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Convenient, Bismuth Mediated, One-pot, Two Component Synthesis of 2,6-Disubstituted-3,4-Dihydropyrans

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Convenient, Bismuth Mediated, One-pot, Two Component Synthesis of 2,6-Disubstituted-3,4-Dihydropyrans

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by

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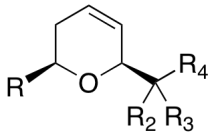
Abstract

The synthesis of *cis*-2,6-dihydropyrans is successfully accomplished through tandem Intramolecular silyl-Modified Sakurai (ISMS)/silyl-Prins type reaction, mediated by $Bi(OTf)_3$. A variety of epoxides and vinyl silanols prove effective in providing *cis*-2,6-dihydropyrans in moderate to good yield and excellent diasterioselectivities. Scope, limitations, and mechanistic considerations of the protocol are described herein. Additionally, within the development of this methodology, the catalytic process involving $Bi(X)_3$ salts was investigated.



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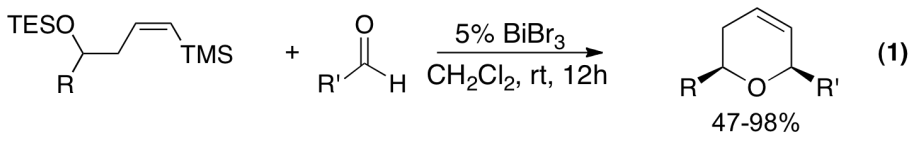
Introduction

Current concerns surrounding the chemical industry, in particular in the field of chemical synthesis, involve atom economy and the use of caustic substances. Modern synthetic protocols attempt to both improve efficiency and decrease environmental degradation through the use of mild reagents. To this end, we have focused our attention on the consolidation of multi-step reactions into cascade sequences, otherwise known as one-pot, multi-component reactions (MCRs). These sequences streamline synthetic processes by combining into one reaction flask what formerly required multiple reactions and isolation sequences. With this goal in mind, we described a protocol (Eq.1) in which 6-membered cyclic ethers were constructed via a bismuth tribromide mediated intermolecular addition followed by intramolecular silyl-modified Sakurai reaction (ISMS).



(1)

The method proved to have excellent diastereoselectivity toward *cis*-2,6-disubstituted dihydropyrans. The search for environmentally friendly organic catalysts led to the chemically benign bismuth (III) compounds (BiX_3)[1] that exhibit extraordinary chemical properties including low toxicity,[2] water stability ($Bi(OTf)_3$),[3] low cost, and ease

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[1] Lian, Y.; Hinkle, R.J.; *J. Org. Chem.* **2006**, *71*, 7071-7074.
[2] Hua, R. *Current Organic Synthesis,* **2008**, *5,* 1-27.
[3] Gaspard-Iloughmane, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 2517-2532.

of preparation and use.[4] In addition, they have been used successfully in a wide range of organic reactions.[2,3,4] Similarly, cyclic ethers such as the dihydropyran motif (DHP) desribed in **1** and tetrahydropyrans (THP) are common in many pharmacologically relevant bioactive molecules.[5] A number of these molecules, including but not limited to: kendomycin,[6] phorboxazole,[7] leucasandrolide,[8] and ambruticin,[9] have been successfully synthesized a variety of ways. Therefore, it is worthwhile to provide a method of synthesizing such a common moiety as the DHP through a noncorrosive, concise protocol.

With this intention, Hinkle and coworkers next described a protocol (eq. 2) in which the *cis*-DHP was located at the α-position of a carbonyl compound as a convenient handle for further functionalization.[10] The synthesis described once again utilized the principles mentioned above (eq. 1), but expanded the protocol to include an initial Mukaiyama aldol reaction between commercially available silyl enol ethers and (*Z*)-4-(trimethylsilyl)but-3-enal. The Mukaiyama adduct subsequently undergoes ISMS to afford the product in good to excellent yield. Furthermore, the process tolerated a variety of functionalization including both hindered and aromatic alkyl groups and electron rich methoxy groups. The convenience and success of MCR's was highlighted.

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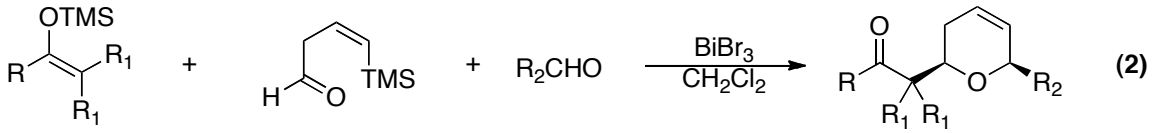
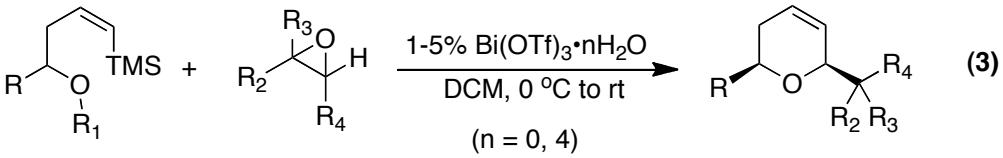
[4] Bhatia, K.A.; Eash, K.J.; Leonard, N.M.; Oswald, M.C.; Mohan, R. S. *Tetrahedron Lett.* **2001**, *42*, 8129-8132.
[5] Kang, E.J.; Lee, E. *Chem. Rev.* **2005,** *105*, 4348−4378.
[6] Funahashi, Y; Kawamura, N; Ishimaru, T. JP Patent 08231551 [A2960910], 1996.
[7] Searle, P.A.; Molinski, T.F.; Brzezinski L.J.; Leahy, J.W. *J. Am. Chem. Soc.* **1996**, *118,* 9422–9423.
[8] D'ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Helv. Chim. Acta.* **1996**, *79,* 51–60.
[9] Ringel, S.M.; Greenough, R.C.; Roemer, S.; Connor, D.; Gutt, A.L.; Blair, B.; Kanter G.; von Strandtmann, M. *J. Antibiot.* **1977**, *30*, 371–375.
[10] Hinkle, R.J.; Lian, Y.; Speight, L.C.; Stevenson, H.E.; Sprachman, M.M.; Katkish, L.A.; Mattern M.C. *Tetrahedron*, **2009**, *65*, 6834-6839.



(2)

Invigorated by the success of these published methodologies, we looked to improve upon them. This was done by the inclusion of an epoxide as a substitute for the aldehyde shown in eq. 1. Along with far greater stability than the corresponding aldehyde, the expoxides investigated are both commercially available and relatively inexpensive. Additionally, the *in situ* rearrangement of the epoxide provided a convenient step in which to explore the properties of bismuth and its role as a catalyst in such reactions.



(3)

R = alkyl, aryl
R_1 = H, TES
R_2, R_3, R_4 = alkyl, aryl

Despite evidence of the Lewis acidic nature of bismuth compounds, debate continues over the mechanism by which these compounds catalyze organic reactions.[11,12] In many bismuth mediated reactions, it is unclear whether the Bi(III) is acting as a Lewis acid or merely producing a Brønsted acid (H-X) *in situ*, which in turn acts as the catalyst. This investigation couples the expansion of the synthetic pathway (eq.3) with the

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[11] Ollevier, T.; Lavie-Compin, G. *Tetrahedron Lett.* **2004**, *45*, 49-52.
[12] Yin, S.; Shimada, S. *Chem. Commun*. **2009**, 1136–1138.

detection of the catalytic species in bismuth (III) reaction sequences. Investigations into both the development of methodology described and the elucidation of the role of bismuth in such chemical transformations are described herein.

Background

Bismuth (III) Catalysis

With the goal of advancing green chemistry, the use of bismuth catalysts particularly halides and triflates, caught our attention. Its location in proximity within the periodic table to the toxic heavy metals, such as mercury, lead and thallium, has caused it to be overlooked in terms of catalytic ability due to the assumption of toxicity by association.[13] This is, however, far from the truth. Bismuth chloride, for example, is actually less toxic than table salt, with an LD_{50} of 3334 mg/kg.[14] This fact alone makes bismuth incredibly attractive as an alternative to harsh catalysts commonly used in organic transformations.

Bismuth, the heaviest stable element, is fairly rare (64^{th} most abundant element), but easily obtained as a byproduct of the copper and tin refining processes.[15] Additionally, bismuth oxides are common ingredients in cosmetic products, and bismuth is one of the active ingredients in medications for gastric ailments such as Pepto-Bismol®. Obviously, since it is non-toxic and non-carcinogenic,[16] bismuth derivatives would be an appealing

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[13] Gaspard-Iloughmane, H.; Le Roux, C. *Eur. J. Org. Chem.* **2004**, 2517-2532.
[14] As listed in the MSDS provided by Sigma-Aldrich Chemical Corp., St. Louis, MO.
[15] Leonard, N.M.; Wieland, L.C.; Mohan, R.S. *Tetrahedron.* **2002**, 58, 8373-8397.
[16] Irwing-Sax, N.; Bewis, R.J. *Dangerous Properties of Industrial Materials*; Van Nostrand Reinhold: New York, 1989; pp 283-284

alternative to harsh, noxious catalysts, such as trimethylsilyl trifluoromethanesulfonate (TMSOTf), for the pharmaceutical industry.

The low toxicity of bismuth compounds can be explained by their insolubility in neutral aqueous solutions such as those found in biological systems.[17] Its use would eliminate the need to painstakingly remove trace amounts of catalyst, which is both costly and time–consuming.

Current literature shows that $Bi(X)_3$ type compounds replaced Lewis acids such as $TiCl_4$ and $InCl_3$ in common organic protocols such as the Mukaiyama Aldol reaction.[18,19] Customary Lewis acids such as the aforementioned are corrosive in nature and difficult to use. As relatively air-stable, crystalline solids, $BiBr_3$, $BiCl_3$ and $Bi(OTf)_3$ are much simpler to use. Although relatively inexpensive, $Bi(OTf)_3$ is commercially available and can be prepared easily in house at low cost and high yield.[7] Due to their extraordinary properties, they have gained popularity in a variety of areas of organic synthesis. Efficient methods mediated by bismuth compounds, including simple protection/deprotections,[20] Friedel-Crafts,[21] Diels-Alder,[22] transesterifications,[23] rearrangments[24] and acylations,[25] have been reported (Scheme 1).

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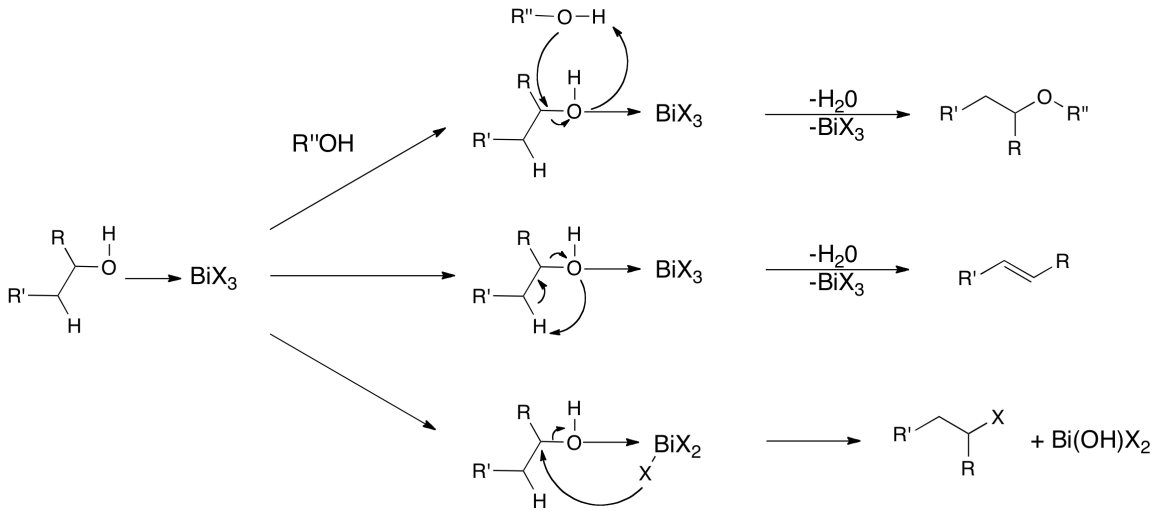
[17] Salvador, J.A.R.; Pinto, R.M.A.; Silvestre, S.M. *Current Organic Synthesis*, **2009**, *6*, 426-470.
[18] Peidro, L.; Le Roux, C.; Laporterie, A.; Dubac, J. *J. Organomet. Chem.* **1996**, *52*, 397-399.
[19] Sanderson, J.; Bayse, C.A. *Tetrahedron* **2008**, *64*, 7685-7689
[20] Kadam, S.T.; Kim, S.S. *J. Organomet. Chem*. **2009**, *694*, 2562-2566
[21] Angelini, E.; Cesarino, B.; Bartoccini, F.; Lucarini, S.; Piersanti, G. *J. Org. Chem.* **2008**, *73*, 5654-5657
[22] Labrouillere, M.; Le Roux, C.; Gaspard, H.; Laporterie, A.; Dubac, J. *Tetrahedron Lett.* **1997**, *38*, 8871-8874.
[23]Gowravaram, S.; Rangavajjula, S.; Peddabuddi, G.; Bhikshapathi, M.; Jhillu, S.Y. *Helv. Chim. Acta.* **2011**, *94*, 119-121
[24] Mouhtady, O.; Gaspard-Iloughmane, H.; Roques, N.; Le Roux, C. *Tetrahedron Lett.* **2003**, *44*, 6379-6382.
[25] Dumeunier, R.; Marko, I.E. *Tetrahedron Lett*. **2004**, *45*, 825-829.

Scheme 1. Simple Transformations Mediated by $Bi(X)_3$[19]



Although these compounds exhibit the incredible qualities mentioned above, bismuth salts do hydrolyze to give 2 equivalents of the corresponding acid (eq.4).[26] Ollevier et al. report a bismuth triflate-mediated epoxide ring opening performed under aqueous conditions in which, they mention that aqueous solutions of bismuth salts are acidic.

$$BiX_3 + H_2O \longrightarrow BiOX + 2\,HX \qquad (4)$$

X = Cl, Br, I, OTf

This is due to the production of triflic acid *in situ*, so it is possible that the Brønsted acid created from this hydrolysis is, in fact, the catalytically active species in the reaction.[11] Bajwa et al. reported a deprotection scheme (eq. 5) of the *tert*-butylsilyl (TBS)

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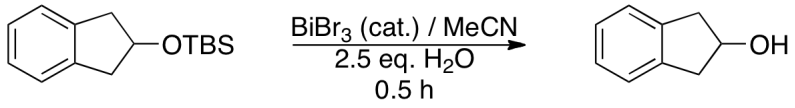
[26] Bajwa, S.J.; Vivelo, J.; Slade, J.; Repic, O.; Blacklock, T.; *Tetrahedron Lett.* **2000**, *41*, 6021-6024.

group through the use of catalytic $BiBr_3$ in acetonitrile with 2.5 eq. of water. These authors claimed that is evidence of Bi(III) acting as a precatalyst and generating H-X *in situ.*[26]



(5)

Many protocols involving BiX_3, particularly bismuth triflate ($Bi(OTf)_3$), have reported bismuth as the progenitor of the true catalyst.[18,27] Kelley and co-workers report that the reactivity of $Bi(OTf)_3$ with respect to hydroalkoxylation mirrors that of triflic acid. They propose a mechanism (Scheme 2) for the synthesis of *trans*-tetrahydrofurans involving the *in situ* generation of two separate catalytic species involving TfOH and TMSOTf. It is suggested that the TMSOTf, produced from $Bi(OTf)_3$ and the silyl nucleophile, is the true catalyst for the addition step.[28] On the other hand, Sanderson and Bayse described the study of the Lewis acidic nature of $Bi(X)_3$ salts with respect to carbonyls and alcohols. Their density functional theory (DFT) findings provided support for the formation of a Lewis complex with each example (X= Cl, Br, I).[19]

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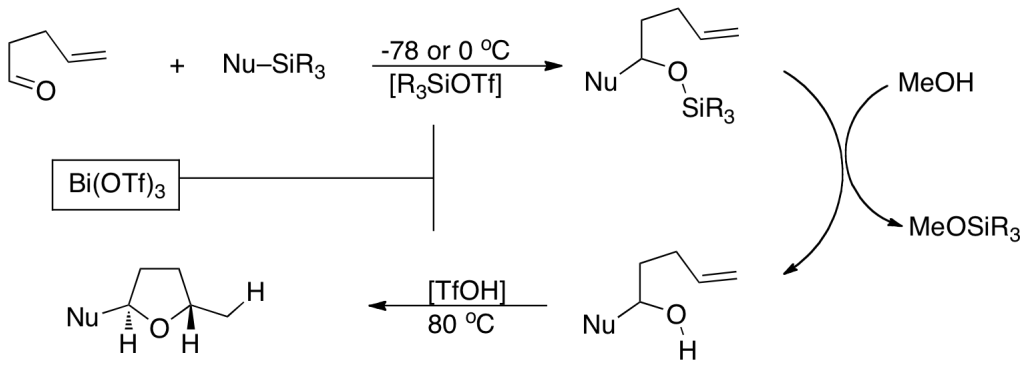
[27] (a) Ollevier, T.; Nadeau, E. *J. Org.* **2004**, *69*, 9292-9295. (b) Komeyama, K.; Miyagi, M.; Takaki, K. *Chemistry Letters*, **2009**, *38*, 224-225. (c) Ghosh, R.; Maiti, S.; Ghosh, S.; Mukherjee, A.K. *Synthesis*, **2007**, *2*, 0190-0196.
[28] Kelley, B.D.; Allen, J.M.; Tundel, R.E.; Lambert, T.H. *Org. Lett.* **2009**, *11*, 1381-1383.

Scheme 2. Proposed Mechanism of Multicatalytic Tetrahydrofuran Synthesis[28]



Ambiguity still surrounds the catalytic cycle of bismuth compounds and lack of consensus within the literature demands further investigation. Due to the lack of definitive evidence of the true active species and the increase in prevalence of organic transformations involving bismuth (III) compounds, the definitive elucidation of their catalytic pathway is a worthy goal.

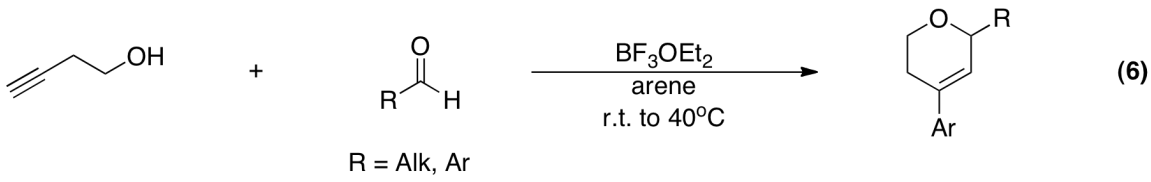
Typical Methods Toward Dihydropyrans

The literature describes several strategies toward the synthesis of disubstituted dihydropyran heterocycles. In a review on strategies for the formation of 6-membered heterocycles, Clark and Santos outline a variety of approaches to the tetrahydropyran scaffold including hetero-Diels-Alder, Michael Reactions, reductions of cyclic hemi-ketals, and even Williamson ether syntheses.[29]

Reddy and Saikia developed a method similar to that described herein. They recently published a method for the construction of 4-aryldihydropryrans via a

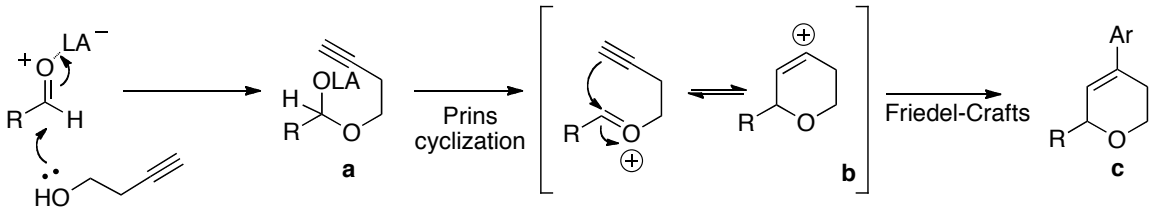
[29] Clarke, P.A.; Santos, S. *Eur. J. Org. Chem.* **2006**, 2045-2053.

combination Prins/Friedel-Crafts reaction using boron trifluoride etherate (eq. 6). Homopropargylic alcohols in combination with aromatic-aldehydes in the presence of BF_3•OEt_2 brings about the cyclization with good to excellent yield. Optimization studies included the screening of several nonhalogenated Lewis acids such as TMSOTf, $Sc(OTf)_3$, $In(OTf)_3$ and $Bi(OTf)_3$; none was efficient in catalyzing the transformation, however. The limitations to this method include failure of ketones and aldehydes with electron-donating groups on the aromatic ring to react favorably. Electon-withdrawing groups such as methoxy groups bonded to an aromatic ring stabilize the carbocation at the benzylic position, thus facilitating oxina-[3,3]-sigmatropic rearrangement.



(6)

Scheme 3. Proposed Prins-Friedel-Crafts Mechanism[30]



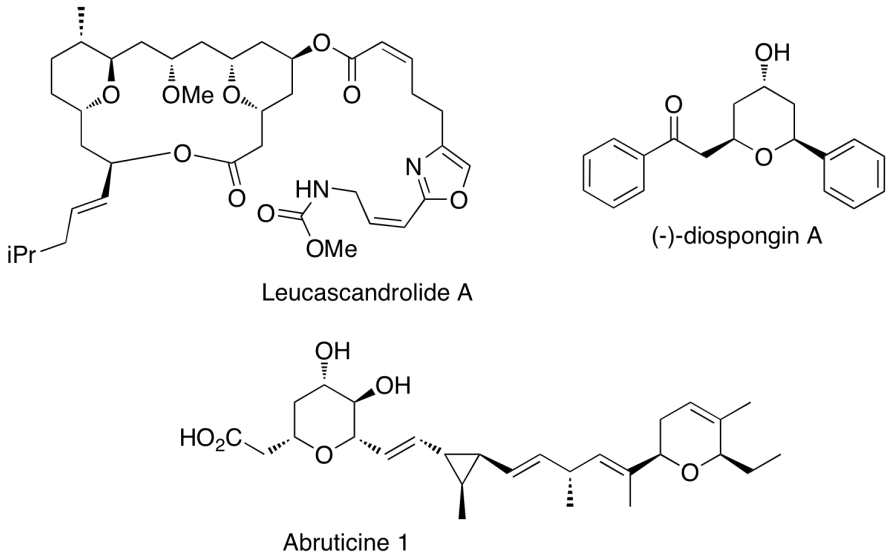
The authors propose a mechanism (Scheme 3) involving initial Lewis acid activation of the aldehyde. This activation allows for nucleophilic attack by the alcohol (**a**) followed by Prins cyclization, resulting in the formation of an oxocarbenium ion

intermediate (**b**). The cation is trapped through a Friedel-Crafts reaction, affording the 2,4-dihydropyran (**c**).[30]

Biologically Active Cyclic Ether Containing Natural Products

As mentioned in the introduction, heterocycles are amazingly common among biologically active small molecules. Several compounds with promising biological activity feature 2,6-dihydropyrans or scaffolds that can easily be accessed through dihydropyran intermediates. These include the diospongins, Leucascandrolide A and Ambruticine 1 (Figure 1).

Figure 1. DHP Containing Natural Products

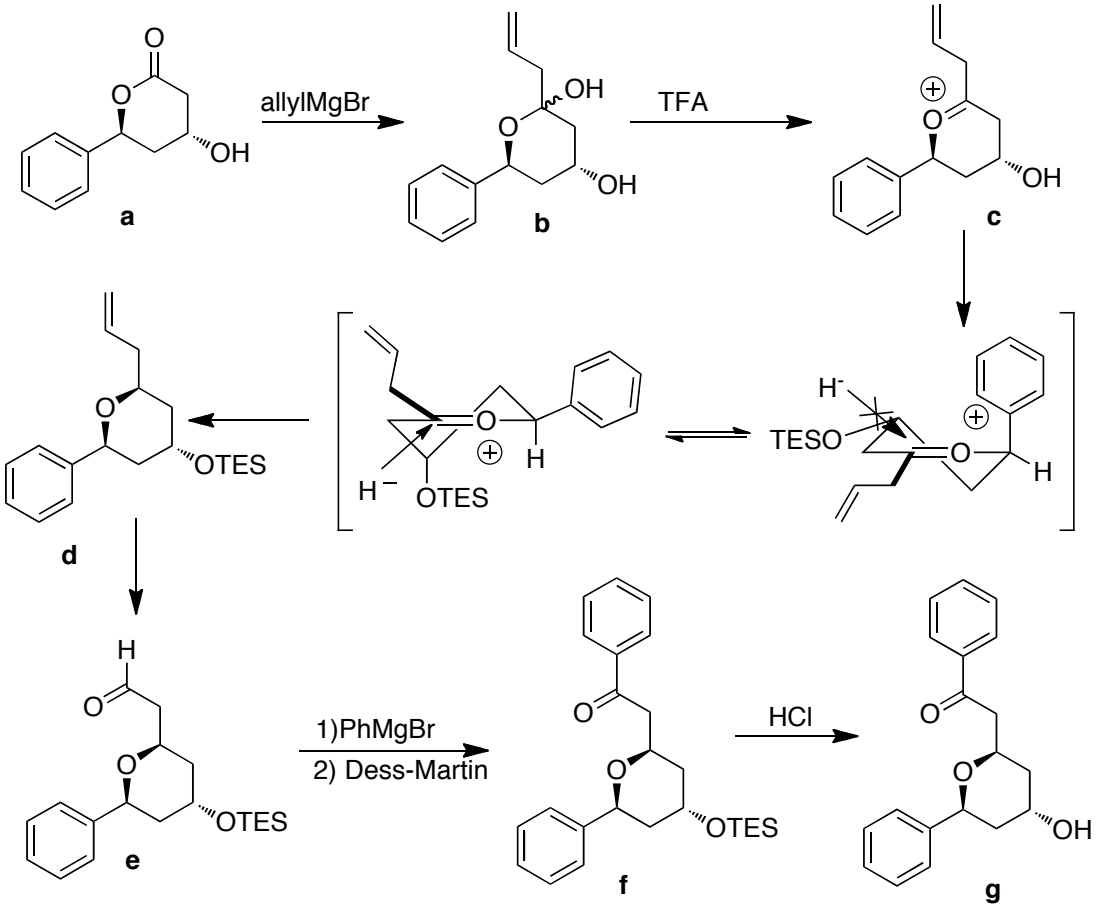


[30] Reddy, U.C.; Saikia, A.K. *Synlett*, **2010**, *7*, 1027-1032.

The diospongins have high anti-osteoporotic activity.[31] Sawant and Jennings report that (-)-diaspongin B exterts powerful inhibitory activity on bone resorption. These molecules would offer the convenience of a small molecule natural product as an effective treatment for osteoporosis. A total synthesis was published by the same authors of both (-)-diospongin A and (-)-diospongin B, deriving the pyran ring system by reduction of an oxocarbenium cation intermediate formed from a commercially available lactone (**a**). In the case of (-)-diospongin A, the lactone carbonyl was first treated with allylmagnesiumbromide followed by trifluoroacetic acid (TFA) to afford the allylated oxocarbenium cation (**c**). Next, the oxocarbenium cation was reduced with Et_3SiH, which occurred by stereoselective axial attack of the hydride. This occurs because the more stable half-chair conformation places the phenyl ring in the pseudoequatorial position. Axial attack of the hydride then gives the *cis*-dihydropryan ring (**d**). Oxidative cleavage of the alkene by ozonolysis (**e**) and subsequent alkylation with PhMgBr followed by Dess-Martin oxidation (**f**) and deprotection of the hydroxyl moiety gives the final product (**g**) in a reported 85% yield (Scheme 4).[31]

[31] Sawant, K.B.; Jennings M.P. *J. Org. Chem.* **2006**, *71*, 7911-7914.

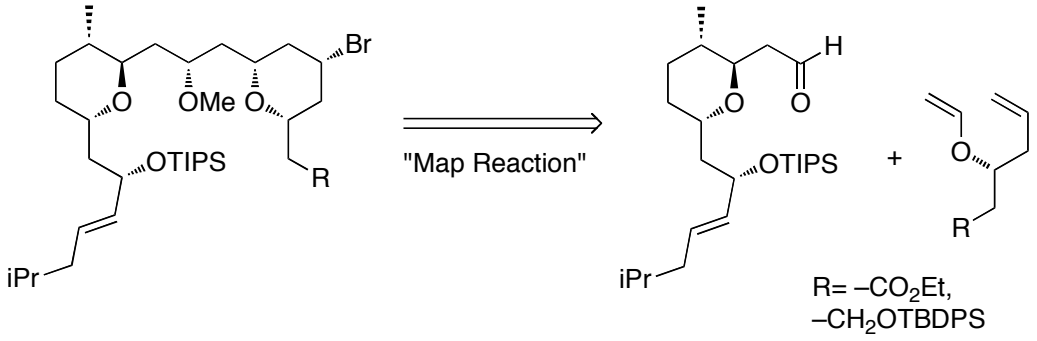
Scheme 4. Synthesis of (-)-Diospongin A



Conveniently, the three-component synthesis described herein, could provide a simple alternative method to the construction of the *cis*-pyran ring structure. Unlike the sequence of reactions described above, we have developed a concise reaction scheme, which can be conducted in a single (one-pot) reaction vessel. Furthermore, the olefin formed within the ring could be used as a handle to further functionalize this compound. Alternative functional groups could serve to enhance the anti-osteoporotic qualities of the diospongins.

Leucasandrolide A is a structurally interesting natural product isolated from calcareous sponges called *L. caveolata*. Today, chemical synthesis is the only source of the compound and it is now believed that leucasandrolide A is produced by opportunistic microbial colonies. Of the compounds isolated from this class of sponges, leucasandrolide shows the greatest biological activity – high cytotoxicity in vitro against human KB tumor cell lines (IC_{50}: 50 ng/mL) and P388 leukemia cell lines (IC_{50}: 250 ng/mL). It has also shown potential anti-fungal activity.[32] Due to its promising biological properties and the lack of natural sources, its is necessary to develop a concise total synthesis of leucasandrolide A. Rychnovsky and coworkers recently completed an elegant total synthesis of leucasandrolide A along with investigations of the Mukaiyama aldol-Prins (MAP) reaction (Figure 2).[33] Discussion herein will focus on the MAP reaction and the construction of the *cis*-tetrahydropyran.

Figure 2. Retrosynthetic Approach to the *cis*-THP of Leucasandrolide A[33]



[32] D'Ambrosio, M.; Guerriero, A.; Debitus, C.; Pietra, F. *Hel*V. *Chim. Acta* **1996**, *79*, 51-60.
[33] Van Orden, L.J.; Patterson, B.D.; Rychnovsky, S.D. *J. Org. Chem.* **2007**, *72*, 5784-5793.

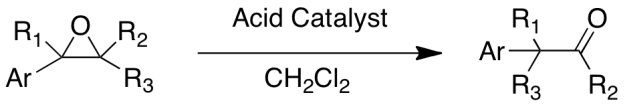
This novel method for the synthesis of the *cis*-THP involves the coupling of an initial Mukaiyama aldol protocol with a Prins cyclization. The synthetic route described was an improvement of the original MAP reaction developed by Rychnovsky in 2001.[34] The MAP reaction outlined in Figure 2 required the use of a Lewis acid that can act as a source of bromide ions to trap the cyclized THP carbenium ion after the initial Mukaiyama aldol coupling. If the Lewis acid involved is not reactive enough or cannot produce bromide ions, then the oxocarbenium ion, formed as an intermediate, will be trapped by an extra equivalent of the initial aldehyde. This major limitation was shown with the failure of tin tetrabromide initiate substrate conversion.[33] A solution to the shortcomings of many of the common synthesis of THP/DHP containing scaffolds would be the use of catalytic bismuth halides or triflates. This would eliminate the need for harsh Lewis acids and anhydrous reaction conditions to produce oxocarbenium ions.

[34] Kopecky, D.J; Rychnovsky, S. D. *J. Am. Chem. Soc.* **2001,** *123,* 8420-8421.

Results and Discussion

Initial Epoxide Rearrangements

Initially, we examined simple epoxide rearrangements (eq. 7), under a variety of conditions.[35] The reaction was pertinent to the overall synthesis, in that it generates the active aldehyde. The epoxide electrophile chosen required a moiety with the ability to stabilize the positive charge generated on the adjacent carbon during the opening of the ring (e.g., an aryl substituent).[35] Due to this stipulation, only those epoxides that possessed substituents such that the formation of a cation would result in either a benzylic or tertiary cation could be utilized. Without this stability, the rearrangement was unfavorable due the lower energy of a secondary carbocation (Scheme 5).



(7)

Bhatia and co workers fully describe the epoxide rearrangements catalyzed by $Bi(OTf)_3$.[35] By testing various epoxides with remarkably low mole percentages of catalyst, they developed a reaction that is both regioselective and highly catalytic. The following mechanism shows the Lewis acid-mediated ring opening, followed by a migration, finally affording the desired aldehyde (Scheme 5).[35] We were able to both confirm and further explore the effects of BiX_3 compounds by comparing the reactions under various conditions.

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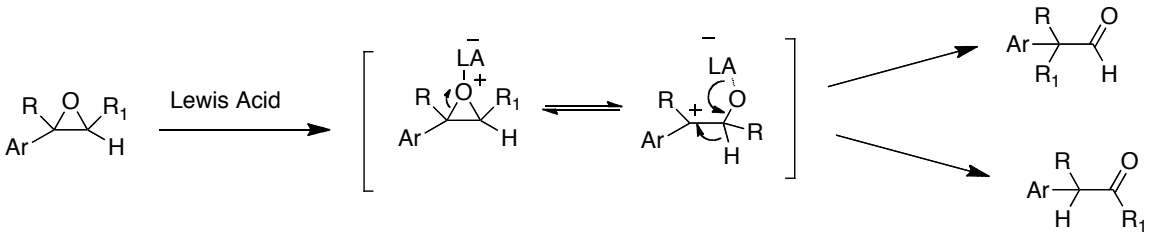
[35] Bhatia, K.A.; Eash, K.J.; Leonard, N.M.; Oswald, M.C.; Mohan, R. S. *Tetrahedron Lett.* **2001**, *42*, 8129-8132.

Scheme 5. Epoxide Ring-Opening/ Rearrangement



In the aryl substituted epoxide rearrangement, the products are dependent on the migratory aptitude[36] of one of the substituents β- to the aromatic ring, giving either a ketone or aldehyde as the final product.

As shown in Table 1, all the reactions attempted proceeded cleanly, rapidly, and in high yield. Each epoxide afforded only one product (with the exception of some aldol byproducts with styrene oxide –entries 4 and 5),[37] showing high regioselectivity with respect to migration. This was exemplified by *trans*-stilbene oxide (entries 1–3), where the phenyl group demonstrated complete migratory preference over the hydride shift (entries 1–3).[38] Regarding catalyst loading, we were able to use as little as 0.001 mol% $Bi(OTf)_3$ at dilute concentrations and the reaction still proceeded smoothly. Interestingly, even 1 mol% TfOH catalyzed the rearrangement in extremely high yield and comparative rapidity. Although we cannot claim that bismuth is only initiating the formation of a Brønsted acid based on this data alone, it remains impossible to justify bismuth as solely a Lewis acid in organic reactions.

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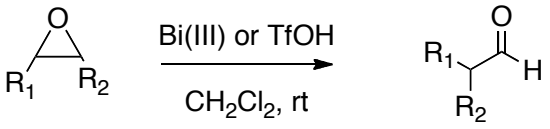
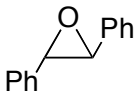
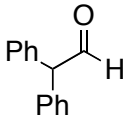
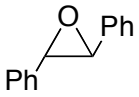
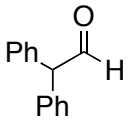
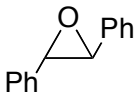
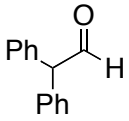
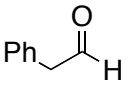
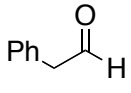
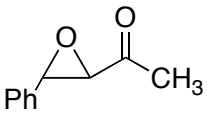
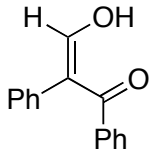
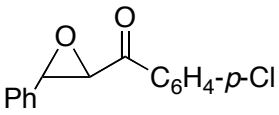
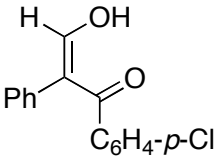
[36] Maruoka, K.; Ooi, T.; Yamamoto, H. *Tetrahedron*, **1992**, *48*, 3303-3312.
[37] *Unpublished Results* – Stephen Ammann
[38] Maruoka, K; Murase, N.; Bureau, R.; Ooi, T.; Yamamoto, H. *Tetrahedron*, **1994**, *50*, 3663-3672

Table 1. Epoxide Rearrangement Studies



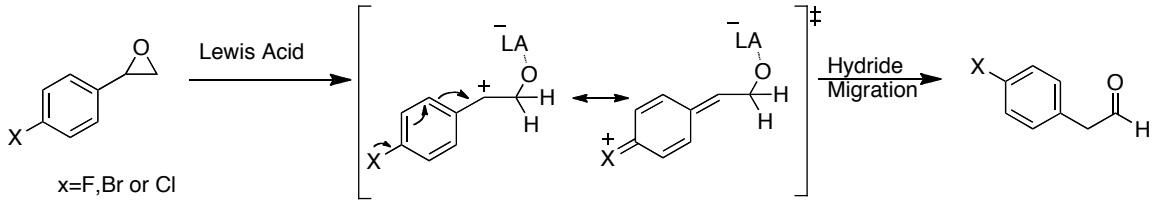
entry	epoxide	catalyst	product	Yield (%)[a]
1		0.1% $Bi(OTf)_3 \cdot 4H_2O$		92[b]
2		5% $Bi(OTf)_3$		99
3		1% TfOH		95
4		1% TfOH		*
5		0.1% $Bi(OTf)_3$ $4H_2O$		*
6		0.1% $Bi(OTf)_3 \cdot 4H_2O$		89[b]
7		0.1% $Bi(OTf)_3 \cdot 4H_2O$		92[b]

[a] Isolated yields
[b] K.A. Bhatia et al., Tetrahedron Letters, 42, **2001**, 8129-8132
* GC/MS analysis showed conversion with aldol formation (Jacob P. Perkinson – *Unpublished Results*)

Each of the reactions shown in Table 1, proceeds in under 5 min, and any amount of dilution (0.5-0.1 mM) or reduction of temperature (0°C and -78°C) failed to slow the reaction rate. This made the study of kinetics impractical. However, when the same reaction was attempted using the milder $BiBr_3$, the ring opening/rearrangement proceeded, but much more slowly (5hr.) and rarely went to completion. Thus, even though this particular study was inconclusive with regard to whether bismuth mediates the reaction or acts solely as a source of TfOH as a catalyst, we were able to show that the production of TfOH *in situ* would indeed cause the reaction to proceed.

Interested in the limitations of the epoxide rearrangements, we expanded the reagents to commercially available halogenated styrene oxides. We hypothesized that these reagents would indeed undergo complete rearrangement to the aldehyde under mildly acidic conditions if the halogen were located at the *para* position. This would allow for stabilization of the carbocation through resonance, outweighing the inductive destabilization (Scheme 6).

Scheme 6. Rearrangement of Halogenated Epoxides

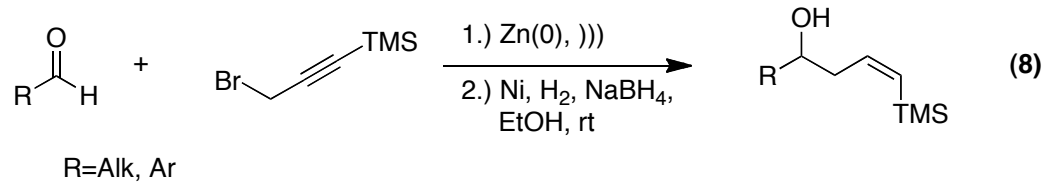


As anticipated, when subjected to 1 mol% of both TfOH and $Bi(OTf)_3$, bromophenyl oxirane and fluorophenyl oxirane showed complete transformation to the

desired aldehyde, along with the formation of aldol byproducts (identified by GC/MS analysis of crude reaction material).[39]

Synthesis of Vinyl Silanol Reagents

Thanks to the efforts of Shane E. Lewis and Jacob P. Perkinson, along with others, a rapid synthetic pathway was developed toward the desired (Z)-vinyl silanol used as reagents in the general synthesis of DHP's described herein (eq. 8).



(8)

Commercially available aldehydes were treated with propargyl bromide and zinc (0), providing the alcohol, which, after purification by flash chromatography, can easily be carried onto the next step. The subsequent reduction under nickel-catalyzed conditions (P-2 catalyst) affords the corresponding (*Z*)-vinyl silanol (Table 2). The reduction with nickel was chosen primarily because it produces excellent (Z):(E) ratios (≥95:5).[40] Also, this reduction method has a very low tendency to over-reduce to the alkane. The (Z) isomer was chosen based on previous work in intramolecular cyclizations and the work by Dobbs et al.[41] Mechanistic justification for this limitation will be discussed in the

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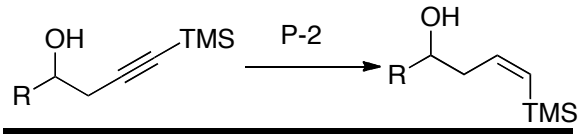
[39] *Unpublished Results* – Jacob P. Perkinson

[40] Semeyn, C.; Blaauw, R. H.; Hiemstra, H.; Speckamp, W. N. *J. Org. Chem*. **1997**, *62*, 3426−3427.

[41] Dobbs, A.P.; Guesné, S.J.J.; Martinovic, S.; Coles, S.J.; Hursthouse, M.B. *J. Org. Chem.* **2003**, *68*, 7880-7883.

following sections. Some of the substrate was protected with triethylsilane (using imidizole and TESOTf) while some was left as the free alcohol.

Table 2. Hydrogenation of Alkynyl Silanols



Entry	R	Yield[a]
1	CH_2CH_2Ph	81
2	*n*-Butyl	90
3	*n*-Ethyl	72
4	*n*-Heptyl	95
5	*p*-CF_3Ph	85
6	CH_2Cl	88

[a] Isolated yields of pure products

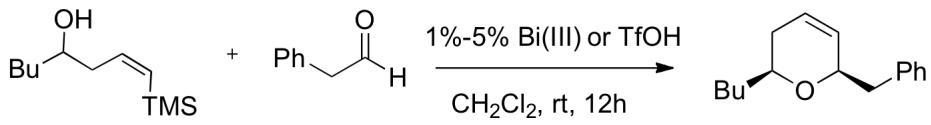
The scope of the synthesis allowed for successful, gram-scale production of starting material. Alkyl, aryl and even electron deficient aldehydes (entries 5 and 6) were tolerated, affording the desired vinylsilanol in excellent yield.

Comparison Studies

Prior to attempting the complete one pot synthesis, we again studied the effect of both catalyst loading and different catalysts on the tandem cyclization (Table 3). The free alcohol version of the vinylsilanol was added to the aldehydes resulting from the above-mentioned epoxide rearrangements, particularly phenylacetaldehyde, giving 6-benzyl-2-butyl-3,6-dihydro-2*H*-pyran as the product. Each reaction was carried out with both 1 mol% and 5 mol% catalyst. The following catalysts were chosen for comparison: TfOH,

$Bi(OTf)_3 \bullet 4H_2O$ (prepared in lab), $Bi(OTf)_3$ (anhydrous – commercially available), and $BiBr_3$. The catalysts were chosen from an interest in the catalytic mechanism. Triflic acid was chosen because of its likely production from the hydrolysis of bismuth triflate (eq. 4). Each time triflic acid was used (even at 0.01mol%); the product was formed in good yield. Additionally, the reaction proceeded smoothly with very little byproduct formation. Both the $Bi(OTf)_3 \bullet 4H_2O$ synthesized in this work and the commercially available $Bi(OTf)_3$ and that produced in laboratory gave moderate yields at 1 mol%. In addition, the product was produced along with the formation of unfavorable silane derived byproducts (i.e., TMS-O-TMS). Conversely, when catalyst loading was increased to 5 mol%, the synthesized bismuth triflate gave good isolated yield. This could be due to the formation of an increased amount of triflic acid produced *in situ* from hydrolysis of bismuth triflate.

Table 3. Comparison of Catalyst Loading on Tandem Reaction



catalyst	mol %	Yield (%)[a]
TfOH	1%	87
$Bi(OTf)_3 \bullet 4H_2O$	1%	45
$Bi(OTf)_3$	1%	50
$BiBr_3$	1%	61
TfOH	5%	82
$Bi(OTf)_3 \bullet 4H_2O$	5%	78
$Bi(OTf)_3$	5%	66
$BiBr_3$	5%	75

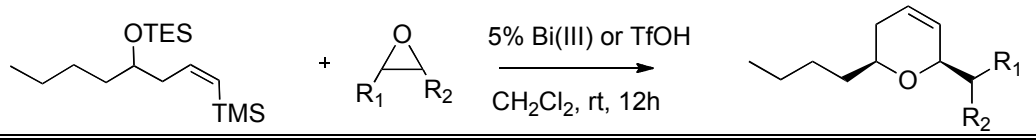
[a] Isolated yields of pure *cis*-isomers after flash chromatography

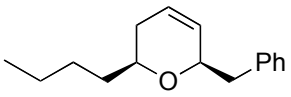
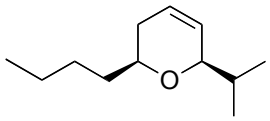
Interestingly, the commercial $Bi(OTf)_3$ still did not give a yield comparable to TfOH. $BiBr_3$ was also successful in generating product, which was consistent with our previously published results using this catalyst.[1] Clearly, this study points to $Bi(OTf)_3$ as an initiator of TfOH. Since even trace amounts of triflic acid can cause the reaction to proceed, it is plausible that the bismuth is only generating the catalyst (TfOH- Brønsted acid) in the reaction instead of acting as a Lewis acid. Consistent with that sentiment, the hydrated bismuth triflate gave better yields. We ran this reaction twice using diphenylacetaldehyde (product from rearrangement of *trans*-stilbene oxide). The first reaction was conducted with 5 mol% $Bi(OTf)_3 \bullet 4H_2O$, resulting in 52% yield of 6-benzhydryl-2-butyl-3,6-dihydro-2*H*-pyran with inseparable silane derivatives. Second, we attempted the same reaction with 5mol% $BiBr_3$ (39% yield). All products were also formed diastereoselectively with preference toward the *cis*-dihydropyran product.

After studying the two components of the reaction separately, we turned to the one-pot synthesis. Due to higher yields resulting from greater amounts of catalyst, we chose to run all reactions using 5mol%, once again trying each of the four catalysts for each substrate. First, we used the triethylsilane-protected vinylsilanols in the intramolecular silyl-modified Sakurai sequence. The results of these reactions are listed in Table 4. All of the reactions were run for 12 h at room temperature.

Due to the success of the previous reactions, isobutylene oxide was added as a new substrate. Surprisingly, each reaction afforded significantly decreased yield and a high percentage of inseparable silane byproducts. For the aforementioned reasons, we turned our attention to the free alcohol substrate.

Table 4. Epoxide Rearrangement Followed by ISMS Using TES - Protected Vinylsilanol



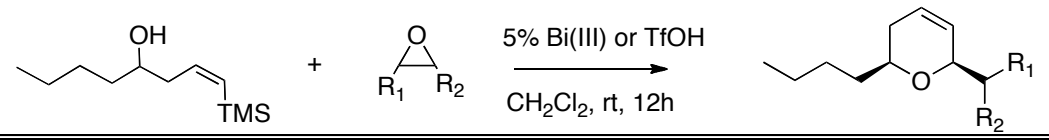
epoxide	product	catalyst	Yield (%)[a]
		TfOH	46
		$Bi(OTf)_3 \bullet 4H_2O$	56
		$Bi(OTf)_3$	45
		$BiBr_3$	NR[b]
		TfOH	70
		$Bi(OTf)_3 \bullet 4H_2O$	66
		$Bi(OTf)_3$	84
		$BiBr_3$	NR[b]

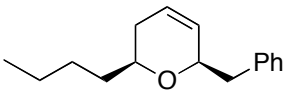
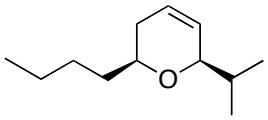
[a] Yields based on purified products that contain traces of inseparable silane derivatives.
[b] Desilylated alcohol recovered.

We expected that the unprotected vinylsilanols would produce less of the unwanted silane byproducts. Luckily, this was the case (Table 5) and any byproducts formed could be removed under reduced pressure (high vacuum 0.1-0.5 mm Hg). In addition, these substrates showed an increase in product yield when TfOH was used. However, there was no improvement in yield with any of the other catalysts. Not surprisingly, $BiBr_3$ failed to induce even the initial ring opening. After 12h, the reaction run with 5 mol% $BiBr_3$ had only formed bismuth oxides and the ^1H NMR spectrum showed only starting material. Clearly, $BiBr_3$ (or HBr) is not a strong enough catalyst to induce both the epoxide ring opening and the rearrangement giving the aldehyde needed for the ISMS. From the success of the TfOH catalyzed reaction in comparison with the low yields generated by both types of $Bi(OTf)_3$ one can once again hypothesize that

bismuth is acting solely as the initiator of a Brønsted acid which, in turn, promotes the reaction.

Table 5. Epoxide Rearrangement Followed by ISMS Using the Free Alcohol



epoxide	product	catalyst	Yield (%)[a]
		TfOH	78
		$Bi(OTf)_3 \bullet 4H_2O$	41
		$Bi(OTf)_3$	40
		$BiBr_3$	NR[b]
		TfOH	52
		$Bi(OTf)_3 \bullet 4H_2O$	59
		$Bi(OTf)_3$	44
		$BiBr_3$	NR[b]

[a] Isolated yields of pure *cis*-isomers after flash chromatography.
[b] Desilylated alcohol recovered.

In an effort to explore the nature of $Bi(OTf)_3$ in the overall reaction scheme, experiments were run with the desire to determine effects of hydrolysis of the Lewis acid and protodesilylation (Table 6).[42] Preliminary studies focused on the production of HBr and TfOH *in situ*.[43] Consistent with the hypothesis that the Lewis acid acts as a source of HX, which in turn functions as the catalyst or initiator, the use of 15 mol% 2,6-di-*tert*-

[42] Evans, P.A.; Cui, J.; Gharpure, J.S.; Hinkle, R.J. *J. Am. Chem. Soc.* **2003**, *125*, 11456-11457.
[43] Grimster, N.P.; Wilton, D.A.A.; Chan, L.K.M.; Godfrey, C.R.A.; Green, C.; Owen, D.R.; Gaunt, M.J. *Tetrahedron*, **2010**, *66*, 6429-6436.

butyl-4-methylpyridine (DTBMP) completely suppressed the reaction (entries 4,8).[44] DTBMP functions as an acid scavenger, neutralizing any HX formed in the reaction flask.[25] To understand the role of DTBMP after it had interacted with the acid, the protocol was attempted using DTBMP-TfOH as a mediator (entries 10-11). This resulted in no observable reaction. Next, we attempted to eliminate any adventitious water by running the reaction with both 3 and 4 Å sieves. This seemed to have no effect on the reaction, resulting in moderate yields. Unfortunately this contradicts the results of DTBMP. If the Lewis acid were producing the active catalytic species (HX) through hydrolytic interactions with adventitious H_2O, then presumably, both the sieves and acid scavenger would suppress the reaction. As this was not the case, a new hypothesis was adopted involving the production of HX *in situ* through interactions between the Lewis acid and the hydroxyl group on the vinyl silanol (Figure 3). This coordination results in the loss of a ligand (-X) by the bismuth compound as it initiates Lewis acidic interactions with the lone pairs of the hydroxyl. Consistent with the observed experimental results, sieves would have no effect on the reaction under this model, while DTBMP would neutralize any HX produced by any mechanism.

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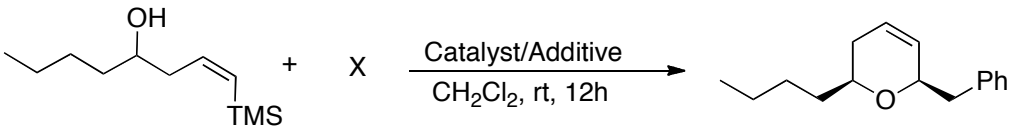
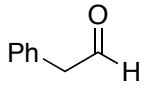
[44] Wabnitz, T.C.; Yu, J.; Spencer, J.B. *Chem Eur. J.* **2004**, *10*, 484-493.

Table 6. Elucidation of the Effects of HX Produced *in situ*

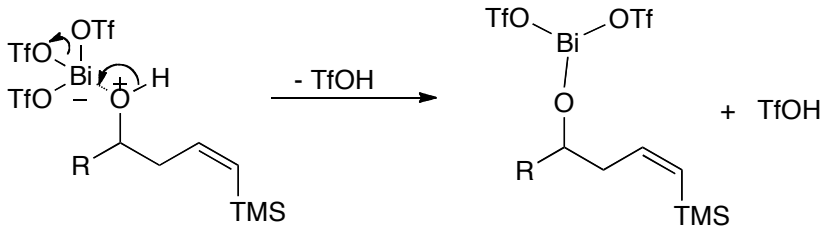


entry	X	catalyst	mol%	additive	(%) yield
1		$BiBr_3$	15	–	66
2		"	"	3Å sieves[a]	0
3		"	"	4Å sieves[a]	0
4		"	"	DTBMP[b]	0
5		$Bi(OTf)_3 \cdot nH_2O$	5	–	41
6		"	"	3Å sieves[a]	48
7	"	"	"	4Å sieves[a]	53
8	"	"	"	DTBMP[b]	0
9	"	$Bi(OTf)_3$	"	4Å sieves[a]	47
10	"	DTBMP•HOTf[c]	"	–	0
11	"	"	10	–	0
12	"	TfOH	"	–	78
13	"	TMSOTf	"	–	57

[a] activated by heating at 100 °C under reduced pressure.
[b] 15 mol % 4,6-di-*tert*-butyl-4-methylpyridine.
[c] 4,6-di-*tert*-butyl-4-methylpyridinium triflate.

This study also indicates that Bi(III) salts act only as the progenitor of the active catalyst. What is still unclear is whether the catalytic species is HX or TMSX, since TMSOTf does indeed catalyze the same reaction to afford products in moderate yields. Through GC/MS analysis, it was determined that 10 mol% TfOH, TMSOTf, $Bi(OTf)_3$ and $BiBr_3$ will all promote the desilylation of the olefin, presumably generating TMSBr or TMSOTf *in situ*. It was shown that 10 mol% TMSOTf also catalyzes the reaction to appreciable yield (entry 13). Further investigations are underway to determine the precise role of TMSOTf.

Figure 3. Production of TfOH

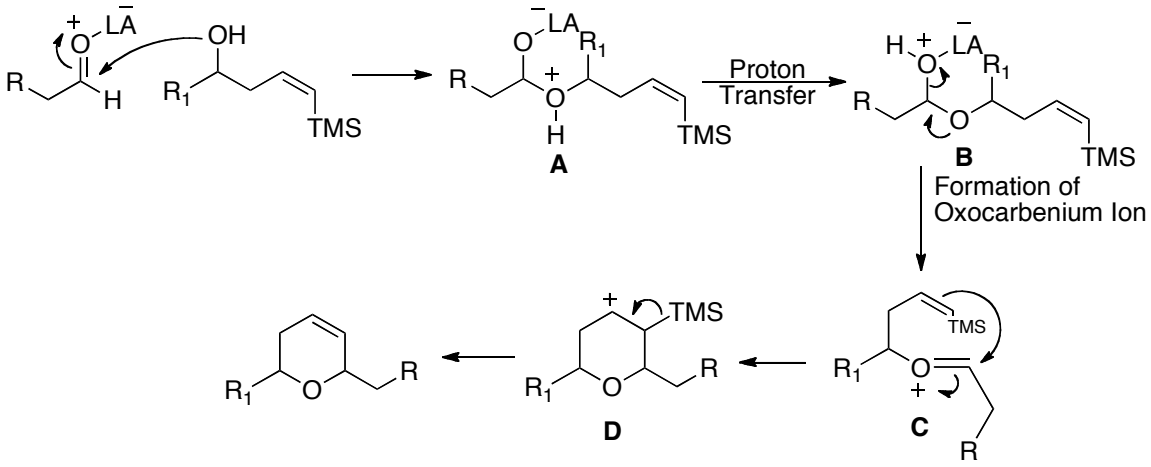


Mechanistic Considerations

The mechanism for cyclizations of this type – ISMS/Prins – has been well documented in the literature. Originally developed by Markó et al., the Intramolecular silyl-Modified Sakurai reaction offers a simple route to dihydropyran containing structures.[45] The basic mechanism, following the rearrangement of the epoxide, is initiated by nucleophilic attack of the carbonyl carbon by the hydroxyl on the vinyl silane to produce intermediate **A** and proton transfer affords **B** (Scheme 7). Elimination of water drives the formation of the oxocarbenium ion intermediate, **C**. This integral pseudo-6 membered intermediate allows for attack by the π electrons of the olefin to afford a tetrahydropyranyl cation, **D**. Finally, elimination of the trimethylsilane provides the dihydropyran.

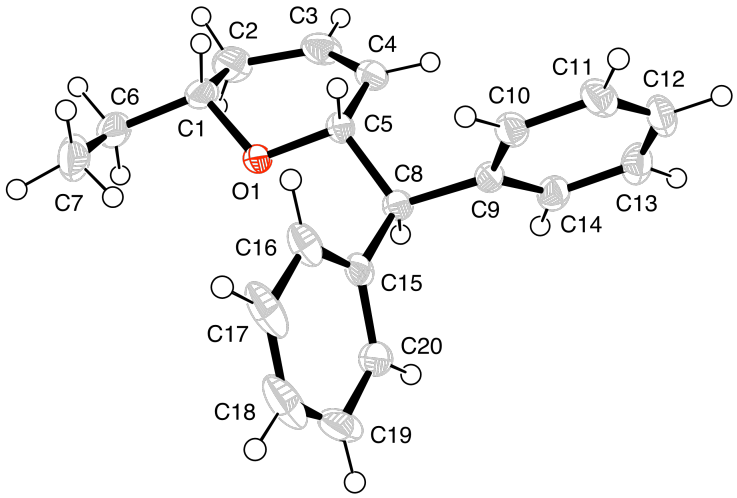
[45] Markó, I.E.; Mekhalfia, A.; Bayston, D.J.; Adams, H. *J. Org. Chem.* **1997**, *57*, 2211-2213.

Scheme 7. ISMS/Prins Mechanism



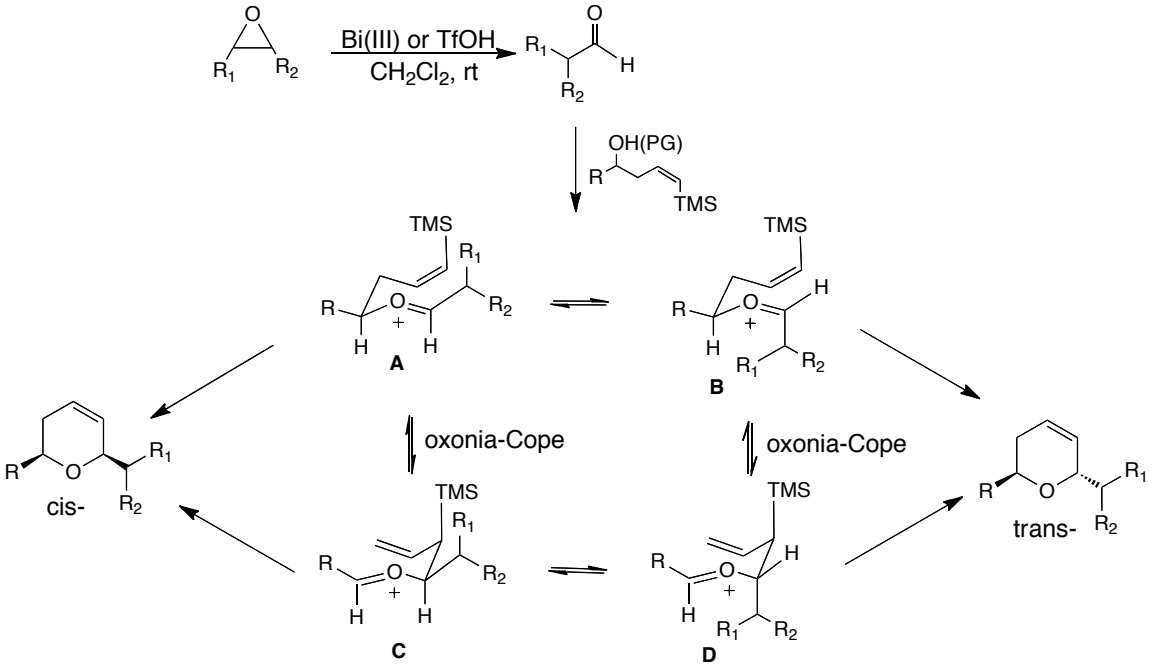
Relative stereochemistry resulting from the cyclization was excellent. Only the *cis* diastereomer was observed in both GC/MS and ^{1}H NMR analysis of crude reaction mixtures. Stereochemistry was further confirmed by X-ray crystallographic analysis of isolated product (Figure 4).

Figure 4. X-ray Crystal Structure of *cis*-DHP (Table 7 entry 11)



This structure shows that both substituents on the ring are in the favored pseudo-equatorial position, eliminating diaxial interactions within the ring. The diastereoselectivity supports the findings of Dobbs and coworkers.[46] In a 2002 publication of a silyl-Prins methodology toward dihydropyrans, Dobbs reports finding no evidence of the formation of *trans*-diastereomers in crude reaction mixtures.[46] Generally, the *cis*-steroselectivity can be explained by the formation of the *(E)*- oxocarbenium ion (Scheme 8). In order to eliminate diaxial interactions, both of the groups adjacent to the heteroatom orient themselves in pseudo-equatorial positions. Stabilization of the β-silyl cation that forms subsequent to cyclization drives the axial positioning of the TMS moiety. As a result of favorable p-orbital overlap, the axial orientation allows for far greater cationic stabilization than if the silane were in an equatorial conformation.[1]

Scheme 8. Justification of *cis*-Stereochemistry



[46] Dobbs, A.P.; Martinovic, S. *Tetrahedron Lett.* **2002**, *43*, 7055-7057.

The formation of an oxocarbenium ion facilitates the assembly of a pseudo-6-membered transition state. The transition state allows for [3,3] sigmatropic oxonia-Cope rearrangements forming C.[47] Cyclization of either **A** or **C** affords the *cis*-diastereomer, both products forming through the same β-silyl cation. Intermediates **B** and **D** show the formation of a *(Z)*-oxocarbenium ion in which one of the substituents flanking the oxygen is placed in the unfavorable pseudoaxial position.[1]

Reaction Scope

Pleased with the preliminary studies involving the overall methodology, we attempted to show the utility of the protocol by testing a variety of substrates under the reaction conditions (Table 7). We were encouraged that both aryl and alkyl vinyl silanes were tolerated. The epoxides tested were limited by stabilization of the cation as mentioned in the discussion of epoxide rearrangements. Even with this limitation, both aryl and alkyl epoxides could be used. Yields range from moderate to good and diastereoselectivities were excellent for each product. Only the *cis* diastereomer was identified through both ^{1}H NMR and GC/MS analysis of crude reaction mixtures. Overall yields comparing 5% $Bi(OTf)_3$ and 10% TfOH were comparable across the spectrum of reagents tested. This supports the hypothesis outlined above – Bismuth triflate acts as a source of TfOH.

Although the substrates examined all resulted in the desired product, the yields overall were lower than expected. Low yields and high ratios of reaction byproducts

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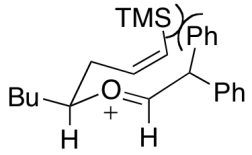
[47] Jasti, R.; Rychnovsky, S.D. *J. Am. Chem. Soc.* **2006**, *128*, 13640-13648.

prompted the examination of crude reaction mixtures to determine the complications. We began with the substrate that resulted in the lowest yields: *trans*-stilbene oxide. Despite the rapidity of the rearrangement, this epoxide afforded low yields of DHP products regardless of the vinyl silanol with which it was reacted. The low yields can be explained by steric hindrance within the intermediate (Figure 5). The silyl group tethered to the olefin on the vinyl silane would be close in space to one of the phenyl rings bonded to the oxocarbenium ion. Steric interaction could impede the formation of the oxocarbenium ion. This could result in a variety of side reactions including the degradation of starting material. Further investigation into the precise reason behind this limitation is necessary.

Figure 5. Proposed Steric Hindrance Limiting the Transformation of *trans*-Stilbene Oxide to the Desired DHP Product

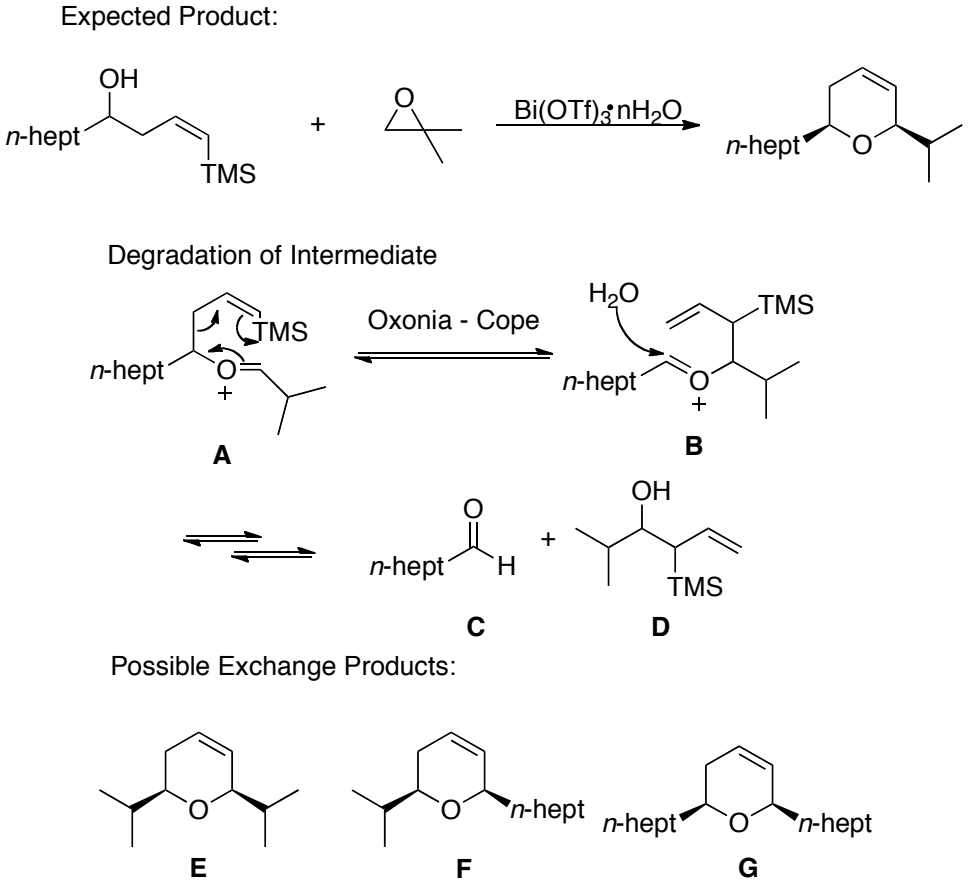


We were next able to identify the source of one side reaction that leads to decreased yield of desired product (Scheme 9). Entry 13 (Table 7) resulted in an inseparable mixture of desired product and 7. Rychnovsky et al. recently described the fragmentation of the pseudo-6 membered transition state produced by the formation of the oxocarbenium ion.[48] Immediately following the formation of the oxocarbenium ion, there is competition between the π electrons of the olefin and other molecules with

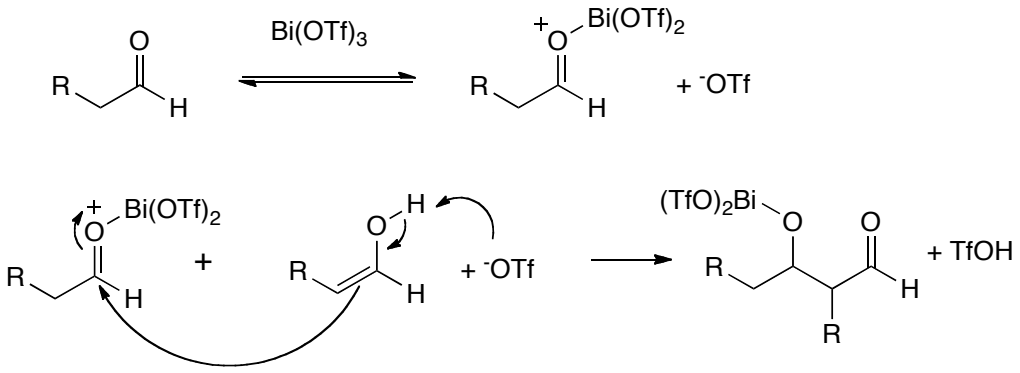
[48] Jasti, R; Rychnovsky, S.D. Org. Lett., **2006**, *10*, 2175-2178.

nucleophilic character (such as adventitious H_2O) for attack of the electrophilic oxocarbenium ion. Attack of the olefinic π electrons affords the desired product while attack by H_2O would result in the regeneration of the starting material. However, intramolecular Oxonia-cope rearrangement of the transition facilitates the degradation of the transition state. This fragmentation causes the formation of new aldehyde and vinyl silanol precursors. New fragments can then undergo a Prins cyclization affording two novel DHP's (**E** and **G**). GC/MS analysis of pure DHP product subjected to catalyst and alkyl substituted aldehydes showed no rearrangement or side-chain exchange. Therefore, once the cyclization is complete, the fragmentation is halted.

Scheme 9. Oxocarbenium Ion Fragmentation

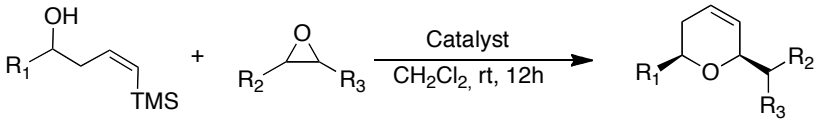


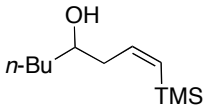
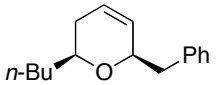
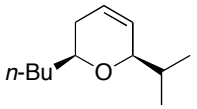
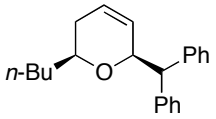
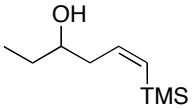
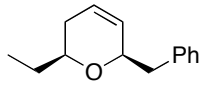
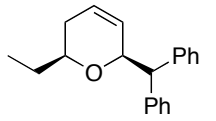
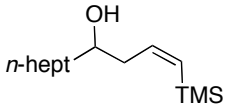
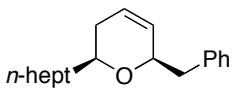
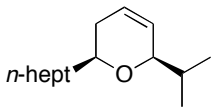
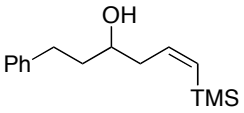
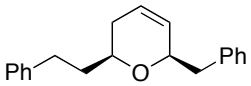
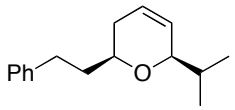
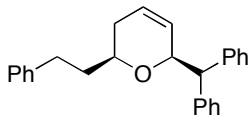
Scheme 10. Formation of Aldol Byproducts



Finally, from the initial epoxide rearrangement study, the production of aldol adducts *in situ* was expected (Scheme 10). This was compensated for by the addition of 2.0 equivalents of epoxide. Along with the production of an unwanted byproduct, aldol formation releases TfOH into the reaction pot. This is yet another source of Brønsted acid. Although a limitation to the overall scheme, we argue that the addition of epoxides is worthwhile because of their greater stability in comparison to aldehydes. Aldehydes have a susceptibility to both aldol formation and oxidation to carboxylic acids over time. The use of aldehydes in organic reactions often requires distillation of the reagant prior to its use in order to remove impurities such as aldol products. There are far fewer of such concerns with the use of epoxides since they cannot undergo aldol reactions nor can they be further oxidized. Ease of use makes epoxides an attractive alternative to aldehyde precursors.

Table 7. Synthesis of 2,6-Disubstituted-3,4-Dihydropyrans



entry	vinylsilane	epoxide	product	yield(%)[a,b]	yield(%)[a,c]
7				56	58
8				66	70
9				31	27
10				53	50
11				28	29
12				59	ND[g]
13				57[e]	65[e]
14				NR[f]	62
15				ND[g]	60
16				ND[g]	NR[f]

[a] All the reactions were carried on 0.5 mmol scale in 5.0 mL CH_2Cl_2 at room temperature using 2.0 equiv of the corresponding aldehyde. Isolated yield of pure *cis*-isomers only, after flash column chromatography.
[b] 5% $Bi(OTf)_3$.
[c] 10% TfOH.
[d] Diastereomeric ratios were determined by ^1H NMR analysis of crude reaction mixtures.
[e] 8/2 mixture of product and inseparable 2,6-diheptyl-3,6-dihydro-2H-pyran.
[f] Trace product identified by ^1H NMR analysis of crude reaction mixtures.
[g] Yields for this entry were not determined.

Interested in the biological implications of these small molecules, we next moved toward the elaboration of the central motif. Gribble outlines the expanding utility of organohalogens.[49] Recent increase in discoveries of organohalogen natural products suggests a novel source of bio-molecules with medicinal properties. Contrary to the former belief that organohalogens are found infrequently in living organisms, today more than 3800 halogenated organic molecules have been discovered.[49] While most biologically produced organohalogens are found in marine-life, a wide variety of organisms actually produce these molecules. Plants, bacteria, insects and even humans produce halogen derivatized organic molecules.

Of these molecules, many are showing promise as drug candidates. Cryptophycin A, isolated from green algae, is a particularly potent anti-cancer drug candidate.[49] Additionally, for many of these molecules, the halogens play an active role in the biological mechanism. For example, it was shown by Kubanek et al. that removal of all bromines on the carbon backbone of bromophycolides results in the elimination of any measurable cytotoxicity.[50] Many have shown biological properties such as antimalarial, antibacterial, antitubercular, anticancer, and antifungal activity.[51] Due to the rise in research attention in the field of organohalogens because of their biological activity, and the success of the initial rearrangments of the halogenated epoxides, we expanded our protocol to include both these epoxides and halogenated vinyl silanes (Table 8).

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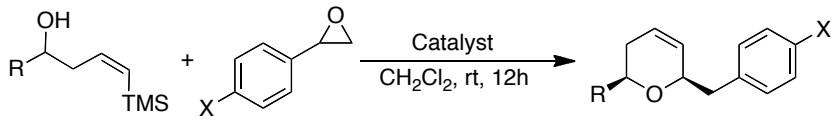
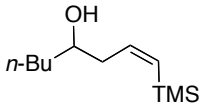
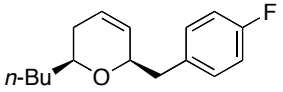
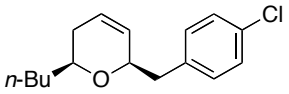
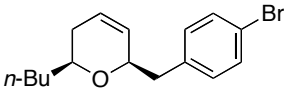
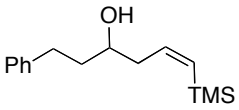
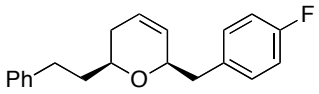
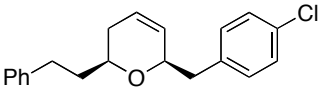
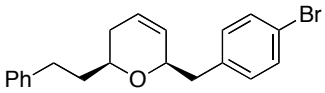
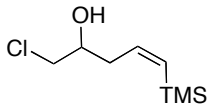
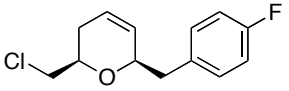
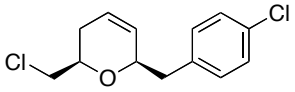
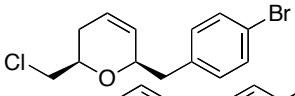
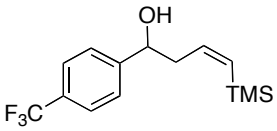
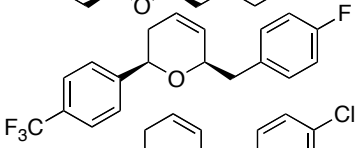
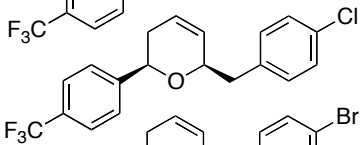
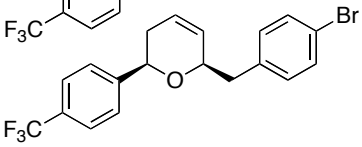
[49] Gribble, G.W. *Chemosphere* **2003**, *52*, 289-297.
[50] Kubanek, J.; Prusak, A.C.; Snell, T.W.; Giese, R.A.; Fairchild, G.R.; Aalbersberg, W.; Hay, M.E. *J. Nat. Prod.* **2006**, *69*, 731-735
[51] Lin, A.; Stout, E.P., Prudhomme, J.; Le Roch, K.; Fairchild, C.R.; Franzblau, S.G.; Aalbersberg, W.; Hay, M.E.; Kubanek, J. *J. Nat. Prod.* **2010**, *73*, 275-278.

The application of halogens to the overall scheme resulted in poor to moderate yields. Not surprisingly, simple alkyl side chains (entries 16-18) afforded the best yields with both 5% $Bi(OTf)_3$ and 10% TfOH. Unfortunately, entries 19-27 gave only trace product formation when catalyzed by $Bi(OTf)_3$. Entries 22-27 failed to convert to any appreciable amount under either catalytic condition. The destabilizing effect of the electron-withdrawing groups on either side of the oxocarbenium ion explains the disappointing yields for these entries.

Table 8. Halogenated Dihydropyran Derivatives



entry	vinylsilane	X	product	yield(%)[a,c]	yield (%)[a,d]
16		F		47	45
17		Cl		49	50
18		Br		41	46
19		F		<10[e]	60
20		Cl		<10[e]	56
21		Br		<10[e]	53
22		F		<10[e]	<25
23		Cl		<10[e]	<19
24		Br		NR[e]	<10
25		F		NR[e]	<10[f]
26		Cl		NR[e]	<10[f]
27		Br		NR[e]	<10[f]

[a] All the reactions were carried on 0.5 mmol scale in 5.0 mL CH_2Cl_2 at room temperature using 2.0 equiv of the corresponding aldehyde. Isolated yield of pure *cis*-isomers only, after flash column chromatography.

[c] 5% $Bi(OTf)_3$.

[d] 10% TfOH.

[e] trace product identified by both GC/MS and NMR analysis of crude reaction - evidence of startng material, desilylation and aldol formation.

[e] Perkinson, J.P., *Unpublished results.*

Conclusion and Future Direction

We have successfully developed a simple, one-pot synthesis of *cis*-dihydropyrans using catalytic quantities of $Bi(OTf)_3$. Following the push toward environmentally friendly synthetic methods, we further showed the utility and convenience of using bismuth salts to mediate organic transformations. Although yields sometimes were sometimes lower than those produced by triflic acid and trimethylsilyl-triflate, the limitation was outweighed by its ease of use. The harsh, corrosive nature of both TfOH and TMSOTf make them extremely cumbersome to use and dangerous for the environment.

In an effort to promote the use of bismuth catalysts, we investigated the catalytic role they play in such reactions. Interestingly, it was determined that BiX_3 compounds act as progenitors of the true catalytic species. Investigations toward the identity of the catalytic species are currently underway. Both NMR and FTIR techniques are being used to better understand the nature of the catalyst. Attempts will be made to determine whether solely TfOH or TMSOTf or a combination of both is promoting the cyclization.

With an interest in the activity of natural products containing cyclic ethers in mind, our group would like to test the activity of the small molecules described herein. We hope that the library of disubstituted dihydropyrans synthesized in the course of developing this methodology with show interesting biological activity against malicious diseases such as malaria, cancer and osteoporosis. It would also be beneficial to show the utility of this scheme in the synthesis of a small natural product.

Experimental Section

All reagents and substrates were used as received unless otherwise noted. Solvents used include dichloromethane (distilled from CaH_2), anhydrous diethyl ether (purchased from Fisher Scientific), and anhydrous ethanol (purchased from Aaper Alcohol). Isobutylene oxide, *trans*-stilbene oxide, nickel acetate and trifluoromethane-sulfonic acid (TfOH) were purchased from Acros Organics, Inc. Bismuth bromide, bismuth triflate, styrene oxide, 2-(4-fluorophenyl)-oxirane, 2-(4-chlorophenyl)-oxirane, 2-(4-bromophenyl)-oxirane were purchased from Aldrich Chemical Company, Inc. Trimethylsilyl-trifluoromethansulfonic acid was obtained from GFS Chemicals, Inc. Bismuth triflate tetrahydrate ($Bi(OTf)_3 \bullet 4H_2O$) was also synthesized in house, from triflic acid and triphenylbismuth(purchased from Gelest, Inc.).[12] (Z)-1-(4-(trifluoromethyl)-phenyl)-4-(trimethylsilyl)but-3-en-1-ol, (*Z*)-6-(trimethylsilyl)hex-5-en-3-ol, (*Z*)-1-(trimethylsilyl)oct-1-en-4-ol, (Z)-1-(trimethylsilyl)undec-1-en-4-ol were prepared in house by Jacob P. Perkinson and Shane E. Lewis. ^{13}C NMR spectra were recorded with the aid of an APT experiment in which methylene (2 H) and quaternary carbons (0 H) are even (e) and methyl (3 H) and methane (1 H) carbons are odd (o). Coupling constants were determined by the method outlined by Hoye, et al.[3] and relative stereochemistry was established by x-ray crystallography. Thin layer chromatography was performed on Sorbent Technologies general-purpose silica gel on glass. Flash column chromatography was performed using Sorbent Technologies chromatographic silica gel (200-475 MESH) and through the use of Biotage - Isolera One flash purification system. Unless otherwise

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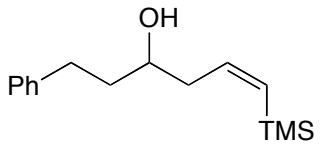
[1] Labrouillere, M.; Le Roux, C.; Gaspard, H.; Laporterie, A.; Dubac, J.; Desmurs, J. R. *Tetrahedron Lett.* **1999**, *40*, 285-286.
[2] Repichet. S.; Zwick. A.; Vendier, L.; Le Roux. C.; Dubac, J. *Tetrahedron Lett*. **2002**, *43*, 993-995.
[3] Hoye, T. R.; Zhao, H. *J. Org. Chem.* **2002**, *67*, 4014-4016.

noted, all experiments were conducted under argon atmosphere. All compounds were judged to be >95% homogeneous by ^{1}H NMR spectroscopy.

General procedure of hydrogenation

The following reactions were carried out under hydrogen. $Ni(OAc)_2 \cdot H_2O$ (1.0 equiv) was added to degassed EtOH and stirred for 5 minutes with hydrogen balloon sparging. After the addition of a solution of 0.539M $NaBH_4$ (2.5 equiv) and 0.097 NaOH, the solution was stirred for 5 more minutes under continuous hydrogen sparging. TMS-alkyne-ol (5.0 equiv) was injected after adding ethylenediamine (5-12 drops). The solution was stirred for 4 hours under hydrogen. To the completed reaction, 2-5 scoops of activated carbon were added along with excess EtOH. The solution was then filtered over celite and concentrated *in vacuo*. The reaction was then washed with brine (4×50 mL) and back-extracted with diethyl ether (3×50 mL), followed by drying over $MgSO_4$. The combined organic layers concentrated *in vacuo* to afford the desired product, which was sufficiently pure to carry on to subsequent reactions.

Preparation of (*Z*)-1-phenyl-6-(trimethylsilyl)hex-6-en-3-ol (Table 2, entry 1)

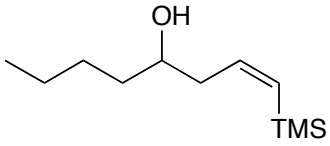


Chemical Formula: $C_{15}H_{24}OSi$
Exact Mass: 248.16
Mol. Wt.: 248.44
C, 72.52; H, 9.74; O, 6.44; Si, 11.30

According to the general procedure, 1-phenyl-6-(trimethylsilyl)hex-5-yn-3-ol (1.38 g, 5.6 mmol, 5.0 equiv) was treated with $Ni(OAc)_2 \cdot H_2O$ (0.28 g, 1.12 mmol, 1.0 equiv), 0.539M

$NaBH_4$ (5.21 mL, 2.8 mmol, 2.5 equiv) and ethylenediamine (10 drops) to afford 1.13 g (81%) of pure TMS-alkene-ol as a pale yellow oil.); IR (neat) 3353(s), 3023(s), 2954(s), 1604(s), 1496(s), 1454(s), 1248(s), 1053(m), 834(m), 763(s), 698(s) cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ 7.10 – 7.25 (m, 5H), 6.25 (m, 1H), 5.64 (dt, *J* = 14.1, 1.2 Hz, 1H), 3.63 (m, 1H), 2.57 – 2.81 (m, 2H), 2.20 – 2.35 (m, 2H), 1.67 – 1.80 (m, 2H), 1.56(m, 1H) 0.07 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.2 (o), 142.2(e), 133.4(o), 128.6(o), 126.0(o), 70.7(o), 41.5(e), 38.7(e), 32.3(e), 0.5(o).

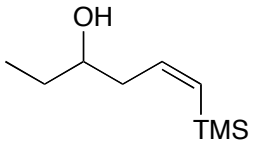
Preparation of (*Z*)-1-(trimethylsilyl)oct-1-en-4-ol (Table 2, entry 2)



Chemical Formula: $C_{11}H_{24}OSi$
Exact Mass: 200.16
Mol. Wt.: 200.39
C, 65.93; H, 12.07; O, 7.98; Si, 14.02

According to the general procedure, 1-(trimethylsilyl)oct-1-yn-4-ol (1.35 g, 6.9 mmol, 5.0 equiv) was treated with $Ni(OAc)_2 \cdot H_2O$ (0.34 g, 1.38 mmol, 1.0 equiv), 0.539M $NaBH_4$ (6.4 mL, 3.45 mmol, 2.5 equiv) and ethylenediamine (7 drops) to afford 1.23 g (90%) of pure TMS-alkene-ol as a pale yellow oil. IR (neat) 3371(s), 2957(s), 2931(s), 2861(m), 1607(s), 1409(s), 1380(s), 1249(s), 1040(s), 858(s), 838(s), 763(s). ^1H NMR (400 MHz, $CDCl_3$) δ 6.33 (1H, ddd, *J* = 14.4, 7.2, 7.2 Hz), 5.71 (1H, d, *J* = 14 Hz), 3.63-3.72 (1H, m), 2.25 – 2.39 (2H, m), 1.24 – 1.55 (6H, m), 0.90 (3H, t, 6.0 Hz), 0.15 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.5(o), 133.0(o), 71.5(o), 41.6(e), 37.0(e), 28.2(e), 23.1(e), 14.4(o), 0.7(o).

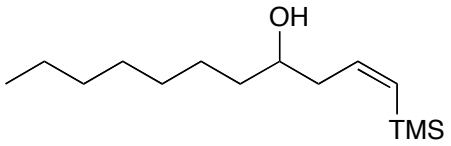
Preparation of (*Z*)-6-(trimethylsilyl)hex-5-en-3-ol (Table 2, entry3)



Chemical Formula: $C_9H_{20}OSi$
Exact Mass: 172.13
Mol. Wt.: 172.34
C, 62.72; H, 11.70; O, 9.28; Si, 16.30

According to the general procedure, 6-(trimethylsilyl)hex-5-yn-3-ol (2.28 g, 13.40 mmol, 5.0 equiv) was treated with $Ni(OAc)_2 \cdot H_2O$ (0.67 g, 2.68 mmol, 1.0 equiv), 0.539M $NaBH_4$ (12.43 mL, 6.70 mmol, 2.5 equiv) and ethylenediamine (7 drops) to afford 1.67 g (72%) of pure TMS-alkene-ol as a pale yellow oil. IR (neat) 3375(s), 2964(s), 2929(s), 2865(m), 1601(s), 1355(s), 1250(s), 1040(s), 858(s), 840(s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.33 (quint. *J* = 7.2 Hz, 1H), 5.66 (dt, *J* = 14.0, 1.2 Hz, 1H), 3.50-3.62 (m, 1H), 2.25 – 2.39 (m, 2H), 1.79 (s, 1H), 1.37 – 1.59 (m, 2H), 0.95 (t, 7.4 Hz, 3H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.7(o), 132.8(o), 72.8(o), 40.9(e), 29.9(e), 10.2(o), 0.4(o).

Preparation of (Z)-1-(trimethylsilyl)undec-1-en-4-ol (Table 2, entry 4)



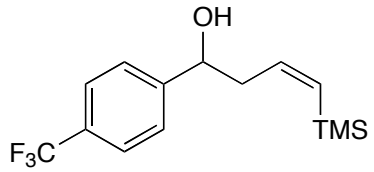
Chemical Formula: $C_{14}H_{30}OSi$
Exact Mass: 242.21
Mol. Wt.: 242.47
C, 69.35; H, 12.47; O, 6.60; Si, 11.58

According to the general procedure, 1-(trimethylsilyl)undec-1-yn-4-ol (2.00 g, 8.32 mmol, 5.0 equiv) was treated with $Ni(OAc)_2 \cdot H_2O$ (0.41 g, 1.66 mmol, 1.0 equiv), 0.539M

$NaBH_4$ (7.72 mL, 4.16 mmol, 2.5 equiv) and ethylenediamine (12 drops) to afford 1.91 g (95%) of pure TMS-alkene-ol as a pale yellow oil. IR (neat) 3380(s), 2961(s), 2931(s), 2865(m), 1345(s), 1250(s), 872(s), 834(s). ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.34 (quint., *J* = 7.4 Hz, 1H), 5.68 (d, *J* = 14.1 Hz, 1H), 3.44-3.76 (m, 1H), 2.22 – 2.39 (m, 2H), 1.60(s, 1H), 1.10 – 1.50 (m, 12H), 0.88 (t, 6.4 Hz, 3H), 0.15 (9H, s); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6(o), 133.0(o), 71.5(o), 41.5(e), 37.2(e), 32.0(e), 29.8(e), 29.5(e), 25.9(e), 22.9(e), 14.3(o), 0.5(o).

Preparation of (Z)-1-(4-(trifluoromethyl)phenyl)-4-(trimethylsilyl)but-3-en-1-ol

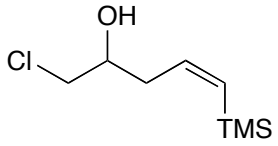
(Table 2, entry 5)



Chemical Formula: $C_{14}H_{19}F_3OSi$
Exact Mass: 288.12
Mol. Wt.: 288.38
C, 58.31; H, 6.64; F, 19.76; O, 5.55; Si, 9.74

According to the general procedure, 1-(4-(trifluoromethyl)phenyl)-4-(trimethylsilyl)but-3-yn-1-ol (3.12g, 10.9 mmol, 5.0 equiv) was treated with $Ni(OAc)_2{\cdot}H_2O$ (0.55 g, 2.20 mmol, 1.00 equiv), 0.539M $NaBH_4$ (10.2 mL, 5.50 mmol, 2.5 equiv) and ethylenediamine (12 drops) to afford 2.68 g (85%) of pure TMS-alkene-ol as a pale yellow oil. IR (neat) 3365(br), 2958(vs), 2898(s), 1923(m), 1621(s), 1418(s), 1166(s), 836(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (dd, *J* = 47.7, 8.0 Hz, 4H), 6.31 (td, *J* = 14.0, 7.4 Hz, 1H), 5.76 (d, *J* = 14.1 Hz, 1H), 4.80 (t, *J* = 6.4 Hz, 1H), 2.56 (t, *J* = 7.2 Hz, 2H), 2.29 (s, 1H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.0(e), 143.0(o), 134.5(o), 130.0(e), 126.3(o), 125.6(o), 123.0(e), 73.2(o), 43.4(e), 0.3(o).

Preparation of (*Z*)-1-chloro-5-(trimethylsilyl)pent-4-en-2-ol (Table 2, entry 6)



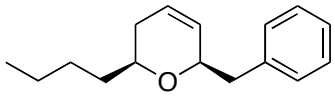
Chemical Formula: $C_8H_{17}ClOSi$
Exact Mass: 192.07
Mol. Wt.: 192.76
C, 49.85; H, 8.89; Cl, 18.39; O, 8.30; Si, 14.57

According to the general procedure, 1-chloro-5-(trimethylsilyl)pent-4-yn-2-ol (1.59 g, 8.3 mmol, 5.0 equiv) was treated with $Ni(OAc)_2 \cdot H_2O$ (0.41 g, 1.7 mmol, 1.0 equiv), 0.539M $NaBH_4$ (7.75 mL, 4.18 mmol, 2.5 equiv) and ethylenediamine (9 drops) to afford 1.417 g (88%) of pure TMS-alkene-ol as a pale yellow oil. IR (neat) 3398(m), 2956(s), 2898(s), 1608(m), 1430(s), 1250(m), 839(m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 6.30 (td, *J* = 14.3, 7.3 Hz, 1H), 5.65 (dt, *J* = 14.0, 1.5 Hz, 1H), 3.85-3.93 (m, 1H), 3.65 (dd, *J* = 7.3, 3.7 Hz, 1H), 3.51 (dd, *J* = 6.8, 4.4 Hz, 1H), 2.40-2.46 (m, 2H), 2.19 (d, *J* = 4.4 Hz, 1H), 0.14 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6(o), 133.9(o), 71.3 (o), 49.9(e), 38.2(e), 0.4(o).

General procedure for the synthesis of dihydropyrans:

Catalyst (TfOH, TMS-OTf, $BiOTf_3$, $BiBr_3$ – 0.010-0.050 equiv) was weighed into 15 mL round bottom flask and 5 mL CH_2Cl_2 was added via syringe. The solution was cooled to 0 ^oC using an ice water bath. Vinylsilane (1.0 equiv) and epoxide (1.1-2.0 equiv) were added sequentially. The mixture was warmed to rt slowly. After stirring for 12 h, the solution was filtered through a small SiO_2 pipette column with CH_2Cl_2 as eluent and concentrated *in vacuo* again. The product was then purified by column chromatography.

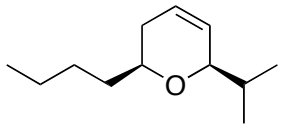
Preparation of *cis*-6-benzyl-2-butyl-3,6-dihydro-2H-pyran (Table 7, entry 7)



Chemical Formula: $C_{16}H_{22}O$
Exact Mass: 230.17
Mol. Wt.: 230.35
C, 83.43; H, 9.63; O, 6.95

According to the general procedure, (*Z*)-1-(trimethyl silyl)oct-1-en-4-ol, (0.100 g, 0.50 mmol, 1.00 equiv) was treated with styrene oxide (0.120 g, 1.00 mmol, 2.0 equiv) to provide 0.067 g (58%) of *cis*-isomer as a colorless oil, after purification by column chromatography (95:5 petroleum ether:ethyl ether, R_f = 0.57): IR (neat) 3029(m), 2955(s), 2929(s), 2860(m), 1454(m), 1184(m), 1085(s), 1064(s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.18-7.31 (m, 5H), 5.76-5.81 (m, 1H), 5.61 (dm, *J* = 10.3 Hz, 1H), 4.31 (m, 1H), 3.48-3.54 (m, 1H), 2.99 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.68 (dd, *J* = 13.5, 7.0 Hz, 1H), 1.92-1.98 (m, 2H), 1.22-1.64 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.5(e), 129.7(o), 129.4(o), 128.2(o), 126.2(o), 125.2(o), 76.0(o), 74.3(o), 42.3(e), 36.1(e), 31.6(e), 28.0(e), 23.1(e), 14.5(o); Anal. calcd. For $C_{16}H_{22}O$ (230.35): C 83.43, H 9.63; Found: C 83.51, H 9.67.

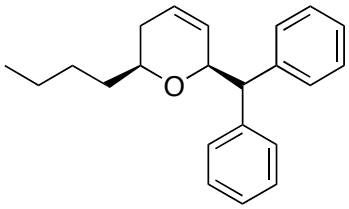
Preparation of *cis*-2-butyl-6-isopropyl-3,6-dihydro-2H-pyran (Table 7, entry 8)



Chemical Formula: $C_{12}H_{22}O$
Exact Mass: 182.17
Mol. Wt.: 182.30
C, 79.06; H, 12.16; O, 8.78

According to the general procedure, (*Z*)-1-(trimethylsilyl) oct-1-en-4-ol, (0.100 g, 0.500 mmol, 1.00 equiv) was treated with isobutylene oxide (0.072 g, 1.00 mmol, 2.0 equiv) to provide 0.057 g (63%) of *cis*-isomer as a colorless oil, after purification by column chromatography (95:5 petroleum ether:ethyl ether, R_f = 0.62): IR (neat) 3031(m), 2957(s), 2929(s), 2868(s), 1465(m), 1366(m), 1185(m), 1080(s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80-5.85 (m, 1H), 5.66 (dq, *J* = 10.3, 1.5 Hz, 1H), 3.84-3.88 (m, 1H), 3.44-3.51 (m, 1H), 1.90-1.94 (m, 2H), 1.71-1.79 (dq, *J* = 6.6, 5.5 Hz, 1H), 1.25-1.60 (m, 6H), 0.93 (d, *J* = 5.5 Hz, 3H), 0.92 (d, *J* = 5.5 Hz, 3H), 0.90(t, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.6(o), 125.6(o), 79.8(o), 74.0(o), 36.2(e), 33.0(o), 31.8(e), 28.1(e), 23.1(e), 18.3(o), 14.5(o); Anal. calcd. For $C_{12}H_{22}O$ (182.30): C 79.06, H 12.16; Found: C 79.06, H 12.22.

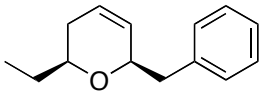
Preparation of *cis*-6-benzhydryl-2-butyl-3,6-dihydro-2H-pyran (Table 7, entry 9)



Chemical Formula: $C_{22}H_{26}O$
Exact Mass: 306.20
Mol. Wt.: 306.44
C, 86.23; H, 8.55; O, 5.22

According to the general procedure, (*Z*)-1-(trimethyl-silyl)oct-1-en-4-ol, (0.100 g, 0.500 mmol, 1.00 equiv) was treated with *trans*-stilbene oxide (0.108 g, 0.55 mmol, 1.1 equiv) to provide 0.047 g (31 %) of *cis*-isomer as a colorless powder, after purification by column chromatography (95:5 petroleum ether:ethyl ether, R_f = 0.43); IR (neat) 3060(m), 3026(m), 2954(s), 2926(s), 2858(s), 1599(m), 1495(s), 1451(s), 1369(m), 1187(m), 1094(s), 745(s), 699(s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.13-7.37 (m, 10H), 5.74-5.78 (m, 1H), 5.55 (dq, *J* = 10.3, 1.5 Hz, 1H), 4.78-4.83 (m, 1H), 3.97 (d, *J* = 8.4 Hz, 1H), 3.52-3.59 (m, 1H), 1.88-1.99 (m, 2H), 1.18-1.54 (m, 6H), 0.84 (d, *J* = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.5(e), 142.1(e), 129.01(o), 128.97(o), 128.93(o), 128.4(o), 127.9(o), 126.4(o), 126.12(o), 126.06(o), 76.9(o), 74.5(o), 56.6(o), 35.9(e), 31.7(e), 28.1(e), 22.8(e), 14.5(o); Anal. calcd. For $C_{22}H_{26}O$ (306.44): C 86.23, H 8.55; Found: C 85.85, H 8.53.

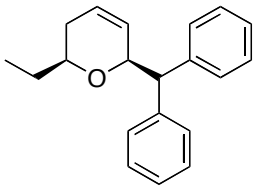
Preparation of *cis*-6-benzyl-2-ethyl-3,6-dihydro-2*H*-pyran (Table 7, entry 10)



Chemical Formula: $C_{14}H_{18}O$
Exact Mass: 202.14
Mol. Wt.: 202.29
C, 83.12; H, 8.97; O, 7.91

According to the general procedure, (*Z*)-6-(trimethylsilyl)hex-5-en-3-ol (0.100 g, 0.580 mmol, 1.0 equiv.) was reacted with styrene oxide (0.139 g, 1.16 mmol, 2.0 equiv) to provide 0.062 g (53%) of *cis*-isomer as a pale yellow oil, after purification by column chromatography (95:5 petroleum ether:ethyl ether, R_f = 0.52): IR (neat) 3030(m), 2963(s), 1496(m), 1185(m), 1086(s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.25-7.37 (m, 5H), 5.85 (ddd, *J* =10.2, 1.6 Hz, 1H), 4.36-4.39 (m, 1H), 3.51 (q, *J* = 6.6 Hz, 1H), 3.05 (dd, *J* = 13.7, 6.6 Hz, 1H), 2.75 (dd, *J* = 13.5, 7.2 Hz, 1H), 2.00-2.03 (m, 2H), 1.51-1.71 (m, 2H), 1.00 (t, *J* = 7.6 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.6(e), 129.8(o), 129.6(o), 128.3(o), 126.3(o), 125.3(o), 76.0(o), 75.6(o), 42.3(e), 31.0(e), 29.2(e), 10.1(o); HRMS (CI) calcd for $(C_{14}H_{18}O)Na$ $(M + Na)^+$ = 225.1250, Found = 225.1250.

Preparation of *cis*-6-benzhydryl-2-ethyl-3,6-dihydro-2*H*-pyran (Table 7, entry 11)

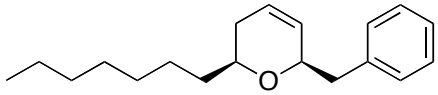


Chemical Formula: $C_{20}H_{22}O$
Exact Mass: 278.17
Mol. Wt.: 278.39
C, 86.29; H, 7.97; O, 5.75

According to the general procedure (*Z*)-6-(trimethylsilyl)hex-5-en-3-ol (0.100 g, 0.58

mmol, 1.0 equiv.) was treated with *trans*-stilbene oxide (0.228g, 1.16 mmol, 2.0 equiv) to provide 0.047 g (29%) of *cis*-isomer as colorless crystals after purification by column chromatography (95:5 petroleum ether: ethyl ether, R_f = 0.47): IR (neat) 3055(m), 2985(s), 2306(s), 2306(s), 1599(s), 1495(s), 1265(m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.16-7.37(m, 10H), 5.74-5.79(m, 1H), 5.56 (dd, *J* = 10.2, 1.6 Hz, 1H), 4.80-4.83 (m, 1H), 3.98 (d, *J* = 8.2 Hz, 1H), 3.48 (q, *J* = 7.0 Hz, 1H), 1.92-1.96 (m, 2H), 1.34-1.52 (m, 2H), 0.87 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.7(e), 142.2(e), 129.2(o), 129.1(o), 128.6(o), 128.0(o), 126.5(o), 126.2(o), 76.9(o), 75.9(o), 56.6(o), 31.2(e), 29.2(e), 10.3(o); HRMS (CI) calcd for $(C_{20}H_{22}O)Na$ $(M + Na)^+$ = 301.1563, Found = 301.1563.

Preparation of *cis*-6-benzyl-2-heptyl-3,6-dihydro-2*H*-pyran (Table 7, entry 12)

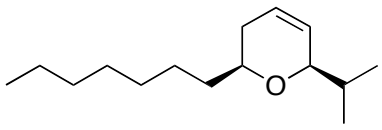


Chemical Formula: $C_{19}H_{28}O$
Exact Mass: 272.21
Mol. Wt.: 272.43
C, 83.77; H, 10.36; O, 5.87

According to the general procedure (Z)-1-(trimethylsilyl)undec-1-en-4-ol (0.075 g, 0.31 mmol, 1.0 equiv) was treated with styrene oxide (0.041 g, 0.34 mmol, 1.1 equiv.) to provide 0.050 g (59%) of *cis*-isomer as a pale yellow liquid after column chromatography (95:5 petroleum ether: ethyl ether, R_f = 0.56): IR (neat) 3029(s), 2858(s), 1604(s), 1495(m), 1185(m),1085(s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 7.19-7.31 (m, 5H), 5.79 (dm, *J* = 10.2 Hz, 1H), 5.60 (dm, *J* = 10.0 Hz, 1H), 4.29-4.33 (m, 1H), 3.48-3.54 (m, 1H), 2.99 (dd, *J* = 13.7, 6.6 Hz, 1H), 2.68 (dd, *J* = 13.7, 7.4 Hz, 1H), 1.93-1.98 (m, 2H), 1.27-1.62 (m, 12H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7(e),

129.8(o), 129.6(o), 128.3(o), 126.3(o), 125.3(o), 76.0(o), 74.3(o), 42.3(e), 36.3(e), 32.0(e), 31.5(e), 29.8(e), 29.5(e), 25.7(e), 22.9(e), 14.4(o); HRMS (CI) calcd for $(C_{19}H_{28}O)Na$ $(M + Na)^+$ = 295.2032, Found = 295.2033.

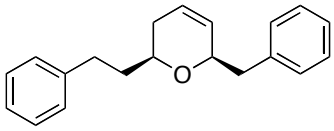
Preparation of *cis*-2-heptyl-6-isopropyl-3,6-dihydro-2*H*-pyran (Table 7, entry 13)



Chemical Formula: $C_{15}H_{28}O$
Exact Mass: 224.21
Mol. Wt.: 224.38
C, 80.29; H, 12.58; O, 7.13

According to the general procedure (Z)-1-(trimethylsilyl)undec-1-en-4-ol (0.150 g, 0.62 mmol, 1.0 equiv.) was treated with isobutylene oxide (0.089 g, 1.23 mmol, 2.0 equiv.) to provide 0.072 g (52% yield) of *cis*-isomer and 0.018 g (11%) of inseparable (2S,6R)-2,6-diheptyl-3,6-dihydro-2H-pyran as a pale yellow liquid, after column chromatography (95:5 petroleum ether: ethyl ether, R_f = 0.72): IR (neat) 3035(s), 2972(s), 1467(s), 1186(s), 1076(m) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.80-5.86 (m, 1H), 5.67 (dq, *J* = 10.16, 1.6 Hz, 1H), 3.83-3.88 (m, 1H), 3.44-3.51 (m, 1H), 1.89-1.94 (m, 2H), 1.75 (dh, *J* = 5.5, 1.4 Hz, 1H), 1.20-1.60 (m, 12H), 0.93 (d, *J* = 4.5 Hz, 3H), 0.9 (d, *J* = 4.7 Hz, 3H), 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 128.8(o), 125.8(o), 79.8(o), 74.0(o), 36.4(e), 32.9(o), 32.1(e), 31.7(e), 29.9(e), 29.5(e), 25.7(e), 22.9(e), 18.2(o), 14.3(o) HRMS (CI) calcd for $(C_{15}H_{28}O)_2Na$ $(2M + Na)^+$ = 471.4173, Found = 471.4166

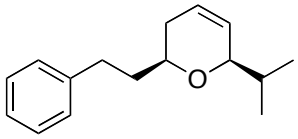
Preparation of *cis*-6-benzyl-2-phenethyl-3,6-dihydro-2H-pyran (Table 7, entry 14)



Chemical Formula: $C_{20}H_{22}O$
Exact Mass: 278.17
Mol. Wt.: 278.39
C, 86.29; H, 7.97; O, 5.75

According to the general procedure, (*Z*)-1-phenyl-6-(trimethylsilyl)hex-5-en-3-ol (0.100 g, 0.40 mmol, 1.00 equiv) was treated with styrene oxide (0.100g, 0.80 mmol, 2.0 equiv), to provide 0.069g (62%) of *cis*-isomer as a colorless oil, after purification by column chromatography (95:5 petroleum ether:diethyl ether, R_f = 0.64): IR (neat) 3062(s), 3028(s), 2923(s), 2858(s), 1603(s), 1495(s), 1454(s), 1084(s), 1064(s), 747(s), 699(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.07 – 7.37 (m, 10H), 5.78 – 5.82 (m, 1H), 5.65 (dq, *J* = 10.4, 1.4 Hz, 1H), 4.27 – 4.29 (1H, m), 3.47 (1H, ddd, *J* = 14, 9.2, 4.8Hz), 2.98 (1H, dd, *J* = 13.4, 7.8Hz), 2.64 – 2.81(3H, m), 1.74 – 2.08 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.4(e), 138.9(e), 129.8(o), 128.7(o), 128.5(o), 128.3(o), 126.4(o), 125.9(o), 125.3(o), 76.0(o), 72.9(o), 42.3(e), 37.8(e), 31.7(e), 31.5(e).

Preparation of *cis*-2-phenethyl-6-isopropyl-3,6-dihydro-2H-pyran (Table 7, entry 15)



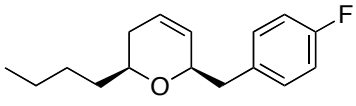
Chemical Formula: $C_{16}H_{22}O$
Exact Mass: 230.17
Mol. Wt.: 230.35
C, 83.43; H, 9.63; O, 6.95

According to the general procedure, (Z)-1-phenyl-6-(trimethylsilyl)hex-5-en-3-ol (0.100 g, 4.00 mmol, 1.00 equiv) was treated with isobutylene oxide (0.06 g, 0.80 mmol, 2.0

equiv) to provide pure product 0.054g (60%) of *cis*-isomer as a colorless oil, after purification by column chromatography (95:5 petroleum ether:diethyl ether; R_f = 0.67). IR (neat) 3028.0(s), 2959.6(s), 2649.2(s), 2360.9(s), 1940.7(s), 1603.8(m) 1096.7(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 – 7.31 (5H, m), 5.80 – 5.84 (1H, m), 5.67 (1H, dt, *J* = 10, 1.2 Hz), 3.85 (1H, dd, *J* = 3.4, 1.4 Hz), 3.48 (1H, dddd, *J* = 14, 4.4 Hz), 2.69 – 2.86 (2H, m), 1.72 – 2.04 (5H, m), 0.97 (6H, d, *J* = 6.8 Hz); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.6(e) 129.0(o), 128.8(o), 128.5(o), 125.8(o), 125.6(o), 79.7(o), 72.6(o), 37.8(e), 33.0(o), 31.8(e), 31.7(e), 18.4(o), 18.1(o); HRMS (CI) calcd for $(C_{16}H_{22}O)Na$ $(M + Na)^+$ = 253.1563, Found = 253.1556.

Preparation of *cis*-2-butyl-6-(4-fluorobenzyl)-3,6-dihydro-2*H*-pyran

(Table 8, entry 16)



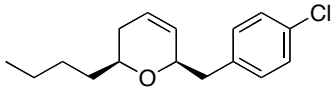
Chemical Formula: $C_{16}H_{21}FO$
Exact Mass: 248.16
Mol. Wt.: 248.34
C, 77.38; H, 8.52; F, 7.65; O, 6.44

According to the general procedure, (Z)-1-(trimethylsilyl)oct-1-en-4-ol (0.100 g, 0.50 mmol, 1.00 equiv) was treated with 2-(4-fluorophenyl)-oxirane (0.140g, 1.00 mmol, 2.00 equiv), to provide 0.058g (47%) of *cis*-isomer as a colorless oil, after purification by column chromatography (95:5 petroleum ether:ethyl ether, Rf: 0.51): IR (neat) 3035(s), 2932(s), 2861(s), 1601(s), 1510(s), 1222(s), 1157(s), 1072(s), 843(s), 713(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.23 (t, *J* = 6.8 Hz, 2H), 6.99 (t, *J* = 8.8 Hz, 2H), 5.79-5.84 (m, 1H), 5.61 (d, *J* = 10.2 Hz, 1H), 4.26-4.32 (m, 1H), 3.48-3.56 (m, 1H), 2.93 (dd, *J* = 7.0, 6.6 Hz, 1H), 2.70 (dd, *J* = 7.0, 6.6 Hz, 1H), 1.92-1.99 (m, 2H), 1.28-1.65 (m, 6H), 0.91 (t, *J*

= 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 134.3(e), 131.2(o), 131.1(o), 129.4(o), 125.6(o), 115.1(o), 114.9(o), 75.8(o), 74.3(o), 41.3(e), 36.0(e), 31.4(e), 27.9(e), 22.9(e), 14.3(o); HRMS (CI) calcd for $(C_{16}H_{21}FO)Na$ $(M + Na)^+$ = 271.1469, Found = 271.1462.

Preparation of *cis*-2-butyl-6-(4-chlorobenzyl)-3,6-dihydro-2*H*-pyran

(Table 8, entry 17)

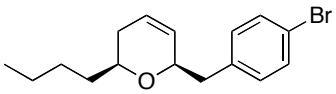


Chemical Formula: $C_{16}H_{21}ClO$
Exact Mass: 264.13
Mol. Wt: 264.79
C, 72.57; H, 7.99; Cl, 13.39; O, 6.04

According to the general procedure, (Z)-1-(trimethylsilyl)oct-1-en-4-ol (0.100 g, 0.50 mmol, 1.00 equiv) was treated with 2-(4-chlorophenyl)-oxirane (0.12 mL, 1.00 mmol, 2.00 equiv), to provide 0.065g (49%) of *cis*-isomer as a colorless oil, after purification by column chromatography (95:5 petroleum ether:ethyl ether, Rf: 0.56): IR (neat) 3032(s), 2933(s), 2861(s), 1493(s), 1184(s), 1091(s), 833(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.21 (dd, *J* = 14.0, 7.0 Hz, 4H), 5.76-5.82 (m, 1H), 5.58 (d, *J* = 10.2 Hz, 1H), 4.27 (s, 1H), 3.45-3.54 (m, 1H), 2.89 (dd, *J* = 7.0, 6.6 Hz, 1H), 2.68 (dd, *J* = 7.4, 6.3 Hz, 1H), 1.91-1.96 (m, 2H), 1.25-1.62 (m, 6H), 0.91 (t, *J* = 6.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.29(e) 132.1(e), 131.2(o), 129.4(o), 128.4(o), 125.7(o), 75.6(o), 74.3(o), 41.5(e), 36.0(e), 31.4(e), 27.9(e), 22.9(e), 14.3(o); HRMS (CI) calcd for $(C_{16}H_{21}ClO)Na$ $(M + Na)^+$ = 287.1173, Found = 287.1170.

Preparation of *cis*-6-(4-bromobenzyl)-2-butyl-3,6-dihydro-2*H*-pyran

(Table 8, entry 18)

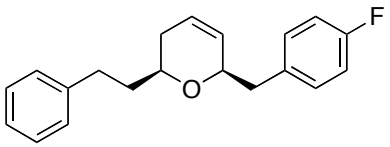


Chemical Formula: $C_{16}H_{21}BrO$
Exact Mass: 308.08
Mol. Wt: 309.24
C, 62.14; H, 6.84; Br, 25.84; O, 5.17

According to the general procedure, (Z)-1-(trimethylsilyl)oct-1-en-4-ol (0.100 g, 0.50 mmol, 1.00 equiv) was treated with 2-(4-bromophenyl)-oxirane (0.200g, 1.00 mmol, 2.00 equiv), to provide 0.063g (41%) of *cis*-isomer as a colorless oil, after purification by column chromatography (95:5 petroleum ether:ethyl ether, Rf: 0.46): IR (neat) 3032(s), 2959(s), 2861(s), 1652(s), 1489(s), 1368(s), 1184(s), 1072(s), 1012(s), 712(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, *J* = 8.2, Hz, 2H), 7.15 (d, *J* = 8.6 Hz, 2H), 5.77-5.84 (m, 1H), 5.58 (d, *J* = 10.2 Hz, 1H), 4.25-4.31 (m, 1H), 3.46-3.54 (m, 1H), 2.89 (dd, *J* = 7.4, 6.3 Hz, 1H), 2.68 (dd, *J* = 7.0, 6.6 Hz, 1H), 1.92-1.97 (m, 2H), 1.25-1.63 (m, 6H), 0.90 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.7(e), 131.6(o), 131.3(o), 129.3(o), 125.7(o), 120.2(e), 75.5(o), 74.3(o), 41.6(e), 36.0(e), 31.4(e), 27.9(e), 22.9(e), 14.3(o); HRMS (CI) calcd for $(C_{16}H_{21}BrO)Na$ $(M + Na)^+$ = 331.0668, Found =331.0664.

Preparation of *cis*-6-(4-fluorobenzyl)-2-phenethyl-3,6-dihydro-2*H*-pyran

(Table 8, entry 19)

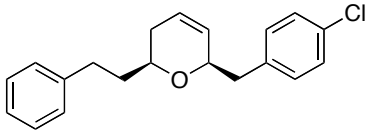


Chemical Formula: $C_{20}H_{21}FO$
Exact Mass: 296.16
Mol. Wt: 296.38
C, 81.05; H, 7.14; F, 6.41; O, 5.40

According to the general procedure, (*Z*)-1-phenyl-6-(trimethylsilyl)hex-5-en-3-ol (0.124 g, 0.50 mmol, 1.0 equiv) was treated with 2-(4-fluorophenyl)-oxirane (0.138g, 1.00 mmol, 2.0 equiv), to provide 0.088 g (60%) of *cis*-isomer as a colorless oil, after purification by column chromatography (95:5 petroleum ether:diethyl ether, R_f = 0.53): IR (neat) 3024(s), 2929(s), 1946(s), 1889(s), 1724(s), 1601(s), 1496(s), 1157(s), 838; ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.95 – 7.30 (m, 9H), 5.75 – 5.82 (1H, m), 5.60 (d, *J* = 10.2 Hz, 1H), 4.18 – 4.25 (m, 1H), 3.39 ‑ 3.48(m, 1H), 2.88 (dd, *J* = 13.9, 7.6Hz, 1H), 2.59–2.77(m, 3H), 1.70 – 2.07 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3(e), 134.5(e), 134.4(e), 131.2(o), 131.1(o), 129.6(o), 128.7(o), 128.5(o), 126.4(o), 125.9(o), 125.5(o), 115.1(o), 114.9(o), 75.8(o), 72.8(o), 41.3(e), 37.7(e), 31.7(e), 31.4(e); HRMS (CI) calcd for $(C_{20}H_{21}FO)Na$ $(M + Na)^+$ = 319.1469, Found = 319.1465.

Preparation of *cis*-6-(4-chlorobenzyl)-2-phenethyl-3,6-dihydro-2*H*-pyran

(Table 8, entry 20)

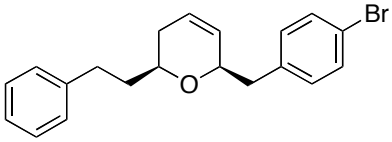


Chemical Formula: $C_{20}H_{21}ClO$
Exact Mass: 312.13
Mol. Wt.: 312.83
C, 76.79; H, 6.77; Cl, 11.33; O, 5.11

According to the general procedure, (*Z*)-1-phenyl-6-(trimethylsilyl)hex-5-en-3-ol (0.124 g, 0.50 mmol, 1.0 equiv) was treated with 2-(4-chlorophenyl)-oxirane (0.155 g, 1.00 mmol, 2.0 equiv), to provide 0.087g (56%) of *cis*-isomer as a pale yellow oil, after purification by column chromatography (95:5 petroleum ether:diethyl ether, R_f = 0.43): IR (neat) 3024(s), 2924(s), 1721(s), 1602(s), 1493(s), 1368(s), 1185(s), 1017(s), 835(s), 746(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.09 – 7.32 (m, 9H), 5.77 – 5.83 (m, 1H), 5.62 (dt, *J* = 10.2, 1.2 Hz, 1H), 4.23-4.28 (m, 1H), 3.42-3.50 (m, 1H), 2.98 (dd, *J* = 13.4, 7.8 Hz, 1H), 2.64 – 2.81(m, 3H), 1.74 – 2.08 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3(e), 137.3(e) 132.1(e), 131.2(o), 129.5(o), 128.7(o), 128.5(o), 128.4(o), 125.9(o), 125.6(o), 75.6(o), 72.9(o), 41.5(e), 37.7(e), 31.7(e), 31.4(e); HRMS (CI) calcd for $(C_{20}H_{21}ClO)Na$ $(M + Na)^+$ = 335.1173, Found = 335.1171.

Preparation of *cis*-6-(4-bromobenzyl)-2-phenethyl-3,6-dihydro-2*H*-pyran

(Table 8, entry 21)

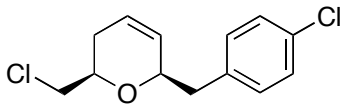


Chemical Formula: $C_{20}H_{21}BrO$
Exact Mass: 356.08
Mol. Wt.: 357.28
C, 67.23; H, 5.92; Br, 22.36; O, 4.48

According to the general procedure, (*Z*)-1-phenyl-6-(trimethylsilyl)hex-5-en-3-ol (0.124 g, 0.50 mmol, 1.0 equiv) was treated with 2-(4-bromophenyl)-oxirane (0.199 g, 1.0 mmol, 2.0 equiv), to provide 0.099 g (53%) of *cis*-isomer as a pale yellow oil, after purification by column chromatography (95:5 petroleum ether:diethyl ether, R_f = 0.48): IR (neat) 3024(s), 1652(s), 1489(s), 1454(s), 1368(s), 1185(s), 746(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.08 – 7.50 (m, 9H), 5.78 – 5.83 (m, 1H), 5.61 (dm, *J* = 10.16 Hz, 1H), 4.25 (dm, *J* = 1.6 Hz, 1H), 3.42-3.55 (m, 1H), 2.60 – 2.95(m, 4H), 1.72– 2.10 (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 142.3(e), 137.8(e), 131.6(o), 131.3(o), 129.5(o), 128.7(o), 128.5(o), 125.9(o), 125.6(o), 120.2(e), 75.5(o), 72.9(o), 41.6(e), 37.7(e), 31.7(e), 31.4(e); HRMS (CI) calcd for $(C_{20}H_{21}BrO)Na$ $(M + Na)^+$ = 379.0668, Found = 379.0663.

Preparation of *cis*-6-(4-chlorobenzyl)-2-(chloromethyl)-3,6-dihydro-2*H*-pyran

(Table 8, entry 23)

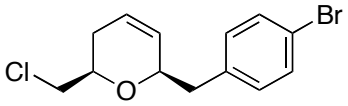


Chemical Formula: $C_{13}H_{14}Cl_2O$
Exact Mass: 256.04
Mol. Wt. 257.16
C, 60.72; H, 5.49; Cl, 27.57; O, 6.22

According to the general procedure, (*Z*)-1-chloro-5-(trimethylsilyl)pent-4-en-2-ol (0.096 g, 0.50 mmol, 1.0 equiv) was treated with 2-(4-chlorophenyl)-oxirane (0.155 g, 1.0 mmol, 2.0 equiv), to provide 0.032 g (<20%) of inseparable 8:2 mix of *cis/trans*-isomers as a pale red oil, after purification by column chromatography (95:5 petroleum ether:diethyl ether, R_f = 0.37): IR (neat) 3036(s), 2928(b), 2361(s), 1653(s), 1491(s), 1430(s), 1184(s), 805(s); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.16 – 7.30 (m, 4H), 5.76 – 5.86 (m, 1H), 5.62 (dquart, *J* = 10.16, 1.95 Hz, 1H), 4.31 – 4.45 (m, 1H), 3.80 (quin, *J* = 6.3, 1H), 3.49 – 3.61 (m, 2H), 2.88 – 2.98 (m, 1H), 2.68 – 2.78(m, 1H), 2.05 – 2.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 136.6(e), 132.3(e), 131.2(o), 131.0(o), 129.1(o), 128.5(o), 127.2(o), 124.6(o), 75.8(o), 73.8(o), 47.1(e), 41.2(e), 28.7(e); HRMS (CI) calcd for $(C_{13}H_{14}Cl_2O)Na$ $(M + Na)^+$ = 279.0314, Found = 279.0309.

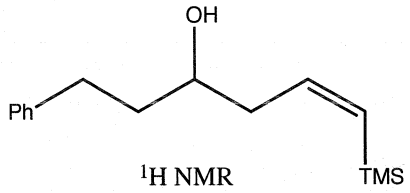
Preparation of *cis*-6-(4-bromobenzyl)-2-(chloromethyl)-3,6-dihydro-2*H*-pyran

(Table 8, entry 24)

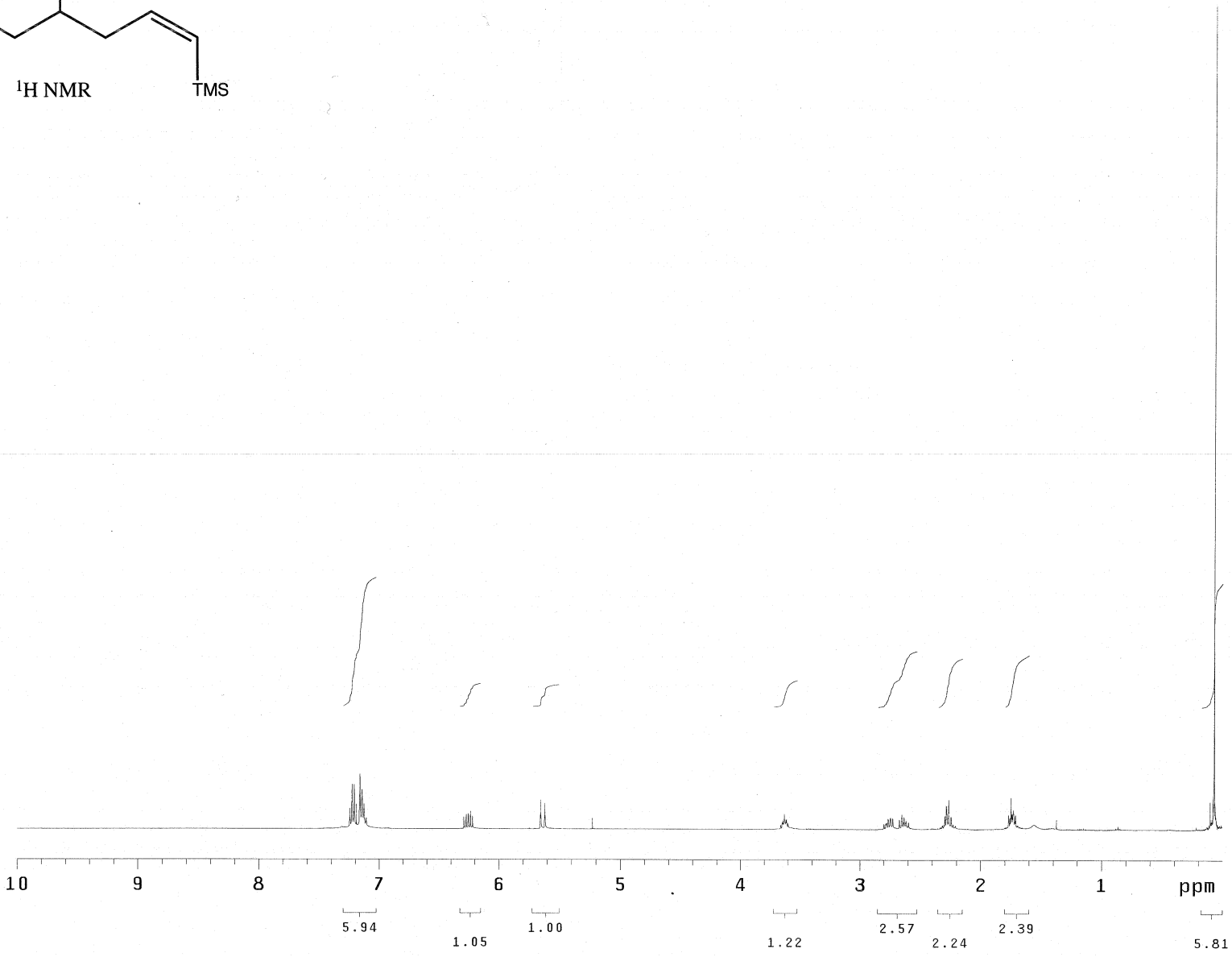


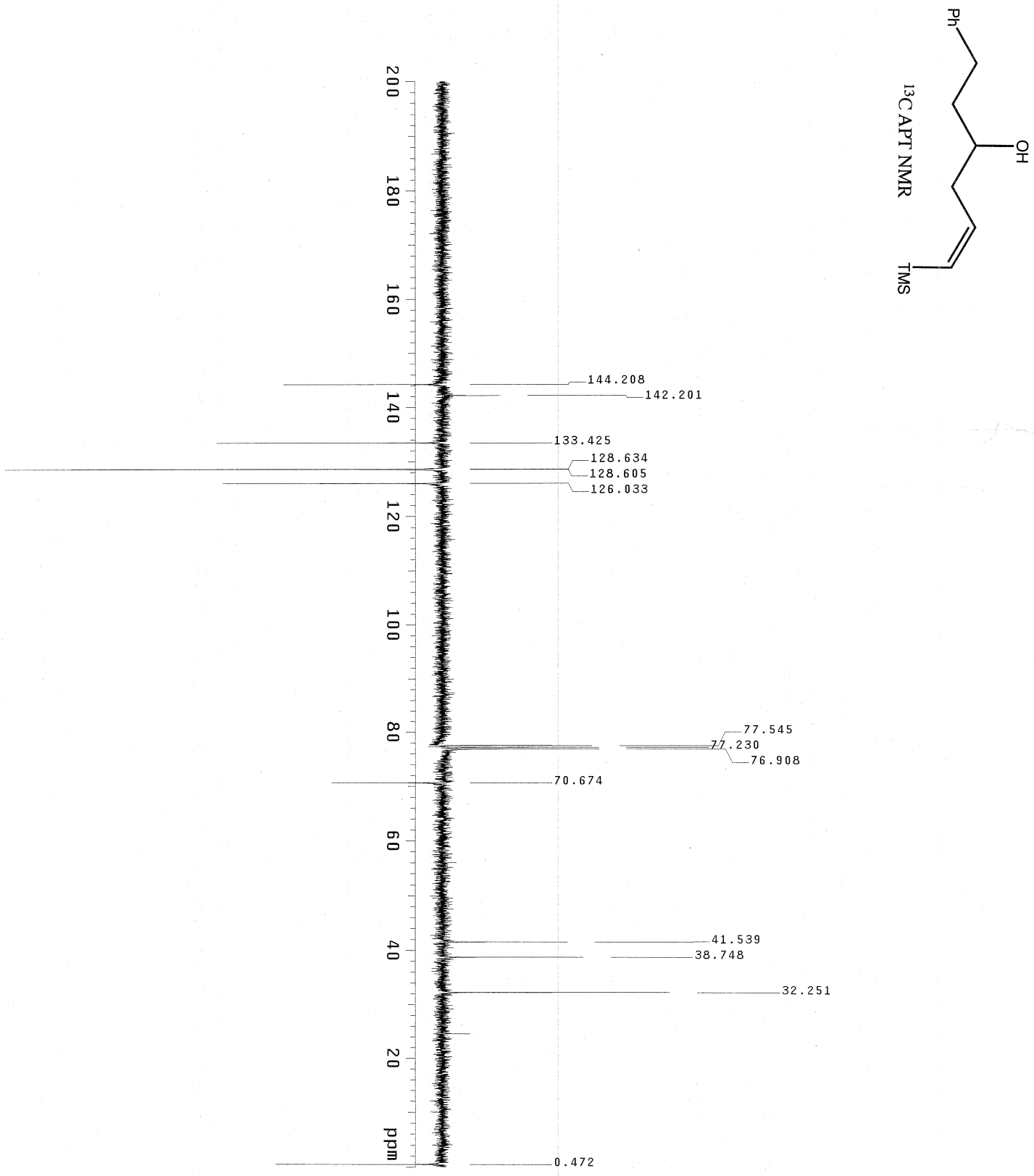
Chemical Formula: $C_{13}H_{14}BrClO$
Exact Mass: 299.99
Mol. Wt. 301.61
C, 51.77; H, 4.68; Br, 26.49; Cl, 11.75; O, 5.30

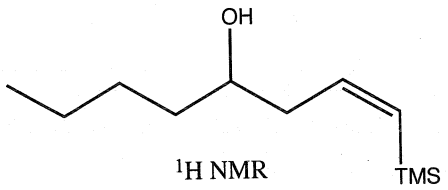
According to the general procedure, (*Z*)-1-chloro-5-(trimethylsilyl)pent-4-en-2-ol (0.096 g, 0.50 mmol, 1.0 equiv) was treated with 2-(4-bromophenyl)-oxirane (0.199 g, 1.0 mmol, 2.0 equiv), to provide 0.029 g (<20%) of inseparable 9:1 mix of *cis/trans*-isomers as a yellow oil, after purification by column chromatography (95:5 petroleum ether:diethyl ether, R_f = 0.34): IR (neat) 3034(s), 2921(s), 2855(s), 2361(s), 1653(s), 1393(s), 1011(s), 801(s)^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, *J* = 8.21 Hz, 2H), 7.151 (d, *J* = 8.21 Hz, 2H), 5.78 – 5.86 (m, 1H), 5.62 (dd, *J* = 10.16, 1.56 Hz, 1H), 4.31-4.44 (m, 1H), 3.80 (quin, *J* = 6.25 Hz, 1H), 3.48 – 3.64 (m, 2H), 2.88 – 2.98 (m, 1H) 2.66–2.79(m, 1H), 2.05 – 2.11 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.1(e), 131.6(o), 131.5(o), 129.1(o), 124.6(o), 120.4(e), 75.7(o), 73.8(o), 47.1(e), 41.3(e), 28.7(e); HRMS (CI) calcd for $(C_{13}H_{14}BrClO)Na$ $(M + Na)^+$ = 322.9809, Found = 322.9804.



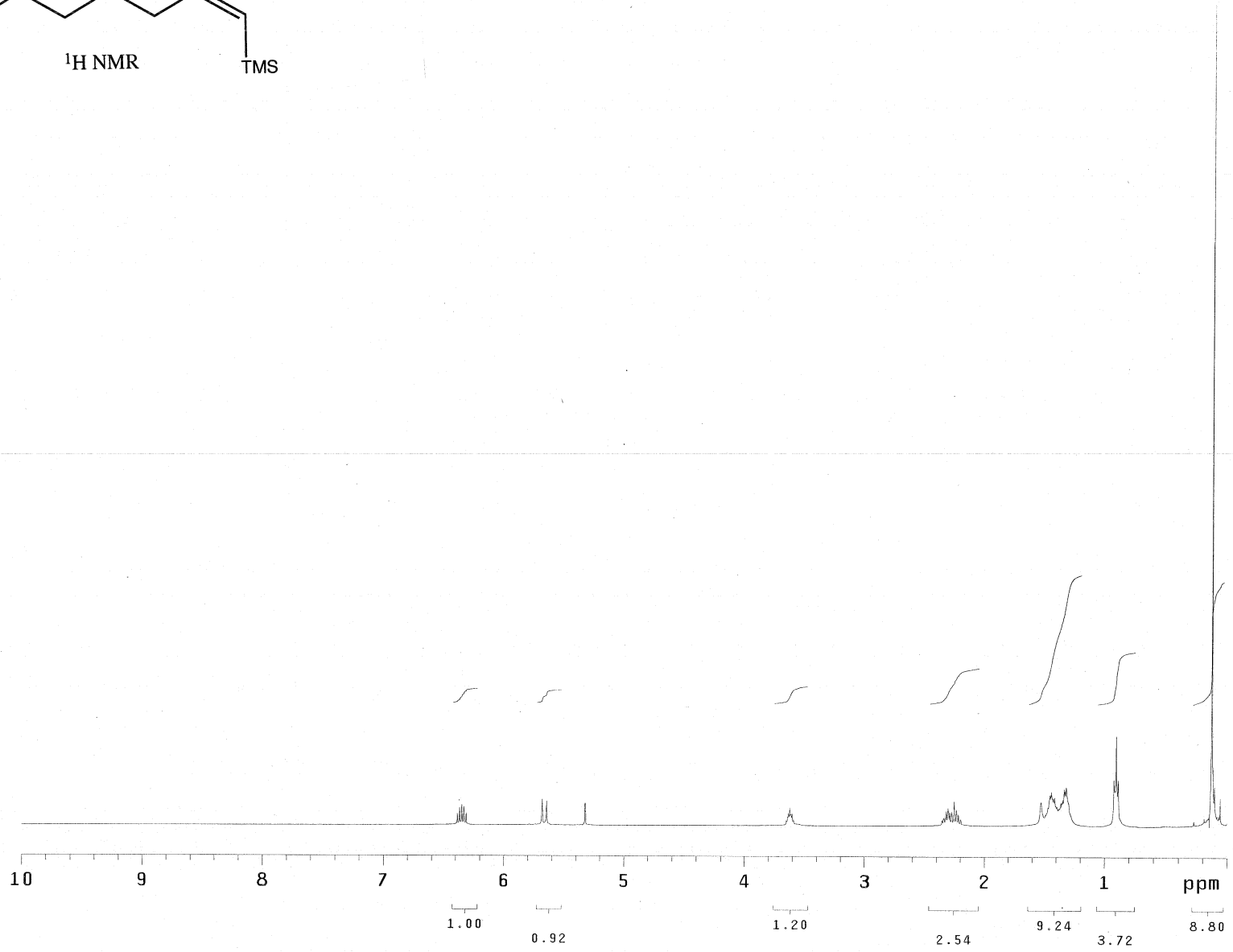
^{1}H NMR



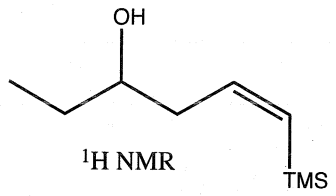

Ph
OH
TMS
^{13}C APT NMR
200
180
160
140
120
100
80
60
40
20
ppm
144.208
142.201
133.425
128.634
128.605
126.033
77.545
77.230
76.908
70.674
41.539
38.748
32.251
0.472



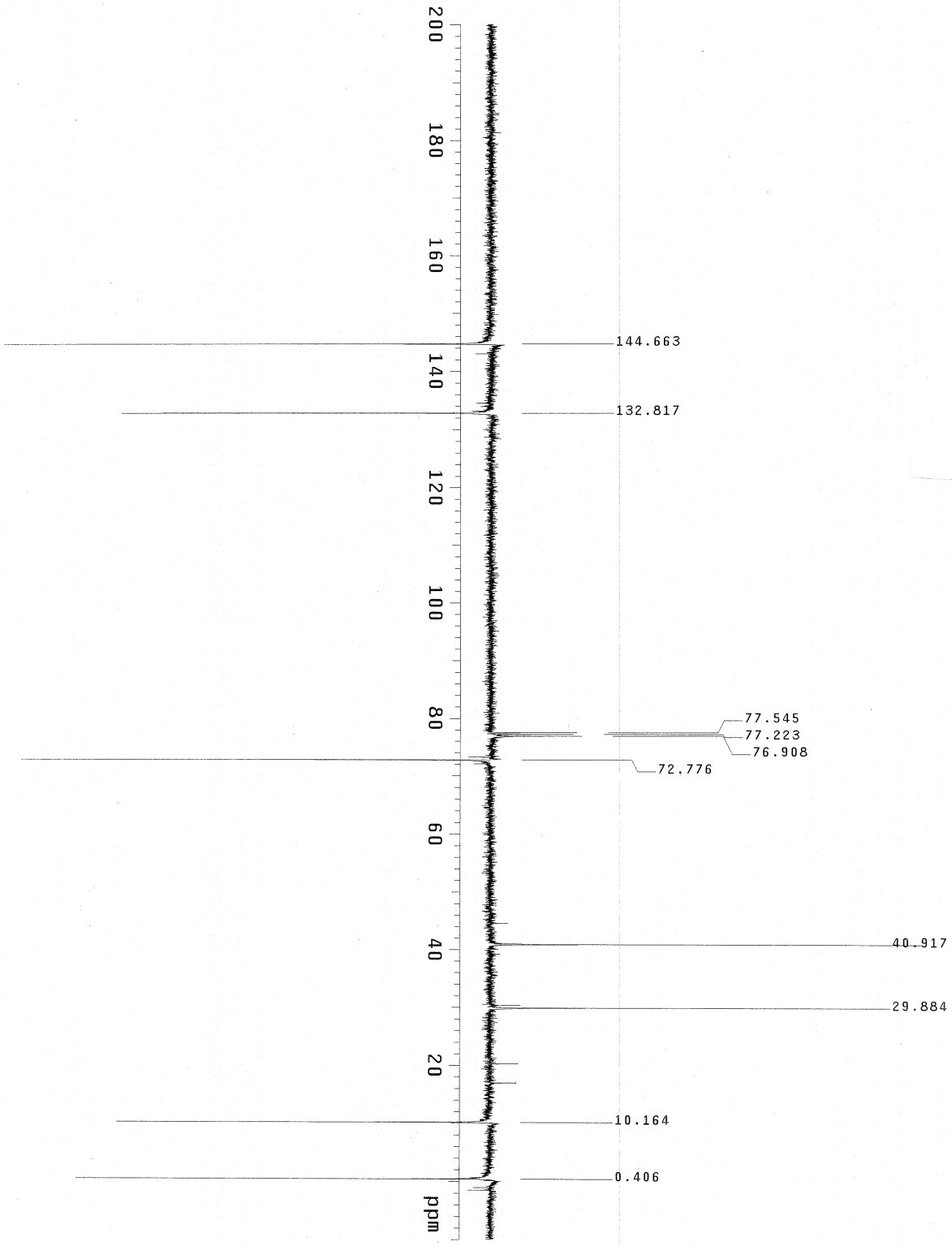
^{1}H NMR

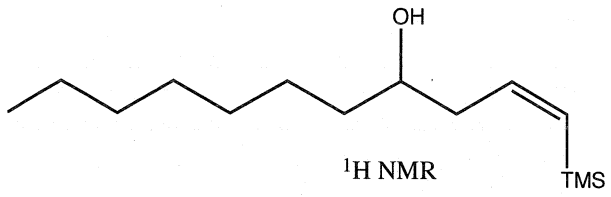


^{13}C APT NMR
OH
TMS
144.455
132.952
77.548
77.230
76.912
71.497
41.551
37.031
28.212
23.078
14.441
0.662
ppm

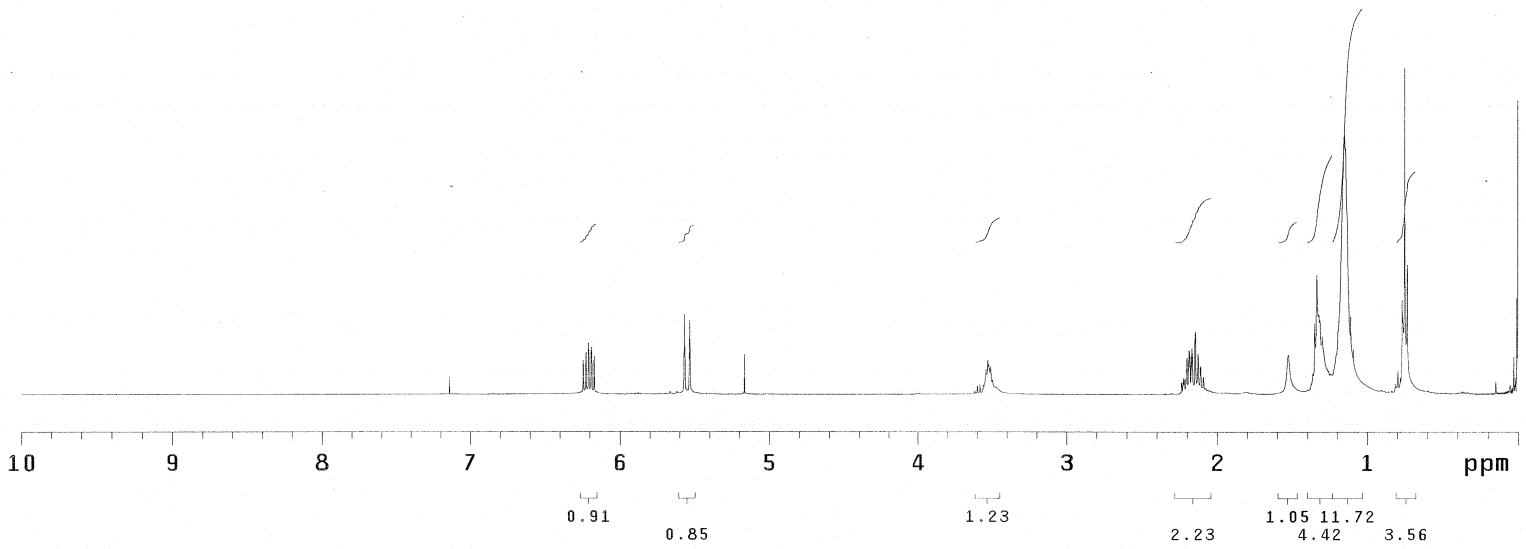


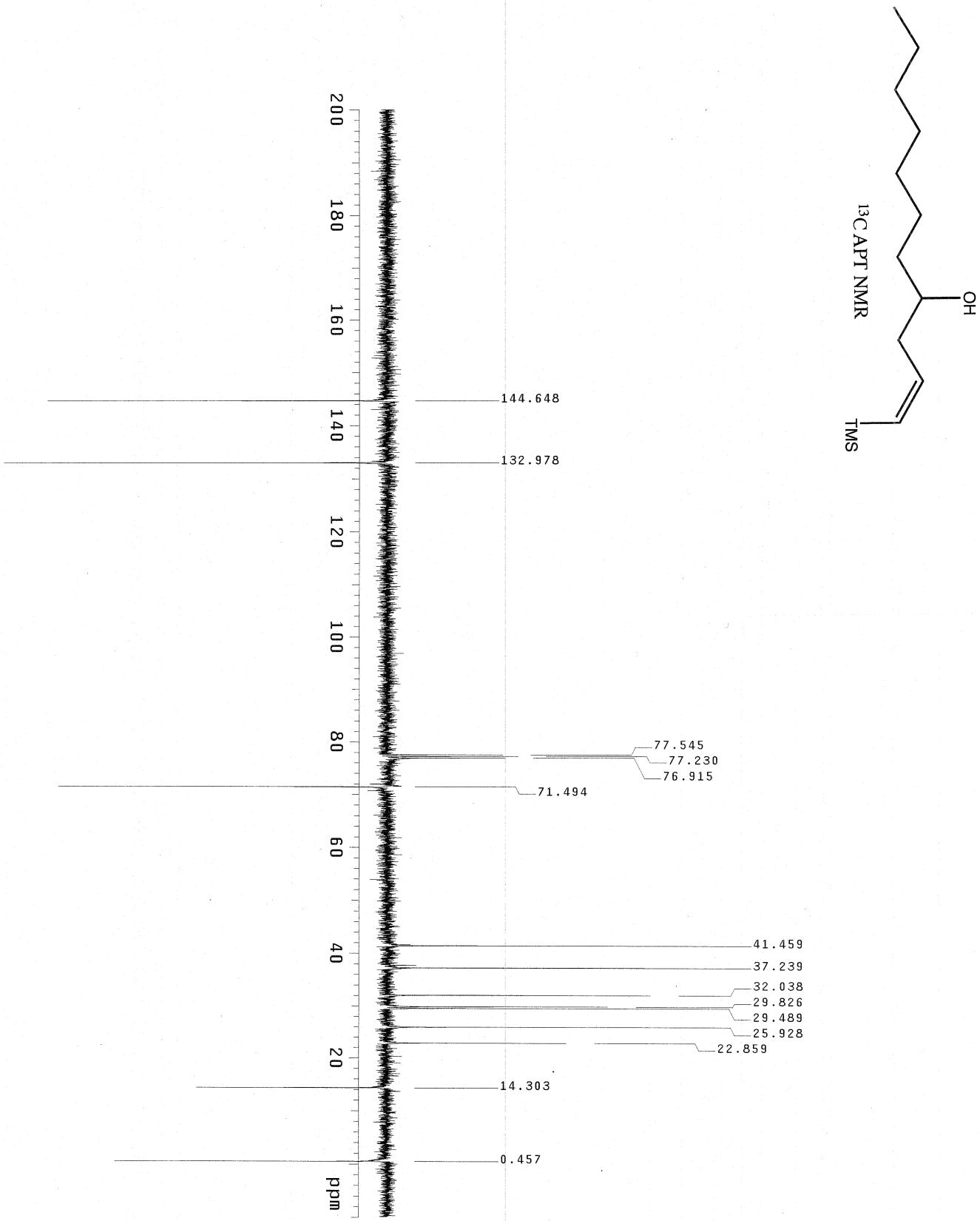
^{1}H NMR

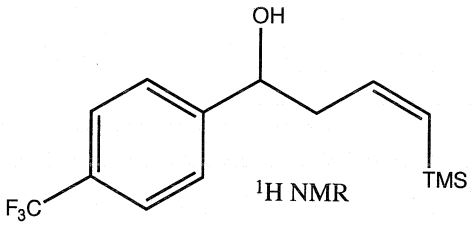

^{13}C APT NMR
OH
TMS
200
180
160
140
120
100
80
60
40
20
ppm
144.663
132.817
77.545
77.223
76.908
72.776
40.917
29.884
10.164
0.406



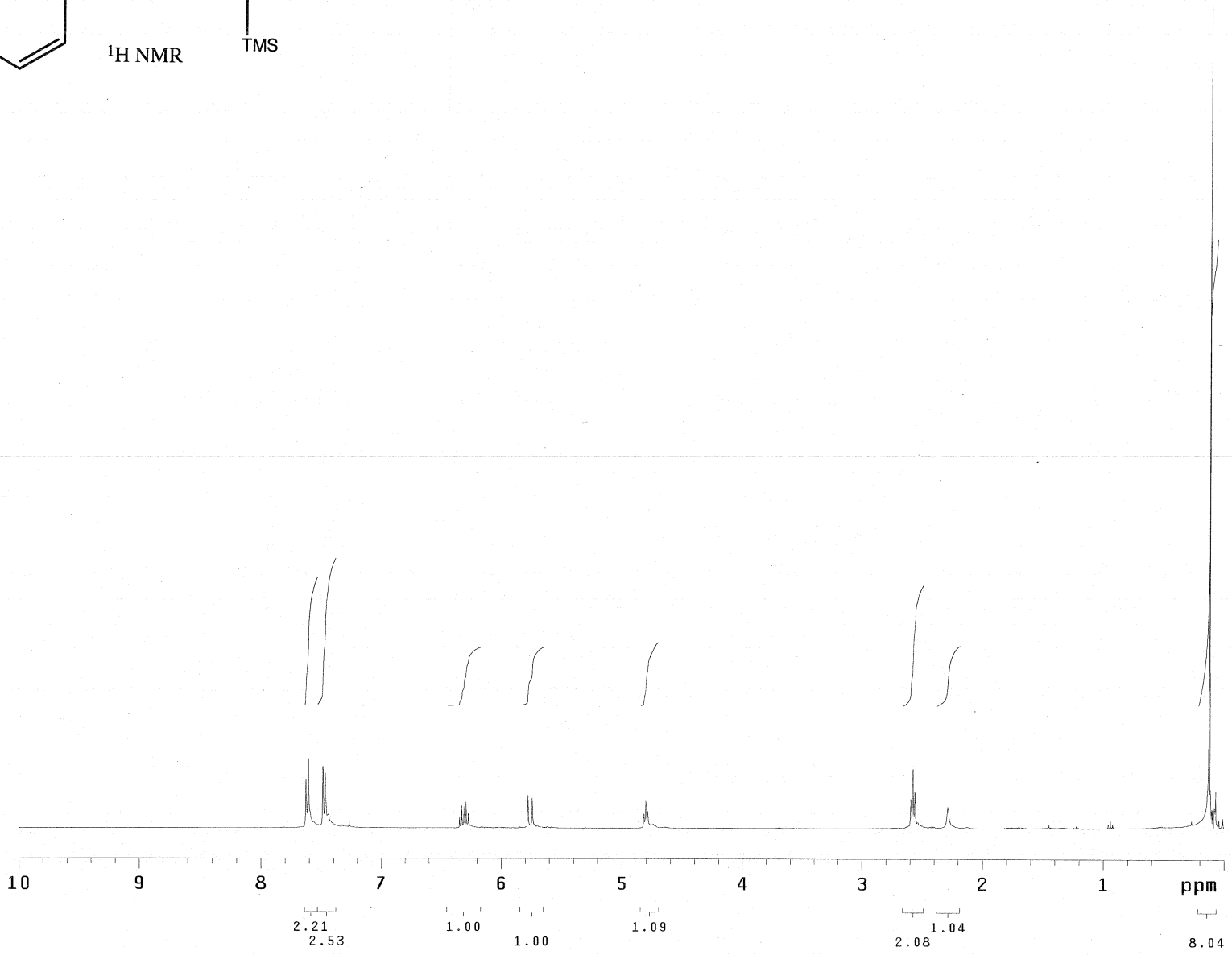
^{1}H NMR

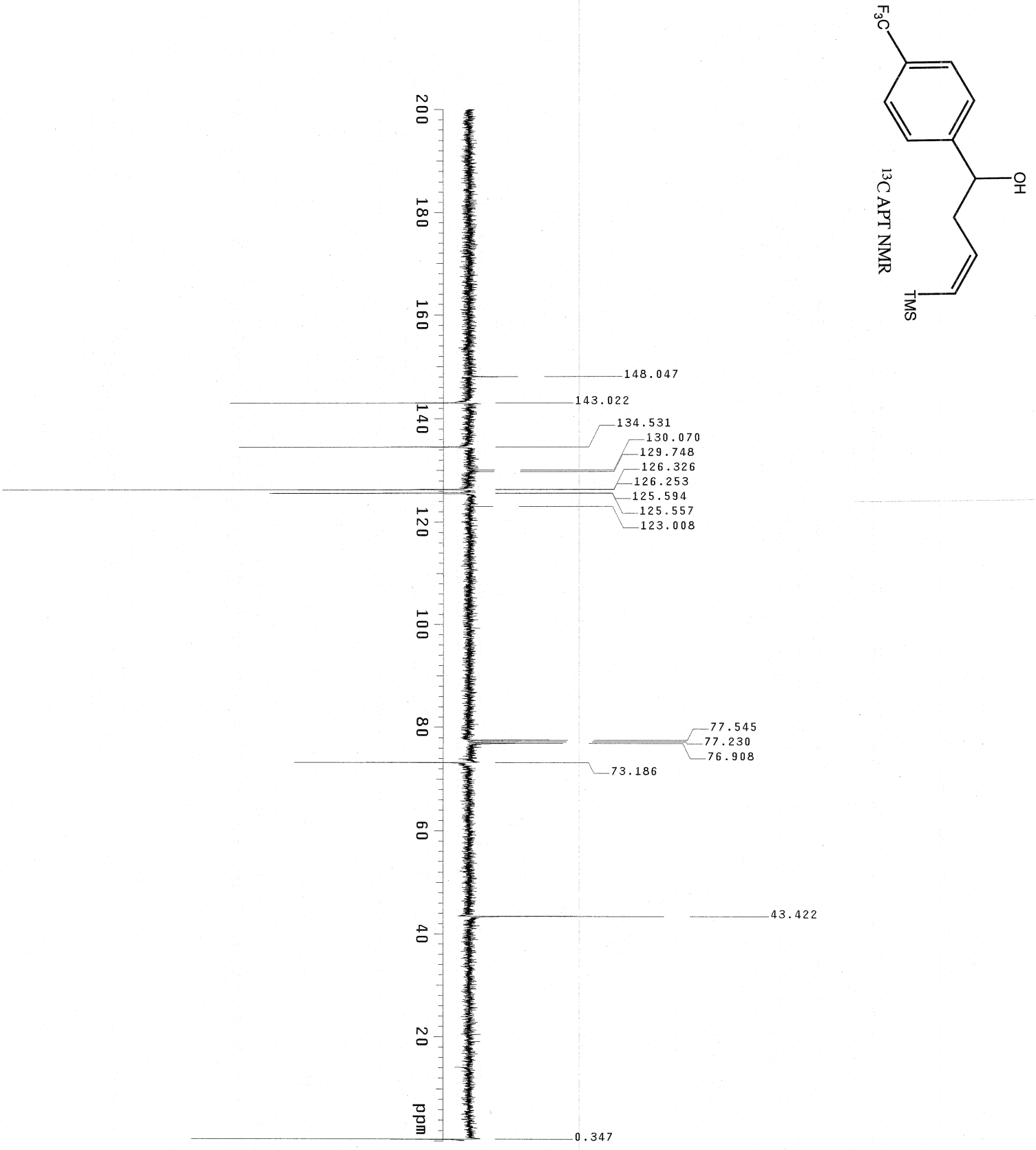


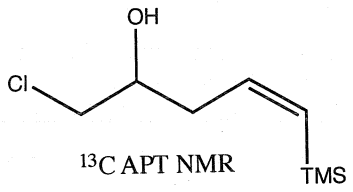

^{13}C APT NMR
OH
TMS
200
180
160
140
120
100
80
60
40
20
ppm
144.648
132.978
77.545
77.230
76.915
71.494
41.459
37.239
32.038
29.826
29.489
25.928
22.859
14.303
0.457



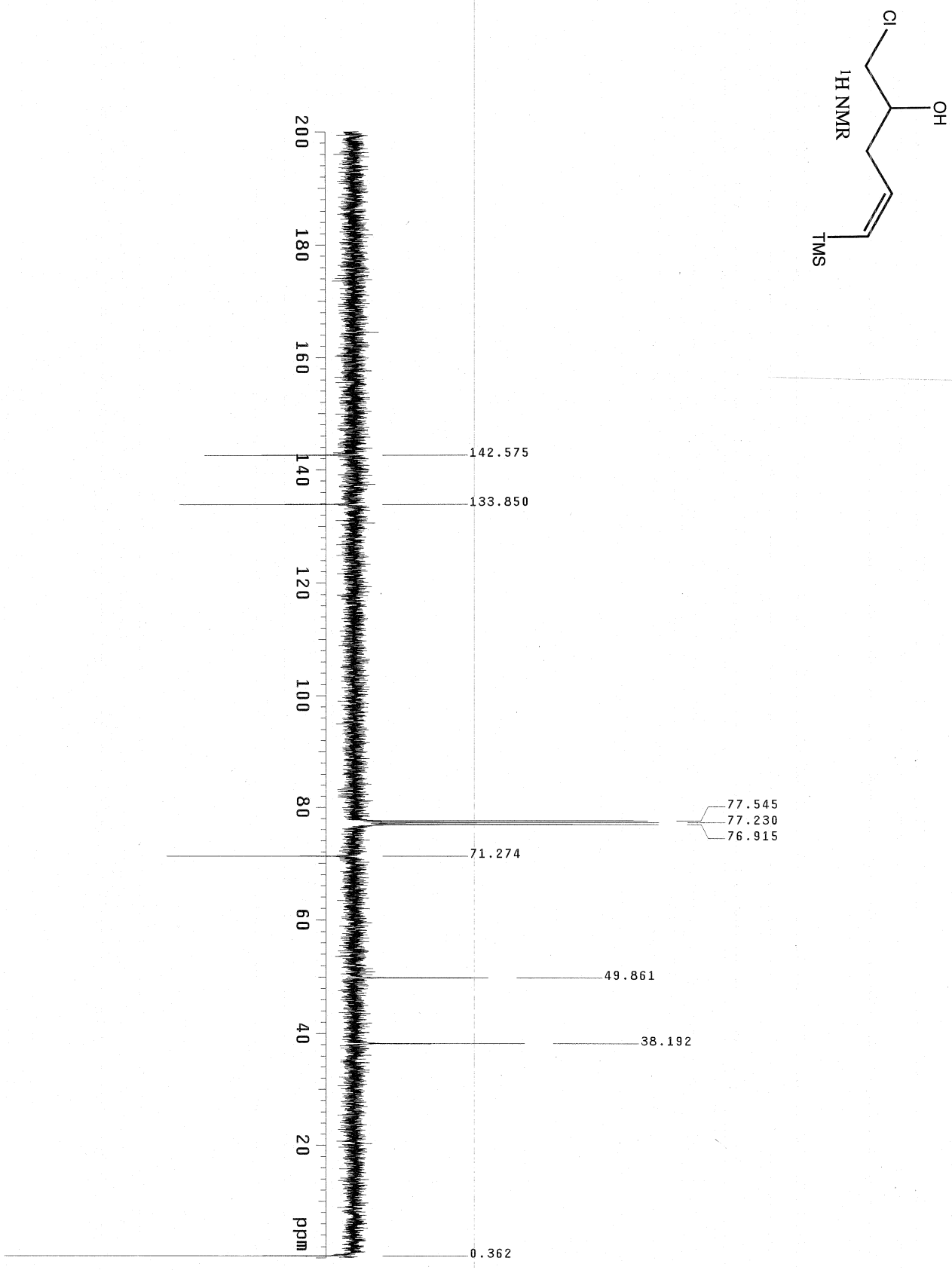
^{1}H NMR

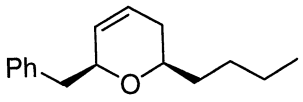



^{13}C APT NMR
F_3C
OH
TMS
200
180
160
140
120
100
80
60
40
20
ppm
148.047
143.022
134.531
130.070
129.748
126.326
126.253
125.594
125.557
123.008
77.545
77.230
76.908
73.186
43.422
0.347

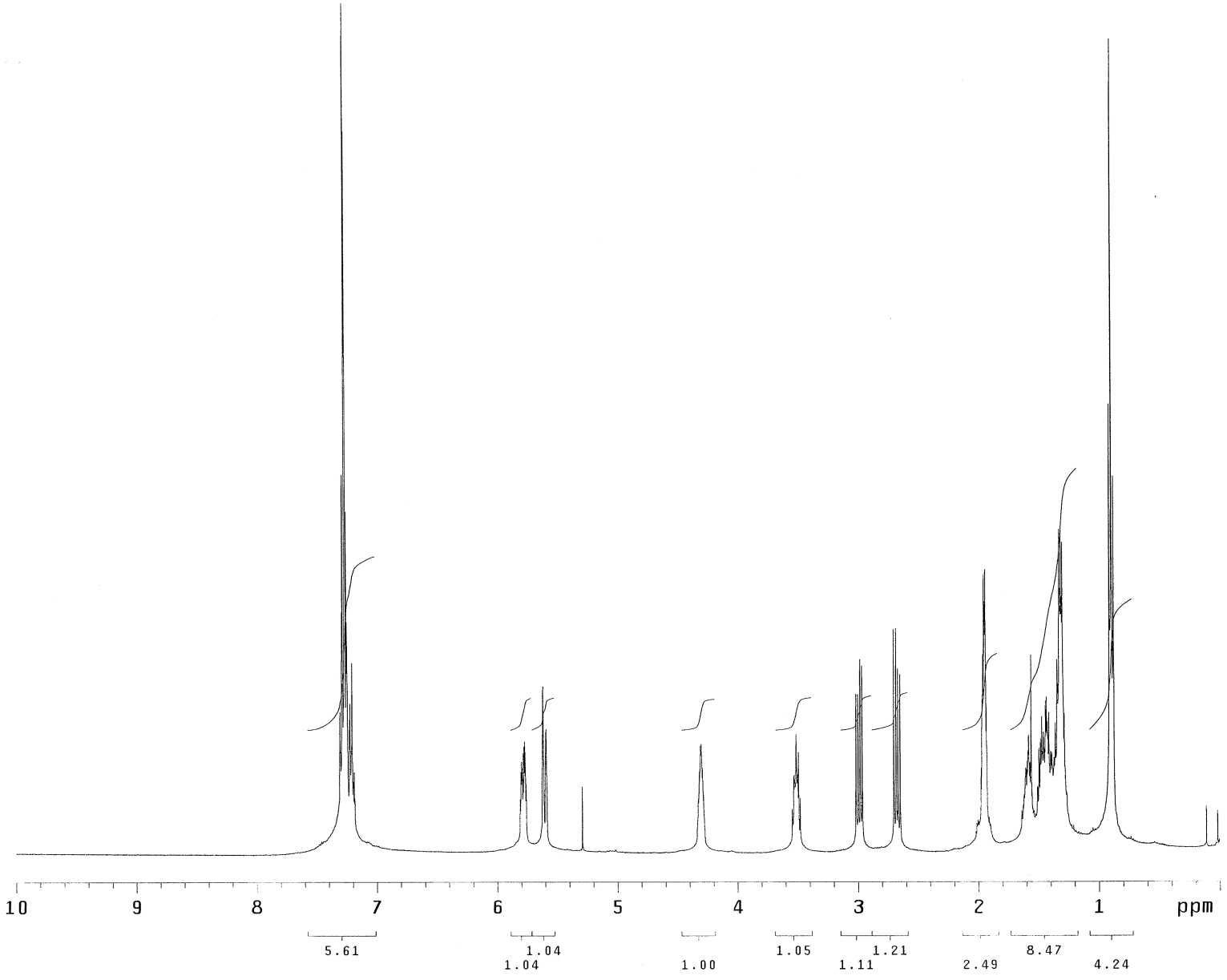


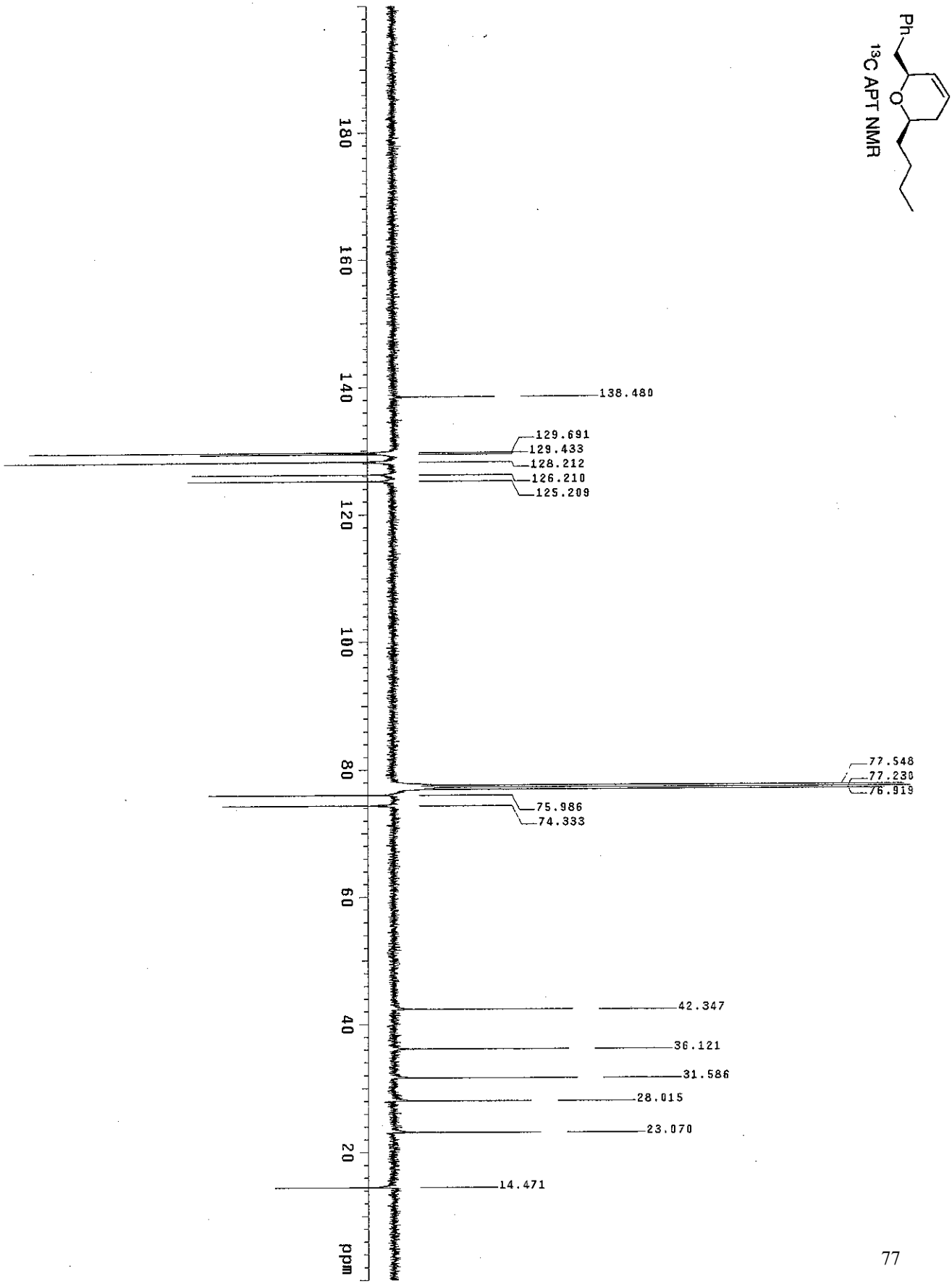
^{13}C APT NMR

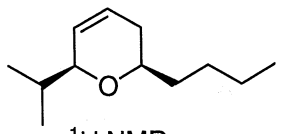

Cl
OH
TMS
^{1}H NMR
200
180
160
140
120
100
80
60
40
20
ppm
142.575
133.850
77.545
77.230
76.915
71.274
49.861
38.192
0.362



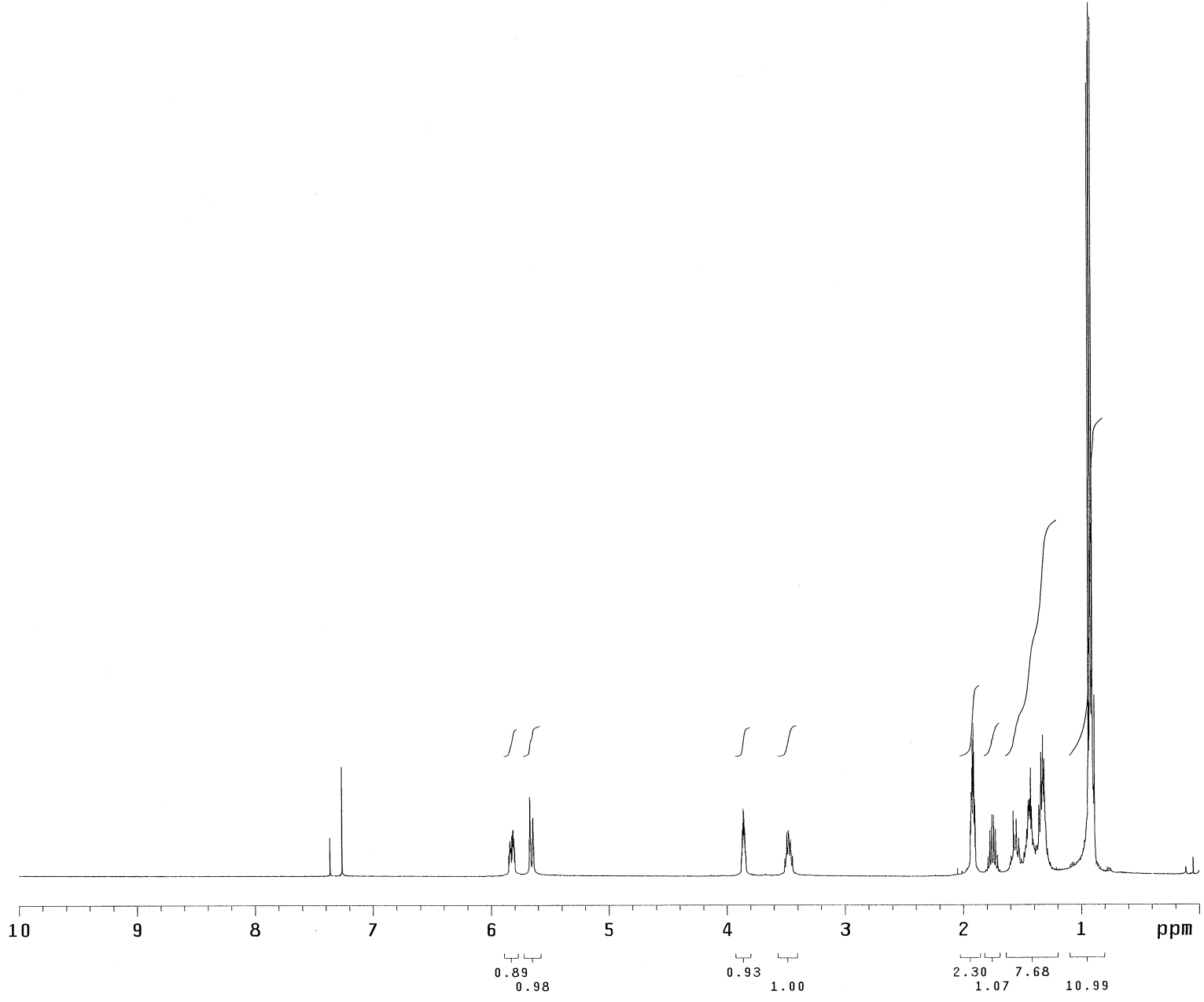
^{1}H NMR

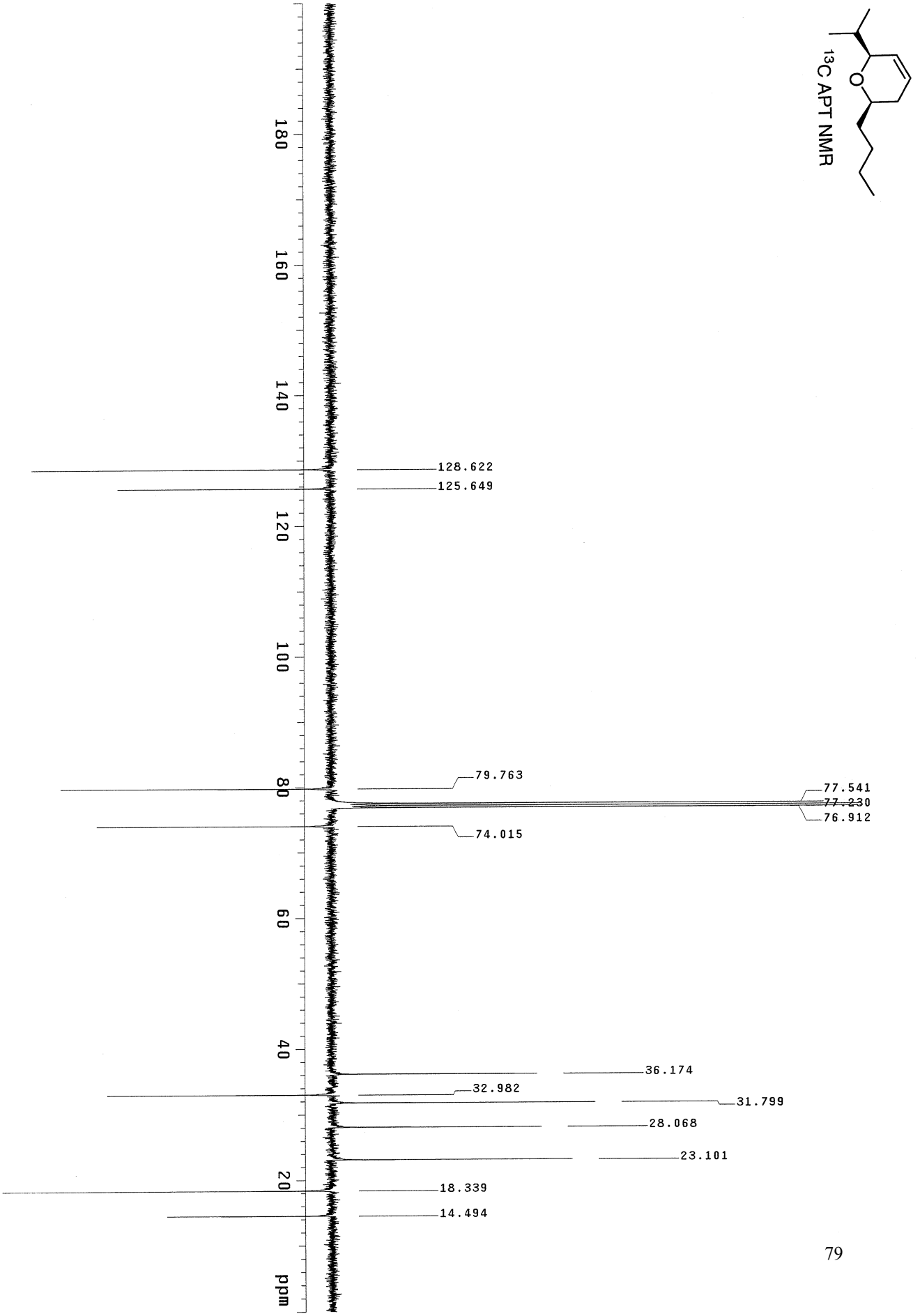


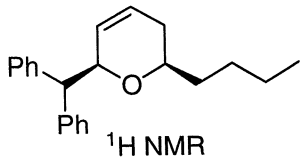

Ph
O
^{13}C APT NMR
180
160
140
120
100
80
60
40
20
ppm
138.480
129.691
129.433
128.212
126.210
125.209
77.548
77.230
76.919
75.986
74.333
42.347
36.121
31.586
28.015
23.070
14.471



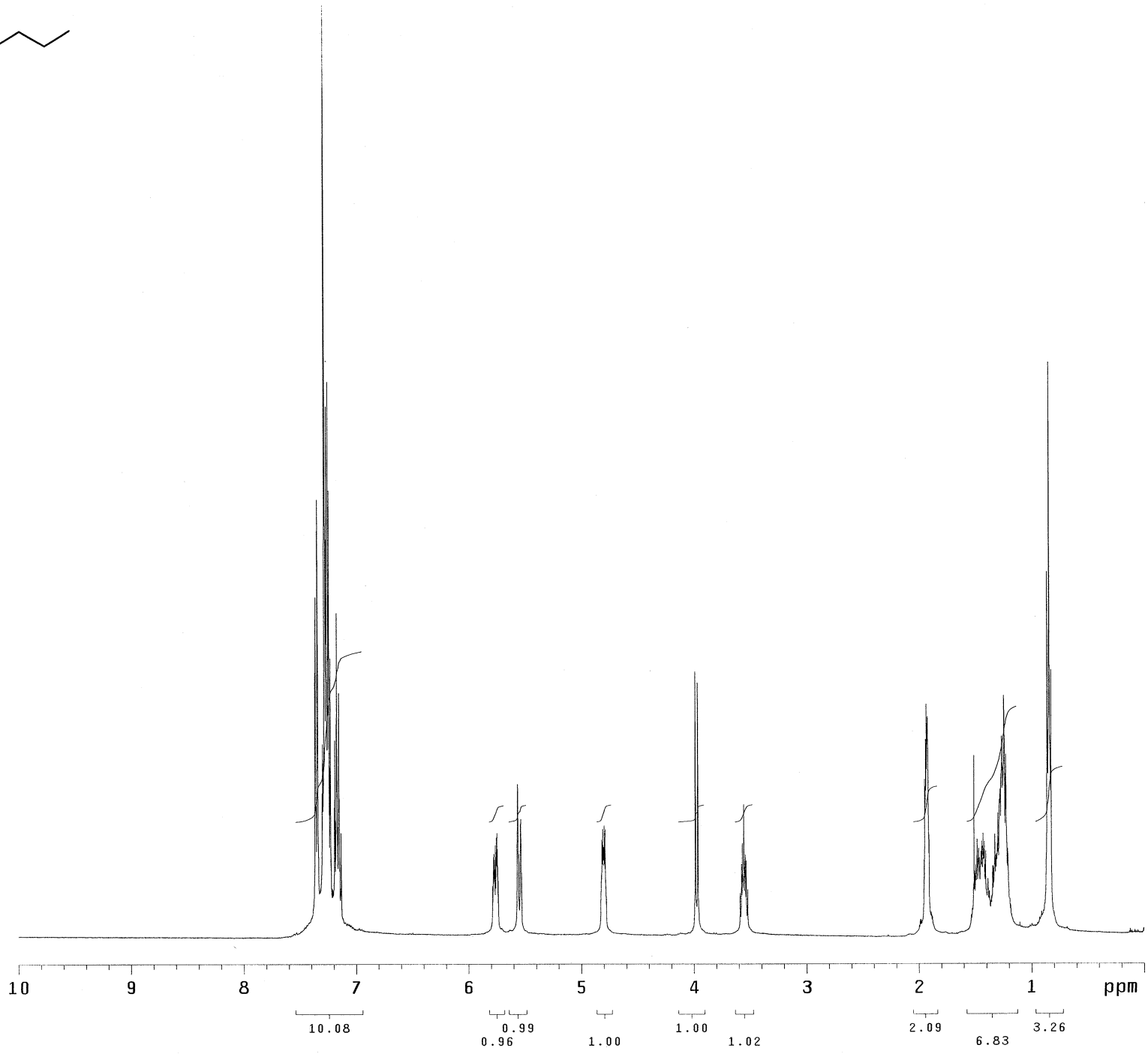
^{1}H NMR

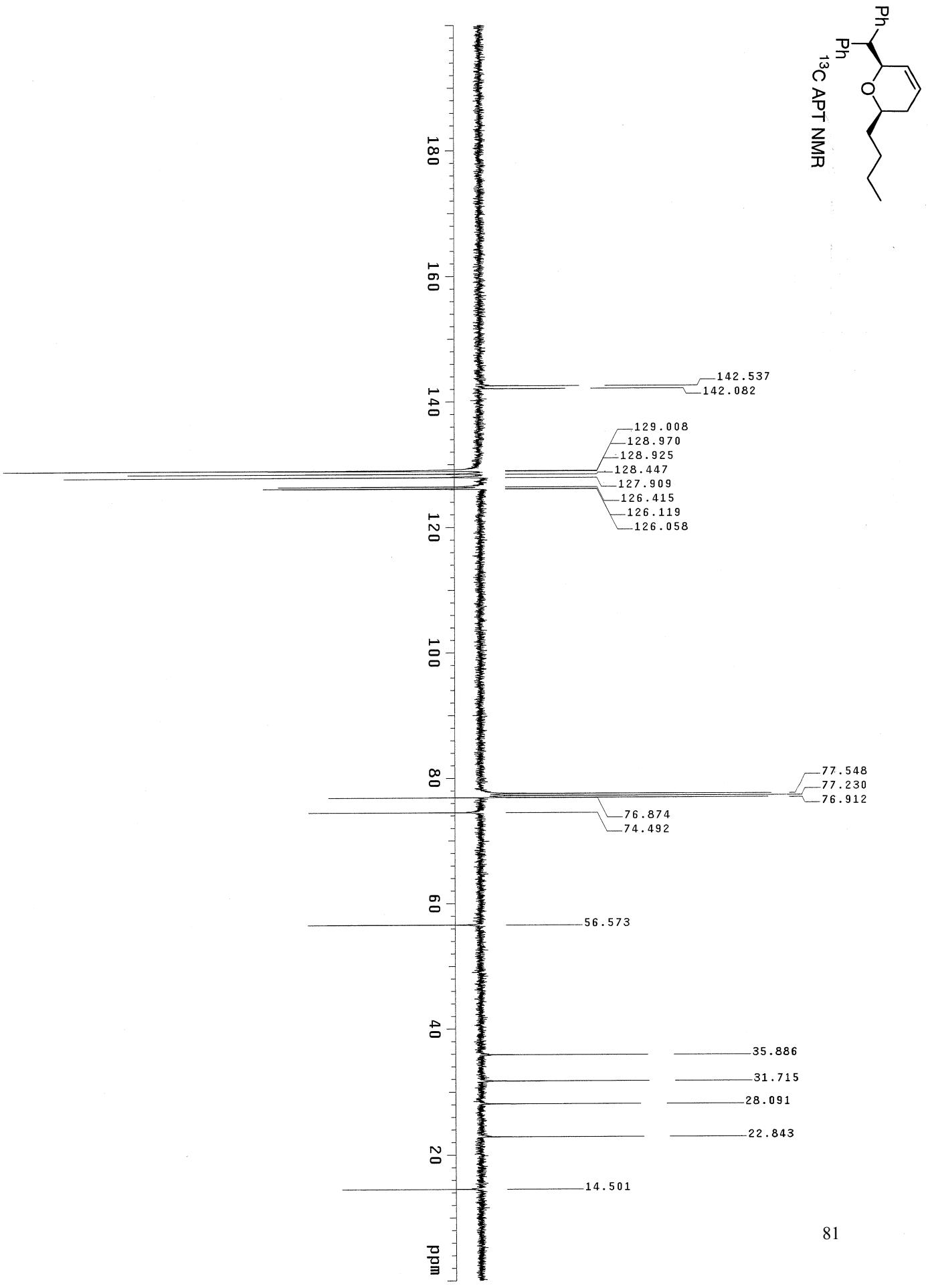


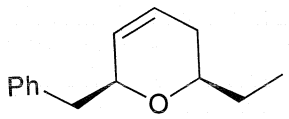

^{13}C APT NMR
O
180
160
140
120
100
80
60
40
20
ppm
128.622
125.649
79.763
77.541
77.230
76.912
74.015
36.174
32.982
31.799
28.068
23.101
18.339
14.494



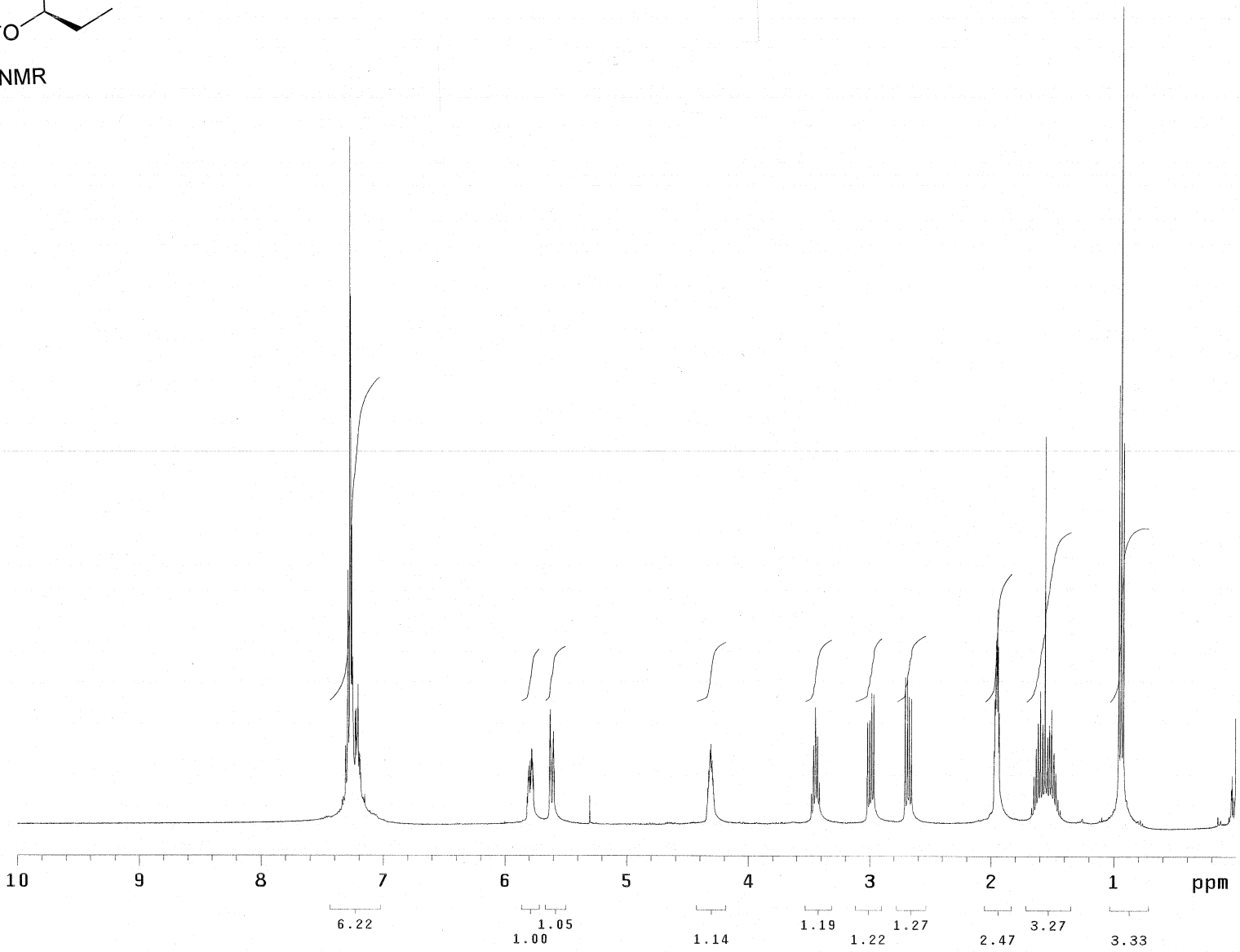
^{1}H NMR

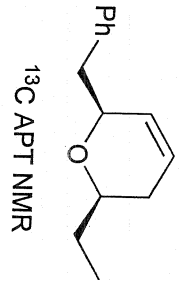



Ph
Ph
O
13C APT NMR
180
160
140
120
100
80
60
40
20
ppm
142.537
142.082
129.008
128.970
128.925
128.447
127.909
126.415
126.119
126.058
77.548
77.230
76.912
76.874
74.492
56.573
35.886
31.715
28.091
22.843
14.501

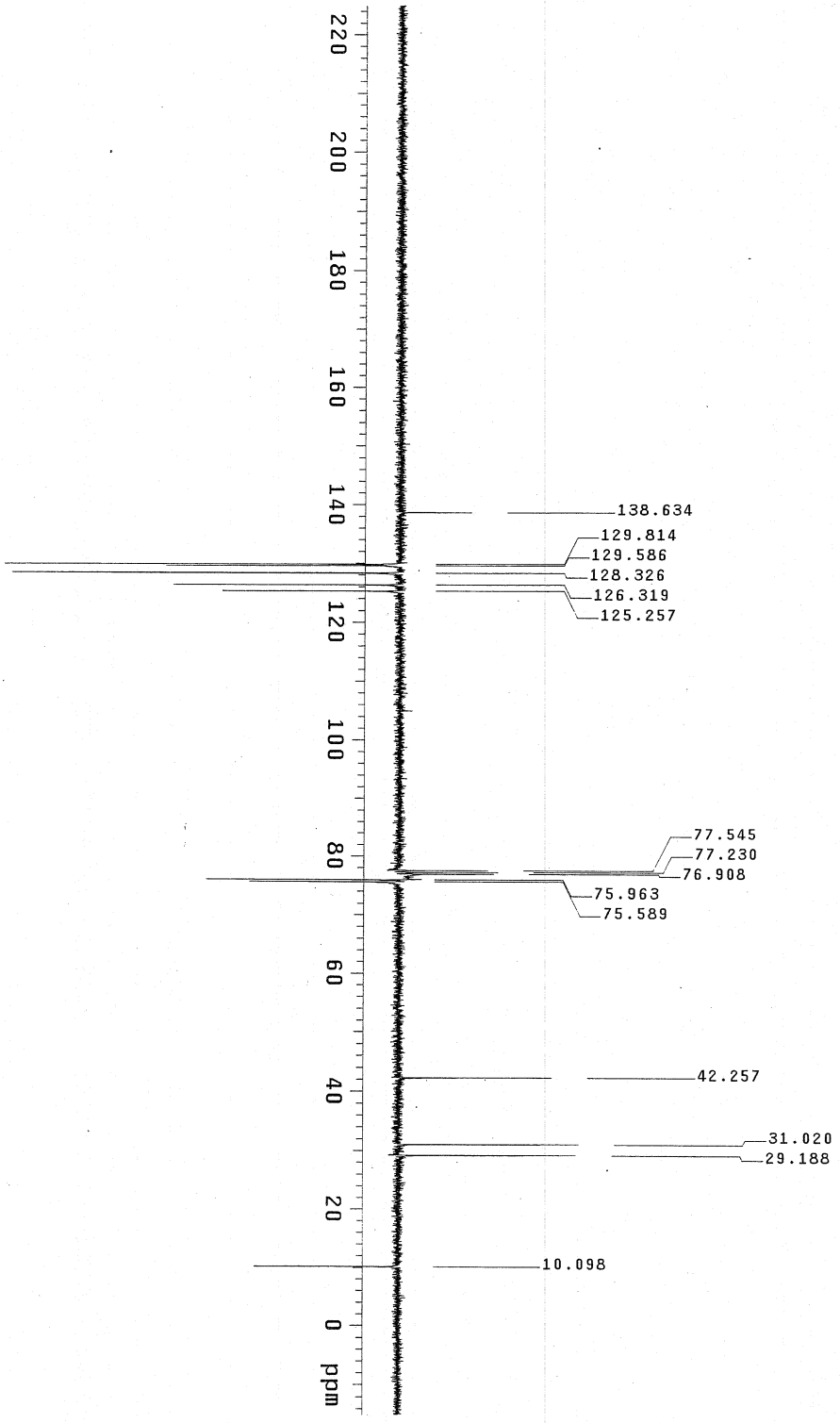


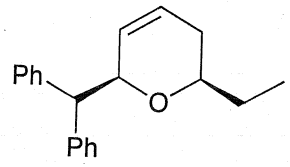
^{1}H NMR



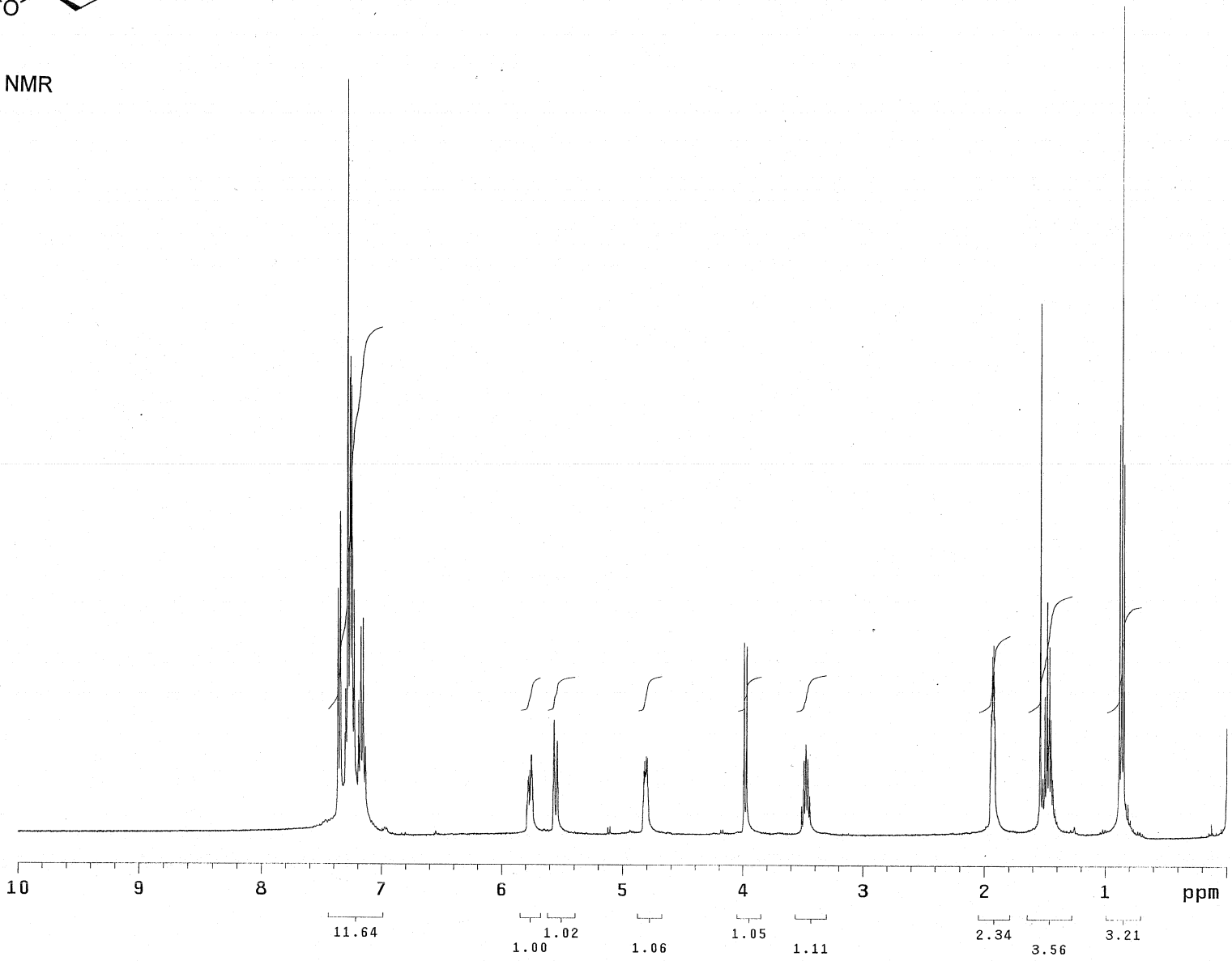

Ph
O

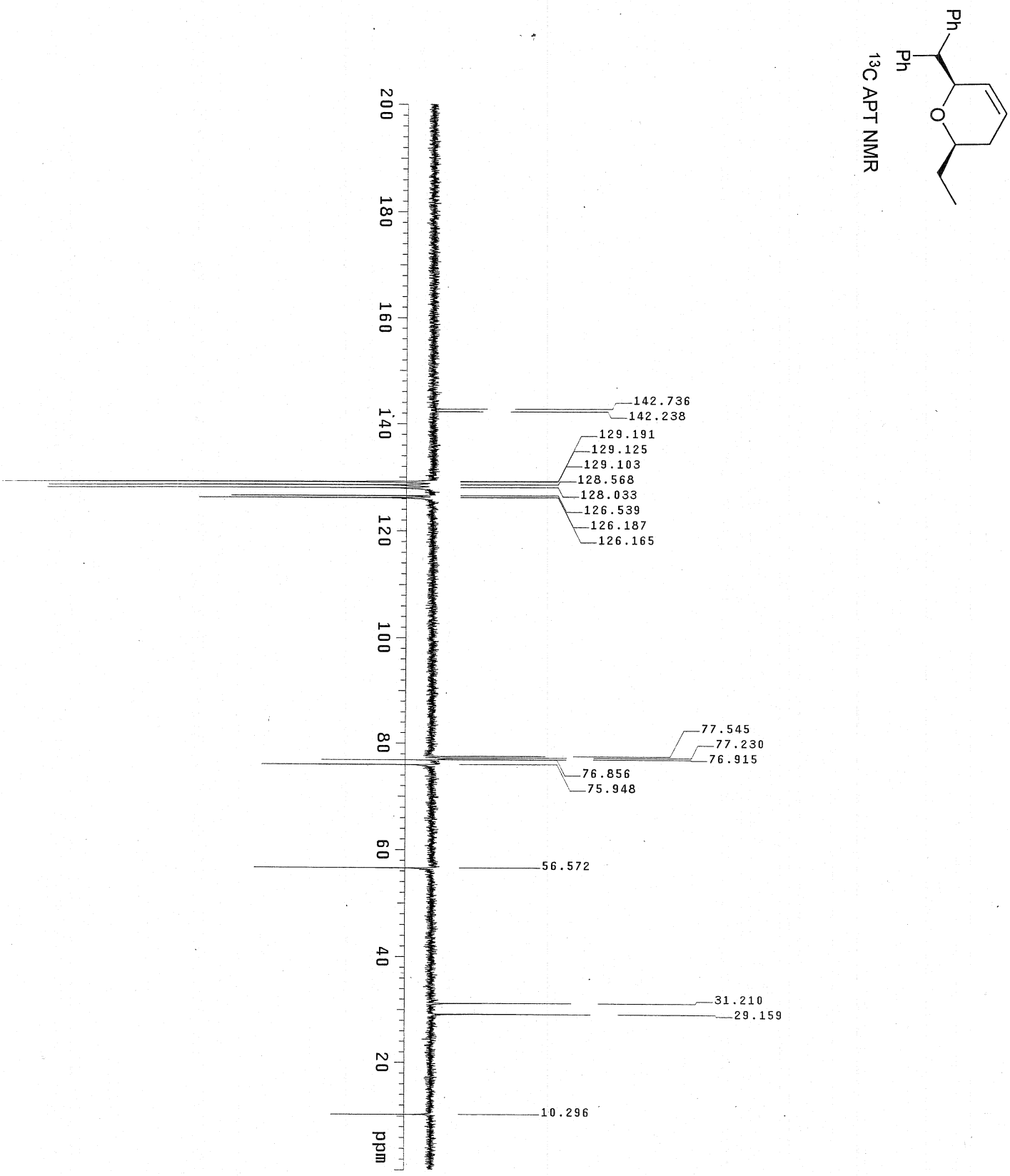
^{13}C APT NMR

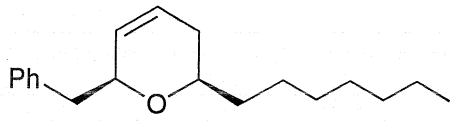

220
200
180
160
140
120
100
80
60
40
20
0
ppm
138.634
129.814
129.586
128.326
126.319
125.257
77.545
77.230
76.908
75.963
75.589
42.257
31.020
29.188
10.098



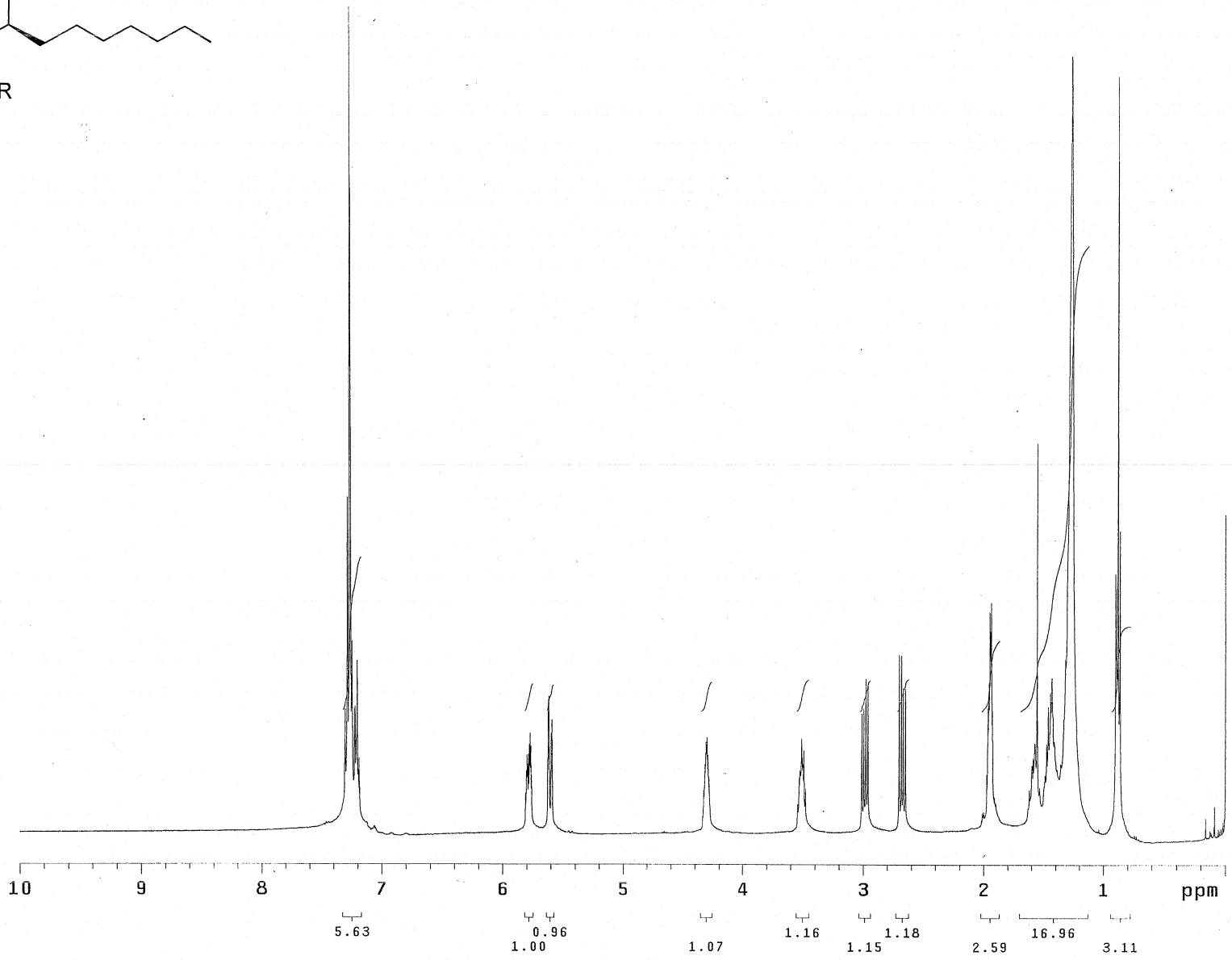
^{1}H NMR

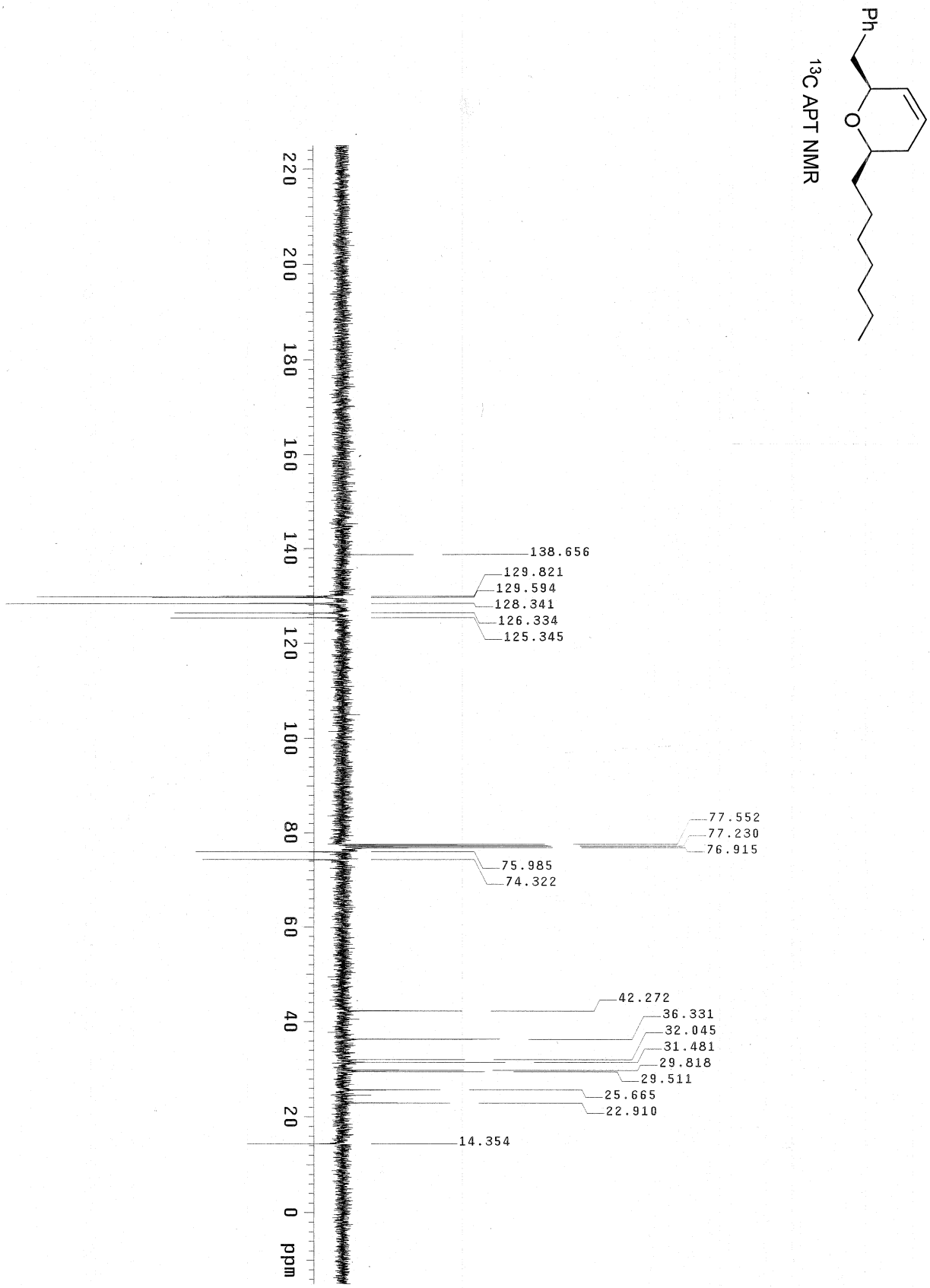


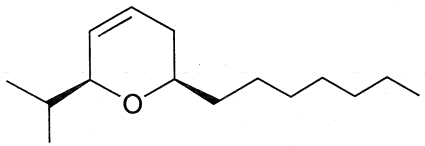

Ph
Ph
O
13C APT NMR
200
180
160
140
120
100
80
60
40
20
ppm
142.736
142.238
129.191
129.125
129.103
128.568
128.033
126.539
126.187
126.165
77.545
77.230
76.915
76.856
75.948
56.572
31.210
29.159
10.296



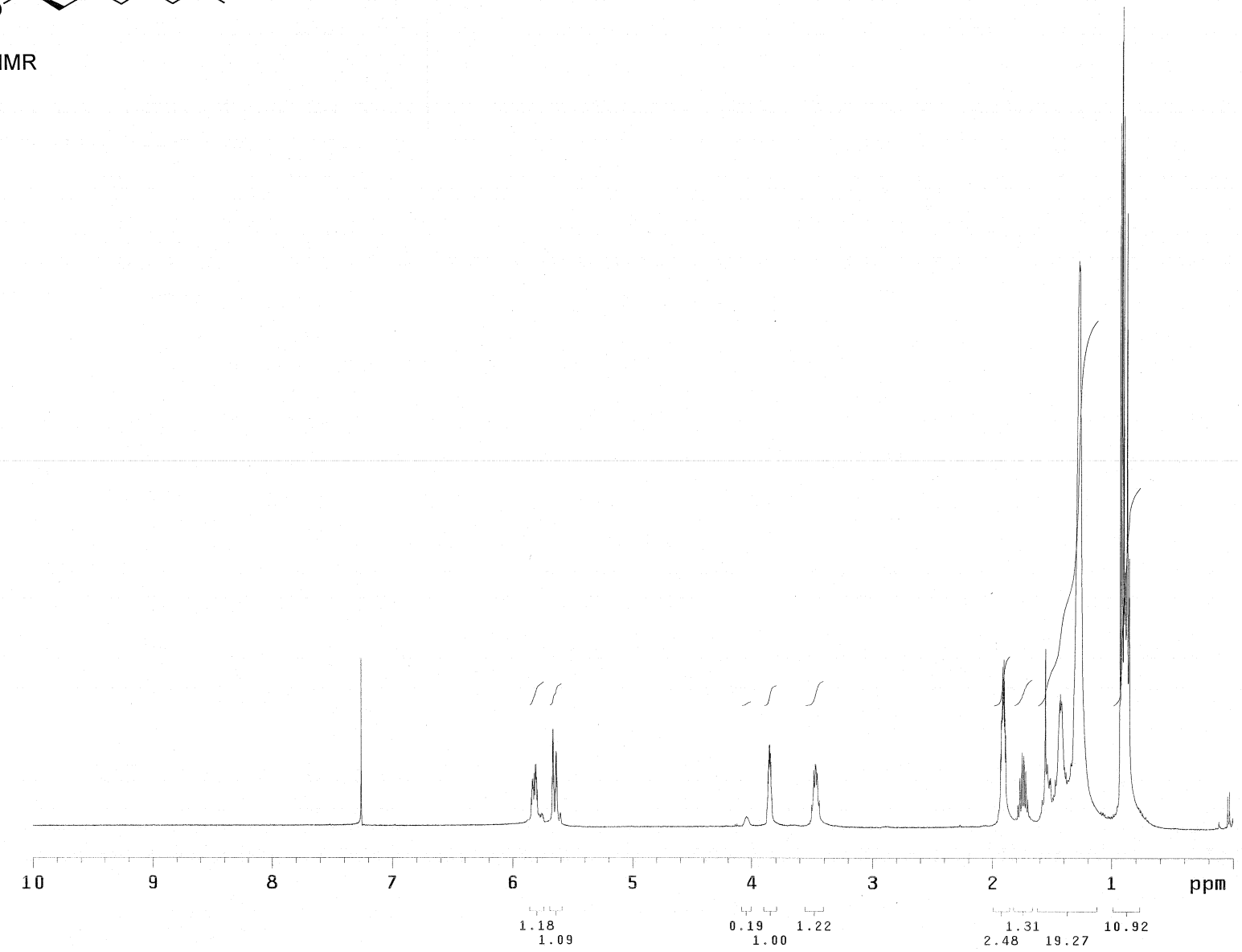
^{1}H NMR

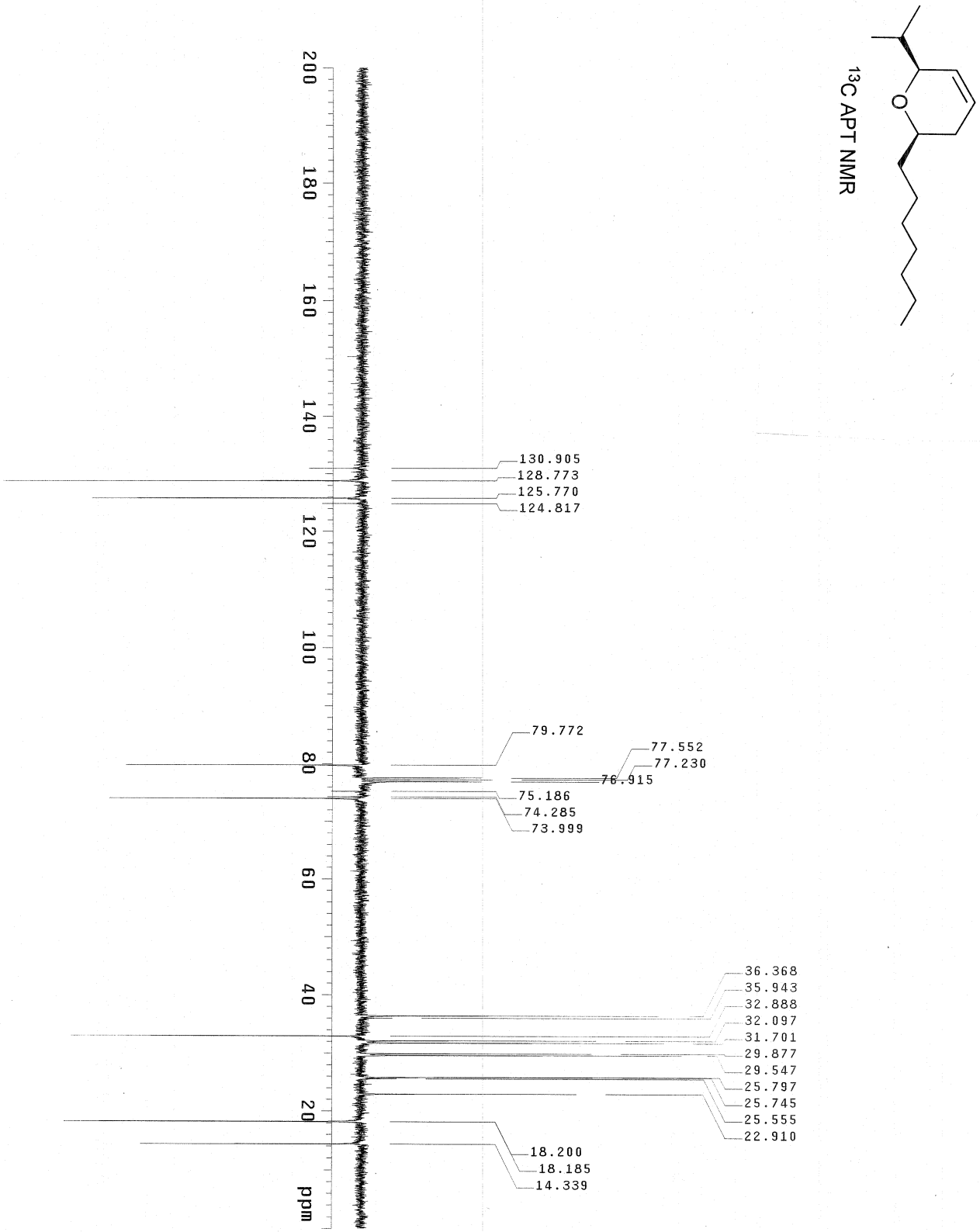



Ph
O
^{13}C APT NMR
220
200
180
160
140
120
100
80
60
40
20
0
ppm
138.656
129.821
129.594
128.341
126.334
125.345
77.552
77.230
76.915
75.985
74.322
42.272
36.331
32.045
31.481
29.818
29.511
25.665
22.910
14.354



^{1}H NMR




^{13}C APT NMR
O
200
180
160
140
120
100
80
60
40
20
ppm
130.905
128.773
125.770
124.817
79.772
77.552
77.230
76.915
75.186
74.285
73.999
36.368
35.943
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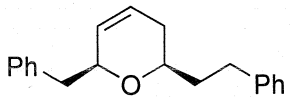
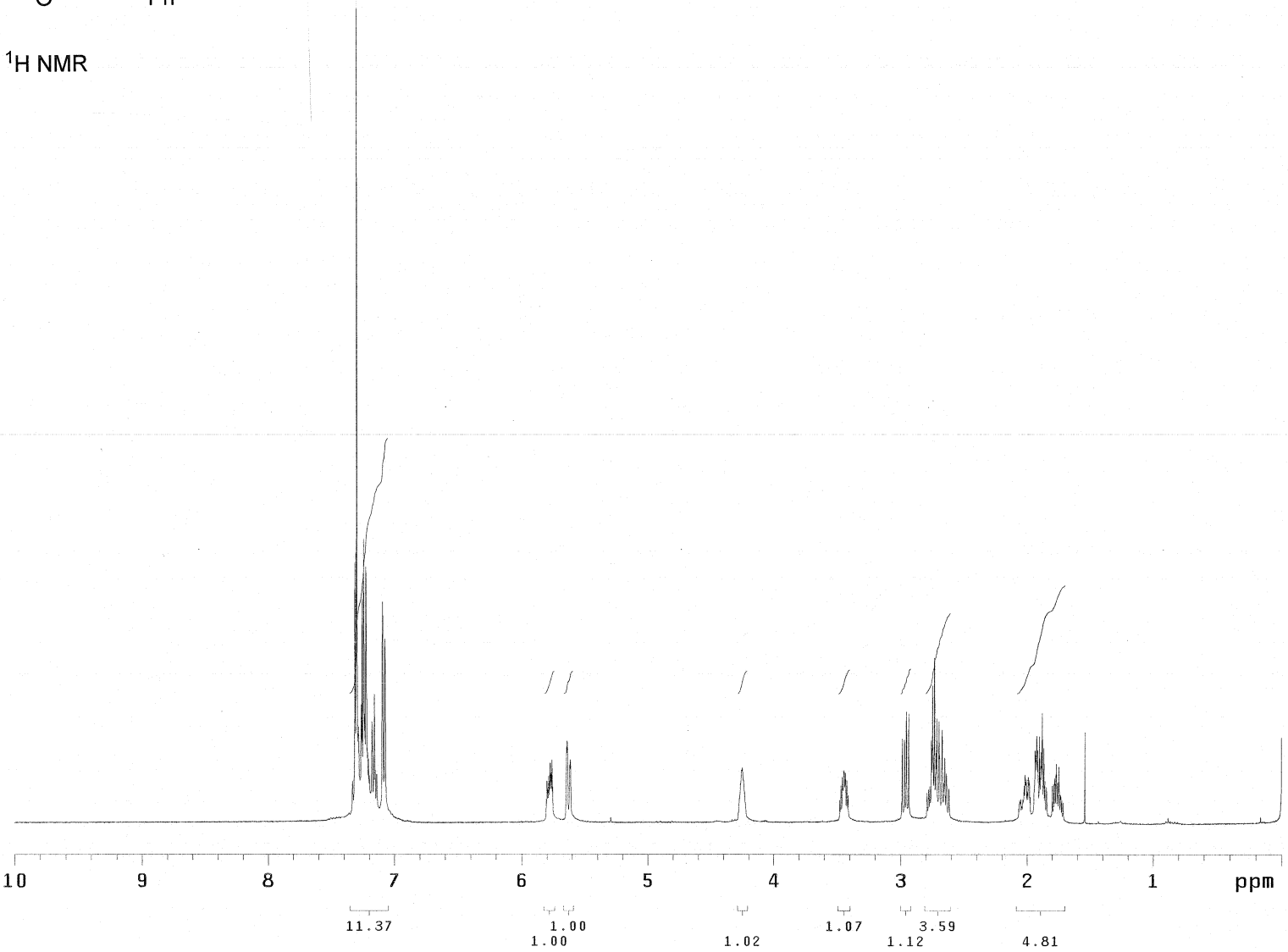
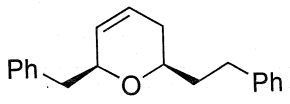
25.745
25.555
22.910
18.200
18.185
14.339

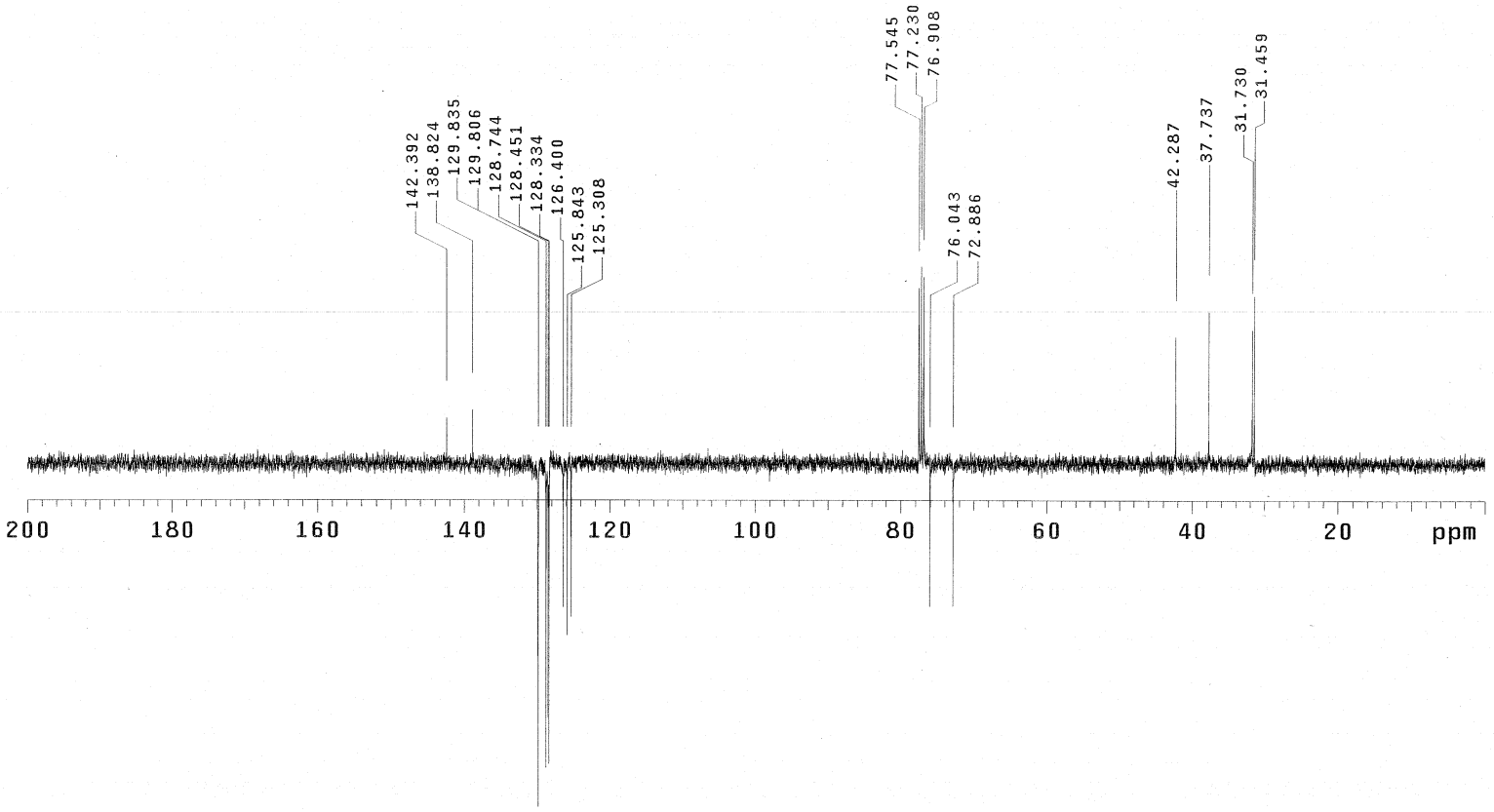


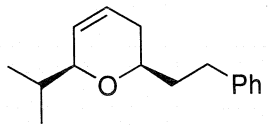
^{1}H NMR



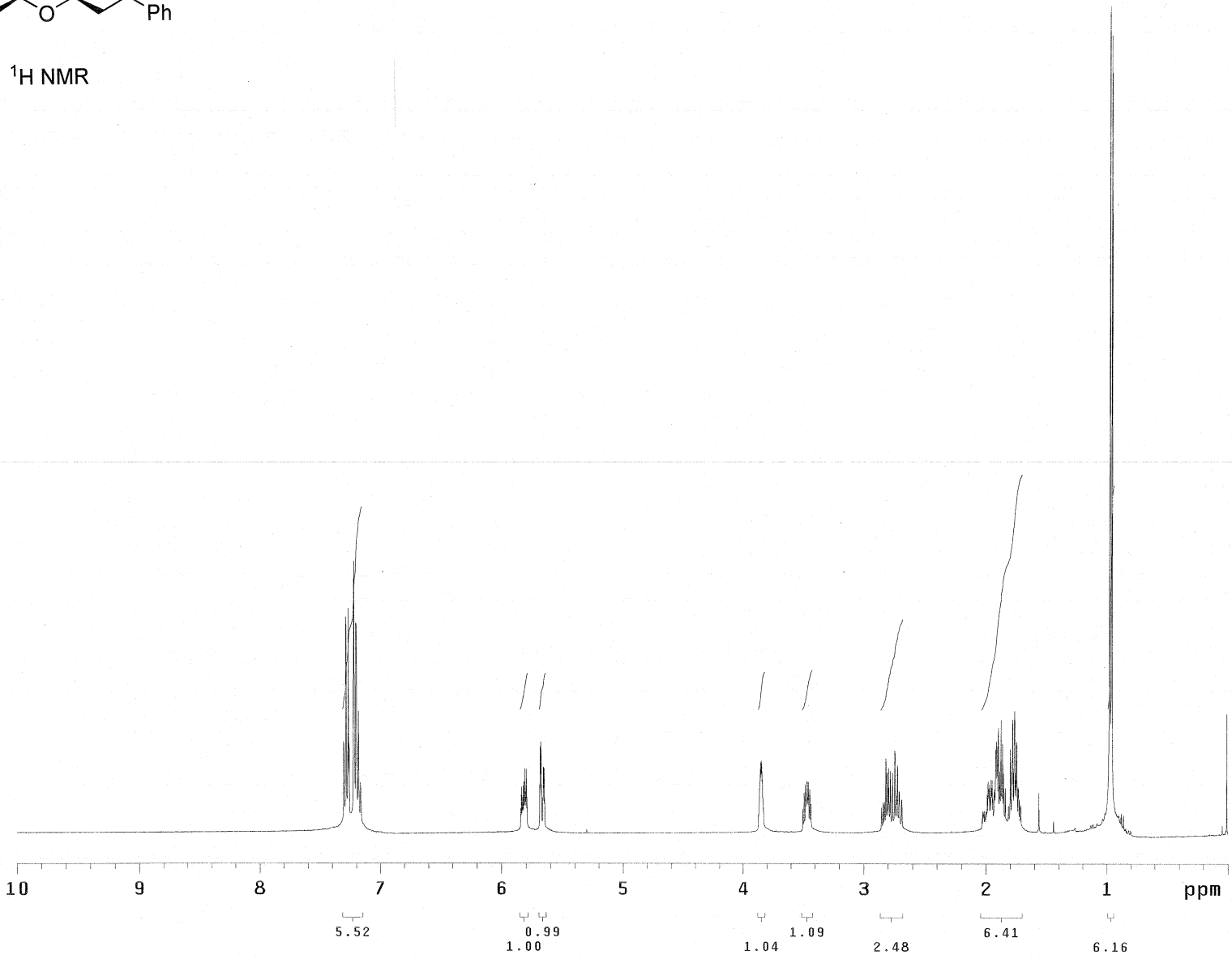

Ph
O
Ph

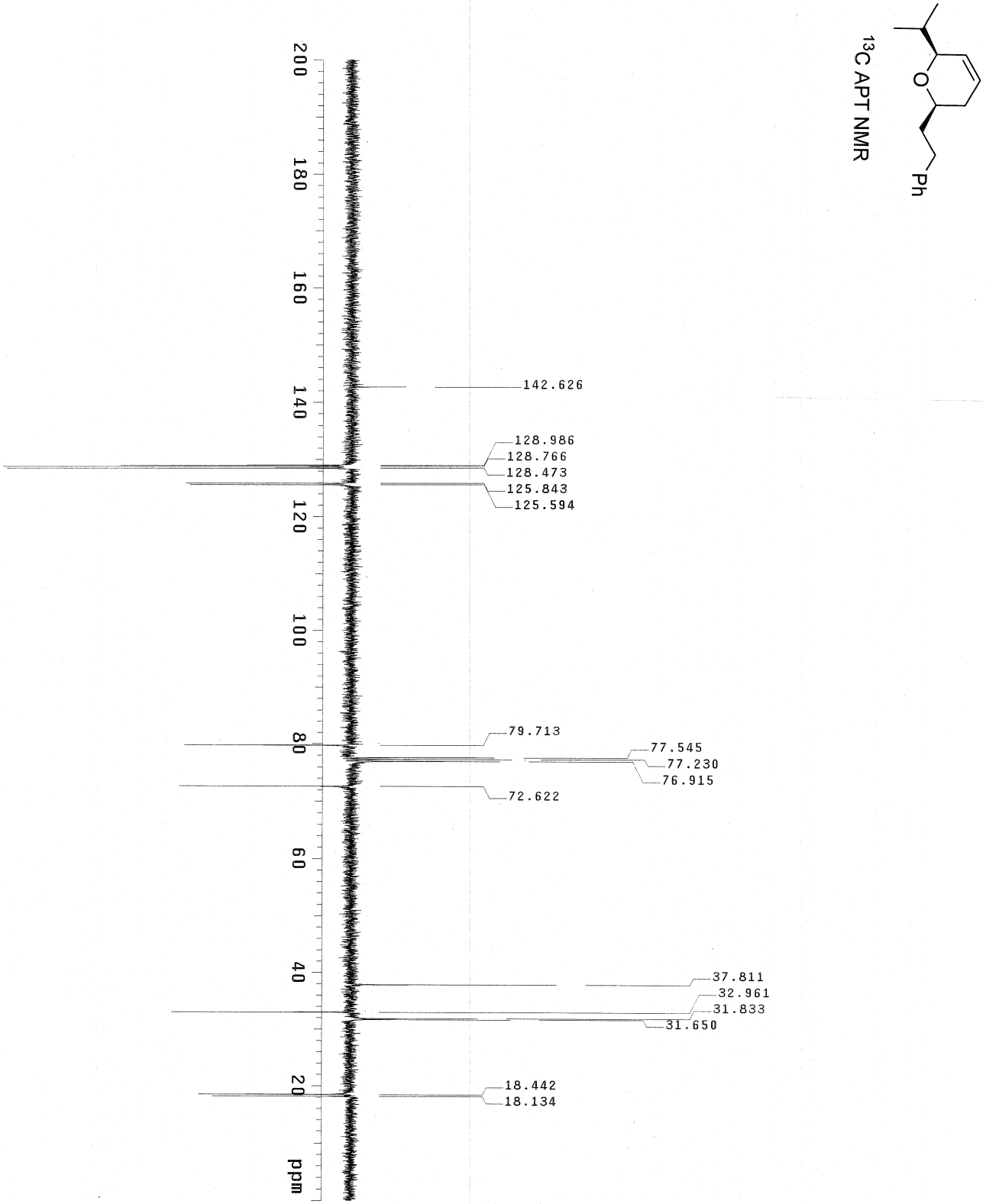
^{13}C APT NMR

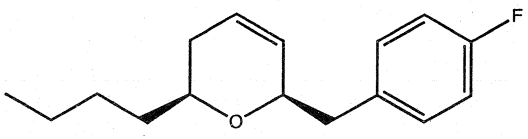

142.392
138.824
129.835
129.806
128.744
128.451
128.334
126.400
125.843
125.308
77.545
77.230
76.908
76.043
72.886
42.287
37.737
31.730
31.459
200
180
160
140
120
100
80
60
40
20
ppm



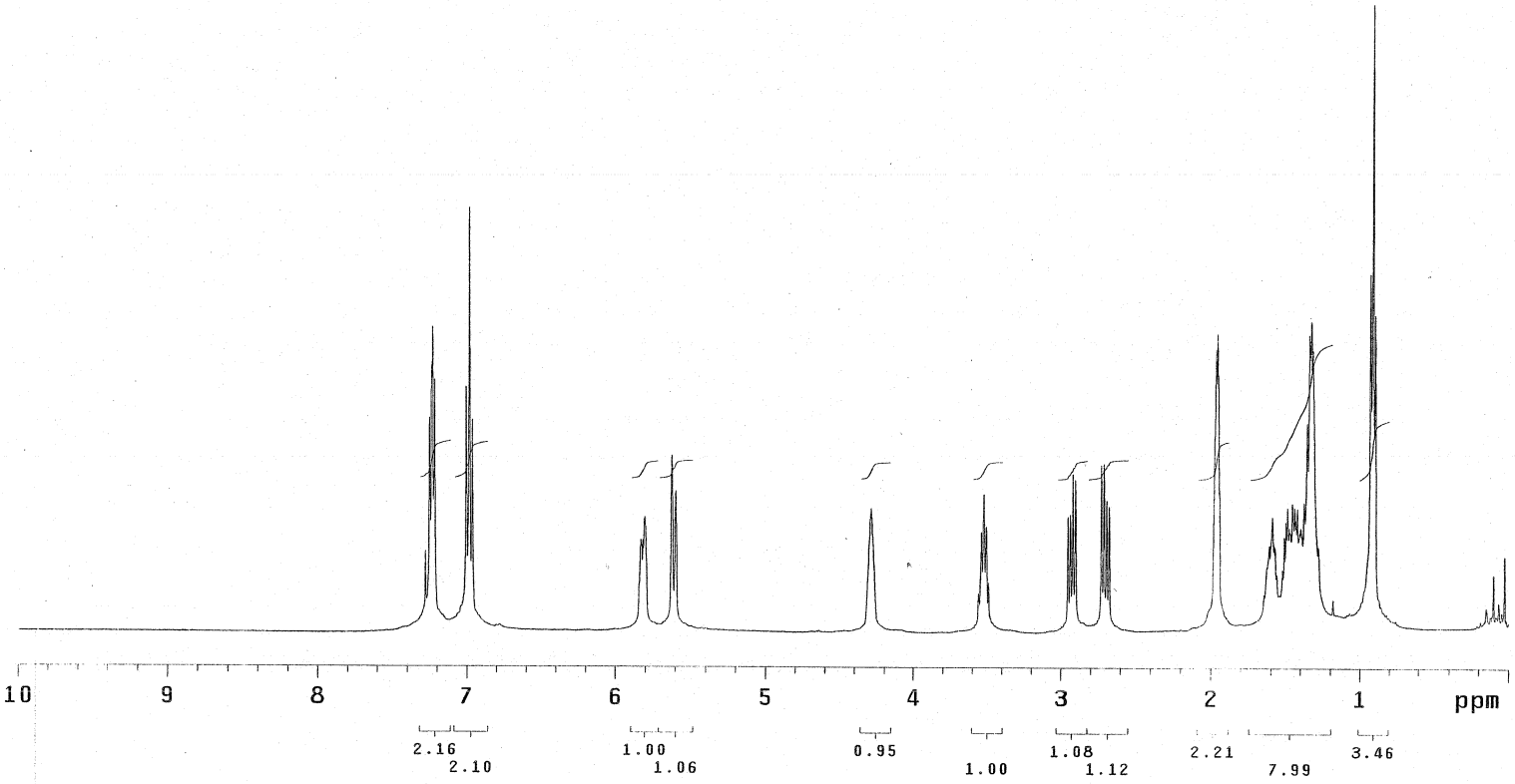
^{1}H NMR



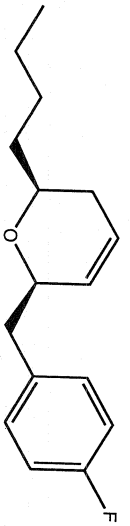

^{13}C APT NMR
O
Ph
200
180
160
140
120
100
80
60
40
20
ppm
142.626
128.986
128.766
128.473
125.843
125.594
79.713
77.545
77.230
76.915
72.622
37.811
32.961
31.833
31.650
18.442
18.134

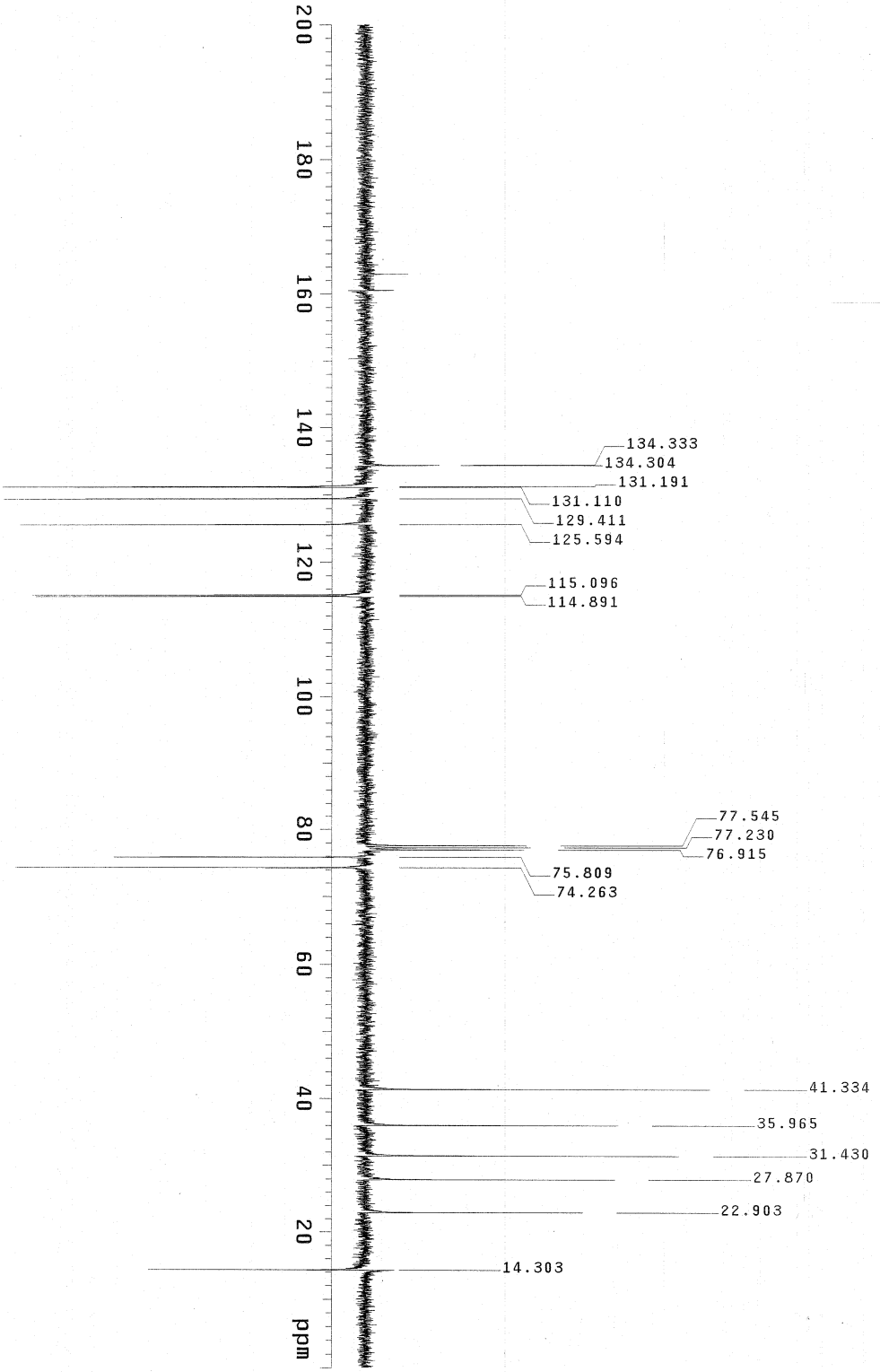


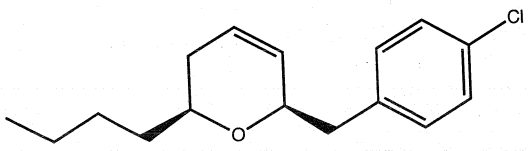
^{1}H NMR



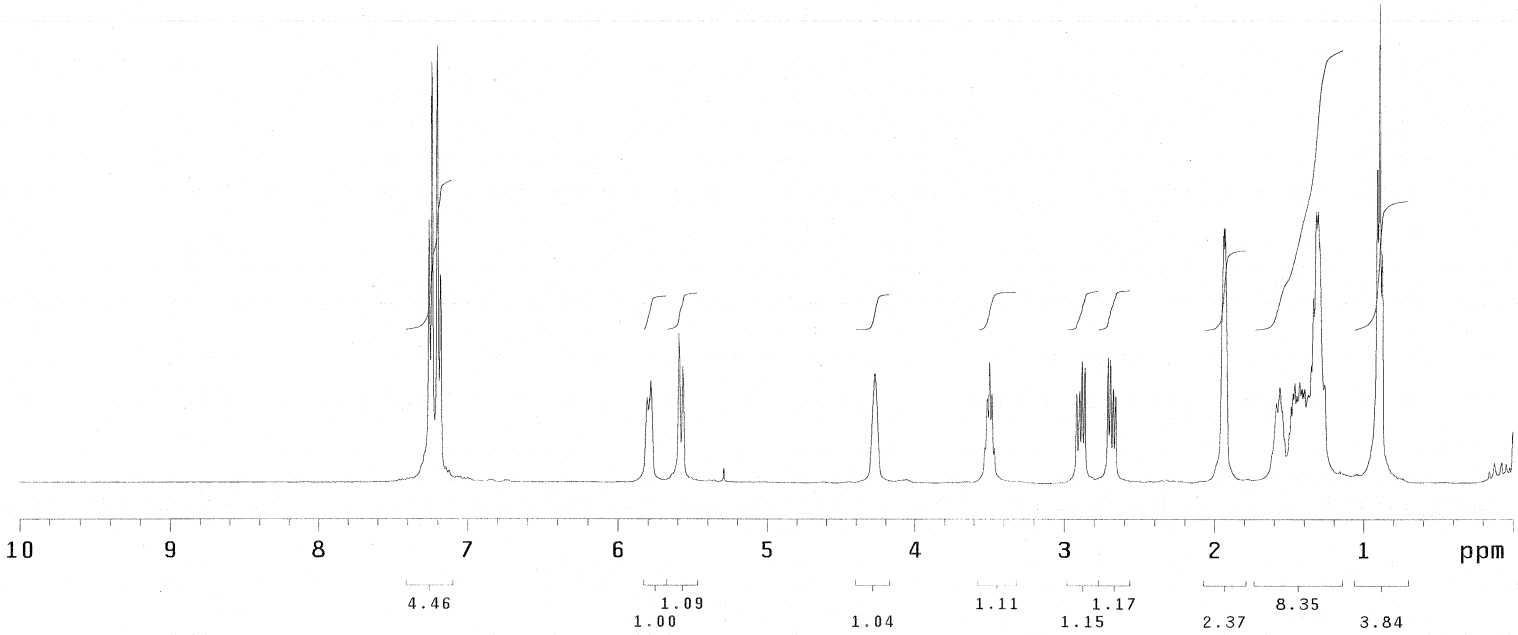
^{13}C APT NMR


O
F

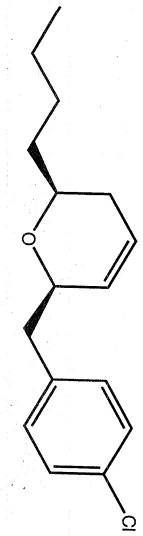

200
180
160
140
120
100
80
60
40
20
ppm
134.333
134.304
131.191
131.110
129.411
125.594
115.096
114.891
77.545
77.230
76.915
75.809
74.263
41.334
35.965
31.430
27.870
22.903
14.303

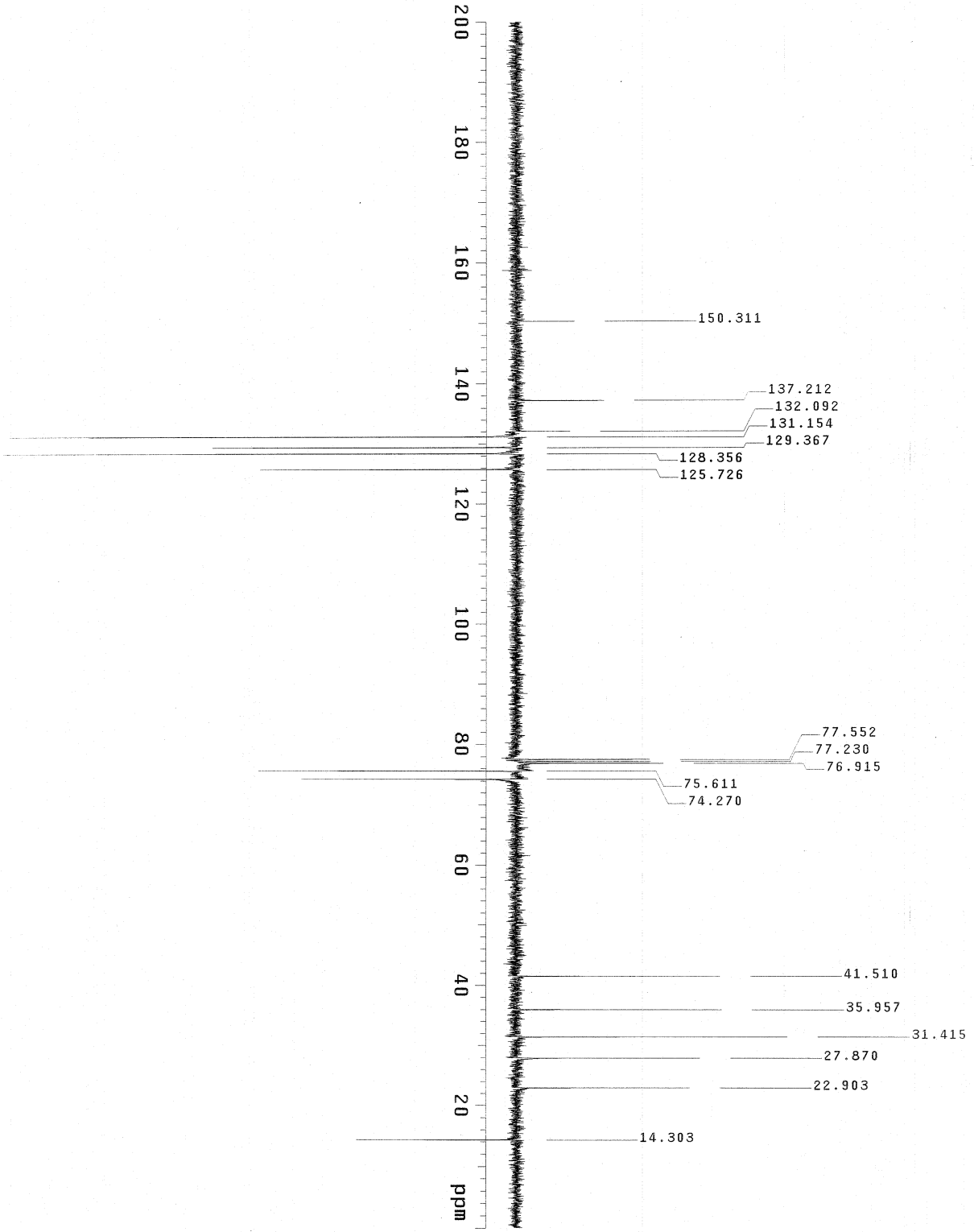


^{1}H NMR



^{13}C APT NMR


O
Cl


200
180
160
140
120
100
80
60
40
20
ppm
150.311
137.212
132.092
131.154
129.367
128.356
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76.915
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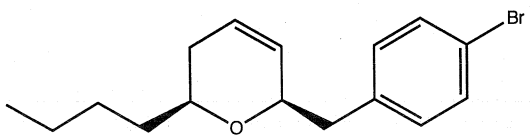
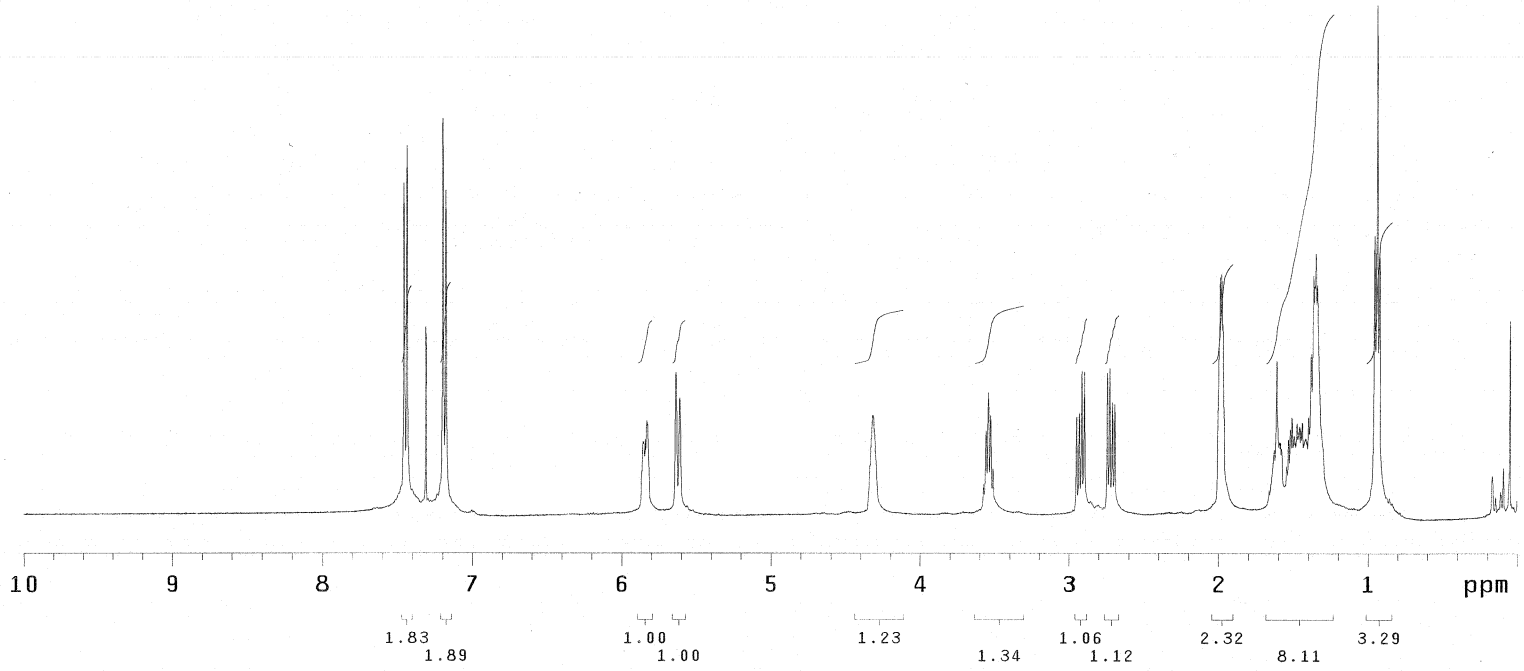
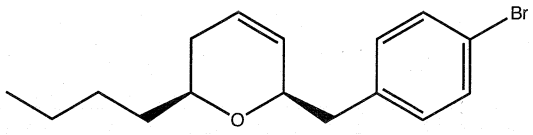
41.510
35.957
31.415
27.870
22.903
14.303

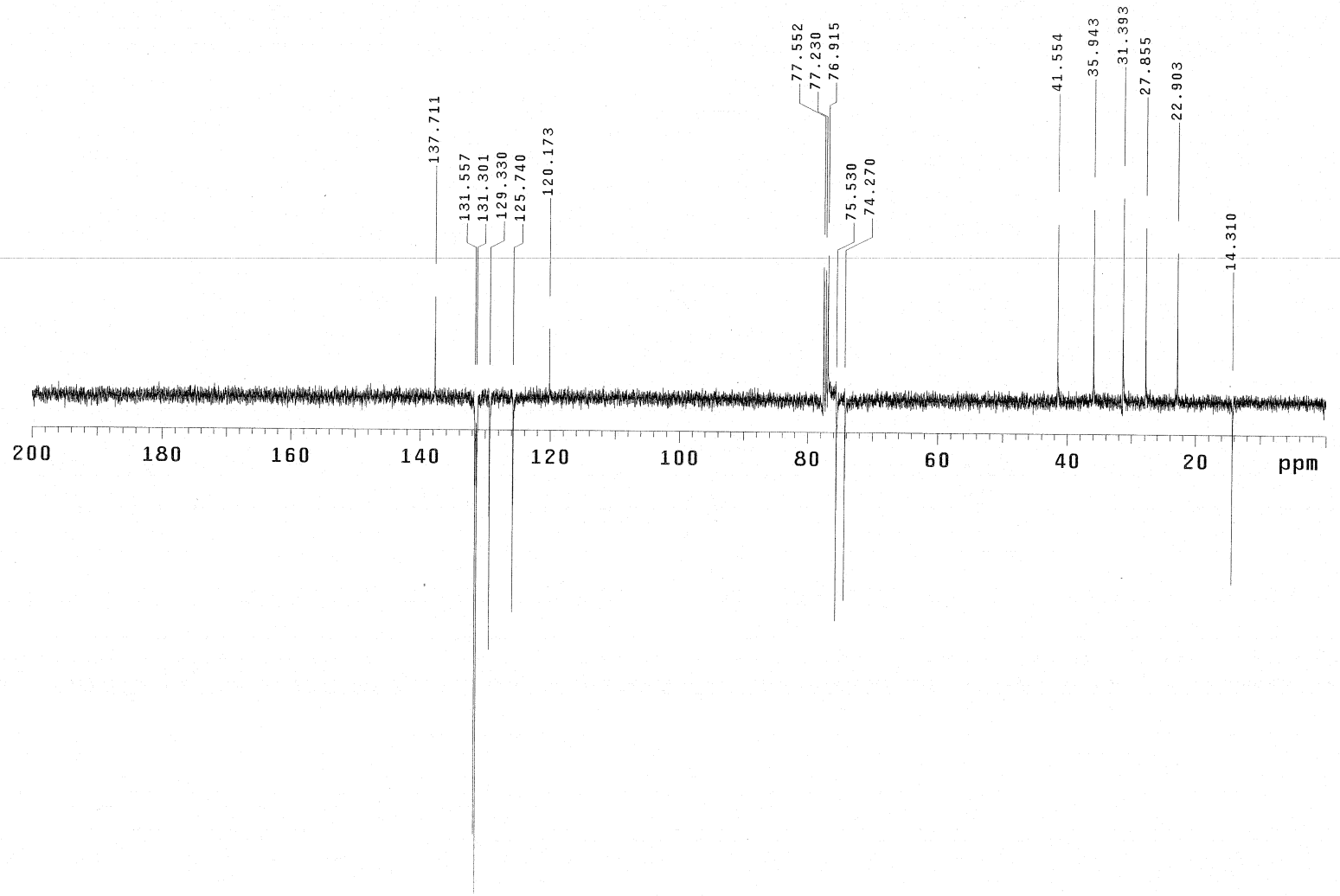

Br
O

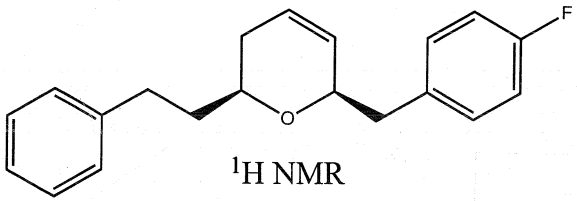
^{1}H NMR


10
9
8
7
6
5
4
3
2
1
ppm
1.83
1.89
1.00
1.00
1.23
1.34
1.06
1.12
2.32
8.11
3.29

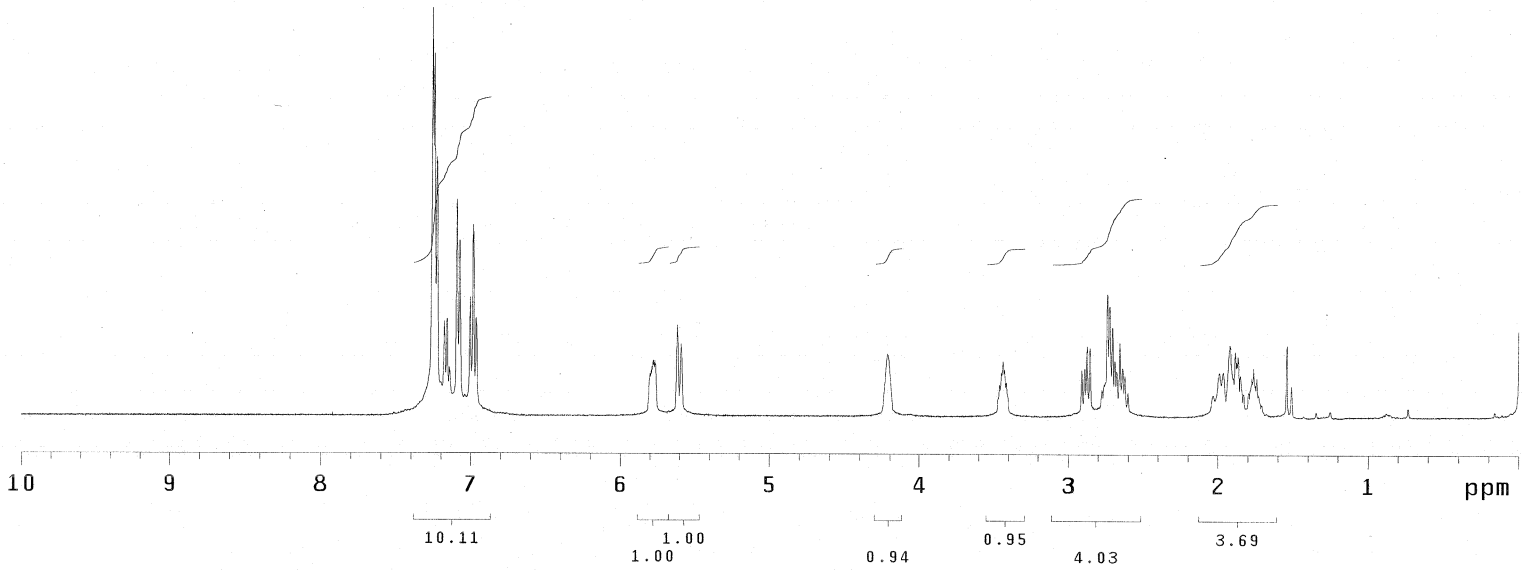

Br
O

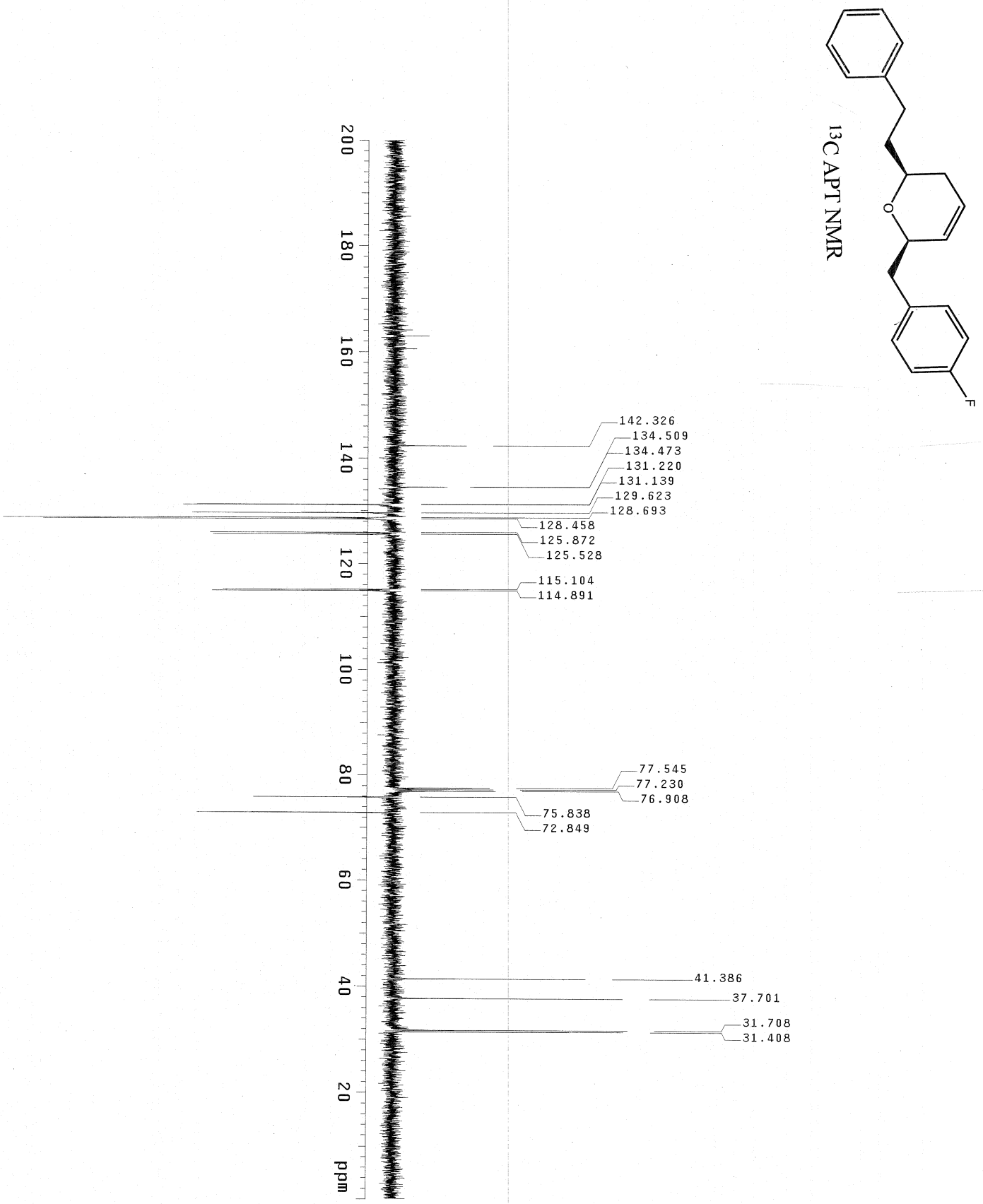
^{13}C APT NMR

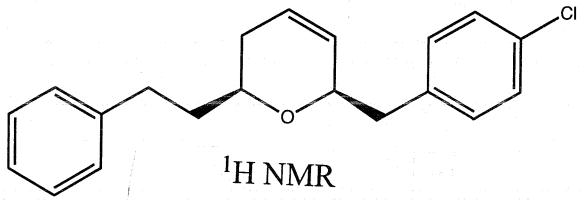

137.711
131.557
131.301
129.330
125.740
120.173
77.552
77.230
76.915
75.530
74.270
41.554
35.943
31.393
27.855
22.903
14.310
200
180
160
140
120
100
80
60
40
20
ppm



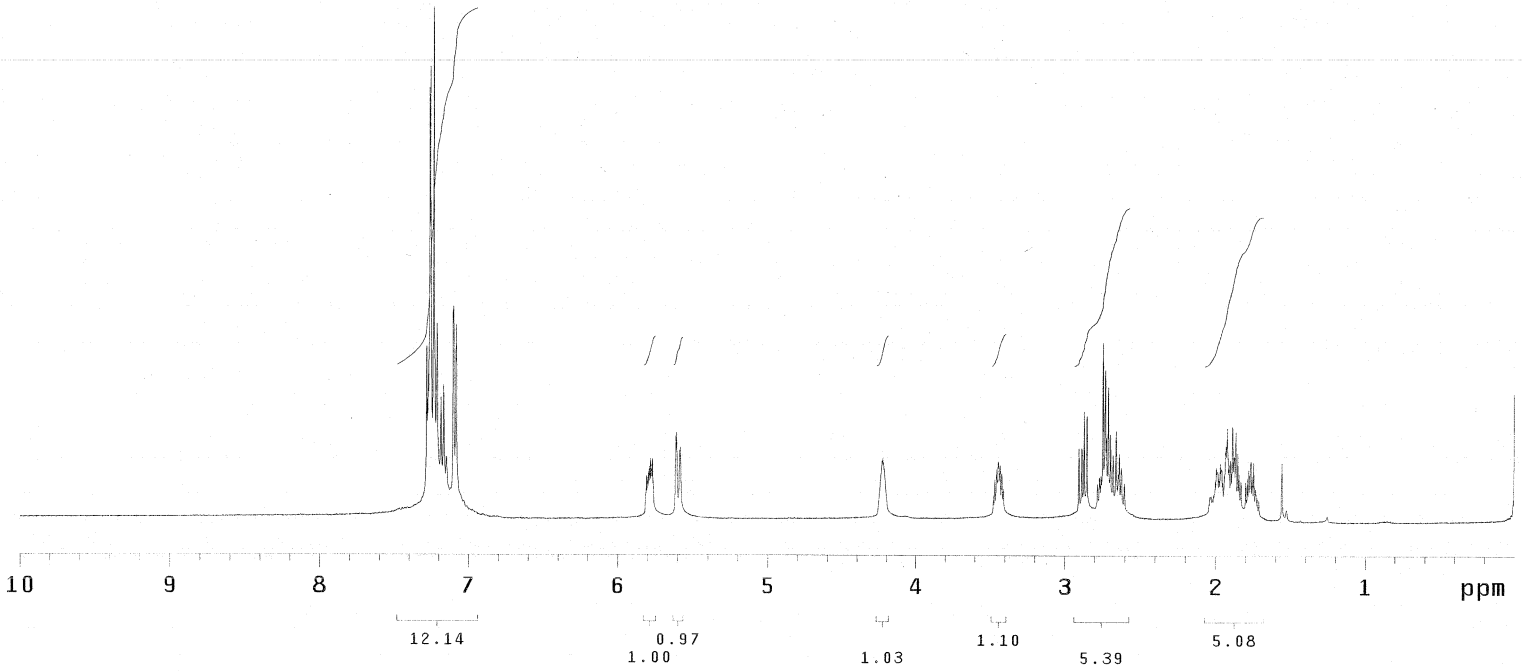
^{1}H NMR

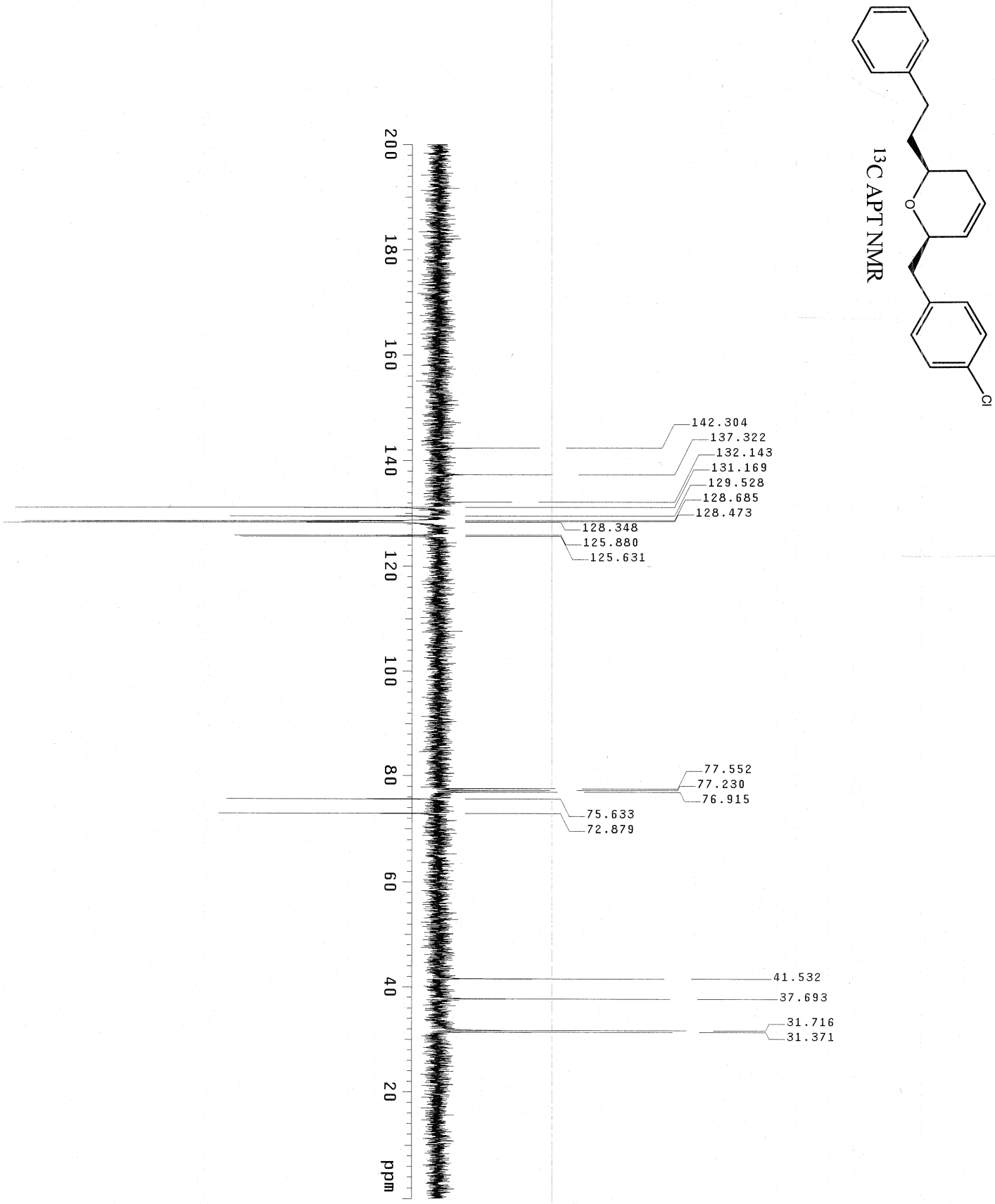



^{13}C APT NMR
O
F
200
180
160
140
120
100
80
60
40
20
ppm
142.326
134.509
134.473
131.220
131.139
129.623
128.693
128.458
125.872
125.528
115.104
114.891
77.545
77.230
76.908
75.838
72.849
41.386
37.701
31.708
31.408



^{1}H NMR




^{13}C APT NMR
O
Cl
200
180
160
140
120
100
80
60
40
20
ppm
142.304
137.322
132.143
131.169
129.528
128.685
128.473
128.348
125.880
125.631
77.552
77.230
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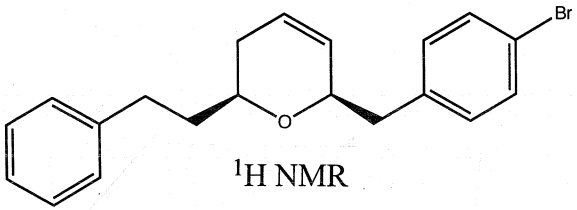
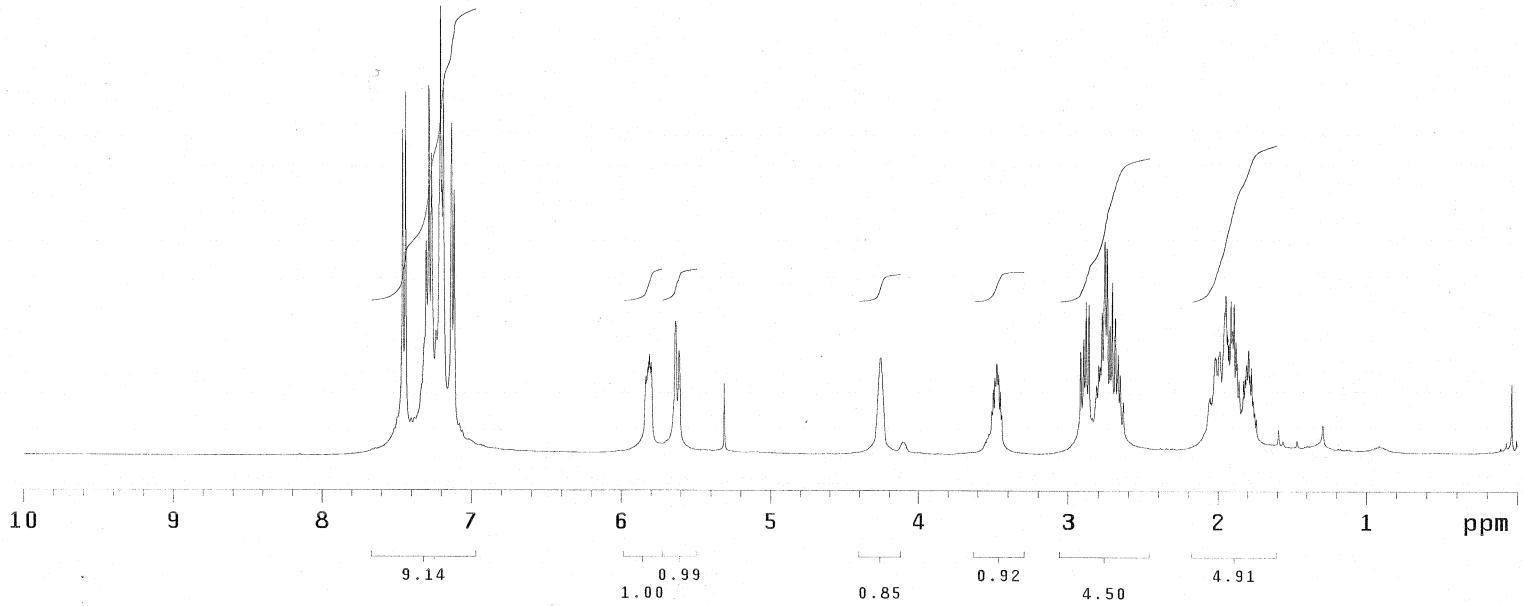
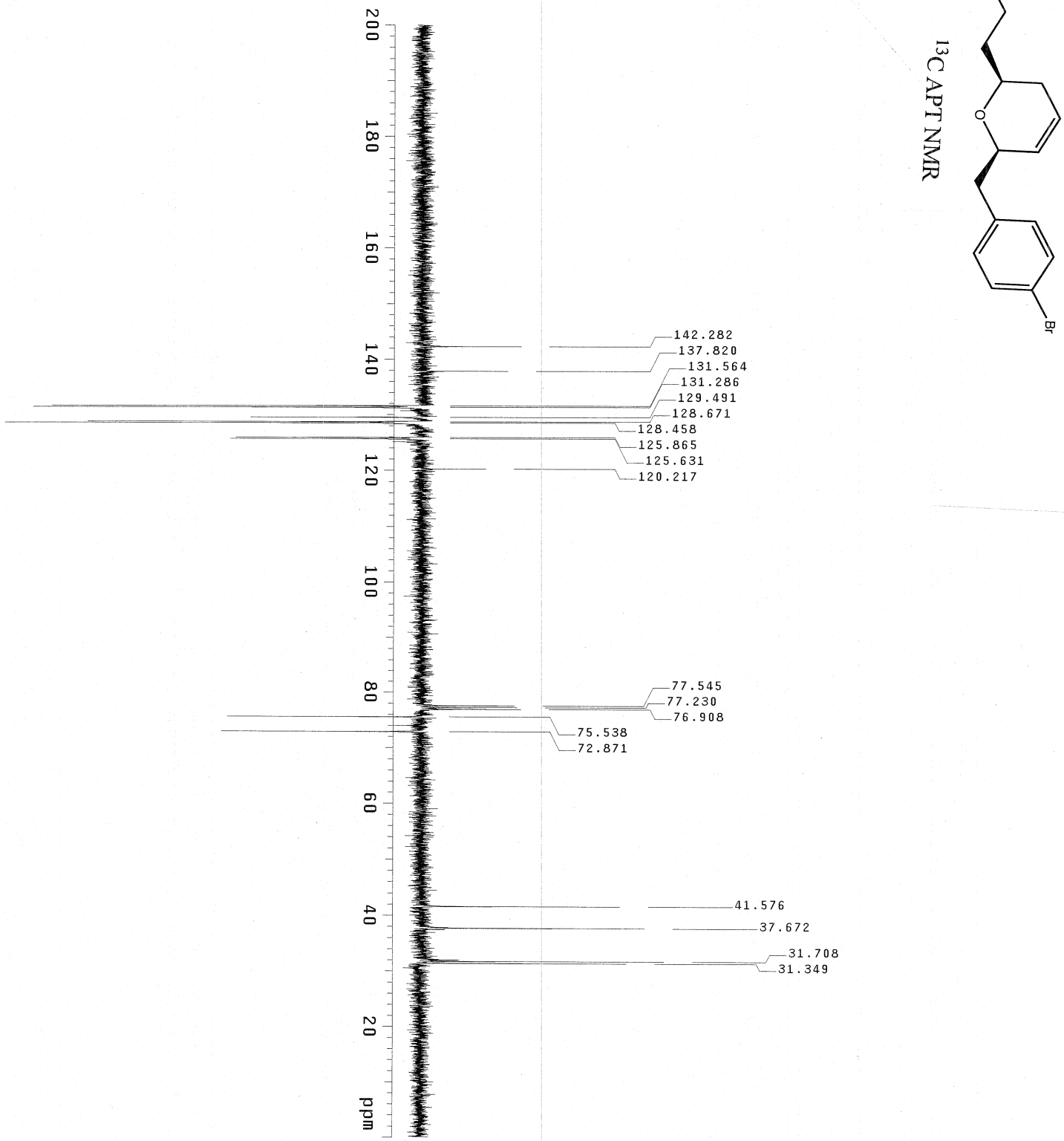
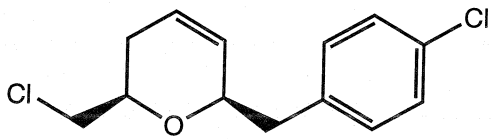
75.633
72.879
41.532
37.693
31.716
31.371



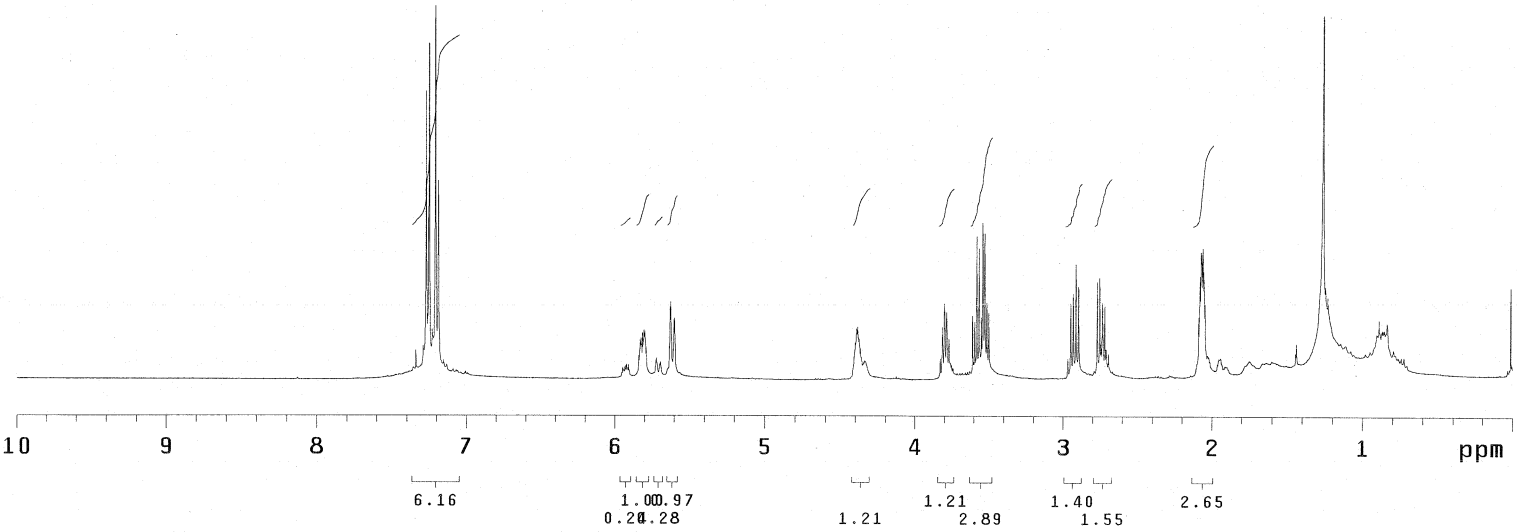
^{1}H NMR

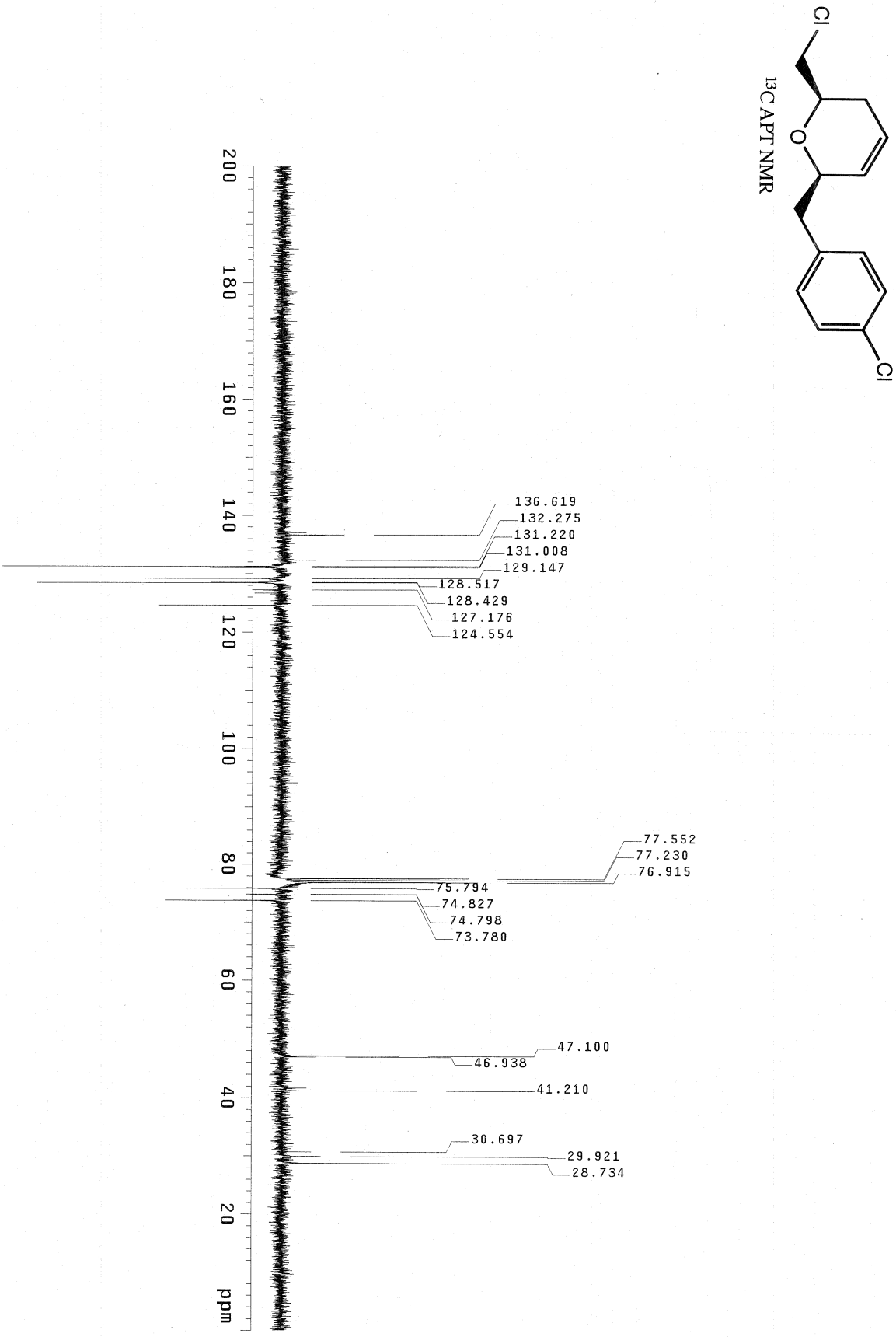


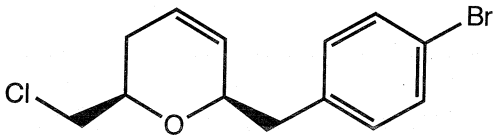

^{13}C APT NMR
O
Br
200
180
160
140
120
100
80
60
40
20
ppm
142.282
137.820
131.564
131.286
129.491
128.671
128.458
125.865
125.631
120.217
77.545
77.230
76.908
75.538
72.871
41.576
37.672
31.708
31.349


Cl
Cl
O

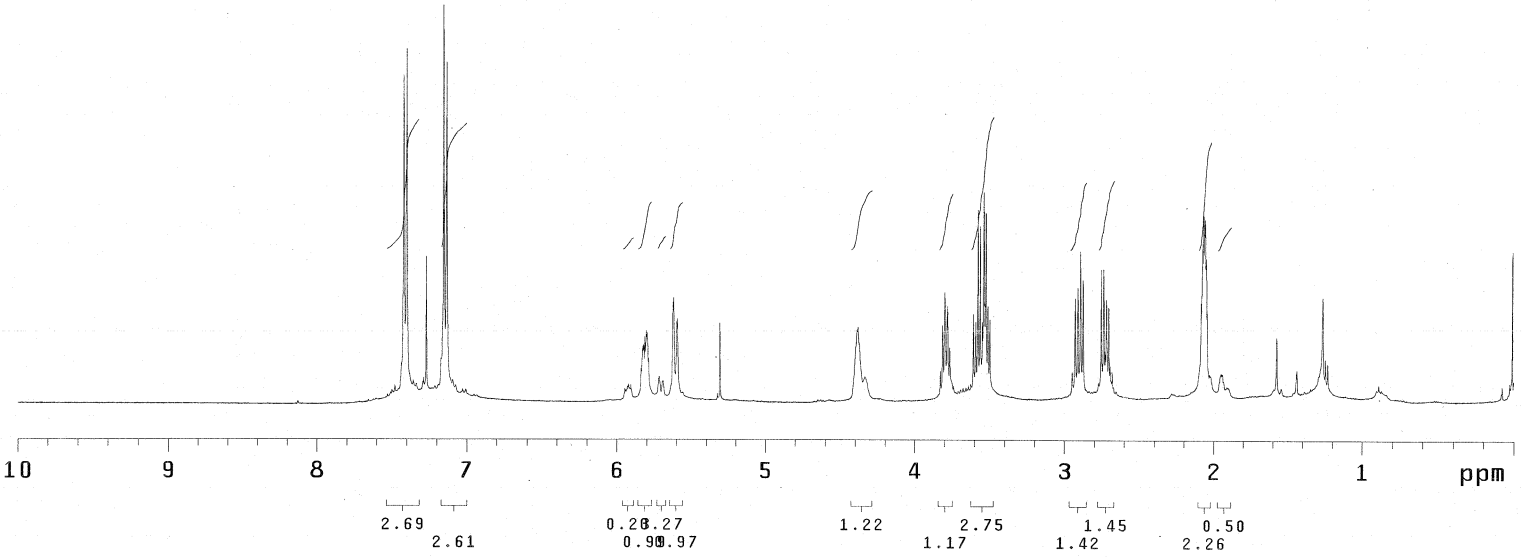
^{1}H NMR


10
9
8
7
6
5
4
3
2
1
ppm
6.16
1.00
0.97
0.20
1.28
1.21
1.21
2.89
1.40
1.55
2.65


^{13}C APT NMR
Cl
O
Cl
200
180
160
140
120
100
80
60
40
20
ppm
136.619
132.275
131.220
131.008
129.147
128.517
128.429
127.176
124.554
77.552
77.230
76.915
75.794
74.827
74.798
73.780
47.100
46.938
41.210
30.697
29.921
28.734


Cl
O
Br

^{1}H NMR


10
9
8
7
6
5
4
3
2
1
ppm
2.69
2.61
0.26
3.27
0.99
0.97
1.22
1.17
2.75
1.42
1.45
2.26
0.50

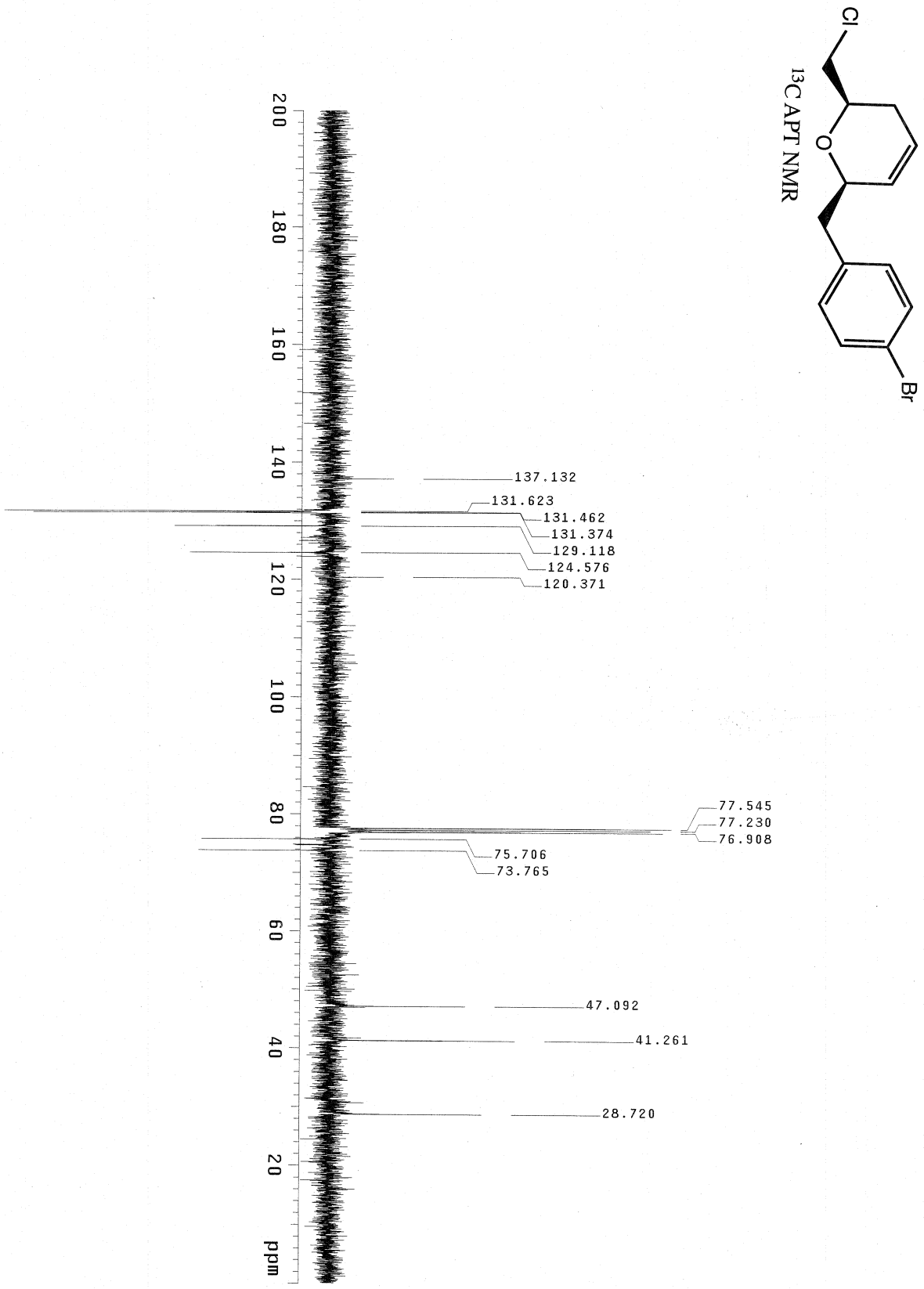

^{13}C APT NMR
Cl
O
Br
200
180
160
140
120
100
80
60
40
20
ppm
137.132
131.623
131.462
131.374
129.118
124.576
120.371
77.545
77.230
76.908
75.706
73.765
47.092
41.261
28.720

Table 1. Crystal data and structure refinement for cc.

Identification code	cc	
Empirical formula	C20 H22 O	
Formula weight	278.38	
Temperature	100(2) K	
Wavelength	1.54178 Å	
Crystal system	Monoclinic	
Space group	Cc	
Unit cell dimensions	a = 17.2161(3) Å	α= 90°.
	b = 5.95830(10) Å	β= 116.2110(10)°.
	c = 17.2485(3) Å	γ = 90°.
Volume	1587.39(5) $Å^3$	
Z	4	
Density (calculated)	1.165 Mg/m^3	
Absorption coefficient	0.533 mm^{-1}	
F(000)	600	
Crystal size	0.28 x 0.26 x 0.15 mm^3	
Theta range for data collection	5.72 to 66.90°.	
Index ranges	-18<=h<=20, -7<=k<=6, -19<=l<=20	
Reflections collected	8161	
Independent reflections	2425 [R(int) = 0.0308]	
Completeness to theta = 66.90°	99.6 %	
Absorption correction	Numerical	
Max. and min. transmission	0.9233 and 0.8672	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	2425 / 2 / 278	
Goodness-of-fit on F^2	1.043	
Final R indices [I>2sigma(I)]	R1 = 0.0283, wR2 = 0.0748	
R indices (all data)	R1 = 0.0284, wR2 = 0.0749	
Absolute structure parameter	0.17(19)	
Largest diff. peak and hole	0.110 and -0.156 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for cc. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z
	U(eq)		
O(1)	8475(1)	3003(2)	9174(1)
	27(1)		
C(1)	9164(1)	3297(3)	8929(1)
	33(1)		
C(2)	9070(1)	5572(3)	8505(1)
	43(1)		
C(3)	8161(1)	5953(3)	7851(1)
	38(1)		
C(4)	7512(1)	4697(2)	7812(1)
	31(1)		
C(5)	7652(1)	2817(2)	8448(1)
	26(1)		
C(6)	10010(1)	3022(3)	9731(1)
	39(1)		
C(7)	10147(1)	721(3)	10135(1)
	46(1)		
C(8)	6971(1)	2796(2)	8794(1)
	24(1)		
C(9)	6070(1)	2480(2)	8058(1)
	24(1)		
C(10)	5832(1)	512(2)	7570(1)
	28(1)		
C(11)	5021(1)	322(3)	6866(1)
	35(1)		
C(12)	4439(1)	2093(3)	6645(1)
	37(1)		
C(13)	4661(1)	4030(3)	7132(1)
	36(1)		
C(14)	5471(1)	4227(2)	7835(1)
	30(1)		

C(15)	7181(1)	1102(2)	9522(1)
	26(1)		
C(16)	7609(1)	-907(2)	9567(1)
	34(1)		
C(17)	7796(1)	-2396(3)	10245(1)
	48(1)		
C(18)	7549(1)	-1933(4)	10880(1)
	54(1)		
C(19)	7121(1)	57(4)	10851(1)
	54(1)		
C(20)	6941(1)	1593(3)	10173(1)
	36(1)		

Table 3. Bond lengths [Å] and angles [°] for cc.

O(1)-C(5)	1.4221(15)
O(1)-C(1)	1.4350(17)
C(1)-C(6)	1.511(2)
C(1)-C(2)	1.514(2)
C(1)-H(1)	1.024(18)
C(2)-C(3)	1.488(2)
C(2)-H(2A)	0.98(2)
C(2)-H(2B)	0.99(2)
C(3)-C(4)	1.322(2)
C(3)-H(3)	0.95(2)
C(4)-C(5)	1.5096(19)
C(4)-H(4)	0.97(2)
C(5)-C(8)	1.5310(18)
C(5)-H(5)	1.051(16)
C(6)-C(7)	1.508(3)
C(6)-H(6A)	0.95(2)
C(6)-H(6B)	1.007(19)
C(7)-H(7A)	1.01(2)
C(7)-H(7B)	0.99(2)
C(7)-H(7C)	0.95(3)
C(8)-C(9)	1.5214(18)
C(8)-C(15)	1.5251(17)
C(8)-H(8)	0.985(17)
C(9)-C(10)	1.395(2)
C(9)-C(14)	1.395(2)
C(10)-C(11)	1.393(2)
C(10)-H(10)	0.992(16)
C(11)-C(12)	1.387(2)
C(11)-H(11)	1.004(19)
C(12)-C(13)	1.379(2)
C(12)-H(12)	0.952(19)
C(13)-C(14)	1.391(2)
C(13)-H(13)	0.974(19)
C(14)-H(14)	0.98(2)

C(15)-C(16)	1.389(2)
C(15)-C(20)	1.389(2)
C(16)-C(17)	1.389(2)
C(16)-H(16)	0.984(19)
C(17)-C(18)	1.365(3)
C(17)-H(17)	1.07(2)
C(18)-C(19)	1.385(3)
C(18)-H(18)	0.97(3)
C(19)-C(20)	1.408(3)
C(19)-H(19)	0.89(3)
C(20)-H(20)	0.963(19)

C(5)-O(1)-C(1)	112.43(9)
O(1)-C(1)-C(6)	107.72(11)
O(1)-C(1)-C(2)	109.01(13)
C(6)-C(1)-C(2)	113.16(13)
O(1)-C(1)-H(1)	109.8(11)
C(6)-C(1)-H(1)	108.0(11)
C(2)-C(1)-H(1)	109.1(10)
C(3)-C(2)-C(1)	110.77(13)
C(3)-C(2)-H(2A)	112.4(12)
C(1)-C(2)-H(2A)	107.3(12)
C(3)-C(2)-H(2B)	112.4(14)
C(1)-C(2)-H(2B)	107.6(12)
H(2A)-C(2)-H(2B)	106.1(18)
C(4)-C(3)-C(2)	122.32(14)
C(4)-C(3)-H(3)	121.4(14)
C(2)-C(3)-H(3)	116.3(13)
C(3)-C(4)-C(5)	121.54(14)
C(3)-C(4)-H(4)	123.2(11)
C(5)-C(4)-H(4)	115.2(11)
O(1)-C(5)-C(4)	111.06(11)
O(1)-C(5)-C(8)	107.06(10)
C(4)-C(5)-C(8)	112.62(11)
O(1)-C(5)-H(5)	108.1(9)
C(4)-C(5)-H(5)	108.5(8)

C(8)-C(5)-H(5)	109.3(9)
C(7)-C(6)-C(1)	114.37(14)
C(7)-C(6)-H(6A)	111.8(11)
C(1)-C(6)-H(6A)	104.4(12)
C(7)-C(6)-H(6B)	110.3(10)
C(1)-C(6)-H(6B)	107.4(10)
H(6A)-C(6)-H(6B)	108.3(15)
C(6)-C(7)-H(7A)	112.2(13)
C(6)-C(7)-H(7B)	112.7(13)
H(7A)-C(7)-H(7B)	107.3(18)
C(6)-C(7)-H(7C)	112.9(15)
H(7A)-C(7)-H(7C)	110(2)
H(7B)-C(7)-H(7C)	101(2)
C(9)-C(8)-C(15)	112.83(10)
C(9)-C(8)-C(5)	110.50(10)
C(15)-C(8)-C(5)	112.49(11)
C(9)-C(8)-H(8)	107.2(10)
C(15)-C(8)-H(8)	107.6(9)
C(5)-C(8)-H(8)	105.9(10)
C(10)-C(9)-C(14)	118.49(13)
C(10)-C(9)-C(8)	121.76(11)
C(14)-C(9)-C(8)	119.69(12)
C(11)-C(10)-C(9)	120.55(13)
C(11)-C(10)-H(10)	119.1(9)
C(9)-C(10)-H(10)	120.4(9)
C(12)-C(11)-C(10)	120.12(14)
C(12)-C(11)-H(11)	119.0(11)
C(10)-C(11)-H(11)	120.9(11)
C(13)-C(12)-C(11)	119.85(14)
C(13)-C(12)-H(12)	119.7(10)
C(11)-C(12)-H(12)	120.4(10)
C(12)-C(13)-C(14)	120.18(14)
C(12)-C(13)-H(13)	122.0(11)
C(14)-C(13)-H(13)	117.8(11)
C(13)-C(14)-C(9)	120.79(13)
C(13)-C(14)-H(14)	118.8(11)

C(9)-C(14)-H(14)	120.4(11)
C(16)-C(15)-C(20)	118.42(13)
C(16)-C(15)-C(8)	122.91(12)
C(20)-C(15)-C(8)	118.67(13)
C(15)-C(16)-C(17)	121.15(16)
C(15)-C(16)-H(16)	120.4(11)
C(17)-C(16)-H(16)	118.4(11)
C(18)-C(17)-C(16)	120.54(19)
C(18)-C(17)-H(17)	120.8(13)
C(16)-C(17)-H(17)	118.6(13)
C(17)-C(18)-C(19)	119.55(16)
C(17)-C(18)-H(18)	118.5(14)
C(19)-C(18)-H(18)	121.9(14)
C(18)-C(19)-C(20)	120.29(18)
C(18)-C(19)-H(19)	122.2(15)
C(20)-C(19)-H(19)	117.5(15)
C(15)-C(20)-C(19)	120.04(17)
C(15)-C(20)-H(20)	119.0(11)
C(19)-C(20)-H(20)	121.0(11)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$)for cc. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2 a^{*2} U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}
	U^{23}	U^{13}	U^{12}
O(1)	19(1)	41(1)	20(1)
	-4(1)	8(1)	-5(1)
C(1)	24(1)	51(1)	28(1)
	-12(1)	14(1)	-9(1)
C(2)	36(1)	61(1)	36(1)
	-2(1)	19(1)	-19(1)
C(3)	43(1)	46(1)	28(1)
	0(1)	19(1)	-12(1)
C(4)	29(1)	42(1)	22(1)
	0(1)	11(1)	-3(1)
C(5)	19(1)	35(1)	21(1)
	-3(1)	7(1)	-4(1)
C(6)	23(1)	59(1)	35(1)
	-13(1)	13(1)	-8(1)
C(7)	24(1)	59(1)	45(1)
	-12(1)	5(1)	4(1)
C(8)	23(1)	26(1)	23(1)
	-2(1)	10(1)	-3(1)
C(9)	21(1)	31(1)	23(1)
	2(1)	10(1)	-4(1)
C(10)	26(1)	32(1)	25(1)
	2(1)	10(1)	-3(1)
C(11)	33(1)	43(1)	25(1)
	-1(1)	9(1)	-13(1)
C(12)	23(1)	54(1)	27(1)
	11(1)	3(1)	-9(1)
C(13)	24(1)	42(1)	39(1)
	14(1)	11(1)	4(1)
C(14)	26(1)	33(1)	32(1)
	4(1)	14(1)	-2(1)

C(15)	18(1)	36(1)	21(1)
	-1(1)	4(1)	-10(1)
C(16)	31(1)	31(1)	26(1)
	0(1)	1(1)	-6(1)
C(17)	41(1)	41(1)	32(1)
	6(1)	-10(1)	-15(1)
C(18)	42(1)	62(1)	31(1)
	18(1)	-8(1)	-26(1)
C(19)	37(1)	101(2)	20(1)
	-2(1)	9(1)	-36(1)
C(20)	23(1)	57(1)	26(1)
	-5(1)	10(1)	-12(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for cc.

	x	y	z
	U(eq)		
H(1)	9131(13)	2070(30)	8499(12)
	34(4)		
H(2A)	9478(15)	5620(30)	8253(13)
	55(6)		
H(2B)	9269(16)	6710(40)	8967(15)
	54(5)		
H(3)	8073(14)	7120(40)	7447(14)
	47(5)		
H(4)	6925(12)	4860(30)	7369(13)
	36(4)		
H(5)	7631(10)	1280(30)	8138(10)
	23(4)		
H(6A)	9995(13)	4150(30)	10112(13)
	38(4)		
H(6B)	10489(12)	3390(30)	9569(11)
	33(4)		
H(7A)	10681(16)	650(40)	10711(15)
	56(6)		
H(7B)	9651(16)	220(40)	10233(15)
	55(6)		
H(7C)	10165(17)	-430(40)	9760(17)
	68(7)		
H(8)	6989(11)	4300(30)	9036(10)
	28(4)		
H(10)	6238(11)	-780(30)	7723(10)
	24(4)		
H(11)	4855(12)	-1070(30)	6500(12)
	38(4)		
H(12)	3880(12)	1960(30)	6172(12)

	33(4)		
H(13)	4259(12)	5280(30)	7011(12)
	33(4)		
H(14)	5610(12)	5610(30)	8182(12)
	39(5)		
H(16)	7800(12)	-1290(30)	9122(12)
	38(5)		
H(17)	8117(15)	-3940(40)	10249(15)
	58(6)		
H(18)	7700(16)	-2990(40)	11351(16)
	63(6)		
H(19)	6934(16)	400(40)	11243(17)
	59(6)		
H(20)	6644(13)	2980(30)	10147(12)
	37(4)		

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Vita

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