 mL), dried (Na_2SO_4), filtered, and concentrated (rotary evaporator) to give 8.0 g (0.038 mol, 67%) of a light brown colored liquid **52**. IR (neat) 1650 (C=O) cm^{-1} [lit[3] IR 1660 (C=O) cm^{-1}]; ^1H NMR ($DCCl_3$), δ 1.16 (s, 6 H, $(CH_3)_2C$), 1.8 (m, 2 H, CH_2-CH_2-S), 2.0 (s, 3 H, CH_3), 2.28(s, 3 H, CH_3-C=O) 2.8 (m, 2 H, CH_2-CH_2-S), 6.1 [d, J = 16.3 Hz, 1 H,H(4)], 7.3 [d, J = 16.3 Hz, 1 H, H(3)].

4-Thia-ß-ionol (53). A 500-mL, three-necked, round-bottomed flask was equipped with a condenser, a magnetic stirrer and an addition funnel. A suspension of 3.0 g (0.029 mol) of $LiAlH_4$ in 100 mL of ether was cooled to 0-5°C in an ice bath (30 min). To this cold, stirred suspension was added 4-thia-ß-ionone (**52**, 8 g, 0.038 mol) in 50 mL of ether. The reaction mixture was stirred at 0-5°C for 5 h, and then it was poured slowly onto 200 g of ice. Cautiously, 30 mL of 6 *M* HCl was added to make the solution slightly acidic. The aqueous layer was extracted with ether (5 x 100 mL). The combined organics were washed with brine (2 x 100 mL), dried (Na_2SO_4), filtered and concentrated (rotary evaporator) to give 5 g (0.023 mol, 62 %) of a reddish brown liquid **53**. IR (neat) 3700-3150 (O-H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.05 (s, 6 H, $(CH_3)_2C$), 1.31 (d, J = 6.3 Hz, 3 H, CH_3-CH), 1.85 (m, 2 H, CH_2-CH_2-S), 1.87 (s, 3 H, CH_3), 2.83 (m, 2 H, CH_2-CH_2-S),

4.35 (m, 1 H, *CH*-OH), 5.4 [dd, J = 15.87 Hz, J = 6.55 Hz, 1 H, H(4))], 6.04 [d, J = 15.87, 1 H, H(3)] [lit[3] bp 85-90/0.1 mm for ß-ionol].

4-Thia-ß-cyclogernyltriphenylphosphonium Bromide (54). A 250-mL, single-necked flask was equipped with a magnetic stirrer and a condenser. To a stirred solution of 5 g (0.023 mol) of 4-thia-ß-ionol (**53**) in methanol was added 14 g (0.04 mol) of triphenylphosphine hydrobromide all at once, and the reaction mixture was stirred at room temperature for 24 h. Methanol was evaporated under reduced pressure (rotary evaporator), and the resulting thick, oily slurry was kept under vacuum (25°C/10 mm) for 2 h. This oil was triturated with ether (100 mL) to obtain 13 g (0.024 mol) of a yellow solid **54.** ^{1}H NMR ($DCCl_3$) δ 0.82 (s, 3 H, CH_3), 0.91 (s, 3 H, CH_3), 1.49 (dd, 3 H, CH_3-CH), 1.3 (m, 2 H, CH_2.CH_2-S), 2.7 (m, 2 H, CH_2-CH_2-S), 3.2 (bs, 3 H, CH_3), 5.0 (m, 1 H, CH_3-*CH*), 6.44 [m, 1 H, H(4)], 6.81 [m, 1 H, H(3)], 7.2-8.0 (m, 15 H, Ar-H).

2-Methyl-4-phenoxy-2-butanol-*1,2'*-$^{14}C_2$ (58*). A 50-mL three-necked round-bottomed flask was equipped with a magnetic stirrer, a rubber septum and a cold finger. To 0.0698 g (2.91 mmol) of Mg turnings in (0.5 mL) of dry ether was added methyl iodide (^{14}C, 2.5 mg, 1 mCi, 56.6 mCi/mmol sp. act., ICN) along with 10 mL of dry ether followed by the addition of 0.531 g (3.74 x 10^{-3} mol) of H_3CI. After stirring at room temperature for 30 min, the reaction mixture was treated with 0.150 g (8.32 x 10^{-4} mol) of methyl 3-phenoxypropionate (**57**) [76] in 5 mL of dry ether. After 24 h of stirring, the grey-colored reaction mixture was poured onto 20 g of crushed ice. Ether (20 mL) was added followed by slow addition of saturated NH_4Cl solution (~40 mL). When the pH of the mixture was made neutral to litmus, the organic layer was separated. Extraction

(ether, 10 x 10 mL) of the aqueous layer followed. The combined organic layer and extracts were washed with water (3 x 10 mL), saturated $NaHCO_3$ (3 x 10 mL), and saturated NaCl (20 mL). After drying (Na_2SO_4) and filtering, the solution was concentrated to give 0.190 g (9.99 x 10^{-4} mol) of a light yellow-colored oil. This slightly impure **58*** was used in the next step without further purification since all spectral properties were identical to those of the unlabelled material [lit[76] IR 3620-3140 (O-H) cm^{-1} for the unlabelled compound].

4,4-Dimethylchroman-*9,10*-$^{14}C_2$ (59*). A 25-mL, three-necked round-bottomed flask was equipped with a magnetic stirrer, an addition funnel and a condenser. To a suspension of 0.163 g (1.23 x 10^{-3} mol) of $AlCl_3$ in 2 mL of freshly distilled H_3CNO_2 was added 0.170 g (9.43 x 10^{-4} mol) of slightly impure **58*** in 5 mL of freshly distilled H_3CNO_2. After stirring for 24 h at room temperature, the dark red reaction mixture was cooled in an ice-water bath for a few minutes. Treatment with HCl (6 M, ~10 mL) to a pH acidic to litmus produced two layers. Stirring of the mixture continued for 10 min and then ether (10 mL) was added. Extracts (ether, 10 x 10 mL) of the aqueous layer, combined with the original organic layer, were washed with water (5 x 10 mL), saturated $NaHCO_3$ (4 x 10 mL), and saturated NaCl (15 mL). After drying (Na_2SO_4), the solution was concentrated to a light brown-colored oil (0.160 g, 9.86 x 10^{-4} mol) which was slightly impure **59*** via spectral analysis.[76] This material was used without further purification in the synthesis of **40*** [lit[76] 74-80°C/0.7 mm].

4,4-Dimethylchroman-6-yl Methyl Ketone-*9,10,11*-$^{14}C_3$ (40*). A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer and a cold finger. To 1.57 mg (2 x10^{-5} mol, 1 mCi, 50 mCi/mmol sp. act., ICN) of $H_3C^{14}C(O)Cl$ in 5 mL of freshly distilled H_3CNO_2 was added 0.093 g (1.18 x 10^{-3} mol) of freshly distilled acetyl

chloride. To this solution was added 0.160 g (9.86×10^{-4} mol) of the above 4,4-dimethylchroman (**59***) in 10 mL of freshly distilled H_3CNO_2. Slow addition of $AlCl_3$ (0.197 g, 1.48×10^{-3} mol) to the stirred solution followed. After stirring at room temperature for 10 h, the solution was cooled (ice-water bath). Cautious addition of of 6 *M* HCl (Ca 10 mL) followed until the solution was just acidic to litmus. The combined organic layer and the ether extracts (10 x 10 mL) of the aqueous layer were washed with water (5 x 10 mL), saturated $NaHCO_3$ (3 x 10 mL), and saturated NaCl (15 mL). After this solution was dried (Na_2SO_4), filtered, and concentrated, a light brown oil (0.165 g, 8.08×10^{-4} mol) remained. This slightly impure **40*** showed the characteristic IR band for the C=O group (1650 cm^{-1}) along with other spectral properties which confirmed the known structure.[76] The sample of **40*** was used without further purification [lit[76] IR (neat) 1685-1675 (C=O) cm^{-1}; lit[55] 1670 (C=O) cm^{-1}]. Since our preparation was slightly impure, the C=O values did not match exactly.

α,4,4-Trimethylchroman-6-methanol-*9,10,11-$^{14}C_3$* (**60***). A 50-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer and a condenser. To a stirred suspension of 0.042 g (1.10×10^{-3} mol) of $LiAlH_4$ in 2 mL of dry ether was added ketone **40*** from above in 5 mL of dry ether. The mixture was held at reflux for 24 h with about 15 mL of ether being added periodically to maintain volume. After the mixture was allowed to cool to room temperature, it was chilled (ice-water). Addition of 6 M HCl was performed until the mixture was slightly acidic to litmus. The combined organic layer and ether (10 x 10 mL) extracts were washed with water (5 x 10 mL), saturated $NaHCO_3$ (3 x 10 mL), and saturated NaCl (20 mL) solution. After the solution was dried (Na_2SO_4), it was filtered and concentrated (rotary evaporator) to a thick brown oil which was slightly impure alcohol **60*** as indicated by spectral analysis.[80] The compound was used directly in the next step [lit[76] IR (neat) 3640-3140 (O-H) cm^{-1} for the unlabelled compound **60**].

[1-(4,4-Dimethylchroman-6-yl)ethyl]triphenylphosphonium Bromide-*9,10,11-$^{14}C_3$* **(61*).** A 50-mL, single-necked, round-bottomed flask was equipped with a magnetic stirrer and a condenser. A mixture of 0.120 g (5.82×10^{-4} mol) of alcohol **60*** in methanol (25 mL) and 0.230 g (6.69×10^{-4} mol) of triphenylphosphine hydrobromide[4] was stirred at room temperature for 24 h. Evaporation (rotary evaporator) of the methanol left a light brown oil which was triturated repeatedly with dry ether (~25 mL) until a solid formed. Filtration of the mixture provided a fair yield of **61*** (0.210 g, 3.95×10^{-4} mol, 68%). The IR spectrum of this salt **61*** [149-153°C (dec)] was essentially identical to that reported for the unlabelled compound [lit[76] mp 149-155°C (dec)] and thus the former was used immediately in the final condensation to produce **28*.**

Ethyl (*E*)-4[2-(3,4-Dihydro-4,4-dimethyl-2*H*-1-benzopyran-6-yl)-1-propenyl]benzoate-*9,10,11,20-$^{14}C_4$* **(28*).** A 50-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer a condenser and a rubber septum. To a solution of *n*-butyllithium (1.5 mL of 1.0 molar in hexanes, Aldrich) was added to 0.200 g of phosphonium salt **60*** (approximately 0.150 g of labelled material and 0.050 g of cold material) in dry ether (20 mL) over a period of 2 min. The resulting dark red mixture was cooled to -78°C (dry ice-acetone bath), and then 0.085 g (0.477 mmol) of ethyl 4-formylbenzoate [4-OHC-$C_6H_4{}^{14}CO_2Et$] (**64***) in ether (5 mL) was added. A cream-colored mixture formed, and this was stirred at -78°C for 10 min and then was allowed to rise to room temperature with stirring over 24 h. A suspension formed and was filtered. The filtrate and one ether wash (25 mL) of the filtered solid were combined and evaporated (rotary evaporater) to a yellow oil. Chromatography of this oil was effected on a Chromatotron [4 mm plate, silica gel 60 PF_{254} containing gypsum] using 200 mL of hexanes:ethyl acetate (9:1) as eluent. Two bands with the highest R_f values (0.75 and

0.70) were collected, and the solvent was evaporated (rotary evaporator) in each case to give colorless oils. The oils appeared to be identical via TLC analysis and were combined and dissolved in a minimum amount of hot absolute ethanol (~5 mL). The solution stood at room temperature for 1 h, and then it was refrigerated (2 days). A white solid was deposited and this was filtered to obtain 13.2 mg (10%) of **28***. The specific activity was determined on a 10 μL aliquot (prepared by dissolving 7.3 mg of **28*** in 4 mL of HPLC grade methanol) via the use of a TRI-CARB liquid scintillation analyzer (model 1900-CA, Packard Instrument Company, Downers Grove, IL). The specific activity of was 0.15 mCi/mg or 4.28 x 10^{-5} mCi/mmol. An average count of 6043.8 DPM (disintegrations/minutes) was obtained. A mixture melting point determination of this material with an authentic sample of cold **28** did not show a depression (mp 72-73°C).[76]

Ethyl *p*-Toluate-^{14}C=*O* (63*). A 50-mL, single-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle and a condenser. To a mixture of 0.015 g (1.10 x 10^{-4} mol, 0.5 mCi, 4.5 mCi/mmol sp. act., Sigma) of *p*-toluic acid-^{14}C=*O* (**62***) and 0.290 g (2.13 x 10^{-3} mol) of *p*-toluic acid was added 10 mL of absolute alcohol and 20 mL of dry benzene along with 1 mL of conc. sulfuric acid. After boiling the solution for 24 h, the near theoretical amount of water was collected via a Dean-Stark trap. Water (~20 mL) was added to the solution which had been allowed to cool to room temperature. The combined organic layer and ether extracts (10 x 10 mL) were washed with water (3 x 10 mL), saturated $NaHCO_3$ (3 x 10 mL), and brine (20 mL). After the solution was dried (Na_2SO_4), filtered, and concentrated (rotary evaporator), a light yellow liquid remained and was used immediately in the next step. The weight of the oil was 0.380 g (quantitative). IR (neat) 1720 [broad] (C=O) cm^{-1} [lit[76] IR (neat) 1745 (C=O) cm^{-1}].

Ethyl 4-Formylbenzoate-$^{14}C(O)OEt$ (64*). A 25-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer and a condenser. A solution of the oil **63*** (0.380 g, 2.31 x 10^{-3} mol) in 5 mL of freshly distilled acetic anhydride and 5 mL of glacial acetic acid was cooled to 0°C (ice-water bath). Concentrated H_2SO_4 (0.2 mL) was added along with 0.693 g of CrO_3 in three equal portions over a period of 30 min. Care was taken to maintain the temperature below 5°C during the addition. When the addition was complete, a dark green reaction mixture remained which was stirred for 1 h at 0°C. Decomposition was effected by slowly pouring the mixture onto crushed ice (25 g) and then adding (very slowly) 50 mL of cold water. A green-colored solution formed, and this was extracted with $HCCl_3$ (10 x 10 mL). The extracts were washed with water (3 x 10 mL), 5% Na_2CO_3 (3 x 10 mL), and brine (20 mL). The dried (Na_2SO_4) solution was filtered and concentrated to give 0.385 g of a yellow oil. Water (10 mL), 95% ethanol (10 mL), and concentrated H_2SO_4 (0.5 mL) were added, and the resulting solution was held at reflux for 1 h. After cooling to room temperature, the solution was diluted with water (10 mL) and then extracted with $HCCl_3$ (10 x 10 mL). The extracts were washed with water (3 x 15 mL), 10% $NaHCO_3$ (3 x 10 mL), and brine (20 mL). When dried (Na_2SO_4), the solution was filtered and concentrated (rotary evaporator) to give 0.090 g (36.8%) of **64*** which was used in the Wittig reaction with the anion from salt **61*** to yield **28*.** IR (neat) 1725 [broad] C(=O)OEt and (HC=O) [lit[76] IR (neat) 1740 C(=O)OEt, 1680 (HC=O) cm^{-1}].

Methyl 4-(Carboxymethylmercapto)butyrate (77). A 25-mL, three-necked, round-bottomed, flask was equipped with a magnetic stirrer, a rubber septum and a condenser. Into this system was placed MeOH (5 mL), which was cooled to 0-5°C (ice-water bath), and then 1.03 g (19.1 mmol) of NaOMe was added in two portions over a 15-min period. Methyl thioglycolate (**76**, 2.00 g, 18.8 mmol) was added by syringe to this

cold, stirred solution, and the reaction mixture was stirred at 0-5°C for 15 min. Methyl 4-chlorobutyrate (**75**, 2.50 g, 18.24 mmol) was added by syringe, and the resulting reaction mixture was stirred at the same temperature for 10 min. It was then allowed to warm to the room temperature over a period of 3 h. The reaction mixture turned cloudy over this period. It was allowed to stand overnight, and solid NaCl precipitated which was filtered (gravity). The residue was washed with MeOH (25 mL). The filtrates and washings were combined and evaporated (rotary evaporator) to yield a viscous residue which was dissolved in 20 mL of ether:water (1:1). The organic layer was separated, washed with water (2 x 10 mL), dried ($MgSO_4$), filtered, and concentrated (rotary evaporator) to give a colorless liquid **77** (3.29 g 87%). IR (neat) 1740 (C=O) cm^{-1} [lit[80] 1740 broad (C=O) cm^{-1}]; ^1H NMR ($DCCl_3$) δ 1.94 [m, 2 H, H(3)], 2.44 [t, 2 H, H(2)], 2.68 [t, 2 H, H(4)], 3.23 [s, 2 H, H(6)], 3.68 [s, 3 H, H(8)], 3.74 [s, 3 H, H(9)]; ^{13}C NMR ($DCCl_3$) ppm 29.93 [C(3)], 31.71[C(2)], 32.51[C(4)], 33.09 [C(6)], 51.55[C(8)], 52.31 [C(9)], 170.75 [C(1)], 173.27 [C(7)].

2-Carbomethoxythiacyclohexan-3-one (78). A 25-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, condenser, and an addition funnel. A suspension of 1.05 g (0.019 mol) of NaOMe in ether (10 mL) was added with stirring and cooling to 0-5°C in ice bath. To this stirred suspension was added 2.00 g (0.096 mol) of methyl 4-(carboxymethylmercapto)butyrate (**77**). The thick, yellow-colored suspension was stirred at 0-5°C for 1 h and then was allowed to warm to room temperature over a period of 3 h. Water (10 mL) and glacial acetic acid (4 mL) were slowly added to the reaction mixture. The organic layer was separated, and the aqueous layer was extracted with ether (10 mL). Combined organics were washed with saturated $NaHCO_3$ (3 x 10 mL) and with brine (10 mL). The organics were dried ($MgSO_4$), filtered and concentrated (rotary evaporator) to give 1.03 g of the colorless liquid **78**. IR (neat) 1740, 1720 (C=O

ester free and hydogen bonded), 1660 (C=O ketone) cm^{-1}[lit[80] 1745, 1715, 1645 (C=O, ester and ketone) cm^{-1}]; ^1H NMR ($DCCl_3$) δ 2.13 [m, 2 H, H(5)], 2.40 [t, 2 H, H(4)], 2.81 [t, 2 H, H(6)], 3.69 [s, 1 H, H(2)], 3.81 (s, 3 H, CH_3), 12.1 (s, 1 H, OH).

Attempted Alkylation of 78. A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser and a rubber septum. A suspension of 0.173 g (0.007 mol) of NaH (50% dispersion in mineral oil) in 40 mL of dry benzene was cooled to 0-5°C (ice bath). To this cold stirred suspension was added 0.270 g (0.0014 mol) of 2-carbomethoxythiacyclohexan-3-one (**78**). A gas was observed to form in the suspension. The mixture was stirred at 0-5°C for 30 min, and then 3.06 g (0.027 mol) of CH_3I was added slowly by syringe. The mixture was stirred at same temperature for 10 min and then allowed to warm to the room temperature over a period of 36 h. It was then cooled in ice bath and MeOH (10 mL) and water (10 mL) were added. The organic layer was separated and the aqueous layer was extracted with ether (3 x 10 mL). The combined organic solutions were dried (Na_2SO_4), filtered and concentrated (rotary evaporator) to give 0.075 g of a yellow colored oil **78**. This oil was similar to the starting material as it had IR bands at 1740, 1715, 1640 cm^{-1}. This reaction was carried out with 4-6 equivalents of CH_3I, but the result was similar in all cases. ^1H NMR ($DCCl_3$) δ 2.13 [m, 2 H, H(5)], 2.40 [t, 2 H, H(4)], 2.81 [t, 2 H, H(6)], 3.69 [s, 1 H, H(2)], 3.81 (s, 3 H, CH_3).

Methyl 4-Chloro-2,2-dimethylbutyrate (80). A 300-mL, three-necked, round-bottomed flask was equipped with an addition funnel, rubber septum and a condenser. Freshly distilled diisopropylamine (10.12 g, 0.001 mol) in 50 mL of THF was cooled to -78°C (dry ice-acetone bath), and then 10 mL of a 10 M solution of *n*-BuLi was added dropwise by syringe. The resulting yellow-colored solution was stirred at -78°C for 1 h. Methyl isobutyrate (8.17 g, 0.001 mol, Aldrich) was then added over a period of 10 min,

and stirring was continued at same temperature for 1 h. After this time, 15.0 g (0.0015) of 1-bromo-2-chloroethane (Lancaster) in 25 mL of THF was added over a period of 15 min. After stirring for an additional 10 min at -78°C, the reaction mixture was allowed to warm to the room temperature over a period of 24 h. A solid formed and was filtered off. The solid melted at 142-144°C and weighed 500 mg; no further work was done with this solid. It was then cooled in an ice bath, and water (100 mL) was added followed by concentrated HCl (25 mL). The organic layer was separated and washed with 10% HCl (2 x 50 mL). The combined aqueous layer was extracted with CH_2Cl_2 (3 x 100 mL). The original organic layer, along with the organic extracts, were dried (Na_2SO_4), filtered, and concentrated (rotary evaporator) to give a colorless liquid **80** which was distilled under vacuum (bp 47-50°C/8 mm, lit[8] bp 80-84°C/15 mm).

Methyl 2,2-Dimethyl-4-(methoxycarbonylmethylmercapto)butyrate (81). A 50-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle and a condenser. To a solution of 1.67 g (0.03 mol) of NaOMe in MeOH (25 mL) was added dropwise 3.29 g (0.03 mol) of methyl thioglycolate (**76**, Aldrich). The reaction mixture was boiled for 0.5 h and then cooled to the room temperature. In an another 100-mL, round-bottomed flask equipped with an addition funnel, condenser and heating mantle was placed a solution of 5 g (0.03 mol) of methyl 2,2-dimethyl-4-chlorobutyrate (**80**) in 25 mL of MeOH. To this was added the earlier reaction mixture of the sodium salt of the methyl thioglycolate (page 37) over a period of 30 min. The new reaction mixture was boiled for 24 h and then was cooled to the room temperature (1 h). The MeOH was evaporated (rotary evaporator). The residue was poured slowly onto ice, and the aqueous solution was acidified with 6 *M* HCl (15 mL) to a pH of about 6. The acidic aqueous solution was extracted with ether (4 x 25 mL). The combined organic extracts were dried (Na_2SO_4), filtered and concentrated (rotary evaporator) to give a light

yellow-colored liquid **81** which was distilled under vacuum (bp 112-115°C/0.02 mm, lit[3] bp 114-117°C/0.25 mm). IR (neat) 1740-1720 (C=O) cm^{-1}.

2-Carbomethoxy-4,4-dimethylthiacyclohexan-3-one (82). A 25-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle and a condenser. To a boiling suspension of 0.344 g of NaH (60% dispersion in mineral oil) in benzene (10 mL) was added 1.0 g (0.004 mol) of methyl 2,2-dimethyl-4-carboxymethylmercaptobutyrate (**81**). The reaction mixture was boiled for 4 h. It was then cooled to the room temperature and poured onto ice. The resulting mixture was made acidic with 6 *M* HCl (10 mL) to a pH of about 6. The aqueous layer was extracted (benzene, 4 x 10 mL), and the combined extracts were dried (Na_2SO_4), filtered, and concentrated (rotary evaporator) to give 0.8 g of an orange-colored liquid **82**. Chomatography on a 2 mm silica gel plate (Chomatotron) with 50 mL of hexane:ethyl acetate (9:1), followed by 50 mL of hexane:ethyl acetate (8:2) as eluent, gave several fractions. The first fraction of 50 mL was collected and concentrated to give 0.32 g of a colorless liquid **82**. IR (neat) 1730-1645 (C=O) cm^{-1} [lit[3] IR 1735-1644 (C=O) cm^{-1}]; ^1H NMR ($DCCl_3$) δ 1.2 [s, 6 H, $(CH_3)_2$], 1.98 [m, 2 H, H(5)], 2.8 [m, 2 H, H(6)], 3.8 (s, 3 H, OCH_3), 12.4 [s, 1 H, OH (enol tautomer)].

Attempted Reaction of 82 with *N*-Phenyltrifluoromethanesulfonimide. A 25-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer, condenser and a rubber septum. A solution of 0.110 g (0.001 mol) of freshly distilled diisopropylamine in 5 mL of THF was cooled to -78°C (dry ice/acetone bath), and 0.11 mL (0.0011 mol) of *n*-BuLi (10 M solution in hexane) was added by syringe. The reaction mixture was stirred at -78°C for an additional 10 min, and then 0.2 g (0.99×10^{-3} mol) of thia ß-keto ester **82** was added in 5 mL of THF by syringe. The resulting mixture was

stirred at the same temperature for 2 h. After this period, 0.378 g (0.0011 mol) of *N*-phenyltrifluoromethanesulfonimide (Aldrich) in 3 mL of THF was added over a period of 5 min. After the addition was complete, the cold bath was removed and the reaction mixture was stirred overnight. Evaporation (rotary evaporator) of the solvent gave a residue which was dissolved in 10% HCl (10 mL). The aqueous layer was extracted with pentane (4 x 10 mL). Combined extracts were washed with 10% HCl (15 mL), 10% NaOH (15 mL) and water (10 mL), after drying (Na_2SO_4), the solution was filtered and evaporated (rotary evaporator) to give 0.15 g of white crystalline solid which showed spectral properties similar to *N*-phenyltrifluoromethanesulfonimide, and the mp of *N*-phenyltrifuoromethane sulfonimide was 99-101°C. The mp of the solid was found to be 100-101 °C.

4,4-Dimethylthiacyclohexan-3-one (83). A 50-mL, two-necked, round-bottomed flask was equipped with a condenser, a magnetic stirrer and a heating mantle. A solution of 2.00 g (9.89×10^{-3} mol) of 2-carbomethoxy-4,4-dimethylthiacyclohexan-3-one (**82**) in 15 mL of 10% H_2SO_4 was boiled for 6 h. The yellow solution was first cooled to the room temperature and then slowly neutralized with 10% NaOH (ca 20 mL) to pH 7. The aqueous layer was extracted with ether (3 x 25 mL). The combined organics were dried (Na_2SO_4), filtered and evaporated (rotary evaporator) to give a light yellow colored liquid **83** . IR (Neat) 1705 (C=O) cm^{-1} [lit[3] 1705 cm^{-1} (C=O)]; ^1H NMR ($DCCl_3$) δ 1.15 [s, 6 H, $(CH_3)_2$], 2.2 [m, 2 H, H(6)], 2.8 [m, 2 H, H(5)], 3.2 [s, 2 H, H(2)].

Attempted Alkylation of 4,4-Dimethylthiacyclohexan-3-one (83). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a rubber septum and a condenser. A solution of 0.7 g (6.92×10^{-3} mol) of freshly distilled diisopropylamine in 10 mL of THF was cooled to -78 °C (dry ice/acetone bath), and to this cooled solution was added 0.7 mL of 10 *M* solution of *n*-BuLi in hexane by syringe. The

resulting yellow-colored solution was stirred at -78°C for 30 min, and then 0.9 g (6.24 x 10^{-3} mol) of 4,4-dimethylthiacyclohexan-3-one (**83**) in 5 mL of THF was added dropwise by syringe. After stirring for 30 min, 0.9 g (6.37 x 10^{-3} mol) of CH_3I in 5 mL of THF was added over a period of 2 min. After the addition was complete, the cold bath was removed, and the reaction mixture was allowed to warm to room temperature over a period of 24 h. After this time, the reaction mixture was cooled in an ice bath and was then quenched with water (10 mL), followed by 6 *M* HCl (5 mL) to a pH of about 3. The aqueous layer was separated and extracted with ether (3 x 25 mL). The combined organics were dried (Na_2SO_4), filtered and concentrated to give a dark oil, which showed spectral properties similar to the starting ketone [lit[3] IR 1705 cm^{-1} (C=O)]. Thus it was concluded that the alkylation did not take place. This reaction was repeated with 2-4 equivalents of CH_3I, but the end result was the same.

Methyl 4-Bromomethylbenzenesulfonate (89). A 50-mL, single-necked, round-bottomed flask was equipped with a magnetic stirrer, a heating mantle, and a condenser. To a boiling solution of 5.0 g (0.02 mol) of methyl *p*-toluene sulfonate (**88**) in CCl_4 (25 mL) was added a mixture of 4.98 g (0.03 mol) of *N*-bromosuccinimide and 0.01 g of dibenzoyl peroxide over a period of 45 min. The resultng brown-colored solution was boiled for 5 h and then cooled to room temperature. Precipitated succinamide was filtered (vacuum) and washed with 25 mL of CCl_4. Combined washings and filtrate were concentrated to give 5.6 g (75%) of white solid. This solid was used without furthur purification in the next step. ^1H NMR ($DCCl_3$) δ 3.9 (s, 3 H, $-OCH_3$), 4.5 (s, 2 H, CH_2-Br), 7.5 (d, 2 H, Ar-*H*), 7.9 (d, 2 H, Ar-*H*).

Ethyl 4-triethylphosphonomethylbenzenesulfonate (91). A 150-mL jacketed flask was equipped with a magnetic stirrer, two condensers, a heating mantle, and toluene

in outer jacket. The mixture of 5.0 g (0.02 mmol) of crude **89** and 4.74 g (0.03 mmol) of triethyl phosphite (**90**) was kept at boiling point of toluene (110°C) for 6 h. The resulting pink-colored solution was cooled to room temperature and then was separated on a 4 mm silica gel using hexane:ethyl acetate (8:2). The third fraction of 150 mL was collected and solvent was evaporated to give 2.1 g (48%) of light-colored oil **91**. IR (neat) 1250 cm^{-1} (P=O). The compound was used directly in the preparation of **47.**

4-Cyano-4-trimethylsilyloxy-3,4-dihydro-2*H*-1-benzopyran (101). A 50-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer and a condenser. To 1.5 g (10 mmol) of 4-chromanone (**100**) in 10 mL of CH_2Cl_2 was added 15 mg (0.23 mmol) of KCN and 15 mg (0.05 mmol) of 18-crown-6 ether. This reaction mixture was cooled in an ice bath and then 1.19 g (12 mmol) of TMSCN was added. The reaction mixture was stirred at 0°C for 10 minutes and was then allowed to warm to room temperature over a period of 24 h. The color changed from light yellow to dark, reddish-brown over this period. The reaction mixture was diluted with CH_2Cl_2 (10 mL). The organics were washed with water (2 x 20 mL), saturated $NaHCO_3$ (2 x 20 mL) and with brine (20 mL). It was dried (Na_2SO_4), filtered and evaporated (rotary evaporator) to 2.1 g (85 %) brown colored liquid. IR (neat) 3110 cm^{-1};^1H NMR ($DCCl_3$) δ 0.2 [s, 9 H, $Si(CH_3)$], 2.4 [m, 2 H, H(3)], 4.35 [m, 2 H, H(2)], 6.8-7.6 [m, 4 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 1.12 [C(Si(*C*H_3)$_3$)], 36.19 [C(2)], 61.2 [C(3)], 117.4 [C(*C*N)]; Aromatic-*C* 120.6, 120.7, 120.9, 128.6, 131.2, 153.4.

4-Cyano-3,4-dihydro-2*H*-1-benzopyran (102). A 100-mL, two-necked, round-bottomed flask was equipped with a condenser and a magnetic stirrer. To a mixture of 3.91 g (36 mmol) of TMSCl, 1.48 g (36 mmol) of CH_3CN, and 5.39 g (36 mmol) NaI was added 1.5 g (6.07 mmol) of 4-cyanochroman (**101**) in 10 mL of hexane. The reaction

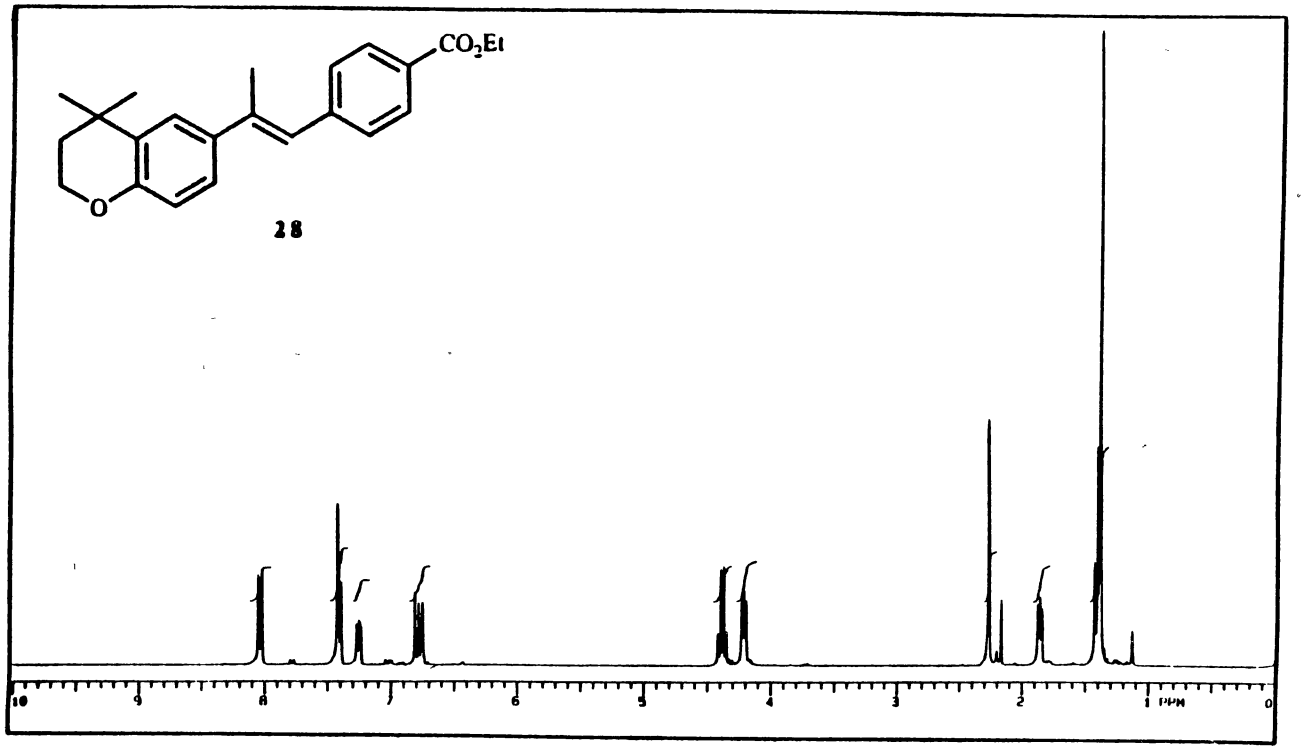
mixture was stirred (30 min) and then 0.22 g of water was added. This heterogeneous mixture was stirred at room temperature for 24 h. The color of the aqueous layer changed to dark red. After 24 h, water (10 mL) was added and the organic layer was separated. The aqueous layer was extracted with ether (3 x 25 mL), and the combined organics were washed with water (2 x 15 mL), 10 % $Na_2S_2O_3$ (3 x 25 mL), and brine (30 mL). It was dried (Na_2SO_4), filtered, and evaporated (rotary evaporator) to dark brown-colored liquid. After purification on the Chromatotron with 200 mL of hexanes:ethyl acetate (9:1), 0.7 g (70 %) of light yellow colored liquid was obtained. IR (neat) 2220 cm^{-1}; ^1H NMR ($DCCl_3$) δ 2.4 [m, 2 H, H(3)], 4.0 [m, 1 H, H(4)], 4.3 [m, 2 H, H(2)], 6.8-7.4 [m, 4 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 26.1[C(3)], 26.8 [C(4)], 63.5 C(3)]; 117.7 [C(*C*N)]; Aromatic *C* 115.1, 120.4, 121.2, 129.3, 129.9, 154.0.

4-Cyano-4-methyl-3,4-dihydro-2*H*-1-benzopyran (103). A 50-mL, two-necked, round-bottomed flask was equipped with a magnetic stirrer and a condenser. To the suspension of 0.12 g (4.84 mmol) of NaH in 10 mL of THF was added 0.7 g of 4-cyanochroman (**102**). The color of the reaction mixture turned dark orange, and after stirring for 15 minutes, 0.68 g of CH_3I was added by a syringe. The resulting reaction mixture was stirred at room temperature for 24 h. It was cooled in an ice bath (15 minutes), and then water (10 mL) was added followed by 5 mL of 10% HCl (pH 5). The organic layer was separated and extracted with ether (3 x 20 mL). The combined organics were washed with water (3 x 25 mL) and brine (40 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated (rotary evaporator) to give dark brown-colored liquid. This liquid was purified on a 4 mm chromatotron plate using 200 mL of hexane:ethyl acetate (9:1) to afford 0.48 g (61 %) of a dark colored liquid. IR (neat) 2220 cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.8 [m, 3 H, C*H*$_3$], 2.3 [m, 2 H, H(3)], 4.3 [m, 2 H, H(2)], 6.8-7.5

[m, 4 H, Ar-H]; ^{13}C NMR ($DCCl_3$) ppm 27.7 [C(9)], 32.0 [C(4)], 34.4 [C(3)], 62.2 [C(2)], 117.7[C(*C*N)]; Aromatic-*C*: 121.3, 121.4, 123.7, 127.7, 129.6, 153.2.

4-Cyano-4-methyl-3,4-dihydro-2*H*-1-benzopyran-6-methyl Ketone (104). A 100-mL, three-necked, round-bottomed flask was equipped with a magnetic stirrer, a condenser, and an addition funnel. To 0.9 g (5.2 mmol) of 4-cyano-4-methyl-3,4-dihydro-2*H*-1-benzopyran (**103**) in 25 mL of CH_3NO_2 was added a solution of 1.73 g (13 mmol) of anhydrous $AlCl_3$ and 0.61 g (7.8 mmol) of $CH_3C(O)Cl$ in 10 mL of CH_3NO_2 over a period of 2 min. The color of the reaction mixture changed to dark reddish brown. This reaction mixture was stirred at room temperature for 24 h. It was then cooled in an ice bath for (15 min), and then 6 *M* HCl (10 mL) was added followed by 10 mL of ether. The organic layer was separated and the aqueous layer was extracted with ether (3 x 15 mL). The combined organic layer was washed with water (2 x 15 mL), saturated $NaHCO_3$, and finally with brine (25 mL). The organic layer was dried (Na_2SO_4), filtered and evaporated (rotary evaporator) to afford a dark brown-colored oil [1.1 g, 57%]. This oil solidified under vacuum (25°C/15 mm). IR (neat) 2200, 1660 cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.82 [s, 3 H], 2.3 [m, 2 H], 2.5 [s, 3 H], 4.4 [m, 2 H], 6.9 [d, J = 8.63 Hz, 1 H], 7.83 [dd, J = 8.66 Hz, J = 2.14 Hz, 1 H], 8.06 [d, J = 2.17 Hz, 1 H]; ^{13}C NMR ($DCCl_3$) ppm 26.3 [C(12)], 27.3 [C(9)], 32.1 [C(4)], 34.1 [C(3)], 62.8 [C(2)], 118.0 [C(*C*N)]; Aromatic-*C*: 121.5, 123.1, 128.7, 130.6, 130.8, 157.3; 196.2 [C(11)].

Plate I



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PLOT/PROCESSING: FN 16 K RE --- sec CD --- sec; LB --- Hz AF --- sec CCD ---; Width 2999 4 Hz/ppm Start 0 Hz/ppm; Reference

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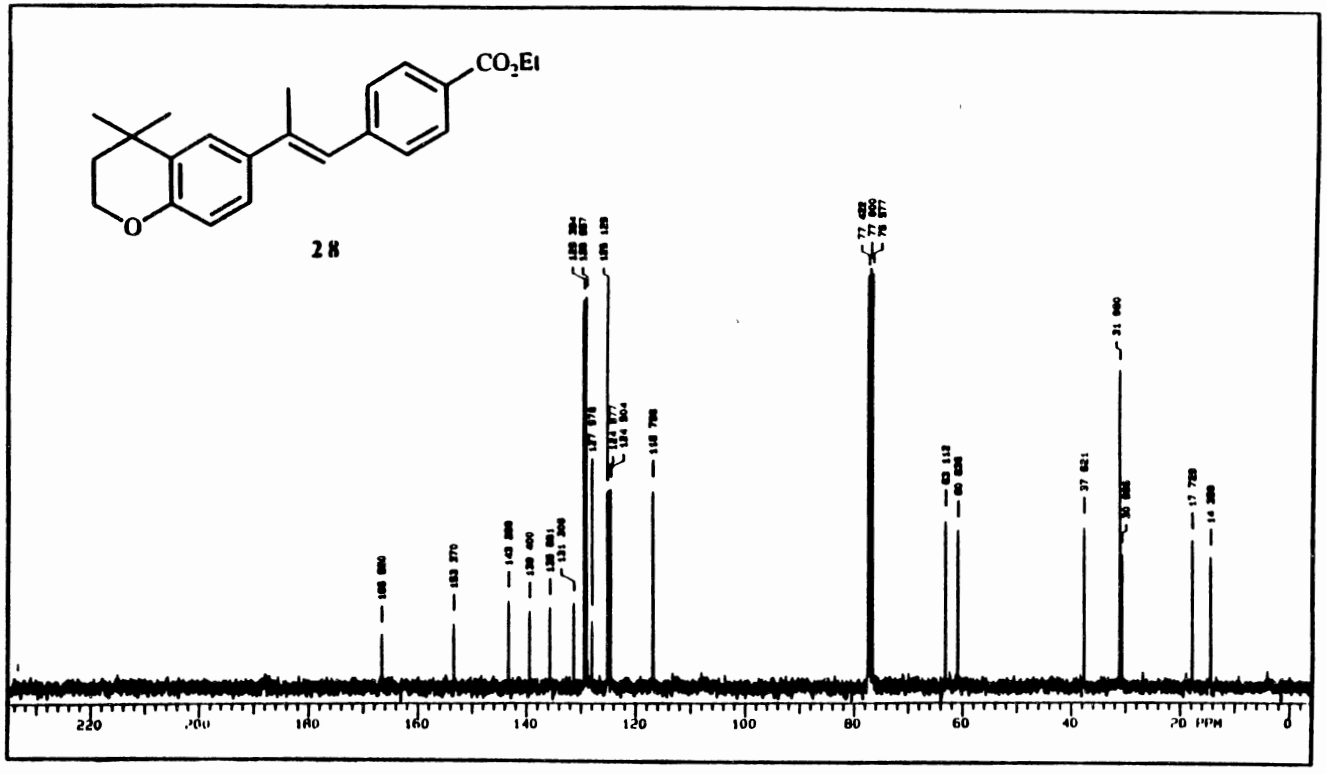
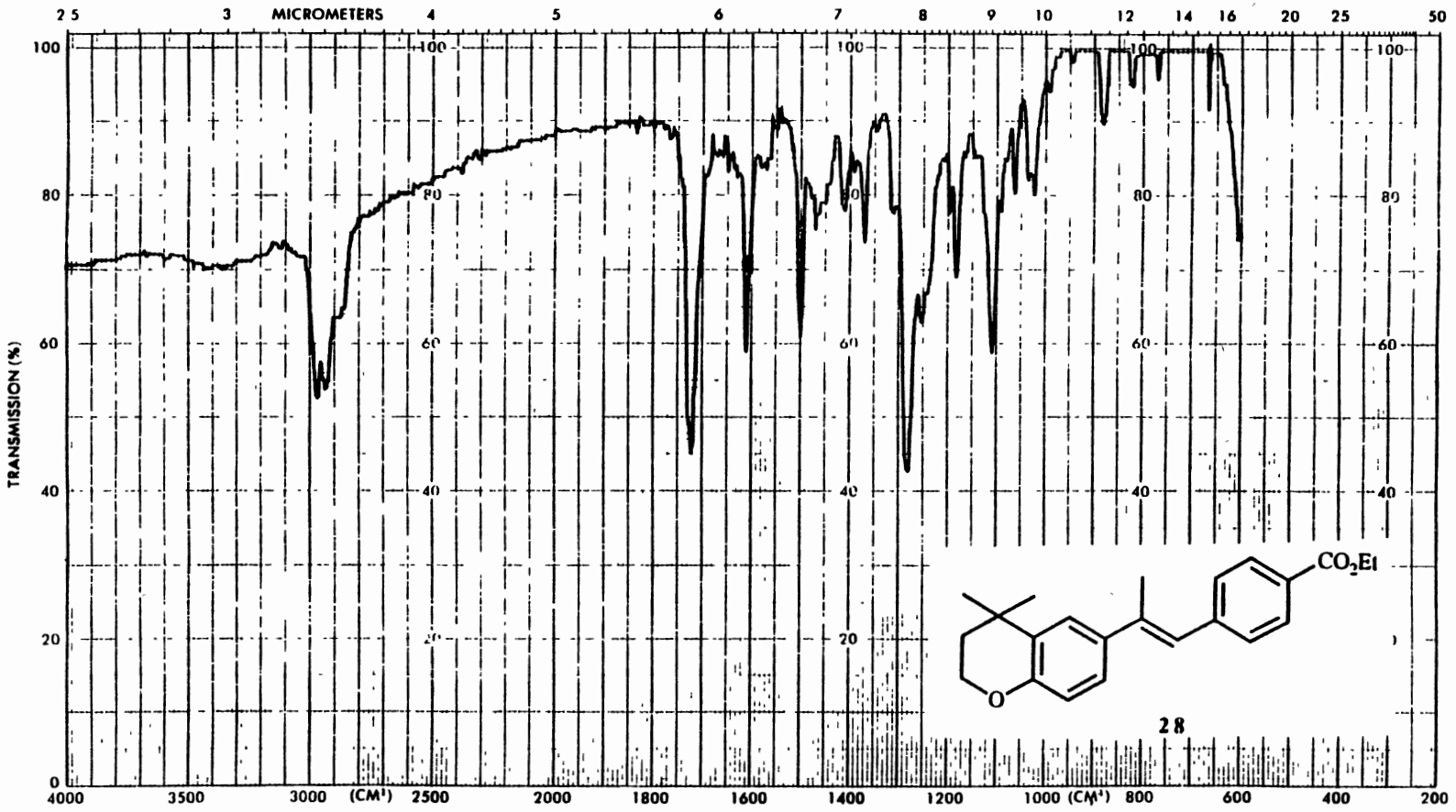
^{1}H NMR Spectrum of **28**

Plate II



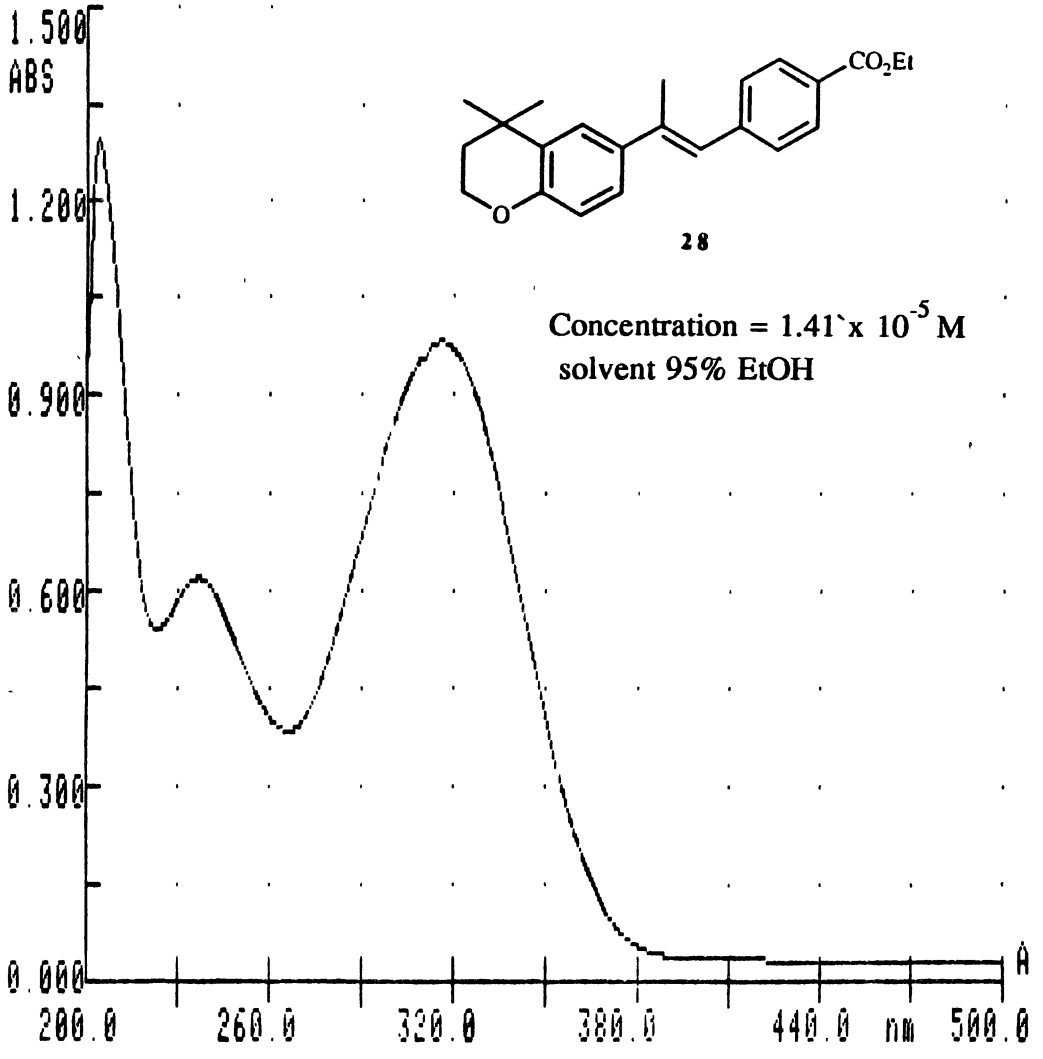
^{13}C NMR Spectrum of **28**

Plate III



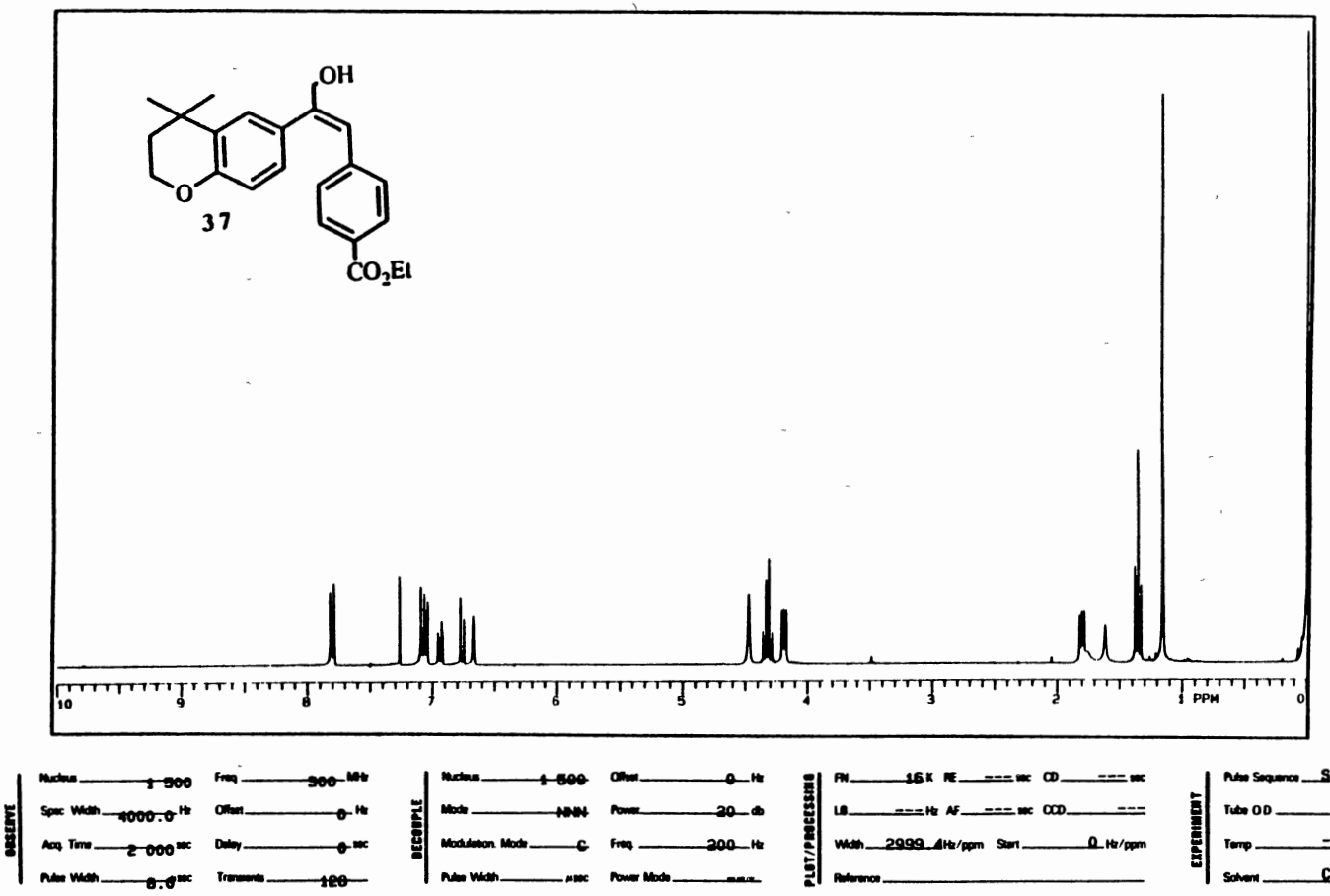
IR Spectrum of **28**

Plate IV



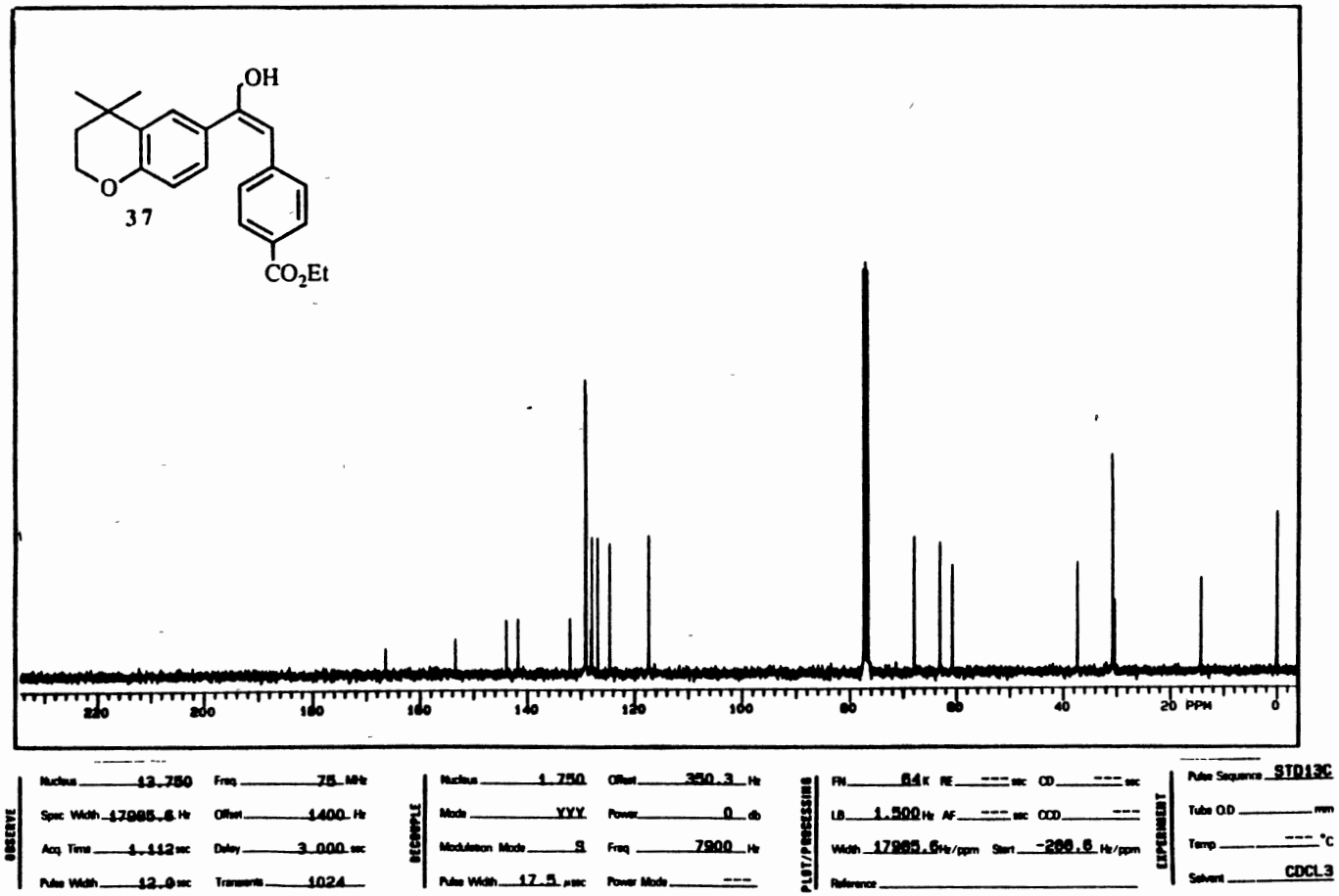
UV Spectrum of **28**

Plate V



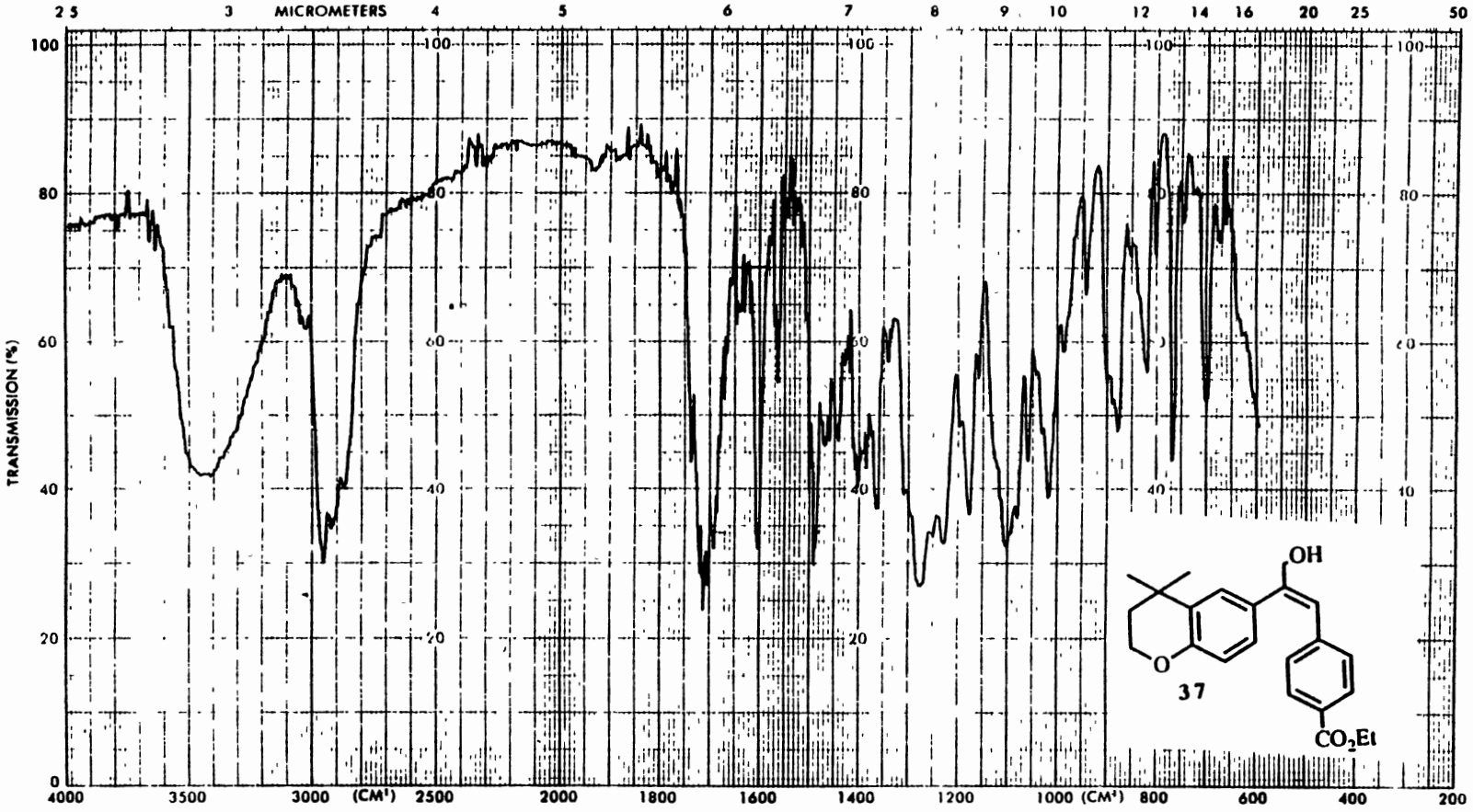
^{1}H NMR Spectrum of **37**

Plate VI



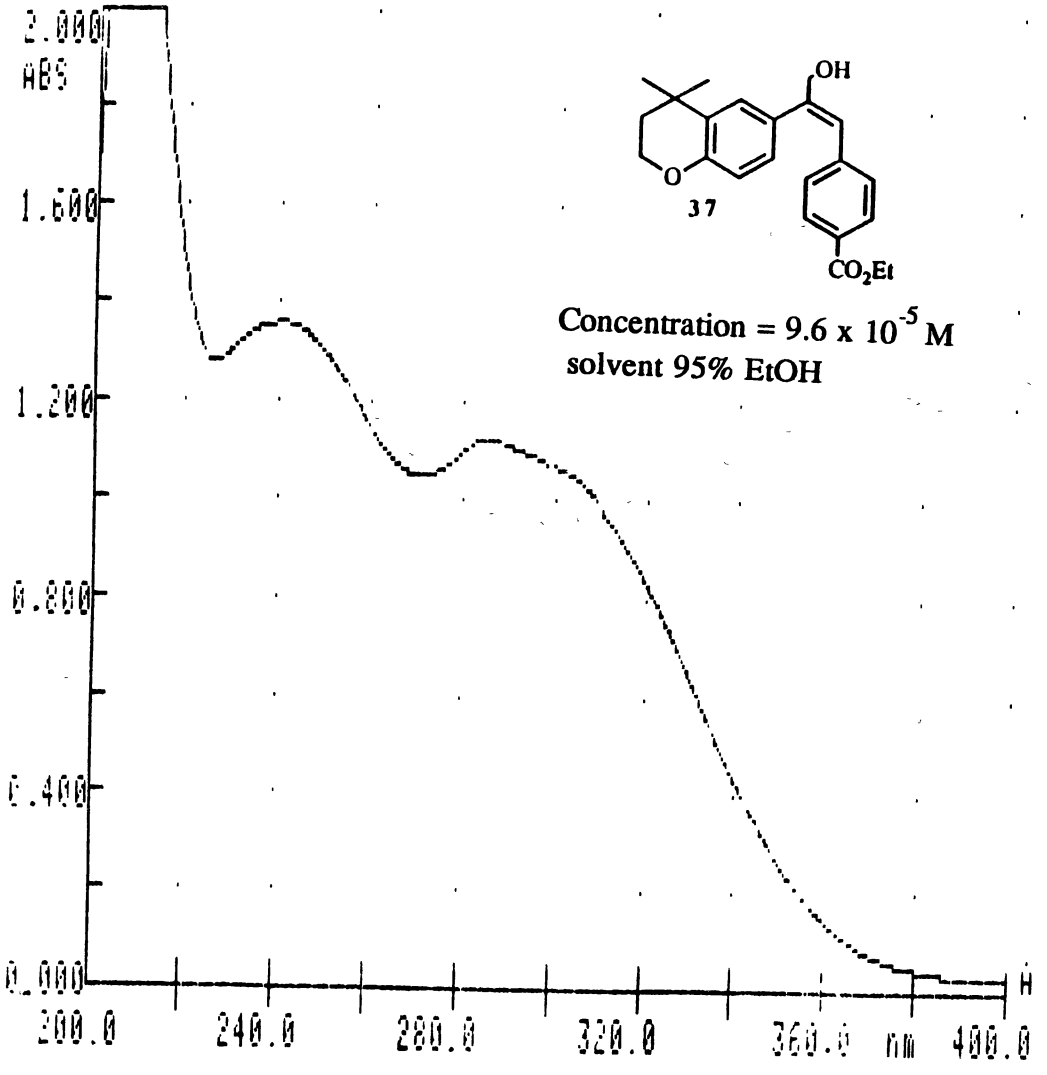
^{13}C NMR Spectrum of **37**

Plate VII



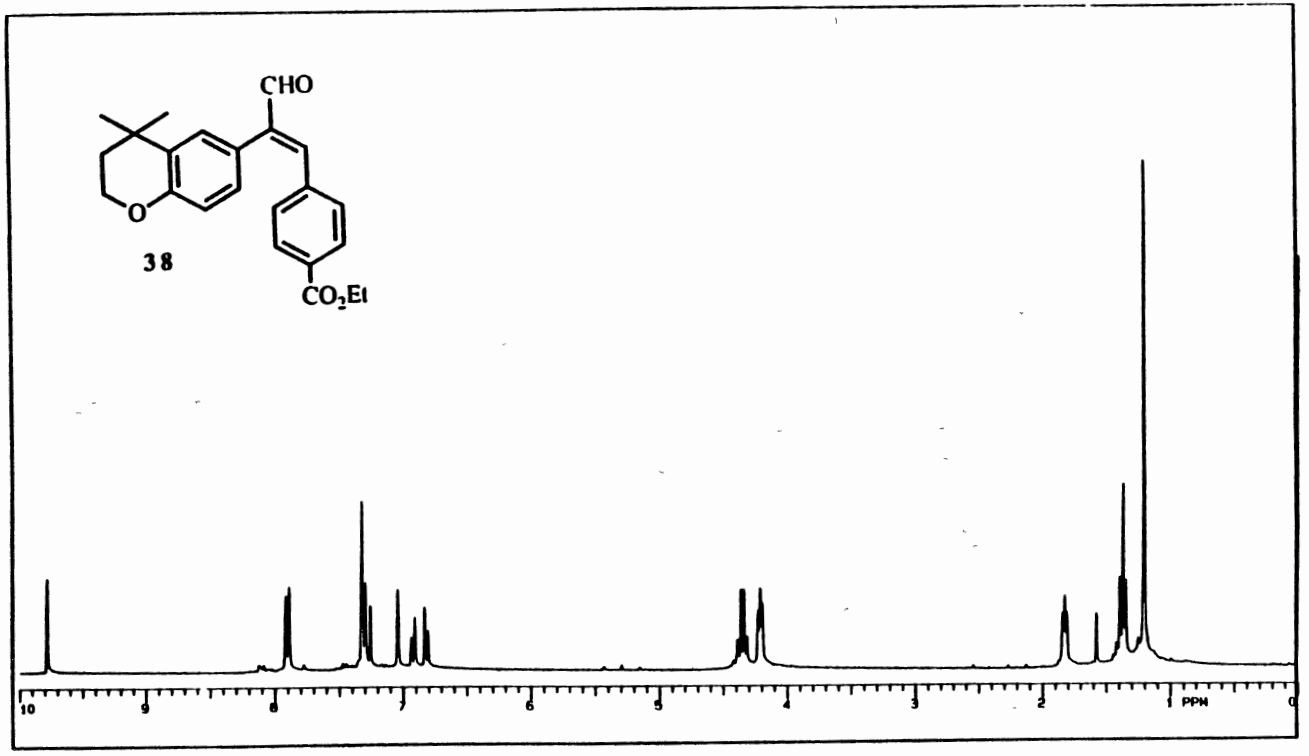
IR Spectrum of **37**

Plate VIII



UV Spectrum of **37**

Plate IX



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

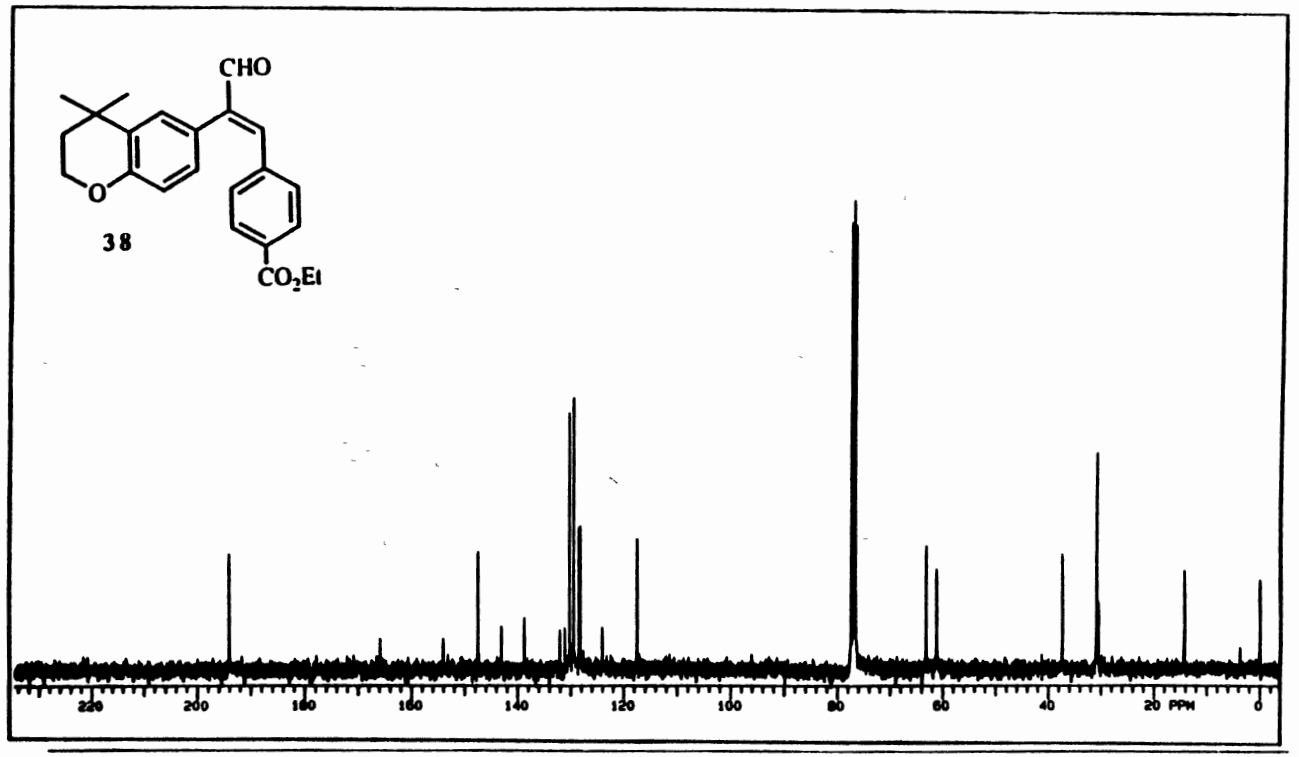
DECOUPLE: Nucleus 1.500 Offset 0 Hz; Mode NNN Power 29 db; Modulation Mode C Freq 200 Hz; Pulse Width ___ μsec Power Mode ---

PLOT/PROCESSING: FN 16K RF ---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

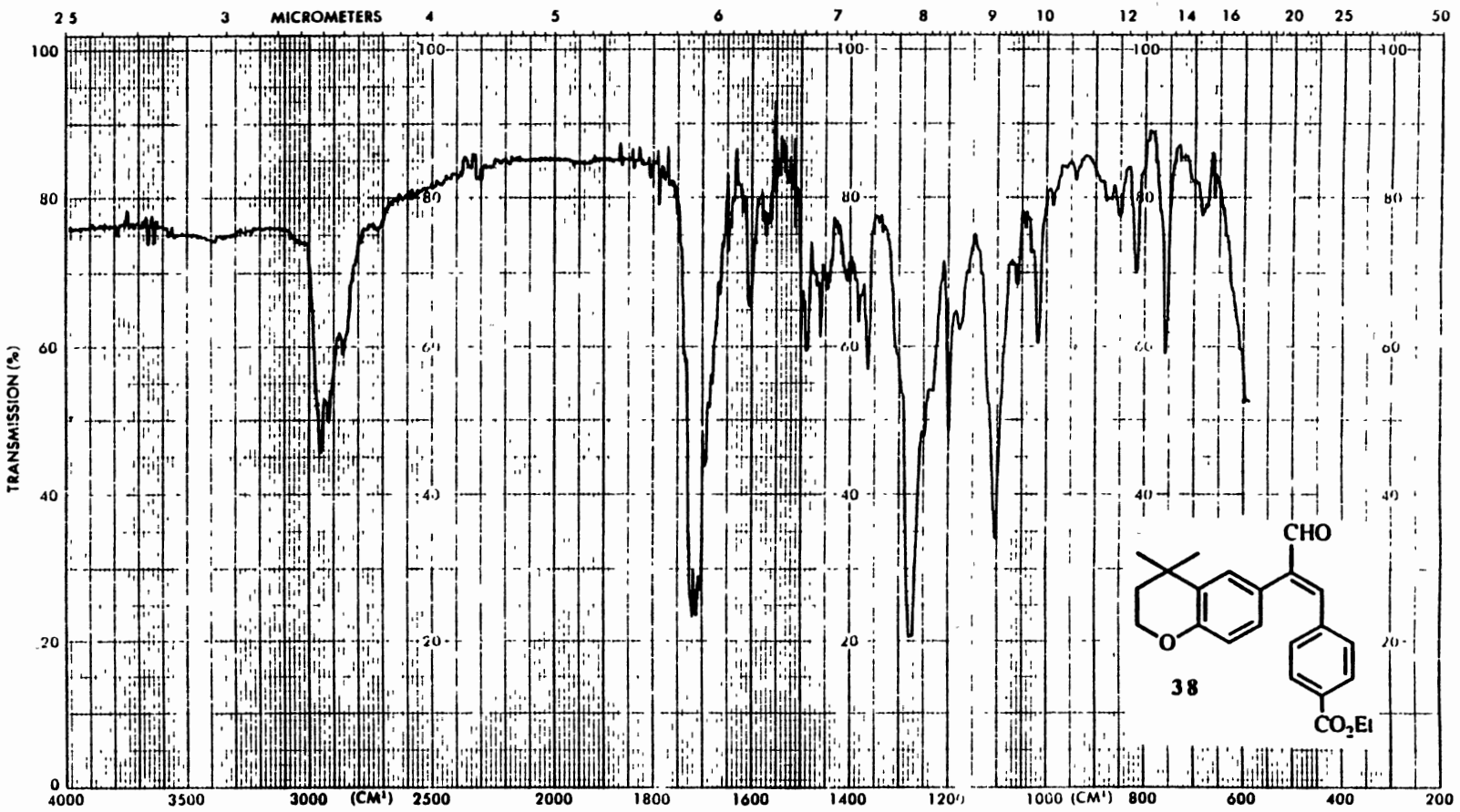
^{1}H NMR Spectrum of **38**

Plate X



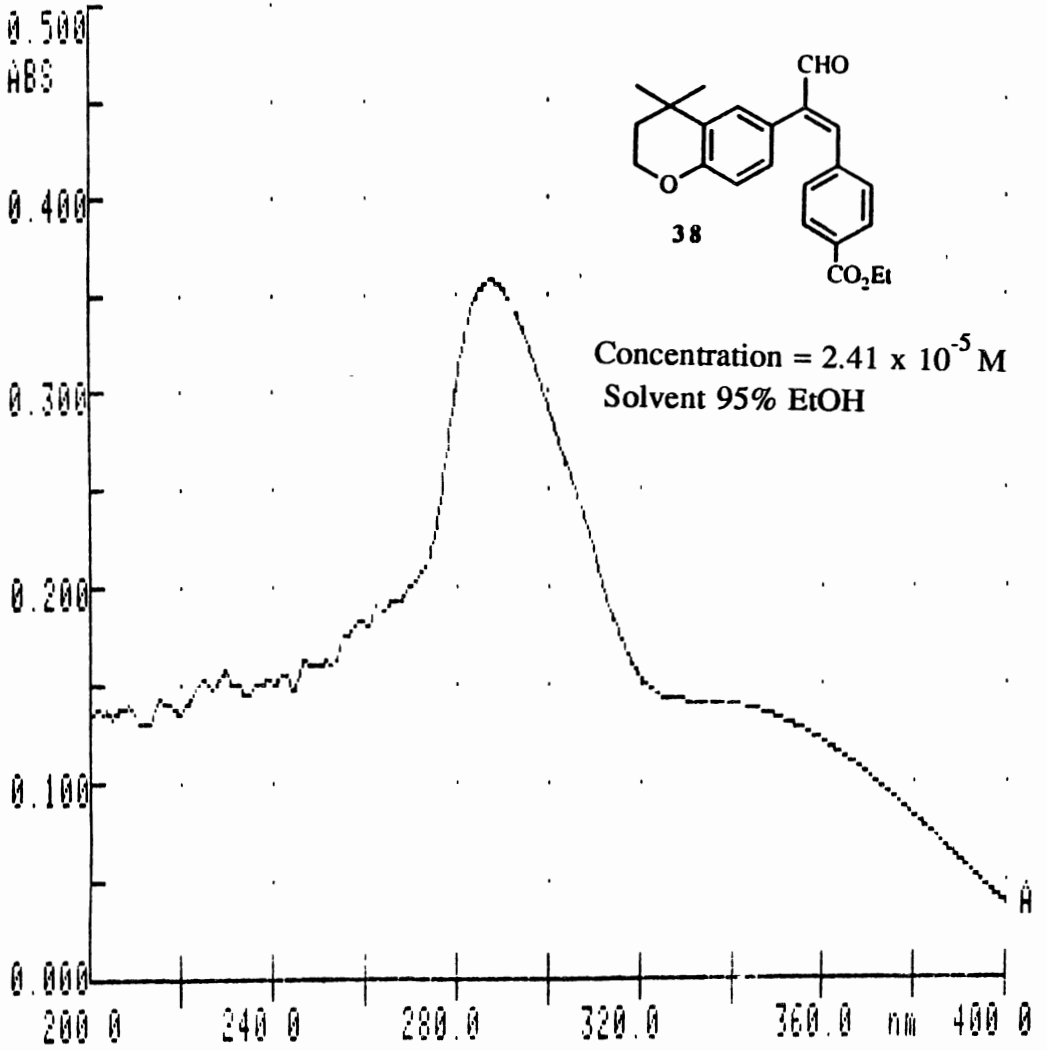
^{13}C NMR Spectrum of **38**

Plate XI



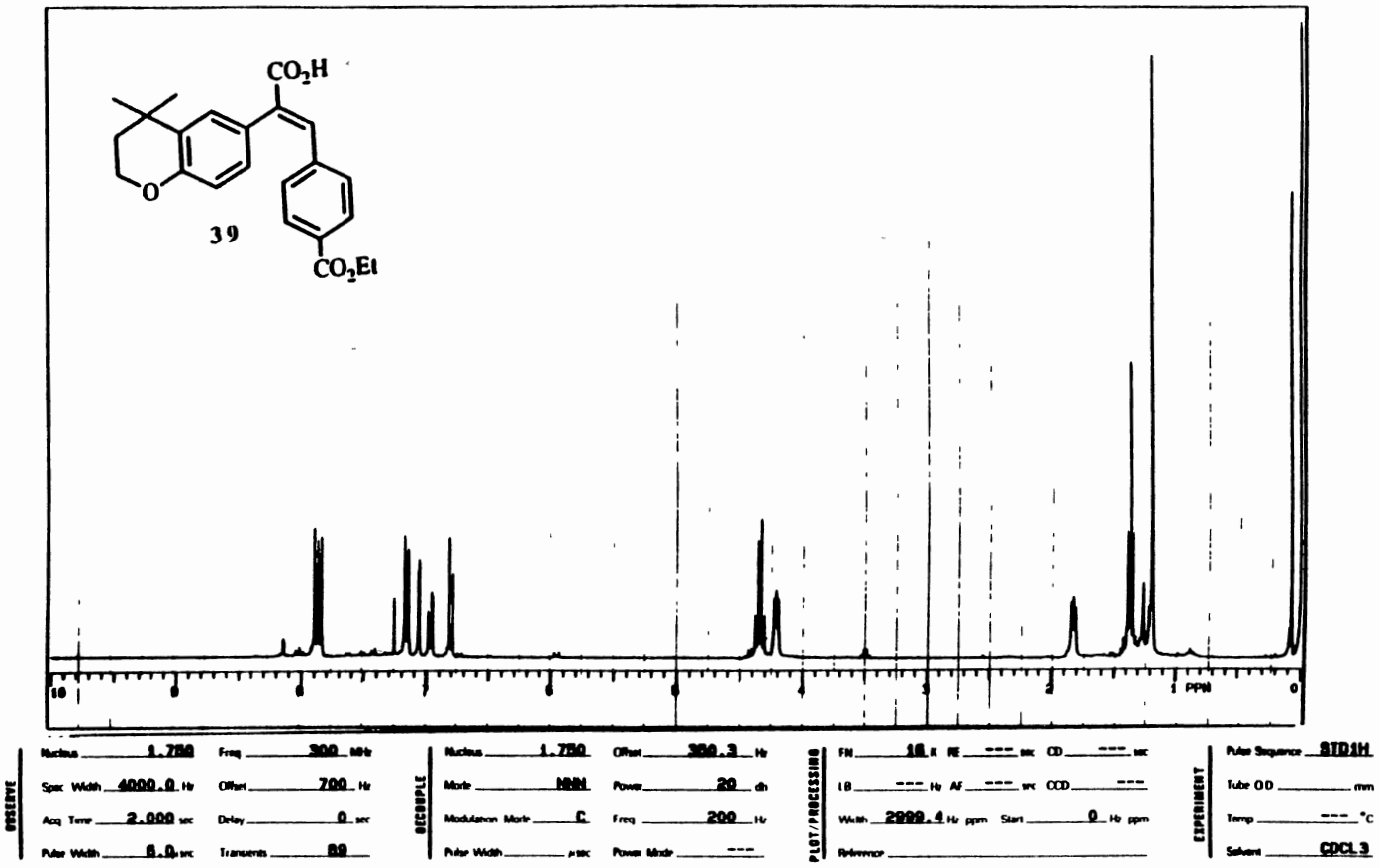
IR Spectrum of **38**

Plate XII



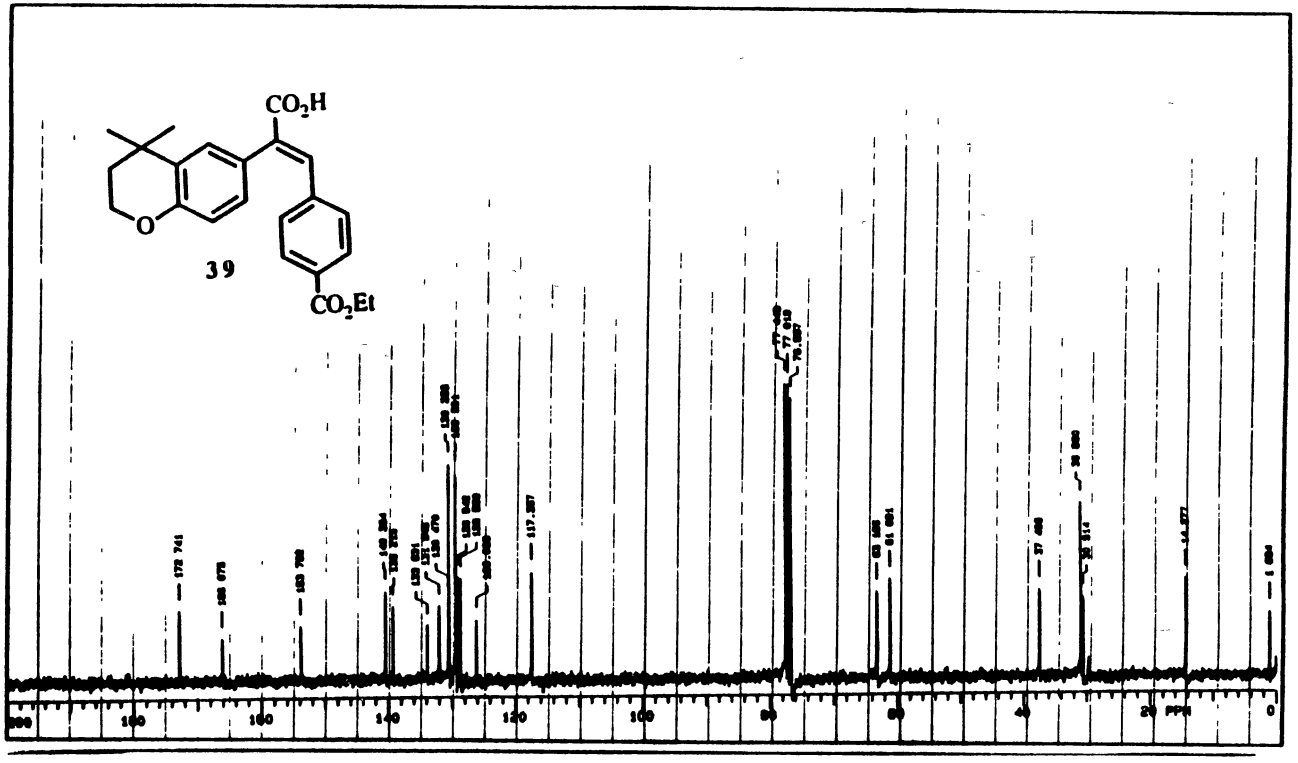
UV Spectrum of **38**

Plate XIII



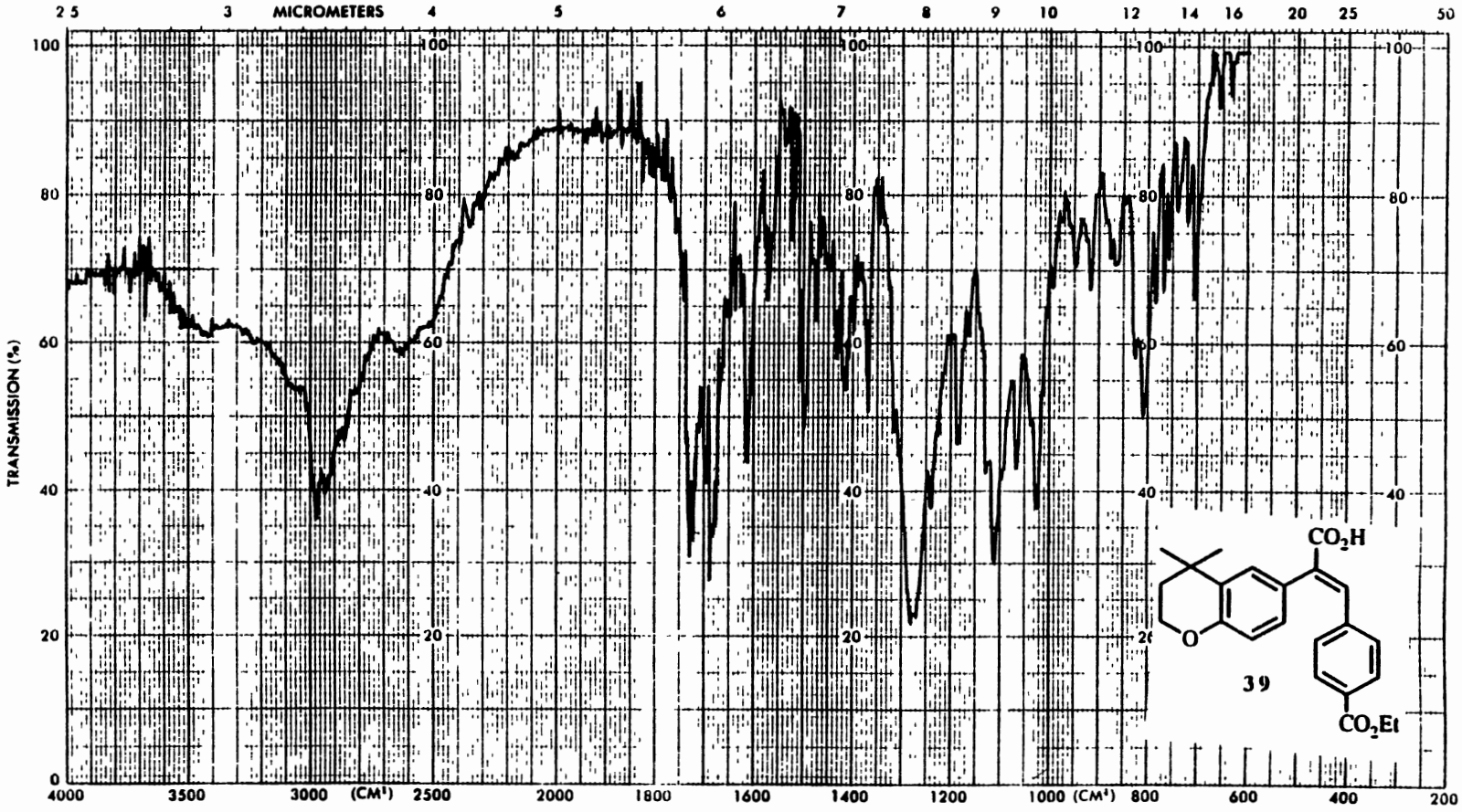
^{1}H NMR Spectrum of **39**

Plate XIV



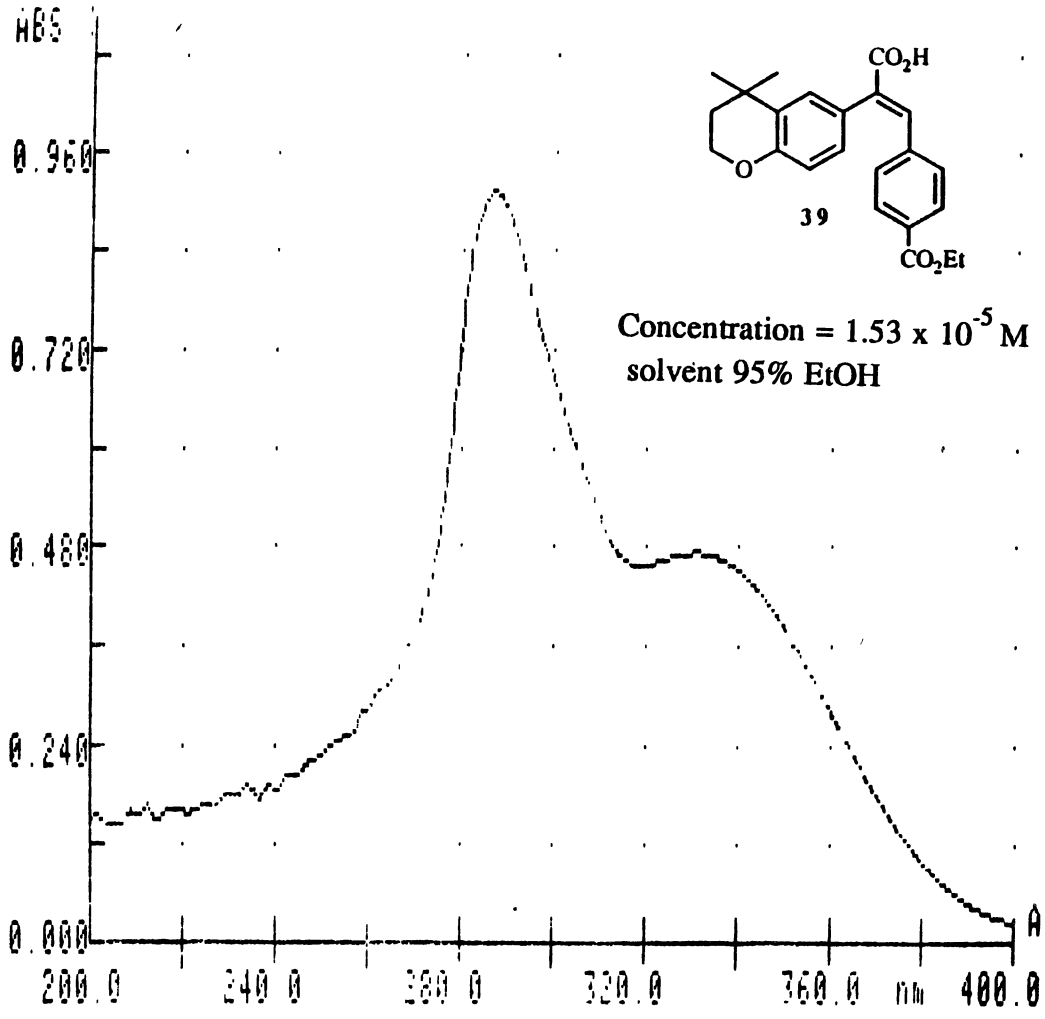
^{13}C NMR Spectrum of **39**

Plate XV



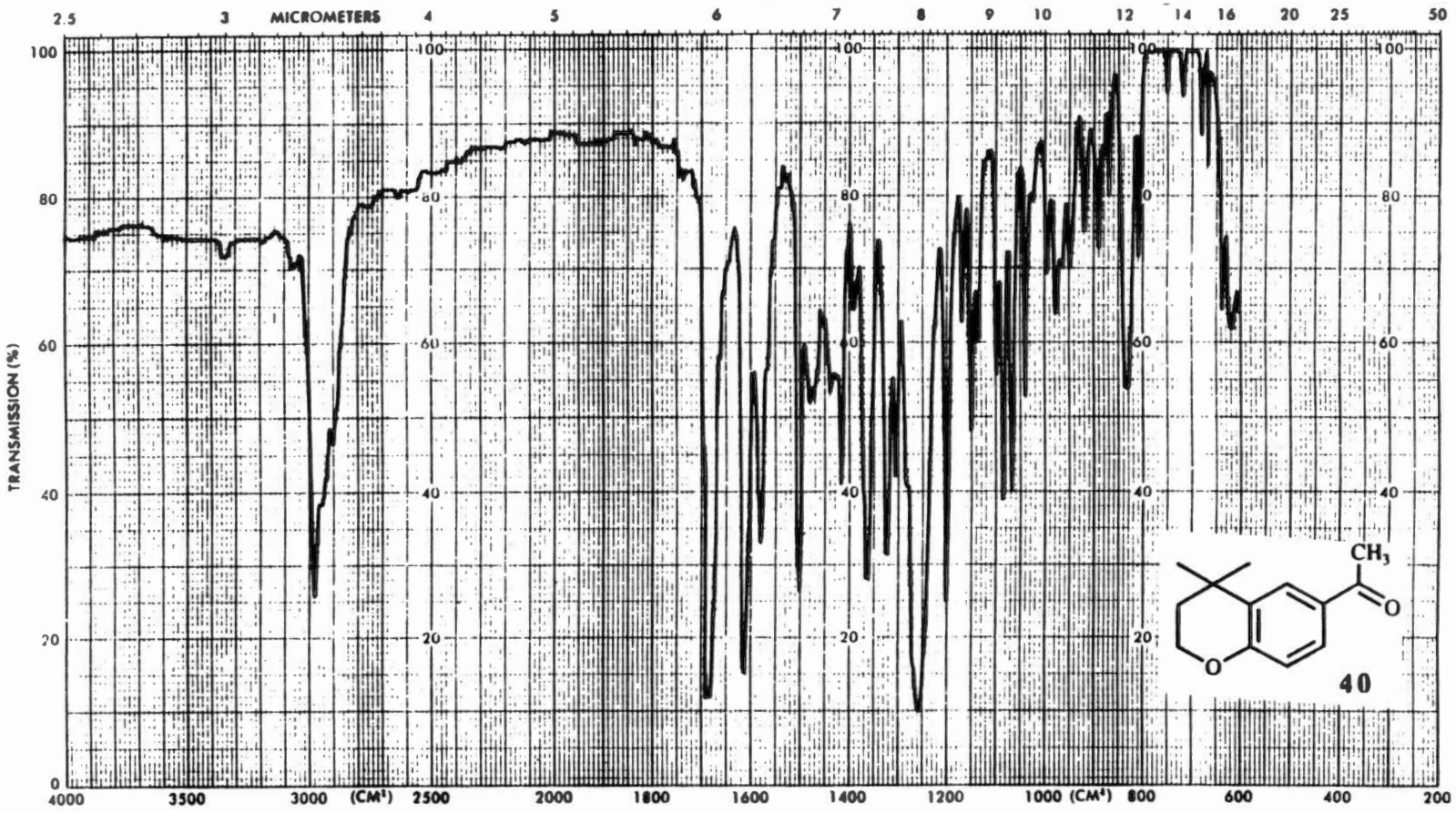
IR Spectrum of **39**

Plate XVI



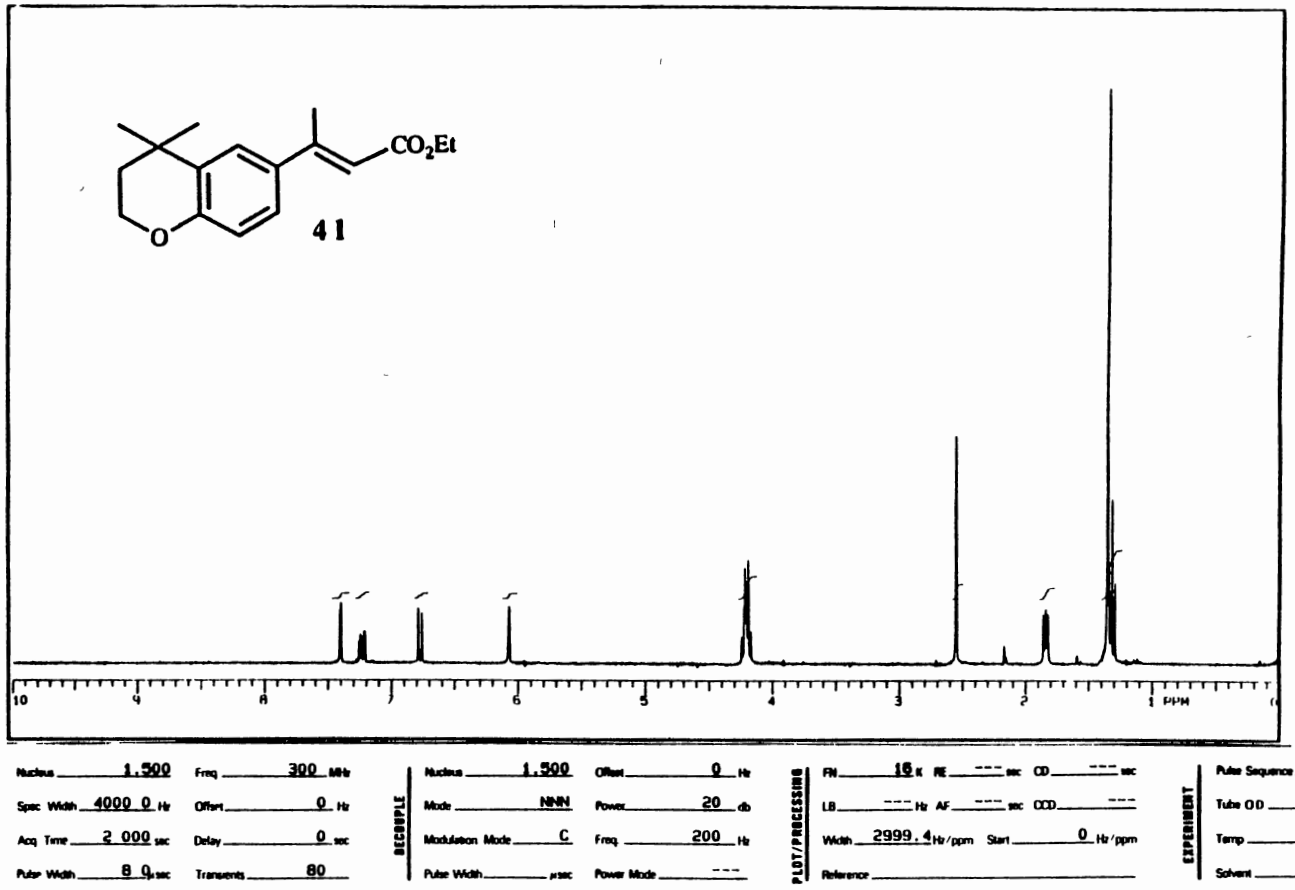
UV Spectrum of **39**

Plate XVII



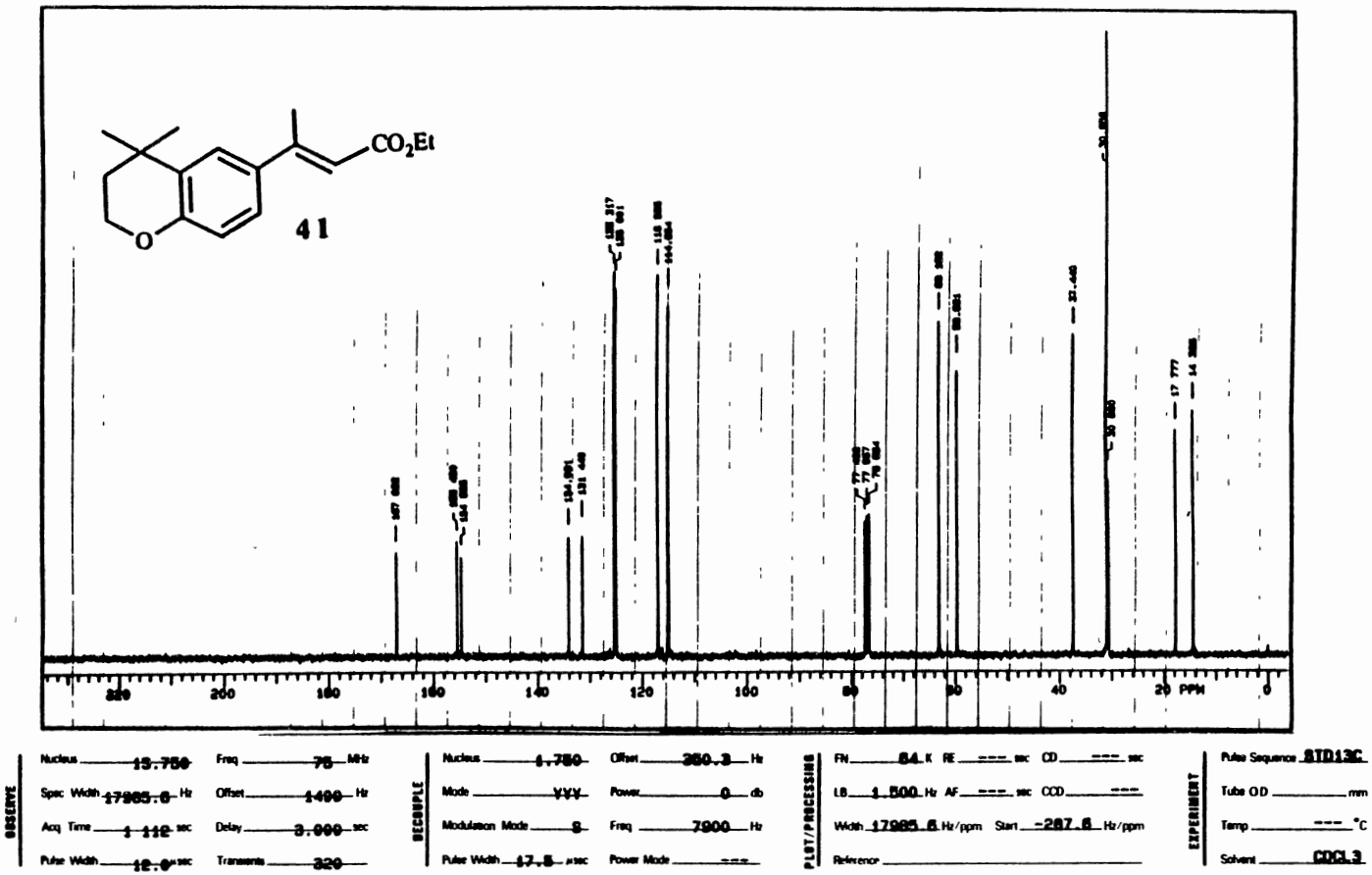
IR Spectrum Of **40**

Plate XVIII



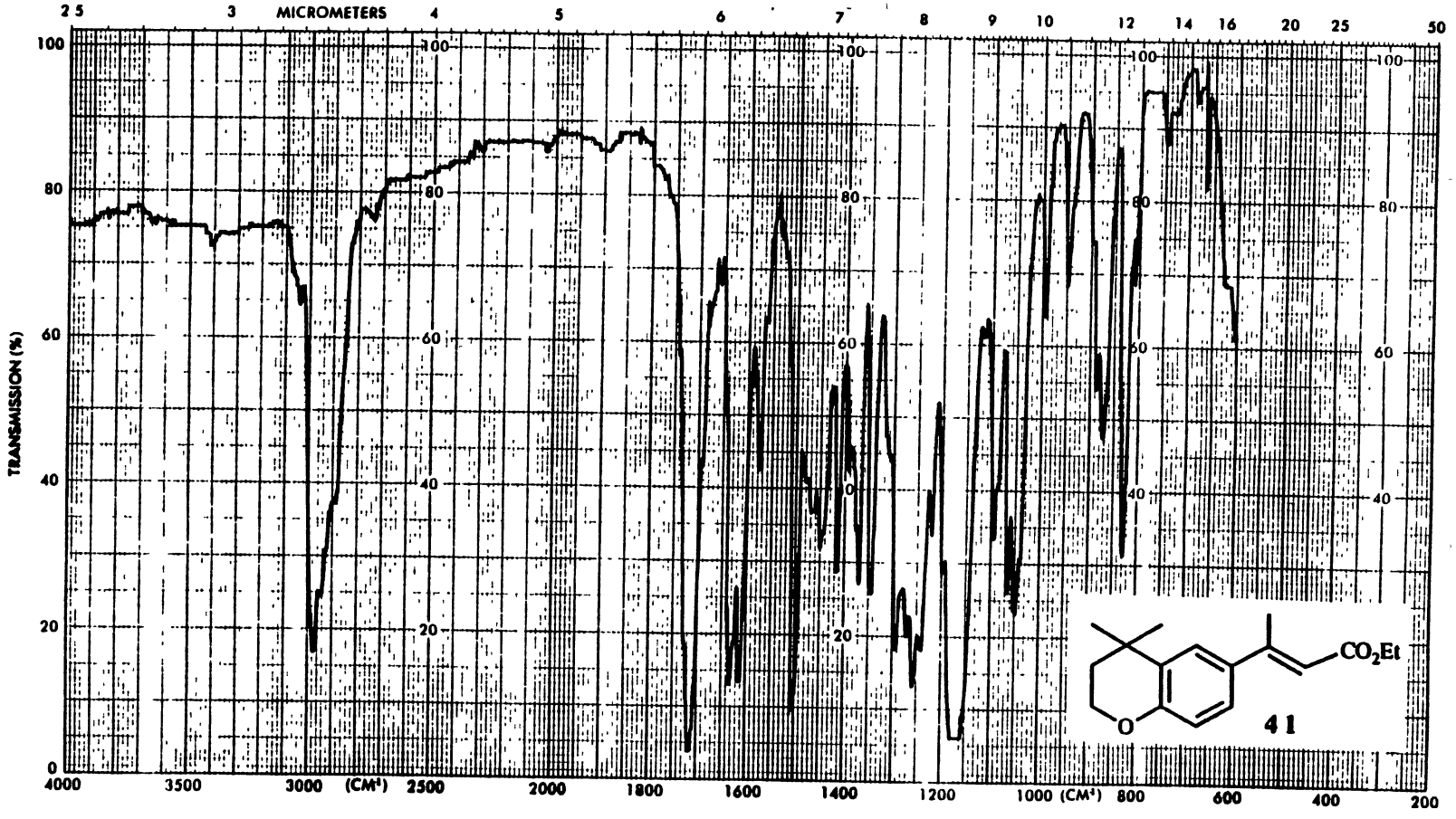
^{1}H NMR Spectrum of **41**

Plate XIX



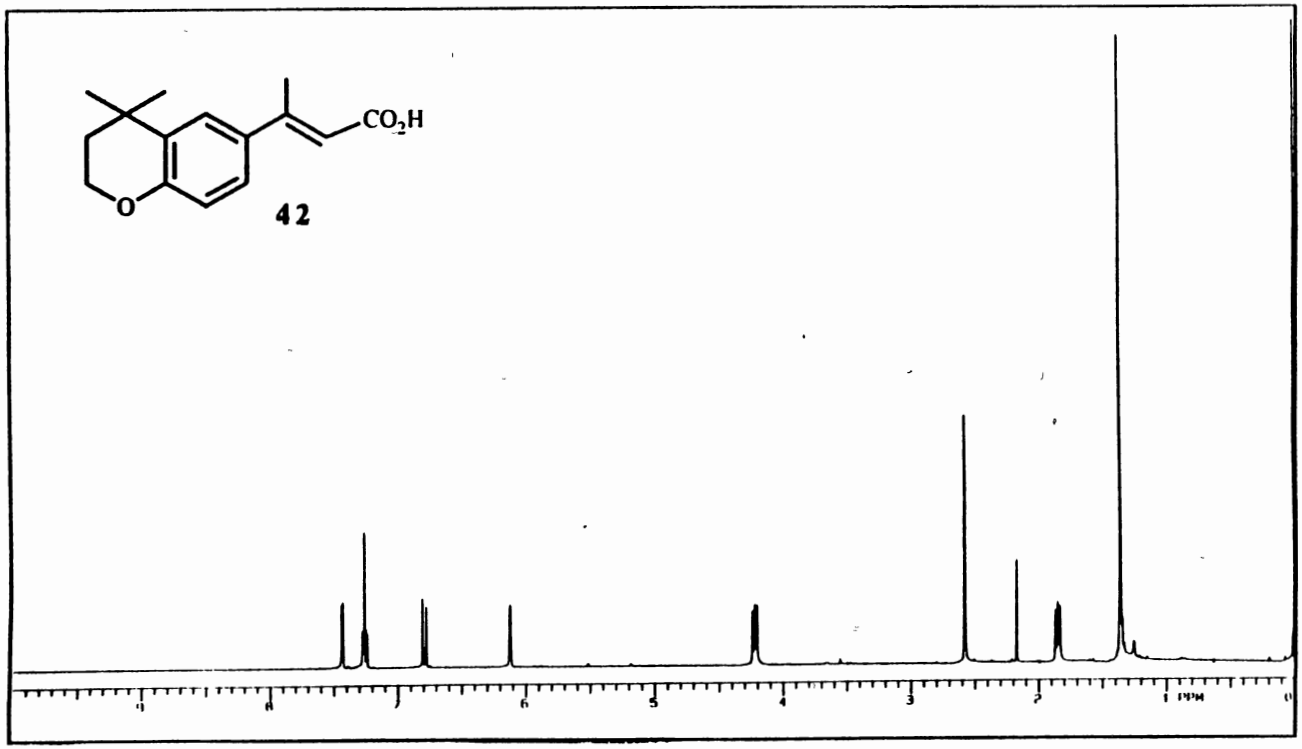
^{13}C NMR Spectrum of **41**

Plate XX



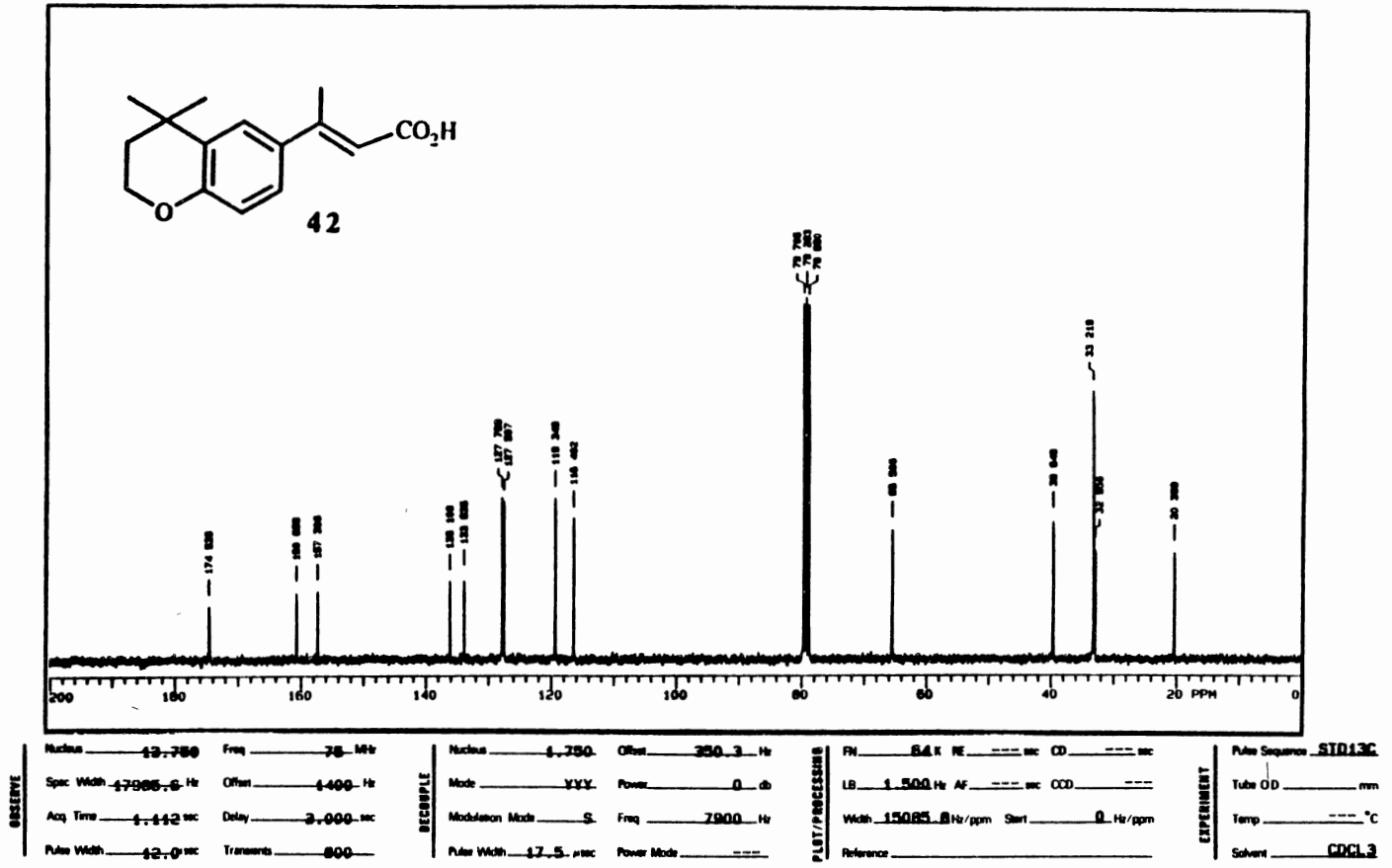
IR Spectrum of **41**

Plate XXI



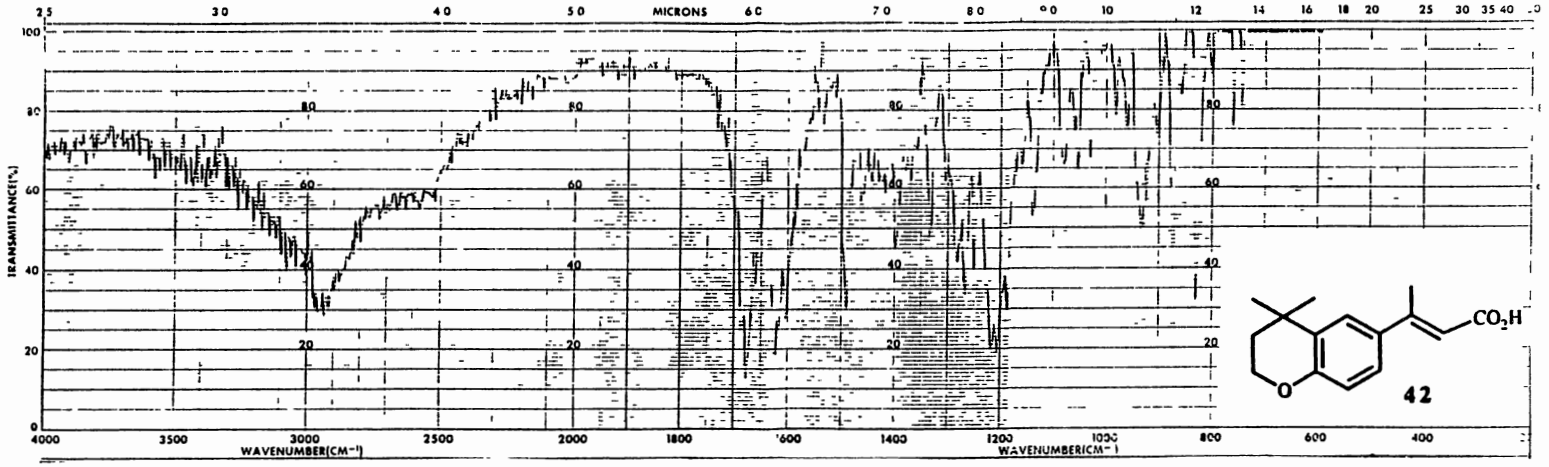
^{1}H NMR Spectrum of **42**

Plate XXII



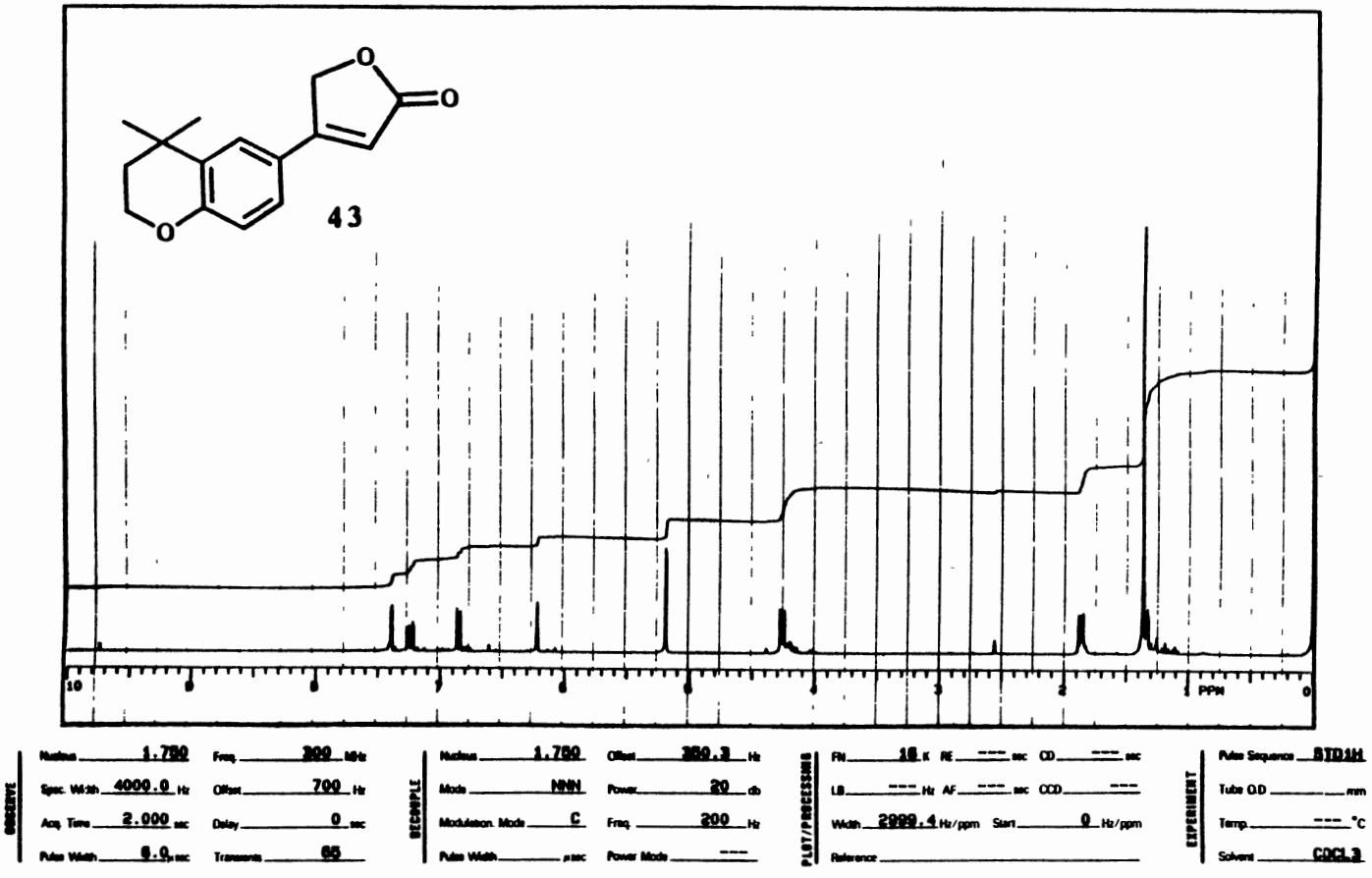
^{13}C NMR Spectrum of **42**

Plate XXIII



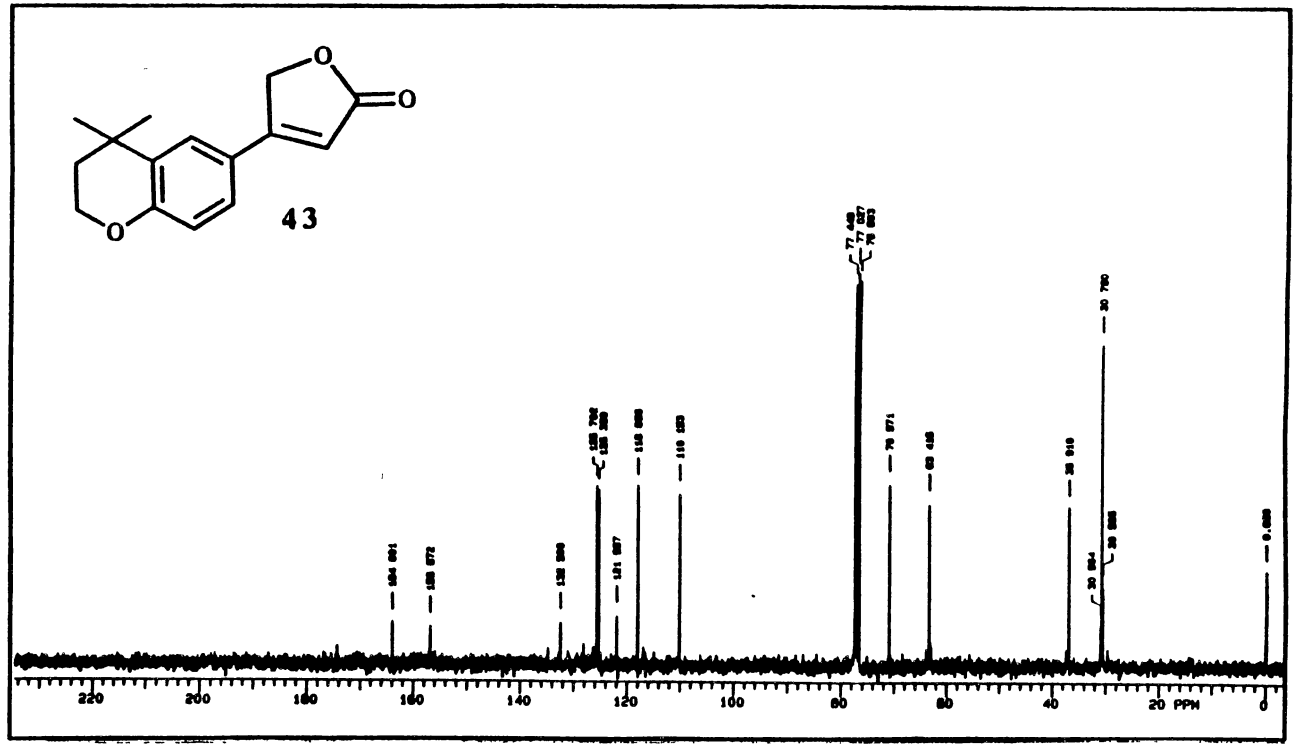
IR Spectrum of **42**

Plate XXIV



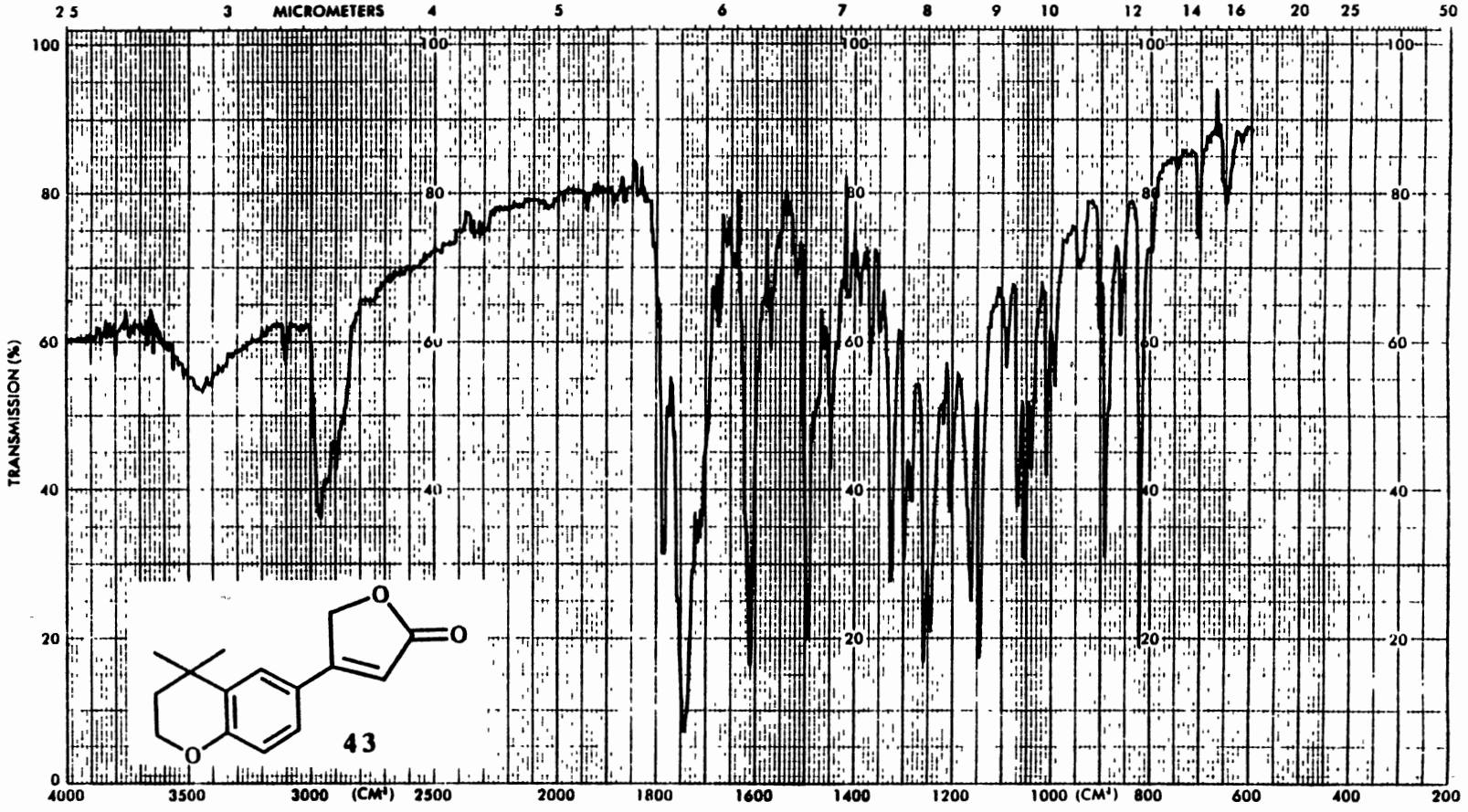
^{1}H NMR Spectrum of **43**

Plate XXV



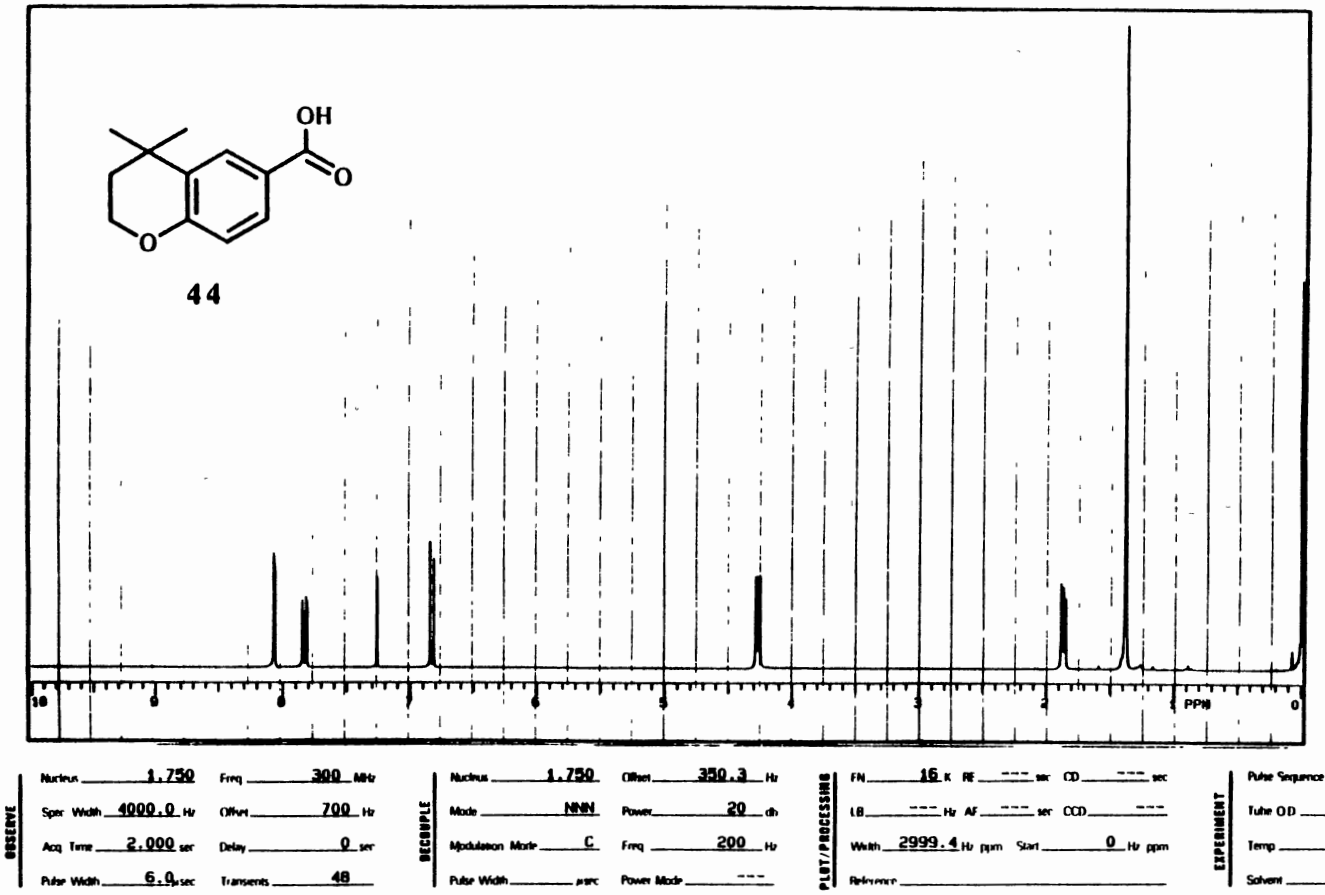
^{13}C NMR Spectrum of **43**

Plate XXVI



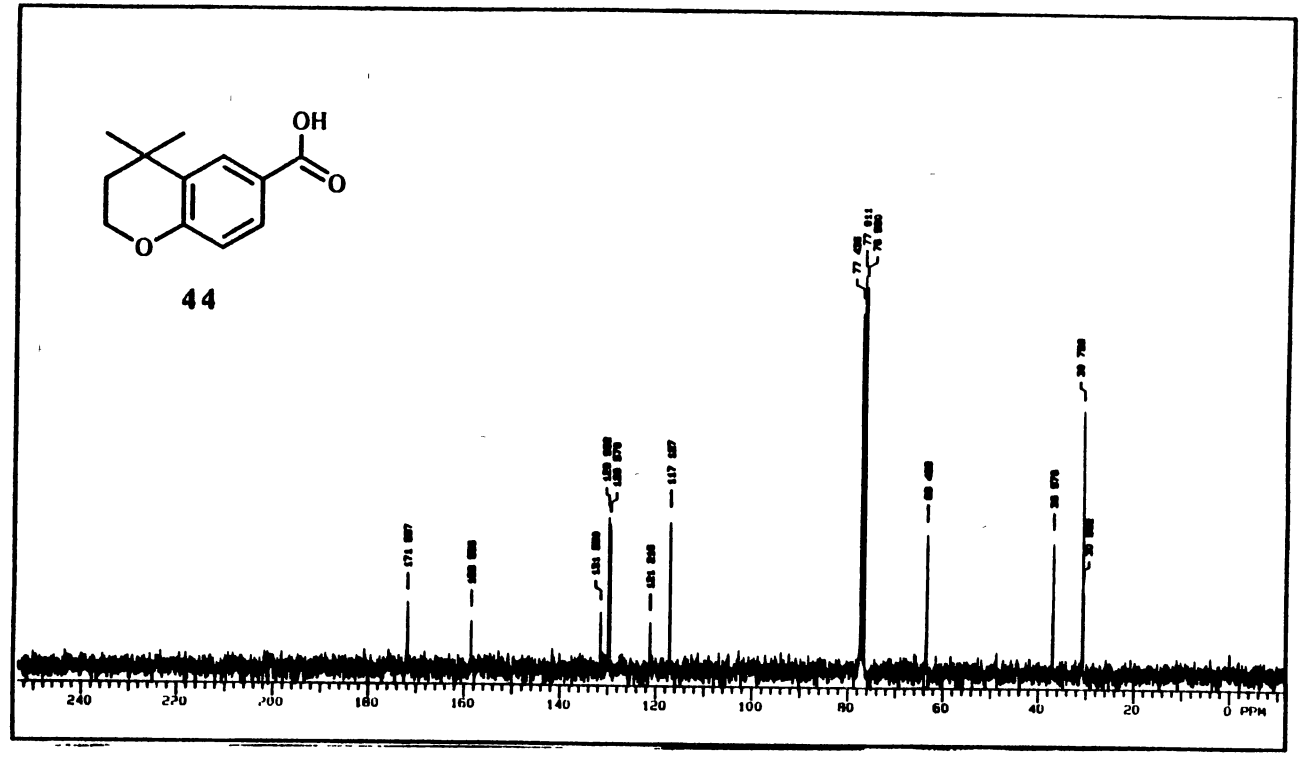
IR Spectrum of **43**

Plate XXVII



^{1}H NMR Spectrum of **44**

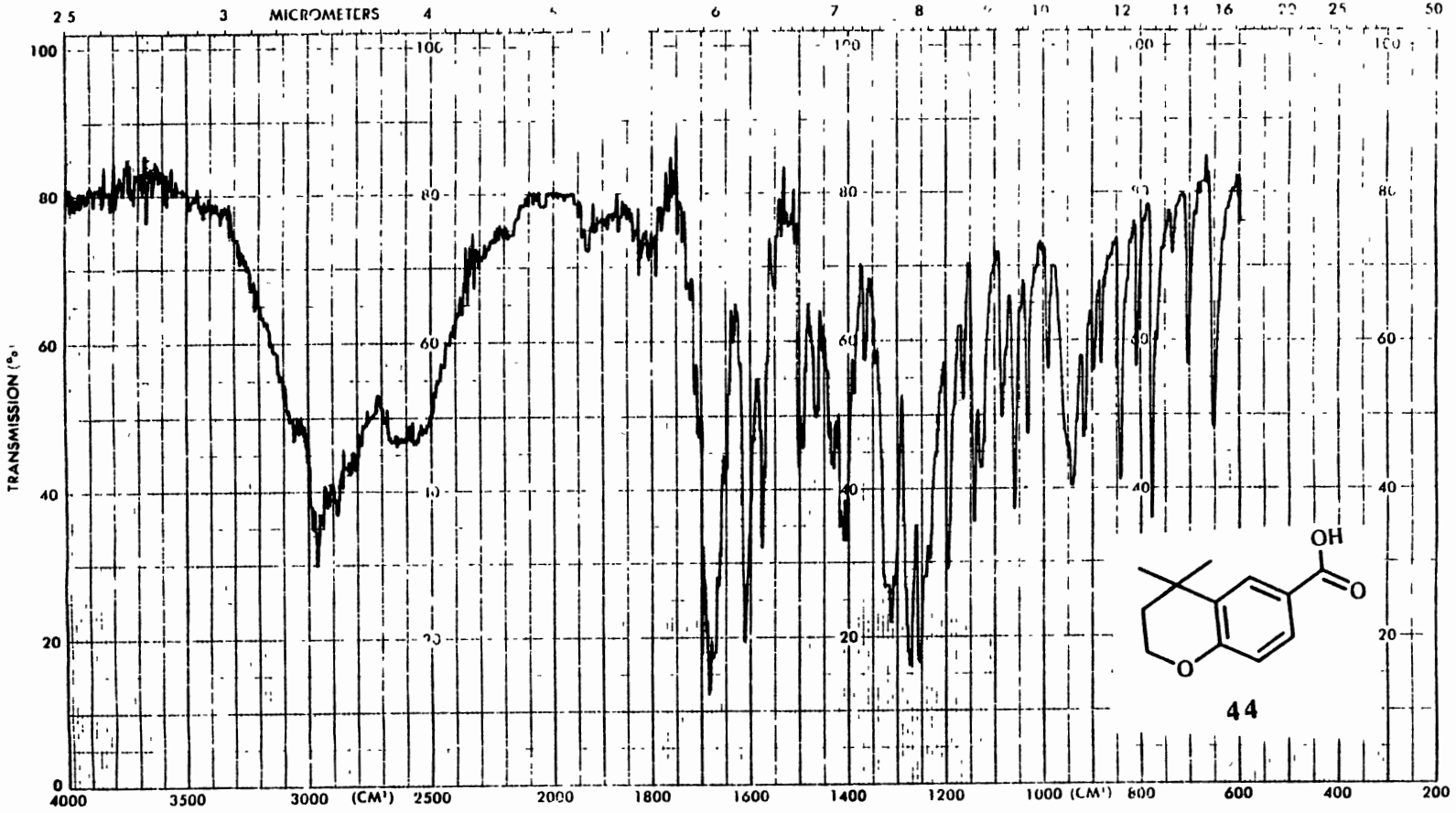
Plate XXVIII



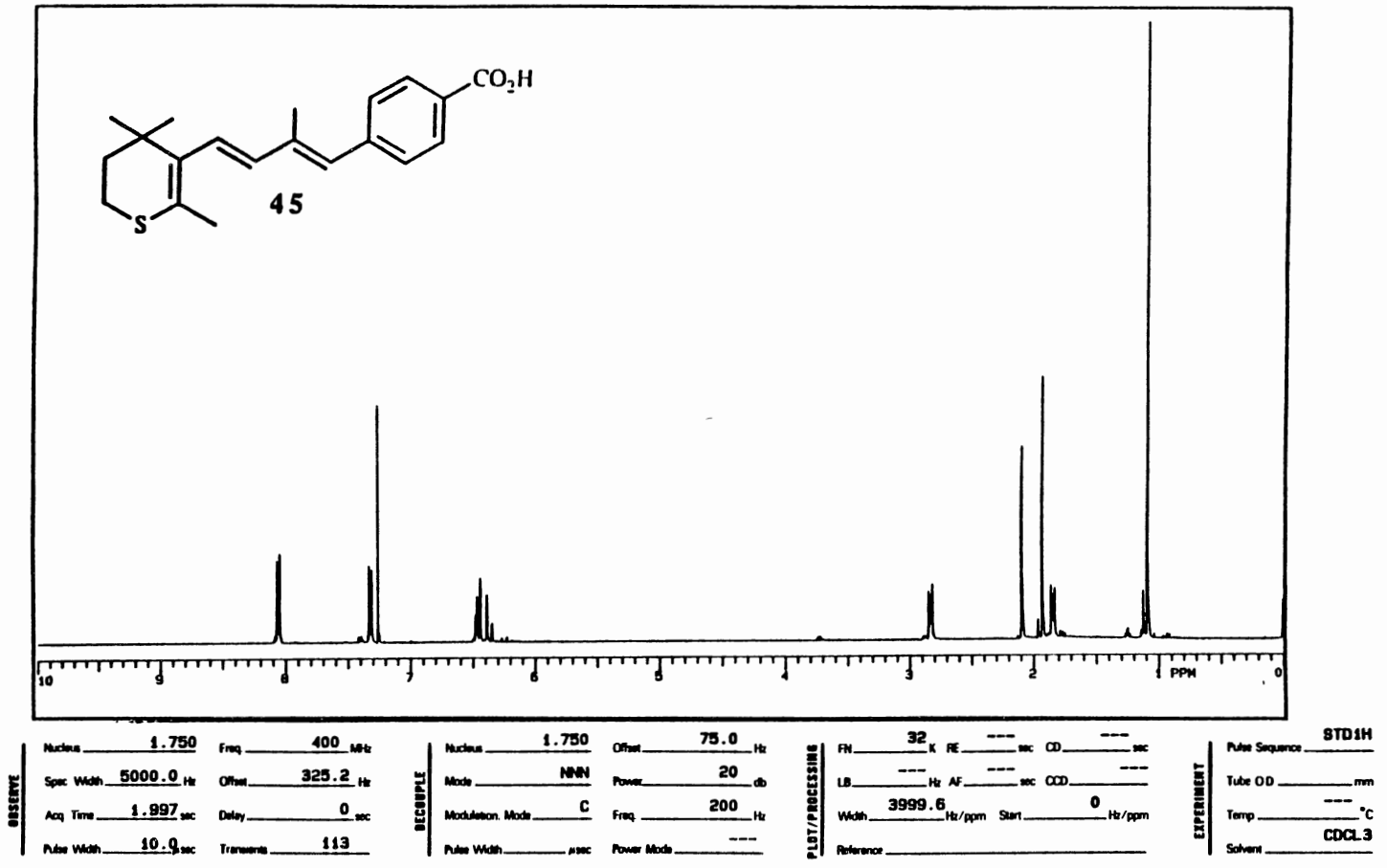
OBSERVE				DECOUPLE				PLOT/PROCESSING				EXPERIMENT	
Nucleus	13 500	Freq	75 MHz	Nucleus	1.750	Offset	350 3 Hz	FN	64 K	RE	--- sec	CD	--- sec	Pulse Sequence	STD13C
Spec Width	20000.0 Hz	Offset	1500 Hz	Mode	YYY	Power	0 db	LB	2 000 Hz	AF	--- sec	CDD	---	Tube OD	--- mm
Acq Time	1.000 sec	Delay	3 000 sec	Modulation Mode	S	Freq	7900 Hz	Width	20000.0 Hz/ppm	Start	-894 2 Hz/ppm	Temp	--- °C
Pulse Width	12.0 µsec	Transients	160	Pulse Width	17 5 µsec	Power Mode	---	Reference				Solvent	CDCL3

^{13}C NMR Spectrum of **44**

Plate XXIX

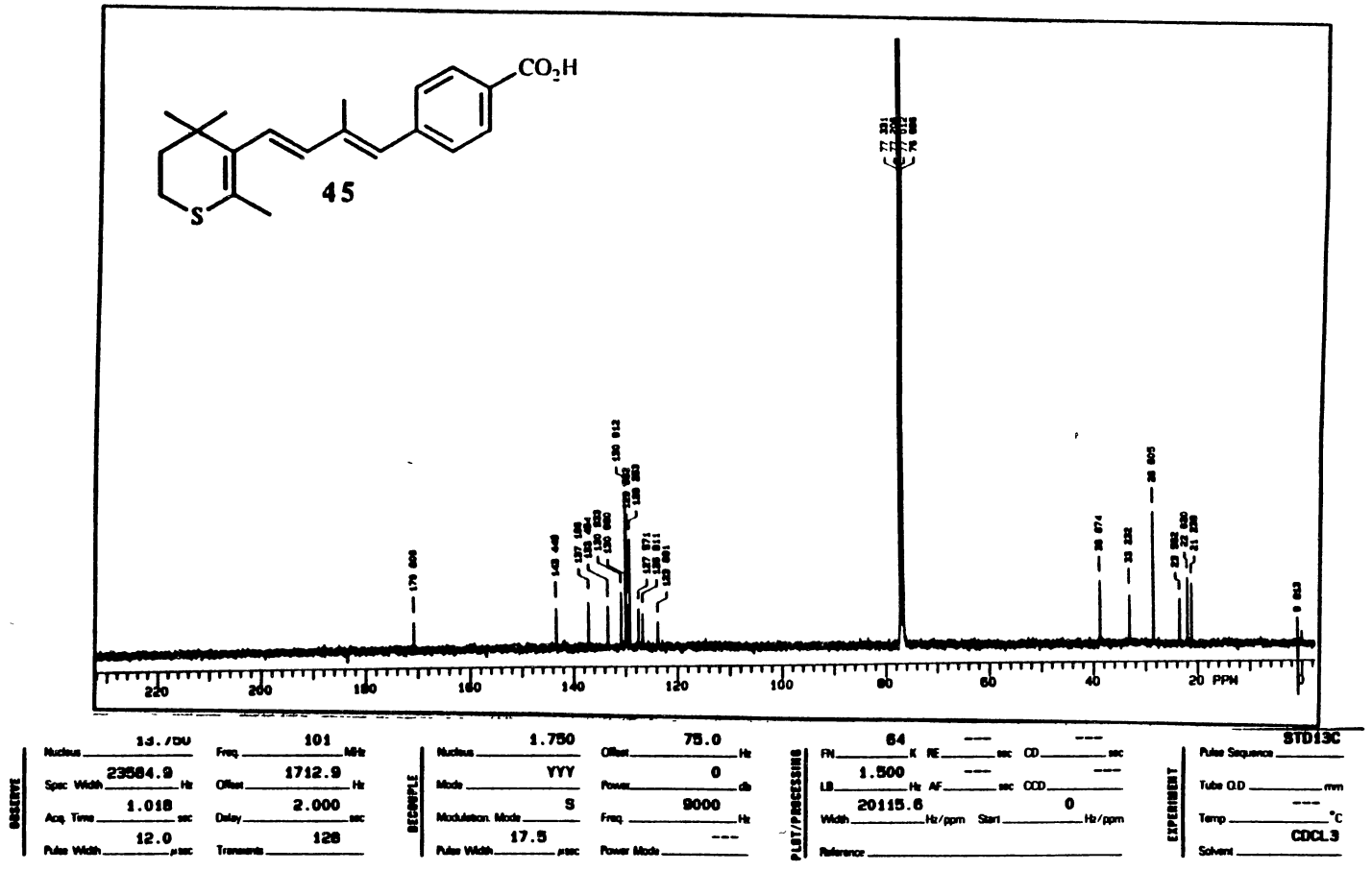


IR Spectrum of **44**



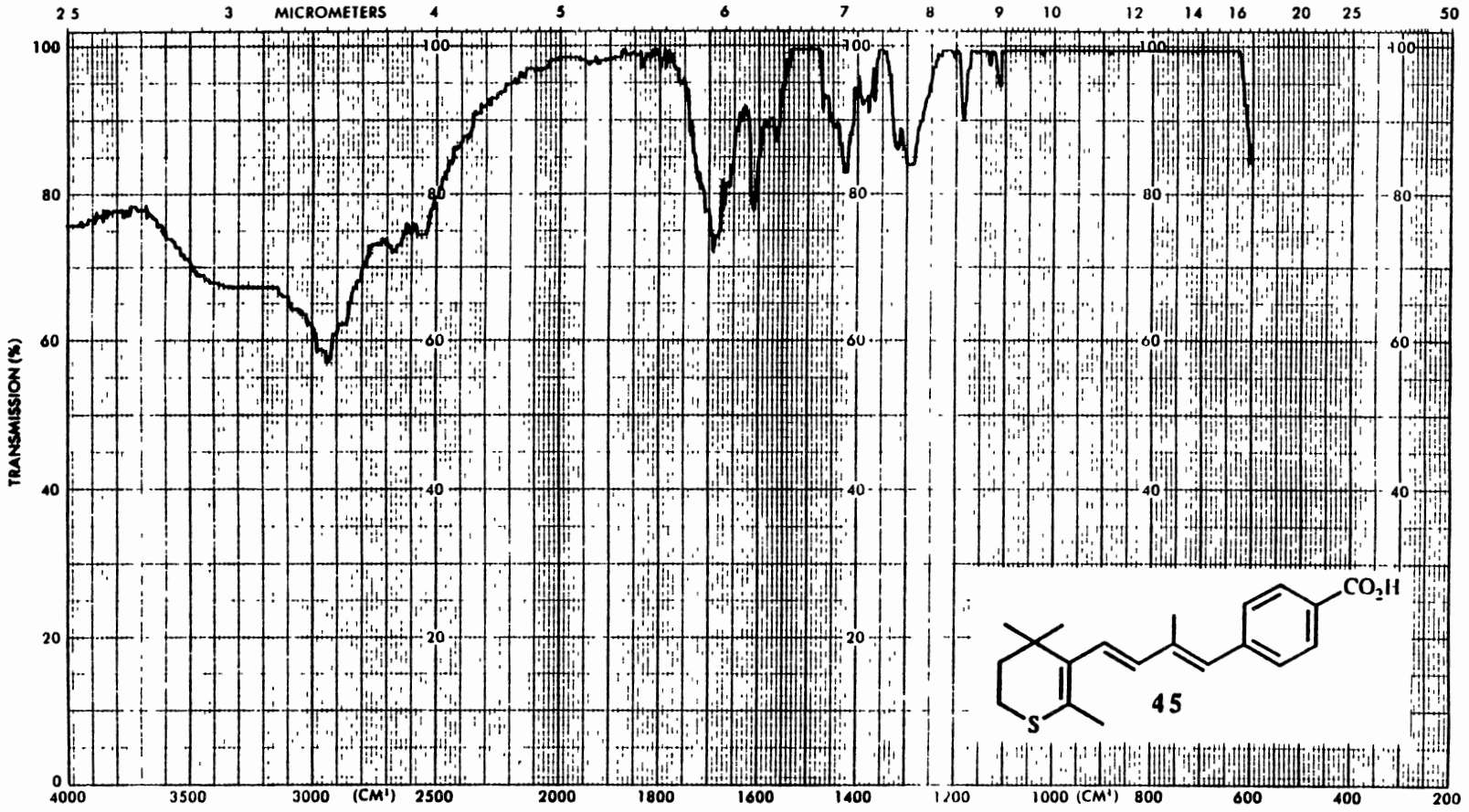
^{1}H NMR Spectrum Of **45**

Plate XXXI



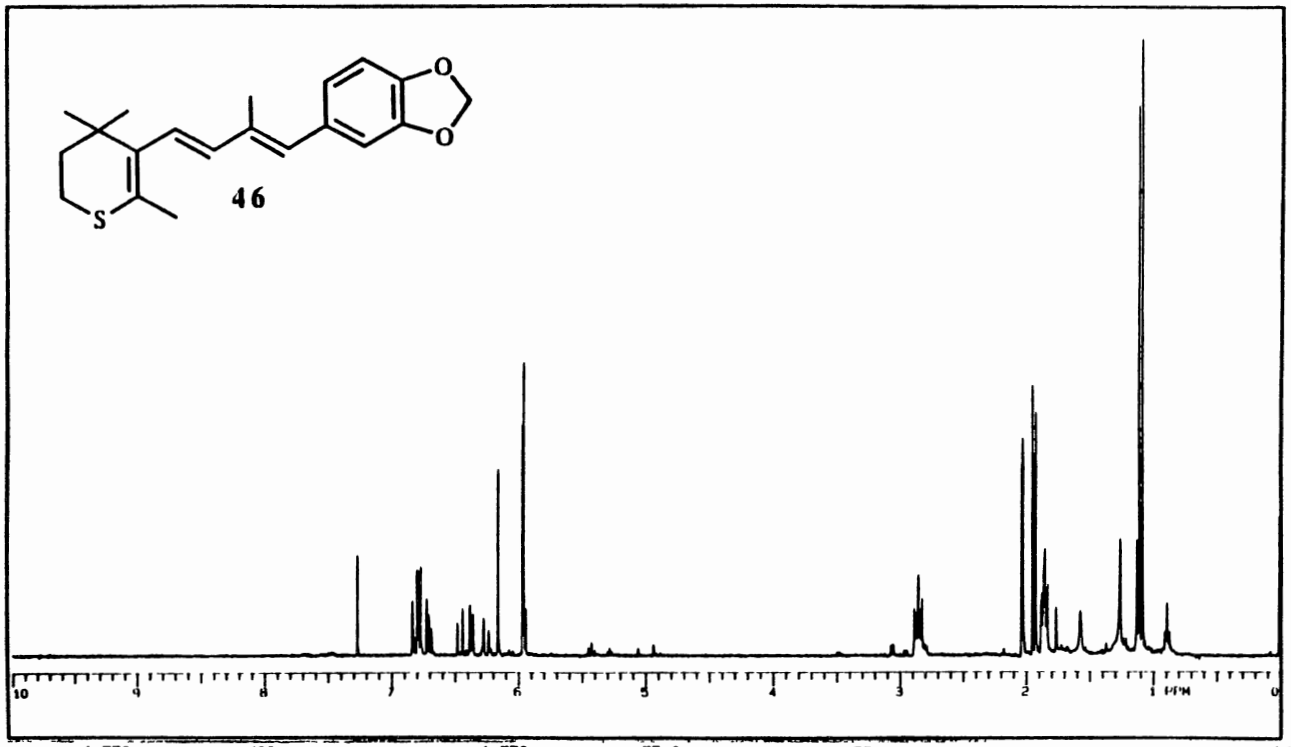
^{13}C NMR Spectrum of **45**

Plate XXXII



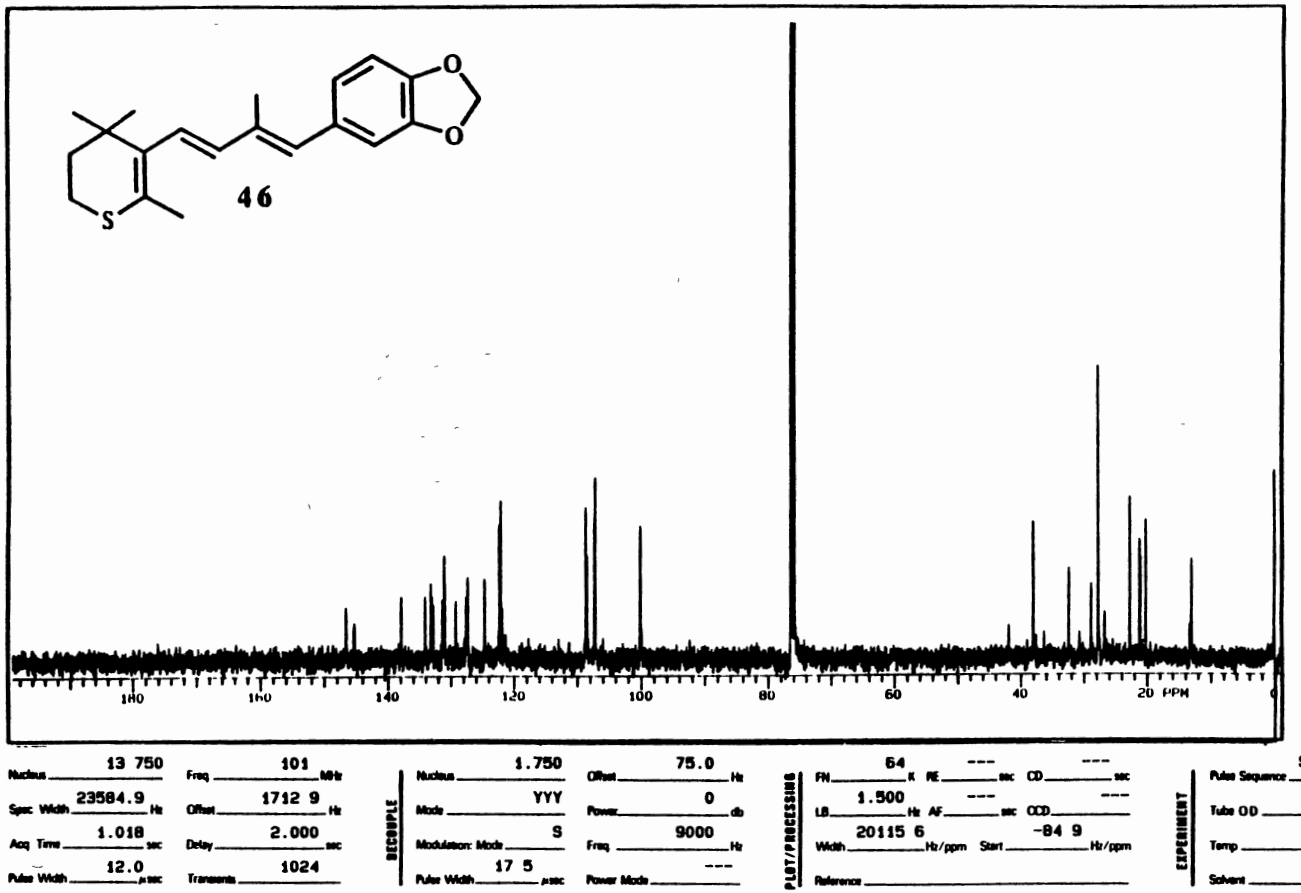
IR Spectrum of **45**

Plate XXXIII



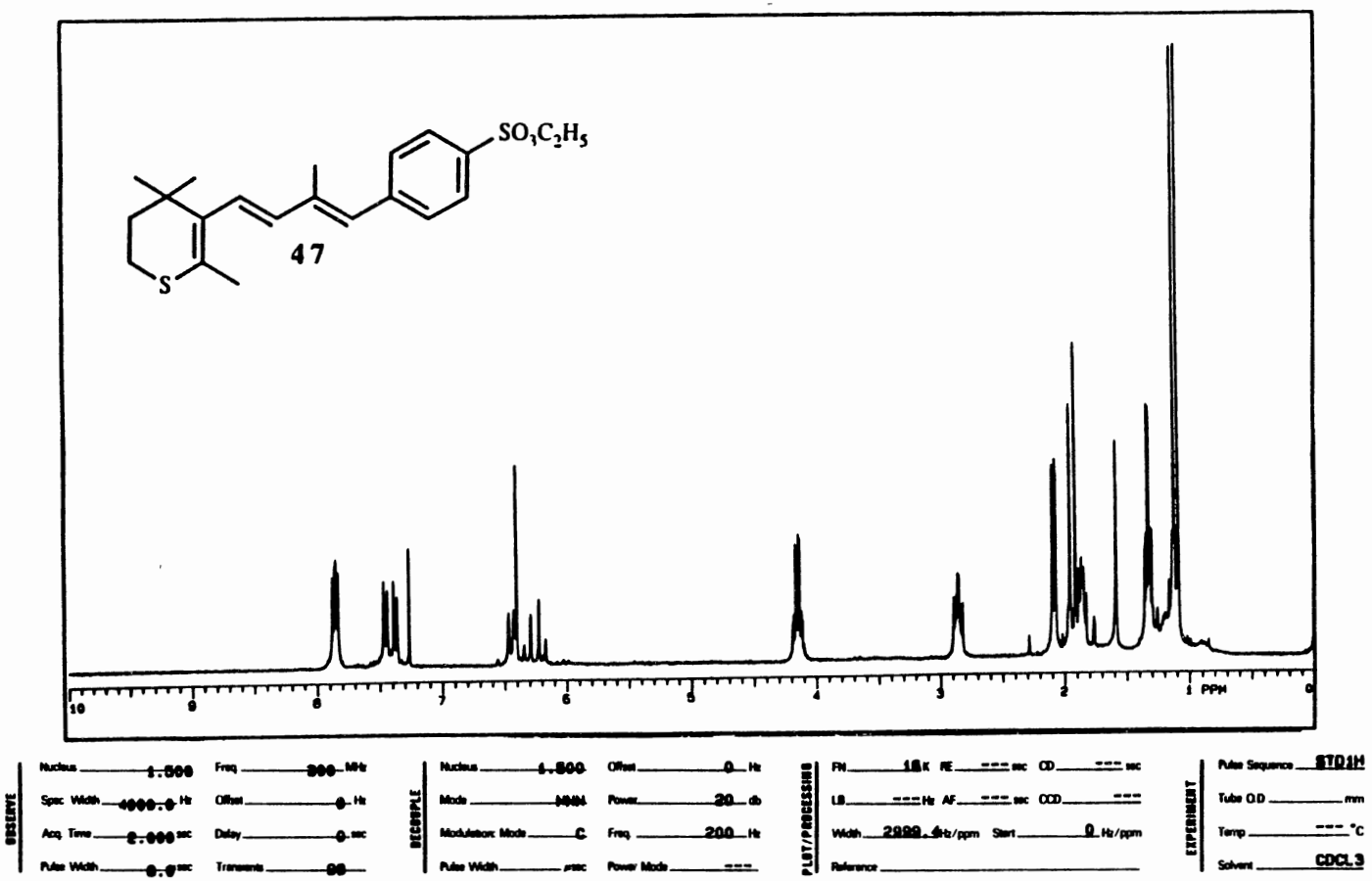
^{1}H NMR Spectrum of **46**

Plate XXXIV



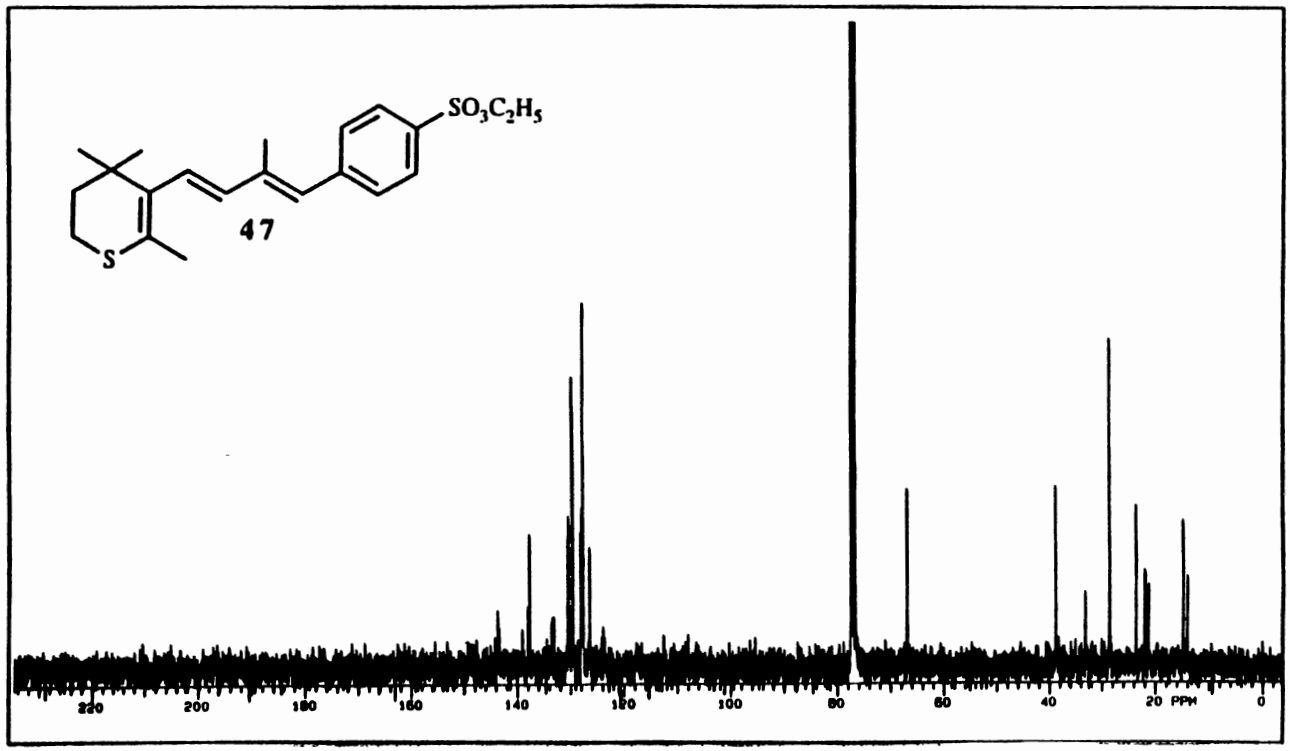
^{13}C NMR Spectrum of **46**

Plate XXXV



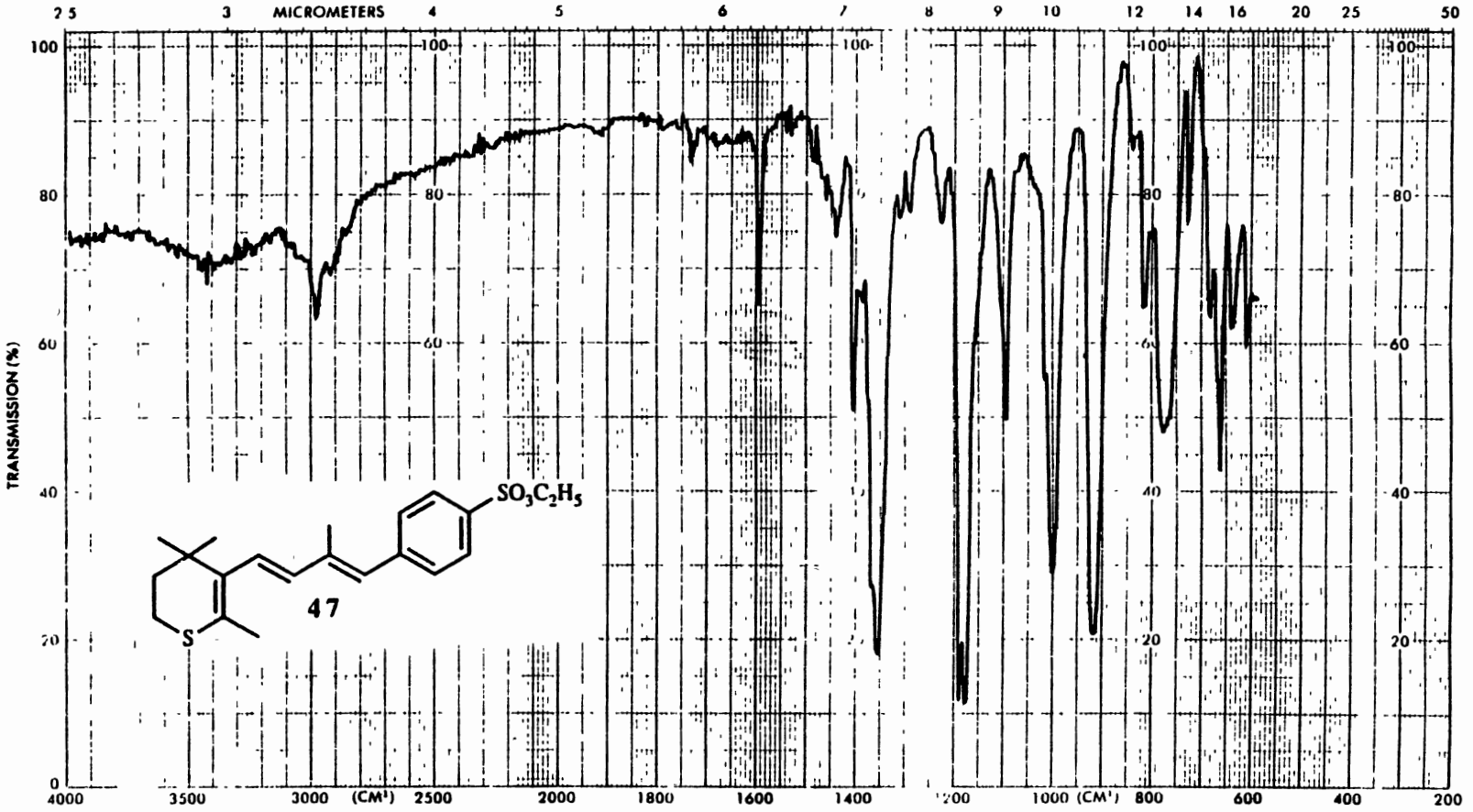
^{1}H NMR Spectrum of **47**

Plate XXXVI



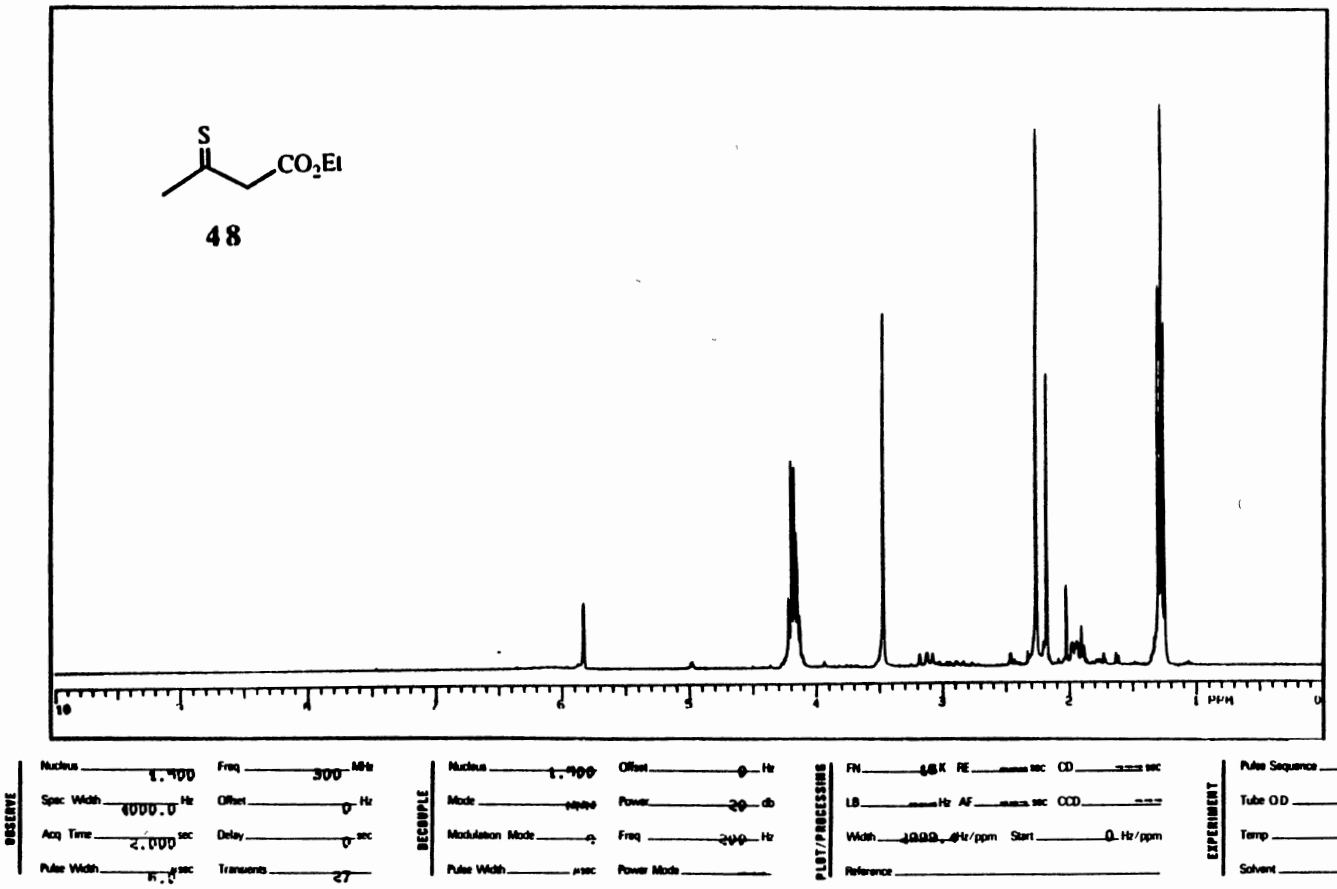
^{13}C NMR Spectrum of **47**

Plate XXXVII



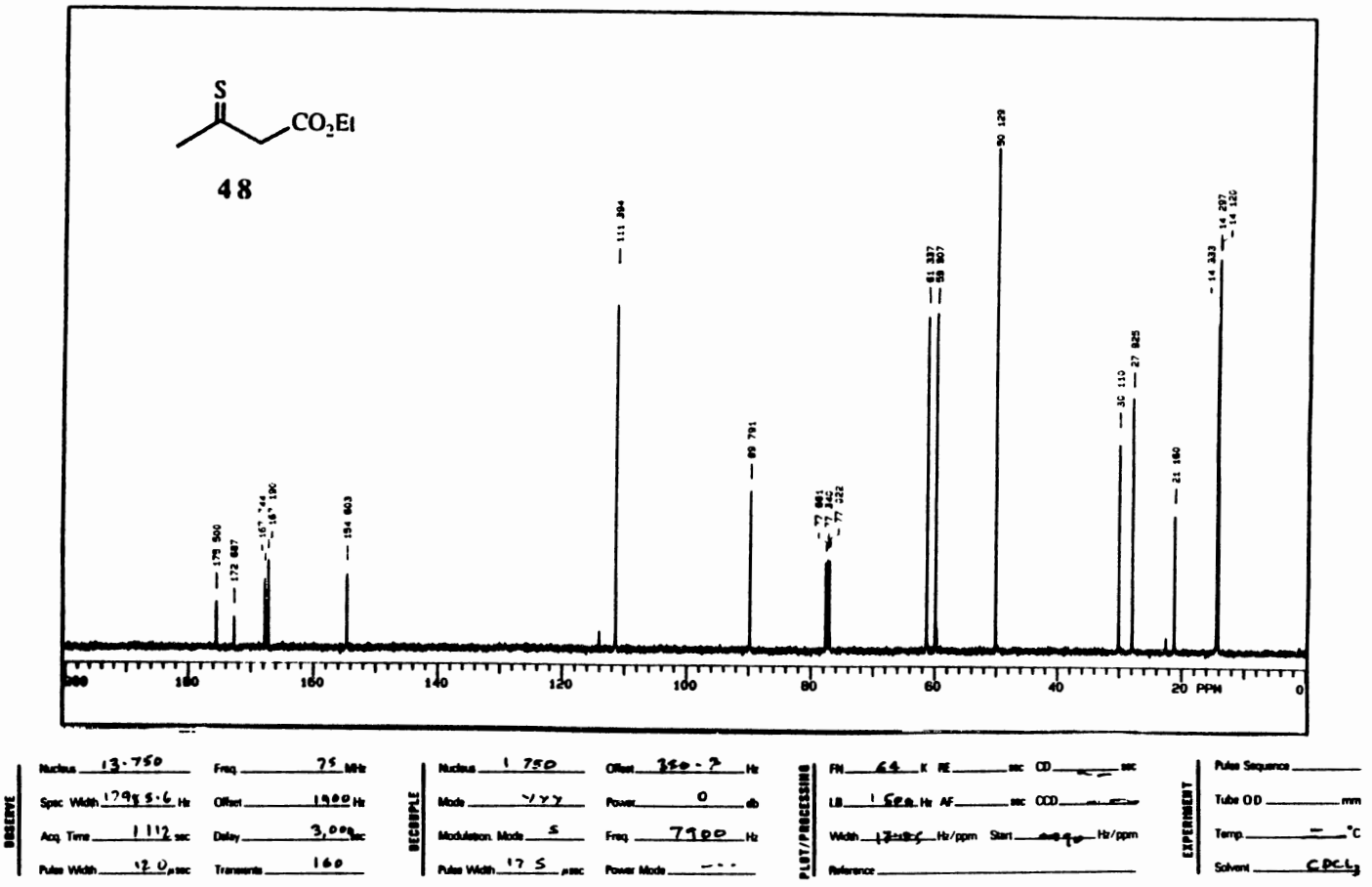
IR Spectrum of **47**

Plate XXXVIII



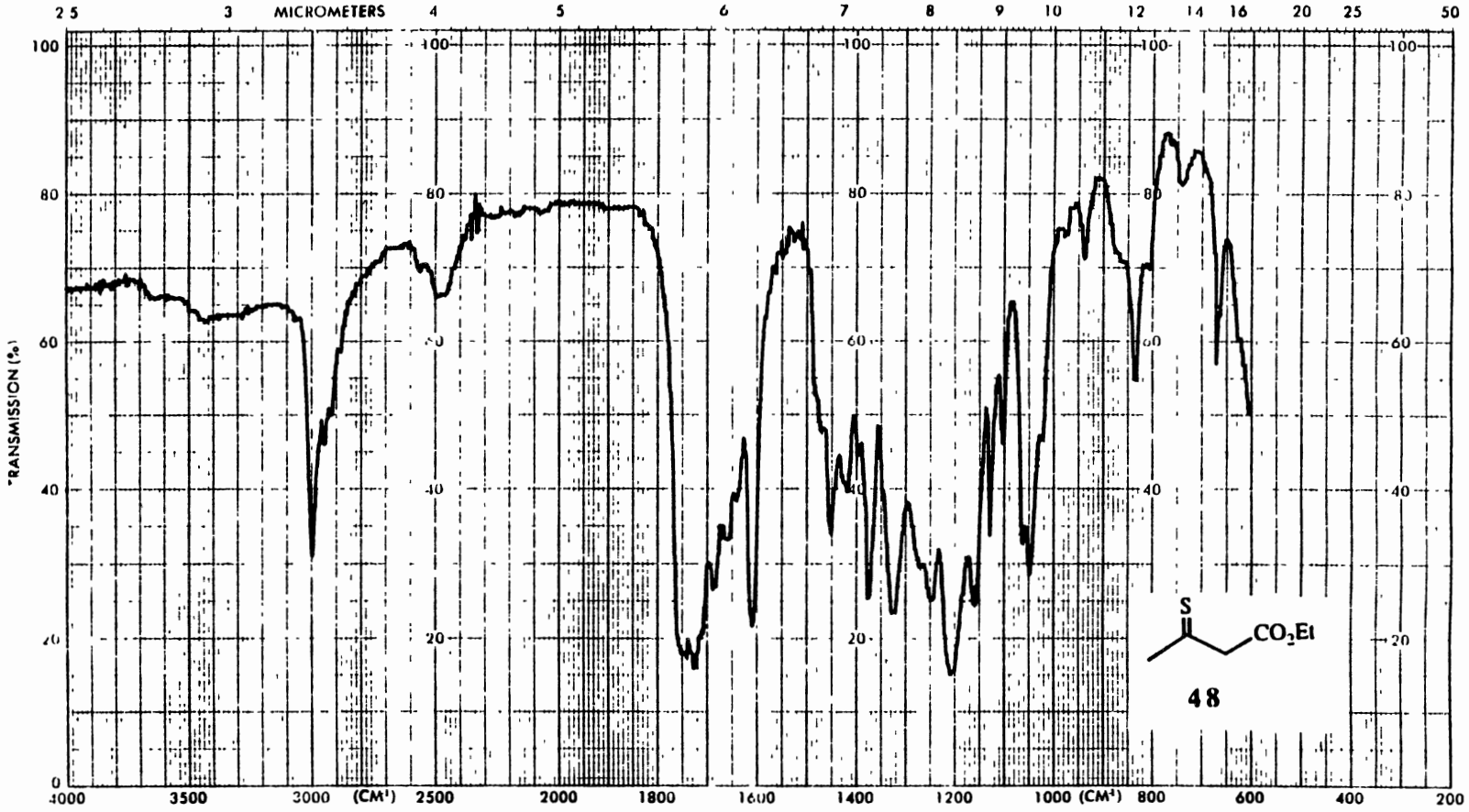
^{1}H NMR Spectrum of **48**

Plate XXXIX



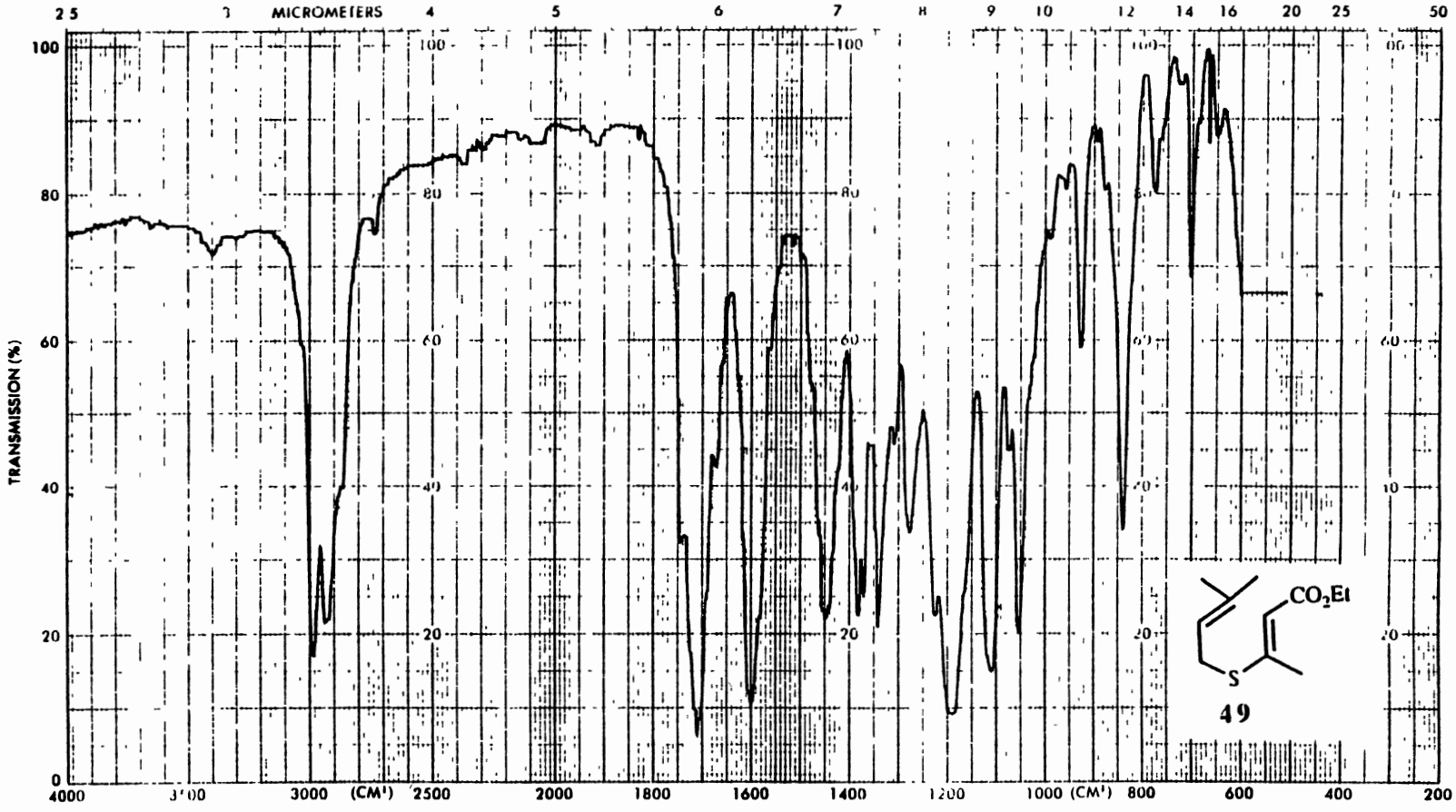
^{13}C NMR Spectrum of **48**

Plate XXXX



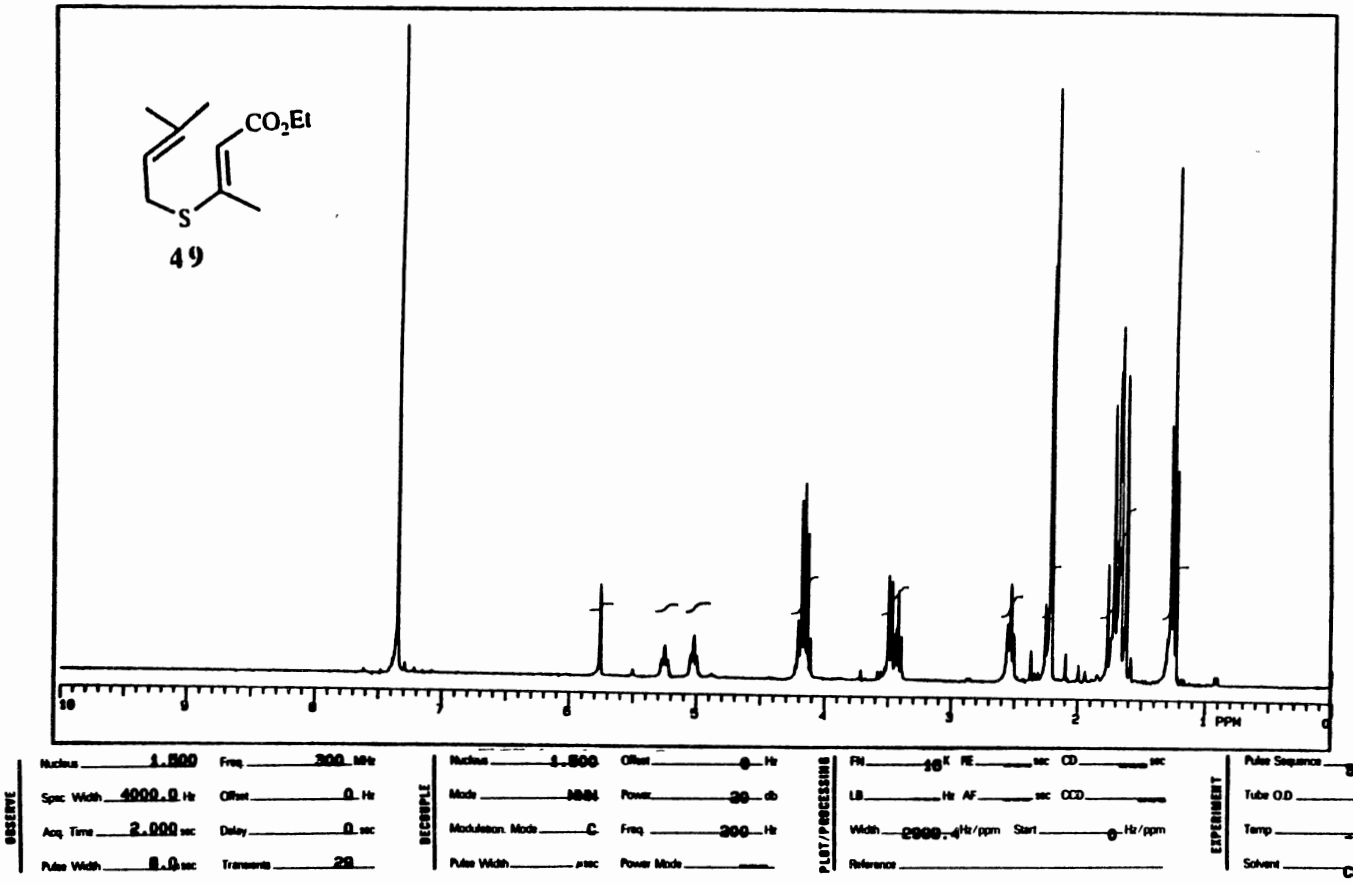
IR Spectrum of **48**

Plate XXXXI



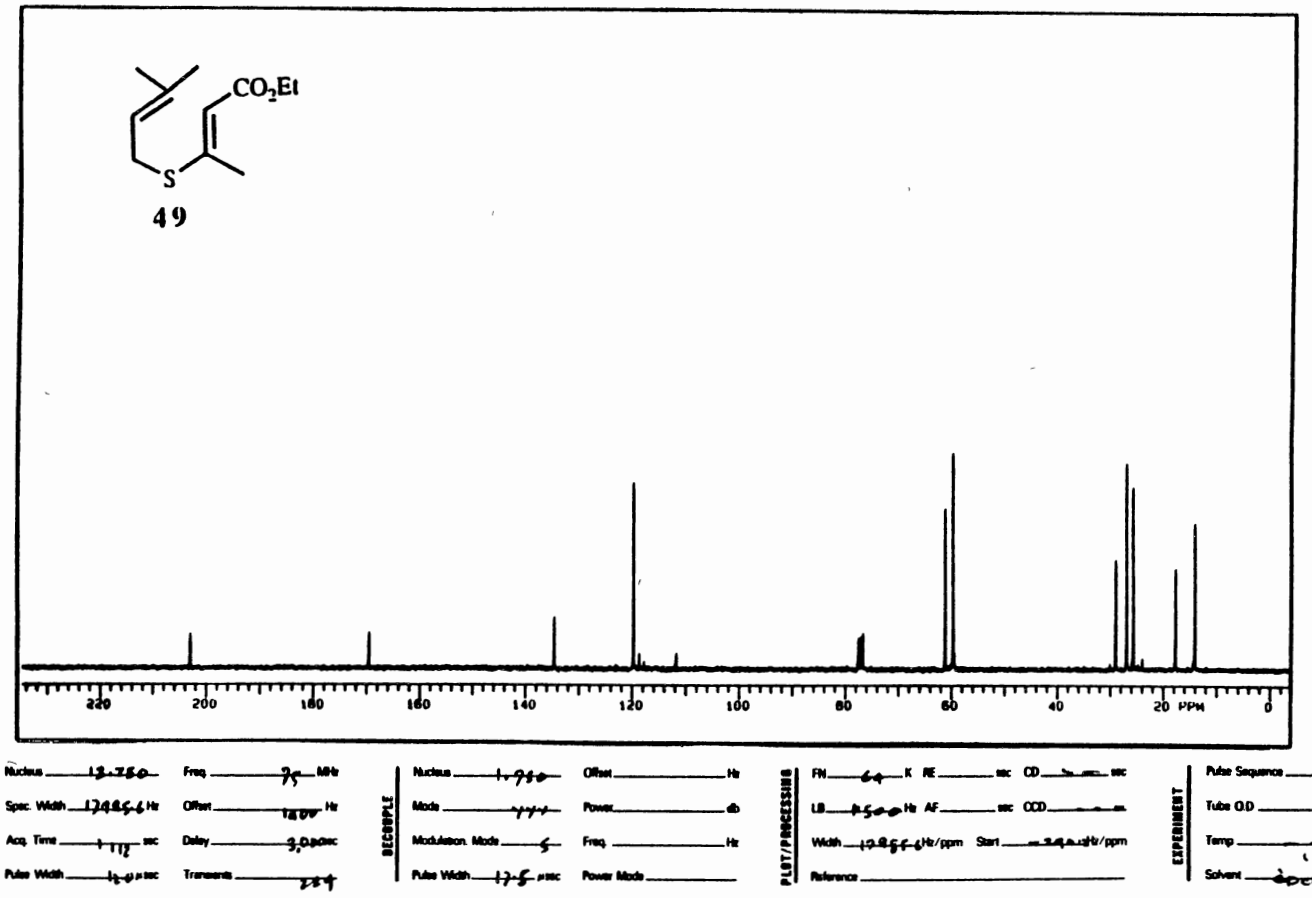
IR Spectrum of **49**

Plate XXXXII



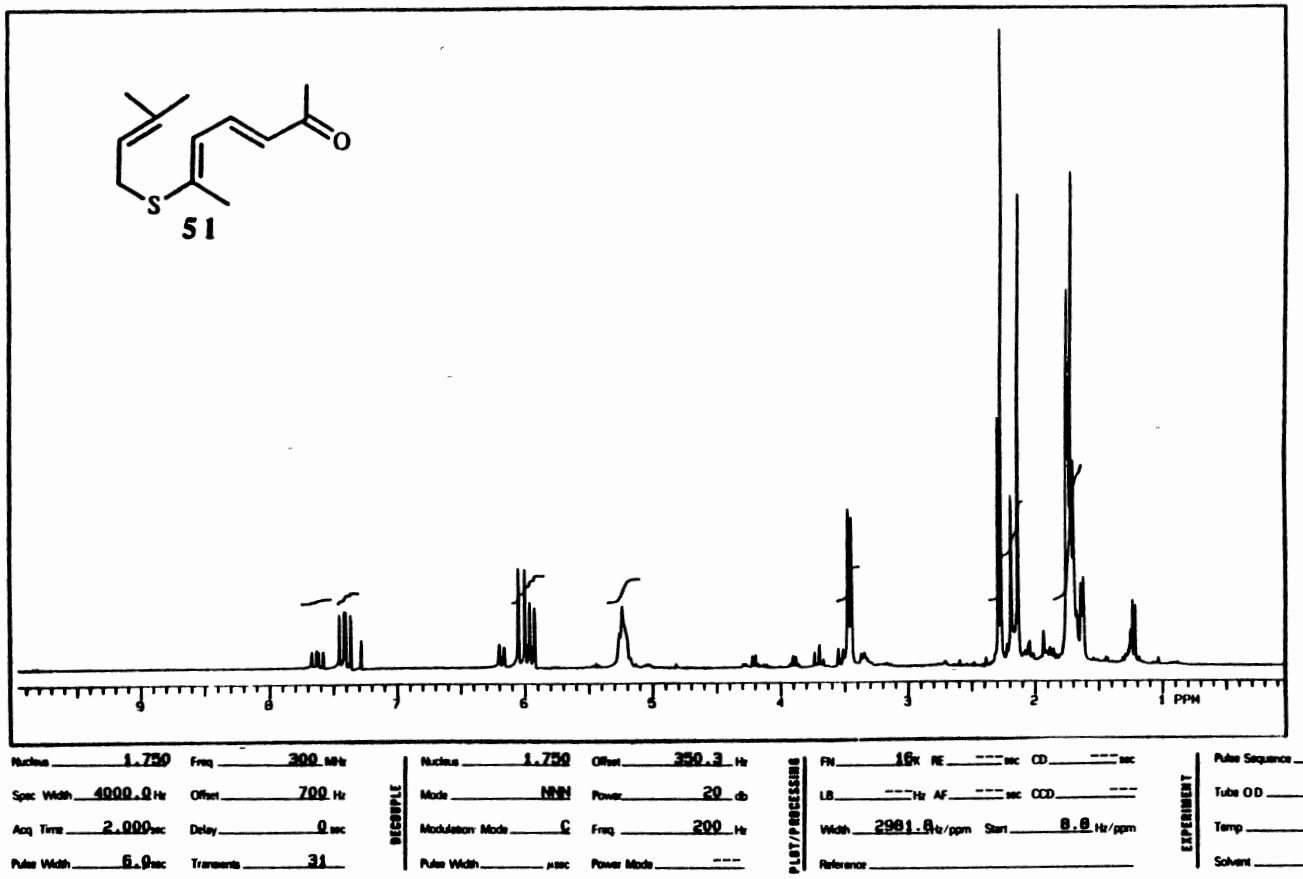
^{1}H NMRSpectrum of **49**

Plate XXXXIII



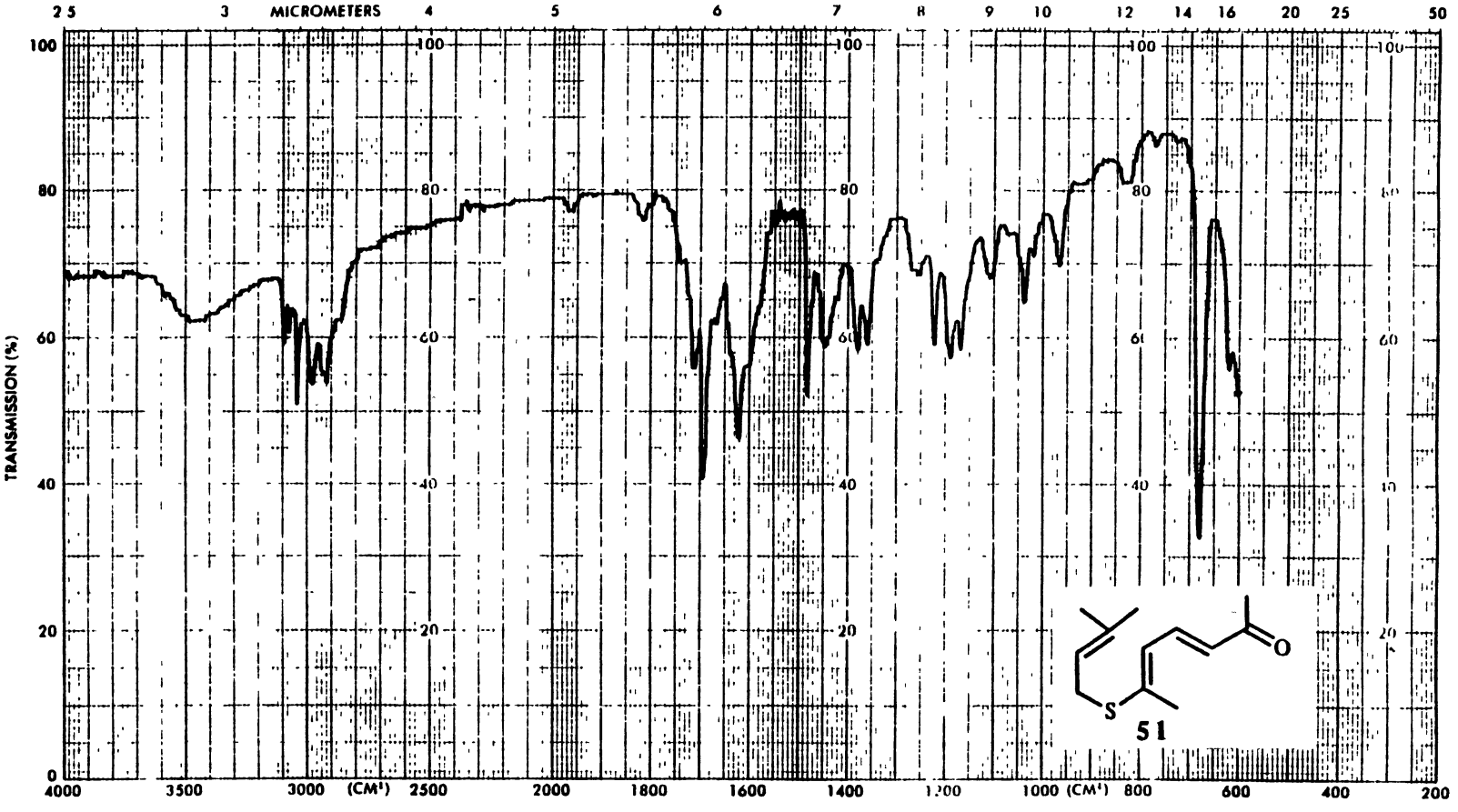
^{13}C NMR Spectrum Of **49**

Plate XXXXIV



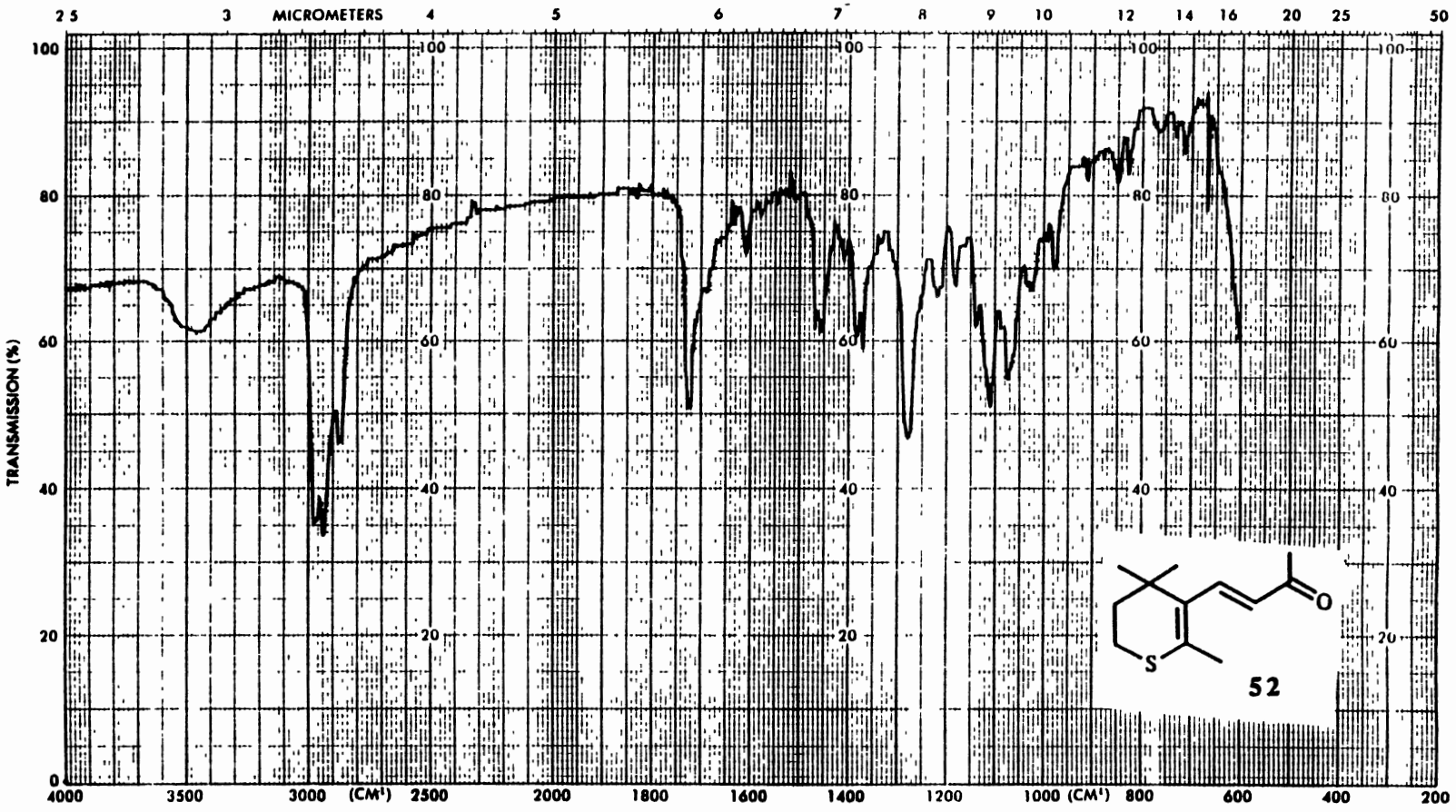
^{1}H NMR Spectrum Of **51**

Plate XXXXV



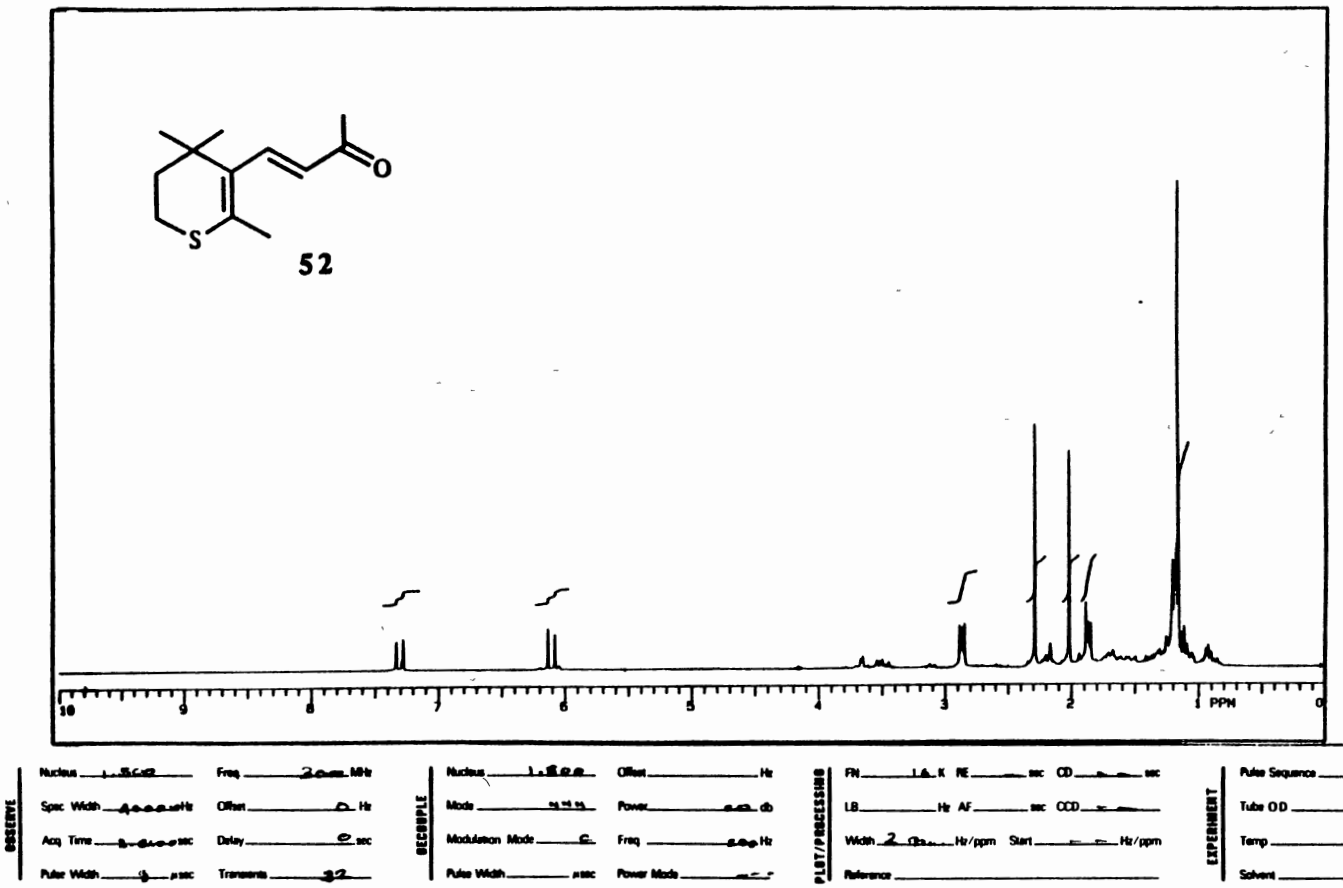
IR Spectrum of **51**

Plate XXXXVI



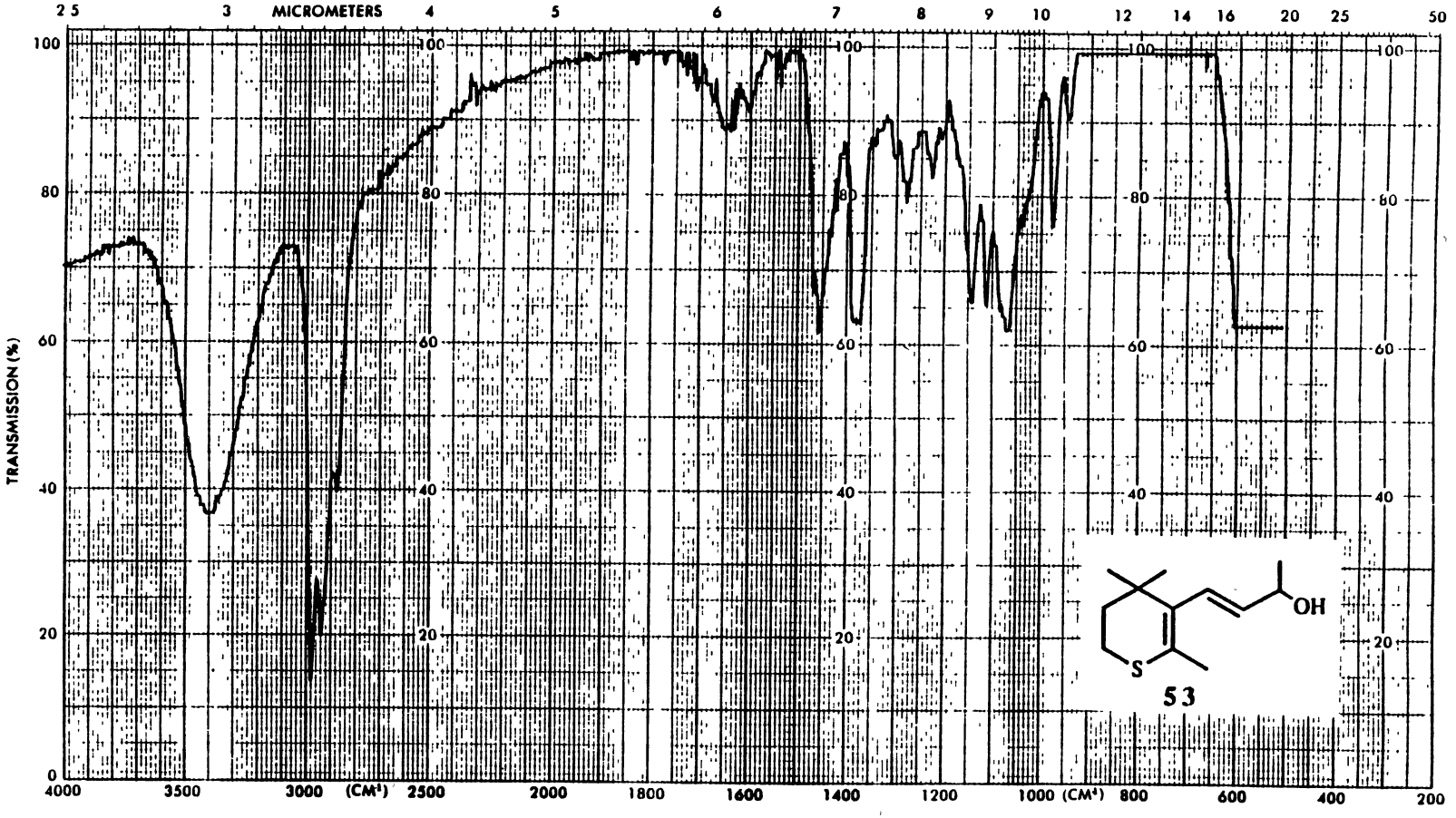
IR Spectrum of **52**

Plate XXXXVII



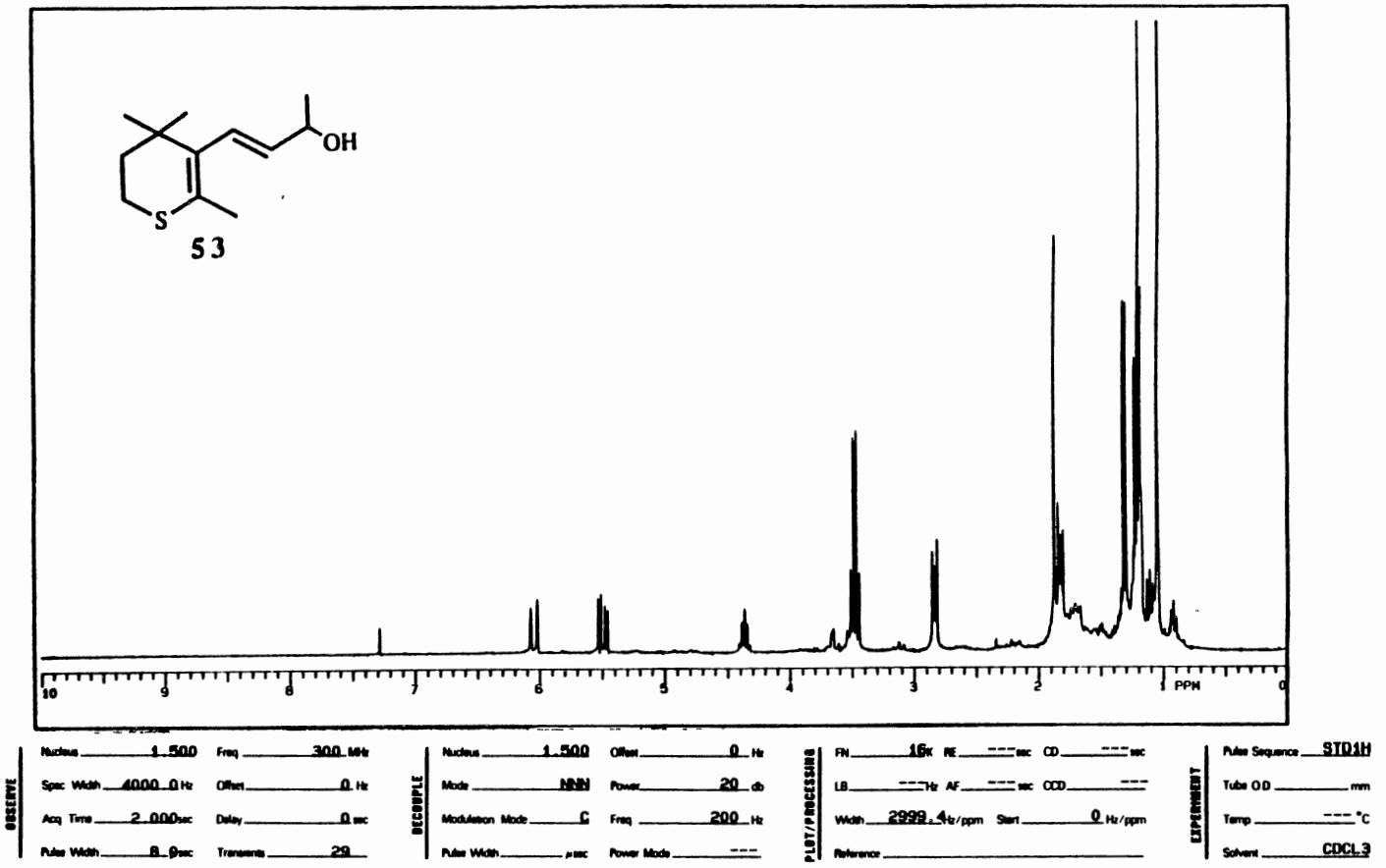
^{1}H NMR Spectrum of **52**

Plate XXXXVIII



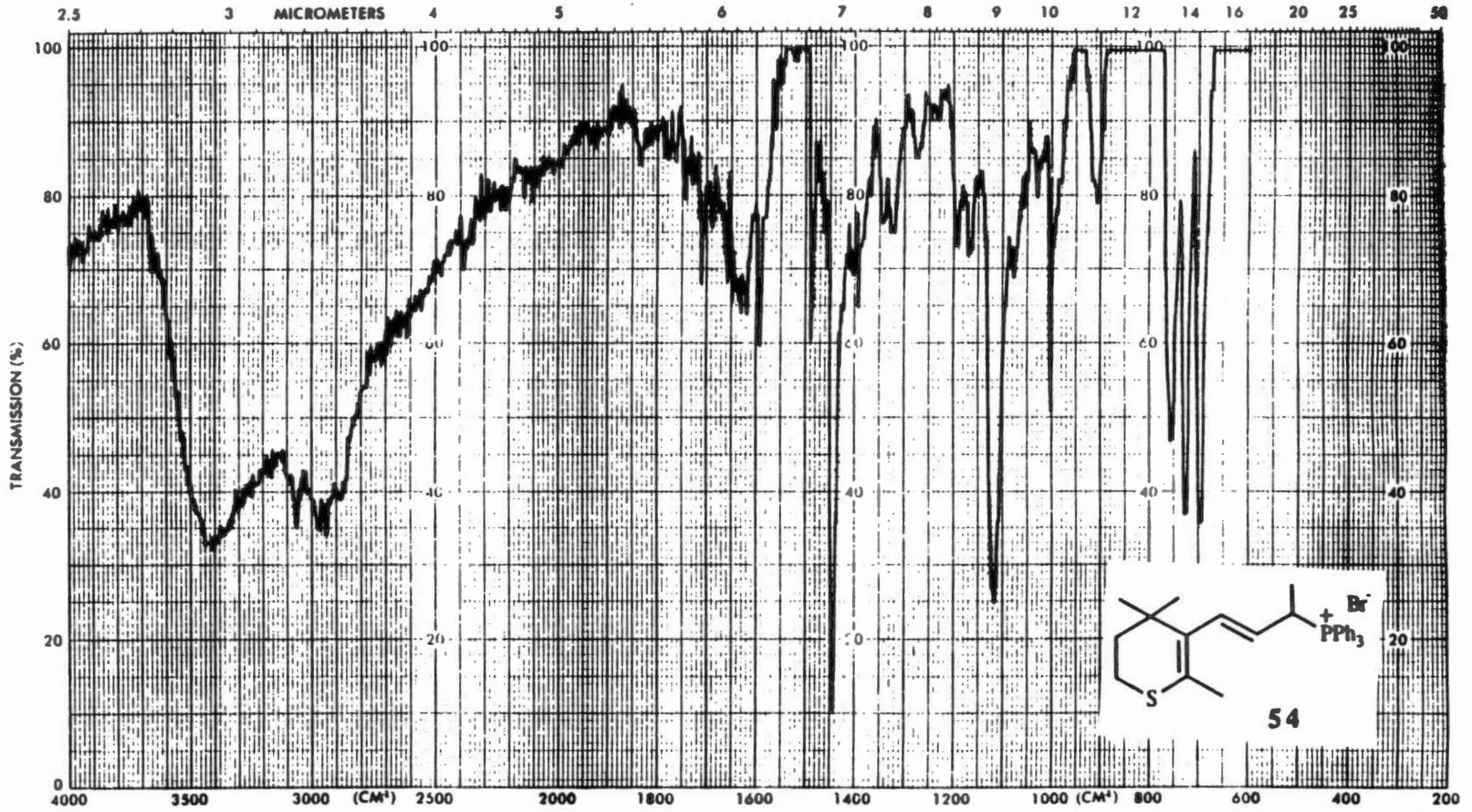
IR Spectrum of **53**

Plate IL

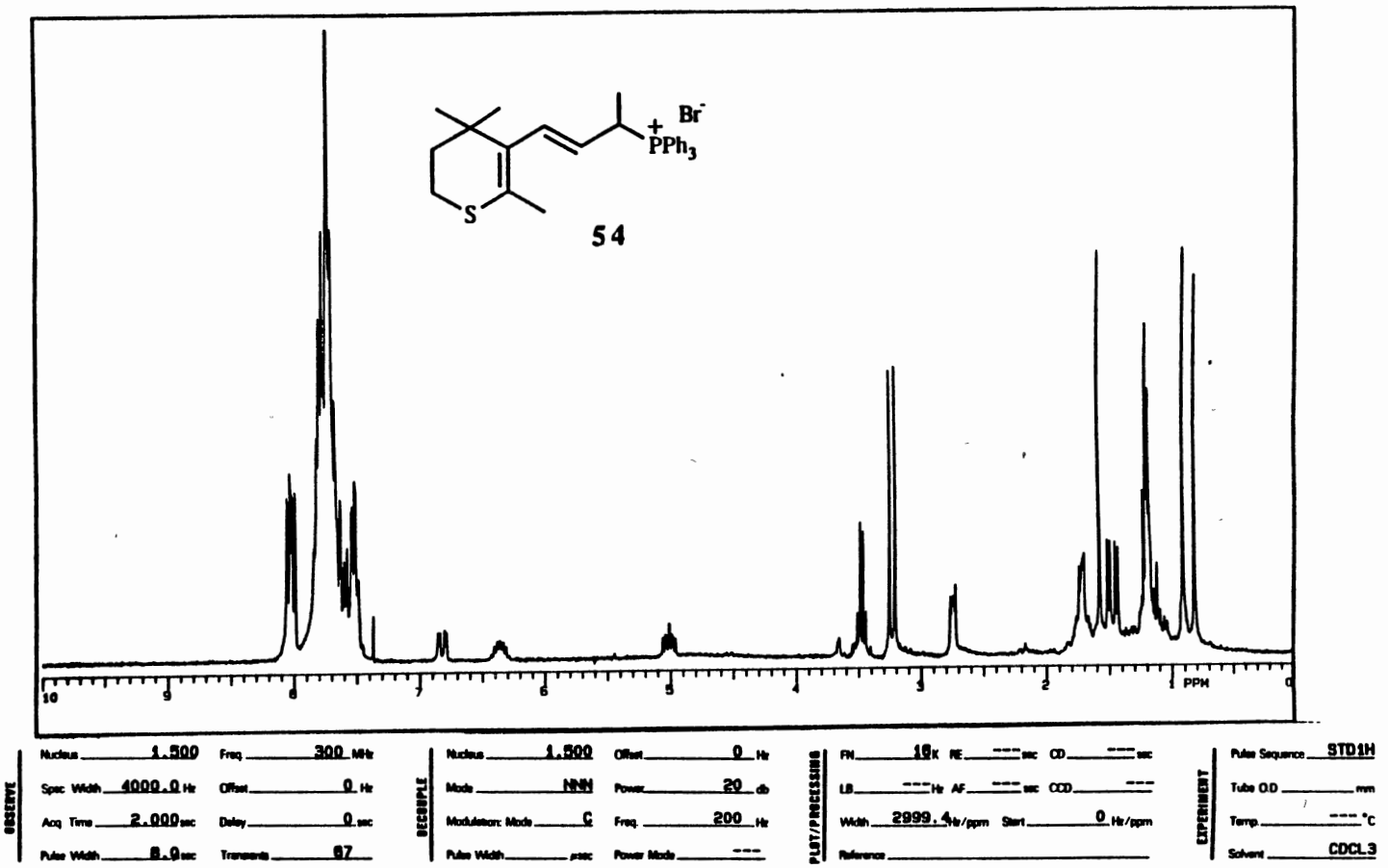


^{1}H NMR Spectrum of **53**

Plate L

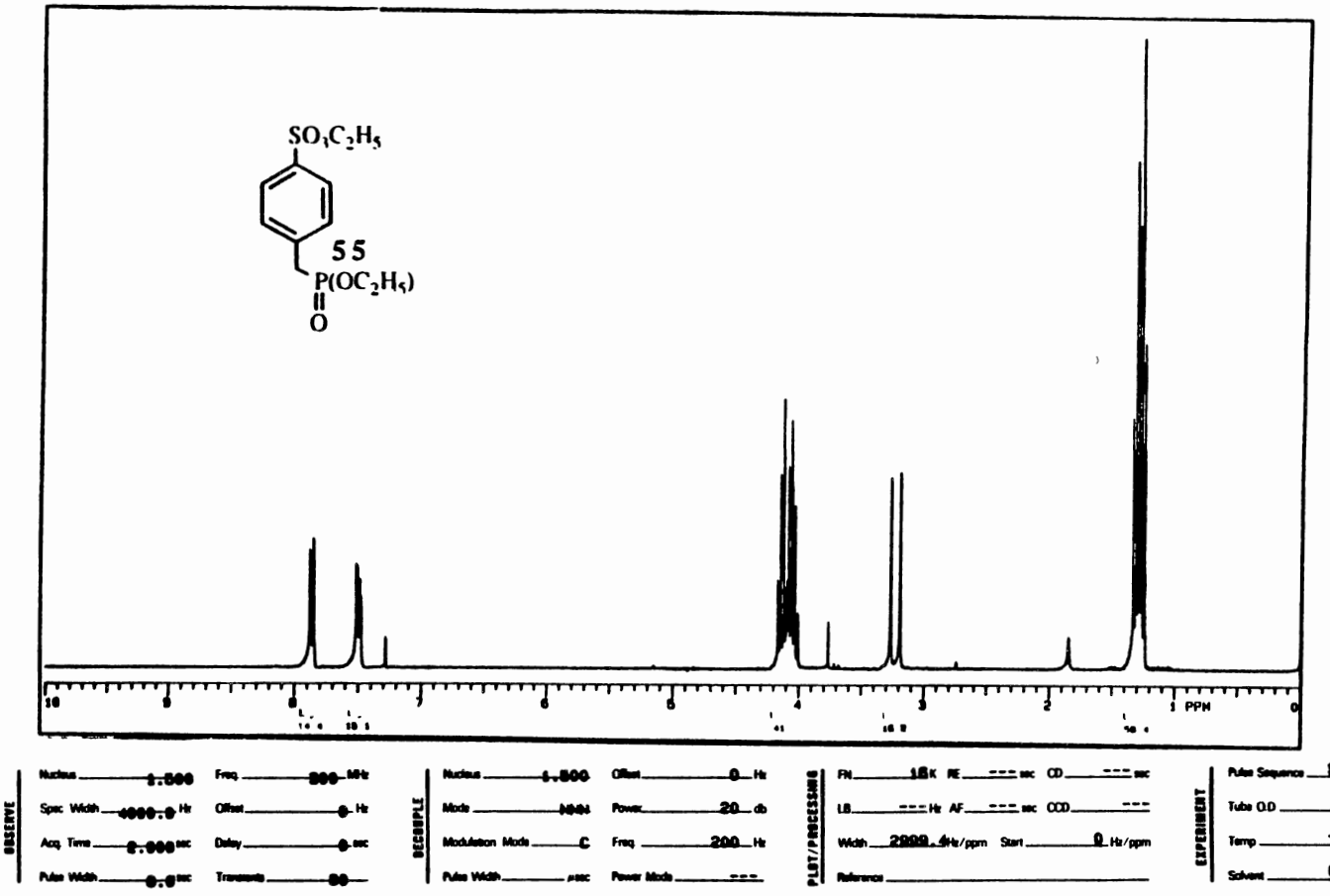


IR Spectrum of **54**



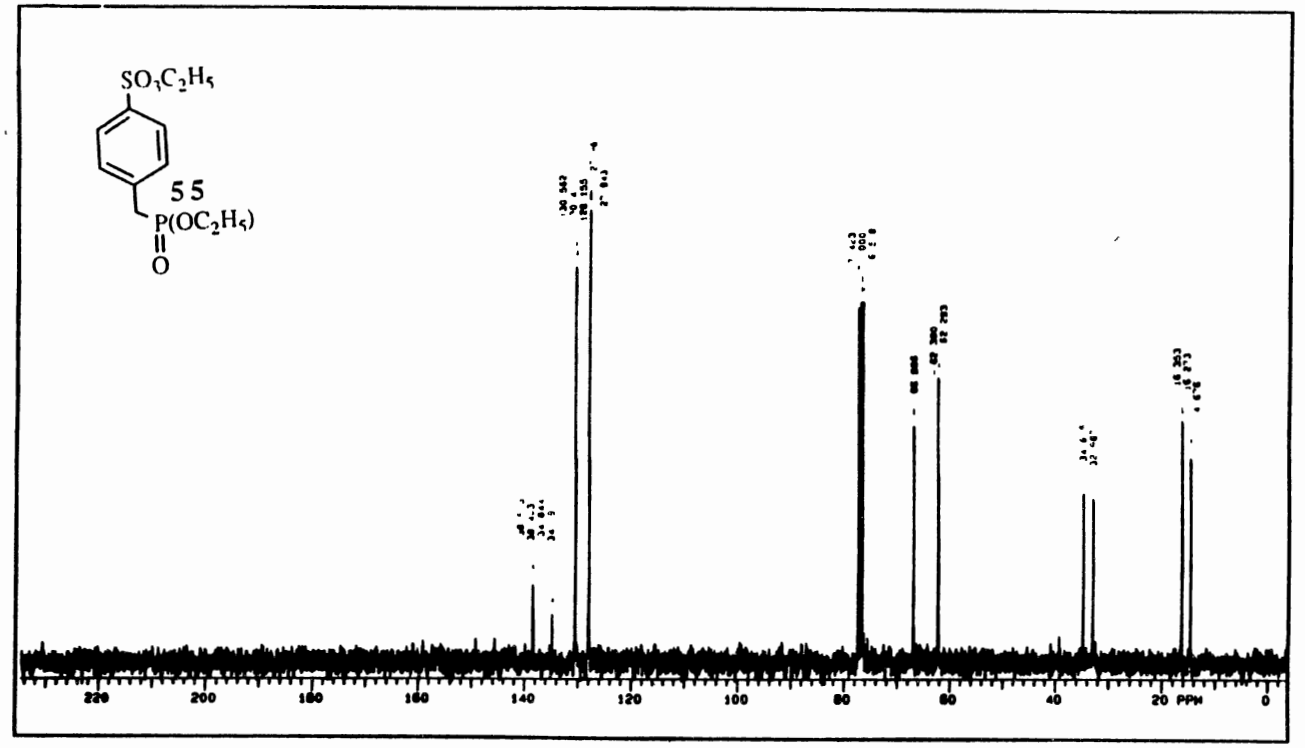
^{1}H NMR Spectrum of **54**

Plate LII



^{1}H NMR Spectrum of **55**

Plate LIII



OBSERVE: Nucleus 13.750 Freq 78 MHz; Spec Width 17985.6 Hz Offset 1400 Hz; Acq Time 1.112 sec Delay 3.000 sec; Pulse Width 12.0 sec Transients 224

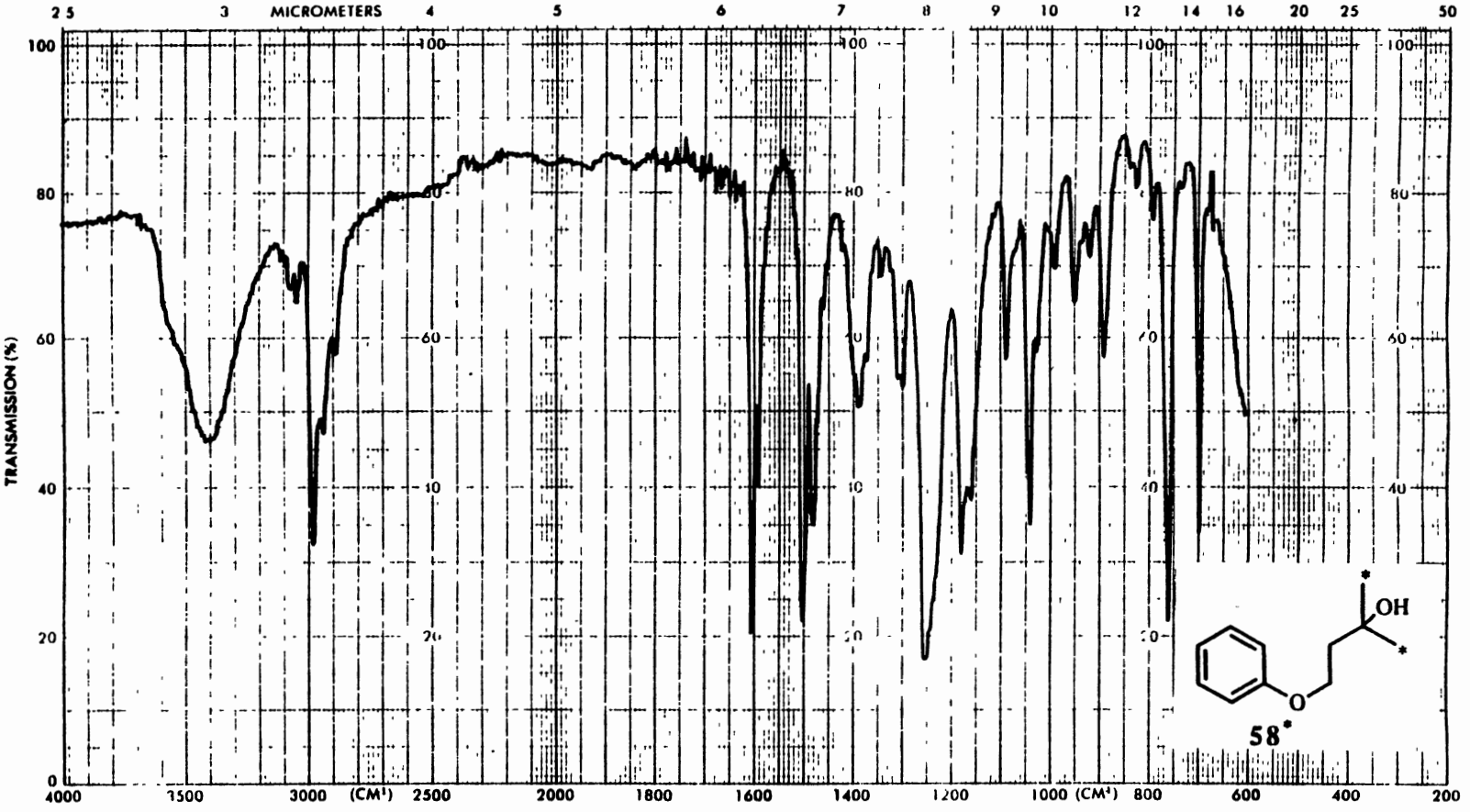
DECOUPLE: Nucleus 1.750 Offset 200.3 Hz; Mode YYY Power 0 db; Modulation Mode S Freq 7900 Hz; Pulse Width 17.5 psec Power Mode ---

PLOT/PROCESSING: FN 64 K RE --- sec CD --- sec; LB 1.000 Hz AF --- sec CCD ---; Width 17985.6 Hz/ppm Start -290.2 Hz/ppm; Reference

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

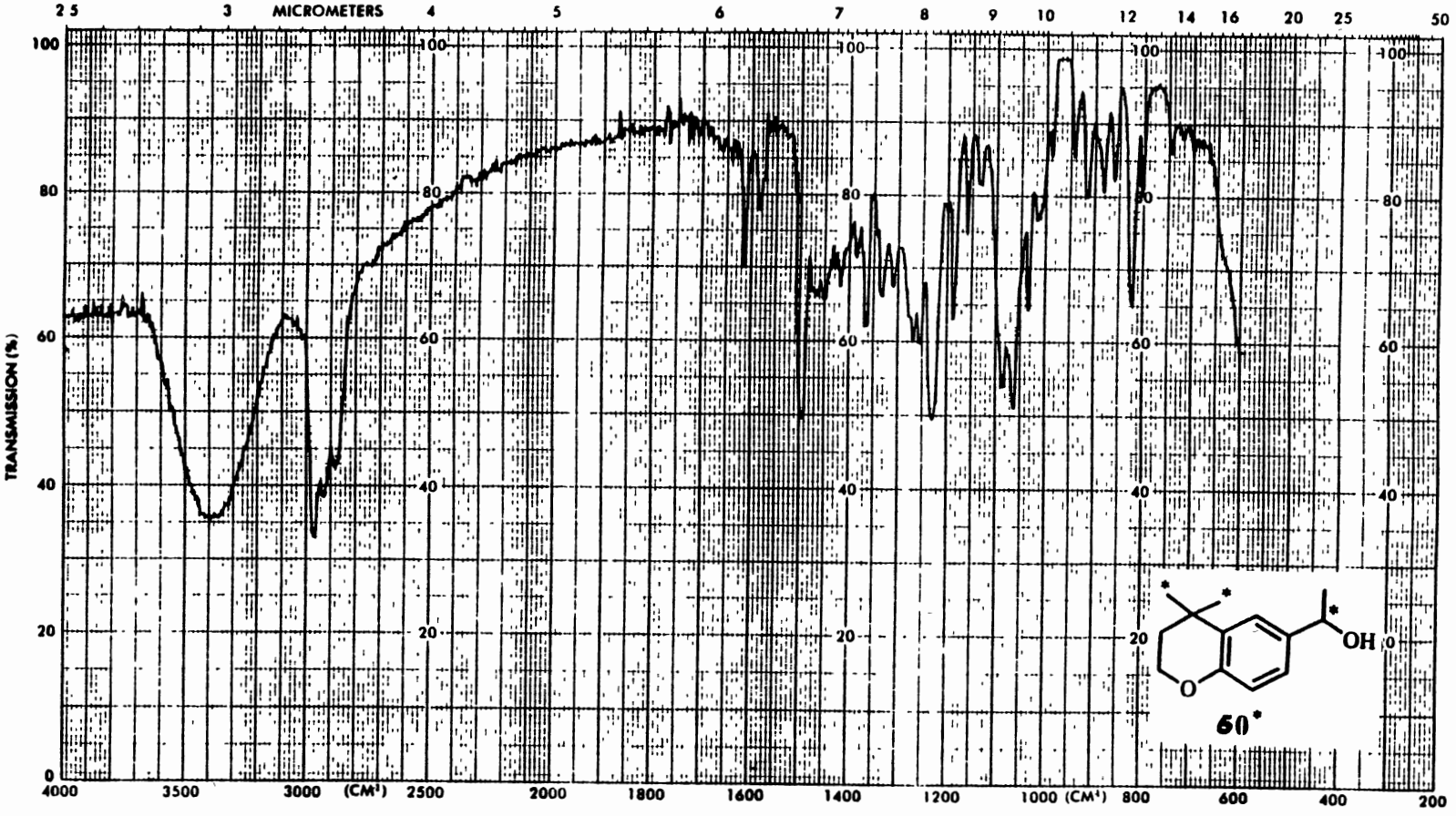
^{13}C NMR Spectrum Of **55**

Plate LIV



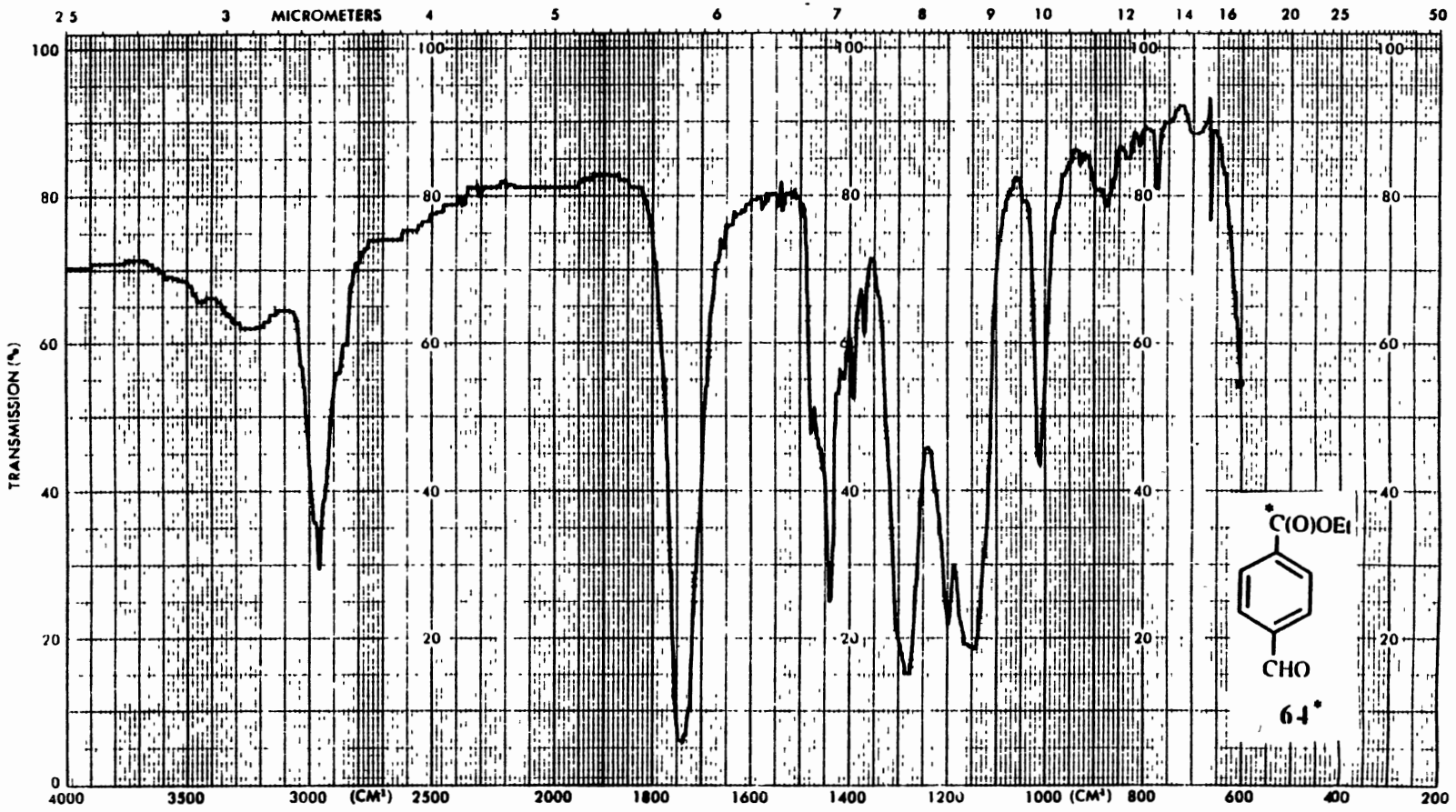
IR Spectrum of **58***

Plate LV



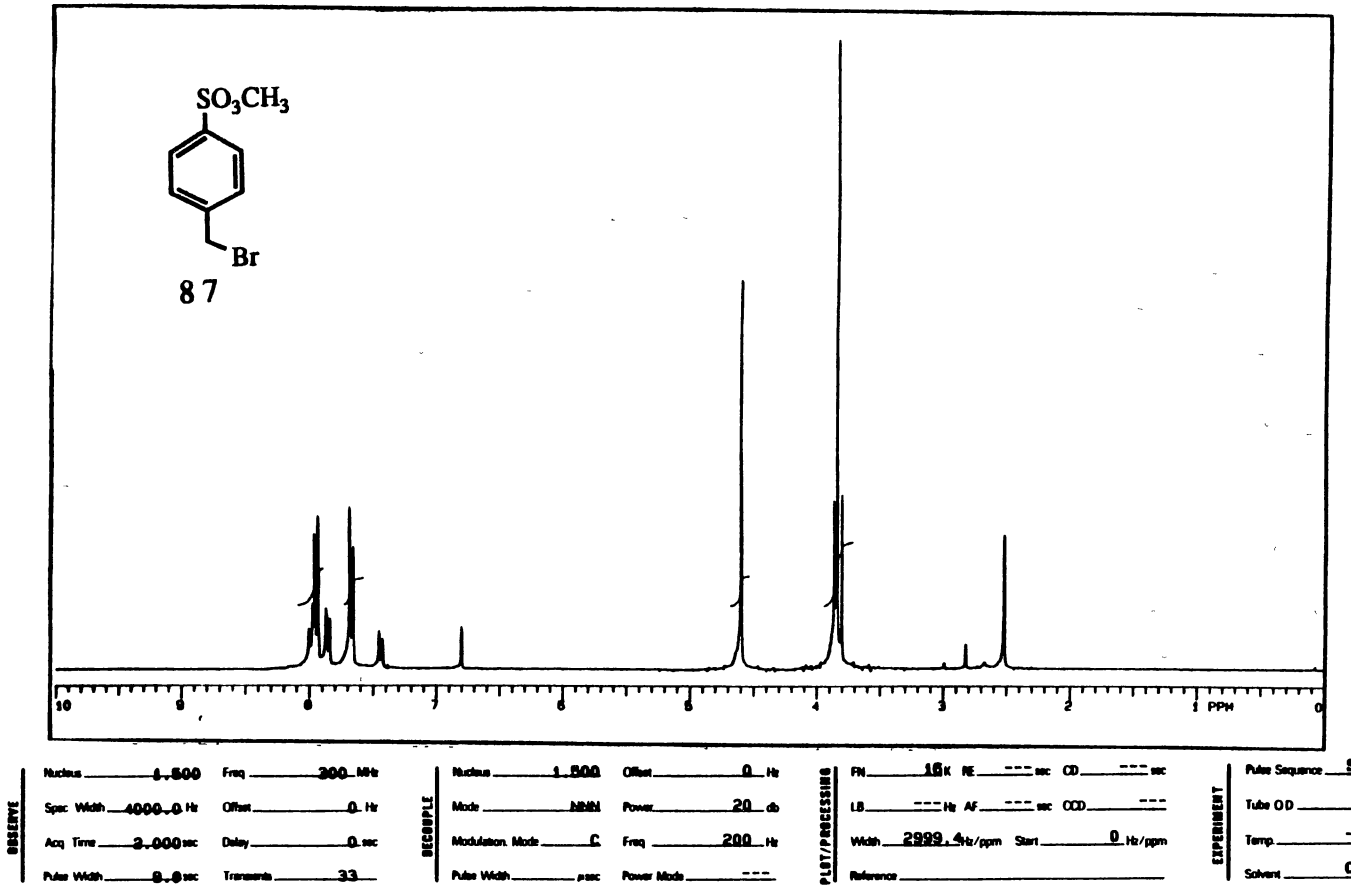
IR Spectrum of **60***

Plate LVI



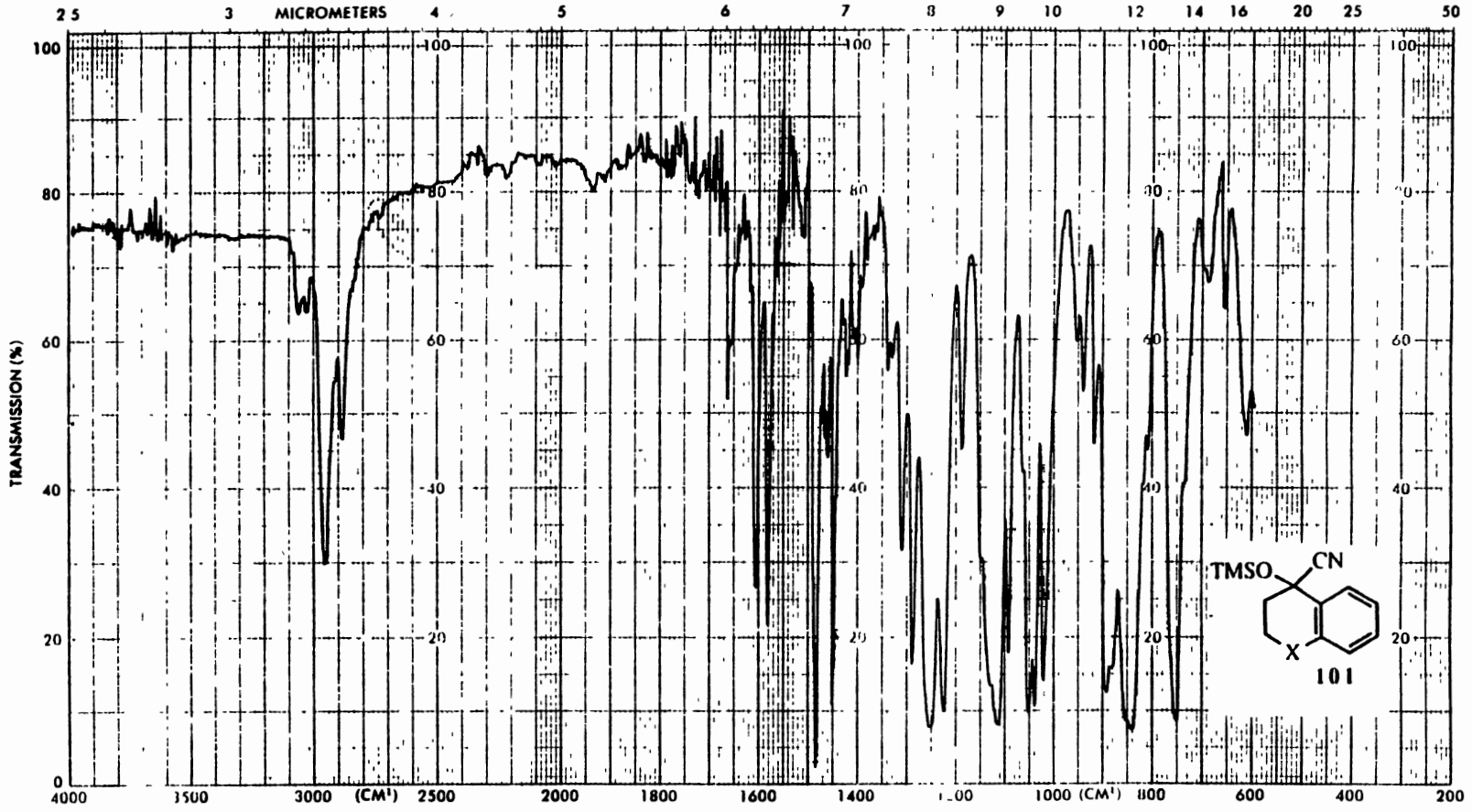
IR Spectrum of **64***

Plate LVII



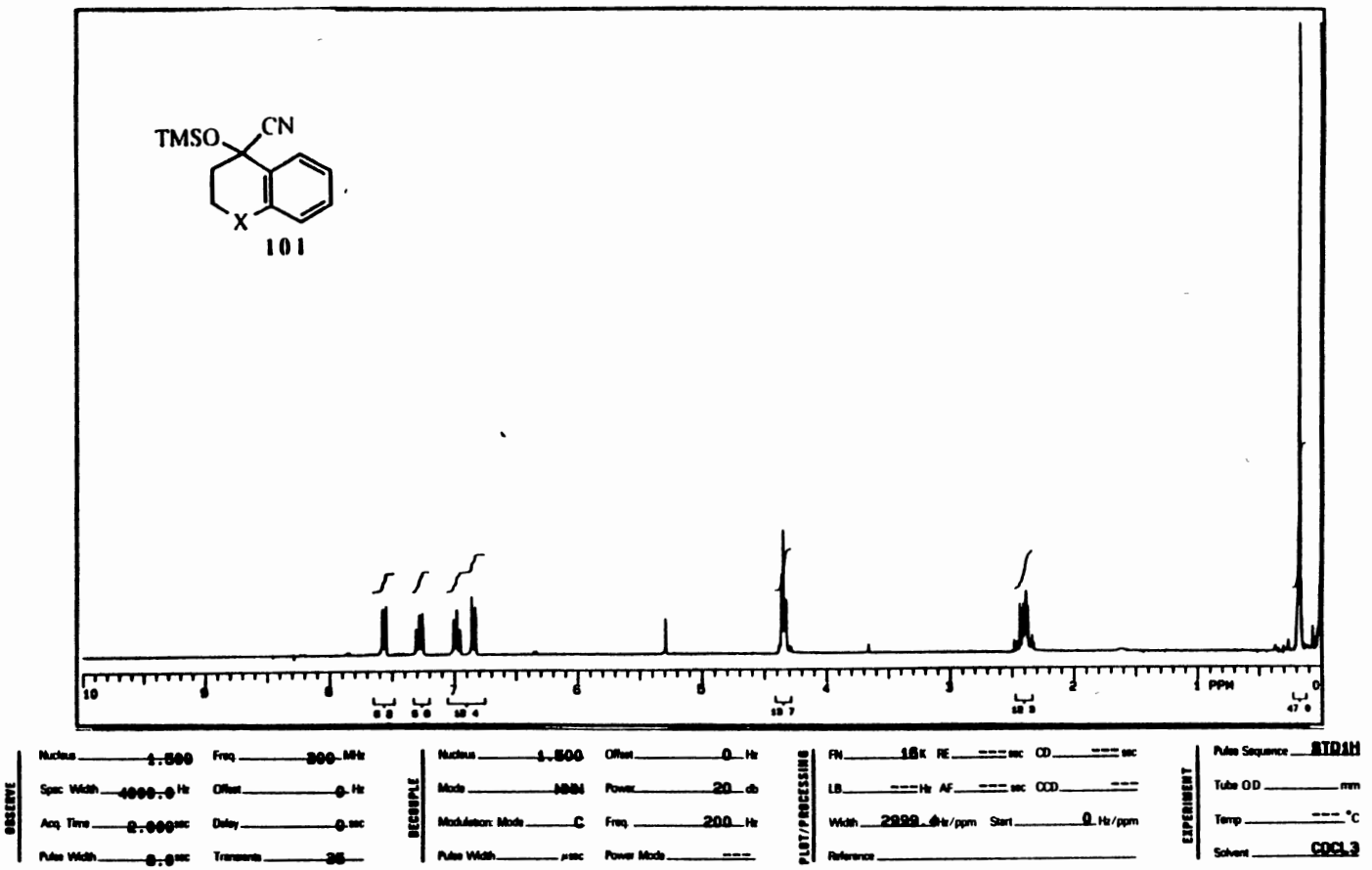
^{1}H NMR Spectrum of **87**

Plate LVIII



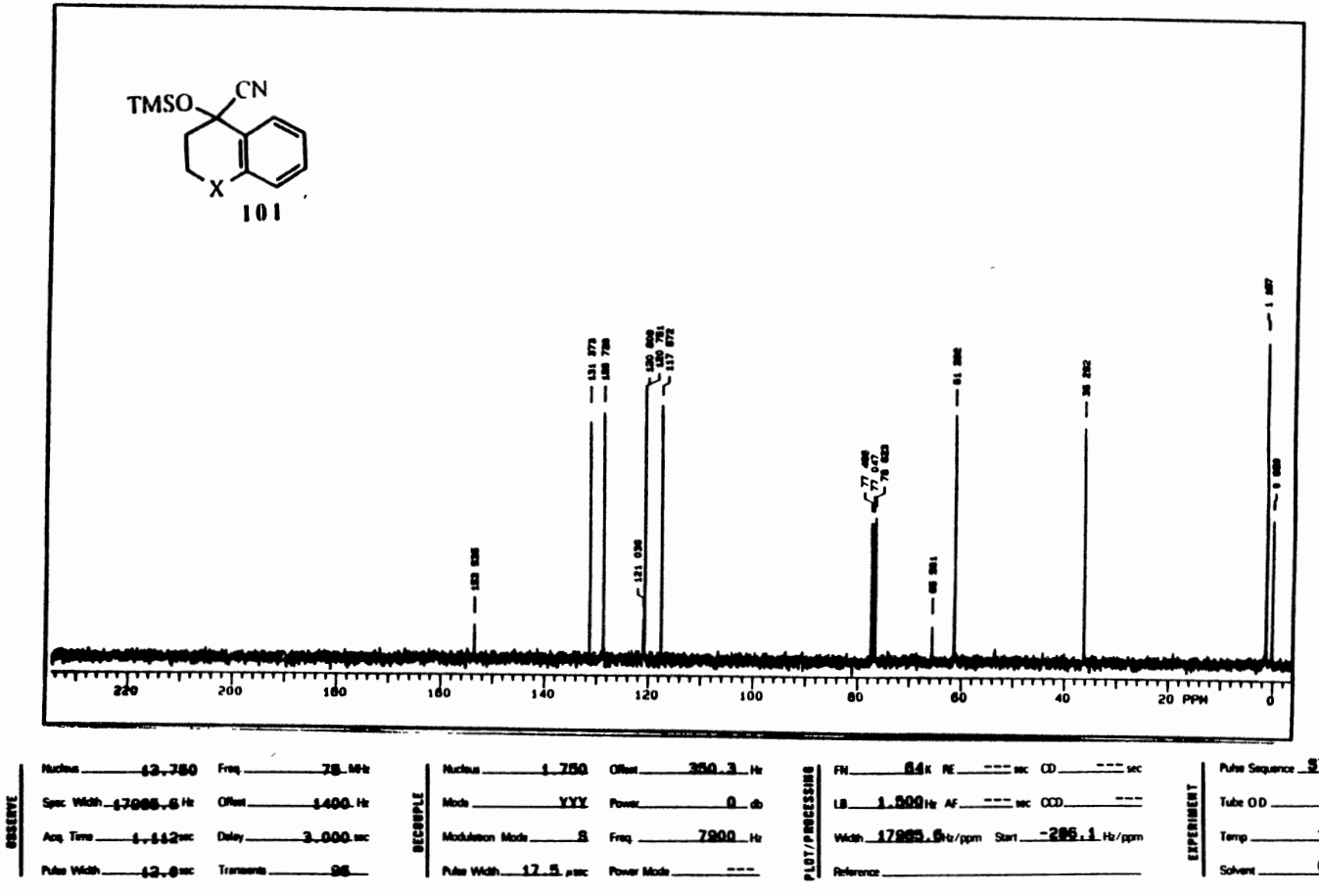
IR Spectrum of **101**

Plate LIX



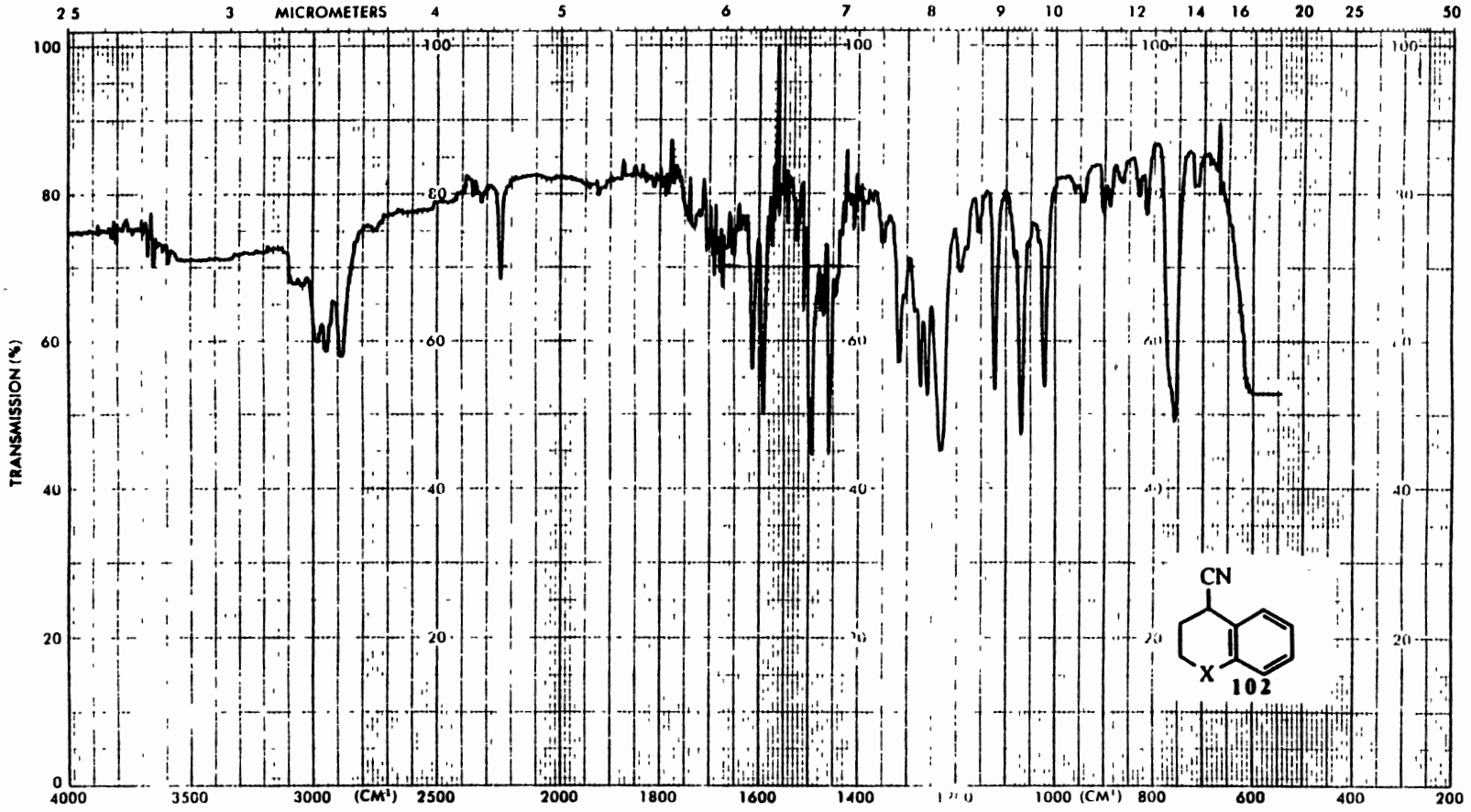
^{1}H NMR Spectrum of **101**

Plate LX



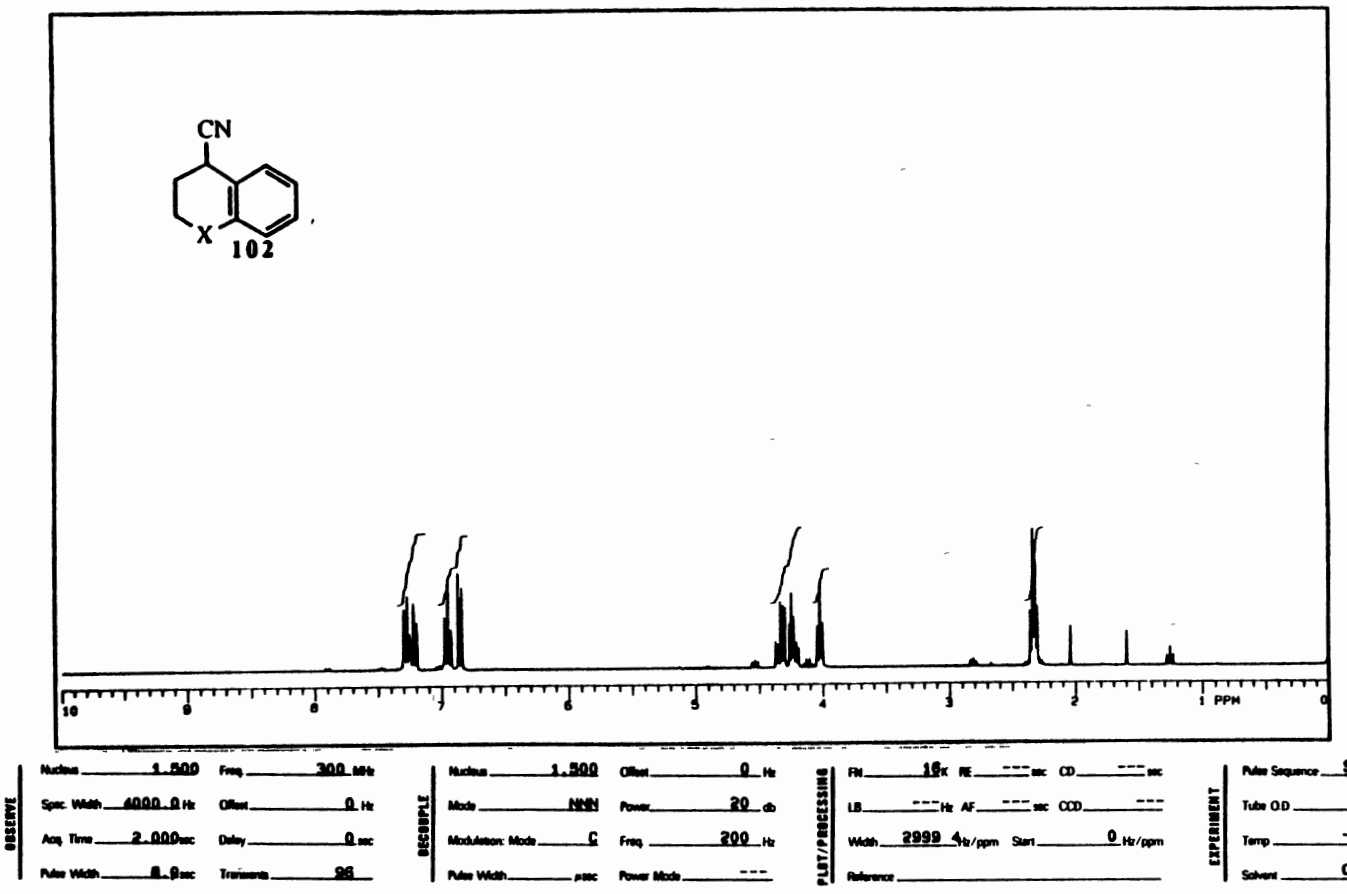
^{13}C NMR Spectrum of **101**

Plate LXI



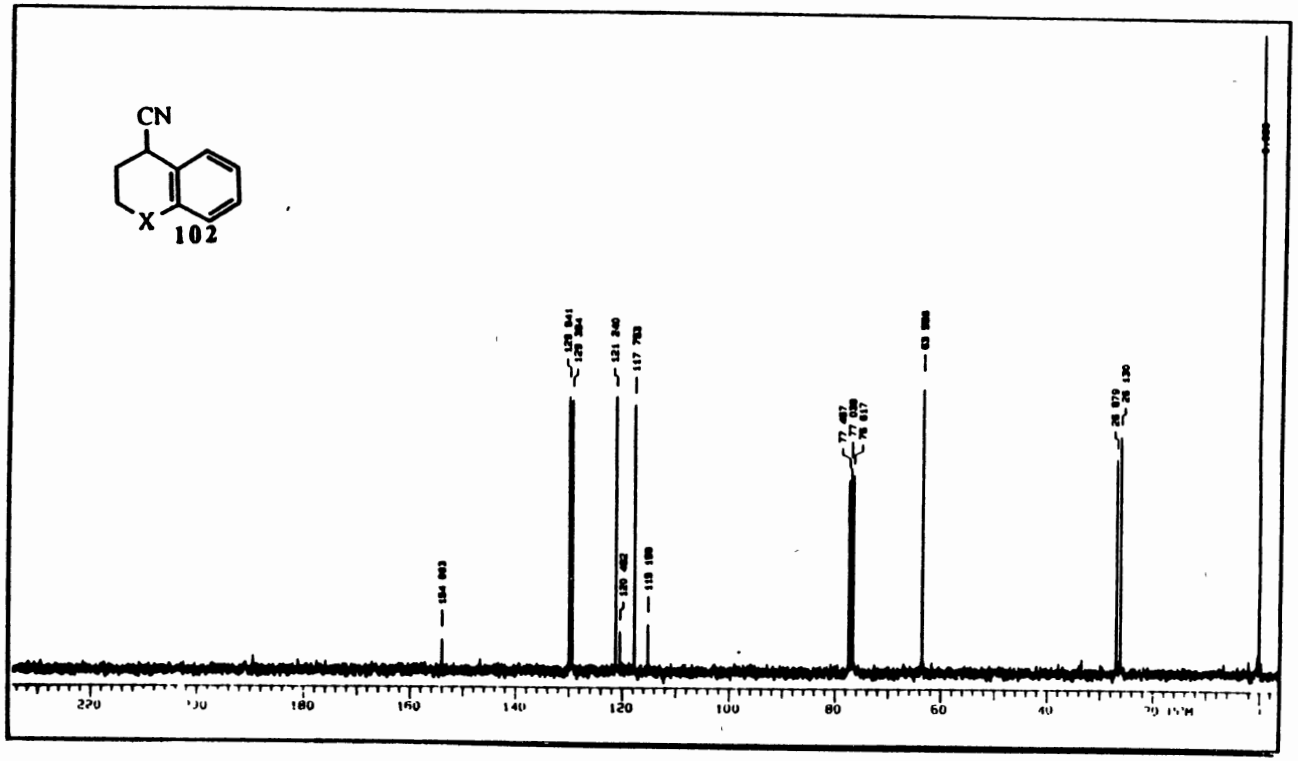
IR Spectrum of **102**

Plate LXII



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

Plate LXIII



OBSERVE: Nucleus 13.360 Freq 75 MHz; Spec Width 17985.6 Hz Offset 1400 Hz; Acq Time 1.117 sec Delay 3.000 sec; Pulse Width 12.0 sec Transients 324

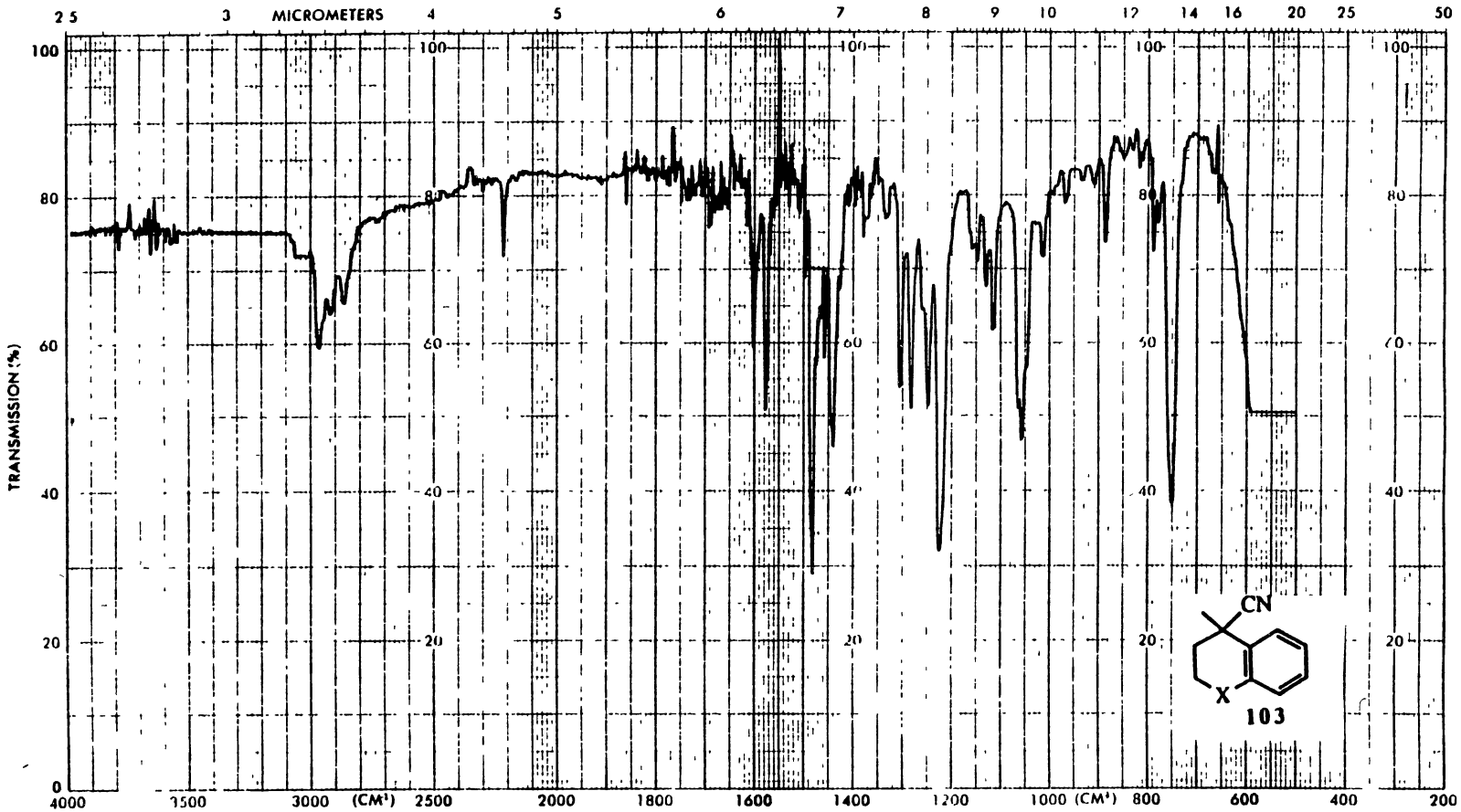
DECOUPLE: Nucleus 1.750 Offset 350.3 Hz; Mode YYY Power 0 db; Modulation Mode S Freq 7900 Hz; Pulse Width 17.5 µsec Power Mode

PLOT/PROCESSING: FN 64K RE --- sec CD --- sec; LB 1.500 Hz AF --- sec OCD ---; Width 17985.6Hz/ppm Start 286.1 Hz/ppm; Reference

EXPERIMENT: Pulse Sequence S1D13C; Tube OD ___ mm; Temp --- °C; Solvent CDCL3

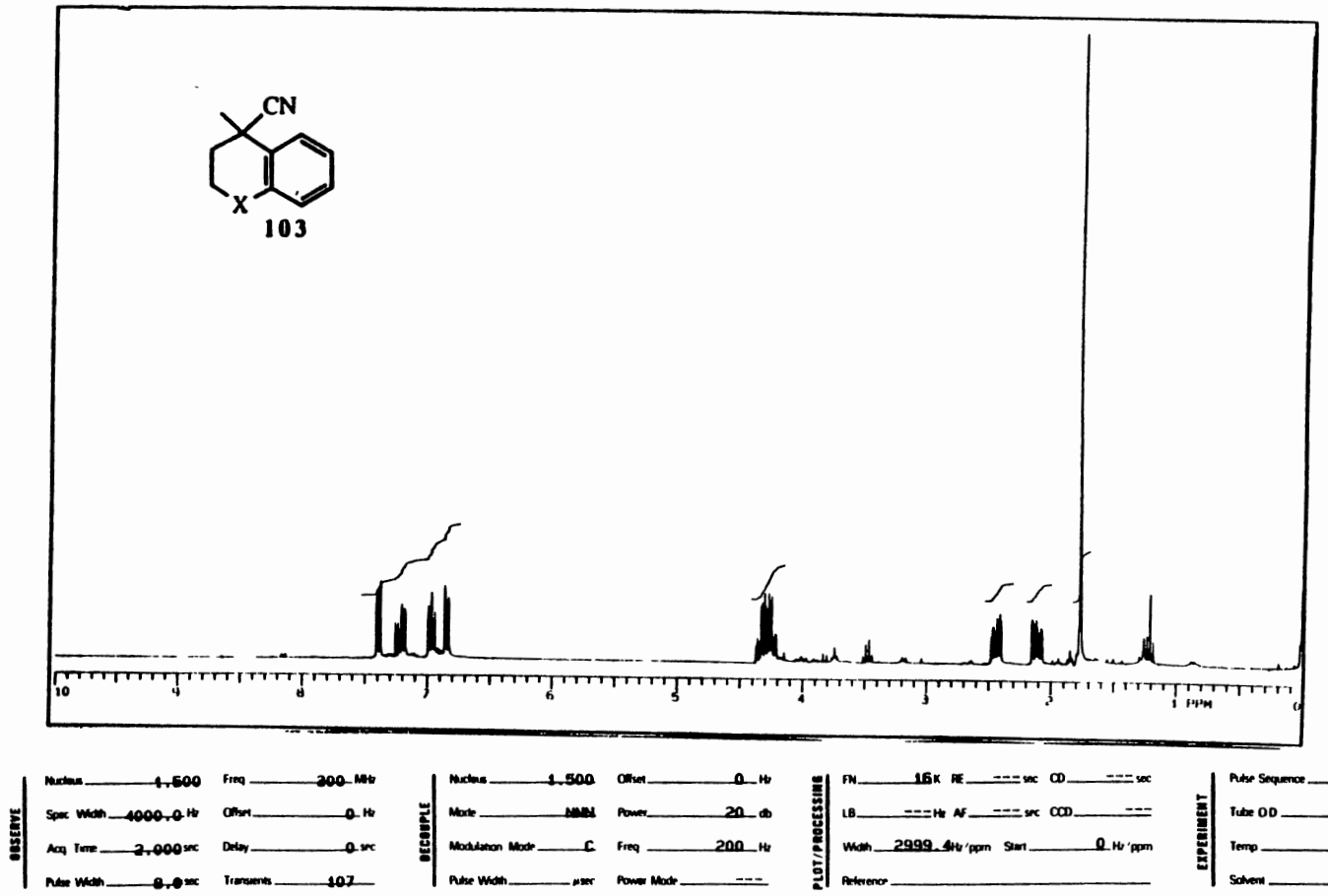
^{13}C NMR Spectrum **102**

Plate LXIV



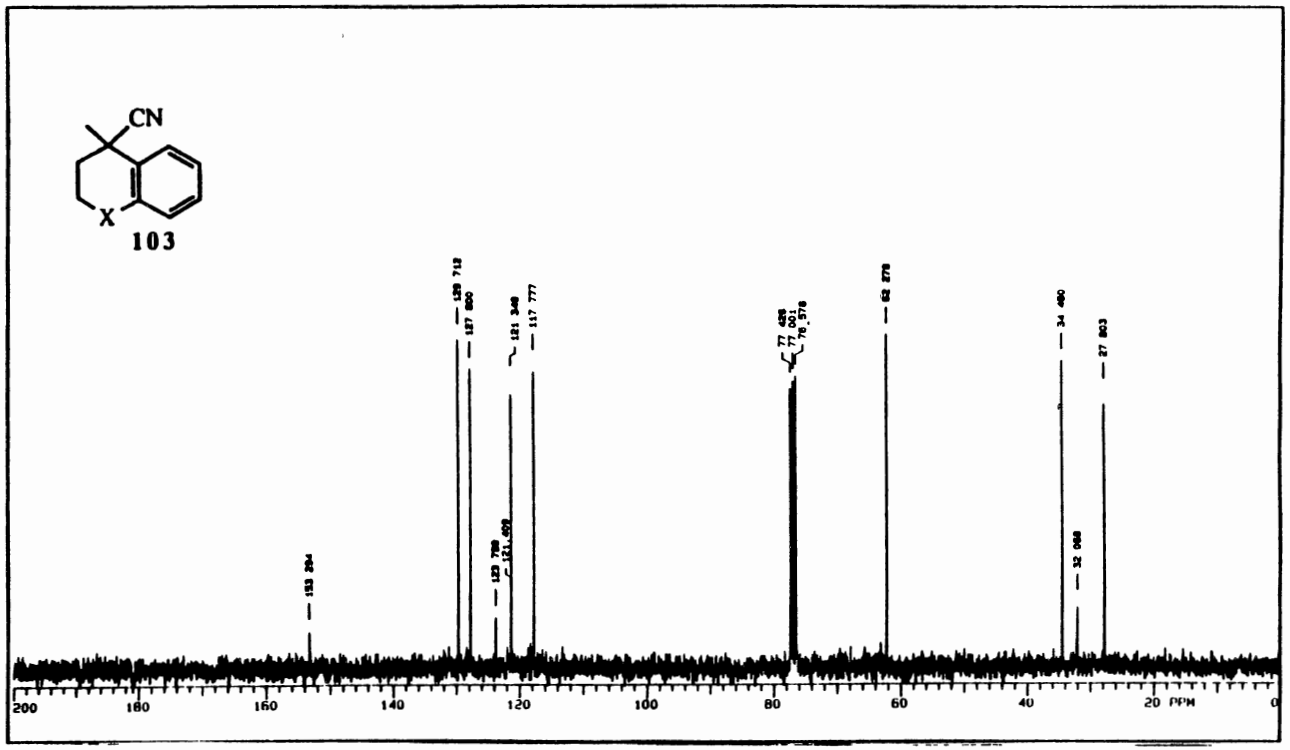
IR Spectrum of **103**

Plate LXV



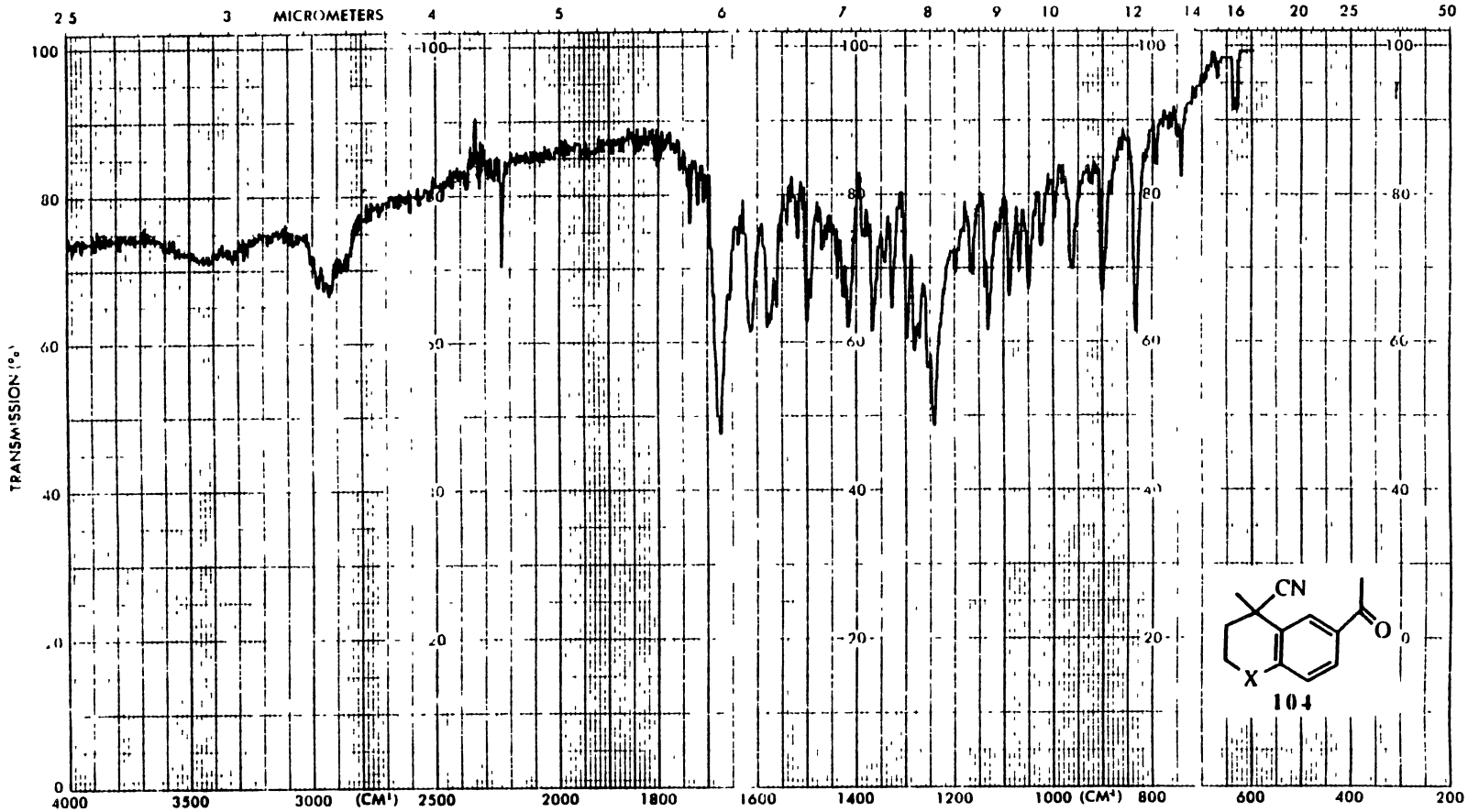
^{1}H NMR Spectrum of **103**

Plate LXVI



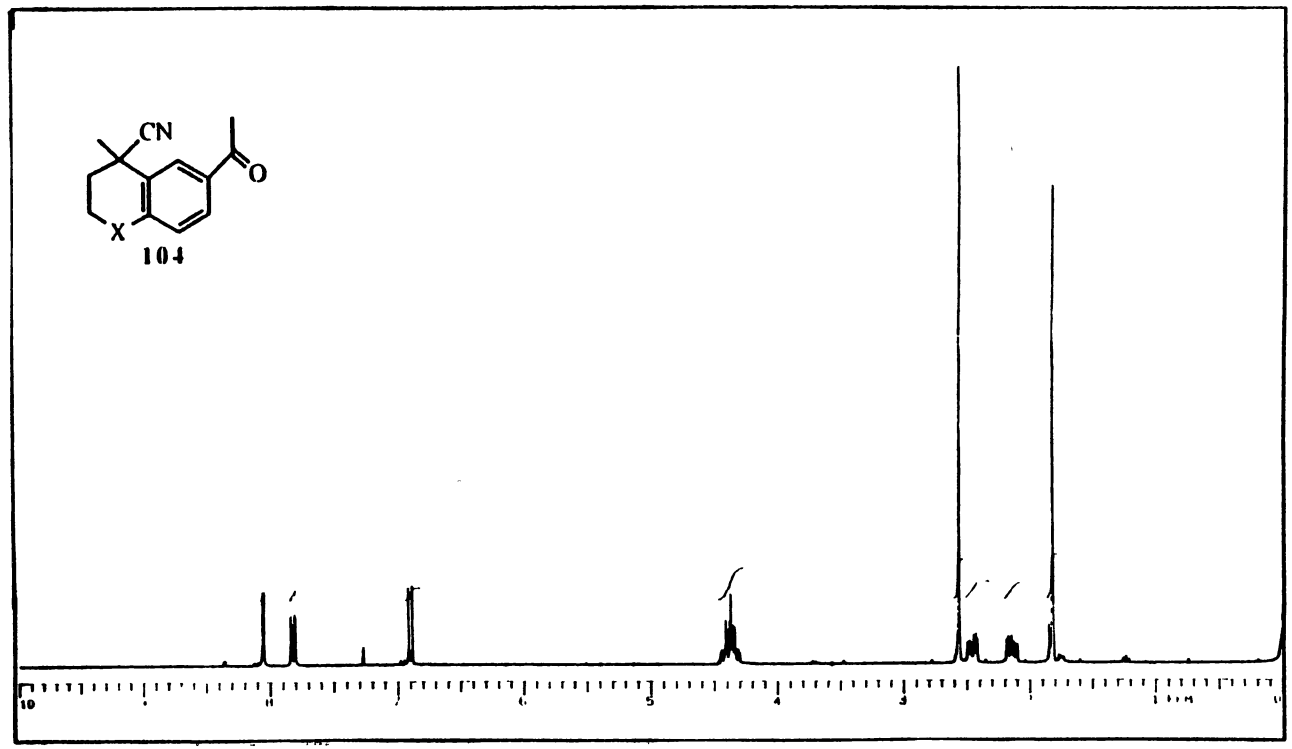
^{13}C NMR Spectrum of **103**

Plate LXVII

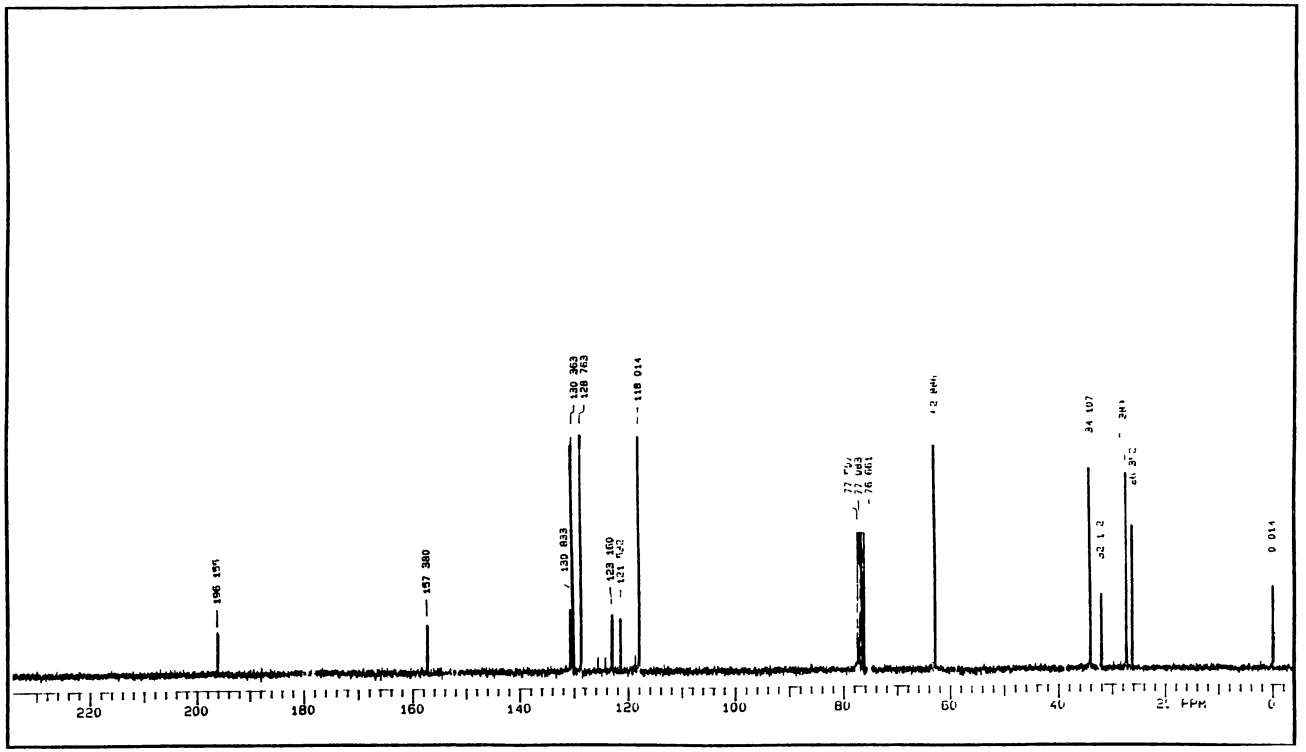


IR Spectrum of **104**

Plate LXVIII



^{1}H NMR Spectrum of **104**



^{13}C NMR Spectrum of **104**.

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VITA

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Doctor Of Philosophy

Thesis: SYNTHESES OF POTENTIAL METABOLITES OF ETHYL (*E*)-4-[2-(3,4-DIHYDRO-4,4-DIMETHYL-2*H*-1-BENZOPYRAN-6-YL)-1-PROPENYL]-BENZOATE, 4-[(ALL-*E*)-2-METHYL-4-(2,6,6-TRIMETHYL-3-THIA-1-CYCLOHEXEN-1-YL)-1,3-BUTADIENYL]BENZOIC ACID AND CERTAIN DERIVATIVES

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