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Transition Metal Promoted Carbometallation of Alkynols

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TRANSITION METAL PROMOTED CARBOMETALLATION OF ALKYNOLS

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by

Douglas W. Moore

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APPROVAL SHEET

This thesis is submitted in partial fulfillment of

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Master of Arts

Douglas W. Moore

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Randolph A. Coleman, Ph.D.

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ABSTRACT

Trisubstituted olefins are a challenging target for stereoselective synthesis. We have modified the components of Ziegler-Natta polymerization systems in order to obtain trisubstituted olefins stereoselectively. A series of ring-substituted bis(cyclopentadienyl)titanium(IV)dichloride compounds was utilized to study the alkylation of 3-butyn-1-ol. As the degree of ring-substitution increased there was an increase in the stereoselectivity of methylation of 3-butyn-1-ol [$(Me_5Cp)_2TiCl_2$ > $(\underline{t}\text{-buCp})_2TiCl_2 \cong (MeCp)_2TiCl_2 \cong Cp_2TiCl_2$]. $(Me_5Cp)_2TiCl_2$ provided a single product, 3-methyl-3-buten-1-ol. Ethylation of 3-butyn-1-ol in these systems was less satisfactory.

Titatium tetrachloride ($TiCl_4$) was investigated with various alkynols, based on 3-butyn-1-ol, in order to determine any effects of alkynol substituents on stereoselectivity of alkylation. The series of alkynols studied all gave single products arising from cis-carbometallation where the methyl group was found on the olefinic carbon atom furthest from the hydroxyl group.

INTRODUCTION

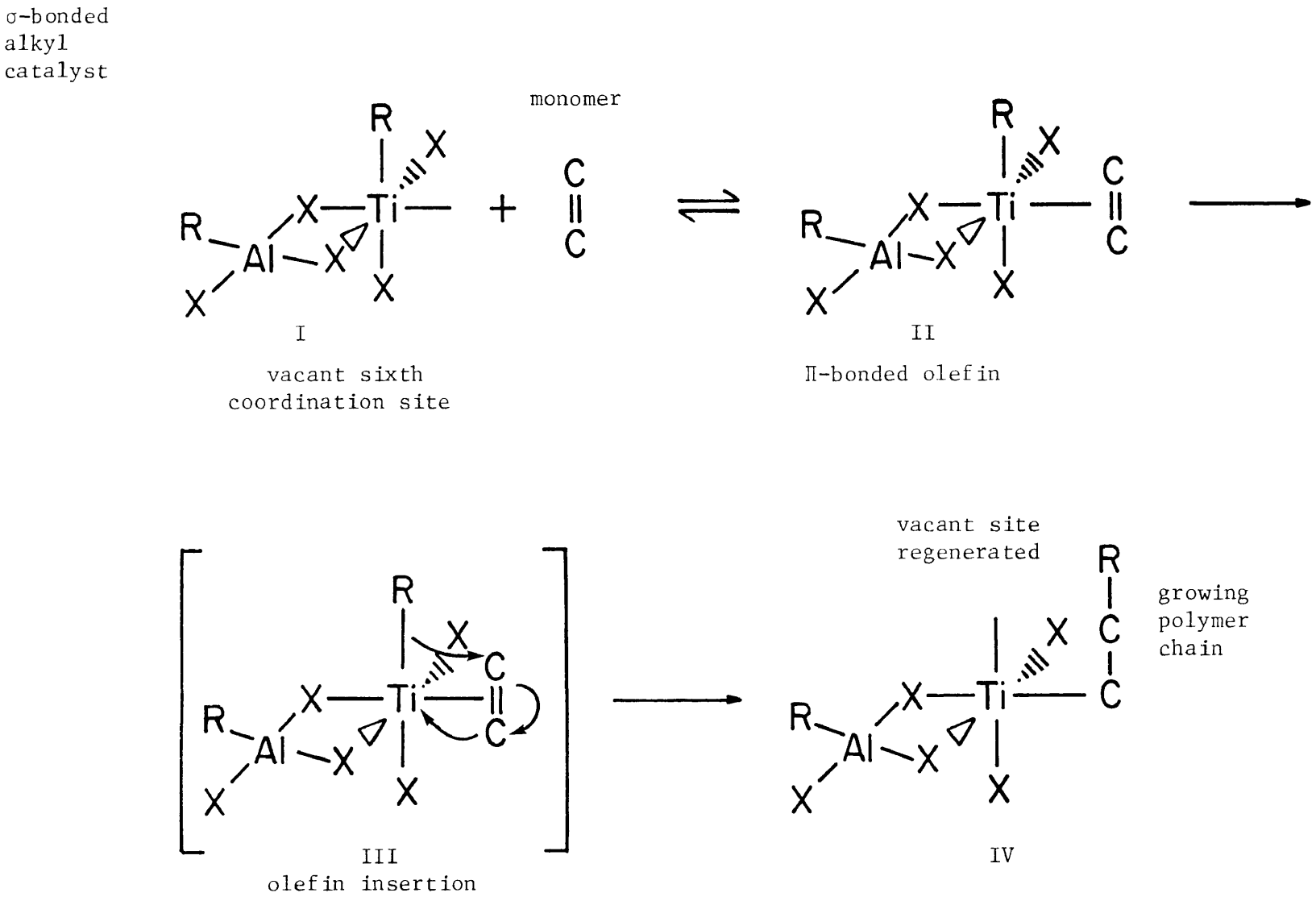
In the early 1950's, Karl Ziegler[1] discovered catalyst systems for facile polymerization of ethylene. The catalyst systems consist of a main group organometallic compound, usually an organoaluminum, and an early transition metal compound. An example is a mixture of titanium tetrachloride and diethylaluminum chloride in an inert organic solvent such as hexane or methylene chloride. When ethylene is added to the catalyst system a facile polymerization occurs which results in linear, high-density polyethylene. Subsequent study of Ziegler type catalysts by Natta[2] showed that they not only convert ethylene into linear, high-density polyethylene, but that they also rapidly convert α-olefins such as propylene in a head-to-tail manner into stereoregular, isotactic polymers, i.e., the configuration at each chiral carbon atom in a polymer chain is the same.

The commonly accepted mechanism for Ziegler-Natta polymerization is given in Figure 1.[3,4] In the presence of an alkylaluminum reagent a titanium (IV) compound forms an alkylated five-coordinate titanium complex (I) via ligand exchange between titanium and aluminum species. The five-coordinate complex (I) is coordinatively unsaturated since titanium (IV) most commonly occurs with a coordination number of six. Thus, the titanium center is considered to have a vacant coordination site. An olefinic monomer can now coordinate through its π-bonded electrons to titanium at the vacant site (II). The olefin becomes activated for carbometallation (III), i.e., addition of the titanium-alkyl moiety across the double bond. This "growth step" increases the chain length of the polymer by one monomer unit and regenerates the vacant site (IV) so that carbometallation of an

Figure 1.

Pathway for Zeigler Catalysis in the Cl_4Ti-Et_2AlCl-Ethylene System

R=Et and X=Cl

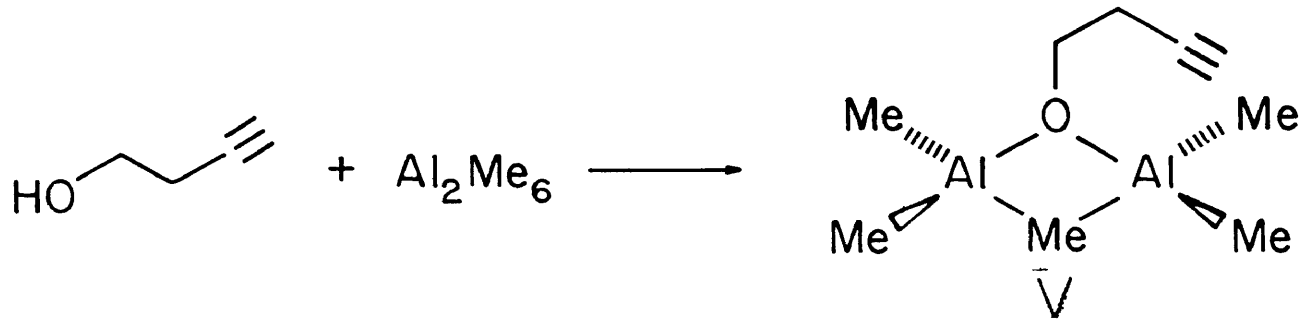


olefin monomer can be repeated. Thus, olefin polymerizations are extremely facile and repetitive carbometallation reactions.

Natta et al.[5] and Miyazawa and Ideguchi[6] have shown that the carbometallation step described in Figure 1 occurs in a cis manner. Their conclusions were based on infrared analysis of polymers which had been formed from selectively deuterated propylene monomers. Thus, the Ziegler-Natta catalyst systems are regioselective and stereoselective as well as facile carbometallating reagents; however, carbometallation is virtually uncontrolled.

The two major goals of synthetic organic chemistry are the extension of carbon frameworks and the functionalization or defunctionalization of carbon frameworks.[7] The former goal is more difficult due to stereochemical variations within a given carbon constitution and fewer well-defined carbon-carbon bond forming reactions.[8] Since carbon-carbon bond formation is facile, regioselective and stereoselective in Ziegler-Natta type catalyst systems, the goal of the research reported herein is to modify Ziegler-Natta catalyst systems in order to control the carbometallation thus obtaining the products of a single carbometallation step. The two approaches toward achieving the goal involve changing the unsaturated substrate and changing the ligand environment of the transition metal such that repetitive carbometallation would be unfavorable. Success in this research would provide a new means of selectively forming carbon-carbon bonds in non-macromolecular synthesis.

Our basic approach to controlled carbometallation, which serves as the basis for the research reported herein, can be illustrated by considering the alkylation of 3-butyn-1-ol via the titanium tetrachloride-trimethylaluminum system. 3-Butyn-1-ol is allowed to react with trimethylaluminum to form the mixed species pentamethyl(3-butyn-1-oxy)dialuminum,



V

Compound V is then allowed to react with titanium tetrachloride. Figure 2 illustrates the chemistry that is envisioned to take place from this point. The titanium tetrachloride and V react to form a binuclear 3-butyn-1-oxy-aluminum-titanium complex in which the titanium has been methylated via ligand exchange, i.e., methyl group-chloride exchange. At this point the significance of choosing to alkylate an unsaturated alcohol is apparent. Coordination of the unsaturated alcoholic substrate through its oxygen atom should favor an intramolecular single-step carbometallation of the triple bond and make polymerization significantly less favorable. Possible carbometallation-protonolysis sequences leading to alkenol products are shown in the proposed intermediate VI in Figure 2. Recent work has demonstrated the potential of this approach.[9]

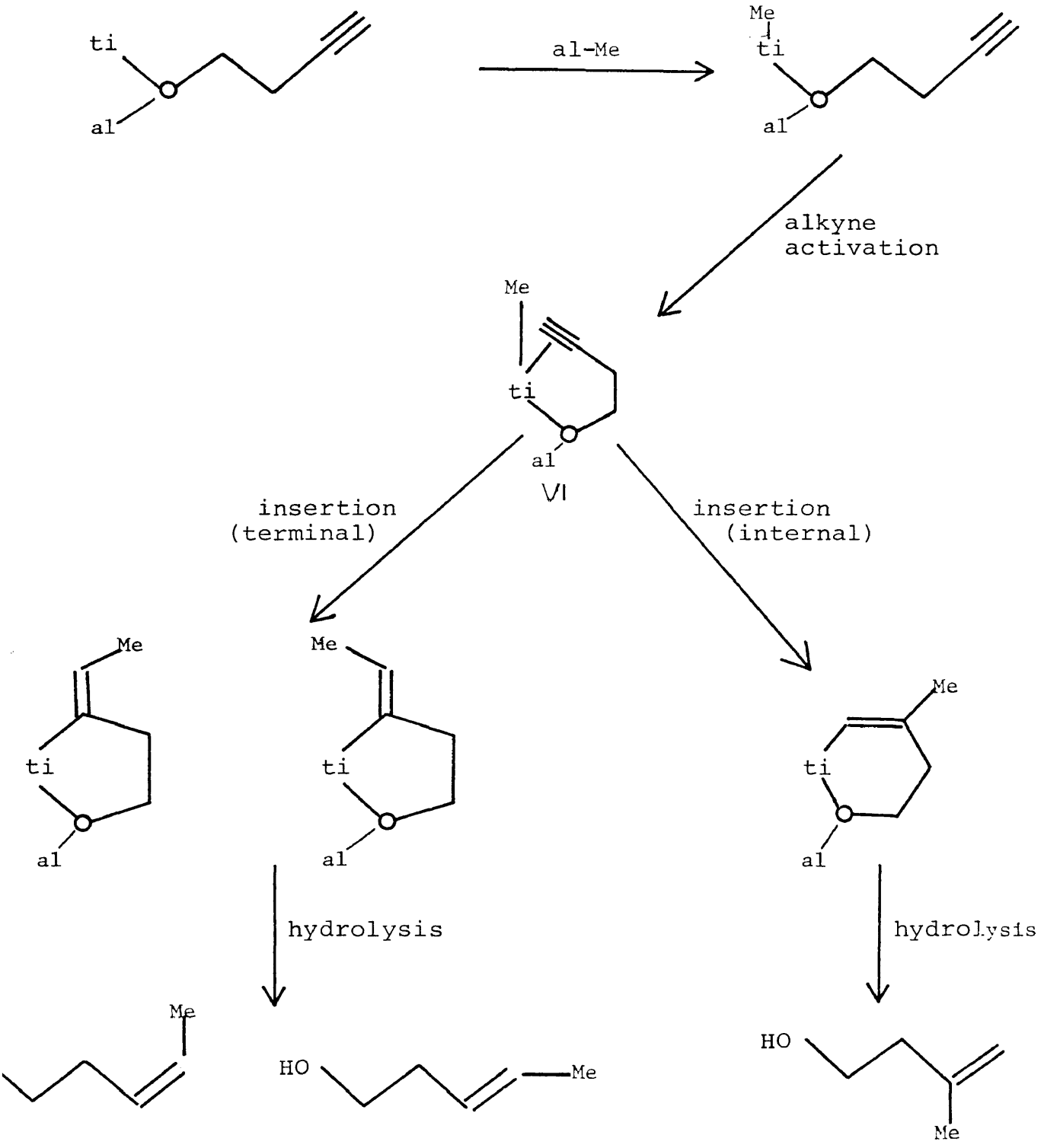


Figure 2. Proposed pathway for the carbometalation of alkynols with titanium-organoalane systems. (The use of ti and al with reacting groups indicates the uncertainty as to the nature of the substitution about the metals in the mixed ligand system. Titanium is assumed to be the alkylating center by analogy to the accepted Ziegler-Natta polymerization mechanism.)

The focus of the research reported in this thesis is twofold. First, the direct stereoselective synthesis of trisubstituted olefins of specific type (Z)-4-methyl-3-alken-1-ol via reaction of internal homopropargyllic alcohols with the titanium tetrachloride-trimethylaluminum Ziegler-Natta type catalyst system was investigated. Preliminary studies indicated that this reagent system holds substantial promise.[9] Second, the substituted cyclopentadienyl complexes bis(η^5-t-butylcyclopentadienyl)titanium (IV) dichloride and bis(η^5-pentamethylcyclopentadienyl)titanium (IV) dichloride were synthesized for use as the transition metal components of Ziegler-Natta carbometallating systems containing either trimethylaluminum or diethylaluminum chloride. These systems were then utilized in carbometallating 3-butyn-1-ol. Earlier work[10] with alkynols had shown that bis(η^5-cyclopentadienyl)- and bis(η^5-methylcyclopentadienyl)titanium dichloride gave excellent yields of carbometallated products, but the regioselectivity was poor. We sought to determine if the substantially greater steric requirements of t-butylcyclopentadienyl and pentamethylcycopentadienyl rings would give improved regioselectivity while retaining excellent overall yield of product.

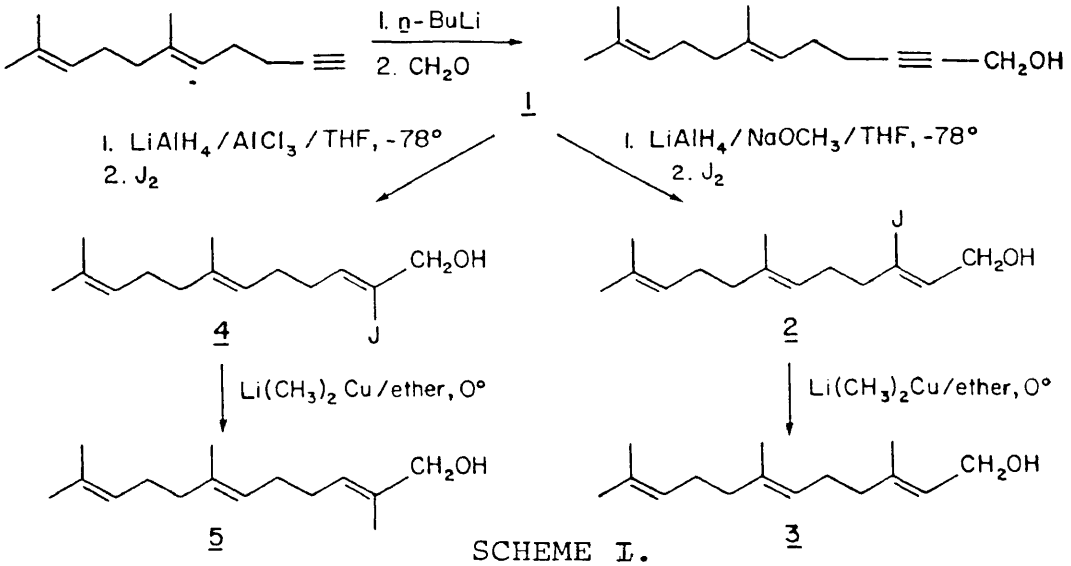
REVIEW

Since this reserach focuses on methods for stereoselective synthesis of di- and trisubstituted olefins, the literature on the subject was reviewed. Before presenting the literature review, certain terms should be clearly defined. The term "stereoselective synthesis" refers to a reaction system which gives predominantly one of two or more possible diastereomeric products. This is to be distinguished from a stereospecific synthesis which means that stereoisomerically different starting materials give rise to stereoisomerically differing products.[11] For the purpose of this paper a "trisubstituted olefin" is an organic molecule containing one or more olefinic linkages having a total of three carbon atoms and one hydrogen atom branching from the olefinic linkage.

The synthetic methods reviewed in this paper are: additions to acetylenes (under which area belongs the experimental work reported herein), some reactions of carbonyl compounds, and some rearrangement reactions. While several other miscellaneous routes to selected trisubstituted olefins have been reported, those discussed here seem to be of more general utility. Only methods for synthesizing trisubstituted olefins will be discussed since such methods are usually readily applied to synthesis of disubstituted olefins. Furthermore, synthesis of trisubstituted olefins offers a greater challenge and generally more interesting products.

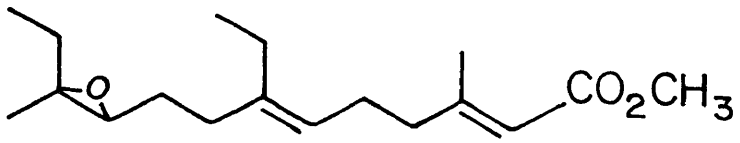
Additions to Acetylenes

Trisubstituted olefins can be formed by addition of carbon groups to acetylenes. One example of this type of reaction is the initial information of a disubstituted vinyl halide from an internal alkyne followed by a coupling reaction (Scheme I). Corey and Posner[12] stereoselectively reduced the acetylenic linkage of a propargylic alcohol (1) with a mixture of lithium aluminum hydride and aluminum chloride (60:1) in THF. Addition of iodine to the organolithium intermediate gave rise to a trans-β-iodo allylic alcohol (4). However, when (1) was reduced with a mixture of lithium aluminum hydride and sodium methoxide (1:2) in THF followed by treatment with iodine, trans-γ-iodo allylic alcohol 2 was obtained. Treatment of alcohols (2) and (4) with lithium dimethyl copper gave the coupled products trans, trans-farnesol (3) and 2,7,11-trimethyl-trans, trans-2,6,10-dodecatrienol (5), respectively. Trans, trans-farnesol is one of the simple, naturally occurring, sesquiterpenoid alcohols and was obtained in 60-75% yield. The key step in the synthesis of (3) was stereoselective formation of the iodo allylic alcohol (2).



SCHEME I.

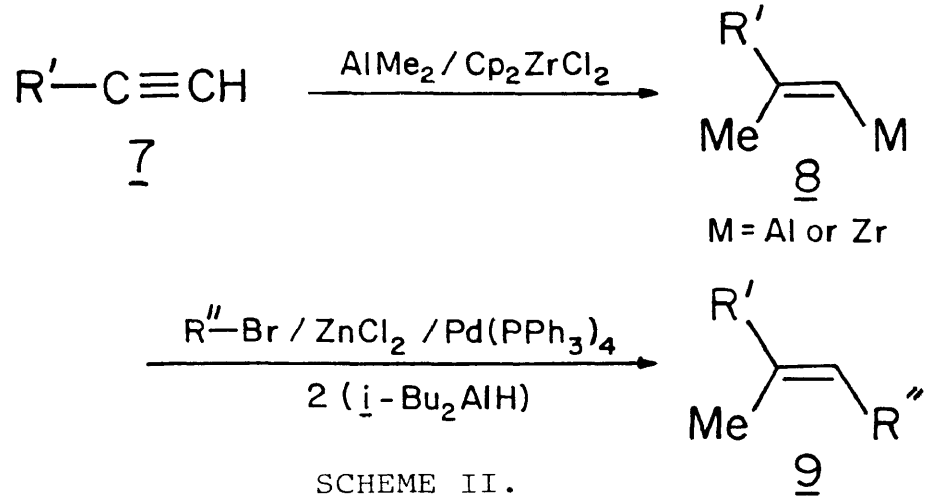
Corey et al.[13] utilized the method in Scheme I twice in a synthesis of cecropia juvenile hormone (6). The juvenile hormone function is



6

to maintain the larval characteristics of insects. Hence, insects exposed to a slight excess of juvenile hormone fail to mature; they die in the larval stage. The potential use of synthetic juvenile hormone as a pesticide appears to offer promise.

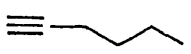
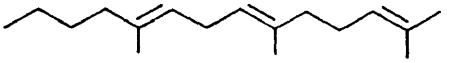
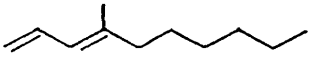
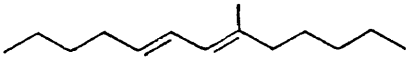
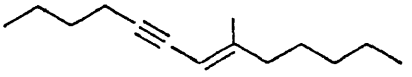
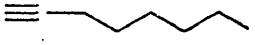
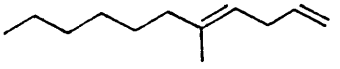
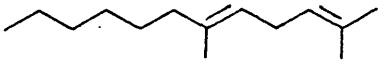
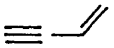
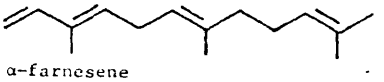
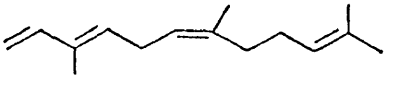
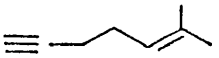
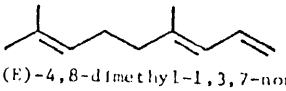
Another means of obtaining an olefin via a coupling reaction is the carbometallation of a terminal acetylene followed by cross-coupling with an organic halide. Negishi et al.[14] have developed a reaction system Scheme II) in which a terminal acetylene (7) is carbometalled via a Ziegler-Natta-type catalyst, $Cp_2ZrCl_2/AlMe_3$ (Cp=η^5-cyclopentadienyl). The carbometallated intermediate (8) is then treated with an organic halide in the presence of tetrakis(triphenylphosphine)palladium(0), $[Pd(PPh_3)_4]$. The resulting product (9) is predominantly the product of cross-coupling of the organometallic intermediate and the organic halide. Table 1 presents a summary of compounds which have been studied by Negishi.



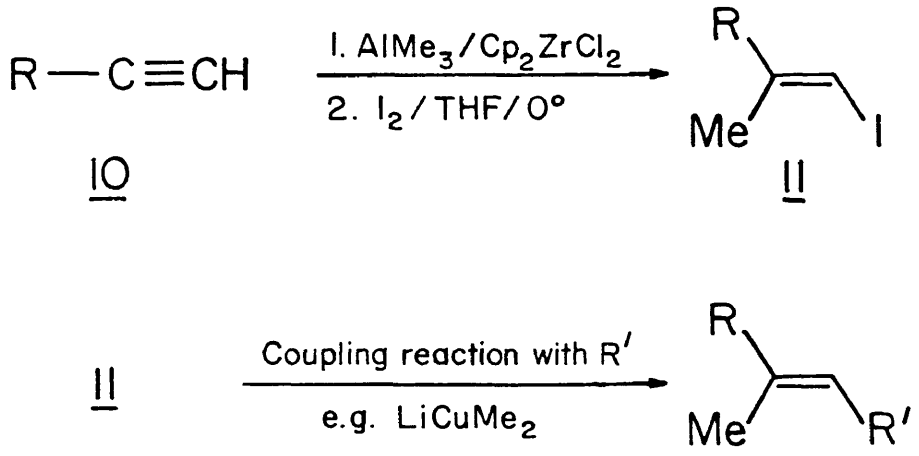
SCHEME II.

TABLE 1

METHYLMETALLATION OF TERMINAL ALKYNES VIA THE $Cp_2ZrCl_2/AlMe_3$ REAGENT FOLLOWED BY $[Pd(PPh_3)_4/ZnCl_2]$ CATALYZED CROSS-COUPLING WITH AN ORGANIC HALIDE TO FORM TRISUBSTITUTED OLEFINS.

Terminal alkyne	Organic halide	Product	
 (1-hexyne)	geranyl chloride $Pd(PPh_3)_4$	 (E,E)-2,6,10-trimethyl-2,6,9-tetradecatriene	(92^6)
 (1-heptyne)	vinyl bromide $Pd(PPh_3)_4$	 (E)-4-methyl-1,3-nonadiene	(73^a)
	(E)-1-iodo-1-hexene $Pd(PPh_3)_4$	 (E,E)-8-methyl-5,7-tridecadiene	(65^a)
	1-iodo-1-hexyne $Pd(PPh_3)_4$	 (E)-8-methyltridec-7-en-5-yne	(90^a)
 (1-octyne)	allyl bromide $Pd(PPh_3)_4$	 (E)-5-methyl-1,4-undecadiene	(90^a)
	isoprenyl chloride $Pd(PPh_3)_4$	 (E)-2,6-dimethyldodeca-2,5-diene	(98^a)
 (butenyne)	geranyl chloride $Pd(PPh_3)_4$	 α-farnesene	(86^b)
	neryl chloride $Pd(PPh_3)_4$		(77^b)
 (6-methyl-5-hepten-1-yne)	vinyl bromide $Pd(PPh_3)_4$	 (E)-4,8-dimethyl-1,3,7-nonatriene	(70^a)

Other work on the formation of trisubstituted olefins from terminal acetylenes has been done by Negishi et al.[15] Instead of forming a vinyl halide from a disubstituted alkyne and subsequent coupling as in Scheme I, a terminal alkyne was carbometallated via $Cp_2ZrCl_2/AlMe_3$ followed by iodinolysis (Scheme III) which gave a vinyl iodide (11) stereoselectively. The vinyl iodide was then allowed to undergo a coupling reaction to form trisubstituted olefins. Reported isolated yields of vinyl iodides range from 70 to 85%. Table 2 is a list of substrates used and products formed in the reaction sequence described in Scheme III.



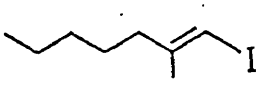
SCHEME III.

TABLE 2

METHYLMETALLATION OF TERMINAL ALKYNES VIA THE $Cp_2ZrCl_2/AlMe_3$ REAGENT FOLLOWED BY IODINOLYSIS TO FORM VINYL IODIDES.

(1-heptyne)

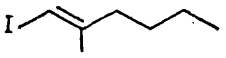
I_2



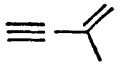
(E)-1-iodo-2-methyl-1-heptene (83[b])

(1-hexyne)

I_2

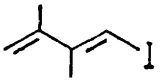


1-iodo-2-methyl-1-hexene (85[b])



2-methylbut-3-en-1-yne

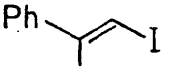
(I_2)



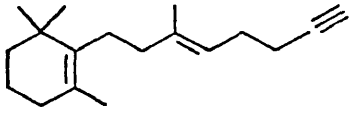
(E)-1-iodo-2,3-dimethyl-1,3-butadiene (70[b])

(phenylacetylene)

I_2

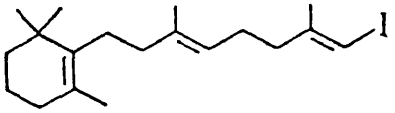


(E)-1-iodo-2-phenylpropene (83[a])

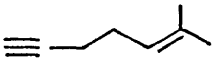


(E)-4-(2,6,6-trimethyl-1-cyclohexenyl)-6-methyloct-5-en-1-yne

I_2

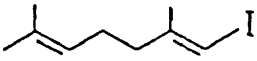


(>70[c])



(6-methyl-5-hepten-1-yne)

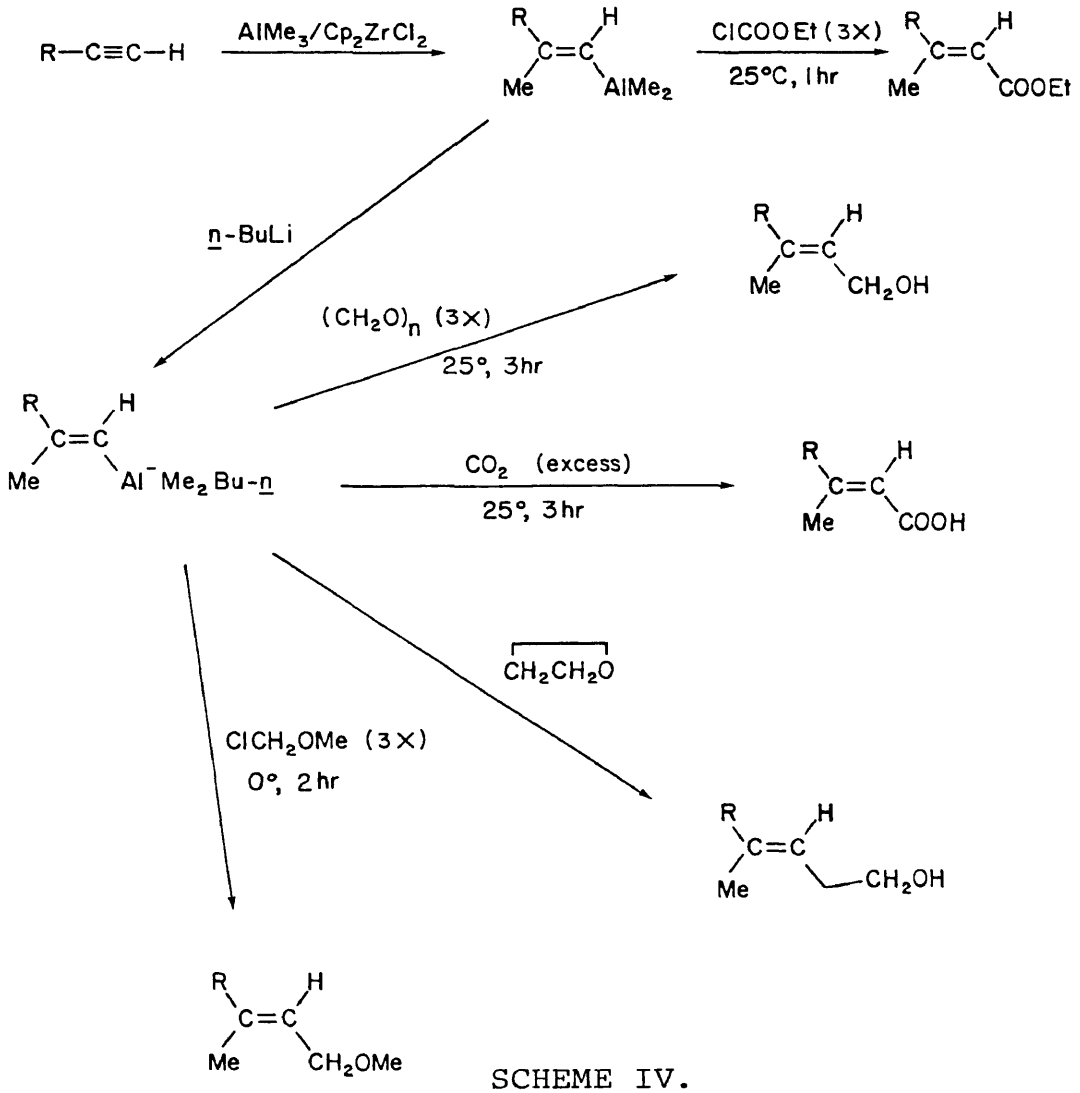
I_2



(E)-1-iodo-2,6-dimethyl-1,5-heptadiene (75[b])

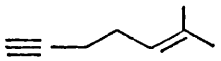
Functionalized terpenoids have been prepared by Negishi by terminating the carbometallation of terminal acetylenes with various carbon homologation reagents.[16] The two or three-step method of this procedure (Scheme IV) offers a slight advantage over Corey's four-step method to olefinic alcohols previously discussed (Scheme I). The basic scheme of the reaction sequence is given in Scheme IV. Specific results are listed in Table 3.

The simplest stereoselective route to trisubstituted olefins has been presented by Thompson et al.[10,17] The group affected direct formation of a trisubstituted olefin by hydroalkylation of an internal (i.e. disubstituted) alkyne. 3-Pentyn-1-ol was allowed to react with diethylaluminum chloride ($AlEt_2Cl$) followed by bis-(η^5-cyclopentadienyl)titanium (IV) dichloride (Cp_2TiCl_2). Protonolysis of the reaction mixture resulted in a mixture of ethylated 3-alken-1-ols. E-4-Methyl-3-hexen-1-ol (12) was formed by ethylation of the unsaturated carbon atom furthest from the hydroxyl group (i.e. terminal alkylation). E-3-Ethyl-3-penten-1-ol (13) was formed by ethylation of the unsaturated carbon atom nearest the hydroxyl group (i.e. internal alkylation). The two products were formed in a relative ratio of 93:7 terminal to internal ethylation and in 85% overall yield. Substituting $(MeCp)_2TiCl_2$ (50 mole percent relative to alkynol) for Cp_2TiCl_2 (75 mole percent relative to alkynol) gave an increase in regioselectivity from 93:7 to 95:5 terminal to internal alkylation but a decrease in overall yield from 85 to 65%. Thompson et al.[18] also reported preparation of 12 via reaction of a 3-pentyn-1-oxy(chloro)bis(2,4-pentanedionato)titatium (IV) complex with diethylaluminum chloride. The yields of alkylated product were modest (44 to 53%) although excellent regioselectivity was noted (terminal alkylation only).

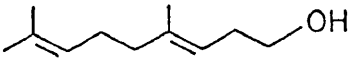
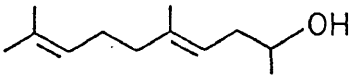
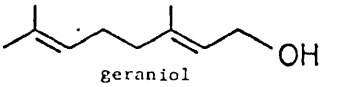
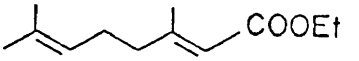

R—C≡C—H
AlMe3/Cp2ZrCl2
ClCOOEt (3X)
25°C, 1 hr
n-BuLi
(CH2O)n (3X)
25°, 3hr
CO2 (excess)
25°, 3hr
ClCH2OMe (3X)
0°, 2 hr
CH2CH2O
Me
AlMe2
COOEt
CH2OH
COOH
Al⁻Me2Bu-n

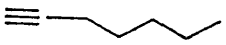
SCHEME IV.

METHYLMETALLATION OF TERMINAL ALKYNES VIA THE $Cp_2ZrCl_2/AlMe_3$ REAGENT FOLLOWED BY FUNCTIONALIZATION WITH VARIOUS CARBON HOMOLOGATION REAGENTS TO FORM TRISUBSTITUTED OLEFINS.

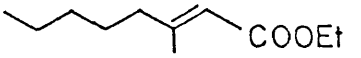
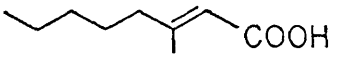
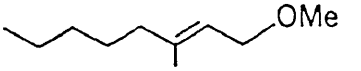
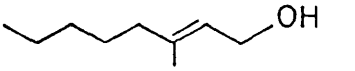


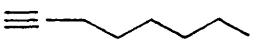
(6-methyl-5-hepten-1-yne)

n-BuLi, CH_2CH_2O		(89[a])
	(E)-4,8-dimethyl-3,7-nonadien-1-ol	
n-BuLi, CH_3CHCH_2O		(82[a])
	(E)-1,4,8-trimethyl-3,7-nonadien-1-ol	
$(CH_2O)_n$, n-Buhi		(87[a])
	geraniol	
ClCOOEt, n-BuLi		(85[a])
	ethyl geranate	

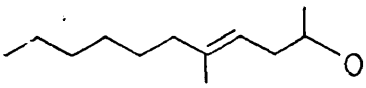
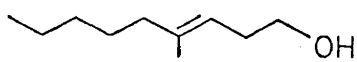


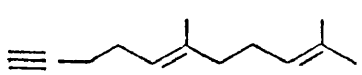
(1-heptyne)

ClCOOEt		(86[a])
	ethyl (E)-3-methyl-2-octenoate	
CO_2, n-BuLi		(64[a])
	(E)-3-methyl-2-octenoic acid	
$ClCH_2OMe$, n-BuLi		(79[a])
	(E)-3-methyl-2-octenyl methyl ether	
$(CH_2O)_n$, n-BuLi		(82[a])
	(E)-3-methyl-2-octen-1-ol	

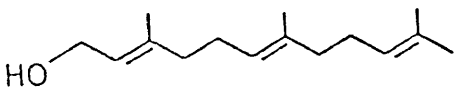


(1-octyne)

n-BuLi, CH_3CHCH_2O		(97[a])
	(E)-5-methyl-4-undecen-2-ol	
n-BuLi, CH_2CH_2O		(78[b])
	(E)-4-methyl-3-nonen-1-ol	



(E)-2,6-dimethylundeca-2,6-dien-10-yne

$(CH_2O)_2$, n-BuLi		(91[d])
	(E,E)-farnesol	

Further study of titanium based alkylation systems has been reported by Thompson et al.[19] 3-Buten-1-ol was alkylated in a titanium tetrachloride-organoaluminum system where the organoaluminum compounds used were $Al(C_2H_5)_3$, $Al(C_2H_5)_2Cl$, $Al(CH_3)_3$, and $Al(CH_3)_2Cl$. In all cases yields of alkylated products were modest and the system gave side products such as the hydrogenated product, 1-butanol (found in both the methylation and ethylation systems) and the β-hydride elimination (subsequent to alkylation) products, trans-3-hexen-1-ol in the ethylation system and trans-3-penten-1-ol in the methylation system. However, in marked contrast to the lack of selectivity with 3-buten-1-ol, preliminary work indicated that alkynol alkylation in a $TiCl_4/AlMe_3$ system was highly selective.[9] For example, Z-4-Methyl-3-hexen-1-ol was prepared stereoselectively from 3-hexyn-1-ol in an isolated yield of 60% and 4-methyl-3-penten-1-ol was obtained in high yield from 3-pentyn-1-ol.

Additions to acetylenes constitute an interesting means of synthesizing di- and trisubstituted olefins. Several methods within this class have been examined. A disubstituted alkyne can be stereoselectively converted to an α,β-disubstituted vinyl halide which can then undergo a coupling reaction to form trisubstituted olefin. A terminal alkyne can be stereoselectively methylmetallated to form a β,β-disubstituted vinyl-metallic intermediate. The intermediate can then be used with an organic halide in a coupling reaction to provide a trisubstituted olefin stereoselectively or can be converted to a vinyl halide itself and then be utilized in a cross-coupling reaction. Lastly, direct carbometallation of a disubstituted alkyne followed by protonolysis gives rise to a trisubstituted olefin.

Some Reactions of Carbonyl Compounds

The carbonyl functionality is prevalent in nature and is often reactive. Hence, the chemistry of the carbonyl functionality is of broad scope. With regard to olefin formation, there are many methods which utilize the carbonyl group. Three of those methods will be discussed here; they are the Wittig reaction, the Cornforth synthesis and the directed aldol condensation.

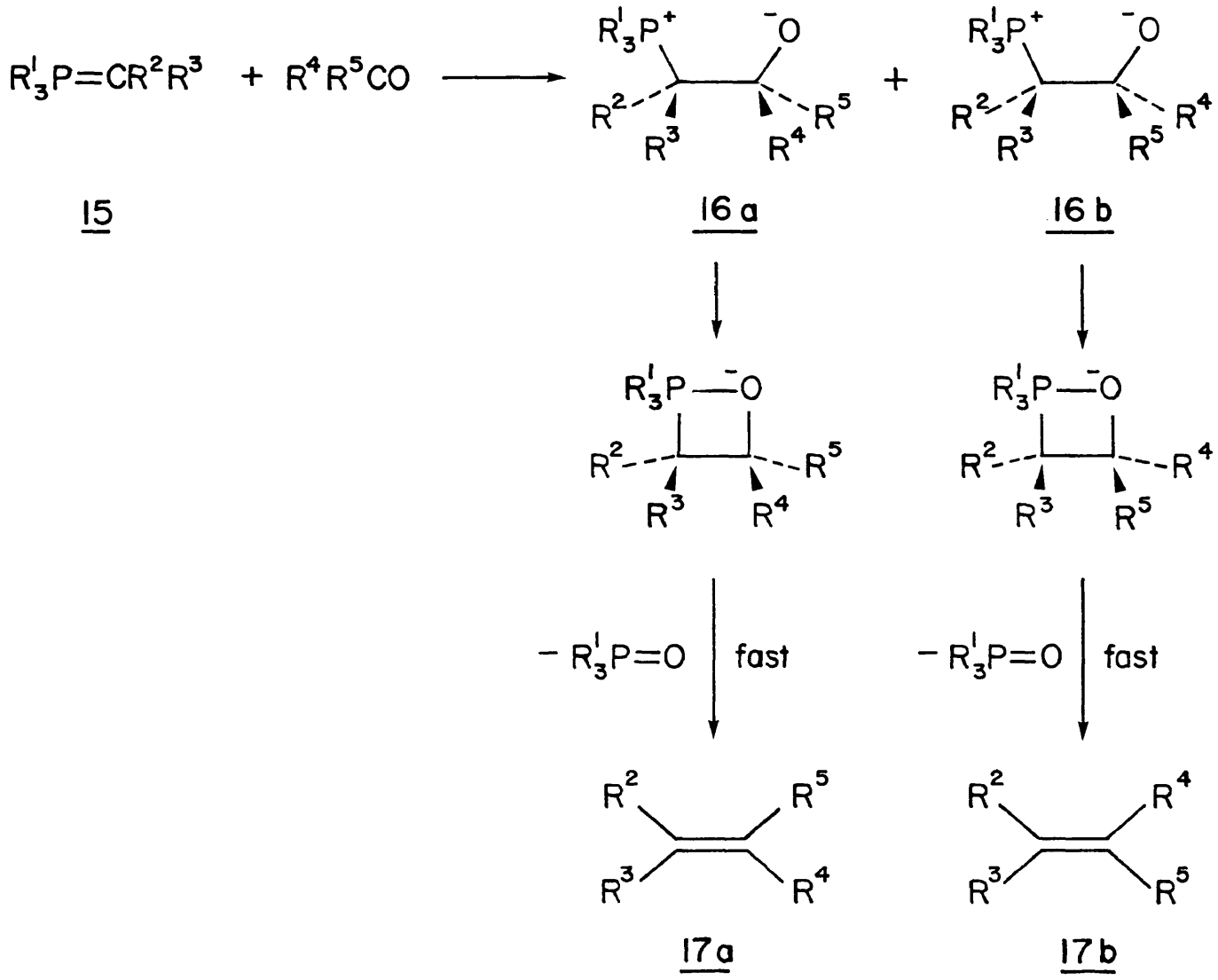
The Wittig reaction is perhaps the most traditional means of preparing olefins. The method involves reaction between a phosphorane (also called a phosphorous ylid) and a carbonyl compound. The advantages of the Wittig reaction are a lack of ambiguity in the location of the olefinic linkage and that the reaction provides simultaneous olefin formation and homologation.[20] The reaction is versatile in the nature and number both of carbonyl compounds and phosphorous ylids which will undergo reaction. The Wittig reaction will proceed with saturated and unsaturated aliphatic aldehydes, aromatic aldehydes, aliphatic and aromatic ketones, thioketones, ketenes, and isocyanates.[21] Over two-hundred different phosphorous ylids have been used in Wittig-type reactions.[22] Some of the disadvantages are: side reactions of ylid with solvent, reduced selectivity due to ions present in solution, fragmentation and intra- or intermolecular reaction of non-stabilized phosphorane intermediates.

The first phosphoranes studies were non-stabilized such as 14 and have been shown to give predominantly cis disubstituted olefins when allowed to react with aldehyde in non-polar solvent.[23] Non-stabilized phosphoranes

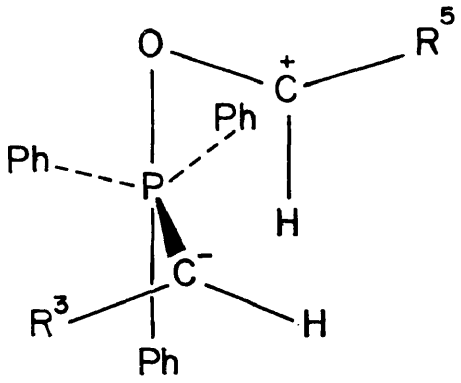
14

are highly reactive in contrast to stabilized phosphoranes which can be isolated, stored in the atmosphere and used in subsequent reactions. Non-stabilized phosphoranes usually contain either alkyl substituents or no substituents on the carbanion; whereas, stabilized phosphoranes usually contain strongly electron-withdrawing groups on the carbanion.

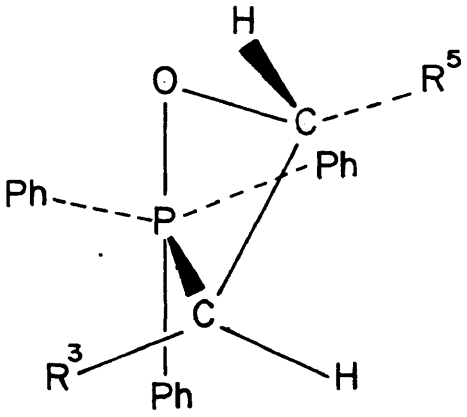
The reaction can be considered to proceed in three steps (Scheme V). Addition of a phosphorane (15) to an aldehyde or ketone gives an intermediate betaine or zwitterion (16). A phosphorous-oxygen bond then forms which leads to rapid cis-elimination of phosphine oxide to form the olefin. Schneider has offered a rationale for the observation that non-stabilized phosphoranes lead to predominantly cis olefins.[24] A priori, it is not obvious that erythro betaine 16b ($R'=C_6H_5$, $R^2=R^4=H$, R^3=organic, R^5=organic) which leads to cis olefin would be more favorable than threo betaine 16a which leads to trans olefin. Assuming the coordination of the oxygen atom to the phosphorous atom prior to nucleophilic attack of the ylid carbon toward the carbonyl carbon, structure 18 can be drawn (Scheme VI). In this configuration the carbon-oxygen bond is in the plane which bisects the phenyl group-phosphorous-carbanion bond angle. The groups on carbonyl carbon are in the plane of the phosphorous-oxygen-carbonyl carbon atoms with the bulkier R^5 pointing away from phosphorous. The R^3 group is directed away from the carbonyl carbon due to steric constraints. For carbon-carbon bonding to occur the cationic group must rotate slightly about the carbon-oxygen bond. Rotation in the clockwise direction (as viewed along the carbon-oxygen axis from carbon toward oxygen) gives structure 19a in which there is the possibility of steric interaction between R^5 and a phenyl group. Rotation of the cationic group in the opposite direction leads to structure 19b in which the steric interaction is minimized. Hence, the intermediate oxaphosphetan 19b is favored over 19a



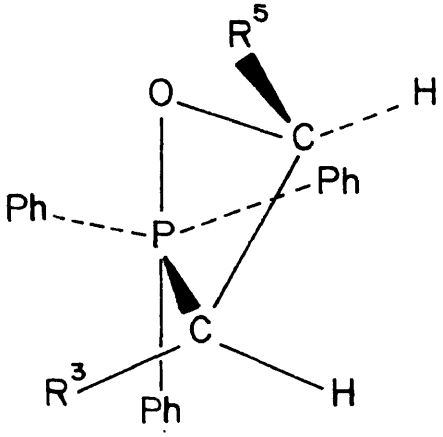
SCHEME V.



18



19a



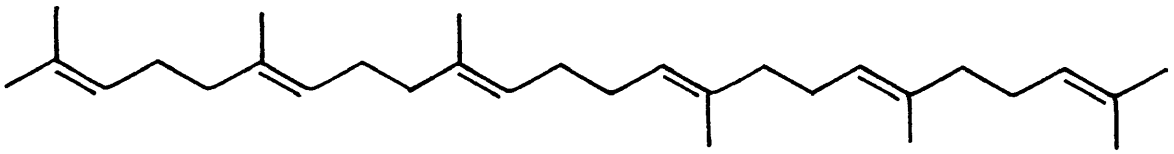
19 b

SCHEME VI.

and elimination of phosphine oxide gives the cis olefin consistent with observation.

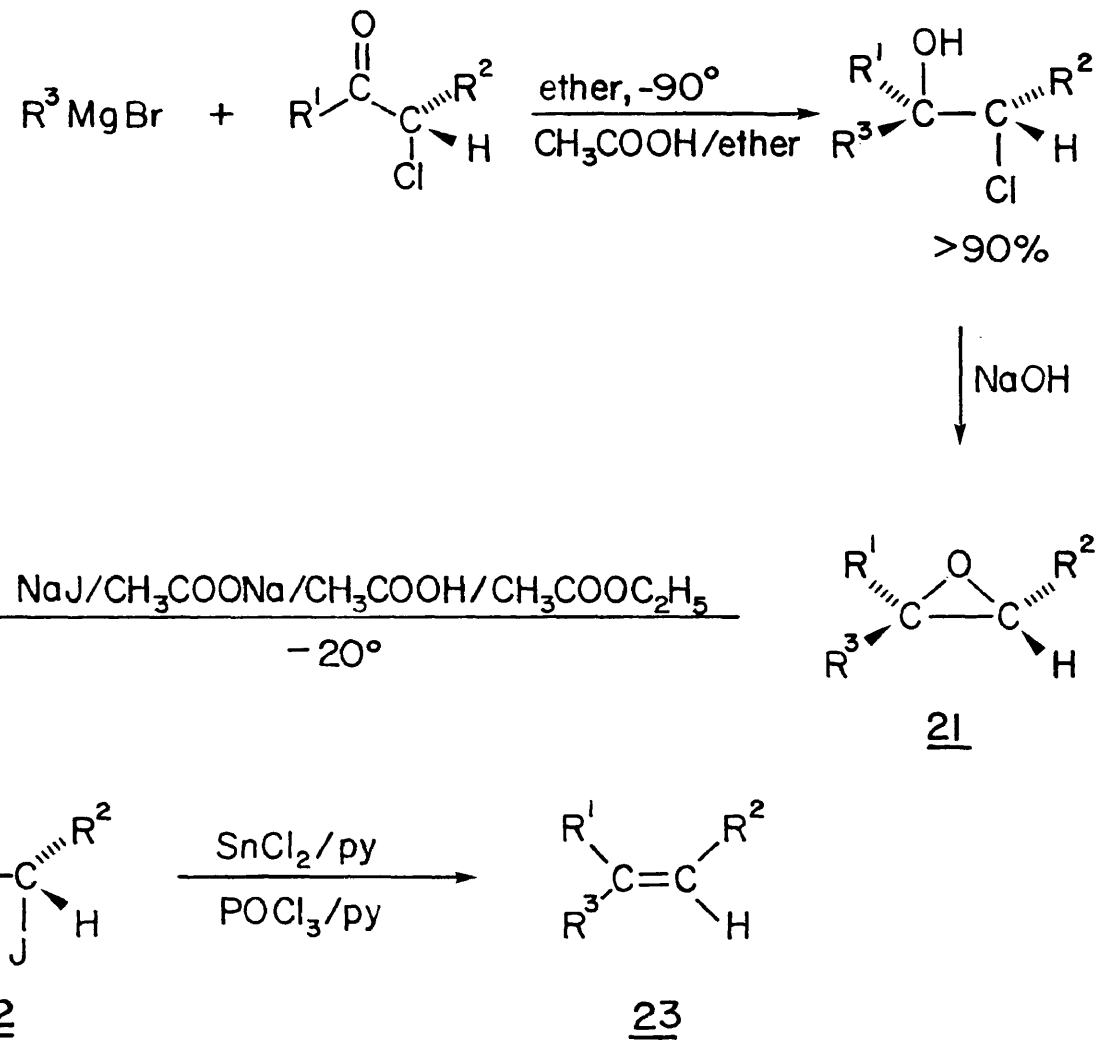
The Wittig reaction can be controlled in order to provide predominantly trans olefin under appropriate conditions of polar solvent and phosphorane stabilization.[25] It can be seen in Scheme VI that if R^3 is an ester group then the carbocation will be attracted toward R^3. In this configuration alkyl group R^5 would favor a position away from R^3 as in 19a thus leading to trans olefin. Other modifications of Wittig reaction systems have been studied and proven to give di-, tri-, and tetrasubstituted olefins in a high degree of stereoselectivity. The modifications include the use of phosphonate carbanions,[26] phosphonamide reagents,[27] phosphonothioate esters[28] and lithium salts added to traditionally stabilized phosphoranes.[29]

Trans-trisubstituted olefins can also be obtained from carbonyl compounds via the Cornforth synthesis. For example, Cornforth et al.[30] were able to prepare squalene (20) with greater than 70% trans geometry at each



20

trisubstituted olefinic linkage. The method involves the low temperature (-70 to -90°C) interaction of a Grignard reagent and an α-chlorocarbonyl compound (Scheme VII). Low temperature permits the α-chlorocarbonyl compound to exist predominantly in an anti-parallel conformation. The molecule has two faces susceptable to nucleophilic attack. The favored side is that which is least sterically hindered. The


R3MgBr
ether, -90°
CH3COOH/ether
OH
Cl
>90%
NaOH
NaJ/CH3COONa/CH3COOH/CH3COOC2H5
-20°
21
SnCl2/py
POCl3/py
22
23

key step toward stereoselectivity is formation of one of the two diastereomeric chlorohydrins. Lower temperatures have been shown to provide higher yields of olefin (90% at -90°C).[31] Converting the chlorohydrin to olefin can be accomplished by the action of sodium hydroxide to form an epoxide (21) which can be converted to an iodohydrin (22) by a mixture of sodium iodide, sodium acetate and acetic and propionic acids. The iodohydrin can then be converted to olefin by stannous chloride and phosphorous oxychloride in pyridine.

The generality of the Cornforth synthesis is limited by the nature of the α-chlorocarbonyl compound. This reagent is generally obtained by acid-catalyzed halogenation of a ketone with N-bromosuccinimide or sulfuryl chloride.[32] The possibility for isomeric α-haloketones exists when there are two α-sites. Usually, however, the halogen adds to the more highly substituted α-carbon in yields of up to 85%. Hence, the Cornforth synthesis appears to be fairly general and gives good yields under mild conditions but does require several steps and reagents.

Another means of forming trisubstituted olefins which involves the transformation of a carbonyl compound via several steps is the directed aldol condensation. In a typical aldol condensation aldehydes undergo base-catalyzed dimerization to β-hydroxyaldehydes (aldols). An aldol gives an α-β unsaturated aldehyde by acid-catalyzed dehydration. Aldehydes and reactive ketones, such as acetone, will undergo reaction to give a mixture of condensation products. Of the four species possible, only dimeric aldehyde and the product of keto-enolate attack on the aldehyde are observed. These intermediates are converted to a mixture of cis and trans-disubstituted olefinic aldehydes upon dehydration.

In the right hand side of Scheme VIII it can be seen that if the enolate ion of acetaldehyde would add to acetone then subsequent dehydration would give a trisubstituted olefin, 3-methyl-2-butenal. Unfortunately, this series of events has not been observed directly. Since the keto-enolate is more nucleophilic than the aldo-enolate, the usual product is ethylidene-acetone (3-penten-2-one) as shown in the left hand side of Scheme VIII.

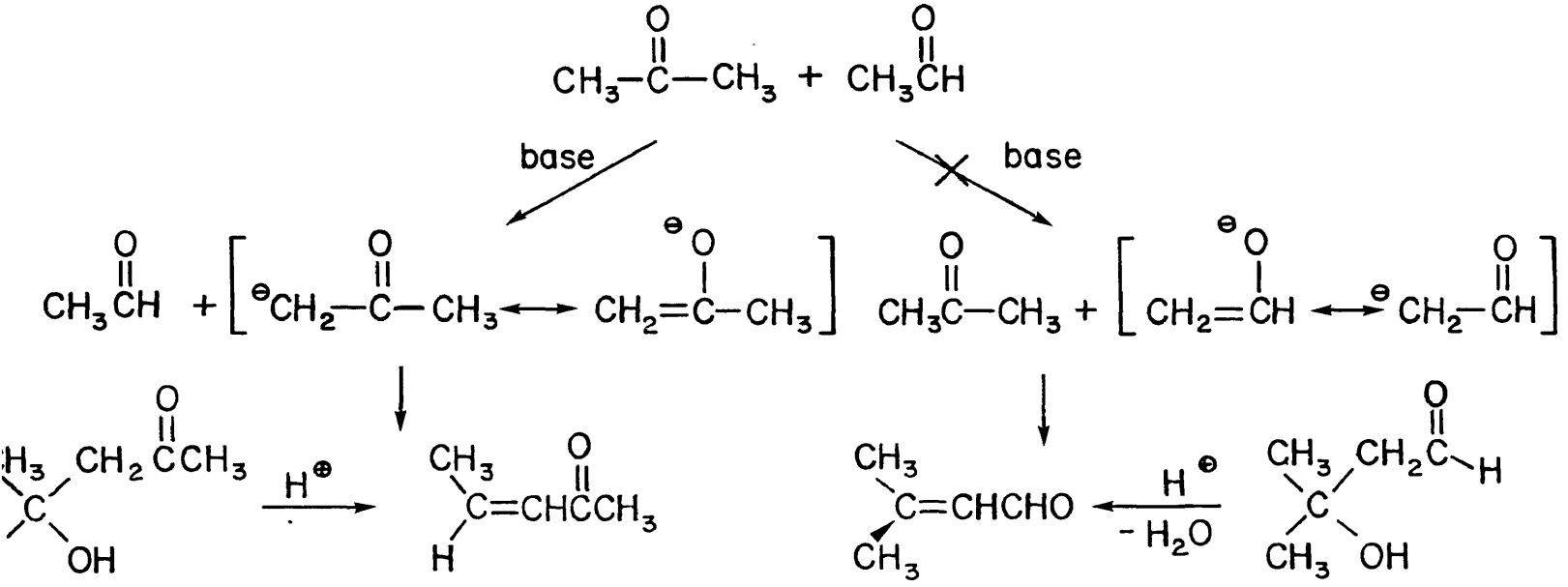
Wittig and Reiff[33] developed a system in which the net reaction is the addition of the enolate ion of an aldehyde to a ketone. The reaction proceeds by converting the aldehyde to an imine (Scheme IX). Metalation of the imine (via a lithium salt) at the α-carbon gives an organolithium reagent which adds to the carbonyl carbon of a ketone. Subsequent acid-catalyzed removal of the imine functionality restores the aldehyde functionality. The final step, acid-catalyzed dehydration, provides a mixture of cis and trans isomers.

Büchi and Wüest[34] were able to increase the stereoselectivity toward the trans-isomer by using t-butylamine in the place of cyclohexylamine.

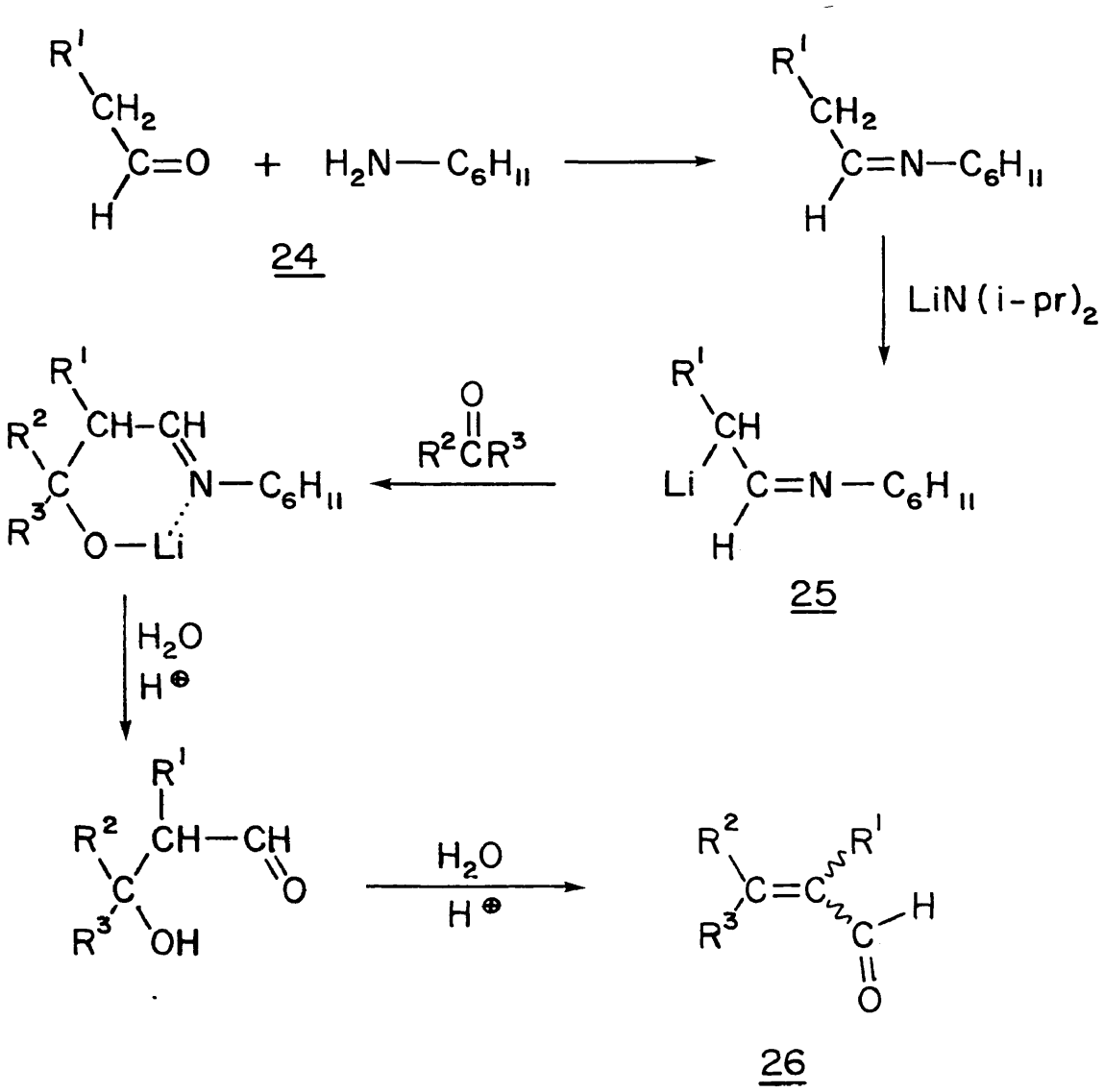
Hence, the directed aldol condensation is useful for the stereo-selective formation of trisubstituted olefins. The method becomes more valuable when it is realized that it provides a pathway for olefination of ketones which is unavailable via stabilized phosphorous ylids.

Rearrangement Reactions

Another class of reactions which has been utilized in the synthesis of trisubstituted olefins is rearrangement reactions. Two important types of rearrangement reactions are the Julia-Johnson synthesis and the Claisen rearrangement. The Julia-Johnson synthesis involves cleavage of



SCHEME VIII.



R^1 = H or organic

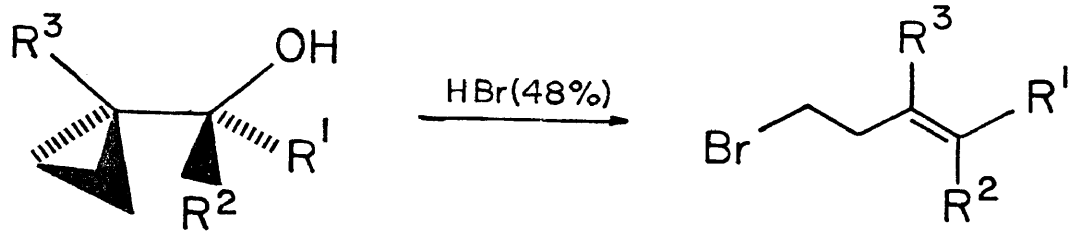
R^2 = organic

R^3 = H or organic

SCHEME IX.

the cyclopropyl ring in cyclopropyl carbinol compounds. The Claisen rearrangement proceeds via intramolecular conversion of allyl vinyl ethers to γ,δ-unsaturated carbonyl compounds.

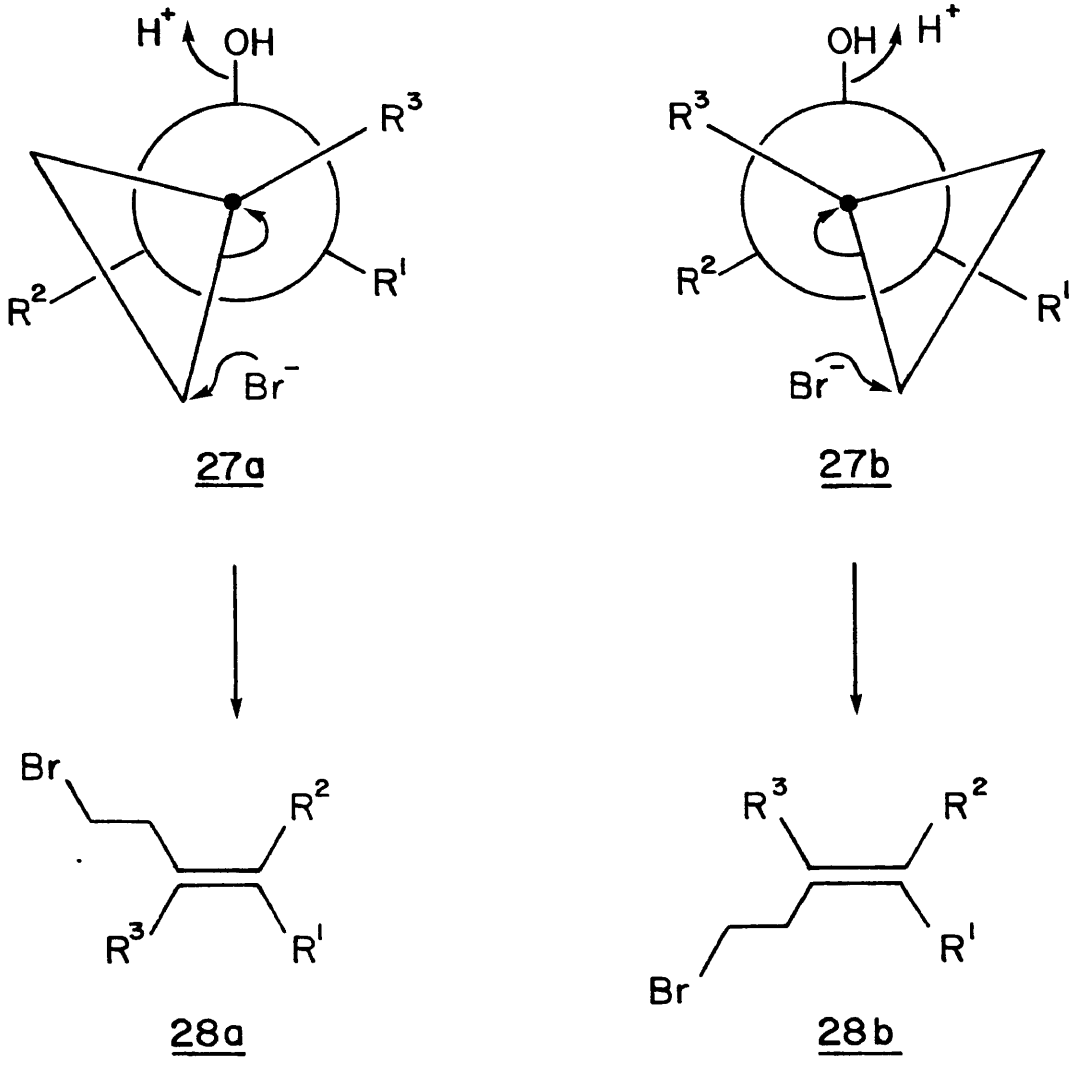
Julia et al.,[35] prepared trans-disubstituted olefins of 90 to 95% stereochemical purity by the reaction of secondary cyclopropyl carbinols (27 R^1=organic, R^2=R^3=H) with 48% hydrobromic acid (Scheme X). The group found that tertiary cyclopropyl carbinols (27 R^1=organic, R^2=organic, R^3=H) did not react stereoselectively; the ratio of trans to cis products was 3:1. Since Julia et al. had shown that the ring opening of secondary



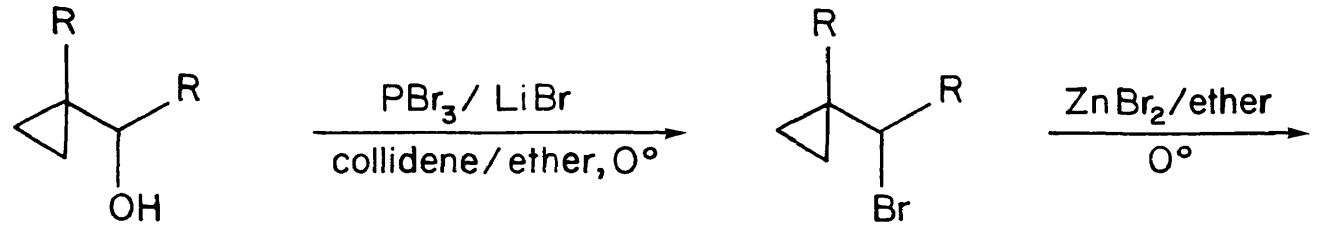
SCHEME X.

cyclopropyl carbinols was highly stereoselective but that tertiary cyclopropyl carbinols failed to shown stereoselectivity under the same conditions, application of the method toward synthesis of trisubstituted olefins needed further development.

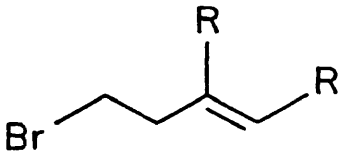
Lack of stereoselectivity in the reaction of tertiary cyclopropyl carbinols can be rationalized by considering the steric interactions between the cyclopropyl ring and substituents R^1 and R^2. The Newman projections below (Scheme XI) show that if R^1 is organic and both R^2 and R^3 are hydrogen then conformation 27a would be sterically favorable over 27b. In conformation


H+
OH
R3
R2
R1
Br−
27a
OH
H+
R3
R2
R1
Br−
27b
Br
R2
R3
R1
28a
R3
R2
R1
Br
28b

SCHEME XI.



29



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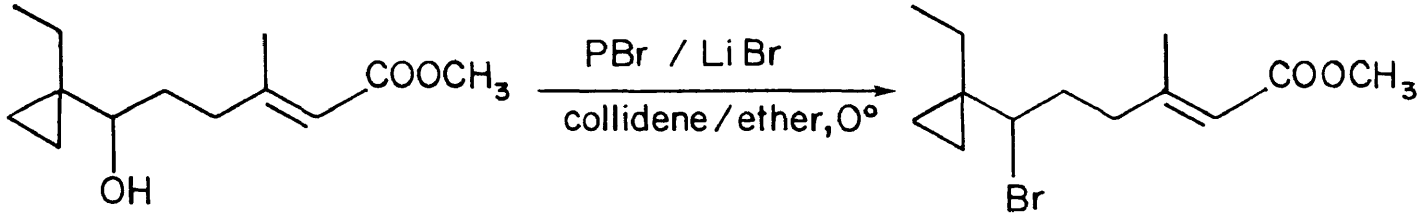
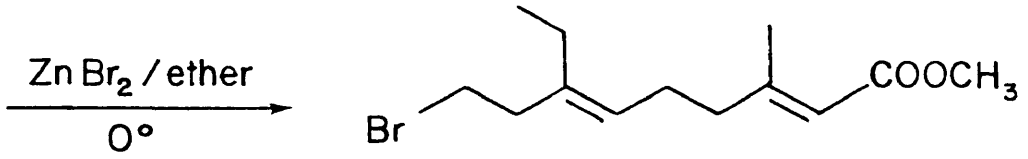
SCHEME XII.



31 32



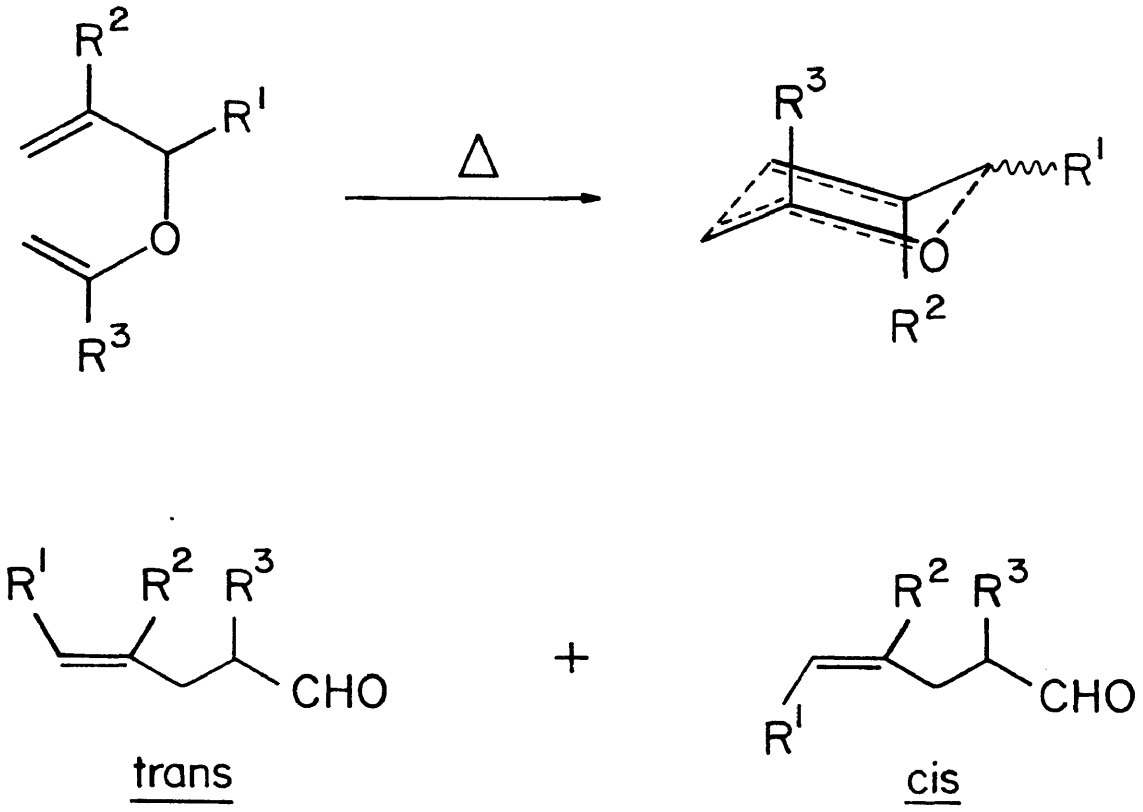
33

SCHEME XIII.

27a there is less overlap between the ring and the organic branch R^1. The olefin resulting from ring-cleavage would then be the trans-olefin 28a. If, however, both R^1 and R^2 are organic then the two conformations 27a and 27b are not as dissimilar as when R^2 is hydrogen. Each conformation would exist in almost equal proportion. Hence, the olefin formed by ring-cleavage would be an almost equal number of cis and trans isomers.

Johnson et al.[31] were able to adapt the ring-opening reaction to effect stereoselective formation of a trans-trisubstituted olefin. It can be seen in Schemes X and XI that if R^1 and R^3 are organic groups and R^2 is hydrogen, then the stereochemistry of ring-opening should not differ greatly from that observed by Julia. The general method employed by Johnson et al. is outlined in Scheme XII. Trans-trisubstituted olefins were obtained in yields of 85 to 90% with only 2 to 4% of the cis isomer. The procedure outlined in Scheme XII was applied successfully in a synthesis of cecropia juvenile hormone (6).[36] In the juvenile hormone synthesis (Scheme XIII) the bromodienic ester 33 was obtained in 87% overall yield as a 96:4 ratio of trans,trans- to trans,cis-products.

Trans-trisubstituted olefins are also available by means of the Claisen rearrangement.[37] In the Claisen rearrangement an allyl vinyl ether undergoes intramolecular rearrangement through a cyclic transition state which resembles a chair conformation of cyclohexane.[38] The products of the thermally induced reaction are Δ^4-alkenals (Scheme XIV). Cis:trans ratios of the alkenals formed at a given temperature can be predicted by comparison of the transition state with the corresponding conformation of cyclohexane at the same temperature. Hence, at 110°C, 34 (R^1=Et, R^2=Me, R^3=H) provided the corresponding alkenals in a cis:trans ratio of



SCHEME XIV.

10:90. The trans product is derived from the transition state having the ethyl groups R^1, in the equatorial conformation. Likewise, at 110°C, ethylcyclohexane exists with 91% of the ethyl groups in the equatorial conformation.[39]

Johnson et al.[40] have shown that an organic substituent, R^3, on the allyl vinyl ether 34 increases the stereoselectivity toward trans products. In a synthesis of squalene (23) substitution of an ethoxy group at position R^3 provided a yield of 92% ester having greater than 98% trans geometry. The method employed not only gave a greater yield of allyl vinyl ether than the unsubstituted selectivity (98% trans vs 86% trans) but also required reduced reaction time (1 hr at 138° vs 61 hr at 83-98°) and a single reaction vessel. Hence, the method of Johnson et al.[40] seems to offer a promising stereoselective route to trisubstituted olefins. However, one of the problems with the Claisen rearrangement in general has been the difficulty of preparing substituted allyl vinyl ethers.

SUMMARY

The olefin functionality is a prevalent and important one and its synthesis offers a great challenge. Many methods for obtaining olefins are known. Some of those methods, especially those related to stereoselective synthesis of trisubstituted olefins, have been reviewed here. The Wittig reaction, the traditional olefin formation method, has wide application within the scope of carbonyl containing compounds. Other transformations of carbonyl compounds have been adapted to olefin synthesis, as have some rearrangement reactions. The emerging usefulness of organometallic reagents has also been applied successfully to olefin synthesis.

EXPERIMENTAL

The goal of the experimental work reported herein is to modify Zeigler-Natta catalyst systems in order to control the carbometallation thus obtaining the product of a single carbometallation step. Two approaches toward achieving the goal were employed. One method involved variations in the unsaturated substrate while keeping the catalyst composition constant. This approach is referred to as alkylation system I. The other approach involved variation of the catalyst composition while keeping the unsaturated substrate constant and is referred to as alkylation system II. Preparation of the ring-substituted bis(η^5-cyclopentadienyl)titanium (IV) dichloride compounds used in alkylation system I is also described.

Alkylation System I: Alkynol + $Al(CH_3)_3$ + $TiCl_4$

Reagents

The alkynols used were: 5-hexyn-3-ol, 5-heptyn-3-ol, 3-heptynl-ol, and 5-methyl-3-hexyn-1-ol which were obtained from Albany International (Farchan Labs). The alkynols were stored at 10°C over Linde 4-A molecular sieves and used without further purification. Reagent grade 1-octanol (Fischer, A-402) and 1-hexanol (Aldrich, H1330-3) were stored over Linde 4-A molecular sieves and used without further purification as standards for glc analysis. Titanium tetrachloride ($TiCl_4$, Fischer, T-308) while in a dry-box was transferred in 2.0 ml portions into 2.5 ml ampules and used without purification. Trimethylaluminum (TMA, Ethyl Corp.) was used without purification. All transfers of neat TMA were performed in a

dry-box due to the pyrophoric nature of alkylaluminum compounds. Methanol (Fischer) was used without purification. A 5% aqueous sulfuric acid solution (v:v) was prepared and was saturated with sodium chloride.

Solvents

Lab grade methylene chloride (CH_2Cl_2, Fischer, D-37) was distilled over phosphorous pentoxide and nitrogen atmosphere. The solvent was stored over Linde 4-A molecular sieves under nitrogen atmosphere. Lab grade, diethyl ether (Et_2O, Fischer) was used without purification.

Stoichiometry and reaction conditions

The alkynol was used in a 15 mmole quantity in this sytem. The ratio of organoaluminum compound to titanium compound and alkynol was 2:1:1, respectively. Experiments were performed at two temperatures in almost all cases, -45°C and -78°C using a hexyl alcohol/dry-ice slush bath and a butyl acetate/dry-ice slush bath, respectively.

Two reaction times were investigated for this system, thirty minutes and also four hours.

Procedure

Preparation of the alkynoxyaluminum reagent.

A 250-ml, three-necked, round-bottomed flask was taken into a dry-box along with a magnetic stirring bar and stoppers for the three necks, a flask containing distilled CH_2Cl_2 and two gas-tight syringes. Using a 50-ml syringe, CH_2Cl_2 (25 ml) was added to the flask. Then, using a 5 or 10 ml syringe, trimethylaluminum (30 mmoles) was added. The flask was then stoppered, brought out of the dry-box and clamped onto

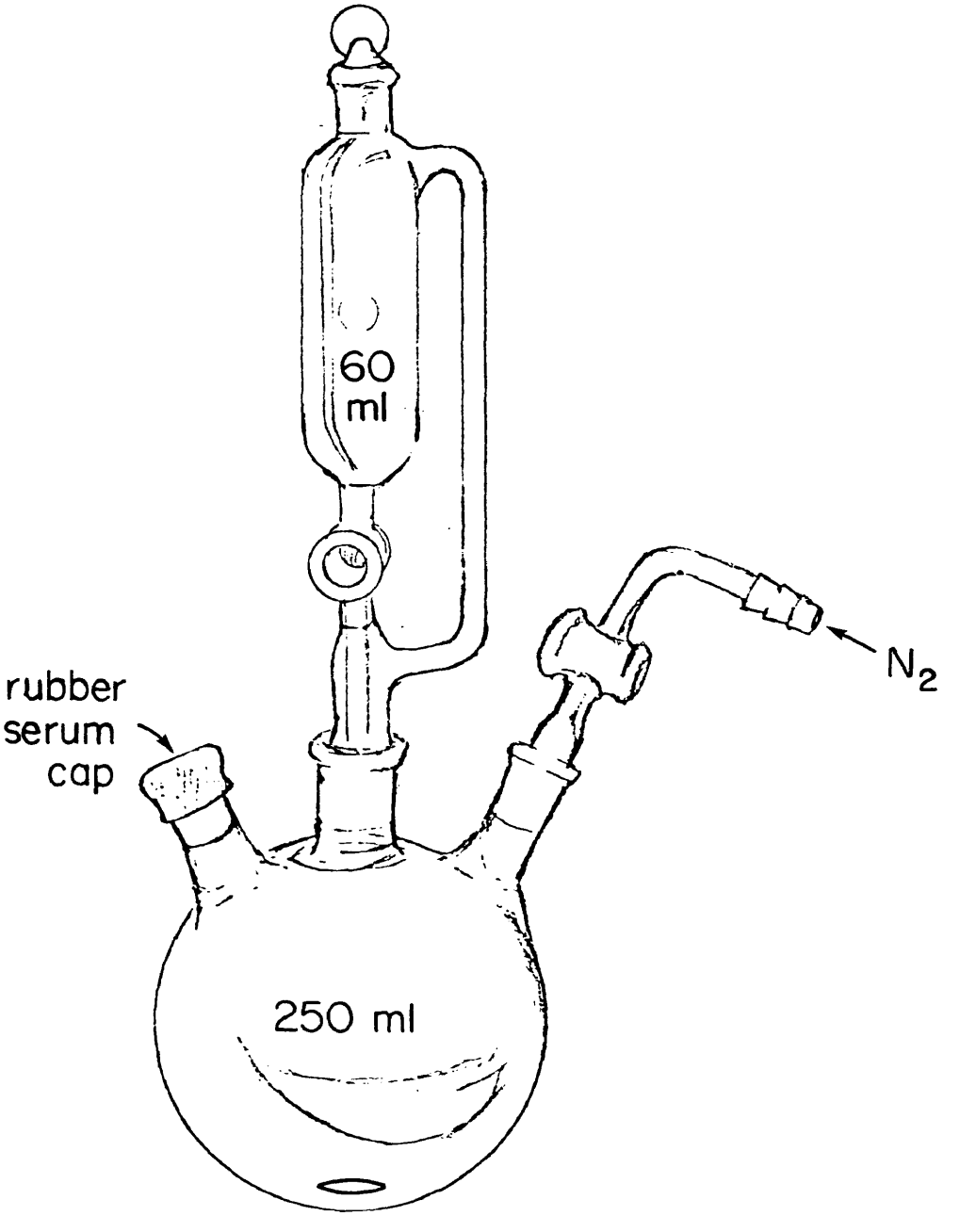
a grid equipped with inert atmosphere lines. One stopper was quickly replaced with a gas inlet joint which provided dry N_2 atmosphere. Another stopper was replaced with a stoppered 60-ml dropping funnel which had been purged of air by dry N_2 and the third stopper was replaced by a rubber serum cap to give the apparatus shown on the following page.

Magnetic stirring and dry N_2 flow were commenced and the flask was cooled to 0°C over an ice-water bath. The dropping funnel was charged with CH_2Cl_2 (25 ml) and with a weighed amount of alkynol (15 mmole). The alkynol solution was then allowed to drip into the flask over a 20 minute period.

Reaction of $TiCl_4$ with the alkynoxyaluminum reagent.

A second 250-ml, three-necked, round-bottomed flask was set up as shown on the following page. The system was purged of air by dry N_2 and the dropping funnel was charged with dry CH_2Cl_2 (50 ml) which was then admitted to the flask. Then $TiCl_4$ (2.0 ml from a sealed glass ampule) was added directly to the flask through the side neck. Magnetic stirring was commenced and the flask was cooled to reaction temperature (-45°C or -78°C). At this point the alkynoxyaluminum reagent was forced through a narrow stainless steel tube using N_2 pressure into the dropping funnel above the $TiCl_4$ solution. The alkynoxyaluminum reagent was then added dropwise to the $TiCl_4$ solution over a period of 10 to 15 minutes. Reaction temperature was monitored and maintained throughout reaction time.

Figure 3.



Termination of reaction and product work-up.

The reaction was terminated by hydrolysis with methanol (10 ml) followed by 5% aqueous H_2SO_4 saturated with NaCl (50 ml). The hydrolyzing reagents were added dropwise through the dropping funnel. At this point a weighed amount of a saturated alcohol was added directly to the product mixture as an internal standard for glc analysis.

The product mixture was filtered over a bed of Celite using a Buchner filtration apparatus. The filtrate was transferred to a separatory funnel and the organic layer was separated and stored in an erlenmeyer flask while the aqueous layer was washed with lab grade ether (5x50 ml). The extracts were added to the organic layer and the whole was dried over $MgSO_4$, filtered, concentrated under reduced pressure and stored at 10°C.

Alkylation System II: 3-Butyn-1-ol + AlR_nCl_{3-n} + (^{5}-$C_5H_{5-m}R_m)_2TiCl_2$

Reagents

The unsaturated substrate, 3-butyn-1-ol, (Albany International) was stored at 10°C over Linde 4-A molecular sieves and was used without purification. Bis(^{5}-cyclopentadienyl)titanium (IV) dichloride (Cp_2TiCl_2) and bis-(^{5}-methylcyclopentadienyl)titanium (IV) dichloride ($(MeCp)_2TiCl_2$ gift from Hercules, Inc.) were used without purification. Bis-(^{5}-tert-butyl-cyclopentadienyl)titanium (IV) dichloride ($(t\text{-}buCp)_2TiCl_2$) and bis-(^{5}-pentamethylcyclopentadienyl)titanium (IV) dichloride ($(Me_5Cp)_2TiCl_2$) were prepared specifically for use in this experimental series. The titanocene dichloride compounds were stored at 10°C as

0.050 M solutions in dry CH_2Cl_2 in 250 ml pop bottles capped with a rubber septum and a two-holed bottle cap. Trimethylaluminum and diethylaluminum chloride (Ethyl Corp.) were used without purification. Transfers of neat organo-aluminum reagents were performed in a dry-box. Solvents, other reagents, and saturated alcohols for glc analysis were used as described for alkylation system I.

Stoichiometries and Reaction Conditions

The ratio of organoaluminum reagent to titanium compound to substrate was 2:0.25:1. Reaction time was two hours at 0°C.

Procedure

While in a dry-box a 250 ml pop bottle containing a magnetic stirring bar was charged with dry CH_2Cl_2 (20 ml) and with an organoaluminum reagent (10 mmoles). The bottle was capped with a Buna N rubber septum and a two-holed bottle cap, removed from the dry-box and clamped to a grid and cooled to 0°C over an ice-water bath. Dry N_2 flow was provided and magnetic stirring was applied. A sample of 3-butyn-1-ol (5 mmoles) was weighed into a 3 cc disposable syringe. The alkynol was slowly and carefully injected into the bottle containing the organoaluminum reagent. Using N_2 pressure the cooled solution of titanium compound was forced through a narrow stainless steel tube into the bottle containing the alkynoxyaluminum reagent. Constant temperature (0°C) and magnetic stirring were maintained for 2 hours. Reaction was terminated by the slow and careful injection of methanol (5 ml) followed by 5% aq. $H_2SO_4 \cdot NaCl$ saturated (10 ml). The work-up of the crude product mixture was the same as that described for alkylation system I beginning with the addition of a weighed amount of 1-heptanol as a standard for glc analysis.

Synthesis of Ring-substituted Bis-(η^5-cyclopentadienyl)titanium (IV) Dichloride Compounds

Bis(η^5-tert-butylcyclopentadienyl)titanium (IV) Dichloride

Reagents

Cyclopentadiene was obtained by heating dicyclopentadiene (Eastman Organic Chemicals, T5068) under reflux conditions. Reagent grade acetone (Fischer, A-18) was stored over Linde 3-A molecular sieves. A 30 to 35% aqueous solution of methylamine (Fischer, M-223) was used without purification. Methyllithium (Aldrich, 19734-3) was used as a 1.5 M solution in diethyl ether. Titanium tetrachloride (Fischer, T-308) was used without purification. Diethyl ether (anhydrous, Fischer, E-1385) was distilled over lithium aluminum hydride. Hexane (Fischer) was used without purification.

Procedure

Preparation of dimethylfulvene[41]

A 500-ml, three-necked, round-bottomed flask was fitted with a reflux condenser and gas inlet, a 25-ml dropping funnel, a stopper and a magnetic stirring bar. The flask was charged with cyclopentadiene (82 ml, 1.0 mole) and then with acetone (73 ml, 1.0 mole). The mixture was cooled to 0°C over an ice-water bath while being magnetically stirred. The dropping funnel was charged with 30-35% aqueous CH_3NH_2 (15 ml) and added dropwise over a period of three minutes.

After reaction had proceeded at 0°C for 15 minutes, the ice-water bath was removed and the mixture allowed to warm naturally for 30 minutes. The mixture was then stored at -10°C overnight, warmed to room temperature the following morning then washed with water (5x50 ml). The organic layer was dried over $MgSO_4$ and vacuum distilled at 23-33 mmHg (bp 50-60°C @ 23-33 mmHg).

Preparation of (tert-butylcyclopentadienyl)lithium.

A 500-ml, three-necked, round-bottomed flask was fitted with a 125-ml dropping funnel, a gas inlet, a rubber serum cap, and a magnetic stirring bar. The system was purged of air by dry N_2. The flask was chared with dimethylfulvene (0.20 mole, 24 ml) and distilled ether (175 ml), then cooled to 0°C over an ice-water bath while stirred magnetically. The dropping funnel was charged with CH_3Li (0.19 mole) which was added dropwise over a period of 20 to 30 minutes. The resulting yellow suspension was stirred for 2 hours at 0°C.

Preparation of bis-(η^5-tert-butylcyclopentadienyl) titanium(IV)dichloride.

A 1-liter, two-necked, round-bottomed flask was fitted with a gas inlet, a rubber serum cap and a magnetic stirring bar. The system was purged of air by dry N_2 and charged with hexane (200 ml) and $TiCl_4$ (10 ml, 0.095 mole). The flask was cooled to 0°C over an ice-water bath. When the $TiCl_4$ solution had cooled, the lithium tert-butylcyclopentadienide previously prepared was added slowly using N_2 pressure to force the liquid through a narrow stainless steel tube. The resulting brown

suspension was stirred at 0°C for 1 hour then cooled to -45°C for several minutes and vacuum filtered using a Büchner funnel. A red-brown solid was collected and extracted overnight in a Soxhlet apparatus with 500 ml of hexanes. The solid was extracted a second time with 200 ml of hexanes plus 50 ml of CH_2Cl_2 again overnight. The residual solid was then removed from the Soxhlet thimble dissolved in 600 ml of CH_2Cl_2 plus 150 ml of hexanes. The CH_2Cl_2 was removed by rotoevaporation under aspirator vacuum and the resulting precipitate (9.377g) collected by suction filtration using a Büchner funnel.

Characterization

Dimethylfulvene was collected by vacuum distillation at 23-33 mmHg (b.p. 50-60°C). The yield based on starting cyclopentadiene was 26%. The proton nmr spectrum of the compound showed chemical shifts of 2.13 (singlet, 6H) and 6.42 (singlet, 4H) ppm.

The yield of $(t\text{-}buCp)_2TiCl_2$ based on starting $TiCl_4$ was 27%. The compound was reddish-orange in color with a fluffy, needlelike appearance. The melting point was 217-223°C. The proton nmr spectrum showed chemical shifts of 1.31 (singlet, 9H) and 6.46 (multiplet, 4H) ppm. See Figure 1 in the Appendix.

Bis(η^5-pentamethylcyclopentadienyl)titanium (IV) Dichloride[43,44,45]

Reagents

A mixture of cis and trans-2-bromo-2-butene (Aldrich, 21, 556-2) was used without purification as was lithium wire (0.32 mm diameter,

Aldrich, 22, 091-4), ethyl acetate (Fischer, E-145S), para-toluene sulfonic acid monohydrate (Fischer, A-320), methyllithium (1.5 M solution in ether, Aldrich, 19,734-3), and solid titanium(III) chloride ($TiCl_3$, Alfa, 27116). All transfers of $TiCl_3$ were performed in a dry-box due to the air-sensitive nature of the compound. Ammonium chloride (NH_4Cl, Fischer, A660) was used as a saturated aqueous solution. A saturated aqueous sodium bicarbonate solution containing sodium carbonate (1.14%, w/v) was prepared. Concentrated (12N) hydrochloric acid (Fischer, A-144C) was diluted to a concentration of 6N.

Solvents

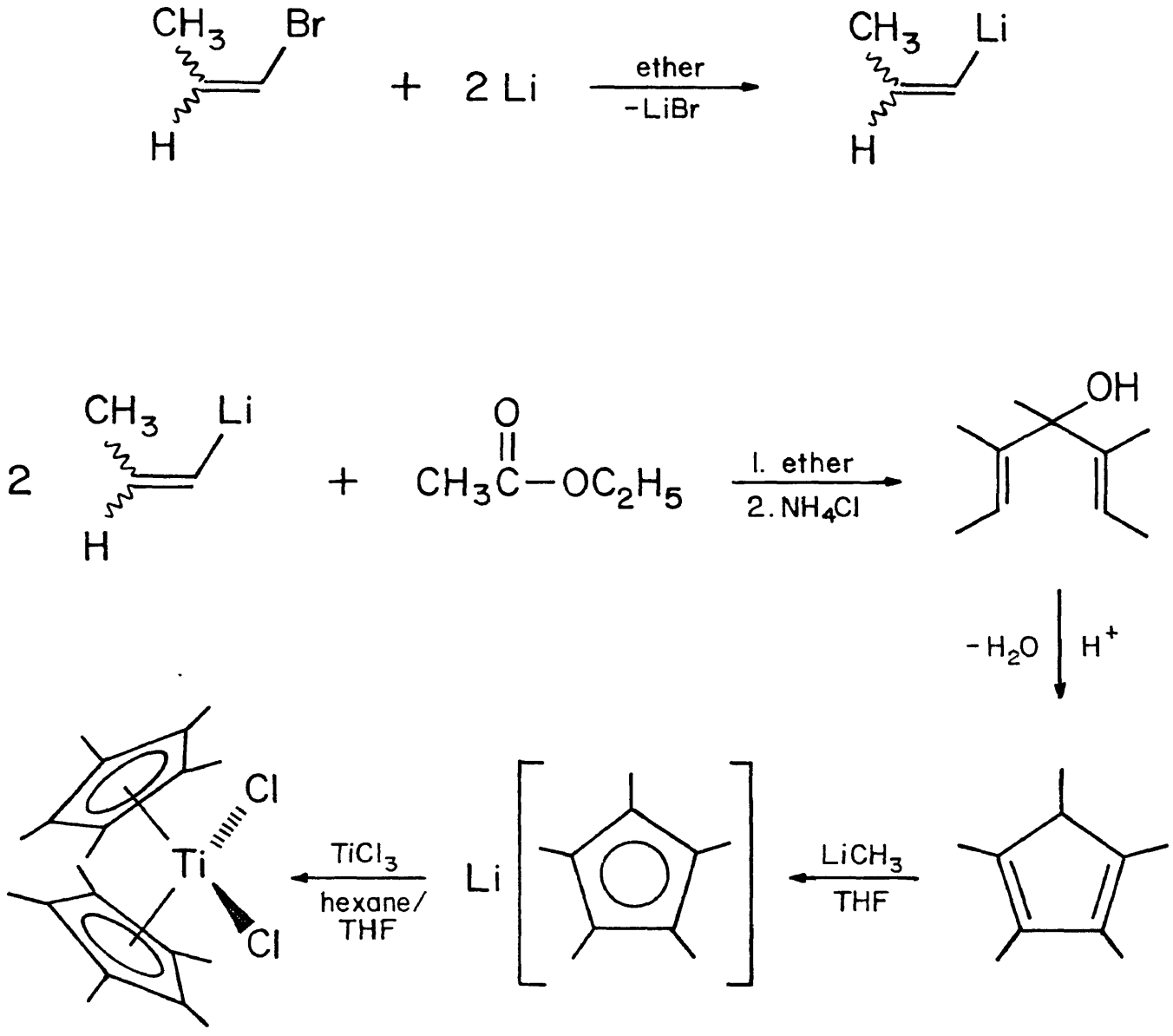
Lab grade ether (Fischer, E-138S) and tetrahydrofuran (THF, Fischer, T-397S) were distilled over lithium aluminum hydride under dry N_2 atmosphere. Hexanes (Fischer, H-291S) and chloroform ($CHCl_3$, Fischer) were used without purification.

Procedure

Formation of 4-hydroxy-3,4,5-trimethyl-2,5-heptadiene.

The reaction sequence is given in Scheme XV.

A 1000 ml, three-necked, round-bottomed flask was fitted with a magnetic stirring bar, a 125 ml dropping funnel, a reflux condenser with gas inlet, and a stopper. The system was purged of air by dry N_2 and charged with dry ether (750 ml). Lithium wire (122 cm,


CH3
Br
H
+ 2 Li
ether
-LiBr
CH3
Li
H
2
CH3
Li
H
+
O
CH3C—OC2H5
1. ether
2. NH4Cl
OH
-H2O
H+
Cl
Ti
Cl
TiCl3
hexane/
THF
Li
LiCH3
THF

SCHEME XV.

0.75 mol) was cut into 1 cm lengths and added directly to the flask. Magnetic stirring and dry N_2 flow were commenced and the dropping funnel was charged with 2-bromo-2-butene (0.37 mol). A small amount (5 ml) of 2-bromo-2-butene was added rapidly to the flask. After several minutes a reflux was noted. The remaining 2-bromo-2-butene was added dropwise at a rate sufficient to maintain gentle reflux. Addition was complete after about 40 minutes.

The dropping funnel was then charged with ethyl acetate (0.187 mol, 18 ml) and an equal volume of dry ether. The ethyl acetate solution was added dropwise over a 20 minute period. Gentle reflux was again maintained. To the resulting mixture was added dropwise through the dropping funnel a saturated aqueous solution of NH_4Cl (100 ml). Addition was carried out over a 30 minute period. This reaction mixture was then added to an erlenmeyer flask containing additional saturated aqueous NH_4Cl (650 ml). The whole was transferred to a 2000-ml separatory funnel. The organic layer was separated and the pH of the aqueous layer was adjusted to about 9 by adding 6N HCl dropwise. The aqueous layer was extracted with lab grade ether (4x75 ml). The extracts were combined with the organic layer, dried over $MgSO_4$, filtered, and concentrated under reduced pressure.

A 500-ml, three-necked, round-bottomed flask was fitted with a magnetic stirring bar, a 60-ml dropping funnel, a reflux condenser with gas inlet and a stopper. The system was flushed of air by dry N_2 and the flask charged with dry ether (75 ml) and

para-toluene sulfonic acid (0.017 mol). Stirring was commenced and the dropping funnel was charged with 4-hydroxy-3,4,5-trimethyl-2,5-heptadiene prepared previously. This was added dropwise over a period of 10 to 15 minutes. The resulting mixture was allowed to stir for 5 minutes and was then poured directly into a flask containing a saturated aqueous solution (200 ml) of $NaHCO_3$ plus Na_2CO_3 (1.75 g). The whole of this mixture was transferred into a separatory funnel and the organic layer was separated. The aqueous layer was extracted with lab-grade ether (3x50 ml) and the extracts were combined with the organic layer. The combined organic layers were then dried over $MgSO_4$, filtered and concentrated under reduced pressure. Vacuum distillation provided pure 1,2,3,4,5-pentamethyl-cyclopentadiene (bp 50-70°C @ 15 mm Hg).

A 1000-ml, three-necked, round-bottomed flask was fitted with a reflux condenser, gas inlet, 60-ml dropping funnel, and an overhead, mechanical stirrer. The flask was charged with dry THF (200 ml) and 1,2,3,4,5-pentamethylcyclopentadiene (0.080 mol). Stirring and dry N_2 flow were commenced and the flask was cooled to 0°C over an ice-water bath. The dropping funnel was charged with methyllithium (0.090 moles) which was added dropwise over a 20 minute period. The resulting yellow suspension of lithium pentamethylcyclopentadienide was stirred at 0°C for 2 hours.

Meanwhile, a 1000-ml, three-necked, round-bottomed flask was taken into a dry-box along with a magnetic stirring bar, two stoppers and a gas inlet. Once in the dry box, $TiCl_3$ (0.030 moles)

was added directly to the flask followed by hexane (50 ml). The flask was removed from the dry box and set up next to the flask containing the lithium pentamethylcyclopentadienide.

A condenser and 125-ml dropping funnel were purged of air by dry N_2 and quickly placed into the outer neck of the flask containing the $TiCl_3$ solution. In the center neck was placed a rubber serum cap. Magnetic stirring and dry N_2 flow were commenced and the flask was cooled to 0^oC over an ice-water bath. The dropping funnel was charged with THF (50 ml) which was added slowly to the $TiCl_3$ solution.

At this point the lithium pentamethylcyclopentadienide was forced through a narrow stainless steel tube using N_2 pressure into the flask containing the $TiCl_3$ solution.

After addition was complete, the resulting suspension of dark purple solid was allowed to warm naturally to room temperature and then was refluxed overnight. After refluxing, the mixture was cooled to 0^oC over an ice-water bath. The dropping funnel was charged with 12 N HCl (160 ml) which was added slowly to avoid spattering and to control reflux. Chloroform (100 ml) was added dropwise to the resulting mixture which had changed from purple to brownish-red in color.

The contents of the flask were transferred into a 2000-ml separatory funnel. The organic layer was separated and the aqueous layer was extracted three times with $CHCl_3$ (total volume 400 ml). The extracts were combined with the organic layer and dried over $MgSO_4$, filtered and concentrated under reduced pressure.

A dark purple solid was precipitated during volume reduction. This solid was extracted overnight in hexane (275 ml) in a Soxhlet apparatus. After extraction was complete the hexane solvent containing the product was cooled to -10°C in a freezer. Fine brown needles were collected by suction filtration through a Büchner funnel (3.123 g).

Characterization

A ^1H nmr spectrum of 1,2,3,4,5-pentamethylcyclopentadiene showed chemical shifts of 1.00 (doublet, J=2 Hz, 3H), 1.80 (singlet, 12H) and 2.47 (multiplet, 1H) ppm. These shifts are in agreement with those reported in the literature.[43] A ^1H nmr spectrum of bis(^{5}-pentamethylcyclopentadienyl)titanium (IV) dichloride showed a single chemical shift at 1.97 ppm (lit. 2.00 ppm).[43] See Figure 2 in the Appendix. The melting point of $(Me_5Cp)_2TiCl_2$ was 263-265°C (lit. 273°C).[44]

A minor product showed a ^1H-nmr spectrum consisting of a single signal at 2.23 (singlet) ppm. Brintzinger[43] reports a value of 2.35 (singlet) ppm for $(Me_5Cp)\ TiCl_3$.

A THF solution of the isolated $(Me_5Cp)TiCl_3$ was analyzed by HPLC under the following conditions:

Solvent system	70/30 hexane/THF
Flow rate	2.0 ml min^{-1}
Injection volume	2.0 l

The chromatogram showed two peaks of retention volume 3.5 m and 4.0 m, respectively. When a small amount of $(Me_5Cp)_2TiCl_2$ was added to the

$(Me_5Cp)TiCl_3$ solution, the peak at 4.0 ml grew. This fact suggested that the two compounds $(Me_5Cp)TiCl_3$ and $(Me_5Cp)_2TiCl_2$ might be separable by preparative HPLC.

Description of Instruments and Equipment used.

A Hewlett-Packard model 5711(FID) gas chromatograph with a flame ionization detector was used for all analytical glc analysis. The system also contained a Hewlett-Packard 3380-S integrator. The columns used were the following purchased from Supelco, Inc.: 10' x 1/8" 10% Carbowax 20M on Supelcoport 80/100 or a series column consising of the 10% Carbowax 20M plus an 8' x 1/8" 10% XE-60 on Supelcoport 80/100.

Preparative separations were performed on a Hewlett-Packard 5750 (TCD) gas chromatograph. The column used was 10' x 1/4" 20% Carbowax 20M on Chromabsorb WHP 80/100.

An Hitachi Perkin-Elmer R20B spectrometer was used for analysis of certain of the compounds and intermediates formed, especially in the synthesis of ring-substituted titanocene dichloride compounds.

A Varian FT-80A nmr spectrometer was used for ^1H and ^{13}C analysis of the isolated products of System I reactions.

Analytical separation of $(Me_5Cp)TiCl_3$ from $(Me_5Cp)_2TiCl_2$ was carried out on a high performance liquid chromatograph manufactured by Waters Associates.

RESULTS AND DISCUSSION

Simple stereoselective routes to molecules containing trisubstituted olefins are not common. Thus, we were pleased to find that several internal homopropargylic alcohols when allowed to react first with trimethylaluminum and then with titanium tetrachloride led, after protonolysis, to good yields of a single stereoisomeric alkenol. Results of these methylation studies are summarized in Tables 4 through 7.

Schiavelli, Plunkett, and Thompson[9] recently reported that 3-pentyn-1-ol and 3-hexyn-1-ol ($HOCH_2CH_2C{\equiv}C\text{-}R$, $R=CH_3$, C_2H_5) when allowed to react with the trimethylaluminum-titanium tetrachloride reagent system led to 4-methyl-3-penten-1-ol and (Z)-4-methyl-3-hexen-1-ol in yields greater than 70%. Both alkynols underwent methylation almost exclusively at the unsaturated carbon atom furthest from the hydroxyl group. Furthermore, the only stereoisomer obtained was that arising from <u>syn</u> or <u>cis</u> addition of a metal-methyl entity. With these preliminary results in mind, we sought to determine if other internal alkynols would undergo similar reaction.

Initially, we chose to extend the reaction to 3-heptyn-1-ol and 5-methyl-3-hexyn-1-ol ($HOCH_2CH_2C{\equiv}C\text{-}R$, $R= -CH_2CH_2CH_3$, and $-CH(CH_3)_2$). Our purpose for choosing these two alkynols was to determine if larger alkyl groups at the 4-carbon would, due to steric bulk, alter the reaction. Two possible steric effects were anticipated: 1) inhibition of the overall carbometallation or 2) formation of a product having the opposite regiochemistry. From the pathway for carbometallation proposed in Figure 2 the possible effects of larger terminal alkyl groups on regioselectivity are unclear. It appears that the overall yield of carbometallated product should decrease with increasing steric constraints about the alkyne functionality. It is well known in Ziegler-Natta

Table 4. Titanium tetrachloride promoted methylation of 3-heptyn-1-ol.

Temp. (°C)	Time (min)	Molar Ratio Ti:Al:ROH	Products	Yield (%)	Starting Alkynol Recovered (%)	Total Mass Balance (%)
-45	30	1:2:1	Z-4-methyl-3-hepten-1-ol(I)	60	14	74
-70	240	1:2:0.5	(I)	66	20	86

Table 5. Titanium tetrachloride promoted methylation of 5-methyl-3-hexyn-1-ol.

Temp. (°C)	Time (min)	Molar Ratio Ti:Al:ROH	Products	Yield (%)	Starting Alkynol Recovered (%)	Total Mass Balance (%)
-45	30	1:2:1	Z-4,5-dimethyl-3-hexen-1-ol(II)	57	34	91
-45	30	1.2:2.4:1.0	(II)	63	34	97
-45	120	1.2:2.4:1.0	(II)	61	29	90
-45	180	1.2:2.4:1.0	(II)	47	22	69
-23	5	1.2:2.4:1.0	(II)	67	25	92
-23	3	1.2:2.4:1.0	(II)	54	32	86
-23	1	1.2:2.4:1.0	(II)	66	24	90
-23	1	1.8:3.0:1.0	(II)	53	9	62

Table 6. Titanium tetrachloride promoted methylation of 5-heptyn-3-ol.

Temp. (°C)	Time (min)	Molar Ratio Ti:Al:ROH	Products	Yield (%)	Starting Alkynol Recovered (%)	Total Mass Balance (%)
-45	240	1:2:1	6-methyl-5-hepten-3-ol(IV)	66	18	84
-78	240	1:2:1	(IV)	41	49	90

Table 7. Titanium tetrachloride promoted methylation of 5-hexyn-3-ol.

Temp. (°C)	Time (min)	Molar Ratio Ti:Al:ROH	Products	Yield (%)	Starting Alkynol Recovered (%)	Total Mass Balance (%)
-45	240	1:2:1	trans-5-hepten-3-ol(III)	46	46	92
-45	30	1:2:1	(III)	61	15	76
-45	5	1:2:1	(III)	58	26	84
-75	240	1:2:1	(III)	36	11	47

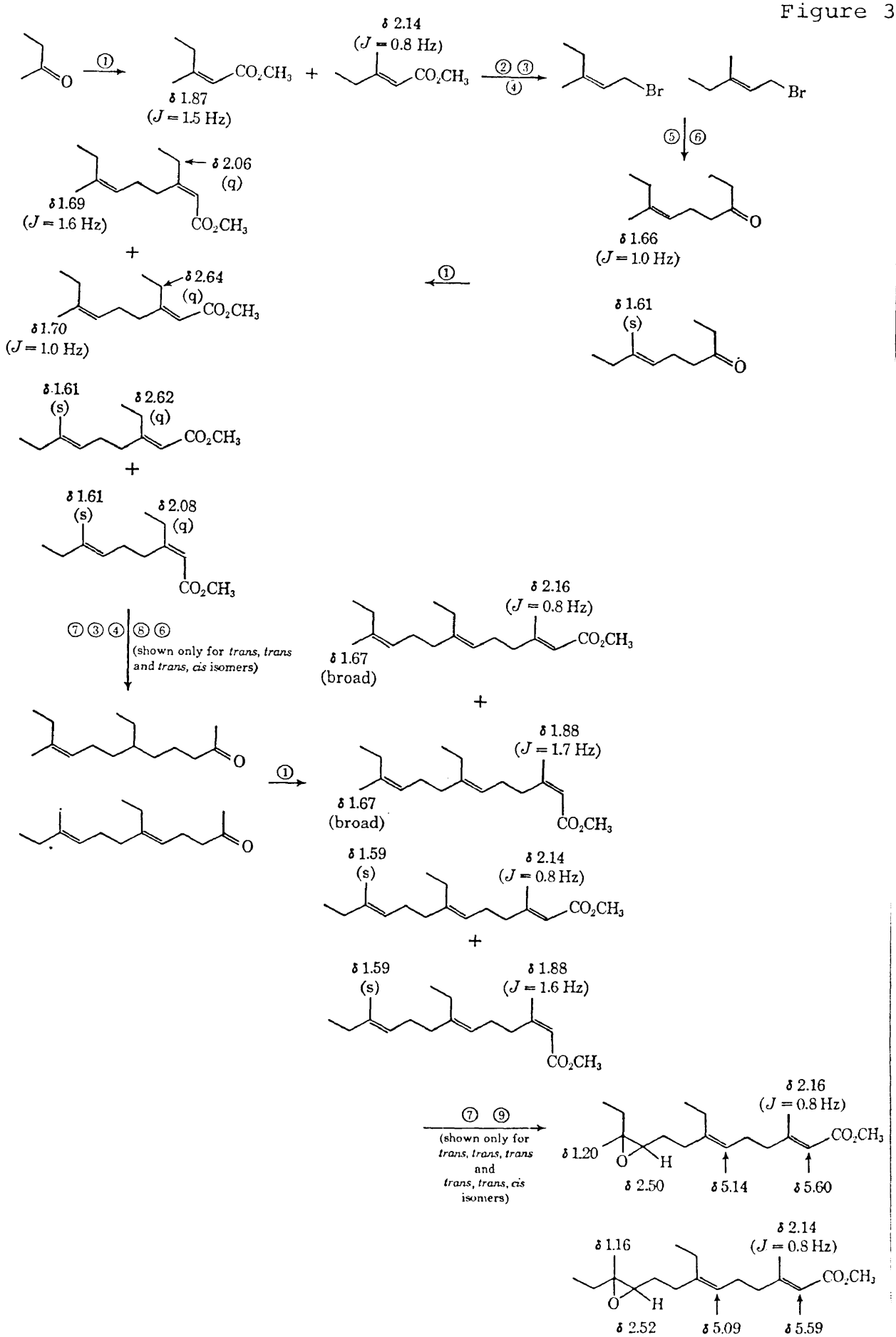


Figure 3. ^{1}H-NMR spectral data from Trost[54] of interest to the characterization of trisubstituted olefins.

olefin polymerization that internal olefins do not homopolymerize. Again, we were pleased to find that 3-heptyn-1-ol and 5-methyl-3-hexyn-1-ol gave ca. 60% yields of a single product, that arising from addition of a methyl group to the 4-carbon in a cis fashion. The respective products were (Z)-4-methyl-3-hepten-1-ol and (Z)-4,5-dimethyl-3-hexen-1-ol. Very recently it has also been shown that 3-nonyn-1-ol under similar conditions gives ca. 70% yield of (Z)-4-methyl-3-nonen-1-ol.[46]

Thus, it appears that the reaction of internal homopropargylic alkynols with the trimethylaluminum-titanium tetrachloride reagent system may provide a general route to the synthesis of (Z)-4-methyl-3-alkenols. This reaction is complementary to that reported recently by Koboyashi, Valente, and Negishi[47] to give (E)-4-methyl-3-alken-1-ols. Their synthesis utilizes the methylzirconation (via Al_2Me_6-$ZrCp_2Cl_2$) of terminal alkynes followed by reaction of a resulting alkenyl-lithium species with an epoxide such as ethylene oxide. The reaction, while consisting of several steps, is nonetheless convenient and efficient, i.e. "single pot". Negishi and coworkers have only studied alkynes with seven or more carbon atoms. In order to prepare the (E) isomer corresponding to (Z)-4-methyl-3-hexen-1-ol, Negishi and coworkers would need to "methylzirconate" the simple alkyne propyne. An unanswered question is whether this could be done without causing oligomerization of the propyne itself since various zirconium compounds have been used effectively as components of Ziegler-Natta polymerization systems.[48]

We also investigated the methylation of 5-heptyn-3-ol ($CH_3CH_2\overset{OH}{C}HCH_2C{\equiv}C\text{-}CH_3$) in order to determine if substituents at the hydroxyl-bearing carbon and terminal olefinic carbon would affect the methylation. Reference to Table 4 shows that this disubstituted secondary alkynol underwent methylation with a similar yield and selectivity to that of the primary alkynols.

Finally, we investigated the methylation of 5-hexyn-3-ol to ascertain any special effect of a carbinol ethyl group alone on the methylation of a terminal alkyne. This substrate, which is analogous to 5-heptyn-3-ol allowed us to readily examine the stereoselectivity of the methylation of an alkynol having a carbinol ethyl substituent. Again, the yield was good and the sole product was (E)-4-hepten-1-ol arising from terminal and cis methyl-metallation (Table 7).

The structural characterization of trisubstituted olefins has been made much easier with the ready availability of proton and particularly, carbon-13, nmr spectroscopy. In summarizing synthetic work related to the juvenile hormone of Hyalophora cecropia, Trost[49] shows that trisubstituted olefins, where one of the substituents is a methyl group, have a distinctive CH_3 proton chemical shift splitting pattern. Reference to the compounds in Figure 3 shows that two structural types need to be considered. When the olefinic

methyl group is trans to a hydrogen the chemical shift tends to be near 1.60 ppm and no coupling with the vinylic proton is observed. However, when the methyl group is cis to the hydrogen the chemical shift is nearer 1.70 ppm and, more significantly, a coupling constant of 1 to 1.5 Hz is usually observed.

Figures 4-7 show the proton nmr spectra for the three trisubstituted alkenols synthesized in this work. When one examines the proton nmr spectra for the products of methylation of 3-heptyn-1-ol and 5-methyl-3-hexyn-1-ol (Figures 5 and 6) prominent olefinic methyl group resonances are observed at 1.63 and 1.70 ppm, respectively. Both peaks are split into doublets with coupling constants of ca. 0.9 and 1.5 Hz, respectively. The product derived from 3-heptyn-1-ol clearly exists in the cis methyl-hydrogen configuration. The observed chemical shift and splitting pattern agree with Trost's observations. The 1.63 ppm shift for the product derived from 5-methyl-3-hexyn-1-ol may appear to offer inconclusive data for the cis configuration; however, the substantial coupling ($J \sim 1.5$ Hz) observed in this signal strongly suggests the cis methyl-hydrogen relationship. A reason for the occurrence of the signal at higher field may be a strong interaction of the olefinic methyl group with the bulky isopropyl group.

The olefinic methyl groups of 6-methyl-5-hepten-3-ol (Figure 4) are of particular interest since one group is cis and the other is trans to a vinylic hydrogen. From Trost's summary, the trans methyl resonance should be near 1.6 ppm; indeed, there is a prominent singlet at 1.63 ppm. Downfield, at 1.73 ppm, is the center of a nicely resolved doublet with coupling constant of ca. 1.1 Hz as expected for a cis methyl group. Likewise, unpublished work[46] for 4-methyl-3-penten-1-ol shows two methyl resonances at 1.64 and 1.72 ppm. Only the latter is split (doublet, $J \cong 0.5$ Hz). Hence, these resonances are assignable to the trans and cis methyl groups, respectively.

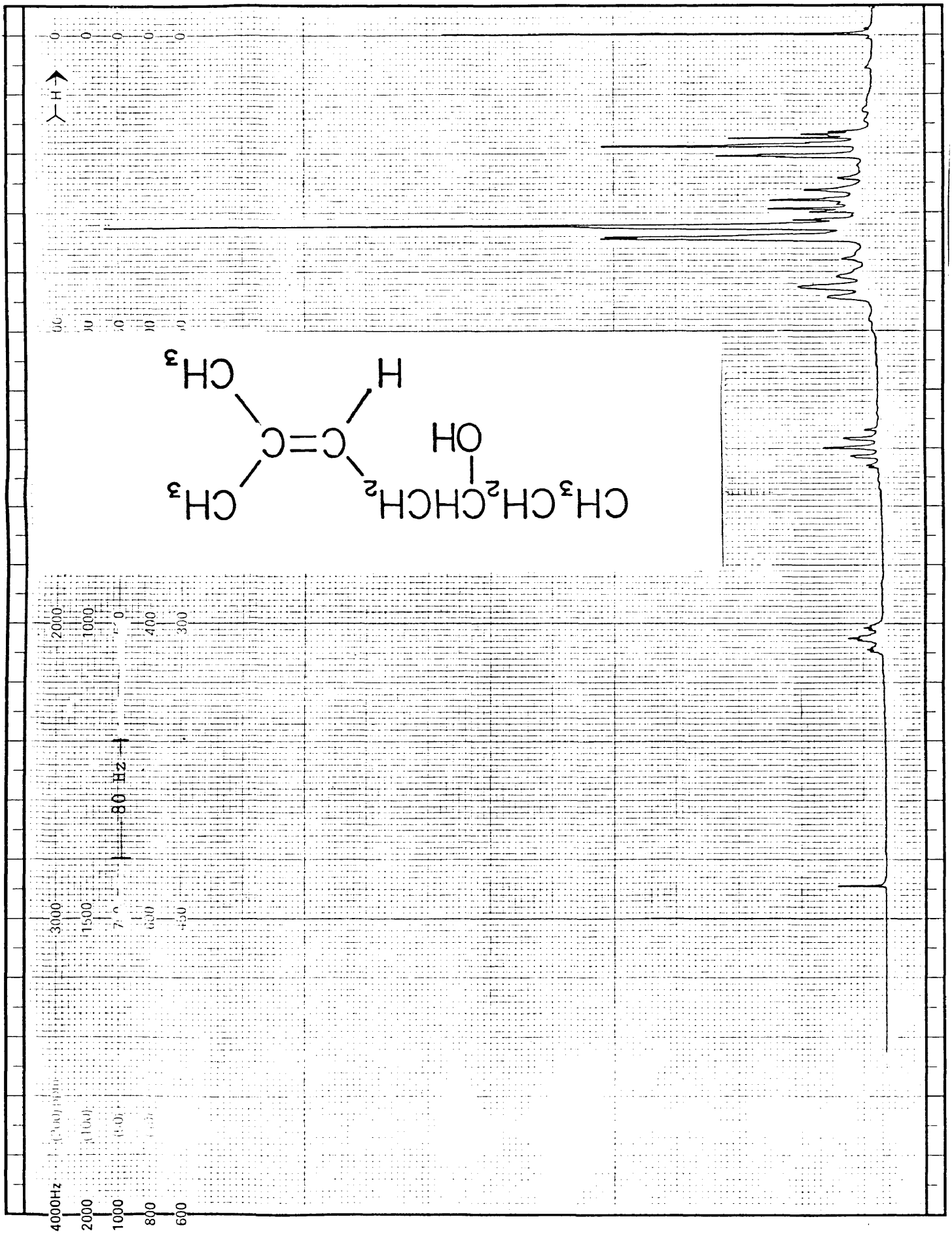


Figure 4. ^{1}H-NMR spectrum of the methylation product from 5-heptyn-3-ol: 6-methyl-5-hepten-3-ol. Solvent: $CDCl_3$.

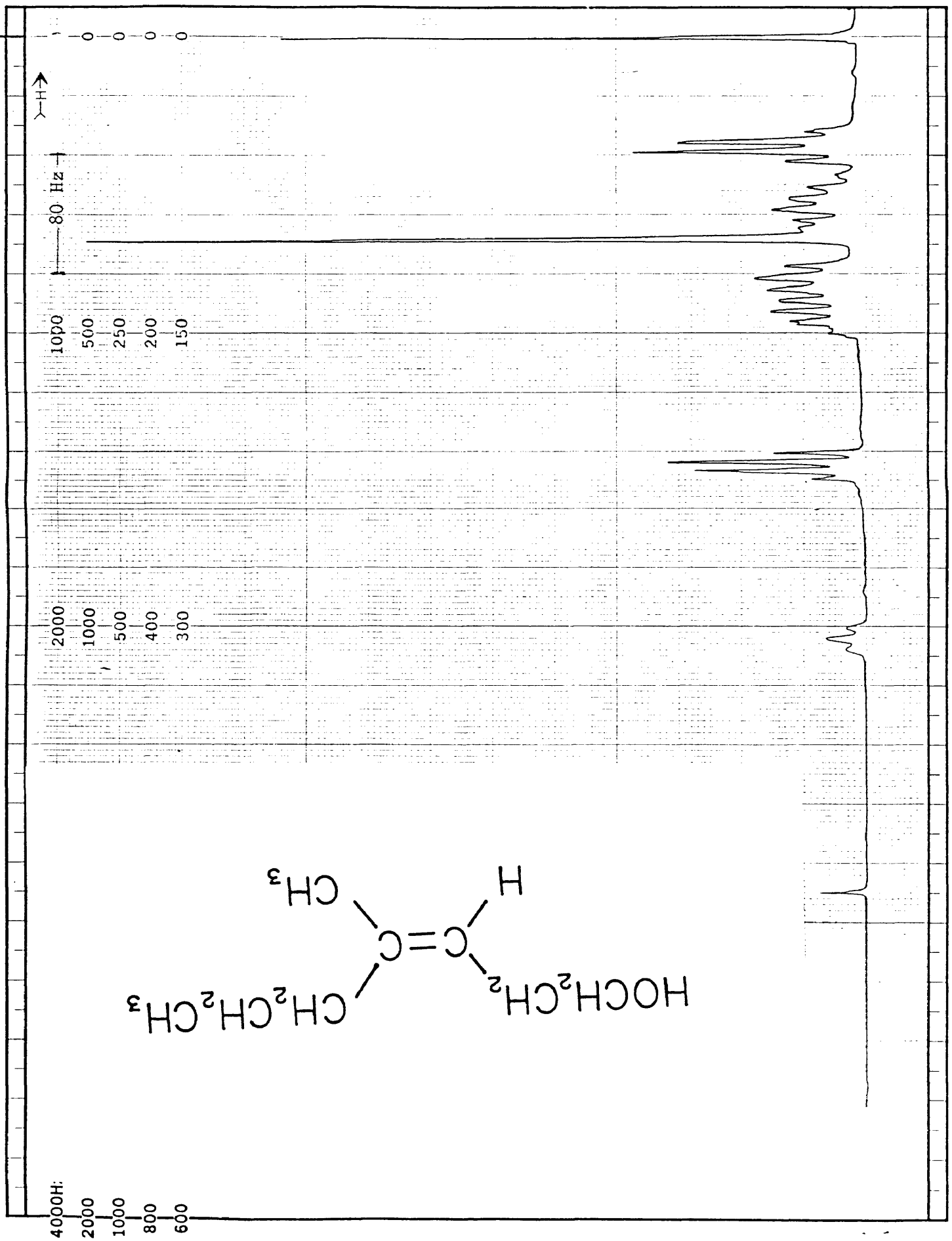


Figure 5. ^{1}H-NMR spectrum of the methylation product from 3-heptyn-1-ol: (Z)-4-methyl-3-hepten-1-ol. Solvent: $CDCl_3$.

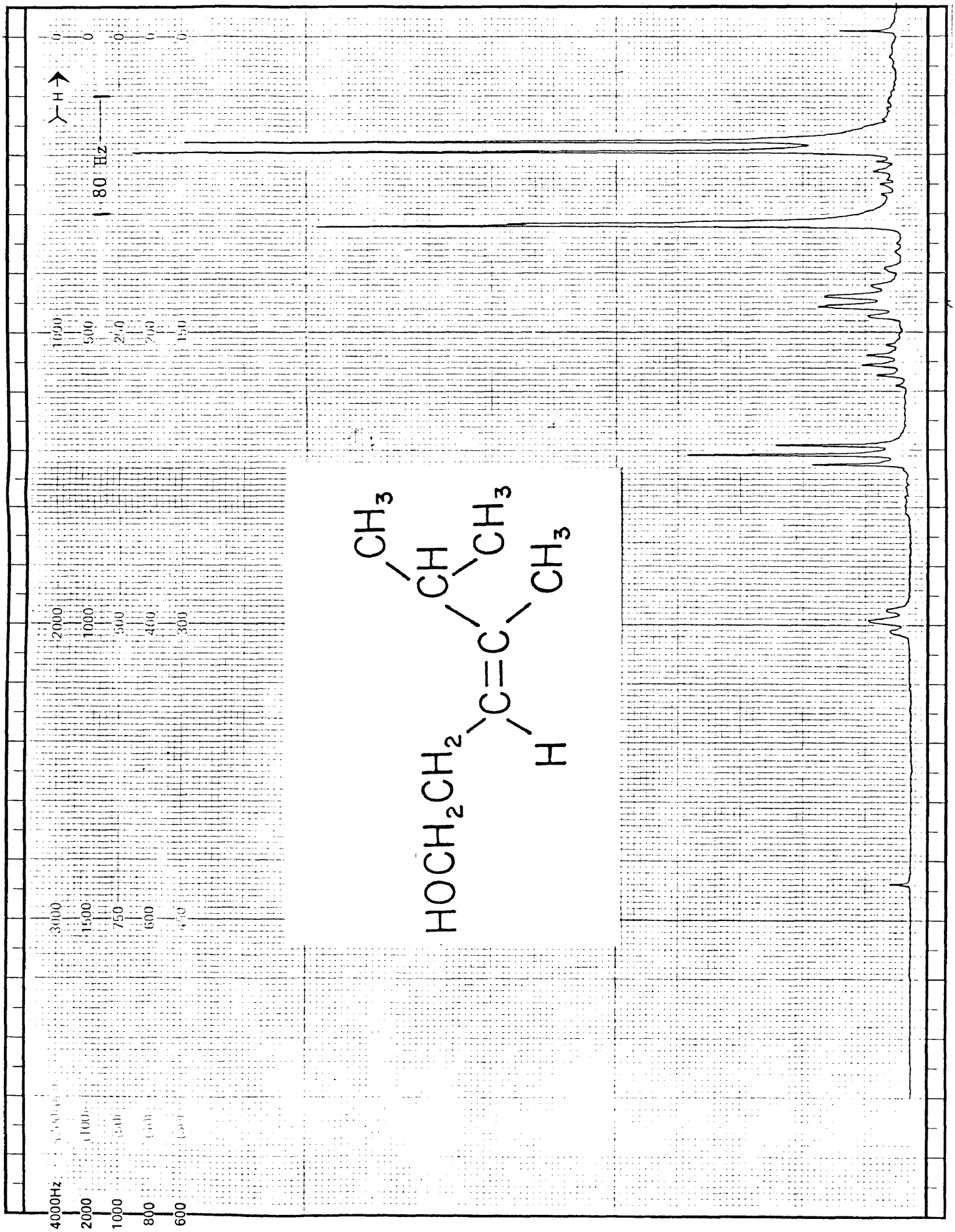
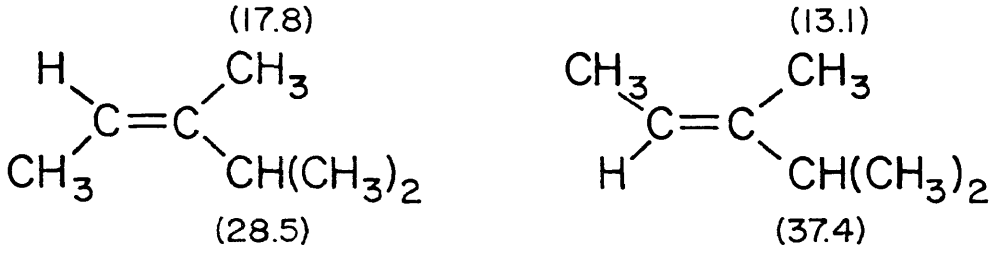


Figure 6. ^{1}H-NMR spectrum of the methylation product from 5-methyl-3-heptyn-1-ol: (Z)-4,5-dimethyl-3-hexen-1-ol. Solvent: $CDCl_3$.

The proton nmr spectrum of the methylated product derived from 5-hexyn-3-ol (Figure 7) offers evidence that the product is (E)-5-hepten-3-ol. There is a doublet centered about 1.70 ppm (J ca. 9 Hz) which can reasonably be assigned to a vinylic methyl group split by a single hydrogen on an adjacent carbon atom. A multiplet centered about 5.5 ppm in the absence of a resonance near the 4.5 to 5.0 ppm range is consistent only with the product arising from terminal methylation.

The ^{13}C-nmr data (Figures 8-11) provide further evidence that the carbometallation reaction took place in the syn fashion to yield trisubstituted olefins with the (Z) configuration. Consider the two model compounds illustrated below.[50] When the methyl group on the same olefinic carbon



(Z)

3,4-dimethyl-2-pentene

as the n-propyl group is cis to the hydrogen, the methyl group ^{13}C shift is 23.9 ppm; when trans the shift is 16.1 ppm. In both isomers the n-propyl methyl resonance is near 14.4 ppm.[50] The ^{13}C nmr spectrum for our product (Figure 10) arising from methylation of 3-heptyn-1-ol shows that the peak at highest field is at 13.8 ppm with the next two peaks occurring at 21.1 and 23.3 ppm. Clearly, the peak at 13.8 ppm arises from the n-propyl methyl group. Comparison with the model (Z) isomer above shows that the peaks at 21.1 and 23.3 ppm are assignable only to the (Z) isomer of the "middle" methylene of the n-propyl group and the olefinic methyl group, respectively. Thus, the product of

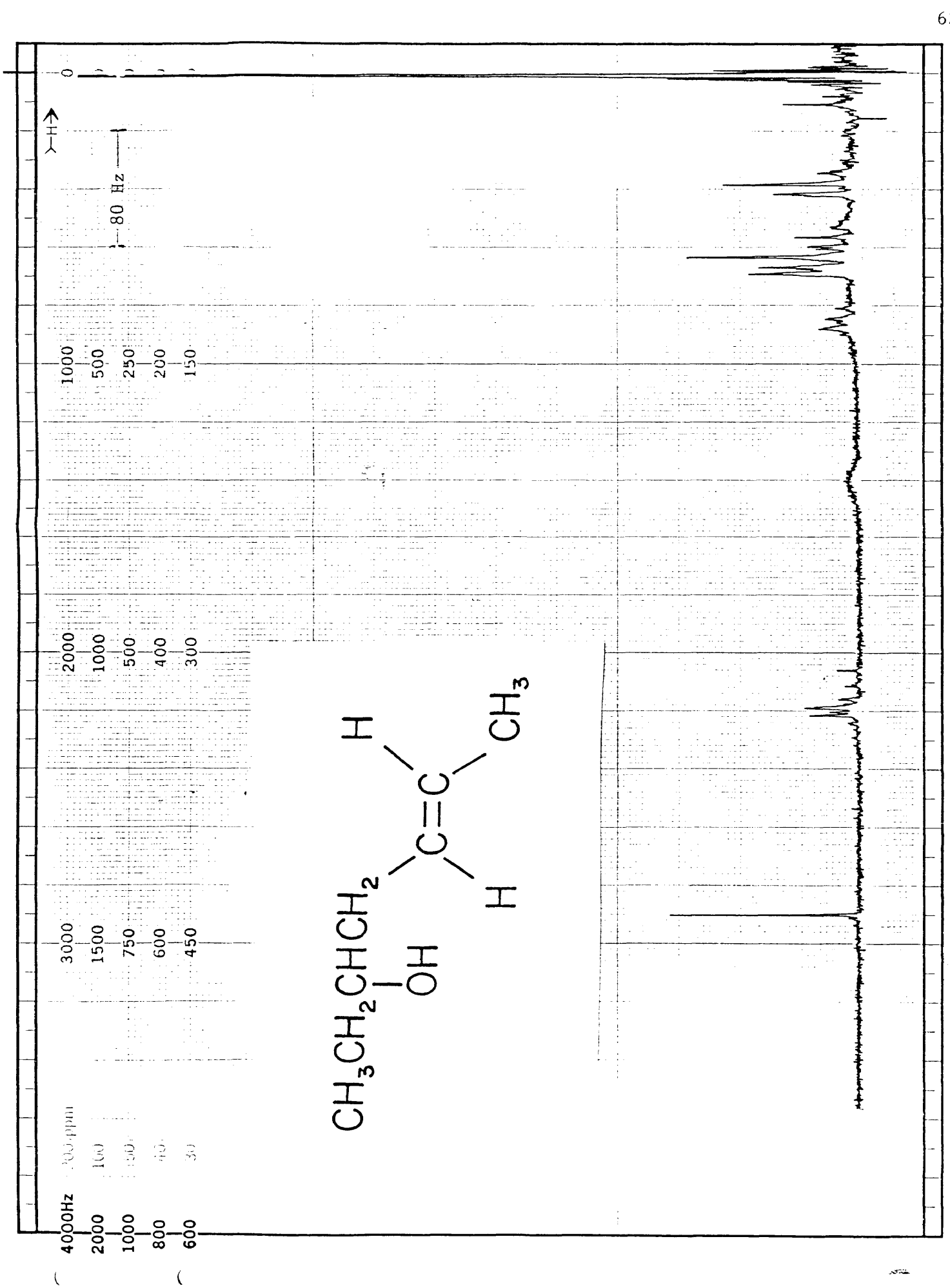


Figure 7. ^{1}H-NMR spectrum of the methylation product from 5-hexyn-1-ol: (E)-5-hepten-3-ol. Solvent: $CDCl_3$.

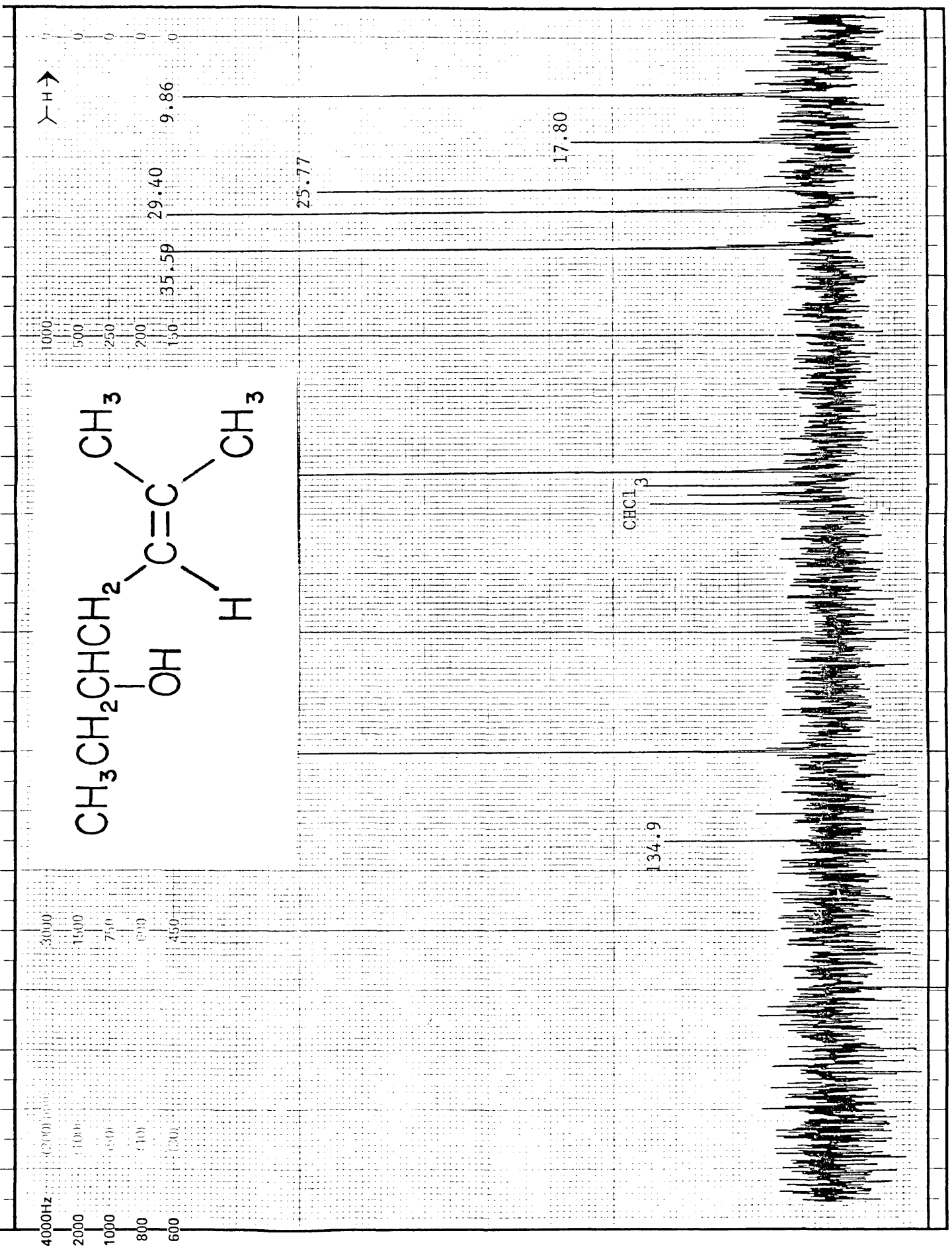


Figure 8. ^{13}C-NMR spectrum of the methylation product from 5-heptyn-3-ol: 6-methyl-5-hepten-3-ol. Solvent: $CDCl_3$.

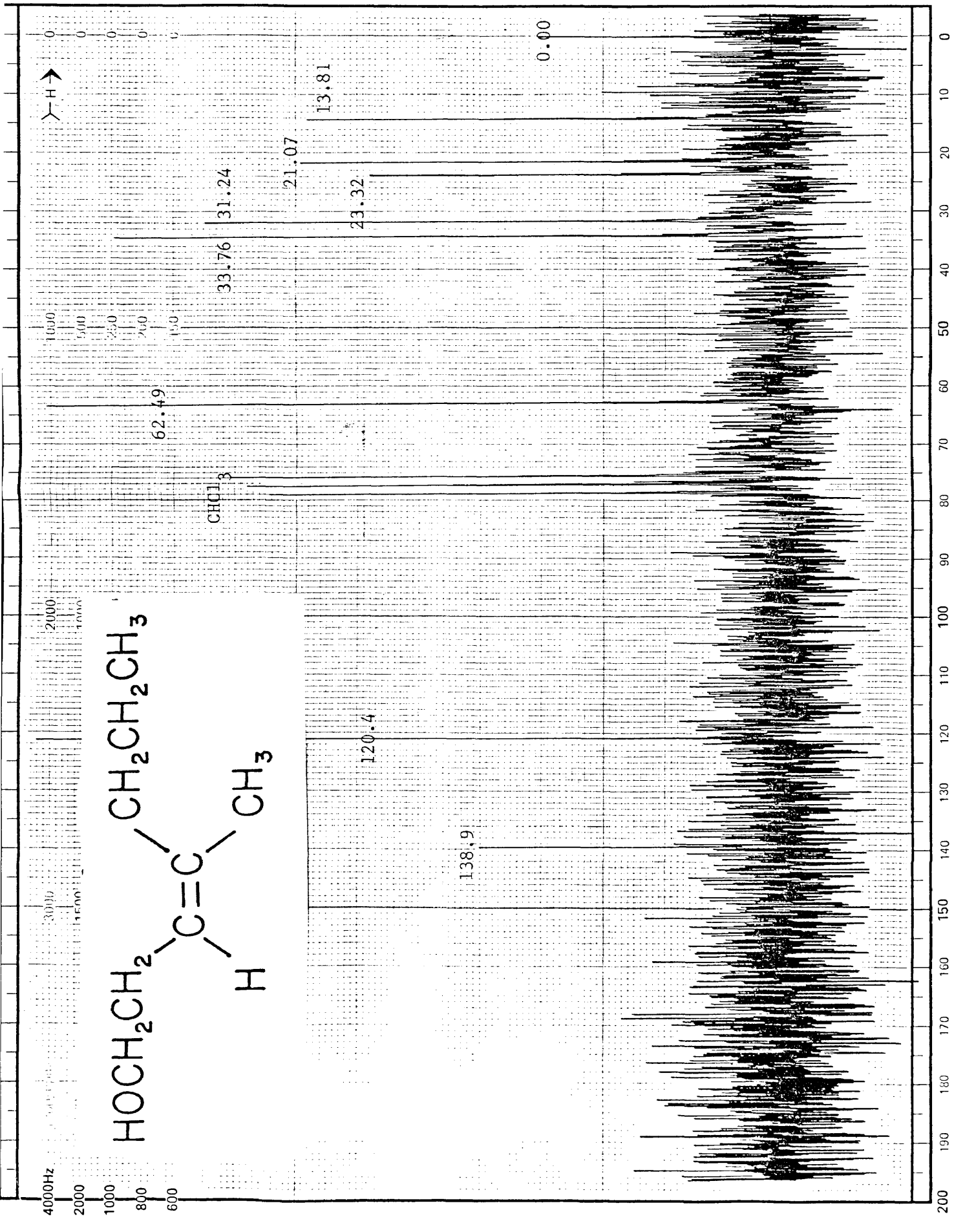


Figure 9. ^{13}C-NMR spectrum of the methylation product from 3-heptyn-1-ol: (Z)-4-methyl-3-hepten-1-ol. Solvent: $CDCl_3$.

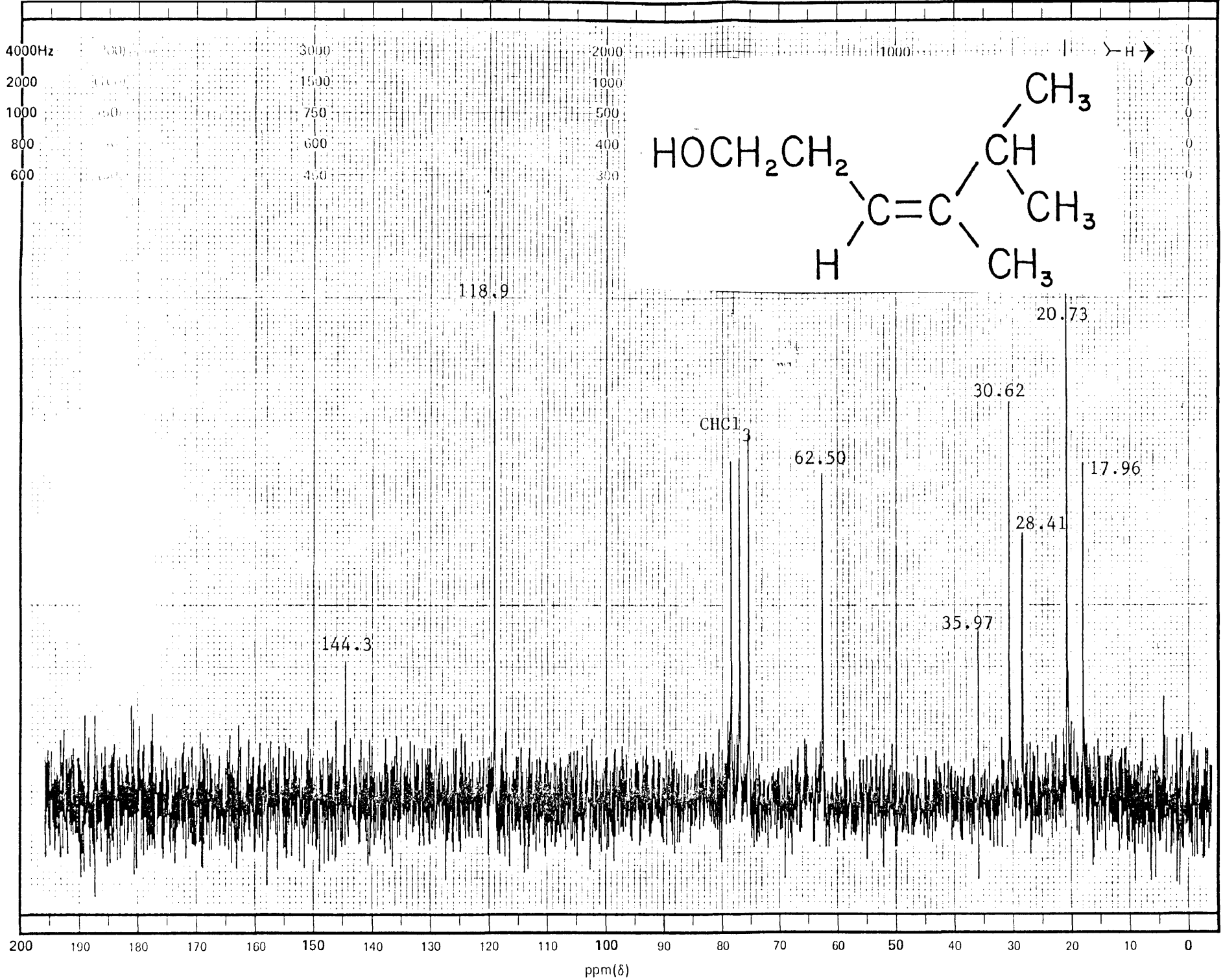


Figure 10. ^{13}C-NMR spectrum of the methylation product from 5-methyl-3-heptyn-1-ol: (Z)-4,5-dimethyl-3-hexen-1-ol. Solvent: $CDCl_3$.

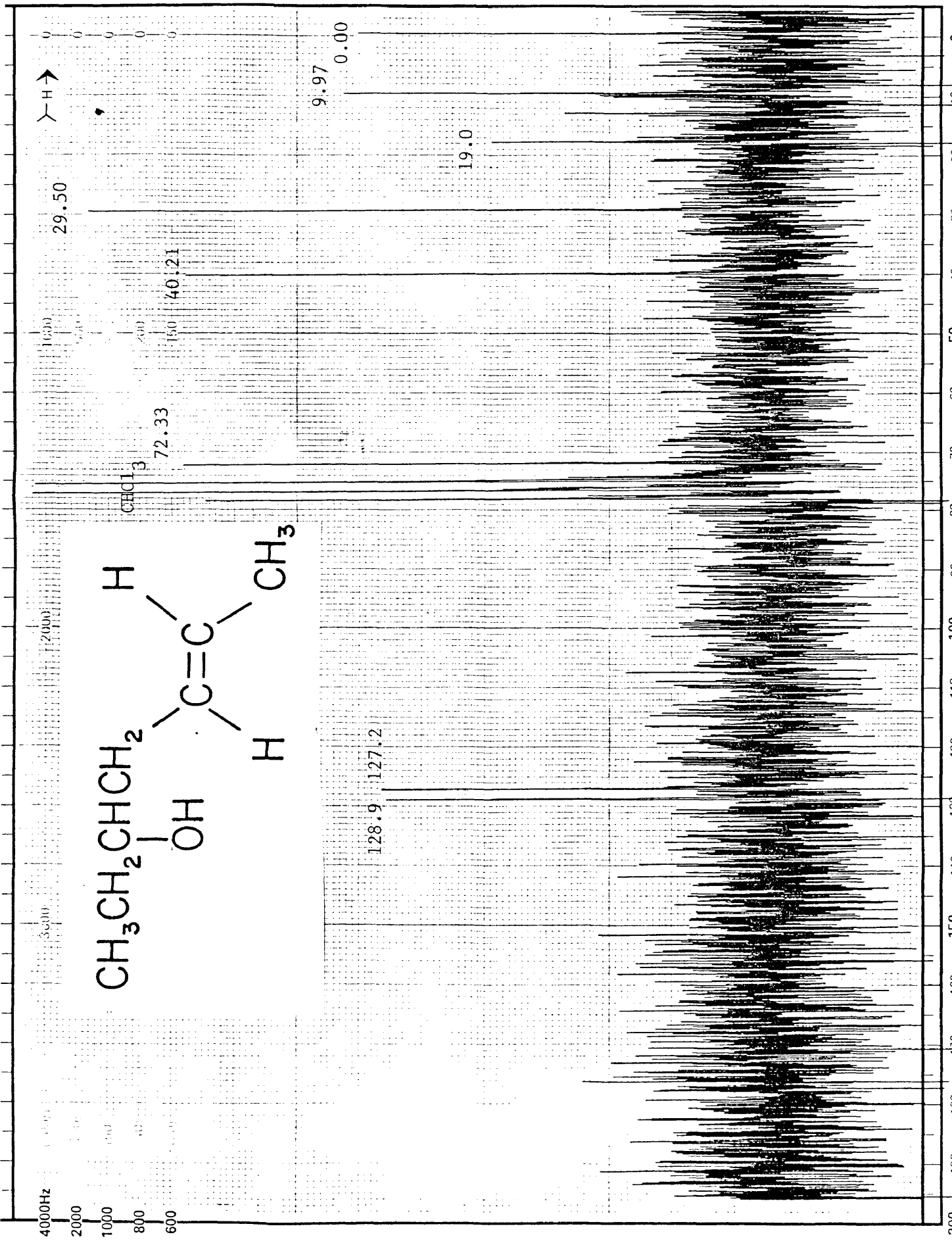
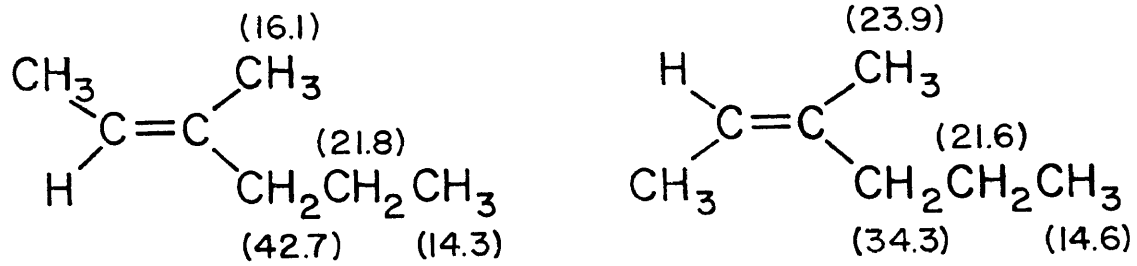


Figure 11. ^{13}C-NMR spectrum of the methylation product from 5-hexyn-1-ol: (E)-5-hepten-3-ol. Solvent: $CDCl_3$.

the carbometallation of 3-heptyn-1-ol is that arising from cis addition.

Two model isomers related to the product of 5-methyl-3-hexyn-1-ol methylation are shown below. In the (Z) isomer where the methyl group

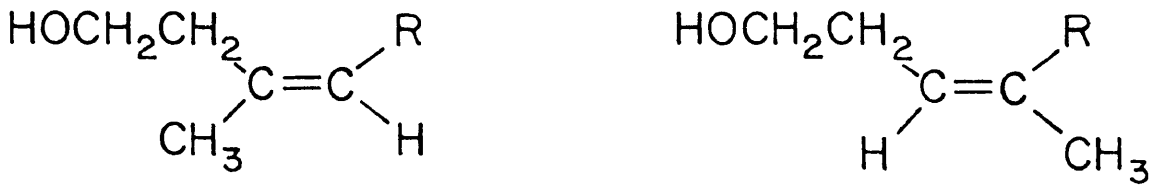


(E) (Z)

3-methyl-2-hexene

is on the same carbon as the isopropyl group and is cis to the hydrogen, the methyl ^{13}C resonance is at 17.8 ppm. The (E) isomer in which the similar methyl group is trans to the olefinic hydrogen has a resonance shifted upfield to 13.1 ppm. For the product of 5-methyl-3-hexyn-1-ol methylation the peak at highest field occurs at 18.0 ppm. This observation together with the ^1H-nmr data clearly confirm the (Z) configuration.

There remains the question of whether the methyl group adds to the 3 or 4 carbon; i.e. are the products (Z)-3-methyl or (Z)-4-methyl-3-alken-1-ols. The question of methyl addition to the 3 or 4 carbon in 3-heptyn-1-ol can



(Z)-3-methyl-3-alken-1-ol (Z)-4-methyl-3-alken-1-ol

be answered from chemical shift additivity relationships for ^{13}C-nmr given by Breitmaier and Voelter.[51] Shift parameters are summarized in Table 8 below. The parameters in Table 8 represent shift contribution to the olefinic carbon atoms (relative to ethylene) due to various carbon containing substituents. From these parameters one can calculate the chemical shifts for the 3-carbon and 4-carbon. In addition to the parameters in Table 8, Schiavelli, et al.[9] determined the group parameters for the hydroxyethyl group in trisubstituted olefins to be α=7.48 and α'=-1.10 ppm. One can now calculate the shifts in (Z)-4-methyl-3-hepten-1-ol to be:

3-carbon shift = 123.3 + 7.48 + 2(-5.14) + (-1.22) + 1.20 = 120.5 ppm

4-carbon shift = 123.3 + 2(6.35) + 6.47 + (-0.66) + (-1.10) = 140.7 ppm.

These calculated shifts are in excellent agreement with the observed shifts of 120.4 and 138.9. A similar calculation for (Z)-3-methyl-3-hepten-1-ol yields shifts of 131.7 (3-carbon) and 128.9 (4-carbon) ppm; clearly this isomer is excluded.

For the product derived from the isopropyl-containing alkynol, the question of methyl group addition at the 3- or 4-carbon is immediately answered from the ^1H-nmr spectrum. The vinylic hydrogen resonance occurs at 5.0 ppm as a well-defined triplet which clearly indicates that it is at the 3-carbon to which a methylene unit is also bound. If the hydrogen was at the 4-carbon, then a doublet should occur due to coupling with the single methine hydrogen of the isopropyl group. Thus, the product from the metal-methylation of 5-methyl-3-hexyn-1-ol is (Z)-4,5-dimethyl-3-hexen-1-ol. The calculated ^{13}C shifts for the 3- and 4-carbons of the methylation product from 5-methyl-3-hexyn-1-ol offer final confirmation that the product is (Z)-4,5-dimethyl-3-hexen-1-ol.

For this isomer:

3-carbon shift = 123.3 + 7.48 + 2(-5.14) + 2(-1.22) = 118.9

4-carbon shift = 123.3 + (-1.10) + 2(6.35) + 2(6.47) = 147.8

These calculated values are in good agreement with the observed values of 118.9 and 144.3 ppm. Assuming methylation takes place at the 3-carbon, the calculated shifts are 129.6 (3-carbon) and 136.4 (4-carbon) ppm which are clearly not in agreement with the observed shifts.

The second emphasis of this research was to investigate the effect of alkyl substituted cyclopentadienyl rings in bis(cyclopentadienyl)-titanium dichlorides as components of alkynol alkylation reagent systems. Thompson and coworkers[53] have reported that bis(η^5-cyclopentadienyl) and bis(η^5-methylcyclopentadienyl)titanium dichlorides when used with diethylaluminum chloride-alkynol solution give excellent yields of ethyl-metallated product. Additionally, the titanium-cyclopentadienyl compound can often be used in less than a stoichiometric amount relative to the alkynol. However, the regioselectivity of the carbometallation was unsatisfactory. While much less data was reported for these systems with trimethylaluminum as the main group alkyl, the yields here were good; however, while the regioselectivity was better, favoring internal methylation, again it was less than desirable. With this background in view we thought that incorporation of a t-butyl group into each ring or incorporation of five methyl groups into each ring might significantly change the regioselectivity to give a single isomer.

Table 8. ^{13}C Chemical Shift Parameters for Different Kinds of Alkenines (Relative to Ethylene).[51]

Parameter	Monosubstituted alkenes	Disubstituted alkenes	1,2-Disubstituted alkenes	Trisubstituted alkenes
α	12.63 ± 0.18	8.75 ± 0.43	2.61 ± 0.12(α+α')	6.35 ± 0.07
β	4.55 ± 0.06	5.90 ± 0.81	6.50 ± 0.05	6.47 ± 0.22
γ	-1.18 ± 0.07	-1.10 ± 0.11	-0.72 ± 0.10	-0.66 ± 0.29
α'	-8.03 ± 0.18	-6.59 ± 0.43	-2.61 ± 0.12(α+α')	-5.14 ± 0.07
β'	-1.95 ± 0.06	-1.86 ± 0.81	-1.82 ± 0.05	-1.22 ± 0.22
γ'	1.41 ± 0.07	1.99 ± 0.11	0.93 ± 0.10	1.20 ± 0.29
c			0.45 ± 0.08	

The solid state molecular structures of $(\eta^5\text{-}C_5H_5)_2TiCl_2$ and $(\eta^5\text{-}C_5H_4CH_3)_2TiCl_2$ are the same, as shown by X-ray crystal structure determination.[54,55,56] In fact, the methyl substituent exerts an "essentially negligible effect on the basic molecular configuration...".[55] On the other hand, the crystal structure for $(\eta^5\text{-}C_5(CH_3)_5)_2TiCl_2$ shows a marked effect due to the methyl substituents.

In $(\eta^5\text{-}C_5H_4CH_3)_2TiCl_2$ the methyl group carbon is essentially in the plane of the cyclopentadienyl ring. In $(\eta^5\text{-}C_5(CH_3)_5)_2TiCl_2$ the methyl group carbon atoms are from 2^o to 20^o out of the plane of the ring and the angle which the rings make with the titanium atom is somewhat larger (137^o) than for the unsubstituted and mono-methyl analogs (ca. 130^o). These distortions have been attributed to a combination of methyl-methyl and methyl-chlorine interactions. The latter type of interaction is of a type which could significantly influence carbometallation at a titanium center; that is, it suggests definite ring interaction with other coordination sites about titanium.

Our expectations for a significant improvement in the regioselectivity with bis(η^5-t-butylcyclopentadienyl)titanium dichloride as a promoter/catalyst for the methylation and ethylation of 3-butyn-1-ol (chosen as the test alkynol for these studies) was not met. Surprisingly, and discouragingly, the t-butyl group had little effect. We were pleased to find that methylation of 3-butyn-1-ol with bis(η^5-pentamethylcyclopentadienyl)titanium dichloride gave a single isomer (3-methyl-3-buten-1-ol) although ethylation with this promoter/catalyst was unsatisfactory. The results of this investigation are presented in Tables 9 through 12.

Table 9. Methylation of 3-butyn-1-ol with trimethylaluminum/titanocene dichloride alkylating reagents.

Titanocene Dichloride	Temp. (°C)	Time (min)	Molar Ratio Ti:Al:ROH	Products (relative ratio)	Yield (%)	Starting Alkynol Recovered (%)	Total Mass Balance (%)
Cp_2TiCl_2	0	120	0.25:2:1	3-methyl-3-buten-1-ol(I) (87) trans-3-penten-1-ol(II) (13)	32	51	83
Cp_2TiCl_2	0	30	0.25:2:1	None		87	
$(MeCp)_2TiCl_2$	20-25	240	0.1:2:1	(I) (74) (II) (26)	75	5	80
$(MeCp)_2TiCl_2$	0	240	0.1:2:1	(I) (72) (II) (28)	50	39	89
$(MeCp)_2TiCl_2$	0	120	0.25:2:1	(I) (79) (II) (21)	56	28	84
$(MeCp)_2TiCl_2$	0	120	0.25:2:1	(I) (81) (II) (19)	31	56	87
$(t\text{-}buCp)_2TiCl_2$	0	120	0.1:2:1	(I) (80) (II) (20)	25	21	46
$(t\text{-}buCp)_2TiCl_2$	0	120	0.25:2:1	(I) (80) (II) (20)	59	8	67
$(t\text{-}buCp)_2TiCl_2$	0	120	0.25:2:1	(I) (II)			
$(Me_5Cp)_2TiCl_2$	0	120	0.25:2:1	(I) (100) (II) (0)	40	7	47
$(Me_5Cp)_2TiCl_2$	-23	5	0.25:2:1	(I) (100) (II) (0)	41	26	67
$(Me_5Cp)_2TiCl_2$		120	0.25:2:1	(I) (100) (II) (0)	49	24	73

Table 6. Ethylation of 3-butyn-1-ol with Bis(η^5-cyclopentadienyl)titanium Dichloride and Diethylaluminum Chloride

Temp. (°C)	Time (min)	Molar Ratio Ti:Al:ROG	Products (relative ratio)[c]	Yield (%)	Starting Alkynol Recovered (%)	Total Mass Balance (%)
0	120	0.25:2:1	3-ethyl-3-buten-1-ol(I) (43) trans-3-hexen-1-ol(II) (57)	71	0	71
0	120	0.1:2.5:1	(I) (II)	90	0	90[a]
0	360	1:2.5:1	(I) (II)	55[b,d]		
0	360	0.5:2.5:1	(I) (II)	85[b]		
0	360	0.25:2.5:1	(I) (II)	78[b]		
0	360	0.1:2.5:1	(I) (II)	80[b]		
0	360	0.1:2.5:1	(I) (II)	88[b]		
-22	360	0.5:2.5:1	(I) (II)	80[b]		
-78	360	0.5:2.5:1	(I) (II)	0[b]		

[a] D. C. Brown et al., J. Org. Chem., 44, 3457 (1979).

[b] L. C. Smedley et al., J. Org. Chem., 42, 4147 (1977).

[c] Ratios not specifically given range between 50/50 and 60/40 for (I)/(II).

[d] Benzene solvent.

Table 11. Ethylation of 3-butyn-1-ol with Titanocene Dichloride and Diethylaluminum Chloride Reagents

Titanocene Dichloride	Temp. (°C)	Time (min	Molar Ratio Ti:Al:ROH	Products	Yield (%)	Starting Alkynol Recovered (%)	Total Mass Balance (%)
$(MeCp)_2TiCl_2$	0	240	0.1:2.0:1.	3-ethyl-3-buten-1-ol(I) (56) trans-3-hexen-1-ol(II) (44)	100	0	100[a]
$(MeCp)_2TiCl_2$	0	120	0.25:2:1	(I) (51) (II) (49)	78	0	78
$(MeCp)_2TiCl_2$	0	120	0.25:2:1	(I) (46) (II) (54)	90	0	90
$(t\text{-buCp})_2TiCl_2$	0	120	0.25:2:1	(I) (43) (II) (57)	80	0	80
$(t\text{-buCp})_2TiCl_2$	0	120	0.25:2:1	(I) (47) (II) (53)	60	19	79
$(Me_5Cp)_2TiCl_2$	0	120	0.25:2:1	(I) (33) (II) (66)	6	70	76

[a] D. C. Brown, et al., J. Org. Chem., 44, 3457 (1979).

In conclusion, it has been demonstrated that the titanium tetrachloride-trimethylaluminum reagent system is very effective in stereo- and regioselectively methylating disubstituted alkynols of the homopropargyllic type to give (Z)-4-methyl-3-alken-1-ol products. This reagent system should be very useful in selective situations involving similar alkynol substrates and extension to other alkylaluminum reagents is a distinct possibility.

While bis(t-butylcyclopentadienyl)titanium dichloride gave essentially no change in regioselectivity when compared to unsubstituted and monomethyl analogs and suggests that monoalkylcyclopentadienyl ligands will not aid regioselectivity, the bis(η^5-pentamethylcyclopentadienyl)titanium dichloride gave a single internally methylated product although the ethylation was unsatisfactory. This preliminary work, however, suggests that there may be useful selective reactions with $(\eta^5\text{-}C_5(CH_3)_5)_2TiCl_2$ and trimethylaluminum. Further work will be needed to establish this.

APPENDIX

NMR Spectra of Selected Alkynols and Cyclopentadienyl Compounds.

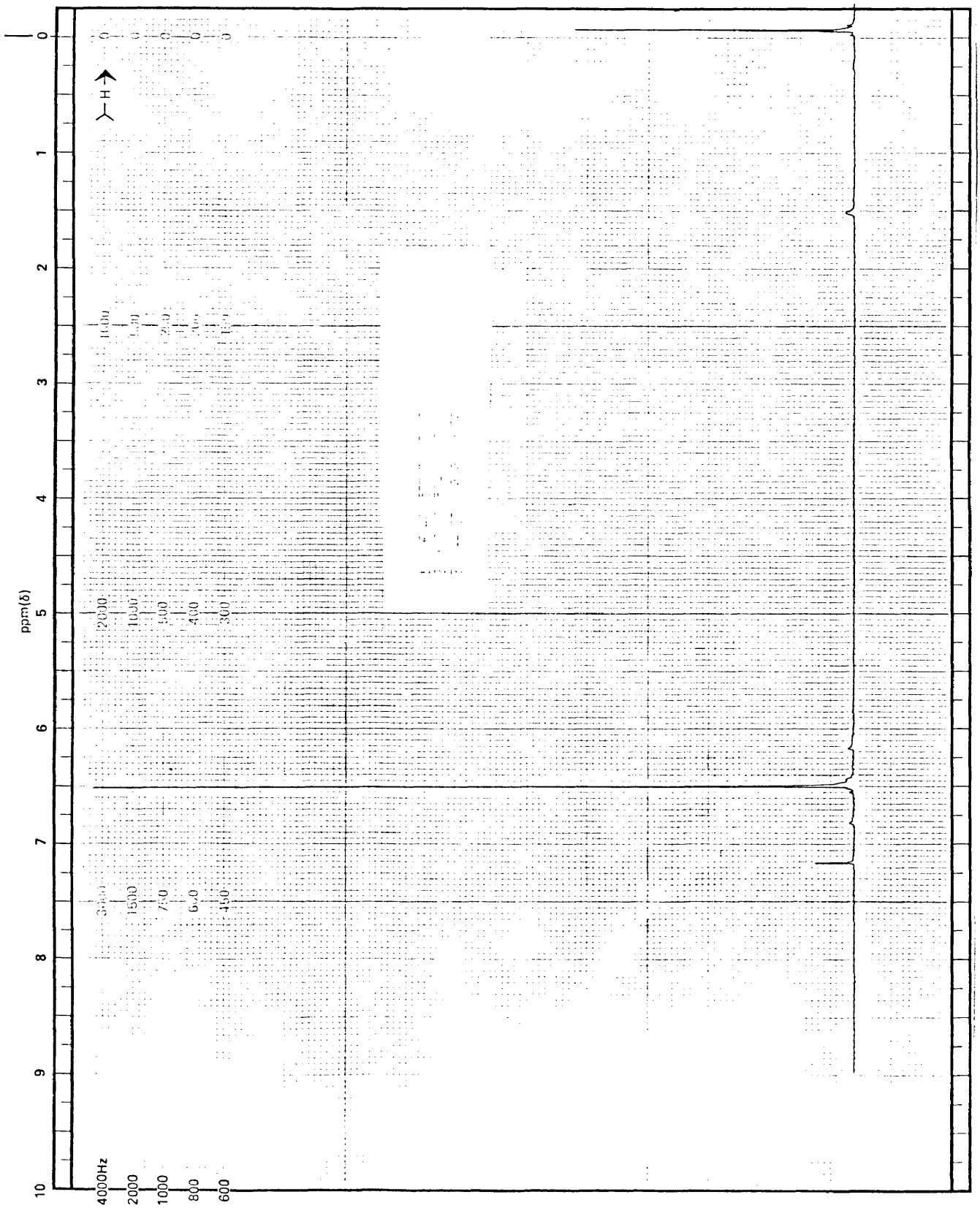


Figure A-1. ^{1}H-NMR spectrum of bis(η^{5}-cyclopentadienyl)titanium dichloride. Solvent: $CDCl_3$.

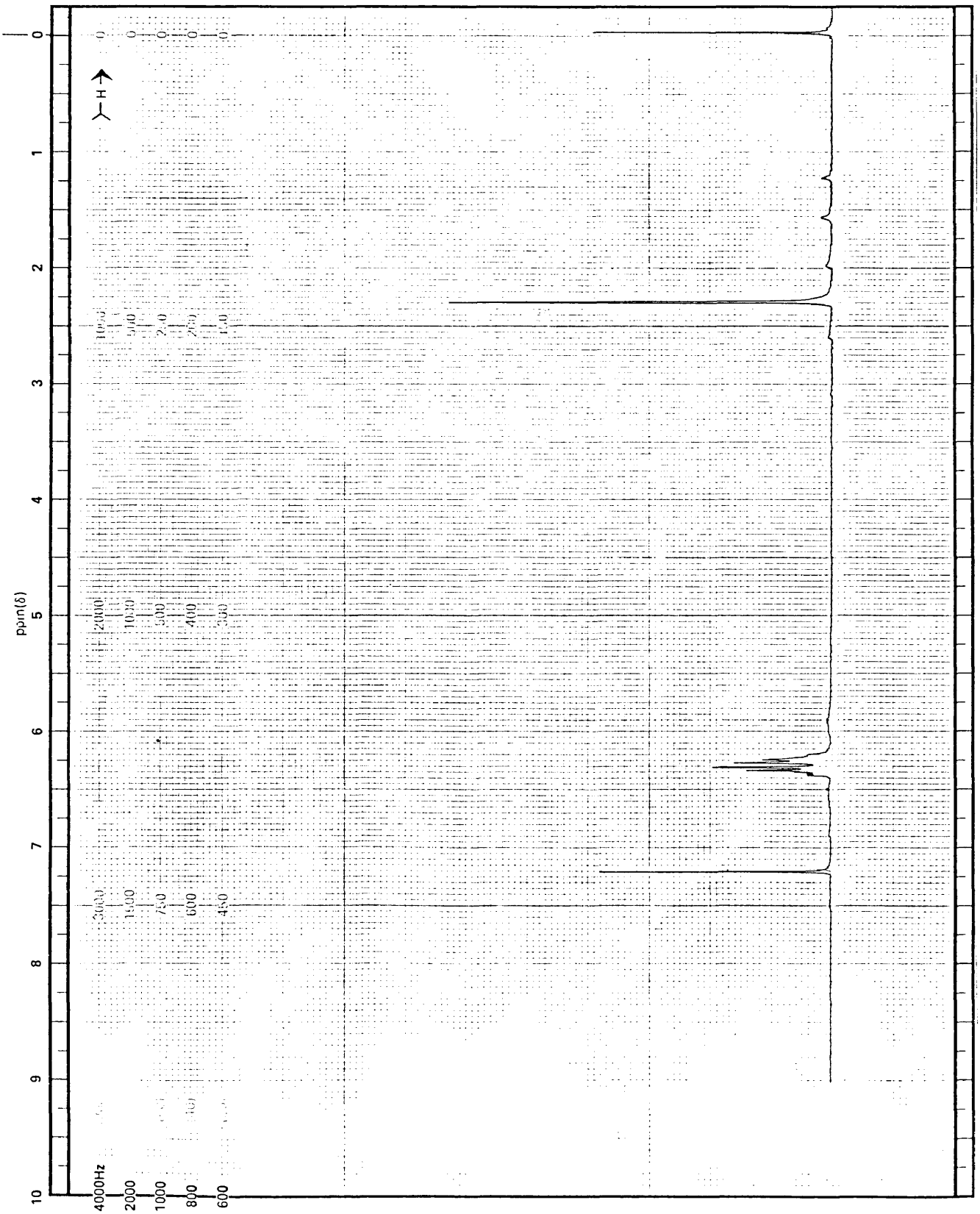


Figure A-2. ^{1}H-NMR spectrum of bis(η^{5}-methylcyclopentadienyl)titanium dichloride. Solvent: $CDCl_3$.

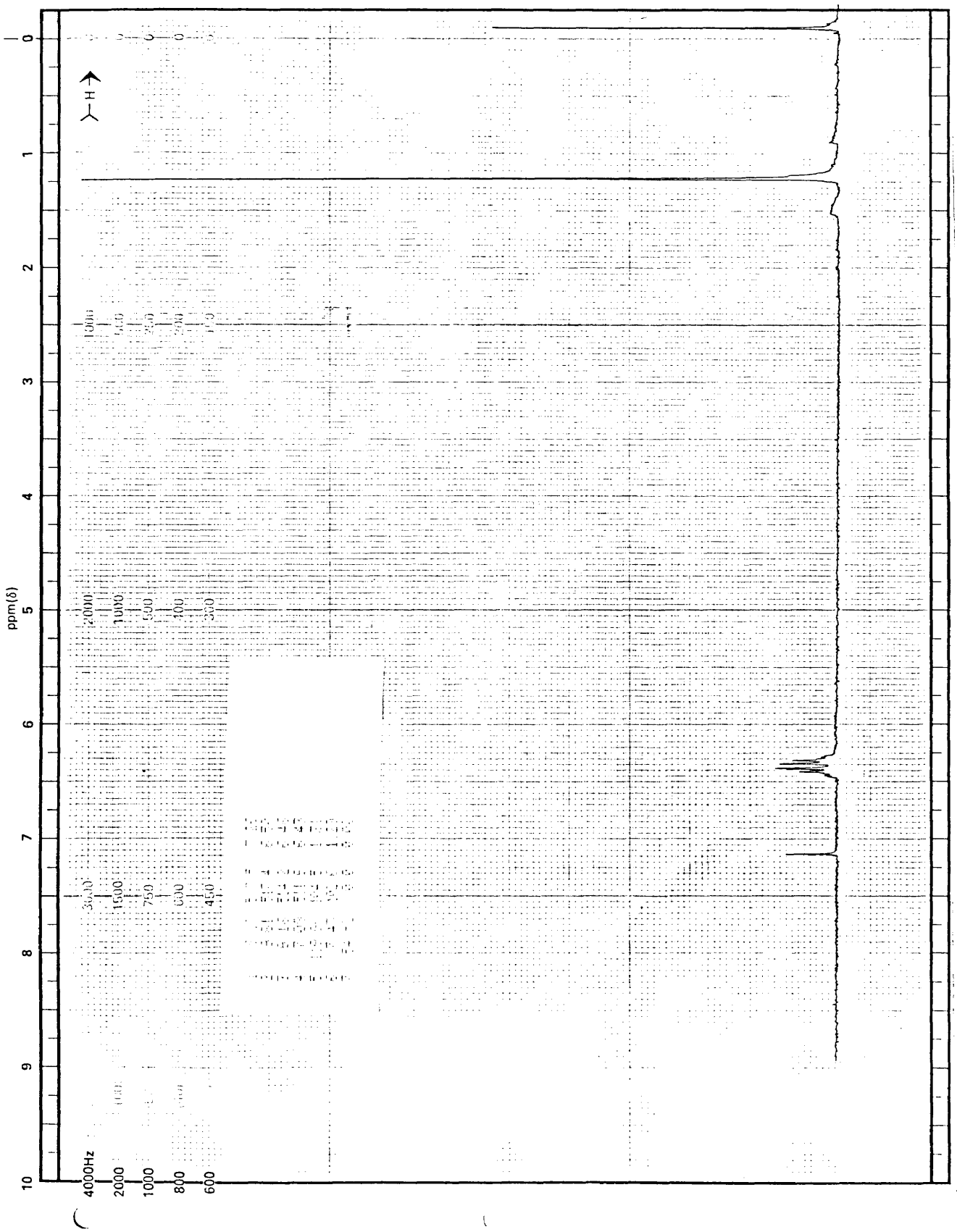


Figure A-3. ^{1}H-NMR spectrum of bis(η^{5}-t-butylcyclopentadienyl)titanium dichloride. Solvent: $CDCl_3$.

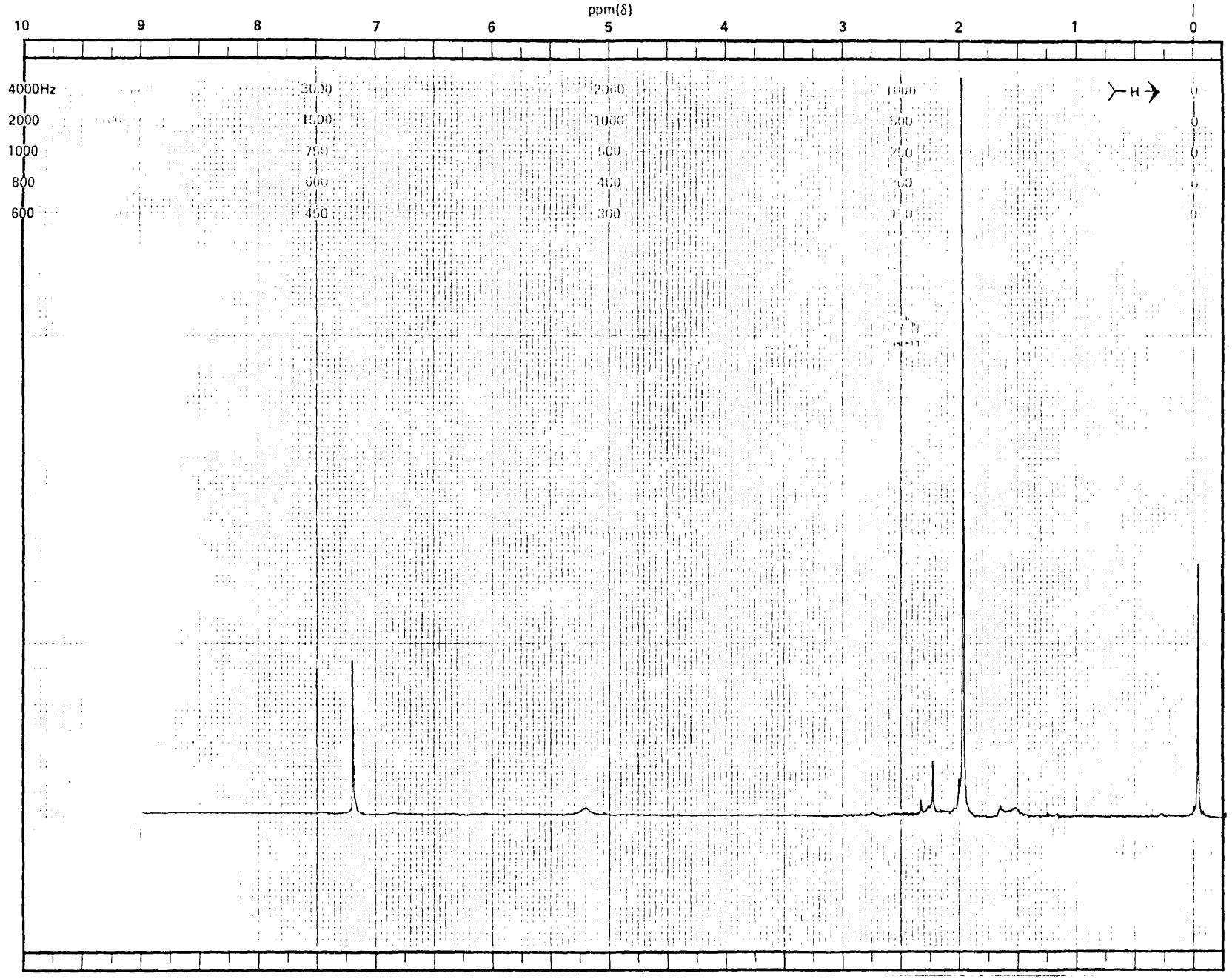


Figure A-4. ^{1}H-NMR spectrum of bis(η^{5}-pentamethylcyclopentadienyl)titanium dichloride. Solvent: $CDCl_3$.

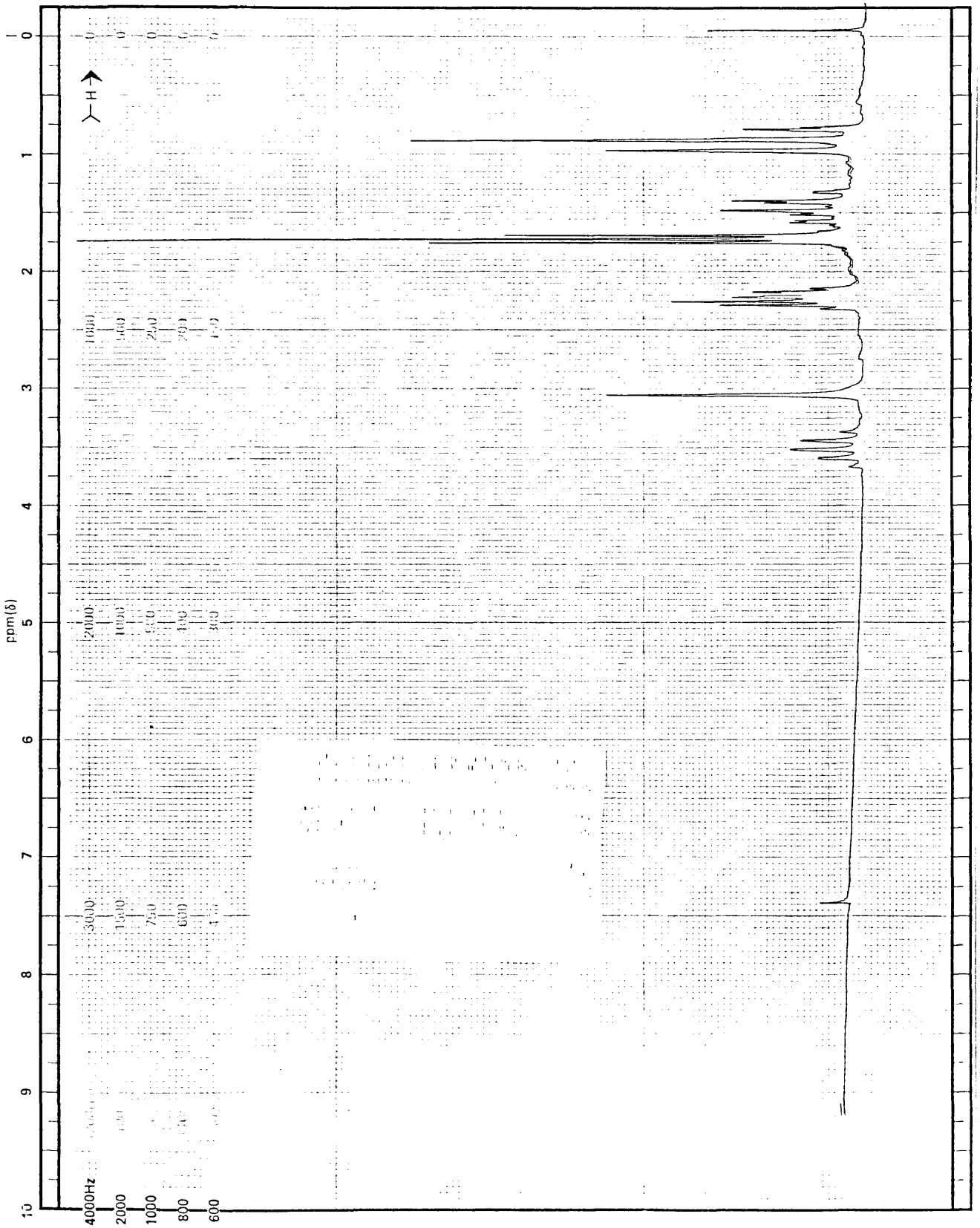


Figure A-5. ^{1}H-NMR spectrum of 5-heptyn-3-ol. Solvent: $CDCl_3$.

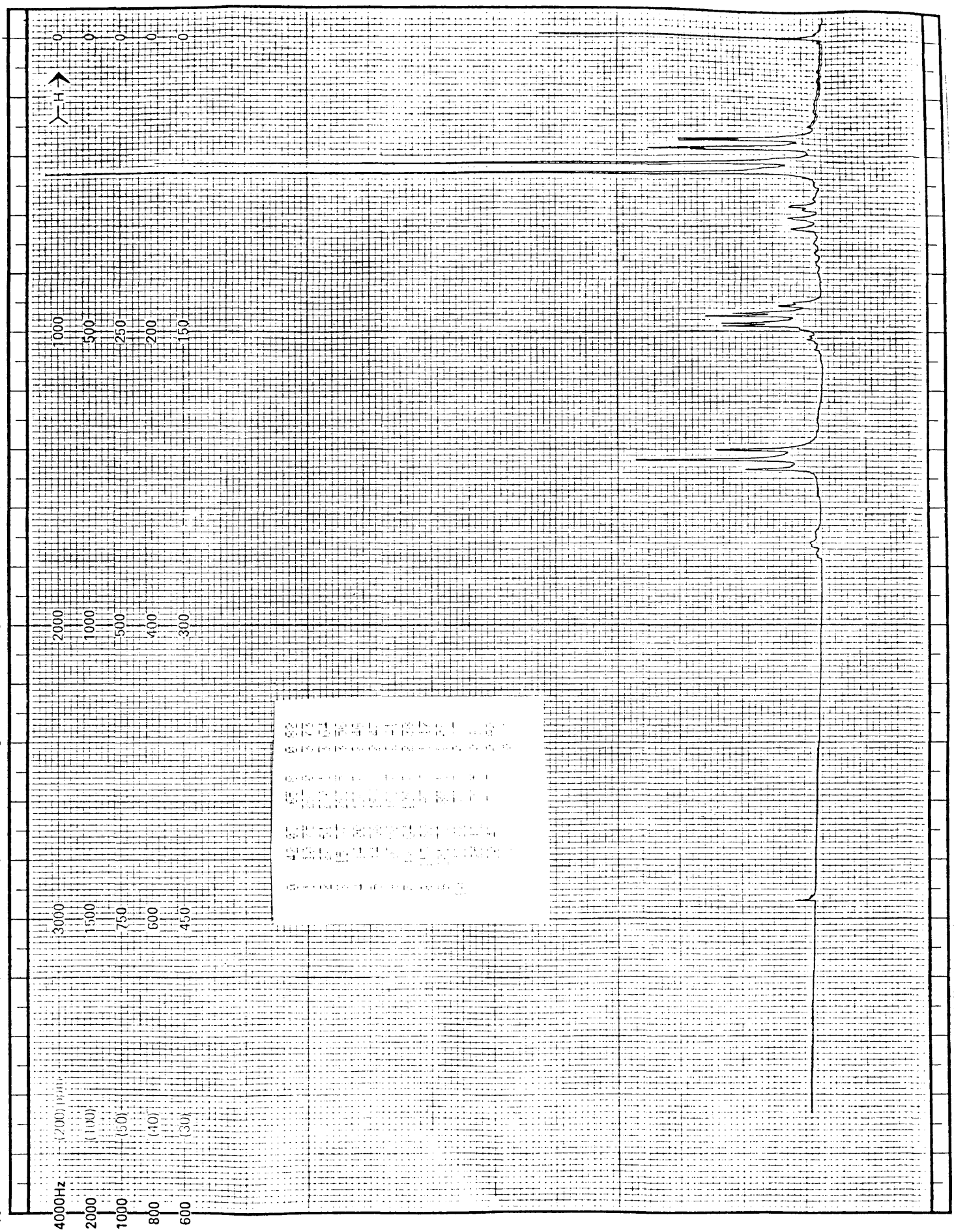


Figure A-6. ^{1}H-NMR spectrum of 5-methyl-3-heptyn-1-ol. Solvent: $CDCl_3$.

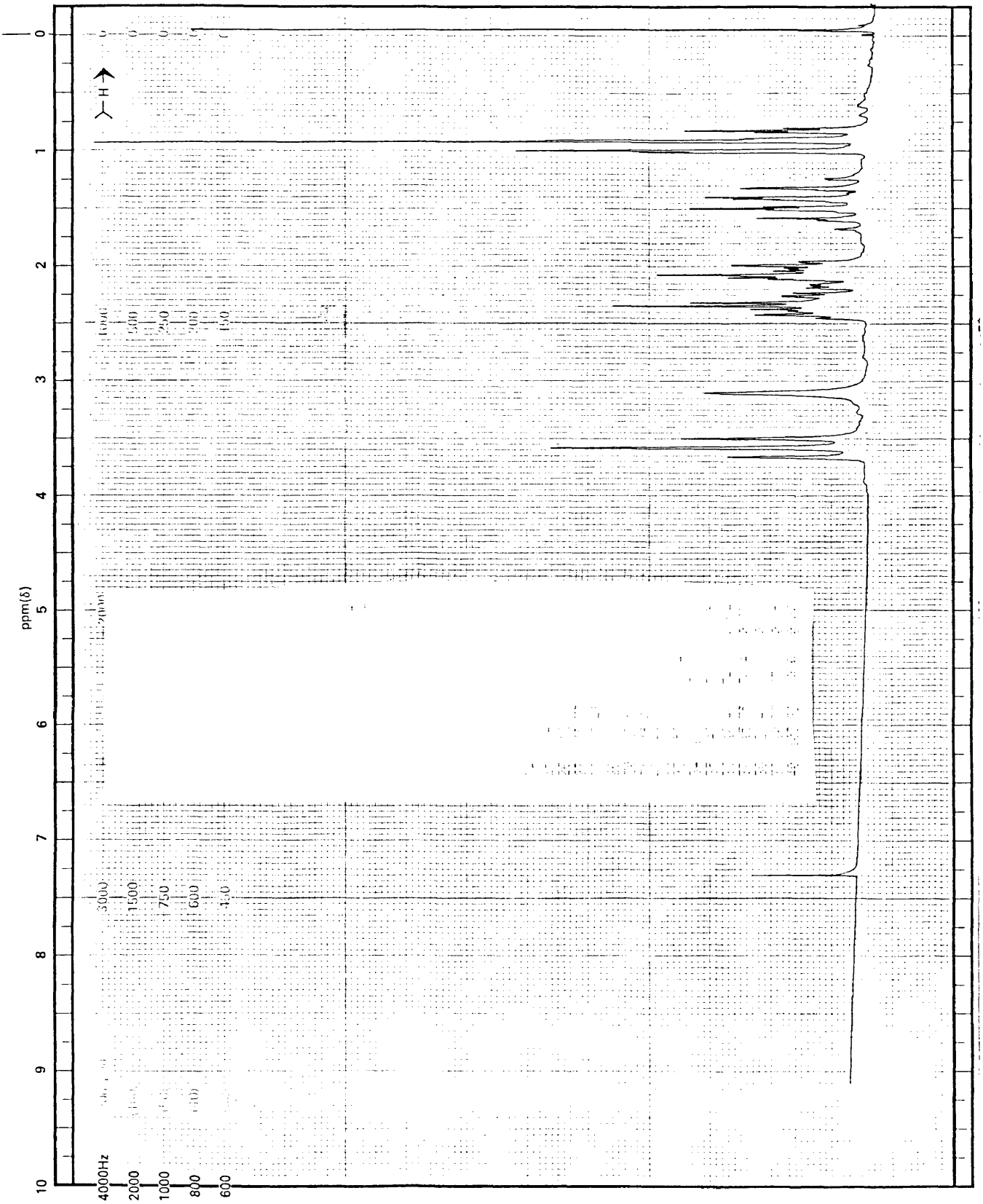


Figure A-7. ^{1}H-NMR spectrum of 3-heptyn-1-ol. Solvent: $CDCl_3$.

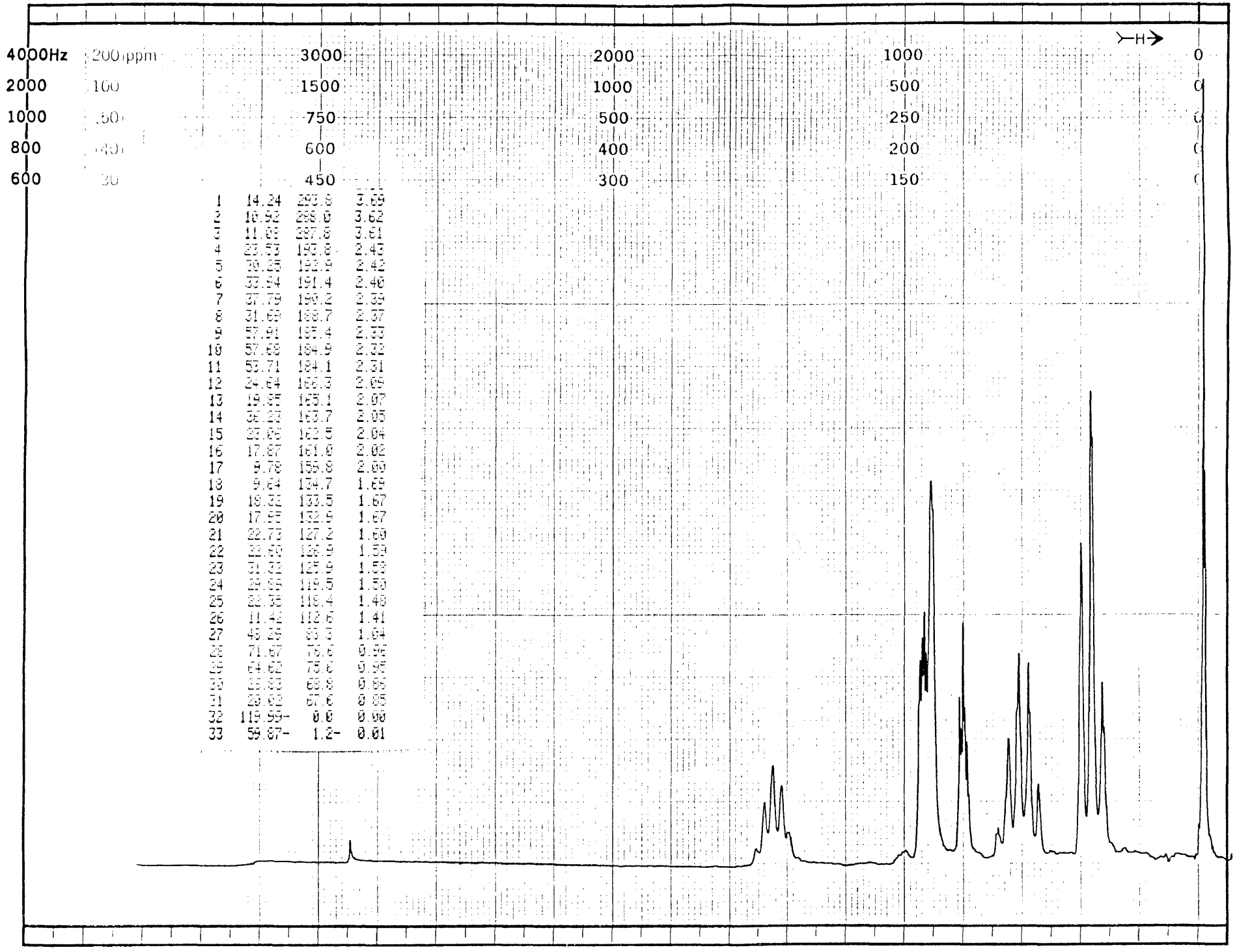


Figure A-8. ^{1}H-NMR spectrum of 5-hexyn-1-ol. Solvent: $CDCl_3$.

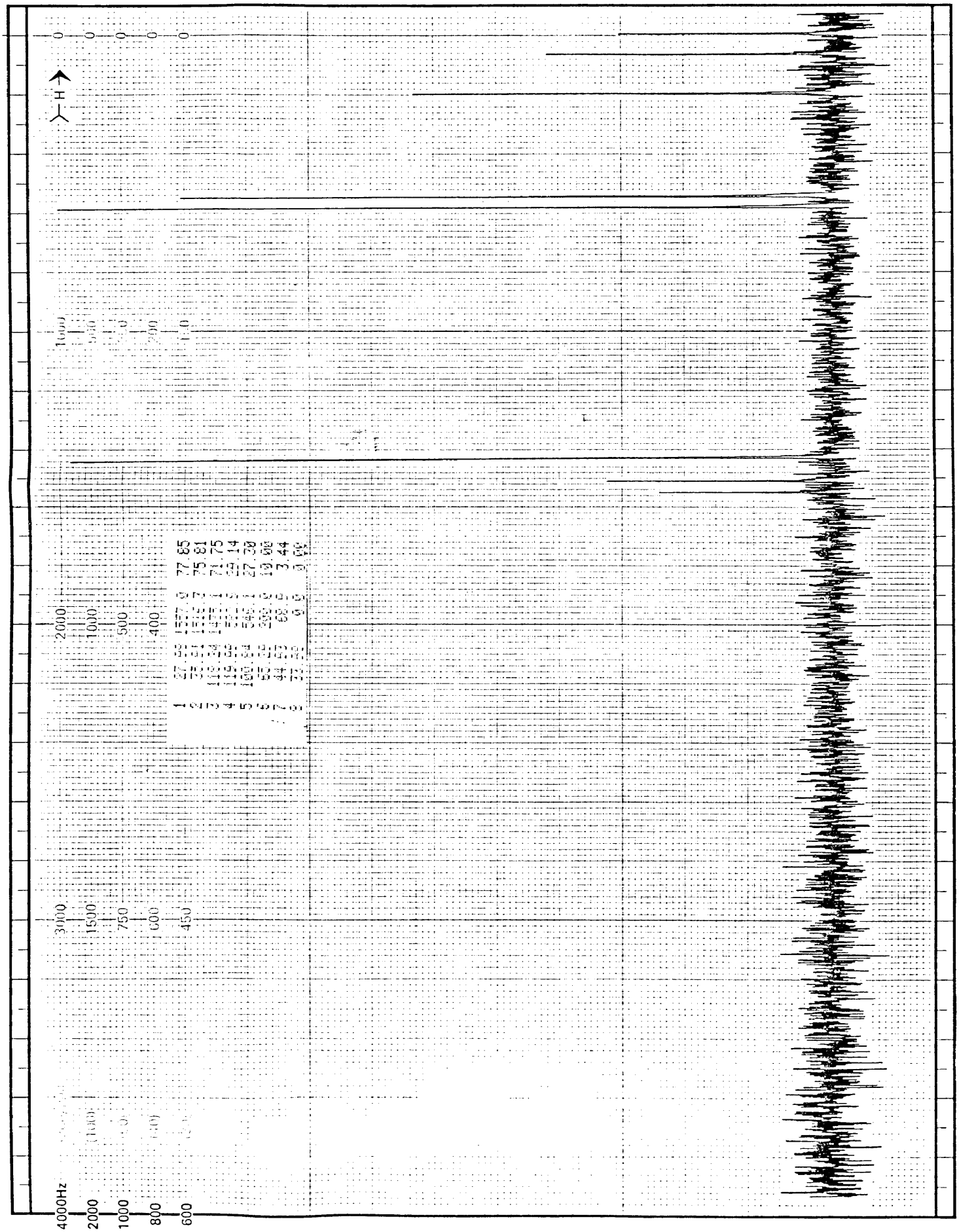


Figure A-9. ^{13}C-NMR spectrum of 5-heptyn-3-ol. Solvent: $CDCl_3$.

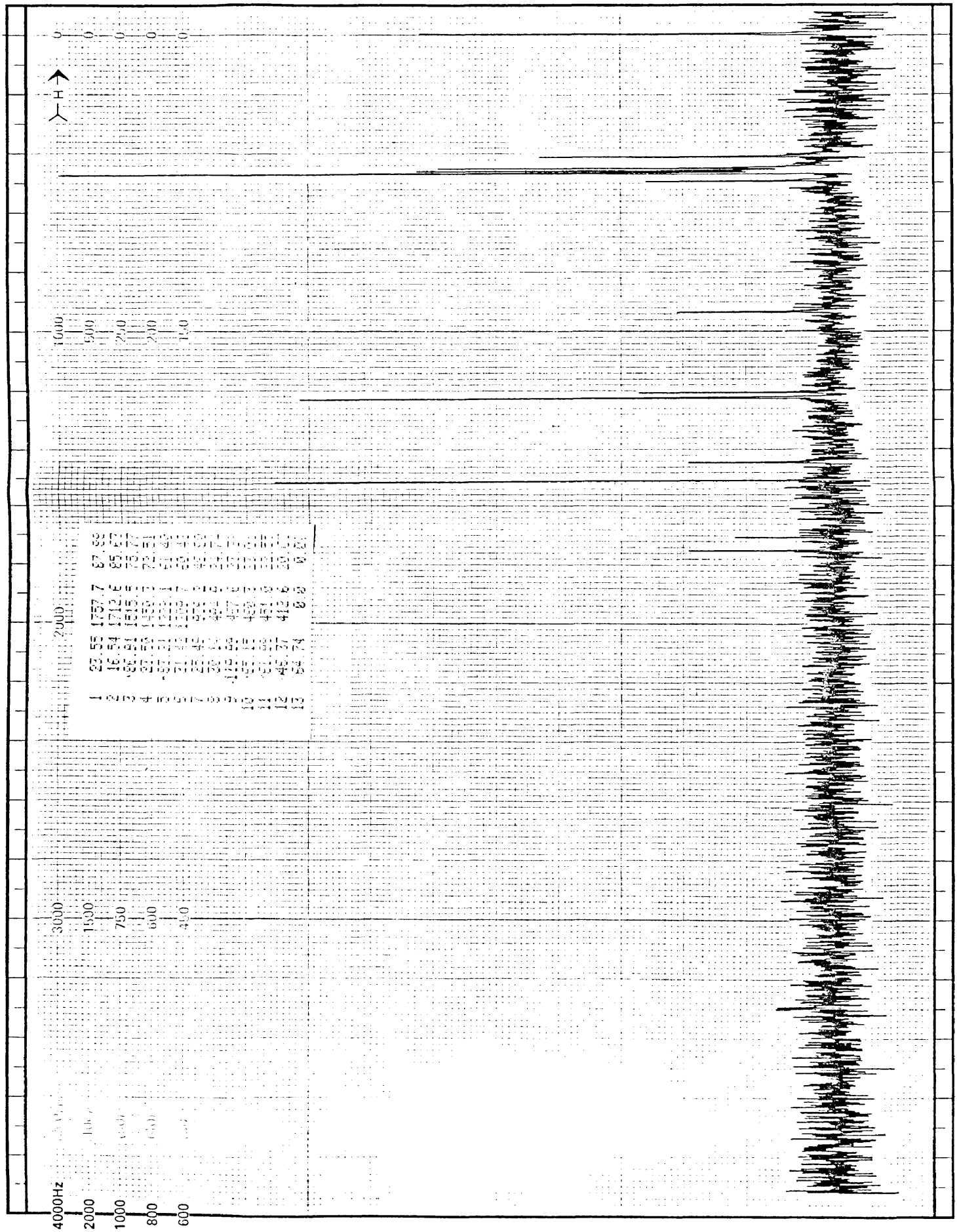


Figure A-10. ^{13}C-NMR spectrum of 5-methyl-3-heptyn-1-ol. Solvent: $CDCl_3$.

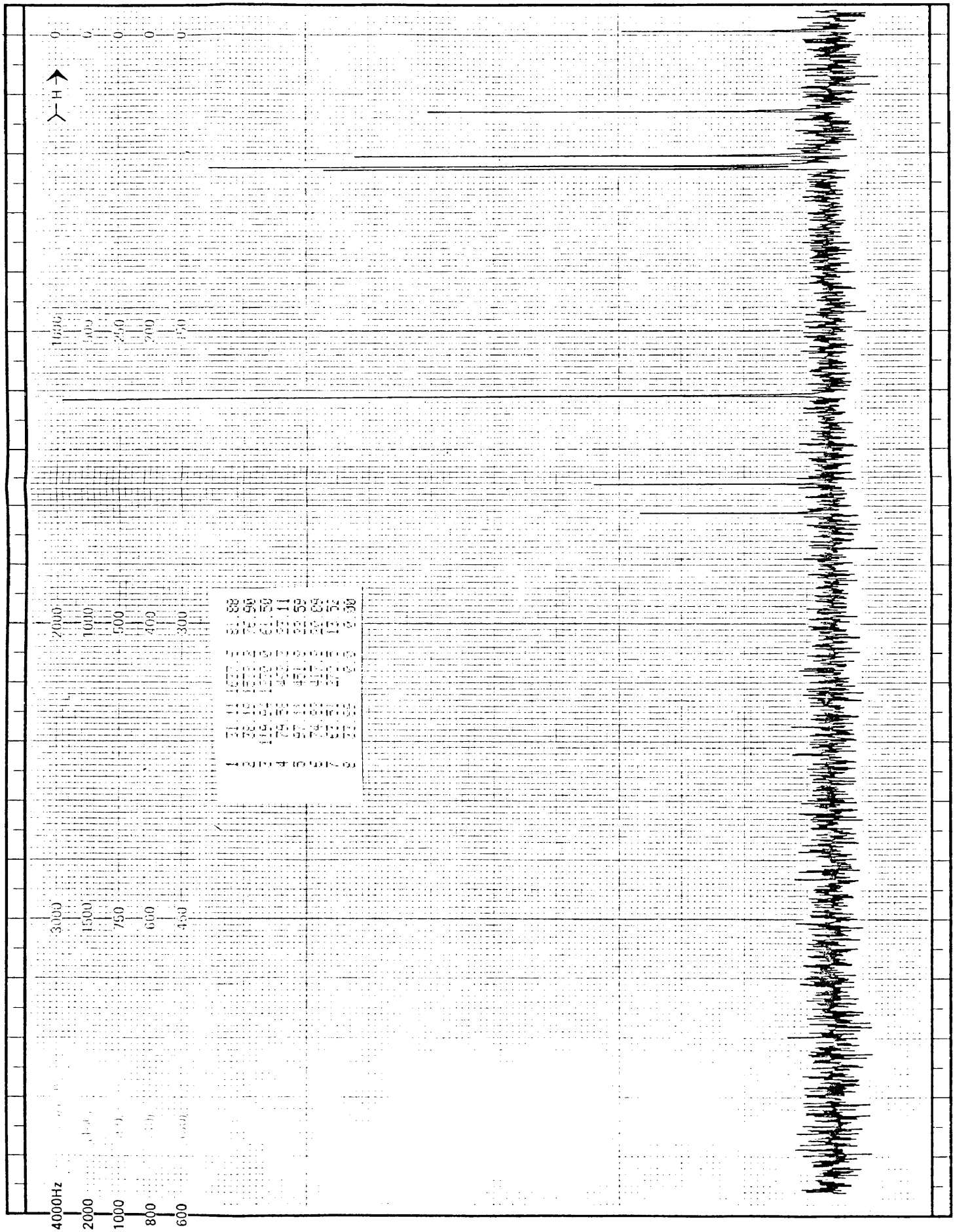


Figure A-11. ^{13}C-NMR spectrum of 3-heptyn-1-ol. Solvent $CDCl_3$.

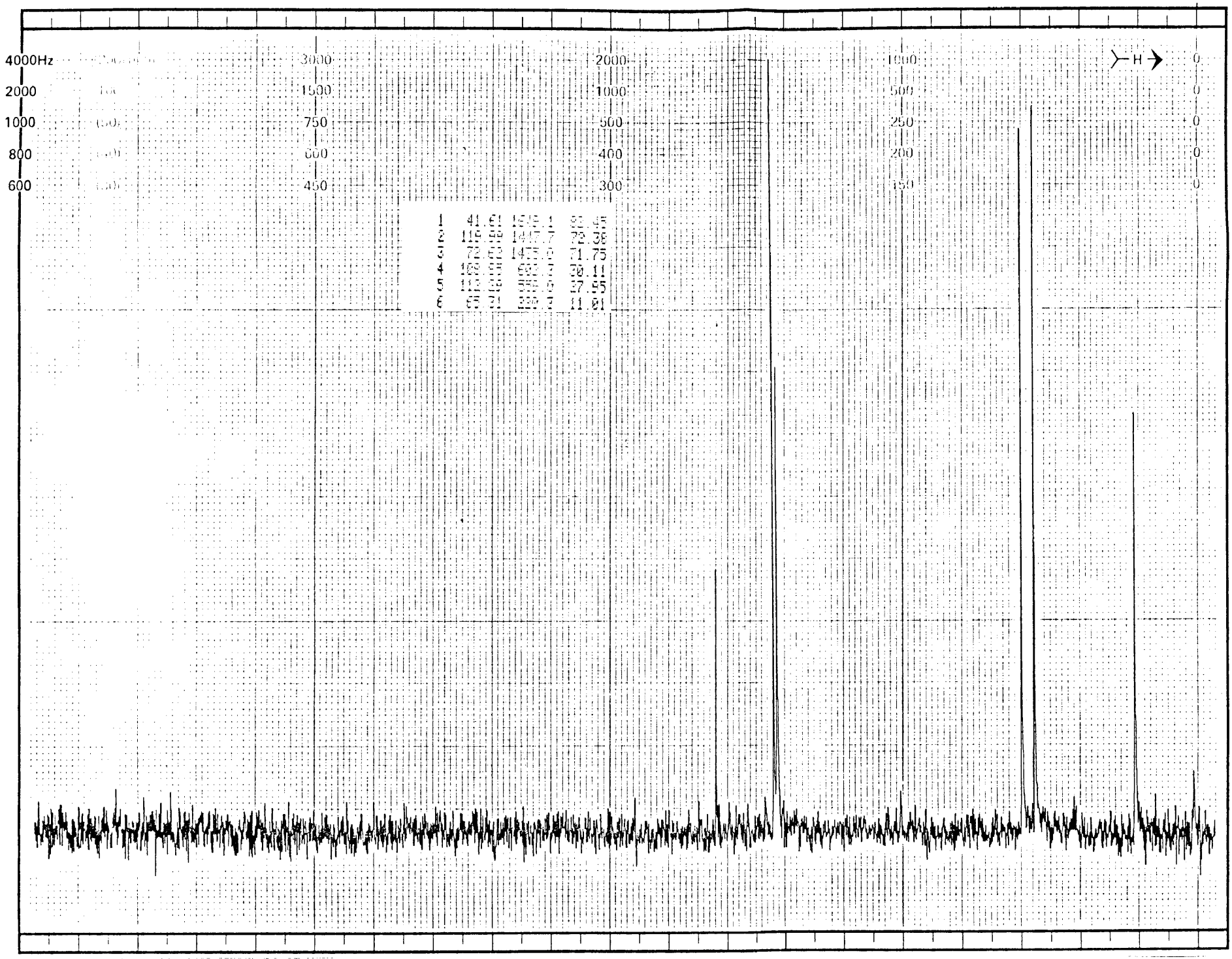


Figure A-12. ^{13}C-NMR spectrum of 5-hexyn-1-ol. Solvent: $CDCl_3$.

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