

A STEREOSPECIFIC APPROACH TO THE SYNTHESIS OF PYRANS

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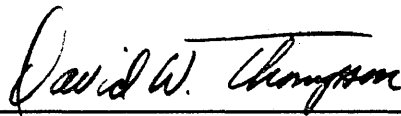
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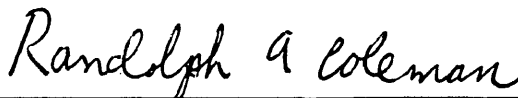
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ABSTRACT

We have investigated methods toward the stereoselective and stereospecific syntheses of 3-methyl-4-halotetrahydropyran, 2,5-dimethyl-4-halotetrahydropyran, and 2,3-dimethyl-4-halotetrahydropyran. The synthetic strategy involves the production of the ethyl vinyl ether or (2-methoxyethoxy)methyl (MEM) acetals of a homoallylic alcohol, followed by Lewis acid promoted cyclization through a resonance stabilized oxacarbocation formed upon cleavage of the acetal linkage. The carbocation and chloride then add across the double bond in a trans fashion. The preeminence of trans addition has important stereochemical implications. First, trans attack at the olefin necessitates an equatorial disposition of the halogen substituent at the 4 position of the product tetrahydropyran unless conformational effects induce chair-chair interconversion. Secondly, attack will proceed such that the cis acetal yields a cis configuration at the 3 and 4 carbons of the tetrahydropyran product; similarly trans acetals yield trans tetrahydropyrans. Thus, cis and trans 2,3-dimethyl-4-halotetrahydropyran are generated from the ethyl vinyl ether acetals of cis and trans-3-penten-1-ol, respectively. Formation of the MEM acetals of the same isomeric alkenols leads similarly to stereospecific production of cis or trans-3-methyl-4-halotetrahydropyran.

In other investigations, the cyclization of the ethyl vinyl ether acetal of 2-methyl-3-buten-1-ol yields a 3:1 cis, trans : cis mixture of 2,5-dimethyl-4-halotetrahydropyran with only small amounts of the other two isomers. MEM acetal cyclization produces a 2:1 trans : cis mixture of 3-methyl-4-halotetrahydropyran. In both cases the isomeric mixtures arise from a variable axial-equatorial orientation of the 3 (or 5) methyl group and are consistent with the predicted conformational stabilities of the isomeric tetrahydropyran products.

A STEREOSPECIFIC APPROACH TO THE SYNTHESIS OF PYRANS

INTRODUCTION

Saturated six membered cyclic ethers, tetrahydropyrans (oxanes), are central features in many naturally occurring products. Typically, oxane syntheses has proven challenging because syntheses of ethers are limited in number. In addition to the obvious similarity to the pyranose sugar series (Figure 1), the tetrahydropyran nucleus is also an important structural feature in molecules such as monensin and lasolocid (Figure 2) belonging to the polyether antibiotic series.¹ Polyether antibiotics are classified as ionophores because of their ability to solvate metal cations such as Na^+ and K^+ and transfer them through non-polar biological media such as the cell membrane.

Pyran nuclei are also prevalent in a variety of insect sex pheromones such as that secreted by the virgin female North American Elm Bark beetle, *Scolytus Multistriatus*. The beetle is known to be the primary agent in the infection of the elm populations of the northeastern United States by *Ceratosystis Ulmi*.² Silverstein first investigated the aggregation pheromone of the species and found the active component to be 2,4-dimethyl-5-ethyl-6,8-dioxabicyclo[3.2.1]octane (Figure 3) and dubbed it multistriatin, after the insect species.³

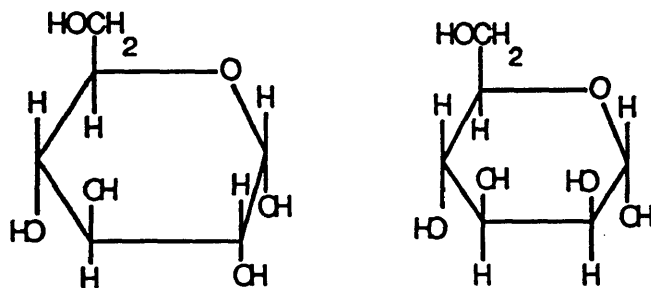


Figure 1 Pyranose sugar structures.

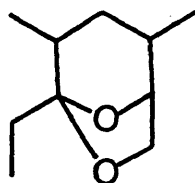
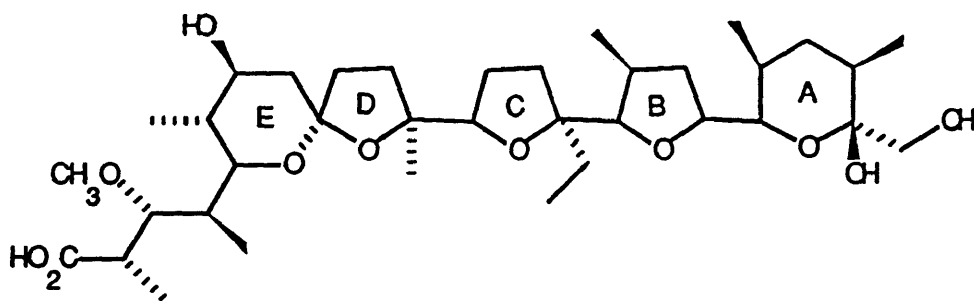
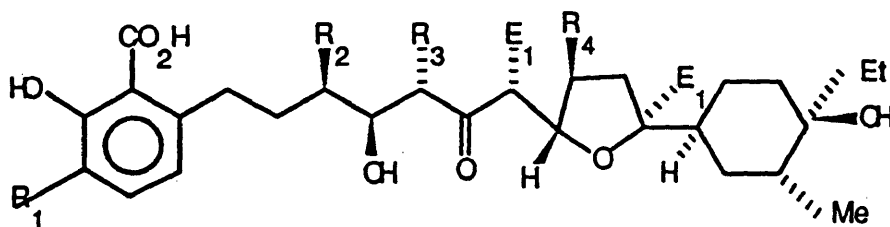


Figure 3 Multistriatin



Monensin

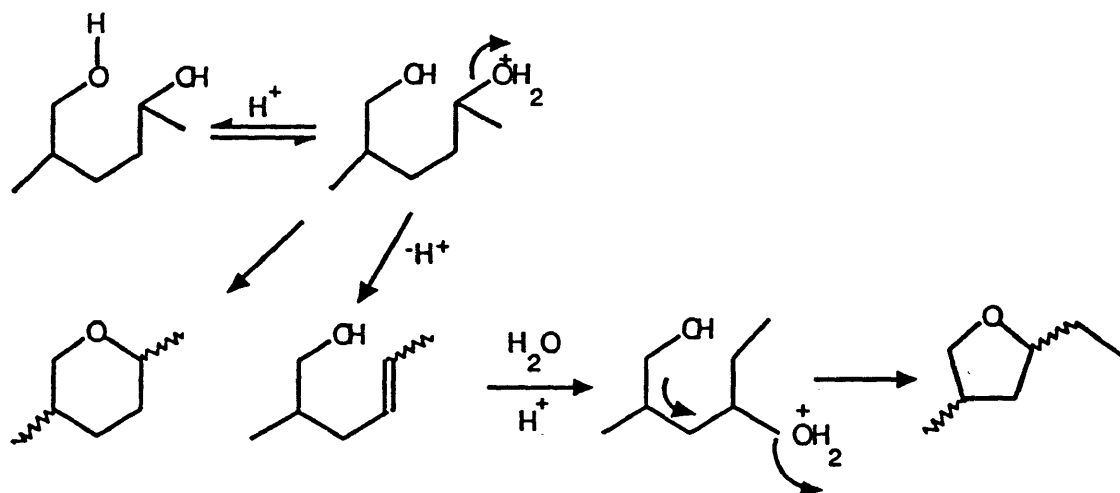


Lasalocid A



Figure 2 Commercially important polyether antibiotics

Synthetic routes to the specifically substituted tetrahydropyrans have typically involved the cyclization of 1,5-diols and related compounds such as 1,5-haloalcohols. However, this type of synthesis is often troubled by unwanted tetrahydrofuran formation and lack of stereospecificity of substituted ring carbons. For example, Ernest Eliel,⁵ in his systematic study of carbon-13 magnetic resonance shifts of tetrahydropyrans, employed a 1,5 diol acid-catalyzed cyclization and generated a mixture of *cis* and *trans*-2,5-dimethyltetrahydropyrans as well as *cis* and *trans*-2-ethyl-4-methyltetrahydrofuran from 2-methyl-1,5-hexanediol:



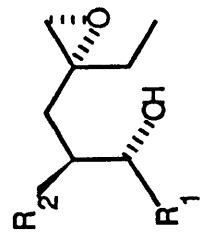
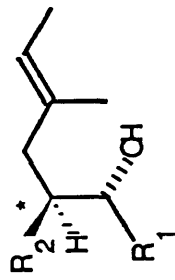
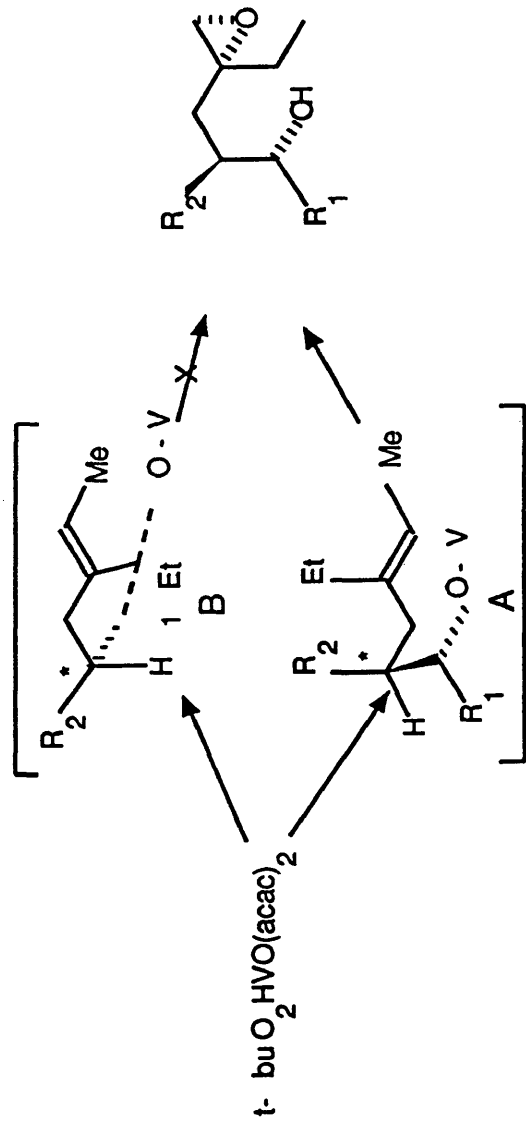
Epoxy olefins or epoxy ketones and aldehydes also serve as popular substrates which can undergo cyclization to produce substituted tetrahydrofuran and tetrahydropyran units, often with the stereospecificity required for natural product synthesis.

For example, to form the tetrahydrofuran ring of lasalocid A, Kishi, et al., used the Sharpless epoxidation to give the epoxide portion of the natural product from the olefinic site. In Scheme 1 below, we see how the stereochemistry is initiated. Of the two pseudoconformations A and B, the major intermediate shown below as A minimizes steric compression between the ethyl group and the pseudoaxial hydrogen in lasalocid-A.

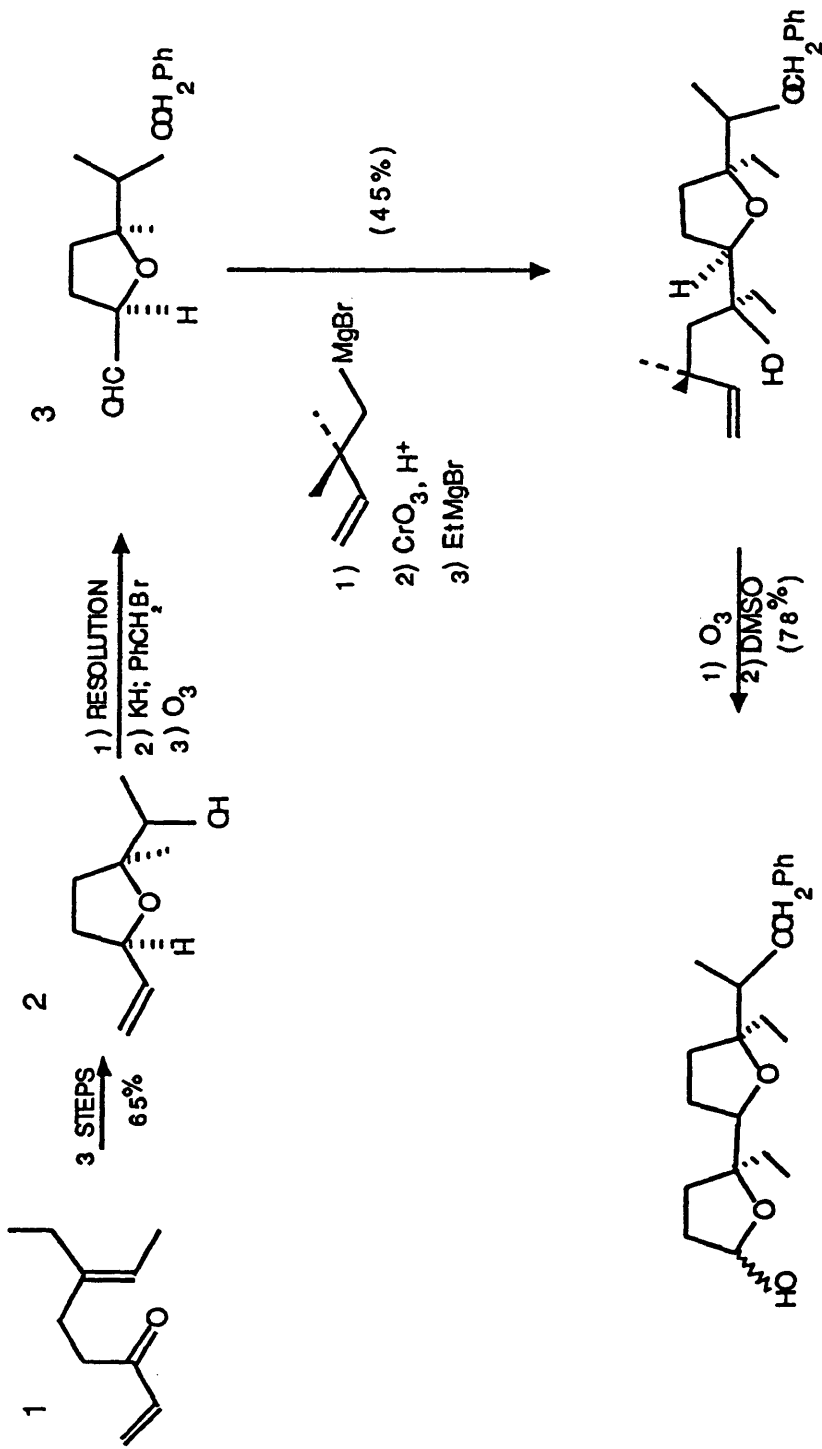
functionality of tetrahydrofuran (3) produces the carbon skeleton for the next tetrahydrofuran ring (4). Ozonolysis followed by dimethylsulfoxide workup and subsequent cyclization yielded the desired tetrahydrofuran.⁷

Scheme 3 shows how the same technique of epoxide ring opening was employed to produce the oxacycles in monensin. Kishi epoxidated intermediate (1) and opened the epoxide with camphor sulfonic acid to produce a 7:2 diastereomeric mixture. Periodate cleavage of the terminal olefin produced the second tetrahydrofuran containing the internal hemiacetal (via hydroxy attack of the aldehyde). The tetrahydrofuran was then reacted with Wittig ylid (4) producing the bishomoallylic alcohol (5). The alcohol was converted to the tetrahydrofuran using N-bromosuccimide and resulting bromide converted with inversion to the alcohol (6) with superoxide. Terminal aldehyde was then formed by osmium tetroxide oxidation of the terminal olefin after protection of the alcohol by $\text{Cl}_3\text{CCOC1}$ in pyridine. The newly formed aldehydic functionality was then protected so that chromic acid oxidation of the secondary alcohol could take place. Methoxide was used to liberate the protecting groups affording a single hemiketal, and trimethylorthoformate gave the cyclic ketal in 53% yield from (1).⁸

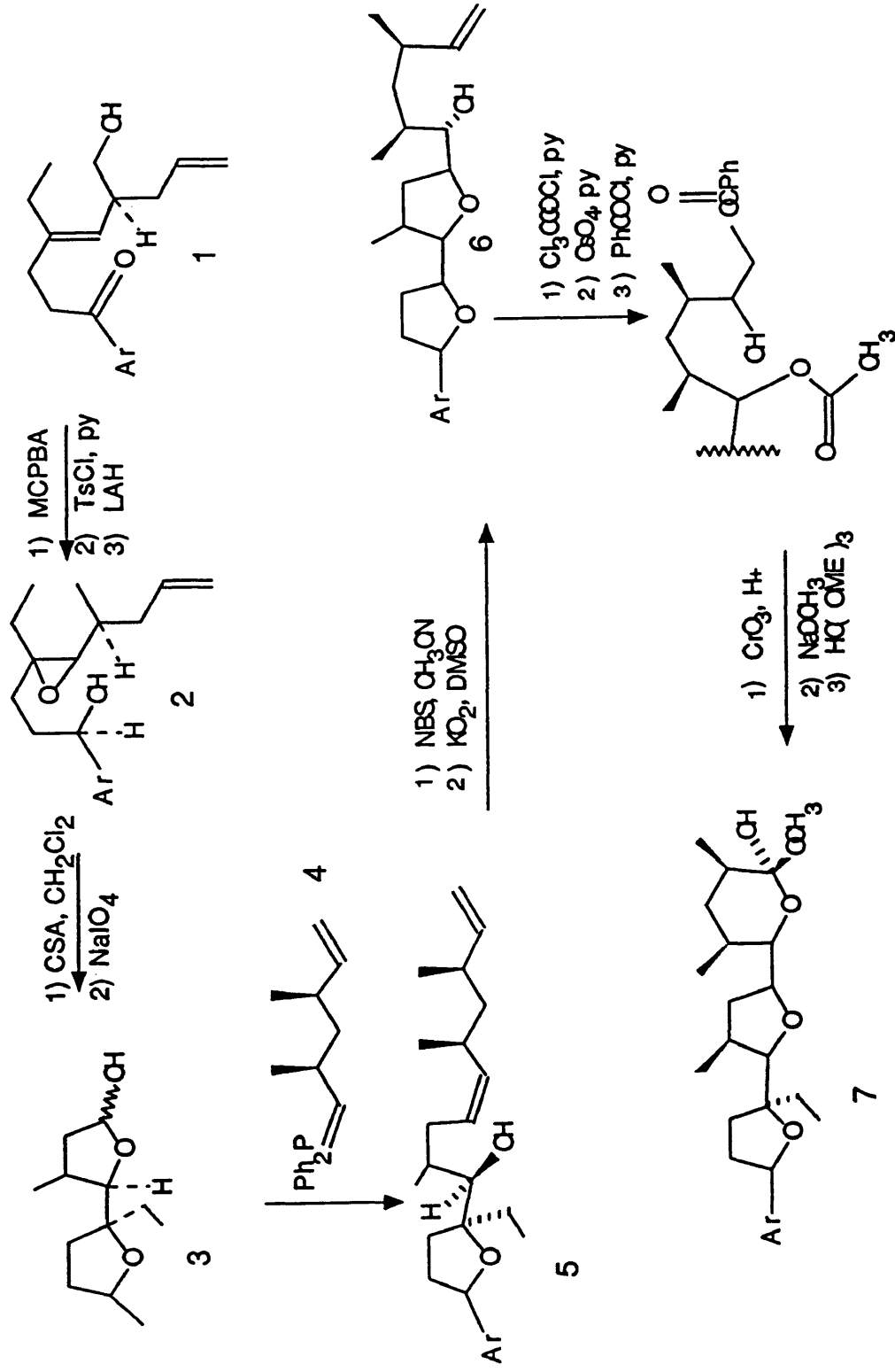
Scheme 1



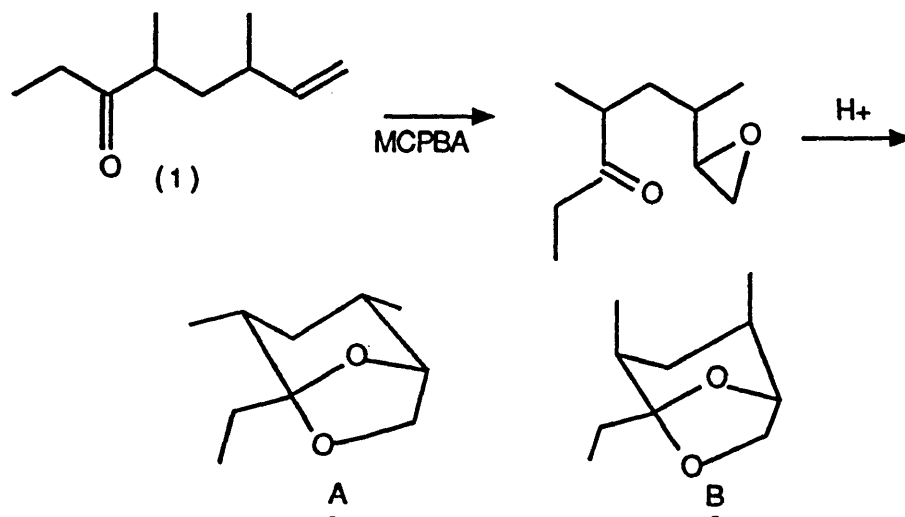
Scheme 2



Scheme 3

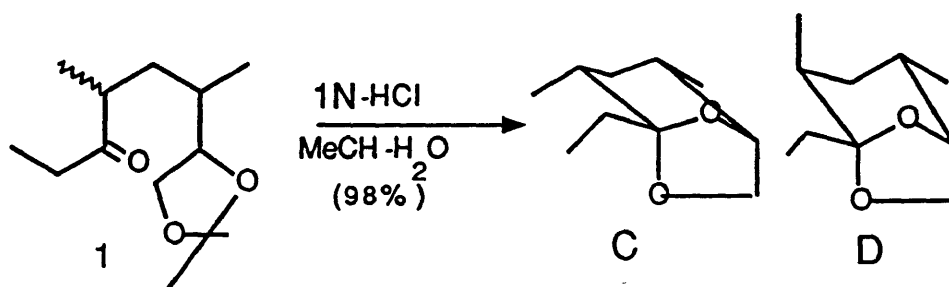


In non-stereospecific attempts to form the tetrahydropyran ring and subsequent ketal linkage of the multistriatin molecule, Silverstein employed metaperchlorobenzoic acid to form the epoxy intermediate from enone (1), (Scheme 4). Acid-catalyzed ketal cyclization forms a 60:40 mixture of isomers A and B, respectively.



Scheme 4

Alternatively, Elliot and Fried employed the diastereomeric ketones (1), (Scheme 5) in another acid-catalyzed cyclization. Acetonide removal produces multistriatin isomers C and D^{9,10}.



Scheme 5

In each of the cyclizations discussed thus far, the method of ring closure involves the formation of a new carbon-oxygen bond, wherein the electron-rich oxygen attacks a nearby electrophilic carbon.

STATEMENT OF THE PROBLEM

While many carbon-oxygen bond forming syntheses of tetrahydropyrans have been reported, relatively few stereoselective approaches have been published. Most commonly the cyclization of 1,5-diols and related compounds have been used to give tetrahydropyrans, stereochemical control in these substrates of the 1,5-diol type is limited to those carbons adjacent to the oxygen atom of the tetrahydropyran product. Thus, stereochemical specificity at the 3,4, and 5 positions must be built into the substrate before cyclization.

Literature reporting carbon-carbon bond forming cyclizations pertinent to our proposed research was scant and dated, usually including no report of the stereochemistry of the tetrahydropyrans produced. The general focus of our work was to investigate the synthetic potential of carbon-carbon bond forming cyclizations.

A survey of the literature and earlier work of our group led us to investigate the stereoselectivity in the production of 2,5-dimethyl-4-halotetrahydropyran (4 possible stereoisomers) from the ethyl vinyl ether acetal of 2-methyl-3-buten-1-ol. Also reported are cyclization studies of the (2-methoxyethoxy)methyl (MEM) acetal of the same alkenol which can give cis and trans isomers of 3-methyl-4-halotetrahydropyran. Both pathways involve the possibility of stereochemical variation of the 3 (or 5)-methyl group leading to an isomeric mixture of products; it is our hope to quantify the expected equatorial orientation of that group upon cyclization.

Separate studies involved the investigation of stereoselectivity in the cyclization of cis and trans unsaturated acetals of homoallylic alcohols to cis and trans tetrahydropyrans.

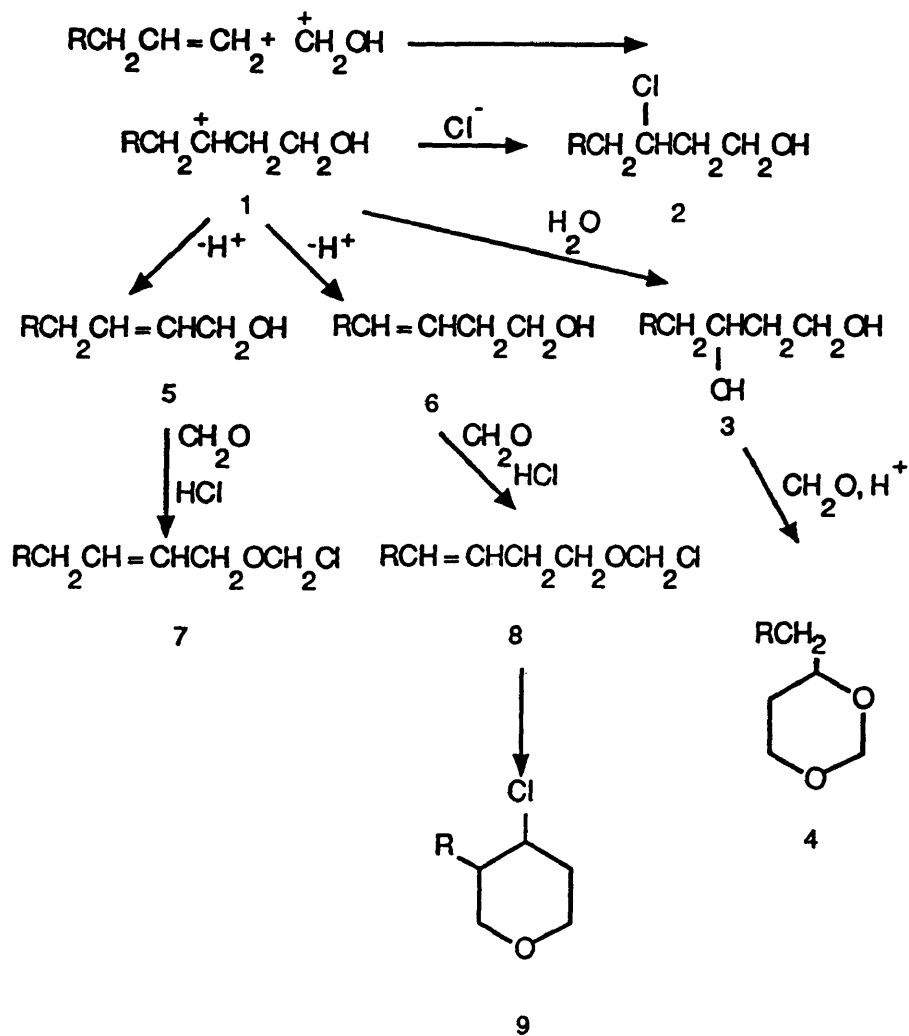
LITERATURE REVIEW

In 1899, Prins first investigated the reactions of olefins with carbonyl-containing compounds under aqueous acidic conditions. By using solutions of acetic, sulfuric, or hydrochloric acid, Prins was able to initiate electrophilic attack at the olefin by a protonated carbonyl species. This is illustrated in Scheme 6 using formaldehyde, hydrochloric acid, and 2-olefins.

The protonated formaldehyde reacts with the nucleophilic site of unsaturation to produce the carbonium ion (1). The ion can then react with hydrogen chloride to produce a chloroalcohol or undergo either a β δ proton elimination. If a δ proton is eliminated a tetrahydropyran (9) can be produced through the addition of a second formaldehyde molecule and hydrogen chloride to produce the α -chloroether (8) followed by cyclization. This cyclization is possible through the loss of chloride anion and subsequent formation of a resonance stabilized oxacarbocation which can then electrophilically attack the olefin. Elimination of the β proton produces the alkyl chloromethyl ether (7). Addition of water produces a 1,3 diol. Addition of the 1,3-diol to another formaldehyde molecule will produce a 1,3 dioxane after a cyclization step(4).

Indeed, the Prins reaction was shown to produce a bewildering variety of products. In addition to those discussed some aldehyde, ketone, and polymer formation was observed.¹¹

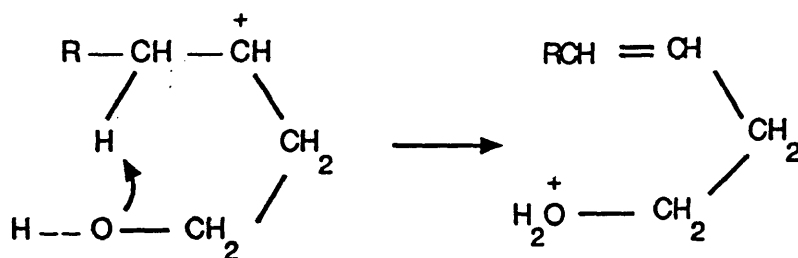
Stapp, in endeavoring to minimize the diversity of products obtained using the classic Prins synthesis, attempted similar reactions in anhydrous media. This modification would eliminate the formation of diols and dioxanes, and hopefully encourage formation of



Scheme 6 The Prins Reaction

tetrahydropyrans. Indeed, Stapp did realize 3-alkyl-4-halotetrahydropyrans from 1-octene, 1-decene, and 1-dodecene at yields of 50-80%. Although these products were produced in high yields, stereochemical control was poor as the reaction produces no more than 60-85% of the trans isomer. This lack of stereoselectivity may arise from a non-specific attack of incoming halide at the 4 position of the pyran ring, or from a non-selective β proton elimination giving rise to a cis-trans mixture of intermediate homoallylic alcohols. This scrambling of stereochemistry is then translated to a cis-trans mixture of the product tetrahydropyrans.

It is interesting to note here the absence of tetrahydrofuran formation that troubles the 1,5-diol and haloalcohol cyclizations. This absence can be explained by proposing a hydroxy-assisted cyclic deprotonation mechanism to produce the homoallylic alcohol from the intermediate carbonium ion as shown in Scheme 8. Such assistance from the hydroxy group is not possible for β proton elimination that would lead to the allylic alcohol and eventually tetrahydrofuran formation.¹¹



Scheme 8

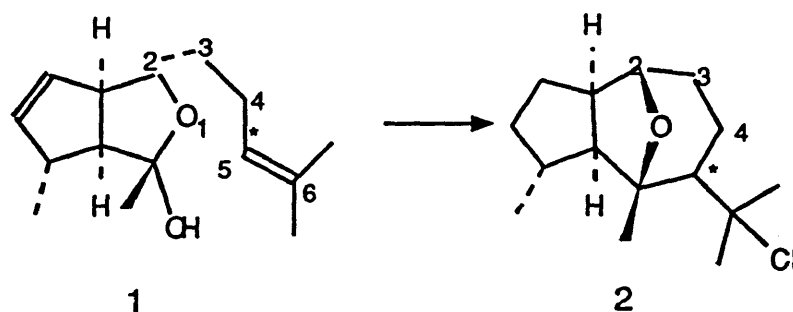
In another attempt to increase the selectivity of Prins' work, Hanschke utilized the chemistry in the Prins reaction by starting with homoallylic alcohols and condensing them with aldehydes and ketones in the presence of protic acid to produce the homoallylic δ -chloroethers (8), (Scheme 6) which then spontaneously cyclize to 4-chlorotetrahydropyrans. By altering the aldehyde or ketone, Hanschke could control substitution at one of the carbons adjacent to the oxygen atom of the tetrahydropyran ring. As in the Stapp modification, no mention is made of stereochemical assignments. summarizes Hanschke's efforts, producing 4-halopyrans in yields of 40-65%.¹²

Table 1

Hanschke's tetrahydropyrans produced from aldehyde-alcohol condensation			
<u>Aldehyde used</u>	<u>Acid</u>	<u>Tetrahydropyran produced</u>	<u>Yield %</u>
Formaldehyde	HCL	4-chlorotetrahydropyran	45
Formaldehyde	HBr	4-bromotetrahydropyran	43
Acetaldehyde	HCl	4-chloro-2-methyl-tetrahydropyran	50
Propionaldehyde	HCl	4-chloro-2-ethyl tetrahydropyran	60
Butyraldehyde	HCl	4-chloro-2-n-propyl tetrahydropyran	65

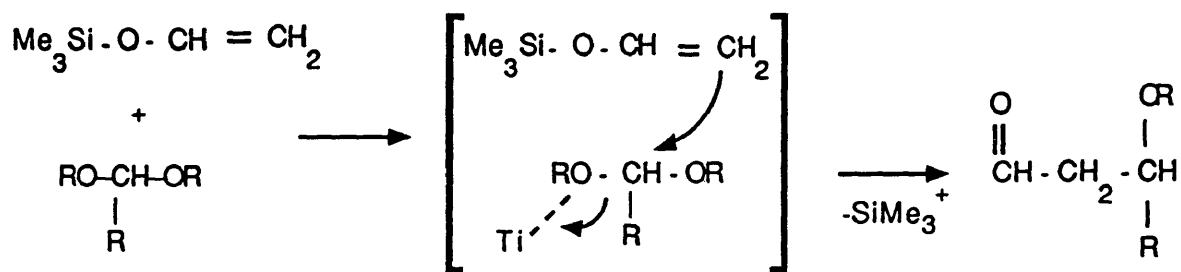
Hudlicky and Coworkers made use of the Prins/Stapp type reaction in an aldehyde-olefin ring closure to produce Guaiane ring systems.¹³ Intermediate 1 of Scheme 9 was produced and treated with SnCl_4 in benzene to yield the cyclic ether (2). Formation of the six-membered ring is favored since electrophilic attack at the double bond to produce the six-membered intermediate generates the more stable tertiary carbonium ion. Seven-membered ring formation produces the more unstable secondary cation.

Scheme 9



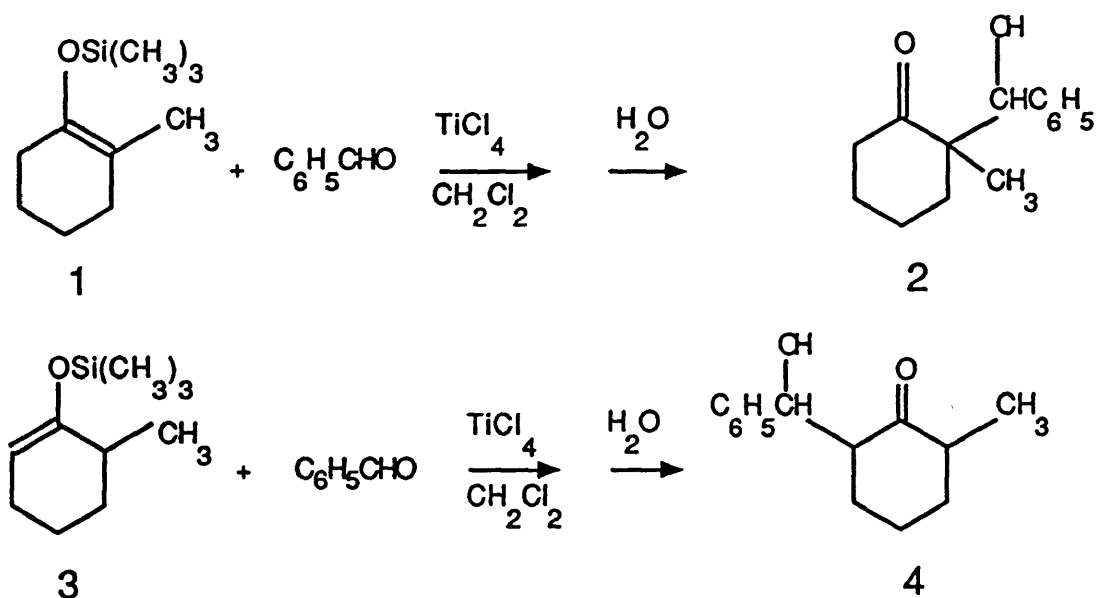
Scheme 10 illustrates Mukaiyama's investigations demonstrating that trimethylsilyl enol ethers react readily with acetals and ketals at -78° in the presence of TiCl_4 to afford β -alkoxy carbonyl compounds in high yields.

Scheme 10

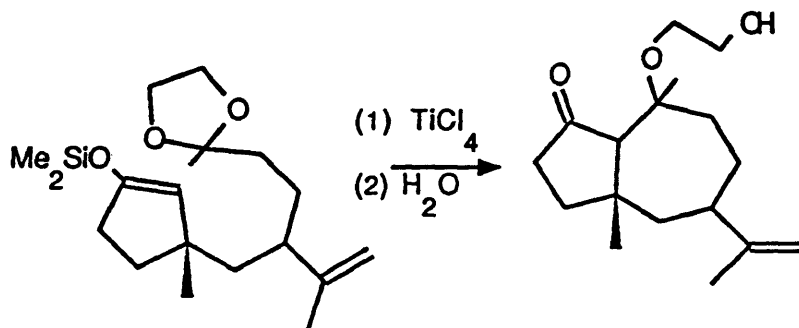


Mukaiyama demonstrated the importance the stability of the developing olefinic cationic center plays in directing the regioselectivity of the reaction terminating nucleophilic addition. He employed the isomers 2-methyl-1-trimethylsilyloxy-1-cyclohexene (1) and 6-methyl-1-trimethylsilyloxy-1-cyclohexene (3) and reacted them with benzaldehyde as shown in Scheme 11. Mukaiyama found that silyl enol ether (1) produced but one regioisomer (2). Isomer (3) similarly produced a single regioisomer. In both cases, the product diastereomers can be obtained only through a regioselective addition of the electrophilic titano-carbonyl species at the olefinic position to the silyl leaving group δ to the silyl leaving group.¹⁴

Scheme 11



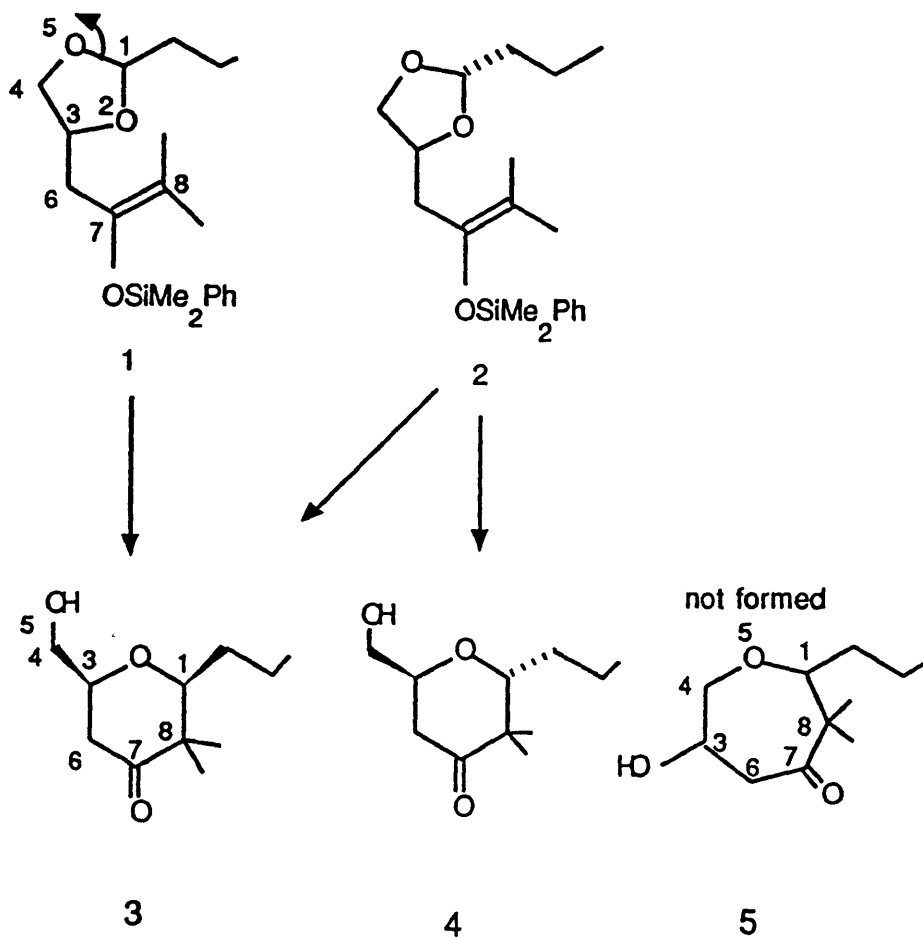
Posner, et al first reported using the intramolecular variation of the Mukaiyama reaction to produce the hydroazulenone (2) in 60% yield from silyl enol ether (1) in his synthetic approach to pseudoguaianes¹⁵:



Cockerill and Kocienski also made use of the silyl enol ether terminator in a TiCl₄ directed cyclization involving the intramolecular variant of the above Mukaiyama reaction in hopes of producing eight-membered cyclic ethers. The synthesis of medium rings poses a classically difficult problem because intermolecular reactions dominate the entropically disfavored ring-like transition state. Galli reports that six-membered ring formation is favored by a factor of ten-thousand over eight-membered.¹⁶ Hence these cyclizations are usually attempted under conditions of high dilution to minimize intermolecular contact.

Kocienski was successful first in producing the tetrahydropyrans by treating dioxolane derivatives (1) and (2) of Scheme 12 with 1-2 equivalents of TiCl₄ in methylene chloride. The expected product tetrahydropyrans (3) and (4) are produced. Kocienski was surprised, though, by the stereospecificity in the production of solely cis tetrahydropyran (3) from cis acetal (1) and both cis and trans tetrahydropyrans, at a 1:1 ratio, from trans starting material (2) when TiCl₄ was used as catalyst. Also promising was the absence of the oxepan-4-one (5), which could potentially result from an alternate acetal fission.¹⁷

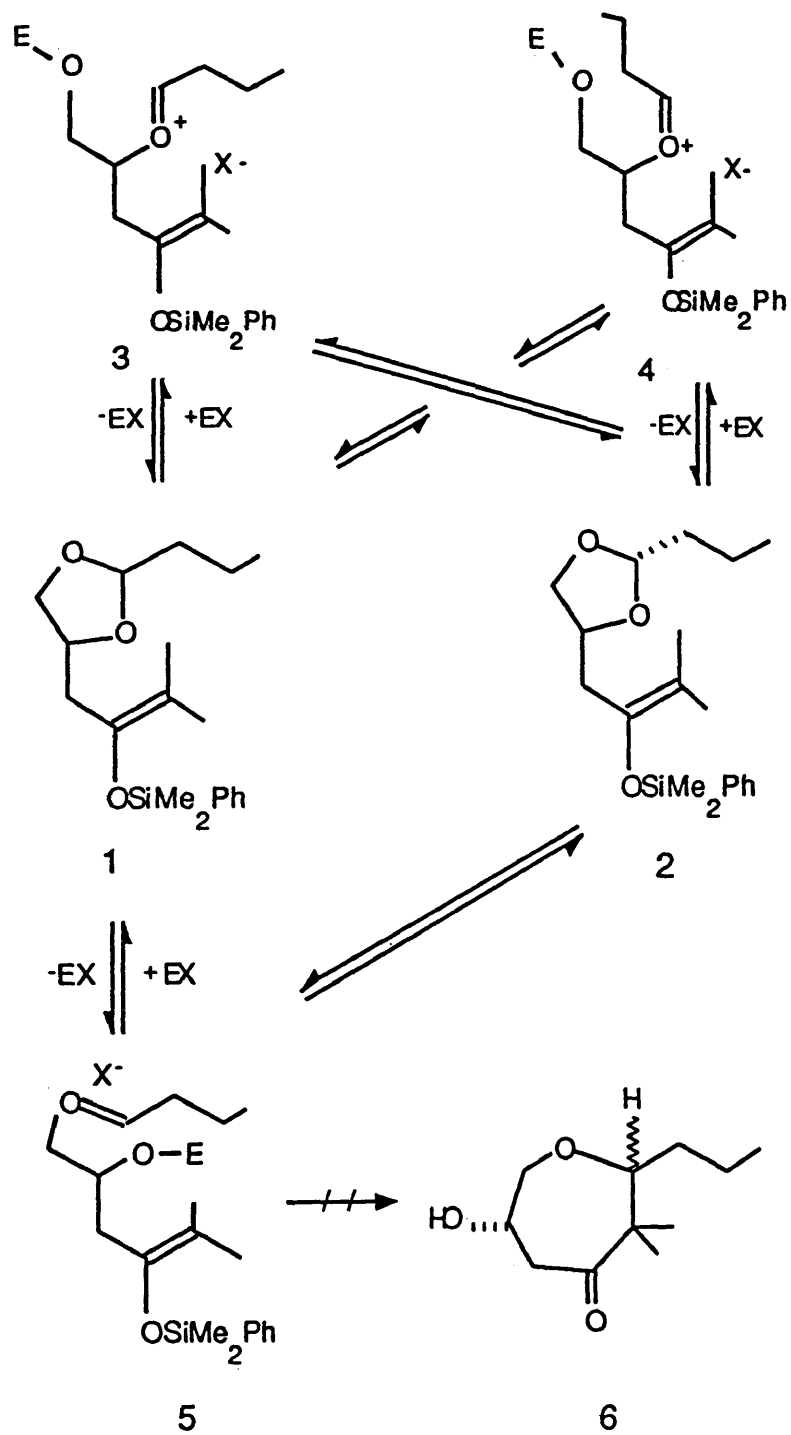
Scheme 12

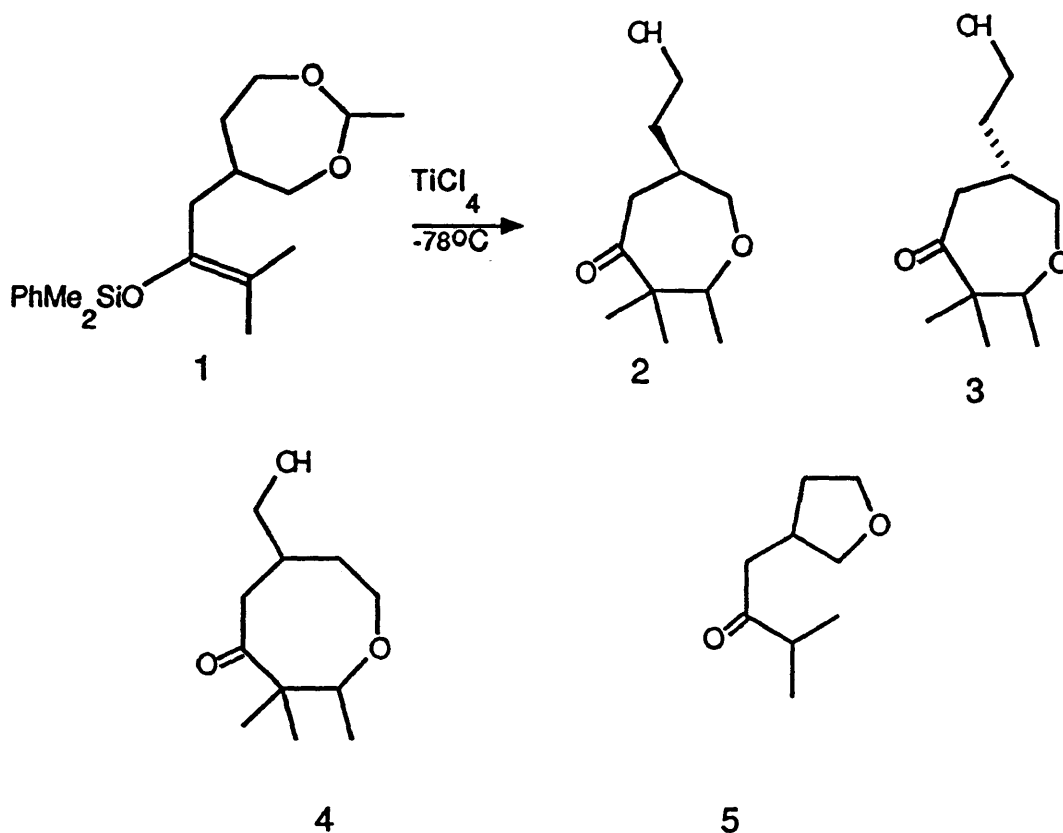


Kocienski was unable to discern the mechanism of cyclization solely from product mixtures and structures. Scheme 13 shows how equilibrium conditions between intermediates in specific pathways destroys the selectivity of the overall reaction and precludes the straightforward elucidation of a discrete mechanism. Electrophilic cleavage of dioxolane (1) and (2) could occur with stereoelectronic control to give the corresponding E and Z oxonium ions (3) and (4) which themselves may cyclize or reverse to isomeric starting material. Uncertainties surrounding the geometry of the intermediate oxonium ions and relative rates of cyclization between the two isomeric intermediates hinder speculation

on the geometry of the acetal or role of the Lewis acid catalyst. Kocienski also points out that the absence of the oxepanone (6) in the product mixture does not confirm regiospecific acetal cleavage. Conceivably, this cleavage could occur, only to be followed by rapid reclosure to starting material and possibly intermediates (3) and (4). He speculates that the relatively slow 7 endo cyclization to give dioxepanone (6) through intermediate oxonium ion (5) may poorly compete with its reversion to starting material. Also, since 30% of the mass of products were polymeric material, it is possible that formation of intermediate (5) may occur, followed by polymerization.

Scheme 13





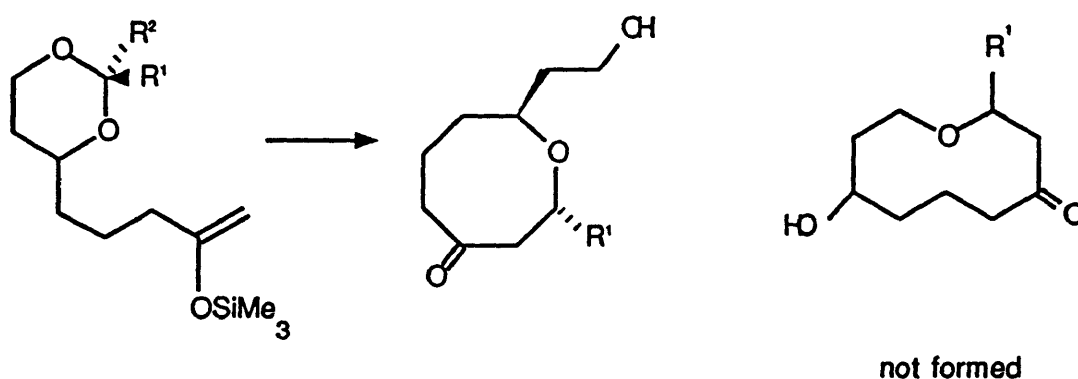
Scheme 14

In order to show that the production of primarily seven-membered rings was possible by the same method, the diastereomeric mixture of dioxepanes (1), (Scheme 14), were reacted with 2 equivalents of TiCl_4 in CH_2Cl_2 at -78° to give the oxepanones (2) and (3) and the oxocanone (4) in 88% yield. Separation was effected after conversion to their dinitrobenzoate derivatives by column chromatography and showed (2), (3), and (4) to be present in a 7:6:4 ratio, respectively. Treatment of the same dioxepanes with 2 equivalents of SnCl_4 , but otherwise similar conditions indicates a dependence of selectivity on Lewis acid employed. SnCl_4 gave 15% of (3) and (2), 20% of the tetrahydrofuran (5), and less than 2% of the oxocanone (4).

Kocienski noticed that in each of the cyclic acetals thus far examined, preference

was given to the formation of the smaller of the two alternative rings. Also puzzling was the formation of but one diastereomer of the oxocanone (4). Cyclic acetal (1), (Scheme 15), as a diastereomeric mixture was therefore synthesized to see if the preference for the smaller rings was observed where either an eight or ten-membered ring is potentially produced. The reaction utilizing TiCl_4 revealed no departure from these observations, as only the 8 endo products are produced in each case as a single diastereomer.

Scheme 15



1) $\text{R}^1 = n\text{-pentyl}$, $\text{R}^2 = \text{H}$

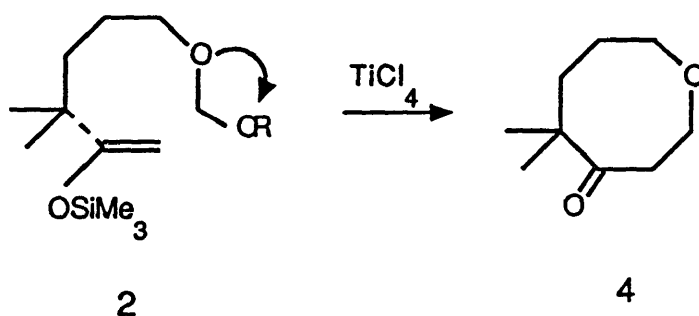
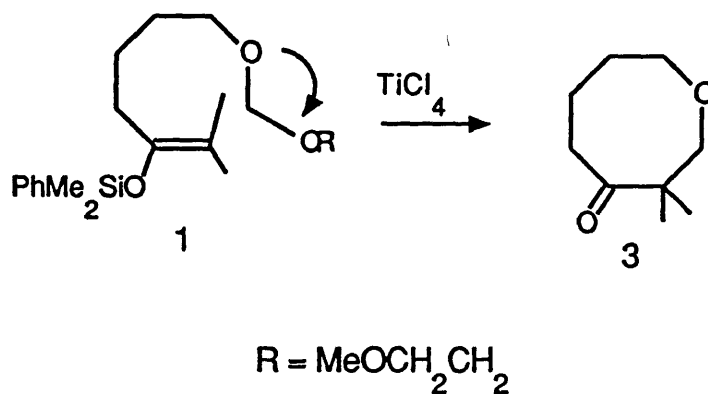
2) $\text{R}^1 = \text{H}$, $\text{R}^2 = n\text{-pentyl}$

3) $\text{R}^1 = n\text{-pentyl}$

5) $\text{R}^1 = n\text{-pentyl}$

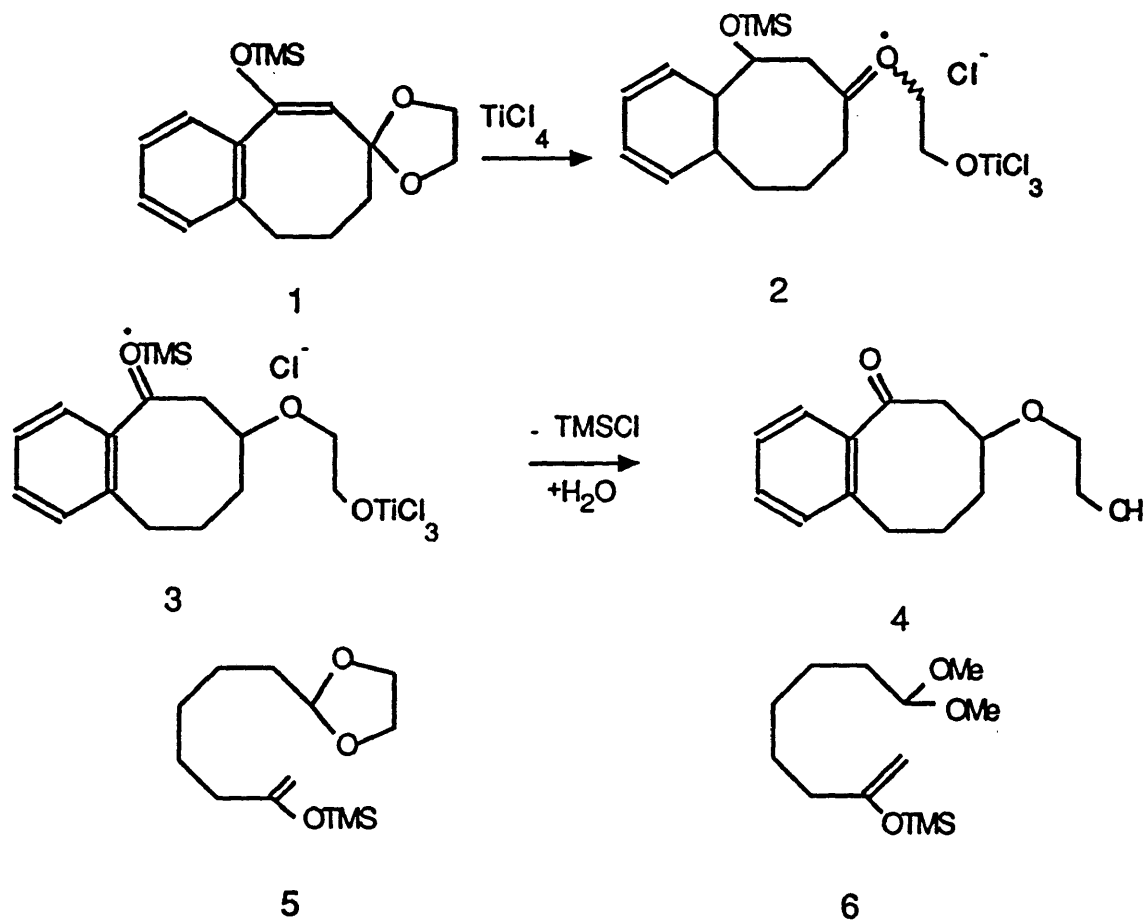
In his next investigations, Kocienski was able to eliminate the ambiguity surrounding the particular mode of acetal cleavage by exploiting the strongly regioselective cleavage in the 2-methoxyethoxymethyl (MEM) ethers induced similarly by TiCl_4 . Oxocanones (3) and (4), (Scheme 16) were unambiguously produced from acetals (1) and (2) in 43% and 55% yield, respectively.¹⁸

Scheme 16



Kocienski then turned his attention to the production of β -alkoxycyclooctanones through the eight-membered exo cyclizations achieved when acetals such as (1) are used to produce the exocyclic ether linkage as shown in Scheme 17. 23 Standard reaction conditions yielded the β -alkoxybenzocyclooctanone (4) in 56% yield, much as one may expect from previous work. Evidence was found to suggest that the yield was deceptively high as cyclization of the enol silanes (5) and (6) yielded only 12-13% of product. The high yield of (4) was explained by the conformational rigidity introduced by the aromatic ring of that precursor holding the reactive functionalities in close proximity.

Scheme 17



In order to maximize the yield of other more conformationally mobile starting molecules, Kocienski studied the effect of the gem-dimethyl substituent placed at various points on the precursor backbone. Fortuitously, the analogous β -gem-dimethyl enol silanes (A) and (B) (Figure 4) underwent TiCl_4 catalyzed cyclization at 43 and 33% yields, respectively. The improvement appears to be an example of the gem-dimethyl effect. The effect can be interpreted by assuming that the "ring-like transition state geometry approximates the lowest energy conformation of the products." These transition states of (A) and (B) occupy the chair boat conformation (Figure 4) with the gem-dimethyl group occupying a sterically unobtrusive "corner site" where they pose no "destabilizing transannular interactions" which could disfavor the achievement of the given transition

state. Conversely, the presence of the gem-dimethyl substituent as shown in the transition states of (C),(Figure 5) and (D),(Figure 6) as shown precludes the formation of chair boat conformation. This is because of steric hindrance between that group and the hydrogens located 4 carbons away. The reactions do occur, albeit through higher energy transition states, suffering accordingly low yields.¹⁹

Figure 4

Transition state of A and B showing geminal dimethyl group occupying sterically favorable "corner Site."

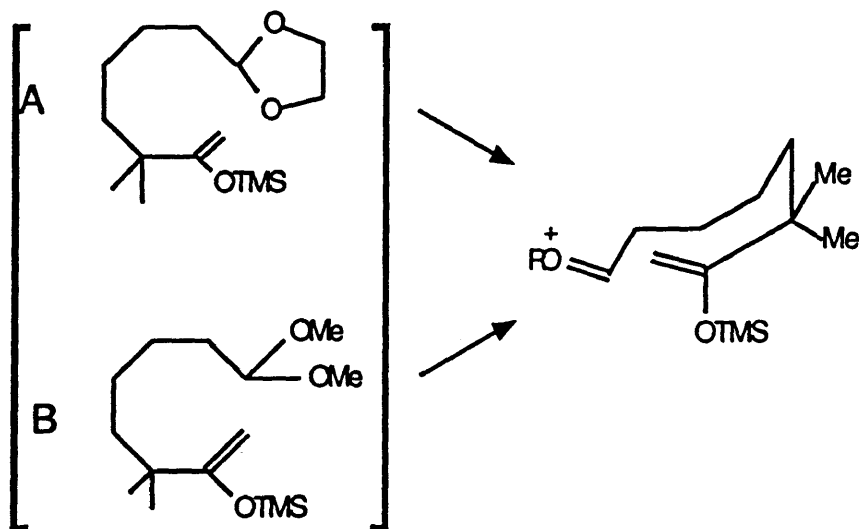


Figure 5

Transition state of C showing steric interference between geminal dimethyl group and nearby hydrogens.

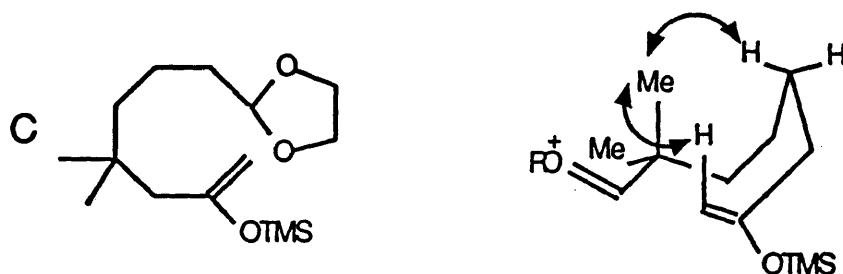
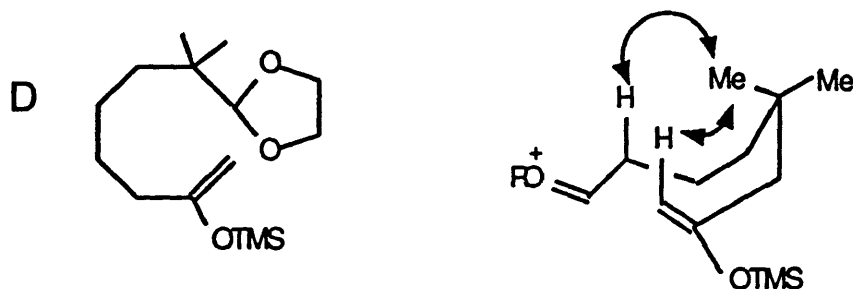


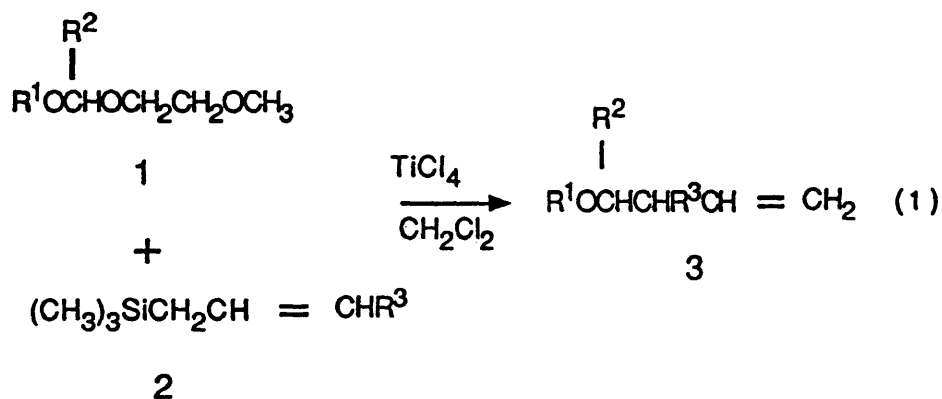
Figure 6

Transition state of D showing steric interference between geminal dimethyl group and nearby hydrogens.



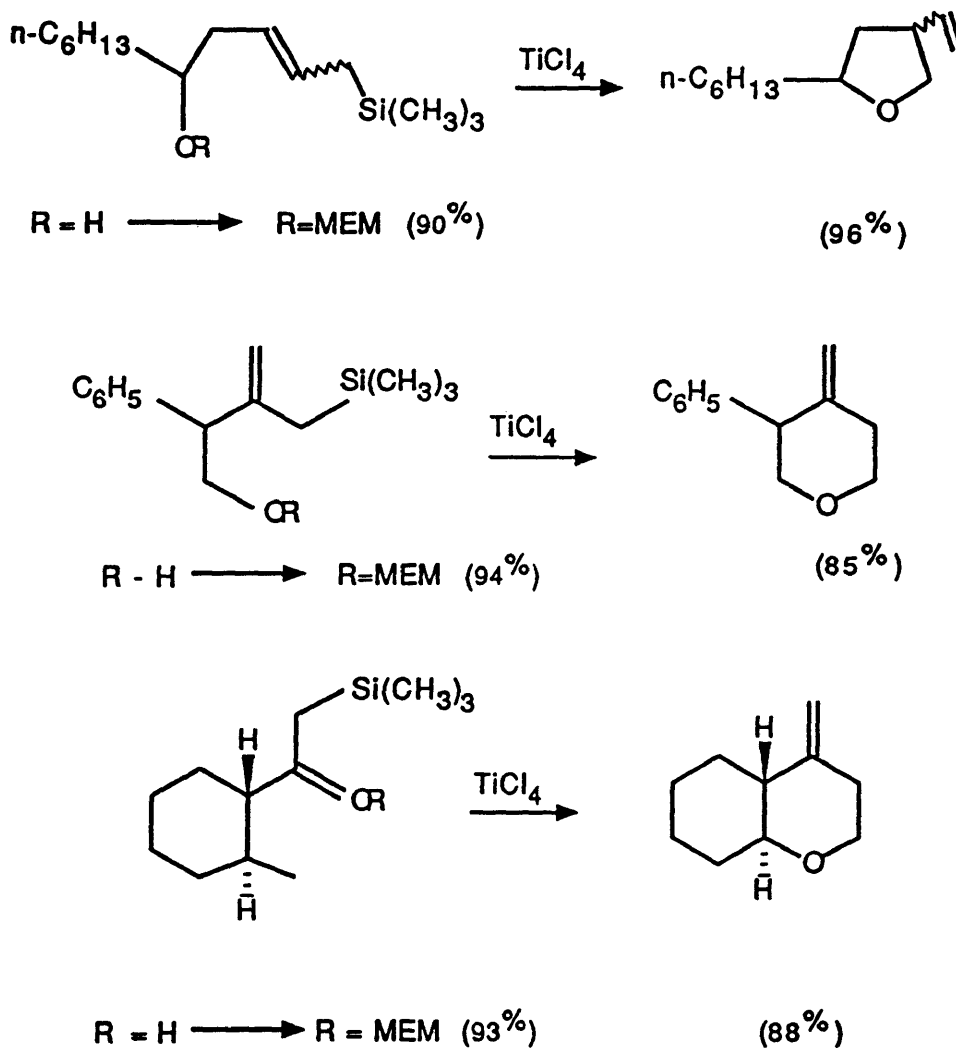
Itoh's Lewis acid promoted formations of homoallyl ethers from unsymmetrical acetals and allylsilanes also provide examples of how the trimethylsilyl terminator can be used to support the formation of a cationic center located β to the silicon atom. Hence, the

regioselective cleavage of (2-methoxyethoxy)methyl acetal (1) below, and subsequent addition of the allylsilyl moiety by way of oxonium ion are followed by the formation of a second cationic center at the favored β carbon. Loss of the trimethylsilyl group produces the homoallylic ether:(3)



As an application to this reaction, Itoh combined the allylsilyl and acetal functionalities on the same molecule to produce an intramolecular oxacycle formation. The hydroxyallylsilanes shown in Scheme 18, were converted to their (2-methoxyethoxy)methyl-substituted allylsilanes by reaction of lithio analogues of the hydroxy allylsilanes with (2-methoxyethoxy)methyl chloride in tetrahydrofuran for 5 hours. The resulting allylsilyl acetals are then treated with 1.1 equivalents of TiCl_4 in CH_2Cl_2 to produce the cyclic ethers indicated.²⁰

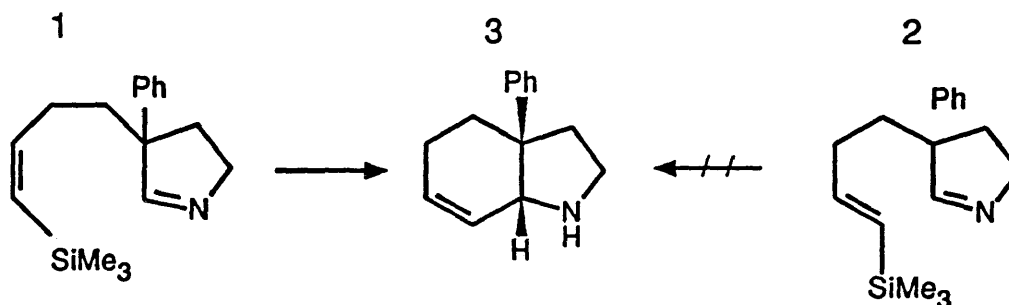
Although the Itoh synthesis is effective in producing the tetrahydrofurans and tetrahydropyrans listed above, no mention is made of stereochemical control as, in each case, only one product stereoisomer is possible.



Scheme 18

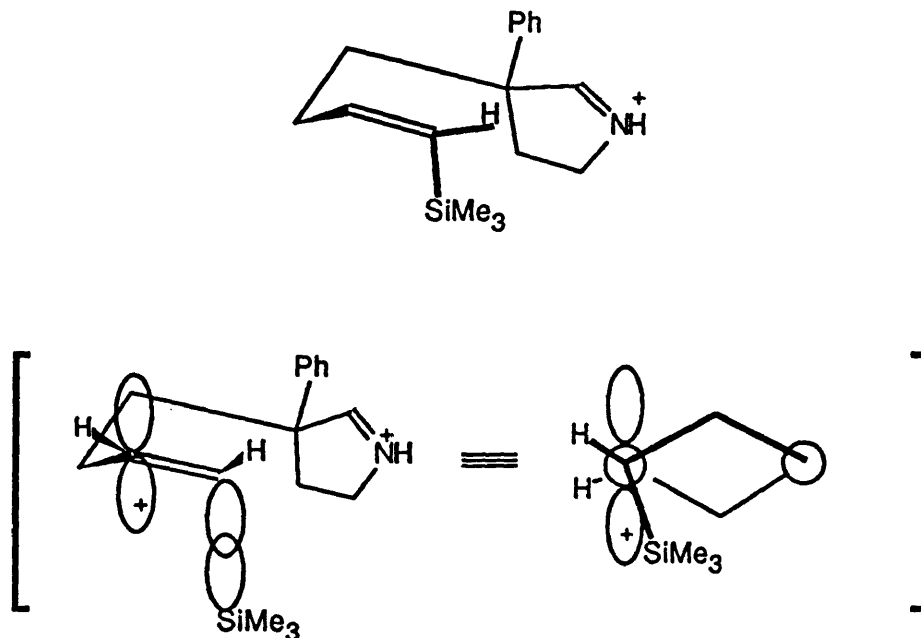
Overman has also made major contributions to the study of cationic cyclizations, although relatively little of his work is directed toward cyclic ether synthesis. Overman's work initially intersects Itoh's in his use of silyl terminators to support β -cations in his intramolecular reaction of iminium ions with vinylsilanes. Trifluoroacetic acid was

employed to effect the stereocontrolled cyclization of the (*Z*)-vinylsilane (1) below by protonation of the nitrogen atom to form the iminium ion. Subsequent formation of the β -silyl cation is followed by loss of the trimethylsilyl group, just as in Itoh's work:



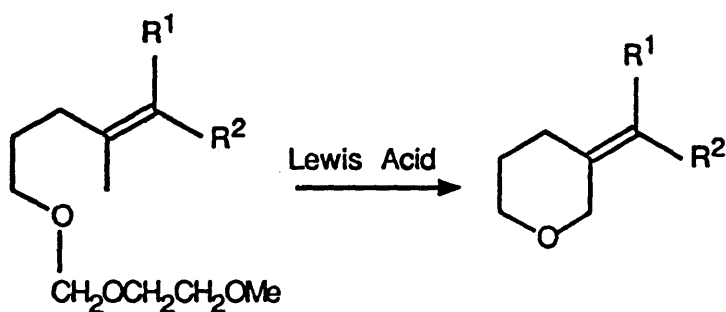
More significant in this synthesis, though, is the light shed on the nature of the β cation stabilizing influence of the silyl terminator by the failure of the (*E*) isomer (2) to yield product. This provides an example of the importance of $[\sigma-\pi]$ stabilization in the cyclization transition state. Scheme 19 shows how only the (*Z*) isomer transition state geometry allows for stabilization of the developing β -cation. Overman's theory is consistent with his and Itoh's cyclizations refuting earlier theories that inductive or other "through-bond" effects are predominant in β -cation silyl stabilization.²¹

Scheme 19



Overman then became interested in using the same technique to produce the five through nine-membered oxacycles using reaction conditions similar to Itoh's to produce the different sized rings from variable substrates. Initial studies employed the use of the (2-methoxyethoxy)methyl ethers to produce acetals such as (1) and (2) below. SnCl_4 catalyst was found to be the most effective, producing (3) and (4) below from (1) and (2) at 89 and

92% yields, respectively. Analysis of products showed the conversion of (1) to (3) and (2) to (4) to be greater than 99.5% stereospecific:



1. $R^1 = H, R^2 = n\text{-Bu}$

2. $R^1 = n\text{-Bu}, R^2 = H$

3. $R^1 = H, R^2 = n\text{-Bu}$

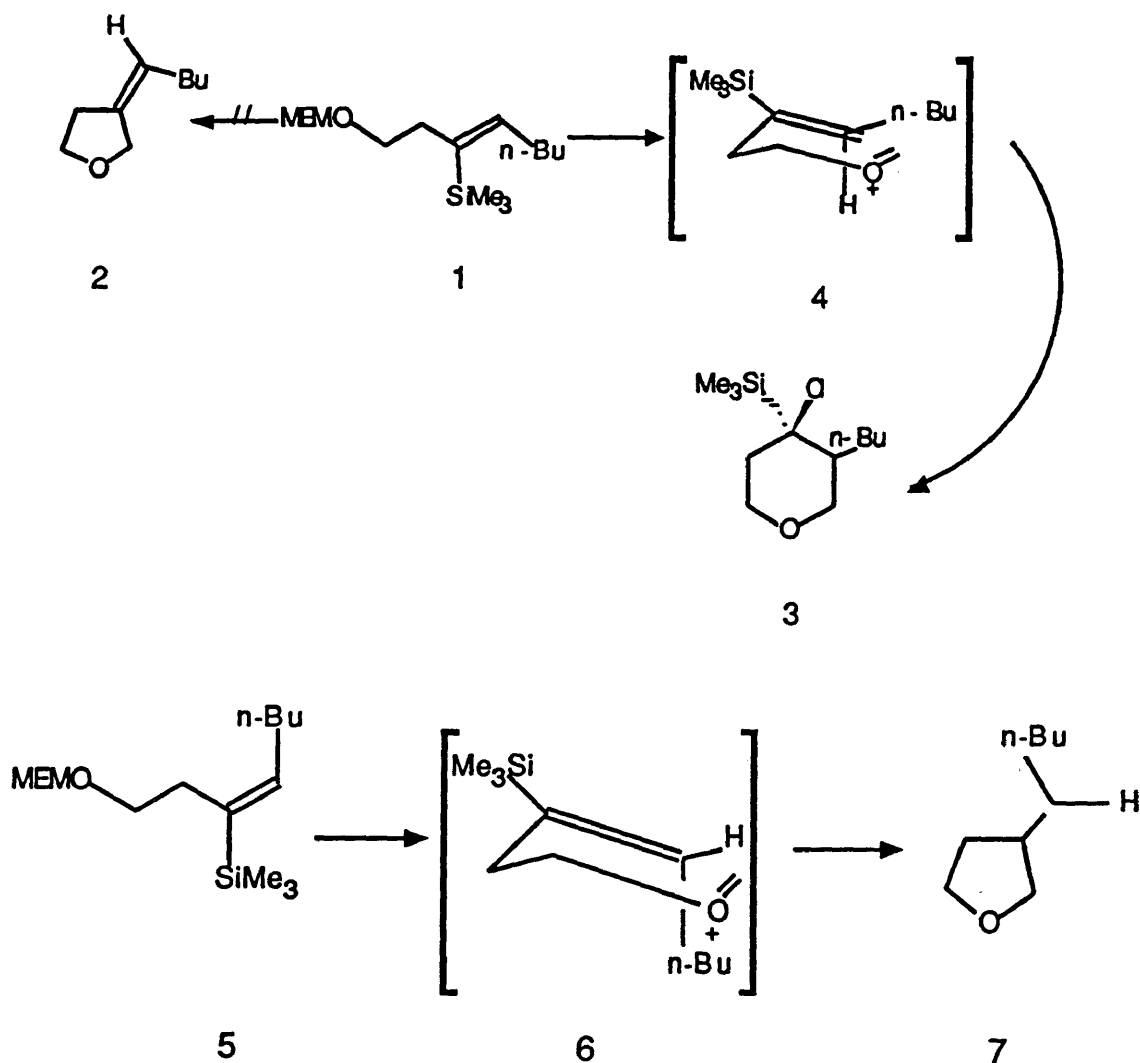
4. $R^1 = n\text{-Bu}, R^2 = H$

Particularly interesting are the somewhat anomalous findings from cyclizations producing the (E)-alkylidene tetrahydrofuran (7), (Scheme 20) from the (E) vinylsilane acetal (1) but the tetrahydropyran (3) from (Z) isomer of the same starting material (1). This unprecedented dependence of exo or endocyclic bond formation on olefin stereochemistry can be rationalized by observing the transition state (4). Tetrahydrofuran formation (via addition of the oxacarbocationic moiety to the carbon atom adjacent to the silicon atom) is unaffected by the substituent pattern at the terminal olefinic carbon. Addition to the β -carbon, however, would be relatively disfavored by steric factors introduced by R^1 and R^2 . Specifically, cyclization of (5) to (7) is allowed because the butyl group can adopt a pseudo-equatorial position while the sterically more demanding pseudo-axial position is occupied in the (Z) acetal transition state (6).²²

Furthermore, the unfavorable geometry of the five-membered Z-acetal transition state dismantles the cation-stabilizing $[\sigma-\pi]$ interactions. This increases the role entropic preference plays in six-membered ring formation and the inductive effect of the relatively

electropositive silicon atom in favoring the tetrahydropyran (3) from (Z)-acetal starting material.

Scheme 20



Tagliavini, in his investigations of allylstannation, discovered that the 2,6-dialkyl-4-halotetrahydropyrans can be synthesized in a $\text{Bu}_3\text{SnCH}_2\text{CH}=\text{CH}_2\text{-RCHO}$ system in the presence of tin(IV) halides., Scheme 21 shows the basic reaction, involving the synthesis

Typical syntheses, undertaken without solvent, involve the addition of 30mmol SnX_4 to a mixture of 30mmol of the original allyl-tin compound and 66mmol of aldehyde. These were then allowed to react for 1 hour at room temperature. Hydrolysis is effected by 2 M Na_2CO_3 before workup.

Table 2 summarizes Tagliavini's work on various starting allyltin compounds. Where appropriate, cis and trans labeling of tetrahydropyrans refers to the stereochemistry across the $\text{CH}(\text{CH}_3)\text{-CH}(\text{Cl})$ -bond. For the most part, formation of the trans isomer is favored.²³

Seamon and Thompson²⁴ also worked with homoallylic alcohols to produce the tetrahydropyran ring, but after first reacting them with the ethyl vinyl ether and (2-methoxyethoxy)methyl chloride to produce their corresponding acetals (Scheme 22). Treatment of the acetals by various Lewis acids yielded quantitative conversion to tetrahydropyrans through the resonance stabilized oxacarbocation attack on the olefin. Either endo or exocyclizations can be promoted, depending on substitution at the olefinic position.

The ethyl vinyl ether and methoxyethoxymethyl (MEM) acetals of various homoallylic alcohols are easily produced using conventional methods. Cyclization of the acetal is facilitated in dry methylene chloride and a four-fold excess of Lewis acid, usually titanium tetrachloride, and proceeds to excellent yields at -45°C and -63°C . The reactions are quenched with 1 N HCL after 40-50 minutes and products isolated via preparative gas chromatography. A typical reaction sequence is shown in Scheme.23

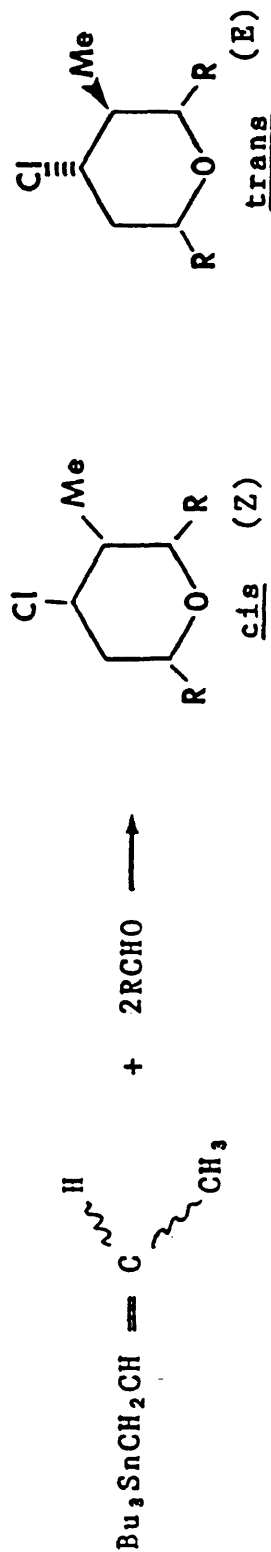
Cyclization of the ethyl vinyl ether acetal of trans 2-vinyl cyclohexanol (Scheme 24) elicits important information on the mechanism of cyclization. NMR spectrometry shows an approximately equal ($50:50 \pm 5$) mixture of diastereomers present in the acetal, but upon cyclization, formation of only one (97%) of four possible diastereomers was observed.³¹ From the comprehensive ^{13}C NMR listings of substituted tetrahydropyrans of Eliel,

Table 2

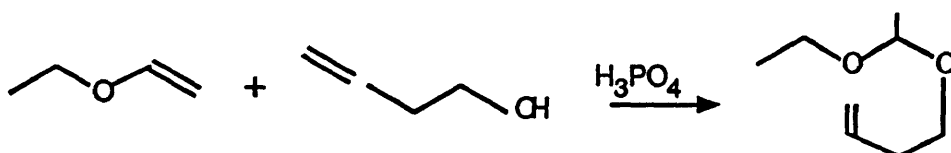
PREPARATION OF 4-CHLORO- AND 4-BROMO-2,6-DIALKYL-3-METHYLTETRAHYDROPIRANS FROM THE SYSTEMS (E/Z)-Bu₃SnCrot + 2 RCHO/SnCl₄(SnBr₄) (Crot = CH₃CH=CHCH₃) IN 1/2.2/1 RATIO "AT" -15°C

RCHO R	Bu ₃ SnCrot E/Z ratio ^a	Time ^c (h)	Tetrahydropyran recovered		Yield (g (%))
			Compound	E/Z ratio ^d	
			X	R	
CH ₃	64/36	2	Cl	CH ₃	3.8 (93)
C ₂ H ₅	66/33	2	Cl	C ₂ H ₅	4.2 (88)
(CH ₃) ₂ CH	33/66	2	Cl	(CH ₃) ₂ CH	4.3 (79)
C ₂ H ₅ (CH ₃)CH	64/36	2	Cl	C ₂ H ₅ (CH ₃)CH	4.5 (73)
(CH ₃) ₂ C	60/40	23	Cl	(CH ₃) ₂ C	4.6 (74)
CH ₃	64/36	2	Br	CH ₃	5.1 (98)
C ₂ H ₅	36/64	2	Br	C ₂ H ₅	5.2 (88)
(CH ₃) ₂ CH	36/64	2	Br	(CH ₃) ₂ CH	6.1 (93)
C ₂ H ₅ (CH ₃)CH	36/64	2	Br	C ₂ H ₅ (CH ₃)CH	5.4 (71)
(CH ₃) ₂ C	36/64	2	Br	(CH ₃) ₂ C	5.6 (73)

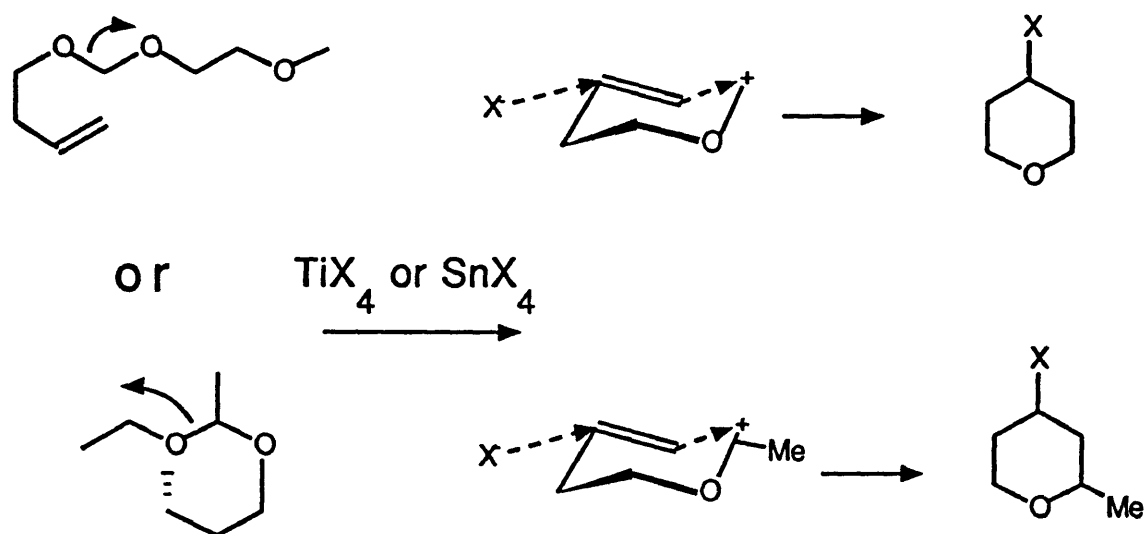
^a All runs have been performed in the absence of solvent with the same amount of reagents: Bu₃SnCrot = SnCl₄ (or SnBr₄) = 25 mmol.; RCHO = 55 mmol. ^b E/Z isomer ratio of Bu₃SnCrot. ^c The period between mixing of the reactants and hydrolysis. ^d The E/Z isomerism refers to the Cl(CH₃)₂-CH(CH₃) bond.



Scheme 22



Scheme 23



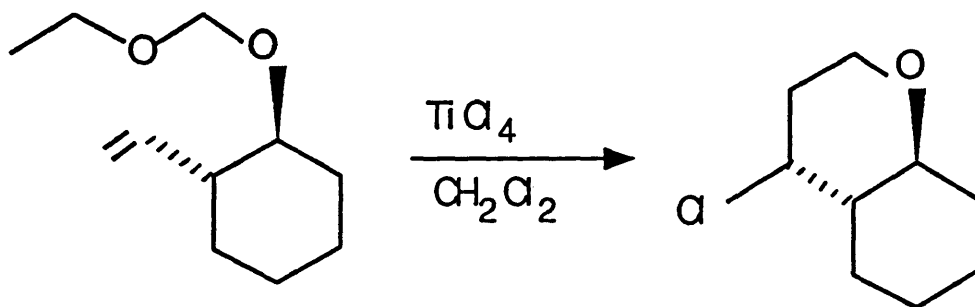
et al ²⁵ one can assign the chemical shift of 22 ppm to an equatorial 2-methyl group. The chloride substituent is also equatorial as indicated by the proton coupling pattern. The exclusive stereochemistry at the 2 carbon is consistent with the formation of a relatively free trigonal oxocarbenium intermediate as illustrated here. The equatorial preference of the methyl substituent is explained in terms of minimizing 1,3 diaxial interactions in the forming tetrahydropyran ring and is consistent with its measured conformational energy of $2.9 \text{ kcal mol}^{-1}$.

If olefinic attack at the electrophilic site were to proceed in a concerted S_N2 fashion, one would expect each of the respective diastereomers, (A) and (B), (Scheme 25) to undergo ring closure with inversion of configuration at carbon-2. Ultimately, concerted attack would yield an equatorial 2-methyl from diastereomer A and an axial 2-methyl from B, resulting in an equimolar mixture of product diastereomers arising from the equimolar diastereomeric mixture of starting acetal. Hence, the production of but one diastereomer effectively eliminates the S_N2 possibility.

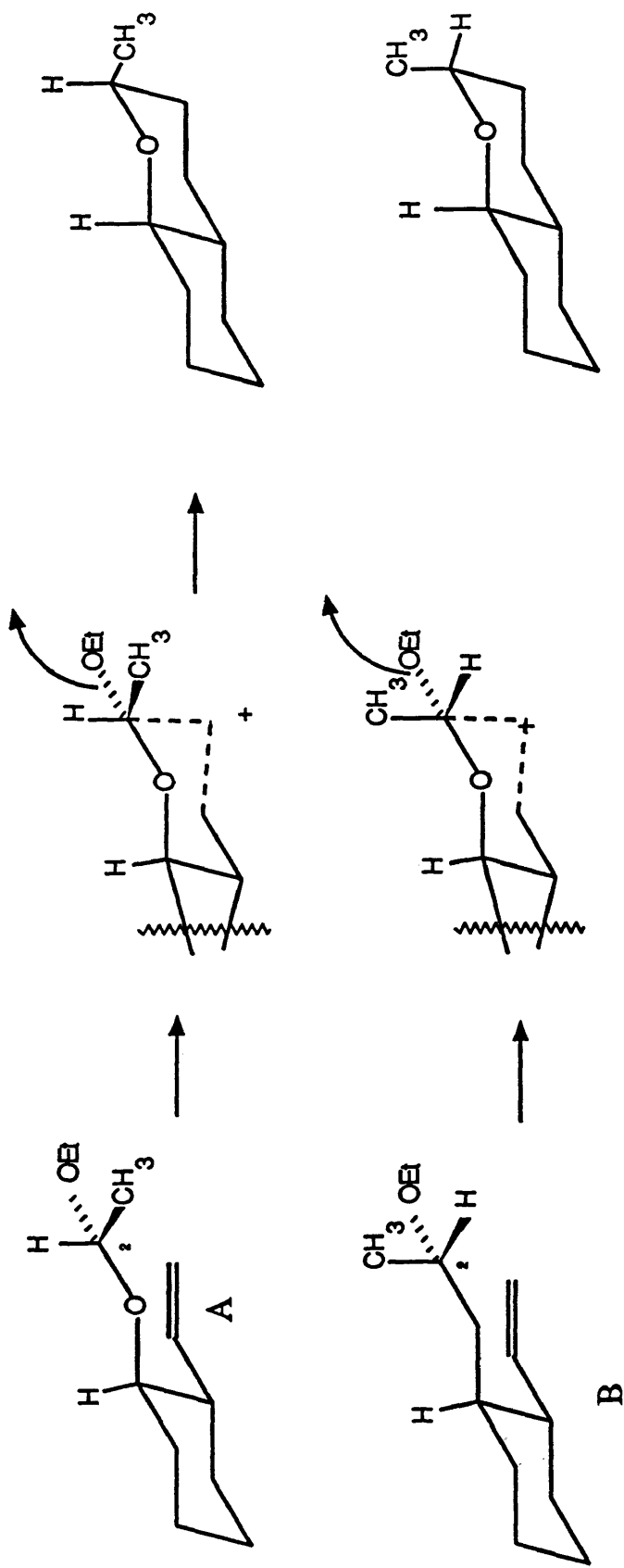
The strong equatorial preference for the chloride despite a rather small conformational stability seems to indicate a significant role of the Lewis acid in assisting chloride ion delivery before a free carbocationic center has time to develop.²⁶

This is consistent with the fact that $TiCl_4$ forms strong acid-base complexes with oxygen atoms. This equatorial attack of halide anion makes for a "trans addition" across the double bond such that the stereochemistry about the former olefinic carbons can be predicted if one anticipates an anti parallel attack of the oxocarbenium and halogen ion.

Scheme 24



Scheme 25



EXPERIMENTAL

All experimental work was directed towards the stereospecific synthesis of variously substituted tetrahydropyrans. First, various homoallylic alcohols were either purchased or prepared using methods described below. Next, these alcohols were converted to their ethyl vinyl ether and (2-methoxyethoxy)methyl acetals. These acetals were then cyclized to produce their corresponding cycle ethers. This experimental section will present the origins of purchased reagents, the preparation of both homoallylic alcohols as well as subsequent acetals, and lastly, the cyclization reactions.

REAGENTS AND SOLVENTS

The homoallylic alcohol 2-methyl-3-buten-1-ol was obtained from Wiley Organics, while the homopropargylic alcohols 3-butyne-1-ol and 3-pentyne-1-ol were supplied by Farchan Laboratories and Albany International, respectively. The alcohols were stored in the refrigerator and used without further purification.

The ethyl vinyl ether (Aldrich D10-620-8) and (2-methoxyethoxy)methyl chloride (Aldrich 19-354-2), as well as 85% phosphoric acid (Fisher, A-242) and N,N-diisopropylethylamine (Aldrich P12,580-6) were used without further purification in acetal preparations.

Titanium tetrachloride (Aldrich 20,856-6), tin tetrachloride (Aldrich 24,995-5) and titanium tetrabromide (Alfa-Ventron) were also used without further purification and handled at all times under nitrogen. Usually, recommended portions of 10 and 20 mmoles were weighed out and sealed in glass ampules which were then broken for use in appropriate reactions. Titanium tetrabromide was kept in a Vacuum Atmospheres Dri-Lab and weighed out at the time of reaction as was the trimethylaluminum (Ethyl Corporation).

1-Heptanol from Eastman Kodak Chemicals was used as an internal standard and

kept at room temperature. Concentrated hydrochloric acid (12 N) was used to prepare 1N hydrochloric acid solution saturated with sodium chloride to destroy the halo(alkoxy)titanium complexes formed during the reaction and upon addition of methanol. Acetic acid (Fisher, A-38), sodium borohydride, and palladium on calcium carbonate both poisoned (Aldrich 20,573-7) and non-poisoned (Aldrich 21,435-3) were all used in the hydrogenation experiment and used as purchased. Aldrich's heavy water and diisobutylaluminum hydride were used in the deuteration experiment. The europium NMR shift reagent $\text{Eu}(\text{fod})_3$ ($\text{fod}=1,1,2,2,3,3,3,\text{heptafluorooctadionate}$) was obtained from Aldrich.

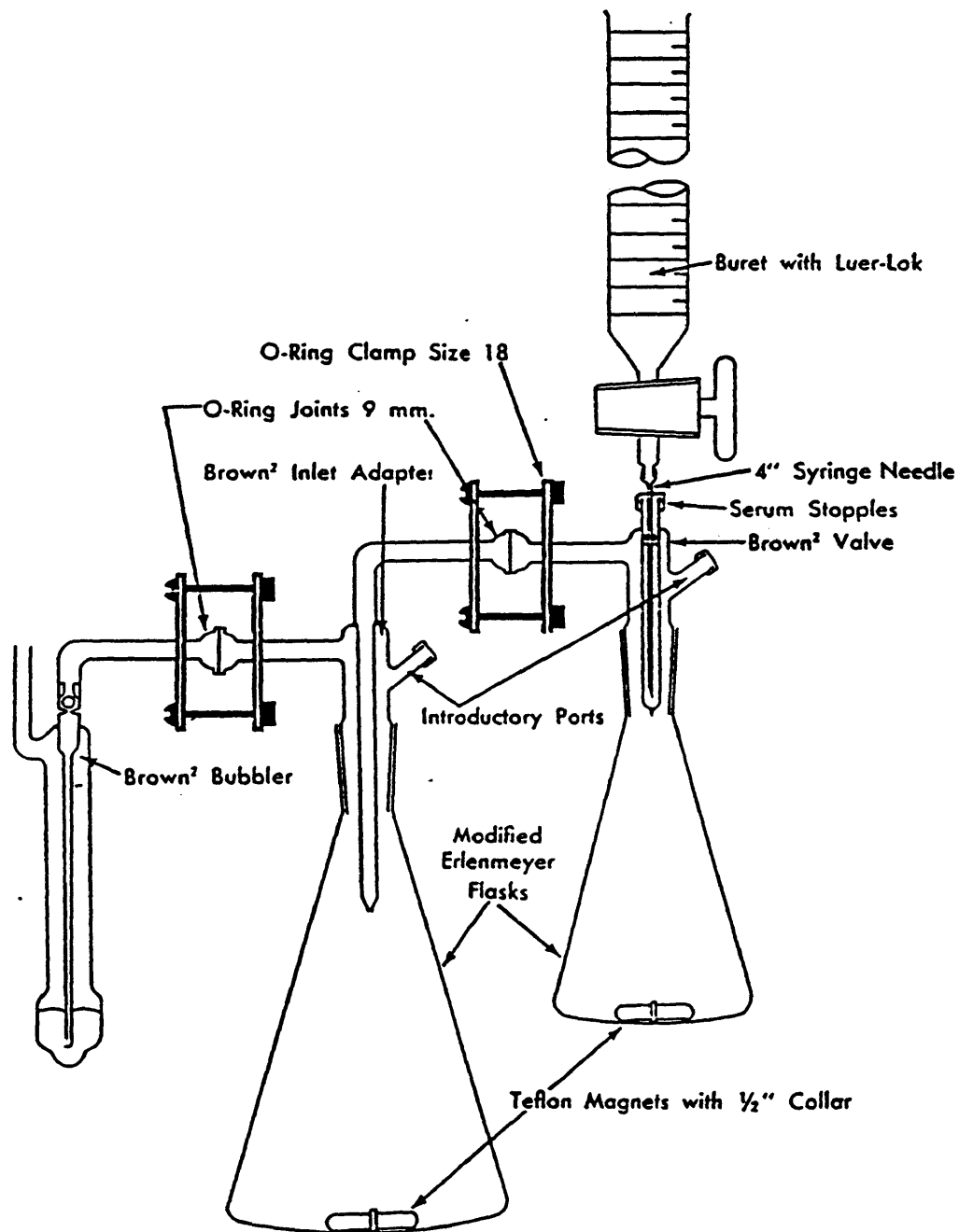
Methylene chloride, supplied by (Fisher, D-37) was used only after careful distillation over phosphorous pentoxide and storage over 4 A molecular sieves. Lab grade ether was used as purchased from Fisher, as was "hexanes".

PREPARATION OF STARTING ALCOHOLS

CIS-3-PENTEN-1-OL

This alcohol was prepared by the hydrogenation of 3-pentyn-1-ol over palladium on calcium carbonate. The Brown² hydrogenation apparatus was employed as shown in Scheme 26. After the apparatus was erected, 24.2 ml of 3-pentyn-1-ol were added to 1.5 grams of palladium on calcium carbonate in the reaction flask at room temperature and atmospheric pressure. The flask was then connected to the adapter and placed over a suitable magnetic stirrer (although stirring was not now begun). The 250 ml buret was filled with 1.00N sodium borohydride solution and attached by means of a 17 gauge transfer needle through a rubber septum cap attached to the verticle port of the "Brown²" hydrogen valve. At this point, 20 ml glacial acetic acid were placed in a 250 ml flask, also equipped with a stirring bar. The flask was attached to the buret port to serve as the hydrogen generator. Approximately 30 ml aqueous borohydride solution was injected by means of syringe needle through the side port into the stirred generator flask to flush the closed system with hydrogen. The stopcock on the buret was opened and vigorous stirring

SCHEMATIC FOR
BROWN² HYDROGENATOR
(External Generation)



Scheme 26

of the reaction solution begun. By monitoring the buret readings, the progress of the reaction was followed and the addition of borohydride solution discontinued when the reaction was complete. The reaction was allowed to proceed for 6 hours after which the pot sample was analyzed by gas chromatography. The palladium catalyst was removed by aid of celite filter and washed with 50 ml methylene chloride. Solvent was removed by rotary evaporation.

Since the chromatogram showed the presence of fully reduced alkanol the catalyst was changed to palladium on calcium carbonate poisoned with lead. The reaction was run again, under identical conditions, and allowed to continue overnight. Inspection of buret, however, showed consumption of only a minimal amount of sodium borohydride solution. Because the presence of alkanol will not adversely effect later reaction schemes, catalyst was switched back to the unpoisoned palladium and reaction allowed to proceed as before to stoichiometric completion (allowing for excess sodium borohydride consumption due to alkanol production). Gas chromatography of final product filtrate showed the presence of both cis and trans alkene and fully saturated alkanol with no evidence of unreacted alkynol. NMR confirms the presence of both cis and trans alcohol due, presumably, to isomerization of cis to trans on the palladium catalyst. Cis predominated over trans in a 3:1 ratio; and 1-pentanol was present at 15% of the total area of the product mixture chromatogram.

TRANS-3-PENTEN-1-OL

This alcohol was prepared by the stereo and regioselective methylation of 3-butyne-1-ol as described below.

Two hundred ml dry methylene chloride and 12 ml trimethylaluminum were added to a dry 500 ml 3-necked round bottom flask in a Vacuum Atmosphere Dri Lab. Outside, under a hood, the flask was attached to a nitrogen inlet, contents brought to 0°C and alcohol added dropwise by syringe through a rubber septum fitted over one of the necks of the flask .

Sixty ml dry methylene chloride and 7 ml titanium tetrachloride were added to a separate "pop" bottle. The bottle was sealed and contents of both the "pop" bottle and round bottom flask brought to -63°C in a chloroform slush bath. After both vessels had reached appropriate temperature, the titanium tetrachloride solution was added via use of a 16 gauge stainless steel transfer needle over a 2-minute period using nitrogen pressure. Care was taken to prevent the leakage of air into the system. After reaction had run for 10 minutes, 20 ml methanol were added slowly to quench, followed by 60 ml HCl saturated with NaCl, also added slowly via dropping funnel.

The solution was then allowed to come to room temperature, extracted with three 100 ml portions of lab grade diethyl ether, and dried using a generous amount of magnesium sulfate. Excess solvent was removed by rotary evaporation. The aqueous purple crusty paste which had formed after solvent evaporation was diluted with 300, H_2O and re-extracted with two 100 ml portions of ether. This second aliquot yielded almost no product. The mixture was then purified by Kugelrohr distillation. Gas chromatography showed the methylated product to be present at 86% by area.

4-METHYL-3-PENTENE-1-OL This alcohol was prepared much in the same way as trans-3-penten-1-ol with the exception that starting material here used was 3-pentyn-1-ol. Four and a half ml of starting alcohol was used and reaction run for 20 minutes. Gas chromatography showed the product to be present at 86% by area, while unreacted 3-pentyn-1-ol occupied 12% area.

CIS-4-DEUTERO-3-BUTEN-1-OL

This deuteration was effected by the diisobutylaluminum hydride reduction of 3-butyn-1-ol employing D_2O in the quenching step to yield the final product.

To a 500 ml round bottom three-necked flask sealed under nitrogen were added 4.8 grams of 3-butyn-1-ol. The flask was brought to 0°C and fitted with a dropping funnel through which 300 ml of 1 N diisobutylaluminum hydride in hexane were added dropwise. The reaction was allowed to come to room temperature and quenched after 12 hours by the

dropwise addition of 100 ml deuterium oxide followed by 100 ml of 1 N HCL saturated with NaCl. The aluminum-alkoxy complex remained undissolved, so approximately 25 ml concentrated sulfuric acid were added, with considerable bubbling before the solid was dissolved. The mixture was extracted with five 100 ml portions lab grade ether and excess solvent removed to yield approximately 2 ml of product. Gas chromatography showed the presence of little unreacted starting material. Unfortunately, the presence of two additional product peaks which have remained unidentified made further synthetic work with the deuterated alkenol impractical.

PREPARATION OF STARTING ACETALS

1-(2-METHOXYETHOXY)METHOXY-2-METHYL-3-BUTENE

A 250-ml three-necked round bottom flask was fitted with a stir bar and nitrogen gas inlet. A ground glass stopper and rubber septum were placed over the other necks. The flask was flushed with nitrogen and methylene chloride (dry) was added. Ten ml (132 mmol) of 2-methyl-3-buten-1-ol were then added via syringe and the flask fitted with a dropping funnel through which 30 ml (170 mmol) were added after the solution was cooled to 0°C in ice water bath. The reaction was allowed to come to room temperature after 1 h and proceed thereafter for 12 h.

To the product mixture were added 100 ml hexanes and the resulting mixture stripped down using rotary evaporation. Another 100 ml hexanes were added, to precipitate out the quaternary amine salt. The salt was filtered off and filtrate extracted with two 40 ml portions of 10% acetic acid. The organic layer was distilled under water aspirator at 97°C and 27 torr and dried with MgSO₄. Potassium carbonate was added to make the mixture slightly basic, insuring preservation of the acetal which is unstable in acidic media. Gas chromatography showed the product peak to dominate the chromatogram at 95% area; the acetal was assumed pure enough for further syntheses.

CIS-1-(2-METHOXYETHOXY)-3-PENTENE

This acetal was prepared in much the same fashion as was the above acetal. Ca. 5

ml cis-3-penten-1-ol were used to generate a solution which was ultimately distilled at 94°C and 25 torr.

PREPARATION OF TRANS-1-(2-METHOXYETHOXY)-3-PENTENE

Again, this preparation is identical to those above. Trans-3-penten-1-ol, produced from the aforementioned carbometallation experiment is used. The final product is distilled on short path at 95°C and 29 torr.

PREPARATION OF 1-(1-ETHOXYETHOXY)-2-METHYL-3-BUTENE

A 100 ml round bottom flask was equipped with a stir bar and suspended over a magnetic stirrer under nitrogen. To the flask are added ca. 5 ml of 2-methyl-3-buten-1-ol, ca. 30 ml ethyl vinyl ether and two drops of 85% phosphoric acid. The reaction stirred for 20 hours at which time an aliquot was removed analyzed by gas chromatography. The analysis showed the presence of essentially product acetal. The reaction was halted by the addition of excess potassium carbonate. The solution was gravity filtered and distilled on vacuum short path to remove excess ethyl vinyl ether and high boiling residue.

PREPARATION OF TRANS-1-(1-ETHOXYETHOXY)-3-PENTENE

The same general method of preparation used in the synthesis of 1-(1-ethoxyethoxy)-2-methyl-3-butene was used here, substituting trans-3-penten-1-ol as prepared above as homoallylic alcohol precursor. After fractional distillation on short path apparatus (88 torr, 110°C), the gas chromatogram showed the product to occupy 85% of the total area.

PREPARATION OF CIS-1-(1-ETHOXYETHOXY)-3-PENTENE

This acetal was prepared in the same fashion as above, using cis-3-penten-1-ol as starting alcohol. The mixture is distilled at 80 torr, 106°C on the short path apparatus.

PREPARATION OF TRANS-1-(1-ETHOXYETHOXY)-4-METHYL-3-PENTENE

The same procedure is used here as in the previous two syntheses; ca. 5 ml of the prepared 4-methyl-3-penten-1-ol produced acetal judged to be ca. 80% pure, with unreacted alkenol occupying ca. 12% area of product chromatogram. Distillation on short path took place at 106°C and 62 torr.

GENERAL PROCEDURE FOR THE CYCLIZATION OF ACETALS TO FORM VARIOUSLY SUBSTITUTED TETRAHYDROPYRAN PRODUCTS

A typical cyclization involved the suspension of a three-necked, 250 ml round bottom flask over a magnetic stirrer and in a dewar flask large enough to house the slush bath which would control the reaction temperature. Chloroform, toluene, or chlorobenzene were utilized for baths at -63°C, -95°C, and -45°C, respectively. A nitrogen gas inlet was fitted to one of the necks and nitrogen blown through the flask to flush the system of any residual moisture. The nitrogen flow rate was then reduced to ca. 120 ml per minute. A tightly fitting rubber septum was placed over another of the necks after ca. 140 ml of freshly distilled methylene chloride and prescribed amount (20 or 40 mmol) of Lewis acid were added. The third neck was then sealed by the appropriate ground glass joint. The flask was then lowered in the dewar and enough bath solvent added to cover the level of

solvent in the round bottom flask. Liquid nitrogen was then added to form a slush bath, bringing the methylene chloride-Lewis acid solution to the desired reaction temperature. After a few minutes, the acetal was added dropwise via syringe through the septum. Care was taken to minimize the amount of acetal dripping down the sides of the flask; most was dropped directly on the surface of the vigorously stirring solution. The slush bath was carefully maintained throughout the course of the reaction.

After the reaction time had elapsed, the mixture was quenched using 5 ml methanol and 50 ml of 1 N HCL saturated with NaCl. The successive addition of methanol and water reduced the bubbling produced as the Lewis acid was destroyed. An acid solution was needed to dissolve the Lewis acid salt and liberate any product still coordinated to it. The reaction continued to stir was allowed to come to room temperature. Typically, an aliquot was removed at this point and analyzed by gas chromatography to insure completion of the reaction. If the run was to be analyzed for yield, a known amount of 1-heptanol as internal standard was added and the flask shaken vigorously to evenly distribute the standard throughout the vessel before analysis.

If the product was to be isolated, the contents of the flask were then transferred to a 250 separatory funnel and the organic and aqueous layers separated. The organic layer is then extracted with three 50 ml portions of diethylether. The combined organics were dried on magnesium sulfate and vacuum filtered into a 500 ml round bottom flask. The solvent was stripped off, and the various tetrahydropyran products isolated by preparative gas chromatography. A discussion of the various reaction conditions, products, and yields is presented in the following section.

CHARACTERIZATION TECHNIQUES

GAS CHROMATOGRAPHY

Analytical gas chromatographic work was performed with Hewlett-Packard models 5710A (fitted with a 30 meter methylsilicone capillary column) and 5790A (packed SP-1000) instruments with flame ionization detectors. The instruments were interfaced with

Hewlett-Packard 3380S and 3390A integrators, respectively. The internal standard technique was employed to determine yields, with response factors estimated from previous work done on similar compounds. Response factors ranged from .9 to 1.1, depending on the number of carbons in the standard compared to that in the unknown.

Preparative chromatographic work was performed on the Hewlett-Packard model 5750 chromatograph interfaced with a strip chart recorder. The instrument was equipped with a 1/4" X 10' 20% SP-1000 column.

NUCLEAR MAGNETIC RESONANCE SPECTROMETRY

A Varian FT-80A nuclear magnetic resonance spectrometer was employed to obtain both C-13 and proton spectra. Higher field work was performed on a Varian XL-300 nuclear magnetic resonance spectrometer.

RESULTS AND DISCUSSION

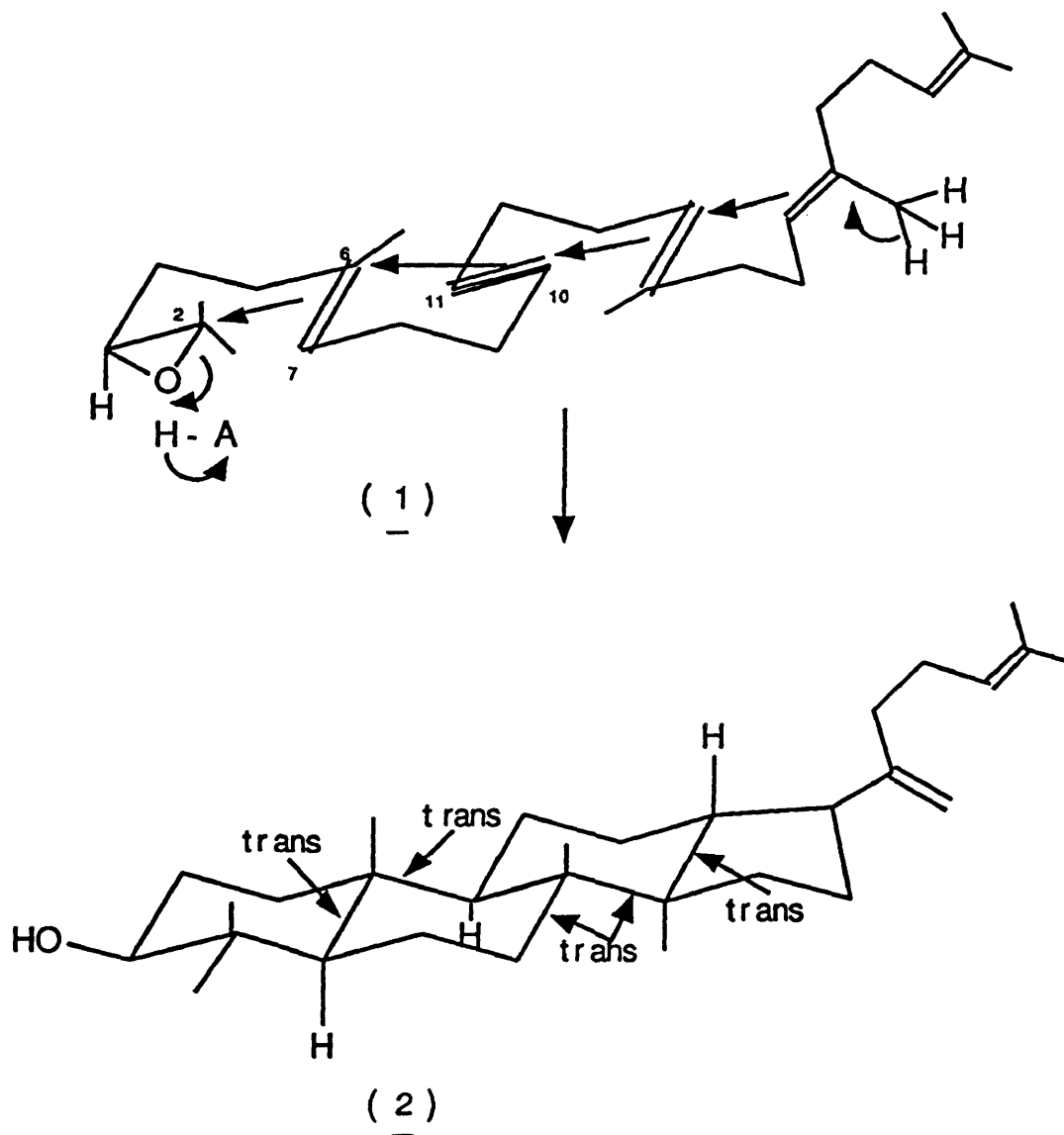
Our research group has made initial contributions to the relatively unexplored area of stereospecific tetrahydropyran syntheses via carbon-carbon bond forming cyclizations. Others such as Itoh,²⁰ Overman,^{21,22} and Kocienski^{17,18,19} have made preliminary contributions in this area. Most stereospecific and stereoselective pathways to tetrahydropyrans have utilized the carbon-oxygen bond forming approach akin to that of Silverstein and Kishi. In these reactions involving carbon-oxygen closure, stereocontrol is usually limited. Desired stereochemical features are normally built into the substrate prior to formation of the final oxacycle.

In earlier efforts of the Thompson group, the ethyl vinyl ether acetal of the parent homoallylic alcohol, 3-buten-1-ol, was found to cyclize predominantly to cis (equatorial, equatorial) 2-methyl-4-chlorotetrahydropyran (Ca. 9:1). Investigations included in this report will cover further stereospecific and stereoselective pathways and attempt to broaden the application of these Lewis acid facilitated cyclizations.

Johnson, in his extensive studies of biomimetic polyene cyclizations, confirmed the hypothesis of Stork and Eschenmoser that the stereochemical course of biological cyclizations could be predicted on stereoelectronic grounds.²⁷ . The dual cyclization occurs to give a trans fused ring system as seen in the naturally occurring triterpenes and steroids. This trans-anti attack is illustrated in the conversion of squalene oxide,(1), (Scheme 27), a known biogenetic intermediate, into the plant triterpenoid. dammaradienol (2) . The Stork-Eschenmoser hypothesis states that electrophilic attack on the 6,7 olefinic bond by the developing cationic center at C-2 will be simultaneously accompanied by nucleophilic attack by the 10,11 double bond.to produce the 6,11 sigma bond. The concerted addition occurs in the same stereochemical sense that molecular bromine adds to

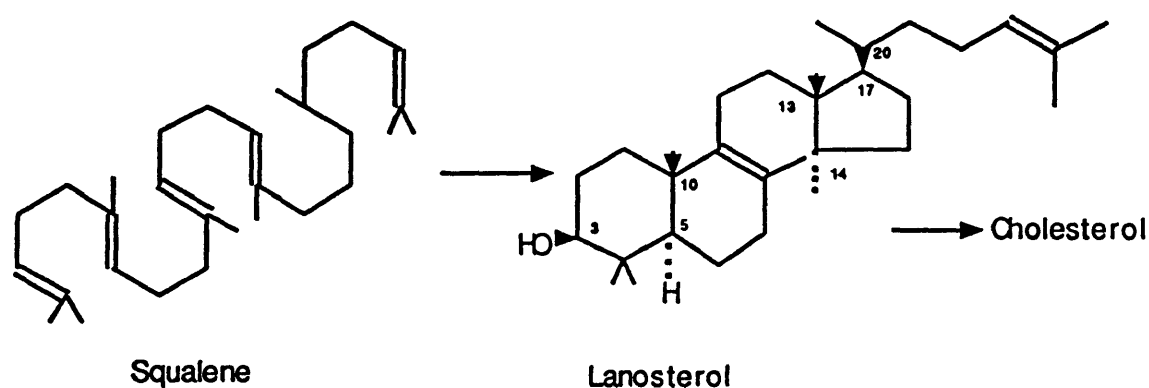
trans-2-butene to give meso-2,3-dibromobutene. A consequence to trans-anti addition is the corollary that a cis-alkene such as (2) will also undergo trans addition to produce the cis-fused bicyclic system.

Scheme 27



Trans-anti parallel attack across the olefin was studied further by Johnson. Below, we see the open-chained polyolefin, squalene, undergoing enzyme catalyzed cyclization to

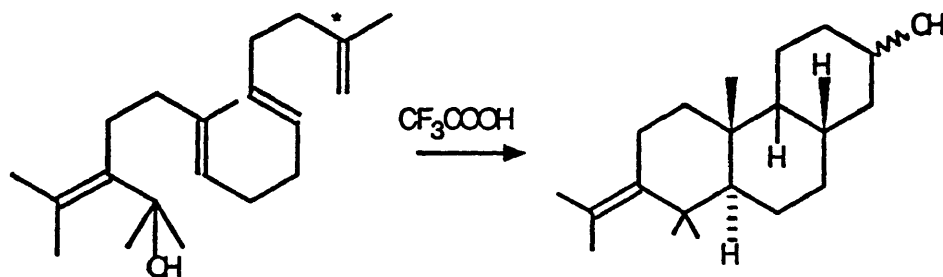
give the tetracyclic material lanosterol, an important intermediate in his total synthesis of cholesterol.²⁸



Noteworthy here is the occurrence of five trans-anti additions to give the four trans-fused rings. Addition of the terminating isopropylidene moiety completes the polycyclization by adding in a pseudo-equatorial fashion. The seven asymmetric centers (at C-3, 5, 10, 13, 14, 17, and 20) are generated such that only 1 of 64 possible racemates is produced.

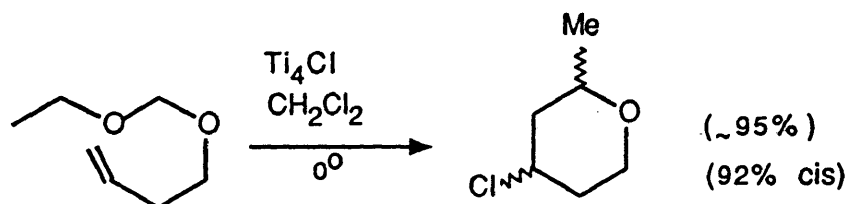
While Johnson's cyclizations tended to yield exclusively all trans cyclic products, variable stereochemistry at the final olefin terminus resulted via the indiscriminate addition of nucleophile. For example, upon trifluoroacetic acid initiated cyclization, the starting tetraenol of Scheme 28 yielded both of the possible all trans epimers, (1) and (2). Presumably, because of the lack of a strong nucleophile under the reaction conditions shown, the carbon marked with an asterisk assumes a planar carbocationic configuration, followed by non-selective nucleophilic addition. Johnson originally avoided the use of strong nucleophiles to minimize the possibility of such a nucleophile prematurely terminating the polycyclization by trapping an intermediate carbon cation.²⁹

Scheme 28



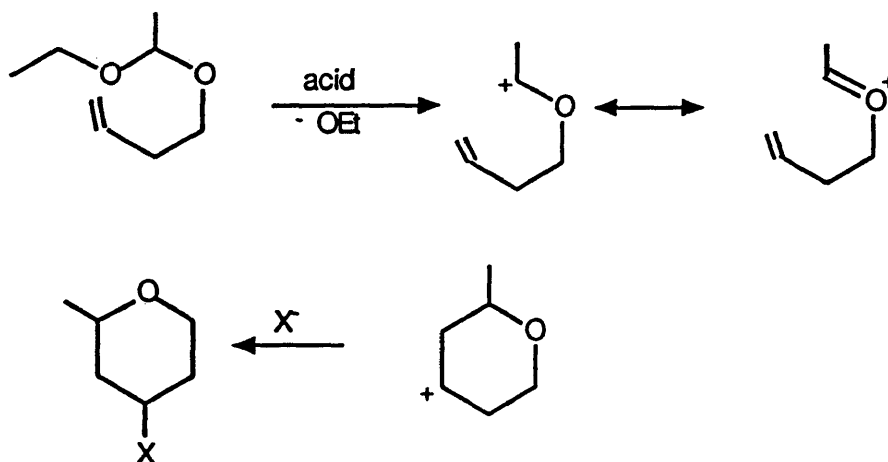
Interestingly, the work of Traynham indicates that in cases of cyclohexyl cationic reactions wherein the nature of the leaving group is not influential, an axial addition of the nucleophile is slightly preferred. Traynham's investigative reaction involved axial and equatorial lead tetracetate oxidative decarboxylations of conformationally locked cyclohexanes. These decarboxylations are carried out via free alkyl cation intermediate to produce the cis and trans alkyl acetates. Analyses of product mixtures showed a preference for the formation of the axial acetate functionality at a ratio of 53:47 from either stereoisomeric starting material. This preference was rationalized on the basis of torsional interactions which deter equatorial addition.

In the earliest work of our group, the ethyl vinyl ether acetal of 3-buten-1-ol was synthesized and cyclized with TiCl_4 to give the corresponding product 2-methyl-4-chlorotetrahydropyran in a 92:8 isomer ratio. The cis (equatorial, equatorial) isomer predominates:²⁴



Clearly, from Traynham's work, a free 4-carbocationic intermediate is not indicated. Rather, the presence of the Lewis acid appears to strongly influence the stereochemistry of chloride addition. This cyclization, analogous to the final closure of the Johnson polycyclizations, demonstrates a preeminence of trans addition. This preference towards trans-addition is not readily explained in terms of the conformational energy of the final tetrahydropyran product since Eliel reports a free energy conformational preference for the equatorial 4-chlorine at a mere .31 kcal/mol.²⁵ Neither can one account for the selectivity of the Lewis acid cyclization by postulating that steric effects posed by the syn-axial protons (1,3 diaxial interactions) sufficiently disfavor an axial addition pathway. Were this the case, the presence of analogous protons in the Johnson cyclization would have had the same effect.

The most reasonable pathway for the Thompson cyclization involves the formation of a primary or secondary oxacarbocation by loss of an alkoxide followed by assisted addition of halide from the Lewis acid promotor:



In order to more fully understand the effects which control the stereochemical outcome of selected cyclizations, the 2-methoxyethoxymethyl (MEM) and ethyl vinyl ether acetals of 2-methyl-3-buten-1-ol were produced in this work. In all cases the MEM acetals

were prepared by reacting MEM chloride and N, N-diisopropylethylamine with a given unsaturated alcohol in methylene chloride. Acetal formation was confirmed by gas chromatography. After removal of the amine hydro-chloride the acetal was isolated by distillation. Ethyl vinyl ether acetals were prepared by the addition of ethyl vinyl ether and alcohol under phosphoric acid catalysis. After neutralization of the reaction mixture, distillation gave the acetal.

Because of variable stereochemistry introduced by the 2-methyl group of the alkenol precursor, two stereoisomers of tetrahydropyran product are possible for the MEM acetal cyclization, four for the ethyl vinyl ether acetal. Stereoisomeric possibilities in their predicted more stable conformations are shown in Scheme 29.

If, as stated by Kocienski, et al,¹⁹ the most favorable ring-like transition state reflects the most stable conformation of the product cycle, we can expect the product distributions to reflect the conformational stabilities of the possible isomers. Below are listed the Eliel's reported conformational stabilities of the monosubstituted tetrahydropyrans most pertinent to our stereochemical predictions. By employing a simple averaging technique using known conformational energies of substituents on the cyclohexane and dioxane rings, Eliel was able to determine the following conformational energies in the tetrahydropyran ring system:²⁵

<u>Substituent</u>	<u>Conformational energy, kcal/mol</u>
2 (6)-methyl	2.86
3 (5)-methyl	1.43
4-chlorine	.31
4-bromine	.34

Hence, upon cyclization of the MEM acetal of 2-methyl-3-buten-1-ol, we expect the product mixture of 3-methyl-4-halotetrahydropyran to be dominated by the trans (equatorial, equatorial) isomer. Indeed, the TiCl_4 promoted cyclization yielded, at 76%, the trans-3-methyl-4-chlorotetrahydropyran in a 68:32 ratio over cis. Use of TiBr_4 , but otherwise similar conditions improved the yield to 86% with a trans:cis ratio of 70:30. These results are consistent with the reported conformational energies for the 4-chlorine (.31 kcal/mol) and 3-methyl (1.44 kcal/mol) substituents, reflecting approximately a net calculated conformational stability of 1.75 kcal/mol for trans-3-methyl-4-chlorotetrahydropyran and 1.78 for the 4-bromo analogue. Table 3 summarizes reaction conditions and products of this and all other cyclizations covered in this report.

Cyclization of the ethyl vinyl ether acetal of the same alcohol introduces another chiral center in the product oxacycle, increasing the number of possible stereoisomers to four. Even if one assumes trans addition across the olefinic region leading to an exclusively equatorial halogen, one still expects four isomers to be produced via variable stereochemistry at carbons 2 and 5.

Cyclization of the ethyl vinyl ether acetal of 2-methyl-3-buten-1-ol yields essentially two diastereomers. This suggests that cyclization ensues to stereospecific results at two of the three asymmetric ring carbons. NMR analysis of product oxacycles reveals the two isomers to be cis, cis and cis, trans-2,5-dimethyl-4-halotetrahydropyran, epimers at carbon 3. If TiCl_4 is used as promotor, the reaction yields 72% product with the cis,trans predominating over the cis,cis isomer in the ratio 78:22. TiBr_4 was more promising, yielding 79% of product, with a similar isomer ratio. The stereochemical results are easily rationalized by taking note of the overwhelming calculated conformational energy of the 2-methyl substituent of 2.86 kcal/mol. Also supportive of these results is earlier work^{26,31} wherein acetal (1), of Scheme 30 cyclizes to essentially one diastereomer despite the potential for stereochemical variation at carbons located adjacent to the oxygen atom. In this example, as in our results, the exclusively equatorial orientation of the

Starting homoallylic alcohol
and preliminary synthesis

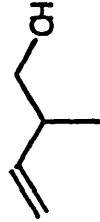
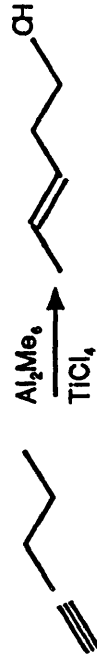
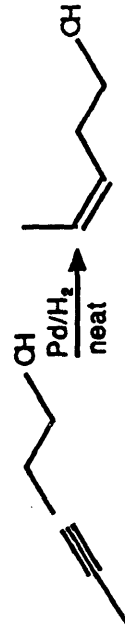


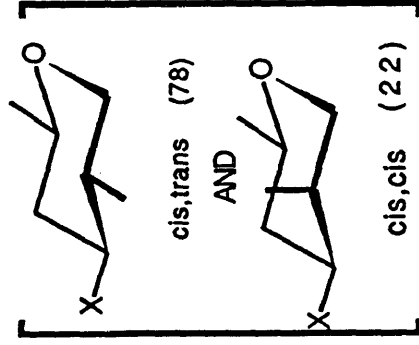
Table 3



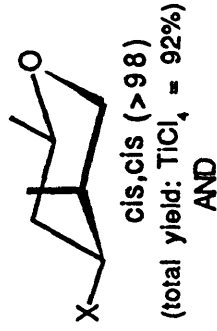
Products from:

ethyl vinyl ether acetals

(isomer percentage of total yield shown in parentheses)

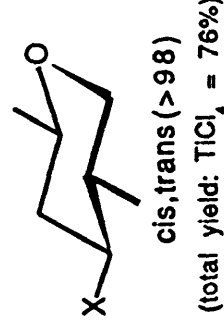


(total yield: $\text{TiCl}_4 = 72\%$
 $\text{TiBr}_4 = 79\%$)



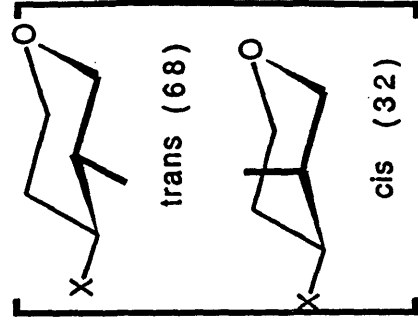
(total yield: $\text{TiCl}_4 = 92\%$)

AND

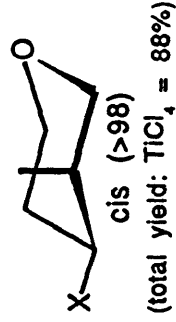


(total yield: $\text{TiCl}_4 = 76\%$)

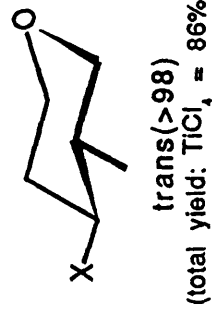
MEM acetals



(total yield: $\text{TiCl}_4 = 76\%$
 $\text{TiBr}_4 = 86\%$)

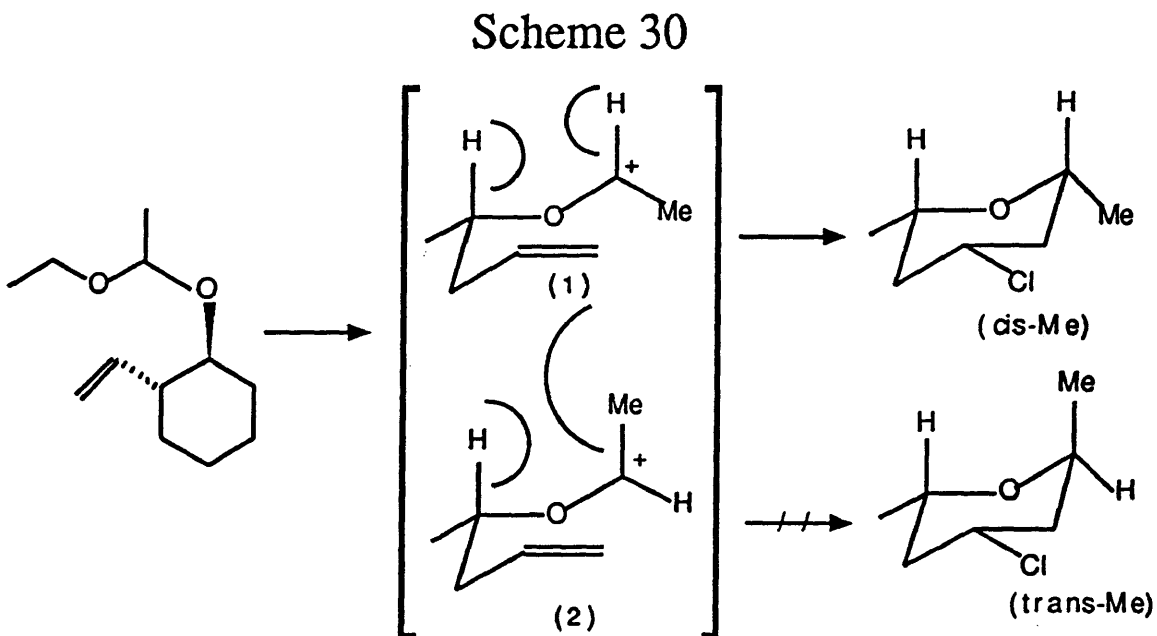


(total yield: $\text{TiCl}_4 = 88\%$)



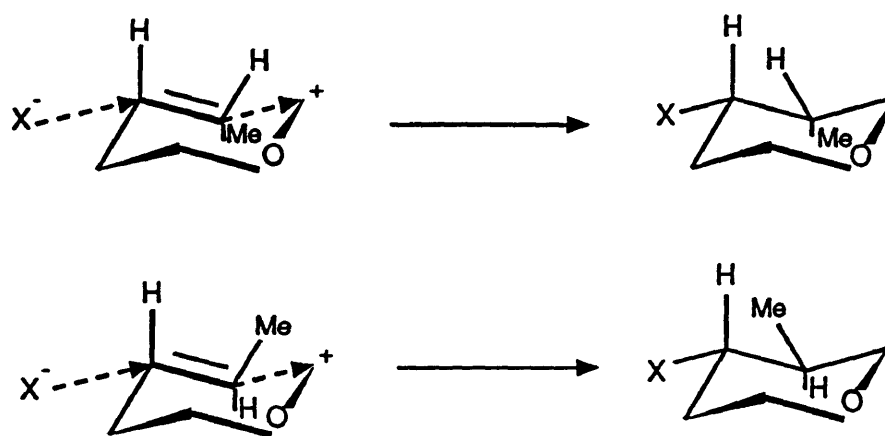
(total yield: $\text{TiCl}_4 = 86\%$)

2-(or 6) methyl group can be rationalized in terms of minimizing severe syn-axial hindrances with nearby hydrogens. Scheme 30, shows how the bulky methyl group of intermediate (1) experiences a severe degree of steric compression compared to that of the pseudo-axial H at intermediate (2)



The fairly specific results obtained in the cyclization producing the 2,5-dimethyl-4-halotetrahydropyran were quite promising in that they confirmed the preeminence of trans-addition leading to stereospecific results at carbon 4 of the product. This being the case, we examined an alternate synthesis leading to completely stereospecific formation of cis and trans-3-methyl-4-chlorotetrahydropyran from the MEM acetals of cis and trans-3-penten-1-ol, respectively. Scheme 31 below shows how trans addition across the double bond allows for the stereochemical integrity of the olefin to be preserved such that a trans olefin yields a trans tetrahydropyran, while cis gives cis.

Scheme 31



Since the internal homoallylic alcohols, cis and trans-3-penten-1-ol were not readily available from commercial sources, a classic hydrogenation of the homopropargylic alcohol, 3-butyn-1-ol, was employed leading to cis-3-penten-1-ol. Palladium on calcium carbonate was employed as catalyst and a mixture of cis and trans alkenol was eventually obtained, with the cis isomer predominating. A much cleaner synthesis, the carbometallation of 3-butyn-1-ol, was employed to give exclusively the trans alkenol.

Separate MEM acetal formations of both the cis and trans alkenols were followed by standard cyclizations at -45°C and found to produce $>98\%$ cis 3-methyl-4-chlorotetrahydropyran (88% yield) and trans 3-methyl-4-chlorotetrahydropyran (86% yield), respectively. Hence, this alternate synthetic route represents a significant improvement over our initial efforts using 3-methyl-2-buten-1-ol wherein both isomers were formed at an ca. 2:1 ratio.

With the ethyl vinyl ether acetal of 2-methyl-3-buten-1-ol, lack of selectivity at the 4,5 portion of the tetrahydropyran ring led to the formation of both cis, trans and cis-2,5-dimethyl-4-halotetrahydropyran. However, we would expect exclusively stereospecific results when the homoallylic precursors cis and trans -4-hexen-2-ol are utilized. Because

of the difficulty attending the syntheses of these alkenol starting materials, particularly cis 4-hexen-2-ol, these syntheses were abandoned though we could envision no complications at the cyclization step previously investigated.

Attention was then turned to the stereospecific synthesis of cis, cis and trans, trans-2,3-dimethyl-4-halotetrahydropyran using the same synthetic strategy of preserving stereochemistry about the double bonds of cis and trans 3-penten-1-ol. Presumably, the cis, cis product tetrahydropyran would possess an axial methyl group in the 3 position, and we hoped to observe the effect of the nearby oxygen on the carbon 13 NMR shift of the 3-methyl group.

Cyclization of the ethyl vinyl ether acetals of both alkenols employing a four-fold excess of TiCl_4 produced cis, cis 2,3-dimethyl-4-chlorotetrahydropyran at 92% yield from cis 1-(1-ethoxyethoxy)-1-pentene, while the isomer was produced at 76% yield from its trans acetal trans, trans substrate. Carbon-13 NMR analysis of the chlorinated cis, tetrahydropyran, confirmed cis, cis stereochemical assignments, and proved interesting as the 3-methyl group shift was observed upfield relative to all other methyl substituent shifts at 6.0 ppm. The finding is puzzling when one takes note of the chemical shift of 11.0 ppm for the axial methyl at carbon 5 of cis, cis-2,5-dimethyl-4-chlorotetrahydropyran. The relatively large discrepancy between the two shifts, despite the similarity in their spatial orientation with respect to the oxygen atom is explained by the γ -gauche upfield shift introduced by the intervening 2-methyl group of cis-2,3-dimethyl-4-chlorotetrahydropyran. The effect, first quantified by Eliel,³² describes the upfield CMR shift introduced by substituents located in γ -gauche orientation from the carbon in question. This topic is further discussed in the following characterization section.

Proton NMR proved to be most beneficial in making concrete stereochemical assignments to the tetrahydropyran products. In each of the spectra, protons located on carbons adjacent to the oxygen atom as well as the 4-proton (always geminal to a halogen atom) elicit chemical shifts furthest downfield, in the range 2.8 to 4.2 ppm. By carefully

examining chemical shifts and splitting patterns of these protons, can we rigorously confirm stereochemistry predicted based on synthetic strategy. In cases where a great deal of overlap is seen in the shifts for these protons, selected samples were evaluated at a higher field (300 MHz).

Particularly helpful in the assignment of stereochemistry is the occurrence of the downfield shift of the equatorial 4-proton of cis-3-methyl-4-halotetrahydropyran. Figures 7 and 8 show a pseudoquartet in the region 4.3-4.5 ppm for both the chlorinated and brominated cis oxacycles. The splitting arises from equivalent couplings with the equatorial proton of carbon 3 and the axial and equatorial protons of carbon 5, measured at ca. 4 Hz. Carbon 13 NMR confirms the equatorial assignment for the 3-methyl by showing its shift at 14.2 and 16.0 ppm for the chloro and bromo tetrahydropyrans, respectively. For the trans isomer, an upfield shift of the axial 4-proton is expected and obscured by overlap with the 2 and 6 hydrogens as shown in Figures 9 and 10. Rigorous stereochemical characterization is unnecessary in this case, as only two isomers can possibly be produced from the given substrate. Again, carbon 13 NMR confirms the expected overwhelming preference for the diequatorial conformer of the trans isomer by

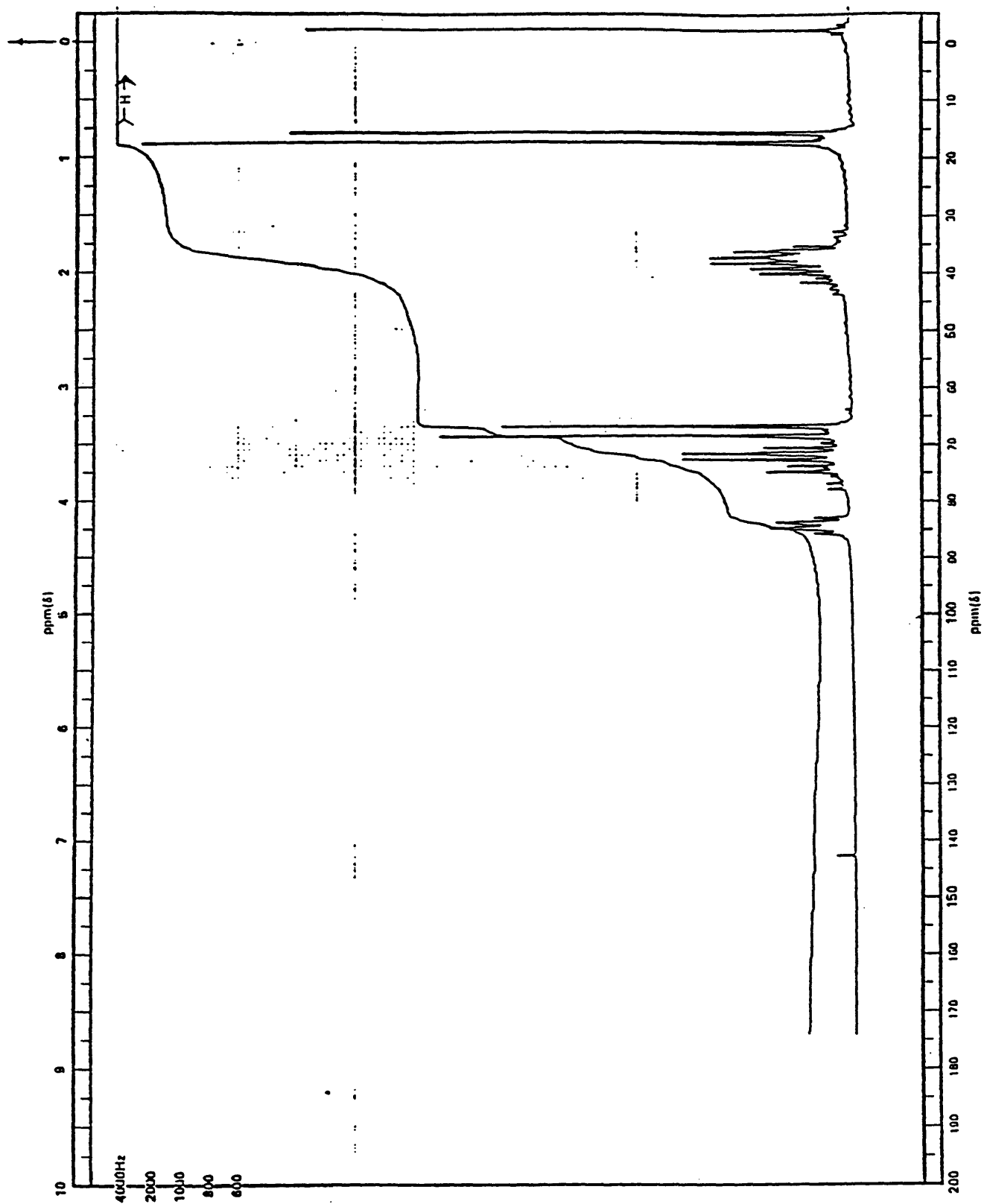


Figure 7 ^1H NMR spectrum of *cis*-3-methyl-4-chlorotetrahydropyran at 80 MHz

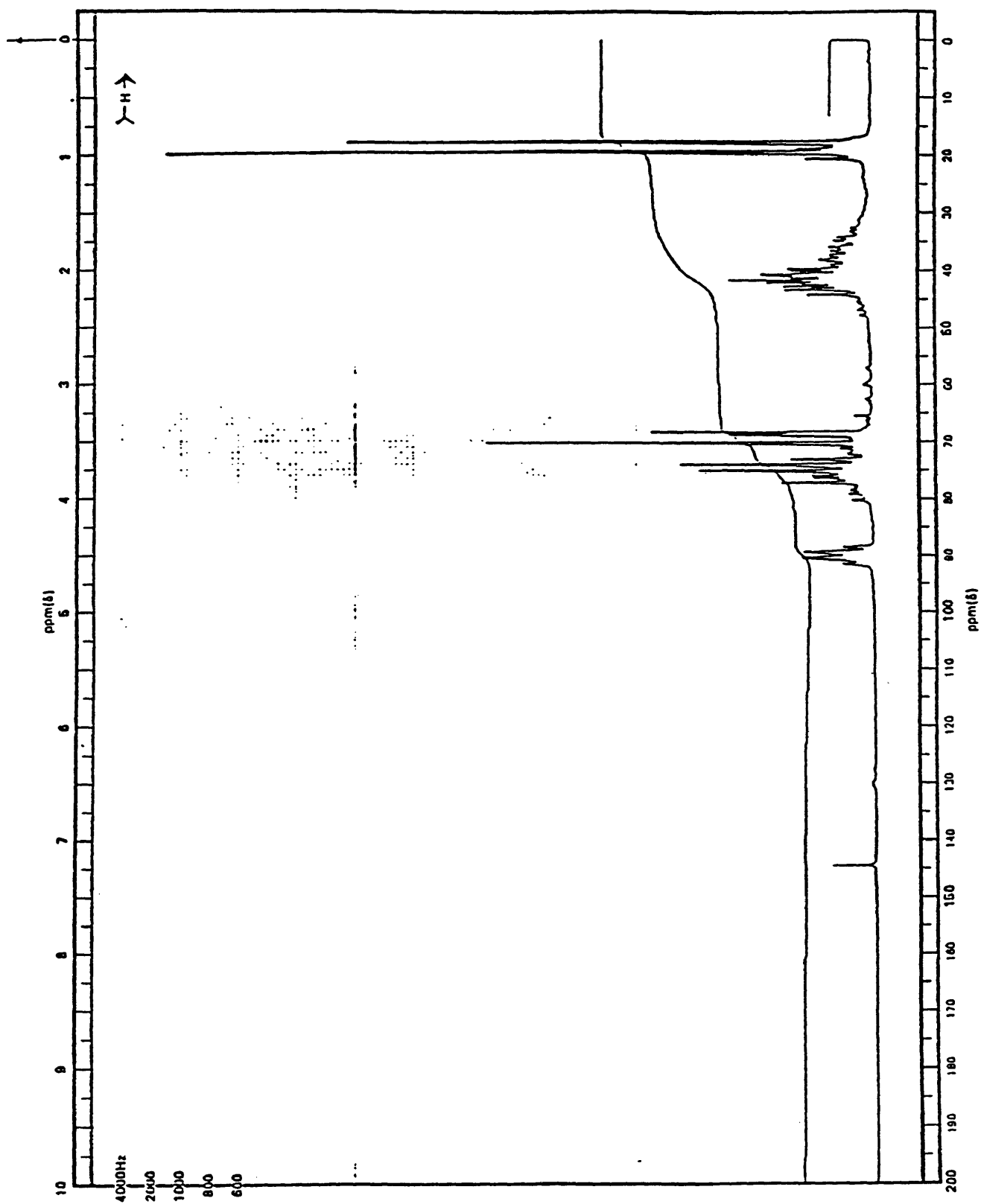


Figure 8 ^1H NMR spectrum of *cis*-3-methyl-4-bromotetrahydropyran at 80 MHz.

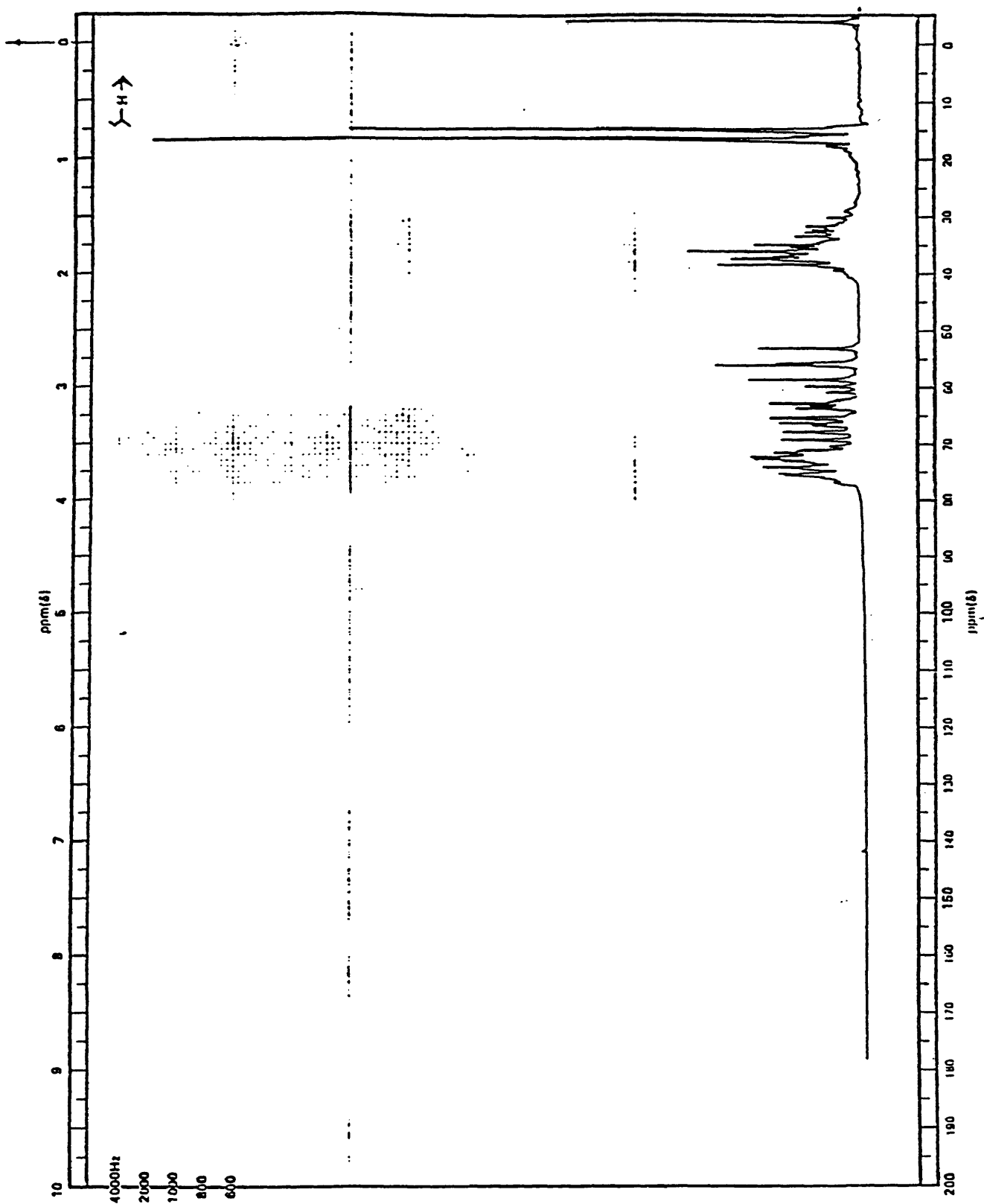


Figure 9 ^1H NMR spectrum of trans-3-methyl-4-chlorotetrahydropyran at 80 MHz.

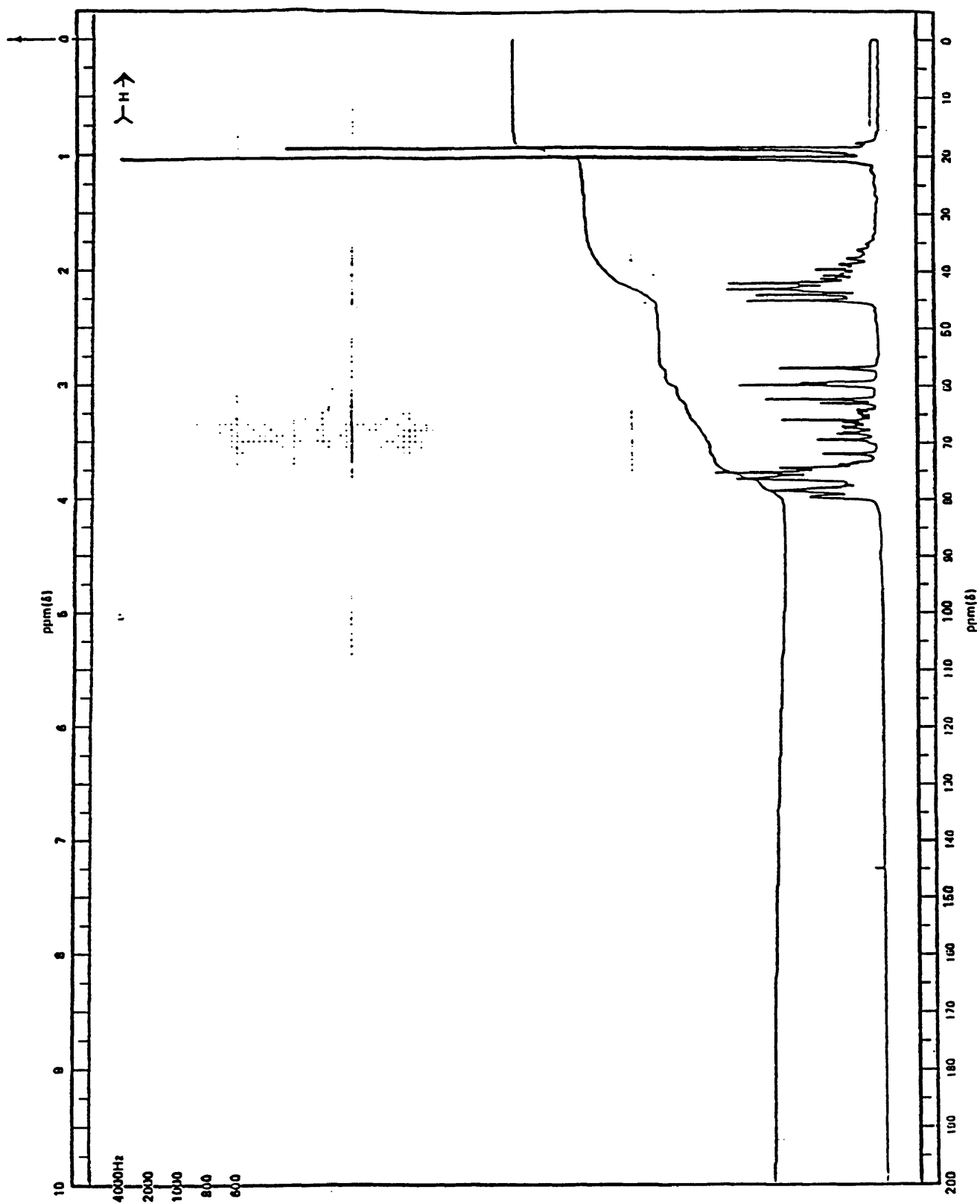


Figure 10 ^1H NMR spectrum of *trans*-3-methyl-4-bromotetrahydropyran at 80 MHz.

showing the 3-methyl shift in the same region as that for the cis isomer.

Upon considering the proton NMR of what was suspected to be cis, cis-2,5-dimethyl-4-chlorotetrahydropyran (Figure 11), a pseudoquintet is observed at 4.2 ppm, the region suspected for the 4-axial proton. The pattern is consistent with that expected for one relatively large coupling constant, and two smaller roughly equivalent couplings. Overlap of peaks accounts for a pseudoquintet appearance. The large and small couplings correspond to the axial-axial and two axial-equatorial couplings predicted for the axial 4-proton. Here, the axial-axial coupling constant is measured at ca. 11 Hz and axial-equatorial at ca. 5.5 Hz. The spectrum (Figure 13) of the bromo analogue shows its 4-axial proton to be shifted downfield relative to the chlorinated compound at 4.4 ppm. This downfield shift is commonly observed. The pattern suggests an axial-axial coupling of 11 Hz and an axial-equatorial coupling of 6.0 Hz.

The axial-axial coupling constant is hereafter referred to as J_{aa} ; axial-equatorial and equatorial-equatorial coupling constants are denoted as J_{ae} and J_{ee} , respectively. Notice that not only do these splittings confirm an axial orientation of the 4-proton, but they also require an axial disposition of the 5-proton. With the correlation to the literature value for the measured C-13 NMR shift of the equatorial 2-methyl at ca. 19 ppm, the structure for cis, cis-2, 5-dimethyl-4-chlorotetrahydropyran is reasonably established.

Concrete assignment was made more difficult in the case of cis, trans-2,5-dimethyl-4-chlorotetrahydropyran since the shift for the 4-proton is further upfield than that observed for the cis, cis isomer and obscured by overlap with the 2 and 6 protons in the 2.5-4 ppm range of Figures 13 and 14. High field NMR at 300 Hz (Figure 15) reveals a triplet of doublets rationalized by two axial-axial couplings ($J_{aa}=11.2$ Hz) and an axial-equatorial coupling of 4.3 Hz, shown enlarged in Figure 15a. Also shown in 15a is the equatorial 6-proton shift at 3.9 ppm. The observed doublet of doublets is accounted for by a geminal coupling of 11.8 Hz and an equatorial-axial coupling of 4.6 Hz. Figure 15b shows the expanded shifts of the axial proton of carbon 2 and the axial proton of carbon 6. The axial

6-proton is accounted for by two approximately equivalent couplings with the vicinal axial proton of carbon 5 and the geminal proton, measured at ca. 11 Hz.

The six-fold shift, suspected to be that for the axial 2-proton, arises from overlapping quartets split by coupling with the axial proton of carbon 3 by 10.9 Hz. The quartets reflect a coupling with the 2-methyl protons at 6.5 Hz. The absence of discrete doublets expected for a smaller coupling with the remaining equatorial 3-proton is not readily explained.

High-field NMR also proved essential to the concrete assignment of both isomers of 2,3-dimethyl-4-chlorotetrahydropyran. Figures 16 and 16a show the shift for the axial proton at carbon 2 of trans, trans-2,3-dimethyl-4-chlorotetrahydropyran at 3.1 ppm. The two overlapping quartets are split by the axial proton at carbon 3. Here, the coupling constant is measured at 9.5 Hz. The coupling with the 3 protons of the 2-methyl group is measured at 6.1 Hz. Figure 16b shows the shift for the axial proton at carbon 4. As suspected, the shift shows a triplet explained by coupling with two axial protons at carbons 3 and 5, both measured at 11.7 Hz. The triplet is then split into two by coupling with the equatorial proton at carbon 5. Here, J_{ae} is measured at 5.0 Hz. Figure 16c accounts for the shift of the equatorial 6-proton at 3.9 ppm. The pattern shows a doublet of doublets of doublets formed by three unequal couplings of 11.7, 5.0, and 1.9 Hz with the geminal, 5-axial, and 5-equatorial protons, respectively. Figure 16d shows the shift of the axial proton of carbon 6 and can be accounted for by proposing a geminal coupling constant roughly equivalent to an axial-axial coupling at ca. 11.8 Hz. The jagged appearance of the shift is explained by the slight inequality of the couplings. The equatorial proton at carbon 5 couples with an equatorial-axial coupling constant of 2.4 Hz to yield the observed doubling of triplets.

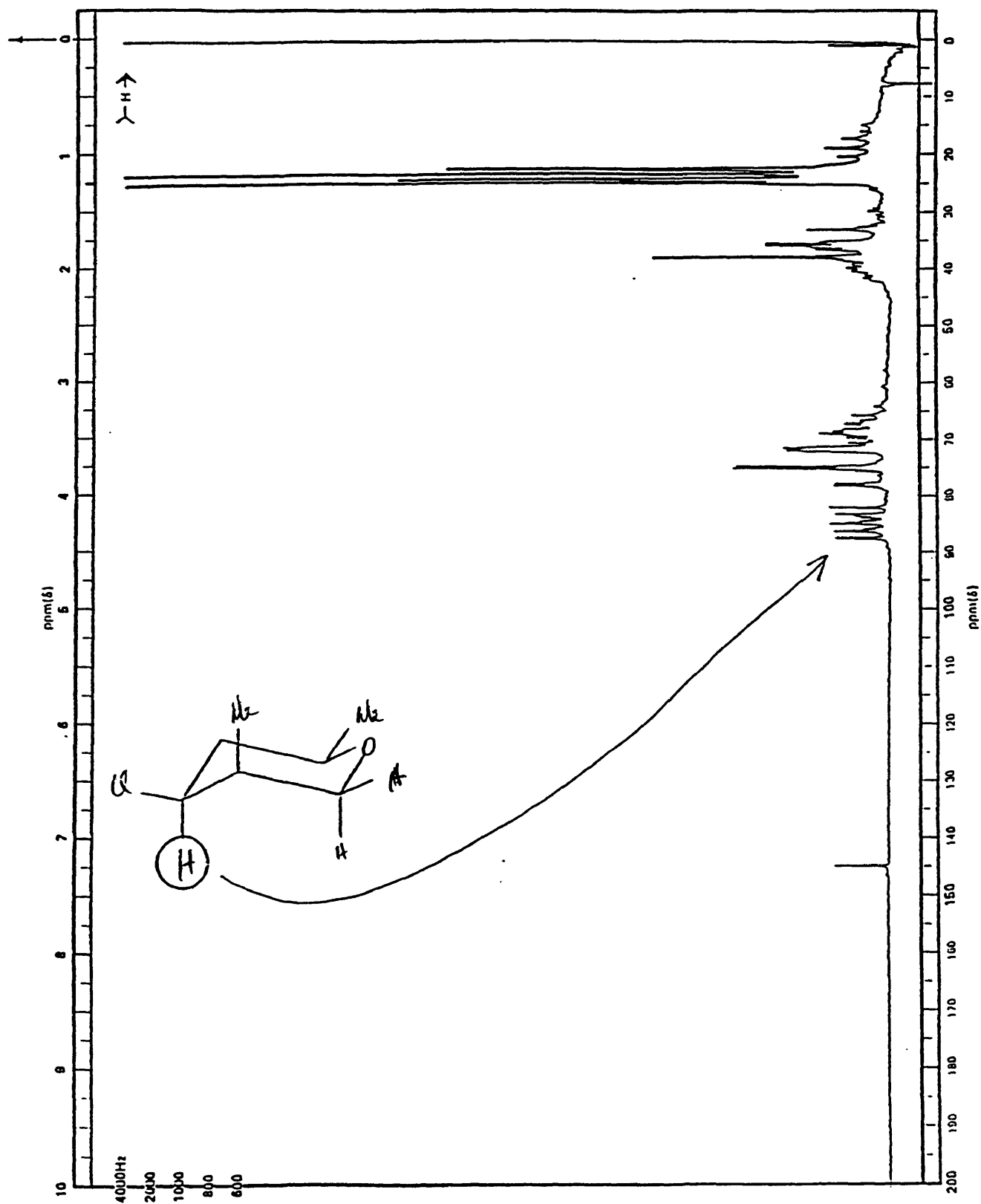


Figure 11 ^1H NMR spectrum of *cis,cis*-2,5-dimethyl-4-chlorotetrahydropyran at 80 MHz.

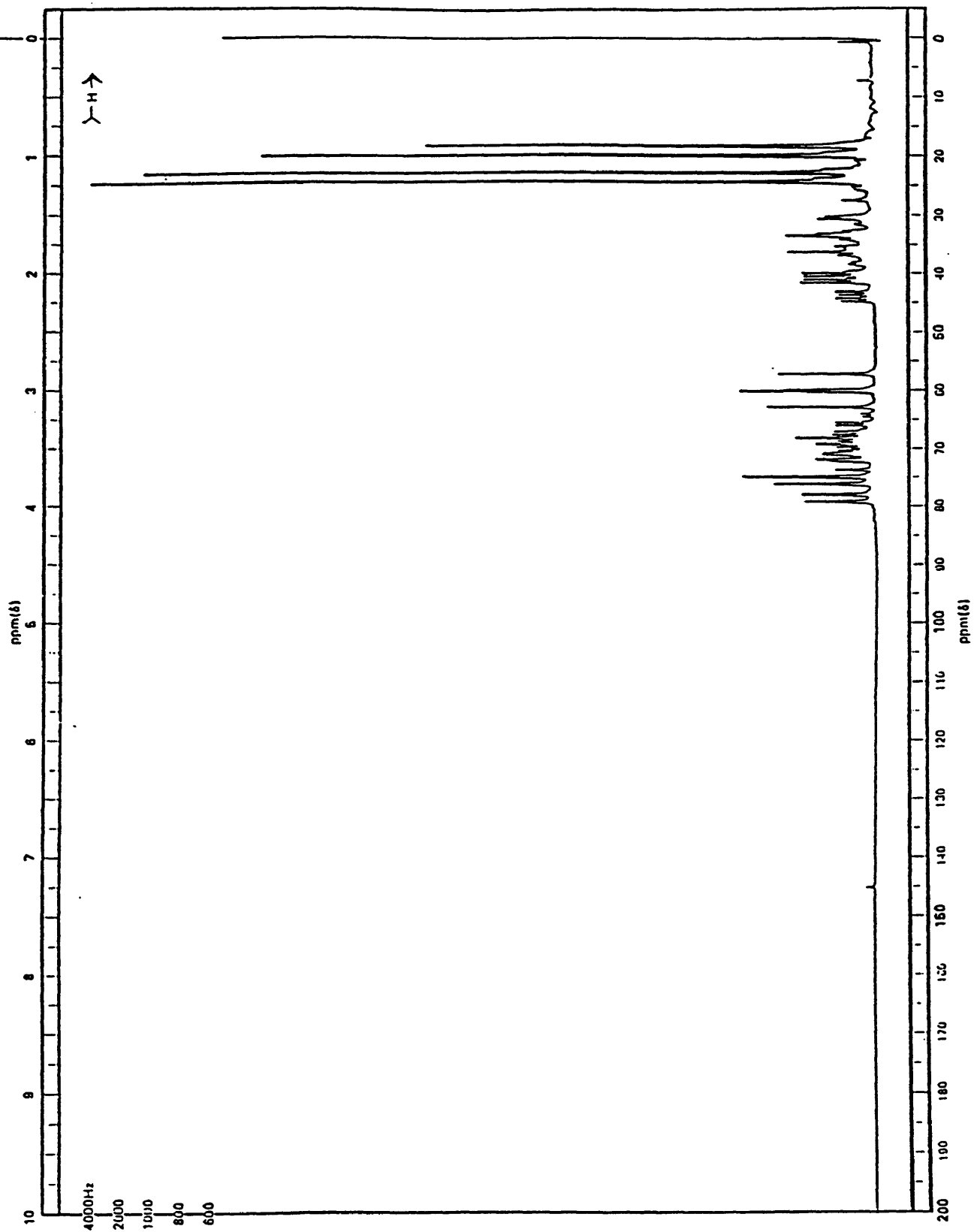


Figure 13 ^1H NMR spectrum of *cis, trans*-2,5-dimethyl-4-chlorotetrahydropyran at 80 MHz.

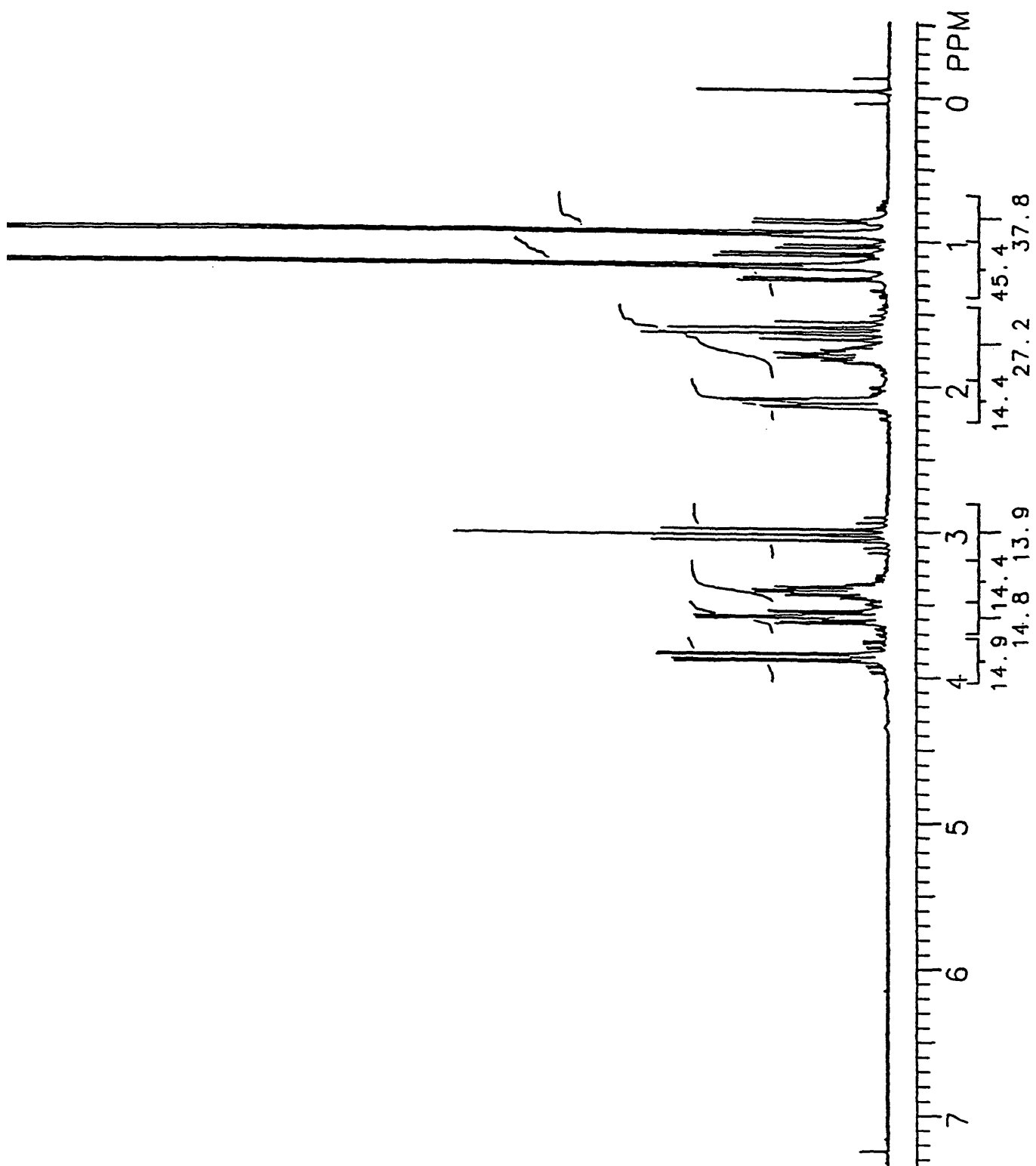


Figure 15
300 MHz.

^1H NMR spectrum of *cis, trans*-2,5-dimethyl-4-chlorotetrahydropyran at

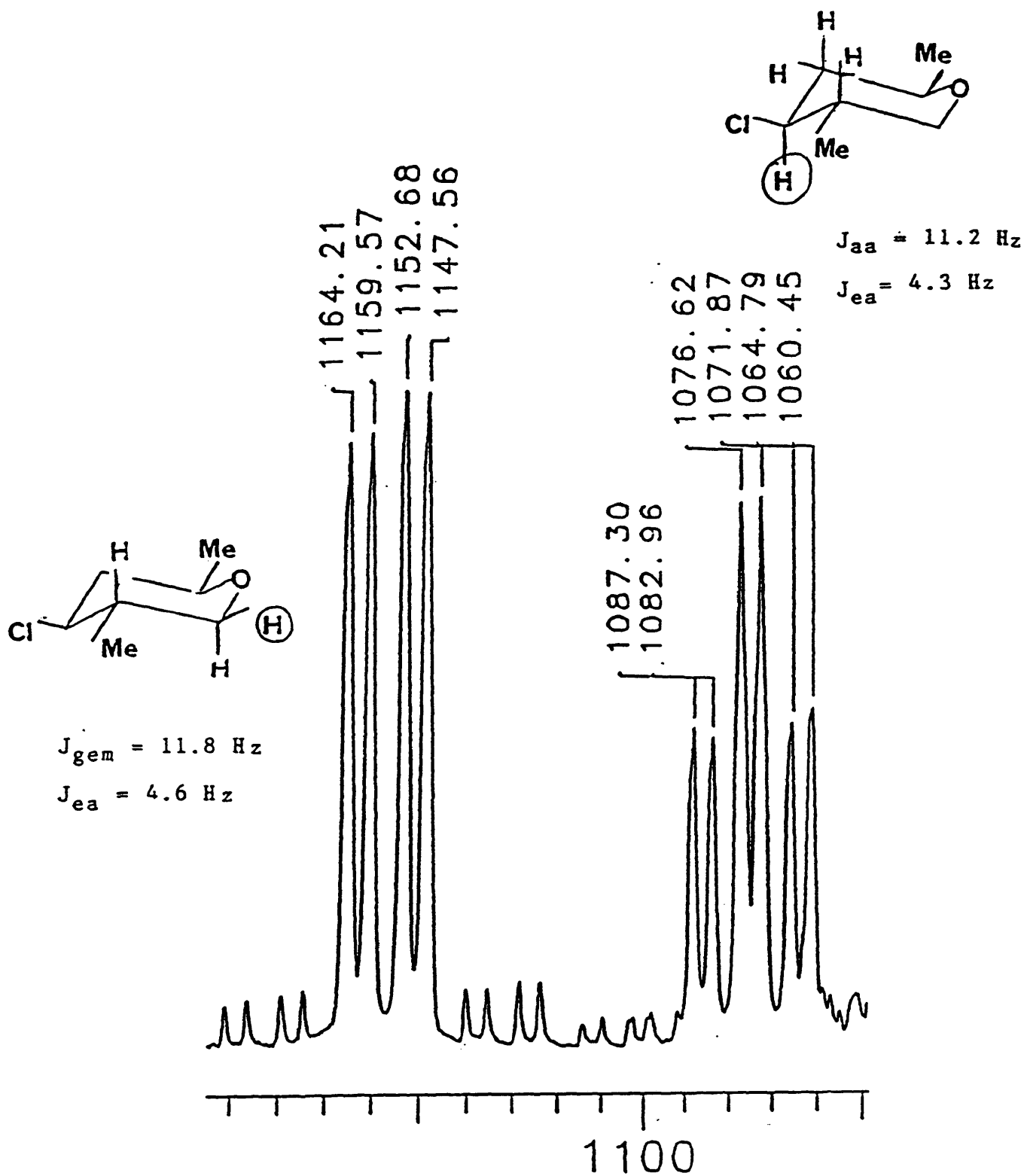


Figure 15a Expanded ^1H NMR shifts of the equatorial proton of carbon 6 (left) and the axial proton of carbon 4 of cis, trans-2,5-dimethyl-4-chlorotetrahydropyran at 300 MHz.

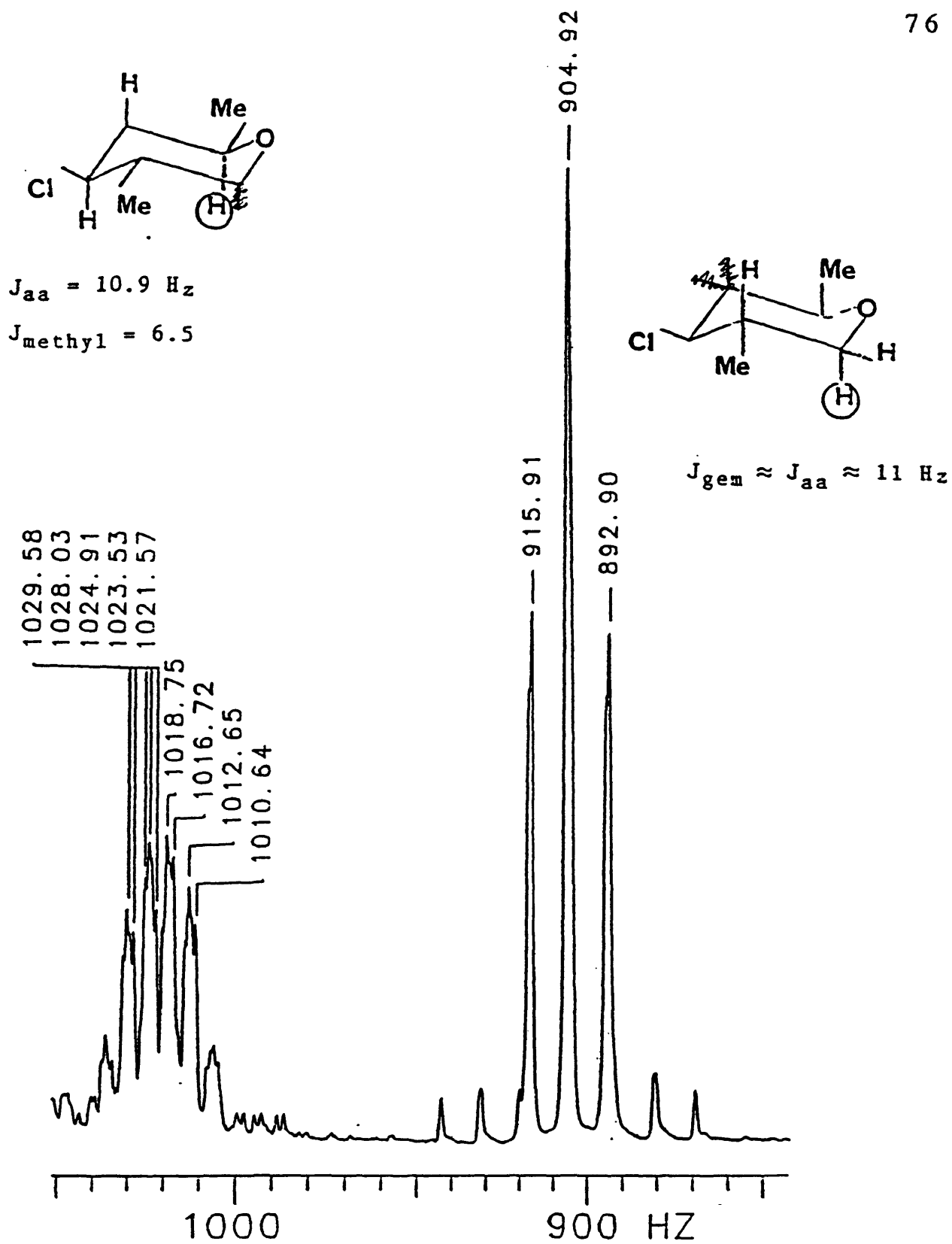


Figure 15b Expanded ^1H NMR shifts of the axial proton of carbon 2 and the axial proton of carbon 6 of *cis, trans*-2,5-dimethyl-4-chlorotetrahydropyran at 300 MHz.

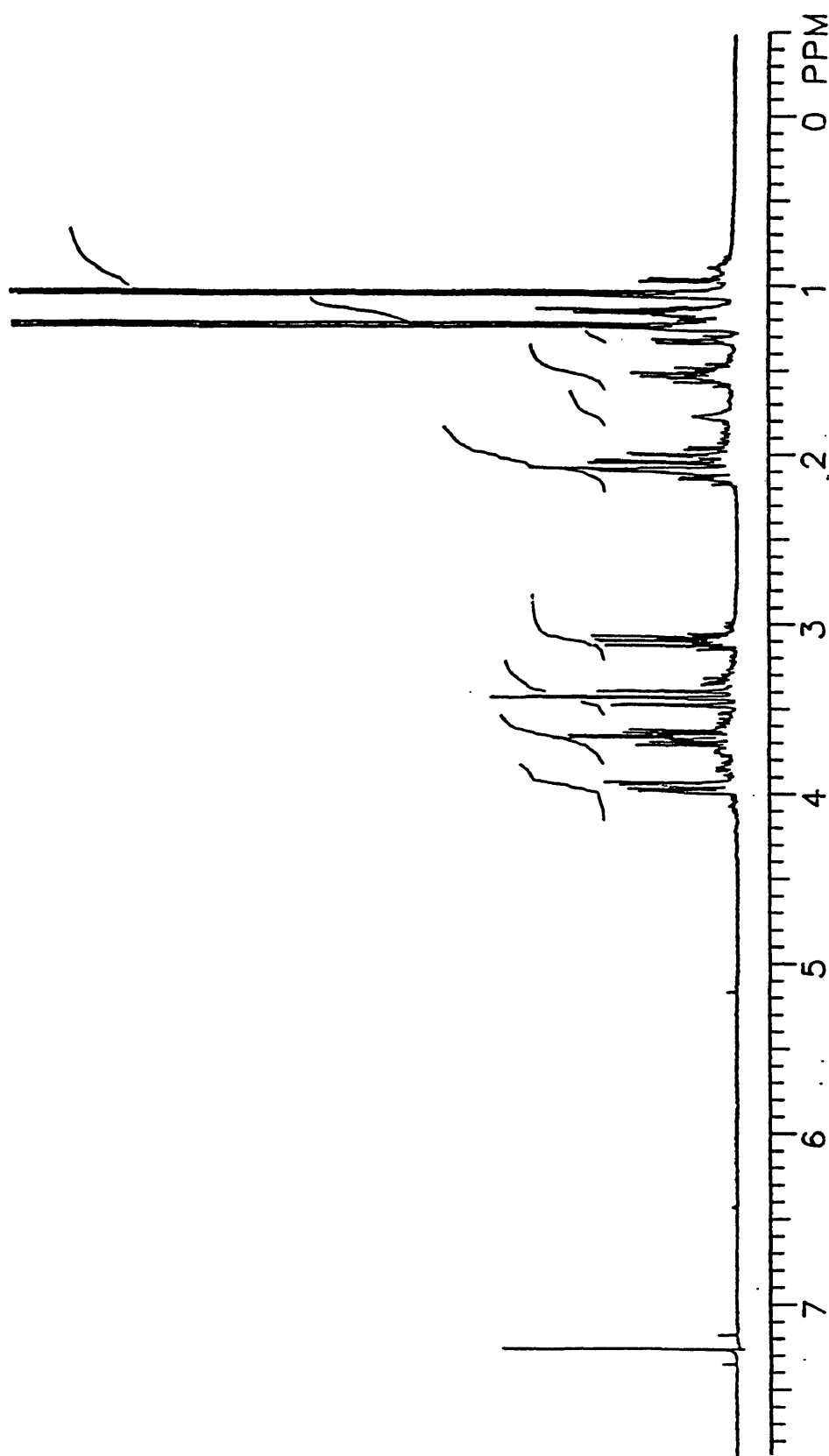
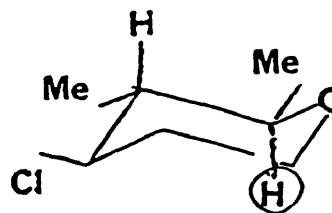


Figure 16 Expanded ^1H NMR spectrum of *trans, trans*-2,3-dimethyl-4-chlorotetrahydropyran at 300 MHz.



$$J_{\text{methyl}} = 6.1 \text{ Hz}$$

$$J_{\text{aa}} = 9.5 \text{ Hz}$$

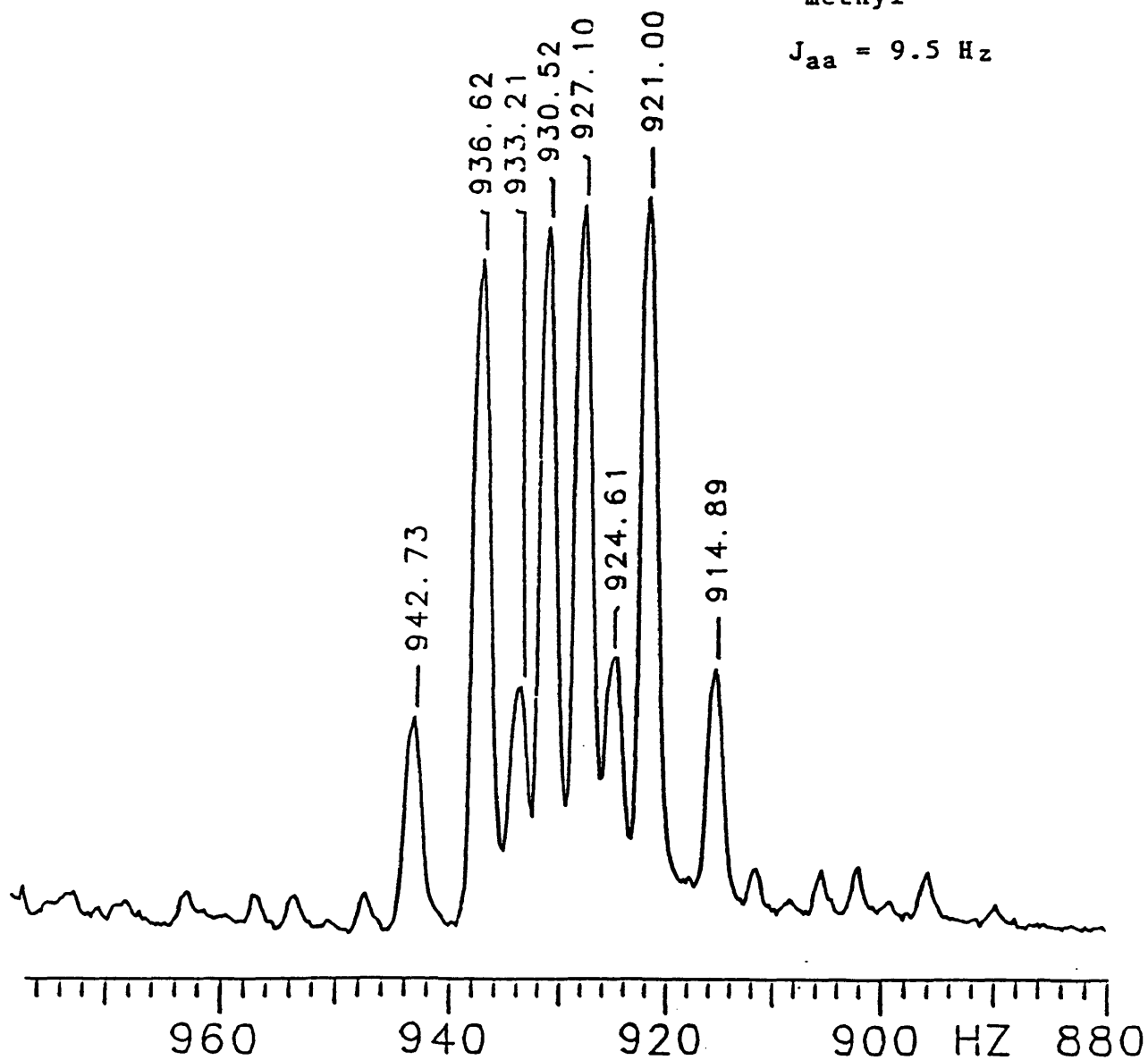


Figure 16a Expanded ^1H NMR spectrum of the axial proton of carbon 2 of trans, trans-2,3-dimethyl-4 chlorotetrahydropyran at 300 MHz.

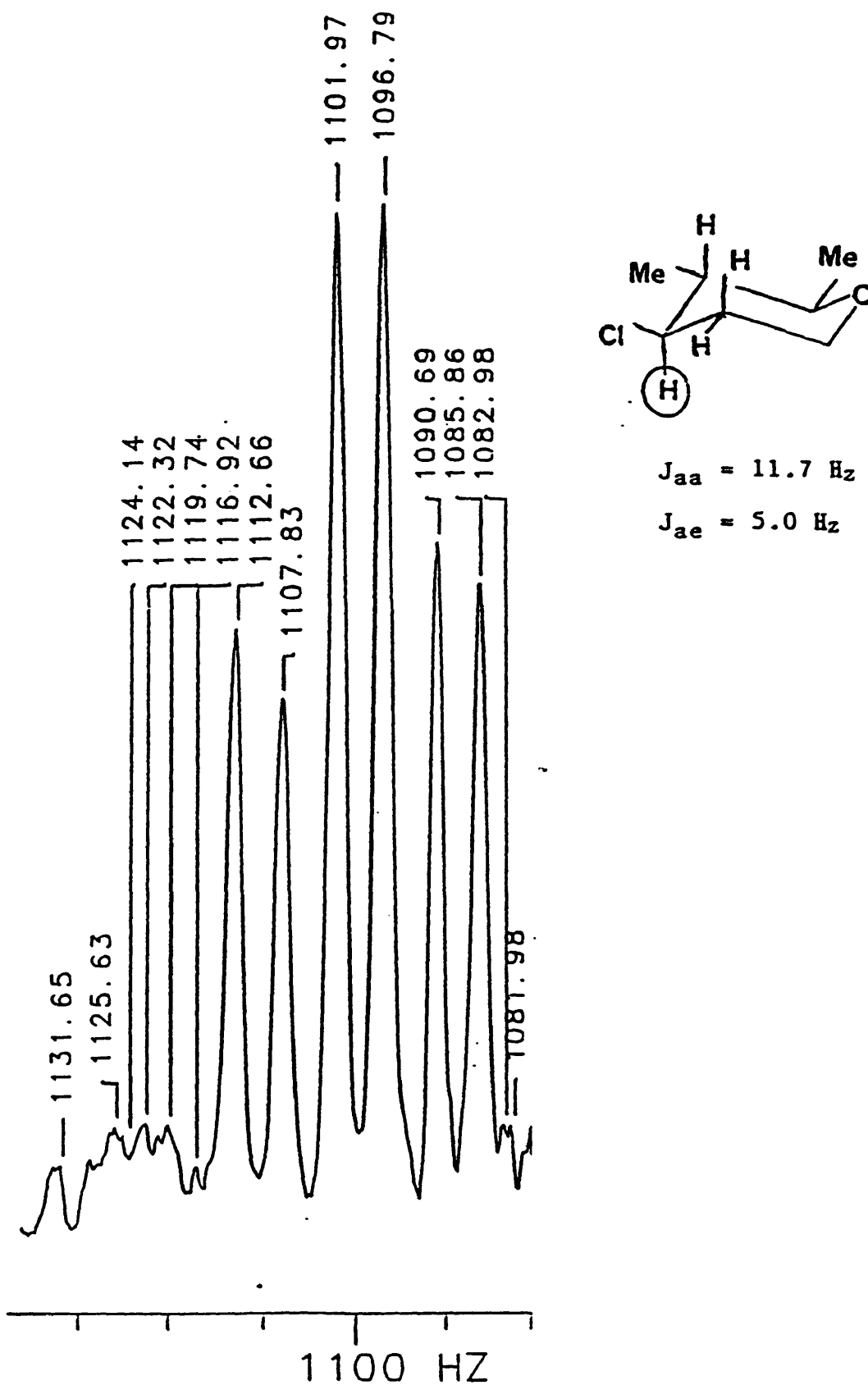


Figure 16b Expanded ^1H NMR shift of the axial proton at carbon 4 of trans, trans-2,3-dimethyl-4 chlorotetrahydropyran at 300 MHz.

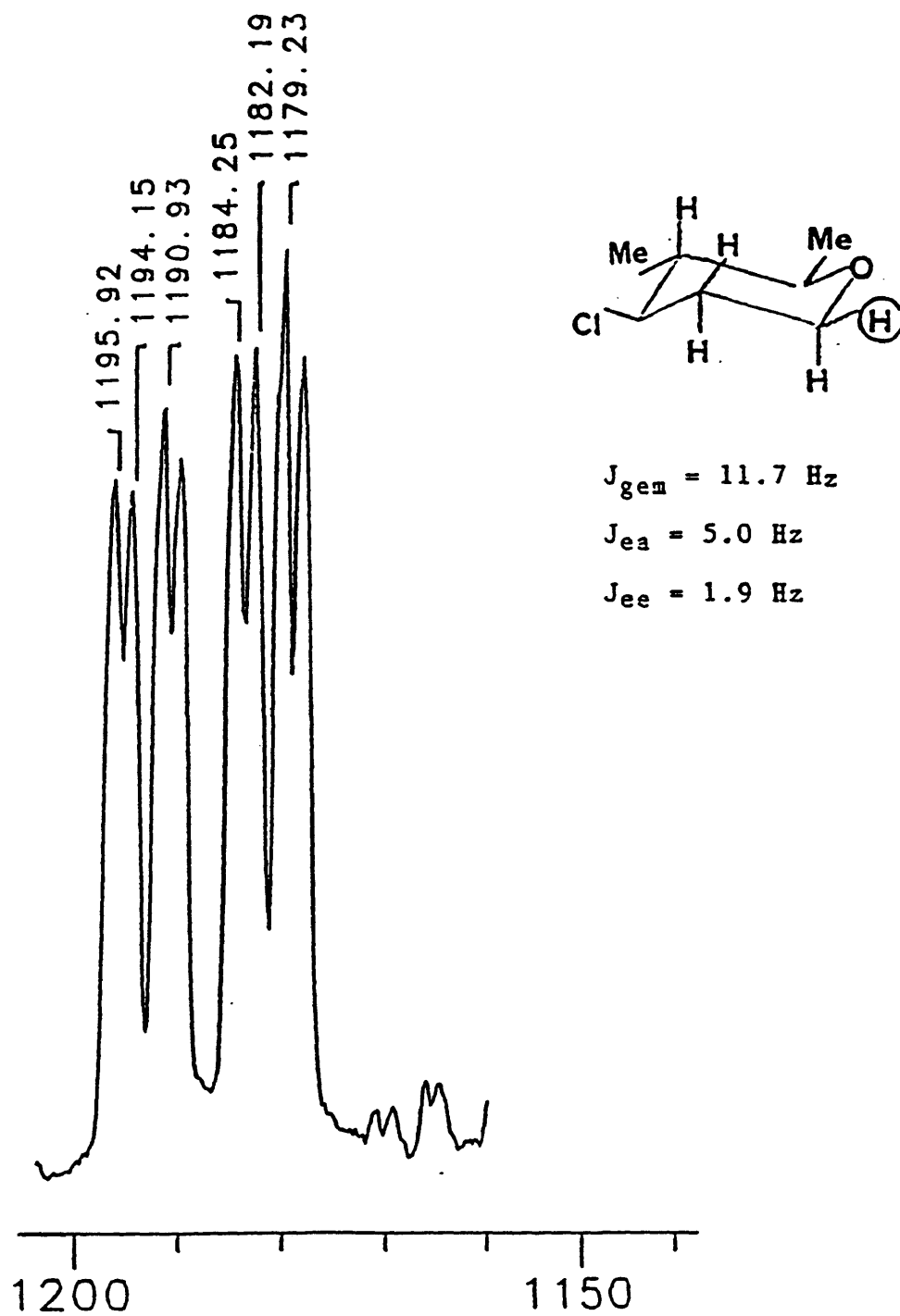


Figure 16c Expanded ^1H NMR shift of the equatorial proton at carbon 6 of trans, trans-2,3-dimethyl-4-chlorotetrahydropyran at 300 MHz.

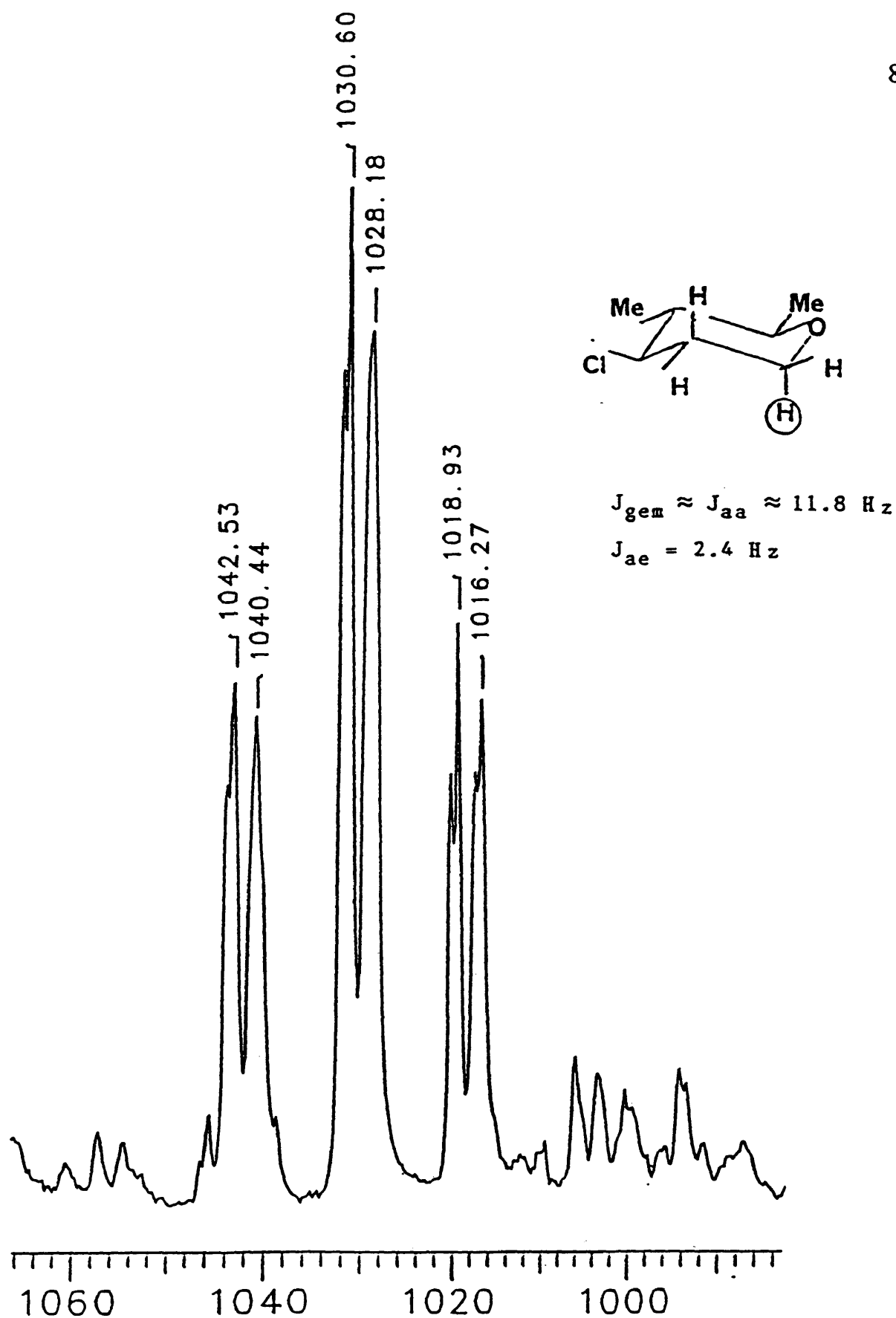


Figure 16d Expanded ^1H NMR shift of the axial proton at carbon 6 of trans,trans-2,3-dimethyl-4-chlorotetrahydropyran at 300 MHz.

The NMR spectrum of cis, cis-2,3-dimethyl-4-chlorotetrahydropyran (Figure 17) also shows overlap in the region of the 2, 4, and 6 hydrogens.

However, examination of the high field shift of the axial protons of carbons 2 and 6 of cis, cis-2,3-dimethyl-4-chlorotetrahydropyran reveals little departure from those of the trans, trans isomer. The 2-axial proton shift shows a quartet with a coupling constant of 6.3 Hz. The quartet is further split by 2.0 Hz by the equatorial proton at carbon 3. The 6-axial shift is nicely accounted for by similarly proposing approximately equivalent couplings with its geminal proton and the axial proton at carbon 5. In this case are the axial-axial and geminal couplings measured at ca. 12 Hz. Figure 17a shows the shift for the axial proton at carbon 4, produced by an equatorial-axial coupling of 4.5 Hz and an axial-axial coupling of 12.5 Hz. As expected, the resulting doublet of triplets at 4.2 ppm occurs downfield relative to the analogous proton of the trans, trans isomer with three unequivalent couplings. Lastly, the pattern for the equatorial proton at carbon 6 is described by couplings of 11.7 Hz for the geminal proton and 5.1 and 1.2 Hz for the axial and equatorial protons of carbon 5, respectively. These interactions produce the doublet of doublets of doublets observed in Figure 17b.

An interesting, albeit unsuccessful, endeavor proved to be the use of the NMR shift reagent, tris(6,6,7,7,8,8,8,-heptafluoro-2,2-dimethyl-3,5-octanedionato)europium in hopes of separating chemical shifts in the region for the 4-axial proton of trans, trans-2,3-dimethyl-4-chlorotetrahydropyran. Figures 18, 19, and 20 show how use of the reagent led to considerable peak broadening with incremental additions of the reagent as to make stereochemical elucidation of the compound impossible by this method.

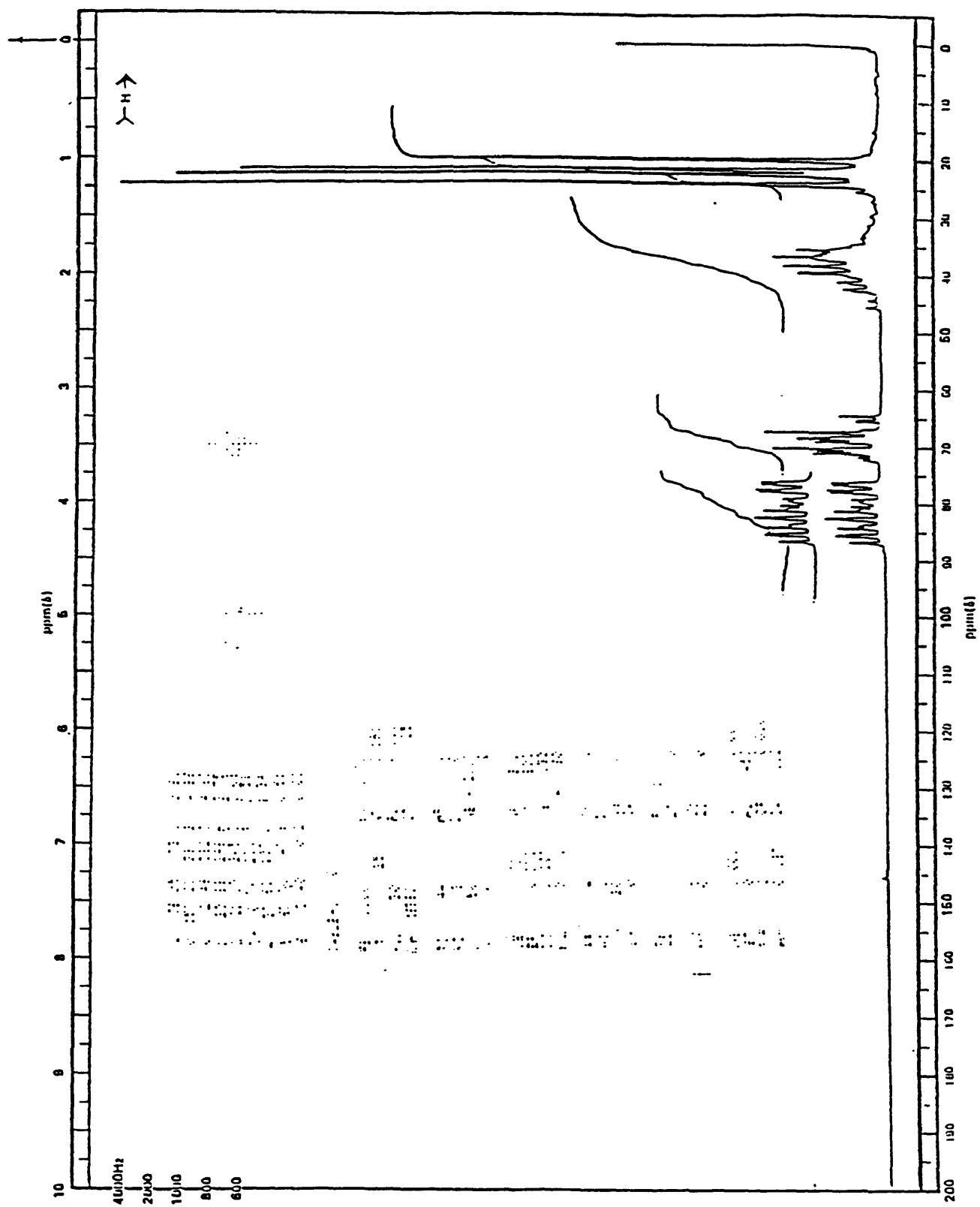


Figure 17. ^1H NMR spectrum of *cis,cis*-2,3-dimethyl-4-chlorotetrahydropyran at 80 MHz.

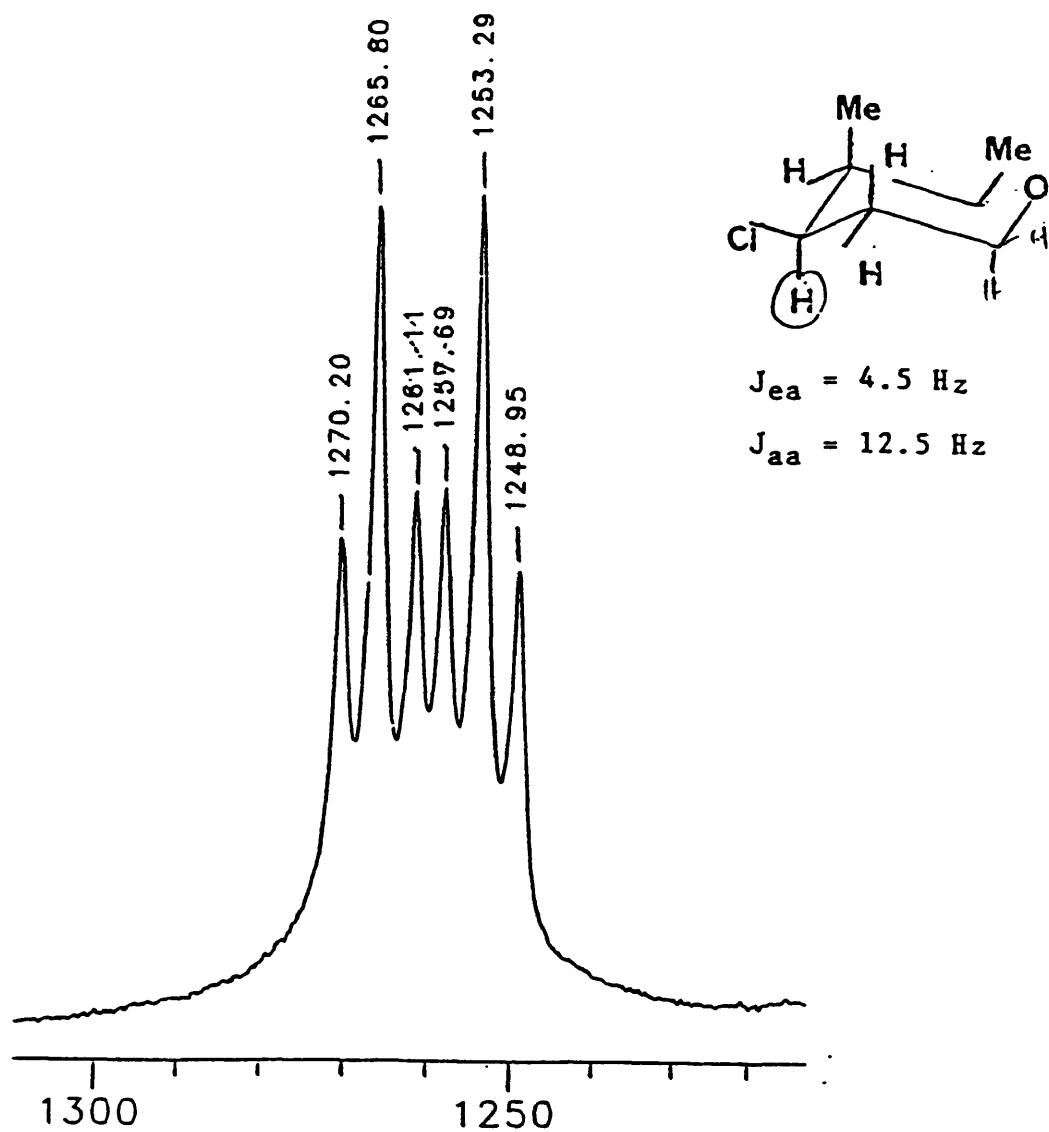


Figure 17a. Expanded ^1H NMR shift of the axial proton at carbon 4 of cis, cis-2,3-dimethyl-4-chlorotetrahydropyran at 300 MHz.

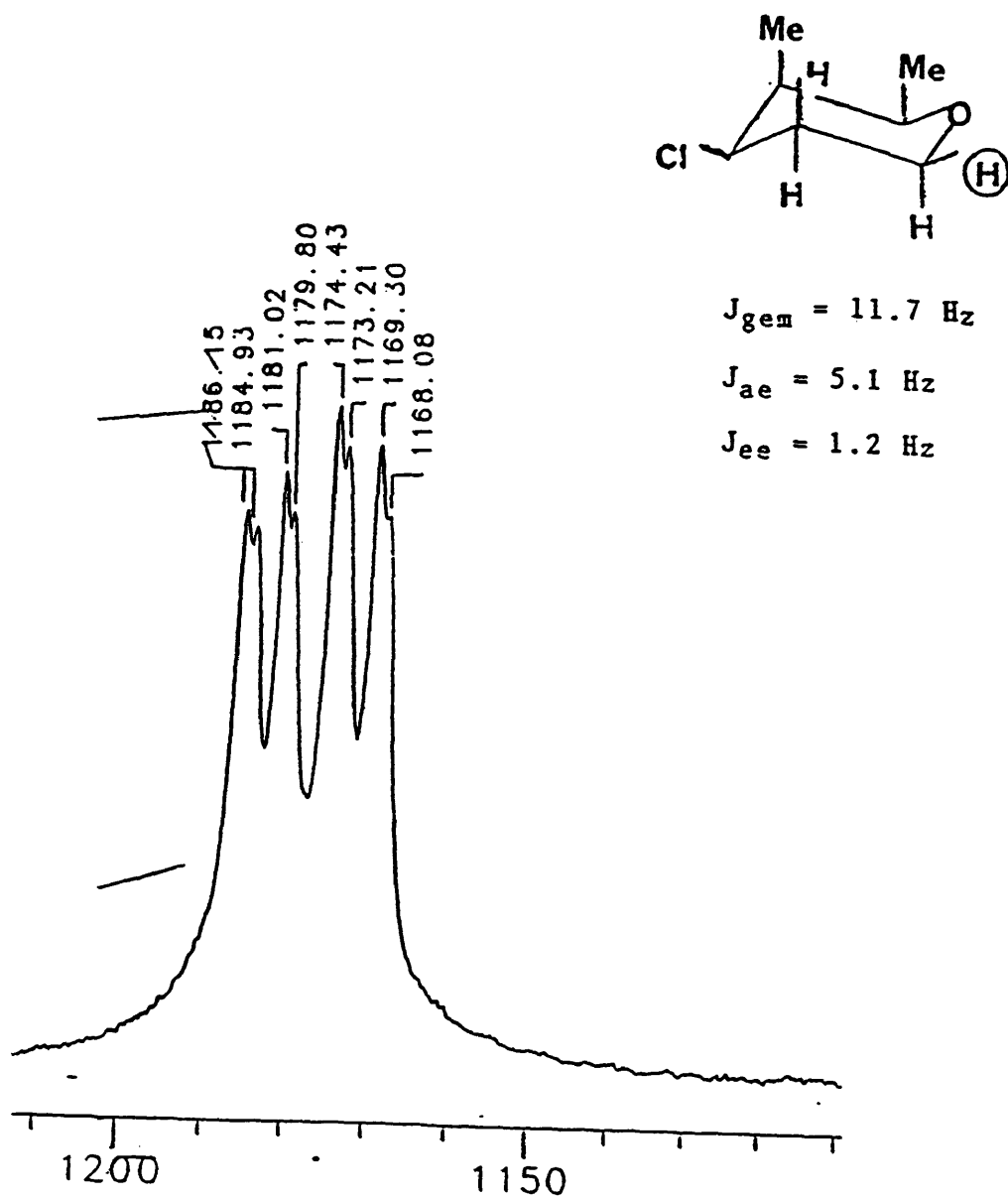


Figure 17b. Expanded ^1H NMR shifts of the equatorial proton at carbon 6 of cis, cis-2,3-dimethyl-4-chlorotetrahydropyran at 300 MHz.

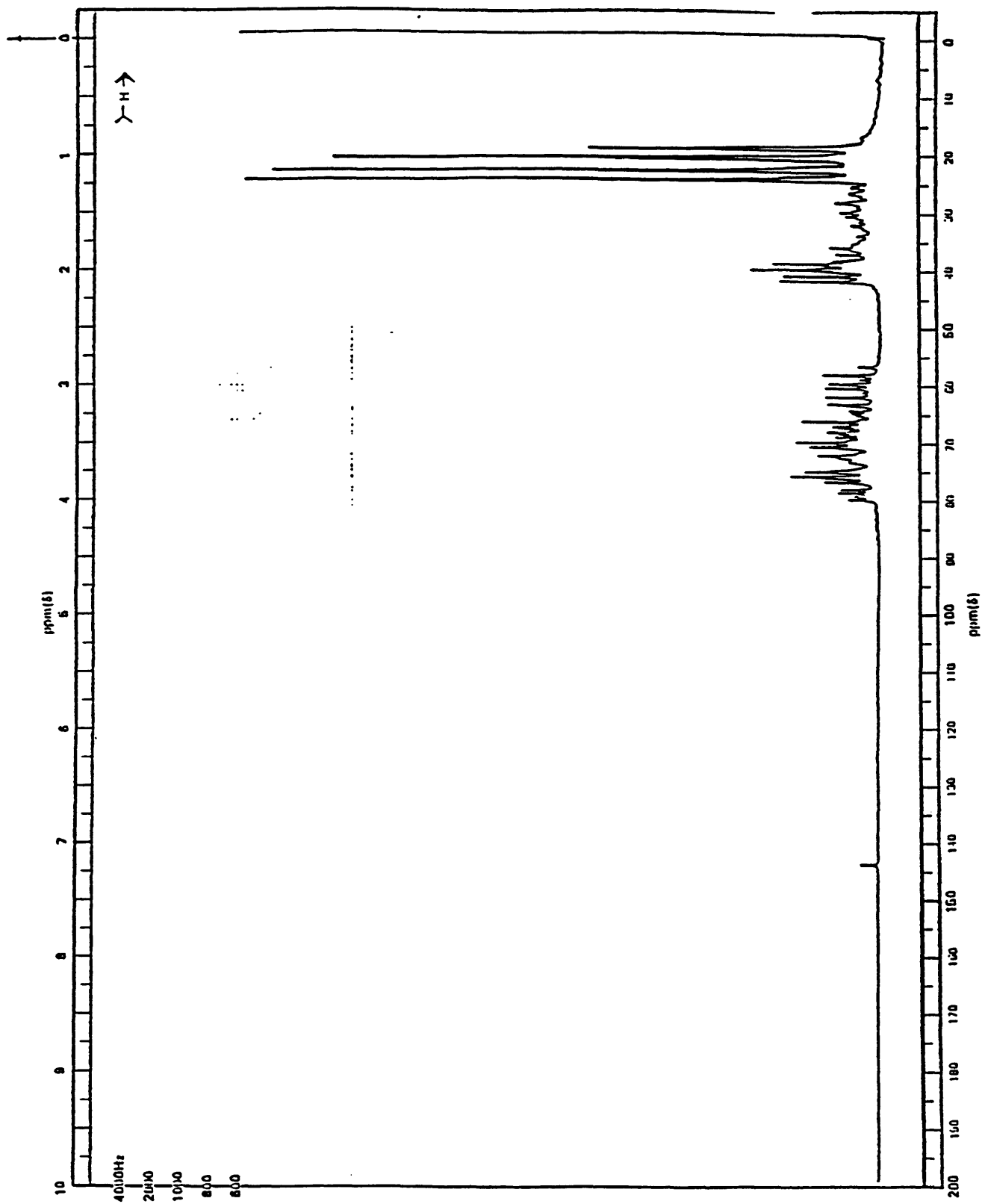


Figure 18 ^1H NMR spectrum of trans,trans-2,3-dimethyl-4-chlorotetrahydropyran at 80 MHz before addition of $\text{Eu}(\text{fod})_3$ shift reagent.

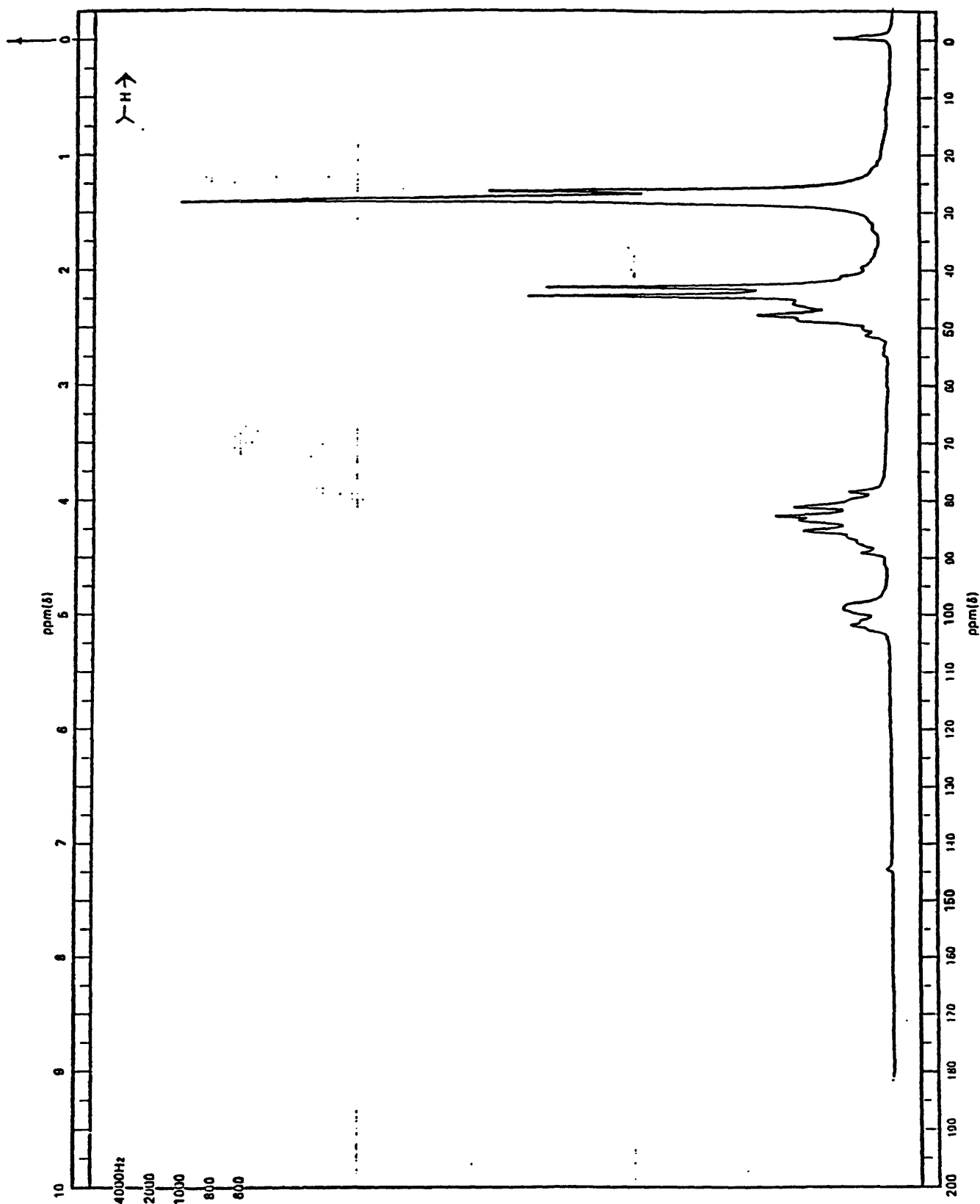


Figure 19 ^1H NMR spectrum of trans, trans-2,3-dimethyl-4-chlorotetrahydropyran at 80 MHz after addition of 30 mg of $\text{Eu}(\text{fod})_3$ shift reagent.

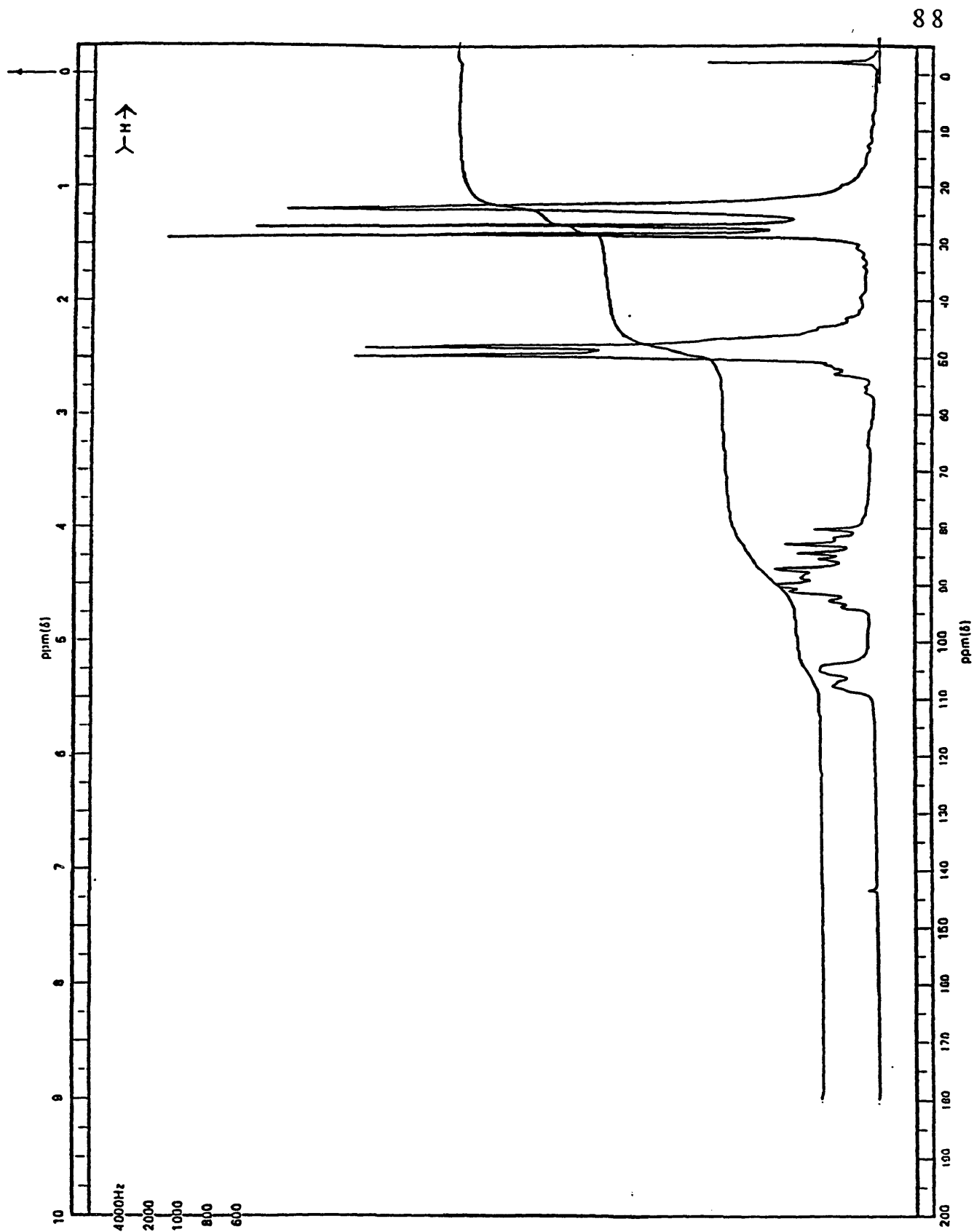


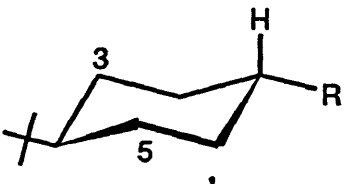
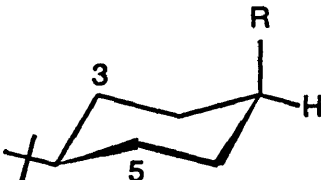
Figure 20 ^1H NMR spectrum of trans, trans-2,3-dimethyl-4-chlorotetrahydropyran at 80 MHz after addition of 60 mg of $\text{Eu}(\text{fod})_3$ shift reagent.

Especially helpful in making stereochemical and conformational assignments were the incremental differences in carbon 13 NMR chemical shifts between stereoisomers and conformers. The documented phenomenon of the γ upfield shift aided particularly in situations such as the distinction between cis, cis and trans, trans-2,3-dimethyl-4-chlorotetrahydropyran. The effect was first described by Eliel as the upfield shift experienced by a carbon atom located γ to a heteroatom compared to its shift when the heteroatom is replaced by a hydrogen or carbon atom. Fortuitously, the effect is substantial when the heteroatom and γ carbon occupy a gauche relationship and minimal when the two atoms are anti-periplanar. Table 4 illustrates Eliel's approach to quantifying shift parameters by noting differences induced on replacement of hydrogen atoms with chlorine on the conformationally locked cyclohexanes. This technique has been employed to derive the substitution parameters for the α and β sites of the cyclohexane ring as well as shown in Table 5.

Since no carbon 13 shift data have been ascertained for the 4-halotetrahydropyrans, we hoped to make tentative predictions for each of the carbons of our 4-halotetrahydropyrans by amending the previously published³² chemical shifts of non-halogenated tetrahydropyrans listed in Table 6. For example, to calculate the carbon 13 chemical shifts of cis, cis-2,3-dimethyl-4-chlorotetrahydropyran, we added the α shift parameter of 33.0 ppm to the published value (30.6 ppm) for the 4 carbon of 2,3-dimethyl tetrahydropyran yielding a calculated chemical shift of 63.6 ppm. Similar addition of the β parameter yields calculated shifts of 43.6 and 32.3 ppm for the 3 and 5 carbons. Finally, the γ -gauche shift parameter of 6 ppm is subtracted from the carbon 3 methyl group for a 6.0 ppm prediction. Note that the chlorine substituent is accurately predicted to have little effect on the anti carbons 2 and 6. Table 7 shows the calculated and observed chemical shifts for each of the stereoisomers of compounds synthesized. In all but a few cases the shifts calculated for all carbons about the tetrahydropyran ring correlate well with those observed for the expected stereoisomer or conformer. The conformational and

stereochemical predictions were based on conformational energies of the collective substituents of the final tetrahydropyran product or general synthetic strategy, respectively. The close correlation of the observed with calculated chemical shifts, in addition to data previously discussed, confirms stereochemical and conformational assignments of product oxacycles covered in this report. Figures 22 through 30 show carbon 13 NMR spectra for each of the tetrahydropyrans covered in Table 7.

Table 4

<u>Shifts Induced on γ Carbons 3 and 5 by Chlorine Substitution</u>		
Reference Compound	(^{13}C)ppm at C3 and C5	Cl Induced γ Shifts (δ chlorinated cmpd - δ reference cmpd)
	R=H 28.0 R=Cl 27.8	(anti) = -.2
	R=CH 22.6 R=Cl 21.2	(gauche) = 6.8*

*Eliel reported that the substitution of an equatorial 1-Cl for an equatorial 1-H on 4-t-butyl cyclohexane shows a negligible effect on carbons 3 and 5 (.2 ppm). Likewise, the substitution of an axial Cl for axial methyl on the same molecule was reported to have little effect (1.4 ppm). There is considerable difference, however, in the upfield shift as induced by an axial 1-Cl and that of an equatorial 1-Cl (6.6 ppm). Eliel can substantiate his claim that the axial 1-Cl induces little or no effect only if he references it to that caused by an axial 1-methyl group, even though the equatorial 1-Cl group is referenced to an equatorial 1-H. This apparent inconsistency is resolved when one notes that the methyl group itself is an inducer of a γ -gauche upfield effect of 5.4 ppm relative to H. Thus, the effect on the 3(5) carbons is explained: an axial 1-Cl induces a 1.4 ppm γ -gauche upfield shift relative to methyl; the methyl induces a 5.4 ppm shift relative to H, for a total of 6.8 ppm. The equatorial 4-Cl induces an upfield shift of .2 ppm relative to H. Hence, the difference in the upfield shifts induced by axial and equatorial 1-chlorine atoms (6.6 ppm) equals the difference between each with respect to their hydrogen analogs $\{(1.4 + 5.4) - .2 \text{ ppm}\}$.

Table 5

Incremental Shifts Induced by Replacement of Hydrogen with Chlorine or Bromine in
conformationally stable Cyclohexane (ppm)

X	$Z_{\alpha a}$	$Z_{\alpha e}$	$Z_{\beta e}$	$Z_{\beta a}$	$Z_{\gamma e}$	$Z_{\gamma a}$
Cl	33	33	11	7	0	-6
Br	25	28	12	8	1	-6

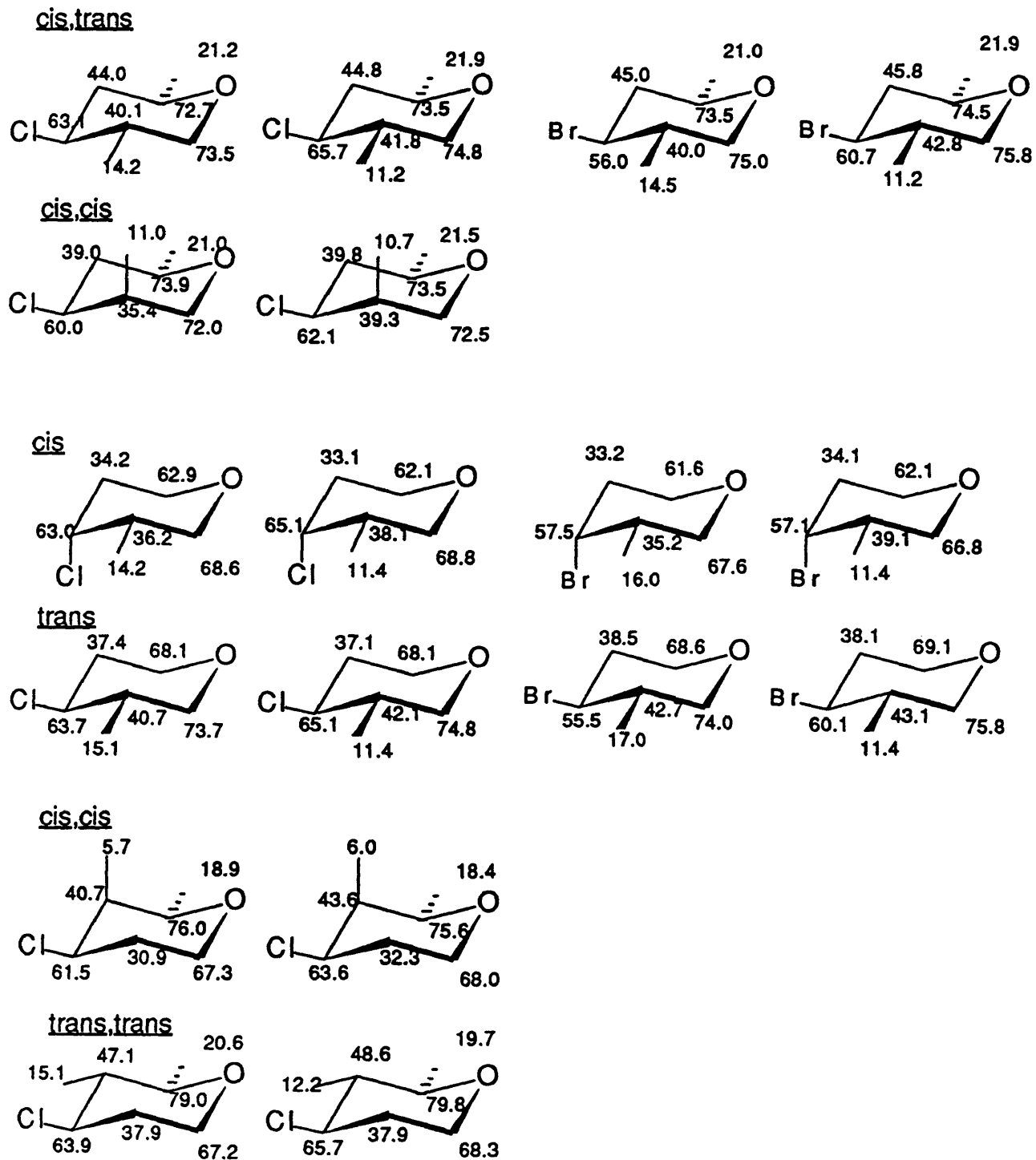
Table from E. Breitmaier and W. Voelter, "¹³CNMR Spectroscopy of Organic Compounds" in ¹³CNMR Spectroscopy, Verlag Chemie, New York, 1978, Chapter 4.

Table 6

Literature Values for Substituted Tetrahydropyrans							
Substituent	C2	C3	C4	C5	C6	2-Me	3(5)Me
None	68.7	26.9	23.8	26.3	68.7		
3-Me	74.8	31.1	32.1	26.1	68.1		17.4
cis-2,3-diMe	75.6	32.6	30.6	21.3	68.0	18.4	12.0
trans-2,3-diMe	79.8	37.6	32.7	26.9	68.3	19.7	18.2
cis-2,5-diMe	73.7	28.8	29.1	28.3	72.5	21.5	16.7
trans-2,5-diMe	73.5	33.8	32.7	30.8	74.8	21.9	17.2

Table 7

Observed and predicted Carbon 13 shifts for substituted Tetrahydropyrans



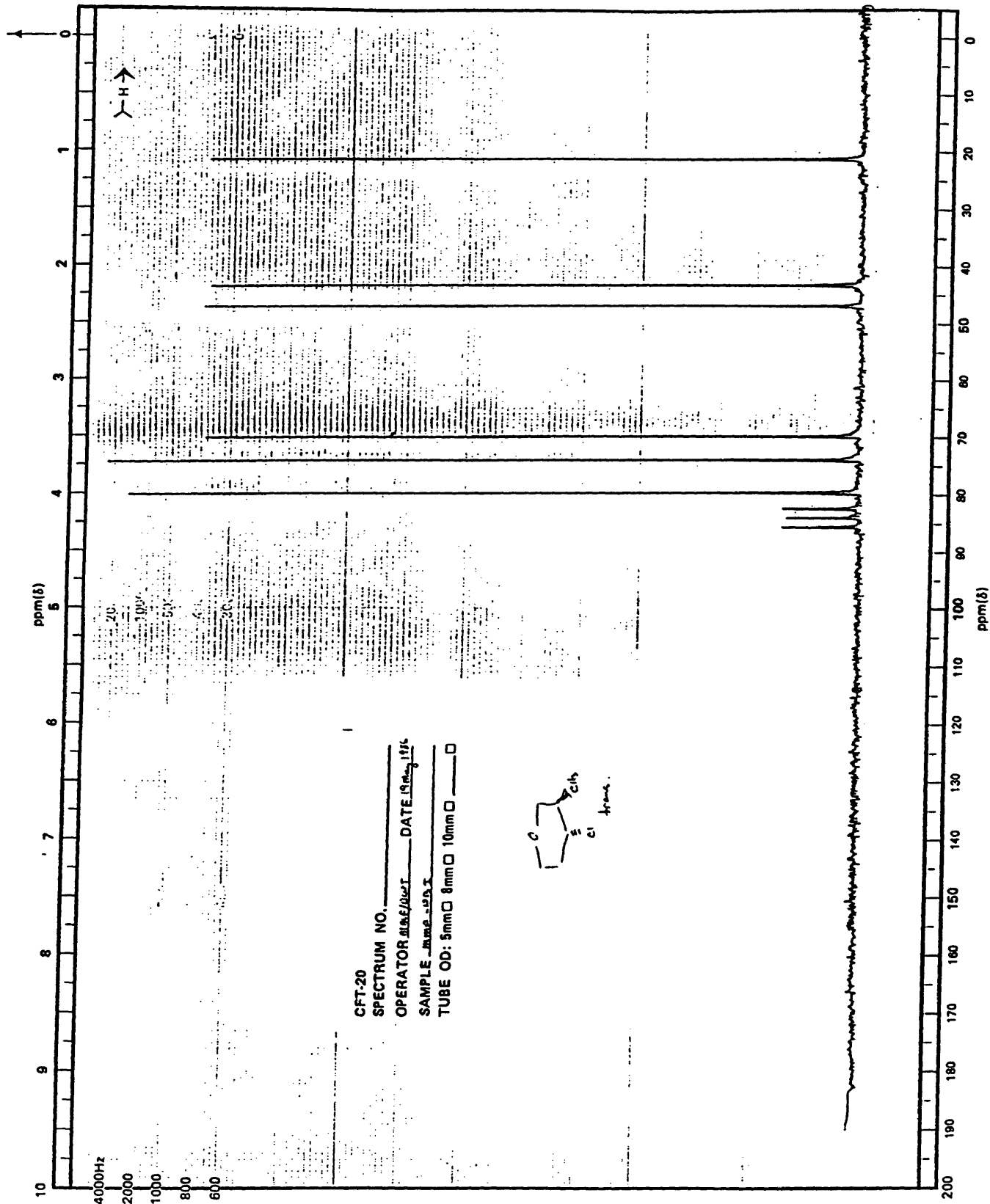


Figure 24

^{13}C NMR spectrum of trans-3-methyl-4-chlorotetrahydropyran at 80 MHz.

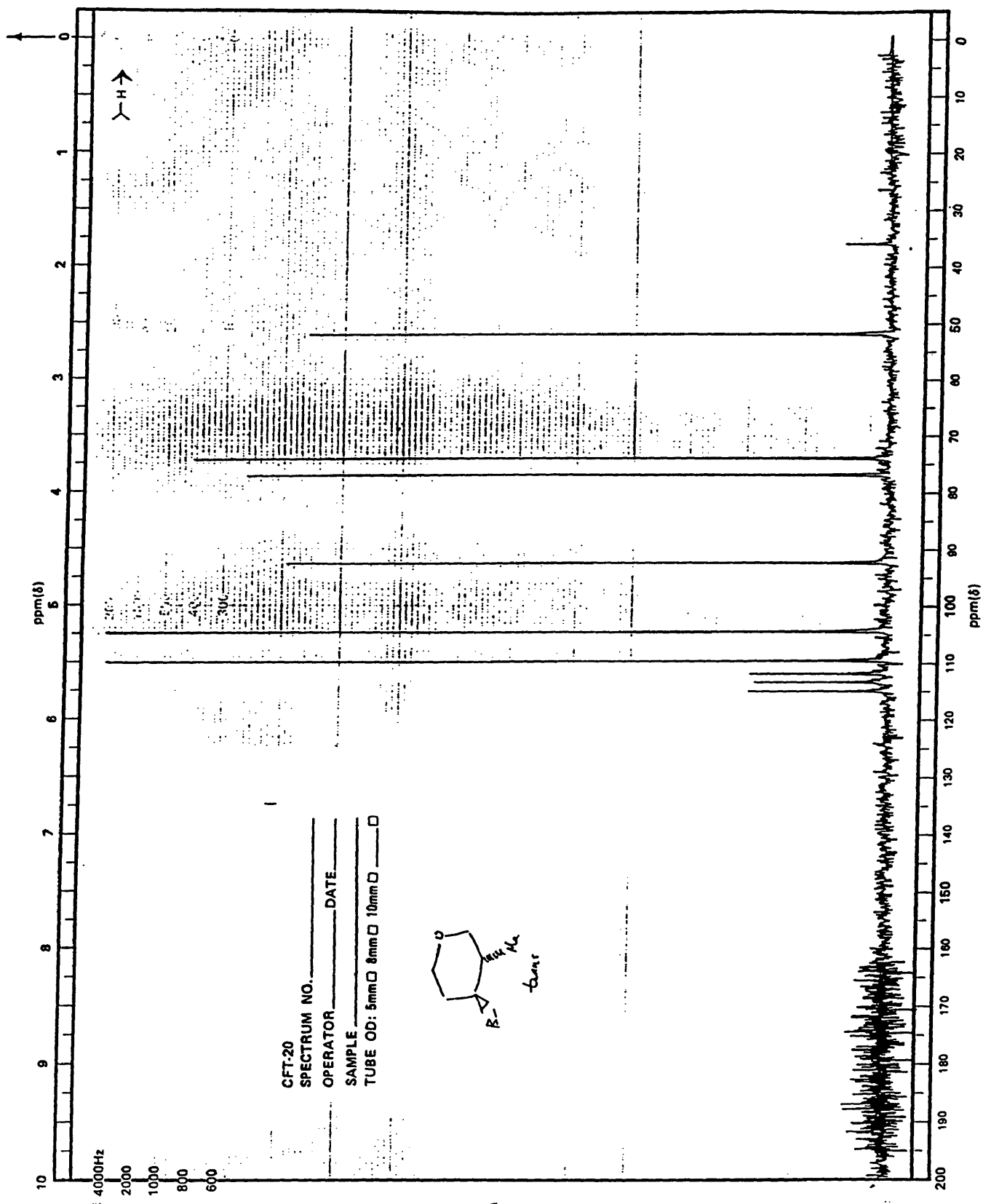


Figure 25 ^{13}C NMR spectrum of trans-3-methyl-4-bromotetrahydropyran at 80 MHz.

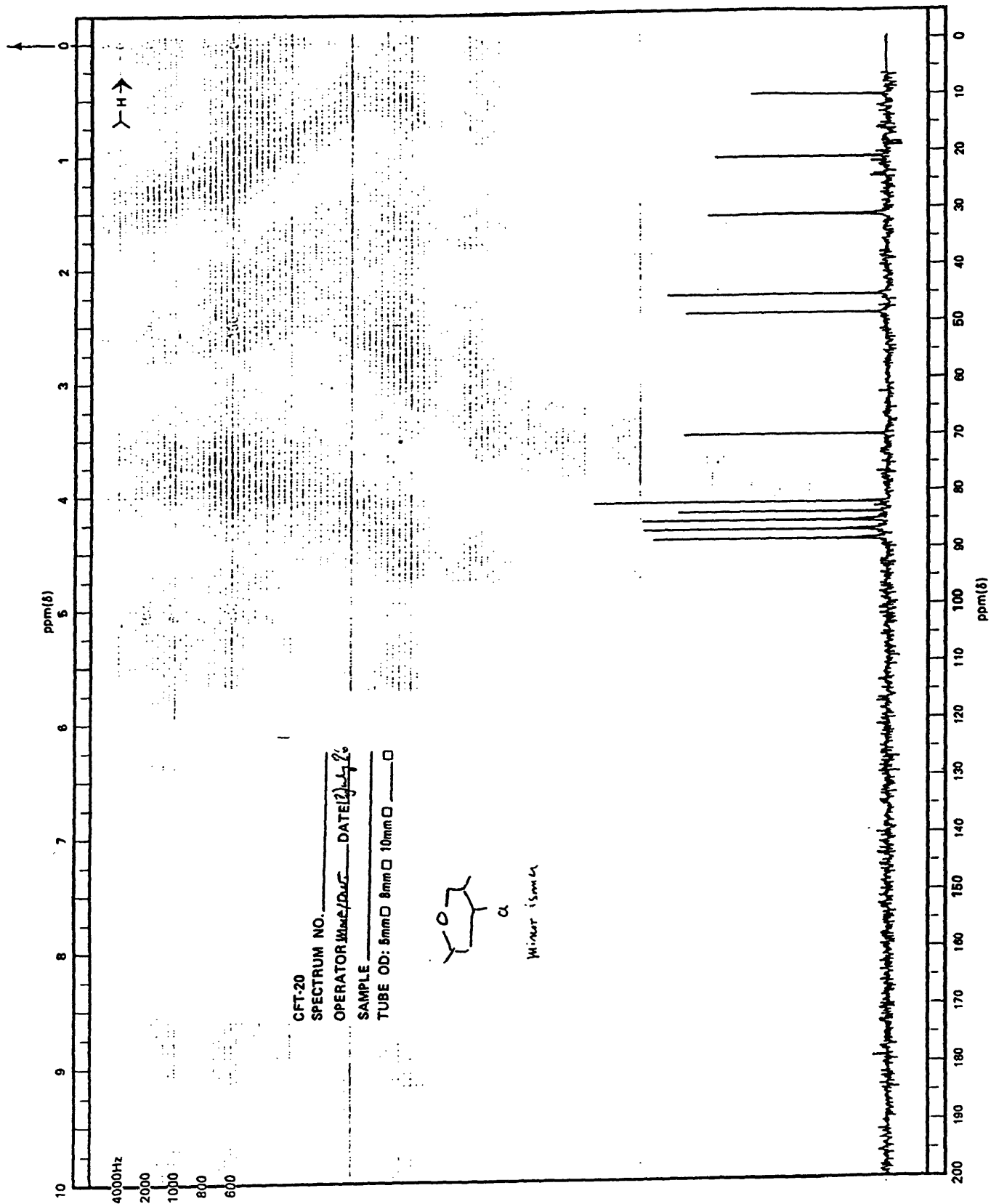


Figure 26 ^{13}C NMR spectrum of cis, cis-2,5-dimethyl-4-chlorotetrahydropyran at 80 MHz.

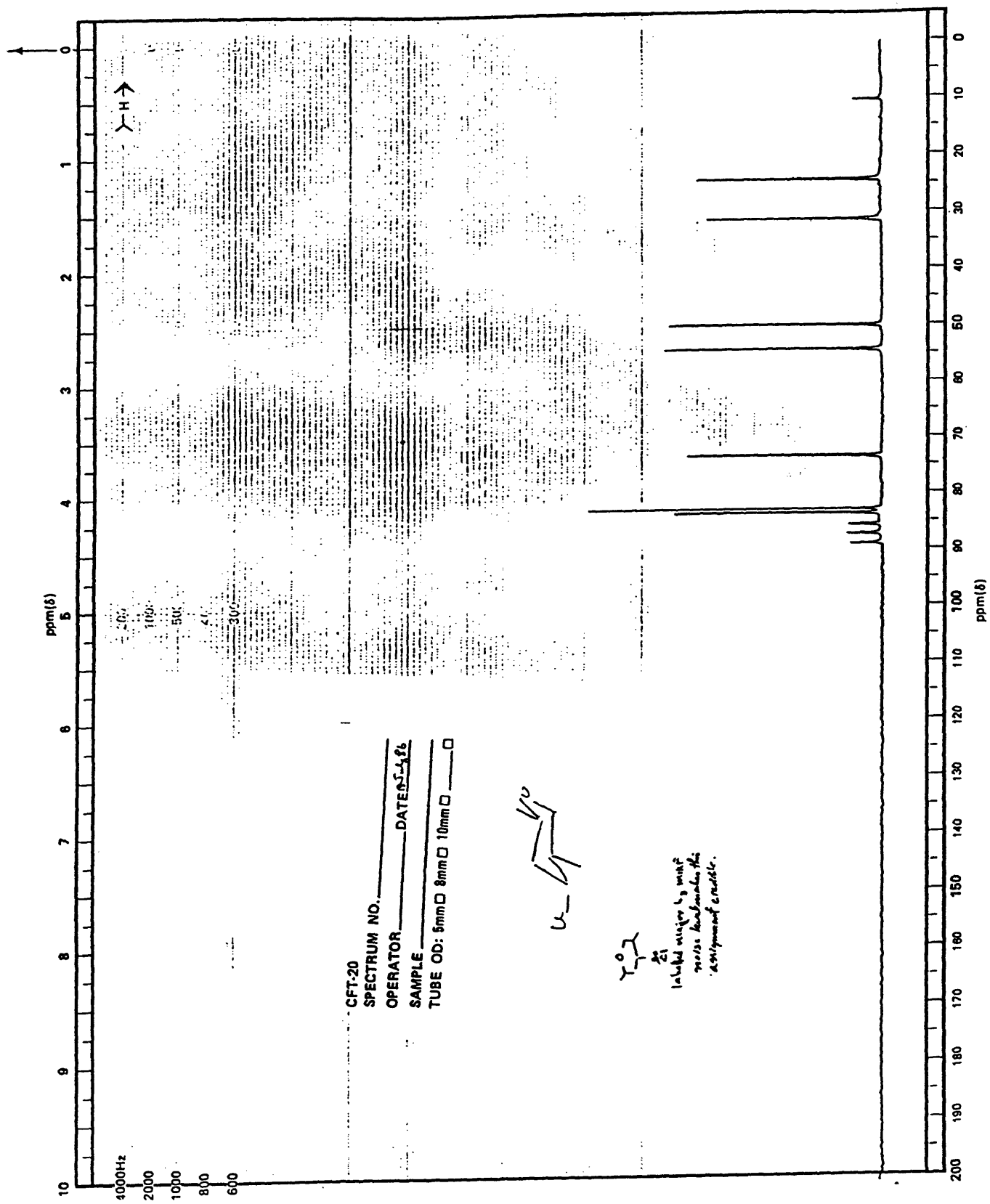


Figure 27
80 MHz.

^{13}C NMR spectrum of cis, trans-2,5-dimethyl-4-chlorotetrahydropyran at

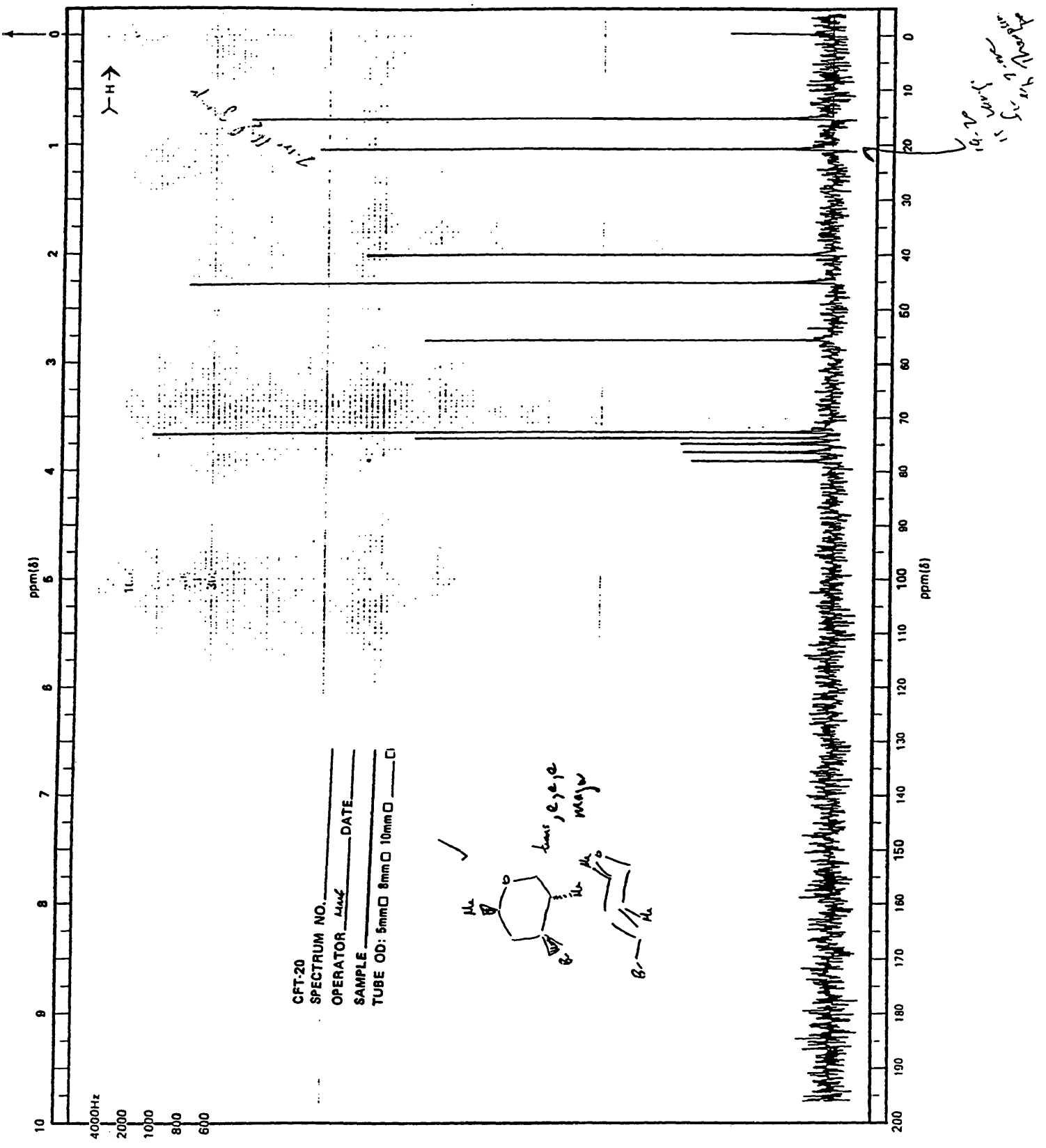


Figure 28 ¹³C NMR spectrum of cis, trans-2,5-dimethyl-4-bromotetrahydropyran (all equatorial) at 80 MHz.

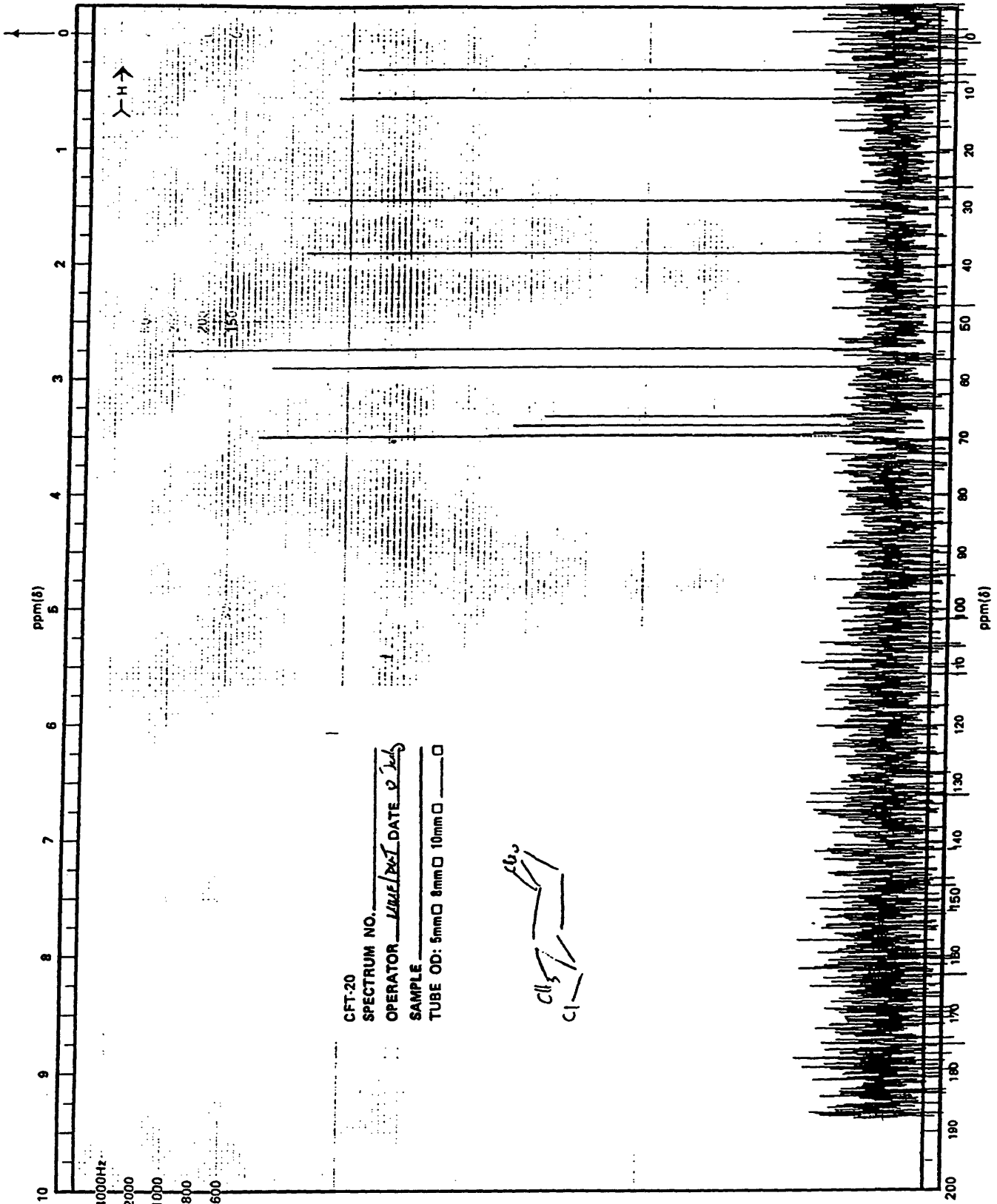


Figure 29
80 MHz.

¹³C NMR spectrum of trans, trans-2,3-dimethyl-4-chlorotetrahydropyran at

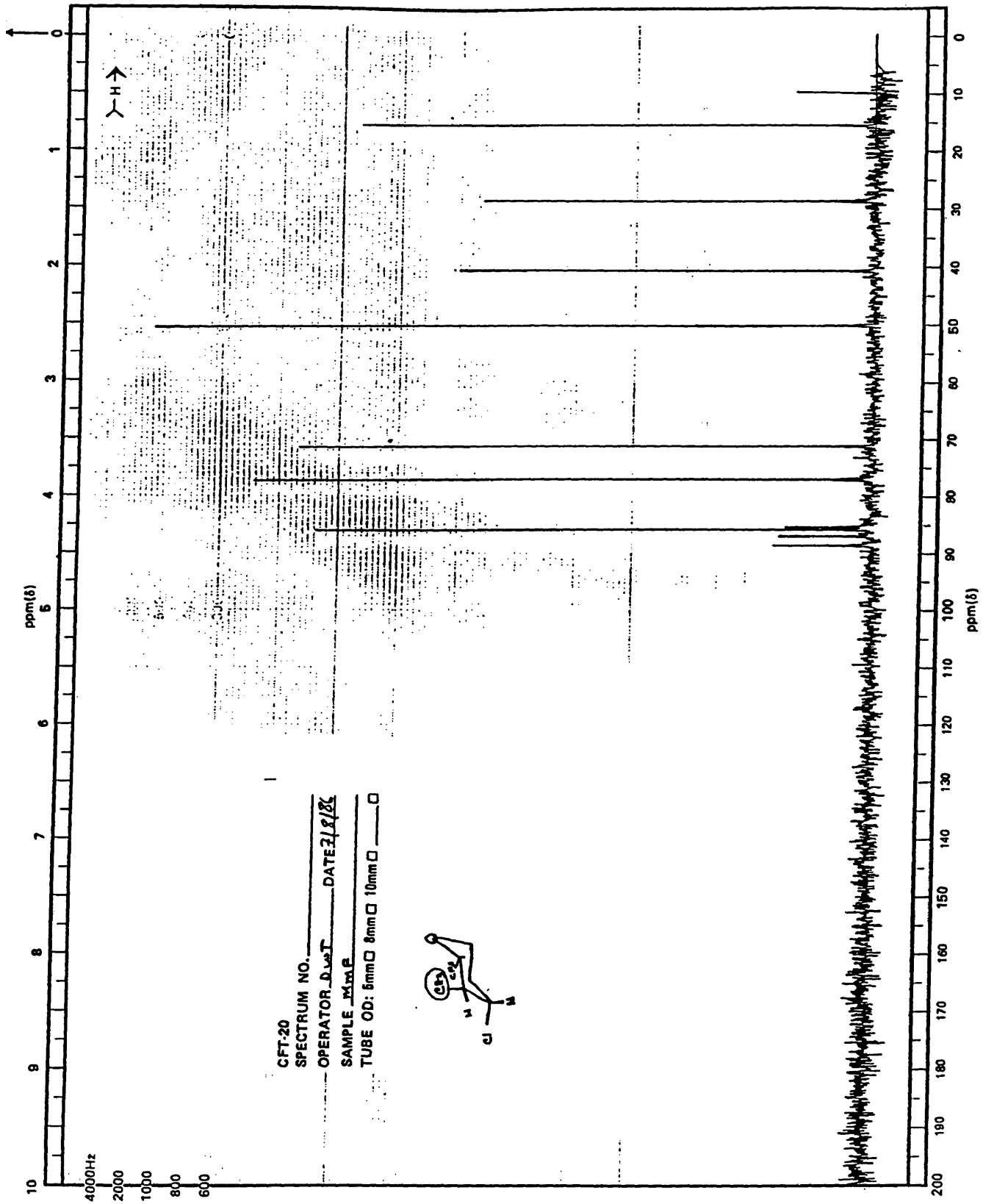


Figure 30. ¹³C NMR spectrum of cis, cis-2,3-dimethyl-4-chlorotetrahydropyran at 80 MHz.

CONCLUSION

We have investigated methods leading to the stereoselective and stereospecific syntheses of 3-methyl-4-halotetrahydropyran, cis and trans 2,5-dimethyl-4-halotetrahydropyran, and cis and trans 2,3-dimethyl-4-halotetrahydropyran. The synthetic strategy involves the production of the ethyl vinyl ether or (2-methoxyethoxy)methyl (MEM) acetals of homoallylic alcohols. Lewis acid promoted cyclization at lower temperatures leads to the formation of a resonance stabilized oxacarocation formed upon cleavage of the acetal linkage followed by addition across the unsaturation in a trans fashion. The preeminence of trans addition has important stereochemical implications. First, trans attack of the olefin necessitates an equatorial disposition of the halogen substituent at the 4 position of the product tetrahydropyran unless conformational effects induce chair-chair interconversion. Secondly, such attack will proceed preserving stereochemical integrity about the double bond such that a cis acetal yields a cis configuration at the 3 (or 5) and 4 carbons of the tetrahydropyran product; similarly trans acetals yield the trans tetrahydropyrans. Thus, cis and trans 2,3-dimethyl-4-halotetrahydropyran are generated from the ethyl vinyl ether acetals of cis and trans 3-penten-1-ol, respectively. Formation of the MEM acetals of the same isomeric alkenols leads similarly to stereospecific production of cis or trans 3-methyl-4-halotetrahydropyran.

In other investigations, the stereoselective cyclization of the ethyl vinyl ether acetal of 2-methyl-3-buten-1-ol yields approximately a 3:1 cis, trans : cis, cis mixture of 2,5-dimethyl-4-halotetrahydropyran while MEM acetal cyclization produces a 2:1 trans : cis mixture of 3-methyl-4-halotetrahydropyran. In both cases the isomeric mixtures arise from a variable orientation of the 3 (or 5) methyl group and are consistent with the predicted conformational stabilities of the isomeric tetrahydropyran products.

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