SYNTHESES, STRUCTURAL ELUCIDATION AND BIOLOGICAL ACTIVITY OF NEW HETEROAROTINOIDS

BY

LYLE WARREN SPRUCE II

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Metropolitan State College

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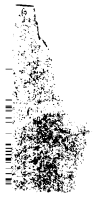

K D Berlin
Thesis Adviser

Richard A. Bunce

Warren T Ford

Don F Kincannon

Norman N. Durham
Dean of the Graduate College

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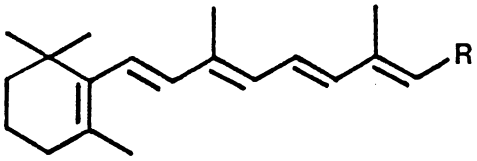
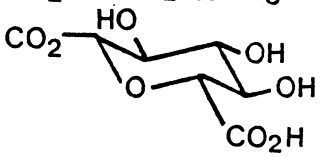
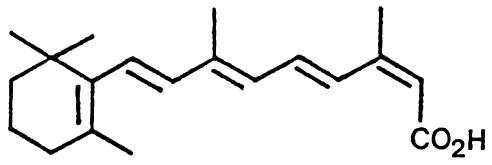
CHAPTER I

INTRODUCTION

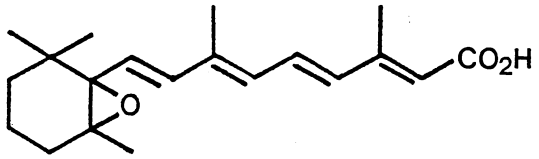
Retinoids are a relatively new class of compounds which have attracted considerable attention in the fields of dermatology[9,16,22,23,33,43,47,66,82,86,87,88,100,132] and oncology.[14,15,23,34,47,69,71,82,91,97] An excellent in depth review was recently published on this dynamic topic and brought together in two volumes the vast amount of data reported up to 1984.[109,110] Originally, these compounds were compared to retinol (**1a**) in terms of structure (as shown for **1a-1i** below) and biological activity. Thus, a general definition for this class of compounds was therefore based on these two intrinsic properties. However, in the search for new retinoids with medicinal applications, many compounds have been prepared which possess structures of dramatic variation. Consequently, the resemblance of many to retinol (**1a**) is remote, and a new definition seems necessary. Sporn and Roberts realized that research on retinoids had exceeded the original scope of studies in terms of significance for nutrition and vision. Thus, in a 1984 symposium on retinoids a new definition for retinoids evolved.[113] They proposed the following: "A retinoid is a



Retinoid	R
1a	CH_2OH
1b	CO_2H
1c	CHO
1d	CH_2OAc
1e	$CH_2OC(=O)(CH_2)_{14}CH_3$
1f	$CH_2OC(=O)(CH_2)_{16}CH_3$
1h	



1g



1i

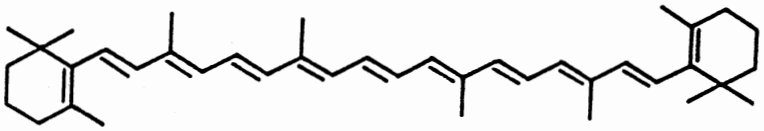
substance that can elicit specific biological responses by binding to and activating a specific receptor or set of receptors".[113] The two classic retinoids which have been examined in binding studies are retinol (**1a**)[109,110] and retinoic acid (**1b**).[109,110,121] However, the experimental studies of the binding process developed by Sporn and Roberts, to determine if a compound was truely a "retinoid", constitute elaborate processes.[109,110] Moreover, Schiff recently reported in a comparison between five retinoids that no correlation existed between biological

activity and binding sites for cellular retinoic acid binding protein (CRABP).[78] Therefore, in this text a specific definition for retinoids will not be cited since at this time there is insufficient evidence to invalidate the candidacy of any synthetic "retinoid" for possible binding studies.

Historical

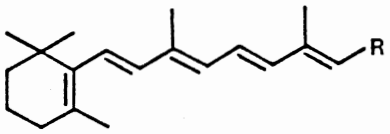
The historical scenario of retinol [**1a** or vitamin A], the parent compound of retinoids, begins at the turn of this century. In 1909, Stepp,[116,117] a professor in Germany, revealed a lipid-soluble material that he proved to be essential for sustaining life in laboratory animals. Stepp performed a critical experiment by extracting animal feed with ether or alcohol, and, after using this feed for his test mice, discovered that the mice died. Thereafter, McCollum and Davis[74,75] reported the presence of a substance which they termed "Fat Soluble A" that occurred in butterfat and egg yolk. They were able to demonstrate that this "Fat Soluble A" promoted life in rats fed fat-deficient diets. Then in 1920, Drummond[35] named this important nutrient "vitamin A". Eleven years later, the structure of vitamin A (**1a**) was elucidated by Karrer and Morf[63] by using structural information for β-carotene (**2**)[61,62,73] established several years earlier.

In experiments that followed, many biological and physiological aspects of vitamin A were uncovered. One



β-Carotene (**2**)

important accomplishment by Wald in 1935 linked vitamin A to the vision process.[125,126] He was able to prove that retinal (**1c**), an oxidatized derivative of vitamin A, was vital in the visual pigments of the eye.



1b R = CO_2H

1c R = CHO

In 1946, Aren and van Dorp[1] synthesized retinoic acid (**1b**), a derivative of vitamin A, and illustrated its biological importance in the promotion of growth in rats. Several groups directed considerable effort to the total synthsis of vitamin A (**1a**), but the most important

contributions were made by two commerial groups, namely those at Hoffmann-La Roche and Company Ltd[56] (1947) and at Badische Anilin und Sodafabrik (BASF)[89] (1960). Isler, of the La Roche group, reported the complete synthesis of vitamin A as shown in Figure 1.[56] The first step was the cyclization step involving pseudoionone (**3**) with acid to give β-ionone (**4**). To β-ionone (**4**) was added a one carbon fragment using Darzens glycidic ester condensation which gave the β-C_{14} aldehyde **5**. This aldehyde was in turn treated with cis-3-methyl-2-penten-4-yn-1-ol (**6**) which gave diol **7**; the latter was subjected to partial hydrogenation over Lindlar catalyst affording the diol **8**. Diol **8** was mono acetylated to **9**, which, after dehydration followed by a rearrangment, gave crystalline vitamin A acetate (**1d**). The final step was achieved smoothly by saponifying **1d** to vitamin A (**1a**).

In 1953, Wittig[131] reported an olefination method which was so efficient that in 1979 he was awarded the Nobel Prize in chemistry. This olefination process prompted Pommer of BASF to attempt another synthesis of vitamin A acetate (**1d**) utilizing the newly discovered Wittig reaction[131] (Figure 2). The key material in this process was β-ionone (**4**) as was true in the Hoffmann-La Roche process. Addition of an acetylene to **4** followed by hydrogenation gave vinyl β-ionol (**11**). The desired phosphonium salt **12** was obtained by treating alcohol **11** with triphenylphosphine and hydrochloric acid. The final step proceeded smoothly

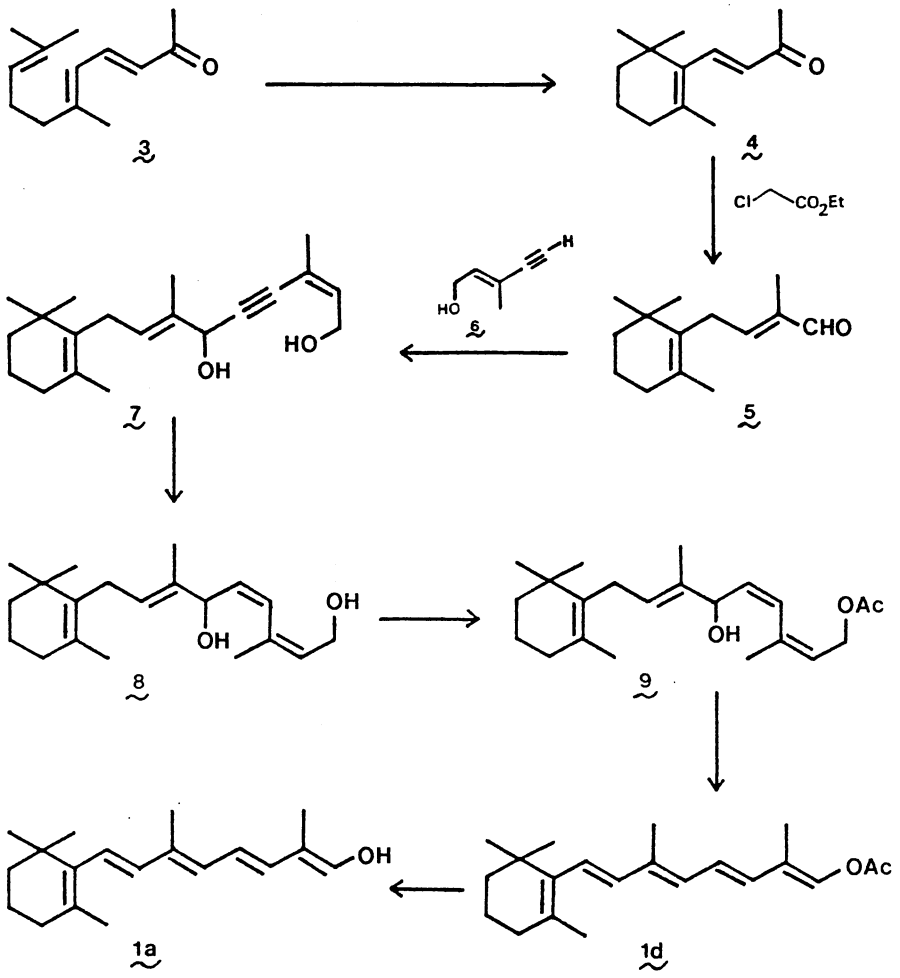


Figure 1. Hoffmann-La Roche Commercial Synthesis of Retinol (**1a**) and Retinyl Acetate (**1d**).

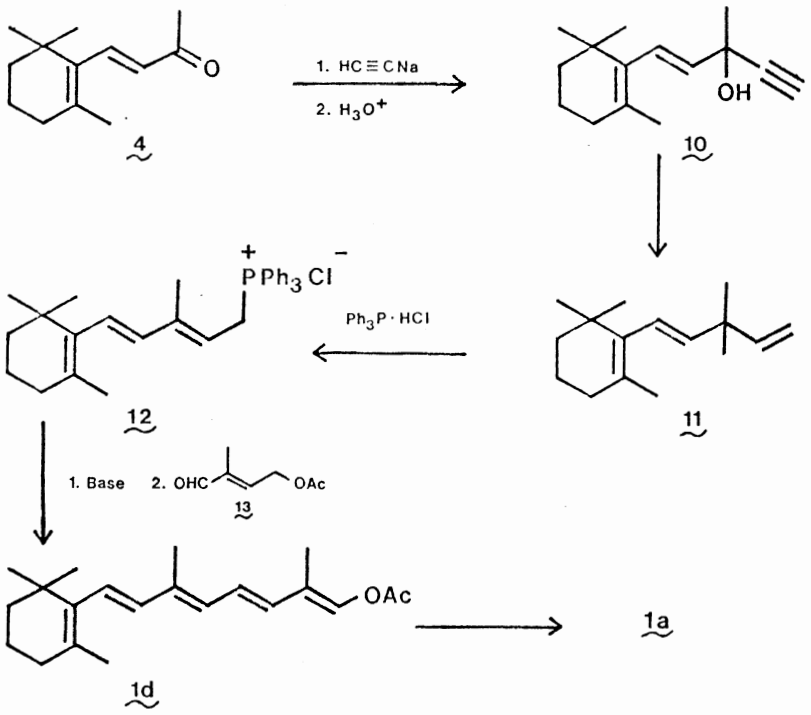


Figure 2. BASF Commerical Synthesis of Vitamin A

through a Wittig type reaction with the anion of **12** and ω-acetoxytiglic aldehyde (**13**) to give vitamin A acetate (**1d**).

The biological interrelationship between certain natural retinoids is shown in Figure 3 and involves retinol (**1a**), retinal (**1c**), and retinoic acid (**1b**). Dietary β-carotene (**2**) was shown by Goodman[45] to be cleaved enzymatically in the intestinal mucosa into two equivalents of retinal (**1c**).

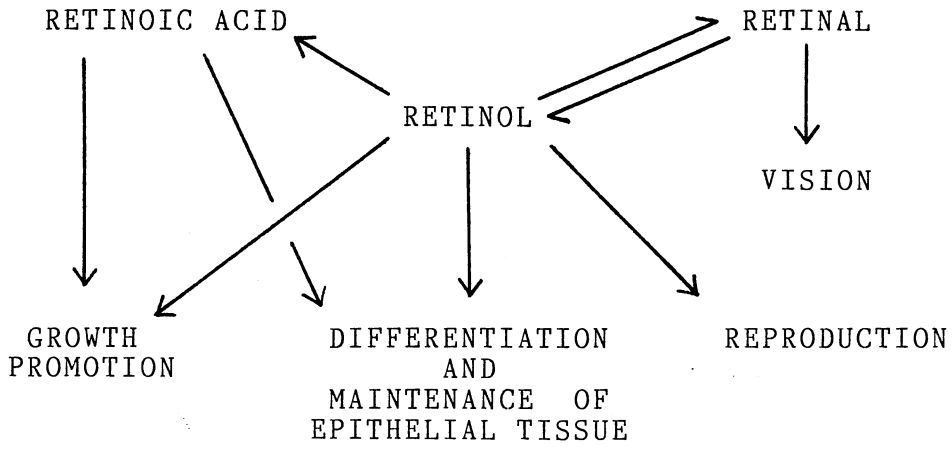


Figure 3. Biological Connection of Vitamin A

Moreover, in the intestinal mucosa retinal (**1c**) was reduced to retinol (**1a**). Retinol (**1a**) was in turn esterified with a long chain fatty acid, usually palmitic acid, and carried in the chylomicrons to the liver for storage.[44]

Retinol (**1a**) is then mobilized from the liver and transported in the plasma while being bound specifically to a transport protein called retinol binding protein (RBP). This protein was first isolated by Goodman[46] and commonly found to be a 1:1 complex with transthyretin (TTR). The primary structures of RBP[93] and TTR[60] are known. TTR is one of the most completely characterized human proteins known, the three-dimensional structure being resolved to 1.8 A in 1978.[11] In contrast, the three-dimensional structure of RBP, however, eluded researchers until recently when the structure was refined to 3.0 A.[80] RBP is defined as containing a β-barrel core as in Figure 4.[80]

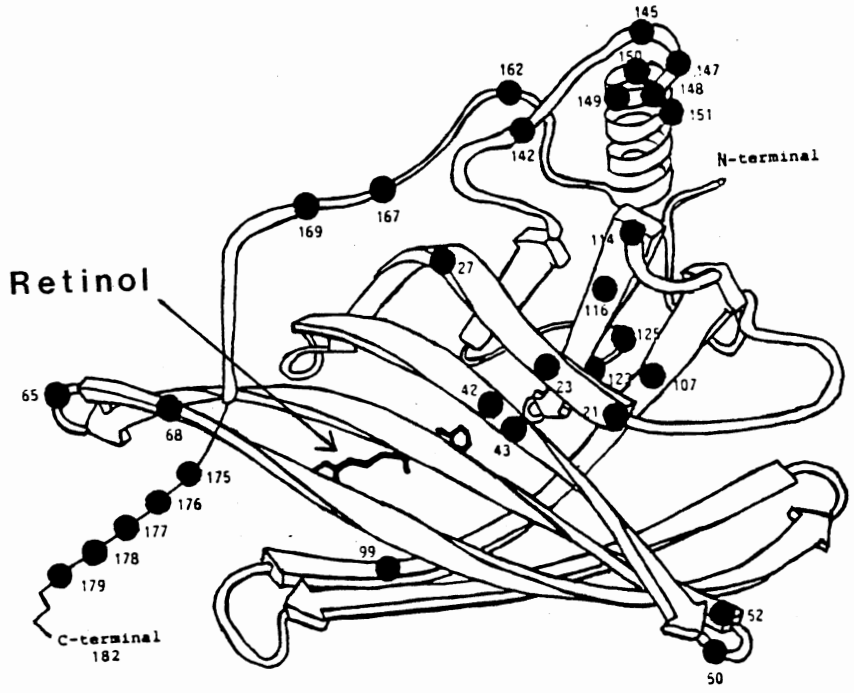


Figure 4. Three Dimensional Structure of RBP[80]

This barrel is open at one end and closed at the opposite end which engulfs the β-ionone ring. The latter eliminates the unfavorable interaction in the polar transporting media.

Retinol (**1a**) is transported in the TTR-RBP complex to peripheral target tissues.[84] The process that governs this mobilization is highly regulated and depends heavily upon RBP synthesis and secretion by the liver. Furthermore,

there is considerable evidence indicating that the translocation of retinol (**1a**) to a cell might also involve recognition of RBP by a specific surface receptor.[54,55,92] Once retinol (**1a**) enters the cell, it complexes with a cellular retinol binding protein (CRBP).[84] This complex is presumed to activate gene expression for cell differentiation and proliferation.[95]

Retinoic acid (**1b**), a biologically active metabolite of retinol (**1a**), is delivered to a cell as a complex with albumin.[108] Once in the cell, **1b** is bound to a new protein known as cellular retinoic acid binding protein (CRABP).[121] In addition to retinol (**1a**) being metabolized by alcohol dehydrogenase at various locations in the body, it is conceivable that metabolism of **1a**, once delievered by RBP to the cell, occurs to give retinoic acid (**1b**) in many target cells.[31] Retinoic acid (**1b**) in a cell can participate in differentiation and growth. It is plausible that a combination of these two processes might be operating independently.

Metabolism of Retinol (1a) and Retinoic Acid (1b)

Since 1931, when the structure of retinol was elucidated, a large number of publications have appeared concerning the metabolism of the natural retinoids.[109,110] Initial investigations were laborious and time-consuming processes which yielded modest results in terms of

resolving the metabolic pathway of retinoids. With the advent of high-pressure liquid chromatography (HPLC) also came quantum leaps in this area affording highly purified retinoids for improved structural diagnosis.

The need to understand the metabolic pathways of retinoids has important ramification regarding active form(s) responsible for the biological activity. In addition, identification of the specific structural sites most vulnerable to biological degradation in a retinoid could afford insight for the medicinal chemist to develop active synthetic analogues.

Metabolism of Retinol (1a)

Retinol (**1a**) has been studied extensively in an effort to determine its physiological mode of action. A portion of one important metabolic pathway was determined early, and revealed the active form in the visionary process as 11-cis-retinaldehyde (**14**).[127] The suggested routes and other metabolites are shown in Figure 5. Metabolites **1b**, **1c**, **1e** and **1f** have been discussed earlier. Surprisingly, an extremely non-polar hydrocarbon was isolated by Bhat in 1979.[10] He reported the identification of anhydoretinol (**15**) as the metabolite of retinol (**1a**) from cultures of spontaneously-transformed, mouse fibroblasts.

Several derivatives are apparently formed intracellularly.[41,8] Retinol (**1a**) can be phosphorylated to retinyl phosphate (**16a**), which in turn is converted to retinyl-

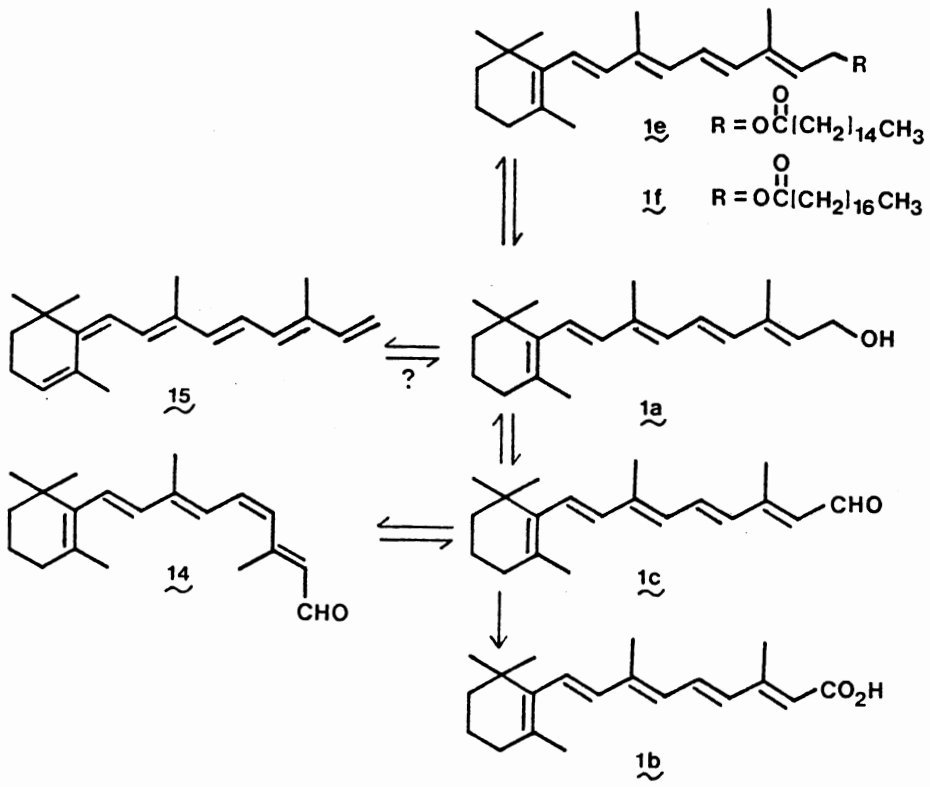


Figure 5. Metabolites of Retinol

mannosyl hydrogen phosphate (**16b**)[41] via the involvment of the cofactor quanosine-5'-diphosphomannose (Figure 6).

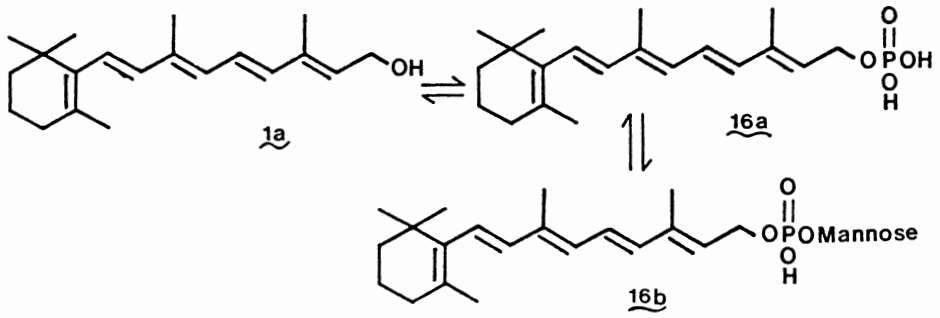


Figure 6. Retinol Metabolites

Metabolism of Retinoic Acid (1b)

Retinoic acid (**1b**) is apparently not reduced biologically to retinol (**1a**) but, **1b** is absorbed unchanged by the blood from the intestine.[39] Moreover, retinoic acid (**1b**) is not stored in appreciable quantities in the body. Kalin[59] determined the distribution of acid (**1b**) in selected mice tissue after a single 10 mg/kg dose. The levels in twelve tissues analyzed reached a maximum between 30 to 120 min and declined after 3 hours. Brain tissue seem to retain retinoic acid (**1b**) longer than the other tissues (i.e. small intestine, liver, lung, fat, kidney heart, spleen, large intestine, muscle, testes, and bladder).

Three metabolites (**17**,**18** and **19**) were observed and identified in the urine of rats given a 27 mg dose of retinoic acid (**1b**) intraperitioneally (Figure 7).[52] All

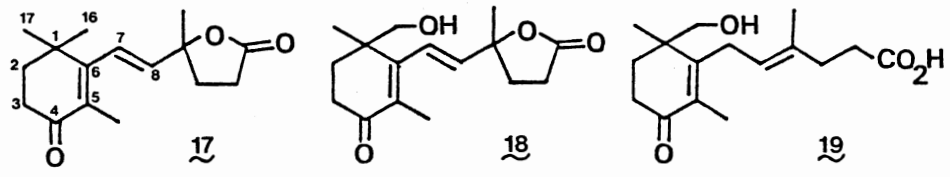


Figure 7. Urinary Metabolites of Retinoic Acid[52]

three of the isolated compounds had a carbonyl group at C(4) and two were lactones with **18** being hydroxylated at C(17). Lactone **17** is apparently a precursor to **18**. The remaining isolated metabolite **19** was a nonconjugated keto acid. Logically, **19** can be lactonized to **18** with concomitant restoration of conjugation.

Rietz[94] reported four other metabolites from rat urine after a pharmacological dose of retinoic acid (**1b**). The metabolites were derivatized with diazomethane to give esters which were characterized (Figure 8). The common

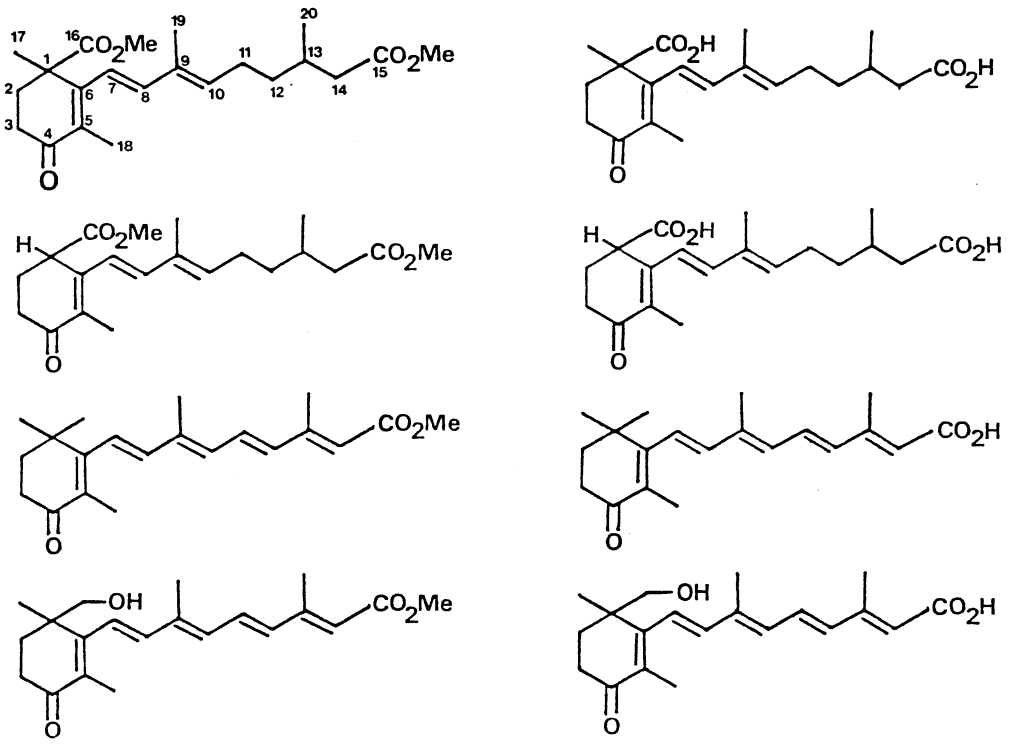


Figure 8.[94] Urinary Metabolites of Retinoic Acid (**1b**) in Rats. (Left) Metabolites After Diazomethane Treatment. (Right) Assumed Structures of Metabolites Before Derivatization.

position metabolized in acid **1b** is C(4) and, to some extent C(16).

An interesting comparison between the studies of Hanni[52] and Rietz[94] is the extent of oxidation of the geminal dimethyls [i.e. at C(16)]. At a pharmacological dose level, the metabolic alcohols experienced additional oxidation to the carboxylic acids with no chain cleavage. With an intraperitioneal dose of 27 mg of **1b** to rats, Hanni[52] observed extensive chain shortening and diminished metabolic oxidation.[52] A plausible conclusion might be that at high levels of retinoic acid (**1b**) the normal pathways are altered to facilitate the excretion of metabolites and **1b** thereby diminishing the latter in the body.

Other metabolites of acid (**1b**) are shown in Figure 9.[110] Several of these natural retinoids have shown biological activity similiar to that of retinoic acid (**1b**).[76,115] One retinoid, namely 13-*cis*-retinoic acid (**1g**), was thought initially to be an artifact of the isolation process. But in 1980, Frolik[40] established that isomerization of acid **1b** to isomeric acid **1g** occurs in the normal metabolic sequence. The importance of this phenomenon was shown in an *in vitro* "liver-metabolizing" system. Using only *all-trans*-retinoic acid (**1b**), the metabolites **20a** and **20b** furnished isomeric 4-oxoretinoic acids **21a** and **21b** whose distribution is concentration dependent. In three tissues studied, at a low initial concentration administered for **1b**, the 13-*cis*-4-oxoretinoic acid (**21b**) was generally the

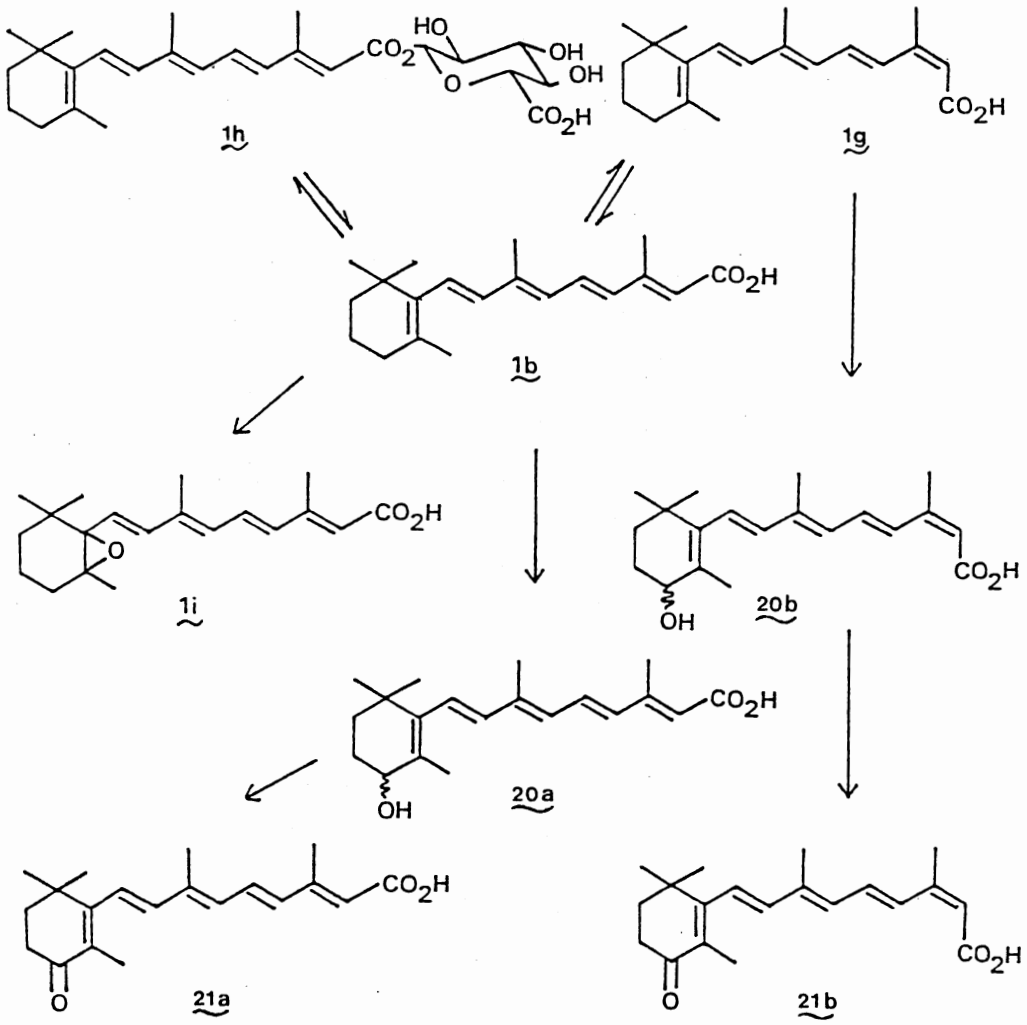


Figure 9. Metabolites of Retinoic Acid (**1b**)[110]

major form while at higher initial concentrations the all-trans-acid **21a** dominated (Table 1). The exact physiological significance of these observation remains unknown. However, since 13-cis-retinoic acid (**1g**) is biologically equivalent to all-trans-retinoic acid (**1b**) in terms of

TABLE 1[40]

CONCENTRAION DEPENDENCE OF ALL TRANS-RETINOIC ACID ON AN IN VITRO CONVERSION TO 4-OXORETINOIC ACID.

Tissue	Initial All-Trans-Retinoic Acid Concentration (M)	Percent of 4-Oxoretinoic Acid	
		13-Cis	Trans
Liver	10^{-7}	27	74
	10^{-8}	59	41
Intestine	10^{-7}	86	14
	10^{-8}	87	13
Testis	10^{-6}	76	24
	10^{-7}	66	34

growth promotion in rats, it is possible, in a manner analogous to the visual process, that isomerization at C(13) is needed for epithelial differentiation.

Another retinoid isolated from metabolism of acid **1b** is retinoyl-β-glucuronide (**1h**). First identified in 1964,[36] ester **1h** was reported to be water soluble and to have biological activity ranging from 30-100% compared to retinoic acid (**1b**) in terms of a growth assay. In the rat vaginal smear assay, retinoyl-β-glucuronide (**1h**) is more active that retinoic acid (**1b**).[115]

In the remaining metabolites from acid **1b**, the common oxidative site is C(4), being oxidized either to a hydroxyl

or to a carbonyl group. Another site attacked is the 5,6 double bond which leads to 5,6-epoxy-5,6-dihydroretinoic acid (**1i**). Preliminary data on epoxide **1i** appeared extremely promising,[76] but it was later determined to possess only 1% of the activity of trans-retinoic acid (**1b**) as evaluated by the tracheal organ culture assay.[81] This assay will be discussed briefly in a later section.

CHAPTER II

RETINOIDS IN CHEMOTHERAPY

Cell differentiation by retinol (**1a**) was first described in 1925 by Wolback.[130] The study revealed that deficiencies of retinol (**1a**) led to changes from normal epithelium to squamous keratinization in mucus membranes.[130] Later, the interrelationship between retinol (**1a**) and cancer was demonstrated by Fujimaki[42] in 1926. He showed that rats fed a vitamin-A deficient diet developed stomach carcinomas. Another study using Syrian golden hamsters linked vitamin A (**1a**) with the inhibition of tracheobronchial tumors.[98] The carcinogen employed was benzo[a]pyrene which was suspended in saline before intratracheal installation. Exposure to such a carcinogen normally produces up to 100% formation of respiratory tract tumors. Of the 46 hamsters treated with vitamin A (**1a**), only two developed detectable tumors.

Another natural retinoid, retinoic acid (**1b**), has been extensively studied.[109,110] Bollag showed that acid **1b** exerted a prophylactic effect on papillomas (originally induced by 7,12-dimethylbenz[a]anthrene) by delaying or diminishing the occurrence of the latter as compared to a control.[12-14] Retinoic acid (**1b**) also accelerated the

healing of wounds in rats.[64,65] These early studies hinted at the overall importance of retinoids in the possible prevention and treatment of certain tissue disorders including cancer. It appeared that the family of natural retinoids might contain significant chemotherapeutic agents to combat the high percentages of deaths from malignancies in the epithelium of patients.[2] Unfortunately, because vitamin A (**1a**) and it esters are stored in the liver, a regulatory process strictly prevents the level of **1a** in the bloodstream from rising proportionally with even massive doses.[84] Moreover, at higher concentrations, natural retinoids become toxic. It is because of this toxicity (known as "hypervitaminosis") that the clinical uses of these natural retinoids are limited. Thus the search for modified retinoids seems a worthy goal. Since the exact mode of action and mechanism of cell differientation is unclear,[104] the question arises as to what structural modifications are likely required to give less toxic retinoids with improved efficacy.

In the search for retinoids with enhanced activity and low toxicity, metabolic pathways and structure-activity relationships of known anticancer agents can serve as guidelines. One might consider three regions in retinol (**1a**) for modification: 1) the trimethylcyclohexenyl or hydrocarbon ring, 2) the polyene or hydrocarbon side chain and 3) the polar terminal group (Figure 10). These regions might be altered in order to accomplish these goals. The

first is to increase the hydrophilicity and overall polarity of the synthetic retinoid. Since both the all-trans-acid **1b** and 13-cis-acid **1g** show acitivity higher than most retinoids in many assays, it is likely that the

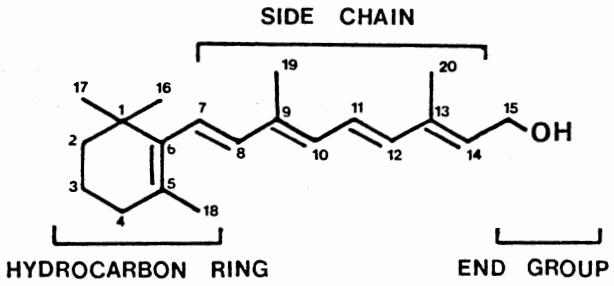
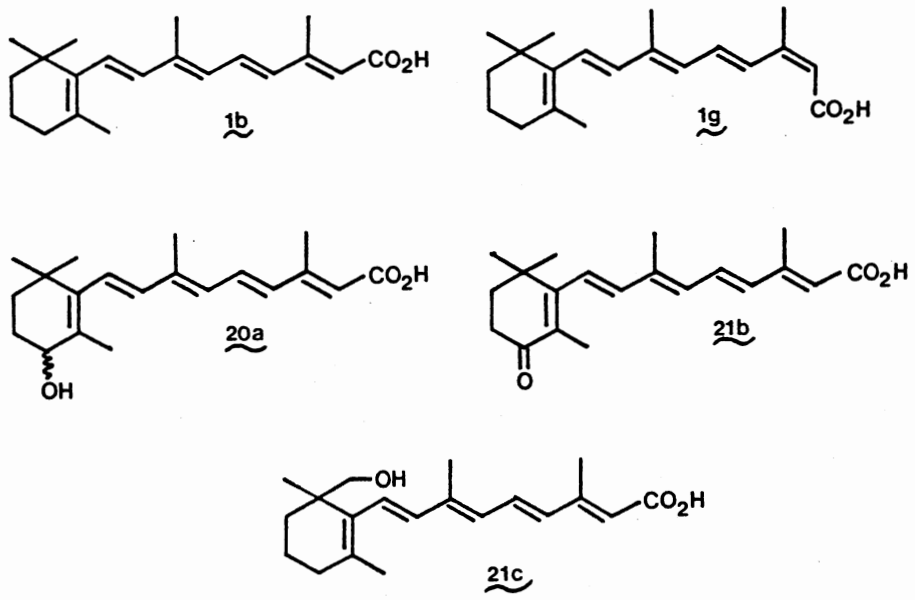


Figure 10. Regions of Structural Modification in Retinol

overall polarity of modified retinoids should be greater than retinoic acid (**1b**) while retaining the same overall geometry and size.

The second objective for structural change is to vary the metabolic oxidative pathway. The oxidation of retinoic acid (**1b**) is known to occur at C(4) to give either the hydroxyl system **20a** or the carbonyl-containing system **21a** (see also Figure 9).[52,94,110] In addition, epoxidation of C(5)-C(6) to give **1i** and hydroxylation of C(16) to give **20c** are known.[52,76] Modifying these positions could allow the modified retinoid to proceed through a different metabolic pathway which might enhance the activity due to higher



concentrations at the target site, for instance, from improved distribution.

Finally, the structure of new retinoids might be changed to block the potential oxidation sites. For instance, if the postion of normal metabolism in acid **1b** is blocked by the presence of a group resistant to oxidation, the usual metabolic path for a retinoid might also be disrupted. This alteration from normal oxidative metabolism could lead to improved effectiveness of the drug.

Assay of Retinoids-The Biological Method

In order to assess the usefulness of a test retinoid, a variety of assays have been developed. Two forms of testing activity of retinoids are available, the in vivo and in vitro methods. Since these analyses vary in accuracy, speed and cost, a full evaluation of new retinoid

analogues require at least two separate assays. Some are described below.[112]

In Vivo Methods

The in vivo methods are extremely important for measuring the biological activity of new retinoids. Results from such an assay can reveal potential use of a test retinoid in chemotherapy. Two common screens are the mouse papilloma assay[14,73] and the ornithine decarboxylase (ODC) assay.[122,123] However, a third but less popular method, is the rat vaginal smear assay.[25,106,115] Each of these tests require only small amounts of retinoid which allows for rapid screening of new synthetic systems.

The mouse papilloma assay is based on a two-stage process involving the dorsal skin with specific initiation and promotion to a carcinogenic state.[32] The test entails use of the initiator 7,12-dimethylbenz[a]anthracene (DMBA) which is applied to the shaven backs of mice twice at 2 week intervals. The promoter croton oil is applied three weeks later and twice a week for 3-8 months which promotes generation of multiple papillomas averaging 3 mm in diameter.[14,73] Treatment with a test retinoid then begins, and, after two weeks, the papillomas are remeasured and the ED_{50} is determined. The ED_{50} is the effective dose required to cause a 50% regression of the papillomas. Some of the important results are shown in Tables II and III.

TABLE II

THE BIOLOGICAL EVALUATION OF RETINOIDS USING THE IN VIVO MOUSE PAPILLOMA ASSAY

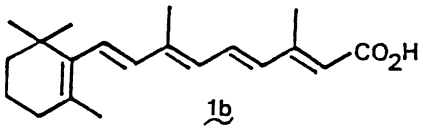
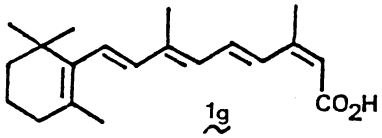
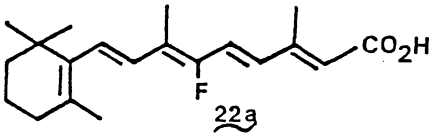
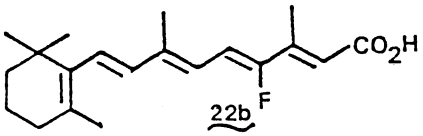
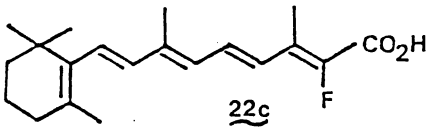
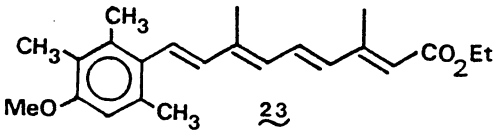
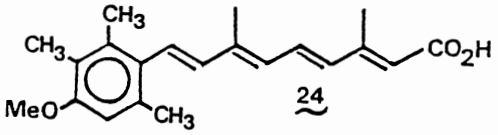
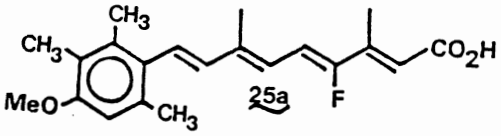
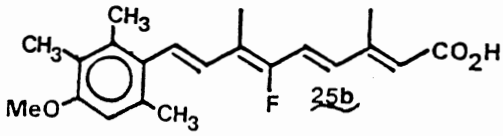
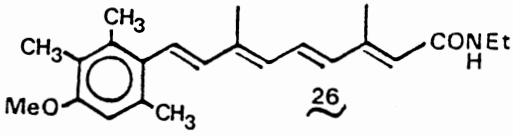
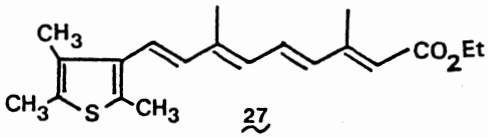
Retinoid	Antipapilloma Activity ED_{50} (mg/kg)/day	Hyper-vitaminosis (mg/kg)/Day	Ref.
 1b	400	80	73
 1g	800	400	84
 22a	<80	200	83
 22b	24.3	100	83
 22c	>20	100	83
 23	25	50	73

TABLE III

THE BIOLOGICAL EVALUATION OF RETINOIDS USING THE IN VIVO MOUSE PAPILLOMA ASSAY

Retinoid	Antipapilloma Activity ED_{50} (mg/kg)/day	Hyper-vitaminosis (mg/kg)/Day	Ref.
 24	12.5 50.0	100 100	83 73
 25a	2.7	25	83
 25b	7.1	50	83
 26	19.2 50	50 100	83 73
 27	75	200	84

One obvious weakness with this assay is the long time required for results. Moreover, the therapeutic efficacy

of 13-cis-retinoic acid (**1g**) is not revealed in this assay as seen in Table II. Acid **1g** has been shown in other assays to be quite active.[8,26,27,81,108] Thus employing two assays for each new retinoid seems crucial to ascertain the level of activity of a potential viable candidate.

A method derived from the mouse papillomas assay is the ornithine decarboxylase assay (ODC) as cited previously.[109] The major advantage of the latter assay is the short time needed to evaluate a retinoid. Verma and Boutwell[122,123] demonstrated that TPA (Figure 11) is an intense promoter of the enzyme ornithine decarboxylase but retinoids were able to inhibit the action of this enzyme. The results of this assay correlate well with the inhibition of papilloma development in the long term experiments with mice.[122,124]

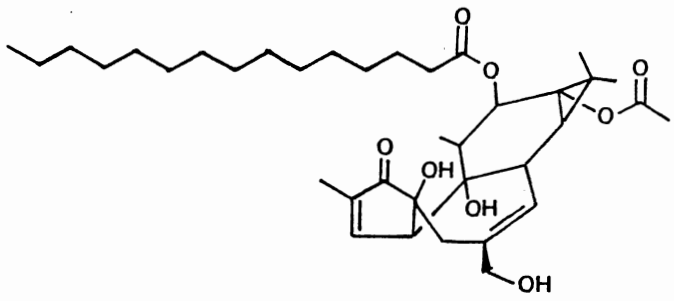


Figure 11. Structure of 12-O-Tetradecanoylphorbol-13-Acetate (TPA)

The procedure used in the quick ODC assay is as follows. To a mouse pretreated with DMBA is applied a test retinoid

at a desired concentration 1 hour before application of 17 nmols of TPA. After 4.5 hours, the mouse is sacrificed and the epidermis is separated and homogenized. The release of labeled CO_2 from [^{14}C]ornithine is determined from homogenized solution. Results for new retinoids are compared to a control and the percent inhibition is determined. Several retinoids are shown in Table IV using the ODC assay.

TABLE IV

ACTIVITY OF RETINOIDS IN THE ORNITHINE DECARBOXYLASE ASSAY

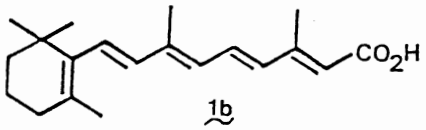
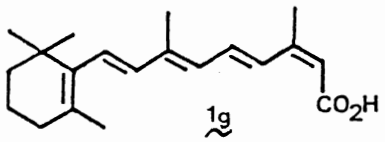
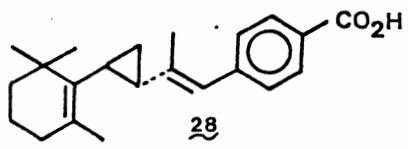
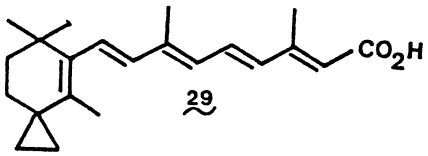
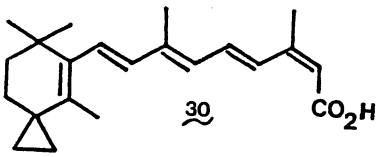
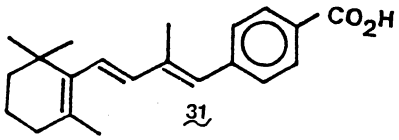
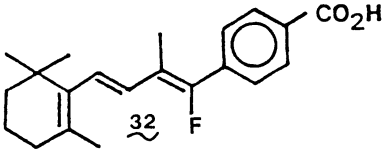
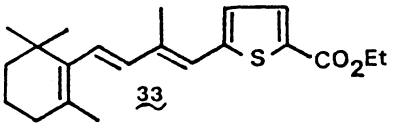
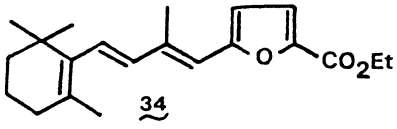
Retinoid	Dose (nmol)	% Inhibition of control	Ref.
 1b	1.7	88 ± 1	29
	1.7	92 ± 2	27
	1.7	92 ± 2	26
 1g	17.0	96 ± 1	27
	1.7	96 ± 1	26
 28	17.0	80 ± 1	29
	1.7	77 ± 0	29

TABLE V

ACTIVITY OF RETINOIDS IN THE ORNITHINE DECARBOXYLASE ASSAY

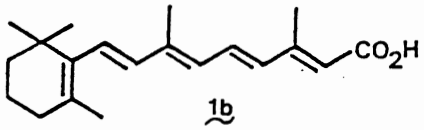
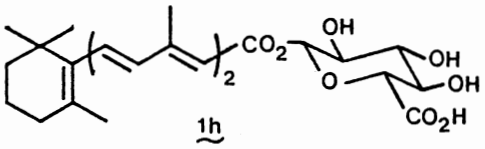
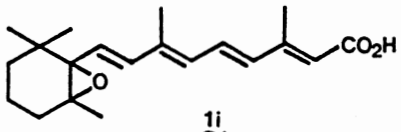
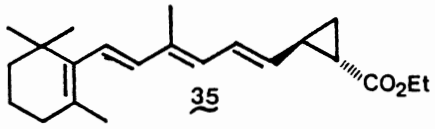
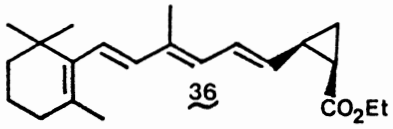
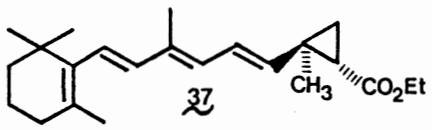
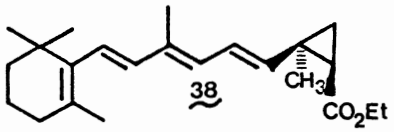
Retinoid	Dose (nmol)	% Inhibition of Control	Ref.
 29	17.0	72 ± 2	27
 30	17.0	67 ± 2	27
 31	17.0	80	28
 32	17.0	82 ± 2	26
 33	17.0 1.7	77 67	28 28
 34	17.0 1.7	9 9	28 28

The final *in vivo* assay discussed herein is the rat vaginal smear assay.[25,106,115] Developed in 1932 by Baumann and Steenbock [7] to determine the presence of retinol (**1a**), the method has become somewhat obsolete with the advent of modern quantitative analytical techniques. However, in 1982, DeLuca[106] was able to increase the sensitivity that had plagued this assay and thereby revived interest in the method for testing new retinoids.

This assay measures the changes in the sensitive vaginal epithelium. Rats used in the assay are vitamin A-deficient and ovariectomized, the latter being done to alleviate the interference from hormonal cycling.[90] The test retinoid is applied topically to the cornified vaginal epithelium and the response is monitored.[106] The response is determined from the vaginal smear by scoring the cells in terms of the *presence* or *absence* of three basic cell types. These types are non cornified epithelial cells, cornified epithelial cells and leukocytes. The scores are plotted against concentrations of retinoid used and the ED_{50} values are determined as the dose observed to give a 50% reversal in cornification[106] (Table VI). Attention should be directed to retinoid **1h**, which is one of the few natural retinoids that posesses biological activity greater than retinoic acid (**1b**). The biological activity of ester **1h** is believed to be the result of the enhanced polarity of the terminal group increasing the concentration of the retinoid at the site of action.[106]

TABLE VI

ACTIVITY OF RETINOIDS IN THE RAT
VAGINAL SMEAR ASSAY

Retinoid	ED_{50} (mol/vagina)	Ref.
 1b	1×10^{-10}	25,106
 1h	8×10^{-10}	106
 1i	2×10^{-10}	106
 35	1.3×10^{-8}	25
 36	2.3×10^{-8}	25
 37	ND (a)	25
 38	ND (a)	25

[a] Not determined, inactive at doses up to 10^{-7} mol/vagina.

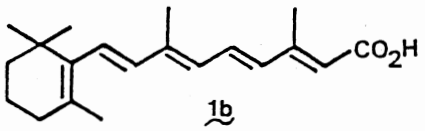
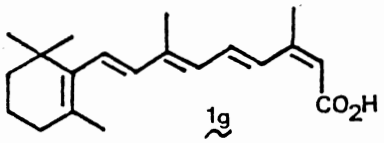
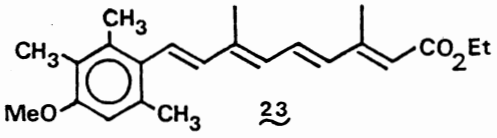
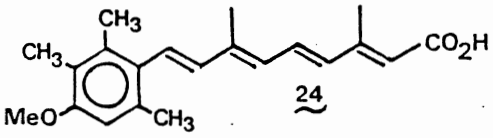
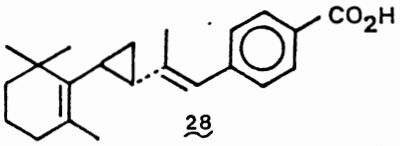
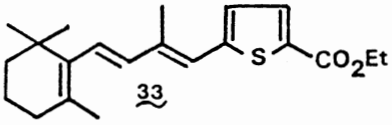
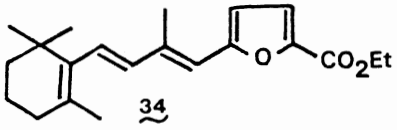
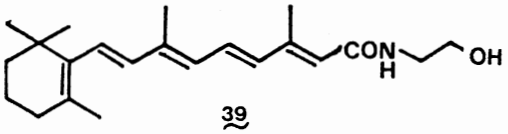
In Vitro Methods

The *in vitro* methods are extremely valuable for screening large numbers of compounds and, unlike *in vivo* methods, exact biological end points are available.[111] The two increasingly important assays are the hamster tracheal organ culture (TOC) assay,[28,29,81,99] and the assay involving the human promyelocytic leukemia cell line (HL-60).[8,108,119] The TOC assay measures the aptitude of retinoids to maintain epithelial cell differentiation in tracheas of hamsters fed a vitamin-A deficient diet.[81] A retinoid is considered *active* if neither keratin or kertohyaline granules are observed and *inactive* if both keratin and keratohyaline are present.[81] Dose response curves are then tabulated to determine the ED_{50} (suppression of keratinization in 50 percent of the cultures). In 1980, Sporn and coworkers reported a collaborative body of data on 87 retinoids from eleven sources around the world.[81] Shown in Table VII are results of important retinoids from Sporn[81] and others more recently published.[28,29,99]

Another *in vitro* method is the use of the human leukemia-60 cell line (HL-60). This cell line, derived from a patient with acute promyelocytic leukemia, is an excellent system for the determination of the activity of a retinoid.[8] Leukemia is believed to prevent normal differentiation and therefore retinoids active in this

TABLE VII

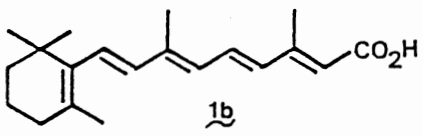
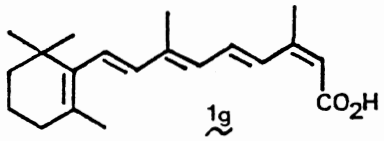
ACITIVITY OF RETINOIDS DETERMINED BY HAMSTER TRACHEAL ORGAN CULTURE

Retinoid	ED_{50} (M)	Ref
 1b	1×10^{-11} 3×10^{-11}	29 81
 1g	3×10^{-11}	81
 23	1×10^{-7} In active in 12/13 cultures	81
 24	5×10^{-9}	81
 28	3×10^{-10}	29
 33	1×10^{-10}	28,99
 34	4×10^{-8}	99
 39	1×10^{-10}	81

assay are good candidates for further study. The procedure for this method involves treatment of HL-60 cells with a test retinoid and nitroblue tetrazolium (NBT), a water-soluble dye, followed by incubation for 4 to 5 days. The differentiated cells produce a superoxide anion reducing NBT to an insoluble dark formazan. Therefore, the percentage of the differentiated cells are easily determined visually. Results are measured by calculating the percent of NBT redution which is directly related to differentiation.[4] The ED_{50} is determined in a similar manner as in the TOC assay. The results with all trans-**1b** and 13-cis-**1g** acids are available in Table VIII.

TABLE VIII

BIOLOGICAL ACTIVITY OF **1b** AND **1g** ACIDS IN THE HL-60 CELL LINE

Retinoid	ED_{50} (M)	Ref
 **1b**	1×10^{-8} 1×10^{-7}	8 108,119
 **1g**	1×10^{-8} 1×10^{-7}	8 108

Arotinoids And Heteroarotinoids. A New Generation of Active Retinoids

Although a large number of modified retinoids have been synthesized and screened for biological activity, only a few have shown promise in pharmacological application. Two basic requirements (discussed earlier) for a retinoid to be potentially useful are activity similiar to retinoic acid (**1b**) and diminished toxicity.

A significant achievement to satisfy the first requirement concerning activity appeared in 1980.[68] Loeliger reported a new class of active retinoids he labeled as "arotinoids". These arotinoids had one common structural feature in that an aromatic ring was fused to the cyclohexyl system and the C(4) position substituted with two methyl groups (Figure 12). These structural modifications block several metabolic sites known to exist for <u>trans</u>-retinoic acid (**1b**).

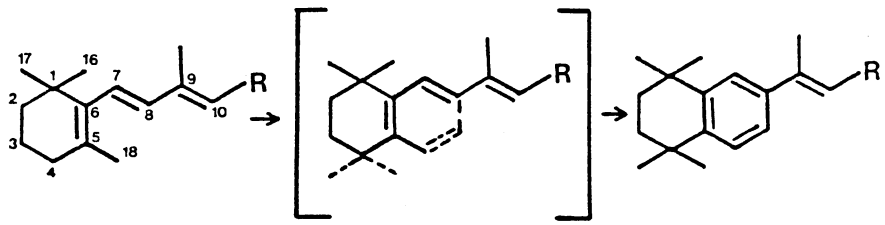


Figure 12. The Conceptual Development in the Conversion of Retinoids to Arotinoids, Blocking the Major Metabolic Postions: C(4) and the C(5)-C(6) Double bond.

The synthesis of these compounds proceeded through two efficient steps, the first being the formation of the appropriate phosphonium bromide as shown below. The second major step was achieved by a Wittig type reation as shown in Figure 13.

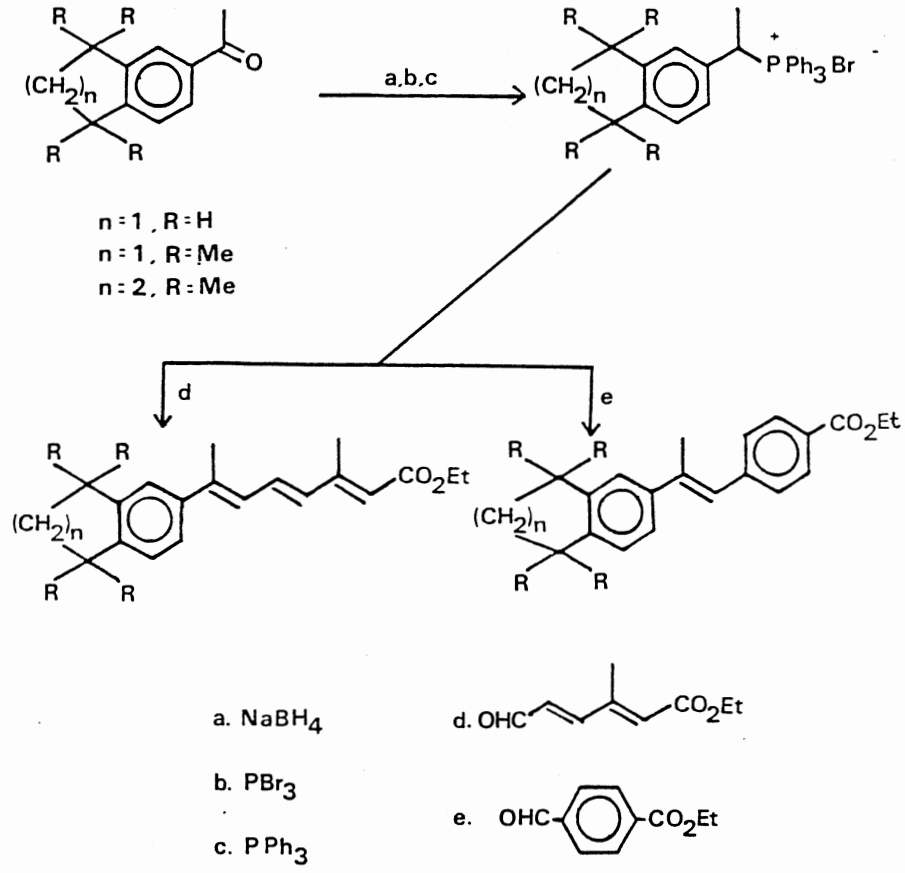
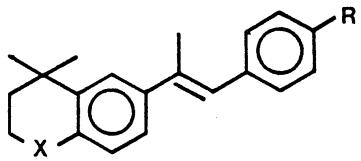


Figure 13. The General Synthetic Route to Arotinoids

Several arotinoids have proven to be extremely active in the mouse papillomas,[68] the TOC,[29,81] the ODC[29] and HL-

60 assays.[119] However, the toxicity of these compounds appears to be severe. Thus these synthetic retinoids showed promise in terms of high activity but the toxicity is above an acceptable level.

A new alteration has been the incorporation of a heteroatom at C(4) to replace the geminal dimethyl group while maintaining the fused aromatic ring (Figure 14). These new retinoids were termed as "heteroarotinoids". The synthesis and biological activities of these new compounds



X = O, S, S→O

Figure 14. General Structure of Heteroarotinoids.

were reported by two groups independently, namely by Berlin[128] and Dawson.[29] These heteroarotinoids appear from preliminary data to have met the two basic requirements described earlier, namely high activity and low toxicity, although the latter is based upon only qualitative observations.

The syntheses of these compounds was accomplished by two separate methods independently. Dawson's synthesis is shown in Figure 15[29] while Berlin's synthetic scheme[128] will be briefly discussed later. The biological data for these compounds are shown in Table IX along with trans-retinoic acid (**1b**) and 13-cis-retinoic acid (**1g**) as the standards for comparison.

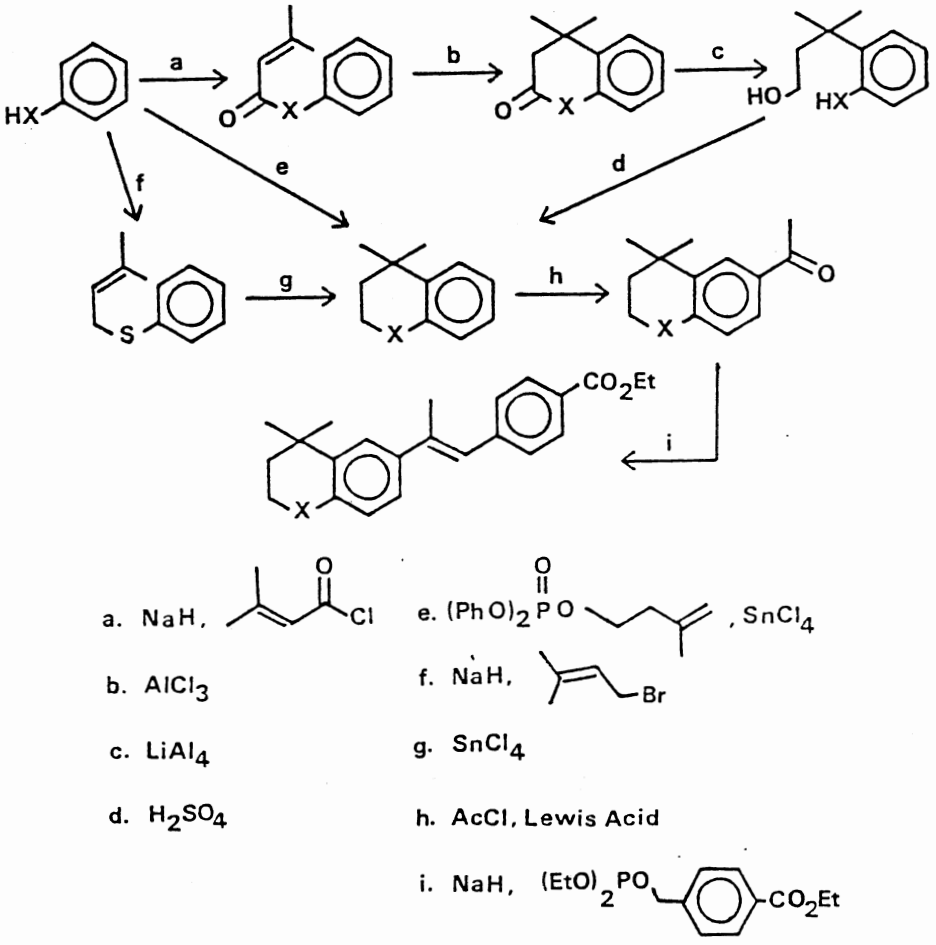


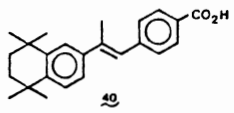
Figure 15.[29] Dawson's Synthesis of the Oxa and Thia-Substituted Heteroarotinoids

TABLE IX

THE BIOLOGICAL ACTIVITY OF SELECTED AROTINOIDS AND HETEROARETINOIDS VIA TOC, ODC AND HL-60 ASSAYS.

Retinoid	TOC ED_{50} (ref.)	ODC % INHIBIT. OF CONTROL (ref.) (1.7 nmol dose)	HL-60 (M) (Ref.)
1b	1×10^{-11} (29)	88 ± 1 (29)	1×10^{-7} (119)
1h	3×10^{-11} (81)	92 (a) 89 (a)	
40	1×10^{-12} (29)	89 ± 1 (29)	3×10^{-7} (119)
41	3×10^{-12} (29)	56 ± 1 (29)	c
42	6×10^{-11} (128)	c	c
43	5×10^{-11} (29)	68 ± 4 (29)	c
44	1×10^{-10} (128)	43[b]	>3×10^{-6} (a)[b]
45	6×10^{-10} (128)	42 ± 6 (29)	>3×10^{-6} (a)
45	2×10^{-10} (29)	c	c
46	1×10^{-10} (128)	c	c

a Unpublished results, Berlin et. al.
b Methyl ester tested
c Not tested



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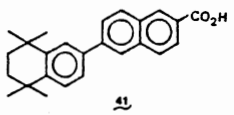

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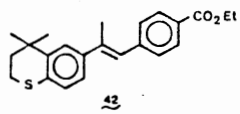

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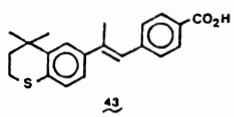

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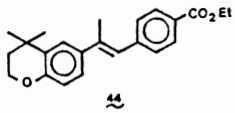

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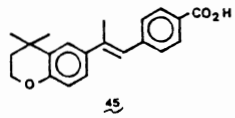

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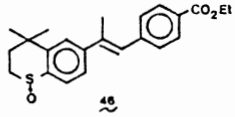


46

The major difference in the activity of the heteroarotinoids is the dramatic results in the preliminary toxicity screening with Swiss mice (Table X). The non-

TABLE X

TOXICITY OF RETINOIC ACID AND SELECTED AROTINOIDS AND HETEROAROTINOIDS IN SWISS MICE.

Retinoid	Dose umol/kg day	% Survivors Day 8	% Survivors Day 15	Mortality Range, Days
Control	0	100	100	
Retinoic Acid (**1b**)	600	95	0	7-13
	300	100	0	10-14
	200	100	63	14-15
	100	100	100	
	67	100	100	
40	30	50	0	6-8
	10	87	0	7-10
	3.3	97	0	7-11
	1.0	100	30	10-15
41	100	100	0	8
	30	100	0	9-12
	10	100	68	10-15
	3.3	100	100	
43	600	100	0	9-10
	300	100	80	14-15
	100	100	100	
	30	100	100	
45	600	70	0	7-10
	300	100	50	12-15
	200	100	90	14
	100	100	100	
	30	100	100	

heterocyclic arotinoid **40** is extremely toxic even at 1.0 umol/kg day which gave a mortality range of 10-15 days.[29] In contrast, with heteroarotinoid **43** (at 300 umol/kg day) the mortality range was 14-15 days. Obviously, if one considers life extension only, **43** is better than **40**. This initial toxicity indicated that arotinoid **40** is greater 300 times more toxic than **43**. A useful comparison is between **43** and trans-retinoic acid (**1b**). The data in Table IX indicates retinoic acid (**1b**) is slightly greater in toxicity than **43**. At a common dose of 300 umol/kg day for both retinoic acid (**1b**) and for **43**, there were no survivors from the experiment with retinoic acid **1b** at the end of two weeks. However, 80% of the animals survived after treatment with heteroarotinoid **43**.[29] The structures of arotinoid **40** and **41** and heteroarotinoids **42** and **46** are shown in Figure 16.

The relationship of retinoids to cancer[109,110] and to epidermal[109,110] disorders is well documented. However, only two retinoids are used in the United States for the treatment of dermatogical conditions but not for cancer. Accutane®, the trade name for 13-cis-retinoic acid (**1g**), is the only retinoid approved for oral use. The other is Tretinoin® [all trans-retinoic acid (**1b**)], but due to its inherent toxicity the use has been accepted for only topical treatment as an ointment. In Europe, Tigason®, a synthetic retinoid, has received considerable attention for treatment of a large number of previously very resistant

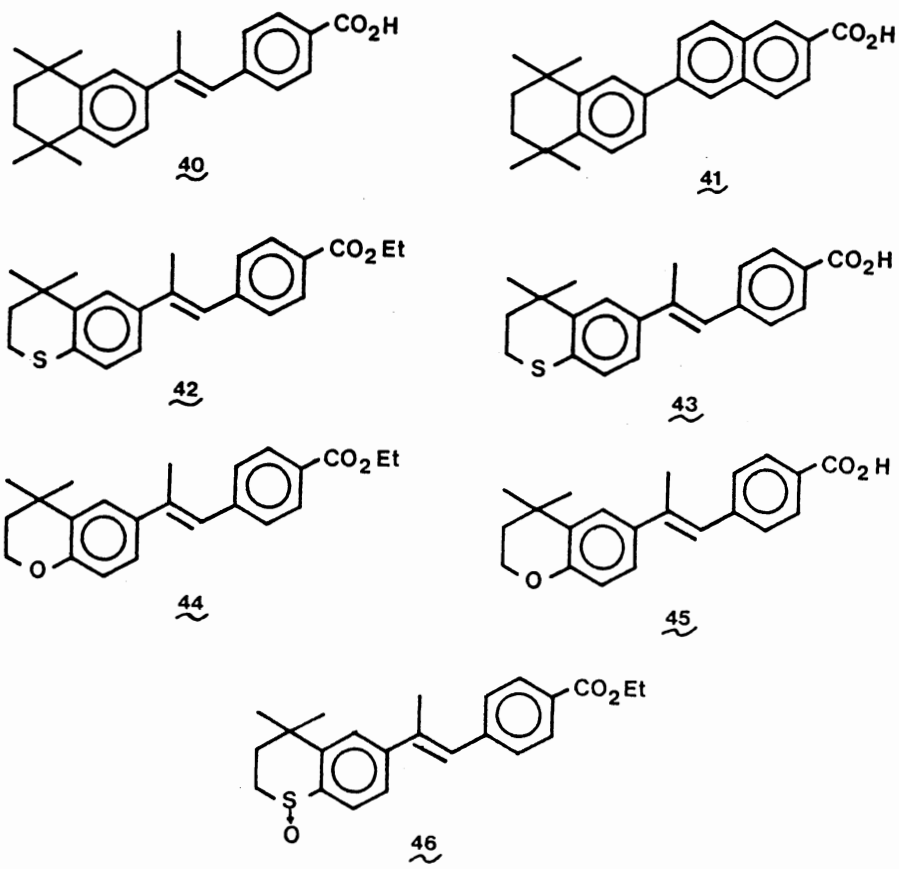


Figure 16. Structures of Reported Arotinoids and Heteroarotinoids

skin disorders.[17] The appropriate structures are shown in Figure 17.

Retinoids used today for the treatment of skin abnormalities have been know for many years. These compounds have been tested by the guidelines set down by the FDA for drug approval in the clinics. Due to the constraints placed on the new retinoids, the usefulness of these compounds is limited for current cancer patients. For

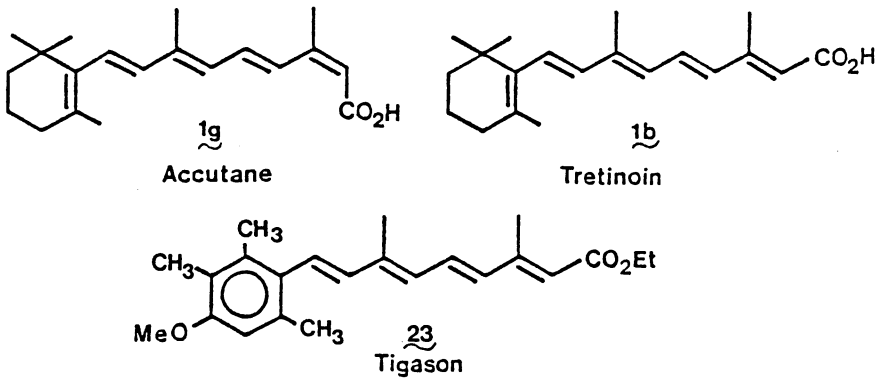
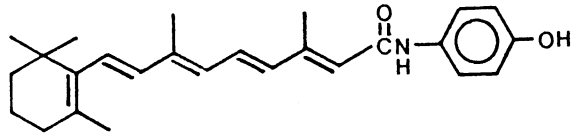


Figure 17. Retinoids used Clinically.

instance, the efficacy of N-(4-hydroxyphenyl)retinamide (**47**) was first reported in 1979 by Moon.[79] This retinoid



N-(4-Hydroxyphenyl)retinamide (**47**)

has been cited as being useful towards dermatogical conditions, bladder papillomas and in women in a high risk class for developing premenopausal breast cancer or fibrocystic disease of the breast.[82] It wasn't, however, until late in 1984 that N-(4-hydroxyphenyl)retinamide (**47**)

started its clinical trials. Therefore, new retinoids that show promise today in preliminary biological screens might, at the earliest, get approval late in this decade or in the early 1990s.

CHAPTER III

RESULTS AND DISCUSSION

Several heteroarotinoids reported by Berlin[128] and Dawson[29] have shown preliminary activity for possible uses in pharmacology. It appears that the sulfur analogues **42** (ester) and **43** (acid) are the most promising due to the diminished toxicity of acid **42** in Swiss mice[29] as compared to several arotinoids and retinoic acid (**1b**). We report herein the syntheses and partial activity of fourteen new heteroarotinoids in which all but two contain a sulfur heteroatom in the ring system. The structures (48-50) are shown in Figure 18 and 19.

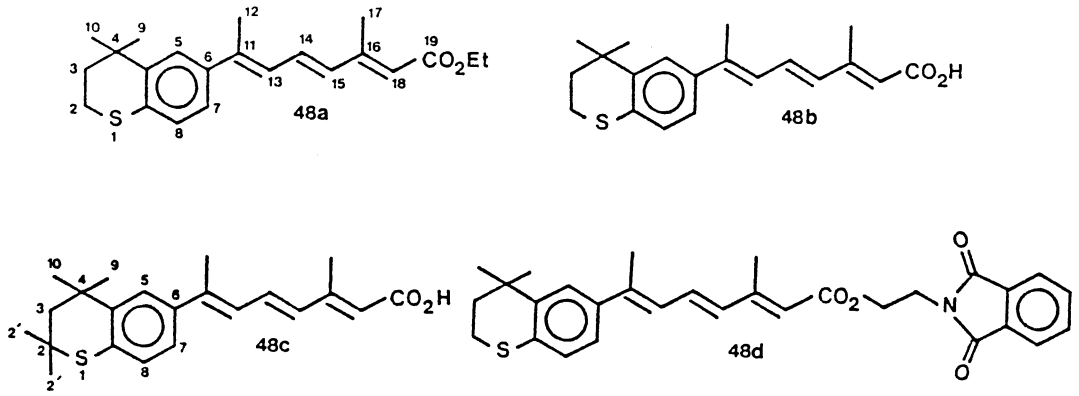


Figure 18. Structures of New Heteroarotinoids.

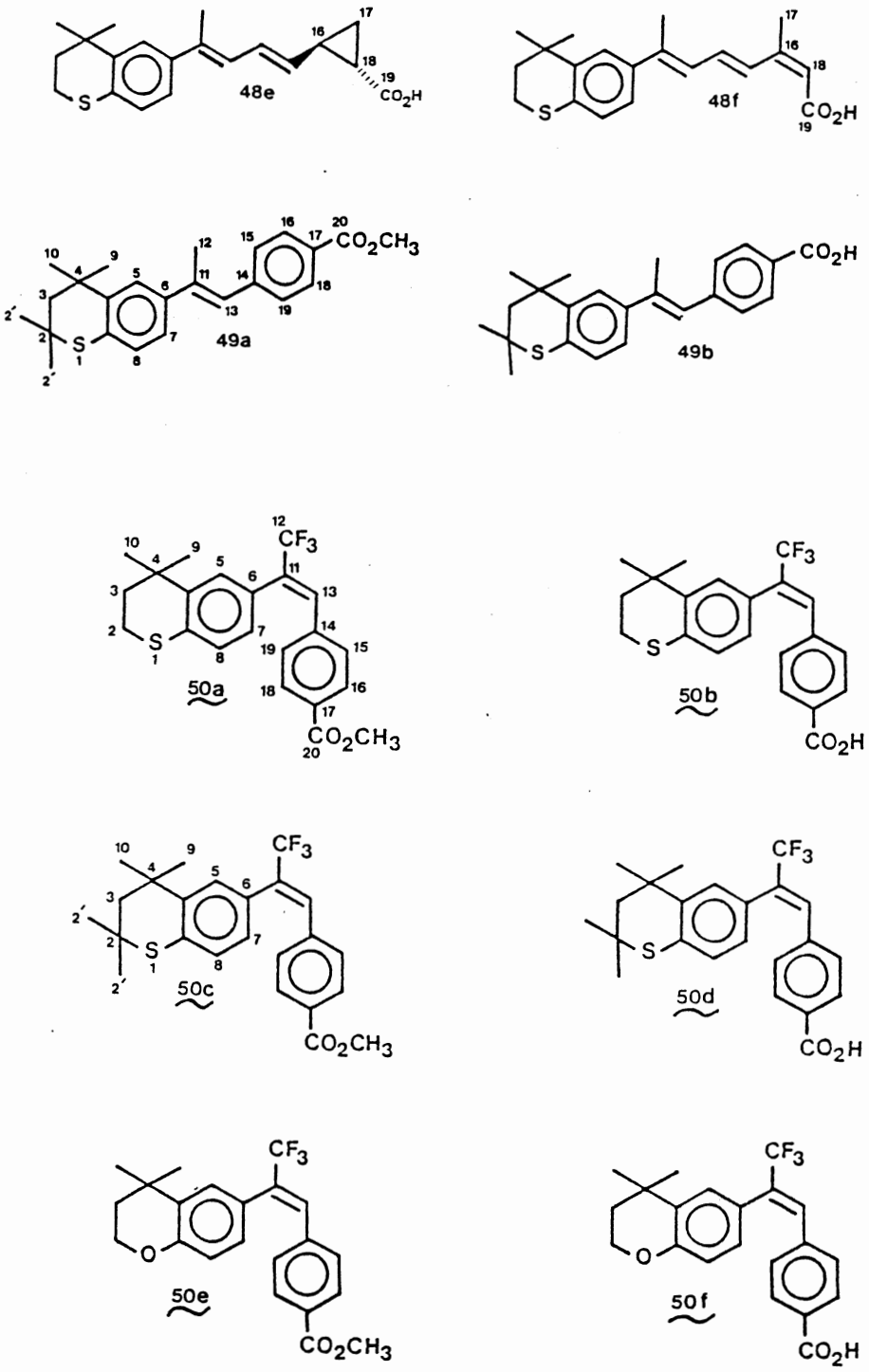
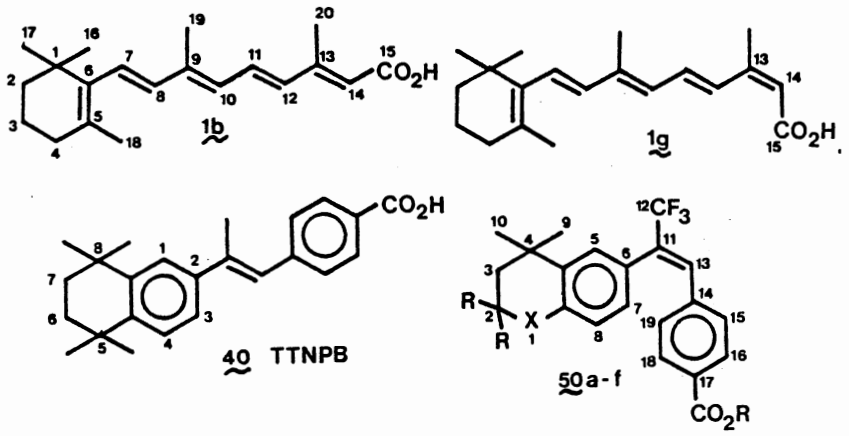


Figure 19. Structures of New Heteroarotinoids

The objectives of this work have been to develop methodology to make very specific alterations in the structures of compounds which could be labeled "hetero-arotinoids". As a first step, we have been able to insert a heteroatom at the 4-position along with the incorporation of an aryl ring fused to the cyclohexyl system as shown in members **48a-f.** This type of molecule retains the side chain as in retinoic acid (**1b**) except for that portion incorporated into the aryl ring. Thus, heterocycles **48-49** allow an assessment of activity in terms of a relationship to block the 4-position which could alter metabolism at that site as well as prevent epoxidation by the presence of the aryl ring. As will be recalled, epoxidation occurs at C(5)-C(6) in retinoic acid (**1b**).

A second group of molecules selected for synthesis involved replacement of part of the side chain with a benzene ring and replacement of the three protons by three fluorine atoms at C(12) as shown in **50a-f.** The presence of a benzene ring in the side chain results in a cisoid arrangement in that portion of the chain. This cisoid arrangement in the side chain has produced useful activity as in 13-<u>cis</u>-retinoic acid (**1g**).[8,26,27,81,108] Thus, the presence of the aryl ring in the side chain of **49a-b** and **50a-f** is reminiscent of that in **28**,[29] **31-34**,[26,28] and **42-46**.[29,128] Fluorine atoms at C(12) certainly will alter the electron density in the double bond at C(11)-C(13) without



making a significant change in the overall geometry at C(12). In view of the known activity of **42-46**, it should now be possible to compare the real effect of the presence of the fluorine atoms in the specific assays.

The third and final change was effected by incorporating a gem dimethyl group at C(2) [this is at C(3) in retinoic acid (**1b**) while the heteroatom occupies the 4-position of retinoic acid (**1b**) in <u>all</u> of these systems] which should also influence the metabolism at that positon and of the heteroatom. Essentially, this later modification simply moves the gem dimethyl group one position from that in (<u>E</u>)-[tetrahydrotetramethyl-2-napthalenyl-1-propenyl]-benzoic acid [TTNPB, (**40**)] followed by adding the heteroatom at the 4-position. The compounds described are **48c**, **49a**, **49b**, **50c** and **50d**. Moreover, it has been possible to insert fluorine atoms at the C(12)-position in an effort to evaluate a second variable within the structure (in terms of effect on

activity) since the proton counterparts were already known.

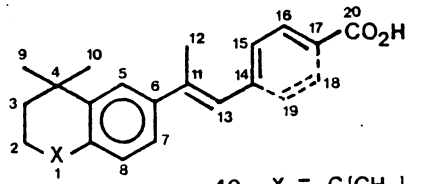
Although we have been successful in the sythnetic strategies which we shall delineate herein, the biological testing data has not been completed. Dr. A. Verma has several of the compounds under examination for activity in the ornithine decarboxylase (ODC) assay[122,123] at the University of Wisconsin, Clinical Cancer Center in Madison, Wisconsin. Dr. T. Breitman, of the National Cancer Institute in Bethesda, Maryland, has several members under investigation in terms of evaluation for these hetero-arotinoids to influence cell differentiation in the HL-60 cell line. The latter is a cell system derived from a patient with acute promyelocytic leukemia.[8]

Synthesis of the New Heteroarotinoids

The fourteen new heteroarotinoids reported herein can be categorized into two groups. One group (**48a-f**) has a triene side chain similar to natural retinoids and the remaining compounds (**49a-b, 50a-f**) have incorporated an aryl moiety to give a locked cisoid rotameric conformation at C(15)-C(16). The aryl group inherently prevents free rotation around C(15)-C(16), fixing the conformation in a cis geometry. This geometry is believed to be partially responsible for biological activity in similar sytems such as acids **40** or **43** (Figure 20).[30]

Analogues **48a-f** were designed to evaluate the activity of heteroarotinoids with the same general side-chain length

as that of retinoic acid (**1b**). The synthesis of these compounds originated from either ketone **51a** or **51b**, the synthesis of which is shown in Figure 21.



40 X = $C(CH_3)_2$

43 X = S

Figure 20. Locked Cisoid Conformation of Acids **40** and **43**

In one of the earliest publications on heteroarotinoids, Berlin[128] first synthesized ketone **51a** by the route shown below. This synthesis began with the condensation of thiophenol (**52**) and ethyl acrylate (**53**) using triethylamine (TEA) as a base to give ester **54**. In the orginal synthesis, sodium ethoxide was employed as the base and gave ester **54** in a yield of 82.5%. In a recent report,[6] triethylamine was used and gave a quantitative conversion. In our hands, however, this was not observed, but yields of approximately 96% were common. Ester **54** was then treated with two equivalents of freshly prepared methylmagnesium iodide, and, after hydroylysis, gave alcohol **55**.

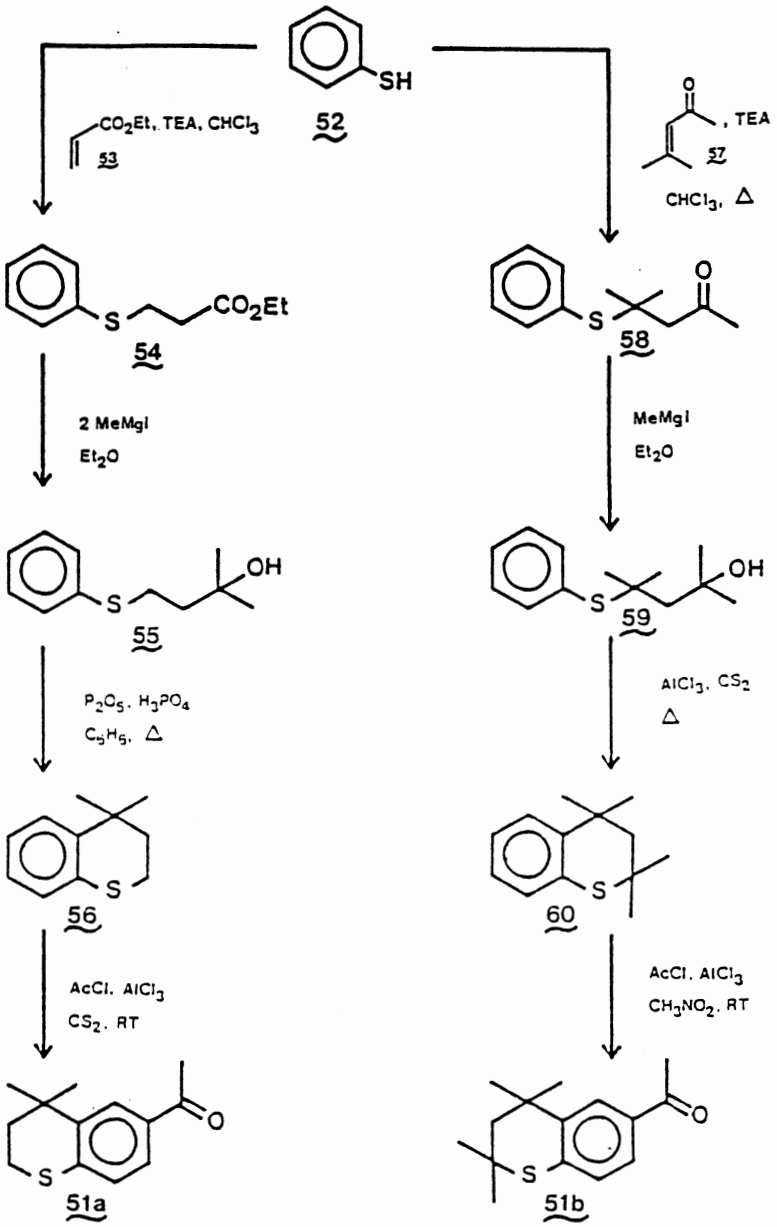


Figure 21. Reaction Sequence for Ketones **51a** and **51b**.

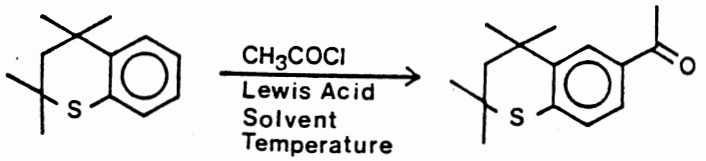
Cyclization of **55** was achieved with polyphosphoric acid generated in situ from phosphorous pentoxide and 85% phosphoric acid in boiling dry benzene. Dimethylthiochroman **56** was obtained after distillation. Acetylation of **56** was effected by treating a solution of the thioether with acetyl chloride in carbon disulfide which gave ketone **51a.**

In parallel fashion, unknown ketone **51b** was acquired as illustrated. Thiophenol (**52**) and mesityl oxide (**57**) were condensed using TEA, but, due to the steric hindrence at the β-position of ketone **57**, a higher reaction temperature was required. The reaction gave the desired 4-methyl-4-thia-phenyl-2-pentanone (**58**) which was treated with methylmagnesium iodide to give alcohol **59.** Cyclization of **59** was achieved by a slightly different method, namely by boiling a suspension of aluminum chloride in CS_2 to which was added alcohol **59.** This led to 2,2,4,4-tetramethylthiochroman (**60**). Unfortunately, acetylation of **60** did not proceed as cleanly as expected. Similiar reaction conditions used to obtain ketone **51a** gave only a mixture of unidentifiable products. Several reaction conditions were scrutinized and are shown in Table XI. The best results employed aluminum chloride and acetyl chloride in nitromethane with **60**, and gave ketone **51b** in a yield of 68.1%. One benefit in the use of nitromethane over carbon disulfide is the formation of a homogenous mixture with aluminum chloride.

The novel synthesis of **48b** and **48c** was accomplished through reaction conditions utilizing ketones **51a** and **51b**,

TABLE XI

ACETYLATION CONDITIONS FOR THIOCHROMAN **60**



LEWIS ACID	SOLVENT	TEMPERATURE (^{o}C)	TIME	RESULTS
$AlCl_3$	CS_2	25	8 h	mixture
$AlCl_3$	CS_2	0	2 h	**51b** (65.0%)
$AlCl_3$	CH_3NO_2	25	12 h	**51b** (68.0%)
$SnCl_4$	CS_2	25	14 d	*

* Incomplete reaction, approximately 50% thiochroman **60** remained unreacted.

as shown in Figure 22. The appropriate ketone (either **51a** or **51b**) was treated with freshly prepared vinylmagnesium bromide in THF and, after hydrolysis, gave the alcohol **61a** or **61b.** Treatment of the proper alcohol with triphenylphosphine hydrobromide (**62**)[24] led to phosphonium salts **63a** or **63b.** In the next step, a Wittig type reaction proceeded smoothly by generation of the ylide of **63a** (or **63b**) with n-butyllithium followed by treatment of the ylide with ethyl β-formyl-crotonate (**64**) at -78^{o}C. The isomeric mixture

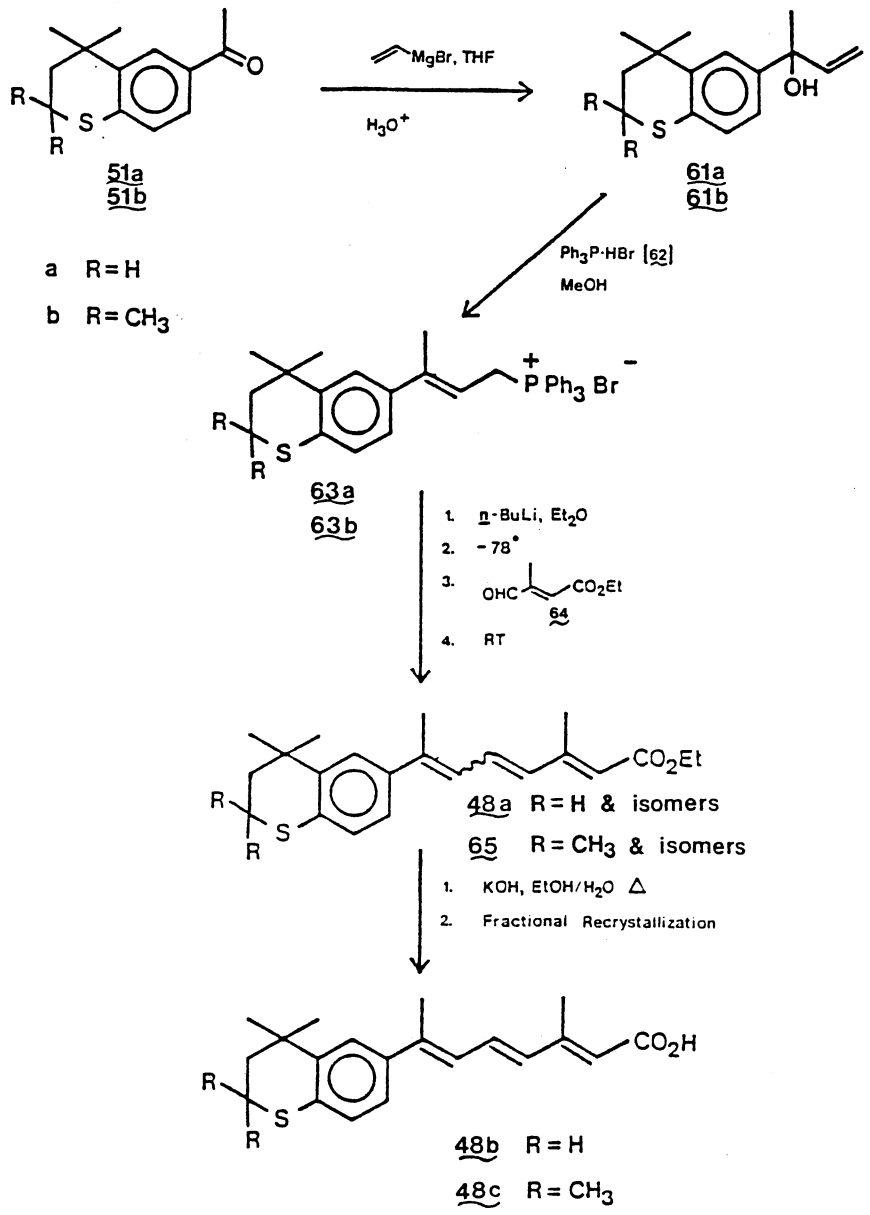


Figure 22. Synthesis of Acids **48b** and **48c**.

(**48a** or **65** plus isomers) of esters produced in this reaction was unresolved by normal chromatographic methods and crystallization techniques. Consequently, this isomeric mixture was saponified using aqueous ethanolic KOH which gave isomerically pure acid **48b** or **48c** after fractional recrystallization.

Esters **48a** and **48d** were prepared from acid **48b** in order to assess the activity imparted by groups on the terminus of the triene side chain. The synthesis of **48a** and **48d** is shown in Figure 23. The all trans-acid **48b** was treated

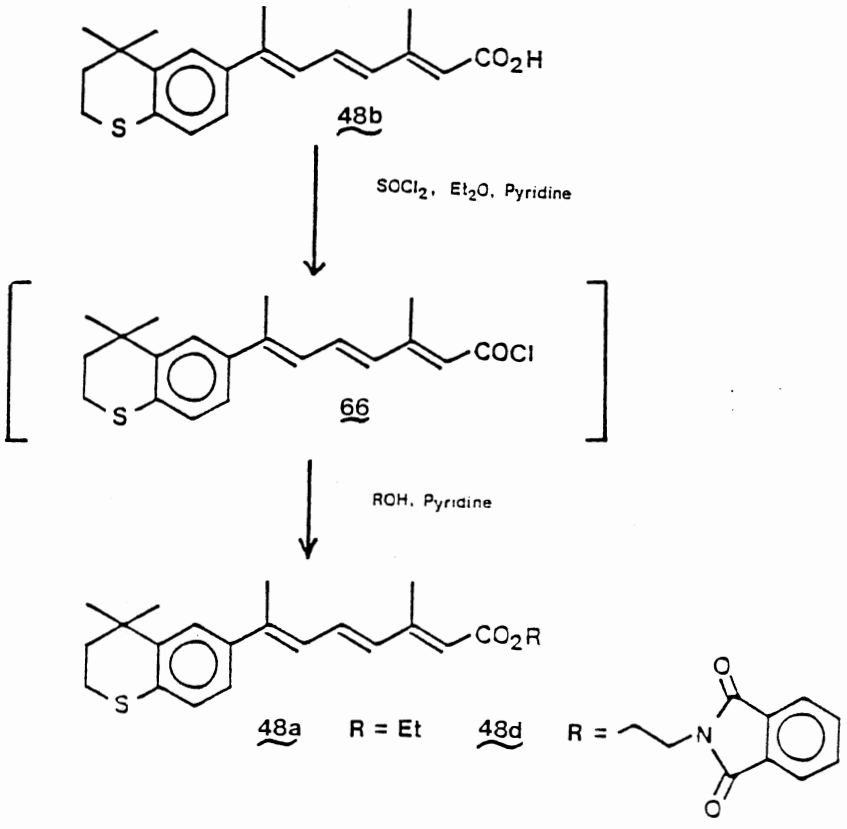
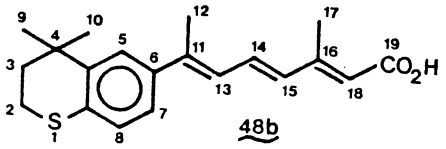
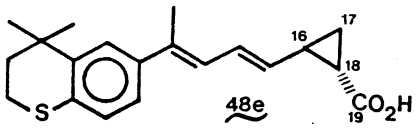


Figure 23. Synthesis of Esters **48a** and **48d**.

with thionyl chloride and pyridine in ether at -10°C. The resulting acid chloride **66** was then allowed to react with the desired alcohol at -20°C and, after chromatography, gave either ester **48a** or **48d**.

Heteroarotinoids **48e** and **48f** were designed to determine if alterations on the C(16)-C(18) double bond would change biological activity with respect to that of **48b** (Figure 24). The incentive for the synthesis of **48f** was, hopefully, to retain the inherent biological characteristics common to 13-cis-retinoic acid (**1g**) while keeping the useful properties of certain sulfur heteroarotinoids, namely ester **42** and acid **43** (Figure 25). Both **48e** and **48f**





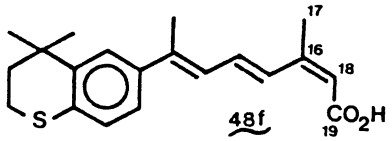
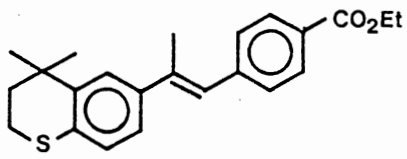


Figure 24. Heteroarotinoid Modifications at the C(16)-C(18) Double Bond.



42 R = Et

43 R = H

Figure 25. Structures of Heteroarotinoids **42** and **43**

were synthesized from the phosphonium salt **63a** as illustrated in Figure 26. The phosphonium salt **63a** was allowed to react with n-butyllithium giving the appropriate ylide. The ylide of **63a** was cooled to -78°C and ethyl trans-2-formylcyclocarboxylate (**67**) was added resulting in an isomeric mixture of esters **68.** Purification of the all trans-ester **68** was unsuccessful and so the mixture was saponified using aqueous methanolic KOH with mild heating. After acidification, the mixture was concentrated to an oil which was crystallized (H_2O:ethanol) to give the all trans-cyclopropanoic acid **48e.** Recently, Curly, DeLuca and Silva reported[24] the synthesis of four cyclopropyl retinoids **35-38** (Figure 27). They indicated later[25] that extensive degradation occurred with these compounds under mildly basic conditions. A major concern of using a base with these esters, as well as with **68,** was the possiblity of epimerzation at the carbon alpha to the CO_2Et group. If this did occur with **68,** then in the crystallization step,

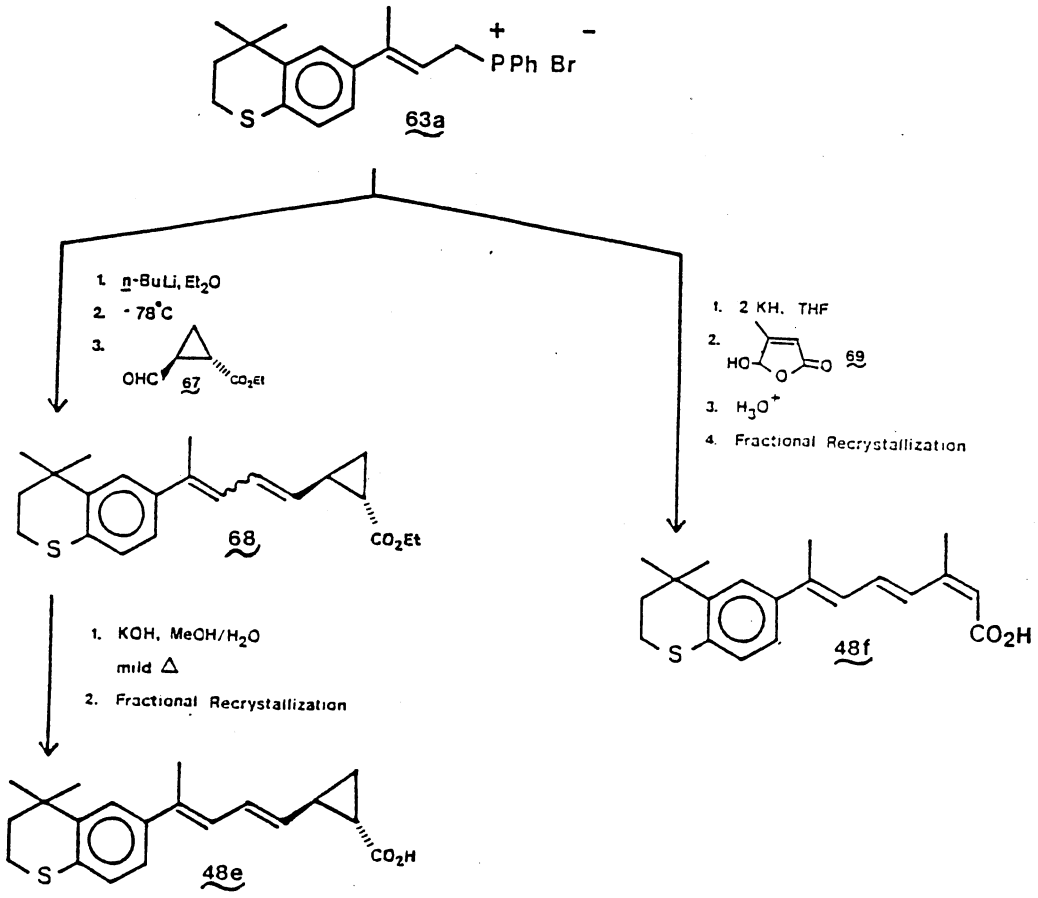
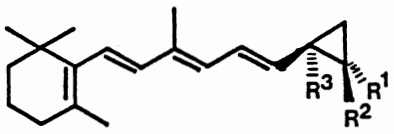


Figure 26. Synthetic Routes to Heterarotinoids **48e** and **48f**.

the unwanted epimer of acid **48e** was apparently removed selectively. The evidence for only one isomer of **48e** was based on ^{13}C NMR analysis which contained the expected number of signals for only **48e** without a duplicate set of signals expected for the other isomer(s). This will be discussed in detail later.



	R^1	R^2	R^3
35	CO_2Et	H	H
36	H	CO_2Et	H
37	CO_2Et	H	CH_3
38	H	CO_2Et	CH_3

Figure 27. Cyclopropane Retinoids.

The synthesis of acid **48f** was accomplished by a different method. The cis double bond at C(16)-C(18) was created by treating 4-hydroxy-3-methylbut-2-enolide (**69**) with one equivalent of potassium hydride which led to potassium cis-3-formylcrotonate (**70**). Another equivalent of potassium hydride was consumed to form the ylide of **63a** which attacked the aldehyde group of **70** and produced the precursor salt of **48f** (Figure 28). After neutralization, a

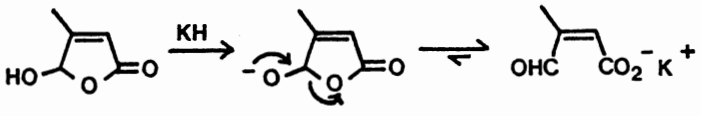


Figure 28. Base Initiated Potassium cis-3-Formylcrotonate (**70**) Formation.

brief iodine treatment of the reaction mixture was implemented to equilibrate the mixture of 14,16-dicis-acid **71** and 16-cis-acid **48f** presumably formed (Figure 29). After fractional recrystallization (ethanol) of the solid product, acid **48f** was obtained. Unlike acid **48b**, the 16-cis isomer **48f** appears to be extremely sensitive to isomerization. It is imperative that, after partial isomerization with iodine, sodium thiosulfate be used to remove any trace of iodine to prevent further isomerization of **48f** to all trans-acid **48b**. The two important reactants (**67**[85] and **69**[21]) used in the synthesis of **48e** and **48f** were

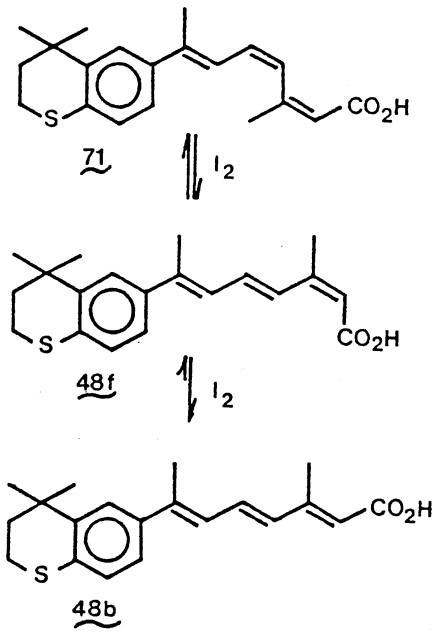


Figure 29. Isomerization of 14,16-dicis-Acid **71**, 16-cis-Acid **47f** and All-trans-Acid **47b**.

either not available commerically (i.e. **69**) or available only as isomeric mixtures (i.e. **67**). Aldehyde **67** could be purchased but was a mixture of cis/trans isomers which had to be separated, a process not cost effective. Therefore, the orginal synthetic route[85] was employed to attain sufficient quantities of pure **67** which is shown in Figure 30. The <u>trans</u>-isomer **67** was separated via a

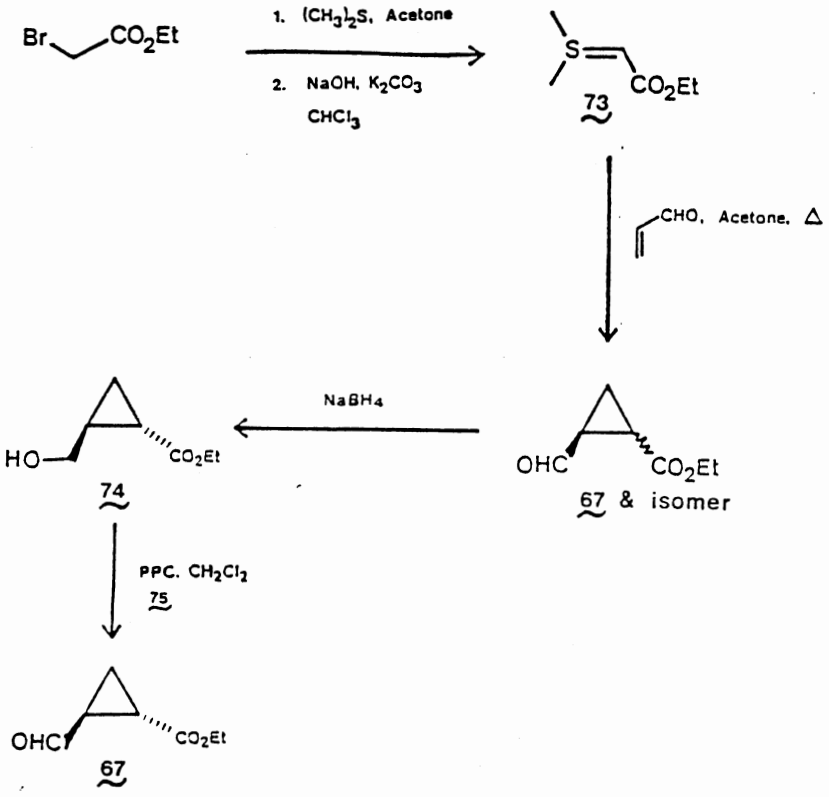


Figure 30. Synthesis of Ethyl <u>Trans</u>-2-Formylcyclopropan-carboxylate (**67**).

chemical means from a reported process.[58] This entailed treatment of the cis/trans mixture of aldehydes with sodium borohydride followed by distillation of the resulting liquid. Isomerically pure ethyl trans-2-hydroxymethyl-cyclopropanecarboxylate (**74**) was obtained in a yield of 41.5%. Presumably, the cis isomer of **74** may suffer an intramolecular transesterification and removed in the distillation along with other rearranged products. Treatment of pure **74** with pyridinium chlorochromate (PCC, **75**) gave the desired aldehyde **67**.

The synthesis of the lactol **69** was accomplished by a known procedure involving the treatment of ethyl β-trans-formylcrotonate (**64**) with boiling 6 N HCl.[21] After distillation of the oily product and recrystallation of the solidified distillate, a low melting (mp 42-43°C) solid was isolated (Figure 31) which proved to be lactol **69**.

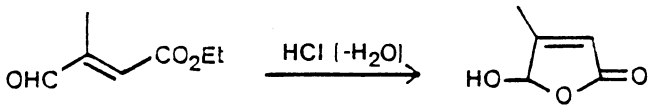
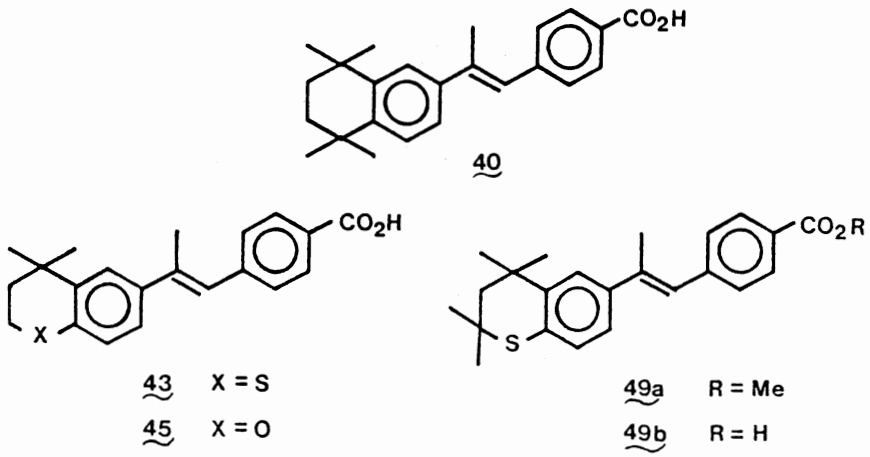


Figure 31. Sythnesis of Lactol **69**

Retinoid **43** has aroused interest in its potential use in chemotherapy.[29,30,128] Previousily unknown but related

trans-ester **49a** and trans-acid **49b** were designed to assess the effect on activity of geminal methyl groups at the C(2) position. This change should serve to inhibit catabolic degradation of the sulfur atom which probably occurs more easily with acid **43**. Thus, **49a** and **49b** are probes for steric requirements at C(2). Biological information gained from this structural modification might lead to future retinoids with efficacy similiar to acid **40** (known to be toxic)[29] with reduced toxicity.



The incorporation of an aromatic ring into the side chain has produced compounds with useful biological activity while possessing greater stablity.[68] For instance acids **43** and **45** had toxicity less than **40**.[29] As a result of the presence of the aromatic ring, the diene portion in the ring is locked into a planar, cisoid conformation. Struc-

tural comparison between retinoic acid (**1b**) and acid **40** revealed remarkable similiarity in the geometrical shapes and suggested a reason why the activities might be similar which has been substantiated (see Figure 32).[119]

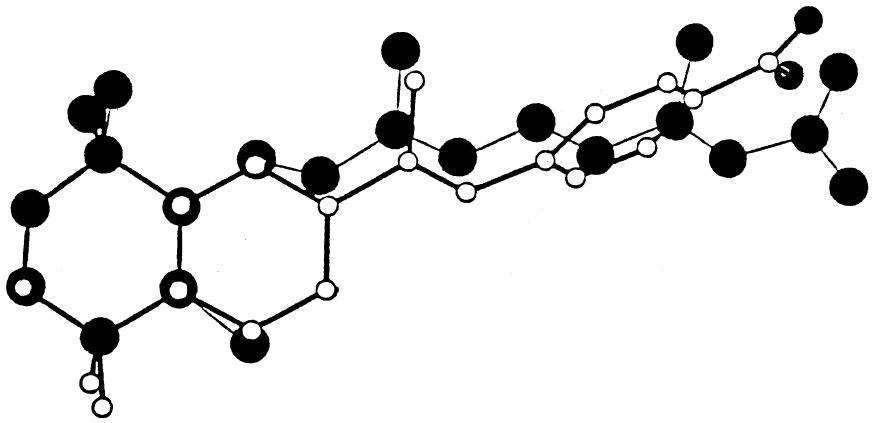


Figure 32.[119] Superimposed Structures of (E)-[Tetrahydro-tetramethyl-2-napthalenyl-1-propenyl]-benzoic Acid (TTNPB, **40**) and Retinoic acid (**1b**).

New retinoid **49a** was prepared by a modified Horner-Emmons reaction.[114] Treatment of ketone **51b** with the anion of dimethyl (4-carbomethoxybenzyl)phosphonate (**76**) in THF in the presence of 15-crown-5 (**77**) afforded ester **49a.** The crude ester was purified by chromatography and fractionally crystallized to give the pure E isomer **49a** as shown in Figure 33. The isomeric purity was assessed by ^{1}H and ^{13}C

NMR analyses which revealed only one signal for the vinylic methyl protons and corresponding carbon. Conversion of ester **49a** to acid **49b** proceeded smoothly by treatment with ethanolic KOH in water at reflux. After neutralization, acid **49b** was isolated and determined by NMR analysis to be the (E)-isomer. Phosphonate **76** was made readily available by the Arbuzov reaction[3] as shown in Figure 34. Treatment

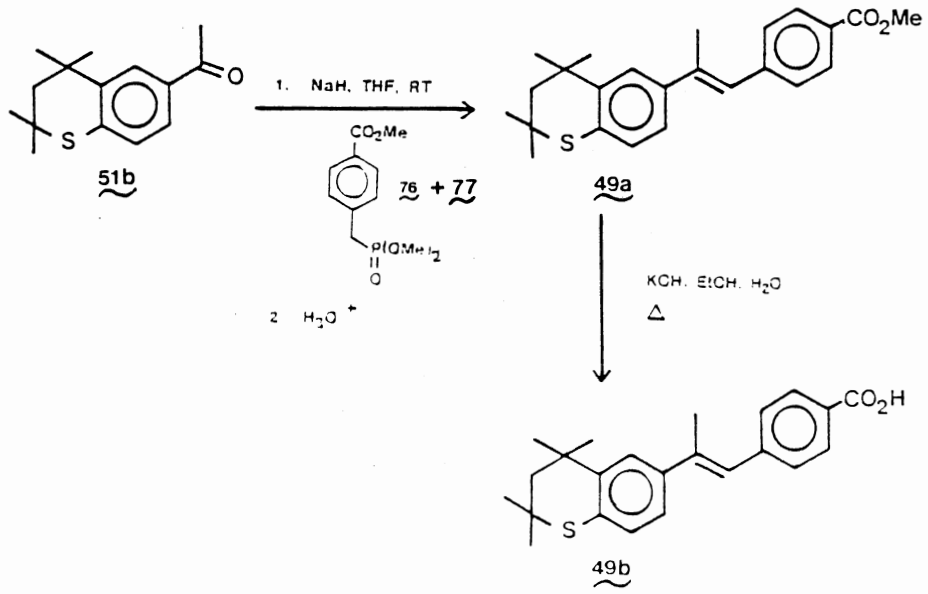


Figure 33. Synthesis of Retinoids **49a** and **49b**.

of ester **78** with N-bromosuccinimide (**79**) in boiling CCl_4 gave bromide **80**. A reaction of trimethyl phosphite (**81**) with **80** gave the important intermediate phosphonate **76**.

The introduction of fluorine for hydrogen is known to

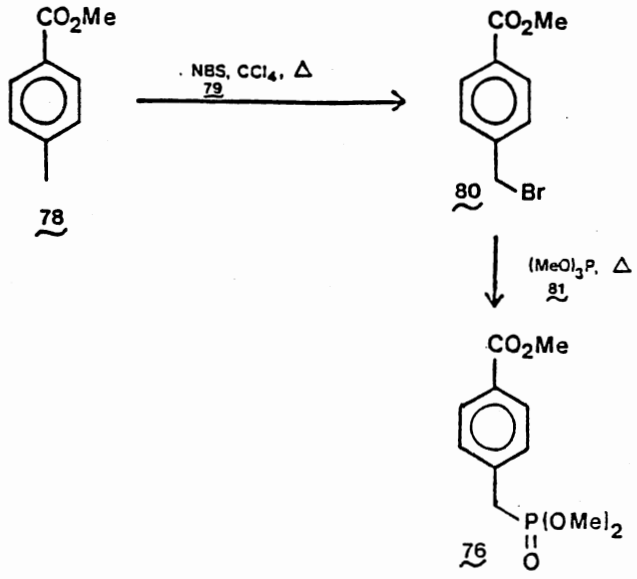


Figure 34. Synthesis of Phosphonate **76.**

alter activity in medicinal agents.[4] The trifluoromethyl-substituted retinoids **50a-f** were of interest because the geometry of the system should not be altered much and yet the electron density will be reduced in the double bond. The impact of such a change on biological activity is unknown in these systems, although some data have been reported in related families.[51,53,77,120,129] All of these known trifluoro-substituted retinoids were synthetic analogues of natural retinoids with hydrogens on one methyl group [C(12)] being substituted with fluorines atoms. Generally, the purpose of a structural modification of this type is two fold. As stated previously, fluorines atoms

change the electronic environment in nearby atoms without appreciable changes in the steric environment, and this could lead to enhanced efficacy. Also, fluorine can be used as a ^{19}F NMR biological probe. Recently, fluorine has been employed as a potential probe in studies on the action of two anesthetics in hopes of revealing drug distribution in tissue and for monitoring metabolic processes.[19] Utilization of fluorine in this manner could lead to information on the mechanism of action by retinoids in cell differentiation.

The synthesis of these previousily unknown, fluorinated retinoids proceeded through the common scheme shown in Figure 35. Similar to the synthesis of ketones **51a** and **51b**, an acid chloride was required. Trifluoroacetyl chloride (**82**), a gas at room temperature, was distilled into a suspension of aluminium chloride in CS_2 containing thiochroman **56** to give the desired ketone **83**. Ketone **83** was then treated with the anion of phosphonate **76** to give retinoid **50a**. NMR analysis (^{19}F) of ester **50a** revealed the presence of only one isomer and suggested that the aryl moieties were <u>syn</u> with respect to each other. This stereochemical designation must be considered tentative in view of a lack of adequate models in this family. The arguments for this assignment are in the NMR section. Ester **50a** was easily converted to acid **50b** with aqueous ethanolic KOH and heat.

Supporting evidence for the conformational assignment

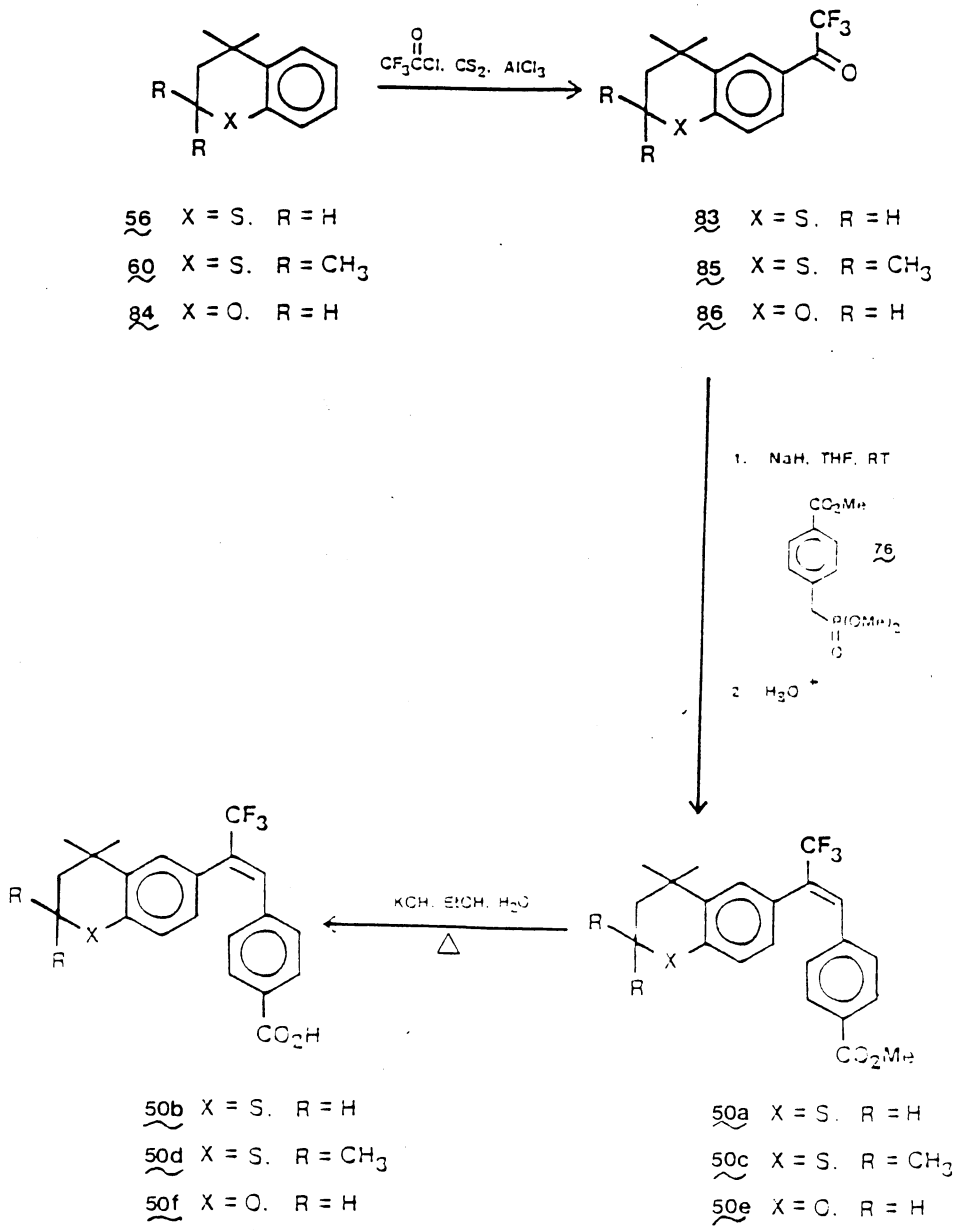


Figure 35. Synthesis of Trifluoromethyl-Substituted Heteroarotinods.

of ester **50a** and acid **50b** was reported by Kossmehl in the synthesis of (E)-(trifluoromethyl)stilbene (**87**).[96] The (E)-isomer **87**, confirmed by X-ray anaylsis, was reported as

the dominate isomer (86:14) with respect to the (Z)-isomer **88** (Figure 36). Also, Liu reported the stablity of the

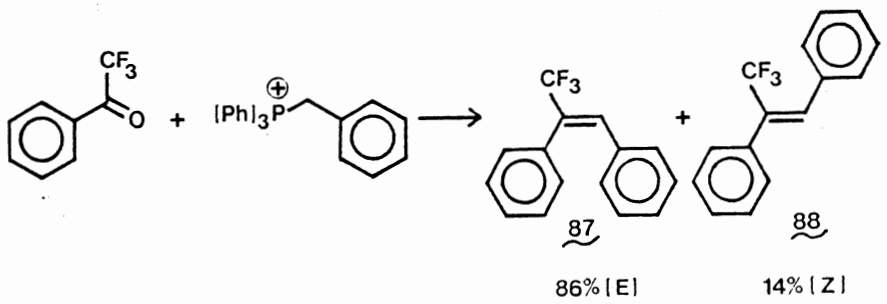


Figure 36. Isomeric Ratio of Trifluoromethyl Stilbenes.[D17]

(E)-isomer with the presence of a vinyl trifluoromethyl group.[5] The remaining trifluoromethyl-substituted retinoids (**50c-f**) were prepared in a manner similar to that of ester **50a** and acid **50b**.

Chroman **84** was prepared by a route similar to that reported by Berlin in 1985[129] (Figure 37). The first step, unlike the orginal reaction sequence, started with phenol (**89**) and ethyl acrylate (**53**) eliminating one step in the orginal scheme. This reaction presumably involved a Michael type addition of phenol (**89**) with ethyl acrylate (**53**) to give ester **90**.[50] Treatment of **90** with methylmagnesium iodide gave 2-methyl-4-phenoxy-2-butanol (**91**). The cyclization of alcohol **91** was then achieved by treatment

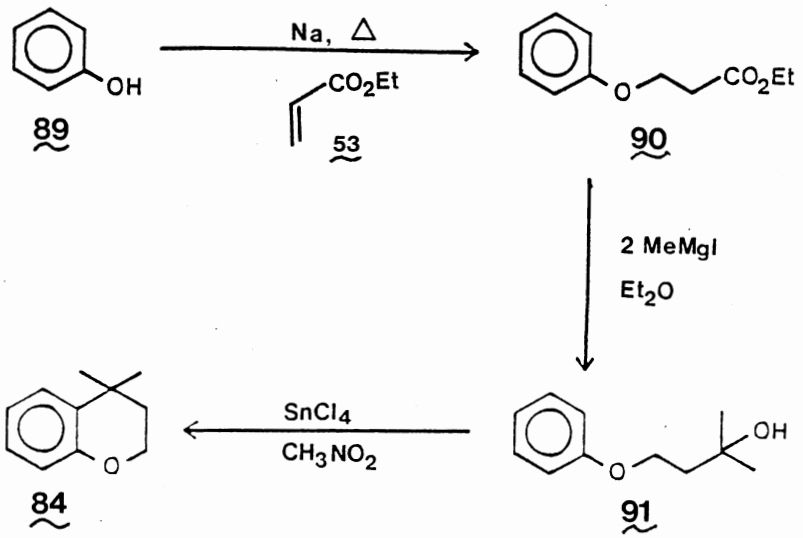


Figure 37. Synthetic Scheme of 4,4-Dimethylchroman (**84**).

with $SnCl_4$ in nitromethane at room temperature to give 4,4-dimethylchroman (**84**).

Structural Elucidation of New Heteroarotinoids Via ^1H And ^{13}C NMR

Natural retinoids characteristically have side chains that consist of a conjugated polyene system. For example, retinoic acid (**1b**), a tetraene, has potentially 16 different (E,Z)-isomers. The stereochemical nature of these double bonds is critical for biological activity.[27,81] Therefore, elucidation of the structures for each new retinoid, prior to biological analyses, is essential.

Heteroarotinoids **48a-f** resemble natural retinoids more than do **49a-b** and **50a-f** (Figures 38 and 39). High isomeric

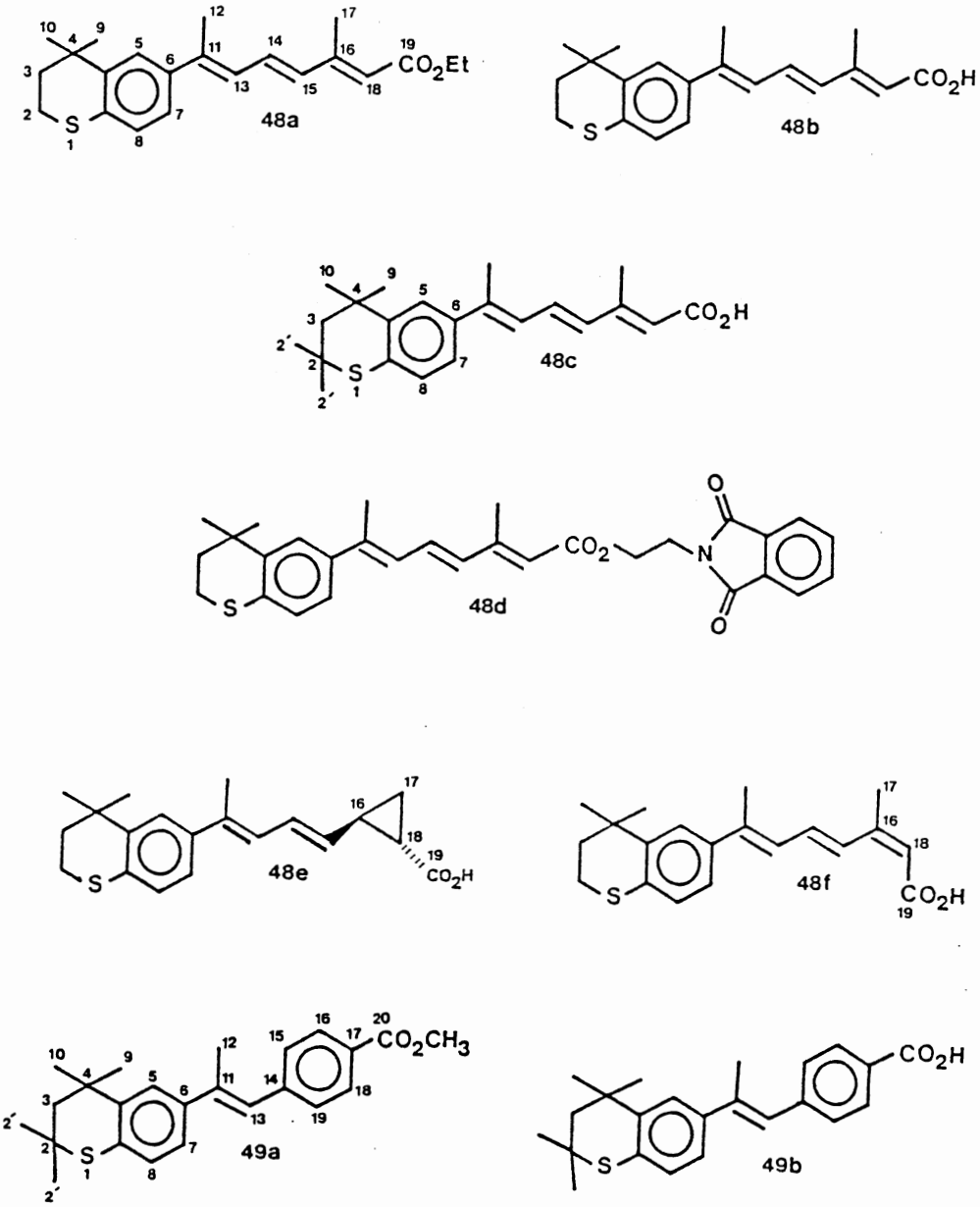


Figure 38. Structures of New Heteroarotinoids **48a-f**, **49a-b** and **50a-b**.

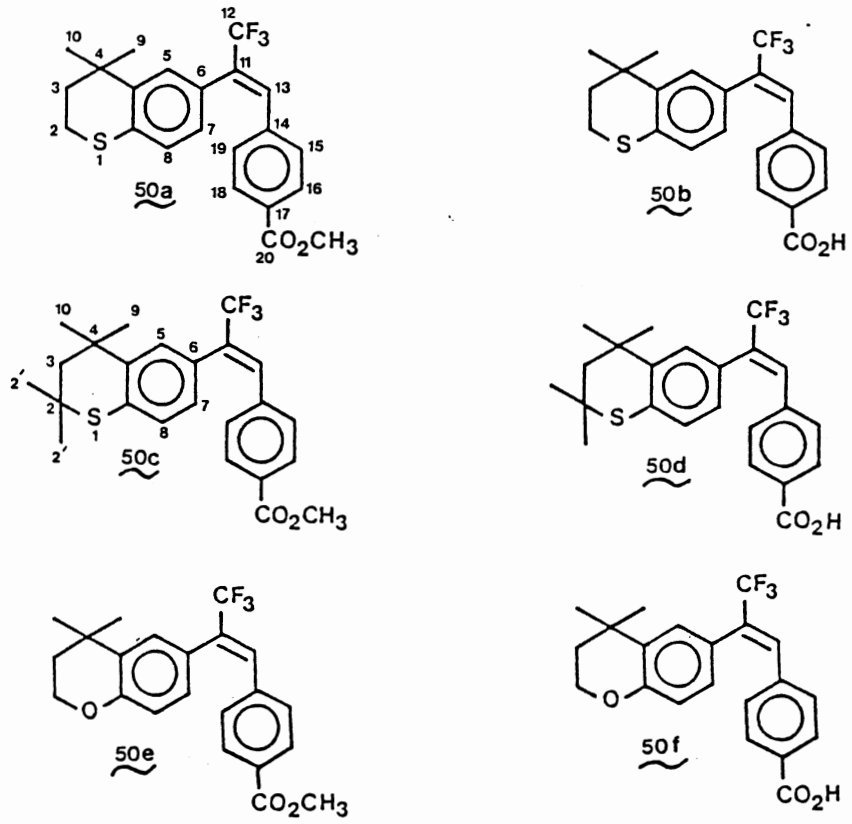


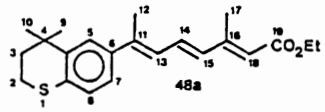
Figure 39. Structures of New Heteroarotinoids **50c-f.**

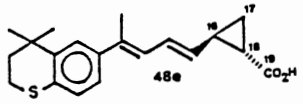
purity of **48a-f** proved difficult to attain compared to that of the remaining new heteroarotinoids **49a-b** and **50a-f.** Discussion of these two groups of retinoids will be conducted separately.

The exact arrangment of a group around the double bond in **48a-f** was determined via NMR spectroscopy. Both ^{1}H and ^{13}C analyses were employed along with a HETCOR 2-dimensional NMR[49] analyses for specific acids **48b** and **48e.** Table XII contains the ^{13}C signals for retinoids **48a-f.**

TABLE XII

^{13}C NMR SIGNALS FOR HETEROAROTINOIDS **48a-f**

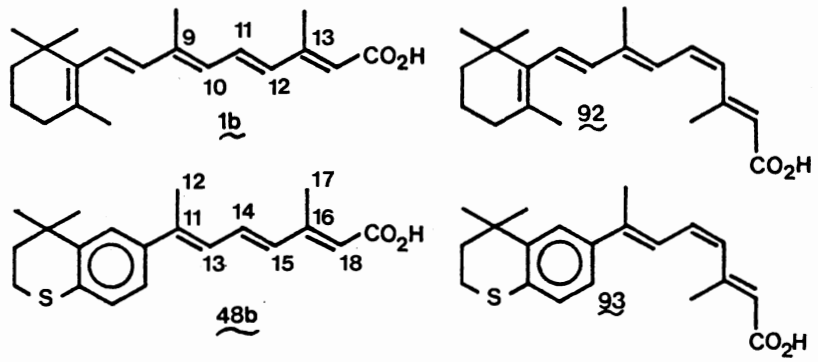




CARBON	HETEROAROTINOIDS **48a**	**48b**	**48c**	**48d**	**48e**	**47f**
2	23.1	23.0	35.7§	23.1	23.1	23.1
2'	-	-	32.6Φ	-	-	-
3	37.6	37.5	54.4	37.6	37.7	37.6
4	33.1	33.0	42.2§	33.1	33.1	33.1
4a	141.7*	141.7*	142.5*	141.8*	141.6*	141.7*
5	123.6	123.6	124.1	123.6	123.6	123.6
6	138.2*	138.1*	139.0*	138.2*	138.8*	138.0*
7	123.4	123.3	123.5	123.4	123.3	123.5
8	126.4	126.4	127.9	126.5	126.4	126.4
8a	131.7*	131.5*	132.9*	131.8*	130.7*	131.9*
9, 10	30.1	30.1	31.7Φ	30.2	30.2	30.2
11	139.9	140.2	140.7	140.1	135.2	140.9
12	16.2	16.1	16.3	16.2	16.9	16.2
13	125.5	125.4	125.7	125.5	125.0	126.0
14	131.1	131.7	132.0	132.0	128.1	133.4
15	135.5	135.4	135.4	134.4	133.1	129.2
16	152.3	154.0	155.1	153.5	26.8	153.7
17	13.8	13.8	14.1	13.9	15.8	21.3
18	118.7	118.3	117.8	117.7	22.4	115.9
19	167.1	170.8	170.8	166.6	179.5	172.1

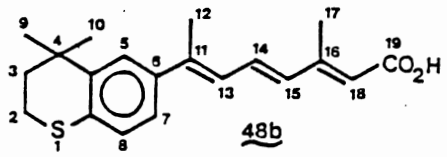
* § Φ Signals may be interchanged in the vertical column.

The all-trans stereochemistry in the side chain of retinoids **48a-d** is supported in terms of reported ppm values for ^{1}H[38,105] and ^{13}C[37,67] signals in corresponding, known natural retinoids. Although these new members have similar spectra with natural reinoids, a portion of the side chain in **48a-f** has been incorporated into an aryl ring. Consequently, there is sufficient variation in the NMR signals to warrant further analyses. Therefore, a HETCOR 2-D plot[49] was employed to verify signal assignments. Analysis of the NMR spectral data and HETCOR plot for acid **48b** established the all-trans stereochemistry which was used as a model for **48a** and **48c-d.** The $^{3}J_{HH}$ values were very helpful in assessing the stereochemistry about the double bonds, particularly isomeric systems related to retinoic acid (**1b**).[101] Coupling constants for all-trans-retinoic acid (**1b**) are 11.5 Hz and 15.0 Hz for H(10,11) and H(11,12), respectively.[101] 11-cis-Retinoic acid (**92**) is similiar to compound **93** which is presumed to be one of the isomers formed in the Wittig reaction as a side product, leading to acid **48b.** Isomer **93** is likely to be present since double bond C(14)-C(15) is formed in this Wittig olefination reaction, but to date however, we have not isolated **93.** Coupling constants for 11-cis-retinoic acid (**92**) are 11.5 Hz and 11.5 Hz for H(10,11) and H(11,12), respectively.[101] Clearly, a difference exists between the $^{3}J_{11,12}$ value for the two isomers of **1b** and **92.** For related acid **48b**, the $^{3}J_{14,15}$ value [similar to $^{3}J_{11,12}$



for acid (**1b**)] is 15.0 Hz supporting the trans juncture in the side chain. Interestingly, the coupling constant for H(13,14) was 12.0 Hz in acid **48b** which corresponds to $^{3}J_{10,11}$ in **1b** which is 11.5 Hz. The HETCOR 2-D plot (Figure 40) for **48b** allows unequivocal correlation of ^{1}H signals to the corresponding ^{13}C signals. The NMR peaks for groups around the thiochromanyl moiety in **48b** are also in agreement with the ^{1}H and ^{13}C signals reported earlier by Waugh and co-workers for **42** and **44-46.**[129] Therefore, the ^{13}C signals for acid **48b** serve as a basis to assign resonances in heteroarotinoids **48a** and **48c-d.**

The ^{13}C assignments for heteroarotinoid **48e** were not readily obvious in comparison to the ^{13}C signals for acid **48b.** Therefore, to elucidate the ^{13}C signals for the two double bonds, a HETCOR 2-D was again used for **48e** (Figure 41). The ^{1}H signal at δ 6.61 was easily assigned as H(14) in view of it splitting pattern (dd, J = 12.0 Hz, J = 15.0 Hz) which is reminiscent of that in acid **48b** for the



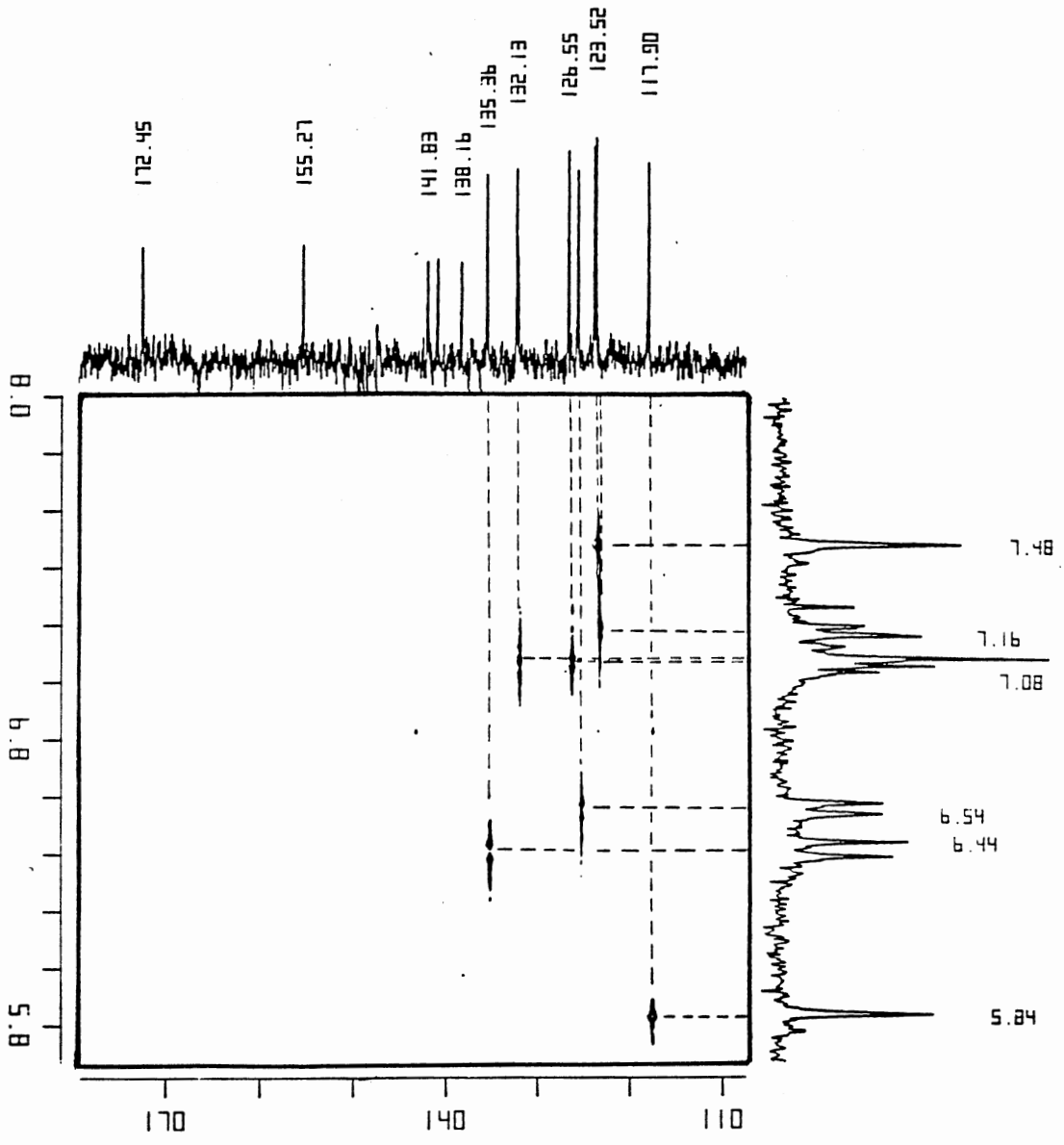
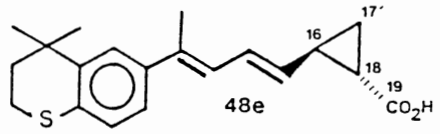


Figure 40. HETCOR-2D Plot of Acid (48b).

corresponding H(14). Although the ^{1}H signal at δ 5.34 in **48e** had a similar splitting pattern, the magnitude of the coupling constants (J = 9.0 Hz, J = 15.0 Hz) indicated that this signal was associated with H(15). The smaller $^{3}J_{HH}$ value of δ 5.34 arises from the coupling of H(15) with H(16) of the cyclopropyl moiety. Finally, the signal at δ 6.34 is a doublet with a coupling constant of 12.0 Hz for H(13). Clearly, the coupling constants define the correctness of the assignments. Moreover, the trans stereochemistry of the double bonds in **48e** is established as identical to that observed in acid **48b.** In addition, the ^{13}C assignments could be obtained from the HETCOR 2-D plot. These values are shown in Table XII. The ^{13}C values for the cyclopropyl portion of acid **48e** paralleled those for ethyl <u>trans</u>-2-formylcyclopropanecarboxylate (**67**). An off-resonance spectrum of ester **67** clearly made the assignments easy (Table XIII). Interestingly, C(2) in ester **67** was a doublet of doublets. This observation was surprising in view of the fact the ^{13}C decoupled spectra clearly gave only one set of signals for the expected isomerically pure ester **67.** Since both C(2) and C(4) gave similar multiplicities, it is apparent that these carbons are adjacent to each other. A splitting of this type was reported by Gray[48] in 1969 for simple acetyl compounds (i.e. acetaldehyde). Therefore, the assigned values for acid **48e** are shown in Table XII.



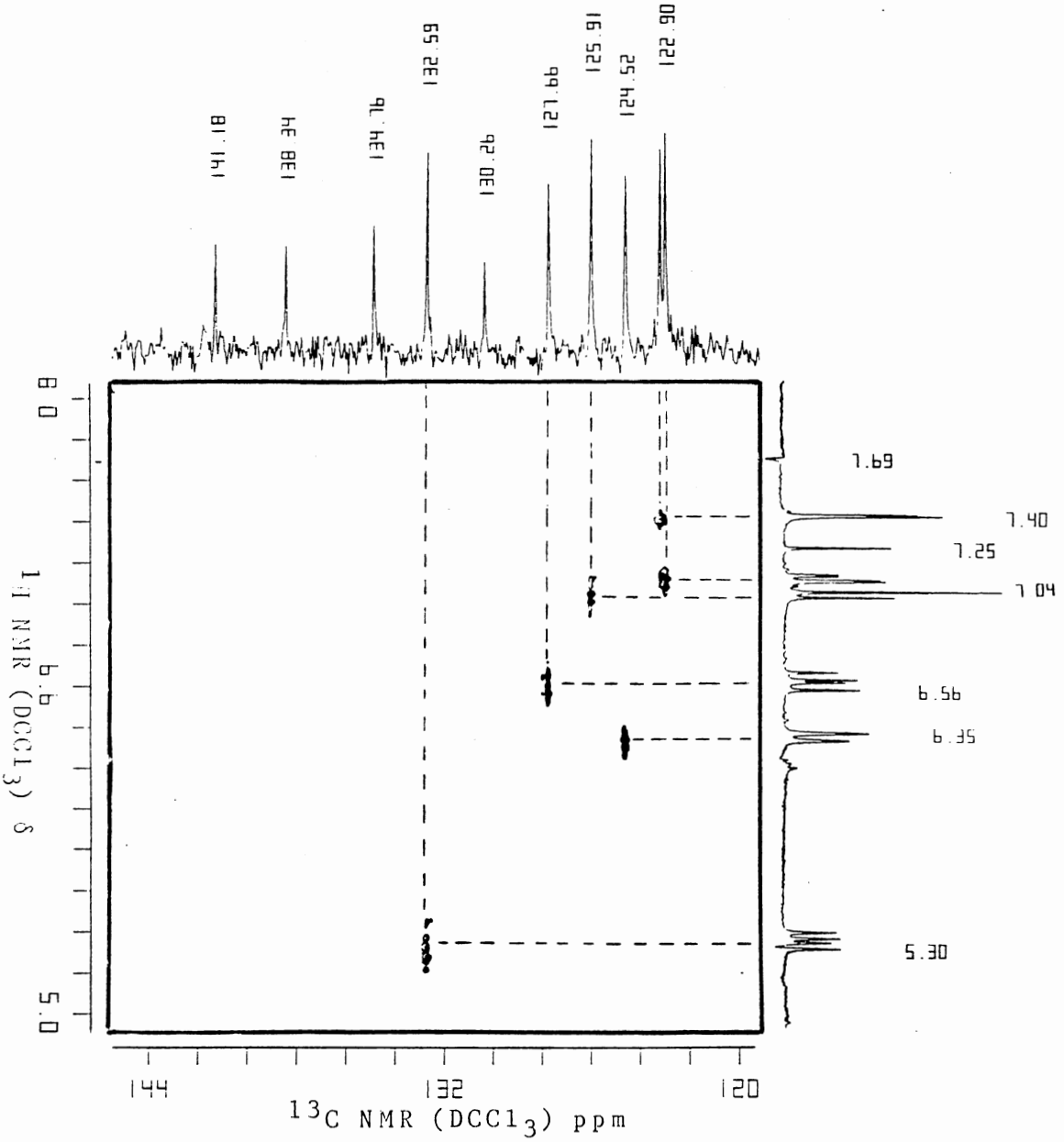
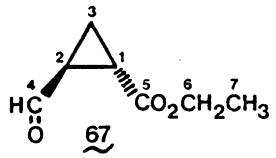


Figure 41. HETCOR 2-D Plot of Acid **48e**

TABLE XIII

^{13}C DATA FOR ETHYL
TRANS-2-FORMYLCYCLOPROPANECARBOXYLATE (**67**)



67

Carbon	^{13}C (ppm)	Multiplicity
1	22.2	d
2	30.7	dd
3	14.8	t
4	198.3	dd
5	171.1	s
6	61.3	t
7	14.2	q

Finally, the ^{13}C assignments for 16-cis acid **48f** were based on similar values found for acid **48b** and 13-cis-retinoic acid (**1g**).[37] Figure 42 shows the similarities in ^{13}C resonances that exist between these retinoids. Predictably, certain signals closer to the terminus (the five carbons of the chain) of acid **48f** coincide with those values of acid **1g** while certain signals for **48f** show similarities in the signals in the thiochromanyl portion as

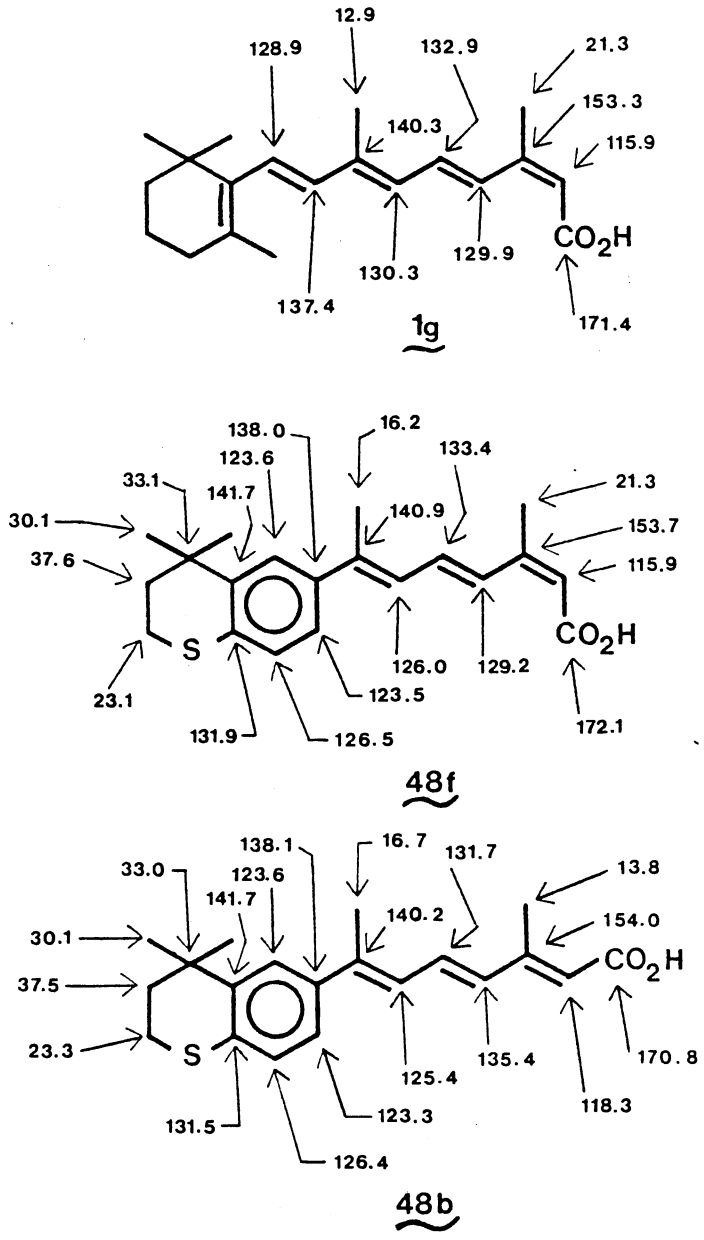
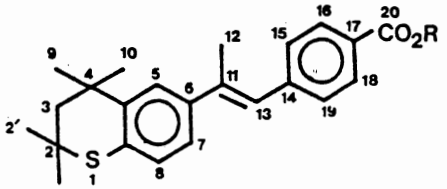


Figure 42. Comparison Between **1g**, **48b** and **48f**.

found in acid **48b**. The reliability of the ^{13}C values for acid **1g** was established by Englert through the use of a

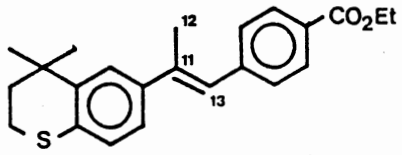
lanthanide shift reagent and selective ^{1}H decoupling experiments.[37]

Heteroarotinoids **49a-b** are very close in structure to ester **42** previously reported by our group. The ^{1}H, ^{13}C



49a R = Me

49b R = H



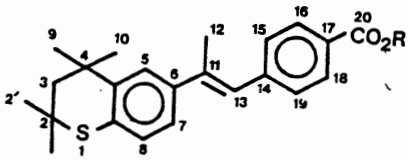
42

and X-ray data revealed a trans arrangement for the isolated double bond [C(11)-C(13)] in **42.**[129] In general, the ^{13}C assignments for ester **49a** and acid **49b** were made by comparison to ester **42** as shown in Table XIV.

The determination of the stereochemistry for compounds **50a-f** is tentative and awaiting an X-ray analysis of **50c.** However, several arguments can be made to deduce the group orientation about the isolated double bond. In the retinoids previously discussed (**48a-f, 49a-b**), all possessed an allylic carbon and hydrogens. Initially, NMR analysis gave an indication of the number of isomers pre

TABLE XIV

^{13}C NMR RESONANCES FOR
HETEROAROTINOIDS **49a** AND **49b**



49a R = Me
49b R = H

Carbon	Heteroarotinoids (ppm) **49a**	**49b**	**42**
2	42.1§	42.2§	23.0
2'	32.6Φ	32.7Φ	-
3	54.4	54.4	37.6
4	35.6§	35.7§	33.1
5	124.2	124.4	124.0
7	123.7	123.7	123.7
8	127.9	128.0	126.4
9, 10	31.6Φ	31.7Φ	30.2
12	17.6	17.7	17.6
13	125.9	125.8	125.7
15, 19	128.9*	129.2*	128.9*
16, 18	129.1*	130.1*	129.4*
20	167.0	171.7	166.5
21	52.1	-	160.8
nonprotonated Carbons	132.4	126.9	143.0
	139.5	132.5	141.7
	139.6	139.9	139.3
	140.1	140.1	139.2
	142.5	142.5	131.4
	143.2	144.1	128.0

§ Φ * May be interchanged in the vertical column.

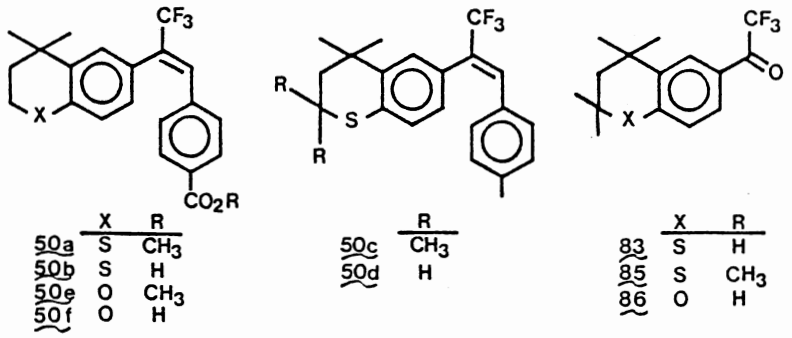
sent (if two ^{13}C signals were present for one allylic carbon, two isomers were present and the same was true for ^{1}H analysis). In retinoids **50a-f**, the trifluoromethyl group complicated the analysis because of coupling between fluorine and the alpha and beta carbons. However, the isomeric purity of these compounds was easily verified by ^{19}F NMR analysis. The presence of only <u>one</u> ^{19}F signal indicated with a high degree of certainty that only one isomer was present. The ^{19}F NMR data for heteroarotinoids **50a-f** are shown in Table XV along with that for the starting ketones **83, 85** and **86.**

There are a few known trifluoromethyl-subsitituted retinoids,[77] but the similarities to **50a-f** are only peripheral. However, valuable information can be obtained from the ^{19}F analysis of the reported isomeric systems **94-97** (Table XVI).[77] A comparison between **94** and **96** indicated that 6.2 ppm separated the two ^{19}F signals. Therefore, a large scan was made from -50.0 to -75.0 ppm (upfield from $FCCl_3$) for the ^{19}F NMR signals in heteroarotinoids **50a-f.** All of our samples displayed resonances within this range although the data did not substantiate specific sterochemistry in the side chain.

As mentioned previously, the trifluoromethyl group on a vinyl carbon (examples are **94-97**)[5] could influence the stereochemistry dramatically. In reported[5] systems containing a CF_3 group, the (<u>E</u>)-isomer dominated (the CF_3 group has priority over the carbon side carbon side chain,

TABLE XV

^{19}F NMR DATA FOR
HETEROAROTINOIDS **50a-f** AND KETONES **83, 85-86.**



	X	R
50a	S	CH_3
50b	S	H
50e	O	CH_3
50f	O	H

	R
50c	CH_3
50d	H

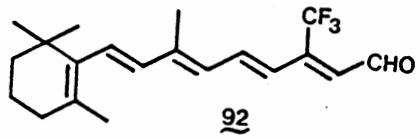
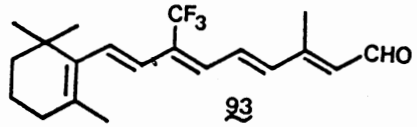
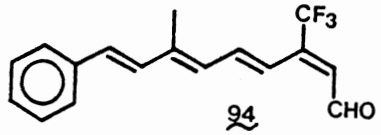
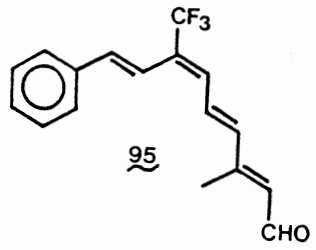
	X	R
83	S	H
85	S	CH_3
86	O	H

Heteroarotinoid	^{19}F (ppm)§	Ketone	^{19}F(ppm)§
50a	-66.60	83	-71.72
50b	-66.61		
50c	-66.59	85	-71.74
50d	-66.61		
50e	-66.80	86	-71.53
50f	-66.82		

§ F_3CCO_2H was the external standard which was referenced to $FCCl_3$.

TABLE XVI

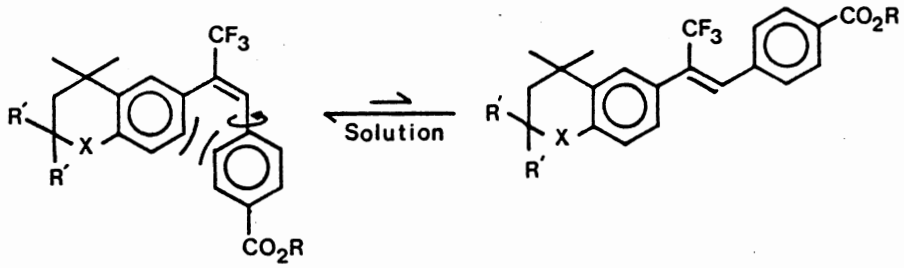
TRIFLUOROMETHYL-SUBSTITUTED
RETINOIDS AND ^{19}F NMR SIGNALS[5]

Retinoid	^{19}F (ppm)*
 92	-58.1
 93	-59.3
 94	-65.3
 95	-64.3

* Referenced to $FCCl_3$.

indicating the E designation). However, it seems logical that in retinoids **50a-f** in which the aryl rings syn to each

other there would be conformation restrictions and the (E)-isomer might slowly isomerize to the spatially more accommodating (Z)-isomer as illustrated. In the solid



state, there appears to be minimal isomerization but in solution, isomerization took place. For example, in heteroarotinoid **50c** such isomerization was observed by ^1H NMR analysis of H(15,19) and H(16,18) in $DCCl_3$, and after approximately 7 days, the isomerized ratio of (E)/(Z) was 87:13. Surprisingly, this final ratio was very similar to that reported for **87** and **88** in Figure 36 [i.e 86(E):14(Z)].[96] The tentative basis for the assignment of the stereochemistry for ester **50c** as being the (E)-isomer (the two aryl rings syn about the double bond) rests on the ^1H shifts for H(15,19) and H(16,18) compared to those in ester **42** (Figure 43). Our contention is that the dramatic shifts in H(15,19) and H(16,18) occur because of the stereochemistry about the double bond and to a lesser

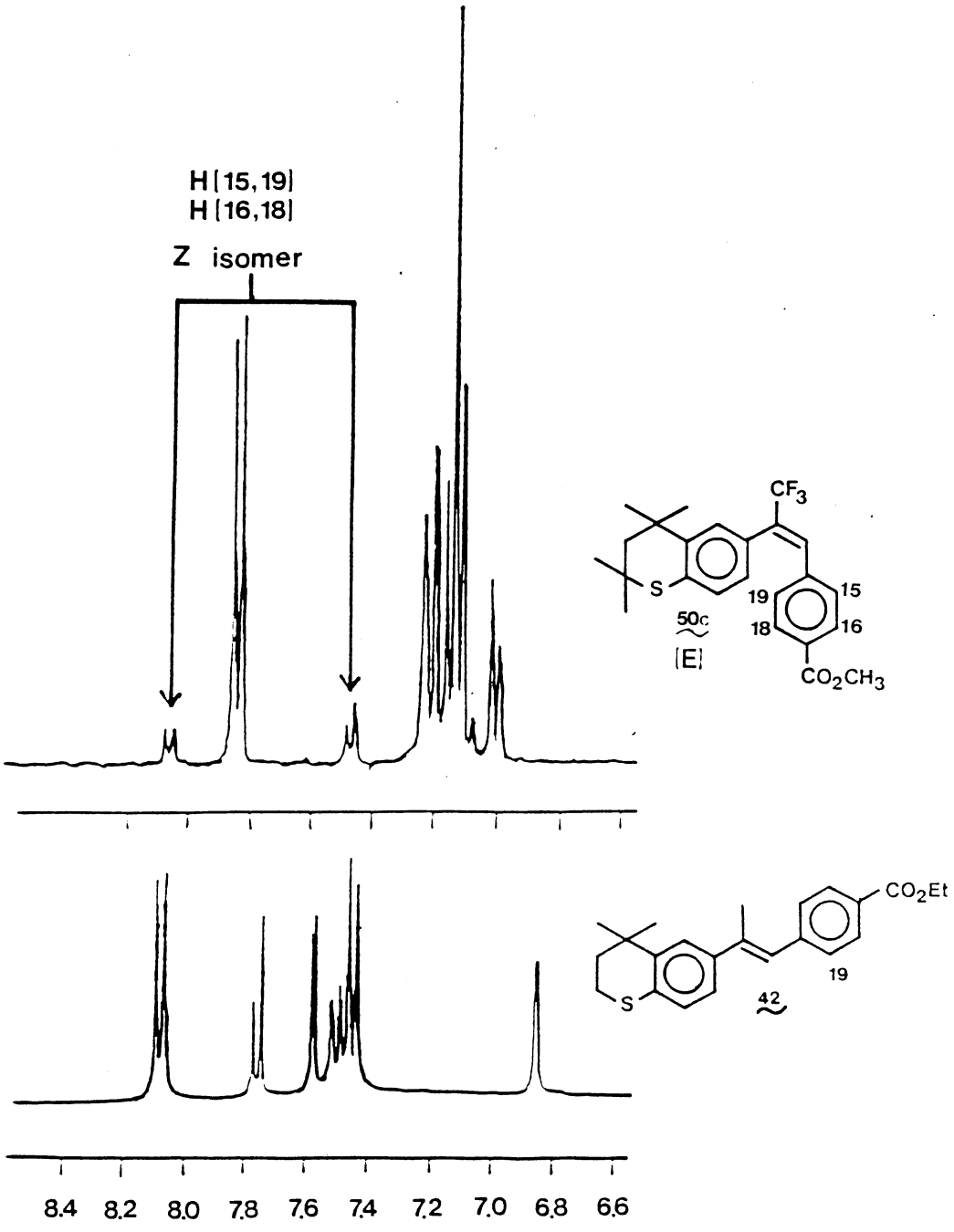


Figure 43. ^{1}H NMR of Ester **42** and E/Z Mixture of Ester 50c.

extent because of the fluorine atoms. Since ester **42** was confirmed as the (E)-isomer by X-ray analysis,[128] but yet the heteroarotinoids **50a-f** have considerably different ^{1}H spectra, it is presumed that **50a-f** exist as (E)-isomers (aryl rings are syn about the double bond in contrast to an anti arrangment as in **42**). The supposition awaits confirmation.

The ^{13}C NMR spectra for heteroarotinoids **50a-f** were not useful in elucidating the stereochemistry about the double bond at C(11)-C(13). Two carbons that were of particular interest, however, were C(11) [the vinyl carbon bonded to the trifluoromethyl group] and C(12) [the carbon bonded to the three fluorine atoms]. In the ^{13}C spectra of **50a-f**, these two carbons were not resolved. Presumably, the fluorine atoms alter the relaxation mechanism for these carbons, thus diminishing the signal intensities. Furthermore, since C(11), and possibly C(12), could be coupled with fluorine, the ^{13}C signal multiplicity will be a quartet with a large J value which could be buried in the baseline noise. Efforts to increase the signal intensity (NMR delay at 10 seconds, normal is 4.0 seconds) proved unsucessful. All the ^{13}C signals are shown in the experimental with ^{1}H NMR signals. A sample of **50c** is currently being examined by X-ray diffraction analysis.

The stereochemical nature of the double bonds present in these newly synthesized heteroarotinoids **48a-f, 49a-b** and **50a-f** may be critical for biological activity. Thus the

elucidation of structures for these new retinoids is essential if a correlation is to be made with biological activity.

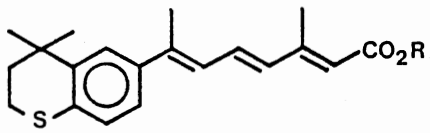
CHAPTER IV

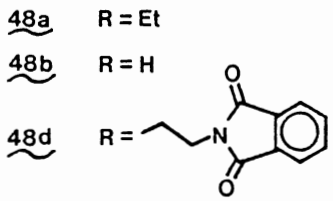
PHARMACOLOGICAL ACTIVITY OF HETEROAROTINOIDS

Although the synthetic objectives of this project were successful, the complete biological analysis of the heteroarotinoids is being conducted in terms of ODC activity by Dr. A. K. Verma at the Department of Human Oncology, University of Wisconsin and activity toward differentiation of HL-60 cells by Dr. T. R. Breitman at the National Cancer Institute. To date, three of the heteroarotinoids (**48a**, **b**, and **d**) have been tested, and the biological analyses for ornithine decarboxylase (ODC) activity[122,124] are shown in Table XVII. The results of this assay correlate well with the inhibition of papilloma development in the long term experiments with mice.[124] The procedure used for these retinoids was slightly different from that described earlier. For completeness, the procedure will be reiterated with small changes. The test retinoids were applied to the shaven backs of the mice 1 hour before application of 10 nmols of TPA (refer to Figure 11). After 5 hours, the mice were killed and the epidermus was separated and homogenized. The release of labeled CO_2 from [$^{14}CO_2$] ornithine was determined from this solution.

TABLE XVII

ODC ACTIVITY OF
HETEROAROTINOIDS **48a, 48b** and **48d**



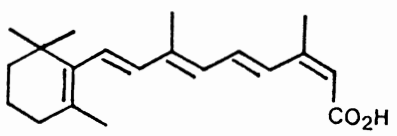


Test System	Retinoid Dose, nmol	ODC Activity	Percent Inhibition
Acetone	0.0	0.00 ± 0.00*	-
Acetone + TPA	0.0	0.90 ± 0.31*	Control
1g$^{\Phi}$ + TPA	17.0	0.10 ± 0.01*	89
48a + TPA	17.0	0.00 ± 0.00*	100
48b + TPA	17.0	0.10 ± 0.01*	89
Acetone	0.0	0.00 ± 0.00§	-
Acetone + TPA	0.0	1.67 ± 0.14§	Control
1g$^{\Phi}$ + TPA	17.0	0.14 ± 0.04§	92
48d + TPA	34.0	0.97 ± 0.13§	42

* nmol CO_2/30 min/mg protein

§ nmol CO_2/60 min/mg protein

$^{\Phi}$ 13-cis-retinoic acid



1g

The greater the amount of $^{14}CO_2$ released the lower the activity of the test retinoid. The retinoids were evaluated in three separate experiments, and the results from the experiments were normalized (% inhibition). This should allow for comparison with the results from other research groups in this field.

Results in Table XVII clearly indicate the importance of this family of retinoids. Ester **48a** at a 17 nmol dose completely inhibited ODC activity. Even acid **48b** was extremely active at the same dose. However, with the incorporation of a large bulky group at the terminus as in **48d**, the activity dropped sharply.

Acid **48b** was also tested in the HL-60 cell line.[108,119] The procedure is identical to that described in an earlier section (pp. 31-34). The dose-response curve of the HL-60 cell line with the standard trans-retinoic acid (**1b**) and acid **48b** is shown in Figure 44. The ED_{50} for trans-retinoic acid (**1b**) was 4.1×10^{-8} M and for acid **48b**, it was 7.2×10^{-8} M.

Heteroarotinoids, **48a** and **48b**, show signs of a bright future in the area of cancer chemotherapy. The incorporation of the sulfur atom in the cyclohexyl ring was shown by Dawson[29] to reduce the toxicity normally associated with this class of compounds. In the ODC assay, both **48a** and **48b** at equivalent doses were at least as potent as 13-cis-retinoic acid (**1g**). Since acid **1g** is clinically being used for treament of cystic acne, it seems logical that both **48a**

and **48b** might someday be used in chemotherapy as well.

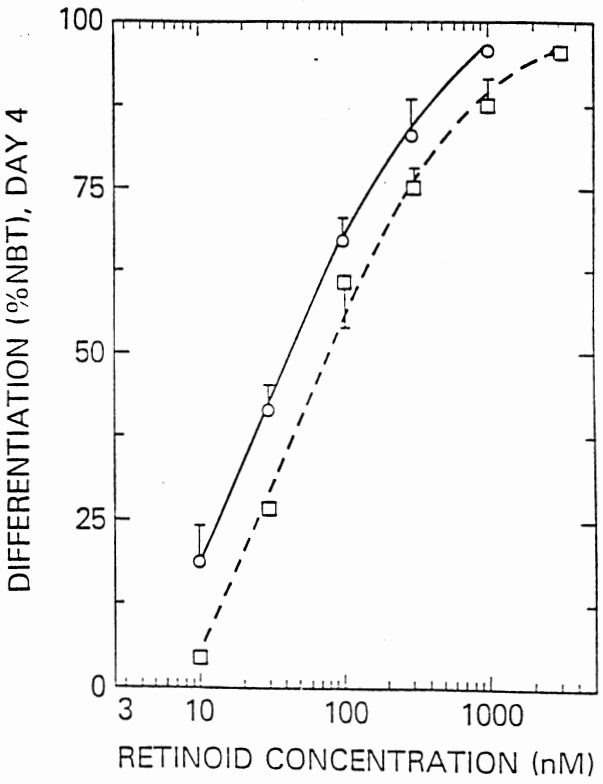
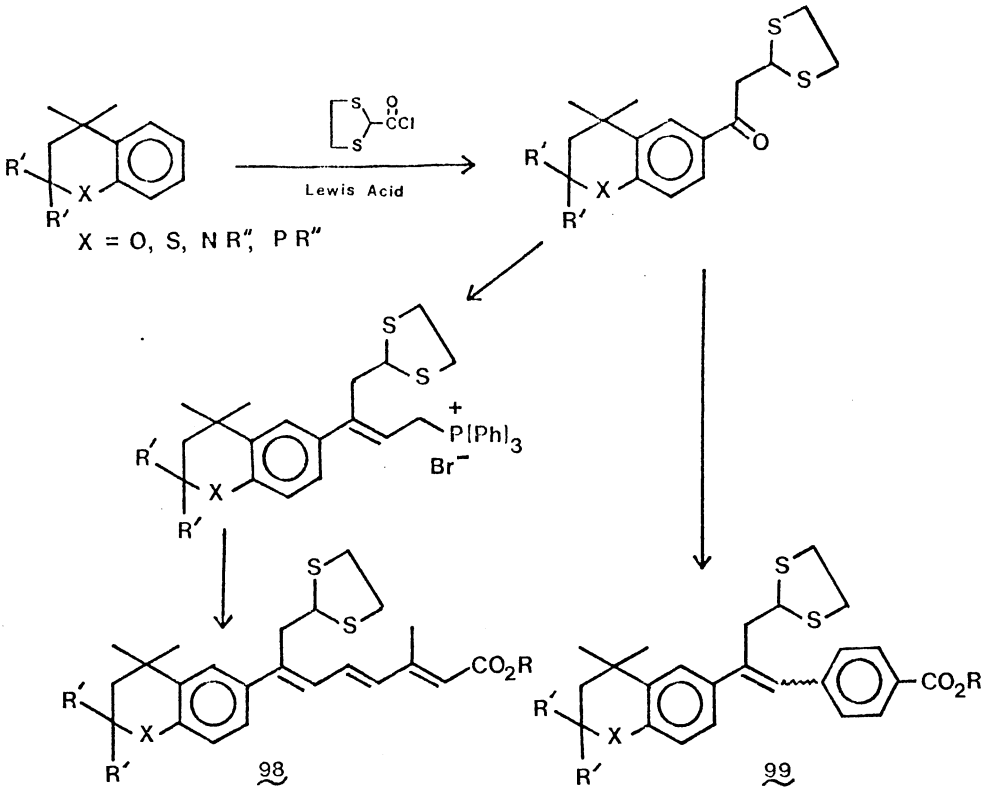


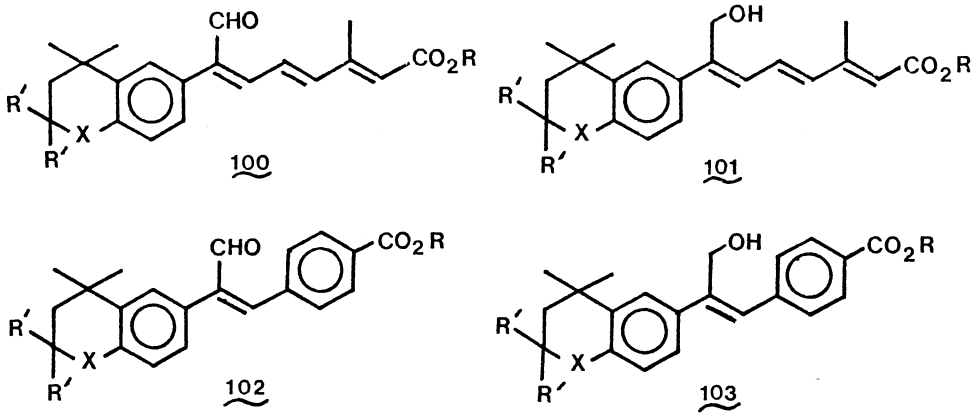
Figure 44. Dose Response Curve For trans-Retinoic Acid (**1b**) (o) And Heteroarotinoid **48b** (□) In The HL-60 Cell Line.

CHAPTER V

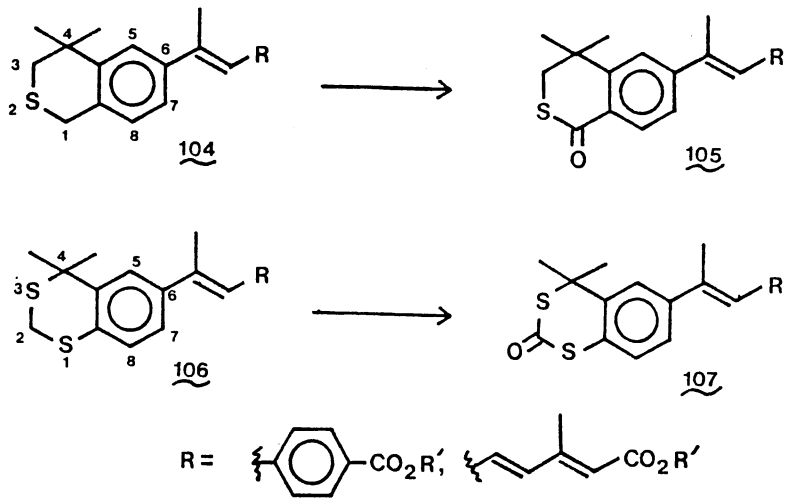
SUGGESTIONS FOR FUTURE WORK

Two main objectives upon which synthetic medicinal chemists have focused with retinoids are activity and toxicity. A major draw back with retinoids appears to be associated with the inherent toxicity. As disclosed herin, there are many retinoids that exist which have good biological activity. Several have activities that are equal to trans-retinoic acid (**1b**) and 13-cis-retinoic acid (**1g**). However, attention needs to be directed at reducing the overall toxicity with these medicinally important compounds. Until the mechanism on epitheal differentiation and cancer is unveiled, one approach to reducing the toxicity is structural modifications, perhaps similar to those of retinoid metabolites. A structural alteration that could prove useful is shown below with the heteranapthyl moiety as a building block leading to retinoids **98** and **99**. There exists many useful reagents to remove the thioacetal group ($HgCl_2$, HgO-BF_3, H_2O_2-HCl, t-BuBr-Me_2SO, PbO_2-BF_3-etherate, Me_2SO-HCl-dioxane and $(PhSeO)_2O$).[70a] Once the aldehyde is obtained, it can be reduced to the target compound.


Lewis Acid
X = O, S, N R", P R"
P[Ph]3
Br−
CO2R
98
99

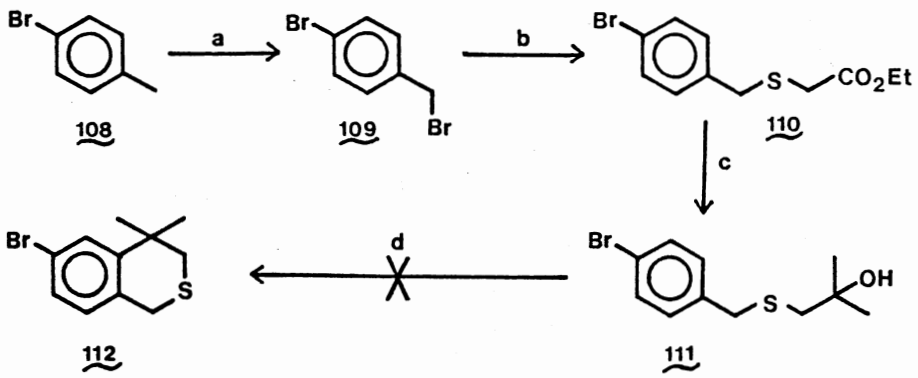

CHO
OH
CO2R
100
101
102
103

Another approach to reducing the toxicity of these compounds is to adopt a "pro drug" concept. This would entail purposefully leaving one or more sites of the retinoid vulnerable to metabolic degradation. The resulting compound(s) would have increased polarity (carbonyl or hydroxyl functionalities) increasing the hydrophilicity leading to presumably a more active retinoid. Two general retinoids of interest might be those shown below.



Sulfur atoms are shown in these structures because of the preliminary evidence suggesting reduction in toxicity in compounds like **43**.[29] Obviousily, retinoid **104** is susceptible to oxidation at C(1) (also at the sulfur atom)

which could lead to thiolactone **105.** Similarily, compound **106** would expectedly give rise to **107.** The synthesis for **104** was briefly explored. The examined synthetic scheme is shown below. Alternative reactions conditions to give the



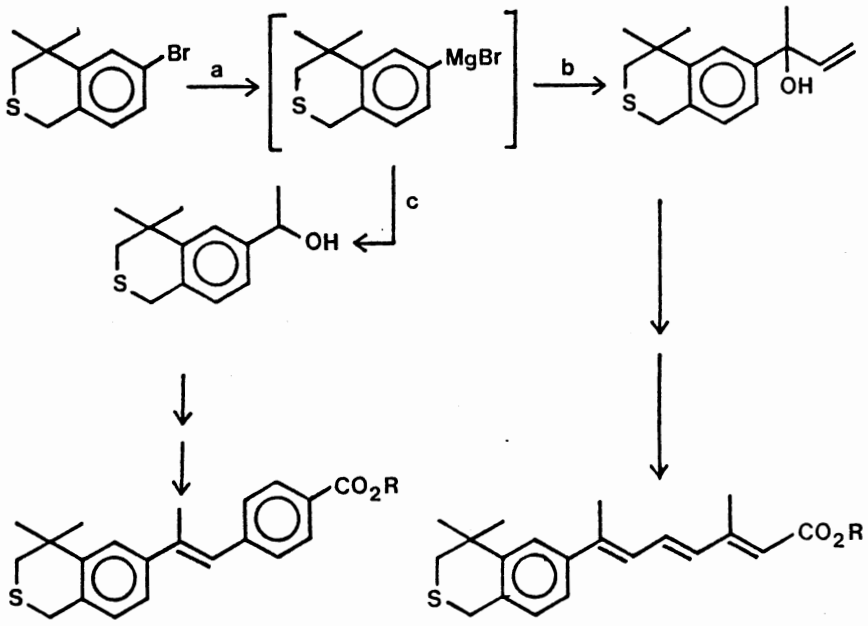
a. NBS, CCl_4, hv, 24 h

b. CH_3ONa, $HSCH_2CO_2Et$

c. 1.) 2 CH_3MgI 2.) H_3O^+

d. H_3PO_4, P_2O_5

the isothiochroman **112** might include bioling **111** in aluminum chloride. Then the Grignard reagent of **112** with the appropreiate carbonyl compound (**113** or **114**) should give alcohols **115** (or **116**) as precursors to the important phosphonium salts and finally the target compounds.



a. Mg/THF

b. 1.) $CH_3C(O)CH{=}CH_2$ (**113**) 2.) H_3O^+

c. 1.) CH_3CHO (**114**) 2.) H_3O^+

CHAPTER VI

EXPERIMENTAL SECTION

General Information

All reactions were carried out in an inert nitrogen atmosphere using magnetic stirring except where otherwise specified. The NMR spectra were taken on a Varian XL-300 NMR spectrometer operating at 299.9485 MHz for ^{1}H, 75.429 MHz for ^{13}C, 121.421 MHz for ^{31}P and at 282.203 MHz for ^{19}F. The ^{1}H and ^{13}C NMR signals are reported in δ values or in ppm, respectively, downfield from tetramethylsilane with $DCCl_3$ as the solvent. The ^{31}P NMR signals are reported in ppm downfield from the external reference of H_3PO_4 and with $DCCl_3$ as the solvent. However, CF_3CO_2H was used as the external standard for ^{19}F which was in turn back referenced to $FCCl_3$. The ^{19}F NMR signals are reported in ppm upfield from $FCCl_3$ with $DCCl_3$ as the solvent. IR data was collected on a Perkin-Elmer 681 IR spectrophotometer. Melting points were obtained using a Thomas Hoover melting point apparatus and are uncorrected. Chromatography was accomplished using a Chromatotron Model 7924 (Harrison Research, 340 Moana Court, Palo Alto, California 94306) as described in the Chromatotron Operation Manual with silica gel, unless otherwise specified. Starting

materials were prepared by modified procedures from the literature (**54**,[57,128] **55**,[128] **56**,[128] **51a**,[128] **58**,[70] **69**,[21] **82**,[20,107] **72**,[85] **67**,[58] **74**,[58] **90**,[128] **84**,[128]).

Certain starting materials and other reagents were obtained form the sources listed below and were used without further purification except where cited: thiophenol (Aldrich, bp 169°C), ethyl acrylate (Aldrich, bp 99°C), triethylamine (Fisher, distilled from KOH: bp 89-90°C), methyl iodide (Fisher, distilled from copper at 41-42°C), P_2O_5 (Fisher, anhydrous white powder), H_3PO_4 (Fisher, 85%), acetyl chloride (Aldrich, bp 52°C), aluminium chloride (Fisher, anhydrous white powder), vinyl bromide (Aldrich, bp 16°C/750 mm), triphenylphosphine (Alfa, mp 79°C), HBr (Matheson, anhydrous, 99.8%), n-butyllithium/hexanes (Aldrich, 1.55 M), thionyl chloride (Eastman, bp 79°C), pyridine (Fisher, distilled from KOH: bp 114-115°C), N-2-hydroxyethylphthalimide (Frinton, mp 128°C), mesityl oxide (Eastman, bp 130°C), NaH (Aldrich, 60% dispersion in mineral oil), dimethyl sulfide (Aldrich, bp 38°C), ethyl bromoacetate (Alfa, bp 159°C), acrolein (Eastman, bp 53°C), sodium borohydride [Aldrich, mp 400°C (dec)]. Anhydrous solvents were obtained by known methods. Ether, THF and thiophene-free benzene were distilled from sodium prior to use. Carbon disulfide was distilled from P_2O_5 before use. Acetone was stored over K_2CO_3 for 24 h and filtered prior to use. All other solvents were obtained in anhydrous

condition and used without further purification. Brine was used as a saturated aqueous solution of NaCl.

Ethyl 3-(Phenylthio)propionate (54)

To a solution of 12.12 g (0.11 mol) of thiophenol (**52**), 10.01 g (0.10 mol) ethyl acrylate (**53**), and 20 mL of dry $HCCl_3$ at 0°C in a 100-mL, one-necked, round-bottom flask was added 0.50 mL of triethylamine. The cold bath (ice) was removed after the addition of triethylamine, and the solution was allowed to stir at room temperature for 3 h. The resulting solution was diluted with 150 mL of ether and washed with 10% NaOH (2 x 50 mL), H_2O (50 mL), and brine (50 mL). The mixture was dried (Na_2SO_4, overnight) and the solvents were removed (rotary evaporator). Vacuum distillation gave 19.36 g (92.1%) of ethyl 3-(phenylthio)-propionate (**54**) as a clear colorless liquid: bp 112-115°C/0.15 mm (lit[57] 117°C/2.5 mm, lit[128] 115-118/0.2 mm); IR (neat) 1740 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.14 [t, 3 H, $CO_2CH_2C\underline{H}_3$], 2.54 [t, 2 H, $C\underline{H}_2CO_2CH_2CH_3$], 3.10 [t, 2 H, $PhSC\underline{H}_2CH_2$], 4.06 [q, 2 H, $CO_2C\underline{H}_2CH_3$], 7.13-7.32 [m, 5 H, Ph-H]; ^{13}C NMR ($DCCl_3$) ppm 13.6 [$CO_2CH_2\underline{C}H_3$], 28.3 [$PhS\underline{C}H_2$], 33.8 [$\underline{C}H_2CO_2CH_2CH_3$], 60.0 [$CO_2\underline{C}H_2CH_3$], 125.8, 128.4, 129.3, 134.8, 170.9 [$\underline{C}$=O].

2-Methyl-4-(phenylthio)-2-butanol (55)

To a freshly prepared solution [42.59 g, (0.30 mol) of methyl iodide, 7.41 g (0.305 g-at) of magnesium] of methyl-

magnesium iodide in 75 mL of ether was added dropwise 21.03 g (0.10 mol) of ethyl 3-(phenylthio)propionate (**54**) in 25 mL of ether in a 500-mL, three-necked, round-bottom flask equipped with a condenser and a nitrogen inlet. The solution was boiled for 1 h and allowed to stir at room temperature for 10 h. The resulting solution was neutralized with 5% H_2SO_4 (pH approx. 6.5); the ether layer was separated and the aqueous layer was extracted with ether (3 x 75 mL). The ether layers were combined and dried (Na_2SO_4, overnight). Solvent was evaporated (rotary evaporator) and vacuum distillation of the residual oil gave 19.02 g (78.5%) 2-methyl-4-(phenylthio)-2-butanol (**55**) as a clear colorless liquid: bp 106-107.5°C/0.15 mm (Lit[128] 93-98°C/0.01 mm); IR (neat) 3400 cm^{-1} (br, O-H); ^1H NMR ($DCCl_3$) δ 1.18 [s, 6 H, $(C\underline{H}_3)_2C$], 1.76 [m, 2 H, $PhSCH_2C\underline{H}_2$], 2.74 [br s, 1 H, O$\underline{H}$], 2.95 [m, 2 H, $PhSC\underline{H}_2$], 7.10-7.36 [m, 5 H, Ph-$\underline{H}$]; ^{13}C NMR ($DCCl_3$) ppm 28.6 [$PhS\underline{C}H_2CH_2$], 29.3 [$(\underline{C}H_3)_2C$], 42.7 [$PhSCH_2\underline{C}H_2$], 70.7 [$(CH_3)_2\underline{C}$], 125.9, 128.9, 136.5.

4,4-Dimethylthiochroman (**56**)

A mixture of 15.00 g (0.076 mol) of 2-methyl-4-(phenylthio)-2-butanol (**55**), 12.75 g of H_3PO_4, 27.0 g (0.190 mol) of P_2O_5 [this is added in three equal portions every 8 h] and 60 mL of anhydrous benzene was boiled for 24 h in a 250-mL, three-necked, round-bottom flask equipped with a

condenser and N_2 inlet. The resulting, cooled (ice bath) heterogeneous mixture was separated and the lower oily layer was extracted with ether (2 x 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL) and then dried (Na_2SO_4, 4 h). Evaporation (rotary evaporator) of the solvent and vacuum distillation of the oil gave 11.68 g (86.0%) of 4,4-dimethylthiochroman (**56**) as a clear colorless liquid: bp 75-82°C/0.1 mm (lit[128] 80-85°C/0.01 mm); ^1H NMR ($DCCl_3$) δ 1.29 [s, 6 H, $(C\underline{H}_3)_2C$] 1.92 [m, 2 H, $PhSCH_2C\underline{H}_2$] 3.00 [m, 2 H, $PhSC\underline{H}_2CH_2$], 6.90-7.32 [m, 4 H, Ph-$\underline{H}$]; ^{13}C NMR ($DCCl_3$) ppm 22.8 [$PhS\underline{C}H_2CH_2$], 29.9 [$(\underline{C}H_3)_2C$], 32.6 [$(CH_3)\underline{C}$], 37.4 [$PhSCH_2\underline{C}H_2$], 123.7, 125.7, 126.1, 126.2, 131.5, 141.5.

6-Acetyl-4,4-dimethylthiochroman (**51a**)

A solution of 10.0 g (0.056 mol) of 4,4-dimethylthiochroman (**56**) and 4.4 g (0.056 mol) of acetyl chloride in 150 mL of dry carbon disulfide was added dropwise over a 45 min period to a stirred suspension of $AlCl_3$ (11.22 g, 0.084 mol) in a 500-mL, three-necked, round-bottom flask equipped with a condenser and N_2 inlet. The resulting yellowish-orange mixture was allowed to stir for 10 h at room temperature; 80 mL of ice water was added and two layers separated. The aqueous layer was extracted with ether (3 x 50 mL); the ether layers were combined and dried (Na_2SO_4, 6 h). After evaporation (rotary evaporator), the resulting light yellow oil was vacuum distilled to give 10.83 g

(87.6%) of 6-acetyl-4,4-dimethylthiochroman (**51a**) as a light yellow viscous oil: bp 168-173°C/2.0 mm (lit[128] 126-130°C/0.02 mm); IR (neat) 1680 cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.31 [s, 6 H, $(C\underline{H}_3)_2C$], 1.89 [m, 2 H, $PhSCH_2C\underline{H}_2$], 2.52 [s, 3 H, $C\underline{H}_3C(O)$] 3.01 [m, 2 H, $PhSC\underline{H}_2CH_2$], 7.11 [d, 1 H, J = 8.1 Hz, H(8)], 7.57 [dd, 1 H, J = 1.7 Hz, J = 8.1 Hz, H(7)], 8.00 [d, 1 H, J = 1.7 Hz, H(5)]; ^{13}C NMR ppm 23.1 [$PhS\underline{C}H_2CH_2$], 26.2 [$\underline{C}H_3C=O$], 29.8 [$(\underline{C}H_3)_2C$], 32.8 [$(CH_3)_2\underline{C}$], 36.8 [$PhSCH_2\underline{C}H_2$], 125.8, 126.2, 132.9, 139.4, 141.7, 196.7 [$CH_3\underline{C}(O)$].

2-(4,4-Dimethyl-6-thiochromanyl)-2-hydroxy-3-butene (**61a**)

To a freshly prepared solution of vinylmagnesium bromide;[102,103] [7.65 g (0.0715 mol) of vinyl bromide was added to 1.75 g (0.0720 g at) of magnesium, in 40 mL of dry THF; the preparation was by the usual procedure for Grignard reagents] was added dropwise 10.5 g (0.0477 mol) of 6-acetyl-4,4-dimethylthiochroman (**51a**) in 25 mL of THF in a 200-mL, three-necked, round-bottom flask equipped with a condenser and N_2 inlet with stirring. The solution was then boiled for 1 h and allowed to stir for 10 h at room temperature. Saturated NH_4Cl solution was added in 1-mL portions until the solution was slightly acidic (pH approx. 6.8), and the layers were separated. The aqueous layer was extracted with ether (4 x 100 mL) and the ether extracts

were combined with the organic layer. The organic solution was washed with 50 mL of H_2O and 50 mL of brine and was then dried (Na_2SO_4, 4 h). The resulting oil (assumed to be quantitative) was used without further purification; IR (neat) 3200-3600 cm^{-1} (O-H); ^1H ($DCCl_3$) δ 1.32 [s, 6 H, $(C\underline{H}_3)_2C$], 1.95 [m, 2 H, $PhSCH_2C\underline{H}_2$], 2.11 [bs, 1 H, O$\underline{H}$], 3.00 [m, 2 H, $PhSC\underline{H}_2CH_2$], 5.14 [dd, 1 H, J = 2.0 Hz, J = 10.5 Hz, $CH=C\underline{H}_2$ (cis)], 5.30 [dd, 1 H, J = 2.0 Hz, J = 15.0 Hz, $CH=C\underline{H}_2$ (trans)], 6.16 [dd, 1 H, J = 10.5 Hz, J = 15.0 Hz, $C\underline{H}=CH_2$], 7.05 [d, 1 H, J = 8 Hz, H(8)], 7.12 [dd, 1 H, J = 2 Hz, J = 8 Hz, H(7)], 7.52 [d, 1 H, J = 2 Hz, H(5)]; ^{13}C ($DCCl_3$) ppm 22.9 [$PhS\underline{C}H_2CH_2$], 29.1 [$\underline{C}H_3COH$], 30.2 [$(\underline{C}H_3)_2C$], 33.1 [$(CH_3)_2\underline{C}$], 37.3 [$PhSCH_2\underline{C}H_2$], 74.5 [$CH_3\underline{C}OH$], 112.1, 123.1, 123.2, 126.2, 130.2, 141.6, 142.1, 144.7.

(E)-3-(1,2,3,4-Tetrahydro-4,4-dimethyl-6-thiochromanyl)-2-butenyl-triphenyl-phoshonium Bromide (**63a**)

To a suspension of 15.6 g (45.4 mol) of triphenyl-phosphine hydrobromide in methanol (100 mL) was added dropwise with stirring to a methanol solution (50 mL) of the previously prepared alcohol **61a** (11.3 g, 45.4 mmol) in a 100-mL, one-necked, round-bottom flask at room temperature (N_2) for 9.5 h. Methanol was removed (rotary evaporator) from the clear solution, ether (approx. 400 mL) was added and crystrallization occurred within a short time. After standing overnight, 26.0 g of white crystals

of salt **63a** formed which were collected, recrystallized (methanol/ether) and dried (24 h, 0.1 mm Hg). The yield of salt **63a** was 25.7 g (98.8% from the allyl alcohol **61a**): mp 268.5-269.5 °C (dec); ^{1}H NMR ($DCCl_3$) δ 1.26 [s, 6 H, $(C\underline{H}_3)_2C$], 1.63 [d, 3 H, J = 4.0 Hz, $C\underline{H}_3C{=}CH$ (trans)], 1.93 [m, 2 H, $PhSCH_2C\underline{H}_2$], 3.02 [m, 2 H, $PhSC\underline{H}_2CH_2$], 4.89 [dd, 2 H, J = 8.0 Hz, J_{PH} = 15.1, $C{=}CHC\underline{H}_2PPh_3$], 5.60 [tq, 1 H, J = 4.0 Hz, J = 8.0 Hz, $CH_3C{=}C\underline{H}CH_2PPh_3$], 6.85 [dd, 1 H, J = 2.0 Hz, J = 8.1 Hz, H(7)], 7.00 [d, 1 H, J = 8.1 Hz, H(8)], 7.17 [d, 1 H, J = 1.7 Hz, H(5)], 7.66-8.00 [m, 15 H, $P(Ph\text{-}\underline{H})_3$]; ^{13}C NMR ($DCCl_3$) ppm 17.0 [$\underline{C}H_3C{=}CH$], 23.0 [$PhS\underline{C}H_2CH_2$], 25.4 [d, J_{CP} = 49 Hz, $C{=}CH\underline{C}H_2$], 30.1 [$(\underline{C}H_3)_2C$], 33.0 [$(CH_3)_2\underline{C}$], 37.4 [$PhSCH_2\underline{C}H_2$], 110.2, 110.3, 117.6, 118.8, 123.4, 123.9, 126.4, 130.2, 130.4, 132.1, 133.9, 134.1, 135.0, 138.0, 138.1, 141.9, 145.4, 145.6; ^{31}P ($DCCl_3$) ppm 21.6, Anal. Calcd for $C_{33}H_{34}SPBr$: C, 69.10; H, 5.98; P, 5.40. Found: C, 69.21; H, 6.07; P, 5.41.

(2E,4E,6E)-3,7-dimethyl-7-(1,2,3,4,-tetrahydro-4,4-dimethyl-6-thiochromanyl)-2,4,6-heptatrienoic Acid (**48b**)

To a stirred suspension of 3.56 g (0.00621 mol) of phosphonium salt **63a** in 50 ml ether was added dropwise n-butyllithium in hexane (4.01 mL, 1.55 M, 0.00621 mol) at room temperature in a 100-mL, three-necked, round-bottom flask equipped with a condenser and N_2 inlet. The

resulting, dark orangish-red solution was cooled to -78°C, and 0.90 g (0.00621 mol) of ethyl (E)-β-formylcrotonate (**64**) in 10 mL of ether was added dropwise in the dark (approx. 5-10 min). The dark red mixture was allowed to warm to room temperature for 10 h and was then diluted with 100 mL of hexane. The solution was filtered and evaporated (vacuum) to give a yellow oil. The resulting oil was added to a solution of 4.5 g (0.0802 mol) of KOH in aqueous ethanol (50 ml 4:1 ethanol/H_2O) and the solution was boiled with stirring in the dark for 45 min. The reddish solution was cooled (RT), treated with 5.0 g of NaCl and extracted with 100 mL of ether. The ether layer was extracted with water (4 x 50 mL), and the combined aqueous layers were acidified slowly with dilute H_2SO_4. At the neutralization point, solid began to form; the aqueous yellow suspension was extracted with ether (3 x 75 mL). The ether layer was dried (Na_2SO_4) and evaporated (vacuum) to give a yellow solid. After fractional recrystallization (abs ethanol), 0.88 g (43.1% from the salt **63a**) of yellow needles of acid **48b** were obtained with a mp of 204-204.5°C (dec); ^{1}H NMR ($DCCl_3$) δ 1.37 [s, 6 H, $(C\underline{H}_3)_2C$], 1.98 [m, 2 H, $PhSCH_2C\underline{H}_2$], 2.25 [s, 3 H, $C\underline{H}_3$], 2.42 [s, 3H, $C\underline{H}_3$] 3.06 [m, 2 H, $PhSC\underline{H}_2CH_2$], 5.86 [br s, 1 H, $C\underline{H}CO_2H$], 6.44 [d, 1H, J = 15 Hz, $C\underline{H}C(CH_3)CHCO_2H$], 6.59 [d, 1H, J = 12 Hz, $PhC(CH_3)C\underline{H}$], 7.09 [d, 1H, J = 7 Hz, H(8)], 7.10 [dd, 1H, J = 12 Hz, J = 15 Hz, CH-C$\underline{H}$=CH], 7.21 [dd, 1H, J = 2 Hz, J = 7 Hz, H(7)], 7.52 [d, 1H, J = 2 Hz, H(5)]; ^{13}C NMR ($DCCl_3$)

ppm 13.8 [$\underline{C}H_3$], 16.1 [$\underline{C}H_3$], 23.0 [PhS$\underline{C}H_2CH_2$], 30.1 [$(\underline{C}H_3)_2C$], 33.0 [$(CH_3)_2\underline{C}$], 37.5 [PhSCH$_2\underline{C}H_2$], 118.3 [$\underline{C}HCO_2H$], 123.3 [C(7)], 123.6 [C(5)], 125.4 [PhC(CH_3)$\underline{C}H$], 126.4 [C(8)], 131.5, 131.7 [CH-$\underline{C}$H=CH], 135.4 [$\underline{C}HC(CH_3)CHCO_2H$], 138.1, 140.2 [Ph$\underline{C}(CH_3)CH$], 141.7, 154.0 [$\underline{C}(CH_3)CHCO_2H$], 170.8 [$\underline{C}O_2H$]. Anal. Calcd for $C_{20}H_{24}O_2S$: C, 73.13; H, 7.36; S, 9.76. Found: C, 73.31; H, 7.37; S, 10.01.

Ethyl (2E, 4E, 6E)-3,7-Dimethyl-7-(1,2,3,4,-tetrahydro-4,4-dimethyl-6-thiochromanyl)-2,4,6,-heptatrienoate (48a)

To a stirred suspension of 503 mg (1.53 mmol) of trans-heteroarotinoic acid **48b** in 8 mL of dry ether was added 0.1420 g (0.00180 mol) of freshly distilled pyridine, and the mixture was cooled to -10°C in a 50 mL, round bottom, three-neck, flask equipped with a condenser and N_2 inlet. A solution of 201 mg (1.69 mmol) of $SOCl_2$ in ether (1 mL) was added and stirring was continued at room temperature for 1 h. The resulting dark red solution was filtered and cooled to -20°C (dry ice/CCl_4). Then 142 mg (1.80 mmol) of pyridine was added and 210 mg (4.59 mmol) of dry ethanol was introduced all at once and stirring was maintained at room temperature for 3 h. The yellow solution was diluted with 25 mL of ether, and the new solution was washed with water (4 x 30 mL); the ether layer was dried (Na_2SO_4, 1 h).

The solvent was removed (rotor evaporator), and the resulting yellow oil was chromatographed on silica gel using hexane/ether (15:1) with the silica gel retaining the trans-heteroarotinoic acid **48b**. The ethyl ester **48a** 492 mg (88.1%) was obtained as a viscous yellow oil; ^{1}H NMR ($DCCl_3$) δ 1.30 [t, 3 H, $CO_2CH_2C\underline{H}_3$], 1.36 [s, 6 H, $(C\underline{H}_3)_2C$], 1.96 [m, 2 H, $PhSCH_2C\underline{H}_2$], 2.22 [s, 3 H, $C\underline{H}_3$] 2.38 [s, 3 H, $C\underline{H}_3$], 3.14 [m, 2 H, $PhSC\underline{H}_2CH_2$], 4.19 [q, 2 H, $CO_2C\underline{H}_2CH_3$], 5.82 [s, 1 H, $C\underline{H}CO_2Et$], 6.39 [d, 1 H, J = 15 Hz, $C\underline{H}C(CH_3)CHCO_2Et$], 6.55 [d, 1 H, J = 12 Hz, $PhC(CH_3)C\underline{H}$], 7.03 [dd, 1 H, J = 12 Hz, J = 15 Hz, CH-C<u>H</u>=CH], 7.07 [d, 1 H, J = 8 Hz, H(8)], 7.18 [dd, 1 H, J = 2 Hz, J = 8 Hz, H(7)], 7.48 [d, 1 H, J = 2 Hz, H(5)]; ^{13}C NMR ($DCCl_3$) ppm 13.8 [$C(\underline{C}H_3)CHCO_2Et$], 14.3 [$CH_2\underline{C}H_3$], 16.2 [$PhC(\underline{C}H_3)CH$], 23.1 [$PhS\underline{C}H_2 2CH_2$], 30.1 [$(\underline{C}H_3)_2C$], 33.1 [$(CH_3)_2\underline{C}$], 37.6 [$PhSCH_2\underline{C}H_2$], 59.6 [$\underline{C}H_2CH_3$], 118.7 [$\underline{C}HCO_2Et$], 123.4 [C(7)], 123.6 [C(5)], 125.5 [<u>C</u>H-CH=CH], 126.4 [C(8)], 131.1 [CH-<u>C</u>H=CH], 135.5 [CH-CH=<u>C</u>H], 138.2, 139.9 [$Ph\underline{C}(CH_3)CH$], 141.7, 152.3 [$\underline{C}(CH_3)CHCO_2Et$], 167.1 [$\underline{C}O_2Et$]. Anal. Calcd for $C_{22}H_{28}SO_2$: C, 74.12; H, 7.92. Found: C, 74.35; H, 8.06.

<u>2-Phthalimidoethyl (2E,4E,6E)-3,7-Dimethyl-7-(1,2,3,4-tetrahydro-4,4-dimethyl-6-thiochromanyl)-2,4,6-heptatrienoate</u>

<u>**(48d)**</u>

To a suspension of 503 mg (1.53 mmol) of <u>trans</u>-heteroarotinoic acid **48b** in 8 mL of dry ether was added 142

mg (1.80 mmol) of freshly distilled pyridine in a 50-mL, three-necked, round-bottom flask equipped with a condenser and nitrogen inlet, and the suspension was cooled to -10°C (NaCl/ice slurry). A solution of 201 mg (1.69 mmol) of $SOCl_2$ in ether (1 mL) was added. The solution was stirred at room temperature for 1 h. The resulting dark red solution was filtered and cooled to -20°C (dry ice/CCl_4); 142 mg (1.80 mmol) of additional pyridine was added. Then a bolus of 296 mg (1.55 mmol) of N-2-hydroxyethyl-phthalimide in 8 mL of dry DMF was introduced and the solution was warmed to room temperature; the new solution was allowed to stir for 10 h. The resultant yellow solution was diluted with ether (25 mL) and washed with water (5 x 60 mL); the ether layer was dried (Na_2SO_4, overnight). The solvent was removed (rotor evaporator) and the resulting yellow solid was chromatographed on silica gel (Chromatotran) using $HCCl_3$. The phthalimido-substituted heteroretinoid **48d** [273 mg, (35.6 %)] was a yellow solid: mp 64-65°C; IR (KBr) 1760-1710 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.36 [s, 6 H, $(C\underline{H}_3)_2C$], 1.98 [m, 2 H, $PhSC\underline{H}_2CH_2$], 2.24 [s, 3 H, $C\underline{H}_3$], 2.34 [s, 3 H, $C\underline{H}_3$], 3.06 [m, 2 H, $PhSCH_2C\underline{H}_2$]. 4.03 [t, 2 H, $CO_2CH_2CH_2$], 4.40 [t, 2 H, $CO_2CH_2CH_2$] 5.78 [s, 1 H, $C\underline{H}CO_2CH_2CH_2$], 6.38 [d, 1 H, J = 15 Hz, $C\underline{H}C(CH_3)CHCO_2CH_2$], 6.55 [d, 1 H, J = 12 Hz, $PhC(CH_3)C\underline{H}$], 7.03 [dd, 1 H, J = 12 Hz, J = 15 Hz, CH-$C\underline{H}$=CH], 7.08 [d, 1 H, J = 8 Hz, H(8)], 7.18 [dd, J = 2 Hz,

J = 8 Hz, H(7)], 7.48 [d, 1 H, J = 2 Hz, H(5)], 7.75 [m, 2 H], 7.80 [m, 2 H]; ^{13}C NMR ($DCCl_3$) ppm 13.9 [C($\underline{C}H_3$)CH], 16.2 [PhC($\underline{C}H_3$)], 23.1 [PhS$\underline{C}H_2CH_2$], 30.2 [($\underline{C}H_3)_2C$], 33.1 [$(CH_3)_2\underline{C}$], 37.1 [$CO_2CH_2\underline{C}H_2$], 37.6 [$PhSCH_2\underline{C}H_2$], 60.8 [$CO_2\underline{C}H_2CH_2$], 117.9 [$\underline{C}HCO_2CH_2CH_2$], 123.3, 123.4 [C(7)], 123.6 [C(5)], 125.5 [$\underline{C}H-CH=CH$], 126.5 [C(8)], 131.4, 131.8, 132.0 [$CH-\underline{C}H=CH$], 134.0, 135.4 [$CH-CH=\underline{C}H$], 138.2, 140.1 [$Ph\underline{C}(CH_3)CH$], 141.8, 153.5 [$\underline{C}(CH_3)CHCO_2CH_2$], 166.6 [$\underline{C}O_2CH_2CH_2$], 168.0 [$CH_2N(\underline{C}=O)_2$]; Anal. Calcd for $C_{30}H_{31}NO_4S$: C, 71.83; H, 6.23; N, 2.79. Found: C, 71.47; H, 6.31; N, 2.76.

4-Methyl-4-thiaphenyl-2-pentanone (58)

To a solution of 28.64 g (0.26 mol) of thiophenol (52), 24.54 g (0.25 mol) of mesityl oxide (57) and 100 mL of $HCCl_3$ at 0°C (ice) in a 500 mL, three-necked, round-bottom flask was added 1.5 ml of triethylamine. The cold bath was removed (15 min) after the addition of triethylamine and the solution was stirred at room temperature for 1 h. The resulting clear, colorless solution was heated at reflux for an additional 24 h. The new solution was allowed to cool to room temperature and poured into a separatory funnel; the flask was rinsed with 25 mL of ether which was added to the separatory funnel. The mixture was washed with 10% NaOH (2 x 50 mL), and the combined aqueous layers were extracted with ether (3 x 50 mL). The organics were combined, washed with H_2O (50 mL) and brine (50 ml) and

then dried (Na_2SO_4, overnight). The dried solution was filtered and concentrated (rotary evaporator). Following vacuum distillation, 40.14 g (77.1%) of 4-methyl-4-thiaphenyl-2-pentanone (**58**) was obtained as a clear colorless liquid: bp 85-87°C/0.01 mm (lit[70] 94-95°C/0.01 mm); IR (neat) 1730 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.41 [s, 6 H, $C(C\underline{H}_3)$], 2.15 [s, 3 H, O=C-$C\underline{H}_3$], 2.69 [s, 2 H, $C\underline{H}_2C(O)CH_3$], 7.34-7.42 [m, 3 H, Ph-$\underline{H}$], 7.75 [dd, 2 H, J = 3.0 Hz, J = 8.0 Hz, Ph-$\underline{H}$]; ^{13}C NMR ($DCCl_3$) ppm 28.1 [q, $(\underline{C}H_3)_2C$], 31.9 [q, O=C-$\underline{C}H_3$], 46.9 [s, $\underline{C}(CH_3)_2$], 54.2 [t, $\underline{C}H_2C(O)CH_3$], 128.4 [d, C(2')], 128.8 [d, C(4')], 131.4 [s, C(1')], 137.4 [d, C(3')], 205.5 [s, C=O].

2,4-Dimethyl-4-thiaphenyl-2-pentanol (**59**)

To a freshly prepared solution [34.06 g, (0.24 mol) of methyl iodide, 5.83 g (0.24 g at) of magnesium in 100 mL of dry ether] of methylmagnesium iodide in 165 mL of ether was added dropwise 25.00 g (0.120 mol) of 2,4-dimethyl-4-thiaphenyl-2-pentanone (**58**) in 50 mL of ether in a 500-ml, three-necked, round-bottom flask equipped with a condenser and N_2 inlet. The solution was stirred at room temperature for 3 h and poured slowly into a 500-mL beaker half filled with ice. The resulting mixture was neutralized with 5% H_2SO_4 to a pH of approx. 6.5; the ether layer was separated, and the aqueous layer was extracted with ether (3 x 50 mL). The organic layers were combined and dried

(Na_2SO_4, overnight). The solvent was removed (rotary evaporator) and the remaining oil was vacuum distilled to give 20.24 g (75.2 %) 2,4-dimethyl-4-thiaphenyl-2-pentanol (**59**) as a clear colorless liquid: bp 105-109°C/0.075 mm. The material was used without further purification. IR (neat) 3200-3600 cm^{-1} (O-H); ^1H NMR ($DCCl_3$) δ 1.30 [s, 6 H, $(C\underline{H}_3)_2C$], 1.33 [s, 6 H, $(C\underline{H}_3)_2C$], 1.79 [s, 2 H, $PhSC(CH_3)_2C\underline{H}_2$], 3.58 [br s, 1 H, O<u>H</u>], 7.26-7.34 [m, 3 H, Ph-<u>H</u>], 7.57 [dd, 2 H, J = 3.0 Hz, J = 8.0 Hz, Ph-<u>H</u>]; ^{13}C NMR ($DCCl_3$) ppm 30.8 [q, $(\underline{C}H_3)_2C$], 32.2 [q, $(\underline{C}H_3)_2C$], 49.1 [s, $PhS\underline{C}C(CH_3)_2$], 52.4 [t, $PhSC(CH_3)_2\underline{C}H_2$], 71.7 [s, $PhSC(CH_3)_2CH_2\underline{C}$], 128.3 [d, C(2')], 128.6 [d, C(4')], 131.5 [s, C(1')], 137.1 [d, C(3')].

<u>2,2,4,4-Tetramethylthiochroman (60)</u>

To a 500-mL, three-necked, round-bottom flask equipped with a condenser, nitrogen inlet and power stirrer was added 42.8 g (0.32 mol) of $AlCl_3$ in 150 mL of dry CS_2. To the stirred suspension of $AlCl_3$ was added dropwise a solution of 18.0 g (80.2 mmol) 2,4-dimethyl-4-thiaphenyl-2-pentanol (**59**) in 50 mL of CS_2 at room temperature over 15 min. The resulting suspension was heated at reflux for 10 h with stirring. The suspension was allowed to cool to room temperature and poured into a 500-mL beaker half filled with ice, and the mixture was stirred for 5 min. The mixture was separated into two layers; the aqueous layer was extracted with ether (3 x 75 mL). The organic

extracts were combined, extracted with H_2O (50 mL) and brine (50 mL) and then dried (Na_2SO_4, overnight). The solvent was removed (rotary evaporator) and the resulting oil was flash chromatographed using hexane on silica gel. Removal of the solvent (rotary evaporator) gave 14.78g (89.3%) of 2,2,4,4-tetramethylthiochroman (**60**) as a clear, colorless oil. The bp was determined to be 66-68°C/0.075 mm. The oil was used without further purification. ^1H NMR ($DCCl_3$) δ 1.38 [s, 6 H, $C(C\underline{H}_3)_2$], 1.40 [s, 6 H, $C(C\underline{H}_3)_2$], 1.94 [s, 2 H, $PhSC(CH_3)_2C\underline{H}_2$], 7.00-7.20 [m, 4 H, Ph-$\underline{H}$]; ^{13}C NMR ($DCCl_3$) ppm 30.4 [q, $C(\underline{C}H_3)_2$], 31.3 [q, $C(\underline{C}H_3)_2$], 34.2 [s, $Ph\underline{C}(CH_3)_2$], 40.7 [s, $PhS\underline{C}(CH_3)_2$], 53.2 [t, $PhSC(CH_3)_2\underline{C}H_2$], 123.6 [d], 124.5 [d], 125.3 [d], 126.6 [d], 131.3 [s], 141.2 [s].

2,2,4,4-Tetramethyl-6-acetylthiochroman (51b)

A solution of 5.0 g (0.024 mol) of 2,2,4,4-tetramethylthiochroman (**60**) and 1.91 g (0.024 mol) of acetyl chloride in 30 mL of nitromethane was added dropwise to a stirred solution of 6.46 g (0.048 mol) of $AlCl_3$ in 30 mL of nitromethane at 0°C (ice bath) under nitrogen. The ice bath was maintained for 0.5 h, and the resulting yellow solution was then allowed to warm to room temperature with stirring (12 h). The reaction mixture was slowly poured with stirring into a 250-mL beaker, half filled with ice. The new mixture was then transferred to a separatory funnel, and

the aqueous layer was separated and extracted with ether (3 x 50 mL). The combined organics were washed with 50 mL of H_2O and 50 mL of brine. After drying overnight (Na_2SO_4), the solvent was removed (rotary evaporator), and the resulting oil was divided into four equal portions and separated individually using chromatography (silica gel/hexane; Chromatotran). The four purified solutions were combined and concentrated (rotary evaporator) to give 4.10 g (68.1%) of 2,2,4,4-tetramethyl-6-acetylthiochroman (**51b**) as a yellowish oil. The oil was used without further purifications. IR (neat) 1680 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.44 [s, 6 H, $(C\underline{H}_3)_2C$], 1.45 [s, 6 H, $(C\underline{H}_3)_2C$], 1.99 [s, 2 H, $PhSC(CH_3)_2C\underline{H}_2$], 2.59 [s, 3 H, $O{=}C{-}C\underline{H}_3$], 7.18 [d, 1 H, J = 8.0 Hz, H(8)], 7.63 [dd, 1 H, J = 2.0 Hz, J = 8.0 Hz, H(7)], 8.06 [d, 1 H, J = 2.0 Hz, H(5)]; ^{13}C NMR ($DCCl_3$) ppm 26.1 [q, $O{=}C{-}\underline{C}H_3$], 31.5 [q, $(\underline{C}H_3)_2C$], 32.4 [q, $(\underline{C}H_3)_2C$], 35.3 [s, $Ph\underline{C}(CH_3)_2$], 42.2 [s, $PhS\underline{C}(CH_3)_2$], 53.7 [t, $PhSC(CH_3)_2\underline{C}H_2$], 125.7 [d], 126.2 [d], 127.4 [d], 133.6 [s], 139.7 [s], 142.1 [s], 196.3 [s, $\underline{C}{=}O$].

3-(1,2,3,4-Tetrahydro-2,2,4,4-tetramethyl-6-thiochromanyl)-2-butenyltriphenylphosphonium Bromide (**63b**)

To a freshly prepared solution of vinylmagnesium bromide [2.58 g (0.024 mol) vinyl bromide and 0.59 g (0.024 g at) magnesium, in 50 mL of THF; the procedure was the same for as a normal Grignard reagents][103] was added dropwise 3.00 g

(0.012 mol) 2,2,4,4-tetramethyl-6-acetylthiochroman (**51b**) in 30 mL of THF in a 200-mL, three-necked, round-bottom flask equipped with a condenser and N_2 inlet (stirred). The solution was heated at reflux for 1 h and then allowed to cool to room temperature. The resulting metallic-colored solution was poured into ice and neutralized carefully with 5% H_2SO_4 to a pH of 6.5. The aqueous layer was separated and extracted with ether (3 x 50 mL), and the organics were combined. The organic layer was washed with H_2O (50 mL) and brine (50 mL) and was then dried overnight (Na_2SO_4). Removal (rotary evaporator) of the solvent gave an oil which was dissolved in 20 mL of methanol; the new solution was added dropwise to a cold (ice bath) suspension of 4.15 g (0.012 mol) of triphenylphosphine hydrobromide (**62**)[24] in 10 mL of methanol. The ice bath was removed after the addition and the resulting light purple suspension was allowed to warm to room temperature during 4 h. The dark purple reaction mixture was evaporated under reduced pressure (rotary evaporator) and gave a thick purple oil which solidified upon trituration with 20 mL of ether and scratching. A dark orange solid formed which was filtered and recrystallized (methanol and ether) to give 4.70 g (65.1%) of **63b** as a tan, powdery solid, suitable for further reactions: mp 224-225°C (dec.), an analytical sample was obtained by the technique of vapor diffusion recrystallization using methanol/ether; mp 227.0-227.5°C

(dec). ^{1}H NMR ($DCCl_3$) δ 1.36 [s, 6 H, $(C\underline{H}_3)_2C$], 1.42 [s, 6 H, $(C\underline{H}_3)_2C$], 1.67 [d, 3 H, J = 4.0 Hz, $C\underline{H}_3C{=}CH$ (trans)], 1.94 [s, 2 H, $PhSC(CH_3)_2C\underline{H}_2$], 4.85 [dd, 2 H, J = 8.0 Hz, J_{PH} = 15.0 Hz, $C{=}CHC\underline{H}_2PPh_3$], 5.64 [tq, 1 H, J = 4.0 Hz, J = 8.0 Hz, $CH_3C{=}C\underline{H}CH_2PPh_3$], 6.89 [dd, 1 H, J = 2.0 Hz, J = 8.0 Hz, H(7)], 7.02 [d, 1 H, J = 8.0 Hz, H(8)], 7.19 [d, 1 H, J = 2.0 Hz, H(5)], 7.70-7.99 [m, 15 H, $P(Ph\text{-}\underline{H})_3$] ^{13}C NMR ($DCCl_3$) ppm 16.9 [$\underline{C}H_3C{=}CH$], 25.4 [d, J_{CP} = 49.9 Hz, $C{=}CH\underline{C}H_2$], 31.6 [$(\underline{C}H_3)_2C$], 32.4 [$(\underline{C}H_3)_2C$], 35.5 [$Ph\underline{C}(CH_3)_2$], 42.1 [$PhS\underline{C}(CH_3)_2$], 54.1 [$PhSC(CH_3)_2\underline{C}H_2$], 110.1, 110.5, 116.2, 119.6, 123.1, 123.9, 124.0, 127.6, 130.0, 130.4, 132.8, 132.9, 133.5, 133.9, 134.9, 135.0, 138.5, 138.7, 142.3, 144.9, 145.4.

(2E, 4E, 6E)-3,7-Diemthyl-7-(1,2,3,4-tetrahydro-2,2,4,4-tetramethyl-6-thiochromanyl)-2,4,6-heptatrieneoic Acid (**48c**)

To a suspension of 1.50 g (2.5 mmol) of phosphonium salt (**63b**) in 10 mL of dry ether was added dropwise at room temperature n-butyllithium (1.80 mL, 1.39 M, 2.5 mmol in hexane) and 5 mL of ether in a 50-mL, three-necked, round-bottom flask equipped with a condenser and nitrogen inlet. The resulting, dark orangish-red solution was cooled to -78°C (dry ice and acetone), and 0.39 g (2.75 mmol) of ethyl trans-β-formylcrotonate (**64**) in 15 mL of ether was added dropwise (approx. 5 min) in the dark. The mixture was allowed to warm to room temperature with stirring over

10 h. The yellow suspension was diluted with 50 ml of hexane; the solution was filtered and passed through a plug of anhydrous Na_2SO_4 (in a filter funnel) and evaporated (rotary evaporator) to give a organish-yellow thick oil. To this oil was added 20 mL ethanol, and the new solution was added all at once to a mixture of KOH (2.70 g, 0.048 mol) in 4 mL of H_2O; the new mixture was heated to reflux for 45 min. The final dark red solution was cooled to room temperature and then diluted with 50 mL of H_2O and 5.0 g of NaCl; this new mixture was extracted with 100 mL of ether. The ether layer was extracted with H_2O (3 x 25 mL), and the combined yellow aqueous layers were acidified (pH approx. 3-4) slowly with 5% H_2SO_4. However, at the neutralization point, the solution became cloudy; the aqueous solution was extracted with ether (2 x 50 mL). The combined organics were extracted with H_2O (25 mL) and brine (25 mL) and then dried (Na_2SO_4, overnight). After evaporation (rotor evaporator), the yellow solid was fractionally recrystallized (abs. ethanol) to give 0.267 g (30.0 % from the phosphonium salt **63b**) of **48c** as a grainy yellow solid: mp 224.5-225°C (dec). ^{1}H NMR ($DCCl_3$) δ 1.42 [s, 12 H, $(C\underline{H}_3)_2C$], 1.97 [s, 2 H, $PhSC(CH_3)_2C\underline{H}_2$], 2.25 [s, 3 H, $C\underline{H}_3$], 2.41 [s, 3 H, $C\underline{H}_3$], 5.86 [brs, 1 H, $C\underline{H}CO_2H$], 6.43 [d, 1 H, J = 15.0 Hz, $C\underline{H}C(CH_3)$, 6.58 [d, 1 H, J = 12.0 Hz, $PhC(CH_3)C\underline{H}$], 7.09 [d, 1 H, J = 8.0 Hz, H(8)], 7.10 [dd, 1 H, J = 12.0 Hz, J = 15.0 Hz, CH-C$\underline{H}$=CH], 7.21 [dd, 1 H, J =

2.0 Hz, J = 8.0 Hz, H(7)], 7.51 [d, 1 H, J = 2.0 Hz, H(5)]; ^{13}C NMR ($DCCl_3$) ppm 14.1 [$\underline{C}H_3$], 16.3 [$\underline{C}H_3$], 31.7 [$(\underline{C}H_3)_2C$], 32.6 [$(\underline{C}H_3)_2C$], 35.7 [$(CH_3)_2\underline{C}Ph$], 42.2 [$PhS\underline{C}(CH_3)_2$], 54.4 [$PhSC(CH_3)_2\underline{C}H_2$], 117.8 [$\underline{C}HCO_2H$], 123.5, 124.1, 125.7 127.9, 132.0, 132.9, 135.4, 139.0, 140.7, 142.5, 155.1 [$\underline{C}(CH_3)CHCO_2H$], 170.8 [$\underline{C}O_2H$]. Anal. Calcd for $C_{22}H_{28}O_2S$: C, 74.12; H, 7.92; S, 8.99. Found: C, 74.09; H, 7.95; S, 9.26.

Methyl (E)-4-[2-(2,2,4,4-Tetramethyl-6-thiochromanyl)-propenyl]-1-benzoate (49a)

To a suspension of 10 mL of dry THF and NaH (19 mg, 60% as mineral dispersion, 4.9 mmol) in a 50-mL, three-necked, round-bottom flask with a N_2 inlet was added dropwise at room temperature a solution of 2,2,4,4-tetramethyl-6-acetylthiochroman [**51b**, 1.10 g, 4.4 mol], dimethyl (4-carbmethoxybenzyl)phosphonate [**76**, 1.25 g, 4.9 mmol), and 15-crown-5 [**77**, 22 mg, 1.0 mmol] in 15 mL of THF. The suspension was stirred at room temperature for 24 hr to give a dark red suspension. This reaction mixture was treated with 1.0 mL of glacial acetic acid; the resulting light yellow solution was combined with 100 mL of brine and the two layers were separated. The aqueous layer was extracted with ether (2 x 50 mL). The organics were combined, washed with H_2O (2 x 50 mL) and brine (50 mL) and finally dried (Na_2SO_4, overnight). The solution was

concentrated and the yellow oil was separated (Chromatotron) using hexanes and silica gel which gave a slightly yellow oil. The oil was crystallized three times using hexane giving 0.66 g (39.2 %) of (**49a**) as white flakes: mp 88.5-89.0°C. IR (KBr) 1720 cm^{-1} (C=O); ^{1}H NMR ($DCCl_3$) δ 1.43 [s, 12 H, $(C\underline{H}_3)_2C$], 1.97 [s, 2 H, $PhSC(CH_3)_2C\underline{H}_2$], 2.28 [d, 3 H, J = 1.0 Hz, $C\underline{H}_3C{=}CH$ (trans)], 3.93 [s, 3 H, $CO_2C\underline{H}_3$], 6.82 [d, 1 H, J = 1.0 Hz, $CH_3C{=}C\underline{H}$ (trans)], 7.13 [d, 1 H, J = 8.0 Hz, H(8)], 7.23 [dd, 1 H, J = 2.0 Hz, J = 8.0 Hz, H(7)], 7.42 [d, 2 H, J = 8.0 Hz, H(15,19)], 7.53 [d, 1 H, J = 2.0 Hz, H(5)], 8.04 [d, 2 H, J = 8.0 Hz, H(16,18)]; ^{13}C NMR ($DCCl_3$) ppm 17.6 [$\underline{C}H_3C{=}CH$], 31.6 [$(\underline{C}H_3)_2C$], 32.6 [$(\underline{C}H_3)_2C$], 35.6 [$(CH_3)_2\underline{C}Ph$], 42.1 [$PhS\underline{C}(CH_3)_2$], 52.1 [$CO_2\underline{C}H_3$], 54.4 [$PhSC(CH_3)_2\underline{C}H_2$], 123.7 [C(7)], 124.4 [C(5)], 125.9 [$CH_3C{=}\underline{C}H$], 127.8, 127.9 [C(8)], 128.9 [C(15, 19)], 129.1 [C(16,18)], 132.4, 139.5, 139.5, 140.1, 142.5, 143.2,167.0 [$\underline{C}O_2CH_3$]. Anal. Calcd for $C_{24}H_{28}SO_2$: C, 75.75; H, 7.42. Found: C, 75.70; H, 7.41.

(E)-4-[2-(3,4-Dihydro-2,2,4,4-tetramethyl-2H-1-benzopyran-6-yl)-1-propenyl]-benzoic Acid (**49b**)

Methyl (E)-4-[2-(2,2,4,4-tetramethyl-6-thiochromanyl)-propenyl]benzoate [**49a**, 0.150 g, 0.394 mmol] was heated to reflux under nitrogen in an aqueous-ethanol (2.4 mL-10 mL) solution of KOH (0.105g, 1.9 mmol) for 1 h in a 25-mL,

three-necked, round-bottom flask. After cooling to room temperature (30 min), the resulting solution was diluted with ether (50 mL) and 50 mL of brine. The two layers were separated and the organic layer was washed with H_2O (2 x 25 mL). The combined aqueous layers were acidified with 5% H_2SO_4 to give a cloudy solution which was extracted with ether (3 x 50 mL). The extracts were washed with H_2O (25 mL) and brine (50 mL)and then dried (Na_2SO_4, overnight); concentration gave a white solid which, after recrystallization (95% ethanol), gave 0.112 g (78.1%) of **49b** as white needles: mp 147-148°C; ^1H NMR ($DCCl_3$) δ 1.46 [s, 12 H, $(C\underline{H}_3)_2C$], 1.99 [s, 2 H, $PhSC(CH_3)_2C\underline{H}_2$], 2.32 [d, 3 H, J = 1.0 Hz, $C\underline{H}_3C{=}CH$ (trans)], 6.84 [d, 1 H, J = 1.0 Hz, $CH_3C{=}C\underline{H}$ (trans)], 7.15 [d, 1 H, J = 8.0 Hz, H(8)], 7.25 [dd, 1 H, J = 2.0 Hz, J = 8.0 Hz, H(7)], 7.48 [d, 2H, J = 8.0 Hz H(15,19)], 7.57 [d, 1 H, J = 2.0 Hz, H(5)], 8.14 [d, 2 H, J = 8.0 Hz, H(16, 18)]; ^{13}C NMR ($DCCl_3$) ppm 17.7 [$\underline{C}H_3C{=}CH$], 31.7 [$(\underline{C}H_3)_2C$], 32.7 [$(\underline{C}H_3)_2C$], 35.7 [$(CH_3)_2\underline{C}Ph$], 42.2 [$PhS\underline{C}(CH_3)_2$], 54.4 [$PHSC(CH_3)_2\underline{H}_2$], 123.7 [C(7)], 124.4 [C(5)], 125.8 [$CH_3C{=}\underline{C}H$], 126.9, 128.0 [C(8)], 129.2 [C(15, 19)], 130.1 [C(16, 18)], 132.5, 139.9, 140.1, 142.5, 144.1, 171.7 [$\underline{C}O_2H$]. Anal. Calcd for $C_{23}H_{26}SO_2$: C, 75.37; H, 7.21. Found: C, 75.06; H, 7.21.

Trifluoroacetyl chloride (82)

To 10.00 g (0.074 mol) of anhydrous sodium trifluoroacetate in a three-neck, round-bottom flask equipped with a

condenser and nitrogen inlet was added dropwise 12.3 mL of $POCl_3$ (20.29 g, 0.132 mol) over 10 min (caution foaming). A slow stream of nitrogen was passed over the solid through the condenser into a dry ice/acetone trap which condensed the volatile trifluoroacetyl chloride at -78°C (dry-ice/acetone) in a 10-mL, round-bottom flask equipped with a drying tube ($CaSO_4$). After the initial reaction had subsided (approx. 20 min), the reaction mixture was heated under gentle reflux for 1 h to give about 5.0 ml of trifluoroacetyl chloride (**83**) which distilled over as a clear colorless liquid. This liquid was used directly without further purification (lit[20,107] mp -146°C, bp -27°C, amide mp 74-75°C).

4,4-Dimethyl-6-thiochromanyl Trifluoromethyl Ketone or 1-(3,4-Dihydro-4,4-dimethyl-2H-1-benzothiopyran-6-yl)-2,2,2-trifluoro-ethanone (83)

To a suspension of 4,4-dimethylthiochroman [**56**, 3.57 g, 0.020 mol), $AlCl_3$ (5.33 g, 0.040 mol) and CS_2 (35 mL) in a 50-mL, three-necked, round-bottom flask equipped with a dry-ice condenser was added (stream of N_2) 1.5 mL of trifluoroacetyl chloride (**82**) over 30 min. After 1 h from the start of the reaction, an additional 1.5 mL of trifluoroacetyl chloride (**82**) was added to the dark, orangish suspension over 30 min. The resulting mixture was stirred for an addidtional 30 min and was poured into ice;

two layers separated. The aqueous layer was extracted with ether (3 x 50 ml); the ether layers were combined, washed with brine and dried (Na_2SO_4, 6 h). After evaporation (rotor evaporator), the resulting yellow oil was separated (Chromatotron) using hexanes on silica gel to give 1.73 g (31.5%) of **83** as a viscous yellow oil which was used without further purification. IR (neat) 1720 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.33 [s, 6 H, $(C\underline{H}_3)_2C$], 1.83 [m, 2 H, $PhSCH_2C\underline{H}_2$], 3.07 [m, 2 H, $PhSC\underline{H}_2CH_2$], 7.20 [d, 1 H, J = 8.0 Hz, H(8)], 7.68 [dd, 1 H, J = 8.0 Hz, J = 1.0 Hz, H(7)], 8.14 [d, 1 H, J = 1.0 Hz, H(5)]; ^{13}C NMR ($DCCl_3$) ppm 23.2 [$PhS\underline{C}H_2CH_2$], 29.3 [$(\underline{C}H_3)_2C$], 32.8 [$(CH_3)_2\underline{C}$], 36.2 [$PhSCH_2\underline{C}H_2$], 116.7 [q, $^1J_{CF}$ = 291.6 Hz, $\underline{C}F_3$], 125.2, 126.5, 126.7, 127.5, 142.2, 143.8, 178.8 [q, $^2J_{CF}$ = 34.5 Hz, $\underline{C}$=O]; ^{19}F NMR ($DCCl_3$) ppm -71.72 [$C\underline{F}_3$].

Methyl (E)-4-[2-trifluoromethyl-2-(4,4-dimethyl-6-thiochromanyl)ethenyl]benzoate (**50a**)

To a suspension of 10 ml of THF and NaH (0.080 g, 60% as mineral dispersion, 2.01 mmol) in a 50-mL, three-necked, round-bottom flask equipped with a condenser and N_2 inlet was added dropwise at room temperature a solution of 4,4-dimethyl-6-thiochromanyl trifluoromethyl ketone [(**83**), 0.50 g, 1.82 mmol], dimethyl (4-carbmethoxybenzyl)phosphonate [(**76**), 0.52 g, 2.01 mmol], and 15-crown-5 [(**77**), 0.11g, 0.50 mmol] in 15 mL of THF. The suspension was stirred (room temperature) for 24 h to give a dark red suspension.

The reaction mixture was treated with 1.0 mL of glacial acetic acid, and the resulting light yellow solution was combined with 100 mL of brine; two layers separated. The aqueous layer was extracted with ether (2 x 50 mL) and dried (Na_2SO_4, overnight). The solution was concentrated (rotor evaporator) and the yellow oil was separated (Chromatotron) using hexanes and silica gel which gave a slightly yellow oil. The oil was crystallized three times using hexanes giving 0.45 g (61.2%) of **50a** as a white powder: mp 83.5-84.5°C. ^{1}H NMR ($DCCl_3$) δ 1.15 [s, 6 H, $(C\underline{H}_3)_2C$], 1.92 [m, 2 H, $PhSCH_2C\underline{H}_2$], 3.02 [m, 2 H, $PhSC\underline{H}_2CH_2$], 3.89 [s, 3 H, $CO_2C\underline{H}_3$], 6.96-7.30 [m, 6 H], 7.86 [d, 2 H, J = 8.0 Hz]; ^{13}C NMR ppm 23.1 [$PhS\underline{C}H_2CH_2$], 30.1 [$(\underline{C}H_3)_2C$], 32.9 [$(CH_3)_2\underline{C}$], 37.4 [$PhSCH_2\underline{C}H_2$], 52.2 [$CO_2\underline{C}H_3$], 118.4, 126.7, 127.1, 127.4, 128.4, 129.4, 129.8, 131.9, 133.5, 138.4, 142.6, 166.4; ^{19}F NMR ppm -66.60 [$C\underline{F}_3$]. Anal. Calcd for $C_{22}H_{21}O_2SF_3$: C, 65.01; H, 5.21; F, 14.02. Found: C, 65.24; H, 5.49; F, 14.02.

(E)-4-[2-(Trifluoromethyl)-2-(4,4-dimethyl-6-thiochromanyl)ethenyl]benzoic acid (**50b**)

Methyl (E)-4-[2-(trifluoromethyl)-2-(4,4-dimethyl-6-thiochromanyl)ethenyl]benzoate [**50a**, 0.2074 g, 0.510 mmol) was heated to reflux under nitrogen in an aqueous-ethanol (3 mL-12 mL) solution of KOH (0.844 g, 15.0 mmol) for 1 h in a 15-mL, three-necked, round-bottom, flask (stirring).

After cooling to room temperature, the resulting solution was diluted with ether (50 mL) and brine (50 mL). Two layers separated and the organic layer was washed with H_2O (2 x 25 mL). The combined aqueous layers were acidified with 5% H_2SO_4 to give a cloudy solution which was extracted with ether (3 x 50 mL). The extracts were washed with H_2O (25 mL) and brine (50 mL) and then dried (Na_2SO_4, overnight). Concentration (rotor evaporator) gave a white solid, which, after recrystallization (95% ethanol), gave 0.162 g (81.0%) of **50b** as a white powder: mp 223.5-224.0°C. IR (KBr) 1700 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.16 [s, 6 H, $(C\underline{H}_3)_2C$], 2.94 [m, 2 H, $PhSCH_2C\underline{H}_2$], 3.03 [m, 2 H, $PhSC\underline{H}_2$], 6.95-7.30 [m, 6 H], 7.95 [d, 2 H, J = 8.0 Hz]; ^{13}C NMR ($DCCl_3$) ppm 23.1 [$PhS\underline{C}H_2CH_2$], 30.1 [$(\underline{C}H_3)_2C$], 32.9 [$(CH_3)_2\underline{C}$], 37.3 [$PhSCH_2\underline{C}H_2$], 126.6, 127.1, 128.3, 128.9, 129.9, 130.0, 131.6, 133.6, 139.3, 142.6, 170.7 [$\underline{C}O_2H$]; ^{19}F NMR ($DCCl_3$) ppm -66.61 [$C\underline{F}_3$]. Anal. Calcd for $C_{21}H_{19}O_2SF_3$: C, 64.27; H, 4.88; F, 14.52. Found: C, 64.08; H, 5.04; F, 14.25.

6-Trifluoroacetyl-4,4-dimethyl-chroman (**86**)

To a suspension of 4,4-dimethylchroman [**84**, 5.00 g, 0.02 mol), $AlCl_3$ (10.66 g, 0.04 mol) and CS_2 (60 mL) in a 100-mL, three-necked, round-bottom flask equipped with a dry-ice condenser was added with stirring (stream of nitrogen) 2.5 mL of trifluoroacetyl chloride (**82**) over 30 min. After

1.5 h from the start of the reaction, an additional 2.5 mL of trifluoroacetyl chloride (**82**) was added to the yellowish-orange suspension over 30 min. The resulting mixture was stirred for an additional 1 h and poured into ice, two layers separated. The aqueous layer was extracted with ether (3 x 75 mL); the ether extracts were combined, washed with brine, and dried (Na_2SO_4, overnight). After evaporation (rotor evaporator), the resulting orangish oil was separated (Chromatotron) using hexanes on silica gel to give 2.74 g (53.1%) of **86** as a light orange solid: mp 41.5-42.5°C. The Ketone was used without further purification. IR (KBR) 1720 cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.33 [s, 6 H, $(C\underline{H}_3)_2C$], 1.82 [m, 2 H, $PhOCH_2C\underline{H}_2$], 4.26 [m, 2 H, $PhOC\underline{H}_2CH_2$], 6.83 [d, 1 H, J = 8.0, H(8)], 7.77 [dd, 1 H, J = 8.0 Hz, J = 1.0 Hz, H(7)], 8.06 [d, 1 H, J = 1.0, H(5)]; ^{13}C NMR ($DCCl_3$) ppm 30.7 [$(\underline{C}H_3)_2C$], 30.9 [$(CH_3)_2\underline{C}$], 36.9 [$PhOCH_2\underline{C}H_2$], 64.3 [$PhO\underline{C}H_2CH_2$], 118.0 [q, $^1J_{CF}$ = 291.3 Hz, $\underline{C}F_3$], 123.4, 130.8, 131.2, 133.5, 161.5 [C(8a)], 180.2 [q, $^2J_{CF}$ = 34.0 Hz, $\underline{C}(O)CF_3$]; ^{19}F NMR ($DCCl_3$) ppm -71.53 [$C\underline{F}_3$].

Methyl (E)-4-[2-(trifluoromethyl)-(4,4-dimethyl-6-chromanyl)ethenyl]benzoate (**50e**)

To a suspension of 10 ml of dry THF and NaH (0.16 g 60% as mineral dispersion, 3.9 mmol) in a 50-mL, three-necked, round-bottom flask was added dropwise (room temperature) a solution of 4,4-dimethyl-6-chromanyl trifluoromethyl ketone

[**86**, 1.00 g, 3.87 mmol], dimethyl (4-carbomethoxybenzyl)-phosphonate [**76**, 1.01 g, 3.9 mmol], and 15-crown-5 [**77**, 0.22 g, 1.0 mmol) in 15 mL of dry THF. The new suspension was stirred at room temperature for 16 h to give a red suspension. This reaction mixture was treated with 1.0 mL of glacial acetic acid, and the resulting light yellow solution was combined with 100 mL of brine and the two layers separated. The aqueous layer was extracted with ether (2 x 50 mL) and the organics were combined and washed with H_2O (2 x 50 mL) and brine (50 mL). After drying (Na_2SO_4, overnight), the solution was concentrated to a yellow oil which was separated (Chromatotron) using hexanes and silica gel and gave a slightly yellow oil. After treatment with decolorizing carbon for 20 min in boiling ether, the resulting mixture was filtered, condensed (rotor evaporator) and, after crystallization from gave hexane, gave 0.52 g (34.4%) as a white crystalline solid: mp 94.5-95.0°C. IR (KBr) 1720 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.18 [s, 6 H, $(C\underline{H}_3)_2C$], 1.81 [m, 2 H, $PhOCH_2C\underline{H}_2$], 3.88 [s, 3 H, $CO_2C\underline{H}_3$], 4.21 [m, 2 H, $PhO\underline{C}H_2CH_2$], 6.81 [d, 1 H, J = 8.0 Hz, H(8)], 7.00 [dd, 1 H, J = 8.0 Hz, J = 1.0 Hz, H(7)], 7.11 [s, 1 H, $PhC(CF_3)C\underline{H}$], 7.12 [d, 1 H, J = 8.0 Hz, H(16,18)], 7.20 [d, 1 H, J = 1.0 Hz, H(5)], 7.86 [d, 2 H, J = 8.0 Hz, H(15,19)]; ^{13}C NMR ($DCCl_3$) 30.5 [$(CH_3)_2\underline{C}$], 30.8 [$(\underline{C}H_3)_2C$], 37.3 [$PHOCH_2\underline{C}H_2$], 63.2 [$CO_2\underline{C}H_3$], 52.2 [$PhO\underline{C}H_2CH_2$], 117.6 [C(8)], 123.6, 128.1 [C(7)], 128.9 [$PhC(CF_3)\underline{C}H$], 129.4 [C(16,18)], 129.8 [C(15,19)], 131.5

[C(5)], 134.3, 138.6, 154.3, 166.5; ^{19}F NMR ($DCCl_3$) ppm -66.80 [C$\underline{F}_3$] Anal. Calcd for $C_{22}H_{21}O_3F_3$: C, 67.69; H, 5.42; F, 14.60. Found: C, 67.94; H, 5.42; F, 14.90.

(E)-p-[2-(Trifluoromethyl)-2-(4,4-dimethyl-6-chromanyl)ethenyl]benzoic acid (**50f**)

Methyl (E)-p-[2-(trifluoromethyl)-2-(4,4-dimethyl-6-chroman)ethenyl]benzoate [**50e**, 0.1645 g, 0.421 mmol) was heated to relux under nitrogen in an aqueous-ethanol (1.0 mL-3.0 mL) solution of KOH (0.48 g, 8.5 mmol) for 1 h. After cooling to room temperature, the resulting solution was diluted with ether (50 mL) and brine (50 mL). Two layers were separated, and the organic layer was washed with H_2O (2 x 25 mL). The combined aqueous layers were acidified with 5% H_2SO_4 to give a cloudy solution which was extracted with ether (3 x 50 mL). The extracts were washed with H_2O (25 mL) and brine (50 mL) and then dried (Na_2SO_4, overnight); concentration (rotor evaporator) gave a white solid, which, after recrystallization (95% ethanol), gave 0.1276 g (80.5%) of **50f** as a white crystalline solid: mp 207.5-208.0°C; ^{1}H NMR ($DCCl_3$) δ 1.18 [s, 6 H, ($C\underline{H}_3)_2C$], 1.82 [m, 2 H, $PhOCH_2C\underline{H}_2$], 4.22 [m, 2 H, $PhOC\underline{H}_2CH_2$], 6.81 [d, 1 H], 7.01 [dd, 1 H], 7.09 [d, 1 H], 7.15 [d, 2 H], 7.22 [d, 1 H], 7.92 [d, 2 H]; ^{13}C NMR ($DCCl_3$) ppm 30.5 [$(CH_3)_2\underline{C}$], 30.8 [($\underline{C}H_3)_2C$], 37.2 [$PhOCH_2\underline{C}H_2$], 63.2 [$PhO\underline{C}H_2CH_2$], 117.6, 123.5, 128.1, 128.8, 128.9, 129.9,

130.0, 131.4, 131.5, 132.4, 139.6, 154.3, 170.8 [$\underline{C}O_2H$]; ^{19}F NMR ($DCCl_3$) ppm -66.82 [$C\underline{F}_3$]. Anal. Calcd for $C_{21}H_{19}O_3F_3$: C, 67.02; H, 5.09; F, 15.14. Found: C, 66.75; H, 5.14; F, 14.95.

Trifluoroacetyl-2,2,4,4-tetramethyl-6-thiochromanyl (**85**)

To a suspension of 2,2,4,4-tetramethylthiochroman [(**60**), 2.50 g, 0.012 mol), $AlCl_3$ (3.23 g, 0.024 mol) and 30 mL of CS_2 in a 100-mL, three-necked, round-bottom flask equipped with a dry ice condenser was added (stream of nitrogen) 1.5 mL of trifluoroacetyl chloride (**82**) over 30 min (stirred). After 1 h from the start of the reaction, an additional 1.5 mL of trifluoroacetyl chloride (**82**) was added to the dark orange suspension over 30 min. The resulting mixture was stirred for an additional 1 h and poured into ice; two layers separated. The aqueous layer was extracted with ether (3 x 50 mL): the ether layers were combined, washed with brine and dried (Na_2SO_4, 6 h). After evaporation (rotary evaporator), the resulting yellow oil was separated (Chromatotron) using hexanes on silica gel to give 0.75 g (20.3%) of **85** as a viscous yellow oil which was used without further purification. Ketone was used without further purification. IR (neat) 1715 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 1.21 [brs, 12 H, ($C\underline{H}_3)_2C$], 1.98 [s, 2 H, $PhSC(CH_3)_2C\underline{H}_2$], 7.21 [d, 1 h, J = 8.0 Hz, H(8)], 7.69 [dd, 1 H, J = 8.0 Hz, J = 1.0 Hz, H(7)], 8.15 [d, 1 H, J = 1.0

Hz, H(5)]; ^{13}C NMR ($DCCl_3$) ppm 31.6 [($\underline{C}H_3)_2C$], 32.4 [($\underline{C}H_3)_2C$], 35.4 [Ph$\underline{C}(CH_3)_2$], 42.9 [PhS$\underline{C}(CH_3)_2$], 53.3 [PhC$(CH_3)_2\underline{C}H_2$], 116.9 [q, $^1J_{CF}$ = 291.2 Hz, $\underline{C}F_3$], 126.2, 126.9, 127.9, 128.5, 143.0, 144.4, 179.0 [q, $^2J_{CF}$ = 34.0 Hz, $\underline{C}(O)CF_3$]; ^{19}F NMR ($DCCl_3$) ppm -71.74 [$C\underline{F}_3$].

Methyl (E)-4-[2-(trifluoromethyl)-2-(2,2,4,4-tetramethyl-6-thiochromanyl)-ethenyl]-benzoate (**50c**)

To a suspension of 10 mL of dry THF and NaH (0.0723 g, 60% dispersion in mineral oil, 1.81 mmol) in a three-necked, round-bottom flask equipped with a condenser and N_2 inlet was added dropwise at room temperature a solution of trifluoroacetyl-2,2,4,4-tetramethyl-6-thiochromanyl [**85**, 0.50 g, 1.64 mmol], dimethyl (4-carbmethoxybenzyl)-phosphonate [**76**, 0.465 g, 1.81 mmol] and 15-crown-5 [**77**, 0.11 g, 0.5 mmol] in 15 mL of dry THF. This suspension was stirred at room temperature for 16 h to give a dark red suspension. The mixture was treated with 1.0 mL glacial acetic acid, and the resulting light yellow solution was combined with 100 mL of brine; two layers separated. The aqueous layer was extracted with ether (2 x 50 mL) and dried (Na_2SO_4, overnight). Concentration (rotor evaporator) of the solution gave a yellow oil was separated (Chromatotron) using hexanes and silica gel; a slightly yellow oil resulted. The oil was crystallized with hexanes

and the recrystallized twice using hexanes to give 0.339 g (47.7%) of **50c** as clear colorless prisms: mp 87.0-87.5°C. IR (KBr) 1740 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.21 [s, 6 H, $(C\underline{H})_3)_2C$], 1.42 [s, 6 H, $(C\underline{H}_3)_2C$], 1.94 [s, 2 H, $PhSC(CH_3)C\underline{H}_2$], 3.89 [s, 3 H, $CO_2C\underline{H}_3$], 6.98-7.30 [m, 6 H], 7.86 [d, 2 H]; ^{13}C NMR ($DCCl_3$) ppm 31.4, 32.6, 35.3, 42.2, 52.2, 54.1, 126.7, 128.5, 128.9, 129.4, 129.9, 131.9, 132.0, 134.3, 138.4, 143.2, 166.4; ^{19}F NMR ($DCCl_3$) ppm -66.59 [$C\underline{F}_3$]. Anal. Calcd for $C_{24}H_{25}SO_2F_3$: C, 66.34; H, 5.86; F, 13.12. Found: C, 66.28; H, 5.86; F, 12.77.

(E)-4-[2-(Trifluoromethyl)-2-(2,2,4,4-tetramethylthio-6-chromanyl)ethenyl]-benzoic acid (**50d**)

Methyl (E)-4-[2-(trifluoromethyl)-2-(2,2,4,4-tetramethyl-6-thiochromanyl)ethenyl]benzoate [**50c**, 0.150g, 0.345 mmol) was heated to reflux with stirring under nitrogen in an aqueous-ethanol (2 mL-10mL) solution of KOH (0.40, 7.13 mmol) for 1 h in a 25-mL, three-necked, round-bottom flask equipped with a condenser and N_2. After cooling to room temperature (30 min), the resulting solution was diluted with ether (50 mL) and brine (50 mL). Two layers were separated and the organic layer was washed with H_2O (2 x 25 mL). The combined aqueous layers were acidified with 5% H_2SO_4 to give a cloudy solution which was extracted with ether (3 x 50 mL). The extracts were washed with H_2O (25 mL) and brine (50 mL) and then dried (Na_2SO_4, 6 h);

concentration gave a white solid which, after recrystallization (95% ethanol), gave 0.1135 g (78.2%) of **50d**: mp 169.0-170.0°C. ^{1}H NMR ($DCCl_3$) δ 1.21 [s, 6 H, $(C\underline{H}_3)_2C$], 1.42 [s, 6 H, $(C\underline{H}_3)_2C$], 1.93 [s, 2 H, $PhSC(CH_3)_2C\underline{H}_2$], 6.97-7.30 [m, 6 H], 7.92 [d, 2 H]; ^{13}C NMR ($DCCl_3$) ppm 31.7, 32.7, 35.7, 42.1, 54.5, 123.8, 124.5, 125.9, 127.0, 128.0, 129.2, 130.2, 132.6, 140.0, 140.1, 142.6, 144.1, 171.7; ^{19}F NMR ($DCCl_3$) ppm -66.61 [$C\underline{F}_3$]. Anal. Calcd for $C_{23}H_{23}SO_2F_3$: C, 65.70; H, 5.51; F, 13.56. Found: C, 65.86; H, 5.53; F, 13.47.

(2Z, 4E, 6E)-3,7-Dimethyl-7-(1,2,3,4-tetrahydro-4,4-dimethyl-6-thiochromanyl)-2,4,6-heptatrienoic Acid (**48f**)

To a stirring suspension of KH (0.214 g, 24% mineral oil dispersion, 5.35 mmol) in 6.0 mL of dry THF was added salt **63a** (1.54 g, 2.68 mmol) at room temperature in a 50-mL, three-necked, round-bottom flask equipped with a condenser and nitrogen inlet. After 20 min, the resulting dark red mixture was cooled in an ice bath for 10 min and 4-hydroxy-3-methylbut-2-enolide[21] [**69**, 0.45 g, 2.68 mmol] was added in 8.0 mL of dry THF dropwise (5 min). The reaction mixture was allowed to warm to room temperature overnight with stirring. The dark reaction mixture was poured into 50 mL of ice water and the resulting solution was extracted with (2 x 25 mL). The combined organics was extracted with

H_2O (2 x 25 mL) while the aqueous layers were combined and acidified with 5% H_2SO_4 to approximately pH 4.0. The cloudy yellow solution was extracted with ether (3 x 50 mL); the ether solutions were combined and washed with H_2O (2 x 25 mL). This new solution was treated with a small crystal of I_2 for 2 min followed by immediate quenching with 5% sodium thiosulfate (2 x 25 mL). The resulting solution was washed with H_2O (25 mL), brine (25 mL) and dried Na_2SO_4 (4 h). The mixture was concentracted and the yellow oil was crystallized twice (abs ethanol) to gave 0.31 g (35.2 %) of acid **48f** as a yellow solid: mp 172.5-173.0°C (dec). IR (KBr) 1675 (C=O) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.36 [s, 6 H, $(C\underline{H}_3)_2C$], 1.96 [m, 2 H, $PhSC\underline{H}_2CH_2$], 2.14 [s, 3 H, $C\underline{H}_3$], 2,23 [s, 3 H, $C\underline{H}_3$], 3.03 [m, 2 H, $PhSCH_2C\underline{H}_2$], 5.71 [brs, 1 H, $C\underline{H}CO_2H$], 6.69 [d, 1 H, J = 9 Hz, $PhC(CH_3)C\underline{H}$-CH=CH], 7.07 [d, 1 H, J = 7 Hz, H(8)], 7.08 [dd, 1 H, J = 9.0 Hz, J = 15.0 Hz, CH-C$\underline{H}$=CH], 7.21 [dd, 1 H, J = 7.0 Hz, J = 2.0 Hz, H(7)], 7.51 [d, 1 H, J = 2.0 Hz, H(5)], &.86 [d, 1 H, J = 15 Hz, $C\underline{H}C(CH_3)CHCO_2H$]; 16.2 [$PhC(\underline{C}H_3)$], 21.3 [$C(\underline{C}H_3)CHCO_2H$], 23.1 [$PhS\underline{C}H_2CH_2$], 30.2 [$(\underline{C}H_3)2C$], 33.1 [$(CH_3)_2\underline{C}$], 37.6 [$PhSCH_2\underline{C}H_2$], 115.9 [$\underline{C}HCO_2H$], 123.5 [C(7)], 123.6 [C(5)], 126.0 [$PhC(CH_3)\underline{C}H$], 126.4 [C(8)], 129.2 [$\underline{C}HC(CH_3)CHCO_2H$], 131.9 [C(8a)], 133.4 [$\underline{C}H$=CHC$(CH_3)CHCO_2$], 138.0 [C(6)], 140.9, 141.7, 153.7 [$C(CH_3)CHCO_2H$], 172.1 [$\underline{C}O_2H$]. Anal. Calcd for $C_{20}H_{24}O_2S$: C, 73.13; H, 7.36; S, 9.76. Found: C, 73.32; H, 7.32; S, 9.93.

Dimethyl (Carboethoxymethyl)sulfonium Bromide (72)

A solution of 57.00 g (0.92 mol) of dimethyl sulfide 132.50 g (0.795 mol) ethyl bromoacetate and 250 mL of dry acetone was stirred at room temperature in a 1000-mL, round-bottom, three-neck flask under a nitrogen atmosphere for 24 h. The resulting white precipitate was filtered, washed with ether (100 mL), and dried under high vacuum (0.1 mm, RT) for 24 h in a desicator ($CaSO_4$) to give 146.80 g (80.6%) of **72**: mp 82.0-82.5°C (lit[85] mp 78-80°C). ^1H NMR ($DCCl_3$) δ 1.35 [t, 3 H, $OCH_2C\underline{H}_3$], 3.52 [s, 6 H, $(CH_3)_2S$], 4.53 [q, 2 H, $OC\underline{H}CH_3$], 5.52 [s, 2 H, $C\underline{H}CO_2Et$]; ^{13}C NMR ($DCCl_3$) ppm 13.2, 23.3, 43.7, 62.4, 163.3.

Ethyl (Dimethylsulfuranylidene)-acetate - (EDSA) (73)

To a solution of 140.0 g (0.611 mol) of dimethyl (carboethoxymethyl)sulfonium bromide (**72**) in 486 mL of $HCCl_3$, which was stirred at 0°C (ice bath) was added all at once a mixture of 365 ml of saturated K_2CO_3 and 48.9 mL of 12.5 N NaOH (0.611 mol). The ice bath was removed after 10 min, and the biphase reaction mixture was stirred for 30 min. The mixture was transferred to a separatory funnel, and the lower aqueous layer was removed and the chloroform layer was then dried (K_2CO_3, 2 h). Evaporation (rotor evaporator) of the solvent at 25°C gave an oil but residual

solvent was removed under high vacuum (0.10 mm, RT, 30 min) to give 88.80 g (98.0%) of ylide **73** (lit[85] ^{1}H NMR ($DCCl_3$) δ 1.2 [t, 3 H], 3.9 [q, 2 H], 2.7-2.8 [s with shoulder, 7 H]) as an almost colorless liquid. The ylide must be used directly or stored under nitrogen at 0°C; ^{13}C NMR ($DCCl_3$) ppm 14.1, 29.5, 31.4, 56.5, 168.8.

Ethyl cis/trans-2-Formylcyclopropan-carboxylate (67)

To a solution of 44.40 g (0.30 mol) of EDSA **73** in 250 mL of dry boiling acetone was added dropwise acrolein (16.80 g, 0.30 mol) over 15 min in a 500 mL, three-necked, round-bottom, flask. The resulting light orange solution was heated for an additional 15 min, the solvent was removed and the residual oil was vacuum distilled to give 14.99 g (35.2%) of an isomeric mixture [84:16 trans-cis, via ^{13}C NMR (no NOE) of the aldehyde carbon at 198.0 and 199.5 ppm respectively] of **67** as a clear colorless liquid: bp 57-62°C/1.0 mm.

Ethyl trans-2-Hydroxymethylenecyclo-propancarboxylate (74)

To a stirred solution of 12.00 g (0.084mol) of the mixture of isomers of ethyl 2-formylcyclopropancarboxylate (**67**) in 65 mL of 95% ethanol was added in four equal portions 6.39 g (0.168 mol) of $NaBH_4$ over 30 min in a 200-mL,

three-necked, round-bottom, flask. The resulting suspension was stirred for an additional 2 h; the mixture was filtered and the filtrate was evaporated (rotor evaporator) to give a colorless liquid. The crude alcohol was distilled to give 5.05 g (41.5%) of ethyl trans-2-hydroxymethylenecyclopropancarboxylate (**74**) as a clear colorless liquid: bp 127-131°C/20 mm (lit[58] 121-123°C/20 mm); ^{1H} NMR ($DCCl_3$) δ 0.86 [m, 1 H], 1.20 [m, 1 H], 1.25 [t, 3 H, $CO_2CH_2C\underline{H}_3$], 1.56 [m, 1 H], 1.91 [m, 1 H], 2.31 [m, 1 H], 3.46 [m, 1 H], 3.62 [m, 1 H], 4.13 [q, 2 H, $CO_2C\underline{H}_2CH_3$]; ^{13}C NMR ($DCCl_3$) ppm 12.6, 14.1, 18.3, 24.2, 60.6, 64.3, 174.0.

Ethyl trans-2-Formylcyclopropan-carboxylate (**67**)

To a 200-mL, three-necked flask equipped with a condenser, nitrogen inlet and power stirrer was added 4.00 g (27.7 mmol) of ethyl trans-2-hydroxymethylenecyclopropan-carboxylate (**74**), 8.97 g (41.6 mmol) of pyridinium chlorochromnate (**75**) and 80 mL of CH_2Cl_2. The mixture immediately became black with insoluble reduced reagent which caused stirring to become difficult. After 2 h, the mixture was diluted with 50 mL of ether, and the flask was rinsed with an additional 50 mL of ether. The resulting solution was evaporated (rotor evaporator), depositing more reduced reagent. The residue was taken up in 25 mL of ether and filtered through a 20 mm column of florasil with

ether (approx. 250 mL) as the eluent. After concentration (rotor evaporator), an oil was obtained which, upon distillation, gave 2.55 g (64.7%) of ethyl trans-2-formylcyclopropancarboxylate (**67**) as a clear, colorless liquid: bp 134-136°C/20 mm (lit[58] 100-102°C/20 mm). IR (neat) 2740 cm^{-1} [CHO, C-H strech], 1703 cm^{-1} [C=O]; ^1H NMR ($DCCl_3$) δ 1.28 [t, 3 H, $CO_2CH_2CH_3$], 1.52 [m, 1 H, H(3)], 1.60 [m, 1 H, H(3)], 2.28 [m, 1 H, H(1)], 2.43 [m, 1 H, H(2)], 4.19 [q, 2 H, $CO_2CH_2CH_3$], 9.31 [d, 1 H, CHO]; ^{13}C NMR ($DCCl_3$) ppm 14.2 [q, CH_3], 14.8 [t, C(2)], 22.2 [d, C(1)], 30.7 [dd, C(2)], 61.3 [t, CO_2CH_2], 171.1 [s, CO_2CH_2], 198.3 [d, CHO].

(2E,4E,6E)-3,7-methyl-(1,2,3,4,-tetrahydro-4,4-dimethyl-6-thiochromanyl)-2,4,6-heptatriene-2,3-dihydro-3-desmethyl-2,3-methylene-carboxylic Acid (**48e**)

To a stirred suspension of 6.05 (10.6 mmol) of phosphonium salt **63a** in 60 mL of dry ether was added dropwise n-butyllithium (6.81 mL, 1.55 M, 10.6 mmol) in hexane at room temperature in a 200-mL, three-necked, round-bottom flask equipped with a condenser and N_2 inlet. The resulting, dark orangish-red solution was cooled to -78°C (dry-ice, acetone), and 1.50 g (10.6 mmol) of ethyl trans-2-formylcyclopropancarboxylate (**67**) in 20 mL of ether was added dropwise in the dark. The mixture was allowed to

warm to room temperature with stirring over 12 h. The almost colorless suspension was diluted with 50 mL of hexanes, filtered, and concentrated. The resulting oil was passed through a 15 cm column containing a slurry of silica gel using 1:1 ether:hexanes. Removal (rotor evaporator) of the solvents gave 3.06 g of the crude esters **68** as a thick oil. To 0.50 g (1.40 mmol) of this oil was added 10 mL of methanol, and this new solution was added to a mixture of KOH (0.28 g, 4.21 mmol) in 2 mL of H_2O. Heating this mixture to a gentle reflux followed for 30 min. The clear resultant solution was allowed to cool (30 min) to room temperature, was diluted with 50 mL of H_2O and 5.0 g of NaCl, and was finally extracted with 100 mL of ether. The ether layer was extracted with H_2O (3 x 25 mL), and the combined aqueous layers were acidified slowly with 5% H_2SO_4 (approx. pH 3). At the neutralization point, the solution became cloudy. The aqueous solution was extracted with ether (2 x 50 mL); the organics were combined, extracted with H_2O (25 mL) and brine (50 mL). After drying (Na_2SO_4, overnight), evaporation (rotor evaporator) of the ether gave a slightly colored oil which was crystallized (ethanol:H_2O) to give 0.98 g (28.2%) of acid **48e** (recrystallized from ethanol:H_2O) as a tan solid: mp 149.5-152.0°C; ^{1}H NMR ($DCCl_3$) δ 1.12 [m, 1 H], 1.33 [s, 6 H, $(C\underline{H}_3)_2C$], 1.51 [m, 1 H], 1.69 [m, 1 H], 1.95 [m, 2 H, $PhSCH_2C\underline{H}_2$], 2.20 [m, 1 H], 2.12 [s, 3 H, $PhC(C\underline{H}_3)$], 3.02 [m, 2 H, $PhSC\underline{H}_2CH_2$], 5.34 [dd, 1 H, J = 9.0 Hz, J = 15.0

Hz, PhC(CH_3)CHCH=C<u>H</u>], 6.34 [d, 1 H, J = 12.0 Hz, PhC(CH_3)C<u>H</u>], 6.61 [dd, 1 H, J = 12.0 Hz, J = 15.0 Hz, CH-C<u>H</u>=CH], 7.04 [d, 1 H, J = 8.0 Hz, H(8)], 7.12 [dd, 1 H, J = 8.0 Hz, J = 2.0 Hz, H(7)], 7.43 [d, 1 H, J = 2.0 Hz, H(5)]; ^{13}C NMR ($DCCl_3$) ppm 15.9, 16.9, 22.4, 23.1, 26.8, 30.2, 33.1, 37.7, 123.3, 123.6, 125.0, 126.4, 128.1, 130.7, 133.1, 135.2, 138.8, 141.6, 179.5. Anal. Calcd for $C_{20}H_{24}SO_2$: C, 73.13; H, 7.37. Found: C, 73.09; H, 7.52.

<u>Ethyl 3-Phenoxypropionate (90)</u>

The procedure used was similiar to that described by Hall and Stern.[50] To a solution of 47.0 g (0.50 mol) of phenol (**89**) and 50.0 g (0.50 mol) of ethyl acrylate (**53**) was added 0.60 g (0.02 g at) of metallic sodium at RT in a 200-mL, three-necked, round-bottom flask equipped with a condenser and N_2 inlet. Heating was started after the sodium had dissolved and the solution temperature was brought to approximately 95°C (slightly lower than the bp of **53**). After 36 h, the resulting solution was cooled and 0.5 mL of acetic acid in 100 mL of H_2O was added. The new mixture was extracted with ether (3 x 100 mL), the organic layers were combined and dried (Na_2SO_4, 12 h). Ether was removed (rotary evaporator) and the resulting oil was vacuum distilled to give 36.32 g (37.4 %) ethyl of 3-phenoxypropionate (**90**) as a clear colorless liquid: bp 139-142°C/11 mm (lit[50] 142°C/11 mm); IR (neat) 1740 cm^{-1} (C=O);

^{1}H NMR ($DCCl_3$) δ 1.15 [t, 3 H, $CO_2CH_2C\underline{H}_3$], 2.65 [t, 2 H, $C\underline{H}_2CO_2CH_2CH_3$], 4.10 [m, 4 H], 6.75-7.25 [m, 5 H, Ph-$\underline{H}$].

2-Methyl-4-Phenoxy-2-butanol (91)

To a freshly prepared solution [70.14 g, (0.494 mol) of methyl iodide, 12.01 g (0.494 g at) of magnesium] of methylmagnesium iodide in 300 mL of dry ether was added dropwise 32.00 g (0.165 mol) of ethyl 3-phenoxypropionate (**90**) in 150 mL of ether in a 1000-mL, three-necked, round-bottom flask equipped with a condenser and N_2 inlet. The solution was boiled for 1 h and allowed to stirr at room temperature for 10h. The resulting solution was neutralized with 5% H_2SO_4 (pH approx. 6.5); the ether layer was separated, and the aqueous layer was extracted with ether (3 x 100 mL). The ether layers were combined and dried (Na_2SO_4, overnight). Solvent was evaporated (rotary evaporator), and vacuum distillation of the residual oil gave 24.06 g (80.9%) of 2-methyl-4-phenoxy-2-butanol (**91**) as a clear, colorless liquid; bp 85-86.5°C/0.2 mm (lit[128] 81-84°C/0.07 mm); IR (neat) 3130-3610 cm^{-1} (O-H); ^{1}H NMR ($DCCl_3$) δ 1.26 [s, 6 H, $(C\underline{H}_3)_2$], 1.95 [t, 2 H, $PhOCH_2C\underline{H}_2$], 2.90 [brs, 1 H, O$\underline{H}$], 4.12 [t, 2 H, $PhOC\underline{H}_2$], 6.80-7.40 [m, 5 H, Ph-$\underline{H}$]; ^{13}C NMR ($DCCl_3$) ppm 29.6, 41.6, 65.0, 70.3, 114.4, 120.9, 129.4, 158.3.

4,4-Dimethylchroman (**84**)

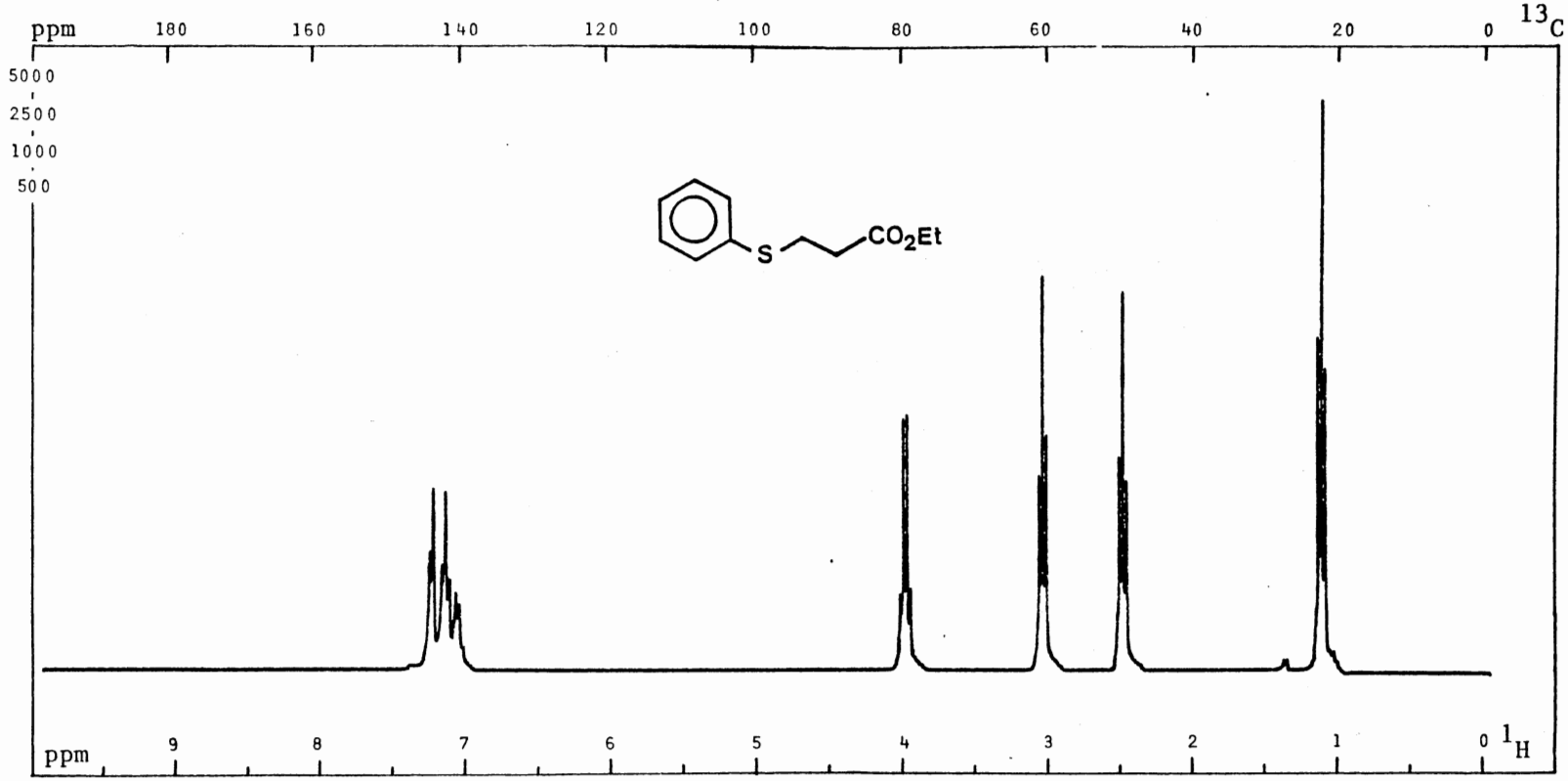
To a 500-mL, three-necked, round-bottom flask equipped with a condenser, N_2 inlet and power stirrer was added 23.01 g (0.173 mol) of $AlCl_3$ in 100 mL of freshly distilled, dry nitromethane. To the stirred solution of $AlCl_3$ was added dropwise a solution of 23.00 g (0.128 mol) of 2-methyl-4-phenoxy-2-butanol (**91**) in 125 mL of dry nitromethane at RT over 30 min and the mixture was stirred for 24 h. To the new solution was added 200 mL 6 N HCl. The resulting mixture was separated and the aqueous layer extracted with ether (3 x 75 mL). The organics were combined, extracted with H_2O (50 mL) and brine (50 mL) and then dried (Na_2SO_4, overnight). The solvent was removed (rotorary evaporator) and the resulting brown oil was vacuum distilled to give 13.40 g (64.5%) of 4,4-dimethylchroman (**84**) as a clear colorless liquid: 54-55°C/0.2 mm (lit[128] 74-80°C/0.7 mm); ^1H NMR ($DCCl_3$) δ 1.30 [s, 6 H, $(C\underline{H}_3)_2$], 1.82 [m, 2 H, $PhOCH_2C\underline{H}_2$], 4.18 [m, 2 H, $PhOC\underline{H}_2CH_2$], 6.70-7.30 [m, 4 H, Ph-$\underline{H}$]; ^{13}C NMR ($DCCl_3$) ppm 30.4, 31.0, 37.6, 63.1, 117.0, 120.3, 126.8, 127.0, 131.7, 153.5.

Dimethyl (4-Carbmethyoxybenzyl)-phosphonate (**76**)

The procedure used was similiar to that described by Dawson for diethyl (3-carbethoxybenzyl)phosphonate.[29] To a

250-mL, three-necked, round-bottom flask equipped with a condenser was added 15.8 g (0.13 mol) trimethyl phosphite and 25.7 g (0.11 mol) methyl bromomethylbenzoate (**80**). A stream of N_2 was swept over the mixture and the flask was slowly heated to 150°C with an oil bath over 1 h (caution: MeBr is evolved during the reation causing the mixture to bubble violently if heated to fast). The resulting mixutre was then heated to 190°C for 30 min and then allowed to cool to RT while maintaining the N_2 atmosphere (about 30 min). After vacuum distillation (138-147°C/0.075 mm) 17.7 g (61.0%) of dimethyl (4-carbomethoxybenzyl)phosphonate (**76**) was obtained as a thick, viscous, clear, colorless oil: IR (neat) 1740 cm^{-1} (C=O); ^1H NMR ($DCCl_3$) δ 3.24 [d, $^2J_{PH}$ = 21 Hz, 2 H, $P(O)C\underline{H}_2$], 3.67 [d, $^3J_{PH}$ = 11 Hz, 6 H, $PO_2C\underline{H}_3$], 3.88 [s, 3 H, $CO_2C\underline{H}_3$], 7.37 [dd, $^3J_{HH}$ = 8 Hz, $^4J_{PH}$ = 3 Hz, 2 H, Ph-H (ortho)], 7.97 [d, $^3J_{HH}$ = 8 Hz, 2 H, Ph-H (meda)]; ^{13}C NMR ($DCCl_3$) ppm 32.3 [d, $^1J_{PC}$ = 136.9 Hz, $P(O)\underline{C}H_2$], 51.8 [d, $^2J_{PC}$ = 26.4 Hz, $PO_2\underline{C}H_3$], 52.1 [$CO_2\underline{C}H_3$], 128.1, 128.2, 128.9, 129.1, 136.0, 136.4, 165.8; ^{31}P ($DCCl_3$) ppm 25.38.

PLATE I



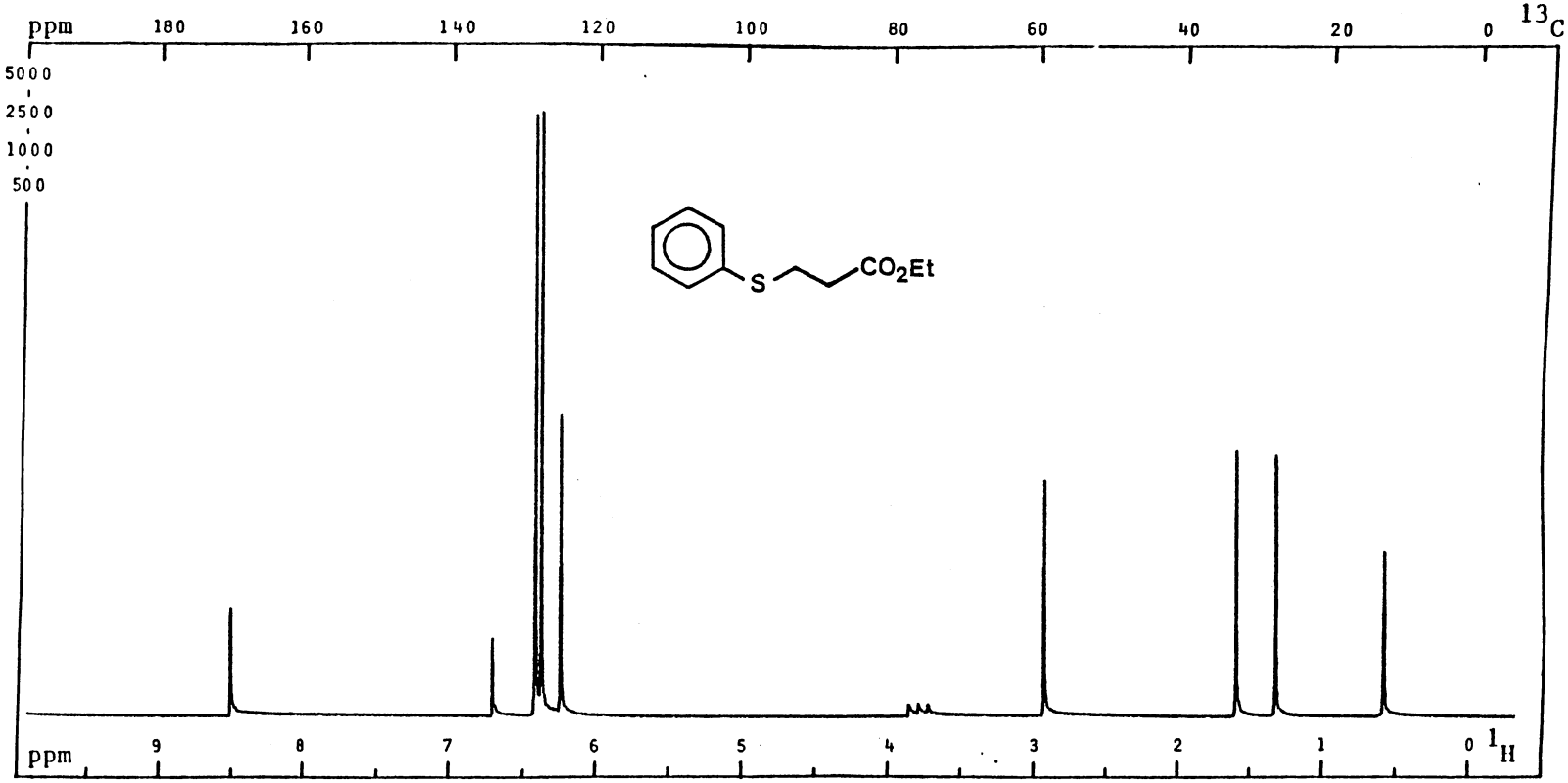
^{1}H NMR Spectrum of **54**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.948 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 12 K; PW/RF: 25.0 µs/dB; SO: 0 Hz; FB: - Hz; Lock: $DCCl_3$; Delay: 0 s.

DC: N ; Gated Off: ; Offset: Hz; RF: - W/dB; NBW: 0 Hz; LB: - .

PLATE II



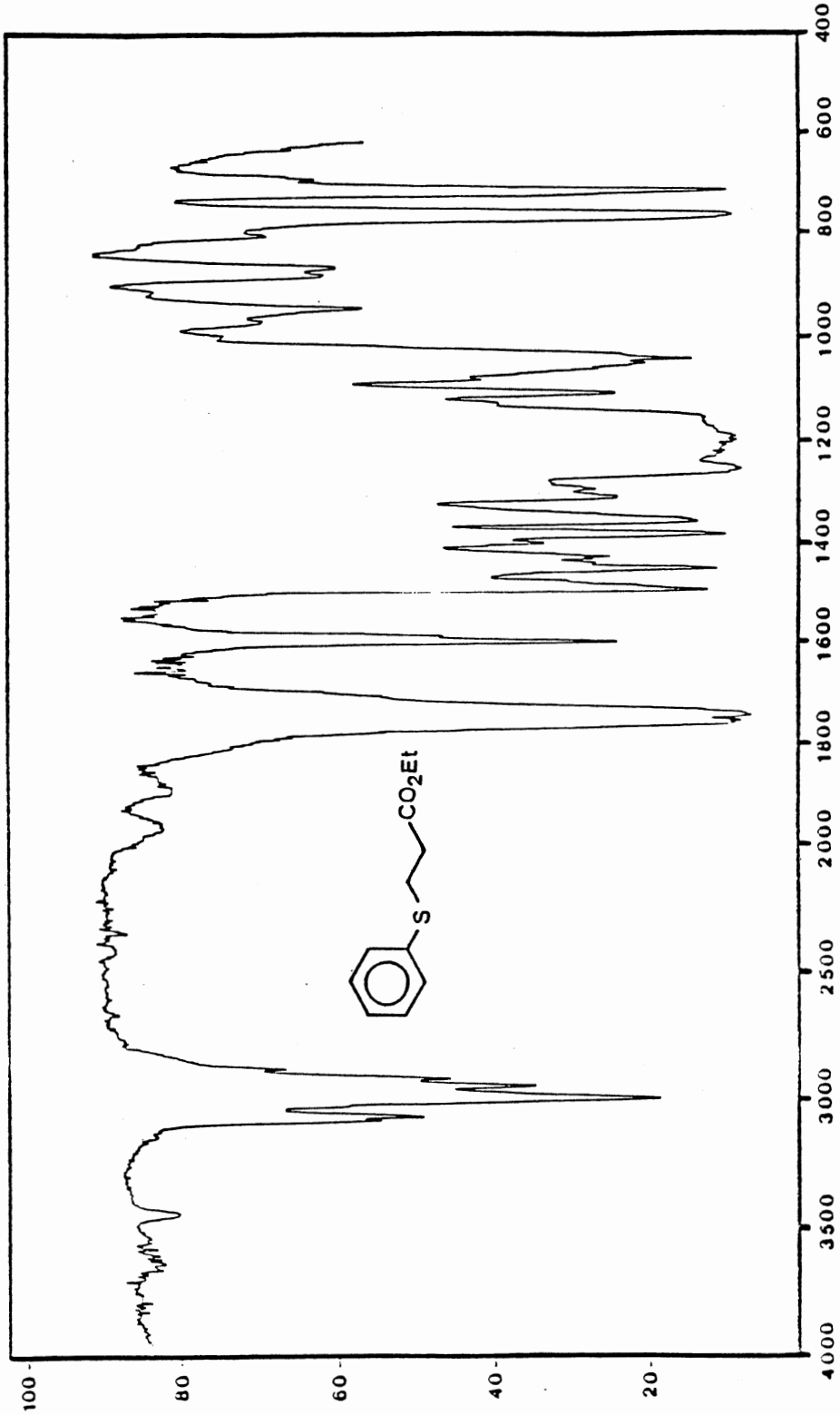
^{13}C NMR Spectrum of **54**

PFT X CW _ ; **Solvent:** $DCCl_3$; **SF:** 75.429 **MHz; WC:** 15085.9 **Hz; T:** RT **°C; NT:** 12

Size: 20 **K; PW/RF:** 12.0 **µs/dB; TO:** 1000 **Hz; FB:** - **Hz; Lock:** $DCCl_3$ **; D1,D5:** 4.0 **s.**

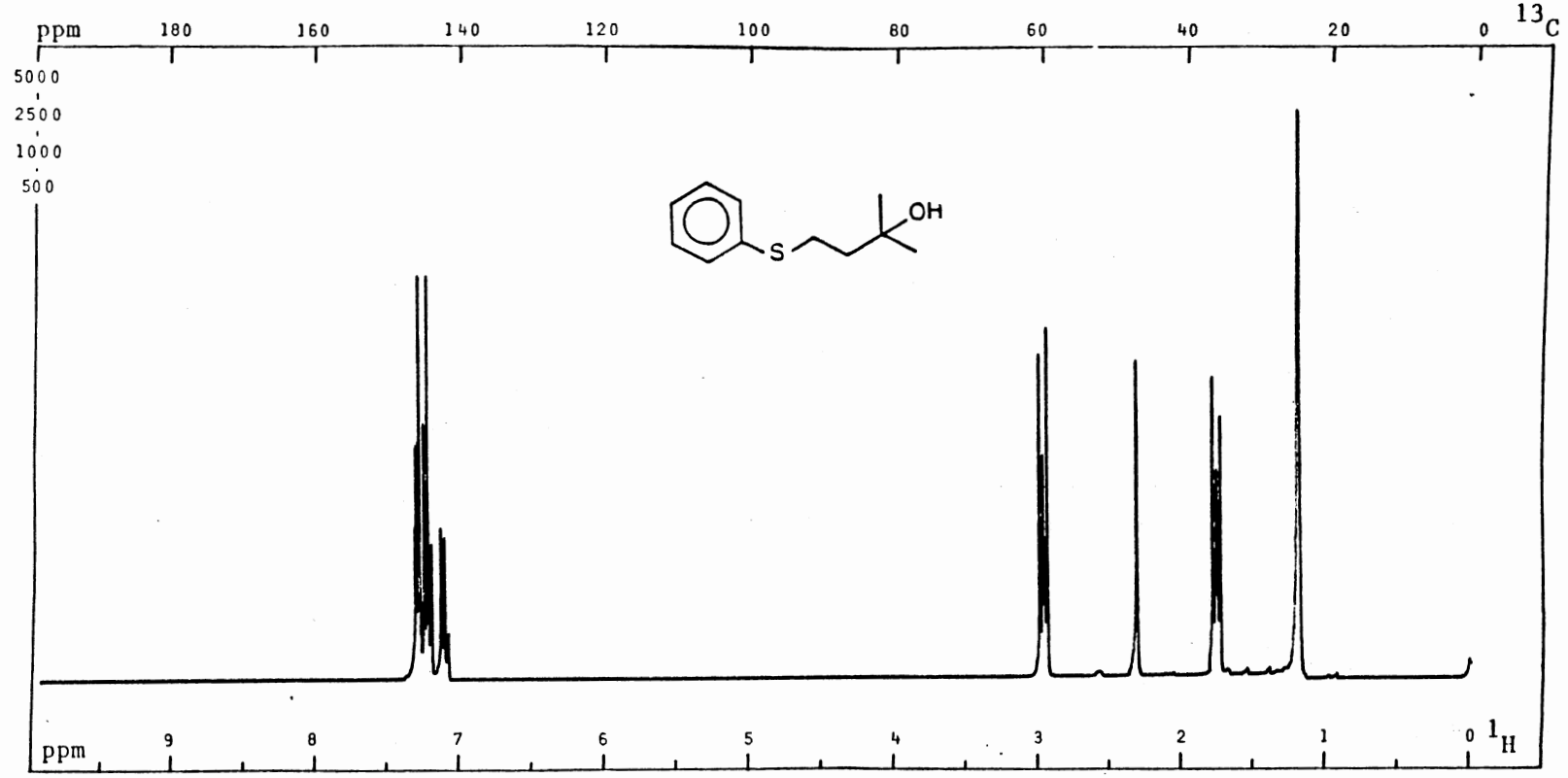
DC: Y, N ; **Gated Off:A or D ; DO:** 0 **Hz; RF(Power):** 10 **W/dB; NBW:** 200 **Hz; LB:** 3.0 **Hz.**

PLATE III



IR Spectrum of 54

PLATE IV



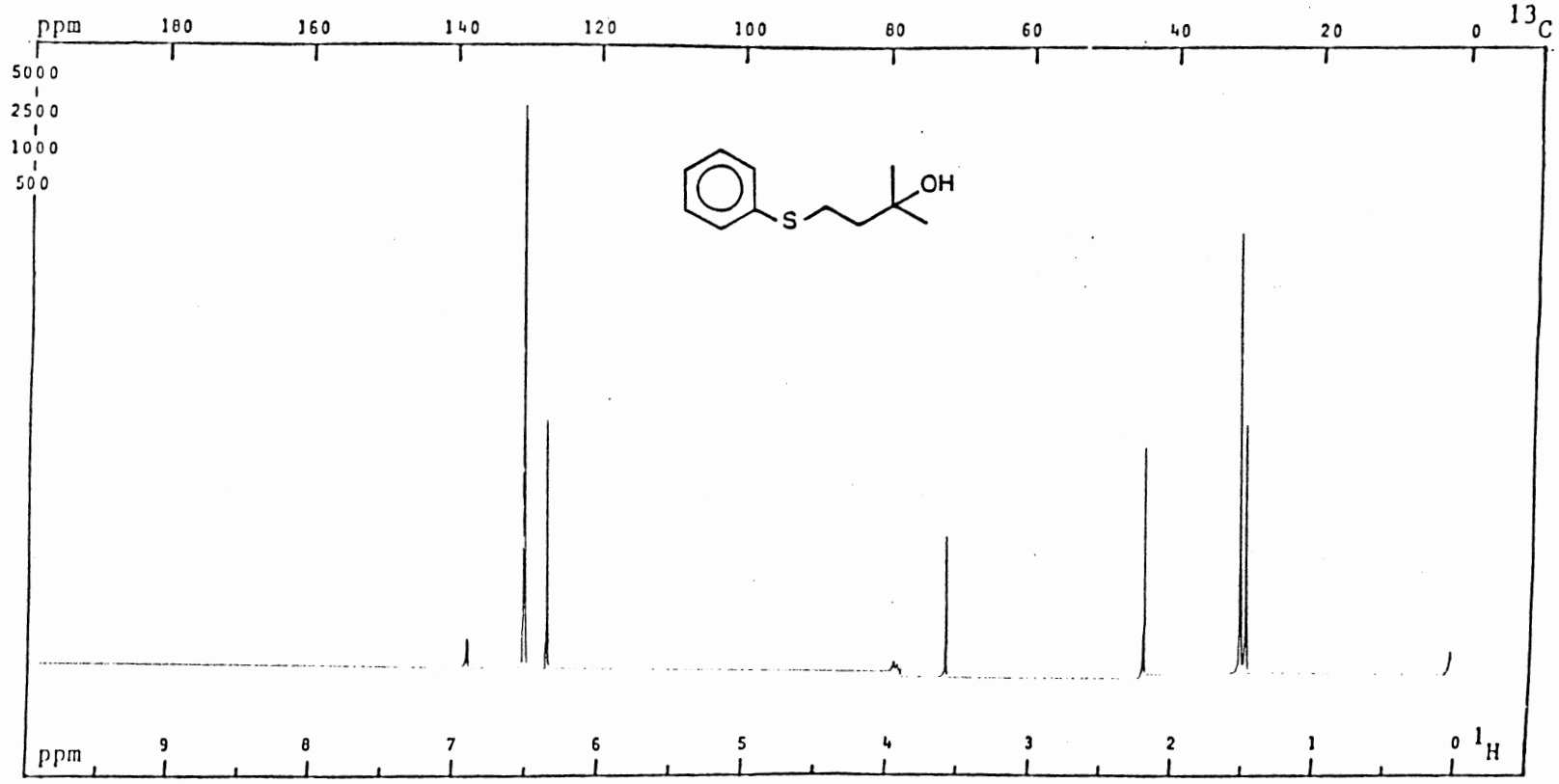
^{1}H NMR Spectrum of **55**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 2999.948 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 8 K; PW/RF: 5 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE V



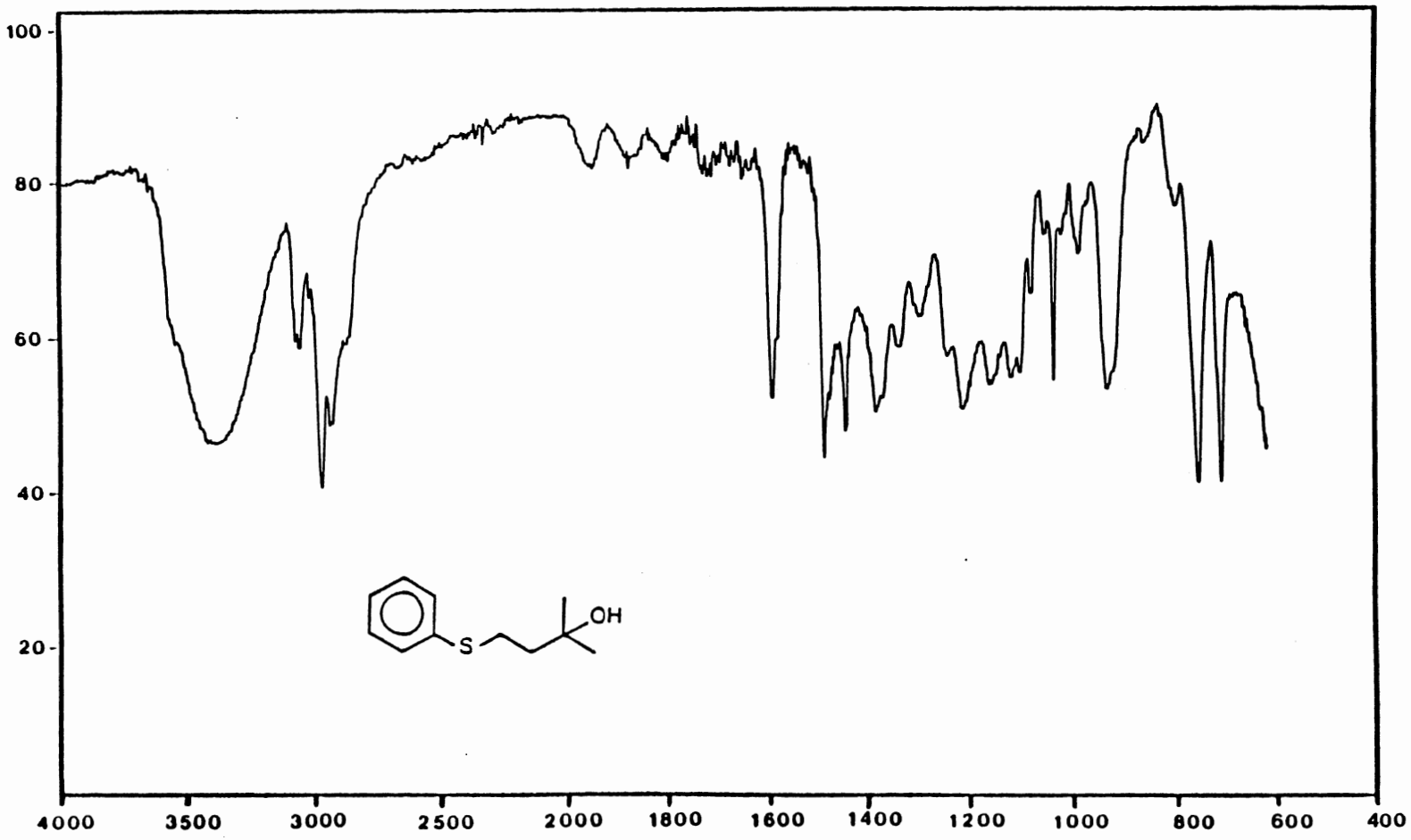
^{13}C NMR Spectrum of 55

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9Hz; T: RT °C; NT: 300

Size: 8 K; PW/RF: 9 µs/dB; TO: 10000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.0 s.

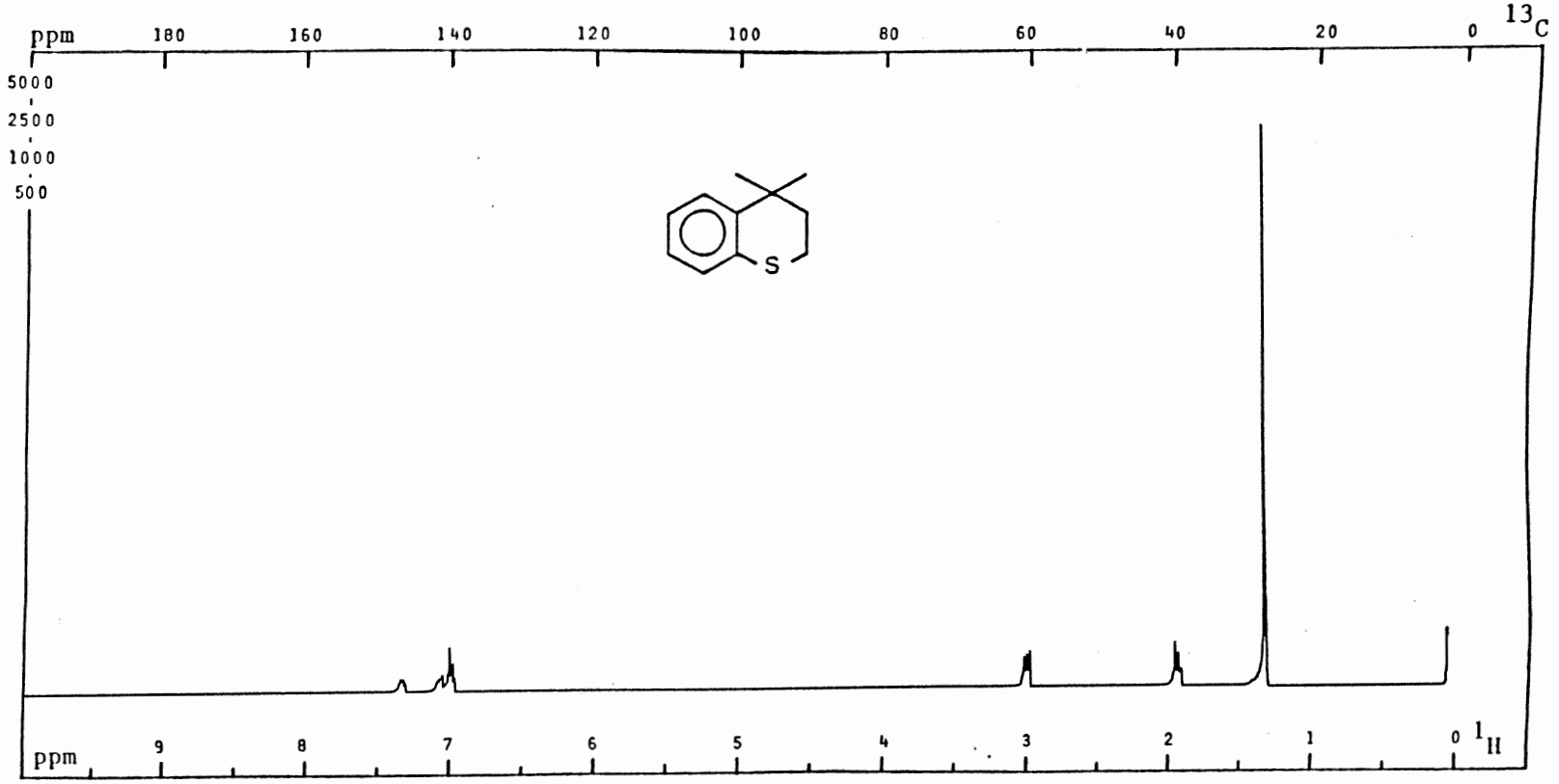
DC: Y, N ; Gated Off:A or D ; DO: Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: 1.0 Hz.

PLATE VI



IR Spectrum of 55

PLATE VII



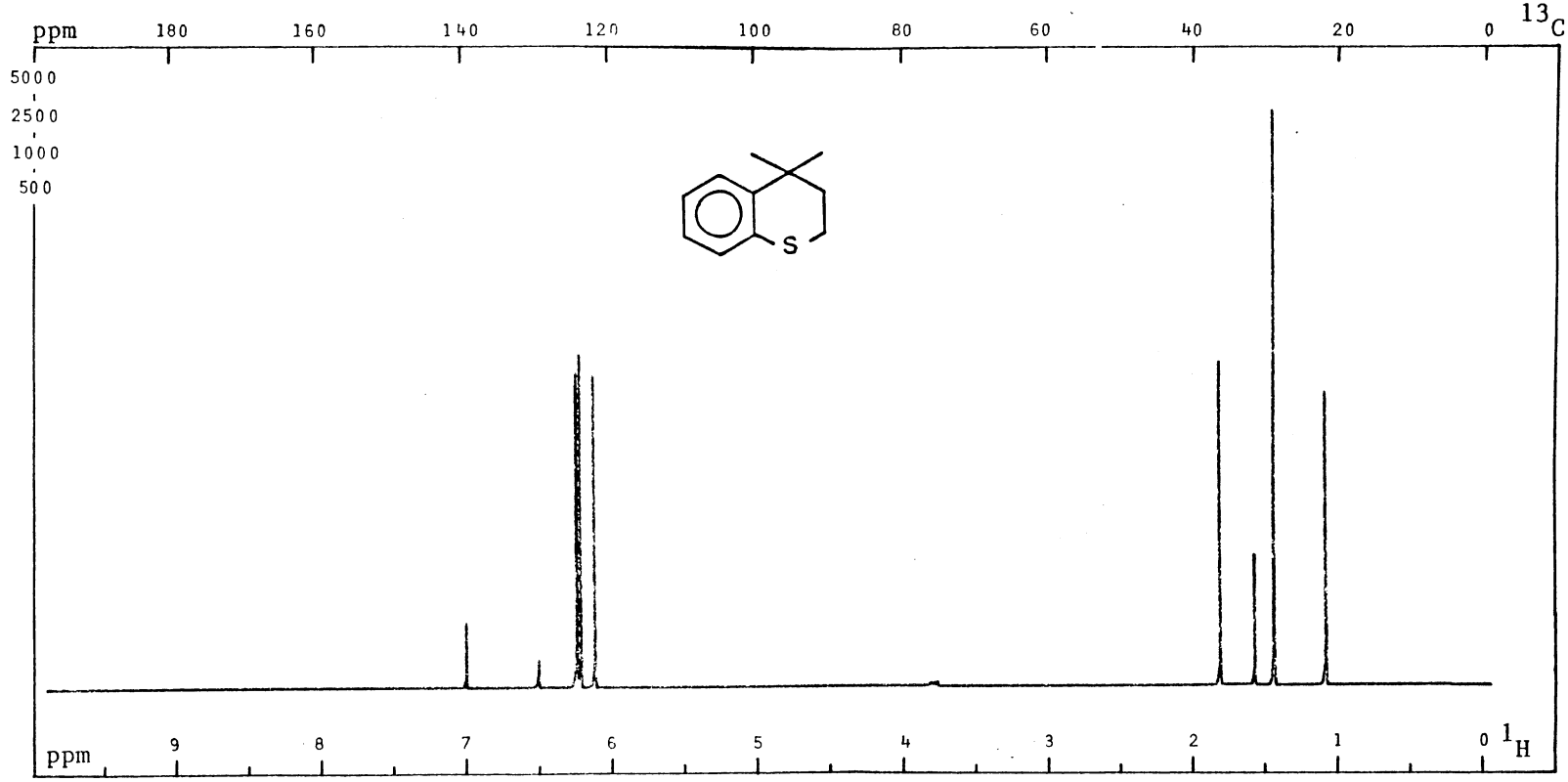
^{1}H NMR Spectrum of **56**

PFT X CW _ ; **Solvent:** $DCCl_3$; **SF:** 299.9485 **MHz; WC:** 2999.4 **Hz; T:** RT **°C; NT:** 8 .

Size: 8 **K; PW/RF:** 9 **µs/dB; TO:** 0 **Hz; FB:** - **Hz; Lock:** ^{2}H **; D1,D5:** 0 **s.**

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

PLATE VIII



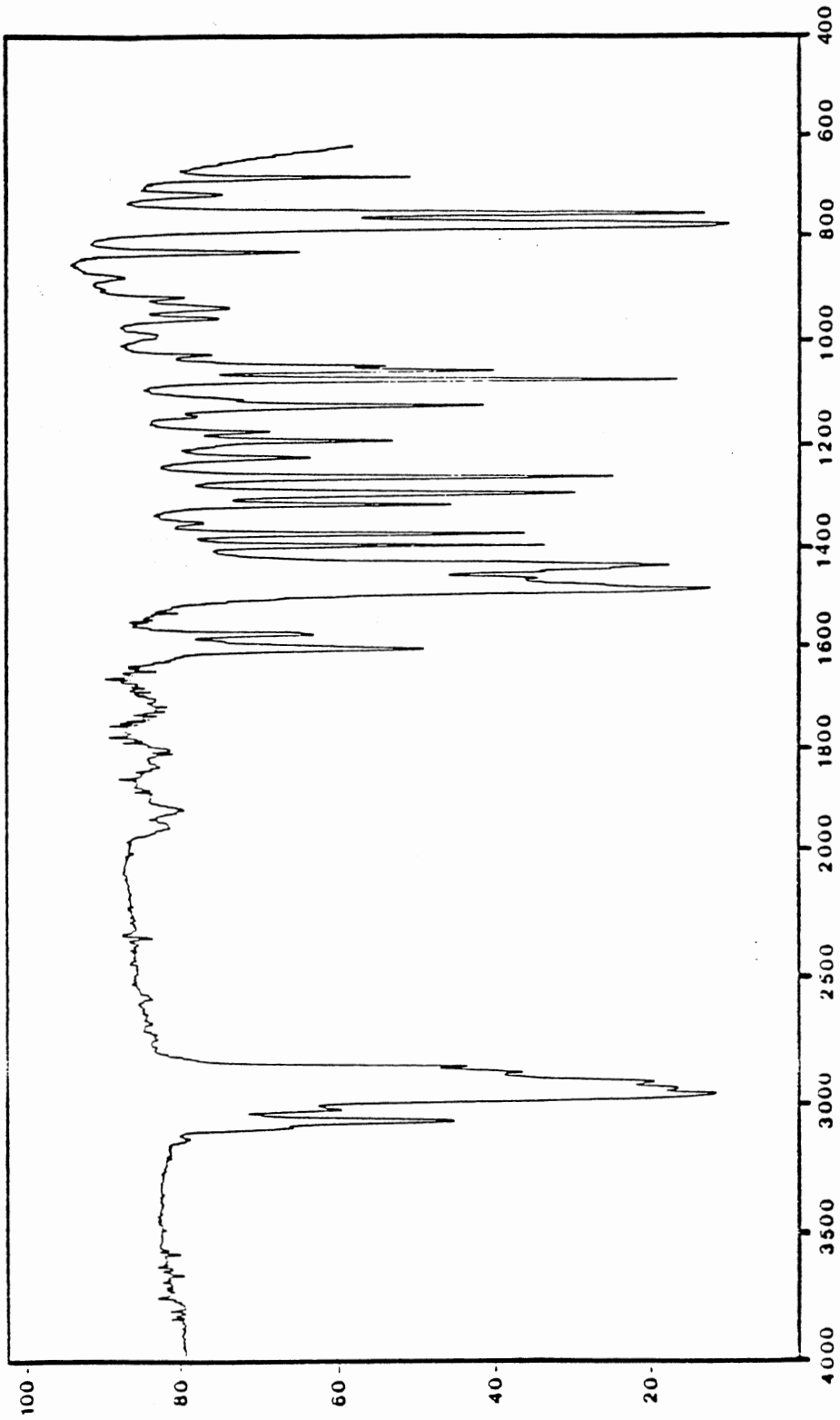
^{13}C NMR Spectrum of **56**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 300 .

Size: 20 K; PW/RF: 12 µs/dB; SO: 1000 Hz; FB: - Hz; Lock: ^2H ; Delay: 4.0 s.

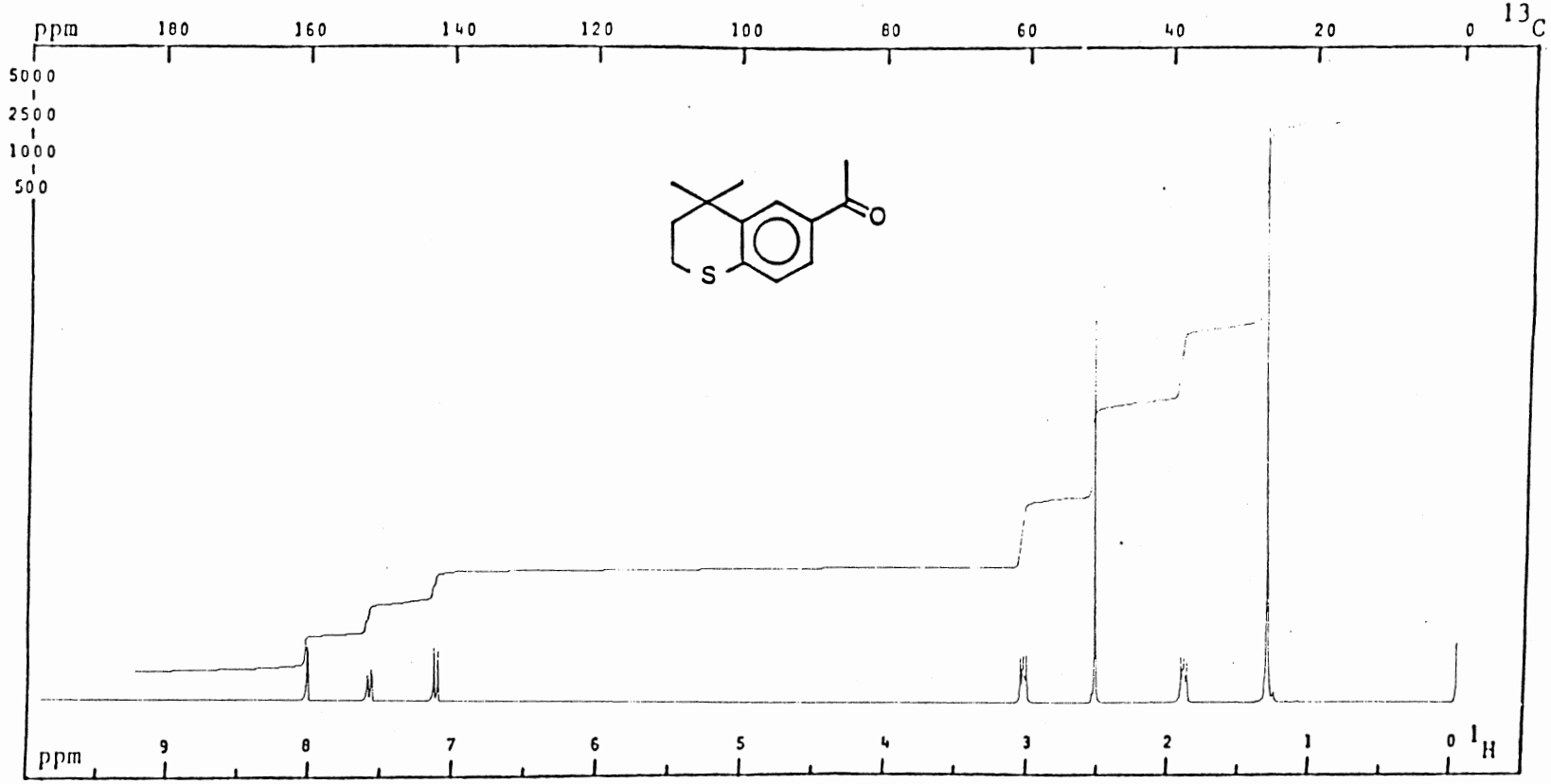
DC: Y ; Gated Off: ; Offset: Hz; RF: 10 W/dB; NBW: 200 Hz; LB: 1.0 .

PLATE IX



IR Spectrum of 56

PLATE X



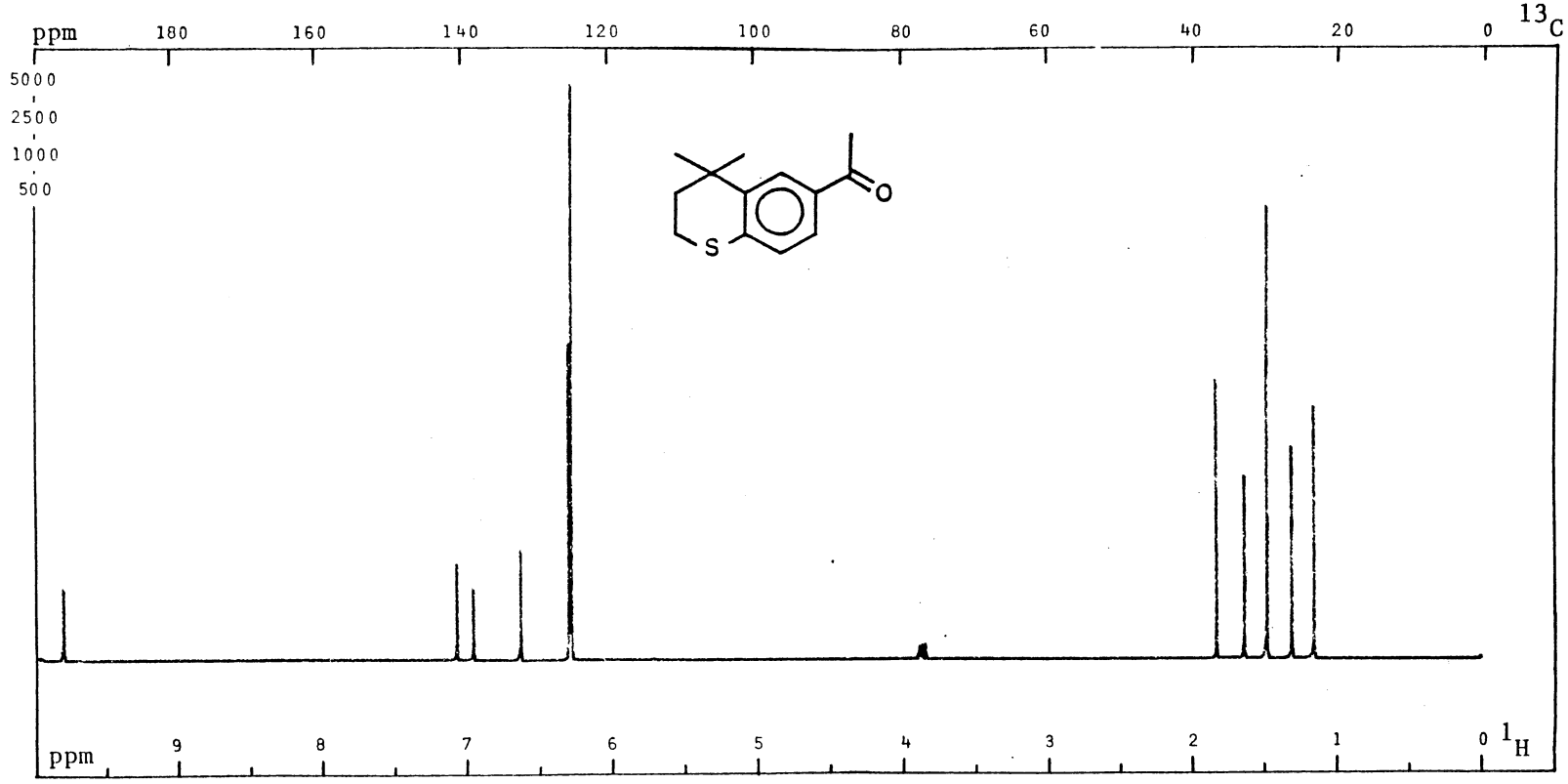
^{1}H NMR Spectrum of **51a**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.948 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16 .

Size: 12 K; PW/RF: 8.0 μs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0.5 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: - Hz.

PLATE XI



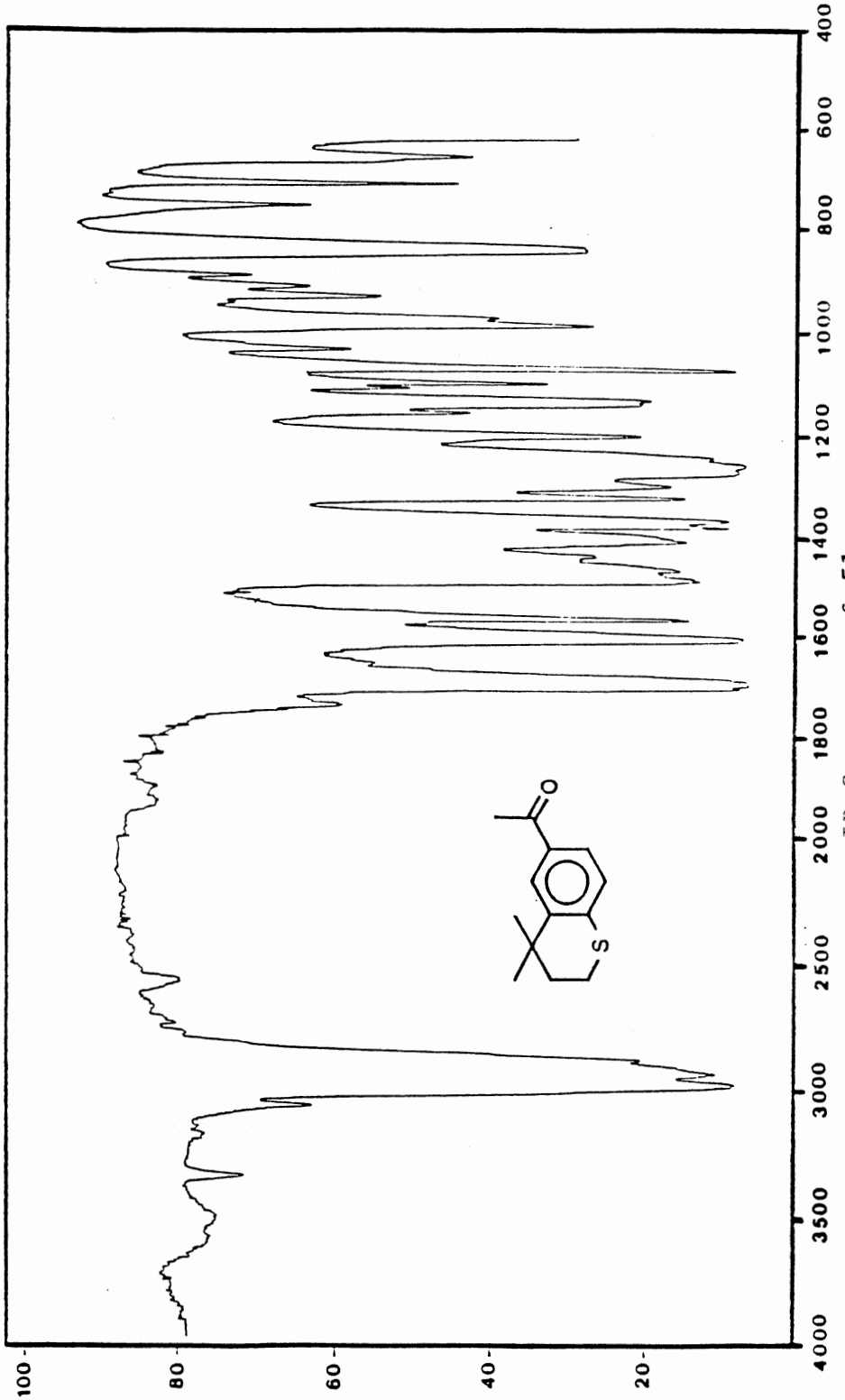
^{13}C NMR Spectrum of **51a**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9Hz; T: RT °C; NT: 300 .

Size: 20 K; PW/RF: 12 μs/dB; SO: 1000 Hz; FB: _ Hz; Lock: ^2H ; Delay: 4.0 s.

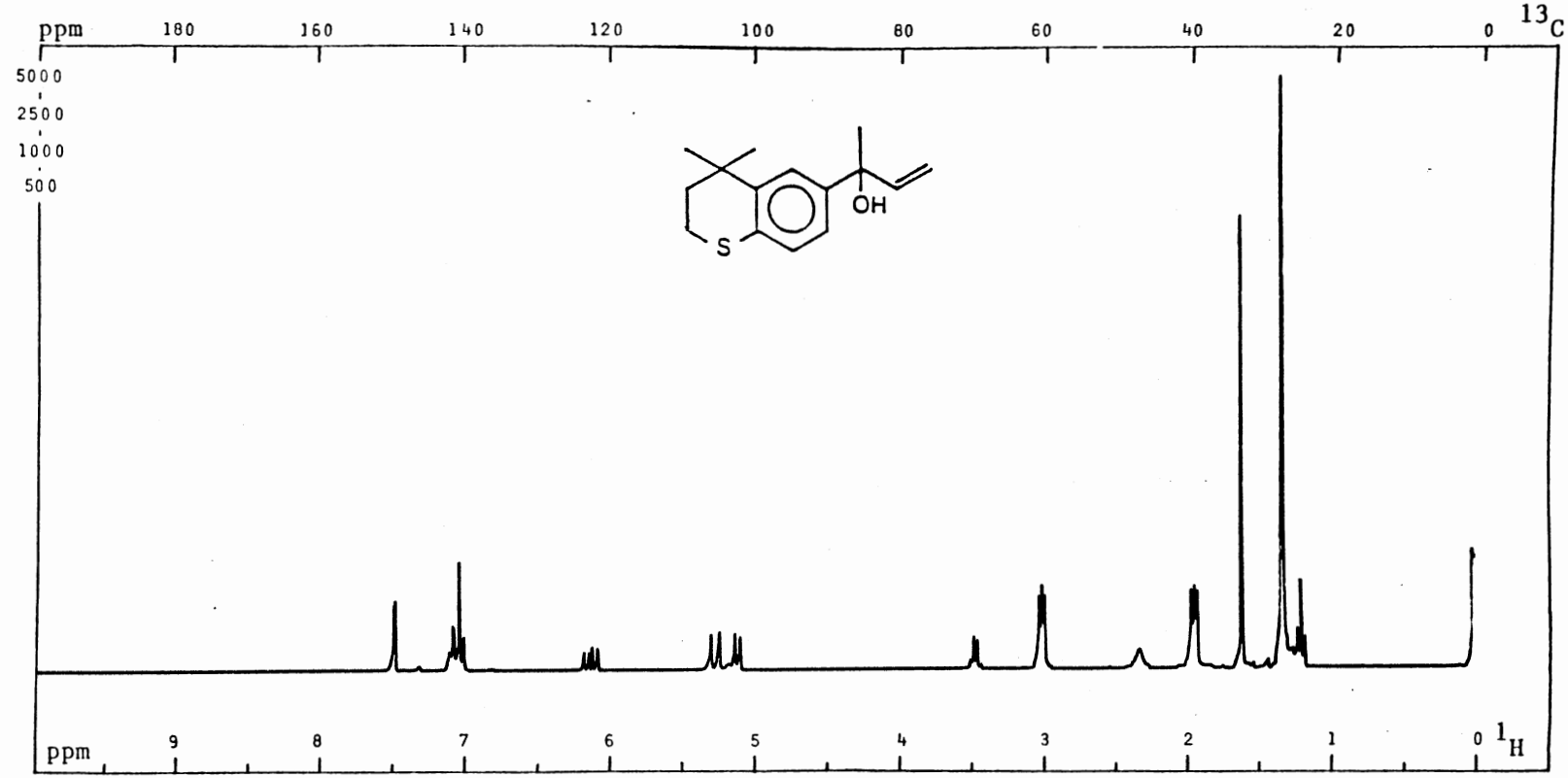
DC: Y ; Gated Off: ; Offset: Hz; RF: 10 W/dB; NBW: 200 Hz; LB: 1.0 .

PLATE XII



IR Spectrum of **51a**

PLATE XIII



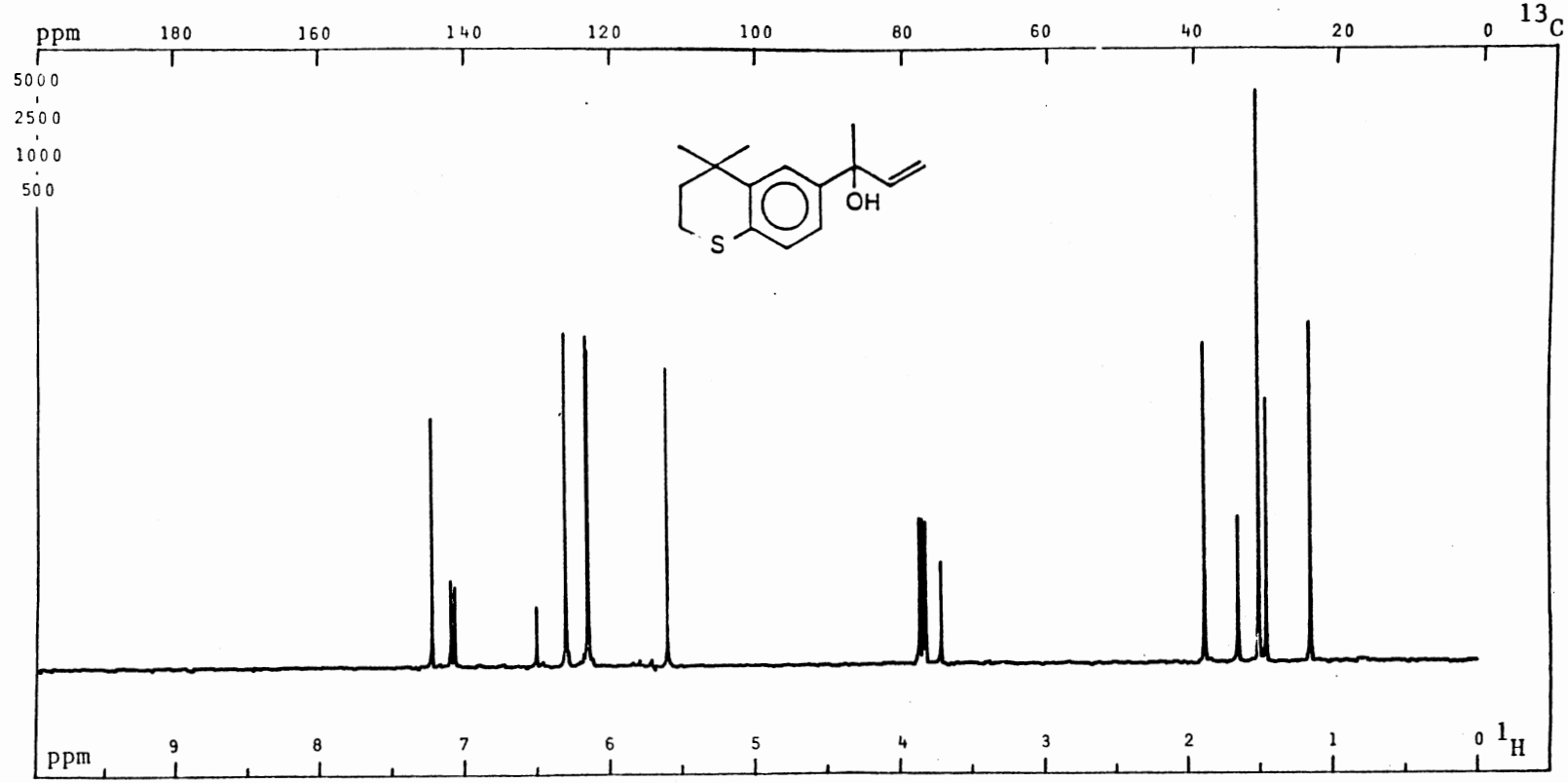
^{1}H Spectrum of **61a**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.948 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16 .

Size: 12 K; PW/RF: 8.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0.5 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: - Hz.

PLATE XIV



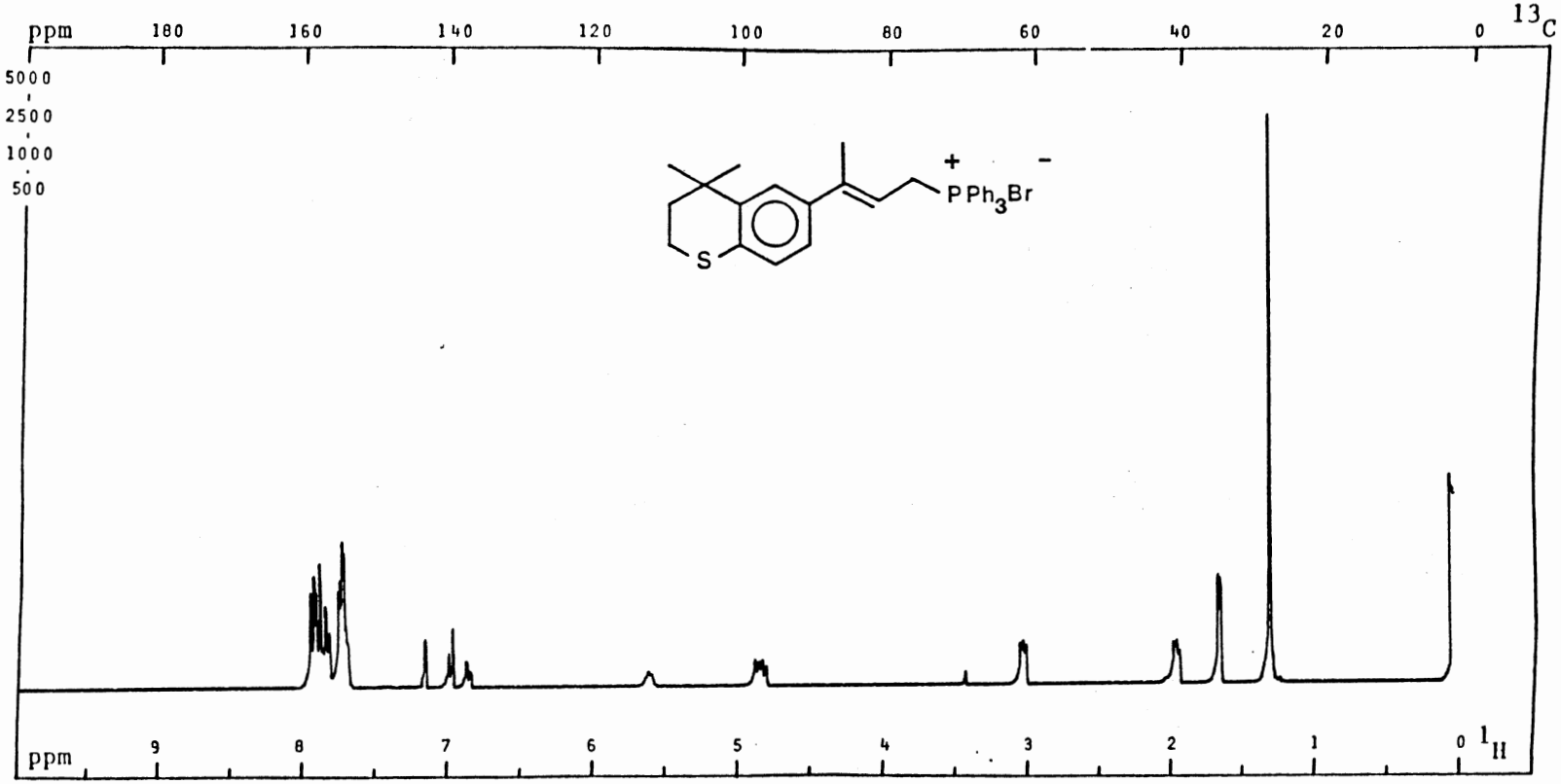
^{13}C Spectrum of **61a**

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

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

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: 1.5 Hz.

PLATE XV



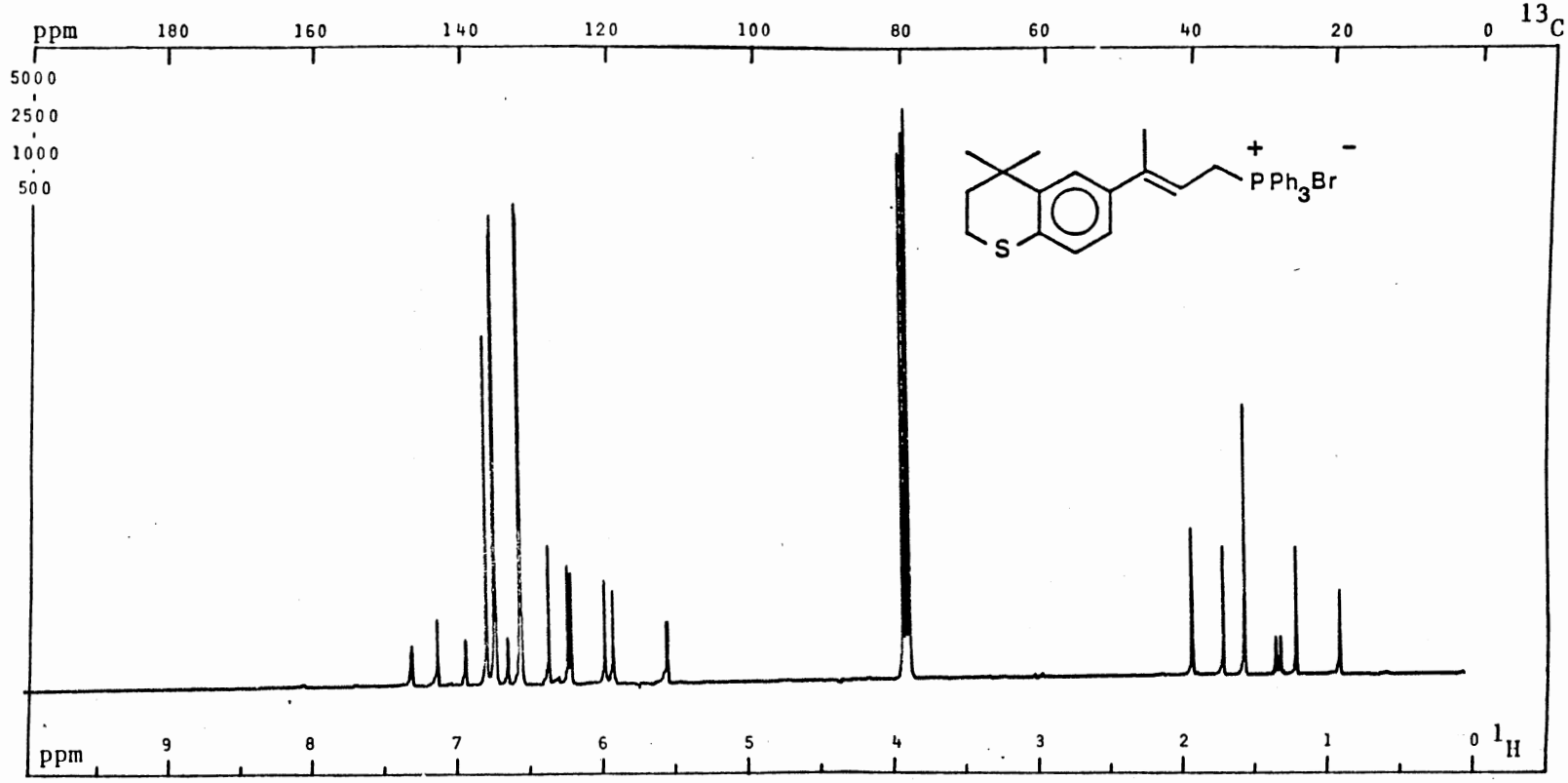
^{1}H Spectrum of **63a**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 8 K; PW/RF: 5 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE XVI



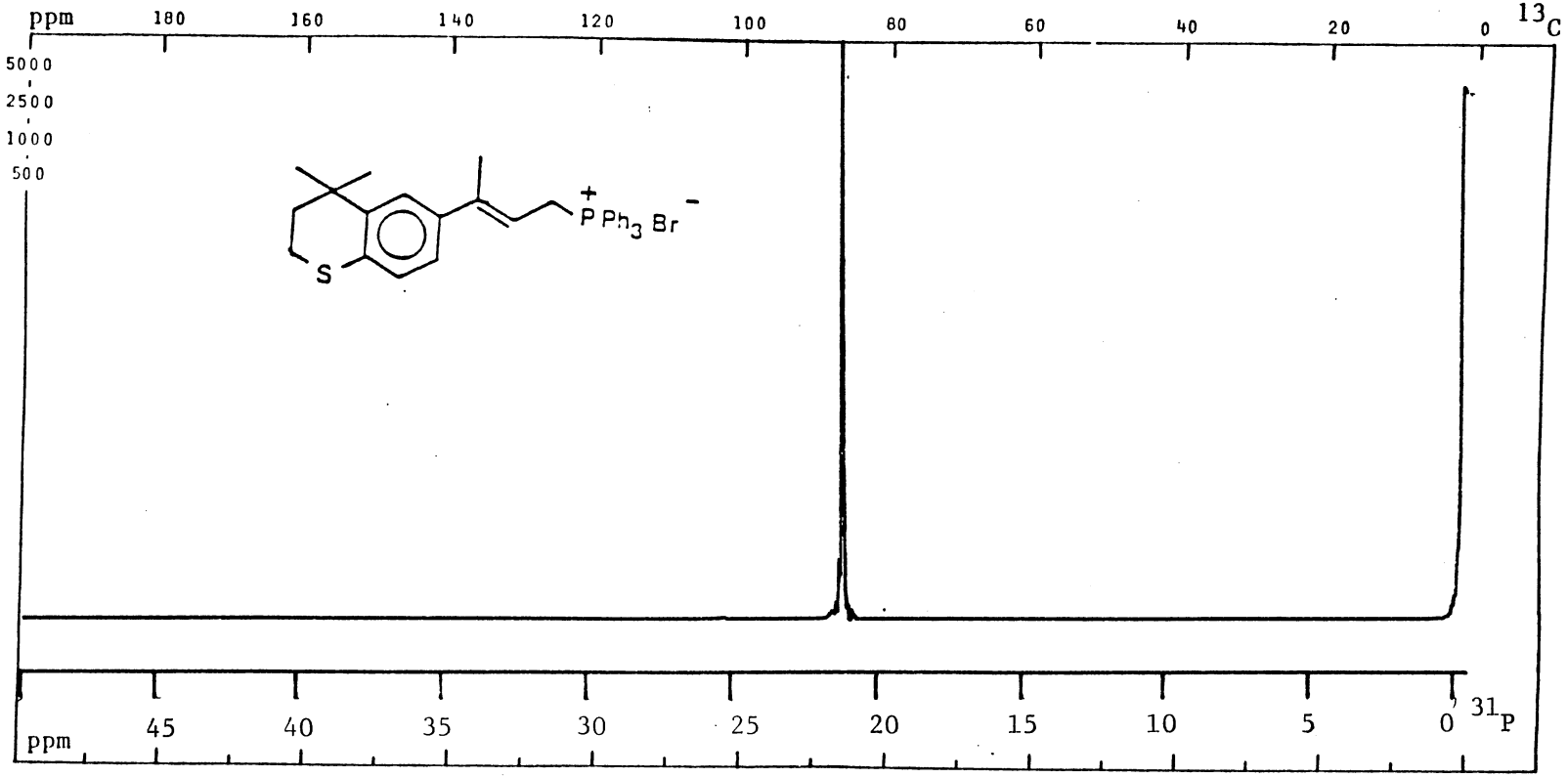
^{13}C NMR Spectrum of **63a**

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

Size: 20 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 5.0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

PLATE XVII



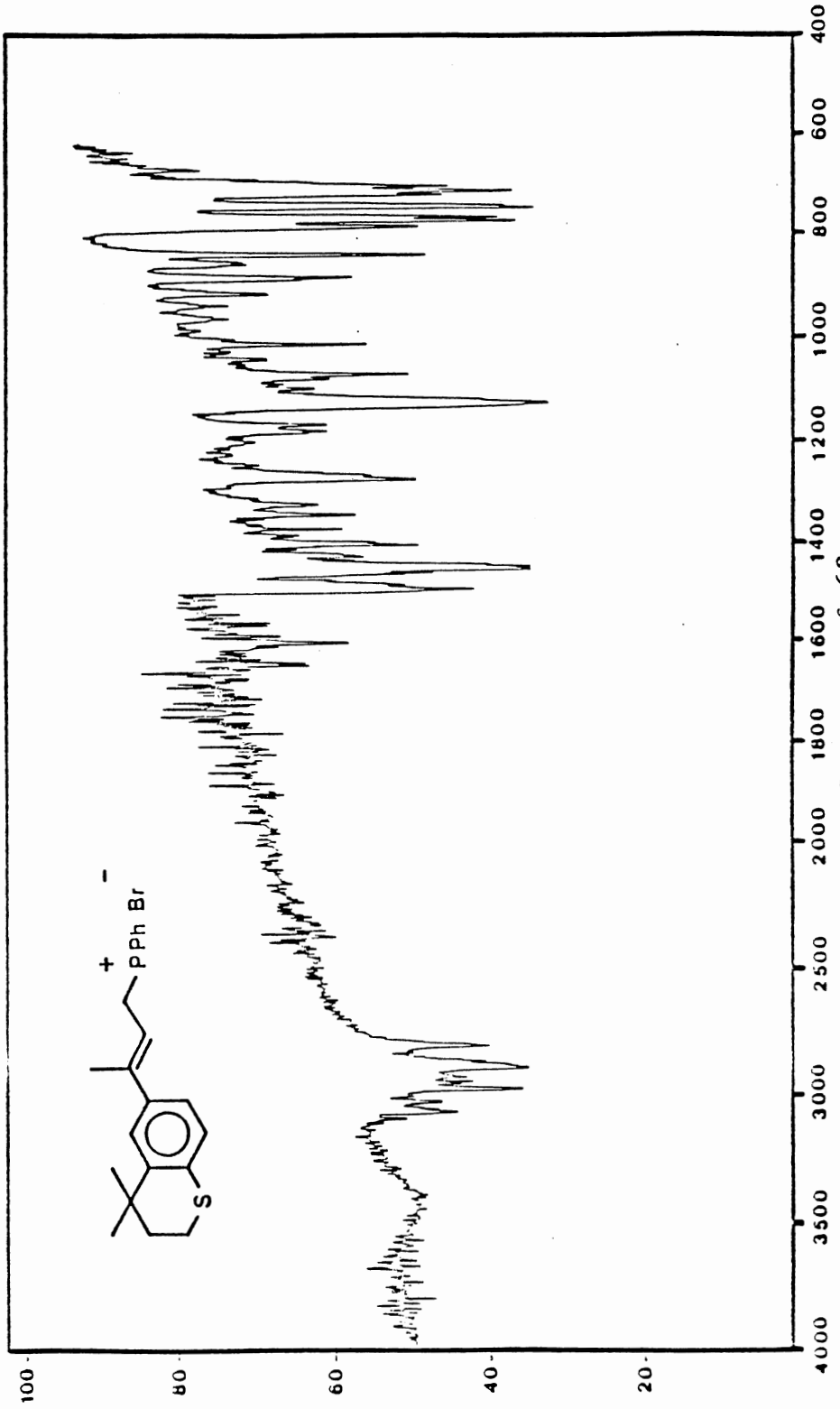
^{31}P NMR Spectrum of **63a**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 121.421 MHz; WC: 6071.0 Hz; T: RT °C; NT: 16 .

Size: 9998 K; PW/RF: 16.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ; D1,D5: 6.0 s.

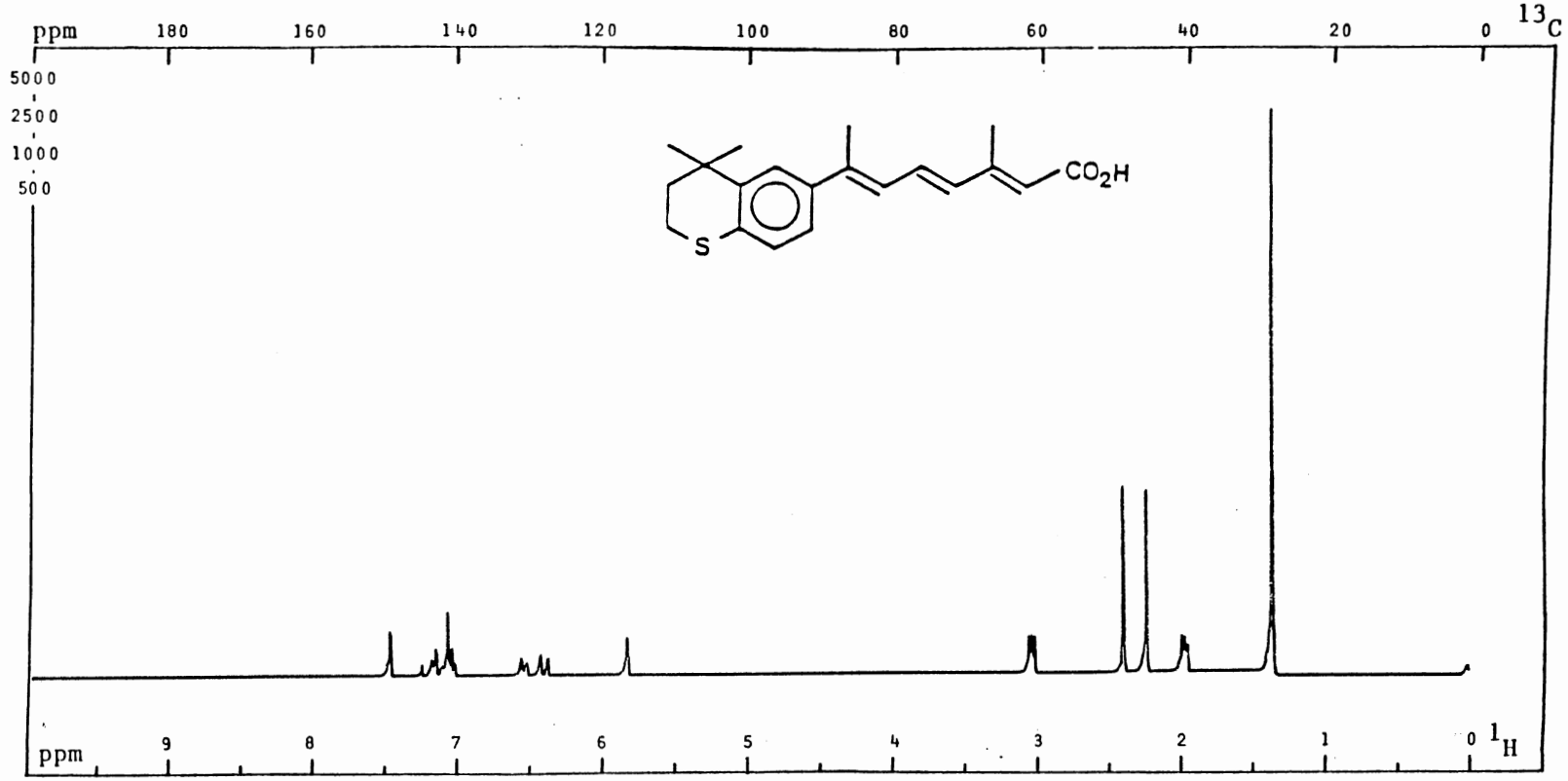
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 1.061 Hz.

PLATE XVIII



IR Spectrum of **63a**

PLATE XIX



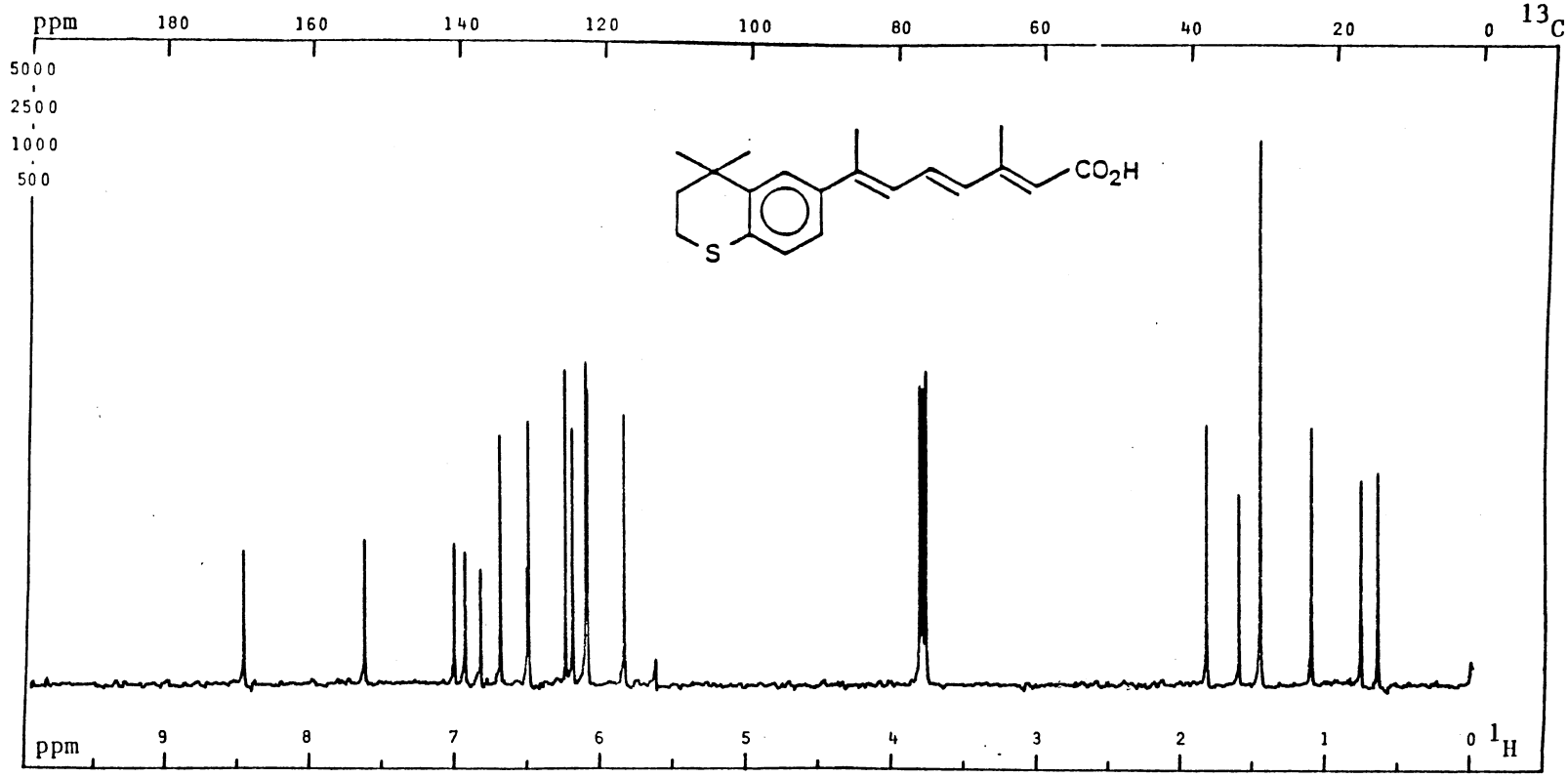
^{1}H Spectrum of **48b**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 100 .

Size: 18 K; PW/RF: 20 μs/dB; TO: 0 Hz; FB: -- Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE XX



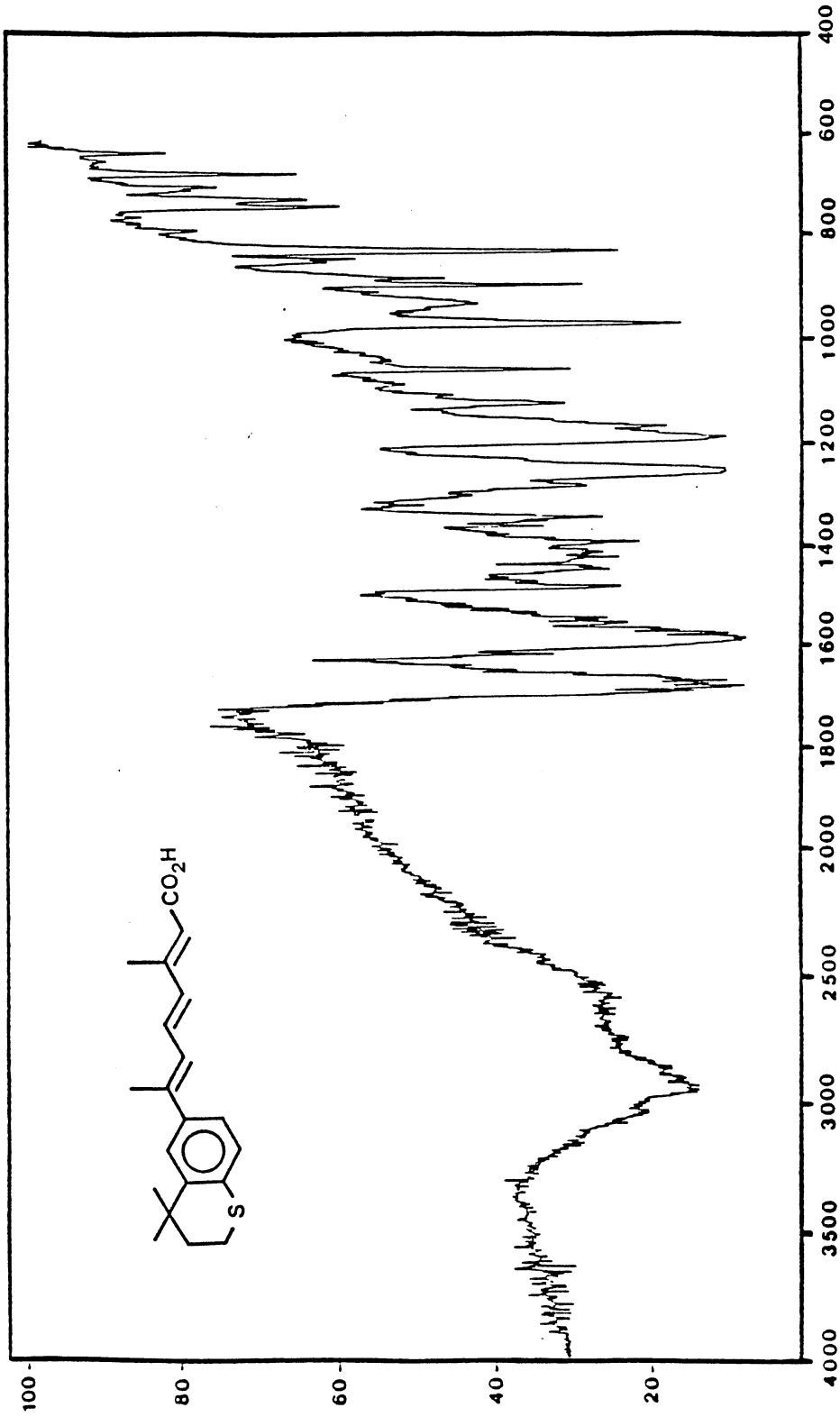
^{13}C Spectrum of **48b**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085 Hz; T: RT °C; NT: 100 .

Size: 16 K; PW/RF: 12 μs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.0 s.

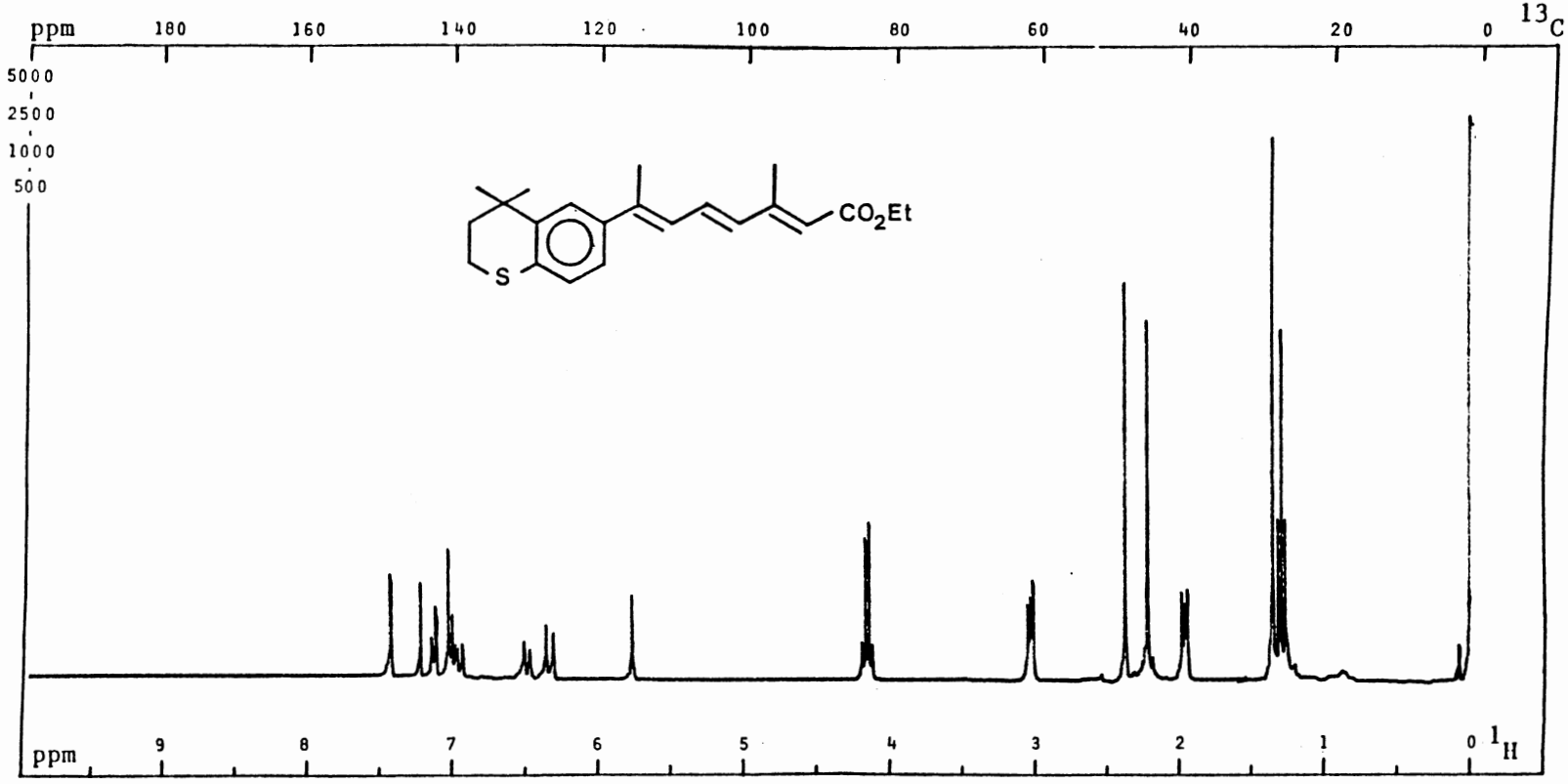
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 4.0 Hz.

PLATE XXI



IR Spectrum of 48b

PLATE XXII



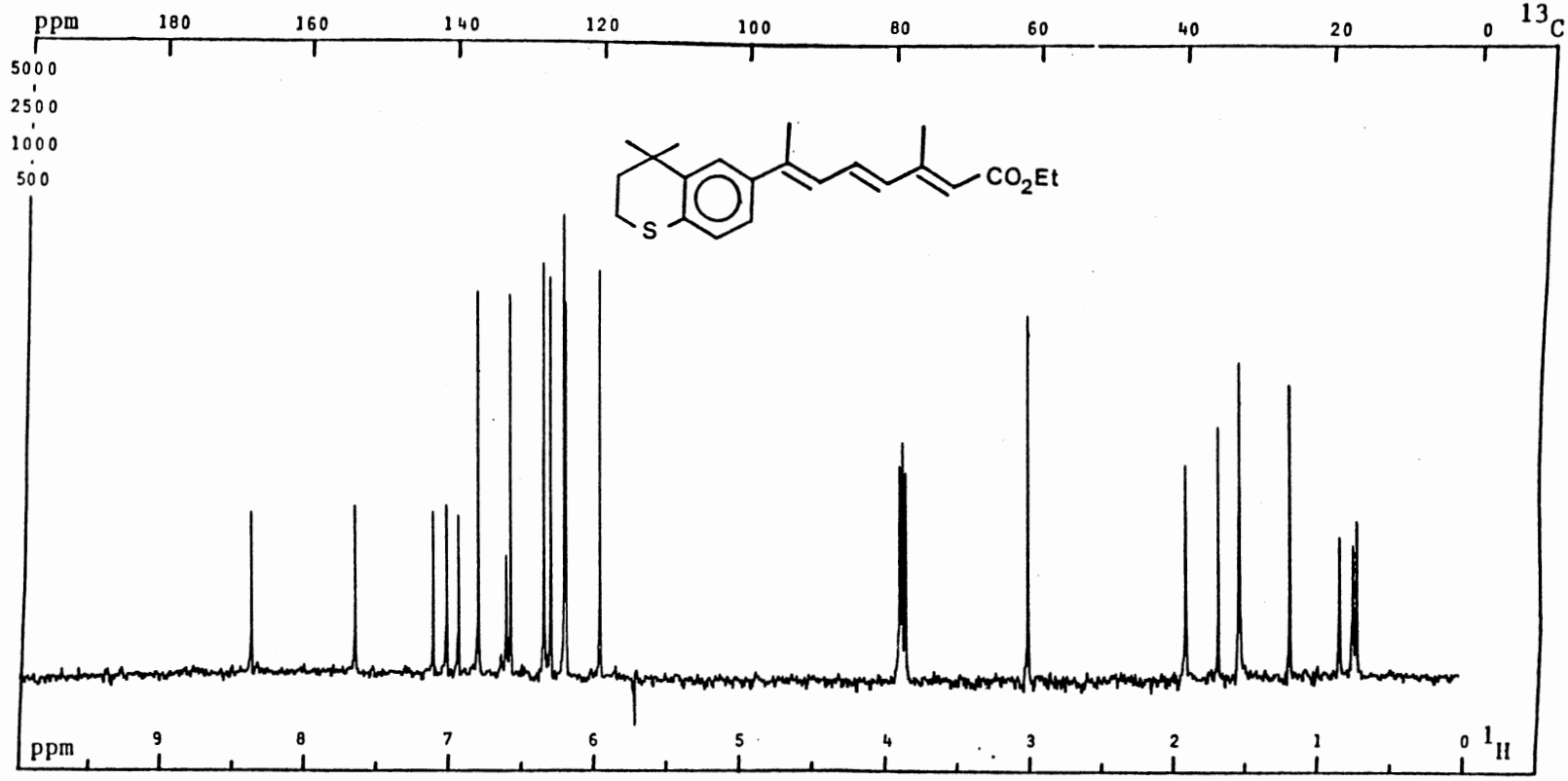
^{1}H Spectrum of **48a**

PFT X CW _ ; Solvent: $DCCl_3$; SF:299.9429 MHz; WC: 2999.4 Hz; T: RT °C; NT: 40 .

Size: 12 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ;D1,D5: 0 s.

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

PLATE XXIII



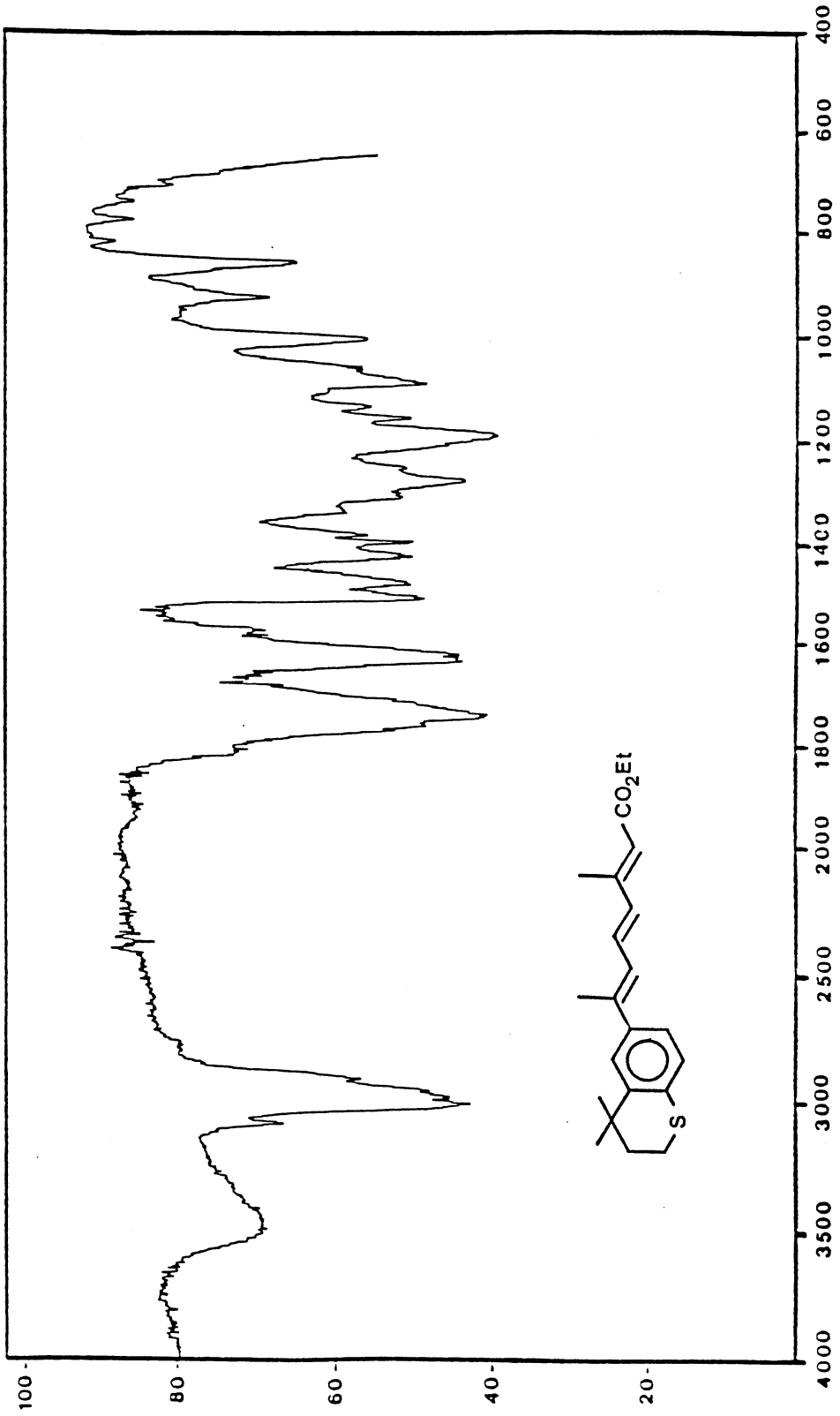
^{13}C NMR Spectrum of **48a**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9Hz; T: RT °C; NT: 1120 .

Size: 20 K; PW/RF: 35 µs/dB; TO: 1000Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.0 s.

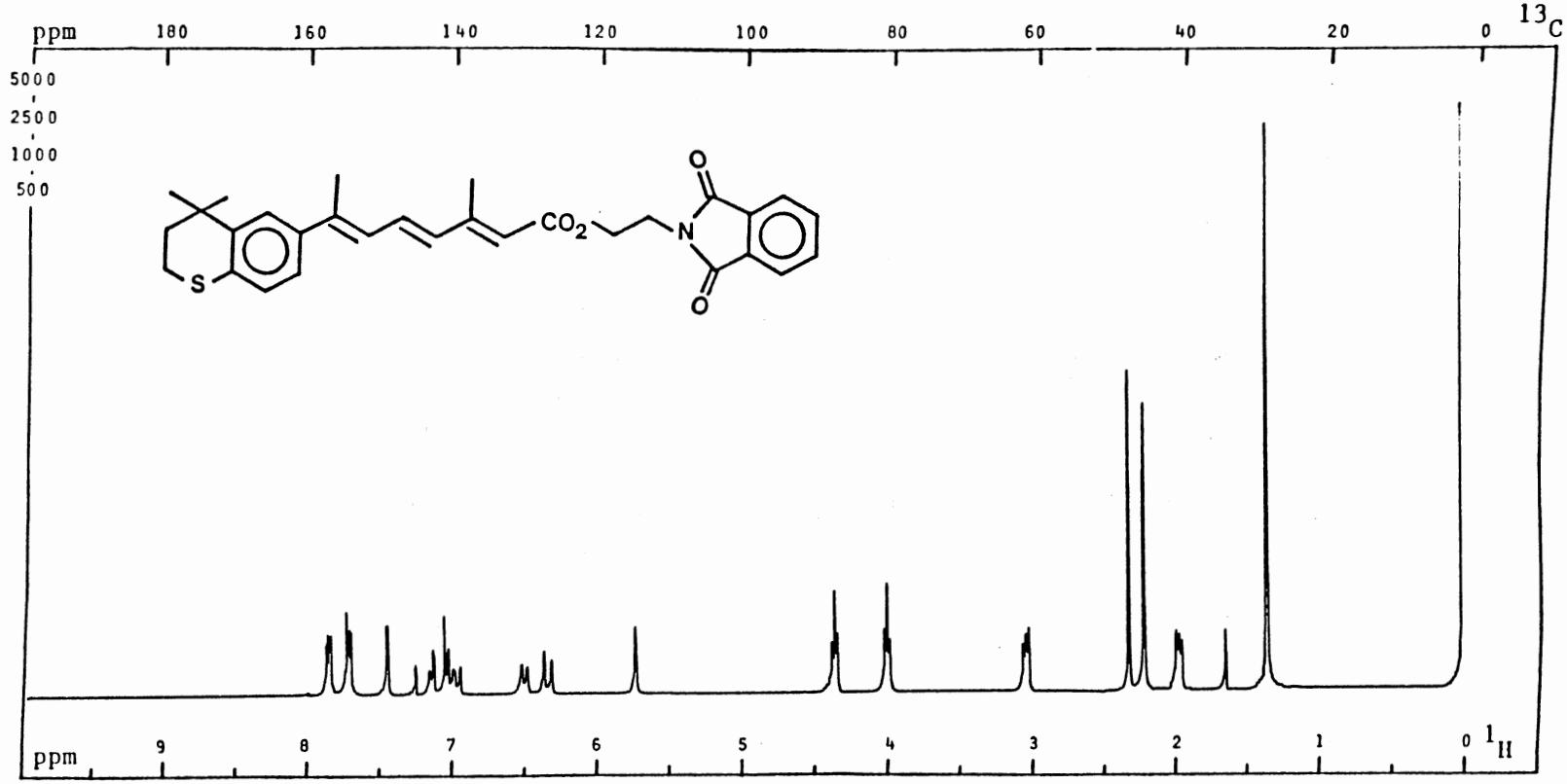
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.5 Hz.

PLATE XXIV



IR Spectrum of **48a**

PLATE XXV



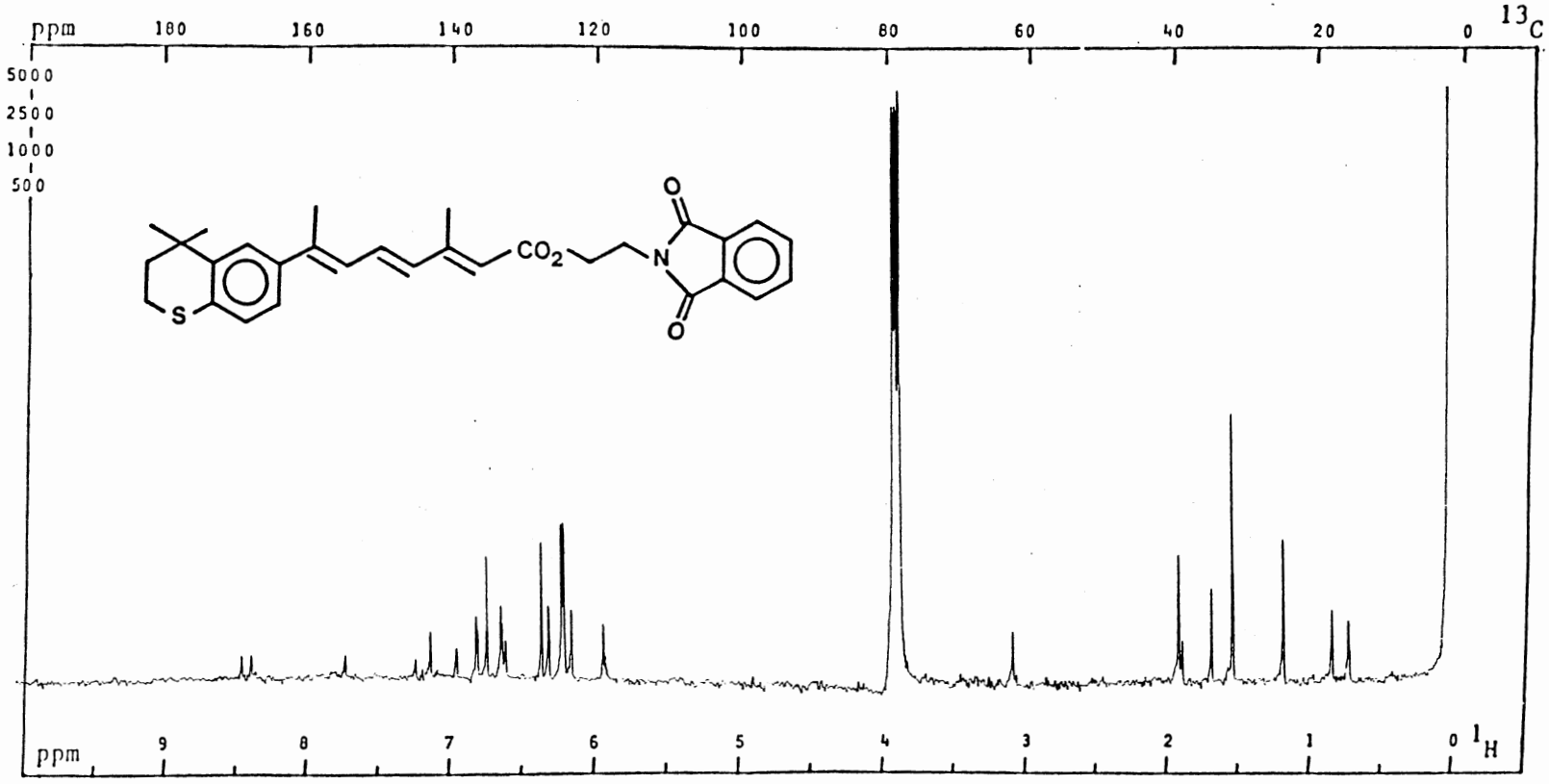
^{1}H NMR Spectrum of **48d**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 8 K; PW/RF: 6.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: 0 Hz; LB: - Hz.

PLATE XXVI



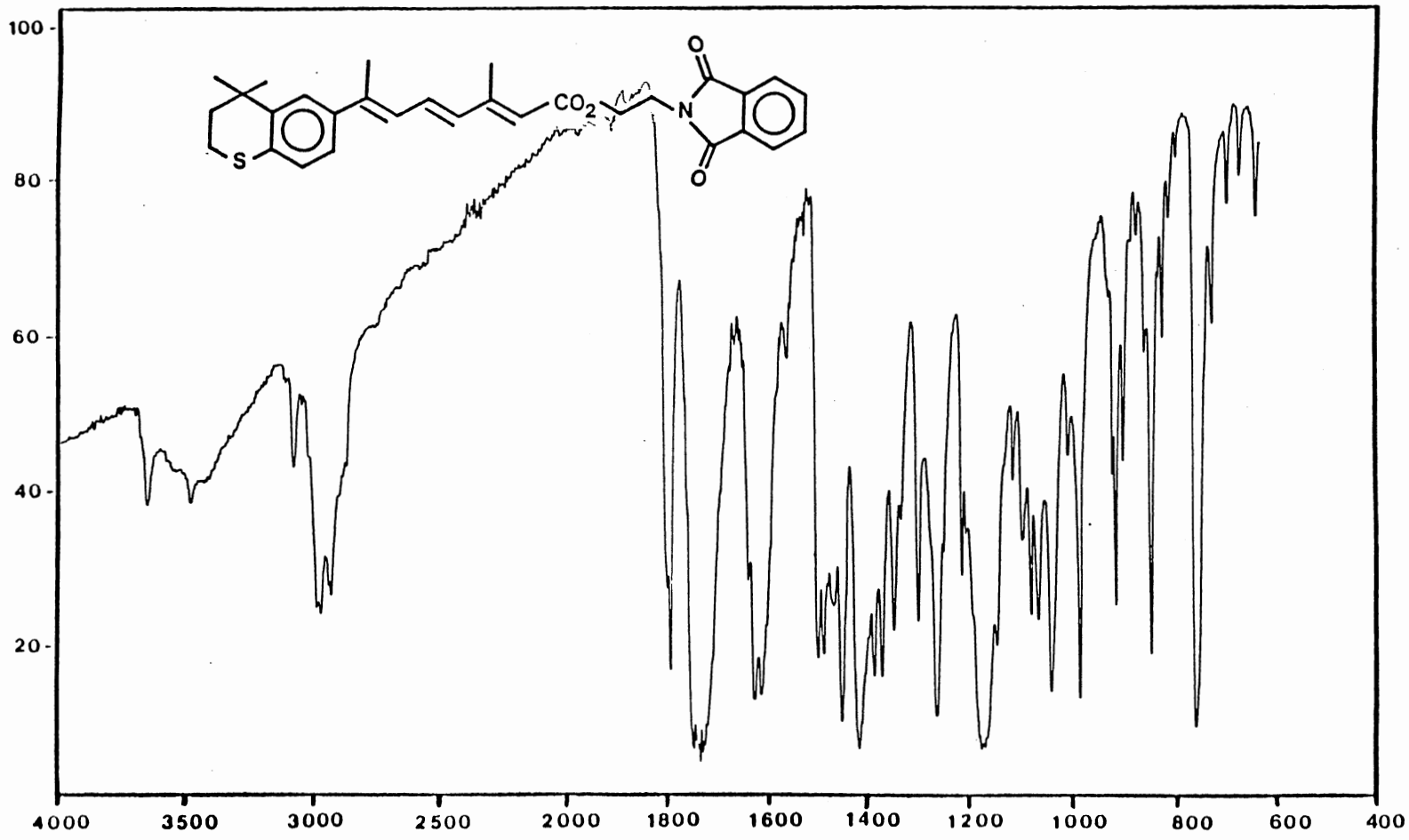
^{13}C NMR Spectrum of **48d**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 1000 .

Size: 16 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: _ Hz; Lock: ^2H ; D1,D5: 4.0 s.

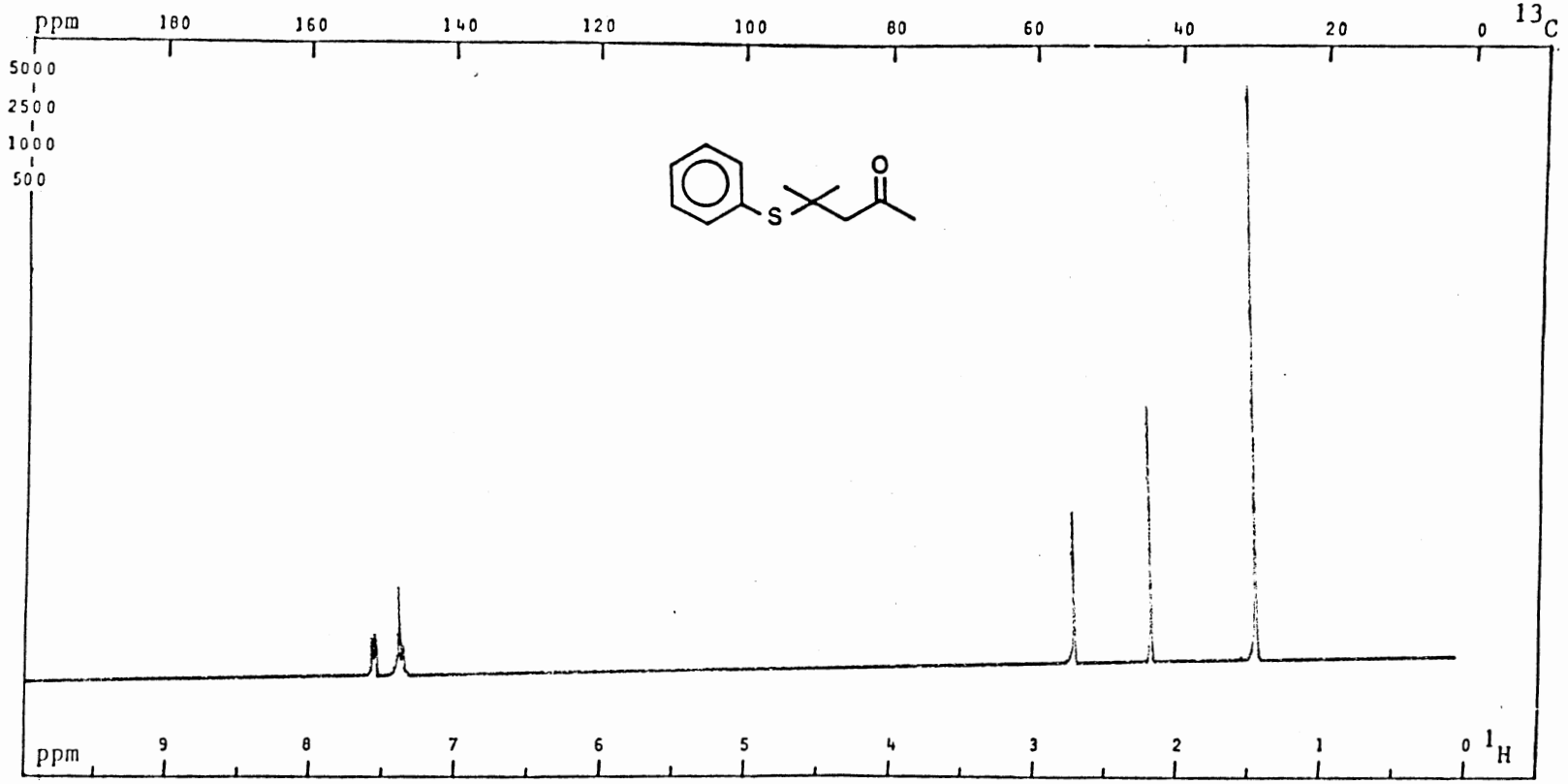
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

PLATE XXVII



IR Spectrum of 48d

PLATE XXVIII



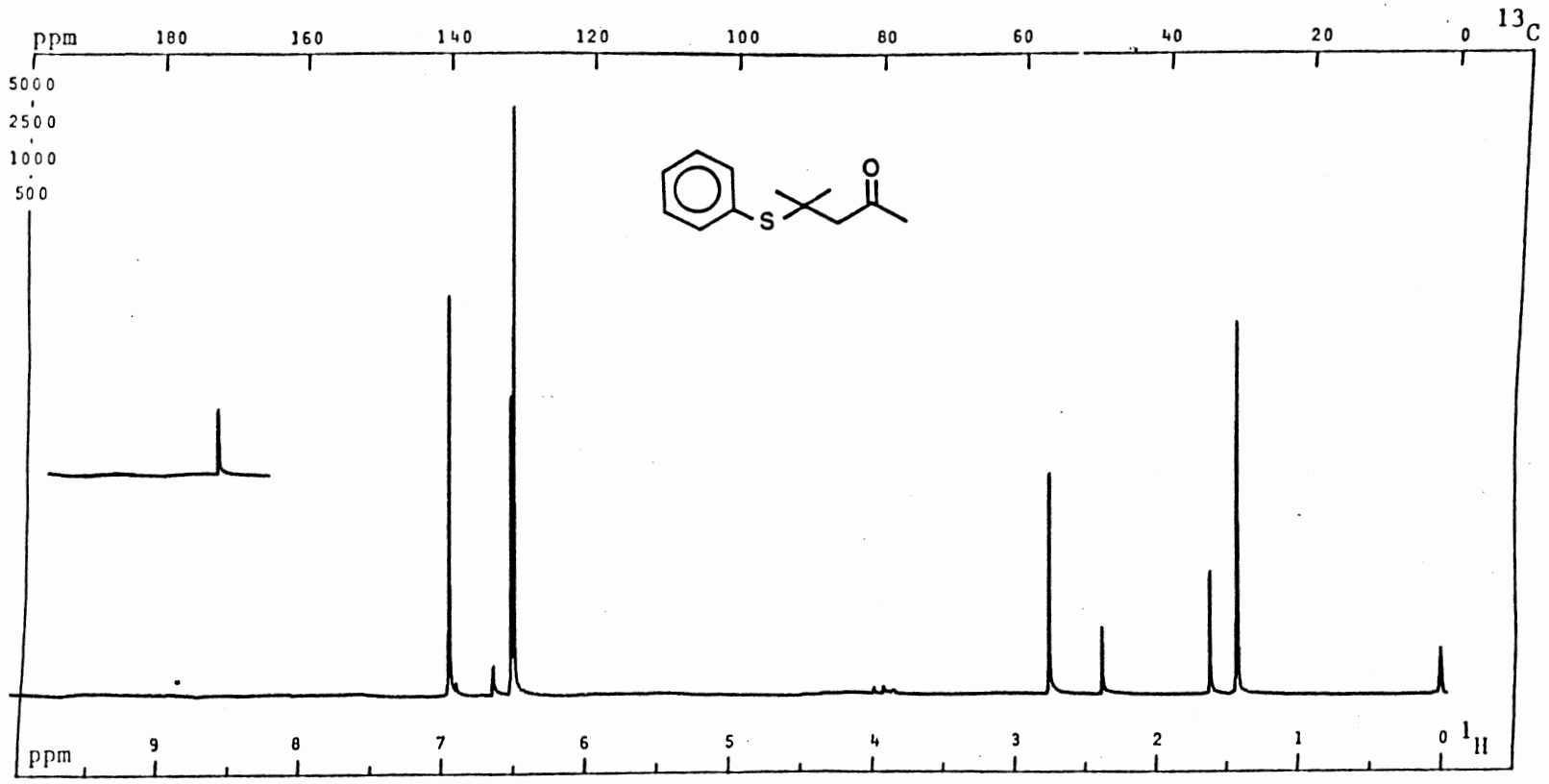
^{1}H NMR Spectrum of **58**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 12 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE XXIX



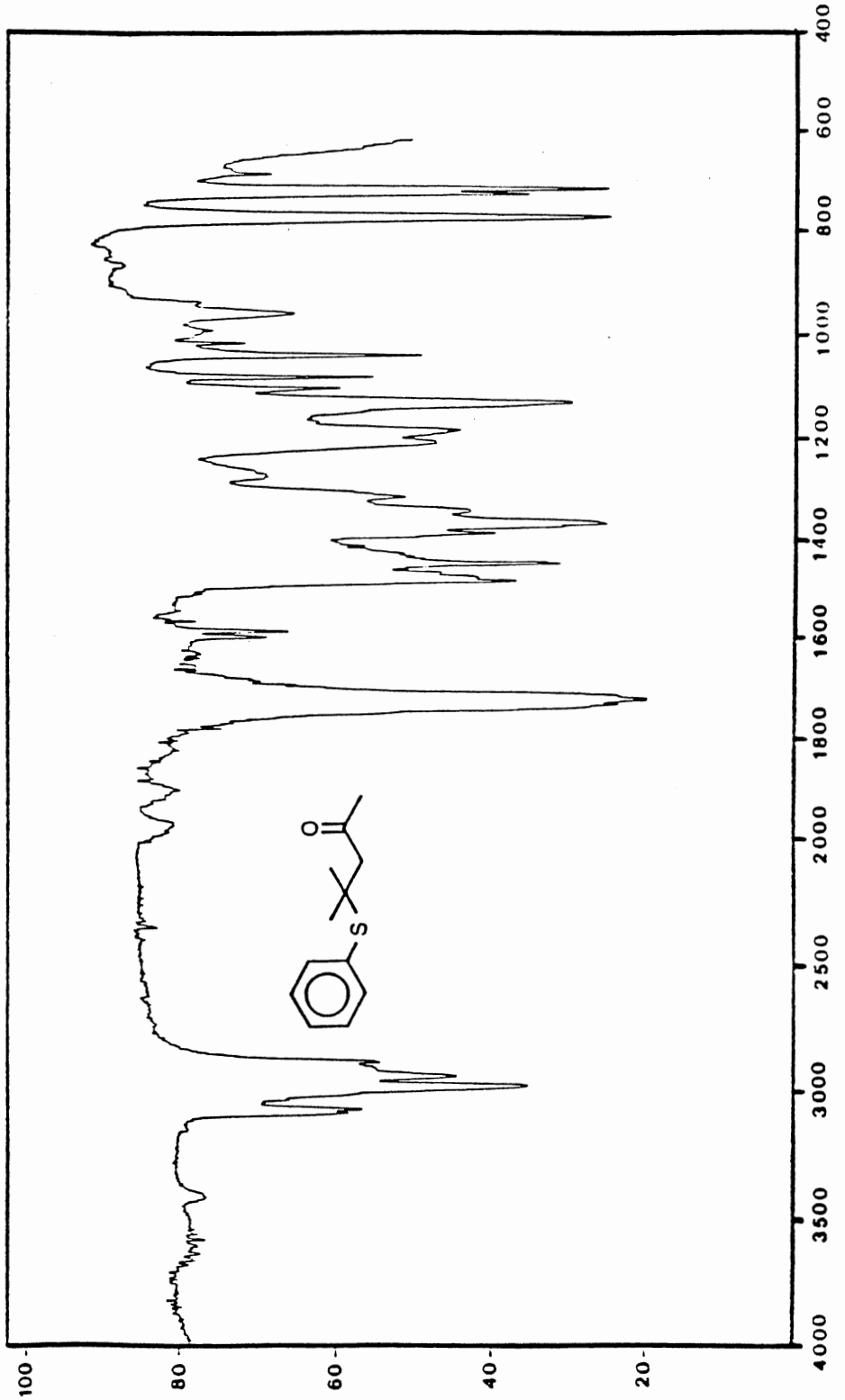
^{13}C NMR Spectrum of **58**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 1500 .

Size: 8 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 10 s.

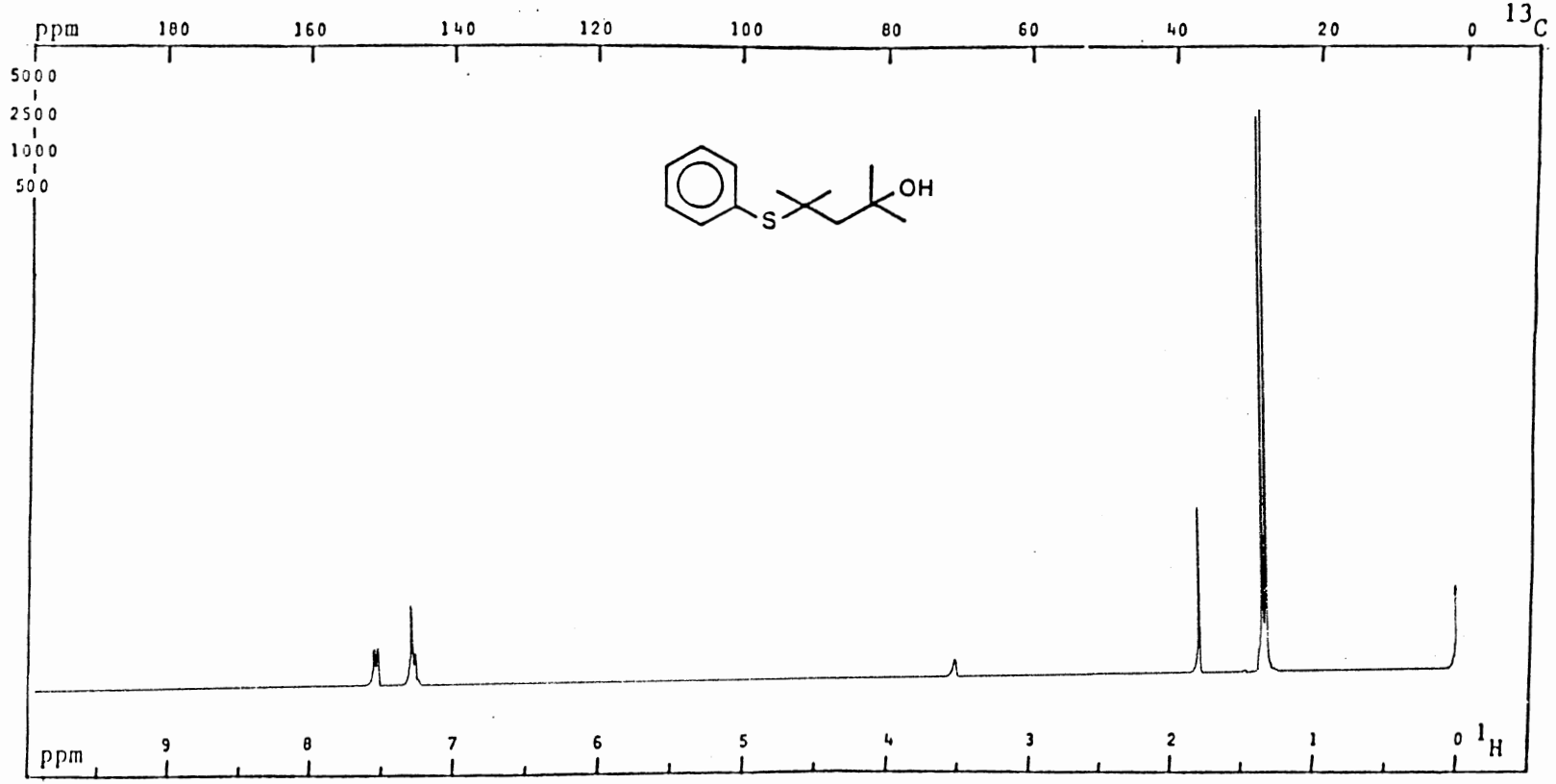
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: - Hz.

PLATE XXX



IR Spectrum of **58**

PLATE XXXI



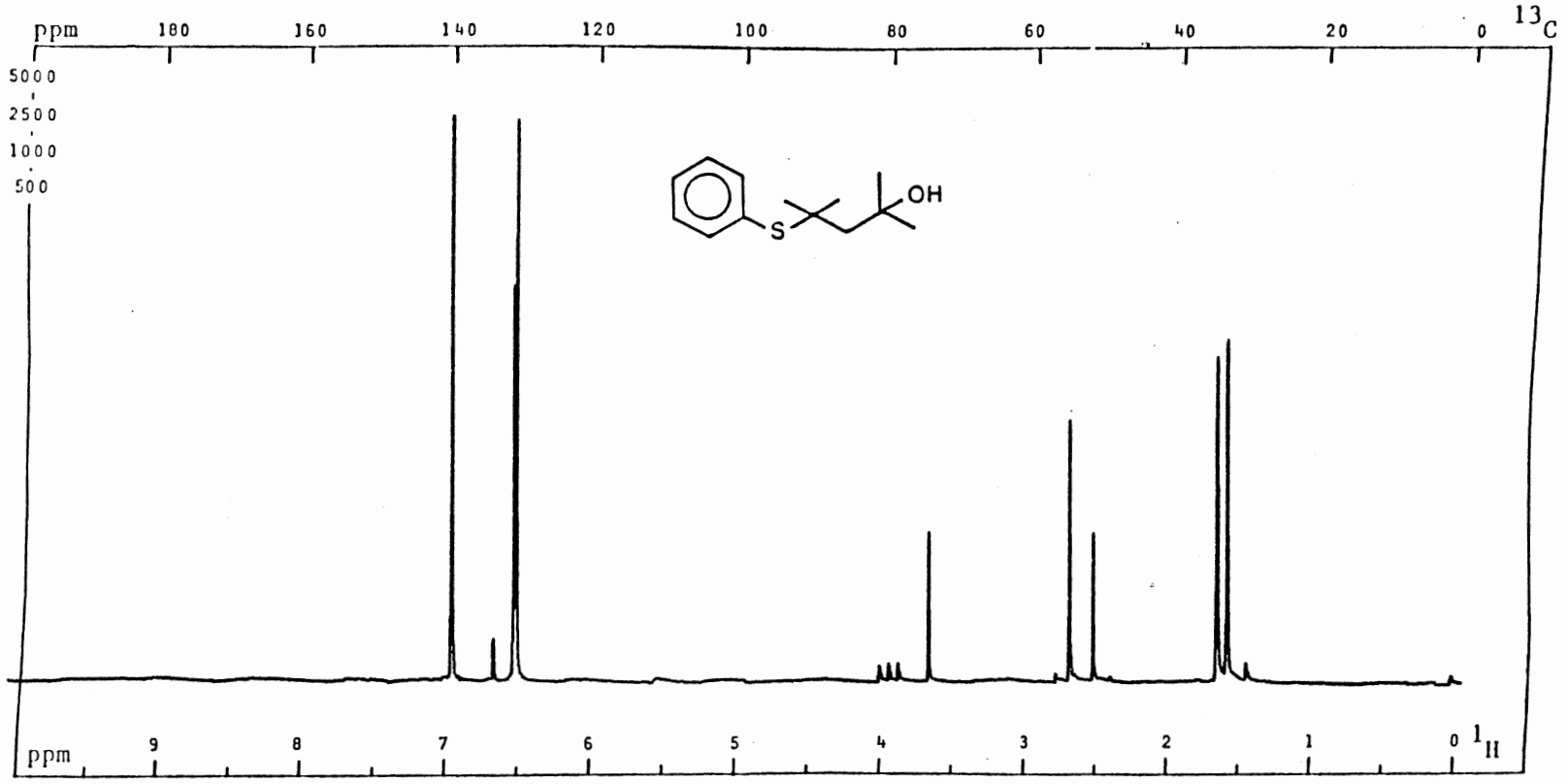
^{1}H NMR Spectrum of **59**

PFT _X_ CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 299.4 Hz; T: RT °C; NT: 4

Size: 12 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE XXXII



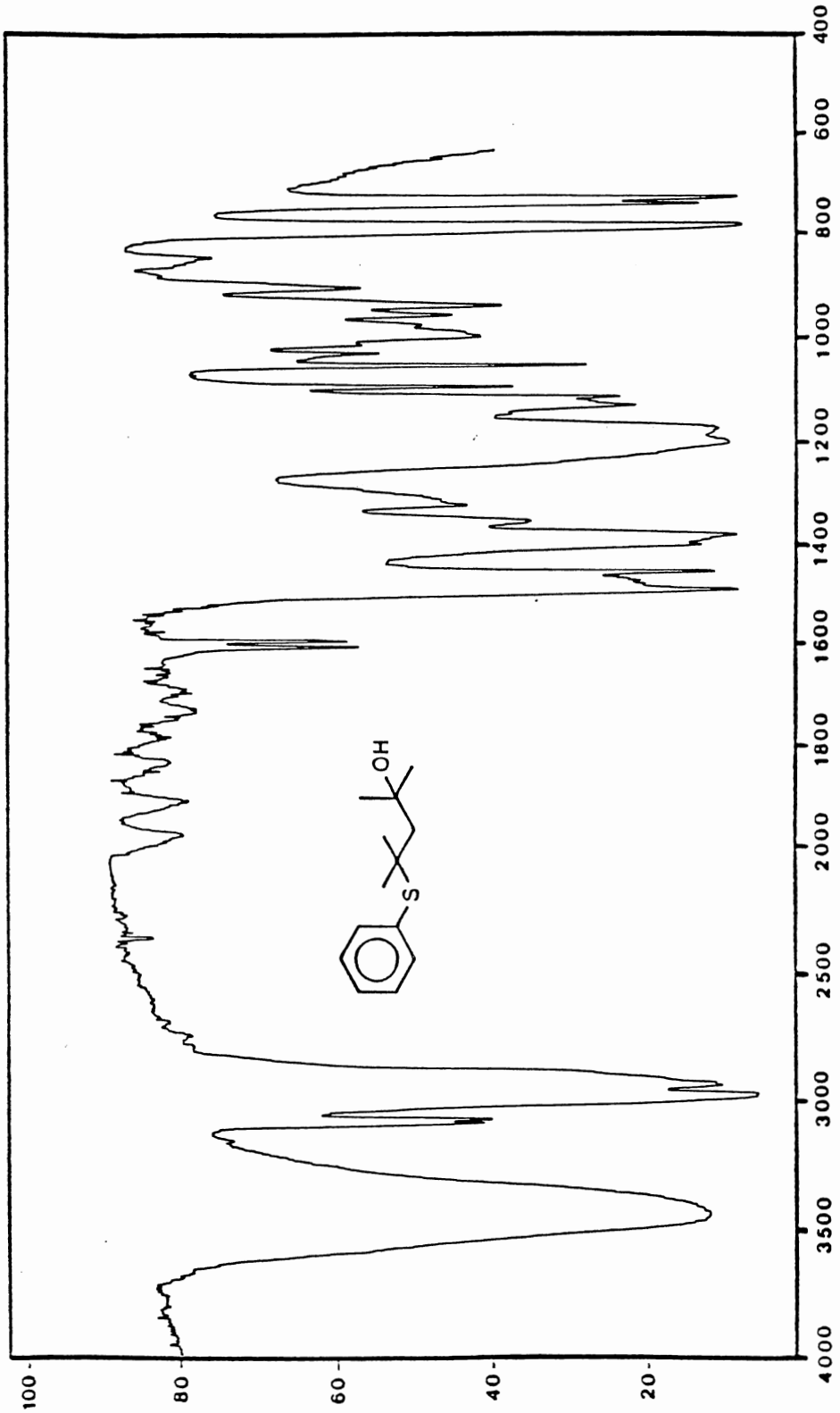
^{13}C NMR Spectrum of **59**

PFT _X_ CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 752 .

Size: 8 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.0 s.

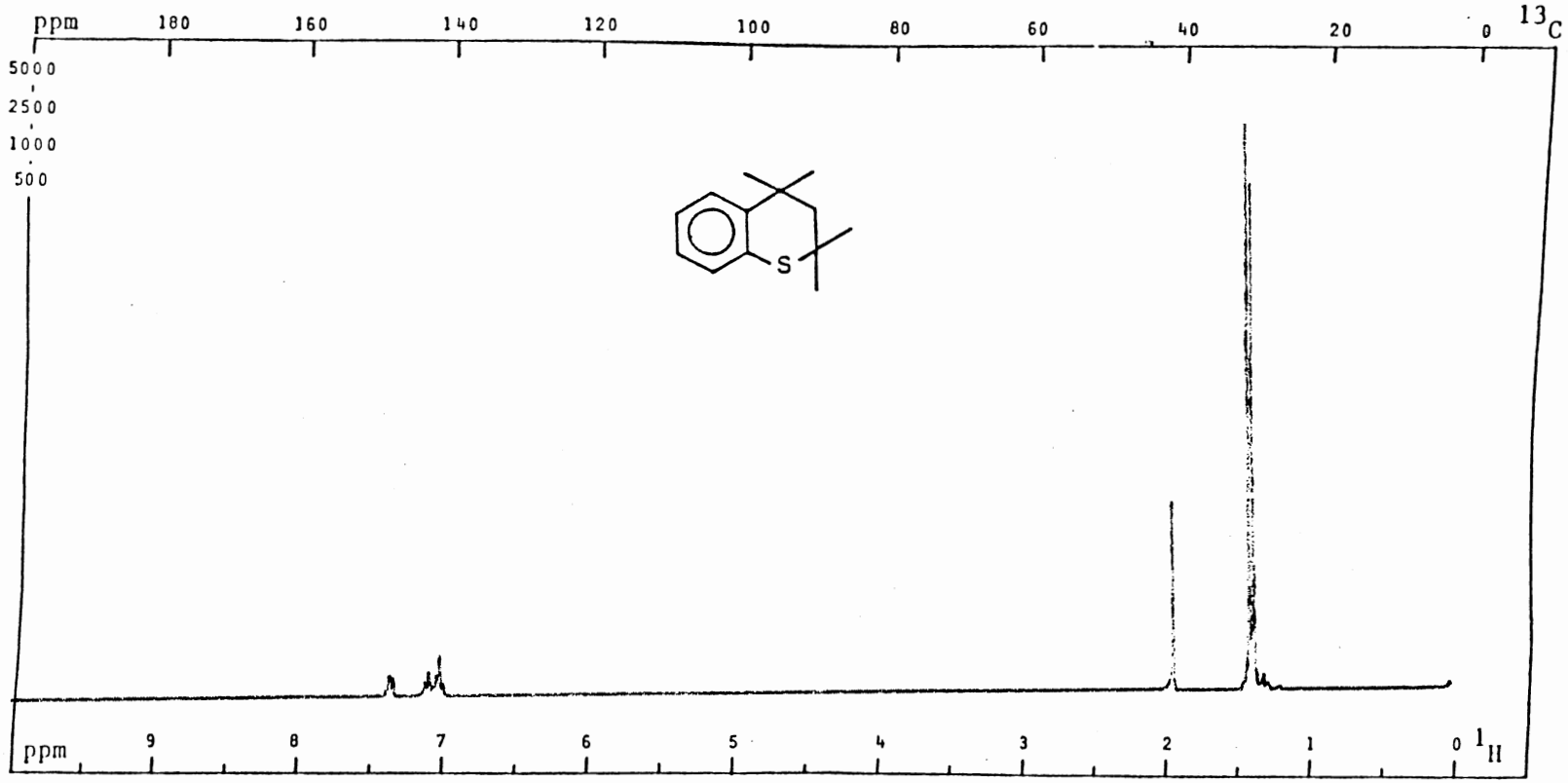
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: -- Hz.

PLATE XXXIII



IR Spectrum of 59

PLATE XXXIV



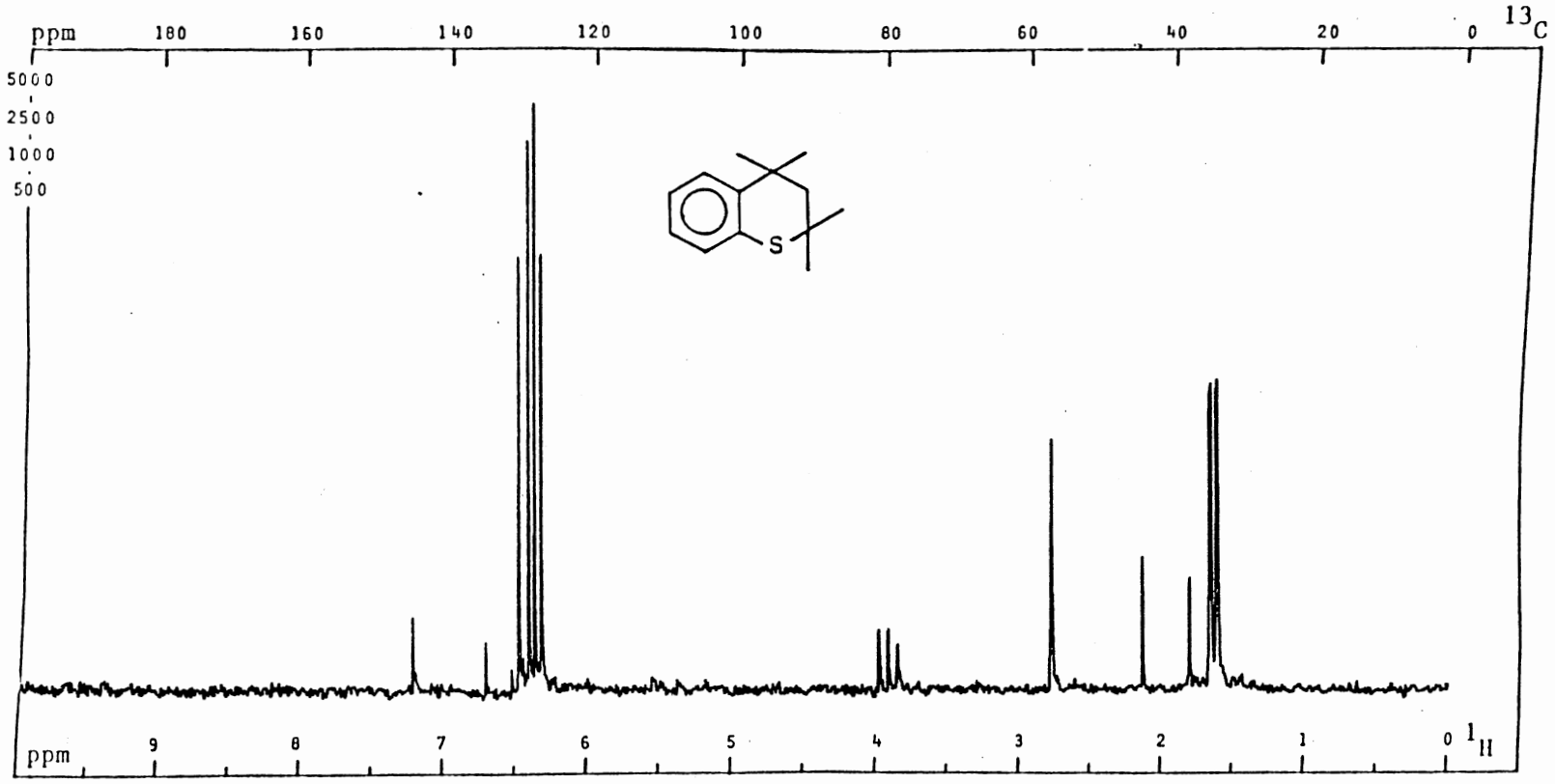
^{1}H NMR Spectrum of **60**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 15085.9 Hz; T: RT °C; NT: 4 .

Size: 12 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE XXXV



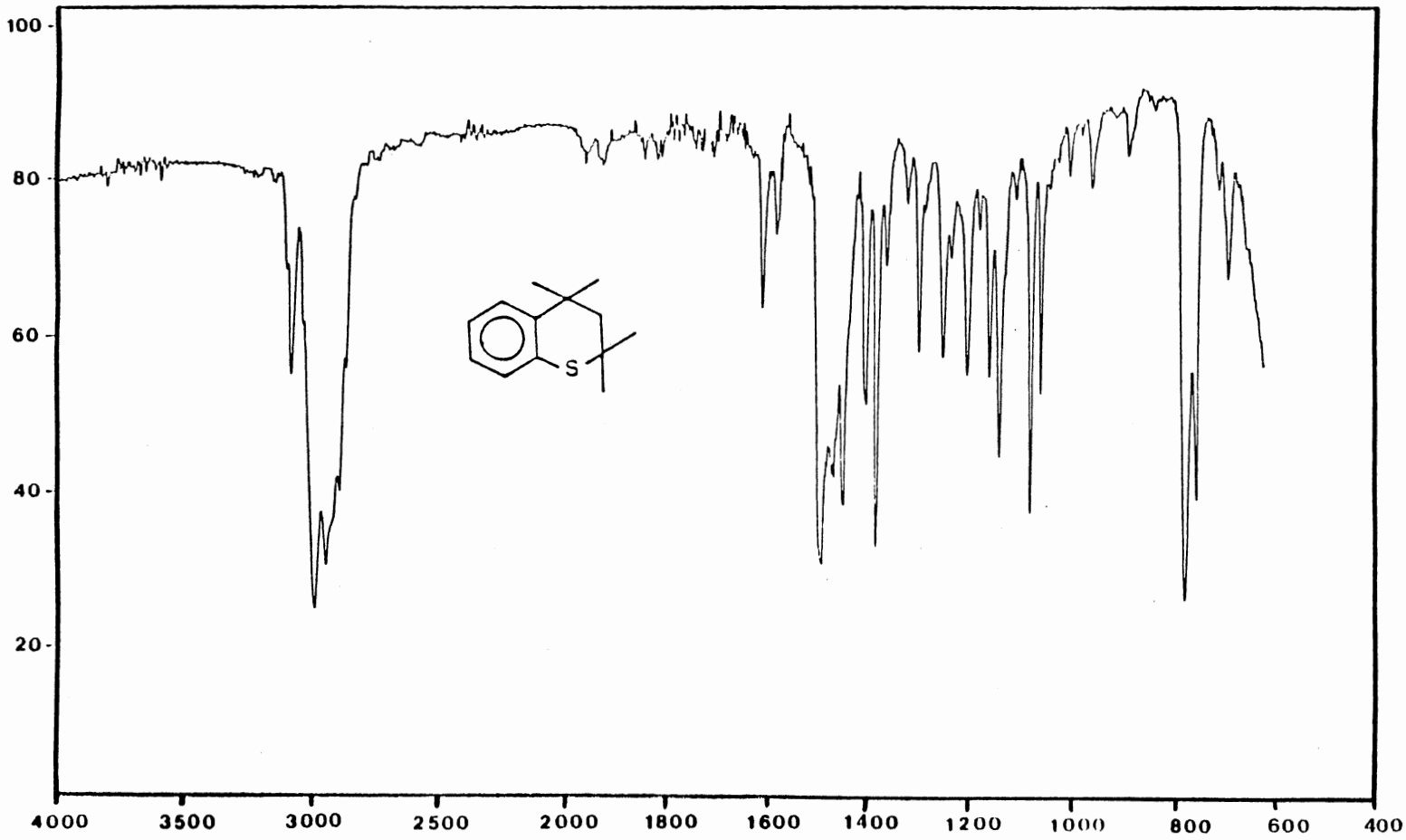
^{13}C NMR Spectrum of **60**

PFT _ ^{X}CW _ ; Solvent: $^{DCCl}_{3}$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 1200

Size: 8 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 4.0 s.

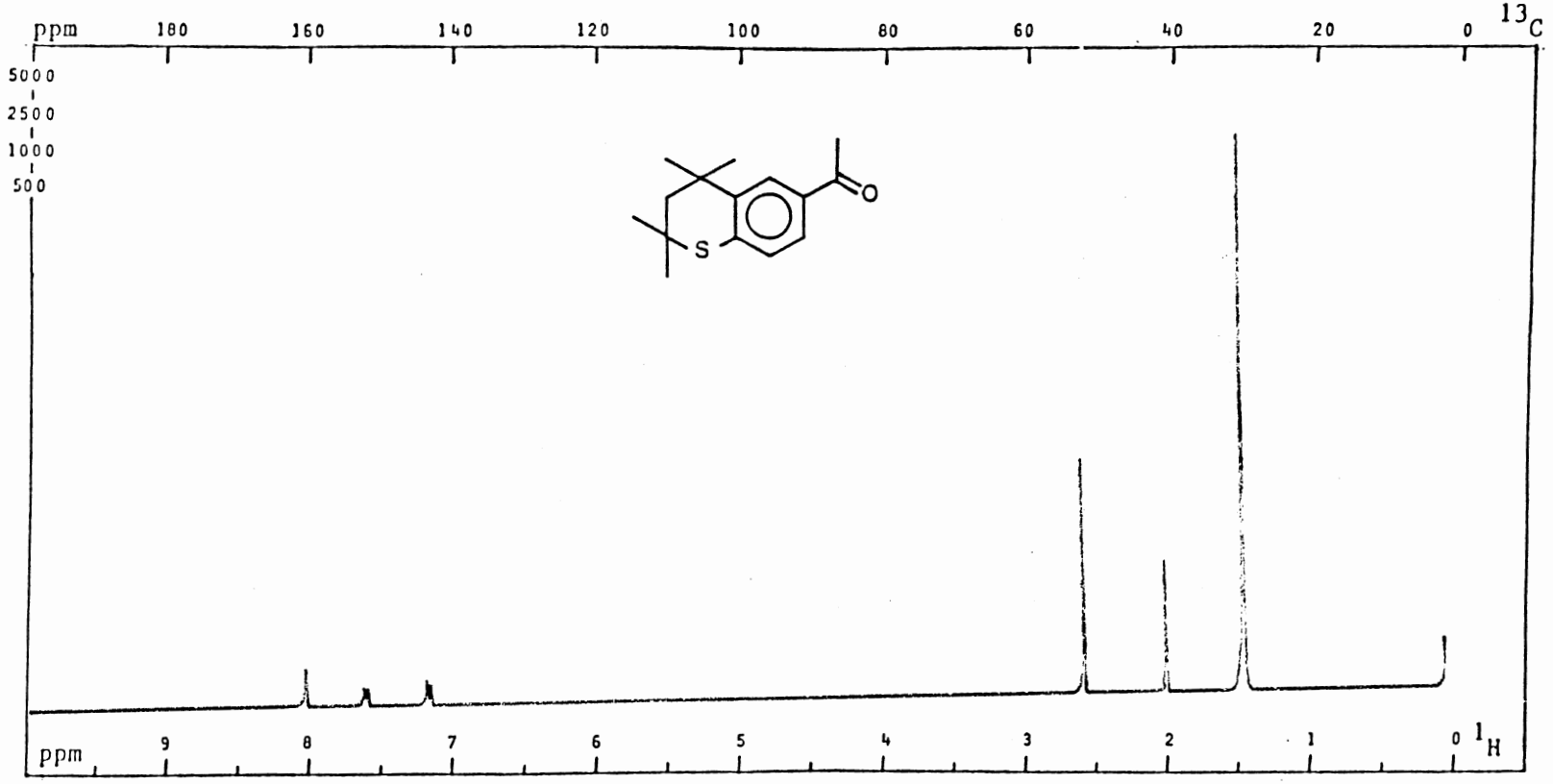
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: - Hz.

PLATE XXXVI



IR Spectrum of **60**

PLATE XXXVII



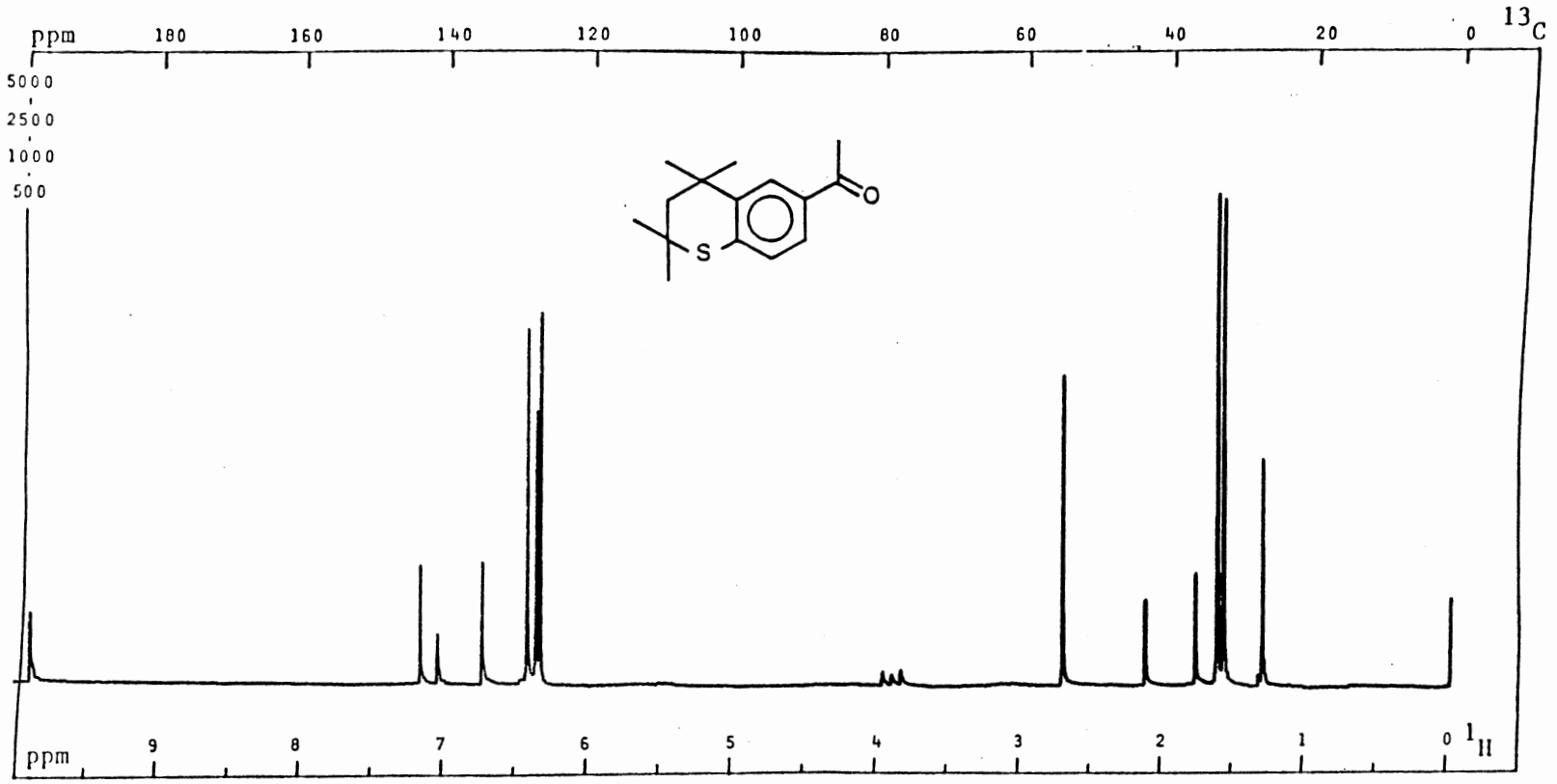
^{1}H NMR Spectrum of **51b**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 4 .

Size: 12 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE XXXVIII



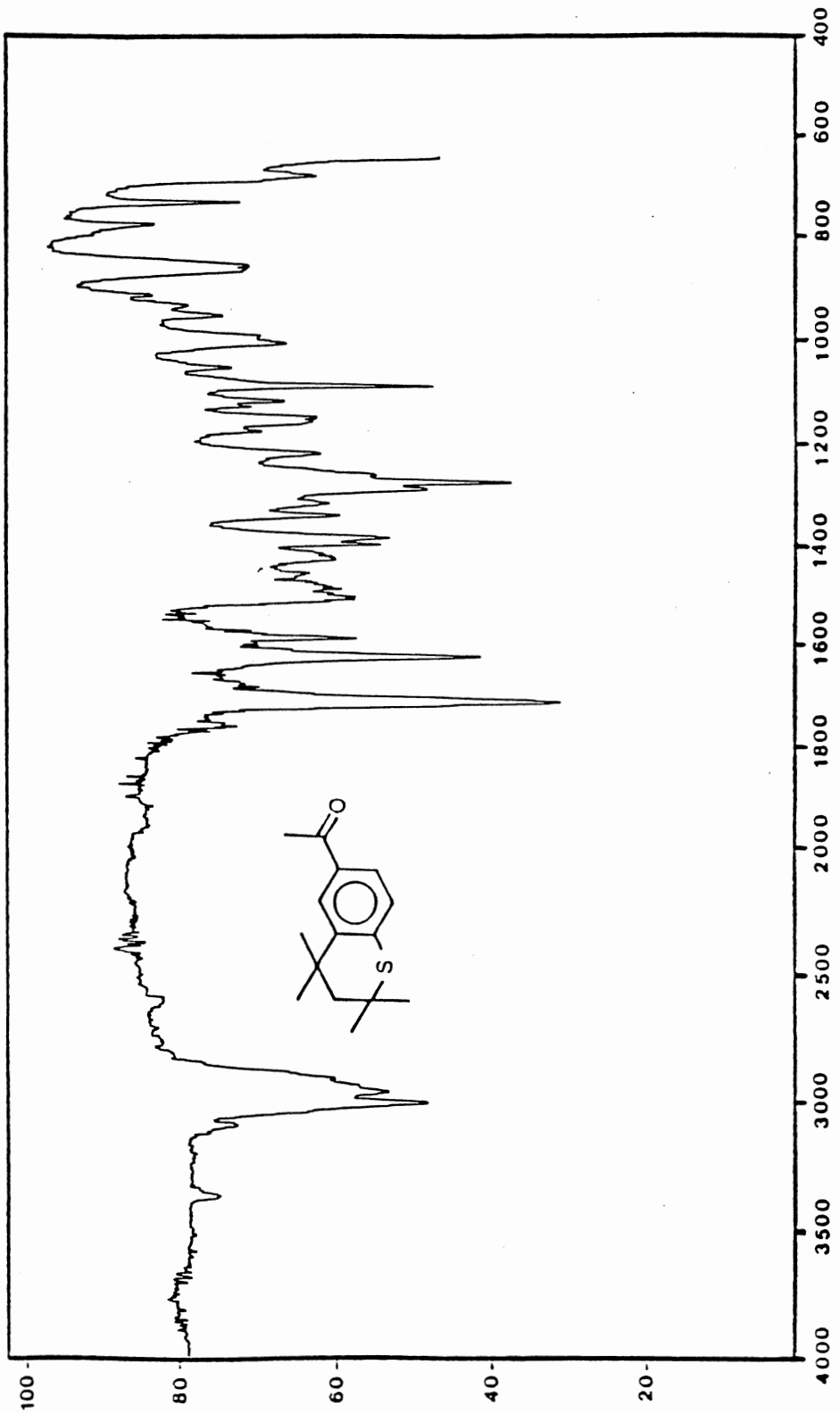
^{13}C NMR Spectrum of **51b**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 500 .

Size: 8 K ; PW/RF: 12 μs/dB; TO: 1000Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.0 s.

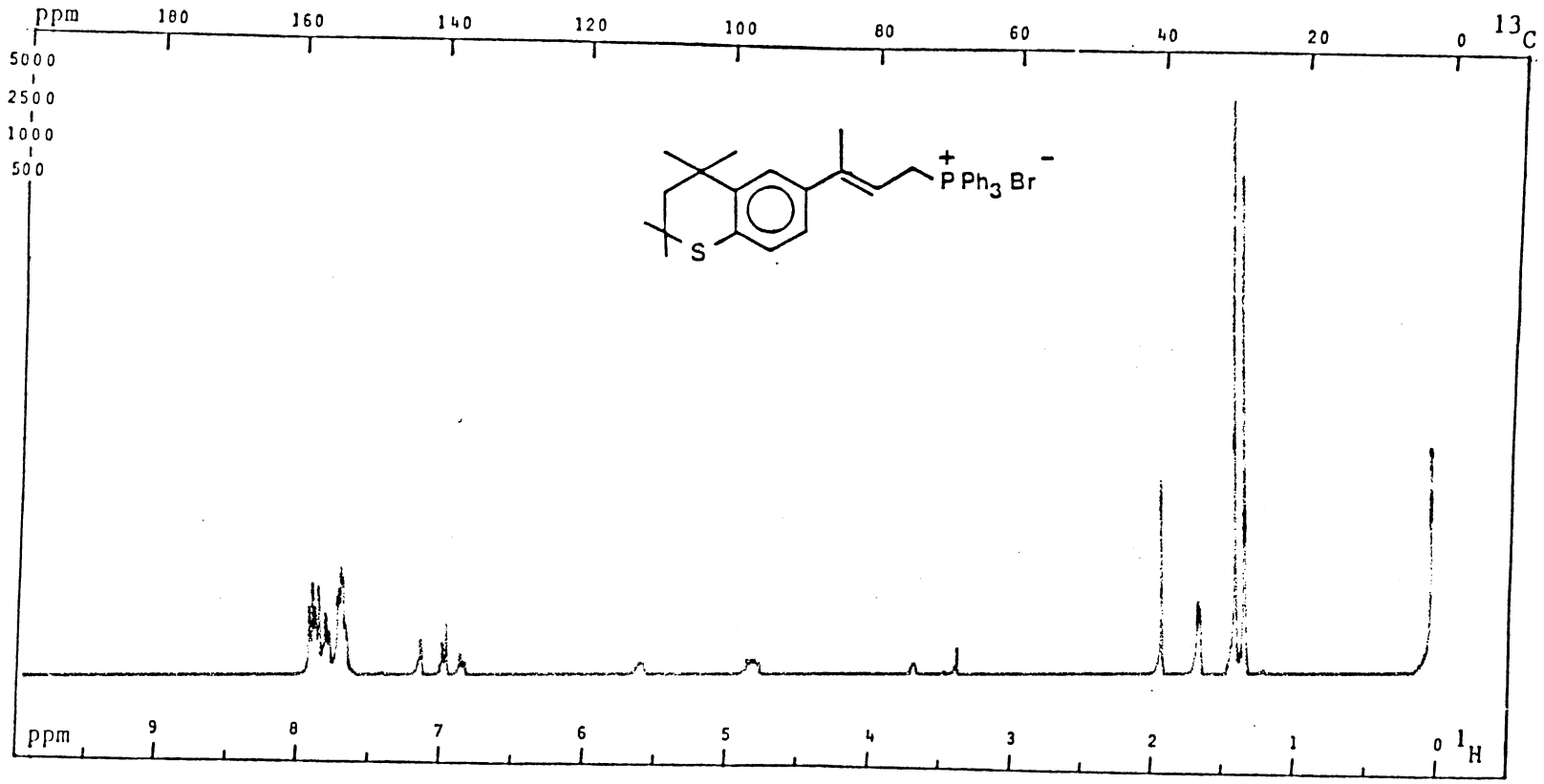
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: - Hz.

PLATE XXXIX



IR Spectrum of 51b

PLATE XXXX



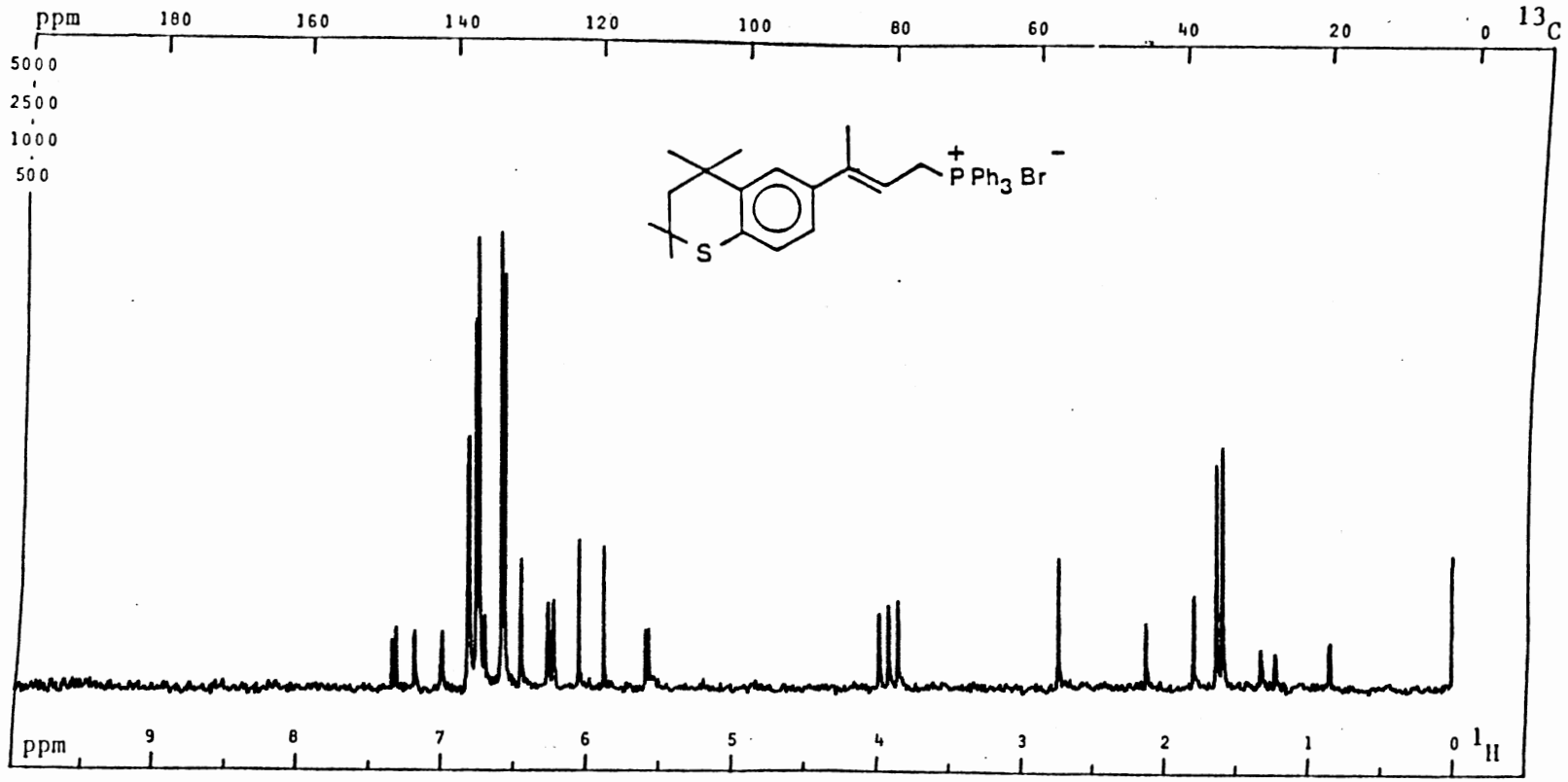
^{1}H NMR Spectrum of **63b**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9429 MHz; WC: 2999.4 Hz; T: RT °C; NT: 4 .

Size: 12 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE XXXXI



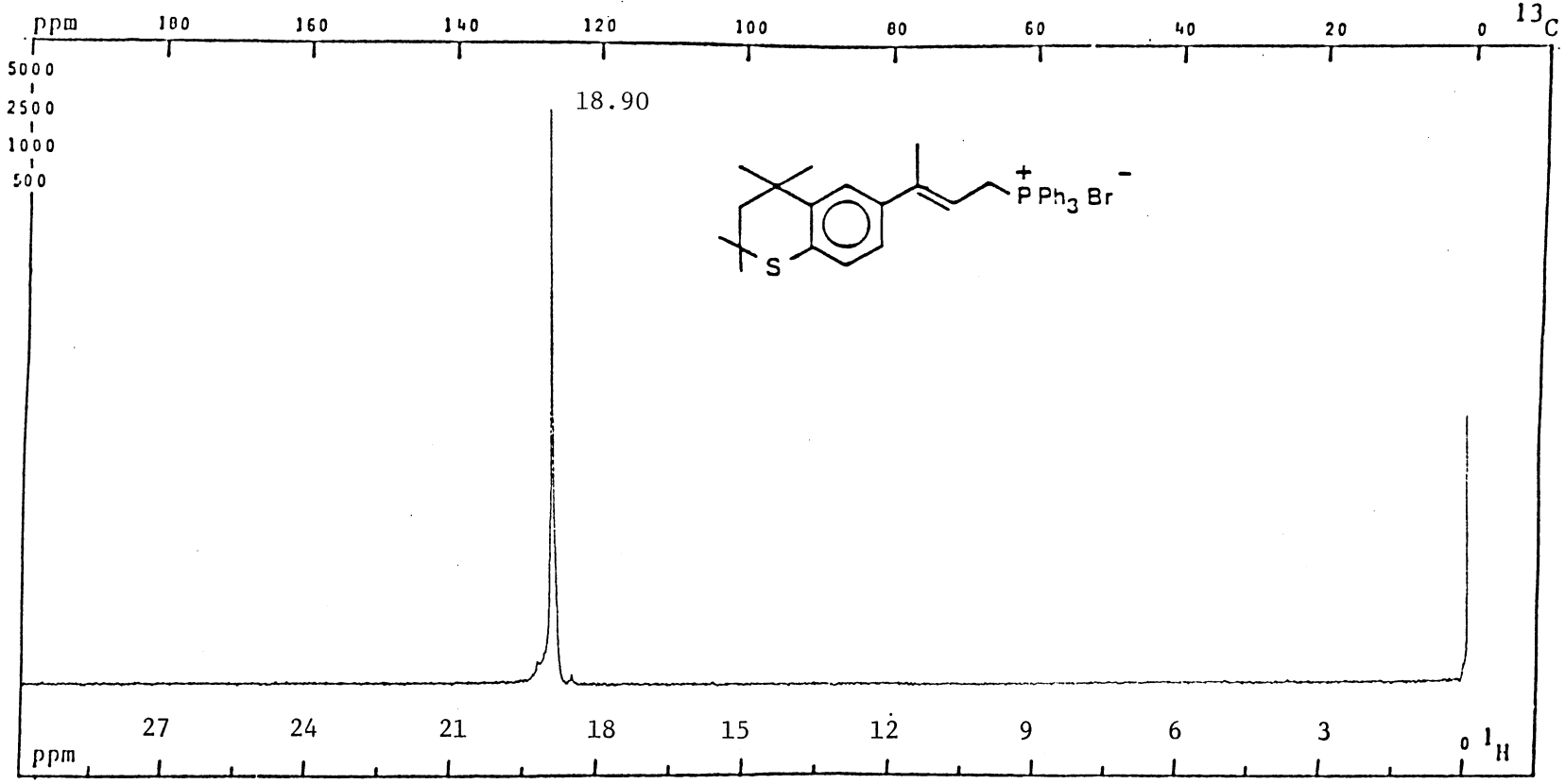
^{13}C NMR Spectrum of **63b**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 1600 .

Size: 8 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: - Hz.

PLATE XXXXII



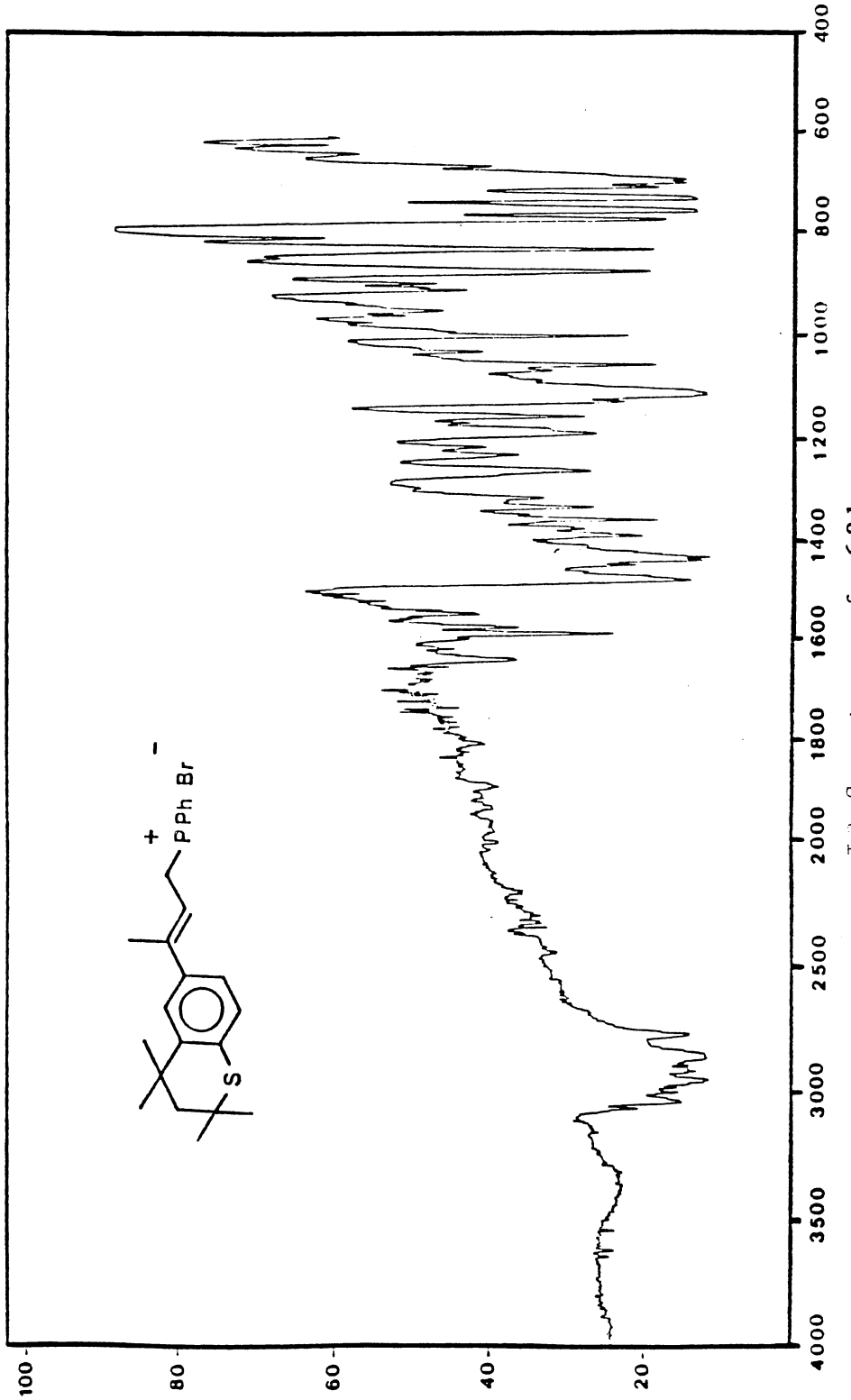
^{31}P NMR Spectrum of **63b**

PFT X CW _ ; Solvent: $DCCl_3$; SF:121.421 MHz; WC: 3642.6 Hz; T: RT °C; NT: 200 .

Size: 12 K; PW/RF: 14 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ; D1,D5: 2.0 s.

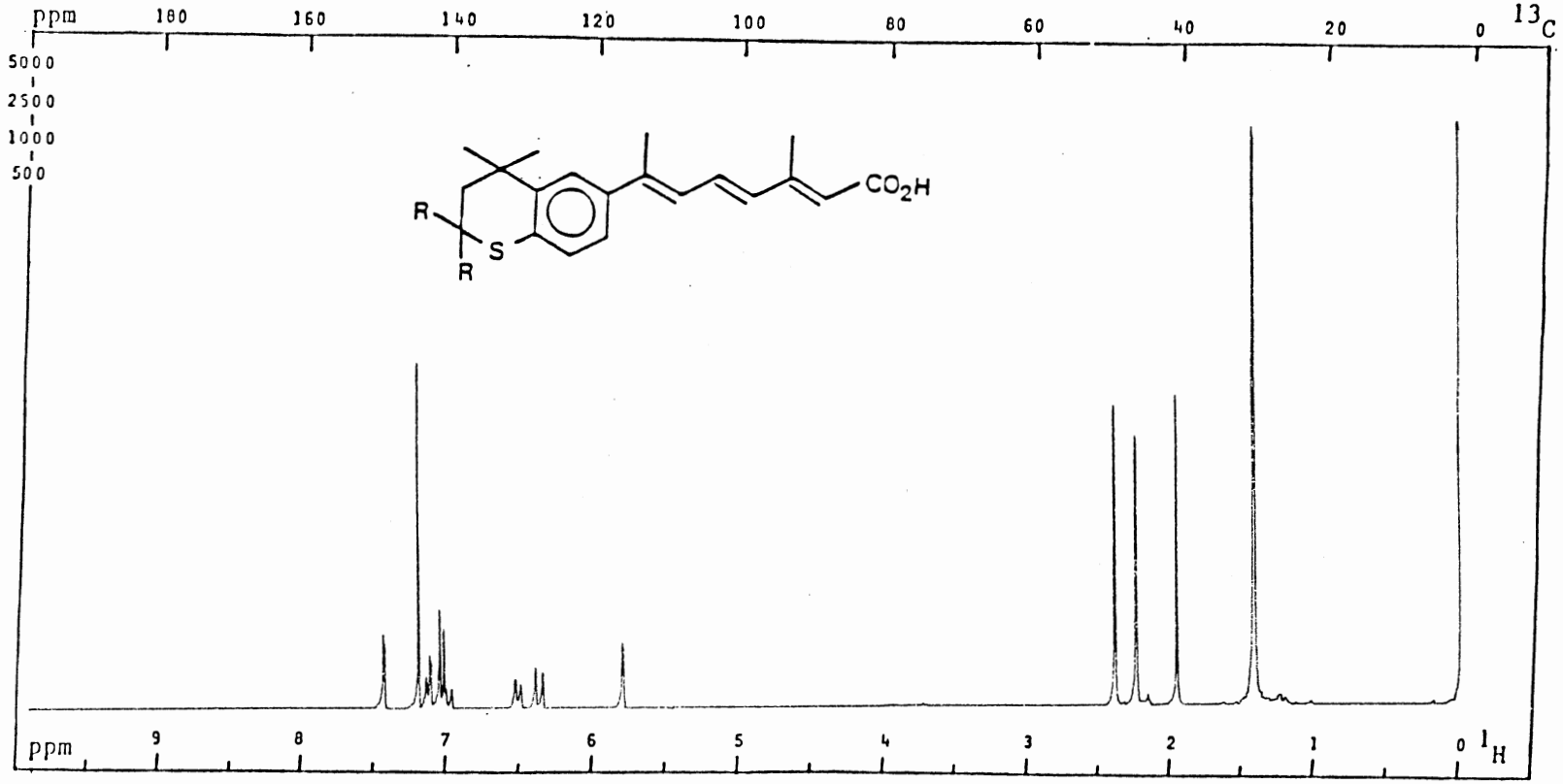
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: Hz.

PLATE XXXXIII



IR Spectrum of **63b**

PLATE XXXXIV



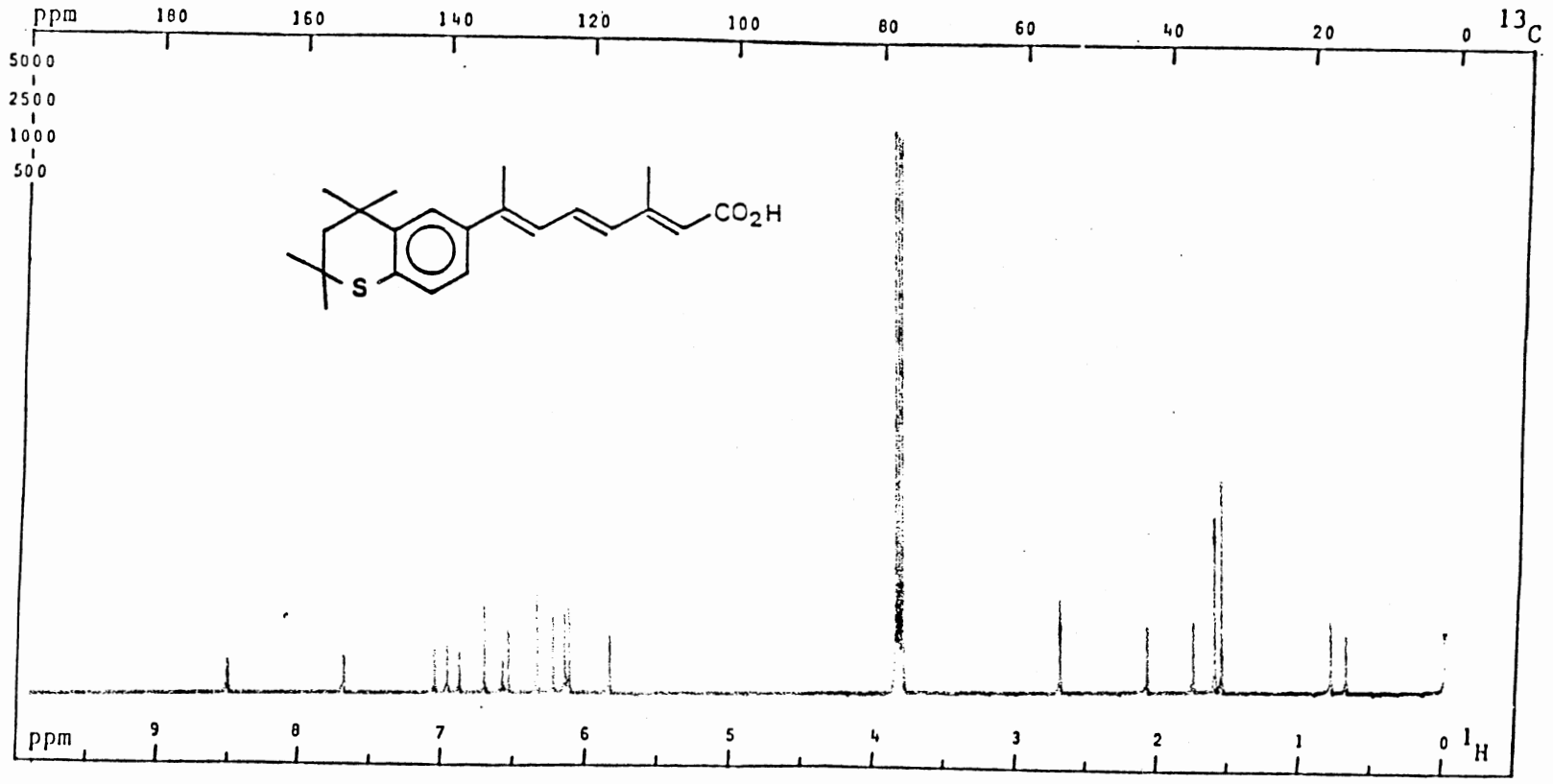
^{1}H NMR Spectrum of **48c**

PFT X CW _ ; Solvent: $DCCl_3$; SF:299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 4 .

Size: 12 K; PW/RF: 5 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE XXXXV



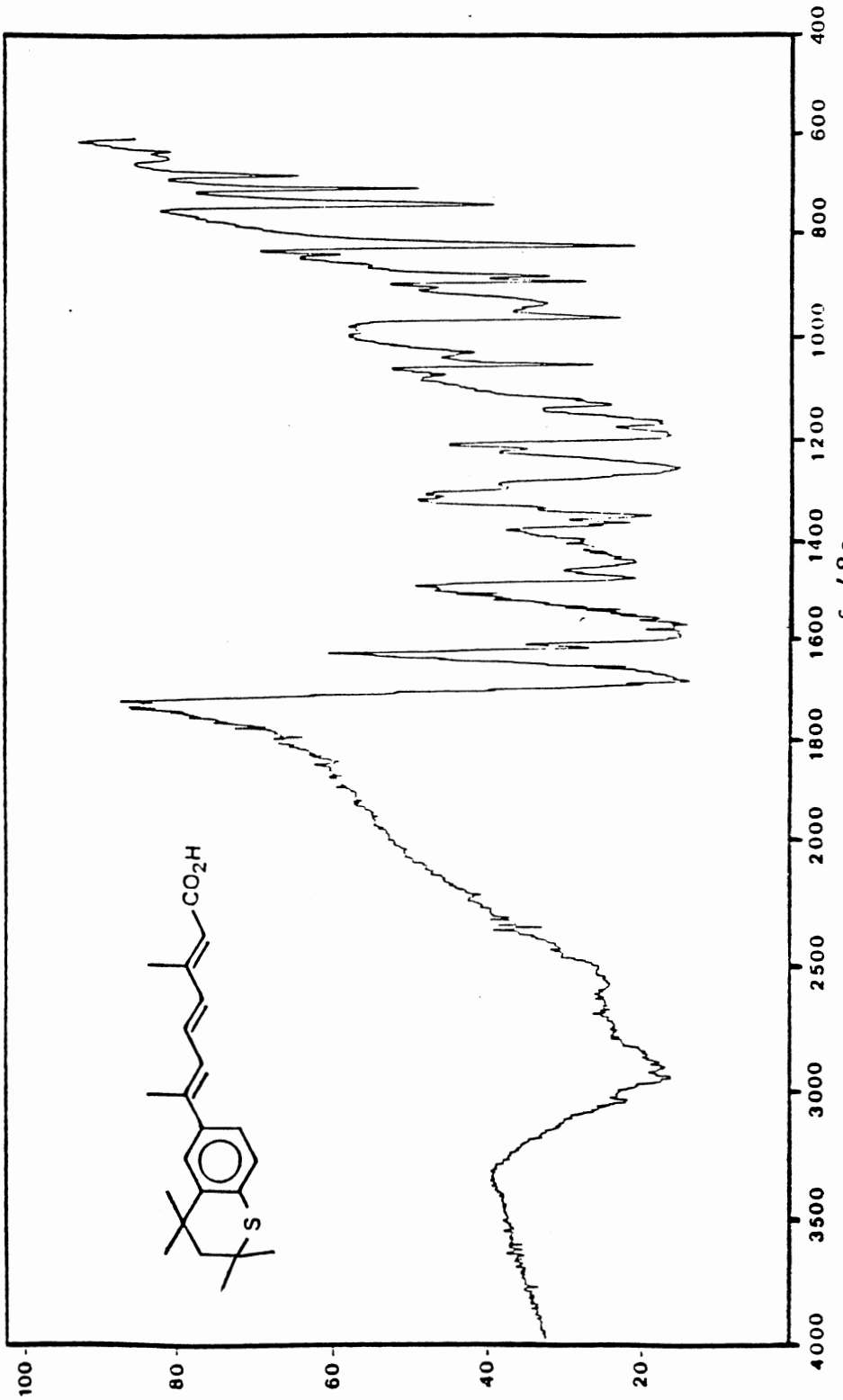
^{13}C NMR Spectrum of **48c**

PFT _XCW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 1600 .

Size: 8 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.0 s.

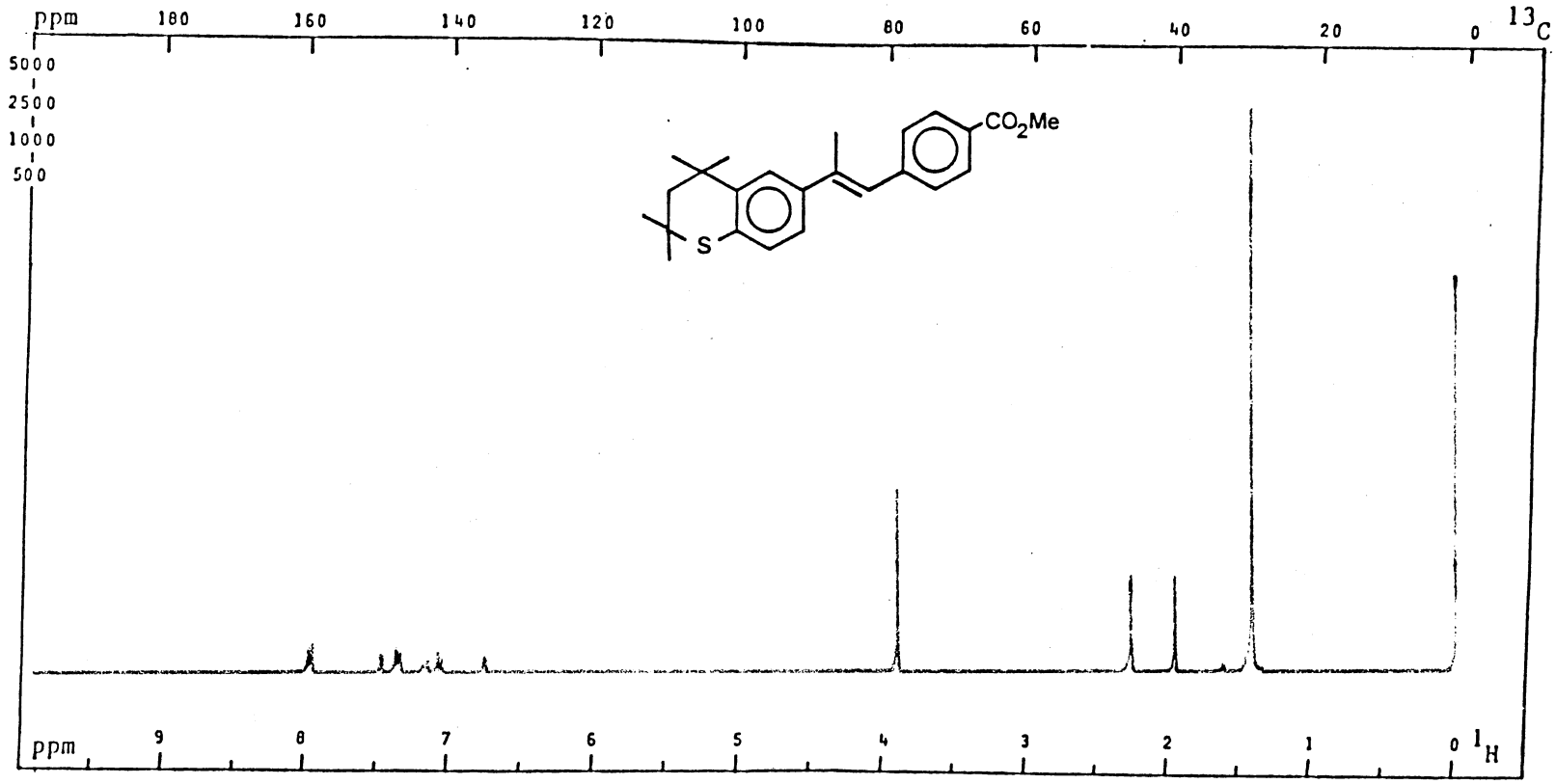
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: - Hz.

PLATE XXXXVI



IR Spectrum of **48c**

PLATE XXXXVII



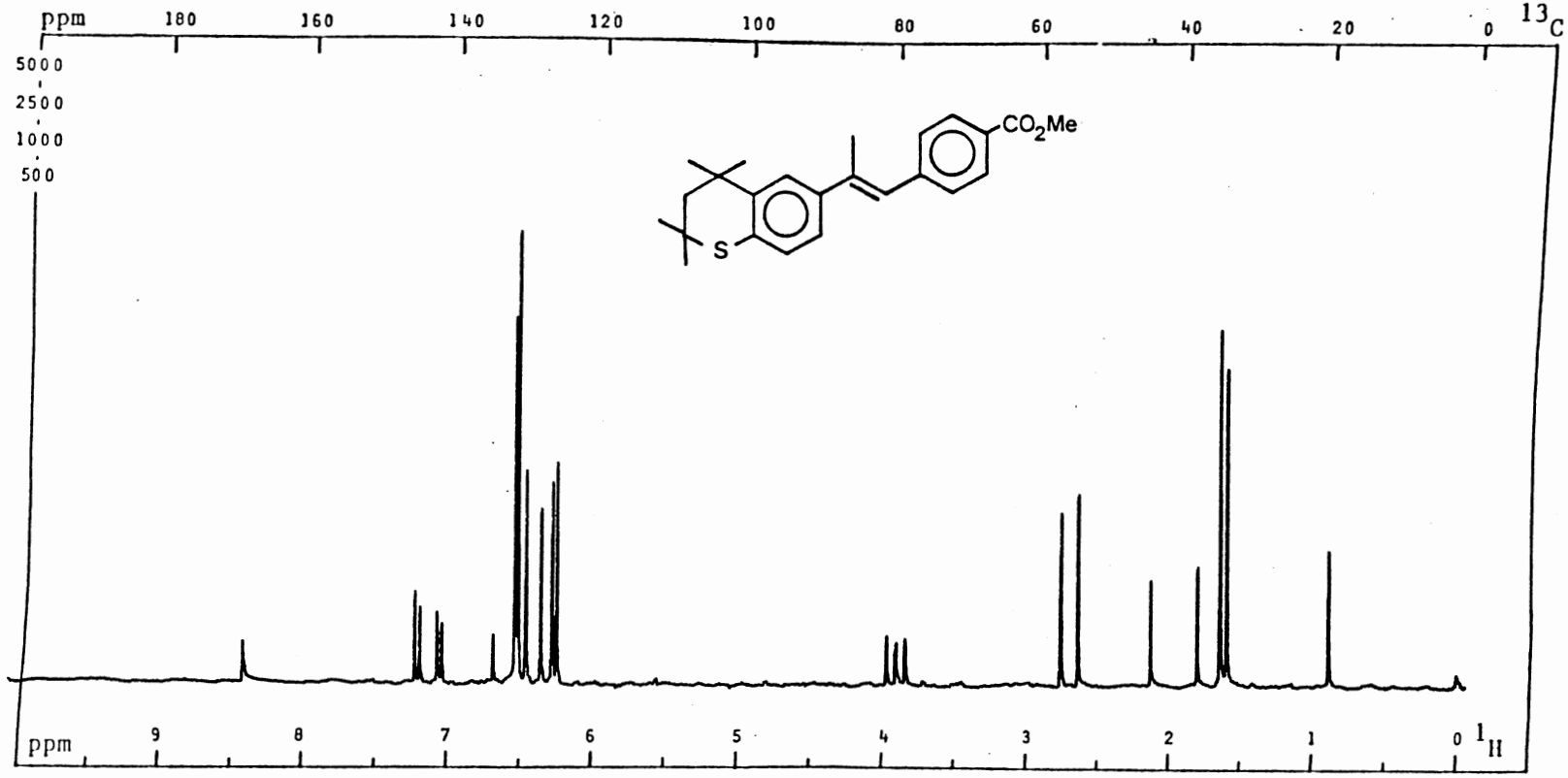
^{1}H NMR Spectrum of **49a**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9284 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16 .

Size: 16 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE XXXXVIII



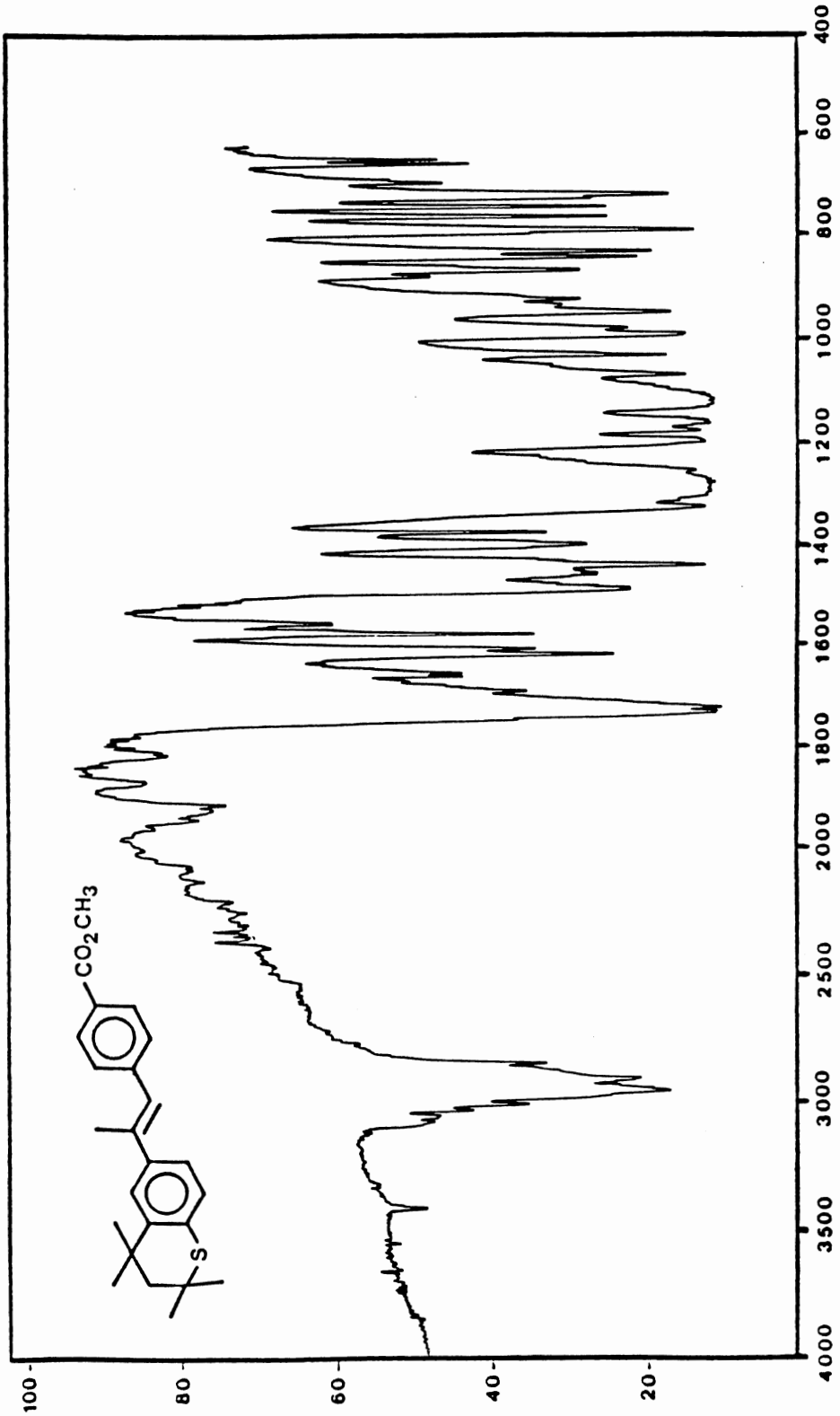
^{13}C NMR Spectrum of **49a**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 200 .

Size: 20 K; PW/RF: 12 μs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 5.0 s.

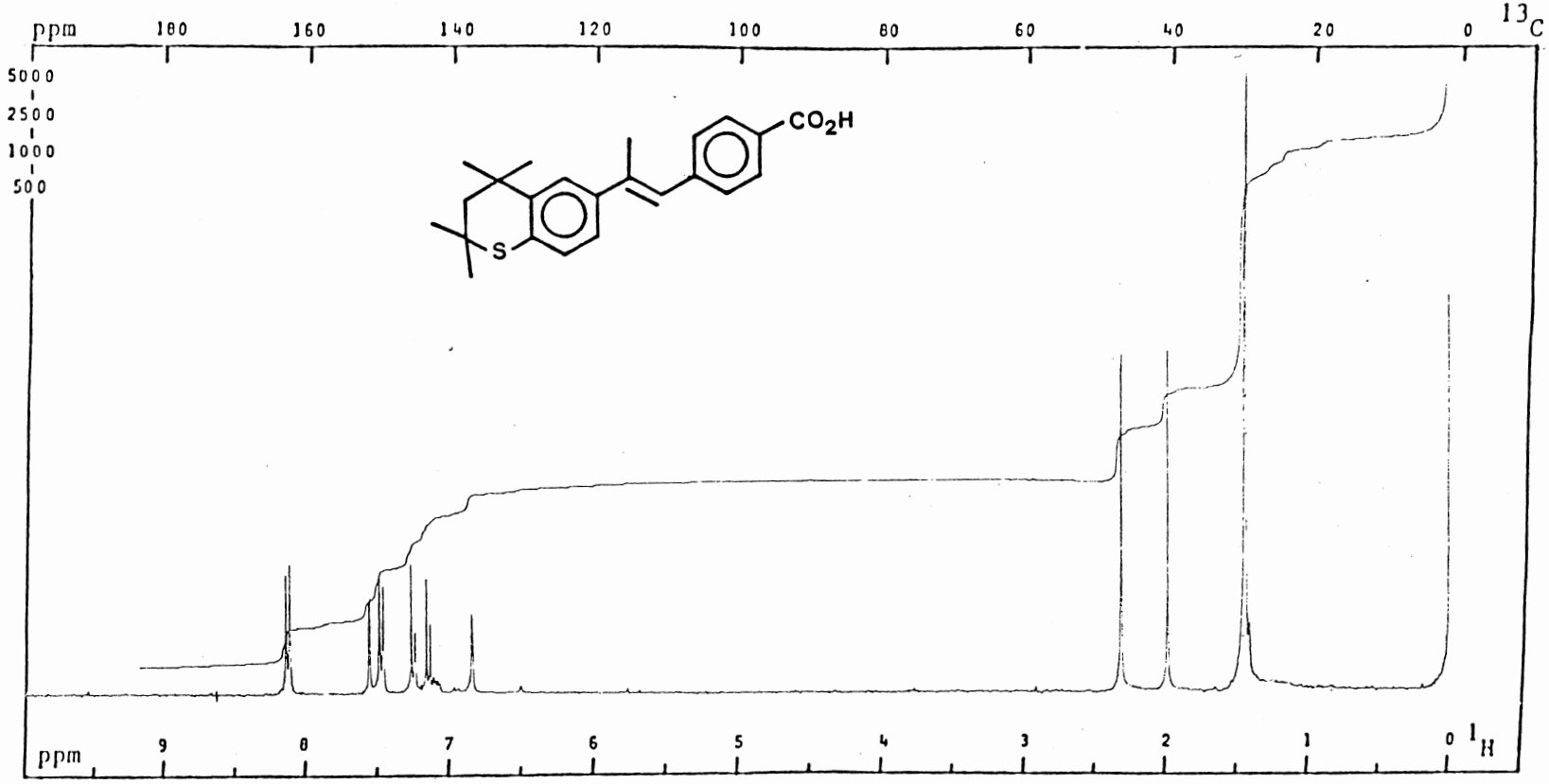
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

PLATE IL



IR Spectrum of **49a**

PLATE L



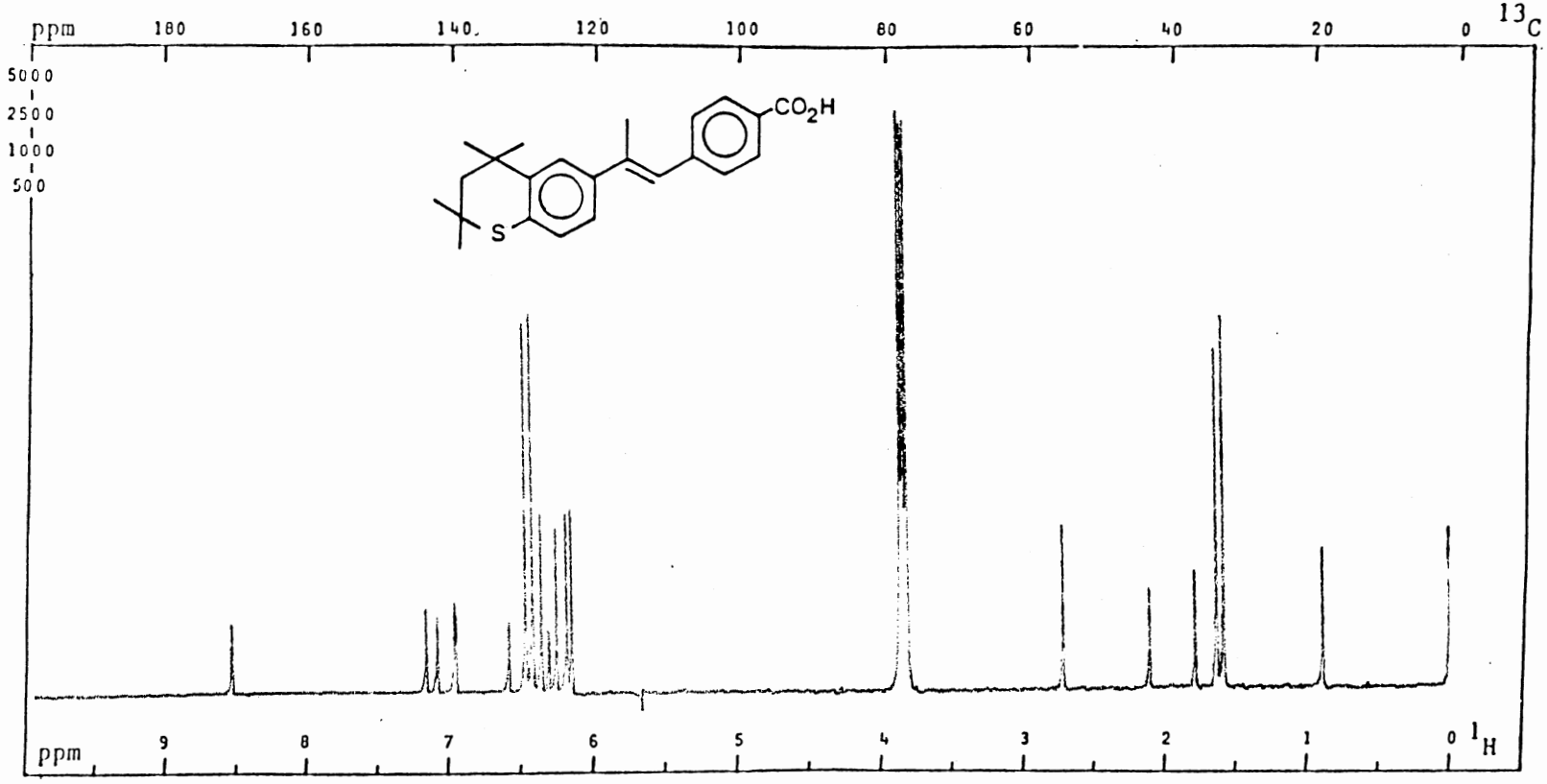
^{1}H NMR Spectrum of **49b**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 16 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE LI



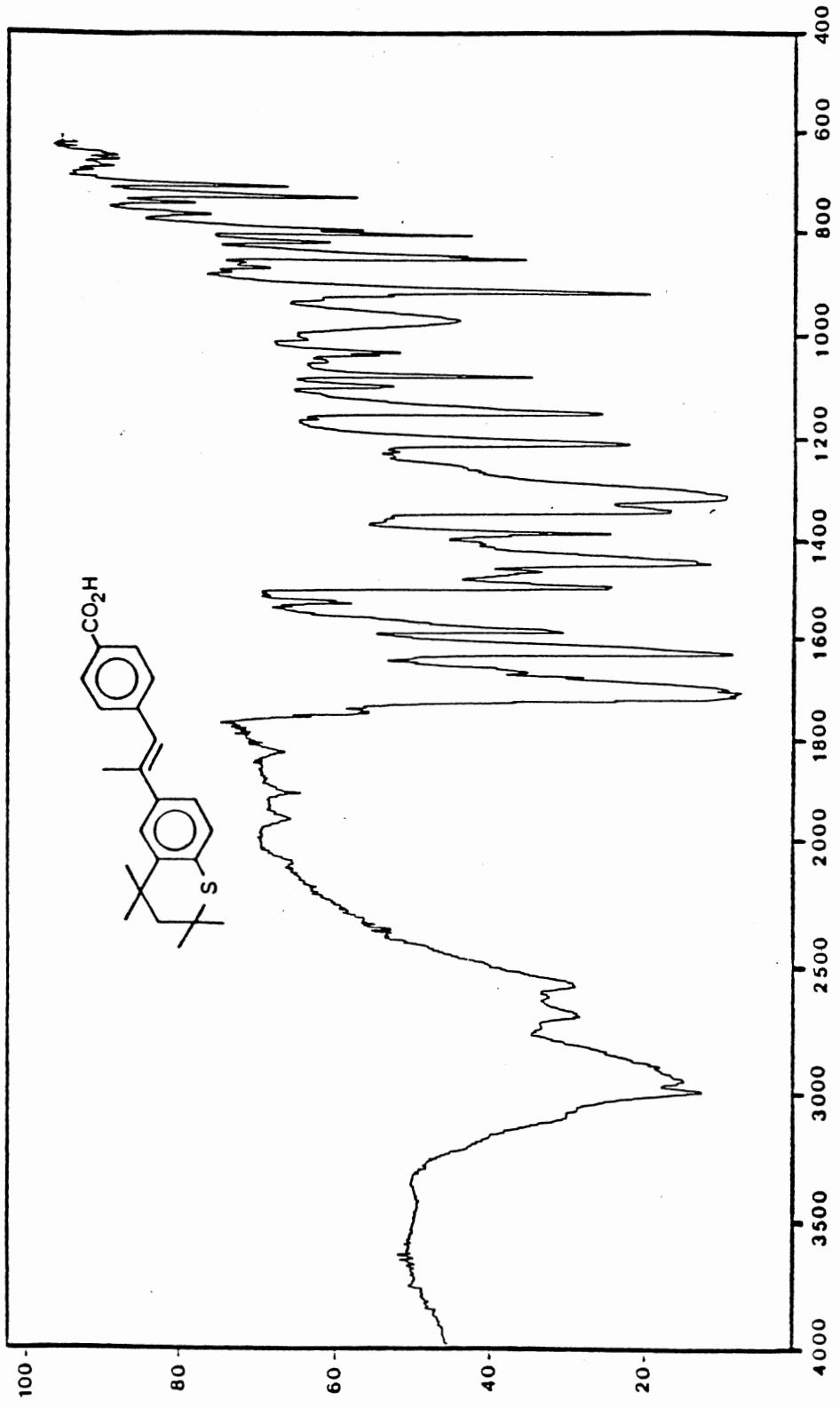
^{13}C NMR Spectrum of **49b**

PFT _XCW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 12 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

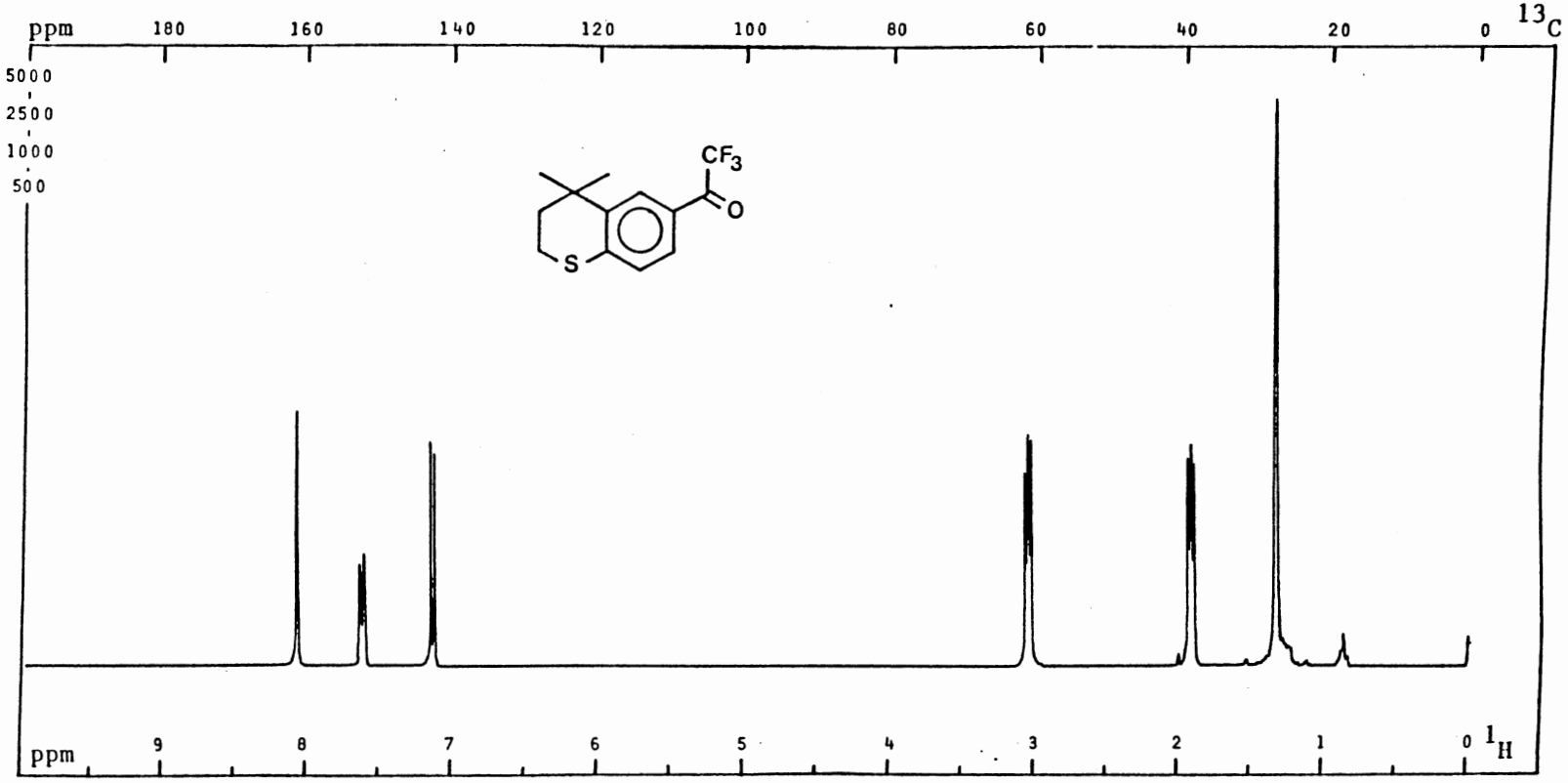
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: 3.0 Hz.

PLATE LII



IR Spectrum of **49b**

PLATE LIII



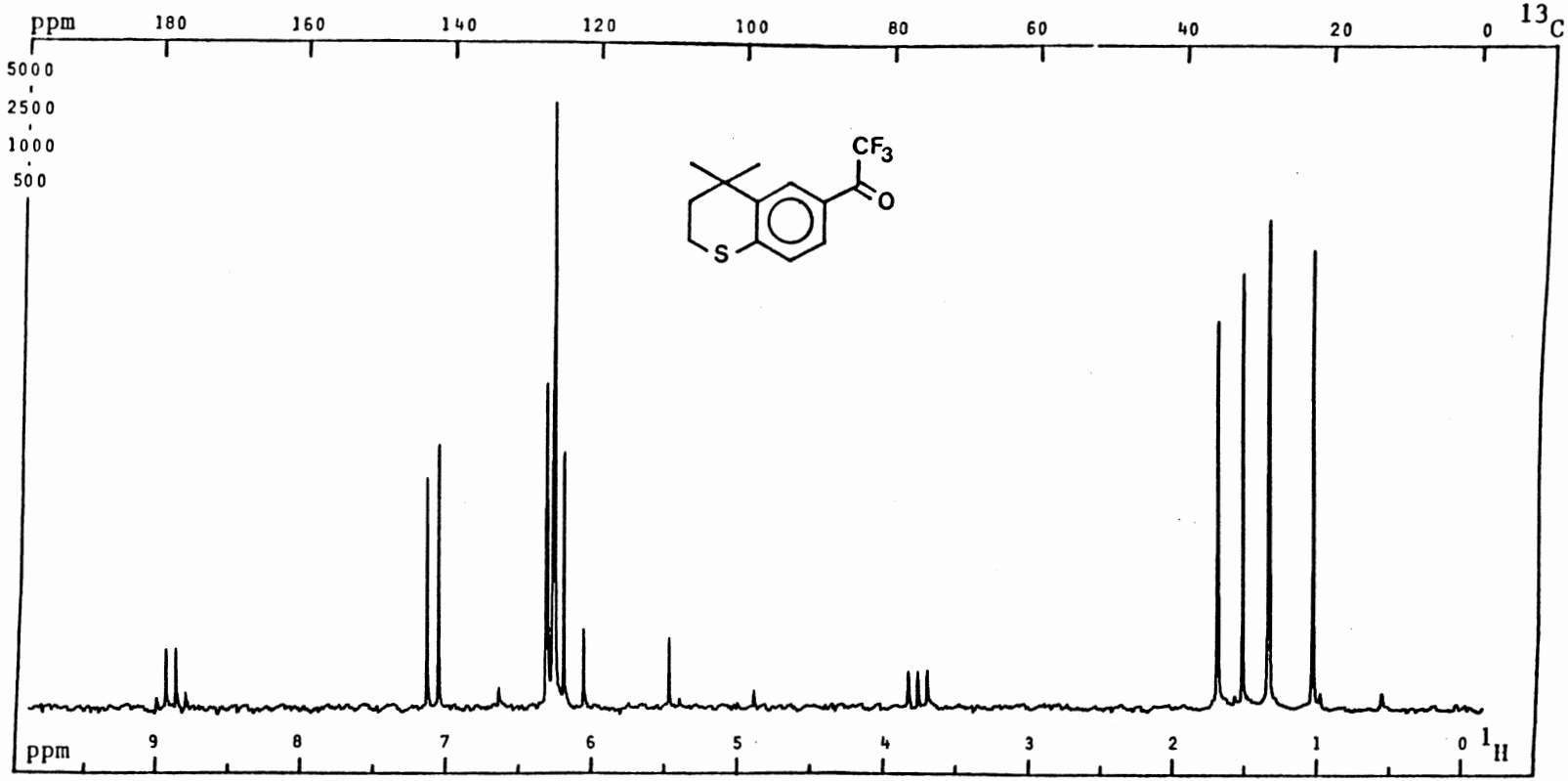
^{1}H NMR Spectrum of **83**

PFT X CW _ ; **Solvent:** $DCCl_3$; **SF:** 299.9485 **MHz; WC:** 2999.4 **Hz; T:** RT **°C; NT:** 12

Size: 12 **K; PW/RF:** 5.0 **µs/dB; TO:** 0 **Hz; FB:** - **Hz; Lock:** ^{2}H **; D1,D5:** 0 **s.**

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

PLATE LIV



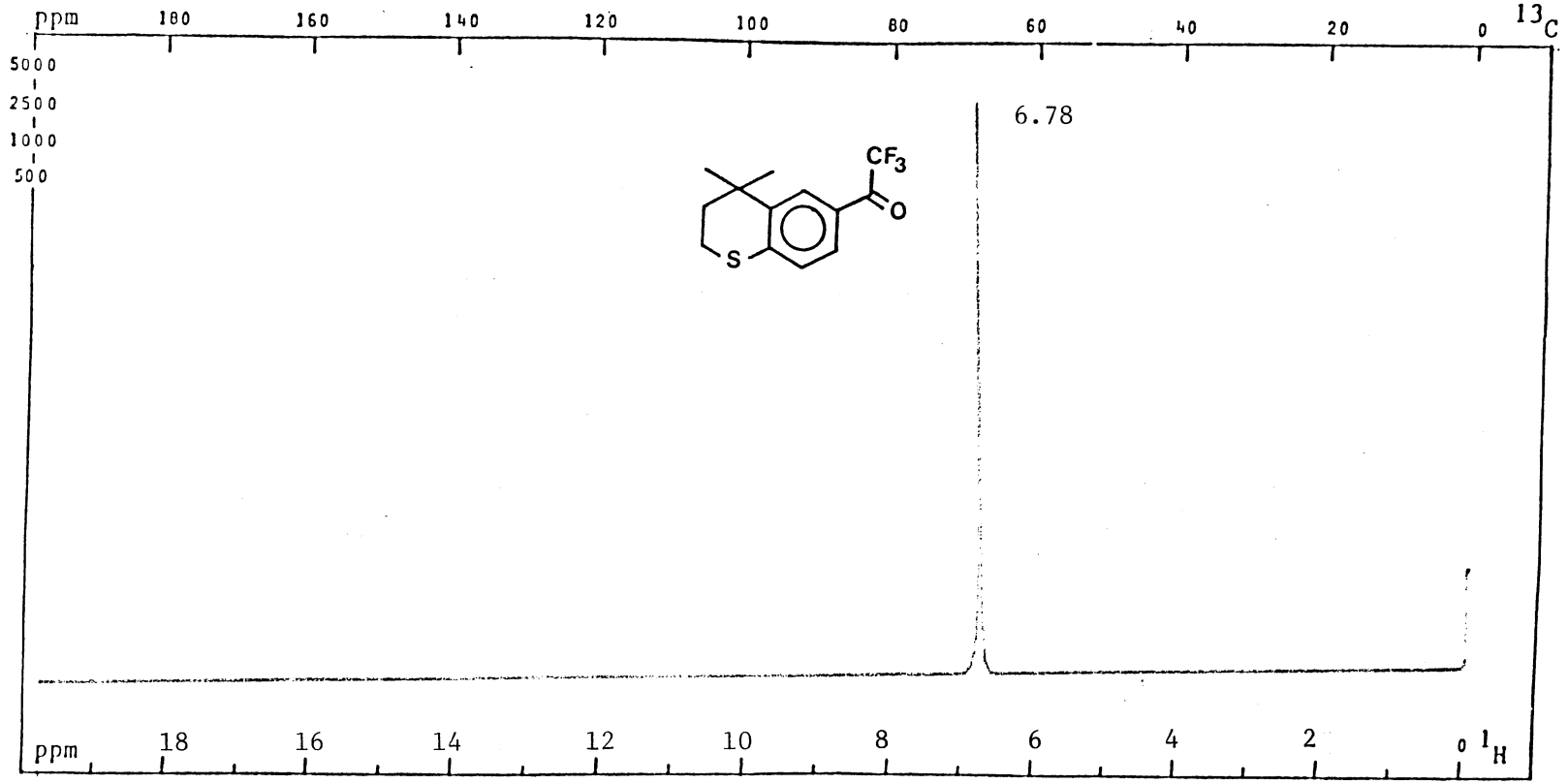
^{13}C NMR Spectrum of **83**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 600

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

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

PLATE LV



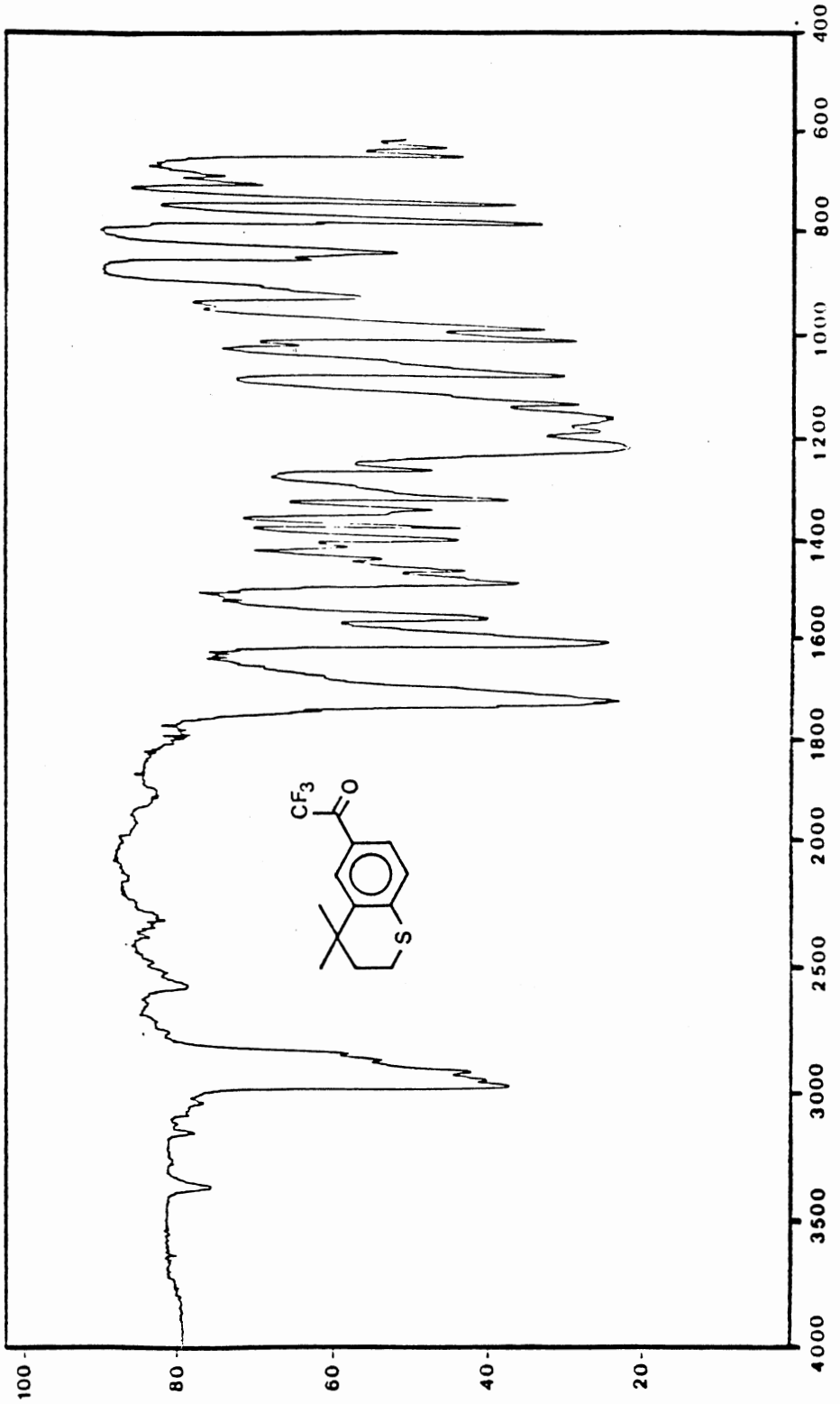
^{19}F NMR Spectrum of **83**

PFT _XCW _ ; Solvent: $DCCl_3$; SF:282.203 MHz; WC: 5644.1 Hz; T: RT °C; NT: 8 .

Size: 2 K; PW/RF: 7 µs/dB; TO: Hz; FB: - Hz; Lock: ;D1,D5: 2.0 s.

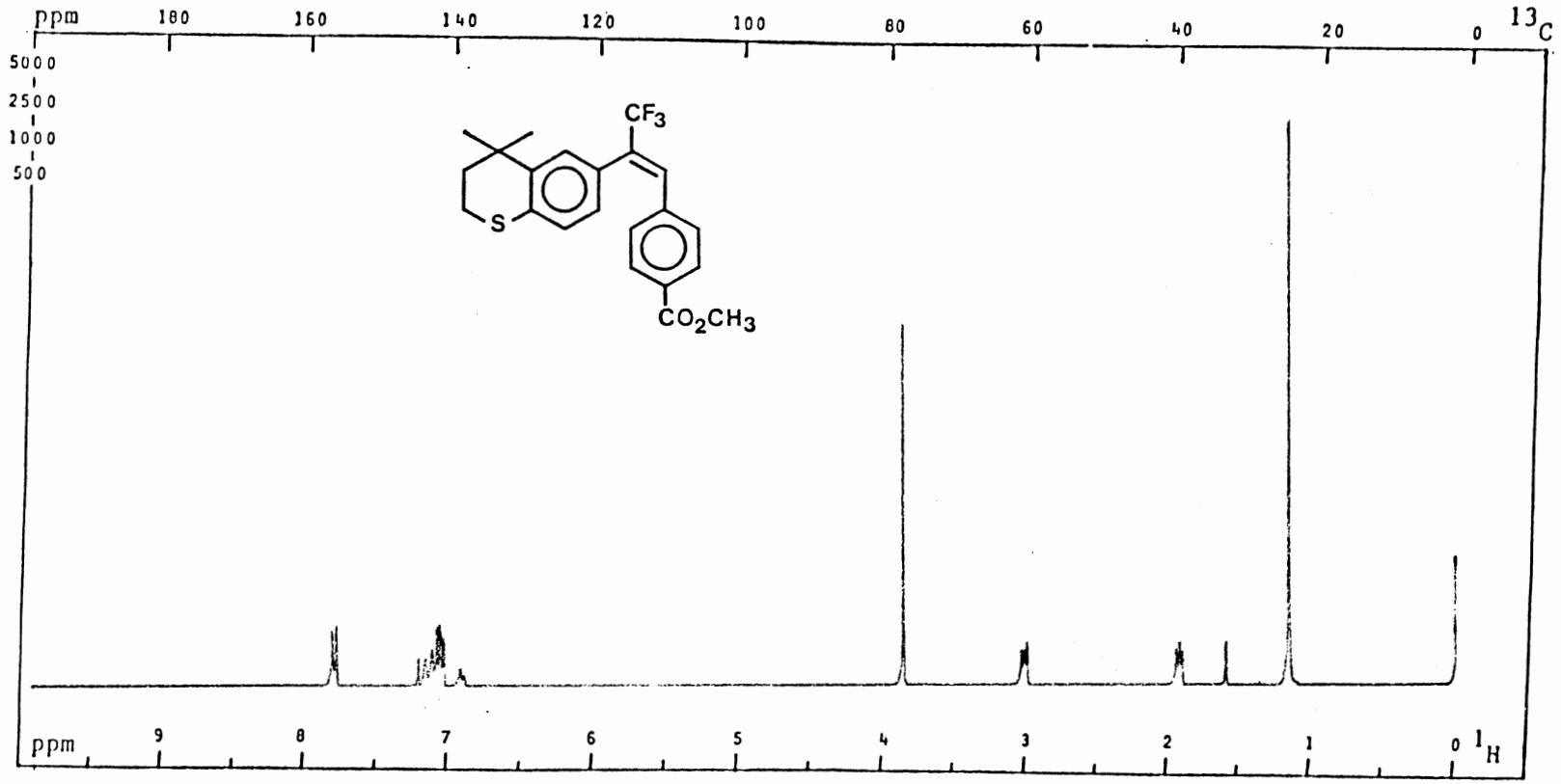
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 2.0 Hz.

PLATE LVI



IR Spectrum of **83**

PLATE LVII



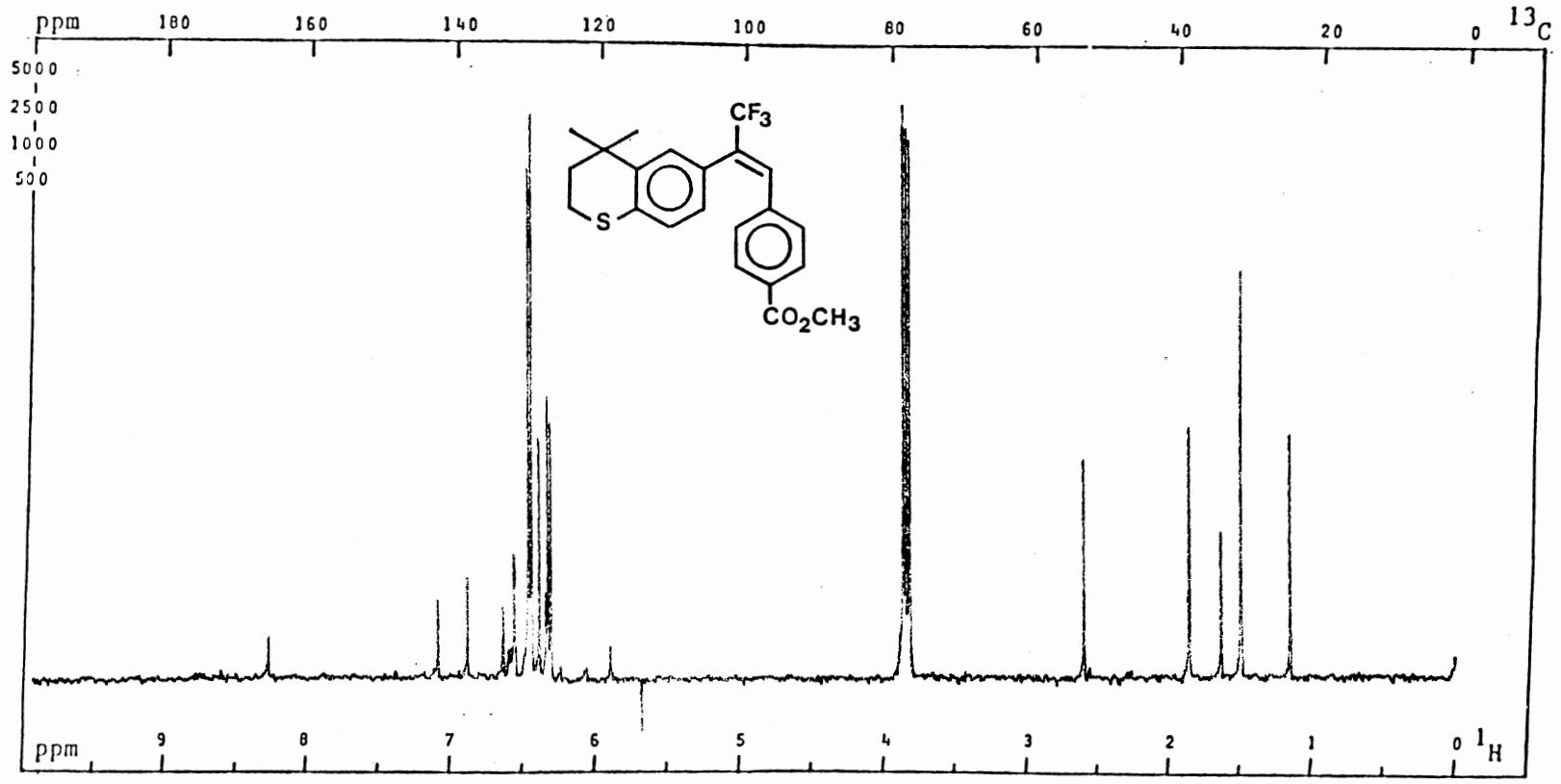
^{1}H NMR Spectrum **50a**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 16 K; PW/RF: 6 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE LVIII



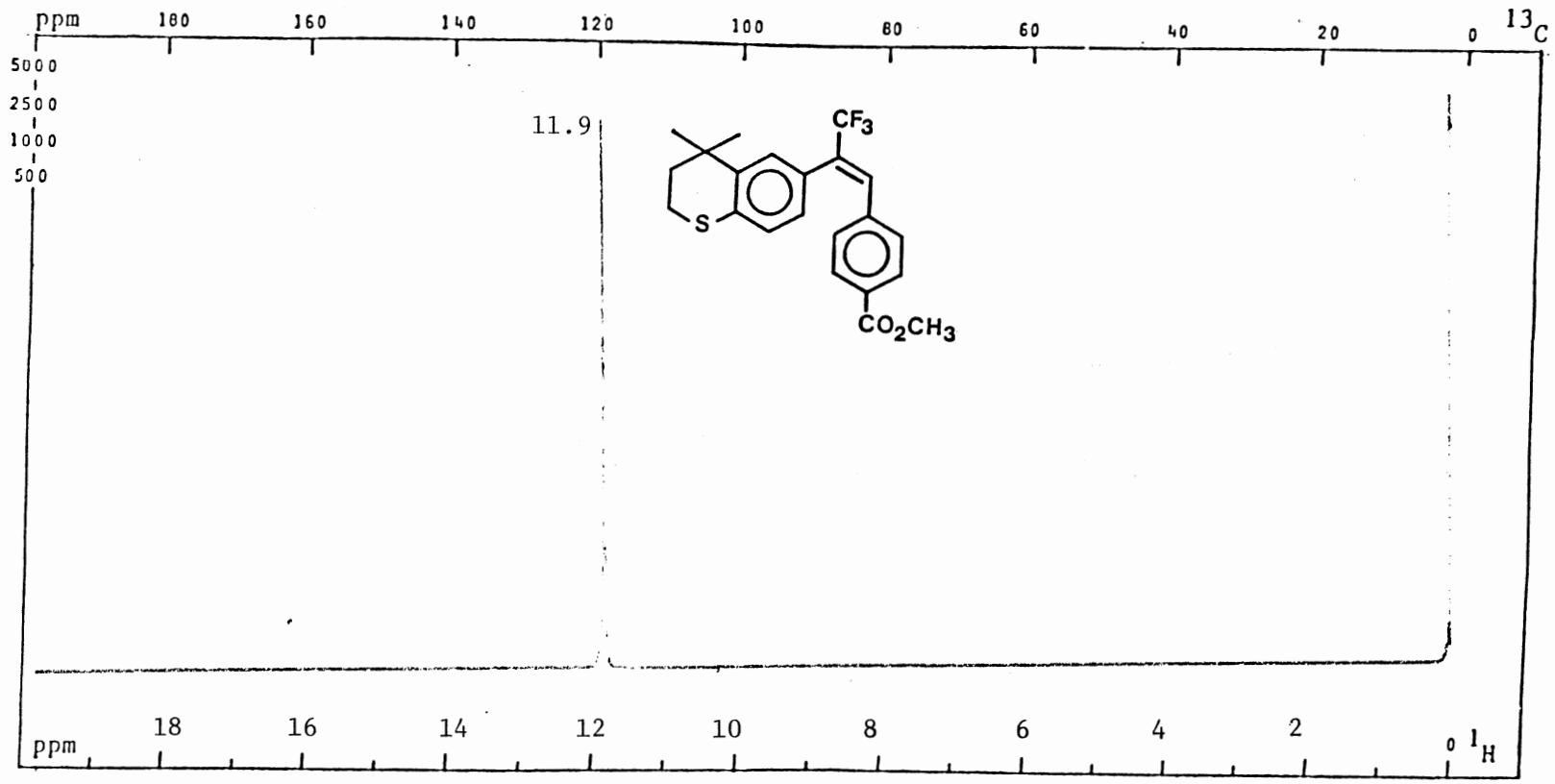
^{13}C NMR Spectrum of **50a**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 1000 .

Size: 8 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

PLATE LIX



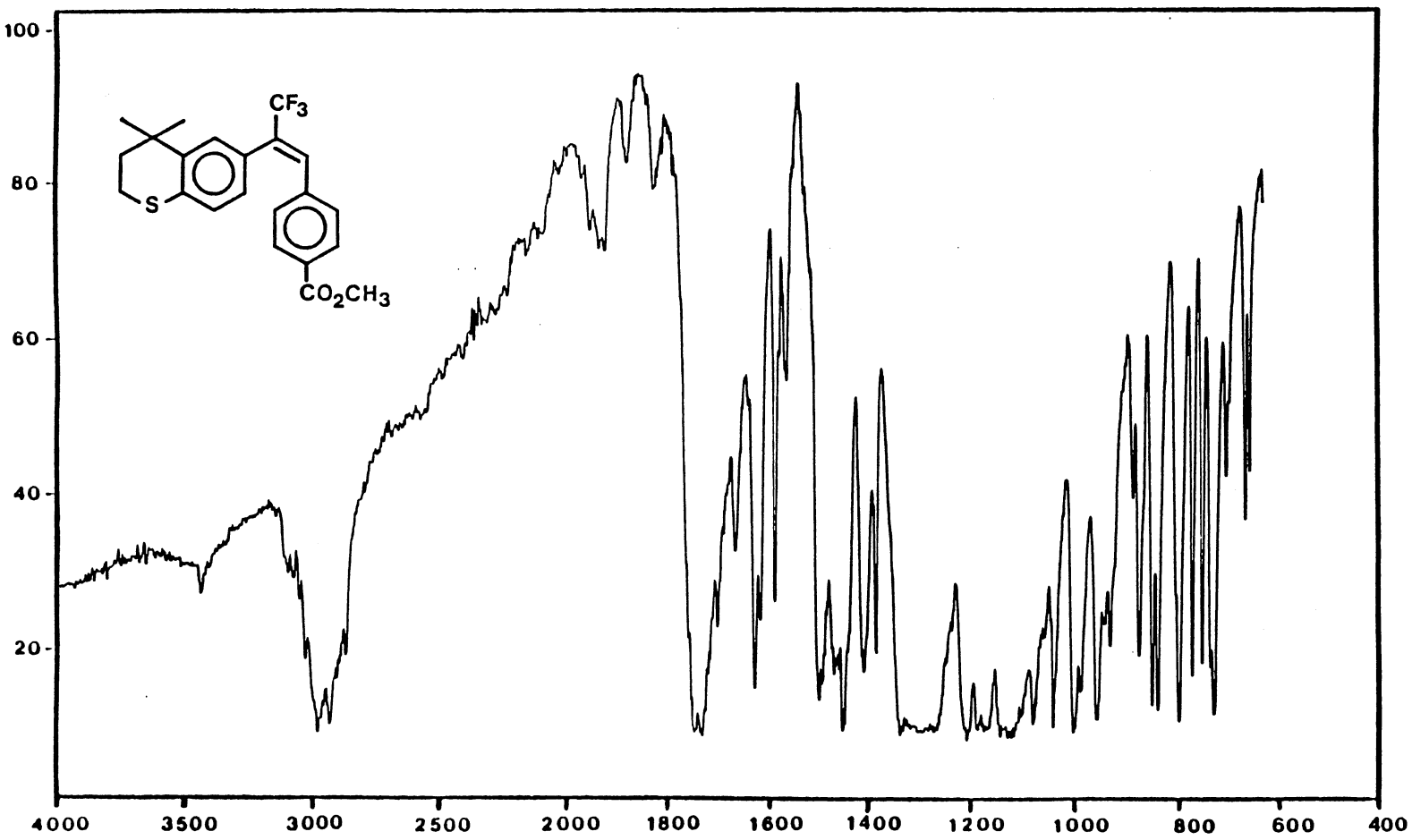
^{19}F NMR Spectrum of **50a**

PFT X _ CW _ ; Solvent: $DCCl_3$; SF: 282.203 MHz; WC: 5644.1 Hz; T: RT °C; NT: 8

Size: 2 K; PW/RF: 7.0 µs/dB; TO: Hz; FB: - Hz; Lock: ; D1,D5: 2.0 s.

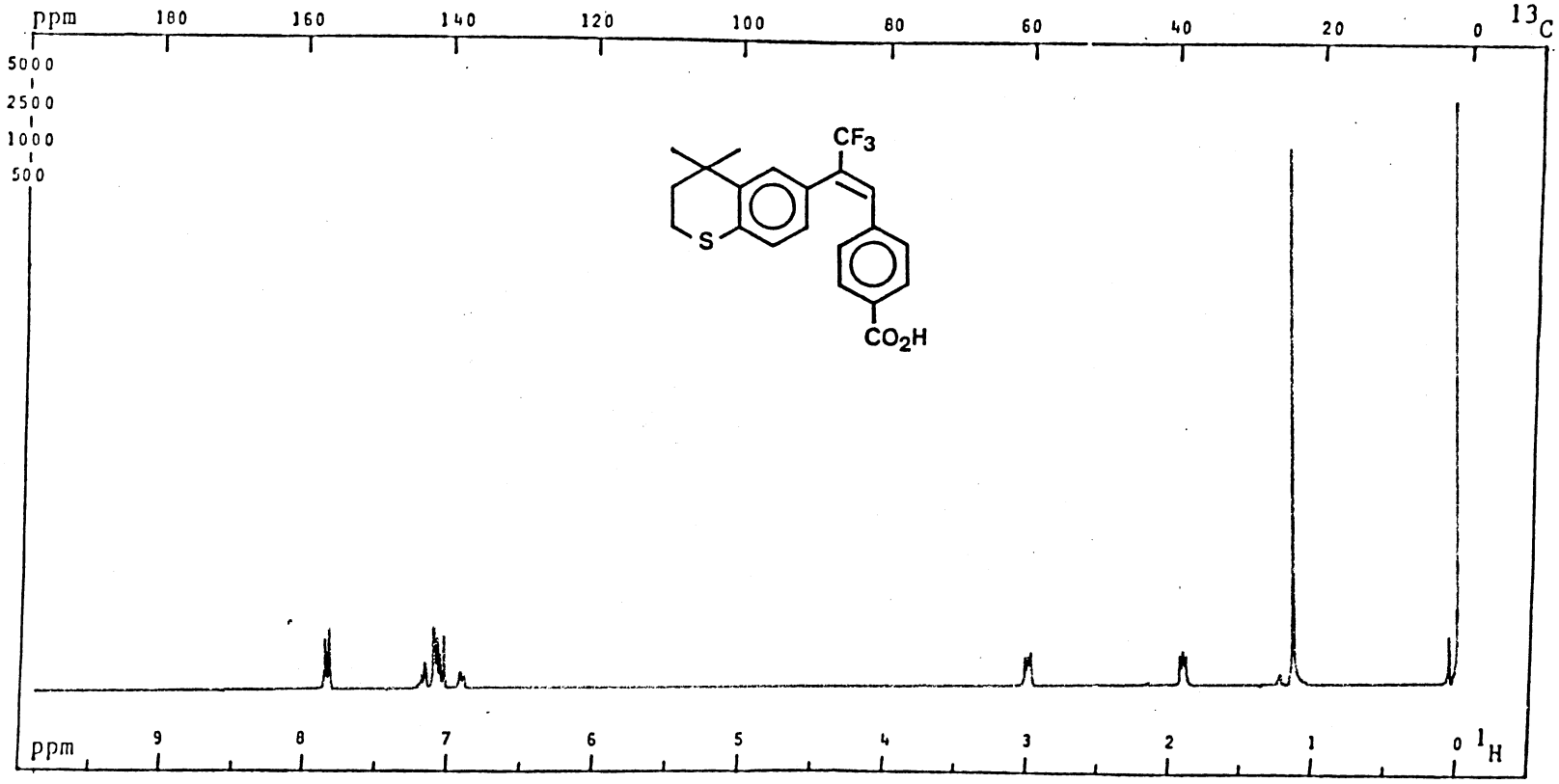
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 2.0 Hz.

PLATE LX



IR Spectrum of 50a

PLATE LXI



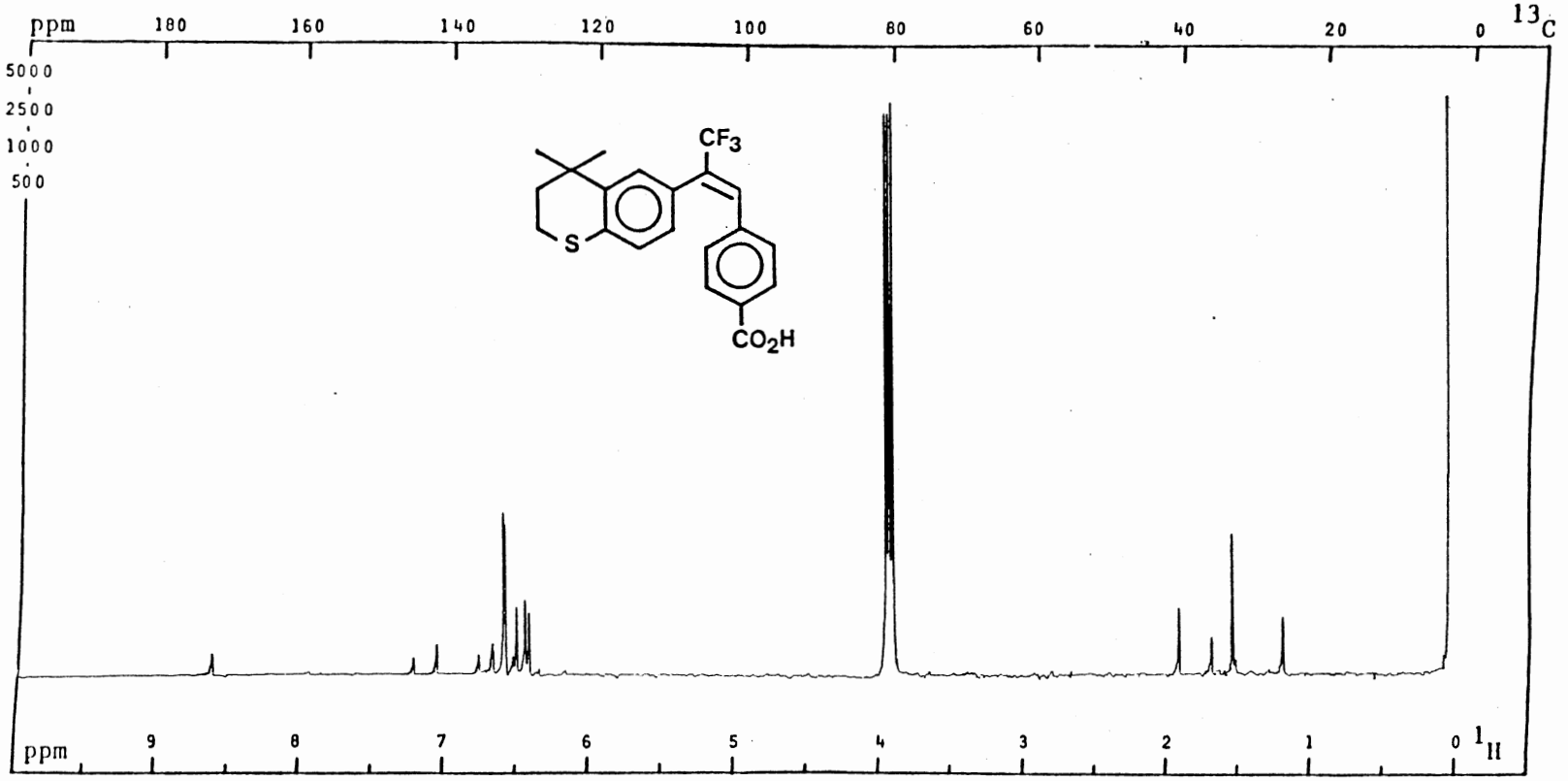
^{1}H NMR Spectrum of **50b**

PFT _X_ CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: ^{16}K; PW/RF: 6 μs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE LXII



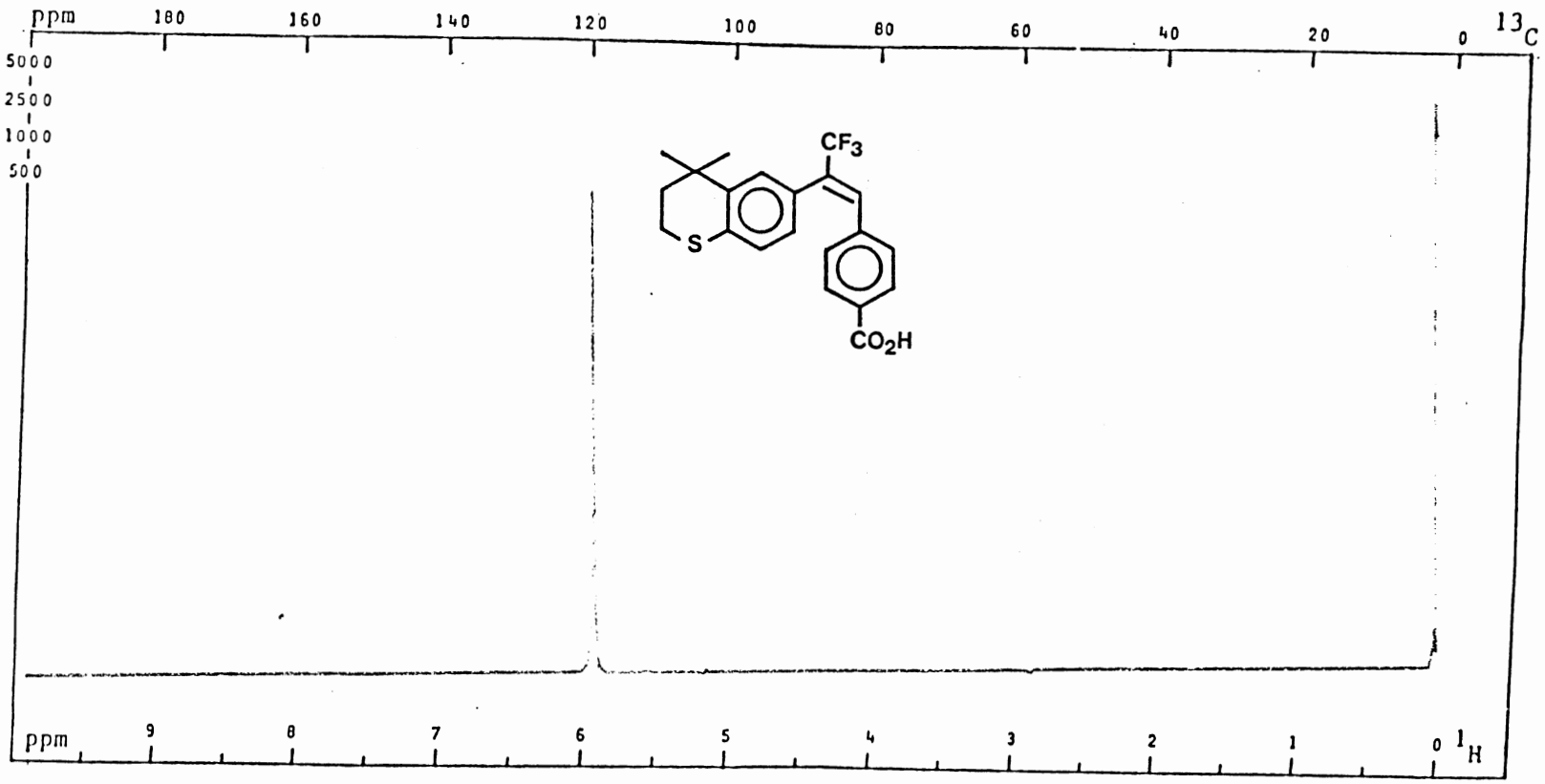
^{13}C NMR Spectrum of **50b**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 1000

Size: 8 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

PLATE LXIII



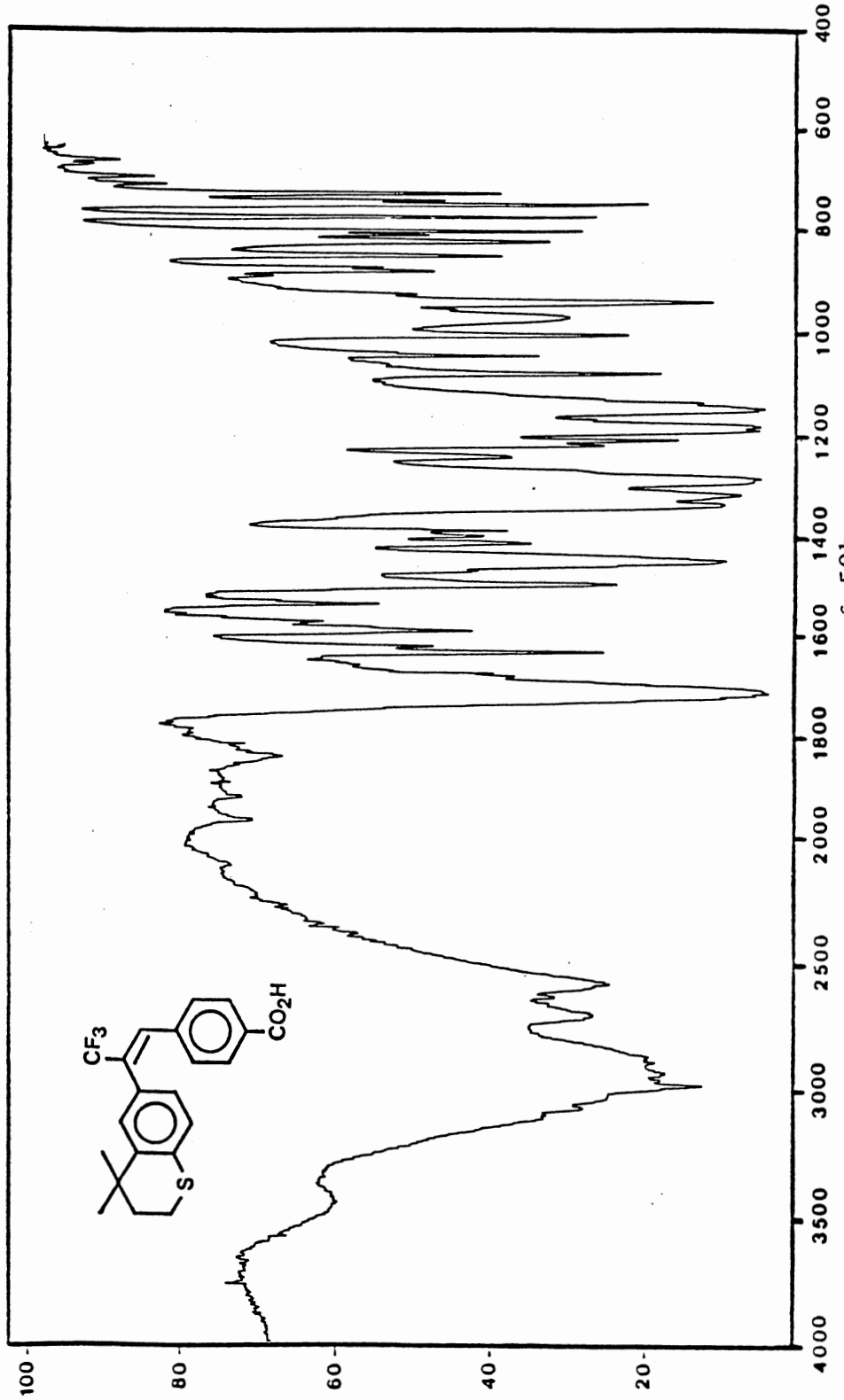
^{19}F NMR Spectrum of **50b**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 282.203 MHz; WC: 5644.1 Hz; T: RT °C; NT: 8 .

Size: 2 K; PW/RF: 7.0 μs/dB; TO: Hz; FB: Hz; Lock: ; D1,D5: 2.0 s.

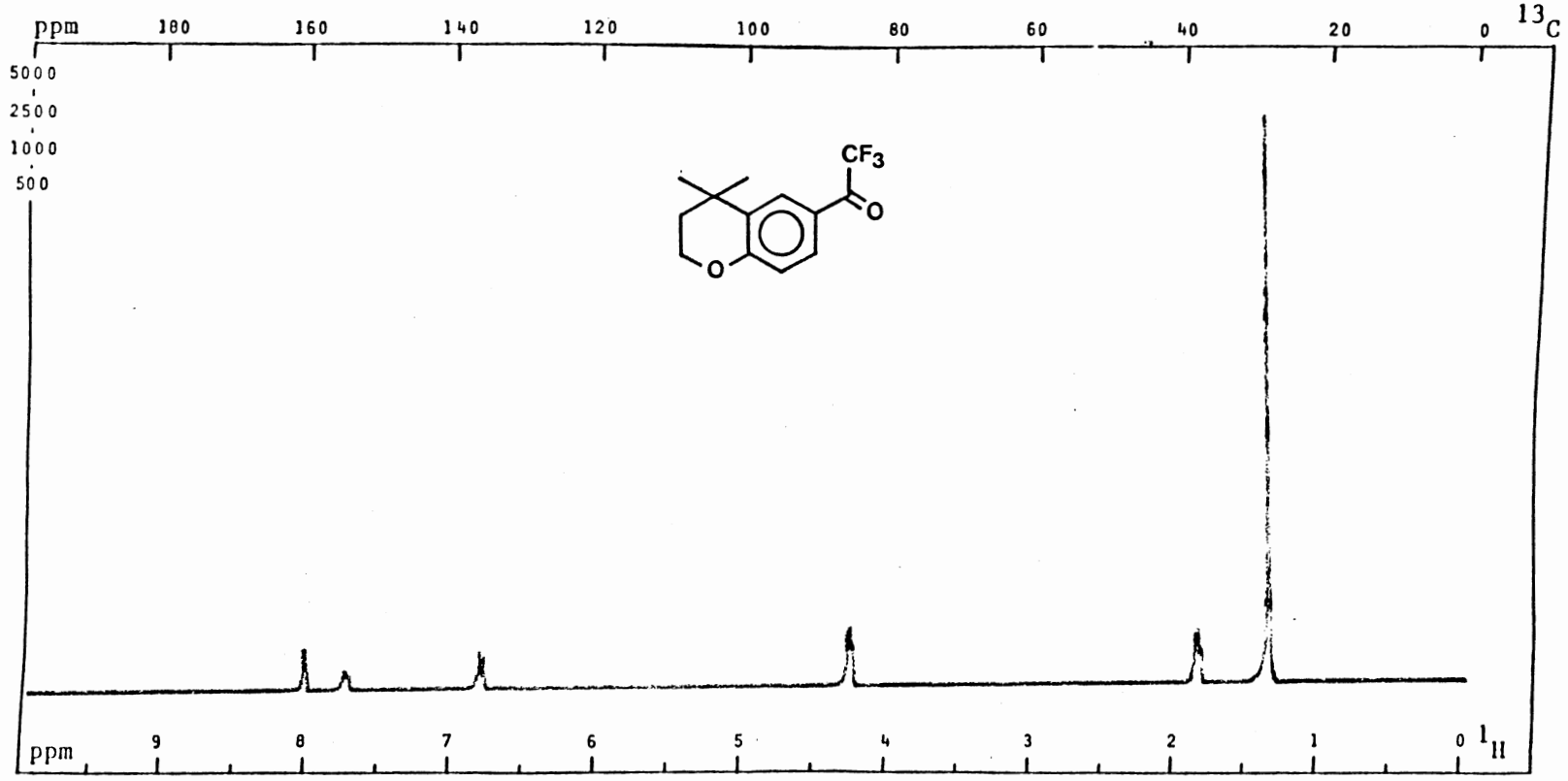
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 2.0 Hz.

PLATE LXIV



IR Spectrum of 50b

PLATE LXV



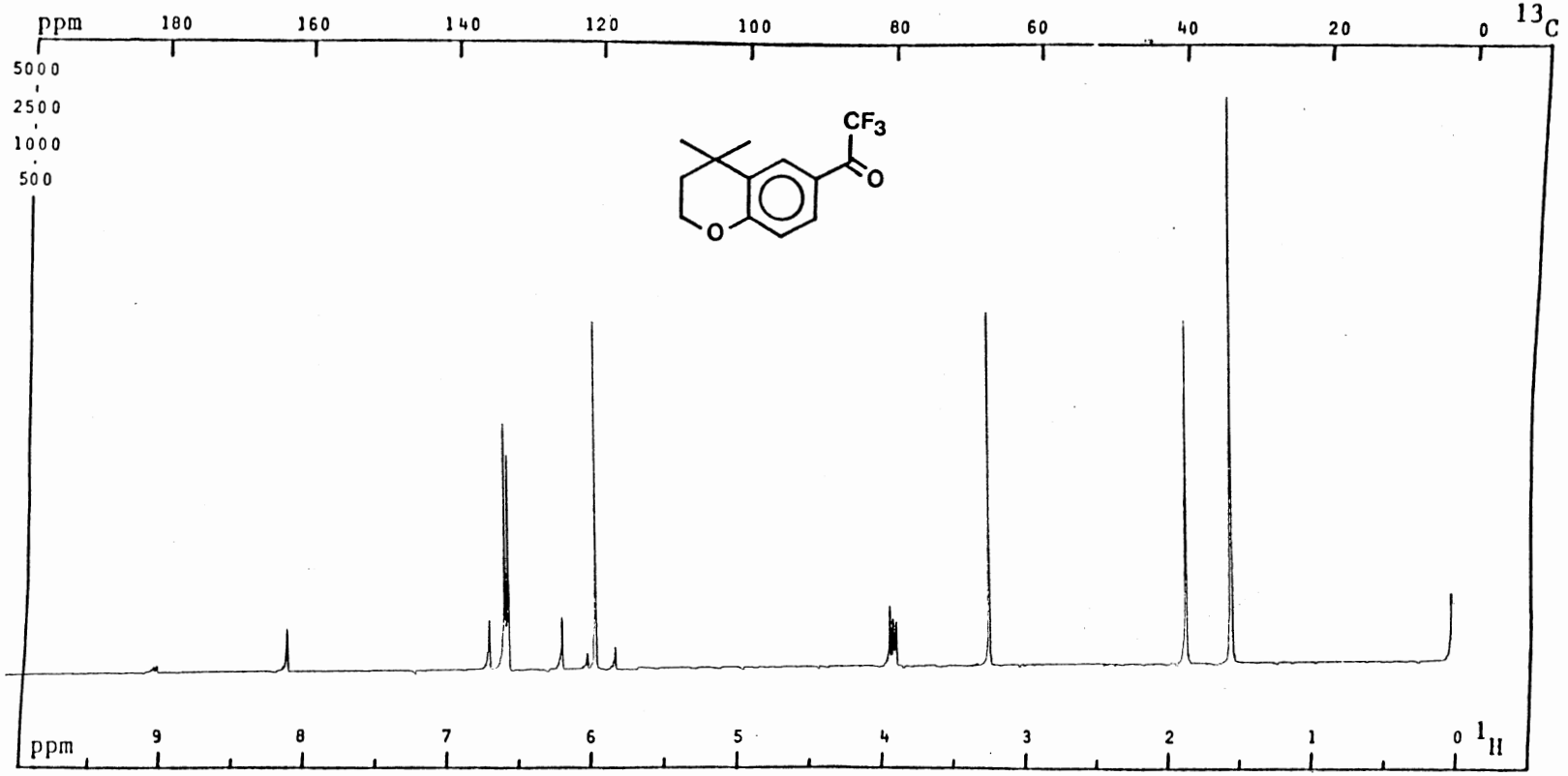
^{1}H NMR Spectrum of **86**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9284 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 8 K; PW/RF: 6.0 μs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0.5 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 13 W/dB; NBW: 0 Hz; LB: - Hz.

PLATE LXVI



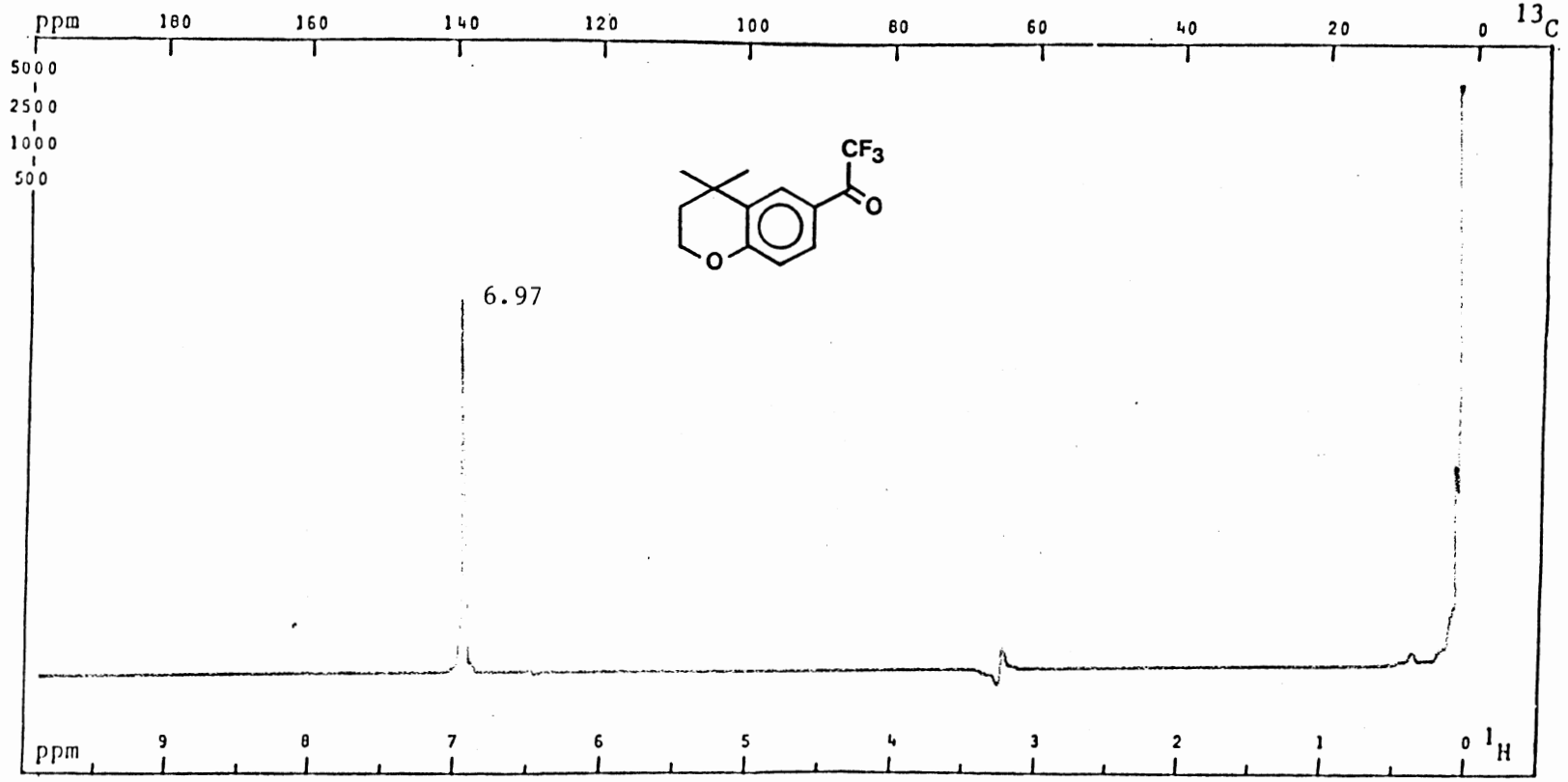
^{13}C NMR Spectrum of **86**

PFT _X_ CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 500 .

Size: 8 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 4.0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: 1.0 Hz.

PLATE LXVII



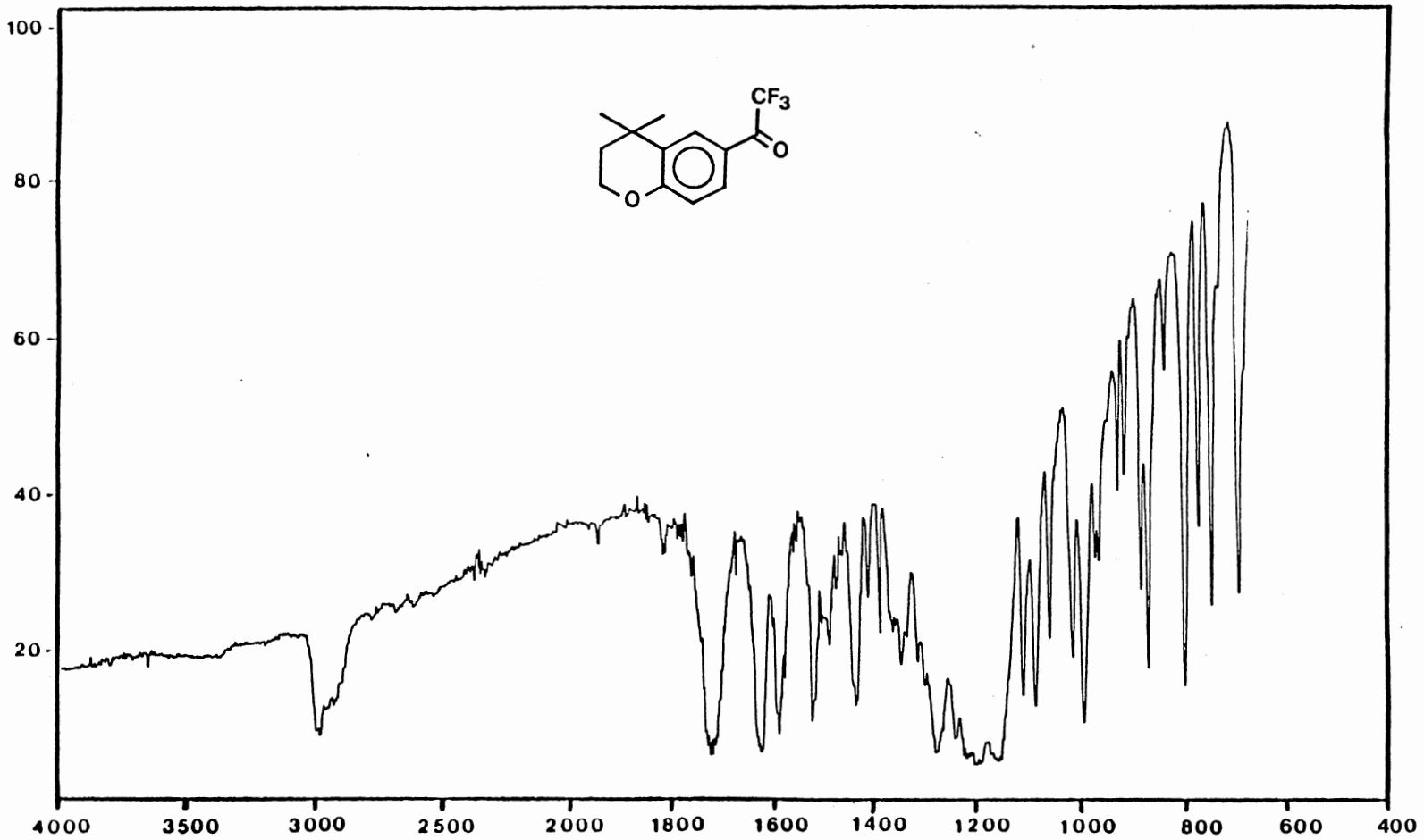
^{19}F NMR Spectrum of **86**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 282.203 MHz; WC: 2822.0 Hz; T: RT °C; NT: 1 .

Size: 1.6K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: Hz; Lock: ^2H ; D1,D5: 2.0 s.

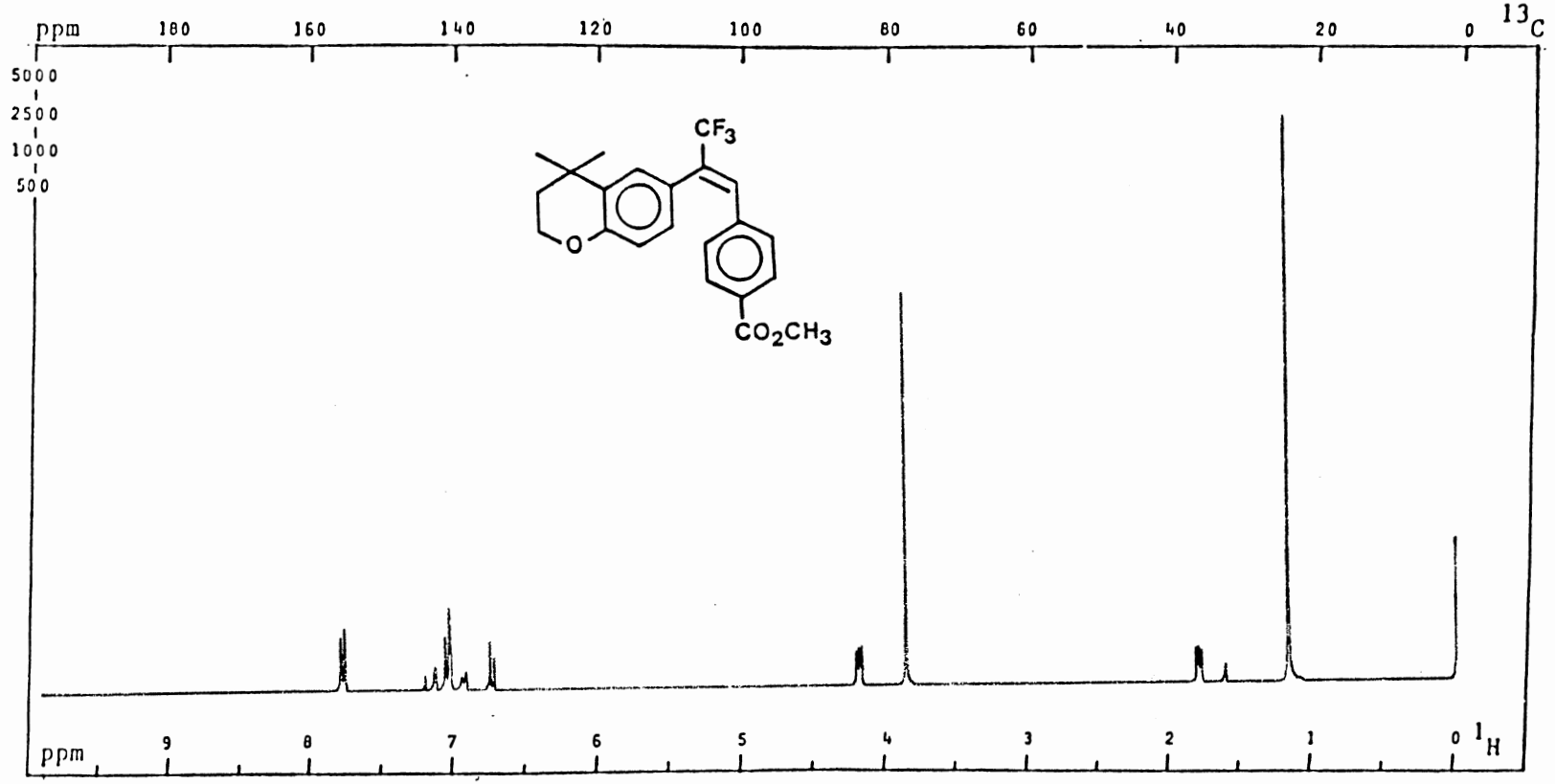
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: Hz; LB: 2.0 Hz.

PLATE LXVIII



IR Spectrum of 86

PLATE LXIX



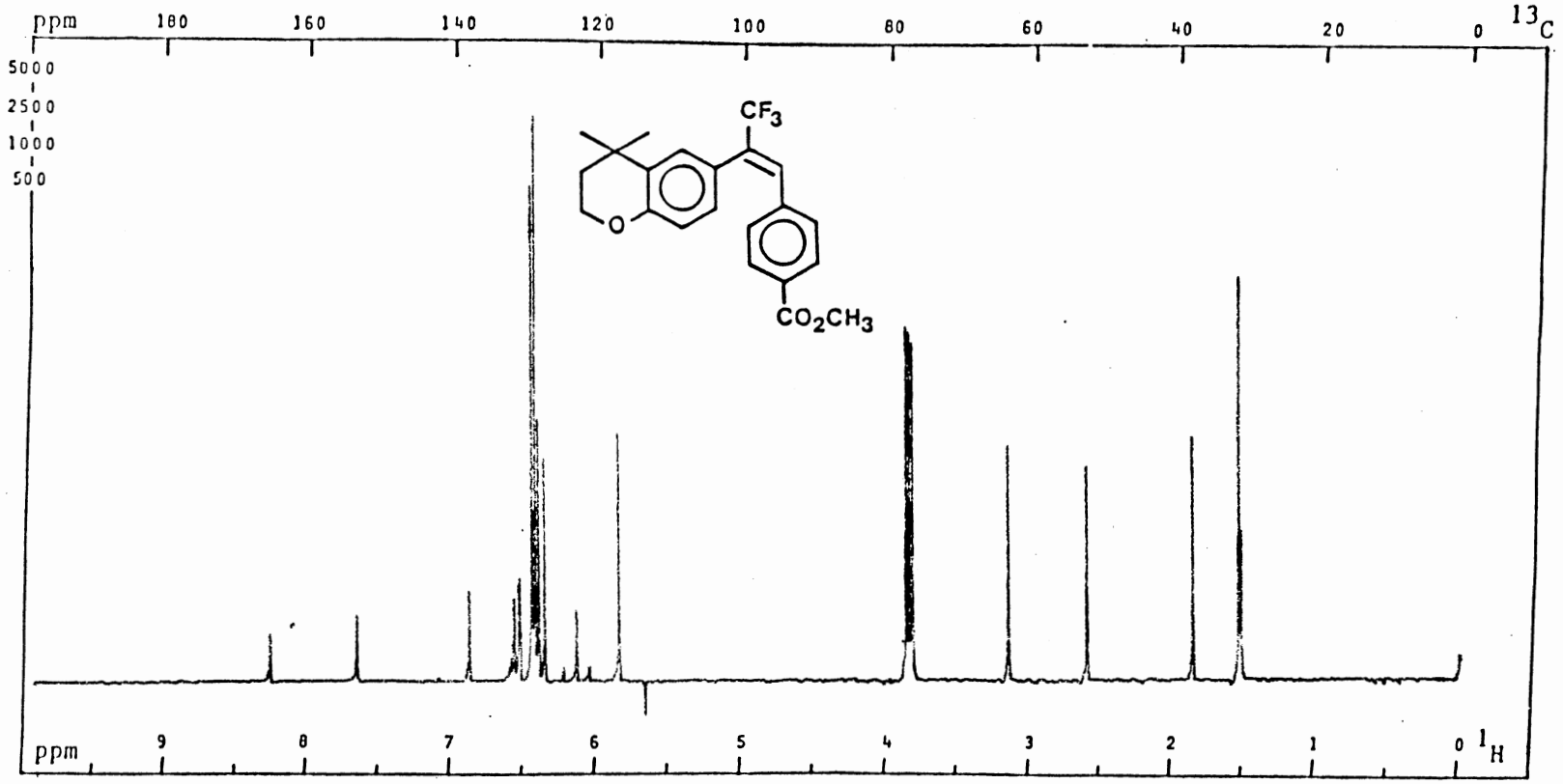
^{1}H NMR Spectrum of **50e**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 4

Size: 8 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE LXX



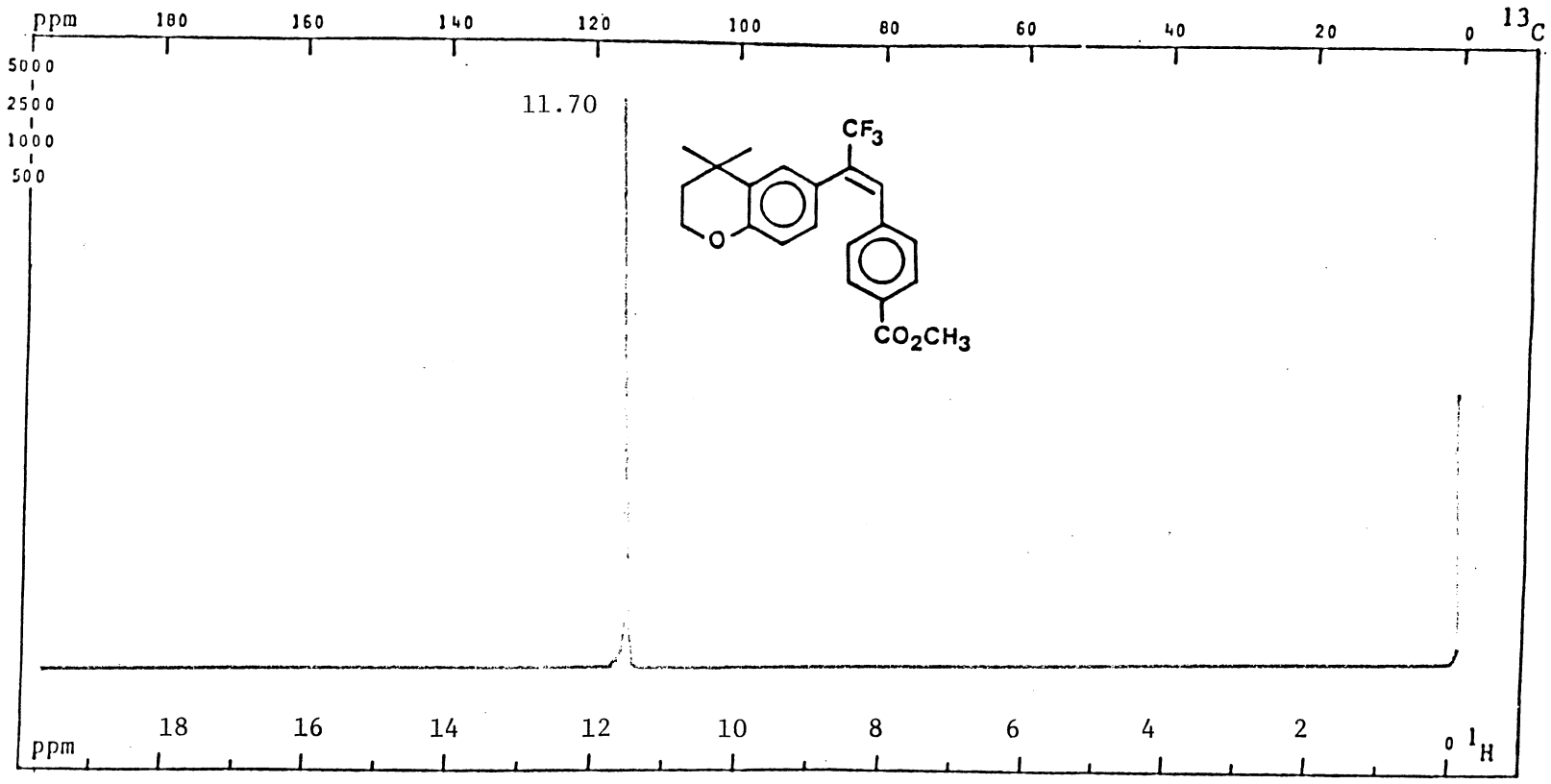
^{13}C NMR Spectrum of **50e**

PFT X CW _ ; Solvent: $DCCl_3$; SF:75.429 MHz; WC: 15085.9Hz; T: RT °C; NT: 6064

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

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

PLATE LXXI



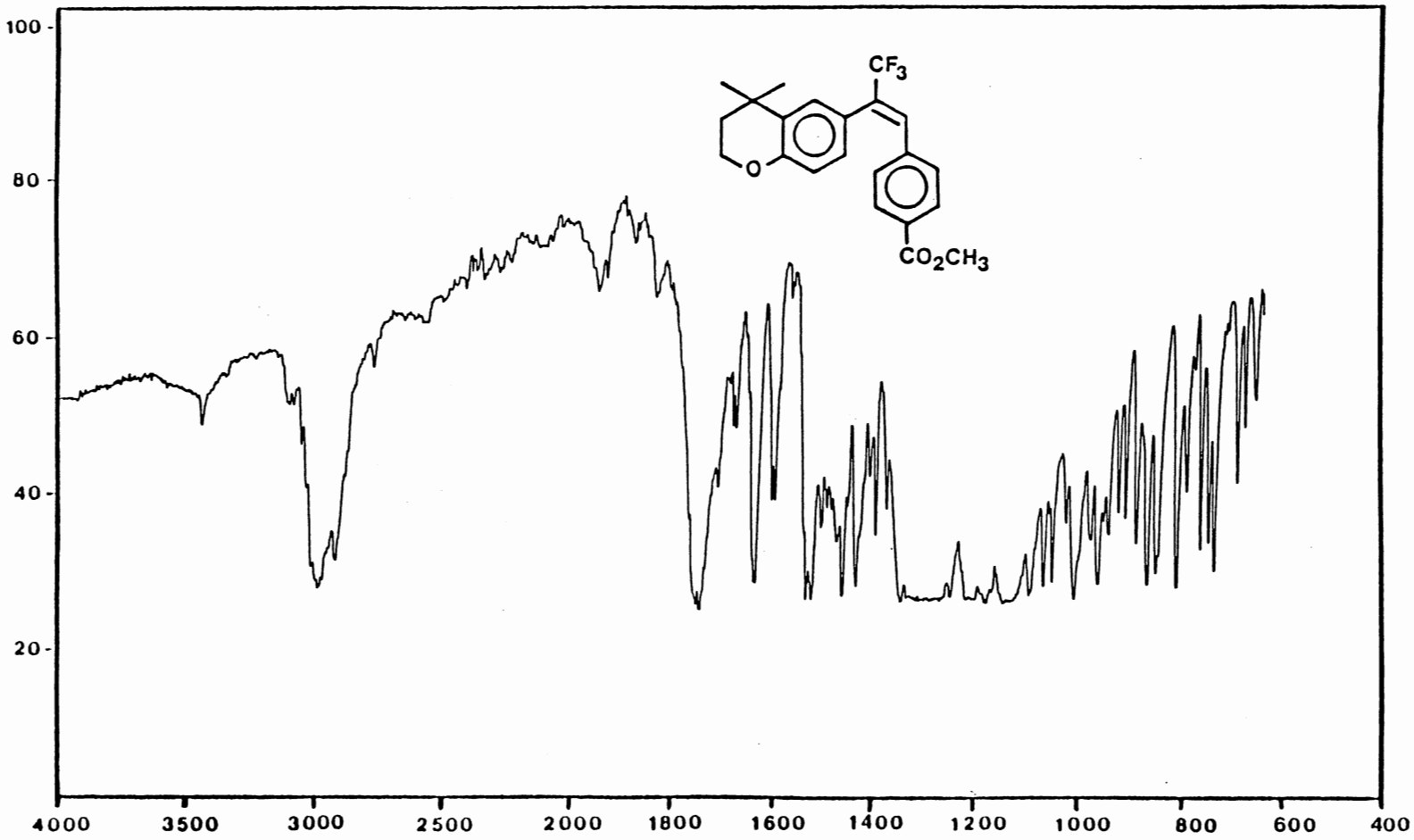
^{19}F NMR Spectrum of **50e**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 282.203 MHz; WC: 5644.1 Hz; T: RT °C; NT: 8

Size: 2.5 K; PW/RF: 7.0 μs/dB; TO: Hz; FB: - Hz; Lock: ; D1,D5: 2.0 s.

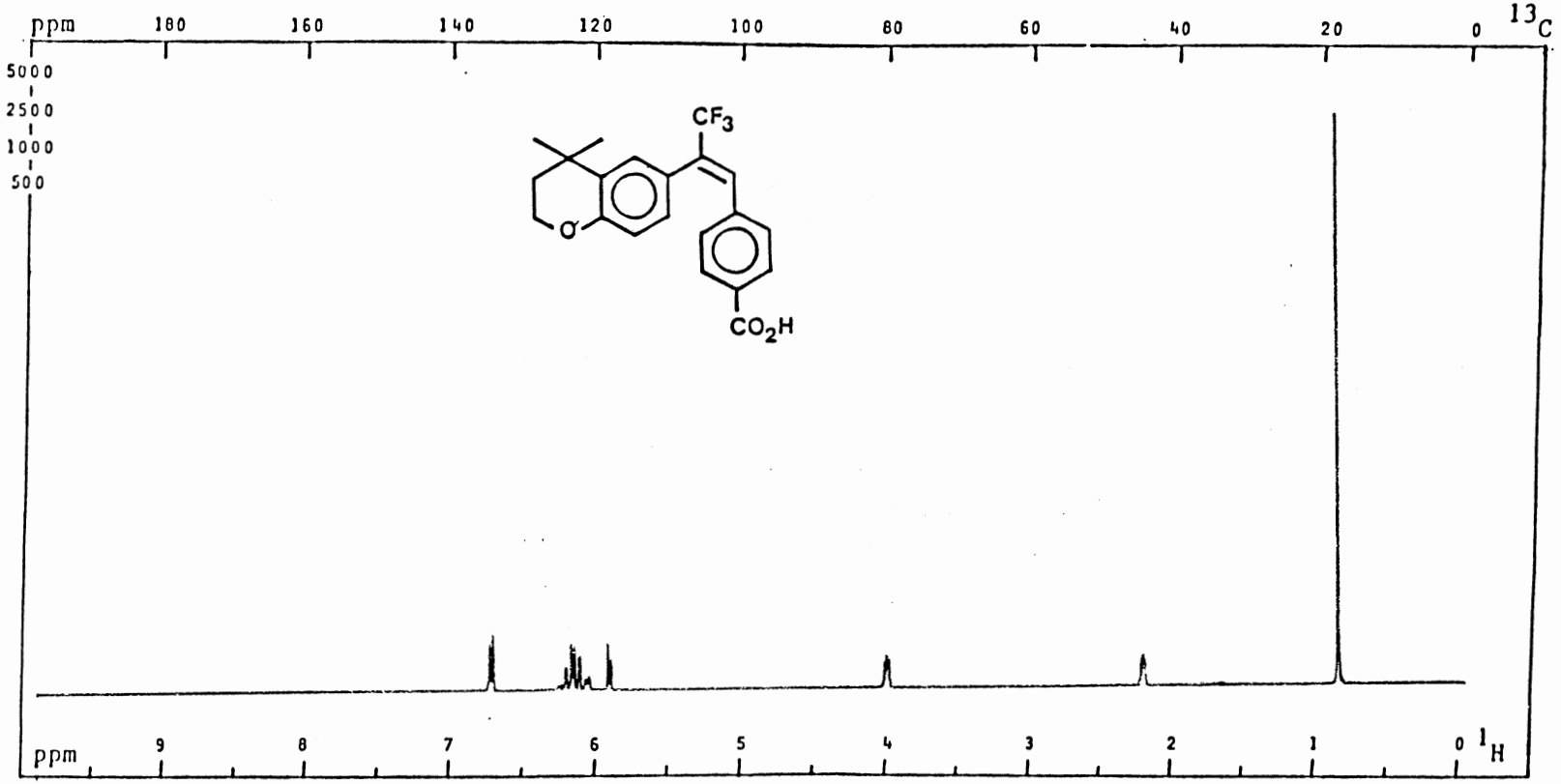
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): W/dB; NBW: Hz; LB: 2.0 Hz.

PLATE LXXII



IR Spectrum of 50e

PLATE LXXIII



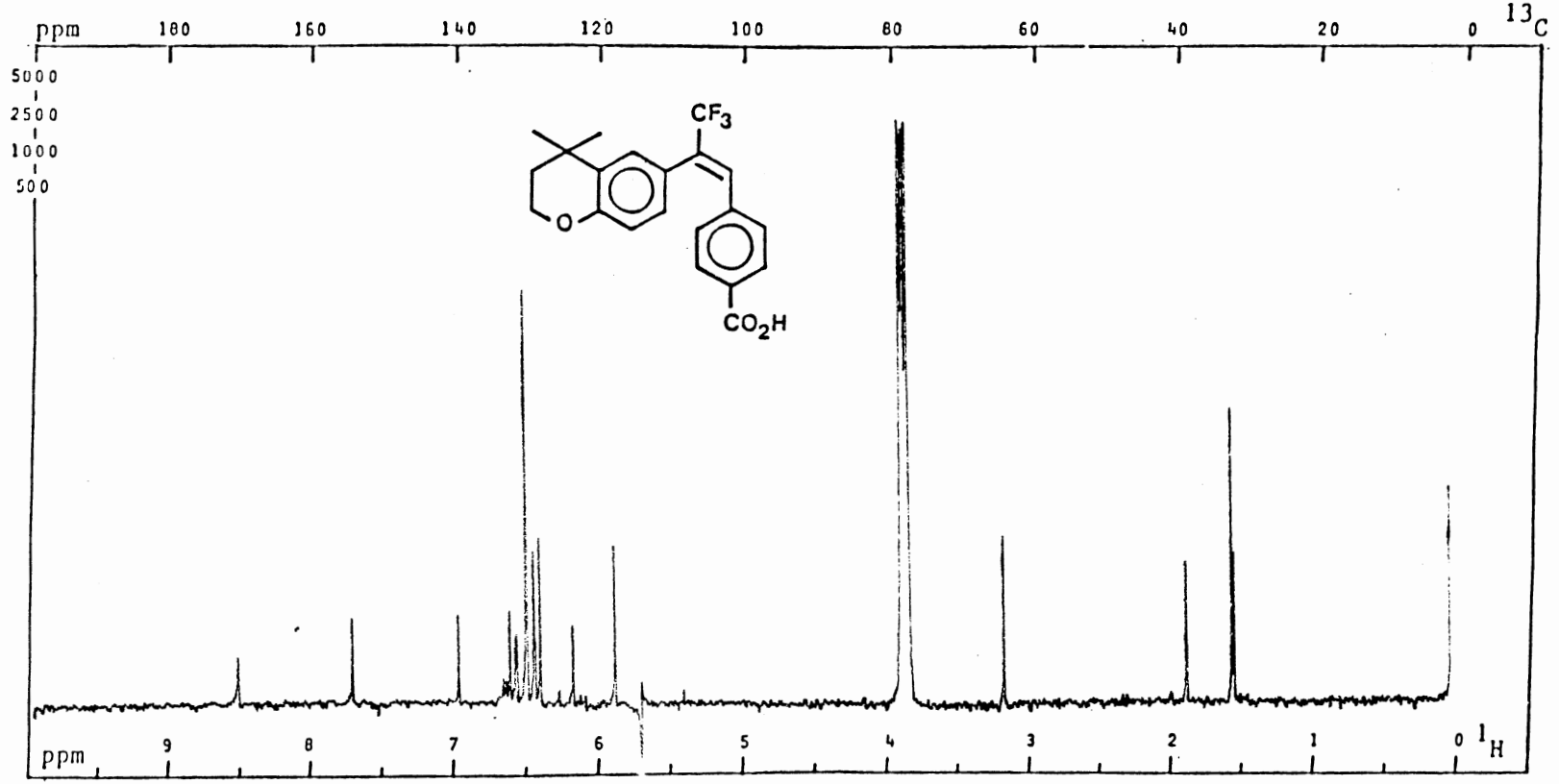
^{1}H NMR Spectrum of **50f**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 16

Size: 12 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE LXXIV



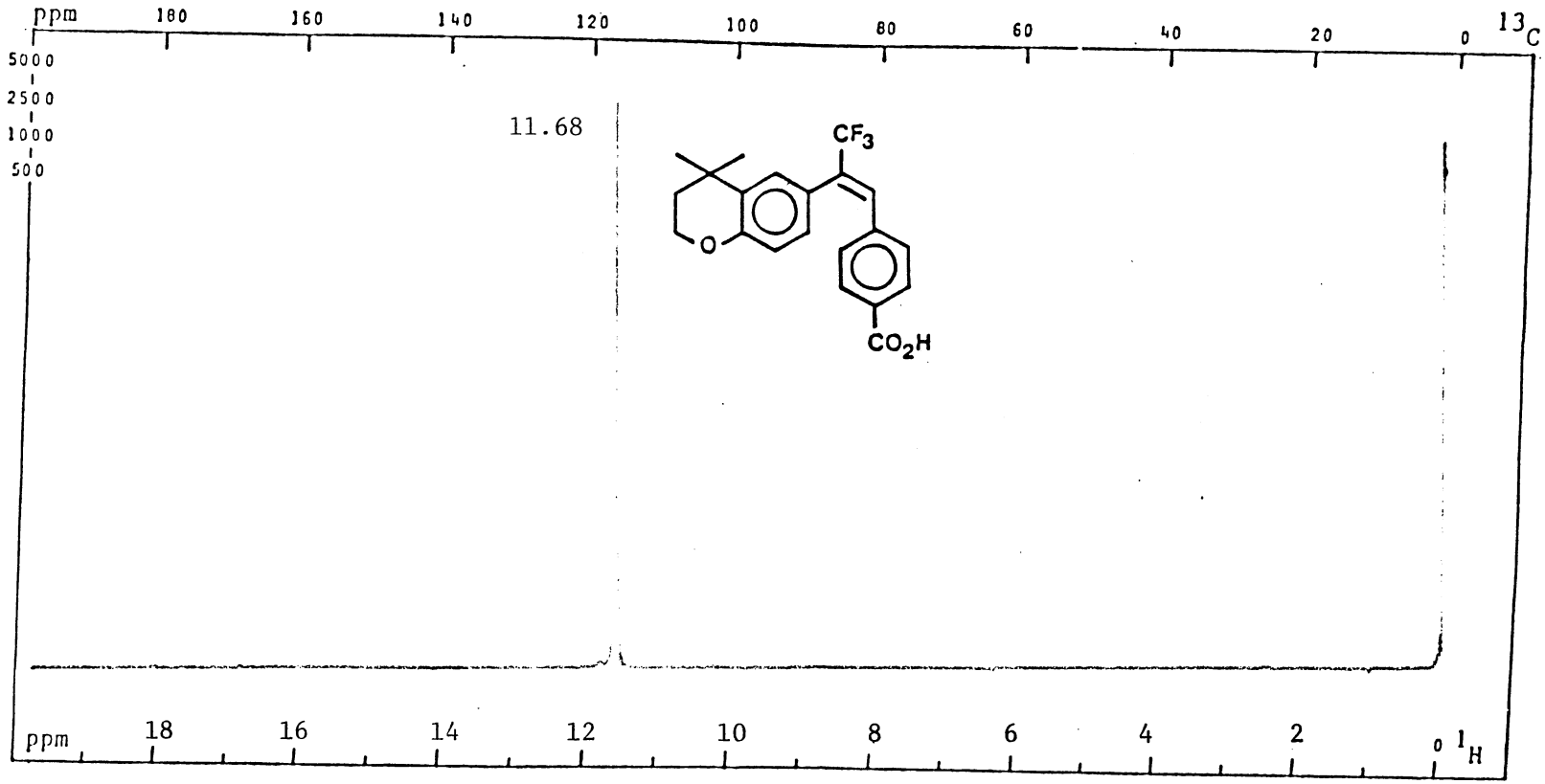
^{13}C NMR Spectrum of **50f**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 6064 .

Size: 20 K; PW/RF: 12.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 9.0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

PLATE LXXV



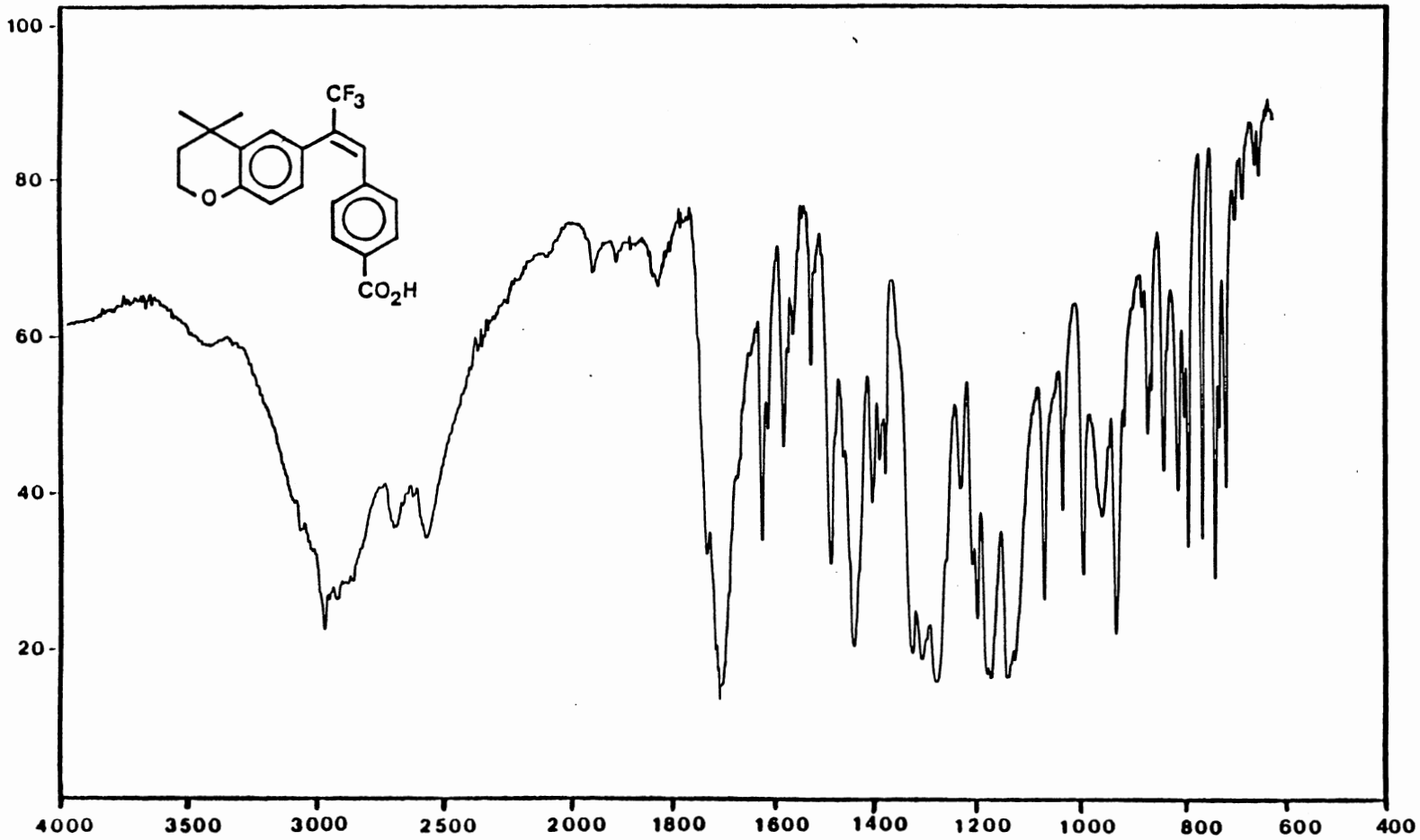
^{19}F NMR Spectrum of **50f**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 282.203 MHz; WC: 5644.0 Hz; T: RT °C; NT: 8 .

Size: 2560K; PW/RF: 7.0 μs/dB; TO: Hz; FB: - Hz; Lock: ; D1,D5: 2.0 s.

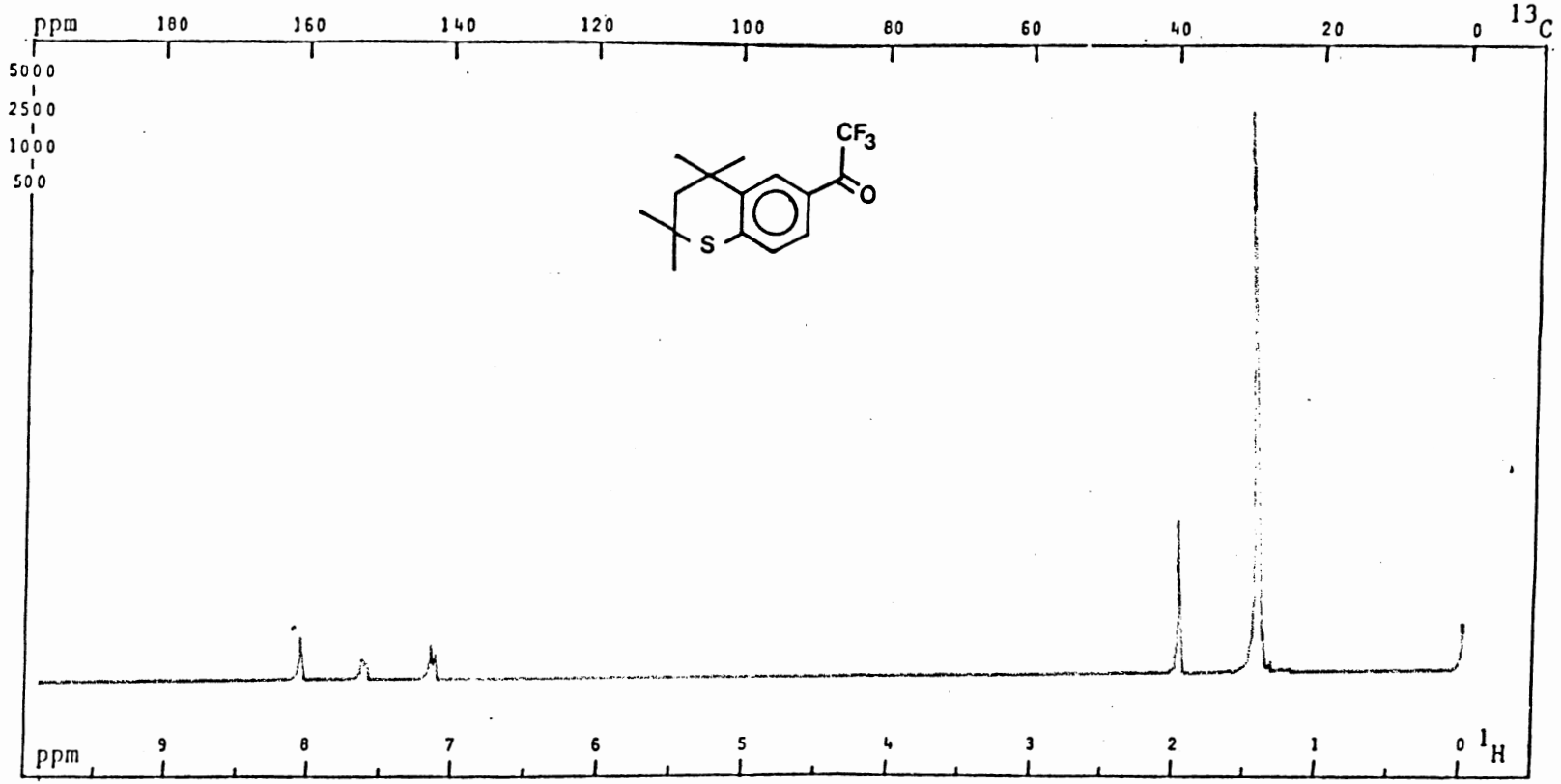
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): W/dB; NBW: Hz; LB: 2.0 Hz.

PLATE LXXVI



IR Spectrum of **50f**

PLATE LXXVII



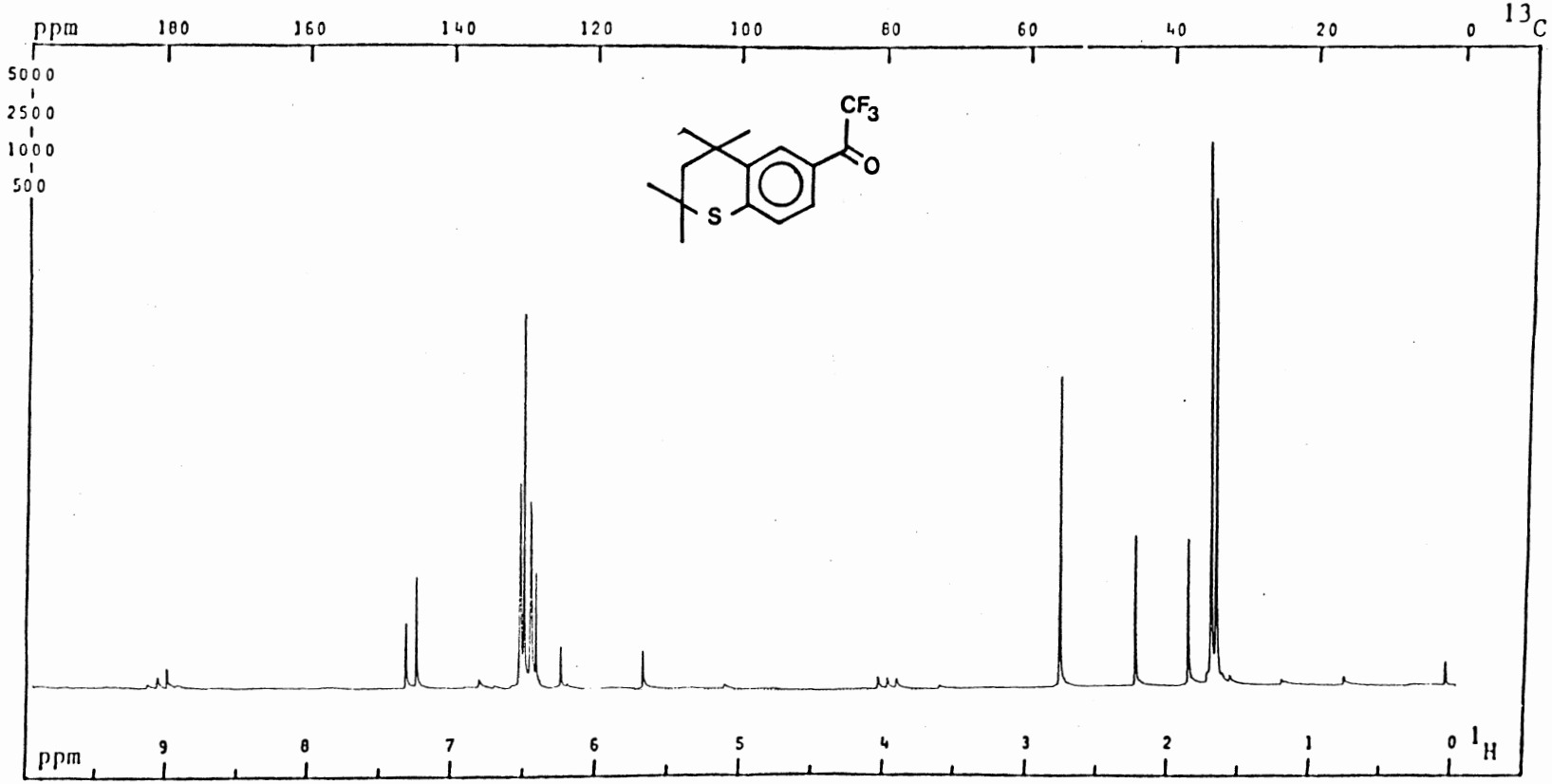
^{1}H NMR Spectrum of **85**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 8 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE LXXVIII



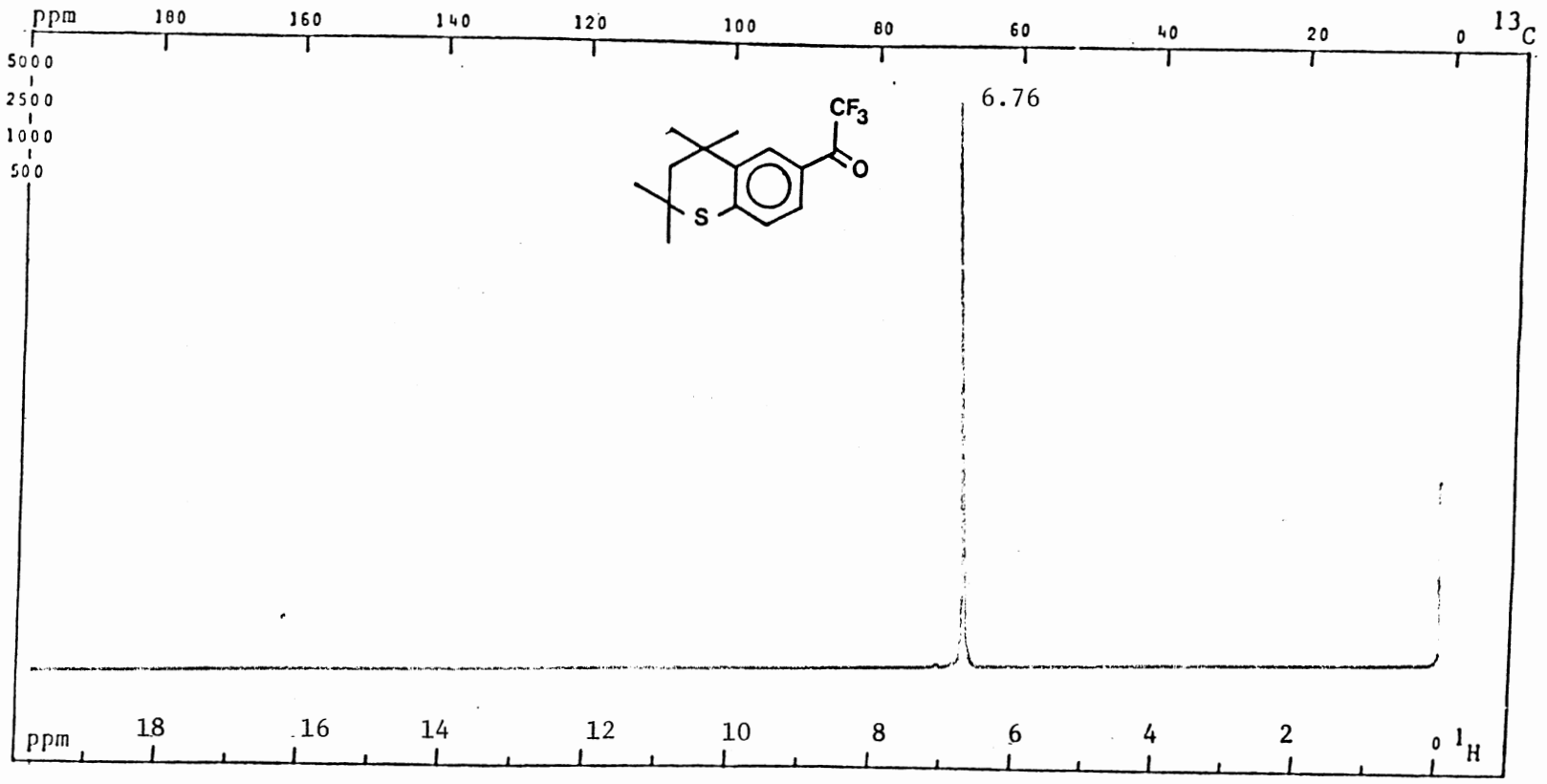
^{13}C NMR Spectrum of **85**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC:15085.9 Hz; T: RT °C; NT: 300 .

Size: 20 K; PW/RF: 8.0 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.0 s.

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

PLATE LXXIX



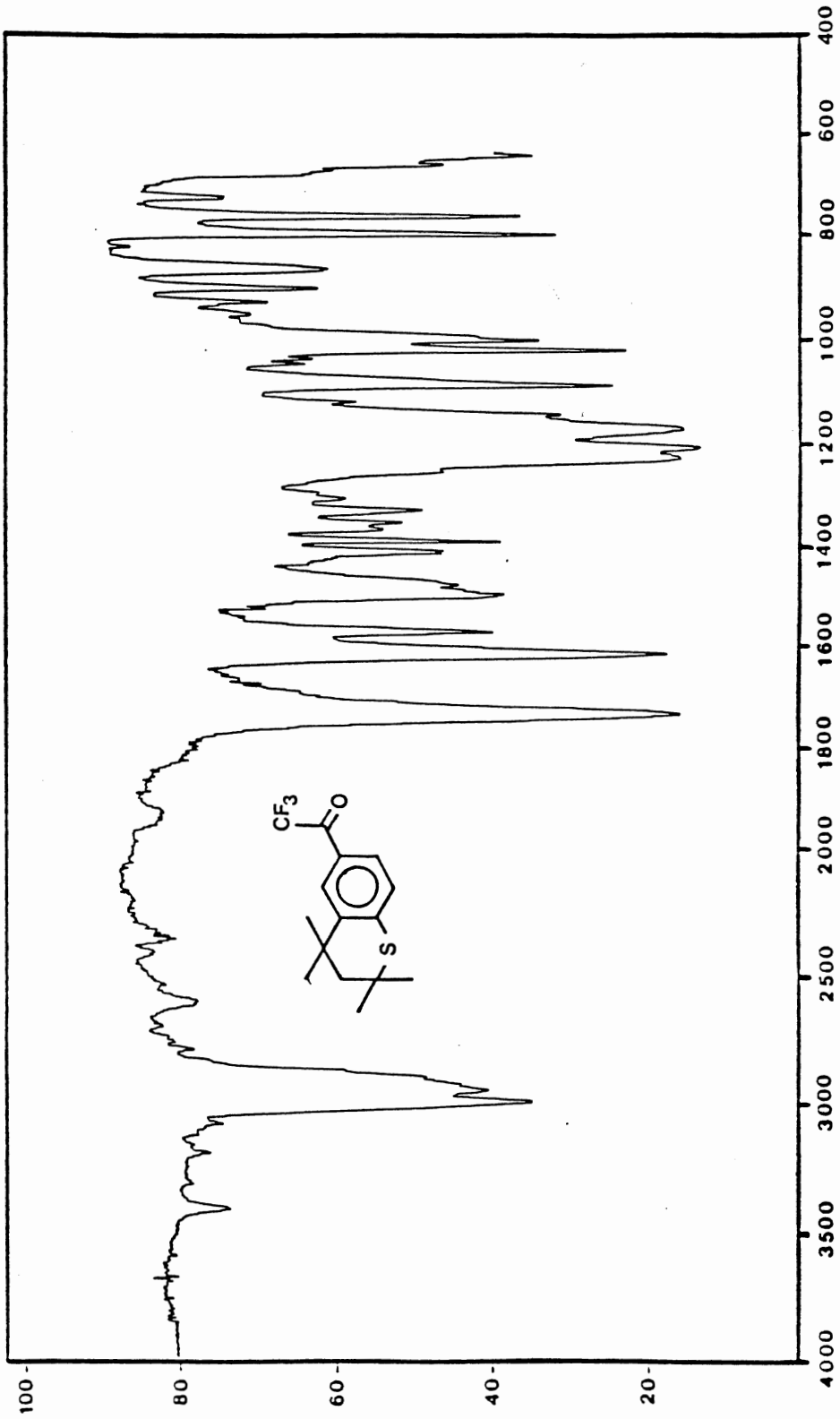
^{19}F NMR Spectrum of **85**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 282.203 MHz; WC: 5644.1 Hz; T: RT °C; NT: 8.0 .

Size: 2.5 K; PW/RF: 7.0 µs/dB; TO: Hz; FB: - Hz; Lock: ; D1,D5: 2.0 s.

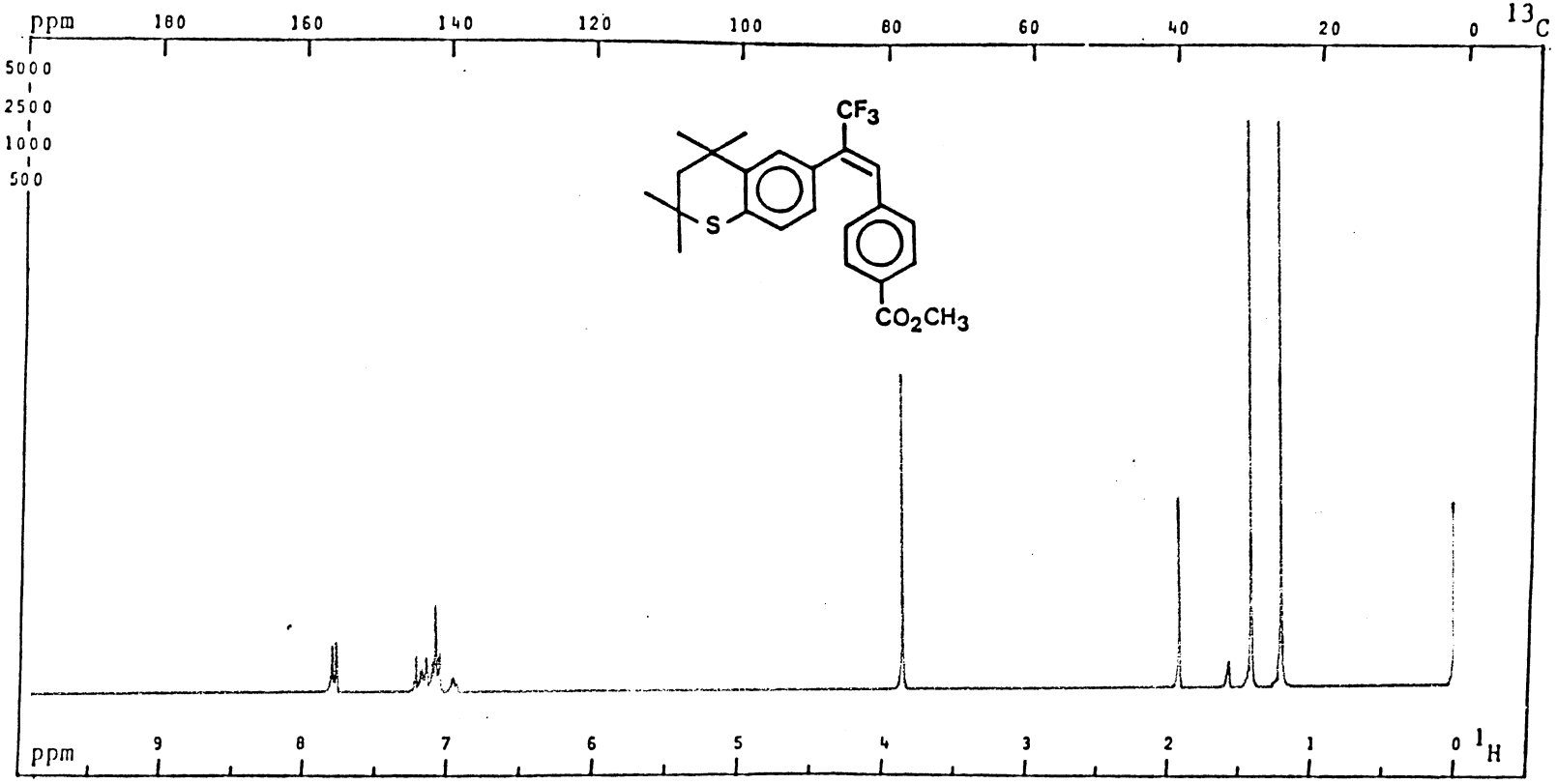
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): W/dB; NBW: Hz; LB: 2.0 Hz.

PLATE LXXX



IR Spectrum of 85

PLATE LXXXI



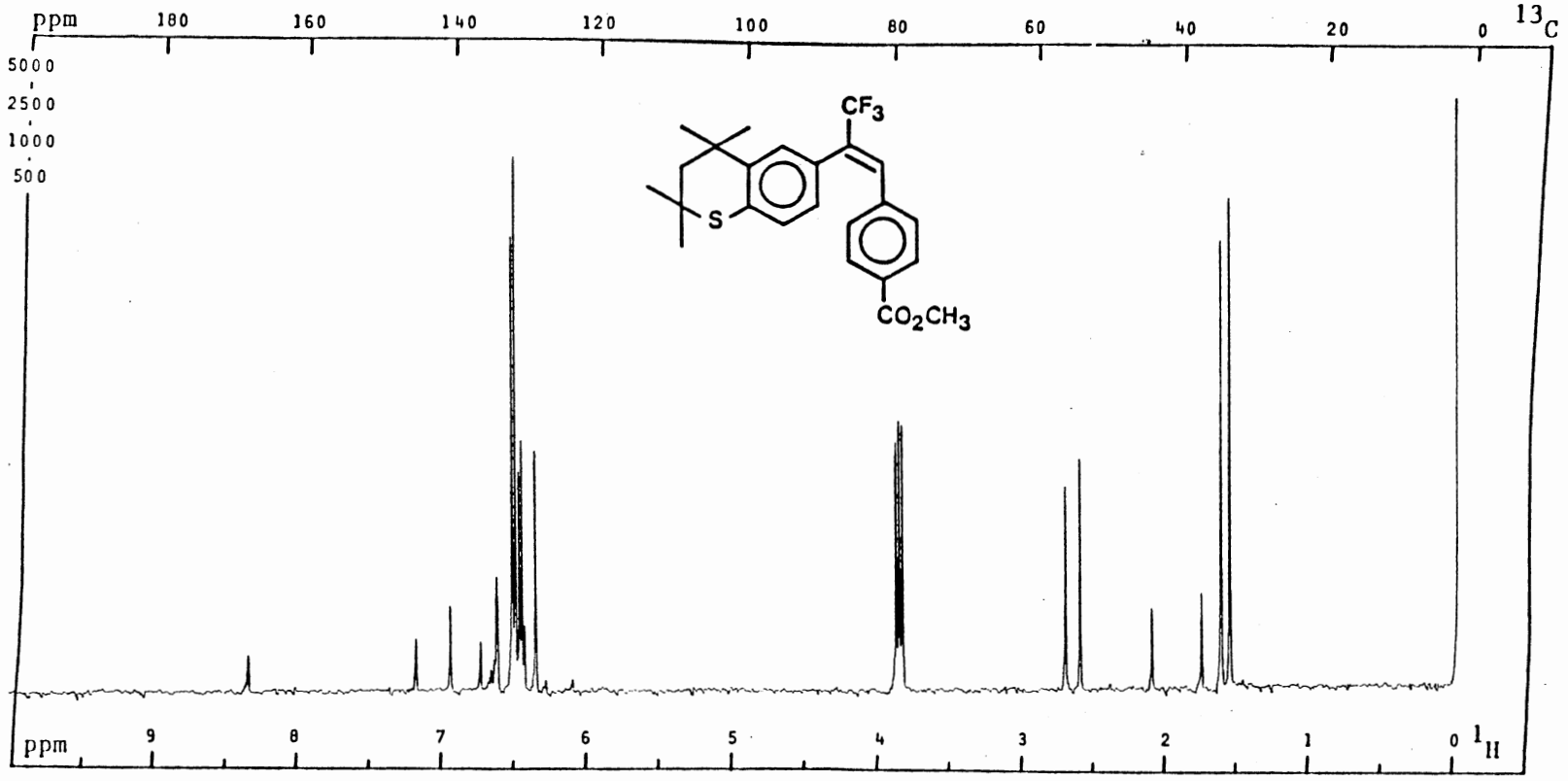
^{1}H NMR Spectrum of **50c**

PFT X CW _ ; Solvent: $DCCl_3$; SF:299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 12 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE LXXXII



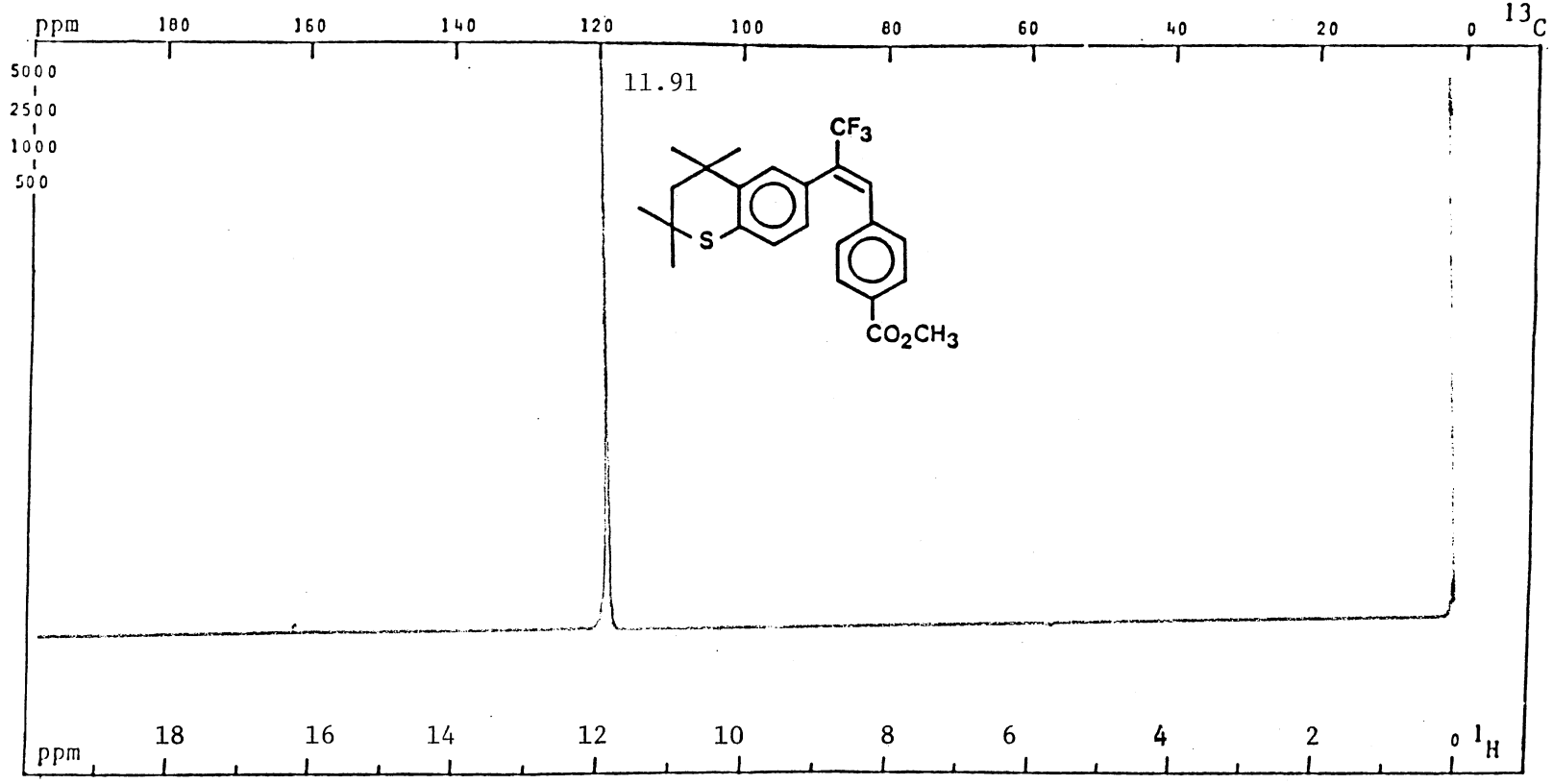
^{13}C NMR Spectrum of **50c**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 6064 .

Size: 20 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 9.0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 10 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

PLATE LXXXIII



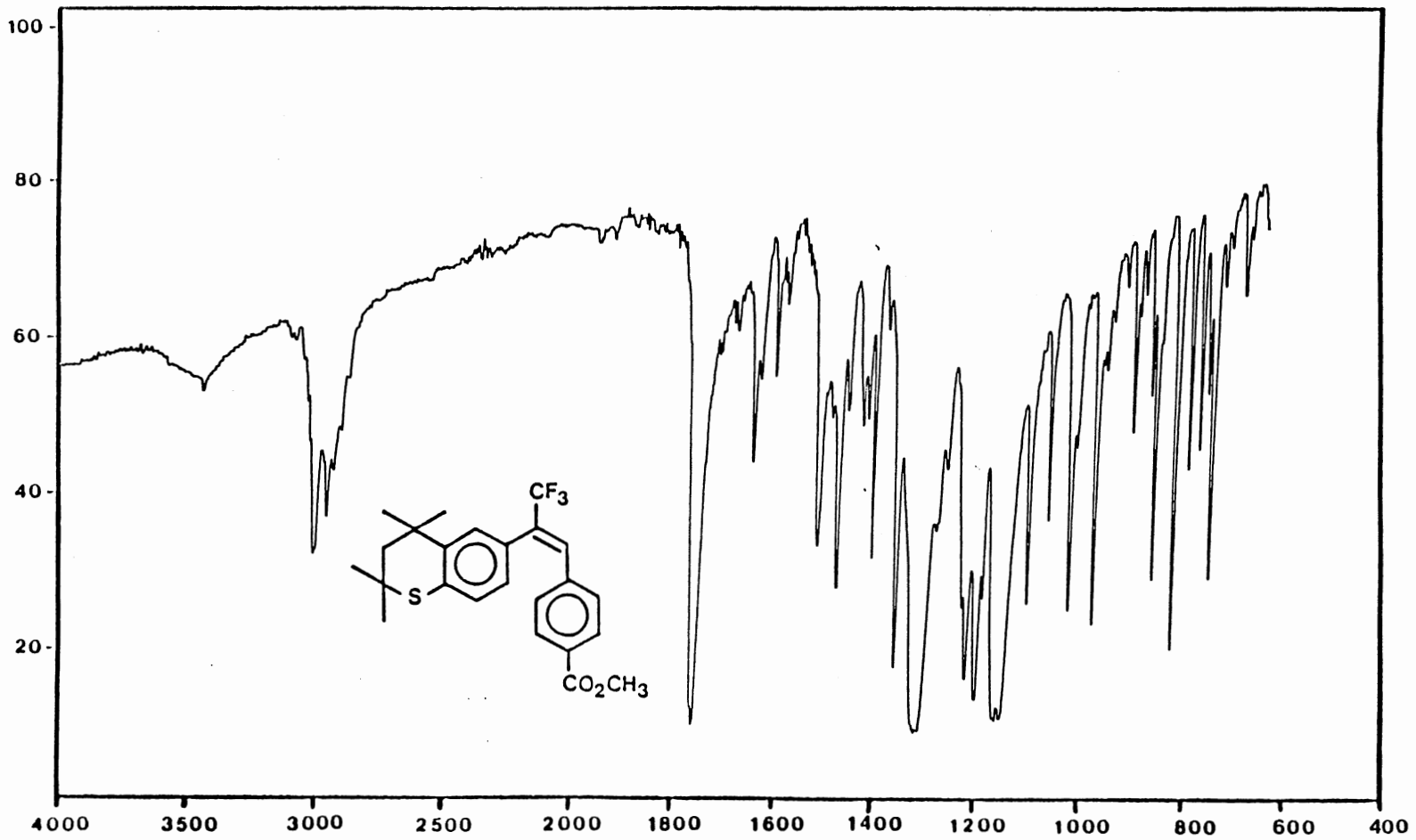
^{19}F NMR Spectrum of **50c**

PFT _X_ CW _ ; Solvent: $DCCl_3$; SF: 282.203 MHz; WC: 5644.1 Hz; T: RT °C; NT: 12

Size: 2.5K; PW/RF: 7.0 μs/dB; TO: Hz; FB: - Hz; Lock: ; D1,D5: 2.0 s.

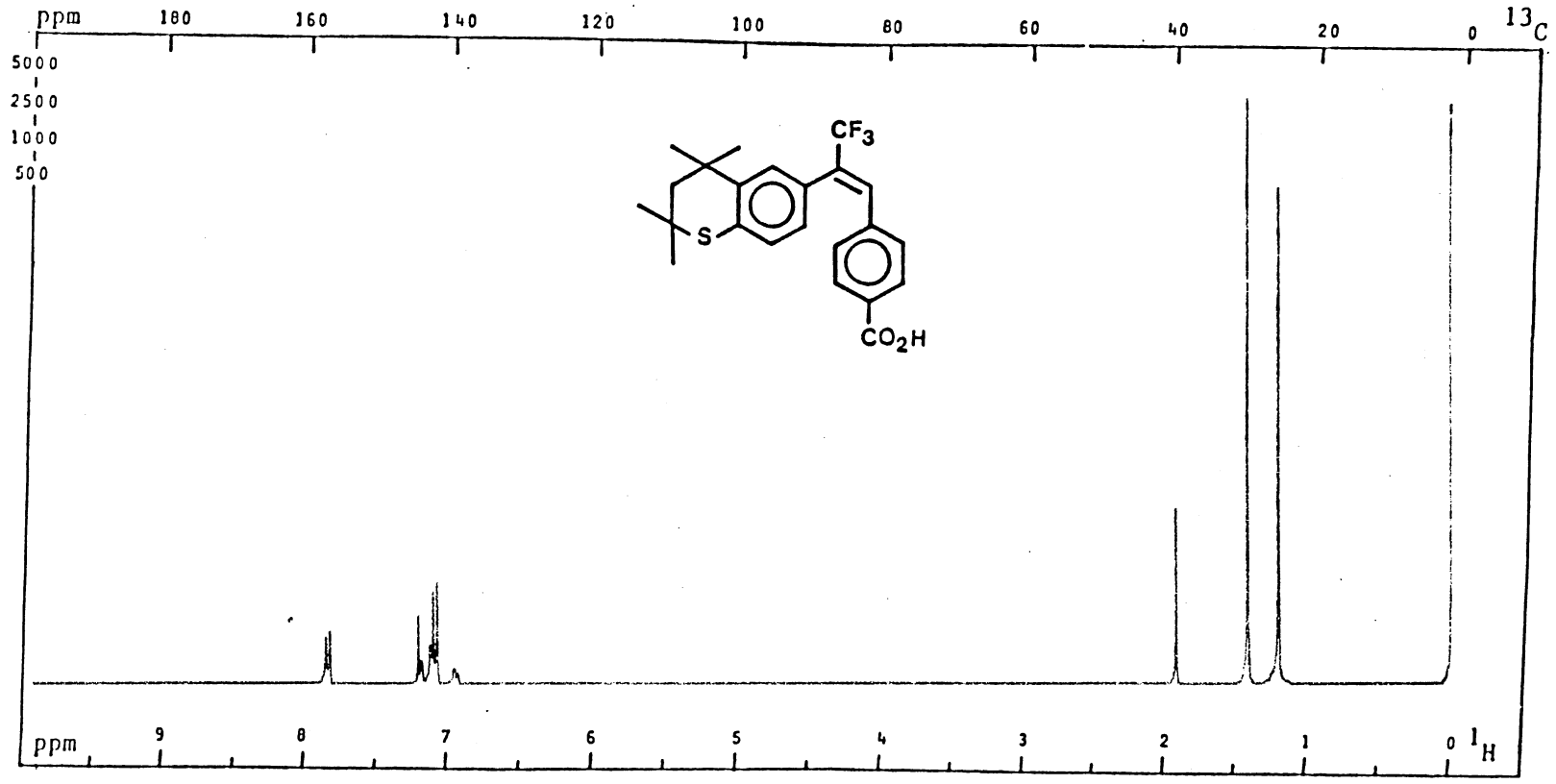
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): W/dB; NBW: Hz; LB: 2.0 Hz.

PLATE LXXXIV



IR Spectrum of **50c**

PLATE LXXXV



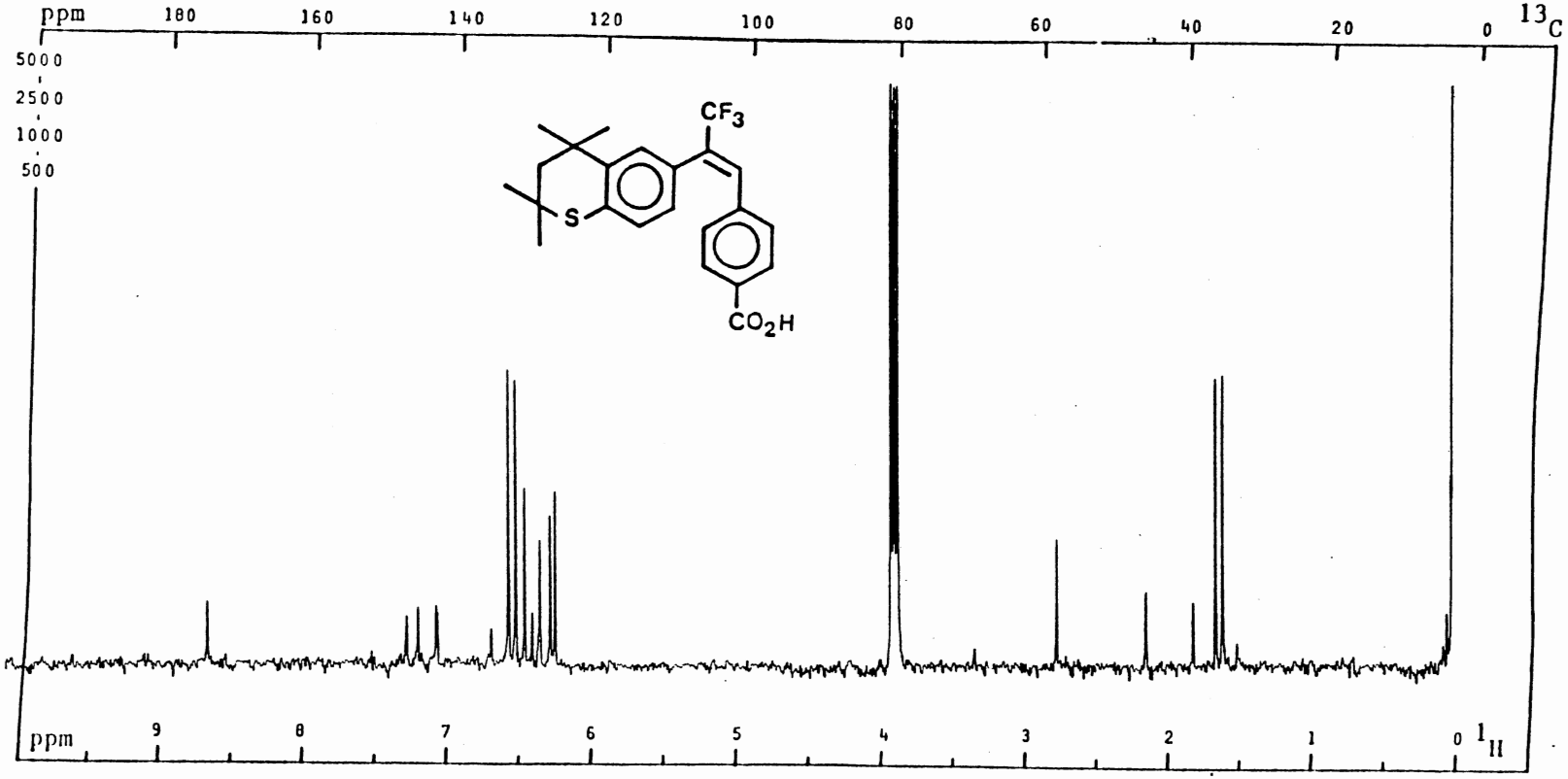
^{1}H NMR Spectrum of **50d**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 16 K; PW/RF: 6.0 μs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE LXXXVI



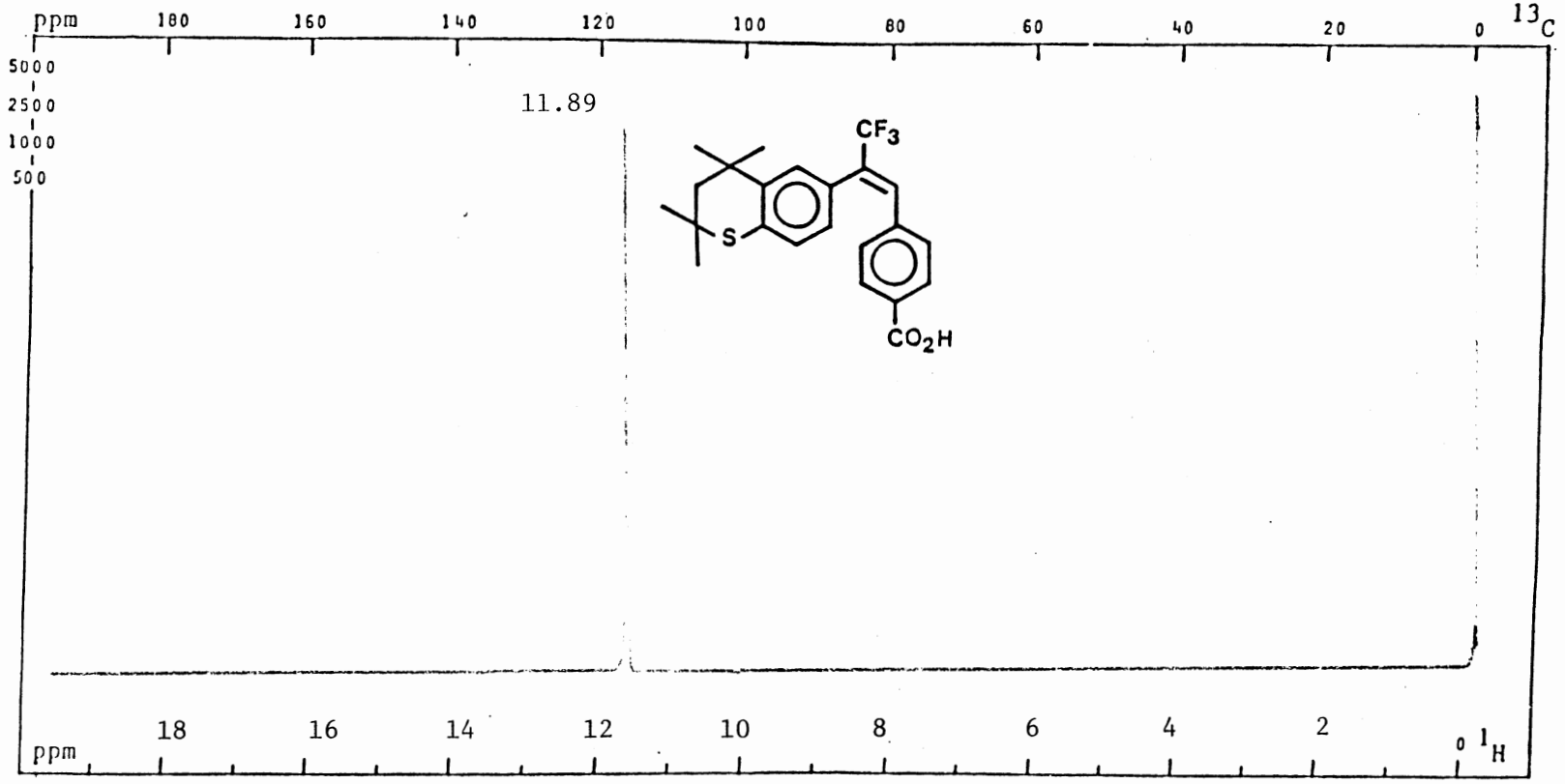
^{13}C NMR Spectrum of **50d**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 6064 .

Size: 20 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 9.0 s.

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

PLATE LXXXVII



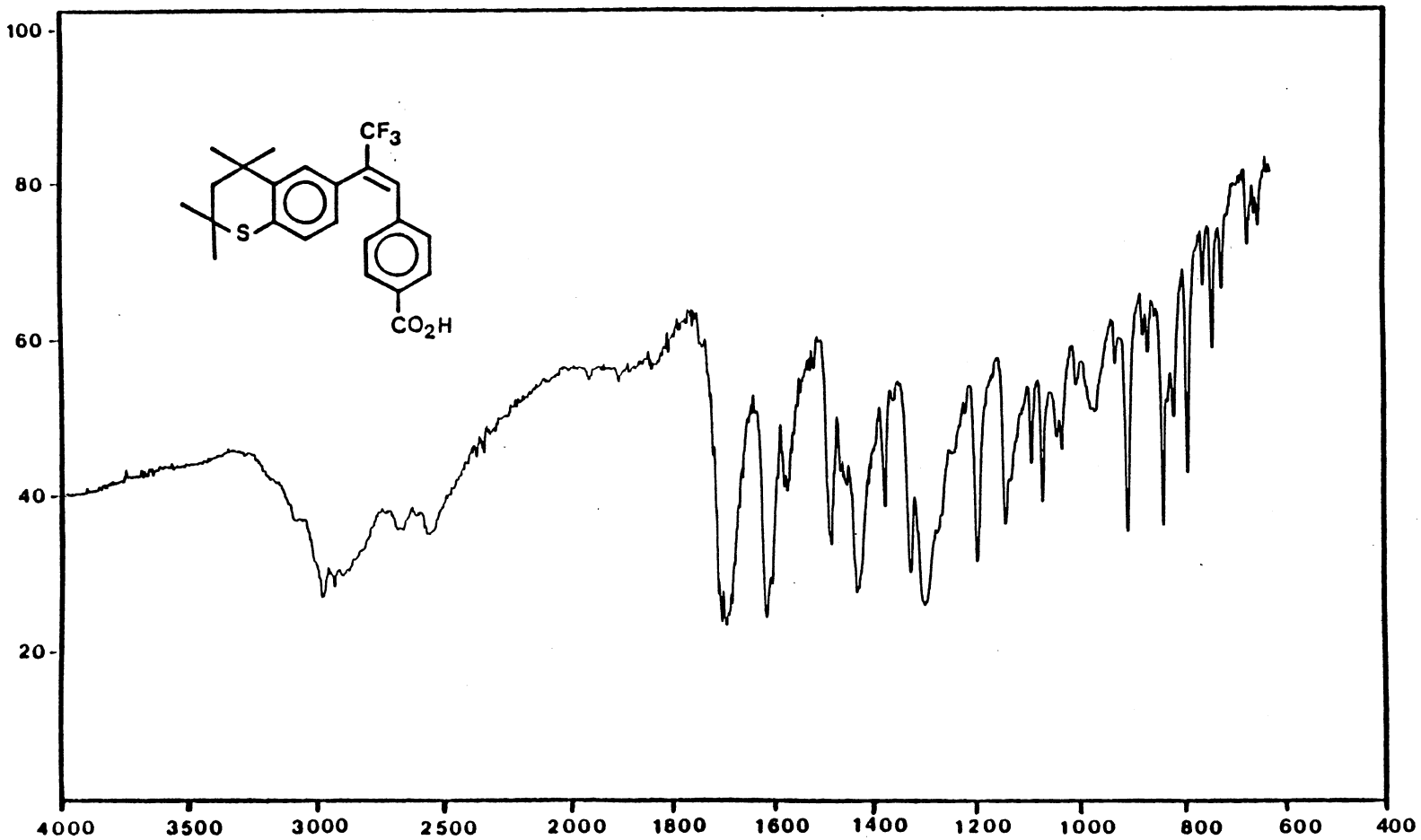
^{19}F NMR Spectrum of **50d**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 282.203 MHz; WC: 5644.1 Hz; T: RT °C; NT: 8 .

Size: 2.5 K; PW/RF: 7.0 µs/dB; TO: Hz; FB: - Hz; Lock: ; D1,D5: 2.0 s.

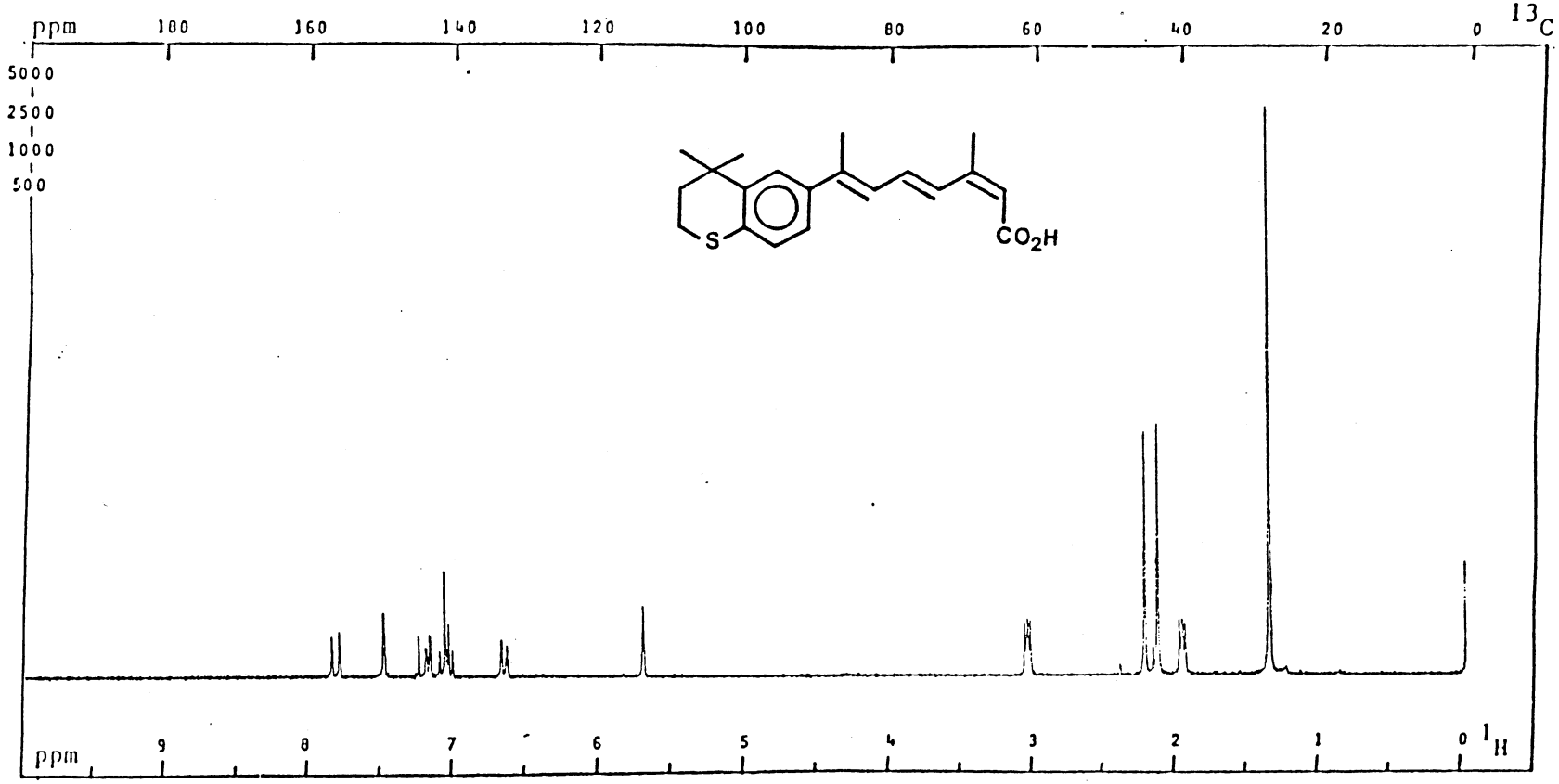
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): W/dB; NBW: Hz; LB: 2.0 Hz.

PLATE LXXXVIII



IR Spectrum of **50d**

PLATE LXXXIX



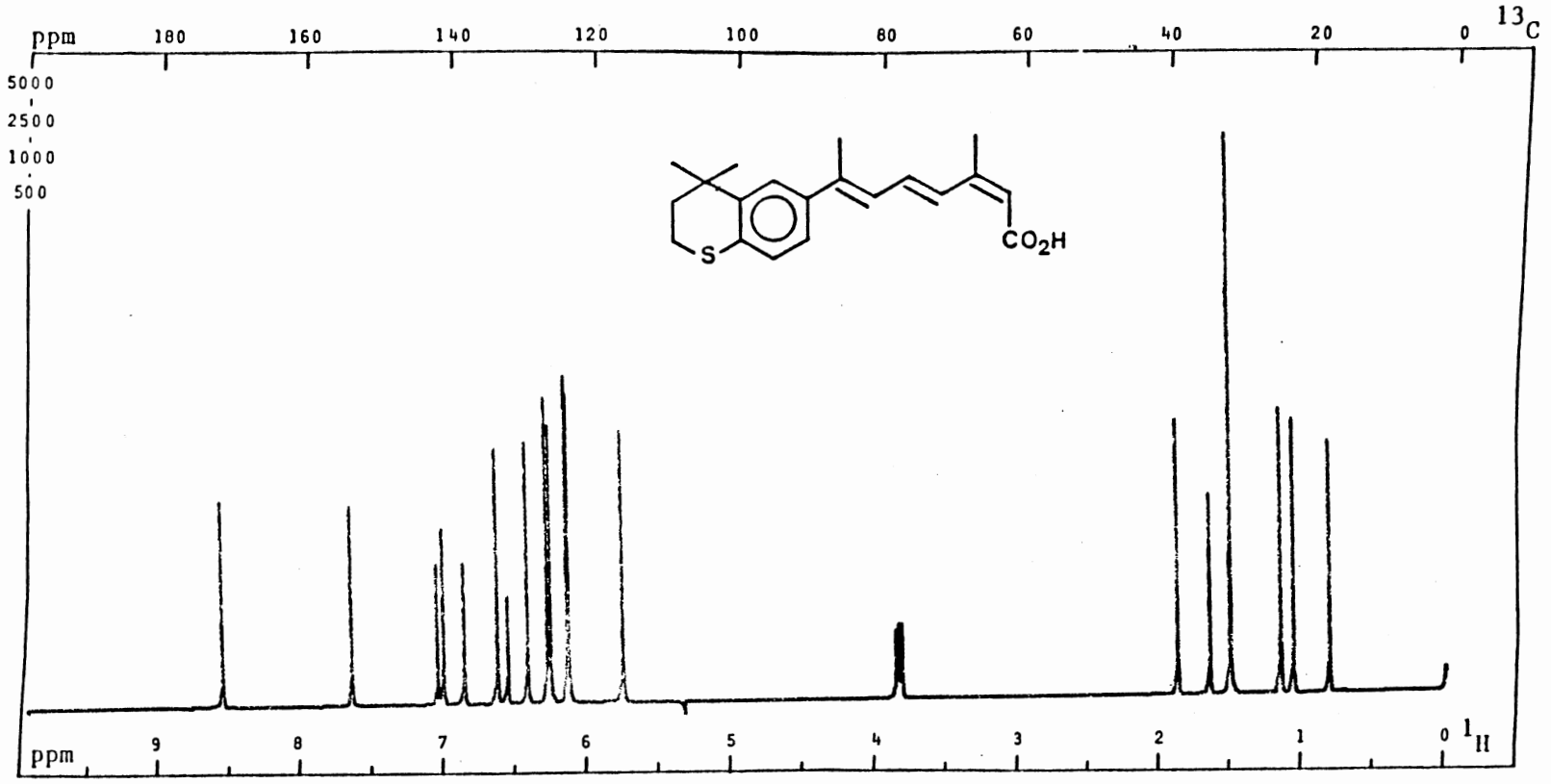
^{1}H NMR Spectrum of **48f**

PFT _ X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8

Size: 32 K; PW/RF: 5.0 μs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE LXXXX



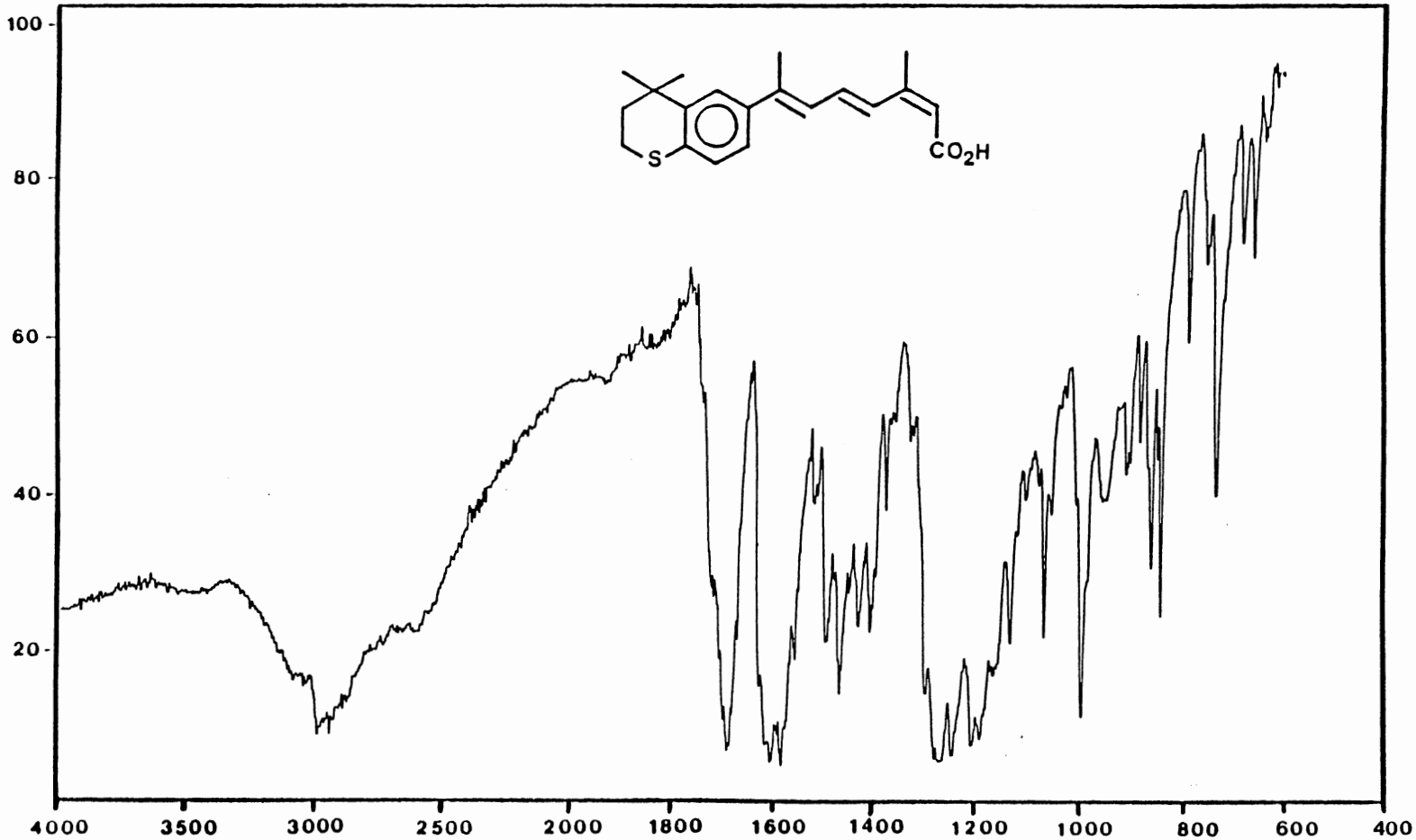
^{13}C NMR Spectrum of **48f**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9Hz; T: RT °C; NT: 5600 .

Size: 20 K; PW/RF: 14 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.0 s.

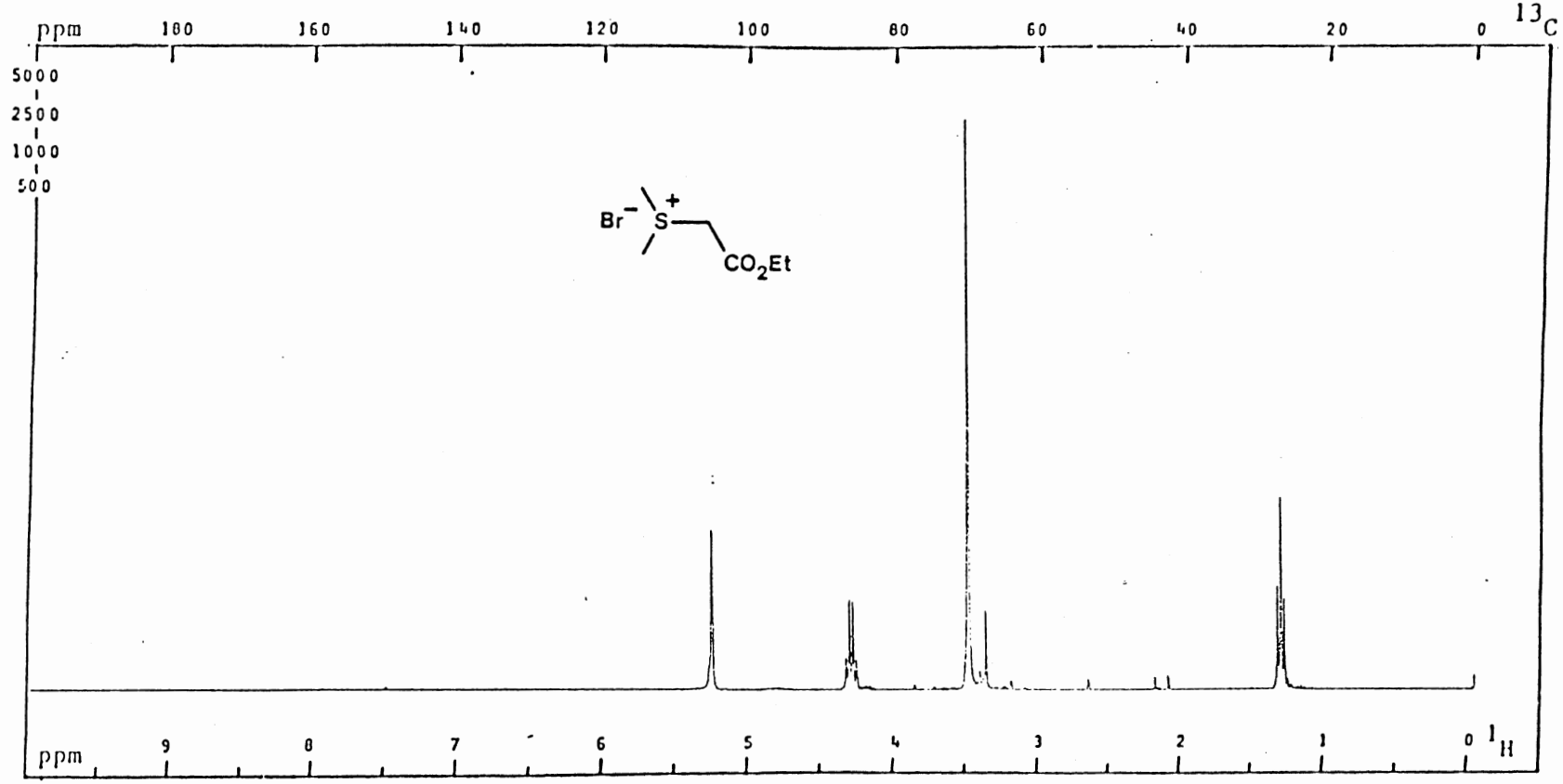
DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: - Hz.

PLATE LXXXXI



IR Spectrum of **48f**

PLATE LXXXXII



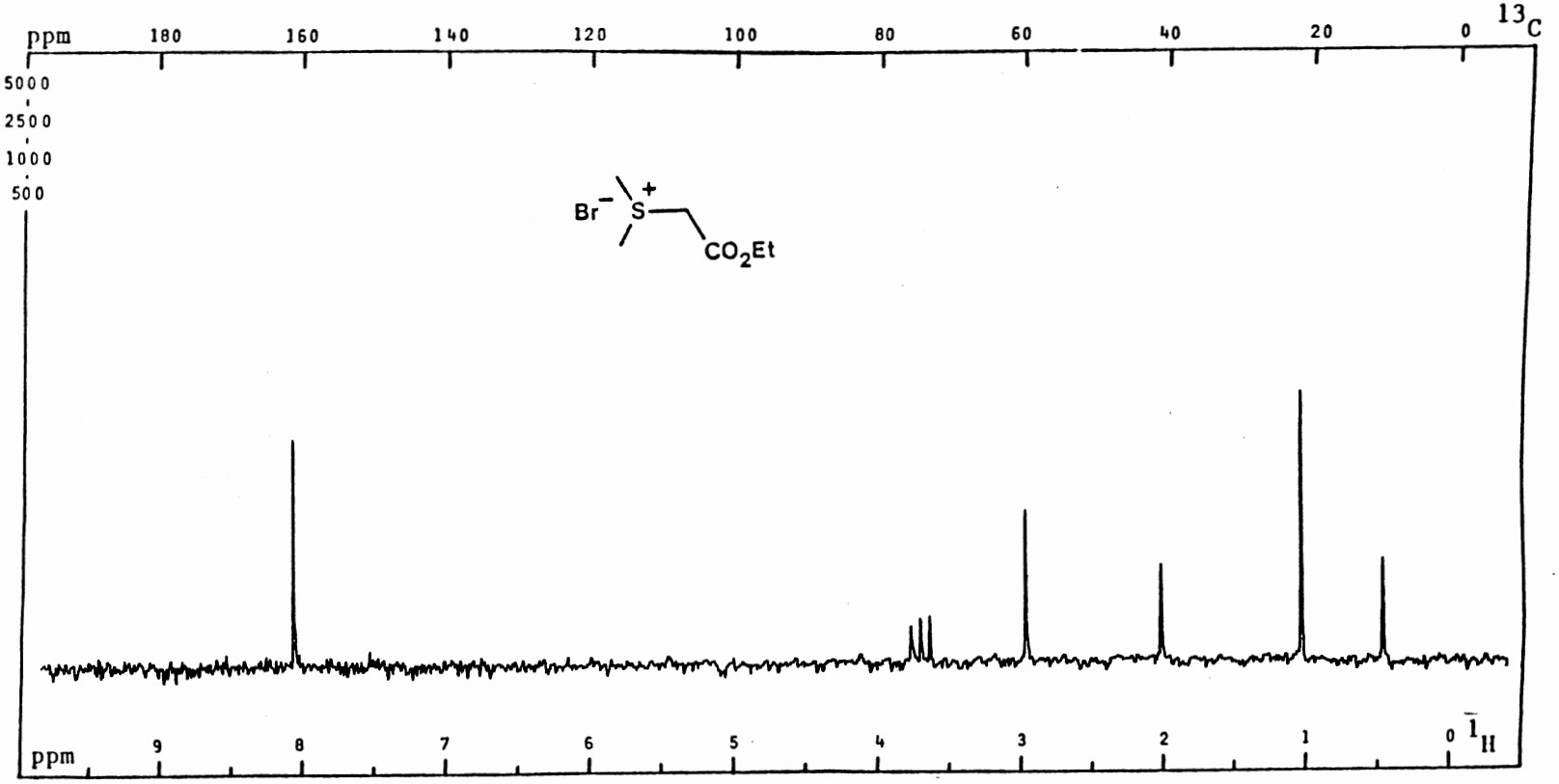
^{1}H NMR Spectrum of **72**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8

Size: 16 K; PW/RF: 6.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE LXXXXIII



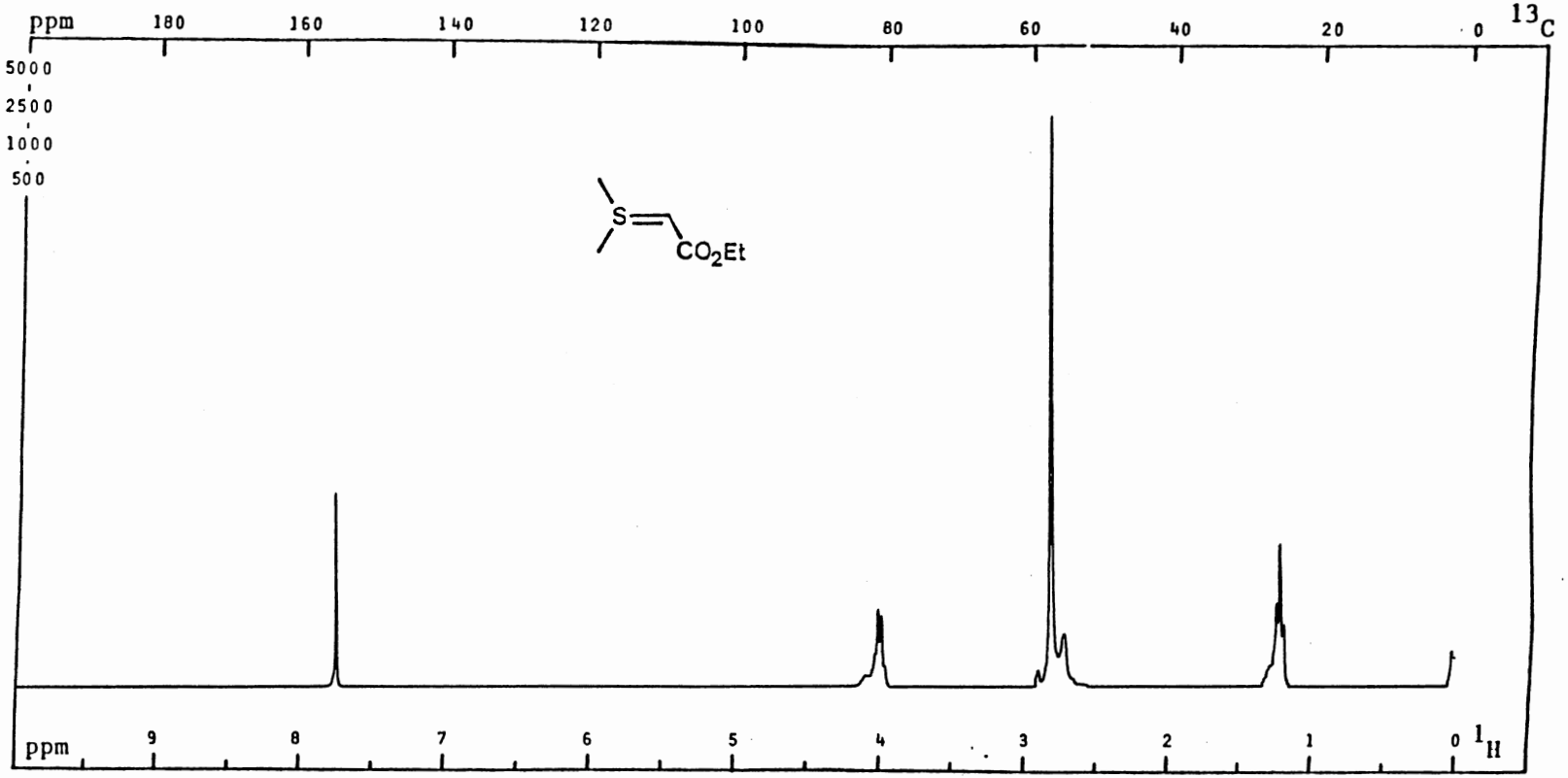
^{13}C NMR Spectrum of **72**

PFT _X_ CW _ ; **Solvent:** $DCCl_3$; **SF:** 75.429 **MHz; WC:** 15085.9 **Hz; T:** RT **°C; NT:** 100

Size: 8 **K; PW/RF:** 12 **µs/dB; TO:** 1000 **Hz; FB:** - **Hz; Lock:** ^2H **; D1,D5:** 4.0 **s.**

DC: Y, N ; Gated Off:A or D ; DO: 0 **Hz; RF(Power):** 20 **W/dB; NBW:** 200 **Hz; LB:** 4.0 **Hz.**

PLATE LXXXXIV



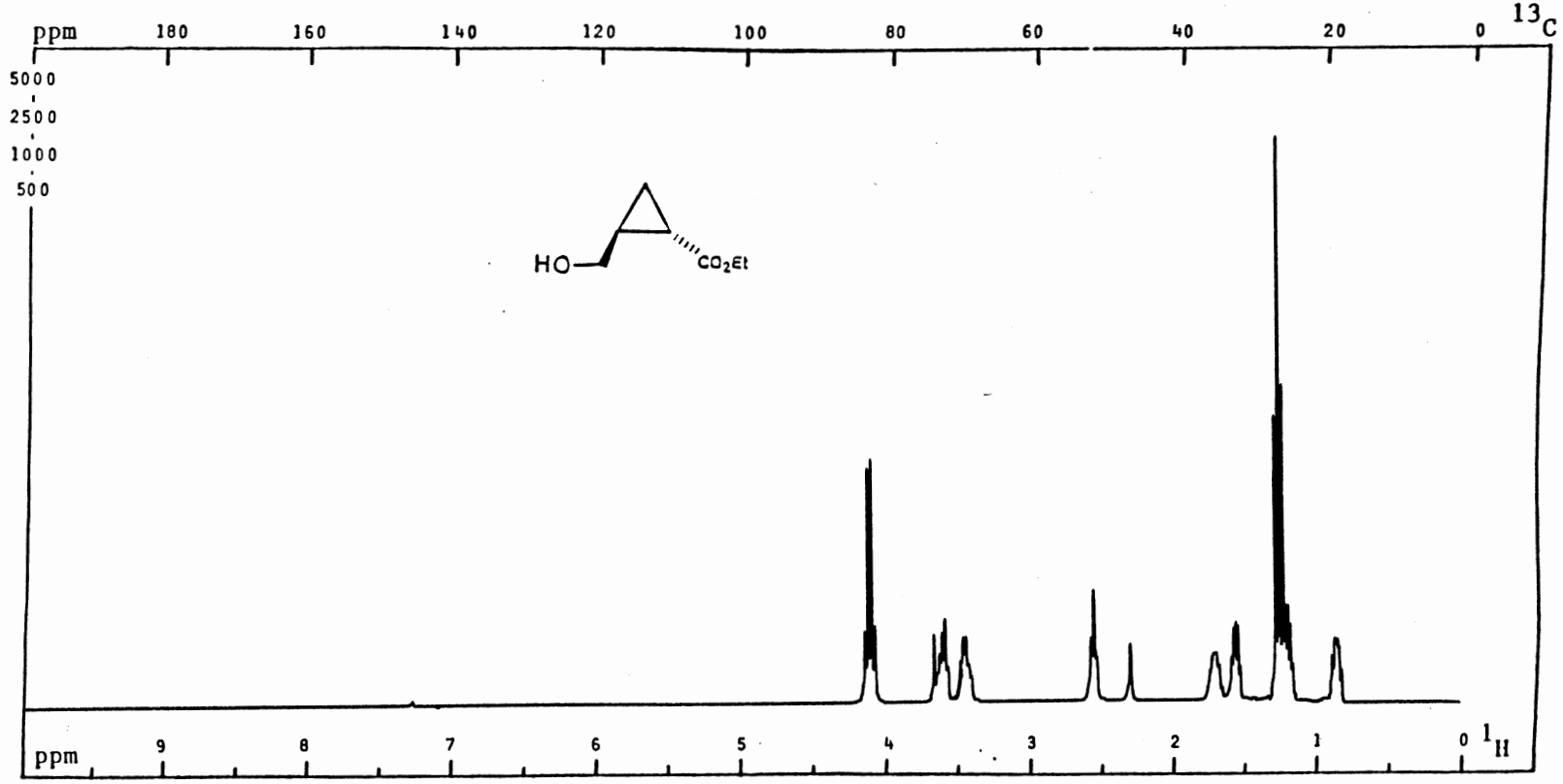
^{1}H NMR Spectrum of **73**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485MHz; WC:2999.4 Hz; T: RT °C; NT: 8 .

Size: 12 K; PW/RF: 8.0 μs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ;D1,D5: 0 s.

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

PLATE LXXXXV



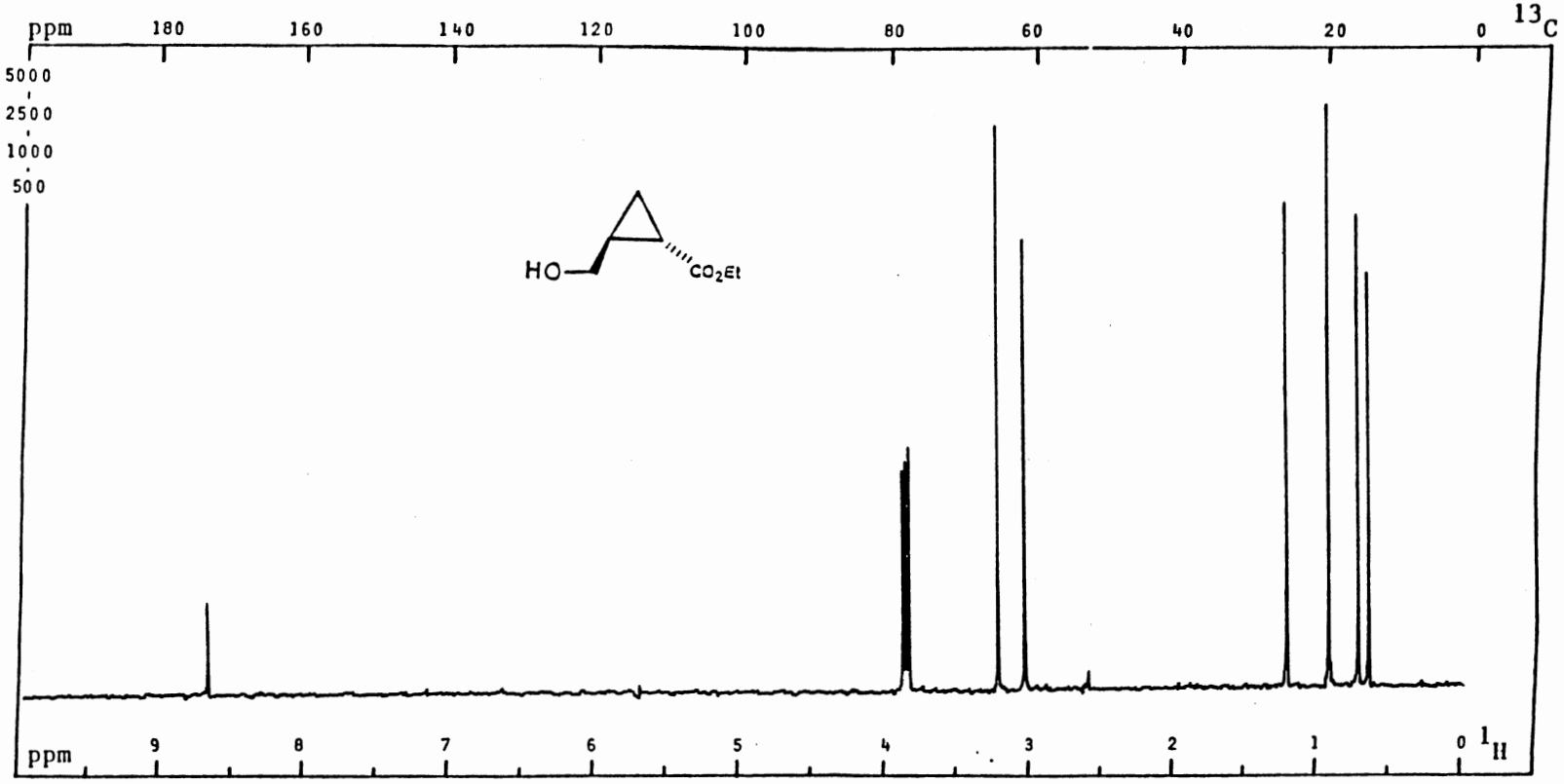
^{1}H NMR Spectrrum of **74**

PFT _X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 12 .

Size: 12 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ;D1,D5: 0 s.

DC: Y, N ; Gated Off:A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: 0 Hz; LB: 0.5 Hz.

PLATE LXXXXVI



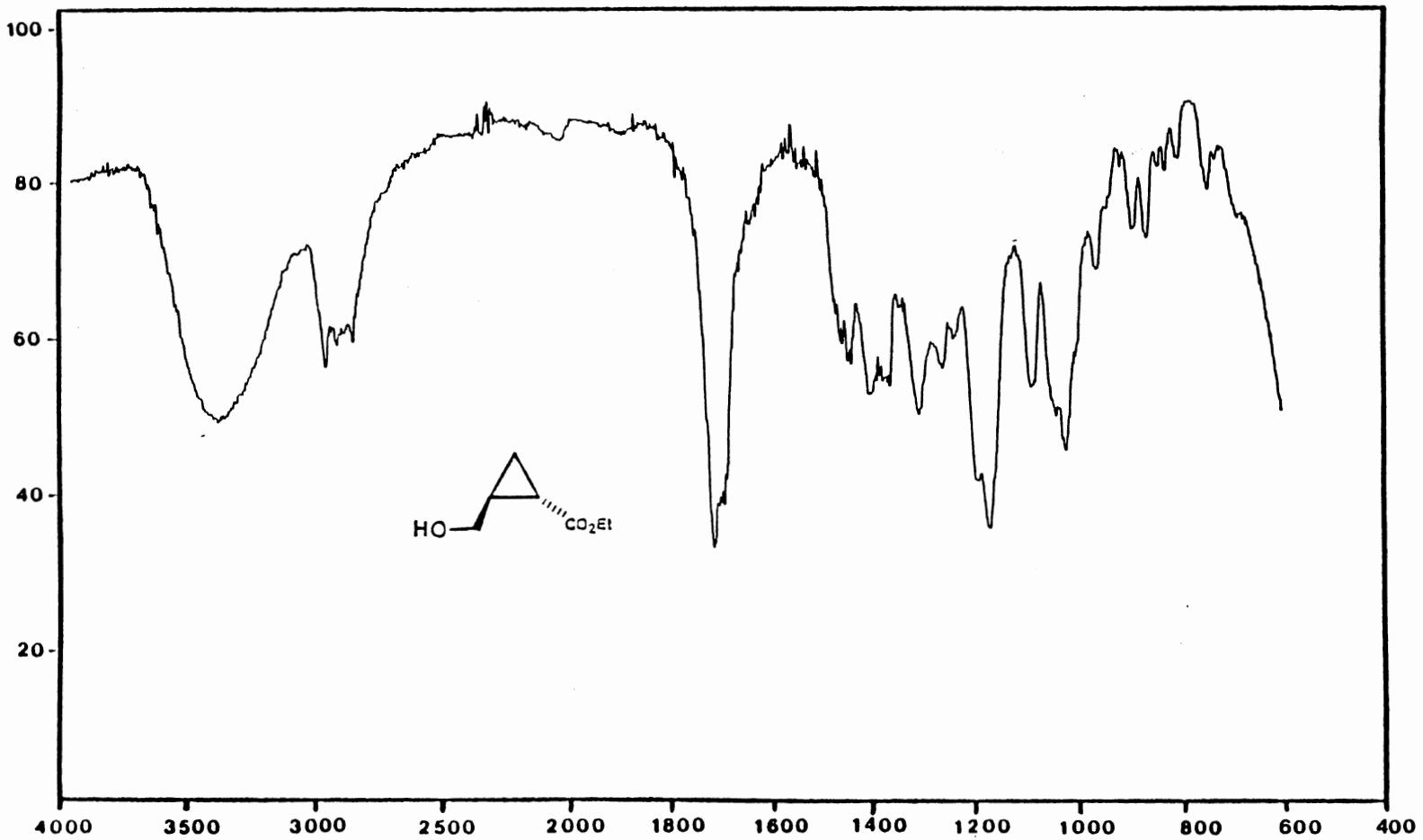
^{13}C NMR Spectrum of **74**

PFT _X_ CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 1000 .

Size: 20 K; PW/RF: 12 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 0 s.

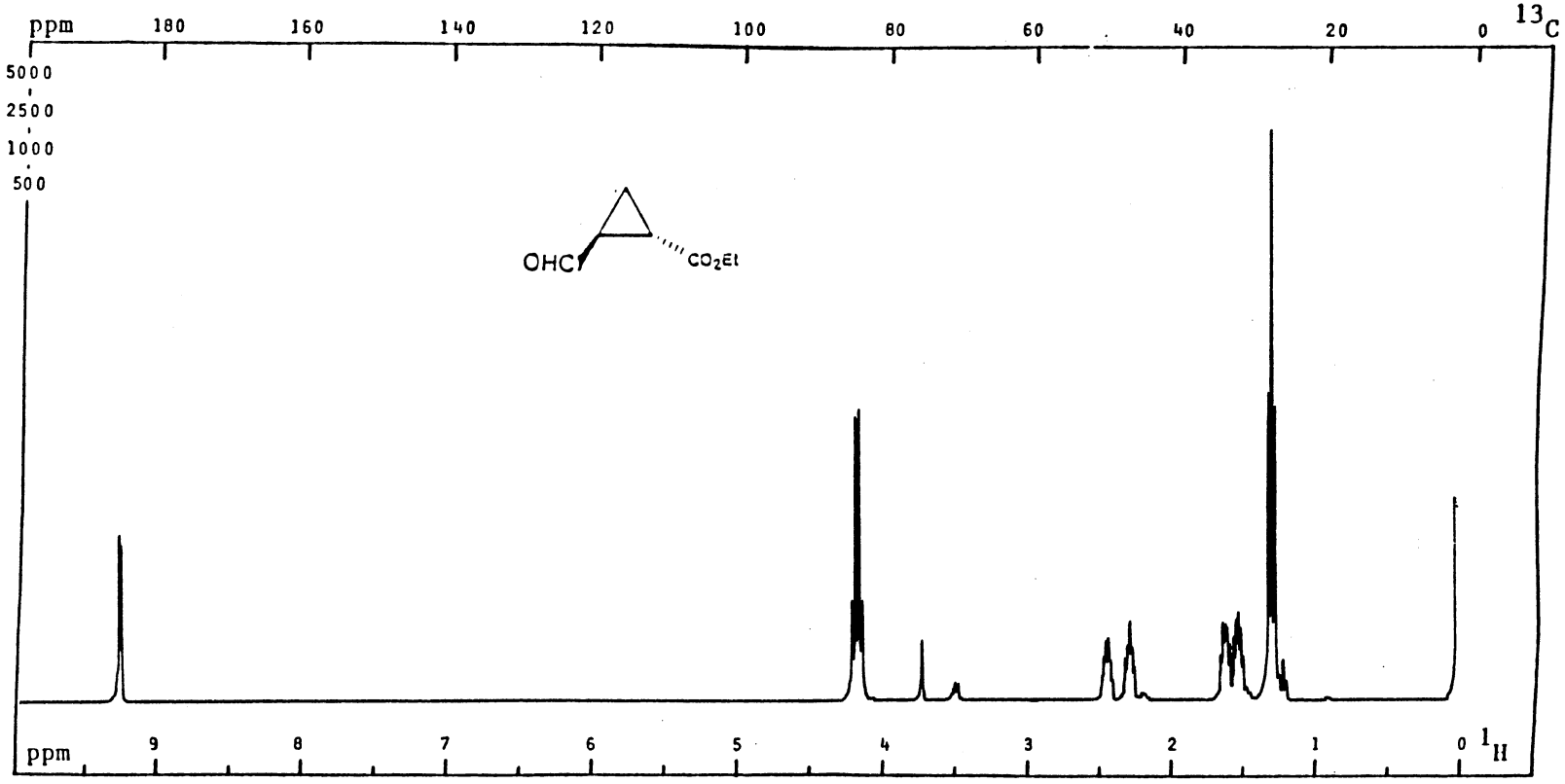
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 1.0 Hz.

PLATE LXXXXVII



IR Spectrum of 74

PLATE LXXXXVIII



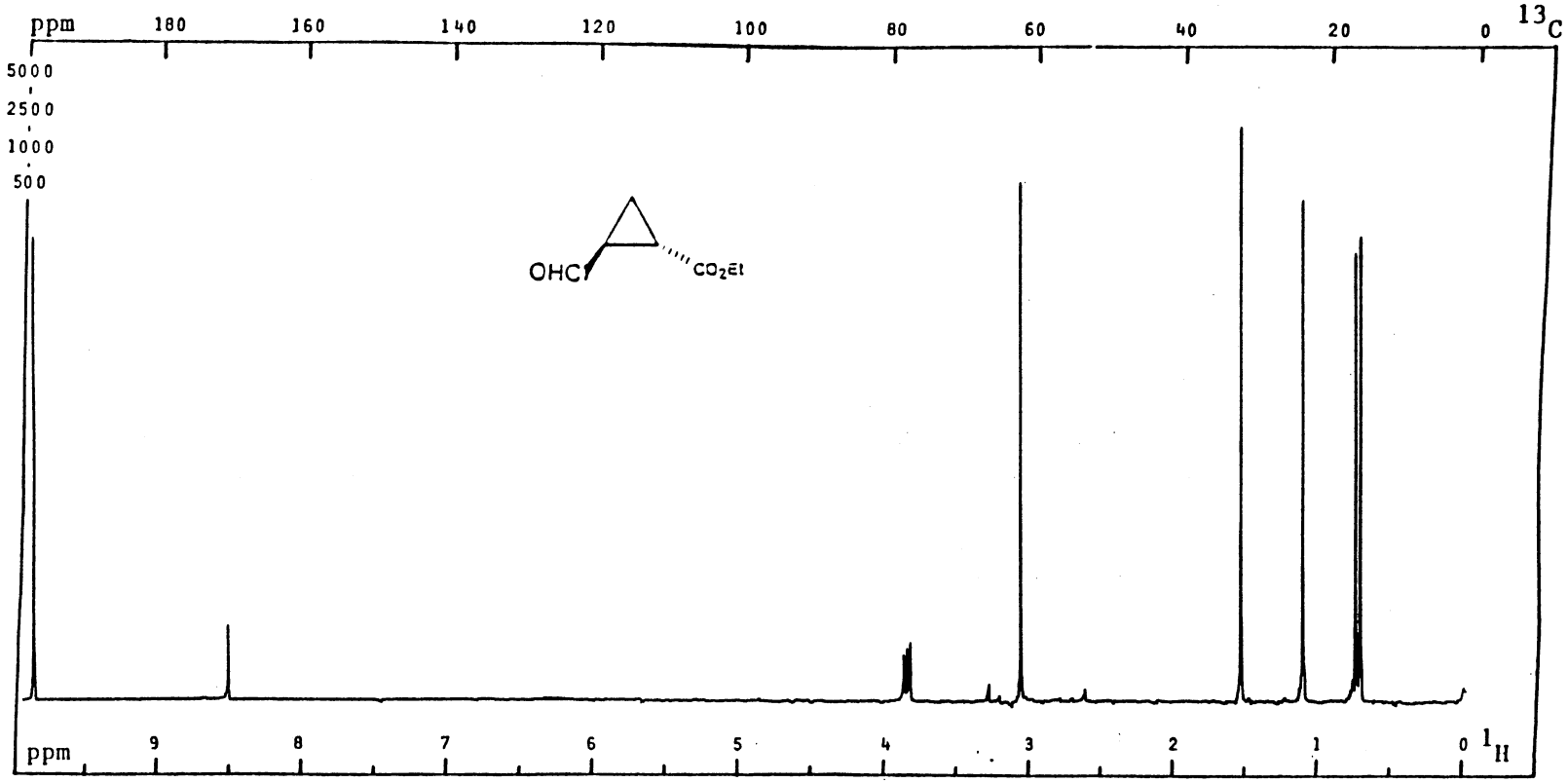
^{1}H NMR Spectrum of **67**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 12 .

Size: 12 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 15 W/dB; NBW: 0 Hz; LB: 0.5 Hz.

PLATE IC



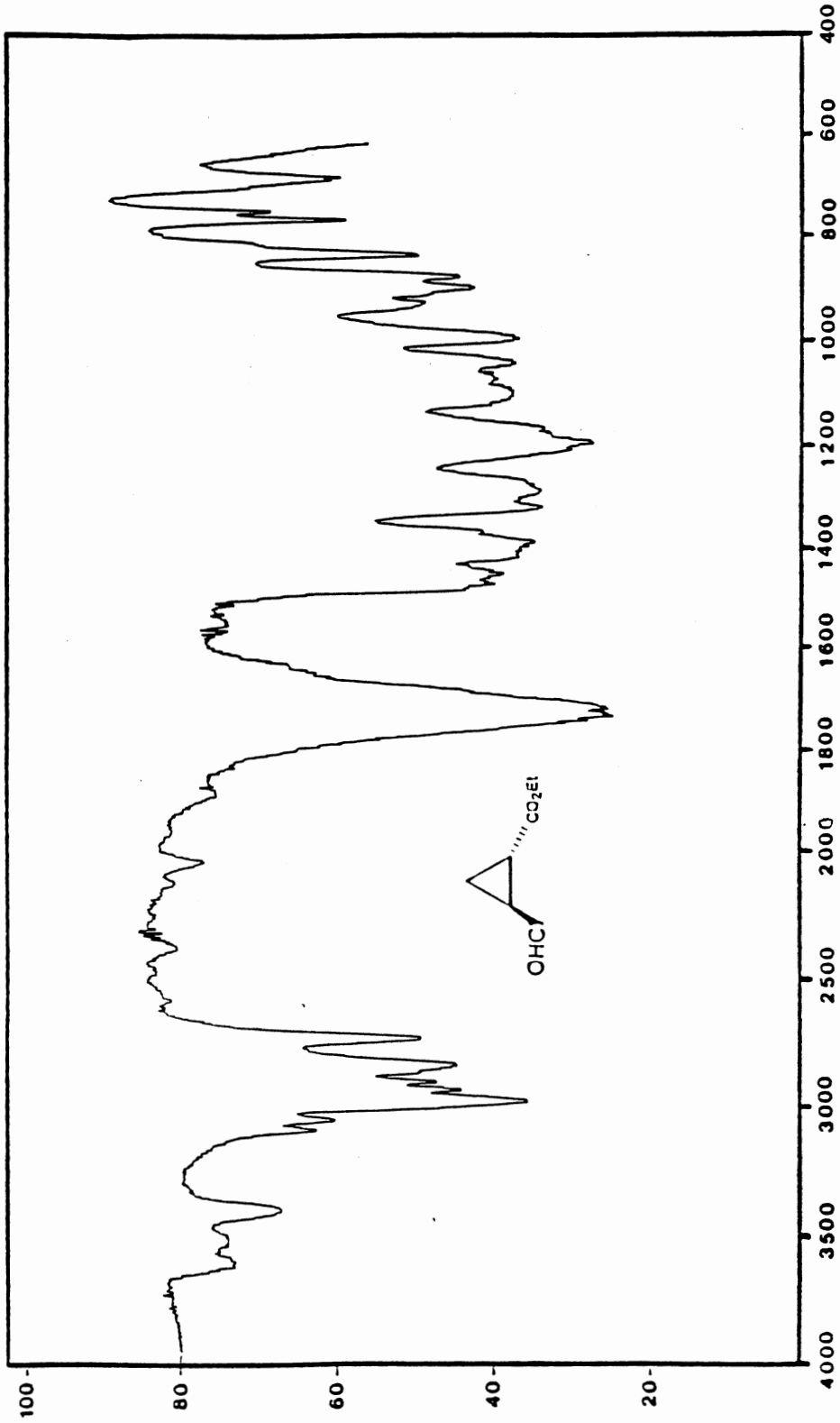
^{13}C NMR Spectrum of **67**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 600 .

Size: 16 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 4.0 s.

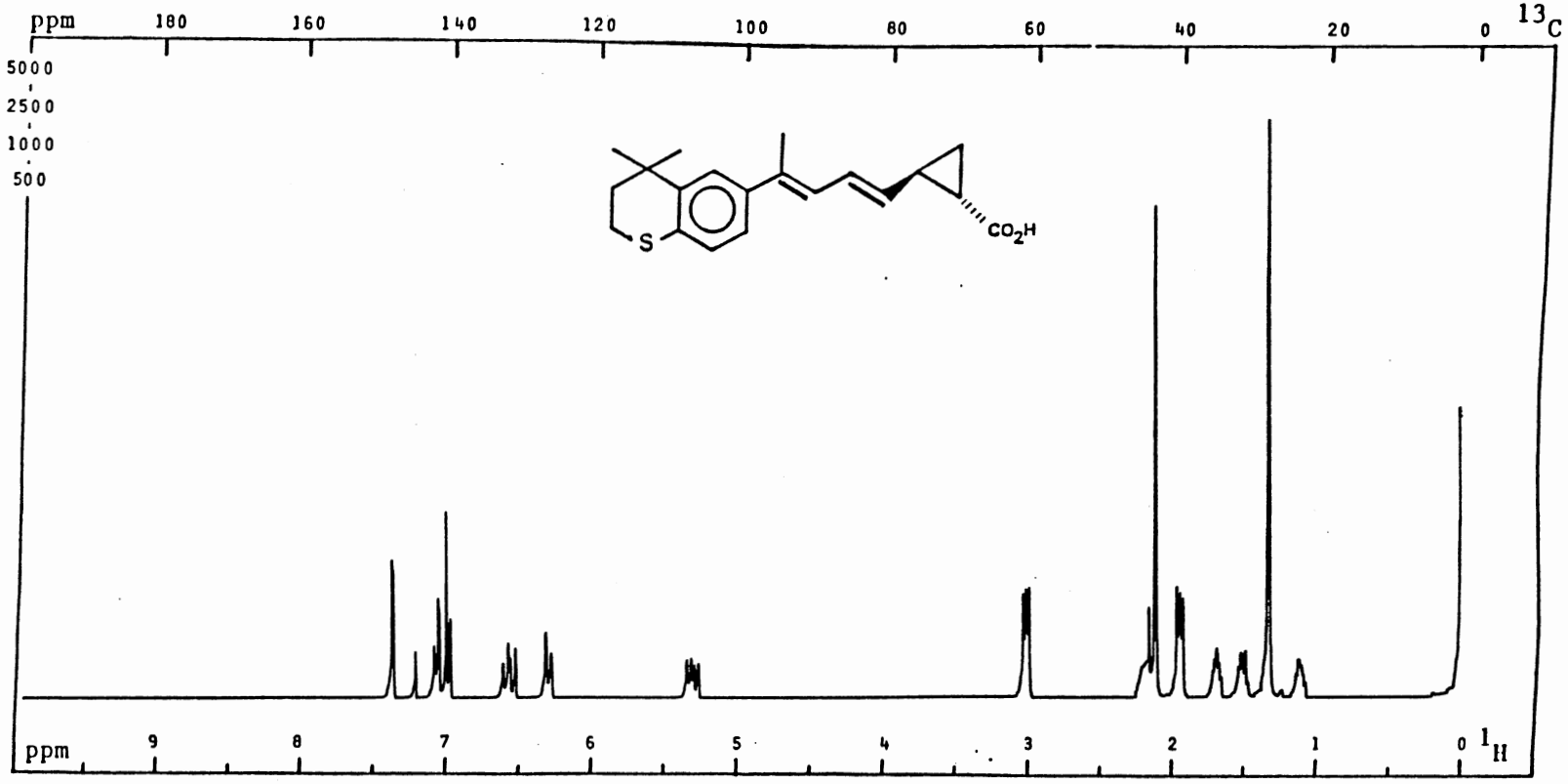
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 1.5 Hz.

PLATE C



IR Spectrum of 67

PLATE CI



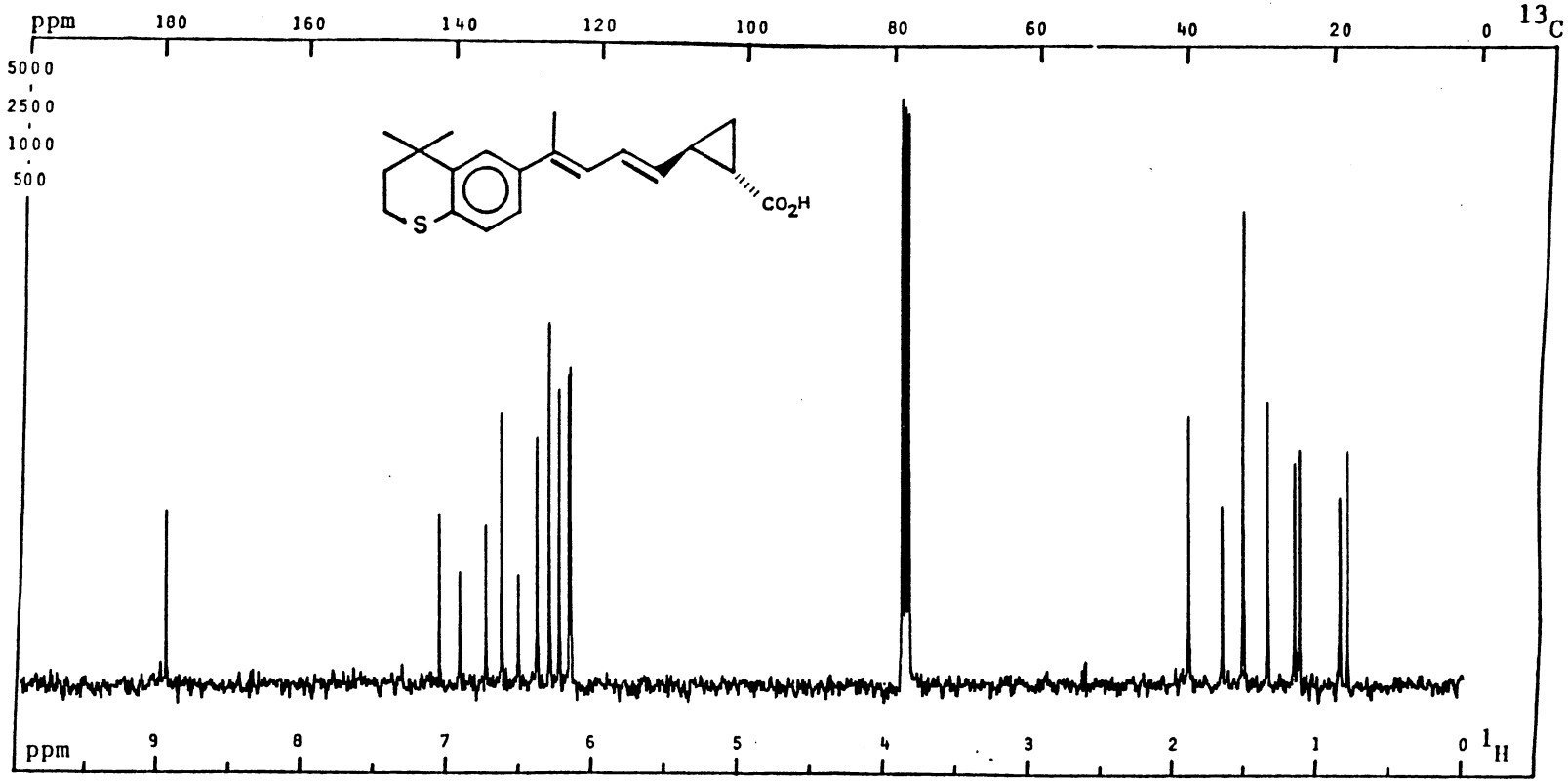
^{1}H NMR Spectrum of **48e**

PFT _X_ CW ___ ; **Solvent:** $DCCl_3$; **SF:** 299.9485 **MHz; WC:** 2999.4 **Hz; T:** RT **°C; NT:** 32

Size: 16 **K; PW/RF:** 5.0 **µs/dB; TO:** 0 **Hz; FB:** - **Hz; Lock:** ^{2}H **; D1,D5:** 0 **s.**

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

PLATE CII



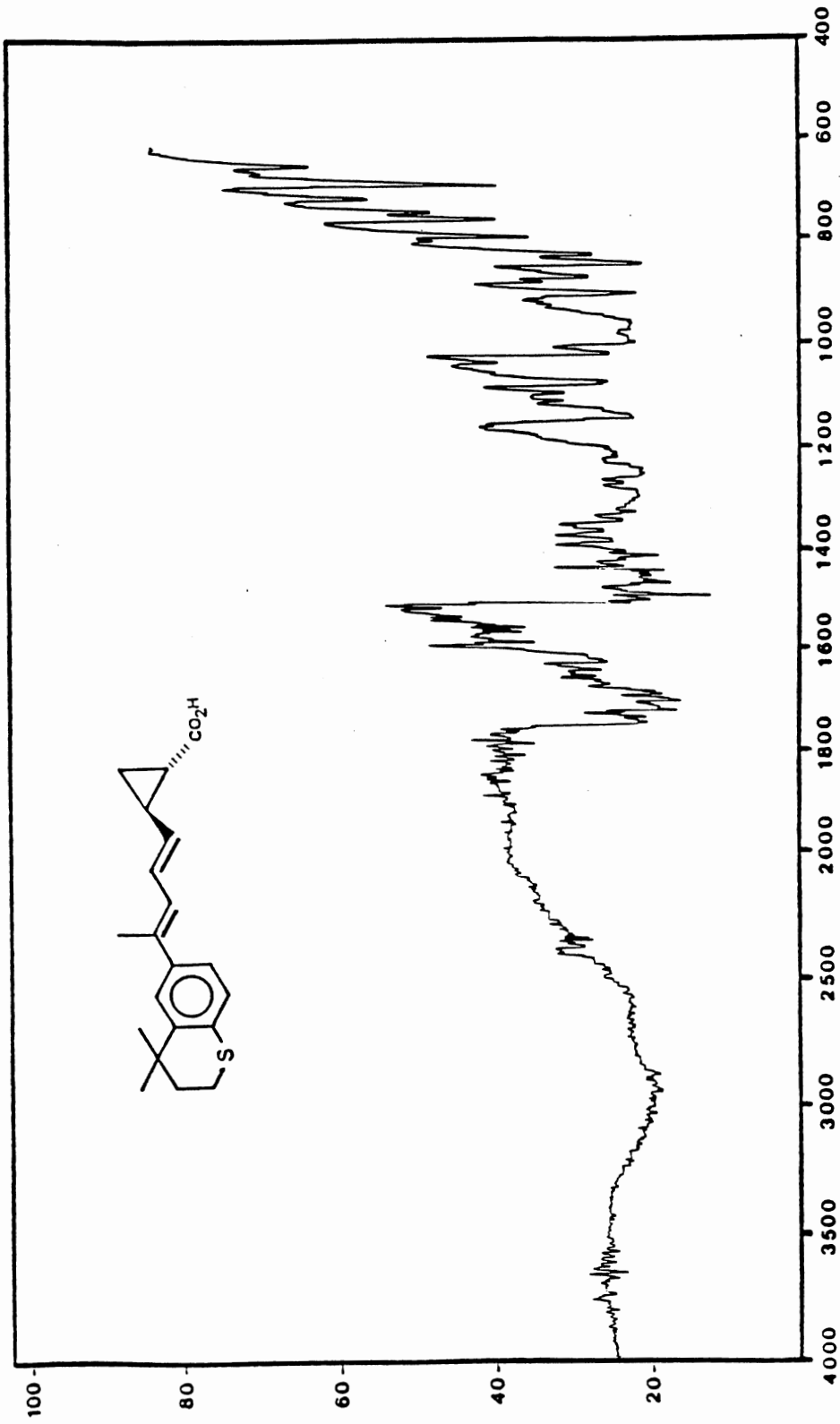
^{13}C NMR Spectrum of **48e**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 1000 .

Size: 16 K; PW/RF: 12 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.0 s.

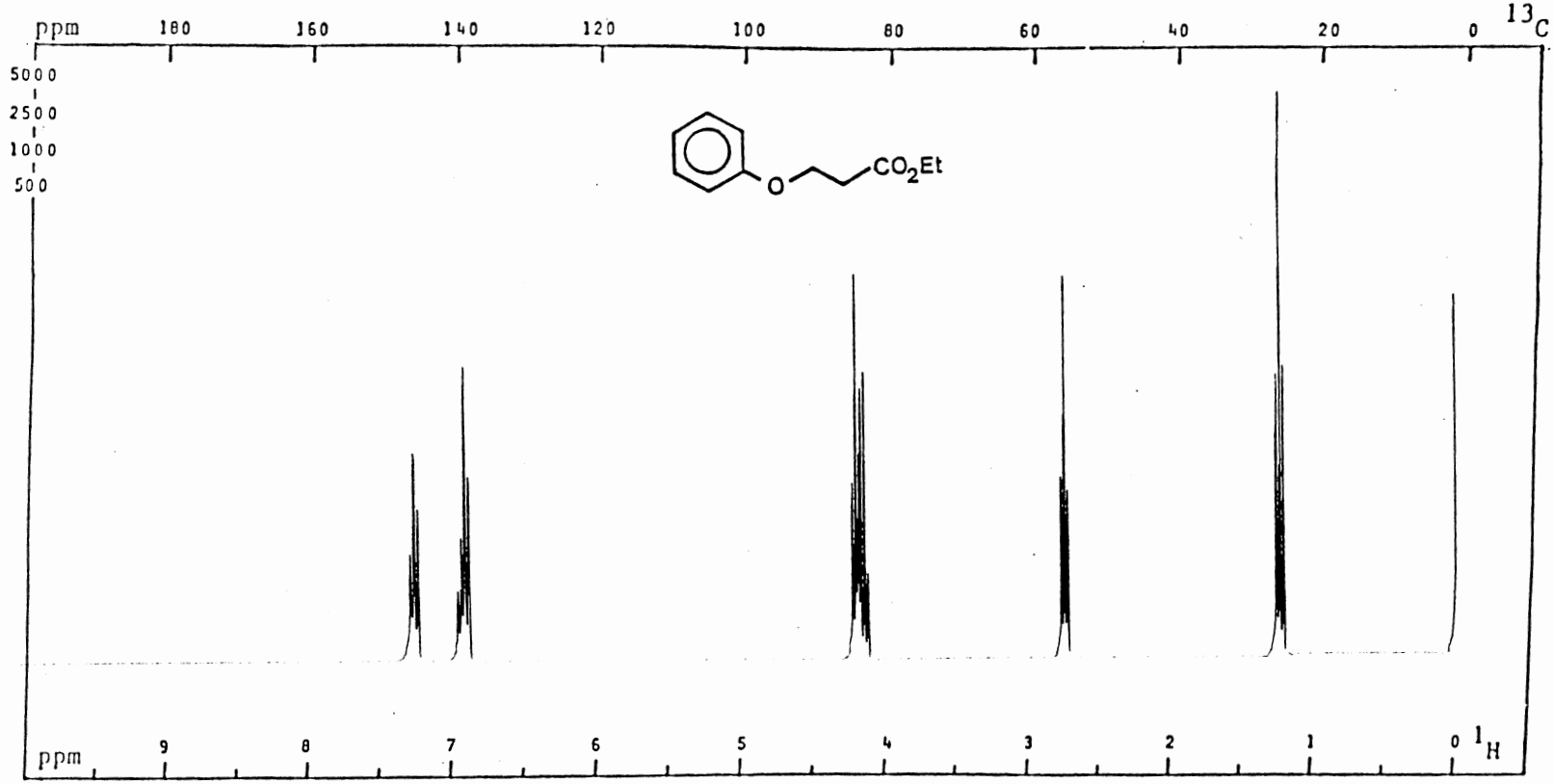
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

PLATE CIII



IR Spectrum of **48e**

PLATE CIV



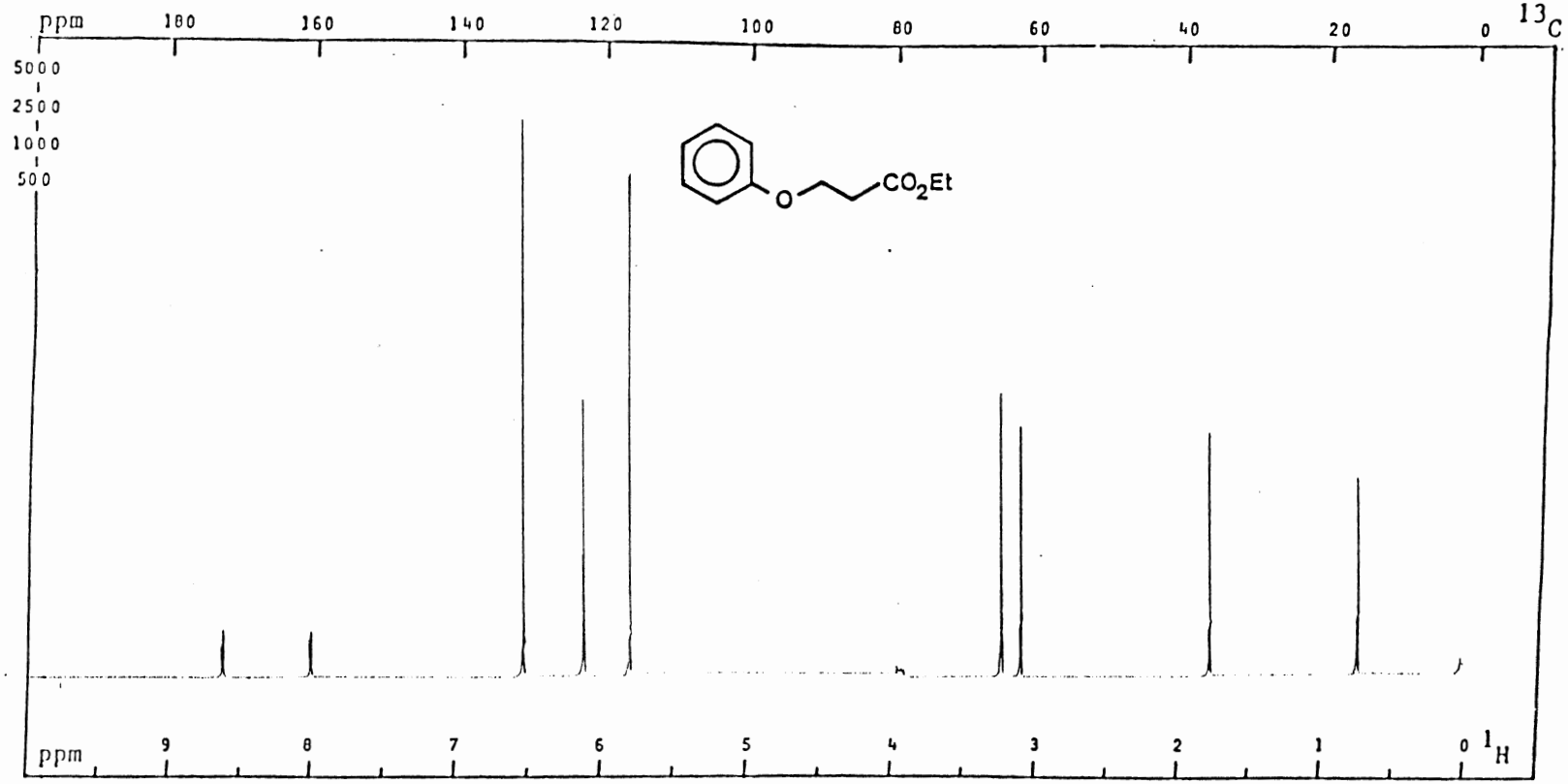
^{1}H NMR Spectrum of **90**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8

Size: 8 K; PW/RF: 5.0 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE CV



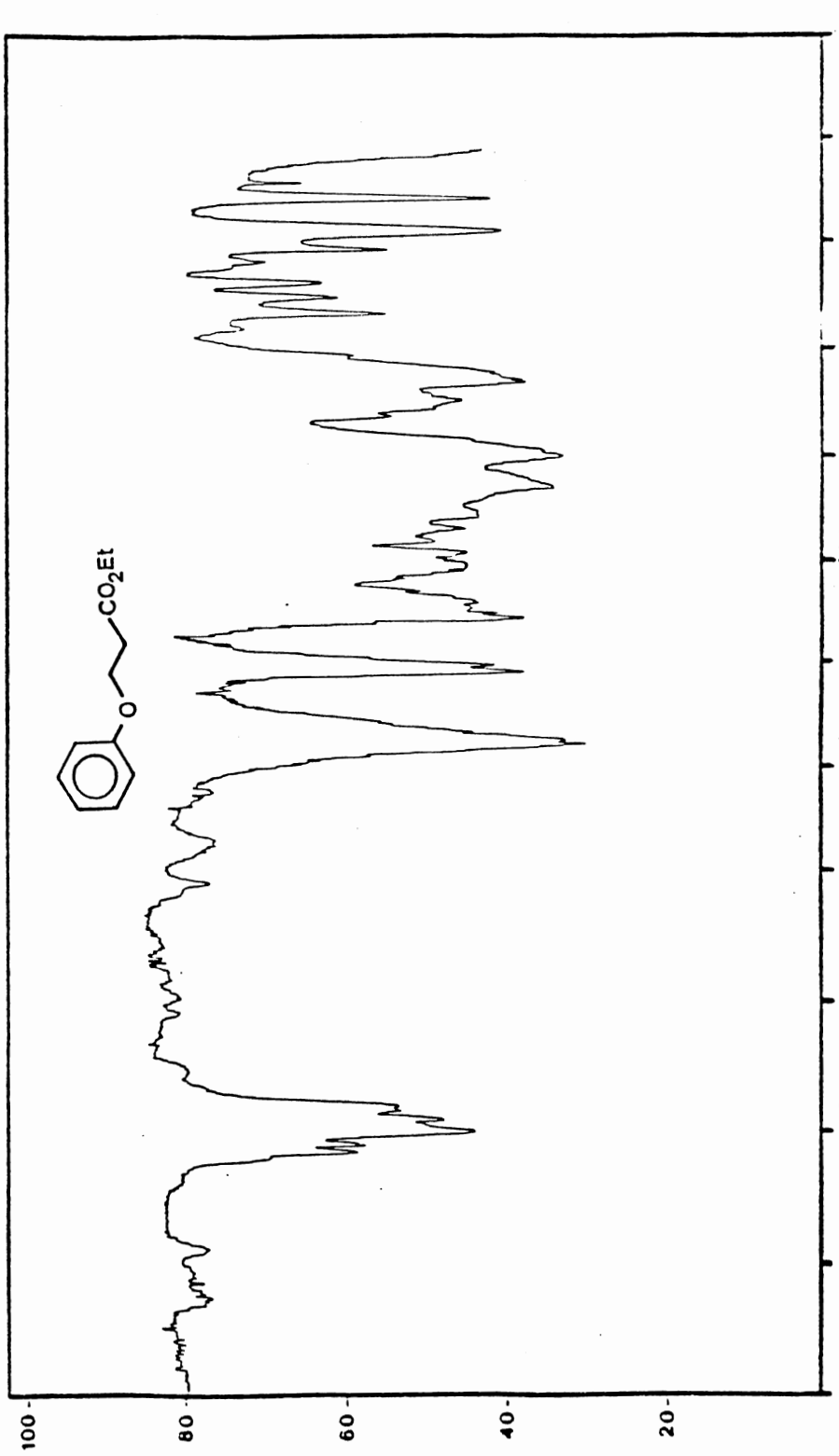
13C NMR Spectrum of **90**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 300 .

Size: 20 K; PW/RF: 8.0 μs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.0 s.

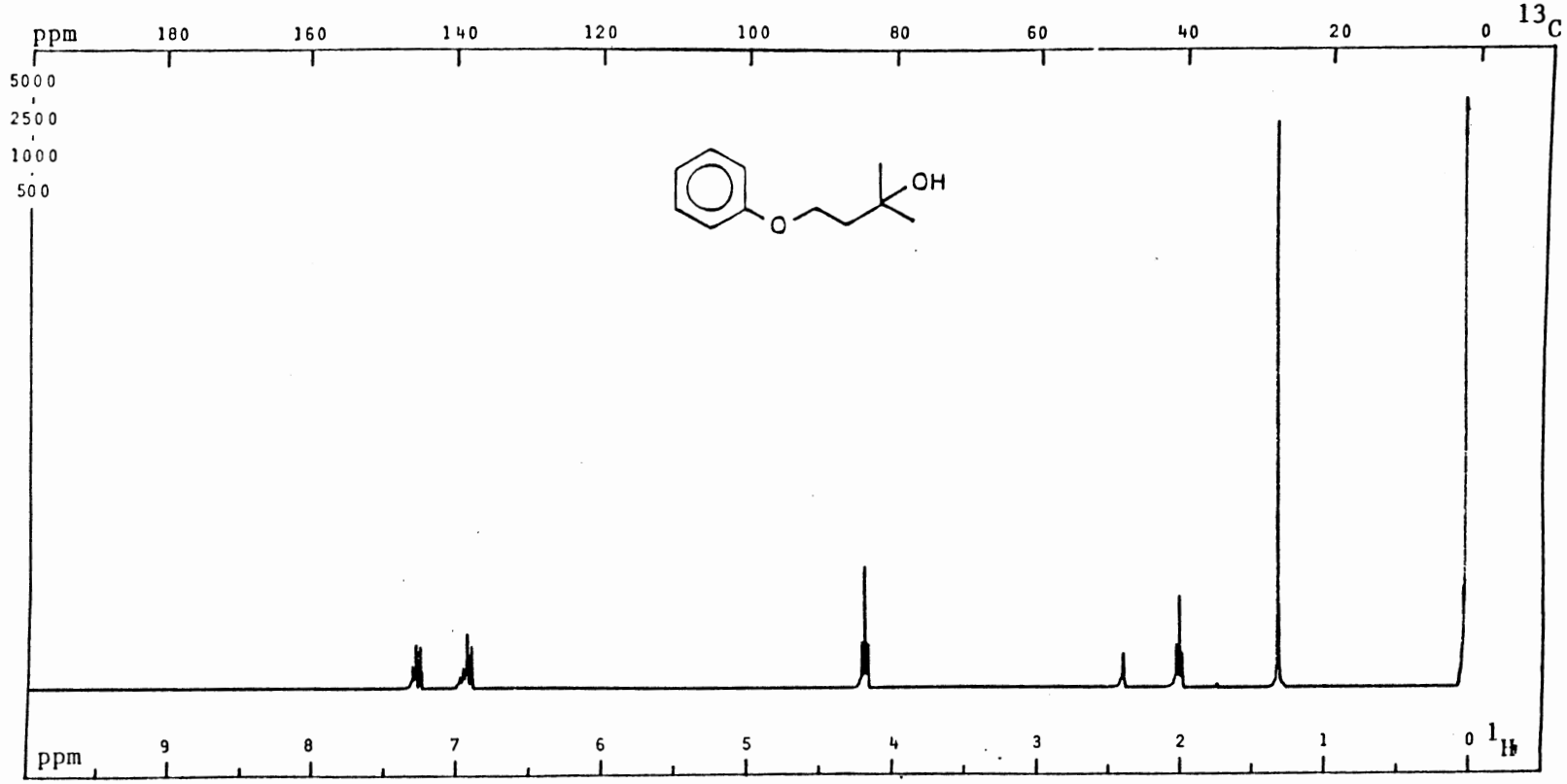
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

PLATE CVI



IR Spectrum of **90**

PLATE CVII



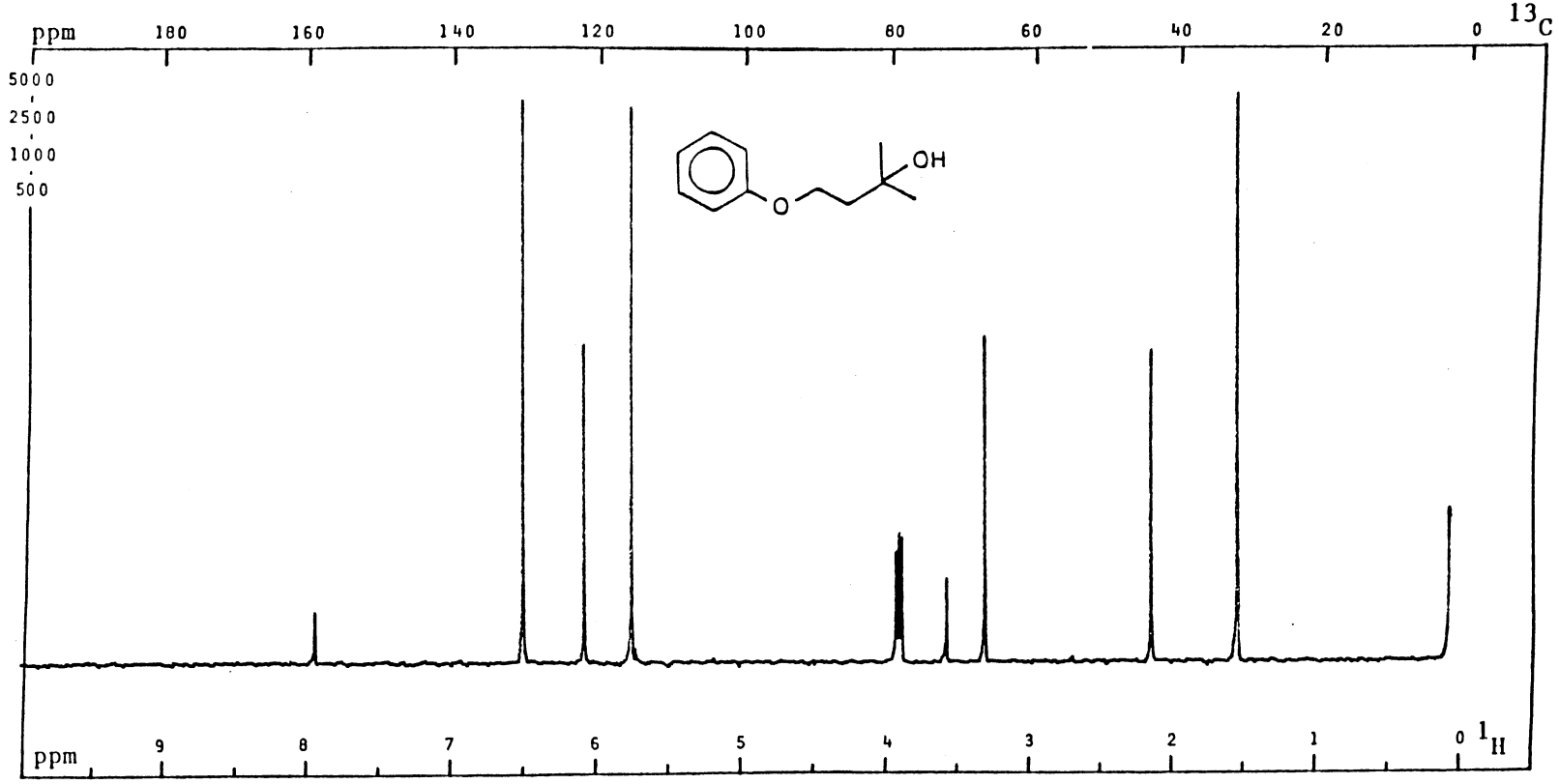
^1H NMR Spectrum of **91**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8 .

Size: 12 K; PW/RF: 12 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 0 s.

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

PLATE CVIII



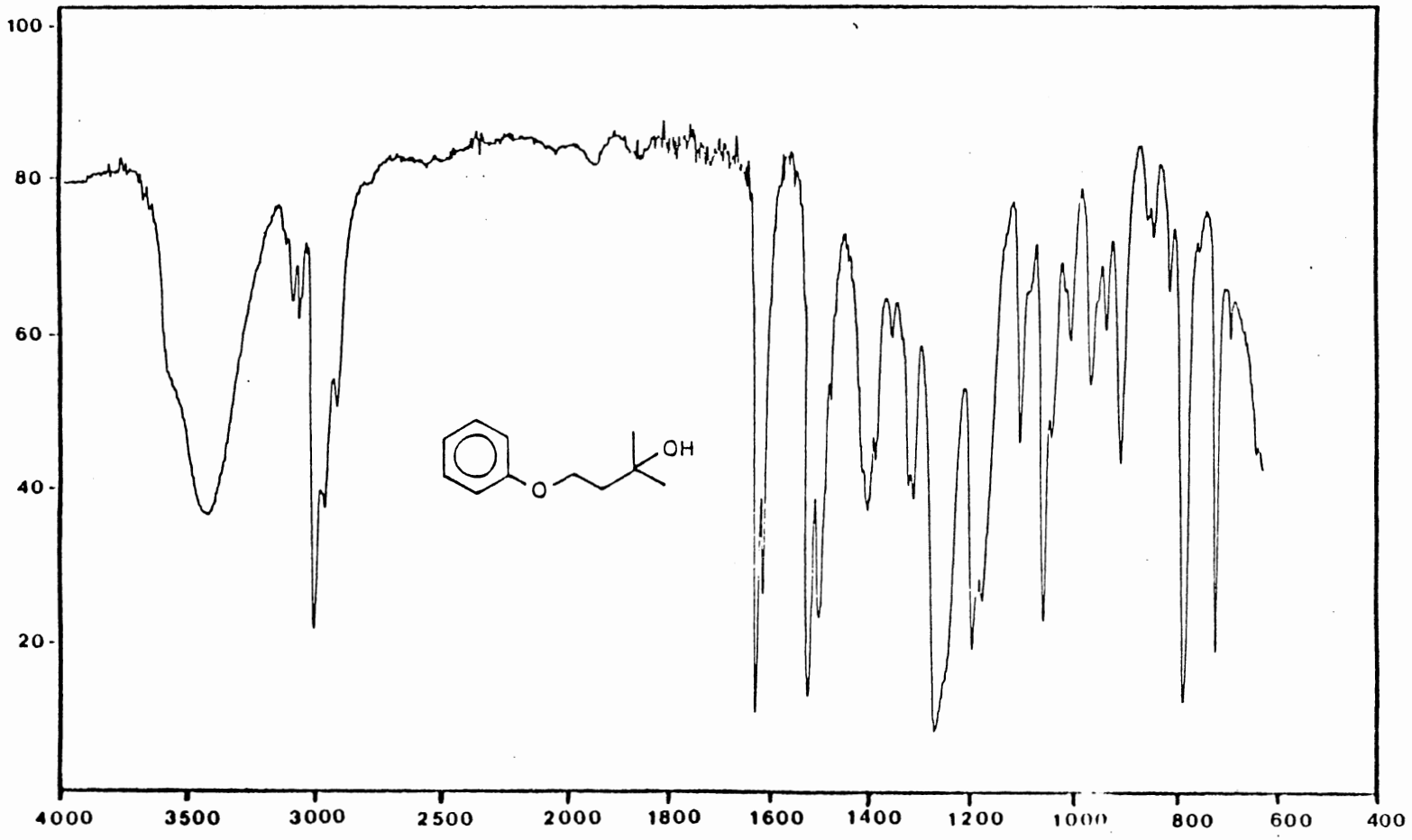
^{13}C NMR Spectrum of **91**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 600 .

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

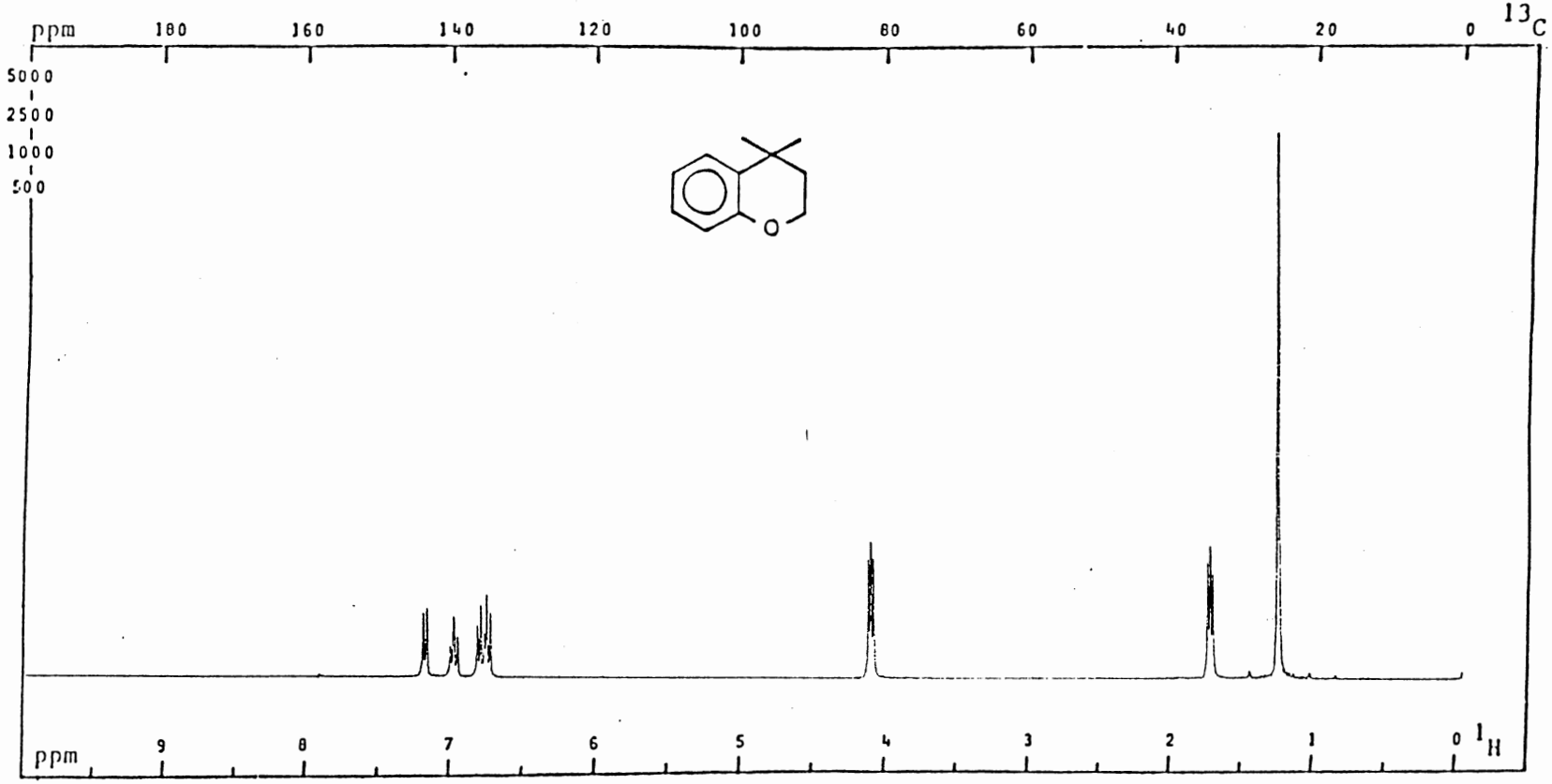
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 2.0 Hz.

PLATE CIX



IR Spectrum of **91**

PLATE CX



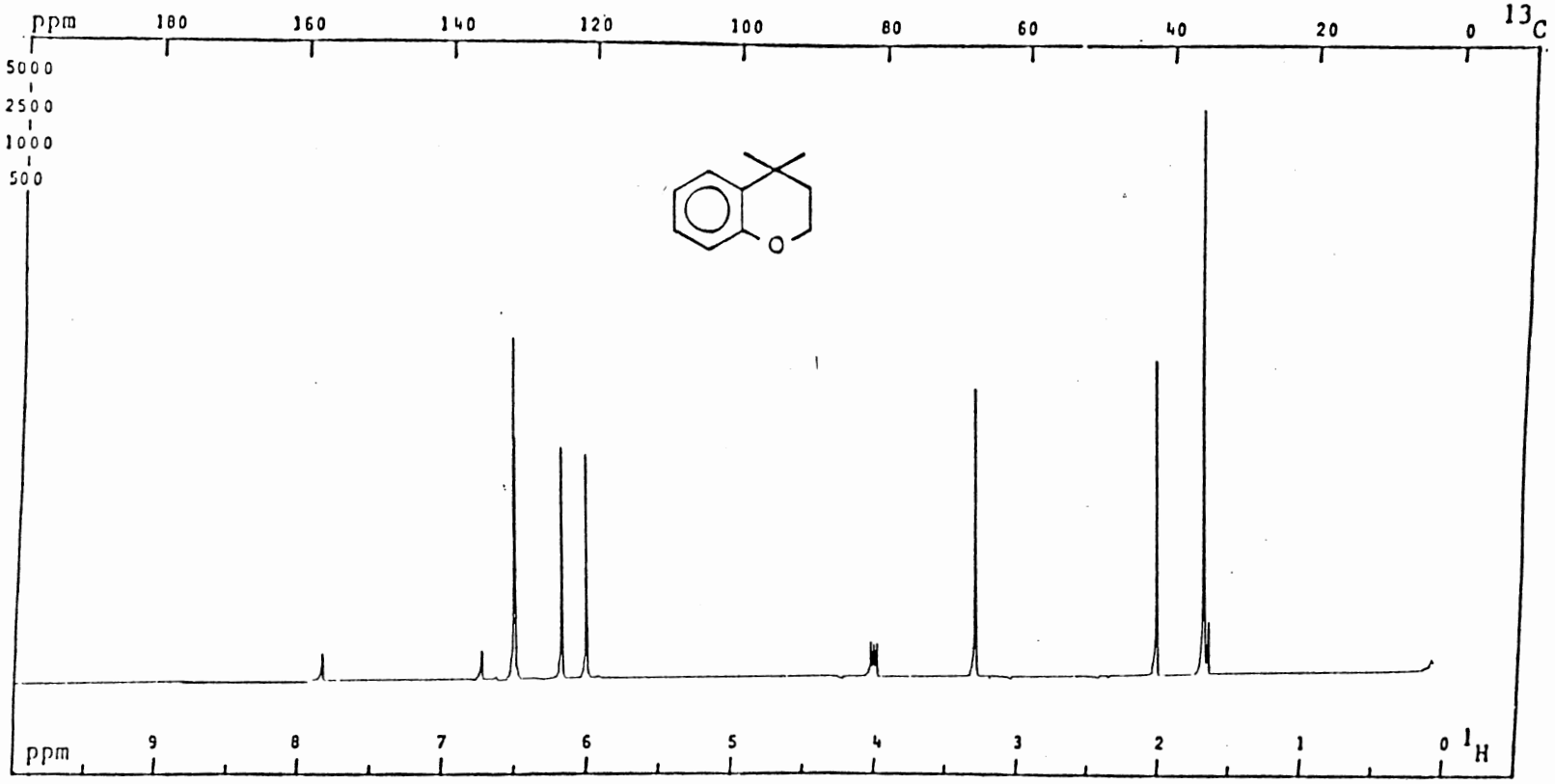
^1H NMR Spectrum of **84**

PFT _X_ CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8

Size: 12 K; PW/RF: 12 µs/dB; TO: 0 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 0 s.

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

PLATE CXI



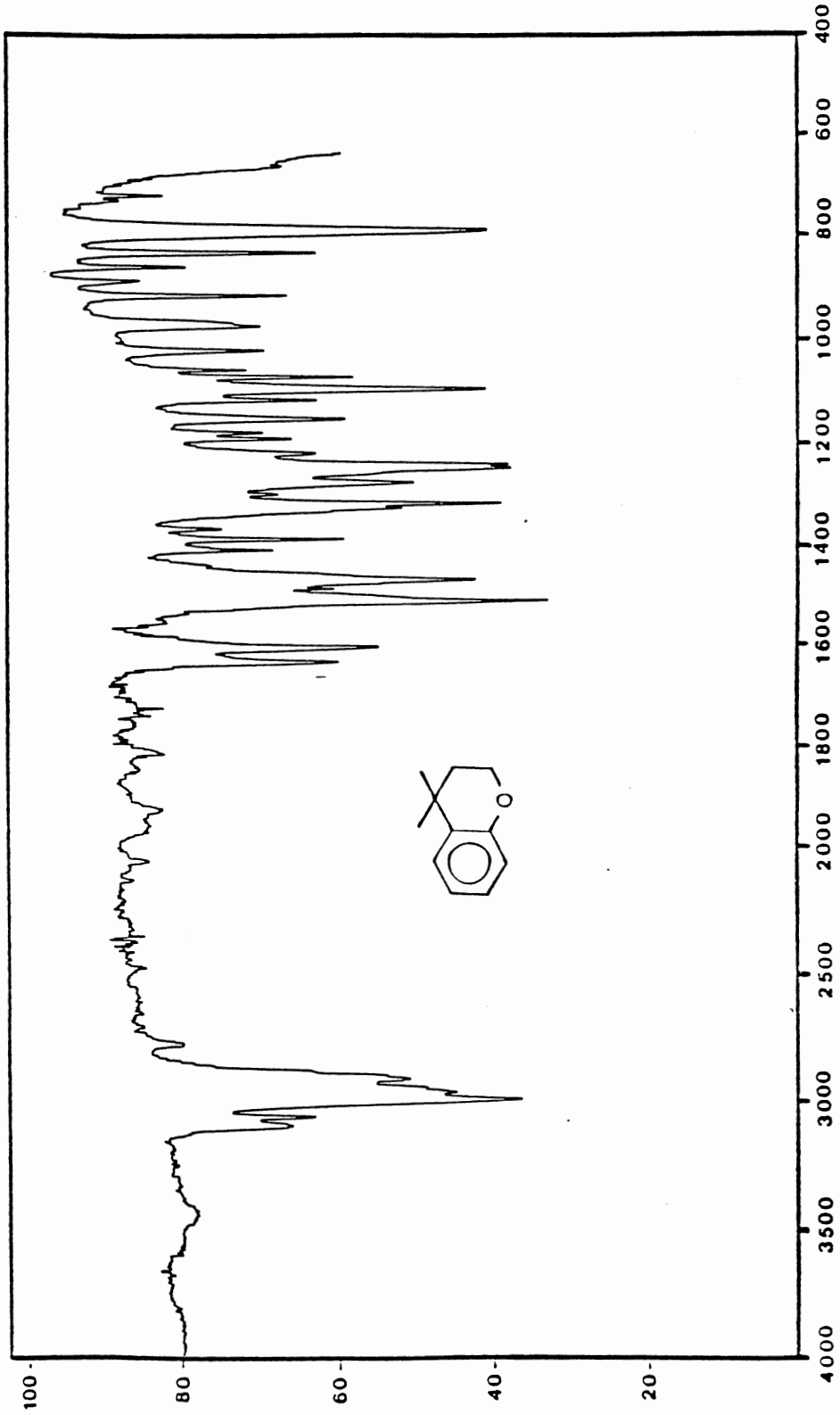
^{13}C NMR Spectrum of **84**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 600 .

Size: 16 K; PW/RF: 12 µs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.0 s.

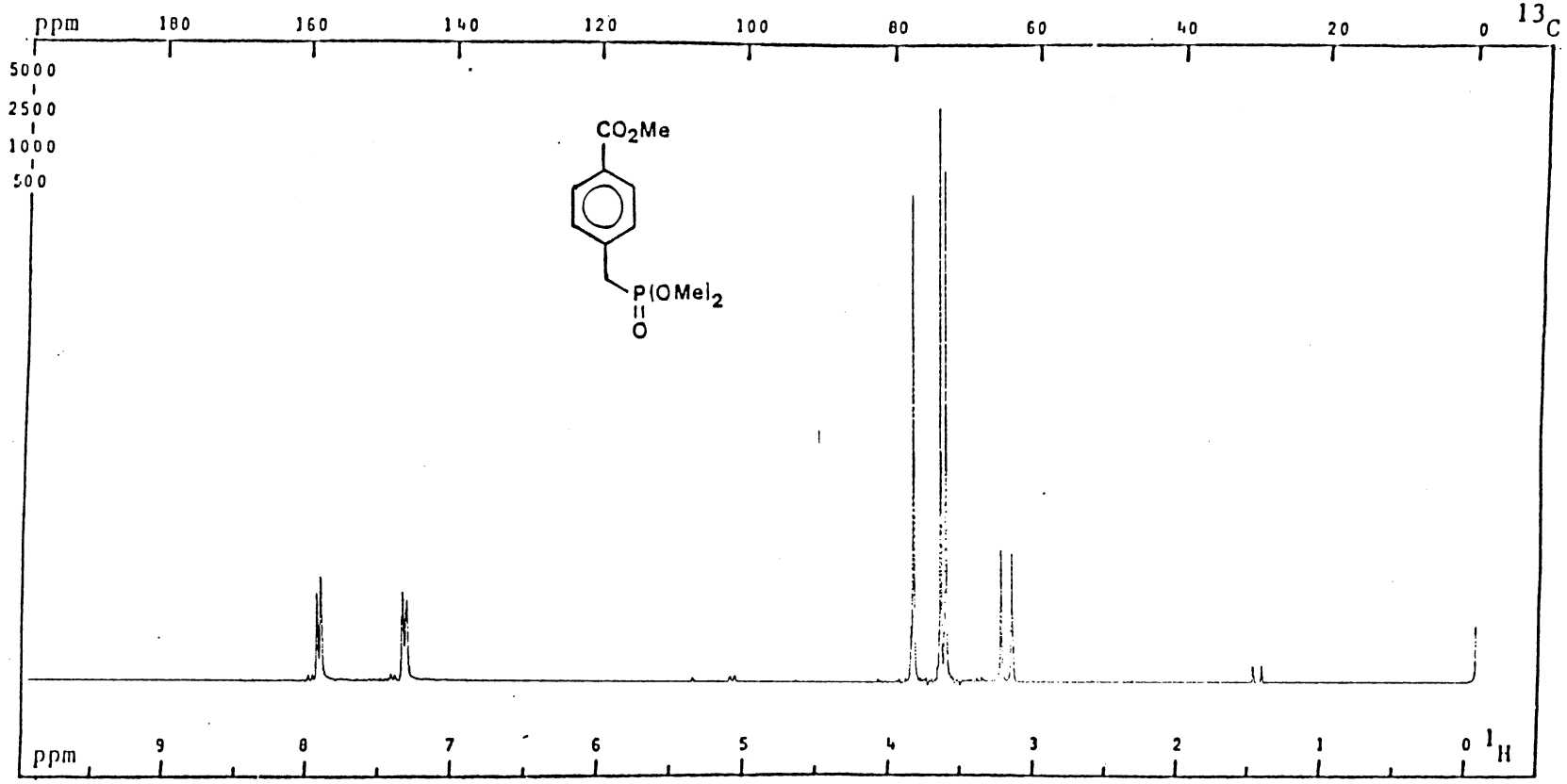
DC: Y, N ; Gated Off: A or D ; DO: 0 Hz; RF(Power): 20 W/dB; NBW: 200 Hz; LB: 1.5 Hz.

PLATE CXII



IR Spectrum of 84

PLATE CXIII



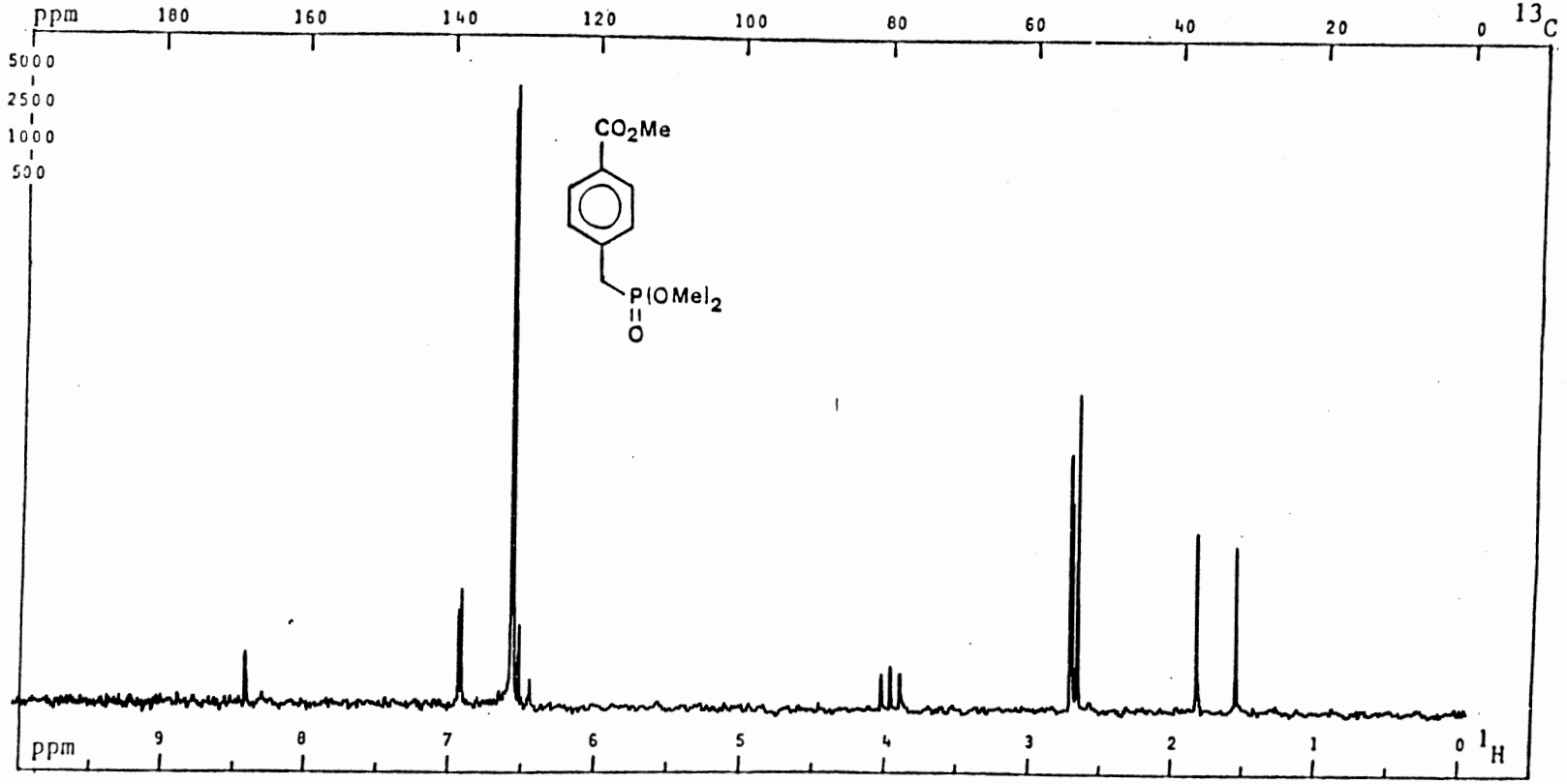
^{1}H NMR Spectrum of **76**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 299.9485 MHz; WC: 2999.4 Hz; T: RT °C; NT: 8

Size: 16 K; PW/RF: 6.0 μs/dB; TO: 0 Hz; FB: - Hz; Lock: ^{2}H ; D1,D5: 0 s.

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

PLATE CXIV



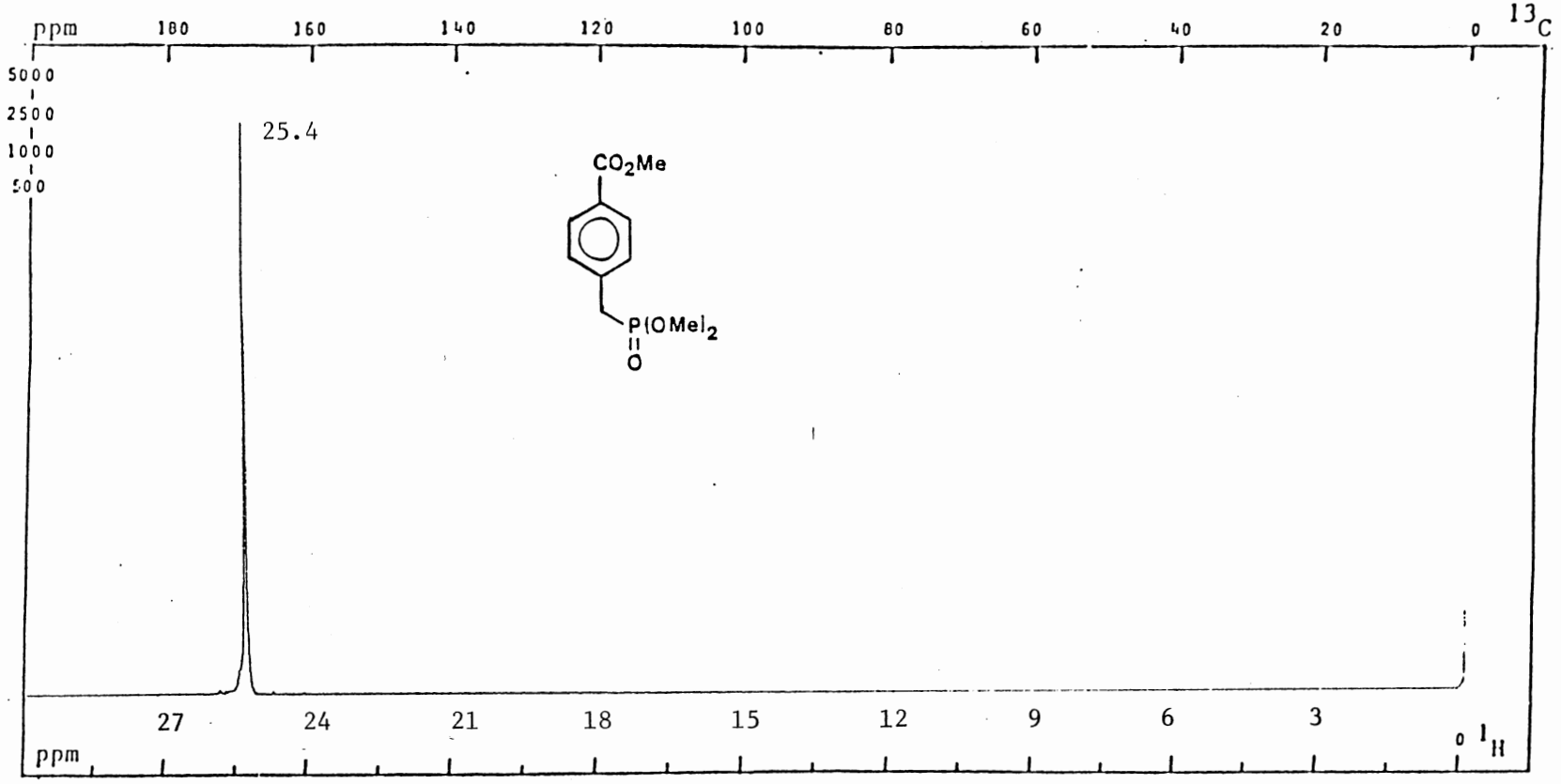
^{13}C NMR Spectrum of **76**

PFT _X_ CW _ ; Solvent: $DCCl_3$; SF: 75.429 MHz; WC: 15085.9 Hz; T: RT °C; NT: 300 .

Size: 20 K; PW/RF: 8.0 μs/dB; TO: 1000 Hz; FB: - Hz; Lock: ^2H ; D1,D5: 4.0 s.

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

PLATE CXV



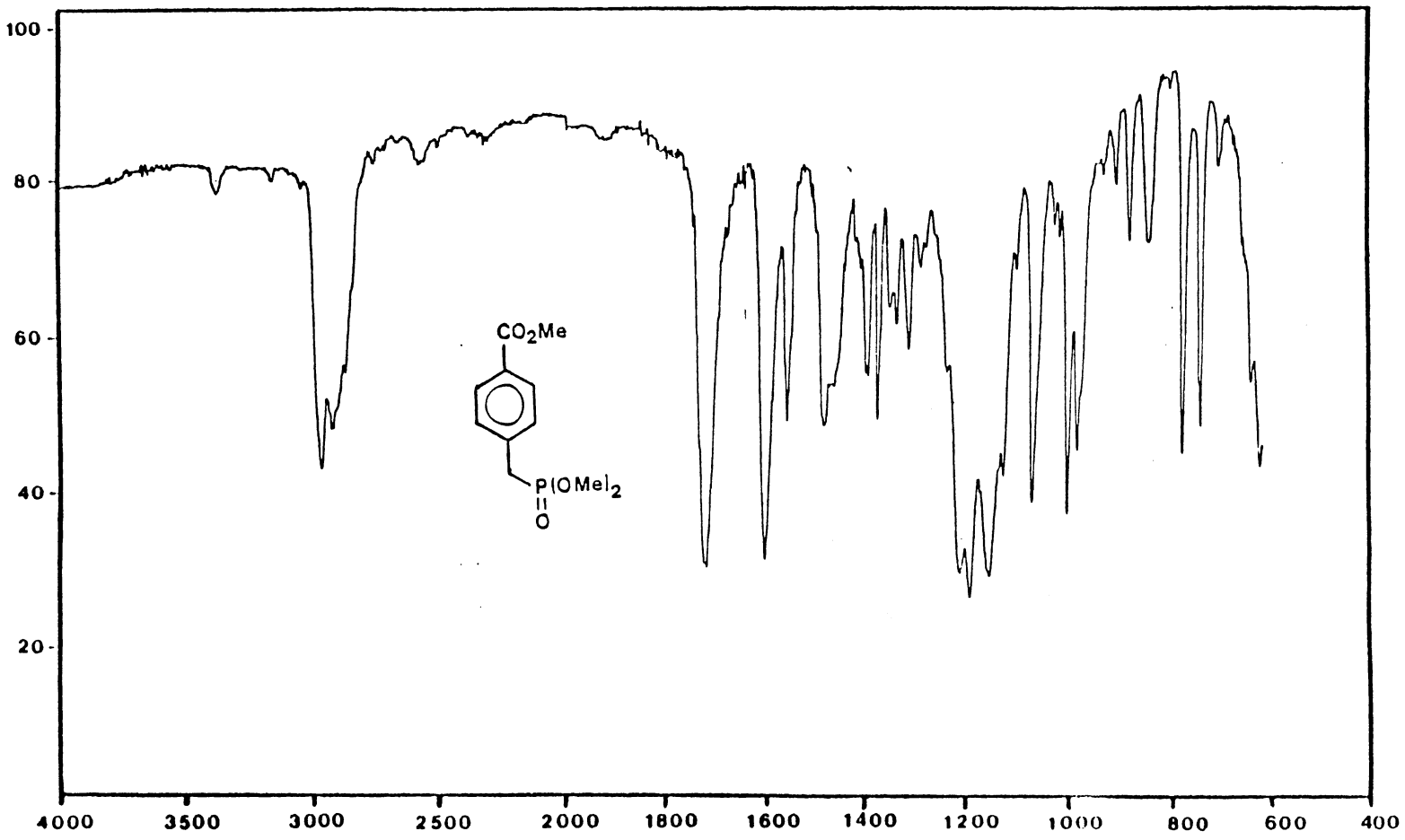
^{31}P NMR Spectrum of **76**

PFT X CW _ ; Solvent: $DCCl_3$; SF: 121.421 MHz; WC: 3642.6 Hz; T: RT °C; NT: 16

Size: 12 K; PW/RF: 14 µs/dB; TO: Hz; FB: - Hz; Lock: ; D1,D5: 2.0 s.

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

PLATE CXVI



IR Spectrum of **76**

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VITA

LYLE W. SPRUCE

Candidate for the Degree of

Doctor of Philosophy

Thesis: SYNTHESES, STRUCTURAL ELUCIDATION AND BIOLOGICAL ACTIVITY OF NEW HETEROAROTINOIDS

Major Field: Chemistry

Biographical:

Personal Data: Born in Denver, Colorado, May 28, 1959, the son of Norman and Alice Spruce.

Education: High School; Abraham Lincoln High School; Denver, Colorado, June, 1977; B.S., Metropolitan State College; Denver, Colorado, 1982; completed requirements for the Doctor of Philosophy degree at Oklahoma State University, May, 1987.

Professional Experience: Teaching Assistant, Oklahoma State University, 1982-85. Research Assistant, 1985-86.