

BI(III) INITIATED CYCLIZATION REACTIONS AND IODONIUM  
FRAGMENTATION KINETICS

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A Thesis

Presented to

The Faculty of the Department of Chemistry  
The College of William and Mary in Virginia

In Partial Fulfillment

Of the Requirements for the Degree of  
Master of Science

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by

Yajing Lian

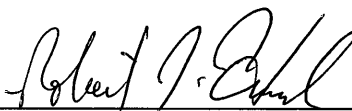
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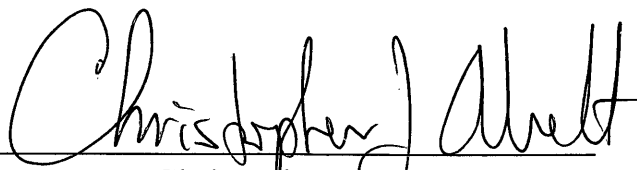
## APPROVAL SHEET


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

Chapter I: Generation of vinyl cations is facile by fragmentation of vinyl iodonium salts. We used  $^1\text{H}$  NMR spectroscopy to examine reaction rates for fragmentation reactions of (*Z*)-2-methyl-buten-1-yl(aryl)iodonium triflates (aryl=  $\text{C}_6\text{H}_5$ -, 4-( $\text{CF}_3$ ) $\text{C}_6\text{H}_4$ -, 3,5-( $\text{CF}_3$ ) $_2\text{C}_6\text{H}_3$ -) and their deuterium analogs in  $\text{CDCl}_3$ . A special salt effect and  $\alpha$ - $\text{d}_1$  and  $\beta$ -methyl- $\text{d}_3$  isotope effects were verified to exist. The mechanism involving concerted aryliodonio departure and *trans*-methyl shift leading to the secondary rather than primary vinyl cations was supported and the product distribution was also explained. The high  $\alpha$ - $\text{d}_1$  isotope effect and the inverse  $\beta$ -methyl- $\text{d}_3$  isotope effect for solvolysis of (*Z*)-2-methyl-1-butenyl (3,5-bis(trifluoromethyl) phenyl)iodonium triflate indicate that solvolysis of this particular compound may occur *via* a primary vinyl cation.

Chapter II: The title acid was isolated in 1979 and has been a popular synthetic target from then on. We recently finished a novel synthetic approach to the title acid catalyzed by  $\text{BiBr}_3$ . Bismuth(III) compounds can initiate tandem cyclization-addition reactions of  $\gamma$ -silyloxy aldehydes and ketones. For the silyl ketene acetal reactions with  $\gamma$ -silyloxy aldehydes, the diastereoselectivities range from 5:1 to 6:1 for tetrahydropyran products and *trans*-isomers are preferred. For reductive etherification reactions of  $\beta$ -keto esters containing a pendant triethylsilyl ether group, the *cis*- isomers are the major products and the diastereoselectivities are greater than 30:1. The diastereoselectivities appear to be related to the nucleophilicity of silane nucleophiles. The greater the nucleophilicity, the lower the stereoelectronic preference for axial attack.

Chapter III:  $\text{BiBr}_3$  initiated reactions of various aldehydes and vinylsilanes showed that the reactions generally provided *cis*-dihydropyrans in good yields and excellent stereoselectivities. The low *cis*- selectivities were observed only with electron rich anisaldehyde as the electrophile. On the other hand, electron poor aromatic aldehydes gave excellent yields and stereoselectivities. When vinyltrimethylsilanes are reacted with phthaldehyde, only one carbonyl group reacted. Another useful reaction related to this Prins cyclization is a reaction involving a two-step sequence catalyzed by  $\text{BiBr}_3$ . Addition of enol ethers or ketene silyl acetals to (*Z*)-4-(trimethylsilyl)but-3-enal, followed by addition of a second aldehyde results in 2,6-disubstituted dihydropyrans in good yields and excellent diastereoselectivities.

**Bi(III) Initiated Cyclization Reactions and Iodonium  
Fragmentation Kinetics**

## INTRODUCTION

Many carbon species are present in chemical reactions, such as carbanions and carbonium ions (i.e., carbocations). In Hinkle's lab, we were focused on the vinyl cations, which could be generated by fragmentation of alkenyl iodonium salts. Vinyl cations were not generally accessible until the triflate leaving group was introduced. The leaving abilities of arylidonio groups are much greater than triflate and make the generation of vinyl cations from iodonium salts more practical than from triflates. We and other groups have reported several solvolytic reactions that involve vinyl cations as intermediates using iodonium salts as precursors. An important question in vinyl cation chemistry is whether primary vinyl cations can be generated under thermal conditions, because the bridging participation of neighboring groups and the rearrangements from primary vinyl cations to more stable secondary vinyl cations can occur easily. Many tools are used as probes to detect these unstable intermediates.

Oxocarbenium ions are another type of cationic intermediates and critical for the stereoselective synthesis of cyclic ethers. These oxocarbenium ions are generated by Lewis acids initiated conditions, follow by nucleophilic attack to obtain the cyclic ethers. The conformations of oxocarbenium ions are presented as pseudoaxial chair-like intermediates and these conformations control the reaction selectivities. The anomeric effect should be accounted for in determining the geometries of products. The following thesis investigates both vinyl cationic and oxocarbenium intermediates.

# CHAPTER I

## SECONDARY ISOTOPE EFFECTS AND MECHANISM(S) OF FRAGMENTATION OF ALKENYL IODONIUM SALTS

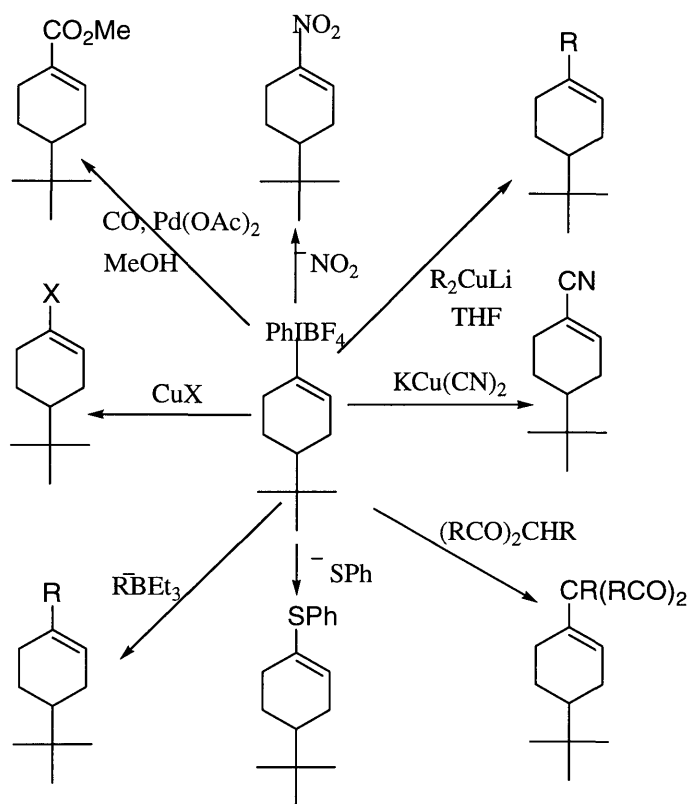
### Background for Iodonium Salts:

The organic chemistry of polyvalent iodine compounds has experienced explosive development during the last 10-15 years<sup>1</sup>. This interest in iodine compounds is mainly due to the very useful oxidizing properties of polyvalent organic iodine reagents and their environmental-friendly character as well as commercial availability. Several areas of organic polyvalent iodine chemistry have attracted significant interest and research activity. These areas include the synthetic applications of the Dess-Martin periodinane and similar oxidizing reagents based on iodine(V), the use of iodosylbenzene in the transition-metal-catalyzed biomimetic oxygenations, catalytic imidations with iodonium imides, azidations with azidoiodanes, the chemistry of benziodoxoles and benziodazoles, and synthetic and mechanistic studies as well as synthetic applications of alkynyl and alkenyl iodonium salts.

Several types of iodonium salts exist: diaryl, alkyl, dialkyl, alkyl(aryl), alkynyl(aryl), and alkenyl(aryl). In this thesis, I focus on the alkenyl(aryl) iodonium salts. Ochiai and co-workers have reported a number of the many reactions that these salts

undergo in which retention of configuration at the double bond is common (**Figure 1.1**)<sup>2</sup>.

**Figure 1.1:** Substitution reactions with alkenyl(aryl)iodonium salts

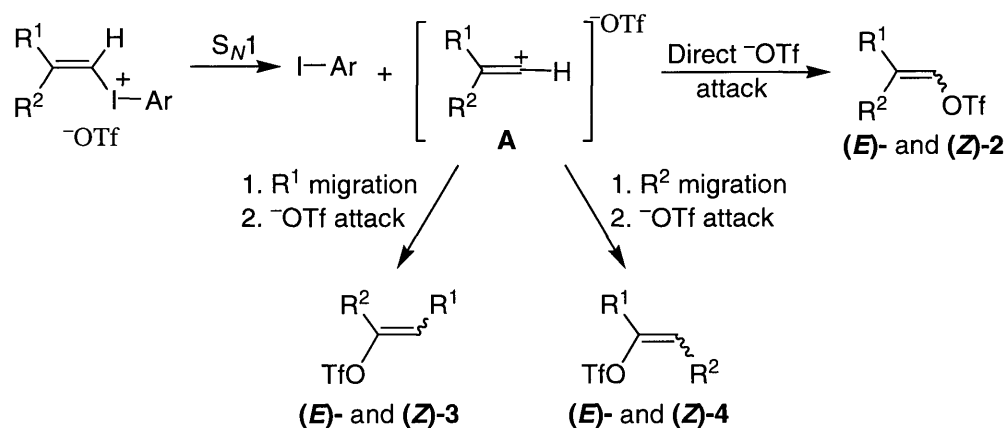


Carbocation chemistry has been explored largely through studies of solvolysis reactions of appropriate precursors. This also involves vinyl cation chemistry, and the development was greatly accelerated by the introduction of a “super” leaving group, triflate, in this field in the 1970s. However, the leaving nucleofugality of aryliodonio group is even  $10^6$  greater than triflate<sup>3</sup>. Therefore, The enormously enhanced nucleofugality of the iodonio group allowed studies of simpler, more labile vinyl cations. We focus on whether the primary vinyl cation is generated in the solvolysis of  $\beta,\beta$ -disubstituted vinyliodonium salts.

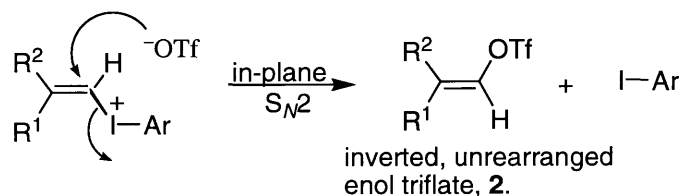
Four mechanisms have been discussed with regard to fragmentation mechanisms leading to the six enol-triflate isomers: (a)  $S_N1$  departure of the aryliodonio moiety<sup>4</sup>; (b) in-plane  $S_N2$  reaction; (c) out-of-plane  $S_N2$  reaction also termed “ligand coupling”; and (d) concerted alkyl migration and aryliodonio- nucleofuge departure. These mechanisms are shown, respectively in **Schemes 1.1-1.4**.

The Hinkle and Okuyama groups had reported rearrangement products that could have occurred by  $S_N1$  fragmentation of various iodonium salts. If a true  $S_N1$  process were occurring, it would lead to a primary vinyl cation (**A**, **Scheme 1.1**). Migration of a  $\beta$ -alkyl group would then provide a more stable secondary vinyl cation.

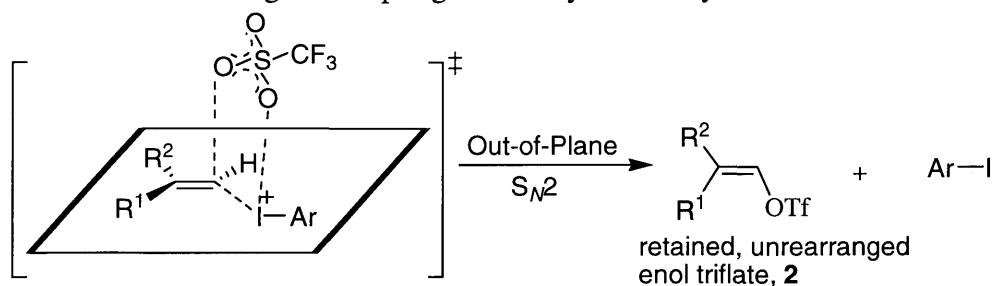
**Scheme 1.1:**  $S_N1$  departure of the aryliodonio moiety in solvolysis of vinyliodonium salts



An in-plane  $S_N2$  mechanism has been reported to proceed with weakly basic nucleophiles such as bromide ion.<sup>5</sup> This process leads to complete inversion at the  $\alpha$ -carbon and is supported by computational studies using MP2 calculations with polarized double-zeta basis sets.

**Scheme 1.2:** In-plane  $S_N2$  in solvolysis of vinyliodonium salts

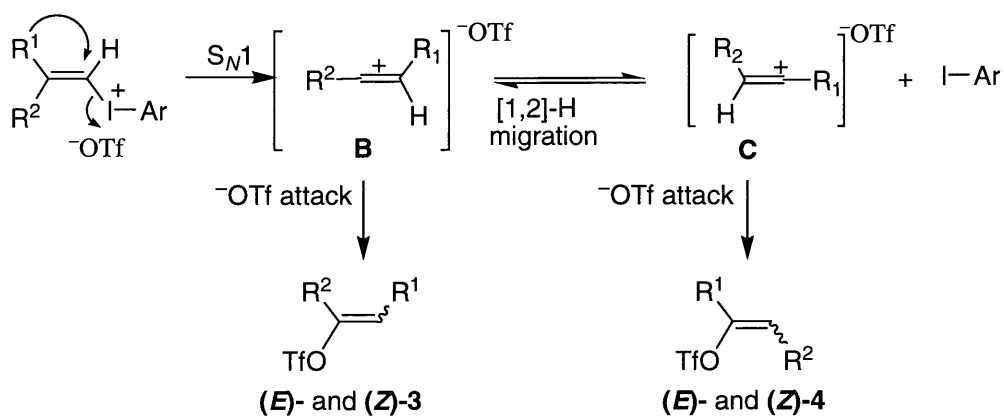
A third mechanism has been studied computationally, is possible for iodonium salts and is sometimes referred to as ligand coupling (LC).<sup>6,7</sup> The nucleophile (the triflate counter ion in the solvolysis) attacks the  $\pi^*$  orbital at the  $\alpha$ -carbon perpendicular to the plane defined by the alkene; this leads to displacement of the aryliodonio- moiety and net retention of configuration in the unrearranged product (e.g., product **2**). As was found for acetate, the triflate counter-ion likely is involved in partial coordination with the iodine, forming a  $\lambda^3$ -iodane complex<sup>6,8</sup> and reductive elimination occurs to form the retained, unrearranged enol triflate, **2**, as well as the aryl iodide byproduct.

**Scheme 1.3:** Ligand coupling in solvolysis of vinyliodonium salts

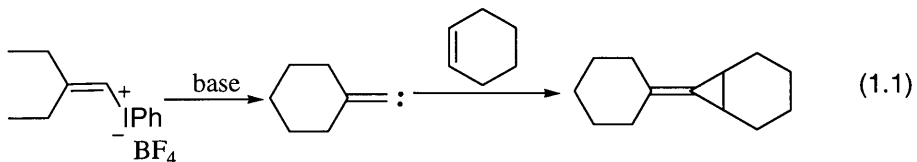
The fourth mechanism related to the  $S_N1$  process involves departure of the aryliodonio- moiety in which there is concerted migration of the *trans*-alkyl group<sup>9</sup>. The concerted migration results in the formation of a linear secondary vinyl cation (**B** or **C** in

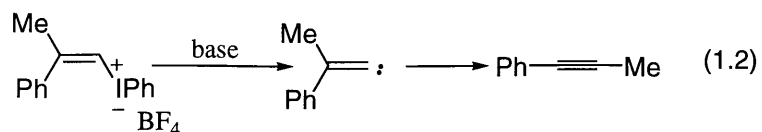
**Scheme 1.4**), that is attacked by the triflate counter ion; this results in two of the four “rearranged” triflate isomers (*(E)*- and *(Z)*-**3**). The secondary vinyl cation can also undergo a rapid [1,2] hydride shift, which provides another secondary vinyl cation; this linear cation is also attacked from both sides by triflate, resulting in two additional “rearranged” isomers.

**Scheme 1.4:** Concerted mechanism in solvolysis of vinyliodonium salts

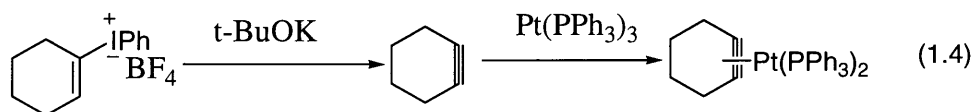
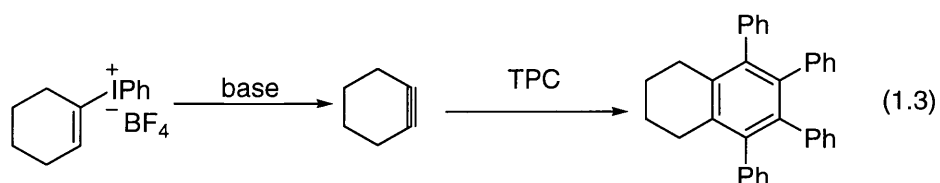


Under different conditions, several mechanisms are also proposed to explain the data. Among these mechanisms, the generation of alkylidene carbene under basic condition is an important one. With moderate bases, such as pyridine,  $\alpha$ -monosubstituted alkenyl iodonium salts generate carbenes, which can be trapped by cyclohexene<sup>9</sup> (eq **1.1**) or rearrange to form the alkyne<sup>10</sup> (eq **1.2**).





Another important intermediate in the solvolysis of alkenyl iodonium salts is the formation of cycloalkyne intermediate, which is generated by  $\beta$ -elimination from the cycloalkenyl iodonium salts under basic conditions. The cycloalkyne is unstable and can be trapped by TPC (tertaphenylcyclopentadienone),<sup>11</sup> (eq 1.3) or in the presence of  $\text{Pt}(\text{PPh}_3)_3$  in THF at 0 °C (eq 1.4).



## Background for isotope effects:

Secondary deuterium isotope effects have been used extensively in the study of solvolytic reactions.<sup>12</sup> Isotope effects are classified into primary isotope effect and secondary isotope effects. Here, we will discuss the  $\alpha$ -isotope effect and  $\beta$ -isotope effect, which are the two major components of the secondary isotope effect.

Recently, with the development of model setting technical methodology and computer applications in the quantum calculation, the field of kinetic isotope effects (*KIEs*) have recently reappeared and attracted much attention. Several points are important in the model calculations, which are listed below (Below are listed modified descriptions of isotope effect details taken from the book written by Collins and Bowman)<sup>12</sup>:

- 1) Expected at the extremes of the temperature, all factors in the equation  $\ln(HRR) = MMI \times EXC \times ZPE$  contribute to the effect significantly in the general condition. Here, *MMI* (mass, moment of inertia) term includes the products of molecular weights and moments of inertia to appropriate powers above; the *EXC* (excitation factor term) includes the product over that part of the harmonic oscillator partitions function which accounts for the population statistics of the upper levels; and the *ZPE* (zero point energy term) accounts for the difference in vibrational zero point energy between the reactants and the transition state<sup>13</sup>.
- 2) If a substantial difference in the properties between reactant and transition state,

complicated temperature dependencies are expected<sup>14</sup>.

- 3) Isotope effect studies do not appear to be appropriate for the determining the geometric structure of the transition state, especially for three dimensions.
- 4) Isotope effects are essentially caused by changes in the force constants related to motions at the position of isotopic substitution during the process from reactant to transition state.
- 5) For isotope effect calculations on large molecular systems, it is possible to omit those parts of the molecule which are far away from the position of isotopic substitution without significantly changing the calculated value of the effect.

The size of kinetic effects is directly related to the isotope mass ratio. Therefore hydrogen isotopes show the largest effects, the magnitude of  $\alpha$ - or  $\beta$ - isotope effects expressed as the ratio  $k_H/k_D$  ranges from approximately 0.95 to 1.25 per deuterium atom. All cases in which this ratio is greater than 1, which means that the deuterated substrate reacts slower than the protiated one, are called “normal” effects. Effects showing rate ratio  $k_H/k_D$  of less than 1 are called “inverse” effects. Several major points should be pointed out for the application of secondary isotope effects.

- 1) Since the “leaving degree” of the departing group has an effect on differences between the solvolytic and direct displacement mechanisms, secondary  $\alpha$ -deuterium isotope effects are believed to be a qualitative tool for distinguishing between these two mechanisms. Different leaving groups reach different degrees of bond breaking

in the transition states and give rise to different magnitudes of the effect. The better leaving groups, the bigger value of  $\alpha$ -isotope effect<sup>15</sup>.

- 2) Secondary  $\beta$ -isotope effects are associated with hyperconjugation involving the interaction of the empty  $p$ -orbital at the cationic ion center and the adjacent carbon-hydrogen (deuterium)  $\sigma$ -bond. Usually,  $\beta$ -effects range from 10 to 20 % per deuterium atom, but are not exactly cumulative<sup>16</sup>. Another aspect is the inductive effect, which is very small and opposite direction compared to the hyperconjugation.
- 3) The inverse  $\beta$ -isotope effect may be ascribed to the effectively shorter length of the carbon-deuterium bond relative to the carbon-hydrogen bond. This indicates that secondary effects might be due to the steric effect in origin. In another aspect, that deuterium is more electropositive than hydrogen, leading to a view that some isotope effects may be due to an inductive effect. Finally, that  $\text{CD}_3$  is less delocalized than  $\text{CH}_3$ , leading to a view in terms of hyperconjugative effects<sup>17</sup>.
- 4) The fact that electronic factors play an important role is shown by methyl substitution in the  $\alpha$ - and  $\beta$ - position. The driving force for participation is greatly decreased by  $\alpha$ -methyl substitution, but increased by  $\beta$ -substituent. In other words, the  $\beta$ -substituent can participate in the transition state in the case that there is no  $\alpha$ -substituent at the carbon with leaving group.
- 5) If in an anchimerically assisted reaction, the participating group G changes to a group G1 which has the property of increasing the stability of the intermediate, the partial bond formation in the transition state between G1 and the reacting carbon will occur

at a greater distance than will be the case with G. The corresponding activated complex will be more reactant-like (Hammond), but G1 will not therefore bear less charge than G. In other words, charge delocalization can occur simultaneously or closely follow the ionization step, but bridging might lag behind<sup>18</sup>.

- 6) Bridging can reduce the usual magnitude of both  $\alpha$ - and  $\beta$ - secondary (the  $\beta$ - secondary effect of the no bridging group attached to the  $\beta$ - carbon) deuterium isotope effect, and both  $\alpha$ - and  $\beta$ - effects will disappear if bridging is very advanced in the reaction transition state. However, if the participation group is the  $\beta$ - secondary deuterium isotope effect (the  $\beta$ - secondary effect of the bridging group attached to the  $\beta$ - carbon) accounted for, the  $\beta$ - effect will increase.

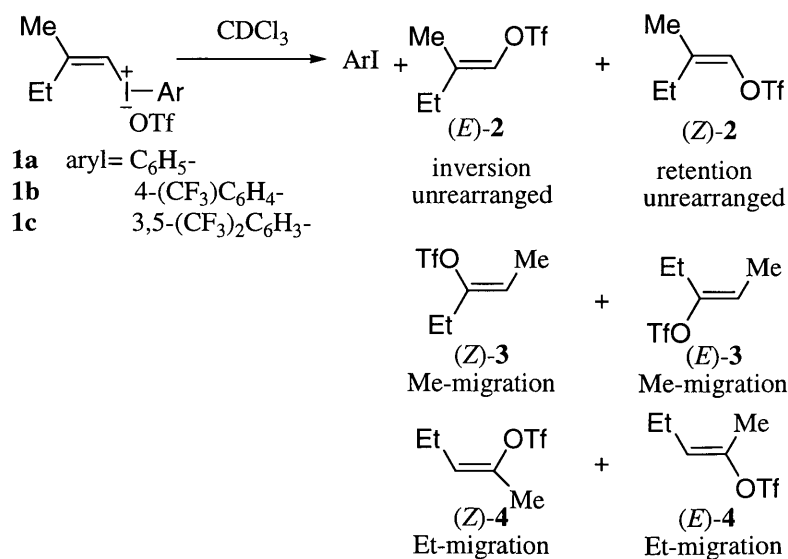
If the distance between the leaving group and the reacting center in the transition state is larger than a critical value, the  $\alpha$ - effects are practically the same for all compounds having the same leaving group, regardless of the structure and nucleophilicity of solvent. In the case of neighboring group participation, a reversal of this phenomenon should be observed. Thus, if neighboring factors cause a reduction of the  $\alpha$ - effect, the participation must be advanced enough so that the distance between the neighboring group and the reacting center is less than a critical value<sup>19</sup>.

## Solvolysis of (*Z*)-2-methylbuten-1-yl(aryl)iodonium triflates:

Secondary deuterium isotope effects have been used as an effective tool in organic mechanistic analysis.<sup>12</sup> Our interest was in the study of solvolysis of iodonium salts. If this solvolysis generates vinyl cations in the solution then  $\alpha,\beta$  deuterium isotope effects should be observed. In previous work,<sup>20</sup> the solvolysis of (*Z*)-2-methylbuten-1-yl(aryl)iodonium triflates (aryl = C<sub>6</sub>H<sub>5</sub>-, 4-(CF<sub>3</sub>)C<sub>6</sub>H<sub>4</sub>-, 3,5-(CF<sub>3</sub>)<sub>2</sub>C<sub>6</sub>H<sub>3</sub>-) in CDCl<sub>3</sub> produced six enol triflate isomers and the fragmentation reaction was found to be the first order substrate in solvolysis. Several details of this reaction were still uncertain, however. Based on isotope effects, we now propose a more reasonable mechanism to explain the solvolysis of these iodonium salts. In addition,  $\alpha$ -d<sub>1</sub> and  $\beta$ -methyl-d<sub>3</sub> compounds were synthesized through the same method.<sup>21</sup>

The fragmentation products of (*Z*)-2-methylbuten-1-yl(aryl)iodonium triflates included aryl iodide and six enol triflate isomers (**Scheme 1.5**).

**Scheme 1.5:** Solvolysis of (*Z*)-2-methylbuten-1-yl(aryl)iodonium triflates in CDCl<sub>3</sub>



As previously shown, four mechanisms have been discussed with regard to fragmentation mechanisms leading to the six enol triflate isomers<sup>20</sup>: (a)  $S_N1$  departure of the aryliodonio moiety; (b) in-plane  $S_N2$  reaction; (c) out-of-plane  $S_N2$  reaction also termed “ligand coupling”; and (d) concerted alkyl migration and aryliodonio- nucleofuge departure. Only products resulting from unrearrangement could be explained by mechanisms (b) and (c), so mechanisms (a) and (d) were more plausible. Departure of the aryliodonio moiety would produce a primary vinyl cation. Due to the high energy of primary vinyl cation, the mechanism was deemed to be unlikely. Okuyama and co-workers used chiral cyclohexylidenemethyliodonium salts to argue that primary vinyl cations were not involved as an intermediate.<sup>22</sup> Their results supported mechanism (d) involving  $\beta$ -alkyl migration. This concerted mechanism (d) was also supported by our secondary isotope effect.

### Special salt effect:

Three kinds of ion-pairs are common in solution (**Figure 1.2**): (a) tight ion-pair; (b) solvent-separated ion-pair; and (c) free ions.<sup>23</sup> From **Table 1.1**, it is apparent that adding salts increase the solvolytic rate. Generally, the reaction rate of tight ion pair is not affected by presence of additional salts, so the tight ion-pair seemed impossible as an intermediate in solution. Since addition of tetrabutylammonium trifluoromethane sulfonate which participated in the reaction increases the reaction rate, it can be concluded that common ion effect did not occur, otherwise, the equilibrium would shift to

left and inhibit the dissociation into free ions and the subsequent fragmentation. Now, it seems clear that solvent-separated ion-pair was the main species in  $\text{CDCl}_3$ . This salt effect of increasing reaction rate was actually called “special salt effect”. Different salts affected the reaction rate differently, possibly due to their different abilities to solvate the iodonium salts.

**Table 1.1:** Salt effects in solvolysis of (Z)-2-methylbuten-1-yl(4-trifluoromethyl-phenyl)iodonium triflate, **1b** in  $\text{CDCl}_3$  at 55 °C

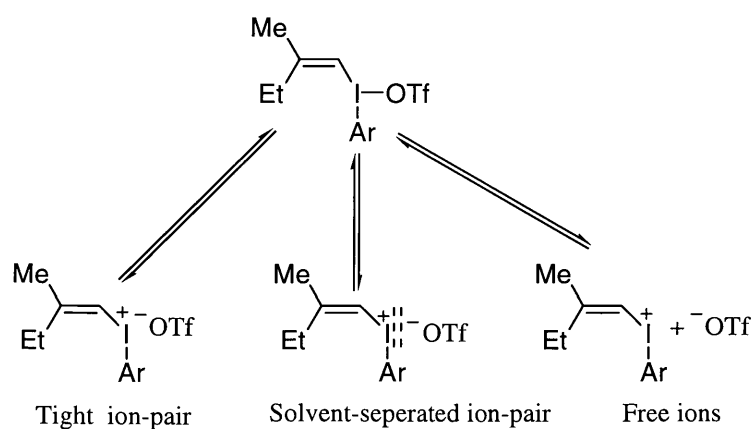
rate constants( $\times 10^5$ ) <sup>a</sup>	additional salts		
	$\text{Bu}_4\text{NOTf}$	$\text{Bu}_4\text{NBF}_4$	$\text{Bu}_4\text{NPF}_6$
$k_s$ <sup>b</sup>	$8.06 \pm 0.39$	$12.5 \pm 0.79$	$10.3 \pm 1.1$
$(k_s/k_H)$ <sup>c</sup>	$1.22 \pm 0.10$	$1.89 \pm 0.17$	$1.56 \pm 0.19$

<sup>a</sup> additional salt is 1.0 equivalent to iodonium salts.

<sup>b</sup> rate constants determined in presence of salt listed

<sup>c</sup> ratio of rate constant in presence of salt vs. rate constant in absence of salt

**Figure 1.2:** Three kinds of ion pairs in solution



## Isotope effects:

**Table 1.2:** Rates and isotope effects in solvolysis of (Z)-2-methylbuten-1-yl(aryl) iodonium triflates and their deuterium compounds in CDCl<sub>3</sub> at different temperatures.

		Temp. (°C)			
		60 °C	55 °C	50 °C	40 °C
<b>k × 10<sup>5</sup> Sec<sup>-1</sup></b>					
<b>Reagents</b>					
	H	2.79±0.24			
	D	2.12±0.14			
	K <sub>H</sub> /K <sub>D</sub>	1.32±0.14			
	H	2.79±0.24			
	D	2.29±0.19			
	K <sub>H<sub>3</sub></sub> /K <sub>D<sub>3</sub></sub>	1.22±0.14			
	H	12.7±0.77	6.61±0.45	2.95±0.27	
	D	8.94±0.87	4.78±0.27	2.35±0.21	
	K <sub>H</sub> /K <sub>D</sub>	1.42±0.16	1.38±0.12	1.26±0.16	
	H	12.7±0.77	6.61±0.45	2.95±0.27	
	D	11.0±0.36	6.31±0.51	2.74±0.05	
	K <sub>H<sub>3</sub></sub> /K <sub>D<sub>3</sub></sub>	1.15±0.08	1.07±0.11	1.08±0.10	
	H	70.0±4.2		15.0±1.3	2.48±0.22
	D	46.4±4.4		8.37±0.34	1.47±0.12
	K <sub>H</sub> /K <sub>D</sub>	1.51±0.17		1.78±0.17	1.69±0.20
	H	70.0±4.2		15.0±1.3	2.48±0.22
	D	71.7±4.2		16.5±1.0	2.69±0.04
	K <sub>H<sub>3</sub></sub> /K <sub>D<sub>3</sub></sub>	0.97±0.08		0.91±0.09	0.92±0.08

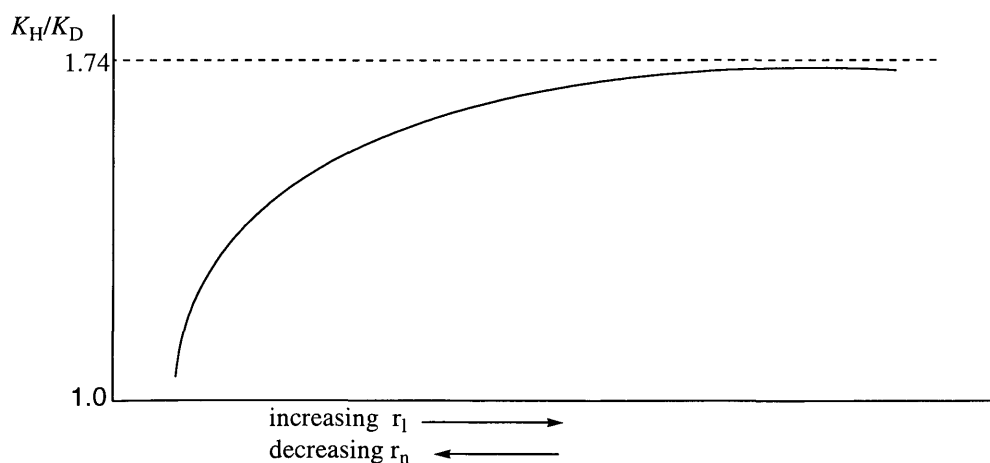
The kinetic order for this reaction is first order.

All experiments were performed at least three times. The rate constants listed are average numbers

A number of different iodonium triflates and their deuterated analogs were thermally fragmented in  $\text{CDCl}_3$  and kinetic rates were measured by  $^1\text{H}$  NMR spectroscopy. The data are listed in **Table 1.2**. Due to the largely different solvolysis rates among these compounds and the limited boiling point of  $\text{CDCl}_3$ , the fragmentation temperatures are not consistent.

From **Table 1.2**, the  $\beta$ -methyl- $\text{d}_3$  isotope effect decreased from 1.22 to 0.97 with addition of an additional  $\text{CF}_3$  group in aromatic ring; it could then be concluded that  $\beta$ -methyl group participated in the transition state, and mechanism d is supported. The fact<sup>20</sup> that (*E*) iodonium triflate isomers solvolyzed in  $\text{CDCl}_3$  more quickly than the (*Z*)-stereoisomers also supported this conclusion. Since the migratory aptitude of ethyl group is greater than that of methyl group and the participation of the larger ethyl group in the departure of leaving group would increase the fragmentation rate.

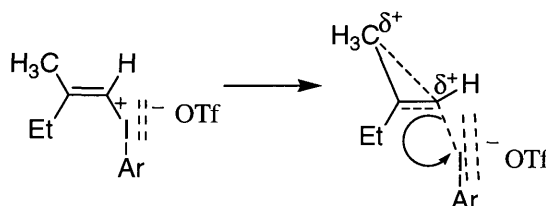
**Figure 1.3:** Possible correlation between the magnitude of  $\alpha$  isotope effects and degree of bonding in the transition state<sup>24</sup>



$r_1$  presents the distance between leaving group and the reaction center  
 $r_n$  presents the distance between neighbor participating group and the reaction center  
 estimated maximum value for secondary isotope effect is 1.74.

The y-axis represents the  $\alpha$ -deuterium isotope effect ( $K_H/K_D$ ) as it reaches a maximum value of 1.74. This value is attained when the distance between the leaving group and carbon to which it is bonded is large. At the same time, the distance between the migrating group and cationic carbon is also large. Therefore, no anchimeric assistance is involved. For the data obtained from fragmentations, only the bis(trifluoromethyl)phenyl iodonium salt, **1c**, approaches this maximum value and neighboring group participation is likely small, or even absent. For the other two salts with phenyl and 4-trifluoromethylphenyl groups (**1a** and **1b**, respectively), more anchimeric assistance is indicated by their lower  $k_H/k_D$  values. **Figure 1.4** shows the progress to the transition state.

**Figure 1.4:** Concerted process in the solvolysis of (*Z*)-2-methylbuten-1-yl(aryl) iodonium triflates

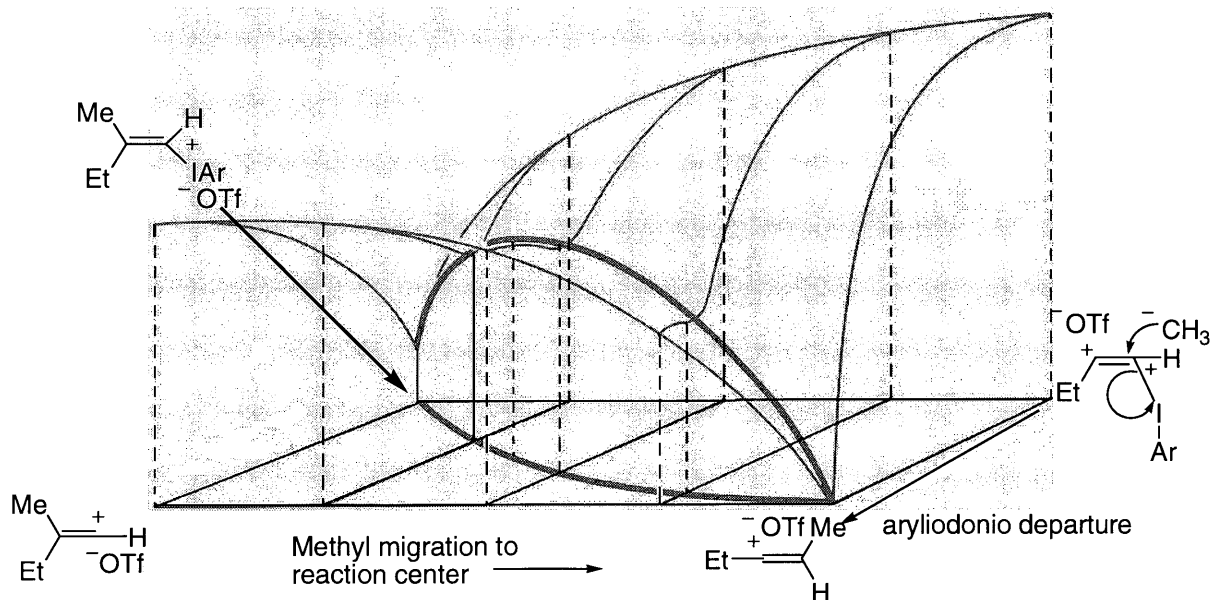


We had earlier reported that increasing the electron withdrawing nature of the aromatic ring (i.e., additional  $\text{CF}_3$  groups) would significantly increase the rates of fragmentation.<sup>20</sup> For this experiment, the  $\alpha$  isotope effect increases from 1.32 to 1.51 at  $60^\circ\text{C}$  with the increasing leaving ability of the aryl iodonio group. However, the  $\beta$ -methyl- $\text{d}_3$  isotope effect is opposite, and decreases from 1.22 to 0.95 with increasing

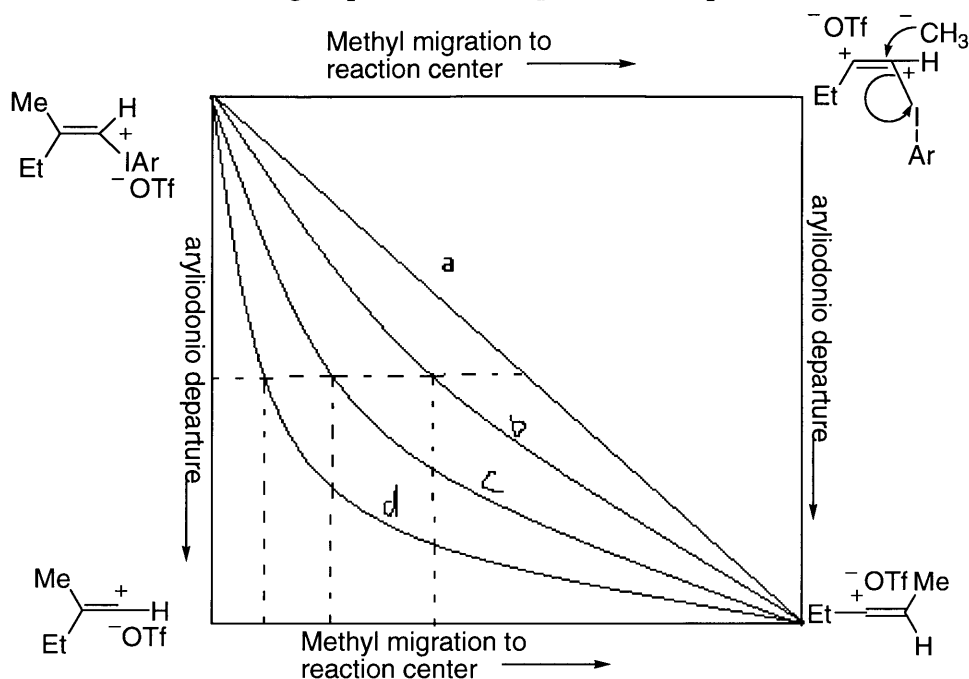
nucleofugality of the arylidonio group. This phenomenon can be explained by transition state theory.

According to transition state theory,<sup>25</sup> making the arylidonio group a better leaving group should raise the energy along the back edge of arylidonio group leaving coordinate (**Figure 1.5**). As leaving group ability increases, the transition state structure moves toward the front and toward the left of the energy surface, and the reaction coordinate projection onto the horizontal plane becomes a curved line. A better leaving group would bend this curve more strongly (**Figure 1.6**).

**Figure 1.5:** Energy surface and reaction coordinate for a hypothetical concerted process for solvolysis of iodonium salts in which energy has been raised along the back edge to simulate the effect of changing to a better leaving arylidonio group. The shape of the transition state is nearer to the left edge<sup>12</sup>.



**Figure 1.6:** Projection on the horizontal plane of the reaction coordinate for the energy surface. The new transition state coordinates correspond to a structure in which arylidonio group is still in the process of departure



Curve (a) represents synchronous process, the degree of arylidonio group departure is the same as the degree of methyl group participation in the transition state.

Curve (b) represents the reaction coordinate of salt **1a**

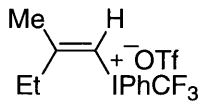
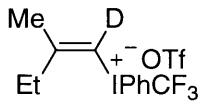
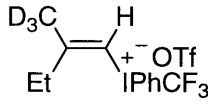
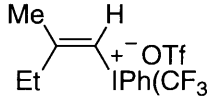
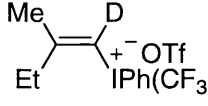
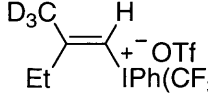
Curve (c) represents the reaction coordinate of salt **1b**

Curve (d) represents the reaction coordinate of salt **1c**

As the arylidonio group is departing, the degree of the methyl group participation decreases with the increasing leaving ability of arylidonio group. Because bridging can reduce the usual magnitude of the  $\alpha$  deuterium isotope effect,<sup>26</sup> the smaller  $\alpha$  isotope effect can be explained by a greater degree of methyl migration in the transition state. That was the reason why the  $\alpha$  isotope effect would increase from 1.32 to 1.51, as  $\text{CF}_3$  groups are added to the arylidonio moiety. For the neighboring methyl group, the effect is opposite. The greater degree of methyl group participation in the transition state will lead to the higher  $\beta$ - $\text{d}_3$  isotope effect, so the isotope effect decreases from 1.22 to

1.15 and to 0.95 in this solvolysis for CD<sub>3</sub> analogs of **1a-1c** respectively. The inverse isotope effect for compound **C** might be due to the more electron-donating ability for CD<sub>3</sub> group than CH<sub>3</sub> group.<sup>27</sup> This electron effect could help stabilize the vinyl cations by hyperconjugation and enhance the reaction rate.

**Table 1.3:** Activation parameters for salts used in this study.

	$E_a$ (Kcal/mol)	$\Delta G^\ddagger$ (Kcal/mol)	$\Delta H^\ddagger$ (Kcal/mol)	$\Delta S^\ddagger$ (Cal/mol)
	31.2	25.6	30.6	13.5
	28.6	25.8	27.9	6.3
	29.8	26.3	29.2	8.9
	34.6	24.7	34.0	28.9
	35.7	25.0	35.1	31.3
	34.1	25.3	33.5	25.5

The temperature used in calculation was the vague temperature.

Calculations show that primary vinyl cations are significantly less stable than their secondary isomers.<sup>20</sup> Participation of the neighboring methyl group in the transition state can help stabilize the intermediate vinyl cations. The efficiency of stabilization is dependent on the degree of *trans*-methyl bridging. Therefore, the activation energy for

compound **1b** should be smaller than compound **1c**. However, the participating effect for activation entropy change in transition state is inverse, the methyl participation would decrease the number of degree of rotation and vibration freedom. As a result, the more the methyl group migration contributions in the transition state, the fewer the degrees of freedom, and the  $\Delta S^\ddagger$  of compound **1b** would be smaller. These conclusions are support by the results (**Table 1.3**).

### Products distribution

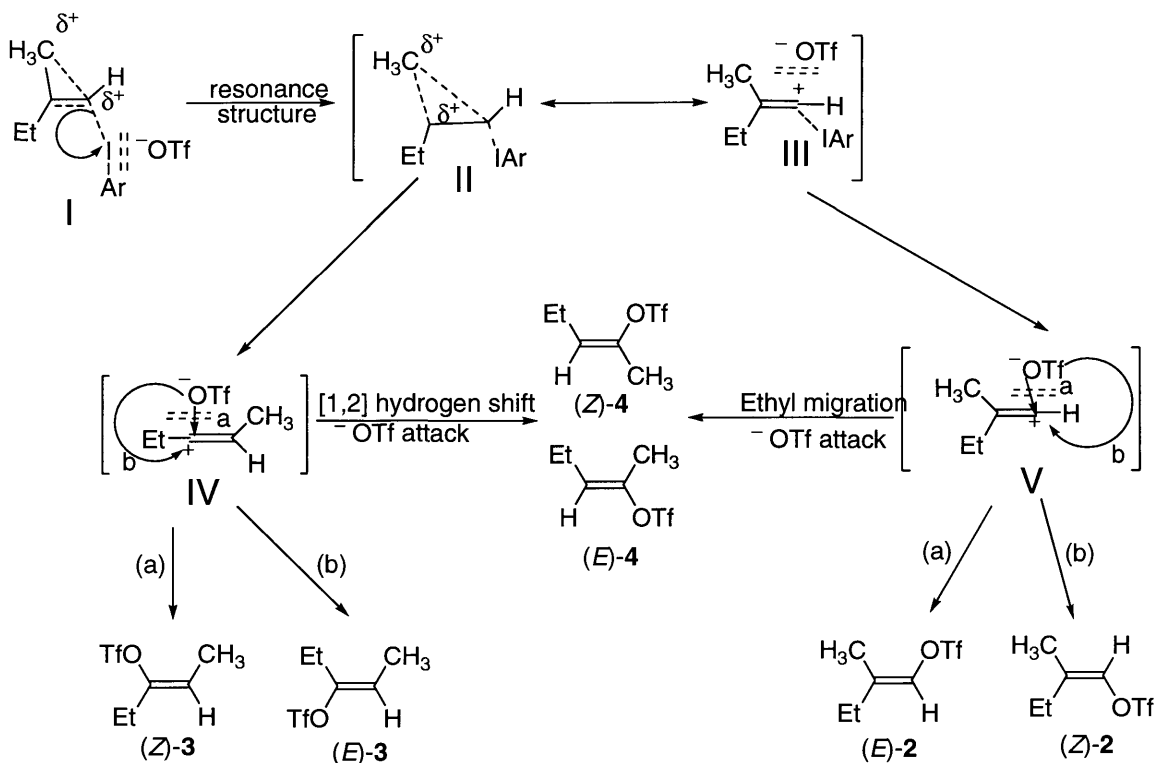
**Table 1.4:** Relative percentages of fragmentation products of (*Z*)-2-methylbuten-1-yl (aryl)iodonium triflate salts in CDCl<sub>3</sub> treated with basic alumina at 60 °C

Yield (%) enol-triflates		Iodonium salts		
		<b>1a</b>	<b>1b</b>	<b>1c</b>
unrearranged	( <i>E</i> )- <b>2</b>	34.0	21.2	9.4
	( <i>Z</i> )- <b>2</b>	7.2	4.6	3.3
	( <i>E</i> )- <b>2</b> +( <i>Z</i> )- <b>2</b>	41.2	25.8	12.7
	( <i>E</i> )- <b>2</b> / <i>(Z)</i> - <b>2</b>	4.7	4.6	2.9
Methyl migration	( <i>Z</i> )- <b>3</b>	31.5	38.7	42.1
	( <i>E</i> )- <b>3</b>	5.2	9.8	12.1
	( <i>Z</i> )- <b>3</b> +( <i>E</i> )- <b>3</b>	36.7	48.6	54.2
	( <i>Z</i> )- <b>3</b> / <i>(E)</i> - <b>3</b>	6.1	4.0	3.5
Ethyl migration	( <i>Z</i> )- <b>4</b>	17.1	17.7	23.7
	( <i>E</i> )- <b>4</b>	5.1	8.3	9.4
	( <i>Z</i> )- <b>4</b> +( <i>E</i> )- <b>4</b>	22.2	26.0	33.1
	( <i>Z</i> )- <b>4</b> / <i>(E)</i> - <b>4</b>	3.3	2.1	2.5

If the triflate anion and vinyl cations were totally free in solution, the yield of same geometrical isomers of regiochemically identical enol-triflate isomers should be the same. For example, the ratio of (*E*)-**2**/*(Z)*-**2**, (*Z*)-**3**/*(E)*-**3**, (*Z*)-**4**/*(E)*-**4**, should be around 2.5, 2.4, 2.7 (accounting for the electronic and steric effects, the ratios come from the enol triflate generations in which triflate group has no interaction with vinyl groups). But in fact, only the ratio of ethyl migration products is similar as **Table 1.4**. The ratio of unrearranged and methyl migration isomers were significantly different. The isomers, such as (*E*)-**2** and (*Z*)-**3** in which triflate groups were opposite to the original arylidonio groups were produced in higher yield than the ones (*Z*)-**2** and (*E*)-**3** in the unrearranged and methyl migration products.

Therefore, we proposed that the triflate anion and the vinyl cations should form an ion pair. They were at the same side of the double bond. The resonance theory would help to illustrate the results (**Figure 1.7**).

**Figure 1.7:** The total mechanism of solvolysis of (*Z*)-2-methylbuten-1-yl(aryl)iodonium triflates



According to the resonance theory, the transition state could be expressed in two resonance structures, II and III as **Figure 1.7** shows. Then, the two structures lead to two different vinyl cations, IV and V independently. The triflate anion has some weak interaction with the cation and is on the other side of the double bond, opposite to the original arylidonio group. Obviously, process **a** is easier than process **b** and caused the yield of product (*E*)-2 or (*Z*)-3 higher than their isomeric products (*Z*)-2 or (*E*)-3. However, the products designated as those arising from ethyl migration involve two possible rearrangement processes subsequent to the rate-determined step. The anion can attack the linear secondary vinyl cations from two directions without selectivity (**Table 1.4**).

### Primary vinyl cations:

In a previous report,<sup>20</sup> the calculated gas phase energies of several vinyl cations were described, including some primary vinyl cations. The primary vinyl cations had much higher energies than secondary vinyl cations, so it seemed that the generation of primary vinyl cations was extremely unlikely. It was very interesting that calculations showed that  $\beta,\beta$ -dimethyl-substituted primary vinyl cation provided a remarkable 24 Kcal/mol methyl stabilization energy over the monosubstituted  $\beta$ -methyl primary vinyl cation, so  $\beta,\beta$ -disubstituted primary cations seemed possible. Loddar and co-workers have reported that primary vinyl cations could be generated through photochemical process,<sup>28</sup> but no firm evidence exists for the intermediacy of primary vinyl cations under thermal conditions. In current work, the  $\alpha$  isotope effect of compound, **1c** was found to be 1.51 at 60 °C. More interesting, the effect increased to 1.78 at 50 °C. The calculated maximum secondary isotope effect is 1.74 at 25 °C, and it may be that solvolysis of compound **1c** involves a primary vinyl cation without the participation of the methyl group in the transition state. The fact that  $\beta$  methyl-d<sub>3</sub> isotope effect was inverse supports this possibility. In order to bolster this mechanism as a possibility, we plan to calculate the transition state for **1c** by using Gaussian 98w and calculate the angular value of methyl-double bond to make sure that whether methyl group could participate in the transition state.

If present in solution, resonance theory indicates that it should be possible to

capture the primary vinyl cation under thermal conditions. Unfortunately, the trapping reagent must be poorly nucleophilic to avoid promotion of the in-plane vinylic  $S_N2$  reaction and the trapping agent must react with vinyl cations quickly enough, otherwise the primary vinyl cation would rearrange to form the more stable secondary vinyl cation. Thus far, we have attempted to trap the cation with many reagents and none was successful.

## Conclusions:

We examined the fragmentation of (*Z*)-2-methylbuten-1-yl(aryl)iodonium triflates and analogous deuterated compounds in CDCl<sub>3</sub> and determined that vinyl cations were formed in solution. We used <sup>1</sup>H NMR spectroscopy to examine the reaction rate, establish the special salt effect, and measure  $\alpha$ -d<sub>1</sub> and  $\beta$ -methyl-d<sub>3</sub> isotope effects. The concerted *trans*-alkyl migration and aryliodonio- nucleofuge departure mechanism was verified by the result. First, CDCl<sub>3</sub> solvent molecules penetrated into iodonium salts to form the solvent-separated ion pairs. Then, the aryliodonio group departed. At the same time, the methyl group would participate in the transition state and triflate anion would transfer to the other side to interact with positively charged carbenium ion as an ion pair. In addition, the degree of *trans*-methyl group participation is dependent on the leaving ability of the aryliodonio group. According to resonance theory, the transition state structure we propose can explain the different product yields. The activation energy and entropy changes in the transition state also support the structure.

The generation of primary vinyl cations was highly doubtful in solution, due to their high energy. The only example in which such an ion might exist is during the fragmentation of salt, **1c**. This is under continuing investigation.

## Experimental Section

**General methods:** Reactions were carried out under nitrogen atmosphere unless otherwise indicated.  $^1\text{H}$  and  $^{13}\text{C}$  NMR spectra were recorded on a Varian Mercury 400 spectrometer, and chemical shifts are reported in ppm downfield from internal TMS or residual protons in the  $\text{CDCl}_3$ . IR spectra were obtained on a Perkin-Elmer 1600 FTIR, neat on NaCl plates purchased from International Crystal Laboratories. Melting points were obtained on a MelTemp apparatus and are uncorrected. Gas chromatography separation were achieved using a GOW-MAC Series 580 gas chromatography with 12' x 0.25" OD column (60/80 Chromosorb W, 15 % SF-19).

**Materials:** Dichloromethane was distilled from  $\text{CaH}_2$ , and Fisher hexanes and ethyl ether were used as received. All reagents were used as received unless otherwise noted. 1-Butyne, tributyl tin chloride, 1,2-dibromoethane, 1-iodo-3, 5-bis(trifluoromethyl)benzene and tetrabutylammonium trifluoromethanesulfonate were purchased from Aldrich Chemical Co. Iodobenzene diacetate, aluminum oxide (basic, 150 mesh), 4-iodobenzotrifluoride, trimethylsilyl cyanide, tetrabutylammonium tetrafluoroborate and tetrabutylammonium hexafluorophosphate were purchased from Acros division of Fisher Scientific. 2-Methyl-d<sub>3</sub>-1-butyne was bought from CDN Isotopes INC

**Kinetic Procedures:** Chloroform-d was filtered through a short plug of basic aluminum

oxide to remove any acidic impurities and then placed in a NMR tube. 1,2-dibromoethane (2  $\mu$ L) was added as an internal standard. The variable temperature probe on the 400MHz NMR was set to the appropriate temperature and the chloroform-d was allowed to equilibrate to the probe temperature. Then the alkenyl(aryl)iodonium triflate (ca. 15 mg) was added into the NMR tube and the timing begun. Spectra were obtained at timed intervals through at least one half-life. Integration was used to determine the concentrations of each species at time t.

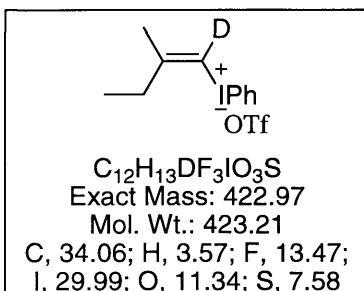
The rate constants ( $k$ ) were determined from the slope of the first-order rate law point:  $\ln[A]_t$  vs time. The concentration at time t ( $[A]_t$ ) was determined by the relative integration of the leaving iodonium salts to that of the internal standard. The time was considered to be the halfway through the pulse sequence for each spectrum. Any rate constants taken from plots with  $R^2$  value exceeding 0.9500 and a rate constant within 10% of the other values were used in determining the average rate constant at each temperature.

### **General Procedure for the Preparation of Alkenyl(aryl)-iodonium Triflates:**

Cyano(aryl)iodonium triflate (0.23 g) was weighed into a 25 mL round-bottom flask equipped with a stir bar. Dichloromethane (2 mL) was injected *via* syringe and the suspension was cooled to  $-43$  °C. Butenyl-tri-n-butylstannane was added *via* syringe slowly until the solid dissolved completely. After 30 min, Et<sub>2</sub>O (1.0 ml) was injected and stirred for additional 5 min, and then 10.0 mL pre-cooled hexane was injected. The white

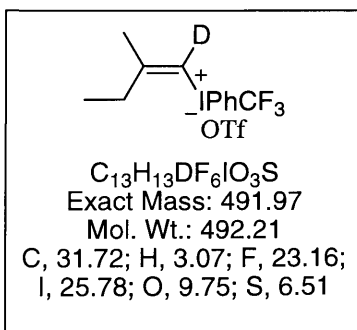
precipitate was collected by filtration and washed with 5.0 mL Et<sub>2</sub>O under nitrogen until it reached rt to provide a white powder.

### Synthesis of (Z)-2-Methyl-1-deuterio-1-Butenyl(phenyl)iodonium Triflate.



According to the general procedure, cyano(phenyl)-iodonium triflate (0.23 g, 0.60 mmol) was reacted with (Z)-2-methyl-1-deuterio-1-butenyl-tri-n-butylstannane to provide 0.215 g (85%) white powder. mp 90-92 °C.; IR (neat): 3083, 3064, 2979, 2947, 2882, 1467, 1443, 1254, 1165, 1029, 992, 900, 740, 637 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz) δ: 7.95 (d, *J* = 8.4 Hz, 2H), 7.61 (t, *J* = 7.2 Hz, 1H), 7.49 (t, *J* = 7.2 Hz, 2H), 2.51 (q, *J* = 7.2 Hz, 2H), 2.18 (s, 3H), 1.01 (t, *J* = 7.2 Hz, 3H); <sup>13</sup>C (CDCl<sub>3</sub>, 100MHz) δ: 162.1, 134.7, 132.21, 132.28, 119.8 (q, *J* = 317 Hz), 111.9, 94.6 (t, *J* = 31 Hz), 33.5, 23.1, 12.5.

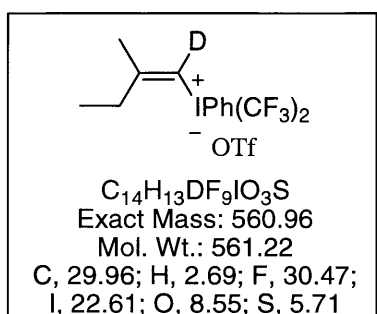
### Preparation of (Z)-2-Methyl-1-deuterio-1-Butenyl(4-trifluoromethylphenyl)-iodonium Triflate.



According to the general procedures, cyano(4-trifluoromethylphenyl) iodonium triflate (0.22 g, 0.5 mmol) was reacted with (Z)-2-methyl—deuterio-1-butenyl-tri-n-butylstannane to provide 0.183 g (74%) white powder. mp 80-82 °C; IR (neat): 3102, 3057, 2994, 2957, 2922, 1593, 1437, 1399, 1322, 1259, 1171, 1067, 1030, 1001, 897, 824, 758, 721, 637 cm<sup>-1</sup>; <sup>1</sup>H NMR

(CDCl<sub>3</sub>, 400MHz)  $\delta$ : 8.21 (d,  $J$  = 8.4 Hz, 2H), 7.69 (d,  $J$  = 8.4 Hz, 2H), 2.48 (q,  $J$  = 7.6 Hz, 2H), 2.19 (s, 3H), 1.02 (t,  $J$  = 7.6 Hz, 3H); <sup>13</sup>C (CDCl<sub>3</sub>, 100MHz)  $\delta$ : 163.0, 135.0, 133.9 (q,  $J$  = 33.4 Hz), 128.70 (d,  $J$  = 4 Hz), 124.6 (q,  $J$  = 271 Hz), 120.2 (q,  $J$  = 317 Hz), 115.7, 94.9 (t,  $J$  = 31 Hz), 33.5, 23.1, 12.4

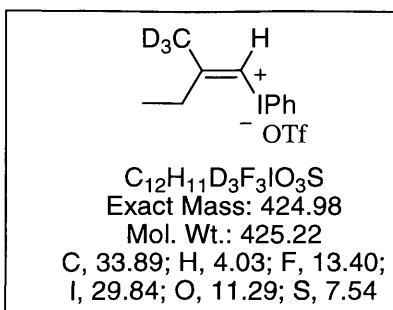
**Preparation of (Z)-2-Methyl-1-deuterio-1-Butenyl(3,5-bis(trifluoromethyl)phenyl)-iodonium Triflate.**



According to the general procedure, cyano(3,5-bis(trifluoromethyl)phenyl)iodonium triflate, (0.22 g, 0.5 mmol) was treated with (Z)-2-methyl-deuterio -1-butenyl-tri-n-butylstannane to provide 0.185 g (66%) white powder. mp 69-71 °C; IR (neat): 3088, 3042, 2979, 2950,

2888, 1464, 1436, 1344, 1276, 1143, 1109, 1084, 1030, 890, 841, 759, 687 cm<sup>-1</sup>; <sup>1</sup>H NMR (CDCl<sub>3</sub>, 400MHz)  $\delta$ : 8.47 (s, 2H), 8.04 (s, 1H), 2.51(q,  $J$  = 7.6 Hz, 2H), 2.18 (s, 3H), 1.02 (t,  $J$  = 7.6 Hz, 3H); <sup>13</sup>C (CDCl<sub>3</sub>, 100MHz)  $\delta$ : 163.0, 135.0, 133.8 (q,  $J$  = 33.4 Hz), 128.7(d,  $J$  = 3.8 Hz), 123.2 (q,  $J$  = 271 Hz), 120.2 (q,  $J$  = 317 Hz), 115.7, 94.9 (t,  $J$  = 31 Hz), 33.5, 23.1, 12.4.

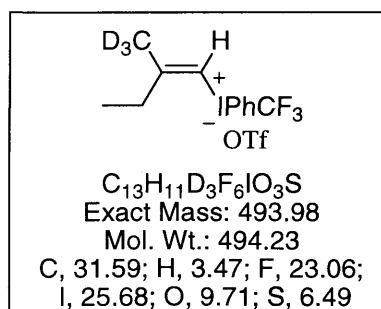
### Preparation of (Z)-2-trideuteriomethyl-1-Butenyl(phenyl)iodonium Triflate.



According to the general procedure, cyano(phenyl)iodonium triflate (0.22 g, 0.5 mmol) was reacted with (Z)-2-trideuteriomethyl-1-butenyl-*tri-n*-butylstannane to provide 0.191 g (87%) white powder. IR (neat): 3068,

2976, 2941, 2880, 1567, 1472, 1444, 1258, 1169, 1029, 991, 834, 739, 679  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 400MHz)  $\delta$ : 7.95 (d,  $J = 8.4$  Hz, 2H), 7.62 (t,  $J = 7.2$  Hz, 1H), 7.48 (t,  $J = 7.2$  Hz, 2H), 6.70 (s, 1H), 2.50 (q,  $J = 7.2$  Hz, 2H), 1.02 (t,  $J = 7.2$  Hz, 3 H);  $^{13}C$  ( $CDCl_3$ , 100MHz)  $\delta$ : 161.8, 134.5, 132.13, 132.10, 110.2 (q,  $J = 317$  Hz), 111.7, 94.8, 33.3, 12.3.

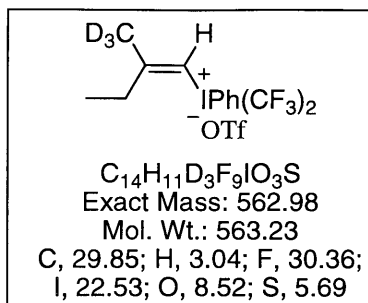
### Preparation of (Z)-2-trideuteriomethyl-1-Butenyl(4-trifluoromethylphenyl)iodonium Triflate



According to the general procedure, cyano-(4-trifluoromethylphenyl)iodonium triflate (0.22 g, 0.5 mmol) was reacted with (Z)-2-trideuteriomethyl-1-butenyl-*tri-n*-butylstannane to provide 0.165 g (65%) white powder. IR (neat): 3082, 2989, 2953, 1399, 1323,

1260, 1226, 1170, 1142, 1067, 1029, 1001, 910, 831, 720, 668, 637  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 400MHz)  $\delta$ : 8.09 (d,  $J = 8.4$  Hz, 2H), 7.67 (d,  $J = 8.4$  Hz, 2H), 6.73 (s, 1H), 2.46 (q,  $J = 7.6$  Hz, 2H), 1.00 (t,  $J = 7.6$  Hz, 3H);  $^{13}C$  ( $CDCl_3$ , 100MHz)  $\delta$ : 162.7 134.8, 133.7 (q,  $J = 33.4$  Hz), 128.5 (d,  $J = 3.8$  Hz), 123.0 (q,  $J = 271$  Hz), 120.0 (q,  $J = 318$  Hz), 115.5, 95.3, 33.4, 12.2

**Preparation of (Z)-2-trideuteriomethyl-1-Butenyl(3,5-bis(trifluoromethyl)phenyl)-iodonium Triflate.**



According to the general procedure, cyano(3,5-bis-(trifluoromethyl)phenyl)iodonium triflate (0.22 g, 0.5 mmol) was treated with (Z)-2-trideuteriomethyl-butenyl-tri-n-butylstannane to provide 0.110 g (38%) white powder. IR (neat): 3076, 2981, 2944, 1340, 1273, 1180, 1084, 1030,

891, 841, 732, 687, 637  $cm^{-1}$ ;  $^1H$  NMR ( $CDCl_3$ , 400MHz)  $\delta$ : 8.46 (s, 2H), 8.04 (s, 1H), 6.89 (s, 1H), 2.51 (q,  $J = 7.6$  Hz, 2H), 1.03 (t,  $J = 7.6$  Hz, 3H);  $^{13}C$  ( $CDCl_3$ , 100MHz)  $\delta$ : 163.1, 134.9, 134.0 (q,  $J = 34.1$  Hz), 125.6, 121.9 (q,  $J = 271$  Hz), 129.8 (q,  $J = 316$  Hz), 112.7, 96.31, 33.4, 12.2.

## REFERENCES

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- <sup>1</sup> Stang, P. J.; Zhdankin, V. V. *Chem. Rev.* **2002**, *102*, 2523-2584
- <sup>2</sup> Ochiai, M.; Sumi, K.; Takaoaka, Y.; Kunishima, M.; Nagao, Y.; Shiro, M.; Fujita, E. *Tetrahedron* **1988**, *44*, 4095-4112.
- <sup>3</sup> Okuyama, T.; Takino, T.; Sueda, T.; Ochiai, M. *J. Am. Chem. Soc.* **1995**, *117*, 3360-3367.
- <sup>4</sup> Hinkle, R. J.; McNeil, A. J.; Thomas, Q. A.; Andrews, M. N. *J. Am. Chem. Soc.* **1999**, *121*, 7437-7438.
- <sup>5</sup> Okuyama, T.; Sato, K.; Ochiai, M. "Reactions of 2,2-Dialkylvinyl Iodonium Salt with Halide Ions," *Bull. Chem. Soc. Jpn.* **2000**, *73*, 2341-2349.
- <sup>6</sup> Okuyama, T.; Yamataka. *Can. J. Chem.* **1999**, *77*, 577-583.
- <sup>7</sup> Okuyama, T.; Yamataka, H.; Ochiai, M. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2761-2769.
- <sup>8</sup> Fujita, M.; Sakanishi, Y.; Nishii, M.; Yamataka, H.; Okuyama, T. *J. Org. Chem.* **2002**, *67*, 8130-8137.
- <sup>9</sup> Fujita, M.; Sakanishi, Y.; Okuyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 9190-9191.
- <sup>10</sup> Gronheid, R.; Lodder, G.; Ochiai, M.; Sueda, T.; Okuyama, T. *J. Am. Chem. Soc.* **2001**, *123*, 8760-8765.
- <sup>11</sup> Fujita, M.; Kim, W. H.; Sakanishi, Y.; Fujiwara, K.; Hirayama, S.; Okuyama, T.; Ohki, Y.; Tatsumi, K.; Yoshioka, Y.; *J. Am. Chem. Soc.* **2004**, *126*, 7548-7558.

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- <sup>12</sup> For review see: C. J. Collins and N. S. Bowman, Ed., "Isotopes Effects in Chemical Reactions" Van Norstrand Reinhold Co. New York, N. Y. **1970**.
- <sup>13</sup> Wolfsberg, M.; Stern, M. J. *Pure Appl. Chem.* **1964**, 8, 225.
- <sup>14</sup> (a) Stern, M. J.; Spindel, M.; Monse, E.U. *J.Chem. Phys.* **1968**, 48, 2908. (b) Monse, E. U.; Spindel, M.; Stern, M. J. *Advan. Chem. Ser.* **1969**, 89, 148. (c) Huang, T. T.; Kass, W. J.; Buddenbaum, W. E.; Pankwich, P. E. *J. Phys. Chem.* **1968**, 72, 4431.
- <sup>15</sup> Streitwieser, A. J.; jagow, R. H.; Fahey, R.C.; Suzuki, S. *J. Am. Chem. Soc.* **1958**, 76, 2326.
- <sup>16</sup> (a) Shiner, V. J.; Humphrey, J. S. *J. Am. Chem. Soc.* **1963**, 85, 2416. (b) Shiner, V. J.; Murr, B. L.; Heinemann *J. Am. Chem. Soc.* **1963**, 85, 2413.
- <sup>17</sup> (a) Thornton, E. R. *Ann. Rev. Phys. Chem.* **1966**, 17, 349. (b) Stern, M. J.; Wolfsberg, M. J. *Pharm. Sci.* **1965**, 54, 849. (c) Weston, R. E. *Science*, **1967**, 158, 332.
- <sup>18</sup> (a) Streitser, A.; *Solvolytic Displacement Reactions*, Mcgraw-Hill Co. New York **1962**, pp. 174-175. (b) Winstein, S. *J. Am. Chem. Soc.* **1965**, 87, 381.
- <sup>19</sup> Shiner, V. J.; Rapp, M. W.; haleiv, E. A. Wolfsberg, M. *J. Am. Chem. Soc.* **1970**, 90, 7171.
- <sup>20</sup> (a) Hinkle, R. J.; McNeil, A. J.; Thomas, Q. A. and Andrews M. N. *J. Am. Chem. Soc.* **1999**, 121, 7437-7438. (b) Hinkle, R. J.; Mikowski, A. M. *ARKIVOC* **2003**, 201-212. (c) McNeil, A. J.; Hinkle, R. J.; Rouse, E. A.; Thomas, Q. A.; Thomas, D. B. *J. Org. Chem.* **2001**, 66, 5556-5565.

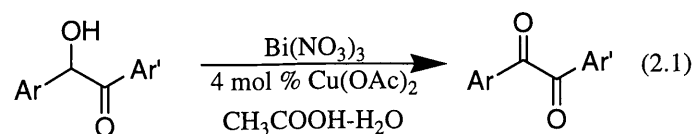
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- <sup>21</sup> Zhdankin, V. V.; Scheuller, M. C.; Stang, P. J. *Tetrahedron Lett.* **1993**, *34*, 6853-6856;  
Hinkle, R. J.; Stang, P. J. *Synthesis* **1994**, 313-316.
- <sup>22</sup> Fujita, M; Sakanishi, Y.; Nishii, M.; Okuyama, T. *J. Org. Chem.* **2002**, *67*, 8138-8146
- <sup>23</sup> Review: Szwarc, M. Ed. “*Ions and Ion pairs in Organic Reactions*”; Wiley, New York,  
Vol. 1 **1972**.
- <sup>24</sup> Bigeleisen, J.; Wolfsberg, M. *Adv. Chem. Phys.* **1958**, *1*, 2326
- <sup>25</sup> (a) Thornton, E. R. *J. Am. Chem. Soc.* **1967**, *89*, 2915; (b) More O’Ferrall, R. A. *J. Chem. Soc. B* **1970**, 274; (c) Jencks, W. P. *Chem. Rev.* **1972**, *72*, 705
- <sup>26</sup> Creary, X. *J. Org. Chem.* **1976**, *41*, 3740-3743.
- <sup>27</sup> Stang, P. J.; Dueber, T. E. *J. Am. Chem. Soc.* **1973**, *95*, 2686-2687.
- <sup>28</sup> Fujita, M; Sakanishi, Y.; Nishii, M.; Okuyama, T. *J. Org. Chem.* **2002**, *67*, 8138-8146.

## CHAPTER II

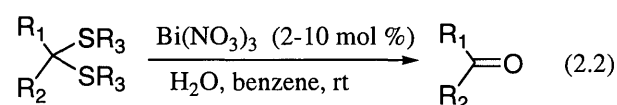
**BiBr<sub>3</sub> INITIATED CYCLIZATION-ADDITION REACTIONS:  
EFFECT OF Π-NUCLEOPHILE ON OXOCARBENIUM ION  
ADDITION AND TOTAL SYNTHESSES OF  
(+)-(S,S)-(cis-6-METHYLTETRAHYDROPYRAN-2-YL)ACETIC  
ACID AND ITS *trans*-DIASTEREOMER**

## Background of Bismuth(III):

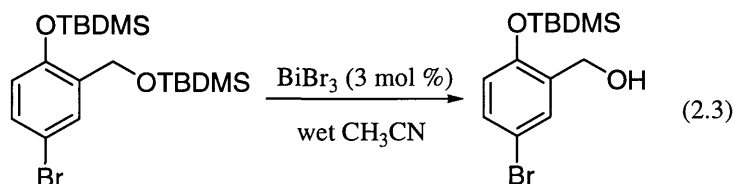
Bismuth is the 83<sup>rd</sup> element in the periodic table and is the heaviest stable element. Although bismuth is a relatively rare element, many bismuth(III) compounds are commercially available and are relatively inexpensive. In contrast to other heavy metal counterparts, bismuth is non-toxic and non-carcinogenic. Other advantages of bismuth compounds include their ability to tolerate small amounts of moisture and consequently their ease of handling. Furthermore, compared to other strong Lewis acids used at low temperature, bismuth(III) catalyzed reactions are run at room temperature. Therefore, bismuth(III) compounds have recently become intensively used in organic synthesis<sup>1</sup>, especially in industry. In the presence of Cu(OAc)<sub>2</sub>, Bi(NO<sub>3</sub>)<sub>3</sub> is a powerful oxidant and can be used to convert secondary alcohols into ketones<sup>2</sup> (eq 2.1).



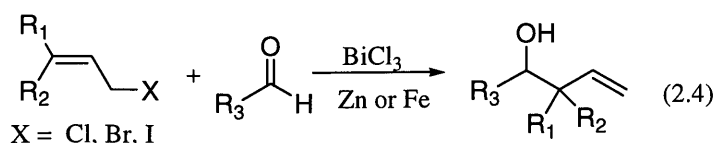
Bismuth(III) compounds have also been studied as effective catalysts or initiators in organic synthesis<sup>3</sup>, and several important applications have been developed. Bi(III) salts can also be used for removal of common protecting groups, such as *S,S*-acetals<sup>4</sup> (eq 2.2). Most common methods for this deprotection require other toxic heavy metals, such as mercury(II) and an oxidizing reagent. Therefore, the use of air-stable and non-toxic bismuth salts offers significant improvements.



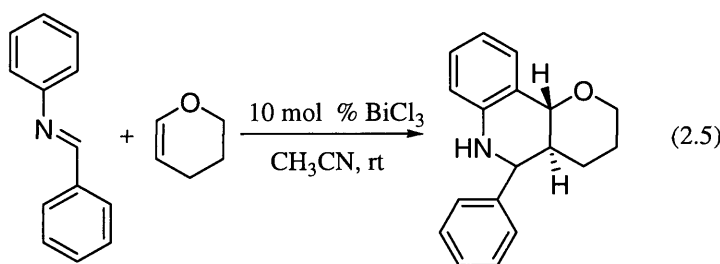
Another example is selective cleavage of alkyl TBDMS groups in the presence of aryl TBDMS groups in wet CH<sub>3</sub>CN using BiBr<sub>3</sub> as a catalyst<sup>5</sup> (eq 2.3). It should be mentioned that TBDMS groups are not affected by BiCl<sub>3</sub> or Bi(CF<sub>3</sub>COO)<sub>3</sub> in methanol. Thus, it is clear that solvent plays an important part in determining selectivity.



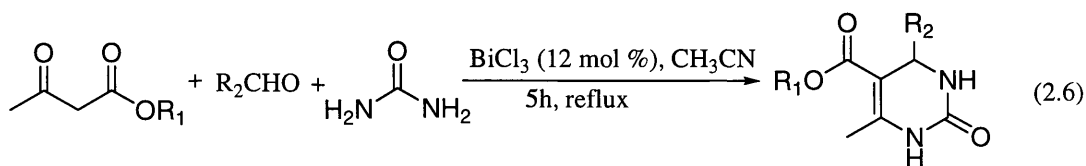
Bismuth triflate has recently been reported to be an efficient catalyst for Friedel-Crafts acylation of a variety of substituted benzenes<sup>6</sup>. Bi(III) salts also have important applications in additions of allyl groups to carbonyl groups<sup>7</sup> (eq 2.4) and aldol condensations<sup>8</sup>. The allylation of aldehydes initiated by Bi(III) and active metals proceeds under mild conditions to afford the corresponding homoallylic alcohols in good yields. This reaction is specific for aldehydes and does not occur with carboxylic acids, nitriles and esters.



Diels-Alder and the aza-Diels-Alder reactions can be catalyzed by catalytic amounts of Bi(III) salts to form cyclohexenes as well as heterocycles. The reactions have many applications in natural product synthesis. For instance, reactions of *N*-aryl aldimines with nucleophilic olefins afford the quoline derivatives in high yields<sup>9</sup> (eq 2.5).



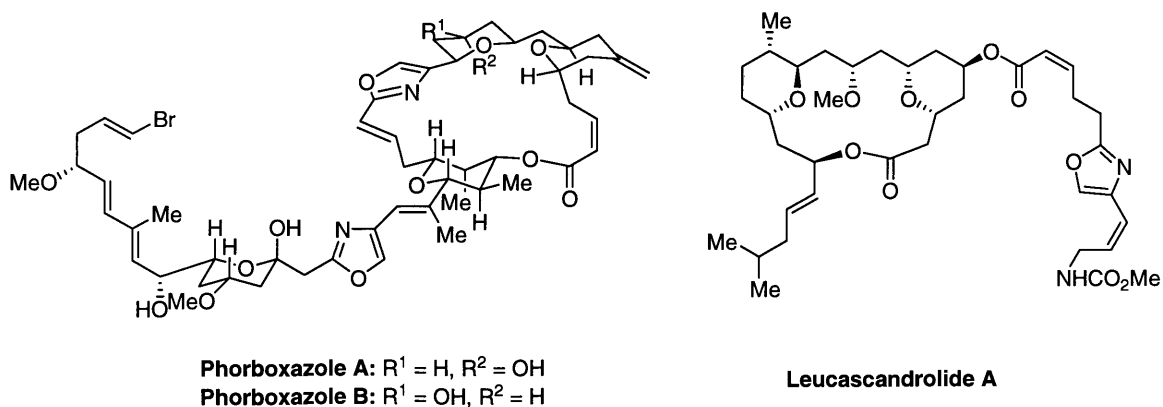
Carbon-heteroatom bond forming reactions occur efficiently with Bi(III) catalyst. The types of C-X bonds formed include bonds between carbon and nitrogen, carbon and oxygen, carbon and sulfonate, as well as carbon and halogen. For example, BiCl<sub>3</sub> has been found to be an attractive catalyst for the Biginelli reaction<sup>10</sup> (eq 2.6). Dihydropyrimidiones have attracted recent attention due to their interesting biological properties. The classic method for their synthesis is Biginelli condensation reaction which usually results in poor to low yield. However, using BiCl<sub>3</sub> as a catalyst, the yield increases to 80-95 %.



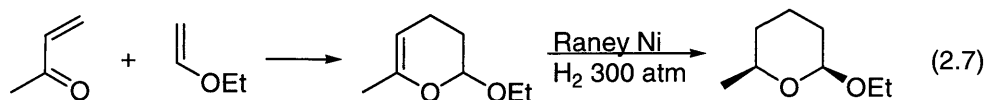
## Background for tetrahydropyrans:

In 1979, Bruno Maurer, Alfred Grieder, and Walter Thommen successfully isolated and synthesized a small cyclic carboxylic acid, (+)-(*S,S*)-(cis-6-methyltetrahydro-pyran-2-yl)acetic acid, from the glandular secretion of the civet cat<sup>11</sup> (*Viverra civetta*). This natural product is a disubstituted, six-membered cyclic ether with stereocenters at the 2- and 6- positions and has been used as a model compound for developing methodology towards 2,6-disubstituted tetrahydropyrans. Cyclic ethers containing tetrahydropyran ring are prevalent in many natural and pharmacological products. For instance, several recently discovered antitumor, antifungal, and antimetabolic compounds contain either or both tetrahydropyran and tetrahydrofuran rings. For example, Phorboxazole<sup>12</sup> has three tetrahydropyran rings and Leucascandrolide A<sup>13</sup> contains two tetrahydropyran rings (**Figure 2.1**). Therefore, it is worthy goal to develop new synthetic methodology toward tetrahydropyran rings.

**Figure 2.1:** Natural products containing *cis*- and *trans*- cyclic ethers

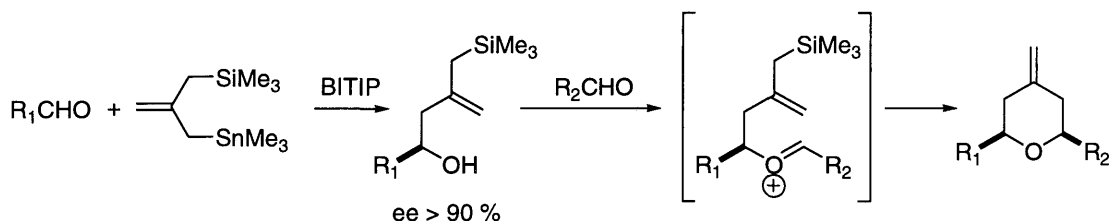


Many methods have been developed towards cyclic ethers. For example, a hetero Diels-Alder reaction followed by reduction of the resulting alkene was employed to give the required 2,6-disubstituted tetrahydropyran ring<sup>14</sup> (eq 2.7).



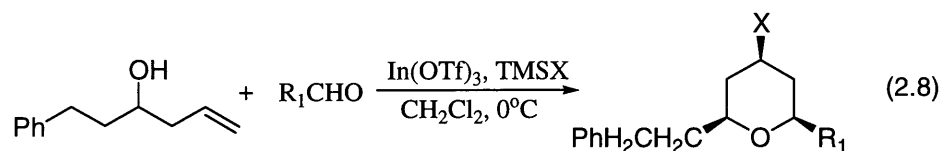
Keck showed that 2,6-*cis*-disubstituted-4-methylenetetrahydropyrans could be synthesized in three steps from commercially available starting materials<sup>15</sup> (**Scheme 2.1**). The greater reactivity of the stannane affords an allylsilane after initial Lewis acid activated allylation of the aldehydes. Subsequent addition of a second aldehyde produces an oxocarbenium ion intermediate that undergoes intramolecular allylation to generate the observed products with high diastereoselectivity. The BITIP, a BINOL titanium tetrakispropoxide catalyst, is the most suitable for the reaction of stannane with aldehydes and results in high enantioselectivity (ee > 90 %).

**Scheme 2.1:** Keck's pyran annulation process



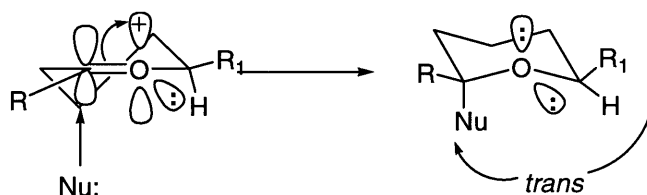
As a third example, Prins cyclizations in silyl additives with suppression of epimerization were reported by Loh<sup>16</sup> (eq 2.8). The oxocarbenium ion for Prins cyclization is generated by the nucleophilic attack of alcohol to aldehyde under Lewis

acid initiated condition. The intermediate carbocation is then trapped by halide using a trimethylsilyl halide additive.



Generally, approaching the synthesis of a disubstituted THP through nucleophilic attack of an oxocarbenium ion is desirable because it typically gives good diastereoselectivity. The Kishi group theorized that the nucleophile would preferentially attack the oxocarbenium ion from the axial direction<sup>17</sup> (**Figure 2.2**). The oxocarbenium ion in which the R<sub>1</sub> group is pseudoequatorial is more stable than when the R<sub>1</sub> group is pseudoaxial. Therefore, the transition state shown in **Figure 2.2** is the more stable one of the two possible structures. The nucleophile then attacks from the axial direction, or *trans* to the R<sub>1</sub> group. Due to the axial approach of various nucleophiles, they were able to synthesize several C-glycopyranosides with greater than 10:1 diastereoselectivity in favor of *trans*-diastereomers.

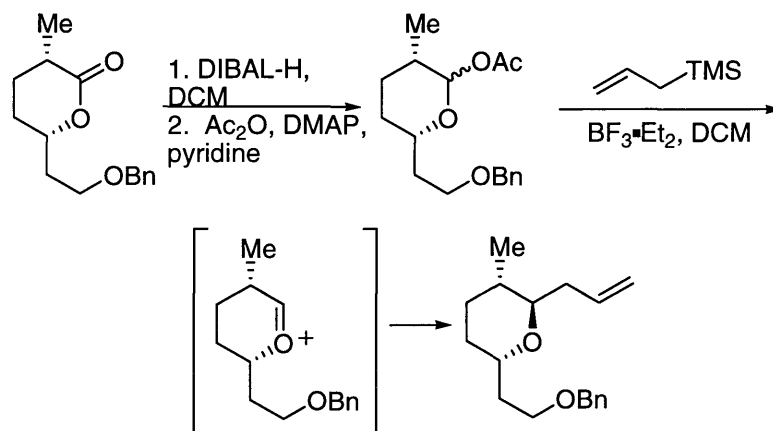
**Figure 2.2** Kishi's proposed conformation for attack of nucleophiles.



Probably the most common strategy towards the synthesis of *trans*-2,6-disubstituted THP systems is used by Kopecky and Rychnovsky. This approach

involves three steps from  $\delta$ -substituted lactone<sup>18</sup> (**Scheme 2.2**): (a) generation of lactone; (b) partial reduction and acylation of the lactol; and (c) addition of nucleophile to the oxocarbenium ion formed by Lewis acid initiated allylation.

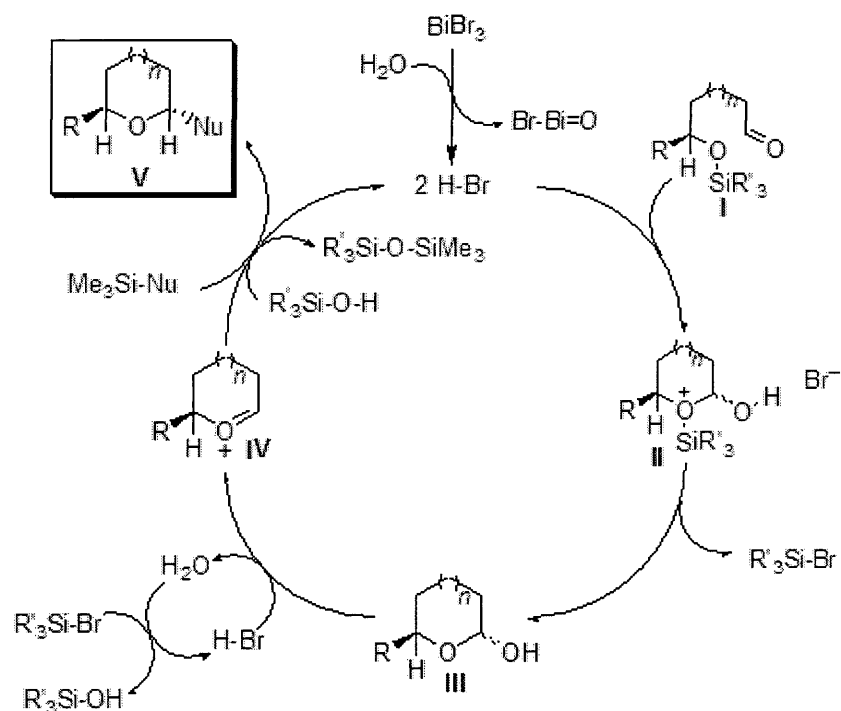
**Scheme 2.2:** Synthesis of leucasandrolide A fragment



## Reaction mechanism:

The mechanism of tandem cyclization/addition reaction was proposed by Evans *et al.*<sup>19</sup> (**Scheme 2.3** and **Figure 2.3**). Bismuth bromide in the presence of water will generate two equivalents of hydrogen bromide, which promotes the intramolecular nucleophilic attack on the aldehyde carbonyl. The lone pair on the oxygen of the trialkylsiloxy moiety will attack the electrophilic carbonyl carbon; the acidic hydrogen from the Brønsted acid will assist the formation of **II**. This intermediate is then proposed to undergo *in situ* desilylation to afford the lactol **III**. At this point, acid-catalyzed dehydroxylation of the lactol leads to the oxocarbenium ion. The oxocarbenium ion is then subject to nucleophilic attack to furnish the cyclic ether.

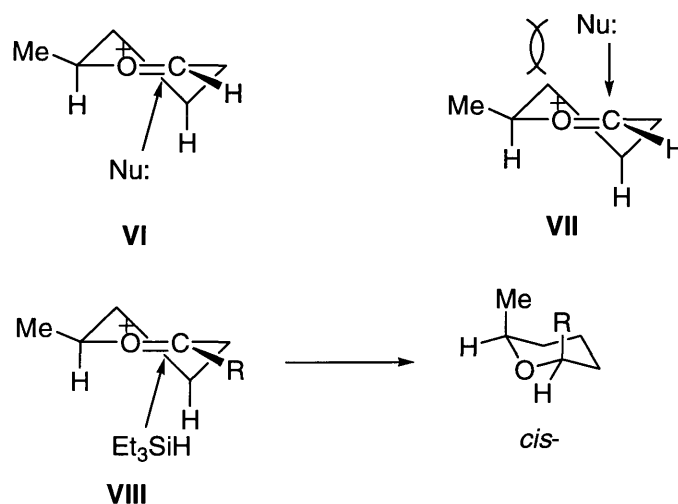
**Scheme 2.3:** Proposed Catalytic cycle for BiBr<sub>3</sub>-Induced Tandem Reaction.



The nucleophiles would attack the oxocarbenium ion from axial direction, as discussed in the Kishi theory above. Due to the interaction between the attacking nucleophile and pseudoequatorial methyl group (**Figure 2.3**), transition state **VI** is favored over transition state **VII**. Therefore, the *trans*-isomers are the major products for these tandem cyclization addition reactions. *Trans/cis* ratios of  $\geq 99:1$  were consistently obtained in this report for the THP allylation reaction<sup>19</sup>.

If triethylsilane ( $\text{Et}_3\text{SiH}$ ) is used as a nucleophile with a ketone substrate, it can be considered as a hydrogen anion and prefers to attack from the opposite direction of methyl group leading to *cis*-isomer (path **VIII**), and this is also consistent with Kishi's model for axial addition.

**Figure 2.3:** The stereoselectivity for oxocarbenium ion intermediate reaction with nucleophile

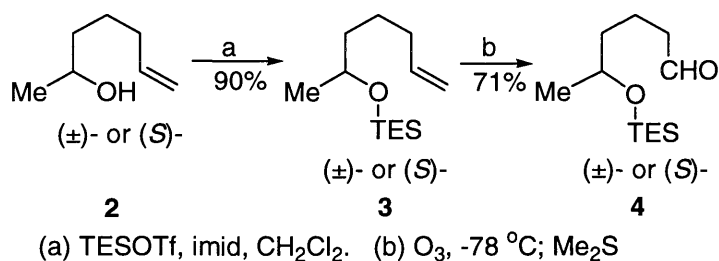


## Synthetic strategy toward “Civet acid”

### Synthesis of $\delta$ -silyloxy aldehyde, **4**

We began our synthesis toward the common intermediate, **4** by Grignard addition to propylene oxide using CuI as a catalyst, which afforded the known alcohol, **2**<sup>20</sup> with high regioselectivity (**Scheme 2.4**). The hydroxyl moiety was protected as the triethylsilylether, **3**, and was ozonolyzed subsequently to provide the desired key compound,  $\gamma$ -silyloxy aldehyde, **4** in good yield.

**Scheme 2.4.** Synthesis of aldehyde intermediates in the construction of an acid component of Civet Cat secretion.

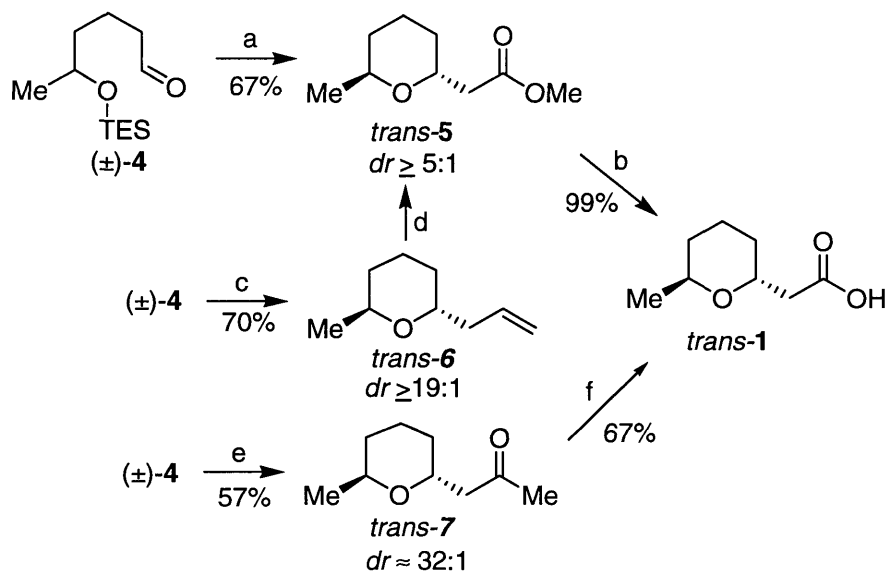


We were first concerned with the synthesis of the *trans*-diastereomer *via* three different BiBr<sub>3</sub> initiated tandem cyclization/addition reactions (**Scheme 2.5**). The first approach involved addition of CH<sub>2</sub>=C(OTMS)OMe to an intermediate oxocarbenium ion. This extension of the allylation methodology<sup>19</sup> to include a ketene silyl acetal as a nucleophile resulted in the desired cyclization/addition product, *trans*-**5**, with *dr* = 5-6/1. The selectivity was low, compared to the high diastereoselectivity for allylation. We first hypothesized that the low selectivity was due to the equilibration of the product from

*trans*- isomer to more stable *cis*- isomer under weak Lewis acid condition (**Scheme 2.6**).

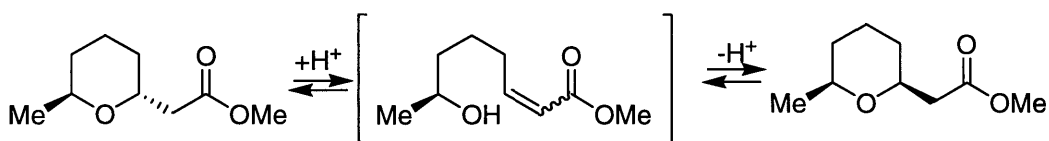
Therefore, two attempts were made to confirm our hypothesis. Conducting the reaction

**Scheme 2.5.** Conversion of aldehyde **4** to intermediates to (*trans*-6-methyltetrahydropyran-2-yl)acetic acid.



(a) 15% BiBr<sub>3</sub>, CH<sub>2</sub>=C(OTMS)OMe, CH<sub>3</sub>CN. (b) NaOH, MeOH, H<sub>2</sub>O. (c) BiBr<sub>3</sub>, H<sub>2</sub>C=CHCH<sub>2</sub>-TMS, CH<sub>3</sub>CN. (d) O<sub>3</sub>, NaOCH<sub>3</sub>, CH<sub>3</sub>OH; Me<sub>2</sub>S. (e) BiBr<sub>3</sub>, CH<sub>2</sub>=C(OTMS)CH<sub>3</sub>, CH<sub>3</sub>CN. (f) NaOBr, dioxane/H<sub>2</sub>O.

**Scheme 2.6.** Possible *trans*- to *cis*- equilibration pathway.



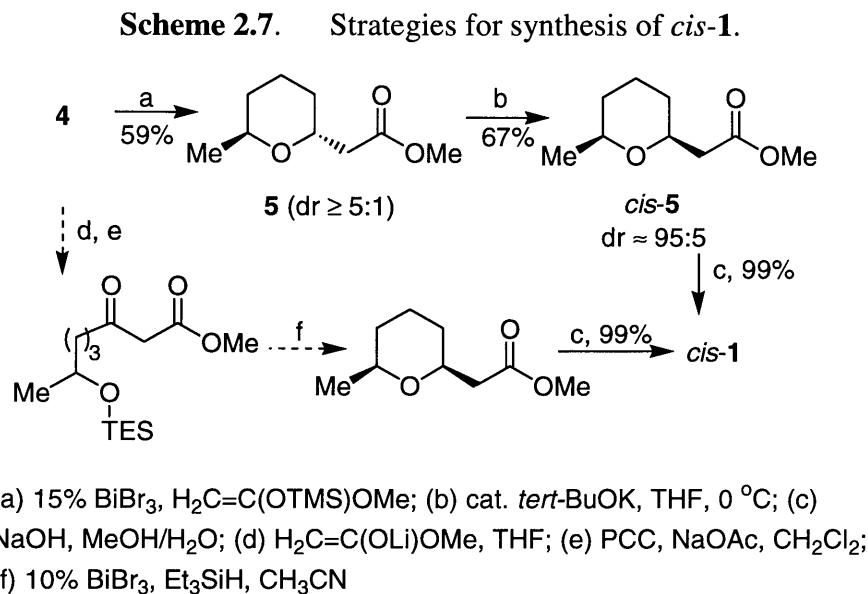
in NMR tubes under the same conditions as the reported procedure, but using CD<sub>3</sub>CN as solvent instead of CH<sub>3</sub>CN showed that the *trans/cis* ratio remained constant even after 16 h at rt. Furthermore, addition of imidazole up to three times amount of BiBr<sub>3</sub> immediately before work-up did not improved the selectivity. These experiments indicated that the elimination-addition pathway was not the reason for lower selectivity. Thus, we believe

that the reduced diastereoselectivity is due to a kinetic effect rather than a thermodynamic equilibration effect. Finally, basic hydrolysis (NaOH) of the disubstituted THP, *trans-5*, directly gave *trans-1* in high isolated yield by the method of Nussbaumer and Frater<sup>21</sup>.

Due to the low selectivity for ketene silyl acetal nucleophile with oxocarbenium ion, we then turned our attention toward another approach to the *trans*-isomer involving conversion of the allylated THP (*trans-6*) to *trans-1* (**Scheme 2.5**). Allylation of **4** under standard conditions (10% BiBr<sub>3</sub>, 3.0 equiv CH<sub>2</sub>=CH-CH<sub>2</sub>-TMS, CH<sub>3</sub>CN, RT) did provide *trans-6* in high selectivity, but the volatility of this product made isolation difficult. Although we did carry this intermediate to *trans-1*, the modest isolated yield after basic ozonolysis (35% for two steps) urged us to try a third route toward the unnatural *trans*- diastereomer. Addition of the commercially available silyl enol ether of acetone (CH<sub>2</sub>=C(OTMS)CH<sub>3</sub>) to **4** directly afforded *trans-7* with *dr* = 32:1 and in reasonable yield. However, we failed to convert the methyl ketone to the corresponding acid under bromoform conditions described by Ley *et al*<sup>22</sup>, because this reaction led to mixtures of *trans-1* and *cis-1*. Due to the difficult separation of the two diastereomeric acids, we returned to the addition of silyl ketene acetal to afford *trans-5* directly. After chromatographic separation of the isomers, basic hydrolysis of the methyl ester afforded *trans-1* in quantitative yield. Thus, we synthesized *trans-1* in as few as four steps from alcohol, **2**.

Our initial efforts toward the natural (*S,S*)-*cis*-diastereomer (*cis-1*), were directed toward two alternative sequences (**Scheme 2.7**): a) equilibration from *trans-5* to

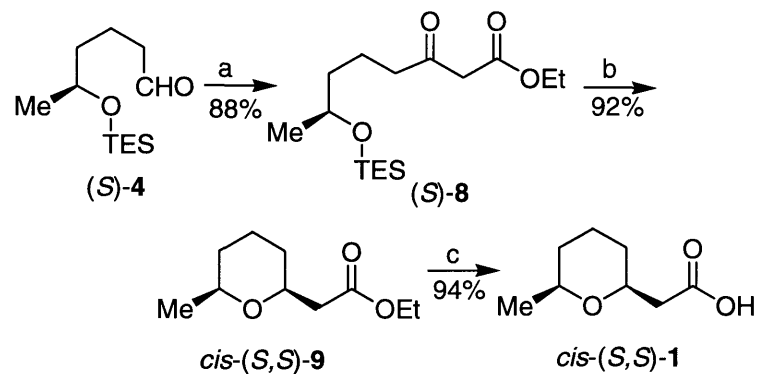
*cis*-**5** with *t*-BuOK/THF followed by basic hydrolysis of the ester to provide acid *cis*-**1**; and b) direct addition of the lithium enolate of methyl acetate to aldehyde, **4**, followed by PCC oxidation of the resulting crude alcohol to afford the desired  $\beta$ -keto methyl ester required for reductive etherification.



Unfortunately, the equilibration with *t*-BuOK from *trans*- to *cis*- isomers resulted in moderate yield, and possibly due to some hydrolysis. This second route with lithium enolate only provided low yields for the enolate addition step, possibly because the TES protecting alcohol reacted with the lithium enolate. Therefore, without any further optimization for this route, we turned our synthesis to the final approach *via* Bi(III) catalyzed reductive etherification. We converted (*S*)-**4** to  $\beta$ -keto ester (*S*)-**8**, using Roskamp's protocol<sup>23</sup>. This mild reaction provided the  $\beta$ -keto ester in excellent yield as a mixture of keto- and enol- forms. Reductive etherification initiated by BiBr<sub>3</sub> with

triethylsilane provided the desired cyclic ester, *cis*-(*S,S*)-**9** in high yield and excellent selectivity. Finally, basic hydrolysis gave the title compound *cis*-(*S,S*)-**1** in excellent overall yield (**Scheme 2.8**).

**Scheme 2.8.** Stereoselective conversion of aldehyde **4** to *cis*-(*S,S*)-**1**.



(a) 1.2 equiv.  $\text{N}_2\text{CHCO}_2\text{Et}$ , 15%  $\text{SnCl}_2$ ,  $\text{CH}_2\text{Cl}_2$ . (b) 2.0 equiv.  $\text{HSiEt}_3$ , 15%  $\text{BiBr}_3$ ,  $\text{CH}_3\text{CN}$ . (c)  $\text{NaOH}/\text{MeOH}/\text{H}_2\text{O}$

## Diastereoselectivity discussion:

Compared the lower diastereoselectivity for addition of the silyl ketene acetal nucleophile to the intermediate oxocarbenium ion, high *trans*- selectivity was generally observed when using allyltrimethylsilane and triethylsilane (>99:1). It is interesting to find that these reaction selectivities appear to be inversely proportional to the nucleophilicity parameters described by Mayr and co-workers<sup>24</sup>. The  $\pi$ -nucleophilicity parameter decreases from approximately 8.51 to 5.41 and to 1.79, for  $\text{CH}_2=\text{C}(\text{OTMS})\text{OMe}$ ,  $\text{CH}_2=\text{C}(\text{OTMS})\text{Me}$ ,  $\text{CH}_2=\text{CHCH}_2\text{-TMS}$ , respectively. The diastereoselectivity in this series, however, increases from 5–6:1 to 32:1 and to  $\geq 99:1$ . Our data show that the greater the nucleophilicity, the lower the stereoelectronic preference for axial attack. The observed trend between  $\pi$ -nucleophilicity and the observed diastereoselectivity is displayed in **Table 2.1** and strongly indicates that the selectivity is likely a kinetic effect of nucleophilic addition.

**Table 2.1:** Diastereoselectivity of cyclization-addition reactions of  $\pi$ -nucleophiles and aldehyde, **4**

Nucleophile	Product	<i>trans</i> -/ <i>cis</i> - <sup>a</sup>	$\pi$ -Nucleophilicity parameter, $N^p$
		99:1	1.79
		32:1	5.41
		5-6:1	~8.5 <sup>c</sup>

<sup>a</sup> The ratio was determined by capillary GC of crude reaction mixtures before chromatography.

<sup>b</sup> Nucleophilicity parameters obtained from Ref. 22 and therein.

<sup>c</sup> This parameter is an estimate.

Although increases in the nucleophilicity of substrates decreased the diastereoselectivities, added Bu<sub>4</sub>NOTf reversed this effect slightly (**Table 2.2**). To ensure that the increased selectivities were not merely due to increases in ionic strength of the solvent, 5-100 % of Me<sub>4</sub>NClO<sub>4</sub> was added in a separate series. As **Table 2.2** shows, the effect appears to be due to the triflate anion rather than just ionic strength. We do not yet know the reason for this salt effect.

**Table 2.2:** Effects of Bu<sub>4</sub>NOTf and Me<sub>4</sub>NClO<sub>4</sub> additives on diastereoselectivities in the tandem cyclization-addition reaction involving aldehyde **4** and the silyl ketene acetal derived from methyl acetate.<sup>a</sup>

entry	additive	mol %	ratio of ( <i>trans/cis</i> ) <sup>b</sup>	yield(%) <sup>c</sup>
1	Bu <sub>4</sub> NOTf	0	5.8:1	63
2	-----	5	6.3:1	65
3	-----	15	6.7:1	61
4	-----	100	7.8:1	56
5	Me <sub>4</sub> NClO <sub>4</sub>	5	5.5:1	58
6	-----	15	5.2:1	60
7	-----	50	5.3:1	61
8	-----	100	5.5:1	53

<sup>a</sup>All the tandem reactions were carried on 0.5 mmol scale in CH<sub>3</sub>CN at room temperature using 3.0 equiv of CH<sub>2</sub>=C(OTMS)OMe and initiated 15% BiBr<sub>3</sub>. <sup>b</sup>The ratio of diastereomers was determined by GLC analysis of crude reaction mixtures. <sup>c</sup> Isolated yield of combined *trans*- and *cis*- isomers.

In conclusion, we established routes from chiral aldehyde, (*S*)-**4** to 2,6-disubstituted tetrahydropyran compounds in good yields and moderate to high diastereoselectivities. The key step of each route is initiated by BiBr<sub>3</sub> and the resulting

stereochemistry is consistent with axial addition to a cyclic oxocarbenium ion. However, compared to both allyl trimethylsilane or triethyl silane ( $\text{Et}_3\text{SiH}$ ), the more reactive silyl ketene acetal nucleophile results in lower diastereoselectivity. The nucleophilicity parameters described by Mayr *et al.*<sup>24</sup> for  $\text{CH}_2=\text{CHCH}_2\text{-TMS}$ ,  $\text{CH}_2=\text{C}(\text{OTMS})\text{Me}$  and  $\text{CH}_2=\text{C}(\text{OTMS})\text{OMe}$  indicate that the axial approach of a nucleophile is dictated by the relative nucleophilicity of the silanes: the greater the nucleophilicity, the more rapid the addition and less discriminating the approach to the oxocarbenium ion.

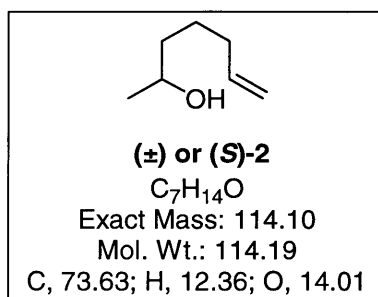
The applications of Bi(III) methodology to *trans*-**1** and *cis*-**1** show the flexibility afforded by tandem cyclization-addition reactions of  $\delta$ -silyloxy carbonyl compounds. The generally low toxicity of most Bi(III) compounds and their ease of use are noteworthy and their applications toward oxocarbenium ion intermediates affords a convenient alternative to typical Lewis acids such as TMSOTf.

## EXPERIMENTAL SECTION

**General Information.** All reagents were used as received unless otherwise noted. Dichloromethane was distilled from  $\text{CaH}_2$  and tetrahydrofuran was purified *via* a SolvTec<sup>®</sup> solvent purification system. Chloroform-d, copper cyanide, (*S*)- and racemic propylene oxide, phenylacetaldehyde, 1-butenylmagnesium bromide (1.0 M in THF), 4-pentenylmagnesium bromide, triphenylphosphine, bismuth(III) bromide, methyl trimethylsilyl dimethylketene acetal, PCC and  $\text{Me}_2\text{S}$  were purchased from Aldrich Chemical Company, Inc. Imidazole and 2,6-lutidine were purchased from Acros Organics and both triethylsilyl chloride (TES-Cl) and triethylsilyl triflate (TES-OTf) were purchased from GFS Chemicals. Methanol, acetonitrile, hexanes, ethyl acetate, sodium hydroxide, sodium bicarbonate, and hydrochloric acid were purchased from Fischer and used as received. All NMR spectroscopic data were obtained using a Varian Mercury 400 MHz nuclear magnetic resonance spectrometer and chemical shifts are reported in ppm downfield from TMS and referenced to either internal TMS or residual protons from the NMR solvent ( $\delta = 7.26$  and  $77.23$  for  $^1\text{H}$  and  $^{13}\text{C}$ , respectively in  $\text{CDCl}_3$ ).  $^{13}\text{C}$  NMR spectra were recorded with the aid of an APT sequence in which methylene and quaternary carbons = e (even) and methyl and methine carbons = o (odd). IR spectra were obtained on a Digilab FTS7000 FT-IR spectrometer using NaCl plates purchased from International Crystal Laboratories. GC-MS traces were recorded on a

Hewlett-Packard 5890 Series II Gas Chromatograph with an Ultra-1 crosslinked (methyl silicone gum; 12 m x 0.2 mm x 0.33 mm) column, equipped with a 70 eV HP 5971A mass selective detector. Thin layer chromatography was performed on Sigma-Aldrich general-purpose silica gel on glass and for flash chromatography was performed using Sorbent Technologies chromatographic silica gel (200-475 MESH). Melting point was recorded by a Mel-Temp<sup>®</sup> apparatus and were uncorrected.

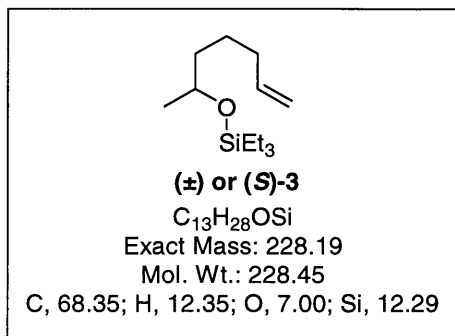
**Preparation of racemic or (*S*)-6-Hepten-2-ol ((±)-2 or (*S*)-2):**



A mixture of propylene oxide (0.60 mL, 8.6 mmol, 1.0 equiv.) and CuCN (0.038 g, 0.42 mmol) in THF (16 mL) was added to a flame-dried 100 mL round bottom flask under argon. The solution was cooled to  $-78\text{ }^{\circ}\text{C}$  using a dry ice/acetone bath and 3-butenylmagnesium bromide (0.5 M in THF, 26.0 mL, 12.8 mmol, 1.5 equiv) was added slowly. The solution was allowed to stir and warm to rt over 12 h. Aqueous  $\text{NH}_4\text{Cl}$  was added, and the solution was extracted with  $\text{Et}_2\text{O}$  (3 x 50 mL). The combined organics were washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated *in vacuo*. The product was purified by column chromatography (8:2 hexanes-EtOAc,  $R_f = 0.67$ ; 9:1 hexanes-EtOAc,  $R_f = 0.34$ ) to afford 0.982 g, (86%) as a colorless liquid: IR (neat): 3349 (br), 3078(w), 2969 (s), 2932 (s), 2861 (s), 1416(w), 1122 (m), 910 (s)  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  5.81 (ddt,  $J = 27.1, 10.6, 6.6$  Hz, 1H), 4.98 (dq,  $J = 17.2, 1.8$  Hz;  $J = 9.5, 1.1$  Hz, 2H), 3.80 (m, 1H), 2.06 (m, 2H), 1.45 (m, 4H), 1.19 (d,  $J = 6.0$

Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ , ppm):  $\delta$  138.3(o), 114.4(e), 67.4(o), 38.5(e), 33.6(e), 24.9(e), 23.2(o). For (**S**)-**2**:  $[\alpha]_{\text{D}}^{25} +12.15$  (c 2.91,  $\text{CHCl}_3$ ).

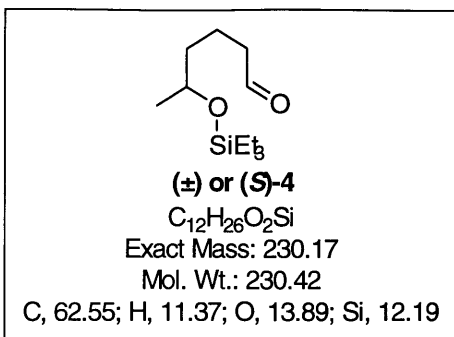
**Preparation of ( $\pm$ )-triethyl(hept-6-en-2-yloxy)silane (( $\pm$ )-**3** or (**S**)-**3**):**



A solution of 6-hepten-2-ol (**2**) (0.610 g, 5.34 mmol) in freshly distilled  $\text{CH}_2\text{Cl}_2$  (11 mL) was placed in a flame-dried round bottom flask under argon. Imidazole (0.52 g, 7.64 mmol) was added to the solution and the solution was cooled to 0 °C using

an ice water bath. TESOTf (1.45 mL, 6.41 mmol) was added to the cooled solution and the mixture was allowed to warm to rt and stir. When starting material was consumed (~1 h, TLC), aqueous  $\text{NaHCO}_3$  (ca. 10 mL) was added, the product was then extracted with  $\text{CH}_2\text{Cl}_2$ , washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated *in vacuo*. The resulting silanol was purified by column chromatography (95:5 hexanes:ethyl acetate,  $R_f = 0.64$ ) to provide 1.102 g (90%) of (**S**)-**3** as a colorless liquid; IR (neat): 3078(w), 2956(s), 2817(s), 1416(w), 1239(w), 1135(m), 1011(m), 910(m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.81 (dddd,  $J = 16.8, 10.2, 6.6, 6.6$  Hz, 1H), 5.00 (dm,  $J = 17.2$  Hz, 1H), 4.94 (dm,  $J = 10.2$  Hz, 1H), 3.74-3.83 (m, 1H), 2.01-2.07 (m, 2H), 1.25-1.45 (m, 4H), 1.13 (d,  $J = 5.9$  Hz, 3H), 0.96 (t,  $J = 8.1$  Hz, 9H), 0.59 (q,  $J = 7.7$  Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 139.0(o), 114.4(e), 68.6(o), 39.5(e), 34.1(e), 25.5(e), 24.2(o), 7.2(o) 5.3(e); For (**S**)-**3**:  $[\alpha]_{\text{D}}^{25} + 9.53$  (c 1.29,  $\text{CHCl}_3$ ).

**Preparation of (±)-5-(triethylsilyloxy)hexanal ((±)-4 or (S)-4):**

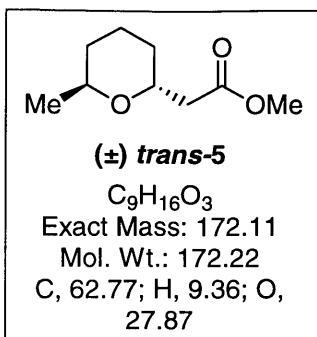


Alkene **3** (0.415 g, 1.82 mmol, 1.0 equiv),  $CH_2Cl_2$  (25 mL), and methanol (5 mL) were added to an oven-dried round bottom flask equipped with a stir bar. The solution was cooled to  $-70\text{ }^\circ\text{C}$  using a dry ice/acetone bath.  $NaHCO_3$  (~0.1 g) was added and  $O_3$

was bubbled through the solution for approximately 15 minutes.  $O_2$  was then bubbled through the solution for 15 minutes followed by argon.  $Me_2S$  (excess, 0.8 mL) was added and the mixture warmed to rt and stirred for 48 h. The mixture was filtered through Celite and concentrated. The product was purified by column chromatography (9:1 hexanes:ethyl acetate,  $R_f = 0.30$ ) to afford 0.308 g (74 %) of (±)-**4** as a colorless oil; IR (neat): 2957(s), 2878(s), 2814(m), 2716(m), 1728(s), 1140(m), 739(s)  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$ : 9.77 (t,  $J = 2.0$  Hz, 1H), 3.77-3.86 (m, 1H), 2.44 (dt,  $J = 7.3, 1.8$  Hz, 2H), 1.68-1.78 (m, 1H), 1.58-1.62 (m, 1H), 1.40-1.50 (m, 2H), 1.15 (d,  $J = 6.2$  Hz, 3H), 0.96 (t,  $J = 8.1$  Hz, 9H), 0.60 (q,  $J = 7.7$  Hz, 6H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$ : 202.6(o), 68.3(o), 44.2(e), 39.3(e), 24.1(o), 18.7(e), 7.3(o), 5.3(e). For (S)-**4**:  $[\alpha]_D^{25} + 12.76$  (c 1.05,  $CHCl_3$ ).

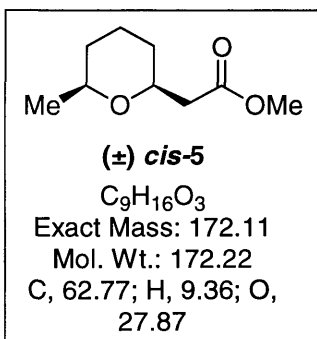
**Preparation of (±) methyl *trans*-2-(6-methyl-tetrahydro-2H-pyran-2-yl)acetate (*trans*-5):**

Aldehyde **4** (0.040 g, 0.17 mmol, 1.0 equiv) was added to an oven-dried test tube equipped with a micro stir bar *via* preweighed syringe. Acetonitrile (2.0 mL) was



added under an argon atmosphere followed by a solution of BiBr<sub>3</sub> (0.10 mL, 0.176 mmol, 10.2 %) in acetonitrile (prepared by dissolution of 0.079 g, 0.18 mmol BiBr<sub>3</sub> in 1.0 mL acetonitrile). Silyl ketene acetal (0.031 g, 0.211 mmol, 1.2 equiv) was then added via syringe in two equal portions. After the reaction stirred for ~2 h, the solvent was evaporated and the reaction mixture filtered through a plug of silica gel using CH<sub>2</sub>Cl<sub>2</sub> as eluant. After removal of the solvent *in vacuo*, the diastereomers were separated by column chromatography (9:1 hexanes-ethyl acetate, R<sub>f</sub> = 0.34 for *trans*-isomer and 0.44 for *cis*-isomer) to afford 0.020 g (68%) of *trans*-5 as a colorless oil: IR (neat): 2936(s), 2869(m), 1741(s), 1288(m), 1168(m), 1049(m), cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>): δ 4.18 (tdd, *J* = 8.8, 6.2, 3.7 Hz, 1H), 3.87 (dq, *J* = 12.8, 6.2, 3.7 Hz, 1H), 3.62 (s, 3H), 2.61 (dd, *J* = 14.7, 8.1 Hz, 1H), 2.37 (dd, *J* = 14.6, 5.9 Hz, 1H), 1.61 (m, 2H), 1.26 (m, 4H), 1.11 (d, *J* = 6.6 Hz, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 171.9(e), 68.2(o), 67.7(o), 51.9(o), 39.2(e), 31.5(e), 29.9(e), 19.8(o), 18.5(e).

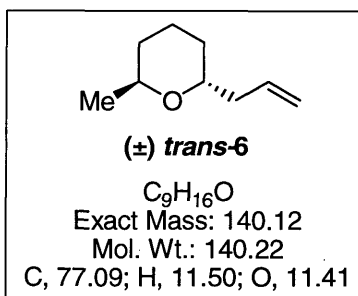
**Preparation of (±) methyl *cis*-2-(6-methyltetra-hydro-2H- pyran-2-yl)acetate (*cis*-5):**



Ester *trans*-5 (0.077 g, 0.45 mmol, 1.0 equiv) was added *via* a pre-weighed 1.0 mL syringe to a flame dried round bottom flask equipped with a stir bar and under an argon atmosphere. THF (2.1 mL) was added to the flask and the solution was cooled to 0 °C

with an ice/salt water bath. Solid *tert*-BuOK (0.014 g, 0.13 mmol, 28 %) was added to the flask and the solution turned dark orange. The reaction stirred for 1.5 h and was quenched with aqueous NH<sub>4</sub>Cl (~10 mL). The product was extracted with EtOAc (3 x 10 mL), dried (MgSO<sub>4</sub>), and concentrated *in vacuo* to afford 0.051 g (67 %) of *cis*-5 (dr ≥ 19:1) as a colorless oil: IR (neat): 2935(s), 2858(m), 1744(s), 1287(m), 1172(m), 1044(m) , cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>) δ 3.75 (tdd, *J* = 9.5, 5.9, 1.8 Hz, 1H), 3.68 (s, 3H), 3.46 (dq, *J* = 14.3, 3.7, 1.8 Hz, 1H), 2.58 (dd, *J* = 15.0, 7.3 Hz, 1H), 2.39 (dd, *J* = 15.2, 6.0 Hz, 1H), 1.82 (m, 2H), 1.58 (m, 2H), 1.20 (m, 2H), 1.15 (d, *J* = 6.2 Hz, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>) δ 172.0(e), 74.5(o), 74.3(o), 51.9(o), 41.9(e), 33.3(e), 31.3(e), 23.8(o), 22.5(e).

#### Preparation of (±) allyl *trans*-2-6-methyl-tetrahydro-2H-pyran, *trans*-6:

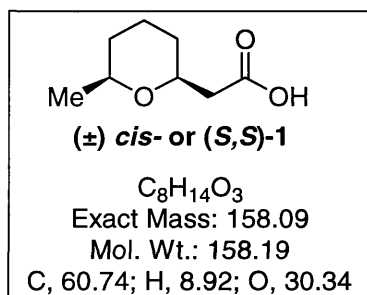


An oven-dried test tube equipped with a micro stir bar was prepared under argon. Aldehyde **4** (0.115 g, 0.50 mmol, 1.0 equiv) was added by preweighed syringe followed by CH<sub>3</sub>CN (4.0 mL). A solution (0.35 mL) of BiBr<sub>3</sub> (100 mg/mL BiBr<sub>3</sub> in CH<sub>3</sub>CN) was added to the reaction mixture, then allyltrimethylsilane (0.16 mL, 1.0 mmol, 2.0 equiv) was added *via* syringe. The reaction was stirred for 2h, then water (30 mL) was added and the mixture was extracted with Et<sub>2</sub>O (2 x 20 mL). The combined ether layers were dried (MgSO<sub>4</sub>) and concentrated *in vacuo*. The product was purified by column chromatography (9:1 petroleum ether:Et<sub>2</sub>O, R<sub>f</sub> = 0.62) to afford 0.049g (70%) of (±)-*trans*-**8** as a colorless oil; IR (neat): 3076(w),

2974(m), 2938(s), 2864(m), 1375(m), 1204(m), 1043(m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.81(dddd,  $J = 16.8, 9.9, 7.0, 7.0$  Hz, 1H), 5.07 (overlapping dm,  $J = 17.2$  Hz, 1H), 5.04 (overlapping dm,  $J = 10.3$  Hz, 1H), 3.93(dqd,  $J = 13.2, 6.6, 3.7$  Hz, 1H), 3.81 (tdd,  $J = 9.2, 6.6, 3.7$  Hz, 1H), 2.42 (dddd,  $J = 14.3, 7.0, 7.0, 3.5, 3.5$  Hz, 1H), 2.21 (dddd,  $J = 14.1, 7.0, 7.0, 3.5, 3.5$  Hz, 1H), 1.60-1.73 (m, 4H), 1.24-1.40 (m, 2H), 1.08 (d,  $J = 6.2$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 135.6(o), 116.5(e), 70.8(o), 67.2(o), 38.2(e), 31.8(e), 29.5(e), 20.0(o), 18.6(e).

**Preparation of *cis*-2-(6-methyl-tetrahydro-2H- pyran-2-yl)acetic acid, ( $\pm$ )-*cis*-1**

**and/or(+)-(*S,S*)-*cis*-1:** Ester **9** (0.128 g, 0.68 mmol) was weighed into a 5 mL round



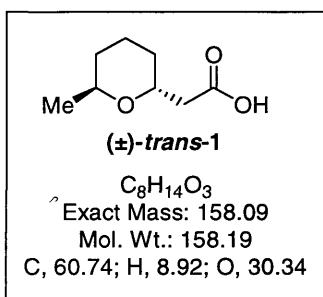
bottom flask, Methanol (1.0 mL) and 10% aqueous NaOH (2.0 mL) solutions were added, the reaction refluxed for 4 h, then washed with ethyl ether to remove neutral impurities. The aqueous layer was acidified with conc.

HCl, extracted with  $\text{Et}_2\text{O}$  (3 x 5 mL) and the organic layers combined. The solution was dried ( $\text{MgSO}_4$ ) and concentrated *in vacuo*, leaving 0.101 g (94%) of ( $\pm$ )-*cis*-**1** as a white solid: m.p. 51–53  $^\circ\text{C}$ ; For (+)-(*S,S*)-*cis*-**1** as a colorless, viscous oil: IR (neat) 3079(br, s), 2973(s), 2935(s), 2863(s), 1714(s), 1206(m), 1071(m),  $\text{cm}^{-1}$ ;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$  3.77 (tdd,  $J = 9.9, 4.8, 1.8$  Hz, 1H), 3.55(dqd,  $J = 10.7, 6.2, 1.8$  Hz, 1H), 2.56 (dd,  $J = 15.7, 7.7$  Hz, 1H), 2.49 (dd,  $J = 15.9, 5.1$  Hz, 1H), 1.83 (m, 2H), 1.57 (m, 2H), 1.24 (m, 2H), 1.18 (d,  $J = 6.2$  Hz, 3H).  $^{13}\text{C}$ -NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$  175.1(e), 74.8(o), 74.2(o),

41.6(e), 33.1(e), 31.1(e), 23.6(e), 22.4(o); Anal. cal. For  $C_8H_{14}O_3$  (158.19): C60.81, H9.01; Found: C60.74, H8.92. For (+)-(*S,S*)-*cis*-1:  $[\alpha]_D^{25} +19.35$  (c = 5.78,  $CHCl_3$ ), Lit:  $[\alpha]_D^{25} +18.6$  (c 2.77,  $CHCl_3$ ), <sup>ref</sup>  $[\alpha]_D^{31} +20.5$  (c 1.23,  $CHCl_3$ ).

**Preparation of ( $\pm$ ) *trans*-2-(6-methyl-tetrahydro-2H-pyran-2-yl)acetic acid, ( $\pm$ )**

***trans*-1:** *Trans*-ester **5** (0.086 g, 0.50 mmol) was weighed into a 5 mL round bottom



flask. Methanol (0.70 mL) and 10% aqueous NaOH (1.50 mL)

solution were then added, the solution refluxed for 3 hours,

then washed with ethyl ether to remove neutral impurities. The

aqueous layer was then acidified with concentration HCl,

extracted with ethyl ether (3 x 20 mL), the combined ether

layers dried ( $MgSO_4$ ) and concentrated *in vacuo*, leaving 0.079 g (99%) of *trans*-1 as a

colorless, viscous oil: IR (neat, NaCl): 3051(br, s), 2937(s), 2873(s), 2657(br, m), 1712(s),

1209(m), 1047(m)  $cm^{-1}$ ;  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$  11.45( br, s, 1H), 4.26 (tdd,  $J = 8.8,$

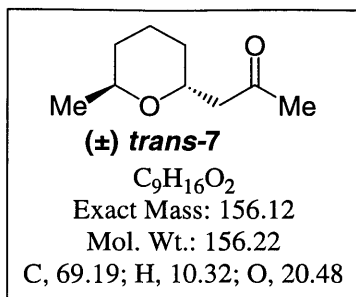
6.6, 4.0 Hz, 1H), 4.01(dqd,  $J = 12.5, 6.2, 2.9$  Hz, 1H), 2.71 (dd,  $J = 15.0, 8.4$  Hz, 1H),

2.48 (dd,  $J = 15.4, 5.5$  Hz, 1H), 1.71 (m, 2H), 1.64 (m, 2H), 1.37 (m, 2H), 1.21 (d,  $J = 6.2$

Hz, 3H);  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$  176.6(e), 68.1(o), 67.9(o), 39.1(e), 31.2(e),

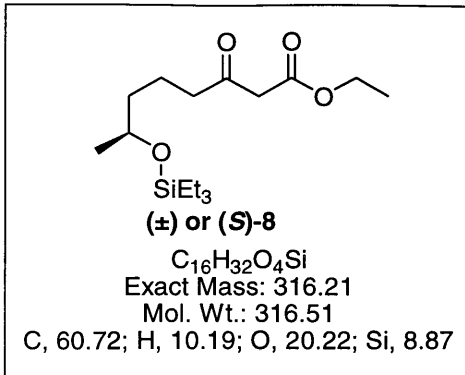
29.9(e), 19.5(o), 18.3(e).

**Preparation of ( $\pm$ ) *trans*-2-(6-methyl-tetrahydro-2H-pyran-2-yl)propan-2-one, 7:**



An oven-dried test tube equipped with a micro stir bar was cooled under argon. Aldehyde **4** (0.089 g, 0.50 mmol, 1.0 equiv) was added *via* pre-weighed syringe followed by acetonitrile (4.0 mL). A solution (0.35mL) of BiBr<sub>3</sub> in acetone (100mg/mL BiBr<sub>3</sub> in acetonitrile) was added to the reaction mixture. Silyl enol ether of acetone (0.20 mL, 1.0 mmol, 2.0 equiv) was then added. After the reaction stirred overnight, the solvent was evaporated, and the reaction mixture filtered through a plug of SiO<sub>2</sub> with CH<sub>2</sub>Cl<sub>2</sub> as eluant. The crude material was concentrated *in vacuo* and the product was purified by column chromatography (9:1 hexanes-ethyl acetate, R<sub>f</sub> = 0.28) to afford 0.045g (57%) of ( $\pm$ )-*trans*-**7** as a colorless oil: IR (neat) 2935(s), 2869(m), 1715(s), 1358(m), 1264(m), 1053(m), cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.27 (tdd, *J*= 8.8, 6.2, 3.7 Hz, 1H), 3.92 (dq, *J* = 12.5, 6.2, 3.7 Hz, 1H), 2.79 (dd, *J* = 15.4, 8.5 Hz, 1H), 2.37 (dd, *J* = 15.0, 5.5 Hz, 1H), 2.12(s, 3H), 1.68 (m, 4H), 1.33 (m, 2H), 1.18 (d, *J*=6.2 Hz, 3H); <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  207.2(e), 67.6(o), 67.5(o), 48.1(e), 31.2(e), 30.5(o), 30.1(e), 19.4(o), 18.3(e).

### Preparation of Ethyl 3-oxo-7-(triethylsilyloxy)octanoate: ( $\pm$ )-8 or (S)-8



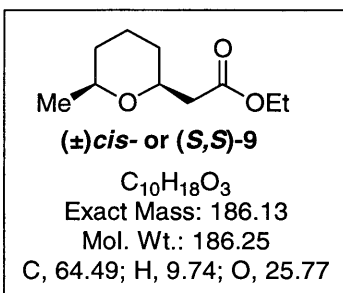
$\text{SnCl}_2$  (14.2 mg, 0.075 mmol, 0.15 equiv) was weighed into a 5 mL round bottom flask.  $\text{CH}_2\text{Cl}_2$  (2.0 mL) and ethyl diazoacetate (63  $\mu\text{L}$ , 0.60 mmol, 1.2 equiv) were then added by syringe. Hexanal 4 (0.115 g, 0.50 mmol, 1.0 equiv) was dissolved in 1.0 mL  $\text{CH}_2\text{Cl}_2$  and added

slowly by syringe. After 1.5 h, the solution was quenched with brine and extracted with  $\text{Et}_2\text{O}$  (3 x 10 mL). The combined organics were dried ( $\text{MgSO}_4$ ), concentrated *in vacuo* and the residue purified by column chromatography (7:3 pentanes:ethyl ether,  $R_f = 0.77$ ) to provide 0.139 g (88%) of ( $\pm$ )-5 as a colorless liquid which contained ~ 15% of the *enol form*; IR (neat): 2959(s), 2878(s), 1748(s), 1721(s), 1644(m), 1239(s), 1138(m), 1036(m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 4.19 (q,  $J = 7.2$  Hz, 2H), 3.75-3.84 (m, 1H), 3.43 (s, 2H), 2.55 (t,  $J = 7.3$  Hz, 2H), 1.57-1.72 (m, 2H), 1.37-1.47 (m, 2H), 1.28 (t,  $J = 7.2$  Hz, 3H), 1.13 (d,  $J = 6.0$  Hz, 3H), 0.95 (t,  $J = 7.8$  Hz, 9H), 0.59 (q,  $J = 7.8$  Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 202.7(e), 167.2(e), 68.4(o), 61.6(e), 49.6(e), 43.4(e), 39.2(e), 24.1(o), 20.1(e), 14.5(o), 7.3(o), 5.3(e); *For the enol form*;  $^1\text{H}$ -NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 12.1 (s, 1H), 4.98 (s, 1H), 4.19 (q,  $J = 7.2$  Hz, 2H), 3.75-3.84 (m, 1H), 2.19 (t,  $J = 7.3$  Hz, 2H), 1.57-1.72 (m, 2H), 1.37-1.44 (m, 2H), 1.29 (t,  $J = 7.2$  Hz, 3H), 1.13 (d,  $J = 6.0$  Hz, 3H), 0.95 (t,  $J = 7.8$  Hz, 9H), 0.59 (q,  $J = 7.8$  Hz, 6H).  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 178.6(e), 94.5(e), 89.3(o), 68.3(o), 60.2(e), 39.3(e), 35.3(e), 24.1(o), 22.8(e), 14.6(o), 7.3(o), 5.3(e); Anal. cal. For  $\text{C}_{16}\text{H}_{32}\text{O}_4\text{Si}$  (316.51): C 60.72, H 10.19; Found: C 60.85, H

10.43; For (*S*)-**5**:  $[\alpha]_D^{25} + 11.44$  (c 2.71, CHCl<sub>3</sub>).

**Preparation of ethyl *cis*-2-(6-methyl-tetrahydro-2H-pyran-2-yl)acetate, ( $\pm$ )-*cis*-**9****

**and/or (+)-(*S,S*)-*cis*-**9**:**



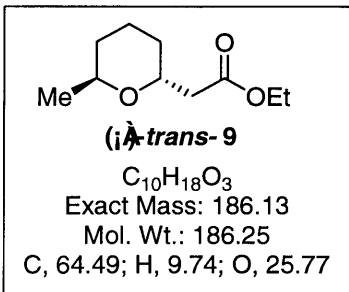
Octanoate **8** (0.137 g, 0.50 mmol, 1.0 equiv) was weighed into a 15 mL round bottom flask and CH<sub>3</sub>CN (4.0 mL) added by syringe. BiBr<sub>3</sub> solution (100 mg/1mL in CH<sub>3</sub>CN) (0.35 mL, 0.075 mmol, 0.15 equiv) and HSiEt<sub>3</sub> (0.16 mL, 1.0 mmol, 2.0 equiv) were added simultaneously. After 1h, solution was

concentrated *in vacuo*, filtered through a small SiO<sub>2</sub> pipette column and concentrated *in vacuo* again. The product was purified by column chromatography (9:1 hexanes-ethyl acetate, R<sub>f</sub> = 0.46) to provide 0.086 g (92%) as a colorless liquid: IR (neat) 2974(s), 2934(s), 2860(m), 1738(s), 1286(s), 1173(s), 1040(s), cm<sup>-1</sup>; <sup>1</sup>H-NMR (400 MHz, CDCl<sub>3</sub>)  $\delta$  4.15 (q, *J* = 7.2 Hz, 2H), 3.77 (tdd, *J* = 9.4, 4.6, 2.1 Hz, 1H), 3.47 (dq, *J* = 12.1, 4.3, 1.6 Hz, 1H), 2.55 (dd, *J* = 15.0, 7.4 Hz, 1H), 2.37 (dd, *J* = 14.8, 5.8 Hz, 1H), 1.82 (m, 2H), 1.58 (m, 2H), 1.26 (t, *J* = 7.2 Hz, 3H), 1.20 (m, 2H), 1.15 (d, *J* = 6.2 Hz, 3H). <sup>13</sup>C-NMR (100 MHz, CDCl<sub>3</sub>)  $\delta$  171.5(e), 74.6(o), 74.3(o), 60.9(e), 41.1(e), 33.2(e), 31.3(e), 23.8(e), 22.4(o), 14.6(o). Anal. cal. for C<sub>10</sub>H<sub>18</sub>O<sub>3</sub>(186.25): C64.59, H9.74; found: C63.97, H9.80.

For (+)-(*S,S*)-*cis*-**5**:  $[\alpha]_D^{25} + 16.43$  (c 2.13, CHCl<sub>3</sub>).

## Preparation of ethyl *trans*-2-(6-methyl-tetrahydro-2H-pyran-2-yl)acetate,

### (±)-*trans*-9:



Cycloether *trans*-6 (0.070 g, 0.50 mmol, 1.0 equiv) was weighed into a 100 mL round bottom flask and  $CH_2Cl_2$  (30.0 mL) added by syringe. NaOH solution (2.0 mol/L in EtOH) (5.0 mL, 10.0 mmol, 20.0 equiv) was added. Cooled the solution to  $-78^\circ C$  and ozone gas was passed through the solution for 1.5 h. Water and  $Et_2O$  was added to the solution and warmed to rt, and then extracted with  $Et_2O$  (3 x 20 mL), the combined ether layers dried ( $MgSO_4$ ) and concentrated *in vacuo*. The product was purified by column chromatography (9:1 hexane-ethyl acetate,  $R_f = 0.36$ ) to afford 0.057g (61%) of (±)-*trans*-6 as a colorless liquid: IR (neat) 2974(s), 2934(s), 2860(m), 1738(s), 1286(s), 1173(s), 1040(s) ,  $cm^{-1}$ ;  $^1H$ -NMR (400 MHz,  $CDCl_3$ )  $\delta$  4.26 (tdd,  $J = 9.9, 6.2, 3.7$  Hz, 1H), 4.15 (q,  $J = 7.3$  Hz, 2H), 3.94 (dq,  $J = 12.8, 6.6, 3.3$  Hz, 1H), 2.67 (dd,  $J = 14.6, 7.4$  Hz, 1H), 2.37 (dd,  $J = 14.6, 6.2$  Hz, 1H), 1.68 (m, 4H), 1.34 (m, 2H), 1.26 (t,  $J = 7.1$  Hz, 3H), 1.18 (d,  $J = 6.6$  Hz, 3H).  $^{13}C$ -NMR (100 MHz,  $CDCl_3$ )  $\delta$  171.5(e), 68.3(o), 67.6(o), 60.6(e), 39.4(e), 31.5(e), 29.9(e), 19.9(o), 18.6(e), 14.6(o).

## REFERENCES

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- <sup>1</sup> For review see Leonard N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373-8397.
- <sup>2</sup> Rigby, W. *J. Chem. Soc.* **1951**, 793-795.
- <sup>3</sup> Komatsu, N. In organobismuth chemistry; Suzuki, H., Matano, Y., Eds.; Elsevier: New York, 2001; pp 371-440.
- <sup>4</sup> Komatsu, N.; Uda, M.; Suzuki, H. *Chem. Lett.* **1997**, 1229-1230.
- <sup>5</sup> Bajwa, J.; Viveló, J.; Slade, J.; Repic, O.; Blacklock, T. *Tetrahedron Lett.* **2000**, *41*, 6021-6024.
- <sup>6</sup> a) Desmurs, J. R.; Labrouillere, M.; Roux, C. L.; Gaspard, H.; Laporterie, A.; Dubac, J. *Tetrahedron Lett.* **1997**, *38*, 8871-8874. b) Repichet, S.; Le Roux, C.; Dubac, J.; Desmurs, J. R. *Eur. J. Org. Chem.* **1998**, 2734-2746.
- <sup>7</sup> Wada, M.; Ohki, H.; Akiba, K. *Bull. Chem. Soc. Jpn* **1990**, *63*, 1738-1747.
- <sup>8</sup> Le Roux, C.; Gaspard-Loughmane, H.; Dubac, J. *J. Org. Chem.* **1993**, *58*, 1835-1839.
- <sup>9</sup> Reddy, B. V.; Srinivas, R.; Yadav, J. S.; Ramalingam, T. *Synth. Commun.* **2001**, *31*, 1075.
- <sup>10</sup> Ramalinga, K.; Vijayalakshmi, P.; Kaimal, T. N. B. *Synlett.* **2001**, *6*, 3167-3170.

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- <sup>11</sup> Maurer, B.; Grieder, A.; Thommen, W. *Helv.Chim. Acta* **1979**, *63*, 44-47.
- <sup>12</sup> a) Searle, P. A.; Molinski, T. F. *J. Am. Chem. Soc.* **1995**, *117*, 8126-8131. b) Searle, P. A.; Molinski, T. F.; Brzeninski, L. J.; Leahy, J. W. *J. Am. Chem. Soc.* **1996**, *118*, 9422-9423. c) Evans, D. A.; Fitch, D. M.; Smith, T. E.; Cee, V. J. *J. Am. Chem. Soc.* **2000**, *122*, 10033-10046.
- <sup>13</sup> D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta* **1996**, *79*, 51-60.
- <sup>14</sup> Kim, Y.; Mundy, B. *J. Org. Chem.* **1982**, *47*, 3556-3557.
- <sup>15</sup> Keck, Gary E.; Covell, Jonathan A.; Schiff, Tobias; Yu, Tao. *Org. Lett.* **2002**, *4*, 1189-1192.
- <sup>16</sup> Chan, K.; Loh, T. *Org. Lett.* **2005**, *7*, 4491-4494.
- <sup>17</sup> Lewis, M.; Cha, J.; Kishi, Y. *J. Am. Chem. Soc.* **1982**, *104*, 4976-4978.
- <sup>18</sup> Kopecky, D. J.; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001**, *123*, 8420-8421.
- <sup>19</sup> Evans, P. A.; Cui, J.; Gharpure, S. J.; Hinkle, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 11456-11457.
- <sup>20</sup> Takahata, H.; Yotsui, Y.; Mamose, T. *Tetrahedron* **1998**, *54*, 13505-13516.
- <sup>21</sup> Nussbaumer, C.; Fráter, G. *Helv. Chim. Acta* **1987**, *70*, 396-401.
- <sup>22</sup> Dixon, D. J.; Ley, S. V.; Tate, E. W. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2385-2394.

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<sup>23</sup> Holmquist, C. R.; Roskamp, E. J. *J. Org. Chem.* **1989**, *54*, 3258-3260.

<sup>24</sup> Mayr, H. Kempf, B.; Ofial, A. R. *Acc. Chem. Res.* **2003**, *36*, 66-77 and references therein.

## CHAPTER III

### BiBr<sub>3</sub>-INITIATED TANDEM ADDITION/SILYL-PRINS REACTIONS TO 2,6-DISUBSTITUTED DIHYDROPYRANS

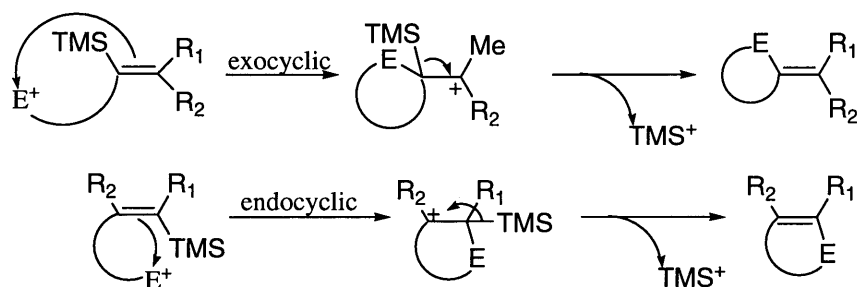
#### Background for vinylsilane:

Recently, organosilicon reagents such as allyl- and vinylsilanes have become powerful substrates in the construction of natural products. In our approach, vinyltrimethylsilanes were used as nucleophiles. Two important factors are concerned regarding the reaction of vinylsilanes. First, the regiochemistry in electrophilic substituted reactions always takes place at  $\alpha$ -carbon<sup>1</sup>. More important, although a rotation around the carbon-carbon single bond may happen when  $\beta$ -silyl cation forms, the lowest energy conformation is where the carbon-silicon  $\sigma$ -bond is coplanar and conjugated with the adjacent vacant  $p$ -orbital of the carbon cation. Therefore, the  $\alpha$ -carbon and  $\beta$ -carbon single bond cannot rotate freely and the configuration at the double bond remains the same as in the starting material<sup>2</sup>. In addition, the stability of reagents in the synthesis of a wide range of natural products makes vinylsilanes particularly important in organic synthesis. The nucleophilicity of vinylsilanes is comparable to that of a corresponding alkene and significantly less than that of allylsilanes. Simple frontier M.O. arguments would suggest that vinylsilanes should be somewhat poorer electron-donors than alkenes<sup>3</sup> as a result of delocalization. This calculation indicates that there is slightly more negative

ionization potential of vinyltrimethylsilane *versus* 3-methyl-1-butene. As a result of the low reactivity of vinylsilanes toward electrophiles and nucleophiles, oxidizing and reducing agents, many chemical reactions can be carried out in the presence of vinylsilanes.

Two distinct modes of cyclization are possible with this particular terminator of vinylsilane: cyclization can occur in an exocyclic or endocyclic mode with respect to the geometry of vinylsilane terminators. In all cyclizations, the silyl group controls the regiochemistry of the double bond in products (**Figure 3.1**).

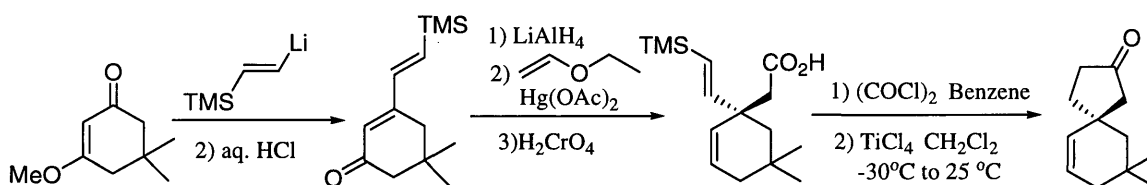
**Figure 3.1:** Two distinct cyclization models for vinylsilanes



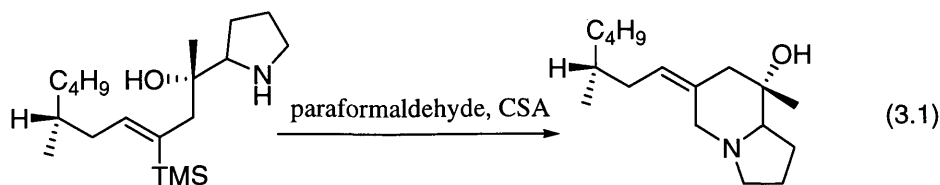
Vinylsilanes have many applications in organic synthesis, either for the synthesis of cyclic or acyclic products. Here, we focus on the cyclic products. For example, the first intramolecular variant of an acylium ion initiated cyclization reaction was reported by Burke for the preparation of spiro[4,5]decadienones<sup>4</sup> (**Scheme 3.1**). Dimedone methyl ether was treated with [ $\beta$ -(trimethylsilyl)vinyl] lithium, followed by aqueous HCl solution to give dienone containing a vinylsilane moiety with high *E* stereoselectivity.

Reduction of the ketone to the allylic alcohol, followed by Claisen rearrangement to generate the intermediate aldehyde, which was oxidized by Jones' reagent to subsequently provide the carboxylic acid. Treatment of the acid with oxalyl chloride in benzene solvent gave an acid chloride which was directly treated with  $\text{TiCl}_4$ . The resulting acylium ion underwent cyclization to give enone in excellent yield.

**Scheme 3.1:** Approach to spiro[4,5]decadienones

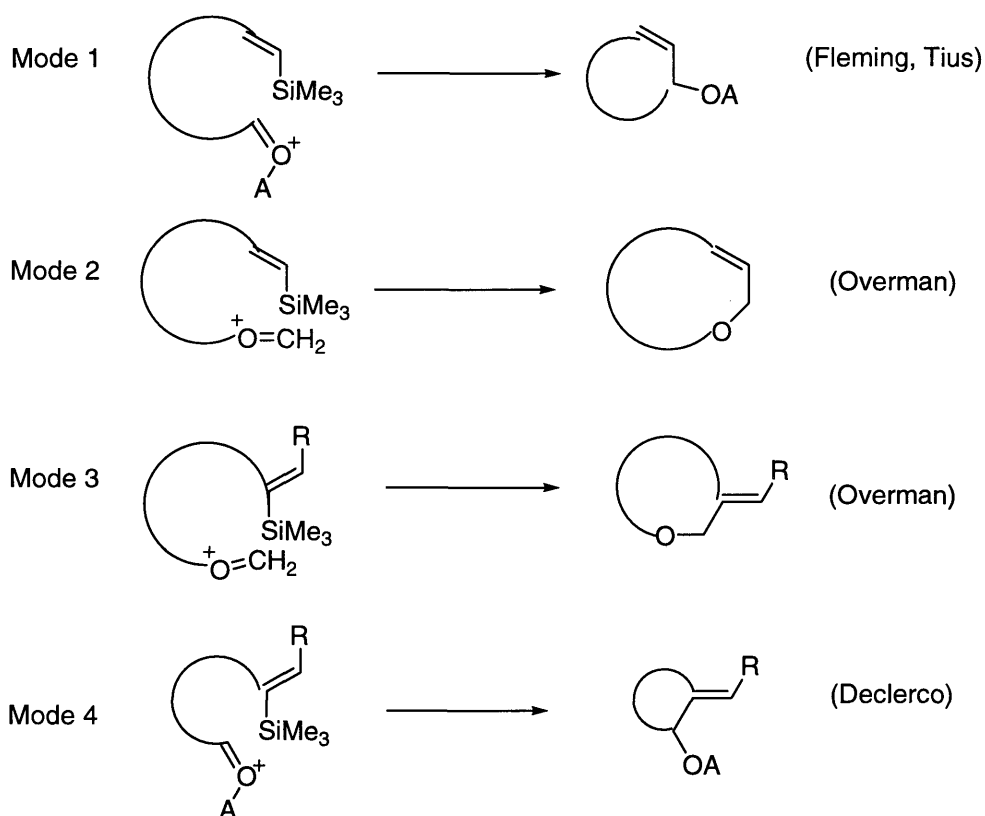


**2) Vinylsilane terminated cyclization with aldehydes and acetals<sup>5</sup>.** Iminium ions can also react with vinylsilanes to give the cyclization products. Compared to the relatively harsh conditions for iminium ion cyclizations with arenes, the iminium ion-vinylsilane cyclization can be accomplished under mild and near-neutral conditions. These cyclizations have been utilized to prepare five-, six- and seven-membered nitrogen heterocycles. For example, in the total synthesis of (+)-Pumiliotoxin 251 D, a vinyl silane cyclization was used to close the six-membered ring under CSA initiated conditions<sup>6</sup> (eq 3.1).



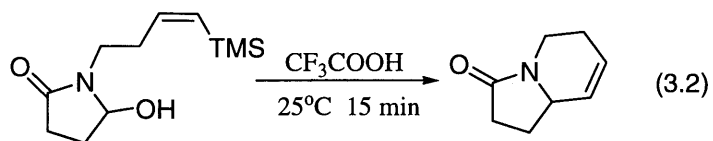
Related cyclizations in which vinylsilanes nucleophilically attack oxocarbenium ion also lead to cyclic ether products. Four models<sup>7</sup> of oxonium ion initiated cyclizations are thereby possible, depending on the orientation of initiating and terminating functions (**Figure 3.2**). All of these reaction modes have been explored, and examples of successful cyclizations have been reported except the last one, the Declerco mode.

**Figure 3.2:** Four possible oxonium ion vinylsilane cyclization models



Acyliminium ions are powerful cyclization initiators and have been used in a wide range of cationic cyclizations. Several methods have been developed to generate acyliminium ions. Among these methods, the most common way is generation from

hydroxylactams. Use of trifluoroacetic acid as solvent initiated rapid cyclization of hydroxylactams to bicyclic lactams in excellent yields<sup>8</sup> (eq 3.2). This reaction provided a nice example of the acid stability of vinylsilanes, due to the strongly acidic condition used.

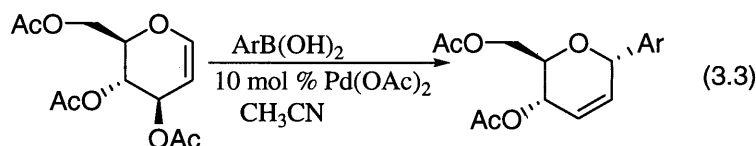


## Background for dihydropyrans:

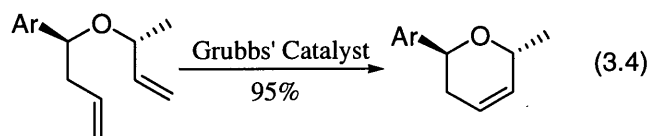
Functionalized pyran systems are important subunits in biologically active compounds. Among these pyran moieties, 2,6-disubstituted dihydropyran systems are important targets in organic synthesis, because they are not only common in many natural products, such as scytophycin C<sup>9</sup>, but also synthetically useful intermediates for polysubstituted tetrahydropyran moieties. Therefore, many methods have been reported to develop the dihydropyrans.

### Palladium mediated reactions to synthesis of C-arylglycosides<sup>10</sup> (eq 3.3).

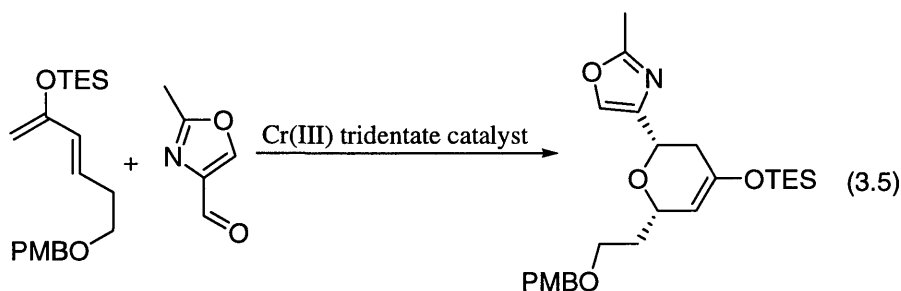
Transmetalation of the phenylboronic acid with Pd(OAc)<sub>2</sub> gives PhPdOAc, which then undergoes *syn* addition the glycal double bond to generate the R-PdOAc intermediate. The intermediate was unstable and *anti* elimination of Pd(OAc)<sub>2</sub> quickly occurred to give C-arylglycosides. The reaction utilized the easy addition of the Ar-Pd complex with an alkene.



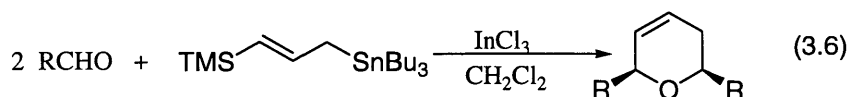
**Ring closing metathesis.** Grubbs' catalyst was used for ring closing metathesis of allylic-homoallylic ethers into dihydropyran<sup>11</sup> (eq 3.4). The problem for this methodology is no diastereomeric center can be introduced during the reaction and both the stereochemical centers must be built into the substrate.



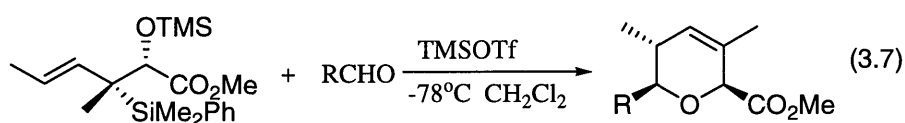
**Asymmetric Hetero-Diels-Alder reaction.** During the total synthesis of Phorboxazoles, a Jacobsen hetero Diels-Alder reaction was used as a key step in the synthesis of an advanced C4-C32 subunit<sup>12</sup> (eq **3.5**). Although the selectivity was good, about one half starting material was recovered even after two days.



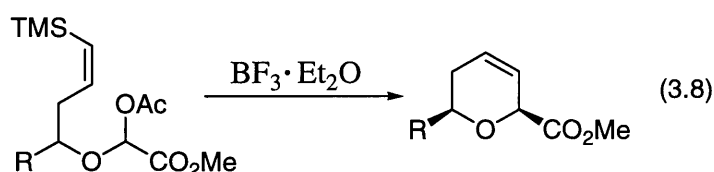
**Prins cyclization methodology.** Among these methods discussed above, the most simple and direct methodology towards the dihydropyran synthesis involves Prins cyclization reactions. Several examples are related to this issue. For example, synthesis of dihydropyrans using a novel carbonyl allylation-Prins cyclization by utilizing 3-trimethylsilylallyltributylstannane leads to high *cis*-diastereoselectivities<sup>13</sup> (eq **3.6**). The greater reactivity of allyl tributylstannane affords allyl silanes after  $\text{InCl}_3$  initiated allylation of one equivalent aldehyde. Subsequent addition of a second equivalent aldehyde generates oxocarbenium ion intermediate that undergoes intramolecular allylation to produce the expected products with high *cis*-selectivity.



Another method involves stereocontrolled [4+2]-annulation access to dihydropyran, starting from crotyl silanes and corresponding aldehydes<sup>14</sup> (eq 3.7). This method is important in the synthesis of fully substituted tetrahydropyrans. An oxocarbenium ion intermediate was generated by nucleophilic attack of trimethylsilyloxy group with electrophilic aldehyde, followed by intramolecular cyclization during which two new stereocenters are formed with high diastereoselectivities.

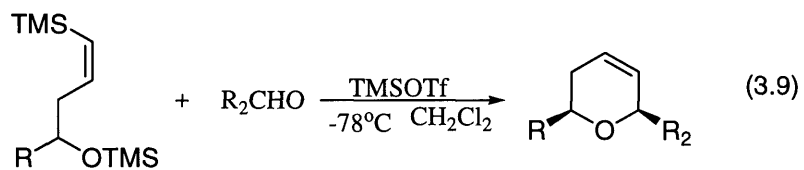


The third construction of 2,6-disubstituted dihydropyrans involves vinylsilane terminated cyclization of ester-substituted oxocarbenium ion intermediates<sup>15</sup> (eq 3.8). It should be noted that the configuration of vinylsilanes has an important effect in the diastereomeric ratio of products. The *Z*-configurations generally led to high *cis*-selectivity, however, the *E*-configuration afforded the *trans* isomer with moderate selectivity.



Yet another method is the intramolecular silyl-modified Sakurai reaction (ISMS).  $\beta$ -Trimethylsilyloxy vinyltrimethylsilanes were reacted with several aldehydes in TMSOTf catalyst<sup>16</sup> (eq 3.9). TMSOTf is a strong Lewis acid, thus, this reaction is

usually carried out at  $-78^{\circ}\text{C}$ . Dobbs and co-workers recently described a variation of this reaction in which they used (*Z*)-4-trimethylsilyl-3-buten-1-ol, an unprotected homoallylic alcohol, and aldehydes were under  $\text{InCl}_3$  initiated condition.<sup>17</sup>



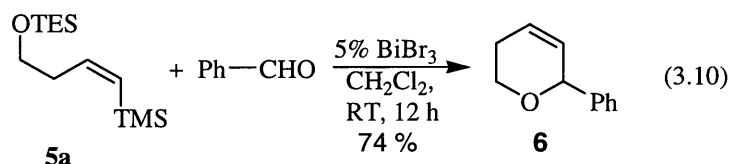
## Synthetic strategy for dihydropyrans

2,6-Disubstituted dihydropyran systems are important targets in organic synthesis. These ring systems are not only present in many natural products, such as scytophycin C1,<sup>9</sup> but are also synthetically useful intermediates for polysubstituted tetrahydropyran ring systems. As previously outlined, many approaches<sup>18</sup> have been reported for dihydropyran synthesis, such as annulating reaction with trimethylsilylallyltributylstannane<sup>18f</sup> and the intramolecular silyl-modified Sakurai reaction (ISMS)<sup>18b,18d</sup> using TMSOTf as catalyst. Dobbs and co-workers<sup>17,18a</sup> utilized the 4-trimethylsilyl-3-buten-1-ols and aldehydes under InCl<sub>3</sub> conditions to obtain the dihydropyran units in good yield with high diastereoselectivities. However, the toxicity of tin compounds in the annulation reaction and the chromatographic overlap of products with the tin derivatives limited its application. TMSOTf as a strong Lewis acid requires strictly anhydrous conditions at low temperature conditions. Indium is also toxic and using 1.0 equiv. makes it expensive as an initiator and causes some environmental problems. In addition, few examples of InCl<sub>3</sub> initiated reactions with aromatic rings have been reported.

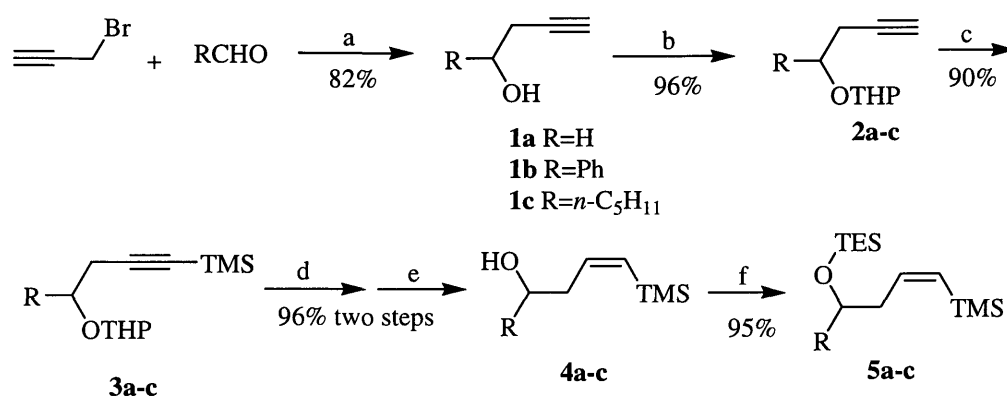
Recently, bismuth compounds, which are convenient, inexpensive, and environmentally friendly sources of Lewis acid, have become studied as effective catalysts in organic synthesis.<sup>19</sup> Many of the reactions that bismuth initiates are simple silyl-protection and deprotection during the reactions. Several groups have described the

synthesis of tetrahydropyran derivatives by using the silyl-protected alcohol and aldehydes and/or ketones.<sup>20</sup> Based on the chemistry involving vinyltrimethylsilane as a nucleophile to attack oxocarbenium ions, it is now possible to synthesize 2,6-disubstituted dihydropyrans using BiBr<sub>3</sub> as an initiator for cyclization reactions.

We initially used the simple (*Z*)-1-trimethylsilyl-4-triethylsilyloxy-butene, **5a** with benzaldehyde, to establish this approach to dihydropyran moiety (eq **3.10**). Fortunately, the cyclization proceeded in excellent yield. We also investigated the use of TBDMS protected alcohol and obtained the desired product in 84 % yield, but extended reaction time under refluxing conditions were required. Therefore, we turned our attention to triethylsilyl protected vinyltrimethylsilanes to react with several aldehydes.

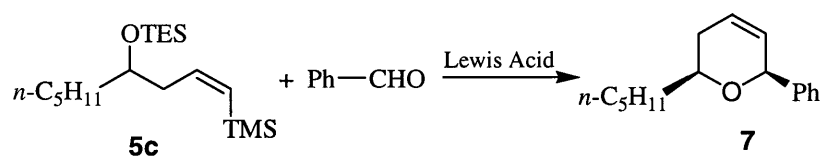


The required  $\beta$ -triethylsilyloxy vinyltrimethylsilane substrates, **5a-c**, (Scheme **3.2**) were synthesized by a six steps process: Propargyl bromide was added to aldehydes under the ultrasonic conditions reported by Lee etc.<sup>21</sup> to obtain the homopropargylic alcohols, **1a-c**. The hydroxyl moiety was subsequently protected as DHP (or TBDMS) ether, **2a-c**, and the alkyne silylated to generate alkyntrimethylsilanes, **3a-c**. DIBAL-H reduction of the silylated alkyne and cleavage of protecting group provided (*Z*)- $\beta$ -hydroxy-vinyltrimethylsilanes, **4a-c**, in good yields and selectivities.<sup>22</sup> The alcohols were then simply reprotected as  $\beta$ -triethylsilyloxy derivatives, **5a-c**.

**Scheme 3.2:** Synthesis of key intermediate, **5** in the construction of dihydropyrans

(a) ICH<sub>2</sub>CH<sub>2</sub>I, Zn, THF, Ultrasonic. (b) DHP, 1 mol % TsOH, CH<sub>2</sub>Cl<sub>2</sub> (c) BuLi, TMSCl, THF.  
 (d) 1.7 equiv. DIBAL-H, Et<sub>2</sub>O, 45 °C. (e) PPTs, EtOH, 55 °C. (f) TESOTf, imid, CH<sub>2</sub>Cl<sub>2</sub>.

Several Lewis acids were examined to optimize this silyl-Prins reaction (**Table 3.1**). Considering that one mole BiBr<sub>3</sub> might generate 2 moles HBr (the same reasoning for TiCl<sub>4</sub>), the amount of other Lewis acids used as initiators were doubled. Of the Lewis acids screened, BiBr<sub>3</sub> in CH<sub>2</sub>Cl<sub>2</sub> afforded the best yields of desired product, **7**.

**Table 3.1:** Optimization for the synthesis of dihydropyran, **7**

entry <sup>a</sup>	Lewis acid	Conditions	dr (GC, <i>cis/trans</i> ) <sup>b</sup>	Yield(%) <sup>c</sup>
1	5% BiBr <sub>3</sub>	Rt	>99:1	70
2	5% BiBr <sub>3</sub> <sup>d</sup>	Rt	>99:1	55
3	10% HCl	Rt	>99:1	45
4	5% TiCl <sub>4</sub>	-78 °C to Rt	>99:1	18
5	10% BF <sub>3</sub>	-78 °C to Rt	>99:1	60
6	10% TMSOTf	-78 °C to Rt	>99:1	54

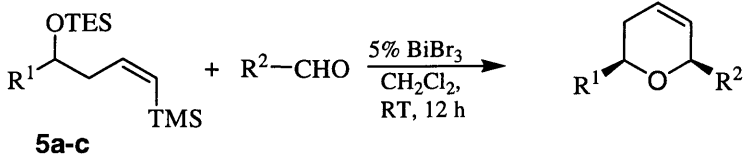
<sup>a</sup> All reactions were carried on 0.5 mmol scale in 5.0 mL CH<sub>2</sub>Cl<sub>2</sub> at room temperature using 2.0 equiv. benzaldehydes.

<sup>b</sup> Diastereomeric ratios were determined by capillary GC analysis of crude reaction mixtures.

<sup>c</sup> Isolated yield of pure *cis*-isomers only, after column flash chromatography.

<sup>d</sup> The reaction was carried in 5.0 mL CH<sub>3</sub>CN instead of CH<sub>2</sub>Cl<sub>2</sub>.

Encouraged by the bismuth results, we turned our attention to the effects of different substituents on both the vinylsilanes and aromatic aldehyde. Both aliphatic and aromatic aldehydes were effective substrates, reacting smoothly with the vinylsilanes to provide the expected dihydropyrans in good to excellent yields. Our data from **Table 3.2** indicate that most reactions provided the *cis*- isomers with high stereoselectivity. In general, the major stereoisomer arises by the cyclization of an *E*-oxocarbenium ion (**I**, **Figure 3.3**) in a chairlike conformation. The electrophilic cyclization is concerted with the addition of the electrophile and nucleophile to the alkene taking place with an synclinal geometry. Precedent<sup>23,18c,18d</sup> indicates that the oxa-Cope rearrangement of **I** to **II** occurs prior to cyclization as shown in **Figure 3.3**. Although the Cope rearrangement is believed to be fast compared to the cyclization process, there should be some distribution between the intermediates **I** and **II**, because different groups would stabilize the oxocarbenium ion energy by different amounts. If phenyl rings are conjugated with the oxocarbenium ion to distribute the positive charge, this would stabilize the oxocarbenium ion by resonance. The TMS group in the axial position would also stabilize the  $\beta$ -cation much more effectively than a TMS in equatorial position are shown in intermediate **III** (**Figure 3.3**), so the conversion from transition state structure **III** to *trans*-isomer is expected to be slow relative to Silyl-Prins from intermediate **II**. This stereoelectronic effect probably explains why the *cis* products were the dominant isomers.

**Table 3.2.** Synthesis of disubstituted dihydropyrans


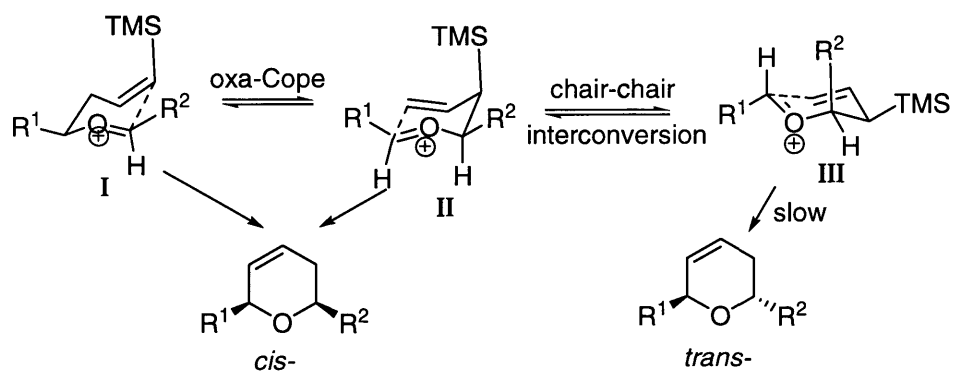
entry <sup>a</sup>	silane R <sup>1</sup>	Aldehyde R <sup>2</sup>	dr (GC, <i>cis/trans</i> ) <sup>b</sup>	Products (Yield, %) <sup>c</sup>
1	H	Ph-	-----	<b>6</b> (74)
2	<i>n</i> -C <sub>5</sub> H <sub>11</sub> -	Ph-	>99:1	<b>7</b> (70)
3	Ph	<i>p</i> -CF <sub>3</sub> Ph-	>99:1	<b>8</b> (82)
4	Ph	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> -	2-3:1 <sup>d</sup>	<b>9</b> (47)
5	Ph	PhCH <sub>2</sub> -	35:1	<b>10</b> (94)
6	Ph	Ph-	4-5:1	<b>11</b> (55)
7	<i>n</i> -C <sub>5</sub> H <sub>11</sub> -	<i>p</i> -CF <sub>3</sub> Ph-	73:1	<b>12</b> (74)
8	<i>n</i> -C <sub>5</sub> H <sub>11</sub> -	<i>p</i> -MeOC <sub>6</sub> H <sub>4</sub> -	2-3:1 <sup>d</sup>	<b>13</b> (58)
9	<i>n</i> -C <sub>5</sub> H <sub>11</sub> -	PhCH <sub>2</sub> -	45:1	<b>14</b> (97)
10	<i>n</i> -C <sub>5</sub> H <sub>11</sub> -	<i>i</i> -Pr-	>99:1	<b>15</b> (88)
11	<i>n</i> -C <sub>5</sub> H <sub>11</sub> -	<i>o</i> -CHOPh-	>99:1	<b>16</b> (98)

<sup>a</sup> All the reactions were carried on 0.5 mmol scale in 5.0 mL CH<sub>2</sub>Cl<sub>2</sub> at room temperature using 2.0 equiv. aldehydes.

<sup>b</sup> Diastereomeric ratios were determined by capillary GC analysis of crude reaction mixtures.

<sup>c</sup> Isolated yield of pure *cis*-isomers only, after column flash chromatography.

<sup>d</sup> Diastereomeric ratios were determined by <sup>1</sup>H NMR spectroscopic analysis of crude reaction mixtures.

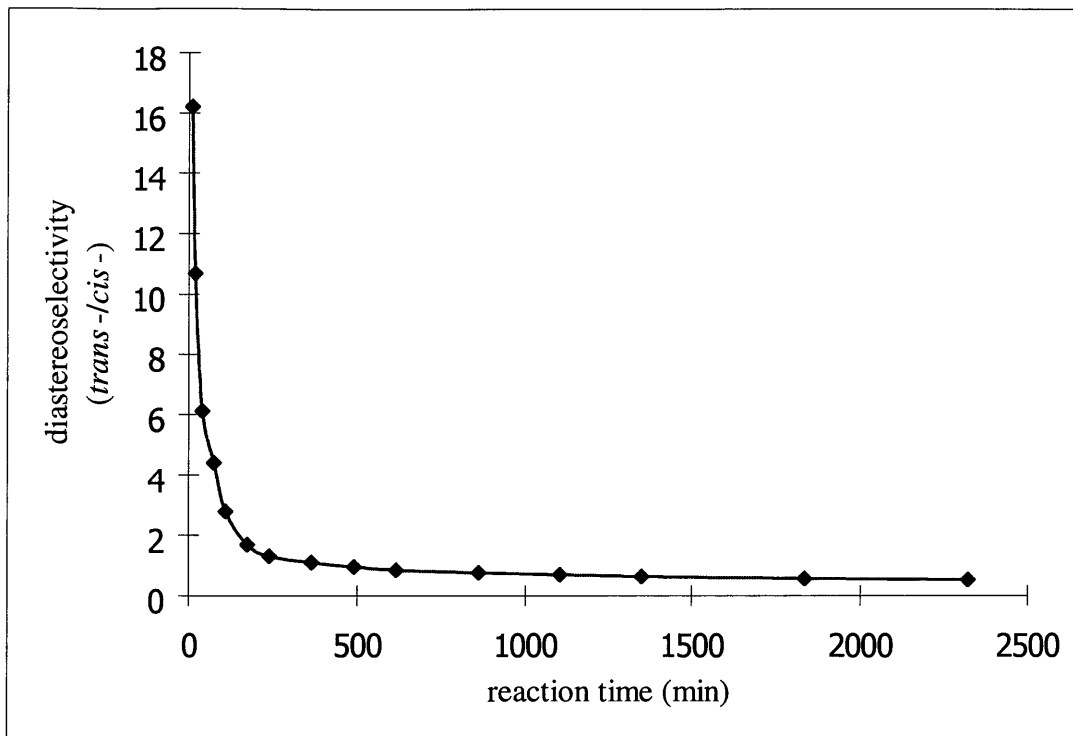
**Figure 3.3:** Possible transition state in Prins cyclizations

The moderate diastereoselectivity of 2,6-diphenyl-3,6-dihydro-2H-pyran (**entry 6**, **Table 3.2**) was significantly different from other highly selective reactions in **Table 3.2**. This product is, however, different from other entries. When either structure **I** or **II** was

the dominant transition state structure, the positive charge of oxocarbenium ion would distribute in either phenyl ring equally. When two phenyl rings were *trans*, it was more effective to distribute the positive charge and the transition state energy was lowered. Therefore, energy difference between *trans*- and *cis*- oxocarbenium ions should be smaller than other entries, and lowered the selectivity.

Compared to aliphatic aldehydes, the use of aromatic aldehydes resulted in somewhat lower yields. It was interesting that introduction of an electron withdrawing group in aromatic rings would increase the yields and electron donating group would decrease the yields (**Entries 2-4, 6-8, Table 3.2**). To our knowledge, no one has reported anisaldehyde as a carbonyl moiety in this ISMS reaction before, possibly because of the low yield. The yield was reasonably good, however, under BiBr<sub>3</sub>-initiated reaction conditions. Surprisingly, the diastereoselectivities for the anisole-derived products (**entries 4 and 8, Table 3.2**) were much lower than those of other reactions and during observation of the reaction by <sup>1</sup>H NMR spectroscopy, it appeared that the *trans*-isomers slowly isomerized to the more stable *cis*- isomer. Therefore, we conducted the reaction between anisaldehyde and (*Z*)-1-(1-(triethylsilyloxy)-4-(trimethylsilyl)but-3-enyl) benzene in an NMR tube using CDCl<sub>3</sub> as solvent and determined the correlation between initial ratio of *trans*-/*cis*- dihydropyran and reaction time (**Figure 3.4**).

**Figure 3.4:** The correlation between reaction time and diastereoselectivity (*trans*-/*cis*-) for entry 4

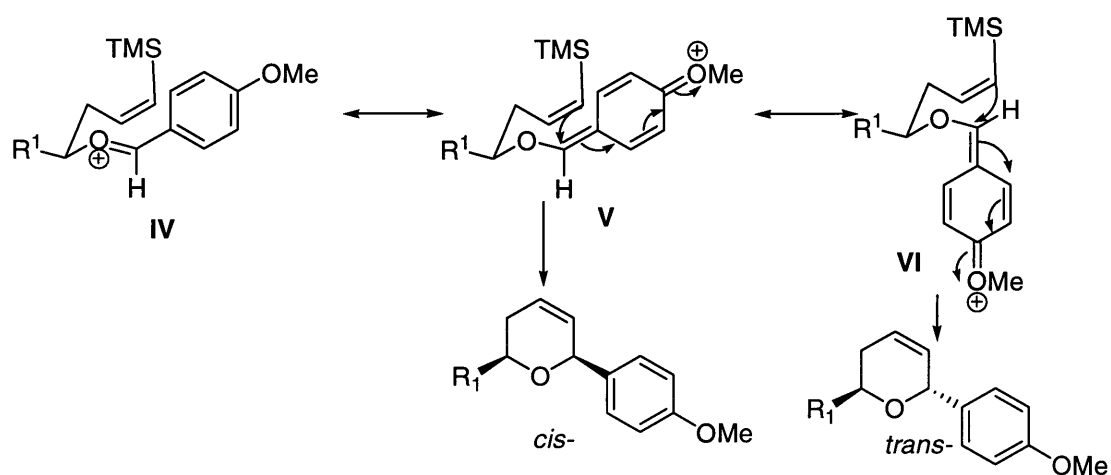


The reaction was carried in 0.1 mmol scale in 1.0 mL  $\text{CDCl}_3$ , using 5%  $\text{BiBr}_3$  as catalyst and 2.0 equiv. anisaldehyde. The  $\text{CDCl}_3$  was passed through  $\text{MgSO}_4$  and basic  $\text{Al}_2\text{O}_3$  to eliminate trace water and acid. The reaction was completed in *Ca.* 110 min, according to the consumption of vinyltrimethylsilane.

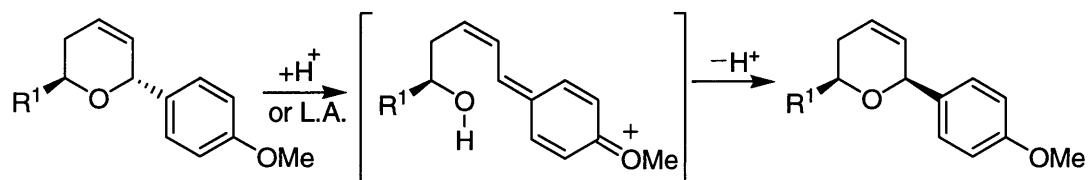
According to **Figure 3.4**, the diastereoselectivity of *trans*-/*cis*- dihydropyran decreased with prolonged reaction time and the *trans* isomer was initially the major product. We propose that the *trans*- isomer is kinetic preferred and it isomerizes to more thermodynamically stable *cis*-isomer. This inverse result is possibly due to the different stabilities of oxocarbenium ion intermediates shown in **Figure 3.5**. The methoxy group at the *para* position of aromatic ring would stabilize the oxocarbenium ion **IV** as **V** and/or **VI**. Due to the steric and/or electrostatic interactions, structure **VI** is more stable than **V**, so the *trans* isomer is dominant in product distribution. It also supports that the initial

control of ISMS reactions is a kinetic effect rather than a thermodynamic factor. Under the weakly acidic (Lewis or Bronsted) reaction condition, the *trans*-isomers then equilibrate to the more stable *cis*-isomers (**Figure 3.6**). The intermediate benzylic cation is electronically stabilized so that even under trace acid conditions, such as normal  $\text{CDCl}_3$ , the isomerization proceeds readily.

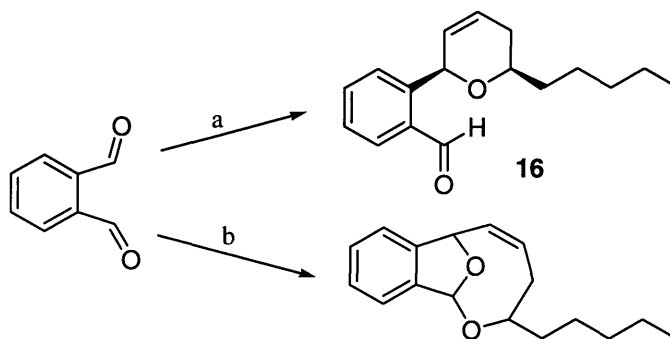
**Figure 3.5:** Possible transition state for reaction with anisaldehyde



**Figure 3.6.** Possible *trans*- and *cis*- equilibration pathway



**Figure 3.7:** Possible products of the reaction between phthalaldehyde and (Z)-4-(triethylsilyloxy)-1-(trimethylsilyl)non-1-ene

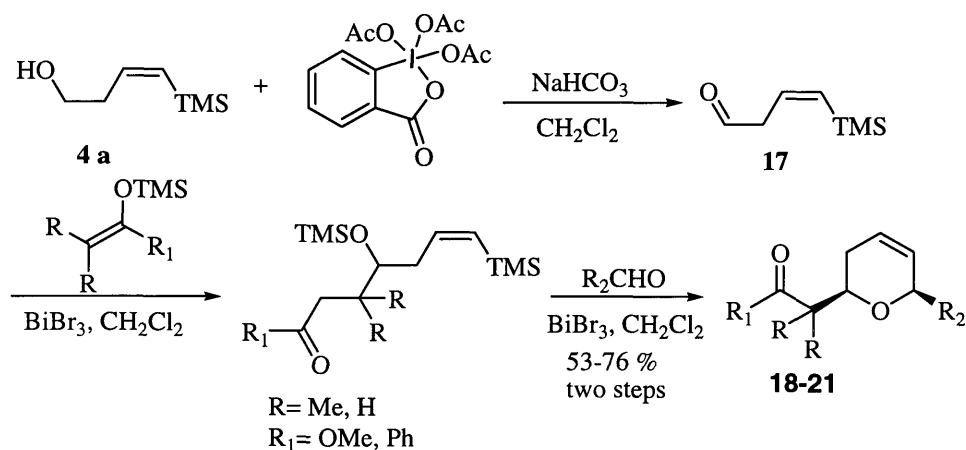


The final example in **Table 3.2** using phthalaldehyde as an electrophile afforded only 2-(6-pentyl-5,6-dihydro-2H-pyran-2-yl)benzaldehyde, **16** (**Table 3.2**, entry **11**). This is surprising since the rapid intramolecular cyclizations occur when phthalaldehyde reacts with other nucleophiles such as allyltrimethylsilane. In this case, isobenzofurans are usually produced (**Figure 3.7**, **Path b**). However, under  $\text{BiBr}_3$  and vinyltrimethylsilane conditions, only one carbonyl group participated in the reaction (**Figure 3.7**, **Path a**). This type of selectivity is powerful in organic synthesis, because the remaining carbonyl group can be converted to other functional groups to provide many useful products. This aspect of vinylsilane chemistry is now under further investigation. This result also supports the fact that the ISMS reaction prefers a six-member ring transition state, otherwise, isobenzofurans involving eight-member ring should be detected.

In other work<sup>24</sup> on the addition of silyl ketene acetals with several aldehydes, TMS protected  $\beta$ -alkoxy esters were the major products under  $\text{BiBr}_3$  conditions using  $\text{CH}_2\text{Cl}_2$  as solvent. Therefore, we developed a two step reaction that utilized the reaction

between enol ethers or ketene silyl acetals with (*Z*)-4-(trimethylsilyl)but-3-enal, **17**, to form the  $\beta$ -trimethylsilyloxy vinyltrimethylsilanes, followed by addition of a second aldehyde results in 2,6-disubstituted dihydropyrans in good yields and excellent diastereoselectivities (**Scheme 3.3** and **Table 3.3**). This approach can introduce two different substitutions at the 2- and 6- positions in dihydropyrans in a single reaction vessel.

**Scheme 3.3:** Synthetic steps for three component one pot reaction



The synthesis of (*Z*)-4-(trimethylsilyl)but-3-enal, **17**, was somewhat challenging, because it was relatively unstable under basic, or strongly acid conditions as well as upon exposure to silica gel. The  $\beta,\gamma$ -unsaturated aldehyde could easily rearrange to the  $\alpha,\beta$ -unsaturated aldehyde. Therefore, PCC as well as PDC oxidation failed to provide the product. At last, we turned our attention to utilizing the Dess-Martin periodinane oxidation using  $\text{NaHCO}_3$  as additive. The product was obtained in good yield with moderate purity and was used without any further purification.

**Table 3.3:** Two step tandem reactions for dihydropyran synthesis

entry	nucleophiles	Aldehyde R <sub>2</sub>	dr (GC, <i>cis/trans</i> ) <sup>a</sup>	Products (Yield, %) <sup>b</sup>
1	R=Me, R <sub>1</sub> =OMe	PhCH <sub>2</sub> -	>99:1	<b>18</b> (64)
2	R=Me, R <sub>1</sub> =OMe	<i>i</i> -Pr-	>99:1	<b>19</b> (53)
3	R=Me, R <sub>1</sub> =OMe	<i>o</i> -CHOPh-	>99:1	<b>20</b> (55)
4	R=H, R <sub>1</sub> =Ph	<i>n</i> -C <sub>5</sub> H <sub>11</sub> -	>99:1	<b>21</b> (76)

<sup>a</sup> Diastereomeric ratios were determined by capillary GC analysis of crude reaction mixtures.

<sup>b</sup> Isolated yield of pure *cis*-isomers only, after column flash chromatography.

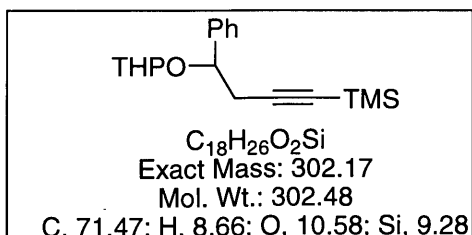
In summary, we have demonstrated a rapid synthesis to 2, 6-disubstituted dihydropyrans in high yield and good selectivity by using a catalytic amount of BiBr<sub>3</sub>, as a mild Lewis acid with extremely low toxicity. When reacted with phthaldehyde, a useful product, 2-(6-pentyl-5,6-dihydro-2H-pyran-2-yl)benzaldehyde is obtained. Different substituents affect the transition state structures and change the distribution of the products differently. Finally, the bismuth(III) initiated three component, one pot tandem addition/cyclization reactions between ketene silyl acetals, silyl enol ether, vinylsilanes and aldehydes afforded a extremely mild and convenient alternatives to other Lewis acids such as BF<sub>3</sub>H<sub>2</sub>O or TMSOTf.

## EXPERIMENTAL SECTION

All reagents were used as received unless otherwise noted. Dichloromethane was distilled from  $\text{CaH}_2$  and THF was purified *via* a Solv-Tek<sup>®</sup> solvent purification system. Propargyl bromide, benzyl aldehyde, chlorotrimethylsilane, imidazole, *p*-anisaldehyde as well as 3,4-dihydro-2H-pyran were purchased from Acros. Hexanal, diiodoethane, *n*-butyllithium and phenylacetaldehyde were purchased from Aldrich Chemical Company, Inc.  $^{13}\text{C}$  NMR spectra were recorded with the aid of an APT sequence in which methylene and quaternary carbons = e (even) and methyl and methine carbons = o (odd). Coupling constants were determined by the method of Hoye, and relative stereochemistry was established by qualitative n.O.e. experiments. Thin layer chromatography was performed on Sigma-Aldrich general-purpose silica gel on glass and flash chromatography was performed using Sorbent Technologies chromatographic silica gel (200-475 MESH). Melting points were recorded by a Mel-Temp<sup>®</sup> apparatus and are uncorrected.

### Preparation of *trimethyl(4-phenyl-4-(tetrahydro-2H-pyran-2-yloxy)but-1-ynyl)silane*,

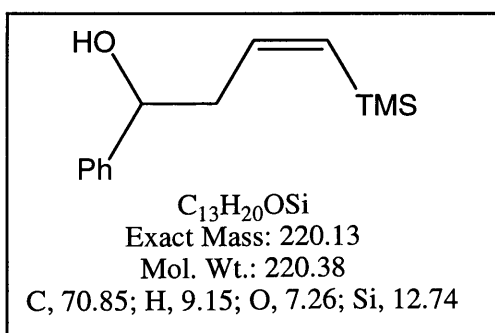
**3b**: A solution of *n*-butyllithium (1.6 M in hexanes, 16.2 mL, 25.9 mmol, 1.4 equiv.) was



added dropwise over 20 min at  $-30\text{ }^\circ\text{C}$  into a solution of 2-(1-phenyl- but-3-ynyloxy)-tetrahydro

-2H-pyran, **2b** (4.26 g, 18.5 mmol in 60 mL THF). The solution was stirred for additional 10 min and was cooled to  $-50\text{ }^{\circ}\text{C}$ . Chlorotrimethyl silane (7.30 mL, 33.3 mmol, 1.80 equiv.) was added over 10 min. After the mixture reached rt, 40 mL water was added slowly and the phases were separated. The aqueous layer was extracted with ether (2 X 30 mL), the organic layer was combined, dried ( $\text{MgSO}_4$ ) and concentrated in *vacuo*. The product was purified by column chromatography (9:1 hexanes:EtOAc,  $R_f = 0.62$ ) to afford 5.26 g (94%) as a colorless liquid ; IR (neat): 3033(w), 2947(s), 2179(m), 1252(m), 1122(m), 1207(s), 980(m), 847(s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.24-7.42 (m, 1H), 5.07, 4.51 (t,  $J = 3.1$  Hz, 1H), 4.85, 4.81 (dd,  $J = 8.1, 5.9$  Hz, 1H), 4.15 (td,  $J = 11.0, 2.9$  Hz, 0.76H), 3.50-3.58 (m, 1H), 3.29-3.35 (m, 0.34H), 2.77, 2.69 (dd,  $J = 16.9, 8.4$  Hz, 1H), 2.55, 2.54 (dd,  $J = 16.8, 5.1$  Hz, 1H), 1.40-1.98 (m, 6H), 0.14, 0.13 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 142.2(e), 140.8(e), 128.3(o), 128.2(o), 128.0(o), 127.4(o), 127.0(o), 126.3(o), 104.4(e), 104.1(e), 98.8(o), 94.5(o), 86.6(e), 86.3(e), 77.0(o), 75.2(o), 62.1(e), 61.5(e), 30.7(e), 30.6(e), 29.9(e), 29.6(e), 25.9(e), 25.7(e), 19.3(e), 19.0(e), 0.62(o), 0.35(o).

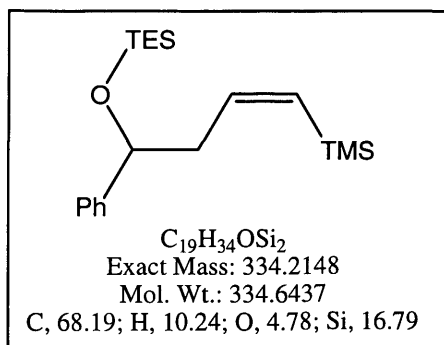
**Preparation of (Z)-1-phenyl-4-(trimethylsilyl)but-3-en-1-ol, 4b.** A solution of



DIBAL-H (20 % w.t. in toluene, 21.9 mL, 26.5 mmol, 1.70 equiv.) was added dropwise at  $0\text{ }^{\circ}\text{C}$  to a solution of trimethyl(4-phenyl-4-(tetrahydro-2H-pyran-2-yl)oxy)-but-1-ynyl)silane, **3b**

(4.72 g, 15.6 mmol) in 60 mL Et<sub>2</sub>O. After stirring for 1 h, the mixture was heated to 45 °C for 20 h. The solution was cooled to 0 °C again and saturated aqueous NH<sub>4</sub>Cl solution (10 mL) was added very slowly. The mixture was acidified until all precipitate had dissolved. The phases were separated and the aqueous layer was extracted by ether (2 X 30 mL). The combined organic layer was dried (MgSO<sub>4</sub>) and concentrated in *vacuo* leaving some colorless oil. The oil was transferred to 250 mL flask and 100 mL ethanol as well as pyridinium toluene-*p*-sulfonate (0.463 g, 1.72 mmol) were added. The mixture was stirred for 12 h at rt and 2 h at 55 °C. The solution was concentrated and the residue was purified by flash chromatography (8:2 hexanes:EtOAc, R<sub>f</sub> = 0.44) to afford 3.30 g (96%) as a colorless liquid ; IR (neat): 3056(br, s), 3024(m), 2957(s), 2899(s),1607(s), 1411(m), 1251(s), 1042(s), 842(s) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.30-7.41 (m, 5H), 6.36 (ddd, *J* = 14.6, 8.1, 7.0 Hz, 1H), 5.75 (dt, *J* = 13.9, 1.5 Hz, 1H), 2.56-2.69 (m, 2H), 2.03 (d, *J* = 2.9 Hz, 1H), 0.10 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 144.0 (e), 143.9(o), 133.5(o), 128.5(o), 127.7(o), 125.9(o), 74.0(o), 43.5(e), 0.6(o).

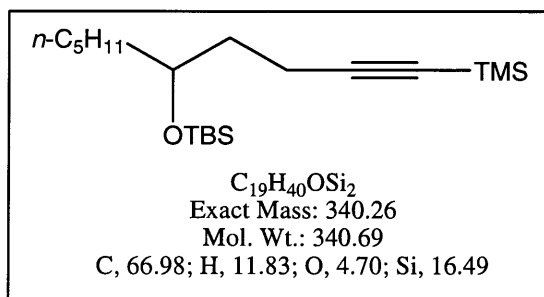
#### Preparation of (Z)-1-(1-(triethylsilyloxy)-4-(trimethylsilyl)but-3-enyl)benzene, **5b**.



A solution of (Z)-1-phenyl-4-(trimethylsilyl)but-3-en-1-ol, **4b** (1.18 g, 5.34 mmol) in freshly distilled CH<sub>2</sub>Cl<sub>2</sub> (11 mL) was placed in a flame-dried round bottom flask under argon. Imidazole (0.52 g, 7.64 mmol) was added to the

solution and the solution was cooled to 0 °C using an ice water bath. TESOTf (1.45 mL, 6.41 mmol) was added to the cooled solution and the mixture was allowed to warm to rt and stir. When starting material was consumed (~1 h, TLC), aqueous NaHCO<sub>3</sub> (ca. 10 mL) was added, the product was then extracted with CH<sub>2</sub>Cl<sub>2</sub>, washed with brine, dried (MgSO<sub>4</sub>), and concentrated *in vacuo*. The resulting silanol was purified by column chromatography (95:5 hexanes:ethyl acetate, R<sub>f</sub> = 0.76) to provide 1.70 g (95%) as a colorless liquid; IR (neat): 2957(s), 2883(s), 1607(m), 1458(s), 1242(s), 1090(s), 1009(s), 840(s) cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ: 7.26-7.36 (m, 5H), 6.34 (td, *J* = 14.3, 7.3 Hz, 1H), 5.60 (d, *J* = 14.3 Hz, 1H), 4.71 (dd, *J* = 7.3, 5.5 Hz, 1H), 2.44-2.64 (m, 2H), 0.91 (t, *J* = 8.0 Hz, 9H), 0.56 (qd, *J* = 8.7, 3.7 Hz, 6H), 0.11 (s, 9H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ: 145.3(e), 145.0(o), 131.1(o), 128.1(o), 127.1(o), 126.0(o), 75.2(o), 44.9(e), 7.2(o), 5.2(e), 0.6(o); Anal. calcd. For C<sub>19</sub>H<sub>34</sub>OSi<sub>2</sub> (334.64): C 68.19, H 10.24; Found: C 68.01, H 10.26.

**Preparation of 5-(tert-butyldimethylsilyloxy)- 1-(trimethylsilyl)dec-1-yne, 3c.** A

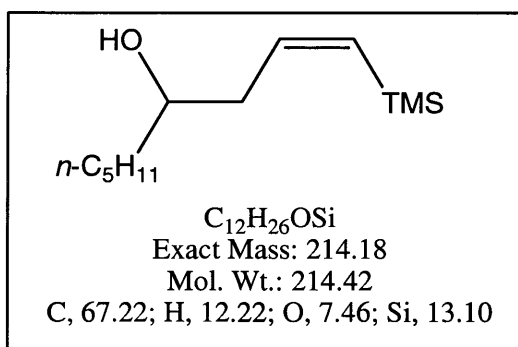


solution of *n*-butyllithium (1.6 M in hexanes, 8.8 mL, 14.0 mmol, 1.4 equiv.) was added dropwise over 15 min at -30 °C into a solution of *tert*-butyl(dec-1-yn-5-yloxy)

dimethylsilane, **2c** (2.83 g, 10 mmol in 45 mL THF). The solution was stirred for additional 10 min and was cooled to -50 °C. Chlorotrimethylsilane (4.0 mL, 18.0 mmol,

1.8 equiv.) was added over 10 min. After the mixture reached rt, 40 mL water was added slowly and the phases were separated. The aqueous layer was extracted with ether (3 X 30 mL), The organic layer was combined and dried ( $\text{MgSO}_4$ ) and concentrated in *vacuo*. The product was purified by column chromatography (95:5 hexanes:EtOAc,  $R_f = 0.40$ ) to afford 5.26 g (94%) as a colorless liquid; IR (neat): 3745(w), 2931(s), 2857(s), 2176(m), 1458(m), 1251(s), 1096(s), 842(s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 3.75-3.81 (m, 1H), 2.34 (d,  $J = 6.1$  Hz, 2H), 1.22-1.62 (m, 8H), 0.90 (t,  $J = 6.8$  Hz, 3H), 0.89 (s, 9H), 0.14 (s, 9H), 0.08 (d,  $J = 7.6$  Hz, 6H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 105.1(e), 86.1(e), 71.4(o), 37.2(e), 32.2(e), 29.1(e), 26.2(o), 25.0(e), 22.9(e), 18.5(e), 14.4(o), 0.5(o), -4.0(o), -4.2(o).

**Preparation of (Z)-1-(trimethylsilyl)non-1-en-4-ol, 4c.** A solution of DIBAL-H (20%

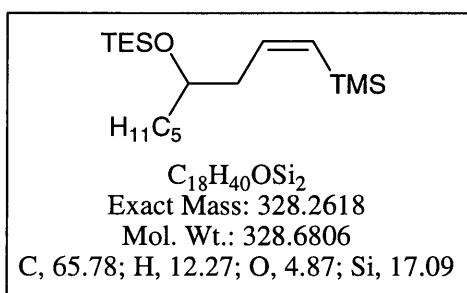


w.t. in toluene, 8.4 mL, 10.2 mmol, 1.7 equiv.) was added dropwise at 0 °C to a solution of 5-(*tert*-butyldimethylsilyloxy)-1-(trimethylsilyl)dec-1-yne, **3c** (2.05 g, 6.0 mmol) in 35 mL  $\text{Et}_2\text{O}$ . After stirring for 1 h, the mixture was

heated to 45 °C for 20 h. The solution was cooled to 0 °C again and saturated aqueous  $\text{NH}_4\text{Cl}$  solution (5 mL) was added slowly. The mixture was acidified until all precipitate had dissolved. The phases were separated and the aqueous layer was extracted by ether (2 X 20 mL). The combined organic layers were dried ( $\text{MgSO}_4$ ) and concentrated in *vacuo*

leaving a colorless oil. The oil was transferred to 100 mL flask and 50 mL ethanol as well as tetrabutylammonium fluoride (2.35 g, 9.0 mmol) were added. The mixture was stirred for 12 h. The solution was concentrated and the residue was purified by flash chromatography (9:1 hexanes:EtOAc,  $R_f = 0.45$ ) to afford 1.01 g (78%) as a colorless liquid; IR (neat): 3349(s, br), 2955(s), 2947(s), 2864(s), 1607(m), 1450(m), 1250(s), 1043(m), 841(s), 764(m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 6.36 (ddd,  $J = 14.6, 8.1, 7.0$  Hz, 1H), 5.70 (d,  $J = 14.3$  Hz, 1H), 3.65-3.71 (m, 1H), 2.24-2.39 (m, 2H), 1.28-1.62 (m, 8H), 0.91 (t,  $J = 6.9$  Hz, 3H), 0.15 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 144.5(o), 132.9(o), 71.5(o), 41.5(e), 37.3(e), 32.2(e), 25.7(e), 23.0(e), 14.4(o), 0.6(o).

**Preparation of (Z)-4-(triethylsilyloxy)-1-(trimethylsilyl)non-1-ene, 5c.** A solution of



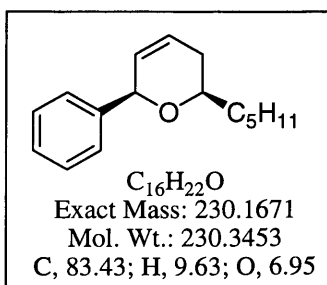
(Z)-1-(trimethylsilyl)non-1-en-4-ol, **4c** (0.69 g, 3.2 mmol) in freshly distilled  $\text{CH}_2\text{Cl}_2$  (10 mL) was placed in a flame-dried round bottom flask under argon. Imidazole (0.33 g, 4.8 mmol) was added to

the solution and the solution was cooled to  $0^\circ\text{C}$  using an ice water bath. TESOTf (0.87 mL, 3.84 mmol) was added to the cooled solution and the mixture was allowed to warm to rt and stir. When starting material was consumed ( $\sim 1$  h, TLC), aqueous  $\text{NaHCO}_3$  (ca. 10 mL) was added, the product was then extracted with  $\text{CH}_2\text{Cl}_2$ , washed with brine, dried ( $\text{MgSO}_4$ ), and concentrated *in vacuo*. The resulting silanol was purified by column chromatography (99:1 hexanes:ethyl acetate,  $R_f = 0.63$ ) to provide 1.01 g (96%) as a

colorless liquid; IR (neat): 2947(s), 2880(s), 1607(m), 1461(m), 1242(s), 1080(s), 1010(s), 841(s), 737(s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ): 6.36 (dt,  $J = 14.3, 7.1$  Hz, 1H), 5.58 (d,  $J = 14.3$  Hz, 1H), 3.73 (dddd,  $J = 5.5, 5.5, 5.5, 5.5$  Hz, 1H), 2.29-2.34 (m, 2H), 1.25-1.50 (m, 8H), 0.98 (t,  $J = 8.0$  Hz, 9H), 0.91 (t,  $J = 7.3$  Hz, 3H), 0.62 (q,  $J = 8.0$  Hz, 6H), 0.14 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 145.4(o), 130.6(o), 72.5(o), 41.5(e), 37.6(e), 32.3(e), 25.5(e), 23.0(e), 14.4(o), 7.3(o), 5.5(e), 0.6(o); Anal. calcd. For  $\text{C}_{18}\text{H}_{40}\text{OSi}_2$  (328.68): C 65.78, H 12.27; Found: C 65.63, H 12.25.

**General procedure for the synthesis of dihydropyrans:**  $\text{BiBr}_3$  (11.2 mg, 0.025 mmol, 0.05 equiv.) was weighed into 10 mL round bottom flask and 5 mL  $\text{CH}_2\text{Cl}_2$  was added via syringe. Aldehyde (1.0 mmol, 2.0 equiv.) and vinylsilane (0.167 g, 0.5 mmol) were added by syringe sequentially. The mixture was stirred for 12 h and was concentrated *in vacuo*, filtered through a small  $\text{SiO}_2$  pipette column with  $\text{CH}_2\text{Cl}_2$  as eluent and concentrated *in vacuo* again. The product was then purified by column chromatography.

**Preparation of *cis*-2-pentyl-6-phenyl-3,6-dihydro-2H-pyran, 7.** According to the

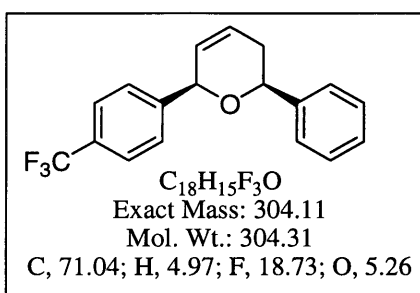


general procedure, benzyl aldehyde (102  $\mu\text{l}$ , 1.0 mmol, 2.0 equiv.) was treated with (Z)-4-(triethylsilyloxy)-1-(trimethylsilyl)non-1-ene, **5c** (0.164 g, 0.5 mmol) to provide 0.081 g (70%) of *cis*-isomer as a colorless liquid,

after purification by column chromatography (97:3 pentane:ether,  $R_f = 0.39$ ); IR (neat):

3032(m), 2926(s), 2857(s), 1450(m), 1180(m), 1074(s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.25-7.39 (m, 5H), 5.88-5.93 (m, 1H), 5.74 (ddq,  $J = 9.9, 2.9, 1.5$  Hz, 1H), 5.15 (m, 1H), 3.69-3.75 (m, 1H), 1.99-2.14 (m, 2H), 1.25-1.70 (m, 8H), 0.88 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 141.9(e), 130.3(o), 128.5(o), 127.8(o), 127.3(o), 124.9(o), 77.9(o), 74.7(o), 36.4(e), 32.2(e), 31.2(e), 25.5(e), 23.0(e), 14.5(o).

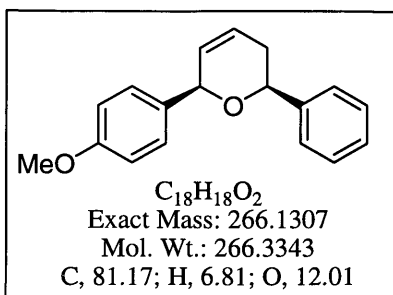
### Preparation of *cis*-2-phenyl-6-(4-(trifluoromethyl)phenyl)-3,6-dihydro-2H-pyran, **8**.



According to the general procedure, *p*-trifluoromethyl benzaldehyde (137  $\mu\text{L}$ , 1.0 mmol, 2.0 equiv.) was treated with (*Z*)-1-(1-(triethylsilyloxy)-4-(trimethylsilyl)but-3-enyl)benzene, **5b** (0.167 g, 0.50 mmol) to

provide 0.125 g (82%) of *cis*-isomer as a colorless oil, after purification by column chromatography (97:3 petroleum ether:ether,  $R_f = 0.42$ ); IR (neat): 3037(m), 2902(m), 2834(m), 1612(m), 1495(w), 1412(m), 1326(s), 1166(s), 1124(s), 1067(s), 828(s), 751(s), 700(s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.62 (d,  $J = 8.4$  Hz, 2H), 7.57 (d,  $J = 8.4$  Hz, 2H), 7.41-7.45 (m, 2H), 7.36 (tm,  $J = 7.7$  Hz, 2H), 7.28 (tt,  $J = 7.0, 1.5$  Hz, 1H), 6.03 (ddq,  $J = 10.3, 5.9, 2.2$  Hz, 1H), 5.81 (ddq,  $J = 10.3, 2.6, 1.5$  Hz, 1H), 5.42-5.46 (m, 1H), 4.83 (dd,  $J = 10.6, 3.7$  Hz, 1H), 2.31-2.39 (dddd,  $J = 17.2, 6.6, 3.3, 3.3, 1.1$  Hz, 1H), 2.42-2.51 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 145.5(e), 142.3(e), 129.9(e, q,  $J = 32.6$  Hz), 129.6(o), 128.5(o), 127.7(o), 127.3(o), 125.9(o), 124.3(e, q,  $J = 269.2$  Hz), 125.5(o, q,  $J = 3.8$  Hz), 125.4(o), 77.8(o), 76.4(o), 33.2(e).

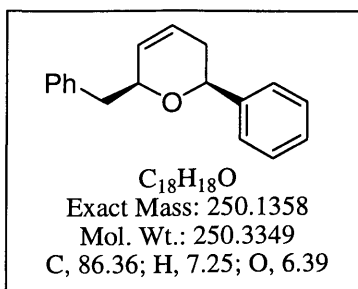
**Preparation of *cis*-6-(4-methoxyphenyl)-2-phenyl-3,6-dihydro-2H-pyran, 9.**



According to the general procedure, *p*-anisaldehyde (0.136 g, 1.0 mmol, 2.0 equiv.) was treated with (*Z*)-1-(1-(triethylsilyloxy)-4-(trimethylsilyl)but-3-enyl)-benzene, **5b** (0.167 g, 0.50 mmol) to provide 0.063 g

(47%) of *cis*-isomer as a white powder, after purification by column chromatography (9:1 pentane:ether,  $R_f = 0.41$ ); IR (neat): 3034(m), 2911(m), 2834(m), 1604(m), 1504(s), 1457(m), 1246(s), 1175(m), 1061(m), 1036(m), 826(m)  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$ : 7.23-7.43 (m, 9H), 6.87-6.91 (m, 2H), 5.97-6.02 (m, 1H), 5.81 (ddq,  $J = 10.3, 2.5, 1.5$  Hz, 1H), 5.31-5.34 (m, 1H), 4.81 (dd,  $J = 10.6, 3.7$  Hz, 1H), 3.80 (s, 3H), 2.39-2.48 (m, 1H), 2.28-2.35 (m, 1H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$ : 159.2(e), 142.7(e), 133.8(e), 130.6(o), 128.6(o), 128.4(o), 127.5(o), 126.0(o), 124.6(o), 113.9(o), 78.0(o), 76.4(o), 55.6(o), 33.3(e); Anal. calcd. For  $C_{18}H_{18}O$  (266.33): C 81.17, H 6.81; Found: C 80.87, H 6.79.

**Preparation of *cis*-6-benzyl-2-phenyl-3,6-dihydro-2H-pyran, 10.** According to the

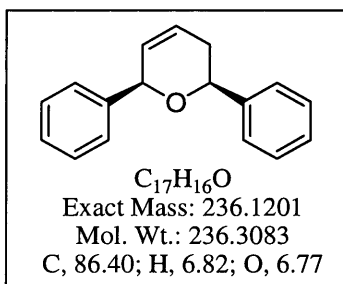


general procedure, Phenylacetaldehyde (0.12 g, 1.0 mmol, 2.0 equiv.) was treated with (*Z*)-1-(1-(triethylsilyloxy)-4-(trimethylsilyl)but-3-enyl)-benzene, **5b** (0.167 g, 0.5 mmol) to provide 0.118 g (94%) of *cis*-isomer as a

colorless liquid, after purification by column chromatography (9:1 pentane:ether,  $R_f =$

0.57); IR (neat): 3032(s), 2918(m), 2827(m), 1739(m), 1489(m), 1443(m), 1080(s), 747(s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.20-7.40 (m, 10H), 5.86-5.91 (m, 1H), 5.83 (ddq,  $J = 10.3, 2.6, 1.5$  Hz, 1H), 4.62 (dd,  $J = 9.2, 5.1$  Hz, 1H), 5.52-5.58 (m, 1H), 3.08 (dd,  $J = 13.5, 6.6$  Hz, 1H), 2.83 (dd,  $J = 13.5, 6.6$  Hz, 1H), 2.18-2.29 (m, 2H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 142.9(e), 138.2(e), 129.8(o), 129.4(o), 128.4(o), 128.2(o), 127.4(o), 126.3(o), 125.8(o), 125.1(o), 76.6(o), 75.9(o), 42.3(e), 33.3(e); Anal. calcd. For  $\text{C}_{18}\text{H}_{18}\text{O}$  (250.33): C 86.36, H 7.25; Found: C 86.32, H 7.44.

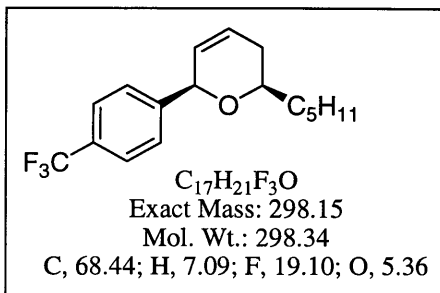
**Preparation of *cis*-2,6-diphenyl-3,6-dihydro-2H-pyran, 11.** According to the general



procedure, benzaldehyde (102  $\mu\text{L}$ , 1.0 mmol, 2.0 equiv.) was treated with (*Z*)-1-(1-(triethylsilyloxy)-4-(trimethylsilyl)but-3-enyl)benzene, **5b** (0.167 g, 0.5 mmol) to provide 0.065 g (55 %) of *cis*-isomer as a colorless liquid, after

purification by column chromatography (97:3 pentane:ether,  $R_f = 0.54$ ); IR (neat): 3031(s), 2898(m), 2823(m), 1494(m), 1451(m), 1064(s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.25-7.46 (m, 10H), 5.97-6.02 (m, 1H), 5.83 (ddq,  $J = 10.3, 2.9, 1.5$  Hz, 1H), 5.37-5.40 (m, 1H), 4.83 (dd,  $J = 10.3, 3.3$  Hz, 1H), 2.41-2.50 (m, 1H), 2.30-2.37 (m, 1H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 142.7(e), 141.6(e), 130.4(o), 128.5(o), 128.4(o), 127.8(o), 127.5(o), 127.2(o), 126.0(o), 124.6(o), 78.4(o), 76.3(o), 33.3(e).

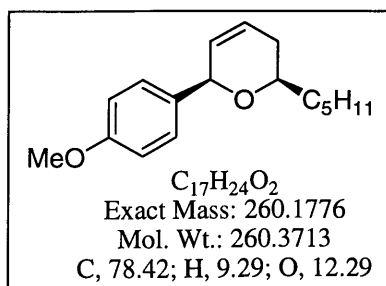
### Preparation of *cis*-2-pentyl-6-(4-(trifluoromethyl)phenyl)-3,6-dihydro-2H-pyran, 12.



According to the general procedure, *p*-trifluoromethylbenzaldehyde (137  $\mu$ L, 1.0 mmol, 2.0 equiv.) was treated with (*Z*)-4-(triethylsilyloxy)-1-(trimethylsilyl)non-1-ene, **5c** (0.164g, 0.50 mmol) to provide

0.110 g (74%) of *cis*-isomer as a colorless liquid, after purification by column chromatography (98:2 petroleum:ether,  $R_f$  = 0.57); IR (neat): 3038(m), 2931(s), 2861(s), 1621(m), 1419(s), 1319(s), 1166(s), 1127(s), 1075(s), 894(m), 831(m)  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$ : 7.59 (d,  $J$  = 8.4 Hz, 2H), 7.49 (d,  $J$  = 8.4 Hz, 2H), 5.93 (ddt,  $J$  = 10.3, 5.1, 2.5 Hz, 1H), 5.70 (dm,  $J$  = 10.3 Hz, 1H), 5.19-5.23 (m, 1H), 3.70-3.76 (m, 1H), 2.01-2.16 (m, 2H), 1.25-1.70 (m, 8H), 0.89 (t,  $J$  = 6.8 Hz, 3H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$ : 145.9(e), 129.9(e, q,  $J$  = 31.8 Hz), 129.4(o), 127.4(o), 125.6(o), 125.5(o, q,  $J$  = 3.8 Hz), 124.3(e, q,  $J$  = 269.6 Hz), 77.2(o), 74.7(e), 36.3(e), 32.2(e), 31.1(e), 25.4(e), 23.0(e), 14.4(o).

### Preparation of *cis*-6-(4-methoxyphenyl)-2-pentyl-3,6-dihydro-2H-pyran, 13.

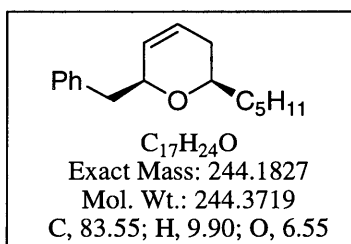


According to the general procedure, *p*-anisaldehyde (0.136 g, 1.0 mmol, 2.0 equiv.) was treated with (*Z*)-4-(triethylsilyloxy)-1-(trimethylsilyl)non-1-ene, **5c** (0.164 g, 0.5 mmol) to provide 0.076 g (58%) of

*cis*-isomer as a colorless liquid, after purification by column chromatography (9:1

pentane:ether,  $R_f = 0.54$ ); IR (neat): 3036(m), 2932(s), 2861(s), 1614(m), 1513(s), 1458(m), 1247(s), 1177(m), 1072(s), 1040(s), 818(m)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.30 (d,  $J = 8.4$ , 2H), 6.88 (d,  $J = 8.8$  Hz, 2H), 5.90-5.95 (m, 1H), 5.74 (ddq,  $J = 9.9$ , 2.6, 1.5 Hz, 1H), 5.11 (m, 1H), 3.80 (s, 3H), 3.68-3.75 (m, 1H), 1.99-2.15 (m, 2H), 1.25-1.70 (m, 8H), 0.89 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 159.2(e), 134.1(e), 130.4(o), 128.7(o), 125.0(o), 114.0(o), 77.4(o), 74.8(o), 36.4(e), 32.2(e), 31.3(e), 25.5(e), 23.0(e), 14.5(o); Anal. calcd. For  $\text{C}_{17}\text{H}_{24}\text{O}$  (260.37): C 78.42, H 9.29; Found: C 78.16, H 9.49.

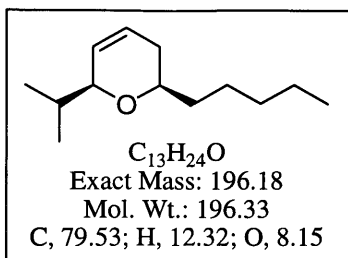
**Preparation of *cis*-6-benzyl-2-pentyl-3,6-dihydro-2H-pyran, 14.** According to the



general procedure, phenylacetaldehyde (0.12 g, 1.0 mmol, 2.0 equiv.) was treated with (*Z*)-4-(triethyl-silyloxy)-1-(trimethylsilyl) non-1-ene, **5c** (0.164 g, 0.5 mmol) to provide 0.119 g (97%) of *cis*-isomer as a colorless liquid,

after purification by column chromatography (97:3 pentane:ether,  $R_f = 0.45$ ); IR (neat): 3032(m), 2929(s), 2859(s), 1450(m), 1183(m), 1080(s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.21-7.33 (m, 5H), 5.79-5.84 (m, 1H), 5.64 (dm,  $J = 10.3$  Hz, 1H), 4.34 (m, 1H), 3.51-3.58 (m, 1H), 3.02 (dd,  $J = 13.5$ , 7.0 Hz, 1H), 2.71 (dd,  $J = 13.5$ , 7.0 Hz, 1H), 1.96-2.01 (m, 2H), 1.25-1.66 (m, 8H), 0.91 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 148.5(e), 129.7(o), 129.5(o), 128.2(o), 126.2(o), 125.2(o), 76.0(o), 74.3(o), 42.3(e), 36.4(e), 32.2(e), 31.6(e), 25.5(e), 23.0(e), 14.4(o).

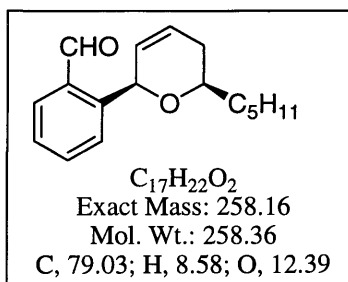
**Preparation of *cis*-6-isopropyl-2-pentyl-3,6-dihydro-2H-pyran, 15.** According to the



general procedure, isobutyl- aldehyde (91  $\mu$ l, 1.0 mmol, 2.0 equiv.) was treated with (Z)-4-(triethyl-silyloxy)-1-(trimethylsilyl)non-1-ene, **5c** (0.164 g, 0.50 mmol) to provide 0.086 g (88%) of *cis*-isomer as a colorless liquid,

after purification by column chromatography (98:2 petroleum:ether,  $R_f$  = 0.68); IR (neat): 3033(m), 2958(s), 2930(s), 2868(s), 1464(m), 1370(m), 1288(w), 1188(m), 1080(s)  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $CDCl_3$ )  $\delta$ : 5.80-5.85 (m, 1H), 5.74 (dq,  $J$  = 10.3, 1.5 Hz, 1H), 3.84-3.88 (m, 1H), 3.45-3.51 (m, 1H), 1.90-1.94 (m, 2H), 1.71-1.79 (ddq,  $J$  = 12.1, 7.0, 1.5 Hz, 1H), 1.25-1.60 (m, 8H), 0.89 (t,  $J$  = 6.8 Hz, 3H);  $^{13}C$  NMR (100 MHz,  $CDCl_3$ )  $\delta$ : 128.6(o), 125.6(o), 79.8(o), 74.0(o), 36.4(e), 33.0(o), 32.2(e), 31.8(e), 25.5(e), 23.0(e), 18.3(o), 14.4(o). Anal. calcd. For  $C_{13}H_{24}O$  (196.33): C 79.53, H 12.32; Found: C 79.17, H 12.29.

**Preparation of *cis*-2-(6-pentyl-5,6-dihydro-2H-pyran-2-yl)benzaldehyde, 16.**

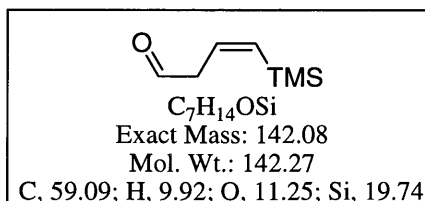


According to the general procedure, Phthalaldehyde (0.134 g, 1.0 mmol, 2.0 equiv.) was treated with (Z)-4-(triethyl-silyloxy)-1-(trimethylsilyl)non-1-ene, **5c** (0.164 g, 0.50 mmol) to provide 0.126 g (98%) of *cis*-isomer as a

colorless liquid, after purification by column chromatography (9:1 petroleum:ether,  $R_f$  =

0.60); IR (neat): 3037(m), 2928(s), 2859(s), 2737(s), 1696(s), 1459(m), 1191(s), 1072(s), 759(s)  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 10.4 (s, 1H), 7.89 (dd,  $J = 7.7, 1.5$  Hz, 1H), 7.61 (dt,  $J = 7.5, 1.5$  Hz, 1H), 7.57 (dt,  $J = 7.5, 1.5$  Hz, 1H), 7.44 (dt,  $J = 7.3, 1.5$  Hz, 1H), 5.89-5.94 (m, 1H), 5.80-5.84 (m, 1H), 5.77-5.79 (m, 1H), 3.77-3.84 (m, 1H), 2.04-2.18 (m, 2H), 1.24-1.69 (m, 8H), 0.88 (t,  $J = 6.8$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 192.7(o), 143.7(e), 134.0(o), 133.8(e), 131.0(o), 129.8(o), 128.2(o), 128.1(o), 125.2(o), 75.1(o), 75.0(o), 36.3(e), 32.2(e), 31.0(e), 25.3(e), 22.9(e), 14.4(o). Anal. calcd. For  $\text{C}_{17}\text{H}_{22}\text{O}_2$  (258.36): C 79.03, H 8.58; Found: C 79.02, H 8.80.

#### Preparation of (Z)-4-(trimethylsilyl)but-3-enal, 17:

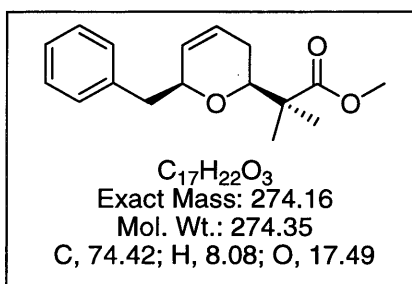


1,1,1-Triacetoxy-1,1-dihydro-1,2-benziodoxol-3(1H)-one (0.512 g, 1.2 mmol, 1.2 equiv.) and  $\text{NaHCO}_3$  (0.420 g, 5.0 mmol, 5.0 equiv.) were weighted into 25 mL round bottom flask and 8 mL  $\text{CH}_2\text{Cl}_2$  was added *via* syringe. (Z)-4-(trimethylsilyl)but-3-en-1-ol, **5a** (0.144 g, 1.0 mmol, 1.0 equiv.) in 3 mL  $\text{CH}_2\text{Cl}_2$  was injected slowly. When starting material was consumed (~0.5 h, TLC), 10 mL  $\text{Et}_2\text{O}$  was poured into the solution and then poured into a mixture consist of saturated  $\text{NaHCO}_3$  (ca. 10 mL), saturated  $\text{Na}_2\text{S}_2\text{O}_3$  (ca. 10 mL),  $\text{H}_2\text{O}$  (ca. 20 mL). The product was then extracted with  $\text{Et}_2\text{O}$  (ca. 50 mL), dried ( $\text{MgSO}_4$ ), and concentrated *in vacuo* to provide 0.129g (91%) as a pale yellow oil. IR (neat): 2957(s), 2725(m), 1682(s), 1412(m), 1250(s), 1119(m), 844(s);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 9.71 (t,  $J = 1.8$  Hz, 1H), 6.44

(dt,  $J = 14.3, 7.3$  Hz, 1H), 5.88 (dt,  $J = 14.3, 1.6$  Hz, 1H), 3.29 (dt,  $J = 7.3, 1.6$  Hz, 2H), 0.14 (s, 9H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 199.4(o), 136.3(o), 135.8(o), 48.1(e), 0.37(o).

**Preparation of *cis*-methyl-2-(6-benzyl-3,6-dihydro-2H-pyran-2-yl)-2-methyl**

**propanoate, 18:**  $\text{BiBr}_3$  (44.8 mg, 0.010 mmol, 0.10 equiv.) was weighed into 25 mL

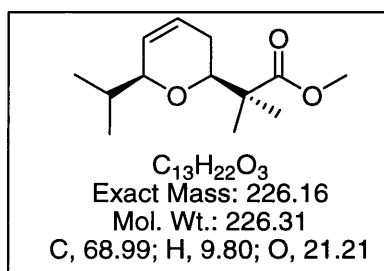


round bottom flask and 10 mL  $\text{CH}_2\text{Cl}_2$  was added *via* syringe. (*Z*)-4-(trimethylsilyl)but-3-enal, **17** (0.142 g, 1.0 mmol, 1.0 equiv.) and dimethyl silyl ketene acetal (0.192 g, 1.1 mmol, 1.1 equiv.) were added by

syringe simultaneously. The mixture was stirred and TLC was used to maintain the reaction until (*Z*)-4-(trimethylsilyl)but-3-enal, **17** was consumed (3 h). Phenylacetaldehyde (0.24 g, 2.0 mmol, 2.0 equiv.) and additional  $\text{BiBr}_3$  (44.8 mg, 0.010 mmol, 0.10 equiv) were added and the mixture was stirred for 12 h. The solution was concentrated *in vacuo*, filtered through a small  $\text{SiO}_2$  pipette column with  $\text{CH}_2\text{Cl}_2$  as eluent and concentrated *in vacuo* again. The product was purified by column chromatography (9:1 petroleum ether: $\text{Et}_2\text{O}$ ,  $R_f = 0.34$ ) to provide 0.175 g (64%) of *cis*-isomer as a colorless oil. IR (neat): 3031(s), 2982(s), 2940(s), 2879(m), 1735(s), 1451(m), 1267(s), 1140(s), 1086(s), 751(m);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.17-7.28 (m, 5H), 5.77-5.82 (m, 1H), 5.63 (dm,  $J = 10.3$  Hz, 1H), 4.27 (br, 1H), 3.77 (dd,  $J = 11.0, 3.3$  Hz, 1H), 3.55 (s, 3H), 2.83 (dd,  $J = 13.9, 8.1$  Hz, 1H), 2.70 (dd,  $J = 13.9, 8.1$  Hz, 1H),

2.06-2.15 (m, 1H), 1.77-1.85 (m, 1H), 1.20 (s, 3H), 1.21(s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 177.2(e), 138.7(e), 129.72(o), 129.69(o), 128.0(o), 126.1(o), 125.0(o), 78.4(o), 76.5(o), 52.0(o), 46.6(e), 42.1(e), 25.4(e), 21.3(o), 20.4(o). Anal. calcd. For  $\text{C}_{17}\text{H}_{22}\text{O}_3$  (274.35): C 74.42, H 8.08; Found: C 74.53, H 8.30.

**Preparation of cis-methyl-2-(6-isopropyl-3,6-dihydro-2H-pyran-2-yl)-2-methyl propanoate, 19:**  $\text{BiBr}_3$  (44.8 mg, 0.010 mmol, 0.10 equiv.) was wighted into 25 mL



round bottom flask and 10 mL  $\text{CH}_2\text{Cl}_2$  was added *via* syringe. (Z)-4-(trimethyl- silyl)but-3-enal, **17** (0.142 g, 1.0 mmol, 1.0 equiv.) and dimethyl silyl ketene acetal (0.192 g, 1.1 mmol, 1.1 equiv.) were added by syringe

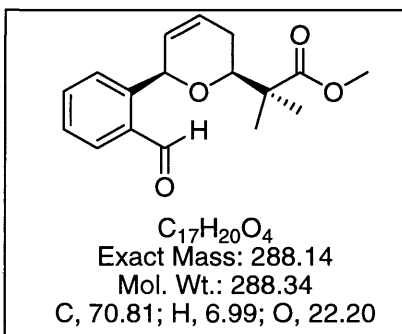
simultaneously. The mixture was stirred and TLC was used to maintain the reaction until (Z)-4-(trimethylsilyl)but-3-enal, **17** was consumed (3 h). Isobutylaldehyde (0.182 mL, 2.0 mmol, 2.0 equiv.) and  $\text{BiBr}_3$  (44.8 mg, 0.010 mmol, 0.10 equiv.) were added and the mixture was stirred for 12 h. The solution was concentrated *in vacuo*, filtered through a small  $\text{SiO}_2$  pipette column with  $\text{CH}_2\text{Cl}_2$  as eluent and concentrated *in vacuo* again. The product was purified by column chromatography (9:1 petroleum ether: $\text{Et}_2\text{O}$ ,  $R_f = 0.52$ ) to provide 0.120 g (53%) of *cis*-isomer as a colorless oil. IR (neat): 2961(s), 1737(s), 1458(w), 1368(w), 1258(m), 1136(m), 1084(m);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 5.80-5.85 (m, 1H), 5.63 (dm,  $J = 10.3$  Hz, 1H), 3.86 (br, 1H), 3.75 (dd,  $J = 10.6, 2.9$  Hz, 1H), 3.67 (s, 3H), 2.04-2.12 (m, 1H), 1.76-1.83 (m, 1H), 1.70 (dtt,  $J = 7.0, 7.0, 5.1$  Hz,

1H), 1.22 (s, 3H), 1.14 (s, 3H), 0.90 (d,  $J = 7.0$  Hz, 3H), 0.86 (d,  $J = 7.0$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 177.4(e), 128.9(o), 125.1(o), 80.0(o), 77.9(o), 52.0(o), 46.7(e), 32.9(o), 25.5(e), 21.2(o), 20.4(o), 18.6(o), 17.5(o). Anal. calcd. For  $\text{C}_{13}\text{H}_{22}\text{O}_3$  (226.31): C 68.99, H 9.80; Found: C 68.29, H 9.61.

**Preparation of *cis*-methyl-2-(6-(2-formylphenyl)-3,6-dihydro-2H-pyran-2-yl)-2-methylpropanoate, 20:**

$\text{BiBr}_3$  (22.4 mg, 0.005 mmol, 0.10 equiv.) was weighed into

25 mL round bottom flask and 5 mL  $\text{CH}_2\text{Cl}_2$  was added



via syringe. (*Z*)-4-(trimethylsilyl)but-3-enal, **17** (0.071

g, 0.50 mmol, 1.0 equiv.) and dimethyl silyl ketene

acetal (0.096 g, 0.55 mmol, 1.1 equiv.) were added by

syringe simultaneously. The mixture was stirred and

TLC was used to maintain the reaction until

(*Z*)-4-(trimethylsilyl)but-3-enal, **17** was consumed (3 h). Phthaldehyde (0.134 g, 1.0

mmol, 2.0 equiv.) and additional  $\text{BiBr}_3$  (22.4 mg, 0.005 mmol, 0.10 equiv.) were added

and the mixture was stirred for 12 h. The solution was concentrated *in vacuo*, filtered

through a small  $\text{SiO}_2$  pipette column with  $\text{CH}_2\text{Cl}_2$  as eluent and concentrated *in vacuo*

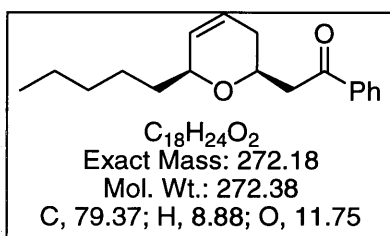
again. The product was purified by column chromatography (8:2 petroleum ether: $\text{Et}_2\text{O}$ ,

$R_f = 0.22$ ) to provide 0.079 g (55%) of *cis*-isomer as a colorless oil. IR (neat): 3743(w),

2980(w), 1733(s), 1698(s), 1558(m), 1464(m), 1266(m), 1195(m), 1139(m), 1077(m),

760(m);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 10.33 (s, 1H), 7.88 (dd,  $J = 7.7, 1.1$  Hz, 1H), 7.56-7.63 (m, 2H), 7.47 (t,  $J = 7.3, 1.5$  Hz, 1H), 5.90-5.95 (m, 1H), 5.85-5.88 (m, 1H), 5.78-5.82 (dm,  $J = 10.3$  Hz, 1H), 4.13 (dd,  $J = 11.0, 3.3$  Hz, 1H), 3.70 (s, 3H), 2.27-2.38 (m, 1H), 1.97-2.04 (dm,  $J = 17.2$  Hz, 1H), 1.29 (s, 3H), 1.22 (s, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 192.7(o), 177.0(e), 143.6(e), 134.0(o), 133.6(e), 131.4(o), 129.7(o), 128.0(o), 127.8(o), 124.7(o), 78.8(o), 75.5(o), 52.2(o), 46.7(e), 25.1(e), 21.4(o), 20.6(o)

**Preparation of *cis*-2-(6-pentyl-3,6-dihydro-2H-pyran-2-yl)-1-phenylethanone, 21:**



$\text{BiBr}_3$  (22.4 mg, 0.005 mmol, 0.10 equiv.) and  $\text{NaI}$  (22.5 mg, 0.015 mmol, 0.30 equiv.) were weighed into 15 mL round bottom flask and 5 mL  $\text{CH}_2\text{Cl}_2$  was added *via* syringe. After ultrasonic for 1 h at rt, (*Z*)-4-(trimethylsilyl)but-3-enal, **17** (0.071 g, 0.50 mmol, 1.0 equiv.) and trimethyl (1-phenylvinyl)oxy silane (0.106 g, 0.55 mmol, 1.1 equiv.) were added by syringe simultaneously. The mixture was stirred and TLC was used to maintain the reaction until (*Z*)-4-(trimethylsilyl)but-3-enal, **17** was consumed (2 h). Hexanal (0.134 g, 1.0 mmol, 2.0 equiv.) and additional  $\text{BiBr}_3$  (22.4 mg, 0.005 mmol, 0.10 equiv.) were added and the mixture was stirred for 12 h. The solution was concentrated *in vacuo*, filtered through a small  $\text{SiO}_2$  pipette column with  $\text{CH}_2\text{Cl}_2$  as eluent and concentrated *in vacuo* again. The product was purified by column chromatography (9:1 petroleum ether: $\text{Et}_2\text{O}$ ,  $R_f = 0.38$ ) to provide 0.104 g (76%) of *cis*-isomer as a colorless oil. IR (neat): 3743(w), 2929(s), 2861(s),

1686(s), 1452(m), 1371(m), 1336(m), 1281(m), 1217(m), 1181(m), 1075(m), 993(m), 751(m);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ )  $\delta$ : 7.98-8.01 (m, 2H), 7.56 (tt,  $J = 7.3, 1.5$  Hz, 1H), 7.44-7.48 (m, 2H), 5.77-5.82 (m, 1H), 5.64 (dm,  $J = 10.3$  Hz, 1H), 4.16-4.23 (m, 1H), 4.08-4.14 (m, 1H), 3.40 (dd,  $J = 15.7, 6.6$  Hz, 1H), 2.98 (dd,  $J = 15.7, 6.6$  Hz, 1H), 2.02-2.18 (m, 2H), 1.18-1.50 (m, 8H), 0.85 (t,  $J = 6.7$  Hz, 3H);  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ )  $\delta$ : 198.5(e), 137.5(e), 130.1(o), 130.6(o), 128.6(o), 128.4(o), 124.2(o), 75.2(o), 71.0(o), 45.4(e), 35.8(e), 32.1(e), 31.6(e), 25.1(e), 22.9(e), 14.4(o). Anal. calcd. For  $\text{C}_{18}\text{H}_{24}\text{O}_2$  (272.38): C 79.37, H 8.88; Found: C 79.22, H 9.01.

## REFERENCES

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- <sup>1</sup> Sommer, L. H.; Bailey, D. L.; Goldberg, G. M.; Buck, C.E.; Bye, T.S.; Evans, F. J.; Whitmore, F. C. *J. Am. Chem. Soc.* **1954**, *76*, 1613.
- <sup>2</sup> Koenig, K.E.; Weber, W. P. *J. Am. Chem. Soc.* **1973**, *95*, 3416.
- <sup>3</sup> Bock, H.; Seidl, H. *J. Organometal. Chem.* **1968**, *13*, 87.
- <sup>4</sup> Burke, S.D.; Murtishaw, C. W.; Dike, M. S.; Smith Strickland, S. M.; Saunders, J. O. *J. Org. Chem.* **1981**, *103*, 6529.
- <sup>5</sup> Tius, M. A.; Sadaquat, A. *J. Org. Chem.* **1982**, *47*, 3163.
- <sup>6</sup> Overman, L.E.; Bell, K.L. *J. Am. Chem. Soc.* **1981**, *103*, 1851.
- <sup>7</sup> a) Denmark, S. E.; Germans, J. P. *Tetrahedron Lett.* **1984**, *25*, 1231. b) Tius, M. A. *Tetrahedron Lett.* **1981**, *22*, 3335. c) Chow, H. F.; Fleming, I. J. *J. Chem. Soc., Perkin Trans. 1* **1984**, 1815. d) Overman, L. E.; Castaneda, A.; Blumenkopf, T. A. *J. Am. Chem. Soc.* **1986**, *108*, 1303.
- <sup>8</sup> Overman, L. E.; Malone, T. C.; Meier, G. P. *J. Am. Chem. Soc.* **1983**, *105*, 6993.
- <sup>9</sup> Roush, W. R.; Dilley, G. J. *Synlett.* **2001**, *SI*, 955-959.
- <sup>10</sup> Ramnauth, J.; Poulin, O.; Rakhit, S.; Maddaford, S. P. *Org. Lett.* **2001**, *3*, 2013-2015.

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- <sup>11</sup> Schmidt, B. *Org. Lett.* **2000**, *2*, 791-794.
- <sup>12</sup> Paterson, I.; Luckhurst, C. A. *Tetrahedron Lett.* **2003**, *44*, 3749-3754.
- <sup>13</sup> Viswanathan, G. S.; Yang, J.; Li, C. *Org. Lett.* **1999**, *1*, 993-995.
- <sup>14</sup> Lowe, J. T.; Panek, J. S. *Org. Lett.* **2005**, *7*, 1529-1532.
- <sup>15</sup> Semeyn, S.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426-3427.
- <sup>16</sup> Marko, I.; Bayston, D. J. *Tetrahedron* **1994**, *50*, 7141-7156.
- <sup>17</sup> Dobbs, A. P.; martinovic, S. *Tetrahedron Lett.* **2002**, *43*, 7055-7057.
- <sup>18</sup> (a) Dobbs, A. P.; Guesne, S. J.; Martinovic, S.; Coles, S.; Hursthouse, M. B. *J. Org. Chem.* **2003**, *68*, 7880-7883. (b) Marko, I. E.; Bayston, D. J. *Tetrahedron* **1994**, *50*, 7141-7156. (c) Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem.* **1997**, *62*, 3426-3427. (d) Marko, I. E.; Dobbs, A. P.; Scheirmann, V.; Chelle, F., Bayston, D. J. *Tetrahedron Lett.* **1997**, *34*, 2899-2902. (e) Brimble, M. A.; Pavia G. S.; Stevenson, R. J. *Tetrahedron Lett.* **2002**, *43*, 1735-1738. (f) Viswanathan, G. S.; Yang, J.; Li, C. *Org. Lett.* **1999**, *1*, 993-995.
- <sup>19</sup> (a) Komatsu, N. In *Organobismuth Chemistry*; Suzuki, H.; Matano, Y., Eds.; Elsevier: New York, 2001; pp 371-440. (b) Leonard, N. M.; Wieland, L. C.; Mohan, R. S. *Tetrahedron* **2002**, *58*, 8373-8397.

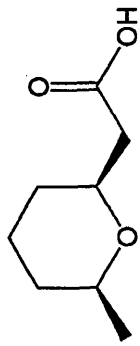
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- <sup>20</sup> (a) Evans, P. A.; Cui, J.; Gharpure, S. J.; Hinkle, R. J. *J. Am. Chem. Soc.* **2003**, *125*, 11456-11457. (b) Evans, P. A.; Cui, J.; Gharpure, S. J.; Polosukhin, A.; Zhang, H.-R. *J. Am. Chem. Soc.* **2003**, *125*, 14702-14703. (c) Evans, P. A.; Cui, J.; Gharpure, S. J. *Org. Lett.* **2003**, *5*, 3883-3885. (d) Komatsu, N.; Ishida, J. Y.; Suzuki, H. *Tetrahedron Lett.* **1997**, *38*, 7219-7222. (f) Hinkle, R. J.; Lian, Y.; Litvinas, N. D.; Jenkins, A. T.; Burnette, D. C. *Tetrahedron* **2005**, *61*, 11679-11685
- <sup>21</sup> Lee, A. S.; Chu, S.; Chang, Y.; Wang, S. *Tetrahedron Lett.* **2004**, *45*, 1551-1553.
- <sup>22</sup> Hoffmann, R. W.; Knopff, O.; Faber, T. *J. Chem. Soc., Perkin Trans.* **2001**, *2*, 1785-1792.
- <sup>23</sup> (a) Jaber, J. J.; Mitsui, K.; Rychnovsky, S. D. *J. Org. Chem.* **2001**, *66*, 4679-4686. (b) Lolkema, L. D. M.; Semeyn, C.; Ashek, L.; Hiemstra, H.; Speckamp, W. N. *Tetrahedron* **1994**, *50*, 7129-7140. (c) Rychnovsky, S. D.; Marumoto, S.; Jaber, J. J. *Org. Lett.* **2001**, *3*, 3815-3818. (d) Castro, P.; Overman, L. E. *Tetrahedron Lett.* **1993**, *34*, 5243-5246. (e) Daub, G. W.; Heerding, D. A.; Overman, L. E. *Tetrahedron* **1988**, *44*, 3919-1930.
- <sup>24</sup> Sprachman, M. M.; Johnson, H. D.; Hinkle, R. J. Unpublish results.

## APPENDIX

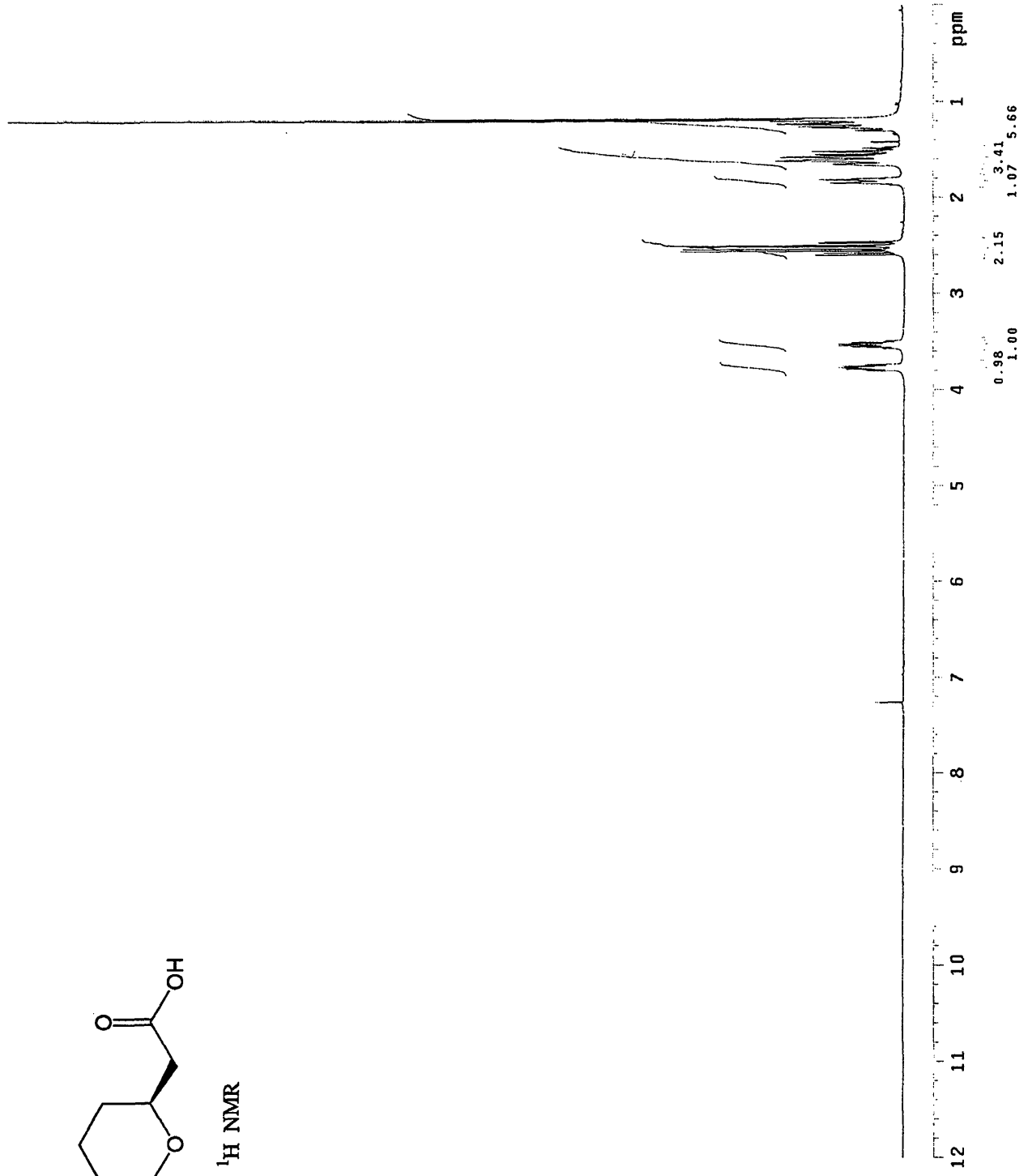
$^1\text{H}$  NMR and  $^{13}\text{C}$  NMR as well as  $^1\text{H}$  NOE spectroscopies are provided as supporting information for chapter II and Chapter III.

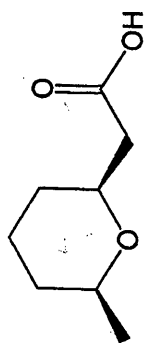
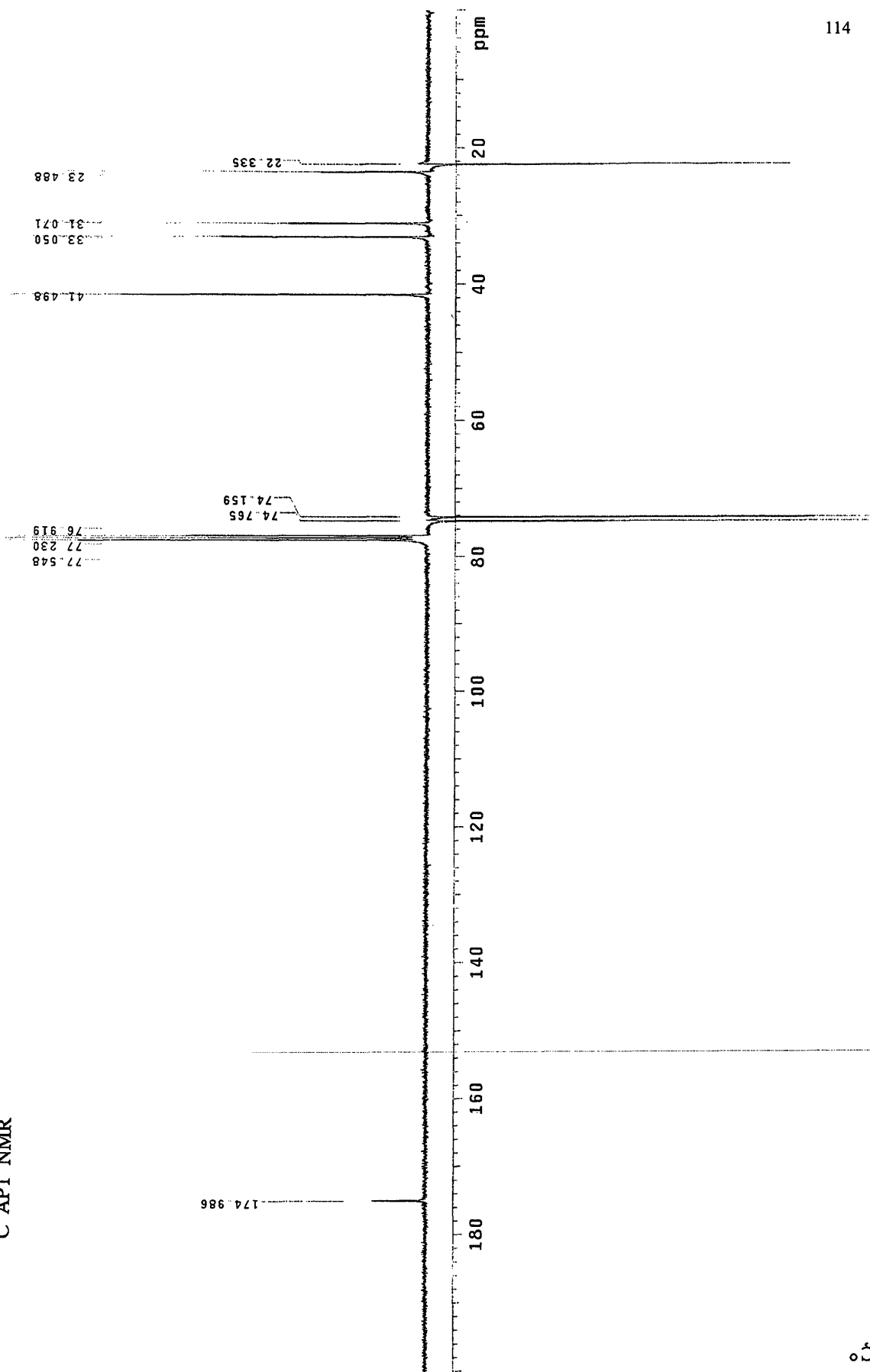
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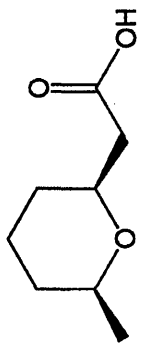
**Chapter II: BiBr<sub>3</sub> initiated cyclization-addition reactions:  
effect of  $\pi$ -nucleophile on oxocarbenium ion addition and total  
syntheses of  
(+)-(*S,S*)-(cis-6-methyltetra-hydropyran-2-yl)acetic acid and its  
*trans*-diastereomer**



<sup>1</sup>H NMR

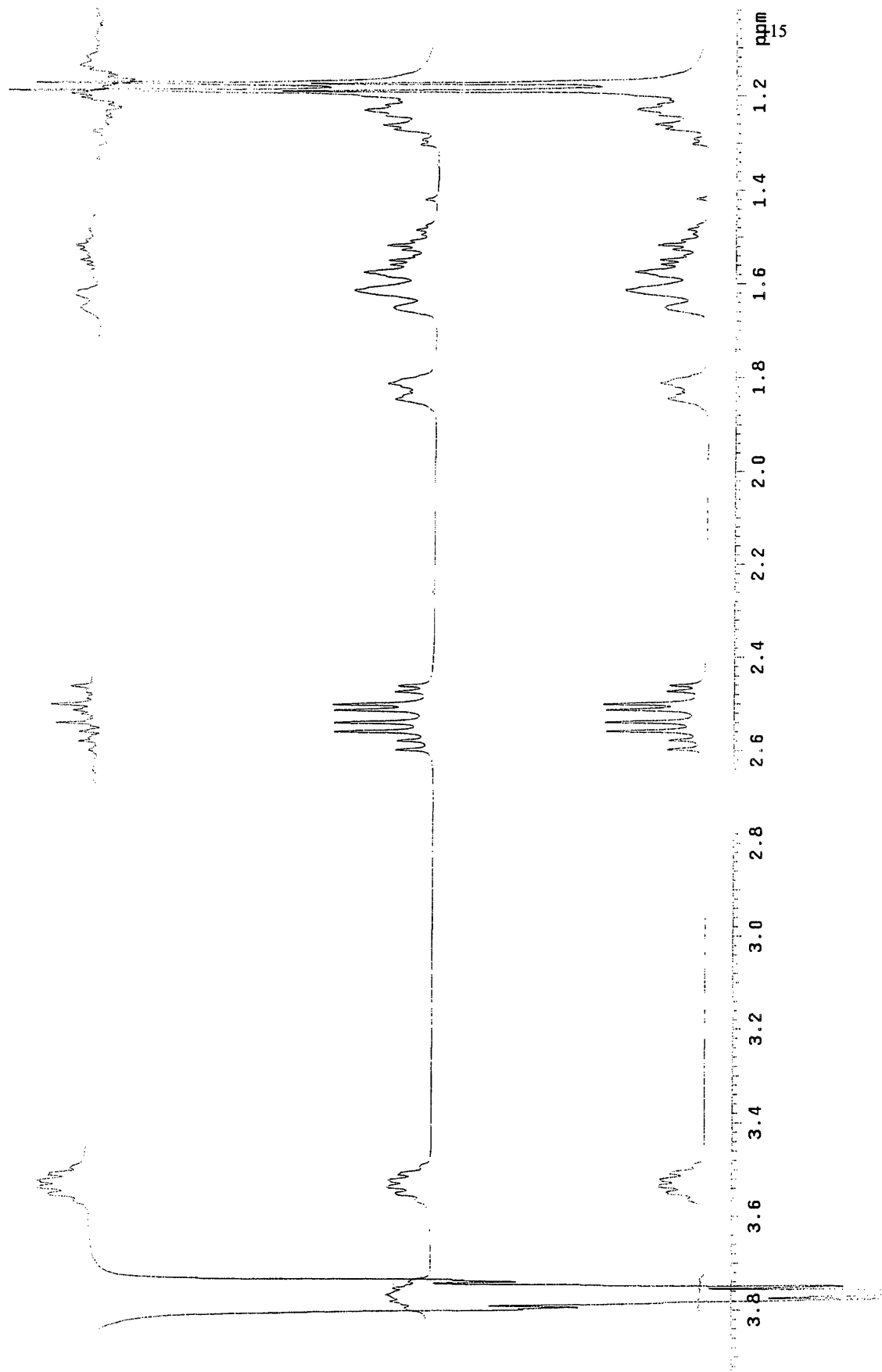


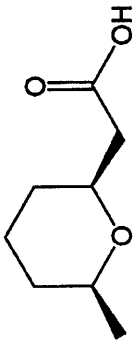
 $^{13}\text{C}$  APT NMR



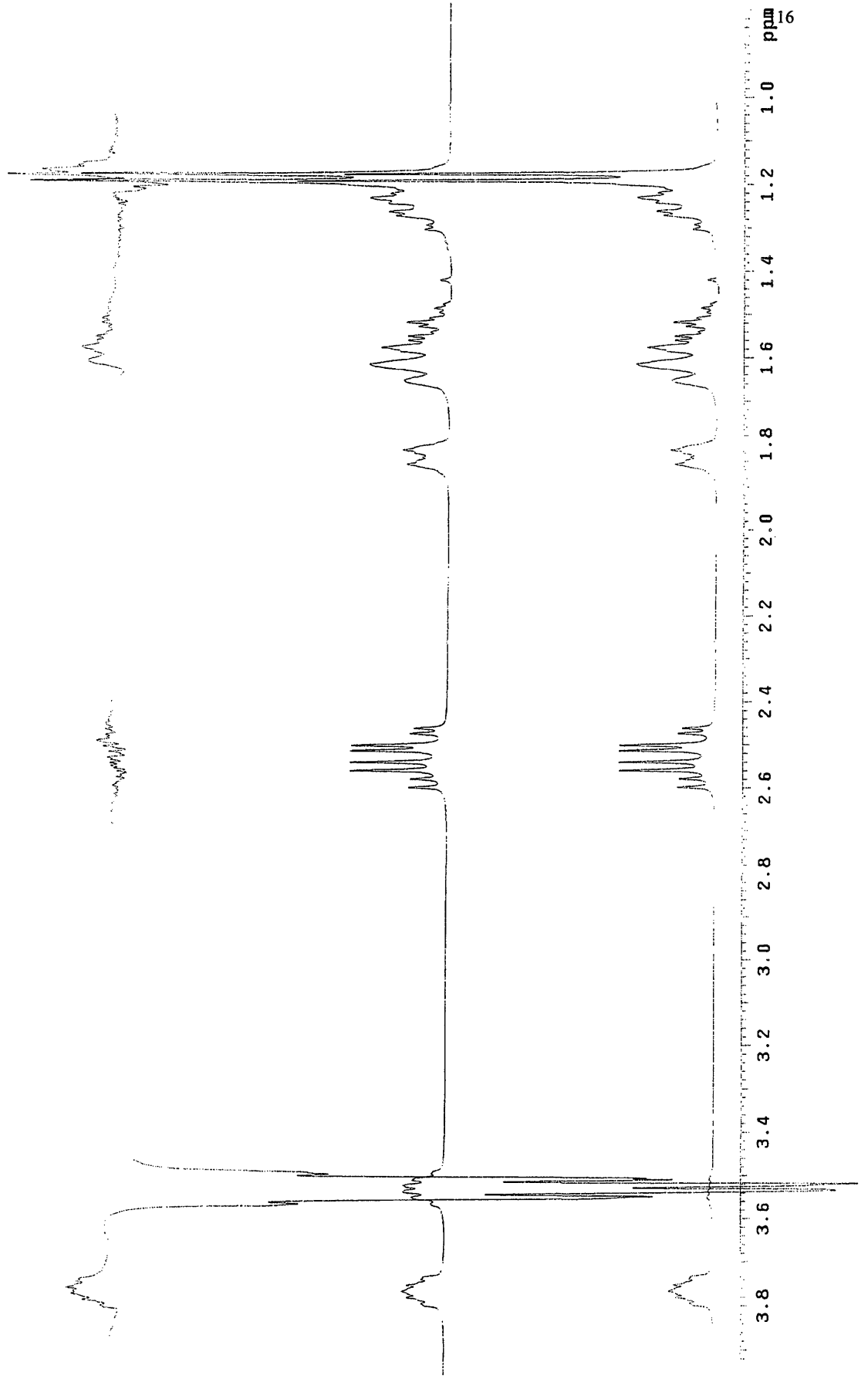
<sup>1</sup>H NOE Spectrum

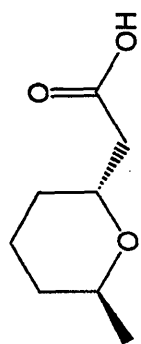
dec= 3.78 ppm



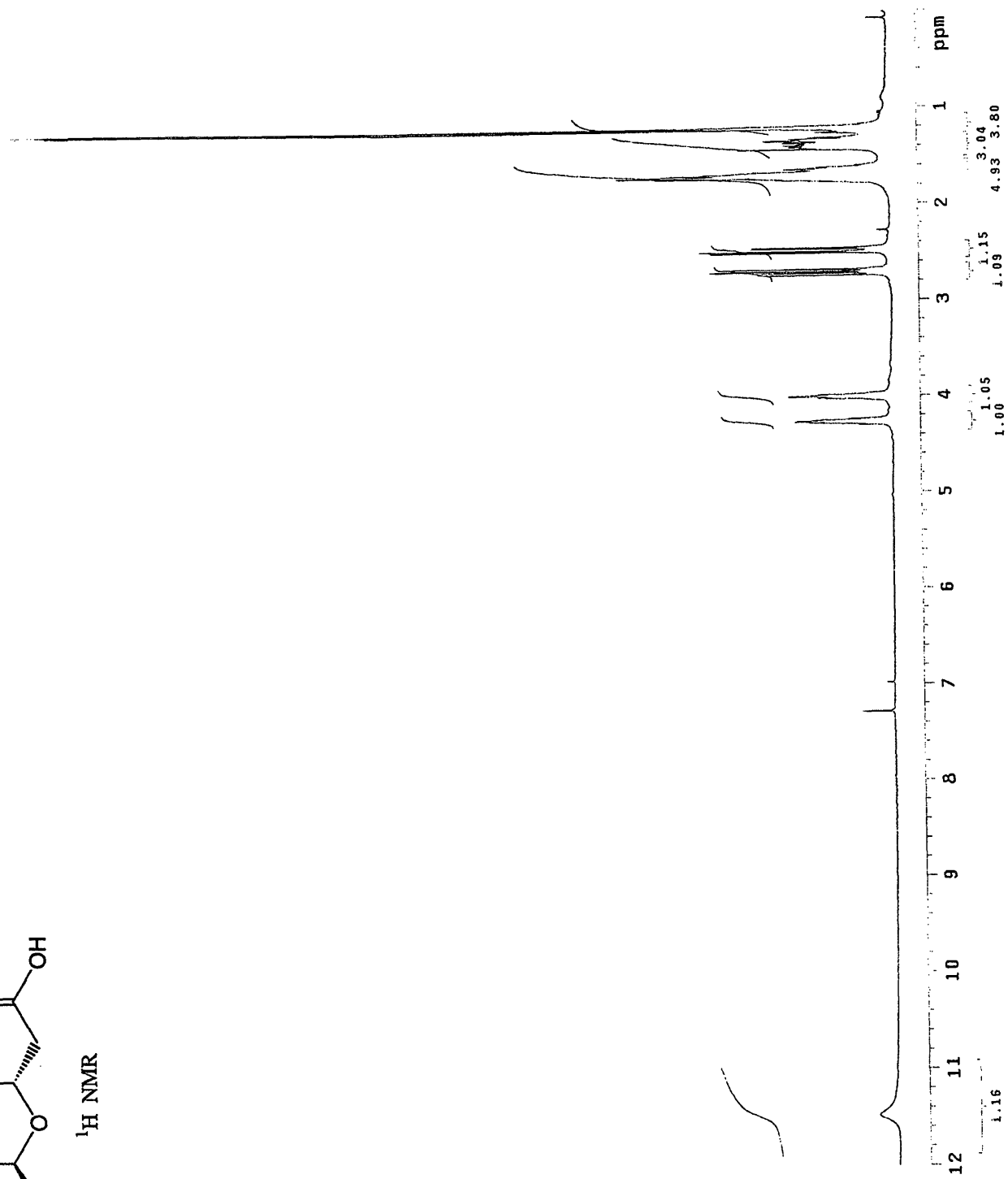


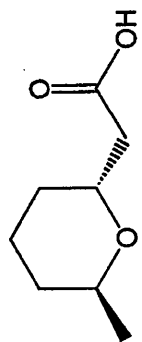
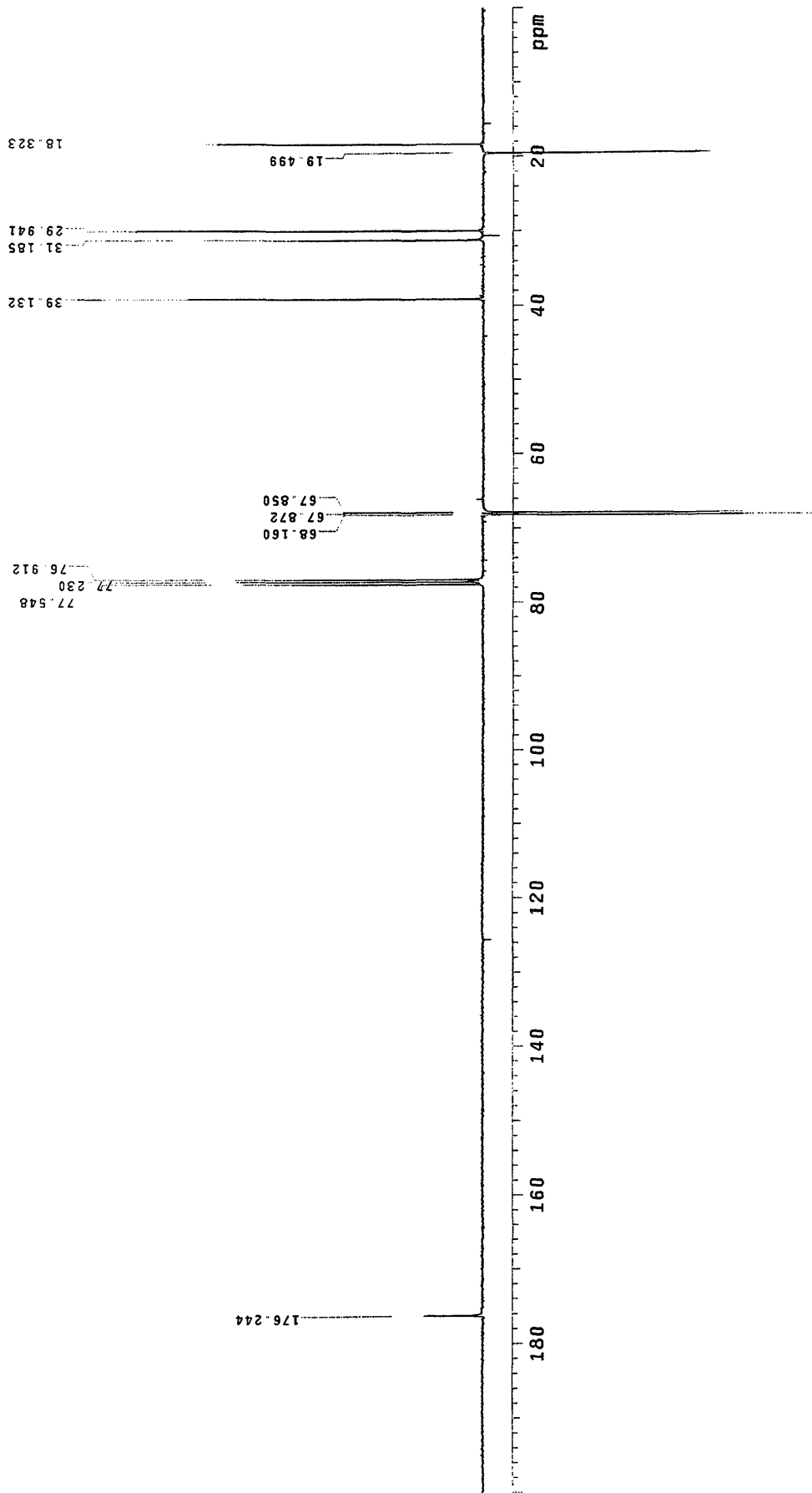
$^1\text{H}$  NOE Spectrum  
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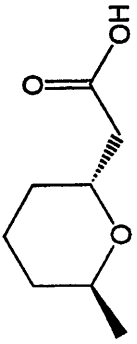




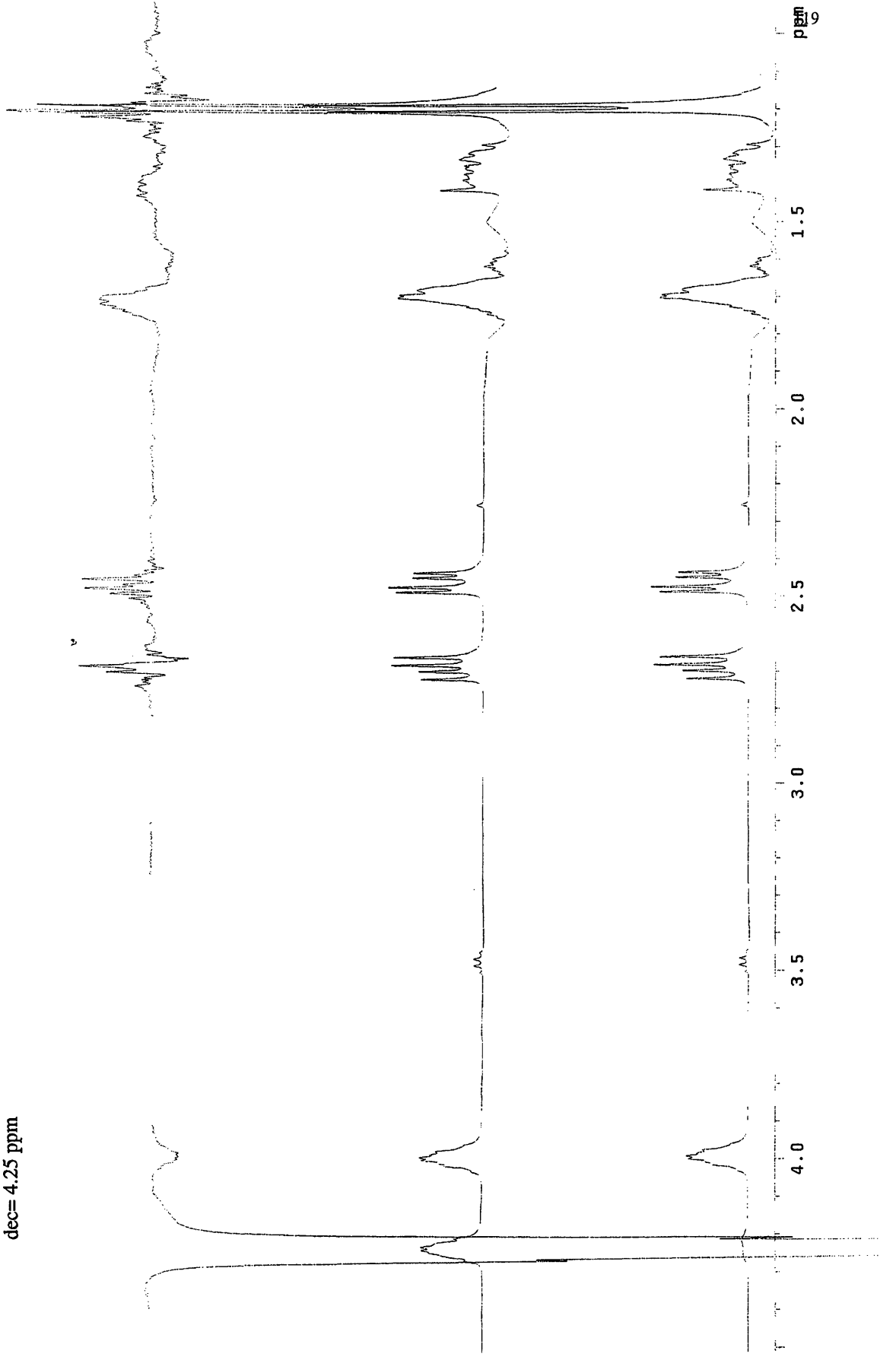
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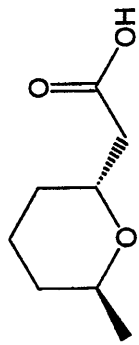


 $^{13}\text{C}$  APT NMR

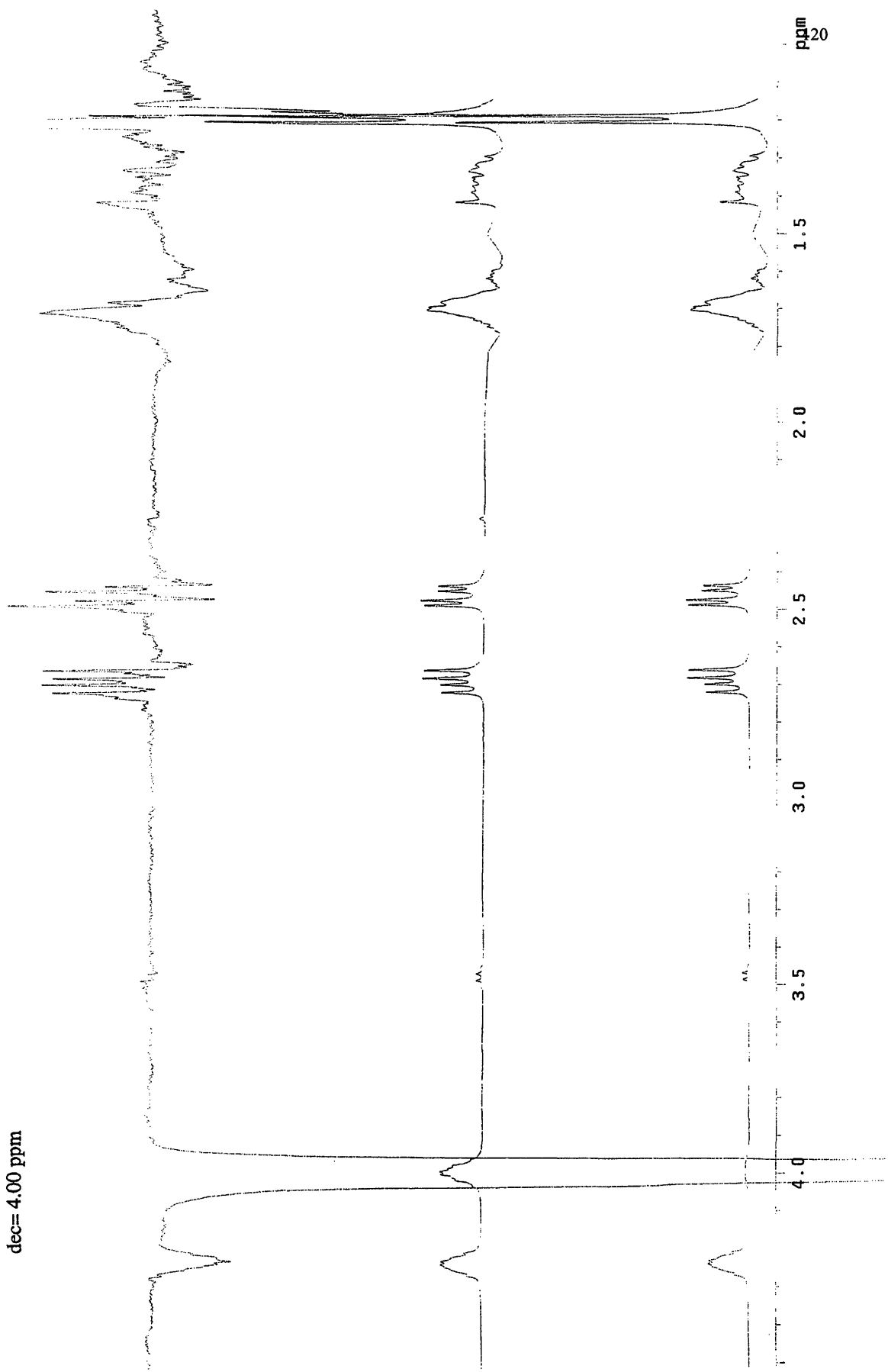


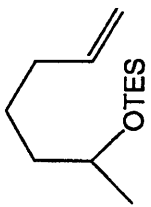
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dec= 4.25 ppm



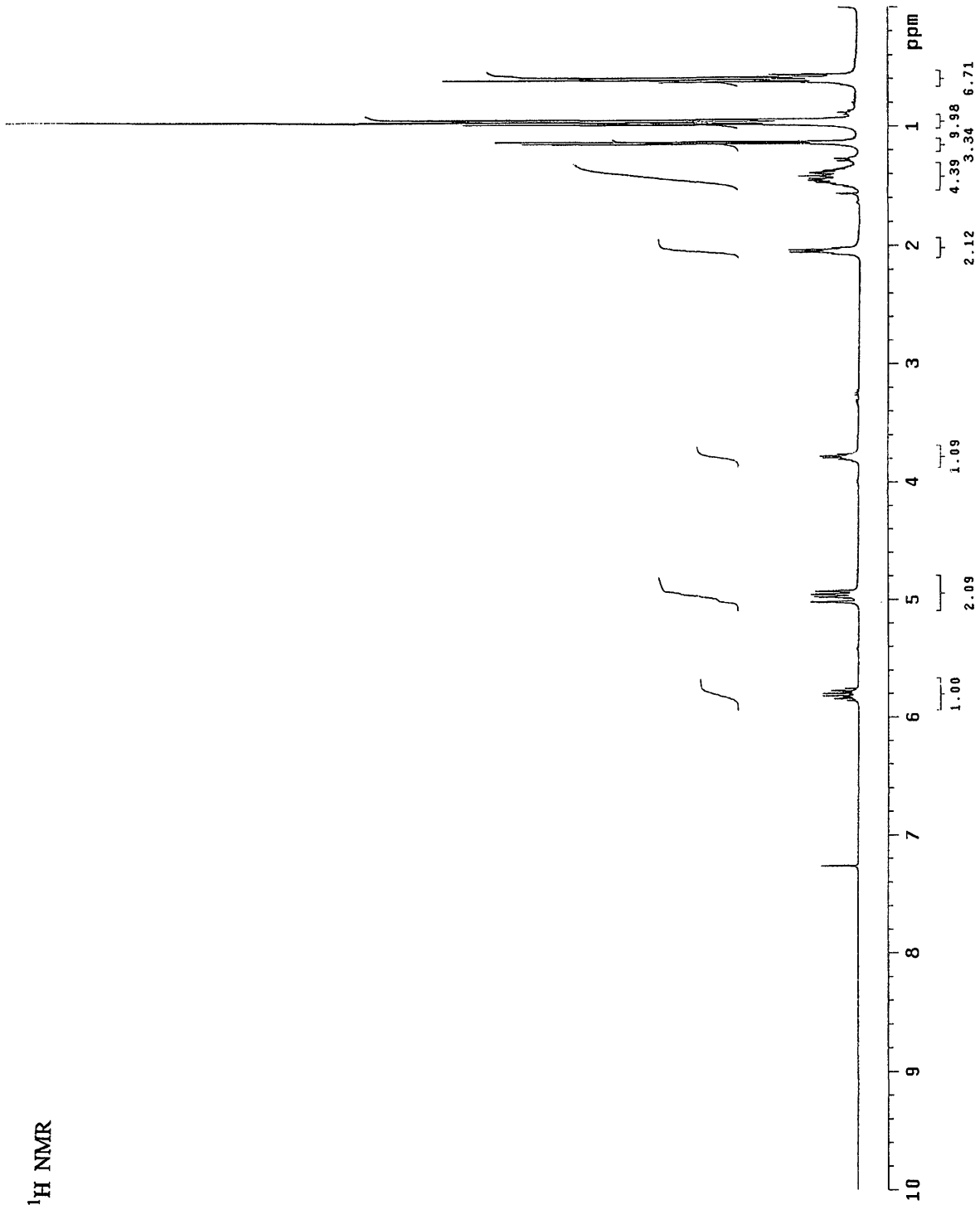


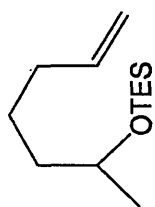
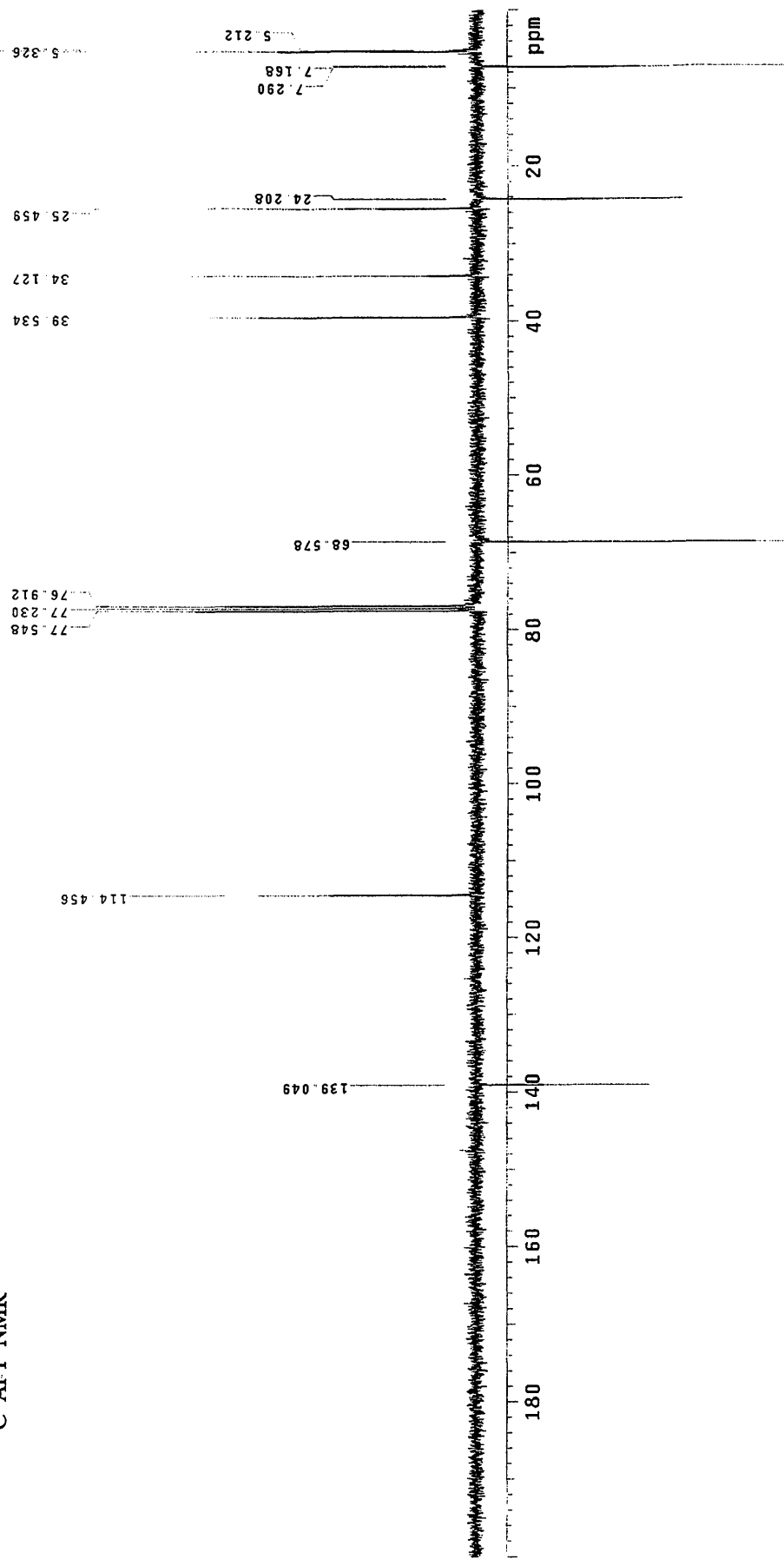
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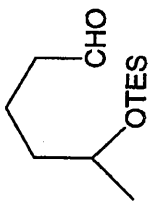


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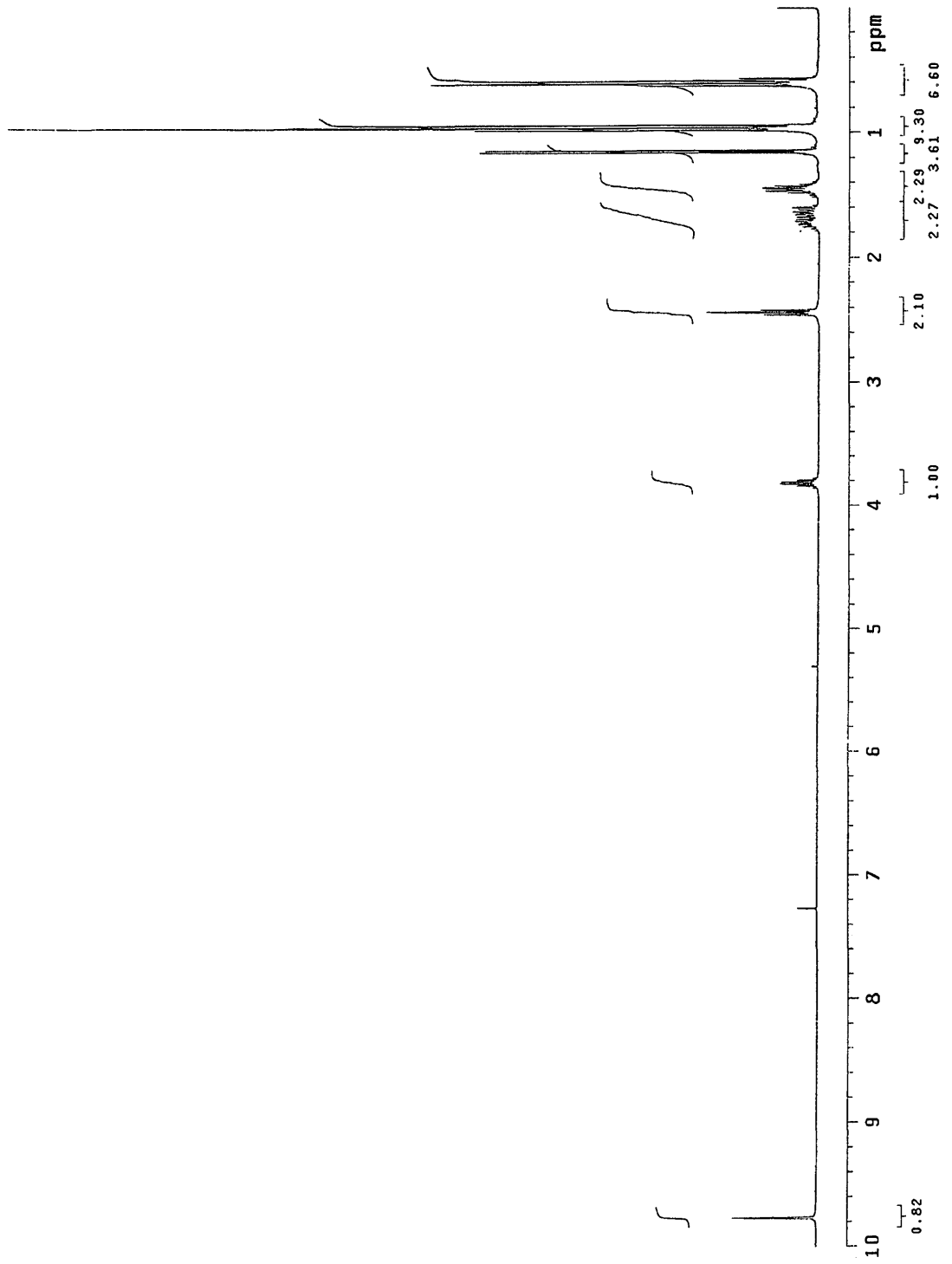


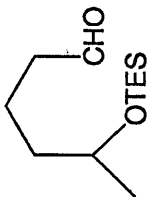


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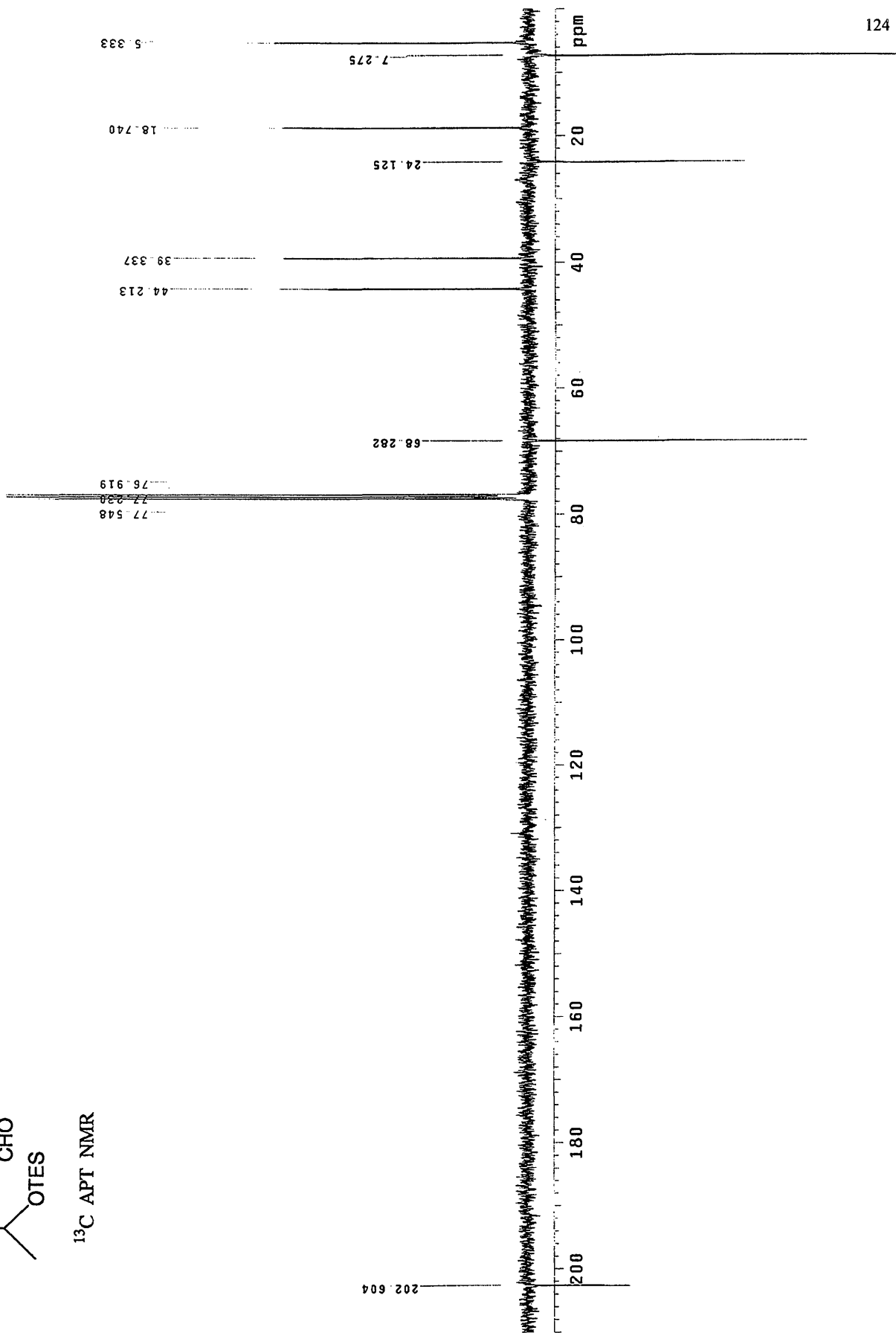


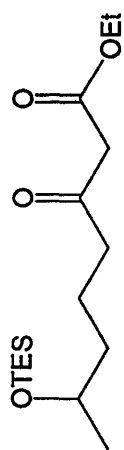
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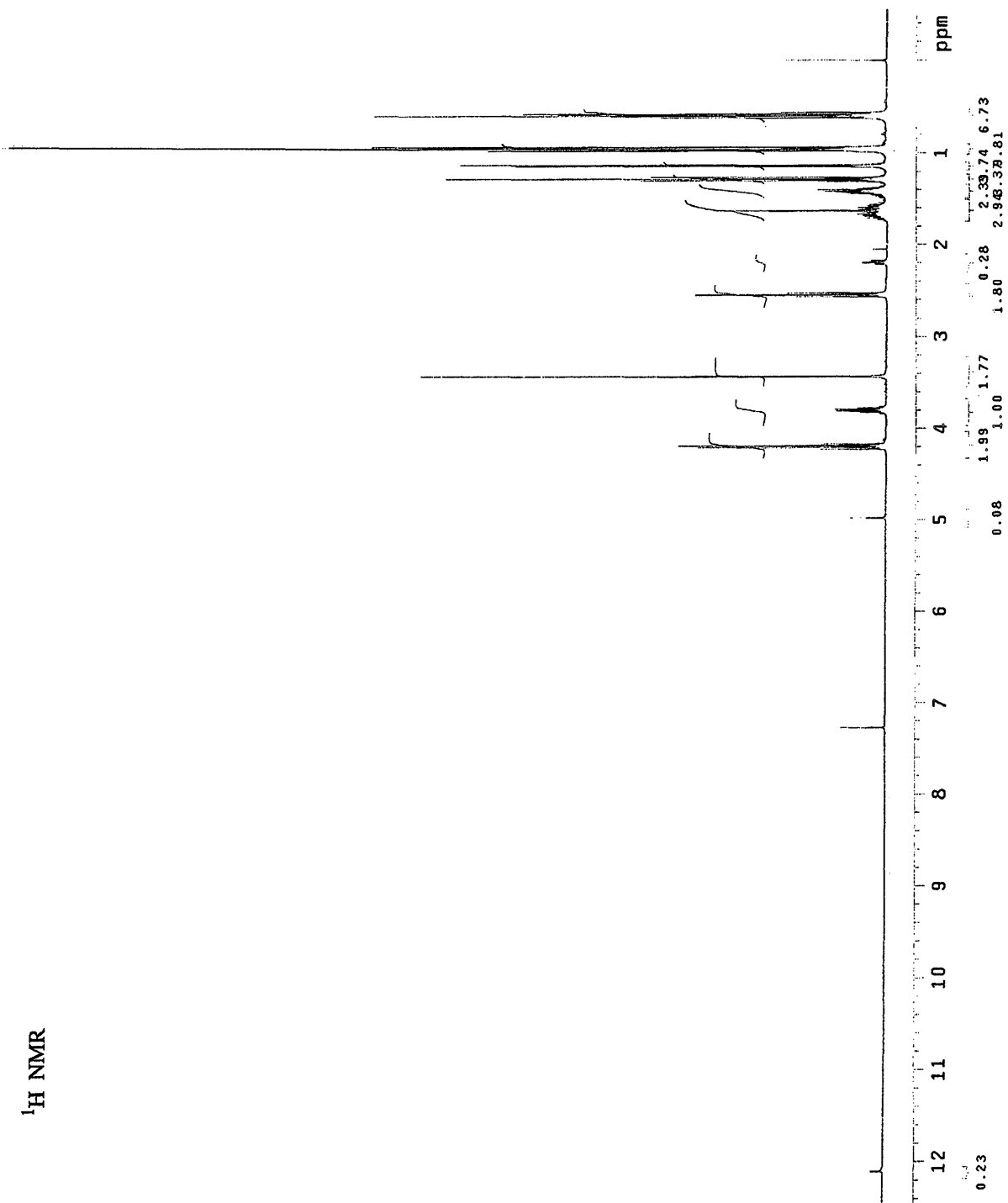


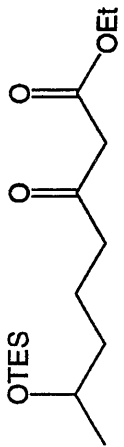
<sup>13</sup>C APT NMR



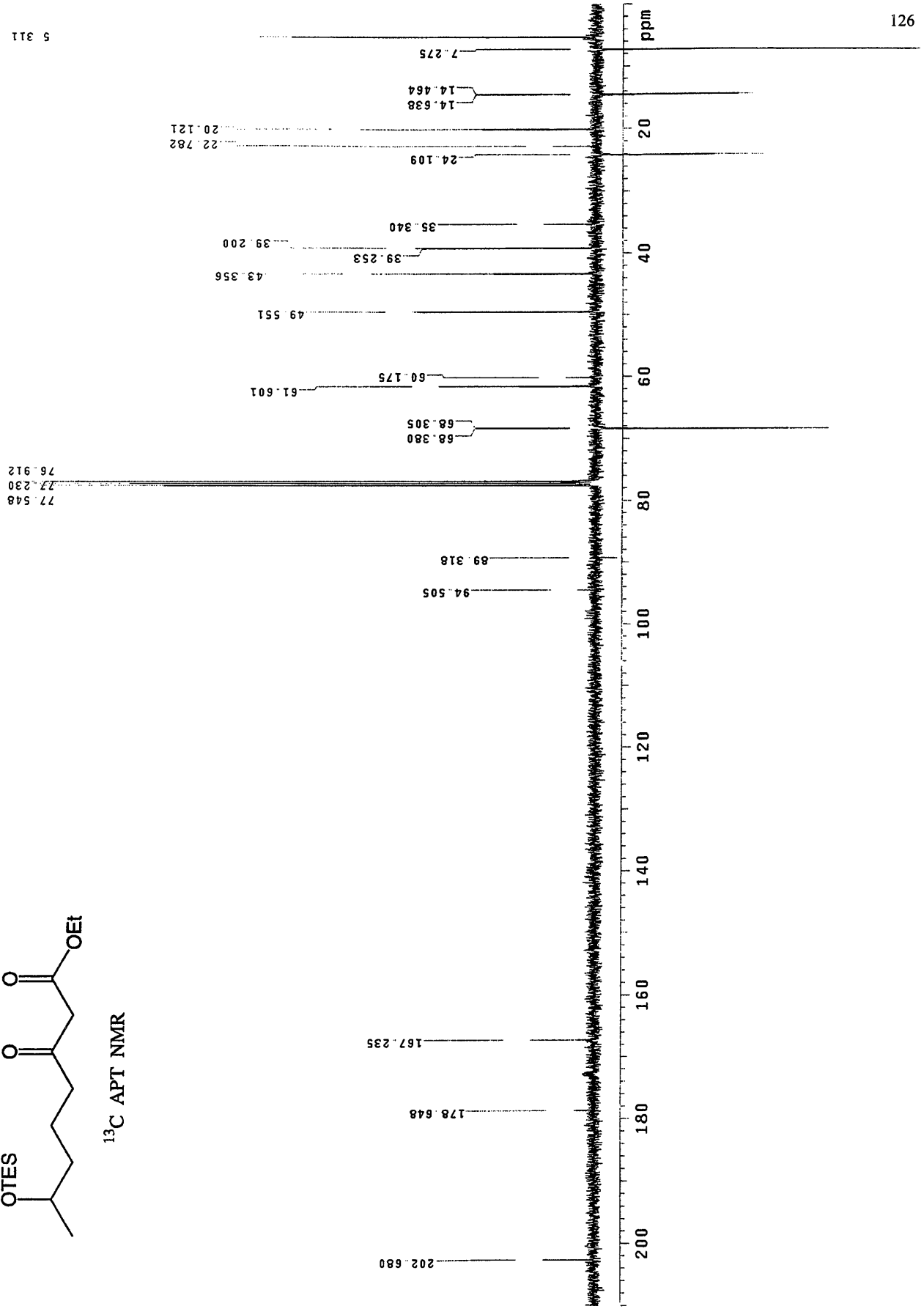


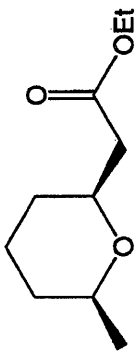
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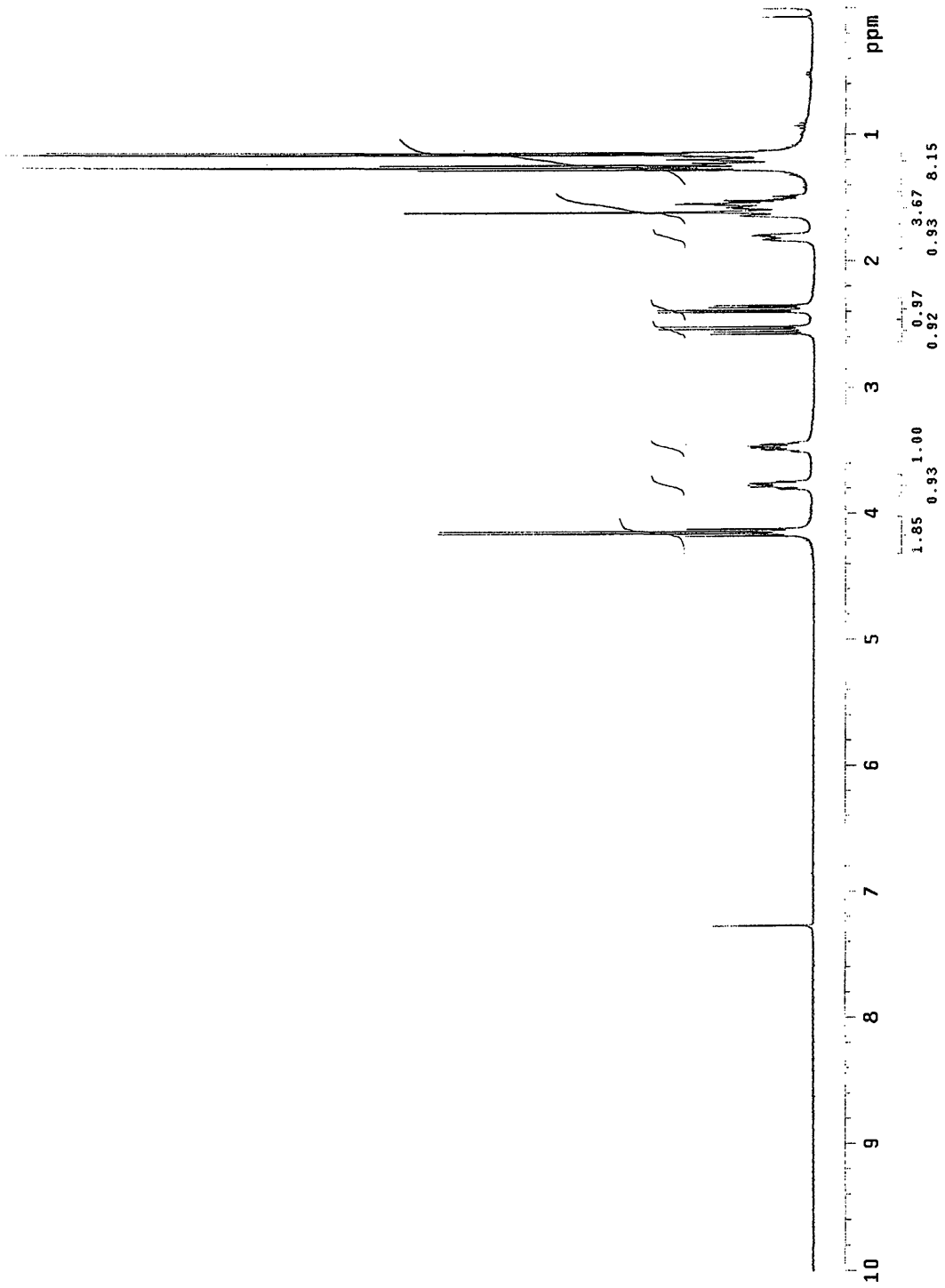


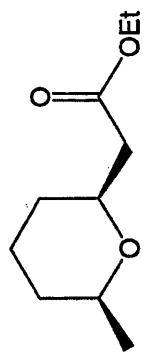
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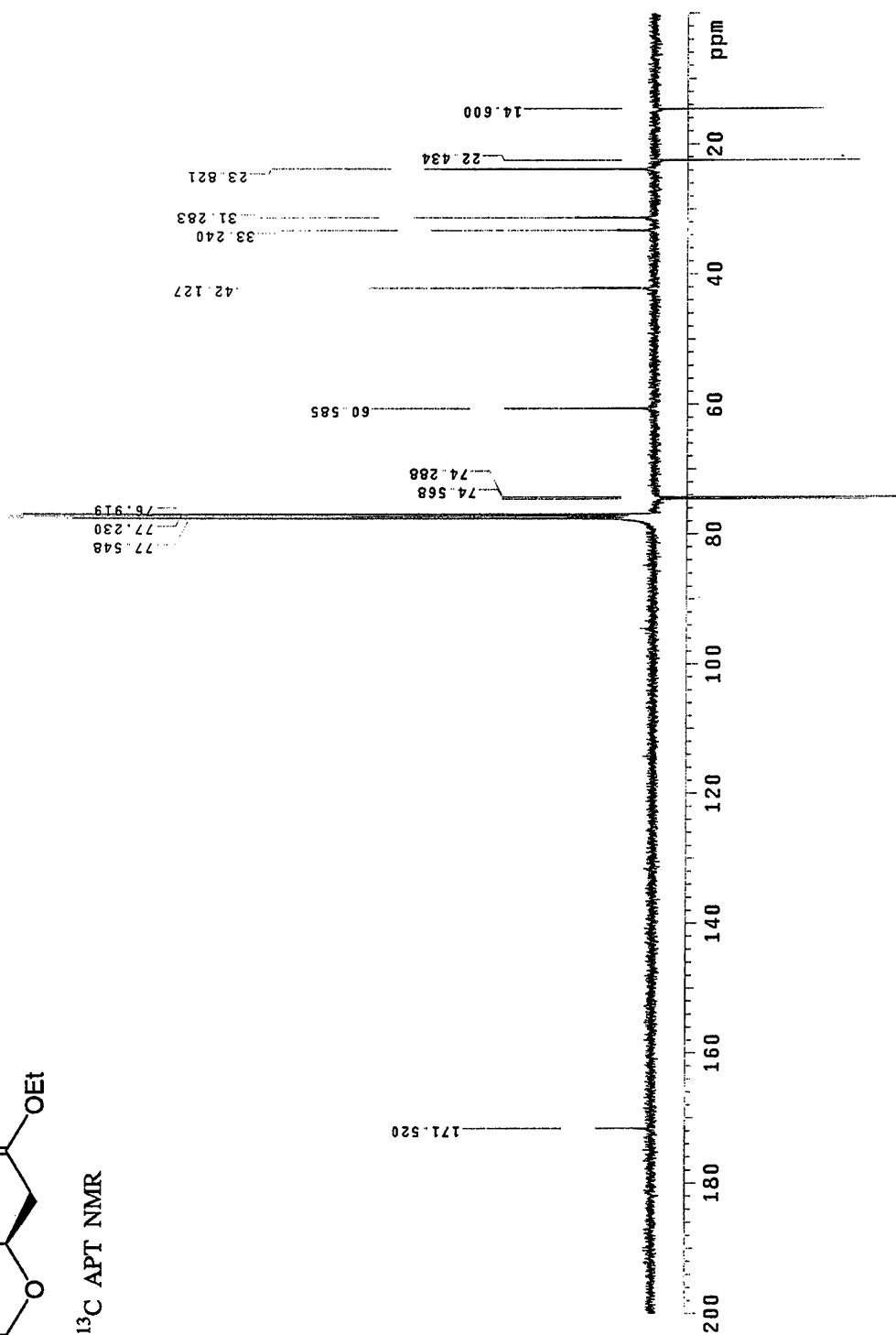


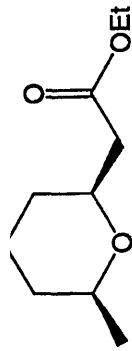
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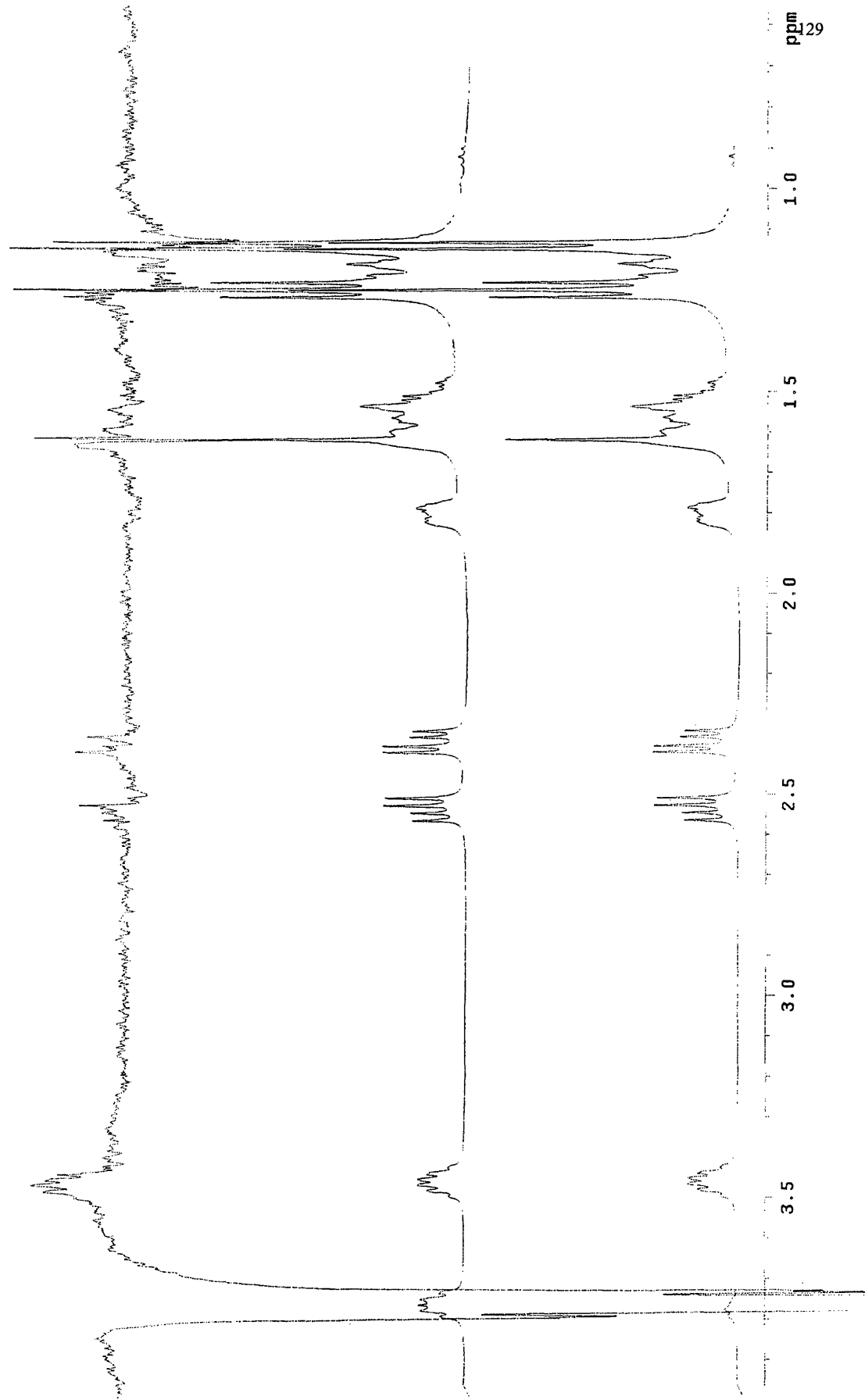


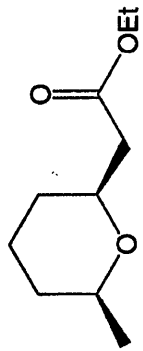
$^{13}\text{C}$  APT NMR



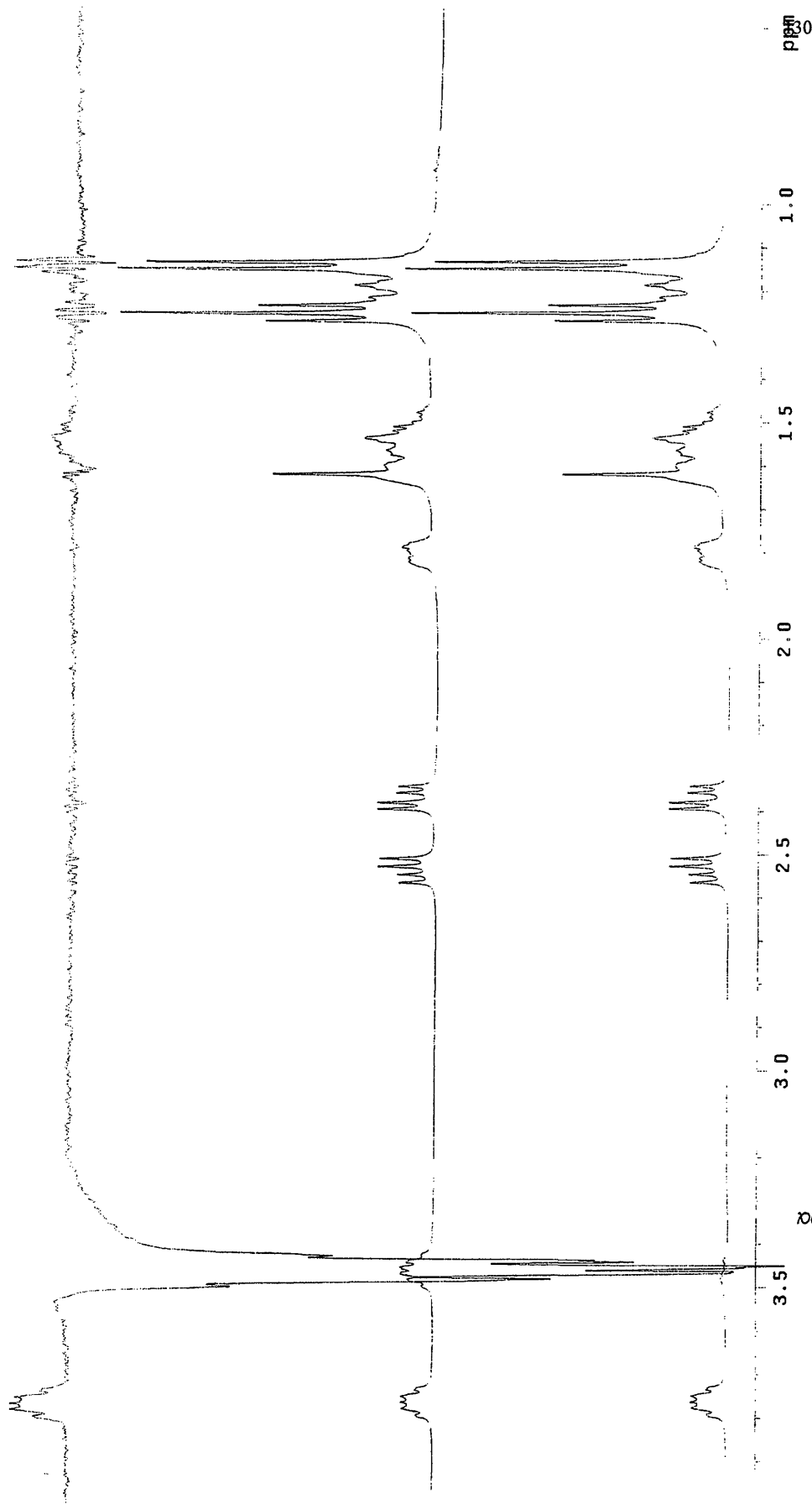


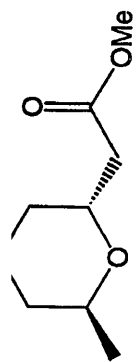
$^1\text{H}$  NOE Spectrum  
dec= 3.78 ppm



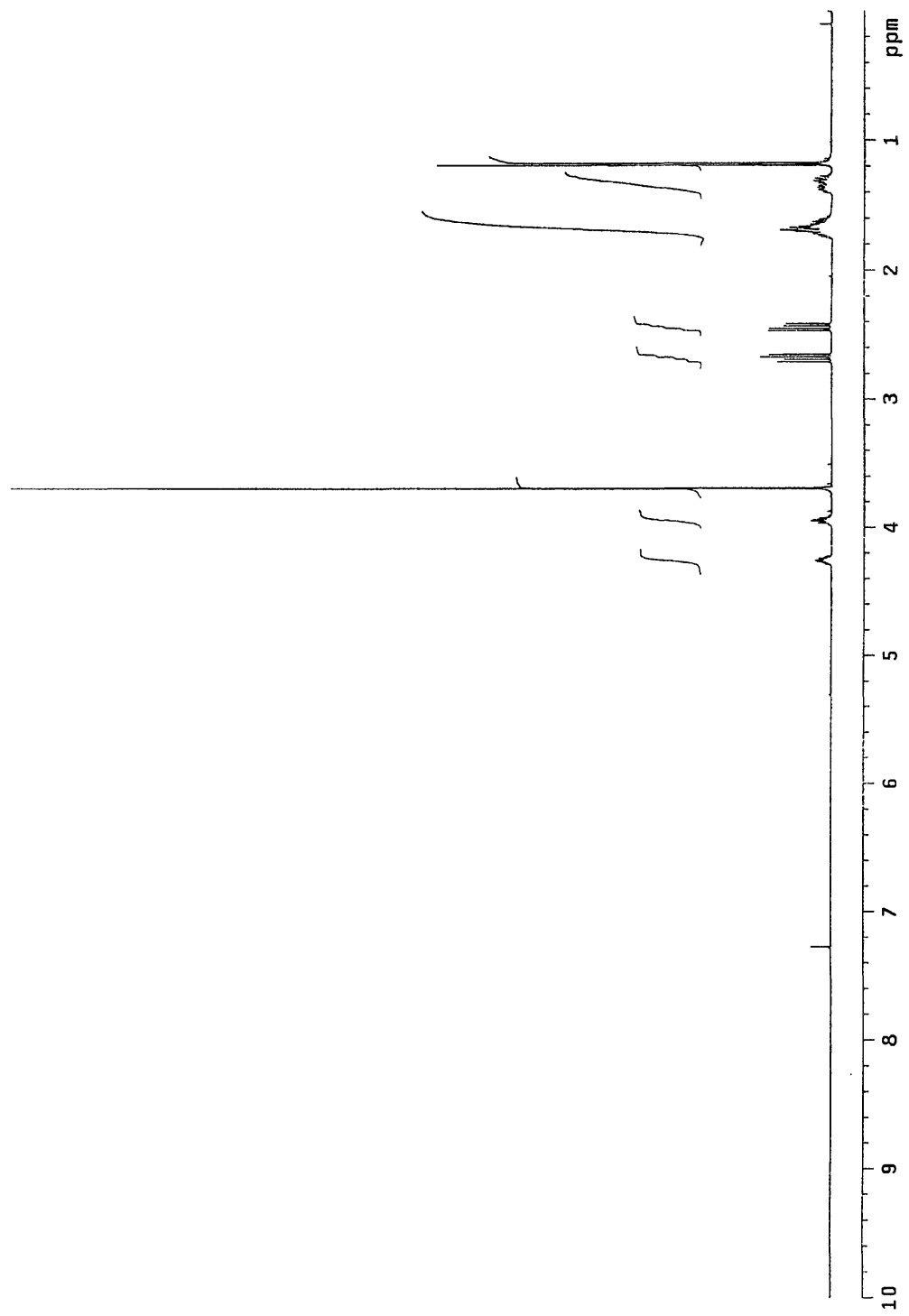


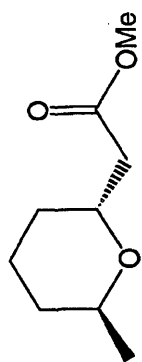
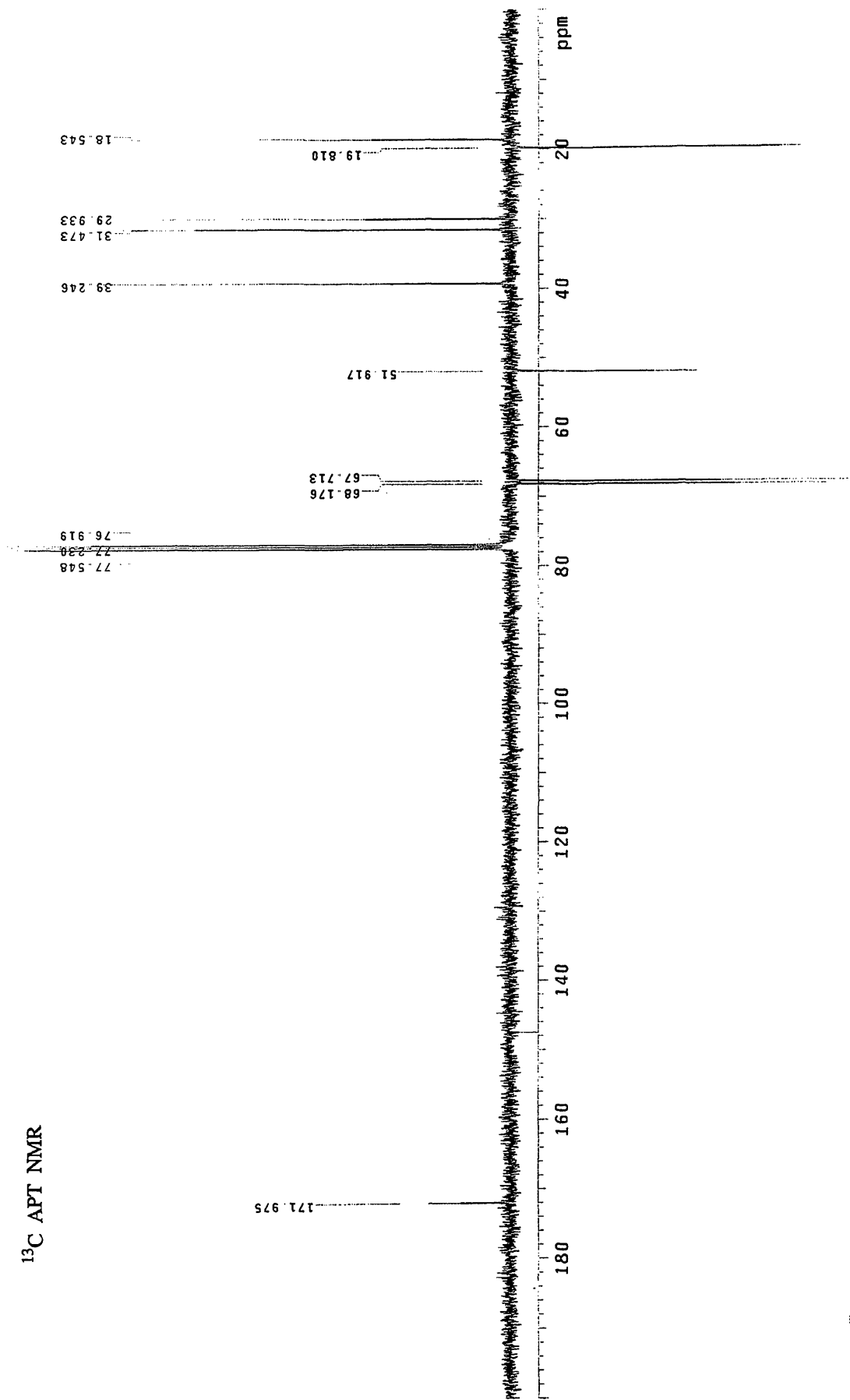
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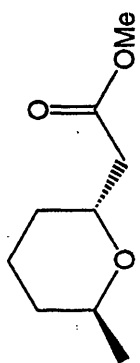




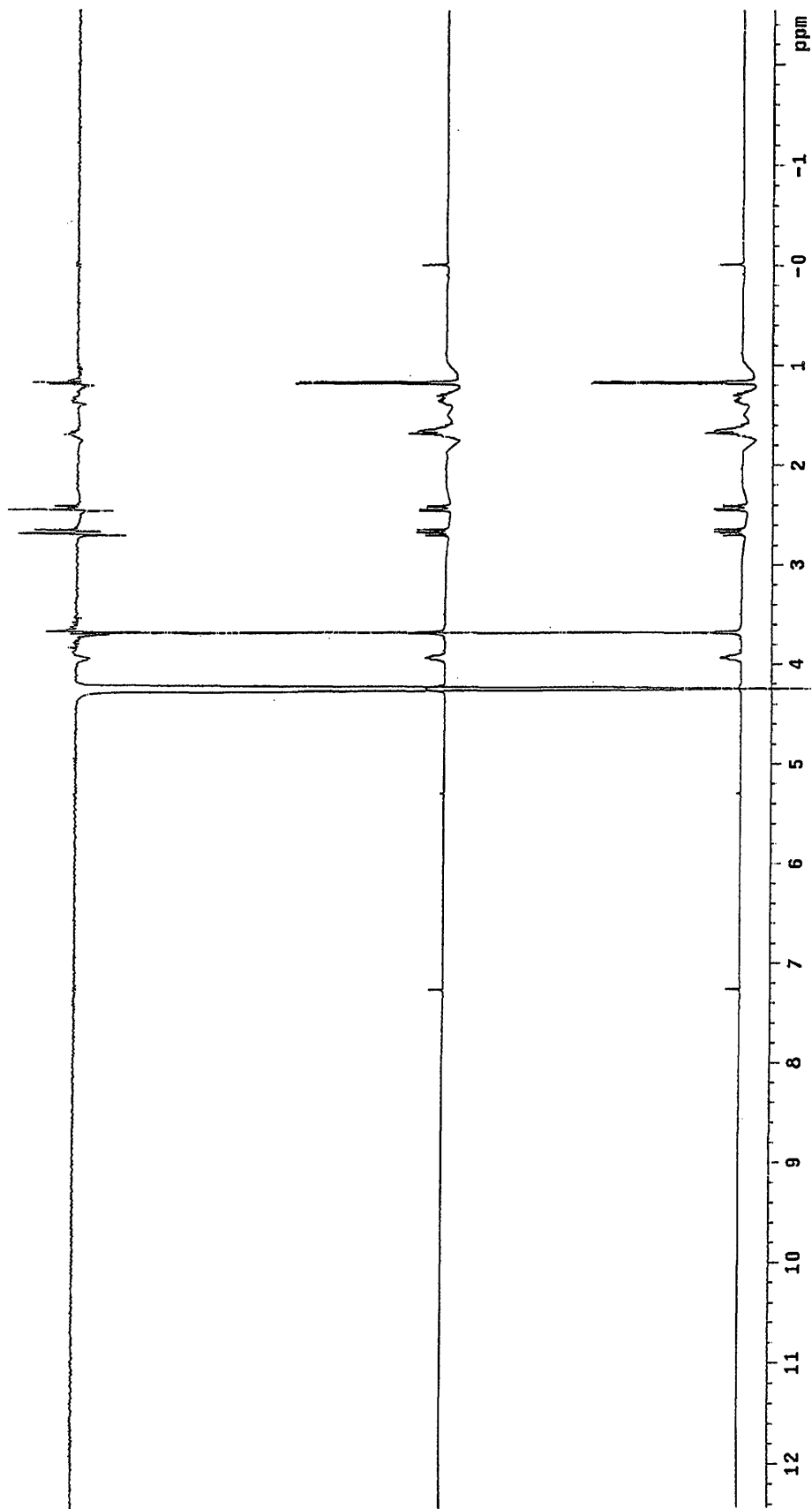
$^1\text{H NMR}$

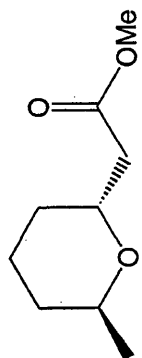


 $^{13}\text{C}$  APT NMR

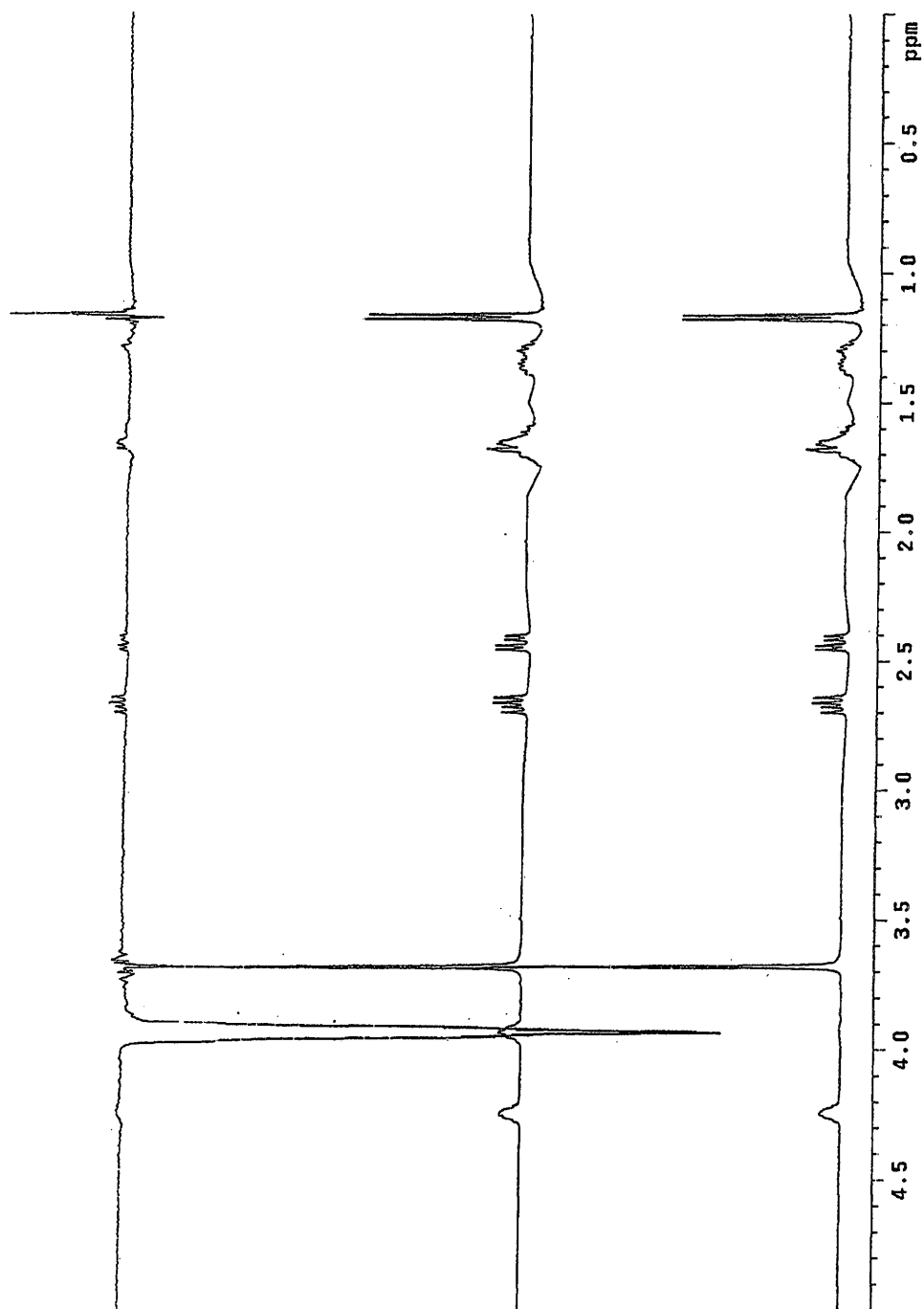


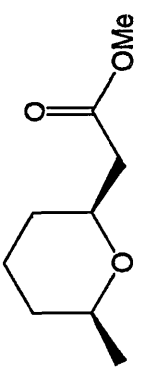
$^1\text{H}$  NOE Spectrum  
dec= 4.24 ppm



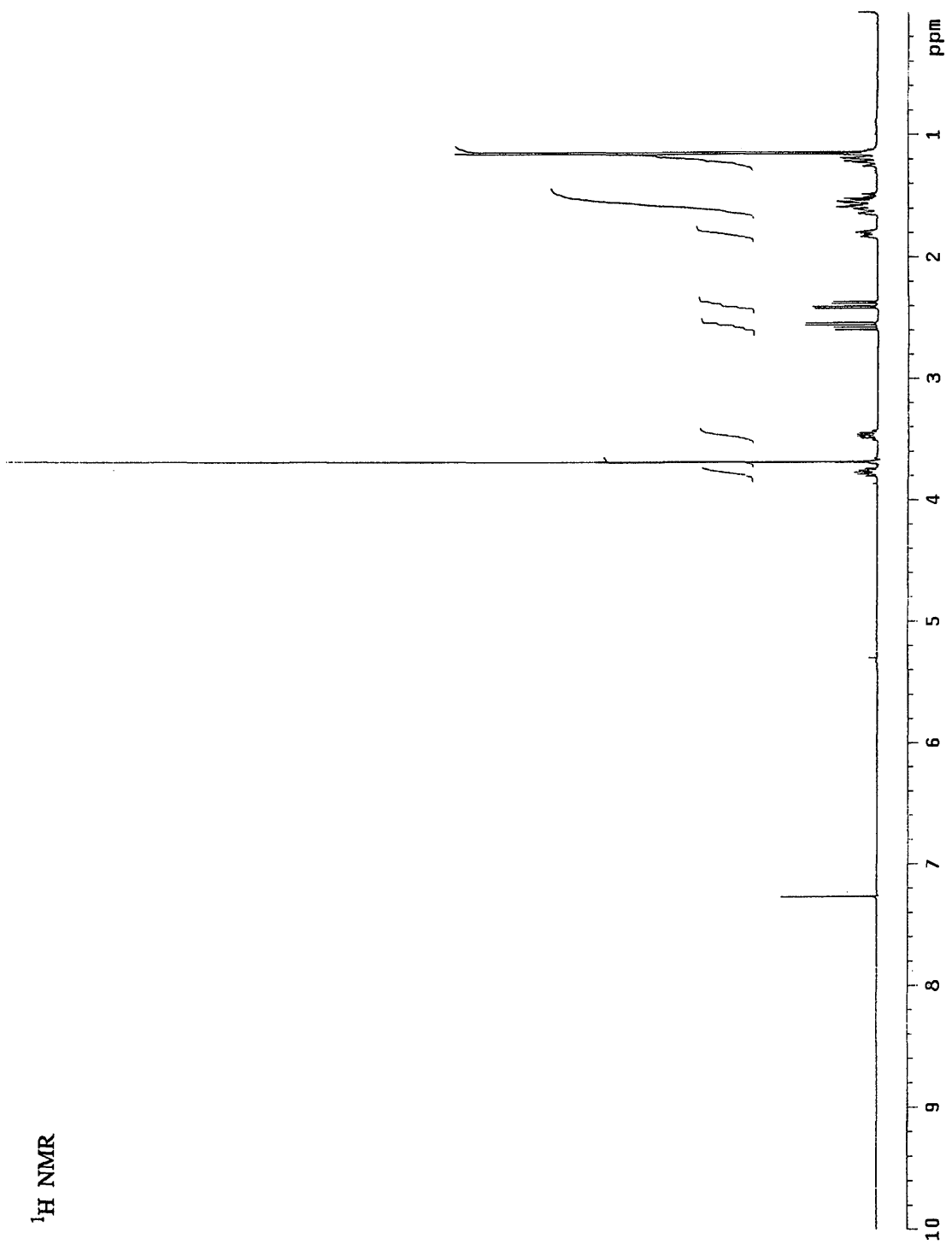


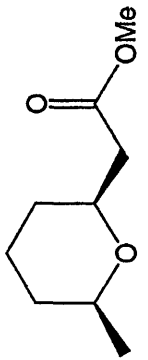
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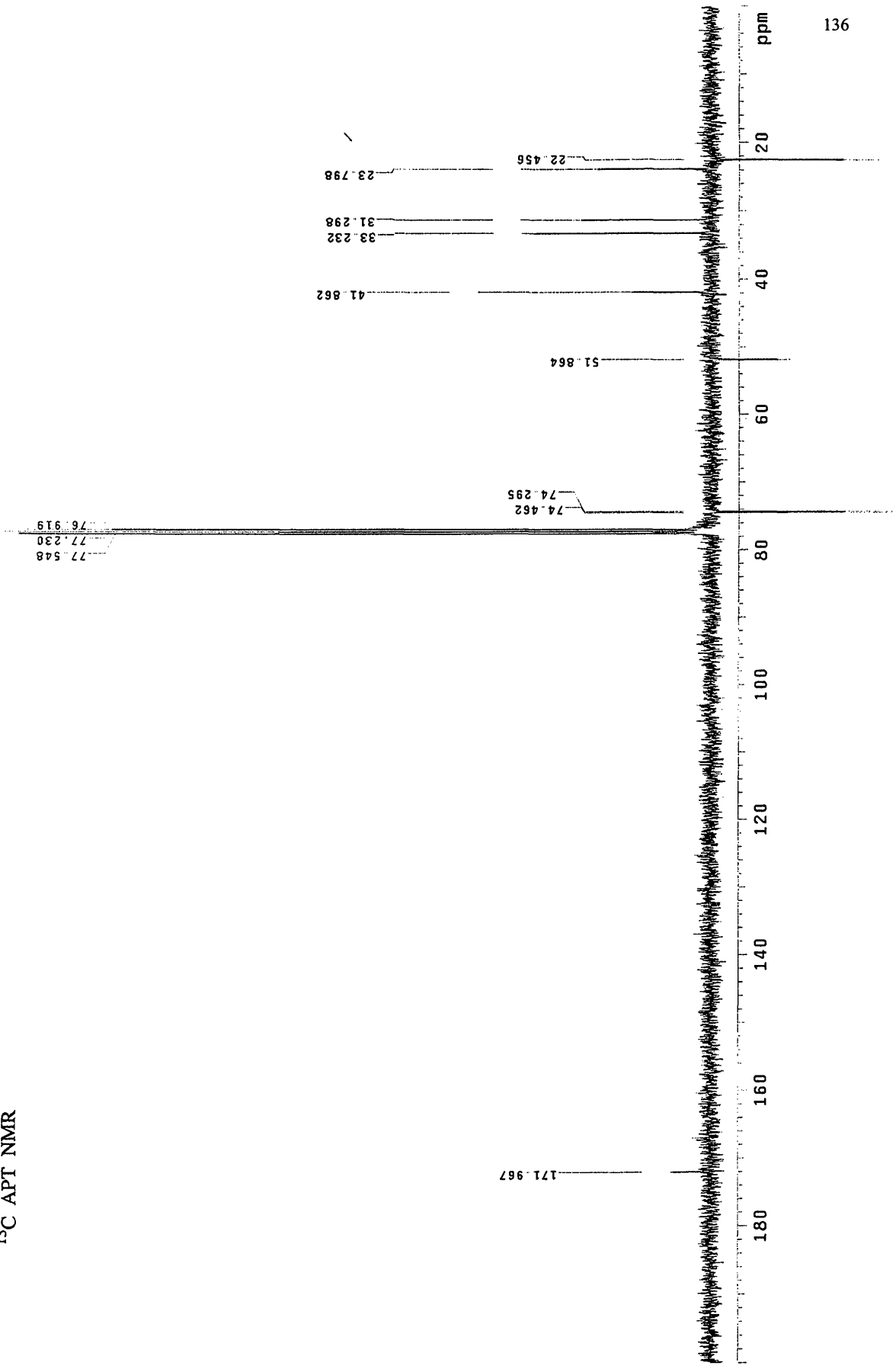


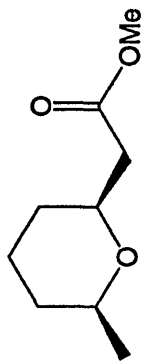
<sup>1</sup>H NMR



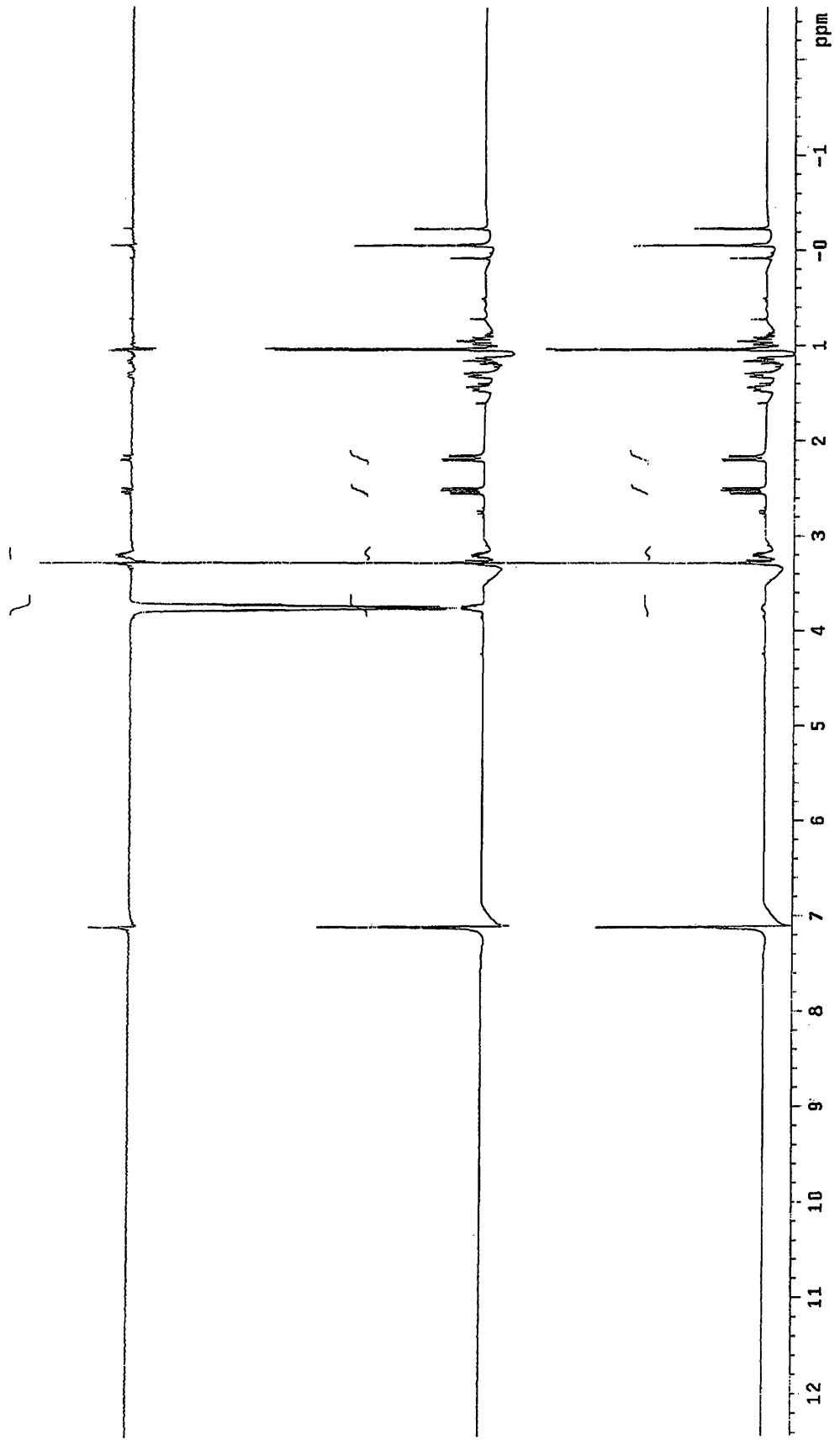


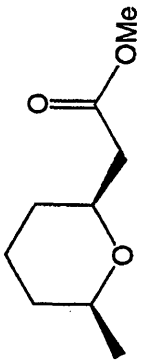
<sup>13</sup>C APT NMR



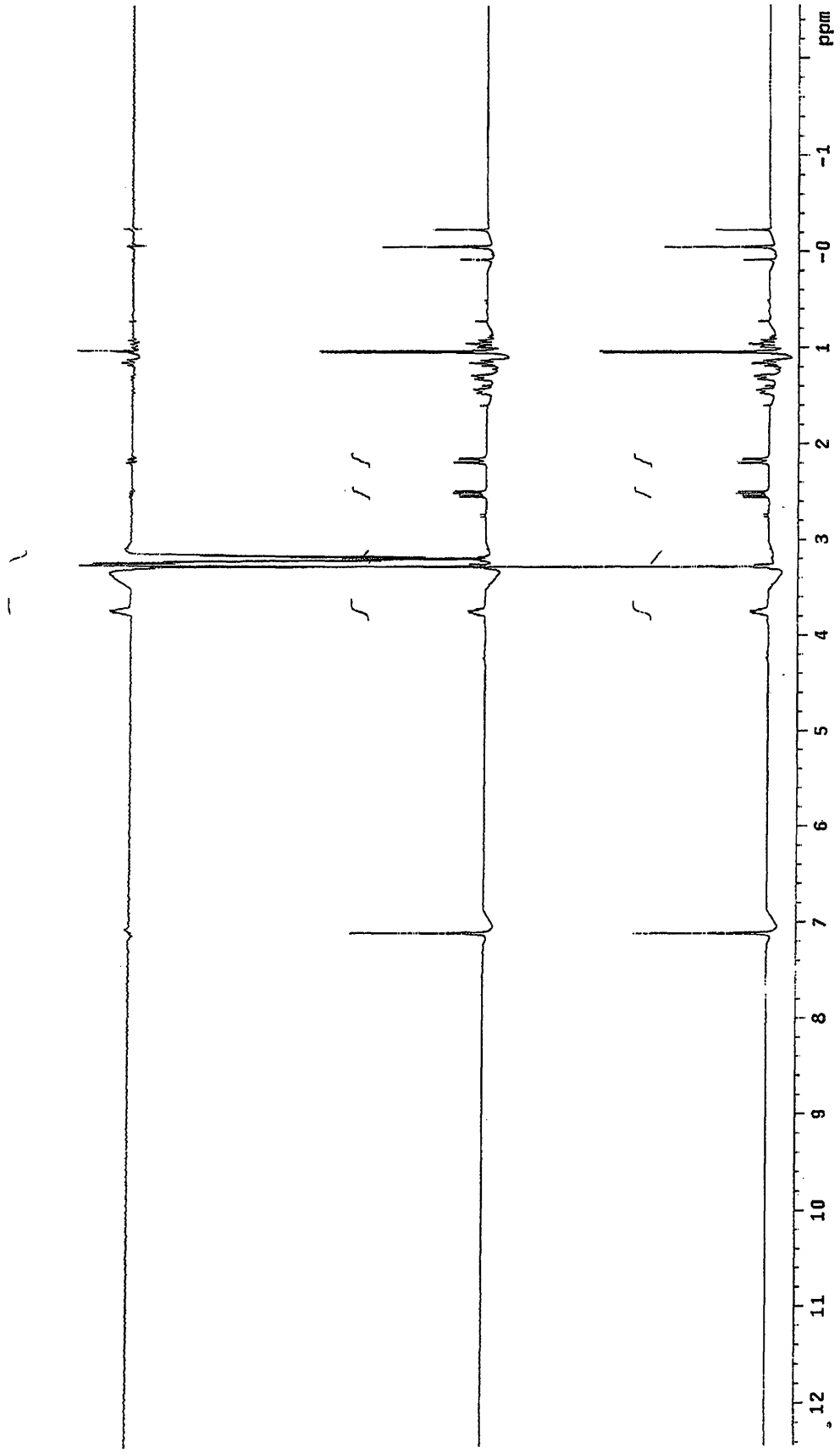


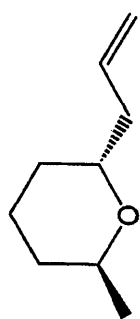
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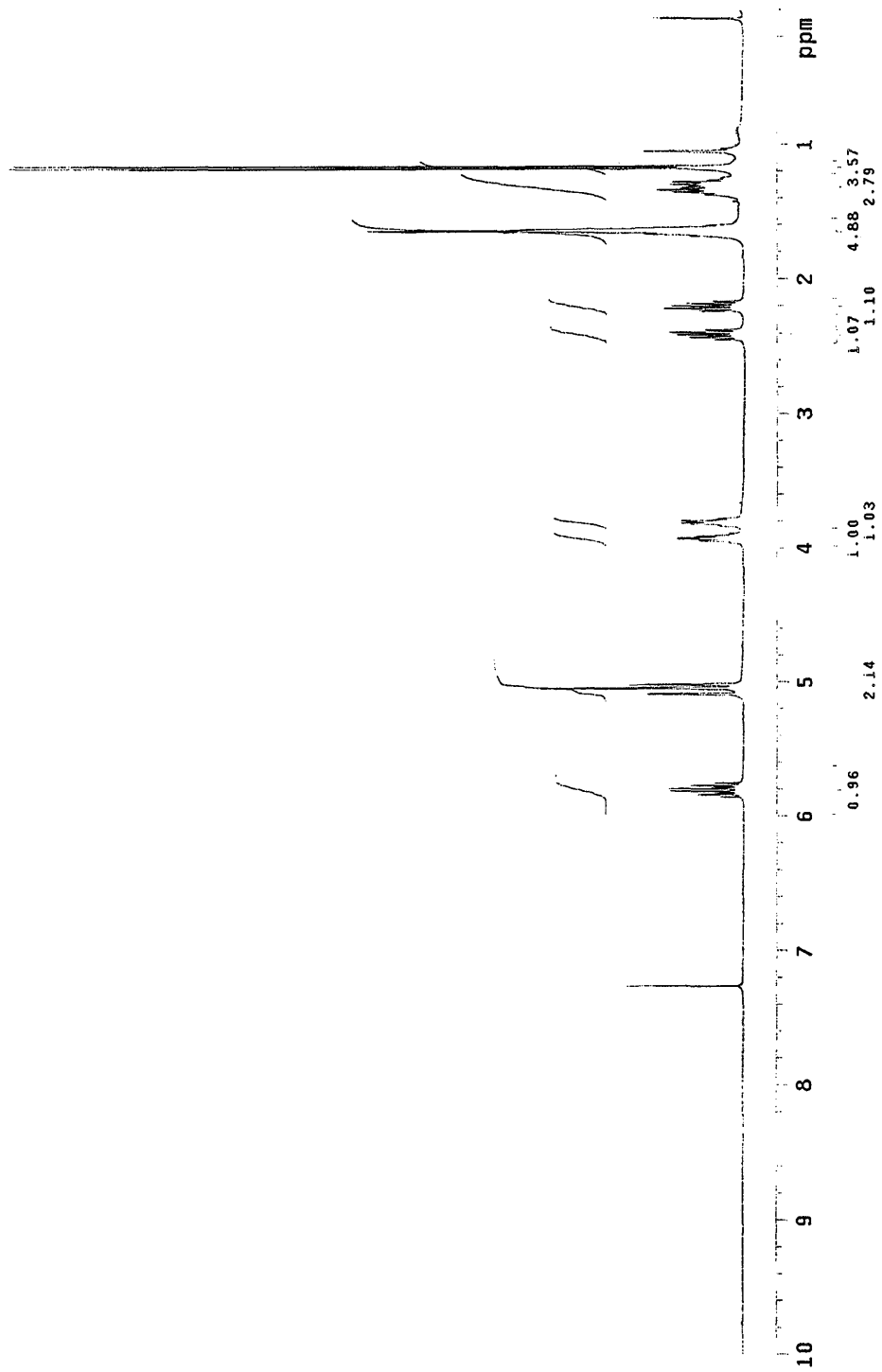


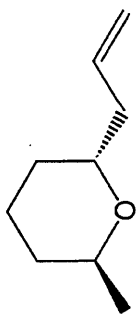
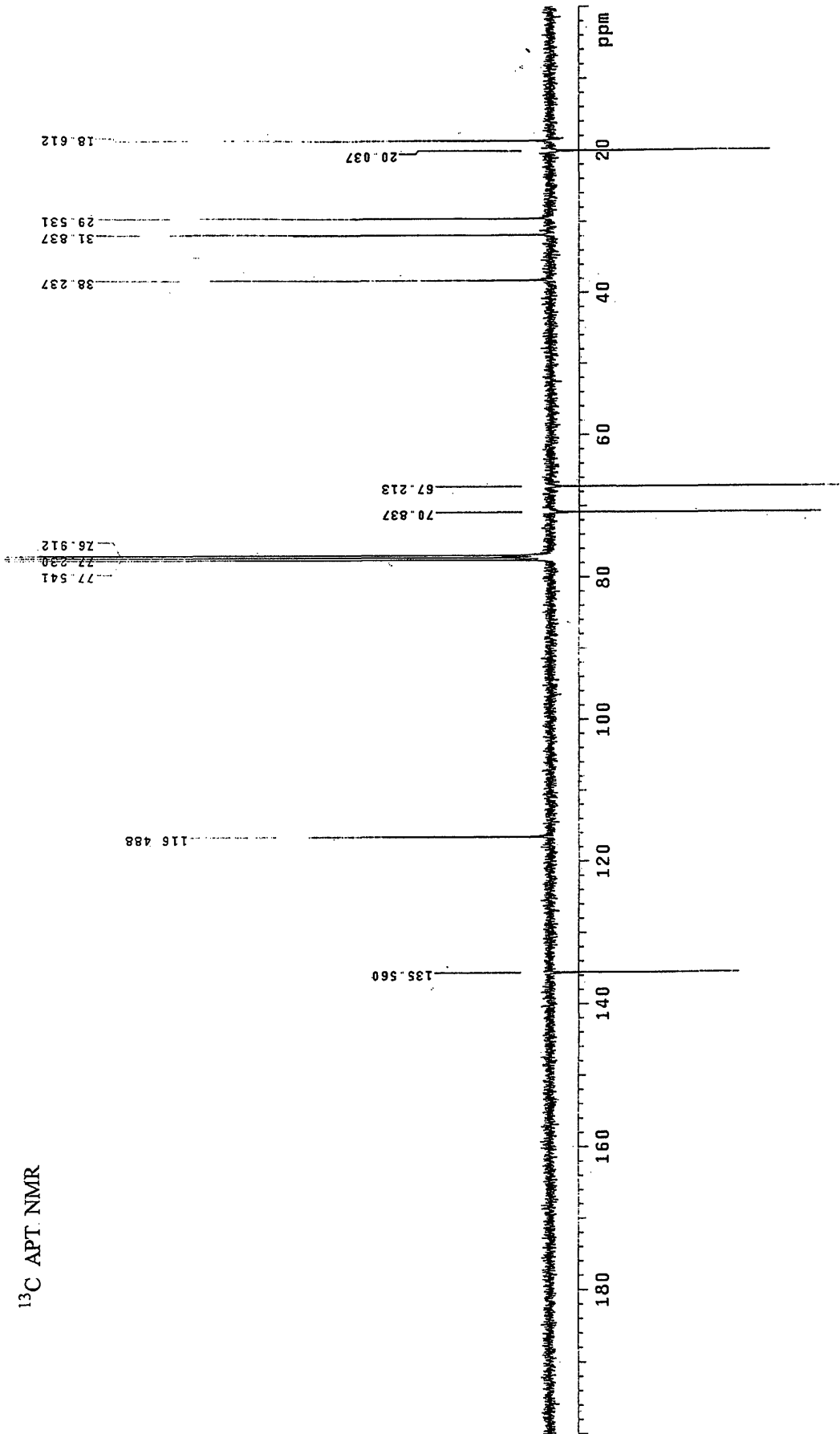
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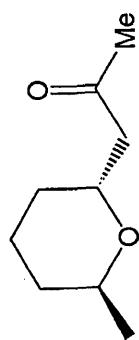




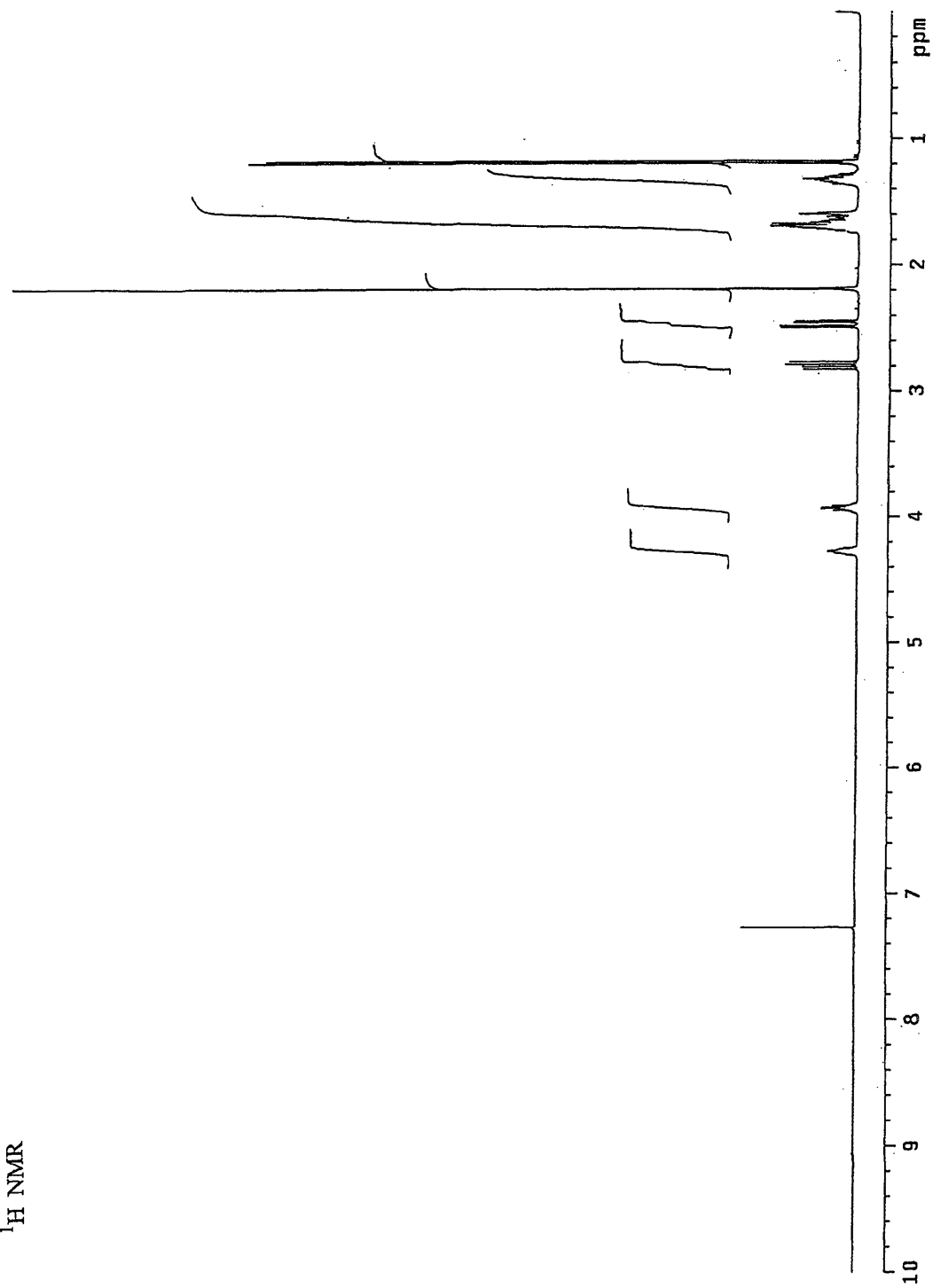
$^1\text{H}$  NMR

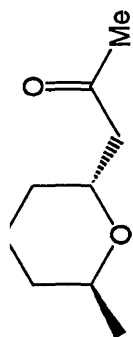


<sup>13</sup>C APT NMR

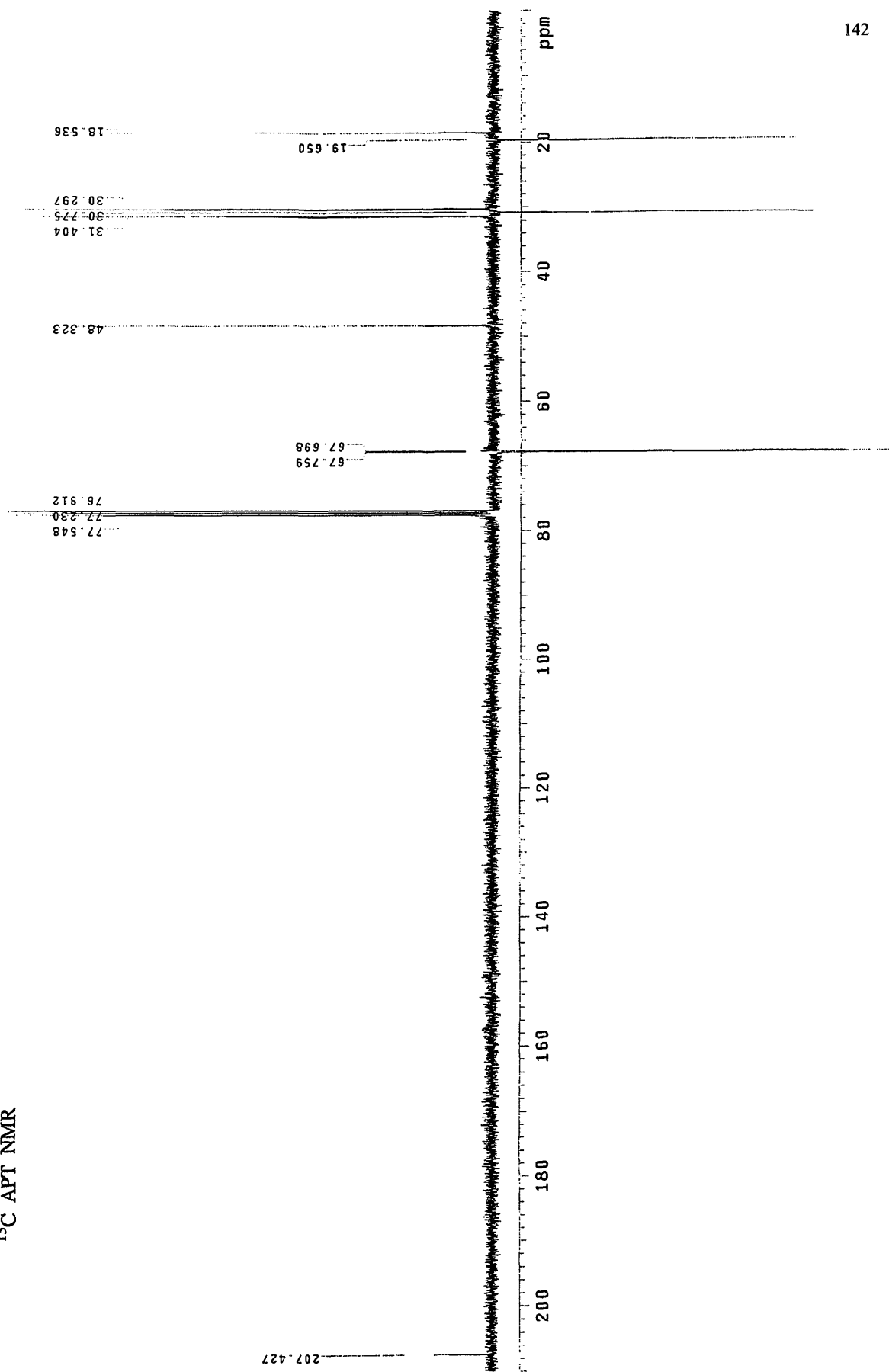


$^1\text{H NMR}$



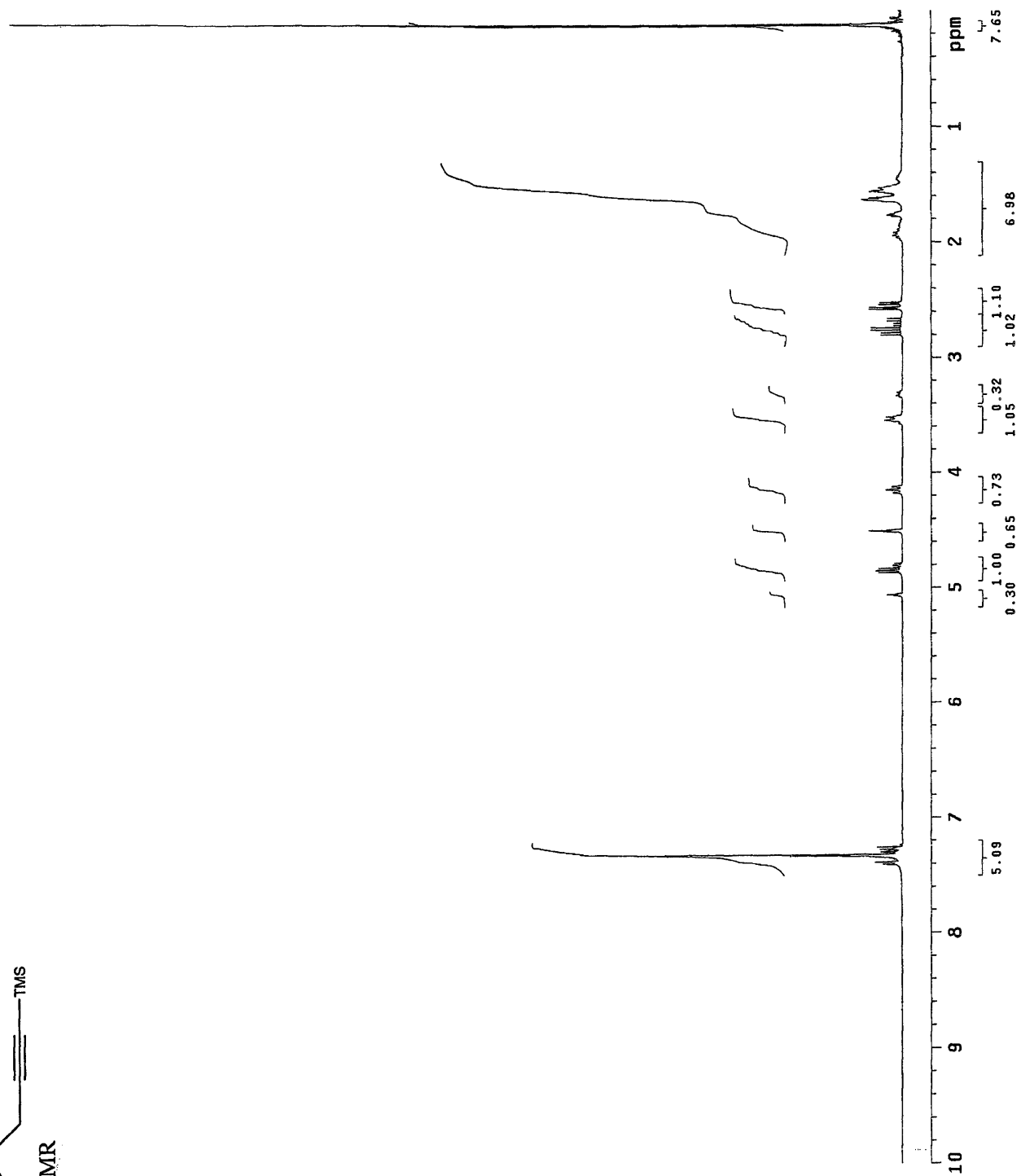
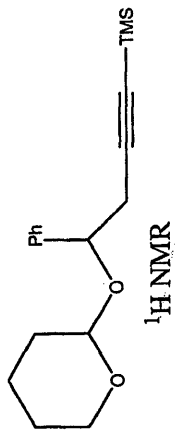


$^{13}\text{C}$  APT NMR

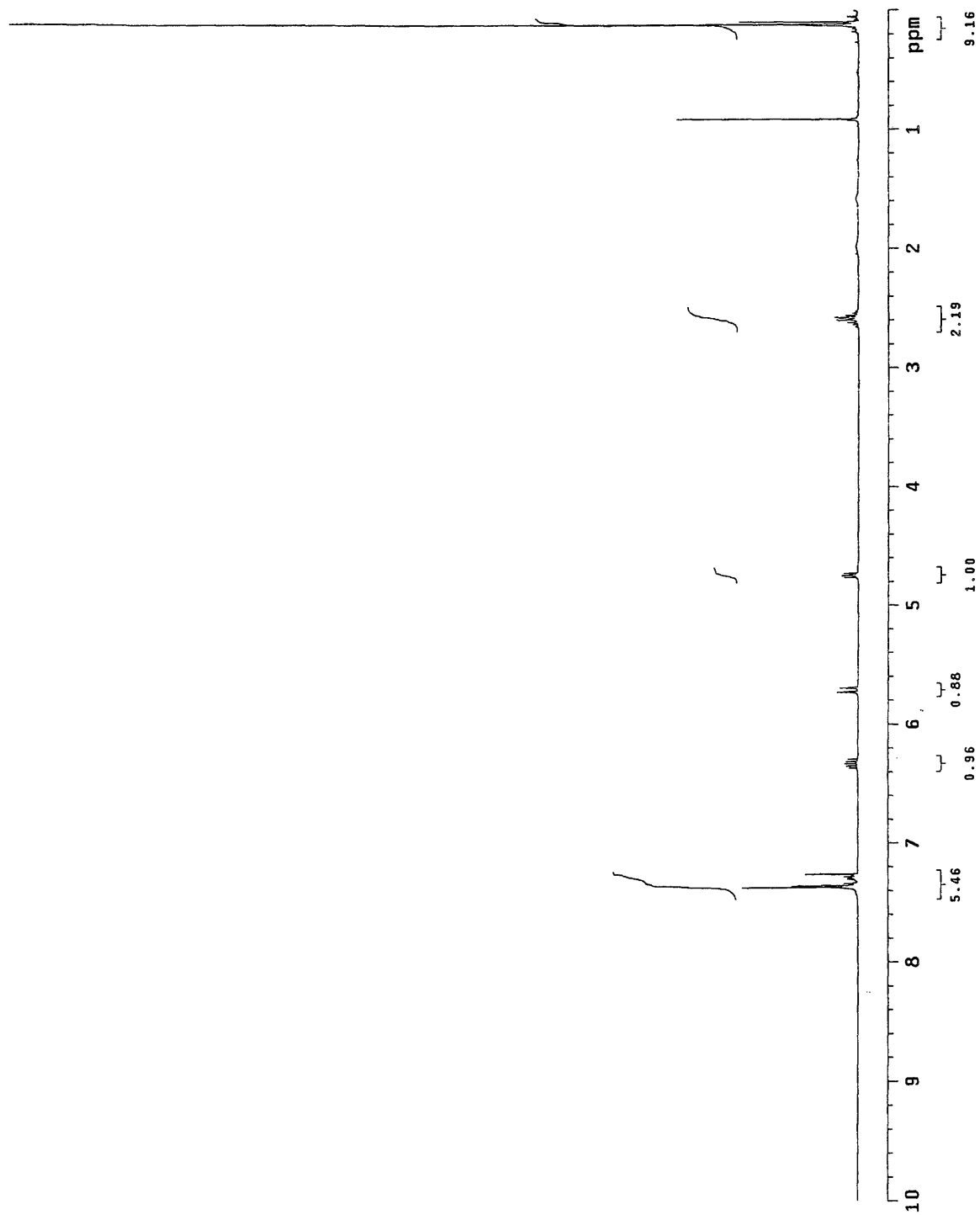
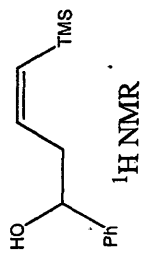


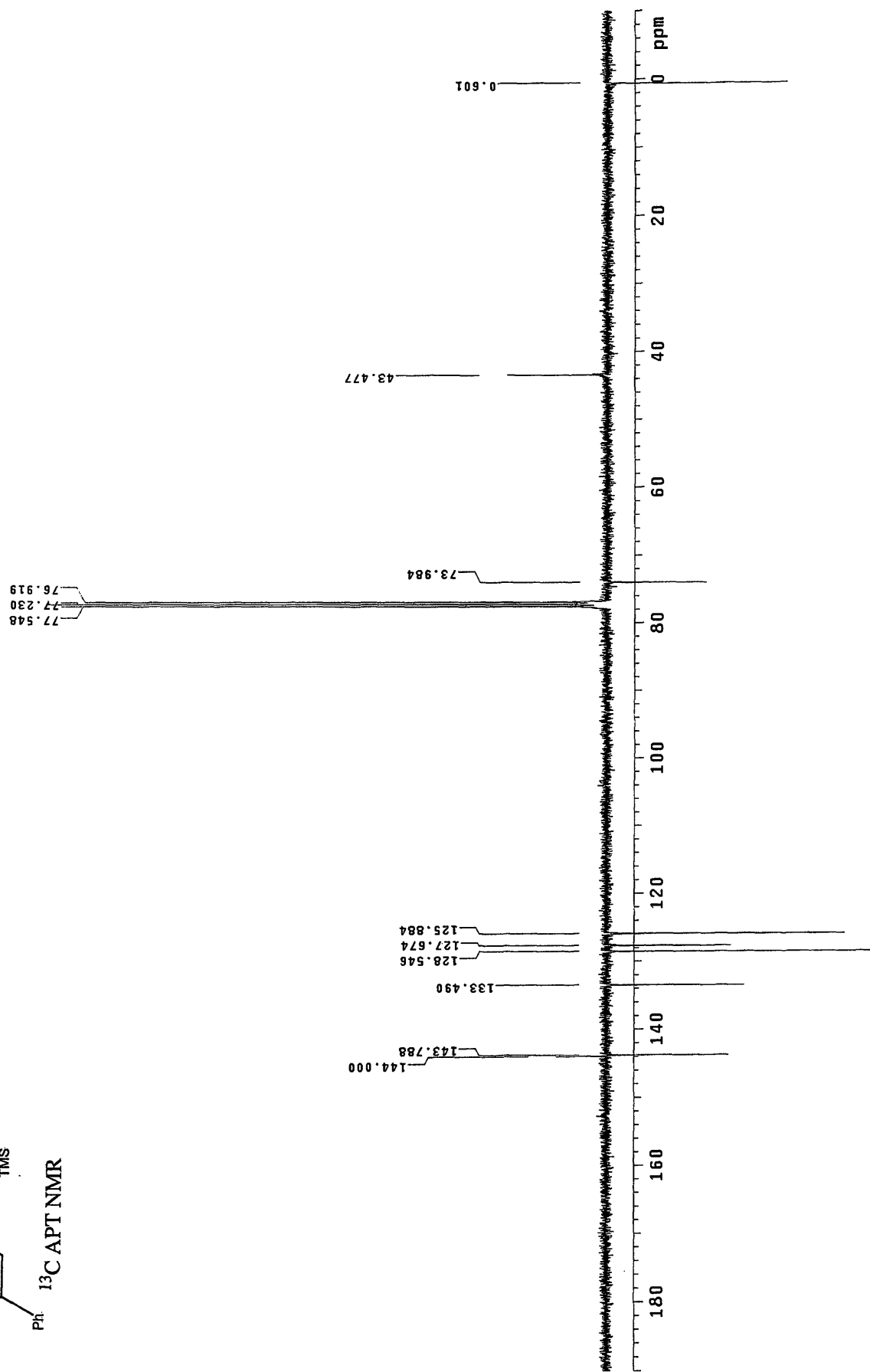
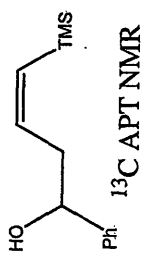
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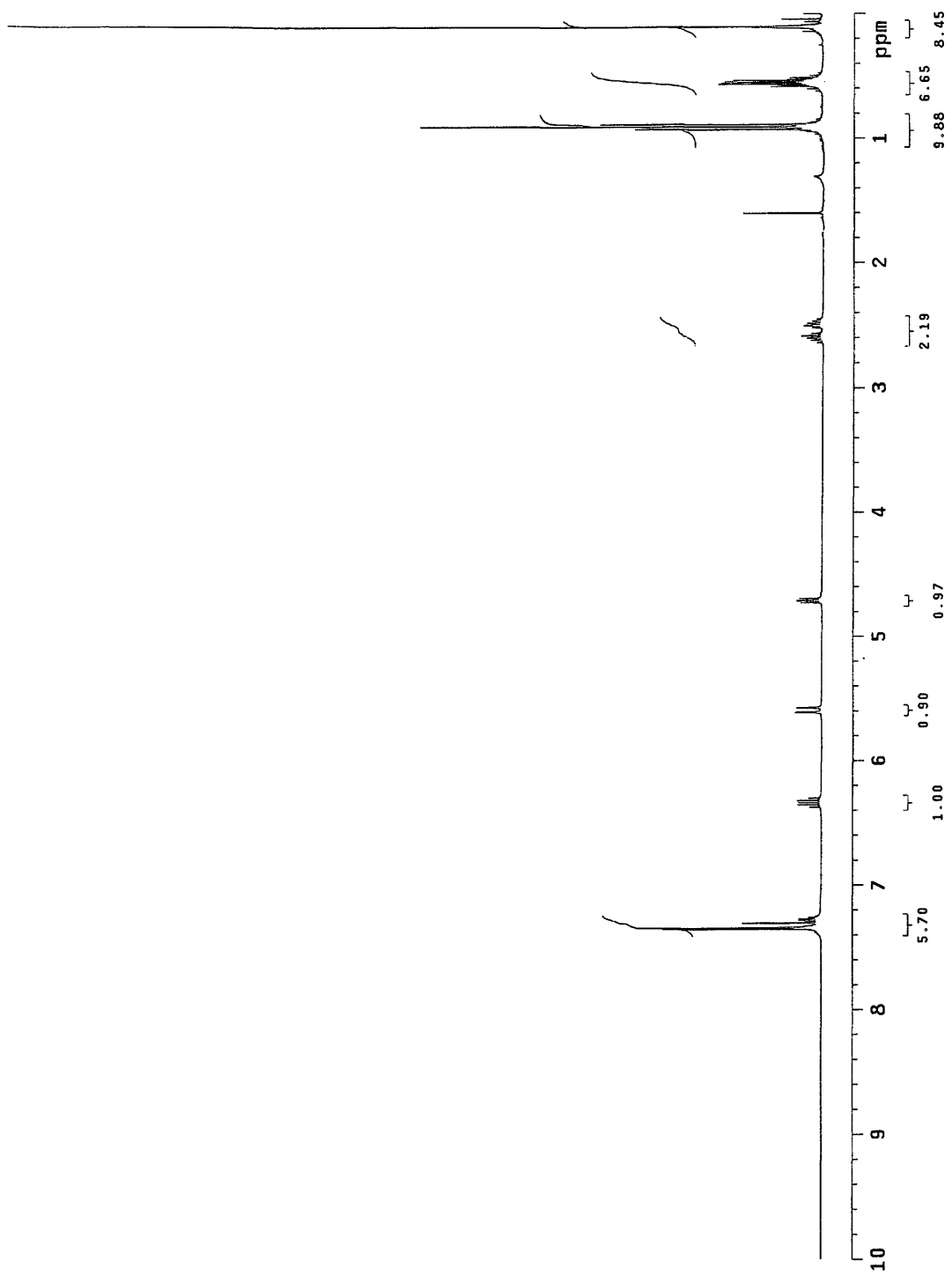
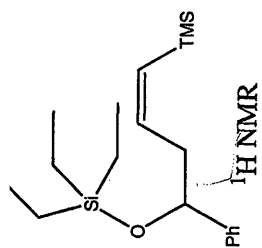
### **Chapter III: BiBr<sub>3</sub>-Initiated Tandem Addition/Silyl-Prins Reactions to 2,6-Disubstituted Dihydropyrans**



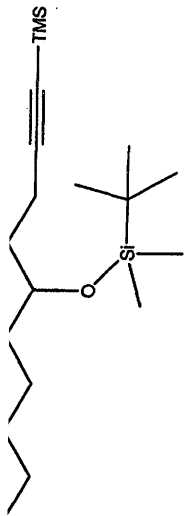
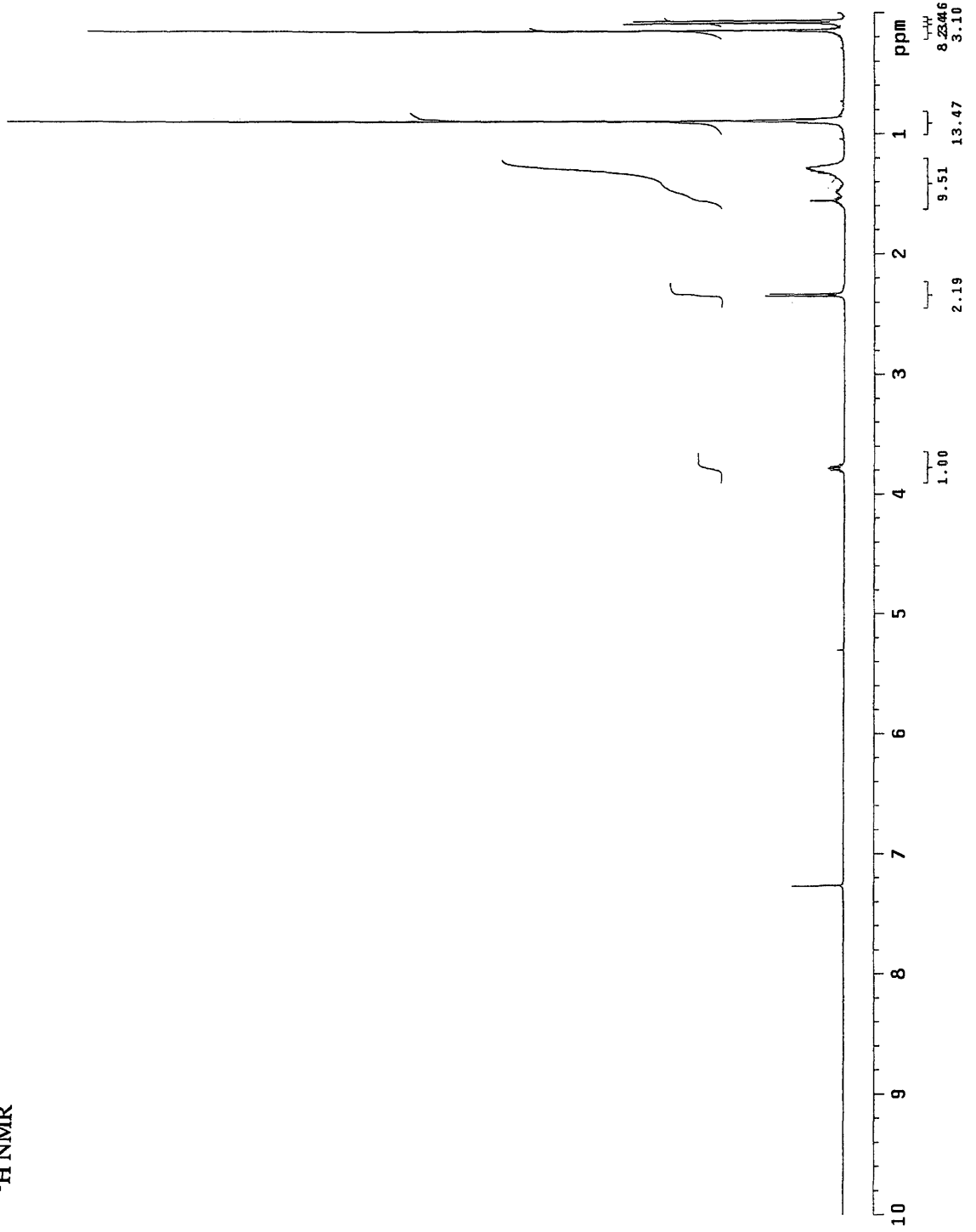


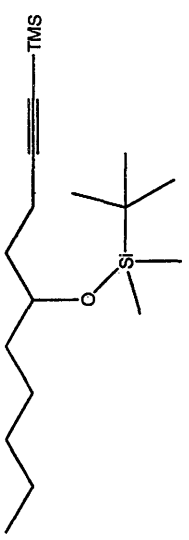




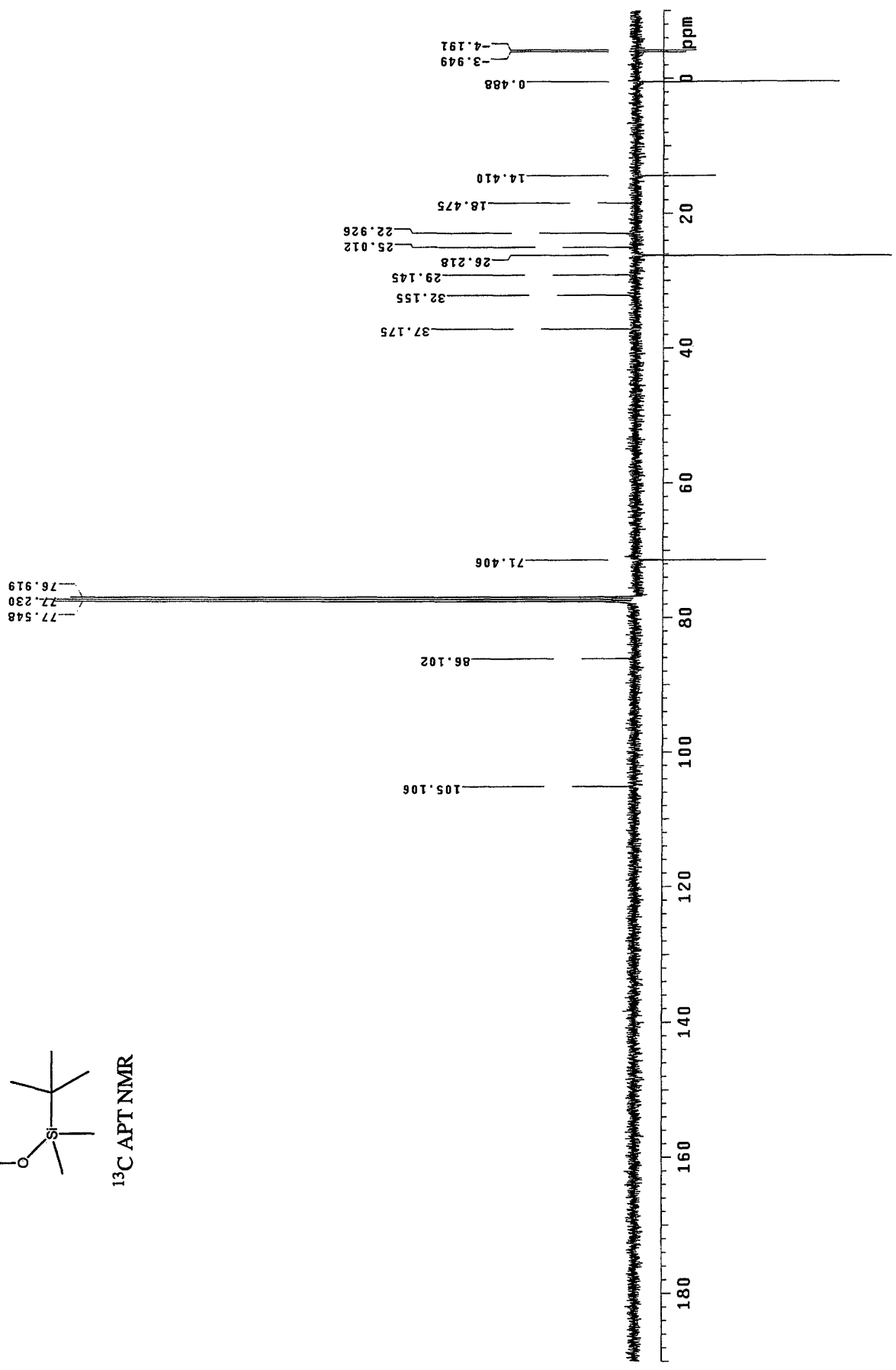


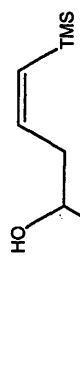


<sup>1</sup>H NMR

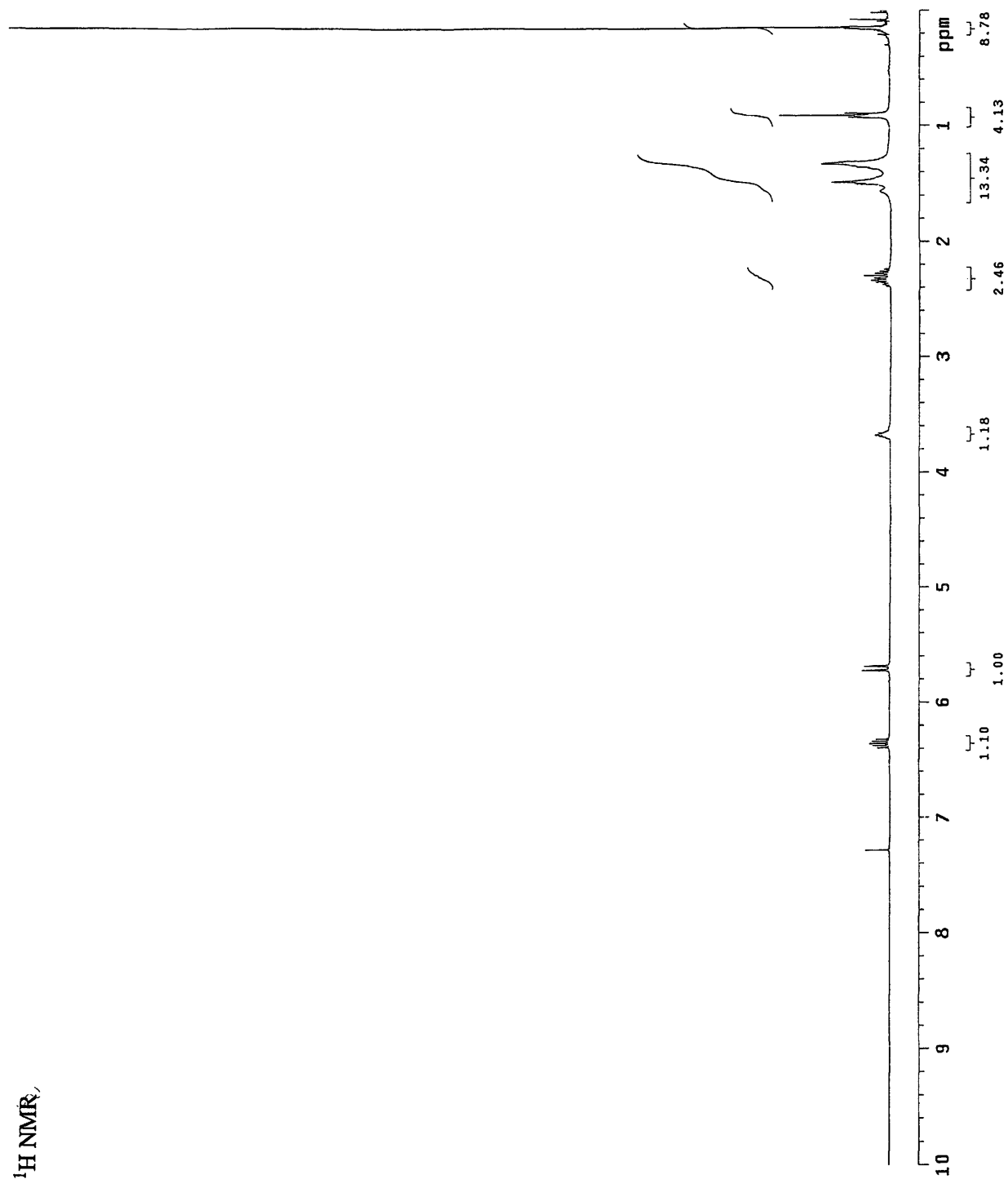


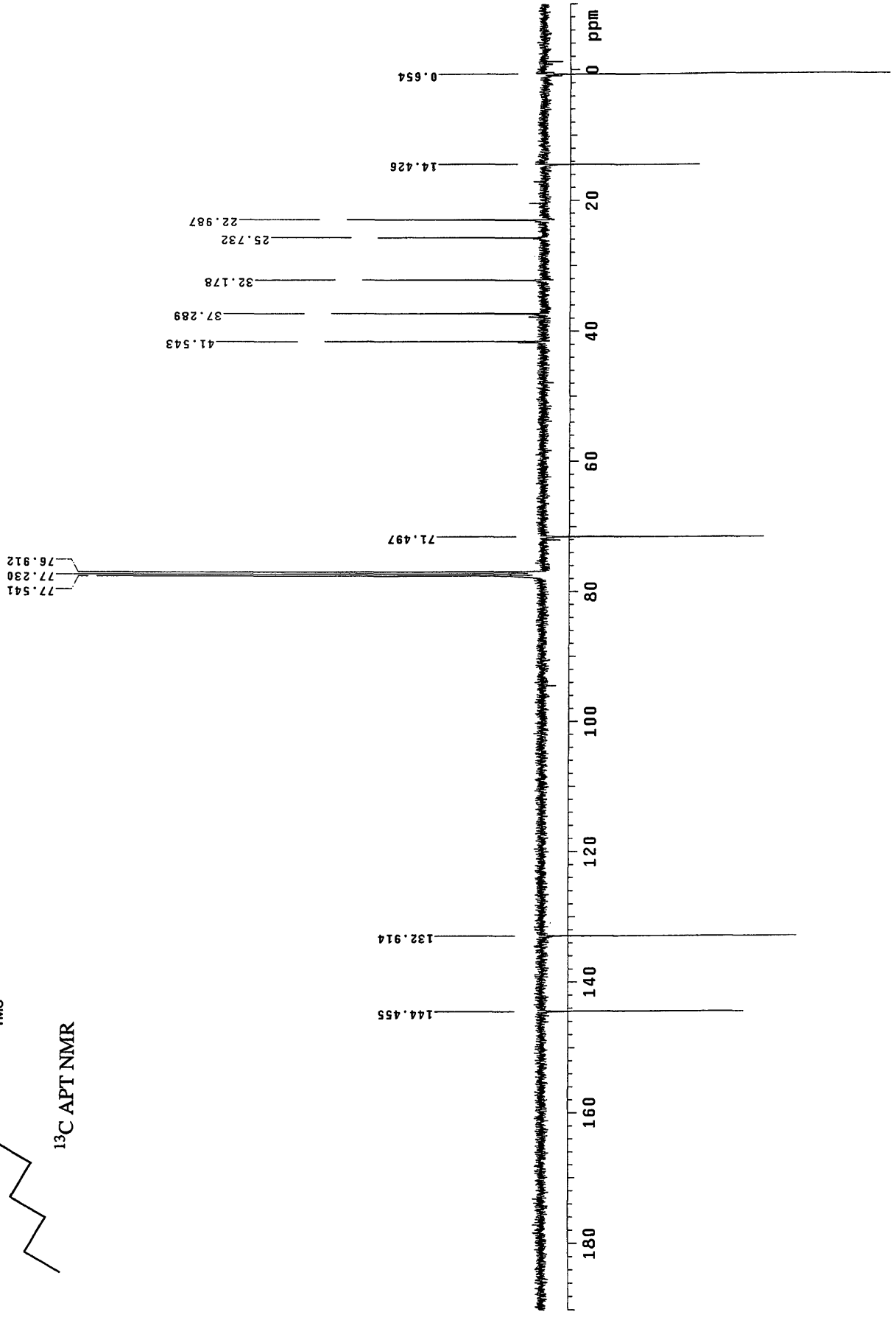
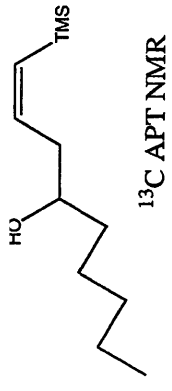
<sup>13</sup>C APT NMR

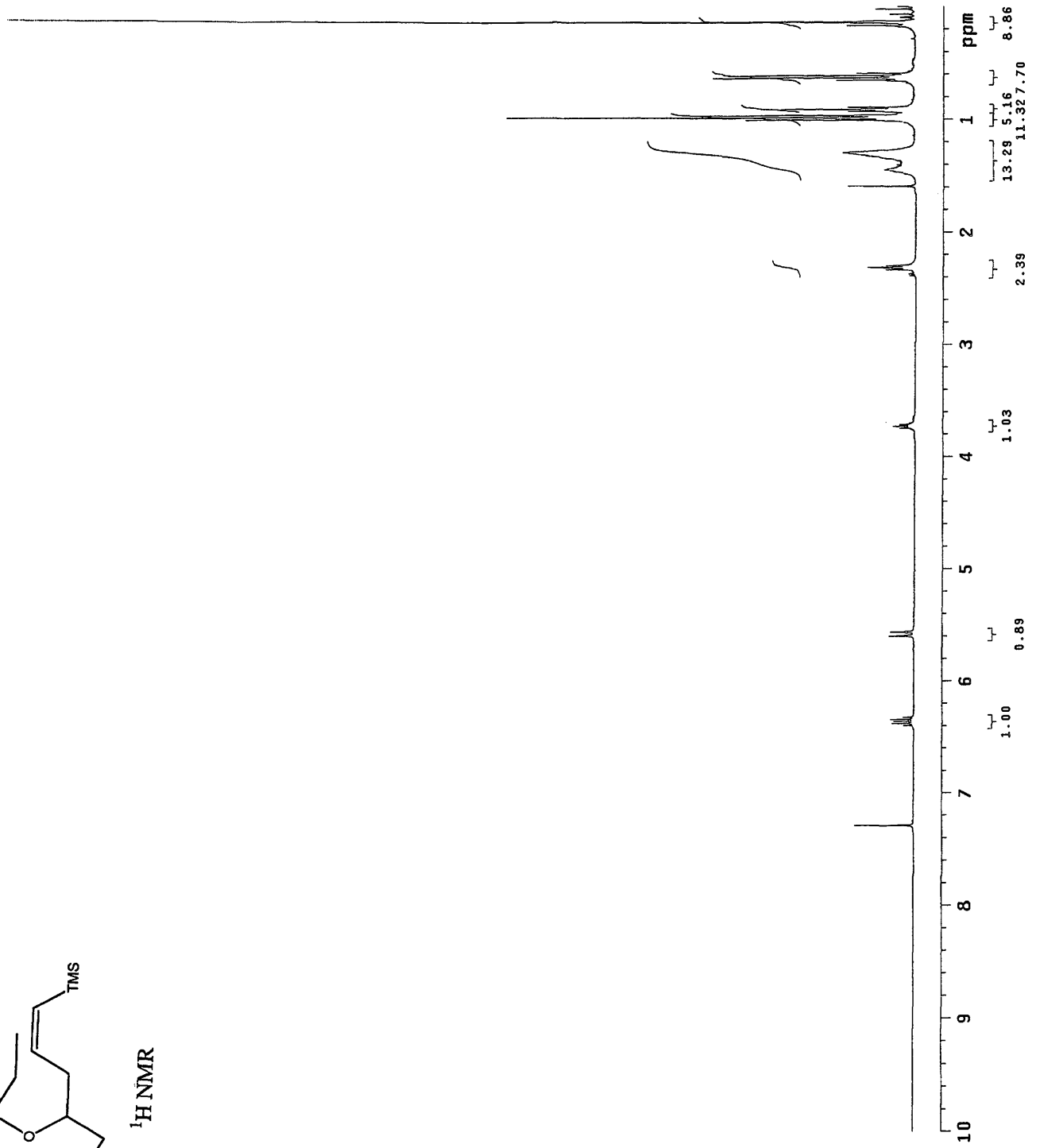
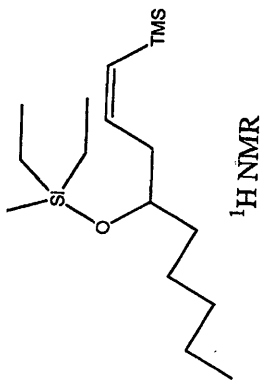


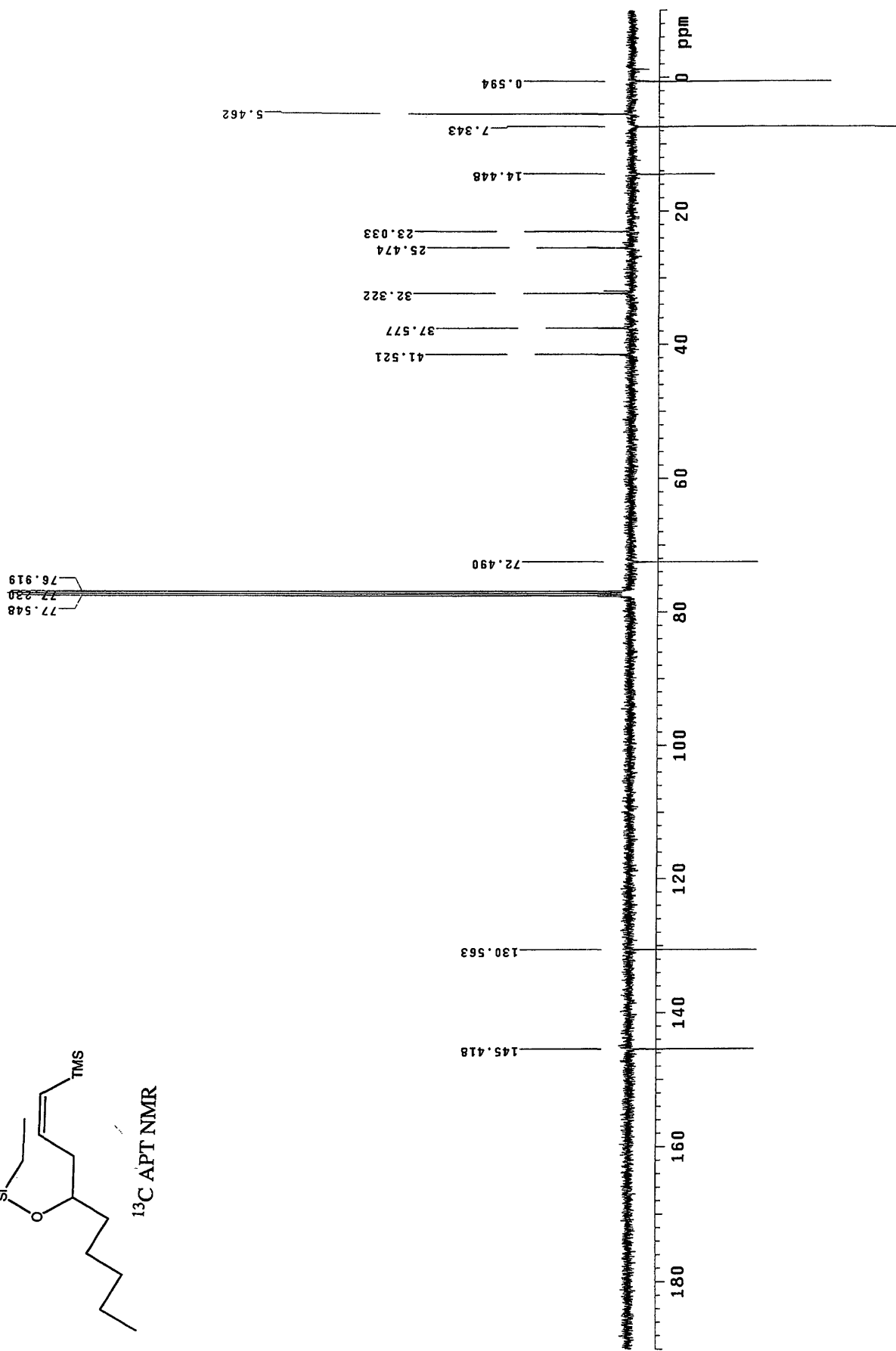
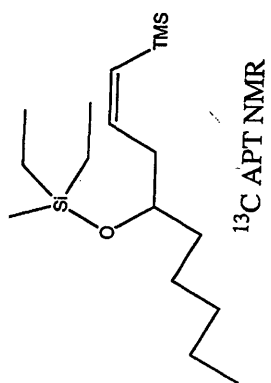


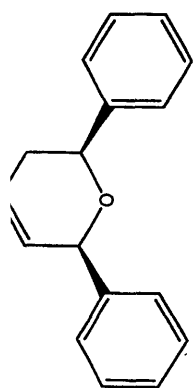
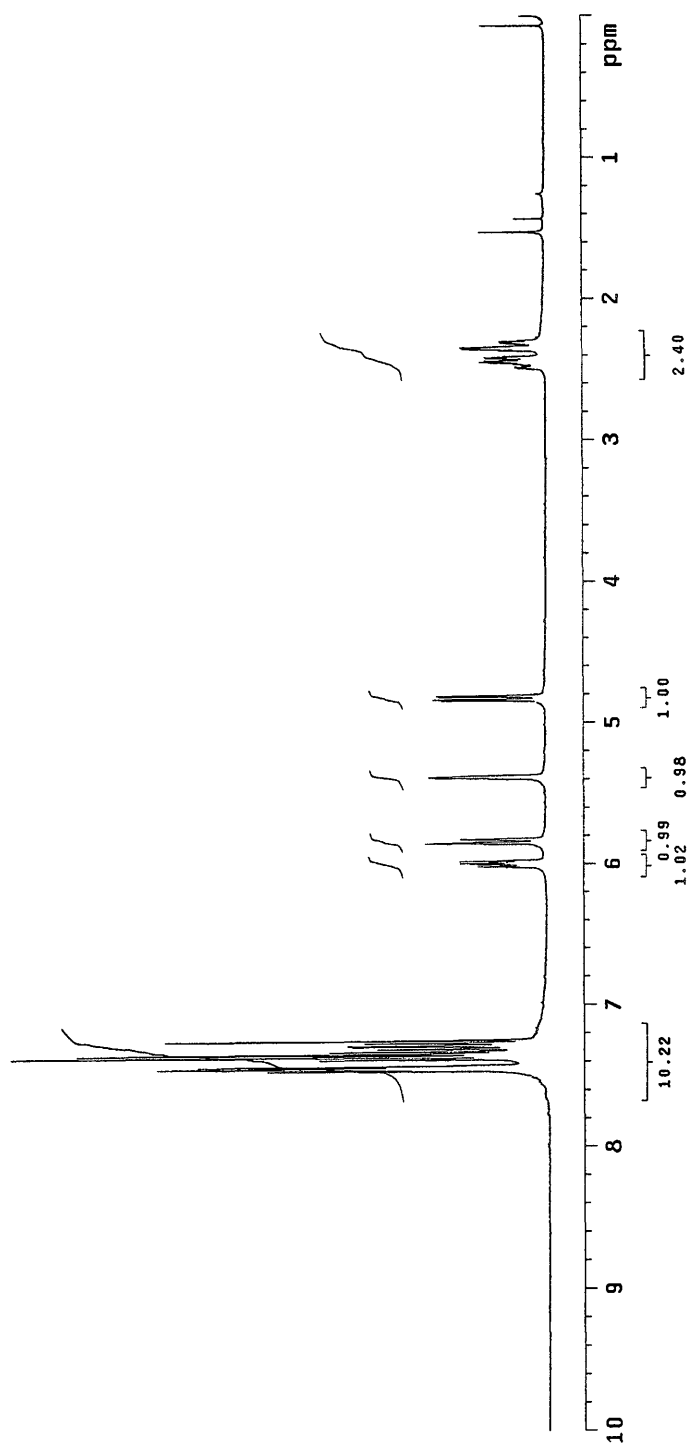
$^1\text{H NMR}$



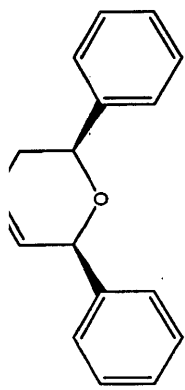




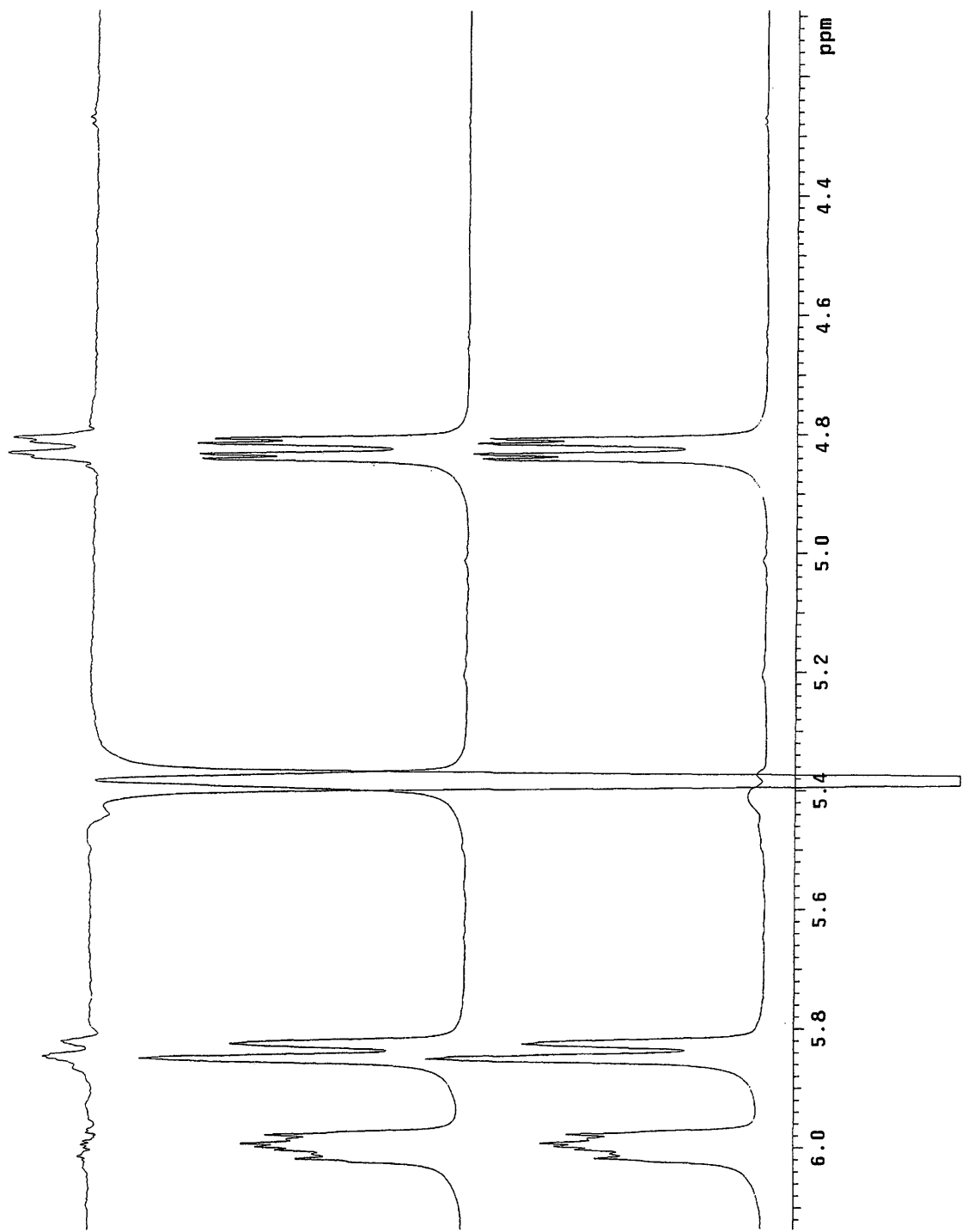


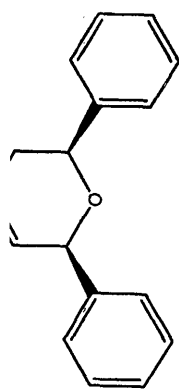
<sup>1</sup>H NMR



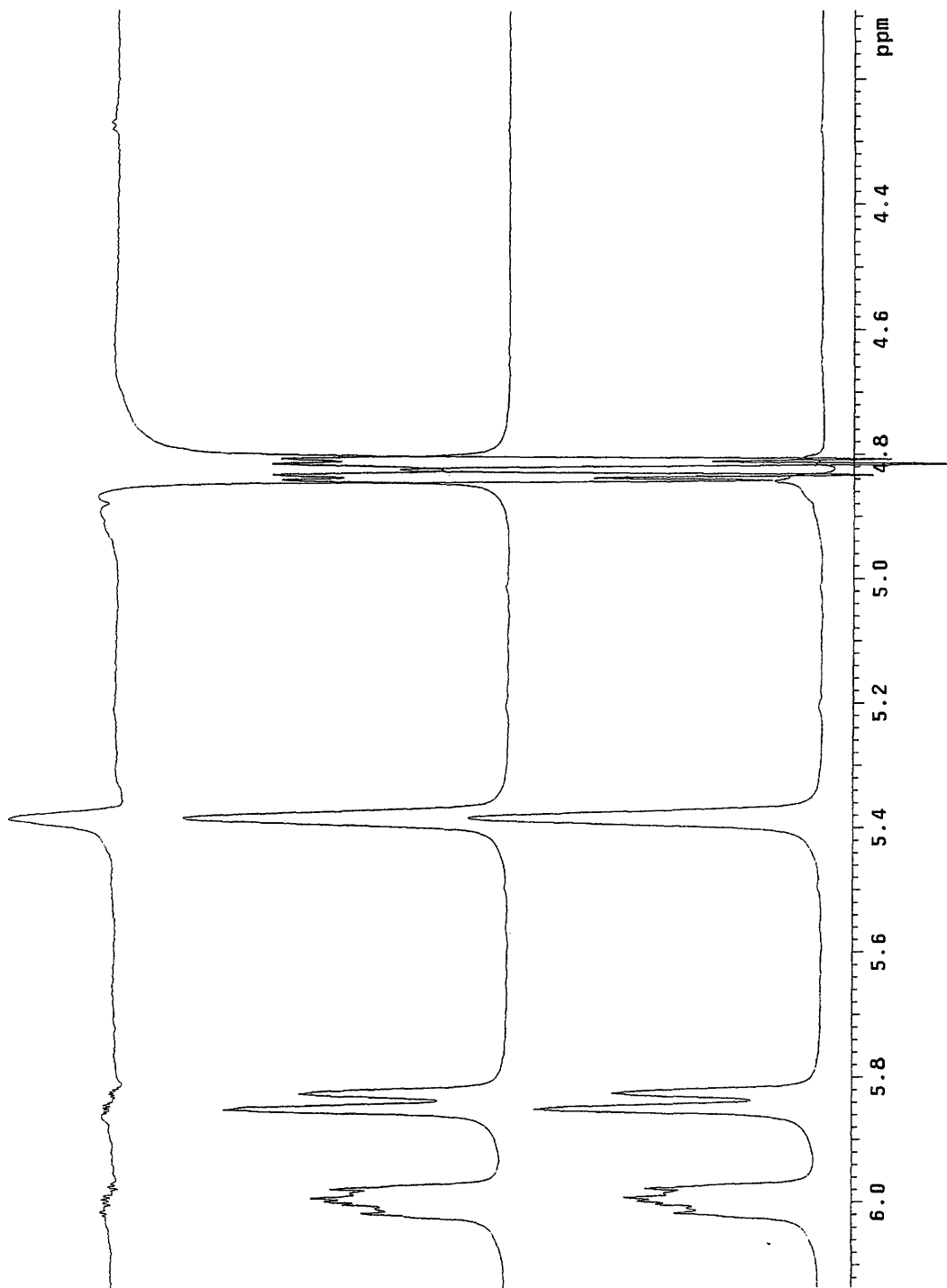


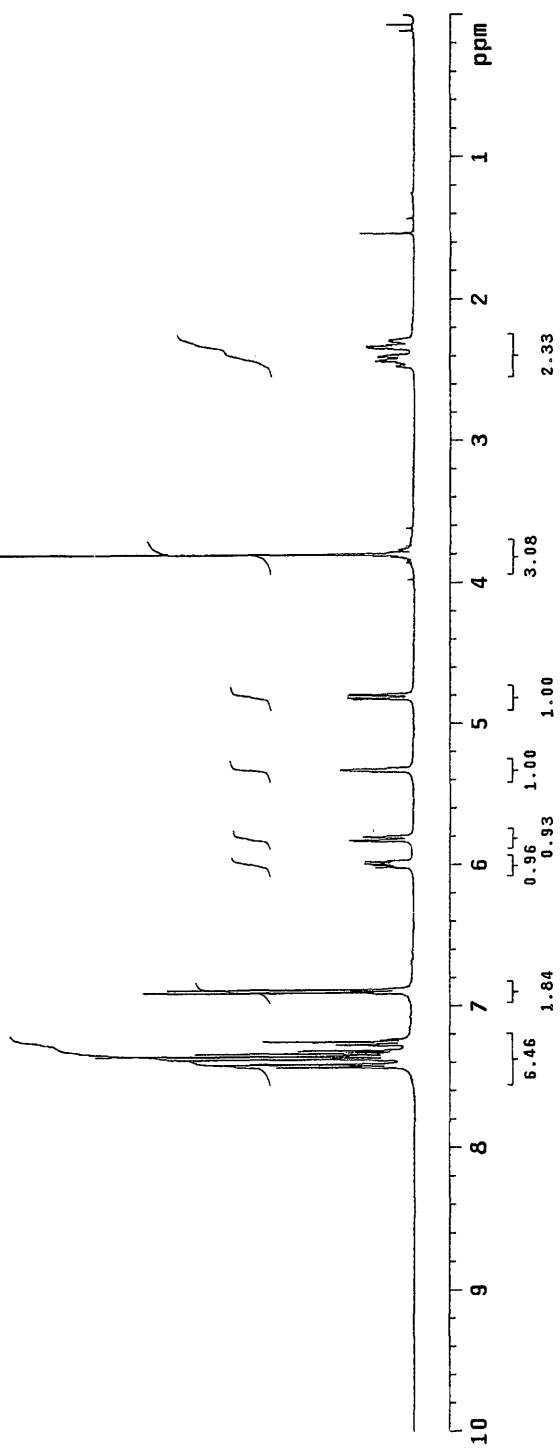
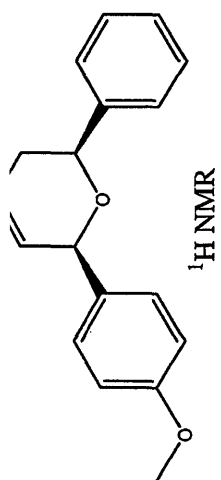
<sup>1</sup>H NOE NMR  
dec = 5.38 ppm

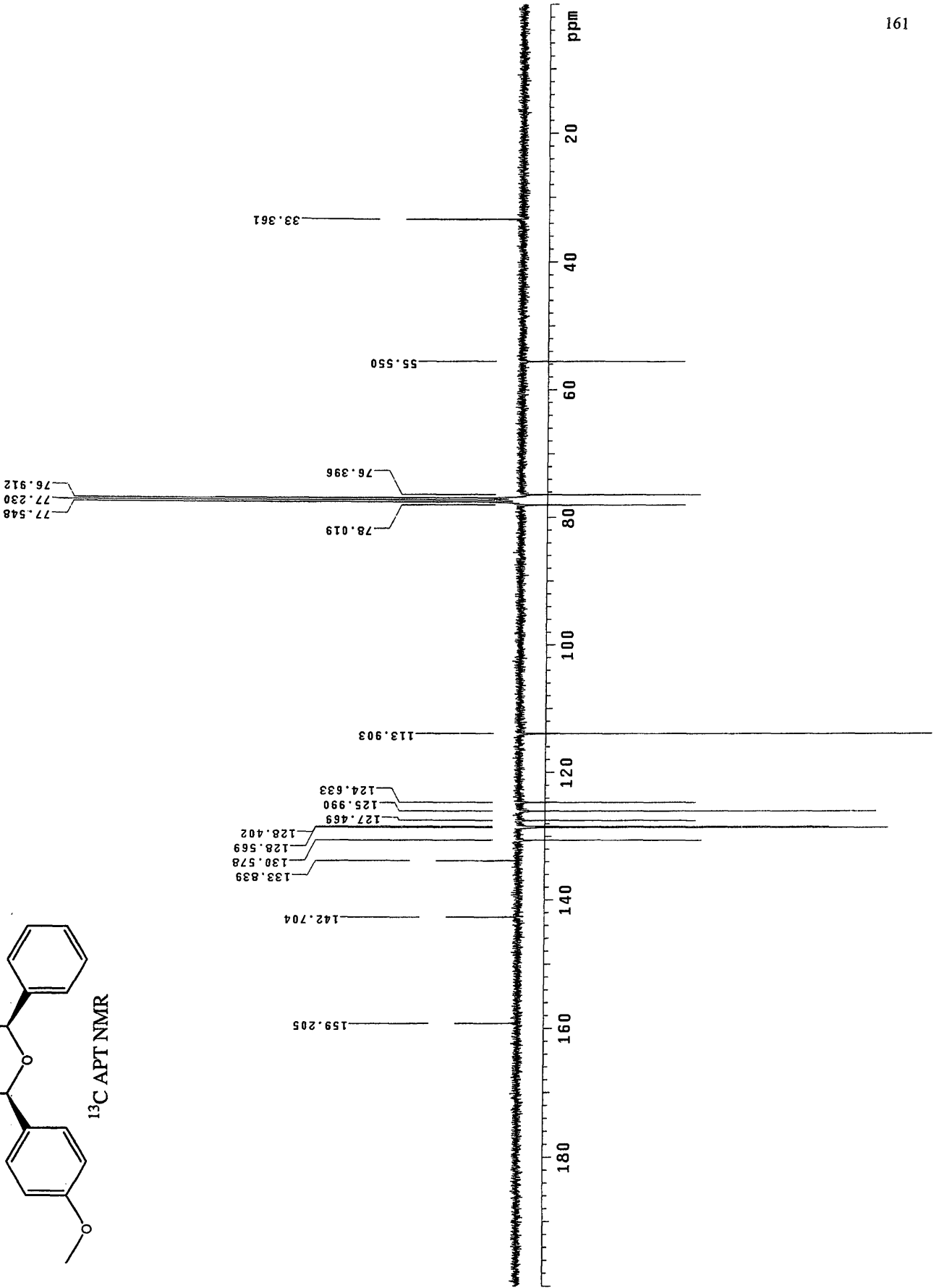
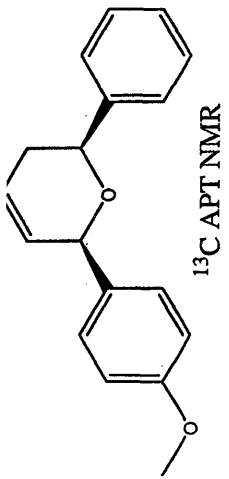


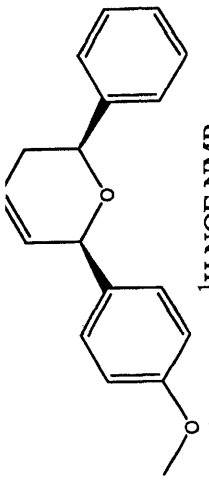


$^1\text{H}$  NOE NMR  
dec = 4.83 ppm



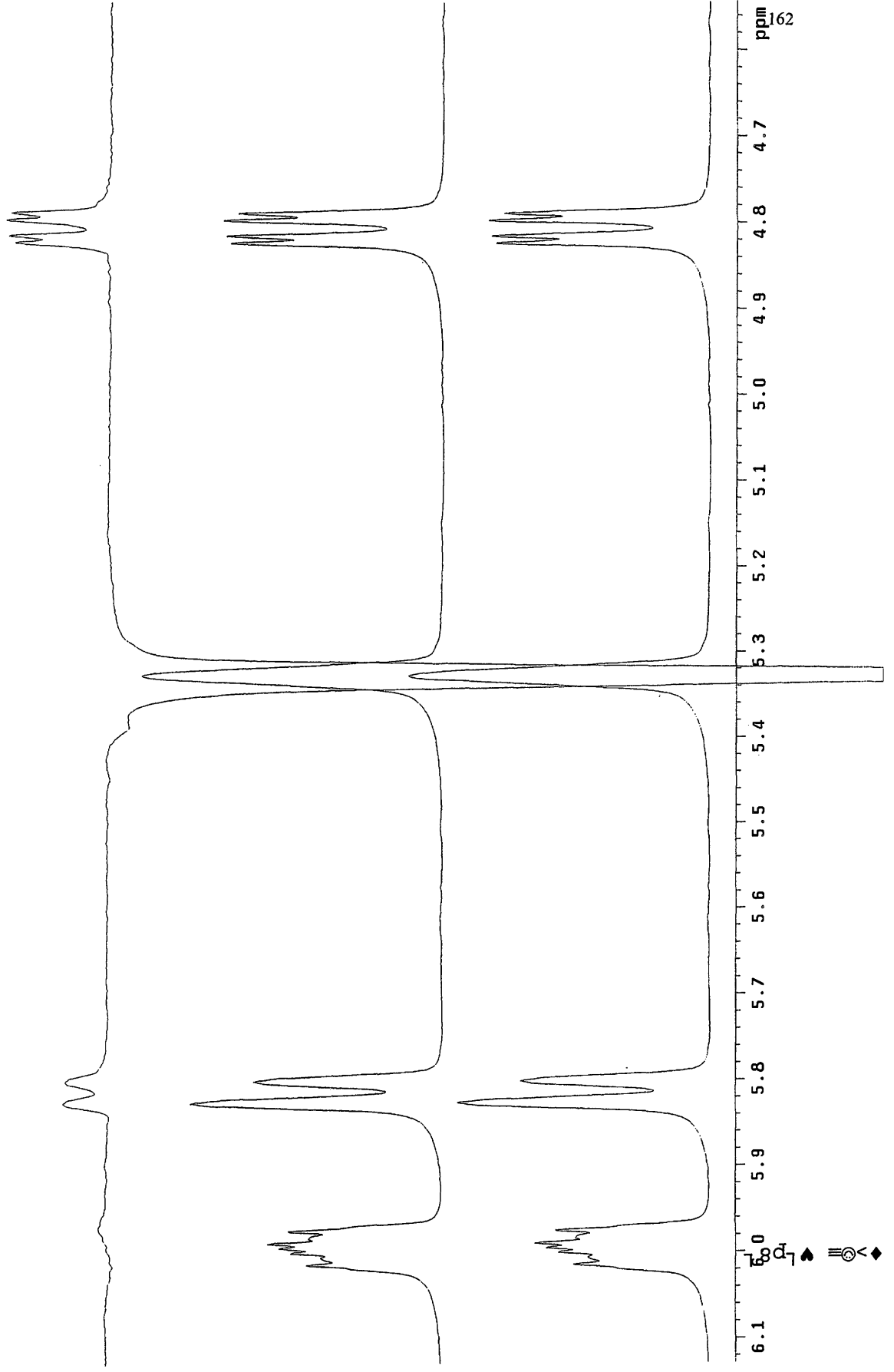


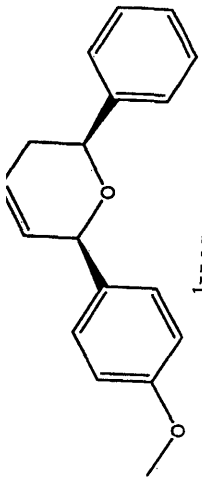




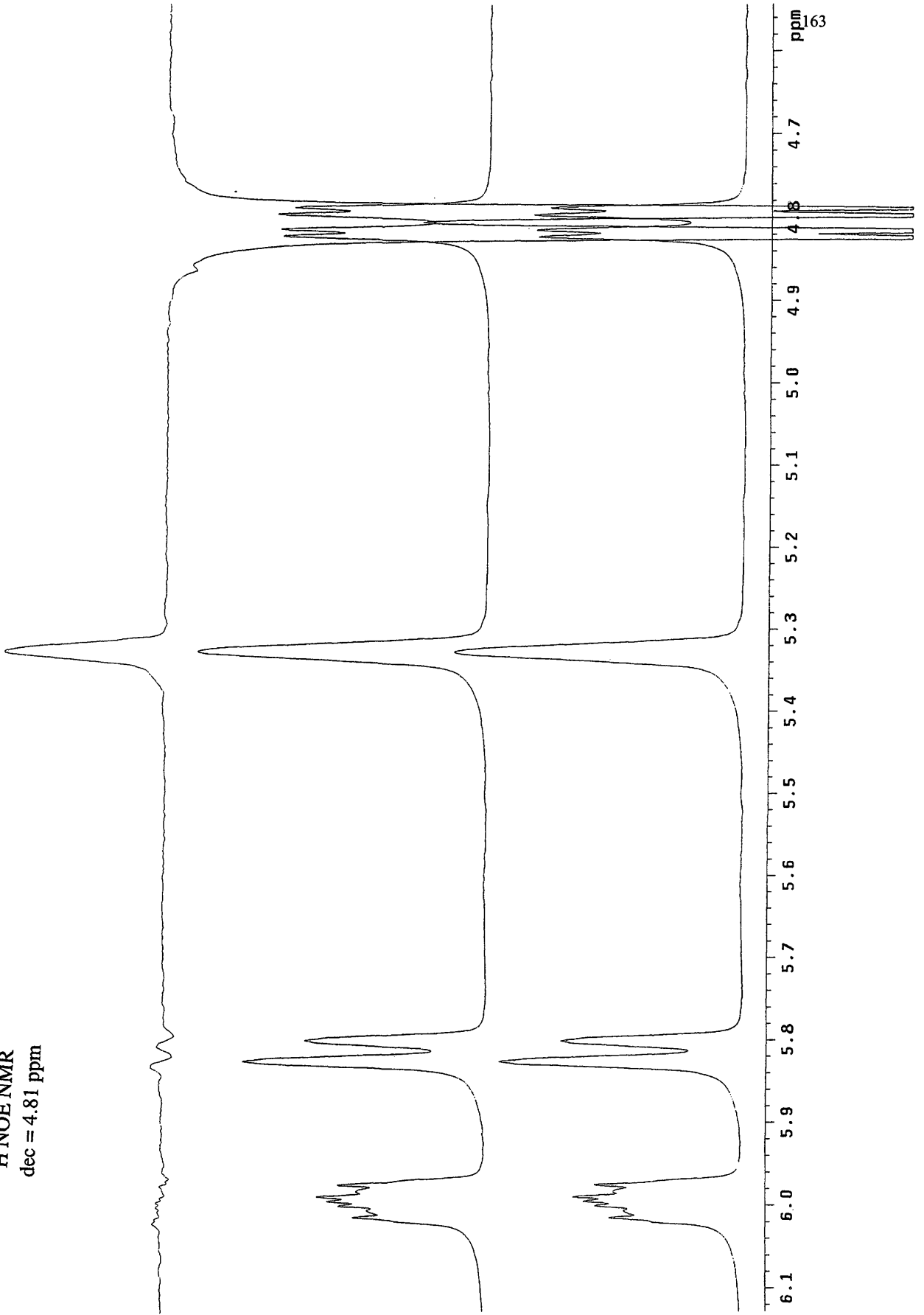
<sup>1</sup>H NOE NMR

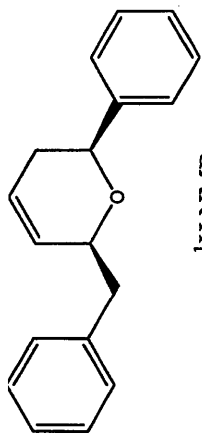
dec = 5.32 ppm



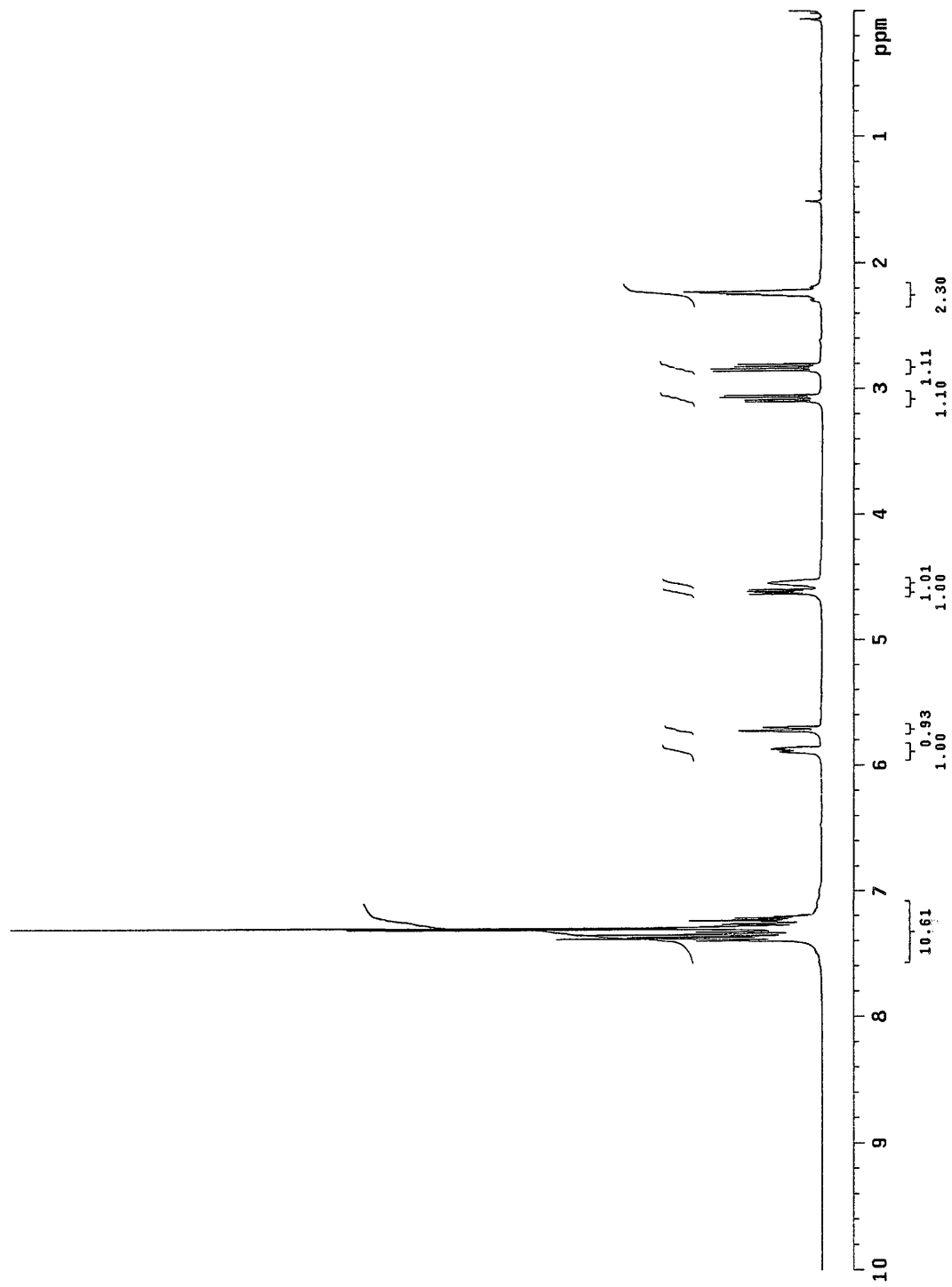


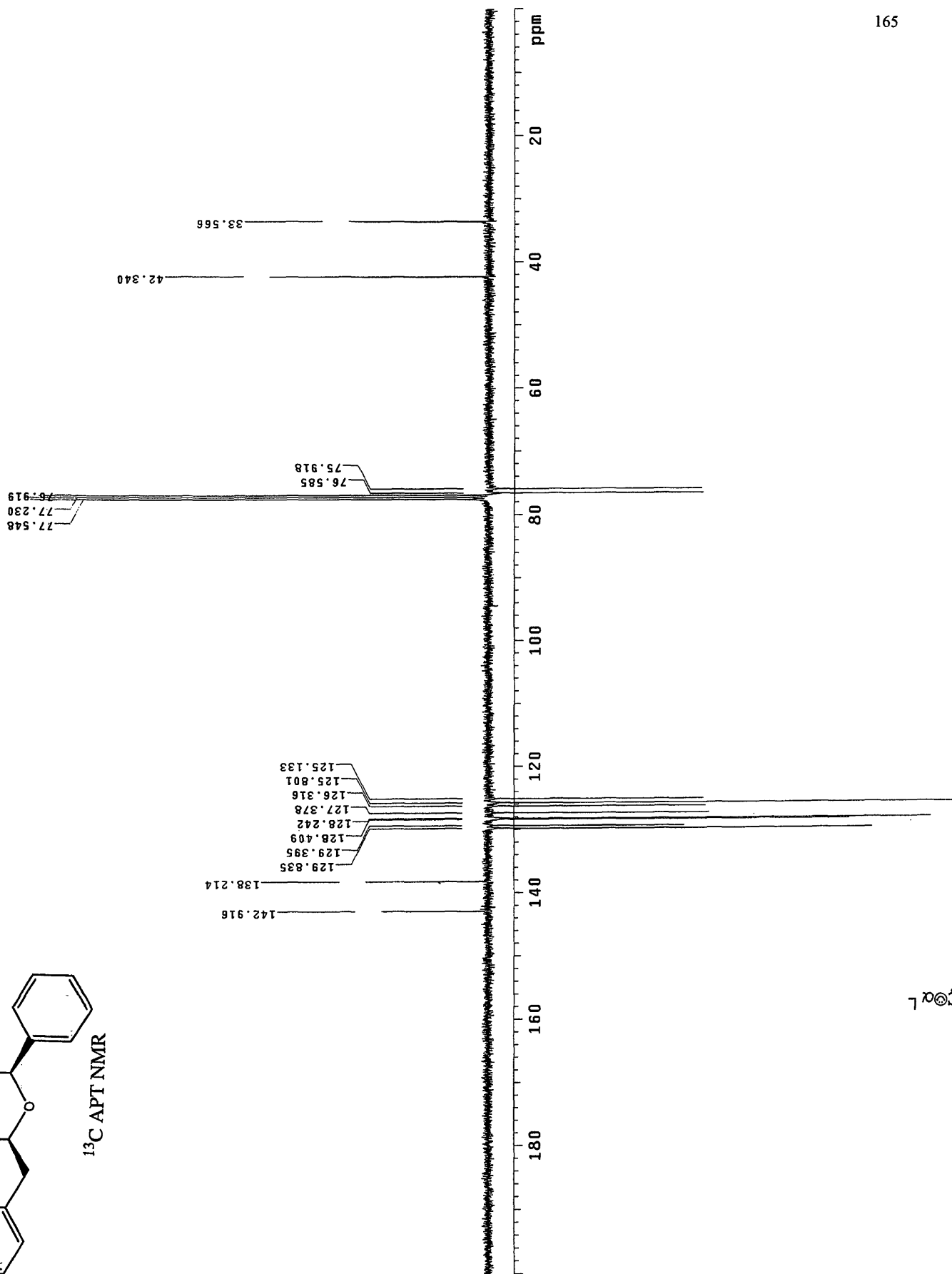
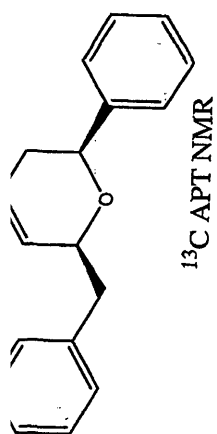
<sup>1</sup>H NOE NMR  
dec = 4.81 ppm

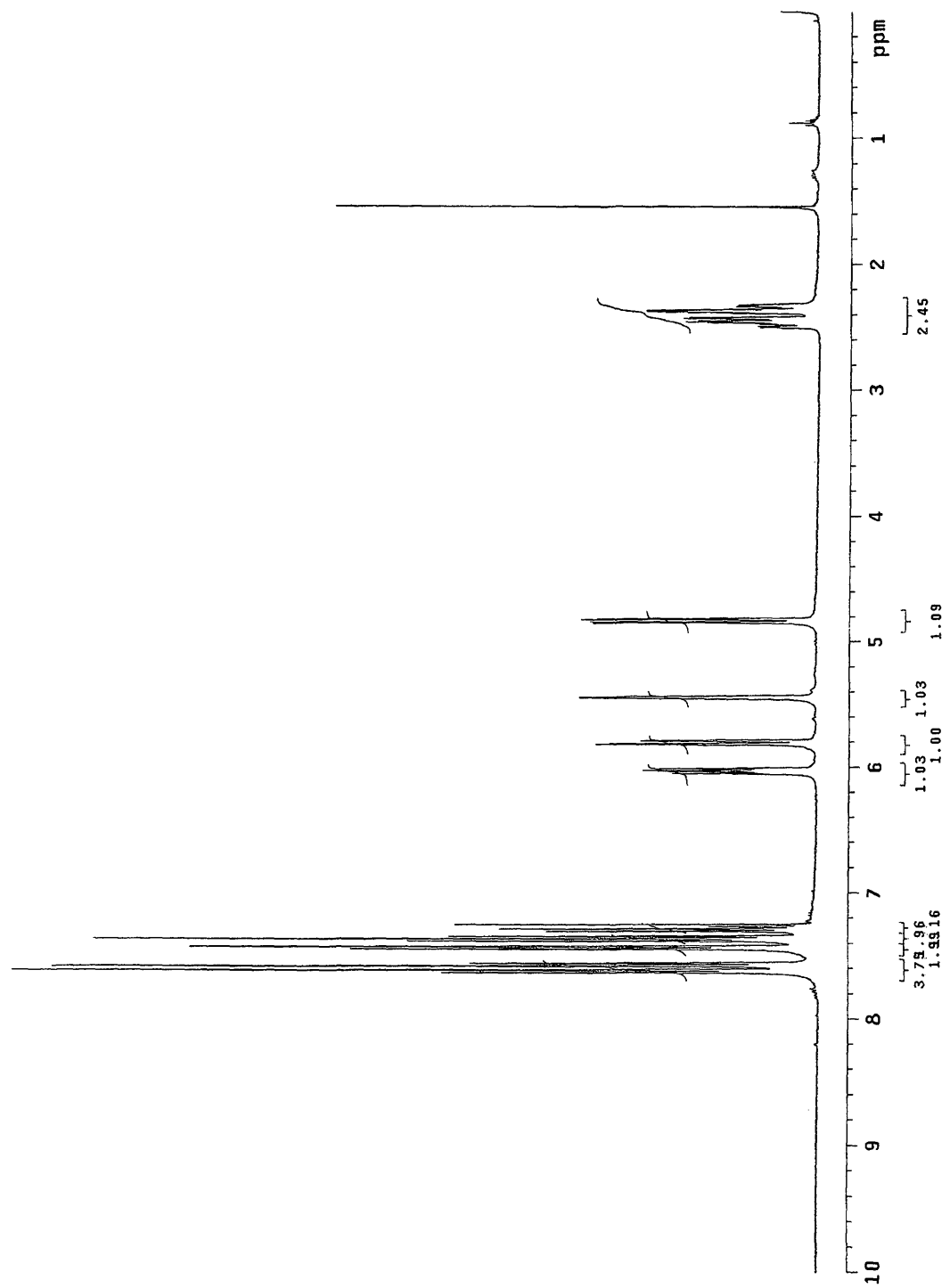
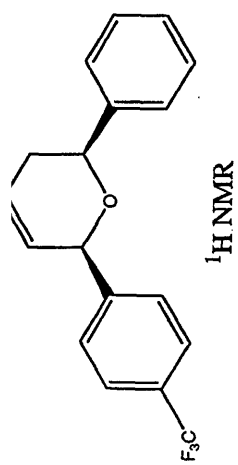


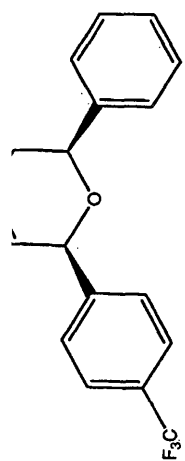
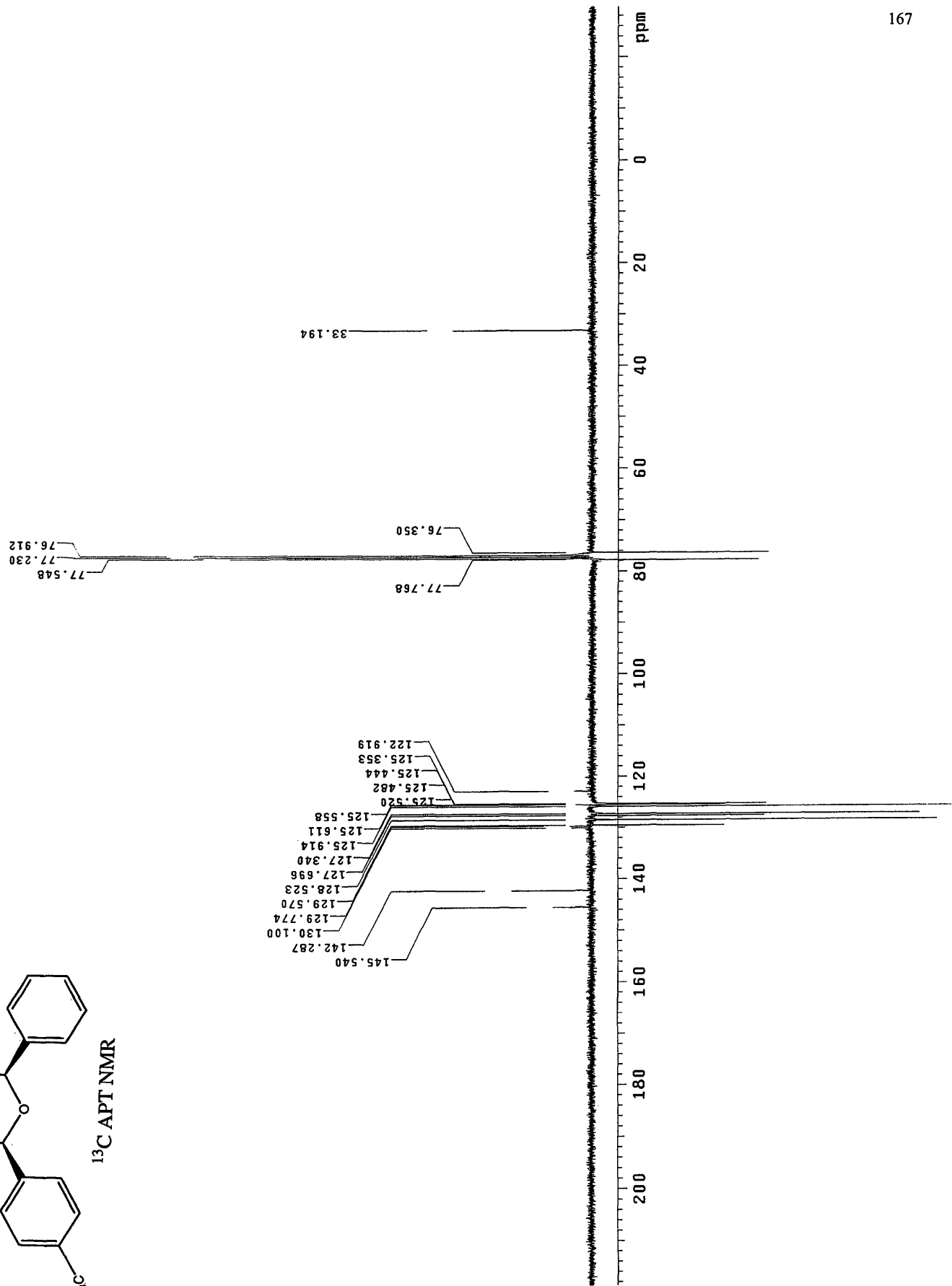


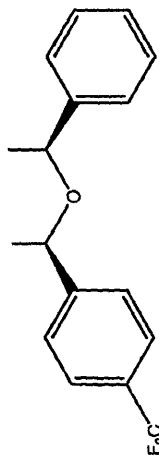
<sup>1</sup>H NMR



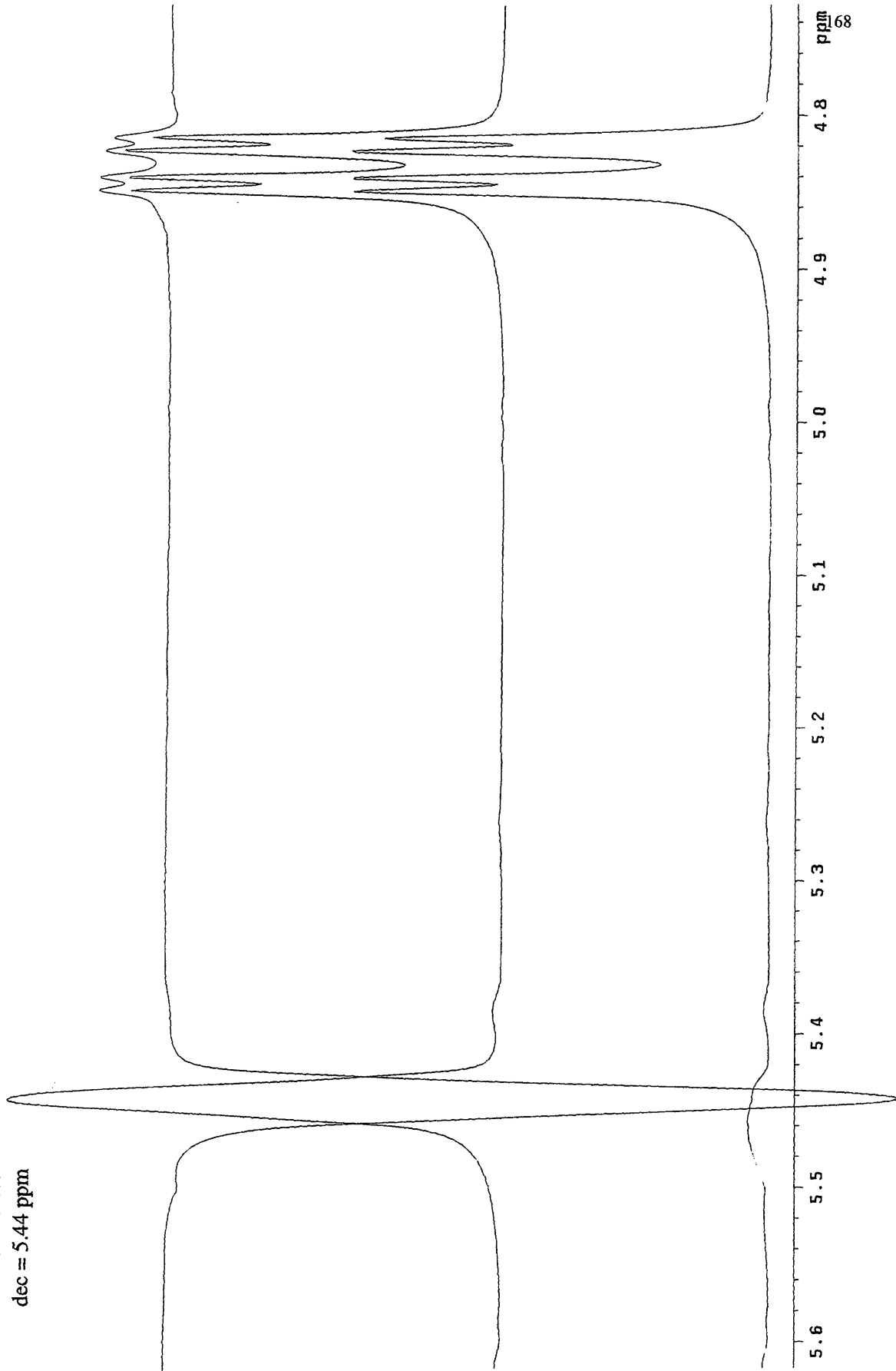




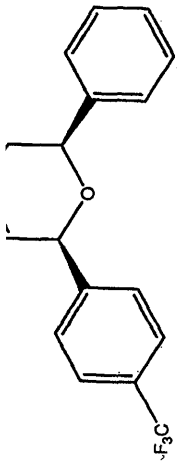
 $^{13}\text{C}$  APT NMR



<sup>1</sup>H NOE NMR  
dec = 5.44 ppm

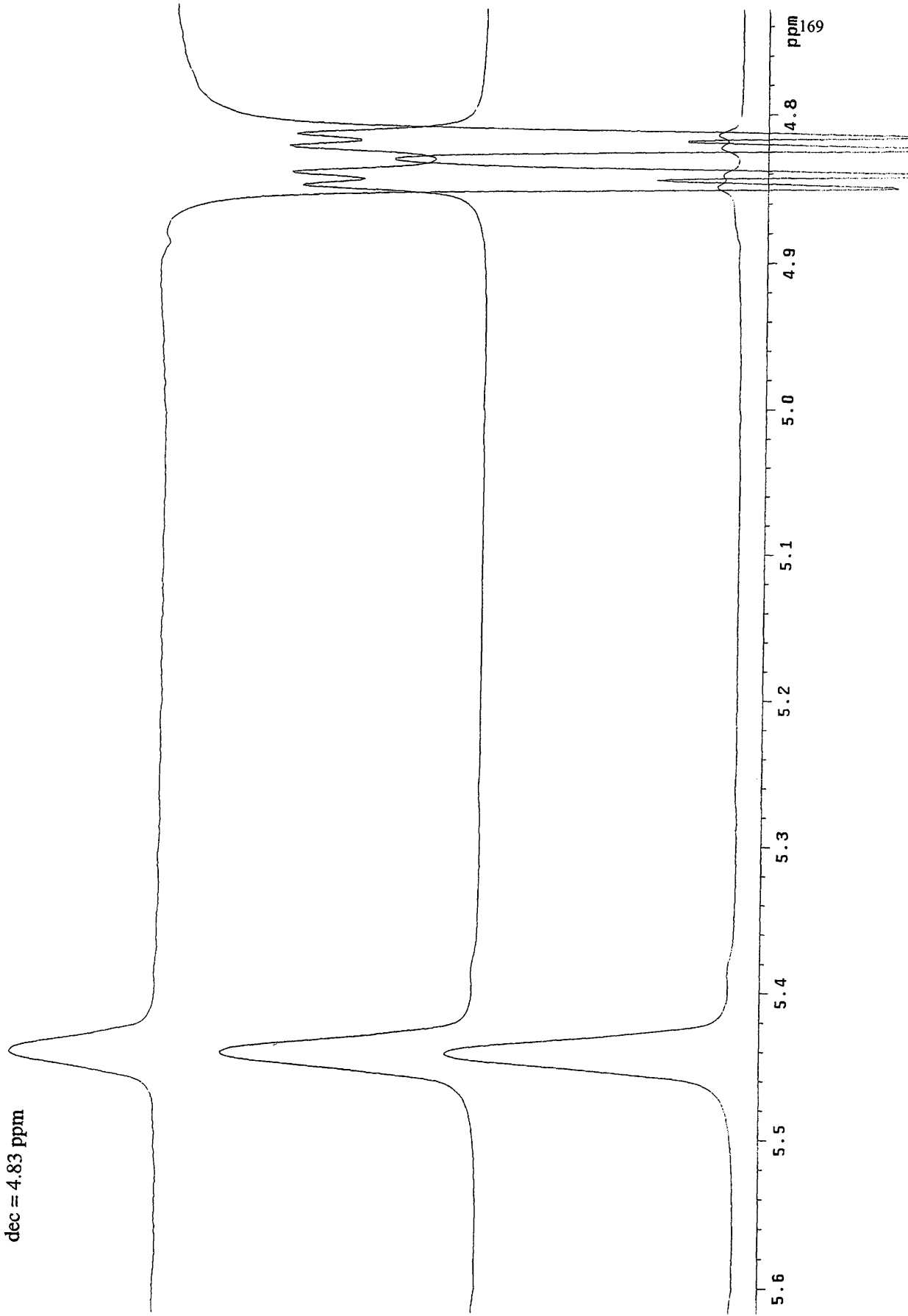


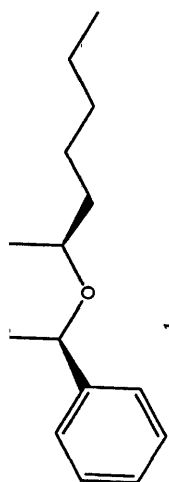
ppm  
68



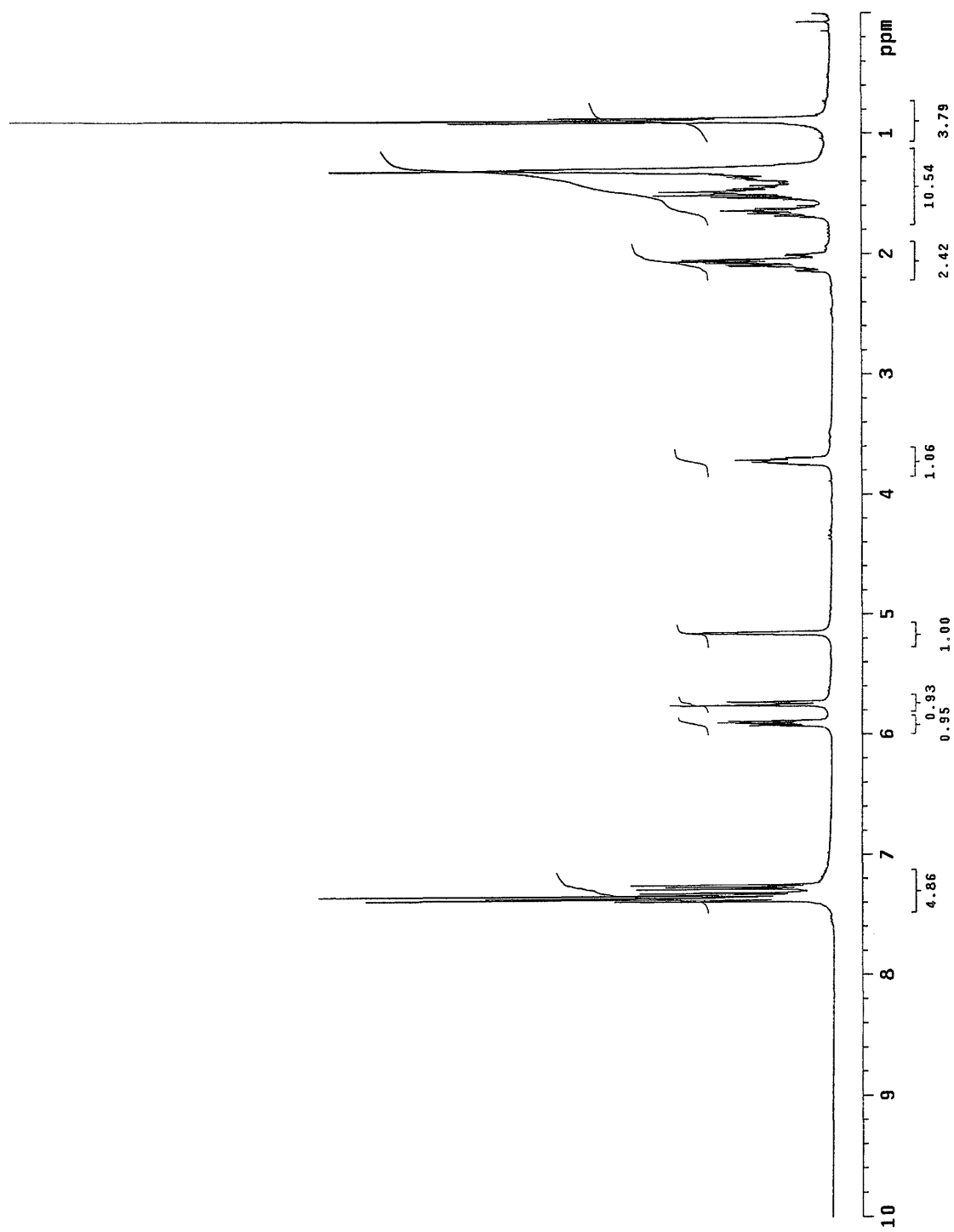
<sup>1</sup>H NOE NMR

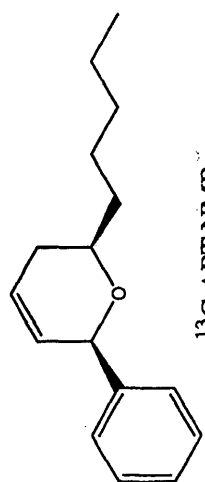
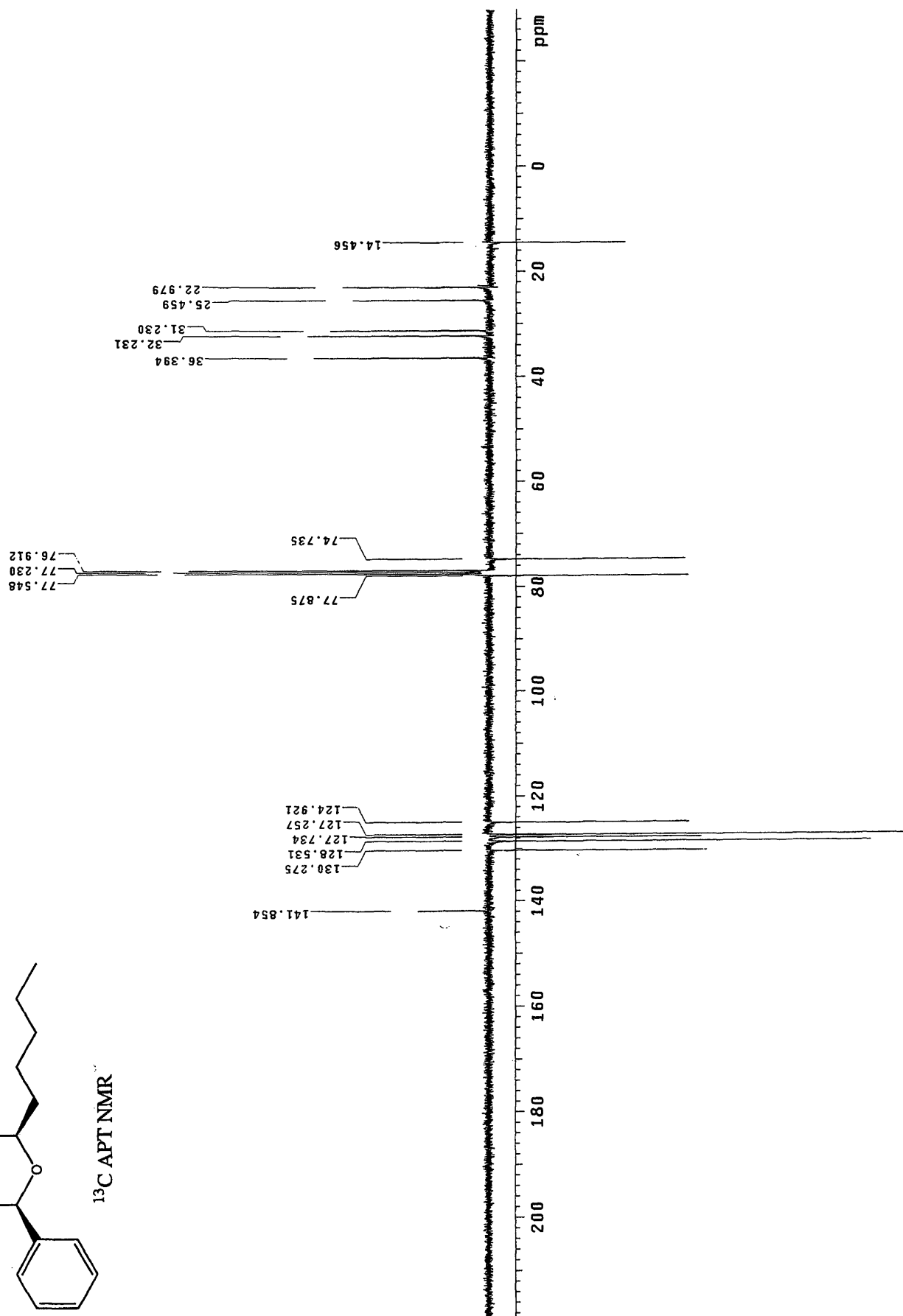
dec = 4.83 ppm

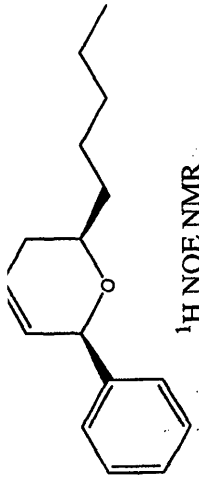




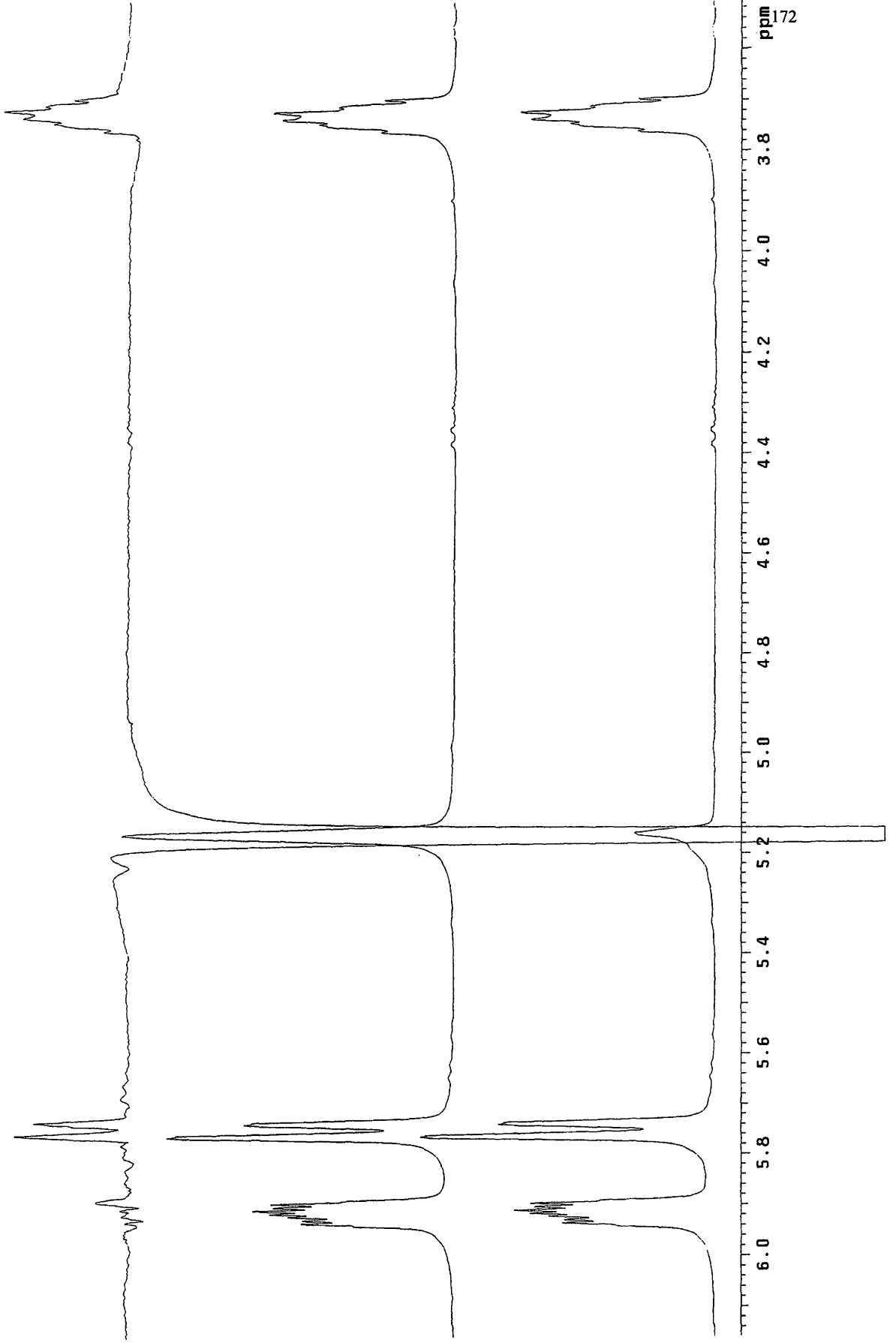
$^1\text{H NMR}$

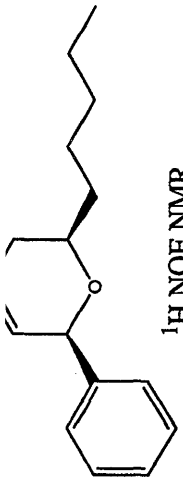


<sup>13</sup>C APT NMR

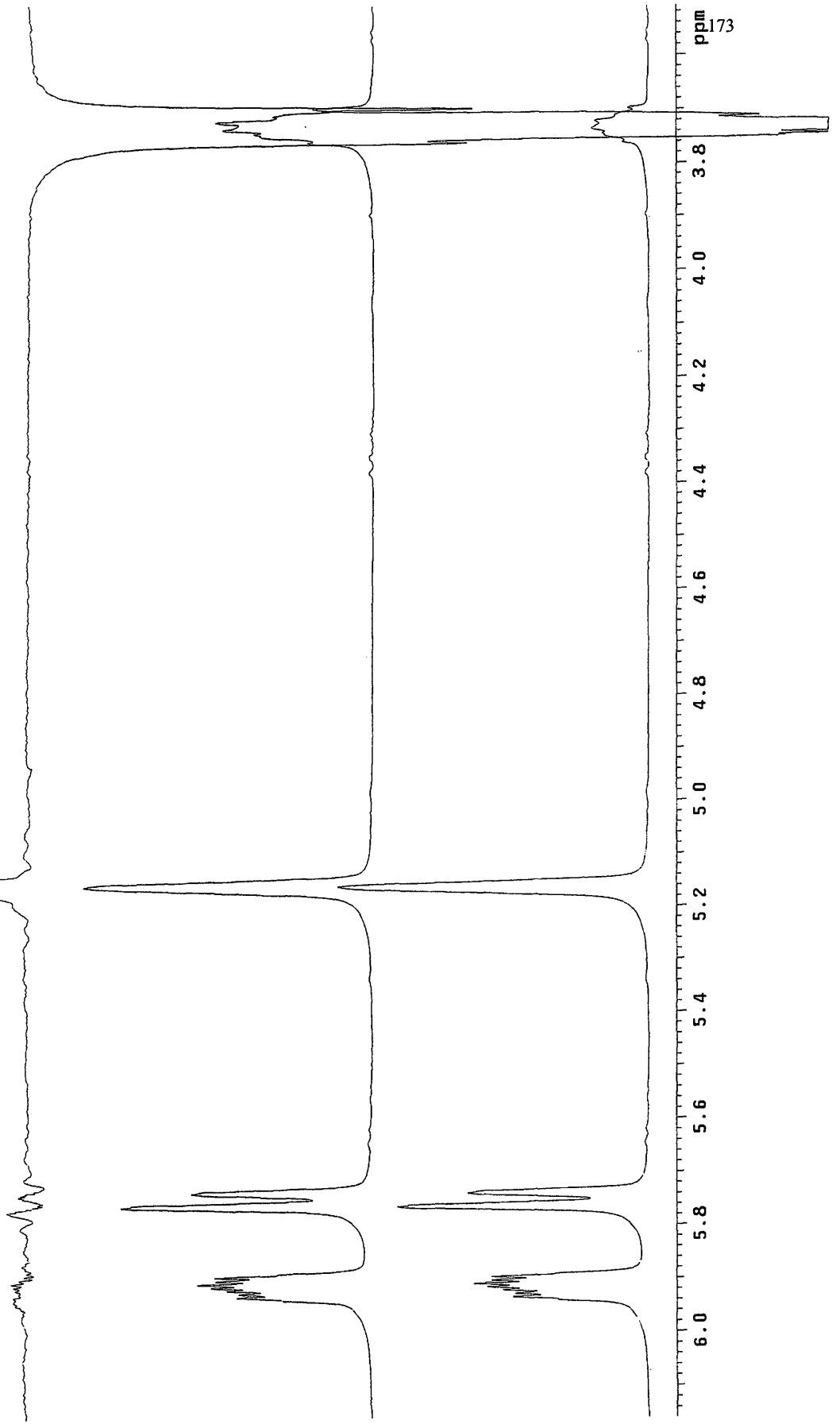


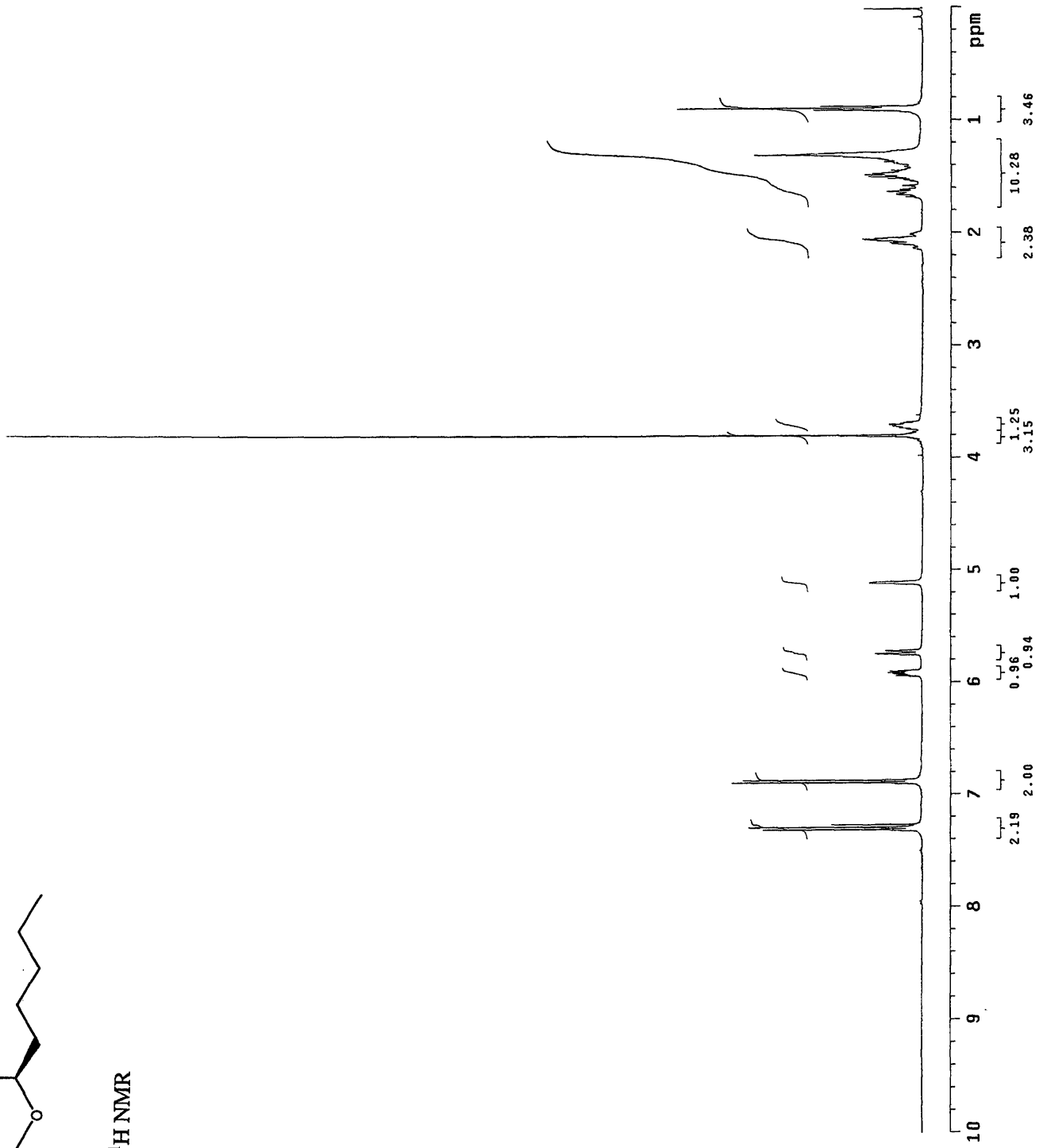
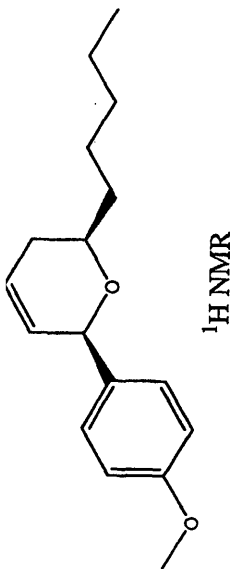
<sup>1</sup>H NOE NMR  
dec = 5.15 ppm

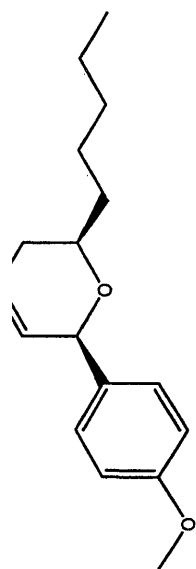
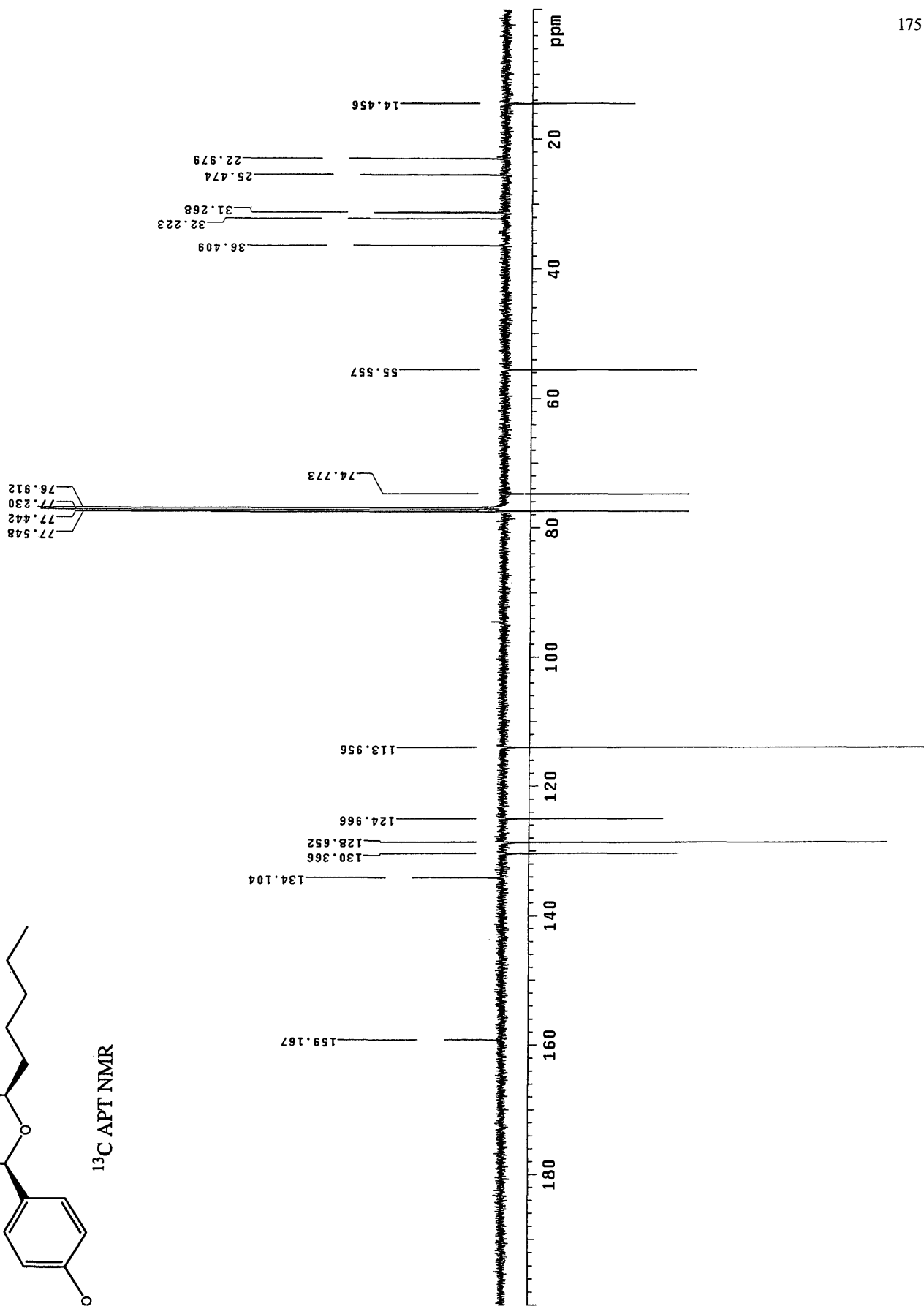


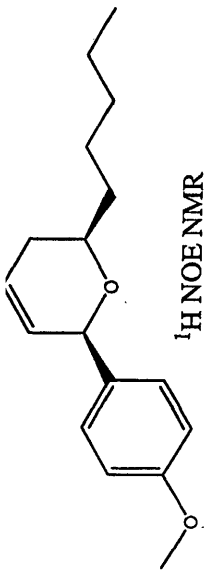


<sup>1</sup>H NOE NMR  
dec = 3.72 ppm

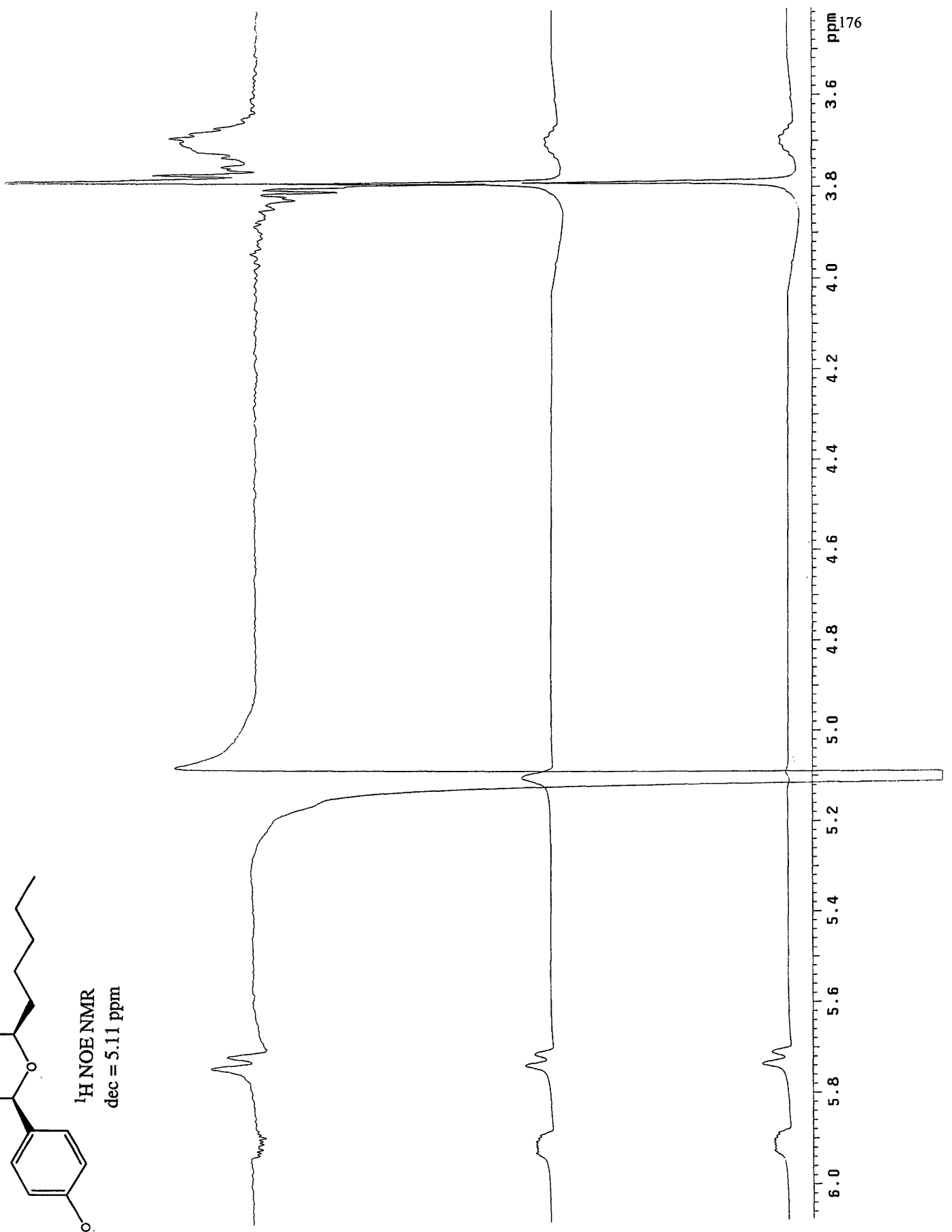


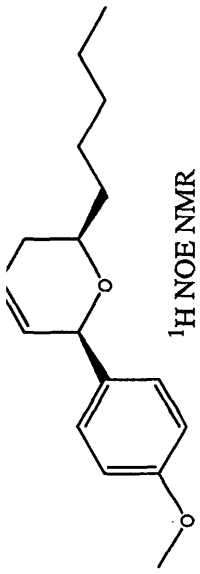


 $^{13}\text{C}$  APT NMR

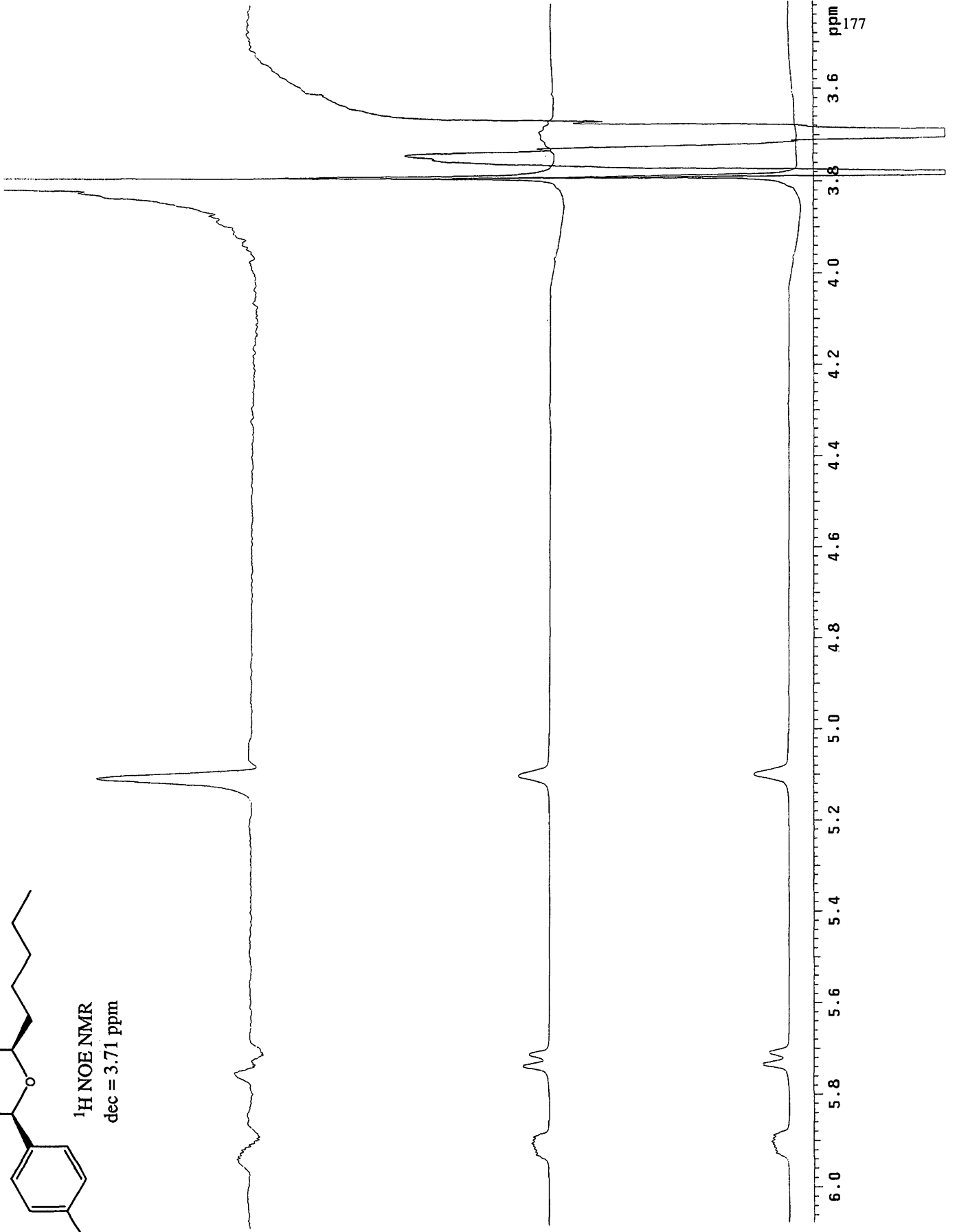


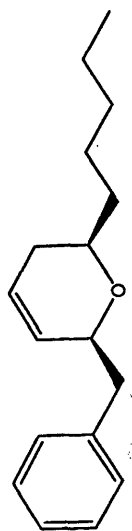
<sup>1</sup>H NOE NMR  
dec = 5.11 ppm



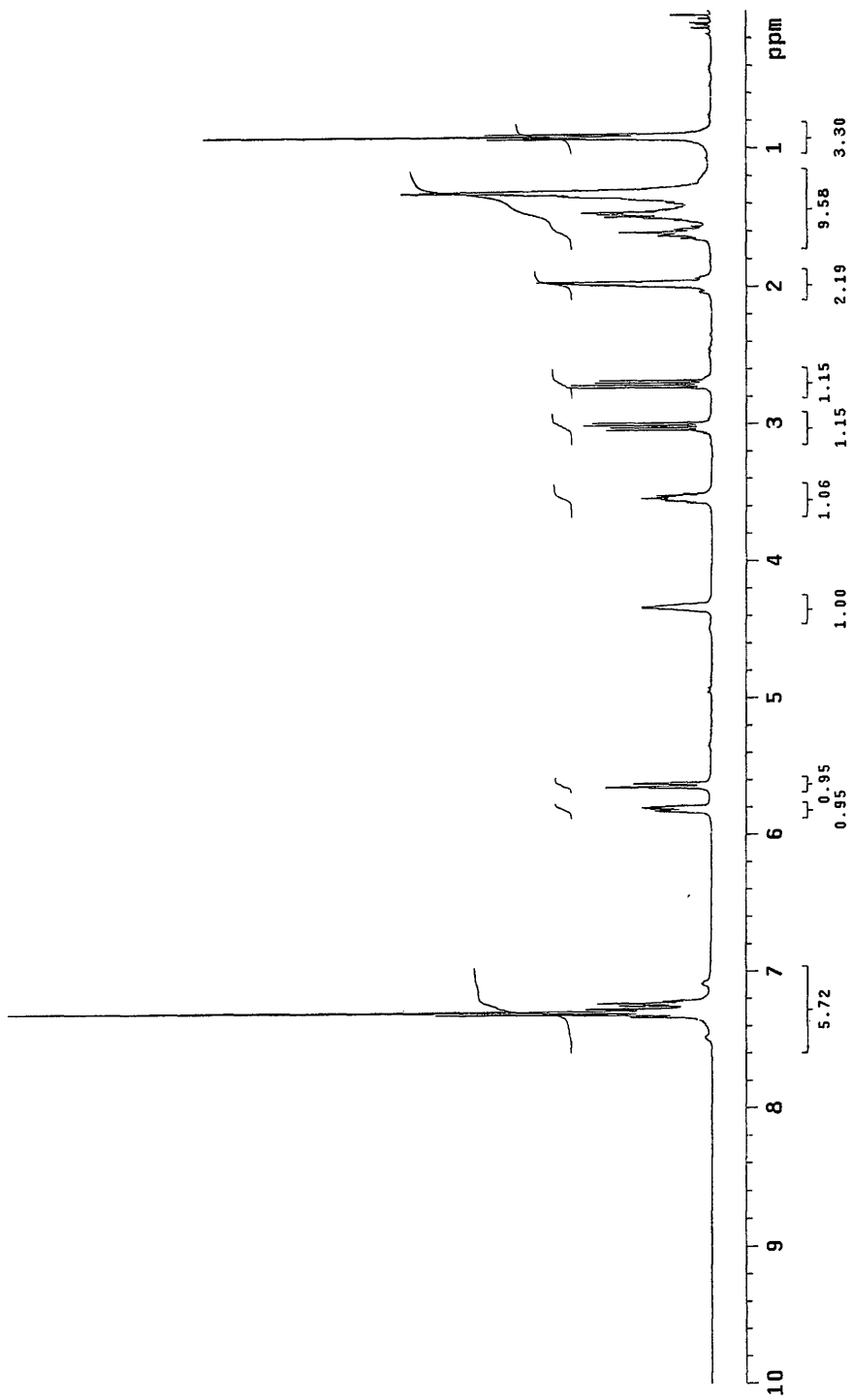


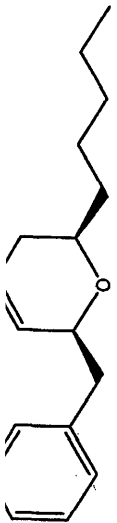
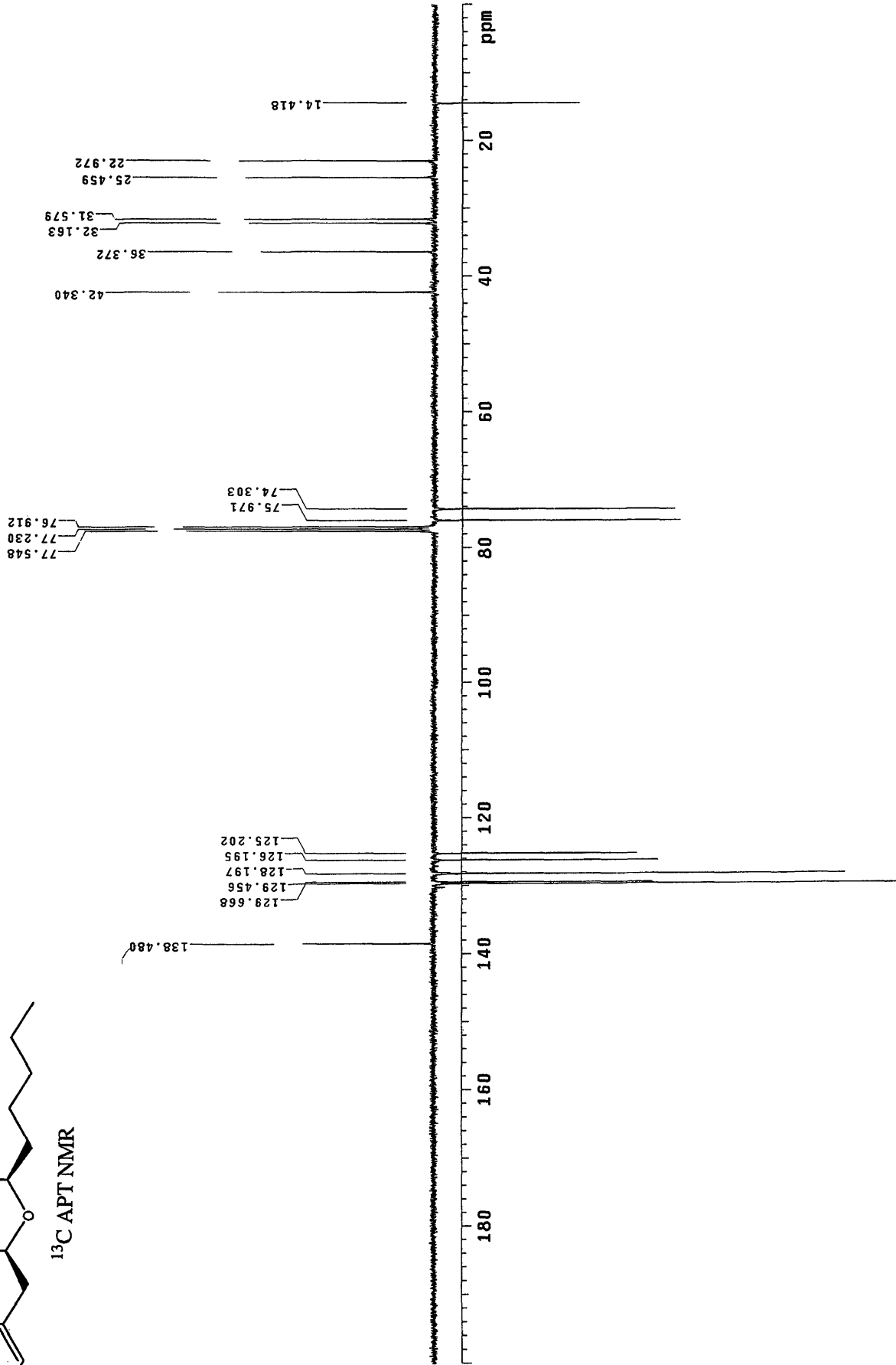
<sup>1</sup>H NOE NMR  
dec = 3.71 ppm

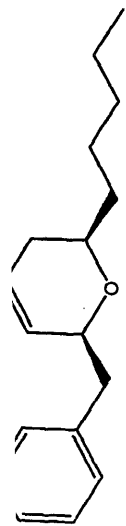




$^1\text{H NMR}$

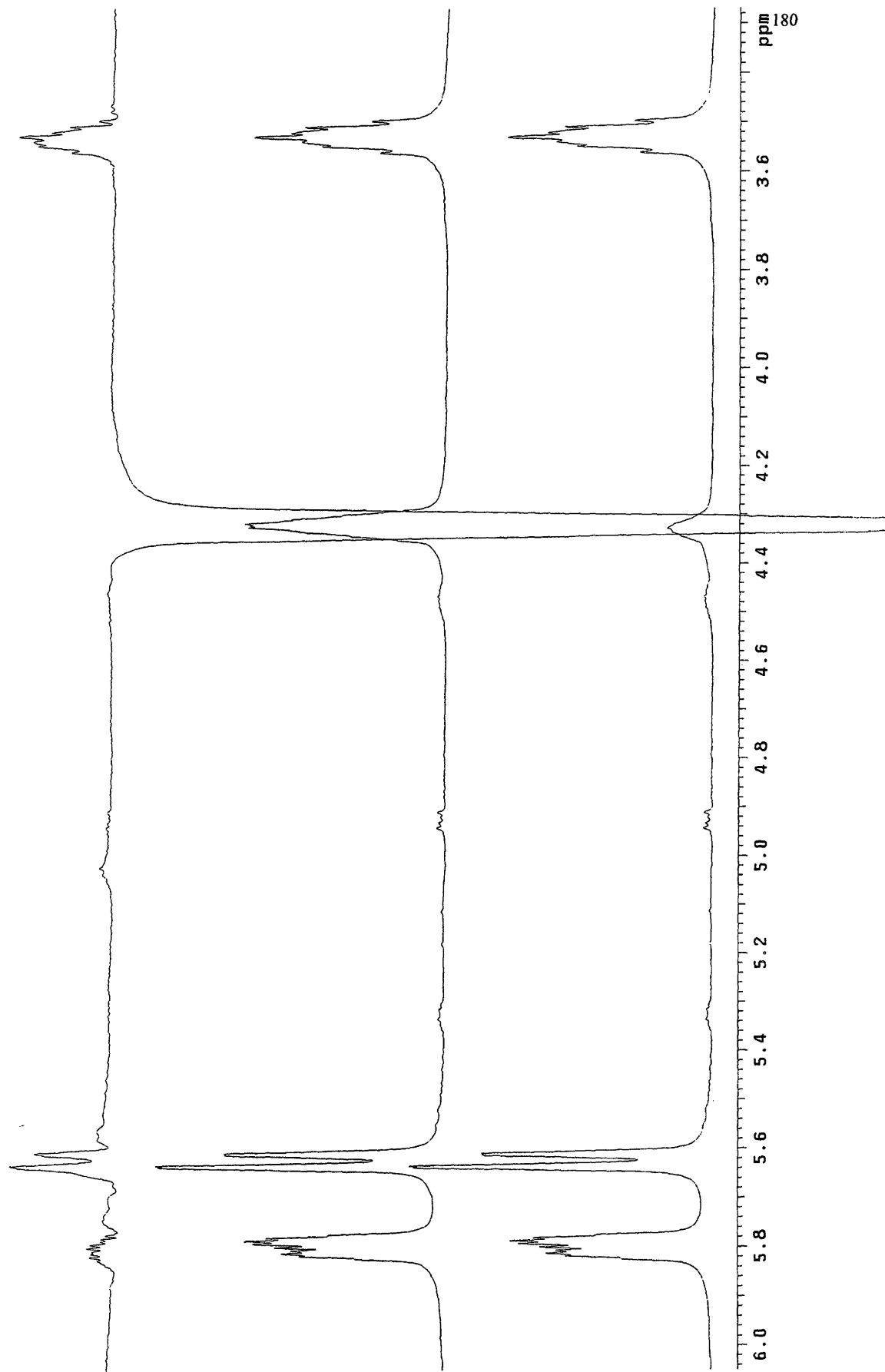


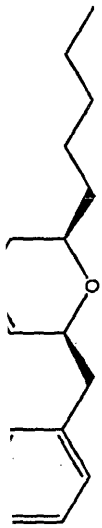
<sup>13</sup>C APT NMR



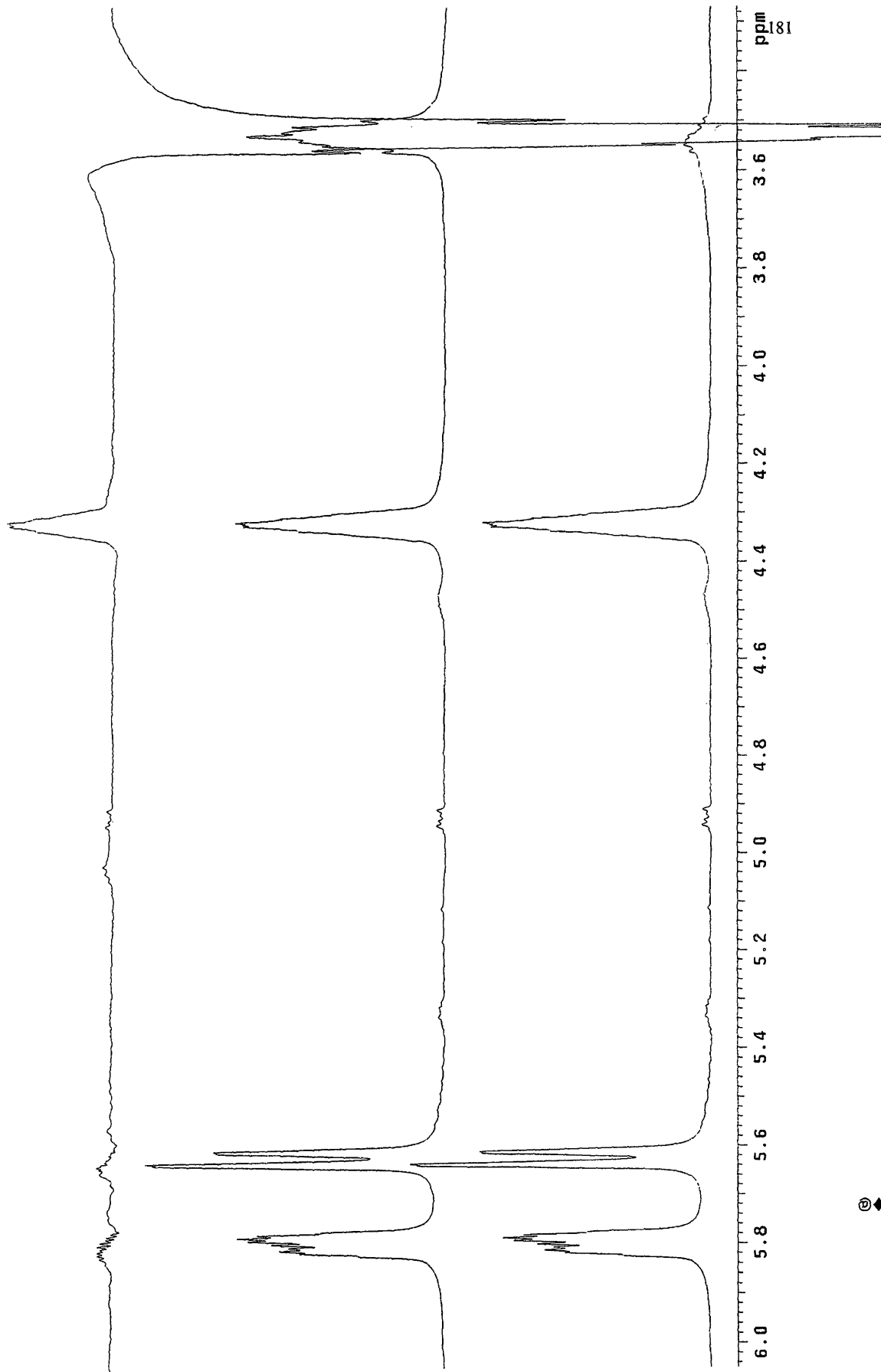
<sup>1</sup>H NOE NMR

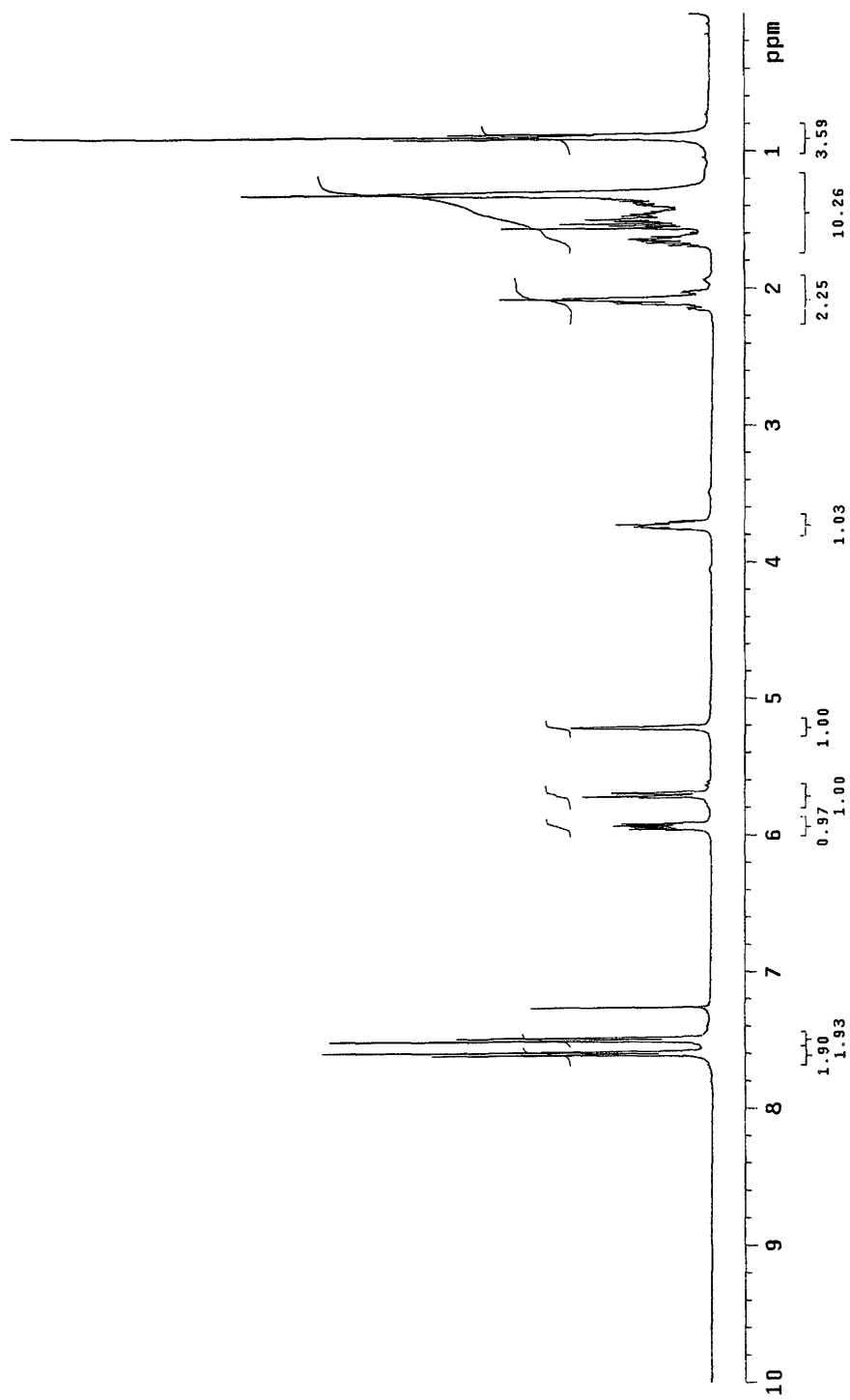
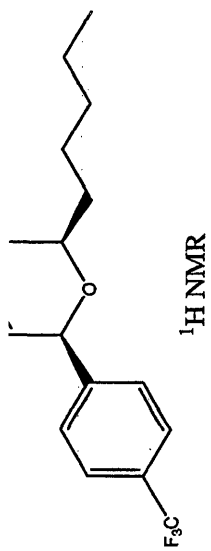
dec = 4.34 ppm

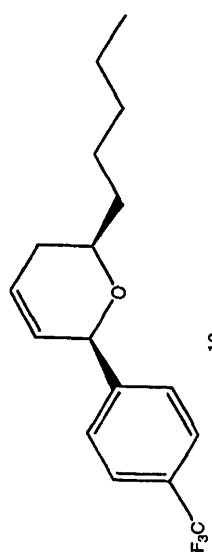
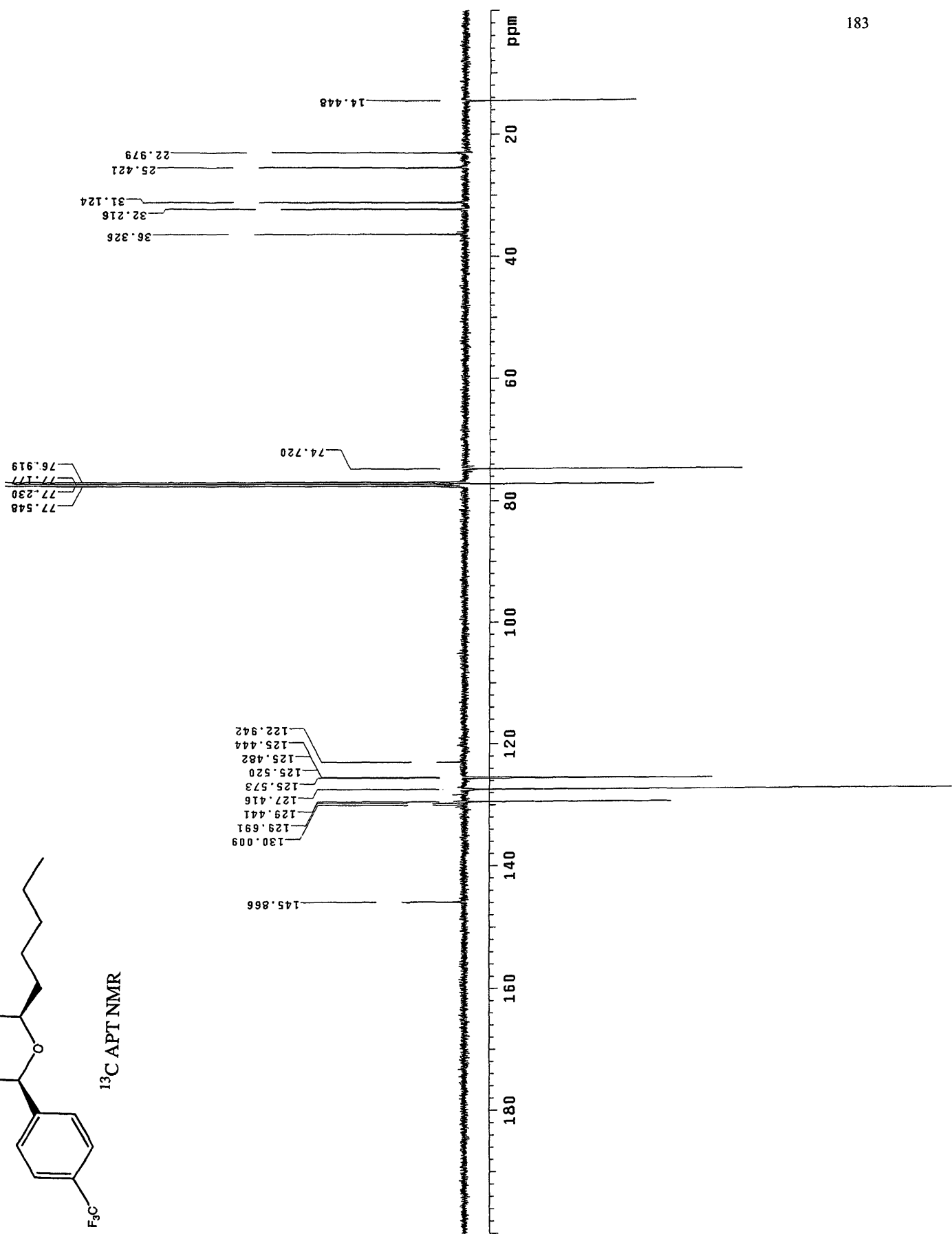


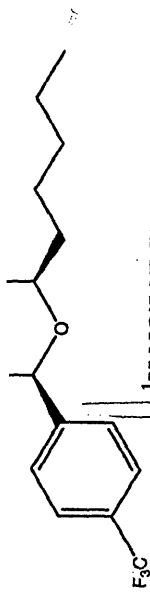


$^1\text{H}$  NOE NMR  
dec = 3.54 ppm

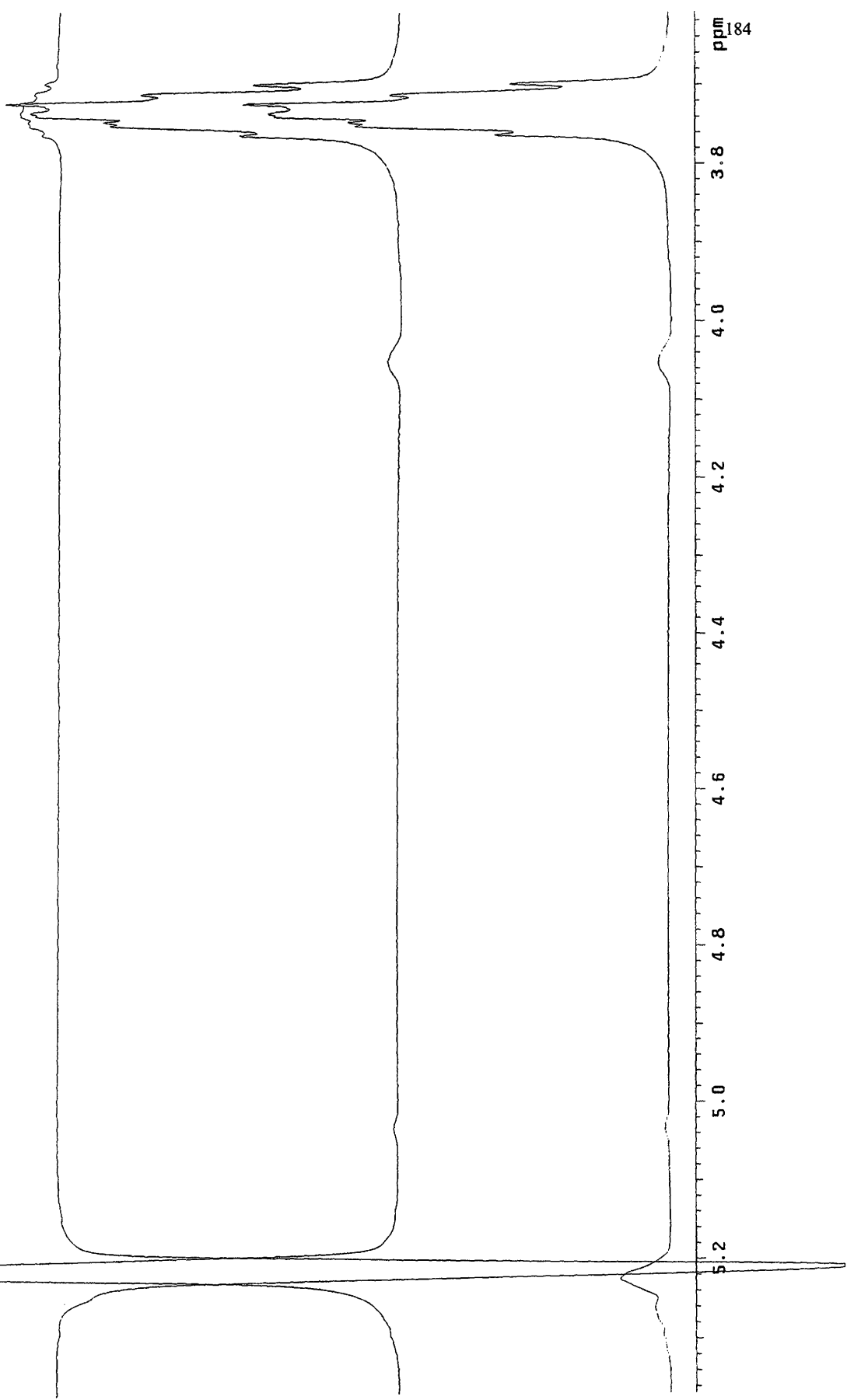


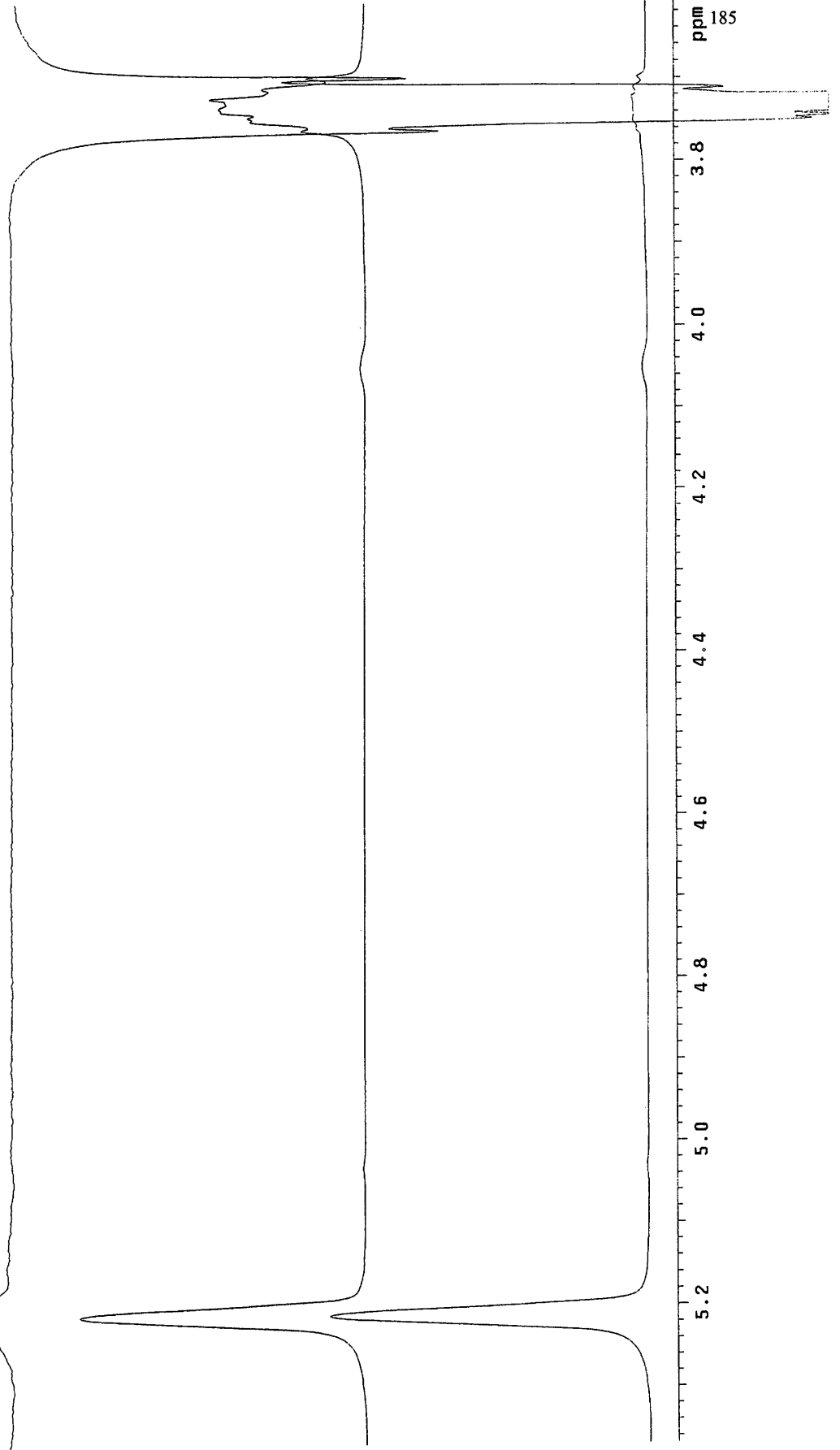
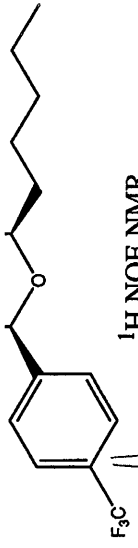


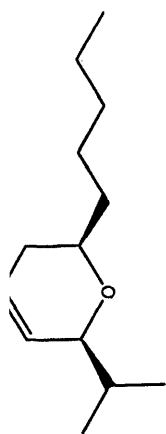
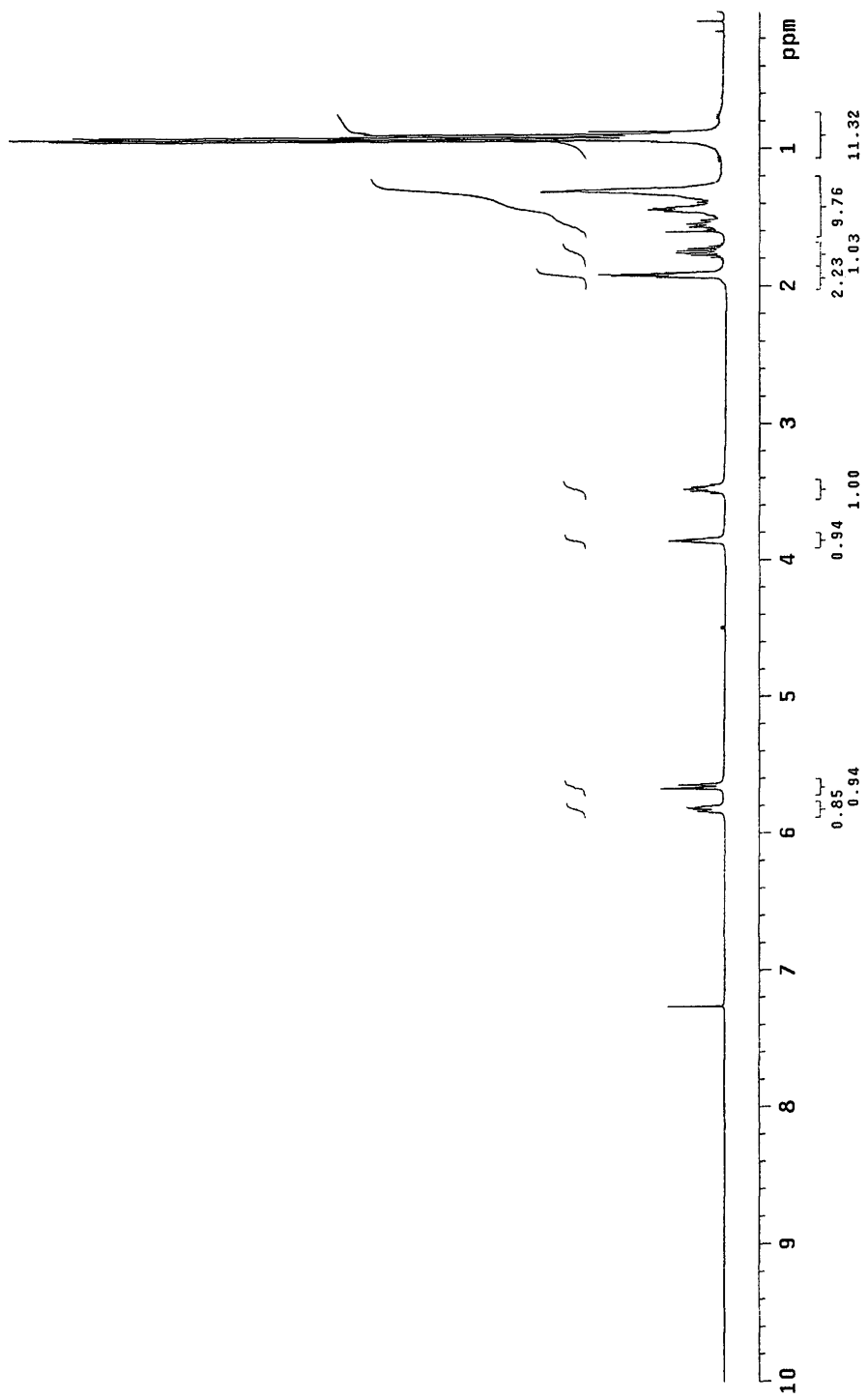
<sup>13</sup>C APT NMR

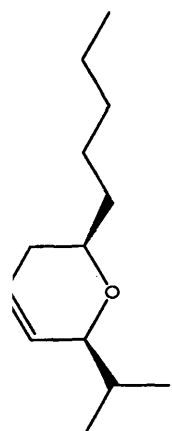
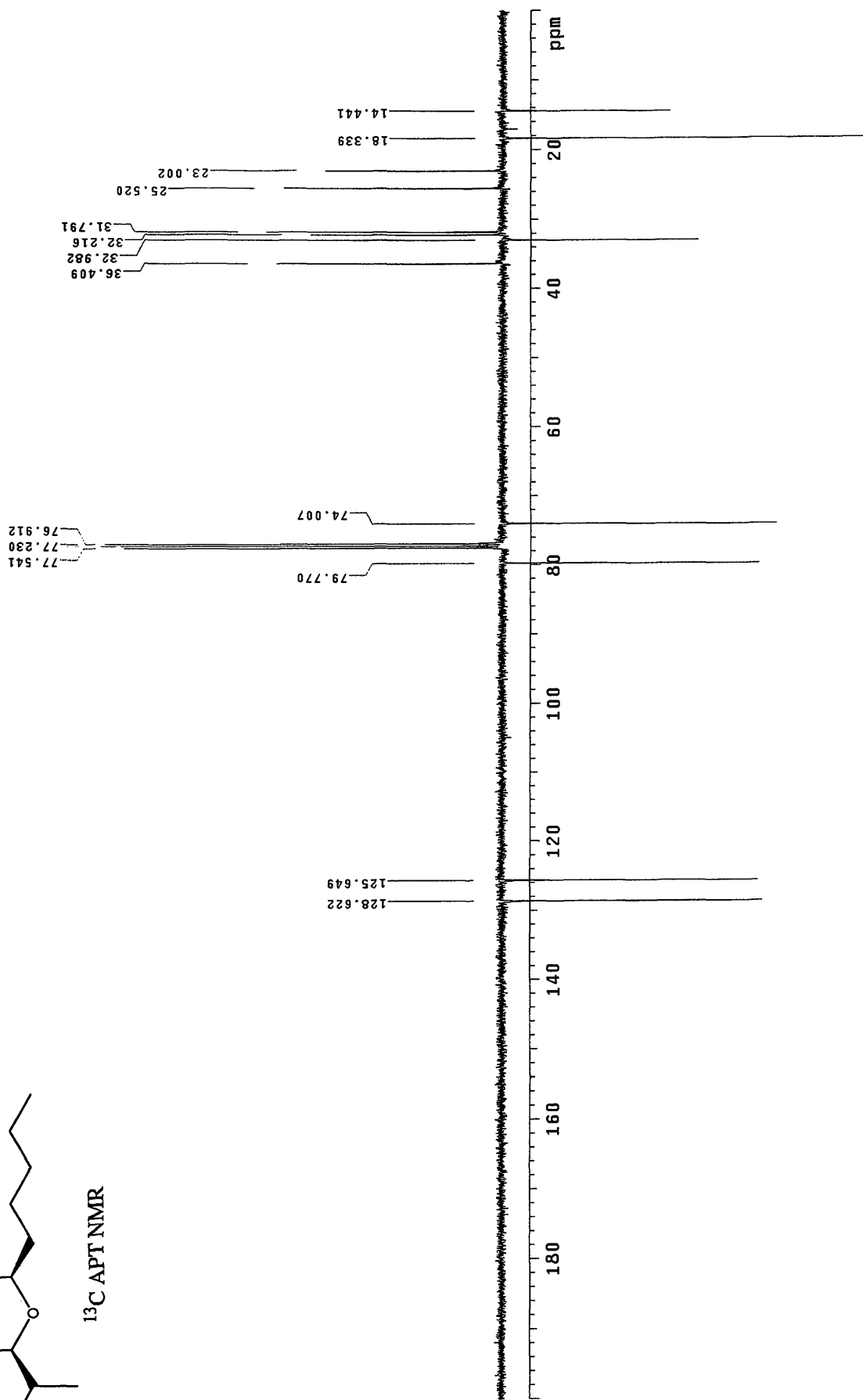


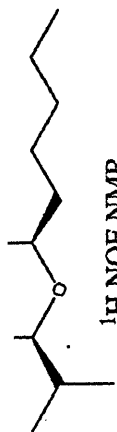
<sup>1</sup>H NOE NMR  
dec = 5.21 ppm



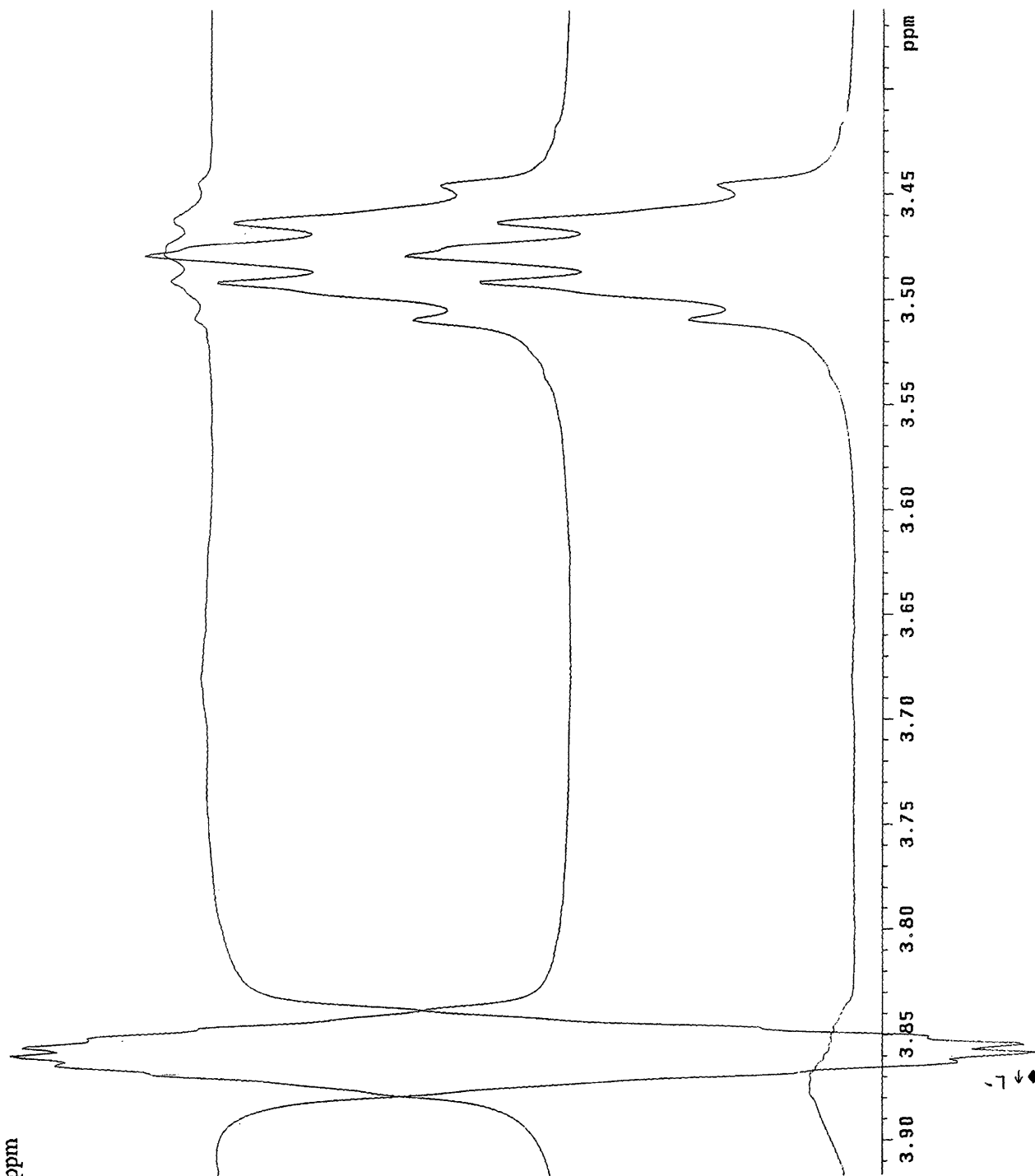


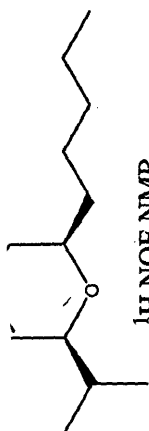
 $^1\text{H NMR}$ 

 $^{13}\text{C}$  APT NMR

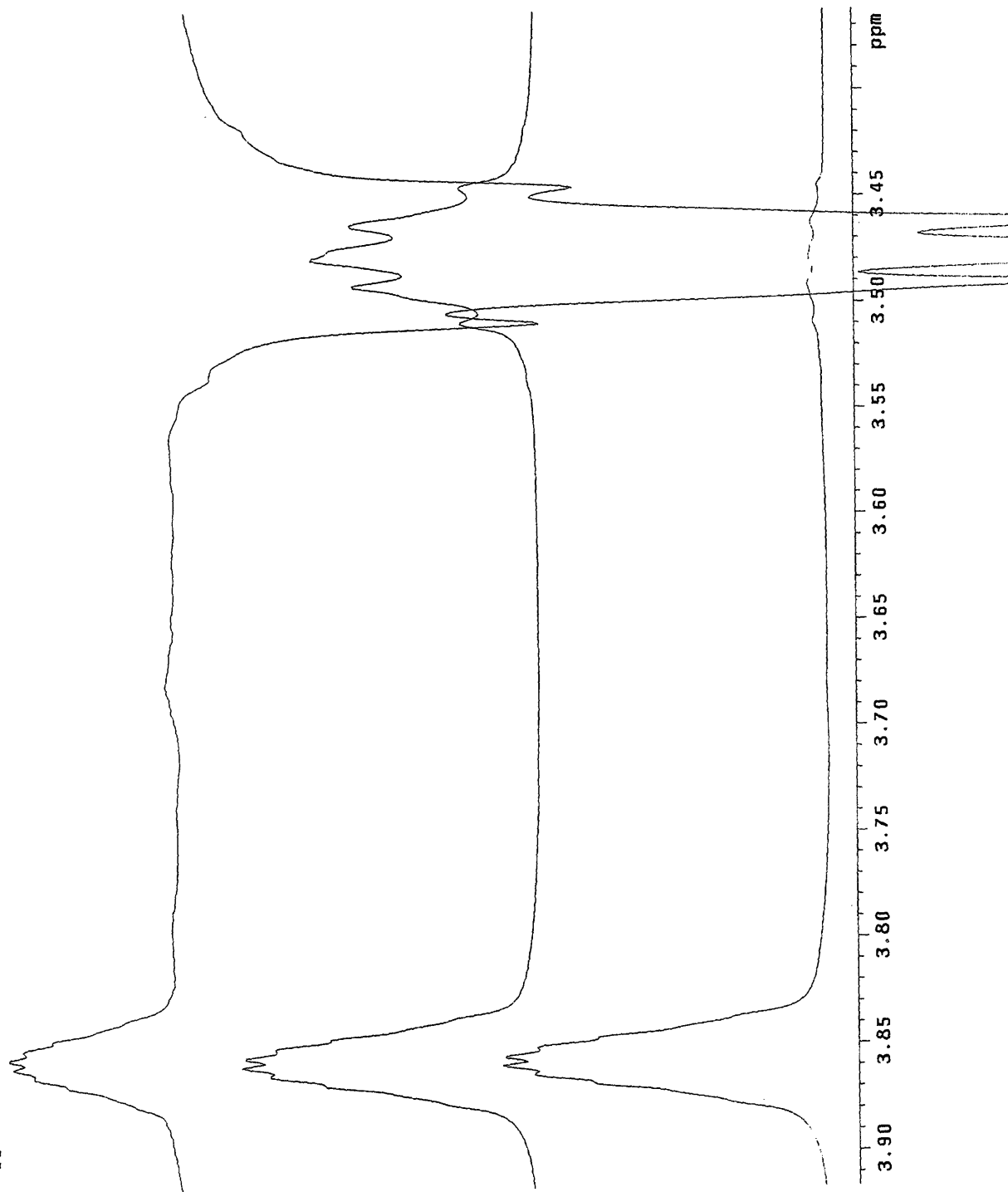


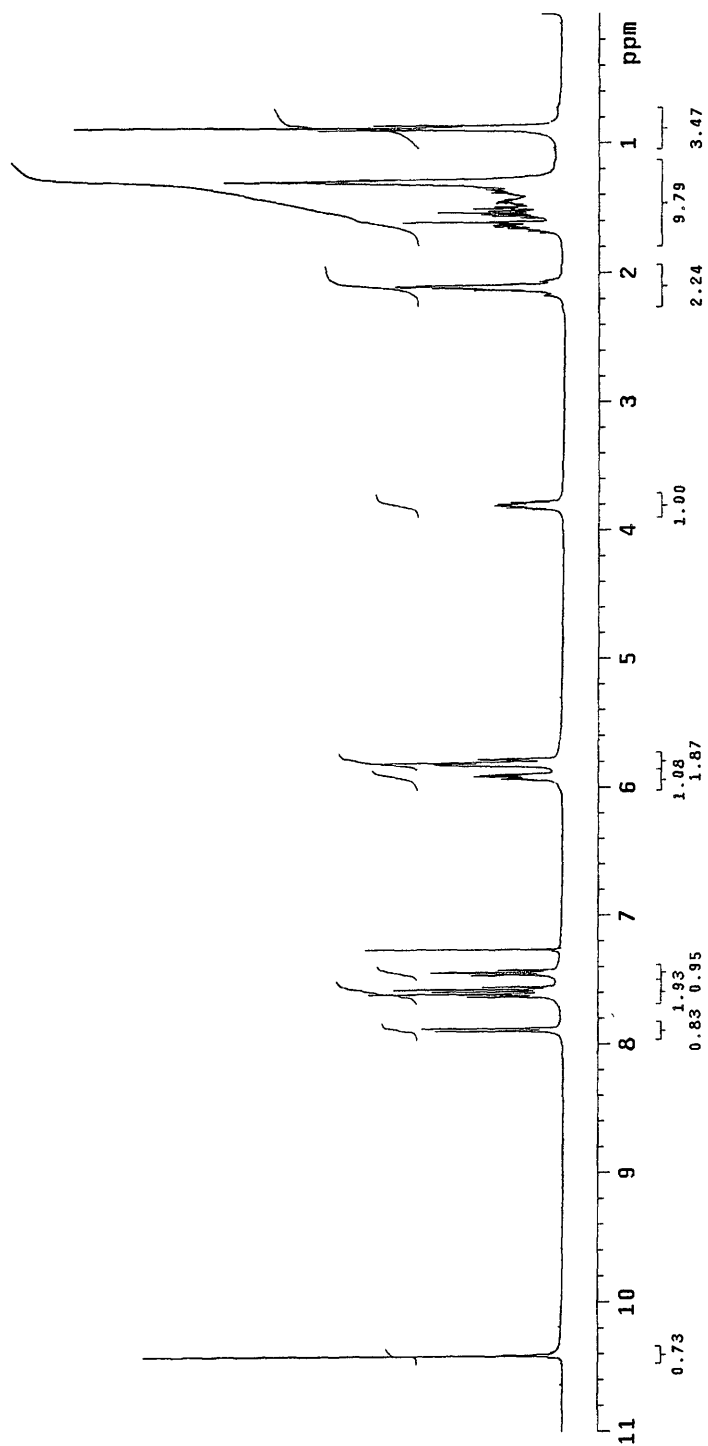
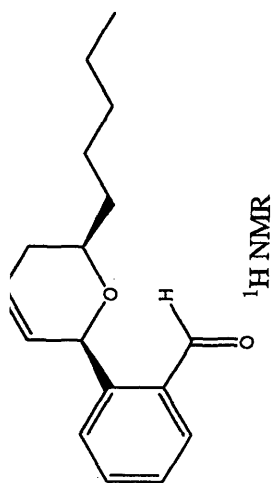
<sup>1</sup>H NOE NMR  
dec = 3.86 ppm

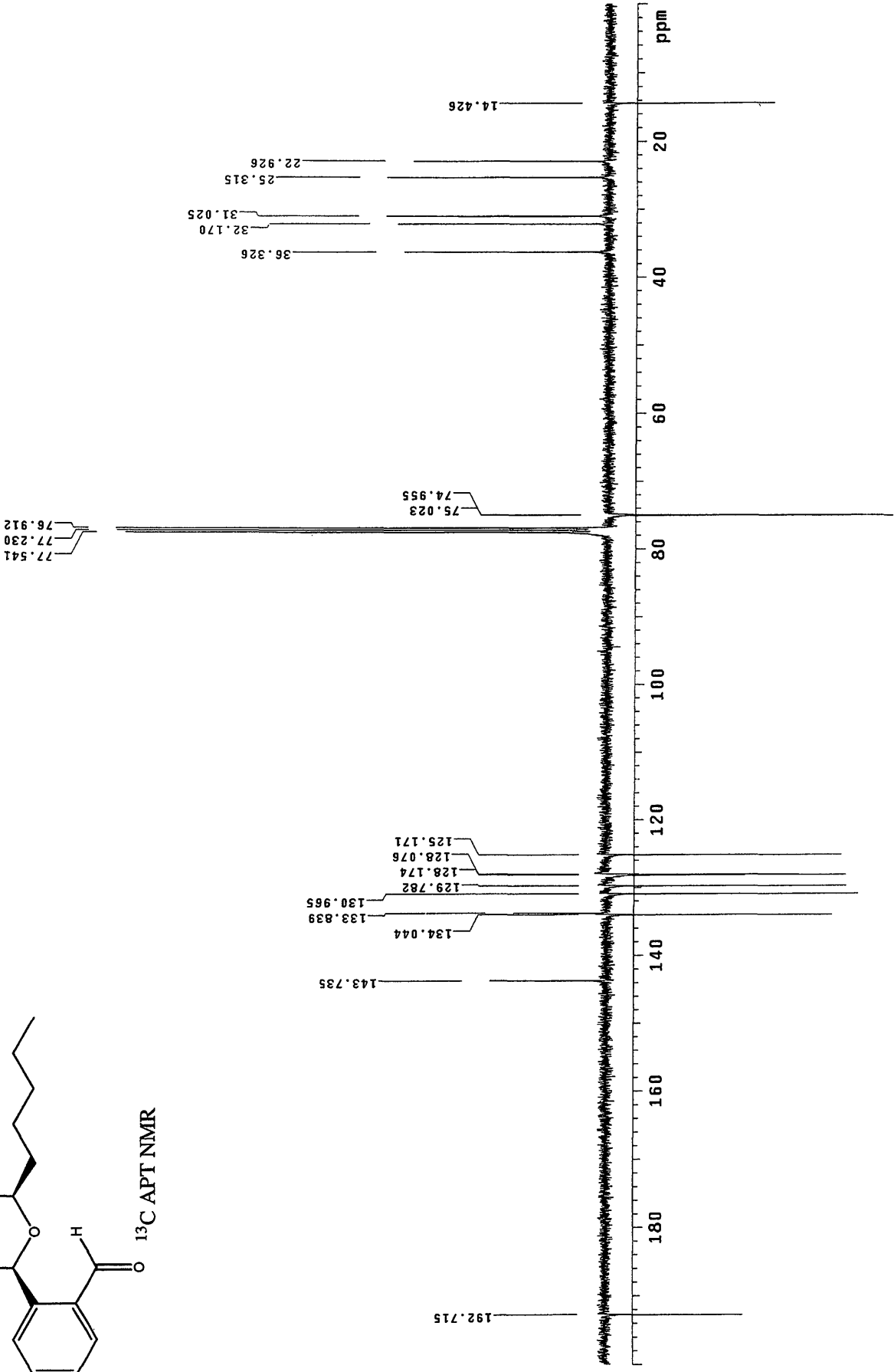
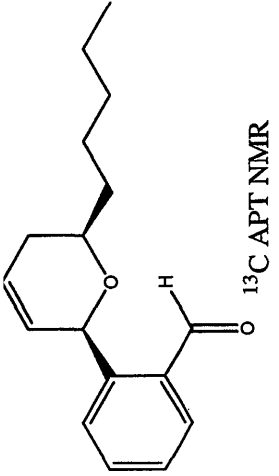


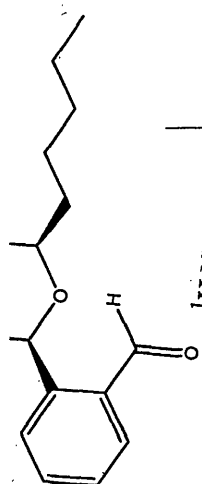


$^1\text{H}$  NOE NMR  
dec = 3.48 ppm

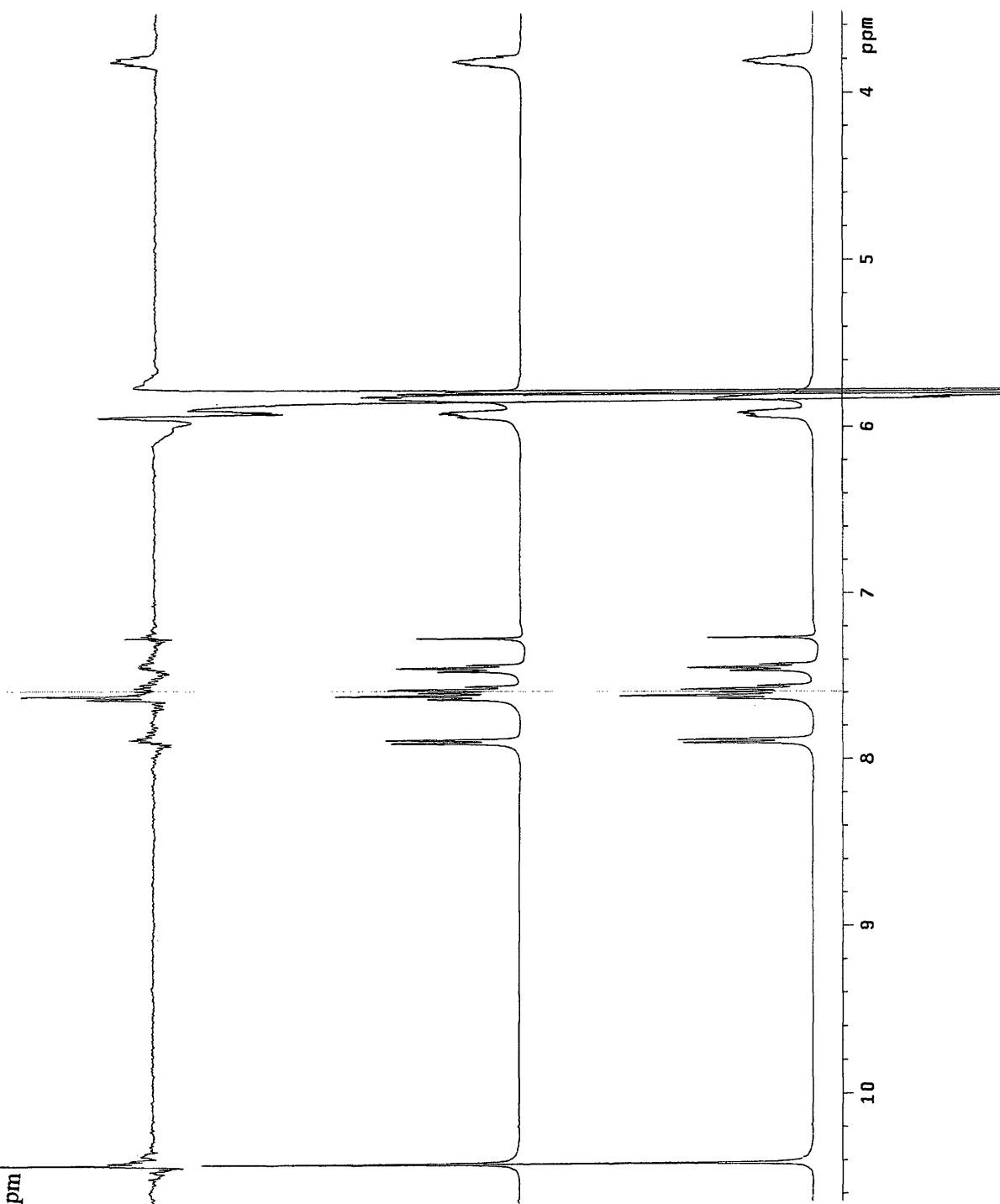


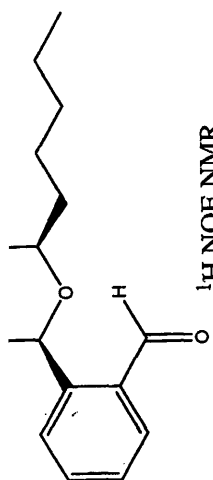




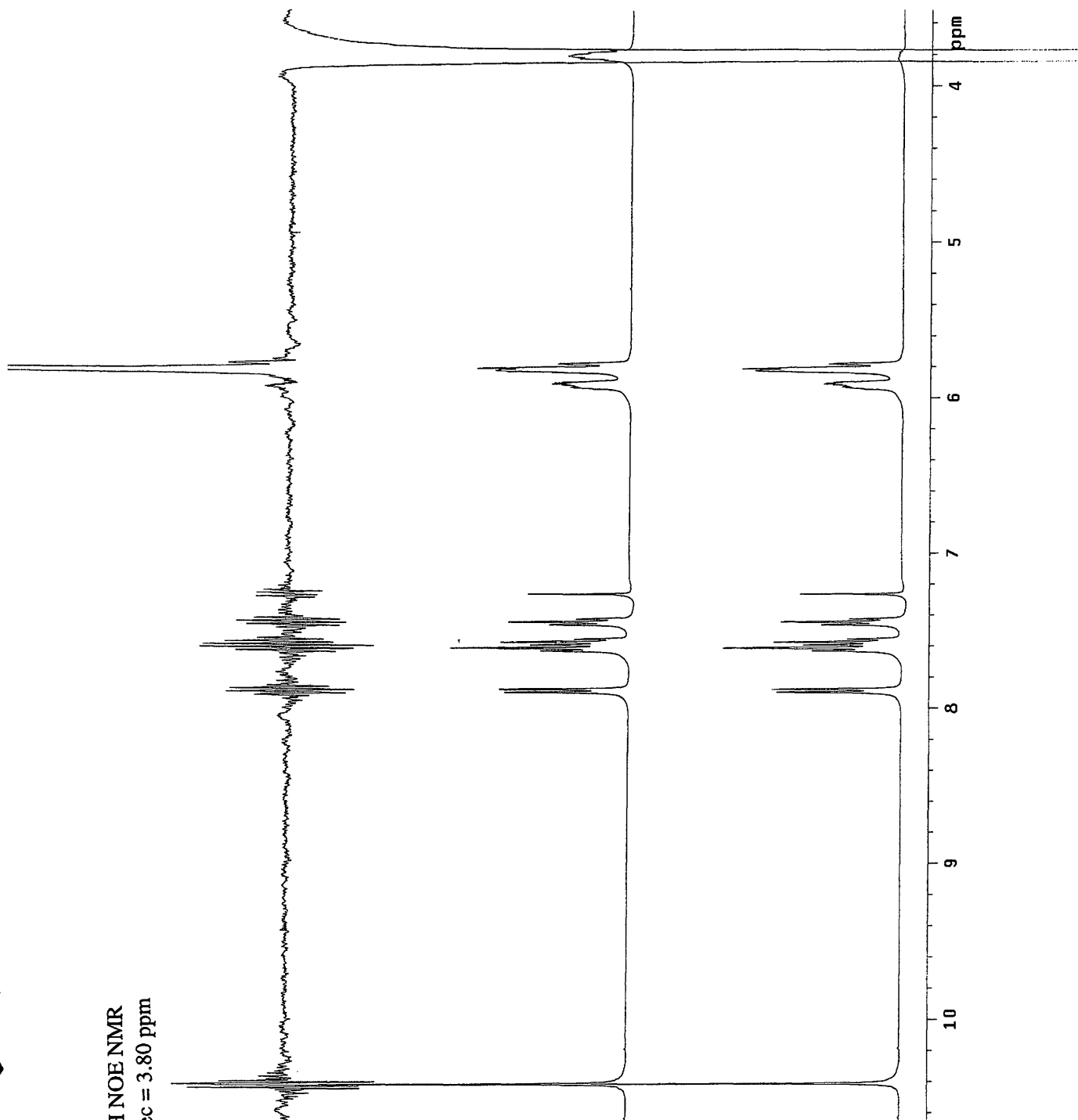


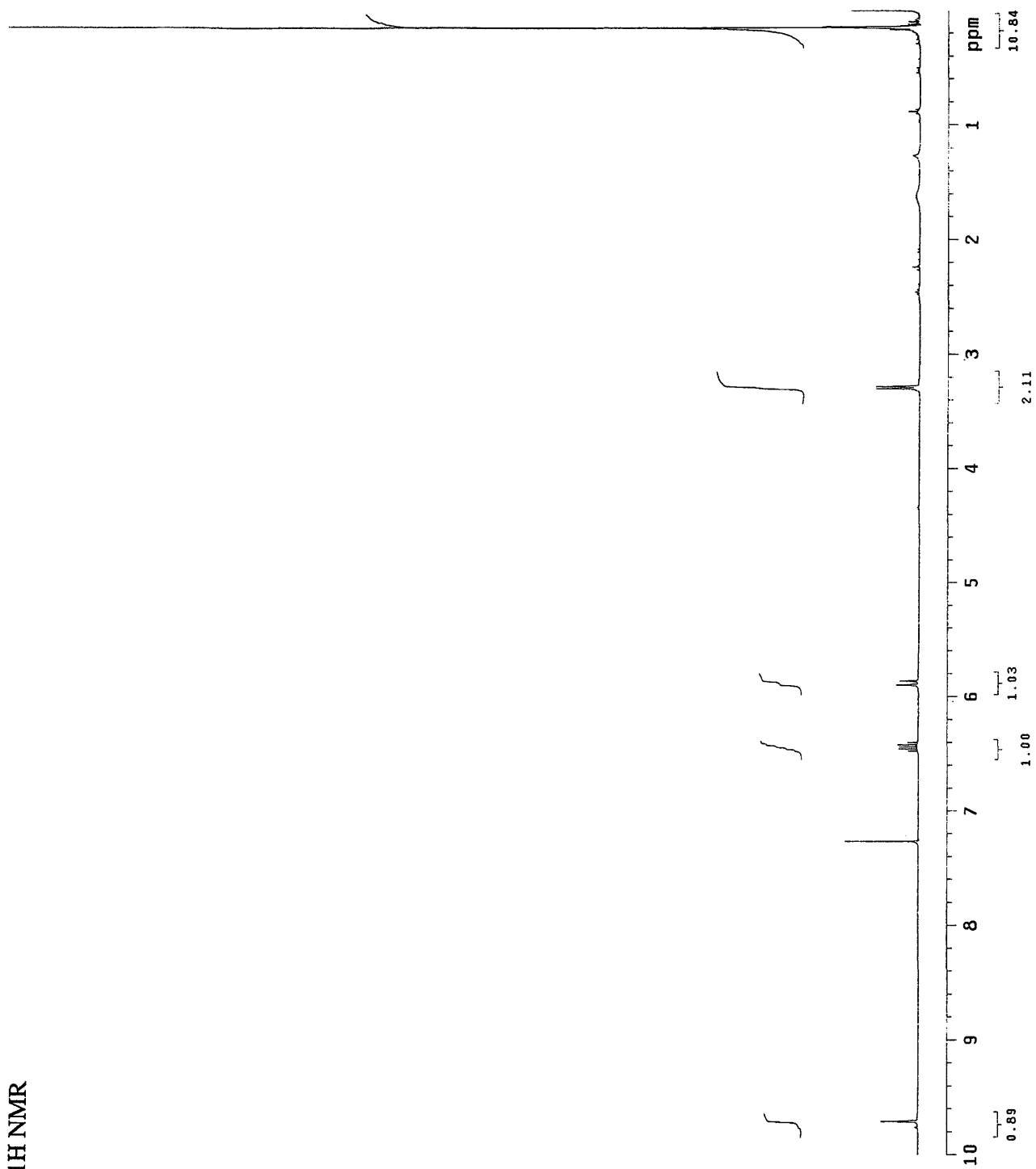
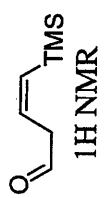
<sup>1</sup>H NOE NMR  
dec = 5.78 ppm

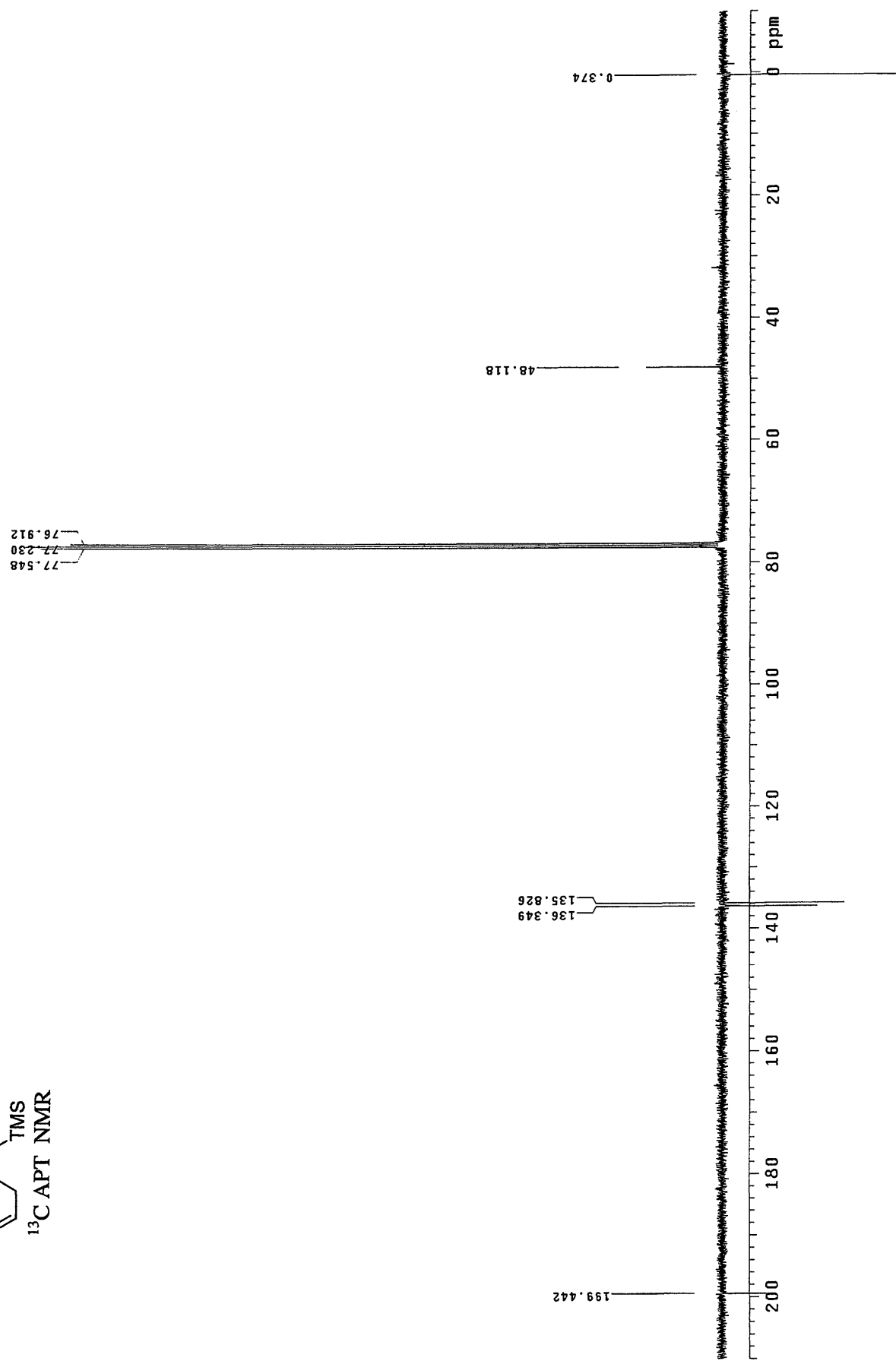
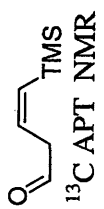




$^1\text{H}$  NOE NMR  
dec = 3.80 ppm

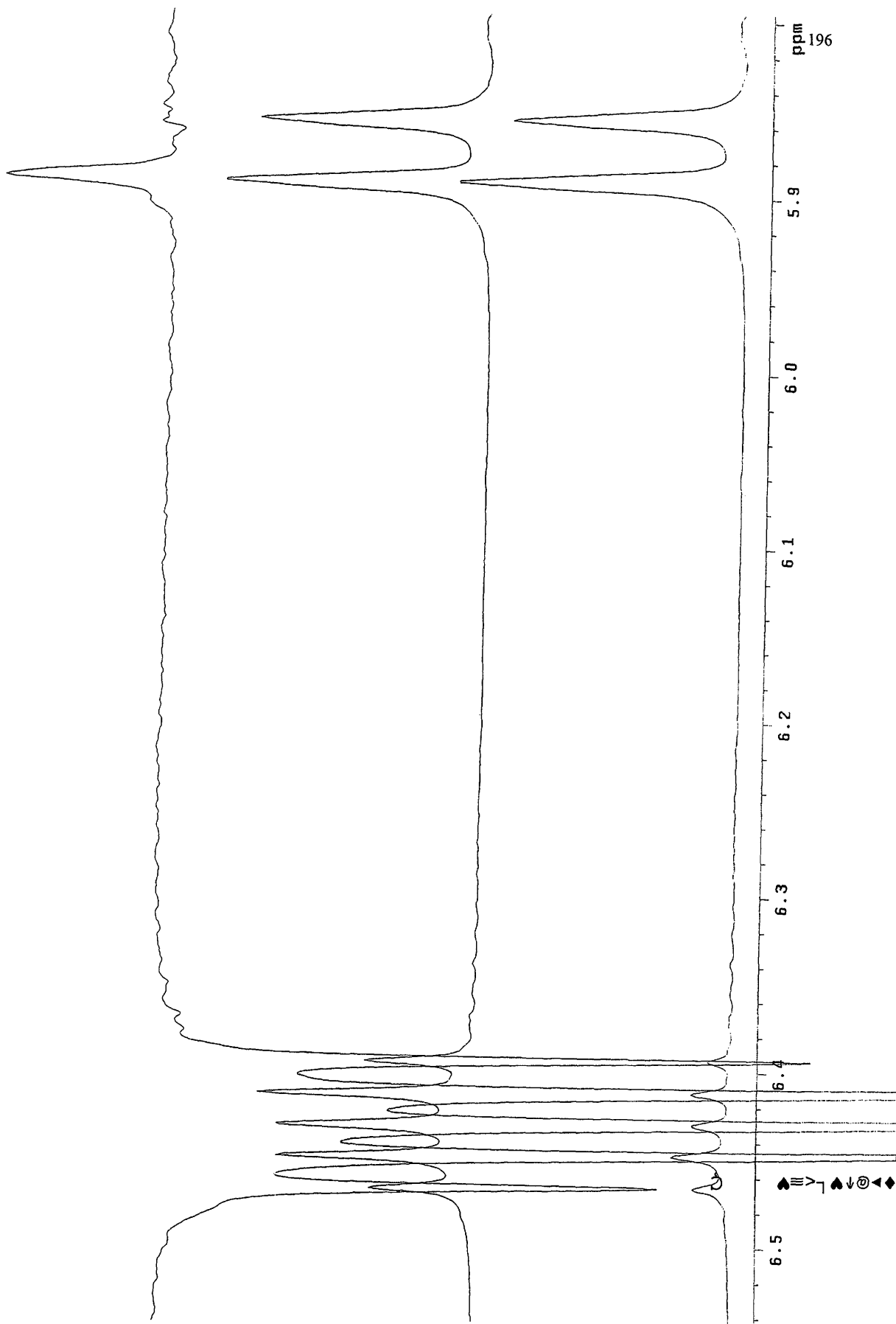




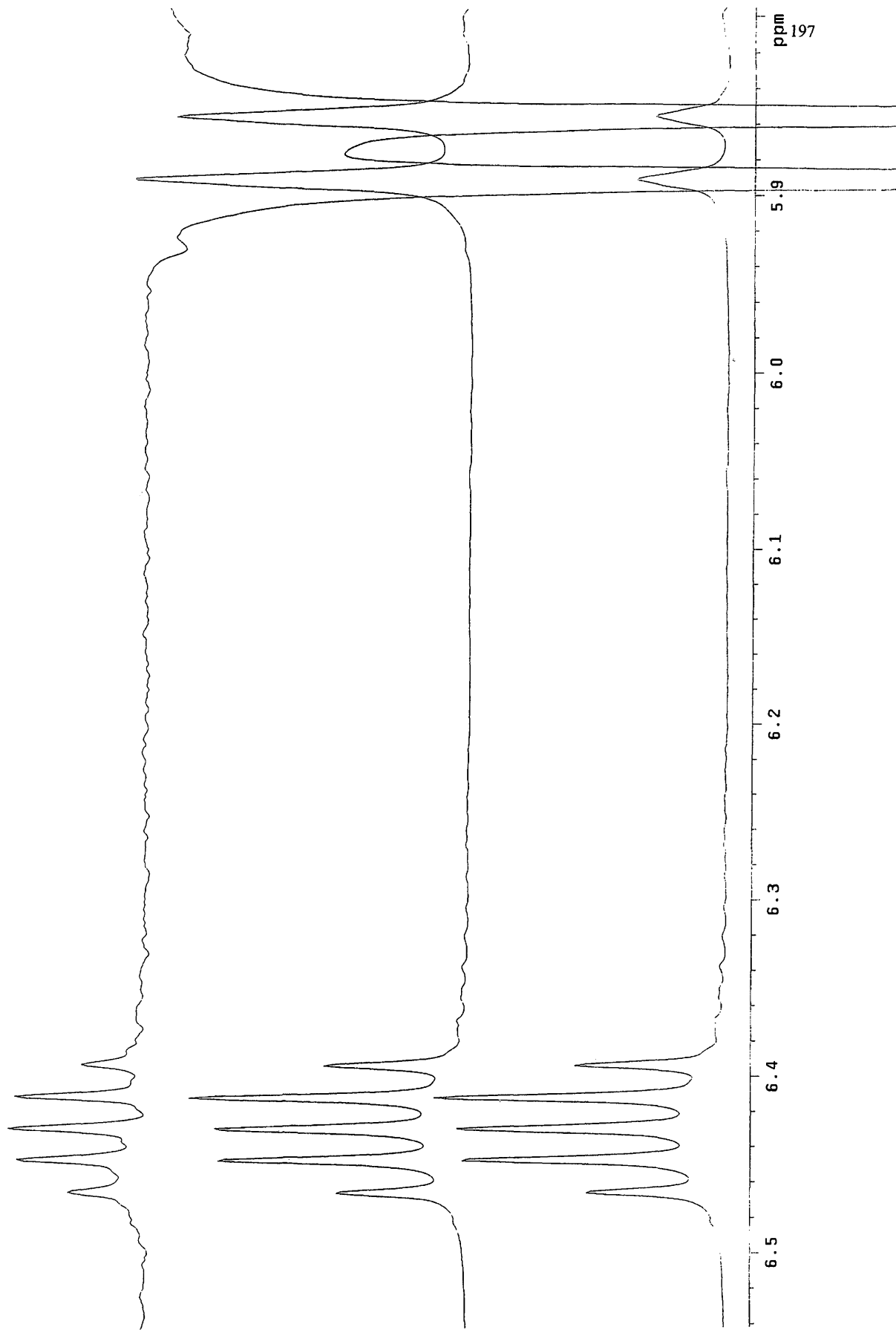


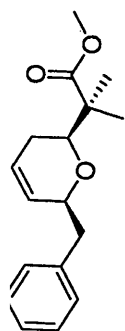
③  
≡  
◀

C=CC(=O)OSi(C)(C)C  
<sup>1</sup>H NOE Spectrum  
dec= 6.44 ppm

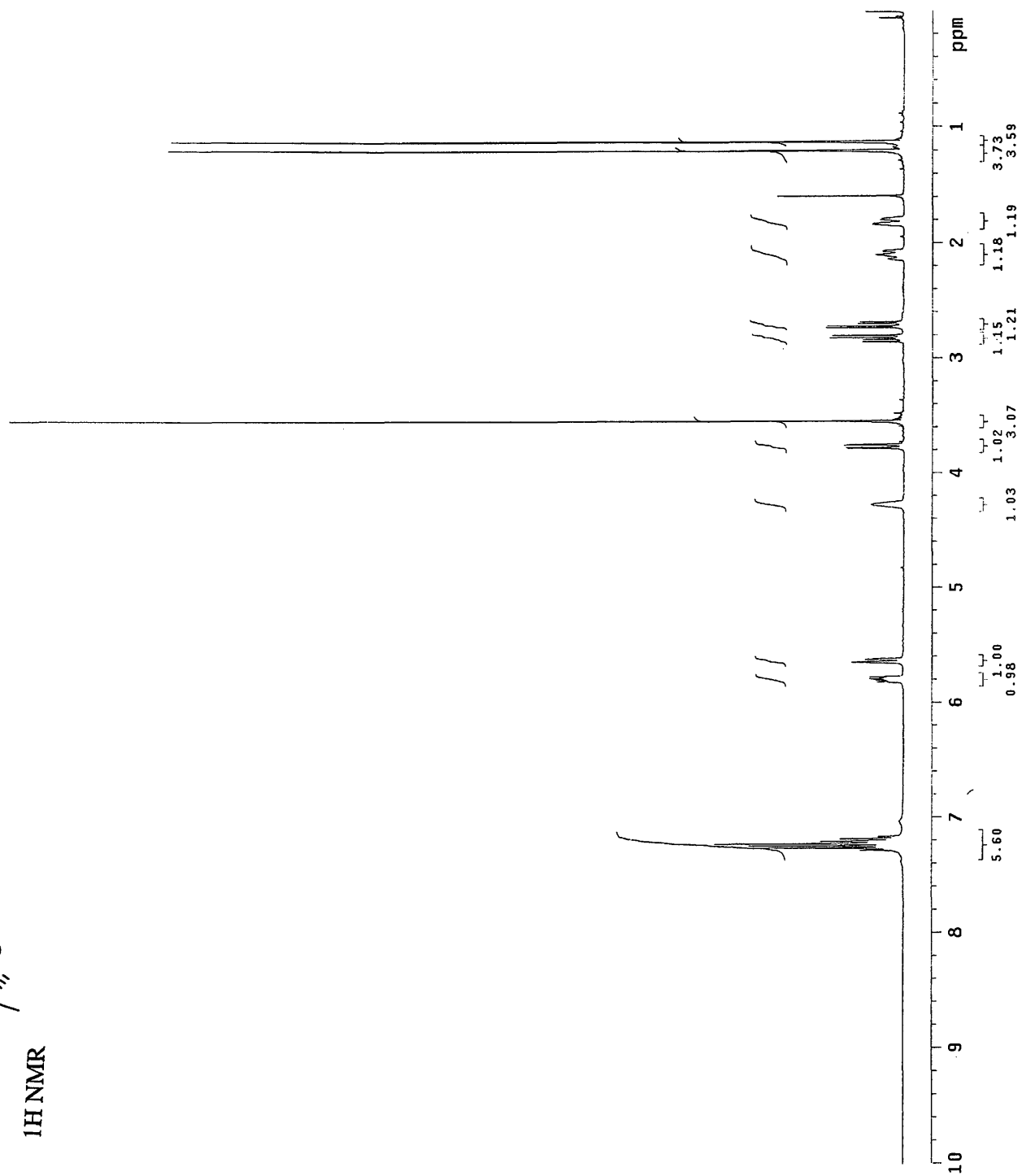


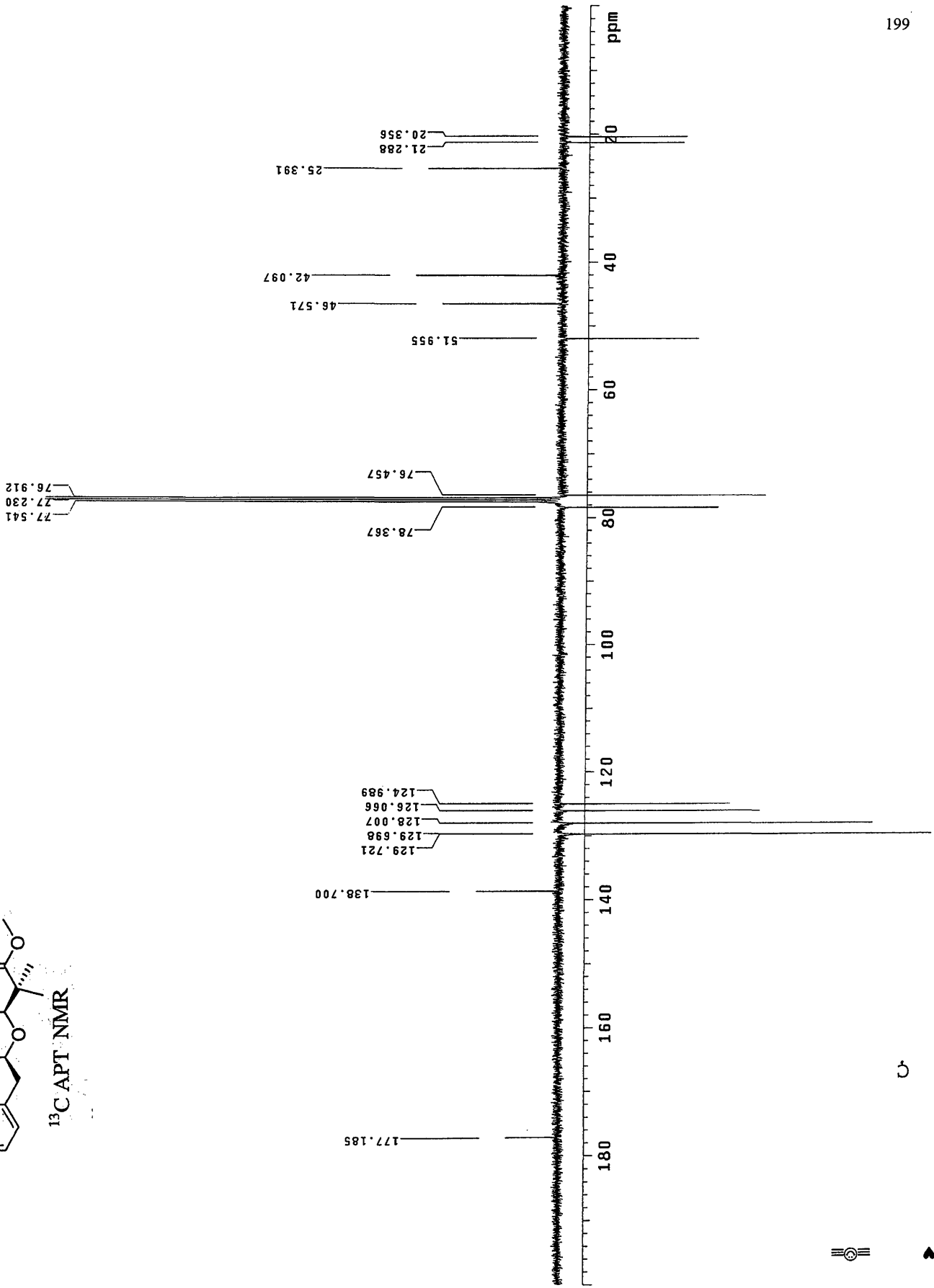
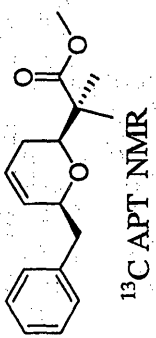
C=CC(=O)O TMS  
<sup>1</sup>H NOE Spectrum  
dec= 5.88 ppm

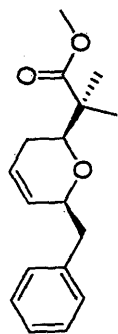




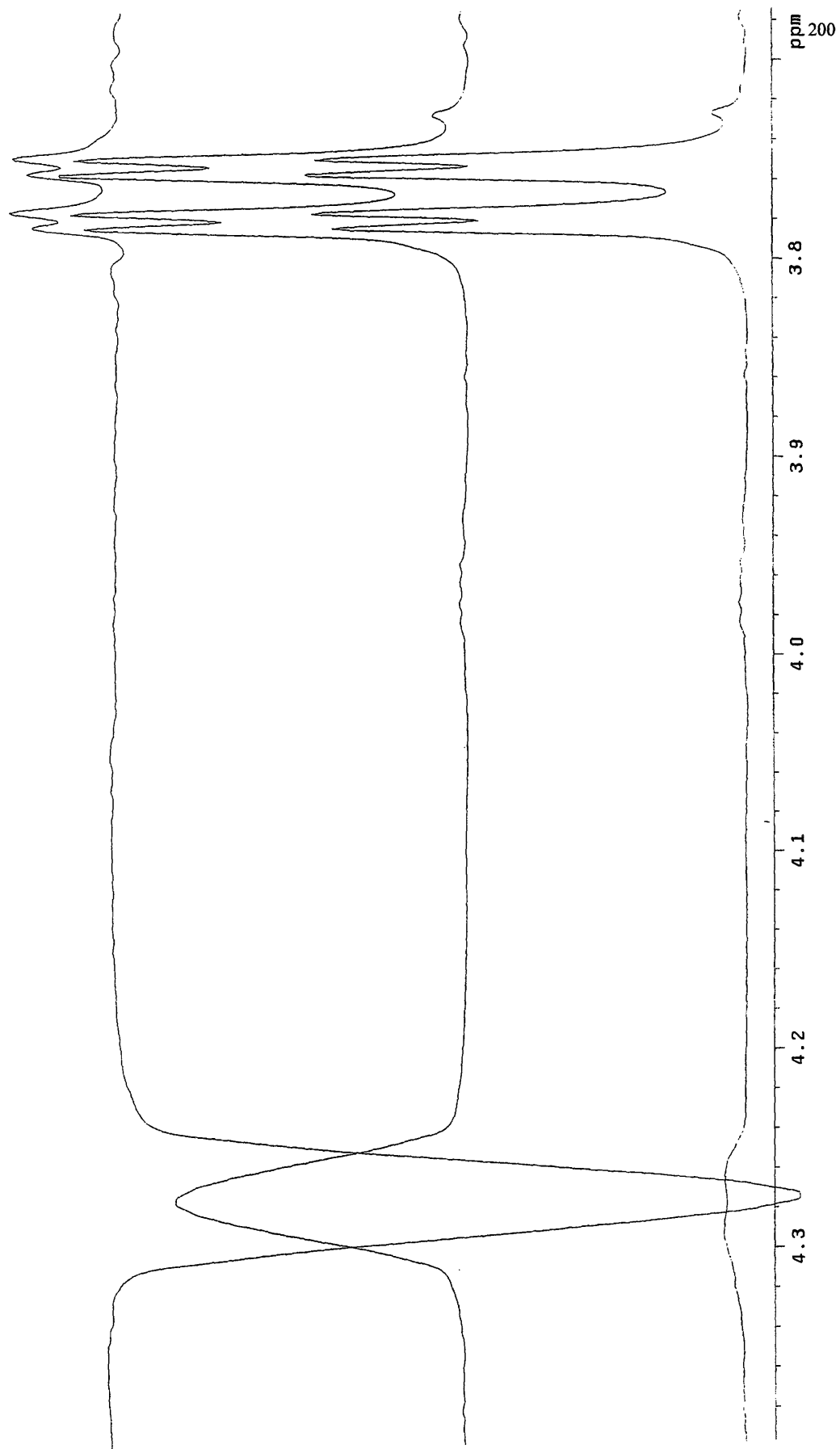
<sup>1</sup>H NMR

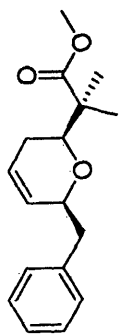




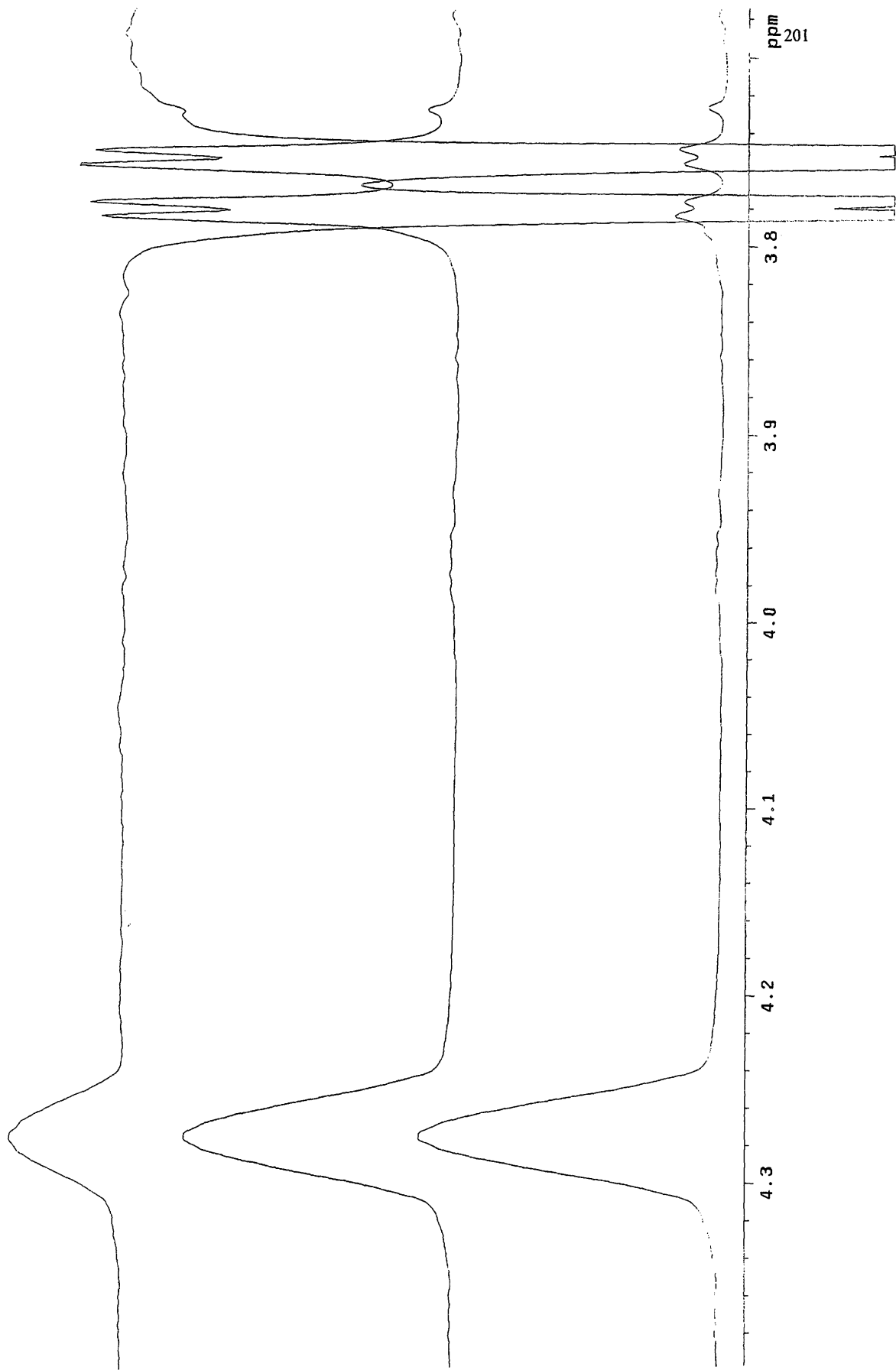


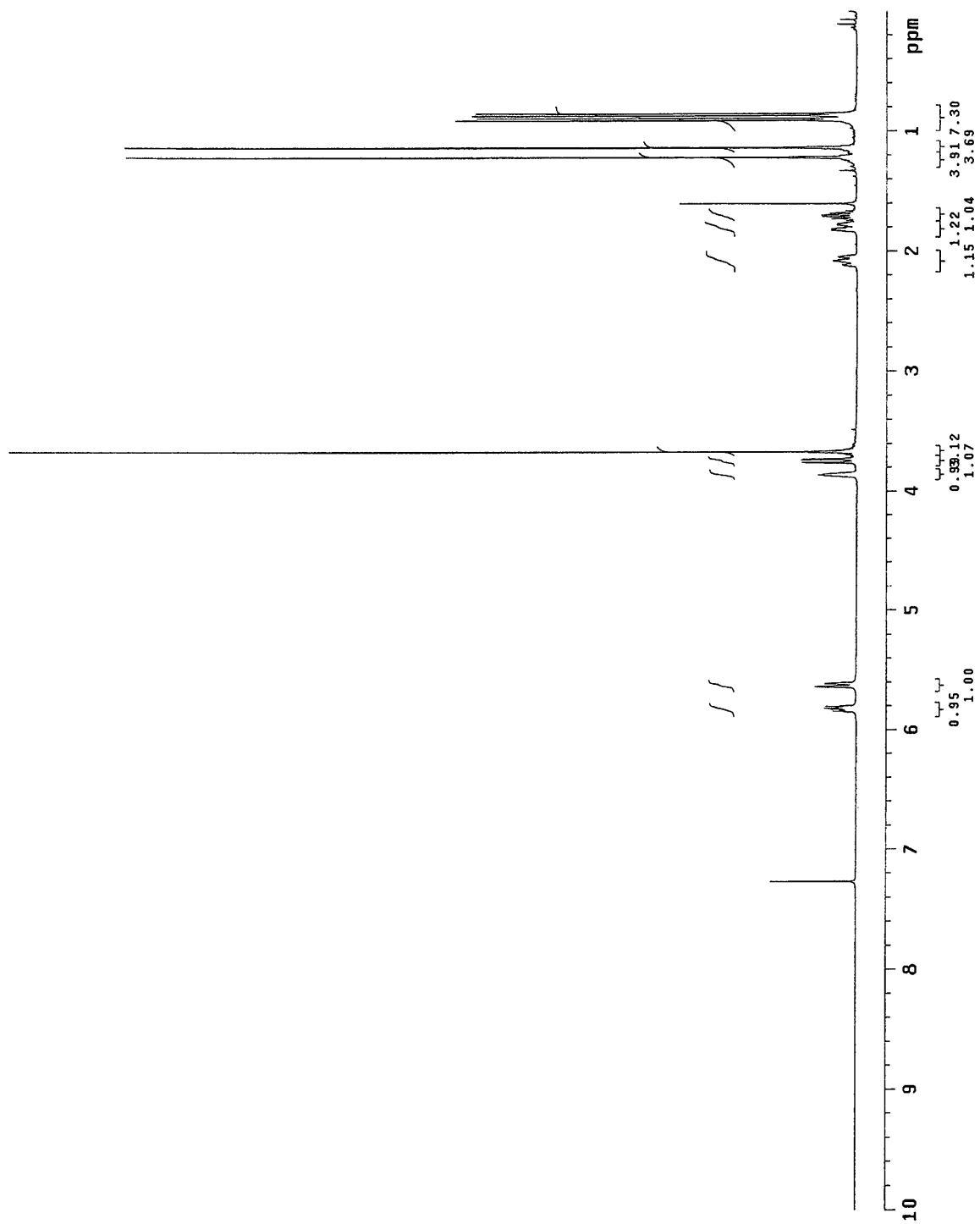
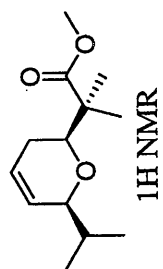
<sup>1</sup>H NOE Spectrum  
dec= 4.27 ppm

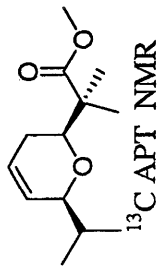
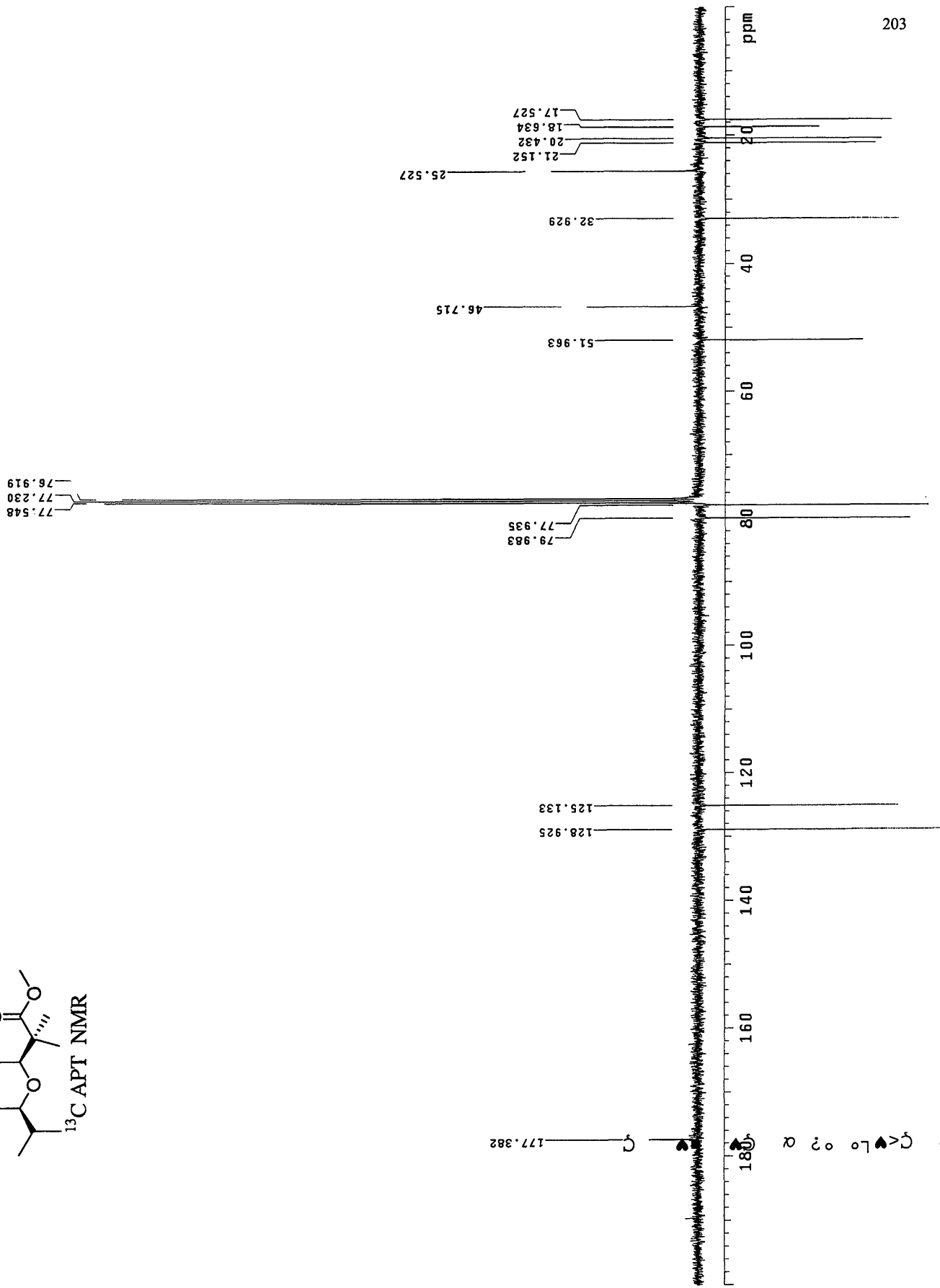


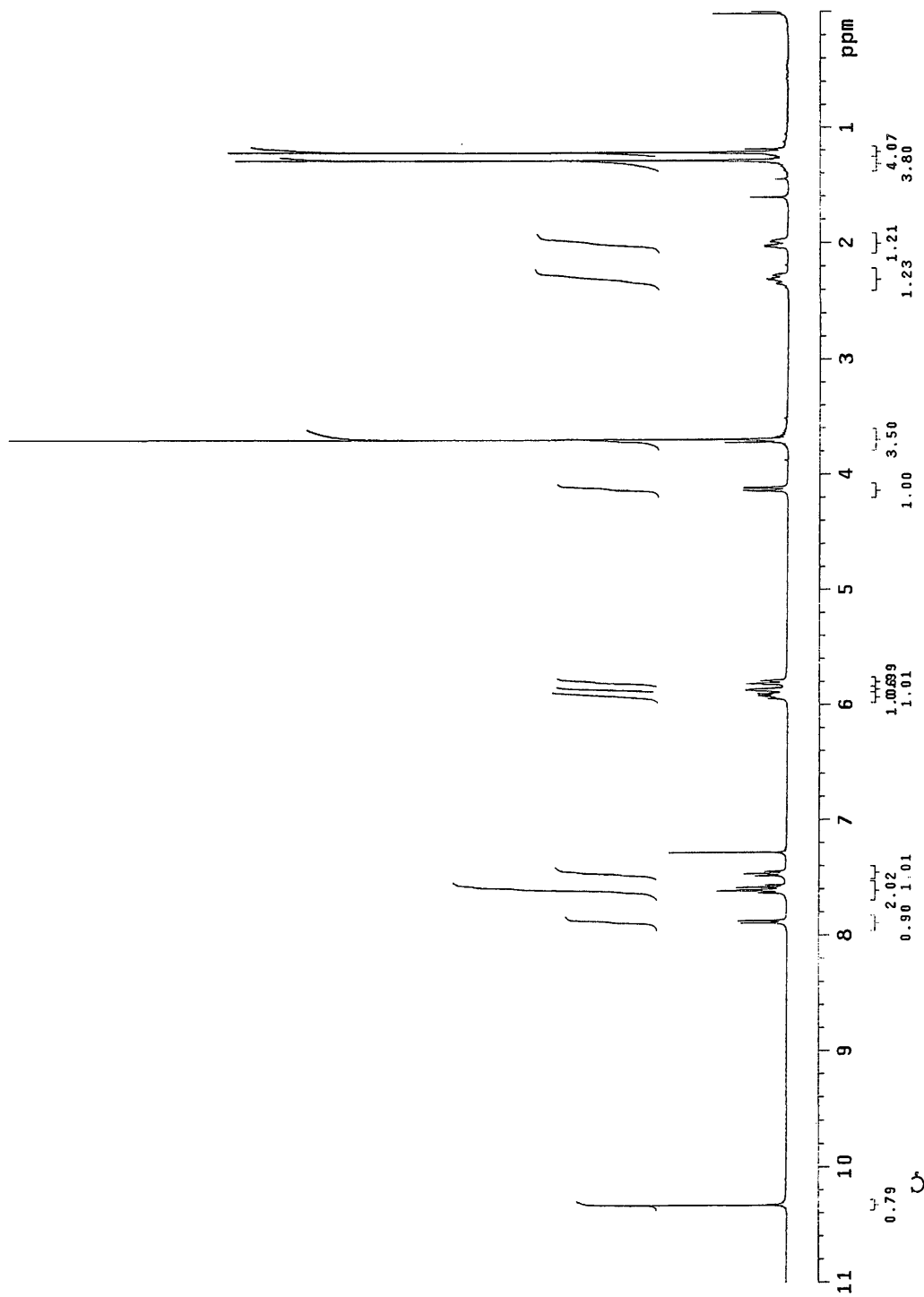
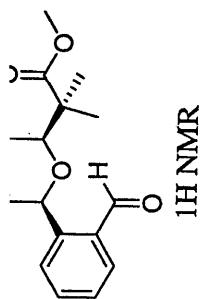


<sup>1</sup>H NOE Spectrum  
dec= 3.77 ppm

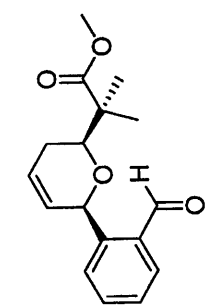




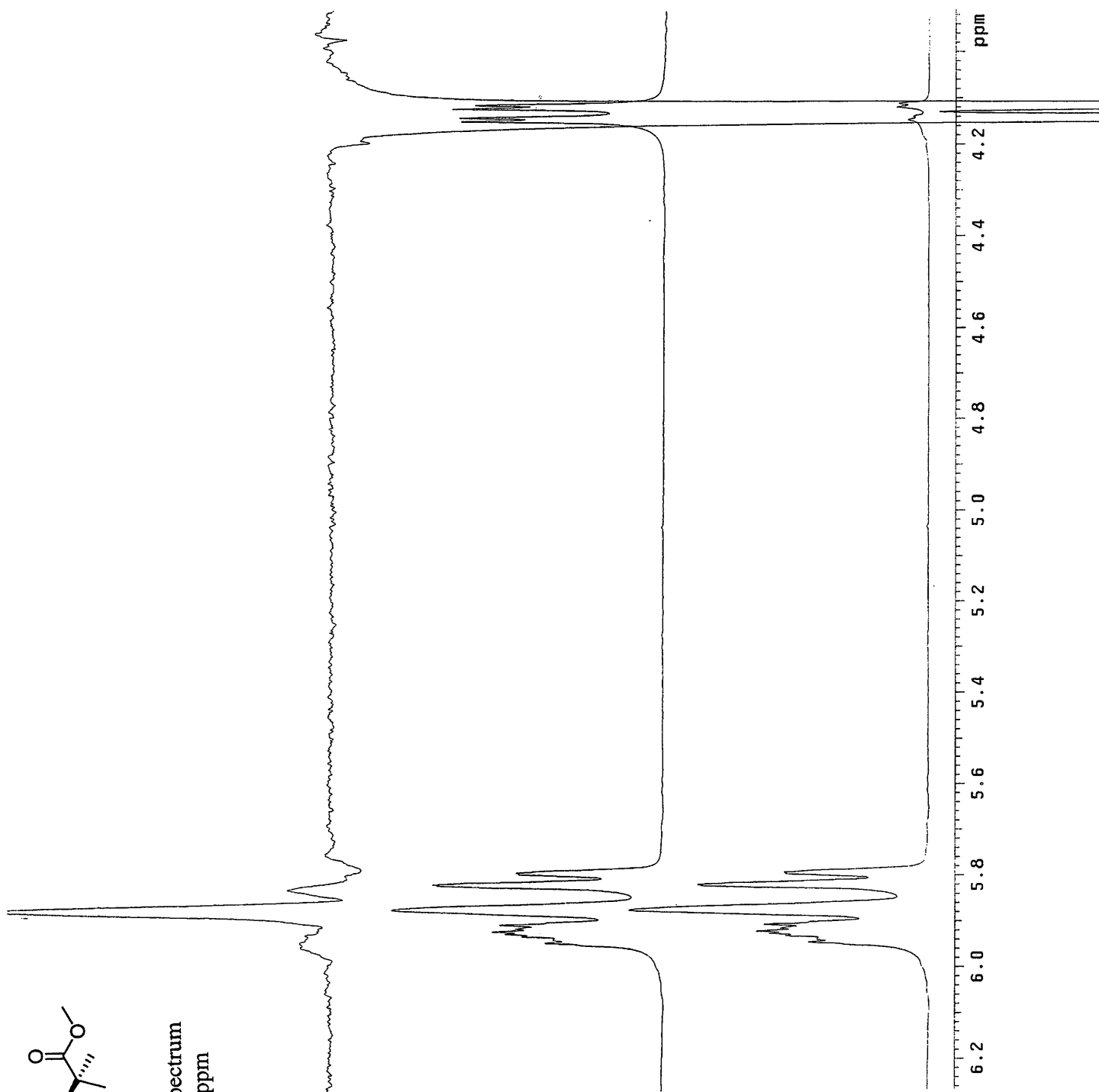


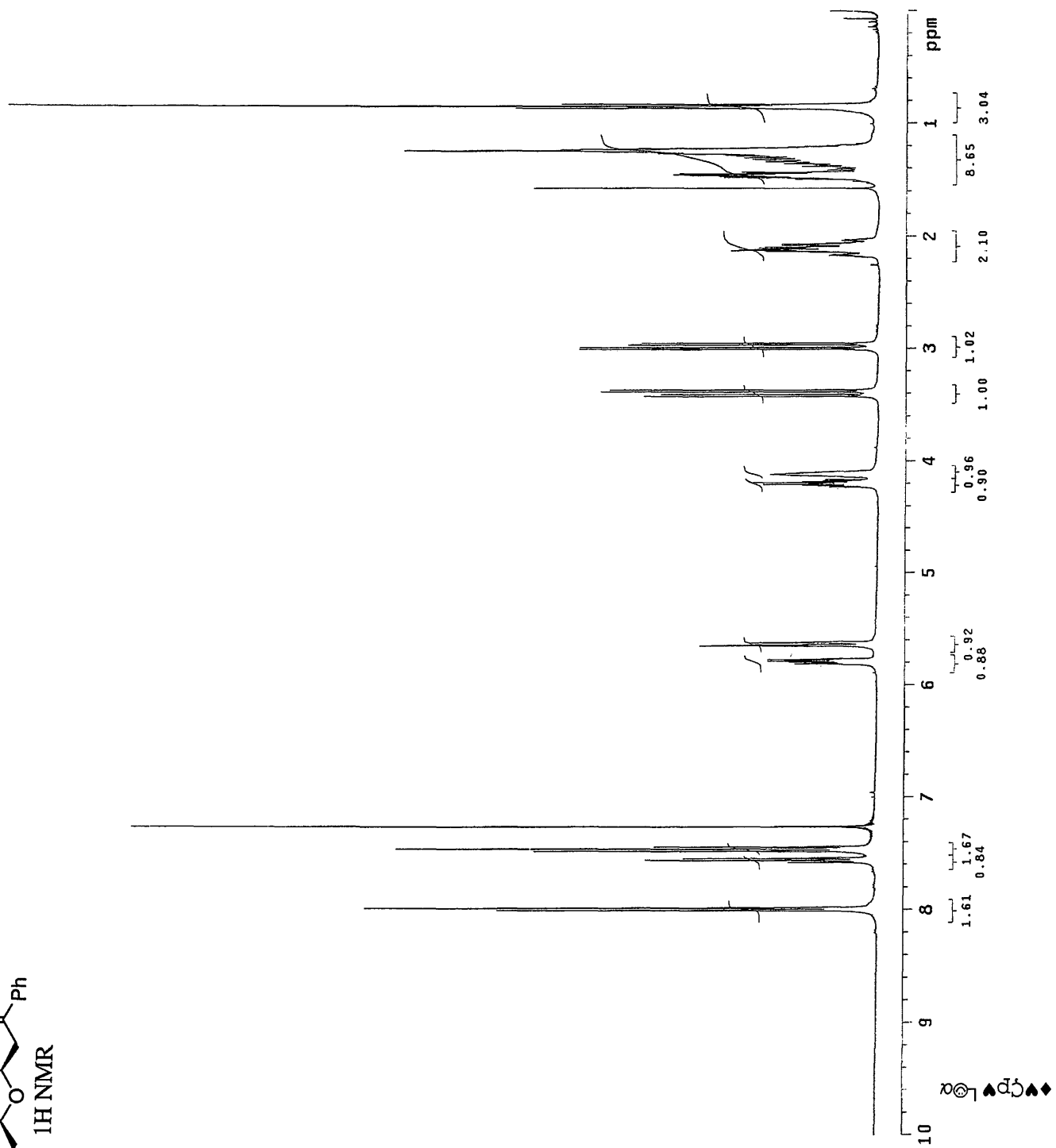
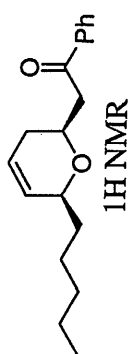


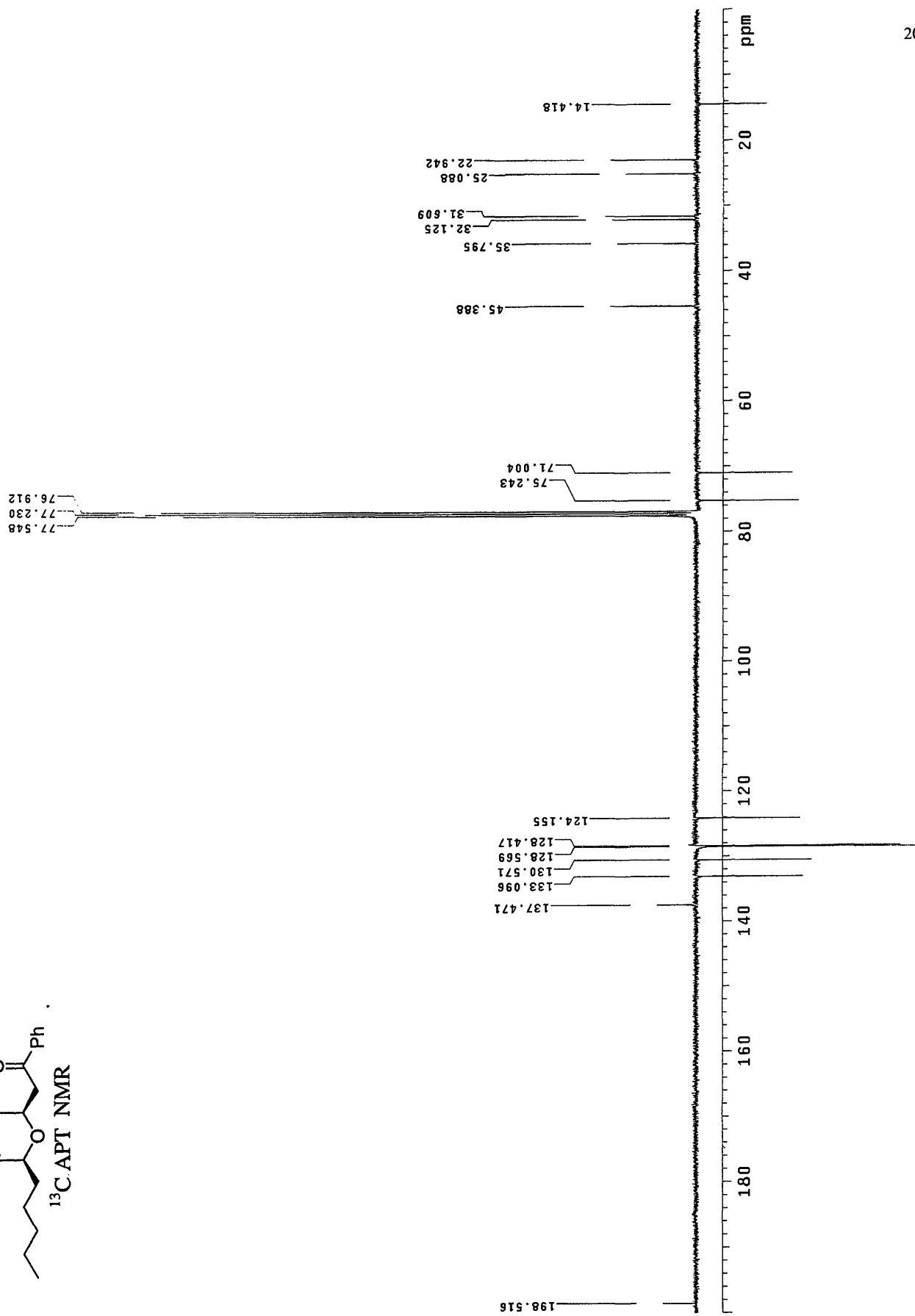
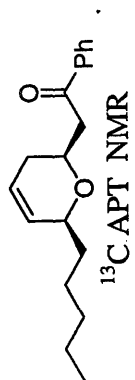




$^1\text{H}$  NOE Spectrum  
dec= 4.13 ppm







## VITA

### Yajing Lian

Yajing Lian was born in Xiamen, P. R. China on November 25, 1981. He graduated from Xiamen Science and Technology High School in June 1999. Yajing received his B.S. of chemistry at Xiamen University, which is situated in Xiamen, in June 2003.

In August 2003, the author entered the College of William and Mary as a graduate assistant in the Department of Chemistry. Yajing carried out his research in Hinkle's Laboratory and he defended his thesis on December 20, 2005 for his master degree. He will go to another graduate school to pursue his Ph. D. degree.