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AN APPROACH TO THE SYNTHESIS OF PYRANS

A Thesis

Presented to

The Faculty of the Department of Chemistry

The College of William and Mary in Virginia

In Partial Fulfillment

Of the Requirements for the Degree of

Master of Arts

---

by

Thomas F. Ball III

1984

APPROVAL SHEET

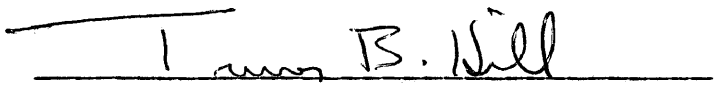
This thesis is submitted in partial fulfillment of the requirements for the degree of

Master of Arts

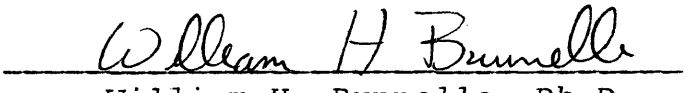
Thomas F.Ball III

Approved, August 1984

David W. Thompson, Ph.D.



Trevor B. Hill, Ph.D.



William H. Bunnelle, Ph.D.

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ACKNOWLEDGEMENT

The author wishes to express his sincere appreciation to Professor David W. Thompson for his direction and encouragement in both the laboratory and classroom, and throughout the writing of this thesis. He also would like to thank Professor William H. Bunnelle for the hours of help and advice throughout the last year and for proof reading this paper. A special thanks is also extended to Sharon Jones and Louise Menges for their valuable assistance in the preparation of the final draft of this work.

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ABSTRACT

We have developed an approach to the synthesis of cyclic ethers involving Lewis acid promoted cyclizations of acetals of homoallylic and homopropargylic alcohols. The purpose of this study was to further investigate this synthesis in order to determine the scope of this reaction as well as gain a greater mechanistic understanding of it.

Various acetals derived from ethyl vinyl ether, MEM chloride, and dihydropyran were prepared using 3-butyn-1-ol, 3-buten-1-ol, 1-allylcyclohexanol, and 1-propargylcyclohexanol. These starting acetals included 2-(3-butyn-1-oxy)tetrahydropyran, 2-(3-buten-1-oxy)tetrahydropyran, 1-(2-methoxyethoxy)-methoxy-3-butyne, 1-(2-methoxyethoxy)methoxy-3-butene, 1-(2-methoxyethoxy)methoxy-1-allylcyclohexane, 1-(2-methoxyethoxy)-methoxy-1-propargylcyclohexane, 1-(1-ethoxyethoxy)-1-allylcyclohexane, and 1-(1-ethoxyethoxy)-1-propargylcyclohexane.

The acetals were cyclized to their corresponding pyrans using titanium tetrachloride in methylene chloride at temperatures ranging from 0 C to -95 C. In general, the yields were good, and, with the exception of the product from 1-(1-ethoxyethoxy)-1-propargylcyclohexane, the pyrans were easily isolated and characterized by NMR spectroscopy.

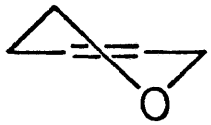
The pyrans synthesized in this study included 4-chloro-2-(4-hydroxybutyl)-5,6-dihydro-2H-pyran, 4-chloro-2-(4-hydroxybutyl)tetrahydropyran, 4-chloro-5,6-dihydro-2H-pyran, 4-chlorotetrahydropyran, 4-chloro-oxaspiro[5.5.]undecane, 4-chloro-oxaspiro[5.5.]-3-undecene, and 4-chloro-2-methyl-oxaspiro[5.5.]undecane.

AN APPROACH TO THE SYNTHESIS OF PYRANS

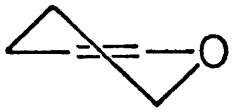
INTRODUCTION

The chemistry of five- and six-membered heterocyclic compounds is not only very interesting but also very important as many natural products have been shown to incorporate this basic structural feature (see Scheme I).[1,a,b,c] The research reported in this thesis is oriented toward the synthesis of one type of heterocyclic species, six-membered cyclic ethers, which are commonly known as pyrans. Several pyran structures are listed below.

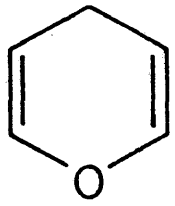
tetrahydro-pyran



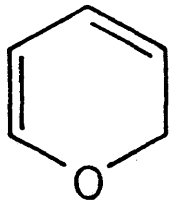
5,6-dihydro-2-H-pyran



3,4-dihydro-2H-pyran



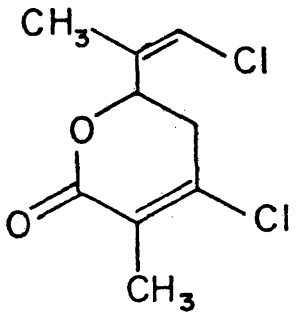
4-H-pyran



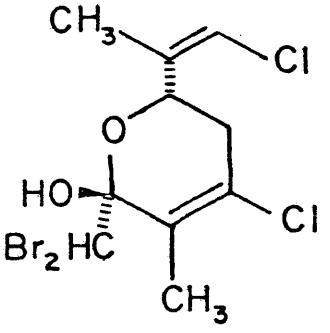
2-H-pyran

Insight into the origin of this research project can be gained by examining the past work of Thompson and coworkers. This research has been directed toward the carbometallation of γ-alkynols using organoalane-titanium reagent systems with a series of papers having been published on this subject.[2] The selectively substituted homoallylic alcohol products of this carbometallation reaction have been produced in good yields. An example of this reaction can be found in Scheme II where the product is (Z)-4-methyl-3-hexen-1-ol (1).

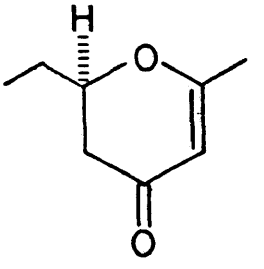
Scheme I



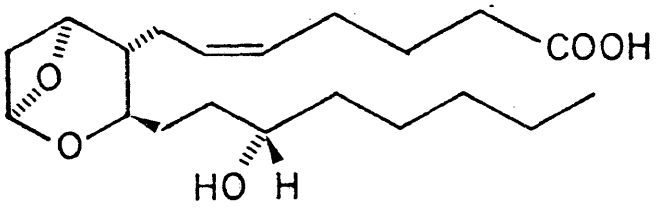
costatolide[1a]



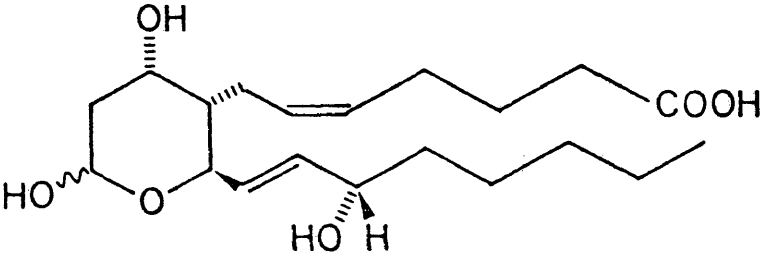
costatone[1a]



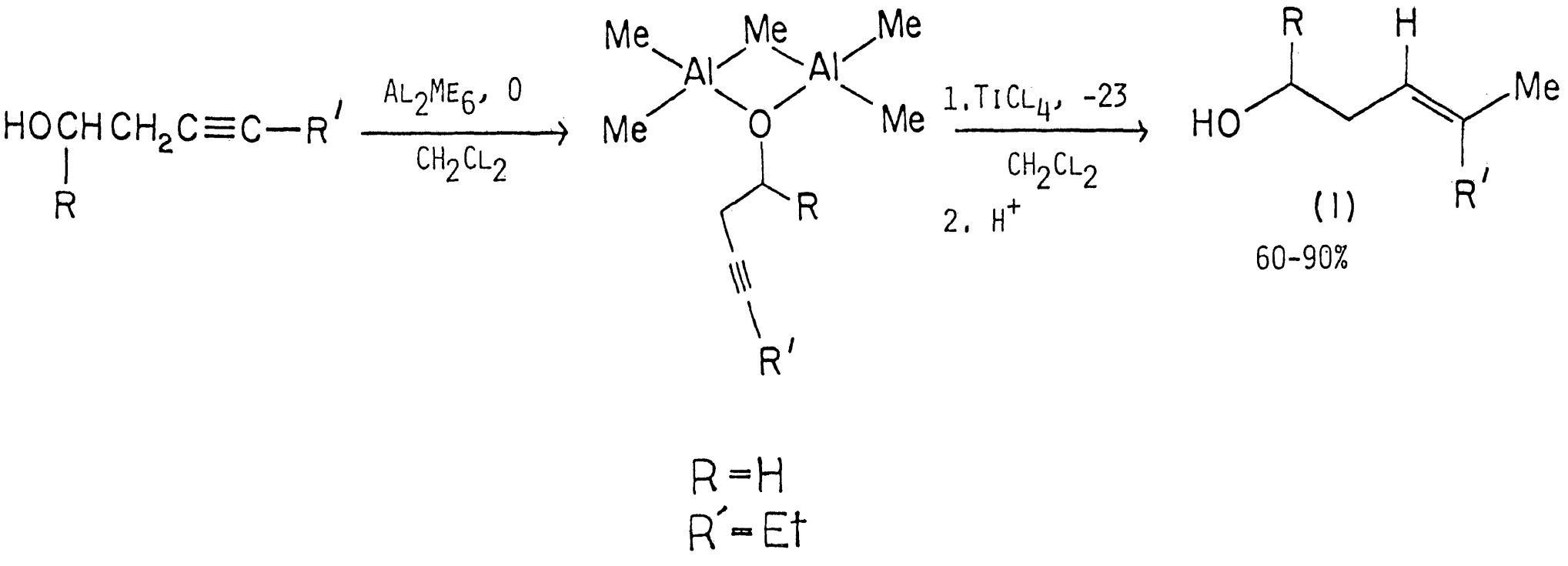
hepaialone[1b]



thromboxane A_2[1c]

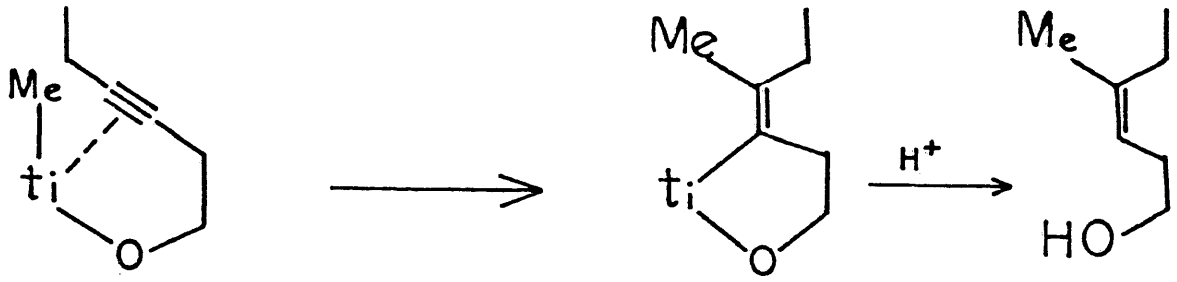


thromboxane B_2[1c]



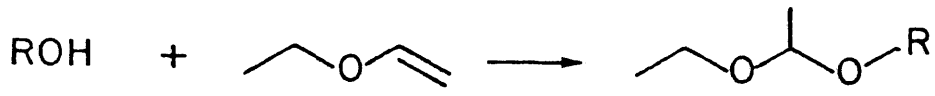
Scheme II. The $TiCl_4$-Al_2Me_6 based methylation of 3-hexyn-1-ol to give (Z)-4-methyl-3-hexen-1-ol.

In an attempt to extend this carbometallation reaction to the synthesis of allylic alcohols, Thompson found that β-alkynols do not carbometallate. This can be explained if the carbometallation is assumed to be an intramolecular process as suggested by Thompson[3] as well as Richey and Moses.[4]



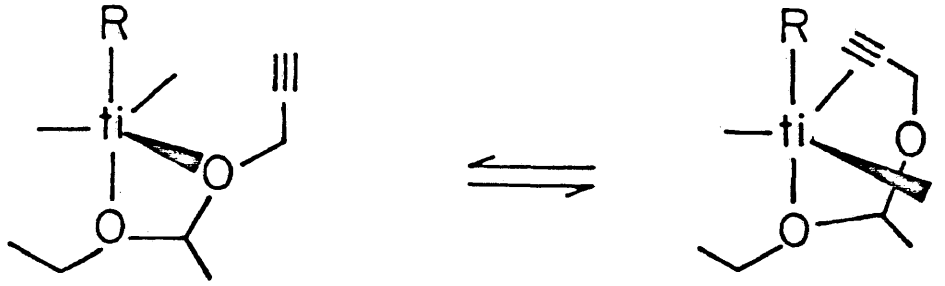
In this case the geometric constraints of the propargyl system would seem to prevent the alkyne group from approaching the titanium center in the proper fashion for titanium-methyl addition.

Hoping to solve the geometric problems effecting the propargyl system, Seamon and Thompson[5] attempted to carbometallate the ethylvinyl ether based acetals (shown below) of the propargyl alcohols rather then the alcohols themselves.



Since bidentate coordination of basic substrates to metal centers was known to occur, it was expected that the

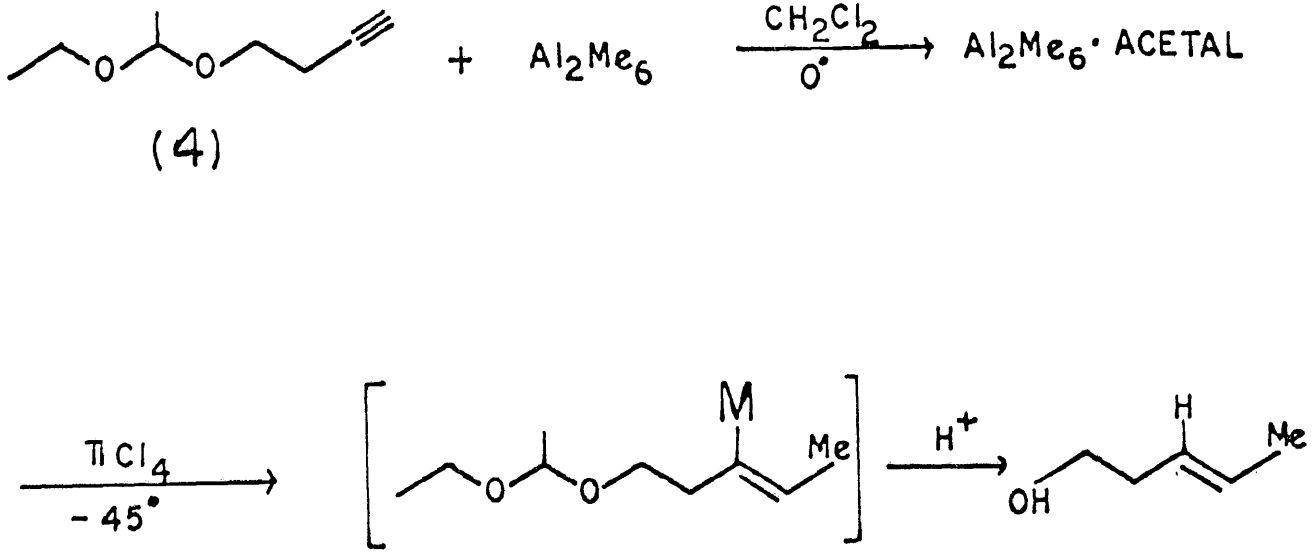
carbometallation of the ethylvinyl ether based acetal of propargyl alcohol would involve an intermediate such as (2) below.



(2) (3)

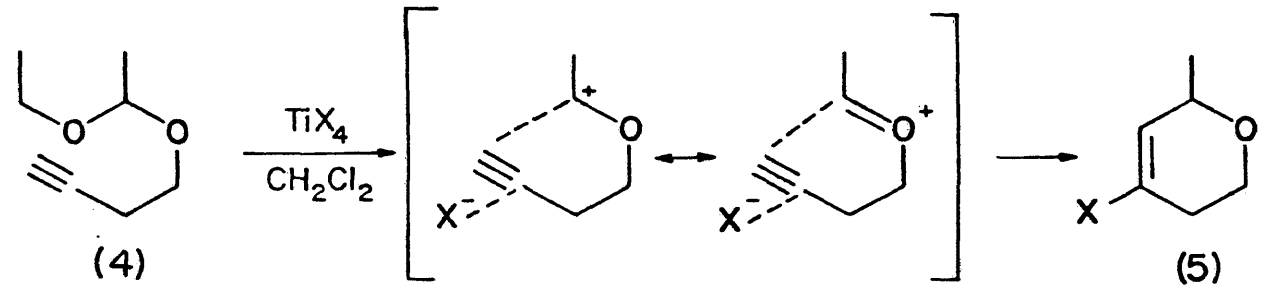
Species such as (2) are labile and, thus, at any given moment may exist as complex (3) which has the appropriate geometry for coordination to the metal and eventual insertion into the metal-alkyl bond.

The investigation involving acetals was begun with the synthesis, and attempted carbometallation, of the ethylvinyl ether based acetal of 3-butyn-1-ol in order to test the effect of the acetal using an alkynol that had been successfully carbometallated in a previous experiment. A stepwise description of the anticipated pathway of this reaction can be seen in Scheme III on the following page. However, when this reaction was carried out, no methyl-substituted alkenol was produced. Another attempt to carbometallate the acetal, this time by first reacting it with titanium tetrachloride and subsequently adding trimethylaluminum, also gave no methyl-substituted alkenol product. However, in the latter experiment a new product, 4-chloro-2-methyl-5,6-dihydro-2H-pyran (5) was produced in

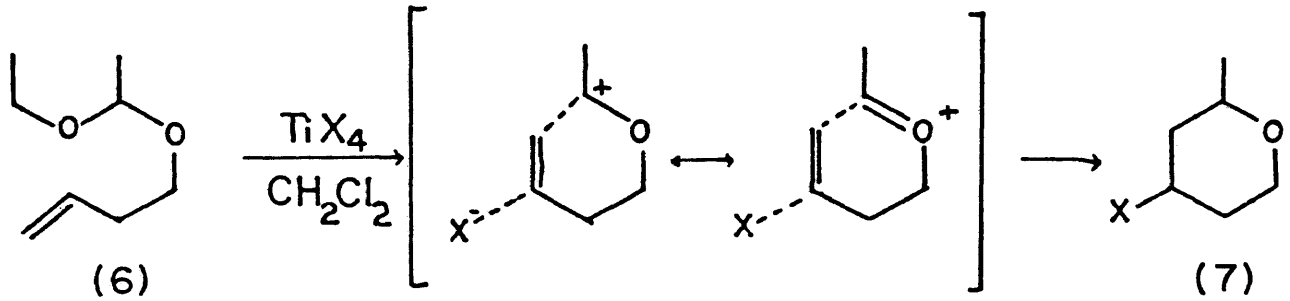


Scheme III. Attempted $TiCl_4$-Al_2Me_6 based methylation of the acetal formed from ethyl vinyl ether and 3-butyn-1-ol.

95% yield.[5,6] A reasonable reaction pathway is illustrated below.



Also, the ethylvinyl ether based acetal of 3-buten-1-ol (6) was cyclized to 4-chloro-2-methyltetrahydropyran (7).[5,6]



The research reported in this thesis represents an extension of these initial studies in an attempt to learn more about, and determine the scope of, this pyran synthesis. Included in this work is the first extension of the titanium tetrachloride promoted cyclization reaction to involve acetals from substrates other then ethylvinyl ether. Herein the cyclization of (2-methoxyethoxy)methyl (MEM) chloride and dihydropyran based acetals of 3-butyn-1-ol and 3-buten-1-ol to the corresponding pyrans were studied.

Also, after examining these simple systems, this cyclization reaction was extended to the synthesis of more complicated "spiro" compounds. Thus, the cyclization of the ethylvinyl ether and MEM chloride based acetals of 1-allylcyclohexanol and 1-propargylcyclohexanol were investigated. In addition, studies on the effect of reaction time, reaction temperature, stoichiometries, and addition sequence were conducted on the cyclizations involving the two dihydropyran based acetals.

LITERATURE REVIEW

Because our research focuses on development of a general method for the synthesis of tetrahydropyrans and 5,6-dihydro-2H-pyrans, it seemed initially that a critical review of other work directed toward the synthesis of these, and other, five- and six-membered cyclic ethers was in order. However, the literature in this area is voluminous[7,8,9], but with most of the reported syntheses of cyclic ethers not involving chemistry which is similar to that involved in our synthesis. Thus this review will be limited to a discussion of two areas of research which are especially related to our synthetic approach.

The first area to be discussed will deal with modifications of the chemistry of the Prins reaction[10] investigated by Stapp.[11,12,13] This work involves a mechanistically similar synthesis of compounds which are analogous to those prepared by our method.

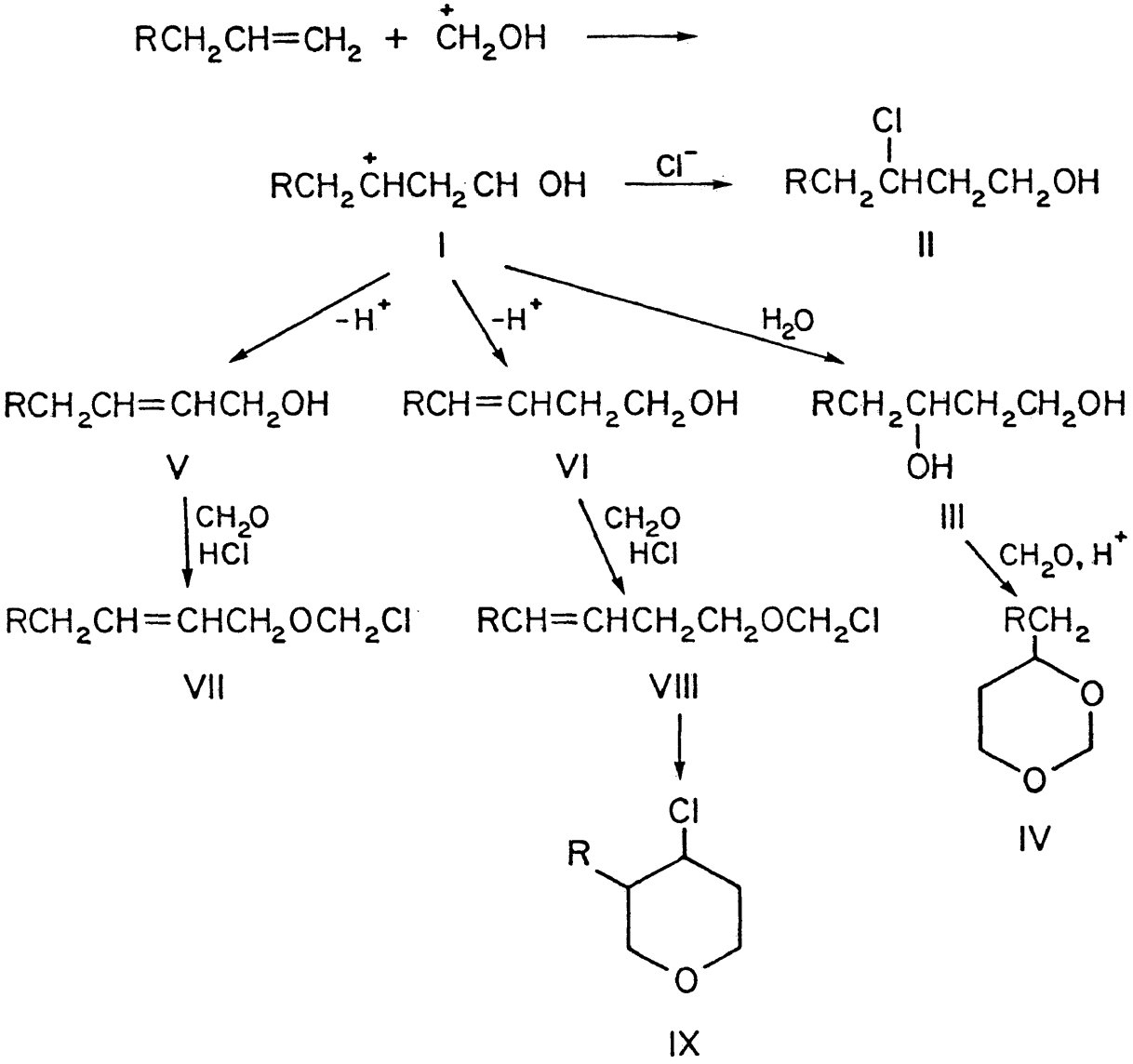
The second body of literature to be discussed will be the work of Johnson and coworkers on biomimetic polyene cyclizations leading ultimately to steroid structures.[19-36] Although their cyclization products are not cyclic ethers, the work involves a similar cyclization mechanism, and is therefore germane to our interests.

Arrundale[14a] and Frazen[14b] have defined the Prins reaction as "those processes which proceed between an olefin

and a carbonyl-containing compound under the acidic conditions existing in aqueous or acetic acid solutions of sulfuric or hydrochloric acid." A wide variety of products have been obtained as discussed below. Also, there have been modifications of the Prins reaction utilizing Lewis acid or thermal conditions to promote the reaction of olefins and carbonyl compounds.[10] In any case this reaction begins with the stepwise addition of a protonated carbonyl species, such as that derived from formaldehyde, to the nucleophilic center in the olefin (see Scheme IV).

Scheme IV shows the different pathways available to the intermediate carbonium ion (I) once it is formed (whether or not this is a free carbonium ion is immaterial at this point). If we assume that the reaction occurs in an aqueous solution of hydrogen chloride, then ion (I) may pick up a chloride ion to form the corresponding chloro alcohol (II). The carbonium ion (I) may also react with water to form a 1,3-diol (III) which can react with additional protonated carbonyl species to yield a 1,3-dioxane (IV). If (I) eliminates a β-proton, the allylic alcohol (V) is formed, and upon further reaction with carbonyl species, this alcohol may eventually yield an allyl chloromethyl ether (VII). If proton elimination occurs in the opposite direction, from the δ-carbon, a homoallylic alcohol (VI) is produced. This homoallylic alcohol (VI) may then react with additional carbonyl species to form the α-chloroether (VIII) which subsequently cyclizes to a tetrahydropyran (IX). This

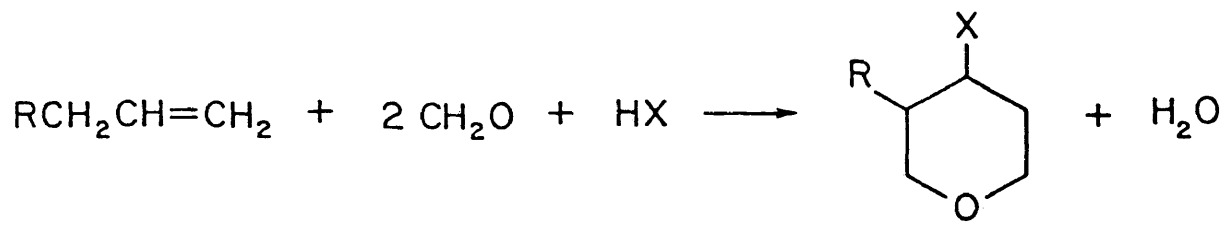
Scheme IV


RCH2CH=CH2 + CH2OH
RCH2CHCH2CH OH
Cl-
RCH2CH(Cl)CH2CH2OH
I
II
-H+
-H+
H2O
RCH2CH=CHCH2OH
RCH=CHCH2CH2OH
RCH2CH(OH)CH2CH2OH
V
VI
III
CH2O
HCl
CH2O
HCl
CH2O, H+
RCH2CH=CHCH2OCH2Cl
RCH=CHCH2CH2OCH2Cl
VII
VIII
IV
Cl
R
O
O
O
IX

cyclization of the α-chloroethers to form tetrahydropyrans is of particular interest to our work because of its similarity to our cyclizations of acetals of homoallylic alcohols to form similar products. The mechanistic similarities are illustrated in Scheme V. The common mechanistic feature is formation of a resonance stabilized carbonium ion which can electrophilically attack the olefinic moiety.

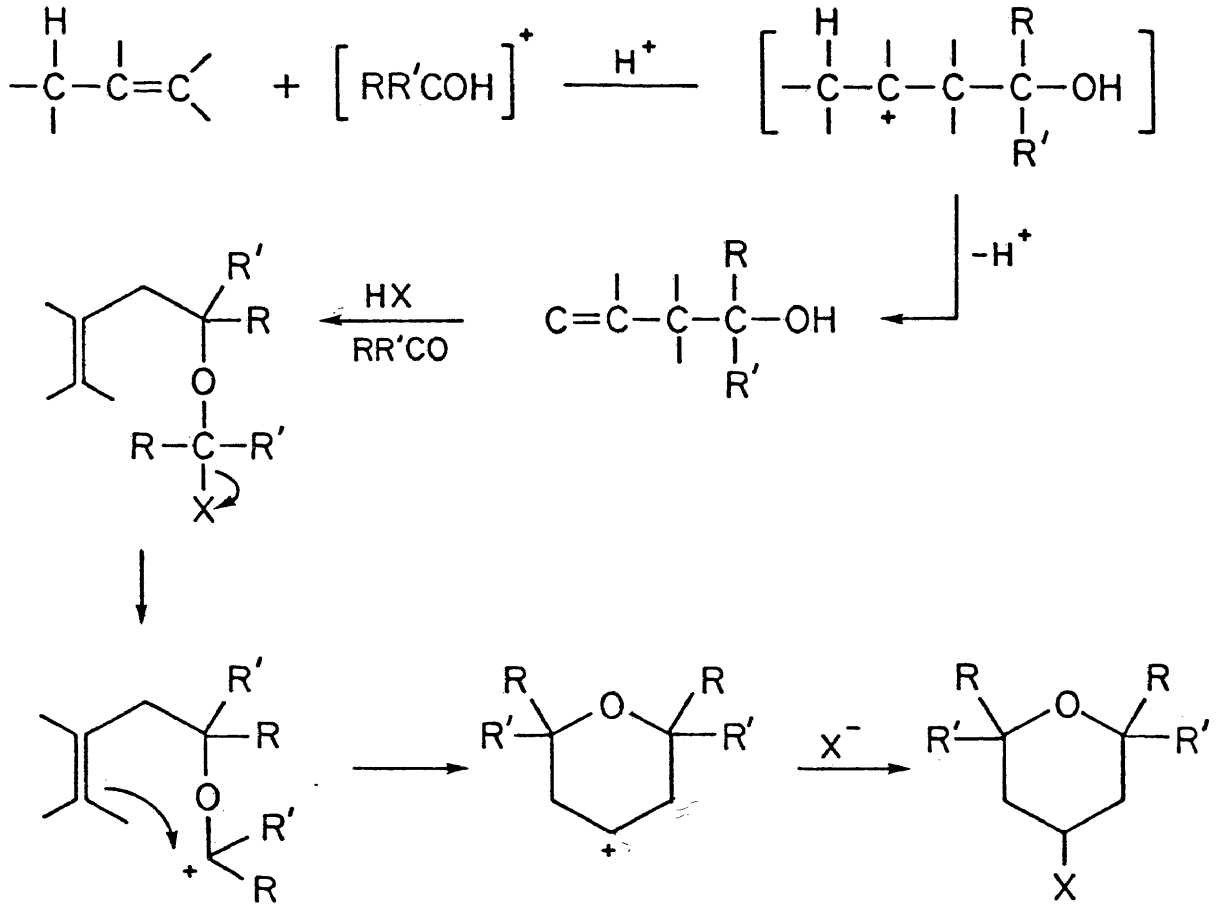
As mentioned earlier and illustrated in Scheme IV the condensation of aldehydes or ketones with olefins in aqueous or acetic acid solutions using mineral acid catalysts may lead to a wide variety of products. In fact, depending on such factors as olefin structure, reactant ratios, and temperature, this conventional Prins reaction generally leads to a complex mixture of 1,3-dioxanes, 1,3-glycols, unsaturated alcohols, and polymers, as well as other higher aldehyde or ketone derived condensation products.[11]

Modifications of the Prins reaction, by Stapp, involving anhydrous media rather than aqueous or acetic acid solutions, have led to the development of a novel synthetic route to 3-alkyl-4-halotetrahydropyrans. This synthesis involves the condensation of 1-olefins with paraformaldehyde and hydrogen halides.[11]

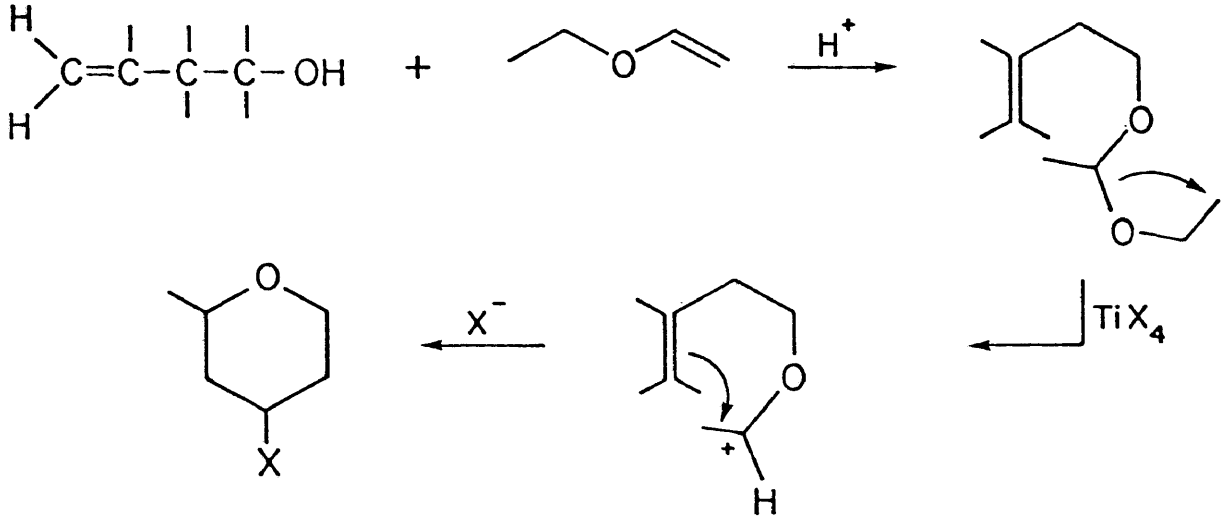


Scheme V

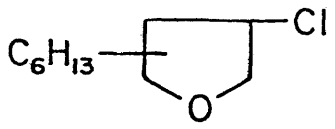
Part A - Prins Reaction



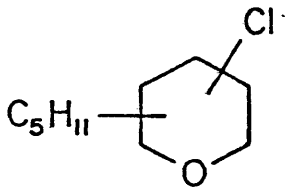
Part B - Acetal Cyclization



In an initial experiment, Stapp saturated a suspension of paraformaldehyde in 1-octene with gaseous hydrogen chloride. Gas chromatographic analysis indicated that two products were obtained from this reaction. Infrared spectroscopy and other chemical analyses, along with the fact that small amounts of tetrahydrofuran and tetrahydropyran derivitives had been isolated as products in conventional Prins reactions, led Stapp to believe that his major product was a mixture of cis/trans isomers of either a chlorohexyltetrahydrofuran (1) or a chloroamyltetrahydropyran (2).



(1)



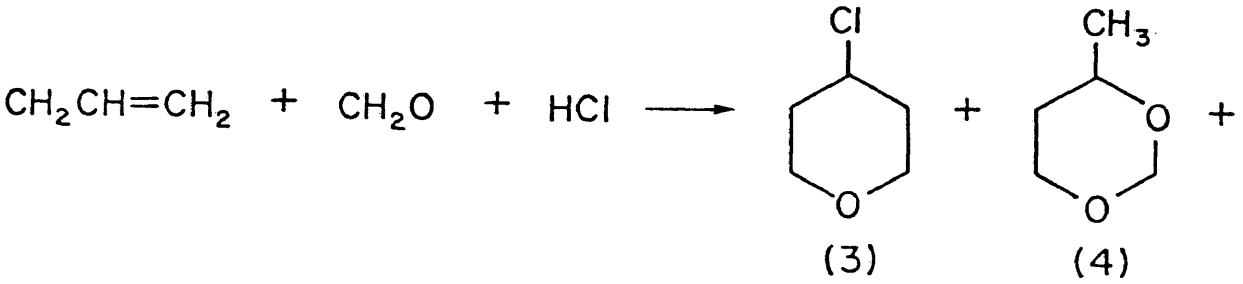
(2)

These products were later determined to be a cis/trans-3-n-amyl-chlorotetrahydropyran mixture by reduction with sodium and methanol to give a single homogeneous product which was identified as 3-n-amyltetrahydropyran by comparison with an authentic sample of that compound. Other products recovered from this reaction included unreacted 1-octene, small amounts of 2-chlorooctene and a chloro alcohol, and some high boiling residue.[11]

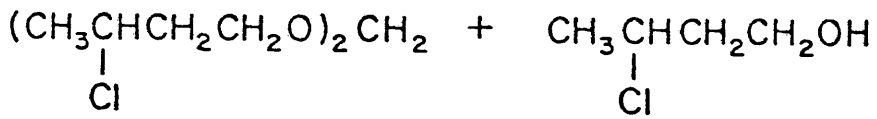
At this point the only structural uncertainty remaining was whether the chlorine occupied the three of four position in the pyran ring. In order to determine the position,

Stapp carried out another reaction, using propylene rather than 1-octene as the olefin component, thus producing a simpler pyran product with no alkyl substituent on the ring. This product was later identified as 4-chlorotetrahydropyran by comparison with authentic samples of 3- and 4-chlorotetrahydropyran using physical properties, glpc retention times, and IR, NMR and mass spectra.

In the condensation of propylene with paraformaldehyde and hydrogen chloride, Stapp[11] also identified several other products in addition to 4-chlorotetrahydropyran. These included 4-methyl-1,3-dioxane (<5%), and bis(3-chloro-1-butoxy)methane and 3-chloro-1-butanol (20-25%). Subsequent experiments showed that if lower mole ratios of formaldehyde to propylene were used, 3-chloro-1-butanol was formed at the expense of the formal. The various products of this reaction are shown below.



(3) (4)



(5) (6)

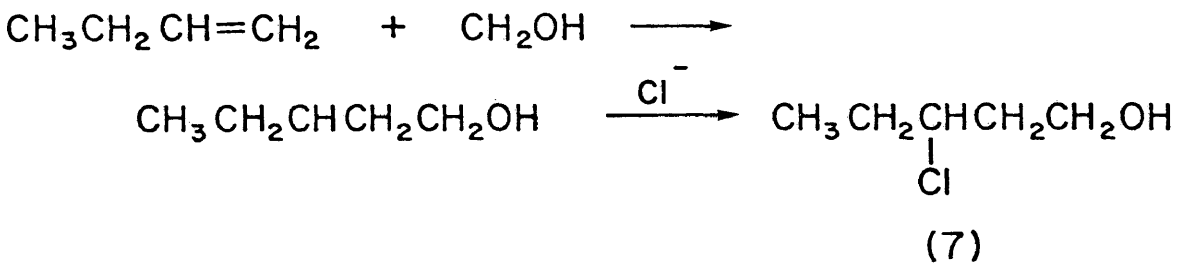
With the structure of the 4-chlorotetrahydropyran product now in hand, the only remaining uncertainty involving products of this reaction was the structure of the

by-product 3-chloroalkanols from 1-olefins higher than propylene. For example, if 1-butene was condensed with paraformaldehyde and hydrogen chloride, two different 3-chloroalkanol by-products are possible. As shown in Scheme VI, if the protonated formaldehyde initially adds to the double bond, followed by chloride ion capture, the resulting product would be 3-chloro-1-pentanol (7), or the formal. However, if the formaldehyde adds to the allylic position followed by Markovnikov addition of hydrogen chloride to the double bond, then the product would be 3-chloro-2-methyl-1-butanol (8). For the reaction of 1-butene, Stapp[11] found that only 3-chloro-1-pentanol was produced. Thus the pathway for formation of the 3-chloro-alkanol by-products is shown by (A) in Scheme VI.

Stapp also investigated the effects that changes in the reaction conditions had on the yield and distribution of products of his modified Prins reaction.[11] He studied the effects of temperature on the yield of 4-chloro-3-propyltetrahydropyran from 1-hexene, formaldehyde, and HCl, and found a substantial increase in yield (18% to 90%) when the temperature was decreased from 0-5 °C to -60--70 °C keeping all other conditions constant. In general, he found that 3-alkyl-4-chlorotetrahydropyrans were isolated, from the condensation of 1-butene, 1-hexene, 1-octene, 1-decene, or 1-dodecene with paraformaldehyde and hydrogen chloride in methylene chloride at -60--70 °C, in yields of 70-80%. Yields of 45-55% were obtained for the

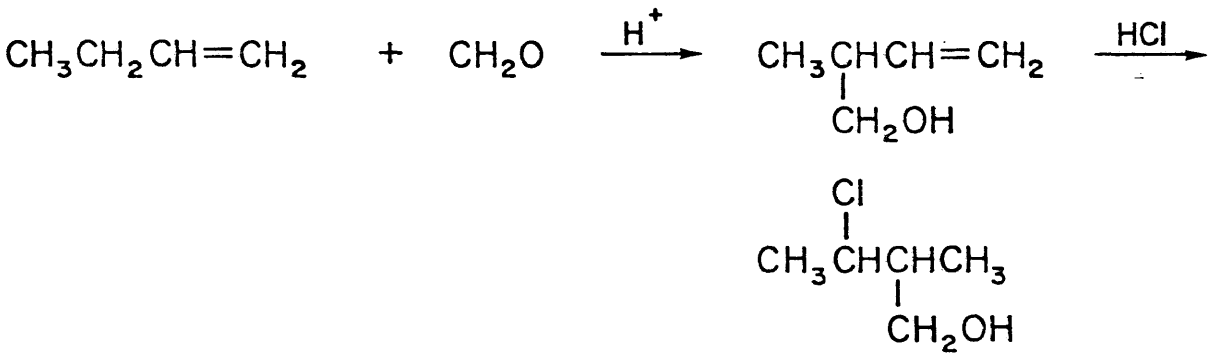
Scheme VI

Part A



(7)

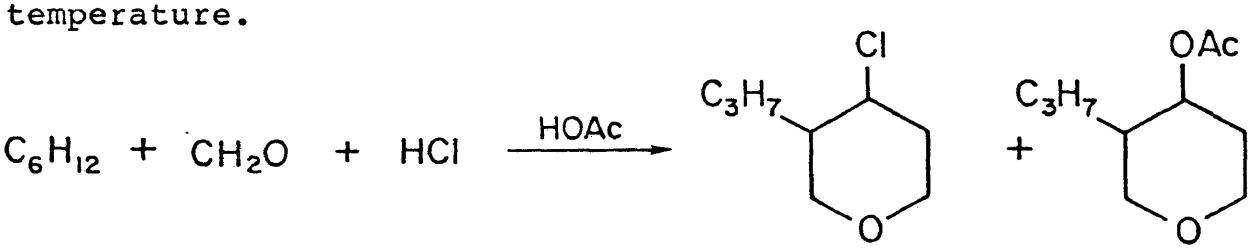
Part B



(8)

synthesis of 4-chlorotetrahydropyran from propylene under the same conditions. Overall, at higher temperatures, the reaction rates were slower, conversions lower, and the workup more complicated then at the lower temperatures. These temperature effects were suprising because of the more vigorous conditions required for success in the conventional Prins reaction.[11]

Stapp also investigated solvent effects in connection with the condensation of 1-olefins with paraformaldehyde. He found that varying the solvent among benzene, methylene chloride, chloroform, pentane, or using no solvent had little effect on the products or yields. However, use of very polar solvents such as liquid sulfur dioxide and sulfolane led to significant improvements in reaction yields. Using acetic acid as the solvent gave difficultly resolvable mixtures of the 4-chloro (9) and 4-acetoxy (10) compounds with ratios being dependent on the reaction temperature.



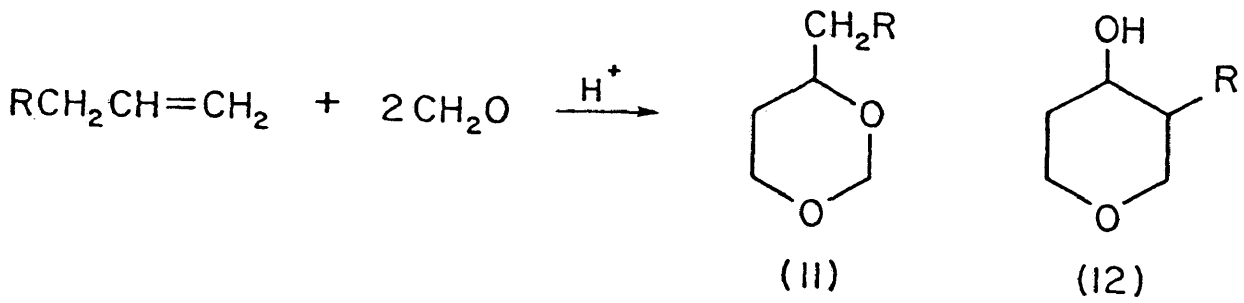
(9) (10)

Stapp also attempted to extend his modification of the Prins reaction to utilize hydrogen flouride and hydrogen bromide.[11]When hydrogen flouride was added to a mixture of 1-hexene and paraformaldehyde in methylene chloride at -65 C, a violently exothermic reaction occured giving a 30%

yield of the 4-flourotetrahydropyran. When hydrogen bromide was used, at 20-30 °C, a smooth reaction produced the 4-bromotetrahydropyran in good yield.

The effects of modifying the carbonyl component of this reaction have been investigated.[11] Using trioxane, the cyclic trimer of formaldehyde, as the carbonyl component, in a reaction with propylene and HCl at -65 °C produced no reaction. Acetaldehyde, used as the carbonyl component under identical conditions, yielded a complex mixture of aldol condensation products, and acetone reacted to give only mesityl oxide, its bimolecular condensation product.

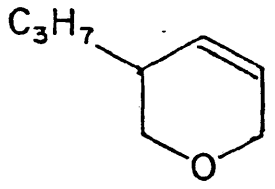
When aqueous formalin was substituted for paraformaldehyde in the synthesis of 4-chloro-3-propyltetrahydropyran from 1-hexene and hydrogen chloride at 0 °C, this product was produced in 35-40% yield.[11] However, purification was difficult. Stapp reports additional work involving the use of formalin as the carbonyl component.[12] Here he uses conditions similar to those used in conventional Prins reactions to synthesize 4-alkyl-1,3-dioxanes (11) and 3-alkyltetrahydropyran-4-ols (12) from 1-olefins.



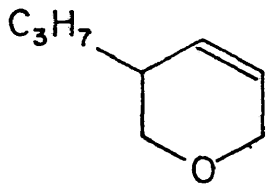
(11) (12)

R = C_2H_5, C_3H_7, C_5H_{11}, C_7H_{15}, or C_9H_{19}

A general procedure for this reaction involves the heating of the 1-olefin (2 mol), 37% formalin (4.9 mol), and sulfuric acid (5 ml) in an autoclave at 150 C for ca. 6 h. When this reaction was carried out using 1-hexene ($R=C_3H_7$), complete conversion of the olefin was obtained, and the major products were identified as 2-hexanol (5%), 4-butyl-1,3-dioxane (44%), and cis,trans-3-propyltetrahydropyran-4-ol (45%). The remaining 6% was made up of hexanal and a mixture of 3,6-dihydro-3-propyl-2H-pyran (13) and 5,6-dihydro-3-propyl-2H-pyran (14).



(13)



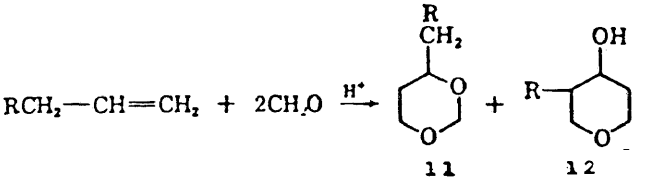
(14)

Table I summarizes the results of this reaction using various olefin starting materials.

The effects of changes in the reaction conditions in the formalin based reaction were investigated using 1-hexene in an attempt to find the optimum conditions for the production of either (11) or (12).[12] Stapp found that, at higher sulfuric acid concentrations, the reaction rates were faster but the by-product formation was greater. Replacing sulfuric acid with phosphoric acid caused a large decrease in the reaction rate. Stapp also found that higher reaction temperatures yielded faster reaction rates but more dihydropyran by-products, while lower temperatures led to

Table I

Condensation of 1-Olefins with Formalin[a]



11 12

R	Conversion, %	Yield,[b] % 11	Yield,[b] % 12
C_5H_9	100	46	42
C_7H_7	100	41	46
C_8H_{11}	85	43	45
C_7H_{15}	53	40	47
C_9H_{19}	39	42	46

[a] Reactions were carried out for 6 hr at 150° using 2 mol of olefin to 4.9 mol of 37% formalin 0.24 *M* in H_2SO_4. [b] Based on reacted olefin.

Table from P.R. Stapp, J. Org. Chem. 1970, 35, 2419.

slower reactions. Overall, attempts to improve the selectivity of the reaction were unsuccessful. However, because of the minimum amount of by-products, and the easy separation of the two major products, Stapp concludes that the reaction utilizing formalin and sulfuric acid is a convenient and useful synthesis of cis,trans-3-alkyltetrahydropyran-4-ols and 4-alkyl-1,3-dioxanes.[12]

In an attempt to extend the modified Prins reaction to include internal olefins, Stapp[13] found that only small amounts of alkylchlorotetrahydropyrans and 1,3-dioxanes were formed in the reaction of 2-butenes with paraformaldehyde and hydrogen chloride at -65 °C. Instead, the major products were a mixture of chloro alcohols and their formals in yields of 45-60%. An investigation of the mechanism of the Prins reaction may give some explanation for the product distributions from both 1-olefins and internal olefins.

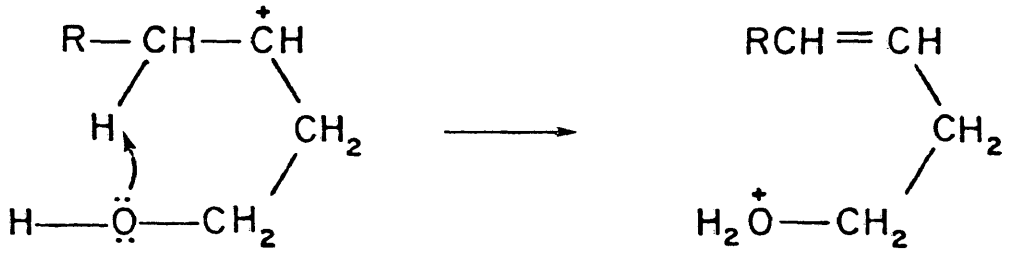
If we can make the reasonable assumption that acids in different media probably catalyze the Prins reaction by the same mechanism, then we may assume that Stapp's modified Prins condensation proceeds by "initial electrophilic attack of a protonated formaldehyde upon a double bond to give an intermediate which has been described as either a free carbonium ion or a solvated trimethylene oxide."[11] According to more recent work,[15] neither of these intermediates can be conclusively ruled out.

The mechanism for the formation of the various products

from either the Prins of modified Prins reactions was shown in scheme IV (page 11) and discussed previously. We can again see from scheme IV that the initial carbonium ion (I) may react with a chloride ion to form a chloro alcohol (II), or it may react with water to form a 1,3-diol (III) and eventually a dioxane (IV). More important to our research, however, is the route involving proton elimination from (I) thus yielding either the allylic alcohol (V) or the homoallylic alcohol (VI). It has previously been shown that homoallylic alcohols cyclize to 4-tetrahydropyranols in the presence of paraformaldehyde and sulfuric acid[16a], and to 4-chlorotetrahydropyrans when reacted with paraformaldehyde and hydrogen chloride.[16b] However, it has also been shown that cyclization of allylchloromethyl ethers, from the reaction of the allyl alcohol (V) with formaldehyde and hydrogen chloride, to the corresponding tetrahydrofuran does not readily occur.[17]

Of even greater interest is the fact that Stapp[11] found neither tetrahydrofuran derivitives, nor the allyl chloromethyl ethers (VII), in his work. This is evidence that deprotonation is not occuring from the β-carbon but only from the δ-carbon in species (I). This result was unexpected because deprotonation to form (VI) does not seem to be thermodynamically more favorable then deprotonation to form (V). To explain this, Stapp[11] proposes a cyclic mechanism for the deprotonation process leading to the homoallylic alcohol, thus making it the kinetically favored

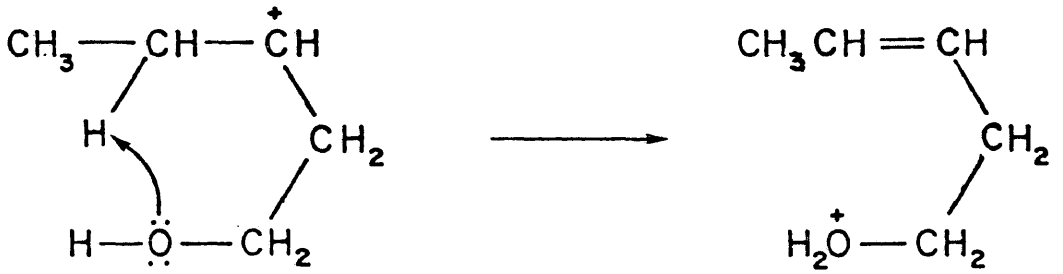
process.



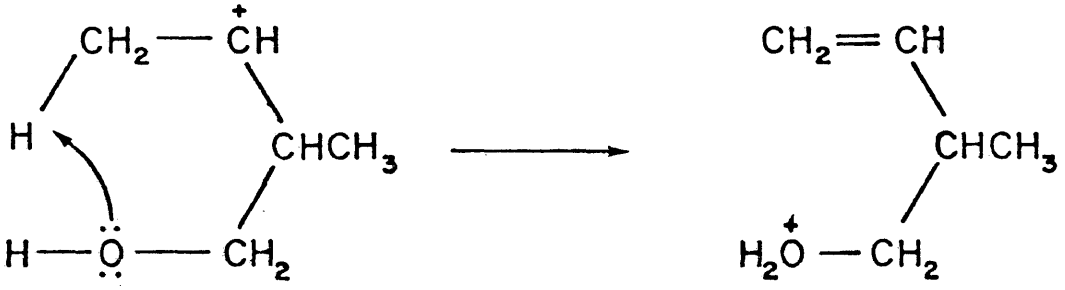
Stapp[11] also found that the yield of alkylchlorotetrahydropyran product in his modified Prins reaction was increased by adding large quantities of chloride ion or increasing the solvent polarity. This showed that this process obeys the Hughes-Ingold generalization which states that "an increase in the ion-solvating power of the medium will accelerate the creation and concentration of charges and inhibit their destruction and diffusion."[18] Thus, since charges are created in the transition state of the Prins reaction, a more polar solvent or additional chloride ions will tend to facilitate that charge formation, and thereby increase the reaction rate.

Stapp fails to offer an adequate explanation of why 1-olefins cyclize to form pyrans while internal olefins tend to favor the formation of chloro alcohols.[13] According to the theory that the formation of the alkylchlorotetrahydropyrans proceeds through the formation of the homoallylic alcohol by cyclic deprotonation[11], Scheme VII on the following page shows the intermediates from

Scheme VII



A C



B D

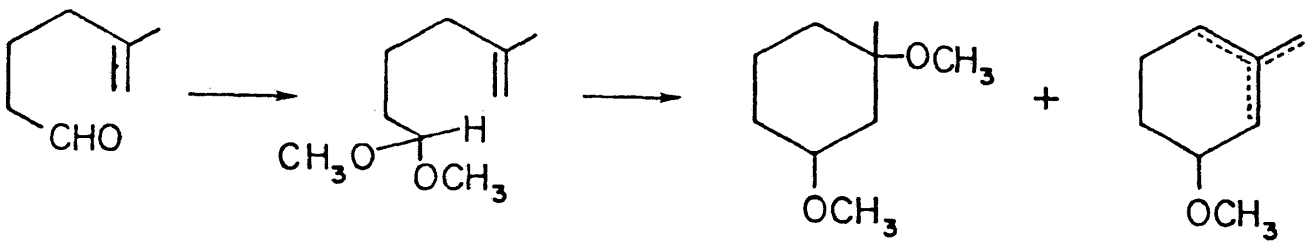
1-butene and 2-butene. This process does not seem to be thermodynamically controlled because, if it was, we would expect the formation of the more stable internal olefin, from deprotonation of (A) to be more favorable then the formation of the less stable terminal olefin (D). Since this is not the case, we must conclude that electronic factors in the transition state must kinetically favor formation of the homoallylic alcohol from (B) while they favor the reaction of (A) with a chloride ion to form the corresponding chloro alcohol. Stapp reports that a present lack of information prevents our determining whether the inductive effect alone of the α-methyl group is enough to cause this great discrepancy in products between 1-olefin cyclizations and internal olefin cyclizations.[13]

In summary, Stapp's work seems to point to the fact that what he views as the crucial step in the Prins reaction, the deprotonation of the initial carbonium ion to form an unsaturated alcohol, is kinetically controlled. This explains why the homoallylic alcohol is formed almost exclusively even though the thermodynamic stability of the allylic alcohol is not very different. Also, it explains why the carbonium ion from internal olefins does not deprotonate to form an unsaturated alcohol even though its corresponding homoallylic alcohol would have an internal double bond, and thus, be more stable then the homoallylic alcohols derived from 1-olefins. The process of deprotonation in internal ofefins seems to be slowed down,

compared to reaction with a chloride ion, by some electronic effects.

Unlike Stapp's work, Johnson's research has not dealt with the synthesis of cyclic ethers, but with biogenetic-like cyclizations of polyolefinic and acetylenic substrates to form five- and six-membered fused ring carbocyclic compounds. Much of his work has been oriented to the synthesis of the basic steroid structure via stereoselective cyclizations. Johnson's work is of interest to us because his cyclizations seem to proceed by a similar mechanism to that involved in our studies.

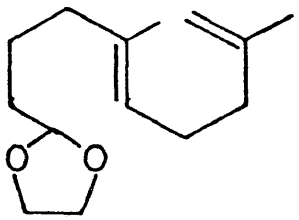
Originally prompted by the fact that certain unsaturated aldehydes of the citronellal type were known to undergo acid-catalyzed cyclizations, Johnson decided to use the aldehyde function to initiate the polycyclizations of polyolefinic systems.[19] The first step was to learn if aldehydes with the olefinic bond in five position would cyclize, and therefore he looked at the cyclization of 5-methyl-5-hexenal (15). Johnson found that, when this aldehyde was



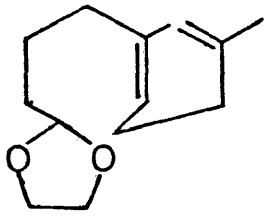
(15) (16) (17) (18)

reacted with hydrogen chloride in methanol at 0 °C for 2 h, the acetal (16) was formed in quantitative yield.[19] However, when this reaction was done at room temperature the aldehyde cyclized yielding a mixture of cis- and trans-dimethylcyclohexane (17) and the olefinic ethers (18).

These encouraging results with the aldehyde cyclization led Johnson to try to extend this reaction to utilize acetals, rather than aldehydes, to initiate cyclization reactions leading to the formation of fused ring compounds. The initial work in this area involved the cyclization of the cis and trans dienic acetals, (19) and (20).[19]

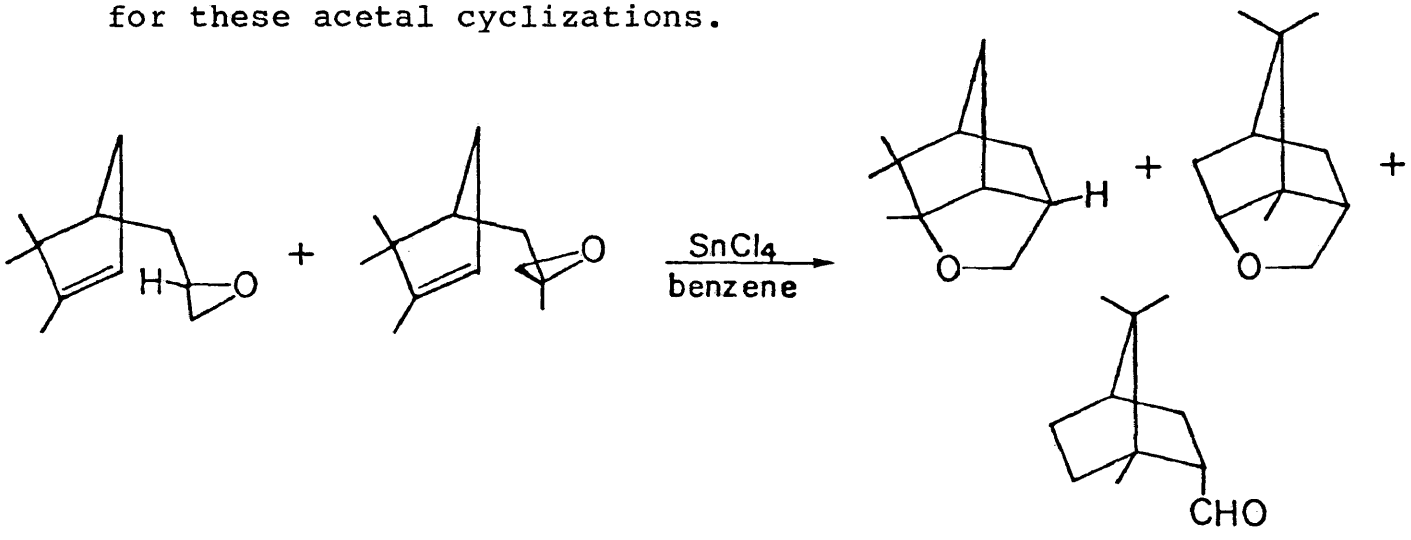


(19)



(20)

Stannic chloride had been shown to be a useful catalyst in promoting the cyclization of epoxy olefins,[20] such as that illustrated below, and was therefore the acid of choice for these acetal cyclizations.



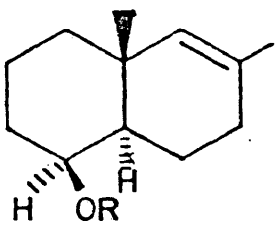
Also, the solvent used for these cyclizations seemed to have a large influence on product ratios. Various solvents (see Table II) were tried, however the benzene-stannic chloride system gave the largest number of isomeric products and thus was studied in detail.

Using gas chromatography, Johnson[19] found, in the stannic chloride-benzene system, that the disappearance of the trans dienic acetal (19) was slow until the amount of stannic chloride present reached 50 mol%, at which time the cyclization became too rapid to follow. The reaction of the trans dienic acetal (19) with stannic chloride (48 mol%) in benzene was carried out at 25 °C for 5 min. Short path distillation yielded a 97% recovery of material showing that little or no polymerization had occured. According to glc analysis, the product mixture contained six different compounds, none of which was starting material. These compounds can be designated A-F in order of increasing glc retention time. Compound A was identified as monocyclic material which composed about 4.5% of the products. The other compounds (B-F) comprised about 93% of the total glc peak area, and were identified as the trans bicyclic compounds listed below.

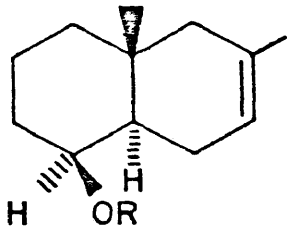
Table II

Ratio of products with the C-5 sustituent axial to products with the C-5 substituent equatorial for the cyclization of trans-dienic acetal (19) in various solvents.

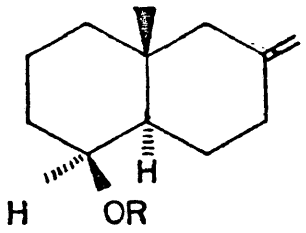
SOLVENT	C-5 AXIAL/EQUATORIAL ISOMER RATIO
PENTANE	1.9
CARBON TETRACHLORIDE	2.2
CARBON DISULFIDE	2.5
CHLOROFORM	2.6
BENZENE	2.8
NITROETHANE	6.9
NITROBENZENE	7.2
NITROMETHANE	8.2
ETHYL ACETATE	9.1
ACETONITRILE	17



B(5%)

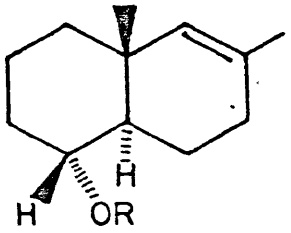


C(63%)

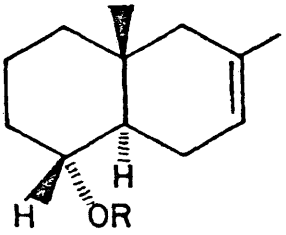


D(3.5%)

R = CH_2CH_2OH



E(1%)

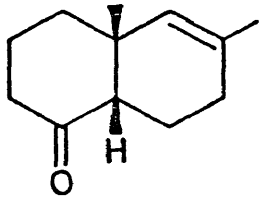


F(21%)

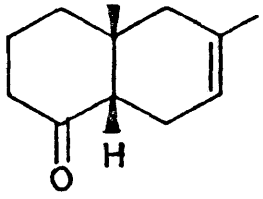
These substances were characterized by degradation to the known dimethyloctalins.

In order to determine if the stereochemistry involved in this reaction is influenced by the configuration of the olefinic bonds in the starting acetal, Johnson also cyclized the cis dienic acetal (20).[19] When this acetal was cyclized under the same conditions used for the previous reaction of (19), the product mixture contained ca. 88.5% bicyclic material by glc. However, none of these products were the same as those produced in the trans-acetal cyclization. Because of the conformational mobility of the cis-bicyclic isomers, they could not be separated easily by chromatography, nor could the configuration at C-5 (axial or equatorial) be determined. Degradation to the corresponding octalones (21) and (22), and conversion to the octalins

showed the positions of the olefinic bonds.



(21)



(22)

The mixture of octalones was composed of 62% of (21), 34% of (22), and 4.5% of a mixture of decalones.[19]

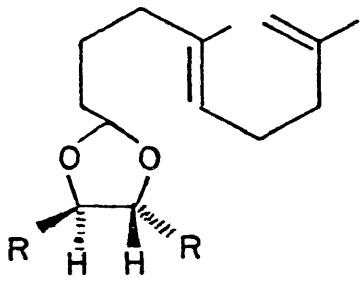
Quantitative gas chromatographic and NMR spectral analysis showed that the octalones from the cyclization of the trans-acetal (19) contained less than 3% cis-octalones, and that the octalones from the cyclization of the cis-acetal (20) contained less than 5% trans-product. Thus this reaction is almost completely stereospecific.[19]

Johnson carried out the cyclization of the trans-dienic acetal (19) in a variety of solvents to examine the effects of the solvent on the product ratios and yields.[19] In general, he found that the more polar solvents gave higher proportions of the C-5 axial isomers. Table II summarizes the solvents studied, and the ratio of C-5 axial to C-5 equatorial products yielded by each. Also, the use of different solvents caused the relative amounts of (B,E) to (C,F) isomers to vary. Of particular interest was the reaction in nitromethane which yielded mostly a single product (C).[19]

Johnson had now shown his cyclization reaction to be

stereospecific with respect to the relative configurations of chiral centers produced at the bridgeheads, and , with certain acetals, to yield polycyclic compounds possessing the "natural configuration."[19,22,23] However, these products were racemic, and since it was known that enzymatic cyclizations of certain compounds, such as squalene, proceeded by asymmetric induction, thus producing enantiomerically pure products, Johnson wanted to achieve this asymmetric induction by non-enzymatic means.

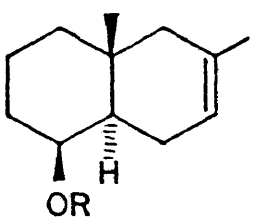
In a study of the amount of asymmetric induction involved in his cyclization process, Johnson examined the reaction of the optically active trans-dienic acetal (23) which differs from the trans-dienic acetal (19) cyclized previously only by the fact that the R groups are methyls rather than hydrogens.[23]



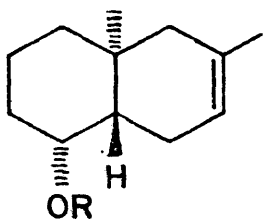
(19), R = H
(23), R = Me

The cyclization of (23) was studied in various solvents, including nitromethane, benzene, and pentane, using stannic chloride.[23] The stannic chloride-benzene system provided the highest amount of asymmetric induction. The reaction of acetal (23) in this system produced two major components identified as the axial hydroxy ether

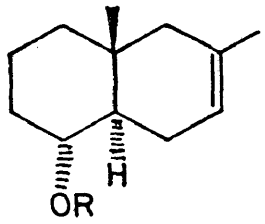
(24a,24b) and the equatorial epimer (25a,25b) in 52% and 21% yields, respectively.[23]



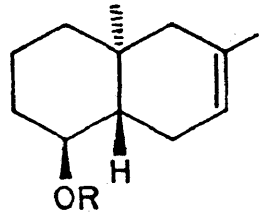
(24a)



(24b)

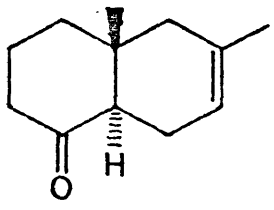


(25a)

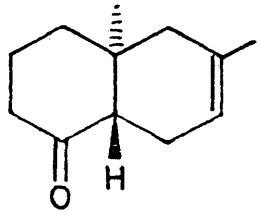


(25b)

Conversion of the above compounds to their corresponding octalones (26a and 26b) was accomplished in order to determine the enantiomeric ratios of products.



(26a)



(26b)

Conversion of the axial hydroxy ether (24a,24b) to the octalones yielded (26a) and (26b) in a 8.5 to 91.5 ratio. Conversion of the epimeric equatorial hydroxy ether (25a, 25b) to the octalones led to a ratio of (26a) to (26b) of 92 to 8. Thus this reaction did proceed with a high degree of asymmetric induction.[23] A summary of the ORD data for this reaction in benzene, nitromethane, and pentane and be found in Table III.

Table III

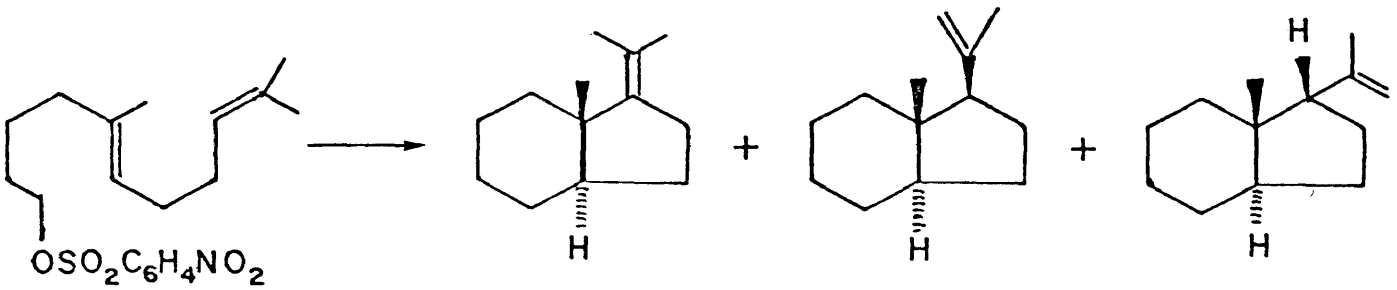
ORD Data and Calculated Enantiomeric Ratios

		ORD data for derived octalones								
		$[\Phi]_{xA}$		$[\Phi]_{yB}$		$[\Phi]_{zC}$			Enantiomeric composition	
Cyclization solvent	Product	x, mμ	A, deg	y, mμ	B, deg	z, mμ	C, deg	c[a]	26a	26b
Benzene	Axial[d]	589	+118	315	+594	222	+9278	0.261	8[b] (7)[c]	92 (93)
	Equatorial[d]	589	−126	313	−577	221	−9379	0.318	92 (94)	8 (6)
Pentane	Axial[e]	589	+126	316	+549	224	+8147	0.261	14 (12)	86 (88)
	Equatorial[e]	589	−119	316	−581	220	−8975	0.278	90 (92)	10 (8)
Nitromethane	Axial[d]	589	+75	314	+365	220	+5580	0.338	25 (24)	75 (76)

[a]Concentration in g/100ml of dioxane solution. [b]Calculated from the value for pure 26b $[\Phi]_{222}$+11180. [c]Enantiomeric ratios in parentheses were calculated from the value for pure 26b $[\Phi]_{222}$+10750. [d]The ORD measurements are an average of three determinations. [e]The ORD measurements are an average of two determinations. [f]The ratio of 26a:26b also reflects the ratios for 24a:24b in the axial series, and 25a:25b in the equatorial series. The values have been rounded off to the nearest whole %.

Table from W.S. Johnson, C.A. Harbert, B.E. Ratcliffe, and R.D. Stipanovic, J. Amer. Chem. Soc. 1976, 98, 6188.

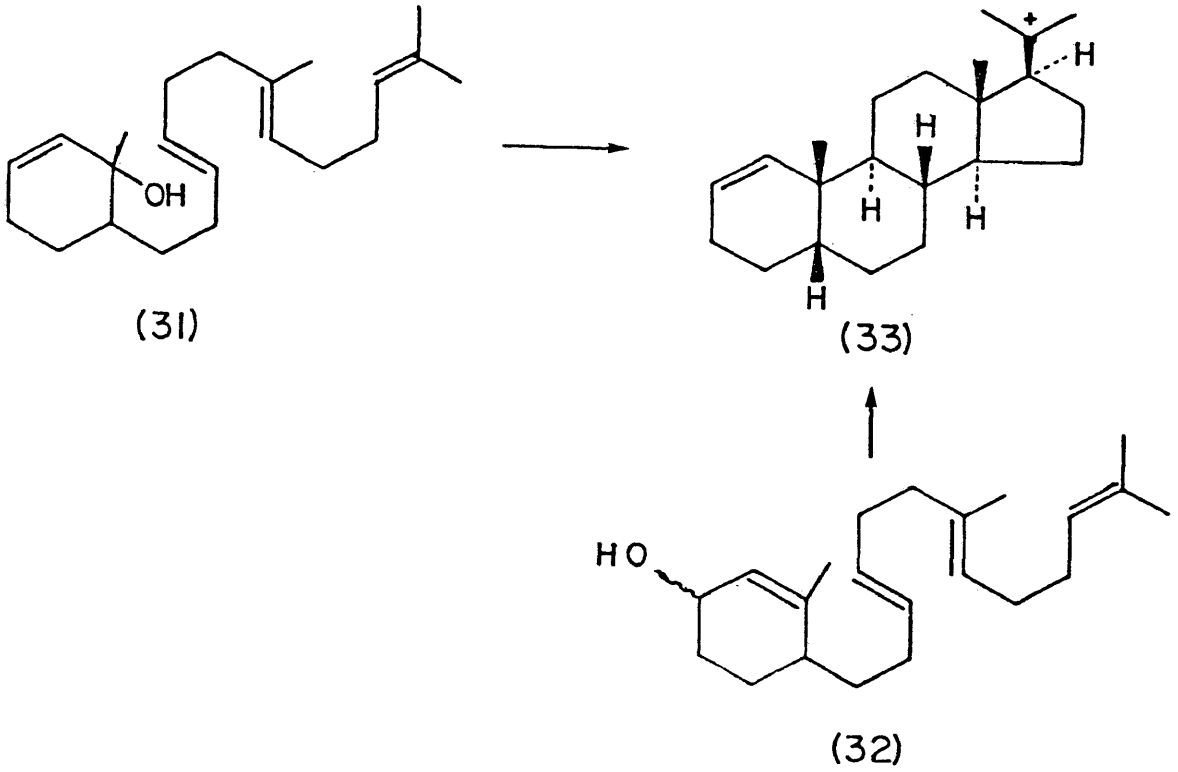
Having developed a stereospecific and enantioselective cyclization of dienic and polyenic acetals to form fused six-membered carbocycles, Johnson's interest turned to extending this reaction to include the synthesis of five-membered rings stereospecifically.[24] This could lead to the production of D-homosteroid ring systems wth five-membered D-rings. Johnson hoped that an appropriately placed isopropylidene terminating group might favor the formation of a five-membered ring over a six due to the preference for forming a tertiary cation over a cyclic secondary cation. Preliminary results from the cyclization of the 1,5-diene (27) shown below were encouraging in that, even though mostly monocyclic products were formed, all of the bicyclic material produced (7.6% yield) contained the trans-hydrindan ring system.[24]



(27) (28) (29) (30)

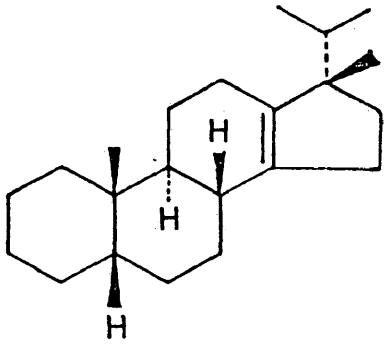
Continuing work in this area, Johnson synthesized and cyclized the tetraenol (31) and its allylic isomer (32) in hopes that the resulting products would contain the cis, anti, trans, anti, trans systems derived from carbonium ion

(33).



(31) (33) (32)

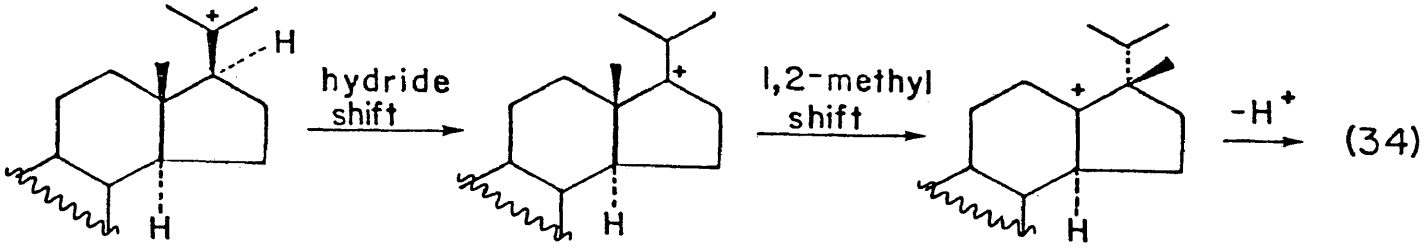
The cyclization of (32) with triflouroacetic acid in methylene chloride at -78 °C for 4.5 h yielded a mixture of hydrocarbon and triflouroacetate. Also, cyclizations of (32) using methylene chloride-stannic chloride or nitromethane-stannic chloride systems yielded the same hydrocarbon product, as did the cyclization of tetraenol (31) in methylene chloride using stannic chloride. This hydrocarbon product represented the only tetracyclic material isolated from the above reaction, and was later identified as compound (34), the product of a facile rearrangement of carbonium ion (33) prior to deprotonation.[24]



(34)

Compound (34) seems to be generated from carbonium ion (33) by a migration of the C-17 (α) hydrogen followed by a 1,2-shift of the C-18 methyl group (Kagi-Miesuler rearrangement).[24] The C-13 cation then deprotonates to form (34). Johnson reports that this sequence of hydride and methyl shifts, followed by elimination of a proton, as shown in Scheme VIII, may be a concerted process.[24]

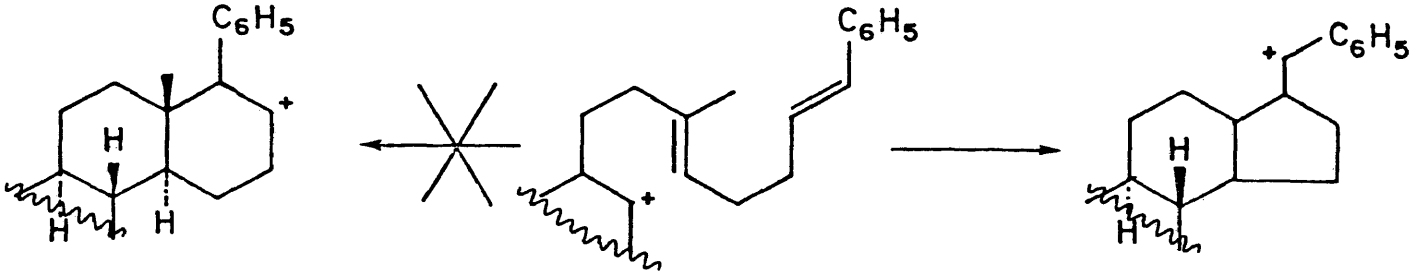
Scheme VIII



(34)

Although the use of the isopropylidene terminating group yielded five-membered rings via biomimetic polyene cyclizations, it was not a useful way to prepare the desired D-homosteroid systems because of the tendency of the product to undergo backbone rearrangement. Thus, Johnson decided to continue his attempt to produce five-membered ring cations

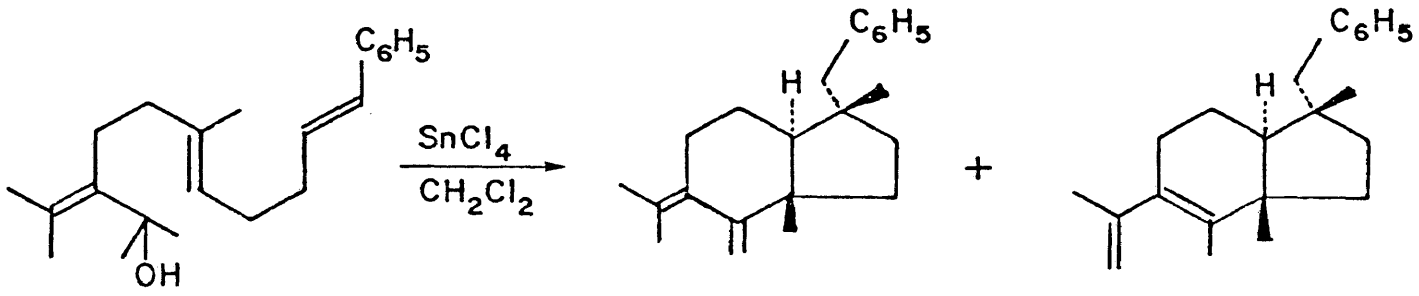
such as (36) by using the styrene terminating group.[25]



(37) (35) (36)

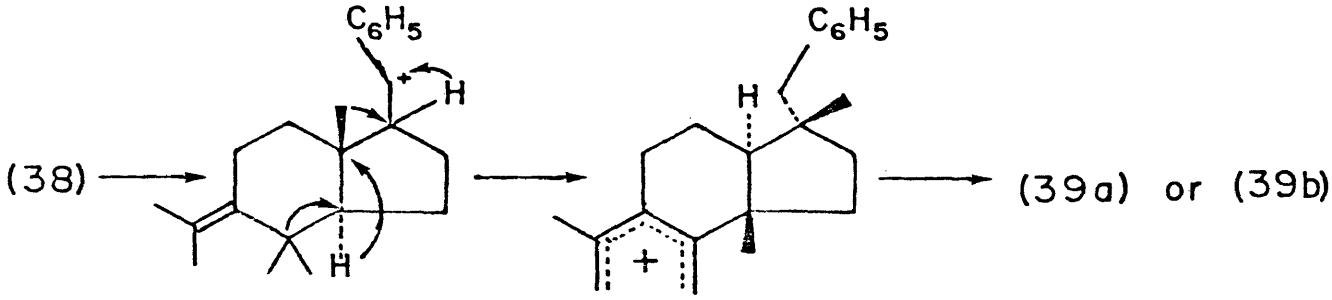
The rational behind this was that cyclization of a compound, as suggested by partial formula (35), with a styrene group incorporated in the molecule, would preferentially lead to the production of the resonance stabilized benzylic cation (36) over the six-membered ring homobenzylic cation (37). Also, the olefinic bond of the styryl group is more nucleophlic than an isolated alkene bond and thus would possibly enhance the cyclization.[25]

The cyclization of (38) using stannic chloride in methylene chloride at -78 °C produced a single hydrocarbon product in 40% yield along with a large amount of high molecular weight material.



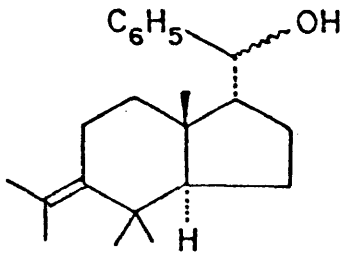
(38) (39a) (39b)

The amount of "polymer" formed was reduced considerably by running the reaction at tenfold dilution. The hydrocarbon product from this reaction was identified as the bicyclic substance (39a) or (39b) which could arise from a series of 1,2-hydride and methyl shifts from the initially formed cation as shown below.



This type of rearrangement is similar to that which occured when using the isopropylidene terminator.[24]

Johnson found, however, that when this cyclization was carried out using triflouroacetic acid rather than stannic chloride, the bicyclic alcohol (40) was formed in high yield.



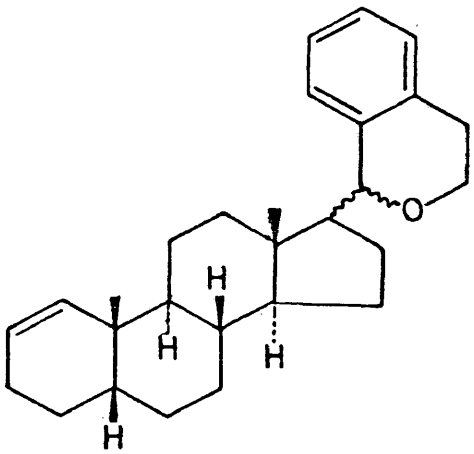
(40)

In another study, Johnson showed that the cyclization of substrates containing the styryl terminator was highly steroselective (>98%) in forming products with the "natural"

(trans) ring fusion.[26] Thus we see that use of the styryl terminator leads to five-membered D-rings[25] with exclusively a C/D trans ring fusion, making this cyclization both regio- and stereoselective.

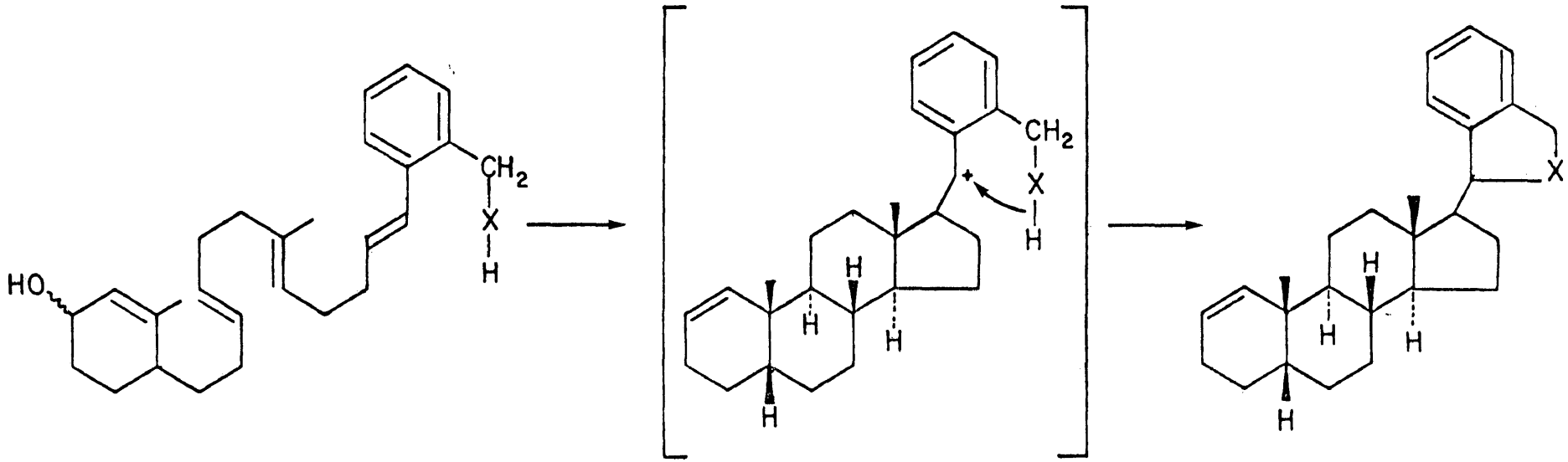
In a further attempt to cyclize a polyene to form a polycyclic compound with the steroid nucleus, Johnson investigated the effect of an appropriately placed internal nucleophile on the reaction.[27] He hoped that by having a nucleophile placed such that it could be intramolecularly delivered only to the site destined for termination, that the cyclization could be better controlled. Thus whereas in nonnucleophilic media, the intermediate benzylic cation tends to polymerize or undergo backbone rearrangement, in more nucleophilic media this cation would be trapped.[27]

To test the effect of an internal nucleophile, Johnson synthesized and cyclized substrates (41) and (42). Scheme IX shows the anticipated pathway of this cyclization. When (41) was cyclized in methylene chloride with stannic chloride it produced, in 73% yield, a mixture of three of the four possible diastereomers (at C-17 and C-20) of type (45).



(45)

Scheme IX



(41) X = $-CH_2O$

(42) X = $-\overset{\overset{O}{\|}}{C}O-$

(43) X = $-CH_2O$

(44) X = $-\overset{\overset{O}{\|}}{C}O-$

One of the isomers was identified as the (17α, C-20(S)) diastereomer, however the others were not positively identified. When substrate (42) was cyclized under similar conditions it was converted (68% yield) into an isomeric mixture of oxygen-sensitive lactones (44).[27]

Thus it is apparent that the use of an internal nucleophile is an effective way to trap the intermediate benzylic cation and thereby form unrearranged steroidal products.

In summary, we see that Johnson has developed a cyclization procedure by which polyenes with olefinic terminating groups may be cyclized to polycyclic compounds. These cyclizations proceed stereo-, regio-, and enantioselectively to yield in many cases fused ring systems possessing "natural" (C/D trans) stereochemistry. When a terminal alkene is used for final ring formation, the final ring is six-membered and is unsaturated because of proton elimination from the final carbocation. In no cases does Johnson report nucleophilic addition to the cation by a halogen from the solvent or catalyst forming a saturated ring. The reason for formation of a six-membered ring in this case is due to the preference for forming a tertiary cyclic cation over a primary cation. Johnson does not report the results of situation where a cyclic secondary cation would be formed because he always uses compounds with an internal substituent in the terminal olefin.

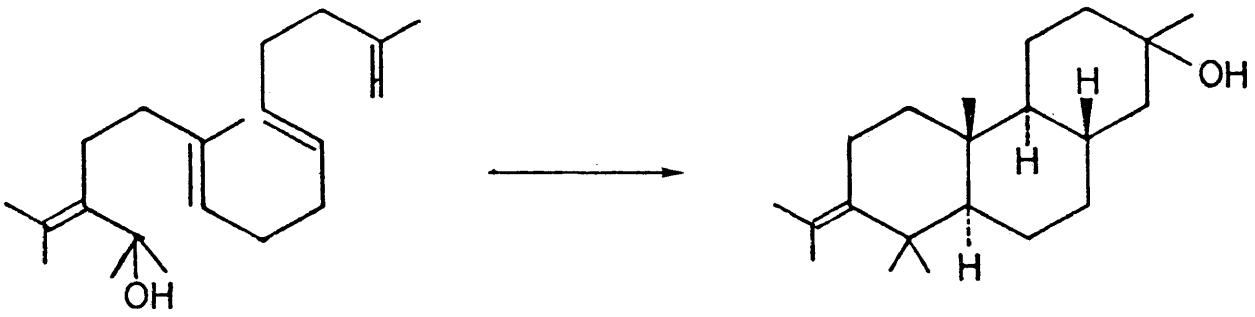
When Johnson uses an internal olefin, such as compounds

possessing the isopropylidene or styryl terminators, he finds that a five-membered ring is formed preferentially over the six-membered product. This seems to be due to the preference for a tertiary cation over a secondary cation in the case of the isopropylidene terminator, and, in the case of the styryl terminator, the resonance stabilization of the benzylic cation is the important factor. However, polymerization and backbone rearrangement present a problem when using these terminators. This problem seems to be alleviated by conducting the reaction in nucleophilic media, especially in the presence of an internal nucleophile where the benzylic cation is trapped before rearrangement can occur.

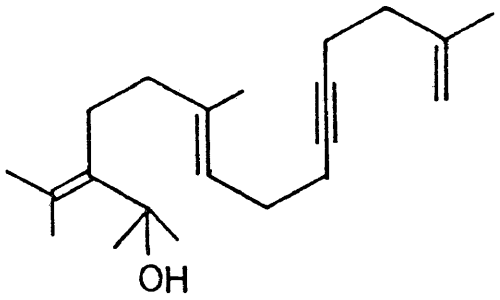
Because of the success achieved in the previously described polyene cyclizations and because it was known that acetylenic bonds can assist the solvolysis of esters with concomitant ring formations,[30] Johnson initiated an investigation of the effect of acetylenic bond participation on biogenetic-like olefinic cyclizations. Since success had been achieved in the acid catalyzed cyclization of (46),[21] Johnson decided to cyclize its acetylenic counterpart (48) shown in Scheme X. It was initially thought that the cyclization would proceed through an intermediate vinyl cation, but it was unclear whether there would be preference for the formation of the six-membered cation (A) or the five-membered cation (B).

When substance (48) was reacted with triflouroacetic

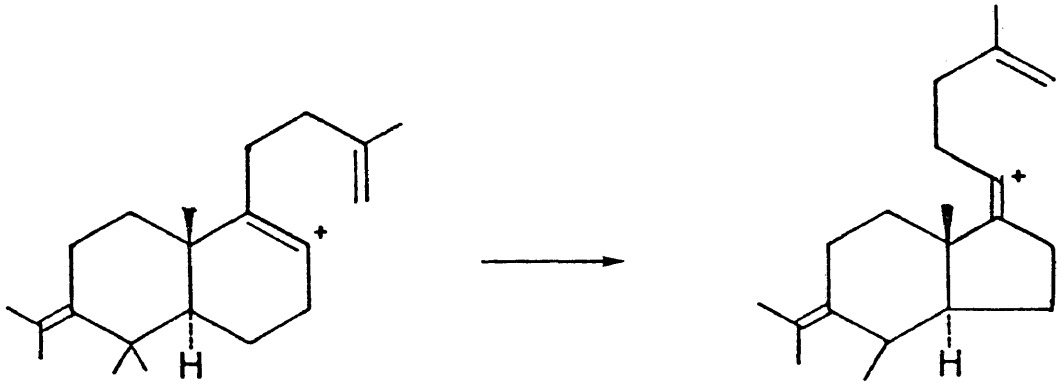
Scheme X



(46) (47)

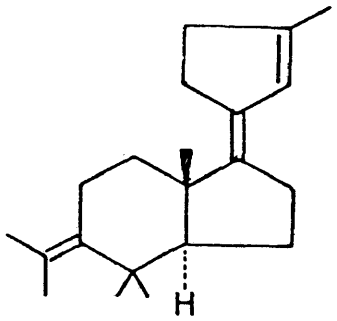


(48)



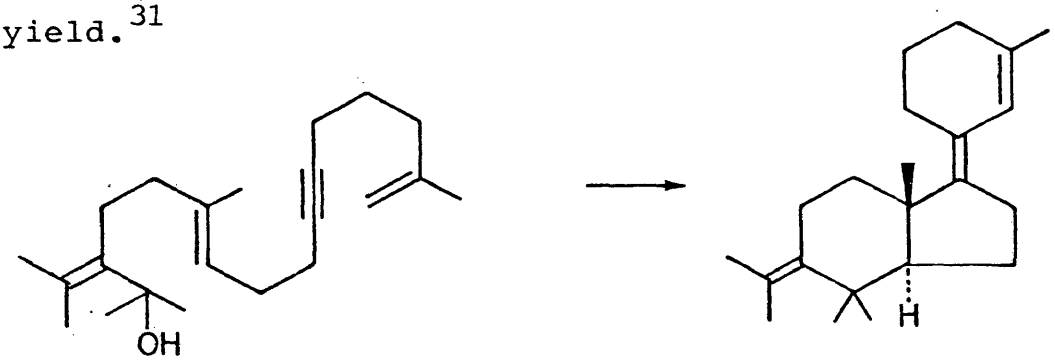
A B

acid in methylene chloride for 5 min at -70 °C, it cyclized to give the tricyclic triene (49) in ca. 70% yield.[31]



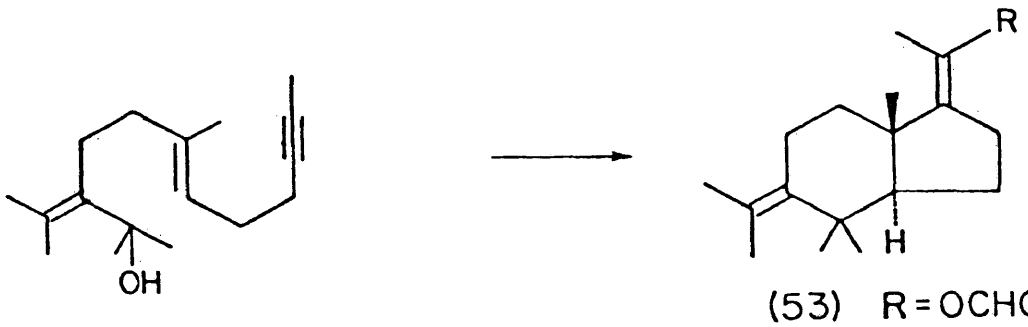
(49)

Also, the trienynol (50) was cyclized under similar conditions with the tricyclic product (51) being produced in 65% yield.[31]



(50) (51)

Johnson continued his investigation of the effect of acetylenic bond participation in these cyclization by looking at the reaction of the simpler dienynol (52) possessing the methyl-acetylenic terminator.



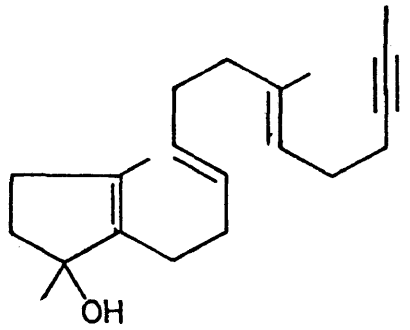
(52)

(53) R = OCHO

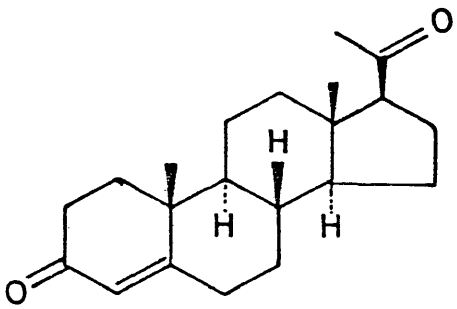
(54) R = $NHCOCH_3$

In this case he varied the procedure in order to provide a nucleophile to react with the intermediate vinyl cation. One experiment involved the cyclization of (52) using formic acid in pentane, thus producing the enol formate (53) in high yield. Another procedure used in cyclizing (52) made use of triflouroacetic acid in acetonitrile (both solvent and nucleophile) and produced, almost quantitatively, the enamide (54).[31]

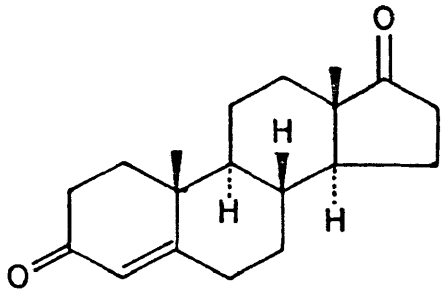
In all of the instances described above, the product of the cyclization had a five-membered ring and was therefore thought to proceed through an intermediate vinyl cation such as B (Scheme X). These results can be attributed to the preferential formation of linear over bent vinyl cations upon cyclization of this type of substrate. These studies also demonstrate that the acetylenic bond participates stereospecifically in biogenetic-like olefinic cyclizations thus forming five-membered ring products having almost exclusively the C/D trans (natural) ring fusion.[31] Johnson extended this work to include the stereospecific cyclization of the trienynol (55) to ultimately produce the natural products dl-progesterone (56) and dl-Δ^4-androstene-3,17-dione (57).[32]



(55)

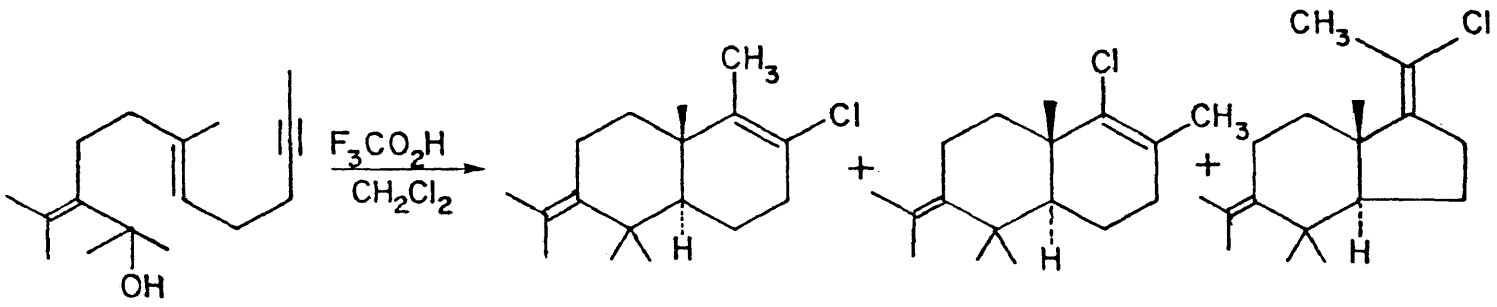


(56)



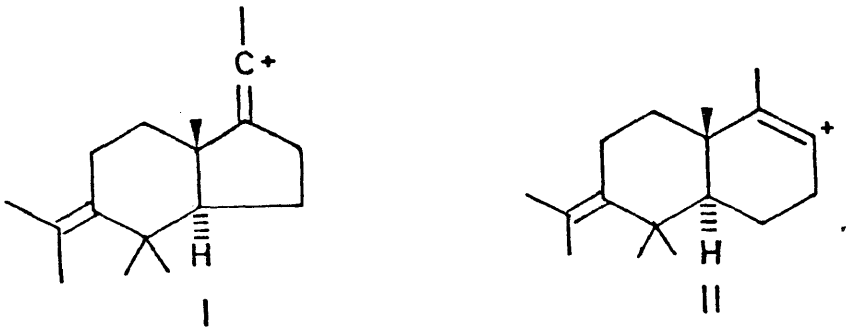
(57)

The above cyclizations of substrates containing the acetylenic terminating group were all conducted under conditions which provided a nucleophile, either intramolecularly, or from the solvent or catalyst, that trapped the intermediate linear vinyl cation thus assuring formation of a five-membered ring. However, when substrate (52) was cyclized in the absence of a good nucleophile, such as with triflouroacetic acid in methylene chloride, the major product (66% yield) proved to be the 6/6 fused ring chlorodiene (58).[33] The product mixture also contained very small proportions of isomers (59) and (60).



(52) (58) (59) (60)

Johnson, in explaining the discrepancy in products from the cyclization in nonnucleophilic media versus nucleophilic media, points out that since the cyclization of (52) proceeds to give, as the primary intermediate, the 6/5 fused ring vinyl cation (I) which is readily trapped by ordinary nucleophiles, this intermediate vinyl cation should also be the product of the reaction in a non-nucleophilic environment.



I II

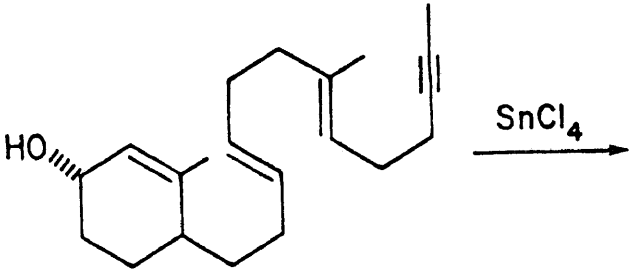
However, when this cation (I) is formed in non-nucleophilic media, there is no good nucleophile present to trap it, and thus it undergoes a Wagner-Meerwein shift[34] rearranging to the 6/6 fused ring cation (II). This 6/6 cation then, in a very slow process, abstracts a chloride ion from the solvent

forming (58). The driving force for this rearrangement could be the relief of torsional strain on going from a 6/5 to 6/6 trans-fused ring system.[33]

Continuing his study of the formation of vinyl halides from vinyl cations, Johnson investigated the effects of a Lewis acid catalyst on the product distributions from the cyclization of dienynol (52).[36] When (52) was reacted with stannic chloride in 1,1-dichloroethylene at -35 C for 45 min, the cyclization proceeded with trapping of the five-membered ring vinyl cation (I) to give as the major product the chlorodiene (60). Also, the cyclization of trienynol (61) under similar conditions yielded as the major product the chlorodiene (62) which comprised ca. 73% of the product mixture. The lesser products from this cyclization included the isomeric chlorodiene (63) (12%) and the C/D cis chlorodiene (64) (15%). The results of this reaction are illustrated in Scheme XI. Thus, the use of a Lewis acid promoter favored formation of the 6/5 fused ring vinyl chloride (62) over its 6/6 fused ring isomer (63). It is important to note that Johnson found evidence that the formation of (63) was not due to stannic chlorid induced isomerization of chlorodiene (62).[36]

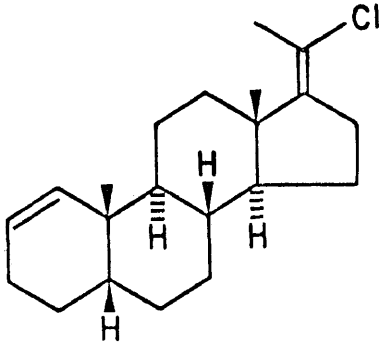
The effect of varying reaction conditions on the product distribution from the cyclization of trienynol (61) was investigated. The use of different solvents such as n-butyl chloride, methylene chloride, chloroform, carbon tetrachloride, 1,1-dichloroethylene, and tetrachloroethylene

Scheme XI

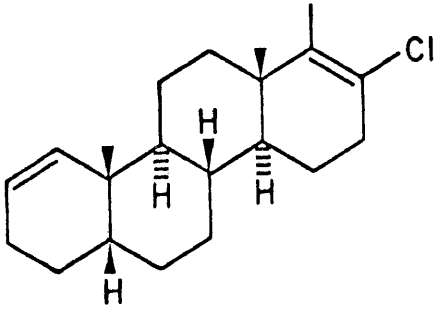


(61)

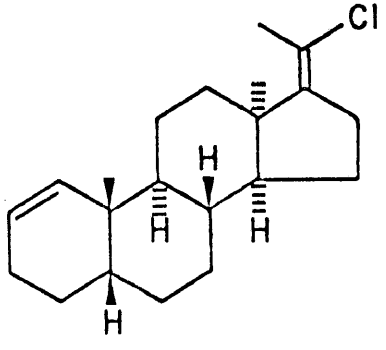
$SnCl_4$



(62)



(63)



(64)

had little effect on the relative amount of C/D cis chlorodiene (64) produced (14-19%) in the cyclization of (61) with stannic chloride at 22 °C for 15 min. However, the ratio of C/D trans chlorodiene products varied considerably with the ratio of the five-membered D-ring product (62) to six-membered D-ring product (63) changing from 46:34 in n-butyl chloride to 75:10 in 1,1-dichloroethylene.

Changing the cyclization temperature had little effect on the relative amount of C/D cis chlorodiene (64) produced. In general, increasing the temperature of the cyclization reaction with stannic chloride in either methylene chloride or 1,1-dichloroethylene favored formation of the C/D trans five-membered ring chlorodiene (62) over its six-membered isomer (63). In contrast, when titanium tetrachloride was used as the catalyst, changing the temperature had no significant effect on product ratios.[36]

Varying the reaction time did not seem to affect the product ratios, nor did changing the concentration of stannic chloride from 0.1 to 2 M in methylene chloride or from 0.1 to 1 M in 1,1-dichloroethylene. Also, the ratio of chlorodienes remained the same when the reaction was accomplished by "inverse addition." "Inverse addition" refers to the addition of the trienynol (61) to a solution of stannic chloride in methylene chloride as opposed to the normal addition where stannic chloride is added to a solution of trienynol in methylene chloride.

The addition of tetra-n-butylammonium chloride to the

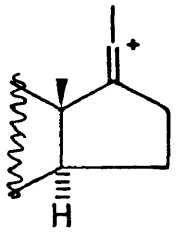
cyclization mixture containing stannic chloride in methylene chloride or titanium tetrachloride in 1,1-dichloroethylene did not effect the product ratios. Adding dry hydrogen chloride to the reaction involving stannic chloride in methylene chloride also had little effect. However, an attempt to cyclize trienynol (61) using only dry hydrogen chloride in methylene chloride afforded only recovered starting material after 15 min at 22 °C.[36]

Although the cyclization of substrates with acetylenic terminators using Lewis acid catalysts and chlorinated solvents produced various chlorine containing products, it was not clear whether the chloride ion was abstracted from the catalyst of solvent. Thus Johnson designed an experiment to determine the origin of the chlorine substituent in the product. First, trienynol (61) was cyclized with stannic bromide in methylene bromide and the three products were identified as the bromodienes analogous to the chlorodienes (62), (63), and (64).[36] Johnson then conducted two "mixed halide" cyclizations where trienynol (61) was cyclized with stannic bromide in methylene chloride and with stannic chloride in methylene bromide. In the first experiment he found a mixture of bromo and chlorodienes in a ratio of 67:33, and in the second the ratio of chloro to bromo products was 91:9. Thus we see that the halogen is abstracted from both the solvent and catalyst, but predominately from the catalyst. It seems that all vinyl cations can react with the halogen

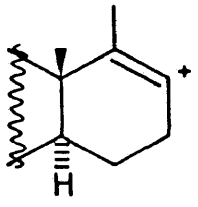
originating from the Lewis acid, but evidence shows that the C/D trans five-membered-ring vinyl cation does not abstract a halogen from the solvent. Further evidence of this can be found in the synthesis of the bicyclic compound where no five-membered ring vinyl chloride (60) was produced from the cyclization with triflouroacetic acid in methylene chloride. However, (60) was the major product when the same reaction was promoted by stannic chloride.[36]

Although the use of the methyl acetylenic terminator in the cyclization reactions led to the stereospecific synthesis of 6/5 trans fused ring compounds, the yields were modest. In hopes of improving the yields, Johnson investigated the use of the phenylacetylenic terminator and found that, while the use of substrates with the phenylacetylenic terminator did cause an improvement in yields of tetracyclic material, it also caused lower stereoselectivity with ca. 20% of the products being the unnatural C/D cis isomers.[35]

Johnson's research lends itself to several mechanistic observations. First, it appears that the kinetically favored intermediate in cyclizations involving the methylacetylenic terminator is vinyl cation (I).



I



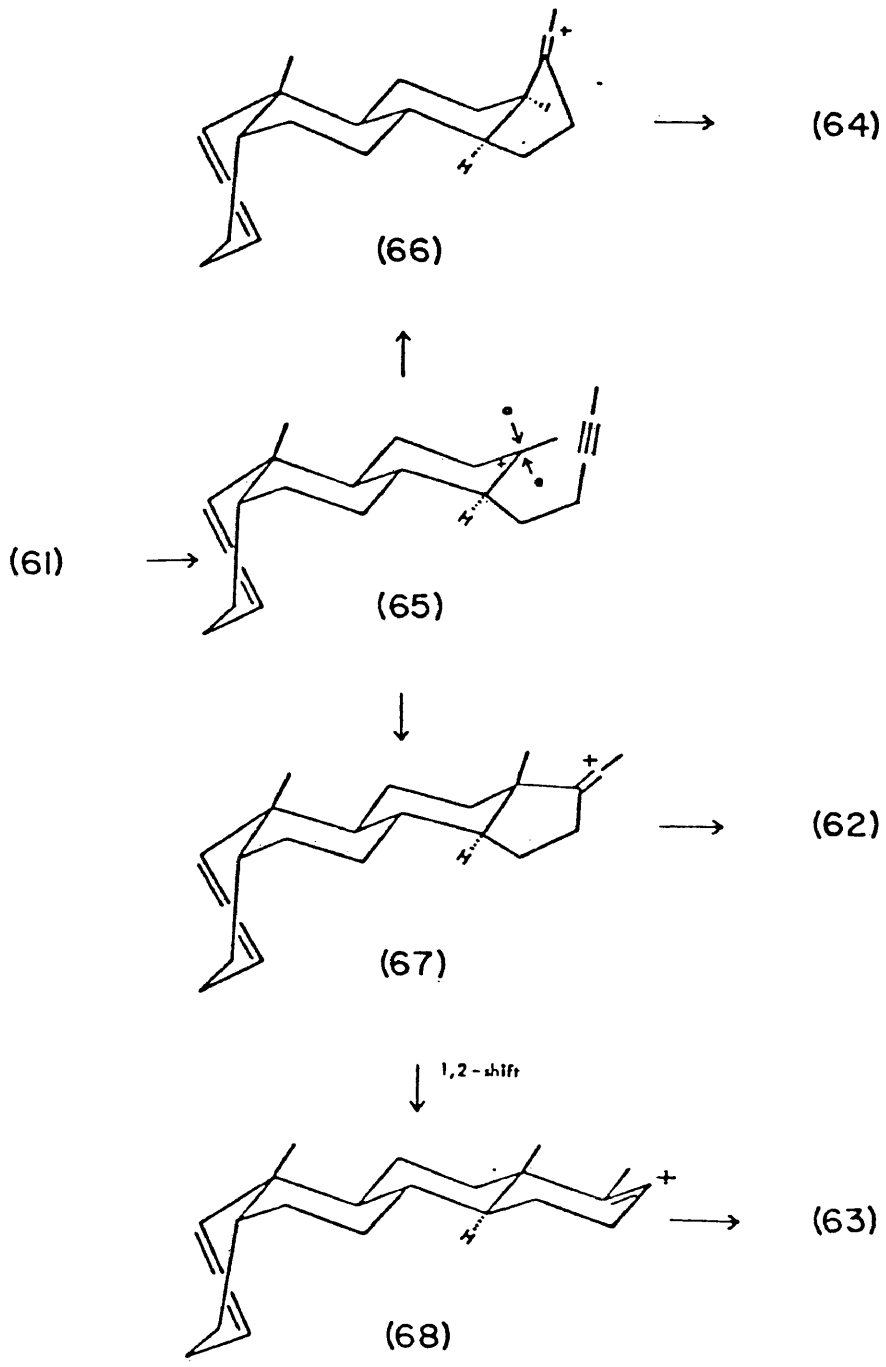
II

However, under certain conditions (I) can undergo Wagner-Meerwein rearrangement to cation (II). Although this requires conversion to the less stable bent vinyl cation, it may be energetically favored due to a relief in torsional strain on going from a 6/5 to a 6/6 trans-fused ring. This reasoning is supported by the fact that no cis-fused six-membered vinyl chloride was observed in any of Johnson's work.

Another mechanistic point is that when substrates, such as (61), with acetylenic terminators are cyclized, the ratio of products is determined by whether attack on a tricyclic cation, such as (65) in Scheme XII, is oriented axially or equatorially. Equatorial attack (indicated by "e") on the ring C-cation by the acetylenic group leads to the C/D trans five-membered ring vinyl cation (67) which can pick up a halogen from the Lewis acid or undergo rearrangement as discussed previously. If axial attack (indicated by "a") occurs, the resulting intermediate is the C/D cis vinyl cation (66) which abstracts a halogen to form (64). The observed 85:15 ratio of C/D trans to C/D cis products seems to be due to steric differences of the axial and equatorial attacks on the intermediate cation (65). The fact that changes in temperature had little effect on the relative amount of C/D cis product formed is evidence that this process has a low activation energy and a negative entropy.[36]

In conclusion, it is clear that the work of both Stapp

Scheme XII



and Johnson provides important information concerning acid-promoted cyclization reactions to form five- and six-membered cyclic compounds. Stapp's modified Prins reaction seems to be an effective way of preparing 4-halotetrahydropyran products, however he does not report the synthesis of any furans, nor does he extend his reaction to the synthesis of dihydropyrans. In fact it is not apparent that his synthesis could be used to produce the unsaturated pyran systems.

Johnson's work involves the synthesis of various fused-ring cyclic compounds including both 6/6 and 6/5 fused ring structures as well as unsaturated rings. However, Johnson's research has dealt entirely with carbocyclic compounds and has not been extended to the synthesis of cyclic ethers even though the incorporation of the oxygen atom should have no significant mechanistic consequences. All of the products of Johnson's cyclization reactions are unsaturated with the final ring either being six-membered with an endocyclic double bond, or five-membered with an exocyclic double bond. Unsaturated systems are of great interest because they are useful for future chemical conversions.

It is hoped that our cyclization reaction to produce cyclic ethers will have the scope of Johnson's cyclization to produce carbocycles as would be anticipated because of the mechanistic similarities between these reactions. It is entirely possible that control over the nature of the

products formed by our synthesis, pyrans vs. furans or unsturated vs. saturated, could be achieved by changing the substituents attached to the terminating alkene or alkyne group, thus changing the nature of the intermediate carbocation.

EXPERIMENTAL

The goal of the experimental work reported herein is to investigate and demonstrate the scope of the Lewis acid promoted cyclization of acetals of homoallylic and homopropargylic alcohols to form tetrahydropyrans and 5,6-dihydro-2H-pyrans. In general, this work involves, first, the synthesis of the starting acetals, and second, the cyclization of these acetals to form the corresponding pyrans.

REAGENTS

The homoallylic alcohol, 3-buten-1-ol, was obtained from Albany International(Farchan Labs) and Wiley Organics in 50g allotments. 3-Butyn-1-ol was purchased from Albany International and Aldrich(13,085-0) in 100g quantities. 1-Allylcyclohexanol, 50g, was obtained from Chemical Samples Co. These alcohols were stored in the refrigerator over Linde 4-A molecular sieves, and used without further purification. Preparation of 1-propargylcyclohexanol required magnesium turnings(Fisher,M-11), propargyl bromide(80 weight percent in toluene (Aldrich, PS-100-1), mercury(II) chloride(Allied Chemical Co.), and cyclohexanone(Fisher). The cyclohexanone was distilled prior to use.

The ethers used in the acetal preparations, ethylvinylether (Aldrich, E5-125-2), dihydropyran(Aldrich,

D10-620-8), and (methoxyethoxy)methyl chloride(Aldrich, 19-354-2), were kept refrigerated and used without purification. Concentrated hydrochloric acid(Fisher, A-144), 85% phosphoric acid (Fisher, A-242), and diisopropylethylamine(Aldrich, D12-580-6)) were used without purification in the various acetal forming reactions.

1-Decanol(Eastman Organic Chemicals), 1-heptanol (Eastman Organic Chemicals), and n-decane(Phillips Petroleum Co.) were used without purification as internal standards in the glc analysis of the various cyclization reactions.

Methanol(Fisher) followed by 3N HCl saturated with NaCl was used to quench the titanium tetrachloride promoted cyclization reactions. Magnesium sulfate(Fisher, M-65) was routinely used as a drying agent. Potassium carbonate(Fisher, P-208) was used as a neutralizing agent in the acetal syntheses.

SOLVENTS

Laboratory grade methylene chloride(Fisher, D-37) was used as the solvent in most cyclization reactions. It was distilled over phosphorous pentoxide under a nitrogen atmosphere, and stored over Linde 4-A molecular sieves. Diethyl ether(Fisher, laboratory grade) was routinely used for extraction purposes. Anhydrous diethylether(Fisher, E-138) was used without purification. Hexanes(Fisher, H-292) was also used without purification.

PREPARATION OF 1-PROPARGYLCYCLHEXANOL

All starting alcohols used in the acetal syntheses were

purchased except for 1-propargylcyclohexanol which was prepared according to the procedure of Brandsma and Verkruijsse[37] as described below. In general this preparation involved the synthesis of the propargylmagnesium bromide Grignard reagent, followed by its addition to cyclohexanone leading to formation of the alcohol upon hydrolysis.

A 1 L round bottom flask with three vertical necks was equipped with a stir bar and suspended over a magnetic stirrer. In one neck was placed a 125 mL dropping funnel in combination with a nitrogen gas inlet. A nitrogen gas outlet was placed in another neck, and in the third neck was placed a glass tube containing a thermocouple wire for monitoring the reaction temperature.

The flask was charged with magnesium turnings(.99 mol) followed by the successive additions of anhydrous diethylether (100 mL) and mercury(II) chloride(5.6 mmol). After stirring for 45 minutes at room temperature, an additional 250 mL of diethylether was added to the flask and the mixture cooled down to 0 °C using an ice-water bath. Once at 0 °C, 5 mL of propargyl bromide was added from the dropping funnel which contained .57 mol of the compound. Following the addition, the temperature inside the reaction flask rose to ca. 10 °C in ca. 2 min. After letting the mixture cool back down to 1 °C, another 2 mL of propargyl bromide was added. This time the temperature rose to ca. 4 °C, and, after allowing it to return to 1 °C, the remainder

of the propargyl bromide was added dropwise over a 2 h period. During this time the reaction temperature varied from 3 °C to 9 °C. After completion of the addition, the ice bath was removed, and the mixture stirred for ca. 30 min.

After the reaction time the mixture was returned to an ice bath, and cooled down to 0 °C. Cyclohexanone(59 mL, .57 mol), in 60 mL of anhydrous diethylether, was placed in the dropping funnel, and added dropwise to the stirring propargylmagnesium bromide reaction mixture over a 1 hour period. At the end of the addition, the ice bath was removed and the mixture allowed to stir while warming to room temperature.

The reaction was quenched by hydrolysis with ca. 200 mL of saturated ammonium chloride solution. The solid magnesium salts were removed by suction filtration, the filtrate poured into a separatory funnel, the layers separated, and the aqueous layer extracted twice with ether. The combined organic layers were dried over magnesium sulfate, filtered into a 500 mL round bottom flask, and concentrated on the rotary evaporator. The mixture was fractionally distilled with the product alcohol collected between 86 °C and 95 °C at 15 torr.

PREPARATION OF STARTING ACETALS

Starting acetals were synthesized by the reaction of homoallylic and homopropargylic alcohols with various ethers. They were isolated in decent yields and high purity by fractional distillation under reduced pressure, and

stored in the refrigerator over potassium carbonate. The acetal products were analyzed by gas-liquid chromatography, and characterized by ^{13}C-NMR spectroscopy, and, on occassion, by IR spectroscopy.

PREPARATION OF 2-(3-BUTYN-1-OXY)TETRAHYDROPYRAN

This acetal was prepared according to the procedure of Cowie, Landor, and Landor .[38]

A 50 mL round bottom flask was equipped with a stir bar and suspended over a magnetic stirrer. To the flask was added 10 mL (132 mmol) of 3-butyn-1-ol, and 13 mL (144 mmol) of dihydropyran. Four small drops (ca. 100 L) of concentrated hydrochloric acid were then added to the flask, and a condenser tube, with a nitrogen inlet in the top, was placed on the flask. The reaction mixture was stirred for ca. 15 minutes and allowed to cool to room temperature. The mixture was then dried and neutralized($MgSO_4$-K_2CO_3), and filtered into a 100 mL distillation flask. The product was fractionally distilled at 100 °C, and 44 torr.

PREPARATION OF 2-(3-BUTEN-1-OXY)TETRAHYDROPYRAN

This acetal was prepared using the same procedure as in the above preparation of the tetrahydropyranyl acetal of 3-butyn-1-ol with the minor differences outlined below. In this reaction we started with ca. 15 mL (175 mmol) of 3-buten-1-ol and ca. 18 mL (193 mmol) of dihydropyran. Also, the reaction vessel was placed in an ice-water bath to prevent the large temperature increase upon addition of acid noticed in the previous preparation. The mixture was

fractionally distilled and the product acetal collected in the range 96 °C-100 °C at 45 torr.

PREPARATION OF 1-(2-METHOXYETHOXY)METHOXY-3-BUTYNE

A 500 mL round bottom flask with three necks was equipped with a stir bar and placed over a magnetic stirrer. One of the necks was fitted with a nitrogen gas inlet, and another with a glass stopper. Methylene chloride (200 mL) was then added to the flask followed by 19 mL (166 mmol) of methoxyethoxymethyl chloride and 10 mL (132 mmol) of 3-butyn-1-ol. Diisopropylethylamine (28.7 mL, 165 mmol) was then added to a 50 mL dropping funnel, and the funnel placed in the third neck of the flask. The stirring reaction mixture was then cooled down to 0 °C using an ice-water bath, and the amine added dropwise from the funnel over a ca. 10 minute period. The reaction was allowed to proceed at room temperature for ca. 45 hours.

After the reaction time, hexanes (100 mL) was added to the reaction mixture, the mixture transferred to a 500 mL single neck round bottom flask, and stripped down on the rotary evaporator in order to remove the methylene chloride. Another 120 mL of hexanes was added to the flask causing the amine salt by-product of the reaction, which was soluble in methylene chloride but not hexanes, to precipitate out as an off-white solid. The salt was then removed by suction filtration and washed several times with hexanes. The filtrate was then extracted with two 75 mL portions of 10 percent acetic acid, the organic layers dried ($MgSO_4$), and

the mixture concentrated using the rotary evaporator. The product was fractionally distilled at 103 °C and 23 torr.

PREPARATION OF 1-(2-METHOXYETHOXY)METHOXY-3-BUTENE

The same procedure used in the above preparation of the MEM ether of 3-butyn-1-ol is used here in the preparation of its olefinic counterpart. In this case, 11.9 mL (139 mmol) of 3-buten-1-ol was reacted with 19.8 mL (173 mmol) of MEM chloride and 30.1 mL(173 mmol) of diisopropylethylamine. The product was fractionally distilled at 85 °C and 20 torr.

PREPARATION OF 1-(2-METHOXYETHOXY)METHOXY-1-ALLYLCYCLOHEXANE

The procedure used here is the same as that used in the synthesis of the previously discussed MEM ethers. In this reaction, 9.2 g (66 mmol) of 1-allylcyclohexanol was reacted with MEM chloride (8.2 g, 66 mmol) and diisopropylethylamine (8.5 g, 66 mmol) in 150 mL of methylene chloride. The product mixture was fractionally distilled and the desired ether collected at 145 °C and 15 torr.

PREPARATION OF 1-(2-METHOXYETHOXY)METHOXY-1-PROPARGYLCYCLOHEXANE

The previously discussed MEM ether preparation was again used here. 1-propargylcyclohexanol (72 mmol) was reacted with MEM chloride (90 mmol) and diisopropylethylamine (90 mmol) in 100 mL of methylene chloride in a 250 mL flask. The product was fractionally distilled at 125 °C and .5 torr, and collected in 65% yield. Analysis by gas-liquid chromatography showed the product to

be ca. 98% pure.

PREPARATION OF 1-(1-ETHOXYETHOXY)-1-ALLYLCYCLOHEXANE

A 100 mL round bottom flask was equipped with a stir bar and suspended over a magnetic stirrer. The flask was then charged with 1-allylcyclohexanol (9.6 g, 69 mmol) and ca. 40 ml (418 mmol) of ethylvinylether. Four small drops(ca. 100 L) of 85% phosphoric acid were then added to the stirring mixture and the flask fitted with a condenser tube and nitrogen gas inlet. The reaction stirred for 72 hours at which time 4 more drops of phosphoric acid were added, and stirring continued for another 24 hours. At this time a generous amount of potassium carbonate was added to the mixture. The product mixture was then gravity filtered, excess ethylvinylether removed by rotary evaporation, and the product acetal obtained in pure form by fractional distillation under reduced pressure.

PREPARATION OF 1-(1-ETHOXYETHOXY)-1-PROPARGYLCYCLOHEXANE

The same basic procedure used in the preparation of the ethylvinylether acetal of 1-allylcyclohexanol described above is used here. In this case 1-propargylcyclohexanol (72 mmol) was reacted with ca. 40 mL of ethylvinylether. The reaction time was 58 hours, and the product was fractionally distilled at 87 °C and .25 torr. Analysis by gas-liquid chromatography showed showed the product, which was isolated in 63% yield, to be ca. 92% pure.

CYCLIZATION OF ACETALS TO FORM PYRAN PRODUCTS

The pyran-forming cyclization reactions were all run

according to the same basic procedure. However, many variations to the procedure were examined. These included changes in reaction conditions, reaction times, stoiciometries, solvents, and, in some cases, in the basic procedure itself. A general cyclization procedure is given below. The specific details of the various cyclizations are given in each case. These details describe only the single set of conditions under which the reaction worked best. In the cyclization descriptions the term Kugelrohr distillation refers to a bulb-to-bulb short path distillation in which the distillation pot is heated with hot air.

A 3-necked 250 mL round bottom flask was equipped with a stir bar and suspended over a magnetic stirrer. To the flask was added 100 mL of dry methylene chloride. The flask was then fitted with a nitrogen gas inlet, glass stopper, and rubber septum cap. A slow rate of nitrogen gas flow was maintained throughout the reaction. X mmoles (x=5,10, or 20) of titanium tetrachloride were then carefully transferred from a sealed ampule to the reaction flask ($TiCl_4$ is very reactive and sensitive to atmospheric moisture and thus should be handled with extreme caution).

A low temperature bath was prepared using a Dewar flask, liquid nitrogen, and either toluene (-95 °C), chloroform (-63 °C), or chlorobenzene (-45 °C). A low temperature bath utilizing ice and distilled water (0 °C) was also used at times. The reaction vessel was then submerged in the bath and the mixture stirred for 5 to 10 minutes to

allow the temperature inside the flask to equilibrate with the bath temperature. At this time the acetal (ca. 10 mmol) was drawn into a 2.5 mL plastic syringe and the syringe weighed. The contents of the syringe were then added, dropwise, to the stirring reaction mixture over a 3-5 minute period, and the syringe weighed again.

The reaction was allowed to proceed for x minutes (x=5, 10, 15, or 60) from the end of the addition, at which time methanol (5 mL) was rapidly added to the vessel from a plastic syringe, followed by 3N HCl saturated with NaCl (50 mL) also from a syringe. The reaction vessel was then removed from the bath, and the mixture allowed to stir rapidly while warming to room temperature. At this point either 1-decanol, 1-heptanol, or n-decane (5 mmol) was added to the mixture as an internal standard. A small aliquot of the organic layer of the reaction mixture was then transferred, by pipet, to a small vial, dried over magnesium sulfate, and used for gas-liquid chromatographic analysis.

REACTION WORKUP AND PRODUCT ISOLATION

The reaction mixture was transferred to a 250 mL separatory funnel, the organic, and aqueous layers separated, and the aqueous layer extracted three times with diethylether. The combined organics were dried($MgSO_4$) and gravity filtered into a 500 mL round bottom flask. The solvent was then stripped off by rotary evaporation, and the desired pyran product isolated by preparative gas-liquid chromatography or Kugelrohr distillation. The products were

characterized by ^{13}C-NMR (decoupled and off-resonance decoupled), ^{1}H-NMR, and IR spectroscopy.

CYCLIZATION OF 2-(3-BUTYN-1-OXY)TETRAHYDROPYRAN TO 4-CHLORO-2-(4-HYDROXYBUTYL)-5,6-DIHYDRO-2H-PYRAN

The tetrahydropyranyl acetal of 3-butyn-1-ol (1.55 g, 10.1 mmol) was added dropwise to a stirring mixture of $TiCl_4$ (20 mmol) in 100 mL of methylene chloride at -95°C. The reaction was allowed to proceed for 15 minutes at which time it was quenched with 5 mL of methanol followed by 50 mL of the saturated 3N HCl solution. 1-Decanol (5 mmol) was then added as an internal standard for glc analysis, and the yield determined to be 60%. The previously described standard workup was employed with the product being isolated by preparative glc using a 6ft. 10% SE-30 column at 200 C. Analysis by glc showed the isolated product to be ca. 95% pure.

CYCLIZATION OF 2-(3-BUTEN-1-OXY)TETRAHYDROPYRAN TO 4-CHLORO-2-(4-HYDROXYBUTYL)TETRAHYDROPYRAN

The tetrahydropyranyl acetal of 3-buten-1-ol (1.46 g, 9.3 mmol) was added dropwise to a stirring mixture of $TiCl_4$ (10 mmol) in 100 mL of methylene chloride at -95 °C. The reaction was allowed to proceed for 15 minutes at which time it was quenched with 5 mL of methanol followed by 50 mL of the saturated 3N HCl solution. 1-Decanol (5 mmol) was then added as an internal standard for glc analysis. The yield for this reaction was calculated to be ca. 92%. Following the standard workup the product was isolated, in ca. 97%

pure form, by Kugelrohr distillation.

CYCLIZATION OF 1-(2-METHOXYETHOXY)METHOXY-3-BUTYNE TO 4-CHLORO-5,6-DIHYDRO-2H-PYRAN

The MEM ether of 3-butyn-1-ol (1.615 g, 10.2 mmol) was added dropwise to a stirring mixture of $TiCl_4$ (20 mmol) in 100 mL of methylene chloride at -45°C. The reaction was allowed to proceed for ca. 20 minutes at which time it was quenched with methanol (8 mL) and the saturated 3N HCl solution (35 mL). 1-heptanol was added as the internal standard and the reaction yield determined to be ca. 88% by glc analysis. The product was isolated by preparative glc using a 10ft. 20% SP-1000 column.

CYCLIZATION OF 1-(2-METHOXYETHOXY)METHOXY-3-BUTENE TO 4-CHLOROTETRAHYDROPYRAN

The MEM ether of 3-buten-1-ol (1.68 g, 10.5 mmol) was cyclized in the presence of $TiCl_4$ (20 mmol). The reaction was run in 100 mL of methylene chloride at 0°C for 15 minutes. After the reaction time, methanol (6 mL) and 3N HCl saturated with NaCl (35 mL) were added to the reaction mixture. 1-heptanol (5 mmol) was added as an internal standard for glc analysis and the yield for the reaction determined to be ca. 87%. The product was was isolated by preparative glc using a 10ft. 20% SP-1000 column.

CYCLIZATION OF 1-(2-METHOXYETHOXY)METHOXY-1-ALLYLCYCLOHEXANE TO 4-CHLORO-OXASPIRO[5.5.]UNDECANE

The MEM ether of 1-allylcyclohexanol (2.65 g, 11.6

mmol) was added dropwise to a stirring mixture of $TiCl_4$ (12 mmol) in methylene chloride (100 mL) at -45°C, and the reaction allowed to run for ca. 20 minutes. After the reaction time, methanol (5 mL), followed by 3N HCl saturated with NaCl (40 mL) was added to the stirring mixture. After allowing the mixture to warm to room temperature, 1-decanol was added as an internal standard for glc analysis and the reaction yield determined to be ca. 88%. The product was isolated in 96% pure form by Kugelrohr distillation.

CYCLIZATION OF 1-(2-METHOXYETHOXY)METHOXY-1-PROPARGYL-CYCLOHEXANE TO 4-CHLORO-OXASPIRO[5.5.]-3-UNDECENE

The MEM ether of 1-propargylcyclohexanol (2.54 g, 11.2 mmol) was added dropwise to a stirring mixture of $TiCl_4$ (20 mmol) in 100 mL of methylene chloride. The reaction temperature was -45°C, and the reaction time 20 minutes. This reaction was quenched with methanol (10 mL) followed by 3N HCl saturated with NaCl (40 mL). 1-Decanol was added as an internal standard for glc analysis, and the yield determined to be ca. 40%. The product was obtained in 97% pure form by Kugelrohr distillation.

CYCLIZATION OF 1-(1-ETHOXYETHOXY)-1-ALLYLCYCLOHEXANE TO 4-CHLORO-2-METHYL-OXASPIRO[5.5.]UNDECANE

The ethylvinylether acetal of 1-allylcyclohexanol (1.51 g, 7.1 mmol) was added dropwise to a stirring mixture of $TiCl_4$ (10 mmol) in methylene chloride (100 mL) at 0°C for 10 minutes. After the reaction time methanol (5 mL) and 3N HCl

saturated with NaCl (40 mL) were added to quench the reaction. N-decane was added as an internal standard for glc analysis and the yield for the reaction determined to be ca. 94%. Kugelrohr distillation yielded a 99% pure product.

CHARACTERIZATION TECHNIQUES

GAS-LIQUID CHROMATOGRAPHY

Analytical gas chromatographic analysis was carried out using Hewlett-Packard models 5710A and 5790A instruments with flame ionization detectors. The chromatographs were interfaced with Hewlett-Packard 3380S and 3390A integrators, respectively. All analyses were carried out using either a 10' x 1/8" 10% Carbowax 20M packed column, a 10' x 1/8" 3% OV 225 packed column, or a 30 meter methylsilicone capillary column.

Employing the internal standard technique, product yields were determined by glc analysis. Using a sample of 4-chloro-2- methyl-5,6-dihydro-2H-pyran, the response factor for this compound, versus a 1-heptanol standard, was calculated to be 1.25. Other response factors were estimated based on previous work done with similar compounds and standards. All quantitative glc analysis was done using the model 5710A chromatograph with the 10% Carbowax 20M column.

Preparative gas-liquid chromatography was carried out on a Hewlett-Packard model 5750 instrumental gas chromatograph equipped with a thermal conductivity detector.

The columns used in preparative separations included a 6' x 1/4" 10% SE-30 and a 10' x 1/4" 20% SP-1000.

NUCLEAR MAGNETIC RESONANCE SPECTROSCOPY

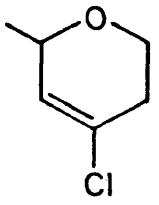
^{1}H and ^{13}C(decoupled and off-resonance decoupled) nuclear magnetic resonance spectra were obtained using a Varian FT-80A NMR spectrometer.

INFRARED SPECTROSCOPY

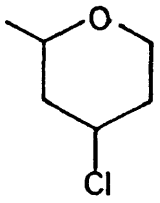
Infrared spectra of many of the intermediate acetals and product pyrans were obtained using a Perkin-Elmer 1320 spectrophotometer.

RESULTS AND DISCUSSION

The work of Seamon[5] resulted in a new approach to the synthesis of six-membered cyclic ethers. This synthesis involves the Lewis acid promoted cyclization of acetals of homoallylic and homopropargylic alcohols, and was first utilized in the preparation of 4-chloro-2-methyl-5,6-dihydro-2H-pyran (1) from the ethyl vinyl ether based acetal of 3-butyn-1-ol. Additional work by Thompson, et al.[6] extended this synthesis to include the cyclization of the ethyl vinyl ether based acetal of the homoallylic alcohol, 3-buten-1-ol, to form 4-chloro-2-methyltetrahydropyran (2).



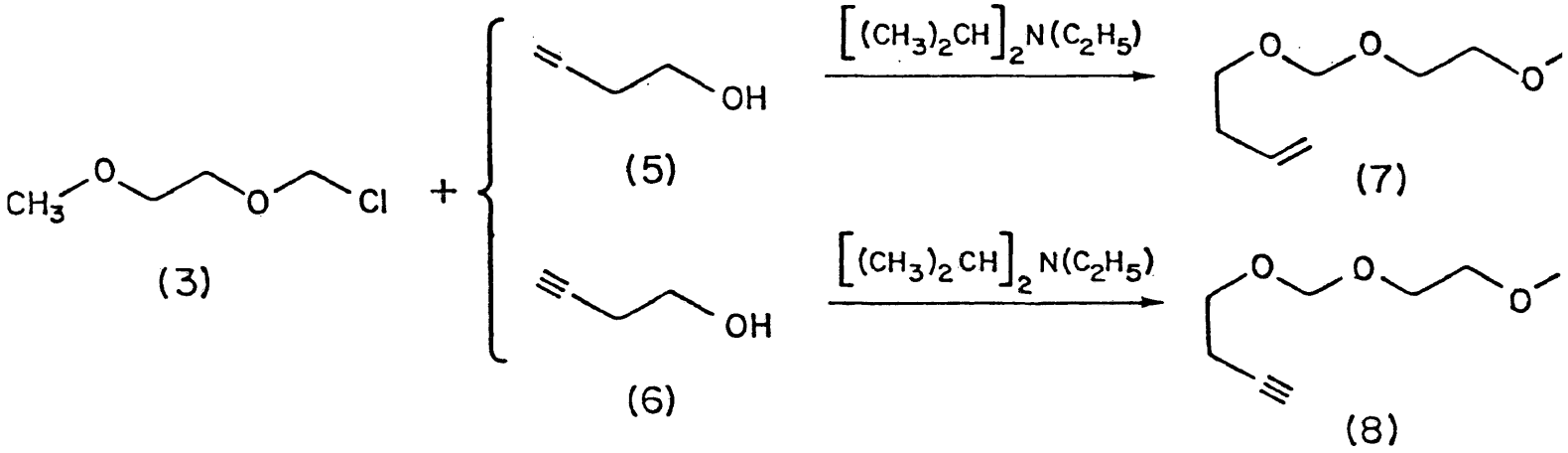
(1)

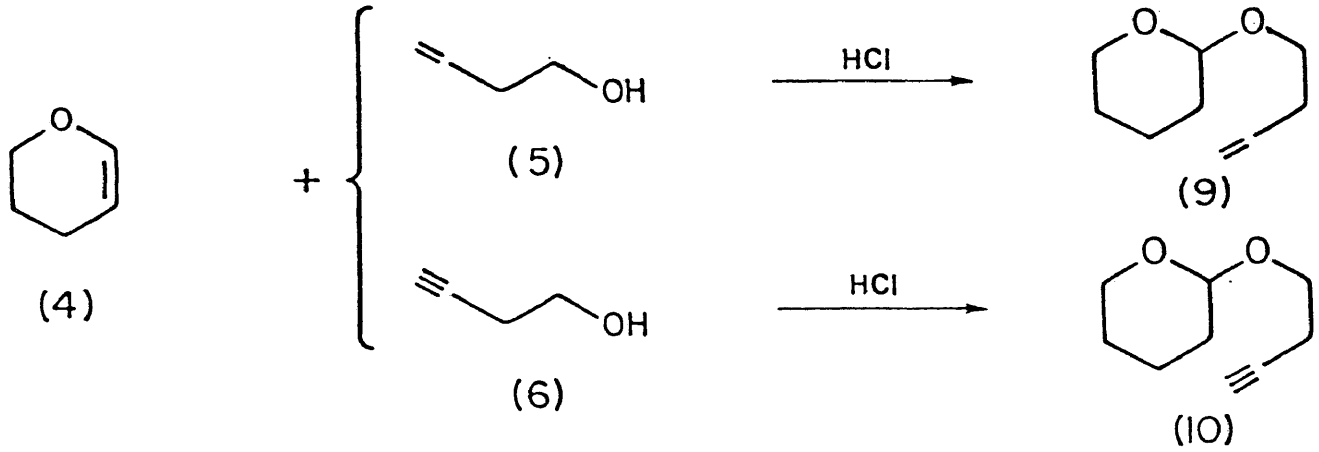


(2)

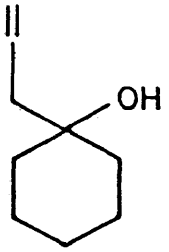
The results reported in this thesis represent an extension of this systhesis to the cyclization of the acetals derived from (2-methoxyethoxy)methyl, "MEM", chloride (3) and dihydropyran (4) in combination with the simple homoallylic and homopropargylic alcohols, 3-buten-1-ol (5) and 3-butyn-1-ol (6), respectively (see Scheme XIII). Also, this synthetic approach was used to

Scheme XIII

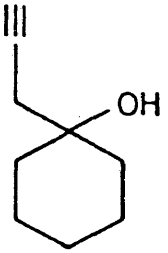

CH3
O
O
Cl
(3)
+
OH
(5)
OH
(6)
[(CH3)2CH]2N(C2H5)
[(CH3)2CH]2N(C2H5)
O
O
O
(7)
O
O
O
(8)


O
(4)
+
OH
(5)
OH
(6)
HCl
HCl
O
O
(9)
O
O
(10)

prepare representative spiro compounds by cyclizing the ethyl vinyl ether and MEM chloride based acetals of 1-allylcyclohexanol (11) and 1-propargylcyclohexanol (12).



(11)



(12)

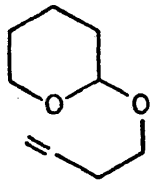
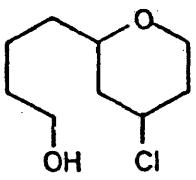
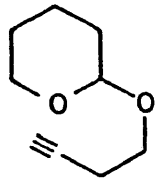
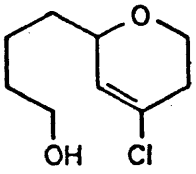
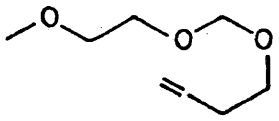
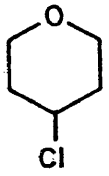
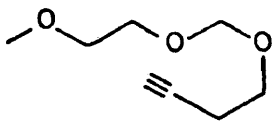
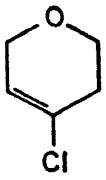
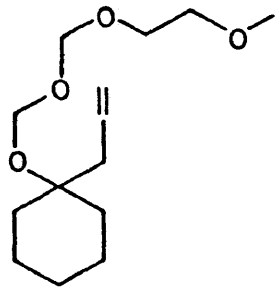
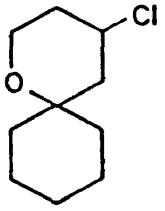
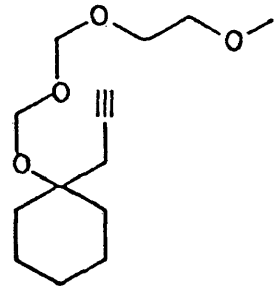
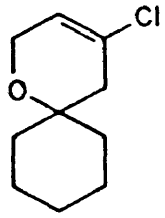
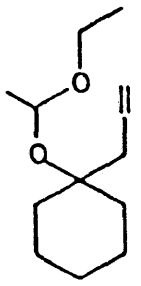
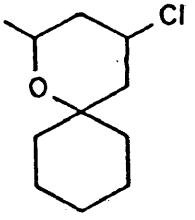
Table IV presents the starting acetals, cyclization products, and reaction yields.

As a first step in our research the starting acetals had to be prepared. The acetals derived from MEM chloride were synthesized by the addition of a small excess of diisopropylethylamine to a mixture of the alcohol and MEM chloride in methylene chloride. The reaction was allowed to proceed for 1-2 d. After the addition of hexanes and removal of methylene chloride, the ammonium salt by-product was removed by filtration, and the desired acetal product isolated by fractional distillation.

The acetals derived from dihydropyran were prepared by the addition of a catalytic amount of concentrated hydrochloric acid to a mixture of the alcohol in a small excess of dihydropyran, the reaction allowed to proceed for 15 min, and then neutralized with potassium carbonate. The products were isolated by fractional distillation.

Finally, the acetals derived from ethyl vinyl ether and

Table IV
Starting Acetals and Products

Starting Acetal	Product Pyran	Yield, %
		92
		65
		87
		88
		88
		40
		94

either 1-allylcyclohexanol or 1-propargylcyclohexanol were synthesized by adding a catalytic amount of 85% phosphoric acid to a mixture of the alcohol in a large excess of ethyl vinyl ether. After a reaction time of 3-4 d and neutralization of excess acid, the acetal products were isolated by fractional distillation. All acetals were characterized by ^{13}C-NMR and the spectra are presented in Figures I-VIII. The IR spectra of the MEM chloride and ethyl vinyl ether based acetals of 1-propargylcyclohexanol are presented in Figures IX and X respectively.

The cyclization of the various acetals were accomplished using the general procedure previously outlined in the experimental section. A variety of reaction conditions were employed in an attempt to optimize the yields and product distributions in these reactions, especially in the cyclizations of the tetrahydropyranyl acetals of 3-buten-1-ol and 3-butyn-1-ol.

The cyclization of the dihydropyran based acetal of 3-butyn-1-ol to 4-chloro-2-(4-hydroxybutyl)-5,6-dihydro-2H-pyran was best accomplished by reacting 1 equivalent of the alcohol with 2 equivalents of titanium tetrachloride at -95°C for 15 min. The desired product, as confirmed by ^{13}C and ^{1}H-NMR and IR spectroscopy (Figures XI-XIV), was produced in 65% yield according to quantitative glc analysis using the internal standard technique.

Variations in reaction conditions such as temperature,

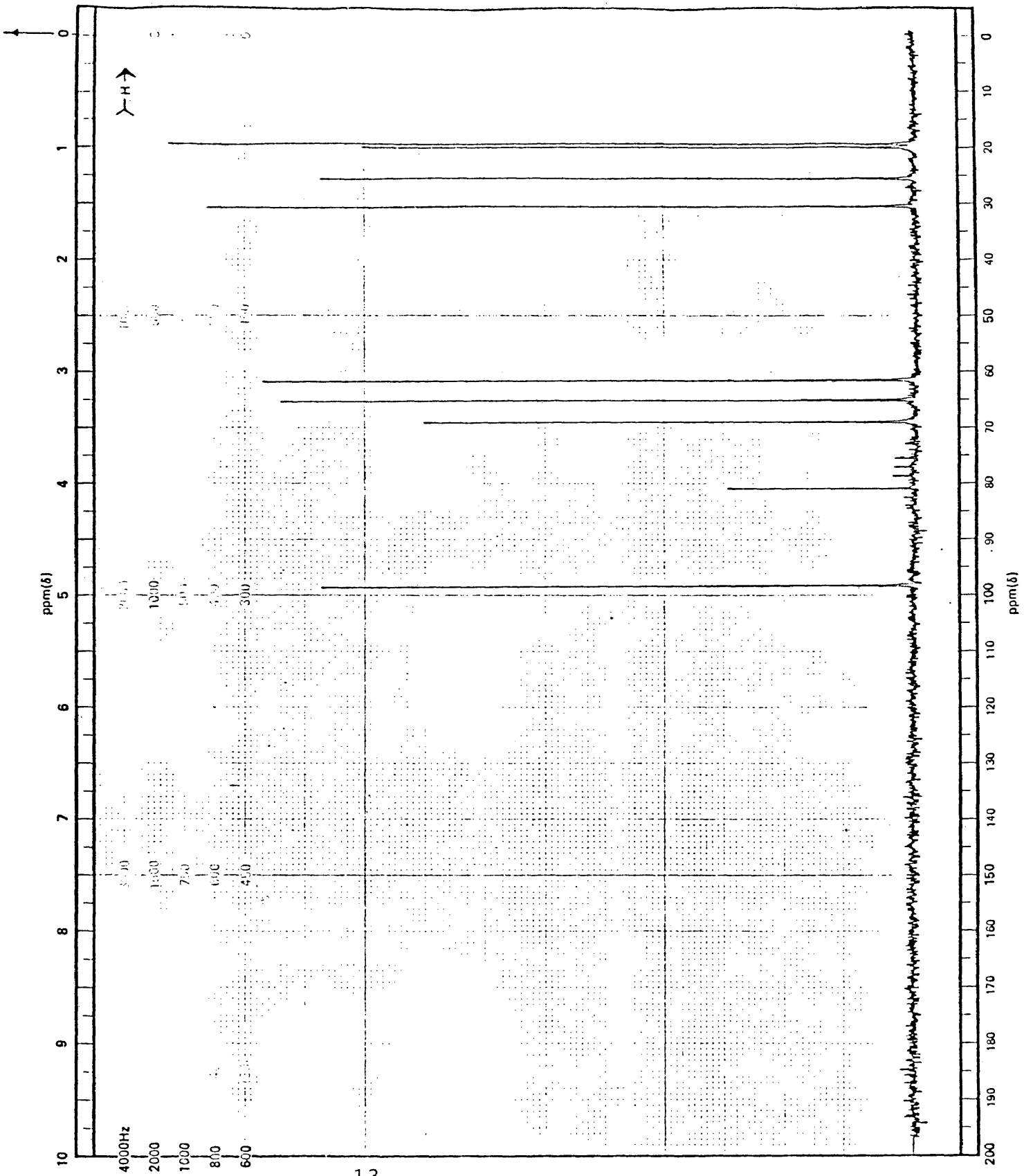


Figure I. Decoupled ^{13}C-NMR Spectrum of 2-(3-Butyn-1-oxy)tetrahydropyran.

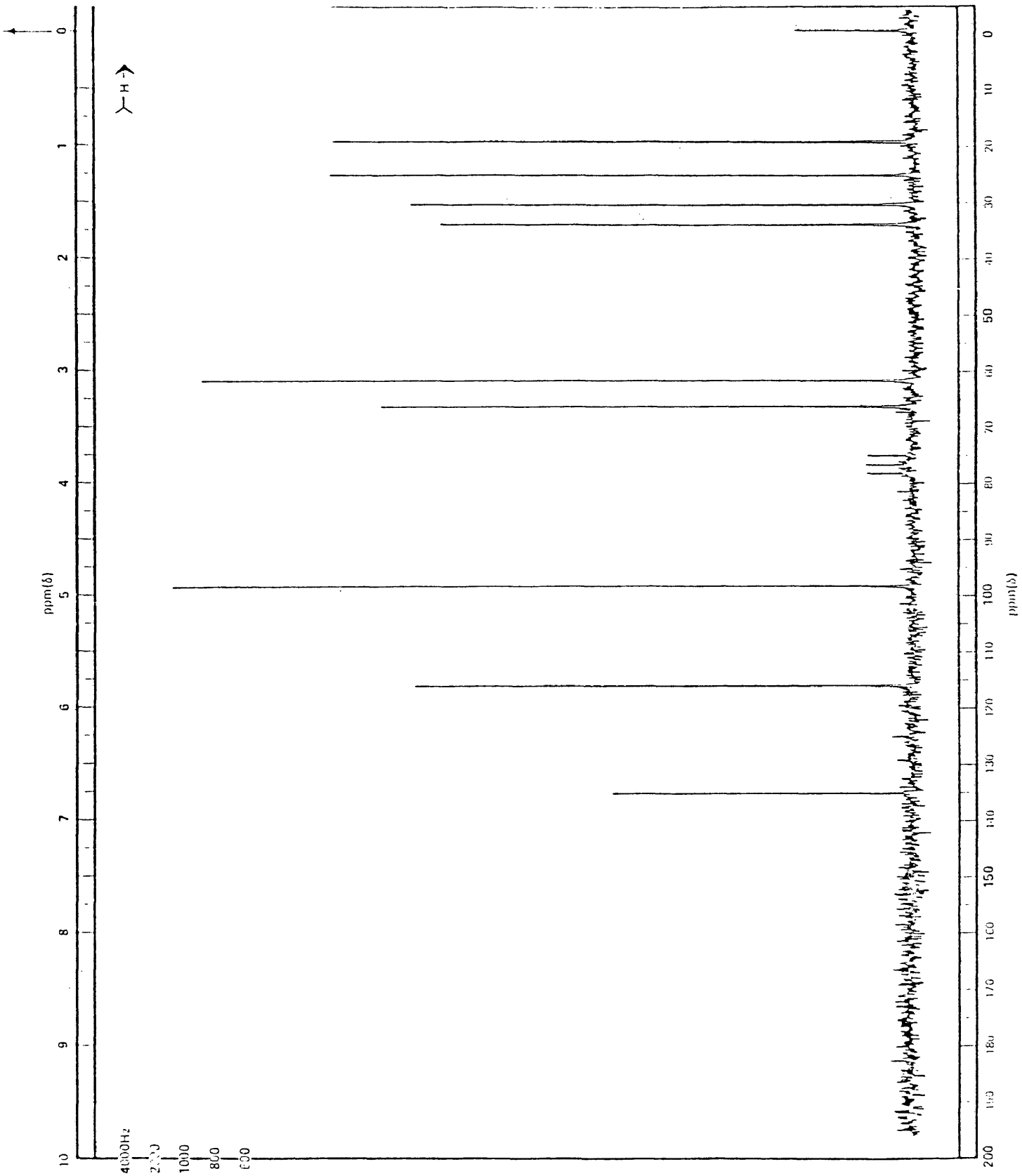


Figure II. Decoupled ^{13}C-NMR Spectrum of 2-(3-Buten-1-oxy)tetrahydropyran.

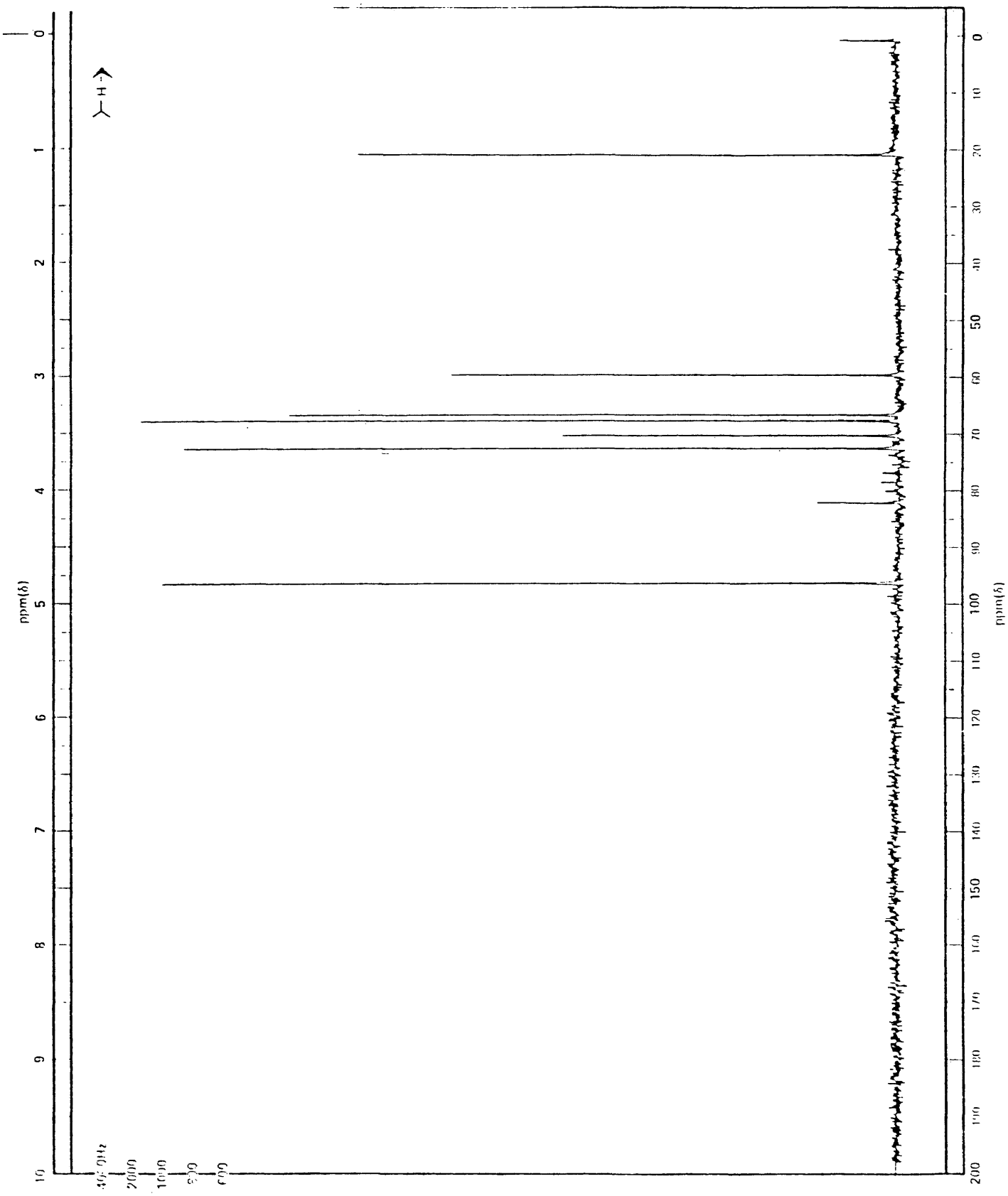


Figure III. Decoupled ^{13}C-NMR Spectrum of 1-(2-Methoxyethoxy)-methoxy-3-butyne.

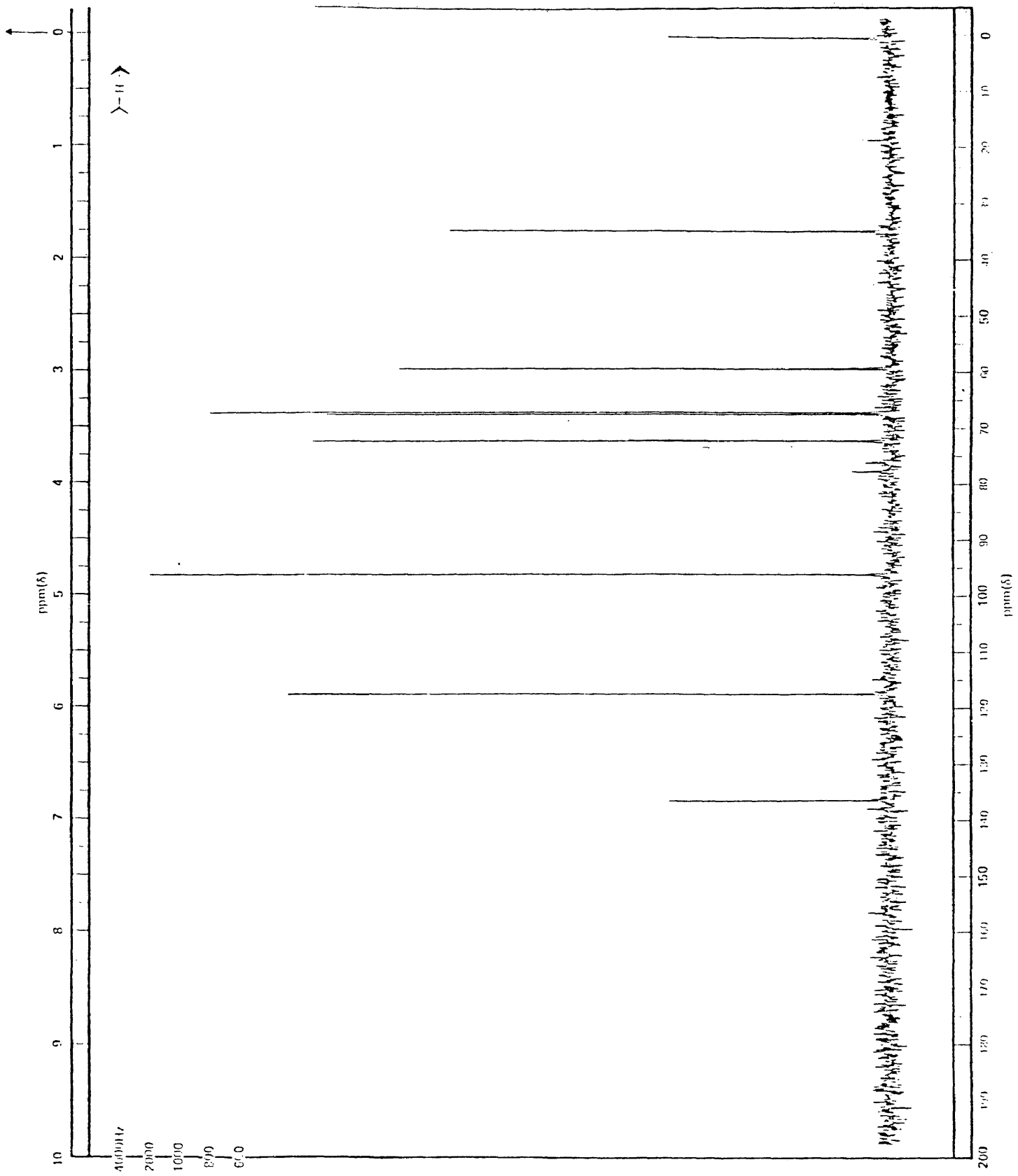


Figure IV. Decoupled ^{13}C-NMR Spectrum of 1-(2-Methoxyethoxy)-methoxy-3-butene.

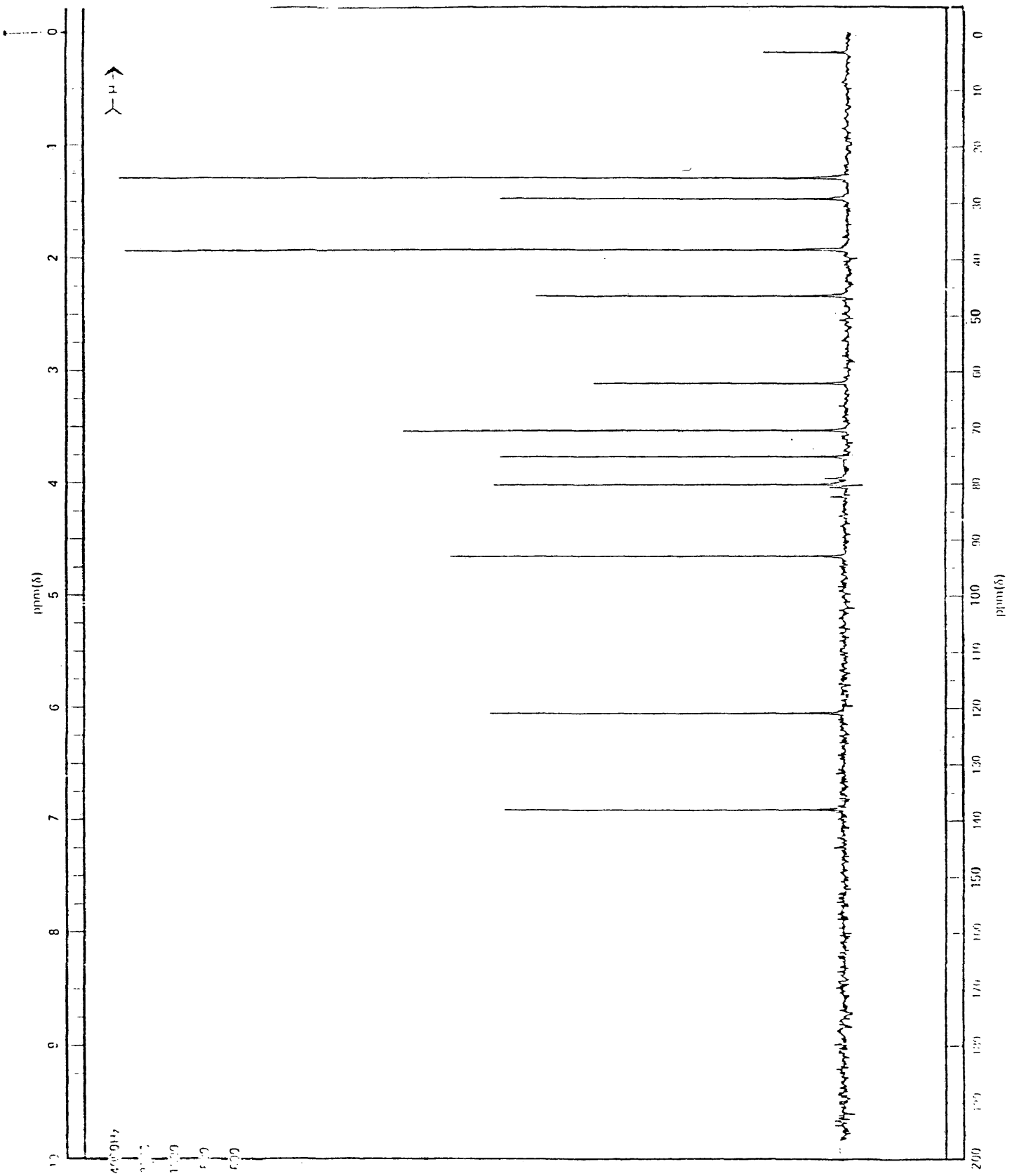


Figure V. Decoupled ^{13}C-NMR Spectrum of 1-(2-Methoxyethoxy)-methoxy-1-allylcyclohexane.

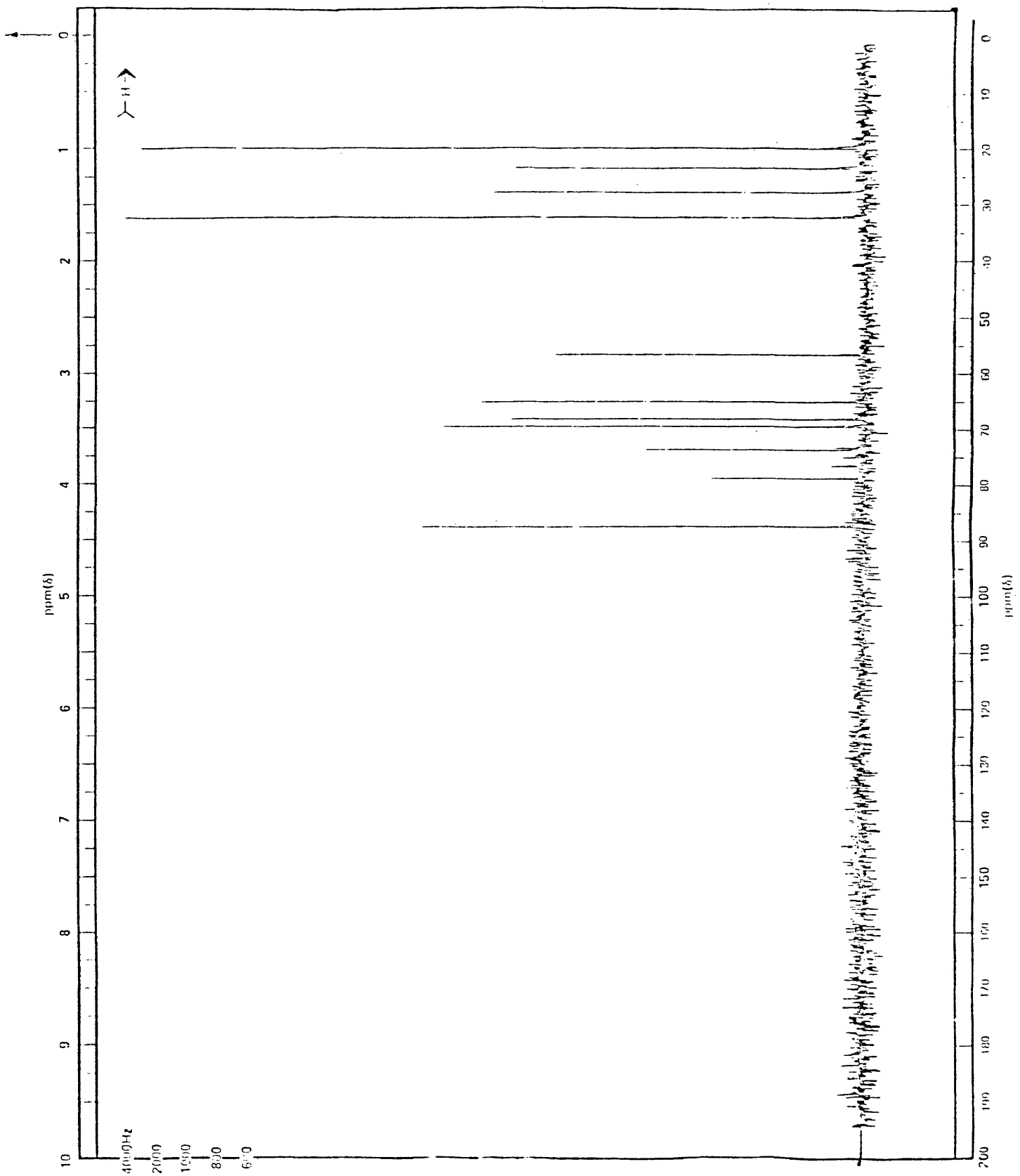


Figure VI. Decoupled ^{13}C-NMR Spectrum of 1-(2-Methoxyethoxy)-methoxy-1-propargylcyclohexane.

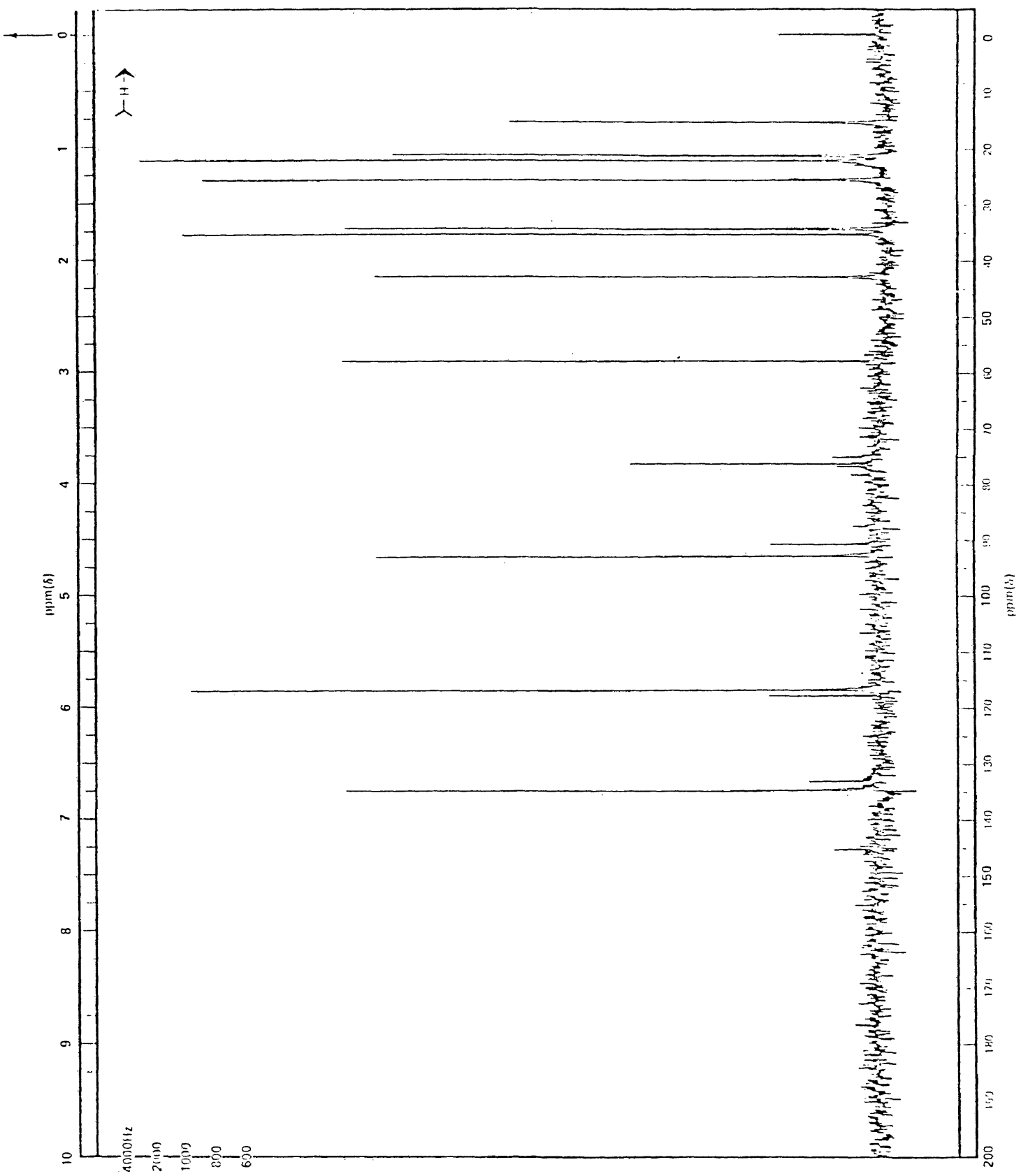


Figure VII. Decoupled ^{13}C-NMR Spectrum of 1-(1-Ethoxyethoxy)-1-allylcyclohexane.

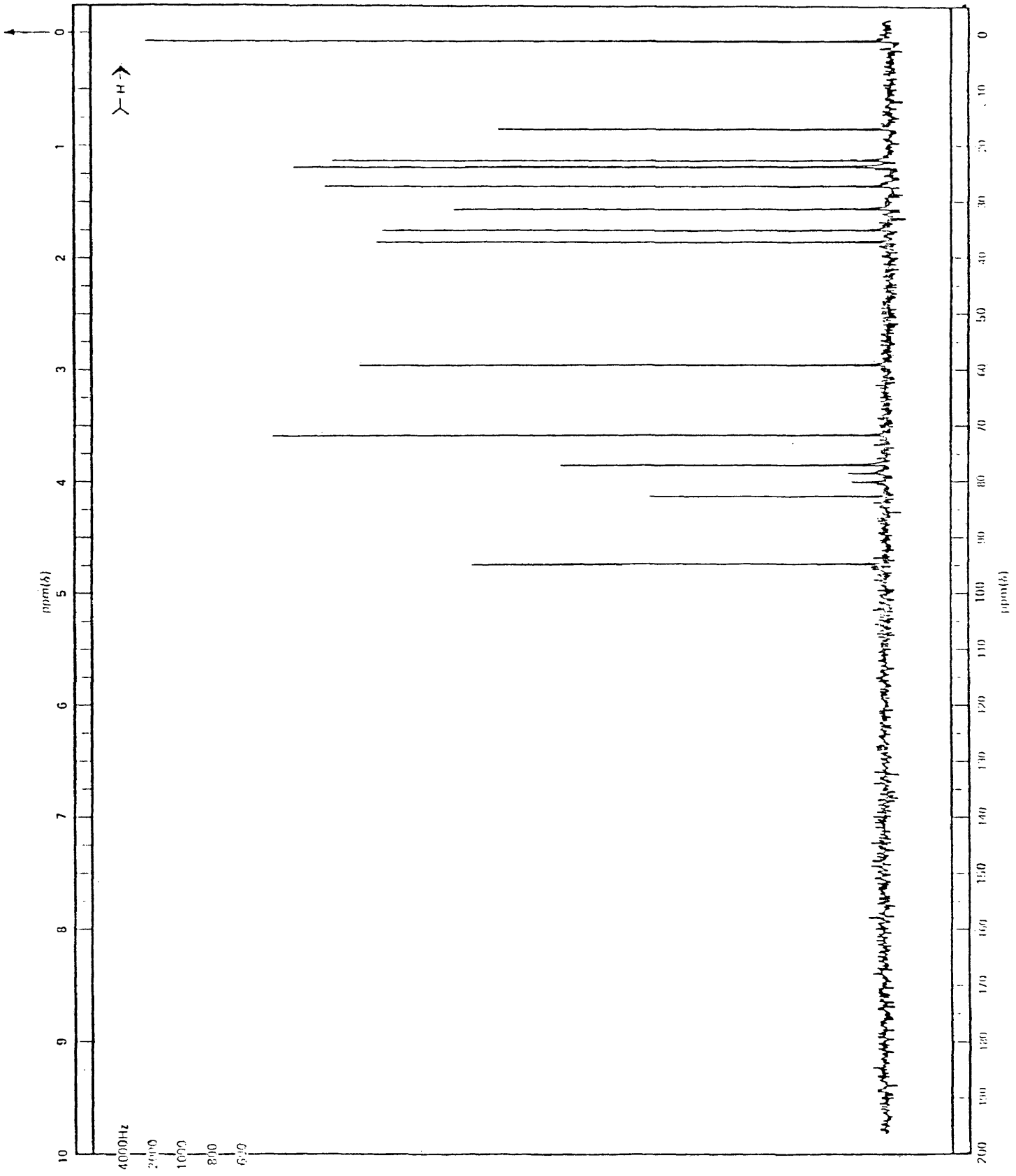


Figure VIII. Decoupled ^{13}C-NMR Spectrum of 1-(1-Ethoxyethoxy)-1-propargylcyclohexane.

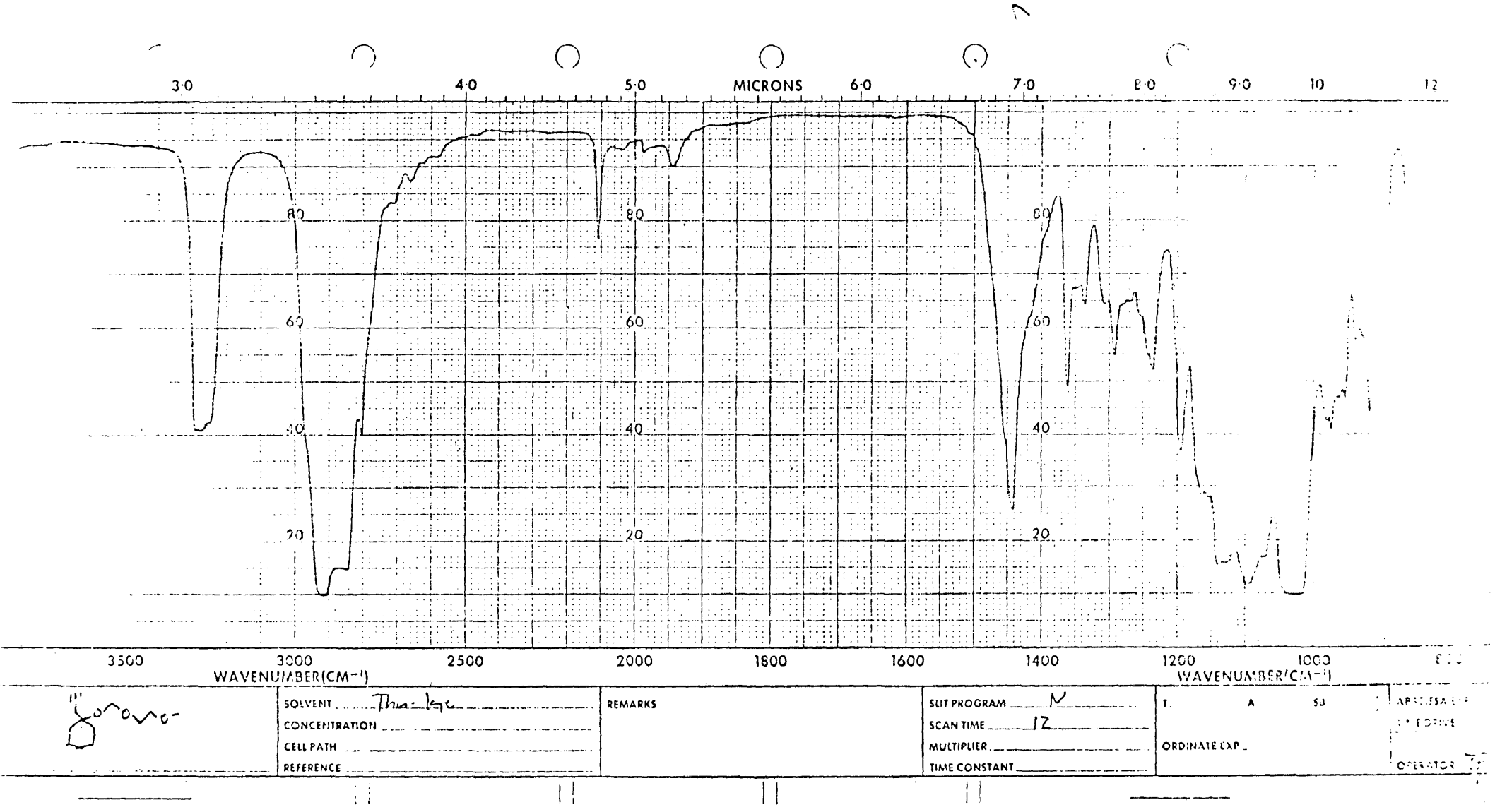


Figure IX. IR Spectrum of 1-(2-Methoxyethoxy)methoxy-1-propargylcyclohexane.

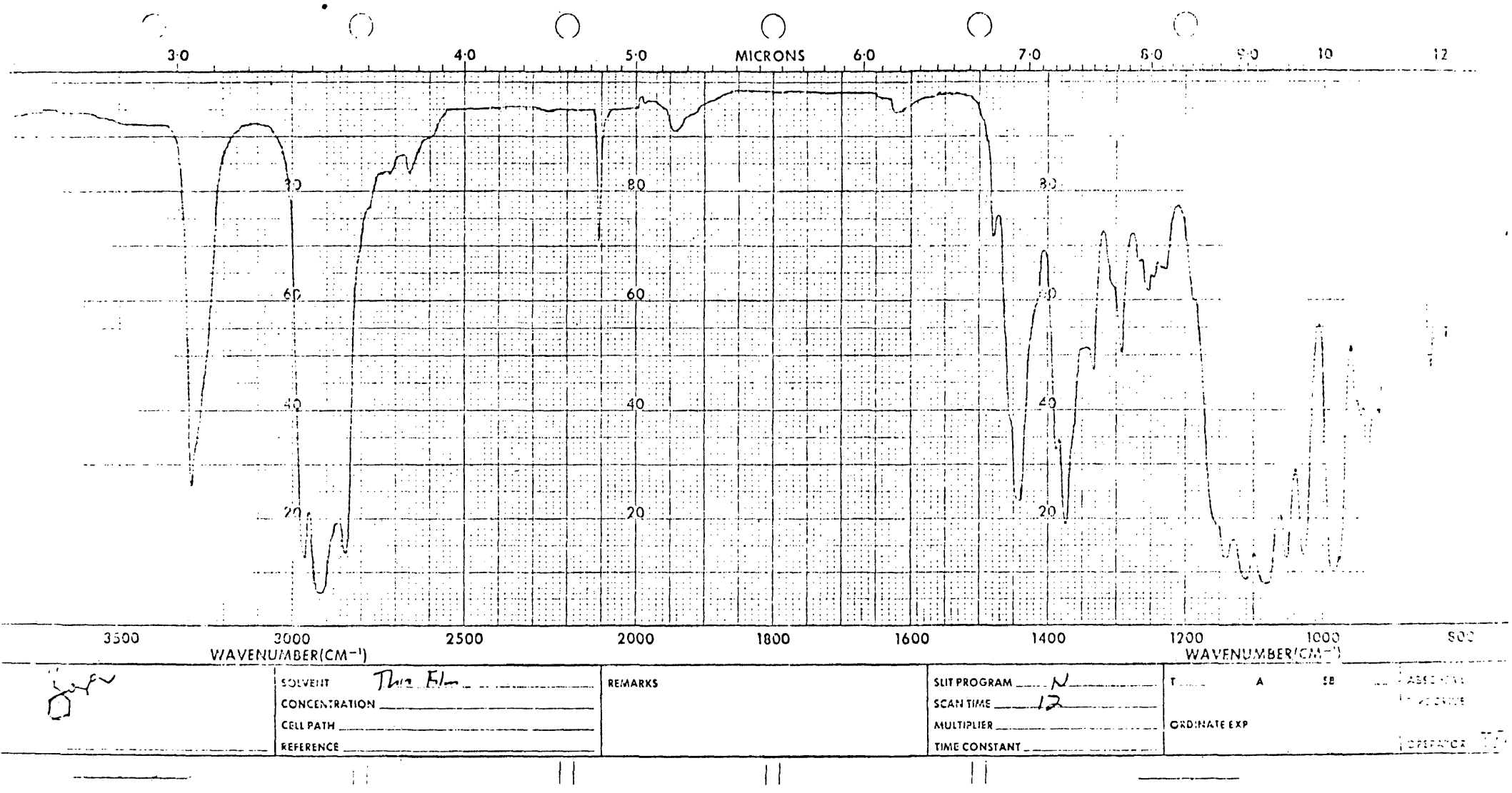


Figure X. IR Spectrum of 1-(1-Ethoxyethoxy)-1-propargylcyclohexane.

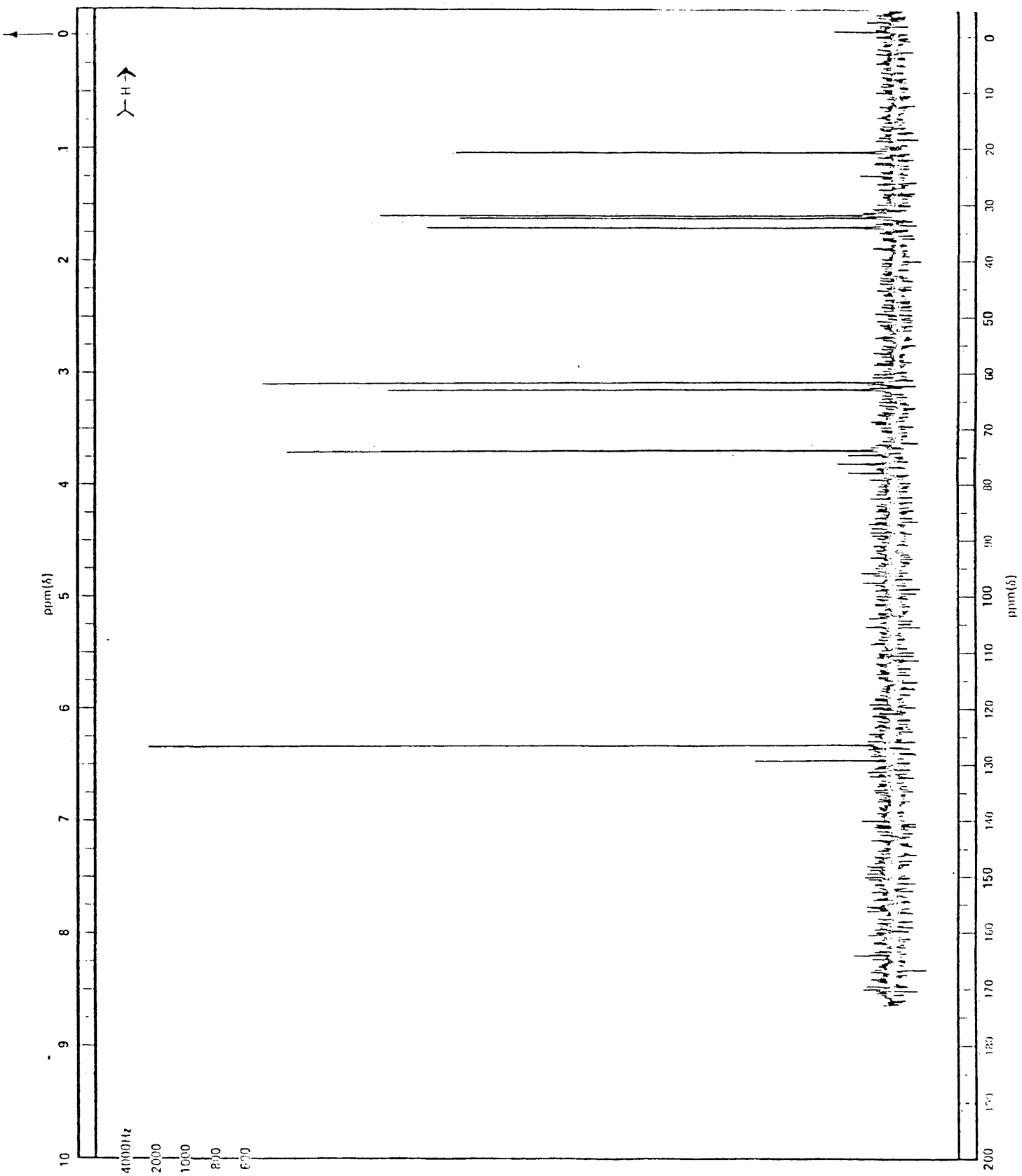


Figure XI. Decoupled ^{13}C-NMR Spectrum of 4-Chloro-2-(4-hydroxybutyl)-5,6-dihydro-2H-pyran.

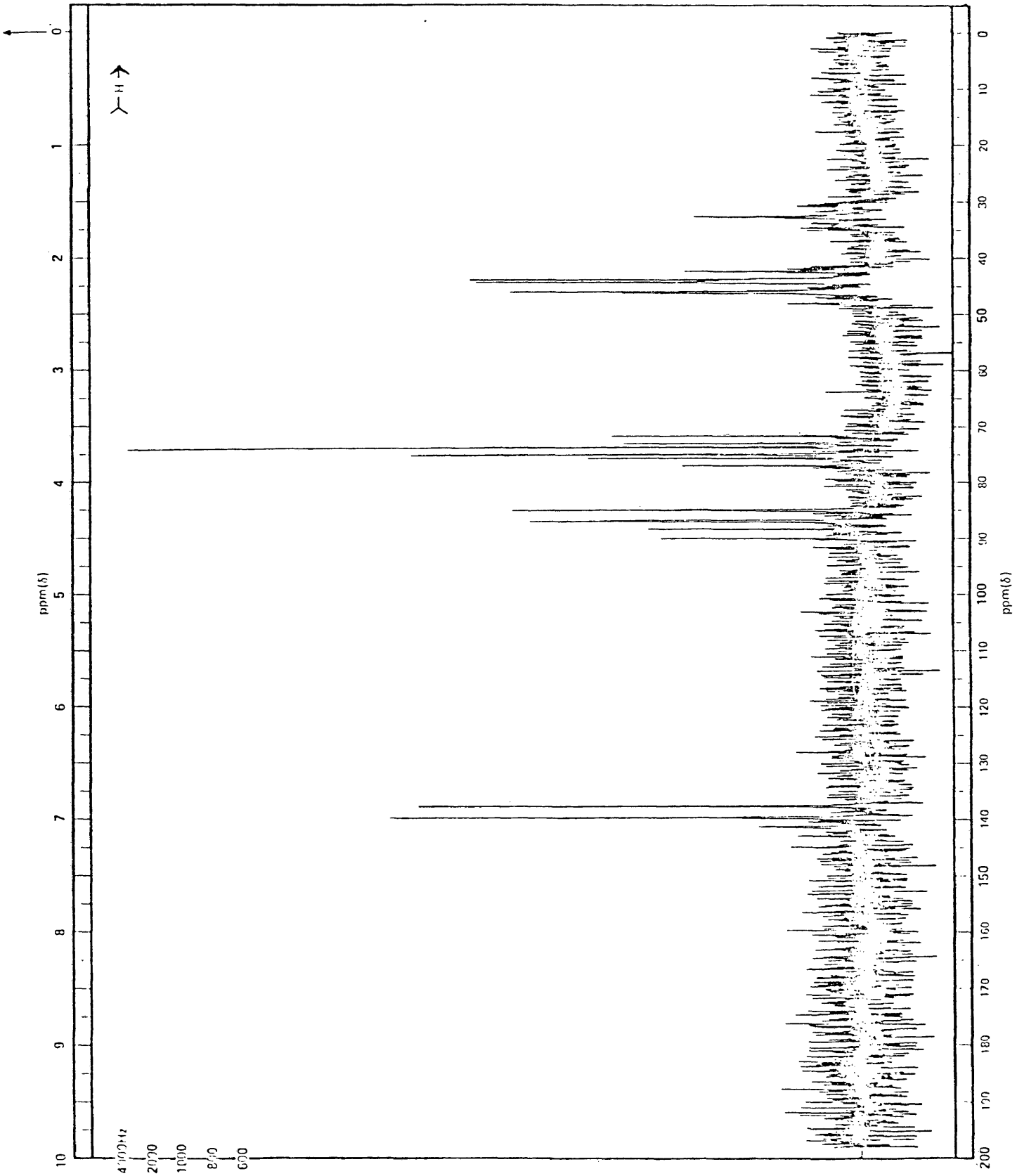


Figure XII. Off-Resonance Decoupled ^{13}C-NMR Spectrum of 4-Chloro-2-(4-hydroxybutyl)-5,6-dihydro-2H-pyran.

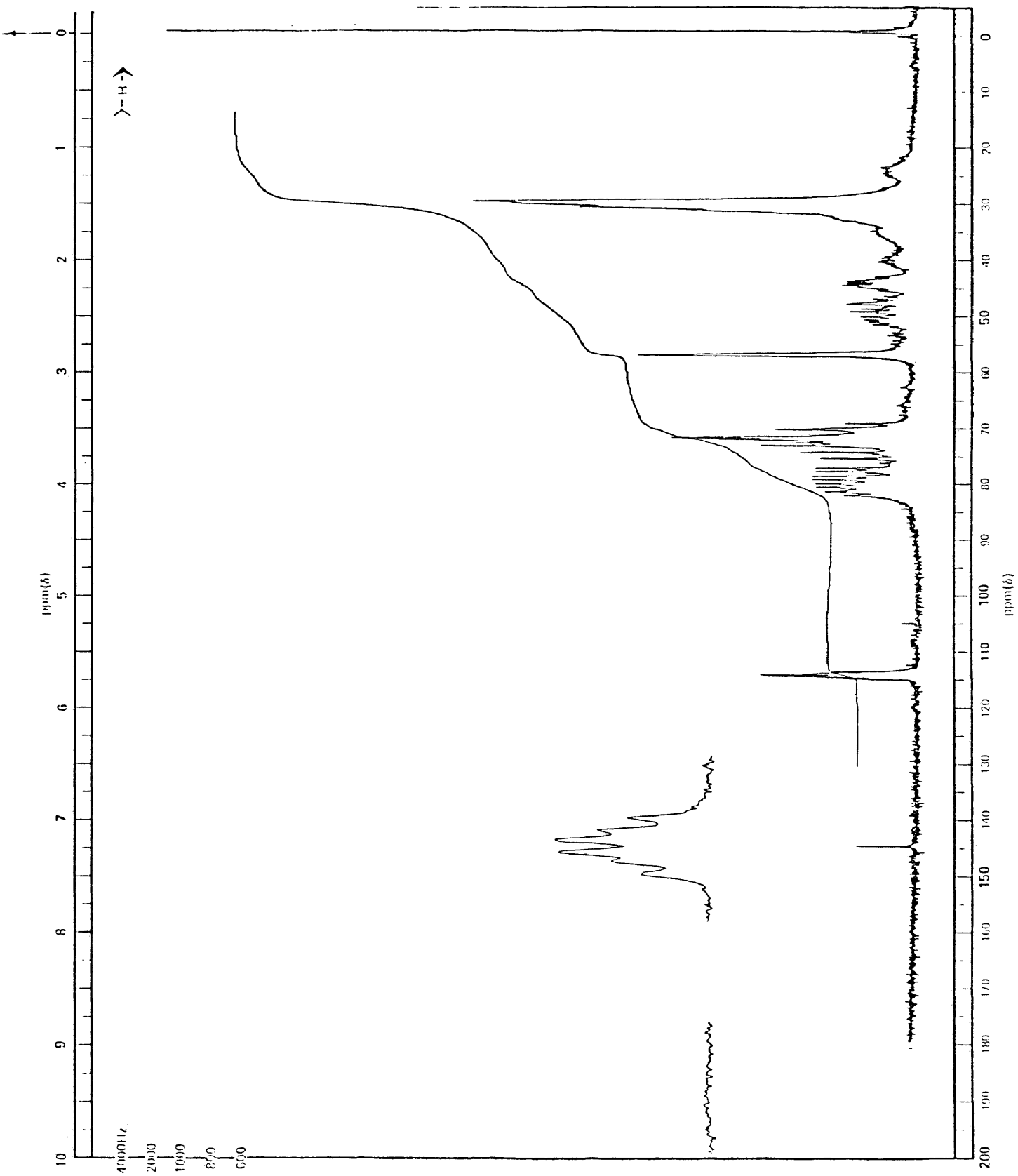


Figure XIII. ^{1}H-NMR Spectrum of 4-Chloro-2-(4-hydroxybutyl)-5,6-dihydro-2H-pyran.

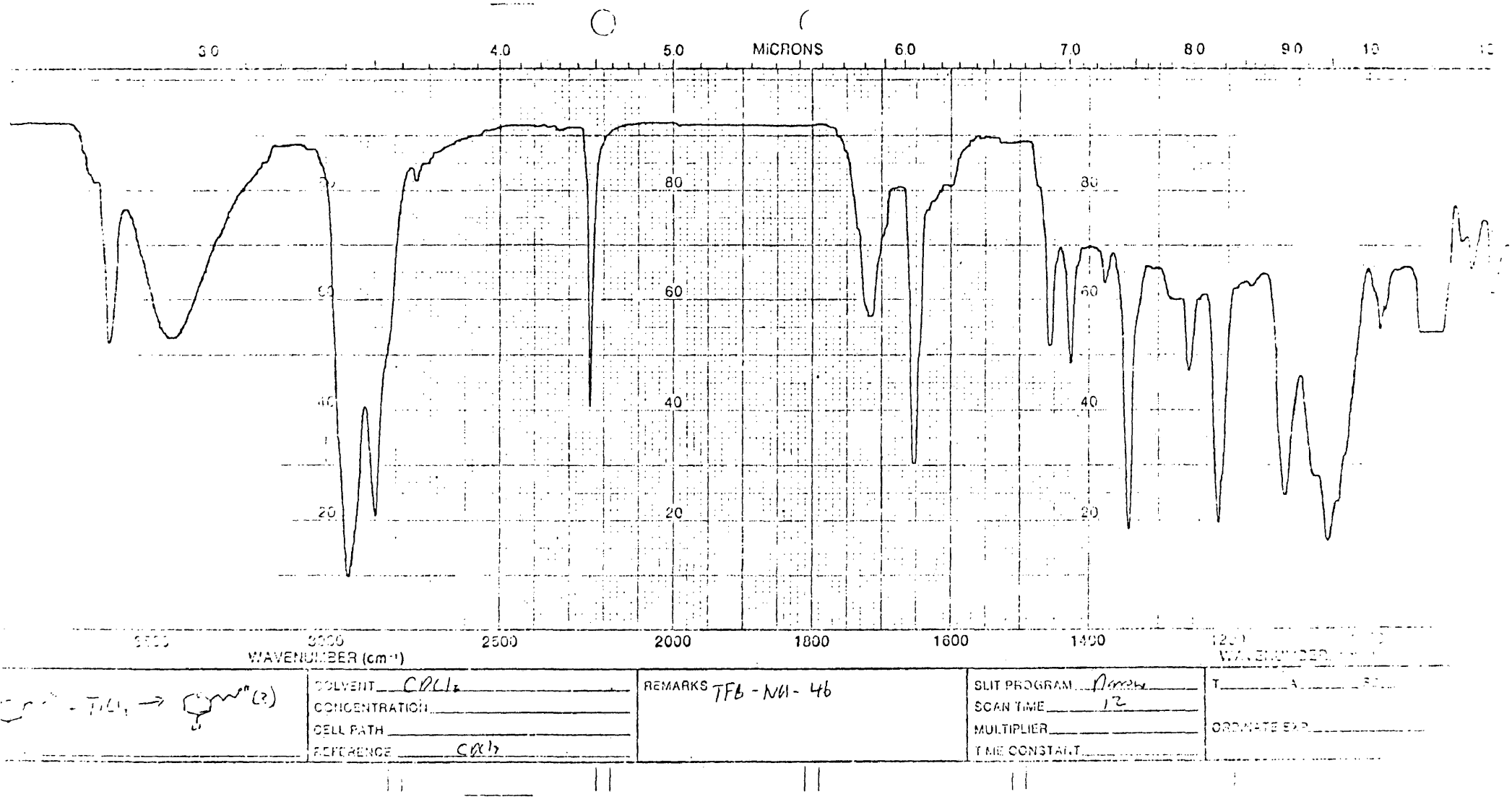


Figure XIV. IR Spectrum of 4-Chloro-2-(4-hydroxybutyl)-5,6-dihydro-2H-pyran.

time and stoichiometries were tried for the above cyclization all resulting in lower yields than 65%. The results of these studies are presented in Table V. In Table V the term "reverse addition" refers to a procedure in which $TiCl_4$ was dissolved in solvent and added to a cooled stirring mixture of acetal in solvent as opposed to the normal addition procedure where the acetal is added to a cooled and stirring solution of $TiCl_4$. We can see from Table V that, in general, lower reaction temperatures led to higher yields of the desired pyran product. Also, the use of $TiCl_4$/acetal ratios of at least 2:1 seemed to have a favorable effect on the yields from this cyclization. Adding the reactants in a "reverse" fashion resulted in significantly lower product yields.

The cyclization of the tetrahydropyranyl acetal of 3-buten-1-ol, at -95°C for 15 min using a 1:1 ratio of $TiCl_4$/acetal, produced the expected product, 4-chloro-2-(4-hydroxybutyl)tetrahydropyran, in 92% yield. This product was characterized by ^{1}H-NMR, ^{13}C-NMR, and IR spectroscopy with the spectra presented in Figures XV-XVIII. Changing the $TiCl_4$/acetal ratio to 2:1 had little effect on the product yield in this reaction, but lowering this ratio to 0.5:1 caused a considerable yield reduction.

The MEM acetal of 3-butyn-1-ol was cyclized to 4-chloro-5,6-dihydro-2H-pyran. Based on the results obtained with the previous cyclization of the acetylenic acetal from dihydropyran and 3-butyn-1-ol, a 2:1 ratio of

Table V

The effect of changes in reaction conditions on the yield of 4-chloro-2-(4-hydroxybutyl)-5,6-dihydro-2H-pyran from the cyclization of the dihydropyran based acetal of 3-butyn-1-ol.

TEMP °C	TIME MIN	$TiCl_4$/ACETAL RATIO	ADDITION MODE	YIELD
-95	15	2:1	NORMAL	65%
-95	15	4:1	NORMAL	54%
-95	15	1:1	NORMAL	44%
-95	15	1:1	NORMAL	46%
-95	15	1:1	REVERSE	17%
-63	15	1:1	NORMAL	42%
-63	15	1:1	REVERSE	33%
-45	2	1:1	NORMAL	<10%
0	5	1:1	NORMAL	<10%

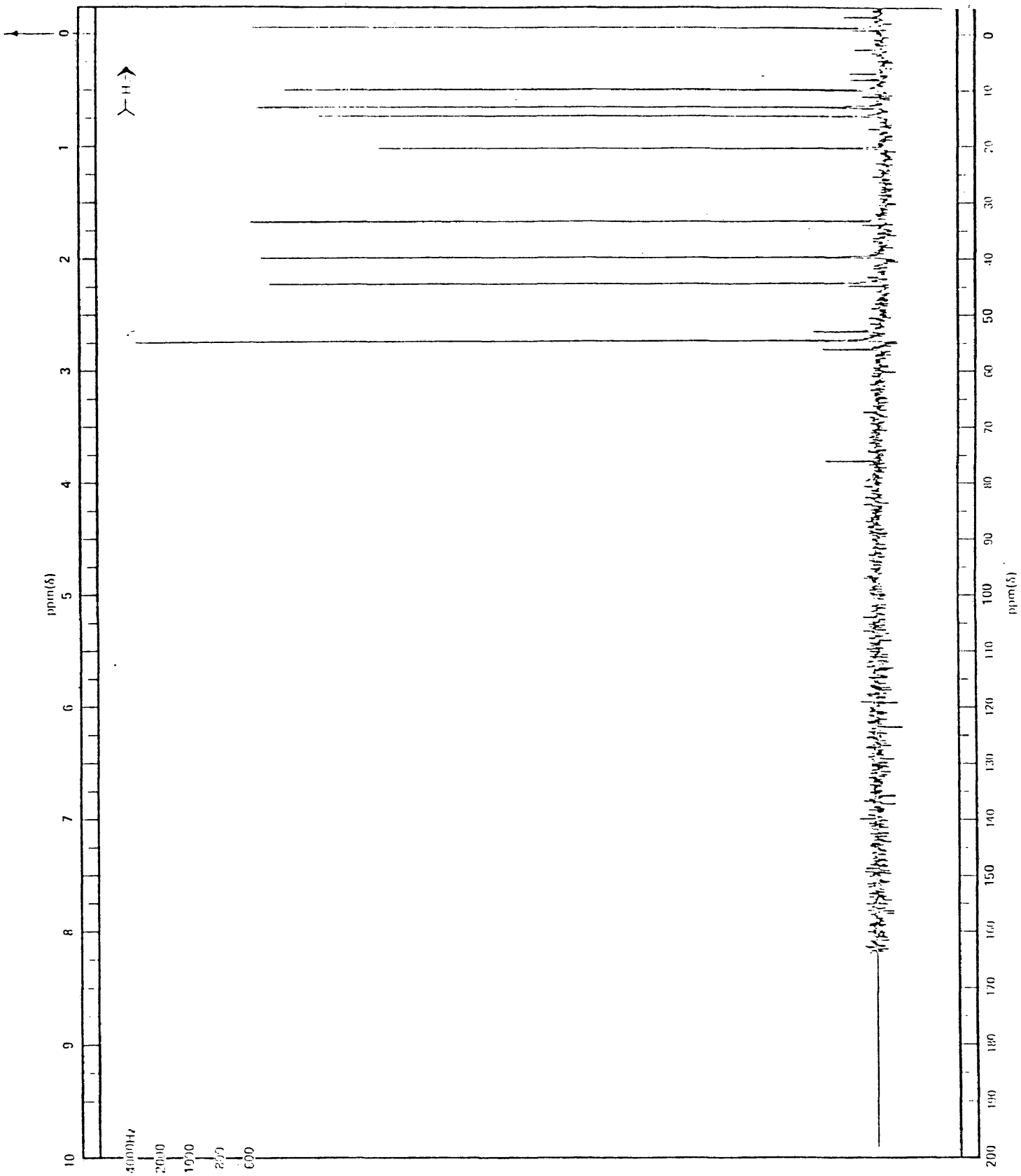


Figure XV. Decoupled ^{13}C-NMR Spectrum of 4-Chloro-2-(4-hydroxybutyl)tetrahydropyran.

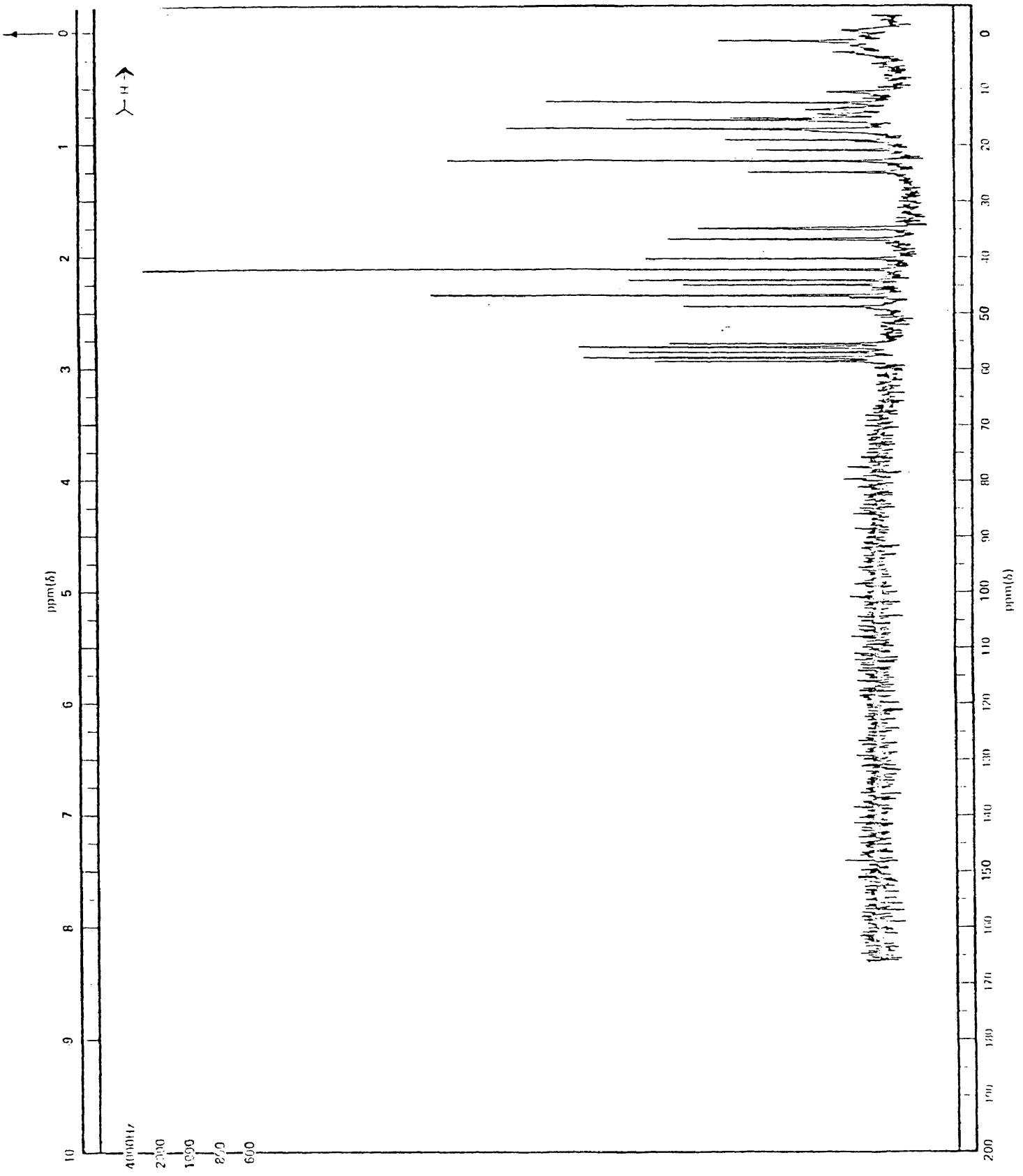


Figure XVI. Off-Resonance Decoupled ^{13}C-NMR Spectrum of 4-Chloro-2-(4-hydroxybutyl)tetrahydropyran.

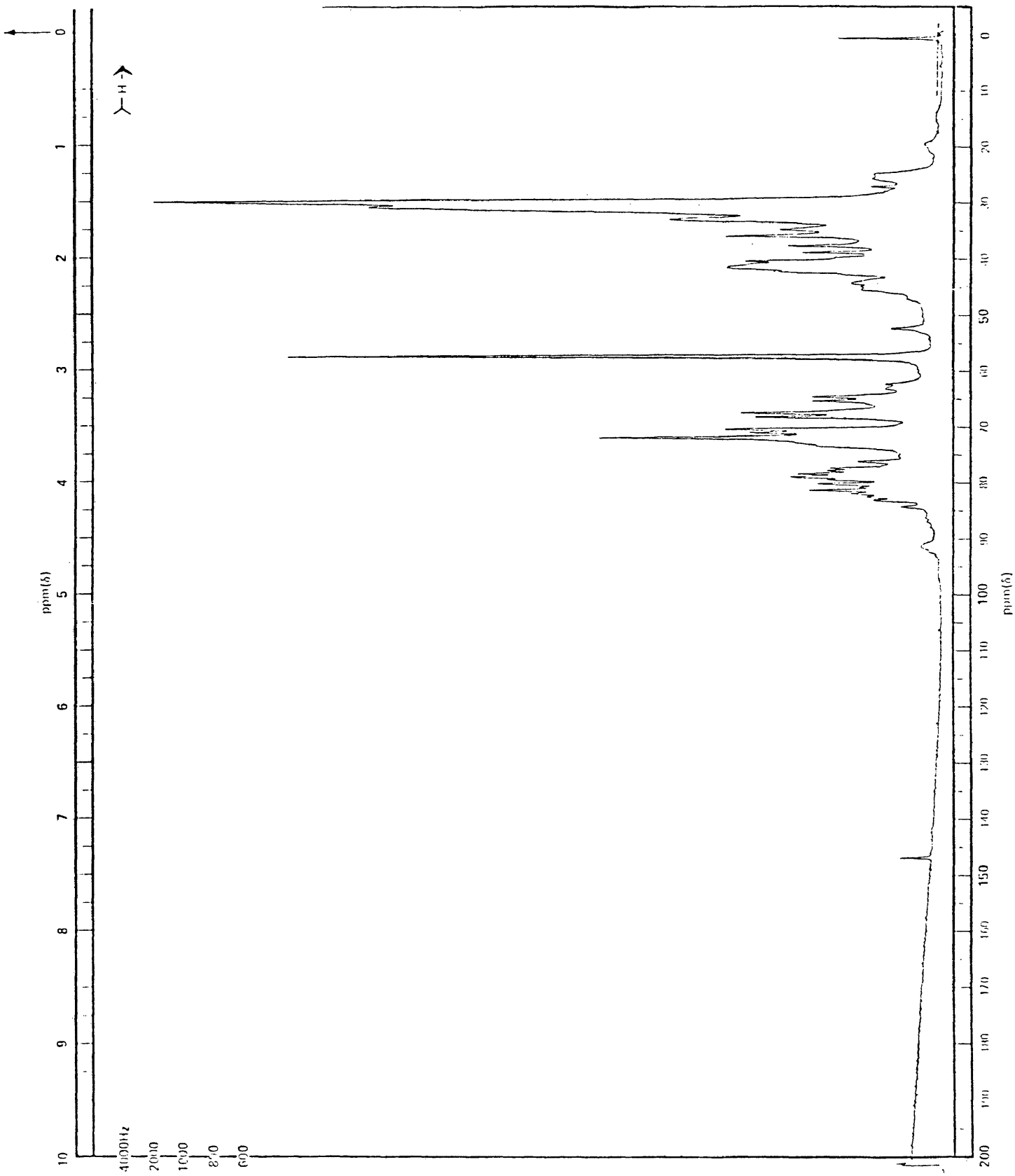


Figure XVII. ^{1}H-NMR Spectrum of 4-Chloro-2-(4-hydroxybutyl)-tetrahydropyran.

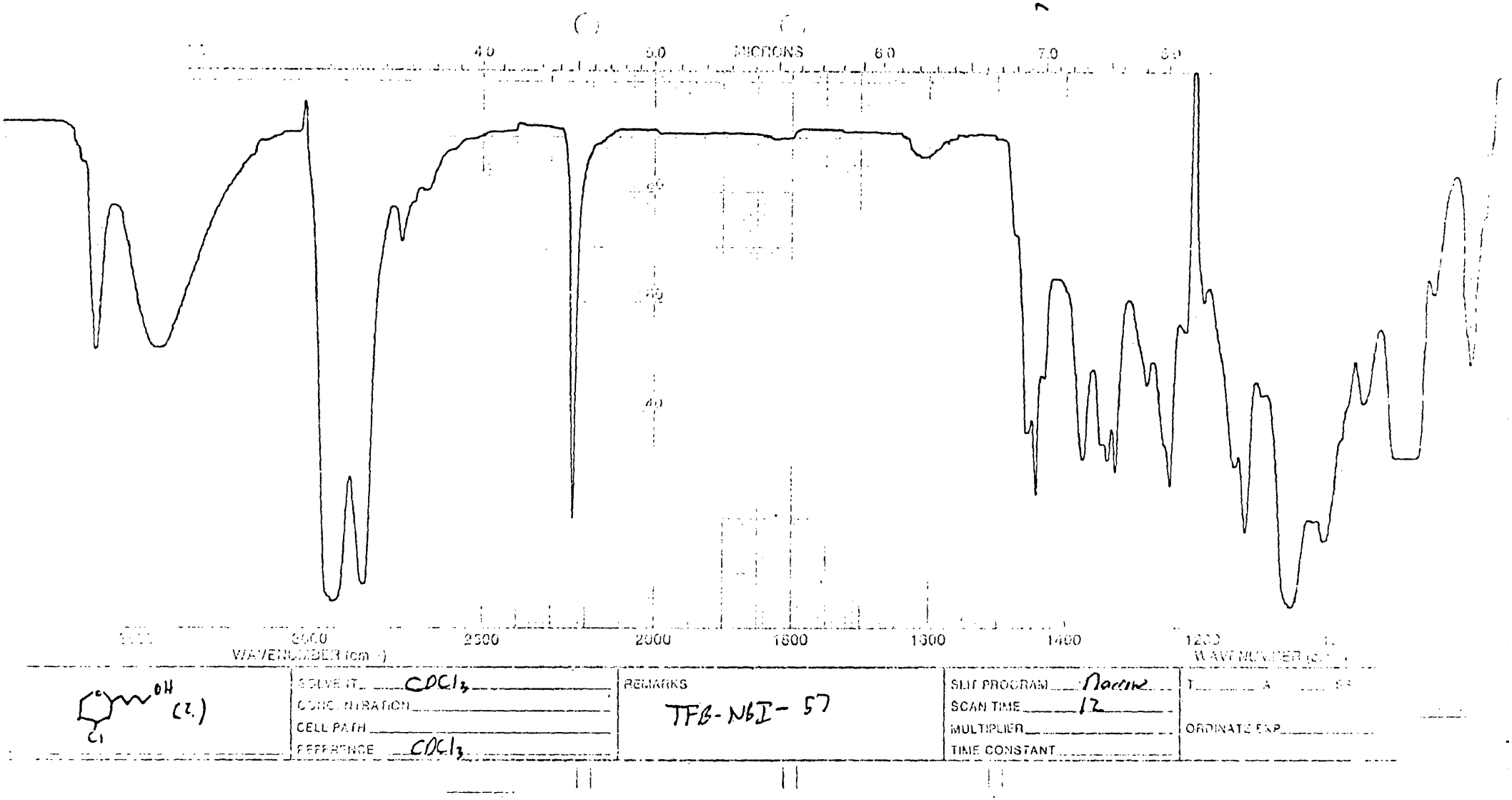


Figure XVIII. Ir Spectrum of 4-Chloro-2-(4-hydroxybutyl)tetrahydropyran.

$TiCl_4$/acetal was employed. This reaction was run at -45°C for 20 min with the expected product, as confirmed by the NMR spectra shown in Figures XIX-XXI, produced in 88% yield. The olefinic counterpart to this acetal, from MEM chloride and 3-buten-1-ol, was cyclized in 87% yield to 4-chlorotetrahydropyran. The ^1H and ^{13}C-NMR spectra used to characterize this product are presented in Figures XXII-XXIV.

The cyclization of the MEM acetal of 1-allylcyclohexanol, using a 1:1 ratio of $TiCl_4$/acetal at -45°C for 20 min, produced in 88% yield the expected product, 4-chloro-oxaspiro[5.5.]undecane. The ^1H and ^{13}C-NMR spectra shown in Figures XXV-XXVII are consistent with the structure of this product. The cyclization of the acetal from MEM chloride and 1-propargylcyclohexanol, when carried out using a $TiCl_4$/acetal ratio of 2:1 at -45°C for 20 min, resulted in the formation of 4-chloro-oxaspiro[5.5.]-3-undecene in 40% yield. The ^1H and ^{13}C-NMR spectra for this compound are presented in Figures XXVIII-XXX.

Finally, the ethyl vinyl ether based acetal of 1-allylcyclohexanol was reacted with 1.4 equivalents of $TiCl_4$ at 0°C for 10 min. This reaction produced 4-chloro-2-methyl-oxaspiro[5.5.]undecane in 94% yield. The ^1H and ^{13}C-NMR spectra used to confirm the structure of this product are shown in Figures XXXI and XXXII. The corresponding acetal from ethyl vinyl ether and

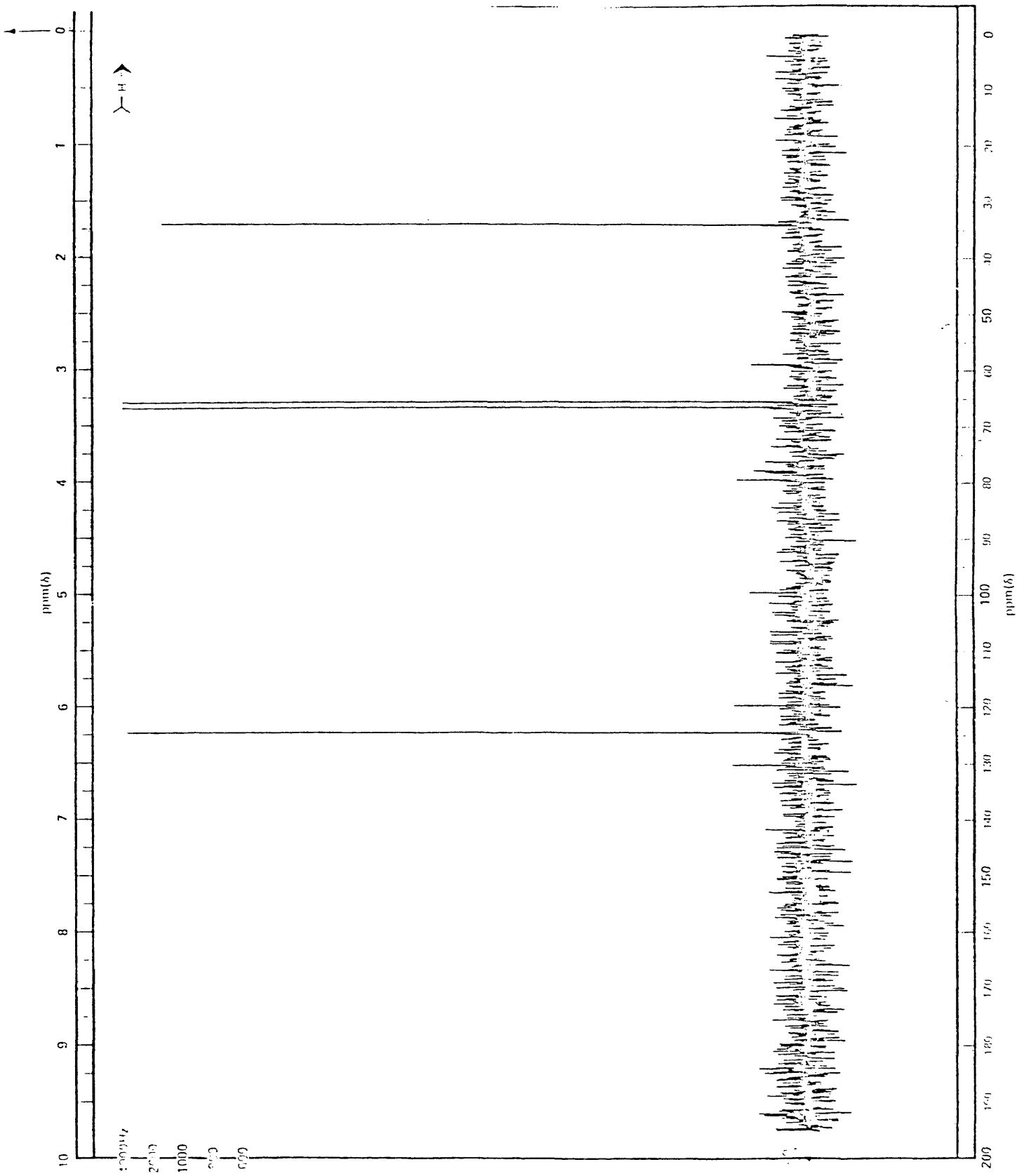


Figure XIX. Decoupled ^{13}C-NMR Spectrum of 4-Chloro-5,6-dihydro-2H-pyran.

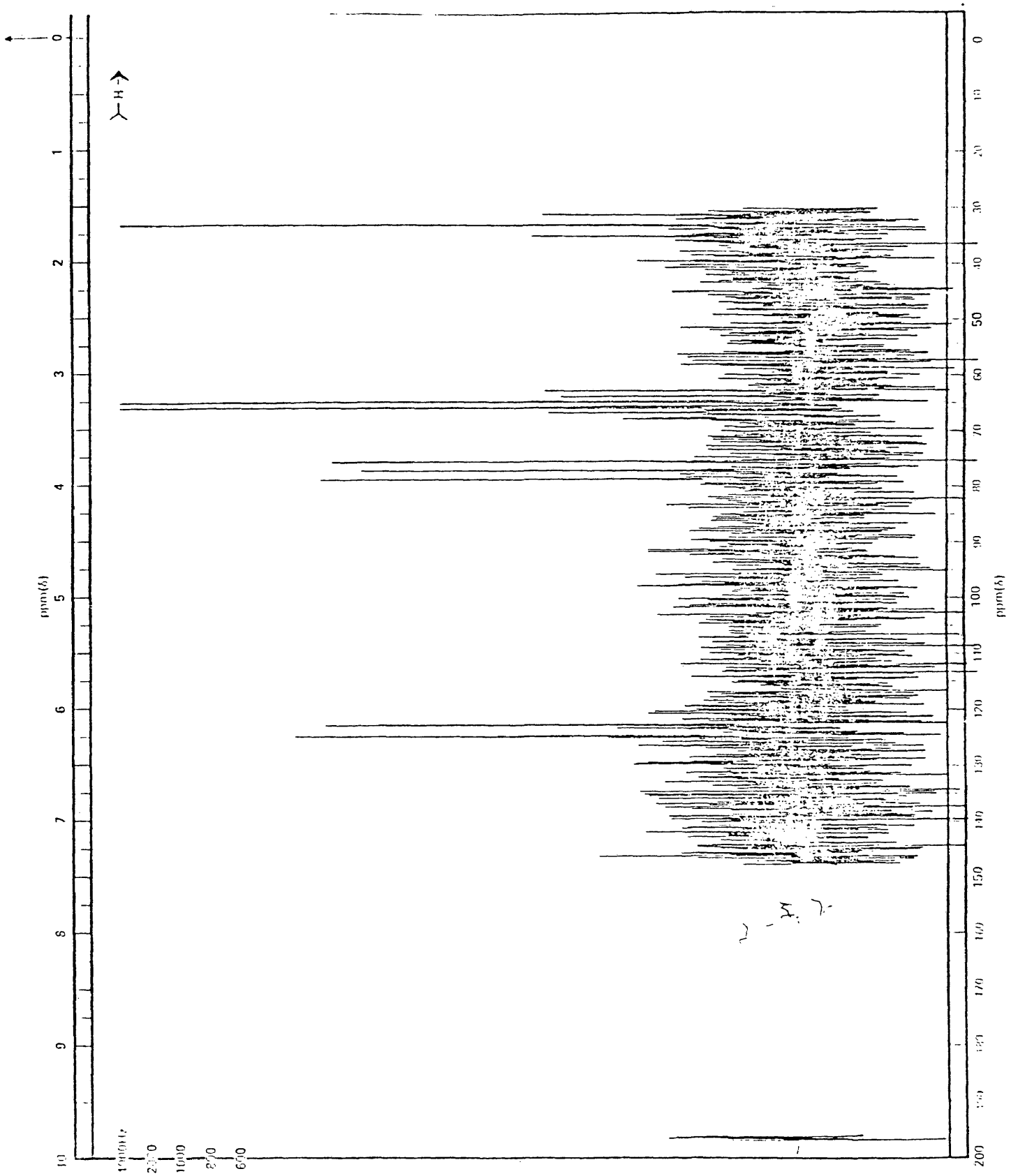


Figure XX. Off-Resonance Decoupled ^{13}C-NMR Spectrum of 4-Chloro-5,6-dihydro-2H-pyran.

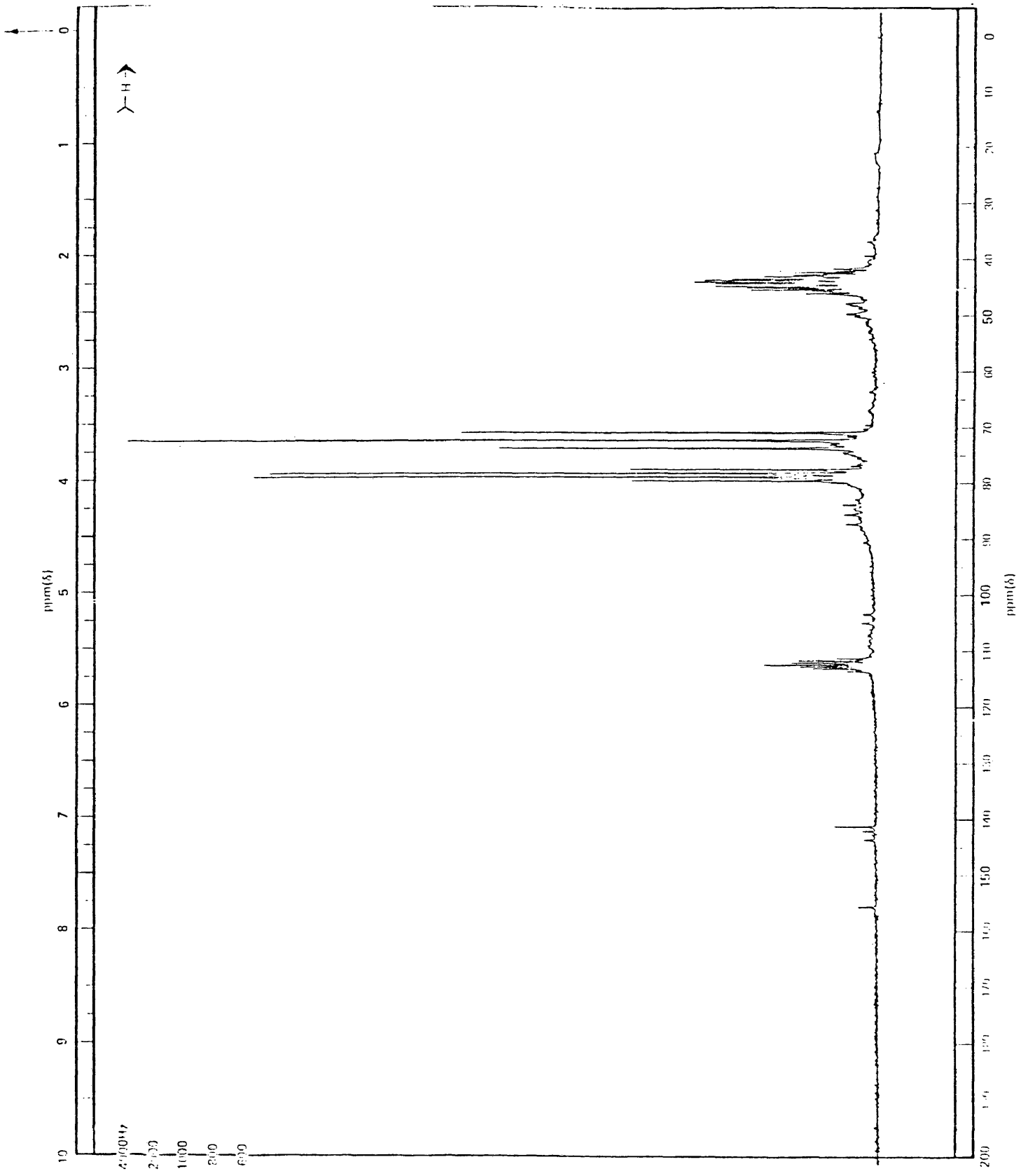


Figure XXI. ^{1}H-NMR Spectrum of 4-Chloro-5,6-dihydro-2H-pyran.

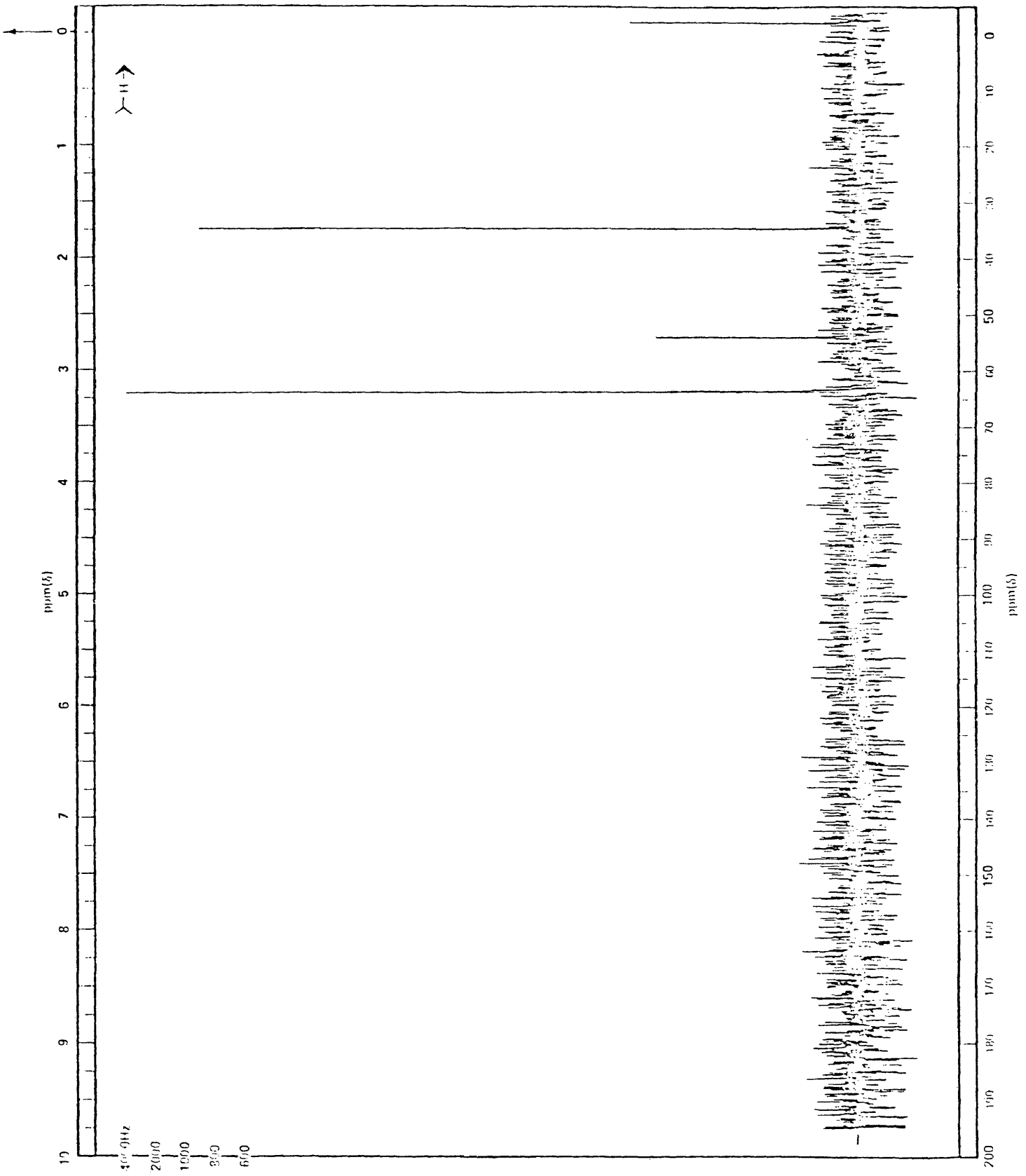


Figure XXII. Decoupled ^{13}C-NMR Spectrum of 4-Chlorotetrahydropyran.

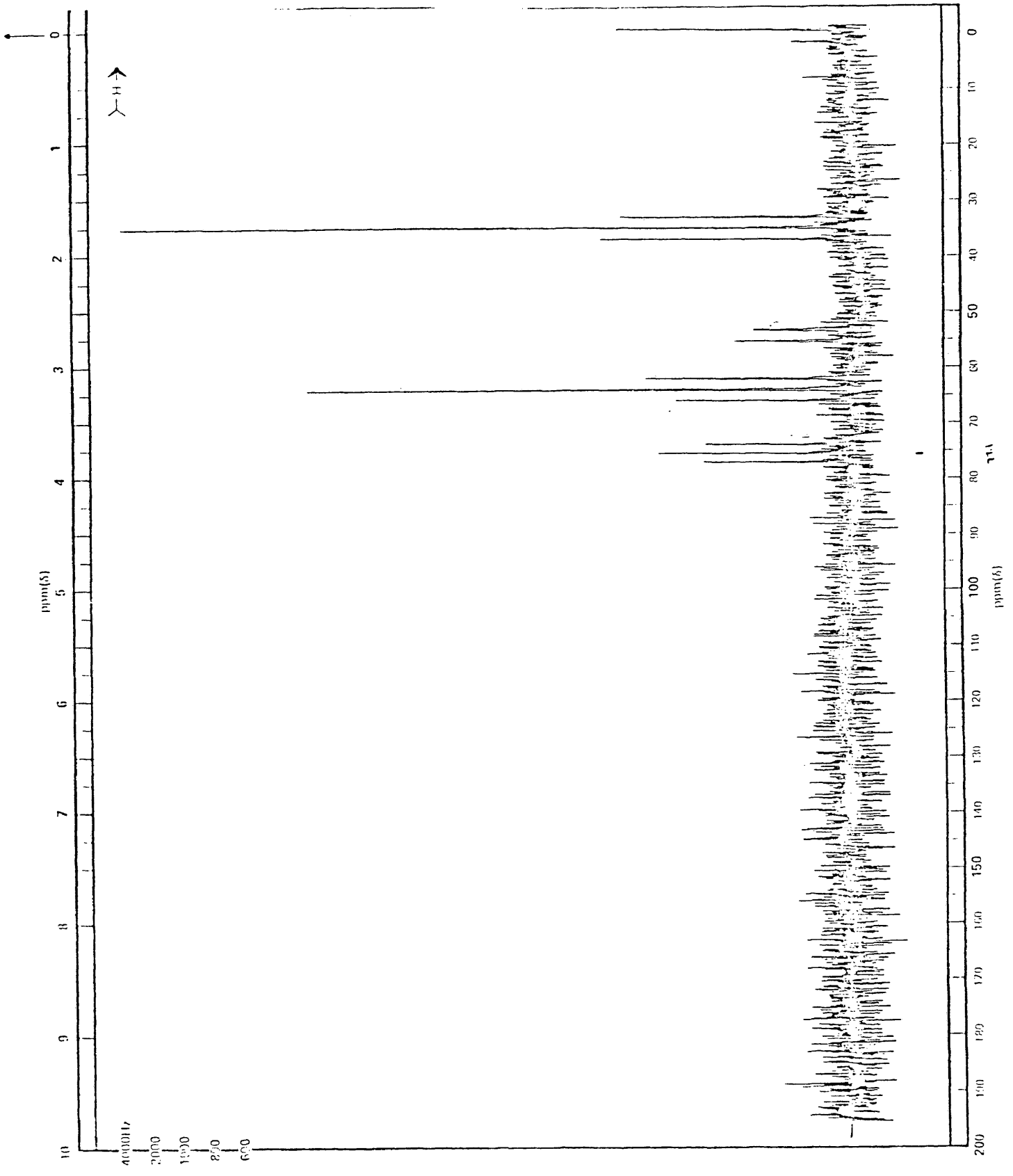


Figure XXIII. Off-Resonance Decoupled ^{13}C-NMR Spectrum of 4-Chlorotetrahydropyran.

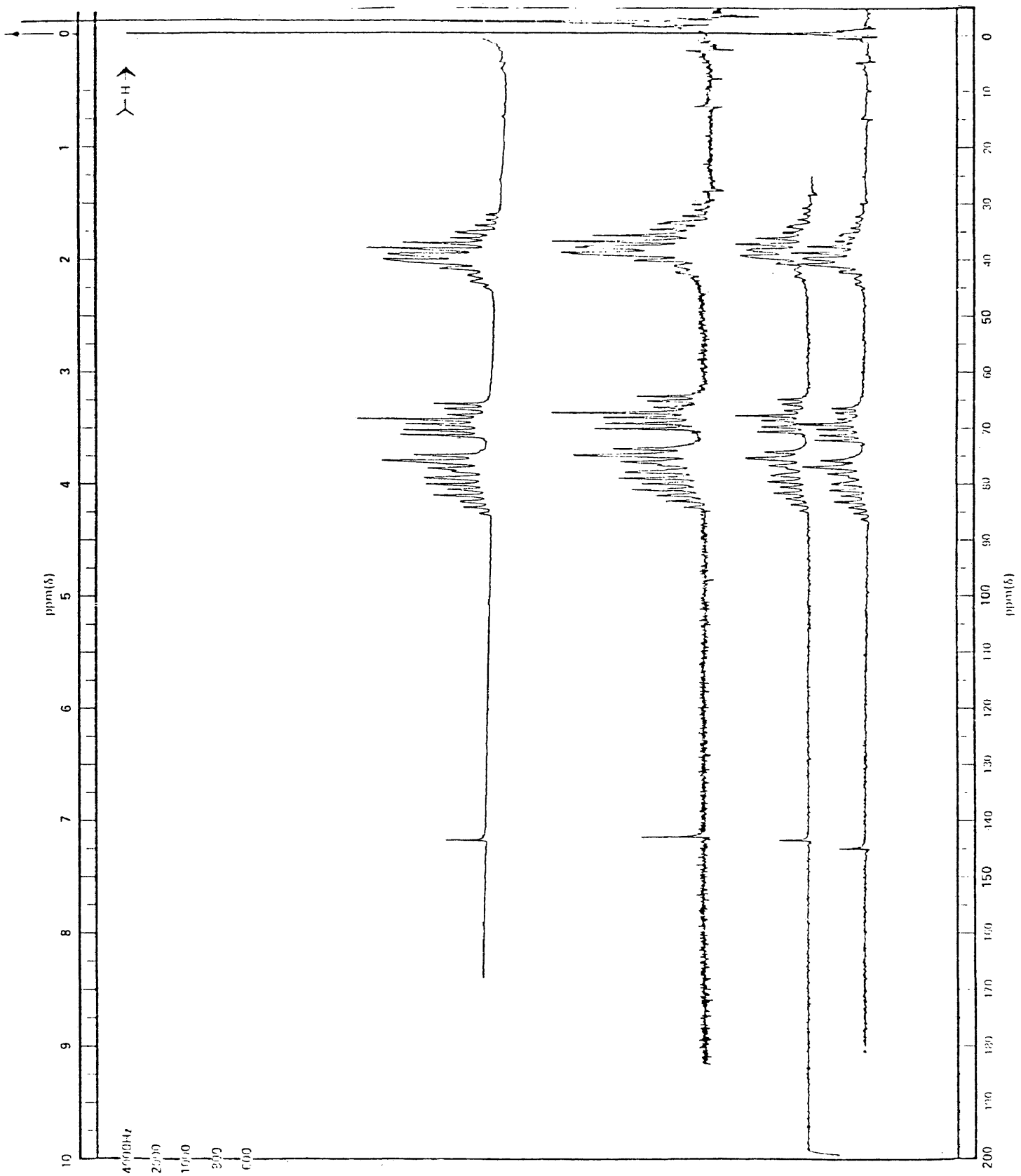


Figure XXIV. ^{1}H-NMR Spectrum of 4-Chlorotetrahydropyran.

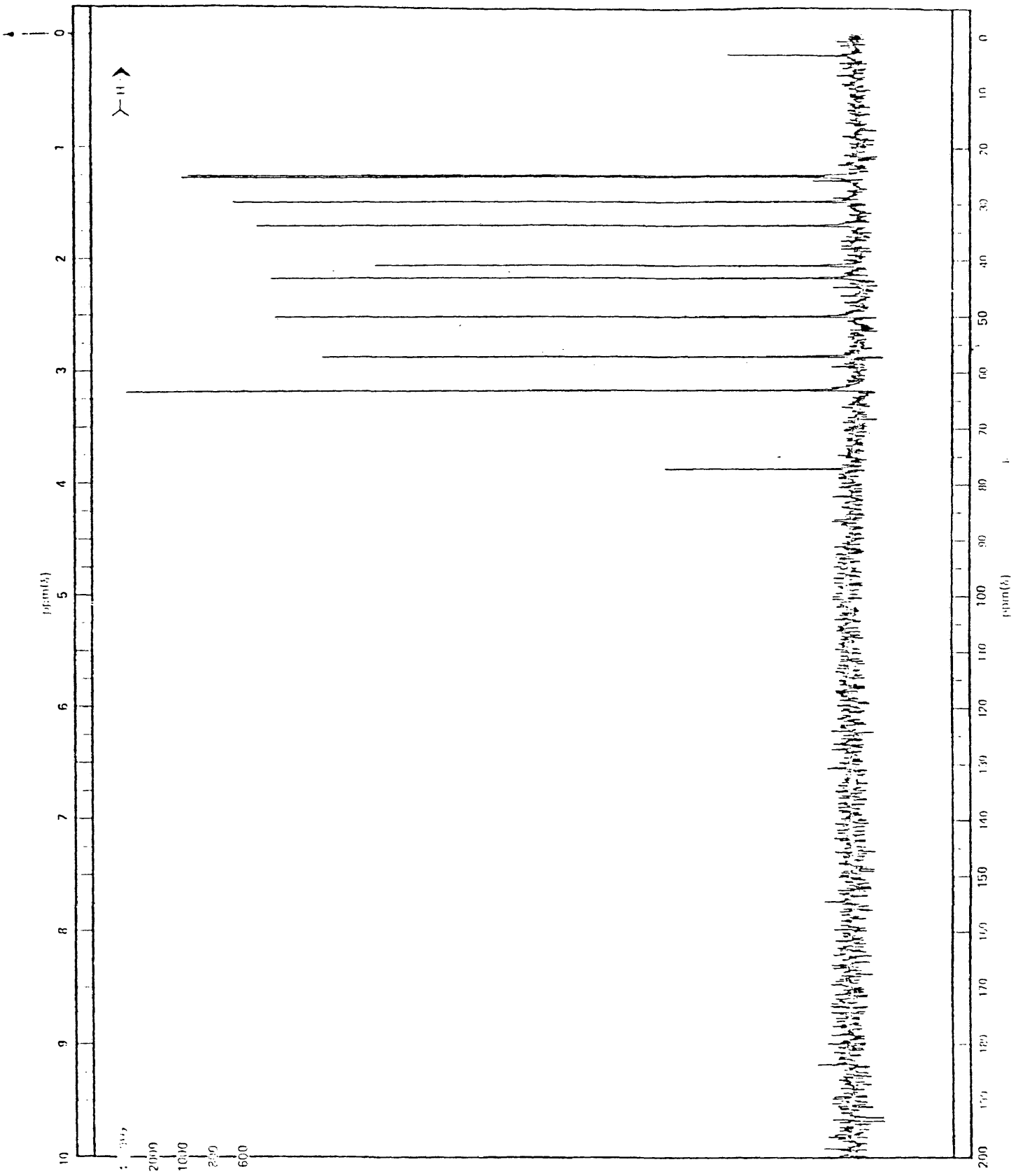


Figure XXV. Decoupled ^{13}C-NMR Spectrum of 4-Chloro-oxaspiro-[5.5.]undecane.

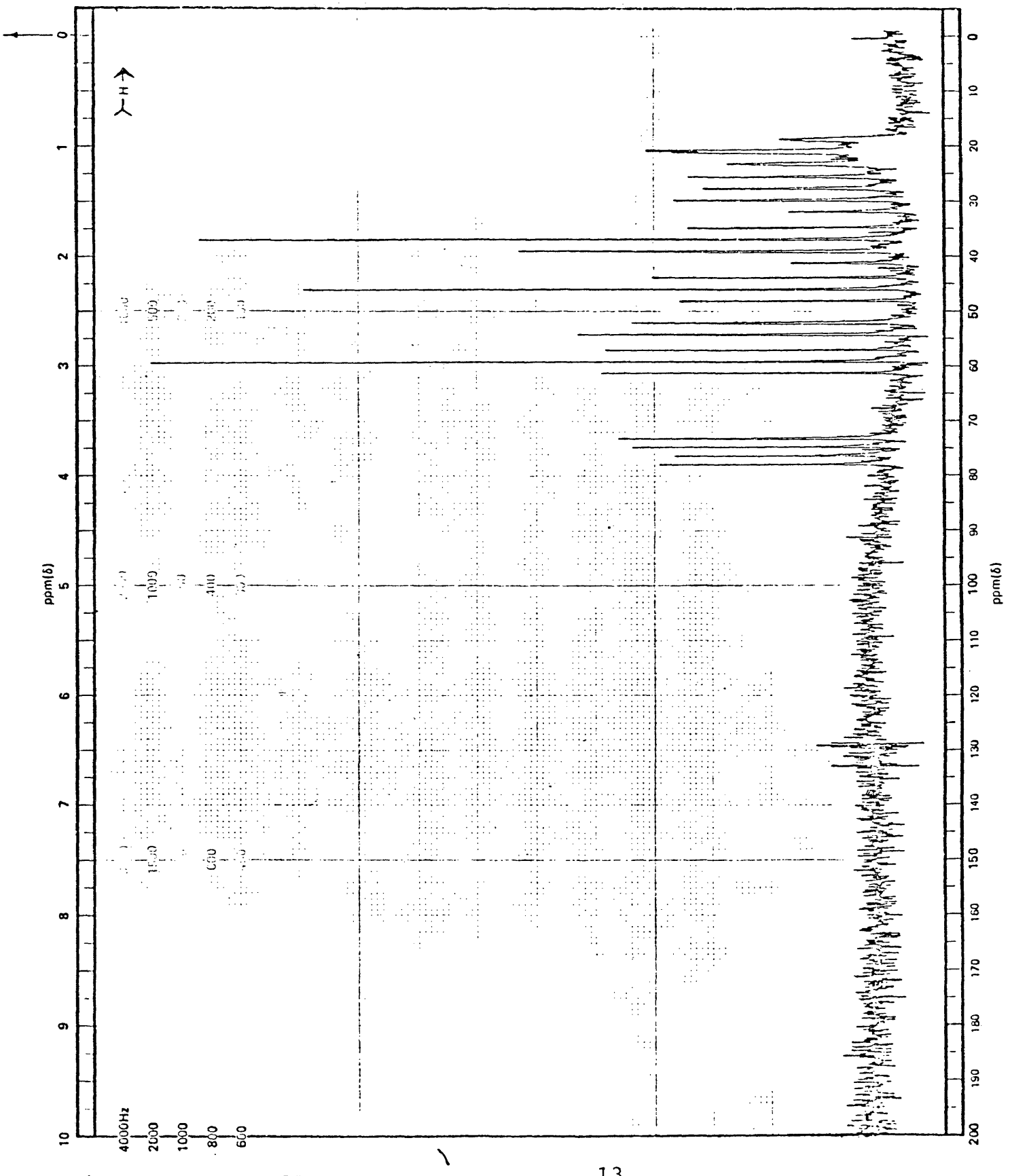


Figure XXVI. Off-Resonance Decoupled ^{13}C-NMR Spectrum of 4-Chloro-oxaspiro[5.5.]undecane.

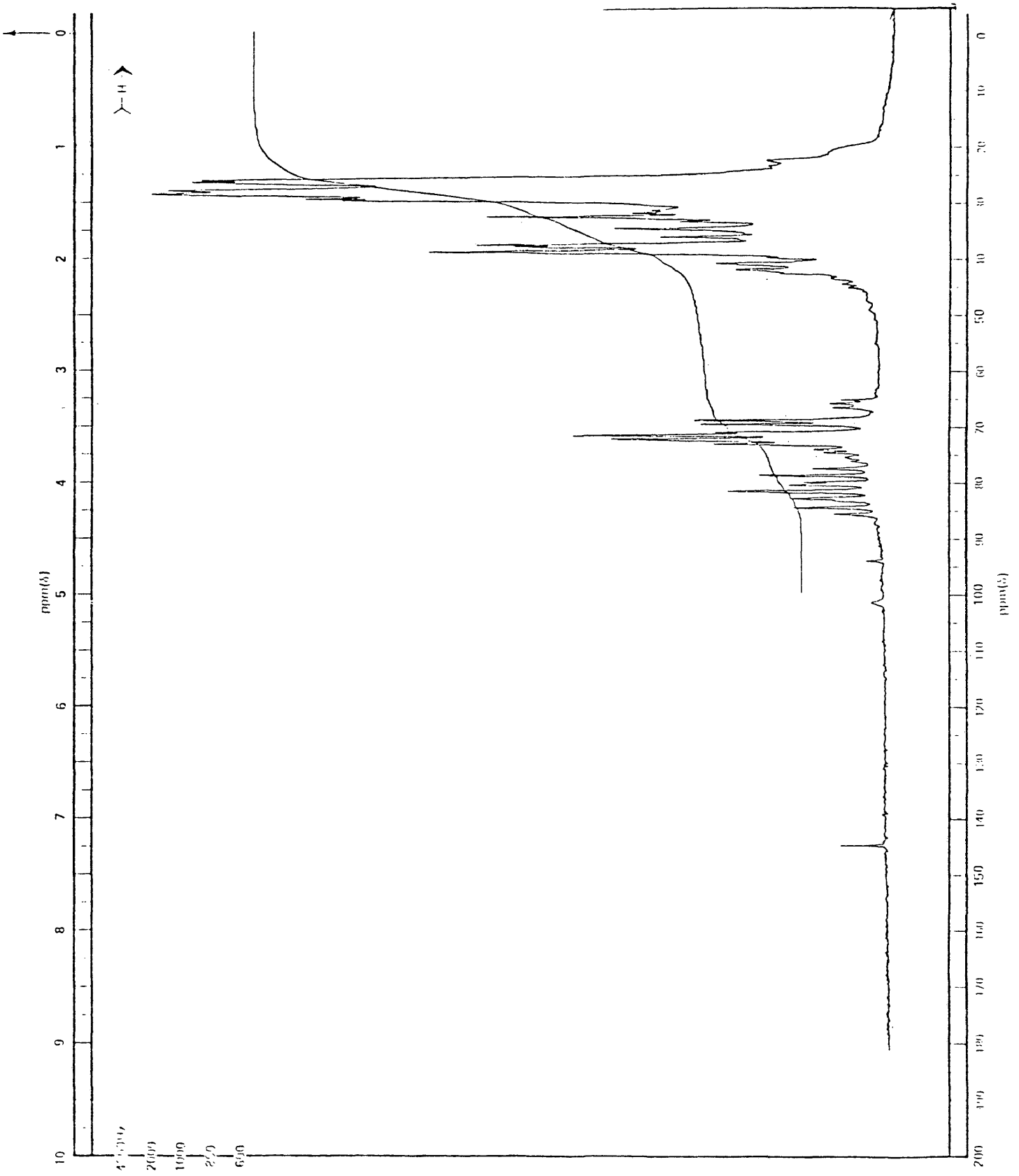


Figure XXVII. ^{1}H-NMR Spectrum of 4-Chloro-oxaspiro[5.5.]undecane.

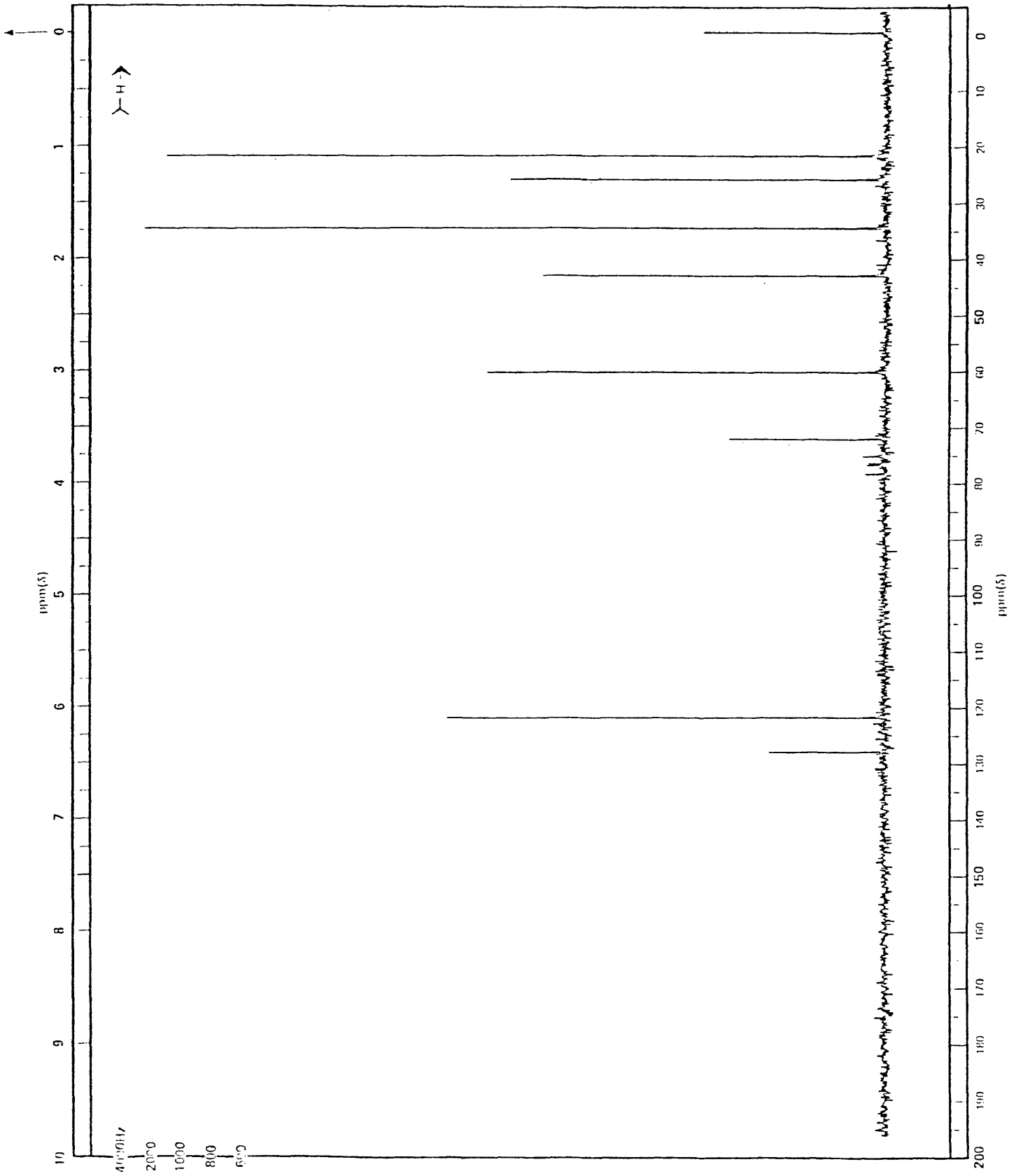


Figure XXVIII. Decoupled ^{13}C-NMR Spectrum of 4-Chloro-oxaspiro[5.5.]-3-undecene.

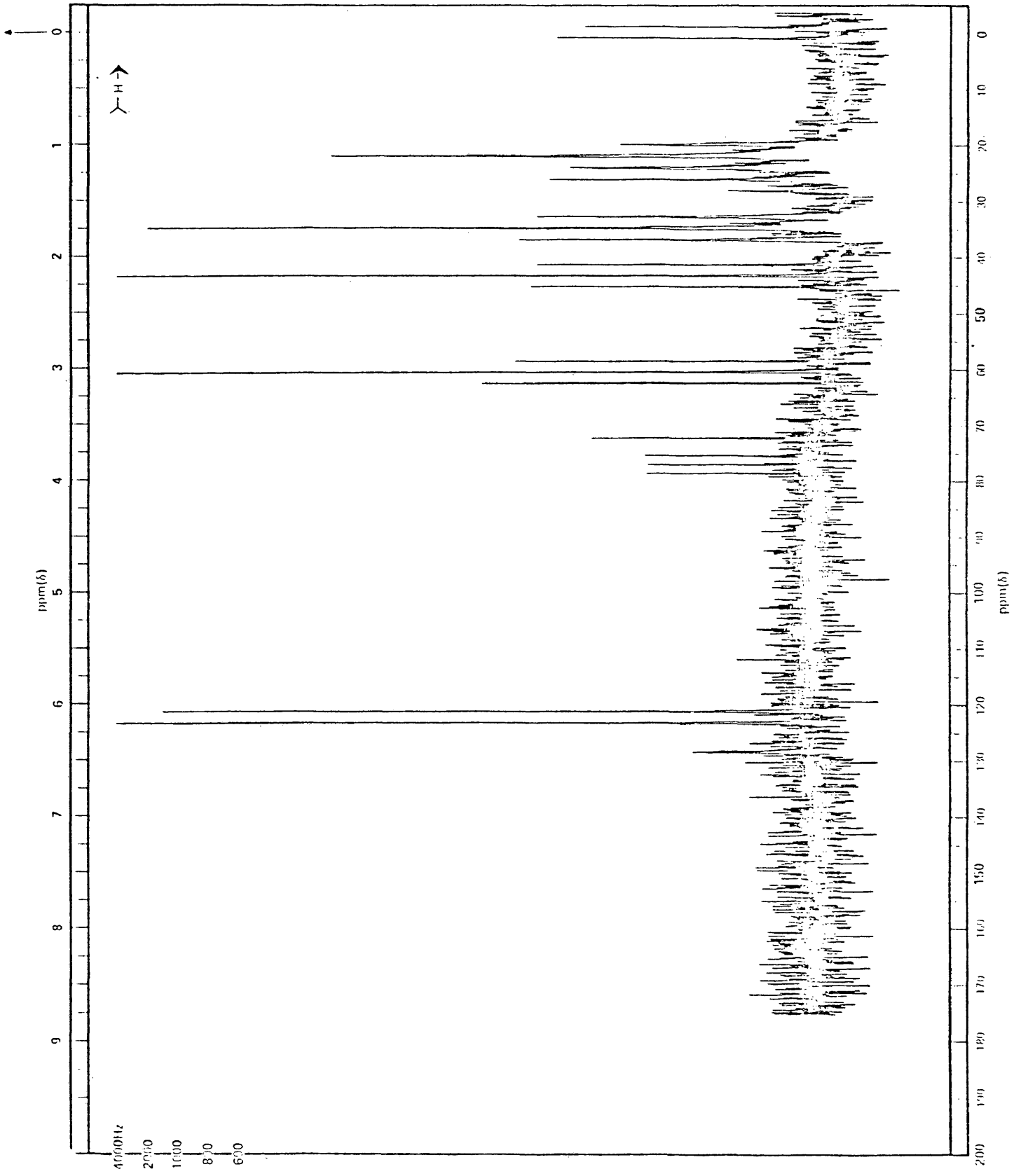


Figure XXIX. Off-Resonance Decoupled ^{13}C-NMR Spectrum of 4-Chloro-oxaspiro[5.5.]-3-undecene.

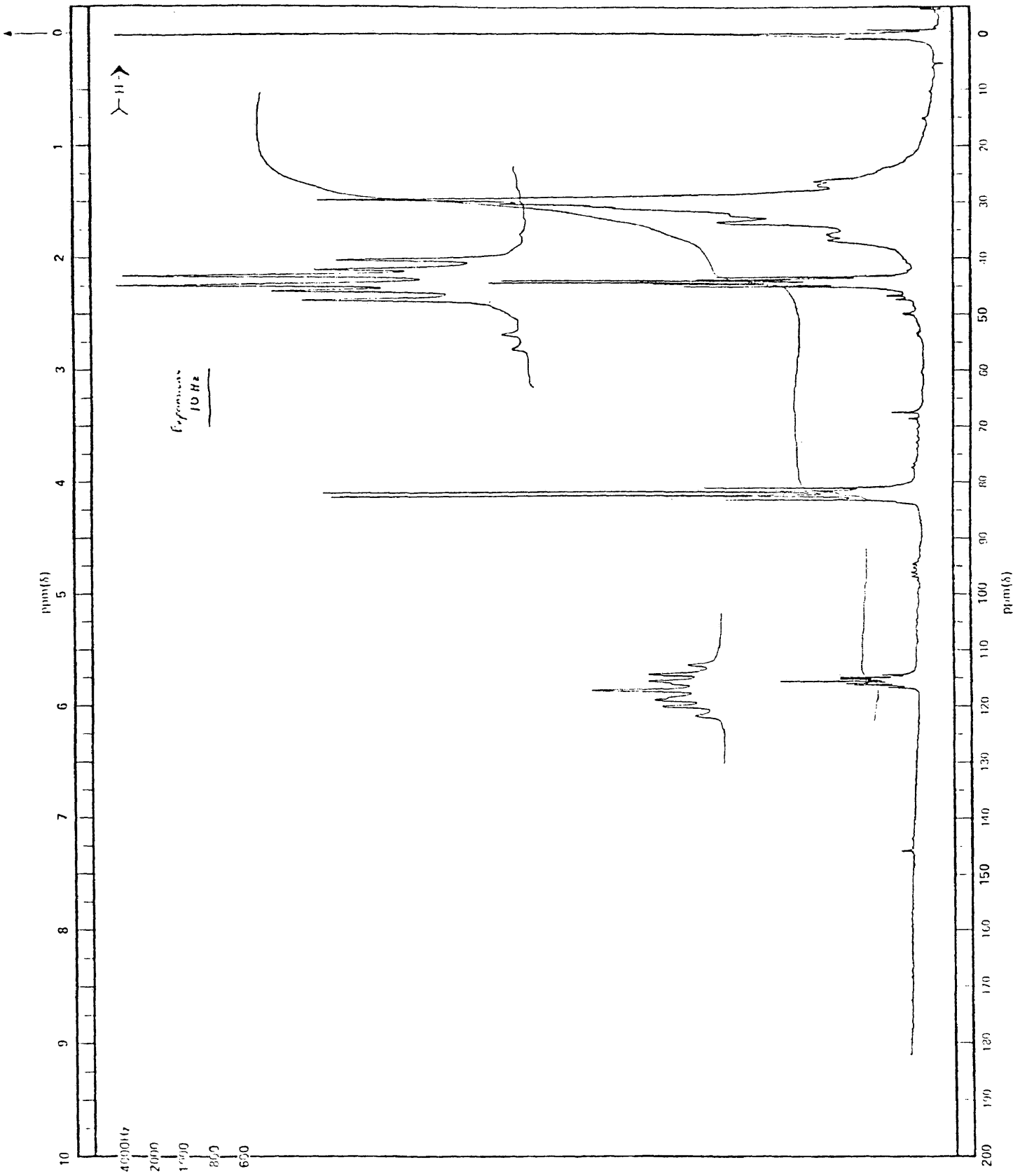


Figure XXX. ^{1}H-NMR Spectrum of 4-Chloro-oxaspiro[5.5.]-3-undecene.

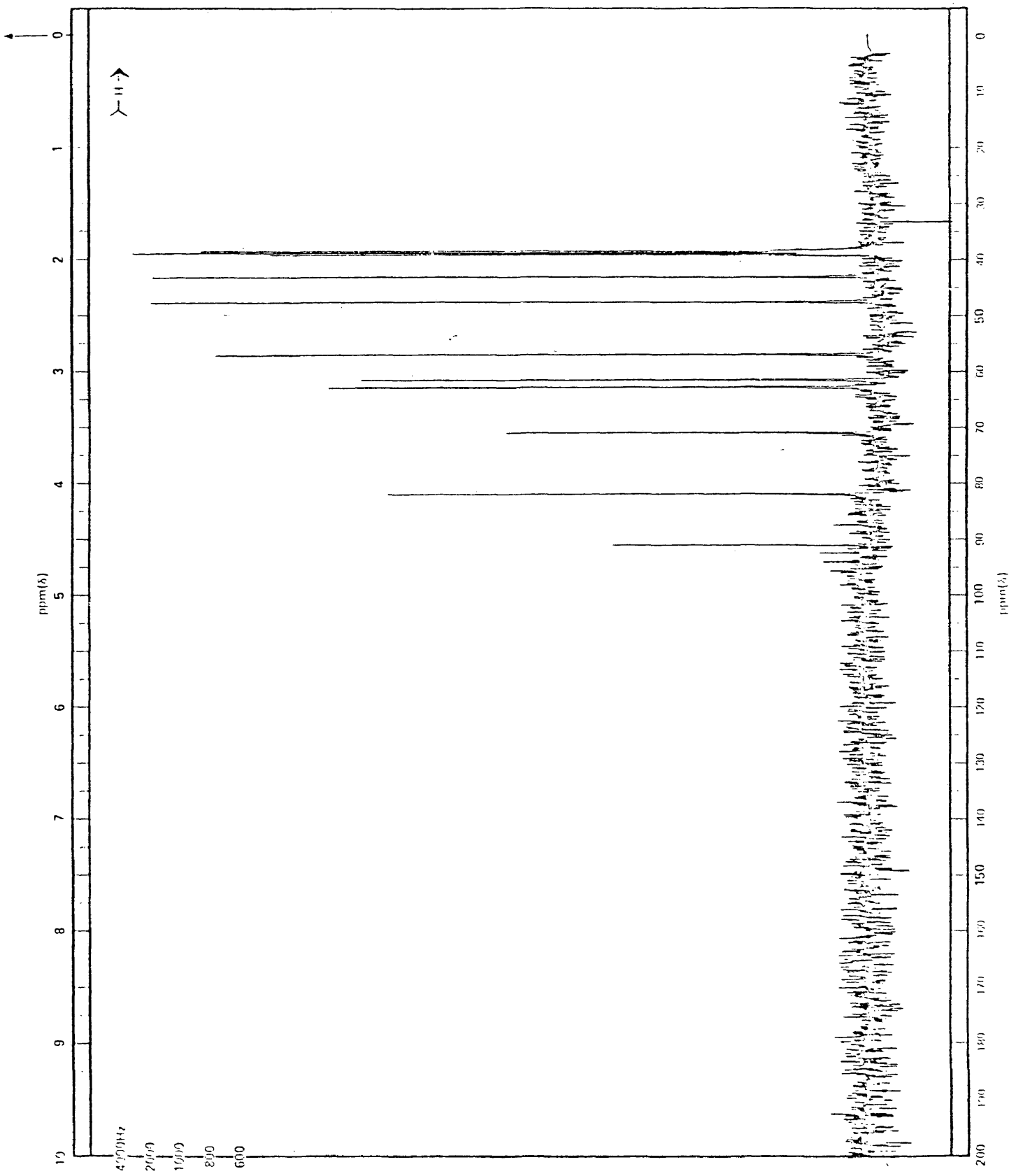


Figure XXXI. Decoupled ^{13}C-NMR Spectrum of 4-Chloro-2-methyl-oxaspiro[5.5.]undecane.

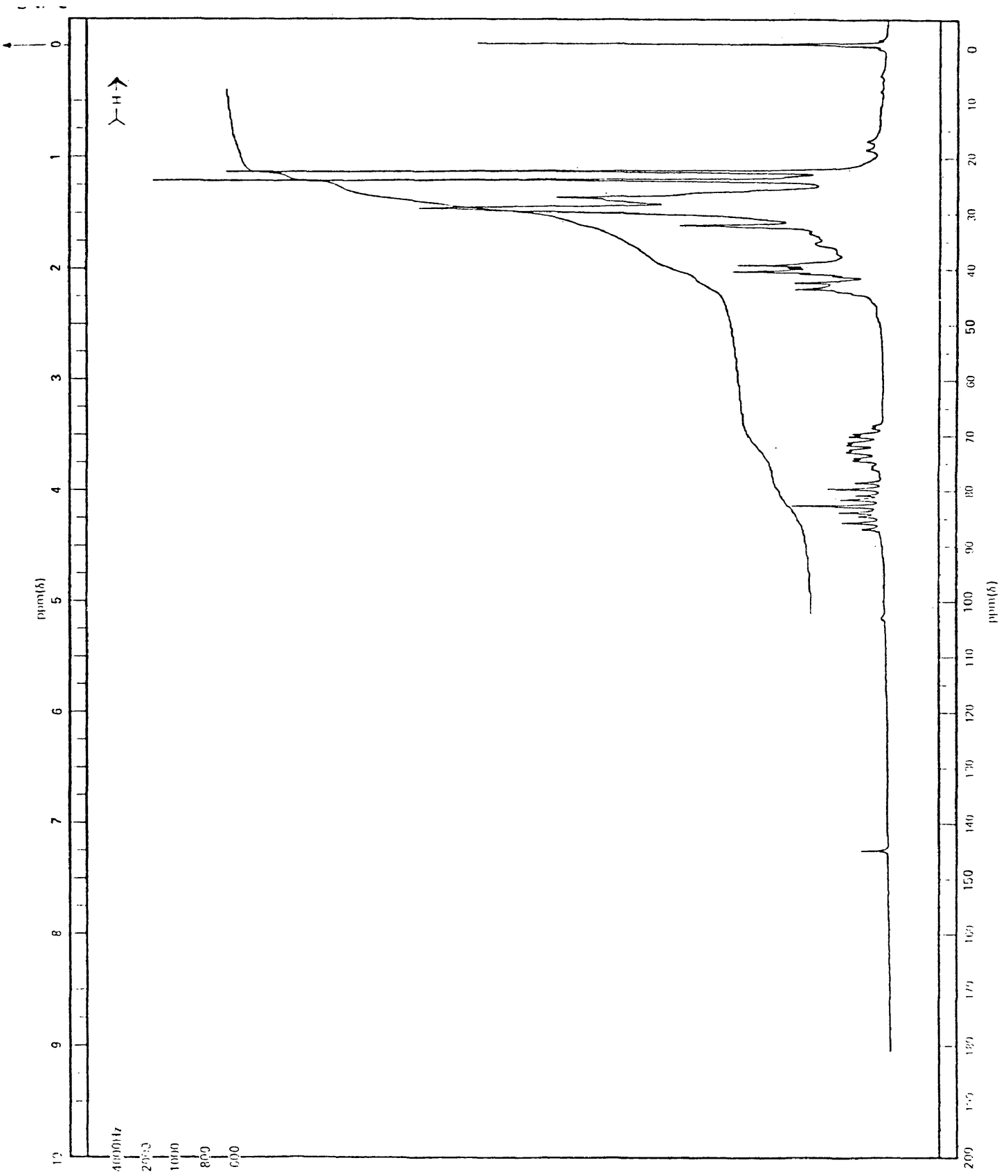


Figure XXXII. ^{1}H-NMR Spectrum of 4-Chloro-2-methyl-oxaspiro-[5.5.]undecane.

1-propargylcyclohexanol reacted to yield a complicated product mixture from which no pyran product could be isolated. A variety of reaction conditions were examined without success.

In general, the olefinic acetals underwent facile cyclizations to produce the corresponding pyrans in high yields. These reactions seemed to proceed very well at temperatures ranging from 0 °C to -95 °C. Also, reacting 1 equivalent of acetal with 1 equivalent of $TiCl_4$ was mostly adequate for the preparation of the desired products in high yield. Increasing the $TiCl_4$/acetal ratio had little effect on the product yields, but lowering this ratio to 0.5:1 caused a decrease in yields.

The reaction of the acetylenic acetals resultd in a more complicated product mixture with the desired products being formed in lower yields. The yields tend to improve and the number of by-products tends to decrease as the reaction temperature becomes lower. At higher temperatures, such as 0 °C, the reaction seems to be quite rapid, and the resulting product mixture very complicated. A $TiCl_4$ to acetal ratio of at least 2:1 is required in order to obtain good yields of the desired pyrans.

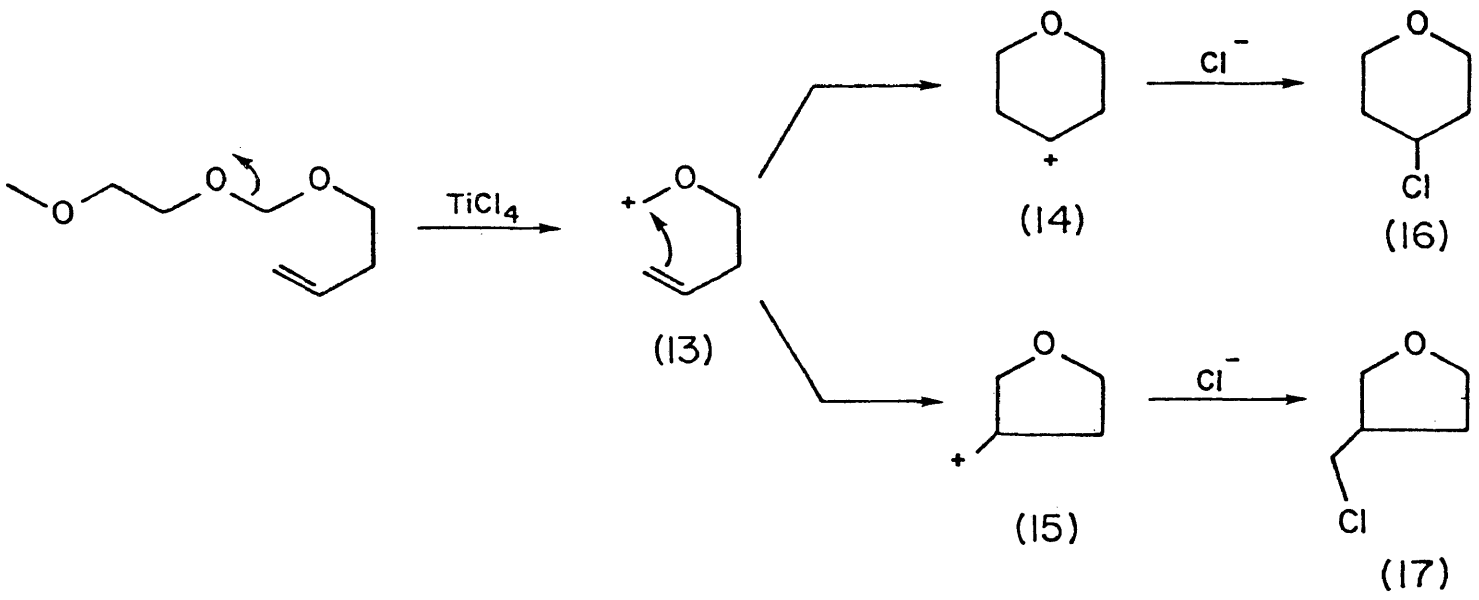
It should be pointed out that, although the NMR spectra presented in this thesis are consistent with the reported structures of the products as shown in Table IV, with one exception they cannot be used to make conclusive distinctions between five- and six-membered cyclic ethers.

Also, in the two compounds which may exist in different isomeric forms, these spectra do not conclusively show which isomer is formed. These structural questions require a more detailed discussion.

Let us first look at the problem of whether pyrans or furans are formed in the cyclization of acetals of homoallylic alcohols. A variety of evidence exists which supports the conclusion that the primary products of these cyclizations are pyrans, not furans. The most significant evidence can be found by examining the product from the cyclization of the MEM acetal of 3-buten-1-ol shown in Scheme XIV. If the terminal olefinic bond attacks the initial carbocation (13) so as to form the intermediate carbocation (14), then the product of the cyclization is 4-chlorotetrahydropyran (16). However, if the double bond attacks (13) such as to form intermediate (15), the resulting product is 3-(chloromethyl)tetrahydrofuran (17). Because of symmetry, ^{13}C-NMR spectroscopy can readily distinguish between these two products (see Figures XXIII and XXIV). The decoupled ^{13}C-NMR spectrum has only 3 lines, and thus the product must be 4-chlorotetrahydropyran (16) because this compound possesses only 3 nonequivalent carbon atoms while its furan isomer should show 5 lines corresponding to its 5 nonequivalent carbons. Also, the splitting patterns seen in the off-resonance decoupled ^{13}C-NMR spetrum are consistent with this pyran product.

This evidence is consistent with what was expected

Scheme XIV



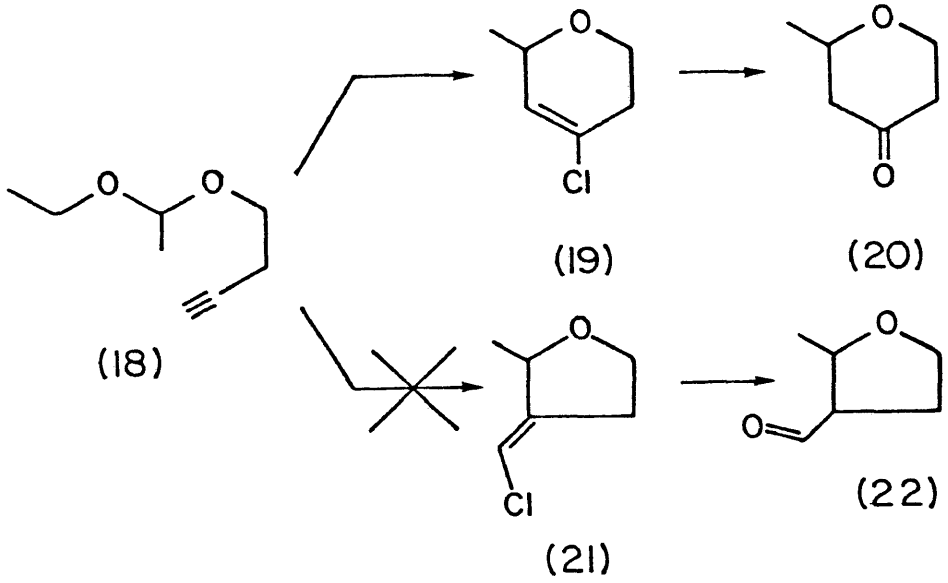
based on results obtained by Stapp[11] and discussed earlier. Stapp found, in a mechanistically similar cyclization based on the chemistry of the Prins reaction, that 4-chlorotetrahydropyran and other six-membered cyclic ethers were formed at the expense of their furan isomers.

An explanation for the formation of pyrans, rather than furans, in olefinic acetal cyclizations can be found by closely examining the cyclization mechanism for the reaction of the MEM acetal of 3-buten-1-ol shown in Scheme XIV. Initial nucleophilic attack on carbocation (13) can proceed to form either the six-membered cyclic cation (14) or the five-membered cyclic cation (15). Since the six-membered cyclic cation precurser to the pyran product is a secondary carbocation while the precurser to the furan product is a primary carbocation, and since secondary cations are favored over primary cations, there seems to be little question that (14) would be formed almost exclusively thus leading to the pyran product (16). In light of the experimental and mechanistic evidence just presented there is little doubt that the cyclizations of acetals of homoallylic alcohols with terminal double bonds, such as those presented in this thesis, result in the formation of exclusively six-membered cyclic ethers.

The nature of the products from the cyclization of acetals of homopropargylic alcohols is not quite as clear as those from the cyclization of olefinic acetals. The NMR data from the products reported in this thesis cannot be

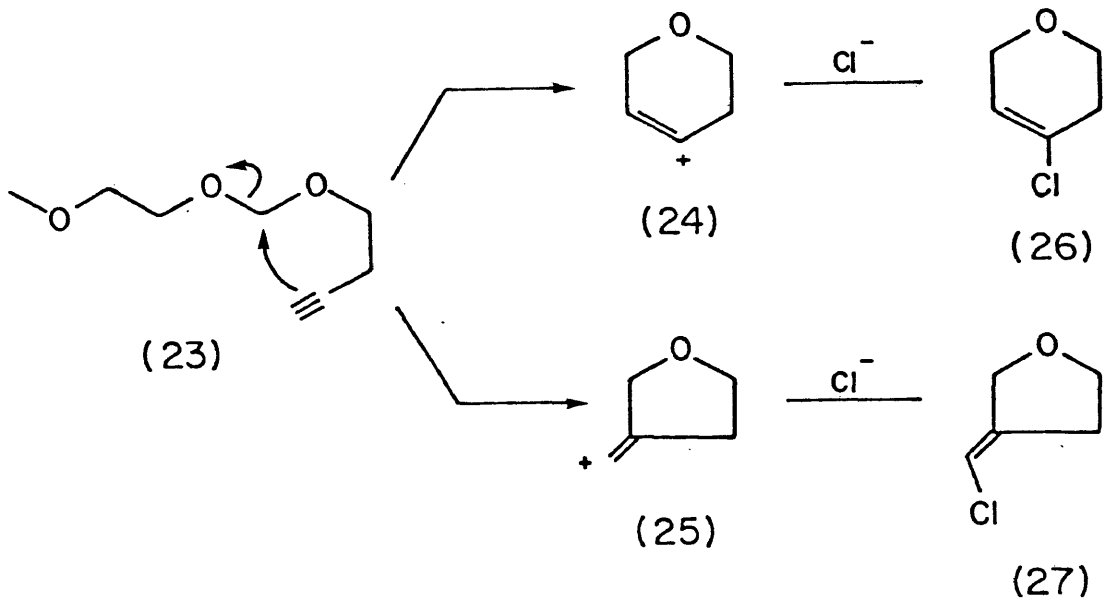
used to make the distinction between pyrans and furans. However, there is evidence from other work as well as mechanistic information which supports the theory that these products are pyrans.

Seamon[5] hydrolized the vinyl chloride product (19) from the cyclization of the ethyl vinyl ether based acetal (18) of 3-butyn-1-ol. The resulting product was the pyrone (20), and not the aldehyde (22), thus showing that the acetal cyclized to 4-chloro-2-methyl-5,6-dihydro-2H-pyran (19).



Other insight can be gained by looking at the mechanism of these cyclizations. As an example, the cyclization of the MEM acetal (23) of 3-butyn-1-ol shown below can result in the formation of either a secondary bent vinyl cation (24) or a primary linear vinyl cation (25) as the intermediate cyclic cation. These cyclic cations can then pick up a chloride ion to form either the pyran (26) or

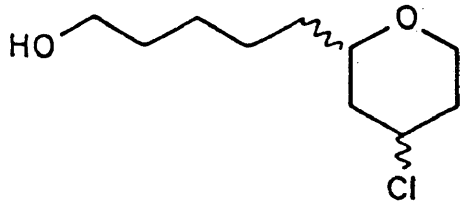
furan (27), respectively.



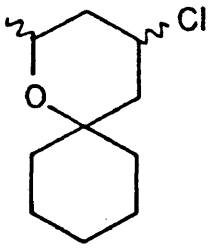
It seems very likely that the formation of (24) would be favored because of the preference for a secondary over a primary cation. This prediction is complicated however by the fact that bent vinyl cations are less stable than linear vinyl cations. Thus, mechanistically it is most likely that acetylenic acetals with terminal triple bonds, such as those described herein, will cyclize to form a secondary bent vinyl cation rather than a primary linear vinyl cation resulting in the formation of pyran products. We cannot, however, be certain about this.

A final uncertainty dealing with the pyran products reported in this thesis concerns the nature of the configurations of the substituents on the pyran ring, and therefore the possibility of isomeric products. All of the unsaturated pyrans reported in Table IV have only one possible isomer and thus require no further consideration.

Also, all of the pyrans prepared from a MEM chloride based acetal have only one possible isomer. Therefore, the only compounds of interest in dealing with this problem are the two tetrahydropyrans shown below.



(28)

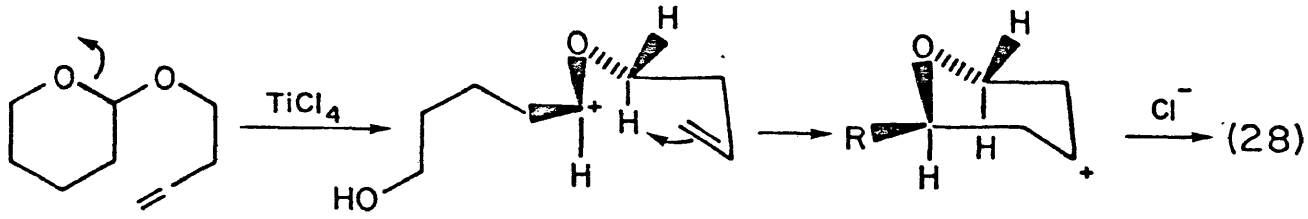


(29)

Both of the above compounds may exist in two isomeric forms. One possible isomer of each has a <u>cis</u> relationship between the alkyl or hydroxybutyl substituent on the 2-position in the pyran ring and the halogen on the 4-position. Thus both substituents are either axial or equatorial (almost certainly equatorial). The other isomer has a <u>trans</u> relationship between these substituents with one being axial and the other equatorial. In each case only one of the two possible isomers is formed, however it is not clear whether this product is the <u>cis</u> or <u>trans</u> isomer.

The fact that only one isomeric form of the above pyran products is formed in cyclization reactions is consistent with the results of another study that showed that in the cyclization of the acetal from ethyl vinyl ether and trans-2-vinyl-cyclohexanol, and other similar acetals, that only one of several possible isomeric products was formed.[39] These results are evidence for the fact that the

intermediate formed initially upon breaking of the carbon-oxygen acetal bond is a trigonal, planar, and relatively free carbocation (31) as shown below.



(30) (31) (32)

Intermediate (31) can exist with the larger hydroxybutyl group in either a pseudo-axial or pseudo-equatorial position. However, it can be assumed that this group prefers the more stable pseudo-equatorial position as depicted by (31) above. This is because 1,3 diaxial steric interactions make the pseudo-axial position very unfavorable. Thus, regardless of the configuration about the asymmetric center in the acetal, it cyclizes stereoselectively to give only a single product because it passes through a trigonal, planar, and thus optically inactive, transition state. In this transition state equilibration to form the more stable, pseudo equatorial, intermediate probably results in the exclusive formation of pyran products with the 2-substituent in the equatorial position.

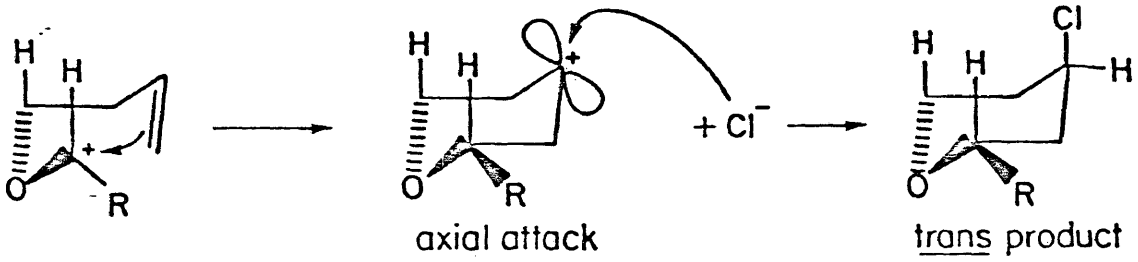
Assuming that the alkyl or hydroxybutyl substituent on

the 2-position in the pyran ring is equatorial, it must be determined if the chloride ion substituent in the 4-position is axial (trans) or equatorial (cis). This orientation is probably dependent on the nature of the mechanism of second carbocation formation and chloride ion attachment. If the mechanism is stepwise with the ring formation, and thus formation of the cationic center on the 4-position in the ring, occuring in a distinct step preceeding chloride ion attachment, then we might expect the chloride ion to occupy the axial position as shown in part A of Scheme XV. Elakovich and Trayham have shown that the nucleophilic capture of a conformationally locked cyclohexyl cation by chloride ion proceeds preferentially to the axial chloride.[40]

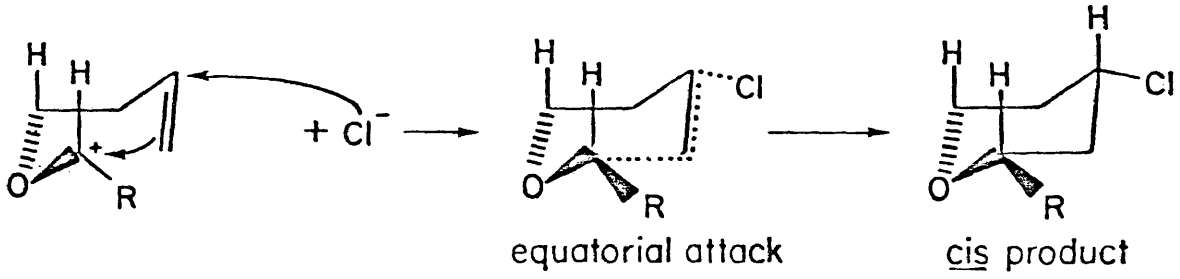
However, if ring formation and chloride ion attachment is a concerted process, as illustrated in part B of Scheme XV, the chloride ion will assume an equatorial orientation in the final product. This is because addition to olefinic bonds occurs in an anti-fashion. At this time a lack of information prohibits us from determining the orientation of the chloro substituent, and thus the mechanism of ring formation. It is fairly clear, however, after reviewing the work of Johnson, that the fact that the product of greatest thermodynamic stability is probably the cis (equatorial/equatorial) product, is probably not a good reason for assuming that the pyrans exist in this form. It is more likely that the nature of the final product is the

Scheme XV

A. Stepwise

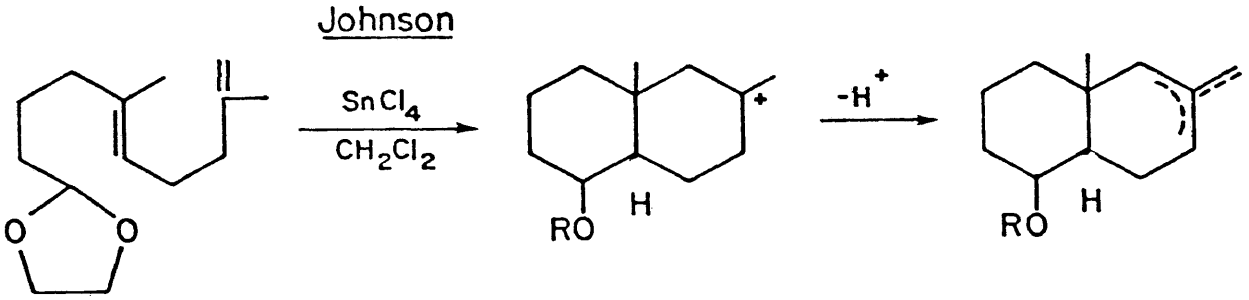


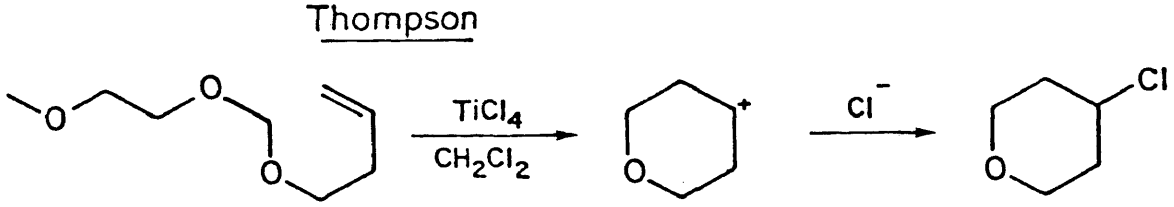
B. Concerted



result of kinetic influences in the transition state.

An important point to note is that the products formed in our cyclizations are always the result of the final carbocation intermediate abstracting a chloride ion from either the solvent or catalyst. In contrast Johnson's work showed that the primary carbocyclic products of his cyclizations of compounds with terminal olefinic bonds under similar reaction conditions were always the result of proton elimination from that final carbocation to form a variety of unsaturated products. An understanding of why Johnson's substrates with terminal olefinic terminators cyclize to yield elimination products while our synthesis leads to substitution products can be gained by examining the pathways shown below.





Johnson's work with terminal olefinic systems utilizes

substrates with a substituent on the olefinic bond such as shown above. Thus the intermediate is always a cyclic tertiary cation. On the other hand, the substrates reported herein cyclize to yield carbocationic intermediates that are secondary. The difference in the effect of a secondary versus tertiary intermediate carbocation must explain the differences in products.

The results in this thesis demonstrate that the cyclization of acetals of homoallylic and homopropargylic alcohols using a Lewis acid promoter offers a facile and stereoselective route to 4-halo-5,6-dihydro-2H-pyrans and 4-halotetrahydropyrans. In general, the yields are good although they are lower for the cyclizations of acetylenic acetals. A variety of substituents can be introduced onto the pyran ring and more complicated substrates, such as spiro pyrans, can be synthesized. Future work in this area will be needed to work out the orientation of the 4-halo substituent on the pyran ring. Also some additional work aimed at improving the yields of the more interesting unsaturated pyrans would be useful. In addition changing the nature of the acetal substrate to include the use of internal double and triple bonds may provide useful mechanistic information about this reaction, as well as extend this synthesis into the preparation of furans.

APPENDIX

Tetrahedron Letters,Vol.25,No.25,pp 2653-2654,1984 0040-4039/84 $3.00 + .00
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THE SYNTHESIS OF 4-HALOTETRAHYDROPYRANS AND 4-HALO-5,6-DIHYDRO-2H-PYRANS VIA THE LEWIS ACID PROMOTED CYCLIZATION OF ACETALS OF HOMOALLYLIC AND HOMOPROPARGYLIC ALCOHOLS

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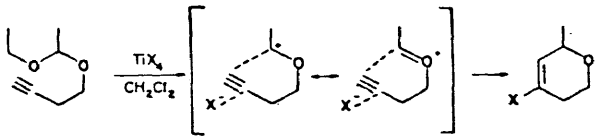
Ethyl vinyl ether, MEM chloride, and dihydropyran based acetals of homoallylic and homopropargylic alcohols cyclize in the presence of Lewis acids to give 4-halotetrahydropyrans and 4-halo-5,6-dihydro-2H-pyrans, respectively.

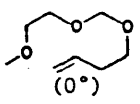
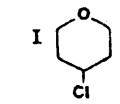
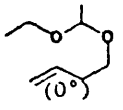
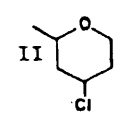
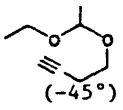
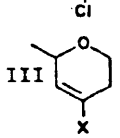
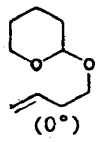
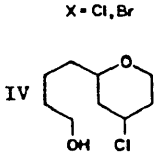
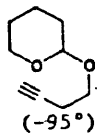
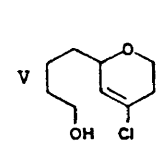
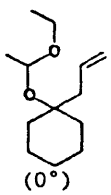
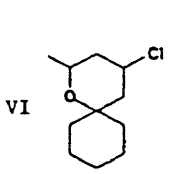
In this paper we report a facile synthesis of the title pyrans via a TiX_4(X=Cl,Br) promoted cyclization of acetals derived from ethyl vinyl ether, 1-chloromethoxy-2-methoxyethane, and 3,4-dihydro-2H pyran with γ-unsaturated alcohols.[1] The synthetic results are summarized in the Table. The cyclizations were accomplished by dissolving 1-2 equivalents of TiX_4 in CH_2Cl_2 (5 mL per 1 mmol TiX_4) followed by dropwise addition of 1 equivalent of the acetal (1 mL per min). The reactions were allowed to proceed 15 min and then were quenched with methanol (5 mL per 10 mmol TiX_4) followed by 30-40 mL of 3N HCl saturated with NaCl. The product pyrans can be isolated from the organic layer by preparative GLC or distillation.

The reaction pathway most reasonably involves a cation-olefin cyclization step as illustrated for the acetal derived from ethyl vinyl ether and 3-butyn-1-ol:



These acetal cyclizations are related to Prins reaction chemistry yielding tetrahydropyrans.[2-4] However, the present approach gives higher yields and offers greater flexibility particularly in the cyclization of γ-alkynol based acetals. While our work was in progress a similar cyclization of the tetrahydropyranyl ether of 3-buten-1-ol catalyzed by $BF_3 \cdot OEt_2$ in trichloroethanol was reported.[5]

Products II, IV, and VI may exist as cis-trans isomers. GLC and NMR data for II indicate two isomers in the ratio 92:8 (presumable cis:trans). For products IV and VI

Acetal [7]	Product	Yield	^{13}C-NMR Data
 (0°)	 I	87	36.9($C_{3,5}$); 56.9(C_4); 66.1 ($C_{2,6}$)
 (0°)	 II	95 (92% cis 8% trans)	21.7(CH_3); 37.2,44.8(C_3 and C_5); 56.0(C_4); 67.3(C_2); 73.4(C_6)
 (-45°)	 III X = Cl, Br	95(Cl)	X=Cl: 20.8(CH_3); 32.8(C_5); 63.8(C_6); 71.0(C_2); 128.0(C_3); 129.4(C_4)
		98(Br)	X=Br: 21.1(CH_3); 35.5(C_5); 65.0(C_6); 72.3(C_2); 119.1(C_4); 133.2(C_3)
 (0°)	 IV	92	21.5, 32.5, 35.9, 37.1, 42.9, 62.5, 67.0(CH_2 carbons); 55.9(C_4); 77.1(C_2)
 (-95°)	 V	65	21.6, 32.8, 33.3, 34.9, 62.8, 63.9(CH_2 carbons); 74.9(C_2); 127.7(C_3); 130.0(C_4)
 (0°)	 VI	94	24.8, 25.1, 25.4, 29.3, 34.0, 43.2, 47.8, 49.1, 57.0, 68.1, 77.1

the GLC and NMR data indicate a single isomer only.

The vinyl halide moiety resulting from the cyclization of the acetylenic acetals allows for further functional development, as demonstrated by the hydrolysis of III to 2-methyl-4-pyrone (aqueous $Hg(NO_3)_2$, 60°C).[6,8]

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1. W. H. Bunnelle, D. W. Thompson, and D. W. Seamon, 35th Sourtheast Regional Meeting of the American Chemical Society, Charlotte, N.C., Nov. 1983; ORG 458.
2. E. Hänschke, Chem. Ber., 1955, 88, 1053.
3. J. Cologne and P. Boisde, Bull. soc. chim. France, 1956, 824.
4. P. R. Stapp, J. Org. Chem., 1969, 34, 479.
5. I. T. Kay and E. G. Williams, Tetrahedron Letters, 1983, 24, 5915.
6. H. Arzoumanian and J. Metzger, J. Organometal. Chem., 1973, 57, C1.

7. The temperature at which the acid promoted cyclization was run is listed under each acetal. Yields determined by GLC. NMR solvent: $CDCl_3$.

8. We thank the donors of the Petroleum Research Fund administered by the American Chemical Society and the Jeffress Memorial Trust for partial support of this work. We thank E. I. DuPont de Nemours and Company, Inc. and the National Science Foundation for funds with which to purchase gas chromatographs.

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REFERENCES

1. a) P.G. Williard, L.A. Grab, and S.E. de Laszlo, J. Org. Chem. 1983, 48, 1123-1125.
   b) I. Kubo and Coworkers, Chemistry in Britian 1984, 6, No. 20, 501.
   c) A. mitra, "The Synthesis of Prostaglandins", John Wiley and Sons, Inc., New York, 1977, p. 304.

2. T.J. Zitzelberger, M.D. Schiavelli, and D.W. Thompson, J. Org. Chem. 1983, 48, 4781 and references therein.

3. A.V. Youngblood, S.A. Nichols, R.A. Coleman, and D.W. Thompson, J. Organomet. Chem. 1978, 146, 221.

4. H.G. Richey, L.M. Moses, and J.J. Hangeland, Organometallics 1983, 2, 1545.

5. D.W. Seamon, College of William and Mary, Honors Thesis, 1983.

6. W.H. Bunnelle, D.W. Seamon, D.L. Mohler, T.F. Ball, and D.W. Thompson, Tetrahedron Lett. 1984,25, 2653.

7. M. Bartok, "Cyclic Ethers," in The Chemistry of Ethers, Supplememt E, John Wiley and Sons, New York, 1980, Chap. 15.

8. M. Bartok and A. Molnar, "Dehydration of Diols," in The Chemistry of Ethers, Supplement E, John Wiley and Sons, New York, 1980, Chap. 16.

9. G. Dittus, W. Lurken, Eu. Muler, and B. Zeeh, in Methoden der Organischen Chemie (Houben-Weyl), Vol. VI/4, Georg Thieme Uerlag, Stuttgart, pp. 11-252.

10. C.W. Roberts in "Friedal-Crafts and Related Reactions," G.A. Olah, Ed., Vol II, Interscience, New York, 1964, Chap. 27.

11. P.R. Stapp, J. Org. Chem. 1969, 34, 479.

12. P.R. Stapp, J. Org. Chem. 1970, 35, 2419.

13. P.R. Stapp and D.S Weinberg, J. Org. Chem. 1969, 34, 3592.

14. a)E. Arundale and L.A. Mikeska, Chem. Rev. 1952, 51, 505, in Ref. 10.
b)V. Frazen and H. Krauch, Chem.-Ztg. 1955, 79, 335, in Ref. 10.

15. a)N.A. Lebel, R.N. Liesemer, and E. Mehmedbasich, J. Org. Chem. 1963, 28, 615, in Ref. 11.
b)F.A. Meneghini, Dissertation Abstr. 1967, 27, 2299B, in Ref. 11.

16. a)E. Hanschke, Chem. Ber. 1955, 88, 1053.
b)J. Colonge, C.R. Acad. Sci., Paris 1955, 240, 1552, in Ref. 11.

17. J. Cologne and P. Boisde, Bull Soc. Chim. Fr. 1956, 23, 824.

18. J. Hine, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N.Y., 1962, pp. 73,157.

19. A. van Gen, K. Wiedhaup, J.J. Swoboda, H.C. Dunathan, and W.S. Johnson, J. Amer. Chem. Soc. 1973, 95, 2656.

20. D.J. Goldsmith, B.C. Clark, Jr., and R.C. Joines, Tetrahedron Lett. 1966, 1149.

21. W.S. Johnson and T.K. Schaaf, Chem. Communs. 1969, 611.

22. W.S. Johnson, K. Wiedhaup, S.F. Brady, and G.L. Olson, J. Amer. Chem. Soc. 1974, 96, 5279.

23. W.S. Johnson, C.A. Harbert, B.E. Ratcliffe, and R.D. Stipanovic, J. Amer. Chem Soc. 1976, 98, 6188.

24. K.A. Parker and W.S Johnson, J. Amer. Chem. Soc. 1974, 96, 2556.

25. W.S. Johnson and L.A. Bunes, J. Amer. Chem Soc. 1976, 98, 5597.

26. W.S. Johnson, L.R. Hughes, and J.L. Carlson, J. Amer. Chem. Soc. 1979, 101, 1281-1282.

27. M.E. Garst, Y. Cheung, and W.S. Johnson, J. Amer. Chem. Soc. 1979, 101, 4404-4406.

28. W.S. Johnson, C.A. Harbert, and R.D. Stipanovic, J. Amer. Chem. Soc. 1968, 90, 5280.

29. P.A. Bartlett, W.S. Johnson, and J.D. Elliott, J. Amer. Chem. Soc. 1983, 105, 2088-2089.

30. P.E. Peterson and R.J. Kamat, J. Amer. Chem. Soc. 1969, 91, 4521, in Ref. 31a.

31. a)W.S. Johnson, M.B. Gravestock, R.J. Parry, R. Myers, T.A. Bryson, and D.H. Miles, J. Amer. Chem. Soc. 1971, 93, 4330-4332.
b)M.B. Gravestock, W.S. Johnson, R.F. Myers, T.A. Bryson, D.H. Miles, and B.E. Ratcliffe, J. Amer. Chem. Soc. 1978, 100. 4268-4273.

32. a)W.S. Johnson, M.B. Gravestock, and B.E. McCarry, J. Amer. Chem. Soc. 1971, 93, 4332-4334.
b)M.B. Gravestock, W.S. Johnson, B.E. McCarry, R.J. Perry, and B.E. Ratcliffe, J. Amer. Chem. Soc. 1978, 100, 4274-4282.

33. W.S. Johnson, M.B. Gravestock, R.J. Parry, and D.A. Okorie, J. Amer. Chem. Soc. 1972, 94, 8604-8605.

34. Products of similar rearrangements have been observed with vinyl cations generated by solvolysis of vinyl triflates. See, for example, W.D. Pfefer, C.A. Bahn, P.v.R. Schleyer, S. Bocher, C.E. Harding, K. Hummel, M. Hanack, and P.J. Stang, J. Amer. Chem. Soc. 1971, 93, 1513, in Ref. 33.

35. W.S. Johnson, L.R. Hughes, J.A. Kliek, T. Niem, and A. Shenvi, J. Amer. Chem. Soc. 1979, 101, 1279.

36. W.S. Johnson, C.E. Ward, S.G. Boots, M.B. Gravestock, R.L. Markezichi, B.E. McCarry, D.A. Okorie, and R.J. Parry, J. Amer. Chem. Soc. 1981, 103, 88-98.

37. L. Brandsma and H.D. Verkruijsse, "Synthesis of Acetylenes, Allenes, and Cumulenes," Elsevier Scientific Publishing Co., Amsterdam, 1981, p.16.

38. J.S. Cowie, P.D. Landor, and S.R. Landor, J. Chem. Soc. Perkin I 1973, p.720.

39. a)M.L. Melany, College of William and Mary, Honors Thesis, 1984.
b)T.F. Ball, M.L. Melany, and D.W. Thompson, Seminar, Virginia Academy of Sciences, University of Richmond, 1984.

40. S.D. Elakovich and J.G. Trayham, J. Org. Chem. 1973, 38, 873-880.