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Synthesis of fluoroalkyl esters

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SYNTHESIS OF FLUOROALKYL ESTERS: POTENTIAL MECHANISTIC PROBES OF SQUALENE SYNTHETASE AND OTHER ENZYMES

by

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B.S., University of California Davis 1974

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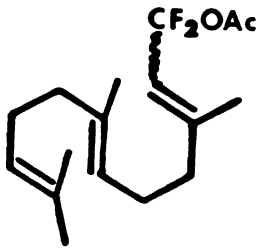
ABSTRACT

Our early artificial substrate studies of the enzyme squalene synthetase using tritium labeled 2-methylfarnesyl pyrophosphate (9) and 3-desmethylfarnesyl pyrophosphate (10) are summarized. The substrate analogues 9 and 10 were both accepted by the enzyme as co-substrates during the second catalytic step producing the products 11-methylsqualene (14) and 10-desmethylsqualene (15), respectively. The chemical syntheses of 14 and 15, and 10,15-didesmethylsqualene (13), which were used in the enzyme product identifications, are presented.

The analogue 4-fluorofarnesyl pyrophosphate (17), the synthesis of which is described, was found to be inactive both as a substrate and as an irreversible inhibitor of squalene synthetase. Arguments concerning the lack of biological activity observed in 17, based on the presence of the highly electronegative fluorine, are discussed.

A new synthetic method has been developed for the synthesis of α-fluoroalkyl esters, compounds which may serve as useful mechanistic probes of squalene synthetase and other enzymes. During the course of this investigation we devised a new and potentially valuable approach to trimethylsilyl protected α-hydroxy aldehydes. We have furthermore shown that these aldehydes serve as precursors to fluoroallyl alcohols which, in turn, are easily converted to halide, amide, acetate, and phosphate derivatives. The synthesis of difluoroacetates 70 and 100, difluorophosphates 94 and 96, and monofluoro analogues 113 and 114 have been achieved.



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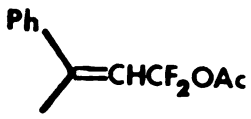

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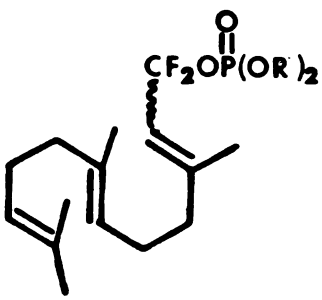
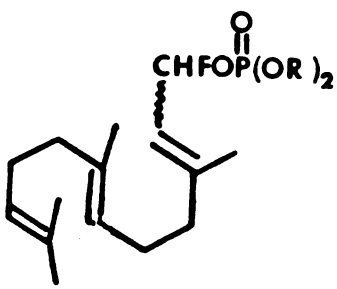


94 (R = Et)

96 (R = Ph)



113 (R = Et)

114 (R = Ph)

to the memory of my stepfather,

Henry P. Krch

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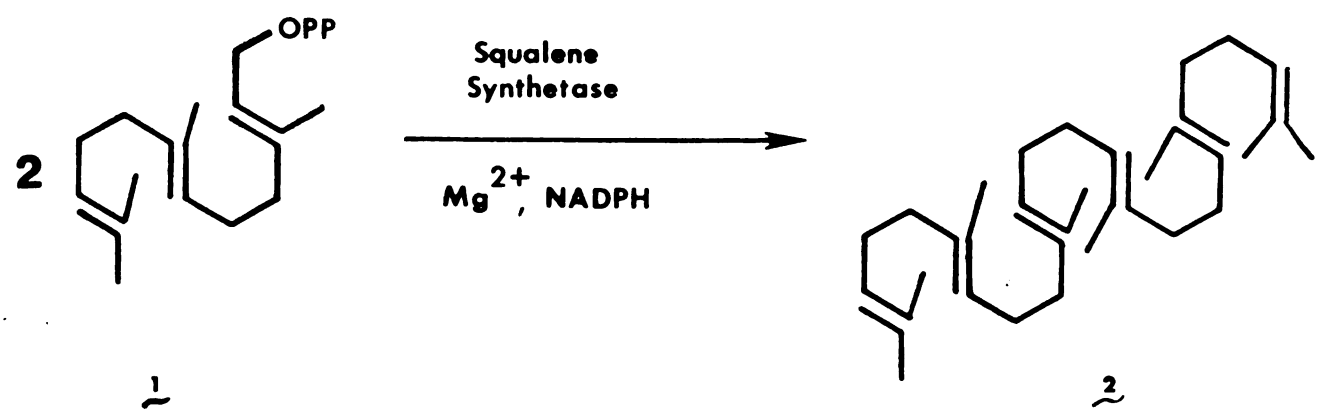
PROLOGUE

I. Introduction

Intensive chemical and biological studies by several research groups have resulted in elucidation of the highly complex acetate to cholesterol biosynthetic pathway.[1] Finely detailed mechanistic information has been obtained for those steps leading to farnesyl pyrophosphate. The relative ease in obtaining the requisite enzymes for these steps has no doubt been a contributing factor in unveiling the enzymes' mechanistic complexities. However, squalene synthetase, the enzyme which couples two farnesyl pyrophosphate residues in a head-to-head fashion yielding the triterpene squalene, has only recently become available in a partially purified state.[2]

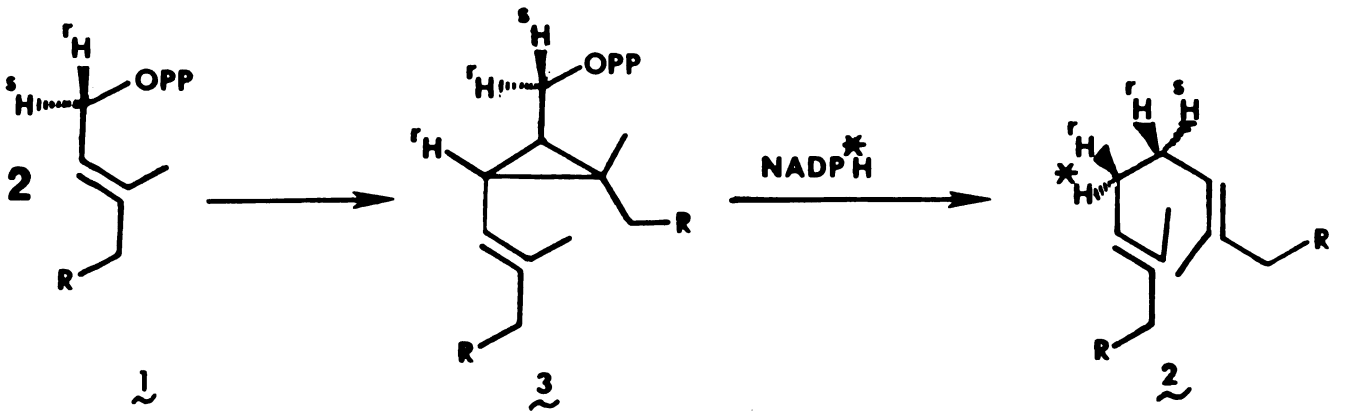
Using crude enzyme extracts, Cornforth and others investigated the intricate molecular transformations involved in the reaction catalyzed by squalene synthetase.[1,3] The gross, overall reaction is simply a symmetrical, reductive coupling of the pyrophosphate esters of two allylic alcohols. The actual enzymatic reaction, however, has been shown to involve the two stereospecific

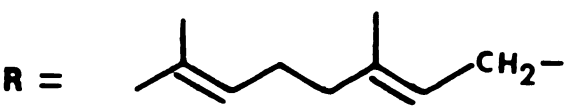


1 2

steps shown in Fig. 1, including formation of an isolable intermediate, presqualene pyrophosphate (3).[4] The overall conversion of 1 to 2 requires the

FIGURE 1



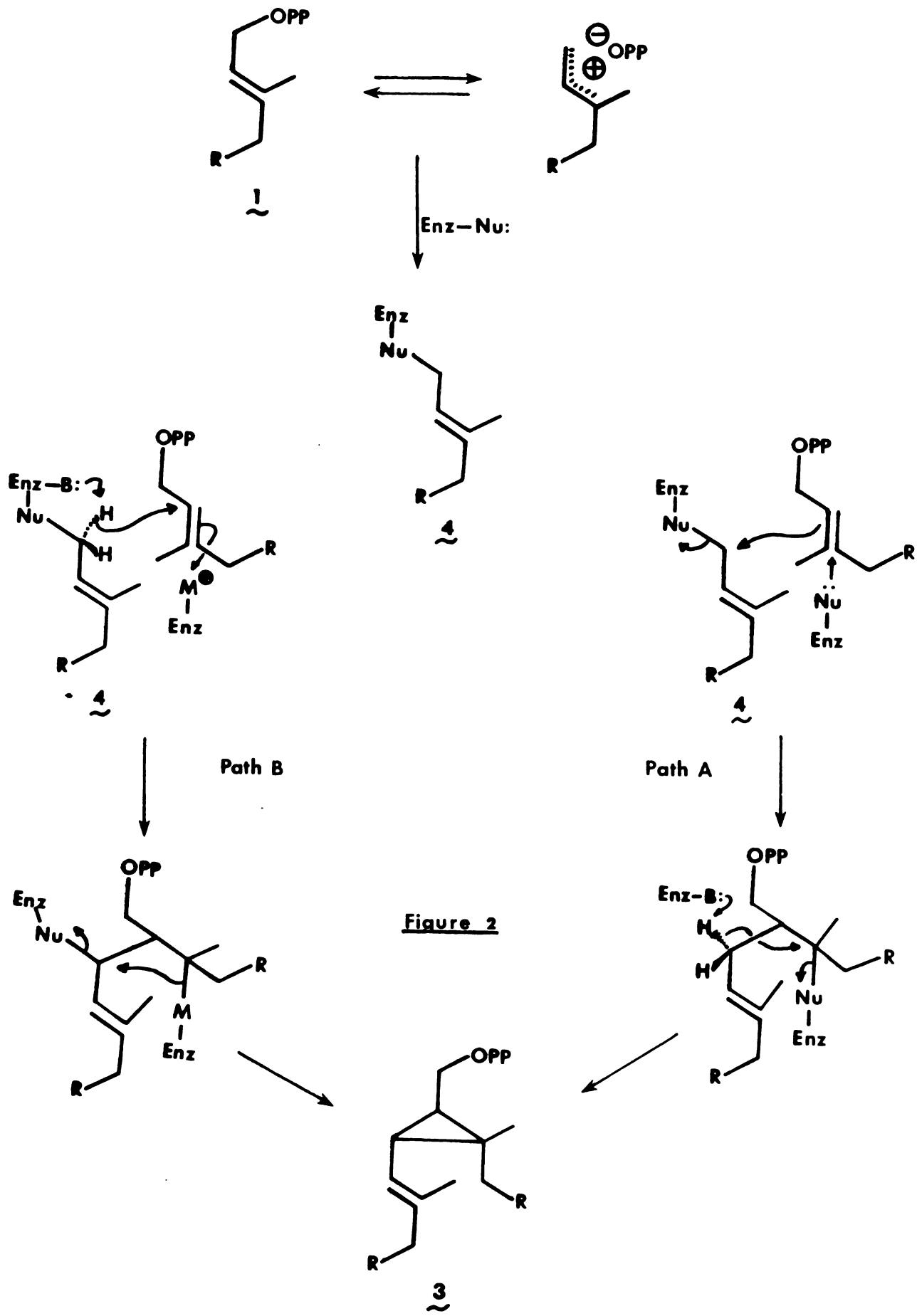


presence of reduced pyridine nucleotides (NADH or, preferably, NADPH) and divalent cations (Mg^{++} or Mn^{++}). If the NADPH cofactor is omitted from an otherwise complete squalene synthesizing microsomal system, no squalene is formed whereas 3 is accumulated.[4] Intermediate 3, on the other hand, is converted to 2 upon supplementation of the incubation with NADPH, suggesting that presqualene pyrophosphate (3) is an actual intermediate. Cornforth initially questioned this interpretation but recent results have verified the role of 3 as an obligatory intermediate.[5]

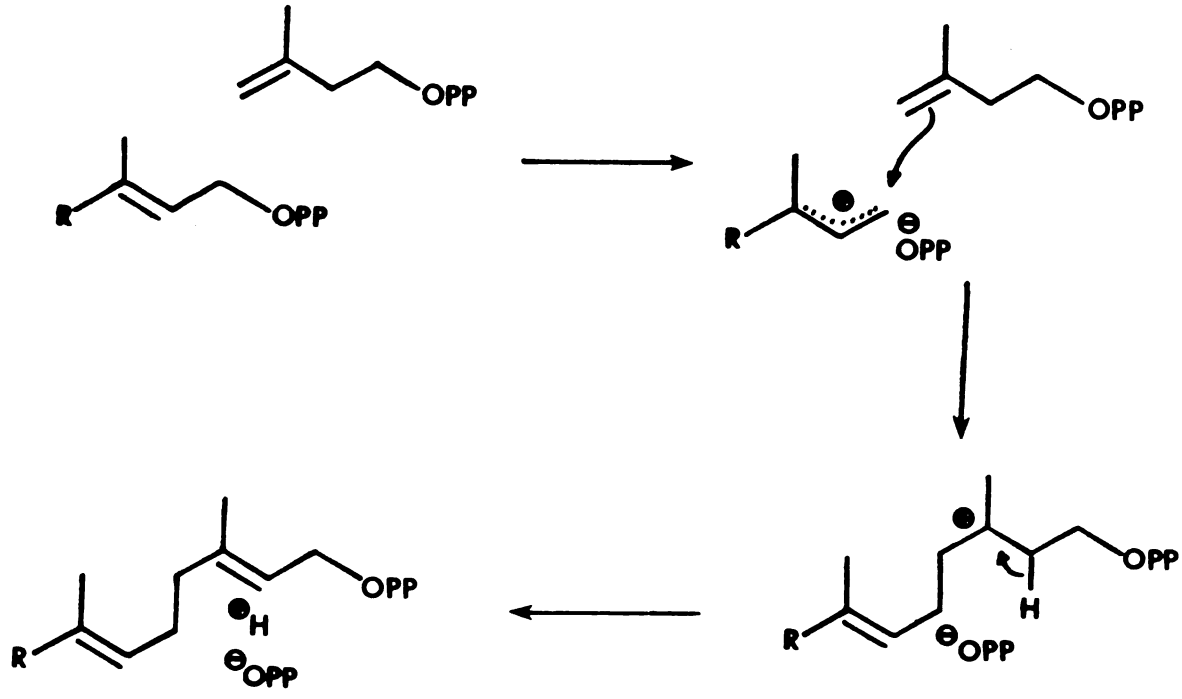
Several mechanisms have been postulated for the formation of squalene (2) from farnesyl pyrophosphate (1)[6]. One can visualize two basic modes for formation of the cyclopropyl ring in 3. The first molecule of 1 bound by the enzyme may initially either accept electrons from the second molecule of 1 that is bound (Path A), or it may donate them (Path B). Recent mechanistic suggestions have been based primarily on a kinetic study of the enzyme by Porter and co-workers[7] using partially purified squalene synthetase. A few of the possible mechanistic variants for formation of 3 are shown in Fig. 2.

Porter's kinetic data[7] strongly support the formation of an initial enzyme-farnesyl complex (4) with synchronous loss of inorganic pyrophosphate. A second unit of 1 is then bound by the enzyme and, in forming presqualene pyrophosphate (3), the C-1 pro-S-proton of the farnesyl unit in 4 is removed. Subsequent formation of squalene (2) from 3 may proceed by way of known cyclopropylcarbinyl cation rearrangements as demonstrated by model solvolytic studies.[6]

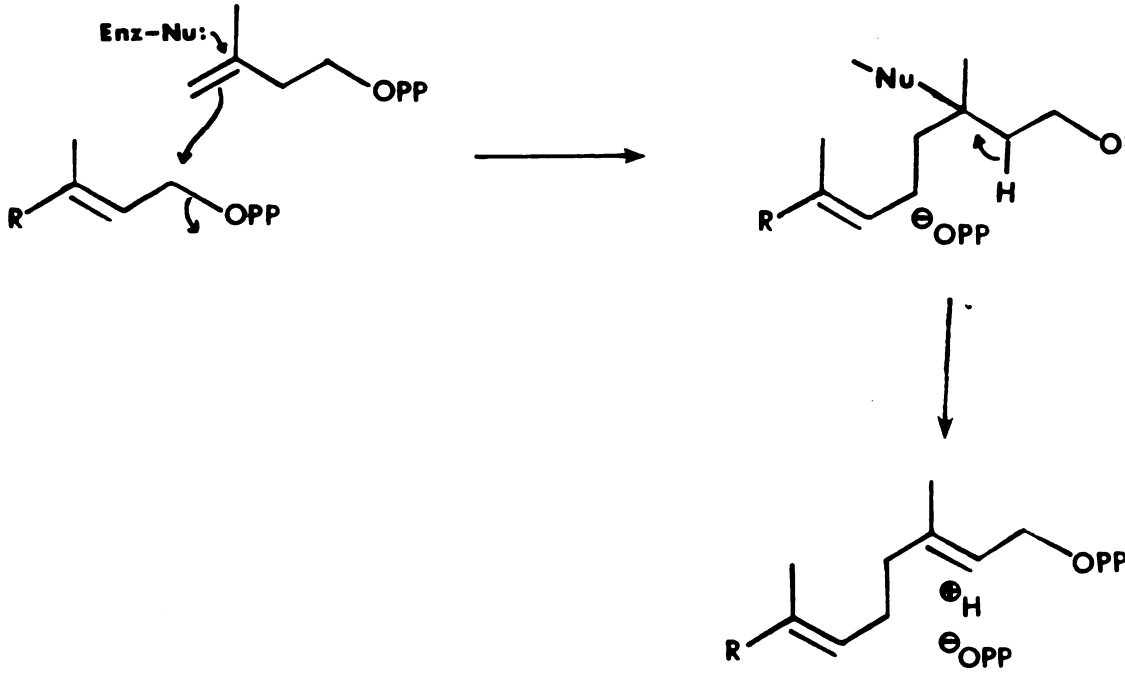
Poulter and Rilling have under taken mechanistic studies of the prenyl transferase catalyzed reactions which directly precede squalene formation in the cholesterol biosynthetic pathway.[8] In their investigations they have attempted to differentiate between two proposed mechanisms for prenyl transferase catalyzed reactions. These two mechanisms differ primarily in their initial, presumably rate determining steps, i.e., the ionization-condensation mechanism (Scheme I) involves initial ion-pair formation from the allyl pyrophosphate residue whereas the condensation-elimination mechanism (Scheme II) proceeds by way of direct displacement of the pyrophosphate moiety assisted, presumably, by a nucleophilic group attached to the enzyme. Poulter and Rilling attempted to distinguish between these two initial enzymatic steps by comparing the chemical and enzymatic behavior of the normal allylic substrate to that of analogues in which the


OPP
R
1
Enz–Nu:
Enz
Nu
4
Enz–B:
H
M
Path B
Path A
Nu
Enz–B:
Figure 2
3

SCHEME I

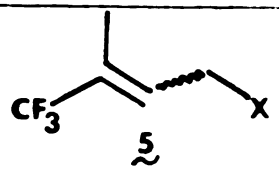
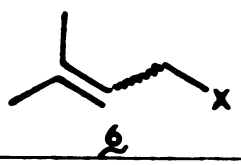


SCHEME II



hydrogens around the C-2 to C-3 double bond have been replaced by fluorine. Theoretically, strongly electronegative fluorines should retard the rate of an initial-ionization mechanism due to destabilization of the carbonium ion which is formed, whereas a condensation-elimination reaction, on the other hand, should not be greatly affected by fluoro substitution since no ionic intermediate is formed. The results of Poulter and Rilling's solvolytic and enzymatic studies using trifluoromethyl analogues 5 and 6 are summarized in Table 1. The rate of

TABLE 1

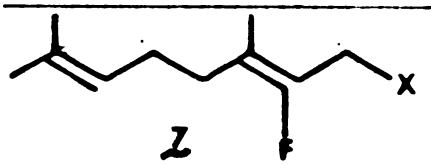
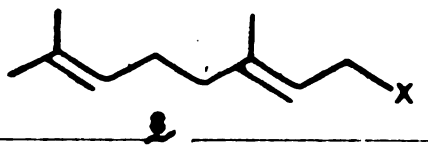
Compound[a]	Relative Rates[b]		
	S_N2	S_N1	Enzymatic
 5	11	1.8×10^{-6}	3×10^{-7}
 6	1	1	1

(a) S_N2 r x n : X = Cl; S_N1 r x n: X = -OMs; Enzymatic r x n: X = -OPP.

(b) S_N2 r x n : $I^{\ominus}$ displacement; S_N1 r x n: H_2O/acetone solvolysis.

S_N1 solvolysis of fluoro analogue 5 (X=-OMs) was found to be ~10^7 times slower than that of the non-fluorinated analogue 6 (X=-OMs). In contrast, essentially identical rate constants were obtained for S_N2 displacements of analogues 5 and 6 (X=-Cl), confirming the expected relative behavior of the fluoro substituted compounds. When either E or Z trifluoromethyl pyrophosphate analogue 5 (X=-OPP) was incubated with isopentenyl pyrophosphate and porcine farnesyl pyrophosphate synthetase (prenyl transferase), the rate of condensation was found to be 3 X 10^7 times slower than that observed with the nonfluorinated substrate 6 (X=-OPP). Consistent as these preliminary results were with an initial ionization mechanism, more detailed kinetic analyses indicated that normal enzymic mechanism was substantially altered by the presence of the trifluoromethyl group. Therefore, in order to strengthen these preliminary findings, Poulter and Rilling carried out similar studies using 2-fluorogeranyl derivatives 7 and 8, the results of which are summarized in Table 2. The results of enzymatic studies, elaborated in this instance by standard kinetic methods, clearly establish that the enzymatic reaction rate using fluoro analogue 7 (X=-OPP), is retarded to a similar degree as that observed in the S_N1 chemical solvolysis study. Poulter and Rilling consequently concluded that the prenyl transferase catalyzed reaction proceeds *via* an ionization - condensation - elimination sequence as shown in Scheme I.[8]

Table 2

Cmpd[a]	Relative Rate[b,c] S_N2	S_N1	Enzymatic
	2	4.4×10^{-3}	8.4×10^{-4}
	1	1	1

(a) S_N2 rxn: x=Cl; S_N1 rxn: X=-OMs; Enzymatic rxn: X=-OPP.

(b) S_N2 rxn: $^{(-)}CN$ displacement; S_N1 rxn: H_2O/acetone.

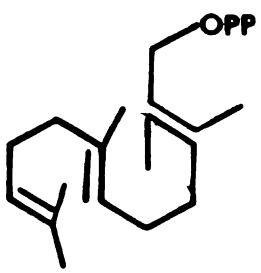
(c) Data taken from reference 8.

The possible existence of mechanistic similarities between the two closely related enzymes, prenyl transferase and squalene synthetase, is a highly intriguing idea, especially since their natural substrates are structurally so similar. In our initial studies of squalene synthetase we have employed mechanistic probes similar to those reported for prenyl transferase. However, we have found that, unlike prenyl transferase which has relatively nonstringent substrate structural requirements, even minor modifications of the substrate farnesyl pyrophosphate are partially or totally unacceptable to the enzyme squalene synthetase.

II Preliminary Substrate Studies of Squalene Synthetase.

The early substrate studies to be described in this section resulted from a collaborative effort with Castillo and Wei. Since these studies have been discussed elsewhere in detail,[1d,9] only a summary is presented here.

During the preliminary stages of our investigation of the enzyme squalene synthetase, Castillo prepared [1-^{3}H]-farnesyl pyrophosphate analogues 9, 10, and 11 as active site probes. All of these analogues, containing only minor structural



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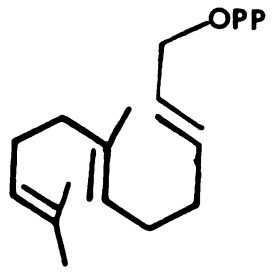

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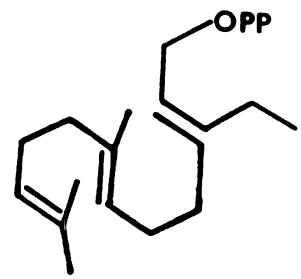

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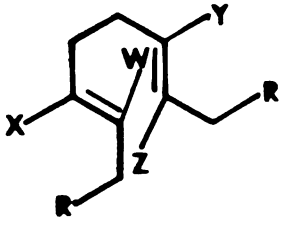
modifications at the C-2 and C-3 carbons, were incubated with an insoluble yeast enzyme preparation. Detailed results indicated that only analogues 9 and 10 yielded tritium labeled, hydrocarbon products, the production of which was absolutely dependent on the presence of NADPH and active enzyme. Furthermore, formation of radio-labeled products could be increased by addition of unlabeled farnesyl pyrophosphate to the incubation medium. Tritium from substrates 9 and 10 was incorporated into hydrocarbon products in approximately 6 and 0.75%, respectively, of the incorporation obtained in standard incubations using [1-^{3}H]-farnesyl pyrophosphate. Both hydrocarbon products behaved similarly to squalene on silica gel thin-layer chromatographic analysis.

Since both NADPH and active enzyme were absolute requirements for the formation of the hydrocarbon products derived from 9 and 10, and since addition of farnesyl pyrophosphate stimulated formation of these products, likely candidates for their structure seemed to be either the symmetrical squalene analogues 12 or 13 derived from two units of the same substrate, and/or the unsymmetrical compounds 14 or 15 due to mixed condensation of the artificial substrates with 1. In order to unambiguously identify the structure of the hydrocarbon products formed from



	W	X	Y	Z
12	Me	Me	Me	Me
13	H	H	H	H
14	Me	Me	H	Me
15	H	H	H	Me

substrates 9 and 10, squalene analogues 12 to 15 were synthesized. Preparation of analogue 12 by Castillo has been described in detail elsewhere.[1d] The details of the synthesis of compounds 13, 14 and 15, prepared by this author, can be found in Appendix A. An outline of the synthesis of these analogues has also appeared in a preliminary communication of this work.[10]

Large scale incubations using [1-^{3}H]-9 were carried out in order to obtain a quantity of product sufficient for structural identification. Preparative glc analysis of the crude product, as illustrated in Fig. 3, demonstrated the presence of 3 major radio labeled peaks. Peak (c), a polar impurity observed in control incubations, was removed by preparative tlc of the sample. The resulting purified product, now containing only approximately equally radiolabeled peaks (a)

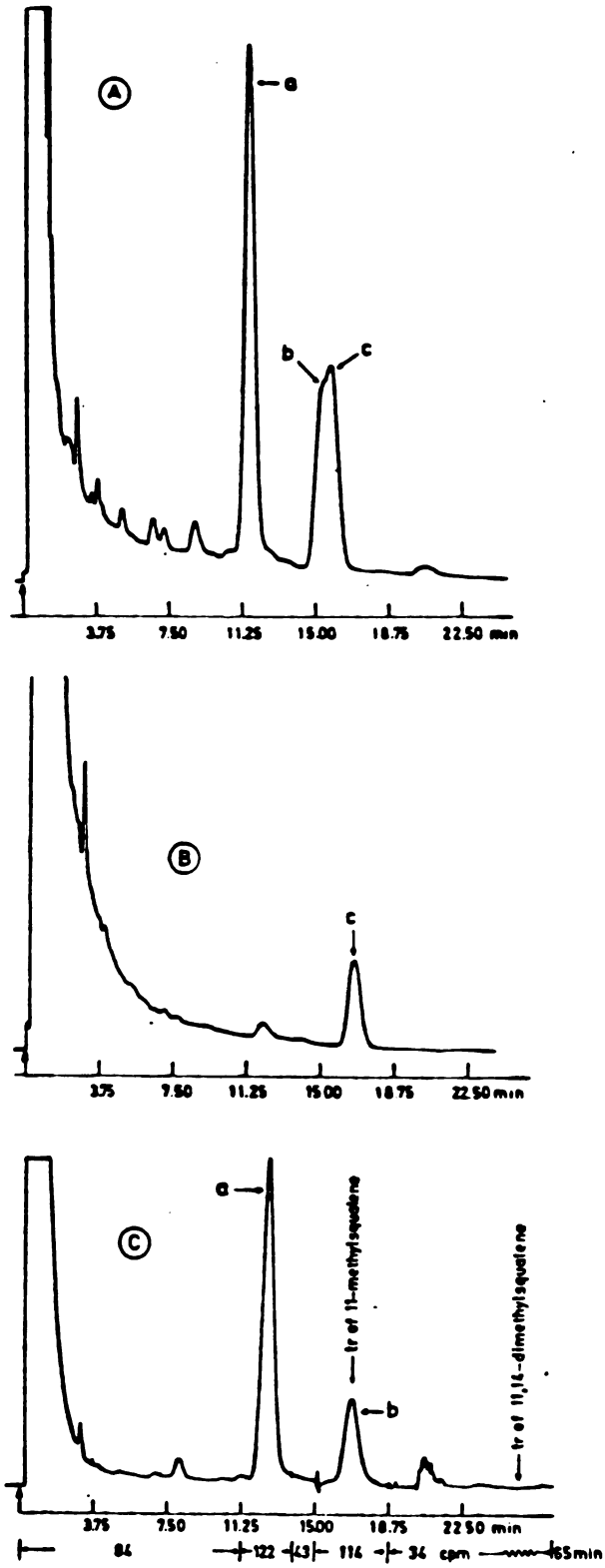


Figure 3 Gc analysis of the mixture obtained by a large scale incubation of 1-^{3}H -2-methylfarnesyl pyrophosphate (A); and of the polar component obtained by tlc separation of this incubation mixture (B). Gc conditions: System A, 220°. (C): GC analysis of the tlc purified labeled hydrocarbon obtained by a large scale incubation of [1-^{3}H]-2-methylfarnesyl pyrophosphate. GC conditions: System C, 200°.

and (b), was subjected to glc-mass spectrometric analysis. Peak (a) consisted primarily of endogeneous squalene, exhibiting the expected molecular ion at m/e 410 as shown in Fig. 4. Nevertheless, a radio labeled compound of unknown structure was assumed to lie buried beneath the squalene peak since the incubation did not contain a source of labeled squalene. The structure of the unknown compound was not determined since it could not be separated from squalene using standard chromatographic techniques. Peak (b), which had a glc retention time identical to that observed for authentic 14, showed a molecular ion at m/e 424 corresponding to $C_{31}H_{52}$. This molecular ion and the associated fragmentation peaks appear 14 mass units higher than those in squalene as shown in Fig. 4, clearly identified peak (b) as 11-methylsqualene (14) formed by unsymmetrical coupling of 1 with [1-^{3}H]-9.

Two separate series of experiments were then carried out in order to determine whether analogue 9 binds as the first or second substrate in the synthesis of 14. These two steps are readily distinguished, since a C-1 proton is exchanged only in the first, and not in the second molecule which binds to the enzyme.[7] In one series of experiments, we were unable to clearly establish whether or not the enzyme was releasing tritium into the incubation medium due to the low specific activity of [1-^{3}H]-9. 1,1-Dideuterofarnesyl pyrophosphate (16) was then synthesized and incubated with unlabeled 9. GLC-mass spectrometric analysis of the resulting product, shown in Fig. 4, indicate a molecular ion at m/e 425 with expected fragmentations giving salient peaks 1 mass unit greater than observed for 14. This result, outlined in Scheme III, established that substrate 9 was being utilized only as a co-substrate in the second catalytic step.

Identification of the radio-labeled hydrocarbon product obtained from incubation of [1-^{3}H]-10 was carried out as previously described. The product, obtained in

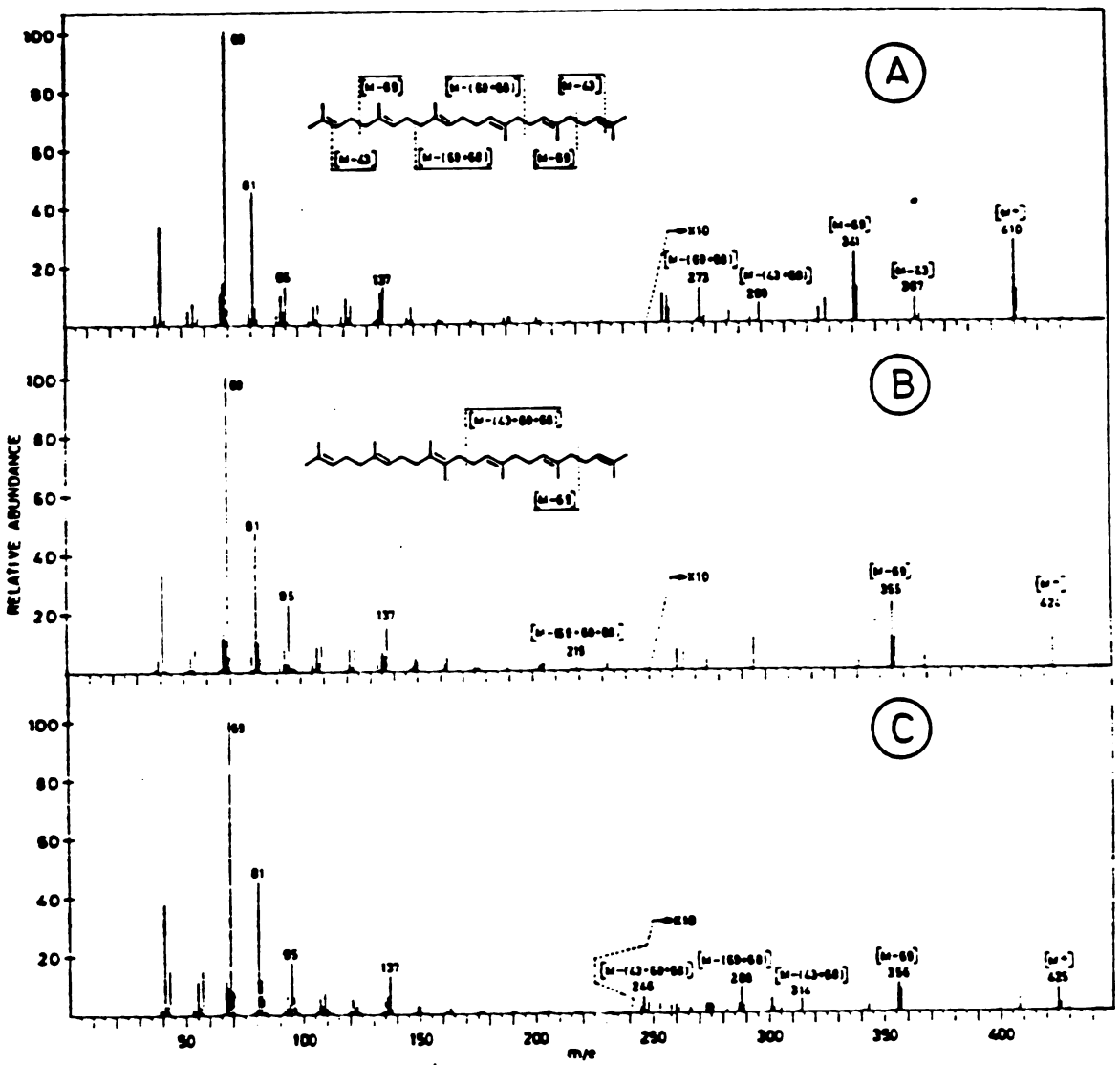
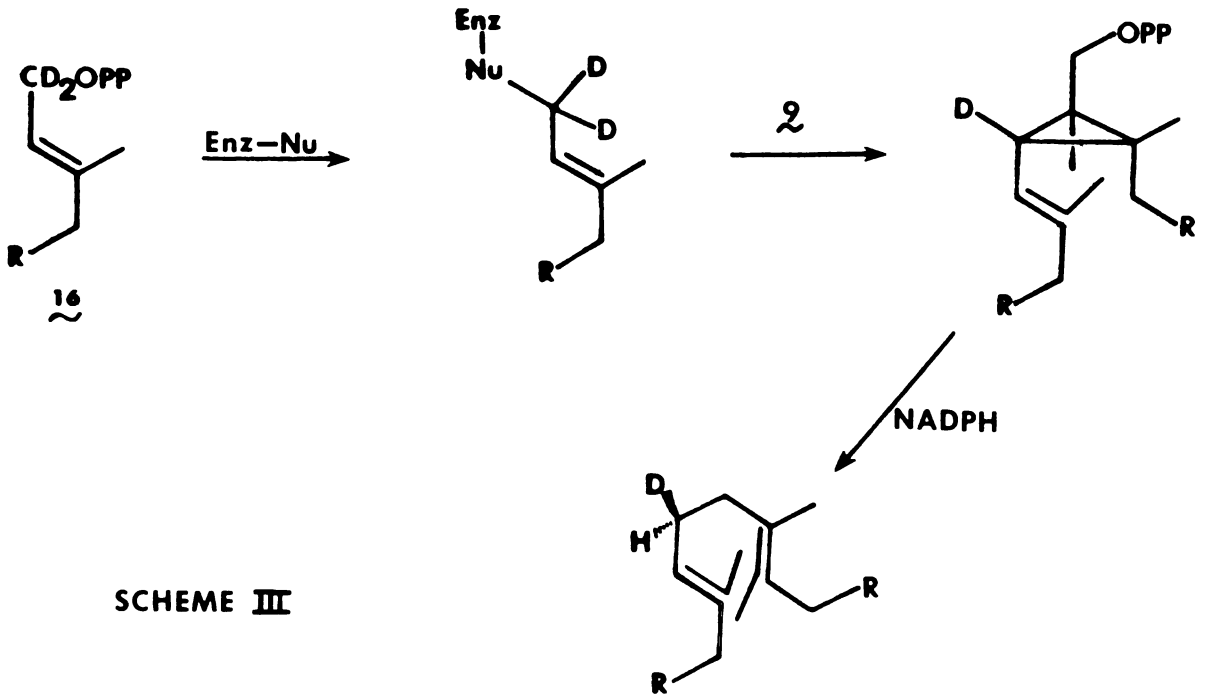


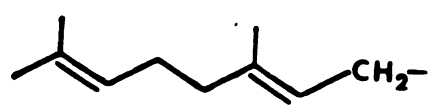
Figure 4. Mass spectra of endogenous squalene (A); the compound obtained by incubation of 2-methylfarnesyl pyrophosphate (B); and the substance obtained by incubation of 2-methylfarnesyl pyrophosphate and 1-dideuterio-farnesyl pyrophosphate (C).

preparative quantities by large scale incubations, and purified by neutral alumina column chromatography, had tlc properties identical to those of squalene.



SCHEME III

11-Methyl-13(S)-deuterosqualene

R = 

Preparative glc analysis (Fig. 5) revealed that peak (b), with a retention time identical to that of 10-desmethyl squalene (15), contained virtually all of the radioactivity. The identity of the radio-labeled product as 15 was verified by glc-mass spectrometric studies. The mass spectra of the product and of authentic 15, presented in Fig. 6, show identical fragmentation patterns. Tritium release experiments using [1-^{3}H]-10 clearly established that statistically significant

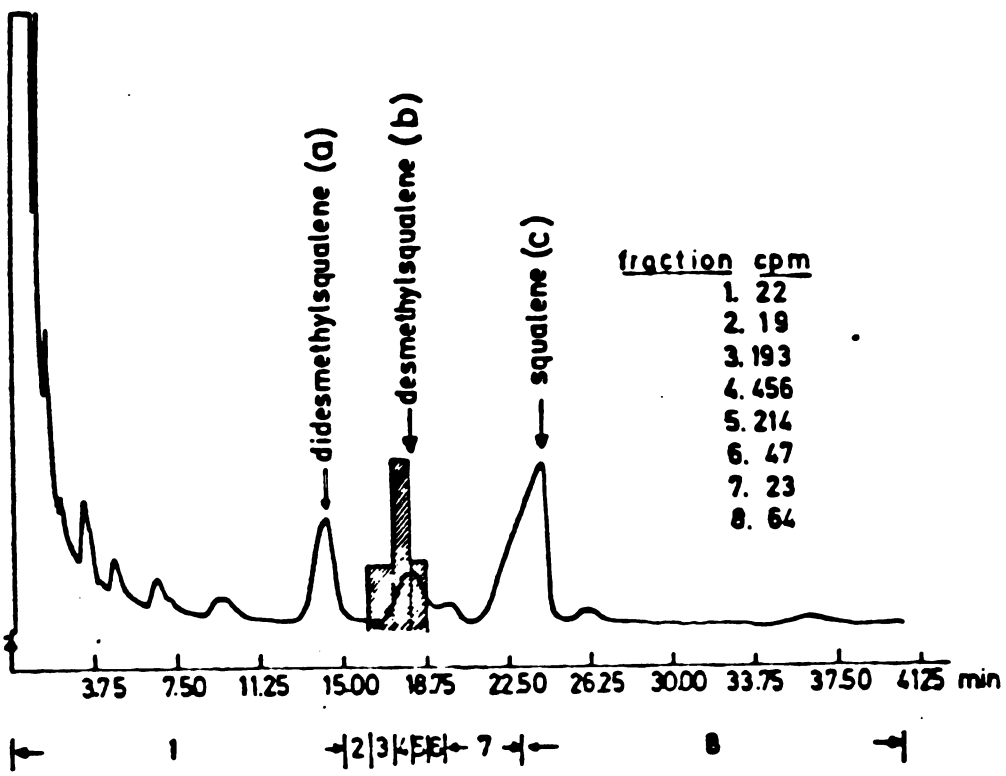


Figure 5. GC analysis of the mixture obtained by a large scale incubation of [1-^{3}H]-3-desmethylfarnesyl pyrophosphate. GC conditions: System C, 190°.

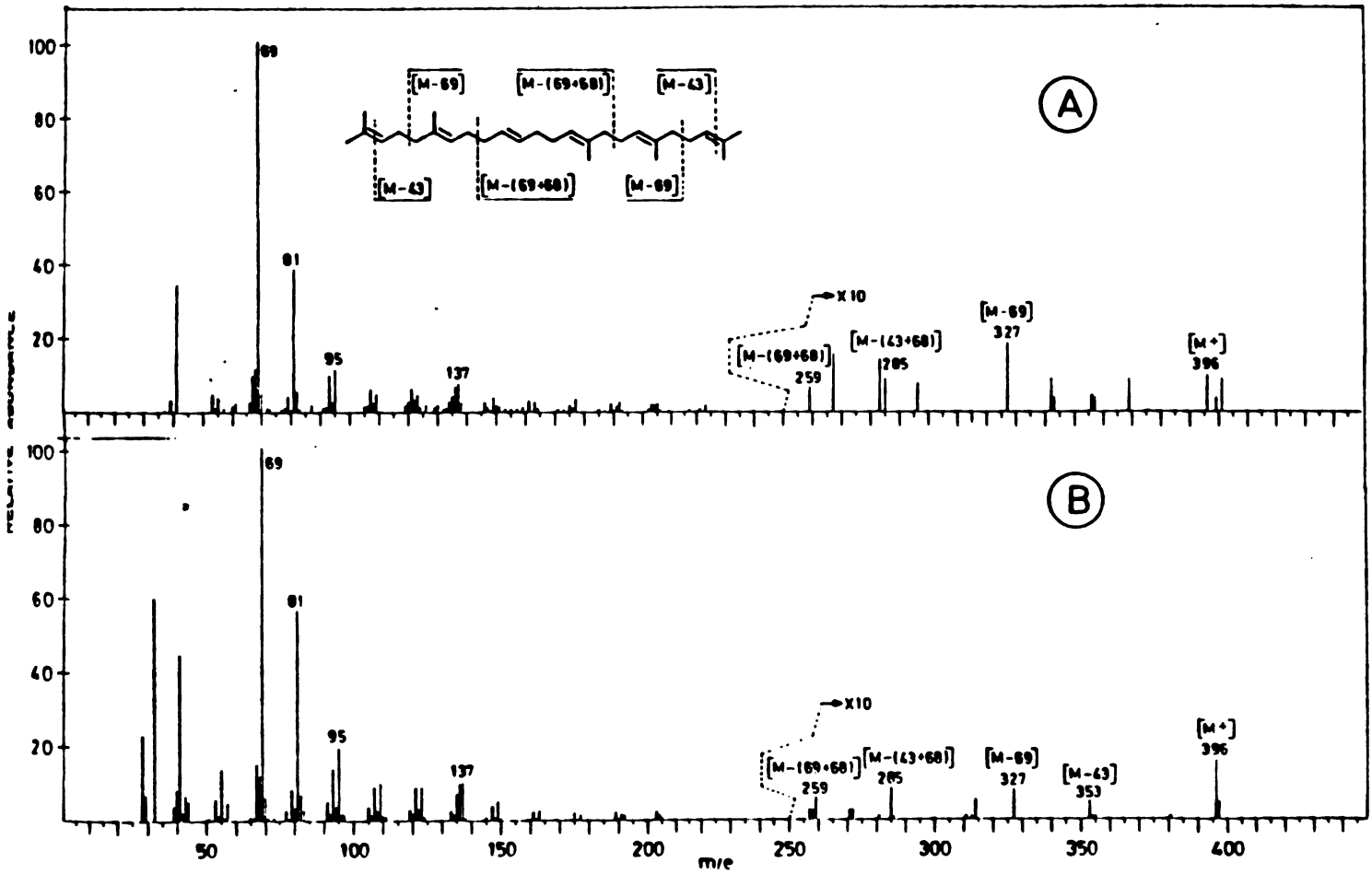


Figure 6. Mass spectra of the substance obtained by incubation of 3-desmethylfarnesyl pyrophosphate (A); and of an authentic sample of 10-desmethylsqualene (B).

amounts of tritium were not being released into the incubation medium. This demonstrated for the second time that an artificial substrate, in this case 10, was only acceptable during the second catalytic step.

Acceptance of both the 2-methyl (9) and desmethyl (10) analogues only as substrates for the second catalytic step, and complete rejection of 11 hints at the existence of a highly stringent structural requirement for initiation of the enzymatic reaction. This, coupled with the fact that analogue 10 is approximately 10 times worse as a substrate than 9, clearly indicates the importance of the 3-methyl group. These results are most consistent with an induced-fit hypothesis in which the C-3 methyl anchors the substrate in a favorable orientation while the C-2 carbon fits into a region of stringent steric requirements. These results also argue favorably for two separate, catalytic sites in the enzyme rather than one, the first, proton exchanging site appearing to be more specific than the second site.

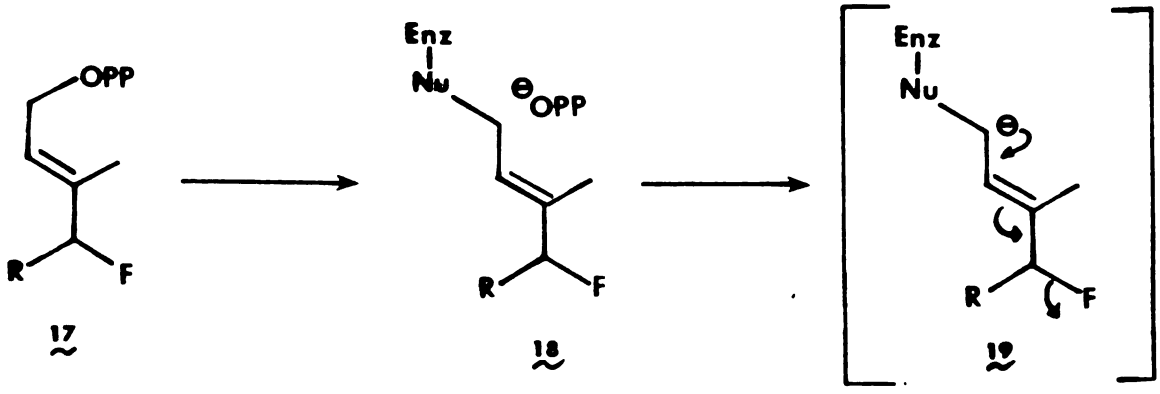
This rather simple explanation of a complicated chain of events may be somewhat naive in light of more recent results. Two groups[10] have demonstrated that the terminal 10,11-double bond in farnesyl pyrophosphate is not required for substrate activity. Lack of the 7-methyl group in 1 is also acceptable by the enzyme.[1e,11] However, Washburn and Kow[10a] have shown that reduction of the 6,7-double bound in 1 is not tolerated by the enzyme. In view of these new findings it is quite possible that the enzymatic mechanism involves some type of intimate assistance from the 6,7-double bond. If this is indeed the case, then the role of the 3-methyl group in the enzymatic reaction may be far more complicated than earlier postulated.

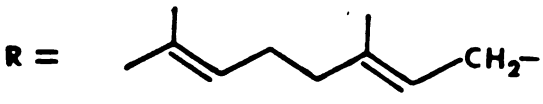
III. 4-Fluorofarnesyl Pyrophosphate. A Mechanistic Probe of Squalene Synthetase

A. Rationale

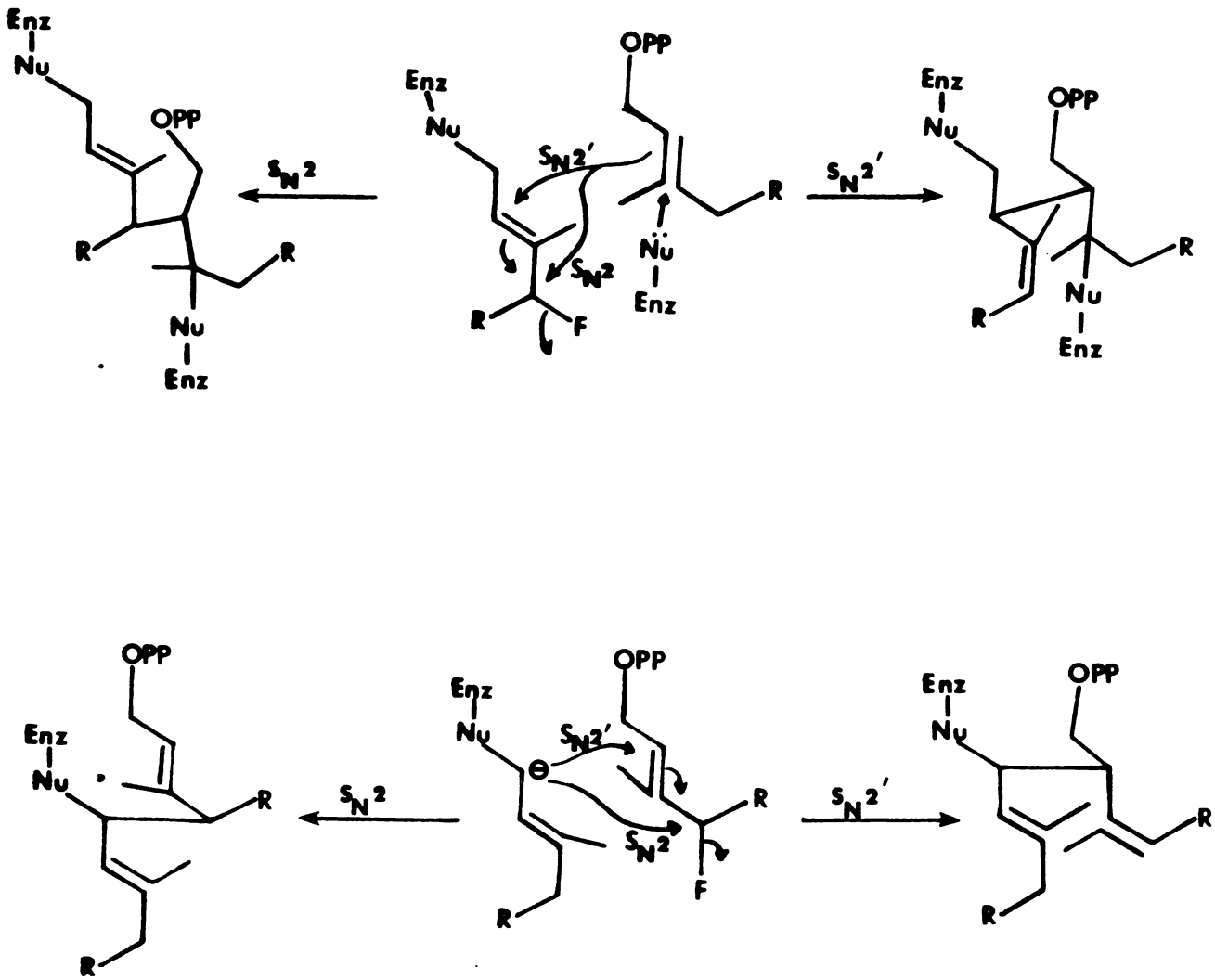
In order to extend our study of the substrate specificity, and to continue our search for potent inhibitors, of squalene synthetase, fluoro analogue 17 was prepared. The details of its synthesis are presented in Appendix B.

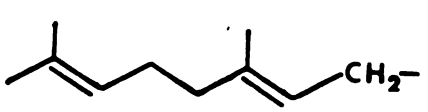
Pyrophosphate 17 could theoretically lead to irreversible inactivation of squalene synthetase. Given an enzyme mechanism such as that in Figure 2 (Path B), for example, on enzymatic removal of the C-1 proton, enzyme complex 18, if formed, would generate allylic carbanion 19. Intermediate 19 might then eliminate fluoride ion, resulting in enzyme inactivation. Other suicidal inactivation schemes of an analogous nature can be invisioned using 17. A few such examples are shown in Scheme IV.





SCHEME IV



R = 

B. Results

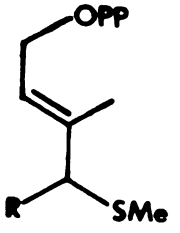
Fluoro analogue 17 was tested as an irreversible inhibitor of squalene synthetase in collaboration with Yost using the previously described procedures.[1d] The results, which indicate that 17 does not measurably inactivate the enzyme, are shown in Figure 7. A ~15% reduction in enzymatic activity relative to controls would be considered statistically significant.

Reversible inhibition studies performed with Wei and Yost using already published procedures, indicate that 17 binds to the enzyme in a manner similar to other, previously studied analogues.[1d,1e] These results are shown in Fig. 8.

Finally, [1-^{3}H]-17, the synthesis of which is described in Appendix B, was totally unacceptable to the enzyme as a substrate when analyzed by our standard procedures.[1d,1e] Substrate activity approximately 0.1% that of 1 would have been detectable using 17.

C. Discussion

Formation of an enzyme-substrate complex analogous to 18 presumably does not occur since fluoro analogue 17 is neither a substrate nor an irreversible inhibitor. These results are similar to those obtained previously with the 4-thiomethyl analogue 20.[1d]



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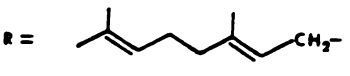


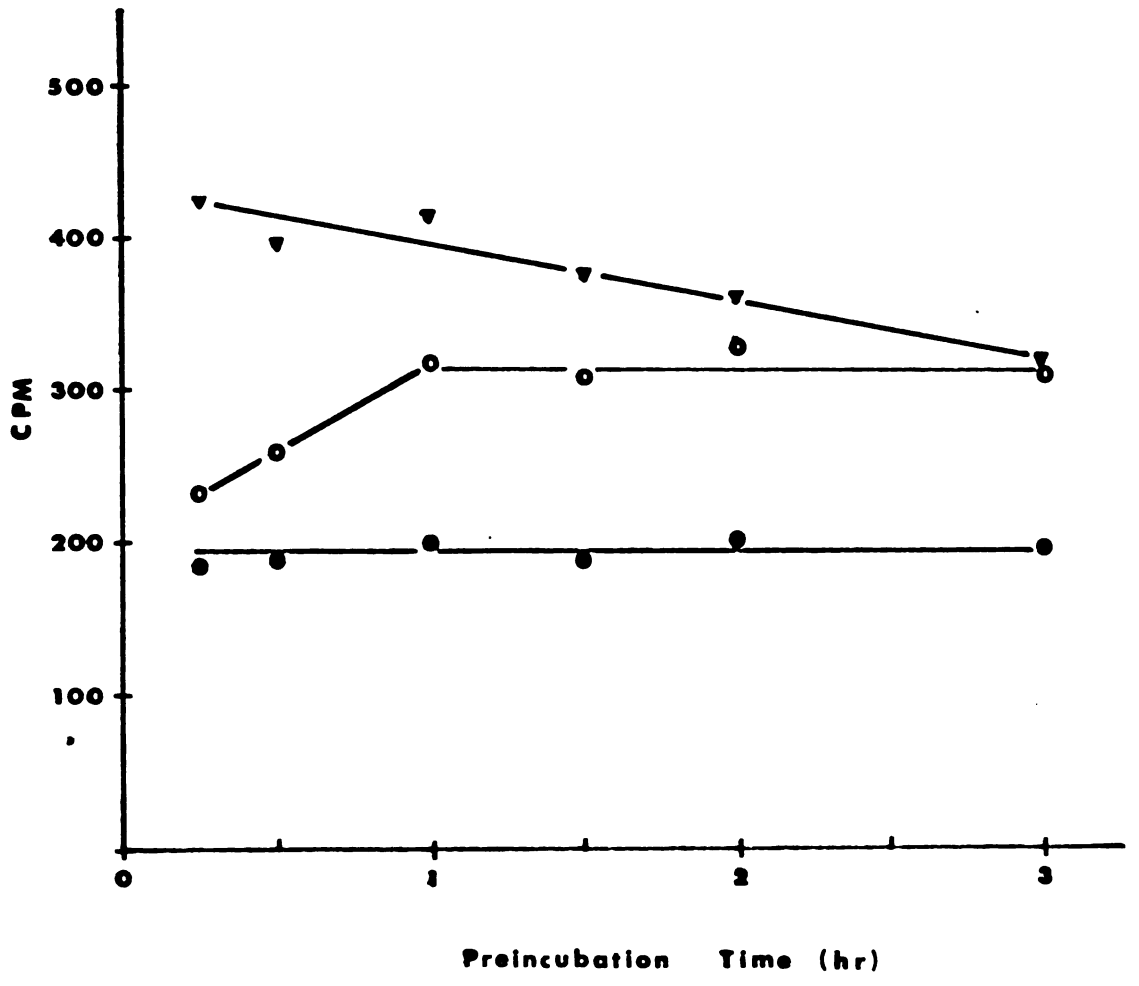


Figure 7

Effect of preincubation of analogues 17(●), 20(○), and control (▼) on squalene synthetase at 37°. Enzyme activity determined using [1-^{3}H]-1, in the normal bioassay[1d].

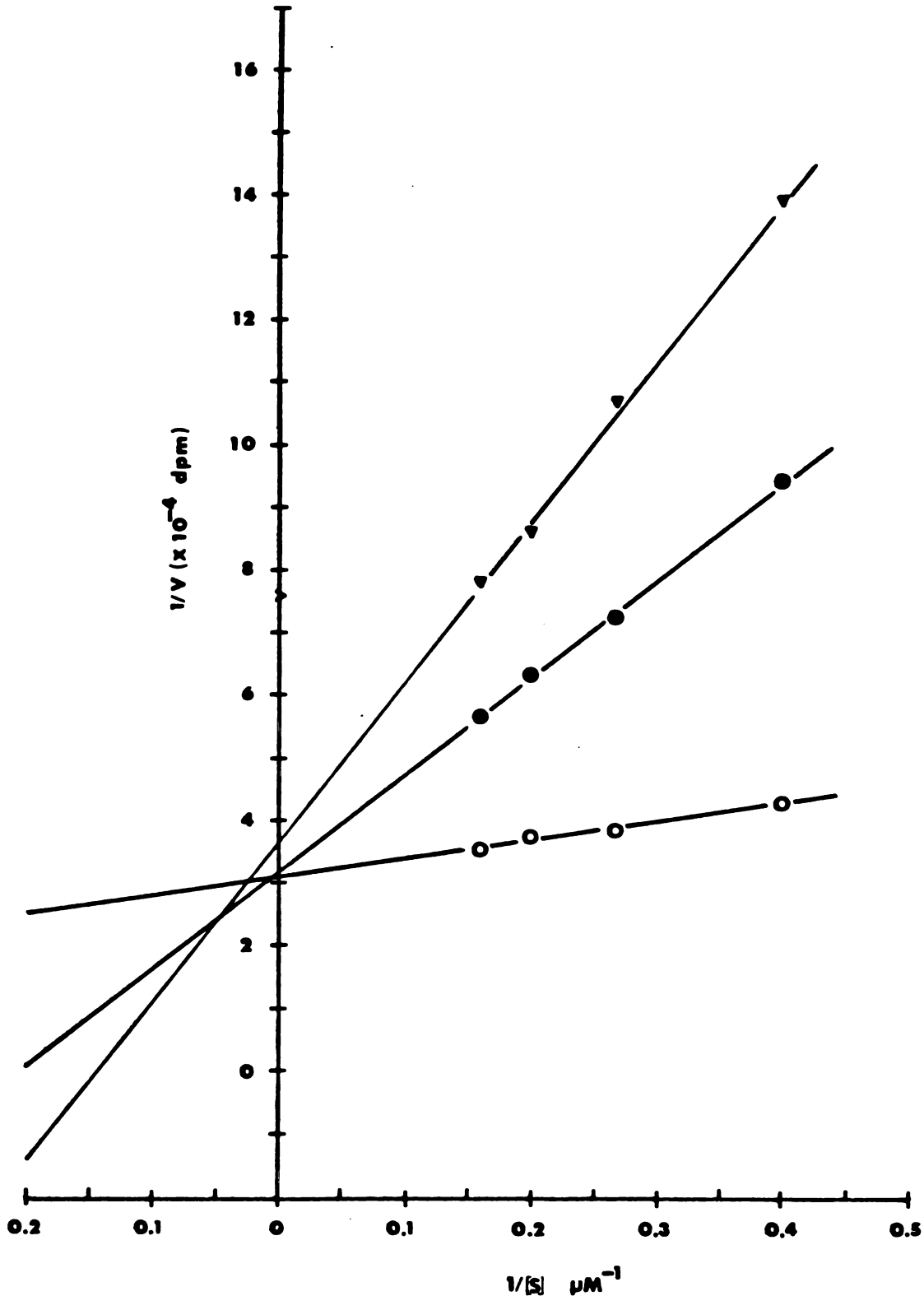
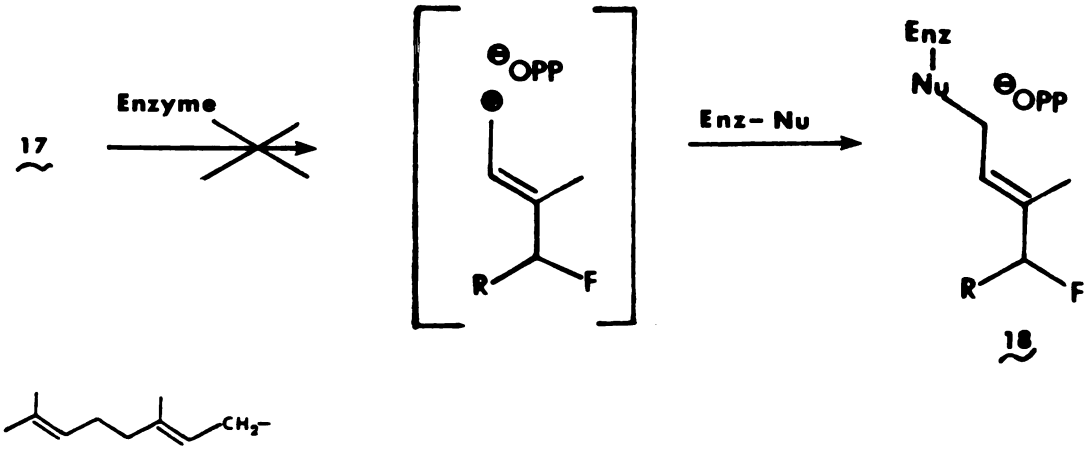


Figure 8.

Lineweaver-Burk plot for 17. [S] is the concentration of [1-^{3}H]-1. Concentration of 17: 0(○); 2 μM(●); and 4 μM(▼).

In the case of analogue 20, the steric bulk of the thiomethyl group can easily be used to rationalize its inactivity. However, a similar steric argument for the inactivity of 17 is virtually excluded by the similarity in size between hydrogen and fluorine.[12] The probable conformational preferences of analogues 1, 17, and 20 were compared using both Dreiding models and computed models based on computer minimization of steric interactions between neighboring substituents, assuming standard bond lengths, angles, and "hard sphere" atomic radii.[13] The results, which neglect electronic effects, suggest that 17 has a favored conformation similar to 1 while that of 20, though probably different, is not separated from it by major steric barriers. It seems unlikely that minor conformational effects are totally responsible for the inability of analogues 17 and 20 to act as substrates or irreversible inhibitors.

A fluorine electronic effect similar to that described by Poulter and Rilling (see Section I), based on the destabilization by a fluorine atom of adjacent cationic transition states, is an attractive alternative explanation for rejection of 17 by the enzyme. Initial ion-pair formation from 17, while reversibly bound to the enzyme, may precede all other enzymatic processes. This



fluorine destabilization effect may be impeding the reaction to such a degree that

product formation is not detectable. Under our normal incubation procedures a substrate less than approximately 10^{-3} as effective as 1 would be undetectable. Poulter and Rillings' fluoro analogues were, in one case, 10^{-7} as effective as the natural substrate (Table 1). However, the greater stability of purified prenyl transferase permitted much longer incubation times than those possible using squalene synthetase.

Alternative explanations for the inactivity of 17, which are based on an electronic perturbation due to the fluorine, are also possible. For example, the ability of the 2,3-double bond to complex to species of an electrophilic nature would also be compromised by the 4-fluoro substituent.

CHAPTER 1

GENERAL INTRODUCTION

The general interest in fluorinated organic compounds, especially within biologically related areas, has grown immensely during the past few years. Fluorine's small size (1.35 vs. 1.10Å for hydrogen)[12] and high electronegativity, as well as its hydrogen bonding properties,[14] its ability to enhance the lipophilic nature of organic molecules[15], and its potential as a leaving group in displacement reactions[16], all contribute to its general importance in medicinal and biochemical applications. A significant proportion of these applications has centered on the use of fluoro substituted analogues in enzyme mechanism[12,14,17] and inhibition[18] studies. Other recent areas of activity include the successful utilization of fluorinated compounds as antibacterials[19], anticarcinogens[20], antiinflammatory agents[21], antiarrythmics[22], and insecticides.[23] Significant advances have also been made in the synthesis of fluorinated juvenile hormones[24], in elucidation of the metabolism of fluoro compounds,[25] and in the employment of fluorine nuclear magnetic resonance techniques[17a,26] for the study of a variety of biological systems.

The increasingly widespread demand for specifically fluorinated compound has resulted in parallel requirements for (1) new, viable synthetic approaches to these compounds,[12] (2) the development of new fluorinated functional groups, and (3) a better understanding of their properties.[27]

CHAPTER 2

The Synthesis of α-Fluoroalkyl Esters

2.1 Introduction

α-Fluoroalkyl carboxylic esters, 21, constitute a group of fluorinated compounds for which virtually no data is available, particularly with regards to their stability and other physical properties. The known derivatives of 21 are presented in Table 3.

$$RCFX-OCOR'$$

21

X = H, F, alkyl

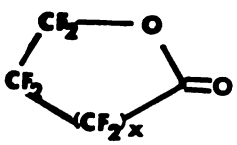
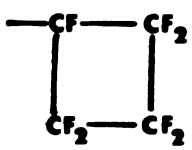
The structurally related α-fluoroalkyl ethers, an example of which is fluoromethyl methyl ether (22)[29], are generally hydrolytically unstable, an instability probably due in part to formation of stabilized oxycarbonium ions such as 23.[29,30]

$$\underset{22}{CH_3OCH_2F} \xrightarrow{H_2O} \underset{23}{CH_3\overset{\bullet}{O}=CH_2} + F^{\ominus}$$

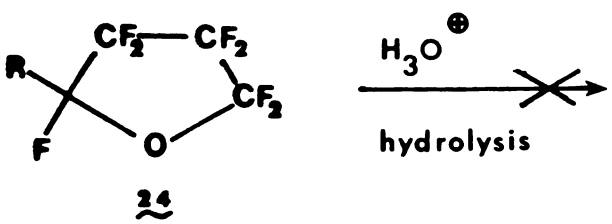
TABLE 3

Some Known α-Fluoroalkyl Esters

RCO_2R^1

R	R^1	Ref
CF_3	$CFHCF_3$	28d
CF_3	CF_2H	28c
CF_3	CF_2CF_3	28d
C_4H_9	CF_2H	28c
Ph	CF_2H	28c
CF_3	CF_2CF_2H	28d
 x = 1, 2		28a
CH_3		28b

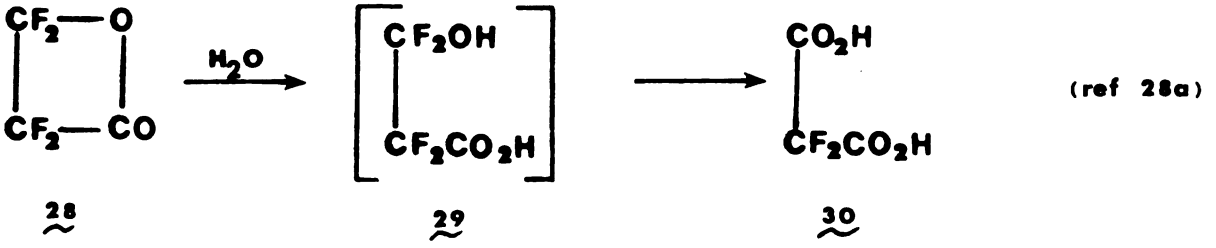
However, hydrolytically inert polyfluorinated ethers such as 24 are also known[31] whose stability may derive from a reduced ability of oxygen to donate its π



24

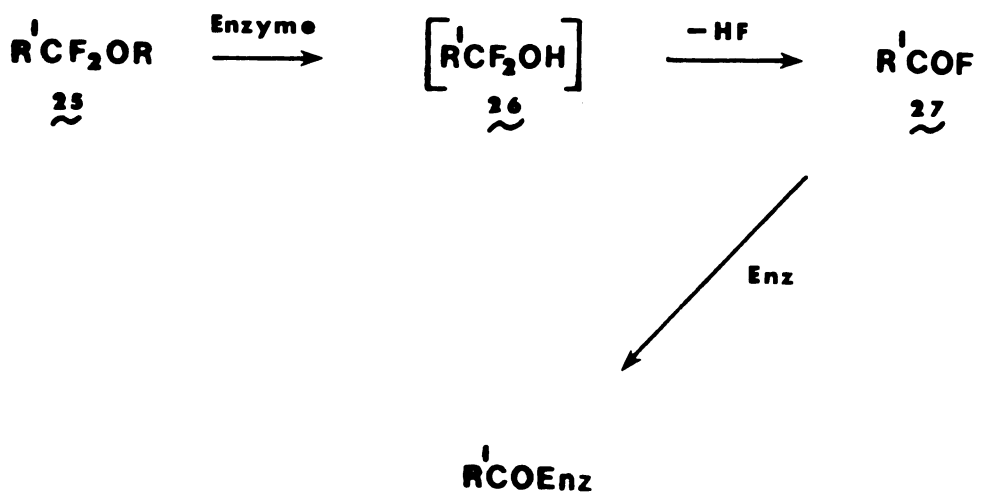
electrons. The electron withdrawing acyl group of an α-fluoroalkyl ester should provide an analogous stabilizing influence, decreasing the ability of the ester oxygen to labilize an α-fluorine by a mechanism analogous to that shown for the formation of 23 from 22.

One of the major goals of pharmaceutical and biochemical research today is to develop new methods by which specific enzymatic processes can be inhibited. The biologically ubiquitious ester functionality is hydrolyzed by numerous enzyme systems, including phosphatases[32] and esterases[33] which hydrolyze phosphorus and carbon esters, respectively. We have recently become interested in the use of α-difluoroalkyl esters as potential inhibitors of these enzymes. In Fig. 9 is shown a general scheme for the possible inhibition of hydrolytic enzymes such as esterases and phosphatases using difluoroesters. Enzymatic hydrolysis of ester 25 would provide α-fluoro alcohol 6, a species known to readily eliminate hydrofluoric acid.[28a,b,34] For example, Hazeldine[28a] has shown that aqueous reagents open fluorinated lactones such as 28 to provide compound 29, a transient species which readily affords diacid 30 following loss of two fluoride anions.



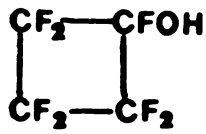
28 29 30 (ref 28a)

FIGURE 9



The recently prepared trifluoromethanol (31)[35], isolable at low temperatures (<-20°C), has been shown to be highly unstable towards loss of hydrofluoric acid at temperatures above -20°C. All attempts to prepare α-fluoroalcohols, except for the recent success with 31, have been unsuccessful[36], although alcohol 32 was prepared and reported to be fairly stable in the absence of moisture.[28b]

31



32

Its abnormal stability may be a function of ring strain and multiple fluorine substitution.

Assuming the normally observed instability of α-fluoroalcohols, loss of HF in 26 (Fig. 9) would provide acyl fluoride 27 which, if sufficiently reactive, could then acylate a nucleophilic group within the enzyme active site resulting in a potential inactivation of the enzyme.

The mode of enzyme inactivation depicted in Figure 9 is highly dependent on the reactivity of acyl fluoride 27. The chemical and biological reactivity of acyl fluorides has been studied.[37] The results of an investigation of the relative solvolysis rates of acetyl halides 33 are given in Table 4.[38] Clearly the fluorinated species was the least reactive under the reaction conditions described. This general trend in the reactivity of acyl halides, ie, F<CI<Br<I is frequently observed.[38] However, a comparative study of the hydrolysis of benzoyl halides indicated that the acyl chloride derivative was hydrolyzed 100X faster than the fluoro analogue under neutral conditions, whereas, under basic conditions the acyl fluoride was hydrolyzed 40% faster than the chloride.[39] The mechanism of nucleophilic addition to acyl halides is known to vary with the experimental conditions.[40] Acyl fluorides have also been found, in some cases, to be biologically more reactive than other acyl halide derivatives[41]. For example, carbamoyl halides

TABLE 4

Relative Solvolysis Rates of Acetyl Halides[38]

$$CH_3COX \xrightarrow[ROH]{HOAc} CH_3CO_2R$$

X	Relative Rate[a]
F	1
Cl	1.4×10^4
Br	2.1×10^5

(a) Solvolyses were performed at 40° in acetic acid using 2-decanol as reagent.

have been employed as inhibitors of hydrolytic enzymes such as acetylcholinesterase.[42] The data in Table 5, taken from this study, show that the acyl fluorides were more reactive as inhibitors than the chloro derivatives.[42] Furthermore, the enzymatic inhibition observed is reportedly due to a nucleophilic acylation process.[42] The results described above, in conjunction with those from other related nucleophilic reactions of acyl halides[40], clearly indicate that acyl fluorides can function as reactive acylating agents, thus indicating the feasibility

TABLE 5

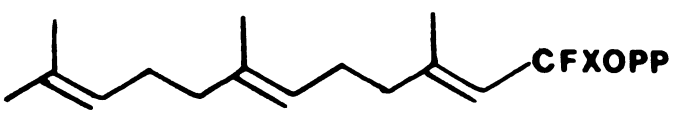
Specific Rate Constants of Carbamoyl Halides As Inhibitors of Hydrolytic Enzymes[a]

Inhibitor		k(1/mol S) AcChE	Human Serum Ch E	Chymotrypsin
Ph_2NCOX	k_F/k_{Cl}	160	89	8
PhMeNCOX	k_F/k_{Cl}	5.4	13	5

(a) Data taken from reference 42.

of the inhibition scheme shown in Fig. 9. Furthermore, such a self-catalyzed inactivation of hydrolytic enzymes would not only be of importance in investigations of the enzymes themselves, but would also be of potential value in drug development.

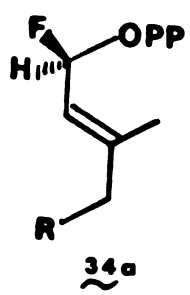
Our initial and still most immediate interest in α-fluoroalkyl esters stems from the promising value of analogues 34 and 35 both as mechanistic probes of the enzyme squalene synthetase and as possible irreversible inhibitors of the enzyme. The suggested role for 34 and 35 as inhibitors is based on the fact, already



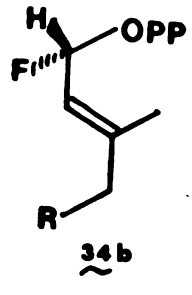
34 (X=H)

35 (X=F)

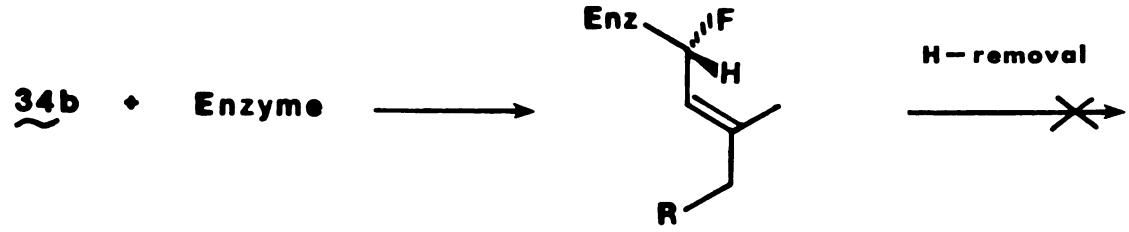
discussed in the Prologue, that the pro-S-hydrogen of the C-1 carbon of farnesyl pyrophosphate (FPP) is exchanged with a hydrogen from NADPH, and that only the FPP unit binding at the first catalytic site of the enzyme undergoes this hydrogen exchange. Assuming that a normal enzyme-substrate complex were formed (Prologue, Section I), analogue 34b would act as an irreversible inhibitor since regeneration of the active site, which requires proton removal, is blocked in this case by the presence of the fluorine atom. On the other hand, 34a could act as a substrate if the enzyme-substrate complex forms, since proton removal is still possible. This mode of inhibition is also valid for difluoroanalogue 35 except that its potential effeciency as an inhibitor would theoretically be twice that of racemic



34a

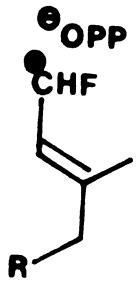


34b



monofluoro analogue 34, assuming 35 formed the enzyme complex equally as well as 34.

As previously discussed in the Prologue, 4-fluorofarnesyl pyrophosphate (17) was neither a detectable substrate nor an irreversible inhibitor of squalene synthetase. One plausible explanation for this lack of biological activity was postulated to be retardation of required ion-pair formation by the electronegative fluorine. Similar ion-pair formation of 34 and 35 giving fluorocarbonium ions 36 and 37, respectively, might therefore be a prerequisite to enzyme inhibition. The possible effects of the fluorines in 36 and 37 poses an interesting question. Instinctively, one is tempted to assume strong destabilization of the carbonium ions due to the adjacent, strongly electron-withdrawing fluorines. However, the results of theoretical calculations, presented in Table 6, suggest the opposite trend. For example, one fluorine may stabilize a carbonium ion by 26-31 kcal/mol



36

37

relative to a hydrogen atom. This stabilization by fluorine has been discussed in a pertinent review.[46] Olah has suggested that donation of non-bonding electrons in the fluorine atom is responsible for the observed stabilization of carbonium ions.[46] Such a resonance stabilizing effect due to fluorine has been

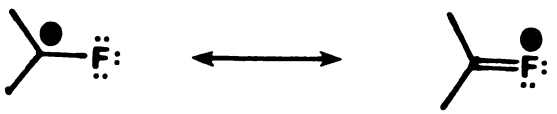
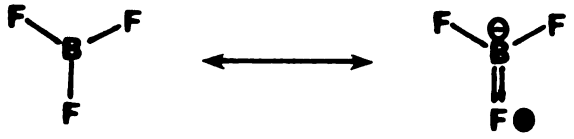


TABLE 6

Theoretical Carbonium Ion Stabilization
Energies Relative to $^{(+)}CH_3$

Ion	S.E. (kcal/mol)	Reference
$^{(+)}CH_3$	0	-
$FCH_2^{(+)}$	27	43
	26	44
	31	45
$F_2CH^{(+)}$	26	43
$F_3C^{(+)}$	14	43
$CH_3O\overset{(+)}{C}H_2$	66	43
$CH_3CH_2^{(+)}$	35	44

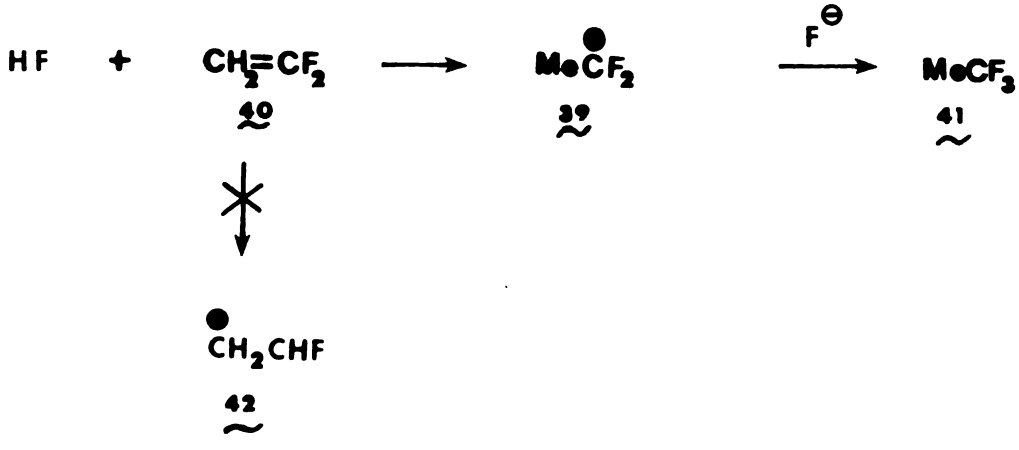
experimentally documented by Onak and co-workers[47] in a study of boron trifluoride by boron-11 nuclear magnetic resonance spectroscopy. Olah's extensive NMR studies



(ref 47)

of fluorocarbonium ions[46] have further confirmed the ability of fluorine to stabilize carbonium ions. Both ions 38 and 39 have been observed using low temperature NMR techniques.[46] Further evidence for the ability of fluorine to

stabilize adjacent carbonium ions, rather than destabilize them, is found in the well studied electrophilic addition to fluoroolefins. These reactions are known to follow the Markovnikoff rule. For example, hydrofluoric acid addition to vinylidene fluoride (40) affords 41 indicating the intermediacy of carbonium ion 39 rather than 42.[46]



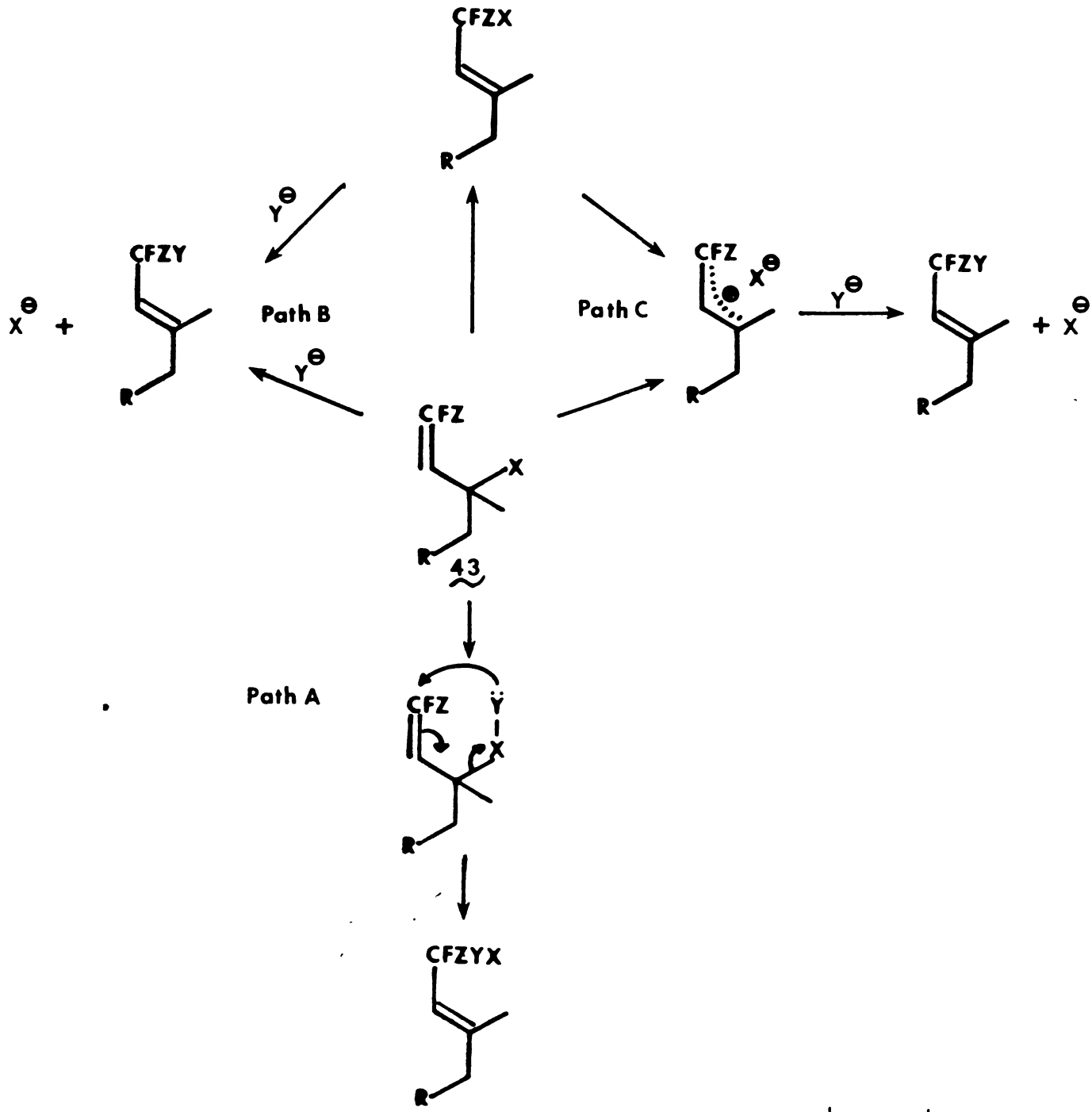
The fluorocarbonium ion studies, taken as a whole, tend to indicate that formation of ion-pairs such as 36 and 37 may be at least as favorable as in the natural, non-fluorinated substrate despite the fact that the purely inductive effect of fluorine in a compound such as 17 substantially decreases the stability of the analogous cation.

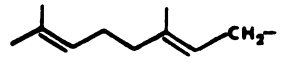
The promise of exciting, multiple uses for α-fluoroalkyl esters such as the farnesyl pyrophosphate derivatives 34 and 35, however, is blocked by a lack of synthetic methodology. The development of suitable preparative methods has therefore been pursued with esters 34 and 35 as the pilot targets. Extension of these studies, and application to specific biomedical problems, are left for future investigations.

2.2 α-Fluorofarnesyl Esters: Synthetic Strategy

The known instability of α-fluoroalkohols (vide supra) precludes their use as precursors to ester derivatives such as phosphates and acetates. Previously reported α-fluoroalkyl esters[28] (Table 3) were prepared by severely restricted procedures suitable primarily for poly fluorinated derivatives. Our basic strategy for the synthesis of α-fluorofarnesyl esters, as illustrated in Fig. 10, is based on three main approaches: (1) allylic transposition of functionality (Path A); (2) nucleophilic displacement reactions under S_N2 or S_N2' conditions (Path B); (3) nucleophilic displacement reactions with ionic intermediates (Path C). Examples of these general transformations in non-fluorinated cases are available.[48] The synthesis of the pivotal precursor 43 was therefore the initial subject of our investigation.

FIGURE 10



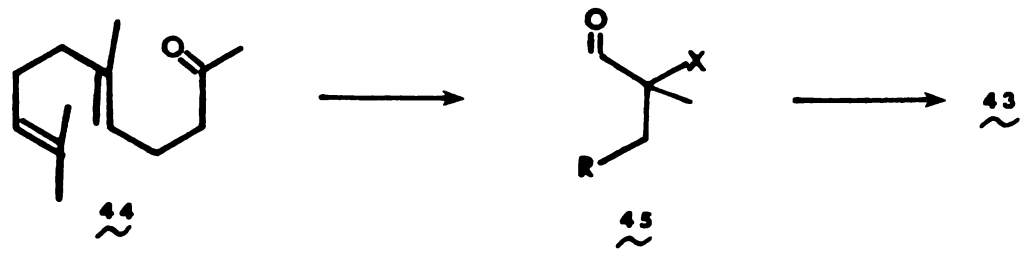
R = 

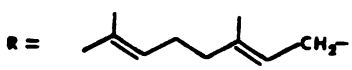
X = halide, OR′

Z = H, F

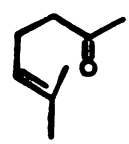
2.3 Synthesis of Precursors

Our initial goal was to use readily accessible E-geranyl acetone (44)[49] as a



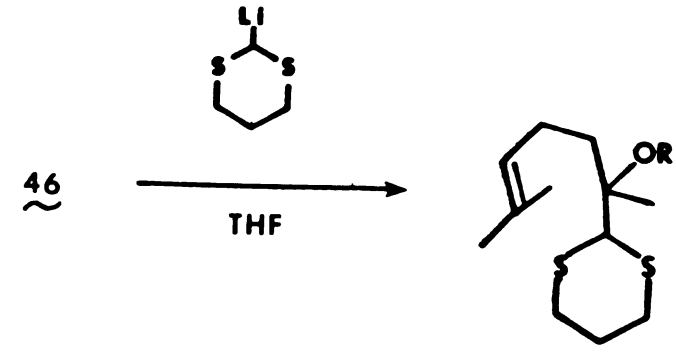


precursor to α-functionalized aldehyde 45 which, in turn, could be transformed into fluoroolefin 43 (X=halide, OR') using one of several procedures.[12,50] The conversion 44 to 45 requires a one-carbon homologation reaction of a carbonyl compound to an α-halo[51] or α-hydroxy[51e,52] aldehyde, transformations for which several methods are available in the literature. Preliminary studies on the conversion of 44 to 45, however, were performed using commercially available ketone 46 as a model rather than geranyl acetone itself (44).



46

Nucleophilic acylation[53] using 1,3-dithiane[52e] as a masked aldehyde group was the first approach attempted. Treatment of ketone 46 with lithio dithiane[52e], followed by aqueous work-up, gave alcohol 47a in 90% yield. Analogue 47b was



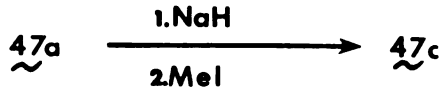
R

47 (a) H

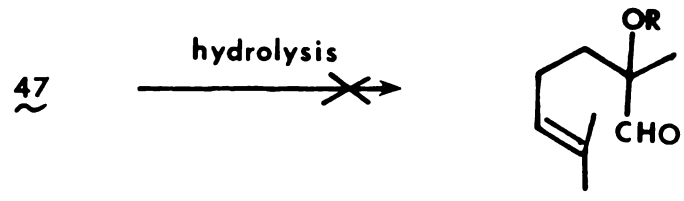
(b) TMS

(c) Me

similarly prepared by quenching the reaction with trimethylsilyl chloride (80% distilled yield). Methyl ether 47c was also conveniently prepared from the



sodium salt of alcohol 47a and methyl iodide (95% yield). Unfortunately, none of these dithiane derivatives (47) afforded the expected aldehydes (48) upon attempted hydrolysis of the dithiane group by standard procedures.[54] Our unsuccessful efforts at hydrolysis of 47c are outlined in Table 7. In each of the



R

48 (a) H

(b) TMS

(c) Me

recorded attempts a complex mixture of polar products was obtained, presumably because the double bond reacted with cationic hydrolysis intermediates. Electron withdrawal by the α-hydroxyl in 47 may reduce the normal rate of hydrolysis sufficiently to make side reactions such as intramolecular cyclizations competitive.

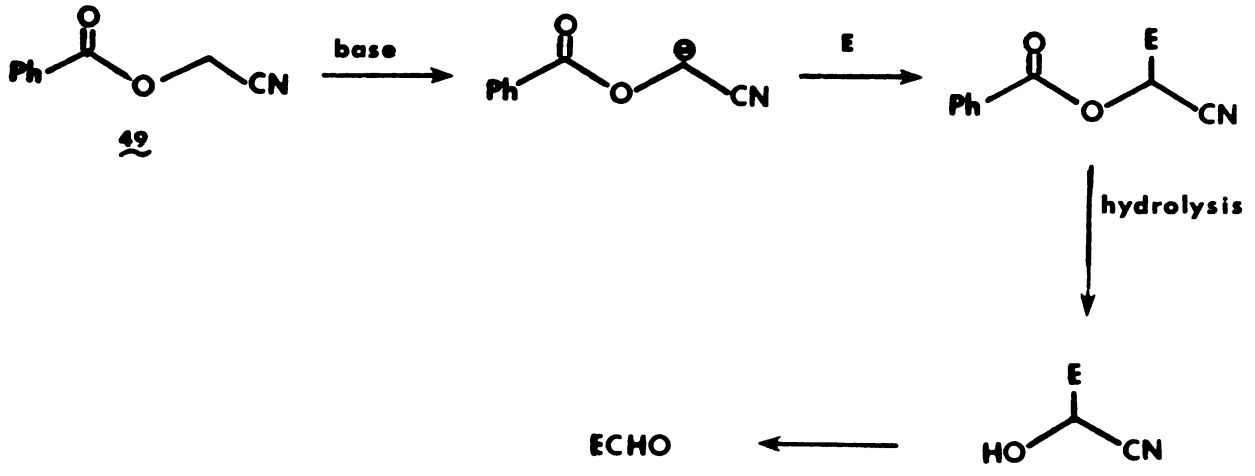
In a different approach we attempted to employ benzoyloxyacetonitrile (49) as a potential acyl carbanion equivalent as shown in Scheme V. Compound 49, prepared by a literature procedure,[55] was metalated using one of several bases and was then treated with an electrophilic reagent (E). The results of these unsuccessful

TABLE 7

Attempted Hydrolysis of 47c

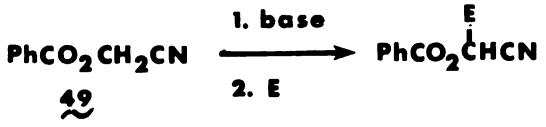
Conditions	Results	Reference
$Ce(NH_4)_2(NO_3)_6$ 20% aq CH_3CN	Complicated mixture	54a
$BF_3 \cdot Et_2O/HgO/THF$ H_2O (2 attempts)	intractable residue	54b
$MeI/CaCO_3/CH_3CN$ H_2O	complicated mixture	54c
$Ce(NH_4)_2(NO_3)_6$ 75% aq CH_3CN	complicated mixture	-
$I_2/NaHCO_3$ dioxane/H_2O	tar	54d
1. MeI/DME 2. $NaOH/H_2O$	complicated mixture	-

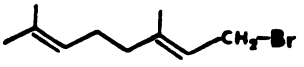
SCHEME V



studies are presented in Table 8. After completion of this work, a report appeared which described a similar lack of success in reactions employing 49.[56]

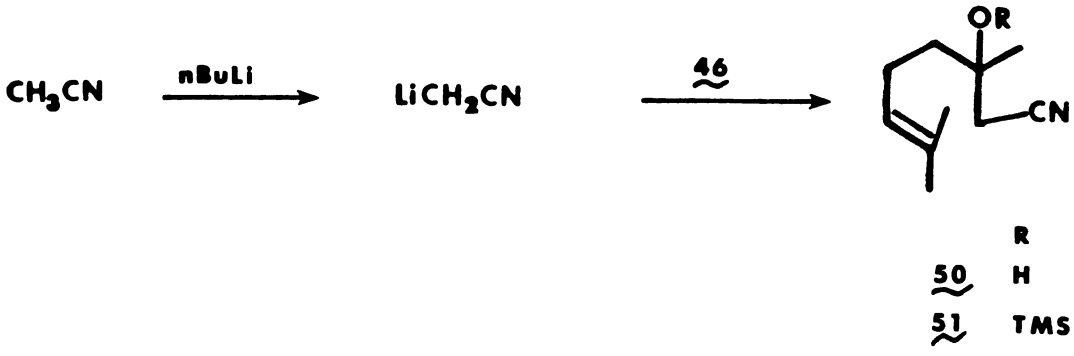
TABLE 8



Metalation Conditions	E	R x n Temp	Results
n-BuLi, THF,-78°	46	-78°	complex mixture
n-BuLi, THF, -20°	46	-78°	complex mixture
LDA[a], THF,-78°		-78°	complex mixture
NaH, hexanes,∿ 60°	MeI	∿60°	no metalation occurred

(a) LDA = Lithium diisopropyl amide

A brief, related study was also made of the metalation of nitrile 50, which was prepared by reaction of lithio acetonitrile[57] with ketone 46. Both 50 and its trimethylsilyl derivative 51 (50/TMS-Cl/pyridine/93% yield) were metalated with n-butyl lithium followed by addition of dibenzoyl peroxide.[58] The results of these unsuccessful experiments are summarized in Table 9.



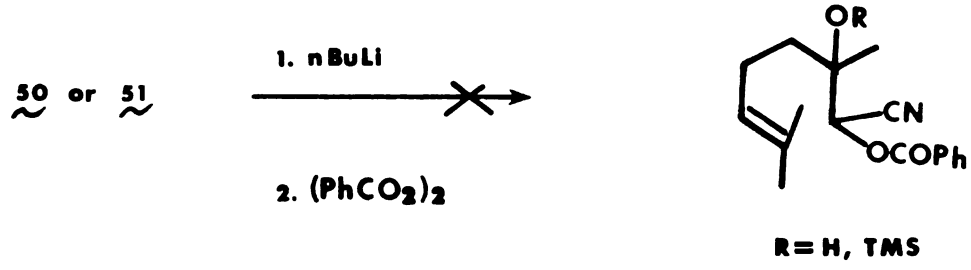
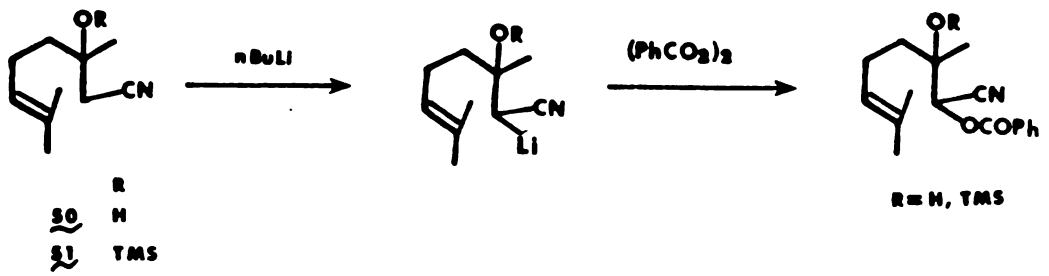
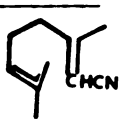


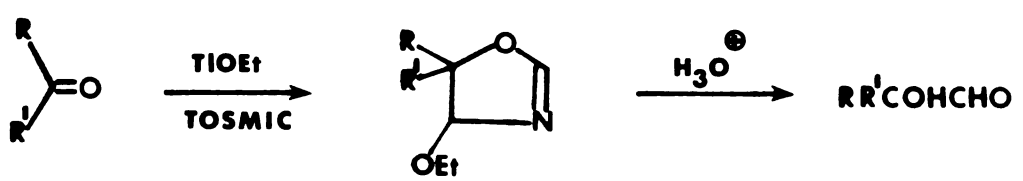
TABLE 9



	R
50	H
51	TMS

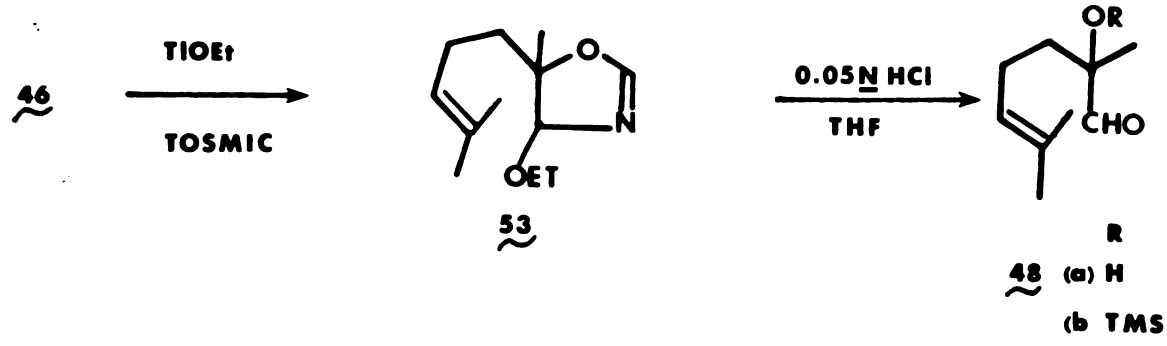
Compound	Metalation Conditions	R x n Temp	Results
51	BuLi (1 eq)/THF -78° → RT	-78°	50 + 
50	BuLi (2 eq)/THF -78° → -20°	-78°	complex mixture

A recent report describes the preparation of 4-ethoxy-2-oxazoline derivatives 52 from reaction of aldehydes and ketones with thallous ethoxide and tosylmethyl isocyanide (TOSMIC).[52d] Mild acid hydrolysis of 52 has been reported to afford



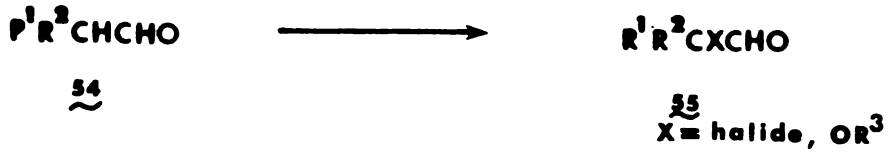
52

α-hydroxy aldehydes,[52d] a functional group combination known to be fairly unstable towards acid or base.[60] In our hands, ketone 46 yielded oxazoline 53 in 80% distilled yield. Mild acid hydrolysis of 53 resulted in a disappointingly low,



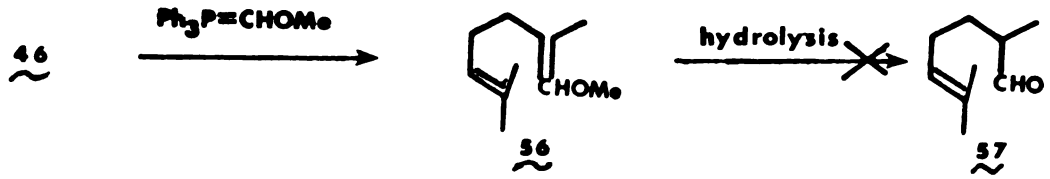
(37%) isolated yield of alcohol 48a. The other, unidentified, products were relatively polar when compared to 48a. α-Hydroxy aldehyde 48a was then converted into trimethylsilyl ether 48b (TMS-Cl, pyridine), obtained in an overall yield of ~30% from ketone 46. Protected α-hydroxy aldehyde 48b was found to be fairly stable to normal chromatographic procedures (glc, tlc) as well as to distillation. The high toxicity of thallous ethoxide, however, and the low yield of the product, constituted strong deterrents to this synthetic scheme. Nevertheless, the stability of 48b stimulated further investigations into its synthesis.

Several procedures have been reported for incorporation of hydroxyl[61] and halide[62] substituents α to an aldehyde group (ie, 54 to 55). Vinyl ether 56, a potential

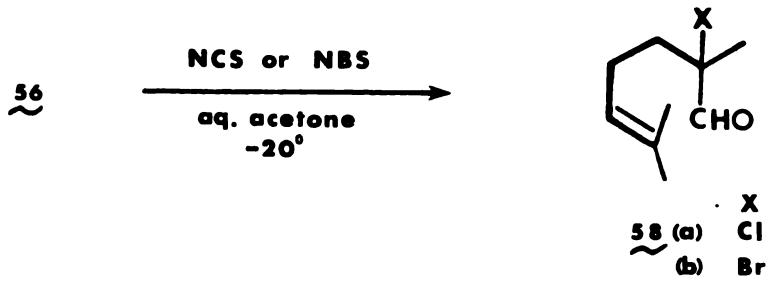


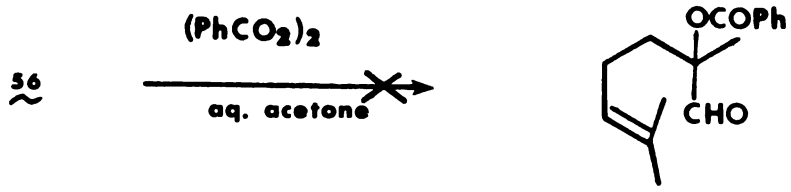
precursor to aldehyde 57, was prepared by reaction of ketone 46 with methoxymethyl-triphenylphosphorane.[63] Ether 56 afforded only complex mixtures of products

upon attempted hydrolysis.[63a] However, vinyl ethers such as 56 have been used



as precursors to α-halo carbonyl compounds.[64] Thus, ether 56 was cleanly and quantitatively converted to α-halo aldehyde 58 using both N-chloro and N-bromo succinimide. Bromide 58b was considerably less stable than chloride 58a, as expected.[62a,65] Ether 56 failed to react with dibenzoyl peroxide under the same conditions used for preparation of the halo derivatives 58.

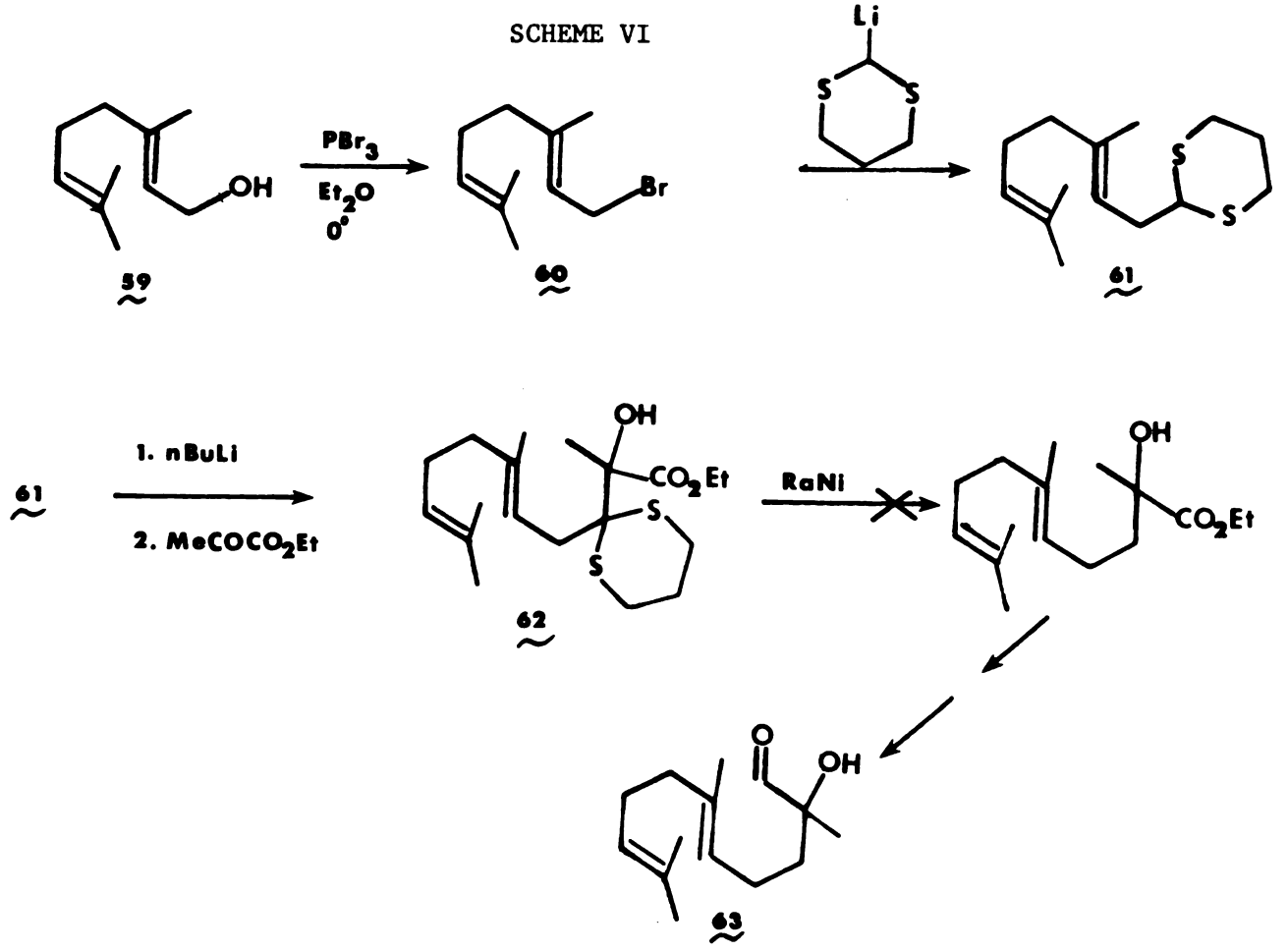




In another, lengthier study, the preparation of a-hydroxy aldehyde 63 was attempted (Scheme IV). E-Geranyl bromide (60) was prepared from commercially

available E-geraniol (59) by reaction with phosphorus tribromide (100% yield).[66] Lithio dithiane, prepared as before by n-butyl lithium treatment of 1,3-dithiane, reacted with bromide 60 to afford geranyl dithiane (61) in 72% distilled yield. Metalation of 61 using n-butyl lithium, followed by addition of ethyl pyruvate,

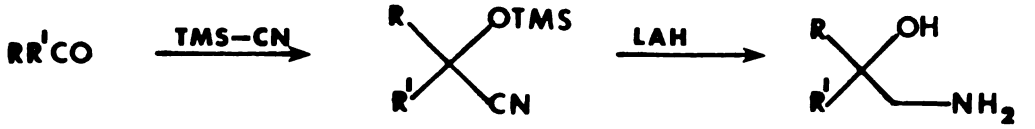
SCHEME VI



provided compound 62 in 31% yield after silica gel chromatography. Removal of the dithiane moiety in 62 using Raney Nickel, however, failed causing us to abandon this approach.

Evans and co-workers have described the preparation of β-hydroxyamines from aldehydes and ketones.[67] The key step in their synthesis is the use of

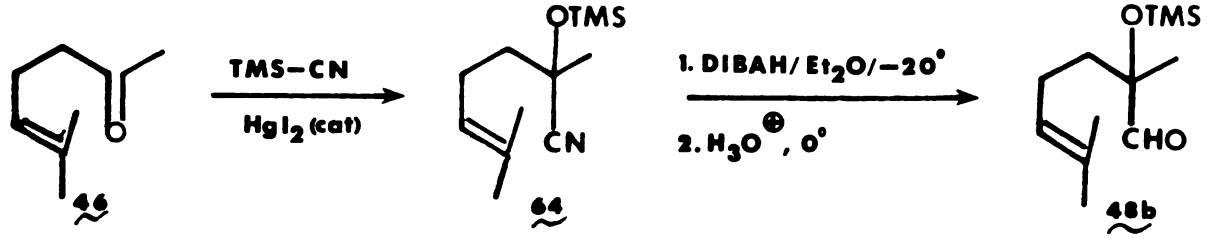
trimethylsilyl cyanide (TMS-CN) to form protected cyanohydrins. It appeared to us that partial reduction of the nitrile in the protected cyanohydrin to the



(ref. 37)

aldehyde oxidation state might be feasible. Diisobutylaluminum hydride (DIBAH) has been used previously for the reduction of nitriles to intermediate imines

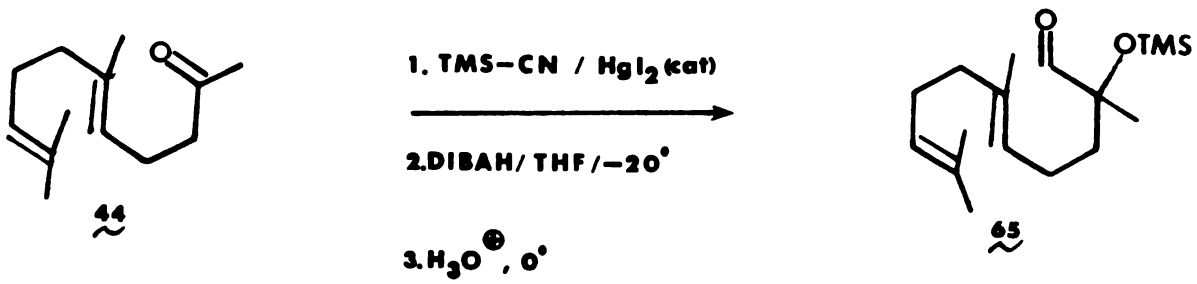
which, in turn, are readily converted to aldehydes upon aqueous work up.[68] Reaction of ketone 46 with TMS-CN using mercuric iodide as catalyst[67] gave trimethylsilyl cyanohydrin 64 in 95% yield. The reduction step was efficiently



46 64 48b

accomplished using a lewis-base solvent such as diethyl ether or tetrahydrofuran (THF) rather than a hydrocarbon solvent (toluene or hexanes), since attempted use of hexanes as solvent at -78°C resulted in a low yield of 48b (28%) contaminated with high boiling products (glc analysis). These side products were shown to be complex amines by their solubility in dilute aqueous acid. In

contrast, the use of ether as solvent provided a 61% distilled yield of aldehyde 48b. Furthermore, carefully controlled hydrolysis at 0°C afforded 48b with the trimethylsilyl group still intact. Product 48b, obtained in this fashion, was identical to the previously synthesized authentic sample. The sequence just described, employing TMS-CN, was repeated using E,E- geranyl acetone(44) instead of ketone 46. In a preliminary study it was observed that replacement of ether by THF in the reduction step provided the aldehyde 65 in even more acceptable yields. Desired α-trimethylsilyloxy aldehyde 65 was, thus, obtained in a one pot synthesis from 44 in overall distilled yields of 84-88%.



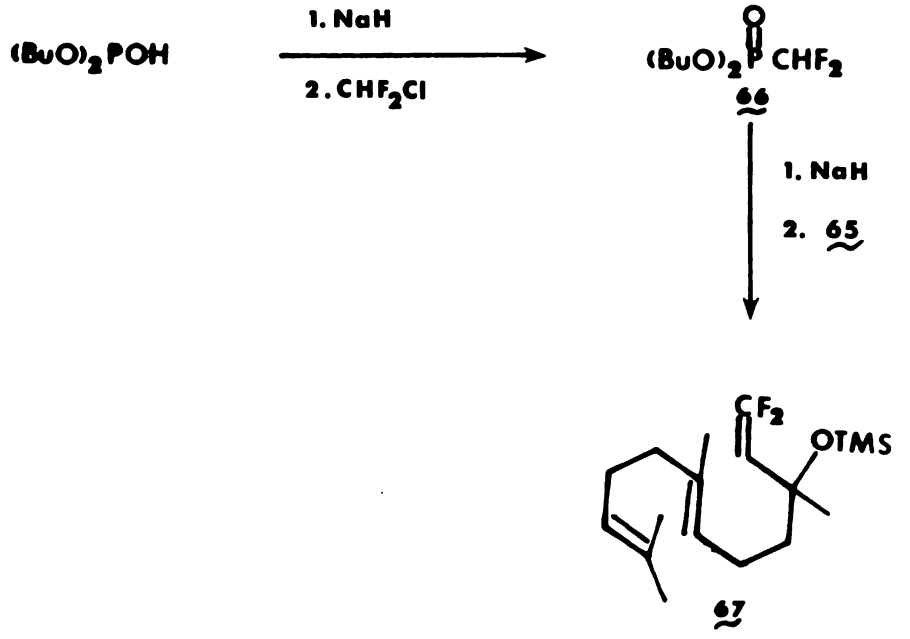
44 65

In our experience, literature procedures suitable for the preparation of aldehyde 65 from 44 are either difficult to reproduce[52d,e] or give low yields of the desired ∝-hydroxy aldehyde product[52a-c]. The sequence 44 to 65 using TMS-CN and DIBAH, which succeeded in the face of the failure of other methods, may prove to be a more general and higher yield preparation of protected ∝-hydroxy aldehydes than these alternative procedures.

2.4 Difluoro Analogues

Several fluoroolefins have been prepared from carbonyl compounds.[50] In an exploratory study, we synthesized the previously described difluorophosphonate 66[69] for attempted use in a Wittig reaction with aldehyde 65.

Sequential treatment of dibutyl phosphite with sodium hydride and chlorodifluoromethane gave phosphonate 66.[69] However, the ylide obtained by reaction of

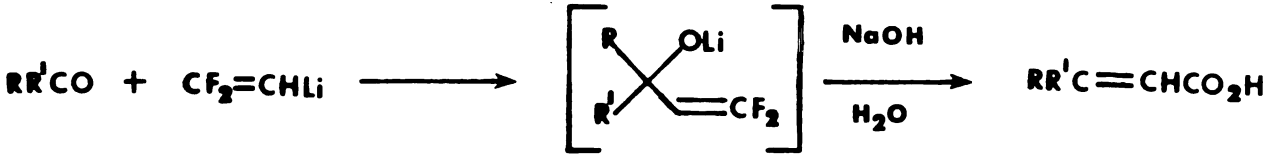


66 with sodium hydride gave only a complex mixture of products upon reaction with aldehyde 65. GLC and tlc studies indicated the absence of the desired product 67.

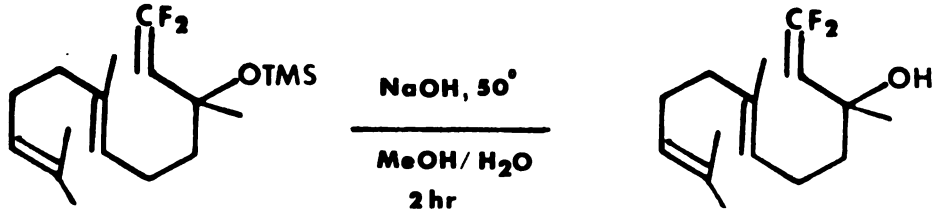
We then turned to a method developed by Naae and Burton[50b] for difluoroolefin synthesis. Reaction of aldehyde 65 with the difluoroylide solution prepared by reaction of dibromodifluoromethane with two equivalents of tris-dimethylamino

phosphine[50b] afforded the desired 1,1-difluoronerolidol derivative 67 in 79% distilled yield. GLC analysis of the distilled product established the presence of aldehyde 66 (∿5%) and alcohol 68 (∿5%) as contaminants. Trimethylsilyl derivative 67 was isolated in analytically pure form using low-pressure-liquid-chromatography (LPLC) on a prepacked silica gel column commercially available from E. Merck. Infrared analysis of pure 67 showed a strong band at 1740 cm^{-1} characteristic of the difluorovinyl group.[50c] The proton NMR of 67 showed a doublet of doublets (J = 26.5 and 6.5 Hz) for the C-2 vinyl proton due to coupling to the two fluorines. A summary of both proton and fluorine NMR data for 67 is presented in Section 2.7.

One potential route to gamma difluorinated alkyl alcohols, such as 67, is suggested by the addition of 2,2-difluorovinyl lithium[70] to aldehydes and ketones. However, in their exploratory study, Tarrant and coworkers[70]



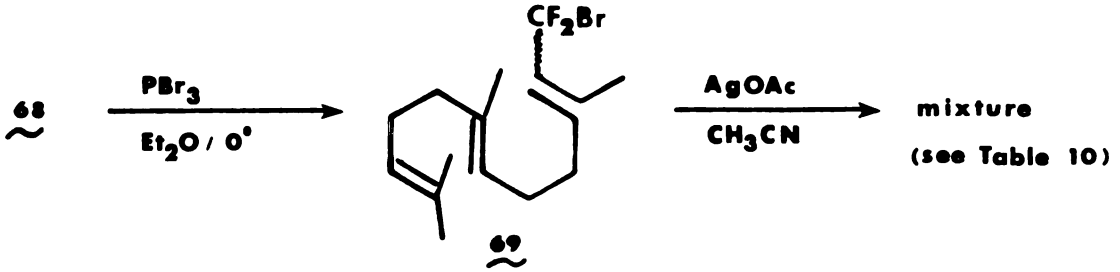
only isolated carboxylic acids resulting from thermal rearrangement, a reaction taking place probably during work-up and suggesting the possible instability of these types of fluoro compounds. In contrast to these results, we were able to prepare difluoroalcohol 68 in virtually quantitative yield by base promoted



67 68

hydrolysis of trimethylsilyl ether 67. We have found, in fact, that pure 68 is stable indefinitely when stored neat at 0°C. However, both 67 and 68 are unstable in acidic environments, decomposing with hydrofluoric acid evolution and formation of complex product mixtures.

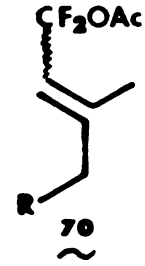
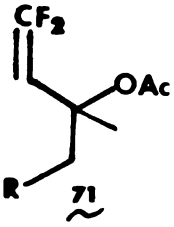
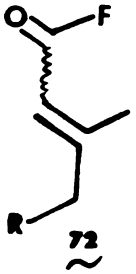
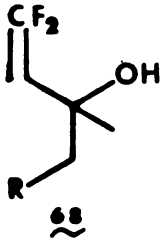
Our initial α-fluorofarnesyl ester synthetic target was acetate derivative 70. Bromide 69, prepared by phosphorus tribromide treatment[71] of tertiary alcohol 68, reacted with silver acetate in acetonitrile to give a mixture of products as judged by glc analysis. The identified products and their relative yields and chromatographic properties are presented in Table 10. Unidentified products,



consisting primarily of non-polar hydrocarbon products, amounted to about 10% of the total crude product obtained. Acyl fluoride 72 was found to be a contaminant formed during the preparation of bromide 69. Table 11 lists several attempts at preparing 69 in hopes of minimizing side product 72.

TABLE 10

Identified Products from the Reaction of Silver Acetate and Bromide 69

Compound	%[a]	R_f[b]	T_r[c] (min)
 70	36 (18)	0.43	9.53[d]
 71	11(5)	0.38	418
 72	51	0.65[d]	E,E 5.57 Z,E 4.76
 68	2	0.20	3.66

(a) GLC yields (isolated yields in parenthesis); (b) tlc (system A, 2% (EtOAc/ 98% hexanes , 2 developments); (c) glc (system A, 150°); (d) isomers not separated.

TABLE 11

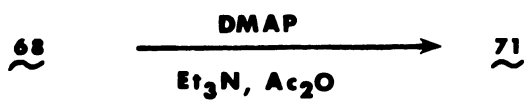
Attempted Preparatin of Bromide 69

Reaction Conditions[a]	Reference	Results[b]
68/PBr_3(ET_2O, 0°)	-	about 50/50[c] (69/72)
68/PBr_3(ET_2O, -20°)	-	mostly 72
68/PBr_3(ET_2O, RT)	-	mostly 72
68/PBr_3/Pyridine (ET_2O,0°)	-	mostly 72
68/PBr_3 (Hexane, 0°)	-	mostly 72
68 + 1.n-BuLi, Et_2O,-20° 2.MsCl, -20° 3.LiBr, 0°	72	complex mixture
71/LiBr (acetone)	-	No reaction (TLC)
71/LiBr/TsOH (acetone)	-	Complex mxture
68/NBS/Ph_3P (ET_2O)	73	No reaction
68/PBr_3/pyridine ET_2O, Pentane,-78°)	71	mostly 72

(a) All reactions conducted under N_2 atmosphere. (b) Results based primarily on tlc evidence. (c) The ratio of 69 to 72 varied (tlc) with the average ratio about 50/50. However, preparative tlc experiments indicated that bromide 69 was converted into acyl fluoride 72 on activated silica gel plates. Both alumina and cellulose tlc plates did not allow the separation of 69 and 72.

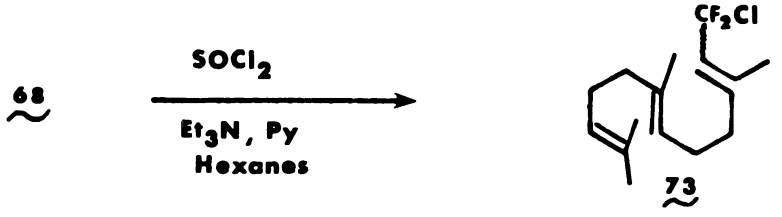
Primary acetate 70 and tertiary acetate 71 were easily isolated from the reaction mixture using LPLC on a silica gel column. The isomeric acetates, obtained in 23% combined yield, were then separated, again using LPLC. The proton NMR spectrum of an isomeric mixture of 70 showed one triplet at 5.60 ppm (J = 10 Hz) for the C-2 vinyl proton split by the two equivalent fluorines. Fluorine NMR studies of 70 showed two doublets for the two possible geometric isomers (J = 10 Hz). The proton NMR of tertiary acetate 71, on the other hand, showed a doublet of doublets centered at 4.67 ppm (J =27 and 5 Hz) for the C-2 vinyl proton. Infrared analysis of primary acetate 70 showed a strong band at 1790 cm^{-1}. This shift of the carbonyl band to higher frequency has been noted for similar fluoroesters.[28d, 74,75] The strong 1740 cm^{-1} infrared band due to the difluorovinyl group was absent in primary acetate 70, whereas in 71 a very broad band at 1740 cm^{-1} was present due to overlapping acetate carbonyl and difluorovinyl absorptions.

An independent synthesis of tertiary acetate 71 was performed using a recently developed procedure for the esterification of highly hindered alcohols.[76] Treatment of alcohol 68 with acetic anhydride, triethylamine, and 4-dimethylamino pyridine[76] (DMAP) afforded acetate 71 in 98% isolated yield. GLC of the reaction mixture indicated the presence of a trace of primary acetate 70. Acetate 71, prepared in this manner, was identical in all respects to the previously prepared compound.



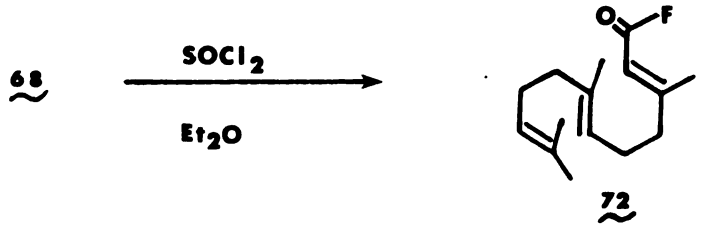
Both 70 and 71 were stable to short exposures to 5% aqueous HCl or NaOH at room temperature. Both acetates could be distilled using a Kugelrohr apparatus.

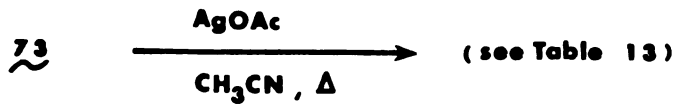
Due to the difficulties encountered in obtaining pure bromide 69, we decided to prepare chloride 73. Using a modified literature procedure,[77] alcohol 68 was treated with thionyl chloride in hexanes in the presence of both pyridine and triethylamine, providing chloride 73 in 87% crude yield.



Contaminants found in the crude product by glc analysis included about 10% of acyl fluoride 72 and about 5% unidentified hydrocarbons. A pure sample of 73 was obtained using LPLC (silica gel). The structure for 73 was confirmed by proton NMR (triplet for C-2 vinyl H giving coupling constant of 12 Hz) and by fluorine NMR (2 doublets, each with 12 Hz coupling) as well as the usual range of spectroscopic and analytical techniques.

In the absence of amine bases, thionyl chloride transformed 68 into acyl fluoride 72 in 89% yield. The fairly unstable 72 was characterized by its proton and fluorine NMR spectra, its infrared spectrum, and by chemical ionization mass spectrometric data. Table 12 summarizes a brief series of experiments showing how the ratio of chloride 73 to acyl fluoride 72 varied with the amine content of the reaction mixture.





Reaction of chloride 73 with silver acetate proceeded slowly in refluxing acetonitrile to provide the mixture of identified products shown in Table 13.

TABLE 12

Effect of Base on the Preparation of Chloride 73

Reaction Conditions[a]	Ratio[b] 72	73
$SOCl_2/Et_2O$	99	1
$SOCl_2$/hexanes pyridine (1 equiv)	~ 20	~ 80
$SOCl_2$/hexanes Et_3N/pyridine (1 equiv. each)	~ 10	~ 90

(a) All reactions conducted under a N_2 atmosphere at room temperature. The $SOCl_2$ was added last to the reaction mixtures. (b) Ratios determined by glc analysis (System A, 150°C).

TABLE 13

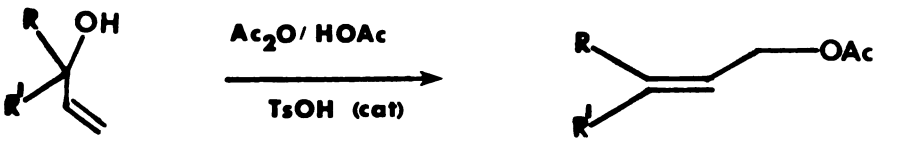
Products From Silver Acetate Reaction of 73

Compound	%[a]
70	38 (18)
71	9 (4)
72	51
68	2

(a) Relative glc yields with isolated yields in parenthesis.

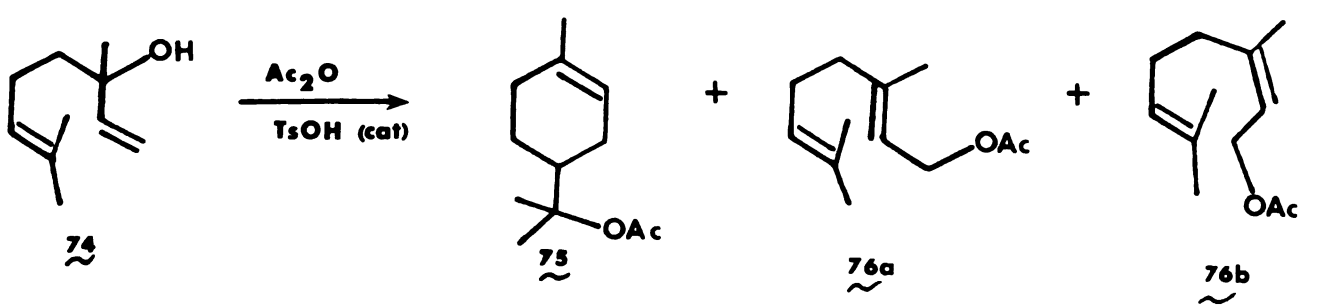
The two silver acetate promoted reactions discussed (using bromide 69 and chloride 73) produced similar ratios of products and furnished virtually equivalent yields of acetates (22-23%). This is rather surprising since bromide 69 was known to be contaminated by larger amounts of acyl fluoride 72. These preliminary results are under further investigation in our laboratories.

Acid catalyzed allylic rearrangement of tertiary vinyl substituted alcohols to the corresponding primary acetates has been studied recently by Babler and coworkers.[48f,g] They found that treatment of tertiary allylic alcohols with



(ref 48f)

acetic anhydride, with or without added acetic acid but in any case in the presence of a catalytic amount of p-toluenesulfonic acid (tosic acid), provided good yields of primary acetate uncontaminated by the tertiary acetate[48f]. They further demonstrated that linalool (74), a terpene structurally related to difluoroalcohol 68, reacted in an abnormal fashion yielding the acetate of α-terpineol (75) as the main product accompanied by smaller amounts of geranyl (76a) and neryl (76b) acetates. Using the reaction conditions described by Babler and Olsen,[48f]



74 75 76a 76b

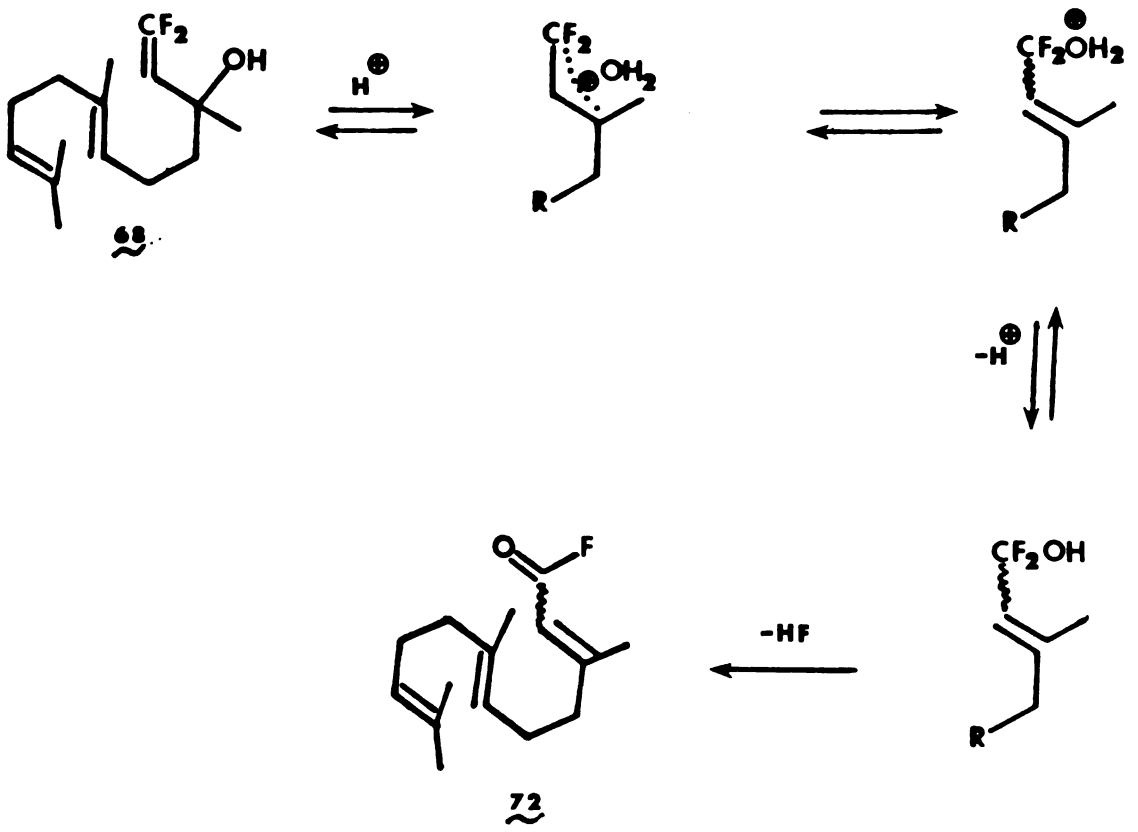
alcohol 68 was transformed into the product mixture shown in Table 14. Other, unidentified hydrocarbon products amounted to about 5% by glc analysis. The primary acetate 70 was obtained in 36-40% isolated yield (LPLC/silica gel). Employment of a solvent in this reaction (hexanes or Et_2O), or a lower reaction temperature (0°C), led to product mixtures dominated almost exclusively by acyl fluoride 72. These results are consistent with the scheme in Fig. 11, which suggests a probable source for the formation of acyl fluoride 72. The postulated scheme is essentially an S_Ni' rearrangement of water from the tertiary carbon to the primary one, a process well established in related studies.[48e,g] The mechanism depicted in Fig. 11 predicts that the acid catalyzed rearrangement of tertiary acetate 71 to primary derivative 70 should proceed without formation

TABLE 14

Acetic Anhydride Reaction of Alcohol 68

Product	%[a]
70	66 (36-40)
71	3
72	30
68	∿ 1

(a) Relative quantities as judged by glc analysis (System A, 150°C). Isolated yields given in parenthesis.



68 72

FIGURE 11

Possible Scheme for the Formation of Acyl Fluoride 72

of acyl fluoride 72. Preliminary studies demonstrated that tertiary acetate 71 did not rearrange thermally to isomer 70 (80°C, benzene, 24 hr.) even in the presence of potassium acetate and 18-crown-6. However, treatment of 71 with acetic anhydride containing a catalytic amount of tosic acid produced primary

$$71 \xrightarrow[\text{TsOH (cat)}]{Ac_2O} 70 + 72$$

acetate 70 in about 75-80% yield as judged by proton NMR and glc analysis. The crude product also contained 10-15% acyl fluoride 72 as well as traces of derivatives 68, 71, and unidentified hydrocarbons. Residual formation of 72 may have been caused by (1) the use of monohydrated rather than anhydrous tosic acid and/or, (2) the work-up procedure which includes 5% sodium hydroxide washes to remove acetic anhydride. Control experiments indicated that 5% NaOH slowly hydrolyzes acetate 70 to acyl fluoride 72. However, glc analysis of the crude product before work-up indicated the presence of 72 in amounts essentially equivalent to those observed after the work-up. The source of 72 is, therefore, most probably due to incorporation of water into the reaction mixture from tosic acid monohydrate.

Analogous acid catalyzed allyl acetate rearrangements are well known in the literature.[78] A possible mechanism for the rearrangement of 71 to 79, based on those proposed for analogous reactions,[78] is shown in Fig. 12. The key step in this proposed mechanism is formation of oxonium ion 71a[78] which then rearranges to eventually form 70.

We briefly studied a recently reported rearrangement of allylic alcohols to homologous amides using N,N-dimethylformamide acetals[79] in order to more generally define the reactions of tertiary alcohol 68. An example of this rearrangement is the conversion of nerolidol (77) to amide 78 using N,N-dimethyl formamide diethyl acetal.[79] In our preliminary study, alcohol 68 was converted into difluoro amide 79 in 35% isolated yield. Other, unrelated studies have clearly demonstrated the thermal instability of 68 at high temperatures, a fact which may account for the low yield and for the non-polar side products which were also observed in this reaction.

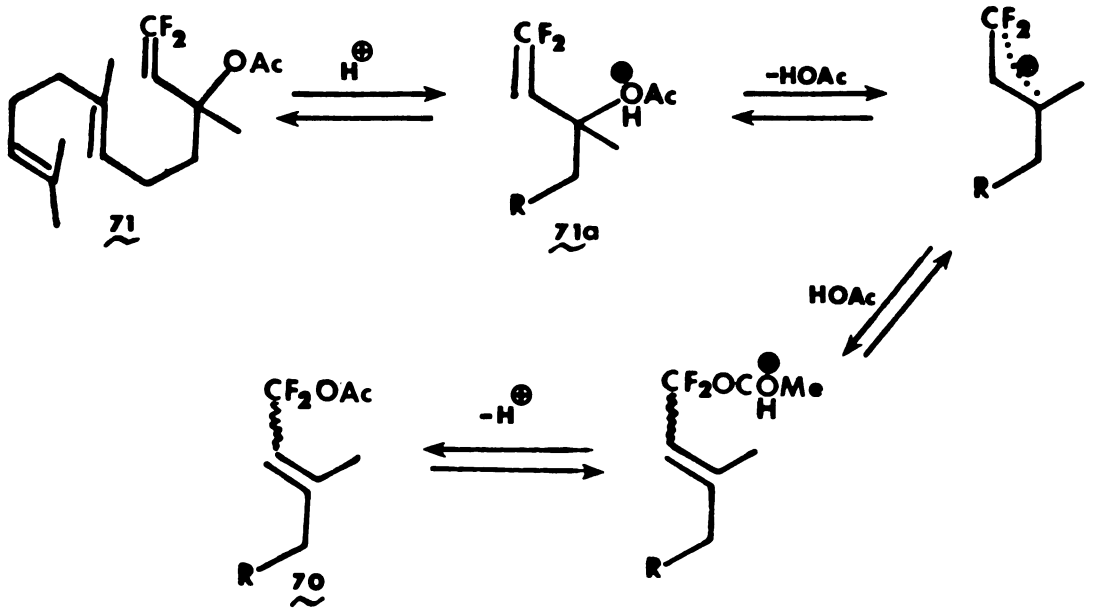
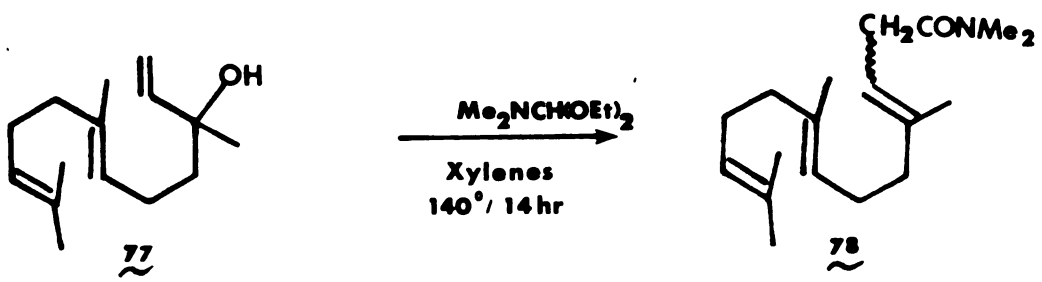
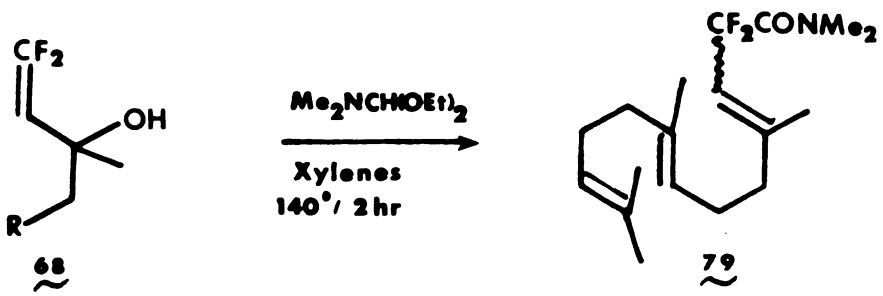


FIGURE 12

Possible Mechanism for Acid Catalyzed Formation of 70

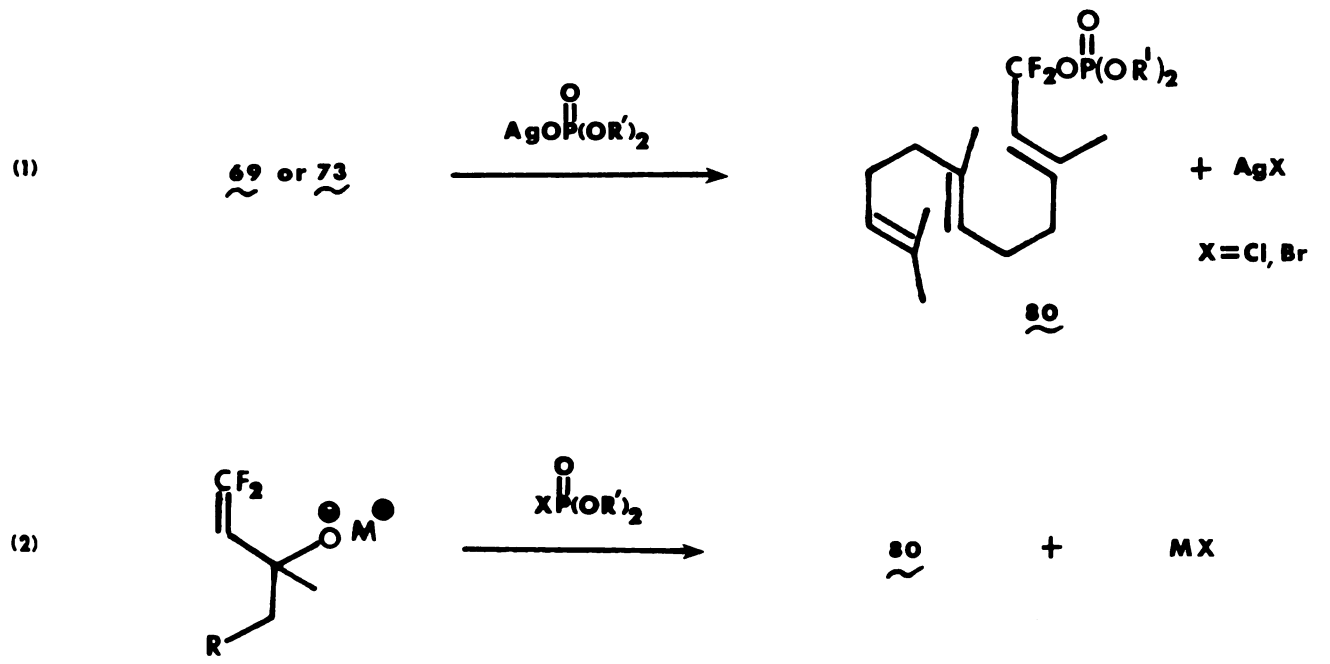


(ref 79)



These impurities, which were not identified in this study, did not contain the amide functionally (No N-Me groups) as judged by NMR analysis. Amide 79 was obtained as a 50:50 mixture of 3-E and 3-Z isomers as indicated by the presence of two doublets (J = 13 Hz) in the fluorine NMR spectrum.

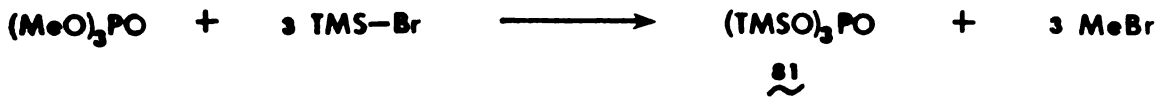
The next, and considerably more ambitious step in our studies, was the attempted preparation of a phosphate ester. The two main avenues selected for the approach to analogues such as 80, shown in Scheme V11, were (1) reaction of the monosilver salt of a phosphate ester with bromide 69 or chloride 73, and (2) reaction of the alkoxy anion of alcohol 68 with an electrophilic phosphate species, followed by allylic transposition. Our initial, and unsuccessful, studies involved the



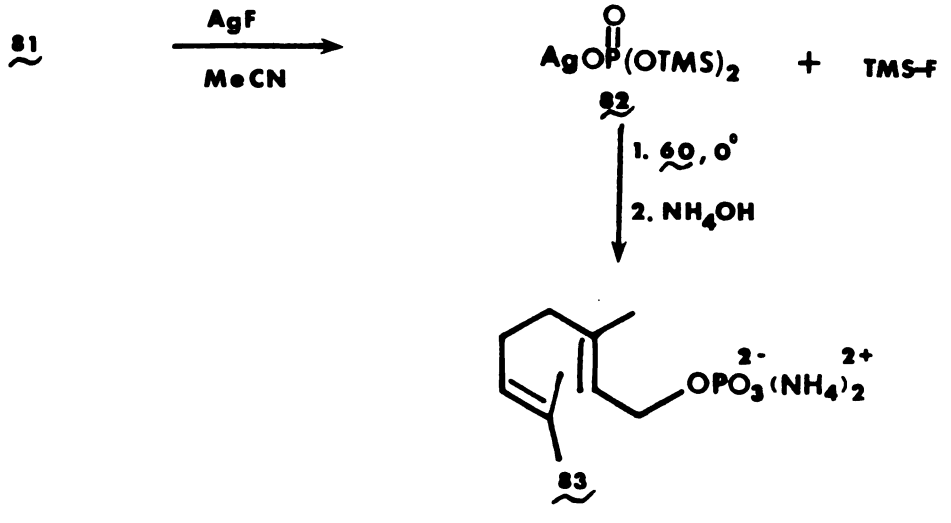
Scheme V11

Possible Approaches to 80

former approach, for which several relevant precedents have been established.[80] The synthesis of nucleophilic phosphate 82 first required the preparation of 81[81] through reaction of trimethyl phosphate with trimethysilyl bromide.[82]

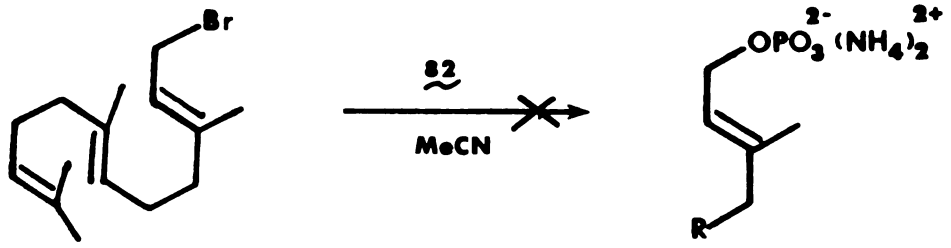


The known ability of fluoride to cleave trimethylsilyl ethers[83] made this approach attractive. GLC analysis of crude 81 showed one major peak with a slighly longer retention time than trimethyl phosphate. Product 81 readily hydrolyzed to polar inorganic phosphate upon addition of water. Addition of silver fluoride to crude 81 in acetonitrile gave monosilver salt 82 as indicated by gradual formation of a grey precipitate. The potential of 82 for preparation of fluorofarnesyl phosphate derivatives was first tested with



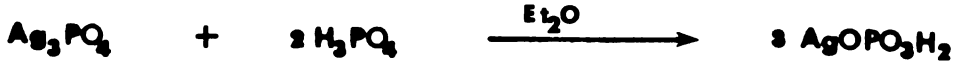
unfluorinated geranyl bromide (60). Reaction of 60 with phosphate salt 82 in

acetonitrile at 0°C furnished geranyl phosphate (83), in about 25% yield, isolated as the diammonium salt. Phosphate 83 was shown to have tlc and NMR properties identical to those of an authentic sample.[1d] A similar reaction employing farnesyl bromide (84) instead of 60, however, failed to produce any organophosphate compound as judged by tlc and NMR analyses. Our poorly reproducible experiments using phosphate 82 prompted our search for a different



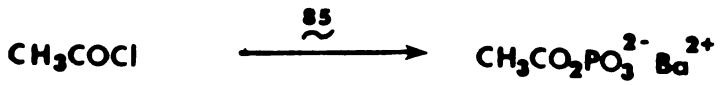
84

nucleophilic phosphate residue. Lipman and Tuttle have reported the preparation and use of monosilver phosphoric acid (85).[80d] They discovered that 85 could be formed by equilibration of 2 equivalents of phosphoric acid with one of trisilver phosphate.[80d]

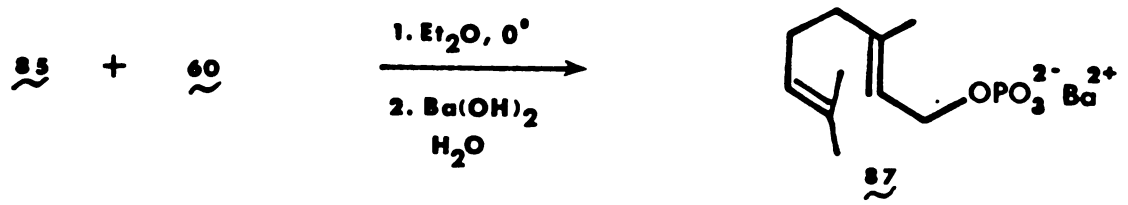


85

They succeeded, furthermore, in preparing acetyl phosphate (86) by treatment of 85 with acetyl chloride, whereas attempted use of trisilver phosphate (instead of 85) in a reaction with acetyl chloride produced polyacetyl phosphates[80d] Reithel has also successfully utilized 85 to prepare β-D-galactose-1-(barium phosphate).[80b]

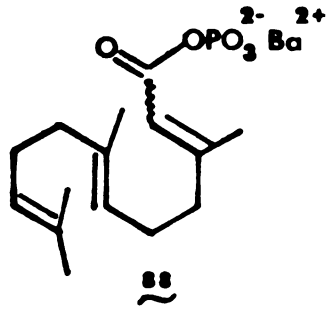


86



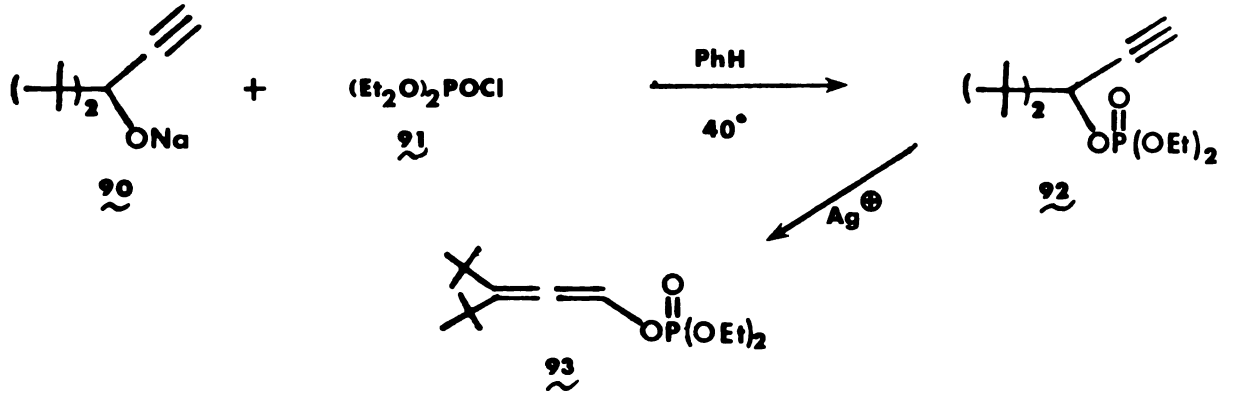
Monosilver phosphoric acid (85) was prepared as described[80d] and the resulting grey slurry allowed to react with geranyl bromide (60). A barium hydroxide work-up furnished the barium salt 87 in about 30-50% yield, contaminated by inorganic phosphate. Product 87 was found to be identical to an authentic sample by tlc and NMR analysis.[1d]

However, attempted preparation of 1,1-difluorofarnesyl phosphate by reaction of crude bromide 69 and 85 yield only inorganic phosphate, neutral hydrocarbon products, and, occasionally, traces of acyl phosphate 88. The structure for 88 was based on its tlc behavior, its infrared spectrum (1720 cm^{-1} band), and NMR studies. The presence of acyl phosphate 88 was thought to be due either to hydrolysis of desired difluorophosphate 89, or more likely, to reaction of acyl fluoride 72 with silver phosphate 85.

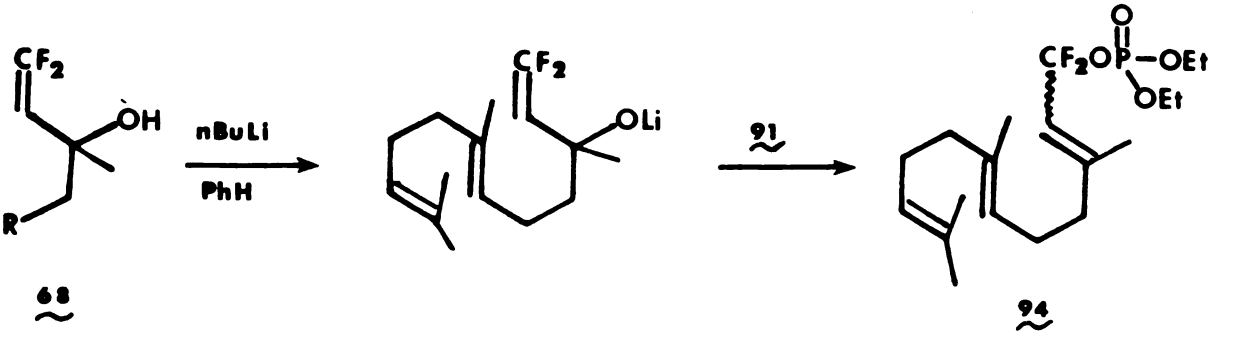


Following these unsuccessful experiments we decided to pursue the second approach shown in Scheme VII. Several groups[48b,84] have reported the synthesis of phosphate derivatives from the sodium salts of highly hindered propargylic alcohols. For example, phosphate ester 92 was prepared by heating the sodium salt 90 in the

presence of diethylchlorophosphate (91).[48d] Oelberg and Schiavelli[48d] have also reported silver ion catalyzed allenyl rearrangements of phosphate esters, as illustrated by their preparation of 93.



We attempted to prepare the tertiary phosphate ester by reaction of the sodium salt of alcohol 68 with chlorophosphate 91. However, after heating 68 with sodium hydride at 40°C for 2 hr, a vigorous, exothermic reaction commenced with simultaneous hydrogen gas evolution. TLC, glc, and NMR analysis indicated that a mixture of products, including acyl fluoride 72, was produced. The lithium salt of 68 was therefore prepared and treated with chlorophosphate 91 at room temperature. To our surprise and delight, no tertiary phosphate was isolated but rather the primary phosphate 94 was directly obtained. Silica gel chrom-



atography (LPLC) of the crude product provided 94 in 22% yield. The 2-E and Z isomers of 94 were cleanly separated by this purification procedure and were fully characterized. The absence of any tertiary phosphate was firmly established by the absence of the difluorovinyl group in the NMR. Both 2-E and Z isomers of 94 showed the characteristic triplet at 5.6 ppm for the C-2 vinyl proton (J = 10 Hz). The fluorine NMR spectrum for each isomer was complicated by an interesting example of multiple long range spin-spin coupling. For each isomer the fluorine NMR signal was an extremely broad (about 0.3 ppm), unresolved multiplet. Off-resonance decoupling experiments[85], as shown in Fig. 13, clearly indicate that complete proton decoupling produces a sharp doublet (J = 6 Hz) in the fluorine NMR resulting from fluorine-phosphorus coupling. This is, to our knowledge, the first observation of F-C-O-P coupling. High field proton decoupling afforded two overlapping doublets (J = 6 and 10 Hz) in the fluorine NMR resulting from coupling of phosphorus and the C-2 vinyl proton to fluorine (Fig. 13).

The major isolated product from this reaction, obtained in about 50% yield, was found to be the previously prepared chloro derivative 73. The source of this side product was puzzling due to the fact that phosphate 94 was found to be inert in a slurry of lithium chloride in benzene. Thus, chloride 73 was not formed by reaction of phosphate 94 and chloride anion. The conversion of alcohol 68 to phosphate 94 was repeated using hexanes as solvent instead of benzene in order to tighten any ion-pair which might be involved in the reaction. Under these conditions chloride 73, though still present by tlc and glc analysis, was, nevertheless, obtained in only about 5% yield as a mixture with other, non-polar impurities. The yield of the phosphate 94, using hexanes as solvent

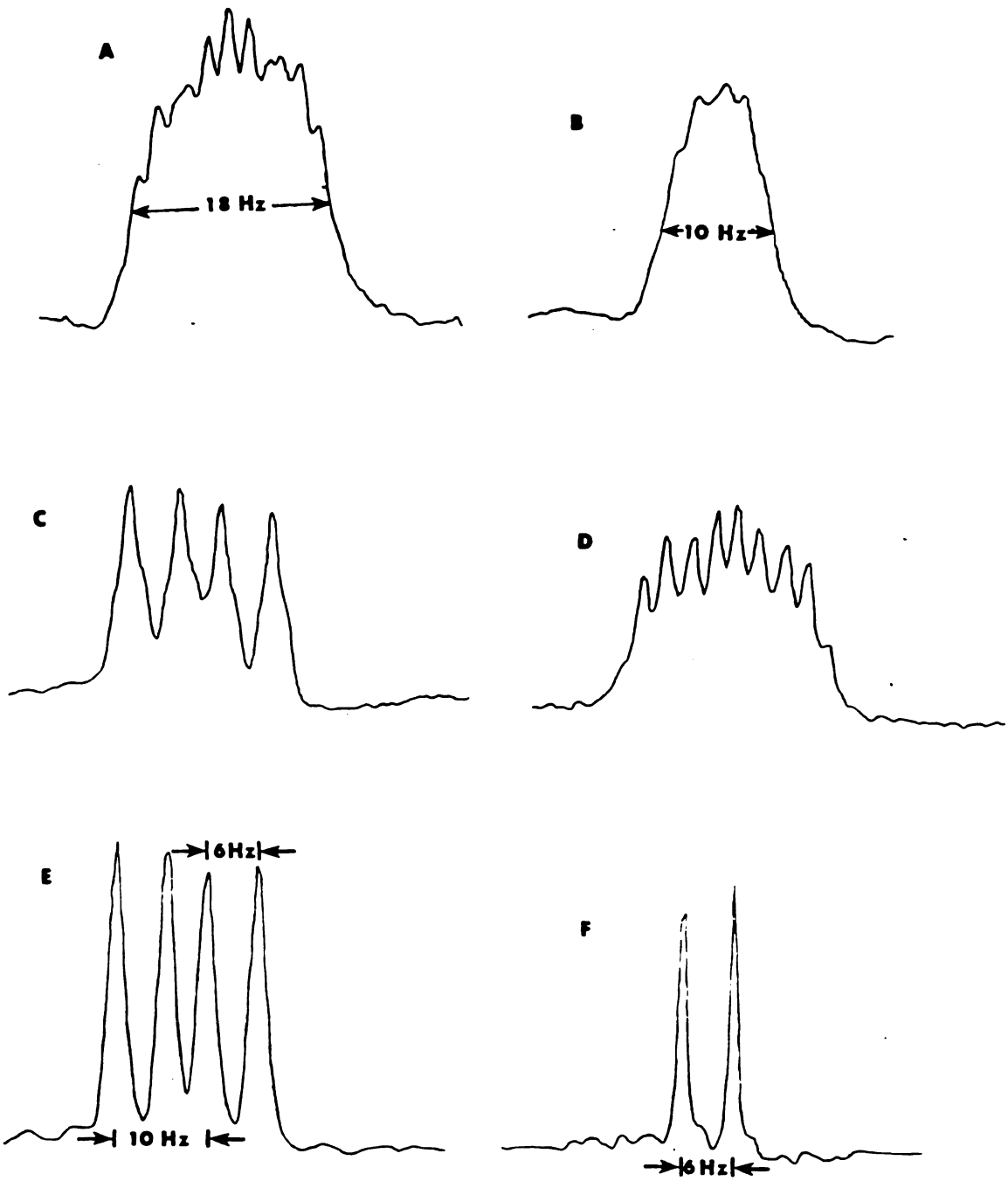


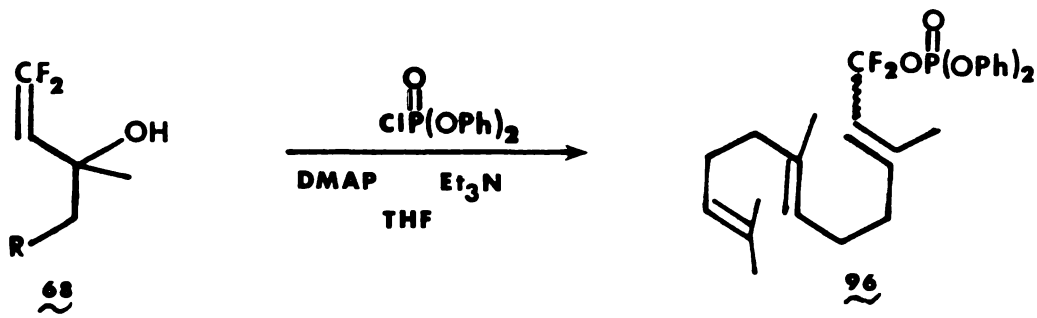
Figure 13

Fluorine-19 NMR spectra of 2-$\underline{Z}$-$\underline{CH}_3$ showing various proton decoupling experiments: (A) Proton coupled spectrum; (B) C-2 vinyl proton decoupled; (C) C-3 methyl protons decoupled; (D) C-4 $\underline{CH}_2$ decoupled; (E) All except vinyl protons decoupled; (F) Completely proton decoupled.

was still a disappointingly low 30%. Some mechanistic possibilities for the reaction leading to 94 are shown in Fig. 14.

In Path A an ion-pair is formed, a species which could allow lithium chloride and phosphate anion to compete as nucleophiles. In hexanes, as compared to benzene, the ion pair would be expected to have increased covalent character, severely retarding nucleophilic competition by lithium chloride in solution. Furthermore, the decreased solubility of lithium chloride in hexanes, relative to benzene, would also aid in preventing formation of 73. Path B postulate formation of a pentacovalent[86] phosphorus intermediate 95. This intermediate 95 could then lead directly to the products as illustrated in Scheme VIII.

Phosphate ester 96 was prepared in an 80% isolated yield from alcohol 68 using diphenylphosphorochloridate, 4-dimethylaminopyridine (DMAP), and triethylamine. The 2-E and 2-Z isomers of 96, obtained in a 2:1 ratio, respectively,



68 96

were easily separated using LPLC on silica gel. The stereochemical assignment for the two isomers of 96 is based on the relative positions of the C-3 methyl and C-4 methylene groups in their NMR spectra (see experimental section).

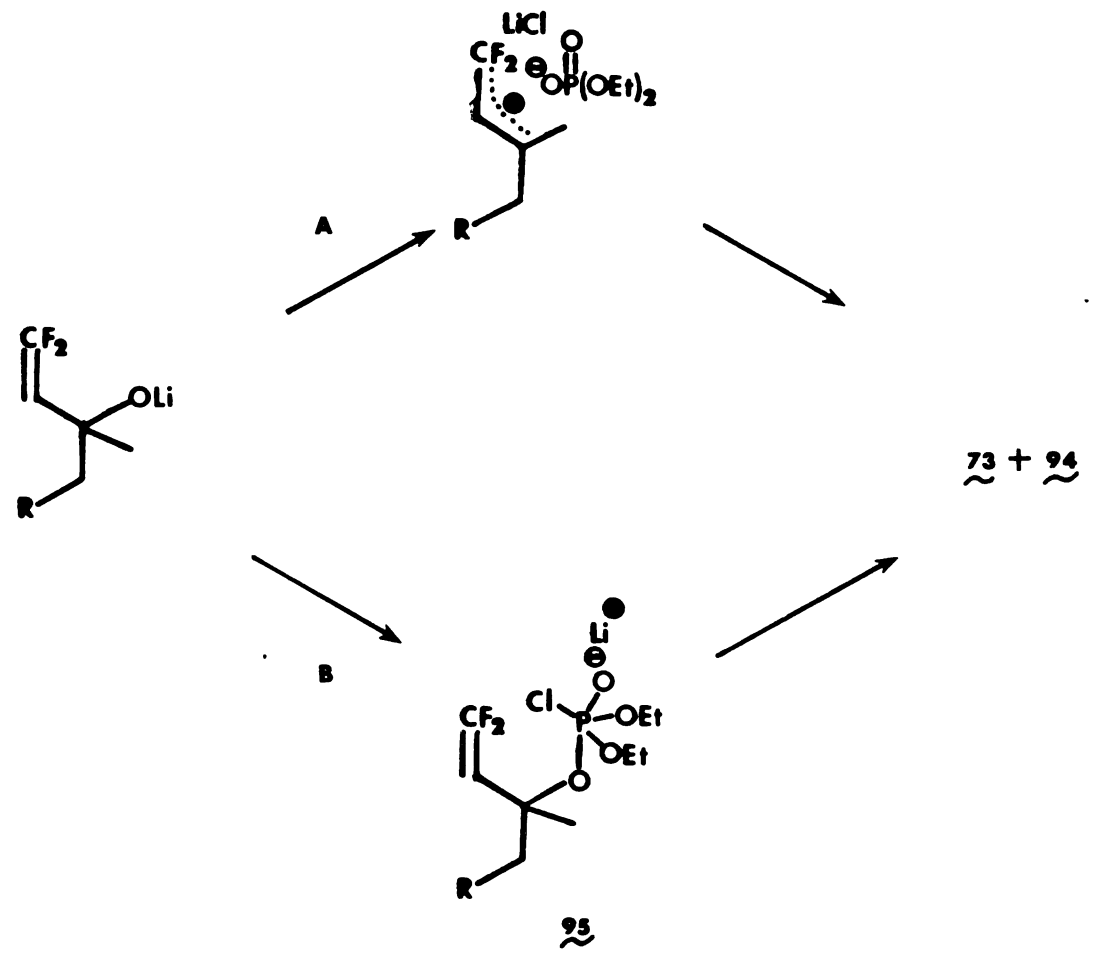
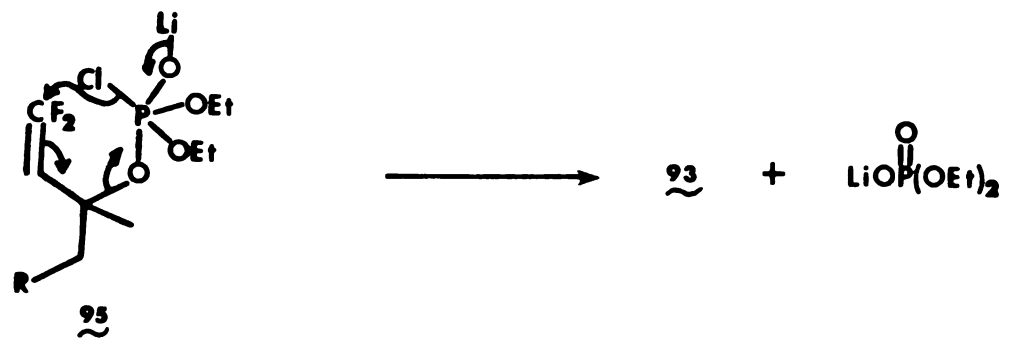
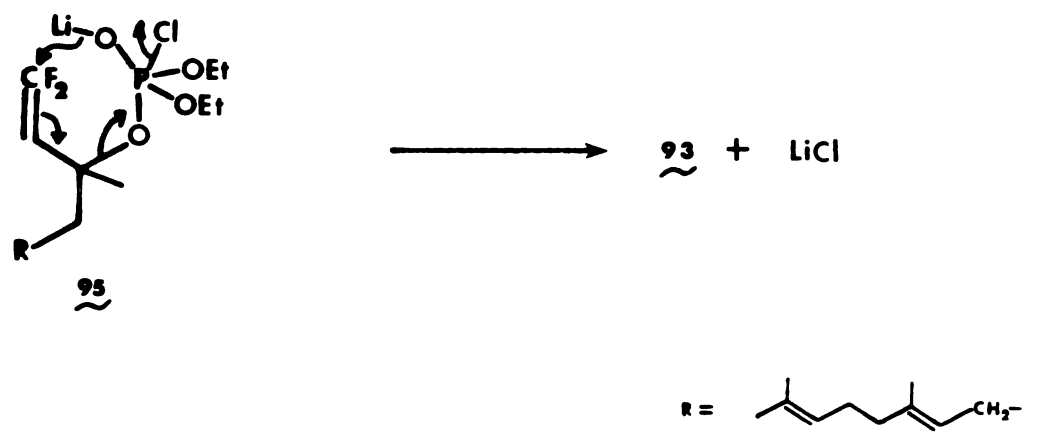


FIGURE 14

Phosphate 96 was further characterized by normal spectroscopic and analytical techniques.

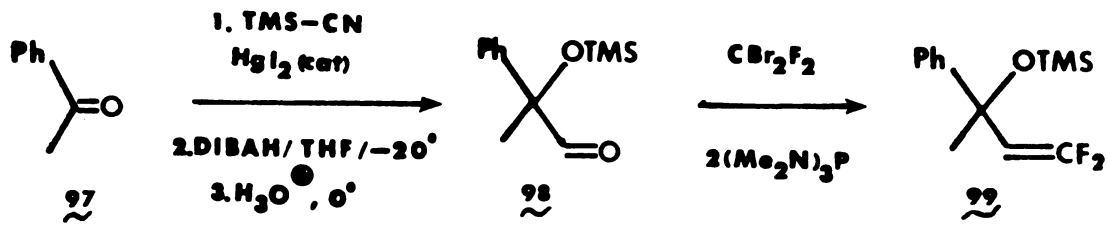




SCHEME VIII

Possible Formation of 94 and 73 Via Pentacoordinate Phosphorus Intermediate 95.

The generality of the previously discussed reactions was briefly investigated in a non-terpenoid model system. In a one pot synthesis, acetophenone (97) was converted to α-trimethylsilyloxy aldehyde 98 in 68-84% yield. GLC and tlc analysis of the product indicated the presence of a polar, unidentified product. The desired product 98, obtained in a pure state using LPLC (silica gel),



was transformed into difluoroolefin 99 in an LPLC yield of 65% using the same procedures used for the preparation of 67. Product 99 was fully characterized by spectroscopic and analytical means including proton and fluorine NMR. As observed in the ^{1}H-NMR spectra of the previously prepared fluoroolefins, the C-3 methyl group was a doublet (J=3Hz) centered at 1.73 ppm. Proton-fluorine off-resonance-decoupling experiments,[85] the results of which are given in Fig. 15, clearly indicate that the fluorine cis to the C-3 methyl group is alone responsible for the observed 3Hz splitting. This cis fluorine atom, which is normally expected to exist as a doublet of doublets in the fluorine NMR, is further split by the C-3 methyl group into quartets (J=3Hz).

An attempt to directly rearrange ether 99 to primary acetate 100 using acetic acid with tosic acid as catalyst failed, the starting ether 99 being recovered virtually intact. The alcohol 101, prepared by base hydrolysis of 99, was

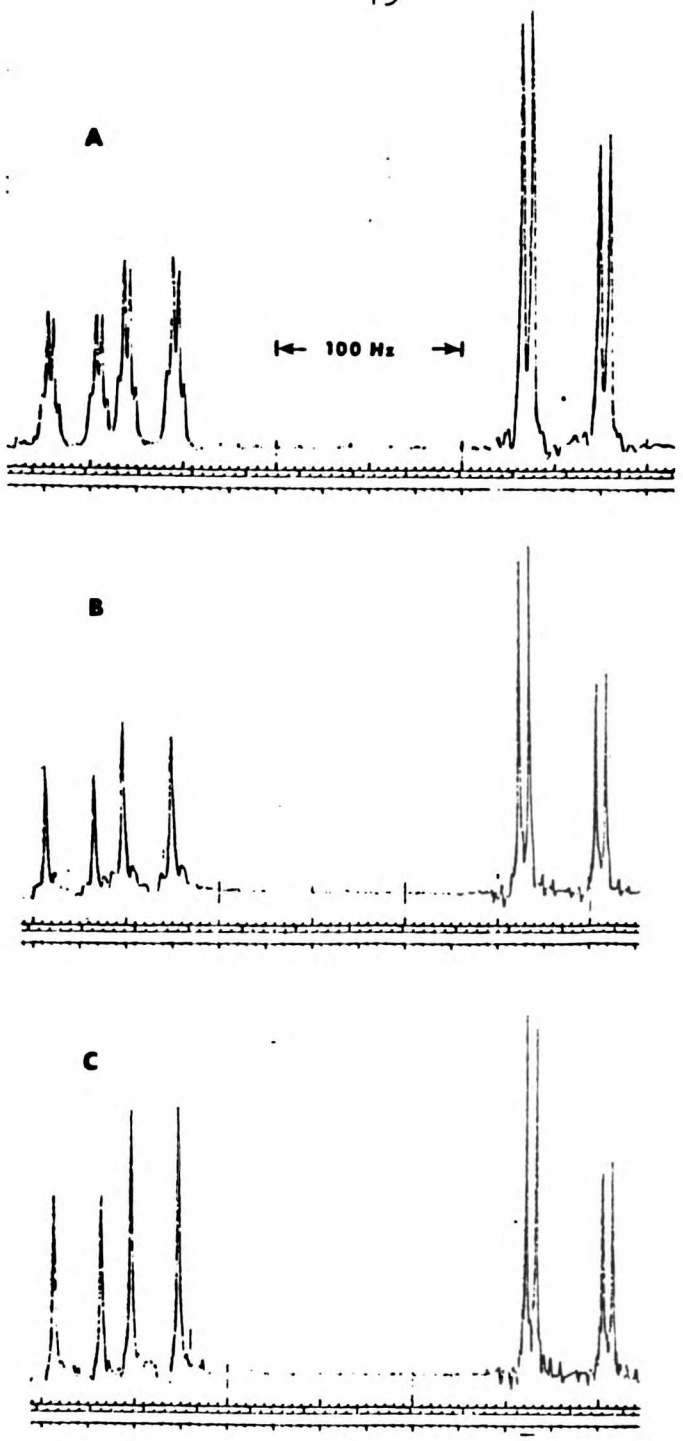
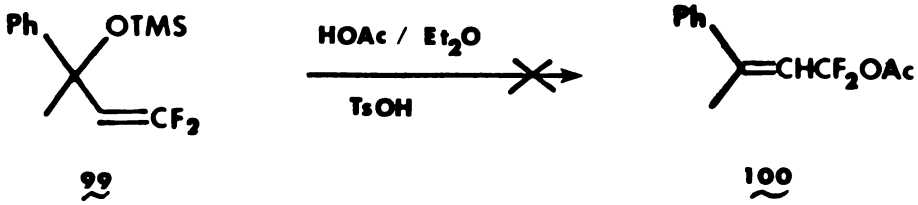


Figure 15

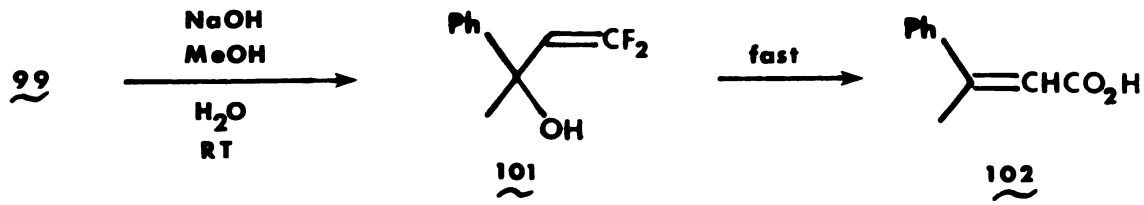
Fluorine-19 NMR spectra of 92 with C-3 methyl proton decoupling: (A) Coupled spectrum; (B) Partially decoupled; (C) Totally decoupled.

highly unstable when exposed to air after aqueous work-up and quickly formed acid 102.



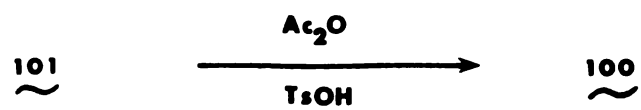
99 100

A similar instability in related compounds has been previously reported.[70] However,



101 102

alcohol 101 decomposed at a much slower rate if maintained for short periods of time (∿1 hr) in a chilled (0°C) hydrocarbon solvent under N_2. The solvent could then be removed and alcohol 101 used immediately. In this fashion, primary acetate 100 was prepared using the standard procedure.

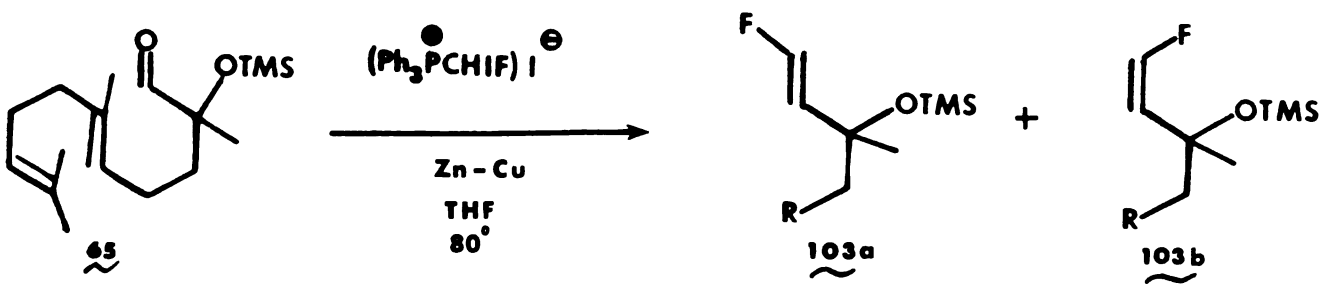


GLC analysis of the crude product indicated the presence of several, unidentified impurities. LPLC on silica gel afforded pure 100 in 24% yield. Proton NMR of 100 showed the expected triplet for the C-2 vinyl proton (J=10Hz) centered at 6.08 ppm. Fluorine NMR showed the expected two doublets (J=10Hz) for the cis and trans isomers (about 50:50 ratio). Acetate 100 was further characterized using normal spectroscopic and analytical procedures. This difluoroalkyl ester was found to slowly decompose with evolution of hydrofluoric acid if kept neat in air. However, 100 was stable in an inert solvent at 0°C.

A summary of NMR data for the fluorocompounds discussed in this section is presented in Section 2.7.

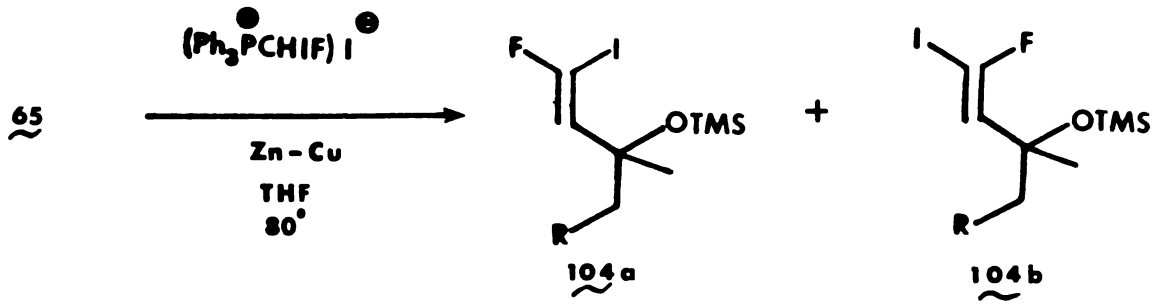
2.5 Monofluoro Derivatives

Monofluoroolefins 103a and 103b were prepared by a method described by Burton and Greenlimb.[50a] Following their procedure, aldehyde 65 was combined with



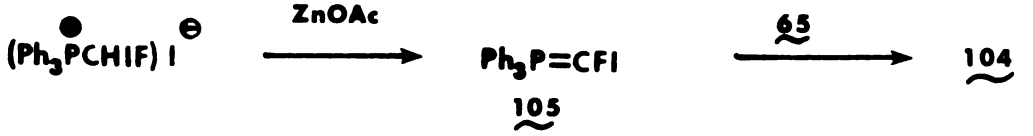
65 103a 103b

fluoroiodomethyl triphenylphosphonium iodide[50a] and zinc-copper couple in THF. Extended periods of heating (days) at about 80°C were required to produce 103 as a mixture of isomers (60:40), contaminated by significant amounts of unknown impurities (glc analysis). LPLC on silica gel furnished the separated isomers in a combined yield of about 14%. The more abundant isomer was found to be the E-isomer (103a), readily distinguished from the Z-isomer (103b) by NMR. The larger coupling observed between the fluorine and C-2 vinyl proton in 103b (J=48Hz) as compared to 102a (J=21Hz), is consistent with observations on numerous analogous fluoroolefins.[50a] The reaction, however, has been found to be erratic and nonreproducible. Recent attempts to repeat this monofluorination sequence have yielded not 103 as the predominant product, but rather the iodofluoroolefins 104a and 104b, in a 60:40 ratio respectively. These iodofluoro products were observed in earlier reactions only as side products, whereas in

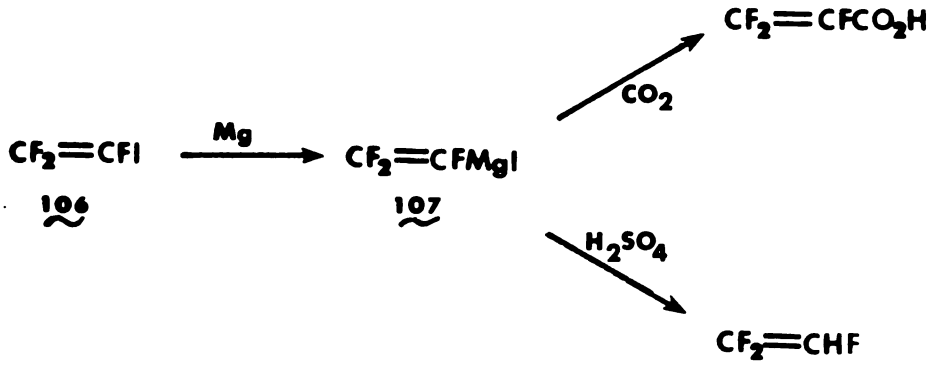


latter reactions only traces of 103 were detectable by glc analysis.

The products 104a and 104b were isolated as separated isomers in a combined yield of 64% using LPLC on silica gel. The structure of the more abundant isomer, 104a, was verified by NMR studies. As expected, 104a exhibited smaller spin-spin coupling between the fluorine and C-2 vinyl proton (J=23 Hz) than that found in 104b (J = 39 Hz). A possible cause for formation of 104 (rather than 103) may be the presence of zinc acetate as an impurity in the zinc-copper couple. This contaminant, if present, might act as a base, forming 104 via ylide 105.



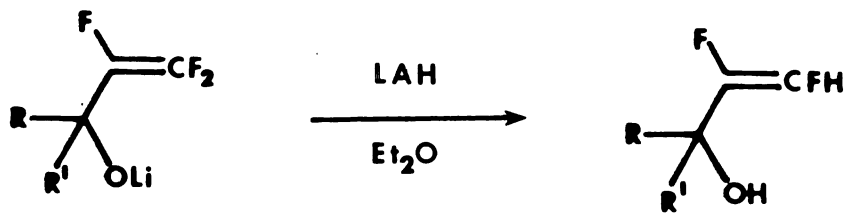
Polyfluorinated iodovinyl compounds are known in the literature.[87] For example, perfluorovinyliodide (106) has been used to prepare Grignard reagent 107, a



potential precursor to a variety of fluorinated compounds.[88] However, monofluoroiodovinyl compounds, such as 104, are virtually unknown. Further investi-

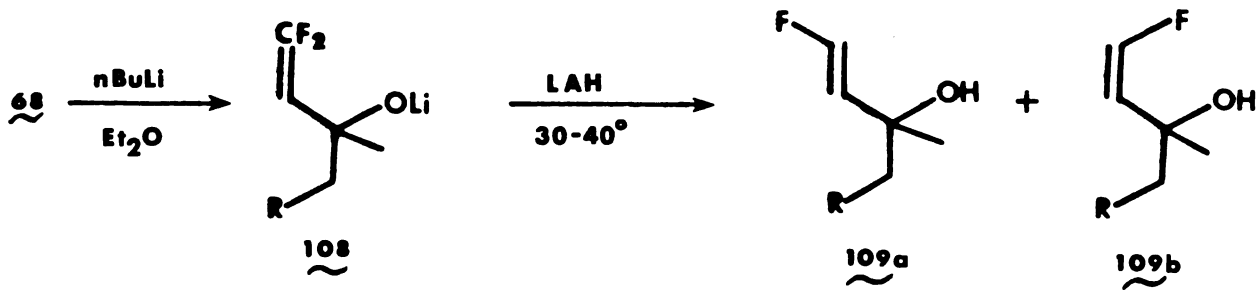
gations involving formation and utilization of iodofluoroolefins are in progress in our laboratories.

A recent study carried out by Normant and coworkers[89] demonstrated that the lithium salts of trifluovinyl carbinols can be conveniently reduced to difluoro analogues using lithium aluminum hydride (LAH). A recent study performed in

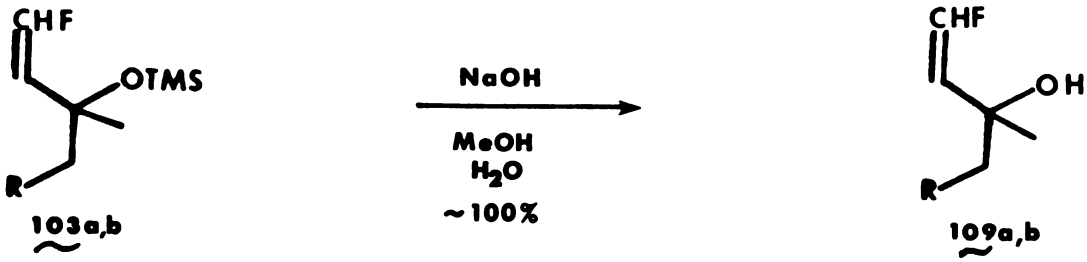


ref 89

our laboratories by Ms. K.S. Prickett has demonstrated that lithium salt 108, obtained by n-butyl lithium treatment of alcohol 68, is readily reduced by LAH to monofluoro alcohols 109a and 109b in about 90% combined yield.[90] Alcohols

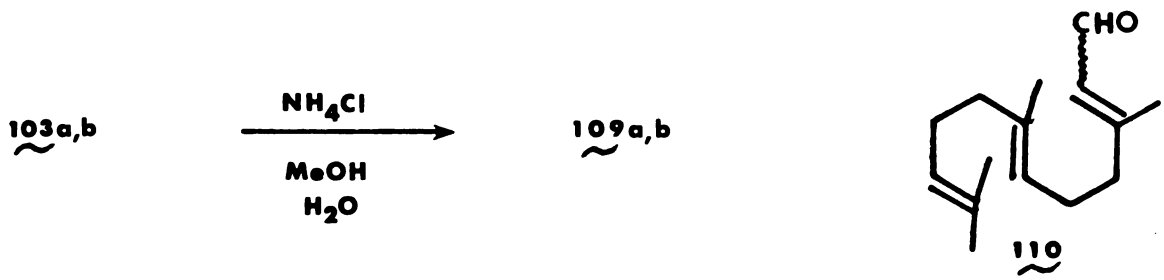


109a and 109b, formed in a 9:1 ratio, respectively, were found to be identical in every way to samples prepared by base promoted cleavage of the trimethylsilyl ether of monofluoroolefins 103a and 103b.

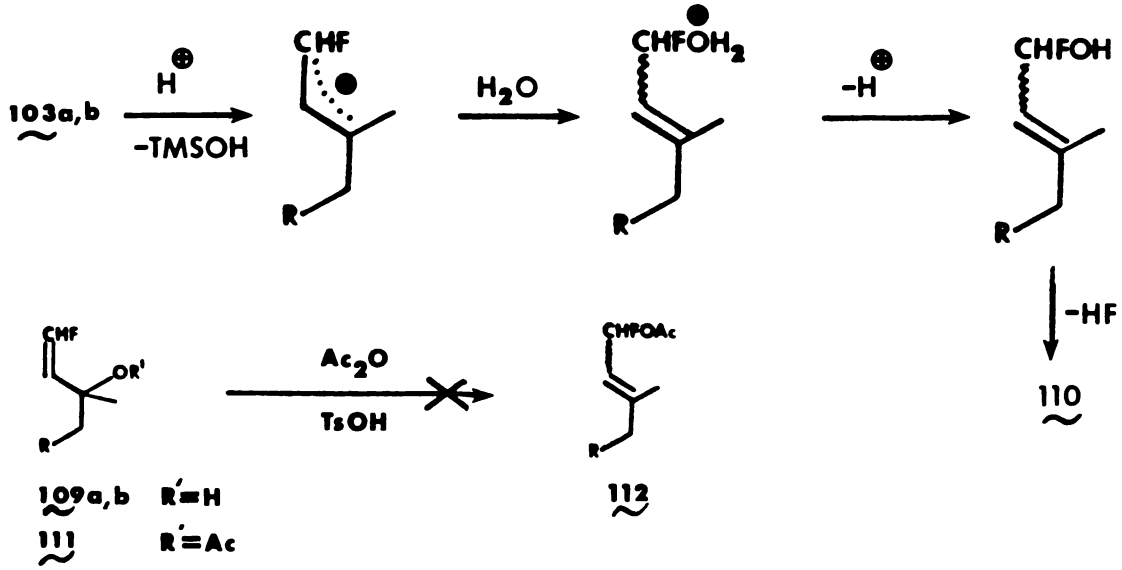


103a,b 109a,b

Hydrolysis of 103a,b under mild acidic conditions on the other hand, afforded not only 109a,b, but also farnesal (110). Formation of aldehyde 110 is probably due



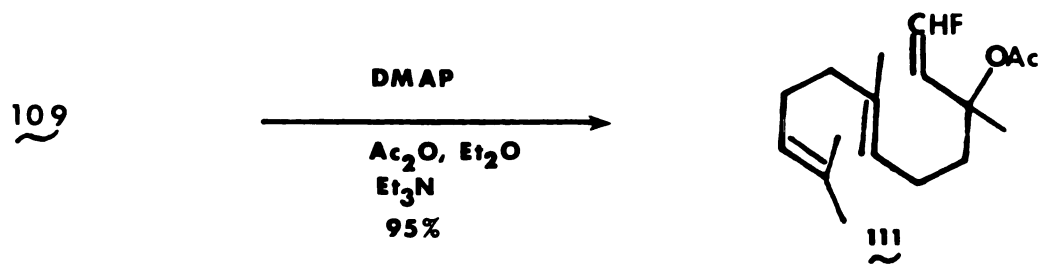
to carbonium ion formation, trapping by water, and subsequent loss of hydrofluoric acid.



Attempted preparation of acetate 112 by rearrangement of tertiary alcohol 109a,b produced a complex mixture of products. An isomeric mixture of acetate 111 also failed to produce the primary acetate derivative 112 upon attempted rearrangement using acetic anhydride and tosic acid. The unsuccessful rearrangement attempts using tertiary acetate 111 were performed by Prickett.[90] Attempted thermal rearrangement of 111 to 112 in xylenes at 120°C led only to a complex mixture.

Our successful rearrangements of both difluoroalcohol 68 and tertiary difluoro acetate 71 to the primary difluoroacetate 70 and, our failures to repeat these reactions in their monofluoro analogues, may point to a subtle difference in the electrophilic nature of vinyl groups containing either one or two fluorines. Linalool (74), a tertiary allylic alcohol containing no fluorines, also failed to undergo rearrangement to form significant amounts of primary acetate derivative, but instead, predominantly formed a tertiary acetate derivative derived from an intramolecular process.[48f] Furthermore, increased fluorine substitution in olefins is known to enhance electrophilic reactions.[30] Thus, the increased electrophilic character of the difluorovinyl group, as in 68 and 71, as compared to monofluoro and non-fluoro analogues 109, 111, and 74, may aid in promoting the desired allylic rearrangement (to form 70) relative to competing intramolecular side reactions. However, one must also note that increased fluorine substitution in terpenoid compounds, such as 74, 109, and 68, may also result in substantial conformational differences in solution. For example, repulsive forces due to increased fluorine substitution may require difluoro analogues 68 and 71 to exist as extended hydrocarbon chains in solution, thus making intramolecular process comparatively difficult. Further experiments aimed at providing increased insight into the effects of fluorine substitution on vinyl groups should be performed.

In a preliminary experiment, tertiary alcohol 109 was transformed into phosphate derivative 113 using the previously described procedure. Phosphate 113, obtained



as separated isomers using LPLC (combined yield of 20%), was characterized by standard techniques. Proton NMR showed a doublet of triplets (J = 57 and about 7Hz) at 6.58 ppm for the C-1 hydrogen. The larger coupling was consistent with the presence of a vicinal fluorine. Furthermore, fluorine NMR studies of the two isomers of 113 indicated very broad doublets (J =57Hz) due to multiple long range spin-spin coupling. Fluorine NMR studies with complete proton decoupling indicated a surprisingly small F-P coupling as shown in Fig. 16. The triplet structure, previously mentioned in the proton NMR for the C-1 hydrogen, is presumably due to the fortuitously equivalent coupling of the C-2 vinyl proton and the phosphorus with the C-1 proton. The C-2 vinyl proton was observed as a broad triplet (J~7Hz) centered at 5.47 ppm. This triplet structure is also probably due to equivalent coupling of the C-1 proton and fluorine with the C-2 vinyl hydrogen.

Phosphate ester 114 was prepared by Prickett[90] using the procedure successfully employed earlier in the synthesis of difluoro analogue 96.[90]

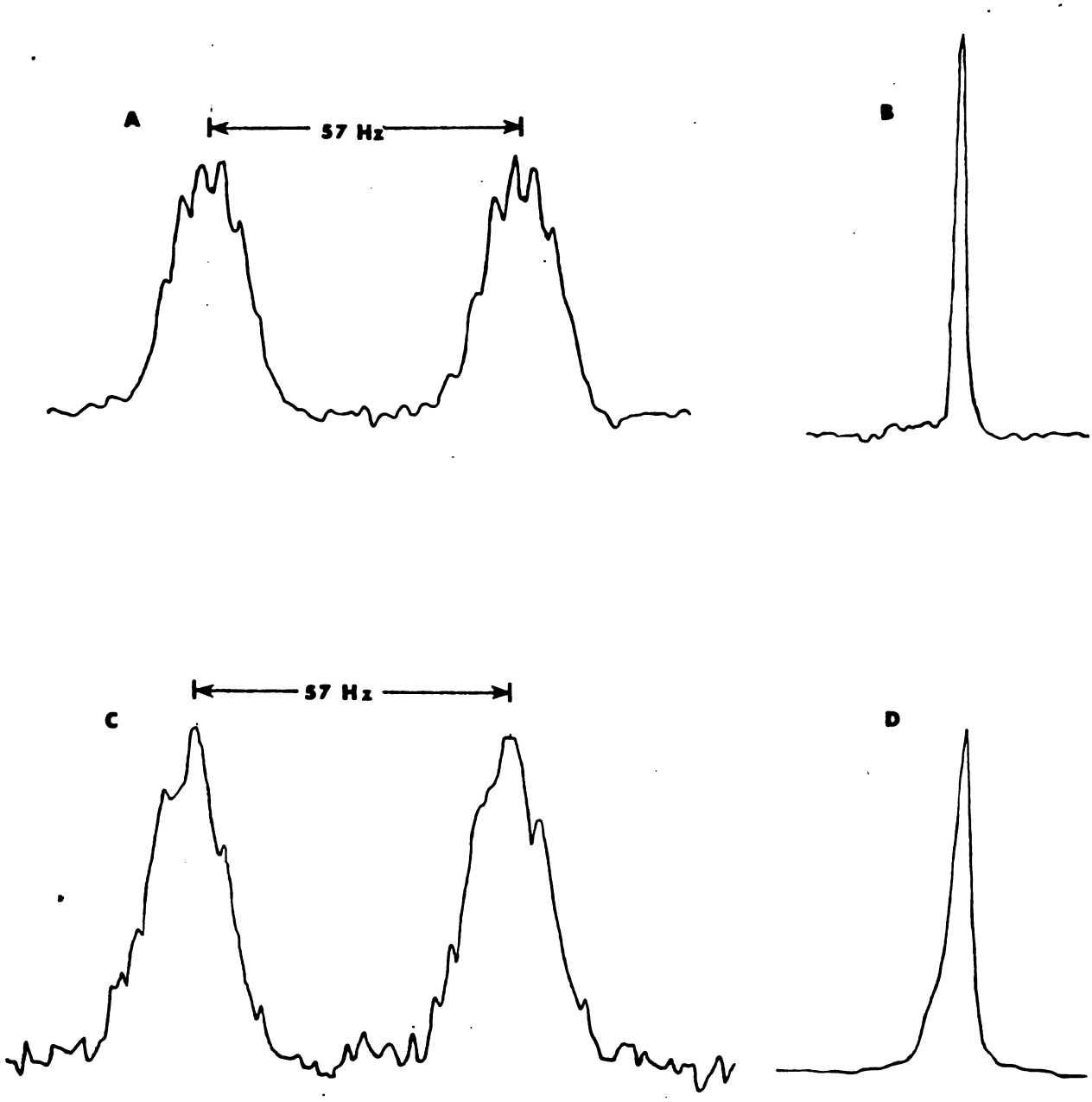
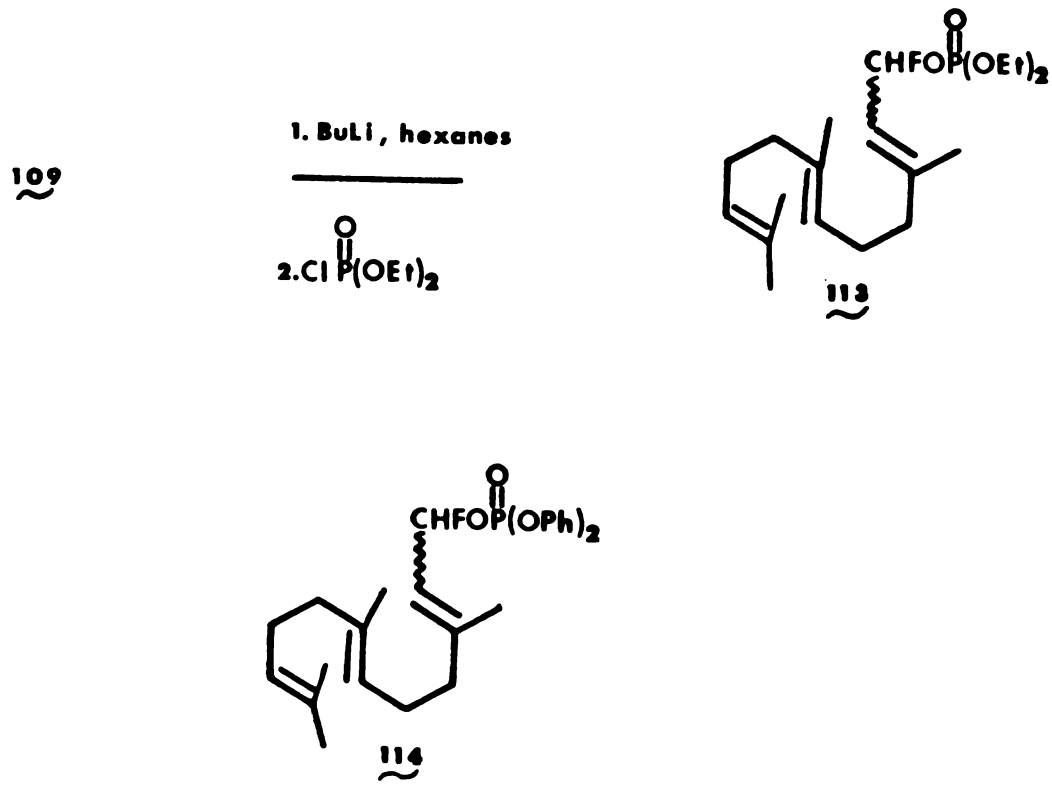


Figure 16

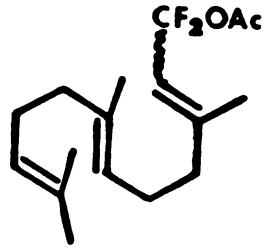
Fluorine-19 NMR spectra of 113 with and without total proton decoupling: (A) Coupled spectrum of 2-E 113; (B) Decoupled spectrum of 2-E 113; (C) Coupled spectrum of 2-Z 113; (D) Decoupled spectrum of 2-Z 113.



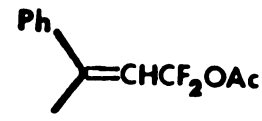
Compound 114, which was obtained in an approximate yield of 50%, was separated into its 2-E and-Z isomers using LPLC on silica gel. The proton NMR spectrum of 114 was totally consistent with the assigned structure and compared well to the spectrum of analogue 113.

2.6 Summary

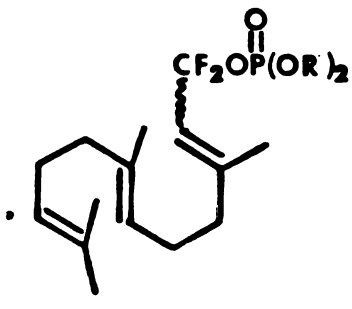
During the course of our investigations we have developed a new and potentially valuable synthetic approach to trimethylsilyl protected α-hydroxy aldehydes. We have also shown that these aldehydes may serve as precursors to fluoroallyl alcohols which, in turn, are easily converted to halide, amide, acetate, and phosphate derivatives. Of primary concern was the successful syntheses of difluoro acetates 70 and 100, and phosphate ester analogues 94, 96, 113, and 114.



70

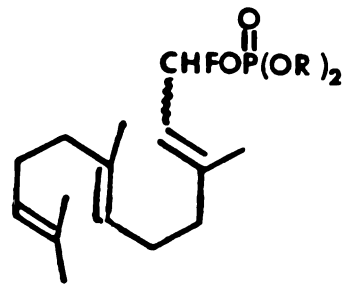


100



94 (R = Et)

96 (R = Ph)



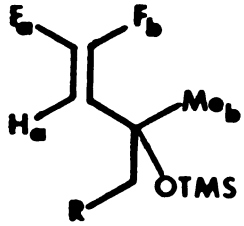
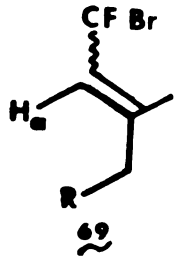
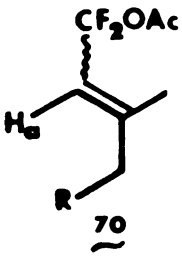
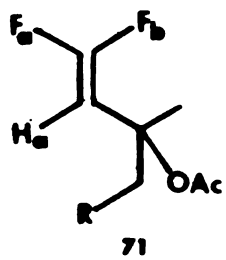
113 (R = Et)

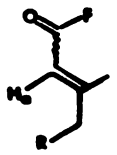
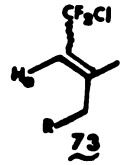
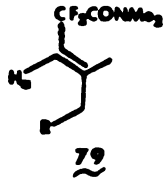
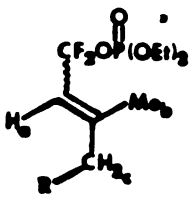
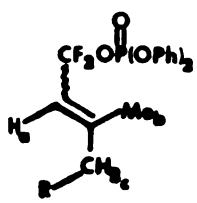
114 (R = Ph)

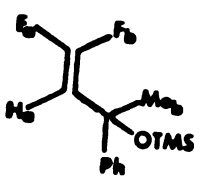
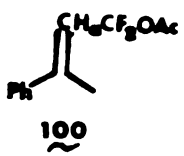
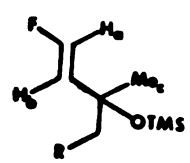
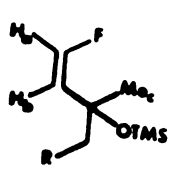
The synthetic approaches described in this thesis provide essential methodology for the preparation of fluoro compounds useful as mechanistic probes of squalene synthetase and other enzymes.

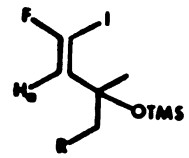
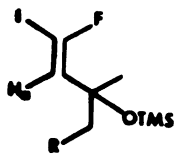
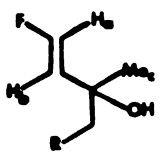
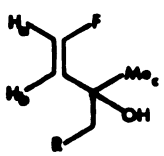
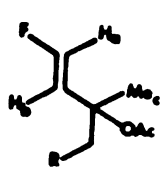
2.7 TABLE 15

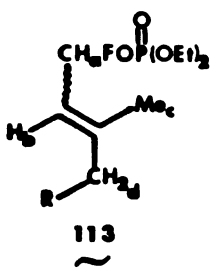
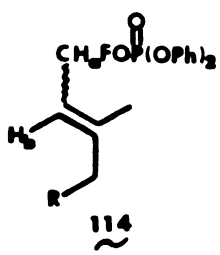
Summary of NMR Data: Fluoro Compounds

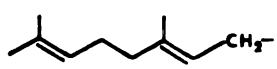
Compound[a]	Chemical[b] Shift (ppm)	Multiplicity	Coupling Constants (Hz)
 67	H_a : 4.38	dd	J_{F_b} (26.5), J_{F_a} (6.5)
	H_b : 1.43	d	J_{F_b} (2.5)
	F_a : 86.8	dd	J_{F_b} (46), J_{H_a} (6)
	F_b : 84.6	dd	J_{F_a} (46), J_{H_a} (27)
 68	H_a : 4.43	dd	J_{F_b} (26) J_{F_a} (6)
	H_b : 1.43	d	J_{F_b} (2)
	F_a : 86.3	dd	J_{F_b} (46), J_{H_a} (6)
	F_b : 84.9	dd	J_{F_a} (46), J_{H_a} (26)
 69	H_a :5.73	t	J_F (12)
 70	H_a : 5.60	t	J_f(10)
	F : 63.3 and 63.7	2d	J_{H_a} (10)
 71	H_a : 4.67	dd	J_{F_b} (27), J_{F_a} (5)
	F_a : 85.72	dd	J_{F_b} (42), J_{H_a} (5)
	F_b : 82.63	dd	J_{F_a} (42), J_{H_a} (27)

Compound[a]		Chemical[b] Shift (ppm)	Multiplicity	Coupling Constants (Hz)
 72		H_a : 5.70	m	
		F :-41.66 and -41.31	2bs	
 73		H_a : 5.68	t	J_F (12)
		F : 42.5 and 42.8	2d	$J_{a\ H_a}$ (12)
 79		H_a : 5.63	t	J_F (13)
		F : 90.73 and 91.51	2d	J_{H_a} (13)
 94	E	H_a : 5.58	t	J_F (10)
		H_b : 1.92	m	
		H_c : 2.13	m	
		F : 55.06	vbm	J_p(∿ 6)[d], J_{H_a} (10)[d]
	Z	H_a : 5.58	t	J_F (10)
		H_b : 1.85	m	
		H_c : 2.28	m	
		F : 54.73	vbm	
 96	E	H_a : 5.52	t	J_F (10)
		H_b : 1.83	m	
		H_c : 2.07	m	
		F : 54.67	vbm	

Compound[a]	Chemical[b] Shift (ppm)	Multiplicity	Coupling Constants (Hz)
96 Z	H_a : 5.48	t	J_F (10)
	H_b : 1.78	m	
	H_c : 2.20	m	
	F : 54.14	vbm	
 99	H_a : 4.63	dd	J_{F_b} (26), J_{F_a} (6)
	H_b : 1.73	d	J_{F_b} (3)
	F_a : 85.92	dd	J_{F_b} (41.5), J_{H_a} (6)
	F_b : 83.27	ddq	J_{F_a} (41.5), J_{H_a} (6) J_{H_b} (3)
 100	H_a : 6.08	t	J_F (10)
	F :63.90 and 63.93	2d	J_{H_a} (10)
 103a	H_a : 6.61	dd	J_F (86), J_{H_b} (11)
	H_b : 5.43	dd	J_F (21), J_{H_a} (11)
	H_c : 1.33	S	
	F : 137.9	dd	J_{H_a} (86), J_{H_b} (21)
 103b	H_a : 6.30	dd	J_F (85), J_{H_b} (6)
	H_b : 4.80	dd	J_F (48), J_{H_a} (6)
	H_c : 1.47	d	J_F (2)
	F : 137.7	dd	J_{H_a} (85), J_{H_b} (48)

Compound[a]	Chemical[b] Shift (ppm)	Multiplicity	Coupling Constants (Hz)
 104a	H_a : 5.95	d	J_F (23)
	F : 60.67	d	J_{H_a} (23)
 104b	H_a : 5.43	d	J_F (39)
	F : 63.17	d	J_{H_a} (39)
 109a	H_a : 6.75	dd	J_F (86), J_{H_b} (10)
	H_b : 5.50	dd	J_F (21), J_{H_a} (10)
	H_c : 1.32	s	
	F : 136	dd	J_{H_a} (86), J_{H_b} (21)
 109b	H_a : 6.13	dd	J_F (85), J_{H_a} (5)
	H_b : 5.08	dd	J_F (47), J_{H_a} (5)
	H_c : 1.42	d	J_F (1.5)
	F : 127	dd	J_{H_a} (85), J_{H_b} (47)
 111	H_a : 6.75	dd	J_F (84), J_{H_b} (11)
	H_b : 5.67	dd	J_F (21), J_{H_b} (11)
	H_c : 1.57	s	
	F : 133	dd	J_{H_a} (84), J_{H_b} (21)

Compound[a]		Chemical[b] Shift (ppm)	Multiplicity	Coupling Constants (Hz)
 113	E	H_a : 6.58	dt	J_F(57), J_p (~7), J_{H_b} (~7)
		H_b : 5.47	bt	J_F (~7), J_{H_a} (~7)
		H_c : 1.82	m	
		H_d : 2.08		
		F : 112.09	bd	J_{H_a} (57)
	Z	F : 110.66	bd	J_{H_a} (57)
 114		H_a : 6.62	dt	J_F (56), J_p (~7) J_{H_b} (~7)
		H_b : 5.35	bt	J_F (~7), J_{H_a} (~7)

(a) R = 

(b) Fluorine chemical shifts in ppm (Ø) upfield from CCl_3F internal standard.

(c) The negative sign for the chemical shift indicates that the fluorine signals are downfield from CCl_3F.

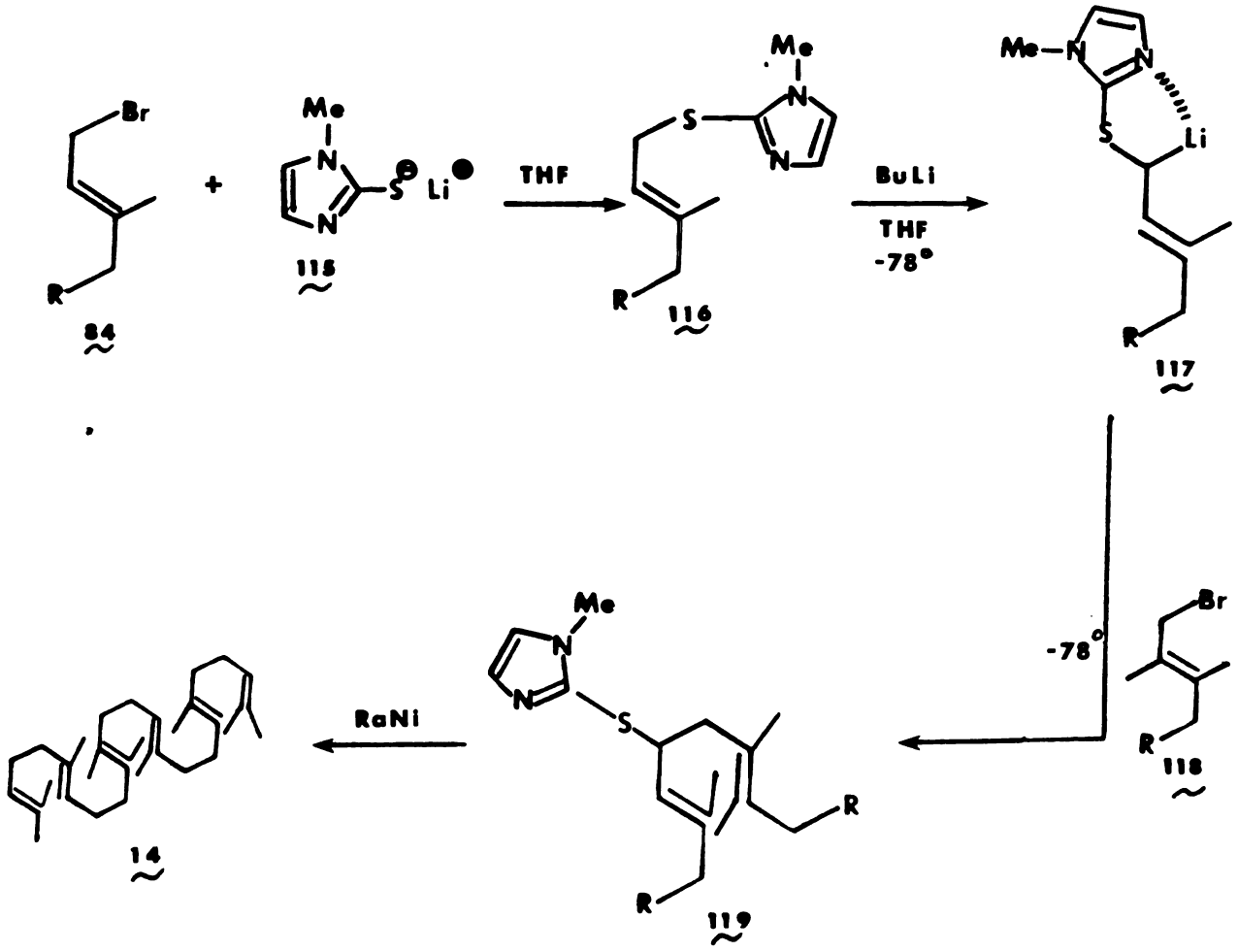
(d) Coupling constants determined from decoupling experiments. See Fig. 13

Appendix A: Synthesis of Squalene Analogues

I. 11-Methyl Squalene (14)

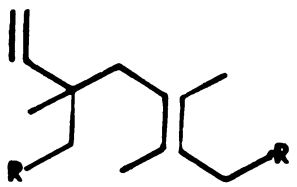
Unsymmetrical squalene analogue 14 was prepared as outlined in Scheme IX. Treatment of all trans-farnesyl bromide (84)[1d] with the lithium salt of 2-mercapto-1-methylimidazole (115) gave 116 in 70% yield following LPLC purification. Low temperature treatment of 116 with n-butyl lithium in THF gave anion 117 which,

SCHEME IX

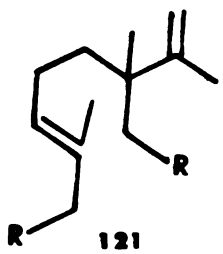


due to the known complexation of the lithium with the nitrogen[91], reacted with trans-2-methylfarnesyl bromide (118)[1d], affording product 119 in 63% yield

(LPLC). Raney nickel desulfurization[92] of 119 then gave 11-methylsqualene (14) in essentially quantitative yield. GLC analysis of crude product 14 showed one major peak under conditions which clearly differentiate between squalene stereo and regioisomers. The total lack of NMR signals both at >5.2 ppm and < 1.6 ppm indicates the absence of regioisomeric impurities such as 120 and 121. Furthermore, the absence of reduced products similar to 123, which can result from

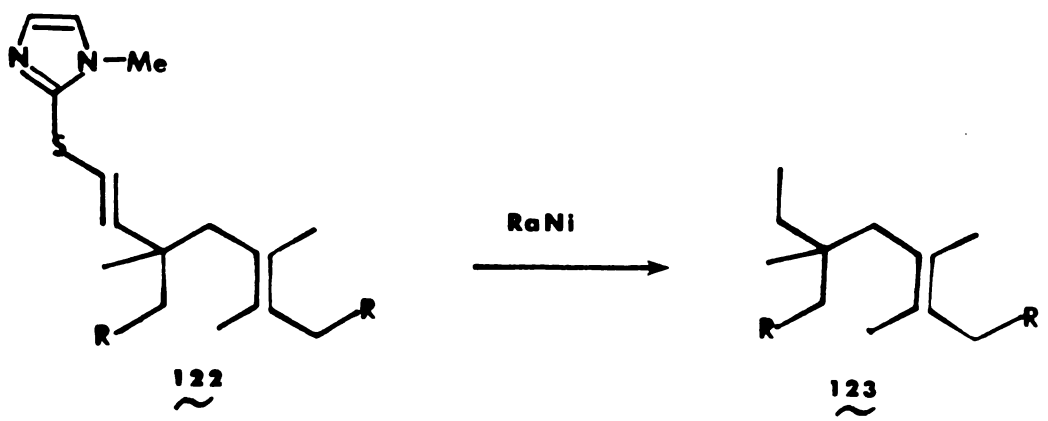


120

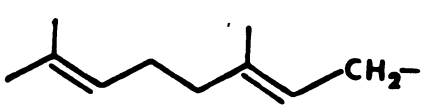


121

Raney nickel reduction of 122, was confirmed by both NMR and mass spectrometric analysis.



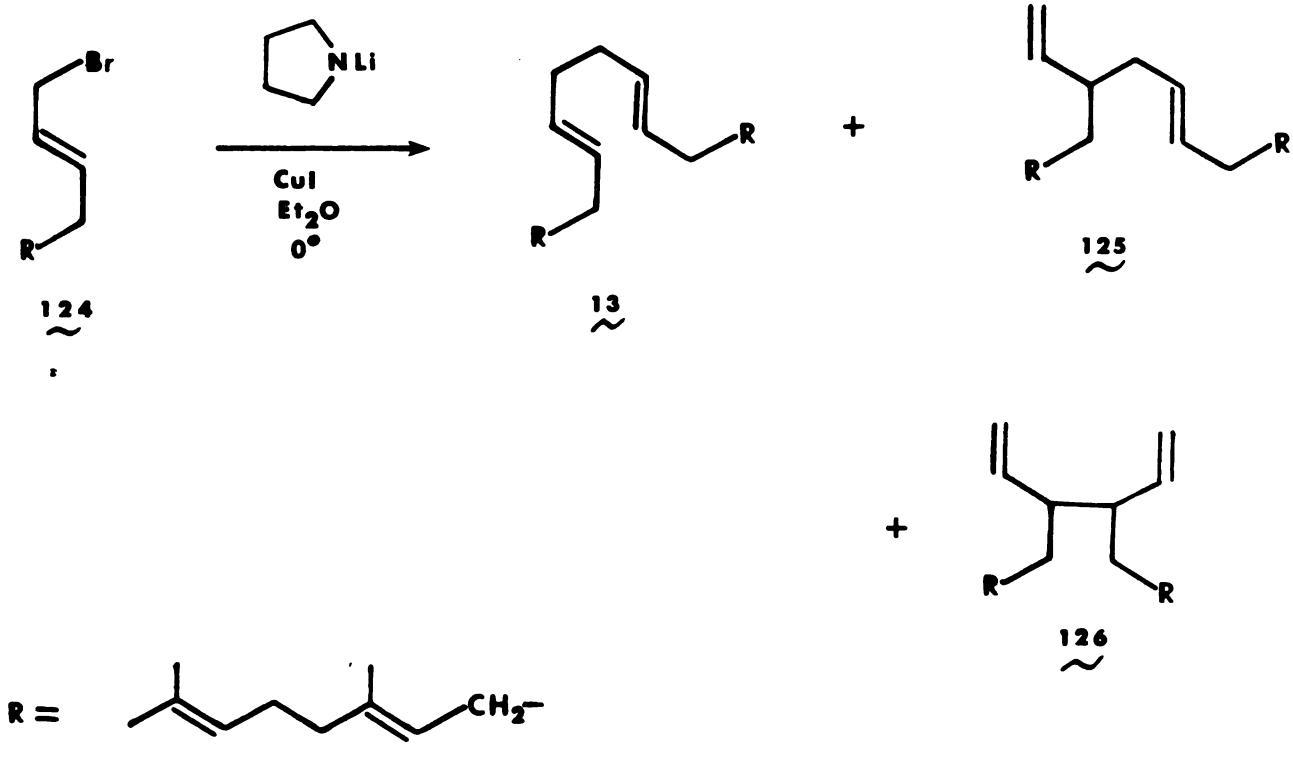
122 123

R = 

II. 10,15-Didesmethyl Squalene (13)

Analogue 13, a previously described symmetrical squalene analogue[93], was prepared according to a recently reported procedure developed by Yamamoto and coworkers.[94] The resulting highly stereospecific but relatively non-regiospecific coupling of allylic bromide 124[1d] is outlined in Scheme X. The coupling reaction is carried out by preparing lithium pyrrolidide (pyrrolidine/n-Buli) followed by sequential addition of cuprous iodide and bromide 124 at 0°C.[94]

SCHEME X



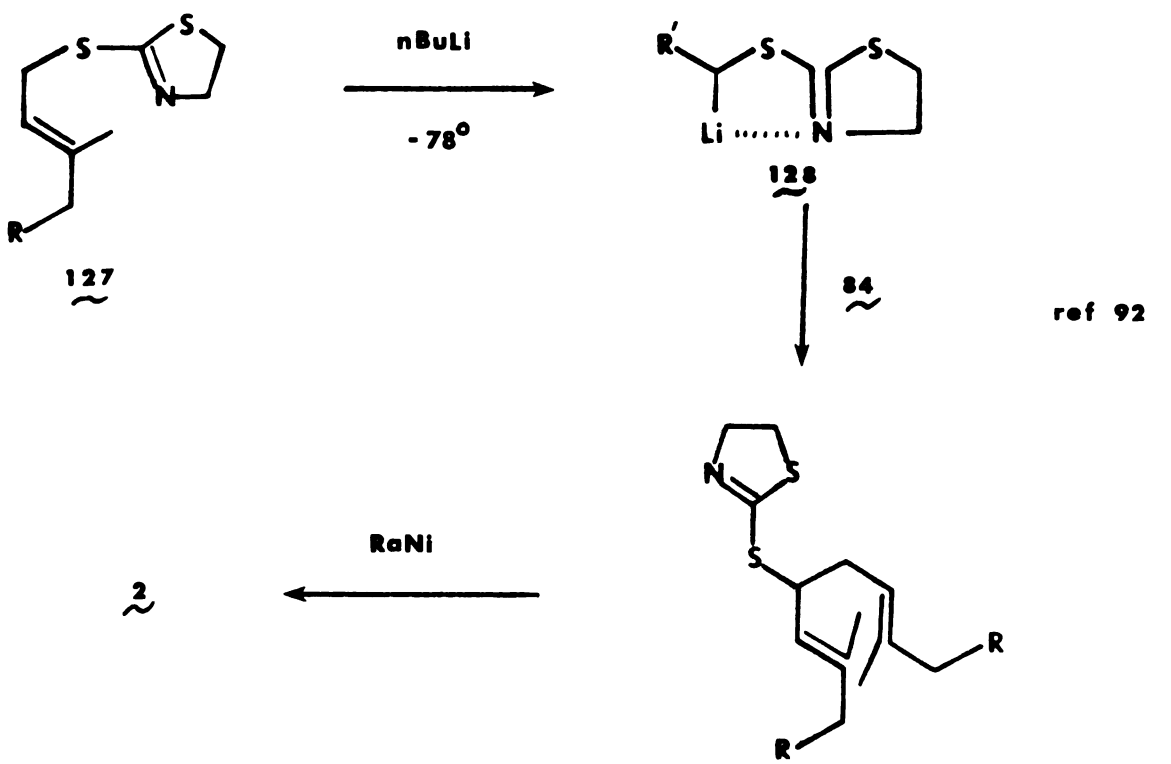
Regioisomers 13, 125, and 126 were obtained in nearly quantitative yield in a 52/39/9 ratio, respectively, as determined by glc analysis. This ratio is quite similar to those previously reported.[94] As expected, analogue 13 had the longest glc retention time.[95] Preparative glc of the crude product mixture gave pure 13.

The trans stereochemical assignment for 13 is based on the presence of an infrared band at 960 cm^{-1} (trans-disubstituted double bond).[96] The product 13 was found to be identical in all respect to previously prepared compound.[94]

III. 10-Desmethylsqualene (15)

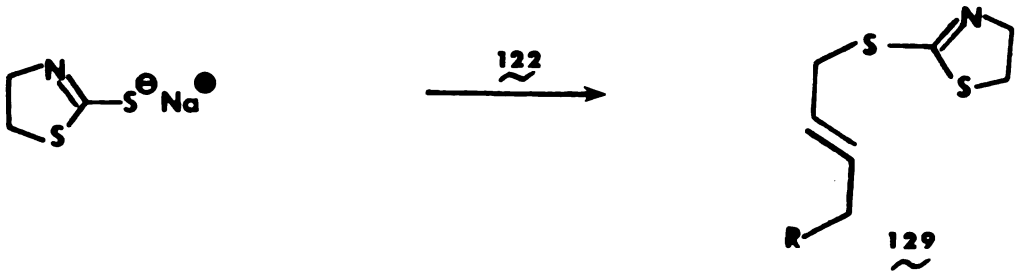
Squalene analogue 15 was prepared by a method similar to that used in the preparation of 11-methyl squalene (14), except that 2-mercaptothiazoline was used instead of 2-mercaptoimidazole. Hirai and co-workers[92] have prepared squalene by this method as shown in Scheme XI.

SCHEME XI

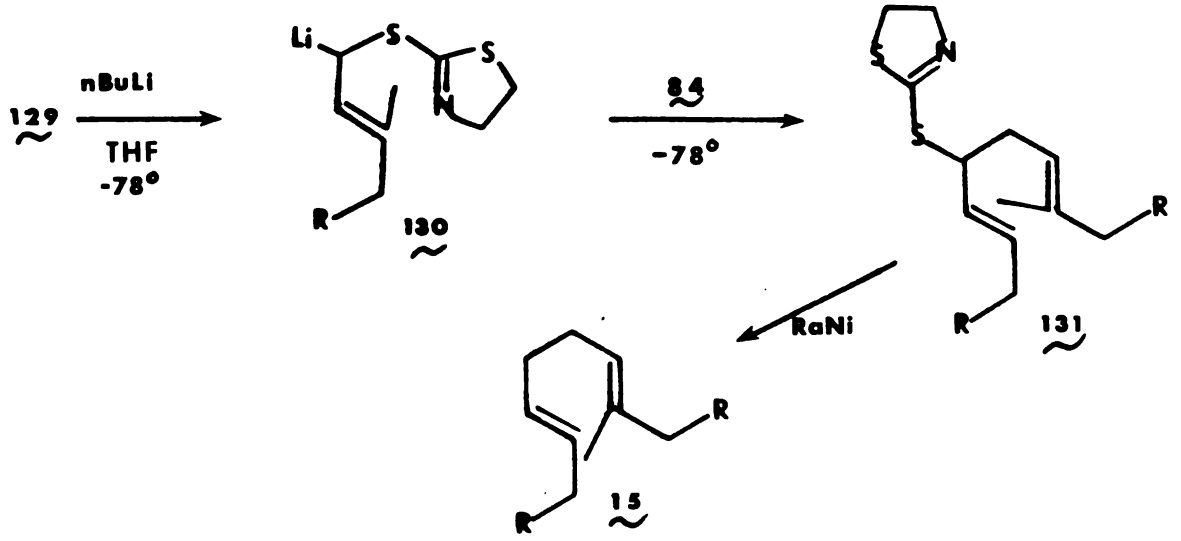


In this, and related reactions, they claimed exclusive α-alkylation (rather than γ) with respect to the sulfur atom and attributed this to a 5-membered chelating ring effect as shown in structure 128.[92]

Compound 129 was prepared by reaction of the sodium salt of 2-mercapto thiazoline with all trans-3-desmethyl farnesyl bromide (124)[1d]. Silica gel chromatography gave pure 129 in about 80% yield. Compound 129 was then treated with n-butyl



lithium at -78° for 1-2 hr, giving lithium salt 130, which, upon addition of bromide 84[1d], gave adduct 131. Product 131, obtained in the rather low but acceptable yield of 44%, was then subjected to Raney nickel desulfurization affording 15, contaminated by 15-20% of impurities as judged by glc analysis.

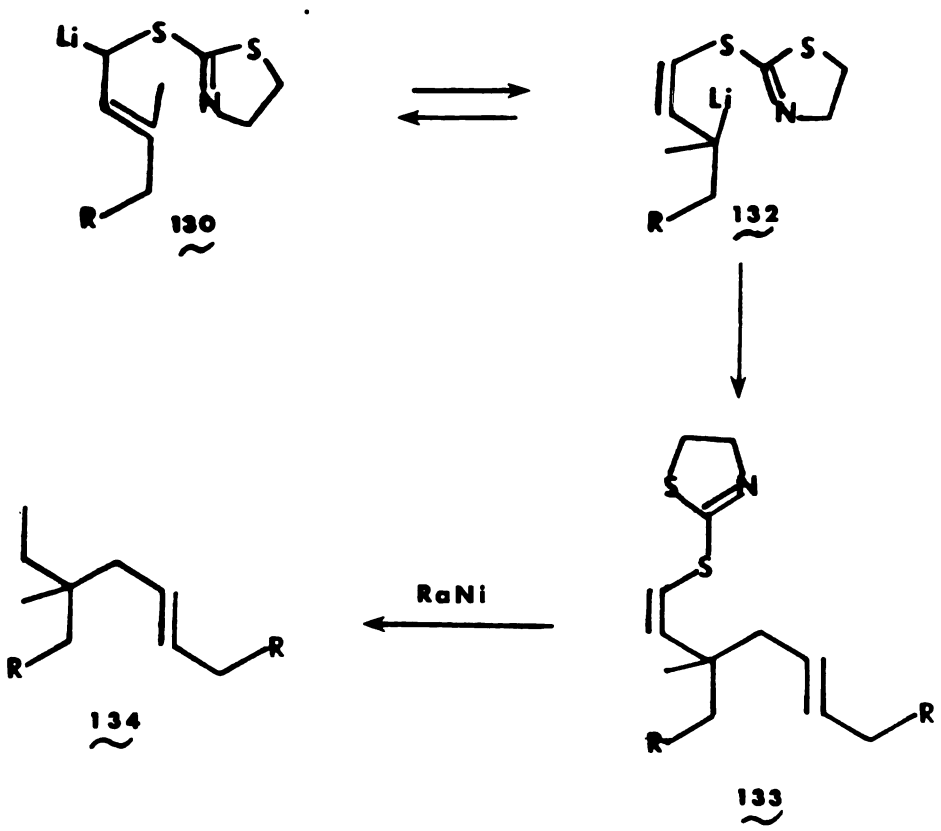


The majority of undesirable impurities were conveniently removed using silica gel column chromatography. The stereochemical assignment for 15 was based on an infrared band at 960 cm^{-1} (trans-disubstituted double bond)[96] and on the

highly preferential formation of a thiourea clathrate.[97]

Thiourea clathration removed a contaminant from all trans 15, as shown in Fig. 17, which was not separable by tlc but which had a slightly longer glc retention time than 15. This impurity was observed to have a mass 2 units greater than 15 by cims analysis. One possible explanation for this impurity was that it resulted from non-regioselective alkylation of 132 with 84 to give 133 as shown in Scheme XII. Subsequent treatment with Raney nickel might then afford

SCHEME XII



reduced product 134. NMR analysis of the crude product mixture showed traces of high field absorptions which possibly were due to 134.

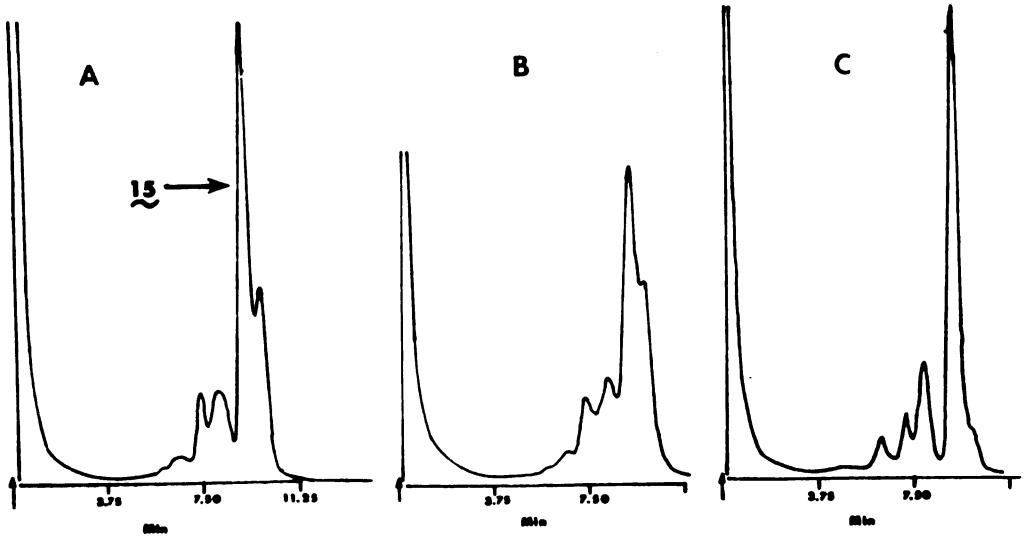
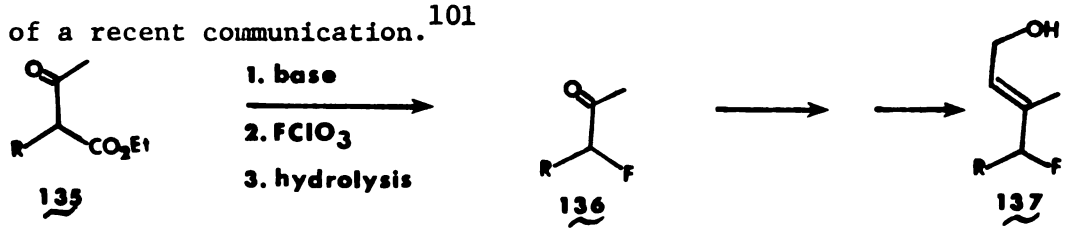


FIGURE 17

Crude 15 (tracing A) was stirred overnight with a saturated solution of thiourea in MeOH. The resulting crystals were filtered and washed with hexanes. Concentration of the hexanes washes afforded an oil (tracing B). The crystals were taken up in water and the resulting solution extracted with hexanes. Evaporation of the organic portion provided a colorless oil (tracing C). GLC system A, 221° C.

Appendix B: Synthesis of 4-Fluorofarnesyl pyrophosphate (17)

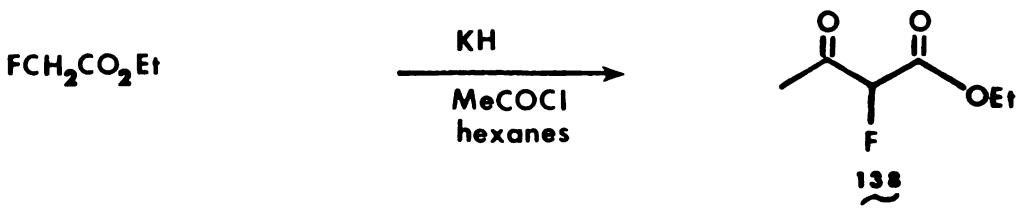
Prior to the outset of this work it had been shown by Machleidt and Grell[98] that ketone 136 could be easily converted to 4-fluorofarnesol (137), the required precursor to title compound 17. However, compound 136 was prepared using the explosively hazardous reagent perchloryl fluoride.[99,100] In order to circumvent this hazardous step we have developed a new method for the synthesis of 136. Our success in this goal and in the subsequent preparation of 137 has been the subject of a recent communication.[101]



135 136 137

The synthesis of 136 was achieved using ethyl 2-fluoroacetoacetate (138), a compound available in moderate yields by base promoted condensation of ethyl fluoroacetate and acetyl chloride.[102] Our extensive studies concerning the condensation of ethyl fluoroacetate and various electrophiles are reviewed in Table 16. We found that the use of potassium hydride as base, rather than sodium hydride, reduced side reactions due to self condensation of the resulting ester enolate. This result was most likely due to the lower temperatures at which KH could efficiently metalate the ester. The use of stronger bases such as n-BuLi, t-BuLi, and LDA for metalation of ethyl fluoroacetate at low temperature (-78°C), however, resulted in complex reaction products.

Although a known toxic compound,[103] ethyl fluoroacetate can be handled safely, using conventional techniques. Treatment of 138 with sodium methoxide in



138

TABLE 16

FCH_2CO_2Et —(1. base; 2. electrophile)→

Reaction Conditions[a]	Electrophile	Results[b]
t-BuLi/THF/-78°C	46/-78°	Complicated mixtures
LDA/THF/-78°	46/-78°	Complicated mixtures
n-BuLi/Et_2O/-78°	46/-78°	Complicated mixtures
KH/pet ether	46/-78°	Complicated mixtures
KH/THF/0°/1.5 hr	CH_3COCl (0° →RT)	Mixture including 138
KH/hexanes/0°	CH_3COCl(0°)	GLC showed about 50% 138
KH/hexanes/-10 to -15°	-	c
2KH/hexanes/about 3 to 10°	CH_3COCl (-78°)	d
nBuLi/hexanes/-78°	CH_3COCl (-78)	Complicated mixture[e]
2NaH/pet ether/0°	CH_3COCl (-78°)	Complex mixture

(a) All reactions conducted under an N_2 atmosphere.

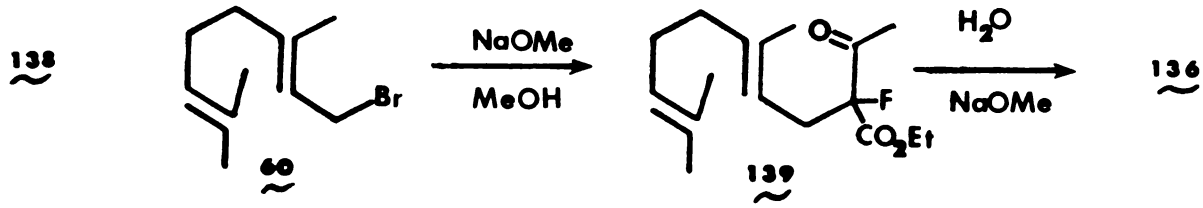
(b) All reactions followed by glc and tlc analysis.

(c) The metalation of the ester was apparently too slow, resulting in polymeric product formation (glc analysis).

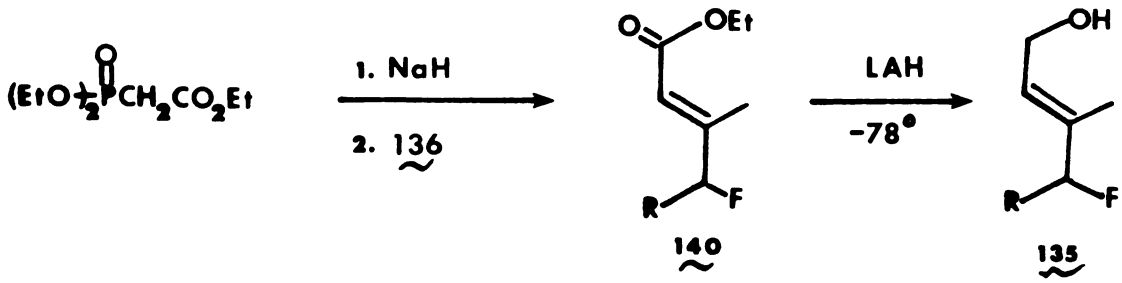
(d) Prior to addition of acetyl chloride, glc analysis indicated only a trace of products due to self condensation. Product 138 was obtained in a 36% distilled yield.

(e) No 138 visible by glc analysis.

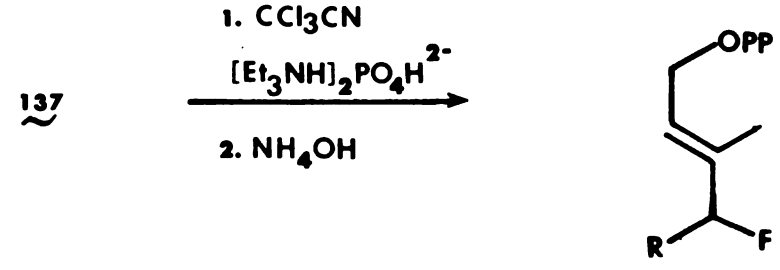
methanol, followed by addition of geranyl bromide (60)[104], gave the intermediate ketoester 139. This substance was hydrolyzed with base in situ, providing ketone 136 in 63% isolated yield. Wadsworth-Emmons[105] condensation of ketone 136 using diethyl 1-carboethoxyethylphosphonate gave fluoro ester 140 as a 9:1 mixture of 2-E and 2-Z isomers which could easily be separated by distillation. The



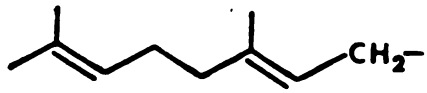
stereochemical assignment was based upon the relative positions of the C-2 vinyl protons in the NMR spectra, that of the major (2-E) isomer appearing at 5.85 ppm, while that of the minor (2-Z) isomer appeared at 5.68 ppm. This downfield shift of the vinyl proton which cis to a fluorine atom has been observed in closely related systems.[106] Low temperature lithium aluminuim hydride reduction of ester 140 afforded 4-fluorofarnesol (137) in 98% yield. Alcohol 137 was then pyrophosphorylated using a standard procedure we have described previously.[1d]



The elemental composition of 17 was verified by quantitative phosphorus analysis.[1d,e] Tritium labeled 17 was prepared by lithium aluminum tritide reduction of ester 140 followed by pyrophosphorylation.



PP= $-P_2O_6^{3-}$

R = 

EXPERIMENTAL

Instrumentation. Proton nuclear magnetic resonance spectra were obtained by either using a Varian A-60A or Varian XL-100 spectrophotometer with signals expressed as parts per million (δ) downfield from the internal standard tetramethylsilane. Fluorine-19 NMR spectra were obtained using a Varian XL-100 instrument at 94.1 MHz with signals expressed as parts per million (ϕ) upfield from a trichlorofluoromethane internal standard. Infrared spectra were obtained using a Perkin Elmer 337 grating spectrophotometer. Chemical ionization mass spectra were obtained using an AEI-MS-9 spectrometer adapted to a chemical ionization mode (isobutane gas). GLC-eims determinations were obtained on a modified AEI-MS-12[107] employing a 6 ft x 2.5 mm glass column containing 2% Dexsil 300 on 80-100 mesh chromsorb GHP as stationary phase. A Packard Tri-Carb Model 3375 spectrometer was used for radioactivity measurements. Melting points were obtained using a Hoover melting point apparatus and are uncorrected. Optical densities were measured using a Gilford adapted Beckman DU Model 2400 spectrophotometer. Spinning band distillations were performed using a Nester-Faust 19 inch Teflon band. A Buchi Kugelrohr apparatus was employed for bulb-to-bulb distillations. A Virtis Unitrap II model was used for general freeze-drying removal of water.

Gas-Liquid Chromatography GLC separations were performed using one of the following systems:

A. Varian 2100 model, flame ionization detectors, 6 ft X 2 mm i.d. glass columns, 3% OV-225 on 100-200 mesh varaport-30, N_2 carrier gas at 18 ml/min flow rate.
B. Same as A except 2.5% Dexsil 300 on 80-100 mesh chromosorb GHP used as stationary phase.

C. Same as A except 5.5 ft X 2 mm i.d. glass splitter with a 10:1 ratio favoring the collector; 2.5% OV-225 on 100-120 mesh chromosorb W; N_2 flow rate 20 ml/min.

D. Varian 90-P; thermal conductivity detector; 10 Ft X 0.2 in i.d. stainless steel column,; 3% OV-225 on 100-200 mesh chromosorb W; He carrier gas at 60 ml/min flow rate.

Thin-Layer Chromatography. The following systems were used:

A. Analtech pre-coated silica gel GF254 glass plates (2.5 X 10 cm; 250 micron thickness) preconditioned by storage over silica gel desiccant in a desiccator.

B. Eastman Kodak plastic-backed silica gel plates with fluorescent indicator.

C. Eastman Kodak plastic-backed cellulose plates.

D. Merck silica gel PF-254 plates (20 X 20 cm; 2mm thickness).

Column Chromatography. Two general methods were employed for column chromatographic separations:

1. Normal glass columns packed with either 70-230 mesh Merck silica gel-60 with basic alumina.

2. Low Pressure Liquid Chromatography (LPLC) using Merck pre-packed silica gel column size B and employing an FMI Lab pump (30 psi max press at 40 ml/min flow rate). When using LPLC for a given separation, the solvent system employed, the flow-rate , and the time required for elution of the given compound will be designated. A Chromatronix Model 220 absorbance detector was used for visualization purposes. Fractions were generally checked for content using tlc and/or glc analysis.

Solvents. Tetrahydrofuran (THF) and dimethoxyethane (DME) were distilled from LAH just prior to use. Diglyme was distilled from LAH at reduced pressure. Trichloroacetonitrile and acetonitrile were distilled from P_2O_5. Triethylamine, diisopropylamine, and 2,2,6,6-tetramethylpiperidine were distilled from calcium hydride. Diethylether used in reactions was Mallinckrodt anhydrous. All other solvents were at least reagent grade and, when drying was required, were stored over Linde 3-A molecular sieves.

Microanalyses. Microanalytical results were obtained from the University of California Microanalytical Laboratory, Berkeley.

General Reaction Procedures. All reactions were conducted under a nitrogen atmosphere in dry glassware unless specified otherwise. Normally, the progress of reactions was monitored by tlc and/or glc analysis. Normal drying and concentration consists of shaking the solution with anhydrous $MgSO_4$, filtration through a sintered-glass filter, and evaporation on a rotary evaporator using water aspirator vacuum.

Presentation of Data. NMR data are presented as follows: chemical shift in δ or $\emptyset$ (multiplicity, integrated intensity, assignment). Infrared data are presented as follows: position of ir band in cm^{-1} (relative intensity and shape). All temperatures are presented as degrees centigrade.

Abbreviations. The following are used in the presentation of NMR data: S = singlet; d = doublet, etc; dd = doublet of doublets; ddq - doublet of doublet of quartets,

etc.; m = multiplet; b = broad. The following abbreviations are used in the presentation of ir data: s = strong; v = very; b = broad; w = weak; m = moderate. R_f is an abbreviation used to described the center of mobility of a compound relative to the solvent front; t_r = glc retention time.

2-(1,3-Dithiane-2-yl)-2-hydroxy-6-methyl-5-heptene (47a)

A solution of 0.1268_g (1.023 mmol) of 1,3-dithiane in 20 ml of THF was treated with 1.07 mmol of n-BuLi at -78°. After warming to -20° for 0.75 hr and recooling to -78°, 0.1494_g (1.184 mmol) of ketone 46 was added. The mixture was slowly warmed to room temperature and stirred 1.5 hr. Water (about 1 ml) was added and the THF removed in vacuo. The residue was taken up in CH_2Cl_2 and washed with water and saturated aqueous NH_4Cl. The organic portion was then treated in the normal fashion to afford 276 mg of a yellow oil (88% yield) which, by glc and tlc analysis, contained trace amounts of ketone 46, 1,3-dithiane, and an adduct due to addition of n-BuLi to 46: tlc (system A, 15% EtOAc/85% hexanes, R_f = 0.32); glc (system A, 180°, T_r = 6.00 min); ir (film) 3450 cm^{-1} (S, OH); NMR ($CDCl_3$) δ1.35 (s, 3H, C-1 Me), 1.64 and 1.69 (2s, 6H, vinyl Me), 1.75-2.30 (m, 6H, $C\underline{H}_2$), 2.43 (bs, 1H, OH), 2.94 (m, 4H, $SC\underline{H}_2$), 4.25 (s, 1H, dithiane C-2H), 5.17 (m, 1H, vinyl H); cims: 247 (MH^+), 229 (MH^+-H_2O).

2-(1,3-dithiane-2-yl)-2-trimethylsilyloxy-6-methyl-5-heptene (47b)

A solution of 3.0152_g (25.079 mmol) of 1,3-dithiane in 150 ml of THF was treated with 26.77 mmol of n-BuLi and 26.76 mmol of ketone 46 as in the preparation of 47a. The lithium salt was then quenched with 5.8_g (53 mmol) trimethylsilyl chloride. After stirring overnight at room temperature,

excess TMS-Cl was removed in vacuo and the residue filtered (hexane washes). Solvent removal left 8.7314$_g$ of yellow oil which was distilled in vacuo to furnish 6.1141$_g$ of 47b as a colorless oil (79%); tlc (System A, 15% EtOAc/85% hexanes, R_f = 0.79); glc (System A, 200°, t_r = 3.7 min); ir (film) 1245, 840, and 755 cm^{-1}; NMR ($CDCl_3$)δ 0.14 (s, 9H, OSiMe), 1.40 (s, 3H, Me), 1.64 and 1.71 (2s, 6H, vinyl Me), 1.75-2.40 (m, 6H, $C\underline{H}_2$), 2.79-2.99 (m, 4H, $SC\underline{H}_2$), 4.17 (s, 1H, $C\underline{H}S_2$), 4.94-5.32 (m, 1H, vinyl H); cims: 319 (MH^+).

2-(1,3-dithiane-2-yl)-2-methoxy-6-methyl-5-heptene (47c).

Alcohol 47a(2.2 891$_g$, 9.29 mmol) in 30 ml of THF was treated with 430 mg (18 mmol) of NaH. H_2 evolution ceased after 1 hr at room temperature and 1 hr at reflux. Then, 28 mmol of MeI was added and, after heating at 40° for 1 hr the reaction was judged complete by glc analysis. Water was added and THF removed giving a residue which was worked up in the normal fashion using Et_2O/H_2O to afford 2.3084g (95%) of a yellow oil, pure by tlc and glc analysis: tlc (System A), 10% EtOAc/90% hexanes, R_f = 0.35), glc (System A, 180°, t_r = 5.25 min); ir analysis showed the absence of an hydroxyl group; NMR ($CDCl_3$) δ 1.32 (s, 3H, $C\underline{H}_3$), 1.65 and 1.71 (2s, 6H, vinyl $C\underline{H}_3$), 2.00 (bm, 6H, $C\underline{H}_2$), 2.81-3.07 (m, 4H, $SC\underline{H}_2$), 3.26 (s, 3H, OMe), 4.35 (s, 1H, dithiane, C-2 H), 4.99-5.35 (m, 1H, vinyl H); cims: 261 (MH^+), 230 (MH^+-MeOH).

3-Hydroxy-3,7-dimethyl-6-octenoic acid nitrile (50)

A solution of 55 mmol of n-BuLi in 40 ml of THF at -78° was treated with 2.0408$_g$ (49.93 mmol) of acetonitrile in 50 ml of THF. In 1 hr 6.3115$_g$ (50.02 mmol) of ketone 46 was added at -78°. The mixture was warmed to room temperature and 2 ml of water added. Solvent removal left a residue which was partitioned between

Et_2O and H_2O. The organic portion was dried and concentrated in the normal way to yield 7.59$_g$ of a yellow oil. Distillation (100-102°, 0.4 mm) gave 5.453g of pale yellow oil (65%): tlc (System A, 20% EtOAc/80% hexanes, R_f = 0.17), glc (System A, 160°, t_r = 7.03 min); ir (film) 3440 (OH), 2955, 2905, 2840, 2250 (m, C N), 1465, 1395 and 1115 cm^{-1}; NMR ($CDCl_3$) δ 1.35 (s, 3H, $C\underline{H}_3$), 1.63 and 1.70 (2s, 6H, vinyl $C\underline{H}_3$), 1.30-2.30 (bm, 4H, $C\underline{H}_2$), 2.52 (s, 2H, $C\underline{H}_2CN$), 2.88 (m, 1H, OH), 5.12 (m, 1H, vinyl H); cims: 168 (MH^+), 150 (MH^+-H_2O).

3-Trimethylsilyloxy-3,7-dimethyl-6-octenoic acid nitrile. (51)

Hydroxy nitrile 50 (20g, 0.120 mol), 46$_g$ (0.24 mol) of trimethylsilyl chloride, and 10.8$_g$ (0.14 mol) of pyridine were combined (external cooling) and stirred at room temperature for 17 hr. Et_2O addition, filtration, and solvent removal left a residue containing some solid. This material was taken up in Et_2O and washed with 5% HCl, water, and brine. Normal drying, filtration, and concentration provided 26.60g of pale yellow oil. Distillation of the crude product yielded 23.9715$_g$ of 51 (86%): glc (System A, 160°, tr = 3.28 min); ir (film) 2250 cm^{-1}; NMR ($CDCl_3$) 0.15 (s, 9H, OTMS), 140 (s, 3H, Me), 1.63 and 1.70 (2s, 6H, vinyl Me), 1.33-2.30 (bm, 4H, $C\underline{H}_2$), 2.48 (s, 2H, $C\underline{H}_2CN$), 5.13 (m, 1H, vinyl H).

4-Ethoxy-5-(4-methyl-3-penten-1-yl)-5-methyl-2-oxazoline. (53)

A slurry of 3.10$_g$ (15.9 mmol) of tosylmethylisocyanide in 30 ml of a 4:1 mixture of DME and EtOH was treated with 4.6$_g$ (18.4 mmol) of thallous ethoxide (caution: highly toxic substance) at room temperature. After 15 min, 2.02$_g$ (16.0 mmol) of ketone 46 was added. A silky white precipitate appeared within about 10 min. The mixture was stirred 24 hr. and then filtered (etheral washings). The combined filtrate was concentrated to an orange, semi-solid residue, taken up in Et_2O, and

washed with water and brine. Normal drying, filtration, and solvent removal gave 2.88g of 53 as a pale orange oil. A portion of this crude product (2.68_g) was bulb-to-bulb distilled (75°, 0.05 mm) to furnish 2.51_g of colorless oil (80% corrected yield). TLC showed two spots more polar than ketone 46 and corresponded to the two possible diasteriomers of 53 (tlc System A, 25% EtOAc/75% hexanes, R_f = 0.23 and 0.34); ir (film) 1630 (s, N = C) and 1110 cm^{-1} (bs); NMR ($CDCl_3$) δ 1.23 (t, J = 7Hz, 3H, $OCH_2C\underline{H}_3$), 1.33 (s, 3H, Me), 1.63 and 1.70 (2s, 6H, vinyl Me); 1.82-2.50 (bm, 4H, allylic $C\underline{H}_2$), 3.42-4.10 (m, 2H, $C\underline{H}_2O$), 4.83-4.93 (m, 1H, C<u>H</u>OEt), 4.83-5.33 (bm, 1H, vinyl H), 6.97 (m, 1H, OC<u>H</u>=N); cims: 212 (MH^+), 166 (MH^+-EtOH).

2,6-Dimethyl-2-hydroxy-5-heptenal. (48a)

A solution of 295 mg (1.40 mmol) of oxazoline 53 in 5 ml of THF was treated with 5 ml of 0.05<u>N</u> HCl at room temperature for 2 hr. at which time the reaction was judged complete (tlc). A normal Et_2O/H_2O work-up provided a crude product which was obtained (80 mg, 37% yield) which was shown to be reasonably free of impurities by glc and tlc analysis; tlc (System A, 25% EtOAc/75% hexanes, R_f = 0.42); glc (System A, 100°, t_r = 5.89 min); ir (film) 3440 (OH) and 1730 cm^{-1} (C = O); NMR ($CDCl_3$) 1.30 (s, 3H, Me), 1.60 and 1.68 (2s, 6H, vinyl Me), 1.75-2.33 (m, 4H, allylic $C\underline{H}_2$), 5.08 (m, 1H, vinyl 1H), 9.58 (s, 1H, C<u>H</u>O); cims: 157 (MH^+), 139 (MH^+-H_2O). A small portion of this product was treated with TMS-Cl/pyridine and, after the normal work-up, the α-trimethylsilyloxy aldehyde 48b was formed which was identical in all respects to the product obtained through DIBAH reduction of nitrile 64.

Methyl 2,6-dimethyl-1,5-heptadien-1-yl ether. (56)

Triphenyl-(methoxymethyl)-phosphonium chloride (17.0533$_g$, 49.75 mmol) in 100 ml of THF was treated with 50.0 mmol of n-BuLi at -78°. After 1 hour, the deep orange solution was treated with 4.0865g (32.38 mmol) of ketone 46 in 15 ml of THF. The reaction was allowed to proceed 4 hrs. at -78° and several hours at room temperature. The reaction mixture was taken up in Et_2O and washed with saturated $NaHCO_3$ and brine. Concentration left a residue to which Et_2O was added. The resulting precipitate was filtered and the filtrate dried and concentrated to a viscous semi-solid. Distillation of this crude product (58-65°, 3-6 mm) afforded 2.8759$_g$ of 56 (58%) which was homogeneous by tlc and glc analysis; tlc (System A, 80°, t_r = 3.90 and 4.61 min for the E and Z isomers-ratio 7:3); ir (film) 2950, 2910, 2850, 1690, 1470, 1380, 1200, 1130, 1050, 980, and 830 cm^{-1}; NMR ($CDCl_3$) 1.52-1.68 (m, 9H, vinyl CH_3), 1.93-2.10 (m, 4H, CH_2), 3.47 and 3.50 (2s, 3H, E and Z-OCH_3), 5.12 (m, 1H, vinyl H), 5.72 (m, 1H, vinyl H); cims: 155 (MH^+).

2-Chloro-2,6-dimethyl-5-heptenal. (58a)

Enol ether 56 (o.7417$_g$, 4.809 mmol), sodium acetate trihydrate (80 mg), and 762 mg (5.71 mmol) of N-chlorosuccinimide were stirred about 5 min. at -16° in 10 ml of acetone/H_2O (9:1). TLC analysis indicated the presence of one spot, less polar than 56. A normal Et_2O/H_2O work-up furnished 0.87$_g$ of colorless oil (100%) which was homogeneous by tlc and glc analysis; tlc (System A, 3% EtOAc/97% hexanes, R_f = 0.34), glc (System A, 80°, t_r = 9.3 min). An analytical sample was prepared by passing the product through 9$_g$ of silica gel (1% EtOAc/ 99% hexanes) to rid the crude product of impurities due to the starting enol ether 56. Bulb-to-bulb distillation of the colorless oil from the silica gel

column provided a pure sample of 58a (70°, 0.50 mm); ir (film) 1740 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.60 (s, 3H, $C\underline{H}_3$), 1.63 and 1.70 (2s, 6H, vinyl Me), 2.00 (m, 4H, $C\underline{H}_2$), 5.05 (m, 1H, vinyl H), 9.40 (s, 1H, C<u>H</u>O).

<u>Anal.</u> Calcd. for $C_9H_{15}ClO$: C, 61.88; H, 8.66; Cl, 20.30. Found: C, 61.76; H, 8.56; Cl, 20.18.

<u>2-Bromo-2,6-Dimethyl-5-heptenal</u> (58b)

Bromide 58b was prepared in 100% yield from 105 mg (0.683 mmol) of 56, 80 mg of NaOAc, and 136 mg (0.762 mmol) of N-bromosuccinimide in the same manner as described for chloride 58a. The crude product, after work-up, was homogeneous by tlc (System A, 10% EtOAc/90% hexanes, R_f = 0.58). Attempted purification using silica gel chromatography resulted in significant loss of product. GLC (System A, 130°C, t_r = 2.89 min); ir (film) 2960, 2920, 2850, 1740 (s), 1450, 1380, 1160, 110, 1060, 910, 800, and 760 cm^{-1}; NMR ($CDCl_3$) δ 1.62 and 1.70 (2s, 6H, vinyl $C\underline{H}_3$), 1.78 (s, 3H, 2-Me), 1.95-2.40 (m, 4H, $C\underline{H}_2$), 5.10 (m, 1H, vinyl H), 8.93 (s, 1H, C<u>H</u>O).

<u>2-Geranyl-1,3-dithiane</u> (61)

n-Butyl lithium (0.110mol) was added to a solution of 12.0782g (0.1005 mol) of 1,3 dithiane in 200 ml of THF at -78°. After stirring 3 hr at -20° and recooling to -78°, 21.9302g (0.1010 mol) of <u>E</u>-geranyl bromide (60) was added. A few ml of water were added after the reaction mixture had stirred 3 hr at -78°. Upon reaching room temperature, the THF was removed <u>in vacuo</u>. The residue was partitioned between Et_2O and water and worked-up in the normal fashion to give 26.15 g of viscous, yellow oil. A portion of this product

(8.31g) was distilled through a short path apparatus with the product collected at a head temperature of 110-130° (0.1mm) and amounted to 5.87g of viscous, yellow oil (72% corrected yield based on 60); tlc (System A, 10% EtOAc/90% hexanes, R_f = 0.59); glc (System A, 190°, E/Z ratio = 95/5); ir (film) 2960, 2900, 2850 (s), 1450, 1375, 1270, 1170, 1105, 1025 (b), and 905 cm^{-1}; NMR ($CDCl_3$)δ 1.68 (m, 9H, vinyl CH_3), 1.83-2.23 (m, 6H, CH_2), 2.47 (t, J = 7Hz, 2H, CH_2-CHS_2), 2.67-3.02 (bm, 4H, dithiane CH_2), 4.11 (t, J=7Hz, 1H, CHS_2), 5.00-5.45 (bm, 2H, vinyl H); cims: 257 (MH^+).

Ethyl 3-(1,3-dithiane-2-yl)-2-hydroxy-2,6,10-trimethylundeca-5,9-dienoate. (62).

A THF solution of 7.73g (30.1 mmol) of 61 at -78° was treated with 31.4 mmol of n-BuLi. The mixture was then stirred for 2 hr at -20° and, after re-cooling to -78°, 4.39g (37.8 mmol) of ethyl pyruvate added. After 2 hr at -78°, the reaction mixture was worked up as described in the preparation of 61 to yield 8.10g of yellow oil. The crude product was chromatographed on 100g of silica gel using a hexanes/EtOAc solvent system. After gradually increasing the concentration of EtOAc from 0 to 4%, the use of 10% EtOAc/90% hexanes resulted in the elution of the desired product 62 (4.8884g, 44% yield); tlc (System A, 10% EtOAc/90% hexanes, R_f = 0.33); glc (System A, 250°, t_r = 5.40 min.); ir (film) 3470 (s, OH) and 1740 cm^{-1} (vs, C = O); NMR ($CDCl_3$) 1.35 (t, J = 7Hz, 3H, OCH_2CH_3), 1.60 (m, 12H, Me), 1.90 (m, 2H, CH_2 in dithiane), 2.10 (m, 4H, allylic CH_2), 2.20 - 3.40 (m, 6H, CH_2 in dithiane and CH-CS_2), 3.92 (s, 1H, OH), 4.30 (g, J = 7Hz, 2H, OCH_2CH_3), 5.15 (m, 1H, vinyl H), 5.55 (bt, J 6Hz, 1H, vinyl H); cims: 373 (MH^+), 355 (MH^+-H_2O).

6-Methyl-5-hepten-2-one cyanohydrin TMS ether (64)

This reaction proceeds smoothly if freshly distilled TMS-CN is utilized. Otherwise, heating and excess reagent are required for completion of the reaction. TMS-CN (86.3 mmol), ketone 46 (10.0g, 79.2 mmol), and about 10 mg of mercuric iodide were combined in the absence of solvent and an exothermic reaction immediately commenced. When the reaction was found complete by glc analysis (a few hr), the crude product was distilled (110-114°, 2-3 mm). A yield of 14.91g of 64 (95%) was obtained based on consumed 46; glc (System A, 100°, t_r = 7.21 min); ir (film) 250 and 760 (Si-Me), 850 cm^{-1} (SiOC); NMR ($CDCl_3$) δ 0.22 (s, 9H, OTMS), 1.57 (s, 3H, Me), 1.62 and 1.70 (2s, 6H, vinyl Me, 2.05 (bm, 4H, $C\underline{H}_2$), 5.08 (m, 1H, vinyl H); cims: 226 (MH^+).

2,6-Dimethyl-2-Trimethylsilyloxy-5-heptenal. (48b)

A solution of 2.25g (10.0 mmol) of 64 stirring at -78° in 25 ml of Et_2O was treated with 13 mmol of diisobutylaluminum hydride (DIBAH). GLC analysis indicated the reaction was complete within 30 minutes. The cold reaction mixture (-78°) was poured into 50 ml of 5% H_2SO_4 and stirred 5 min. at 0°. The layers were separated and the aqueous portion extracted with Et_2O (3x). Combined etheral portions were brine washed, dried, and concentrated to 2.08g of colorless oil. Distillation (bulb-to-bulb, 120°, 2-3 mm) provided 1.30 of colorless oil (61%); tlc (System A, 10% EtOAc/90% hexanes, R_f = 0.57); glc (System A, 100°, t_r = 5.63 min); ir (film) 1733 (C = O), 1250 and 755 (SiMe), and 850 cm^{-1} (b, SiOC); NMR (CDCl) 0.17 (s, 9H, OTMS), 1.30 (s, 3H, $C\underline{H}_3$), 1.62 and 1.70 (2s, 6H, vinyl Me), 1.97 (m, 4H, $C\underline{H}_2$), 5.10 (m, 1H, vinyl H), 9.60 (s, 1H, $C\underline{H}O$); cims:229 (MH^+).

2,6,10-Trimethyl-2-trimethylsilyloxyundeca-5,9-dienal. (65)

A mixture of 155 mmol of TMS-CN, 140.5 mmol of geranyl acetone (44), and about 100 mg of HgI_2 was stirred (exothermic reaction). The use of freshly distilled TMS-CN results in a smooth conversion to the nitrile without any external heating. The reaction is conveniently monitored via glc analysis. The nitrile may be isolated at this stage in distilled yields of better than 90%; tlc (System A, 5% EtOAc/95% hexanes, R_f = 0.59); glc (System A, 150°, t_r = 6.68 min); ir (film) 2950, 2910, 2850, 1460, 1380, 1250, 1180, 1045, 990, 850, and 755 cm^{-1}; NMR ($CDCl_3$) 0.25 (s, 9H, OSiMe), 158 (s, 3H, Me), 1.63 and 1.70 (2s, 9H, vinyl Me), 2.03 (bm, 8H, allylic (H_2), 5.20 (m, 2H, vinyl H); cims: 294 (MH^+);

Anal. Calcd. for $C_{17}H_{31}ONSi$: C, 69.56; H, 10.65; N, 4.77. Found: C, 69.59; H, 10.54; N, 4.57.

Preparation of aldehyde 65 was most successful if the nitrile was reduced in situ following in vacuo removal of excess TMS-CN. Thus, 210 mmol of DIBAH was added to the nitrile stirring at -78° in 300 ml of THF. The reaction mixture was warmed to -20° and followed by glc analysis. When complete, the cold mixture was poured into 800 ml of ice-cold 5% H_2SO_4. The reaction flask was rinsed with 100 ml of Et_2O. The mixture was stirred 30 min. at 0°C and then 200 ml of Et_2O added. Following layer separation the organic portion was concentrated on the rotovap. The aqueous portion was thrice extracted with Et_2O and all organic portions combined, brine washed, dried, and concentrated to afford 39.90, of pale orange oil. A portion of this crude product was distilled through a short path apparatus to give an 88% corrected yield of 65 (bath temp 110-130°, about 0.15 mm) which was homogeneous by tlc and glc analysis; tlc (System A, hexanes - 2 developments, R_f = 0.13); glc (System A, 150°, t_r=

5.39 min). An analytical sample was obtained *via* LPLC (5% EtOAc/95% hexanes, 8 ml/min, 12-18 min elution time); ir (film) 1740 cm^{-1} (C = O); NMR ($CDCl_3$) δ 0.17 (s, 9H, OSiMe), 1.30 (s, 3H, C-3 Me), 1.62 and 1.68 (2s, 9h, vinyl CH_3), 2.00 (m, 8H, allylic CH_2), 5.13 (m, 2H, vinyl H), 9.62 (s, 1H, CHO); cims: 297 (MH^+), 207 (MH^+-TMSOH).

Anal. Calcd. for $C_{17}H_{31}O_2Si$: C, 68.86; H, 10.88. Found: c, 68.83, H, 10.92.

1,1-Difluoronerolidol TMS ether . (67)

Dibromodifluoromethane (about 38g, 181 mmol) was condensed into 250 ml of THF at -78° by using a dry-ice condenser. Then, 54g (330 mmol) of tris-dimethyl-aminophosphine was added and the mixture allowed to warm to room temperature. Aldehyde 65 (20.42g, 68.87 mmol) was then added and was totally consumed within 30 min (glc). The slurry was transferred to a separatory funnel using 300 ml of water and 500 ml of pentane. The aqueous layer was washed with pentane (2 x 200 ml). Combined organic portions were washed with water (3 x 200 ml) and brine (1 x 200 ml), dried, and concentrated to yield 23.59g of orange oil. ^{1}H-NMR analysis indicated that the crude product was about 94% pure. A portion of the crude product (22.023g) was distilled using a short path apparatus providing 19.22g of pale yellow oil (85-96°, 0.05-0.075 mm) judged > 95% pure by glc; tlc (System A, hexanes, 2 developments, R_f = 0.43); glc (System A, 120°, t_r = 7.50 min). An analytical sample was prepared by LPLC (hexanes, 8 ml/min, 10-27 min elution time); ir (film) 1740 cm^{-1} (s, C = CF_2); ^{1}H-NMR ($CDCl_3$) 0.13 (s, 9H, OSiMe), 1.43 (d, J = 2.5 Hz, 2H, C-3 Me), 1.63 and 1.72 (2s, 9H, vinyl Me), 2.03 (bm, 8H, allyl CH_2), 4.38 (dd, J = 26.5 and 6.5 Hz, 1H, CH_2), 4.38 (dd, J = 26.5 and 6.5 Hz, 1H, CH = CF_2), 5.18 (m, 2H, vinyl H); ^{19}F-NMR ($CDCl_3$) 86.8 (J = 46 and 6Hz, F *trans* to OTMS), 84.6

(J = 46 and 27Hz, F cis to OTMS); cims: 331 (MH^+), 321 (MH^+-HF), 241 (MH^+-HF-TMSOH):

Anal. Calcd. for $C_{18}H_{32}F_2OSi$: C, 65.40; H, 9.76. Found: C, 65.33; H, 9.54.

1,1-Difluoronerolidol (68)

A mixture of 10.00g (30.25 mmol) of 67, 50 ml of MeOH, and 13 ml of 15% NaOH (49 mmol NaOH), was stirred at 50° for 2.25 hr at which time the reaction was judged complete by glc analysis. The reaction mixture was immediately partitioned between hexanes and water. The aqueous portion was extracted thrice with hexanes and the combined hexanes portions were washed with water (2x) and brine, dried, and concentrated to afford 7.93g (100%) of 68 as a pale yellow oil, homogeneous by tlc and glc analysis; tlc (System A, 100% EtOAc/90% hexanes, R_f = 0.15); glc (System A, 130°, t_r = 8.58 min); ir (film) 3375 (bs, OH) and 1740 cm^{-1}, (s, C = CF_2); ^{1}H-NMR ($CDCl_3$) 1.43 (d, J 2Hz, 3H, C-3 Me), 1.63 and 1.72 (25, 9H, vinyl Me), 2.05 (bm, 8H, allylic $C\underline{H}_2$), 2.15 (s, 1H, OH),4.43 (dd, J = 26 and 6Hz, 1H, $C\underline{H}$ = CF_2), 5.20 (m, 2H, vinyl H): ^{19}F-NMR ($CDCl_3$) ø 84.9 (dd, J = 46 and 26 Hz, F cis to OH), 86.3 (dd, J = 46 and 6 Hz, F trans to OH); cims: 241 (MH^+-H_2O), 219 (MH^+-HF-H_2O). No parent ion observed.

Anal. Calcd. for $C_{15}H_{24}F_2O$: C, 69.73; H, 9.36. Found: C, 69.63; H, 9.12.

1,1-Difluorofarnesyl Bromide. (69)

Alcohol 68 (201 mg, 0.780 mmol) in 8 ml of Et_2O at 0° was treated with 15 mmol of PBr_3 and stirred 7 hr. The reaction mixture was poured into ice-water and diluted with Et_2O. After separation of layers the organic portion was washed

with ice-cold water and brine, dried, and concentrated to yield 234 mg of pale yellow oil (93%) consisting mainly of 69 by NMR analysis. Preparative tlc experiments indicated that 69 is hydrolyzed to acyl fluoride 72 on silica gel plates. Product 69 should be used immediately after preparation; tlc (System A, 2% EtOAc/98% hexanes, R_f = 0.77); ^{1}H-NMR ($CDCl_3$) 1.63 and 1.70 (2s, 9H, vinyl CH_3), 1.92 (m, 3H, C-3 Me), 2.08 (bm, 8H, allylic CH_2), 5.15 (bm, 2H, vinyl H), 5.73 (t, J = 12 Hz, 1H, C-2 vinyl H).

1,1-Difluorofarnesyl acetate (70) via bromide 69

A solution of bromide 69 (200 mg, 0.62 mmol) in 5 ml of acetonitrile was treated with 130 mg (0.78 mmol) of silver acetate. After stirring overnight the crude mixture was filtered through a Celite pad using hexanes washings. The filtrate was concentrated, giving 175 mg of yellow oil which was shown by glc analysis to consist of the mixture of products shown in Table 10. LPLC of the crude product afforded 45 mg (23%) of a 4:1 mixture of 1° and 3° acetates 70 and 71, respectively (5% EtOAc/95% hexanes, 4 ml/min, 32-42 min. elution time). Acetate 70 was separated from tertiary isomer 71 by LPLC using the same conditions as before; tlc (System A, 5% EtOAc/95% hexanes, R_f = 0.29); glc (System A, 150°, t_r = 9.02 min); ir (film) 1790 (s, C = O) and 1670 cm^{-1} (m, C = C); ^{1}H-NMR ($CDCl_3$) 1.63 and 1.70 (2s, 9H, vinyl CH_3), 1.88 (m, 3H, C-3 Me); 2.07 (bm, 8H, allyl CH_2), 2.15 (s, 3H, COMe), 5.17 (m, 2H, vinyl H), 5.60 (t, J = 10Hz, 1H, C-2 vinyl H); ^{19}F-NMR ($CDCl_3$) ∅ 63.3 and 63.7 (2 d, J = 10 Hz each); cims: 241 (MH^+-HOAc), no parent ion observed.

Anal. Calcd. for $C_{17}H_{26}F_2O_2$: C, 69.97; H, 8.73. Found: C, 68.36; H, 8.75.

1,1-Difluoronerolidol acetate (71)

Alcohol 68 (207 mg, 0.801 mmol), acetic anhydride (3.2 mmol), 4-dimethylamino pyridine (110 mg, 0.90 mmol), and triethyl amine (1.2 mmol) were combined in 5 ml of Et_2O and stirred 2 days at room temperature. The reaction was judged complete by glc and tlc analysis. The mixture was taken up in Et_2O and washed with 5% NaOH and 0.1 N HCl. Normal drying and solvent removal provided 235 mg of yellow oil (98%) which was homogeneous by glc and tlc analysis; tlc (System A, 5% EtOAc/95% hexanes, R_f = 0.24); glc (System A, 140°, t_r = 6.34 min); ir (film) 1740 cm^{-1} (bvs, C = CF_2 and C = O); ^{1}H-NMR ($CDCl_3$) 1.63 and 1.70 (2bs, 12H, $C\underline{H}_3$), 1.97 (m, 8H, $C\underline{H}_2$), 2.02 (s, 3H, COMe), 4.67 (dd, J = 27 and 5 Hz, 1H, $C\underline{H}$ = CF_2), 5.17 (m, 2H, vinyl H); ^{19}F-NMR ($CDCl_3$) ø 82.63 (dd, J = 42 and 27 Hz, F cis to OAc), 85.72 (dd, J = 42 and 5 Hz, F trans to OAc); cims: 301 (MH^+), 241 (MH^+-HOAc);

Anal. Calcd. for $C_{17}H_{26}F_2O_2$: C, 67.97; H, 8.73. Found: C, 68.27; H, 8.56.

Farnesoyl fluoride. (72)

Thionyl chloride (about 1 mmol) was added to 138.7 mg (0.537 mmol) of alcohol 68 stirring in 5 ml of Et_2O at room temperature. The alcohol 68 was totally consumed within 2 hr (glc). A normal Et_2O/H_2O work-up afforded 114 mg of pale yellow oil (89%) which was virtually one spot by tlc (System A, 2% EtOAc/98% hexanes, R_f = 0.55) and two peaks by glc (System A, 150°, t_r = 4.34 and 5.04 min). The product quickly decomposed upon exposure to air; ir (film) 1805 cm^{-1} (s, C = O); ^{1}H-NMR ($CDCl_3$) 1.63 and 1.70 (2s, 9H, vinyl H), about 2.17 (bm, 8H, allylic $C\underline{H}_2$), 2.22 (m, 3H, C-3 Me), 5.15 (m, 2H, vinyl H), 5.70 (m, 1H, C-2 vinyl H); ^{19}F-NMR ($CDCl_3$) ø -41.66 and -41.31 (2 bs, ratio 3:2 for E and Z isomers, respectively); cims: 239 (MH^+), 219 (MH^+-HF).

1,1-Diflurofarnesyl chloride (73)

A solution of 1.56g (6.04 mmol) of alcohol 68, 10 mmol of pyridine, and 10 mmol of triethyl amine in 15 ml of hexanes was treated with 10 mmol of thionyl chloride at room temperature. The reaction was complete after 3 hr (tlc). The crude mixture was taken up in Et_2O and washed with 0.1 N HCl, brine, and saturated $NaHCO_3$. Normal drying and solvent evaporation left 1.47g of yellow oil homogeneous by tlc and glc (88% yield). The product 73 slowly decomposed in air to yield farnesoyl fluoride (72). An analytical sample was prepared via LPLC (hexanes, 8 ml/min, 10-30 min elution time); tlc (System A, pentane, R_f = 0.45); glc (System A, 140°, t_r = 3.28 min); ir (film) 2950, 2910, 1670, 1450, 1385, 1215, 1075, and 965 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.63 and 1.70 (2 s, 9H, vinyl CH_3), 1.92 (m, 3H, C-3 Me), 2.08 (bm, 8H, allylic CH_2), 5.15 (M, 2H, vinyl H), 5.68 (t, J = 12 Hz, 1H, C-2 vinyl H); ^{19}F-NMR ($CDCl_3$) Ø 42.5 and 42.8 (2 d, J = 12Hz each, ratio of 1:2 respectively); cims: 277 (MH^+), 241 (MH^+-HCl), 221 (MH^+-HCl-HF).

Anal. Calcd. for $C_{15}H_{23}F_2Cl$: C, 65.09; H, 8.37; Cl, 12.81. Found: C, 65.35; H, 8.34; Cl, 12.25.

1,1-Difluorofarnesyl acetate (70) via chloride 73

Crude chloride 73 (1.44g, 5.2 mmol) in 15 ml of acetonitrile was treated with 1.00g (5.99 mmol) of silver acetate. After heating at 80° for 8 hr the crude product was filtered through a Celite pad using hexanes washings. Solvent removal afforded 1.294g of orange oil containing the ratio of products shown in Table 13. The crude product was purifed as in the similar reaction via bromide 69 to give 346 mg of a 4:1 mixture of 1° and 3° acetates in a combined

yield of 22%. These acetates were identical in all respects to the products described previously.

1,1-Difluorofarnesyl acetate (70) via alcohol 68

To a solution of approximately 60 mg of tosic acid stirring in 4 ml of acetic anhydride at room temperature was added 260.7 mg (1.009 mmol) of alcohol 68 in 3 ml of acetic anhydride. The reaction was complete within 20 minutes (tlc). The mixture was taken up in water and extracted thrice with pentane. Combined organic portions were washed with saturated $NaHCO_3$ to remove Ac_2O, water, and finally brine. Normal drying and concentration provided 251 mg of pale yellow oil. The glc ratios of identified products are given in Table 14. The crude product was purified by LPLC as described in the preparation of 70 via bromide 69. The LPLC yields of 70, obtained from alcohol 68, ranged from 36-40%. This product 70 was identical in every way to previously described compound.

1,1-Difluorofarnesyl acetate (70) from 71

Tertiary acetate 71 (299 mg, 0.995 mmol) was stirred in 3 ml of Ac_2O at room temperature and then about 50 mg of tosic acid added. The reaction was complete by glc analysis within 30 minutes. The product was taken up in pentane and washed with 5% NaOH (3X), water, and brine. Normal drying and solvent stripping furnished 301 mg of pale yellow oil which was at least 75% 70 by glc and ^1H-NMR studies (75% yield). This product was identical to previously prpepared 70.

2,2-Difluoro-N,N,4,8,12-pentamethyl-3,7,10-tridecatrienoamide (79)

Alcohol 68 (263.6 mg, 1.020 mmol), N,N-dimethyl formamide diethyl acetal (6 mmol), and 1.5 g of 4A molecular sieves (Linde) were combined in 10 ml of xylenes and

heated at 140°C for 2 hours. At this time no alcohol 68 remained (tlc). Filtration (Et_2O washings) gave a filtrate which was concentrated to 313 mg of orange oil. Preparative tlc (System D) was used to isolate the desired product. The band at R_f 0.55 (30% EtOAc/70% hexanes) was excised to yield 111 mg of 79 as a viscous, yellow oil (35%). An analytical sample was prepared via LPLC (25% EtOAc/75% hexanes, 8 ml/min, 18-28 min elution time); tlc (System A, 70% hexanes/30% EtOAc, R_f = 0.51); ir (film) 2970, 2920, 2850, 1680 (vs) and 1070 cm^{-1}; ^1H-NMR ($CDCl_3$) 1.63 and 1.70 (2s, 9H, vinyl CH_3), 1.87 (m, 3H, C-4 Me), 2.13 (bm, 8H, allylic CH_2), 3.10 (m, 6H, NMe_2), 5.15 (M, 2H, vinyl H), 5.63 (t, J = 13 Hz, C-3 vinyl H); ^{19}F-NMR ($CDCl_3$) ϕ 90.73 and 91.51 (2d, J = 13 Hz each, ratio 1:1); cims: 134 (MH^+), 178, 113.

Anal. Calcd. for $C_{18}H_{29}F_2ON$: C, 68.97; H, 9.33; N, 4.47. Found.: C, 96.12; H, 9.08; N, 4.35.

Diethyl 1,1-diflurofarnesyl phosphate (94)

To 257.8 mg (0.998 mmol) of alcohol 68 in 5 ml of hexanes at -78° was added 1.05 mmol of n-BuLi. Upon reaching room temperature, the colorless solution was treated with 1.10 mmol of diethyl phosphorochloridate resulting in an immediate yellow colored solution. In about 15 minutes a precipitate began forming. The mixture was worked-up after 1.5 hr by gravity filtration and concentration of the resulting filtrate providing 258 mg of yellow oil. LPLC purification (30% EtOAc/70% hexanes, 8 ml/min) of the crude product gave 74 mg of a mixture of compounds 68, 72, and 73 (9-24 min elution time) and 118 mg (30% yield) of a mixture of 2-E and Z isomers of 94 (2-E, 30.0 to 37.5 min; 2-Z 39.0 to 45.0 min); tlc (System A, 20% EtOAc/80% hexanes, R_f = 0.19 and

0.15 for the 2-E and 2-Z isomers respectively); glc (System A, 220°, t_r = 3.98 min, the isomers were not separable using glc System A); ir (film) Z-isomer 2970, 2920, 2860, 1670, 1450, 1290, 1250, 1210, 1160, 1105, 1070, 1030, 980, 815, and 800 cm^{-1}; E-isomer ^{1}H-NMR ($CDCl_3$) 1.38 (dt, J = 1 and about 7 Hz, 6H, $POCH_2\underline{CH_3}$), 1.63 and 1.70 (2s, 9H, vinyl Me), 1.92 (m, 3H, C-3 Me), 2.02 (M, 6H, allylic $\underline{CH_2}$), 2.13 (m, 2H, C-H $\underline{CH_2}$), 4.25 p, J = 7 Hz, 4H, $POCH_2CH_3$), 5.15 (m, 2H, vinyl H), 5.58 (+, J = 10Hz, 1H, C-2 vinyl H); ^{19}F-NMR ($CDCl_3$) ø 55.06 (bm); Z-isomer ^{1}H-NMR ($CDCl_3$) 1.37 (dt, J = 1 and 7 Hz, 6H, $POCH_2\underline{CH_3}$), 1.63 and 1.70 (2s, 9H, vinyl Me), 1.85 (m, 3H, C-3 Me), 2.02 (m, 6H, allylic $\underline{CH_2}$), 2.28 (m, 2H, C-4 $\underline{CH_2}$), 4.25 p, J = 7Hz, 4H, $POCH_2CH_3$), 5.18 (m, 2H, vinyl H), 5.58 (t, J = 10 Hz, 1H, C-2 vinyl H); ^{19}F-NMR ($CDCl_3$) ø 54.74 (bm); cims: 395 (MH^+), 375 (MH^+-HF), 203 (MH^+-diethylphosphate-HF).

Anal. Calcd. for $C_{19}H_{33}F_2PO_4$: C, 57.85; H, 8.43; P, 7.85. Found: C, 58.11; H, 8.28; P, 7.76.

Diphenyl 1,1-difluorofarnesyl phosphate (96)

A mixture of 256.1 mg (0.9913 mmol) of alcohol 68, 2.4 mmol of diphenyl phosphorochloridate, 300 mg (2.4 mmol) of p-dimethylaminopyridine (DMAP), and 2.2 mmol of triethylamine in 5 ml of THF was stirred 2 days. At this time glc analysis indicated that only a trace of alcohol 68 remained. The reaction mixture was taken up in Et_2O and washed with water, 5% NaOH 0.1 N HCl (2x), and brine. After normal drying and solvent evaporation there remained 697 mg of pale yellow oil. TLC analysis of the crude product showed two closely spaced spots, the lower of which co-chromatographed with alcohol 68 (System A, 10% EtOAc/90% hexanes, R_f = 0.20 and 0.24). LPLC purification (10% EtOAc/90% hexanes, 8 ml/min, R_f 0.24: 24-31.5 min and R_f 0.20: 31.5-45 min. elution times) provided for

the complete separation of the 2-E and 2-Z isomers of 96 (combined yield of 80%). The lower R_f spot was contaminated by a small amount of alcohol 68 (glc, NMR): ir (film) 1680, 1600, 1495, 1460, 1325, 1255, 1215, 1180, 1155, 1065, 1025, 1010, 955, 935, 755, 730, and 690 cm^{-1}. Proton NMR clearly established that the higher R_f spot (0.24) was the E isomer: ^{1}H-NMR ($CDCl_3$) 1.60 and 1.70 (2s, 9H, vinyl Me), 1.83 (m, 3H, C-3 Me), 2.02 (bm, 6H, allylic CH_2), 5.03 (m, 2H, vinyl H), C-4 CH_2), 5.03 (m, 2H, vinyl H), 5.52 (t, J = 10Hz, 1H, C-2 vinyl H), 7.23 (s, 10H, aromatic); ^{19}F-NMR ($CDCl_3$) Ø 54.67 (vbm); Z-isomer; ^{1}H-NMR ($CDCl_3$) 1.62 and 1.70 (2s, 9H, vinyl Me), 1.78 (m, 3H, C-3 Me), 2.02 (bm, 6H, allylic CH_2), 2.20 (m, 2H, C-4 CH_2), 5.05 (m, 2H, vinyl H, 5.48 (t, J = 10 Hz, 1H, C-2 vinyl H), 7.22 (s, 10H, aromatic); ^{19}F-NMR ($CDCl_3$) Ø 54.14 (vbm); cims: (E-isomer) 491 (MH^+), 241 (MH^+-diphenyl phosphate), 221 (241-HF).

2-Phenyl-2-trimethylsilyloxypropanal (98)

Compound 98 was prepared in 68-84% yield by the same method used to prepare product 65. An analytical sample was prepared by LPLC (10% EtOAc/90% hexanes, 8 ml/min, 9-20 min elution time); glc (System A, 120°, t_r = 4.69 min); ir (film) 1740 cm^{-1} (C = 0); ^{1}H-NMR ($CDCl_3$) 0.10 (s, 9H, OSiMe), 1.60 (s, 3H, CH_3), 7.10-7.50 (bm, 5H, aromatic), 9.35 (s, 1H, CHO); cims-exact mass measurement calcd. for $C_{12}H_{19}SiO_2$: 223.1154. Found: 223.1158.

1,1-Difluoro-3-phenyl-3-trimethylsilyloxy-1-butene. (99)

Product 99 was prepared according to the procedure used to prepare 67. A 65% yield of pure 99 was obtained via LPLC (5% EtOAc/95% hexanes, 8ml/min, 10-12 min elution time) ; glc (System A, 120°, t_r = 1.52 min); ir (film) 1740 (vs,

C = CF_2); ^{1}H-NMR ($CDCl_3$) 0.13 (s, 9H, OTMS), 1.73 (d, J = 3Hz, 3H, Me), 4.63 (dd, J =26 and 6Hz, 1H, vinyl H), 7.17-7.67 (m, 5H, aromatic); ^{19}F-NMR ($CDCl_3$) ø 83.27 (ddg, J = 41.5, 26, and 3Hz, F cis to OTMS), 85.92 (dd, J = 41.5 and 6 Hz, F trans to OTMS); cims: 167 (MH^+-TMSOH): MH^+ not visible.

Anal. Calcd. for $C_{13}H_{18}F_2SiO$: C, 60.90; H, 7.08. Found H, 61.13; H, 6.99.

1,1-Difluoro-3-phenyl-3-methyl-2-butenyl acetate (100)

TMS ether 99 (125.6 mg, 0.50 mmol) was treated with 30 mg (0.75 mmol) of NaOH in about 10 ml of a 4:1 MeOH/water solvent system at room temperature for 30 min. GLC analysis at this time indicated the total absence of 99 in the reaction mixture. The mixture was partitioned between hexanes and water. The aqueous layer was thrice extracted with hexanes and the combined organic portions washed with water (2x) and brine. After normal drying, the solvent was removed until only about 3-5 ml remained. This residue was immediately used in the next step. This solution was added to 3 ml of Ac_2O and the residual hexanes was removed in a N_2 stream. GLC analysis indicated that no acetate products were being formed. Addition of about 30 mg of tosic acid initiated the reaction which was stirred a total of 14 hours at room temperature. The reaction mixture was worked-up as previously described to yield 92 mg of colorless oil. GLC analysis indicated a mixture of several products. LPLC purification (5% EtOAc/95% hexanes, 8 ml/min, 32-36 min elution time) afforded 27 mg of 100 as a colorless oil (24%) which was contaminated by a few % of an impurity which formed upon decomposition of 100. This impurity is probably the acid fluoride derivative. GLC analysis of 100 showed one major peak (System A, 120°, t_r = 10.31 min); ir (film) 1790 (s, C = O), 1660 (m, C = C); ^{1}H-NMR ($CDCl_3$) 2.17 (s, 3H, COMe), 2.22 (m, C-3

Me), 6.08 (t, J = 10Hz, 1H, vinyl H), 7.27 (s, 5H, aromatic); ^{19}F-NMR ($CDCl_3$) ø 63.90 and 63.93 (2 d, J = 10Hz each, ratio 1:1); cims-exact mass measurement calcd. for $C_{12}H_{13}F_2O_2$: 227.0884. Found: 227.0887.

1-Fluoronerolidol TMS ether (103)

Fluoroiodomethyltriphenylphosphonium iodide (4.11g, 7.3 mmol), and Zn-Cu couple[50b] (0.6g, 10 mmol) were all combined in 20 ml of THF and heated at 75° for 14 hours. At this time glc analysis indicated that the reaction was 30-40% complete. An additional 3.3g of phosphonium salt and 1.2g of Zn-Cu couple were added over a 3 day period while heating at 75°. GLC analysis then indicated the total absence of aldehyde 65 in the reaction mixture. Solvent was removed in vacuo and the residue taken up in Et_2O. Filtration and solvent removal gave a reddish residue which was passed through 15g of silica gel (hexanes) to yield 800 mg of a colorless oil. Analytical glc analysis showed two major peaks (System A, 130°, t_r = 6.80 and 7.50 min, ratio 2:3, respectively). The crude product was contaminated by several impurities. A portion of this crude product (25%) was purified by LPLC (hexanes, 8 ml/min, see Table below).

LPLC of Crude 103

Elution Time (Min)	R_f[a]	t_r(min)[b]	Weight (mg)	Composition[c]
		12.50		
12-17	0.52	16.41	-	104a,b
17-20	0.48	3.23	40	103a
20-22	-	-	14	103a,b
22-34	0.41	2.93	31	103b

(a) tlc (System A, hexanes, 2 developments)

(b) glc (System A, 150°)

(c) Determined via glc analysis.

The corrected yield of 103 was 340 mg (15%); ir (film) 2950, 2910, 2950, 1675 cm^{-1} (C = CF); 103a ^{1}H-NMR ($CDCl_3$) 0.12 (s, 9H, OTMS), 1.33 (s, 3H, C-3 Me), 1.60 and 1.68 (2s, 9H, vinyl $C\underline{H}_3$), 2.00 (bm, 8H, $C\underline{H}_2$), 5.10 (m, 2H, vinyl H), 5.43 (dd, J = 21 and 11Hz, 1H, C-2 vinyl H), 5.43 (dd, J = 21 and 11Hz, 1H, C-2 vinyl H), 6.61 (dd, J = 86 and 11Hz, 1H, C-1 vinyl H); ^{19}F-NMR ($CDCl_3$) ∅ 137.9 (dd, J = 86 and 21Hz); 103b ^{1}H-NMR ($CDCl_3$) 0.12 (s, 9H, OTMS), 1.47 (d, J ∿2Hz, 3H, C-3 Me), 159 and 1.66 (2s, 9H, vinyl Me), 1.99 (m, 8H, $C\underline{H}_2$), 4.80 (dd, J =48 and 6 Hz, 1H, C-2 vinyl H), 5.11 (m, 2H, vinyl H), 6.30 (dd, J = 85 and 6Hz, (dd, J = 85 and 48 Hz); cims (mixture of isomers): 313 (MH^+, 223 (MH^+-TMSOH), 203 (MH^+-TMSOH-HF).

Anal. Calcd. for $C_{18}H_{33}FSiO$: C, 69.17; H, 10.64. Found: C, 69.30; H, 10.79.

1-Fluoro-1-iodonerolidol TMS Ether (104)

A mixture of 148 mg (0.50 mmol) of aldehyde 65 and 1.65 g (3 mmol) of fluoroiodomethyltriphenylphosphonium iodide[50b] in 10 ml of THF was heated at 80° for 1 hour at which time no 65 remained (glc analysis). The THF was removed (water aspirator) and the dark solids triturated with Et_2O (4x). Combined etheral portions were washed with water (2x) and evaporated down to a residue which was taken up in hexanes and filtered through a Celite pad. The filtrate was then passed through 2g of silica gel (pet ether). Solvent removal left 140 mg of colorless oil (64%) which was homgeneous by tlc (System A, hexanes - 2 developments, R_f = 0.51) and gave two peaks by glc analysis (System A, 150° t_r = 12.25 and 16.09 min, 104b/104a ratio 2:3); ir (film) 2950, 1245, 1165, 1110, 1040, 840, and 750 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 0.13 and 0.18 (2s, 9H, OTMS), 1.43 (s, 3H, C-3 Me), 1.63 and 1.72 (2s, 9H, vinyl $C\underline{H}_3$), 1.83-2.42 (bm, 8H, $C\underline{H}_2$), 5.13 (m,

2H, vinyl H), 5.43 (d, J = 39Hz, 0.4H, HC = CF trans in 104b), 5.95 (d, J = 23 Hz, 0.6H, HC = CF cis in 104a); ^{19}F-NMR ($CDCl_3$) ø 60.67 (d, J = 27 Hz, 104a), 63.17 (d, J = 39Hz, 104b); cims: 439 (MH^+, 349 (MH^+-TMSOH), 329 (MH^+-TMSOH-HF) 221 (MH^+-TMSOH-HI), 201 (MH^+-TMSOH-HI-HF).

1-Fluoronerolidol (109)

An isomeric mixture of TMS ether 103 (255 mg, 0.816 mmol) was treated with 1.4 mmol of NaOH by the same procedure used to prepare alcohol 68. Product 109 was obtained as 191 mg of pale yellow oil (97% yield); tlc (System A, 10% EtOAc/ 90% hexanes, R_f = 0.24 and 0.28 for the 1-Z and 1-E isomers, respectively); ir (film) 3400 (b, OH) and 1670 (s, C= CHF); 109a ^{1}H-NMR ($CDCl_3$) 1.32 (s, 3H, C-3 Me), 1.63 and 1.70 (2s, 9H, vinyl CH_3), 1.73 (m, 2H, C-4 (CH_2), 2.02 (m, 6H, allylic CH_2), 5.17 (m, 2H, vinyl H), 5.50 (dd, J = 21 and 10 Hz, 1H, C-2 vinyl H), 6.75 (dd, J = 86 and 10 Hz, 1H, C-1 vinyl H): ^{19}F-NMR ($CDCl_3$) ø 136 (dd, J = 86 and 21 Hz); 109b ^{1}H-NMR ($CDCl_3$) 1.42 (d, J ~1.5Hz, 3H, C-3 Me), 1.62 and 1.68 (2s, 9H, vinyl CH_3), 1.75 (m, 2H, C-4 CH_2), 2.05 (m, 6H, allylic CH_2), 5.08 (dd, J = 47 and 5 Hz, 1H, C-2 vinyl H), 5.17 (m, 2H, vinyl Hl, 6.13 (dd, J = 85 and 5 Hz, 1H, C-l vinyl H); ^{19}F-NMR ($CDCl_3$) ø 127 (dd, J = 85 and 47 Hz); cims (isomeric mixture) 223 (MH^+-H_2O), 203 (MH^+-H_2O-HF), no MH^+ observed.

Diethyl 1-fluorofarnesyl phosphate (113)

Phosphate 113 was prepared using 247 mg (1.028 mmol) of alcohol 109a, 1.2 mmol of n-BuLi, and 1.2 mmol of diethylphosphorochloridate as previously described in the synthesis of 94. The crude product was taken up in pentane and washed with water, saturated $NaHCO_3$, and brine. Normal drying and solvent removal

provided 344 mg of yellow oil. TLC analysis of the crude product indicated the presence of starting alcohol 109a, traces of relatively nonpolar impurities and two polar spots (System A, 20% EtOAc/80% hexanes, R_f = 0.18 and 0.12). The two polar components were separated from the mixture using LPLC (30% EtOAc/70% hexanes, 8 ml/min, 30-36 and 48-63 min elution times). The two low R_f components were totally consistent with the 2-E and 2-Z isomers of 113 (19% combined yield); ir (film, R_f 0.12 product) 2960, 2905, 2850, 1690, 1450, 1400, 1270, 1135, 1030 (vbs), 970 (vbs), 900, 810, and 755 cm^{-1}. The lower R_f product (0.12), which was obtained in about 5 fold excess over the higher R_f component (0.18), was most consistent with the 2-E stereochemical assignment; ^{1}H-NMR ($CDCl_3$) 1.37 (t, J = 7Hz, 6H, $OCH_2\underline{CH_3}$), 1.62 and 1.70 (2s, 9H, vinyl Me), 1.82 (m, 3H, C-3 Me), 2.02 (m, 6H, allylic $\underline{CH_2}$), 2.08 (m, 2H, C-4 $\underline{CH_2}$), 4.22 (m, 4H, $O\underline{CH_2}CH_3$), 5.15 (m, 2H, vinyl H), 5.47 (t, J = 7Hz, 1H, C-2 vinyl H), 6.58 (dt, J = 57 and 7Hz, 1H, $\underline{CH}F$); ^{19}F-NMR ($CDCl_3$) ø112.09 (bd, J = 57Hz); cims: 377 (MH^+), 357 (MH^+-HF); Z-isomer (sample decomposed prior to ^{1}H-NMR); ^{19}F-NMR ($CDCl_3$) ø 110.66 (bd, J = 57Hz); cims: 377 (MH^+), 357 (MH^+-HF).

10,15-Didesmethylsqualene (13)

Pyrrolidine (1.50g, 21.1 mmol) in 20 ml of Et_2O was treated at -78° with 23.2 mmol of n-BuLi. After stirring at 0° for 30 min, 2.3115g (12.14 mmol) of cuprous iodide was added in one portion, followed in 30 min, by addition of 1.4329g (5.2818 mmol) of bromide 124[1d] (100% E, E) in 40 ml of Et_2O. Following 4 hours at 0° and 2 hours at room temperature, 30 ml of hexanes was added and the resulting dark slurry filtered. The filtrate was washed with ice-cold 1N-HCl, H_2O, dried, filtered, and concentrated to 0.9997g of yellow

oil. The combined aqueous washings were back extracted (hexanes) to provide a further 51 mg of product (99% yield). GLC analysis indicated three major isomers in a ratio of 9: 39: 52 with retention times 3.53, 4.50, and 5.93 min, respectively (System A, 227°). The longest retention time peak was isolated by preparative glc (System D, 180°) and was shown to be identical to authentic 13[93] in every way; tlc (System A, hexanes, R_f = 0.43); ir (film) 2950, 2900, 1670, 1440, 1370, and 960 cm^{-1}; NMR ($CDCl_3$) 1.60 and 1.69 (2s, 18H, vinyl CH_3), 8.01-8.06 (m, 20H, allylic CH_2), 5.01-5.25 (m, 4H, vinyl H), 5.37-5.53 (m, 4H, vinyl H); cims: 383 (MH^+).

Anal. Calcd. for $C_{28}H_{46}$: C, 87.88; H, 12.12. Found: C, 87.98; H, 11.97.

2-(1-Farnesylthio)-1-methylimidazole (116)

The lithium salt of 2-mercapto-1-methylimidazole was prepared by reaction of 255 mg (2.234 mmol) of 2-mercapto-1-methylimidazole with 2.2 mmoles of n-BuLi using 3 ml of THF as solvent. Bromide 84[1d], (0.55g, 1.93 mmol, 4-isomers), was then added at -78° and the temperature allowed to slowly rise to room temperature. The reaction was judged complete after stirring 1 hr at room temperature (tlc analysis). The work-up consisted of addition of ether followed by water, 15% NaOH, and brine washings. Normal drying and solvent removal provided 0.61g of crude yellow-oil which was purified by LPLC (30% EtOAc/70% hexanes; 4 ml/min; 81-144 min). The product was obtained as 438 mg of a viscous yellow oil (71%). A similar reaction using 92% E,E-84 provided product 116 in 70% yield; tlc (System A, 35% EtOAc/65% hexanes, R_f = 0.49); ir (film) 2940, 2900, 2850, 1670, 1460, 1380, 1280, and 1120 cm^{-1}; NMR ($CDCl_3$) 1.42-

1.83 (m, 12H, vinyl $C\underline{H}_3$), 1.75-2.22 (m, 8H, allylic $C\underline{H}_2$), 3.60 (s, 3H, N-Me), 3.67 (d, J = 8Hz, 2H, S-$C\underline{H}_2$), 5.13 (bm, 2H, vinyl H), 5.37 (t, J = 8Hz, 1H, vinyl H), 6.93 and 7.08 (2d, J = 1 Hz, 2H, C = N-$C\underline{H}_2$), 5.13 (bm, 2H, vinyl H), 5.37 (t, J = 8Hz, 1H, vinyl H), 6.93 and 7.08 (2d, J=1Hz, 2H, C=N-$C\underline{H}_2$); cims: 319 (MH^+), 205 (MH^+-thioimidazole).

Anal. Calcd. for $C_{19}H_{30}N_2S$; C, 71.65; H, 9.49; N, 8.80; S, 10.07. Found: C, 71.98; H, 9.62;N, 8.36; S, 9.61

1-Methylimidazol-2-yl 2,6,10,14,15,19,23-heptametheyl-2,6(E), 10(E),14(E), 18(E),22-tetracosahexaene-12-yl sulfide. (119)

A solution of 320 mg (1.005 mmol) of 116 in 3 ml of THF at -78° was treated with 1.05 mmol of n-BuLi. After stirring 1.75 hr at -78°, 0.32g (1.07 mmol) of bromide 118 was added. In 3 hr the mixture was warmed to room temperature and stirred overnight. The product mixture was then taken up in ether and washed with water and brine, dried, and evaporated down to 0.55g of yellow oil. LPLC purification resulted in 338 mg (63%) of pale yellow oil (30% EtOAc/70% hexanes, 4 ml/min, 30-66 min elution time); tlc (System A; 30% EtOAc/70% hexanes; R_f =0.36); ir (film) 2900, 2910, 2850, 1460, 1380, and 2175 cm^{-1}; NMR ($CDCl_3$) 1.58 and 1.65 (2s, 27H, vinyl $C\underline{H}_3$), 1.80-280 (m, 19H, allylic $C\underline{H}_2$), 3.65 (s, 3H, N-Me), 4.80-5.40 (m, 5H, vinyl H), 6.97 and 7.12 (2d, J = 1Hz, 2H, vinyl imidazole); cims: 537 (MH^+).

Anal. Calcd. for $C_{35}H_{56}N_2S$: C, 78.29; H, 10.51; N, 5.22; S, 5.97. Found: C, 78.20; H, 10.62; N, 5.01; S, 5.64.

11-Methylsqualene (14)

An ice-cold (0°) ethanolic solution of 102.5 mg (0.1909 mmol) of 119 was treated with about 600 mg of Raney Nickel (W-2)[108]. The reaction was judged complete after 20 min (tlc). The slurry was filtered and the filtrate evaporated down to 81.7 mg (110%) of colorless oil, homogeneous by tlc (System A, hexanes, R_f = 0.40); glc (System A, 220°, t_r = 15.4 min, 85% all trans 14); ir (film) 2950, 2910, 2850, 1750, 1450, 1380, and 1250 cm^{-1}; NMR ($CDCl_3$) δ 1.60-1.70 (m, 27H, vinyl CH_3), 1.85-2.30 (m, 20H, allylic CH_2), 5.18 (m, 5H, vinyl H); glc-eims: m/e (% rel. intensity) 424 (1.9), 355 (2.4), 232 (2.7), 219 (1.8), 217 (3.3), 205 (2.8), 204 (2.5), 203 (1.7), 189 (4.0), 163 (5.1), 150 (4.0), 149 (5.3), 137 (16.8), 123 (8.4), 121 (8.5), 110 (2.7), 109 (9.2), 107) (8.7), 95 (24), 81 (47), 69 (100).

2-(3-Desmethylfarnesylthio)-2-thiazoline (129)

The sodium salt of 0.3481g (2.920 mmol) of 2-mercapto-2-thiazoline was prepared in 25 ml of THF using 71.5g (2.98 mmol) of NaH. The salt was cooled to -78° and 0.7190g (2.651 mmol) of bromide 124 (all trans) added in 30 ml of THF. The bromide was totally consumed when checked after 10 hr. at room temperature (tlc). Water was then added and the majority of THF removed in vacuo. A normal Et_2O/water work-up afforded 0.8535g of yellow oil which was chromatograhed on 20g silica gel. Elution, first with hexanes, and then with EtOAc/hexanes (5/95) gave 0.6946g of colorless oil (85% yield); tlc (System A, 10% EtOAc/90% hexanes, R_f = 0.27); ir (film) 2950, 2900, 2840, 1670, 1580, 1440, 1380, 1310, 995, 960 and 920 cm^{-1}; NMR ($CDCl_3$) 1.59 and 1.68 (2s, 9H, vinyl CH_3), 2.00-2.10 (m, 8H, allylic CH_2), 3.33 (t, J = 8Hz, 2H, S-CH_2 in thiazoline ring), 3.73

(d, J = 5 Hz, 2H, allylic $C\underline{H}_2$-S), 4.18 (t, J = 8Hz, 2H, $NC\underline{H}_2$ in thiazoline ring), 5.12 (m, 2H, vinyl H), 5.65 (m, 2H, vinyl); cims: 310 (MH^+), 191 (MH^+-thiothiazoline).

Anal. Calcd for $C_{17}H_{27}S_2N$: C, 65.96; H, 8.79; N, 4.53. Found: C, 66.35; H, 8.96; N, 4.28.

10-Desmethyl-12-(2-thiazoline-2-thio)-squalene (131)

A solution of 0.932 mmol of 129 in 20 ml of THF was cooled to -78° and 3.22 mmol of n-BuLi added. After stirring 1 hr. at -78°, 0.9236 (3.238 mmol) of bromide 84 (89% E, E; 9% Z, E; 2% E, Z) was added. Following reaction at -78° for 3 hr. and overnight at room temperature, a few ml of water were added and the majority of THF removed in vacuo. A normal Et_2O/water work-up gave 1.6178g of orange oil which was chromatographed on 200g of basic alumina. The solvent systems pet-ether, EtOAc/pet-ether (2:98), and finally EtOAc/pet-ether (6:94) then furnished 434 mg (29%) of a pale yellow oil, homogeneous by tlc analysis (System A, 10% EtOAc/90% hexanes, R_f = 0.42); ir (film) 2960, 2910, 2840, 1670, 1570, 1450, 1380, 1300, 990, 960, and 920 cm^{-1}; NMR ($CDCl_3$) 1.61 and 1.71 (2S, 21H, vinyl $C\underline{H}_3$), 2.00-2.30 (m, 16H, allylic $C\underline{H}_2$), 2.25-2.73 (m, 2H, SCHR-$C\underline{H}_2$ in thiazoline ring), 4.24 (t, J = 7Hz, 2H, C = $NC\underline{H}_2$ in thiazoline ring), 4.25 (m, 1H, $SC\underline{H}$), 4.98-5.40 (m, 5H, vinyl H), 5.50-5.80 (m, 2H, vinyl); cims: 514 (MH^+), 395 (MH^+-thiothizaoline).

10-Desmethylsqualene (15)

A slurry consisting of 114.3 mg (0.2224 mmol) of 131, 20ml of absolute EtOH, and about 600 mg of RaNi[108] was stirred 1 hr at 0°. Filtration and solvent removal gave a crude oil which was passed through 5g of silica gel (pet-ether)

affording 15 as a colorless, viscous oil (71%) which proved to be an isomeric mixture by glc analysis. Approximately 60% of this material was all trans 15 based on the experimentally observed fact that trans olefins have longer glc retention times than cis isomers.[95] The majority of impurities were removed by submitting the product to another chromatographic separation using 7g of silica gel (pet-ether); tlc (System A, 5% EtOAc/95% hexanes, R_f = 0.81); glc (System A, 230°, t_r = 6.38 min.); ir (film) 2950, 2900, 2840, 1450, 1380, and 960 cm^{-1}; NMR ($CDCl_3$) 1.58 and 1.67 (2S, 21H, $C\underline{H}_3$), 2.00 (bm, 20H, $C\underline{H}_2$), 5.15 (m, 5H, vinyl H), 5.43 (m, 2H, vinyl H); glc-cims: m/e (% rel. abundance) 396 (1.6), 327 (0.8), 285 (0.9), 259 (0.6), 205 (0.7), 204 (0.9), 203 (1.4), 191 (2.0), 189 (2.1), 177 (1.7), 163 (2.2), 149 (5.0), 137 (10.0), 123 (9.0), 121 (9.0), 109 (10.2), 107 (8.8), 95 (20.0), 81 (56.0), 69 (100).

6,10-Dimethyl-3-fluoro-5(E), 9-undecadien-2-one (136)

Ethyl 2-fluoroacetoacetate (1.092g, 7.37 mmol) was added to 0.40g (7.40 mmol) of sodium methoxide in 15 ml of anhydrous methanol at 0°. After 10 min, 1.54g (7.1 mmol) of bromide 60 was added and the mixture stirred at ambient temperature for 1 hr., at which time no bromide 60 remained (tlc analysis). A solution of 0.40g of sodium hydroxide in 15 ml of water was added and the mixture heated at 60° for 3 hr. Following addition of 50 ml of water, the mixture was exhaustively extracted with dichloromethane. Normal treatment of the combined organic portions gave a crude orange oil which was bulb-to-bulb distilled (75°, 0.20 mm), yielding 0.9532g (63%) of colorless oil (96% pure by glc analysis): tlc (System A, 20% EtOAc/80% hexanes, R_f = 0.62); glc (System A, 120°, t_r = 9.00 min); ir (film) 1730 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.62 and 1.68 (2s, 9H, vinyl $C\underline{H}_3$), 2.00-2.17 (m, 4H, allyl $C\underline{H}_2$), 2.20 (d, J = 4.5 Hz, 3H, $COC\underline{H}_3$, coupled to fluorine),

2.53 (dt, J = 26 and 6Hz, 2H, $C\underline{H}_2CF$), 4.67 (dt, J = 50 and 6Hz, 1H, $C\underline{H}F$), 5.00-5.30 (m, 2H, vinyl H); ^{19}F-NMR ($CDCl_3$) ∅ 189 (dtq, J =50, 26 and 5Hz); cims: 213 (MH^+), 193 (MH^+-HF).

Anal. Calcd. for $C_{13}H_2FO$: C, 73.54; H, 9.97. Found: C, 73.53; H, 9.93.

E,E-4-Fluorofarnesol (137)

A slurry of 80 mg (2.11 mmol) of LAH in 10 ml of Et_2O was cooled to -78°. Then 1.1232g (3.978 mmol) of all trans ester 140 was added. A further 120 mg of LAH was required for completion of the reduction (tlc analysis). The reaction was quenched at -78° by the addition of 200 µl of water and the mixture warmed to room temperature. The addition of 200µl of 15% NaOH was followed in 5 min by 600µl of water. After stirring several min, a small amount of anh. $MgSO_4$ was added. Filtration and solvent removal afforded 0.9384g (98%) of colorless oil: tlc (System A, 10:1-benzene/EtOAc, R_f = 0.26); glc (material decomposed at elevated temperature); ir (film) 3325 cm^{-1} (OH); ^{1}H-NMR ($CDCl_3$) 1.60 and 1.67 (2s, 12H, vinyl $C\underline{H}_3$), 1.98-2.17 (m, 4H, allyl $C\underline{H}_2$), 2.37 (dt, J = 26 and 6Hz, 2H, $C\underline{H}_2CF$), 2.93 (m, 1H, OH), 4.02-4.33 (m, 2H, $C\underline{H}_2O$), 4.37 (dt, J = 48 and 6 Hz, 1H, $C\underline{H}F$), 4.92-5.30 (m, 2H, vinyl H), 5.45-5.82 (m, 1H, vinyl); ^{19}F-NMR ($CDCl_3$) ∅ 176 (dtq, J = 48, 26, and about 6Hz); cims: 241 (MH^+), 223 (MH^+-H_2O), and 221 (MH^+-HF).

Anal. Calcd. for $C_{15}H_{25}FO$: C, 74.95; H, 10.48. Found: C, 74.74; H, 10.43.

Ethyl α-fluoroacetoacetate (138)

A mineral oil suspension of 11.05g (2.76 mmol) of potassium hydride was twice washed with hexanes. Then, 150 ml of hexanes was added and the slurry cooled

to 0°. Ethyl fluoroacetate (14.53g, 137 mmol) was added neat via syringe at a rate slow enough to maintain the reaction temperature at or below 10°. The resulting mixture was stirred 2 hours at about 3° and then cooled to -78°. Acetyl chloride (10.8g, 138 mmol) was added quickly. After 1 hour at -78°, 5 ml of saturated aqueous NH_4Cl was added and the cold slurry slowly warmed to room temperature. Filtration and evaporation of the resulting filtrate resulted in about 15 ml of dark material. Distillation in vacuo (85-91°, 20-21 mm) gave 5.6g of colorless oil (36%); tlc (System A, 20% EtOAc/80% hexanes, R_f = 0.34); glc (System A, 82°, t_r = 7.50 min); ir (film) 2970 (w), 2940 (w), 1770 (s), 1740 (s), 1255, 1220, 1175, 1100,, 1015 (bs), 960, and 855 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 1.32 (t, J = 7Hz, 3H, $CH_2\underline{CH_3}$), 2.02 (S, 0.07H, OH), 2.33 (d, J = 3.5 Hz, 3H, $\underline{CH_3}CO$), 4.15 (g, J = 7Hz, 2H, $\underline{CH_2}O$), 5.30 (d, J = 49Hz, 0.93H,-$\underline{CH}$F). Note that both the ir and ^{1}H-NMR indicate the presence of a few % of the enol form of the keto ester 138;[109] ^{19}F-NMR ($CDCl_3$) Ø 194 (dq, J = 49 and 3.5 Hz); cims: 149 (MH^+).

Ethyl 4-fluorofarnesoate. (140)

Triethylphosphonoacetate (7.450g, 33.2 mmol) was added to 0.85g (35.4 mmol) of sodium hydride in 150 ml of Et_2O at 0°. The mixture was then stirred 1.5 hr at room temperature at which time 7.0101g (33.02 mmol) of ketone 136 was added neat. After 30 min. at room temperature the reaction was judged complete by glc analysis. A few drops of acetic acid were added and, after the normal Et_2O/water work-up, 9.0g of yellow oil remained which was distilled (see Table next page).

VACUUM DISTILLATION

Fraction	Vacuum	Temperature (°C)	Wt(g)	E/Z (glc)
I	0.05 mm	30-95°	trace	-
II	0.05 mm	97-100°	0.7995	60/40
III	0.05 mm	100-104	3.6589	84/16
IV	0.05 mm	104-108	1.7475	93/7
V	0.05 mm	108-110	0.2647	98/2
		Yield: 6.4726$_g$ (69%)		

GLC analysis of the crude product indicated a 90:10 ratio of E:Z isomers, respectively; tlc (System A, 35% EtOAc/65% hexanes, R_f = 0.75, fraction IV); glc (System A, 150°C, E, E-isomer, t_r = 19.1 min; Z, E-isomer, t_r = 11.7 min); ir (film) 1725 and 1660 cm^{-1}); ^{1}H-NMR (E,E-isomer) 1.27 (t, J = 7Hz, 3H, $OCH_2\underline{CH}_3$), 1.60 and 1.68 (2S, 9H, vinyl $\underline{CH}_3$), 1.97-2.20 (bm, 4H, allylic $\underline{CH}_2$), 2.12 (d, J = 2Hz, 3H, C-3 Me), 2.47 (dt, J = 24 and 6Hz, 2H, $\underline{CH}_2CF$), 4.15 (q, J = 7Hz, 2H, $\underline{CH}_2O$), 4.82 (dt, J = 47 and 6Hz, 1H, $\underline{CH}F$), 4.90-5.33 (bm, 2H, vinyl H), 5.85 (m, 1H, vinyl H). The (2vinyl proton in the Z,E-isomer was observed at 4.68 ppm. ^{19}F-NMR ($CDCl_3$, E,E-isomer) ø 180 (dt, J = 47 and 24Hz); cims: 283 (MH^+), 263 (MH^+-HF).

Anal. Calcd. for $C_{17}H_{27}FO_2$: C, 72.30; H, 9.64. Found: C, 72.07; H, 9.50.

4-Fluorofarnesyl pyrophosphate (17)

A solution of 1.030$_g$ (3.43 mmol) of di-(triethylammonium)-phosphate in 50 ml of acetonitrile was added over a period of 3 hours to 273 mg (1.14 mmol) of alcohol 13 and 1.49g (10.3 mmol) of trichloroacetonitrile in 10 ml of acetonitrile. After stirring 20 hours the solvent was removed in vacuo leaving a yellow residue which was dissolved in 10 ml of acetone containing 0.01 N NH_3. Concentrated NH_4OH was added (about 1 ml) resulting in precipitate formation which was subsequently washed thrice with acetone containing 0.01 N NH_3. The solid was dissolved in 2 ml of water (0.01 N NH_3) and chromatographed on 75$_g$ of silica gel using a 9/4/1 (n-propanol/NH_4OH/water) solvent system. The monophosphate salt eluted with 110-120 ml of solvent. Pyrophosphate 17 eluted with 185-220 ml of solvent. Fractions containing 17 (tlc system B, 6/3/1n-propanol/NH_4OH/H_2O, R_f = 0.38) were combined and solvent removed in vacuo to provide 32 mg of white solid. Quantitative phosphorus analysis[1d,1e] indicated 15.1% phosphorus (Expected: 13.7%).

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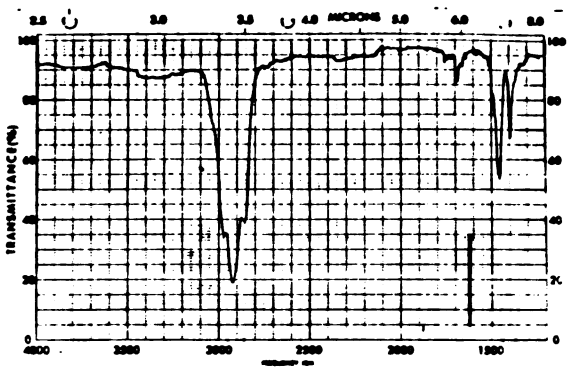

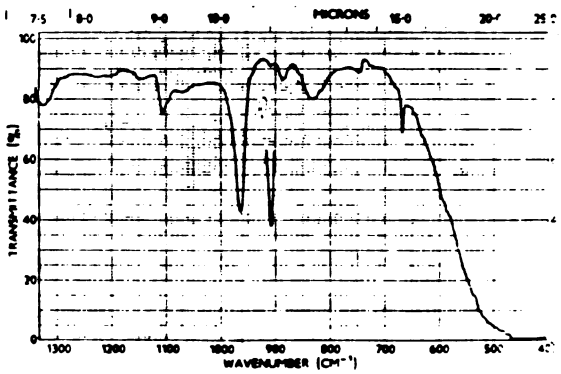

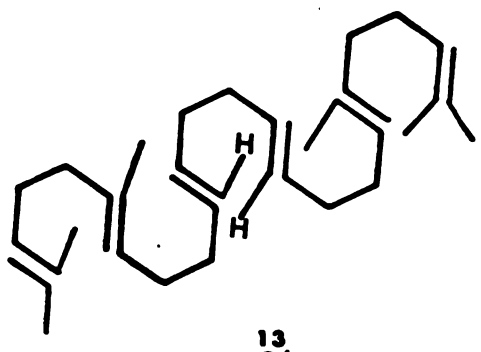

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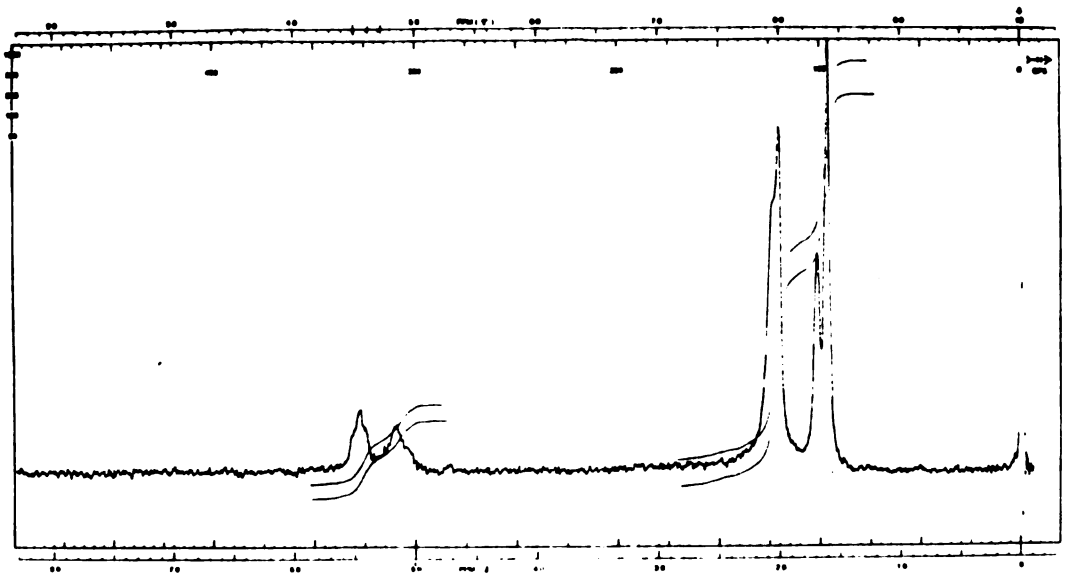

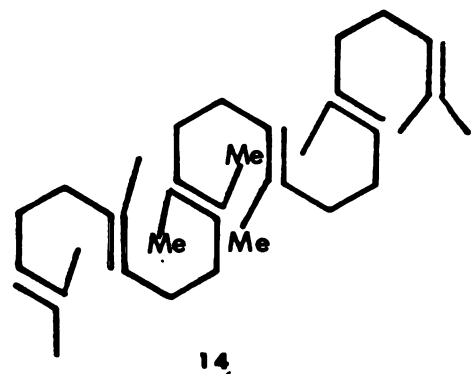

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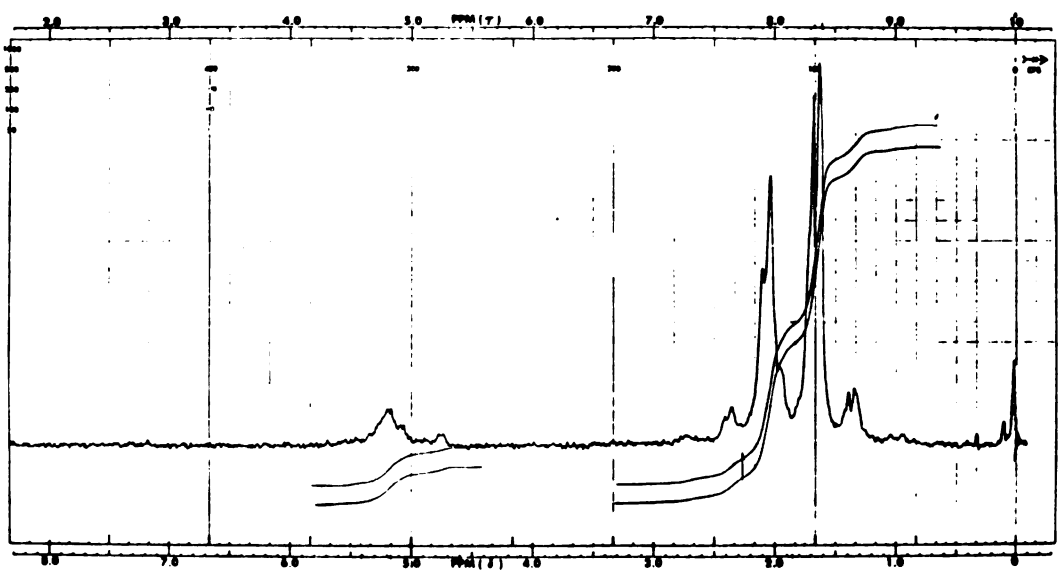

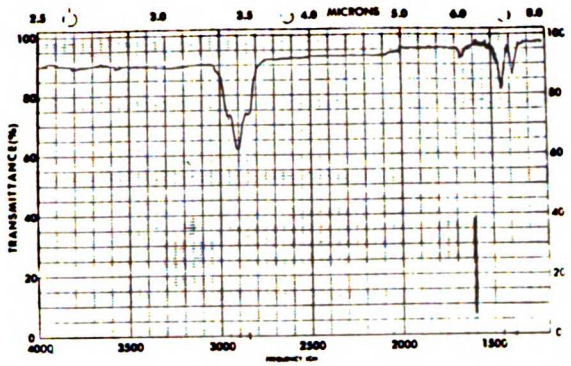
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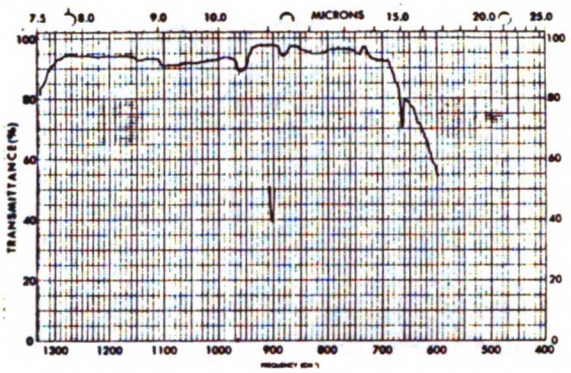
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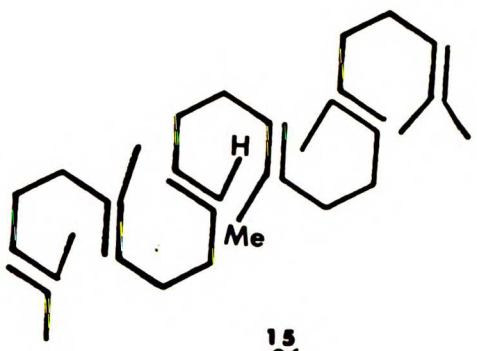
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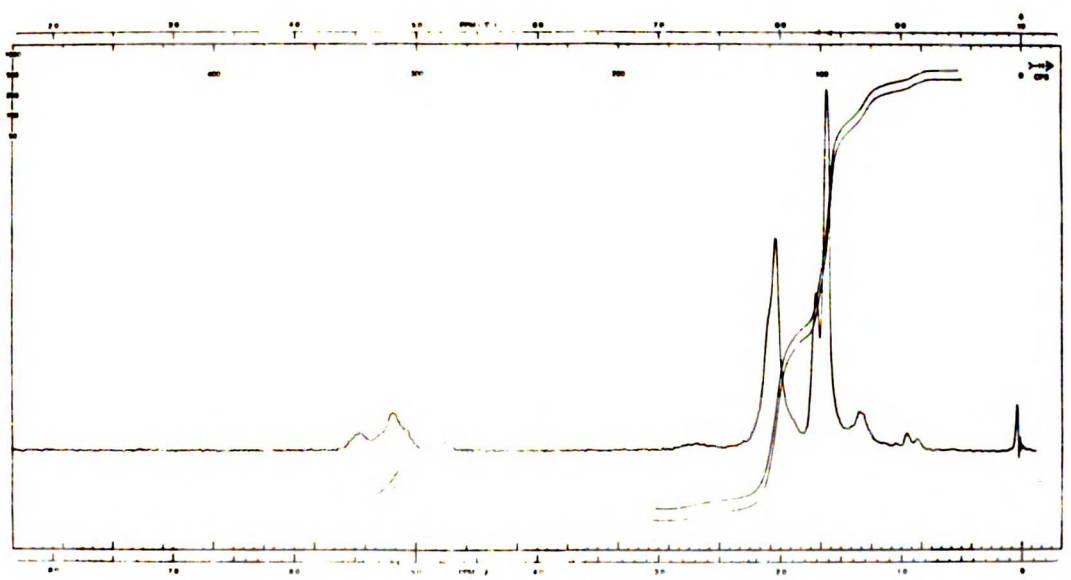

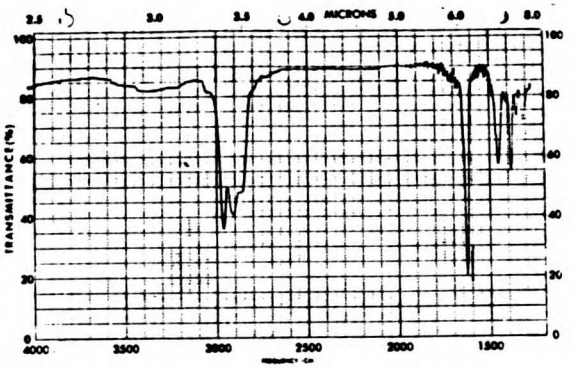
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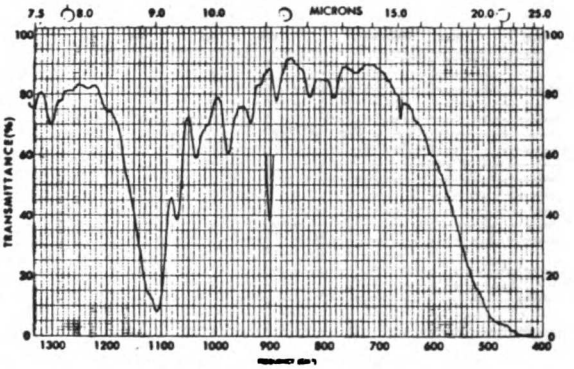
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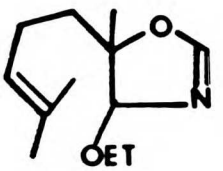
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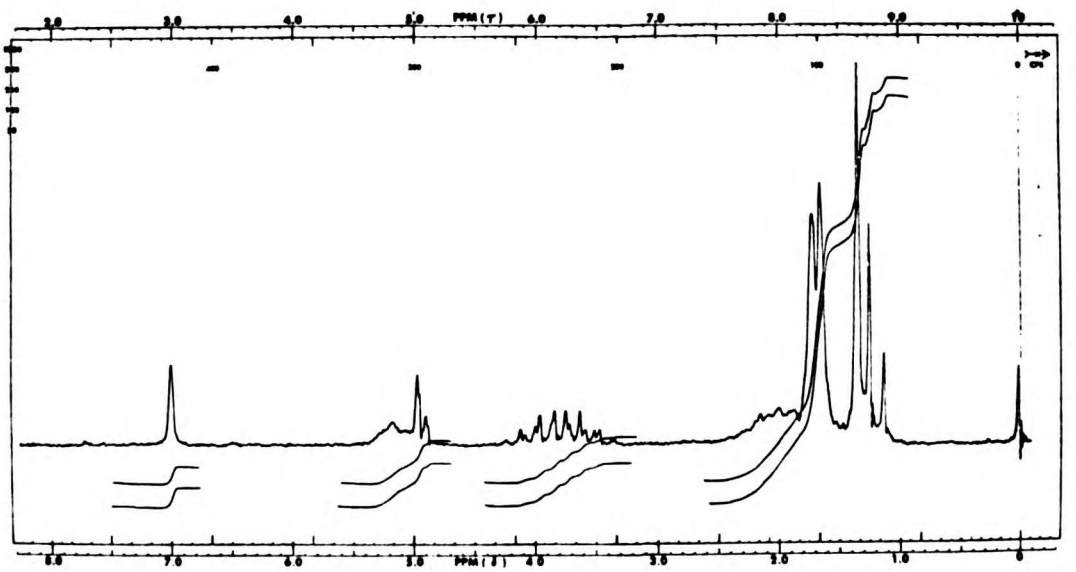
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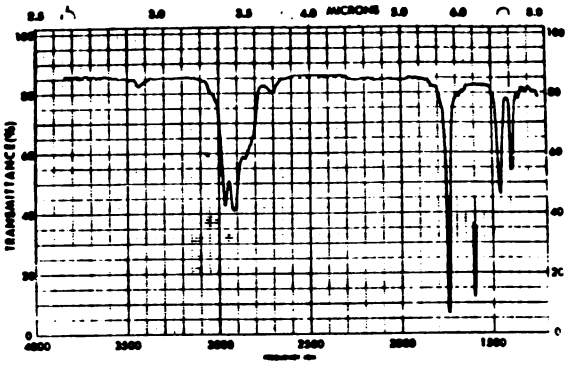

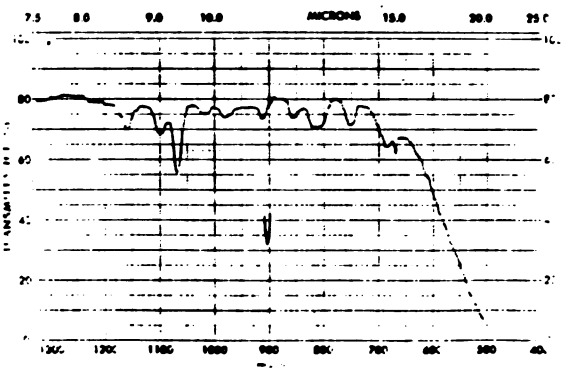

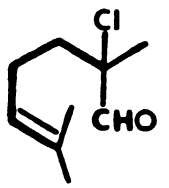

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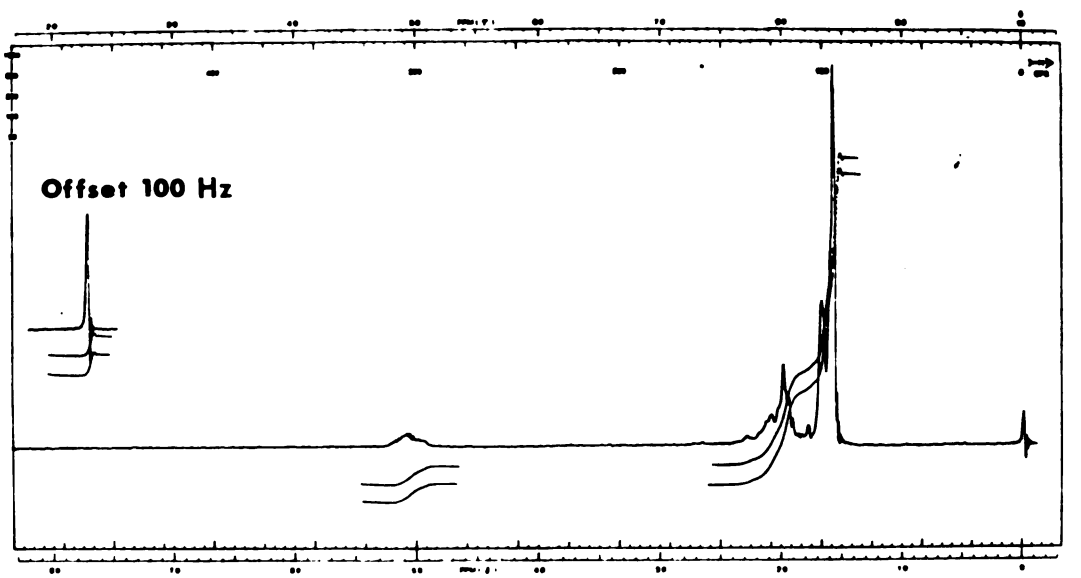

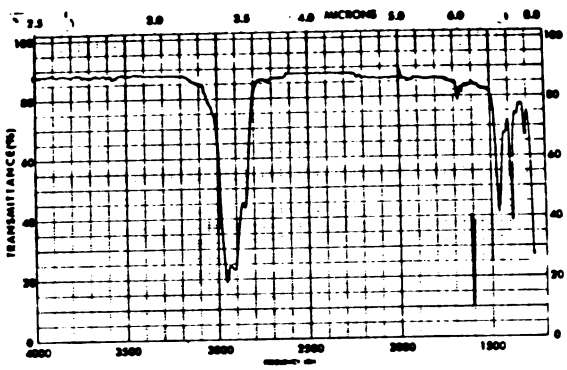

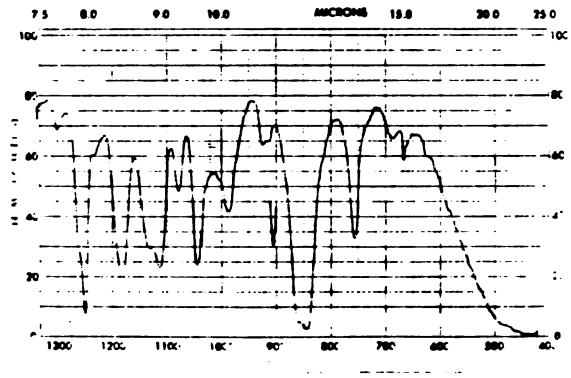

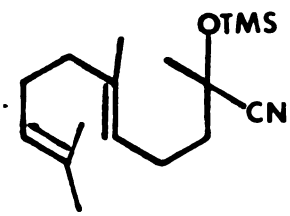
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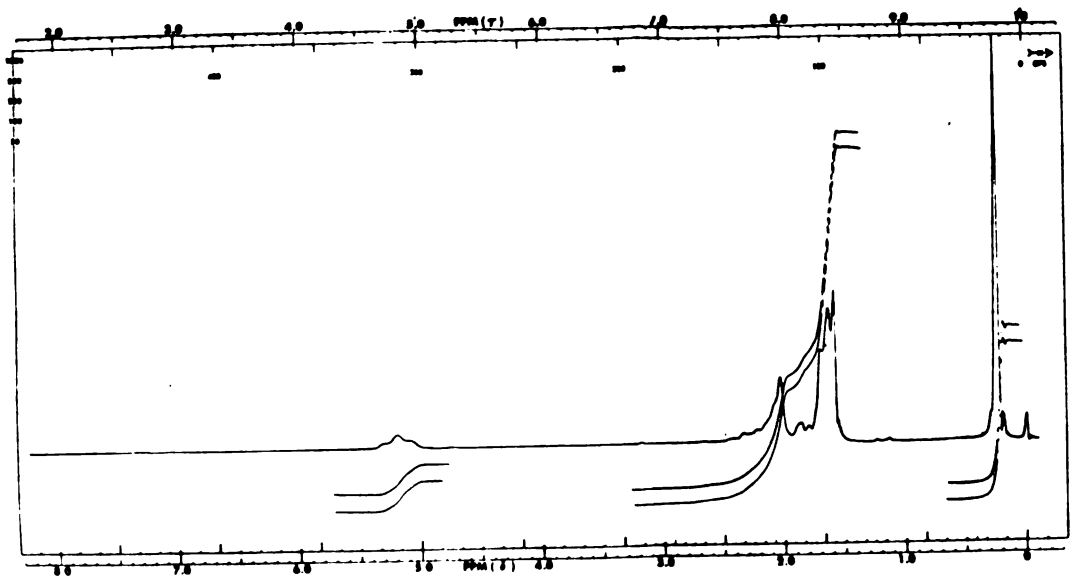

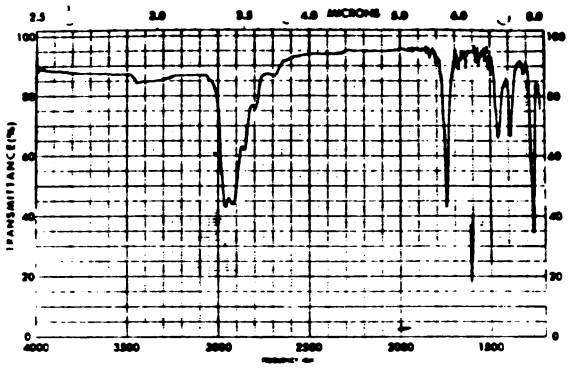

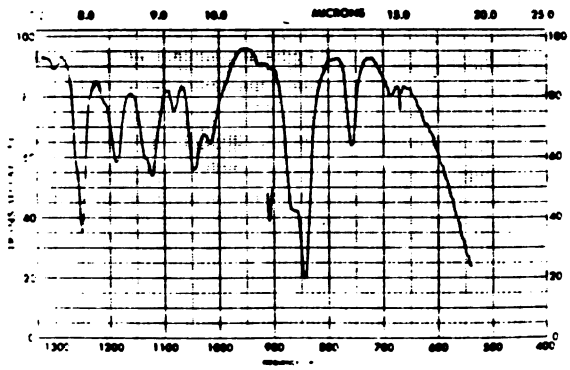

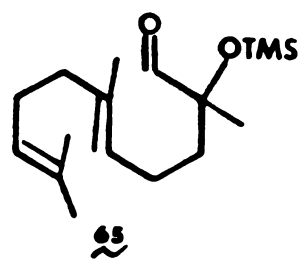

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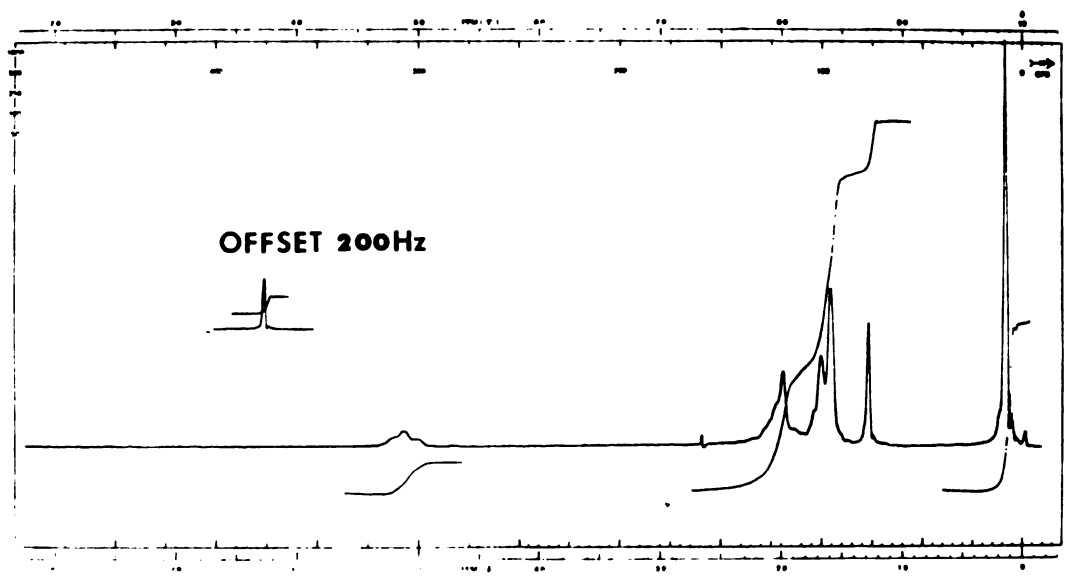
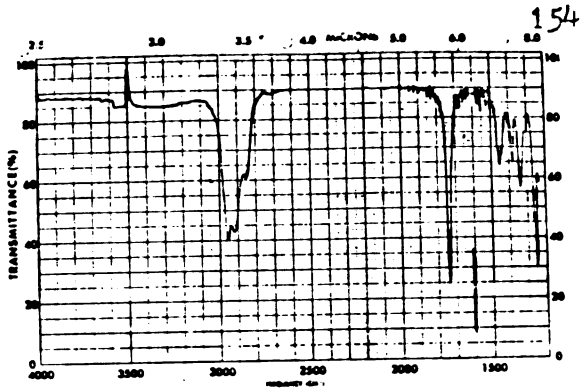
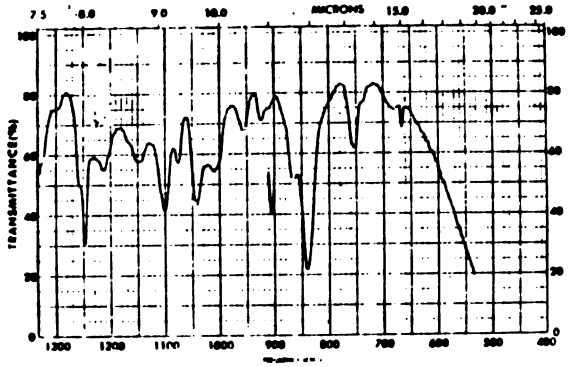
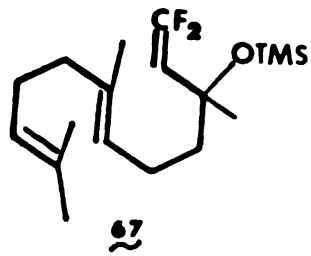
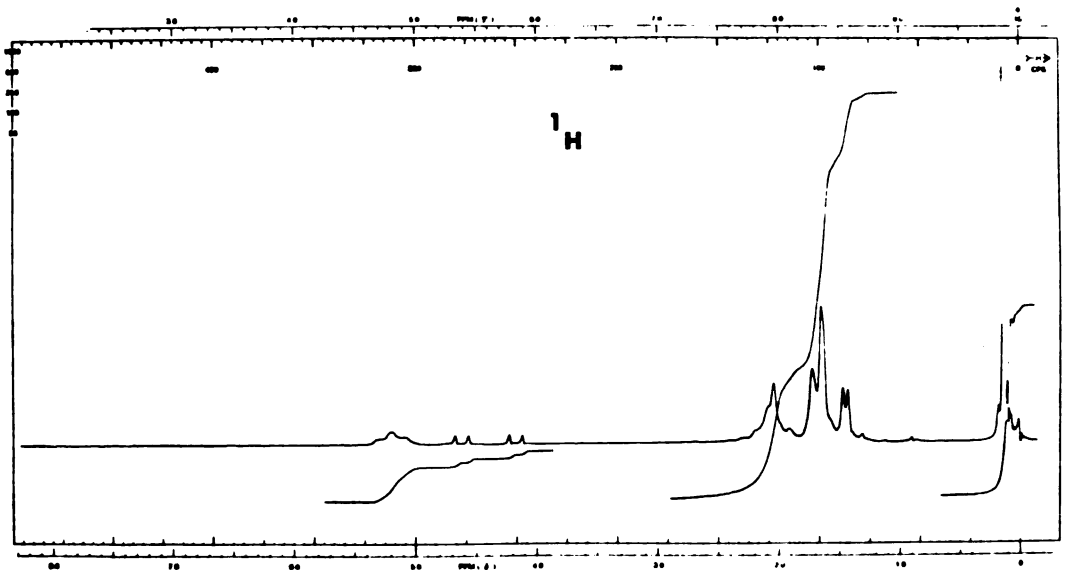


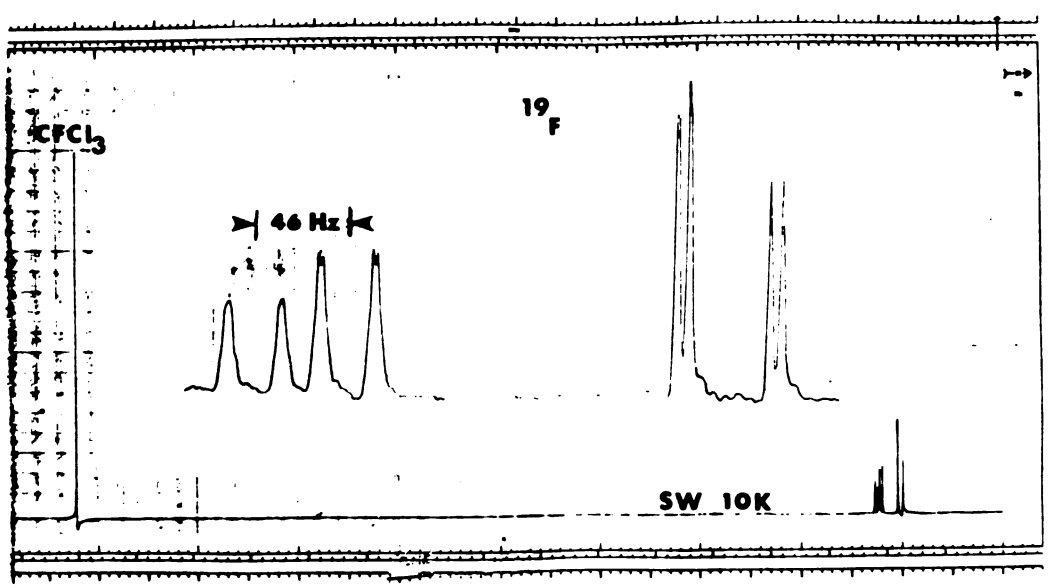

TRANSMITTANCE(%)

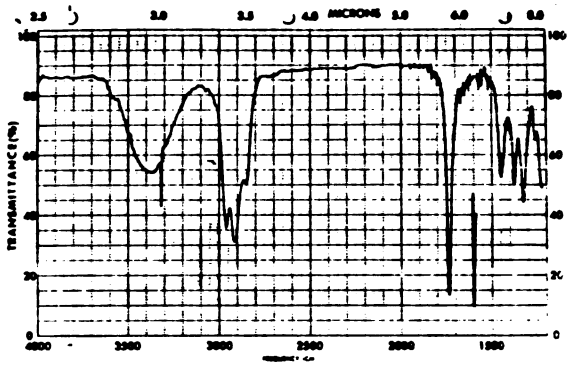

TRANSMITTANCE(%)

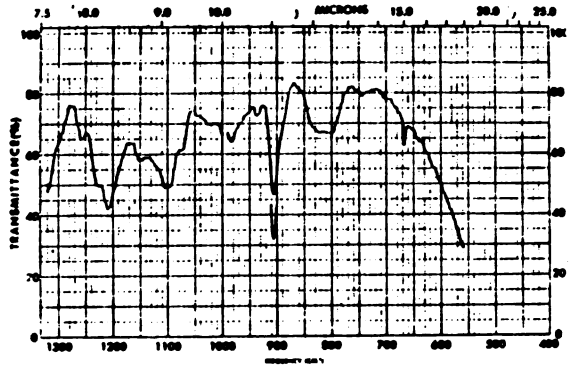

CF2
OTMS

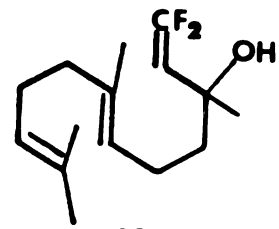
67


1H

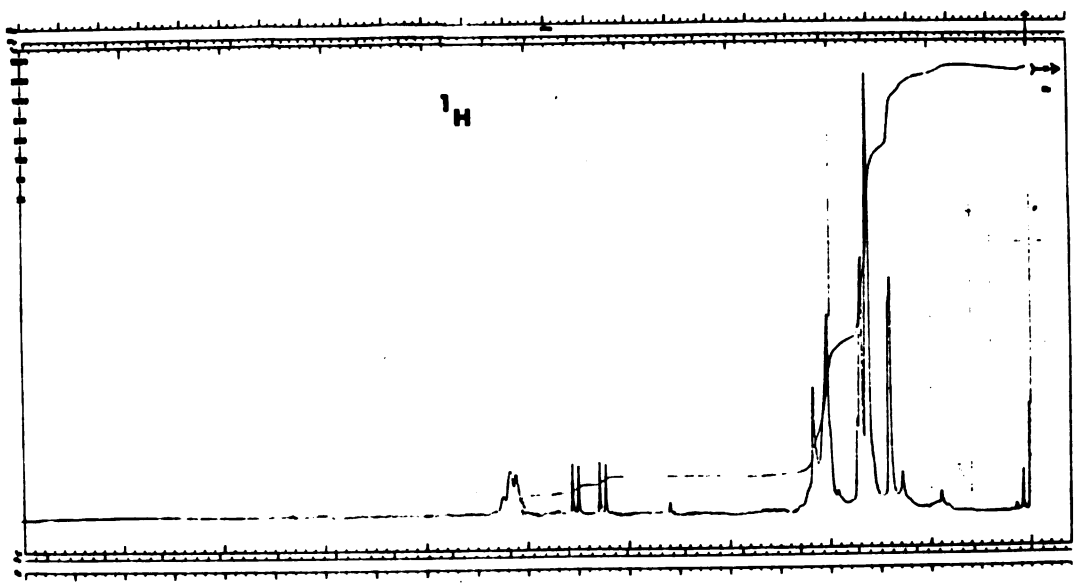

CFCl3
19F
46 Hz
SW 10K

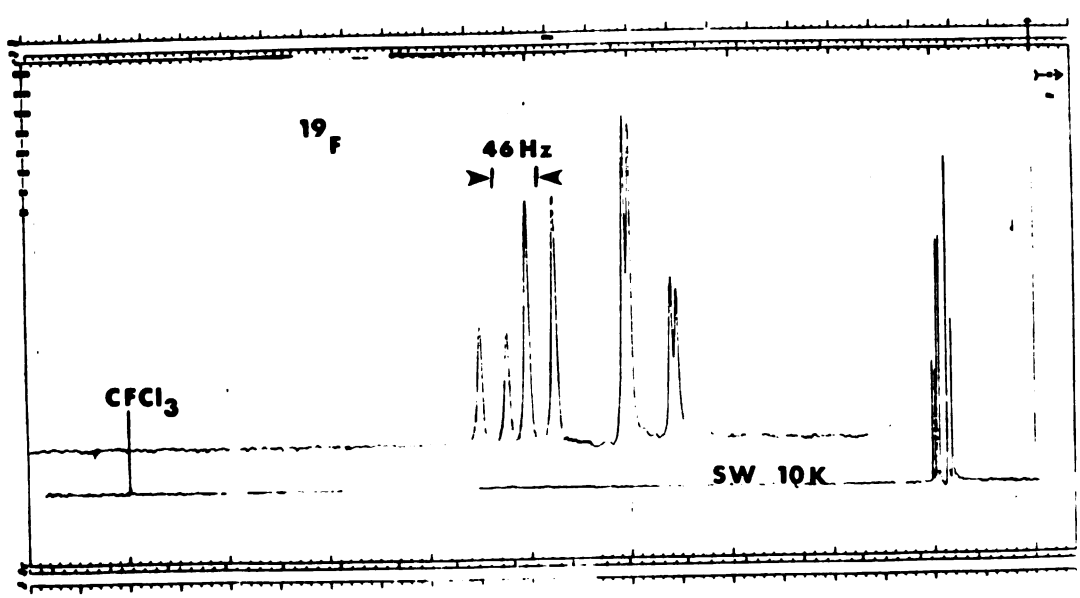


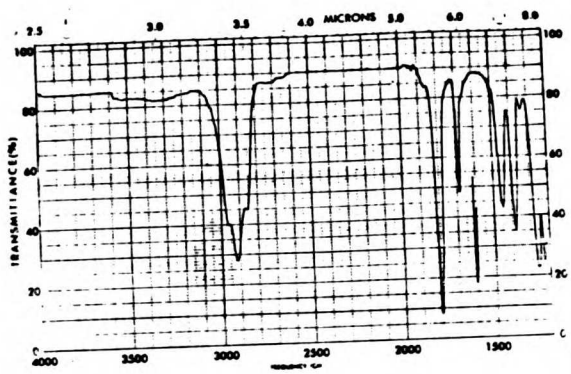


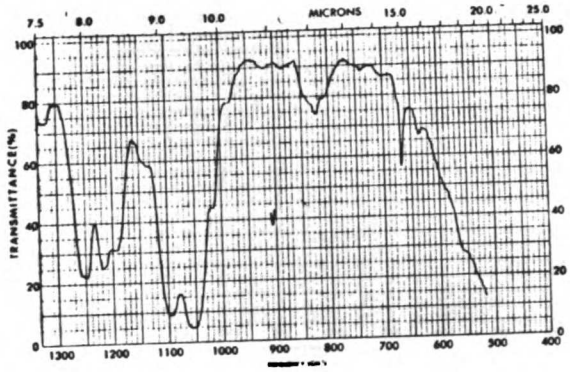


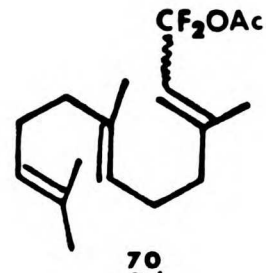
68



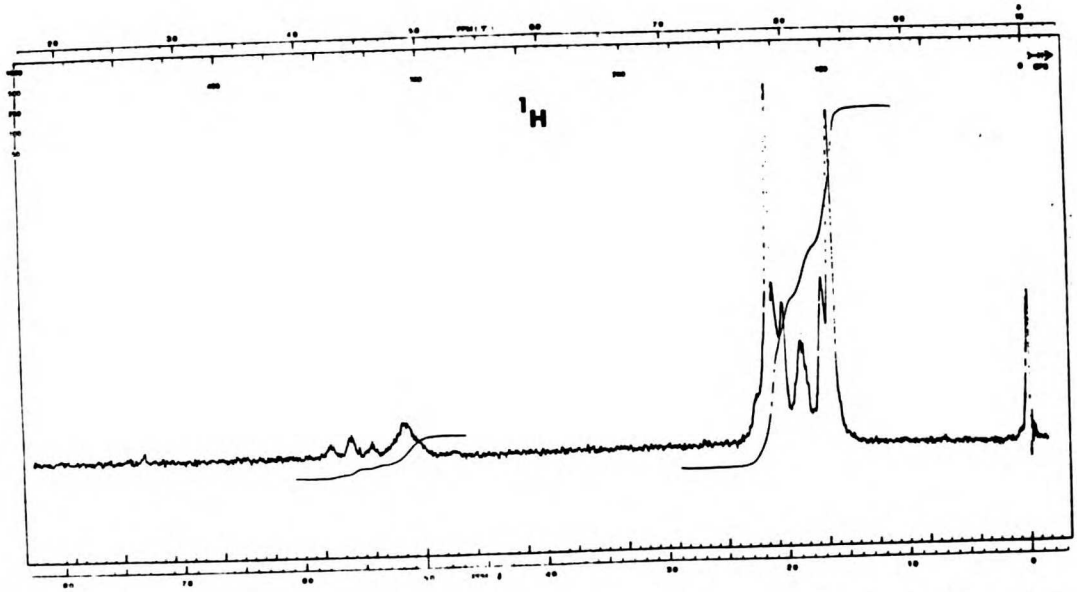


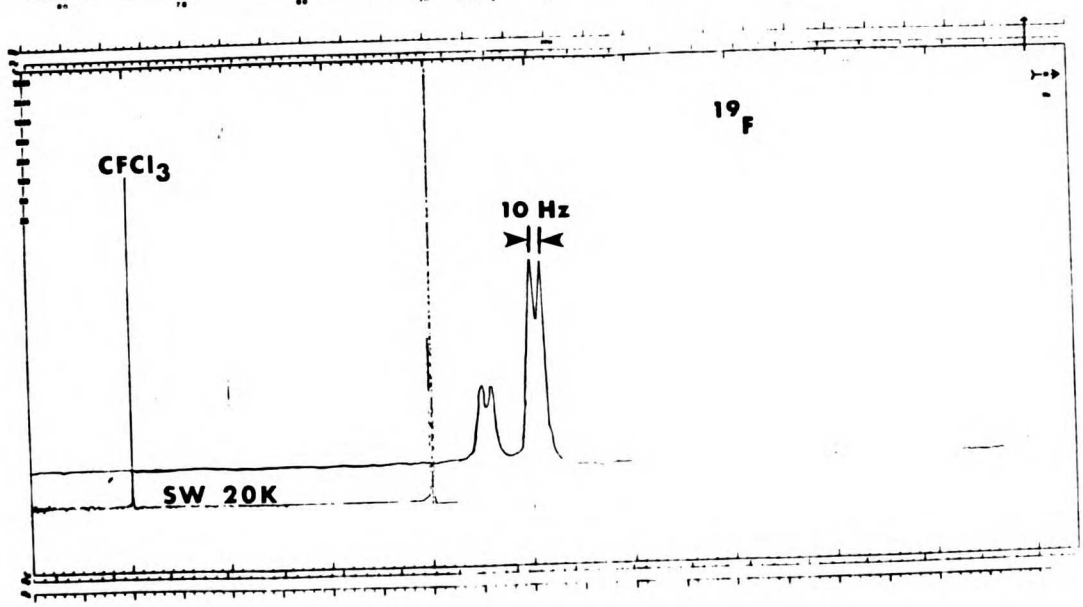

MICRONS
TRANSMITTANCE(%)
4000
3500
3000
2500
2000
1500

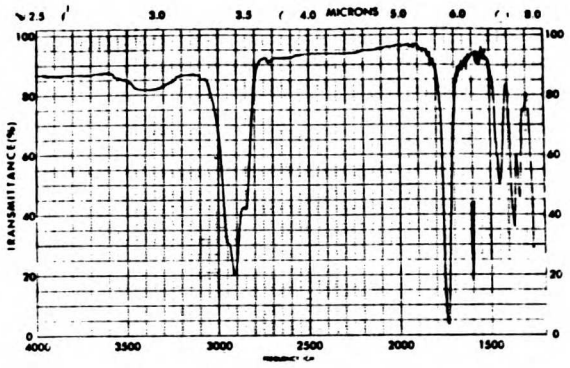

MICRONS
TRANSMITTANCE(%)
1300
1200
1100
1000
900
800
700
600
500
400

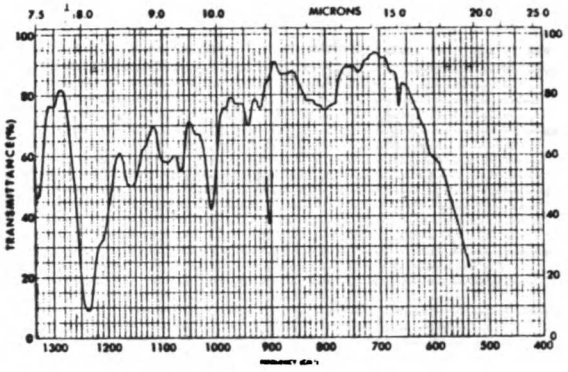

CF_2OAc

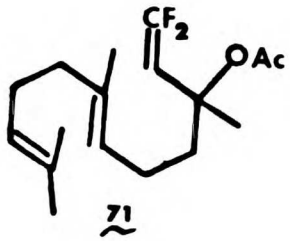
70


^1H

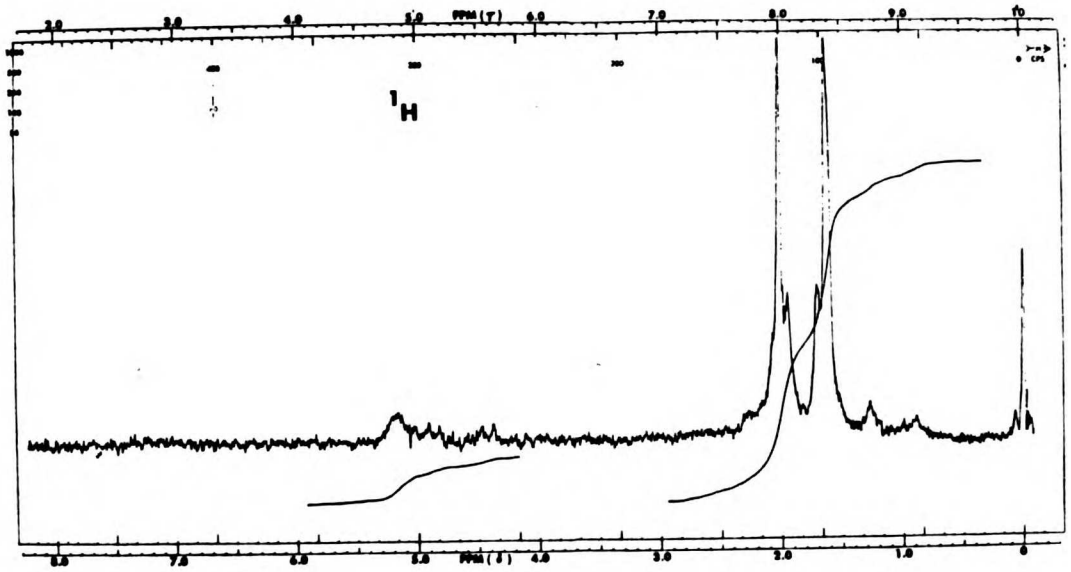

^{19}F
$CFCl_3$
10 Hz
SW 20K

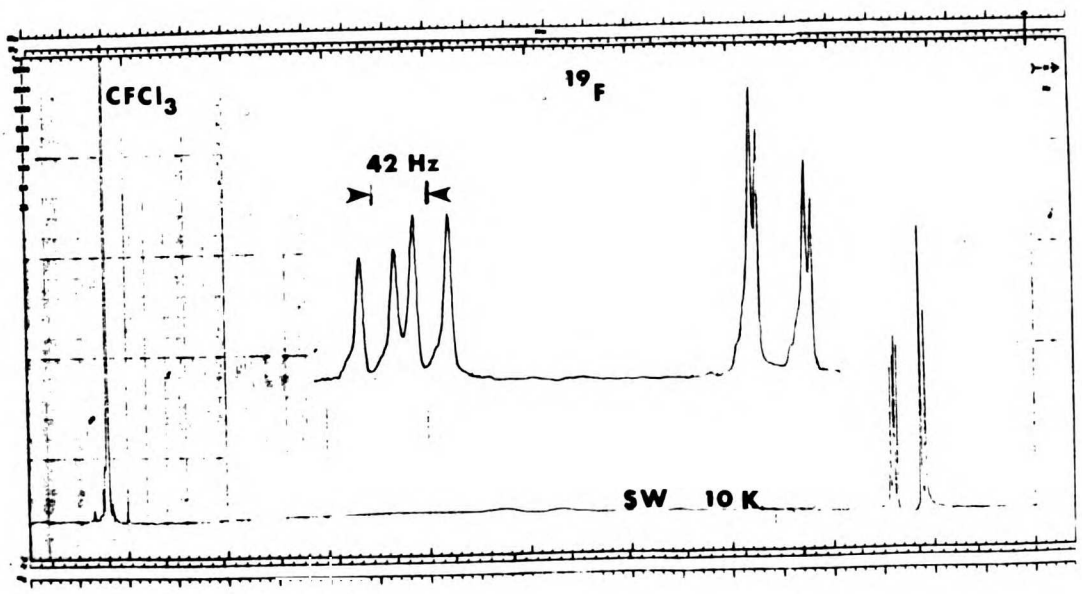

MICRONS
TRANSMITTANCE(%)

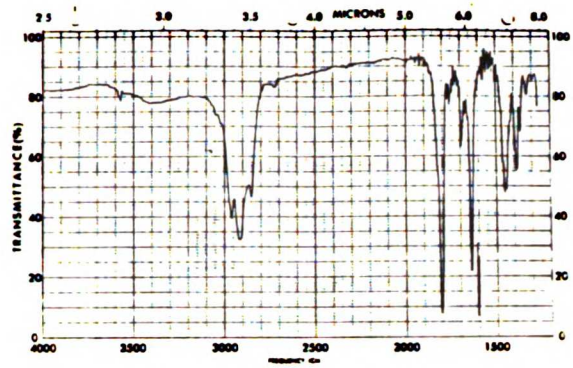

MICRONS
TRANSMITTANCE(%)

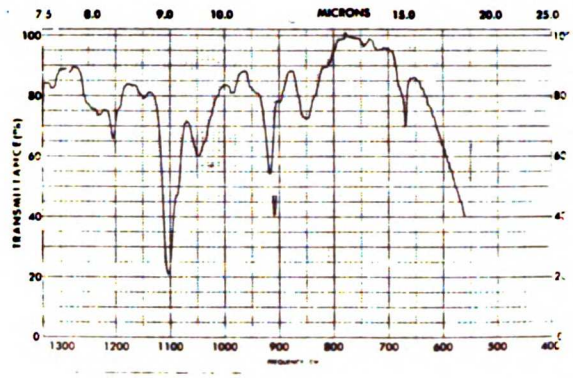

CF2
OAc

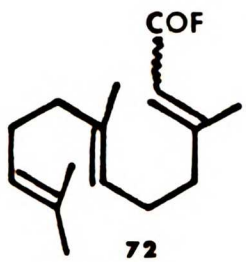
71


1H

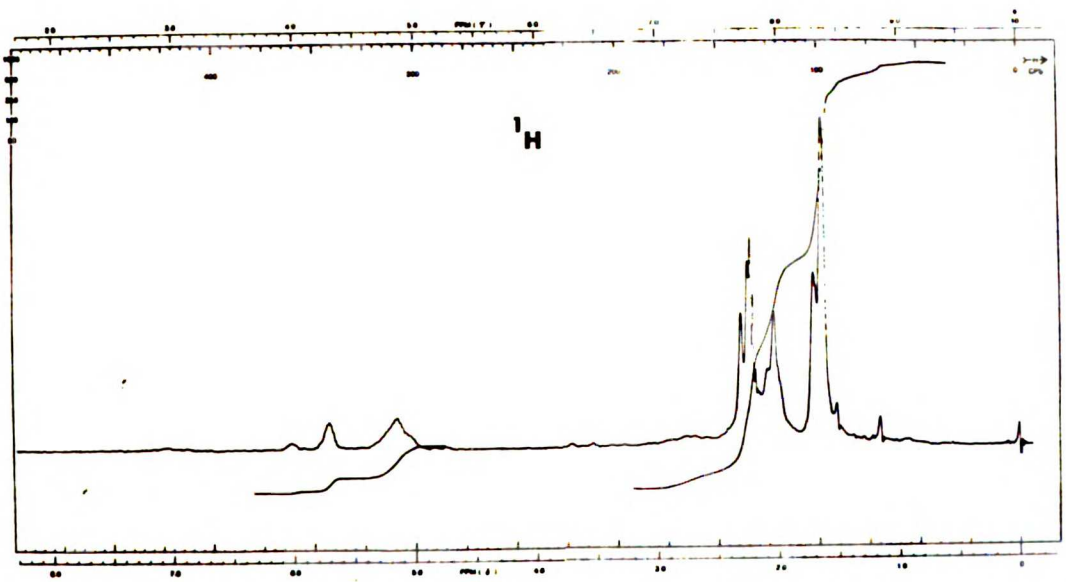

CFCl3
19F
42 Hz
SW 10 K


MICRONS
TRANSMITTANCE(%)
4000
3500
3000
2500
2000
1500


MICRONS
TRANSMITTANCE(%)
1300
1200
1100
1000
900
800
700
600
500


COF

72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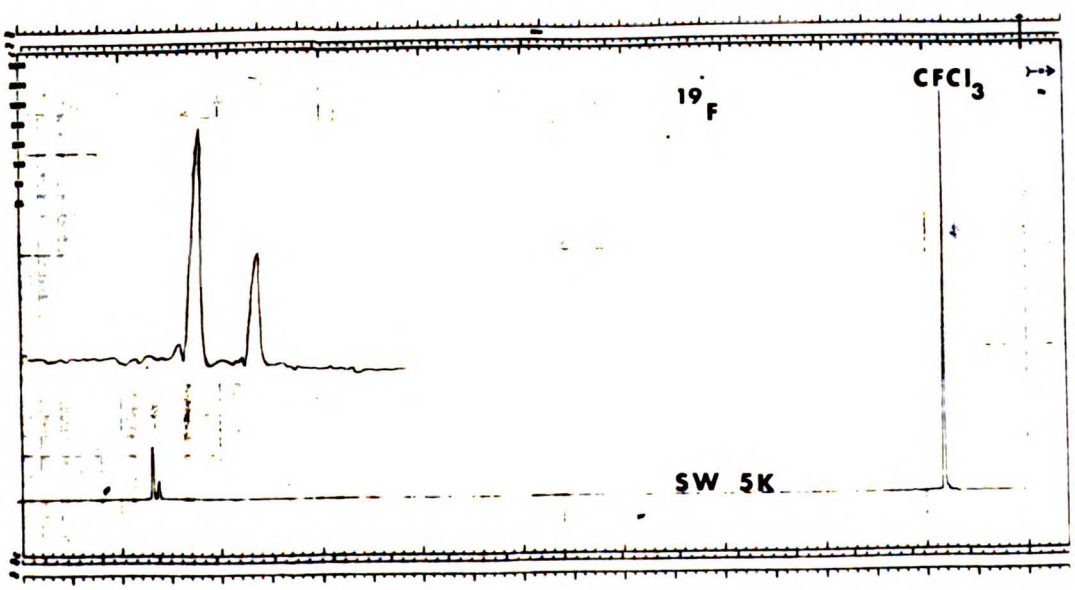
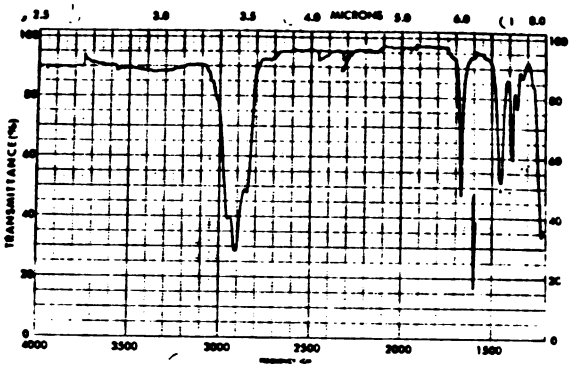
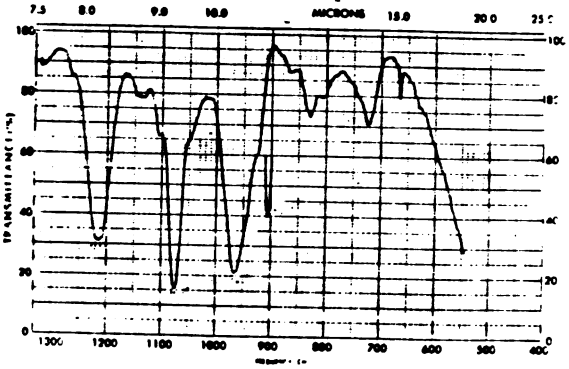
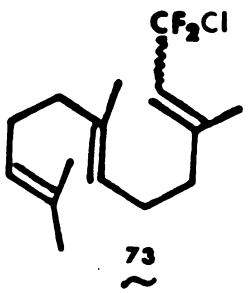
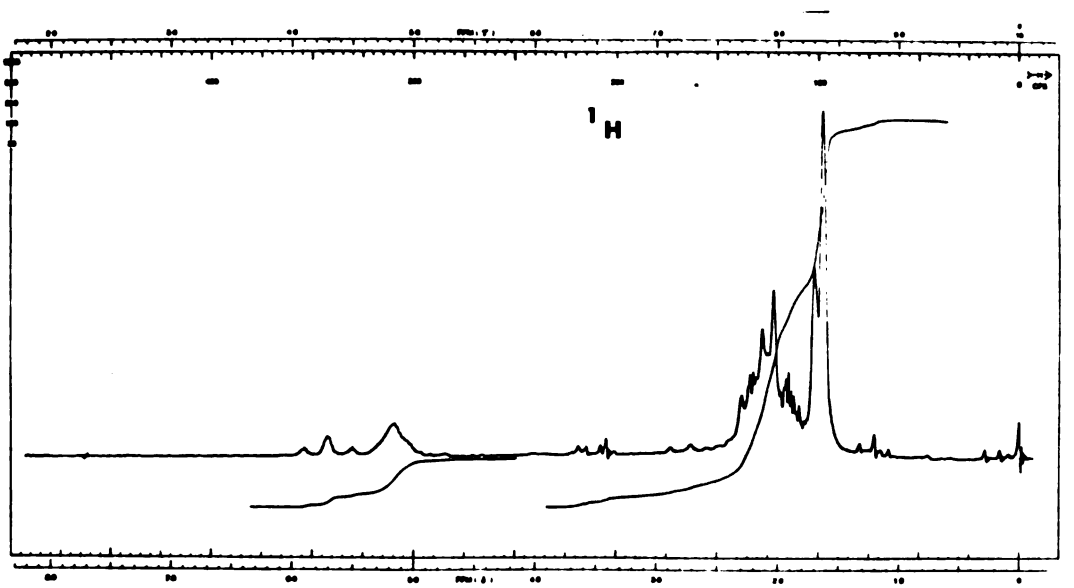

^{19}F
CFCl$_3$
SW 5K

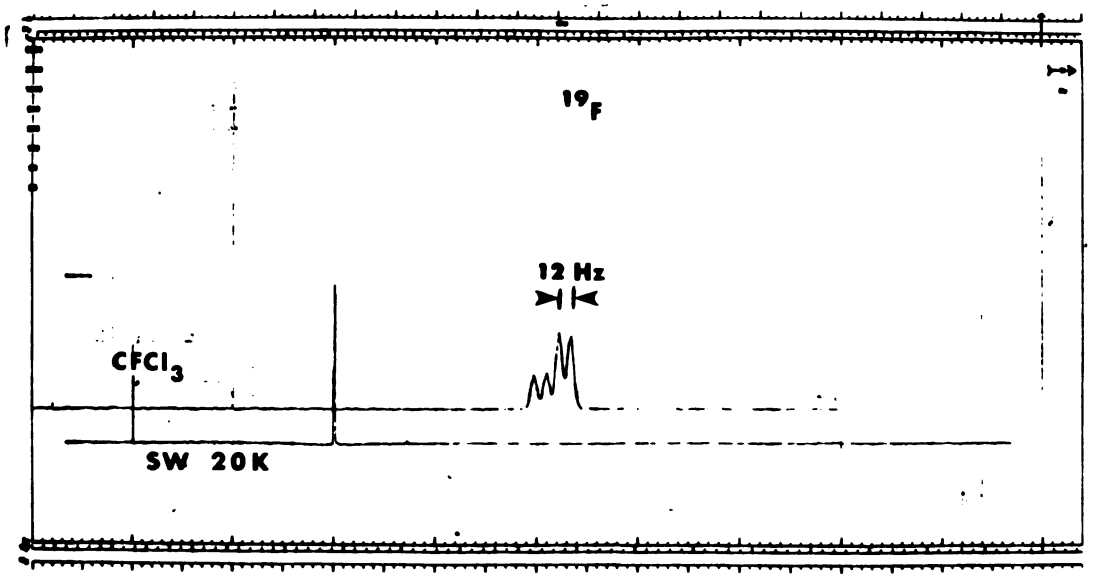

MICRONS
TRANSMITTANCE (%)
4000
3500
3000
2500
2000
1500

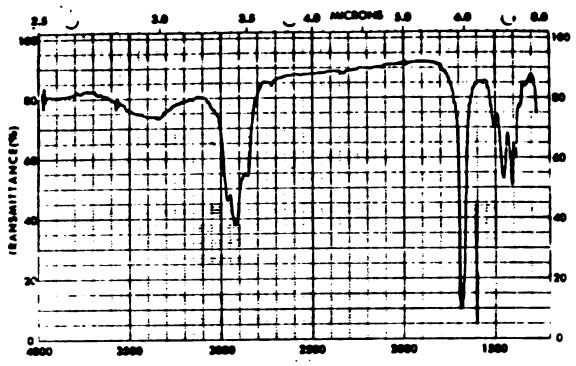

MICRONS
1300
1200
1100
1000
900
800
700
600
500
400

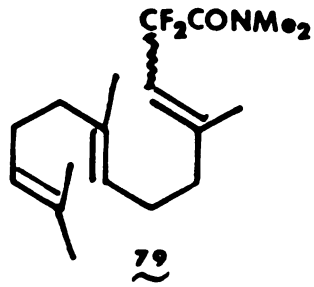

CF_2Cl

73

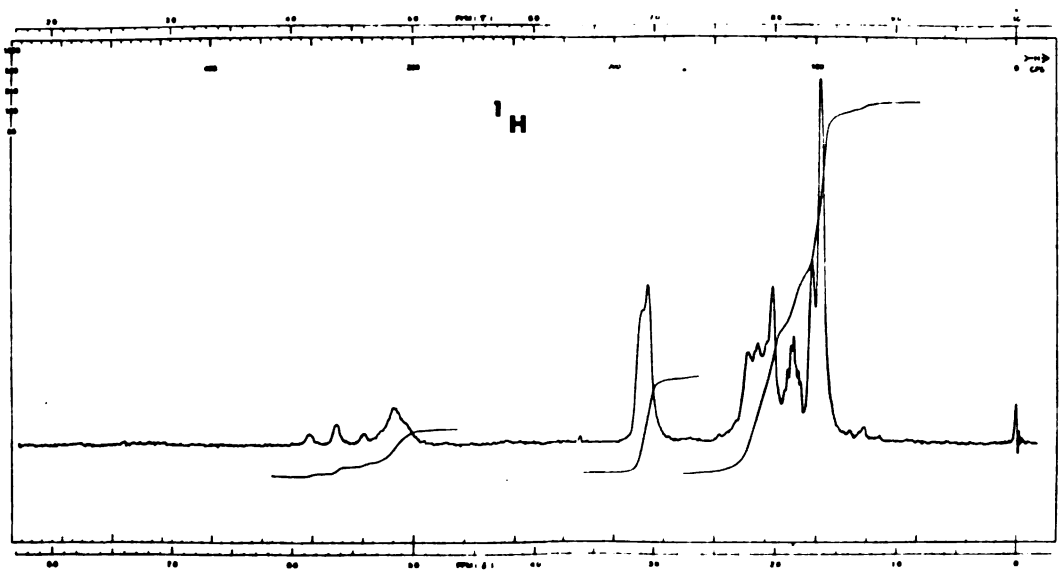

^1H

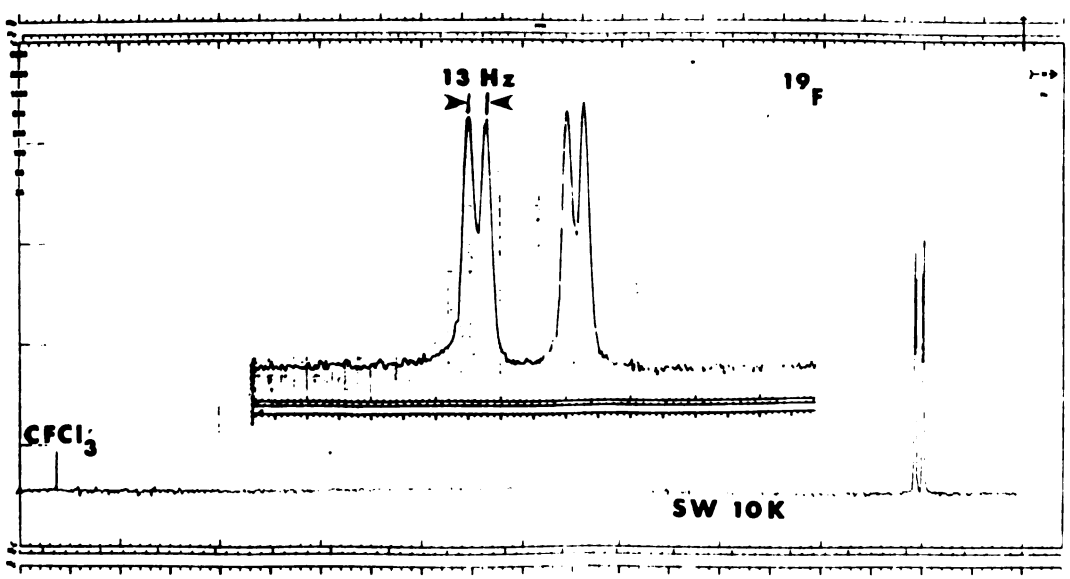

^{19}F
12 Hz
$CFCl_3$
SW 20K

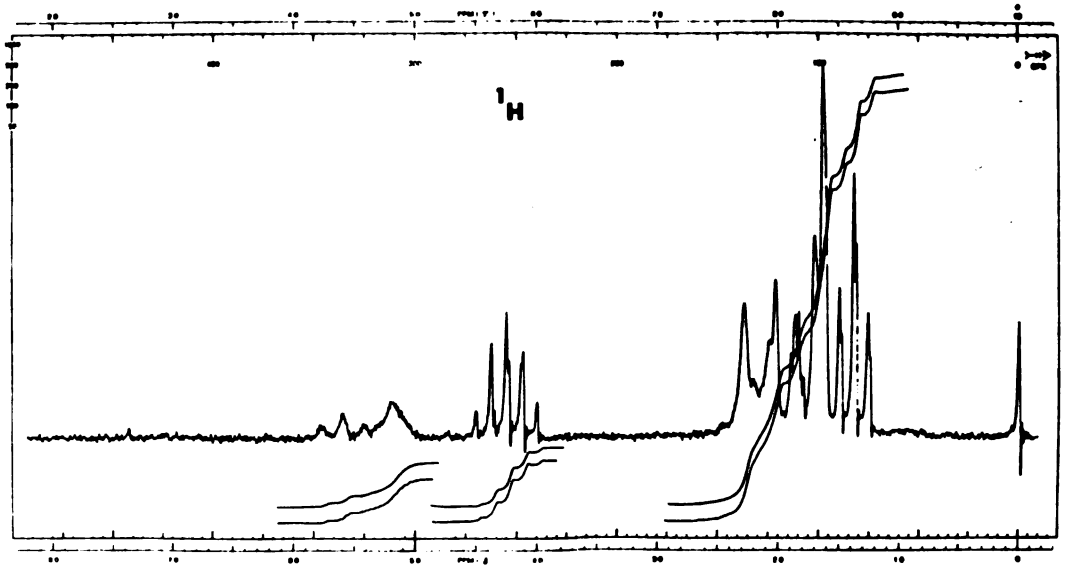


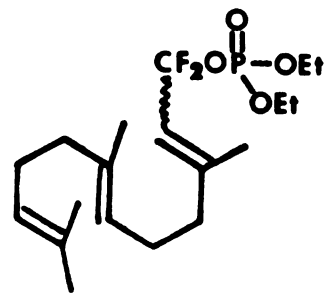


79

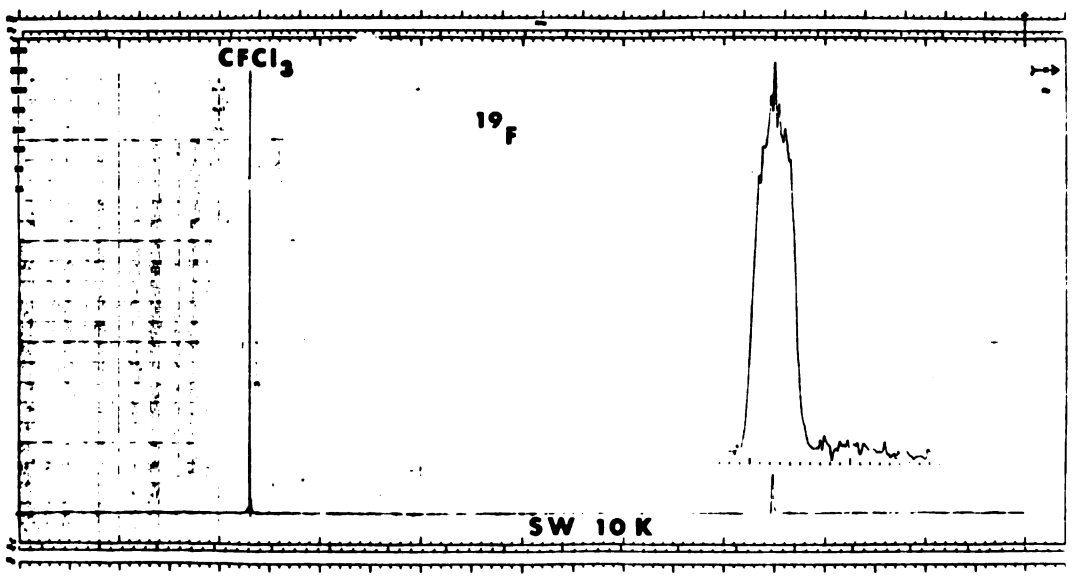


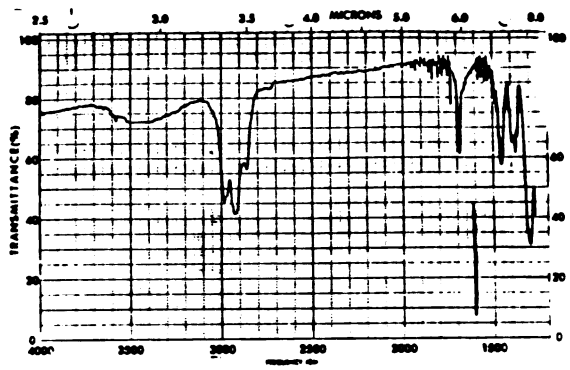


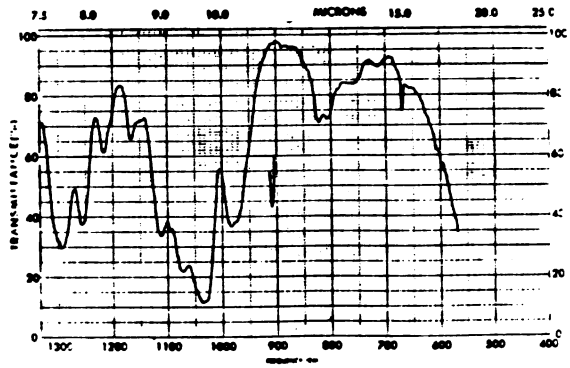


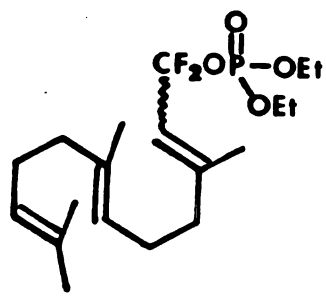


94-Z

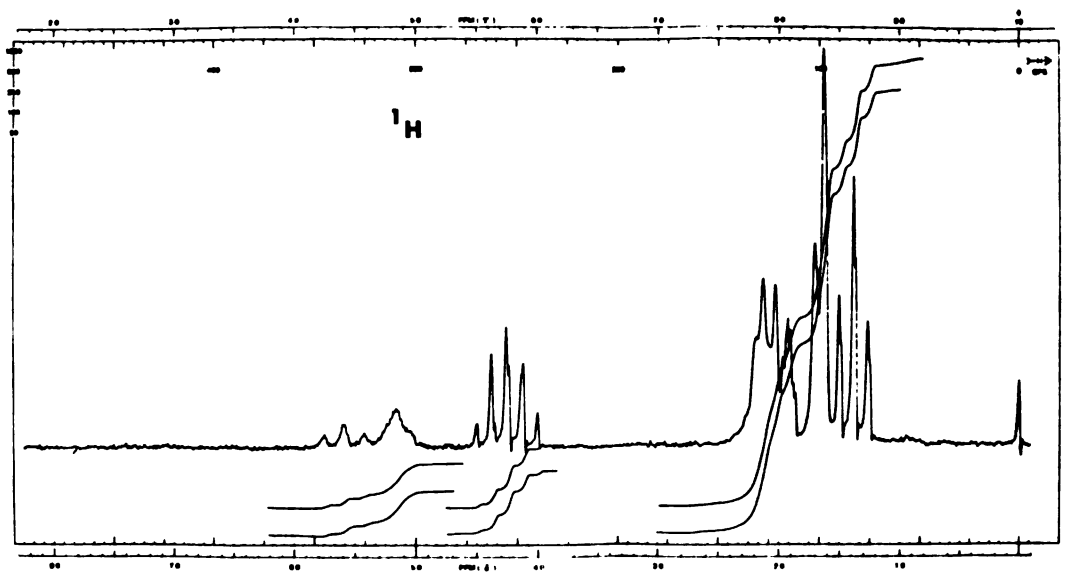


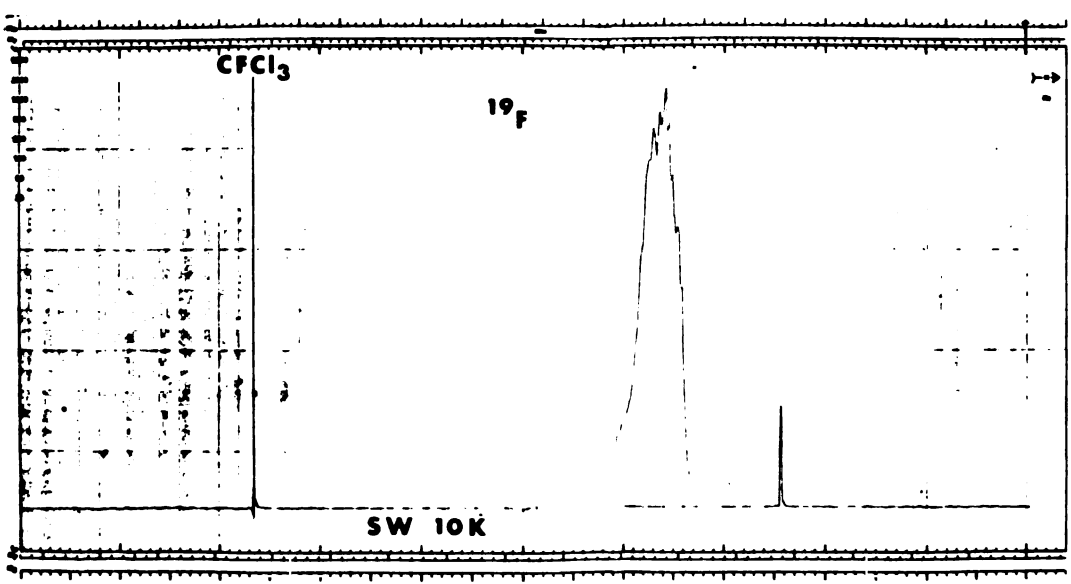


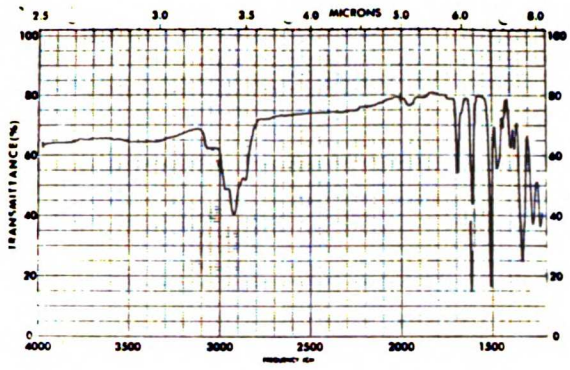


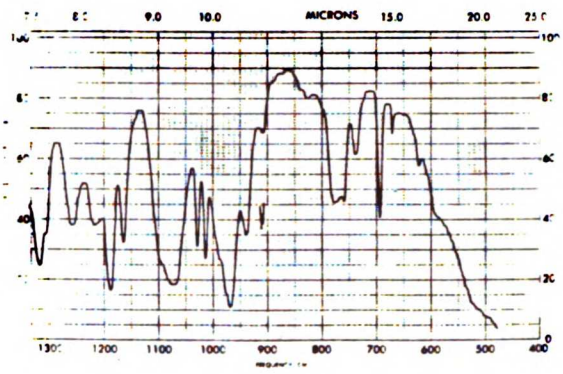


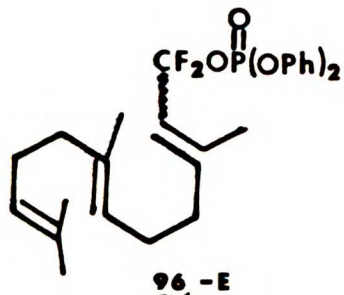
94-E



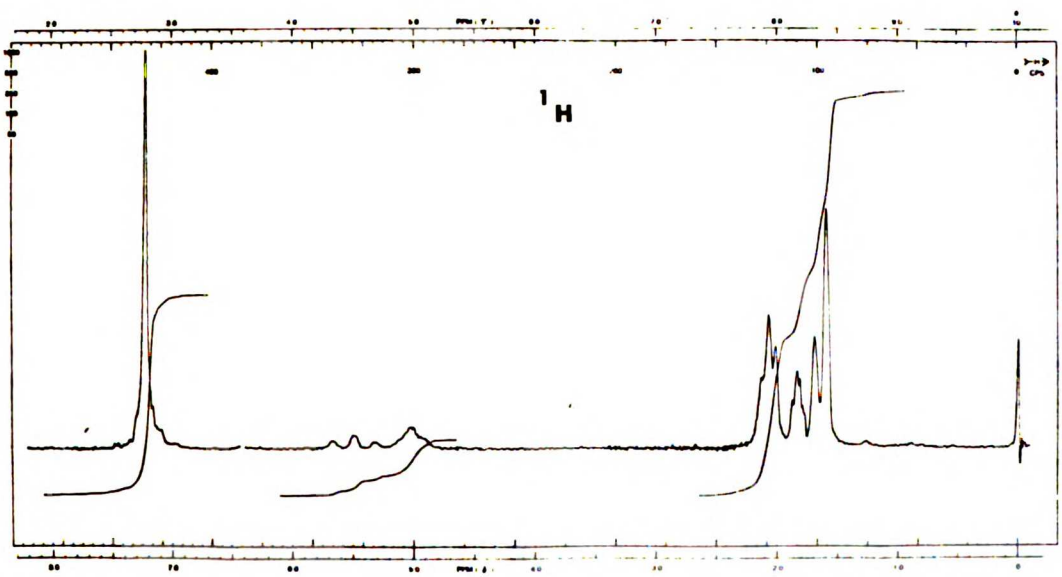


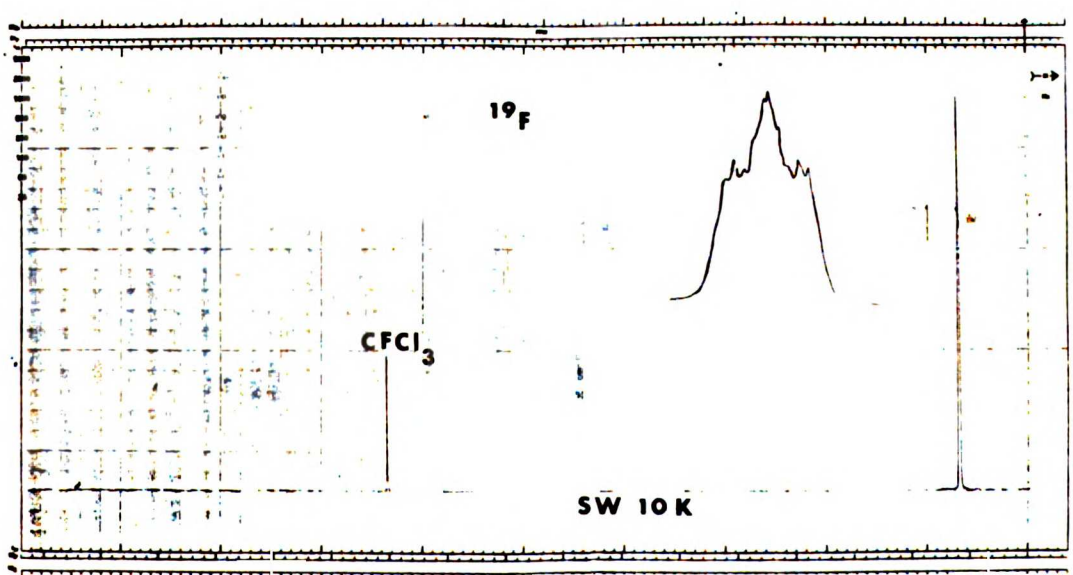

2.5
3.0
3.5
4.0 MICRONS 5.0
6.0
8.0
TRANSMITTANCE(%)
4000
3500
3000
2500
2000
1500

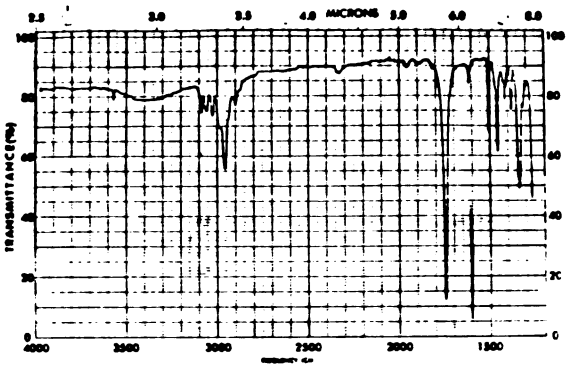

9.0
10.0
MICRONS
15.0
20.0
1300
1200
1100
1000
900
800
700
600
500
400

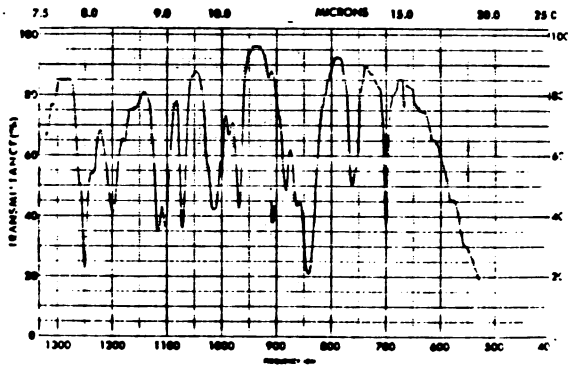

CF2OP(OPh)2

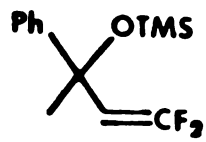
96 -E


1H


19F
CFCl3
SW 10 K







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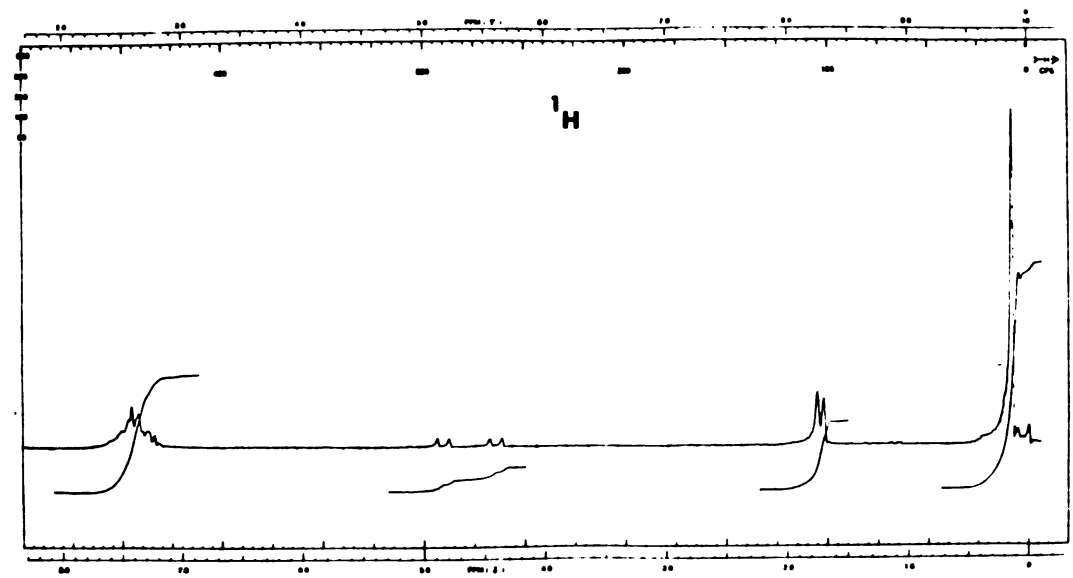

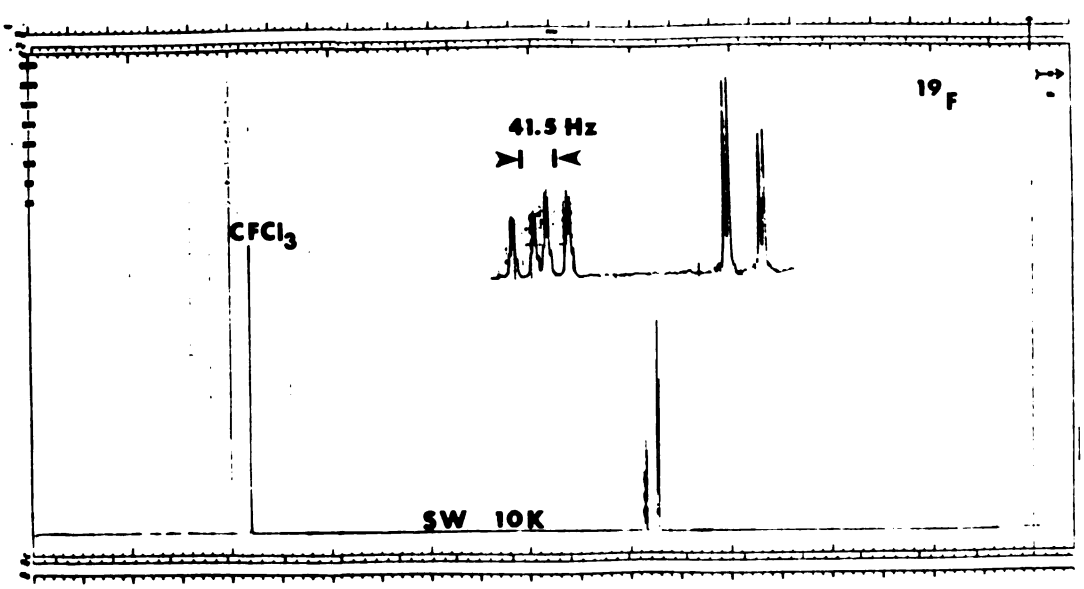

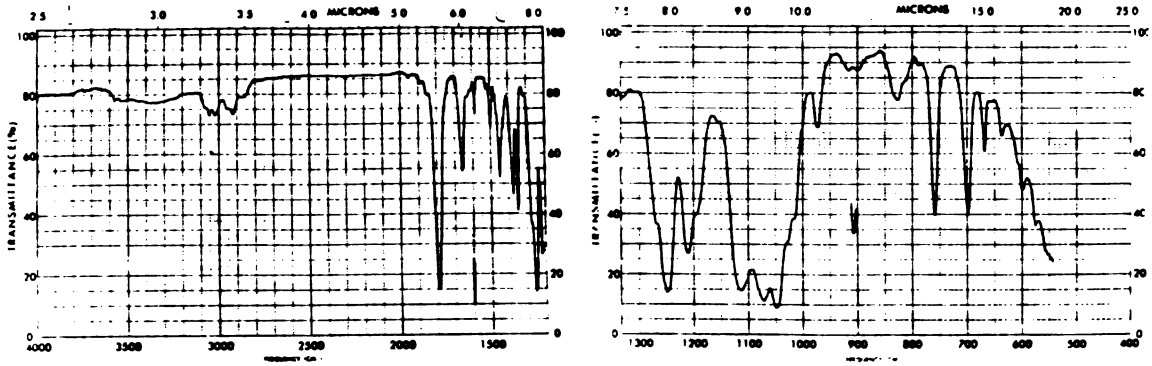

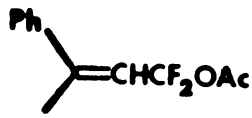

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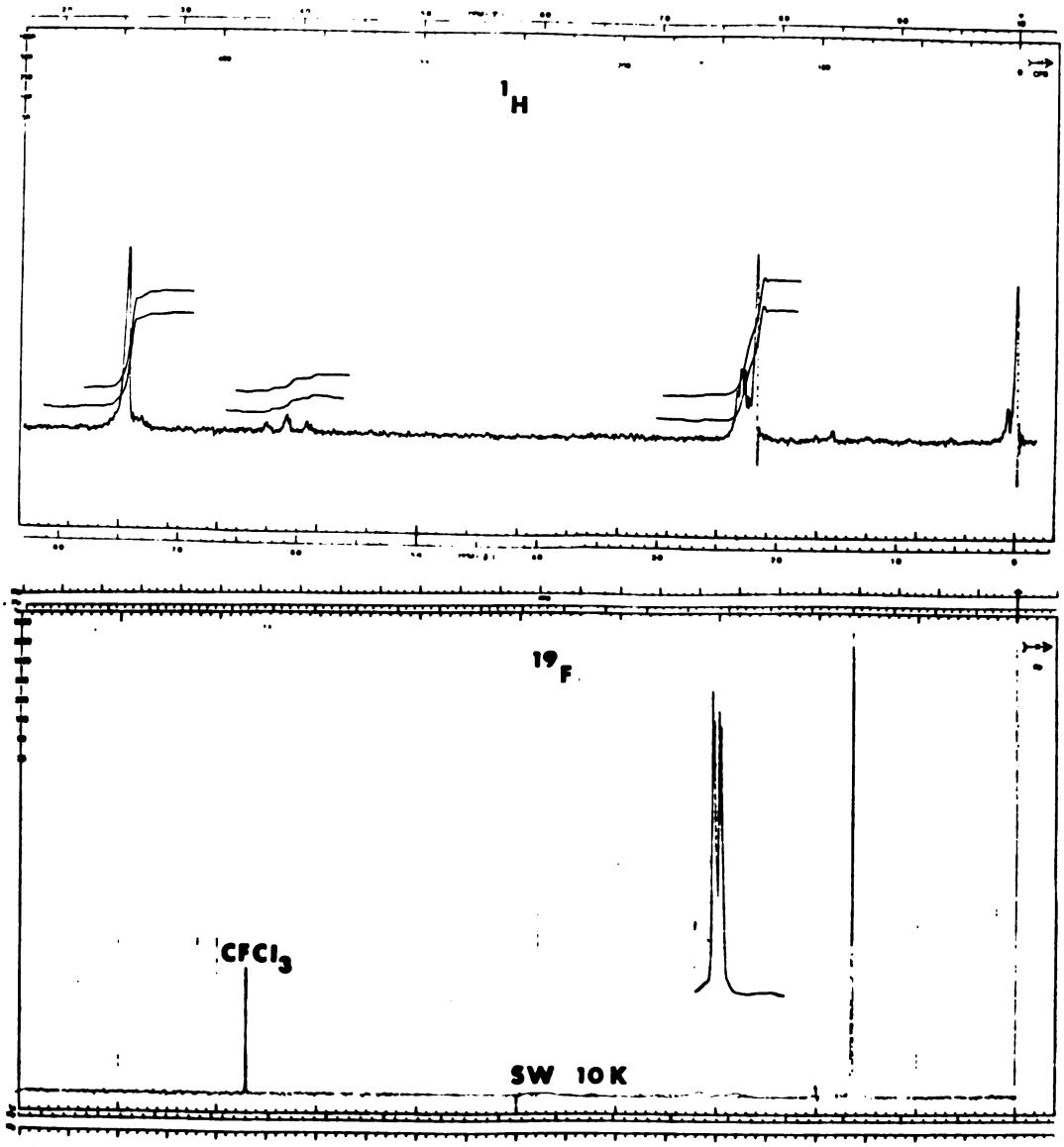
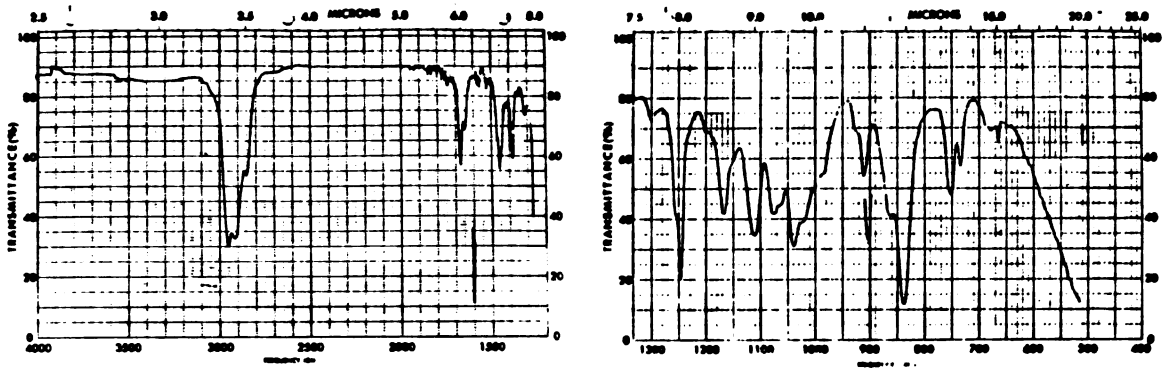
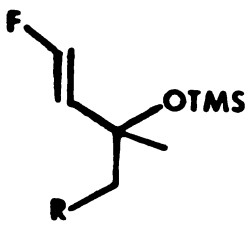
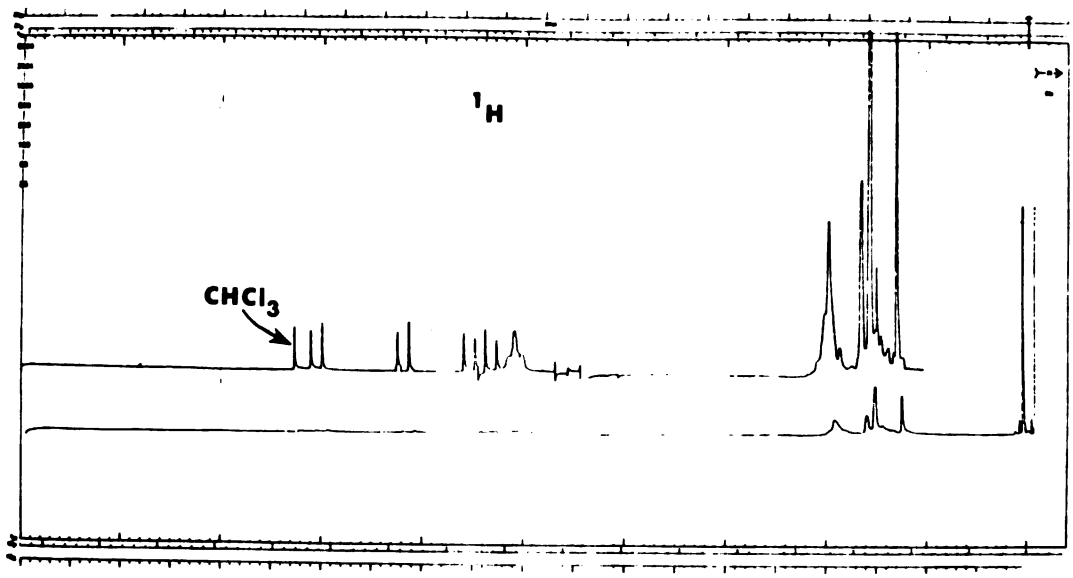
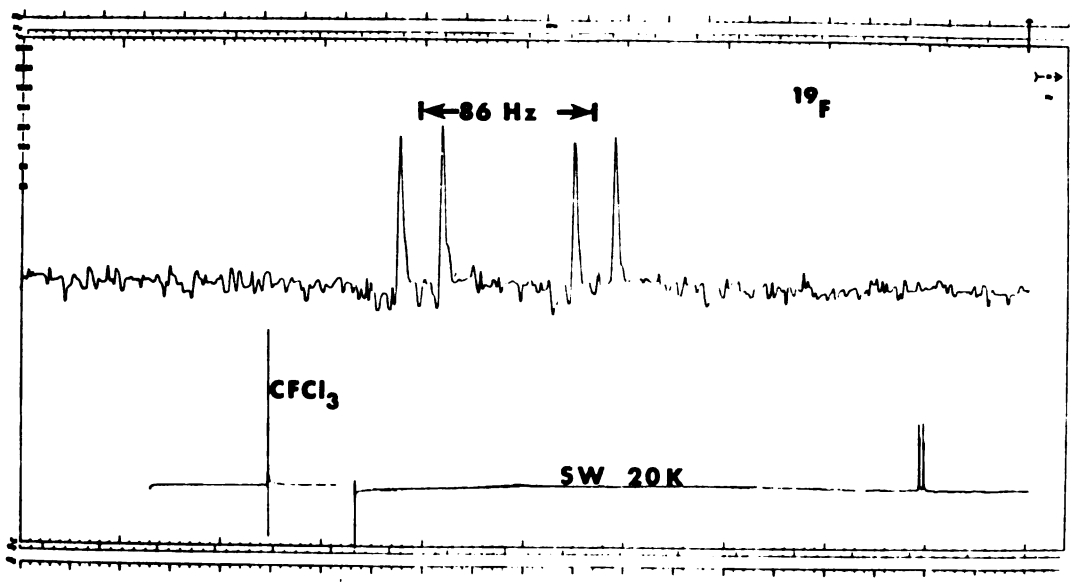


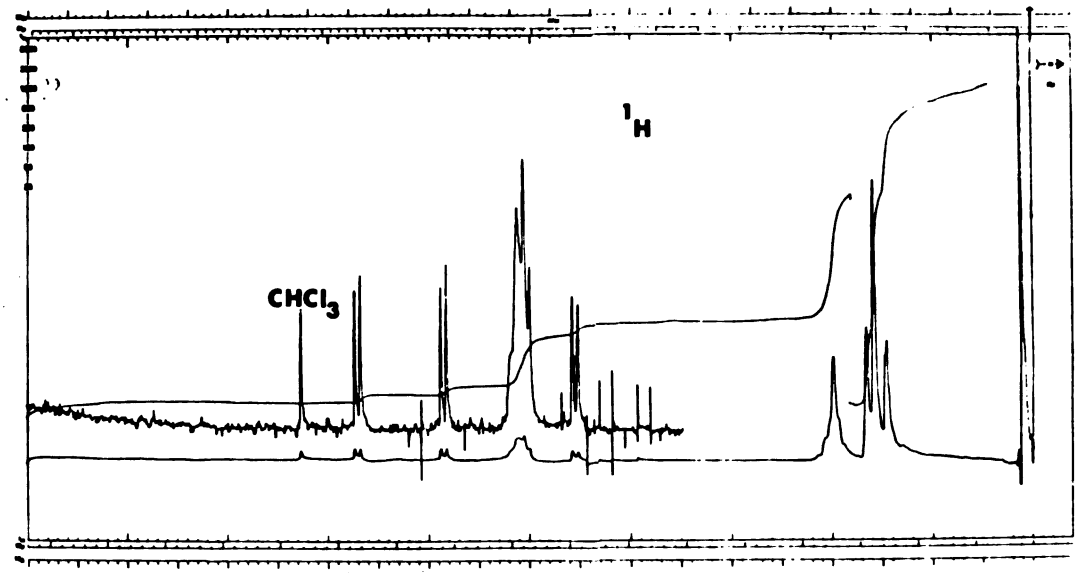


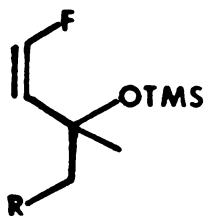


103a

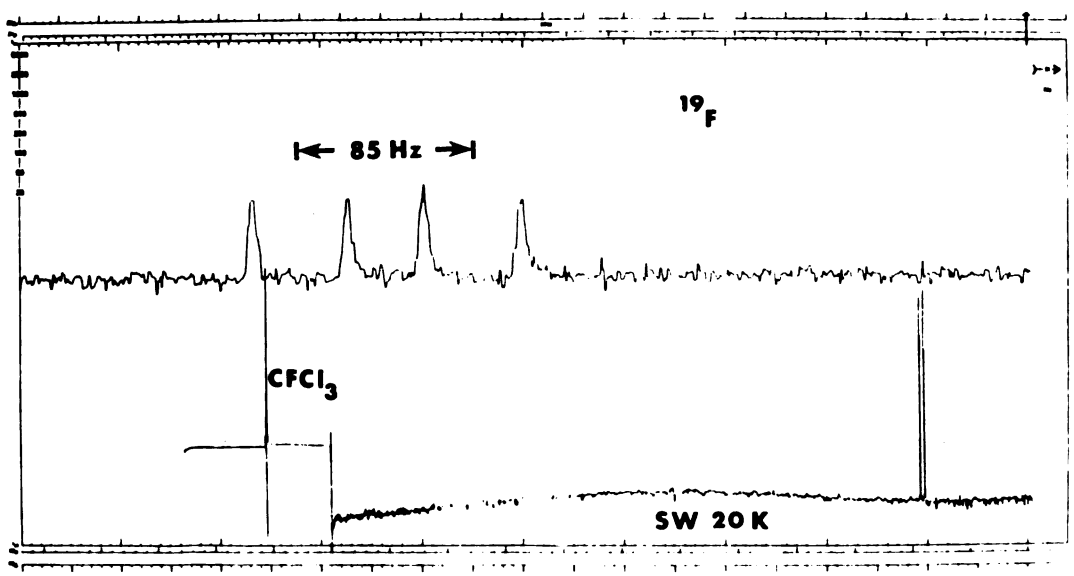


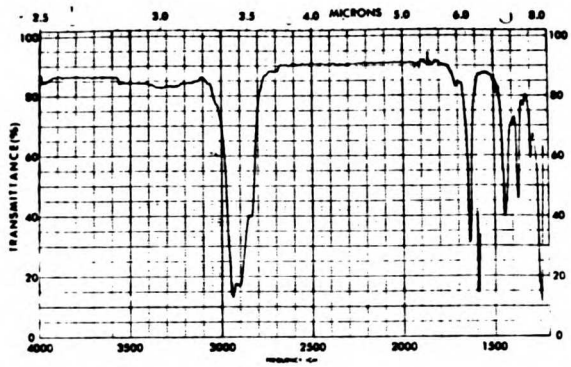


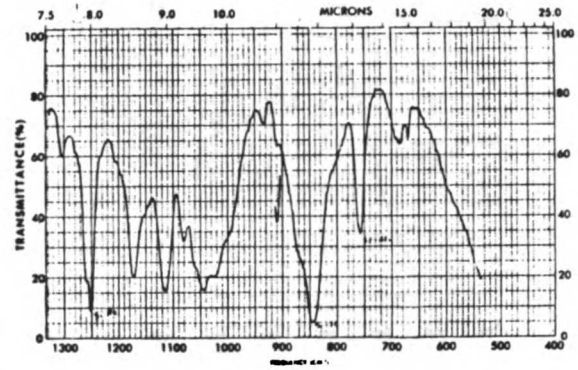


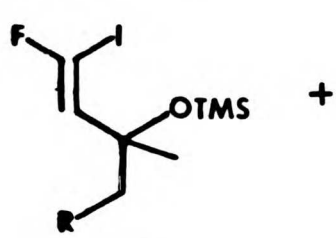


103b

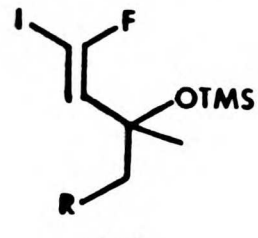



MICRONS
TRANSMITTANCE(%)
4000
3500
3000
2500
2000
1500

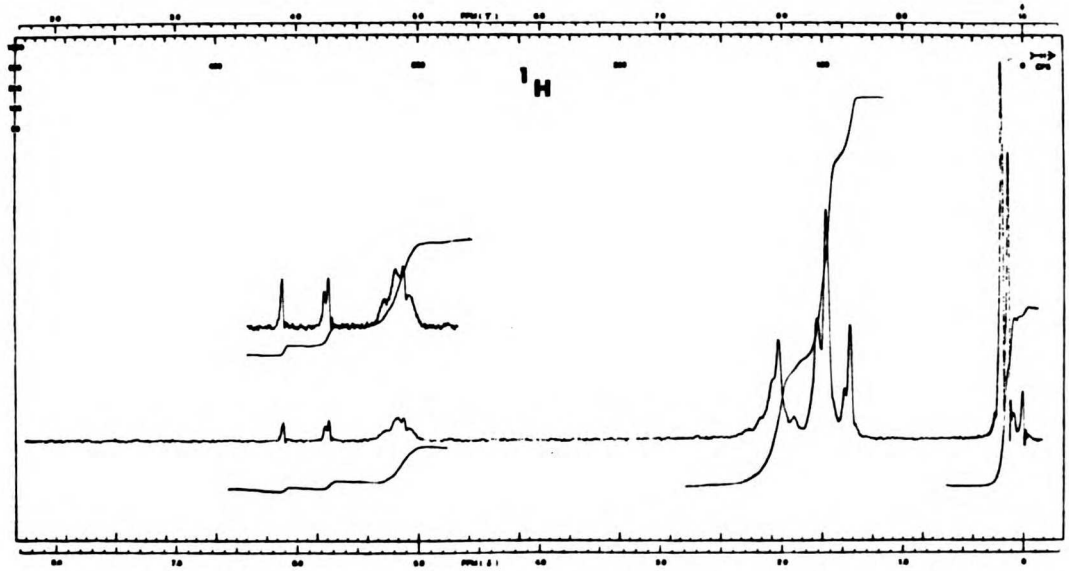

MICRONS
TRANSMITTANCE(%)
1300
1200
1100
1000
900
800
700
600
500
400

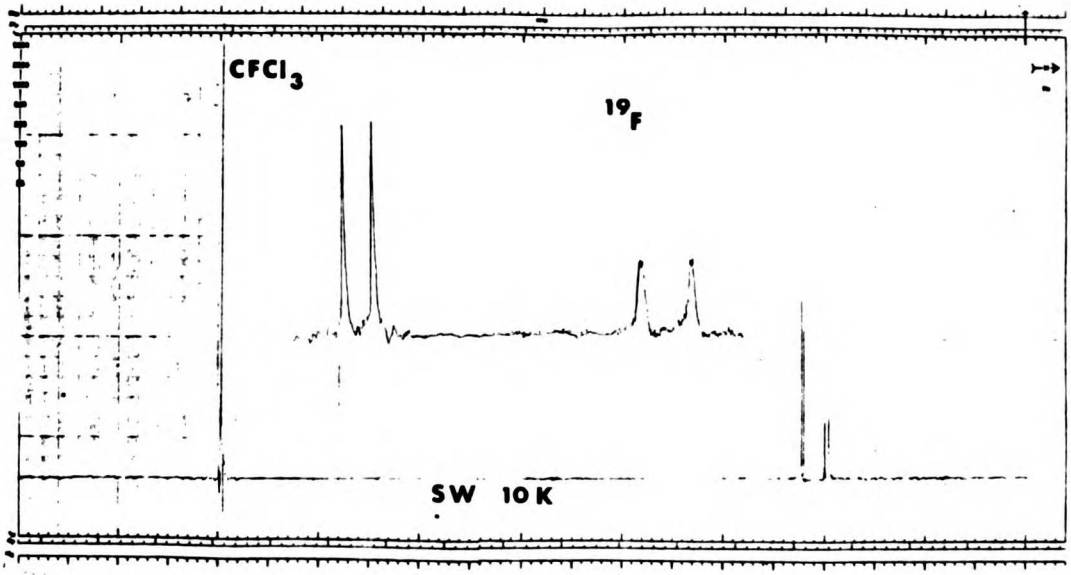

F
I
OTMS
R

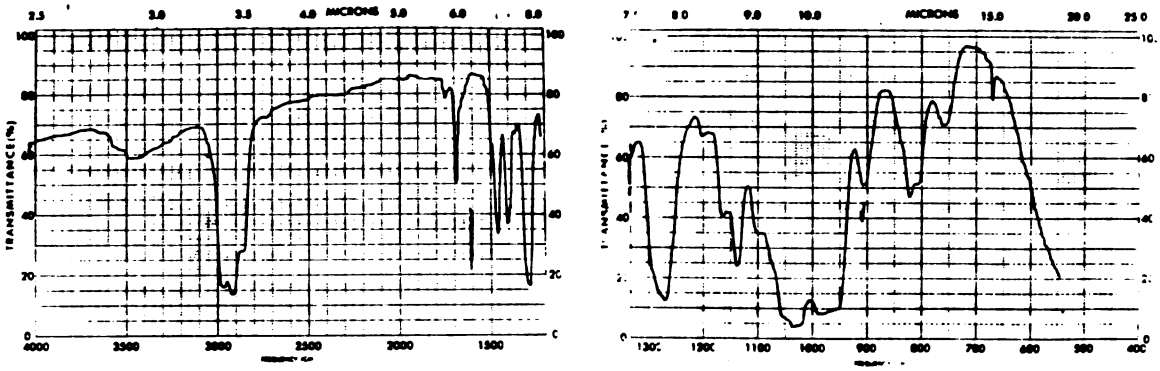
+

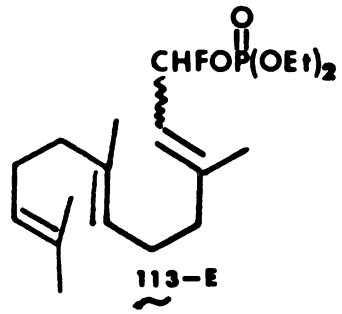

I
F
OTMS
R

104a ~ 104b ~

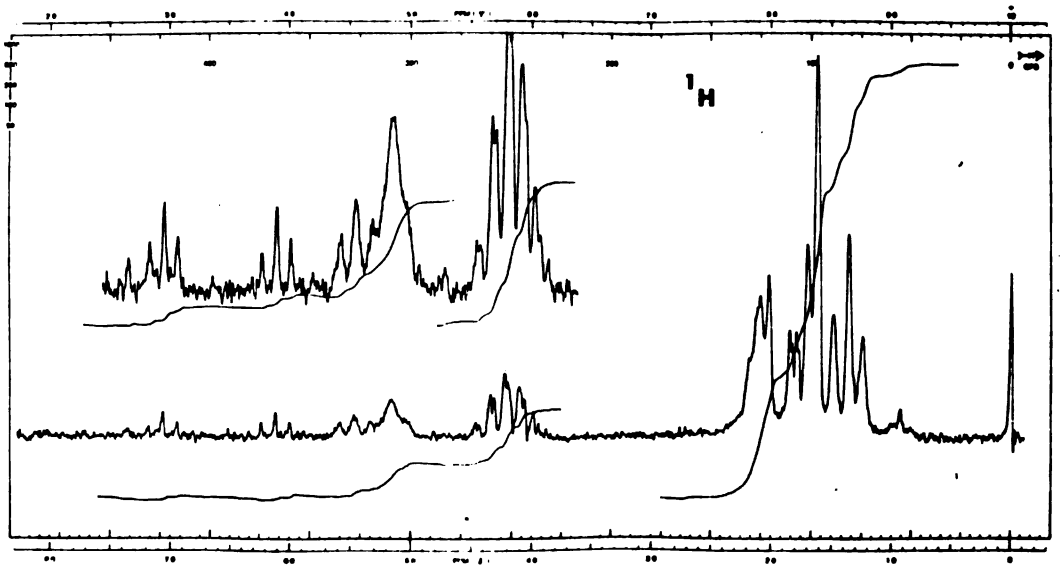

1H

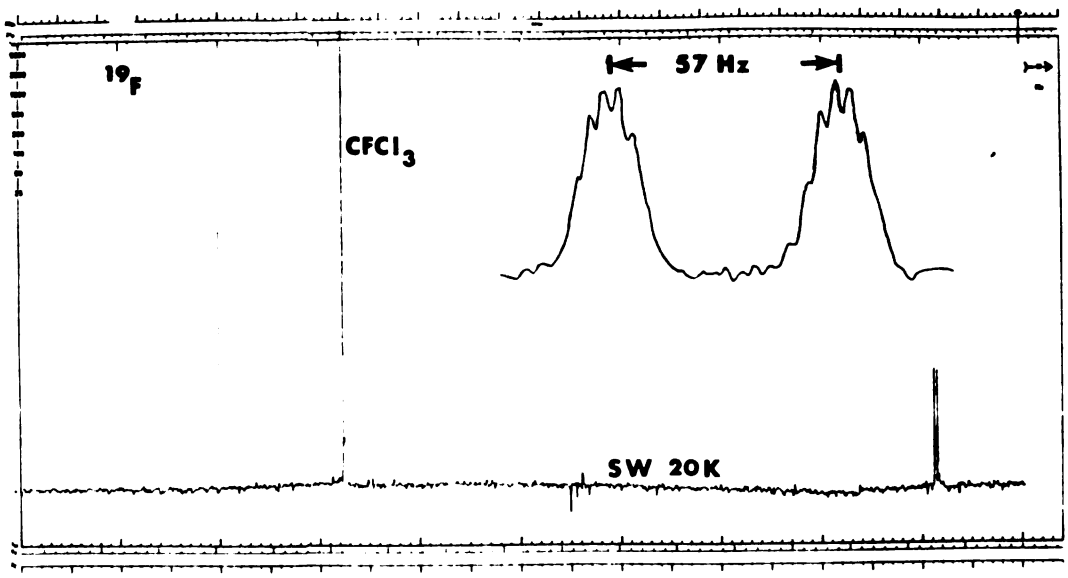

CFCl3
19F
SW 10K

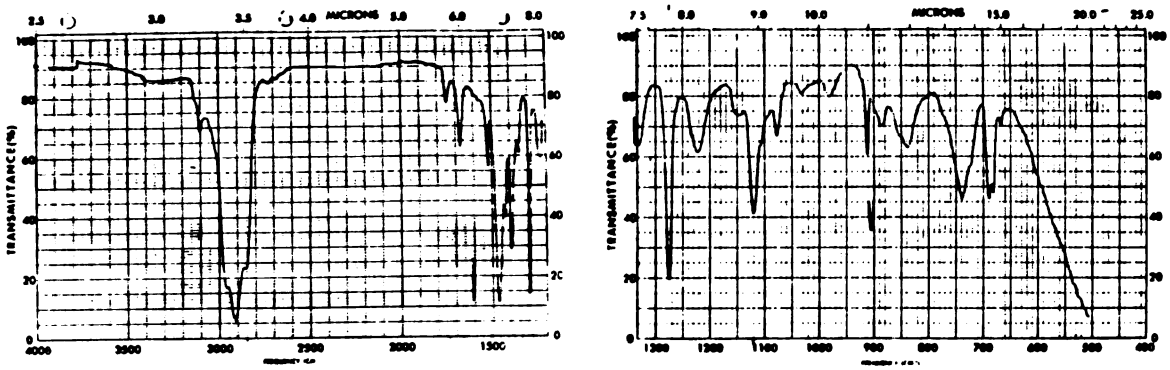


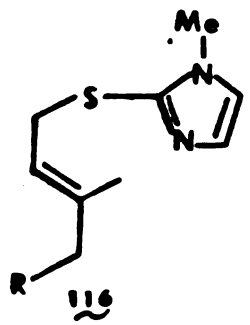


113-E

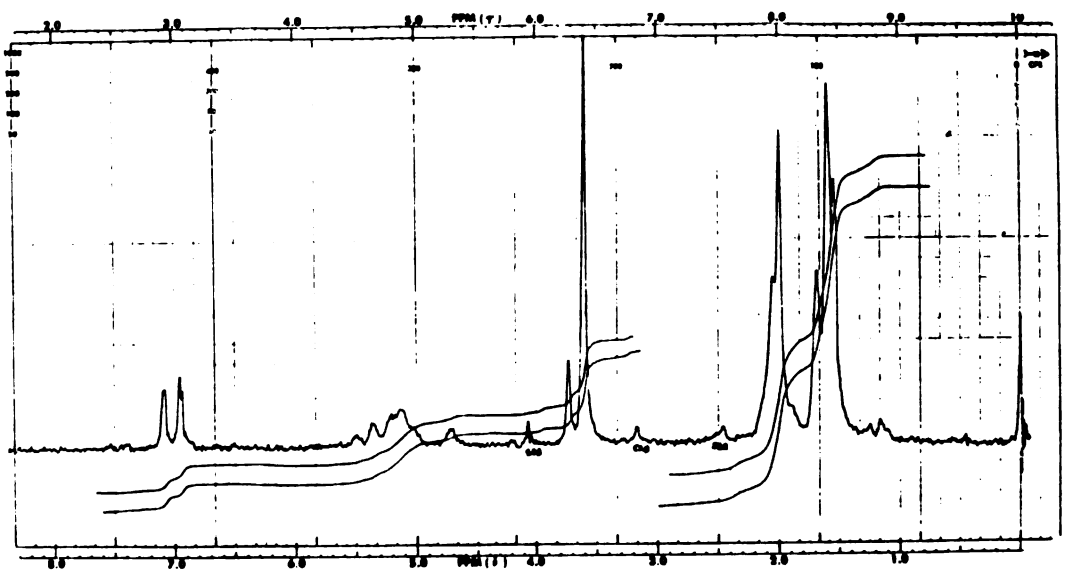


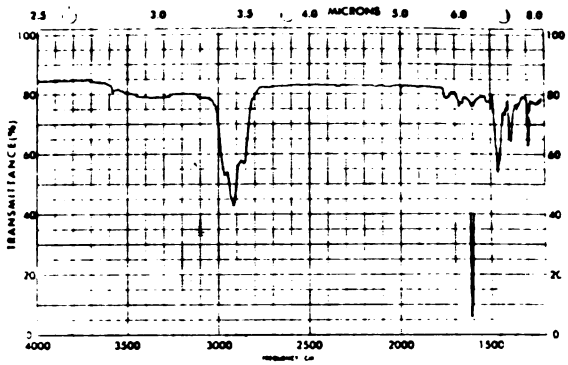


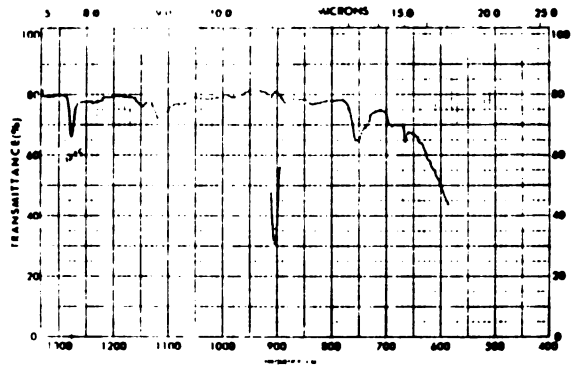


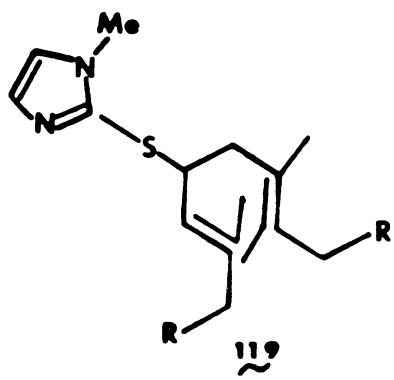


116

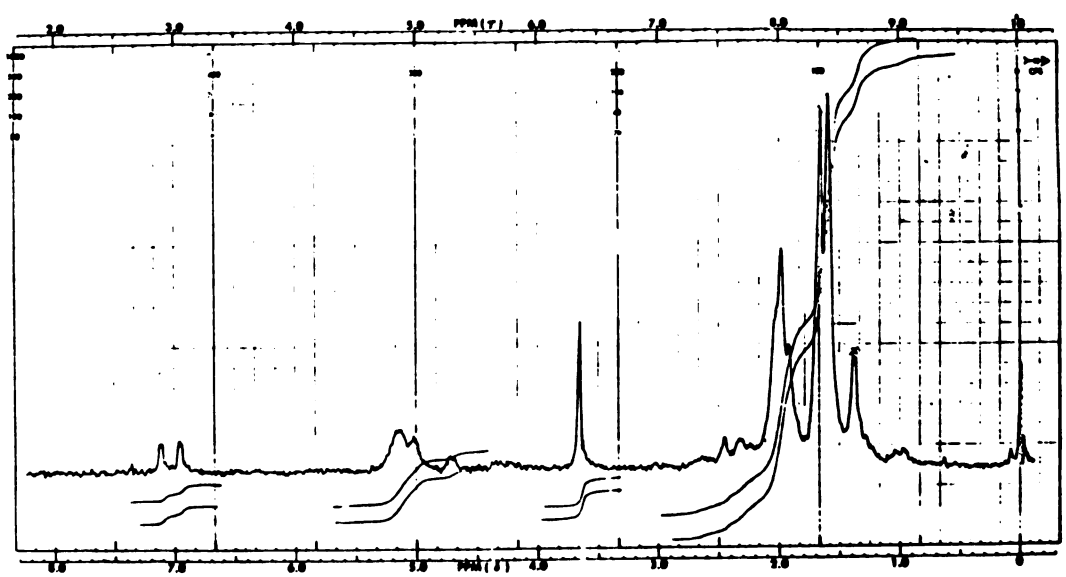


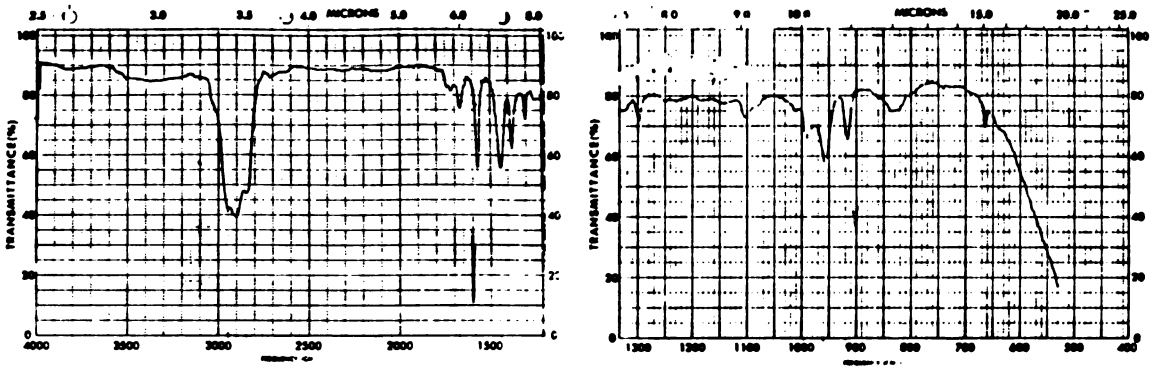


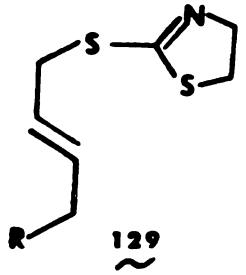




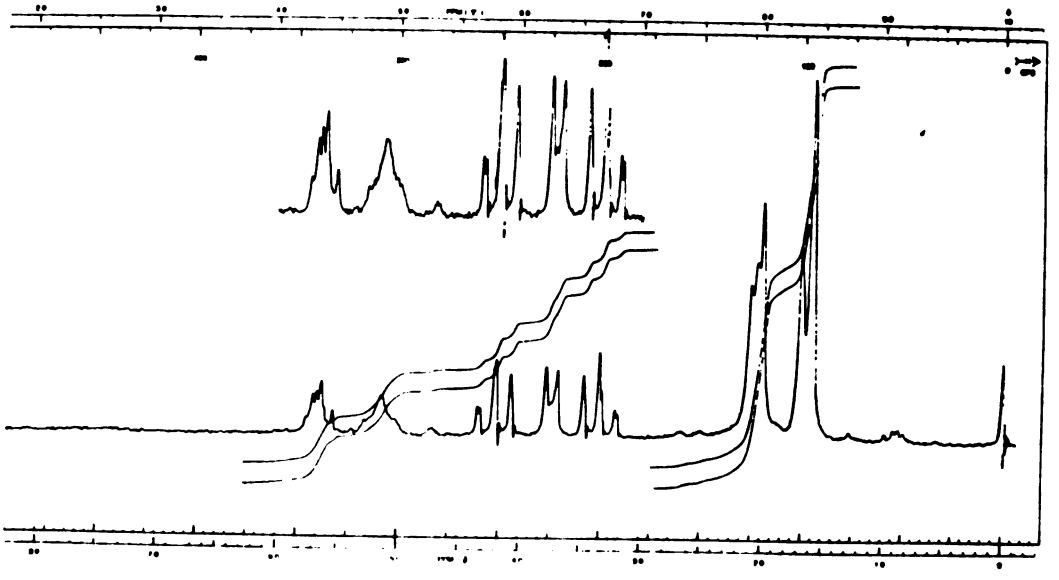
119

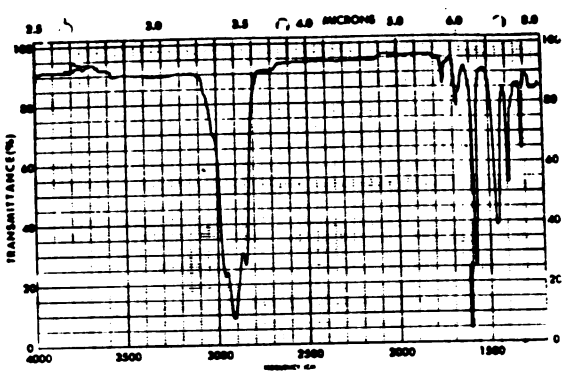


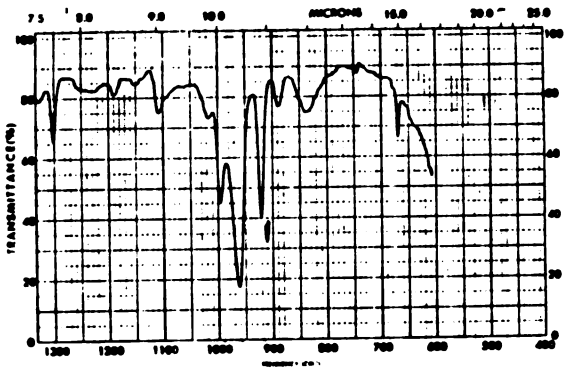

MICRONS
TRANSMITTANCE(%)
4000
3500
3000
2500
2000
1500
1300
1200
1100
1000
900
800
700
600
500
400

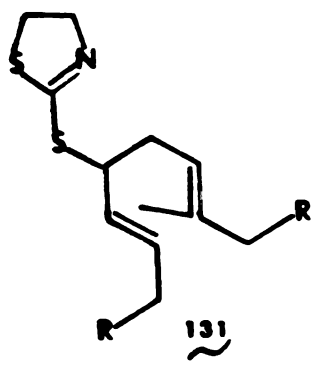

S
N
S
R

129

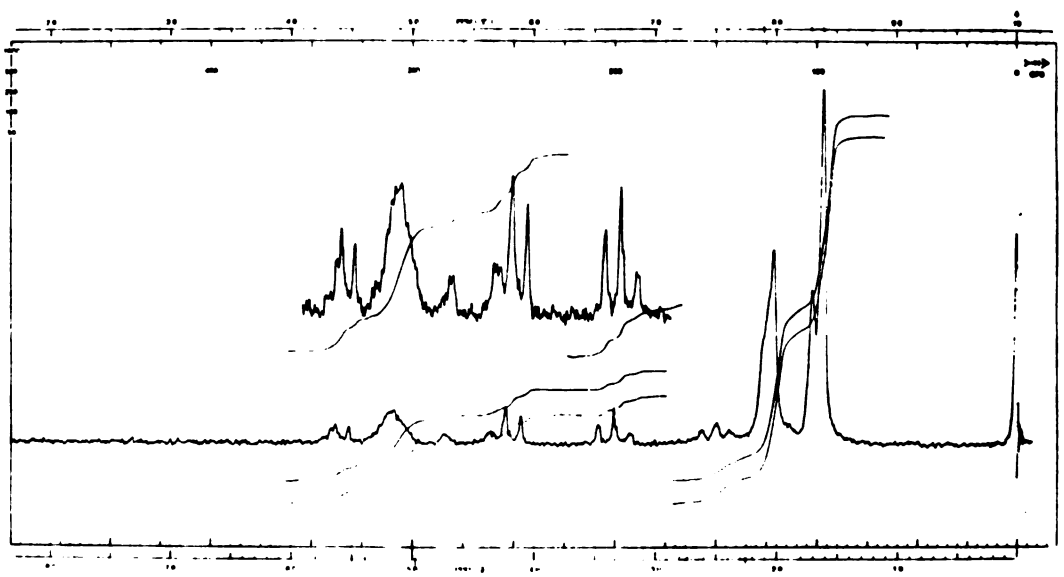


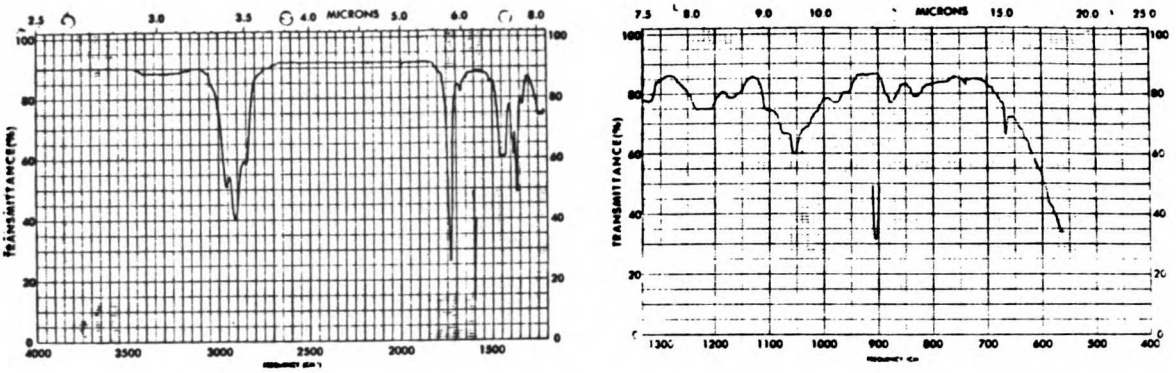


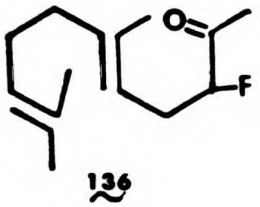




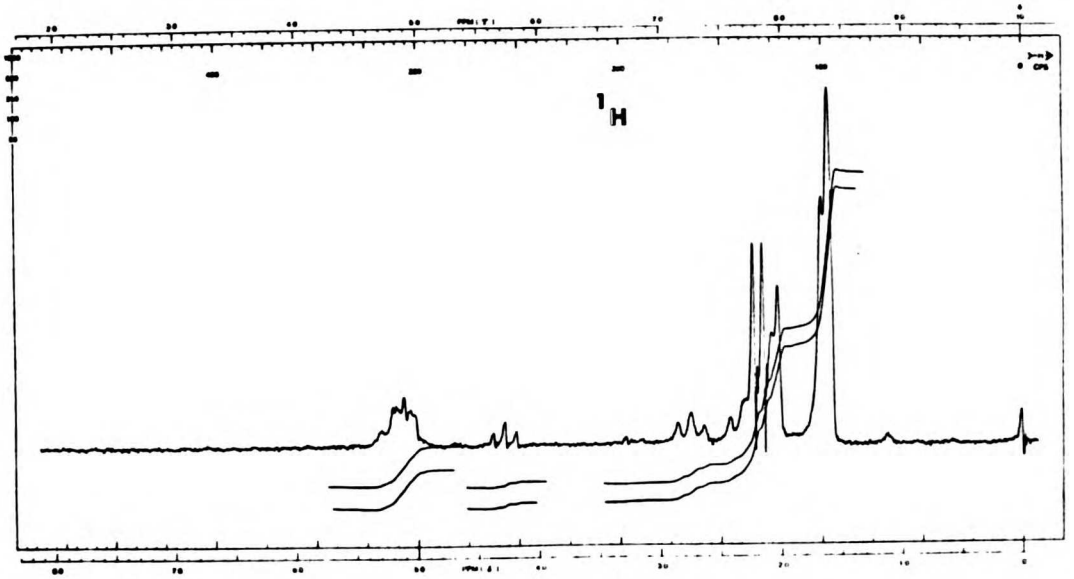
131

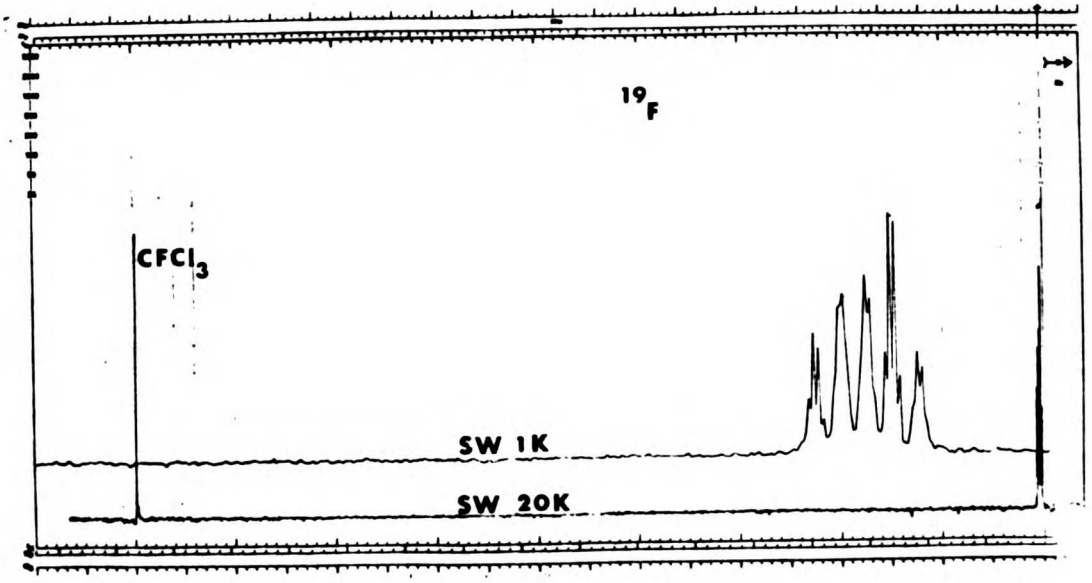


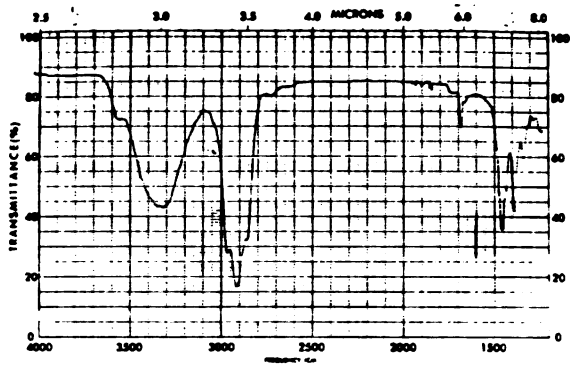

MICRONS
TRANSMITTANCE(%)
MICRONS
TRANSMITTANCE(%)

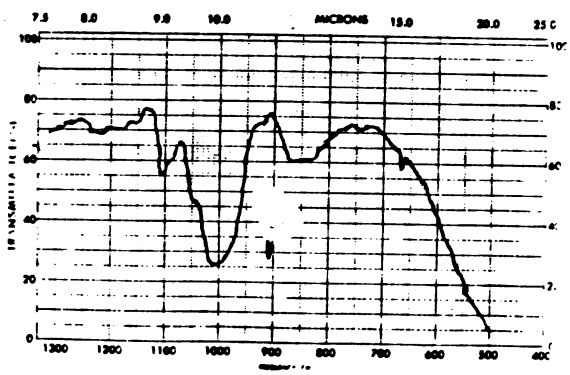

O
F

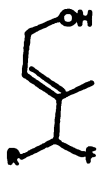
136


1H

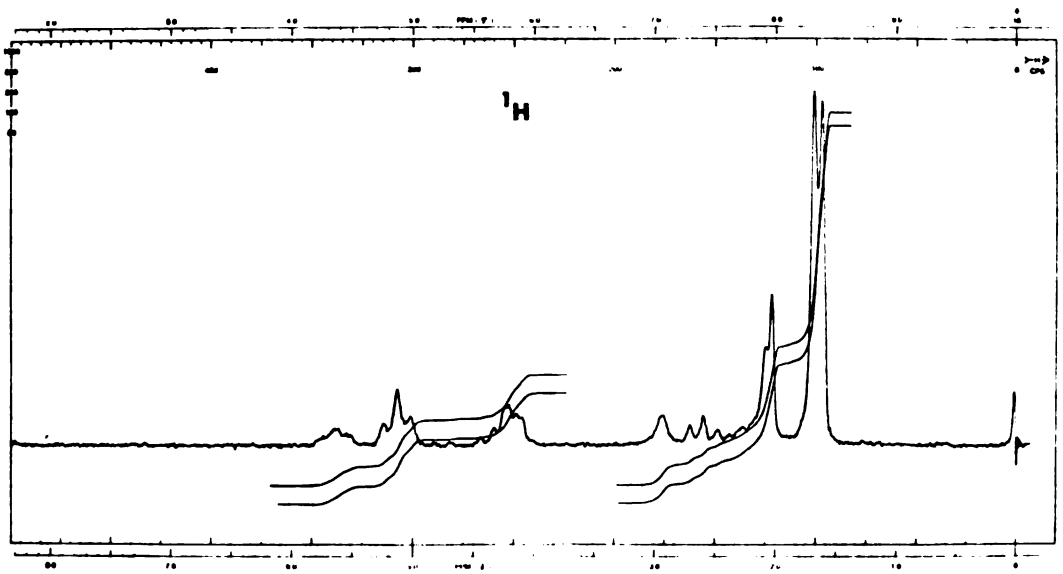

19F
CFCl3
SW 1K
SW 20K

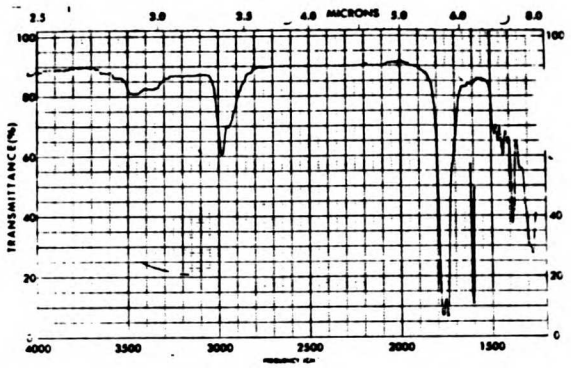


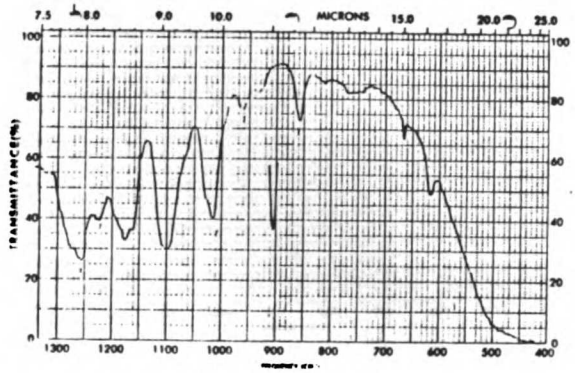


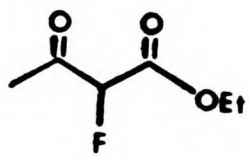


137

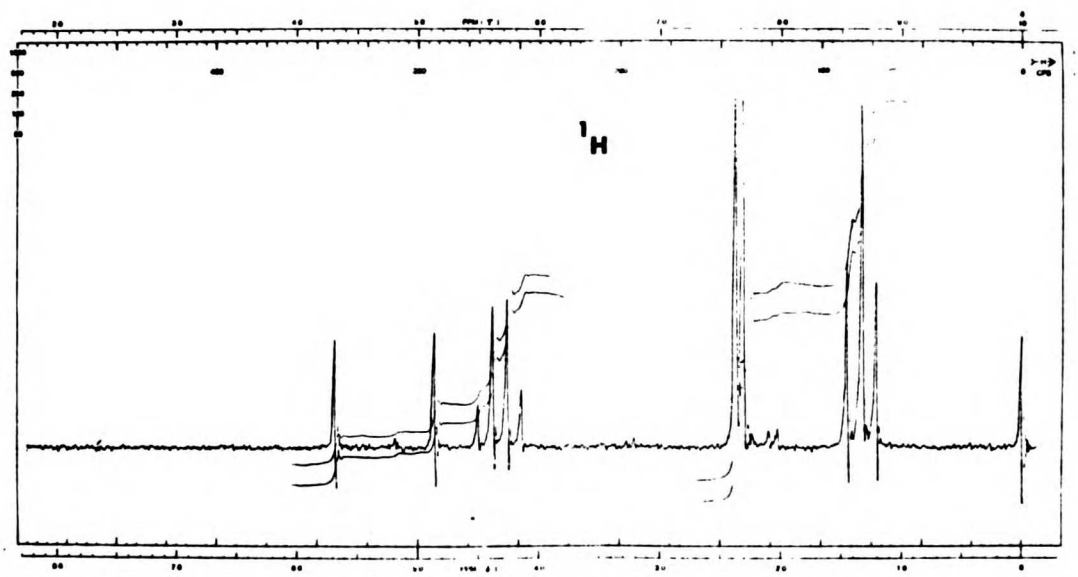


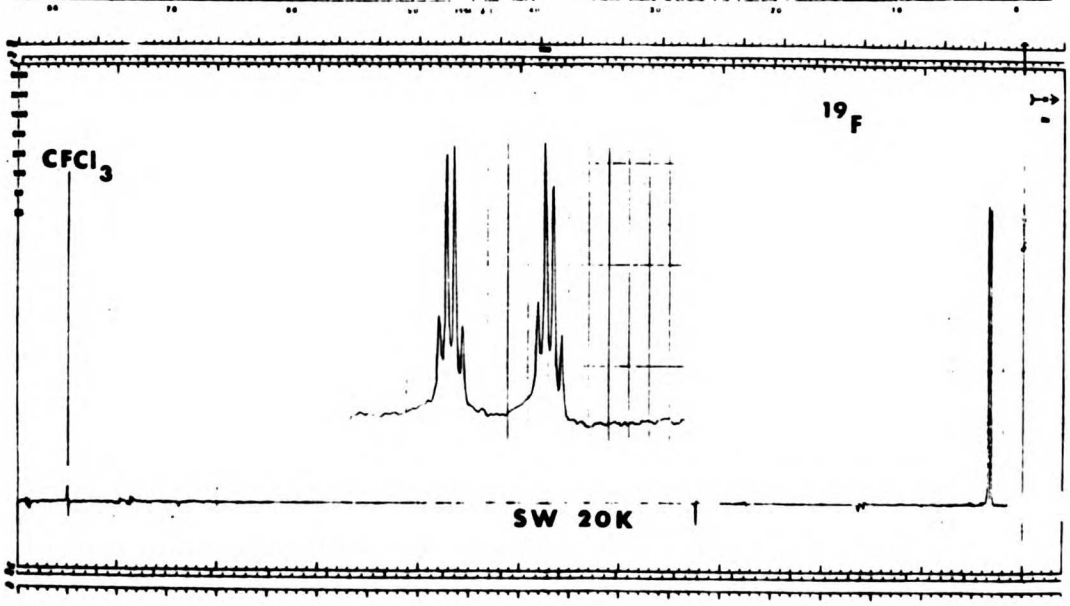

MICRONS
TRANSMITTANCE(%)
4000
3500
3000
2500
2000
1500

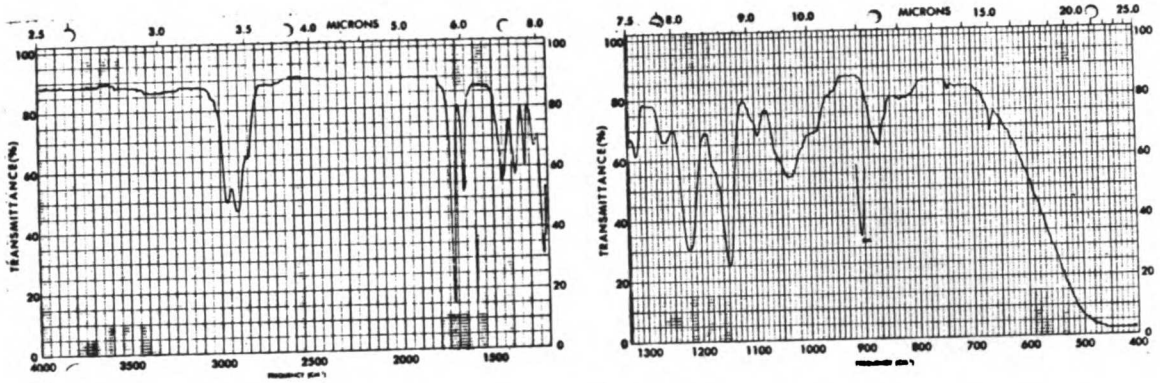

MICRONS
TRANSMITTANCE(%)
1300
1200
1100
1000
900
800
700
600
500
400

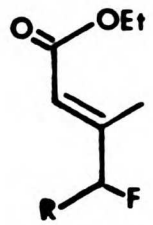

OEt
F

138

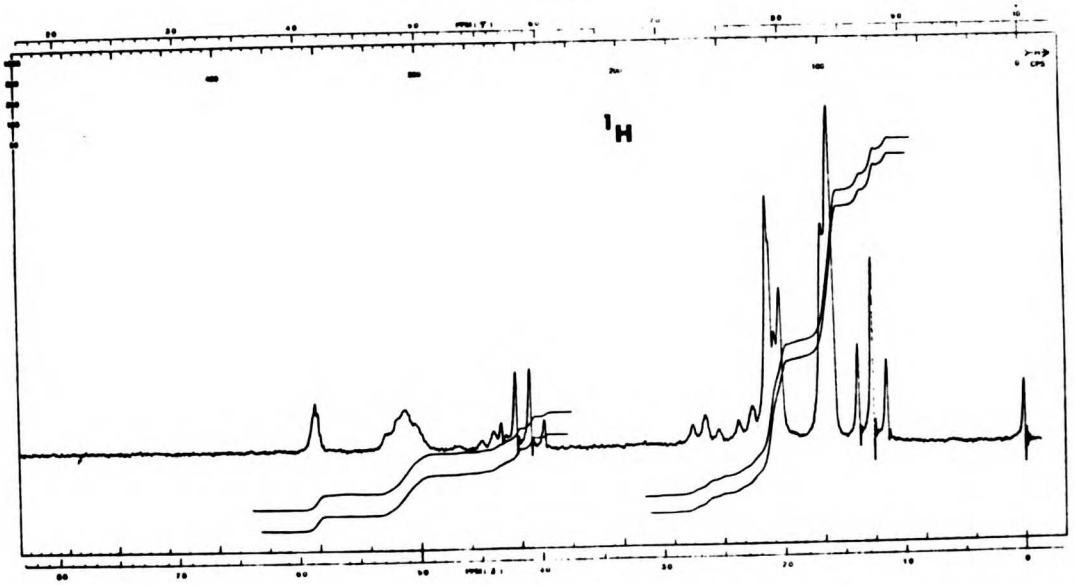

1H


19F
CFCl3
SW 20K


MICRONS
TRANSMITTANCE(%)
MICRONS
TRANSMITTANCE(%)


O
OEt
R
F

140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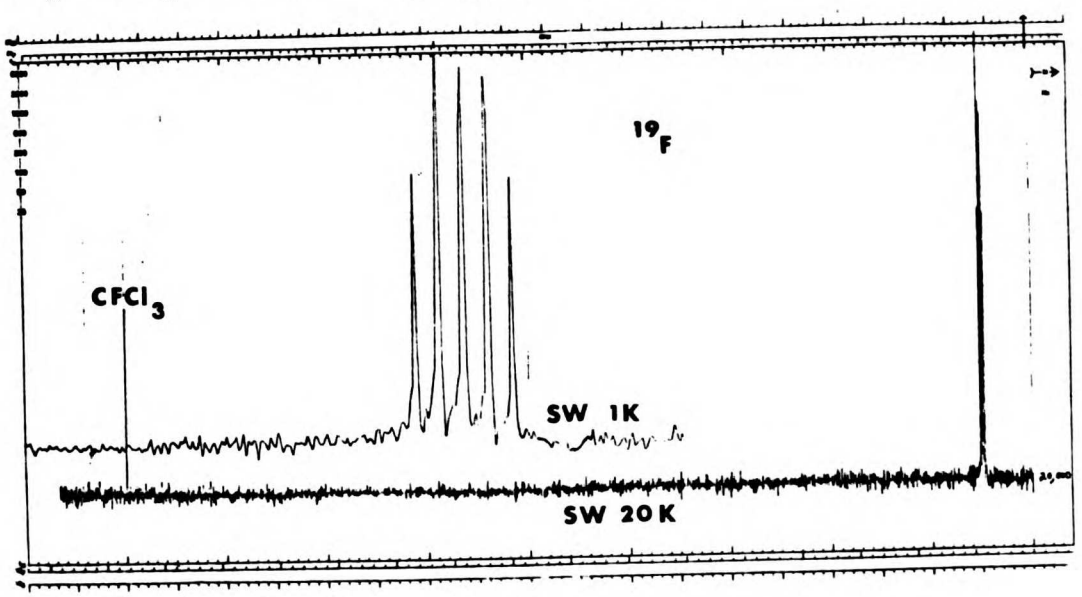
^{19}F
$CFCl_3$
SW 1K
SW 20K