

**THE STEREOSPECIFIC SYNTHESIS OF TETRAHYDROPYRANS
AND TETRAHYDROFURANS**

A Thesis

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The College of William and Mary in Virginia**

**In Partial Fulfillment
Of the Requirements for the Degree of
Master of Arts**

by

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APPROVAL SHEET

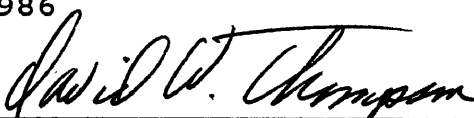
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I dedicate this thesis to my family for their love, support, and encouragement to continue with my studies. It was not always easy, but they were always there. Thank you.

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ABSTRACT

The aim of this study was to cyclize unsaturated acetals in a stereospecific manner to form tetrahydropyrans and tetrahydrofurans. The cyclization, initiated by a Lewis acid, involved formation of an oxocarbenium ion which then attacked the intramolecular double or triple bond to form a ring and an oxocarbenium ion. This oxocarbenium ion was attacked simultaneously by a nucleophile. When the unsaturation was an alkene, the attack on the double bond occurs by trans-addition. The cis starting acetal thereby produces the cis tetrahydropyran and the trans starting acetal produces the trans tetrahydropyran. When the unsaturation was an alkyne, the product mixture contained tetrahydrofurans and a dihydropyran. The ratios of these products varied with starting acetal and temperature.

**THE STEREOSPECIFIC SYNTHESIS OF TETRAHYDROPYRANS
AND TETRAHYDROFURANS**

INTRODUCTION

Tetrahydropyran and tetrahydrofuran nuclei (Figure 1) are important structural features in a



Figure 1. Tetrahydropyran and Tetrahydrofuran Nuclei.

variety of natural products. In addition to the large variety of pyranose and furanose sugars and thromboxanes (Figure 2), tetrahydropyran and tetrahydrofuran nuclei are found in more recently investigated polyether antibiotics such as monensin, lasalocid, and antibiotic X-206 (Figure 3). These antibiotics are useful in controlling coccidia infections in poultry, with monensin cornering 80% of the coccidiostat market. These antibiotics, along with others, are also useful in the improvement of ruminant feed utilization¹.

In Kishi's synthesis of lasalocid, both tetrahydropyran and tetrahydrofuran rings are formed by cyclizations initiated by the opening of an epoxide. In the formation of the tetrahydrofuran ring of lasalocid (1)

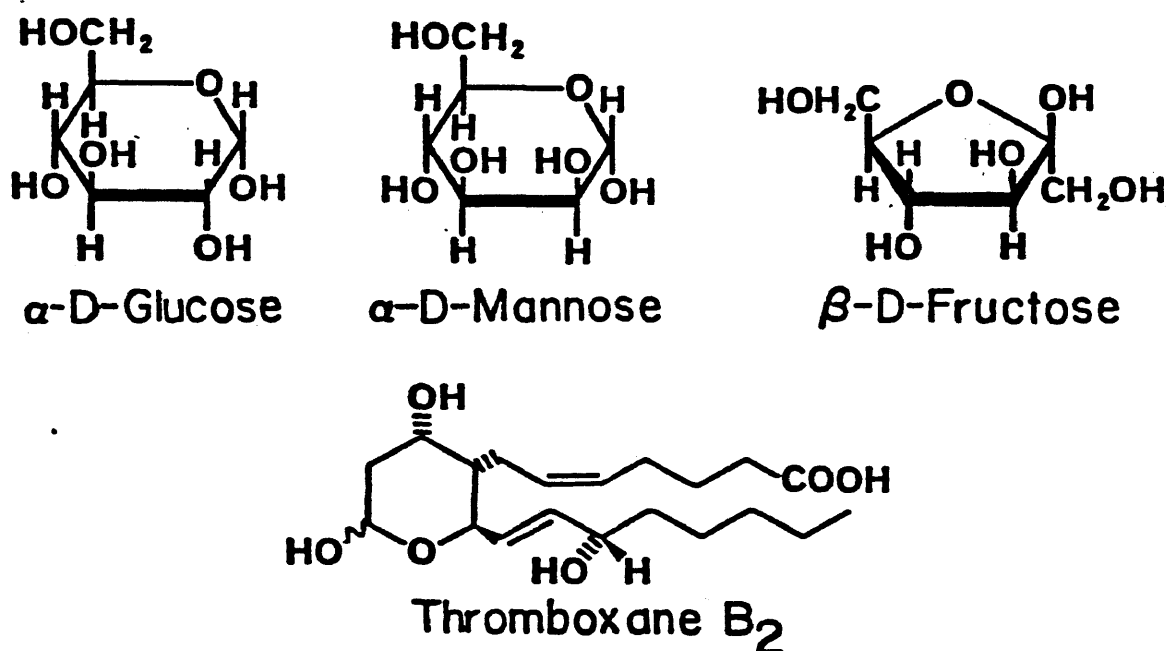


Figure 2. Pyranose Sugars: Glucose and Mannose; Furanose Sugar: Fructose; and Thromboxane B-2.

(Scheme 1), there is an 8:1 ratio of stereoisomers favoring the isomer shown. The tetrahydropyran in lasalocid (3) (Scheme 2) is formed from a ring expansion of the furan (2). This furan is synthesized with a 5:1 ratio of stereoisomers from a hydroxyl attack on an epoxide. In Kishi's synthesis of monensin (Scheme 3), formation of tetrahydrofuran C (4) also is initiated by a ring opening of an epoxide. Ring C is formed with a 7:2 diastereomeric ratio. The tetrahydropyran ring A (5) in Scheme 4 was formed from the oxidation of an alcohol and an ester with a 53% yield. In Still's synthesis of monensin (Scheme 5) the C-ring tetrahydrofuran (6) is formed from the condensation of a diol in a 70% yield².

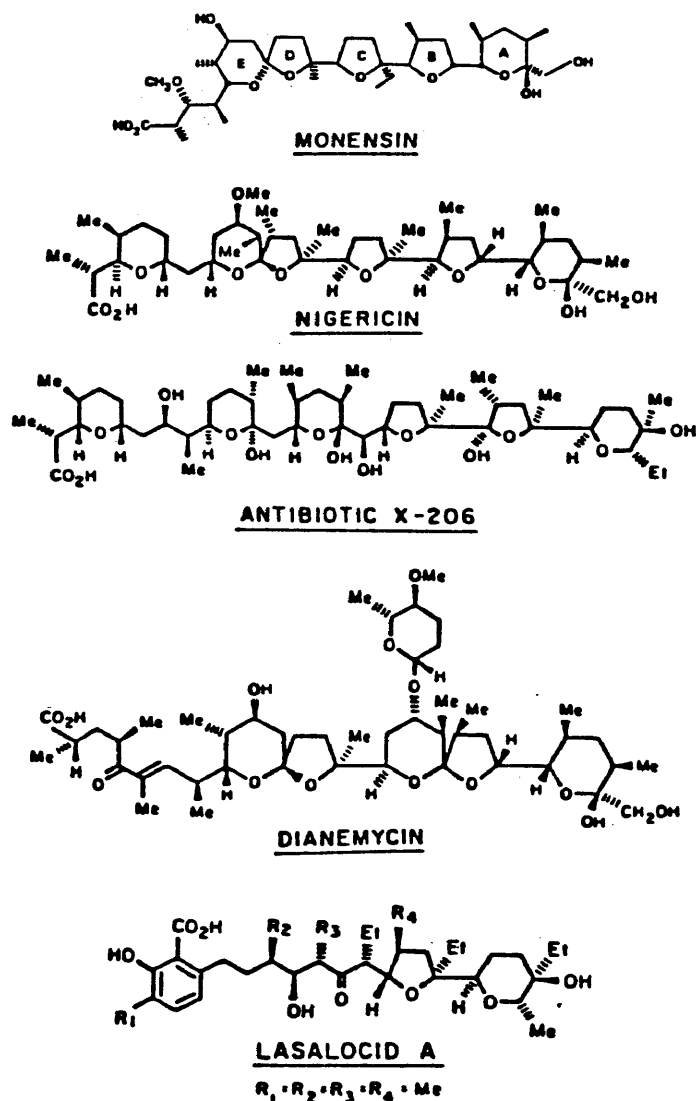
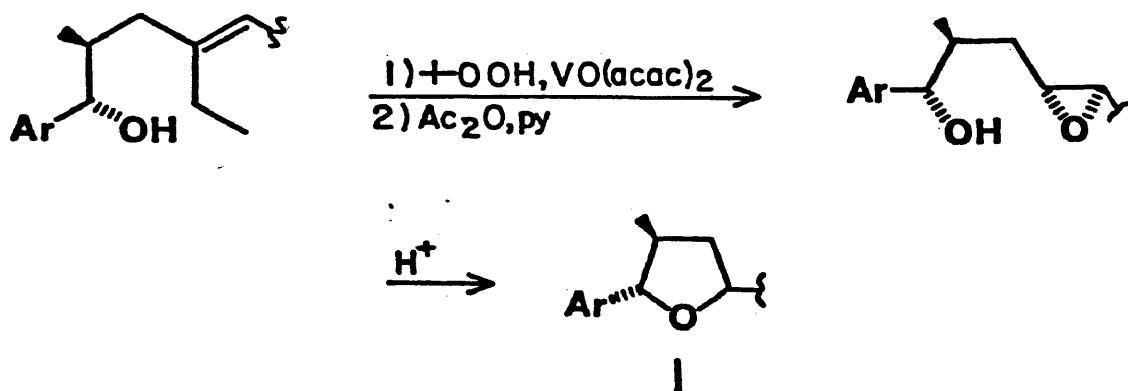
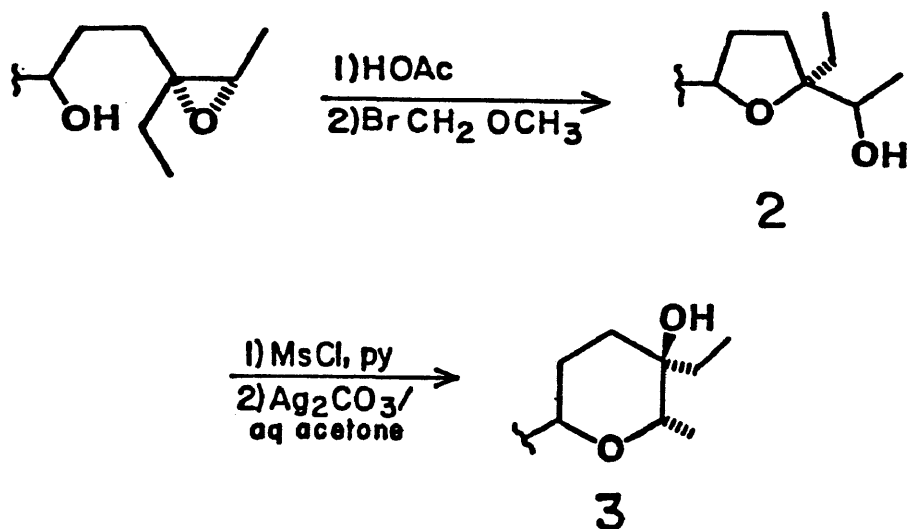


Figure 3. Various Antibiotics Containing Tetrahydropyran and Tetrahydrofuran Nuclei.

In each of these syntheses and indeed in most all syntheses reported of tetrahydropyrans and tetrahydrofurans, a carbon-oxygen bond is formed usually resulting in less than desired stereoselectivity around the ring. Natural syntheses of these nuclei in living organisms, however, is very stereospecific, and use of these molecules in a living



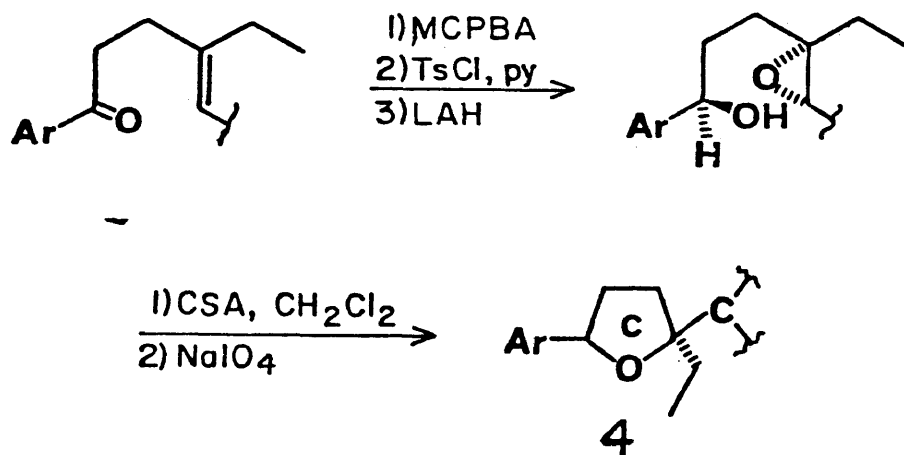
Scheme 1.



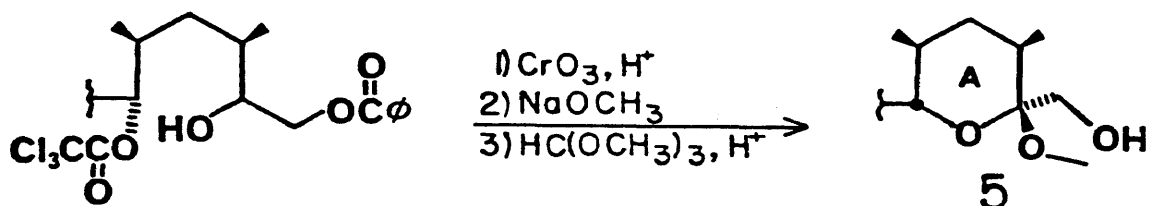
Scheme 2.

system requires a high degree of stereoselectivity. Therefore in this work we report an investigation of a carbon-carbon bond forming cyclization which may give rise to enhanced stereoselectivity.

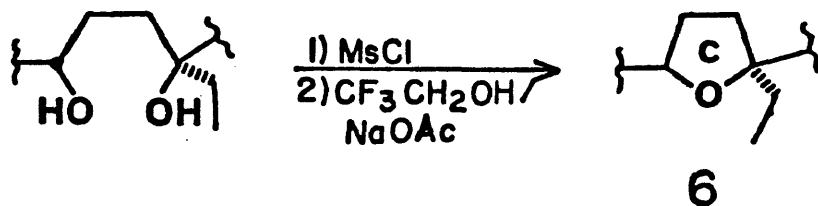
In 1899 Prins³ synthesized tetrahydropyrans by mixing formaldehyde, an olefin, and a protic acid together in an aqueous system. This led to a complex mixture of



Scheme 3.

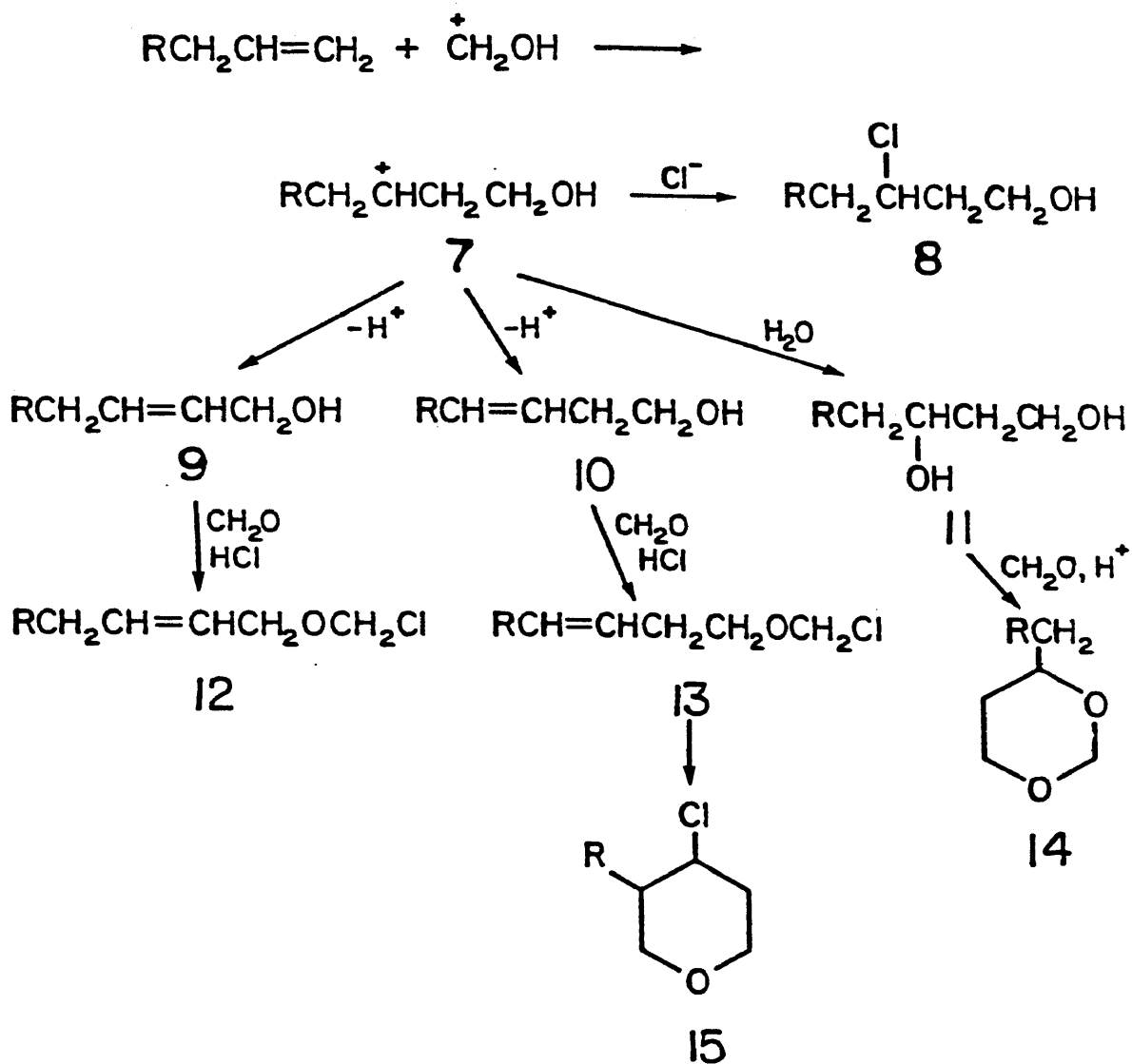


Scheme 4.



Scheme 5.

products as seen in Scheme 6. A protonated formaldehyde attacks the double bond of the alkene to form the cationic alcohol (7). This can then be attacked by an anion from the acid to form a halo-alcohol (8), or it can lose a proton in one of two different ways. It can lose a proton to form the



Scheme 6.

allylic alcohol (9) which can then react with formaldehyde and acid again to form the α -chloroether (12), or it can lose a proton to form the homoallylic alcohol (10). This homoallylic alcohol can also react with formaldehyde and acid to form another α -chloroether (13) which can then cyclize to form the 4-chloro-3-ethyltetrahydropyran (15). In both cases of deprotonation, the cationic alcohol can

lose a proton to form a cis or a trans double bond. Both the cis and the trans isomers of the homoallylic alcohol can then cyclize to form the cis or the trans-3-alkyl-4-halotetrahydropyran. The cationic alcohol (7) also can react with water in the system to form a diol (11) which after attack by protonated formaldehyde can cyclize to form the dioxane (14). With the complex mixture of products formed by the Prins reaction, however, this reaction is not useful for the synthesis of tetrahydropyrans.

In 1969 Stapp³ published a modification of the Prins reaction in which the reaction was performed in an anhydrous medium (therefore eliminating dioxanes) with gaseous hydrogen chloride, formaldehyde, and a terminal olefin. In Stapp's reaction only the homoallylic alcohol (10) is formed from the cationic alcohol (7). The homoallylic alcohol then cyclizes, after reaction with a formaldehyde molecule, to form a cis/trans isomer mixture of 3-alkyl-4-halotetrahydropyran (15). The two isomers of this reaction were resolved on a nonpolar Ucon chromatographic column. Since the lower boiling compound usually elutes first, the trans isomer (which has a lower boiling point according to Crombie and Harper) is expected to comprise 60-85% of the compound and the cis isomer 15-40%. Although good isolated yields of 70-80% of 3-alkyl-4-chlorotetrahydropyran can be obtained for the olefins 1-butene, 1-hexene, 1-octene, 1-decene, and 1-dodecene at -60° to -70°C, their cis/trans stereoselectivity is not

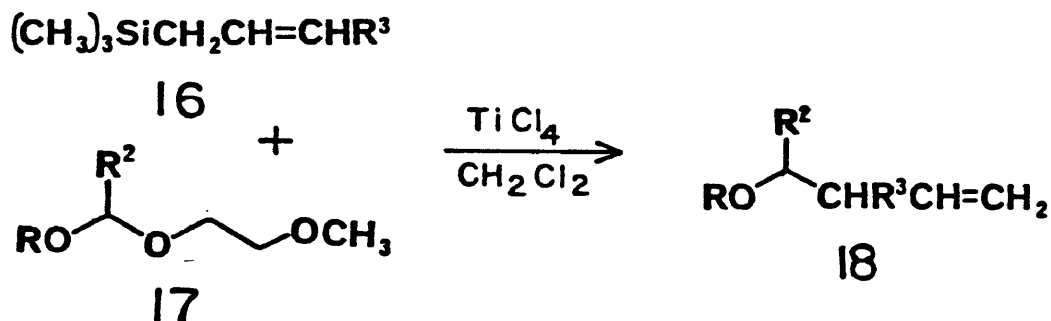
as good as hoped. The effect of raising the temperature of the reaction on stereoselectivity is unknown, however, raising the temperature of the reaction with 1-hexene considerably reduces the product yield (-60° to -70°C (90%), -20° to -30°C (57%), 0° to 5°C (18%)) thus making a change in stereoselectivity with a change in temperature basically useless.

In both Prins' and Stapp's work, a terminal olefin is used as a starting material. As each reaction proceeds a proton is lost to form the homoallylic alcohol, and in the case of the Prins reaction, the allylic alcohol as well. The homoallylic alcohol then can cyclize to form the cis/trans isomers of 3-alkyl-4-halotetrahydropyran³.

Colonge and Boisse⁴ in 1956 reported the cyclization of tetrahydropyrans by reacting a homoallylic alcohol with formaldehyde and hydrogen chloride. By starting with the homoallylic alcohol (10) rather than with the alkene, they avoided the complex mixture of products caused by the loss of a proton to give reactive carbocationic intermediates. Thus they only produced the cyclized product, 3-alkyl-4-chlorotetrahydropyran. Colonge and Boisse, however, never made any reference to the cis/trans ratio in their starting material or in their product, thus the stereoselectivity of their reaction is unknown.

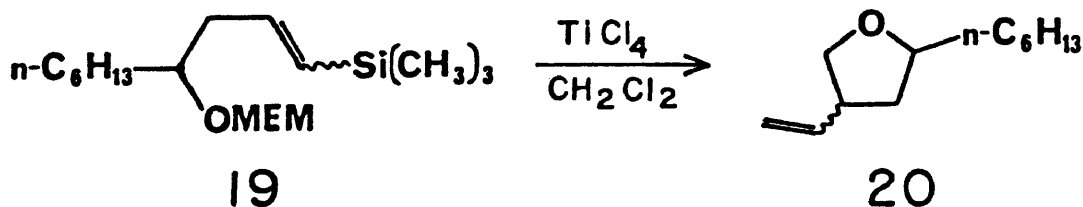
Each of these cyclizations consists of a carbon-carbon bond formation using an electrophilic cationic attack

on a double bond. Itoh's reaction⁵ (Scheme 7) of an allylsilane (16) and a hemiacetal (17) also used an electrophilic attack of a double bond to form a homoallyl ether (18) by way of a carbon-carbon bond formation. He



Scheme 7.

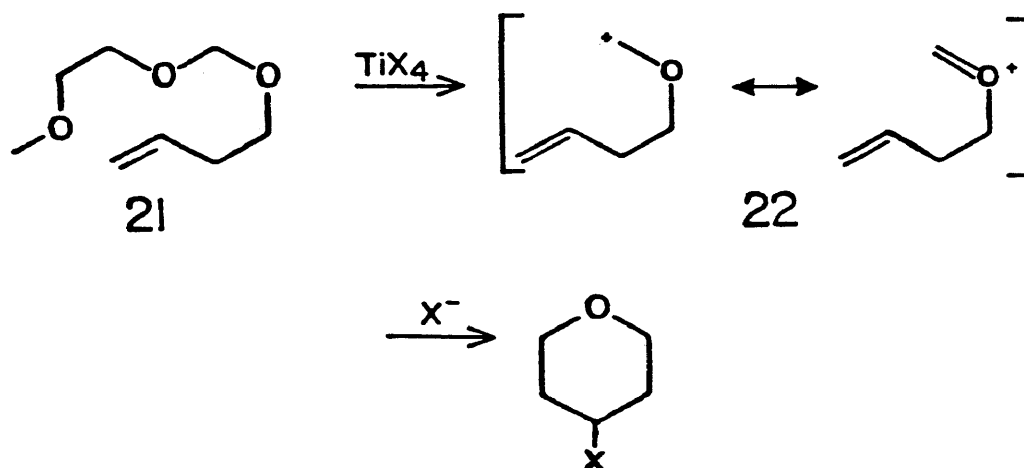
used the Lewis acid TiCl_4 to produce an oxocarbenium ion from (17) which then attacked the double bond of (16) in an intermolecular reaction. Itoh also reacted an allylsilane hemiacetal (19) with TiCl_4 , as seen in Scheme 8, to form a carbocation which attacked the intramolecular double bond to form a tetrahydrofuran (20).



Scheme 8.

In an independent synthesis of tetrahydropyrans, Seamon and Thompson⁶ formed a carbon-carbon bond through cationic attack of a double bond. The cation was

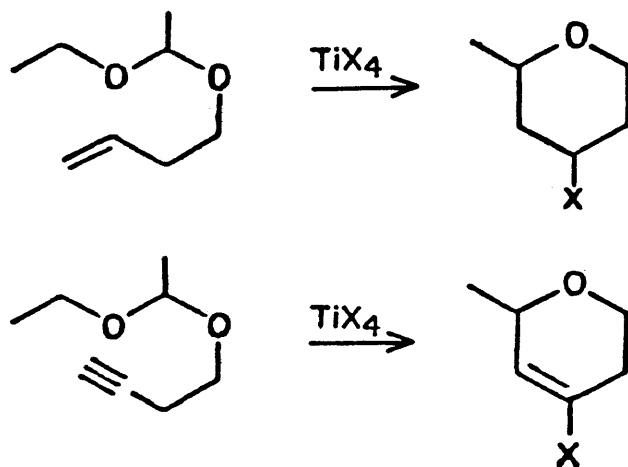
formed by an attack of a Lewis acid on an acetal. To minimize complex mixtures of product through non-stereospecific loss of a proton, they began with a terminal homoallylic alcohol. The alcohol was made into the acetal of methoxyethoxymethyl chloride (MEM Cl) or into the acetal of ethyl vinyl ether. The acetal (21) (Scheme 9) was then subjected to a Lewis acid so as to form the oxocarbenium ion (22) which is stabilized by the adjacent oxygen. The cation attacked the intramolecular double bond



Scheme 9.

to form a new carbon-carbon bond, and the reaction was terminated by a final attack of a halide ion to form the 4-halotetrahydropyran (23) in 96% yields. Other examples of these reactions are found in Scheme 10.

In our own investigation of a carbon-carbon bond forming cyclization to give tetrahydropyrans with enhanced stereoselectivity, we started with either the cis or the trans homoallylic alcohol in order to determine if the



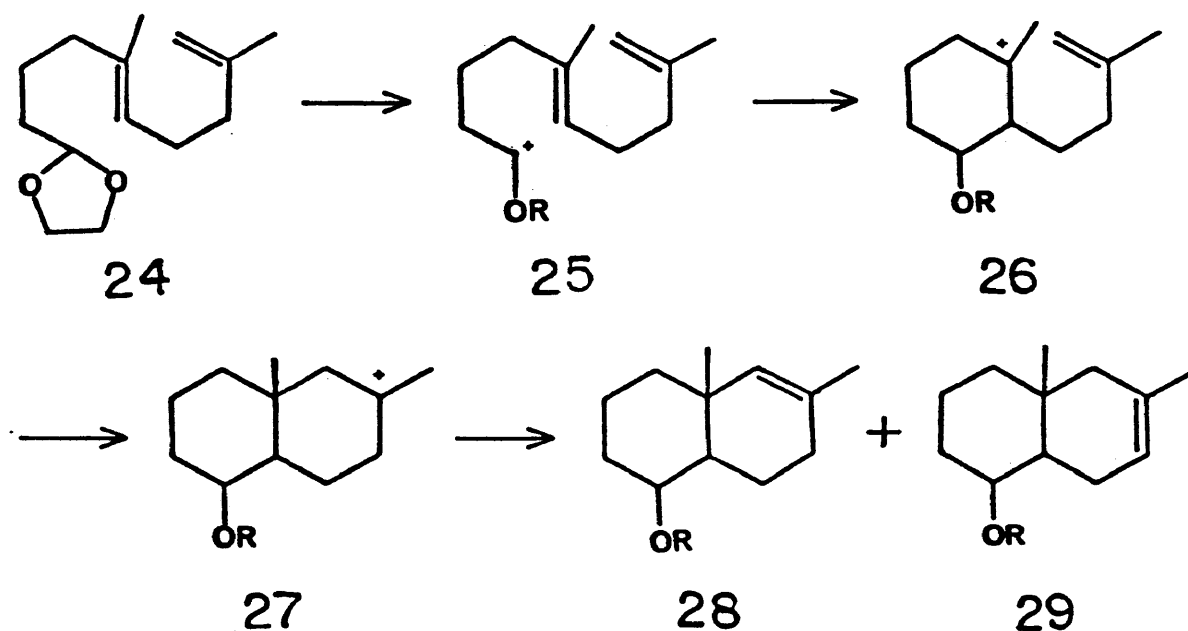
Scheme 10.

cyclization itself is stereospecific and if so to present a facile synthesis of cis or trans-3-alkyl-4-halotetrahydropyran with good yields. We also have studied the effect of cyclization on an internal homopropargylic alcohol in hopes to form a tetrahydrofuran.

LITERATURE REVIEW

The reactions which we have investigated leading to cyclic ethers are cationic cyclizations. Johnson and coworkers have presented detailed studies of cationic polyene cyclizations. These cyclizations often deal with many of the same situations and problems found in making tetrahydropyrans and tetrahydrofurans. Although our synthesis involves an oxygen in a single five or six-membered ring and Johnson's contains just carbons to make a multi-ring structure, both syntheses involve a carbon-carbon bond formation using a cationic electrophilic attack on a double bond.

An example of Johnson's work is seen in Scheme 11. In this case Johnson starts with the acetal (24), which upon reaction with an acid gives the carbocation (25). The OR substituent ($R = \text{CH}_2\text{CH}_2\text{OH}$) is the leftover acetal fragment. This carbocation then attacks the intramolecular, electron-rich double bond to form the cyclic carbocation (26). This carbocation then attacks another intramolecular double bond to form the bicyclic carbocation (27) which eliminates a proton to form the bicyclics (28) and (29)⁷.



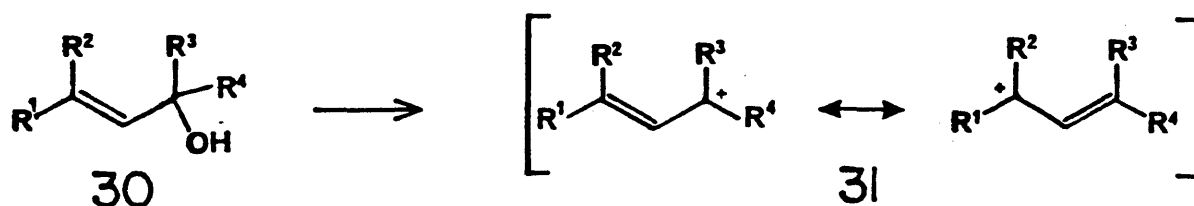
Scheme 11.

The initiating carbocations for these polyene cyclizations can be formed by using 1) an allylic alcohol^{8, 9, 10, 11}, 2) a very good leaving group^{12, 13}, or 3) an acetal^{10, 14, 15}.

Examples of these initiators are discussed below.

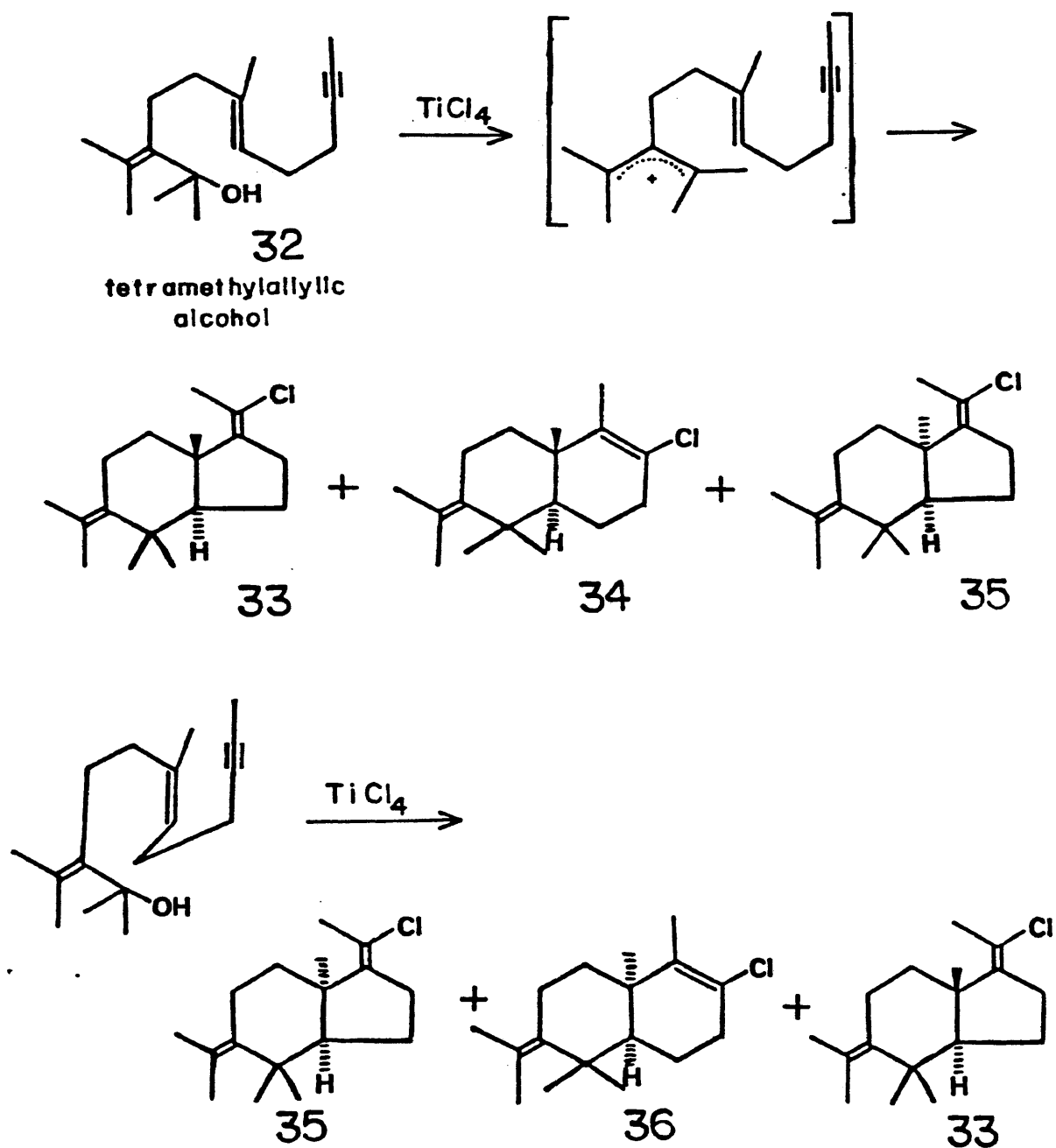
When using an allylic alcohol (30) (Scheme 12), the hydroxyl group is lost as water after protonation. The hydroxyl group also can be lost by complexation with a Lewis acid. Either way the cation (31) is stabilized by delocalization of the charge.

The type of allylic alcohol (tetramethylallylic alcohol, cyclohexenyl alcohol, or cyclopentenyl alcohol) in the starting material affects the stereochemistry of the final product. When Johnson starts with an acetylenic trans diene system with a tetramethylallylic alcohol (32), as seen



Scheme 12.

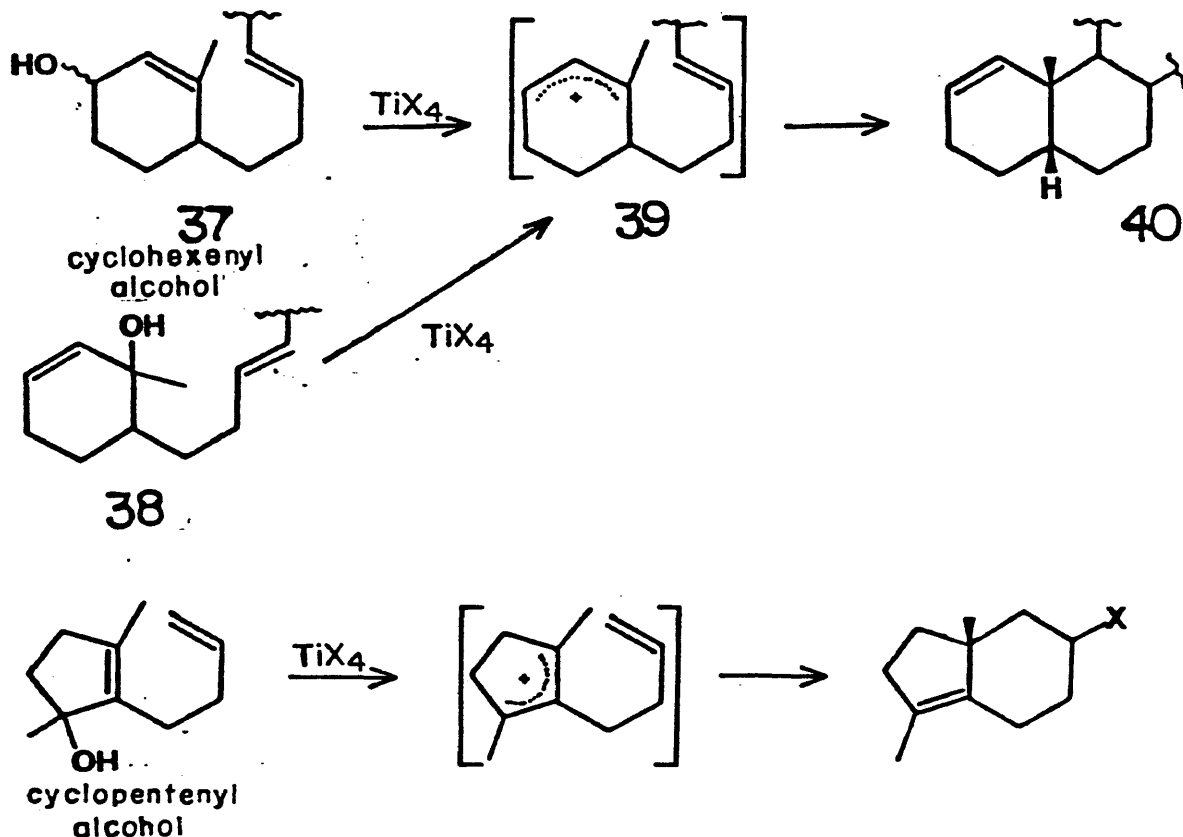
in Scheme 13, the major products have trans-fused A/B rings, as in compounds (33) (75%) and (34) (12%). Eight percent of the product is compound (35) with cis-fused A/B rings^{8, 11}. The acetylenic cis diene system (in Scheme 13) likewise produces products with cis-fused A/B rings, as in compounds (35) and (36), and small amounts of the product with trans-fused A/B rings, compound (33)¹⁶. The cis-fused A/B ring system, however, also can be produced without any trans-fused A/B ring products. When the allylic alcohol is a cyclohexenyl alcohol, as compounds (37) or (38) (Scheme 14), the product has cis-fused A/B rings as in compound (40)⁹. When any of the four trans olefin isomers of (37) or (38) are reacted with a Lewis acid, a carbocation (39) is formed. Because of the steric interference of the free arm with the methyl group attached to the delocalized cation, the free arm double bond can only approach the cation from the side of the ring to which it is attached. This can only give the cis-fused ring system as found in compound (40). The cyclopentenyl initiator is also seen in Scheme 14. Cyclizations initiated by allylic alcohols are synthetically useful because under



Scheme 13.

mild conditions they give yields greater than 50% of fully cyclized product¹⁰.

An initiating carbocation can also be produced by using a very good leaving group. Groups such as nosylate and tosylate are such good electron-withdrawing groups that

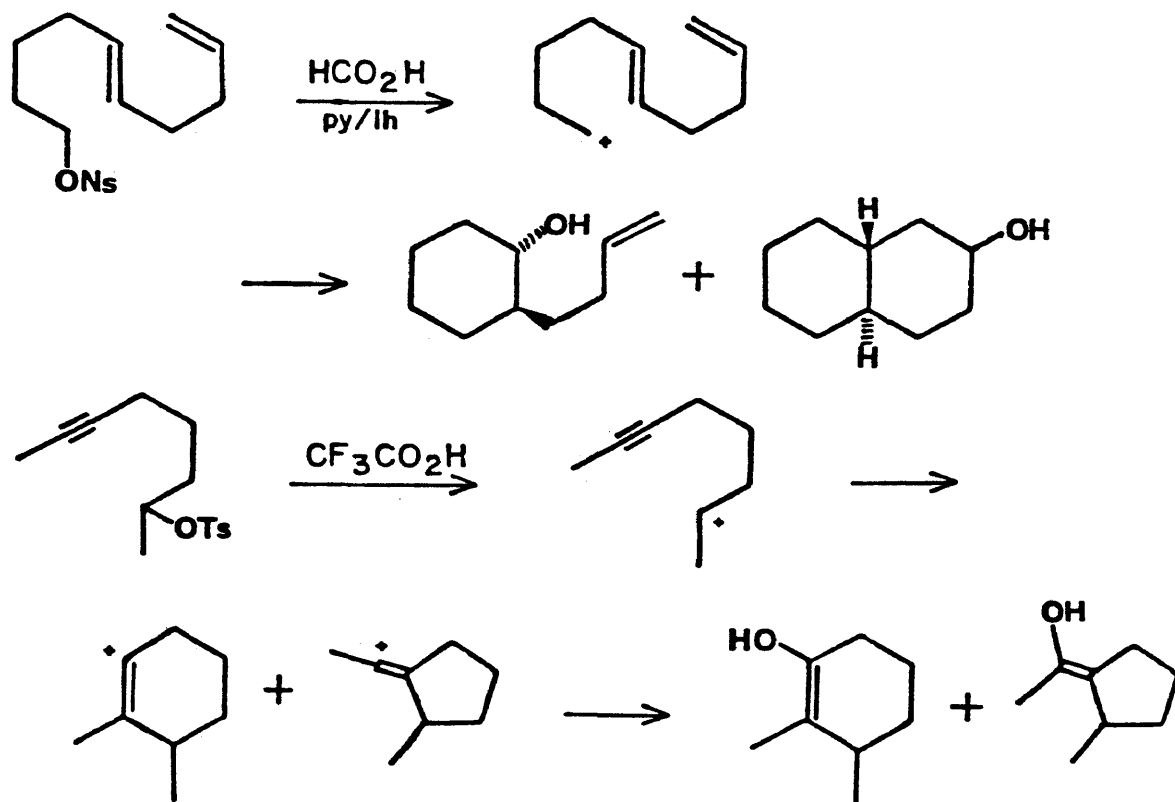


Scheme 14.

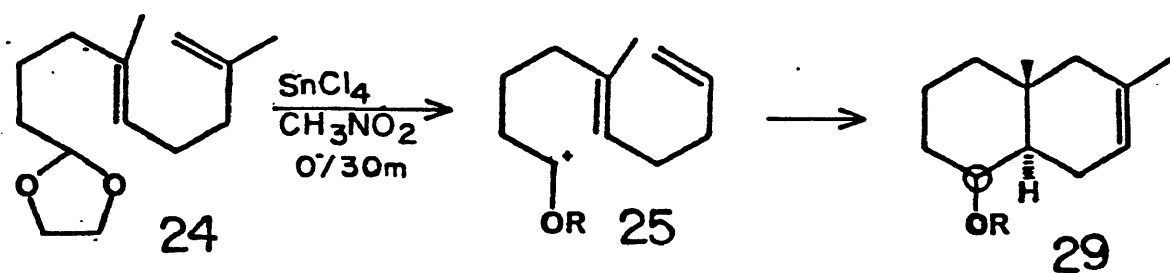
upon attack by a protic acid, they eliminate, leaving even primary carbocations behind (Scheme 15)^{12, 13}.

Unfortunately polyenic sulfonate esters only give small yields of fully cyclized products, thus making them synthetically useless as an initiator for cyclizations¹⁰.

Another approach to a carbocation is the acidic attack of an acetal as seen in Scheme 16. When cyclizing an external acetal (24), the product (29), usually contains a mixture of axial and equatorial configurations of the OR groups ($R = CH_2CH_2OH$) at the site of the circled

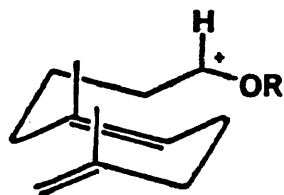


Scheme 15.

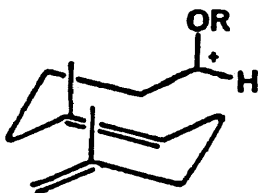


Scheme 16.

carbon. When the OR group takes on a pseudo-equatorial position:



compound (29) contains an equatorial OR group. When the OR group assumes the pseudo-axial position, which is more stable in polar solvents:



compound (29) contains an axial OR group^{7, 14}. The ratio of axial OR groups to equatorial OR groups is shown in Table 1 for a variety of solvents¹⁵.

Table 1. Solvent dependency of an alkoxy substituent position off a cyclohexane

solvent	(axial/equatorial) OR
pentane	1.9
CCl ₄	2.2
CS ₂	2.5
chloroform	2.6
benzene	2.8
nitroethane	6.9
nitrobenzene	7.2
nitromethane	8.2
ethyl acetate	9.1
acetonitrile	17

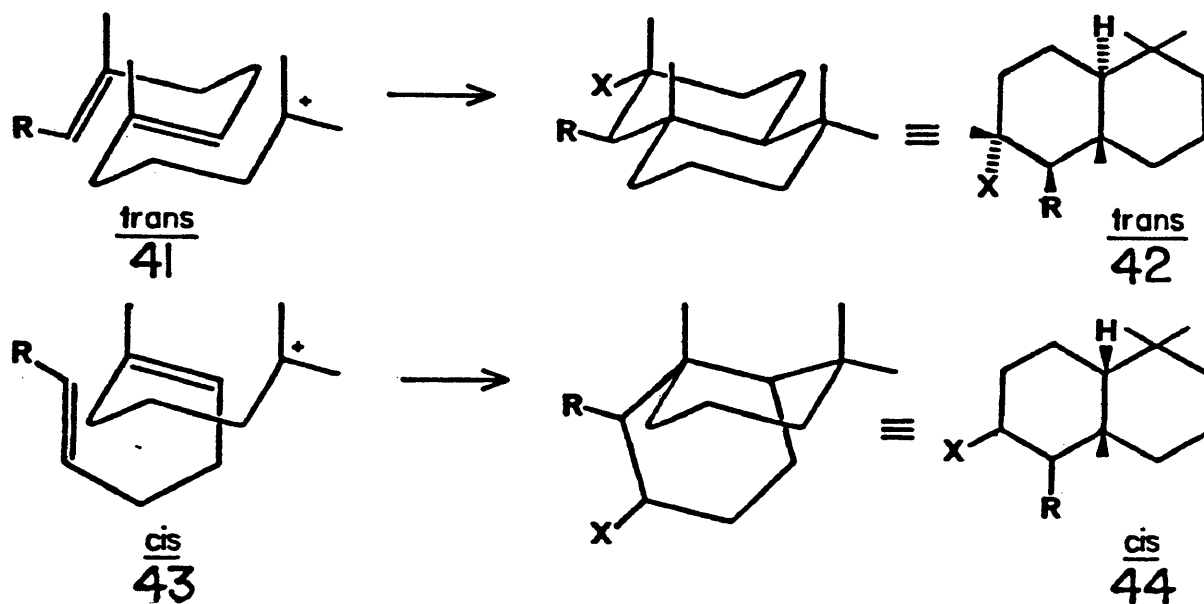
All three types of initiators require an acid to form a carbocation. The acid can be either a protic acid or a Lewis acid, although Lewis acids seem to be preferred for complete reactions¹⁶. Protic acids often allow indiscriminate protonation leading to a variety of products¹⁴ as well as deprotonation leading to

partially cyclized products¹⁰. Protic acids also promote addition and isomerization¹⁰.

In Johnson's cyclizations the electrophilic attack of a double bond occurs stereoselectively as suggested by the Stork-Eschenmoser hypothesis of trans-addition¹². In other words, trans-addition is the concerted addition across a double bond such that a cation is reacting with one carbon of the double bond from a certain direction while an anion is attacking the other carbon of the double bond from just the opposite direction. When a compound with a trans double bond such as (41), (Scheme 17), undergoes trans-addition, the trans-fused product (42) is formed; likewise a compound with a cis double bond, such as (43), forms the cis-fused product (44)¹².

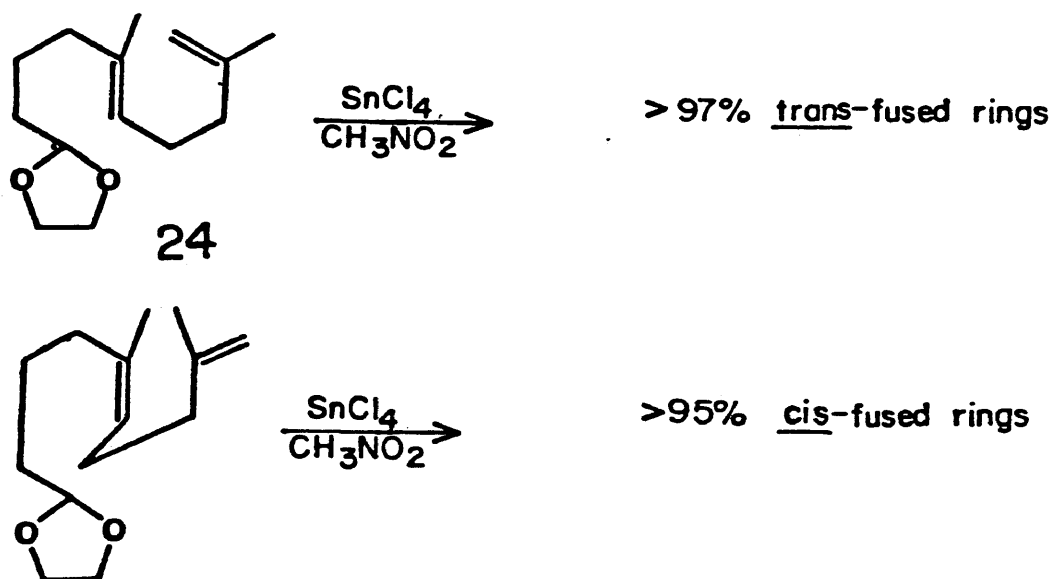
Because the trans and cis starting materials give different products, there can not be a common intermediate such as compound (45). Rather the structures of the products with respect to their starting materials and the similar type of product distribution between cis and trans reactions, suggest similar concerted reactions which allow each isomer to maintain its stereochemical integrity as seen in Scheme 18¹⁵. This is trans-addition¹².

In Johnson's polyene cyclizations, all the rings tend to close via trans-addition except the last ring in the system. If all the rings closed by trans-addition, the only product of the reaction in Scheme 19 would be (48), the product formed by an equatorial attack of the OH group.

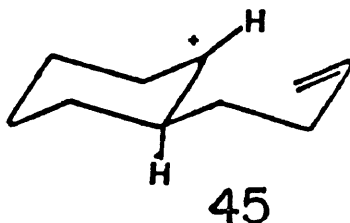


Scheme 17.

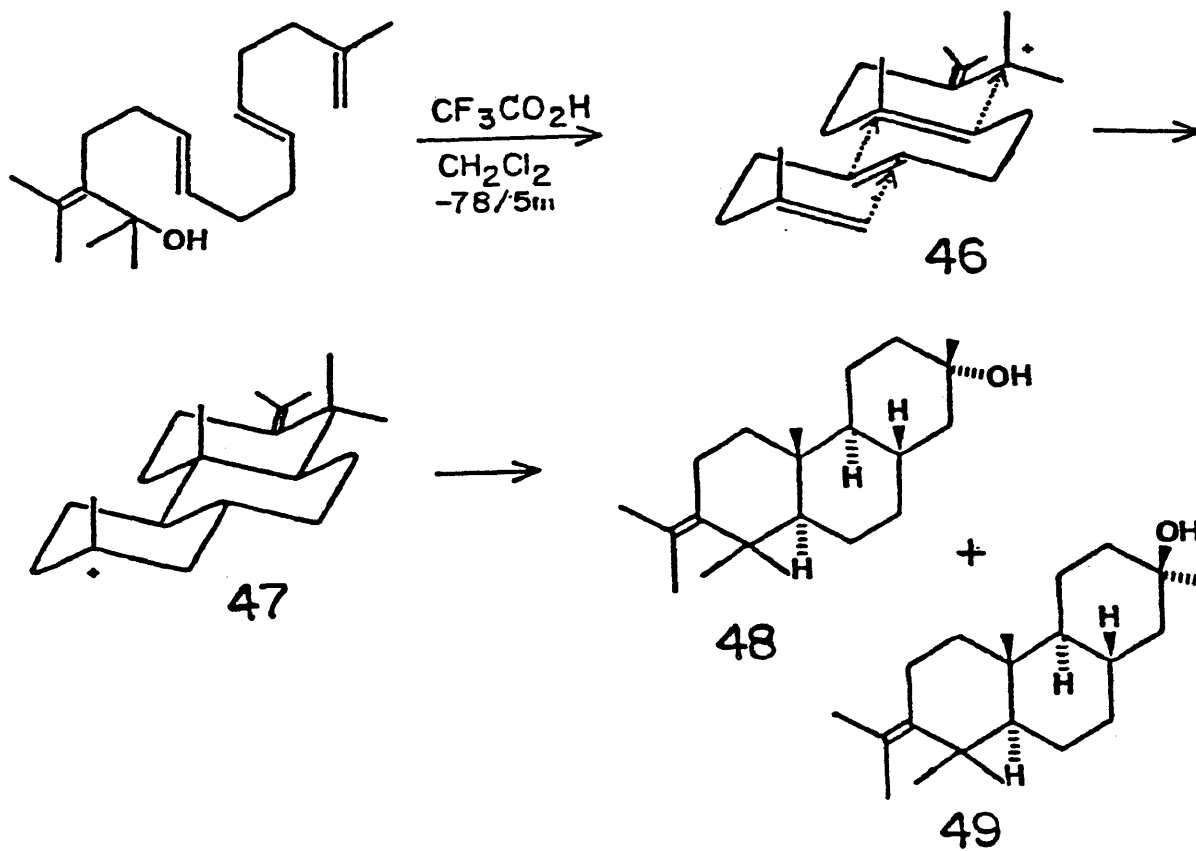
However product (49) is also found in the product mixture. Because of the close proximity of the double bonds to their attacking cations, there tends to be a "concerted" process of trans-addition (46) to give the tricyclic carbocation (47). However, once all the double bonds in a molecule have been attacked by a carbocation, the final cation must be attacked by an external nucleophile in order to terminate the reaction. Nucleophiles are maintained at low concentrations in order to prevent the premature termination of the cyclization, so this final cation (47) has time to obtain a planar confirmation which then can be attacked equatorially or axially by a nucleophile to give products (48) or (49) respectively¹⁷.



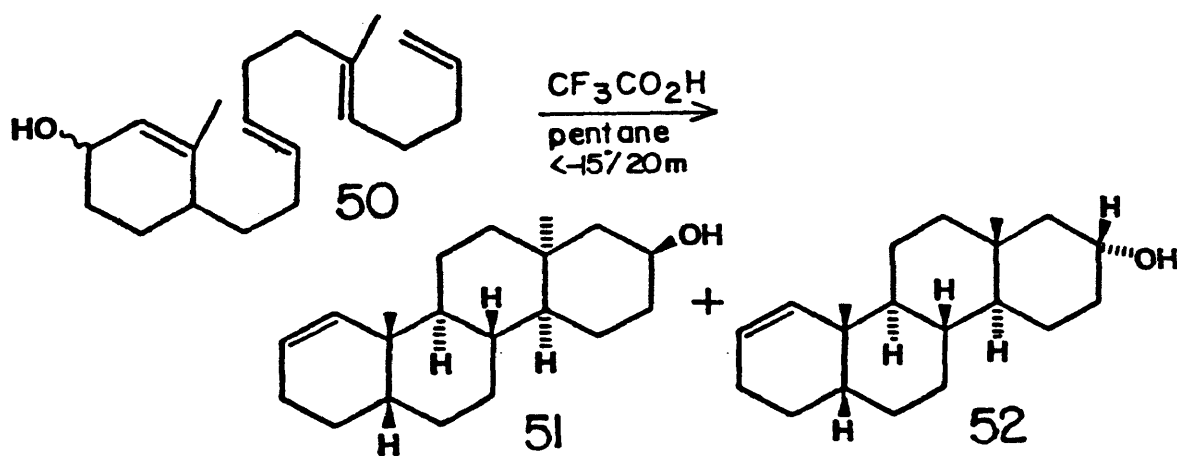
Scheme 18.



In some of Johnson's steroid syntheses, the trans-addition mechanism is not compatible with the final products. For example in Scheme 20 compounds with both cis and trans-fused C/D rings, compounds (51) and (52) respectively, are cyclized from polyene (50), but only compound (52) is expected¹⁸. In other reactions methyl substituents are not where the trans-addition mechanism predicts them to be^{9, 19, 20}. These difficulties are due to rearrangements in the steroid nuclei.

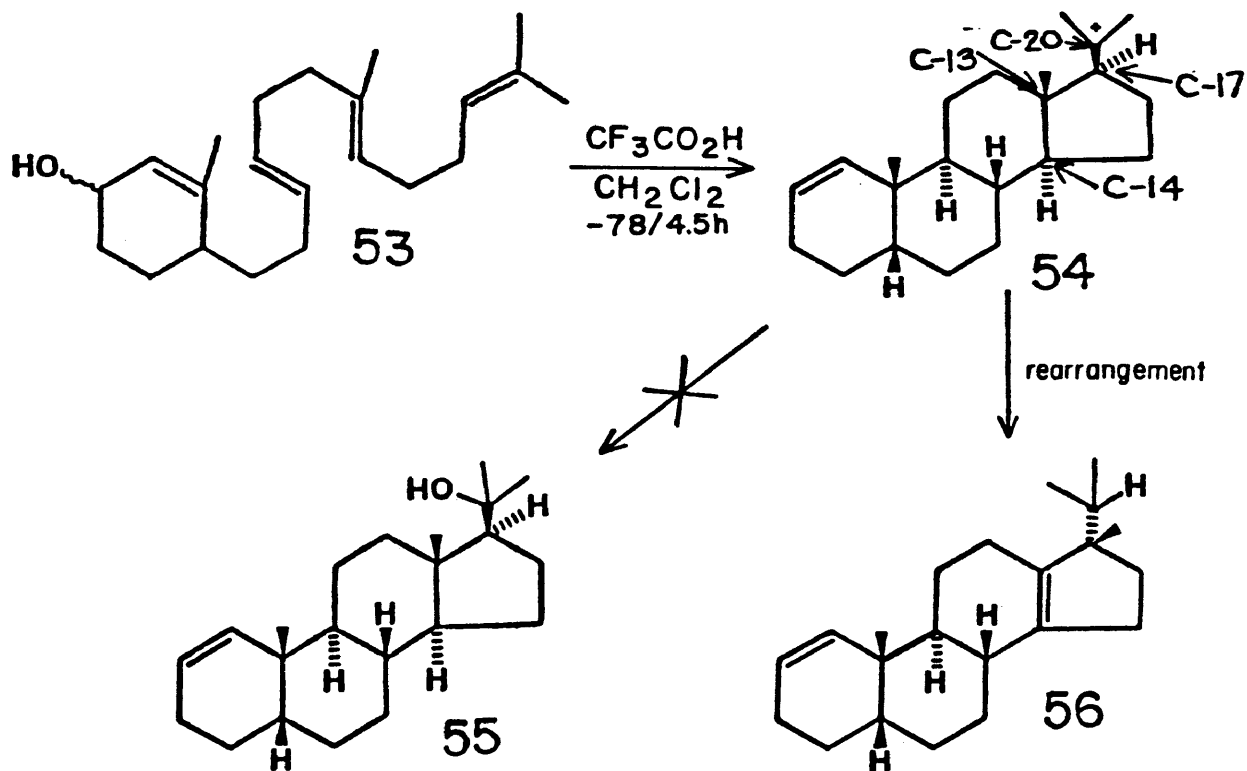


Scheme 19.



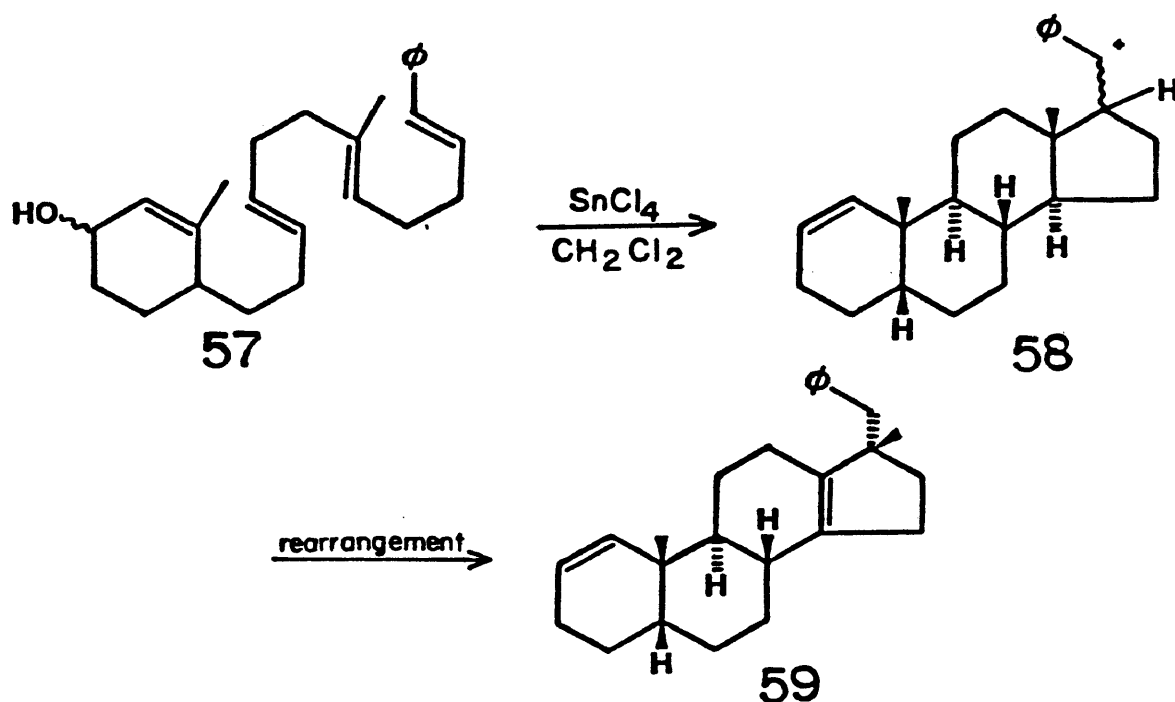
Scheme 20.

In Scheme 21 product (55) is expected for the ring cyclization of (53) with trifluoroacetic acid. However, after cyclization is complete and before nucleophilic attack of the hydroxyl anion, intermediate (54) rearranges. The hydride at C-17 shifts to C-20, the methyl at C-13 shifts to C-17, and there is a deprotonation at C-14 to give (56) in 36% yield. No other hydrocarbons are formed⁹.



Scheme 21.

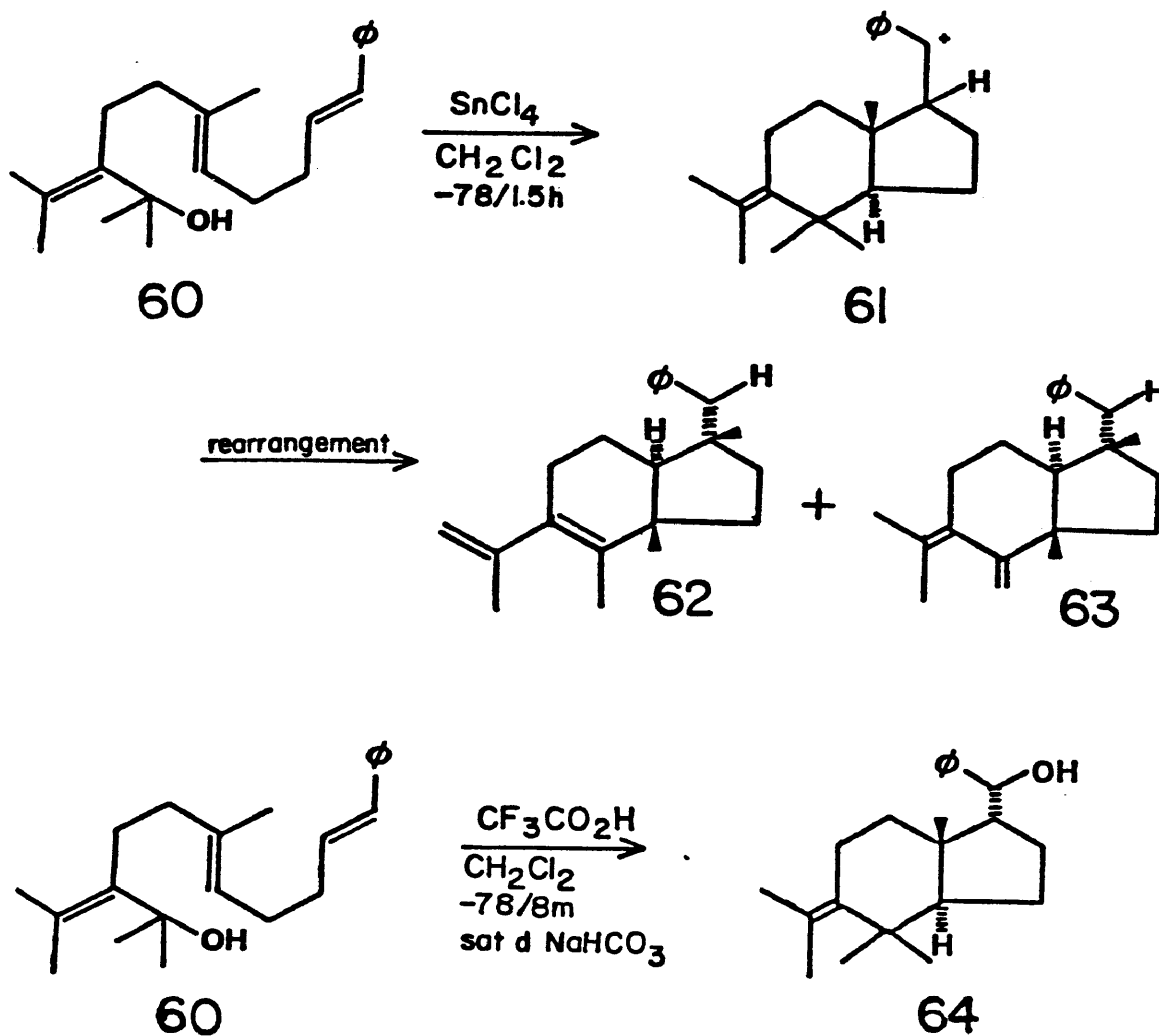
Polyenes terminating with styryl functional groups also tend to undergo rearrangements. In Scheme 22, as in the scheme above, after cyclization of the polyene (57) to give the tetracyclic carbocation (58), there is a hydride and a methyl shift followed by deprotonation to give product (59) in yields of up to 50%¹⁹.



Scheme 22.

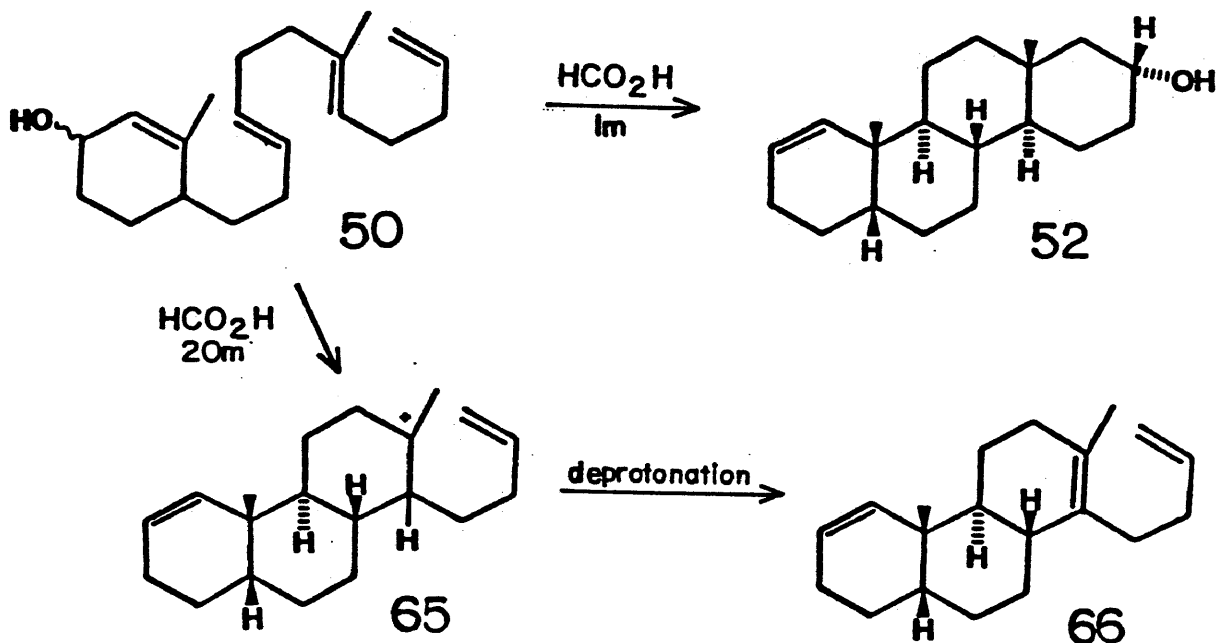
Rearrangements can also be more complex. In Scheme 23 cyclization of the polyene (**60**) occurs using a Lewis acid to give cation (**61**). This is followed by a hydride shift, a methyl shift, a hydride shift, a methyl shift, and finally deprotonation in one of two different directions to give the two unexpected hydrocarbons, (**62**) and (**63**), in 68% combined yield²⁰. Upon treatment with trifluoroacetic acid in methylene chloride, however, compound (**60**) cyclizes to form the expected alcohol (**64**) with no rearrangements²⁰.

The cis-fused C/D rings of compound (**51**) in Scheme 20 are also a product of rearrangements. In



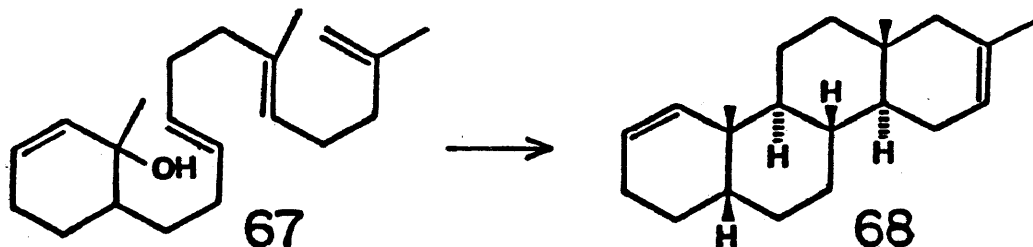
Scheme 23.

short-term reactions (1 min), compound (50) in Scheme 24, can react with formic acid to produce solely the trans-fused C/D ring product (52). In reactions of longer duration (20 min), however, rings A, B, and C are cyclized to form cation (65), and then a deprotonation occurs to form compound (66). This can then be attacked from either side to give both products (51) and (52)¹⁸.



Scheme 24.

Deprotonation, and thus termination of cyclization of compound (**50**) at the tricyclic stage (as in compound (**66**)), could result from inadequate nucleophilicity of the terminal vinyl group. A terminal isopropenyl group should be more nucleophilic and give one product with complete



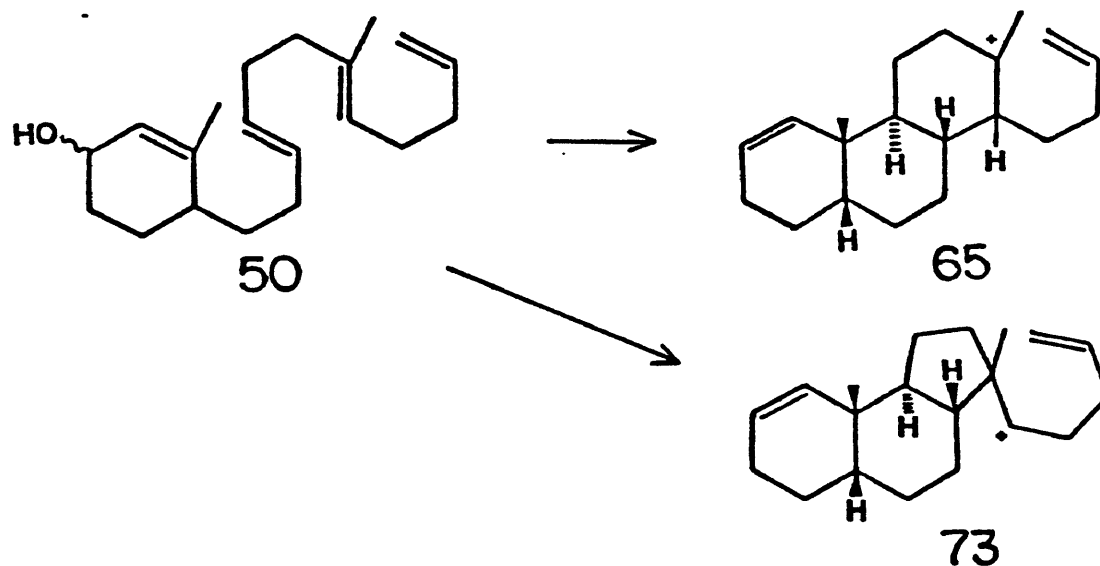
Scheme 25.

cyclization. This can be seen as (**67**) in Scheme 25 undergoes complete cyclization to form (**68**) in 60%

4) solvent^{8,25}, 5) temperature of the reaction⁸, and 6) acid^{8,11,23}.

In internal alkenes, molecules arrange themselves to form the very stable tertiary carbocation rather than the moderately stable secondary carbocation. Therefore in Scheme 27, compound (50) cyclizes so that the C ring is the six-membered ring product, (65), rather than the five-membered ring product, (73)¹⁸.

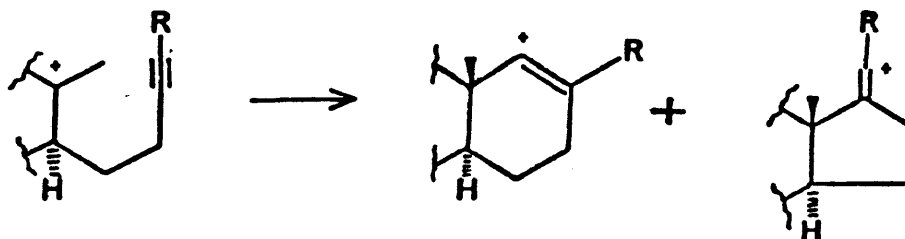
An internal alkyne upon cyclization forms a five or a six-membered ring with a vinyl cation (Scheme 28)²¹. Linear vinyl cations of five-membered rings are 77 kcal more stable than bent vinyl cations of six-membered rings^{13, 21}. Due to the greater stability of six-membered rings over five-membered rings, however, both



Scheme 27.

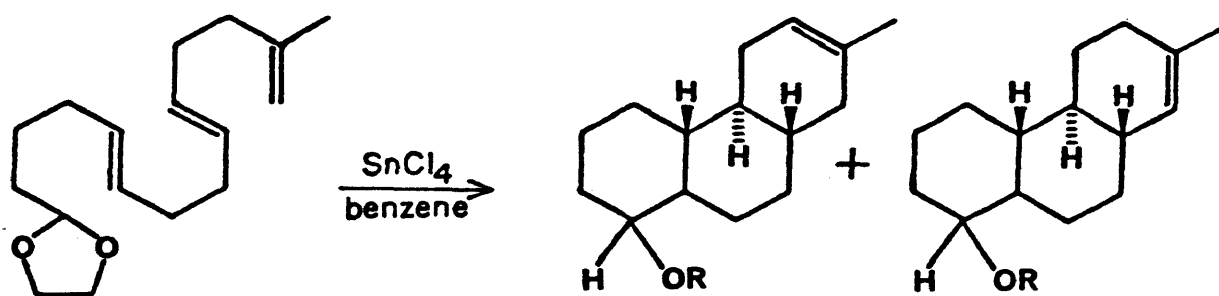
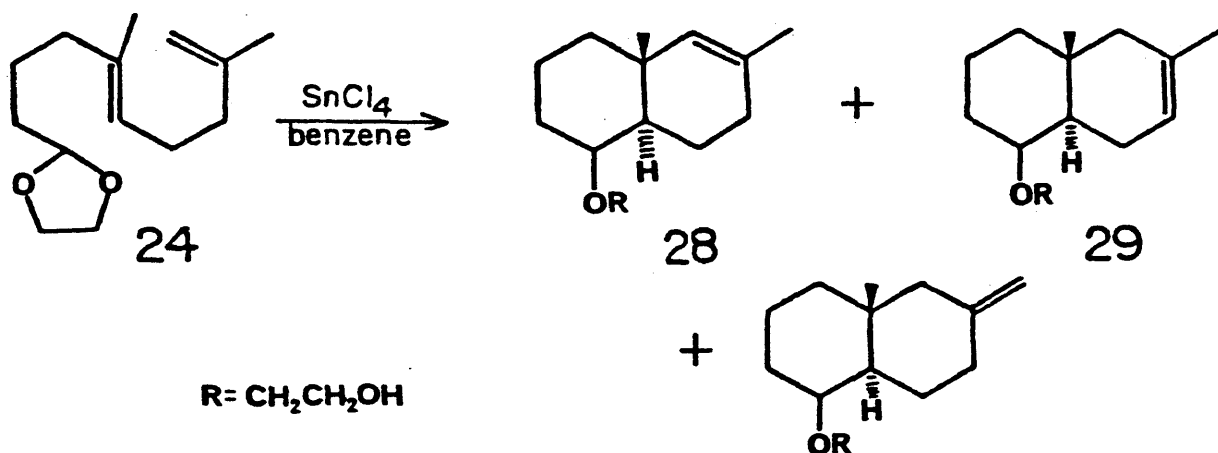
five and six-membered rings with vinyl cations are formed during cyclizations. The ring strain difference

approximately balances the vinyl cation strain difference to make both size rings reasonable and possible. Thus all of Johnson's cyclizations make both five and six-membered rings unless the R group, the chemical moiety after the last unsaturated bond, is a substituent which makes one of the two cations totally improbable²².

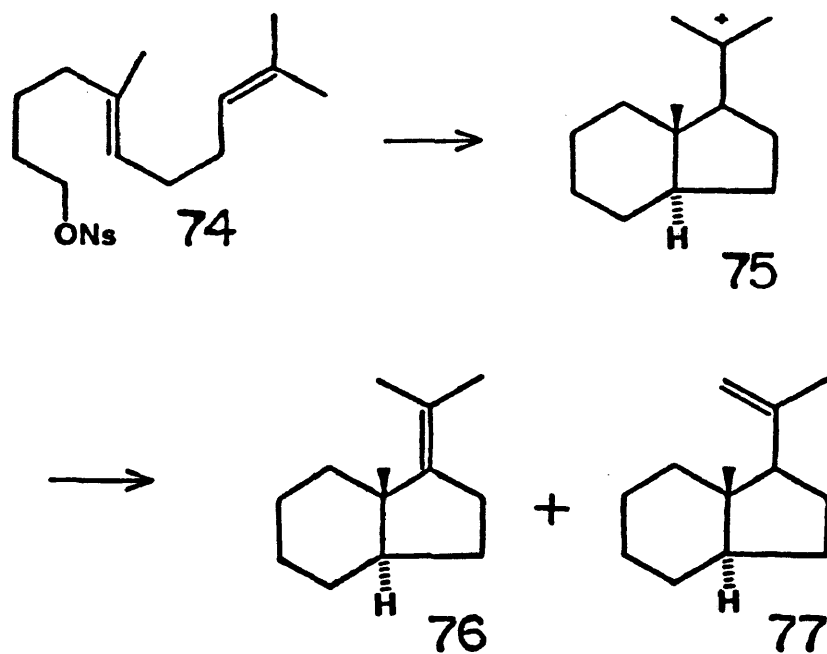


Scheme 28.

Substituents across an alkene often make either the five or the six-membered ring more probable due to the electron-releasing ability of the R group next to the final carbocation formed during cyclization. When the R group is a hydrogen, only six-membered rings are observed (Scheme 29)^{14, 15}. Most of the R groups encountered by Johnson, however, favor formation of five-membered rings over six-membered rings. Internal double bonds, especially those which have two R groups or R=phenyl, tend to form five-membered rings^{9, 10, 19}. When there are two R groups, as in compound (74) (Scheme 30), the five-membered ring intermediate (75) forms a tertiary cation which is more stable than the six-membered ring's secondary cation (78). Therefore, the five-membered ring products (76) and (77) are

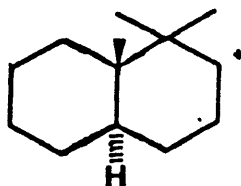


Scheme 29.



Scheme 30.

formed⁹. When R is a phenyl as in compound (57) (Scheme 31), the cation of the five-membered ring (58)

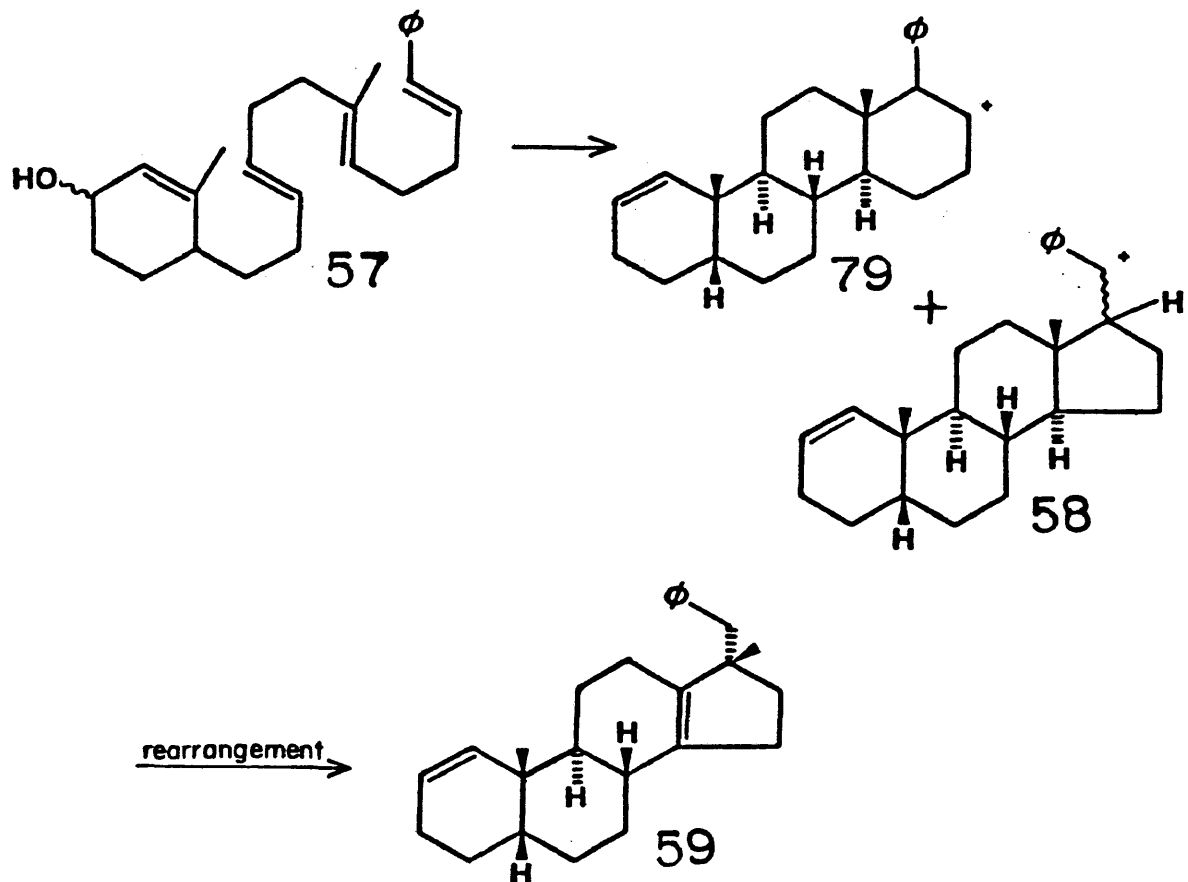


78

forms a resonance-stabilized benzylic cation which is more stable than the six-membered ring homobenzylic cation found in compound (79)^{10,19}. Compound (58) can then rearrange to form compound (59). Substituents off the phenyl ring such as p-methyl can further stabilize the cation as well as make the double bond more nucleophilic and therefore more susceptible to electrophilic attack²⁰.

When (57) is treated with trifluoroacetic acid in methylene chloride at -50° to -25°C, compound (59) is produced in 70% yield. When the aromatic ring contains a p-methyl, the same reaction conditions yield 75% p-methyl (59). When the phenyl ring is an α -naphthyl, the yield of tetracyclic product increases to 81%¹⁰.

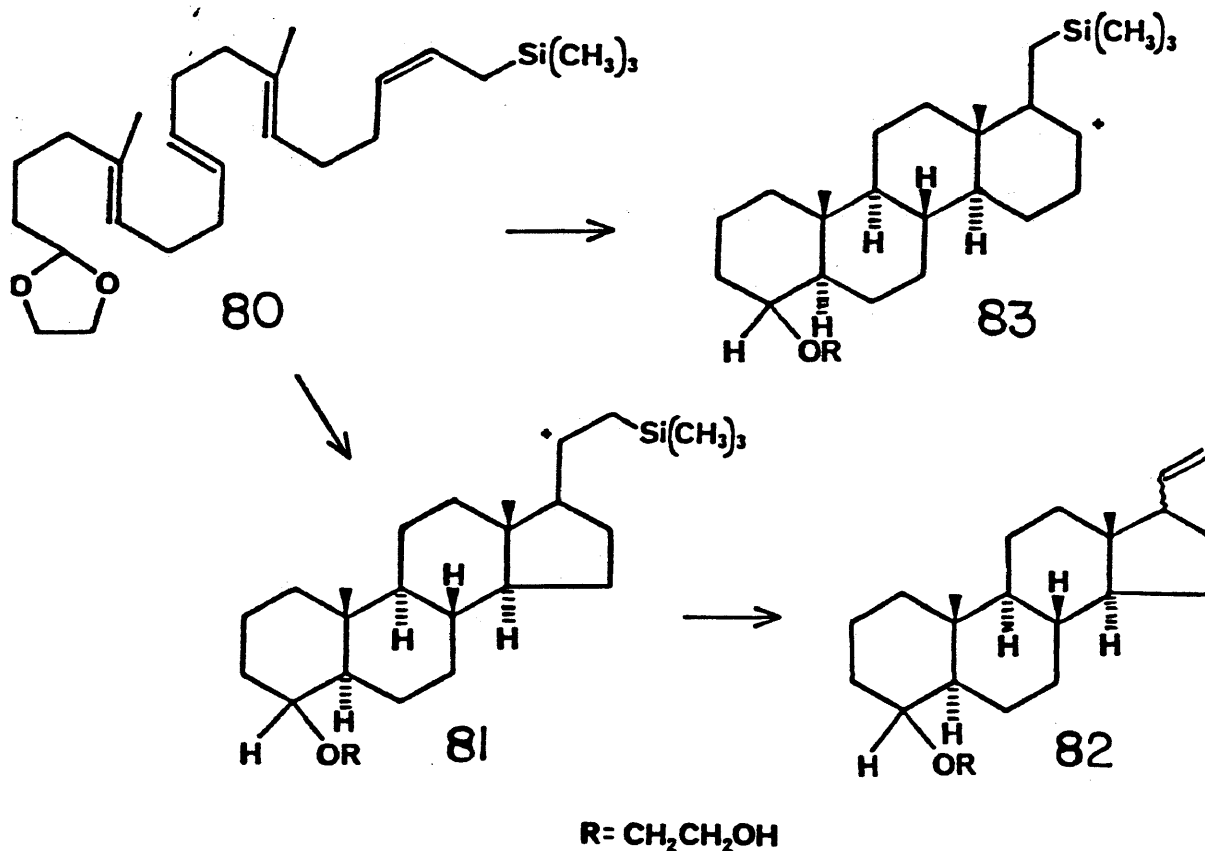
Internal double bonds with a trimethylsilane R group also tend to form five-membered terminal rings. Upon cyclization of (80), (Scheme 32), the five-membered ring product, (81), can eliminate the trimethylsilane functional group to form the double bond in compound (82), whereas the six-membered ring product (83) cannot¹⁶. Therefore



Scheme 31.

the five-membered D-ring of (82) is formed preferentially over the six-membered D-ring.

Alkyl and aryl groups at the terminal end of an alkyne moiety, also affect the five to six-membered ring ratio. When R is a methyl group as in (84) in Scheme 33, mostly five-membered rings products such as (85) are formed²³. When R is a phenyl as in (86) in Scheme 34, the phenyl group stabilizes the five-membered ring carbocation in (88) to the exclusion of six-membered ring

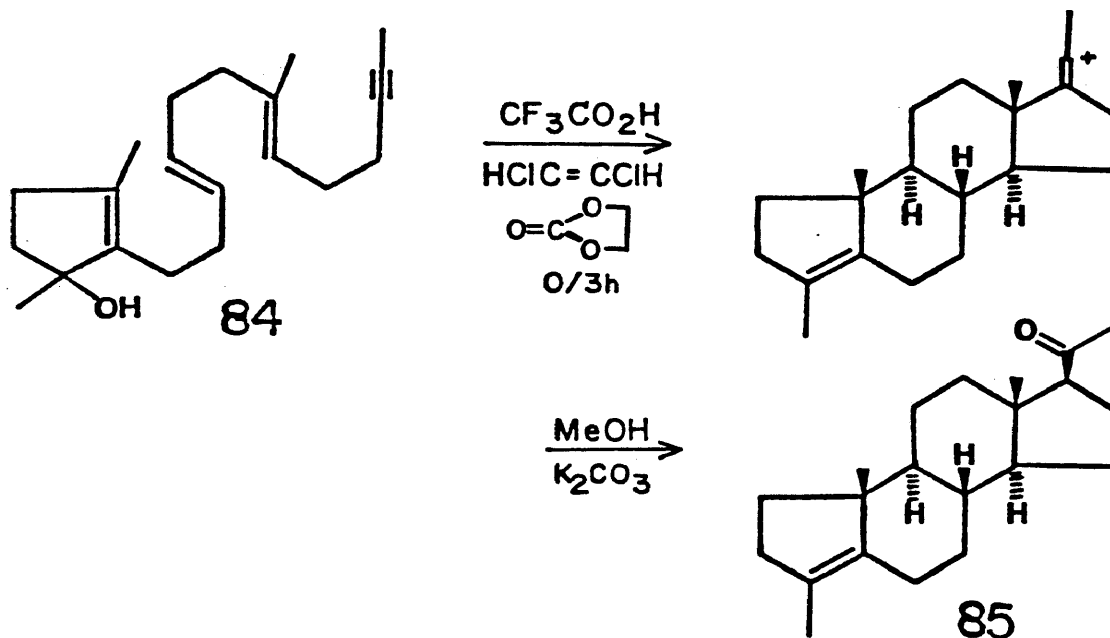


Scheme 32.

carbocations such as found in (87). The six-membered ring carbocation cannot be stabilized by the phenyl ring²⁴.

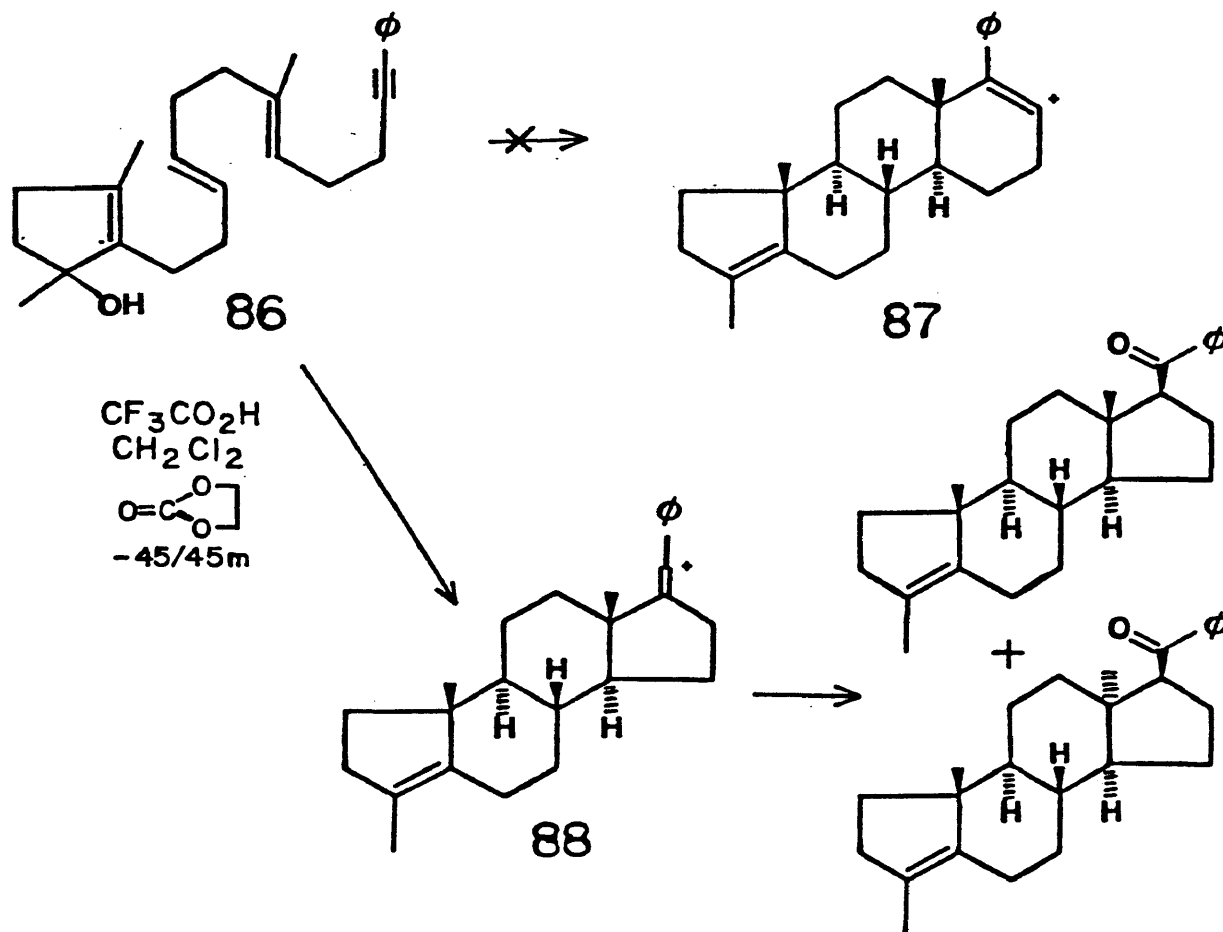
Other cases where five-membered rings are formed preferentially over six-membered rings are found in Scheme 35¹⁰.

According to Johnson, upon cyclization of an alkyne, the five-membered ring cationic intermediate (89) (Scheme 36) is formed first. In reactions without good nucleophiles, this intermediate can then rearrange via a Wagner-Meerwein rearrangement to form the six-membered ring cationic intermediate (90)^{8, 10, 25}. Six-membered



Scheme 33.

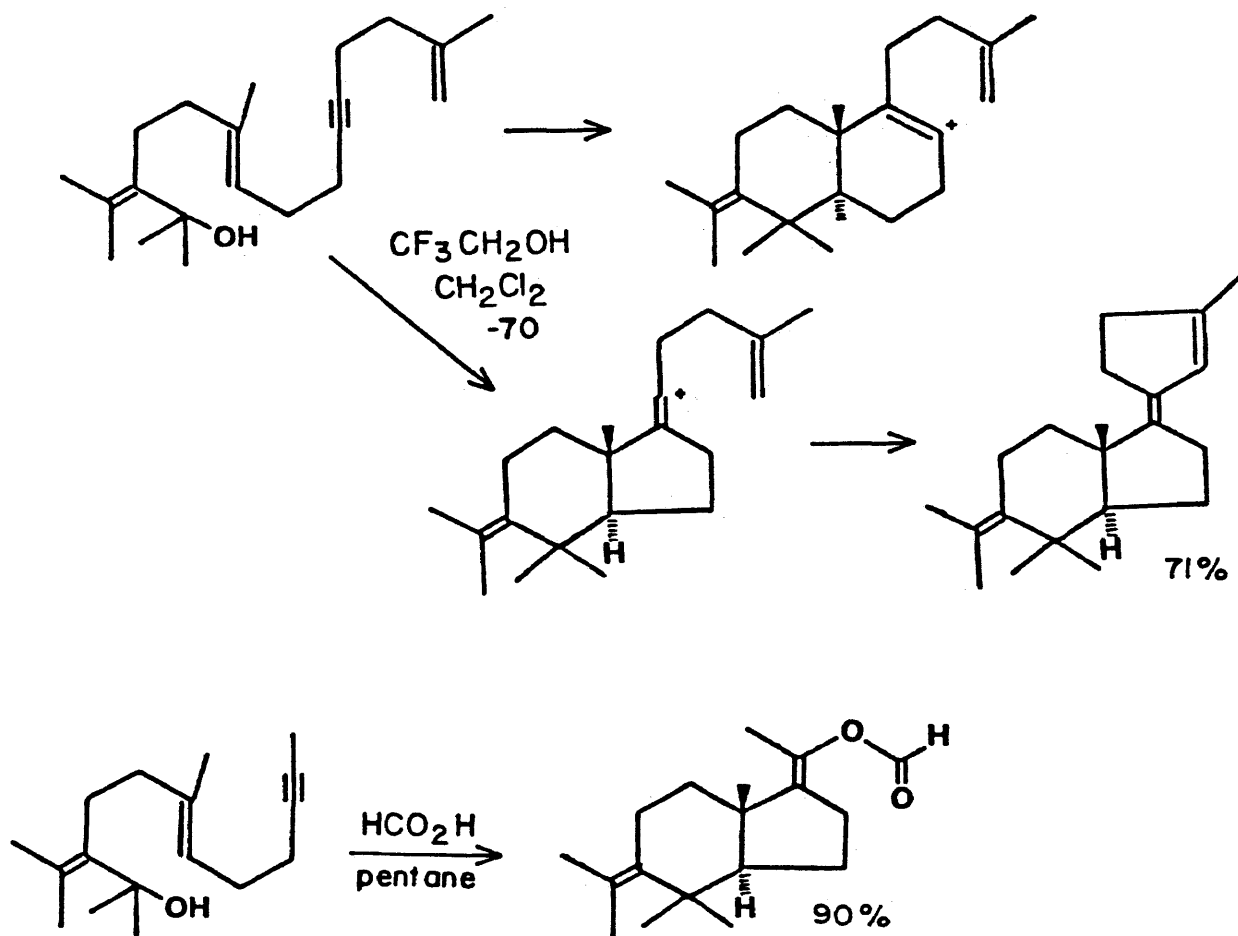
ring cations such as in (91) are not formed during rearrangement because it would require a 1,2 shift of a primary group¹⁰. Intermediates (89) and (90) then equilibrate until a nucleophilic attack terminates the reaction^{8, 25}. More polar solvents tend to favor a shift to the right in equilibrium; whereas in less polar solvents, intermediate (89) tends to be captured almost immediately by a nucleophile. The effects of two different solvents on the formation of five or six-membered rings can be seen in Scheme 37⁸. When the solvent is methylene chloride, the five to six-membered ring ratio is 1:10. When the solvent is 7.5:1 pentane-1,2-dichloroethane, which is less polar than methylene chloride, the ion pair formed between the five-membered ring cation and the acid becomes



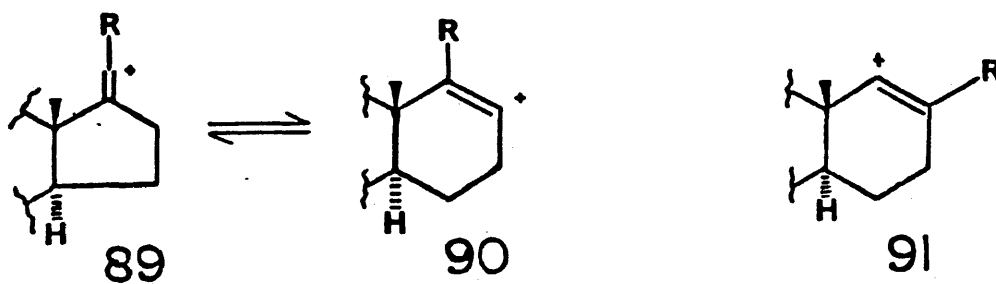
Scheme 34.

tighter, and the cation is more likely to collapse forming (92) rather than to rearrange and extract a chloride from the solvent to form (34)⁸. The ratio of five to six-membered rings for this solvent is 9:1.

The temperature of the reaction also affects the ratio of five to six-membered rings. The cyclization of (93), (Scheme 38), in methylene chloride at -30°C gives a five to six-membered ring product ratio of 51:37. When the reaction temperature is raised to 40°C , the ratio of (94) to (95) is 73:10. When the same reaction is performed in



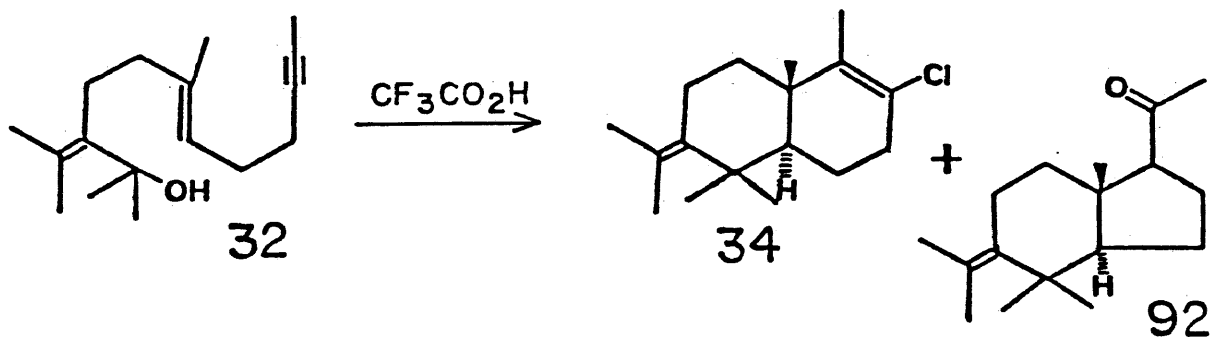
Scheme 35.



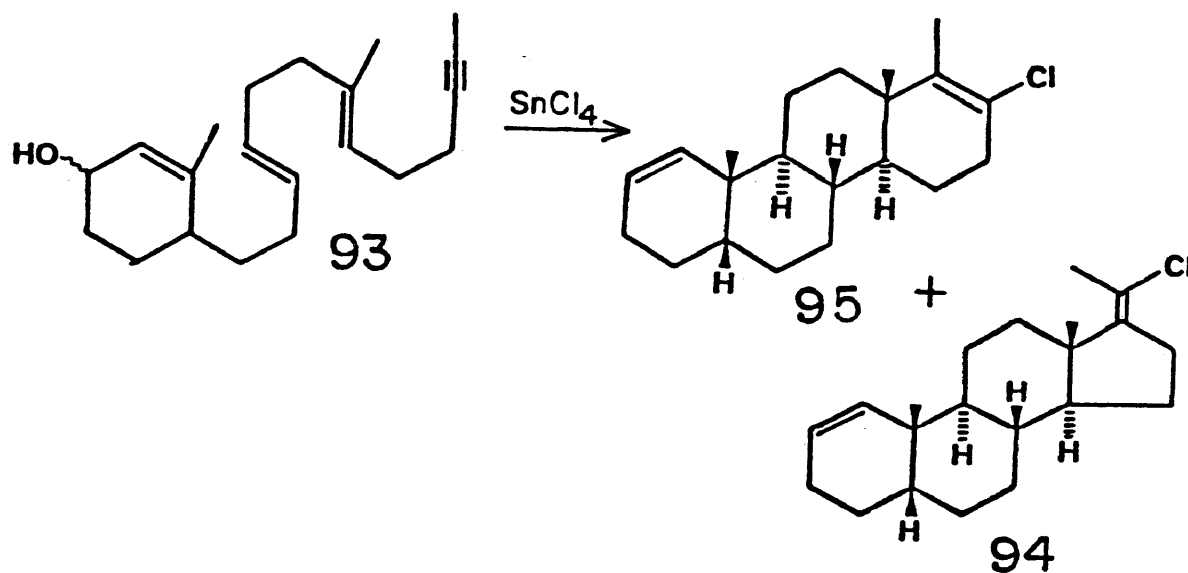
Scheme 36.

1,1-dichloroethane at -78°C , the ratio is 64:21. Raising the reaction temperature in 1,1-dichloroethane to 22°C

increases the five to six-membered ring ratio to $75:10^8$.

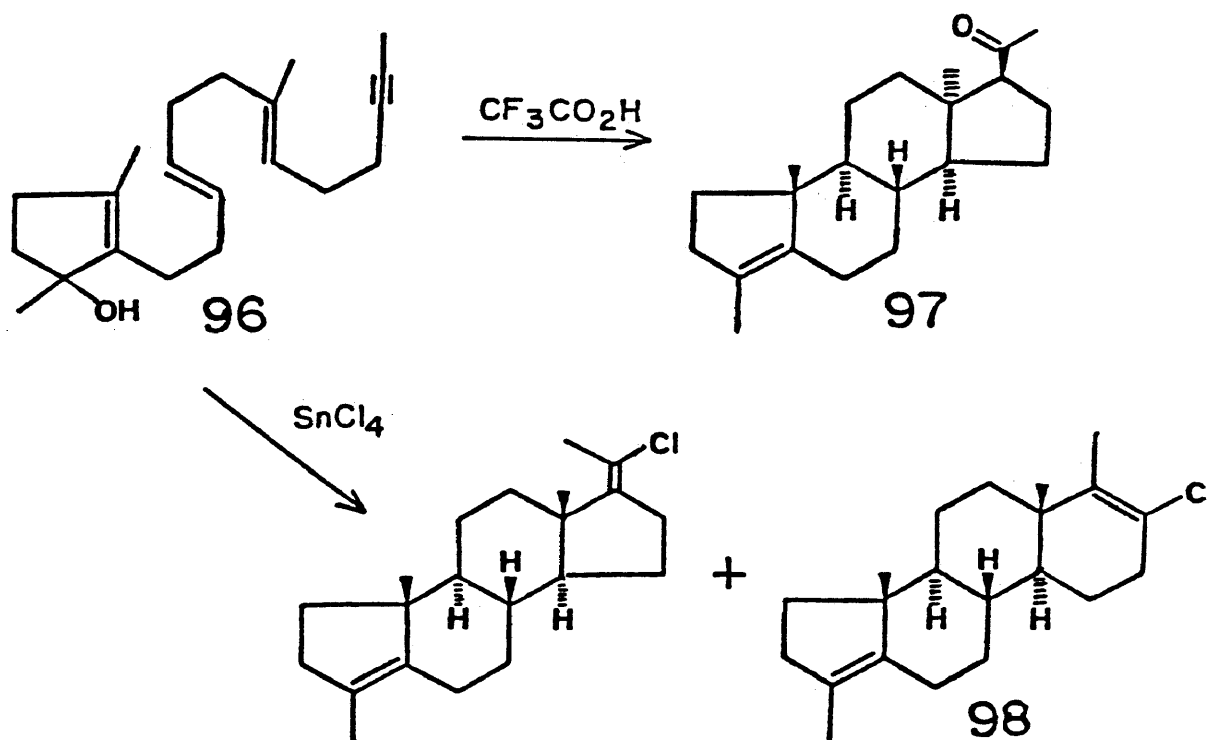


Scheme 37.



Scheme 38.

When compound (96) in Scheme 39 is cyclized by trifluoroacetic acid, only compound (97) is formed. There are no six-membered D-ring products^{23, 26}. When (96) is cyclized with stannic chloride, however, up to 14% of the product mixture has a six-membered D ring as in compound (98)^{8, 23}.

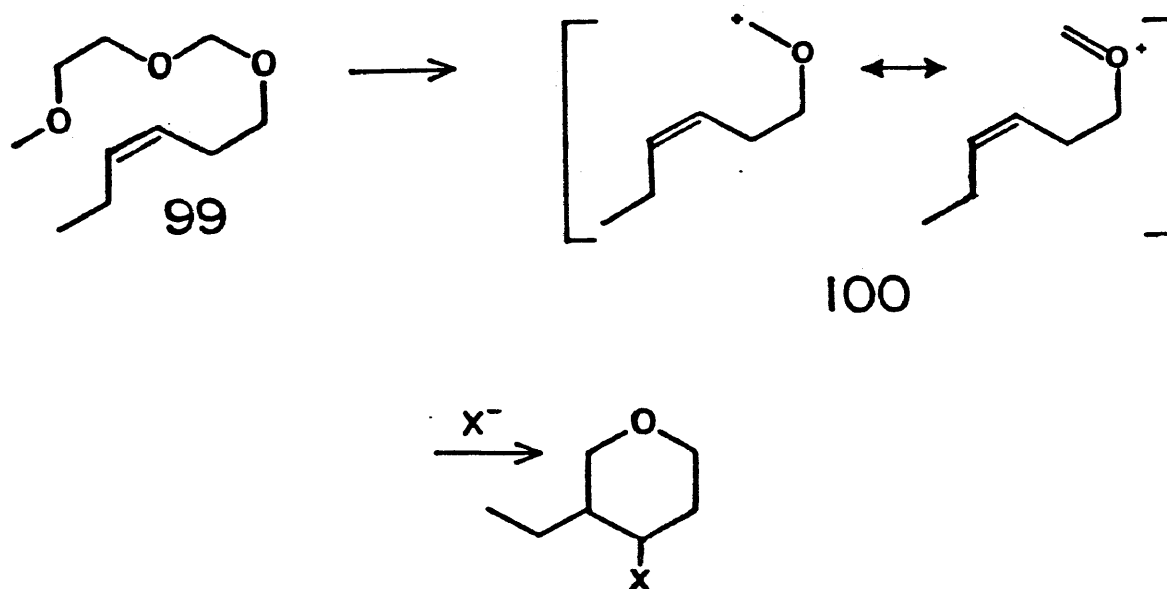


Scheme 39.

As stated previously we are interested in the formation of tetrahydropyrans and tetrahydrofurans. Johnson's work concerning electrophilic cyclizations of cyclohexanes and cyclopentanes is potentially useful for our similar electrophilic cyclization to form tetrahydropyrans and tetrahydrofurans. If Johnson's system and conclusions hold true in our system, as well they might, then several conclusions may be suggested for our system of cyclizations.

In Johnson's cyclizations he uses three types of initiators: an allylic alcohol, a good leaving group, and an acetal^{8 - 15}. In our cyclizations we use an acetal. The acetals are easy to make from an alcohol and an ether, such as ethyl vinyl ether, or from another acetal,

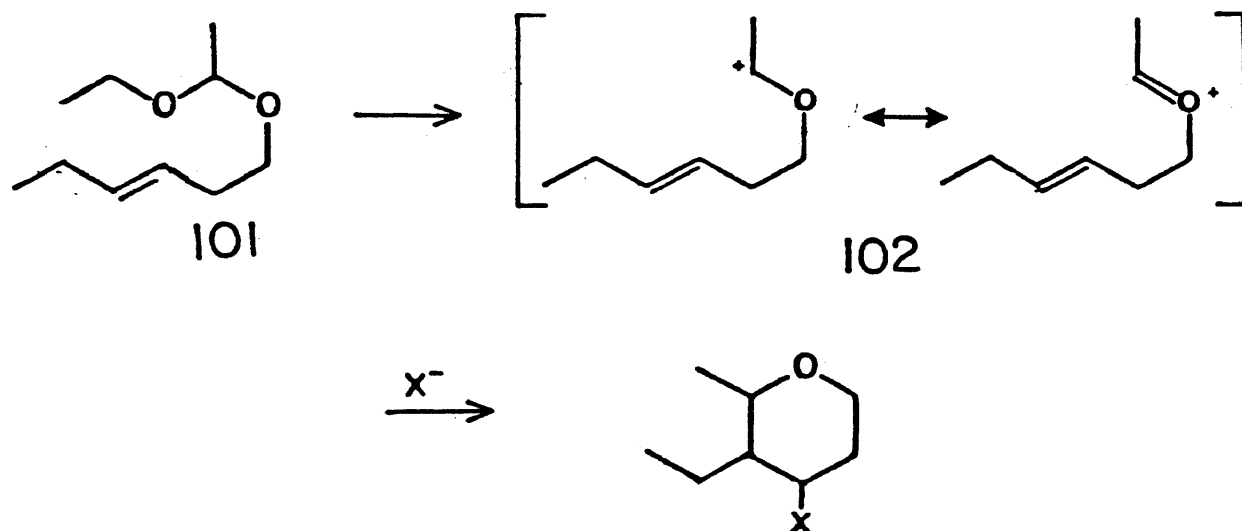
such as methoxyethoxymethyl chloride. By using an internal acetal, rather than an external acetal as Johnson did (see Scheme 29 for an example), we can easily form an oxocarbenium ion which can attack a double bond to form a tetrahydropyran as seen in Scheme 9.



Scheme 40.

By using an internal acetal such as (99) in Scheme 40, we do not expect a mixture of axial and equatorial configurations at the site of the first carbocation as is seen in Scheme 16, because the OR group will be eliminated after protonation leaving the primary oxocarbenium ion (100) behind. When using an internal acetal such as (101) in Scheme 41, the OR group is lost to form the secondary oxocarbenium ion (102). A mixture of axial and equatorial positions for the methyl group is expected after

cyclization for the same reason a mixture of configurations of OR groups is expected in Scheme 16. The carbocation formed by the loss of the OR substituent in each case is stabilized by the adjacent remaining oxygen.



Scheme 41.

Johnson's cyclizations can form both cyclohexanes and cyclopentanes depending on the characteristics of the starting material and the reaction conditions. Johnson's systems cyclize and equilibrate to form the most stable carbocation before termination by a nucleophilic attack^{8, 25}. Thus a cyclopentane with a saturated tertiary carbocation is more stable than a cyclohexane with a saturated secondary carbocation. The major product is the cyclopentane. When Johnson's systems cyclize to form a vinyl cation, then there are more cyclopentanes with linear vinyl cations in the product mixture than cyclohexanes with

bent vinyl cations because linear vinyl cations are more stable than bent vinyl cations^{13, 21}. In this case, though, both cyclohexanes and cyclopentanes are found in the product mixture because of the greater stability of a cyclohexane ring over a cyclopentane ring. When Johnson's systems can cyclize so as to form a carbocation next to an electron-releasing group, they will, thereby stabilizing the carbocations²². We expect that these characteristics in our starting materials will help us predict which product, tetrahydropyran or tetrahydrofuran, should be formed.

As per the Stork-Eschenmoser hypothesis¹², all of Johnson's cyclizations occur such that addition across the double bond occurs in a trans fashion except addition across the final double bond¹⁷. The final double bond is attacked by the carbocation, and then the newly-formed carbocation is given time to obtain a planar conformation before it is attacked by a nucleophile from either an axial or an equatorial position (as in Scheme 19). If this same situation of non-stereoselective addition across the final double bond occurs in our system which only contains one double bond; then we would not expect our system to undergo trans-addition, and we would not expect stereoselectivity in our final product.

The foregoing conclusions are those of Johnson's most applicable to our electrophilic cyclizations to form tetrahydropyrans and tetrahydrofurans. Though all of these

conclusions may be valid for our cyclizations, it is also possible that some or all are not. If they all are valid, then the electrophilic cyclization via cationic attack of a double bond, would produce a mixture of axial and equatorial chloride substituents rather than the hoped for stereoselective tetrahydropyran. Our results and how they relate to Johnson's conclusions are discussed later in this paper.

EXPIREMENTAL

I. REAGENTS

cis-3-Hexen-1-ol was obtained from Chemical Samples Company. trans-3-Hexen-1-ol and 4-phenyl-3-butyn-1-ol were obtained from Wiley Organics. 3-Pentyn-1-ol was obtained from Farchan Labs. These alcohols were kept refrigerated and used without further purification.

The methoxyethoxymethyl chloride used in preparing the MEM acetals and the ethyl vinyl ether used in preparing the ethyl vinyl ether acetals were obtained from Aldrich (19,354-2 and E5,125-2, respectively). These both were kept refrigerated and were used without further purification. Phosphoric acid (85%) (Fisher, A-242) and N,N-diisopropylethylamine (Aldrich, D12,580-6) also were used without further purification in the various acetal preparations. Sodium bicarbonate was used to make the ethyl vinyl ether acetal basic before distillation.

Titanium tetrabromide (ALFA Products, 101582), titanium tetrachloride (Aldrich, 20,856-6), and stannous chloride (Aldrich 20,893-0) were used to cyclize the acetals. They were kept under nitrogen.

The methanol (Fisher, A-412) and the hydrochloric acid (J. T. Baker Chemical Company, 9535-3) were used to quench the cyclizations reactions. Magnesium sulfate from Fisher (M-65) and Aldrich (24,697-2) was used as a drying agent.

1-Heptanol (Eastman Organic Chemicals), 1-octanol (Fisher 702423), and 1-decanol (Eastman Organic Chemicals) were used without further purification as internal standards in the GC analysis of the cyclization reactions.

II. SOLVENTS

Laboratory grade methylene chloride (Fisher D-37), distilled over phosphorus pentoxide (Aldrich 21,470-1) and stored over Linde 4-A molecular sieves, was used as the solvent in all the acetal preparations and in most of the cyclization reactions. Tetrachloroethylene was used as the solvent for some of the cyclizations. Diethyl ether (Fisher, laboratory grade) and 10% acetic acid (Fisher) were used for extractions. Hexanes (Fisher, H-292) were used without further purification.

III. CHARACTERIZATION TECHNIQUES

Gas chromatographic analyses were conducted on Hewlett-Packard models 5710A and 5790A with flame ionization detectors. These chromatographs were interfaced with Hewlett-Packard integrators 3380S and 3390A, respectively.

All analyses were conducted on a 10' x 1/8" 10% Carbowax 20M packed column or a 30 meter methylsilicone capillary column.

Product yields were determined by glc analysis using the internal standard technique. The response factor for 4-bromo-3-ethyltetrahydropyran versus 1-heptanol was estimated to be 1.0. Other response factors were estimated considering previous work on similar compounds and standards. Quantitative glc analyses were conducted on the Hewlett-Packard 5710A chromatograph with the 10% Carbowax 20M column.

Preparative gas-liquid chromatography was conducted on a Hewlett-Packard model 5750 equipped with a thermal conductivity detector. Preparative separations were conducted on 10' x 1/4" 20% SP-1000 and SP-2300 columns.

^1H and ^{13}C nuclear magnetic resonance spectra were obtained by using a Varian FT-80A spectrometer and a Nicolet NTC 360 spectrometer.

IV. PREPARATION OF MATERIALS.

cis-6-(2-methoxyethoxy)methoxy-3-hexene. To 200 ml methylene chloride in a three-neck 500 ml round-bottom flask equipped with a nitrogen inlet, a rubber septum, and a dropping-funnel was added 18.7 g (150 mmol) methoxyethoxy-methyl chloride (MEM Cl). While this was stirred and cooled to 0°C, 10.0 g (100 mmol) cis-3-hexen-1-ol was added via syringe and 19.4 g (150 mmol) N,N-diisopropylethylamine

was added slowly via dropping-funnel. The contents were continuously stirred and allowed to come to room temperature over a 24 h period. Hexanes (100 ml) were added to the solution, and the solution was stripped down on a rotovap. Another 120 ml hexanes were added, and the solution was filtered to remove the salt. The filtrate was then extracted with two 40 ml portions of 10% acetic acid. The organic layer was dried with MgSO_4 , filtered, and stripped down on the rotovap. The organic layer was distilled at 85°C (head), 96°C (oil bath), and 0.2 torr. The product was analyzed by capillary gas chromatography.

trans-6-(2-methoxyethoxy)methoxy-3-hexene. This reaction was conducted in a similar fashion to the preparation of cis-6-(2-methoxyethoxy)methoxy-3-hexene using 14.448 g (116.0 mmol) MEM Cl, 10.990 g (109.8 mmol) trans-3-hexen-1-ol, and 20.7394 g (160.4 mmol) N,N-diisopropylethylamine. The organic layer was distilled at 87°C (head), 90°C (pot), and 0.3 torr.

5-(2-methoxyethoxy)methoxy-2-pentyne. This reaction was conducted in a similar fashion to the preparation of cis-6-(2-methoxyethoxy)methoxy-3-hexene using 17.324 g (139.0 mmol) MEM Cl, 8.301 g (98.69 mmol) 3-pentyn-1-ol, and 19.002 g (147.0 mmol) N,N-diisopropylethylamine. The organic layer was distilled at 125°C (head) and 56 torr.

1-phenyl-4-(2-methoxyethoxy)methoxy-1-butyne. This reaction was conducted in a similar fashion to the preparation of cis-6-(2-methoxyethoxy)methoxy-3-hexene using

19.73 g (158.3 mmol) MEM Cl, 11.657 g (79.742 mmol) 4-phenyl-3-butyn-1-ol, and 19.496 g (150.8 mmol) *N,N*-diisopropylethylamine. The organic layer was distilled at 125-135°C (head) and 250 micrometers.

cis-6-(1-ethoxy)ethoxy-3-hexene. To 50 ml ethyl vinyl ether in a three-neck 250 ml round-bottom flask equipped with a nitrogen inlet, a rubber septum, a reflux tube, and a stirring rod was added 10.256 g (102.5 mmol) cis-3-hexen-1-ol and 3 drops of phosphoric acid. The solution was stirred 60 h with heat and gentle refluxing, after which the solution was made basic with sodium bicarbonate and then distilled. A fraction was collected at 80°C (pot), 79°C (head), and 10-15 torr. The fraction was analyzed by capillary gas chromatography.

trans-6-(1-ethoxy)ethoxy-3-hexene. This reaction was conducted in a similar fashion to the preparation of cis-6-(1-ethoxy)ethoxy-3-hexene using 9.8433 g (98.33 mmol) trans-3-hexen-1-ol. The distillate was collected at 111°C (pot), 112°C (head), and 45 torr.

5-(1-ethoxy)ethoxy-2-pentyne. This reaction was conducted in a similar fashion to the preparation of cis-6-(1-ethoxy)ethoxy-3-hexene using 9.687 g (115.2 mmol) 3-pentyn-1-ol.

1-phenyl-4-(1-ethoxy)ethoxy-1-butyne. This reaction was conducted in a similar fashion to the preparation of cis-6-(1-ethoxy)ethoxy-3-hexene using 9.5 g

4-phenyl-3-butyn-1-ol. Note: this reaction did not form an acetal at all but rather it polymerized.

V. CYCLIZATION STUDIES.

cis-4-Bromo-3-ethyltetrahydropyran. Titanium tetrabromide (4.906 g, 13.35 mmol) was added to 150 ml methylene chloride with stirring in a three-neck 250 ml round-bottom flask equipped with a nitrogen inlet, a rubber septum, and a ground glass stopper. The flask and contents were cooled to -45°C in chlorobenzene bath, and 1.715 g (9.108 mmol) cis-6-(2-methoxyethoxy)methoxy-3-hexene was added via syringe. The contents of the flask were allowed to react for 30 min, and then the reaction was quenched with 5 ml methanol added via syringe and 45 ml 3N HCl/sat'd NaCl. The reaction mixture was extracted with four 50 ml portions of diethyl ether, and the organic layer was dried with MgSO_4 and filtered. A yield analysis on the product mixture using 0.652 g (5.61 mmol) 1-heptanol as a standard indicated 74% cis-4-bromo-3-ethyltetrahydropyran.

cis-4-Chloro-3-ethyltetrahydropyran. This reaction was conducted in a similar fashion as the cyclization to form cis-4-bromo-3-ethyltetrahydropyran using 20 mmol titanium tetrachloride and 1.431 g (7.600 mmol) cis-6-(2-methoxyethoxy)methoxy-3-hexene. The reaction was conducted for 1 h at -95°C in a toluene bath. A yield analysis on the product mixture using 0.797 g (6.859 mmol)

1-heptanol as a standard indicated 81.0% cis-4-chloro-3-ethyltetrahydropyran.

trans-4-Bromo-3-ethyltetrahydropyran. This reaction was conducted in a similar fashion as the cyclization to form cis-4-bromo-3-ethyltetrahydropyran using 5.3 g (14 mmol) TiBr_4 and 1.746 g (9.272 mmol)

trans-6-(2-methoxyethoxy)methoxy-3-hexene. The mixture was allowed to react for 30 min at -45°C in a chlorobenzene bath. A yield analysis, performed on the organic fraction using 0.481 g (4.14 mmol) heptanol, indicated 97.8% trans-4-bromo-3-ethyltetrahydropyran.

trans-4-Chloro-3-ethyltetrahydropyran. This reaction was conducted in a similar fashion as the cyclization to form cis-4-bromo-3-ethyltetrahydropyran using 20 mmol TiCl_4 and 1.971 g (104.7 mmol)

trans-6-(2-methoxyethoxy)methoxy-3-hexene. This reaction was conducted for elemental analysis. Yield analysis data was obtained from the work of T. H. Simpson.

cis,cis-4-Bromo-3-ethyl-2-methyltetrahydropyran. This reaction was conducted in a similar fashion as the cyclization to form cis-4-bromo-3-ethyltetrahydropyran using 4.5 g (12 mmol) TiBr_4 and 1.618 g (9.391 mmol) cis-6-(1-ethoxy)ethoxy-3-hexene. The mixture was allowed to react for 30 min at -45°C . A yield analysis, performed on the organic fraction using 0.476 g (4.10 mmol) 1-heptanol, indicated 92.3% cis,cis-4-bromo-3-ethyl-2-methyltetrahydropyran.

cis,cis-4-Chloro-3-ethyl-2-methyltetrahydropyran.

This reaction was conducted in a similar fashion as the cyclization to form cis-4-bromo-3-ethyltetrahydropyran using 20 mmol TiCl_4 and 2 ml cis-6-(1-ethoxy)ethoxy-3-hexene. This reaction was conducted for elemental analysis. Yield analysis data was obtained from the work of T. H. Simpson.

trans,trans-4-Bromo-3-ethyl-2-methyltetrahydropyran.

This reaction was conducted in a similar fashion as the cyclization to form cis-4-bromo-3-ethyltetrahydropyran using 5.303 g (14.43 mmol) TiBr_4 and 1.830 g (10.62 mmol) trans-6-(1-ethoxy)ethoxy-3-hexene. The mixture was allowed to react for 30 min at -45°C . A yield analysis, performed on the organic fraction using 0.441 g (3.80 mmol) 1-heptanol, indicated >99% trans,trans-4-bromo-3-ethyl-2-methyltetrahydropyran.

3-(1-Chlorovinyl)tetrahydrofuran. This reaction was conducted in a similar fashion as the cyclization to form cis-4-bromo-3-ethyltetrahydropyran using 100 ml methylene chloride, 20 mmol TiCl_4 , and 1.581 g (9.180 mmol) 5-(2-methoxyethoxy)methoxy-2-pentyne. The mixture was allowed to react for 15 min at 25°C . A yield analysis, performed on the organic fraction using 0.928 g (7.13 mmol) 1-octanol, indicated >99% 3-(1-chlorovinyl)tetrahydrofuran.

3-(1-Chloro-2-phenylvinyl)tetrahydrofuran. This reaction was conducted in a similar fashion as the cyclization to form cis-4-bromo-3-ethyltetrahydropyran using

100 ml methylene chloride, 20 mmol TiCl_4 , and 2.051 g (8.754 mmol) 1-phenyl-4-(2-methoxyethoxy)methoxy-1-butyne. The mixture was allowed to react for 30 min at -45°C . The organic fraction was Kugelroored, and the isolated yield indicated 79.9% 3-(1-chloro-2-phenylvinyl)tetrahydrofuran.

3-(1-Chlorovinyl)-2-methyltetrahydrofuran. This reaction was conducted in a similar fashion as the cyclization to form cis-4-bromo-3-ethyltetrahydropyran using 50 ml methylene chloride, 10 mmol TiCl_4 , 1 drop water*, and 0.856 g (5.48 mmol) 5-(1-ethoxy)ethoxy-2-pentyne. The mixture was allowed to react for 10 min at -63°C . A yield analysis, performed on the organic fraction using 0.314 g (2.70 mmol) 1-heptanol, indicated 45.4% 3-(1-chlorovinyl)-2-methyltetrahydrofuran.

* Traces of water enhance the rate of reactions using Lewis acid catalysts²⁸.

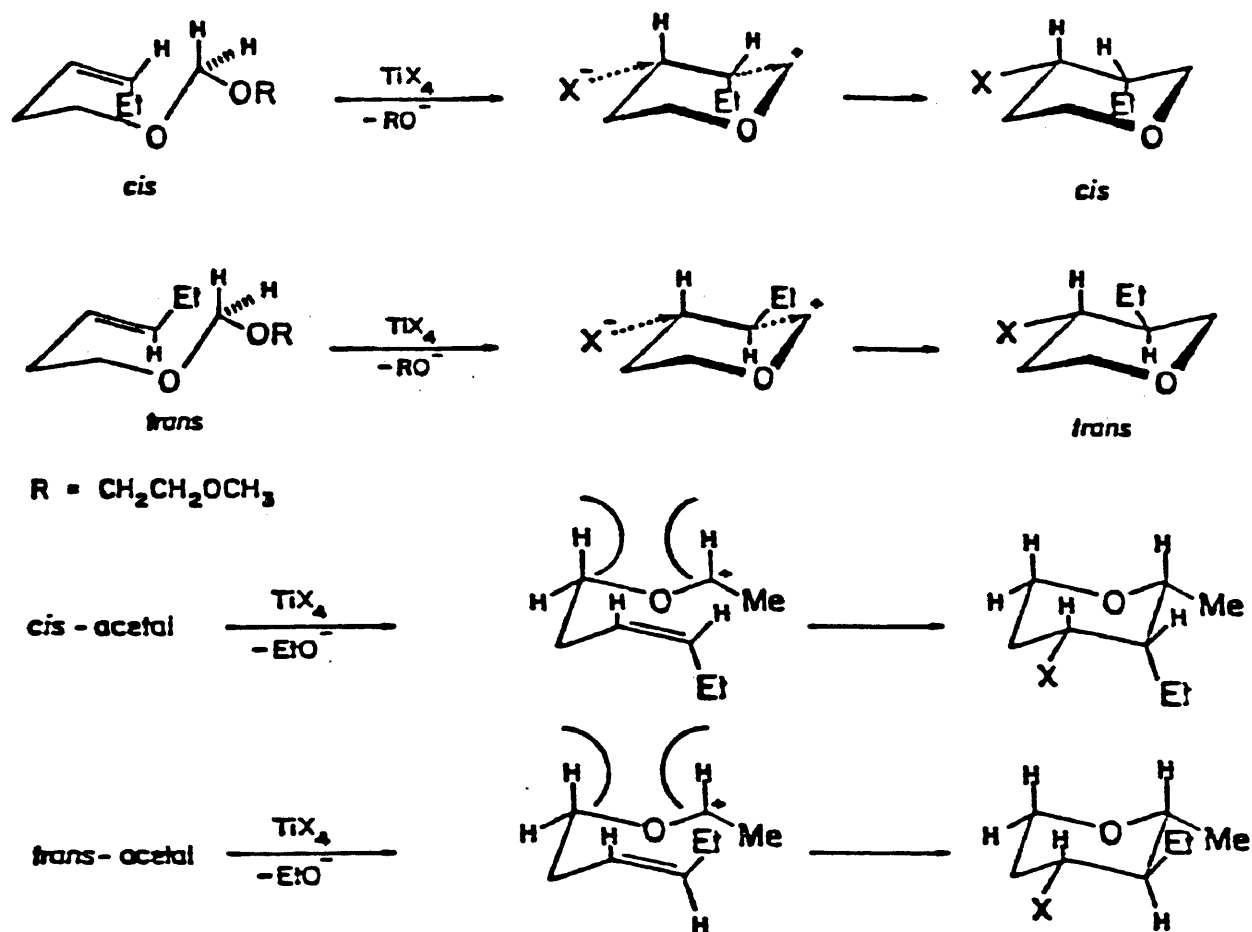
RESULTS AND DISCUSSION

I. CYCLIZATION OF ACETALS DERIVED FROM CIS AND TRANS-3-HEXEN-1-OL AND METHOXYETHOXYMETHYL CHLORIDE AND ETHYL VINYL ETHER

Stapp's³ work as discussed previously consisted of the cyclization of a terminal alkene in the presence of formaldehyde and hydrogen chloride to form a 3-alkyl-4-chlorotetrahydropyran (see Scheme 6). This reaction, however, like that of Prins' earlier work, involved the loss of a proton (whether stereoselectively or not is unknown) and then a cyclization (again whether stereoselectively or not is unknown) to give both cis and trans-3-alkyl-4-halotetrahydropyrans. Because the product is a mixture of cis and trans isomers, this reaction is of minimal interest for the stereoselective production of tetrahydropyrans.

Our goal was to produce a reaction which forms either the cis or the trans-3-alkyl-4-halotetrahydropyran in a stereospecific manner from a cis or trans acetal. If our cyclizations occur by trans-addition across the double bond¹², then the cis acetal should cyclize to produce the cis tetrahydropyran, and the trans acetal should cyclize to produce the trans tetrahydropyran (Scheme 42). In our

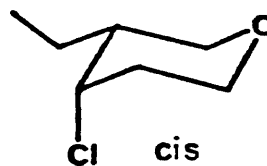
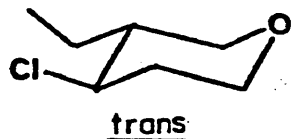
study we have reacted the MEM acetals and the ethyl vinyl ether acetals of cis and trans-3-hexen-1-ol with the Lewis acids titanium tetrachloride (TiCl_4) and titanium tetrabromide (TiBr_4) with the expectation of stereospecifically forming cis and trans-3-alkyl-4-halotetrahydropyrans.



Scheme 42.

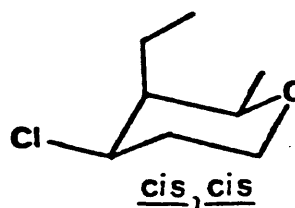
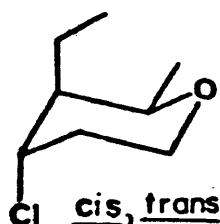
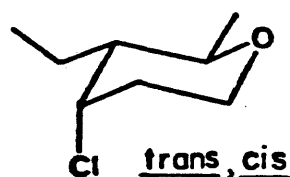
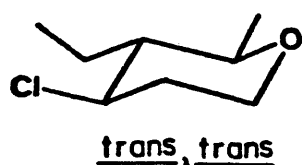
Upon cyclization of the MEM acetals, two isomers can be formed. Either the substituents (3-ethyl and 4-halogen) will be trans to one another and both substituents will be

in an equatorial position or the substituents will be cis to one another. In the latter case conformational energies tabulated by Eliel et. al.²⁷ indicate the ethyl group will prefer the equatorial position over the chloride. The $-\Delta G^\circ$ value for a 3-ethyl substituent on a tetrahydropyran is unknown, but the $-\Delta G^\circ$ value for a 2-ethyl substituent is 2.62 kcal/mole and is similar to the $-\Delta G^\circ$ value of 2.86 kcal/mole for a 2-methyl substituent. On this basis we assume the $-\Delta G^\circ$ value for a 3-ethyl substituent on a



tetrahydropyran is similar to the $-\Delta G^\circ$ value of 1.43 kcal/mole for a 3-methyl substituent. The $-\Delta G^\circ$ value for a 4-chloride is 0.31 kcal/mole. The substituent with the smaller $-\Delta G^\circ$ value occupies the axial position. Thus the chloride occupies the axial position, and the ethyl occupies the equatorial position. The compound, cis-4-chloro-3-ethyltetrahydropyran has a $-\Delta G^\circ$ value of 1.12 (1.43 - 0.31) kcal/mole. The cis configuration where the 3-ethyl is axial and the 4-chloride is equatorial makes up less than 3% of cis-4-chloro-3-ethyltetrahydropyran. The trans configuration where both substituents are axial is very unstable and makes up less than -2% of the trans-4-chloro-3-ethyltetrahydropyran.

Upon cyclization of the ethyl vinyl ether acetals, four isomers are expected to be formed. The expected conformation for the trans,trans isomer has all equatorial substituents. The expected conformation for the cis,trans isomer, the isomer with the methyl and the ethyl cis to one another and the ethyl and the halogen trans to one another, is expected to contain an axial methyl and equatorial ethyl



and halogen substituents. The $-\Delta G^\circ$, calculated with the above conformational energies, for this configuration of the cis,trans isomer is -1.12 ($1.43 + 0.31 - 2.86$) kcal/mole. The negative value indicates that the original assumption of an axial methyl and equatorial ethyl and halogen substituents is wrong and that the conformation should actually have an equatorial methyl and axial ethyl and halogen substituents. The expected conformation for the trans,cis isomer should contain an axial halogen and equatorial methyl and ethyl substituents. This is confirmed by the $-\Delta G^\circ$ value of 3.98 ($2.86 + 1.43 - 0.31$) kcal/mole.

The expected configuration for the cis,cis isomer should consist of an axial ethyl and equatorial methyl and halogen substituents. Again this is confirmed by the $-\Delta G^\circ$ value of 1.74 (2.86 + 0.31 - 1.43) kcal/mole.

The MEM acetals were prepared by reacting MEM chloride and N,N-diisopropylethylamine with either cis or trans-3-hexen-1-ol in methylene chloride. The progress of the reaction was observed by capillary gas chromatography (GC). The organic layer was then separated, distilled, and analyzed by capillary GC to determine its purity. The acetals were identified by ^{13}C nuclear magnetic resonance spectroscopy (NMR).

The ethyl vinyl ether acetals were prepared by reacting ethyl vinyl ether and phosphoric acid with the alcohol. The reaction mixture was then distilled and analyzed by capillary GC for purity.

Both types of acetals were cyclized to form tetrahydropyrans by reacting TiCl_4 or TiBr_4 with an acetal in methylene chloride. The reactions were run at several temperatures for fifteen to thirty minutes, and the progress of the reaction was observed by capillary GC. Upon completion of a reaction, it was quenched with methanol and hydrochloric acid. The product yields were determined for the products, and the products were identified by ^1H and ^{13}C NMR. A listing of the products and their NMR absorptions is presented in Tables 2 and 3.

Table 2. Starting acetals, products, yields, and ^{13}C NMR absorptions for the formation of tetrahydropyrans




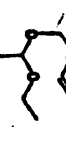




acetal	Lewis acid	major product X, (yield, %)	^{13}C NMR, ($\text{CDCl}_3/\text{Me}_4\text{Si}$)
	TiCl_4	Cl, (94;92% trans)	11.0 (CH_2), 22.3, 36.4 (CH_2), 46.2 (EtCH), 61.5 (ClCH), 67.2, 70.8 (OCH_2)
	TiBr_4	Br, (98;89% trans)	11.1 (CH_2), 24.0, 37.7 (CH_2), 46.2 (EtCH), 54.7 (BrCH), 68.2, 71.4 (OCH_2)
	TiCl_4	Cl, (92;95% cis)	10.7 (CH_2), 21.5, 34.8 (CH_2), 42.8 (EtCH), 60.1 (ClCH), 62.6, 67.0 (OCH_2)
	TiBr_4	Br, (74;87% cis)	10.6 (CH_2), 23.6, 35.1 (CH_2), 42.7 (EtCH), 56.5 (BrCH), 63.3, 67.7 (OCH_2)
	TiCl_4	Cl, (85;96% trans)	9.2 (Et- CH_3), 20.0 (2- CH_2), 21.1, 38.1 (CH_2), 51.8 (EtCH), 60.4 (ClCH), 67.1 (6- CH_2), 76.9 (MeCHO)
	TiBr_4	Br, (>99;98% trans, trans)	9.1 (Et-CH), 20.1 (2- CH_2), 22.6, 39.2 (CH_2), 52.0 (EtCH), 54.0 (BrCH), 68.1 (6- CH_2), 77.1 (MeCHO)
	TiCl_4	Cl, (96;97% cis)	16.0, 19.0 (CH_3), 16.7 (Me CH_2), 32.4 (5- CH_2), 48.3 (EtCH), 62.0 (ClCH), 66.1 (6- CH_2), 76.2 (MeCHO)
	TiBr_4	Br, (>99;98% cis)	15.9, 19.1 (CH_3), 18.0 (Me CH_2), 33.1 (5- CH_2), 48.8 (EtCH), 55.1 (BrCH), 67.2 (6- CH_2), 76.5 (MeCHO)

Table 3. Cyclization products and their ^1H -NMR absorptions

major product X	^1H -NMR
	0.90(CH_3), 3.12(2H_a), 3.40(6H_a), 3.81(4H_a), 3.93(6H_e), 4.02(2H_e)
	0.90(CH_3), 3.51(6H_a), 3.61(2H_a), 3.74(6H_e), 3.86(2H_e), 4.47(4H_e)
	0.89(CH_3 , CH_2), 1.25(CH_3 , CH), 3.29(2H_a), 3.40(6H_a), 3.92(6H_e), 3.94(4H_a) 0.87(CH_3 , CH_2), 1.25(CH_3 , CH), 3.3(2H_a), 3.4(6H_a)
	1.01(CH_3 , CH_2), 1.24(CH_3 , CH), 3.43(6H_a), 3.54(2H_e), 3.94(6H_e), 4.21(4H_a) 1.01(CH_3 , CH_2), 1.23(CH_3 , CH), 3.44(6H_a), 3.57(2H_e), 3.92(6H_e), 4.40(4H_a)

No other acids or solvents were used in these cyclization studies.

On reaction of the MEM acetal (99) (Scheme 40) with TiCl_4 or TiBr_4 , the methoxyethoxide tail is lost leaving the primary oxocarbo-cation (100) behind. This oxocarbo-cation attacks the intramolecular double bond to form a ring and thereby produces another carbocation. This carbocation is then attacked by a nucleophilic chloride or bromide ion from the acid to produce a 3-ethyl-4-halotetrahydropyran.

When the ethyl vinyl ether acetal (101) (Scheme 41) is reacted with TiCl_4 or TiBr_4 , the ethoxide tail is lost to produce a secondary oxocarbo-cation (102). This oxocarbo-cation attacks the intramolecular double bond to form a ring and produces another carbocation as in the MEM cyclization. Again a nucleophilic chloride or bromide ion from the acid attacks the carbocation to form, this time, a 3-ethyl-4-halo-2-methyltetrahydropyran.

It was our hope that the cyclization would be a stereospecific reaction and that the cis acetal would produce a single isomer, while the trans acetal would produce the second product isomer. As seen in Table 2 starting acetals and their products, this was the case. In the MEM acetal cyclizations cis-6-(2-methoxyethoxy)methoxy-3-hexene produced cis-3-ethyl-4-halotetrahydropyran, and trans-6-(2-methoxyethoxy)methoxy-3-hexene produced trans-3-ethyl-4-halotetrahydropyran. In the ethyl vinyl

ether cyclizations cis-6-(1-ethoxy)ethoxy-3-hexene produced cis,cis-3-ethyl-4-halo-2-methyltetrahydropyran and trans-6-(1-ethoxy)ethoxy-3-hexene produced trans,trans-3-ethyl-4-halo-2-methyltetrahydropyran.

In the MEM acetal cyclizations there are only two products: cis and trans-3-ethyl-4-halotetrahydropyran. In the cyclizations where TiCl_4 is used as the Lewis acid, the halogen is a chloride. When TiBr_4 is the Lewis acid,, the halogen is a bromide. In the cyclization reactions, the cis acetal produces the cis tetrahydropyran, and the trans acetal produces the trans tetrahydropyran. This can be seen in the high field ^1H NMR studies of trans and cis-4-chloro-3-ethyltetrahydropyran in Figures 4 and 5, respectively.

The set of peaks at 3.81 ppm in Figures 4 and 4c is the carbon 4 axial hydrogen of trans-4-chloro-3-ethyltetrahydropyran. Its nearest neighbors are two axial hydrogens and one equatorial hydrogen. Axial-axial coupling constants (J_{aa}) usually range from 8 to 10 Hz although J_{aa} can range anywhere from 6 to 14 Hz. Axial-equatorial coupling constants (J_{ae}) range from 0 to 5 Hz with typical values between 2 to 3 Hz. If, as in this case, the two axial-axial coupling constants are equal, then a triplet, formed by the two axial-axial couplings, is expected with each peak split again by the smaller equatorial-axial coupling. This is indeed what is seen in

Figure 4c. The axial-axial coupling constant is 6.1 Hz and J_{ae} is 2.7 Hz. These fall within the expected ranges.

The set of peaks at 4.47 ppm in Figures 5 and 5a is the equatorial hydrogen off carbon 4 in cis-4-chloro-3-ethyltetrahydropyran. Its nearest neighbors are two axial hydrogens and an equatorial hydrogen. If the axial-equatorial couplings and J_{ee} are almost equal (J_{ee} , like J_{ae} , usually ranges from 2 to 3 Hz), then the spectra should look like a quartet. The spectra is indeed an approximate quartet with J_{ee} and both J_{ae} 's approximately equal at 2.0 Hz.

The set of peaks at 3.81 ppm in Figures 4 and 4c and the set of peaks at 4.47 ppm in Figures 5 and 5a identify these compounds as being the trans and the cis products, respectively. Both sets of peaks represent the hydrogen at C-4. In the trans product the hydrogen is axial, but in the cis product the hydrogen is equatorial. Equatorial hydrogens are found further downfield in ^1H NMR than their respective axial counterparts. This along with their peak patterns and coupling constants verifies the product structure of the cyclization of cis-6-(2-methoxyethoxy)methoxy-3-hexene as being cis-4-chloro-3-ethyltetrahydropyran and the product structure of the cyclization of trans-6-(2-methoxyethoxy)methoxy-3-hexene as being trans-4-chloro-3-ethyltetrahydropyran.

Other peaks in the ^1H NMR of trans-4-chloro-3-ethyltetrahydropyran are discussed below. The two sets of peaks in Figures 4a and 4b show the effects of long range coupling between the hydrogens on carbons 2 and 6 through the oxygen atom. The set of peaks centered at 4.02 ppm in Figures 4 and 4a is the ^1H NMR peak of the equatorial hydrogen at carbon 2. It's nearest neighbor is an axial hydrogen at carbon 3. It also couples with its gem hydrogen. The coupling constant for gem hydrogens (J_{gem}) usually ranges from 12 to 15 Hz although J_{gem} can range anywhere from 0 to 30 Hz. In these spectra J_{gem} is usually 7.0 Hz. From these two coupling constants a doublet of doublets is expected in the ^1H NMR. The ^1H NMR actually shows a doublet of doublet of doublets. The coupling constants for these peaks are 7.0, 2.5, and 0.72 Hz. The coupling constant of 7.0 Hz must be the gem coupling, and 2.5 Hz is probably the J_{ae} since 0.72 Hz is rather small (though not unknown) for axial-equatorial couplings. That leaves the coupling constant of 0.72 Hz to be explained. Because carbon-oxygen bond lengths are slightly smaller than carbon-carbon bond lengths, there may be long range coupling between the hydrogens on carbons 2 and 6. These coupling constants would be expected to be very small because of the distance between the hydrogens, and this is what is seen in Figure 4a.

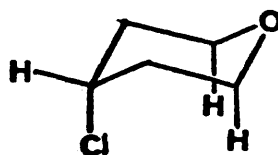
The set of peaks at 3.93 ppm in Figures 4 and 4b also shows long range coupling. These peaks represent the equatorial hydrogen at C-6. It's nearest neighbors are an axial hydrogen, an equatorial hydrogen, and a gem hydrogen. If J_{ee} does not equal J_{ae} , then a doublet of doublet of doublets is expected. However, long range coupling is also involved such that each doublet is split to form the pattern seen in Figure 4b. The coupling constants for this spectra are 7.0 Hz (J_{gem}), 1.9 and 2.6 Hz (J_{ee} and J_{ae}), and 0.7 Hz (long range coupling constant).

The ^1H NMR spectra for the axial hydrogen at C-2 of trans-4-chloro-3-ethyltetrahydropyran is seen in Figures 4 and 4d at 3.12 ppm. This hydrogen has an axial nearest neighbor and a gem hydrogen. The expected (and the actual) spectra is a doublet of doublets with $J_{gem} = 7.2$ Hz and $J_{aa} = 5.4$ Hz. This spectra is too narrow to see any long range coupling.

The ^1H NMR spectra for the axial hydrogen at C-6 is also seen in Figures 4 and 4d at 3.40 ppm. Unfortunately there were impurities in the sample which make this spectra difficult to analyze. This set of peaks is split by axial-axial, axial-equatorial, and gem couplings. If J_{aa} and J_{gem} are close in value, then a doublet of doublet of doublets with overlap of the center four peaks is expected. This can be seen in the set of peaks at 3.40 ppm if closely inspected. The coupling

constants for this set of peaks include $J_{\text{gem}} = 6.8$ Hz, $J_{\text{aa}} = 6.4$ Hz, and $J_{\text{ae}} = 1.4$ Hz.

The ^1H NMR spectra of the cis-4-chloro-3-ethyltetrahydropyran is more ambiguous because of the interaction of the axial chloride with the two axial hydrogens. The spectra of the axial hydrogens at carbons 2 and 6 and the hydrogen gem to the chloride are slightly unusual and confusing. The spectra of the other hydrogens in this compound contain coupling constants which are not usual due to the same 1,3-diaxial interactions.



1,3-diaxial interference

The set of peaks at 3.86 ppm in Figures 5 and 5b represent the equatorial hydrogen at carbon 2 in cis-4-chloro-3-ethyltetrahydropyran. This hydrogen has a gem coupling of 7.0 Hz, an axial-equatorial coupling of 7.0 Hz, and two long range couplings of 1.4 and 0.36 Hz. The axial-equatorial coupling is not in the usual range of 2 to 3 Hz for J_{ae} , because of the 1,3-diaxial interactions between the chloride and the hydrogens at carbons 2 and 6.

The set of peaks at 3.75 ppm in Figures 5 and 5c represent the equatorial hydrogen at carbon 6. This hydrogen has a gem coupling of 7.0 Hz and J_{ee} and

J_{ae} of 1.4 and 2.9 Hz. This gives a doublet of doublet of doublets. Two long range couplings split each of these peaks into a triplet to give the spectra seen in Figure 5c.

The spectra for the axial hydrogen at carbon 2 appears at 3.61 ppm in Figures 5 and 5d. This hydrogen has a gem coupling of 7.0 Hz and an axial-axial coupling of 2.5 Hz to give a doublet of doublets. The long range coupling constant is small and does not completely split the peaks to form the spectra seen in Figure 5d. The value for J_{aa} is very small, and one would expect it to be J_{ee} or J_{ae} . However axial hydrogens are found further upfield than equatorial hydrogens so that this set of peaks must represent an axial hydrogen. One reason for the unusual coupling constants for the hydrogens at carbons 2 and 6 could be the steric effect of an axial chloride to nearby hydrogens. This may not only explain the unusual coupling constants of the spectra of cis-4-chloro-3-ethyltetrahydropyran but also the broad and ambiguous peaks at 4.47, 3.61, and 3.52 ppm.

The set of peaks at 3.52 ppm in Figures 5 and 5e is due to the axial hydrogen at carbon 6. It has a gem coupling of 6.9 Hz and an axial-axial coupling constant of 6.0 Hz. The axial-equatorial coupling constant and the long range coupling constants are very small and unobserved to give a doublet of doublets as seen in Figure 5e. /

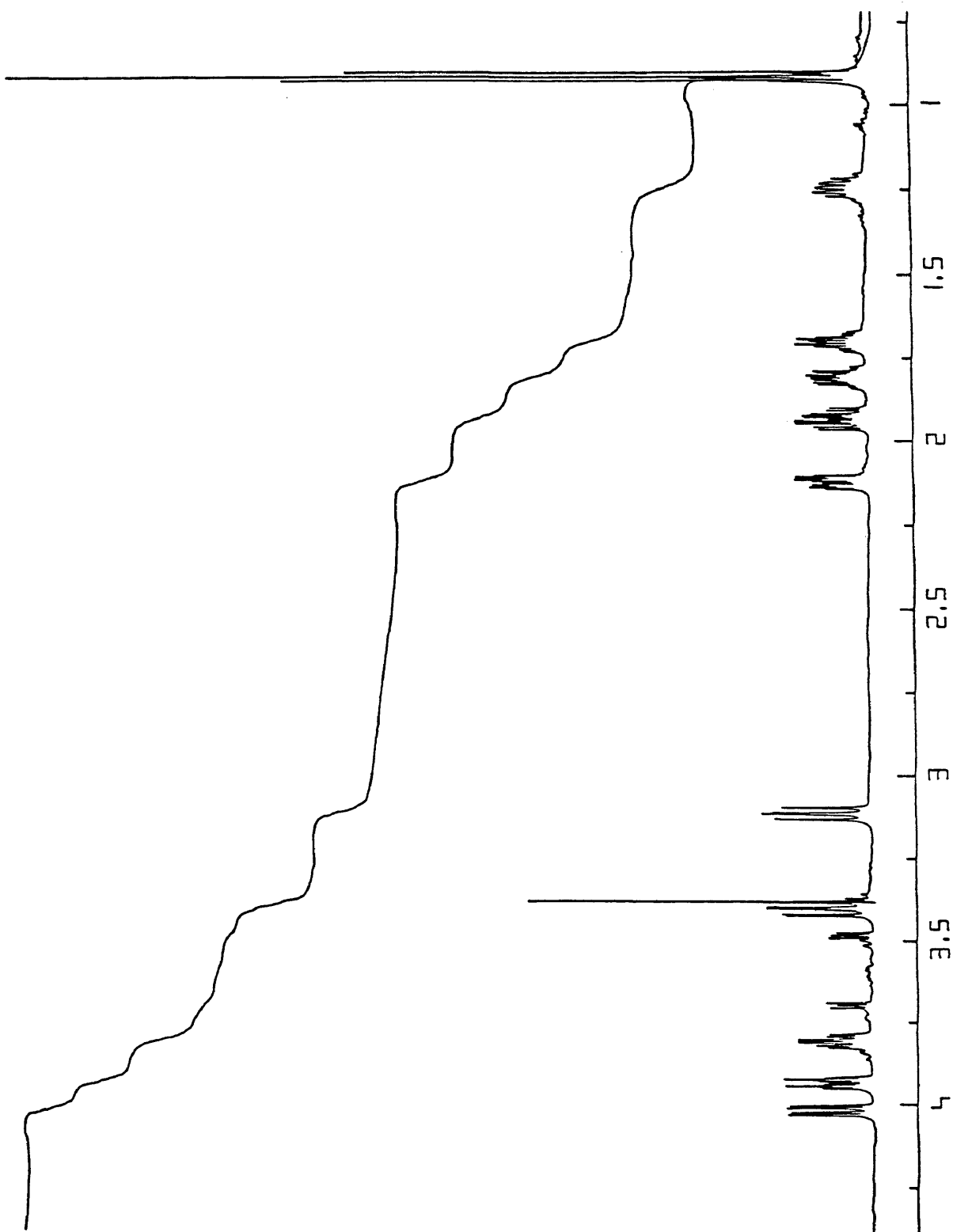


Figure 4. ^1H NMR spectra of trans-4-chloro-3-ethyltetrahydropyran at 60 MHz

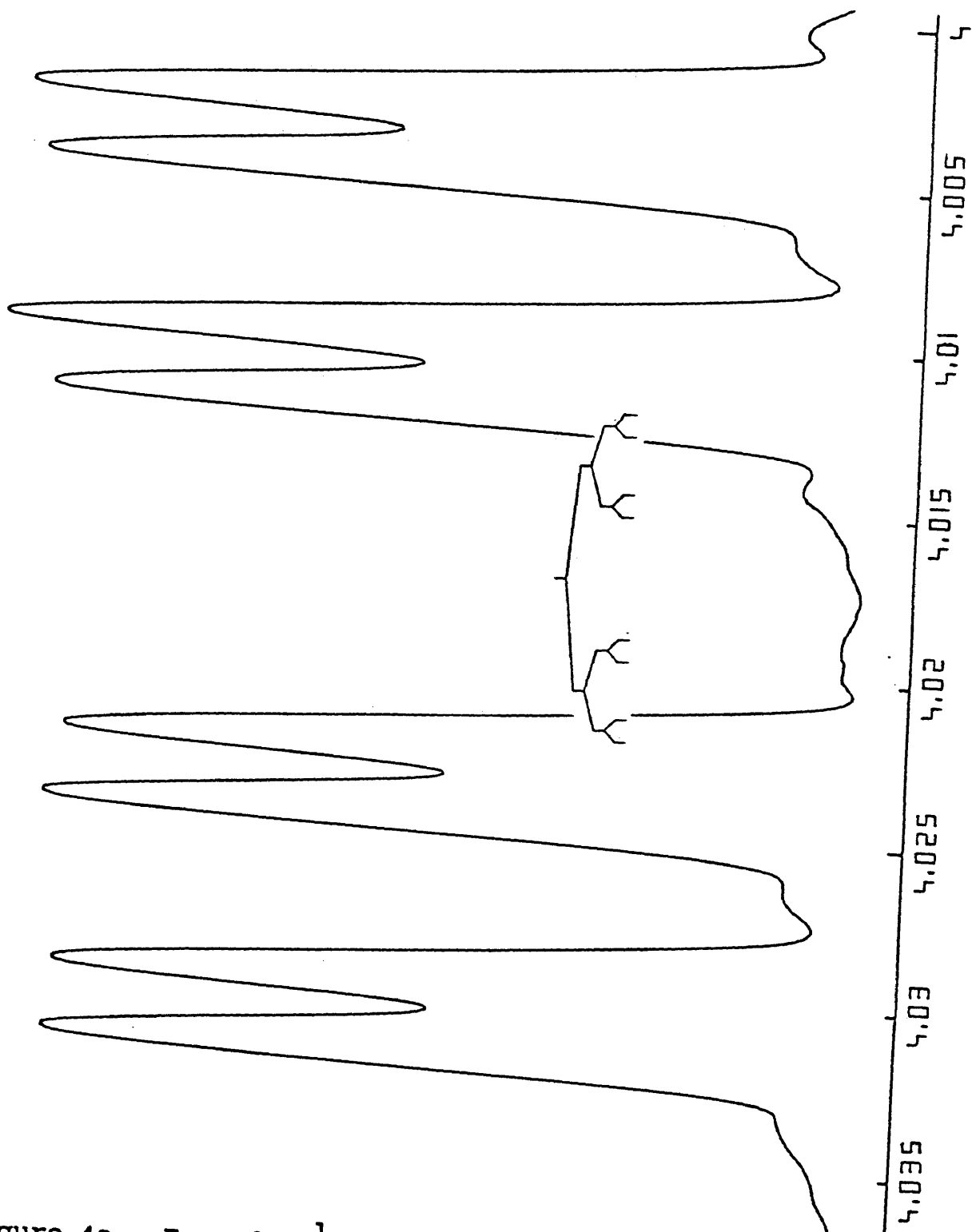


Figure 4a. Expanded ^1H NMR spectra of the equatorial hydrogen at carbon 2 of trans-4-chloro-3-ethyltetrahydropyran at 360MHz

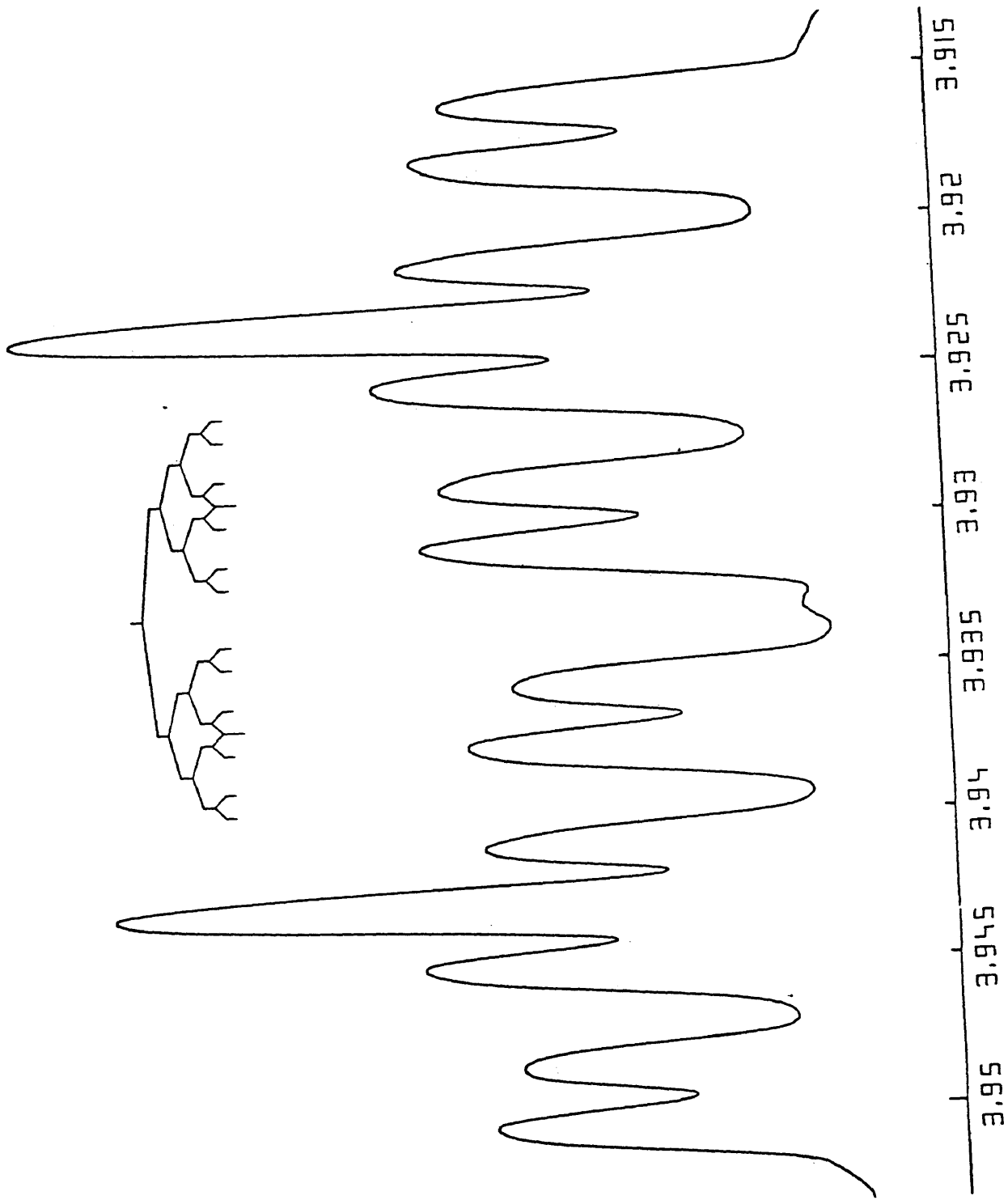


Figure 4b. Expanded ^1H NMR spectra of the equatorial hydrogen at carbon 6 of trans-4-chloro-3-ethyltetrahydropyran at 360MHz

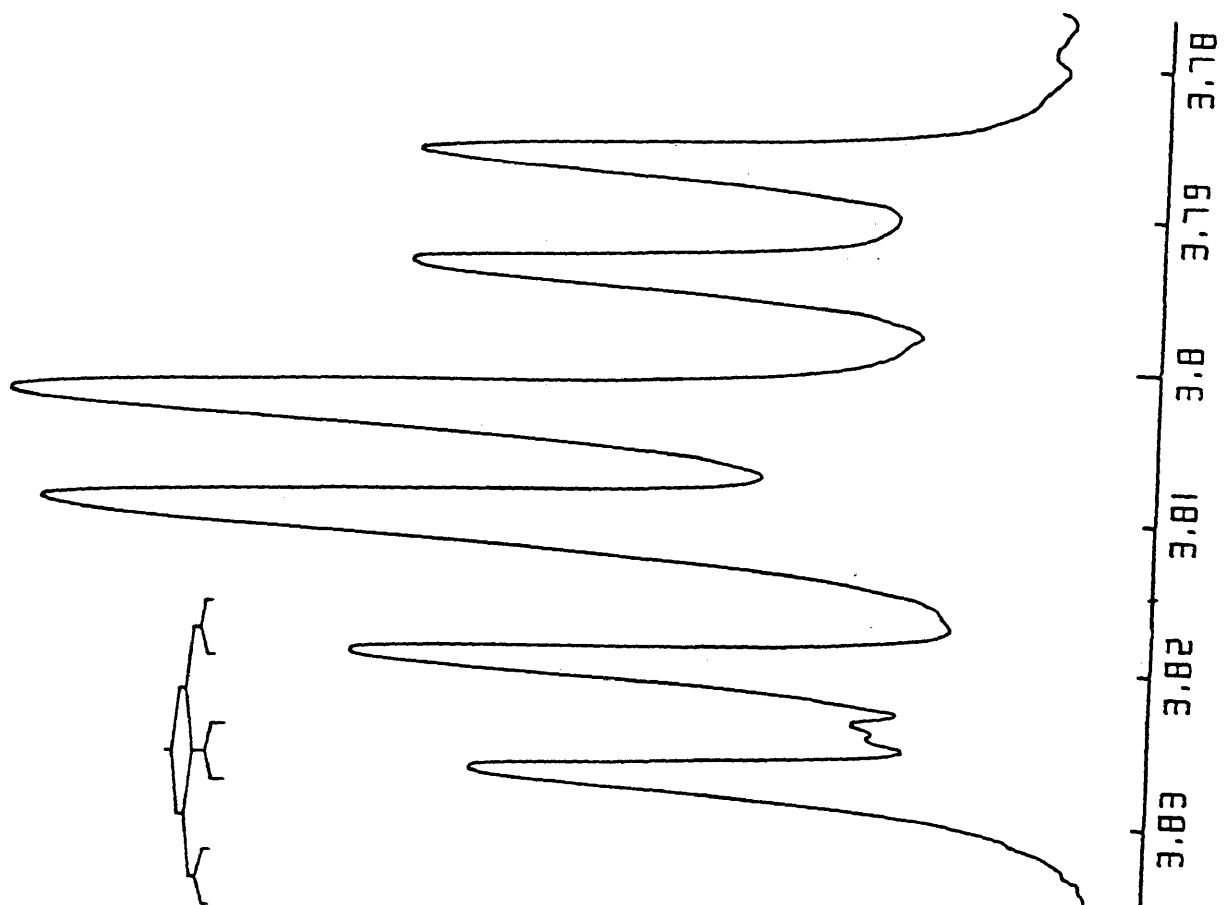


Figure 4c. Expanded ^1H NMR spectra of the axial hydrogen at carbon 4 of trans-4-chloro-3-ethyltetrahydropyran at 360MHz

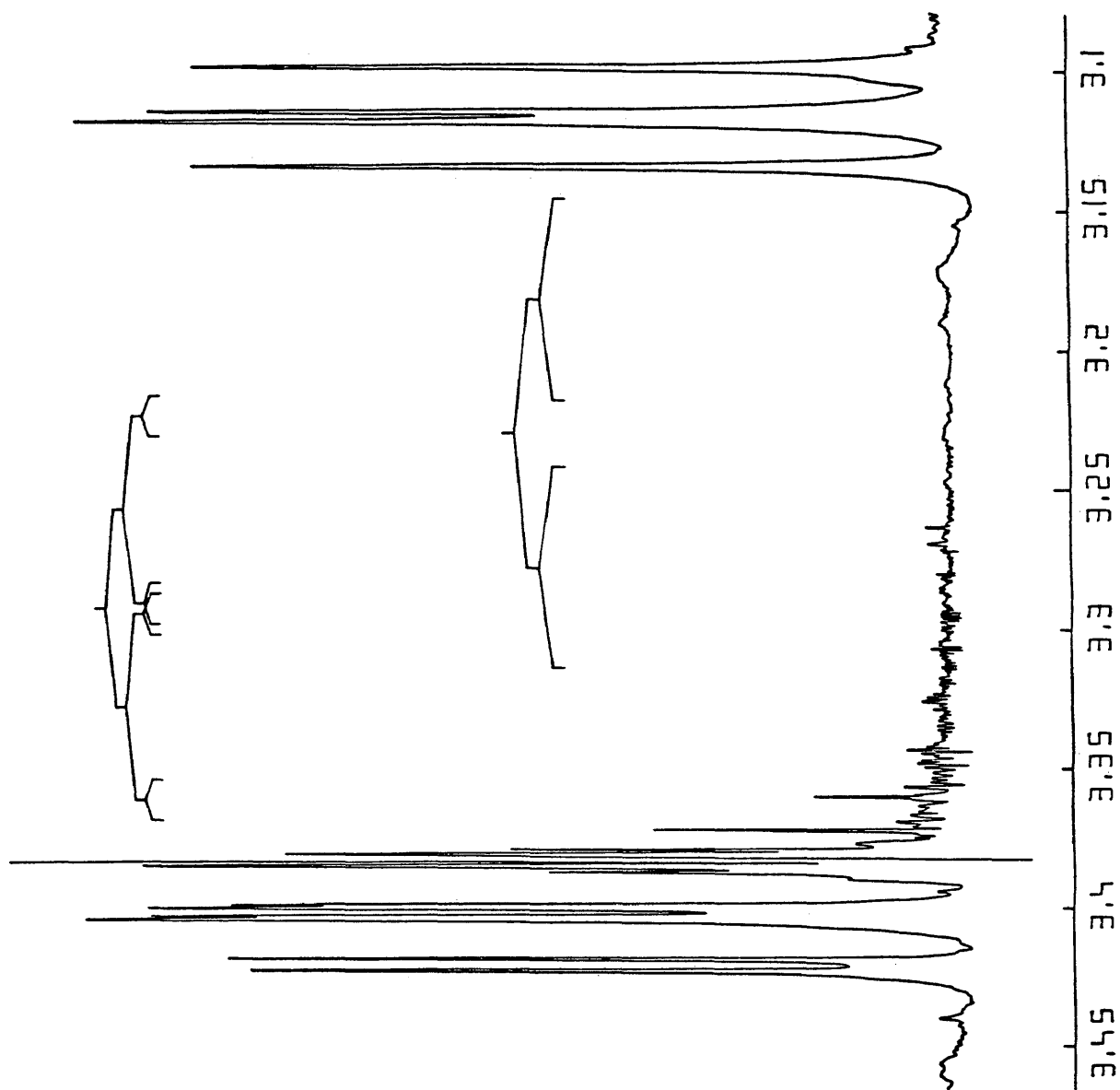


Figure 4d. Expanded ^1H NMR spectra of the axial hydrogens at carbons 2 and 6 of trans-4-chloro-3-ethyltetrahydropyran at 360MHz

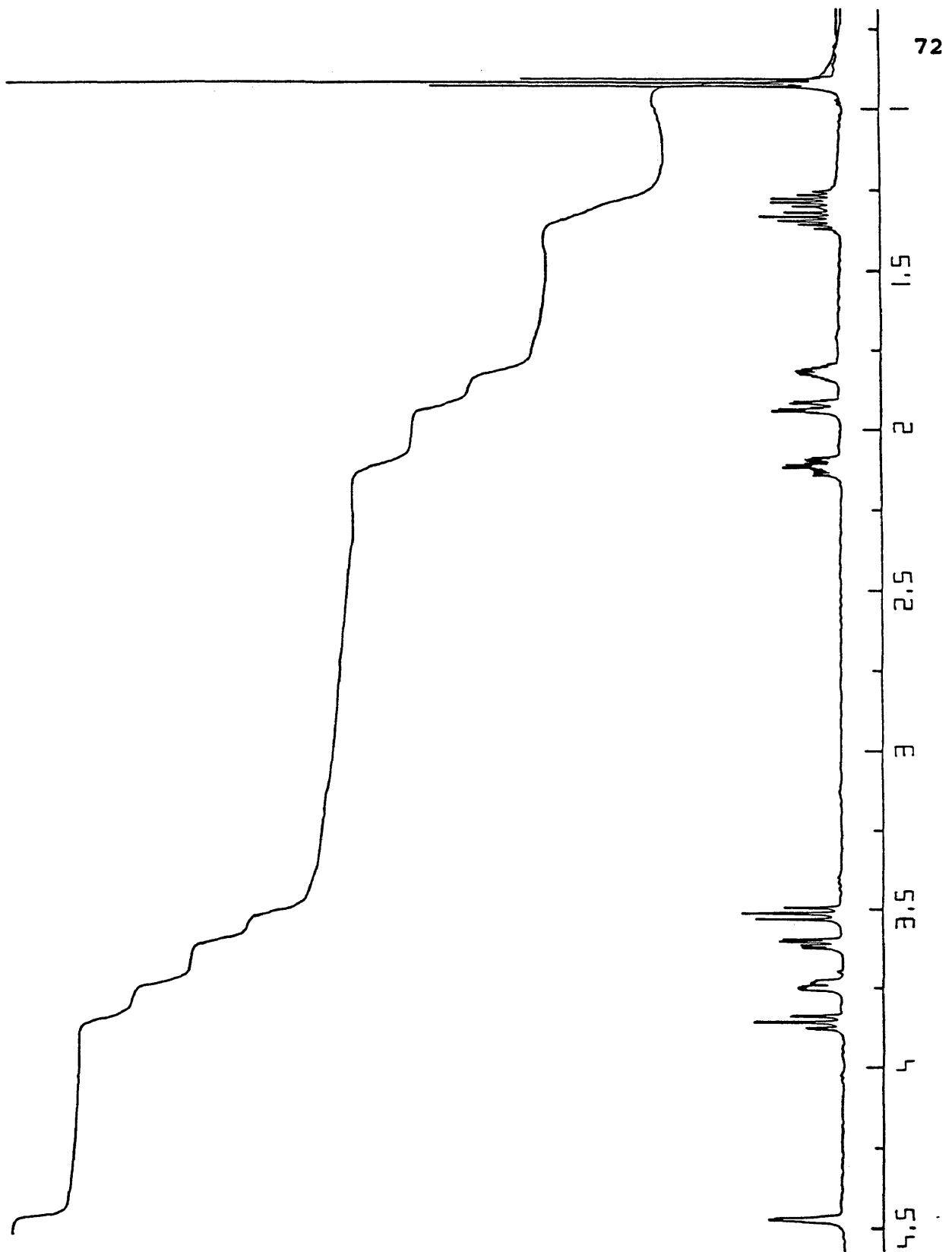


Figure 5. ^1H NMR spectra of *cis*-4-chloro-3-ethyltetrahydropyran at 60 MHz

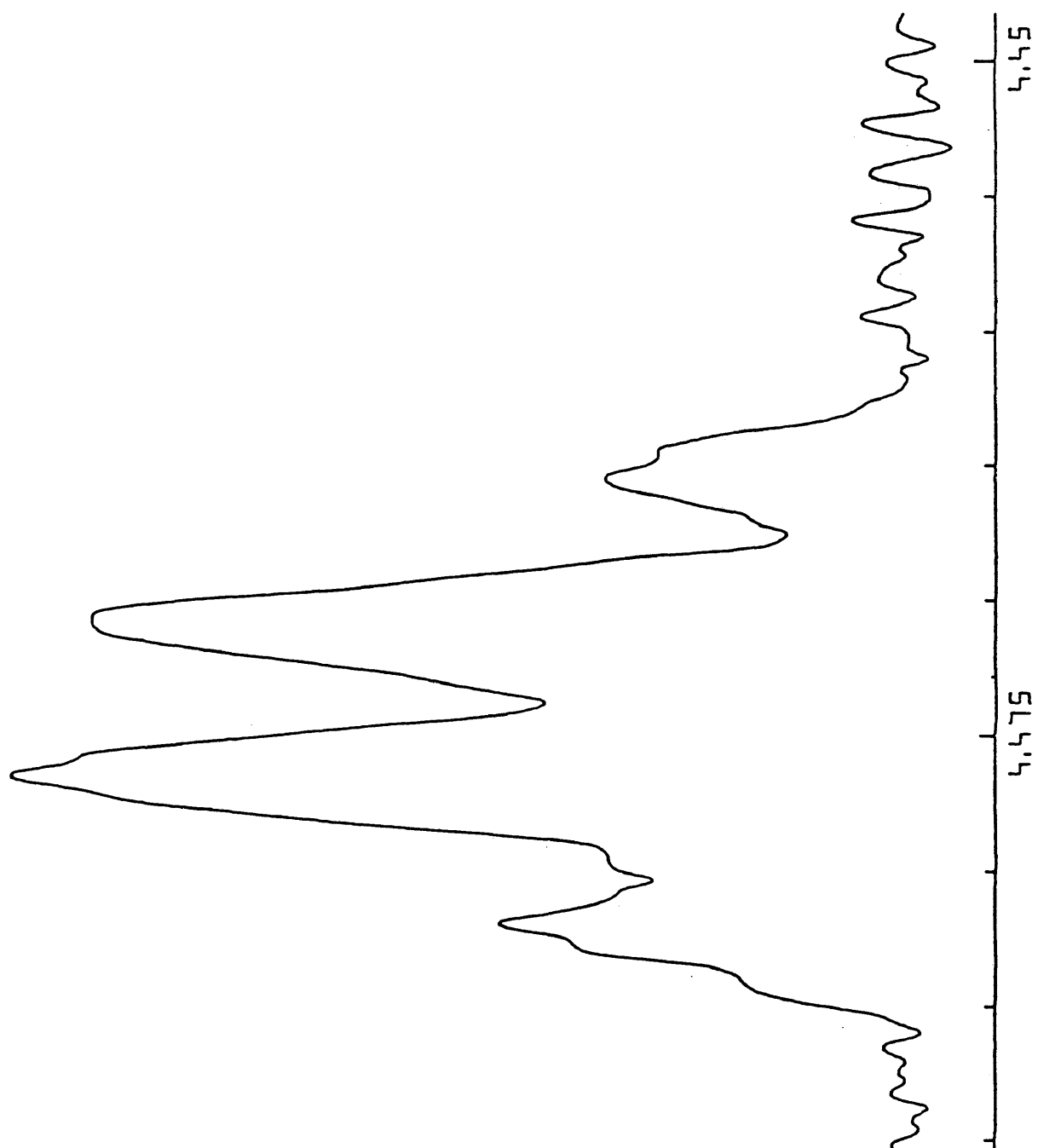


Figure 5a. Expanded ^1H NMR spectra of the equatorial hydrogen at carbon 4 of cis-4-chloro-3-ethyltetrahydropyran at 360MHz

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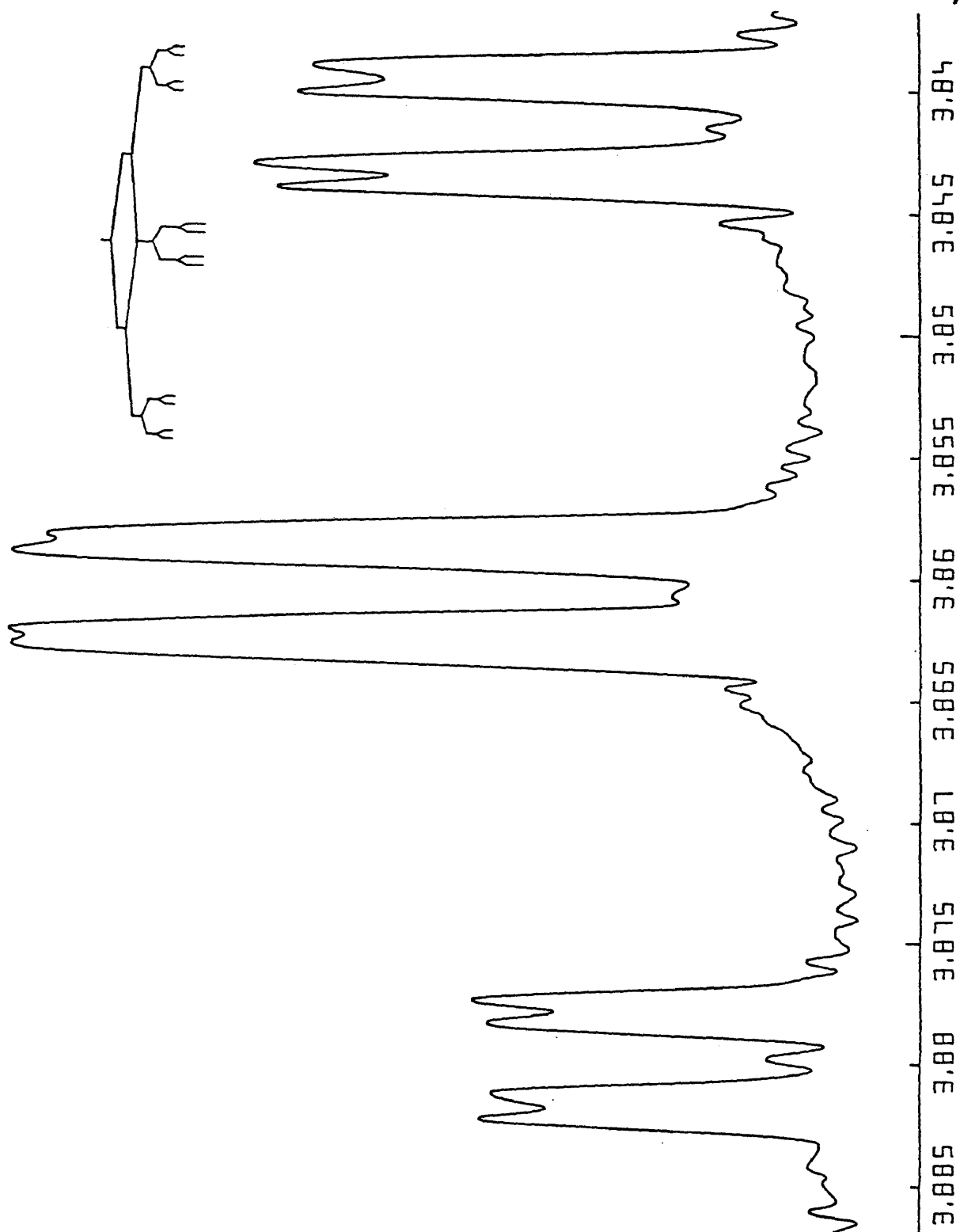


Figure 5b. Expanded ^1H NMR spectra of the equatorial hydrogen at carbon 2 of *cis*-4-chloro-3-ethyltetrahydropyran at 360MHz

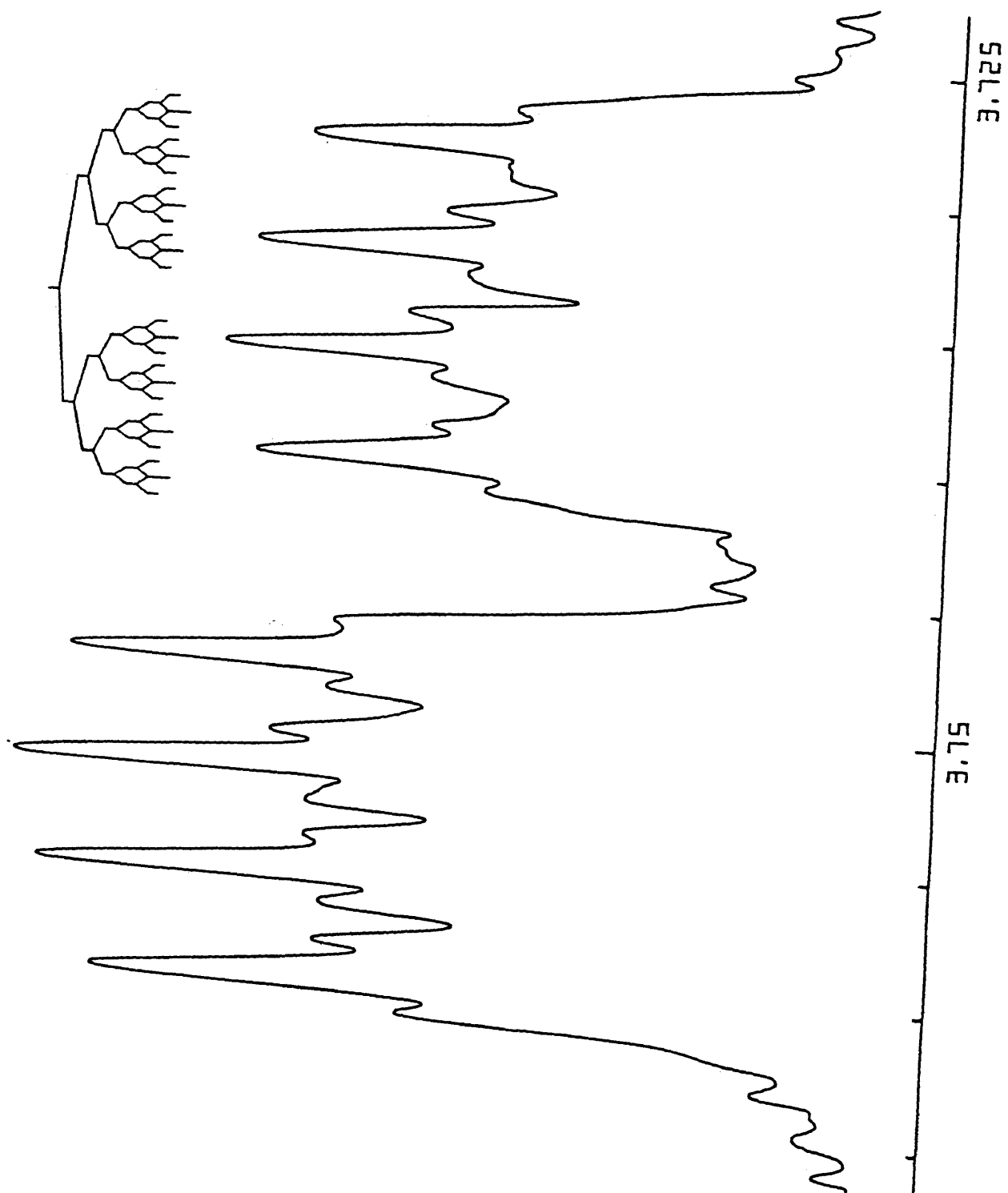


Figure 5c. Expanded ^1H NMR spectra of the equatorial hydrogen at carbon 6 of *cis*-4-chloro-3-ethyltetrahydropyran at 360MHz

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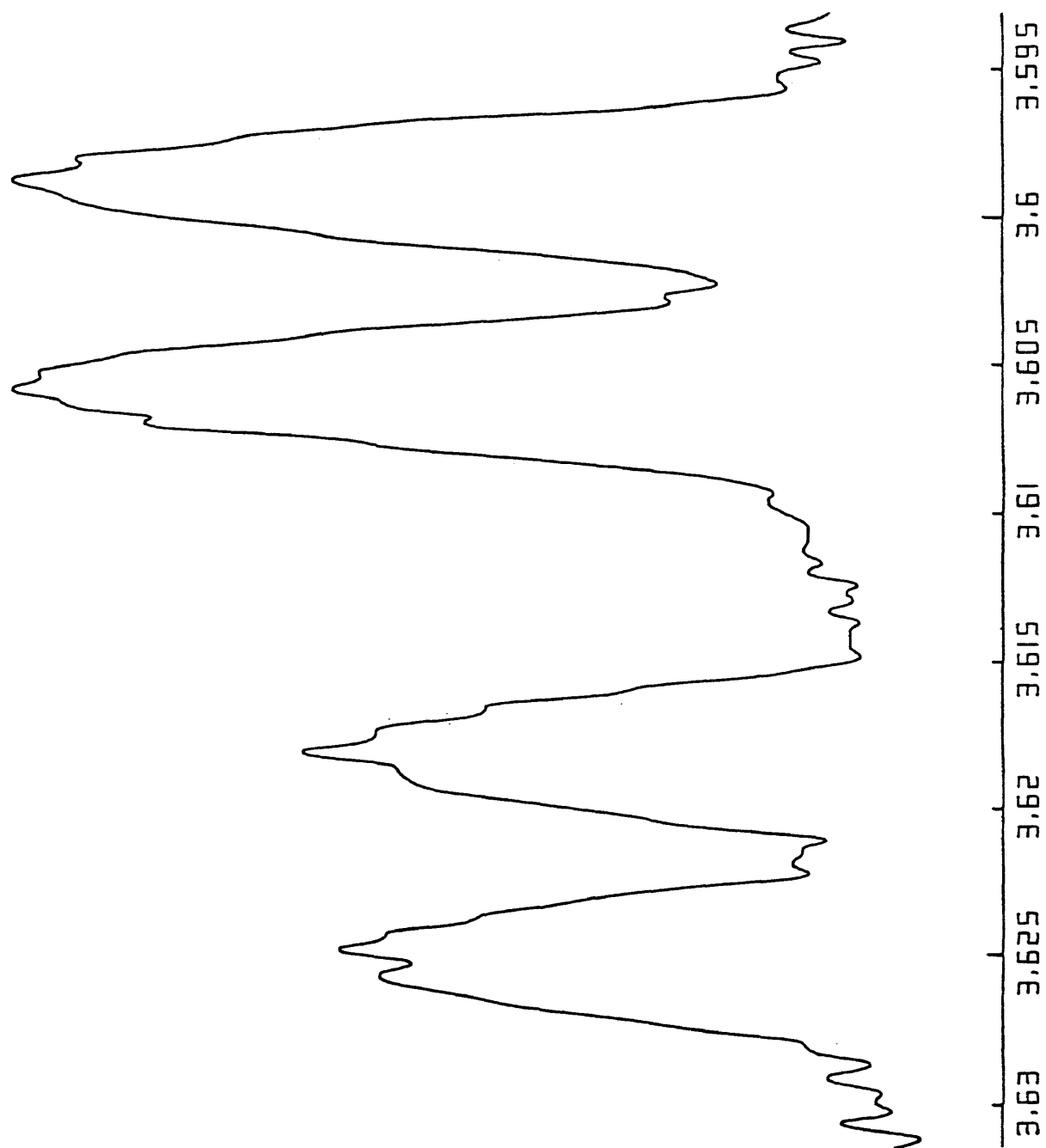


Figure 5d. Expanded ^1H NMR spectra of the axial hydrogen at carbon 2 of *cis*-4-chloro-3-ethyltetrahydropyran at 360MHz

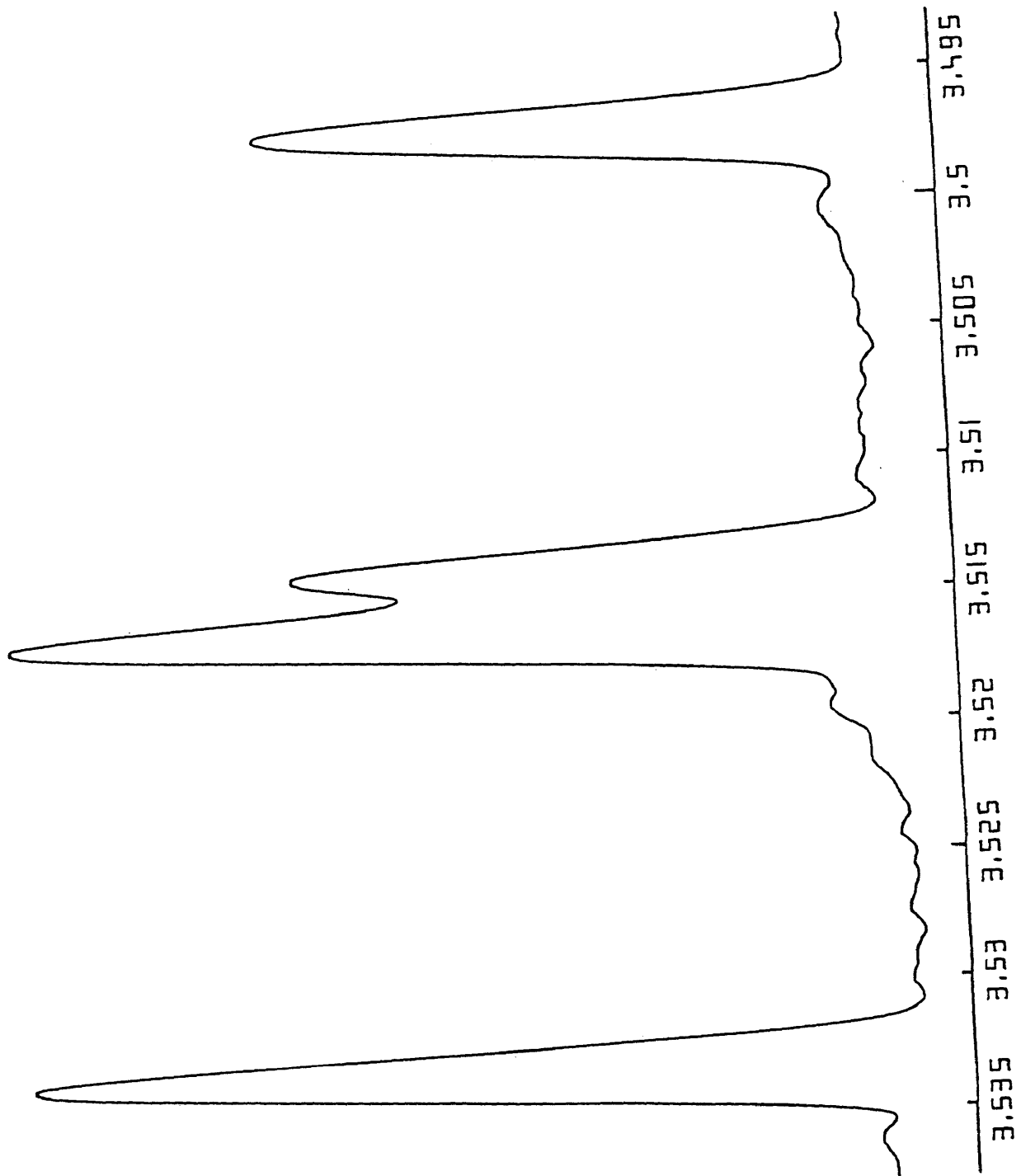
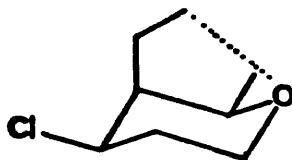


Figure 5e. Expanded ^1H NMR spectra of the axial hydrogen at carbon 6 of cis-4-chloro-3-ethyltetrahydropyran at 360MHz

Four products are expected for the cyclization of the cis and trans ethyl vinyl ether acetals. However, upon cyclization only two products are formed. cis-6-(1-Ethoxy)ethoxy-3-hexene produces cis,cis-3-ethyl-4-halo-2-methyltetrahydropyran, and trans-6-(1-ethoxy)ethoxy-3-hexene produces trans,trans-3-ethyl-4-halo-2-methyltetrahydropyran. There are no cis,trans or trans,cis products. The products of the cyclizations using TiCl_4 and TiBr_4 were identified for both the chloro and the bromo products, respectively, by high field ^1H NMR and are seen in Figures 6 through 9. A listing of starting acetals, products, and peak assignments for both ^1H NMR and ^{13}C NMR is seen in Table 2 and 3.

The ethyl methyl and the 2-methyl peaks, at 0.87 to 1.01 ppm and 1.25 ppm respectively, in Figures 6 through 9 identify the compounds as the cis and the trans isomers. In the cis compounds the ethyl group is axial, and its methyl interacts with the oxygen of the tetrahydropyran. This



Ethyl-oxygen interaction

causes a downfield shift of the ethyl methyl peak to 1.01 ppm. The trans isomer has an equatorial ethyl group and therefore there are no interactions between the ethyl

and the oxygen. For this reason no downfield shift of the ethyl methyl peak is observed, and the methyl peak is found as expected at 0.87 ppm.

In addition to the difference in peak shifts, the order of the peaks in the downfield half of the spectra of cis,cis-3-ethyl-4-halo-2-methyltetrahydropyran is the same as the order of peaks in the downfield half of cis-4-chloro-3-ethyltetrahydropyran except for the absence of the peak for the equatorial hydrogen at C-2.

The spectra for the cis,cis chloro product and the cis,cis bromo product are almost exactly alike except for the shifts of the axial hydrogens at C-4. In the spectra of the bromo product this set of peaks is at 4.40 ppm, while this set of peaks for the chloro product appears at 4.22 ppm. In both of the cis,cis spectra the axial hydrogen at carbon 4 couples with an axial hydrogen and two equatorial hydrogens. The axial-equatorial couplings are both 2.5 Hz for both the chloro and the bromo compounds, and J_{aa} equals 6.9 and 7.1 Hz for the chloro and the bromo compounds, respectively. This forms two triplets as seen in Figures 6, 6a, 7, and 7a.

The equatorial hydrogens at carbon 6 have a gem coupling of 7.1 Hz Cl, 7.2 Hz Br. The equatorial-equatorial and the axial-equatorial couplings are 2.9 Hz Cl, 3.0 Hz Br and 1.7 Hz Cl, 1.5 Hz Br. These coupling constants form a doublet of doublet of doublets. The long range coupling

constants are very small and therefore are unobserved. These spectra are seen at ca. 3.93 ppm in Figures 6b and 7b.

The axial hydrogen at carbon 2 of the cis,cis compounds forms a quartet due to the adjacent methyl. This quartet is then split by an axial-equatorial coupling of 1.3 Hz to form the set of peaks at ca. 3.55 ppm in Figures 6, 6c, 7, and 7c.

The axial hydrogens at carbon 6 appear at ca. 3.45 ppm in Figures 6, 6d, 7, and 7c. In the chloro compound (Figure 6d) J_{aa} equals 6.7 Hz, and J_{gem} equals 6.9 Hz. This forms a doublet of doublets. The axial-equatorial coupling constant (1.7 Hz), then splits each of these peaks to give a doublet of doublet of doublets. In the bromo compound (Figure 7c), J_{aa} and J_{gem} both equal 6.9 Hz to form a triplet. This is split by J_{ae} (1.7 Hz) to form two overlapping triplets.

The assignment of trans,trans-4-chloro-3-ethyl-2-methyltetrahydropyran to Figure 8 and of trans,trans-4-bromo-3-ethyl-2-methyltetrahydropyran to Figure 9 is verified by examination of the spectra. As stated before both of the compounds in these two spectra must be trans between the 2-methyl and the 3-ethyl because of the difference in the chemical shifts of the ethyl methyl at carbon 3. Examination of the high-field spectra, though at times plagued by overlap and sample contamination,

confirms the trans,trans assignment for the chloro and the bromo compounds.

The spectra of the axial hydrogen at carbon 4 and the equatorial hydrogen at carbon 6 are difficult to decipher for both compounds. In the chloro product, the two sets of peaks which represent these two hydrogens overlap as seen in Figures 8 and 8a. In the bromo product, these two sets of peaks are contaminated by impurities in the sample as seen in Figures 9a and 9b which make them very difficult to decipher. Knowing what the spectra of the hydrogens at carbons 4 and 6 should look like, however, it is possible to interpret the overlapping spectra of trans,trans-4-chloro-3-ethyl-2-methyltetrahydropyran in Figure 8a.

The axial hydrogen at carbon 4 has two axial-axial couplings and an axial-equatorial coupling. If the two axial-axial couplings are not equal, and if their difference does not equal J_{ae} , then a doublet of doublet of doublets is expected. If the two axial-axial couplings are not equal, and if their difference does equal J_{ae} , then a doublet, a triplet, and a doublet are expected. If both J_{aa} values are equal, which is often the case, then a split triplet is expected.

The equatorial hydrogen at carbon 6 has a gem coupling, an axial-equatorial coupling, and an equatorial-equatorial coupling. Because this hydrogen has only one wide coupling constant whereas the carbon 4 hydrogen has two wide coupling constants, this spectra

should be narrower than the spectra for the hydrogen at carbon 4. If J_{ae} does not equal J_{ee} in the spectra for the equatorial hydrogen at carbon 6, then a doublet of doublet of doublets is expected. If J_{ae} equals J_{ee} , then two triplets are expected.

Upon examination of the spectra in Figure 8a, it was decided that the axial hydrogen at carbon 4 is represented by a split triplet with two equal J_{aa} values of 6.8 Hz and a J_{ae} value of 2.8 Hz. The equatorial hydrogen at carbon 6 is represented by a doublet of doublet of doublets with $J_{gem} = 7.1$ Hz and J_{ae} and J_{ee} values of 2.8 and 1.9 Hz. The two larger peaks in the spectra are due to the overlap of the two sets of peaks. These two sets of peaks in the bromo compound (Figures 9a and 9b) are indistinguishable from the overlapping impurities.

The spectra of the axial hydrogens at carbon 6 are found at ca. 3.4 ppm in Figures 8, 8b, 9, and 9c. These hydrogens have a gem coupling, an axial-axial coupling, and an axial-equatorial coupling. In the chloro compound these coupling constants are 7.3, 6.9, and 1.3 Hz, respectively. This forms a doublet of doublet of doublets with central overlap. Impurities in the bromo compound make the spectra difficult to be seen, however the four tallest peaks represent a doublet of doublets formed by J_{gem} (8.5 Hz) and J_{aa} (6.9 Hz). The spectra of the bromo compound is too narrow to see the axial-axial coupling.

The spectra of the axial hydrogen at carbon 2 is easily discernible in Figures 8, 8c, 9, and 9c for both the chloro and the bromo compounds. This hydrogen's nearest neighbors are a methyl group and an axial hydrogen. The axial-axial coupling constant of 5.7 Hz splits the quartet formed by the methyl group to produce two overlapping quartets as seen in Figures 8c and 9c. The coupling constant for the quartet is 3.6 Hz.

In these cyclizations of an acetal using a Lewis acid, the cis acetals produced the cis products and the trans acetals produced the trans products. According to Johnson the acetals should cyclize, but because of a lack of nucleophiles a planar carbocation should form which then can be attacked from either side to produce both cis and trans products¹⁷. According to Traynham²⁹ if the cyclized carbocation is free from the stereochemical influence of the leaving group, then there will be a preference for nucleophilic attack from an axial direction. This would lead to a "cis-addition" across the double bond. We do not see a "cis-addition" or a mixture of isomers. Rather all the products seem to stem from a trans-addition. For this reason there must be a mechanism which places the nucleophile in a position to facilitate trans-addition before a planar cation has time to form. An intermediate where the titanium complexes with the oxygens in the acetal would not only aid in initiation of the reaction / (Scheme 37), but would also place a halogen ion in a

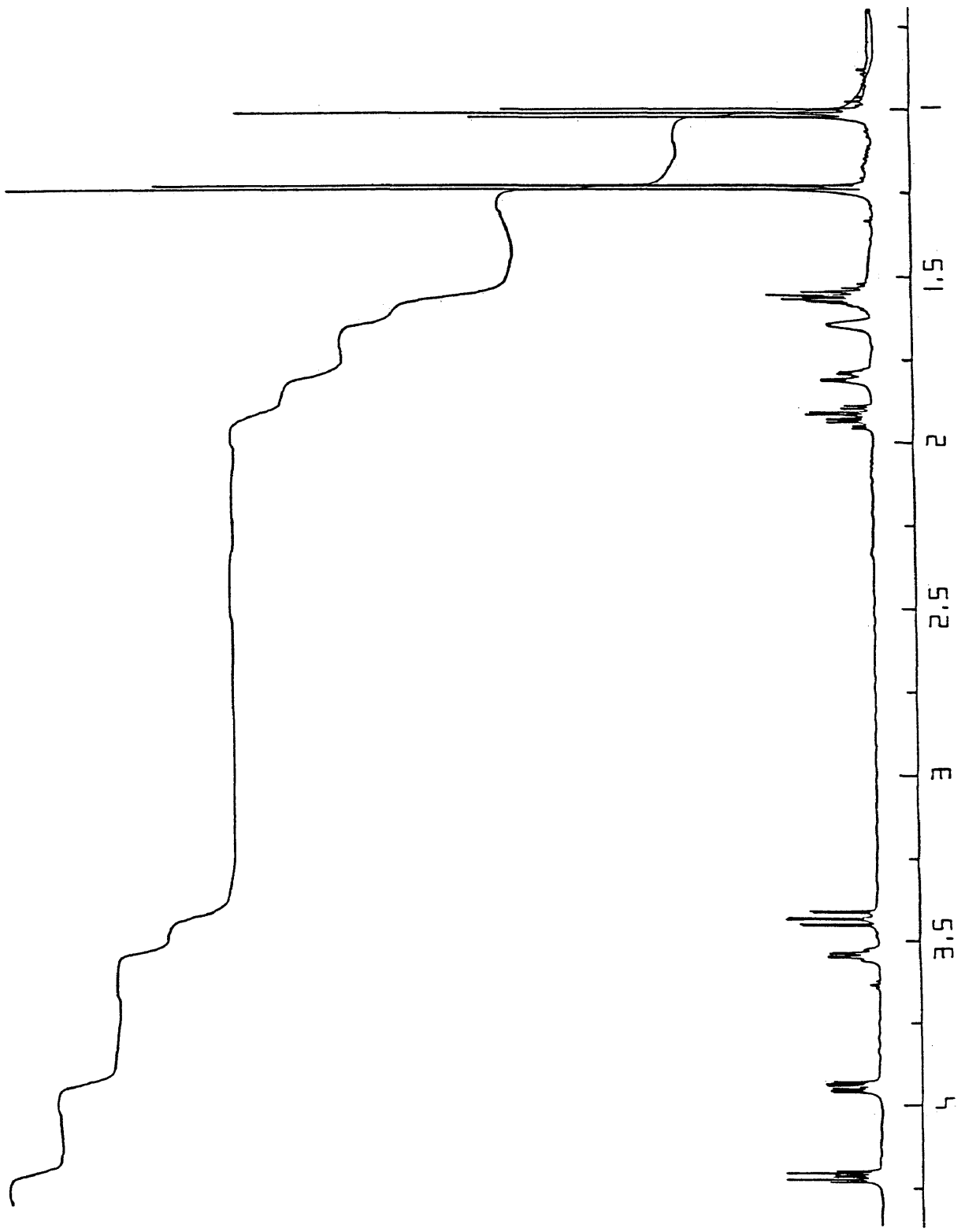


Figure 6. ^1H NMR spectra of cis,cis-4-chloro-3-ethyl-2-methyltetrahydropyran at 60 MHz

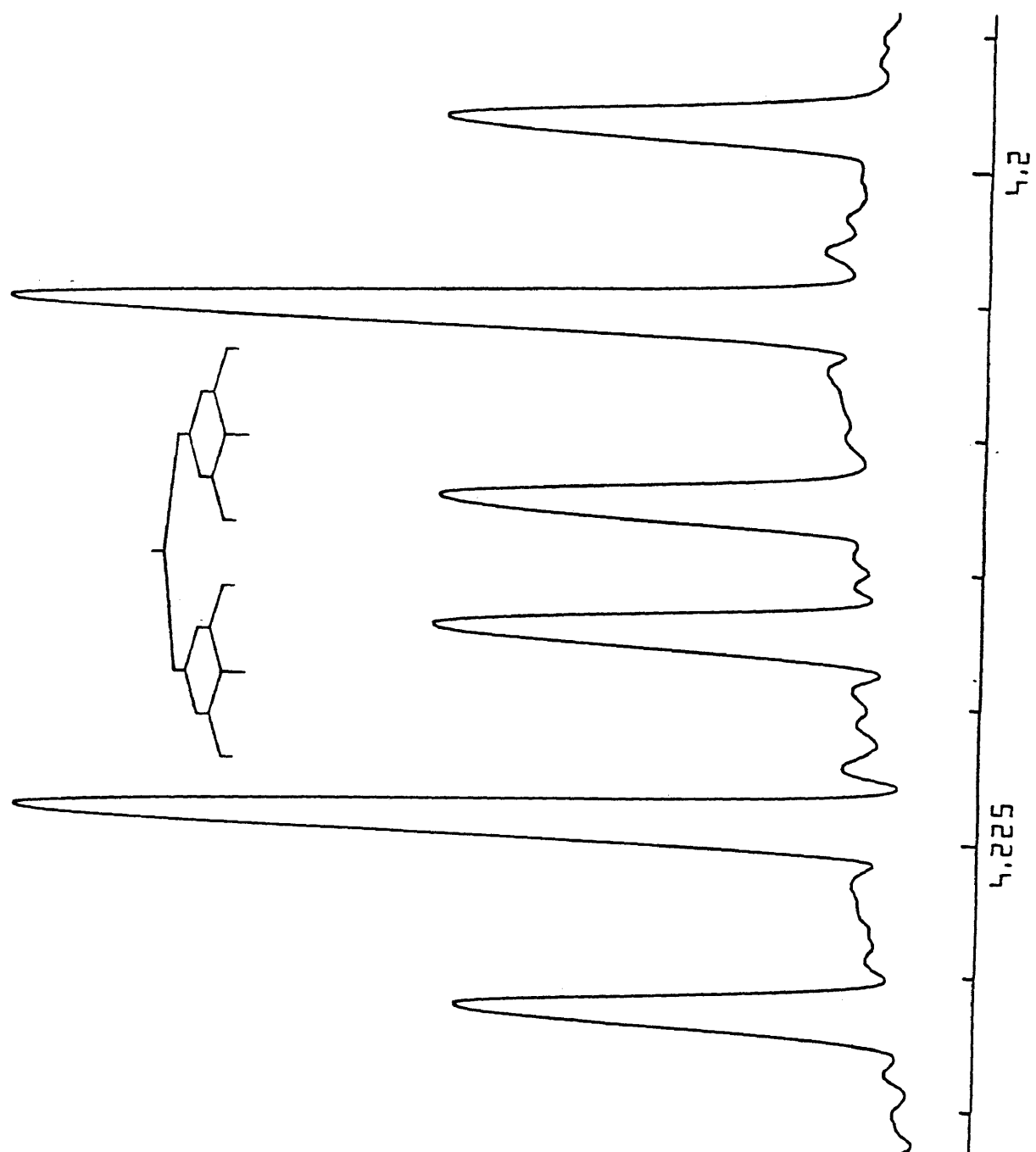


Figure 6a. Expanded ^1H NMR spectra of the axial hydrogen at carbon 4 of *cis,cis*-4-chloro-3-ethyl-2-methyltetrahydropyran at 360MHz

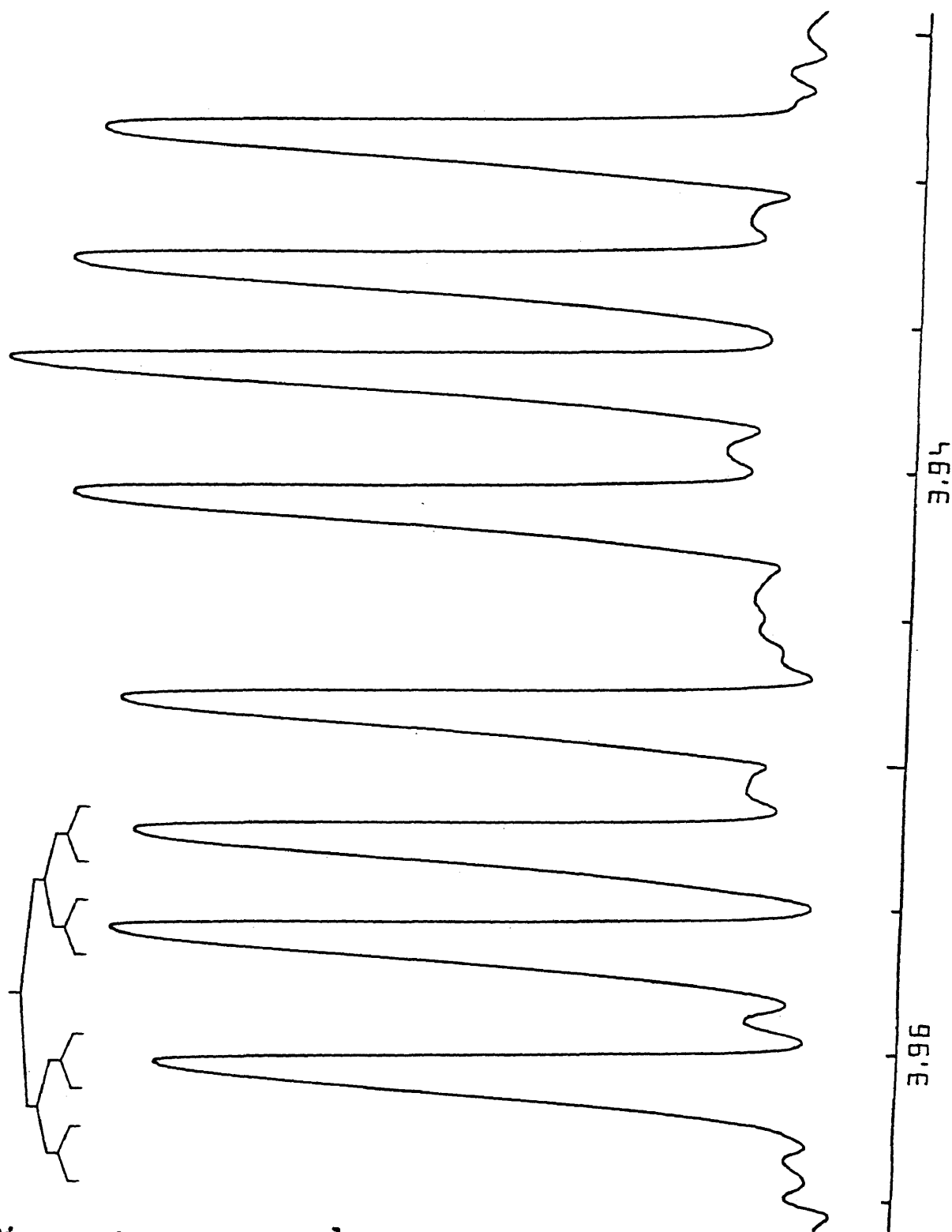


Figure 6b. Expanded ^1H NMR spectra of the equatorial hydrogen at carbon 6 of cis,cis-4-chloro-3-ethyl-2-methyltetrahydropyran at 360MHz

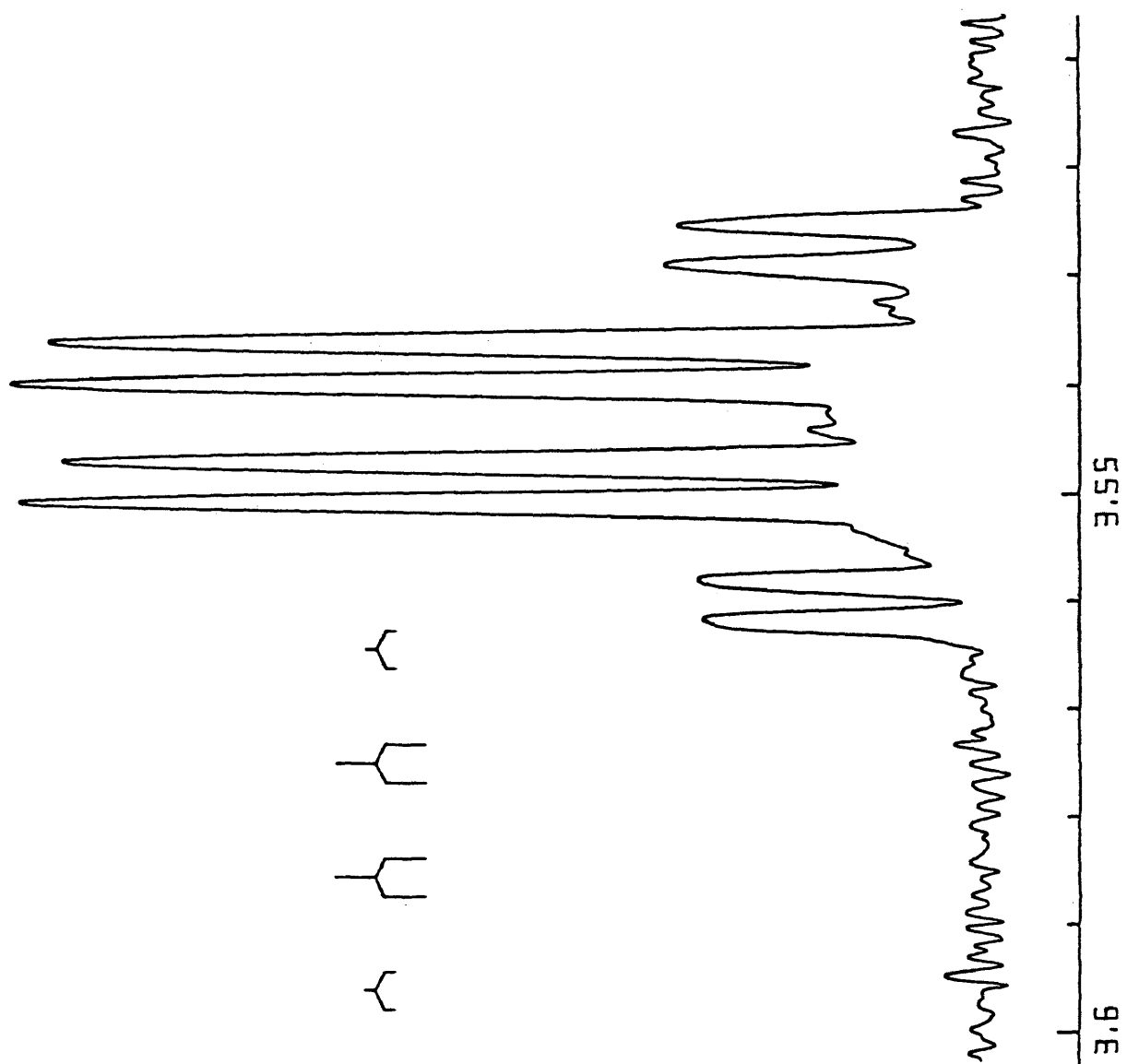


Figure 6c. Expanded ^1H NMR spectra of the axial hydrogen at carbon 2 of cis,cis-4-chloro-3-ethyl-2-methyltetrahydropyran at 360MHz

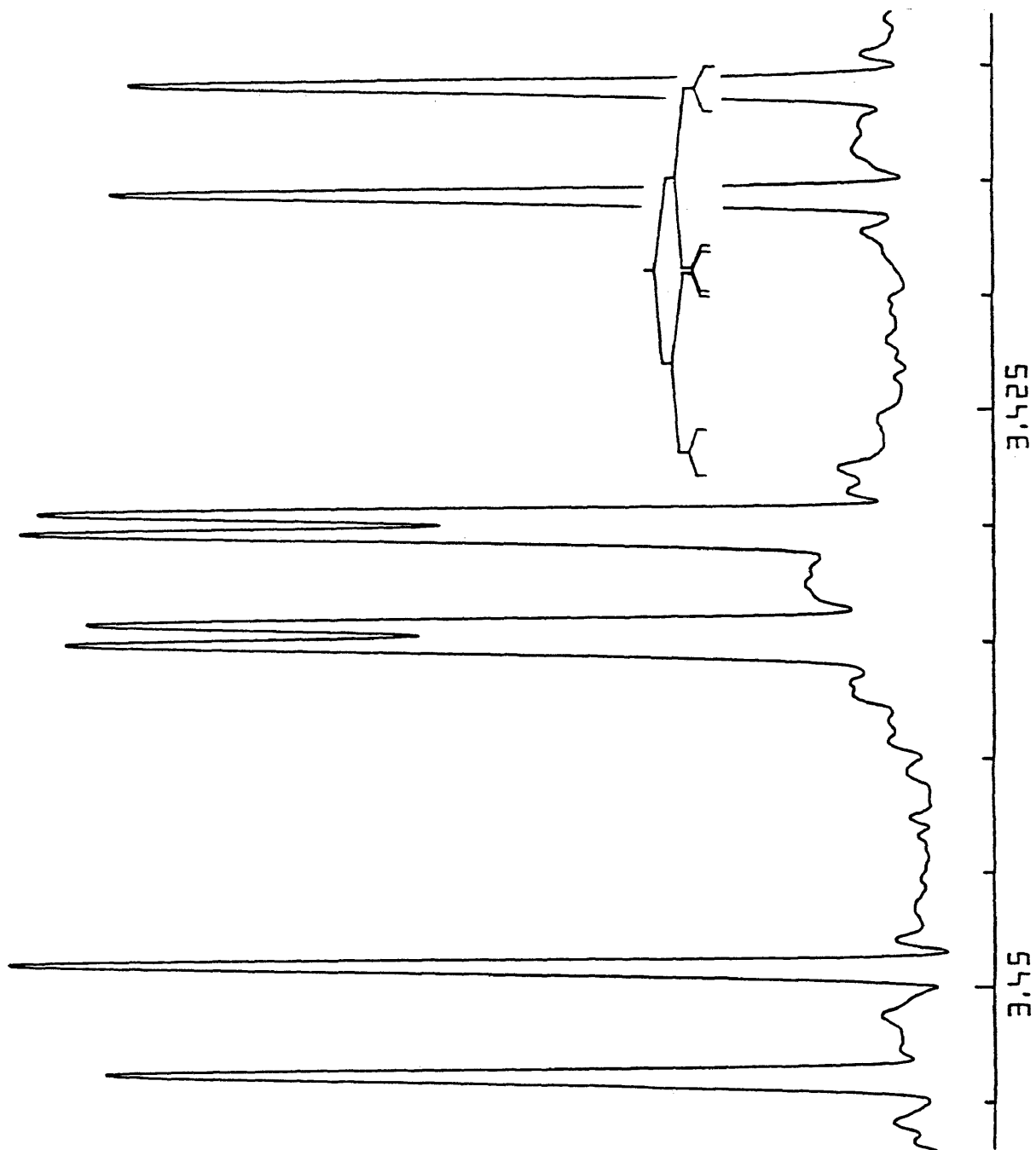


Figure 6d. Expanded ^1H NMR spectra of the axial hydrogen at carbon 6 of cis,cis-4-chloro-3-ethyl-2-methyltetrahydropyran at 360MHz

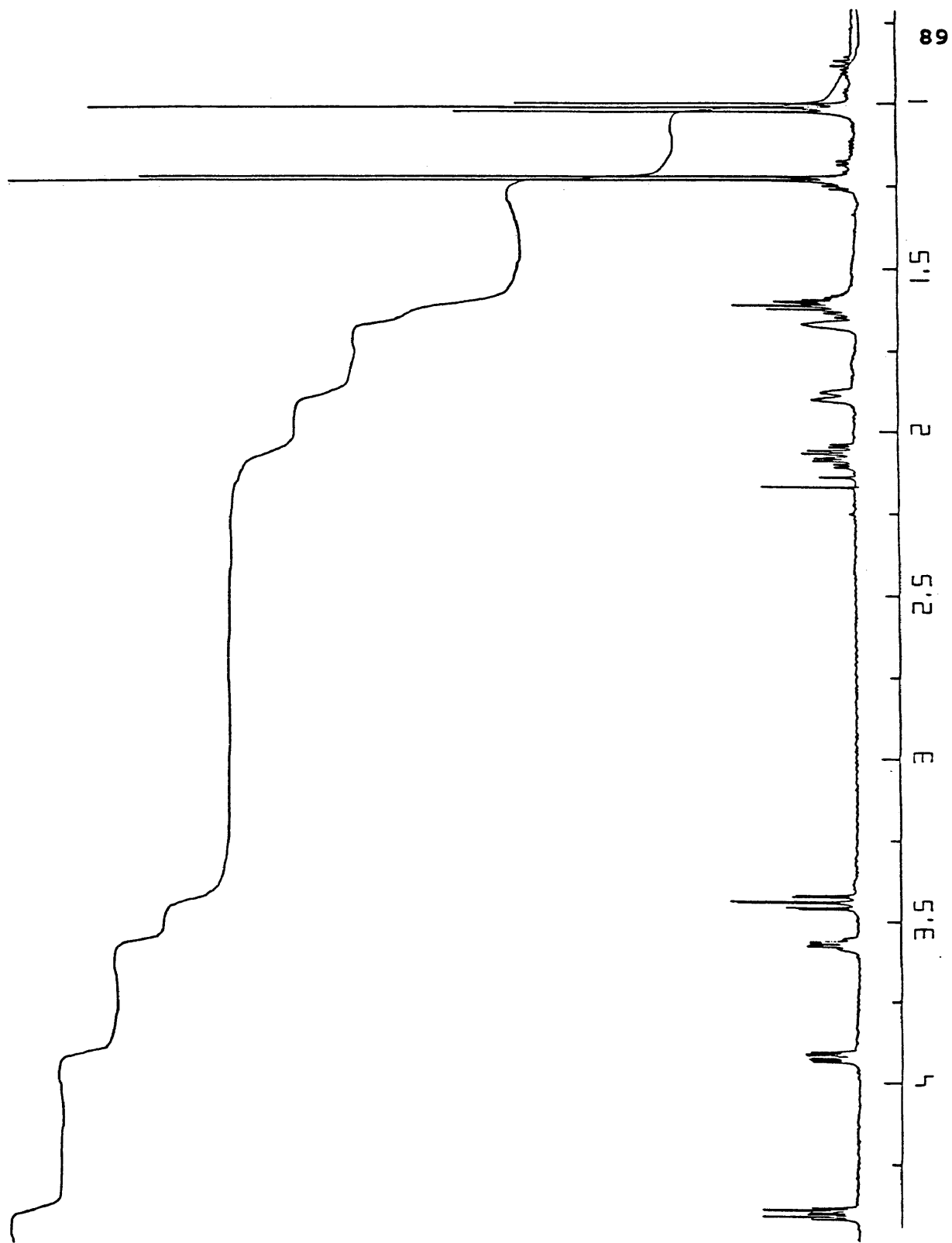


Figure 7. ^1H NMR spectra of cis,cis-4-bromo-3-ethyl-2-methyltetrahydropyran at 60 MHz

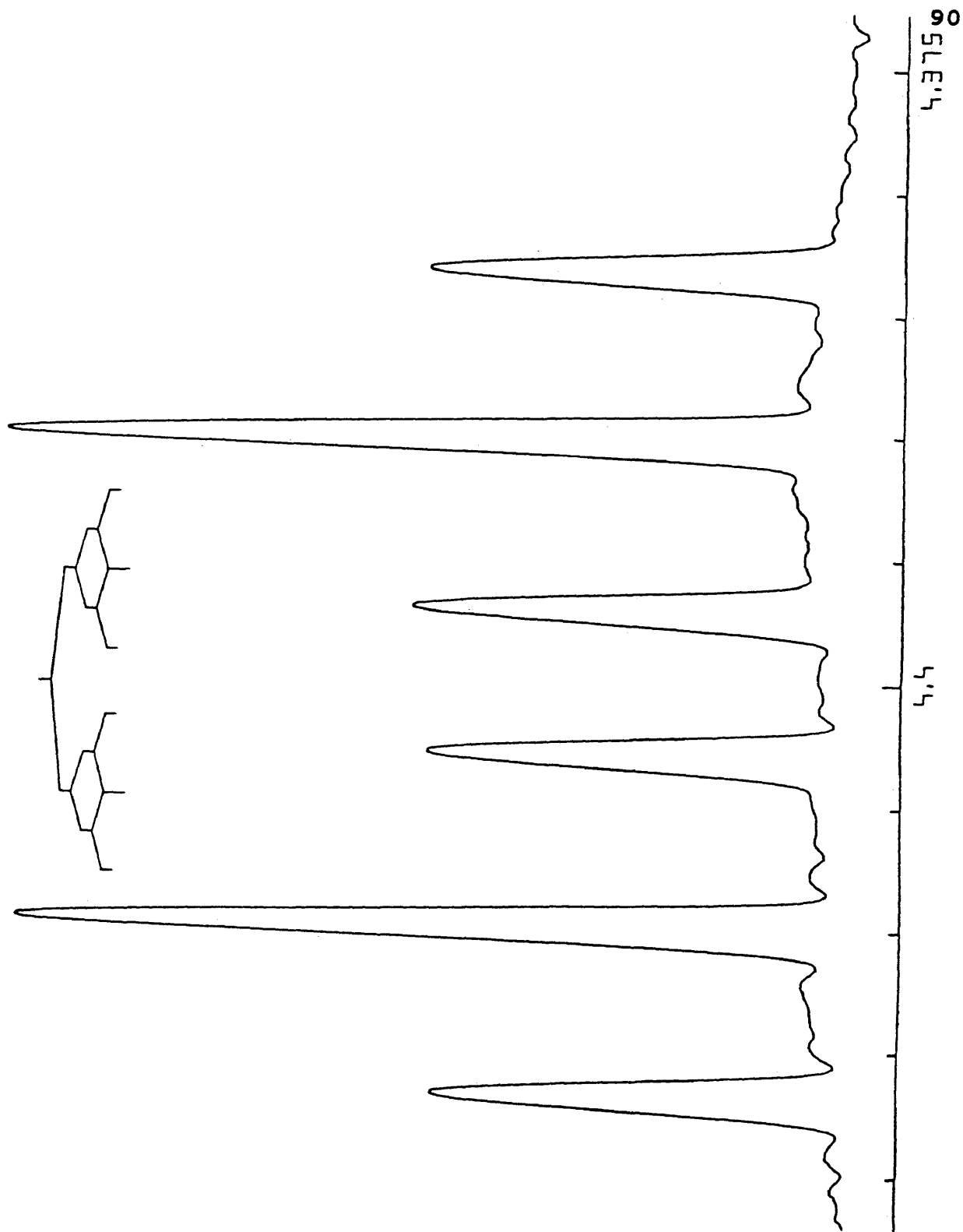


Figure 7a. Expanded ^1H NMR spectra of the axial hydrogen at carbon 4 of *cis,cis*-4-bromo-3-ethyl-2-methyltetrahydropyran at 360MHz

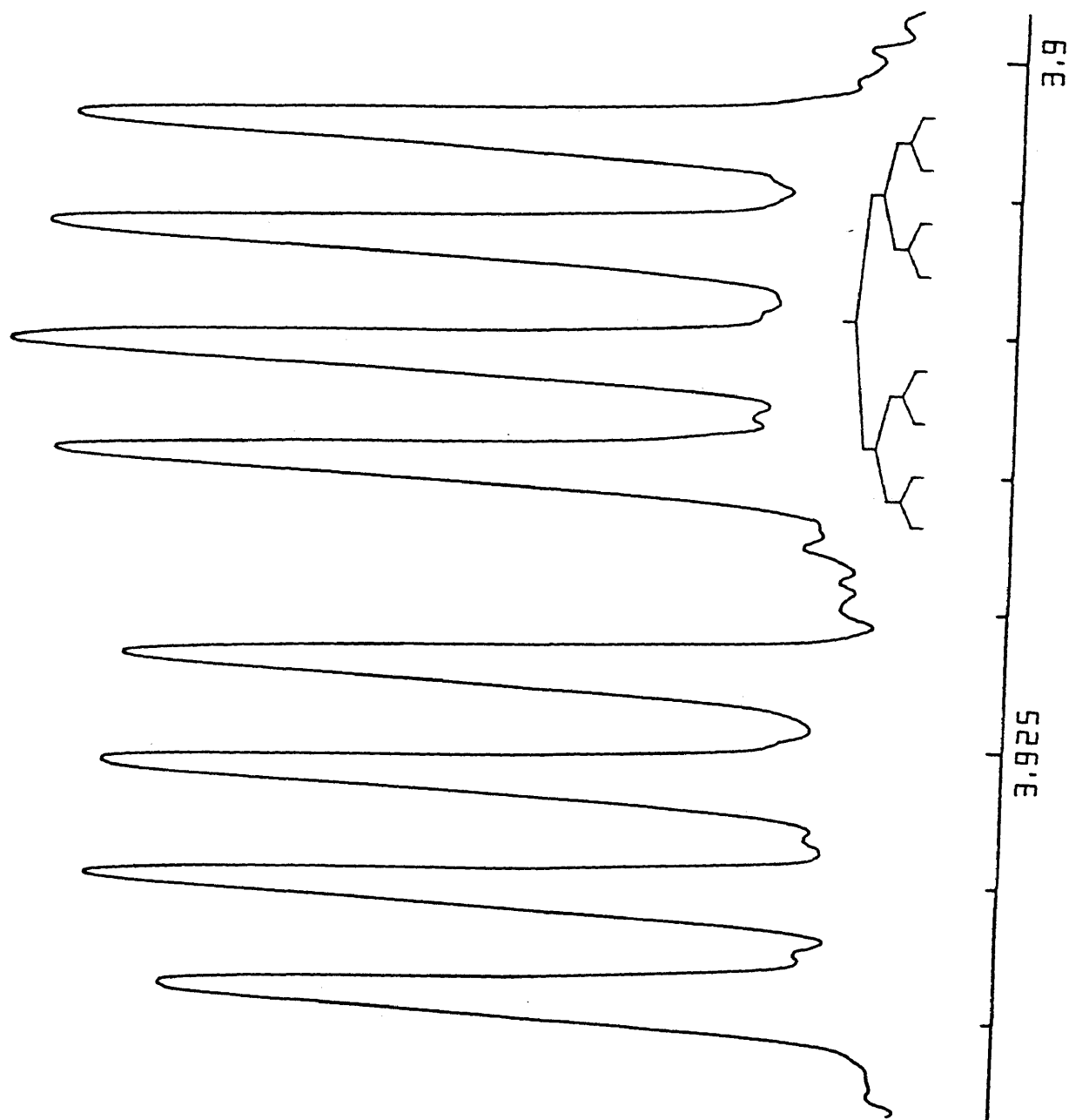


Figure 7b. Expanded ^1H NMR spectra of the equatorial hydrogen at carbon 6 of cis,cis-4-bromo-3-ethyl-2-methyltetrahydropyran at 360MHz

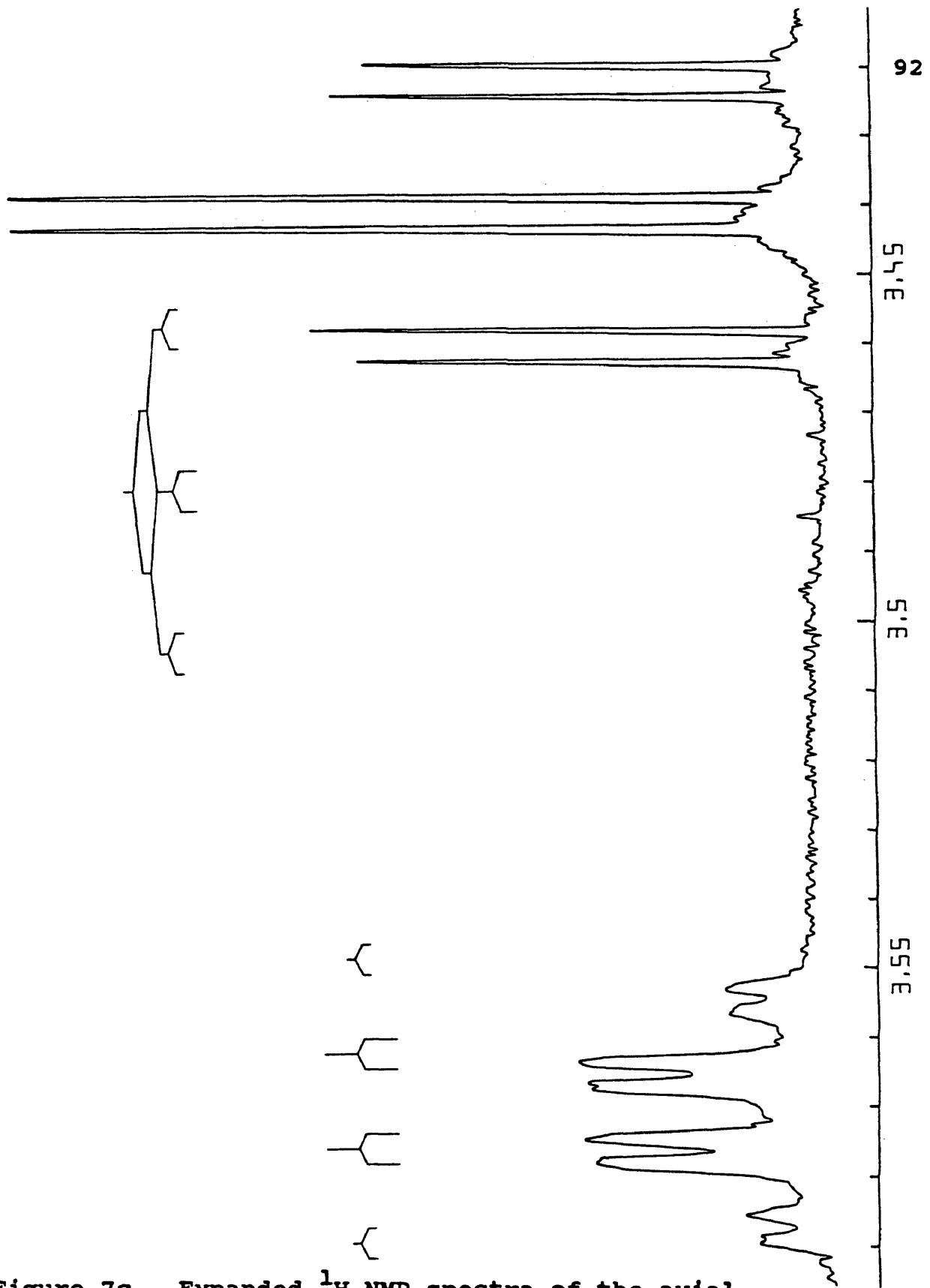


Figure 7c. Expanded ^1H NMR spectra of the axial hydrogens at carbons 2 and 6 of *cis,cis*-4-bromo-3-ethyl-2-methyltetrahydropyran at 360MHz

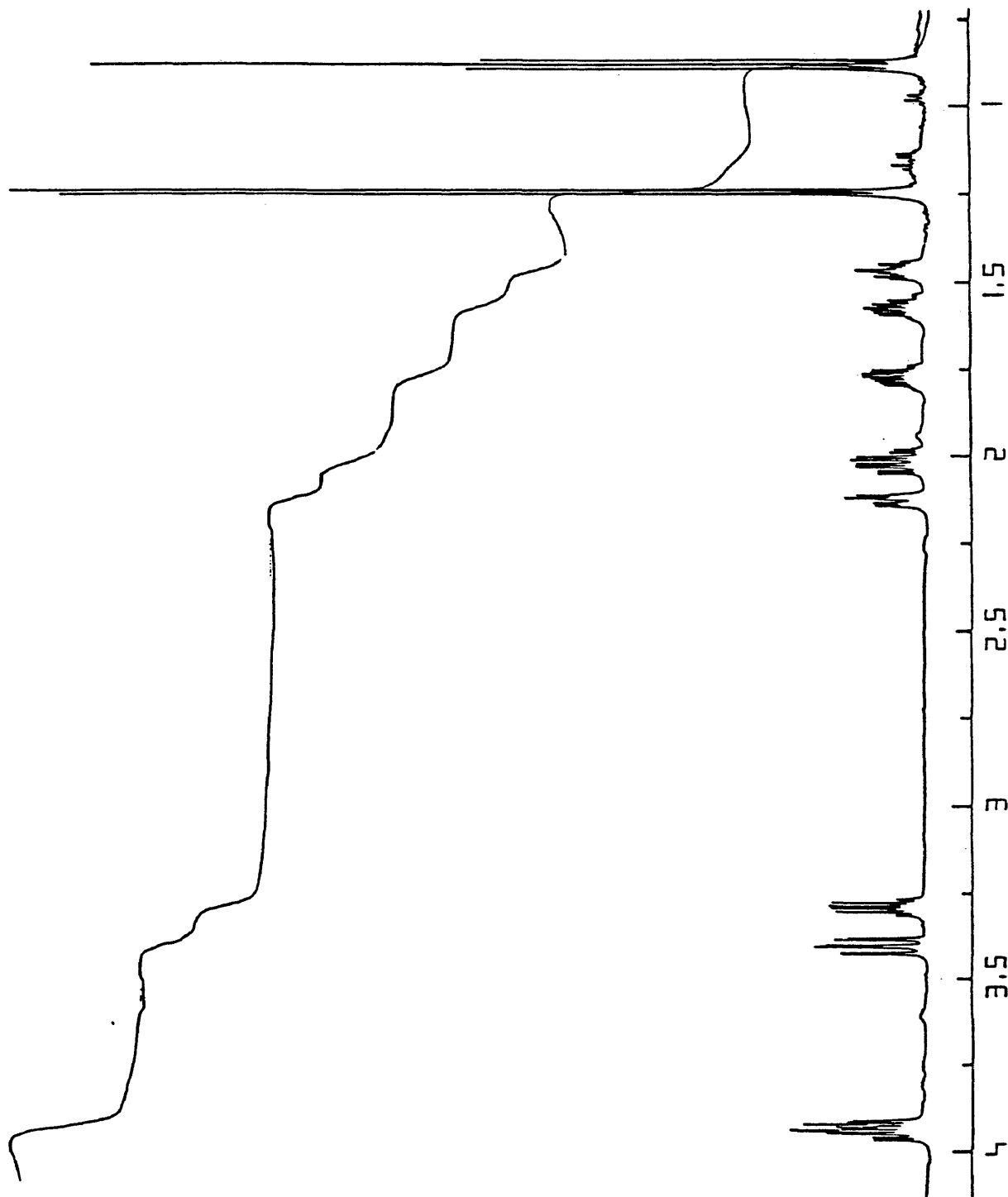


Figure 8. ^1H NMR spectra of trans,trans-4-chloro-3-ethyl-2-methyltetrahydropyran at 60 MHz

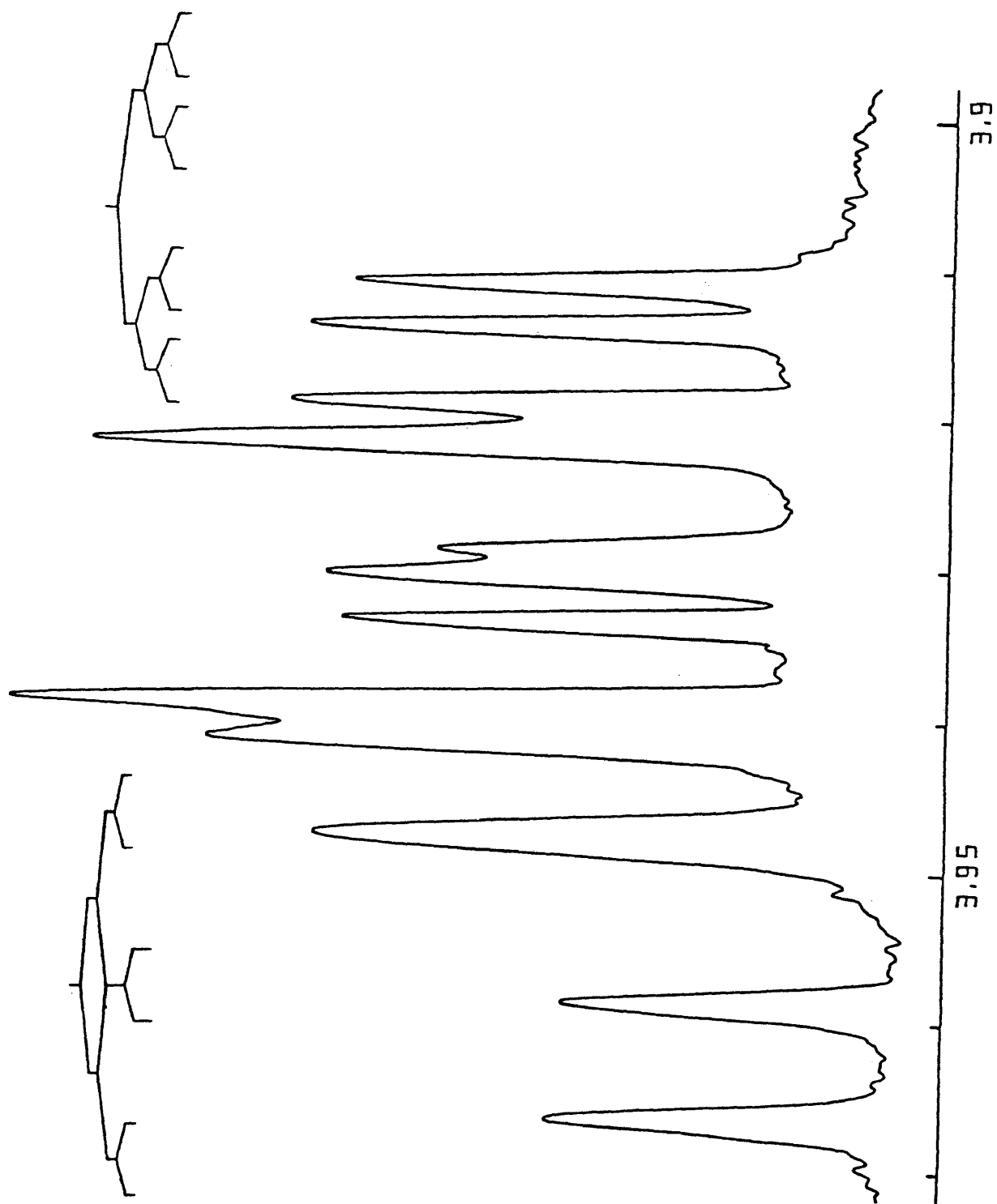


Figure 8a. Expanded ^1H NMR spectra of the axial hydrogen at carbon 4 and the equatorial hydrogen at carbon 6 of trans,trans-4-chloro-3-ethyl-2-methyltetrahydropyran at 360 MHz

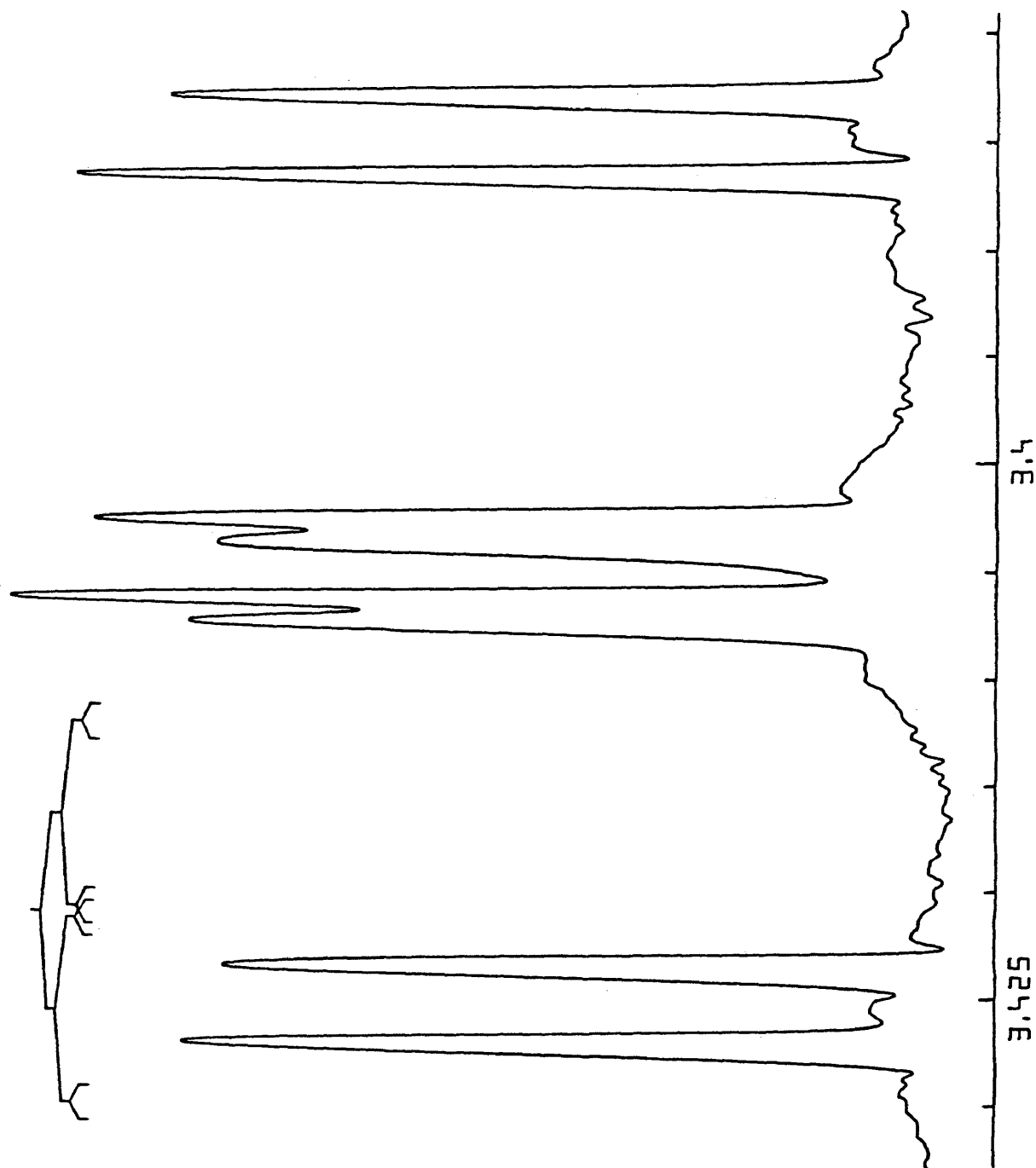


Figure 8b. Expanded ^1H NMR spectra of the axial hydrogen at carbon 6 of trans,trans-4-chloro-3-ethyl-2-methyltetrahydropyran at 360 MHz

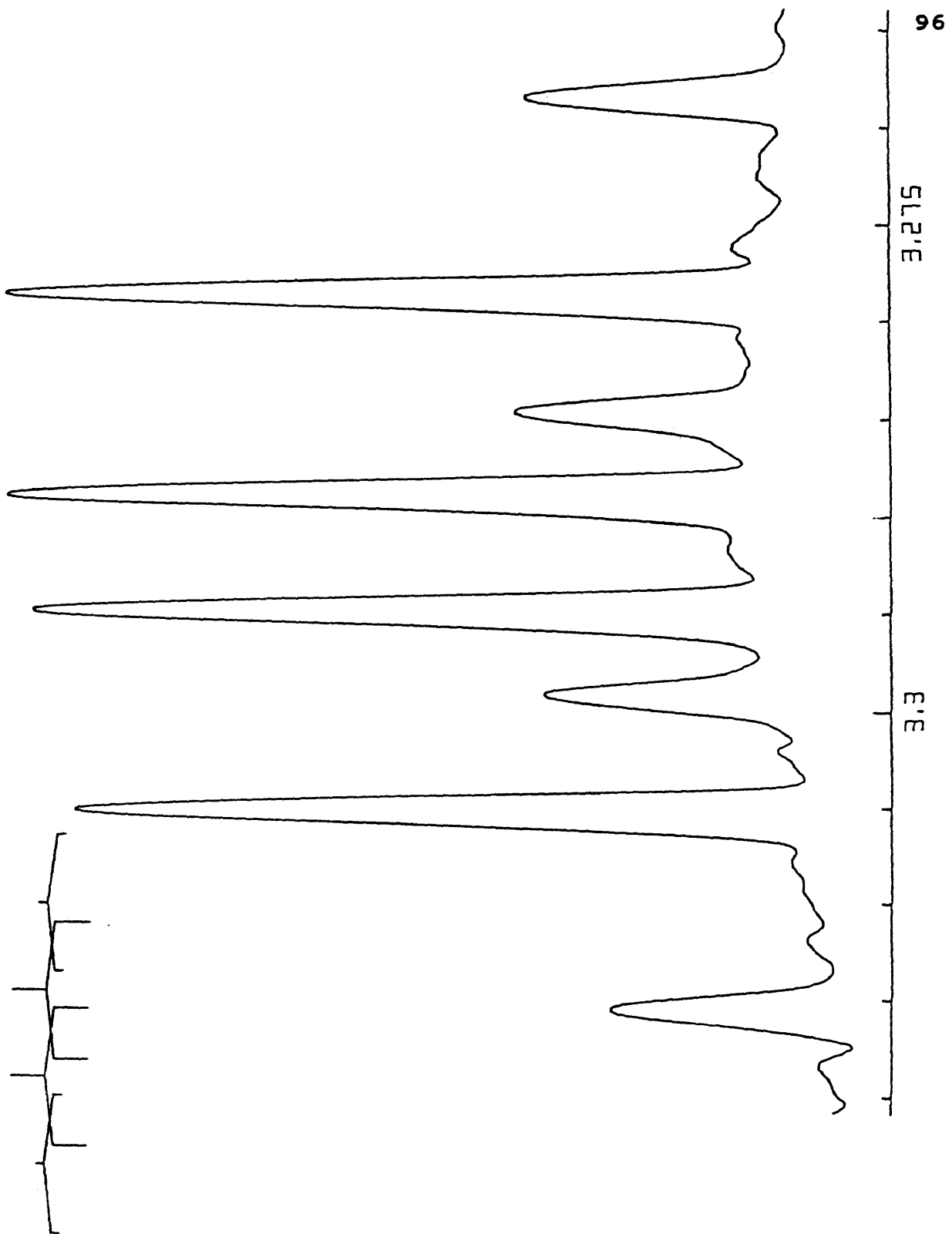


Figure 8c. Expanded ^1H NMR spectra of the axial hydrogen at carbon 2 of trans,trans-4-chloro-3-ethyl-2-methyltetrahydropyran at 360 MHz

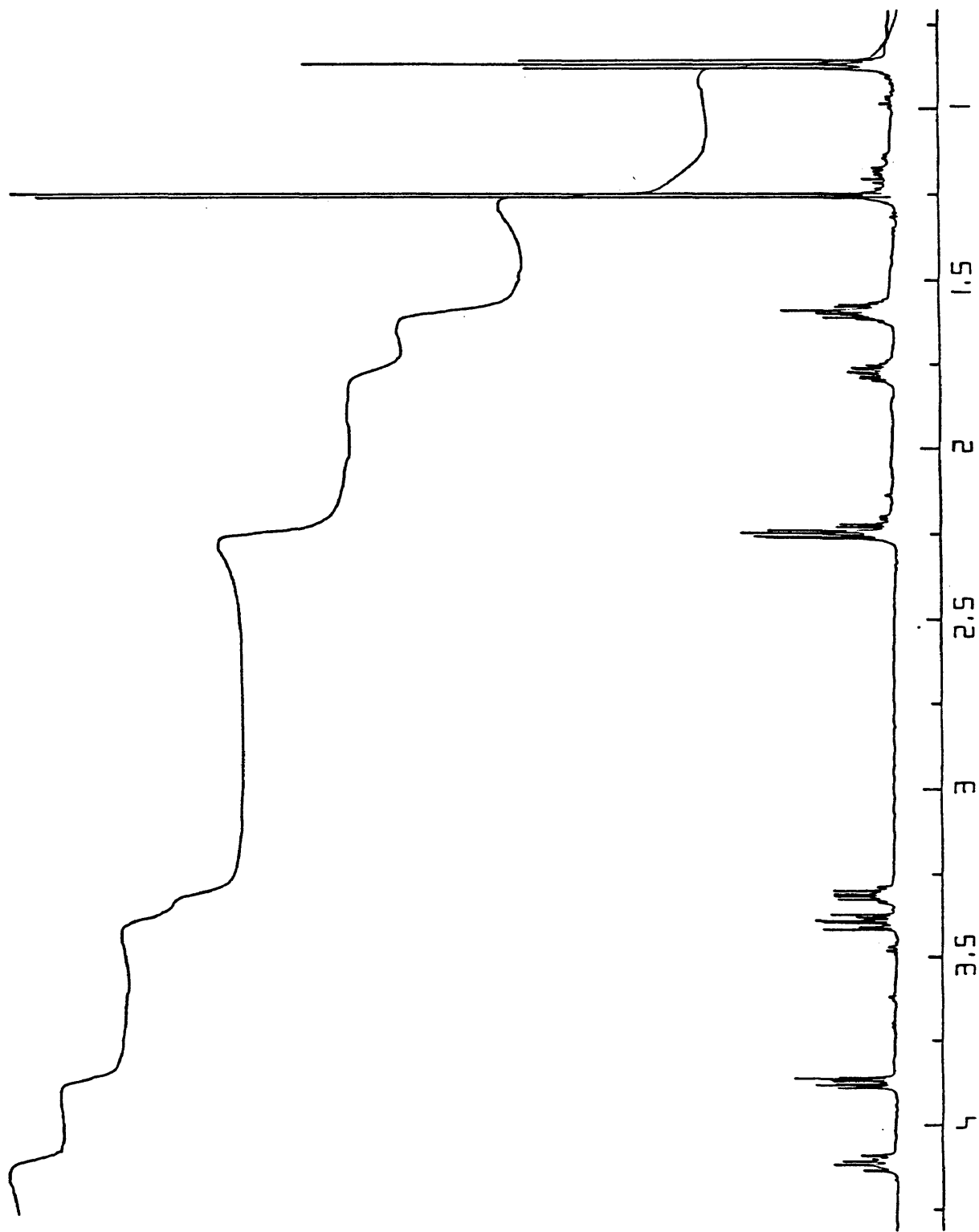


Figure 9. ^1H NMR spectra of trans,trans-4-bromo-3-ethyl-2-methyltetrahydropyran at 60 MHz

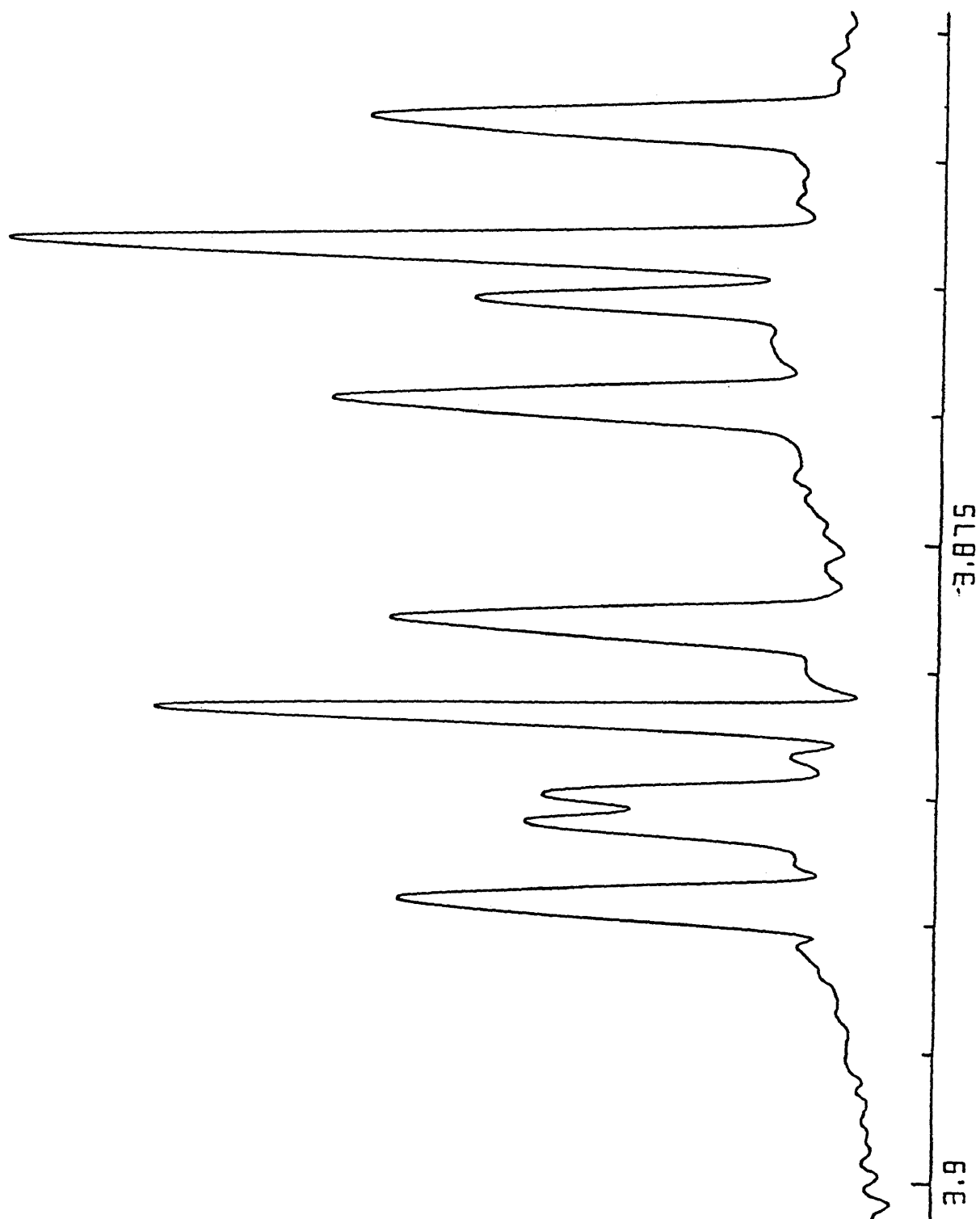


Figure 9a. Expanded ^1H NMR spectra of the axial hydrogen at carbon 4 of trans,trans-4-bromo-3-ethyl-2-methyltetrahydropyran at 360 MHz

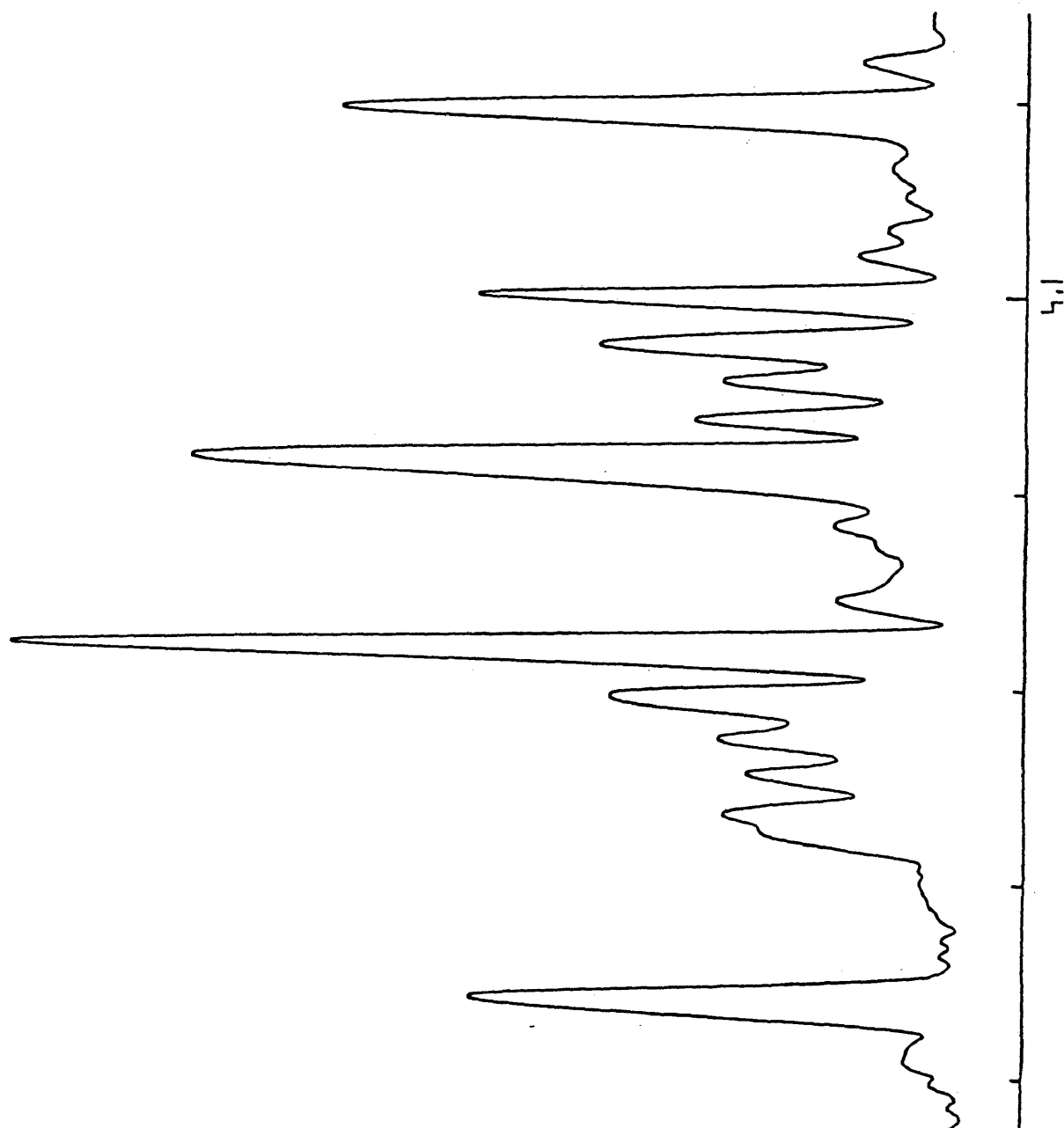


Figure 9b. Expanded ^1H NMR spectra of the equatorial hydrogen at carbon 4 of trans,trans-4-bromo-3-ethyl-2-methyltetrahydropyran at 360 MHz

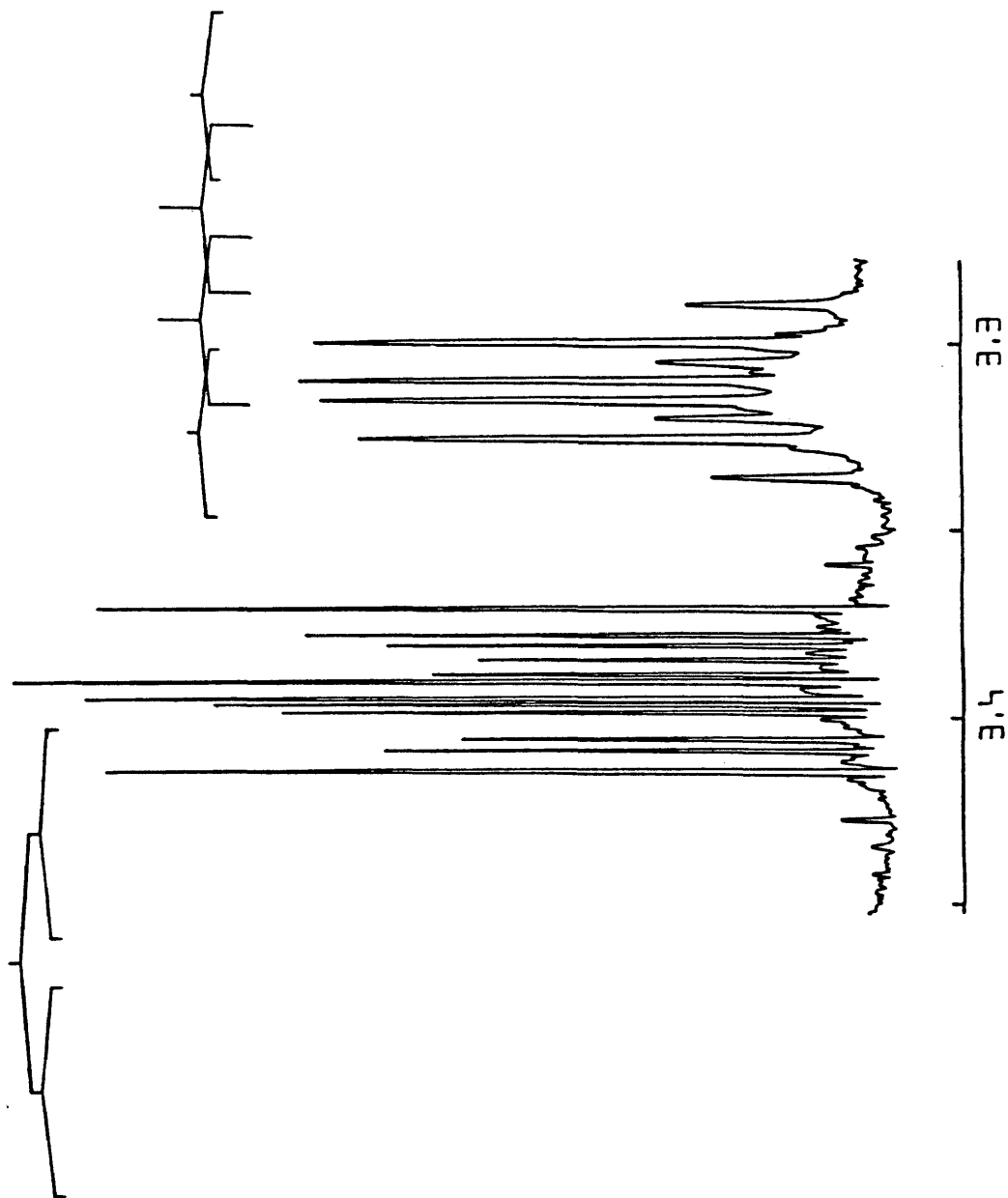
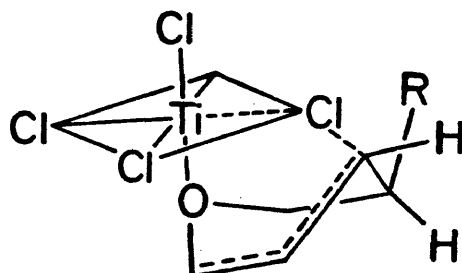


Figure 9c. Expanded ^1H NMR spectra of the axial hydrogens at carbons 2 and 6 of trans,trans-4-bromo-3-ethyl-2-methyltetrahydropyran at 360 MHz

strategic position to act as a terminating nucleophile in the cyclization reaction. This would allow trans-addition and produce a stereospecific reaction for the production of tetrahydropyrans.



Titanium-acetal complex

A titanium-acetal complex which allows trans-addition explains the stereospecificity between the 4-halogen and the 3-ethyl substituents in the MEM and the ethyl vinyl ether cyclizations. However, it does not explain the stereoselectivity between the 3-ethyl and the 2-methyl substituents in the ethyl vinyl ether cyclization. According to our expectations there should be four isomers for the cyclization of the ethyl vinyl ether acetals: the trans,trans isomer, the trans,cis isomer, the cis,cis isomer, and the cis,trans isomer. Only two isomers, however, the trans,trans isomer and the cis,cis isomer are formed. According to Johnson^{7,14,15} in his cyclizations using an external acetal, the pre-cyclized cation assumes a chair conformation with the OR group (the leftover acetal fragment) assuming either an axial or an equatorial position. The ratio of OR groups assuming the

axial position over the equatorial position is dependent on the solvent¹⁵. In our study there is a methyl substituent off the carbocation rather than an OR substituent. Our system is also cyclizing to form a tetrahydropyran rather than a cyclohexane. If our pre-cyclized carbocation also assumes a chair conformation, then we have a system similar to our cyclized tetrahydropyran but with the capability of rotating the methyl substituent on the oxocarbocation to its most stable position. According to the conformational energy of a 2-methyl substituent on a tetrahydropyran ($-\Delta G^\circ = 2.86$ kcal/mole), the carbocation should rotate the methyl so that it assumes an equatorial position. This is what happens. However, because the carbocation has not cyclized yet, no other substituents are affected. The positioning of the methyl group in a pseudo-equatorial position also minimizes the 1,3-diaxial interactions by placing only hydrogens in the axial positions. Upon cyclization via trans-addition, only the cis,cis and the trans,trans isomers are formed from their respective acetals.

II. THE CYCLIZATION OF ACETALS DERIVED FROM ALKYNOLS TO PRODUCE TETRAHYDROFURANS

Johnson's work with polyenes indicated that a cyclopentane could be produced by using a styryl terminator^{10, 19}, a 1,1-disubstituted alkene⁹,

or an internal alkyne^{23, 24}. Each of these, upon cyclization, produces a cation which is more stable when the polyene forms a 5-membered ring than when the polyene forms a 6-membered ring.

In the case of a styryl terminator, both cyclized carbocations are secondary carbocations, so the six-membered ring (which is more stable than the five-membered ring) would be expected as the product. However, in the six-membered ring the phenyl group is too far away from the carbocation to stabilize it, whereas in the five-membered ring, the phenyl group is adjacent to the carbocation and thus can distribute the positive charge around the phenyl ring. Because of the extra stabilization of the carbocation by the phenyl ring, only five-membered rings are formed when using a styryl terminator.

When a 1,1-disubstituted alkene is used, the carbocation formed with the cyclohexane is a secondary carbocation. The carbocation formed upon the cyclization of a five-membered ring, however, is a tertiary carbocation. Because tertiary carbocations are much more stable than secondary carbocations, only the five-membered ring with the tertiary carbocation is formed.

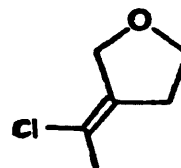
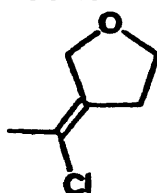
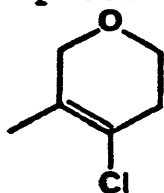
In both of the above cyclizations involving a styryl terminator and a 1,1-disubstituted alkene, cyclopentanes are the only products formed^{9, 10, 19}. However, after cyclization and before termination by a nucleophile, these two systems tend to rearrange via 1,2-methyl and 1,2-hydride

shifts and deprotonations. These can lead to unexpected final products as seen in Schemes 21, 22, 23, and 32. This problem, however, does not seem to occur in cyclizations using an internal alkyne^{23,24}.

In the cyclization of internal alkynes either a six-membered ring with an internal, bent vinyl cation or a five-membered ring with an external, linear vinyl cation is formed. Linear vinyl cations are more stable than bent vinyl cations, but six-membered rings are more stable than five-membered rings^{13, 21}. Because the two energy differences are approximately equal but opposite in sign, both five and six-membered rings are expected.

Our goal was to make a tetrahydrofuran. To avoid undesired rearrangements, we prepared the acetals from alkynols. We used internal triple bonds because terminal triple bonds only produce dihydropyrans.

Upon cyclization of the acetals of 3-pentyn-1-ol, which contain a methylacetylenic terminator, 4-chloro-3-methyl-(2,5)-dihydropyran and the (E) and the (Z) isomers of 3-(1-chlorovinyl)tetrahydrofuran (as seen below, respectively) are expected. The acetals of



4-phenyl-3-butyn-1-ol, which contain a phenylacetylenic terminator, however, are expected to produce only tetrahydrofurans upon cyclization. The six-membered ring

products are not expected in this case because the phenyl substituent is too far removed from the carbocation to stabilize it. In the five-membered ring product, however, the phenyl substituent is adjacent to the carbocation and can therefore stabilize the charge by delocalizing it around the ring.

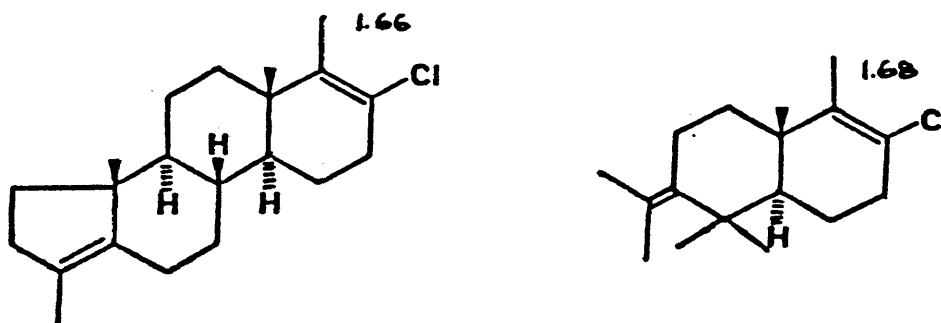
The cyclization of the MEM acetals of 3-pentyn-1-ol and 4-phenyl-3-butyn-1-ol with TiCl_4 or stannous chloride, (SnCl_4), is expected to give both the (E) and the (Z) isomers of the tetrahydrofuran. Cyclization of the ethyl vinyl ether acetals, however, are expected to give mainly the (E) isomer because of the interference of the 2-methyl with the incoming chloride ion.

The acetals of the alkynols were prepared in a similar fashion to the acetals of the alkenols. The preparation of the ethyl vinyl ether acetal of 4-phenyl-3-butyn-1-ol, however, did not form the expected acetal but polymerized instead.

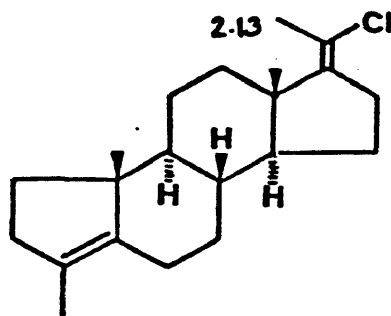
The acetals were cyclized by reacting them with TiCl_4 or SnCl_4 until completion as observed on the capillary GC. At this time the reactions were quenched with methanol and hydrochloric acid. Yields were determined for the products, and the products were identified by ^1H and ^{13}C NMR. These reactions were run at several temperatures to determine the optimum temperature.

Upon cyclization of 5-(2-methoxyethoxy)methoxy-2-pentyne, three products were

observed by gas chromatography. These have been identified as 4-chloro-3-methyl-(2,5)-dihydropyran and the (E) and (Z) isomers of 3-(1-chlorovinyl)tetrahydrofuran, respectively, by ^1H and ^{13}C NMR. The ^1H NMR for the first GLC peak is seen in Figure 10. It is identified as the pyran by the absorption at 1.68 ppm. According to



Johnson^{8, 25}, the vinylic methyl group of similar pyrans absorbs at 1.66 to 1.68 ppm. The ethylenic hydrogens of similar furans, however, absorb further downfield at 2.13 ppm as in the compound below.



The first absorptions in Figures 11 and 12 (1.98 and 2.09 ppm, respectively) identify these two compounds as furans. Each of these absorptions are multiplets due to the

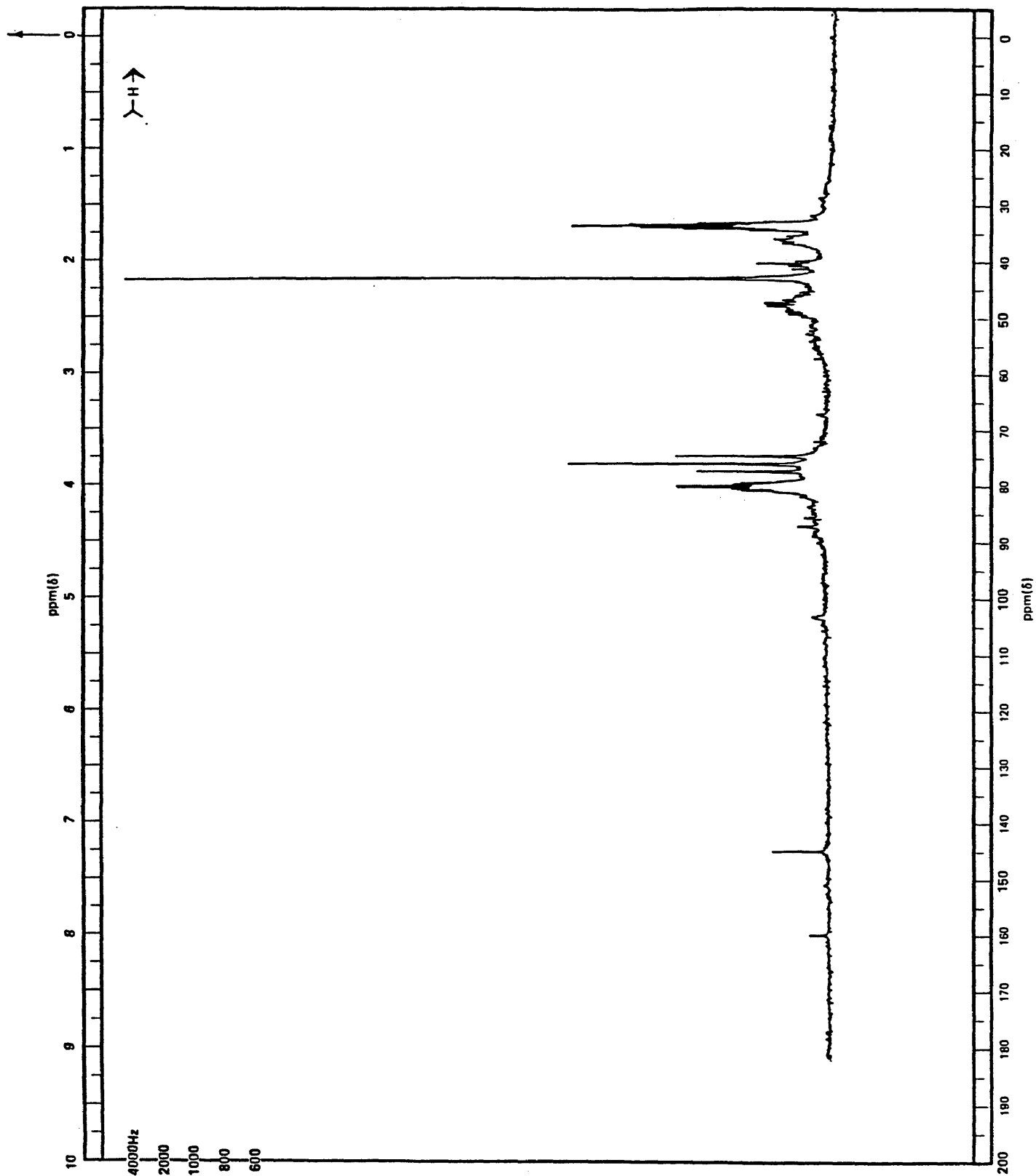


Figure 10. ^1H NMR spectra of 4-chloro-3-methyl-(2,5)-dihydropyran at 60 MHz

long range coupling across the double bond. In Figure 10 the vinylic hydrogens complex with the hydrogens on carbon 5. In Figures 11 and 12, the ethylenic hydrogens couple with the hydrogens on carbons 2 and 4.

Other absorptions in these spectra include the multiplet at 2.38 ppm (Figure 10), 2.60 ppm (Figure 11) and 2.50 ppm (Figure 12) which represents the methylene at carbon 5 in the pyran and the methylene at carbon 4 in the furans. These hydrogens also experience long range coupling through the double bond. The expansion of the spectra in Figure 12 shows a triplet of quartets. This is due to the coupling of the methylene hydrogens at carbon 5 to form a triplet which is then split by the long range methyl coupling to form three quartets.

The obvious triplets at 3.80, 3.88, and 3.95 ppm (Figures 10, 11, and 12, respectively) represent the methylenes at carbon 6 in the pyran and at carbon 5 in the furans. There is no long range coupling.

The multiplets at 4.00, 4.25, and 4.32 ppm (Figures 10, 11, and 12, respectively) represent the methylenes at carbon 1. These also experience long range couplings through the double bond.

The ^{13}C NMR spectras for the first and third GLC peaks are seen in Figures 13 and 14 respectively, The absorptions for two vinylic carbons in the pyran are found at 123.5 and 128.6 ppm in Figure 13. The absorptions for the carbons adjacent to the oxygens are found at 65.4 and

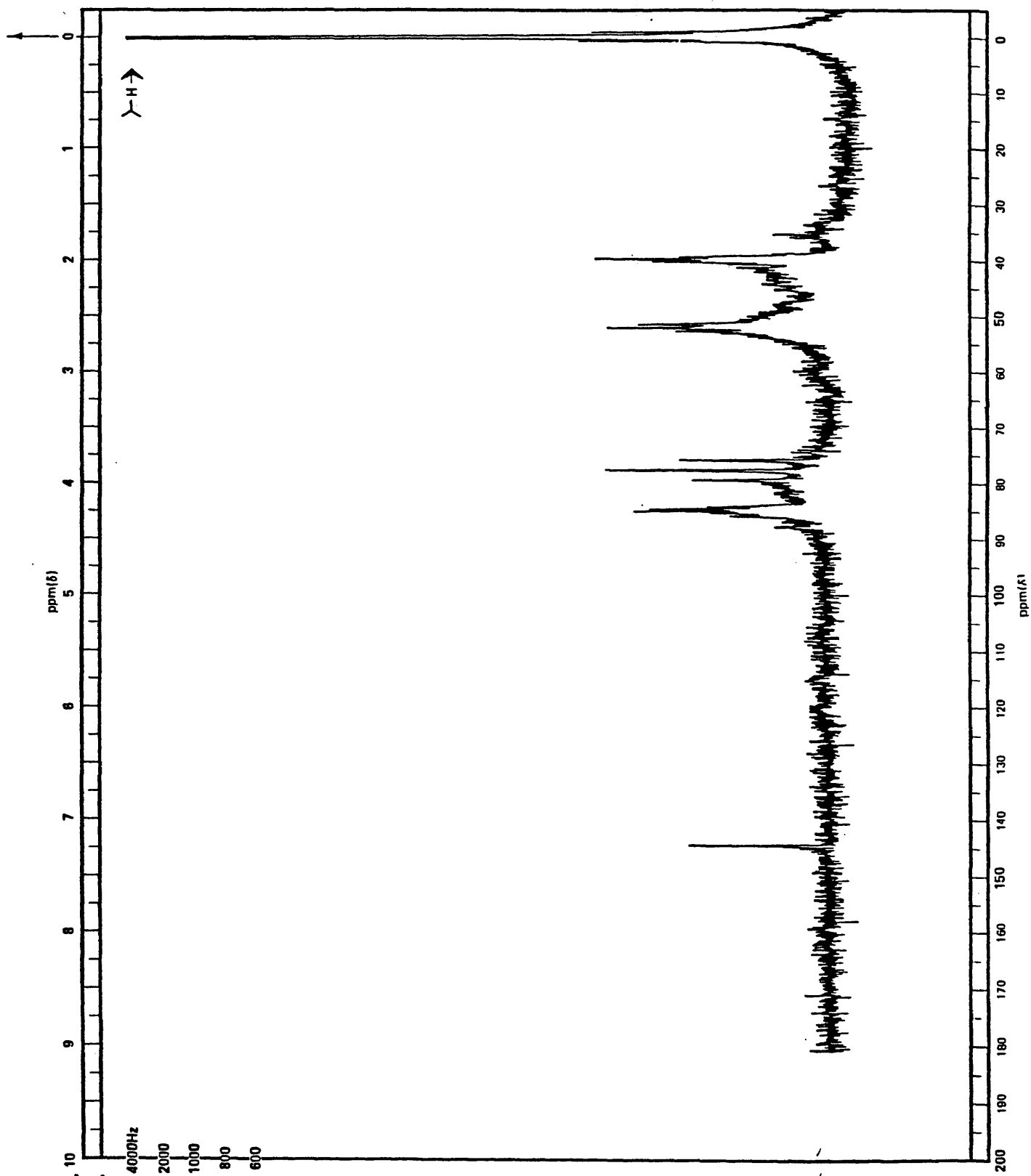


Figure 11. ^1H NMR spectra of (E)-3-(1-chlorovinyl)tetrahydrofuran at 60 MHz

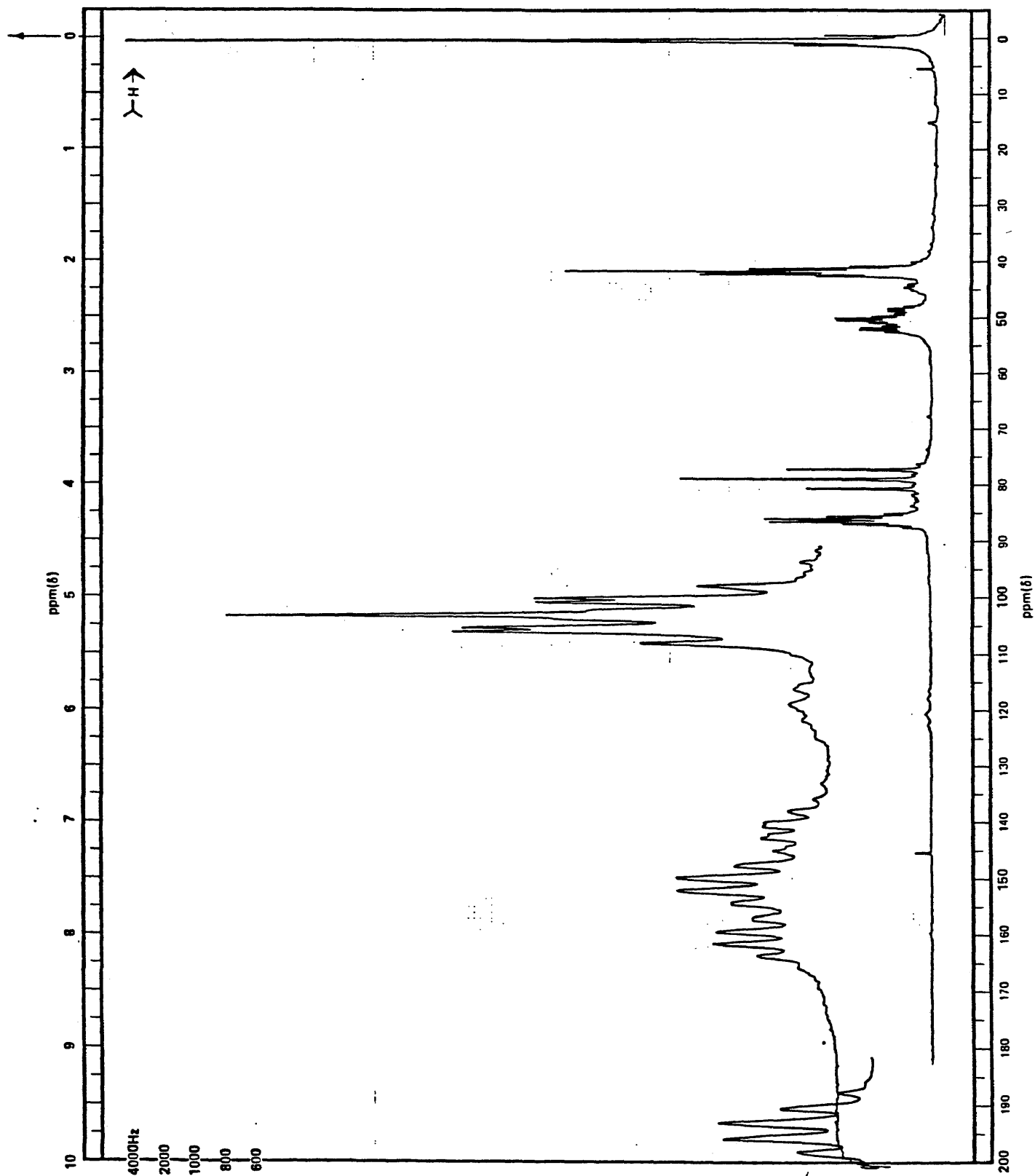


Figure 12. ^1H NMR spectra of (Z)-3-(1-chlorovinyl)tetrahydrofuran at 60 MHz

69.7 ppm. The absorptions for the vinylic methyl and the methylene at carbon 5 are observed at 30.6 and 33.2 ppm.

The absorptions for the two vinylic carbons in the furan are found at 119.7 and 135.8 ppm in Figure 14. The absorptions for C-2 and C-5 are found at 96.5 and 98.1 ppm. The absorptions for the methyl off the double bond and for carbon 4 are at 49.9 and 58.0 ppm.

The ratio of the three products and the overall yield of products formed from the cyclization of 5-(2-methoxyethoxy)methoxy-2-pentyne varies with solvent, Lewis acid, and temperature. When the reaction is conducted in methylene chloride the overall yields are at least 21% greater than when the reaction is conducted in tetrachloroethene.

When TiCl_4 is used as the Lewis acid instead of SnCl_4 to initiate the reaction, the reaction times are shorter, the overall yields are better, and only the three products previously mentioned are formed. At -45°C the cyclization using TiCl_4 is complete in 30 min. The cyclization using SnCl_4 at -45°C , however, is still incomplete after 60 min. When the reaction occurs at 0°C with TiCl_4 , the overall yield is 95.7%. When the reaction is initiated with SnCl_4 , the overall yield is only 52.6%. Another problem with using SnCl_4 , especially at lower temperatures, is that the product mixture contains five products rather than the expected three products.

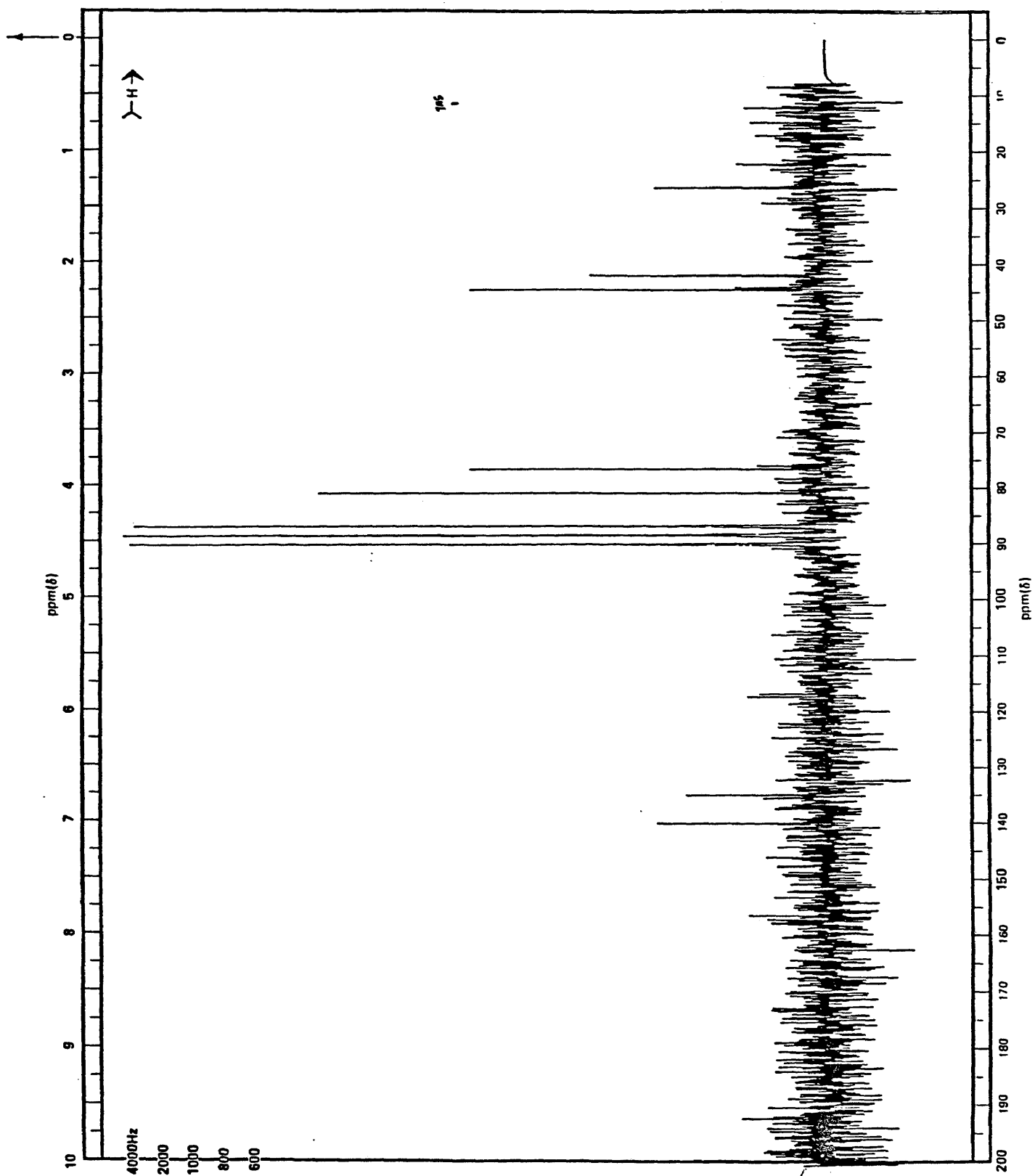


Figure 13. ^{13}C NMR spectra of 4-chloro-3-methyl-(2,5)-dihydropyran at 60 MHz

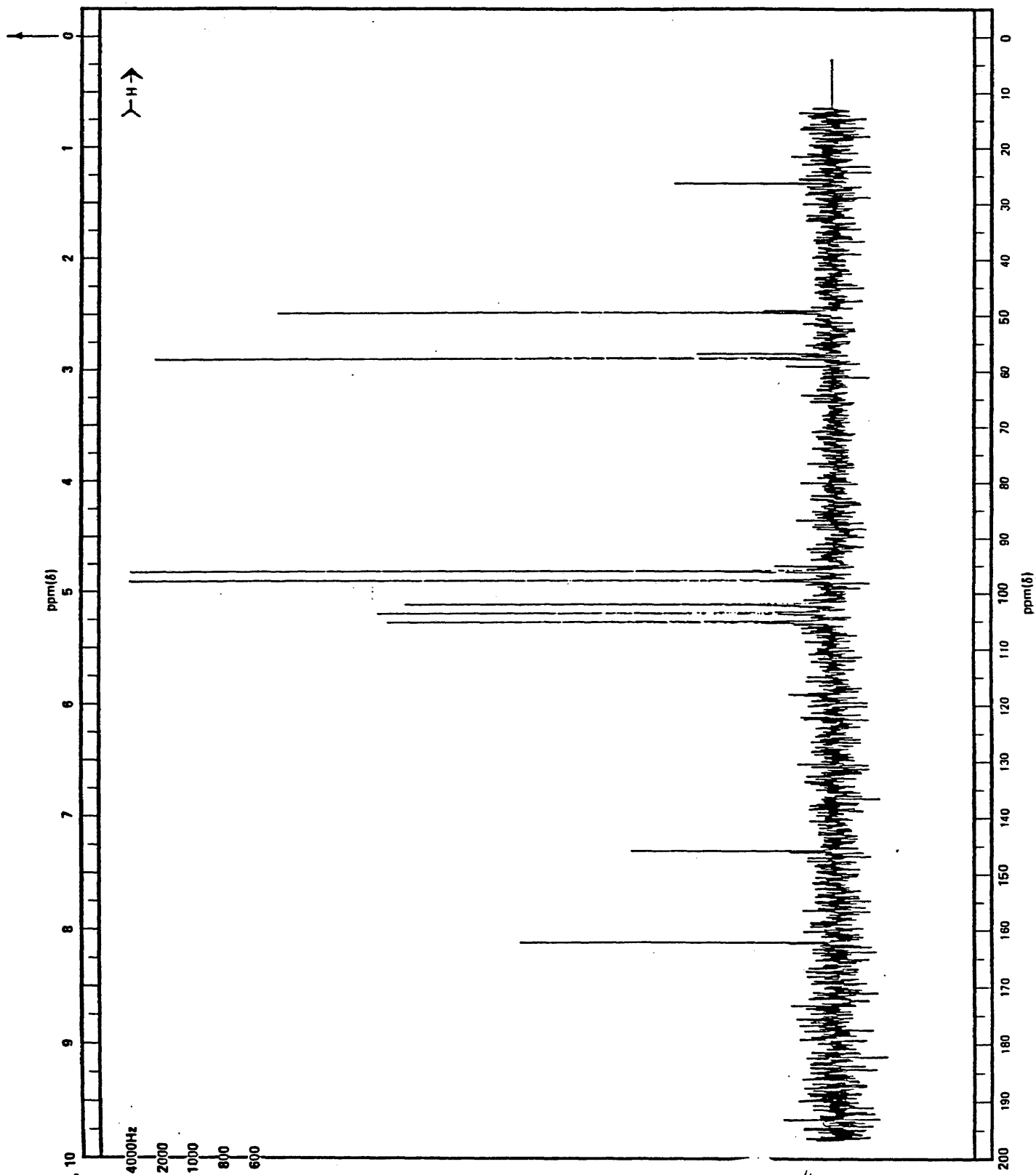
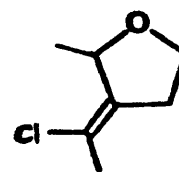
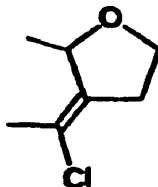
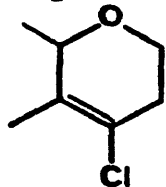


Figure 14. ^{13}C NMR spectra of (Z)-3-(1-chlorovinyl)tetrahydrofuran at 60 MHz

When the reaction temperature is raised, the reaction times are shorter, the yields are better, and the individual yields of the three products vary. At the lower temperatures the reaction times are shorter. At 25°C the reaction is complete in 15 min. At -95°C the reaction is still incomplete after 70 min. As the temperature is raised from -63°C to 25°C, the overall yield increases from 81.9% to over 99%--an increase of over 20%. The individual yields of the three products also vary with temperature. At the lower temperatures, more six-membered rings are formed whereas at the higher temperatures, more five-membered rings are formed. The product yields of the two five-membered rings both increase as the temperature increases. The product yield of the third absorption on the GC spectra increases from 32.1% at -95°C to 46.0% at 25°C. The yield of the second absorption increases from 18.1% at -95°C to 25.1% at 25°C. The individual yields and the overall yields of the cyclizations of 5-(2-methoxyethoxy)methoxy-2-pentyne at various temperatures is seen in Table 4.

Upon cyclization of 5-(1-ethoxy)ethoxy-2-pentyne, three products were observed by gas chromatography. If these products travel through the GC column in the same order as the products in the previous reaction, then the expected order of products versus GC peaks should be 4-chloro-2,3-dimethyl-(2,5)dihydropyran, and the (E) and the (Z) isomers of 3-(1-chlorovinyl)-2-methyltetrahydrofuran (as

seen below, respectively). The tetrahydropyran makes up 30% of the product mixture while the combined yields of the two tetrahydrofurans make up the other 70% according to the GC



spectra. There is very little (Z) isomer according to the spectra.

The (E) isomer and the pyran were difficult to separate using preparative GC techniques. The ^1H and ^{13}C NMR spectra, therefore, contain absorptions for both compounds. The sets of peaks centered at 1.00 ppm in the ^1H NMR spectra seen in Figure 15 are the hydrogens of the 2-methyls in both compounds. The taller two absorptions belong to the furan, and the two shorter absorptions, slightly to the left of each large peak, belong to the pyran. The absorptions at 1.60 ppm is the vinyl methyl hydrogens belonging to the furan. Because of the double bond, it experiences long range couplings with the hydrogens at carbons 2 and 4. This gives the multiplet seen at 1.60 ppm. The absorption at 1.35 ppm is the vinyl methyl hydrogens of the pyran. It also experiences long range couplings through the double bond.

The ^{13}C NMR spectra in Figure 16 also contains absorptions for both the pyran and the furan. The absorptions at 121.1 and 140.3 ppm represent the vinylic carbons in the furan. As in Figures 13 and 14 of

Table 4. Temperature effects on product yields in the cyclization of 5-(2-methoxyethoxy)methoxy-2-pentyne.

Temp (°C)	overall yield, %	individual yields, %		
		4-chloro-3-methyl- (2,5)-dihydropyran	(E)-3-(1-chlorovinyl) tetrahydrofuran	(Z)-3-(1-chlorovinyl)- tetrahydrofuran
-95	90.9	40.7	18.1	32.1
-63	81.9	33.6	17.0	31.3
-45	86.8	33.6	18.7	34.5
0	95.7	31.4	23.2	41.0
25	>99	30.7	25.1	46.0

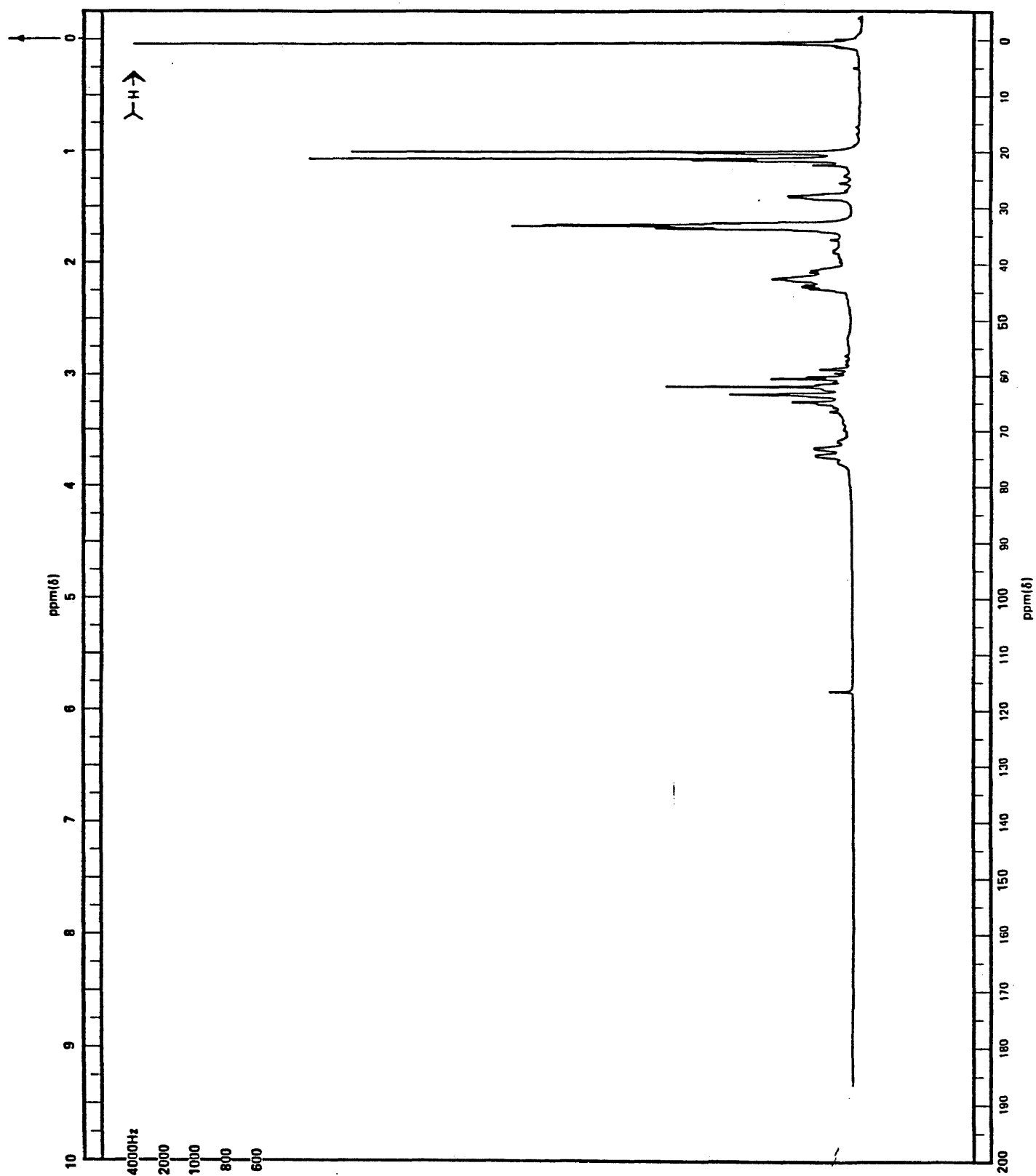


Figure 15. ^1H NMR spectra of 3-(1-chlorovinyl)-2-methyltetrahydrofuran and of 4-chloro-2,3-dimethyl-(2,5) dihydropyran at 60 MHz

4-chloro-3-methyl-(2,5)-dihdropyran and (Z)-3-(1-chlorovinyl)tetrahydrofuran, respectively, the vinyl carbon absorptions are further apart in the tetrahydrofuran, where the double bond is external to the ring, than in the dihydropyran, where the double bond is inside the ring. The other carbon absorptions for the furan are found at 20.0, 22.9, 33.2, 66.4, and 76.1 ppm. The smaller absorptions in this spectra represent the pyran. These absorption are at 15.4, 19.2, 33.6, 62.5, and 74.1 ppm. The vinylic absorptions for the pyran are unobserved.

Upon cyclization of 1-phenyl-4-(1-ethoxy)ethoxy-1-butyne, only two products were observed. These two products are probably the two five-membered ring isomers due to the stabilization of the carbocation by the phenyl ring. These two isomers were difficult to separate by preparative gas chromatography, therefore both the ^1H and the ^{13}C NMR spectras contain absorptions for both isomers.

The ^1H NMR of the (E) and the (Z) isomers of 3-(1-chloro-2-phenylvinyl)tetrahydrofuran is seen in Figure 17. The absorptions for the hydrogens around the phenyl ring are observed at 5.73 ppm. The hydrogens at carbon 2 are observed at 3.33 and 3.48 ppm for the (E) and the (Z) isomers. The narrow triplets are due to long range coupling. Two overlapping sets of triplets (due to the two isomers) are observed at 3.00 ppm. These absorptions are

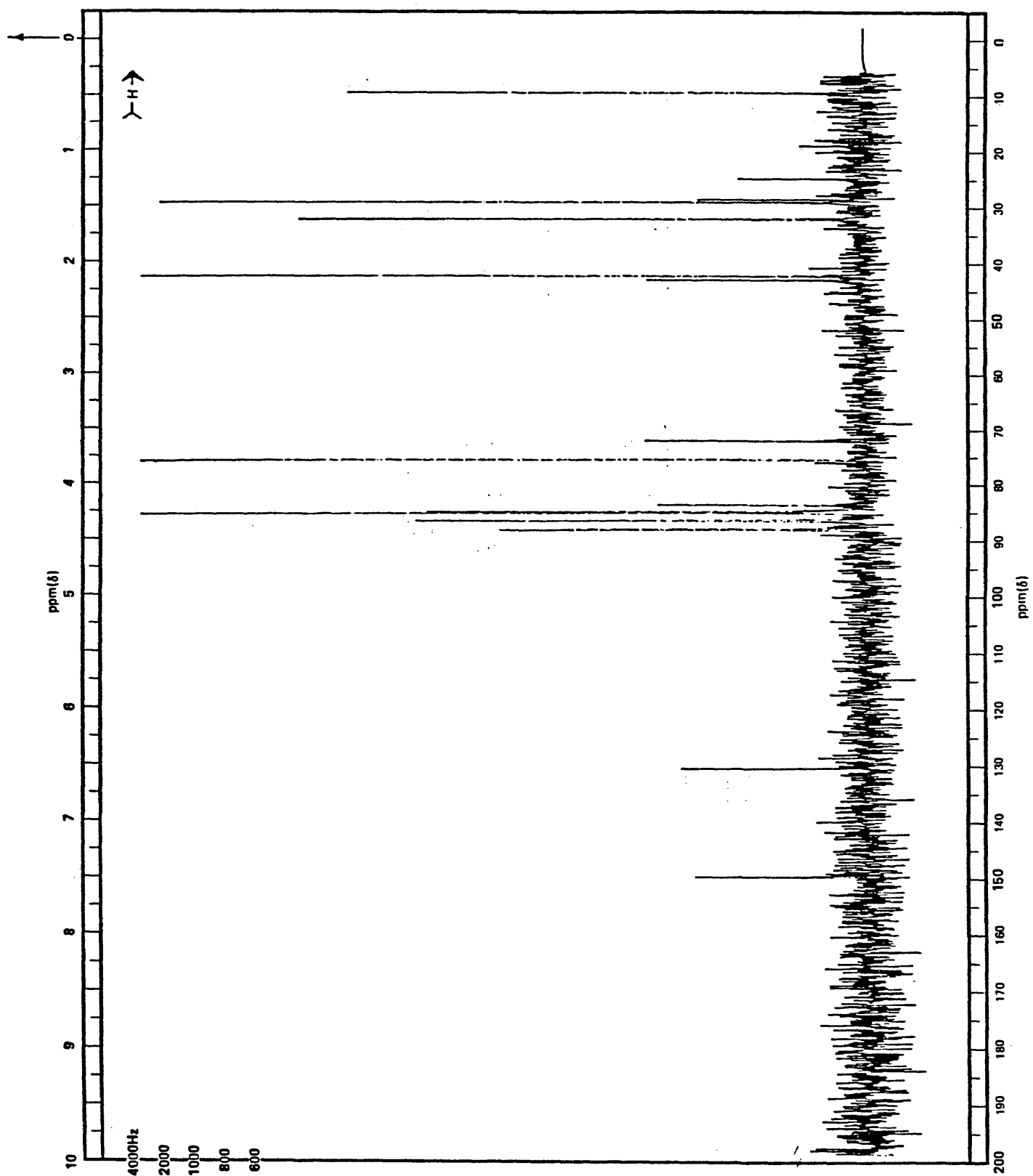


Figure 16. ^{13}C NMR spectra of 3-(1-chlorovinyl)-2-methyltetrahydrofuran and of 4-chloro-2,3-dimethyl-(2,5) dihydropyran at 60 MHz

due to the hydrogens at carbon 5. These hydrogens couple with the hydrogens at carbon 4 and therefore these triplets are not as narrow as those representing the hydrogens at carbon 2. The set of peaks at 2.00 ppm represent the hydrogens at carbon 4.

The ^{13}C NMR of the (E) and the (Z) isomers of 3-(1-chloro-2-phenylvinyl)tetrahydrofuran is seen in Figure 18. One isomer produces the absorptions observed at 72.4, 69.9, and 33.1 ppm. The absorptions at 70.3, 67.9, 34.2 ppm represent the other isomer. The absorption at 128.7 represents the hydrogens off the phenyl ring.

It was our hope to stereospecifically form tetrahydropyrans by a cationic attack of a double bond and to use a similar reaction to form a tetrahydrofuran. In both cases we have succeeded. We have taken an acetal with a cis or trans homoallylic double bond, and upon cyclization, stereospecifically have produced a cis or trans-4-halo-3-ethyltetrahydropyran, respectively. This cyclization is not only dependent on a Lewis acid, such as TiCl_4 or TiBr_4 , for initiation but the stereochemistry of the final products is due to the Lewis acid complexing with the acetal. This complexation allows the chloride or bromide ion to be juxtaposed so that upon formation of the final cation, the nucleophile can attack immediately. It is this immediate attack which prevents the mixture of geometrical isomers in the final product that Johnson observed.

We also have cyclized a homopropargylic acetal with TiCl_4 and SnCl_4 to form tetrahydrofurans and dihydropyrans. By varying the terminal group (methylacetylenic vs. phenylacetylenic) and the reaction temperature, we can produce up to 100% tetrahydrofuran. In this cyclization, as in the cyclization of the homoallylic acetals, the Lewis acid complexes with the acetal to allow immediate placement of the nucleophile upon formation of the final cyclized carbocation.

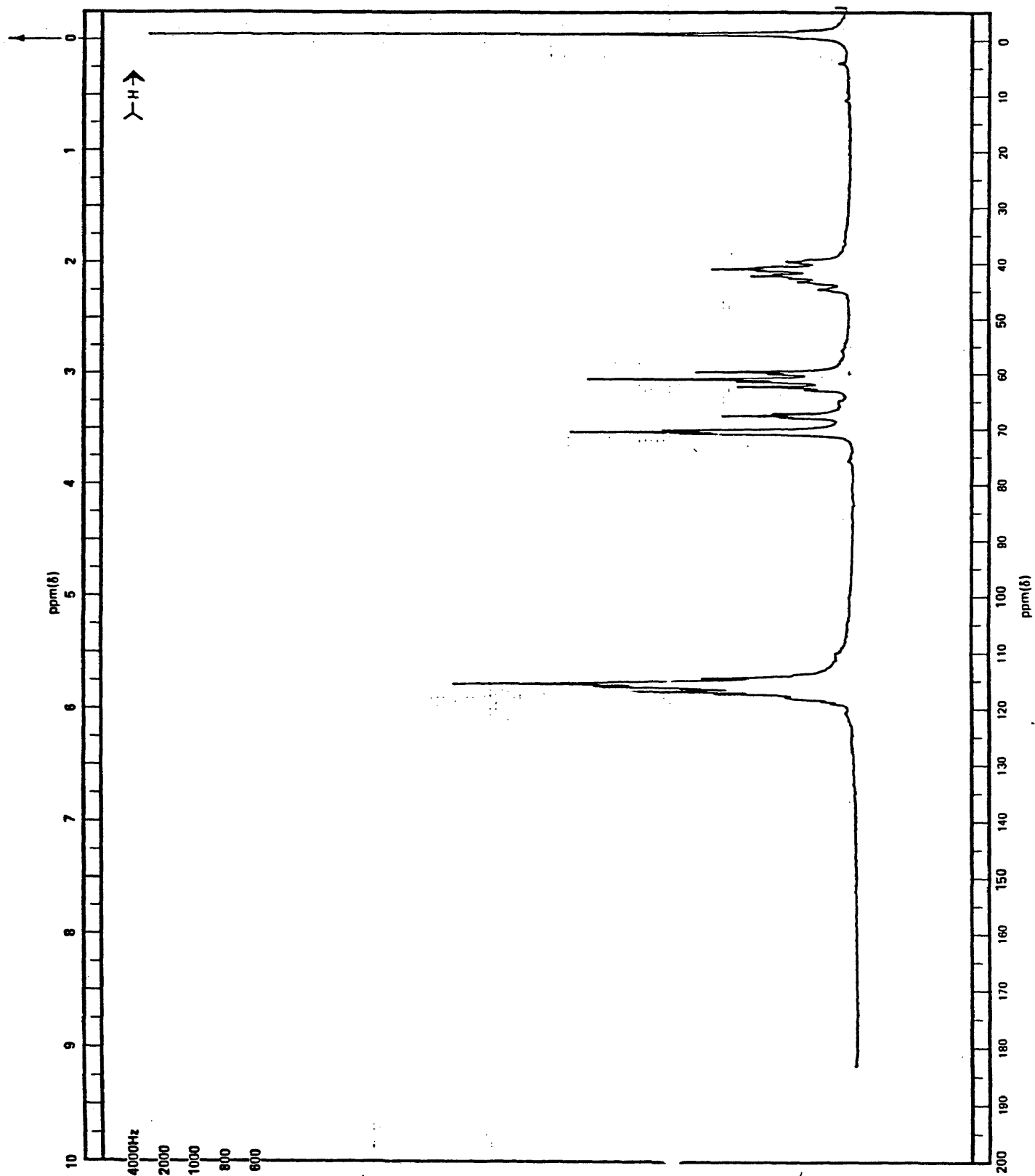


Figure 17. ^1H NMR spectra of 3-(1-chloro-2-phenylvinyl)tetrahydrofuran at 60 MHz

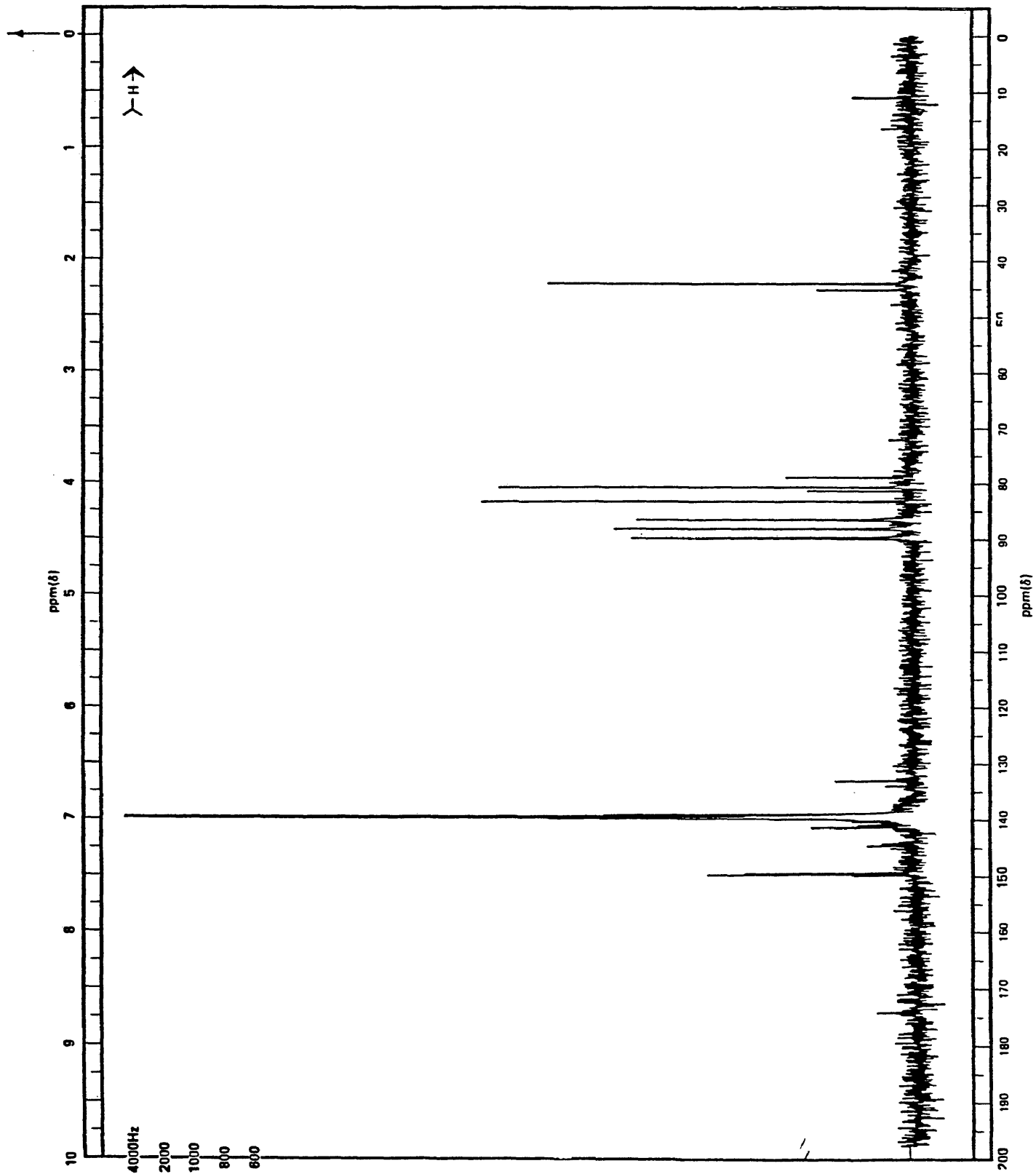
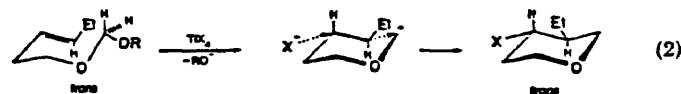
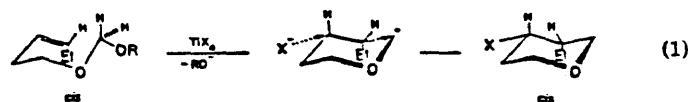


Figure 18. ^{13}C NMR spectra of the (E) and the (Z) isomers of 3-(1-chloro-2-phenylvinyl)tetrahydrofuran at 60 MHz

homoallylic alcohols 3-buten-1-ol and 4-penten-2-ol react with simple aldehydes in the presence of hydrogen halide to give 4-halotetrahydropyrans in yields of 40–65%. No stereochemical characterization was reported.

With the increasing interest in tetrahydropyran nuclei within the natural products area, we wish to report a stereospecific, high-yield approach, related to the above-mentioned chemistry, to the synthesis of *cis*- and *trans*-3-alkyl-4-halotetrahydropyrans. Specifically, we describe the selective synthesis of *cis*- and *trans*-3-ethyl-4-chloro-(bromo)tetrahydropyrans and *all-cis*- and *all-trans*-2-methyl-3-ethyl-4-chloro(bromo)tetrahydropyrans via the Lewis acid promoted carbon-carbon bond-forming cyclization of acetals derived from *cis*- and *trans*-3-hexen-1-ol.

The acetal cyclization reactions we examined are summarized in Table I. The MEM chloride and ethyl vinyl ether based acetals of *cis*- and *trans*-3-hexen-1-ol are readily prepared in high yield by well-established procedures.^{3,4} These acetals are clearly similar to the α -halo ethers proposed by Stapp as intermediates in his tetrahydropyran synthesis. The acetals are rapidly cyclized in the presence of titanium tetrachloride or tetrabromide under mild conditions, and the yields of tetrahydropyran products are excellent.⁵ However, more striking is the excellent selectivity. The *cis* and *trans* MEM chloride acetals give predominately *cis*- and *trans*-3-ethyl-4-halotetrahydropyrans, respectively, with a ca. 9:1 selectivity ratio.⁶ This *cis* to *cis*, *trans* to *trans* reaction pattern can be rationalized by a pathway involving *trans* addition of an oxocarbenium and X⁻ to the unsaturation as illustrated in eq 1 and 2.



A Selective Synthesis of 3-Alkyl-4-halotetrahydropyrans via the Titanium Tetrahalide Promoted Cyclization of Unsaturated Acetals

Summary: A stereospecific, high-yield approach to the synthesis of *cis*- and *trans*-3-ethyl-4-chloro(bromo)tetrahydropyrans and *all-cis*- and *all-trans*-2-methyl-3-ethyl-4-chloro(bromo)tetrahydropyrans via the Lewis acid promoted carbon-carbon bond-forming cyclization of acetals derived from *cis*- and *trans*-3-hexen-1-ol is described.

Sir: In 1969 Stapp¹ reported the synthesis of six 4-halo-3-alkyltetrahydropyrans from the direct reaction of 1-alkenes, paraformaldehyde, and hydrogen halides. While the yields of the tetrahydropyrans were satisfactory, the stereoselectivity was limited with the author stating that "throughout this work 3-alkyl-4-halotetrahydropyrans are *cis*/*trans* isomer mixtures" (60–85% *trans*).¹ The isolation of 3-buten-1-ol from a reaction of propylene, paraformaldehyde, and hydrogen chloride suggested a pathway involving homoallylic alcohols. Indeed, earlier Hanschke^{2a} and Colonge and Boide^{2b} had shown that the terminal

trans addition predominates in cationic polyene cyclizations reported by Johnson et al.¹⁰ In view of stereochemical studies of product formation from conformationally locked 4-*tert*-butylcyclohexenyl cations, it does not appear that a free carbocation at the 4-carbon is involved since this should lead to substantial axial attack of the incoming halogen.¹¹

The ethyl vinyl ether acetals cyclize with almost complete selectivity to one of four diastereomers. The *trans*-acetal gives *all-trans*-2-methyl-3-ethyl-4-halotetrahydropyrans while the *cis*-acetal gives *all-cis*-tetrahydropyran products.¹² The conformations of the *all-trans* products are clearly 2,3,4-equatorial. For the *all-cis* products, the predominant conformation must be equatorial methyl, axial ethyl, equatorial halogen since conformational energies are ca. 2.9 (2-Me), 1.4 (3-Et), and 0.3 kcal/mol (halogen). The *all-trans* and *all-cis* isomers are the products which one would expect on the basis of the observed preference for *trans* addition in tetrahydropyran formation seen above in the 3-ethyl-4-halo analogues and

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(4) Greene, T. W. "Protective Groups in Organic Synthesis"; Wiley-Interscience: New York, 1981; Chapter 2.

(5) For a typical cyclization reaction 15 mmol of an unsaturated acetal dissolved in ca. 100 mL of dry CH₂Cl₂ was treated with 20 mmol of TiCl₄ at -45 °C. The reaction mixture was stirred for 30 min after which 5 mL of CH₃OH followed by 35 mL of 3 N HCl saturated with NaCl was added. The products were extracted with diethyl ether and isolated for spectral analysis by preparative GLC.

(1) Stapp, P. R. *J. Org. Chem.* 1969, 34, 479.

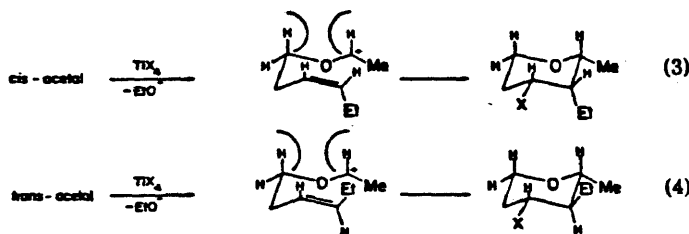
(2) (a) Hanschke, E. *Chem. Ber.* 1955, 88, 1053. (b) Colonge, J.; Boide, P. *Bull. Soc. Chim. Fr.* 1956, 23, 824.

Table I

acetal	Lewis acid	major product (yield, %)	^{13}C NMR, δ ($\text{CDCl}_3/\text{Me}_4\text{Si}$)
	TiCl_4 TiBr_4	X = Cl (94; 92% trans) X = Br (98; 89% trans)	11.0 (CH_3), 22.3, 36.4 (CH_2), 46.2 (EtCH), 61.5 (ClCH), 67.2, 70.8 (OCH_2) 11.1 (CH_3), 24.0, 37.7 (CH_2), 46.6 (EtCH), 54.7 (BrCH), 68.2, 71.4 (OCH_2)
	TiCl_4 TiBr_4	X = Cl (92; 95% cis) X = Br (74; 87% cis)	10.7 (CH_3), 21.5, 34.8 (CH_2), 42.8 (EtCH), 60.1 (ClCH), 62.6, 67.0 (OCH_2) 10.6 (CH_3), 23.6, 35.1 (CH_2), 42.7 (EtCH), 56.5 (BrCH), 63.3, 67.7 (OCH_2)
	TiCl_4 TiBr_4	X = Cl (85; 96% all-trans) X = Br (>99; 98% all-trans)	9.2 (CH_3CH_2), 20.0 (2- CH_3), 21.1, 38.1 (CH_2), 51.8 (EtCH), 60.4 (ClCH), 67.1 (2- CH_2), 76.9 (CH_3CHO) 9.1 (CH_3CH_2), 20.1 (2- CH_3), 22.6, 39.2 (CH_2), 52.0 (EtCH), 54.0 (BrCH), 68.1 (2- CH_2), 77.1 (CH_3CHO)
	TiCl_4 TiBr_4	X = Cl (96; 97% all-cis) X = Br (>99; 98% all-cis)	16.0, 19.0 (CH_3), 16.7 (CH_3CH_2), 32.4 (4- CH_2), 48.3 (EtCH), 62.0 (ClCH), 66.1 (2- CH_2), 76.2 (CH_3CHO) 15.9, 19.1 (CH_3), 18.0 (CH_3CH_2), 33.1 (4- CH_2), 48.8 (EtCH), 55.1 (BrCH), 67.2 (2- CH_2), 76.5 (CH_3CHO)

* Yields determined by GLC (corrected for response factors).

on the basis of the preference for the 2-methyl group to adopt the equatorial site so as to minimize the 1,3-diaxial methyl-hydrogen interaction in a carbocation intermediate (eq 3 and 4).



(6) The product from the cyclization of the *cis*-acetal has a longer GLC retention time than that for the *trans*-acetal; it is expected that the *cis* product have the longer retention time.¹⁷ The *trans*-3-ethyl-4-halo-tetrahydropyrans will exist overwhelmingly in the equatorial-equatorial conformation since the conformational energies of the ethyl group and halogens are ca. 1.4 and 0.3 kcal/mol, respectively.⁸ The conformation of the *cis* isomers will be predominately that with an equatorial ethyl group and axial halogens. This latter situation does exist for the products from the *cis*-acetal cyclization as indicated by the ^1H NMR pattern for the 4-protons. A pseudoquartet is observed which arises from coupling of an equatorial 4-hydrogen (axial X) to the three adjacent equatorial and axial protons with the three coupling constants approximately equal at 4 Hz. For the *trans* products the resonance of the axial 4-hydrogen is shifted upfield as expected,⁹ the splitting pattern is obscured by overlap with the 2- and 6-hydrogens. The ^{13}C NMR shifts for the ethyl group carbons of the *cis* and *trans* products differ only slightly and verify that the ethyl group is essentially in the same (equatorial) disposition in both product isomers; the axial and equatorial methyl carbon shifts for a 3-ethyl group are expected to be significantly separated as seen in the data for *all-cis*- and *all-trans*-2-methyl-3-ethyl-4-halotetrahydropyrans (see Table I, 16.0 vs. 9.2 for halo = Cl and 15.9 vs. 9.1 for halo = Br).

(7) Gambaro, A.; Boaretto, A.; Marton, D.; Tagliavini, G. *J. Organomet. Chem.* 1983, 254, 293.

(8) Eliel, E. L.; Hargrave, K. D.; Pietrusiewicz, K. M.; Manoharan, J. *J. Am. Chem. Soc.* 1982, 104, 3635 and references therein.

(9) Wigfield, D. C.; Feiner, S. *Can. J. Chem.* 1978, 56, 789.

The lack of selectivity in Stapp's synthesis may arise from a nonselective proton elimination to give a *cis-trans* mixture of the homoallylic intermediates and/or the use of hydrogen halide acids which may not lead to selective equatorial additions at the 4-carbon. Preliminary cyclization studies with gaseous hydrogen chloride and hydrogen bromide and acetals of homoallylic alcohols has indicated a substantial lack of selectivity and several by-products. The fact that TiCl_4 and TiBr_4 form strong Lewis acid-base adducts with oxygen-donating substrates may lead to a more concerted and thus selective *trans* (equatorial) delivery of halides to the 4-carbon.¹¹

With the strong preference for *trans* addition of the oxocarbenium and halogen across the double bond and with enhanced 1,3-diaxial interactions across the oxygen, the unsaturated acetal cyclizations hold substantial promise for the selective synthesis of substituted tetrahydropyrans. We are continuing studies in this area with a variety of substituents and Lewis acids.

(11) Elakovich, S. D.; Traynham, J. G. *J. Org. Chem.* 1973, 38, 875.

(12) The products from the cyclization of the *cis*-acetal have 2-methyl ^{13}C NMR chemical shifts in the range 19.0–20.1 ppm. In view of the work of Eliel et al.⁸ and Gambaro et al.⁷ coupled with substituent effects on chemical shifts,¹² these δ values confirm the 2-methyl groups as being equatorial. From the prior results with the *cis* MEM acetals we expect *trans* addition across the unsaturation such that the ethyl group is axial and the halogen is equatorial. In the *cis*-acetal cyclization products, the significant downfield shifts of the ethyl group methyl carbons (~16 ppm relative to those in the *cis*- and *trans*-3-ethyl-4-halotetrahydropyran (~11 ppm) are consistent with axial ethyl dispositions. Furthermore, the halogens are clearly equatorial as indicated by the ^1H NMR patterns for the 4-hydrogens. The width of the patterns are ~22 Hz which necessitates an axial-axial coupling; overall, the patterns are approximated with $J_{ax} \sim 11$ Hz and $J_{ax} \sim 4.2$ and 4.8 Hz. Thus, the *cis*-acetal cyclization products are *all-cis*. Finally, the *cis*-acetal products have longer GLC retention times than their *trans*-acetal congeners. From a similar line of argument *all-trans* products result from *trans*-acetal cyclizations.

(13) Wehrli, F. W. Wirthlin, T. "Interpretation of Carbon-13 NMR Spectra"; Heyden: London, 1976.

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