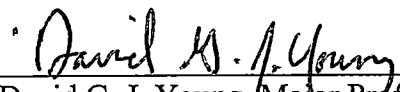


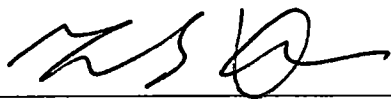
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I am submitting herewith a thesis written by Dongxiang Zeng entitled "Studies Toward the Synthesis of Hyperevolutin A: Nitrile Oxide-Allene Cycloaddition Approach". I have examined the final copy of this thesis for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Master of Science, with a major in Chemistry.


David G. J. Young, Major Professor

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and recommend its acceptance:





Accepted for the Council:


Vice provost and
Dean of Graduate Studies

Studies Toward the Synthesis of Hyperevolutin A:

Nitrile Oxide–Allene Cycloaddition Approach

A Thesis

Presented for the

Master of Science

Degree

The University of Tennessee, Knoxville

Dongxiang Zeng

August 2001

DEDICATION

This thesis is dedicated to my parents, my brother

and

my husband

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ABSTRACT

This thesis described research conducted on the synthesis of hyperevolutin A—an antitumor antibiotic. An introduction related to the structural and synthetic aspects of polyisoprenylated phloroglucinol natural products is given in section 1. The study investigated an unprecedented intramolecular nitrile oxide–allene approach to a hindered bicyclo[3.3.1] ring system as well as the β,β' -tricarbonyl unit. The research results are summarized in section 2 and described in two separate sections—acyclic model and cyclic model. The acyclic model showed that the β,γ -double bond of the allene is more reactive and this result is attributed to thermodynamic preference. In the cyclic model, the α,β -double bond is more reactive as a result of reversed thermodynamic preference. A functionalized core of hyperevolution A was prepared from 2-methylcyclohexanone in 12 steps in 6% overall yield. All experiments related to this research are summarized in section 3.

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ABBREVIATIONS

DMA	<i>N,N</i> -dimethylacetamide
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	<i>N,N</i> -dimethylformamide
DMS	dimethyl sulfide
DMSO	dimethyl sulfoxide
EDA	ethylenediamine
HMPA	hexamethyl phosphoric triamide
LDA	lithium diisopropyl amide
NMR	nuclear magnetic resonance
TBS	<i>tert</i> -butyldimethylsilyl-
TBSCl	<i>tert</i> -butylchlorodimethylsilane
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	trimethylsilyl-
TMSCl	chlorotrimethylsilane

1. Introduction and Background

1.1 Hyperevolutins–polyisoprenylated phloroglucinol natural products

In recent years, the antidepressant activity of *Hypericum perforatum* has led to extensive interest in the study of active components from *Hypericum* genus.¹ Many of these metabolites are biologically active compounds that contain an acylphloroglucinol moiety.² Hyperforin (**1a**) is believed to be the major antidepressant constituent of St. John's wort.³ The structure of hyperforin was determined by spectroscopic methods⁴ as well as by X-ray diffraction, and can be described as a polyisoprenylated phloroglucinol.⁵ The polyisoprenylated phloroglucinol structural feature appears in other natural products obtained from *Hypericum*, as well as sources such as *Garcinia* and *Clusia* (Figure 1). Some of these compounds are biologically active and are currently considered as potential candidates for drugs. For example, some are active against cancer cell lines such as sampsoniones A and I (*Hypericum sampsonii*);⁶ some, such as garsubellin A (**2**) (*Garcinia subelliptica*), which is a potent inducer of choline acetyltransferase (ChAT),⁷ have shown activity against dementia associated with neurodegenerative diseases like Alzheimer's; some, such as nemorosone II (**3**) (*Clusia rosea*),⁸ have potent antibacterial properties and some, such as laxifloranone (**6**)⁹ and the guttiferones,¹⁰ inhibit the cytopathic effects of *in vitro* HIV infection.

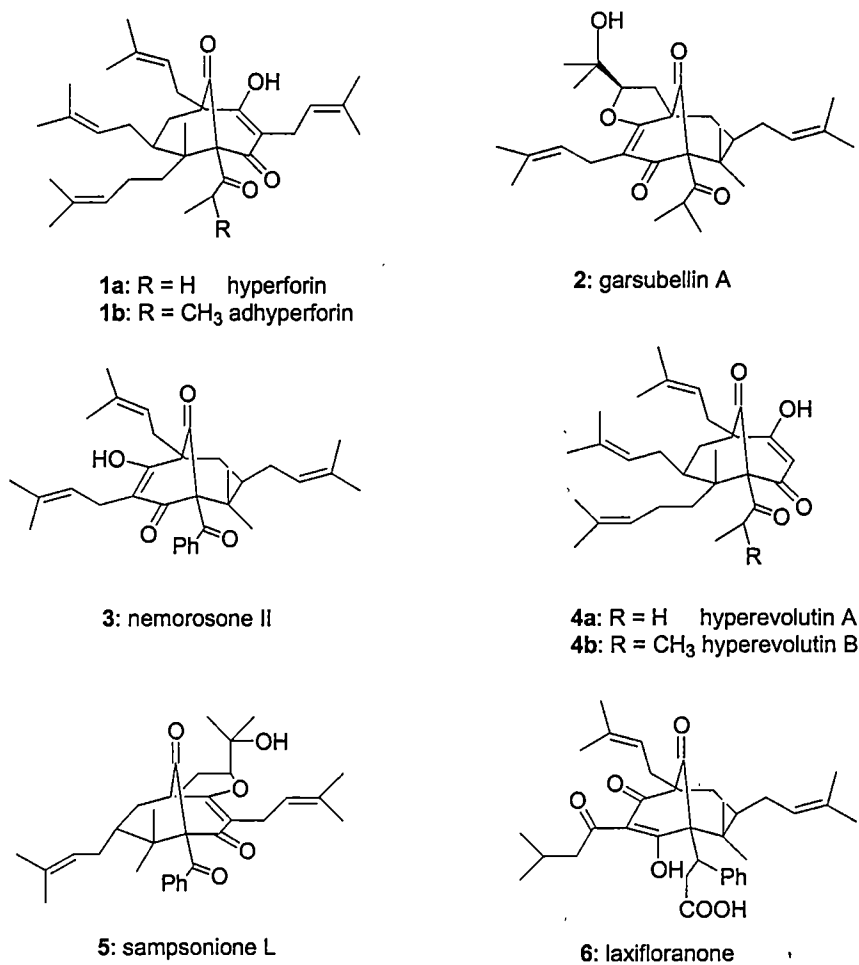
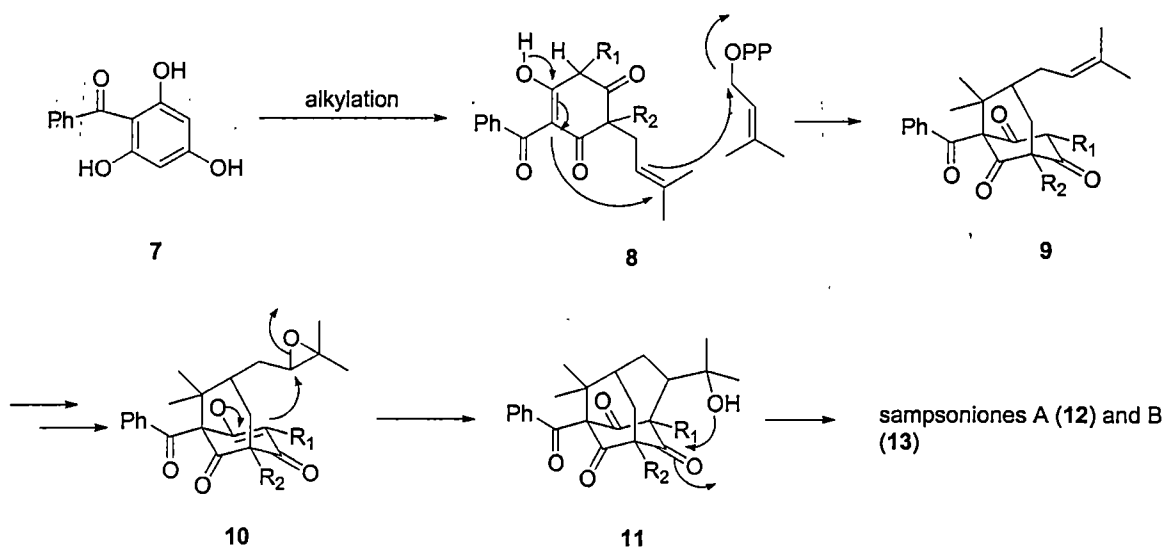


Figure 1. Some polyprenylated acylphloroglucinol natural products.

Among these biologically important compounds, hyperevolutins attracted our special interest. The petroleum ether extract of *Hypericum revolutum*, a shrub native to South-east Africa, displayed significant growth-inhibitory activity against the Co-115 human colon carcinoma cell line.¹¹ Hyperevolutins A (4a) and B (4b) were shown to be the main active components of this extract. The structure of hyperevolutin A was solved through X-ray diffraction (Figure 1) and was shown to exhibit high structural similarity to hyperforin.

No biosynthetic studies on the hyperevolutins have been reported, however, biosynthesis from a simple benzoylphloroglucinol has been proposed, as related to studies on the sampsoniones A–M. The sampsoniones are presumably biosynthesized from biogenetically acceptable 2,4,6-trihydroxybenzophenone (7) (Scheme 1).⁶



Scheme 1. Biosynthesis of sampsoniones proposed by Hu and Sim.

1.2 Polyprenylated acylphloroglucinol natural products; strategies and synthetic studies

While many polyprenylated phloroglucinol related natural products have been isolated, few synthetic studies have been reported. Despite the lack of information, a number of synthetic challenges are found in these structures, including the congested bridgehead carbons and β,β -tricarbonyl subunits. The adjacent quaternary carbons in this framework make the traditional α,α' -annulation strategies for construction of bicyclo [3.3.1]nonan-9-ones insufficient. Moreover, the general preference of O-acylation versus C-acylation precludes the possibility of constructing the tricarbonyl unit by direct acylation by a β -dicarbonyl. It may be possible to avoid the acylation problem by forming a functionalized skeleton first and transforming it to the tricarbonyl via oxidation, but congestion around the bridgehead area and the known sensitivity of the natural product to oxidation by air give reason to believe that a number of synthetic problems would be encountered at the latest stages of the synthetic plan.

1.2.1 Synthesis of tricarbonyls

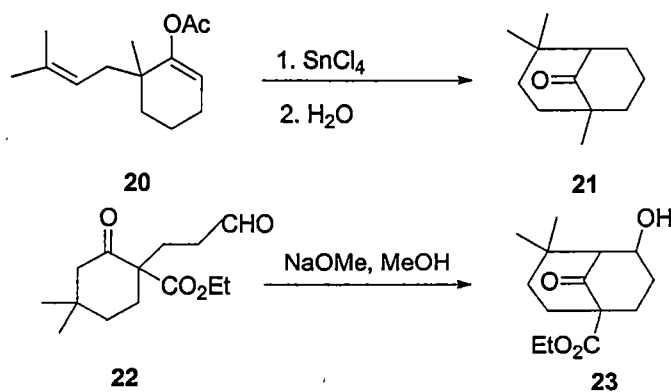
An β,β' -tricarbonyl unit in a tertiary carbon system could be approached by direct acylation using an acid chloride¹² or other special reagents;¹³ however, O-acylation is usually competitive, and there are no examples of quaternary carbons formation or β,β' -tricarbonyl synthesis using this approach. Alternatively, the carbonyls could be

introduced onto an existing hydrocarbon system by oxidation,¹⁴ or one could also approach the tricarbonyl using a chromium-mediated cyclization of an alkyne precursor.¹⁵

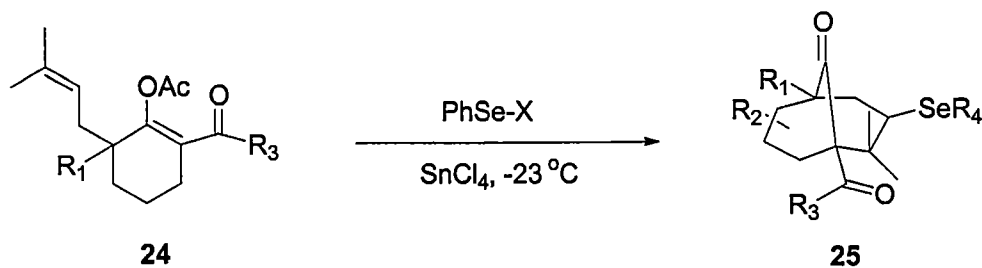
1.2.2 Synthesis of hindered bicyclo[3.3.1]nonanones.

Examples of hindered bicyclo[3.3.1]nonanone formation are rare; however, a few examples bearing two quaternary bridgehead carbons are known using the base-catalyzed aldol condensation.¹⁶ Base and Lewis acid-catalyzed cyclization has also been used to construct a bicyclic core containing one quaternary bridgehead site and one quaternary carbon adjacent to the bridgehead (Scheme 2).¹⁷

Nicolaou's group at the Scripps Research Institute has developed an electrophilic selenium-mediated cyclization strategy to construct the hindered bicyclic core with *gem*-dimethyl groups and the quaternary bridgehead carbons intact both in solution and on



Scheme 2. Exemplary routes to hindered bicyclo[3.3.1]nonan-9-ones.



Scheme 3. Selenium mediated formation of 2,2-dimethylbicyclo[3.3.1]nonan-9-one.

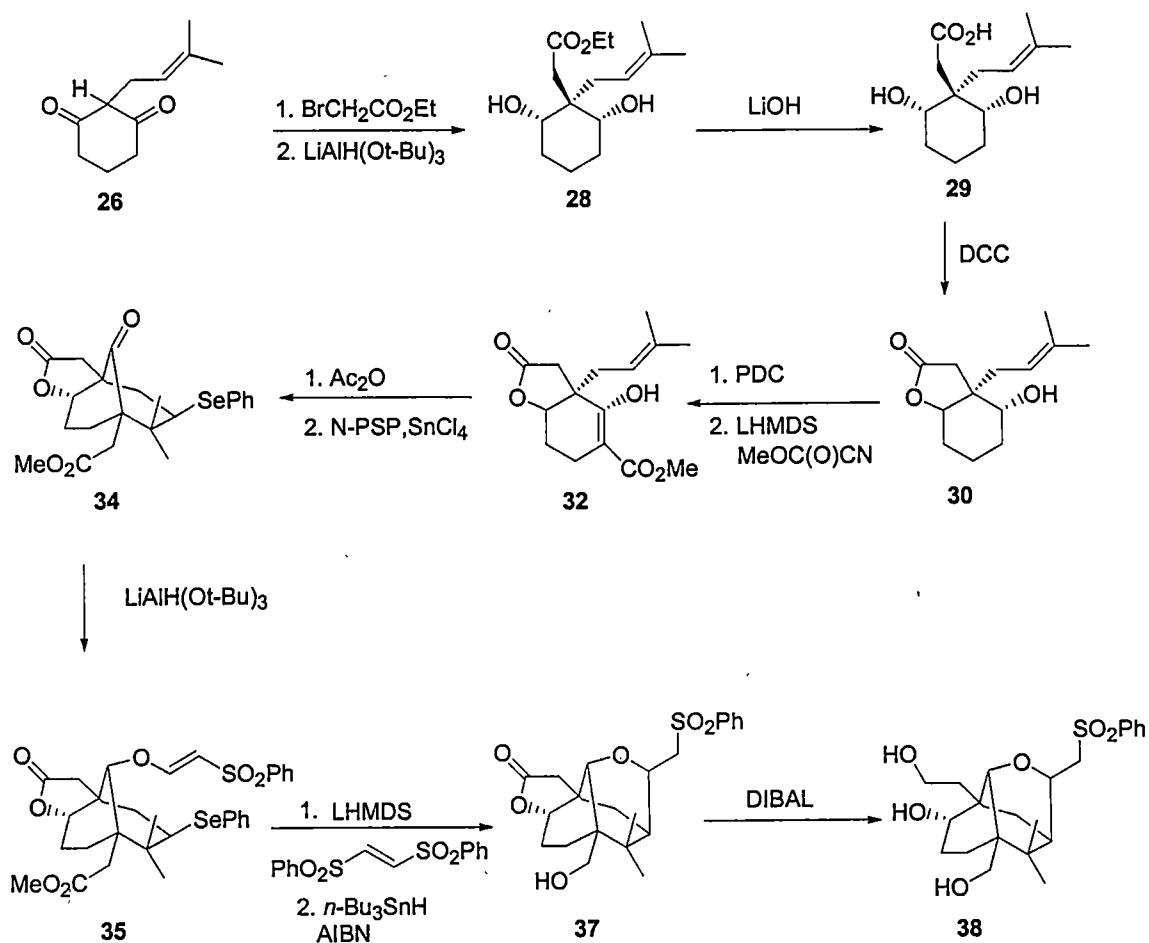
solid support. Thus, a variety of bicyclo[3.3.1]nonan-9-ones have been synthesized using this methodology (Scheme 3).¹⁸

1.2.3 Application in the synthesis of garsubellin A

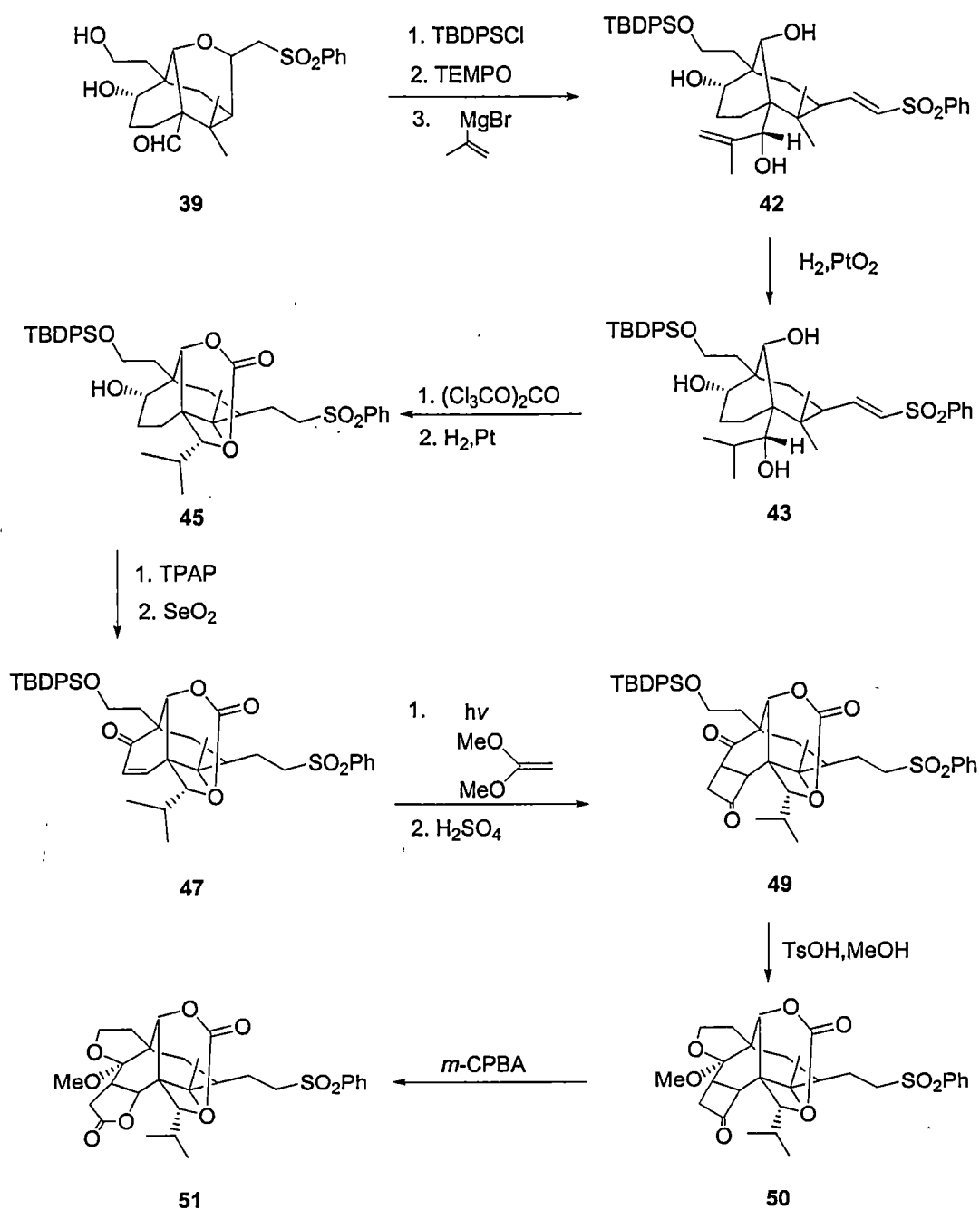
To our knowledge, only one total synthesis of this type of natural products has been reported. A fully functionalized garsubellin A bicyclic core has been assembled using the above-mentioned selenium cyclization methodology; however, a total synthesis has not been completed (Scheme 4, Scheme 5).¹⁹

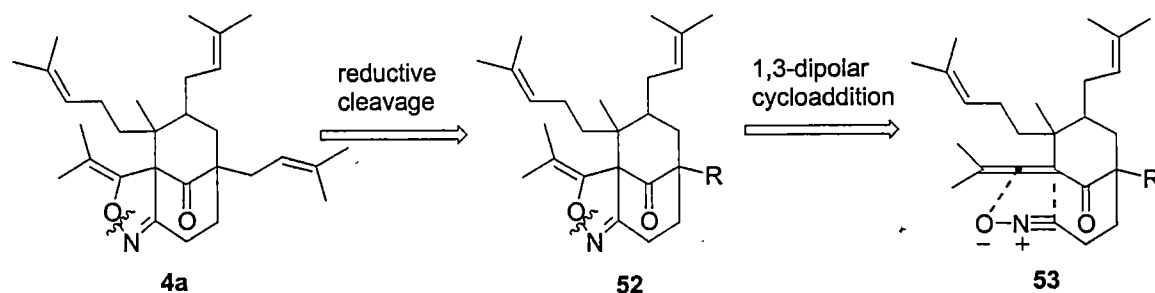
1.2.4 Our strategy toward the synthesis of hyperevolutin A.

Approaches to the total synthesis of hyperevolutin A require methodology for construction of vicinal quaternary centers, as well as the incorporation of a β,β -tricarbonyl group. Our proposed approach addressed the problems simultaneously, using



Scheme 4. Nicolaou's synthesis of the bicyclic core of garsubellin A.

**Scheme 5.** Further elaboration of the bicyclic core of garsubellin A.



Scheme 6. Retrosynthetic analysis of hyperevolutin A.

an intramolecular cycloaddition to close the bicyclic core and introduce latent carbonyl functionality in the form of a dihydroisoxazoline. This approach appeared to circumvent the potential difficulty of late-stage elaboration in a densely functionalized area (Scheme 6).

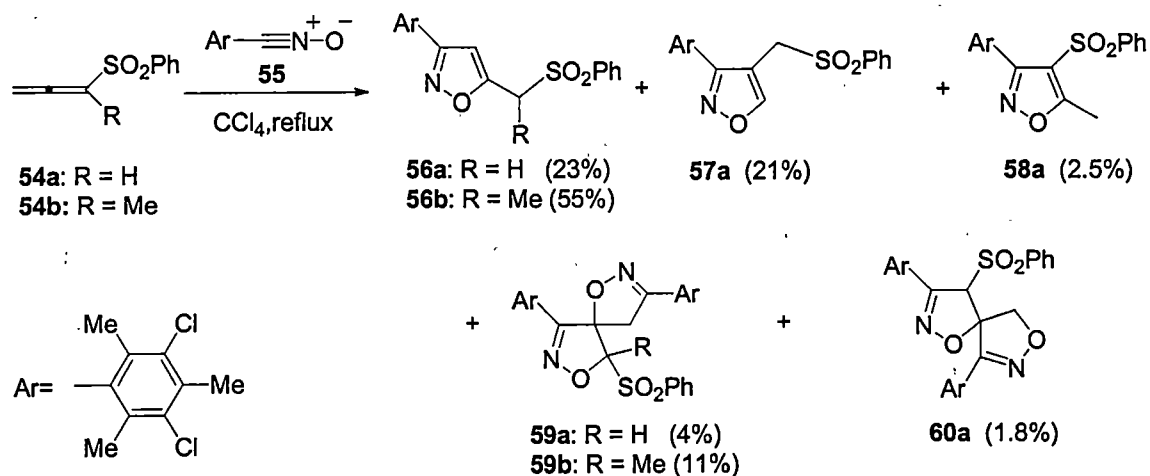
As shown in Scheme 6, the key step of this strategy would be a nitrile oxide–allene cycloaddition (53→52), and a subsequent reductive-cleavage step. Potential problems were that steric repulsion could deter the cycloaddition, and difficulty in opening of the cycloadduct. To place our studies in perspective, a review of nitrile oxide–allene cycloadditions is described in the next section.

1.3 Nitrile oxide–allene cycloadditions: a review of intermolecular approaches.

Cycloadditions using allenes as the dienophiles in the Diels–Alder reaction have been studied extensively,²⁰ but the use of allenes as dipolarophiles has received less attention. Known examples are presented in the schemes which follow; however, the

data is limited and generalizations about the regio- and stereochemical aspects are difficult to draw. The intermolecular processes usually result in complex mixtures of products that include regioisomers and spirocycles, which are formed upon further reaction of monoadducts with a second equivalent of the dipole. Additionally, products resulting from a shift of the double bond can arise if a driving force, such as formation of an aromatic compound, exists.

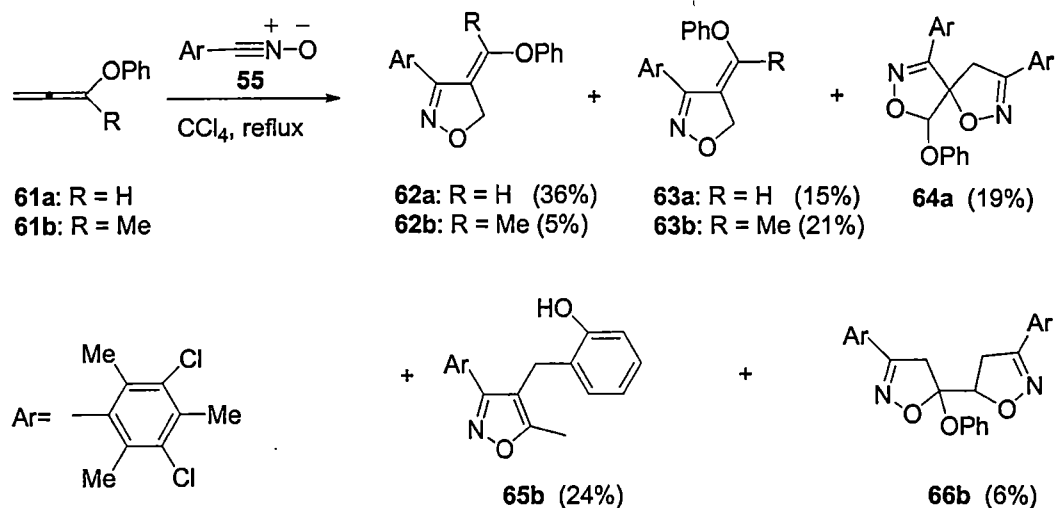
As shown in Scheme 7,²¹ the cycloaddition of allenyl sulfones leads to the isolation of product mixtures in which either or both of the allene double bonds participate as dipolarophiles. Thus, treatment of **54a** with **55** gave 23% **56a**, 21% **57a**,



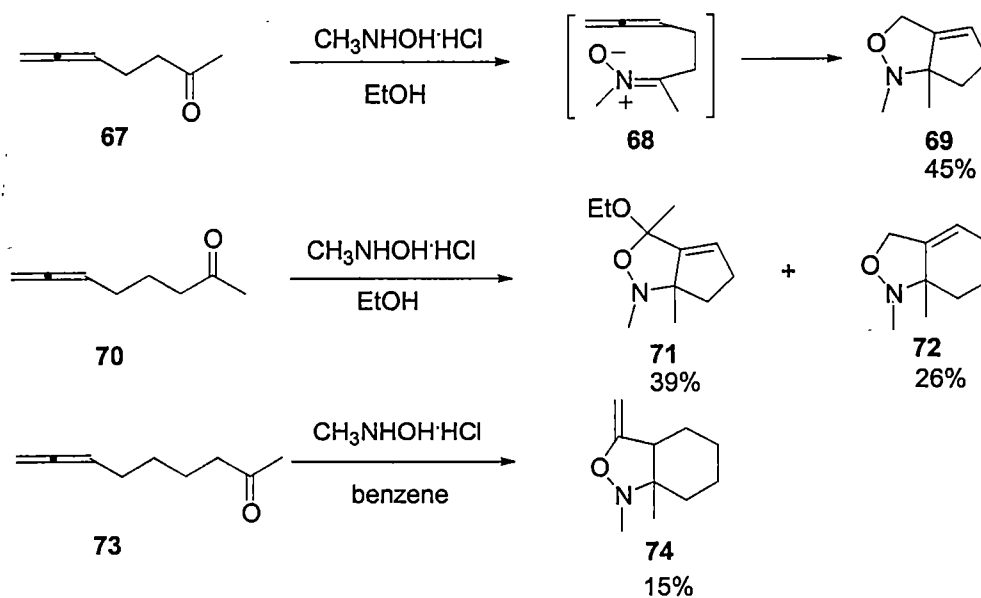
Scheme 7. Cycloaddition of nitrile oxide with an electron deficient allene.

and 2.5% **58a**, along with spirocycles **59a** and **60a**. The studies further suggest that the presence of an α -methyl group suppresses reaction of the α,β -double bond, except when the β,γ double bond has already reacted. These limited examples showed that in the electron deficient allene β,γ -double bond was more reactive than the α,β double bond which is very different from the preference shown in a nitrone-allene cycloaddition. The reason for this preference which deviated from FMO prediction was not clear, and it was suggested that both electronic and steric effects were involved in these reactions. As shown in Scheme 8,²² when allenyl phenyl ether was reacted with benzonitrile-*N*-oxide, the formation of cycloadducts **61a-63a** occurred, in which it was clear that the β,γ -pi bond was more reactive. As expected, the incorporation of an α -methyl group did not significantly effect the outcome (**61b** $\rightarrow$ **62b**, **63b**, **65b**, **66b**) of the cycloaddition.

The lack of appreciable selectivity in intermolecular cycloadditions limits its application to synthesis. It was envisioned, however, that an intramolecular version could impart restrictions on regioselectivity. Consequently, the hypothetical intramolecular variant was viewed as an attractive method. Although an intramolecular nitrile oxide-allene cycloaddition has not been reported previously, reactions of some related nitrones are described in Scheme 9.²³ As depicted, the five- vs. six-membered ring competition shows little selectivity, while the six- vs. seven-membered ring competition demonstrates the six-membered ring is favored (Scheme 9).



Scheme 8. Cycloaddition of a nitrile oxide with an electron rich allene.



Scheme 9. Intramolecular nitrone-allene cycloaddition.

It was decided to study the nitrile oxide–allene cycloaddition, because of the potentially different reactivity of nitrones and nitrile oxides. A number of literature examples of the preparations of various cyclic and polycyclic ring systems through the use of nitrile oxide alkene cycloadditions had been described.²⁴ The cycloaddition had also proved to be an elegant way to construct quaternary carbons and congested ring systems.²⁵ It was anticipated that despite the scarcity of examples, the use of allenes in the [3+2] cycloaddition would be useful in that the additional unsaturation in the product would serve as a handle for further elaboration. Despite the potential, not a single example of an intramolecular nitrile oxide–allene cycloaddition had been reported prior to these studies.

2. Results and discussion

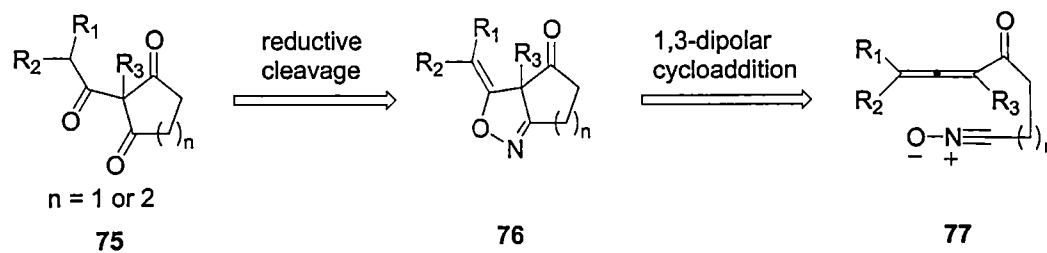
2.1 Acyclic model.

To initiate our studies, intramolecular nitrile oxide–allene cycloaddition was tested on a simple acyclic system. This less complex setting was expected to simplify spectral analysis and eliminate most of the less important problems that would be encountered in the bicyclic core of the real molecule (Scheme 10). It was anticipated that potential effects of the prenyl groups on the cycloaddition would be eliminated in this model.

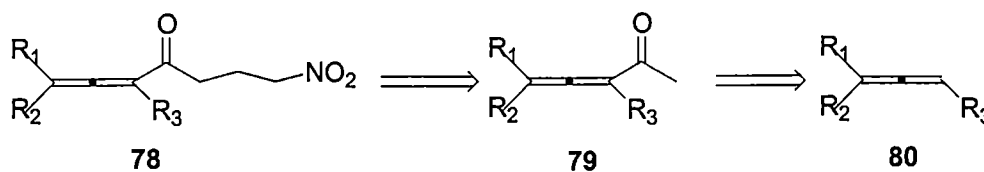
2.1.1 Five-membered ring system

The proposed synthesis of the model system **75** was based on Michael addition of the enolate of allenylketone **79** with nitroethene (Scheme 11). To avoid the possible aromatization of the cycloadduct, R_3 was chosen to be an alkyl group.

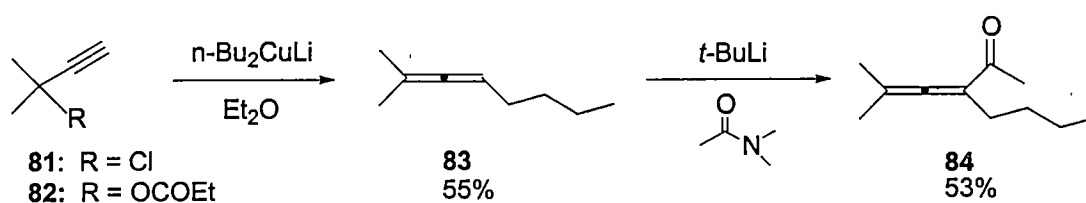
Ketoallene **84** was prepared by a literature method^{26, 27} from either alkyne **81** or **82** in 29% overall yield for two steps (Scheme 12). The yield of ketoallene **84** was lower than reported in the literature due to production of byproduct **87** (Scheme 13). A logical explanation for the formation of **87** is that incomplete deprotonation of **83** is followed by deprotonation of *N,N*-dimethylacetamide (DMA) by unconsumed base to form **86**, which condenses with **84** to produce **87** (Scheme 13).



Scheme 10. Nitrile oxide—allene cycloaddition route to the tricarbonyl unit.



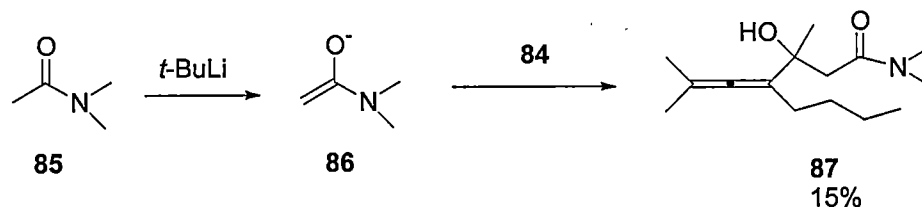
Scheme 11. Retrosynthetic analysis of cycloaddition precursor 78.



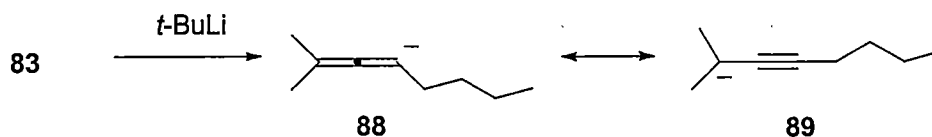
Scheme 12. Synthesis of ketoallene 84.

Optimization experiments did not lead to significant improvement, and were complicated by the fact that at higher temperature the allenyl and propargyl anions resonance forms showed poor regioselectivity (Scheme 14).²⁸

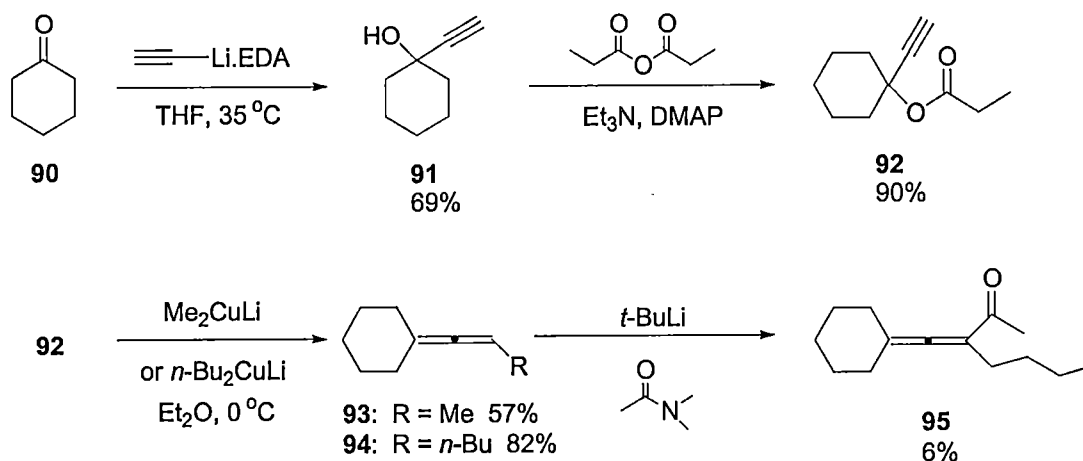
In an attempt to increase the availability of ketoallenes for model studies (Scheme 11), the cyclohexyl allene in Scheme 15 was prepared. Thus, propargyl alcohol **91** was obtained from the addition of lithium acetylide to **90**.²⁹ Alcohol **91** was then treated with propanoic anhydride to afford propanoate **92**³⁰ that was subjected to S_N2' displacement with methyl or butyl cuprate reagents to give **93** or **94**.³¹ Unfortunately, only a small amount of **95** was produced by this reaction sequence (Scheme 15).



Scheme 13. Formation of **87** in the synthesis of **84**.



Scheme 14. Allenyl and propargyl anion resonance forms.

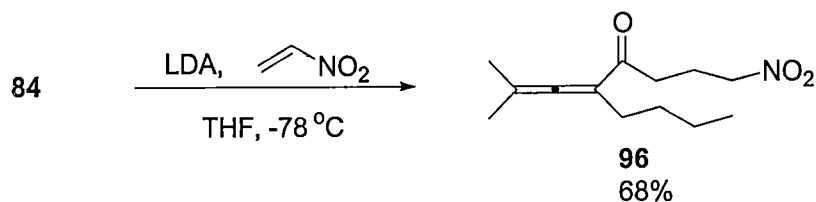


Scheme 15. Preparation of ketoallene 95.

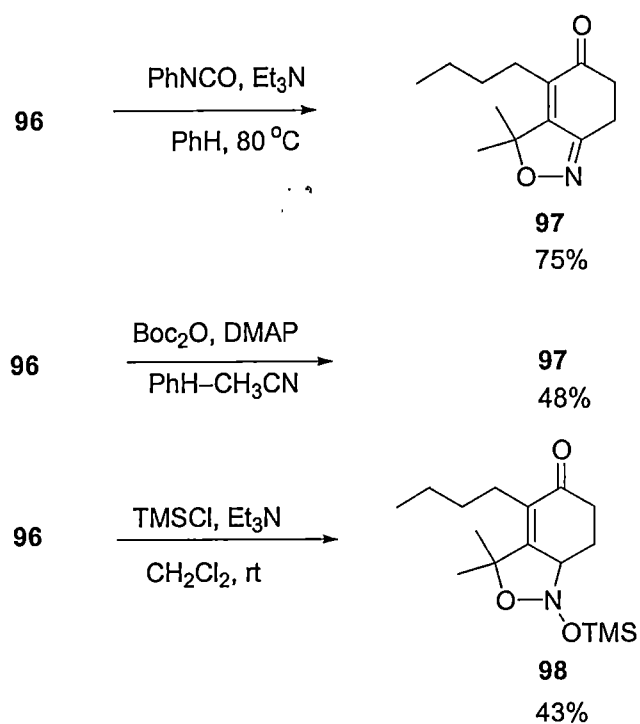
As shown in literature, attempts to generate ketoallene **95** using an allenyl zinc species generated from a propargyl chloride were not regioselective and led to ketoallene and propargyl ketone mixtures (1:1).³²

Despite the low yields of ketoallene **84**, its derived enolate reacted with nitroethene to afford targeted ketone **96** in 68% yield (Scheme 16). The intramolecular cycloaddition was tested on **96** under several sets of conditions, all of which yielded a single cycloadduct (**97** or **98**). The Mukaiyama method gave the best result (Scheme 17).

The data in Scheme 17 supported the idea that the β,γ -double bond is more reactive than the α,β -double bond. This result was consistent with literature cycloadditions of nitrile oxide with electron deficient allenes where β,γ -double bond was more reactive (Figure 2).



Scheme 16. Synthesis of nitroketone 96.



Scheme 17. Cycloadditions of nitroketone 96.

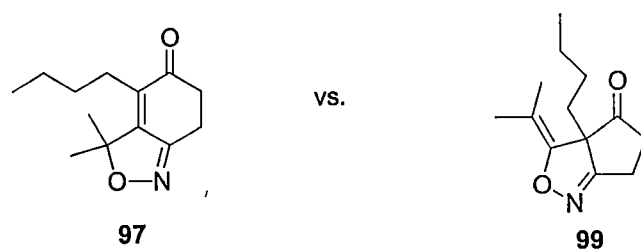


Figure 2. Two possible cycloadducts in an acyclic system.

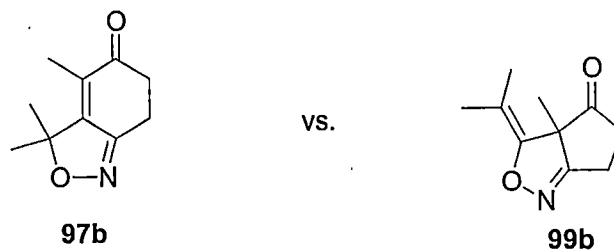


Figure 3. Models for MMX calculations in acyclic system.

Since this regioselectivity could not be explained by FMO theory, it was suspected that steric effect rather than the electronic effect played more important role in the reaction. In retrospect, it was speculated that cycloadduct **97** would gain extra stability from conjugation. An MMX calculation was performed to evaluate the relative stability of these two cycloadducts. To avoid problems that might arise from the flexible *n*-butyl group, models **97b** and **99b** were used in the calculation (Figure 3). The difference in the ΔH_f of these two products suggested that that **97b** (-27.26 kcal/mmol) was favored thermodynamically over **99b** (-14.96 kcal/mmol). The difference in the strain energy (16.55 kcal/mmol for **97b** and 22.30 kcal/mmol for **99b**) accounted for a big part of the difference in the heat of formation of **97b** and **99b**.

Although allylic strain is present in both cycloadducts, by examining the molecular models we found out that there is a difference in the proposed transition states that lead to these two cycloadducts (Figure 4). While the nitrile oxide unit can reach both the allene double bonds geometrically, it was shown that in the transition state of **99** formation there existed a severe interaction between one of the *gem*-dimethyl groups and the incoming nitrile oxide oxygen, which was not present in the transition state leading to

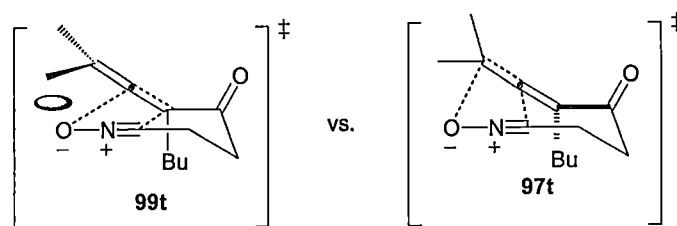


Figure 4. Proposed transition states of cycloadducts **97** and **99** formation.

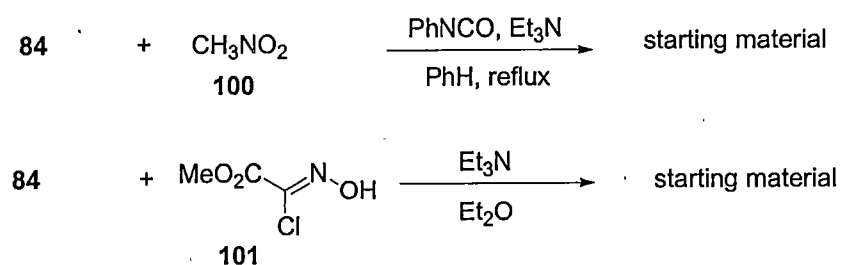
97. Although these transition states were not calculated rigorously, it was suspected that this repulsion could suppress the formation of **99** and favor **97**.

Another possible reason that the formation of cycloadduct **97** is favored over **99** could be that the five-membered ring contains more strain energy than the six-membered ring; thus it is disfavored thermodynamically (Figure 2). This result is consistent with theoretical calculations on the intramolecular nitrile oxide cycloaddition using the tandem QM/MM method³³ that showed that the transition state for forming a five-membered ring involves significant twisting in the forming of the oxazoline ring, while less distortion is involved in the transition state of a six-membered ring. Although literature examples show that allenes bearing electron-withdrawing groups favor reaction of the α,β -double bond in cycloadditions with a dipole such as a nitrone, it is possible that steric effects could outweigh electronic preferences in the present case (Figure 4).

Although the preliminary cycloaddition did not occur at the desired site, it was the first example of an intramolecular nitrile oxide–allene cycloaddition and the reaction

showed excellent regioselectivity. The result was viewed as encouraging, and warranted further design modification to ensure the cycloaddition occurred at the desired site.

To find out whether the α,β -double bond in the allene could participate in a nitrile oxide [3+2] cycloaddition, an intermolecular cycloaddition was attempted using ketone **84** as the dipolarophile and ethyl chlorooxiaoacetate and nitromethane as nitrile oxide precursors because of their known ability to form cycloadducts. In both cases, only starting materials were recovered (Scheme 18). It was possible that failure to produce a cycloadduct was either a function of steric hindrance in the allene or the tendency of methyl nitrile oxide to polymerize. With more questions arising than answers, no conclusions could be drawn; however, the failure of allene **84** to participate suggested that the overall reactivity of allenes was a problem.



Scheme 18. Intermolecular cycloaddition of allene **84** with nitrile oxides.

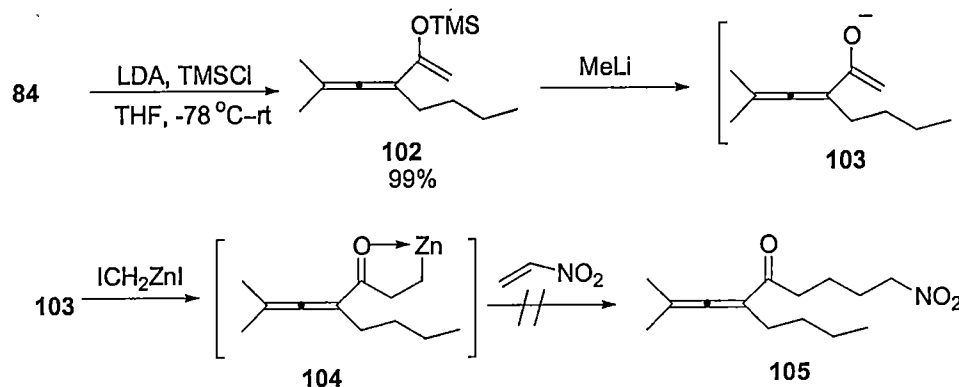
2.1.2 Six-membered ring system

Examples of intramolecular cycloadditions of nitrile oxides with alkenes in the literature showed that six-membered ring formation was favored over the corresponding five- or seven-membered ring.³⁴ With this in mind, it was speculated that an additional carbon in the main chain of the model system would disfavor seven-membered ring formation and lead to the six-membered cycloadduct.

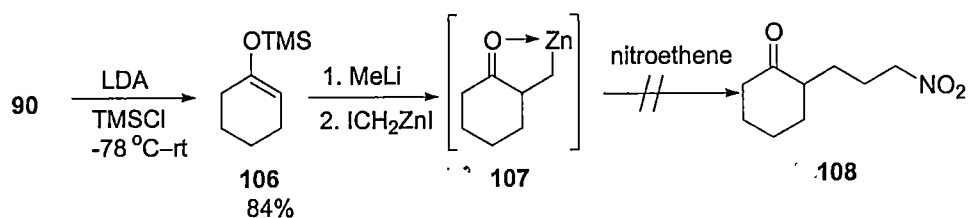
Several methods were envisioned for forming the longer chain. Michael addition of a homoenolate, as opposed to an enolate to nitroethene, appeared to be the most straightforward choice. Homoenolates can be generated in several ways.³⁵ An organozinc homoenolate was explored first in a reaction with nitroethene in an attempt to generate nitro homolog **105** (Scheme 19).³⁶

Unfortunately, production of **105** was unobtainable with or without trimethylsilyl chloride as an additive. To examine the reason for nitro chain installation failure using this method, the same method was tested on cyclohexanone, which also met with failure (Scheme 20).

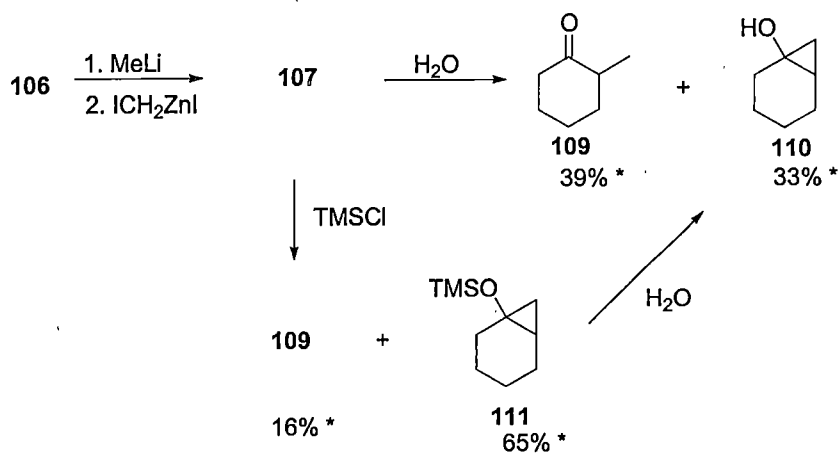
Although the reactions ultimately did not succeed, two compounds were detected without the addition of nitroethene (Scheme 21). The two products suggested that an equilibrium between the homoenolate and the anion **112** exists, which is consistent with the literature observation (Scheme 22).³⁷



Scheme 19. Attempted zinc-homoenolate synthesis of nitroketone 105.



Scheme 20. Homoene-Michael addition to nitroethene.



note: * yield derived by GC

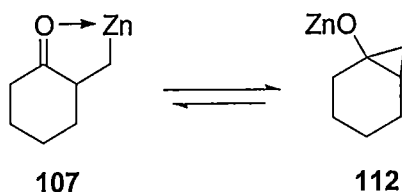
Scheme 21. Reactions of homoenolate 107.

With this information in hand it was speculated that a base-induced polymerization led to decomposition of nitroethene in the presence of **112**.⁴⁰

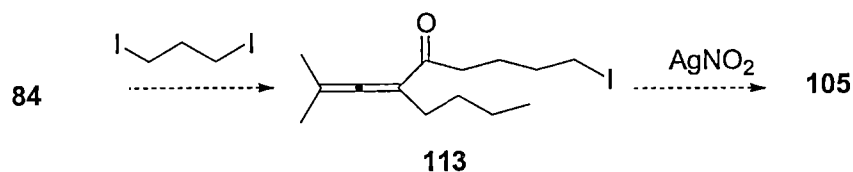
A second approach to homologation was to install the carbon chain of desired length first, and then add the nitro group using a substitution reaction (Scheme 23).

However, the first step was problematic due to the low reactivity of **84**. Thus, when enolate of **84** was exposed to 1,3-diiodopropane, only starting material was recovered.

The third approach used 3-nitropropanal as the electrophile in a reaction with **84**. To avoid proton-transfer from 3-nitropropanal prior to condensation, the Mukaiyama aldol variant was used as the key step.³⁹



Scheme 22. Equilibrium of homoenolate **107** and anion **112**.

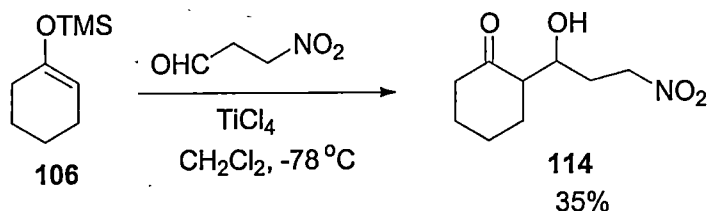


Scheme 23. Proposed installation of nitro side chain by substitution.

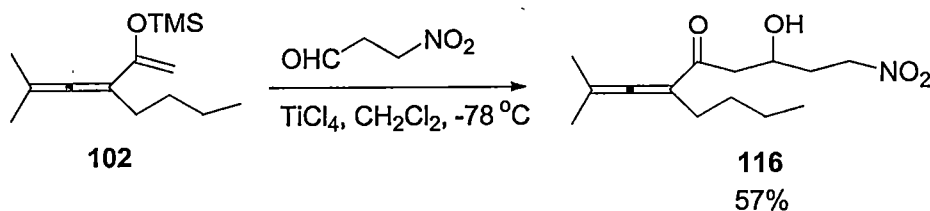
As shown in Scheme 24, it was first tested on cyclohexanone. Thus silyl enol ether **106** was allowed to react with 3-nitropropanal in presence of titanium(IV) chloride to produce the desired nitro alcohol product **114**.

This encouraging result led us to test the aldol condensation on enol ether **102** prepared from ketoallene **84** with 3-nitropropanal catalyzed by TiCl_4 , which yielded aldol **116** in 57% yield (Scheme 25).

There was little precedent of nitrile oxide cycloadditions in presence of a free hydroxyl group; therefore, the alcohol was protected first. Alcohol **116** was protected as trimethylsilyl ether **117** and exposed to phenylisocyanate and triethylamine as shown in Scheme 26. However, no identifiable product was obtained.



Scheme 24. Mukaiyama aldol condensation of **106** with 3-nitropropanal.

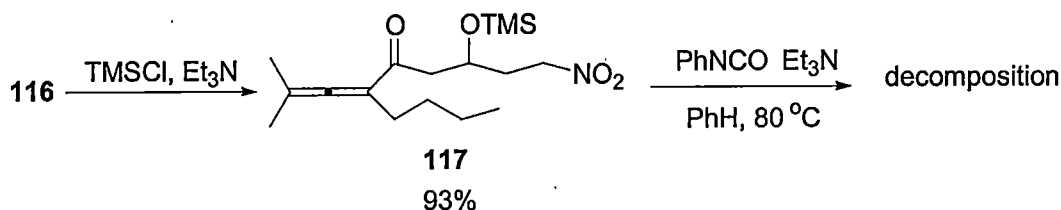


Scheme 25. Preparation of nitroaldol **116**.

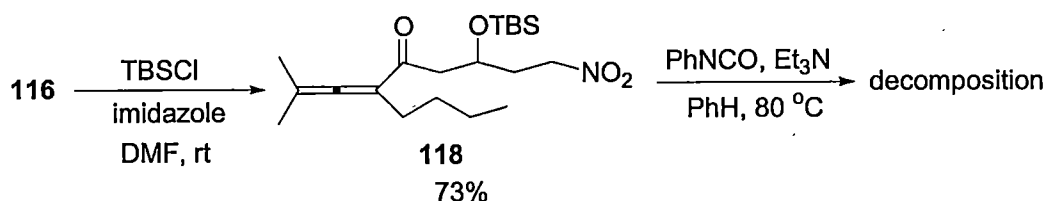
Failure to isolate a cycloadduct could have been an artifact of either the protected hydroxyl or the carbonyl. Two different modifications were therefore envisioned as methods that could lead to a six-membered ring cycloadduct.

Protection group modifications was examined first. Changing from a trimethylsilyl to a *tert*-butyl-dimethylsilyl ether of the alcohol (118), was explored. However, this substrate also decomposed. (Scheme 27).

It was suspected that β -elimination of the $-\text{OSiR}_3$ group in 118 might be a decomposition pathway. In general, if one alkoxy group eliminates, then all the oxygen derivatives eliminate, but that elimination was indeed occurring had not been proven. This being the case, other simple derivatives were examined, because it appeared that



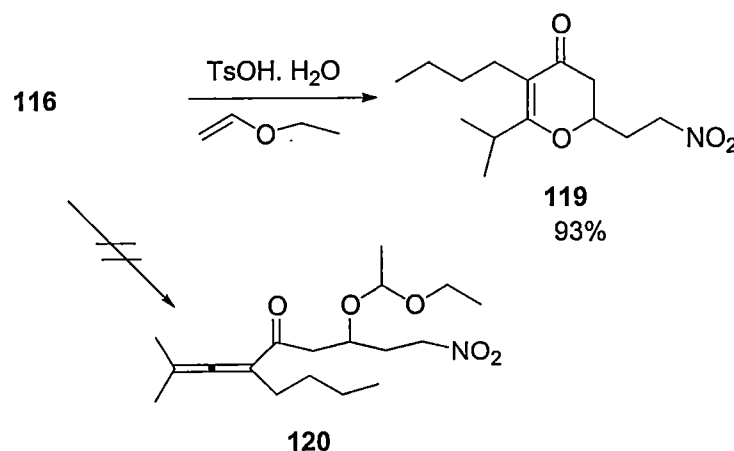
Scheme 26. Preparation and cycloaddition of 117.



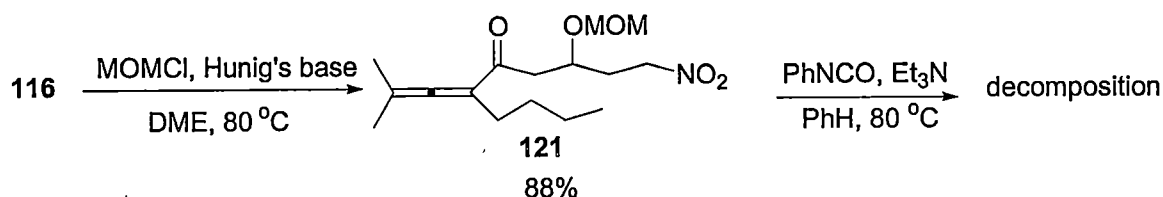
Scheme 27. Preparation and cycloaddition of 118.

they could be readily prepared from the alcohol. An acetal protecting group was the next candidate; however, it was soon found that exposure of **116** to mild acid resulted in the production of dihydropyran **119** in 93% yield (Scheme 28).

Since it was clear that **116** was acid sensitive, acetal formation under basic conditions was studied. Standard procedures for methoxy methyl ether formation from **116** did not give **121**, but experimentation gradually led to the conclusion that chloromethyl methyl ether and dimethoxyethane produced **121** in 88% yield if conducted at 80 °C. Nitro compound **121** was then exposed to phenyl isocyanate, but no cycloadduct was prepared. Indeed an intractable mixture resulted (Scheme 29).



Scheme 28. Attempts to protect the hydroxyl of **116** as an acetal.

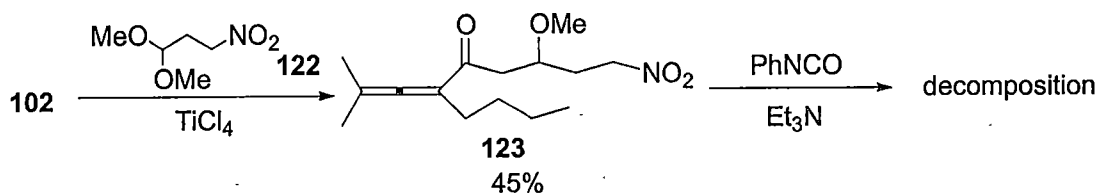


Scheme 29. Preparation and cycloaddition of 121.

As one might suspect, aldol **116** proved to be sensitive. Silyl ether and acetal protecting groups did not survive the reaction conditions for cycloaddition, but protection of the hydroxyl as an ether group was studied next. Benzylation did not succeed, and attempts to alkylate the alcohol using silver oxide failed to produce the methyl ether (Table 1). Enol ether **102** was eventually reacted with acetal **122**, which provided **123**. When the cycloaddition was conducted on this substrate, the reaction was once again, problematic (Scheme 30).

Table 1. Attempted protection of the hydroxyl in 116 as an ether group.

Entry	Reagents	Temperature ($^\circ\text{C}$)	Solvent	Result
1	LDA/BnBr	-78–20	THF	Decomposition
2	NaH/BnBr	65	THF	Decomposition
3	Ag_2O /BnBr	20	DMF/ CH_2Cl_2	Decomposition
4	Ag_2O /MeI/ CaSO_4	20	—	No reaction



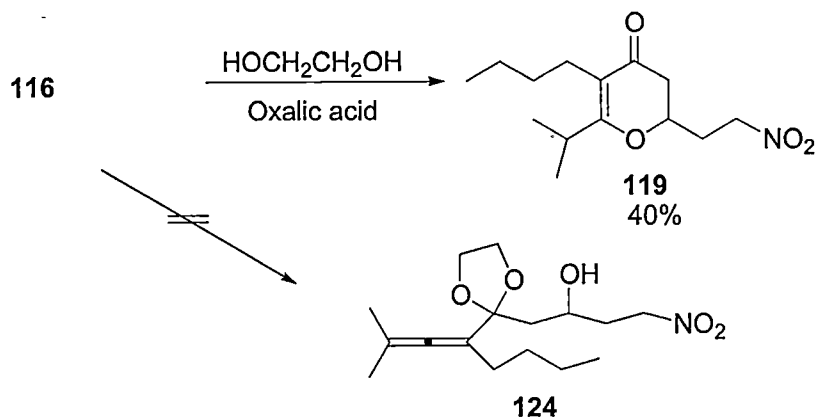
Scheme 30. Preparation of 123 and subsequent cycloaddition attempt.

The previously mentioned β -elimination possibility could not be proven due to the production of a complex mixture in each of the cycloadditions. Using this as the working hypothesis, however, protection of the carbonyl group was undertaken. Attempts to protect the carbonyl as an acetal using an even milder acid failed; however, and the intramolecular cyclization product **119** was isolated together with recovered starting material (Scheme 31).

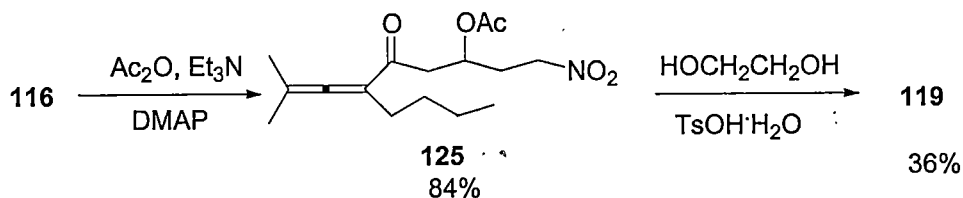
To reduce the nucleophilicity of the free hydroxyl, it was protected as acetate **125**. The acetate could not survive the reaction conditions and **119** was isolated once again (Scheme 32).

As protection failed due to alternative reaction pathways available to the carbonyl group, the carbonyl was reduced with sodium borohydride and cerium(III) chloride heptahydrate at low temperature to provide diol **126**, and subsequently protected as the bis-trimethylsilyl ether **127** using trimethylsilylchloride and triethylamine (Scheme 33).

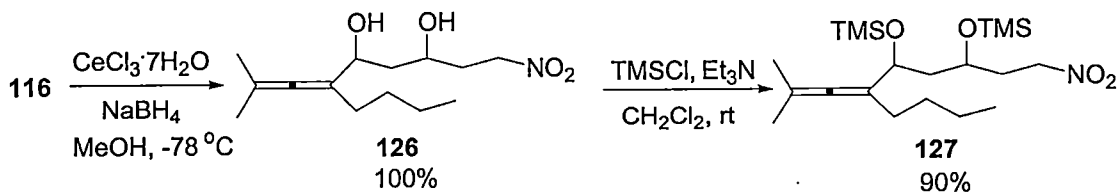
The stereochemistry of the diol was not proven, but assumed to be *syn* based on literature precedent. The protected diol was subjected to cycloaddition conditions, and



Scheme 31. Attempts to protect the carbonyl group of 116 as an acetal.

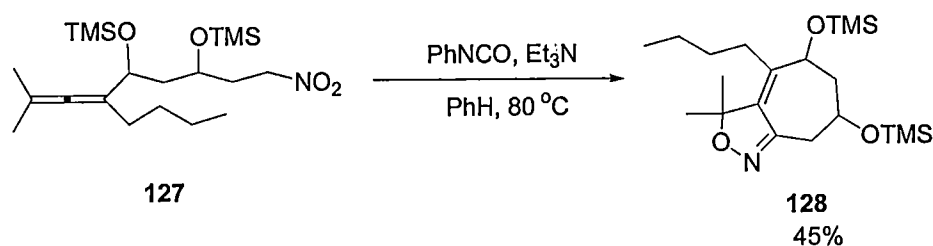


Scheme 32. Preparation of 125 and attempted carbonyl protection.



Scheme 33. Reduction of nitroketone 116 and its protection.

128 was isolated as the sole cycloadduct in 45% yield (Scheme 34). Clearly, the seven-membered ring was favored here, although the allenyl trimethylsiloxy group created additional steric congestion in **127**. The problem may again be the *gem*-dimethyl groups on the allene, which create a steric interaction at the transition state. The drop in the yield was consistent with the literature observation that as the length of the chain increased the efficiency of the reaction decreased.⁴⁰ This result could also be explained by MMX calculations using models shown in Figure 5. The calculations showed that although the ring strain was relieved as the ring size increased from 5 to 6 in **128a**, **128b** ($\Delta H_f = -26.36$ kcal/mol) was still 1.8 kcal/mol more stable than **128a** ($\Delta H_f = -24.51$ kcal/mol).



Scheme 34. Cycloaddition of bis-trimethylsilyl ether **127**.

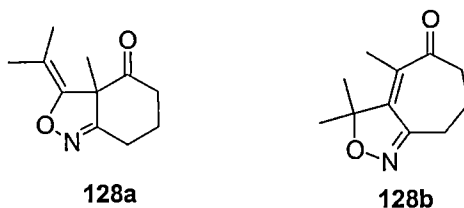


Figure 5. Models of 6/7-membered ring system used in MMX calculations.

The acyclic cycloaddition model did not yield a tricarbonyl compound, but the successful execution of an intramolecular cycloaddition was regarded as encouraging, because it demonstrated that an intramolecular allene–nitrile oxide cycloaddition is feasible.

Furthermore, examination of **130** and **131** (Figure 6), which were the potential products of a cycloaddition involving cyclic allenyl ketones, revealed that other features would be important in the cyclic series.

In the cyclic system, for example, a cycloaddition result comparable to the acyclic model would lead to the formation of bridgehead double bond within a [4.3.1] bicyclic ring system (**131**). This new factor could potentially impact the cycloaddition such that formation of the six-membered ring was favored. MMX calculations on **130** and **131** showed that the thermodynamic preference was reversed in the cyclic system with a 10 kcal/mmol difference in ΔH_f (-32.60 kcal/mmol for **130** and -22.02 kcal/mmol for **131**).

With this in mind, studies on the cyclic model were conducted as described in the next section.

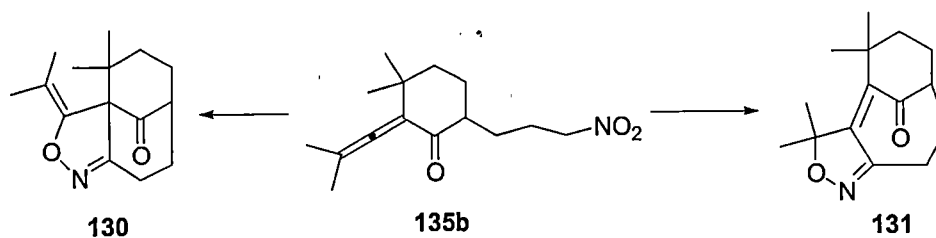
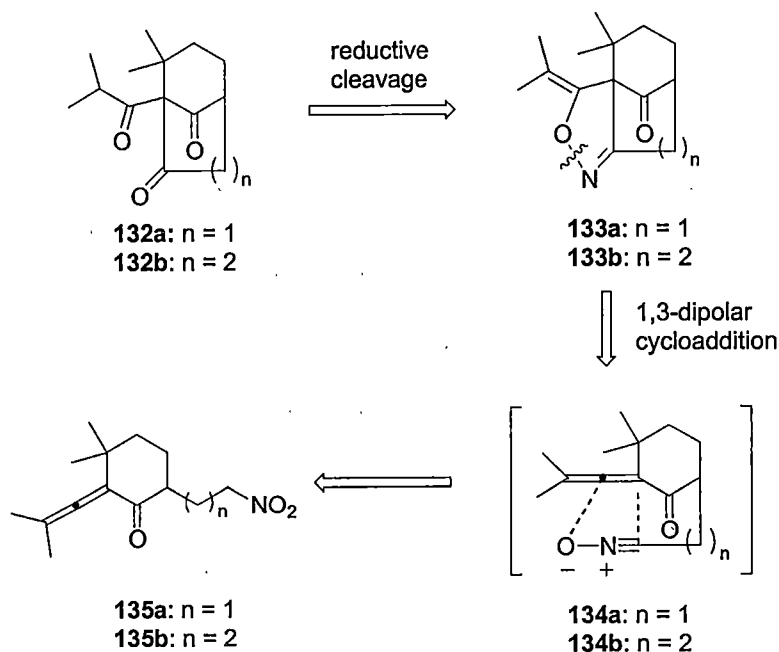


Figure 6. Possible cycloadducts in a cyclic system.

2.2 Cyclic model

It was thought that the prenyl side chains in the real molecule could potentially complicate the cycloaddition by providing other potentially reactive dipolarophile sites. Since the alkenes could be protected if necessary, the desprenyl target molecules **132 (a)** and **(b)** were chosen for studying the assembly of tricarbonyl models (Scheme 35). Importantly, the targets contained all the key structural features in hyperevolutin A, including the bicyclic skeleton, the β,β -tricarbonyl unit and the adjacent quaternary carbons between C1 and C2. Removal of the other functionality permitted us to focus on the cycloaddition itself.

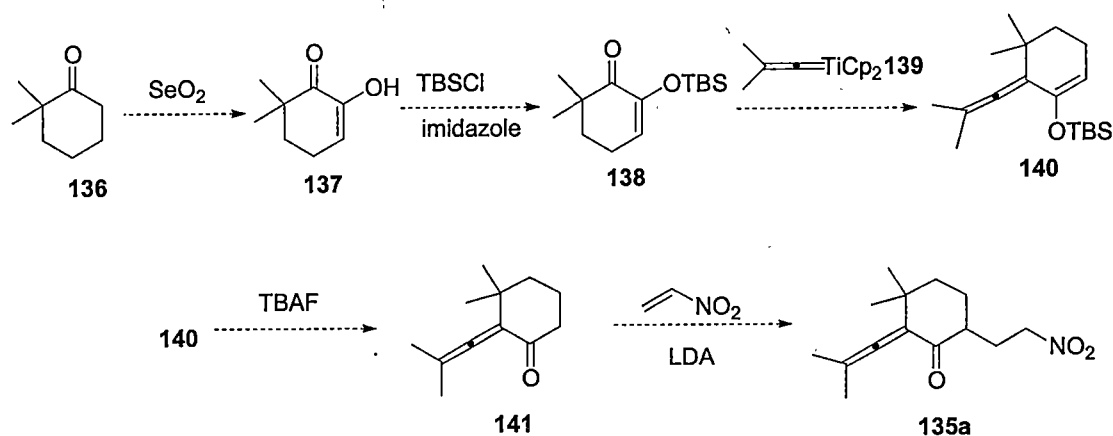


Scheme 35. Retrosynthetic analysis of hyperevolutin A and a strategy for tricarbonyl assembly.

For reasons described previously, it was anticipated that the cycloaddition should occur at the α,β -double bond to avoid formation of a bridgehead alkene in a small ring system. Because a two-carbon chain was more easily introduced than a three-carbon unit, studies were initially conducted on [3.2.1] bicycles as described in Scheme 36.

2.2.1 Direct allenylation approach to cycloaddition precursor 135a

As outlined in Scheme 36, the proposed synthesis of intramolecular cycloaddition precursor 135a started from 2,2-dimethylcyclohexanone (136), envisioning modern titanium chemistry as a means for introducing the allene. Thus, allene 140 was to be formed by application of organotitanium reagent 139⁴¹ to masked diketone 138. Deprotection of 140, followed by Michael addition to nitroethene, was expected to give the desired cycloaddition precursor 135a.

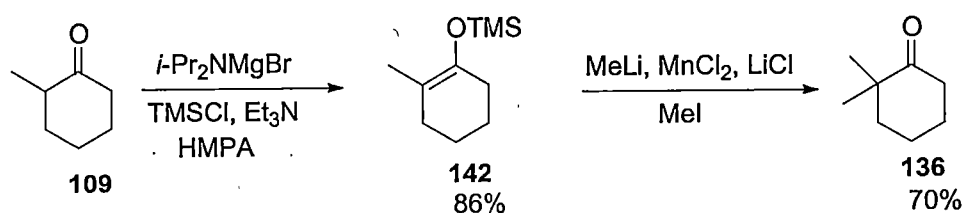


Scheme 36. Proposed allenylation approach to cycloaddition precursor 135a.

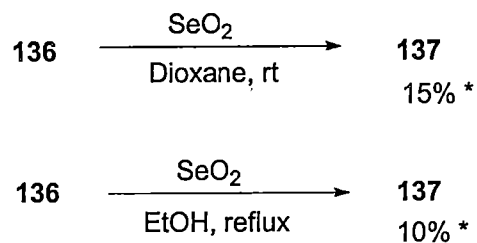
2,2-Dimethylcyclohexanone (**136**) was synthesized using a literature method from 2-methylcyclohexanone in two steps (60% overall yield, Scheme 37).^{42, 43}

Several methods were explored for the oxidation of **136** to diketone **137**, but none gave satisfactory yields. Direct oxidation with selenium dioxide in dioxane at room temperature, for example, did not exceed 15% yield. Substitution of refluxing ethanol for dioxane resulted in a complex mixture of products, where the yield of **137** ranged from 8%–15% by gas chromatography (Scheme 38).

Another literature method⁴⁴ that relied on oxidation of 2-benzal-6,6-dimethylcyclohexanone (**144**)⁴⁵ (Scheme 39) with potassium permanganate produced diketone **137** in 25% yield, probably due to further oxidation of the initial diketone product. Attempts to ozonolyse 2-benzal-6,6-dimethylcyclohexanone gave mostly acyclic products and 4% of **137** (Scheme 40). Possible reasons may involve ozonolysis of the diketone intermediate (Scheme 41).

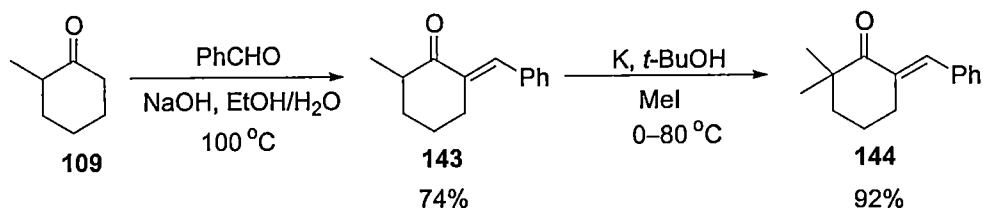


Scheme 37. Synthesis of 2,2-dimethylcyclohexanone (**136**).

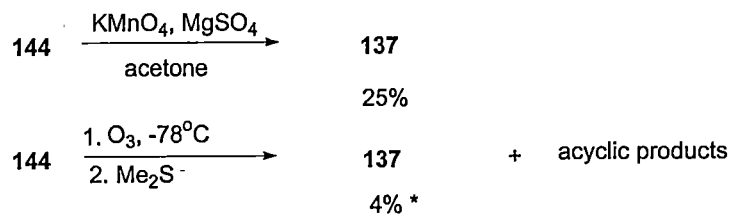


note: * yield derived by GC

Scheme 38. Direct oxidation of 136 by selenium dioxide.

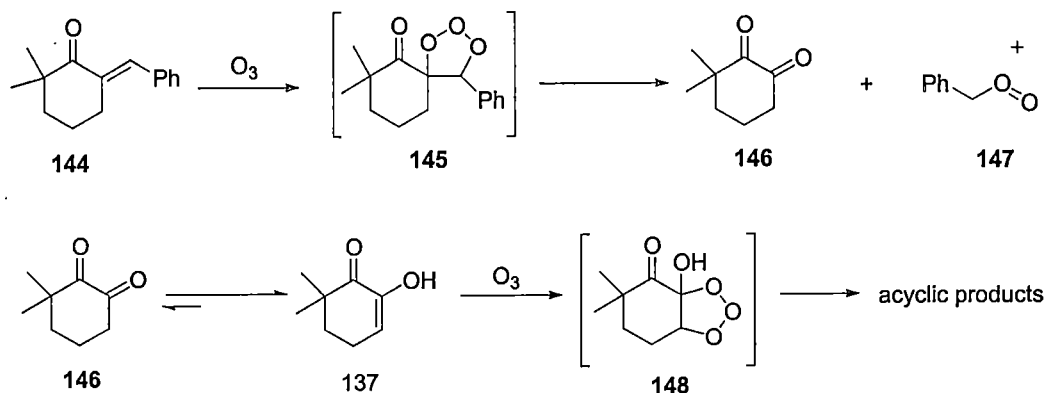


Scheme 39. Synthesis of 2-benzal-6,6 dimethylcyclohexanone (144).



note: * yield derived by GC

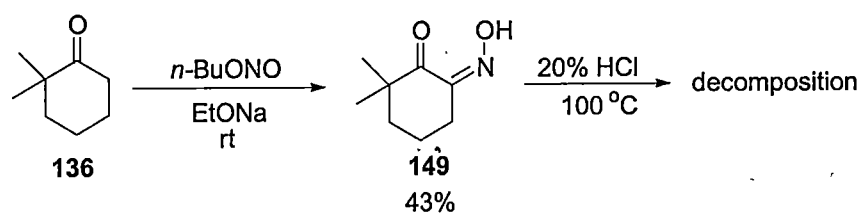
Scheme 40. Synthesis of diketone 137 from 144 by oxidation.



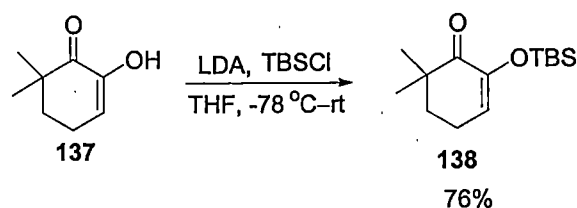
Scheme 41. Ozonolysis of benzylidene compound 144.

An indirect approach employing acidic hydrolysis of α -oximo-dimethylcyclohexanone **149**⁴⁶ did not give the diketone. No further investigations were performed after the low yield of nitrosation was not promising (Scheme 42).

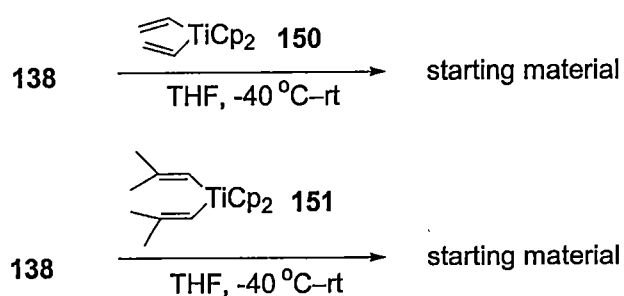
Despite the low yields of diketone **137**, it was decided to investigate the allenylation step anyway. Diketone **137** was subjected to allenylation, following protection of one carbonyl group as a *tert*-butyldimethylsilyl ether **138**. The standard procedure of protecting a hydroxyl group as a *tert*-butyldimethylsilyl ether using TBSCl/imidazole yielded only 10% of **138**; however, treatment of diketone **137** with LDA, followed by TBSCl, produced **138** in 76% yield (Scheme 43). Nevertheless, subjection to alkenyldenetitanocene reagent **150** or **151**⁴⁷ led to recovery of starting material (Scheme 44).



Scheme 42. Synthesis and attempted acidic hydrolysis of 149.



Scheme 43. Synthesis of protected diketone 138.



Scheme 44. Direct allenylation of 138.

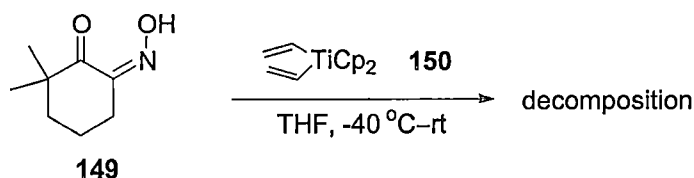
It was suspected that difficulty in allenylation of the diketone derivatives might derive from steric congestion about the carbonyl group of **138**. As shown in Figure 7, severe repulsion exists between the *gem*-dimethyl of the diketone with the inside hydrogen (**152**) or methyl (**153**) of the vinyl titanium.

Oximoketone **149** led to the same result when exposed to the *in situ* generated organotitanium (Scheme 45), possibly due to complications caused by the oxime hydroxyl group. Nevertheless, the same steric interactions found in **152** and **153** (Figure 7) would be expected to exist in the allenylation of **149**.

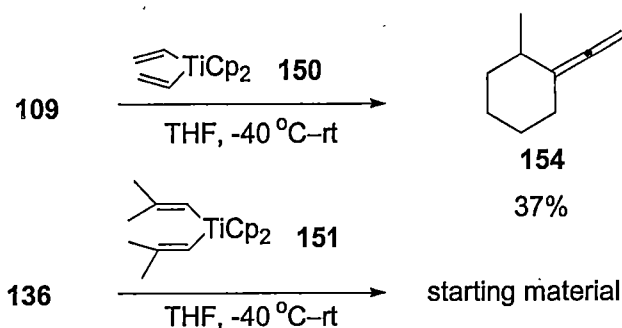
To understand the difficulties of the allenylation reaction, the method was tested on 2-methylcyclohexanone and 2,2-dimethylcyclohexanone. The difference in steric



Figure 7. Steric interaction in the allenylation intermediates.



Scheme 45. Direct allenylation of oximoketone **149**.



Scheme 46. Steric effects on the direct allenylation.

properties was found to cause substantial changes in reactivity toward the titanium reagent. Thus 2-methylcyclohexanone gave allene **154**, but it failed to produce an allene with 2,2-dimethylcyclohexanone (Scheme 46).

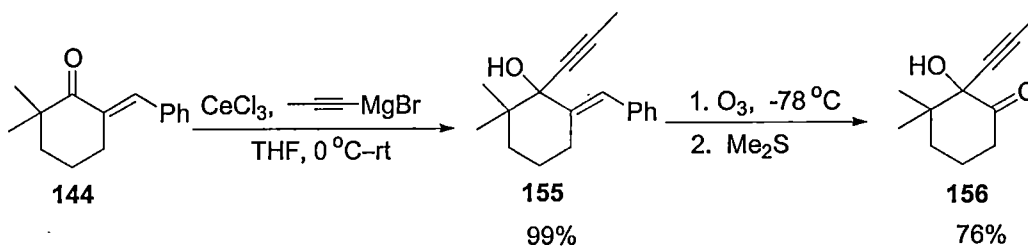
Failure to achieve installation of an allene in 2,2-methylcyclohexanone suggested that it would be even harder to incorporate the allene to a protected and congested diketone setting. Therefore, the direct allenylation approach was abandoned at this stage.

2.2.2 Conjugate substitution approach to cycloaddition precursor **135a**.

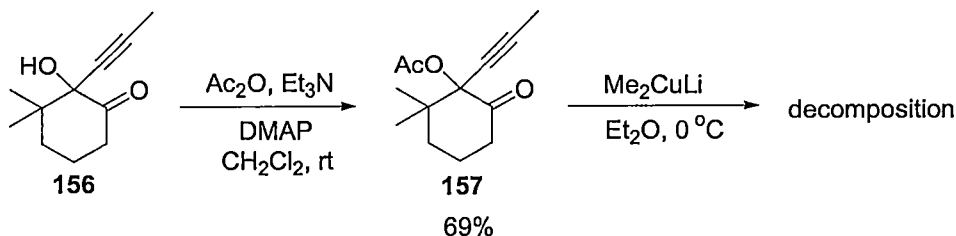
Since the desired ketoallene was not obtained through direct allenylation, a different route was necessary. Thus, 1,2-addition of 1-propynylmagnesium bromide to 2-benzal-6,6-dimethylcyclohexanone (**144**) in the presence of anhydrous cerous chloride⁴⁸ afforded propargyl alcohol **155**. Attempts to generate the acetate of propargyl alcohol **155** resulted in decomposition, probably due to the formation and rearrangement of a

carbocation. To avoid this, the benzylidene fragment was cleaved by ozonolysis to form ketoalcohol **156** (Scheme 47).

However, attempts to produce the acetate of alcohol **156** in refluxing pyridine once again gave decomposition. It was possible that the carbonyl group provided a driving force for rearrangement to the more stable conjugated isomer. However, acetate **157** could be prepared using milder conditions in moderate yield with triethylamine and DMAP at room temperature. Acetate **157** proved to be a dead end; however, since attempts to convert **157** into an allene were not successful, possibly due to conjugate addition to the initial ketoallene product (Scheme 48).



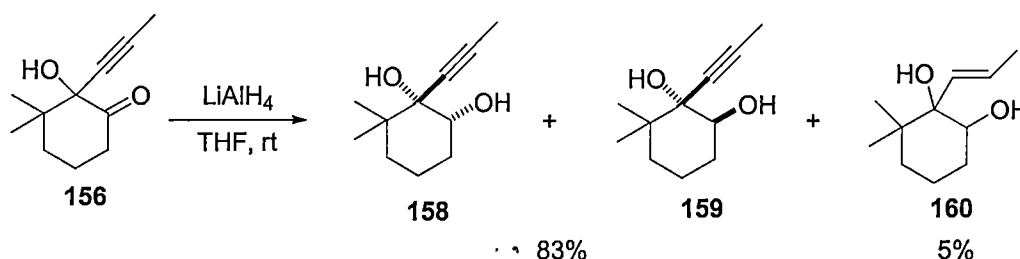
Scheme 47. Preparation of ketoalcohol **156**.



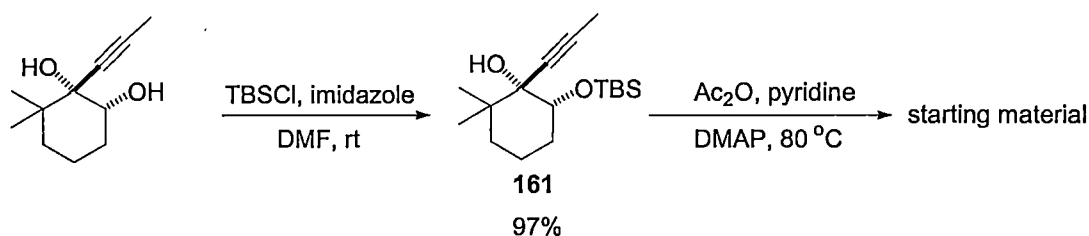
Scheme 48. Preparation and attempted conjugate addition of acetate **157**.

To circumvent problems introduced by the ketone carbonyl, ketone **156** was reduced with lithium aluminum hydride to diols **158** and **159** in 2:1 ratio in 83% combined yield, along with 5% of the overreduced product **160** (Scheme 49). To avoid the overreduction problem, ketone **156** was reduced using a milder hydride source ($\text{NaBH}_4/\text{CeCl}_3 \cdot 7\text{H}_2\text{O}$) at -78°C to yield **158** as the product quantitatively.

Selective protection of the secondary hydroxyl group in the presence of the tertiary hydroxyl group gave **161**, but attempts to prepare the acetate of tertiary alcohol **161** failed to give the desired product, probably due to steric hindrance about the substrate (Scheme 50).

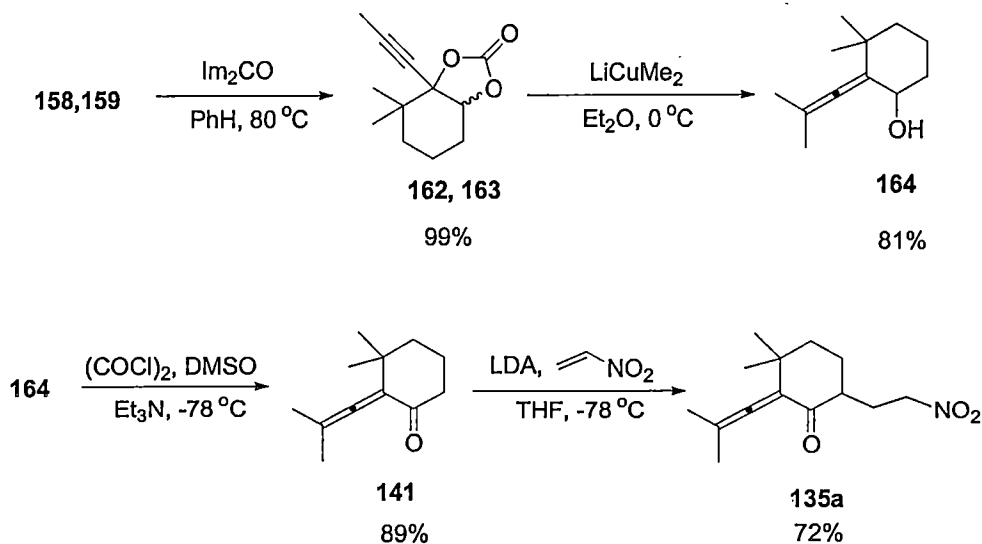


Scheme 49. Reduction of ketone **156** using LiAlH_4 .



Scheme 50. Attempted preparation of the acetate derived from silyl enol ether **161**.

An alternative leaving group was thus employed through the reaction of diols **158** and **159** with carbonyldiimidazole to yield carbonates **162** and **163**. The stereochemistry of carbonate **158** was determined by X-ray diffraction and shown to be *cis* (Figure 8). The carbonates were subjected to S_N2' displacement by methyl cuprate to afford α -allenylalcohol **164** in 81% yield. Allenylalcohol **164** was then transformed to ketoallene **141** by Swern oxidation. Treatment of ketoallene **141** with LDA, followed by conjugate addition to nitroethene, produced the intramolecular cycloaddition precursor nitro ketone **135a** in 72% yield (Scheme 51).



Scheme 51. Preparation of nitroketone **135a**.

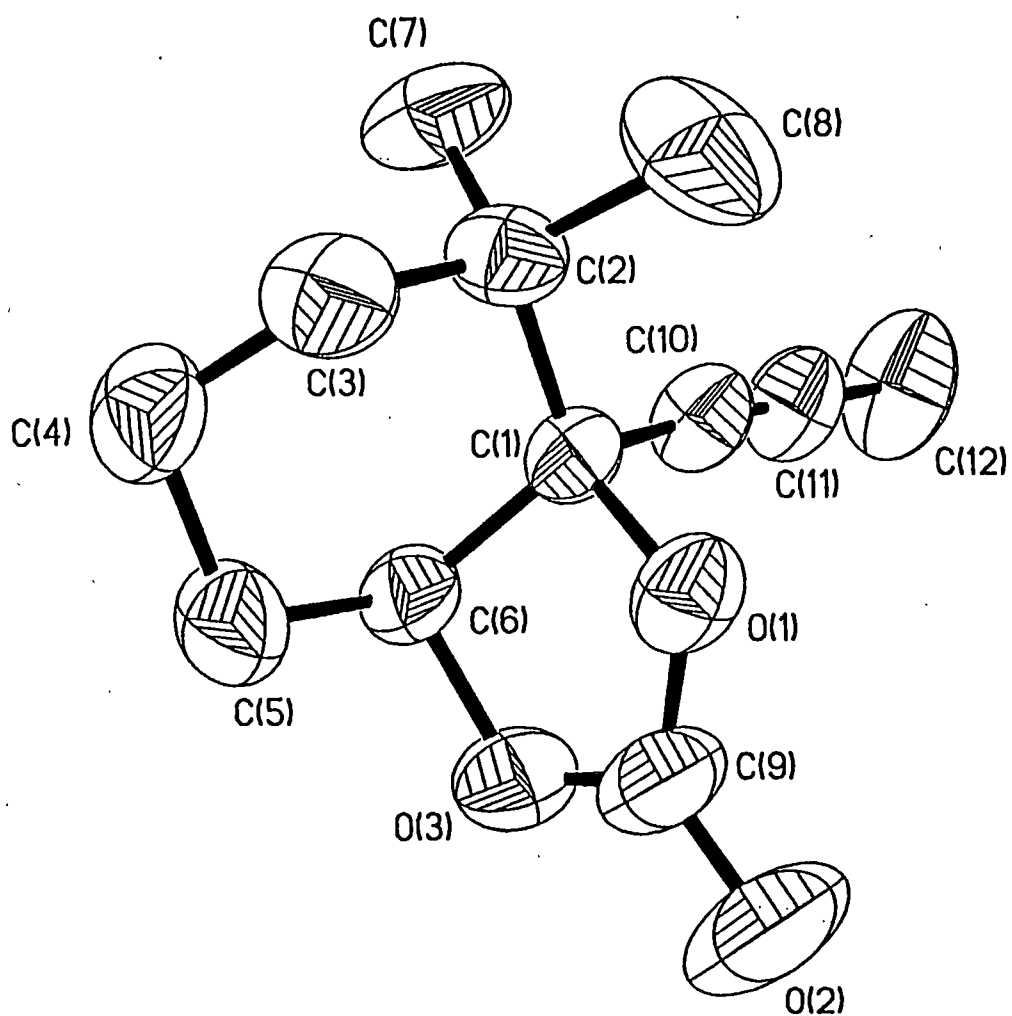


Figure 8. ORTEP view of carbonate **162**, showing 50% thermal ellipsoids. All H atoms are omitted for clarity.

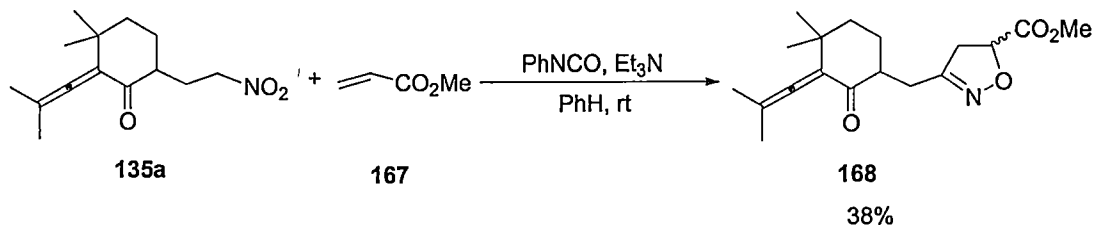
2.2.3 Intramolecular cycloadditions of the cyclic model

Results of the attempted intramolecular cycloaddition of **135a** are summarized in Table 2. As shown, no reaction was observed using TMSCl/Et₃N (silyl nitronate condition ^{49a}), and attempted reaction of the nitrile oxide (generated by phenylisocyanate/triethylamine^{49b} or Boc₂O/DMAP^{49c}) as the dipole systematically resulted in decomposition.

The problem appeared to be a function of the allene, since the nitro group underwent ready cycloaddition with methyl acrylate to afford a mixture of diastereomers **168** (Scheme 52). It is possible, however, that the *gem*-dimethyl group on the allene

Table 2. Intramolecular cycloaddition of nitro ketone 135a

Entry	Substrate	Reagent	Solvent	Temperature (°C)	Results
1	135a	TMSCl/Et ₃ N	CH ₂ Cl ₂	20	No reaction
2	135a	TMSCl/Et ₃ N	PhH	60	No reaction
3	135a	Boc ₂ O/DMAP	toluene	90	Decomposition
4	135a	Boc ₂ O/DMAP	toluene	20	Decomposition
5	135a	PhNCO/Et ₃ N	benzene	50	Decomposition
7	135a	PhNCO/Et ₃ N	chloroform	50	Decomposition
8	135a	PhNCO/Et ₃ N	CH ₂ Cl ₂	20	Decomposition
9	141	LDA/nitroethene/ TMSCl	THF	-78-50	Decomposition



Scheme 52. Intermolecular cycloaddition of nitroketone 135a with methyl acrylate.

interfered with the incoming nitrile oxide oxygen, which deterred the cycloaddition, or that ring strain, as proposed in the acyclic model, prohibited formation of the cycloadduct.

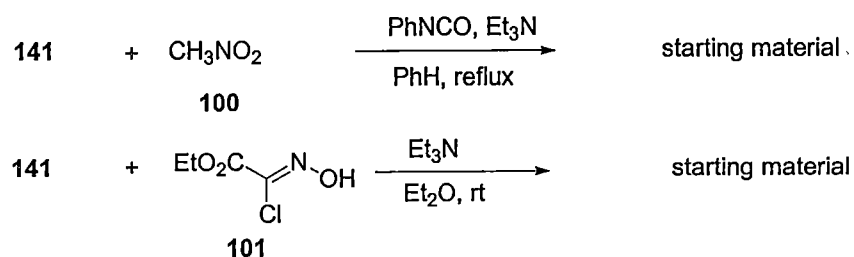
This idea is reinforced by the fact that when ketoallene **141** was reacted with nitromethane in presence of phenylisocyanate and triethylamine in refluxing benzene, or with ethyl chlorooximoacetate at room temperature in ether, only the starting materials were recovered (Scheme 53).

Although the intermolecular cycloaddition failed using **141** as the dipolarophile, the possibility of successful cycloaddition was not eliminated. Since allenes have been reported to react in different types of cycloadditions,⁵⁰ problems with this specific substrate could revolve around steric congestion (allylic strain) in the final product. While the low reactivity of the allene as a dipolarophile could inhibit the cycloaddition, the intramolecular protocol was still viewed as promising under the right conditions.

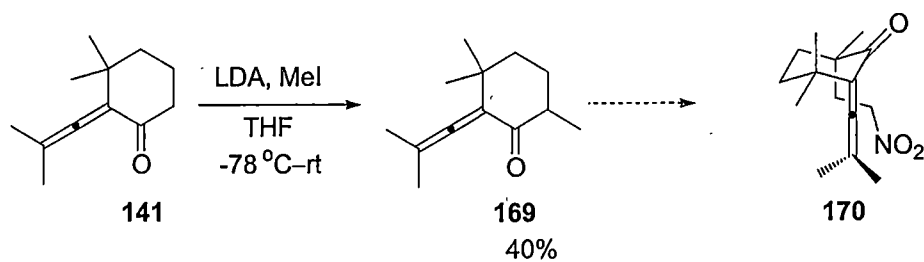
Other reasons for failure were considered, however. For example, the low percentage of axial side chain in **170**, which is required for a successful cycloaddition

could be a problem. To solve this problem, an additional substituent could be introduced to increase the percentage of the axial nitro side chain (Scheme 54). Thus treatment of allenylketone **141** with LDA, followed by alkylation with methyl iodide, afforded allenylketone **169** in 40% yield. However, installation of the nitro side chain turned out to be problematic, probably due to steric congestion around the reacting area.

Another reason could be that the nitrile oxide unit had problem reaching the allene. Although the nitrile oxide unit could reach the α,β -double bond of the allene if the six-membered ring is a perfect chair conformation, the tendency of the allene double bond to conjugate with the carbonyl group would be expected to flatten the ring, and it would be more difficult for the nitrile oxide and allene units to reach each other in such a conformation. An MMX calculation showed that the cyclohexyl ring in a conjugated allene deviated from the ideal chair to a flattened conformation. A local minimum was found for a close-to-chair conformation of **141** (**141b**), and it was a higher energy species compared with a more flattened conformation **141a** (Figure 9, Table 3).



Scheme 53. Intermolecular cycloaddition of ketoallene **141** with nitromethane or ethyl chlorooximoacetate.



Scheme 54. Attempted synthesis of substrate 170.

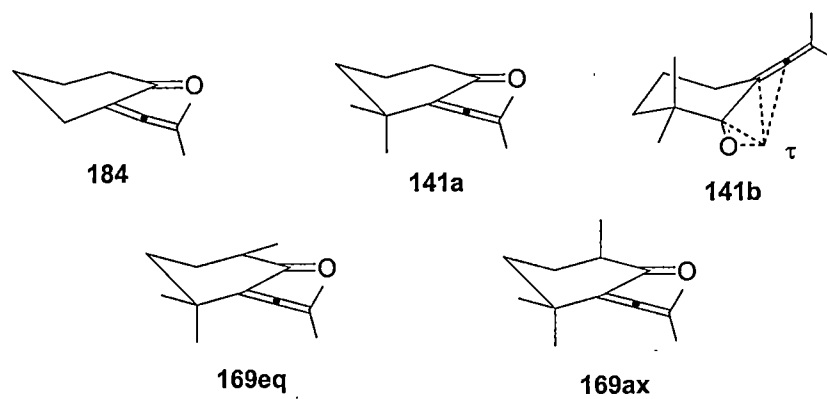


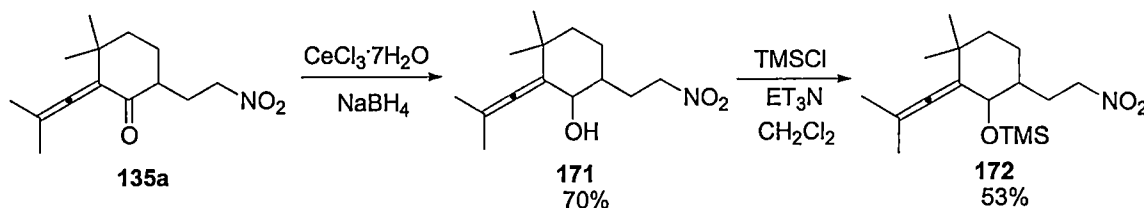
Figure 9. Model conjugated allenes used in MMX calculation.

Table 3. MMX calculation of conjugated allenes.

Entry	Model	Strain energy (kcal/mol)	ΔH_f (kcal/mol)	Dihedral angle τ (°)
1	184	13.08	-9.75	10.15
2	141a	14.06	-24.01	3.68
3	141b	16.37	-21.39	38.05
4	169eq	15.01	-30.82	11.38
5	169ax	16.62	-29.21	8.31

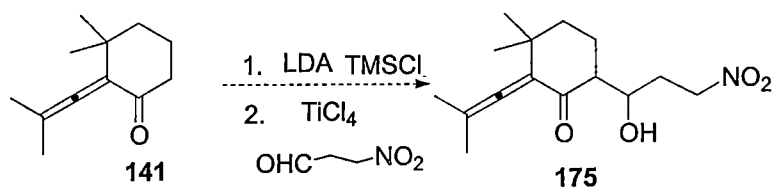
To break the conjugation, nitro ketone **135a** was reduced to alcohol **171** using sodium borohydride and cerium(III) chloride heptahydrate in 70% yield. Alcohol **171** was then protected as silyl ether **172** using trimethylsilyl chloride and triethylamine (Scheme 55). Unfortunately, no cycloadduct was isolated from the reaction of silyl ether **172** with phenylisocyanate and triethylamine in refluxing benzene.

A possible solution that was considered was that an increase in chain length could eliminate the distance problem even in a flattened conformation. To verify this, the chain was homologated using the same method as in the acyclic model (Scheme 56).

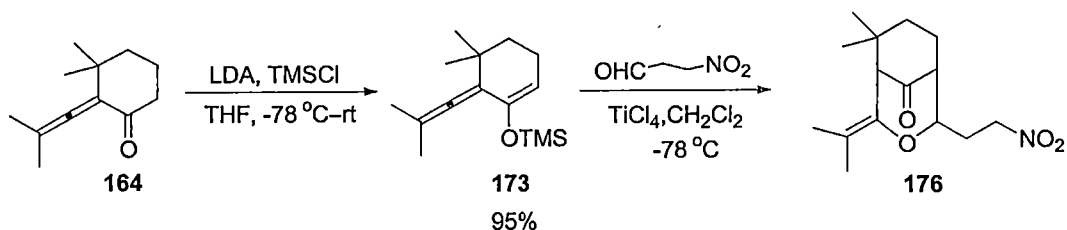
**Scheme 55. Preparation of protected alcohol 172.**

Condensation of the enol ether derived from **141** with 3-nitropropanal, however, did not lead to the isolation of nitroalcohol **175**, but instead a pair of products tentatively assigned structure **176** were isolated, which resulted from the intramolecular cyclization of the nitroalcohol intermediate (Scheme 57).

To stop intramolecular cyclization, nitropropanal dimethyl acetal **122** was used as the nitro source in a synthesis of methoxy compound **177** (44%) (Scheme 58). Treatment of **177** with di-*tert*-dibutylcarbonate and DMAP in refluxing benzene and acetonitrile (2:1) yielded 40% of the cycloadduct **178** (Scheme 58). The reaction of **177** with phenylisocyanate and triethylamine in refluxing benzene gave a comparable yield (30%). In line with our prediction, the formation of a six-membered ring occurred,



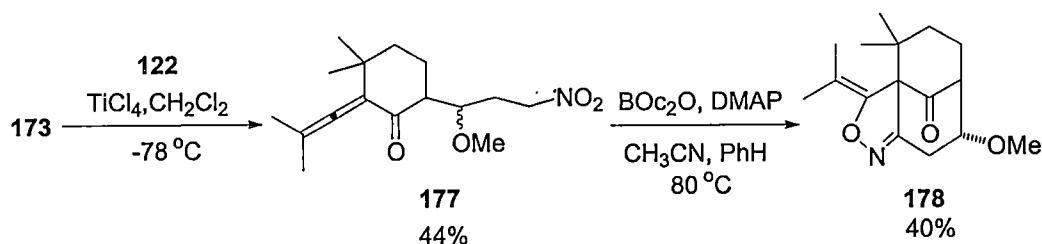
Scheme 56. Proposed preparation of nitroalcohol **175**.



Scheme 57. Aldol condensation of **173** with 3-nitropropanal.

possibly due to avoidance of the bridgehead double bond. Thus, the success of the cycloaddition is consistent with our hypothesis, and the only cycloadduct isolated was the one with the α,β -double bond acting as the dipolarophile. An X-ray single crystal structure was obtained to confirm the assigned structure of the product, and it showed the area around the bridgehead was highly crowded (Figure 10). In crystal the bicyclic ring was in a chair-chair conformation with the methoxy group in an equatorial position. It was surprising that the cycloadduct originated from only one of the methoxy diastereomers, thus the fate of the other has not been determined. β -Elimination of the methoxy group was ruled out, since refluxing the nitro compound **177** with triethylamine in benzene did not show any evidence of elimination after 18 h at 80 °C.

Despite the modest yield, the cycloaddition resulted in construction of the hindered bicyclic core of the hyperevolutins. Furthermore, we were gratified to find that reductive cleavage of the N–O bond in cycloadduct **178** occurred in quantitative yield using hydrogen in the presence of Raney nickel, which afforded the tricarbonyl unit in latent form (**179**) (Scheme 59).



Scheme 58. Preparation and cycloaddition of **177**.

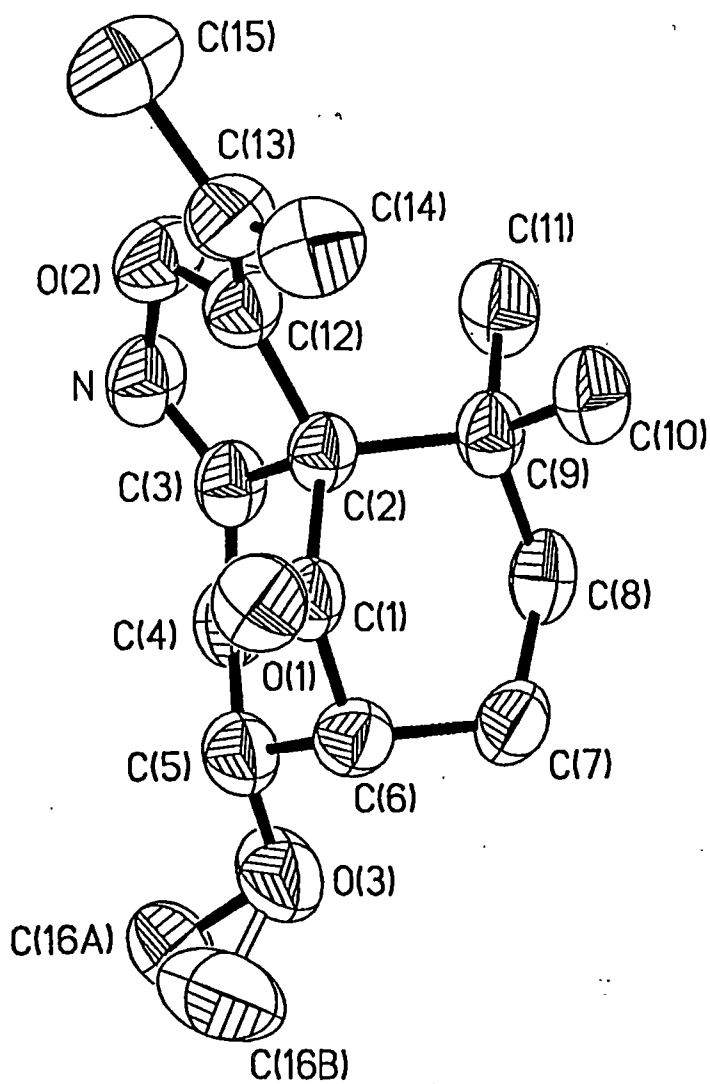
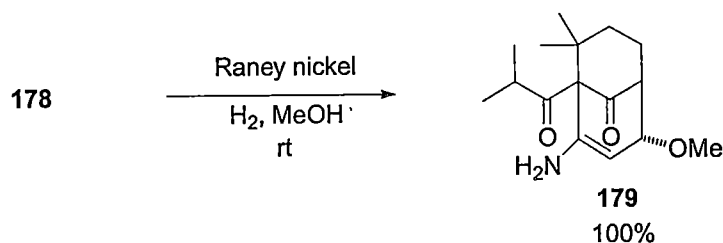


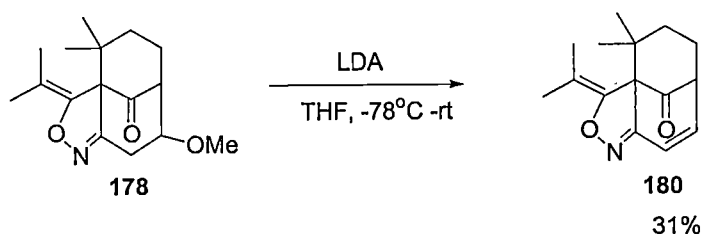
Figure 10. ORTEP view of cycloadduct **178**, showing 50% thermal ellipsoids. All H atoms are omitted for clarity.

Currently, studies related to the hydrolysis of **179** are being explored. Various conditions have been examined, yet so far none has yielded the tricarbonyl (Table 4).

It was speculated that elimination of the methoxy group would disallow the formation of an enamine in the reductive-cleavage step. Thus the cycloadduct was subjected to acid as well as alkine conditions in an attempt to eliminate the methoxy group (Table 5). The reaction under acidic conditions was not clean, and the desired α,β -unsaturated product was not isolated. Refluxing cycloadduct **178** with *tert*-butoxide in *tert*-butanol showed no reaction as well. However, deprotonation with LDA led to the isolation of **180** in low yield (Scheme 60).



Scheme 59. Cleavage of the N–O bond in cycloadduct **178**.



Scheme 60. β -Elimination in cycloadduct **178**.

Table 4. Acidic hydrolysis of enamine 179.

Entry	Substrate	Solvent	Acid	Temperature (°C)	Result
1	179	MeOH/H ₂ O	1N HCl	20	decomposition
2	179	H ₂ O	1N HCl	20	decomposition
3	178	MeOH	Concd HCl	20	decomposition
			H ₂ /Ra Ni		
4	179	MeOH	HNO ₂	20	decomposition

Table 5. Attempted elimination of the methoxy group in cycloadduct 178.

Entry	Solvent	Temperature (°C)	Reagent	Result
1	<i>t</i> -BuOH	20	<i>t</i> -BuOK	No reaction
2	<i>t</i> -BuOH	80	<i>t</i> -BuOK	No reaction
3	benzene	80	TsOH·H ₂ O	Decomposition
4	THF	20	HCl	No reaction
5	THF	80	HCl	No reaction

2.3 Conclusions

In the acyclic model, the β,γ -double bond of the allene is more reactive in an intramolecular nitrile oxide–allene cycloaddition both in the 5- and 6-membered ring system. Molecular mechanics calculations showed that the regioselectivity was a result of thermodynamic preference.

In the cyclic model, the α,β -double bond of the allene is more reactive as a result of reversed relative stabilities of the two cycloadducts. Although a tricarbonyl compound has not yet been isolated, **178** and **180** are functionalized models of hyperforin/hyperevolutin antitumor antibiotics. These compounds were prepared from 2-methylcyclohexanone in 11 or 12 steps, in 6% and 2% overall yields respectively. The tricarbonyls were also prepared in the latent form (**179**) in 12 steps in a 6% overall yield.

3. Experimental Section

3.1 General methods

All melting points were measured on a Thomas-Hoover capillary melting point apparatus and are uncorrected. ^1H and ^{13}C -NMR were recorded on Bruker AC-250 or Varian mercury-300 spectrometers at 250 MHz and 63 MHz, or 300 MHz and 75 MHz respectively and are recorded in part per million from internal tetramethyl silane as the δ scale. The Splitting patterns of the ^1H NMR spectra was reported as follows: s, singlet; d, doublet; dd, doublet of doublets; t, triplet; q, quartet; td, triplet of doublets; h, heptet; m, multiplet. FT-infrared spectra were obtained on an Arid-zone bomem MB100 instrument. The mass spectral analyses were obtained on a Micromass VG Quattro II electrospray instrument at the University of Tennessee. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, Ga or Complete Analysis Labs, Inc., Parsippany, NJ.

All commercial reagents were used without further purification unless otherwise noted. All reactions were conducted under a nitrogen atmosphere unless otherwise noted, and yields refer to isolated yields of material unless otherwise stated.

Tetrahydrofuran, diethyl ether and toluene were distilled from sodium benzophenone ketyl. Methylene chloride, diisopropylamine, chlorotrimethylsilane and benzene were distilled over calcium hydride before use. Acetonitrile and dimethyl sulfoxide were distilled over calcium hydride and stored over 4-Å molecular sieves. *N,N*-dimethylacetamide was distilled over barium oxide and stored over 4-Å molecular sieves.

tert-Butyl alcohol was distilled over potassium *tert*-butoxide before use. 4-dimethylaminopyridine was recrystallized from toluene.

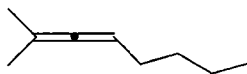
Methylolithium, *n*-butyllithium, *t*-butyllithium, methylmagnesium bromide, vinylmagnesium bromide and 1-propynylmagnesium bromide were titrated with menthol using 1,10-phenanthroline as the indicator on a regular basis.⁵¹

Analytical thin-layer chromatography (TLC) was conducted using Whatman K5F 150A 250 μ m silica gel plates. Column chromatography was performed on ICN Silitech silica gel (63–200 mesh, 60 Å).

Anhydrous oxalic acid,⁵² *n*-butyl nitrite,⁵³ nitroethene,⁵⁴ 3-nitropropanal,⁵⁵ 1,1-dimethoxy-3-nitropropane,⁵⁵ silver oxide,⁵⁶ and a 1M solution of IZnCH_2I in THF⁵⁷ were prepared by literature methods.

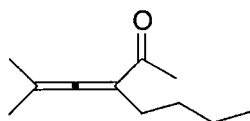
Nomenclature of new compounds was generated using a ChemDraw Ultra program. Molecular mechanics calculations were conducted using a PCMODEL 4.0 program from Serena Software.

Abbreviations for compounds appear as follows: THF (tetrahydrofuran), DMA (*N,N*-dimethyl acetamide), DMF (*N,N*-dimethyl formamide), DMAP (4-dimethylaminopyridine), HMPA (hexamethylphosphoric triamide), TBSCl (*tert*-butyldimethylsilyl chloride), DMSO (dimethyl sulfoxide), HCl (hydrochloric acid).

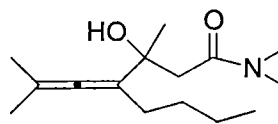


83

2-Methylocta-2,3-diene (83).²⁶ To a suspension of 5.33 g of cuprous iodide (28 mmol) in 60 mL of ether at $-78\text{ }^{\circ}\text{C}$ was added 40.0 mL of a 1.4 M solution of *n*-BuLi in hexane (56 mmol). The resulting black solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 10 min then warmed to $0\text{ }^{\circ}\text{C}$ and 3-chloro-3-methyl-1-butyne (81) in 40 mL of ether was added over a period of 10 min. The mixture was stirred at $0\text{ }^{\circ}\text{C}$ for 2 h and quenched with 100 mL of saturated aqueous NH_4Cl . The aqueous layer was extracted with three 50-mL portions of ether and 50-mL of pentane. The combined organic layers were dried (MgSO_4), and concentrated *in vacuo*. The residue was chromatographed over 45 g of silica gel (eluted with pentane) to afford 1.37 g of **84** as a colorless oil (55%): ^1H NMR (250 MHz, CDCl_3) δ 4.94 (m, 1H), 1.95 (q, $J=6.6\text{ Hz}$, 2H), 1.68 (d, $J=2.8\text{ Hz}$, 6H), 1.34–1.39 (m, 4H), 0.86–0.90 (m, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 201.70 (s), 94.64 (s), 88.79 (s), 31.39 (t), 28.93 (t), 22.09 (t), 20.73 (q, 2C), 14.06 (q).



84

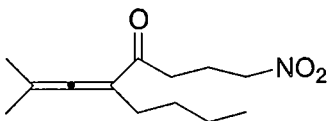


87

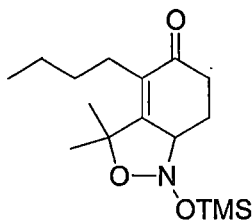
3-Butyl-5-methylhexa-3,4-dien-2-one (84).²⁷ To a solution of 0.461 g (3.72 mmol) of allene **84** in 10 mL of THF at $-78\text{ }^{\circ}\text{C}$ was added 2.65 mL of a 1.4 M solution of *t*-BuLi

in pentane (3.72 mmol). The resulting yellow solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h, warmed to $-50\text{ }^{\circ}\text{C}$, stirred for 1 h, and then re-cooled to $-78\text{ }^{\circ}\text{C}$. *N,N*-Dimethylacetamide (0.34 g, 0.36 mL, 3.91 mmol) was added all at once. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 2.5 h, transferred via cannula to 75 mL of ice-cold aqueous HCl (0.1 M). The aqueous layer was extracted with three 20-mL portions of ether. The combined organic layers were dried (MgSO_4), filtered, and concentrated *in vacuo*. The residue was chromatographed over 2 g of silica gel (eluted with hexane-ethyl acetate, 20:1) to afford 0.324 g of **84** as a colorless oil (53%): ^1H NMR (250 MHz, CDCl_3) δ 2.22 (s, 3H), 2.14 (t, $J=6.5$ Hz, 2H), 1.83 (s, 6H), 1.30–1.33 (m, 4H), 0.89 (t, $J=6.2$ Hz, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 210.19 (s), 200.15 (s), 107.81 (s), 99.43 (s), 30.17 (t), 26.90 (q), 26.34 (t), 22.27 (t), 19.65 (q, 2C), 13.95 (q). Continued elution afforded a colorless oil which crystallized on standing to afford 0.145 g of **87** (15%): mp $41\text{--}42\text{ }^{\circ}\text{C}$; IR (neat) 3383, 2959, 2930, 2871, 1962, 1625, 1459, 1400, 1367, 1157, 1069 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 6.03 (s, 1H), 2.98 (s, 3H), 2.95 (s, 3H), 2.86 (d, $J=15.8$ Hz, 1H), 2.24 (d, $J=15.8$ Hz, 1H), 2.13 (m, 1H), 2.05 (m, 1H), 1.87 (s, 3H), 1.58 (s, 3H), 1.25–1.40 (m, 4H), 1.31 (s, 3H), 0.89 (m, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 195.87 (s), 173.37 (s), 109.14 (s), 97.54 (s), 72.72 (s), 41.18 (t), 36.90 (q), 34.83 (q), 30.11 (t), 28.44 (q), 26.28 (t), 22.20 (t), 20.45 (q), 20.33 (q), 13.86 (q); exact mass calcd for $\text{C}_{15}\text{H}_{27}\text{NO}_2$ m/z 253.2042; found m/z 253.2045.

Anal. Calcd for $\text{C}_{15}\text{H}_{27}\text{NO}_2$: C, 71.15; H, 10.67. Found: C, 71.14; H, 10.58.

**96**

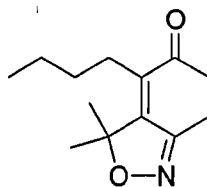
5-Butyl-7-methyl-1-nitroocta-5,6-dien-4-one (96). Diisopropylamine (0.582 g, 0.806 mL, 5.75 mmol) in 15 mL of THF at $-78\text{ }^{\circ}\text{C}$ was treated with 3.76 mL of *n*-BuLi (1.4 M in hexane, 5.27 mmol). The resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 20 min, warmed to $-10\text{ }^{\circ}\text{C}$, stirred for 50 min and then recooled to $-78\text{ }^{\circ}\text{C}$. A solution of 0.795 g (4.79 mmol) of ketone **84** in 6 mL of THF was then added dropwise. The resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h, and a solution of 0.369 g (5.03 mmol) of nitroethene in 4 mL of THF was added. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 4 h and then quenched with 10 mL of 0.5 M HCl. The aqueous layer was extracted with four 40-mL portions of ether. The combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. The residue was chromatographed over 20 g of silica gel (eluted with hexane–ethyl acetate, 15:1) to afford 0.721 g of **96** as a pale yellow oil (68 %): IR (neat) 2956, 2929, 1951, 1673, 1553, 1439, 1364 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.42 (t, $J=6.6$ Hz, 2H), 2.71 (t, $J=6.9$ Hz, 2H), 2.26 (q, $J=6.8$ Hz, 2H), 2.15 (t, $J=7.1$ Hz, 2H), 1.82 (s, 6H), 1.25–1.35 (m, 4H), 0.87–0.93 (m, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 209.53 (s), 200.10 (s), 107.21 (s), 100.56 (s), 74.87 (t), 34.94 (t), 30.08 (t), 26.36 (t), 22.25 (t), 19.57 (q, 2C), 13.89 (q); exact mass calcd for $\text{C}_{13}\text{H}_{21}\text{NO}_3$ m/z 239.1521; found m/z 239.1516.



98

4-Butyl-3,3-dimethyl-1-trimethylsilanyloxy-1,6,7,7a-tetrahydro-3H-

benzo[c]isoxazol-5-one (98). To a solution of 60.9 mg (0.255 mmol) of nitroketone **96** in 1 mL of methylene chloride at room temperature was added 78.1 μ L (56.7 mg, 0.561 mmol) of triethylamine followed by 71.2 μ L (60.9 mg, 0.561 mmol) of chlorotrimethylsilane. The resulting slurry was stirred at room temperature for 18 h. The solvent was removed *in vacuo*, and the residue was chromatographed over 1.5 g of silica gel (eluted with hexane–ethyl acetate, 20:1) to afford 34.3 mg of **98** as a yellow oil (43%): IR (neat) 2958, 2871, 1718, 1452, 1252, 1055, 845 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.22 (m, 1H), 2.85 (td, $J=15.8, 9.8$ Hz, 1H), 2.12–2.28 (m, 3H), 1.80 (s, 3H), 1.73 (s, 3H), 1.54–1.59 (m, 2H), 1.25–1.42 (m, 4H), 0.92 (t, $J=6.8$ Hz, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 205.79 (s), 133.28 (s), 128.89 (s), 92.10 (s), 74.03 (d), 34.36 (t), 27.51 (t), 26.74 (t), 25.56 (t), 23.11 (q), 22.96 (t), 18.94 (q), 14.09 (q), -0.42 (q, 3C); exact mass calcd for $\text{C}_{16}\text{H}_{29}\text{NO}_3\text{Si}$ m/z 311.1917; found m/z 311.1928.

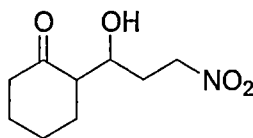


97

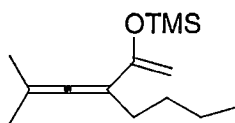
4-Butyl-3, 3-dimethyl-6,7-dihydro-3H-benzo[c]isoxazol-5-one (97). Method A: To a solution of 60.0 mg (0.250 mmol) of nitroketone **96** in 1 mL of benzene at room temperature was added 40.8 μ L (44.7 mg, 0.375 mmol) of phenyl isocyanate, followed by 4.0 μ L (0.025 mmol) of triethylamine. The mixture was stirred at room temperature for 5 min., then heated to 60 °C and stirred for 24 h. The reaction was cooled to room temperature, and 5 mL of ether was added. The mixture was filtered. The filtrate was concentrated *in vacuo* and the residue was chromatographed over 2 g of silica gel (eluted with hexane–ethyl acetate, 5:1) to afford 42 mg of **97** as a yellow oil (75%): IR (neat) 2960, 2933, 2869, 1672, 1631, 1438, 1195, 902 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 2.95 (t, $J=7.4$ Hz, 2H), 2.61 (t, $J=7.4$ Hz, 2H), 2.29 (m, 2H), 1.55 (s, 6H), 1.34–1.37 (m, 4H), 0.89 (t, $J=6.7$ Hz, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 198.69 (s), 156.60 (s), 152.35 (s), 134.83 (s), 85.91 (s), 35.28 (t), 32.19 (t), 25.39 (q, 2C), 25.30 (t), 23.10 (t), 19.97 (t), 13.74 (t); exact mass calcd for $\text{C}_{13}\text{H}_{19}\text{NO}_2$ m/z 221.1416; found m/z 221.1420.

Method B: To a solution of 0.120 g (0.50 mmol) of nitroketone **96** and 0.164 g (0.75 mmol) of di-*tert*-butyldicarbonate in 1 mL of acetonitrile at room temperature was added 6.1 mg (0.050 mmol) of DMAP. The resulting solution was stirred at room temperature for 48 h and then concentrated *in vacuo*. The residue was chromatographed over 2 g of

silica gel (eluted with hexane–ethyl acetate, 10:1) to afford 53.5 mg of **97** as a yellow oil (48%).

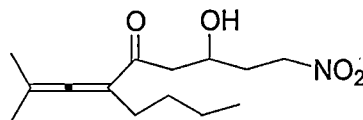
**114**

2-(1-Hydroxy-3-nitropropyl)cyclohexanone (114). To a solution of 240.0 mg (2.32 mmol) of 3-nitropropanal (**122**) in 20 mL of methylene chloride at $-78\text{ }^{\circ}\text{C}$ was added 0.507 mL (880.0 mg, 4.64 mmol) of titanium(IV) chloride, followed by 360.0 mg (2.12 mmol) of enol ether **106**. The resulting solution was stirred at $-78\text{ }^{\circ}\text{C}$ for 4 h, then quenched with aq K_2CO_3 (20 mmol). The aqueous layer was extracted with three 10-mL portions of ether. The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was chromatographed over 5 g of silica gel (eluted with hexane–ethyl acetate, 5:1) to afford 210 mg of **114** as a yellow oil (50%): IR (neat) 3465, 2941, 2866, 1700, 1552, 1449, 1431, 1382, 1310, 1132, 1110, 1055, 940 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.53 (t, $J=6.3\text{ Hz}$, 2H), 4.11 (3.78) (m, 1H), 3.67 (2.91) (m, 1H), 2.35 (m, 3H), 2.06 (m, 4H), 1.93 (s, 1H), 1.41–1.51 (m, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 215.05 (213.98) (s), 72.74 (72.17) (t), 68.63 (66.23) (d), 55.63 (54.77) (d), 42.55 (42.31) (t), 30.87 (30.54) (t), 30.28 (t), 27.50 (27.37) (t), 26.57 (24.57) (t).

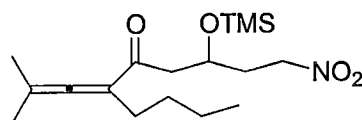


102

(2-Butyl-4-methyl-1-methylenepenta-2,3-dienyloxy)-trimethylsilane (102). A solution of 0.334 mL (0.241 g, 2.39 mmol) of diisopropylamine in 6 mL of THF at -78 °C was treated with 1.75 mL of *n*-BuLi (1.25 M in hexane, 2.19 mmol). The resulting solution was stirred at -78 °C for 20 min, warmed to 0 °C, stirred for 40 min, and recooled to -78 °C. A solution of 0.330 g (1.988 mmol) of ketone **84** in 2.4 mL of THF was added dropwise. The resulting solution was stirred at -78 °C for 1 h. Trimethylsilyl chloride (0.259 g, 0.302 mL, 2.386 mmol) was added. The reaction was warmed to room temperature over 4.5 h. The solvent was removed *in vacuo*. The residue was dissolved in pentane and filtered through a short pad of Florisil (eluted with pentane) to afford 0.468 g of **102** as a colorless oil (99%): IR (neat) 2958, 2931, 2861, 1955, 1604, 1250, 1019, 845 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.37 (s, 1H), 4.27 (s, 1H), 2.08 (t, $J=6.8$ Hz, 2H), 1.72 (s, 6H), 1.33–1.42 (m, 4H), 0.91 (t, $J=7.1$ Hz, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 202.29 (s), 154.75 (s), 103.49 (s), 97.71 (s), 92.13 (t), 30.23 (t), 29.15 (t), 22.41 (t), 20.35 (q, 2C), 13.98 (q), -0.09 (q, 3C); exact mass calcd for $\text{C}_{14}\text{H}_{26}\text{OSi}$ m/z 238.1753; found m/z 238.1755.

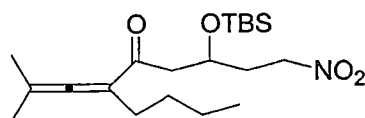
**116**

4-Butyl-7-hydroxy-2-methyl-9-nitronona-2,3-dien-5-one (116). To a solution of 30.6 mg of 3-nitropropanal⁵⁵ (**122**) (0.30 mmol) in 2.5 mL of methylene chloride at $-78\text{ }^{\circ}\text{C}$ was added 35.5 μL (61.5 mg, 0.32 mmol) of titanium(IV) chloride. The mixture was stirred for 10 min before 64 mg (0.27 mmol) of enol ether **102** in 0.5 mL of methylene chloride was added. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 4 h, and then quenched with 5 mL of aq K_2CO_3 (1.5 mmol). The aqueous layer was extracted with three 8-mL portions of ethyl acetate. The combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. The residue was chromatographed over 2 g of silica gel (eluted with hexane–ethyl acetate, 5:1) to afford 35.8 mg of **116** as a pale yellow oil (49%): IR (neat) 3480, 2957, 2930, 2871, 1950, 1663, 1553, 1433, 1385, 1183, 1110 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.54 (t, $J=5.2$ Hz, 2H), 4.06 (m, 1H), 3.59 (s, 1H), 2.83 (dd, $J=17.1$, 2.9 Hz, 1H), 2.62 (dd, $J=17.1$, 8.9 Hz, 1H), 2.00–2.15 (m, 4H), 1.80 (s, 6H), 1.22–1.32 (m, 4H), 0.85 (t, $J=6.8$ Hz, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 210.06 (s), 202.00 (s), 107.59 (s), 100.79 (s), 72.15 (t), 65.17 (d), 44.87 (t), 33.46 (t), 29.91 (t), 26.02 (t), 22.11 (t), 19.43 (q, 2C), 13.79 (q); exact mass calcd for $\text{C}_{14}\text{H}_{23}\text{NO}_4$ m/z 269.1627; found m/z 269.1639.



117

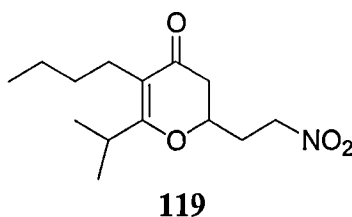
4-Butyl-2-methyl-9-nitro-7-trimethylsilanyloxy-nona-2,3-dien-5-one (117). To a solution of 69 mg of nitro aldol **116** (0.257 mmol) in 1 mL of methylene chloride was added 0.114 mL (83.1 mg, 0.821 mmol) of triethylamine, followed by 0.104 mL of chlorotrimethylsilane (89.2 mg, 0.821 mmol). The mixture was stirred at room temperature overnight, and filtered through 1 g of Florisil (eluted with hexane–ethyl acetate, 10:1) to afford 81.5 mg of **117** as a yellow oil (93%): IR (neat) 2957, 2930, 2863, 1950, 1669, 1555, 1381, 1252, 1109, 844 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.42 (t, $J=6.6$ Hz, 2H), 4.24 (m, 1H), 2.86 (dd, $J=15.2$, 6.3 Hz, 1H), 2.61 (dd, $J=15.2$, 6.8 Hz, 1H), 2.03–2.20 (m, 4H), 1.82 (s, 6H), 1.23–1.32 (m, 4H), 0.86 (t, $J=6.6$ Hz, 3H), 0.07 (s, 9H); ^{13}C NMR (63 MHz, CDCl_3) δ 210.07 (s), 199.22 (s), 108.14 (s), 100.34 (s), 72.12 (t), 66.57 (d), 46.62 (t), 34.41 (t), 29.99 (t), 26.26 (t), 22.17 (t), 19.62 (q, 2C), 13.83 (q), -0.08 (q, 3C); exact mass calcd for $\text{C}_{17}\text{H}_{31}\text{NO}_4\text{Si}$ m/z 341.2022; found m/z 341.2014.



118

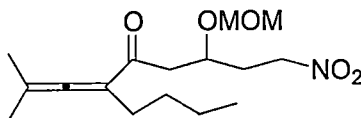
4-Butyl-7-(*tert*-butyldimethylsilyloxy)-2-methyl-9-nitronona-2,3-dien-5-one (118). To a solution of 53.8 mg (0.20 mmol) of nitroaldol **116** and 29.9 mg (0.44 mmol) of imidazole in 0.5 mL of DMF at room temperature was added 36.2 mg (0.24 mmol) of *t*-

butyldimethylsilyl chloride. The mixture was stirred at room temperature for 2 d, followed by chromatography over 1.5 g of Florisil (eluted with hexane–ethyl acetate, 10:1) to afford 56.0 mg of silyl ether **118** as a pale yellow oil (73%): IR (neat) 2956, 2931, 2859, 1950, 1670, 1555, 1465, 1382, 1255, 1097, 837, 777 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.45 (t, $J=7.1$ Hz, 2H), 4.27 (m, 1H), 2.91 (dd, $J=15.1, 5.9$ Hz, 1H), 2.58 (dd, $J=15.0$ Hz, 7.2 Hz, 1H), 2.10–2.15 (m, 1H), 2.05–2.09 (m, 3H), 1.84 (s, 6H), 1.28–1.34 (m, 4H), 0.88–0.90 (m, 3H), 0.86 (s, 9H), 0.06 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 210.09 (s), 199.24 (s), 108.23 (s), 100.41 (s), 71.86 (t), 66.55(d), 46.34 (t), 34.45 (t), 30.00 (t), 26.30 (t), 25.85 (q, 3C), 22.20 (t), 19.66 (s), 17.88 (q, 2C), 13.89 (q), -4.72 (q), -5.03 (q).



5-Butyl-6-isopropyl-2-(2-nitroethyl)-2,3-dihydropyran-4-one (119). To a solution of 53.8 mg (0.2 mmol) of nitroaldol **116** in 1 mL of methylene chloride at room temperature was added 3.8 mg (0.020 mmol) of *p*-toluenesulfonic acid monohydrate, followed by 28.7 μL (21.6 mg, 0.3 mmol) of ethyl vinyl ether. The mixture was stirred at room temperature for 18 h. The solvent was removed *in vacuo*. Ether (5 mL) was added. The resulting solution was washed with three 1-mL portions of brine, and the organic layer was dried (MgSO_4), filtered and concentrated *in vacuo* to afford 50.0 mg of **119** as a colorless oil (93%): IR (neat) 2961, 2933, 2872, 1662, 1600, 1556, 1466, 1433, 1394,

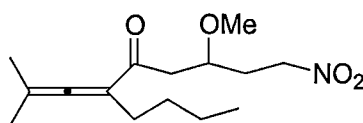
1373, 1352, 1201, 1137, 1101, 1072 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.49–4.65 (m, 2H), 4.23–4.35 (m, 1H), 2.82–2.92 (h, $J=6.8$ Hz, 1H), 2.35–2.53 (m, 3H), 2.01–2.18 (m, 2H), 1.85–1.88 (d, $J=8.2$ Hz, 1H), 1.24–1.28 (m, 4H), 1.09 (d, $J=6.8$ Hz, 3H), 1.07 (d, $J=6.7$ Hz, 3H), 0.62 (t, $J=8.0$ Hz, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 191.45 (s), 175.80 (s), 114.11 (s), 74.66 (d), 71.29 (t), 41.15 (t), 32.27 (t), 31.87 (t), 30.05 (d), 23.30 (t), 22.57 (t), 19.60 (q), 19.42 (q), 13.83 (q); exact mass calcd for $\text{C}_{14}\text{H}_{23}\text{NO}_4$ m/z 269.1627; found m/z 269.1632.



121

4-Butyl-7-methoxymethoxy-2-methyl-9-nitronona-2,3-dien-5-one (121). To a solution of 107.6 mg (0.4 mmol) of nitroadol 116 in 2.5 mL of dimethoxyethane at 0 $^{\circ}\text{C}$ was added 96.6 mg (1.2 mmol) of chloromethyl methyl ether followed by 155 mg (1.2 mmol) of ethyldiisopropylamine. The mixture was then heated at 85 $^{\circ}\text{C}$ for 5 h. Ether (5 mL) and water (5 mL) were added. The aqueous layer was extracted with three 10-mL portions of ether. The combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. The residue was chromatographed over 2 g of silica gel (eluted with hexane–ethyl acetate, 5:1) to afford 110 mg of 121 as a pale yellow oil (88%): IR (neat) 2955, 2931, 2861, 1950, 1669, 1554, 1444, 1382, 1151, 1102, 1035 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.52–4.62 (m, 2H), 4.45–4.51 (m, 2H), 4.07–4.09 (m, 1H), 3.30 (s, 3H), 3.01 (dd, $J=15.2, 6.1$ Hz, 1H), 2.61 (dd, $J=15.3, 7.0$ Hz, 1H), 2.26 (m, 1H), 2.08–2.13 (m, 3H),

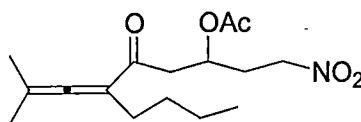
1.81 (s, 6H), 1.22–1.32 (m, 4H), 0.85 (t, $J=6.8$ Hz, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 209.89 (s), 198.97 (s), 107.87 (s), 100.44 (s), 96.41 (t), 72.15 (d), 71.99 (t), 55.67 (q), 44.15 (t), 32.36 (t), 29.99 (t), 26.23 (t), 22.14 (t), 19.55 (q, 2C), 13.80 (q); exact mass calcd for $\text{C}_{16}\text{H}_{27}\text{NO}_5$ m/z 313.1889; found m/z 313.1886.



123

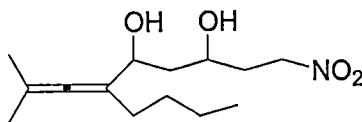
4-Butyl-7-methoxy-2-methyl-9-nitronona-2,3-dien-5-one (123). To a solution of 0.232 g (1.56 mmol) of acetal **122** in 13 mL of methylene chloride at -78 °C was added 0.285 mL (0.493 g, 2.6 mmol) of titanium(IV) chloride dropwise. The solution was stirred at -78 °C for 10 min, and a solution of 0.31 g (1.3 mmol) of enol ether **102** in 2.5 mL of methylene chloride was added. The resulting red solution was stirred at -78 °C for 2 h and quenched with 10 mL of aq K_2CO_3 (13 mmol). The aqueous layer was extracted with three 15-mL portions of ethyl acetate. The combined organic layers were washed with two 10-mL portions of brine, dried (MgSO_4), filtered, and *concentrated in vacuo*. The residue was chromatographed over 5 g of Florisil (eluted with hexanes–ethyl acetate 10:1) to afford 0.165 g (45%) of **123** as a pale yellow oil: IR (neat) 2959, 1948, 1667, 1533, 1448, 1383, 1181, 1156, 1116, 1093, 1042, 917 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.45 (t, $J=7.6$ Hz, 2H), 3.65–3.75 (m, 1H), 3.28 (s, 3H), 2.95 (dd, $J=15.1, 5.5$ Hz, 1H), 2.59 (dd, $J=15.1, 7.2$ Hz, 1H), 2.06–2.16 (m, 4H), 1.81 (s, 3H), 1.27–1.33 (m, 4H), 0.86 (t, $J=7.0$ Hz, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 210.00 (s), 199.42 (s), 108.00 (s),

100.38 (s), 75.06 (d), 72.08 (t), 57.16 (q), 42.84 (t), 32.03 (t), 29.96 (t), 26.25 (t), 22.12 (t), 19.58 (q, 2C), 13.82 (q); exact mass calcd for $C_{15}H_{25}NO_4$ m/z 284.1784; found m/z 284.1783.



125

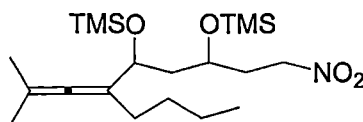
Acetic acid 4-butyl-6-methyl-1-(2-nitroethyl)-3-oxohepta-4,5-dienyl ester (125). To a solution of 53.8 mg (0.20 mmol) of nitroaldol **116** in 150 μ L of methylene chloride at 0 $^{\circ}$ C was added 23.6 μ L (25.5 mg, 0.25 mmol) of acetic anhydride, followed by 30.7 μ L (22.3 mg, 0.22 mmol) of triethylamine and 1 mg of DMAP. The mixture was stirred at 0 $^{\circ}$ C for 3 h, then 3 mL of ether and 2 mL of 1 N HCl were added. The aqueous layer was extracted with three 5-mL portions of ether. The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was chromatographed over 1 g of silica gel (eluted with hexane–ethyl acetate, 10:1) to afford 52 mg of **125** as an oil (84%): IR (neat) 2957, 2929, 2862, 1950, 1743, 1671, 1435, 1375, 1235, 1110, 1028 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 5.25–5.28 (m, 1H), 4.42 (t, $J=7.0$ Hz, 2H), 2.96 (dd, $J=15.6, 6.3$ Hz, 1H), 2.76 (dd, $J=15.6, 7.2$ Hz, 1H), 2.23–2.37 (m, 2H), 2.05–2.10 (m, 2H), 1.99 (s, 3H), 1.82 (s, 6H), 1.26–1.40 (m, 4H), 0.86 (t, $J=6.5$ Hz, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 209.77 (s), 197.90 (s), 170.05 (s), 107.68 (s), 100.77 (s), 71.93 (t), 68.33 (d), 42.91 (t), 31.33 (t), 29.98 (t), 26.23 (t), 22.14 (t), 20.75 (q), 19.57 (q, 2C), 13.82 (q); exact mass calcd for $C_{16}H_{25}NO_5$ m/z 311.1733; found m/z 311.1735.



126

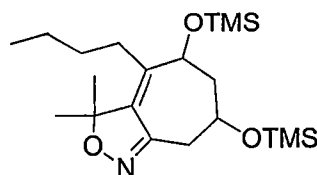
6-Butyl-8-methyl-1-nitronona-6,7-diene-3,5-diol (126). A solution of 107.6 mg (0.4 mmol) of nitroadol **116** and 164 mg (0.44 mmol) of cerium(III) chloride heptahydrate in 10 mL of methanol were stirred at room temperature for 30 min. The reaction mixture was cooled to $-78\text{ }^{\circ}\text{C}$ and 16.6 mg (0.44 mmol) of sodium borohydride was added. The reaction was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h and quenched with 5 mL of sat aq NH_4Cl . The methanol was removed *in vacuo* and the residue was extracted with two 15-mL portions of ether followed by two 15-mL portions of ethyl acetate. The combined organic layers were washed with 10 mL of brine, dried (MgSO_4), and concentrated *in vacuo* to give 109 mg of **126** as a white solid (100%): mp $68\text{--}70\text{ }^{\circ}\text{C}$ (diethyl ether); IR (CCL_4) 3276, 2956, 2925, 2858, 1968, 1554, 1435, 1385 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.52–4.59 (m, 2H), 4.23–4.27 (m, 1H), 4.00–4.10 (m, 1H), 3.40 (s, 1H), 2.80 (s, 1H), 2.07–2.19 (m, 3H), 1.81–1.91 (m, 3H), 1.80 (s, 6 H), 1.34–1.43 (m, 4H), 0.89 (t, $J=6.6\text{ Hz}$, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 195.94 (s), 106.37 (s), 102.01 (s), 72.57 (t), 69.57 (d), 65.82 (d), 40.80 (t), 34.45 (t), 29.89 (t), 28.90 (t), 22.30 (t), 20.84 (q, 2C), 13.94 (q); exact mass calcd for $\text{C}_{14}\text{H}_{25}\text{NO}_4\text{-H}_2\text{O}$ m/z 253.1678; found m/z 253.1690.

Anal. Calcd for $\text{C}_{14}\text{H}_{25}\text{NO}_4$: C, 61.99; H, 9.23; N, 5.17. Found: C, 61.02; H, 8.95; N, 5.00.



127

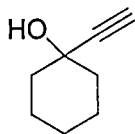
4-Butyl-2-methyl-9-nitro-5,7-bistrimethylsilanyloxynona-2,3-diene (127). To a solution of 36.2 mg (0.134 mmol) of diol **126** in 0.5 mL of methylene chloride at room temperature was added 74.4 μ L (54.0 mg, 0.534 mmol) of triethylamine, followed by 67.8 μ L (58.0 mg, 0.534 mmol) of chlorotrimethylsilane. The resulting slurry was stirred at room temperature for 18 h. The mixture was filtered through a short pad of Florisil to afford 50.1 mg of **127** as a colorless oil (90%): IR (neat) 2957, 2931, 2872, 1555, 1436, 1378, 1251, 1100, 870, 842, 751 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.44 (t, $J=7.1$ Hz, 2H), 4.14 (t, $J=6.8$ Hz, 1H), 3.84 (m, 1H), 1.72–2.06 (m, 6H), 1.69 (s, 3H), 1.66 (s, 3H), 1.26–1.42 (m, 4H), 0.89 (t, $J=4.5$ Hz, 3H), 0.11 (s, 9H), 0.09 (s, 9H); ^{13}C NMR (63 MHz, CDCl_3) δ 198.36 (s), 104.38 (s), 96.74 (s), 72.36 (t), 72.35 (d), 67.43 (d), 44.31 (t), 34.48 (t), 29.90 (t), 25.81 (t), 22.57 (t), 20.63 (q), 20.32 (q), 14.08 (q), 0.27 (q, 6C); exact mass calcd for $\text{C}_{20}\text{H}_{41}\text{NO}_4\text{Si}_2$ m/z 415.2574; found m/z 415.2575.



128

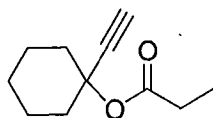
4-Butyl-3,3-dimethyl-5,7-bistrimethylsilanyloxy-5,6,7,8-tetrahydro-3H-cyclohepta[c]isoxazole (128). To a solution of 35.0 mg (0.08 mmol) of ether **127** in 0.5

mL of benzene at room temperature was added 27.5 μ L (30.3 mg, 0.25 mmol) of phenyl isocyanate, followed by 3 μ L of triethylamine. The mixture was heated at 80 $^{\circ}$ C for 22 h. Ether (5 mL) was added and the mixture was filtered. The filtrate was concentrated, and the residue was chromatographed over 2 g of silica gel (eluted with hexane–ethyl acetate, 10:1) to afford 14.2 mg of **128** as a yellow oil (45%): IR (neat) 2958, 2932, 2872, 1459, 1440, 1252, 1090, 882, 842 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.68–4.71 (m, 1H), 4.11–4.14 (m, 1H), 3.10 (dd, $J=14.7$, 5.2 Hz, 1H), 2.58 (dd, $J=14.6$, 8.1 Hz, 1H), 2.12–2.23 (m, 2H), 1.87–1.93 (m, 1H), 1.63–1.66 (m, 1H), 1.53 (s, 3H), 1.48 (s, 3H), 1.26–1.45 (m, 4H), 0.93 (t, $J=6.7$ Hz, 3H), 0.16 (s, 9H), 0.11 (s, 9H); ^{13}C NMR (63 MHz, CDCl_3) δ 154.36 (s), 145.05 (s), 140.07 (s), 86.82 (s), 68.35 (d), 65.69 (d), 48.24 (t), 35.01 (t), 32.36 (t), 30.56 (t), 26.72 (q, 2C), 23.11 (t), 13.90 (q), 0.18 (q, 3C), -0.02 (q, 3C); exact mass calcd for $\text{C}_{20}\text{H}_{39}\text{NO}_3\text{Si}_2$ m/z 397.2469; found m/z 397.2473.

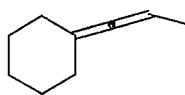
**91**

1-Ethynylcyclohexanol (91).²⁹ To a slurry of 2.71 g (90%, 26.5 mmol) of lithium acetylide ethylenediamine complex in 20 mL of THF at room temperature was added dropwise 2.0 g (20.4 mmol) of cyclohexanone. The reaction was warmed to 35 $^{\circ}$ C, stirred for 20 h and quenched with 20 mL of sat aq NH_4Cl . The aqueous layer was extracted with three 60-mL portions of ether, and the combined organic layers were dried

(MgSO₄) and concentrated *in vacuo*. The residue was chromatographed over 60 g of silica gel (eluted with hexane–ethyl acetate, 20:1 followed by 10:1) to afford 1.70 g of **91** as a colorless oil (69%): ¹H NMR (250 MHz, CDCl₃) δ 2.48 (s, 1H), 2.48 (s, 1H), 1.89–1.94 (m, 2H), 1.63–1.72 (m, 2H), 1.48–1.60 (m, 5H), 1.24–1.27 (m, 1H); ¹³C NMR (63 MHz, CDCl₃) δ 87.71, 72.04, 68.44, 39.67, 25.01, 23.04.

**92**

Propionic acid 1-ethynylcyclohexyl ester (92).³⁰ To 1.51 g (12.18 mmol) of alcohol **91** at room temperature was added 2.14 g (16.44 mmol) of propanoic anhydride, 1.85 g (18.27 mmol) of triethylamine and 0.238 g (1.948 mmol) of DMAP. The mixture was stirred at room temperature for 18 h. Ether (50 mL) and 1 N HCl (10 mL) were added. The aqueous layer was extracted with three 50-mL portions of ether. The combined organic layers were dried (MgSO₄) and concentrated *in vacuo*, and the residue was chromatographed over 50 g of silica gel (eluted with hexane–ethyl acetate, 15:1) to afford 1.98 g of **92** as a colorless oil (90%). ¹H NMR (250 MHz, CDCl₃) δ 2.60 (s, 1H), 2.32 (q, *J*=7.6 Hz, 2H), 2.06–2.16 (m, 2H), 1.82–1.92 (m, 2H), 1.57–1.67 (m, 4H), 1.46–1.57 (m, 1H), 1.31–1.39 (m, 1H), 1.15 (t, *J*=7.6 Hz, 3H); ¹³C NMR (63 MHz, CDCl₃) δ 172.34, 83.80, 74.57, 73.93, 36.73, 28.08, 24.92, 22.20, 8.81.



93

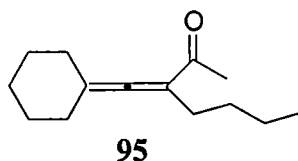
Propenylidenecyclohexane (93).³¹ To a slurry of 0.126 g (0.66 mmol) of cuprous iodide in 2.5 mL of ether at ice-salt temperature was added methyllithium (1.4 M in ether) until a clear colorless solution appeared. A solution of 0.10 g (0.55 mmol) of propanoate **92** in 1 mL of ether was added. The resulting yellow mixture was stirred at 0 °C for 4 h and quenched with 15 mL of sat aq NH₄Cl. The aqueous layer was extracted with four 10-mL portions of ether. The combined organic layers were dried (MgSO₄), concentrated to 1 mL and filtered through a plug of silica gel (eluted with pentane) to afford 38 mg of **93** as a pale yellow oil (57%): ¹H NMR (250 MHz, CDCl₃) δ 4.90 (m, 1H), 2.06–2.08 (m, 4H), 1.53–1.57 (m, 6H), 1.62 (d, *J*=6.8 Hz, 3H); ¹³C NMR (63 MHz, CDCl₃) δ 199.08, 101.86, 83.12, 31.73, 27.49, 26.21, 15.24.



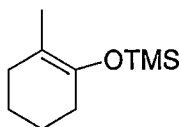
94

Hex-1-enylidenecyclohexane (94).³¹ To a slurry of 3.14 g (16.44 mmol) of cuprous iodide in 90 mL of ether at ice-salt temperature was added 20.6 mL (1.6 M in hexane, 33.0 mmol) of *n*-butyllithium to form a black solution. A solution of 1.98 g (11.0 mmol) of propanoate **92** in 40 mL of ether was added. The resulting blue mixture was stirred at room temperature for 4 h and then quenched with 220 mL of sat aq NH₄Cl. The aqueous layer was extracted with four 75-mL portions of ether. The combined organic layers were

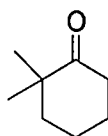
dried (MgSO_4) and concentrated *in vacuo*, and the residue was chromatographed over 15 g of silica gel (eluted with pentane) to afford 1.48 g of **94** as a colorless oil (82%): ^1H NMR (250 MHz, CDCl_3) δ 4.91–4.95 (m, 1H), 2.06–2.11 (m, 4H), 1.91–1.99 (m, 2H), 1.53–1.60 (m, 6H), 1.26–1.39 (m, 4H), 0.85–0.92 (m, 3H).



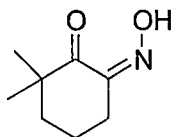
3-Butyl-cyclohexylidenebut-3-en-2-one (95). To a solution of 0.191 g (1.17 mmol) of allene **94** in 2.5 mL of THF at $-78\text{ }^\circ\text{C}$ was added dropwise 0.755 mL of a 1.7 M solution of *t*-BuLi in pentane (1.28 mmol). The resulting solution was stirred for 10 min, and 0.263 mL (0.272 g, 1.517 mmol) of HMPA was added. The orange-red solution was stirred at $-78\text{ }^\circ\text{C}$ for 1 h before 0.163 mL (0.152 g, 1.750 mmol) of *N,N*-dimethylacetamide was added in a single shot. The mixture was stirred for 4 h and quenched with 10 mL of 0.3 M HCl (aq). The aqueous layer was extracted with three 15-mL portions of ether. The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was chromatographed over 8 g of silica gel (eluted with hexanes-ethyl acetate, 20:1) to recover 0.150 g (78%) of allene **94**. Continued elution afforded 14.8 mg of **95** as a colorless oil (6%).³⁴ ^1H NMR (250 MHz, CDCl_3) δ 2.18–2.26 (m, 4H), 2.24 (s, 3H), 2.14 (t, $J=7.2$ Hz, 2H), 1.59–1.66 (m, 6H), 1.30–1.34 (m, 4H), 0.88 (t, $J=7.2$ Hz, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 206.93 (s), 200.00 (s), 107.68 (s), 106.41 (s), 30.69 (t), 30.12 (t), 27.11 (t), 26.84 (q), 26.26 (t), 25.90 (t), 22.18 (t), 13.95 (q).

**142**

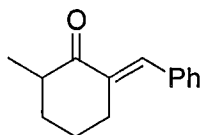
Trimethy-(2-methylcyclohex-1-enyloxy)silane (142).⁴² Diisopropylamine (7.0 mL, 5.05 g, 50.0 mmol) in 160 mL of ether at room temperature was treated with 16.2 mL (3.0 M in ether, 48.6 mmol) of methylmagnesium bromide. The resulting mixture was stirred at room temperature for 3 d. A solution of 2-methylcyclohexanone (4.48 g, 40.0 mmol) in 120 mL of ether was added dropwise and the resulting mixture was stirred for 20 min. To the resulting solution was added 16 mL (13.70 g, 126.0 mmol) of chlorotrimethylsilane, 18 mL (13.07g, 129 mmol) of triethylamine and 3.5 mL (3.60 g, 20.0 mmol) of HMPA in that order. The reaction was stirred at room temperature for 6.5 h, and washed with sat aq sodium bicarbonate. The organic layer was dried (Na₂SO₄), and concentrated *in vacuo*, and the residue was chromatographed over 125 g of silica gel (eluted with hexane–ethyl acetate, 10:1) to afford 6.35 g of **142** as a colorless oil (86%): ¹H NMR (250 MHz, CDCl₃) δ 1.97–2.06 (m, 4H), 1.62–1.71 (m, 2H), 1.60 (s, 3H), 1.57–1.67 (m, 2H), 0.21 (s, 9H); ¹³C NMR (63 MHz, CDCl₃) δ 142.88 (s), 111.71 (s), 30.27 (t), 30.09 (t), 23.77 (t), 23.03 (t), 16.27 (q), 0.64 (q, 3C) (lit⁵⁸).

**136**

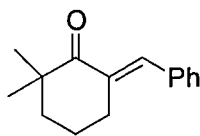
2,2-Dimethylcyclohexanone (136).⁴³ Manganese(II) chloride (9.59 g, 76.22 mmol) and lithium chloride (6.46 g, 152.44 mmol) were baked at 180 °C under vacuum (0.07 mm Hg) for 4.5 h. A solution of 12.75 g (69.29 mmol) of silyl ether **142** in 350 mL of THF was treated at ice-salt temperature with 52.0 mL (1.4 M in ether, 72.76 mmol) of methyllithium. The resulting mixture was warmed to room temperature and stirred for 30 min before a solution of MnCl_4Li_2 (prepared by stirring dried MnCl_2 and LiCl in 120 mL of THF at room temperature for 2 d) was added. The yellow solution was stirred for 30 min and a solution of 4.96 mL (11.31 g, 19.68 mmol) of methyl iodide in 35 mL of THF and 25 mL of DMSO was added. The reaction was stirred overnight and quenched with 75 mL of 1 N HCl. The aqueous layer was extracted with three, 100-mL portions of ether. The combined organic layers were dried (MgSO_4), concentrated *in vacuo*, and the residue was flash chromatographed over 250 g of silica gel (eluted with hexane-ethyl acetate, 50:1) to afford 6.32 g of **136** as a pale yellow oil (70%): ^1H NMR (250 MHz, CDCl_3) δ 2.33 (t, $J=6.4$ Hz, 2H), 1.62–1.67 (m, 6H), 1.05 (s, 6H); ^{13}C NMR (63 MHz, CDCl_3) δ 216.19 (s), 45.12 (s), 41.03 (t), 38.21 (t), 27.49 (t), 25.06 (q, 2C), 21.32 (t) (lit⁵⁹).

**149**

3,3-Dimethylcyclohexane-1,2-dione-1-oxime 149.⁴⁶ To 2.5 mL of absolute ethanol at room temperature was added 0.116 g (5.08 mmol) of sodium metal. After dissolution of sodium was complete, 1.75 mL of ether was added and the solution was cooled to ice-salt temperature. A solution of 0.652 g (5.18 mmol) of dimethylcyclohexanone (**136**) and 0.575 g (5.58 mmol) of *n*-butyl nitrite⁵³ in 6.25 mL of ether was added slowly. The reaction was stirred at room temperature for 5 h and then placed in a freezer (4 °C) overnight. The solvent was evaporated *in vacuo* and the residue was dissolved in 8 mL of water. The aqueous layer was washed with three 3-mL portions of ether, acidified with 1 N HCl to pH=4, and extracted with three 5-mL portions of ether. The organic layer was dried (Na₂SO₄), and evaporation of the solvent afforded 0.350 g of **149** as a yellow solid (43%): mp 115-116 °C (diethyl ether) (lit⁴⁶ 116-116.5 °C); ¹H NMR (250 MHz, CDCl₃) δ 2.62 (m, 2H), 1.61 (m, 4H), 1.10 (s, 1H), 1.01 (s, 6H); ¹³C NMR (63 MHz, CDCl₃) δ 201.48 (s), 153.29 (s), 44.00 (s), 36.75 (t), 24.92 (t), 24.84 (q, 2C), 16.95 (t); exact mass calcd for C₈H₁₃NO₂ *m/z* 155.0946; found *m/z* 155.0952.

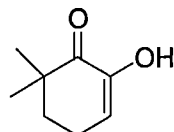
**143**

2-Benzylidene-6-methylcyclohexanone (143).⁴⁵ A solution of 12.0 g (107 mmol) of 2-methylcyclohexanone, 16.7 g (157 mmol) of benzaldehyde and 7.0 g (175 mmol) of sodium hydroxide in a mixture of 65 mL of water and 40 mL of 95% ethanol was heated under reflux for 3 h, cooled to room temperature, and the resulting oil was extracted with three, 50-mL portions of ether. The solvent was removed *in vacuo* and the residue was distilled to afford 15.9 g (74%) of **143** as a pale yellow solid (122-126 °C/0.5 mm Hg): mp 56 °C (lit⁴⁵ 58-60 °C); ¹H NMR (250 MHz, CDCl₃) δ 7.25–7.39 (m, 6H), 2.94–3.03 (m, 1H), 2.65–2.70 (m, 1H), 2.43–2.47 (m, 1H), 2.05–2.09 (m, 1H), 1.86–1.91 (m, 1H), 1.56–1.71 (m, 2H), 1.19 (d, *J*=6.8 Hz, 3H); ¹³C NMR (63 MHz, CDCl₃) δ 204.69 (s), 137.29 (s), 135.79 (s), 134.65 (d), 130.04 (d), 128.22 (d, 2C), 44.28, 31.86, 29.15, 22.67, 16.29.

**144**

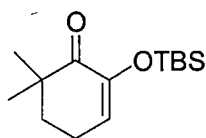
2-benzylidene-6,6-dimethylcyclohexanone 144.⁴⁵ To a solution of 4.85 g (124.0 mmol) of potassium in 125 mL of *tert*-BuOH at room temperature under nitrogen was added

8.25 g (41.25 mmol) of 2-benzal-6-methyl-cyclohexanone **143**. After all the solid dissolved, the mixture was chilled in an ice-salt bath and 14.5 mL of methyl iodide was added. After 10 min, the reaction was heated to reflux for 1.5 h and the solvent was removed *in vacuo*. Water (70 mL) was added, the mixture was filtered, and the residue was washed with 10 mL of water. The damp cake was recrystallized from a solution of 90 mL of methanol and 20 mL of water to afford 8.10 g of **144** as a white solid (92%): mp 80 °C (lit⁴⁵ 80-82 °C); ¹H NMR (250 MHz, CDCl₃) δ 7.29–7.37 (m, 6H), 2.81–2.84 (m, 2H), 1.74–1.78 (m, 4H), 1.17 (s, 6H); ¹³C NMR (63 MHz, CDCl₃) δ 207.85 (s), 136.68 (s), 135.95 (s), 135.29 (d), 130.07 (d), 128.22 (d, 2C), 43.94 (s), 38.36 (t), 29.54 (t), 26.33 (q, 2C), 20.01 (t).

**137**

2-Hydroxy-6,6-dimethylcyclohex-2-one (137).⁴⁴ A solution of 3.48 g of (16.3 mmol) 2-benzal-6,6-dimethyl-cyclohexanone (**144**) in 70 mL of acetone was cooled in an ice bath and a solution of 2.60 g (16.4 mmol) of potassium permanganate and 1.95 g (16.2 mmol) magnesium sulfate in 60 mL of water was slowly added with stirring over 1 h. The reaction was warmed to room temperature and stirred for another 0.5 h. The mixture was filtered, and the filtrate was extracted with three, 20-mL portions of ether. The combined organic layers were washed with 20% NaOH. The basic washes were acidified to pH=4 with 1 N HCl, and the organic acids were extracted with three 30-mL portions of ether.

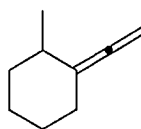
The combined organic layers were washed with 40 mL of saturated aqueous sodium bicarbonate and the solvent was removed *in vacuo* to afford 0.273 g (13%) of **137** as a viscous oil followed by 0.2 g of recovered **144** (6%): ^1H NMR (250 MHz, CDCl_3) δ 6.06 (t, $J=4.5$ Hz, 1H), 2.38 (q, $J=4.7$ Hz, 2H), 2.10 (s, 1H), 1.84 (t, $J=6.0$ Hz, 2H), 1.18 (s, 6H); ^{13}C NMR (63 MHz, CDCl_3) δ 200.82 (s), 145.14 (s), 116.55 (d), 40.73 (s), 36.51 (t), 23.84 (q, 2C), 20.29 (t) (lit⁶⁰); exact mass calcd for $\text{C}_8\text{H}_{12}\text{O}_2$ m/z 140.0837; found m/z 140.0836.

**138**

2-(tert-Butyldimethylsilanyloxy)-6,6-dimethylcyclohex-2-one (138). To a solution of 0.36 mL of (2.42 mmol) diisopropylamine in 4 mL of THF at -75 $^{\circ}\text{C}$ was added dropwise 3.66 mL of a 0.66 M solution of *n*-BuLi (2.416 mmol) over 10 min. The resulting solution was stirred at -75 $^{\circ}\text{C}$ for 0.5 h, warmed to -10 $^{\circ}\text{C}$ over 0.5 h, and then stirred at -10 $^{\circ}\text{C}$ for 0.5 h. A solution of 0.308 g (2.20 mmol) of diketone **137** in 1.5 mL of THF was then added dropwise over 15 min. The reaction mixture was warmed to 5 $^{\circ}\text{C}$ over 20 min, recooled to 0 $^{\circ}\text{C}$, and 0.496 g (3.29 mmol) of TBSCl in 1.5 mL of THF was added. The mixture was stirred at room temperature for 19 h, concentrated *in vacuo* and the residue was flash chromatographed over 3 g of silica gel (eluted with hexane–ethyl acetate, 10:1) to afford 0.42 g of **138** as a pale yellow oil (76%): IR (neat) 2957, 2929,

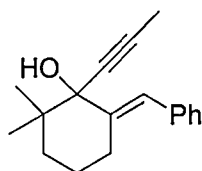
2856, 1684, 1633, 1386, 1362, 1340, 1284, 1213, 1081, 1045, 1005, 835, 783 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 6.07 (t, $J=4.5$ Hz, 1H), 2.36 (q, $J=4.8$ Hz, 2H), 1.79 (t, $J=6.0$ Hz, 2H), 1.12 (s, 6H), 0.93 (s, 9H), 1.19 (s, 6H); NMR (63 MHz, CDCl_3) δ 200.80 (s), 146.42 (s), 125.85 (d), 42.20 (s), 36.43 (t), 25.85 (q, 3C), 24.18 (q, 2C), 21.35 (t), 18.39 (s), -4.88 (q, 2C).

Anal. Calcd for $\text{C}_{14}\text{H}_{26}\text{O}_2\text{Si}$: C, 66.14; H, 10.24. Found C, 66.09; H, 10.28.



154

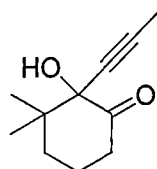
1-Methyl-2-vinylidenecyclohexane (154). To a suspension of 0.50 g (2.0 mmol) of titanocene dichloride in 20 mL of THF at -40 $^{\circ}\text{C}$ was added vinylmagnesium bromide over 2 min. The reaction was warmed to -20 $^{\circ}\text{C}$ over 1.5 h, and then warmed to 0 $^{\circ}\text{C}$ quickly before 0.12 mL (0.112 g, 1.0 mmol) of 2-methylcyclohexanone was added. The reaction was stirred at 0 $^{\circ}\text{C}$ for 10 min, warmed to room temperature, stirred for 50 min. The reaction mixture was concentrated to 1 mL, and 100 mL of pentane was added. The mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was chromatographed over 15 g of silica gel (eluted with pentane) to afford 45 mg of **154** as a yellow oil (37%): ^1H NMR (250 MHz, CDCl_3) δ 4.64 (m, 2H), 2.32 (m, 1H), 1.90–2.10 (m, 2H), 1.75–1.78 (m, 3H), 1.27–1.35 (m, 3H), 1.00 (d, $J=6.6$ Hz, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 106.96, 74.78, 35.84, 33.75, 31.60, 27.15, 26.06, 19.53.



155

6-Benzylidene-2,2-dimethylprop-1-ynylcyclohexanol (155). Cerium(III) chloride heptahydrate (3.90 g, 10.5 mmol) was dried using the literature method,⁵⁴ and 2.14 g (10 mmol) of 2-benzylidene-6,6-dimethylcyclohexanone (**144**) in 180 mL of THF was added at room temperature all at once to the anhydrous cerous chloride. The resulting mixture was stirred at room temperature for 4 h, then cooled to 0 °C and 23 mL (11.5 mmol) of a 0.5 M solution of 1-propynylmagnesium bromide in THF was added. The resulting mixture was gradually warmed to room temperature and stirred overnight. The reaction was quenched with 50 mL of sat aq NH₄Cl. The aqueous layer was extracted with three 25-mL portions of ether. The combined organic layers were washed with 100 mL of brine, dried (MgSO₄), and concentrated *in vacuo*. The residue was flash chromatographed over 50 g of silica gel (eluted with hexane-ethyl acetate, 10:1) to afford 2.40 g of **155** as a pale yellow viscous oil (95%): IR (neat) 3472, 3056, 3023, 2969, 2929, 2864, 2235, 1599, 1457 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 7.18–7.35 (m, 5H), 6.93 (s, 1H), 2.50–2.60 (m, 2H), 2.20 (s, 1H), 1.91 (s, 3H), 1.51–1.68 (m, 4H), 1.12 (s, 3H), 1.08 (s, 3H); ¹³C NMR (63 MHz, CDCl₃) δ 144.99 (s), 137.99 (s), 128.80 (d), 127.86 (d), 126.04 (d), 123.22 (d), 82.83 (s), 80.31 (s), 77.85 (s), 40.58 (s), 35.98 (t), 25.26 (t), 24.59

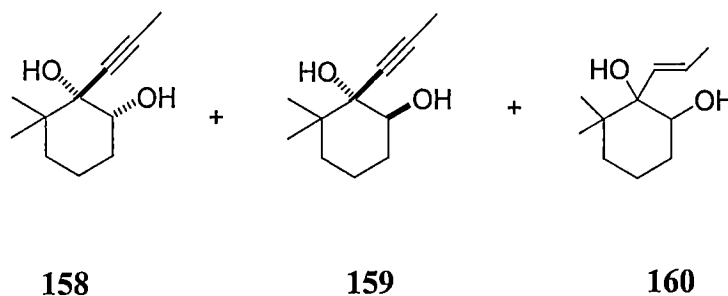
(q), 22.56 (q), 22.24 (t), 3.48 (q); exact mass calcd for $C_{18}H_{22}O$ m/z 254.1671; found m/z 254.1670.



156

2-Hydroxy-3,3-dimethyl-2-prop-1-ynylcyclohexanone (156). A solution of 2.18 g (8.59 mmol) of alcohol **155** in 150 mL of dichloromethane was cooled to -78°C . Ozone was passed through the solution until a light blue color persisted. The solution was then purged with nitrogen until the blue color disappeared. Dimethylsulfide (4 mL) was added. The resulting solution was warmed to room temperature and stirred overnight. The solvent was removed *in vacuo* and the residue was chromatographed over 80 g silica gel (eluted with hexane-ethyl acetate, 40:1) to afford 1.168 g of **156** as a yellow oil which solidified at room temperature (76%): mp $38\text{--}39^{\circ}\text{C}$ (from diethyl ether); IR (neat) 3464, 2964, 2923, 2876, 2227, 1720 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.05 (s, 1H), 2.95–3.09 (m, 1H), 2.36–2.44 (m, 1H), 2.06–2.14 (m, 1H), 1.94 (s, 3H), 1.70–1.92 (m, 2H), 1.40–1.47 (m, 1H), 1.19 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 209.02 (s), 84.01 (s), 79.36 (s), 77.78 (s), 44.00 (s), 35.96 (t), 35.69 (t), 24.85 (q), 21.76 (t), 19.27 (q), 3.61 (q); exact mass calcd for $C_{11}H_{16}O_2$ m/z 180.1150; found m/z 180.1155.

Anal. Calcd for $C_{11}H_{16}O_2$: C, 73.33; H, 8.89. Found: C, 73.30; H, 8.99.



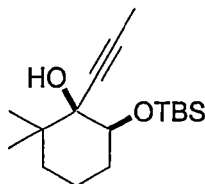
6,6-Dimethyl-1-prop-1-ynylcyclohexane-1,2-diol (158) and (159). Ketone **156** (450 mg, 2.5 mmol) was added at room temperature to a slurry of 474 mg (12.5 mmol) of LiAlH_4 in 7 mL of THF. The mixture was stirred at room temperature for 16 h, quenched with 50 mL of 1 N HCl, and extracted with 100 mL of ether. The combined organic layers were washed with brine, dried (MgSO_4), concentrated *in vacuo* and the residue was chromatographed over 80 g of silica gel (eluted with hexane-ethyl acetate, 5:1) to afford 245.2 mg of **158** as a colorless oil which crystallized on standing: mp 64-65 °C (diethyl ether); IR (CCl_4) 3460, 2945, 2869, 2236, 1460, 1386, 1067, 1044 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 3.80 (t, $J=5.7$, 1H), 2.65 (s, 1H), 2.37 (s, 1H), 1.88 (s, 3H), 1.73 (m, 1H), 1.45–1.57 (m, 4H), 1.12–1.17 (m, 1H), 1.09 (s, 3H), 1.03 (s, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 81.43 (s), 80.12 (s), 76.35 (s), 72.39 (d), 38.48 (s), 32.94 (t), 27.65 (t), 25.78 (q), 23.47 (q), 19.31 (t), 3.50 (q); exact mass calcd for $\text{C}_{11}\text{H}_{18}\text{O}_2$ m/z 182.1307; found m/z 182.1305.

Anal. Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_2$: C, 72.53; H, 9.89. Found: C, 72.62; H, 10.06.

Continued elution using the same solvent produced 132.4 mg of **159** as a white solid: mp 91–92 °C (diethyl ether); ^1H NMR (250 MHz, CDCl_3) δ 3.66 (m, 1H), 2.80 (s, 1H), 1.95 (s, 1H), 1.90–1.99 (m, 1H), 1.90 (s, 3H), 1.48–1.58 (m, 4H), 1.23–1.27 (m, 1H), 1.12 (s, 3H), 0.98 (s, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 84.18 (s), 79.49 (s), 78.24 (s), 73.05 (d), 39.16 (s), 37.02 (t), 32.39 (t), 26.68 (q), 19.93 (q), 19.76 (t), 3.59 (q); exact mass calcd for $\text{C}_{11}\text{H}_{18}\text{O}_2$ m/z 182.1307; found m/z 182.1307.

Anal. Calcd for $\text{C}_{11}\text{H}_{18}\text{O}_2$: C, 72.53; H, 9.89. Found: C, 72.74; H, 10.08.

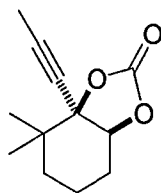
Continued elution afforded 22.3 mg of **160** as a colorless oil (5%): IR (neat) 3457, 3029, 2934, 2865, 1452, 1383, 1364, 1284, 1172, 1159, 1059, 1044, 985, 977, 936, 873 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 5.85–5.90 (m, 1H), 5.50 (d, $J=15.4$ Hz, 1H), 3.77 (m, 1H), 2.03 (s, 1H), 1.86 (d, $J=5.1$ Hz, 3H), 1.44–1.62 (m, 4H), 1.25 (s, 1H), 1.03–1.17 (m, 2H), 0.92 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 132.38 (d), 127.67 (d), 76.48 (s), 70.90 (d), 37.94 (s), 35.18 (t), 28.44 (t), 24.96 (q), 23.30 (q), 19.60 (t), 17.93 (q); exact mass calcd for $\text{C}_{11}\text{H}_{20}\text{O}_2$ m/z 184.1463; found m/z 184.1470.



161

6-(*tert*-Butyldimethylsilyloxy)-2,2-dimethyl-1-prop-1-ynylcyclohexanol (161). To a solution of 18.8 mg (0.103 mmol) of diol **158** in 0.25 mL of DMF at room temperature was added 15.4 mg of (0.223 mmol) imidazole and 18.7 mg (0.124 mmol) TBSCl. The

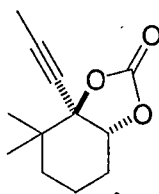
resulting solution was stirred at room temperature for 24 h, and directly chromatographed over 5 g of silica gel (eluted with hexane-ethyl acetate, 5:1) to afford 29.6 mg of **161** as a colorless oil (97%): IR (neat) 3591, 2931, 2858, 2243, 1744, 1463, 1385, 1361, 1252, 1166, 1107, 1061, 1043, 1021, 1006, 982, 835, 777 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 3.74 (dd, $J=10.0$, 5.1 Hz, 1H), 2.54 (s, 1H), 1.85 (s, 3H), 1.46–1.72 (m, 4H), 1.19–1.25 (m, 2H), 1.12 (s, 3H), 0.97 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (63 MHz, CDCl_3) δ 81.99 (s), 79.39 (s), 78.60 (s), 74.45 (d), 38.71 (s), 36.90 (t), 32.38 (t), 26.63 (q), 25.75 (q, 3C), 20.52 (q), 19.66 (t), 18.03 (s), 3.51 (q), -3.89 (q), -4.66 (q); exact mass calcd for $\text{C}_{12}\text{H}_{16}\text{O}_3\text{-C}_4\text{H}_9$ m/z 239.1467; found m/z 239.1474.

**162**

4,4-Dimethyl-3a-prop-1-ynylhexahydrobenzo[1,3]dioxol-2-one (162). A solution of 0.558 g (3.065 mmol) of diol **158** and 1.988 g (12.26 mmol) of carbonyldiimidazole in 45 mL was heated under refluxing benzene for 18 h. The mixture was cooled to room temperature and 30 mL of water was added. The aqueous layer was extracted with four, 15-mL portions of ether and four, 15-mL portions of ethyl acetate. The combined organic layers were washed with 40 mL of water, dried (MgSO_4) and concentrated *in vacuo*. The residue was chromatographed over 8 g of silica gel (eluted with hexanes-ethyl acetate, 5:1) to afford carbonate 632.5 mg of **162** as a white solid (99%): mp 91–92 $^{\circ}\text{C}$ (Et_2O); IR

(CCl₄) 2949, 2874, 2247, 1816, 1390, 1362, 1177, 1027 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 4.59 (t, *J*=6.6 Hz, 1H), 2.11-2.19 (m, 1H), 1.87 (s, 3H), 1.36-1.56 (m, 5H), 1.14 (s, 3H), 1.07 (s, 3H); ¹³C NMR (63 MHz, CDCl₃) δ 154.46 (s), 84.86 (s, 2C), 80.71 (d), 75.35 (s), 36.39 (s), 33.18 (t), 27.51 (t), 25.50 (q), 25.26 (q), 16.49 (t), 3.47 (q); exact mass calcd for C₁₂H₁₆O₃ *m/z* 208.1099; found *m/z* 208.1095.

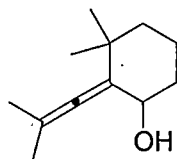
Anal. Calcd for C₁₂H₁₆O₃: C, 69.23; H, 7.69. Found: C, 69.35; H, 7.80. Single crystal structure showed a *cis* relationship.

**163**

4,4-Dimethyl-3a-prop-1-ynylhexahydrobenzo[1,3]dioxol-2-one (163). A solution of 36.4 mg (0.20 mmol) diol **159** and 130 mg (0.80 mmol) of carbonyldiimidazole were heated in 2.5 mL of refluxing benzene for 18 h. The mixture was cooled to room temperature and 3 mL of water was added. The aqueous layer was extracted with four, 4-mL portions of ether and four, 4-mL portions of ethyl acetate. The combined organic layers were washed with 4 mL of water, dried (MgSO₄) and concentrated *in vacuo*. The residue was chromatographed over 4 g silica gel (eluted with hexanes-ethyl acetate, 5:1) to afford 40.0 mg of **163** as a colorless oil which crystallized on standing (96%): mp 74-75 °C (diethyl ether); ¹H NMR (250 MHz, CDCl₃) δ 4.40 (dd, *J*=9.0, 7.05 Hz, 1H), 2.09-2.13 (m, 2H), 2.08 (s, 3H), 1.41-1.91 (m, 4H), 1.19 (s, 3H), 1.08 (s, 3H); ¹³C NMR

(63 MHz, CDCl_3) δ 154.83 (s), 89.41 (s), 88.34 (s), 80.29 (d), 72.97 (s), 38.14 (s), 36.45 (t), 26.59 (q), 25.98 (t), 19.71 (t), 19.59 (q), 3.59 (q); exact mass calcd for $\text{C}_{12}\text{H}_{16}\text{O}_3$ m/z 208.1099; found m/z 208.1098.

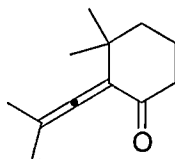
Anal. Calcd for $\text{C}_{12}\text{H}_{16}\text{O}_3$: C, 69.23; H, 7.69. Found: C, 69.15; H, 7.73.



164

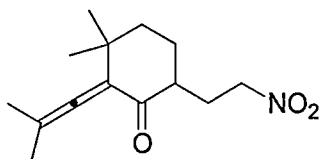
3,3-Dimethyl-2-(2-methylpropenyldene)-cyclohexanol (164). To a suspension of 236.5 mg (1.24 mmol) of cuprous iodide in 5 mL of ether at ice-salt temperature was added methyllithium (1.4 M in ether) such that a yellow precipitate formed and redissolved to give a colorless solution. A solution of 215.0 mg (1.04 mmol) of carbonate **162** in 9 mL of ether was then added, and the resulting mixture was stirred at 0 °C for 5 h followed by quenching with 15 mL of sat aq NH_4Cl . The aqueous layer was extracted with four, 20-mL portions of ether and the combined organic layers were dried (MgSO_4) and concentrated *in vacuo*. The residue was chromatographed over 10 g of silica gel (eluted with hexane–ethyl acetate, 10:1) to afford 151.4 mg of **164** as a colorless oil (81%): IR (neat) 3456, 2957, 2930, 2864, 1813, 1448, 1391, 1361, 1081, 1021 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.10 (dd, $J=10.8, 4.5$ Hz, 1H), 2.15 (m, 1H), 1.92 (s, 1H), 1.75 (s, 3H), 1.74 (s, 3H), 1.43–1.68 (m, 3H), 1.09–1.31 (m, 2H), 1.05 (s, 3H), 1.01 (s, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 192.15 (s), 115.58 (s), 103.18 (s), 66.10

(d), 40.31 (t), 36.76 (t), 35.64 (s), 30.51 (q), 26.55 (q), 21.56 (q), 21.14 (q), 20.17 (t); exact mass calcd for $C_{12}H_{20}O$ m/z 180.1514; found m/z 180.1515.

**141**

3,3-Dimethyl-2-(2-methylpropenylidene)-cyclohexanone (141). To a solution of 132.4 mg (1.04 mmol) of oxalyl chloride in 2.5 mL of methylene chloride at $-78\text{ }^{\circ}\text{C}$ was added 171.8 mg (2.20 mmol) of dimethyl sulfoxide. The resulting mixture was stirred for 30 min and a solution of 149.0 mg (0.83 mmol) of alcohol **164** in 1.5 mL of methylene chloride was added. The resulting slurry was stirred at $-78\text{ }^{\circ}\text{C}$ for an additional 1.5 h and 0.6 mL of triethylamine was then added. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 30 min, warmed to room temperature, stirred for 1.5 h and then 5 mL of water was added. The aqueous layer was extracted with four, 10-mL portions of methylene chloride. The combined organic layers were washed with 30 mL of brine, dried (MgSO_4), and concentrated *in vacuo*. The residue was flash chromatographed over 8 g of silica gel (eluted with pentane-methylene chloride, 1:1) to afford 131.4 mg of **141** as a pale yellow oil (89%): IR (neat) 2958, 2868, 1949, 1679, 1451, 1383, 1180 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 2.41 (t, $J=6.6$ Hz, 2H), 1.85–1.89 (m, 2H), 1.76 (s, 6H), 1.62–1.67 (m, 2H), 1.07 (s, 6H); ^{13}C NMR (63 MHz, CDCl_3) δ 204.86 (s), 201.95 (s), 113.85 (s), 100.89 (s),

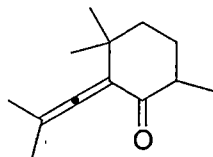
40.33 (t), 37.99 (t), 35.94 (s), 30.18 (q, 2C), 19.58 (q, 2C), 19.30 (t); exact mass calcd for $C_{12}H_{18}O$ m/z 178.1358; found m/z 178.1355.



135a

3,3-Dimethyl-2-(2-methylpropenylidene)-6-(2-nitroethyl)-cyclohexanone (135a). A solution of 219 μ L (1.55 mmol) of diisopropylamine in 4 mL of THF at -78°C was treated with 0.896 mL of *n*-BuLi (1.6 M in hexane, 1.43 mmol). The resulting solution was stirred at -78°C for 30 min, warmed to -20°C , stirred for 40 min, and recooled to -78°C . A solution of 222.0 mg (1.25 mmol) of ketoallene **141** in 1.2 mL of THF was added dropwise over 2 min and the solution was stirred for 1 h. To the resulting solution was added 100.0 mg (1.38 mmol) of nitroethene in 1.2 mL of THF. The reaction was stirred at -78°C for 4 h, quenched with 4 mL of sat aq NH_4Cl , and the aqueous layer was extracted with three, 10-mL portions of ether. The combined organic layers were dried (MgSO_4), concentrated *in vacuo*, and the residue was flash chromatographed over 1 g of silica gel (eluted with hexane-ethyl acetate, 25:1) to afford 224.7 mg of **135a** as a pale yellow oil (72%): IR (neat) 2959, 2932, 2866, 1944, 1679, 1552, 1445, 1385 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.54–4.61 (m, 2H), 2.35–2.43 (m, 2H), 1.94–2.09 (m, 2H), 1.80 (s, 3H), 1.77 (s, 3H), 1.66–1.74 (m, 3H), 1.11 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (63

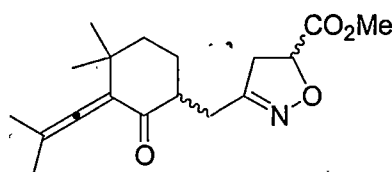
MHz, CDCl_3) δ 203.85 (s), 202.37 (s), 113.51 (s), 101.02 (s), 73.86 (t), 46.55 (d), 37.47 (s), 36.51 (t), 30.11 (q), 29.54 (q), 28.54 (t), 26.27 (t), 19.79 (q), 19.36 (q); exact mass calcd for $\text{C}_{14}\text{H}_{21}\text{NO}_3$ m/z 251.1521; found m/z 251.1517.

**169**

3,3,6-Trimethyl-2-(2-methylpropenylidene)cyclohexanone (169). A solution of 189 μL (136 mg, 1.34 mmol) of diisopropylamine in 2.5 mL of THF at -78°C was treated with 0.859 mL of *n*-BuLi (0.88 M in hexane, 0.76 mmol). The resulting solution was stirred at -78°C for 30 min, warmed to -20°C , stirred for 40 min, and re-cooled to -78°C . A solution of 200.0 mg (1.12 mmol) of ketoallene **141** in 1 mL of THF was then added, and the solution was stirred for 1 h. Methyl iodide (139 μL , 318 mg, 2.24 mmol) was added, and the reaction was stirred at -78°C for 3 h, warmed to room temperature, stirred overnight, and quenched with 5 mL of sat aq NH_4Cl . The aqueous layer was extracted with three 5-mL portions of ether. The combined organic layers were dried (MgSO_4), concentrated *in vacuo*, and the residue was chromatographed over 2 g of silica gel (eluted with hexane-ethyl acetate, 20:1, followed by 10:1) to afford 60 mg of **169** as a colorless oil (40%): IR (neat) 2960, 2928, 2867, 1953, 1684, 1386, 1315, 1263, 1213, 1186, 1153, 1101, 1037, 969, 919 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 2.30–2.37 (m, 1H), 1.92–1.97 (m, 1H), 1.78 (s, 3H), 1.76 (s, 3H), 1.59–1.75 (m, 3H), 1.13 (d, $J=6.7$ Hz,

3H), 1.09 (s, 3H), 1.06 (s, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 204.39 (s), 203.60 (s), 113.68 (s), 100.42 (s), 44.55 (d), 37.49 (t), 36.81 (s), 30.33 (q), 29.66 (q), 28.3 (t), 19.94 (q), 19.60 (q), 15.98 (q) exact mass calcd for $\text{C}_{13}\text{H}_{20}\text{O}$ m/z 192.1514; found m/z 192.1508.

Continued elution using the same solvent afforded 60 mg of **141** (30%).

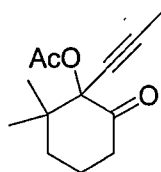


168

3-[4,4-Dimethyl-3-(2-methylpropenylidene)-2-oxocyclohexylmethyl]-4,5-

dihydroisoxazole-5-carboxylic acid methyl ester (168). To a solution of 24.8 mg (0.10 mmol) of nitroallene **135a** and methyl 19.5 mg (0.22 mmol) of acrylate in 0.3 mL of benzene at room temperature was added 16 μL (18 mg, 0.15 mmol) of phenylisocyanate and 3 μL (2.0 mg, 0.02 mmol) of triethylamine. The reaction was stirred at room temperature for 18 h before 5 mL of ether was added. The mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was chromatographed over 2 g of silica gel (eluted with hexane-ethyl acetate, 10:1, followed by 5:1) to afford 12.0 mg of **168** as a mixture of diastereomers (38%): IR (neat) 2957, 2930, 2866, 1948, 1744, 1672, 1598, 1533, 1499, 1440, 1386, 1285, 1215, 1181, 1148, 1036, 922, 873 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.98 (t, $J=7.9$ Hz, 1H), 3.78 (s, 3H), 3.21–3.31 (m, 2H), 2.79–2.85 (m, 1H), 2.62–2.64 (m, 1H), 2.44–2.52 (m, 2H), 1.99–1.03 (m, 1H), 1.79 (s, 3H), 1.76 (s,

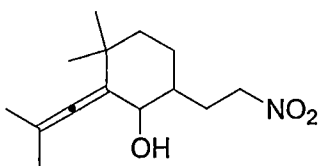
3H), 1.58–1.76 (m, 2H), 1.11 (s, 3H), 1.07 (s, 3H); ^{13}C NMR (63 MHz, CDCl_3) δ 204.37 (204.18) (s), 201.82 (201.63) (s), 170.91 (s), 157.21 (157.15) (s), 113.57 (113.51) (s), 100.98 (s), 76.91 (d), 52.59 (q), 47.70 (47.22) (d), 41.97 (41.61) (t), 37.58 (37.39) (t), 36.66 (36.55) (s), 30.32 (30.23) (q), 29.69 (29.60) (q), 28.05 (27.90) (t), 25.74 (25.54) (t), 19.86 (q), 19.42 (q); exact mass calcd for $\text{C}_{18}\text{H}_{25}\text{NO}_4$ m/z 319.1784; found m/z 319.1786.

**157**

Acetic acid 2,2-dimethyl-6-oxo-1-prop-1-ynylcyclohexyl ester (157). To a solution of 36.0 mg (0.2 mmol) of alcohol **156** in 200 μL of methylene chloride at room temperature was added 23.6 μL (25.5 mg, 0.25 mmol) of acetic anhydride, 34.8 μL (25.3 mg, 0.25 mmol) of triethylamine and a catalytic amount of DMAP in that order. The mixture was stirred at room temperature for 5 d, and 1 mL of sat aq sodium bicarbonate was added. The mixture was extracted with three 5-mL portions of ether. The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo*. The residue was chromatographed over 2 g of silica gel (eluted with hexane–ethyl acetate, 20:1, followed by 10:1) to afford 30.5 mg of **157** as a colorless oil (69%): IR (neat) 2975, 2945, 2875, 2245, 1750, 1434, 1387, 1367, 1308, 1270, 1232, 1195, 1084, 1059, 1036 1019, 981 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 2.74–2.78 (m, 1H), 2.30–2.37 (m, 1H), 2.10 (s, 3H), 1.90 (s, 3H), 1.74–1.87 (m, 3H), 1.59–1.64 (m, 1H), 1.07 (s, 3H), 1.00 (s, 3H); ^{13}C NMR

(63 MHz, CDCl_3) δ 202.42 (s), 168.73 (s), 86.06 (s), 85.03 (s), 73.84 (s), 44.83 (s), 37.08 (t), 34.81 (t), 23.55 (q), 22.94 (t), 22.16 (q), 20.98 (q), 3.79 (q); exact mass calcd for $\text{C}_{13}\text{H}_{18}\text{O}_3$ m/z 222.1256; found m/z 222.1262.

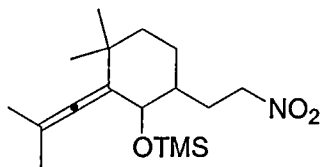
Anal. Calcd for $\text{C}_{13}\text{H}_{18}\text{O}_3$: C, 70.27; H, 8.11. Found: C, 70.27; H, 8.03.



171

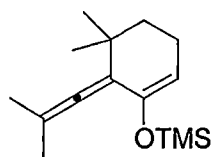
3,3-Dimethyl-2-(2-methyl-propenylidene)-6-(2-nitro-ethyl)-cyclohexanol (171). To a solution of 48.0 mg (0.20 mmol) of nitroketone **135a** in 3 mL of methanol at room temperature was added 81.5 mg (0.22 mmol) of cerium(III) chloride heptahydrate and the solution was stirred for 10 min. The mixture was then cooled to $-78\text{ }^{\circ}\text{C}$ and 7.4 mg (0.2 mmol) sodium borohydride was added. The mixture was stirred at $-78\text{ }^{\circ}\text{C}$ for 1 h, then quenched with 2 mL of sat aq NH_4Cl . The methanol was removed *in vacuo* and the residue was extracted with three 5-mL portions of ether. The combined organic layers were dried (MgSO_4), filtered and concentrated *in vacuo* to afford 35.0 mg of **171** as a colorless oil (70%): IR (neat) 3530, 2958, 2930, 2867, 1963, 1552, 1451, 1383, 1365, 1257, 1190, 1112, 1030 cm^{-1} ; ^1H NMR (250 MHz, CDCl_3) δ 4.42–4.56 (m, 2H), 4.33 (d, $J=2\text{ Hz}$, 1H), 2.19–2.22 (m, 1H); 2.02–2.04 (m, 1H), 1.75–1.91 (m, 1H), 1.70 (s, 3H), 1.67 (s, 3H), 1.44–1.59 (m, 2H), 1.21–1.34 (m, 2H), 1.11 (s, 1H), 1.07 (s, 6H); ^{13}C NMR (63 MHz, CDCl_3) 193.47 (s), 111.44 (s), 102.85 (s), 75.05 (t), 68.81 (d), 38.18 (d), 35.57

(s), 35.02 (t), 30.03 (q), 27.48 (q), 25.41 (t), 24.38 (q), 20.39 (q), 20.92 (q); exact mass calcd for $C_{13}H_{18}O_3$ m/z 253.1678; found m/z 253.1684.



172

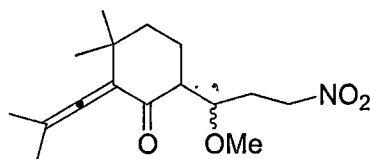
[3,3-Dimethyl-2-(2-methylpropenylidene)-6-(2-nitroethyl)cyclohexyloxy]trimethylsilane (172). To a solution of 34.0 mg (0.134 mmol) of alcohol 171 in 1 mL of methylene chloride at room temperature was added 37.5 μ L (27.2 mg, 0.268 mmol) of triethylamine followed by 34.0 μ L (29.1 mg, 0.268 mmol) of chlorotrimethylsilane. The slurry was stirred at room temperature for 24 h, and chromatographed directly over 2 g of Florisil (eluted with hexane–ethyl acetate, 10:1) to afford 23.0 mg of 172 as a colorless oil (53%): IR (neat) 2957, 2930, 2865, 1965, 1553, 1444, 1382, 1363, 1251, 1189, 1124, 1049, 1027, 988, 915, 880, 841 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 4.45 (t, $J=7.4$ Hz, 2H), 4.22 (d, $J=2.7$ Hz, 1H), 2.11–2.30 (m, 1H); 1.87–1.95 (m, 1H), 1.69 (s, 3H), 1.66 (s, 3H), 1.60–1.62 (m, 1H), 1.46–1.53 (m, 2H), 1.34–1.43 (m, 2H), 1.11 (s, 3H), 0.95 (s, 3H), 0.08 (s, 9H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 197.51 (s), 109.59 (s), 96.01 (s), 74.35 (t), 72.87 (d), 40.57 (d), 38.93 (t), 34.24 (s), 29.93 (q), 29.34 (t), 29.12 (q), 23.85 (t), 21.08 (q), 20.35 (q), 0.09 (q, 3C); exact mass calcd for $C_{13}H_{18}O_3$ m/z 325.2073; found m/z 325.2065.



173

[5,5-Dimethyl-6-(2-methylpropenylidene)cyclohex-1-enyloxy]trimethylsilane (173).

A solution of 0.165 mL (0.119 g, 1.18 mmol) of diisopropylamine in 3 mL of THF at -78 °C was treated with 0.71 mL of a 1.6 M solution of *n*-BuLi in hexane (1.13 mmol). The resulting solution was stirred at -78 °C for 10 min, warmed to 0 °C, stirred 30 min, and recooled to -78 °C. A solution of 0.175 g (0.98 mmol) of ketoallene **141** in 2 mL of THF was added. The mixture was stirred at -78 °C for 1 h and 0.150 mL (0.128 g, 1.18 mmol) of chlorotrimethylsilane was added. The reaction was allowed to warm up to room temperature over 3 h, and then stirred for an additional 18 h. The solvent was removed *in vacuo*. The residue was dissolved in hexane and filtered through 1.5 g of Florisil to afford 0.232 g of **173** as a colorless oil (95%): IR (neat) 2959, 2871, 1951, 1699, 1452, 1386, 1364, 1251, 844 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 5.00 (t, *J*=4.2 Hz, 1H), 2.14 (pt, *J*=6.1 Hz, 2H), 1.73 (s, 6H), 1.44 (t, *J*=6.2 Hz, 2H), 1.03 (s, 6H), 0.14 (s, 9H); ¹³C NMR (63 MHz, CDCl₃) δ 198.59 (s), 145.19 (s), 109.96 (s), 107.26 (d), 99.37 (s), 36.23 (t), 34.15 (s), 28.23 (q, 2C), 21.40 (t), 20.69 (q, 2C), -0.03 (q, 3C).

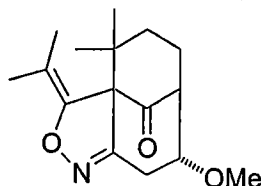


177

6-(1-Methoxy-3-nitropropyl)-3,3-dimethyl-2-(2-methyl-propenylidene)-

cyclohexanone (177). To a solution of 87.1 mg (0.59 mmol) of nitropropanal dimethylacetal⁵⁵ in 5 mL of methylene chloride at -78 °C was added 63.7 μ L (0.110 g, 0.59 mmol) of titanium(IV) chloride. The resulting yellow solution was stirred for 10 min before a solution of 0.121 g (0.48 mmol) of enol ether **173** in 1 mL of methylene chloride was added. The mixture was stirred at -78 °C for 2 h, then quenched with 10 mL of aq K_2CO_3 . The aqueous layer was extracted with three 15-mL portions of ethyl acetate. The combined organic layers were washed with 20 mL of brine, dried ($MgSO_4$), filtered, and concentrated *in vacuo*. The residue was chromatographed over 2 g of silica gel (eluted with hexane–ethyl acetate, 10:1) to afford 62.5 mg of **177** as a mixture of diastereomers (44%): IR (neat) 2959, 1948, 1667, 1553, 1448, 1383, 1156, 1093 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 4.47 (t, $J=6.8$ Hz, 2H), 4.01–4.04 (m, 1H), 3.83–3.90 (m, 1H), 3.28 (s, 3H), 2.71–2.75 (m, 1H), 2.08–2.24 (m, 2H), 1.90–1.92 (m, 1H), 1.78 (s, 3H), 1.76 (s, 3H), 1.48–1.53 (m, 1H), 1.25–1.37 (m, 2H), 1.11 (s, 3H), 1.08 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 205.31 (204.98) (s), 201.90 (201.27) (s), 113.98 (s), 101.29 (101.05) (s), 77.51 (76.49) (d), 73.27 (72.75) (t), 59.28 (57.08) (s), 52.89 (49.98) (d), 37.27 (36.82) (t), 36.00 (35.79) (s), 31.03 (28.94) (t), 30.57 (q), 29.70 (q), 19.63 (19.35)

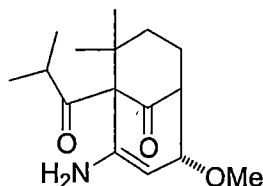
(q, 2C), 18.78 (18.62) (t); exact mass calcd for $C_{16}H_{25}NO_4$ m/z 295.1784; found m/z 295.1776.



178

2-Isopropylidene-7-methoxy-11,11-dimethyl-3-oxa-4-aza-tricyclo[6.3.1.0.^{1.5}]dodec-4-en-12-one (178). To a solution of 29.0 mg (0.098 mmol) of nitroallene 177 and 32.2 mg (0.147 mmol) di-*tert*-butyldicarbonate in 2 mL of benzene and 1 mL of acetonitrile at room temperature was added a catalytic amount of DMAP. The mixture was stirred for 10 min, heated to 80 °C, and stirred for 18 h. Sat aq NH_4Cl (2 mL) was added and the aqueous layer was extracted with three 10-mL portions of ethyl acetate. The combined organic layers were dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was chromatographed over 2 g of silica gel (eluted with hexane–ethyl acetate, 10:1) to afford 11 mg of 178 as a white solid (40%): mp 148–150 °C (MeOH); ^1H NMR (250 MHz, $CDCl_3$) δ 3.59 (m, 1H), 3.36 (s, 3H), 3.22 (dd, $J=16.5, 7.4$ Hz, 1H), 2.95–2.98 (m, 1H), 2.79 (dd, $J=16.5, 10.5$ Hz, 1H), 2.30–2.34 (m, 1H), 1.99–2.03 (m, 2H), 1.82 (s, 3H), 1.80 (m, 3H), 1.46–1.50 (m, 1H), 1.07 (s, 3H), 0.96 (m, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 203.57 (s), 156.88 (s), 144.54 (s), 110.90 (s), 77.87 (d), 73.82 (s), 56.71 (q), 50.25 (d), 48.39 (t), 36.49 (t), 31.75 (q), 26.44 (q), 25.89 (t), 22.29 (q), 22.13 (q), 19.13 (q); exact mass calcd for $C_{16}H_{23}NO_3$ m/z 277.1678; found m/z 277.1673.

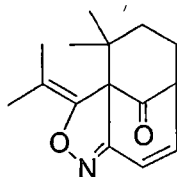
Anal. Calcd for $C_{16}H_{23}NO_3$: C, 69.31; H, 8.30; N, 5.05. Found: C, 69.40; H, 8.38; N, 4.98.



179

2-Amino-1-isobutyryl-4-methoxy-8,8-dimethylbicyclo[3.3.1]non-2-en-9-one (179). A solution of 25.2 mg (0.09 mmol) of cycloadduct **178** and 5 mg of Raney nickel in 3 mL of methanol was stirred under hydrogen for 24 h. The mixture was filtered and concentrated *in vacuo* to afford 25 mg of **179** as a white solid (100%): mp 135-137 °C (MeOH); IR (CCl_4) 3249, 2970, 2932, 2872, 1799, 1722, 1387, 1365, 1099 cm^{-1} ; ^1H NMR (250 MHz, $CDCl_3$) δ 5.17 (d, $J=2.2$ Hz, 1H), 4.15 (dd, $J=6.5, 2.4$ Hz, 1H), 3.34 (s, 3H), 31.2 (s, 2H), 2.93 (t, $J=5.6$ Hz, 1H), 2.59 (h, $J=6.5$ Hz, 1H), 1.92-2.08 (m, 2H), 1.73-1.81 (m, 1H), 1.60 (m, 1H), 1.33 (s, 3H), 1.17 (d, $J=6.5$ Hz, 3H), 1.13 (d, $J=6.5$ Hz, 1H), 1.09 (s, 3H); ^{13}C NMR (63 MHz, $CDCl_3$) δ 214.78 (s), 209.87 (s), 139.04 (d), 101.84 (s), 76.48 (d), 72.84 (s), 56.01 (q), 48.95 (d), 43.79 (s), 39.99 (d), 37.11 (t), 27.62 (q), 23.41 (t), 22.19 (q, 2C), 20.84 (q); exact mass calcd for $C_{16}H_{25}NO_3$ m/z 279.1834; found m/z 279.1827.

Anal. Calcd for $C_{16}H_{25}NO_3$ C, 68.82; H, 8.96; N, 5.02. Found: C, 68.95; H, 9.08; N, 5.03.

**180**

2-Isopropylidene-11,11-dimethyl-3-oxa-4-aza-tricyclo[6.3.1.0^{1,5}]dodeca-4,6-dien-12-one (180). A solution of 50.4 μ L (36.4 mg, 0.36 mmol) of diisopropylamine in 1 mL of THF at -78 °C was treated with 0.306 mL of *n*-butyllithium (1.6 M in hexane, 0.346 mmol). The resulting solution was stirred at -78 °C for 30 min, warmed to -20 °C, stirred for 40 min, and recooled to -78 °C. A solution of 41.4 mg (0.15 mmol) of cycloadduct **178** in 1 mL of THF was added dropwise. The resulting solution was stirred at -78°C for 1 h, warmed gradually to room temperature, and stirred for 1 h before 5 mL of sat aq NH₄Cl was added. The aqueous layer was extracted with three 5-mL portions of ether. The combined organic layers were dried, filtered and concentrated *in vacuo*. The residue was chromatographed over 2 g of silica gel (eluted with hexane–ethyl acetate 20:1) to afford 11.5 mg of **180** as a pale yellow oil (31%): IR (neat) 2934, 2871, 1737, 1617, 1455, 1390, 1370, 1309, 1237, 1118, 1082, 921, 877, 778, 732 cm⁻¹; ¹H NMR (250 MHz, CDCl₃) δ 6.74 (d, *J*=9.5 Hz, 1H), 6.15 (dd, *J*=9.5, 6.0 Hz, 1H), 3.20–3.25 (m, 1H), 2.10–2.19 (m, 1H), 1.94–2.01 (m, 1H), 1.87 (s, 3H), 1.85 (s, 3H), 1.75–1.80 (m, 1H), 1.31–1.38 (m, 1H), 0.95 (s, 3H), 0.88 (s, 3H); ¹³C NMR (63 MHz, CDCl₃) δ 201.85 (s), 159.94 (s), 135.88 (d), 121.57 (d), 121.52 (s), 111.72 (s), 71.72 (s), 50.07 (d), 47.84 (s), 32.23 (t),

25.88 (q), 25.84 (t), 24.58 (q), 21.88 (q), 18.97 (q); exact mass calcd for $C_{15}H_{19}NO_2$ m/z 245.1416; found m/z 245.1426.

Continued elution provided 10 mg of **178** (24%).

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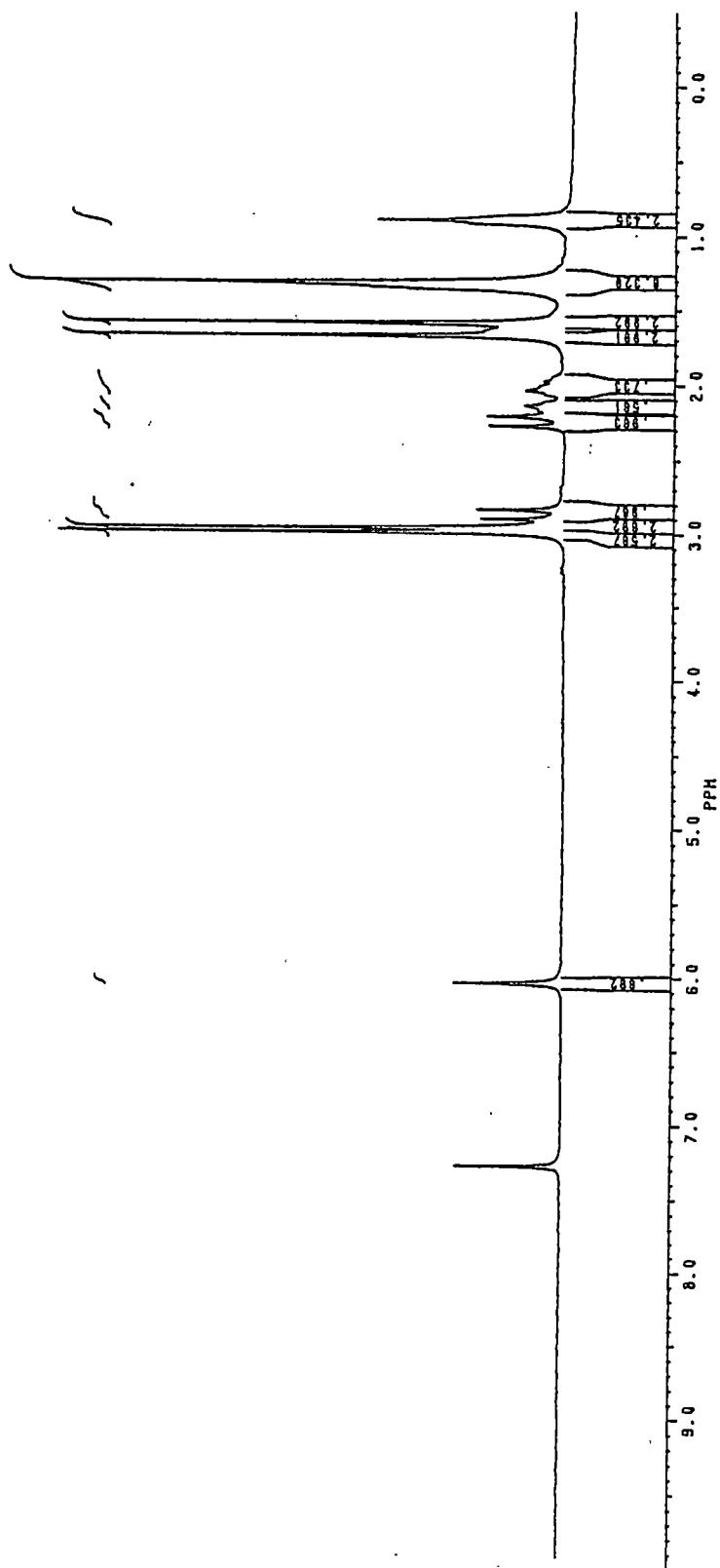
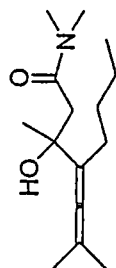
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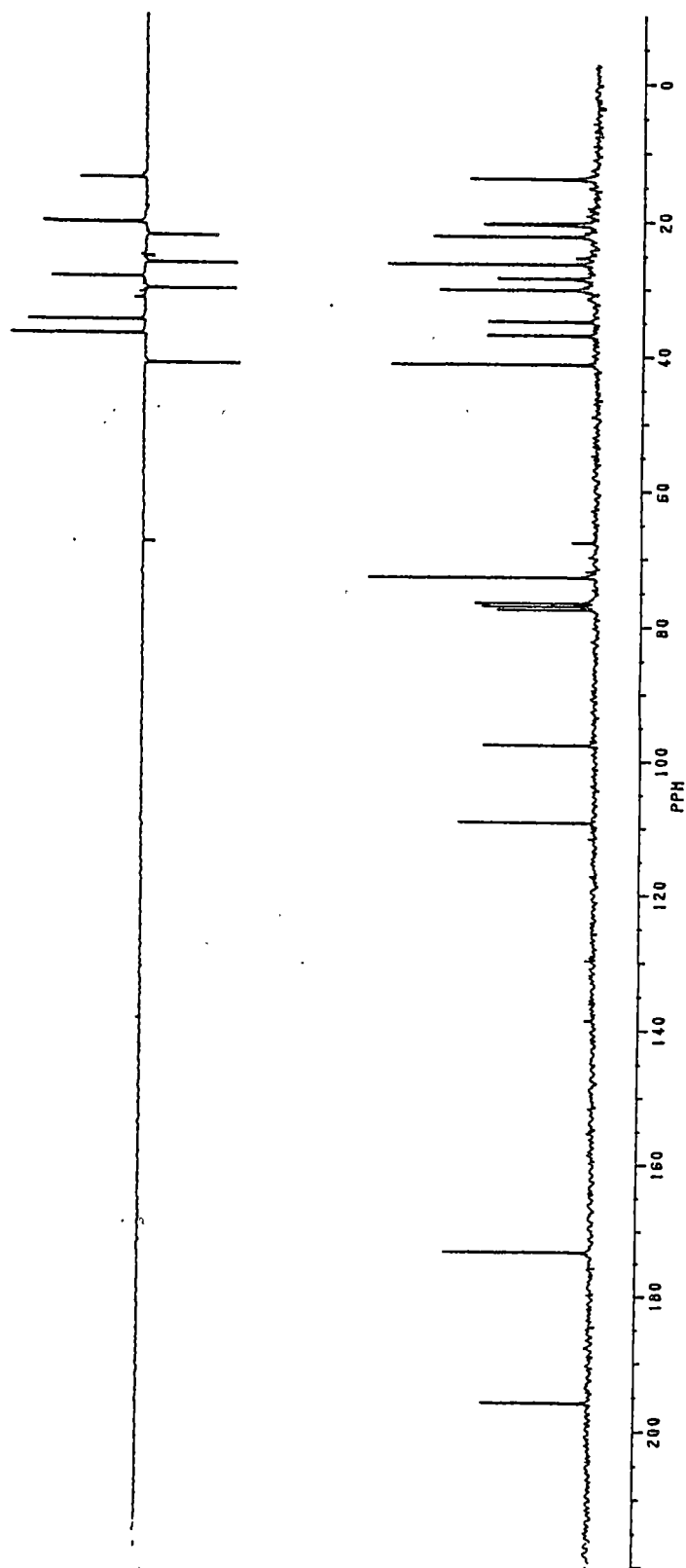
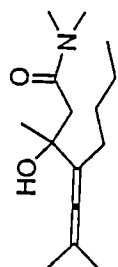
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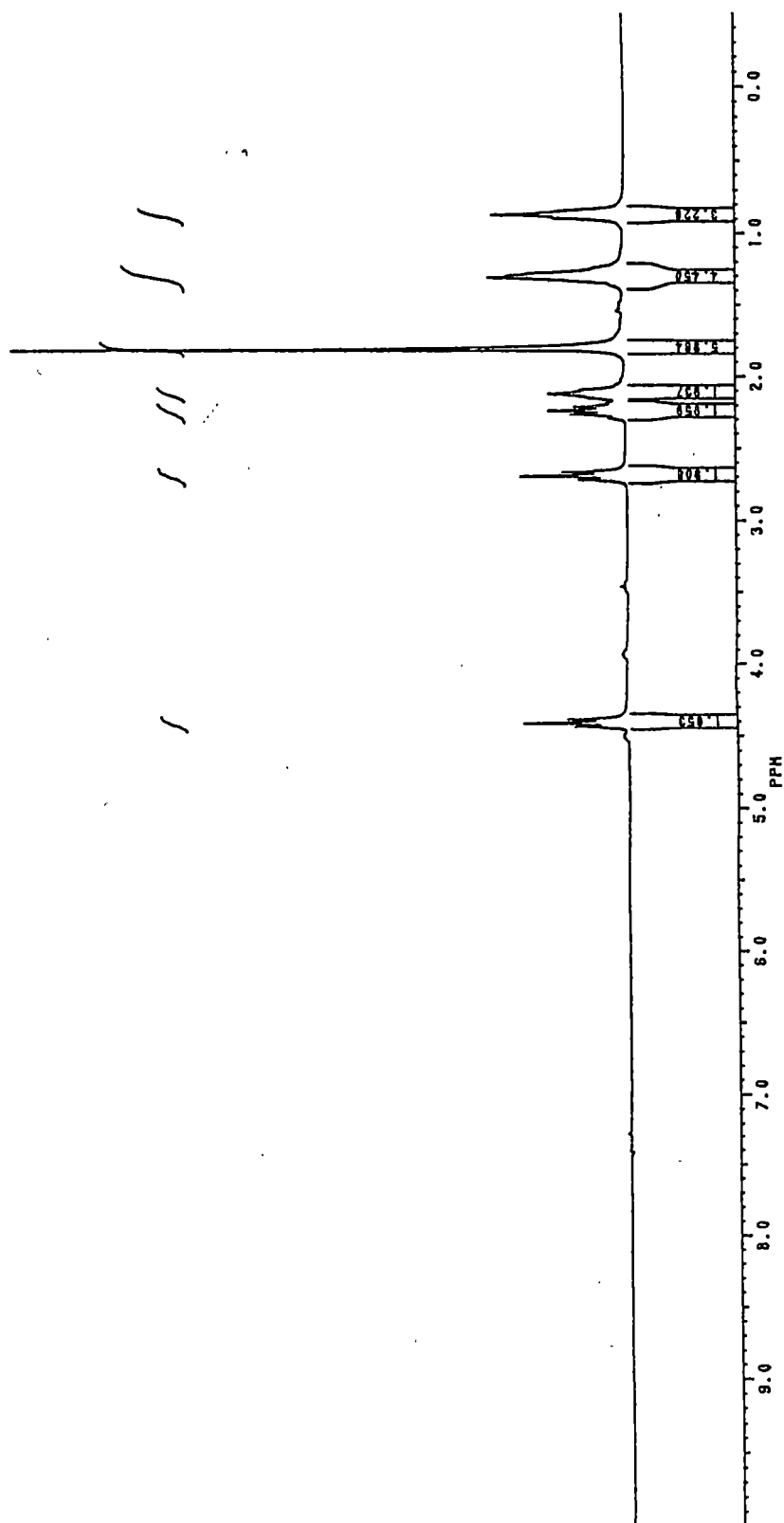
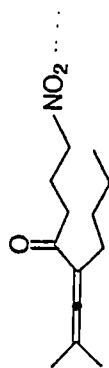
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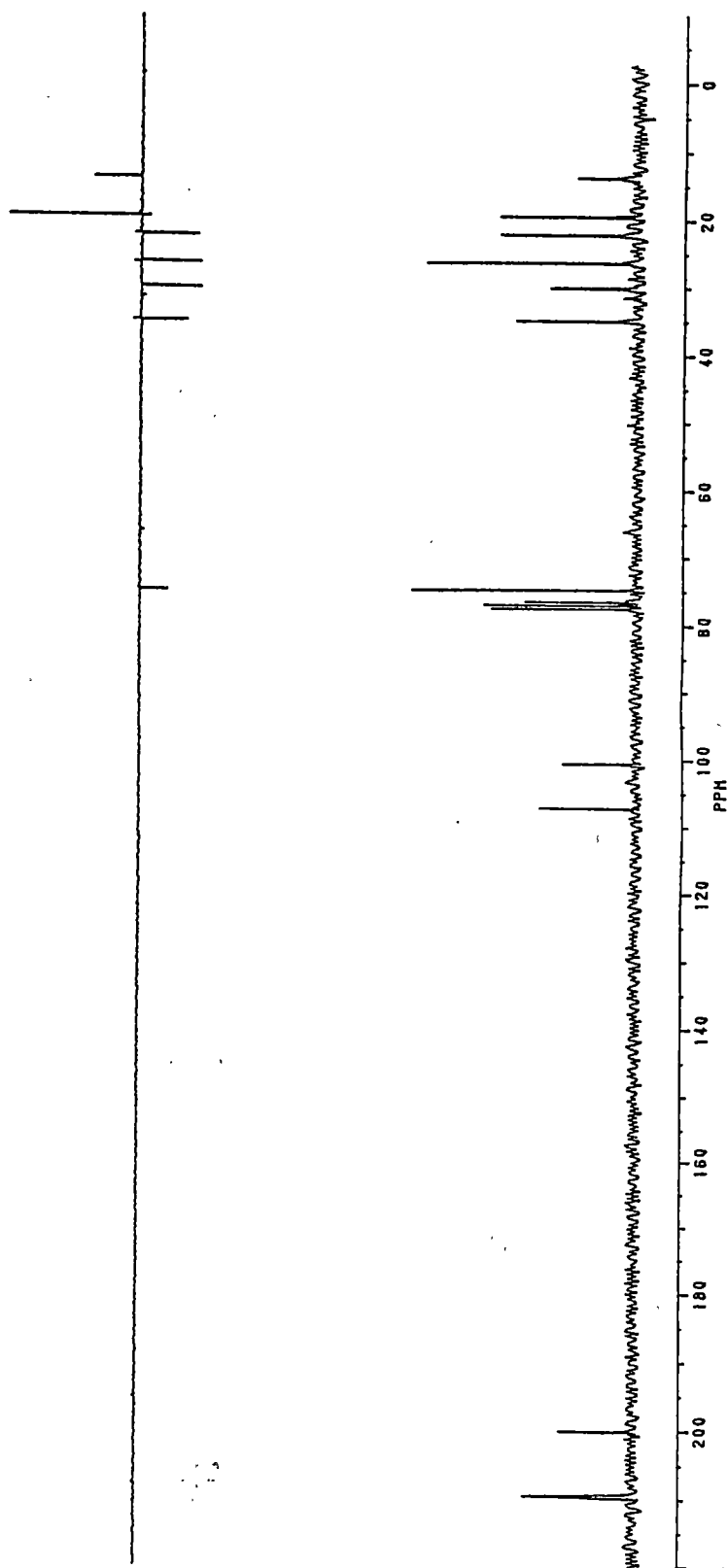
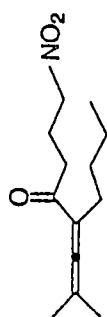
Appendices

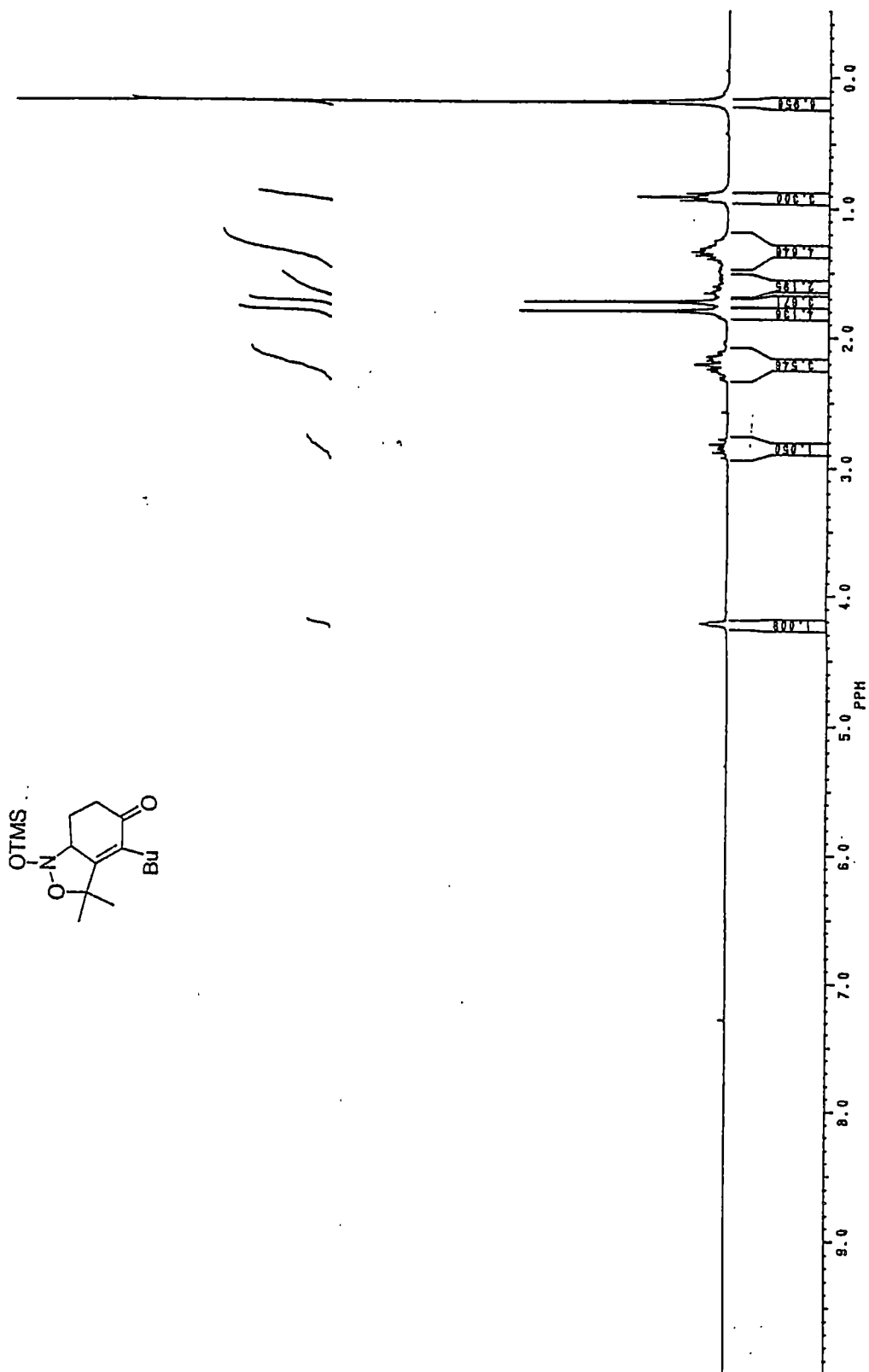
Appendix I. ^1H and ^{13}C NMR spectra for new compounds prepared

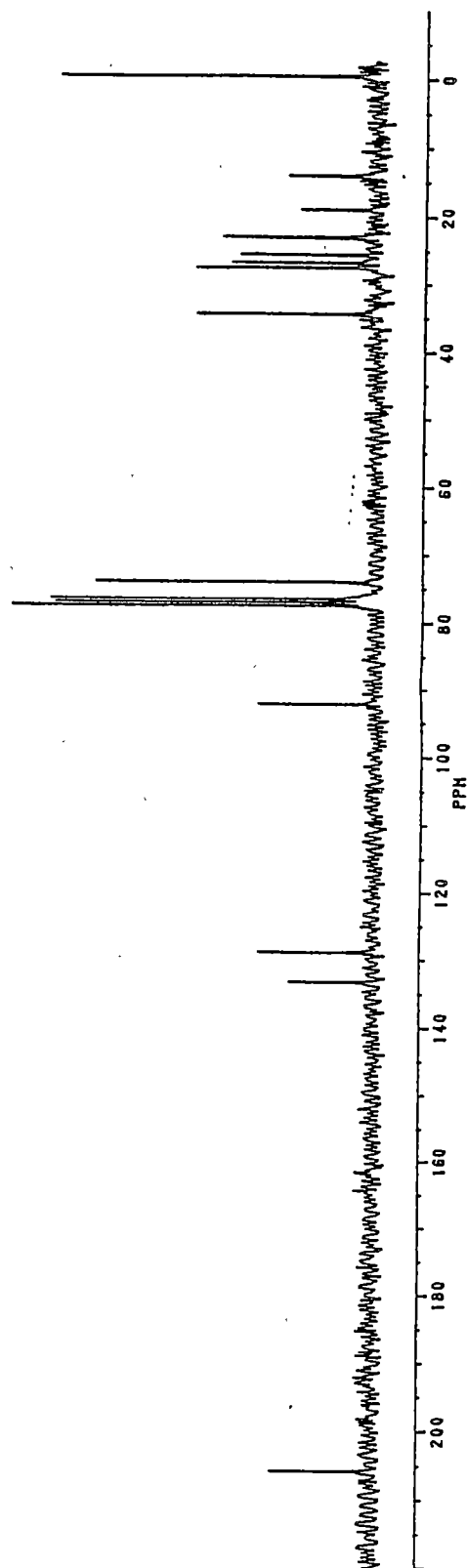
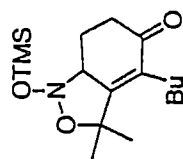


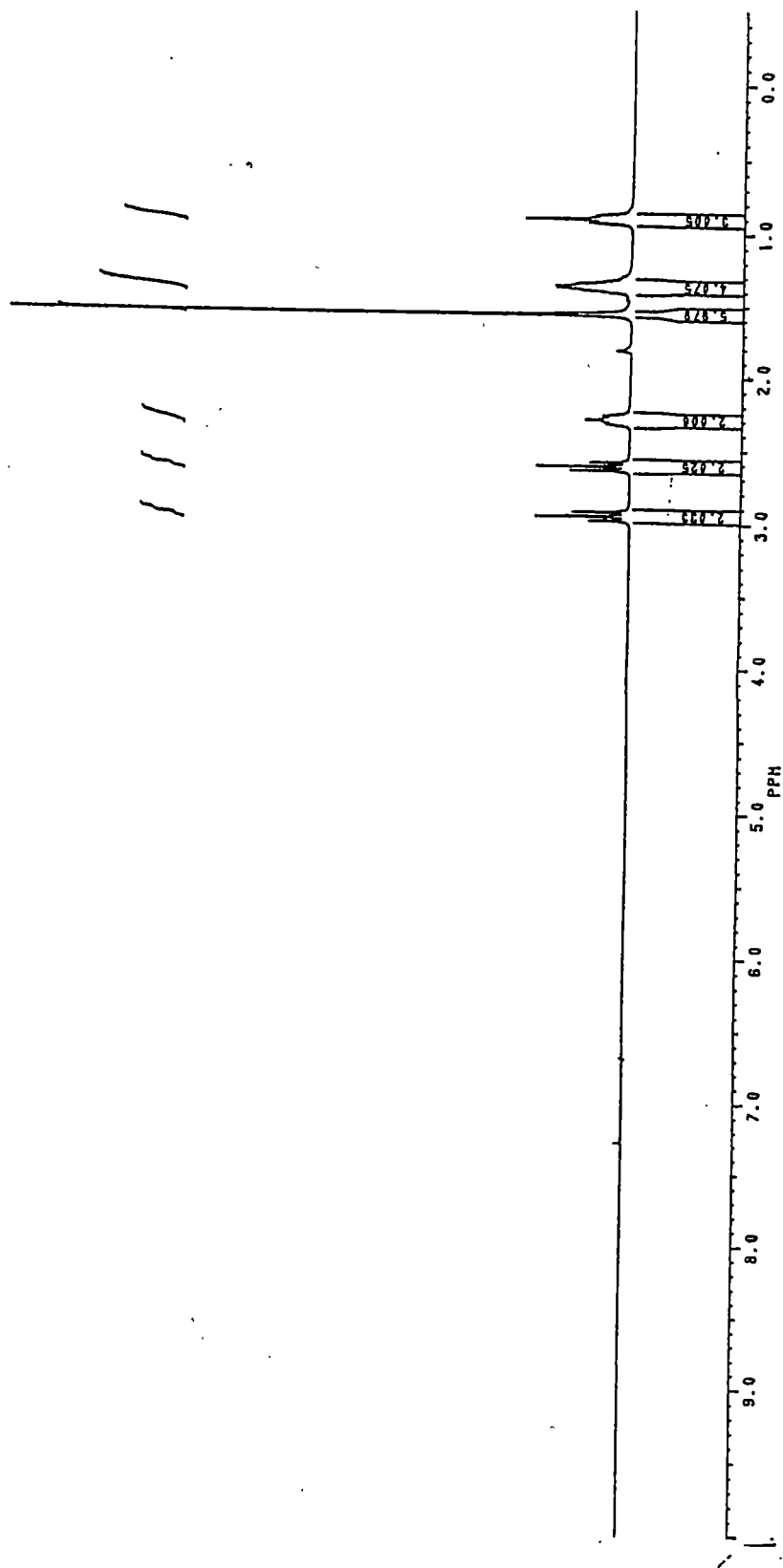
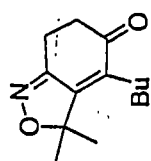


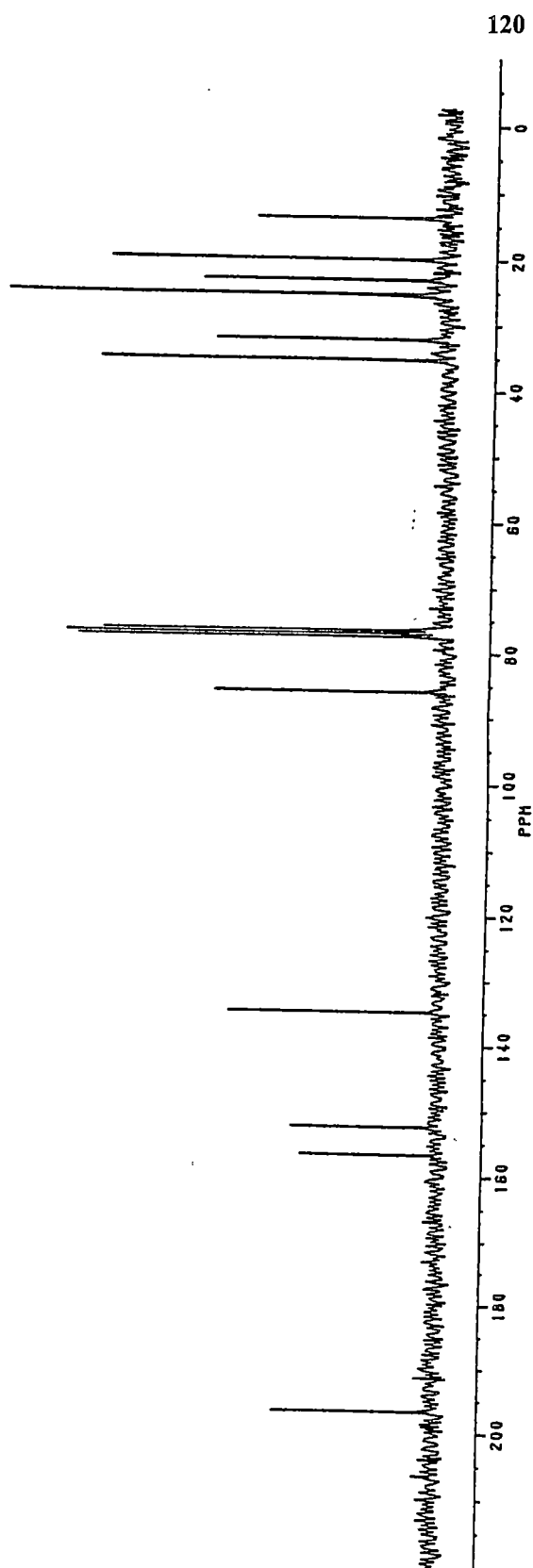
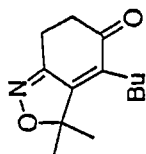


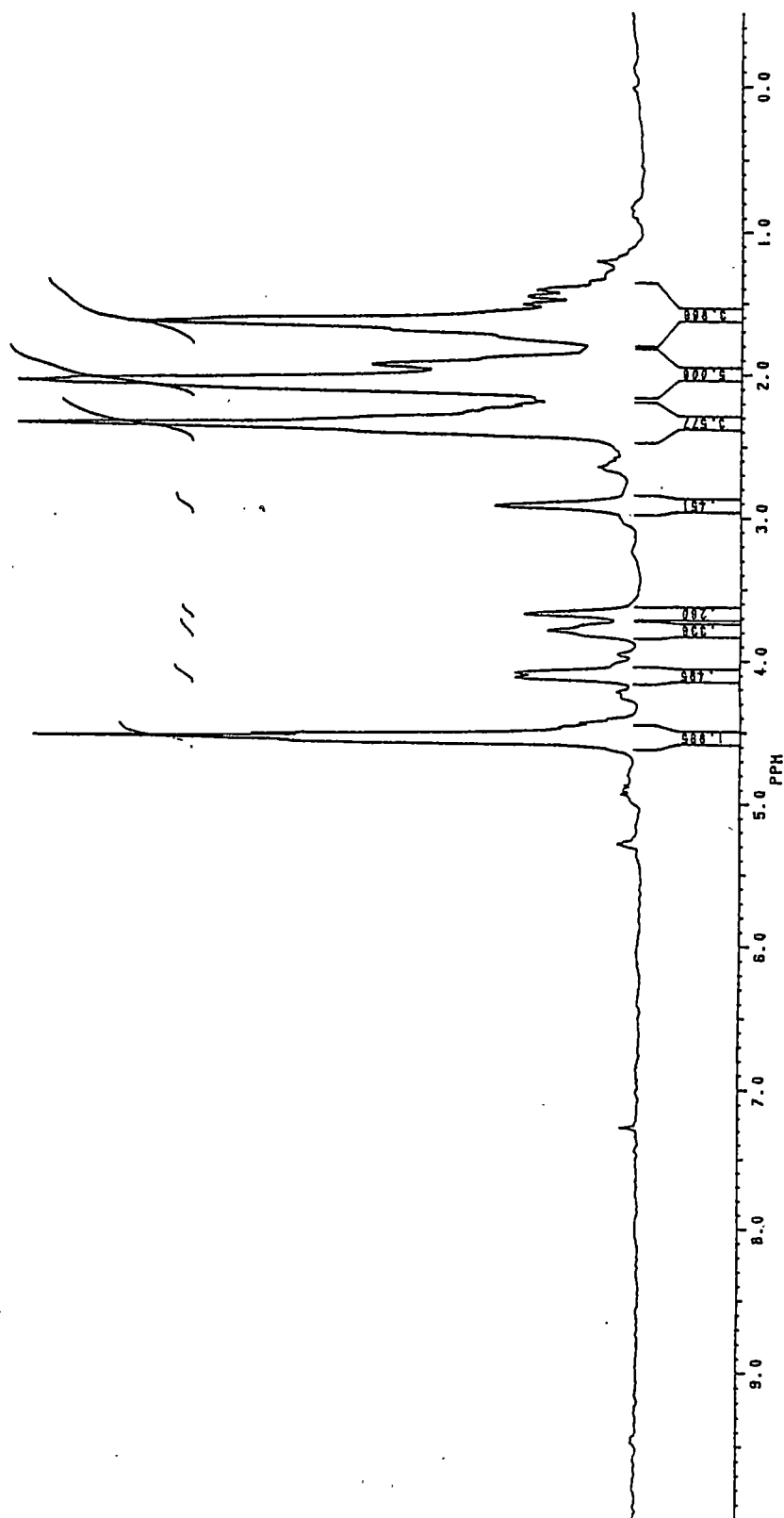
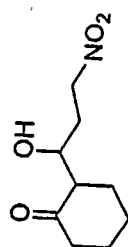


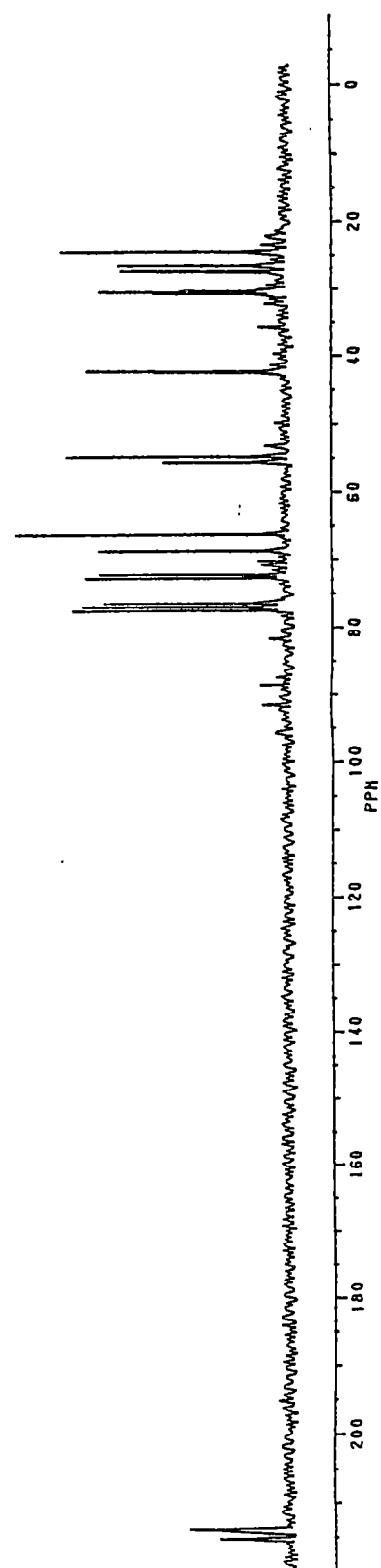
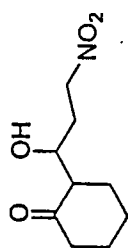


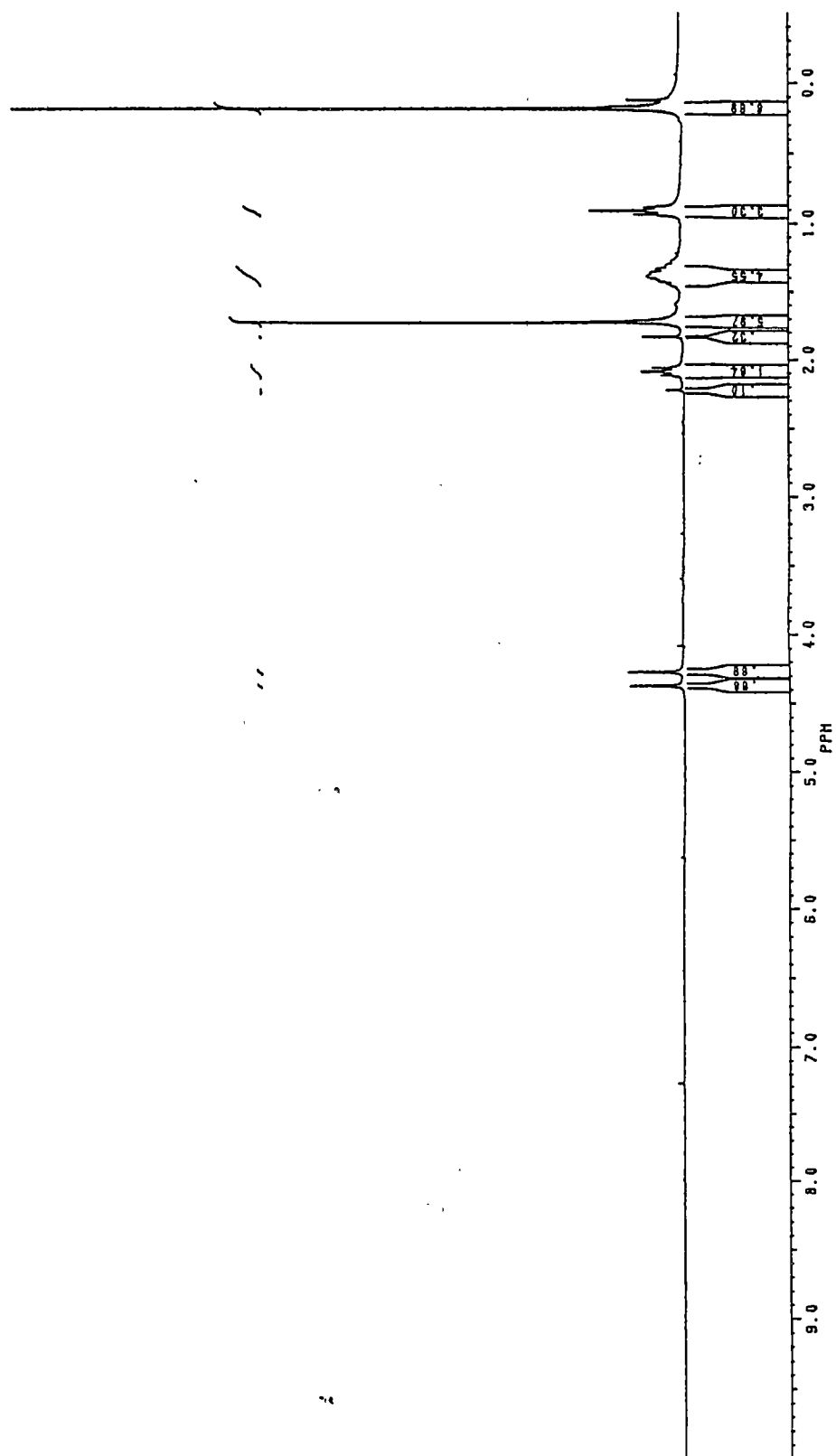
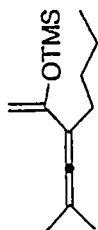


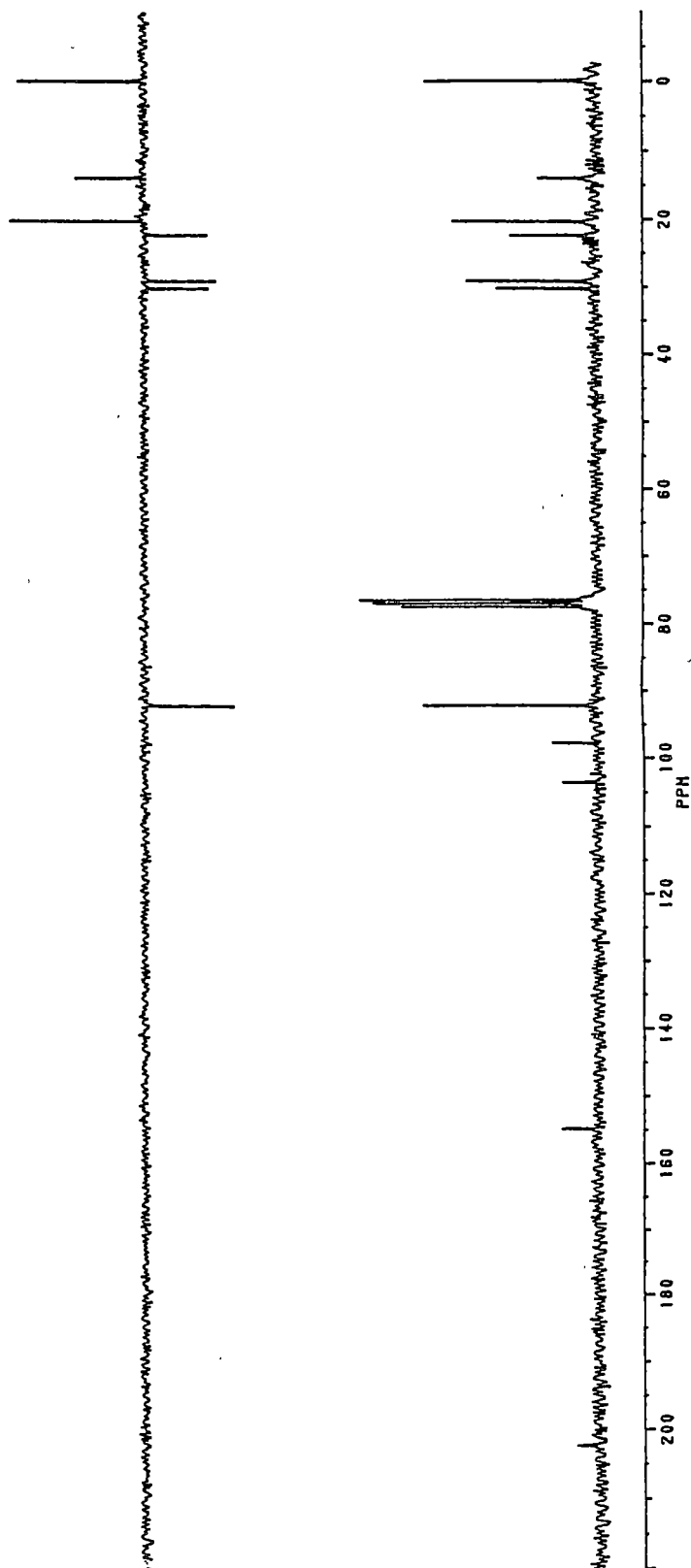
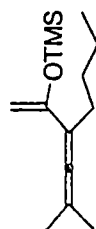


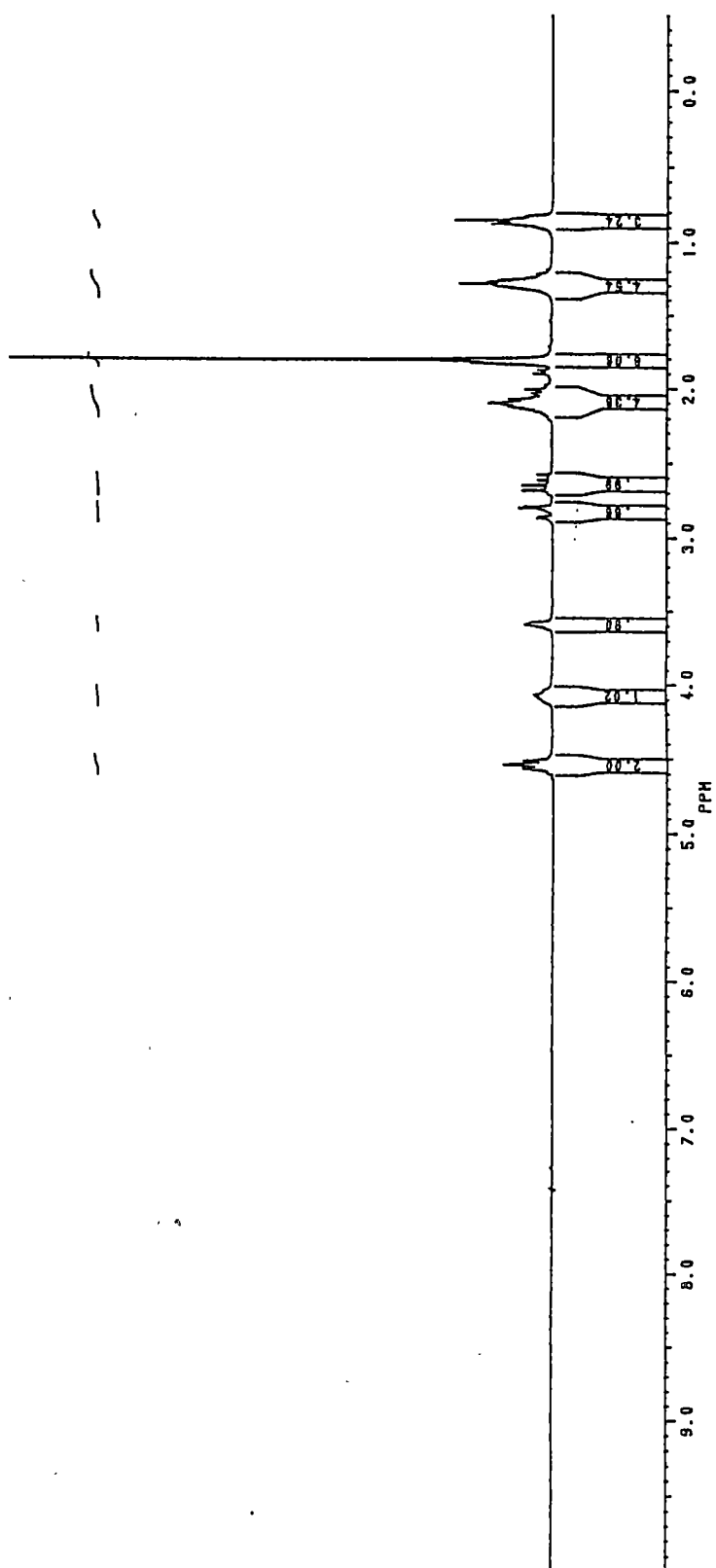
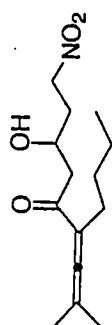


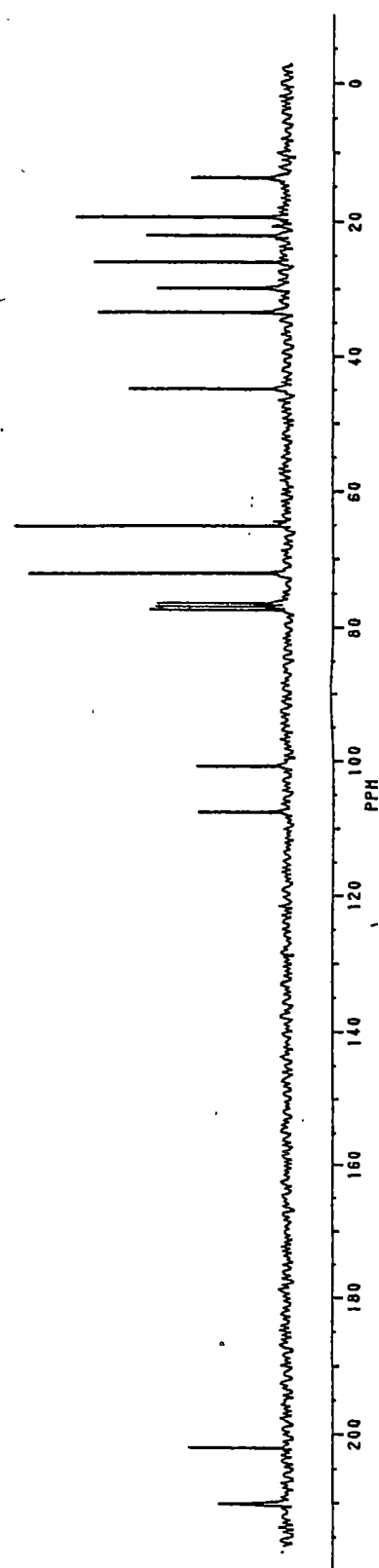
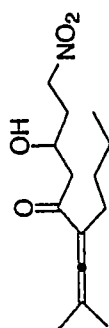


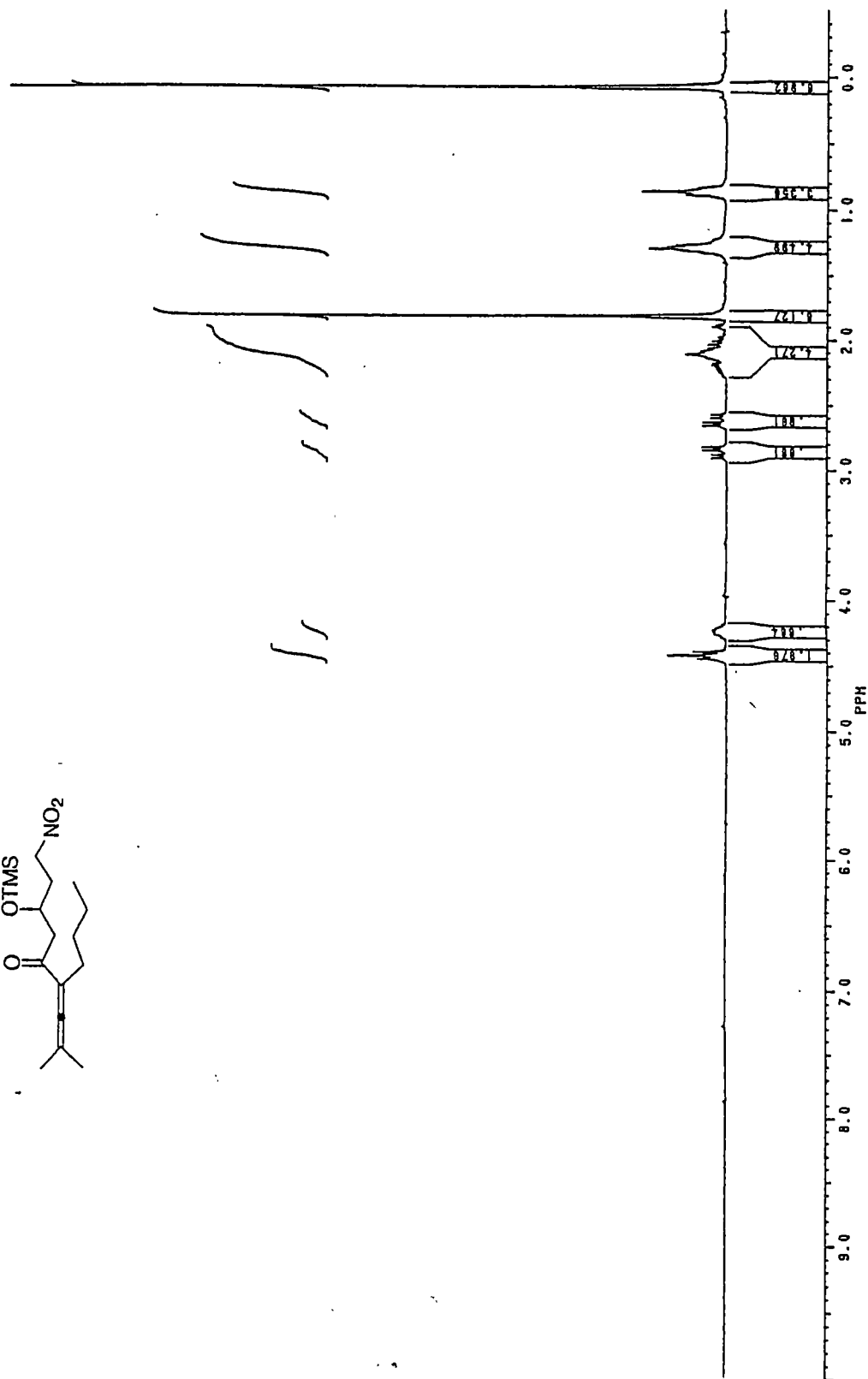
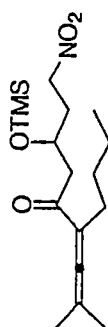


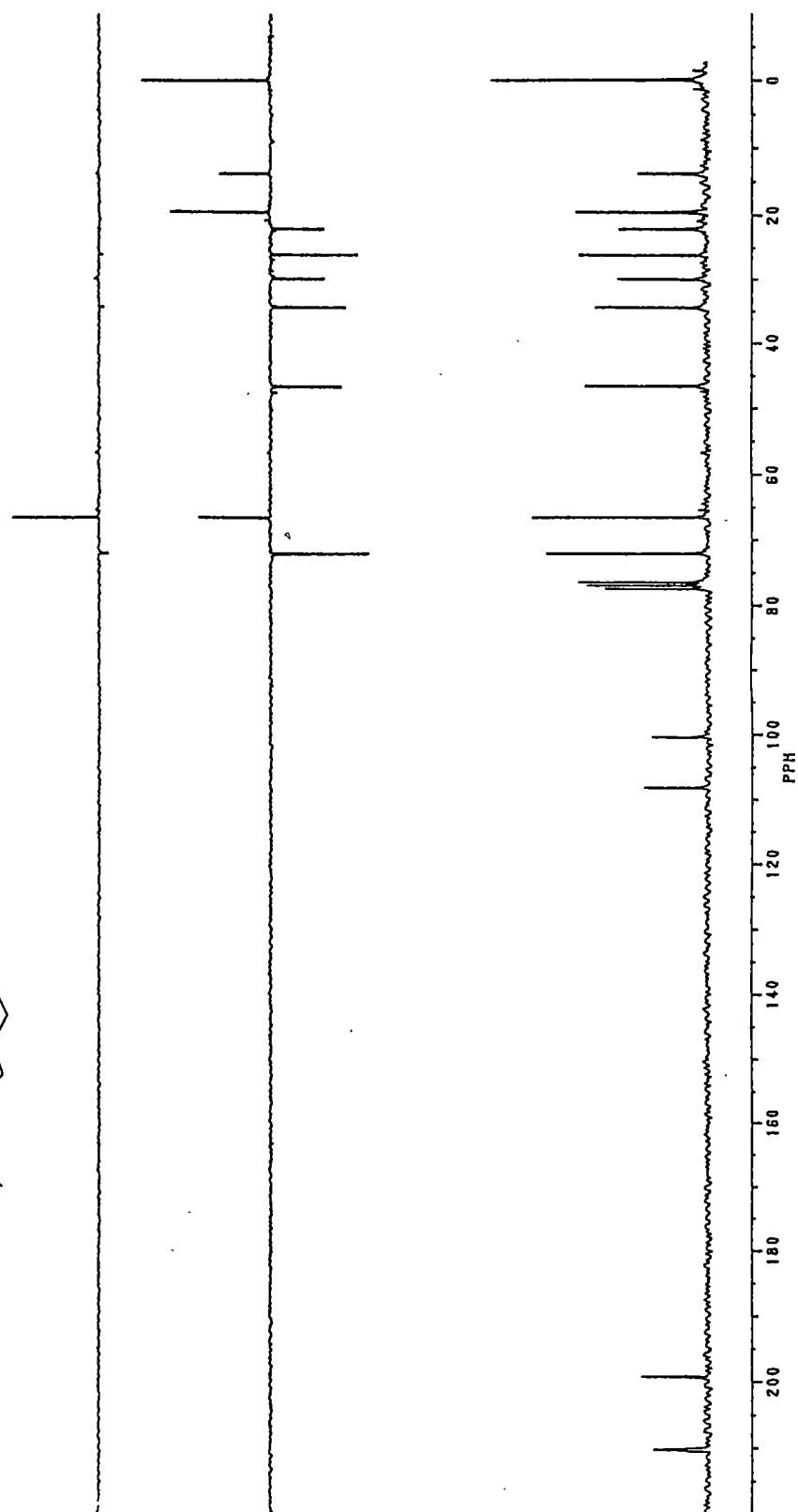
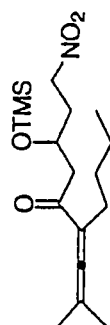


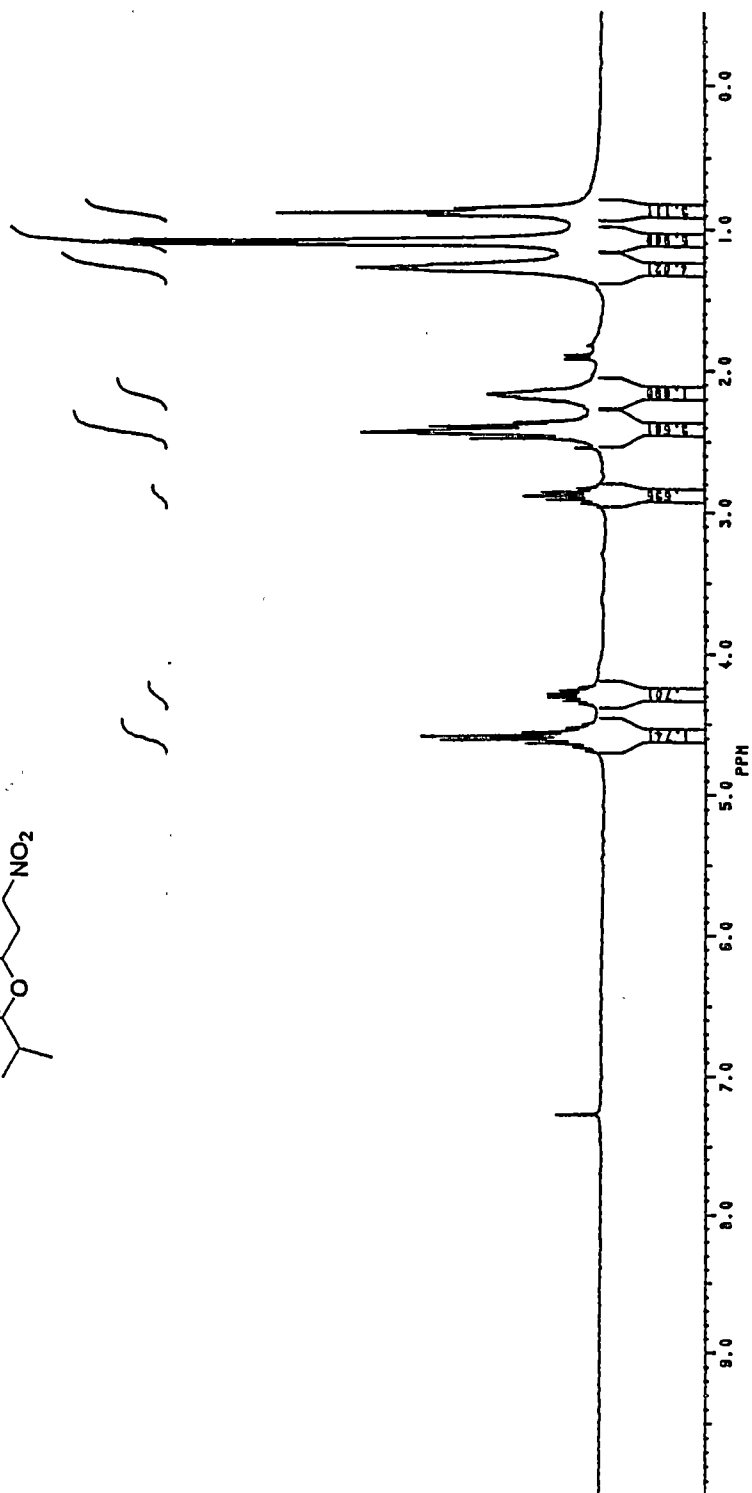
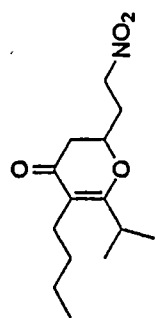


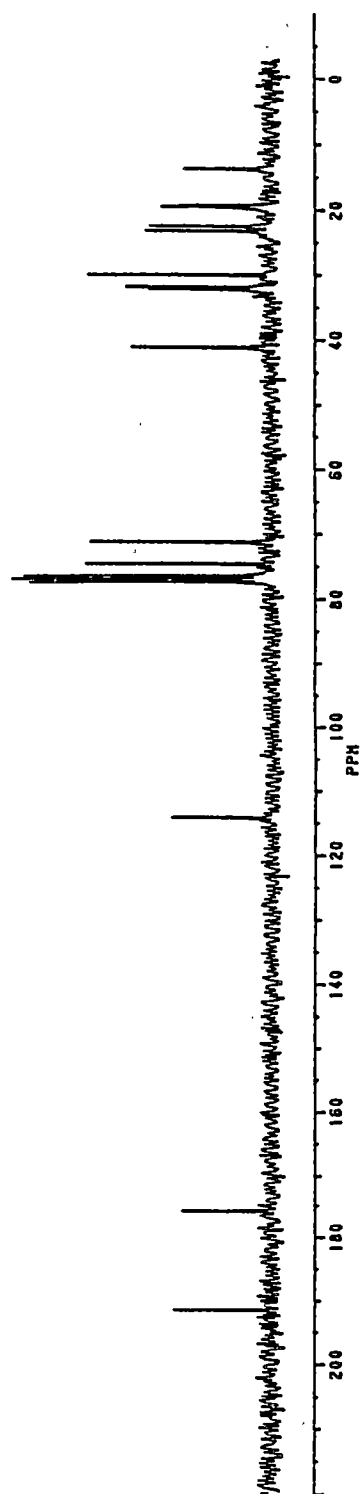
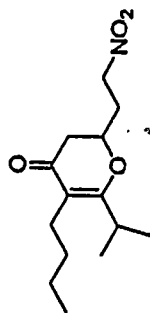


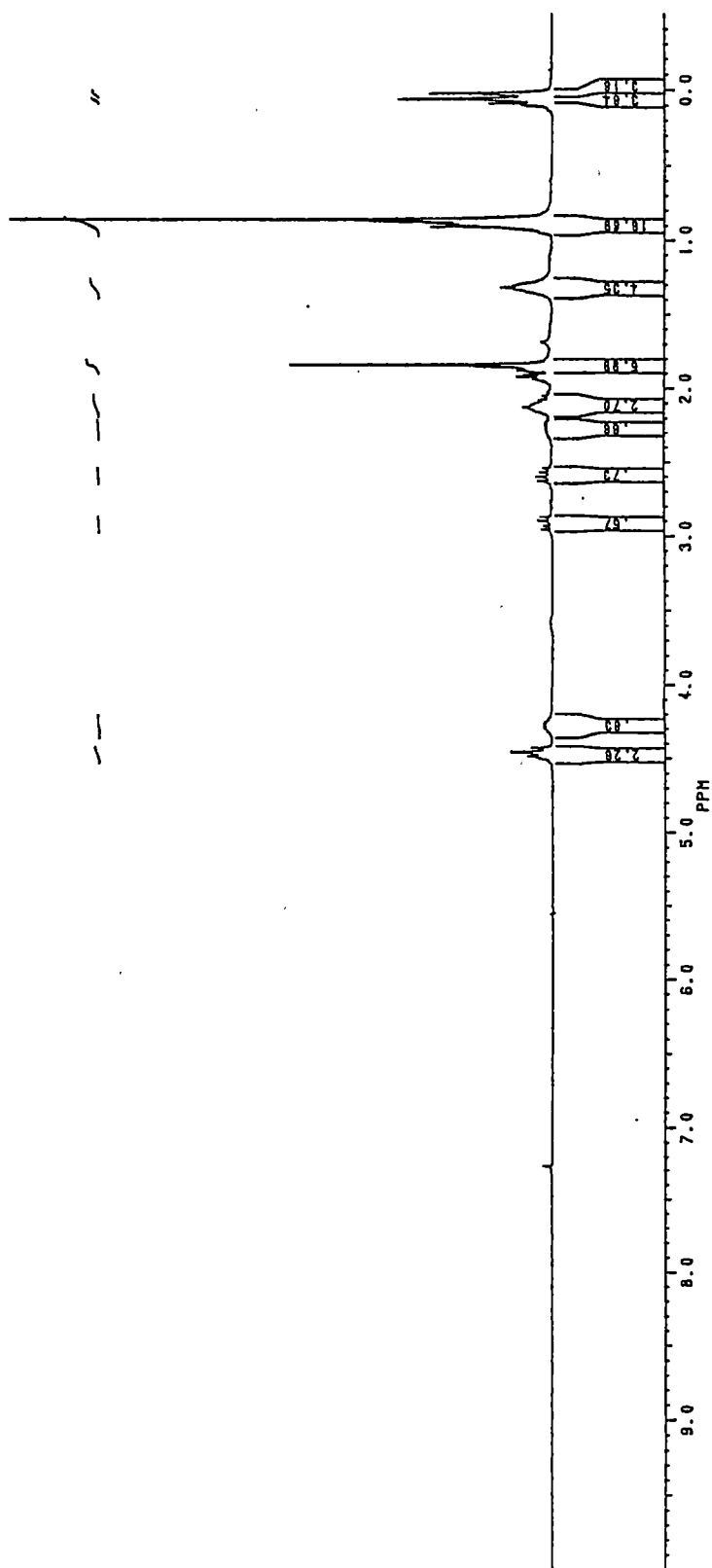
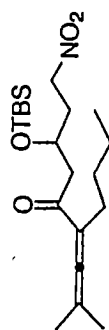


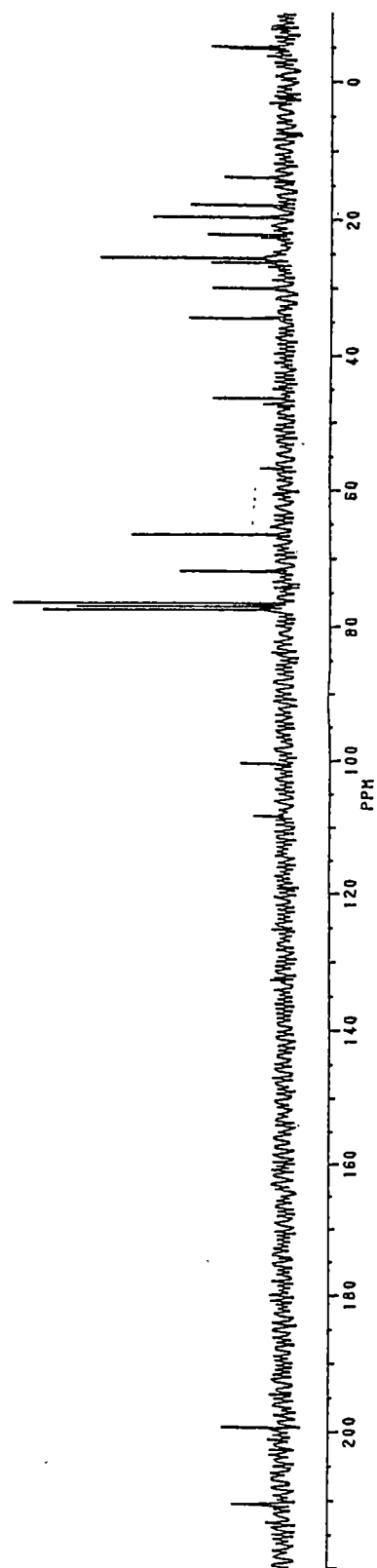
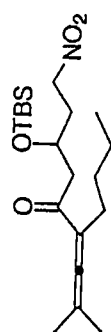


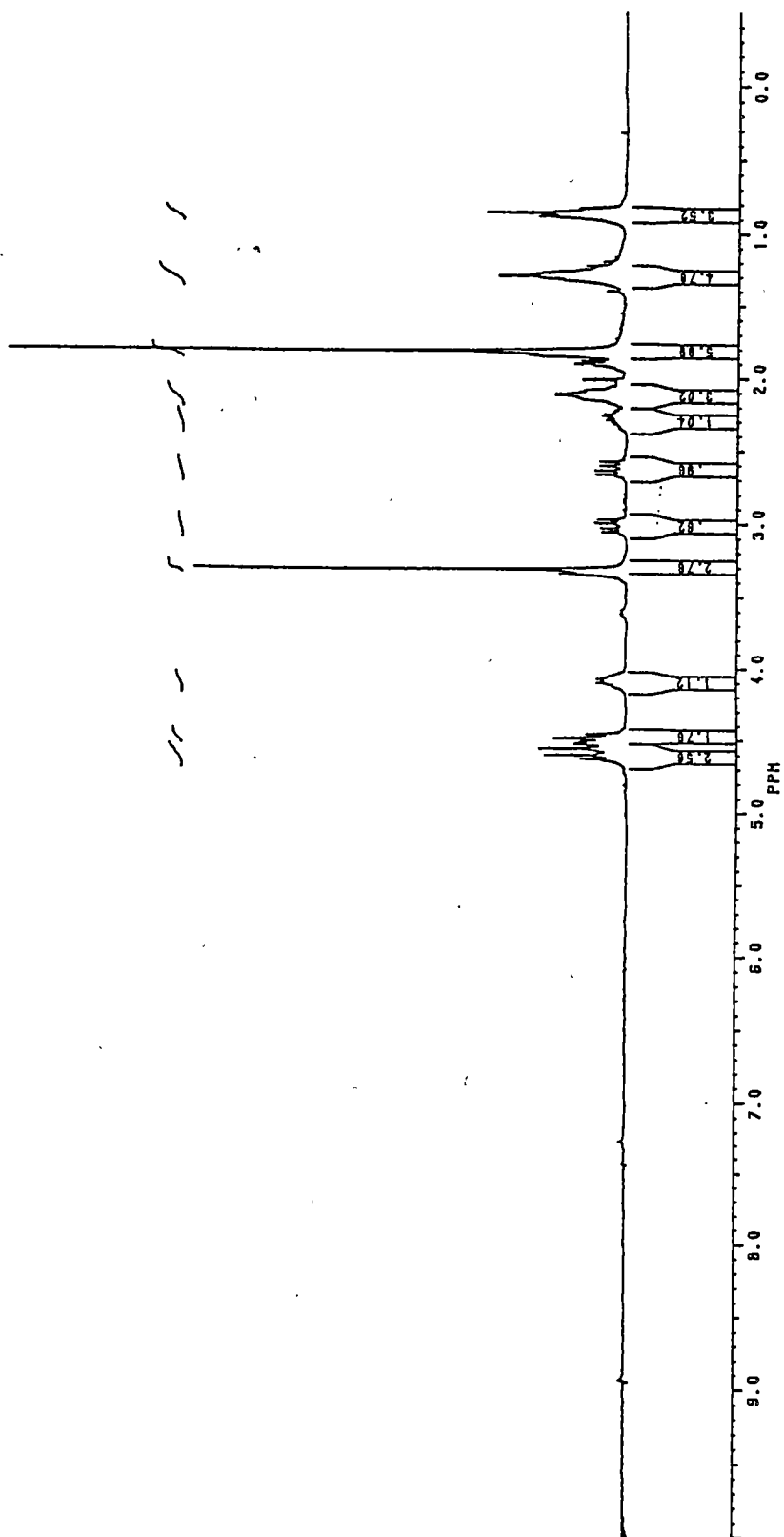
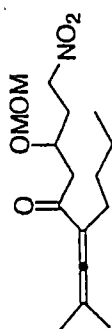


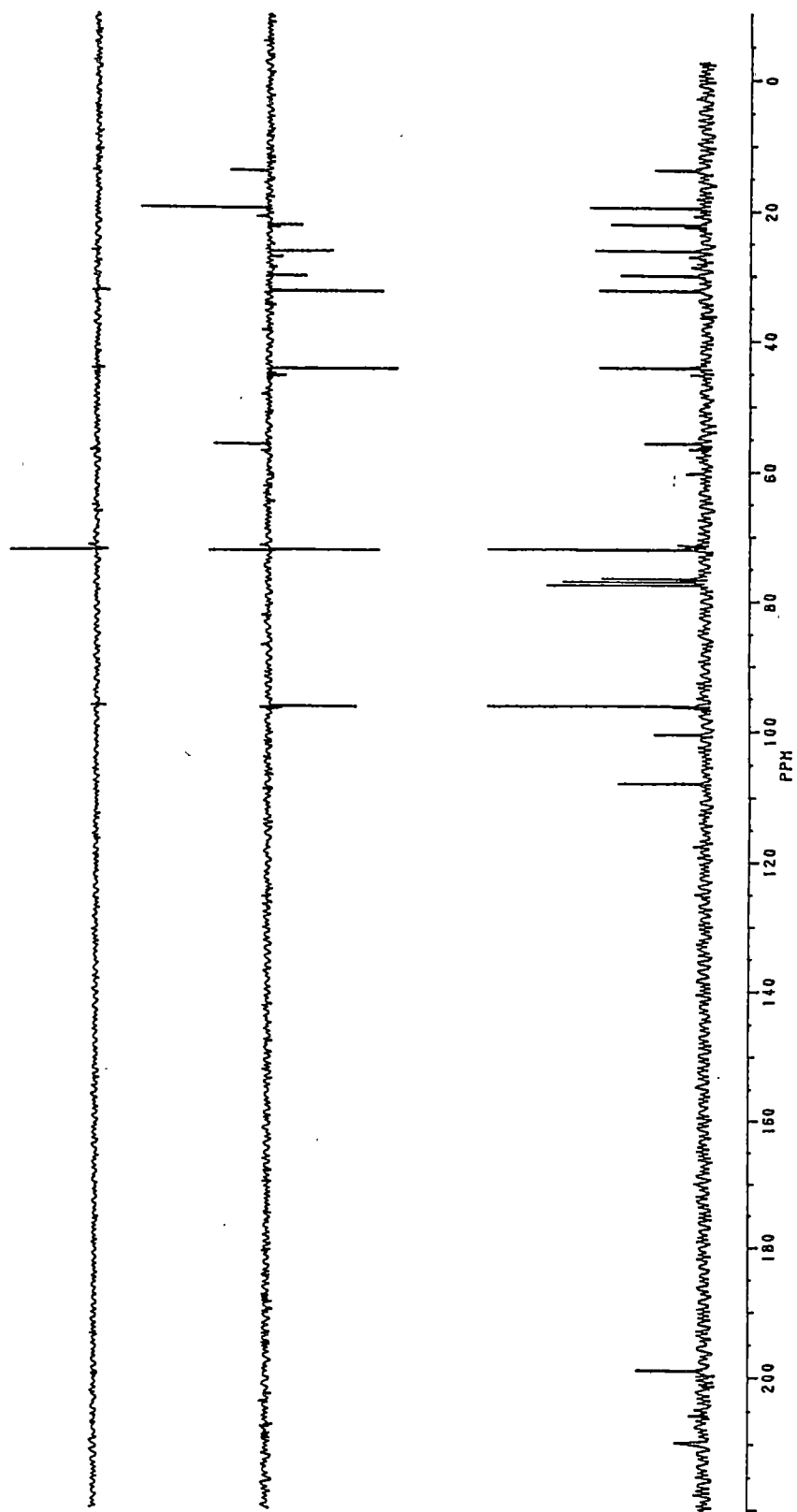
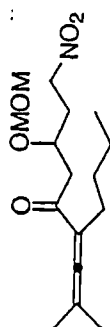


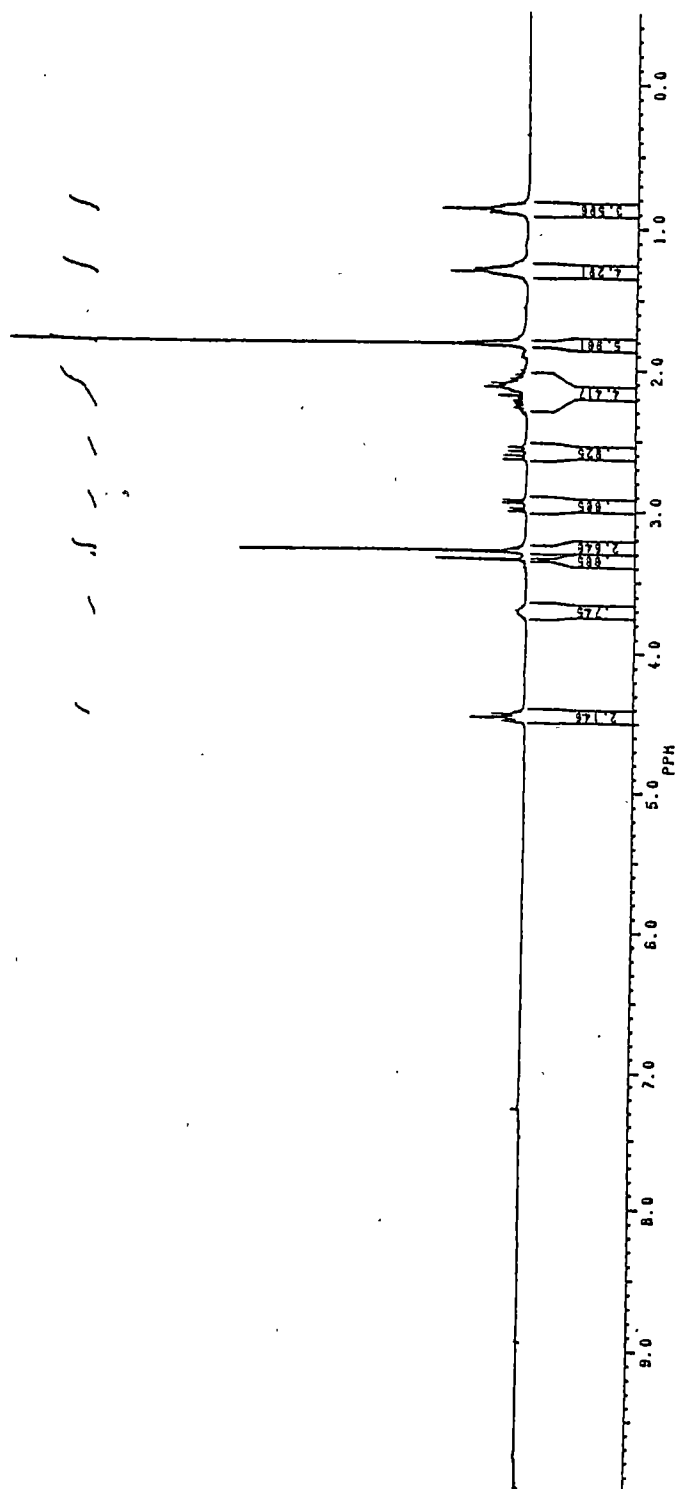
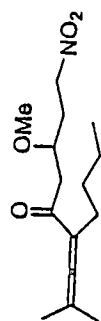


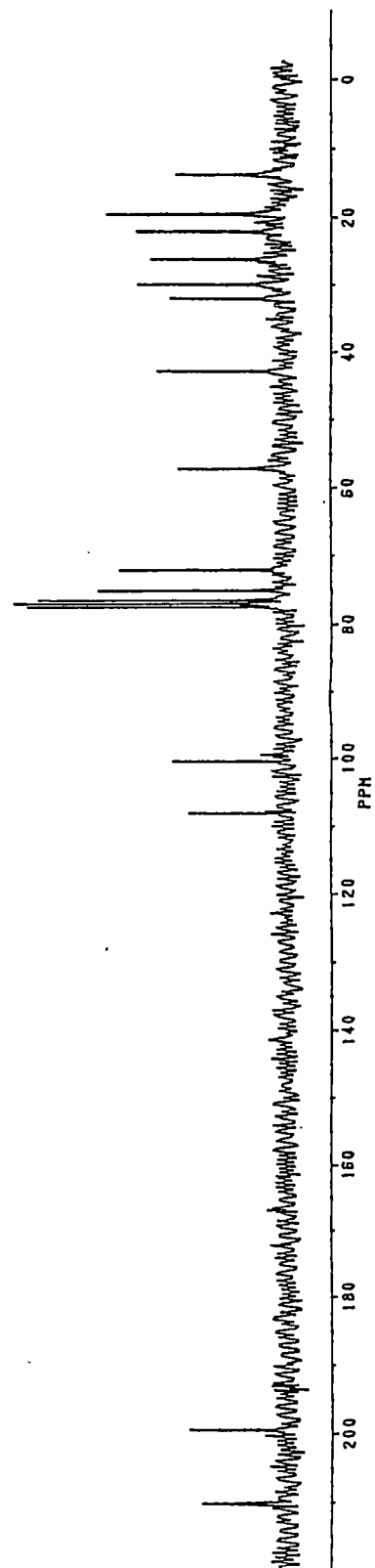
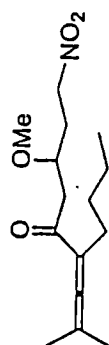


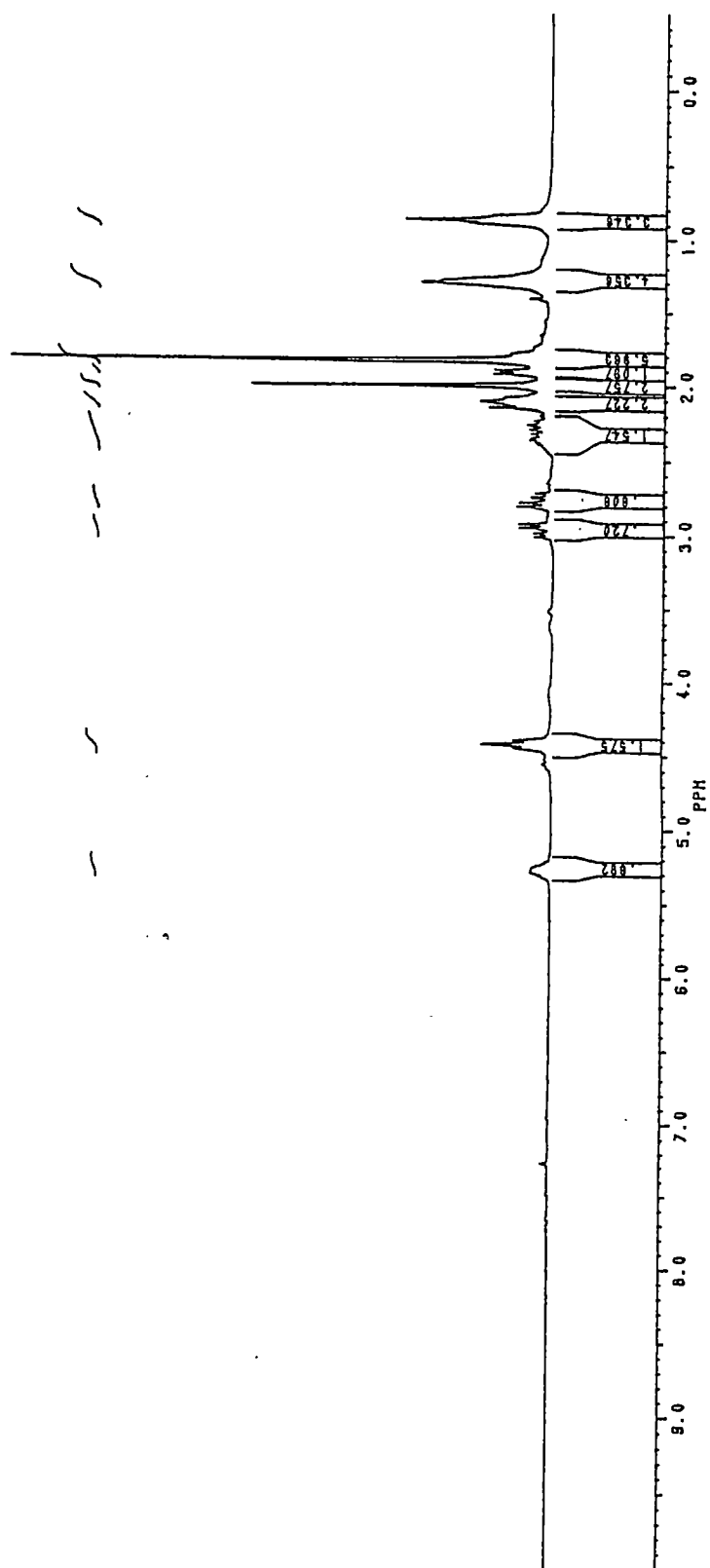
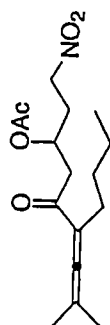


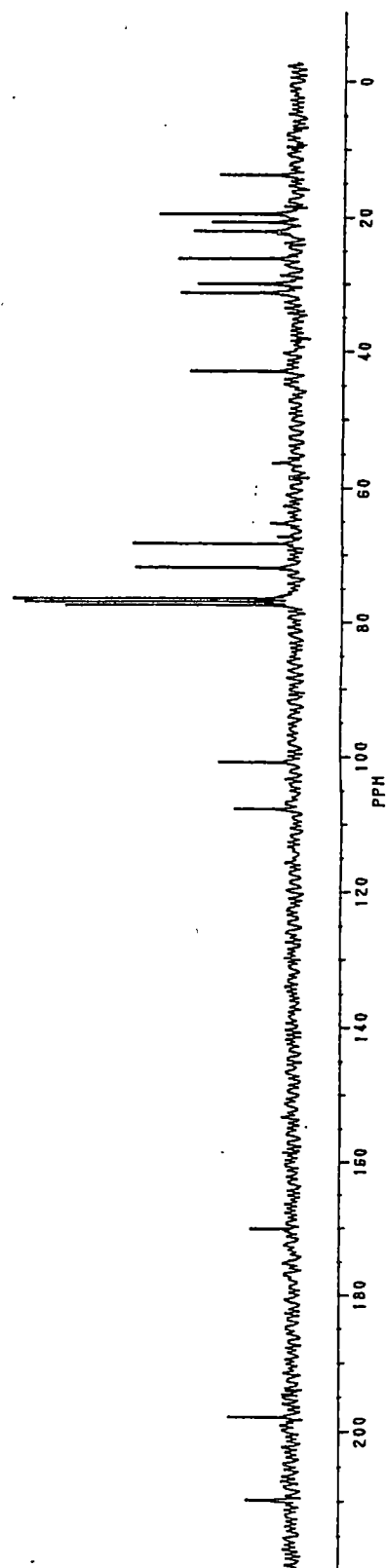
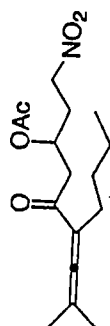


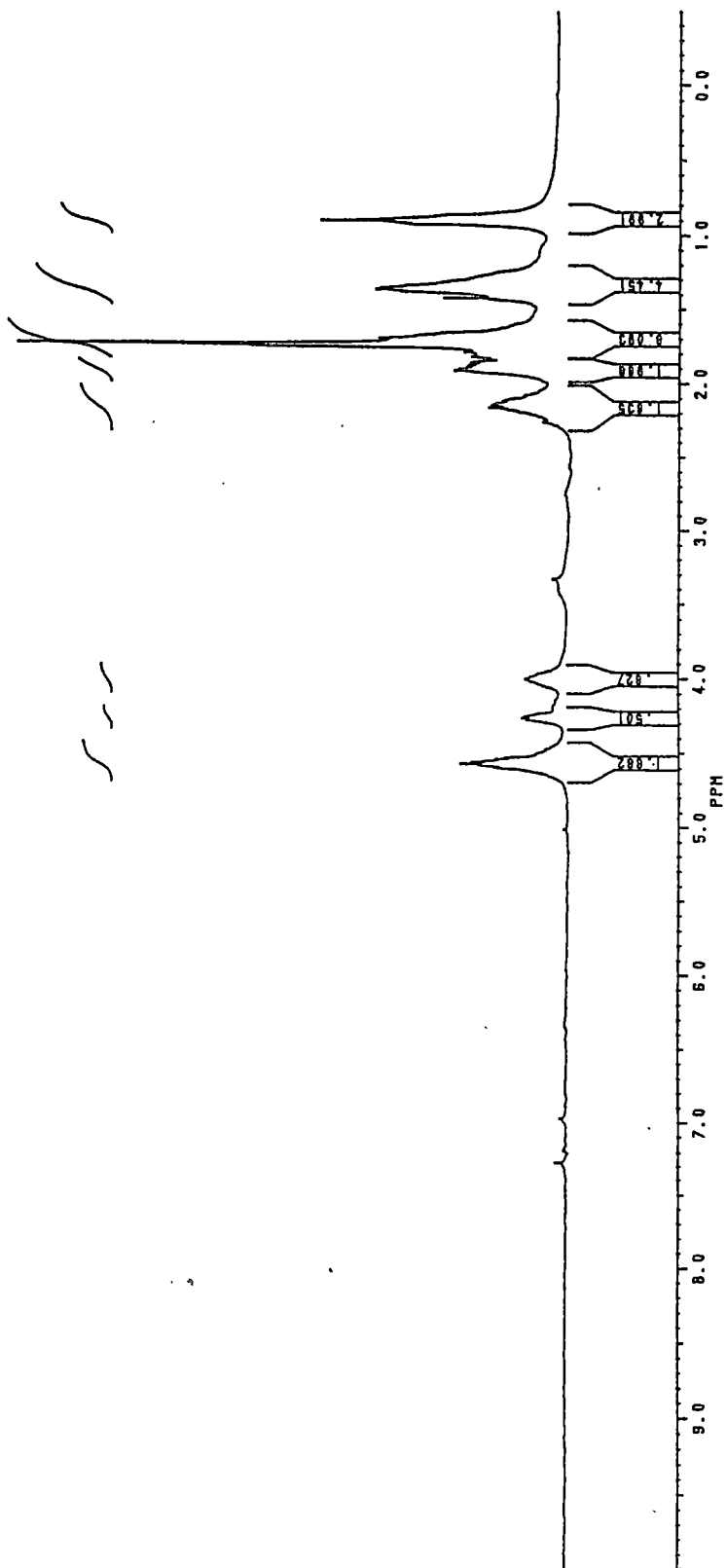
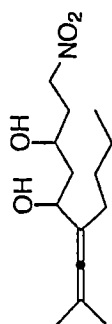


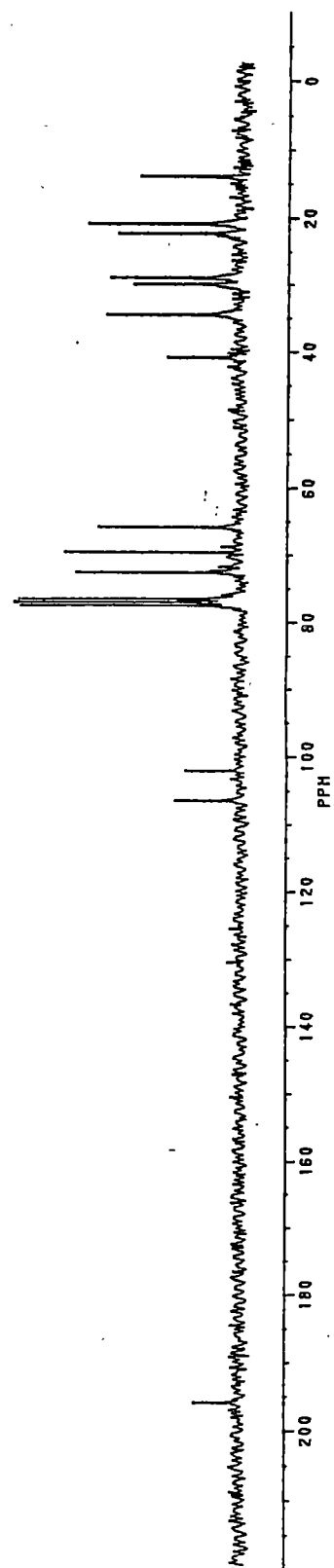
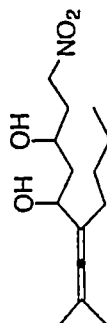


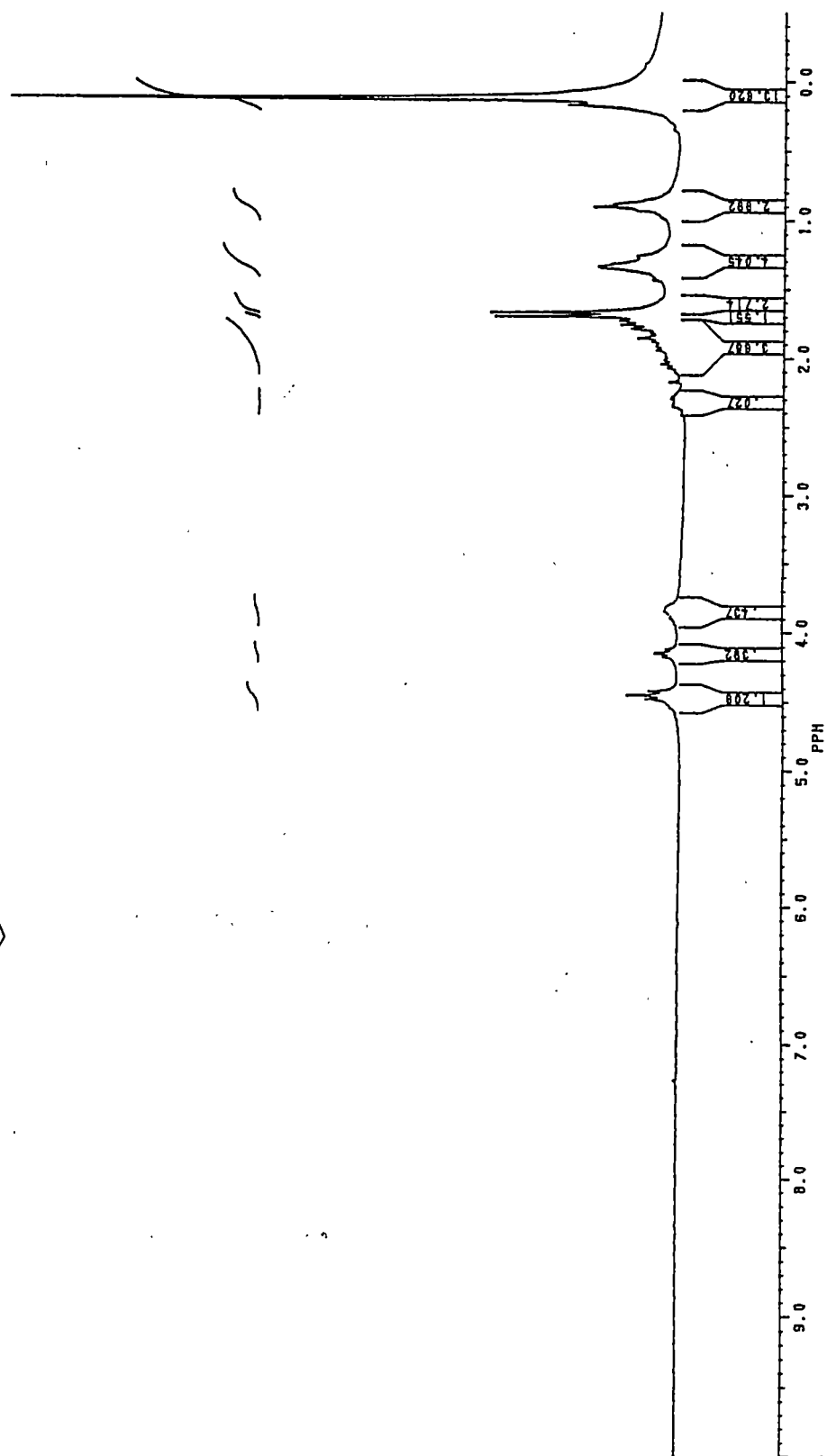
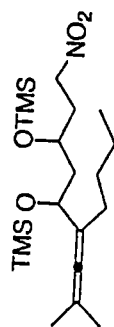


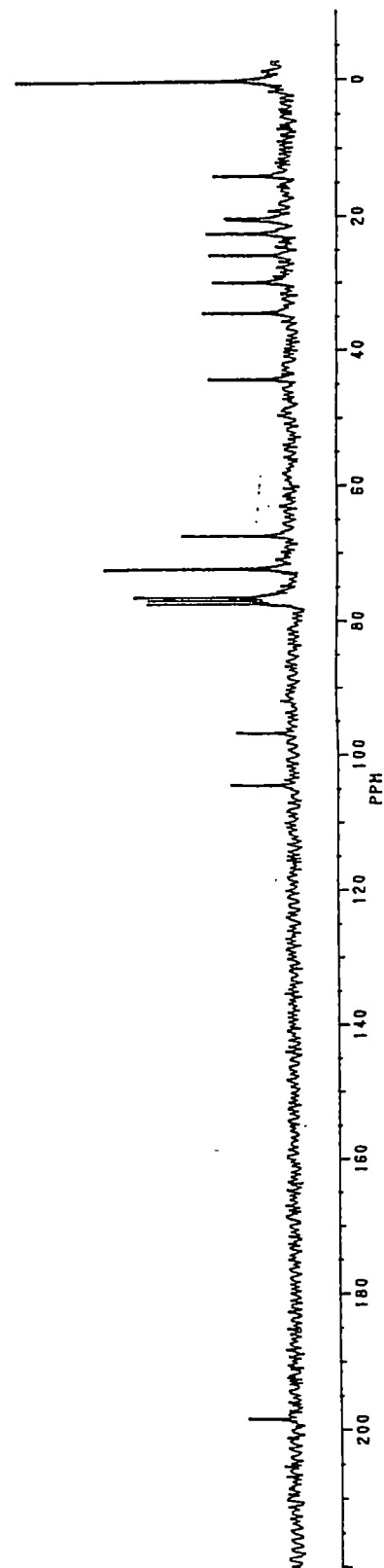
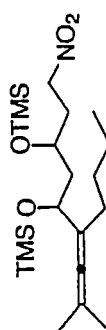


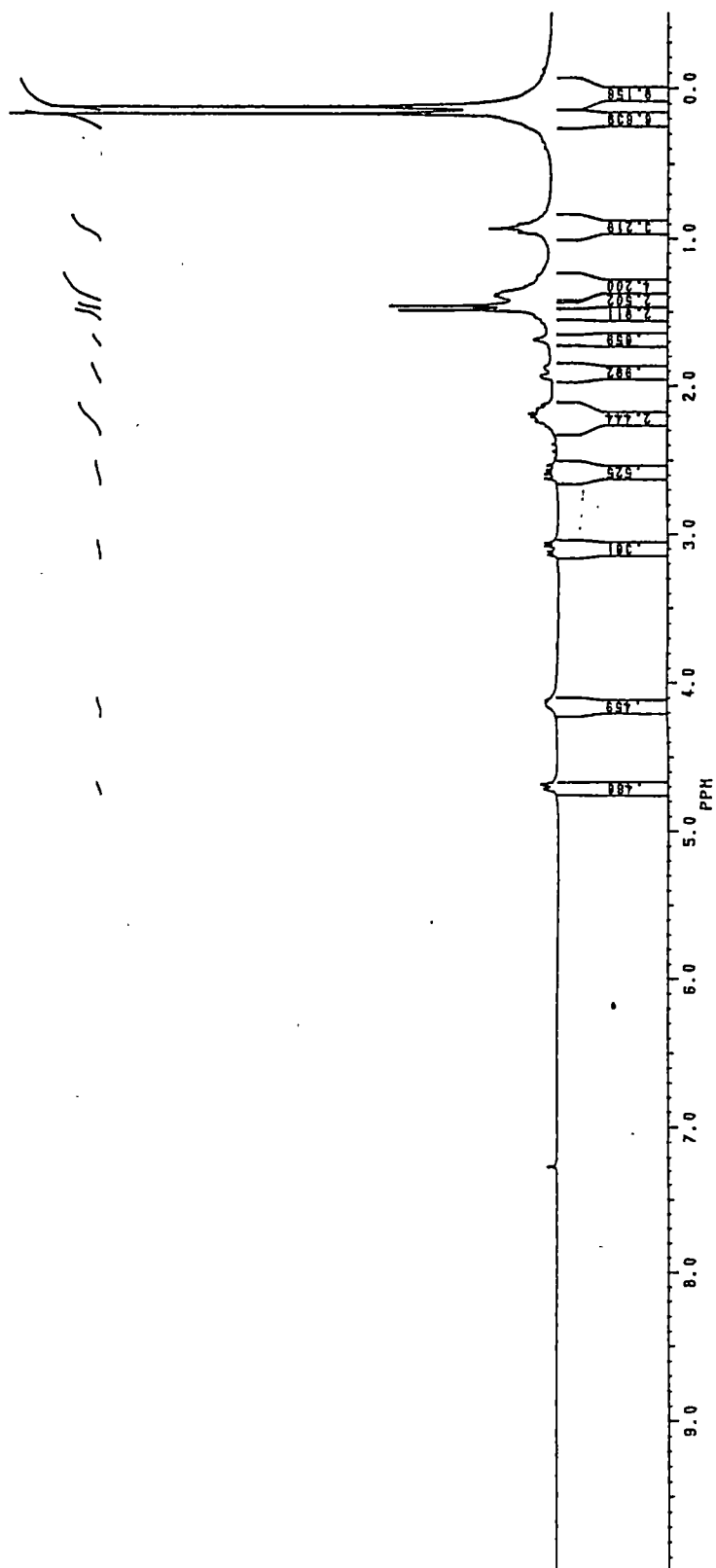
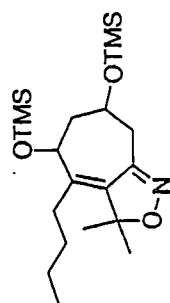


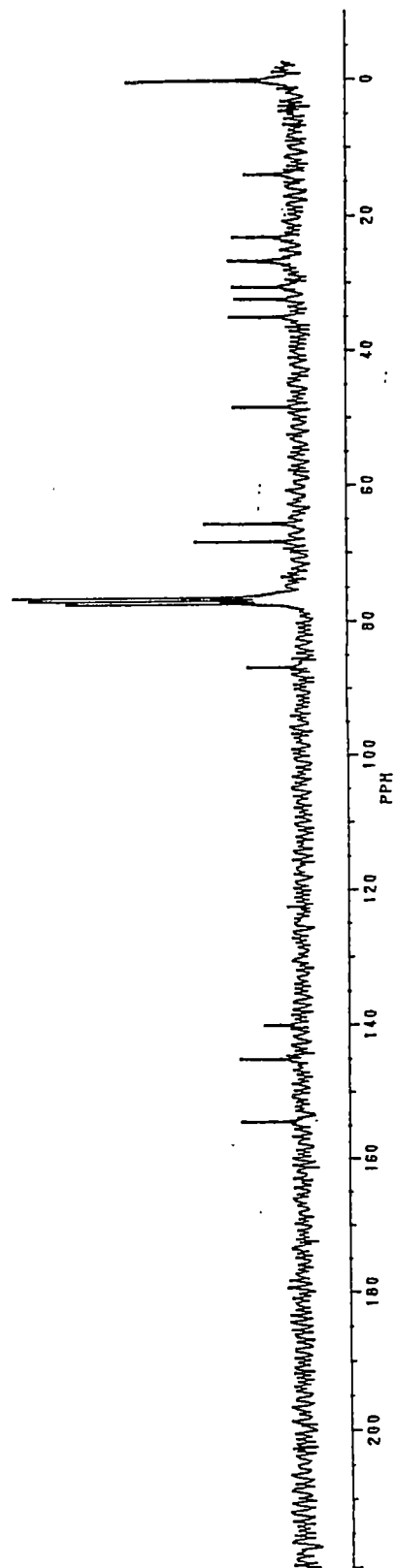
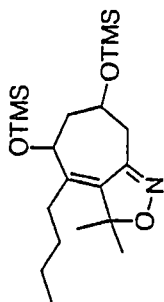


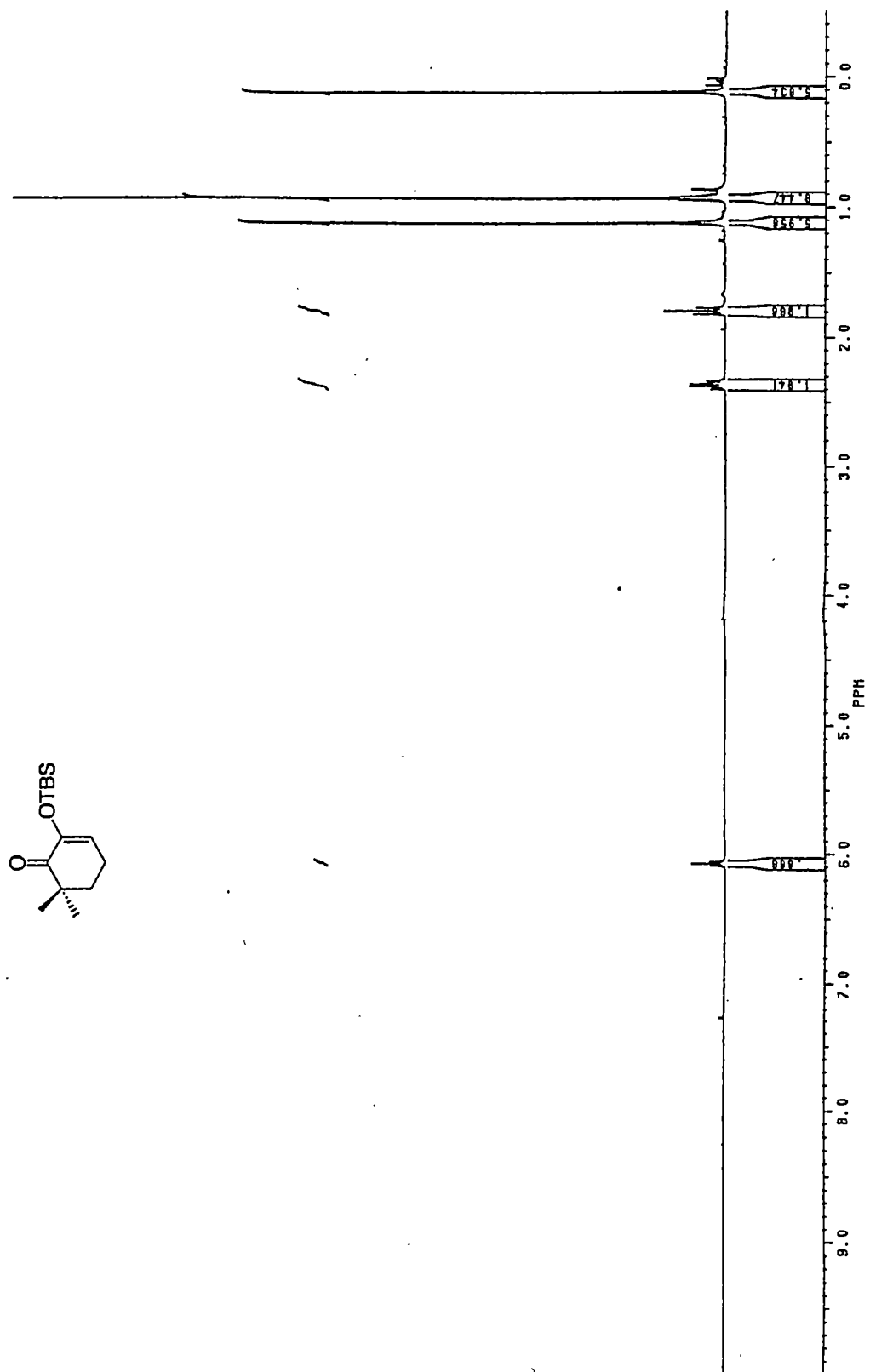




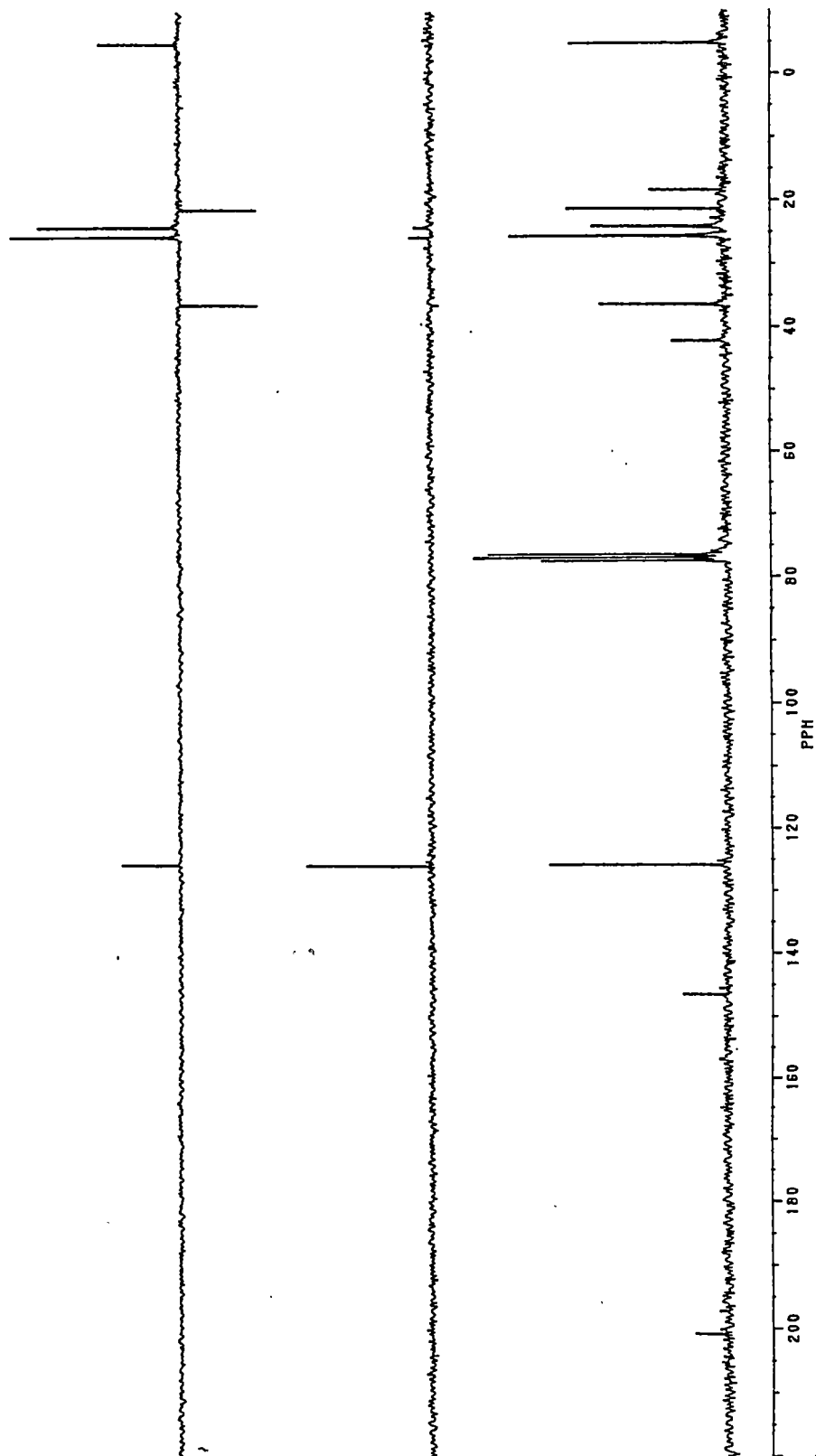
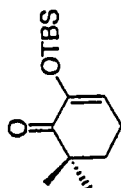


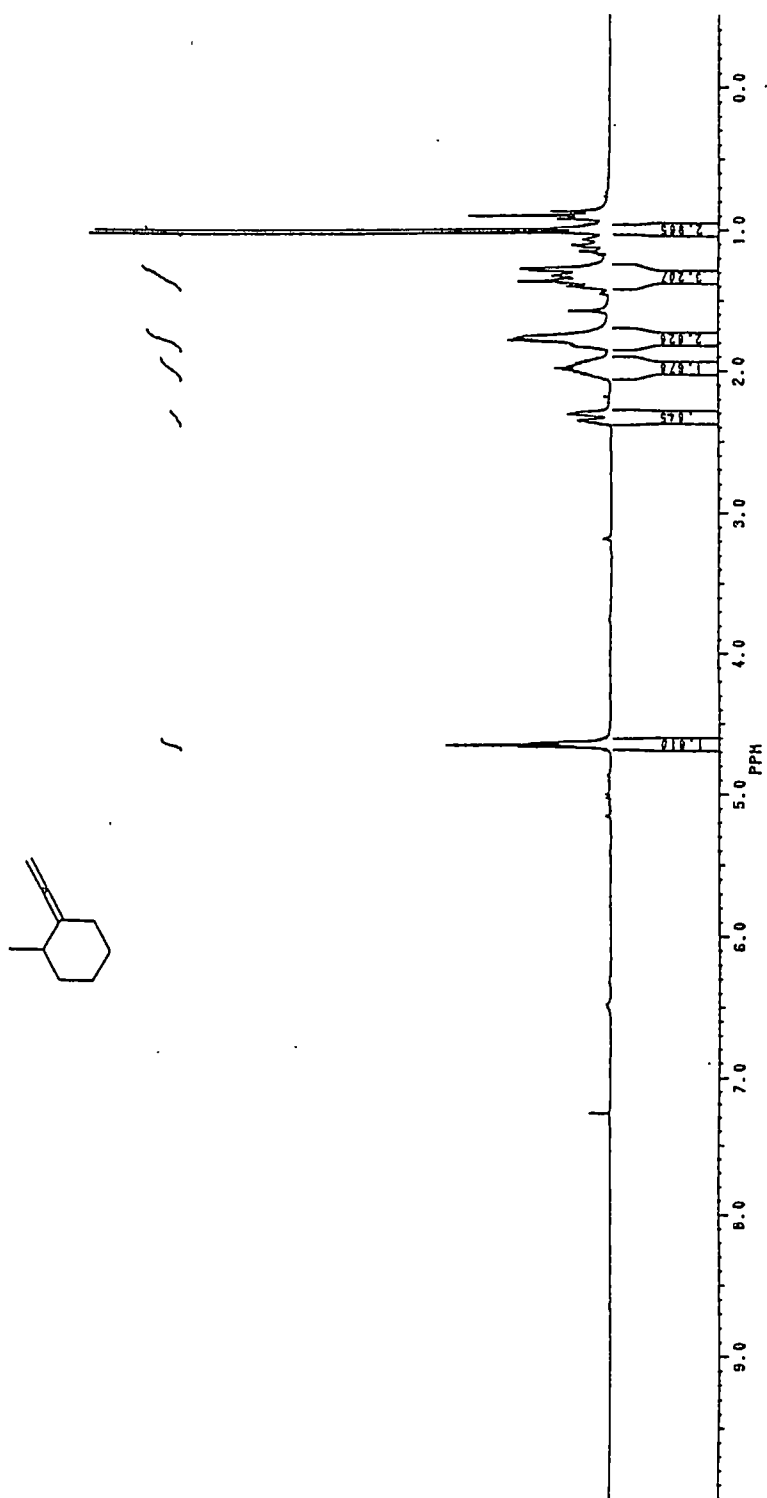


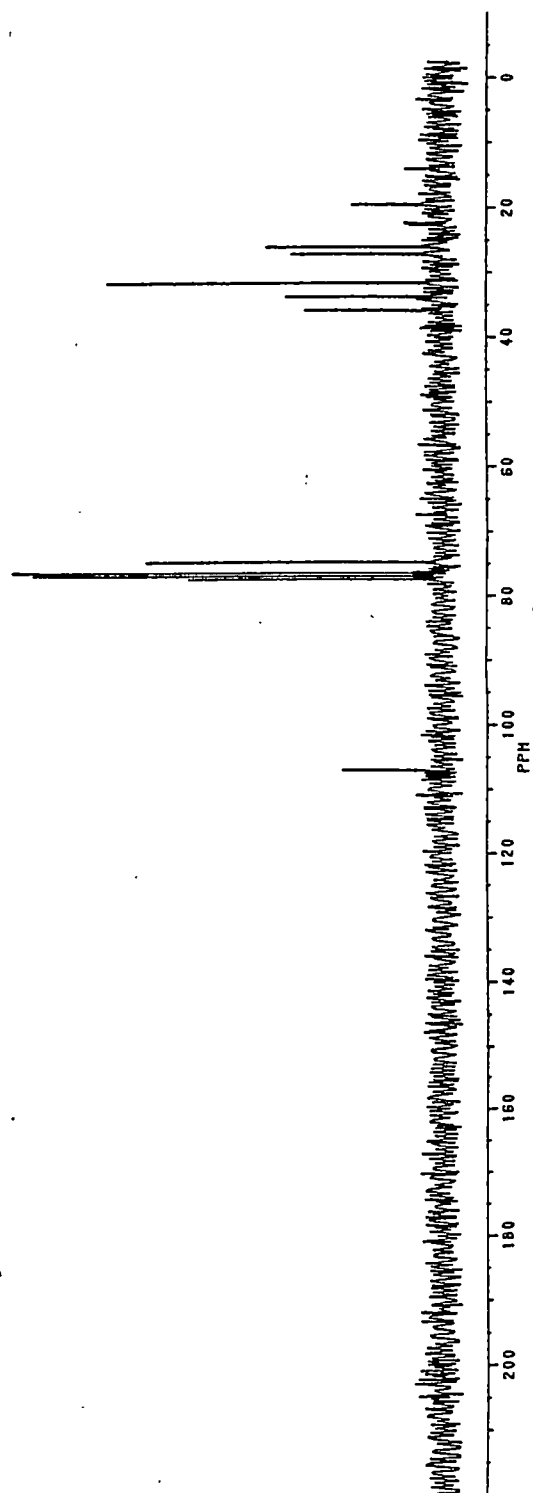
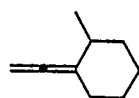


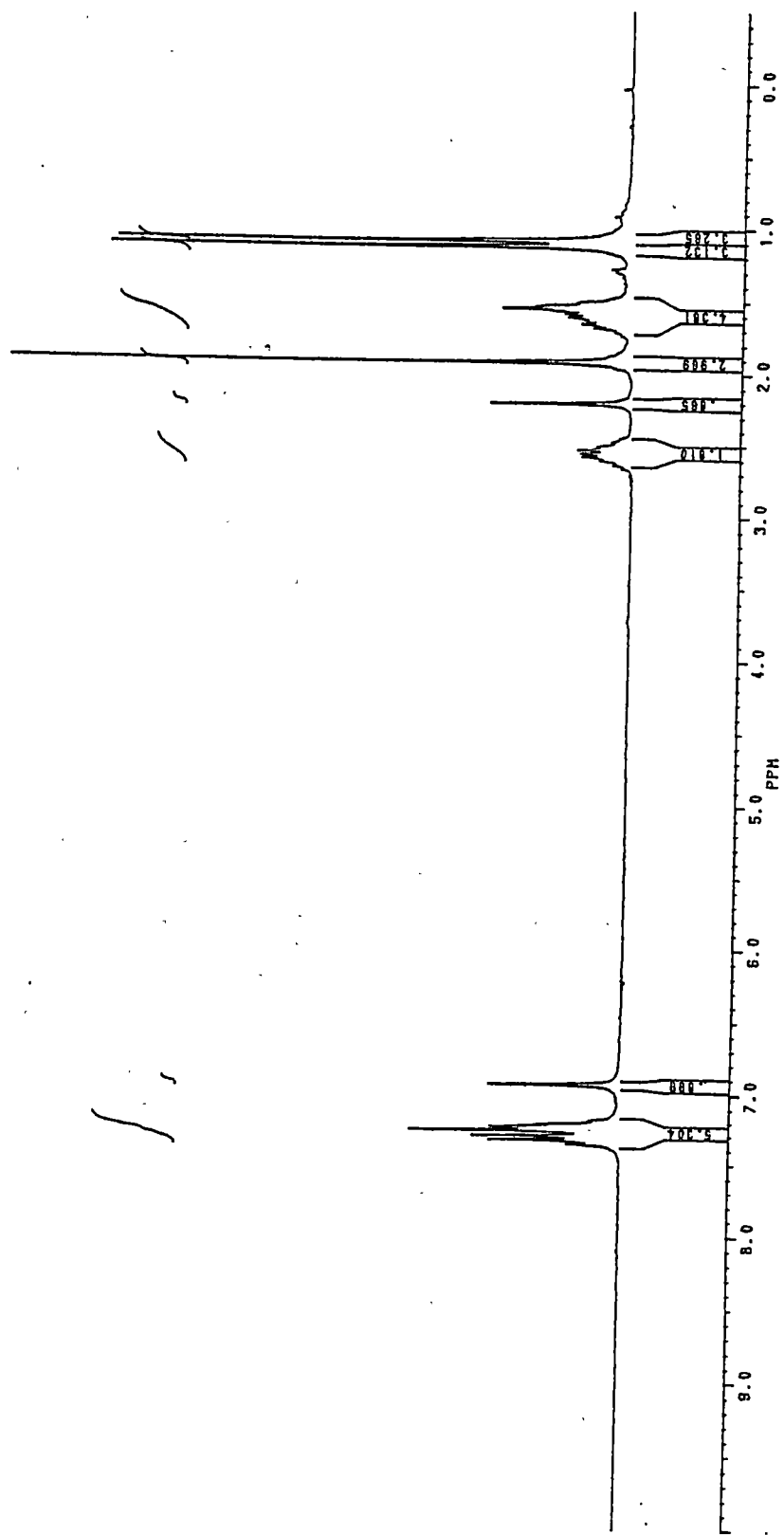
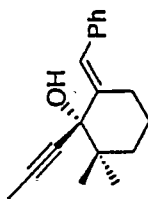


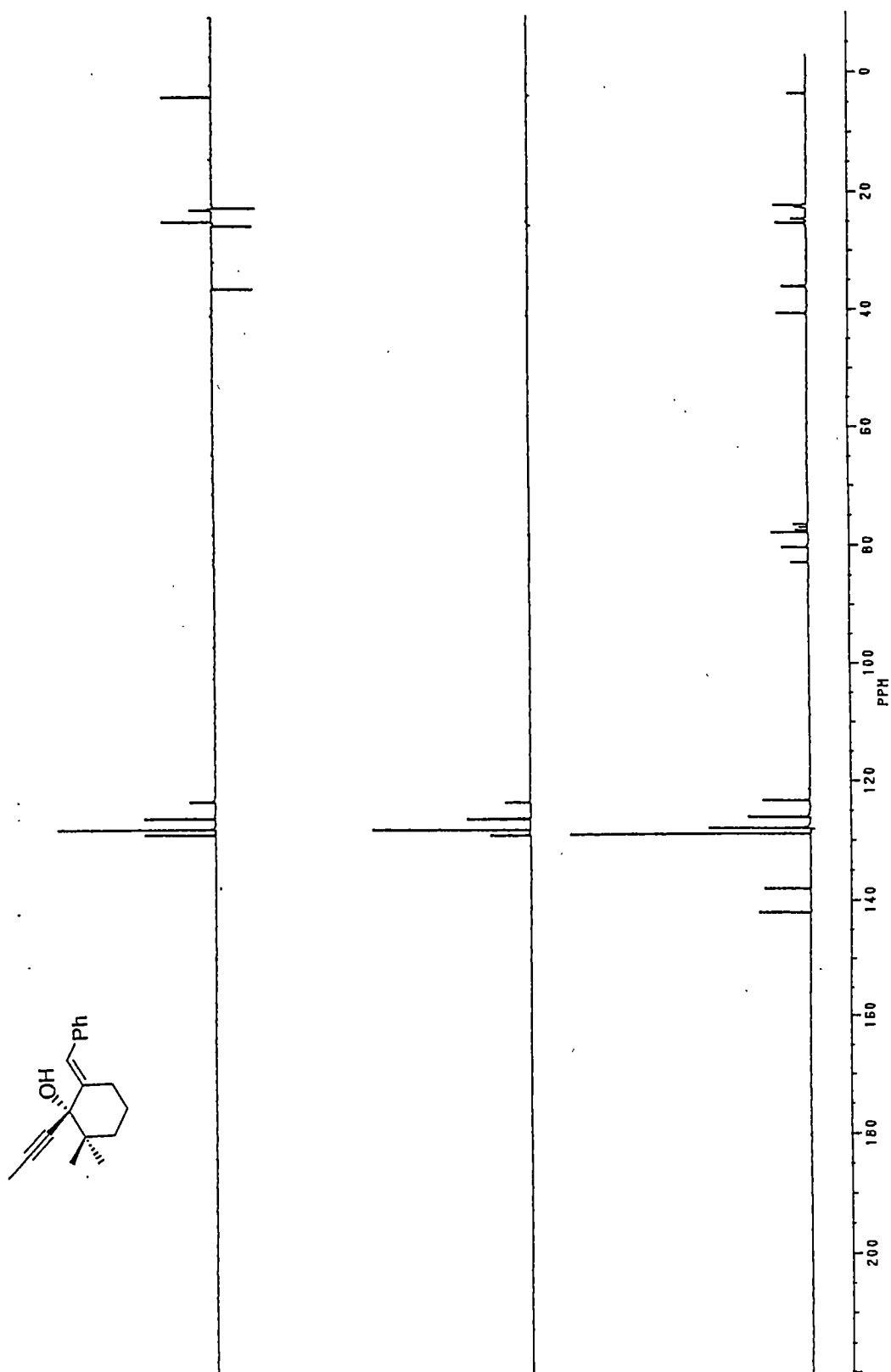
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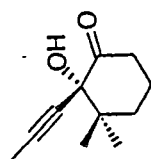
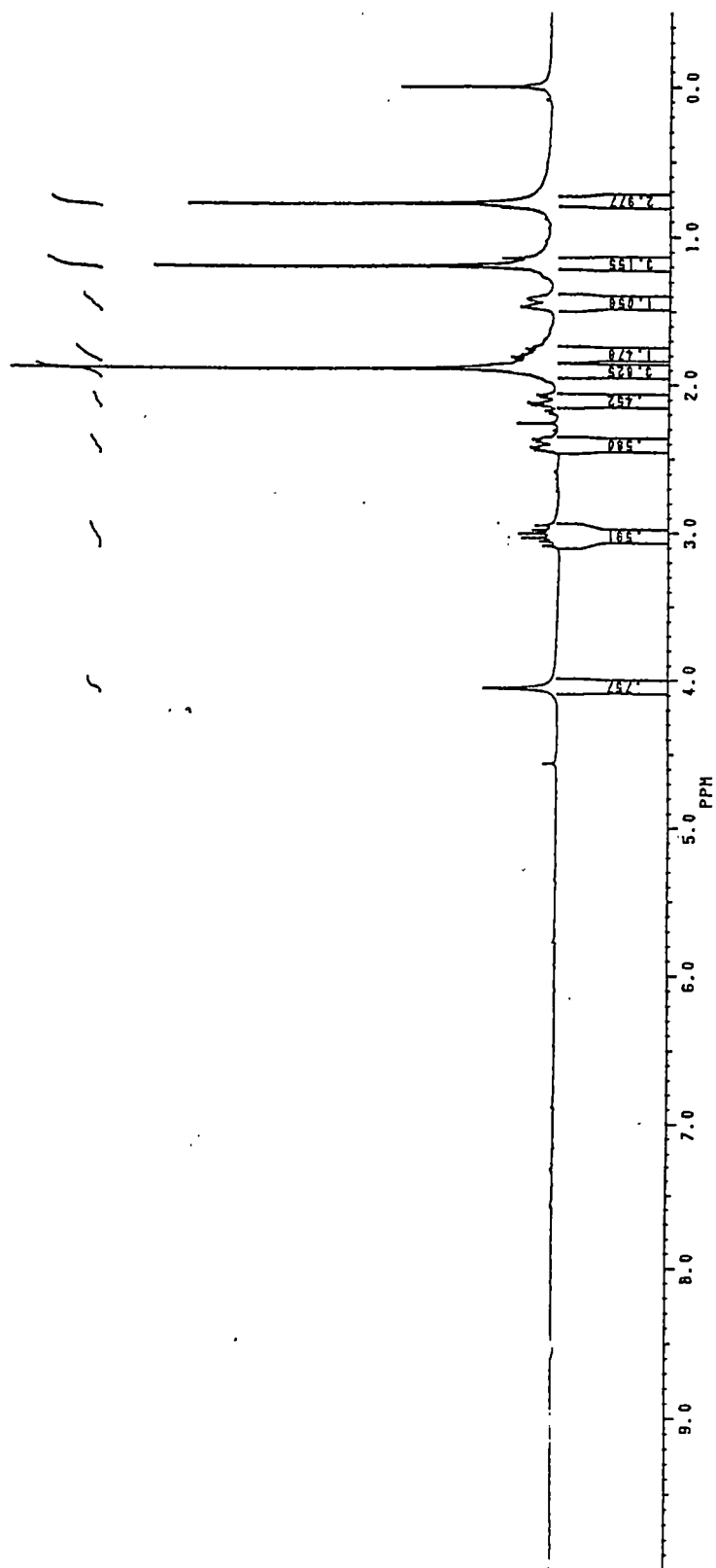


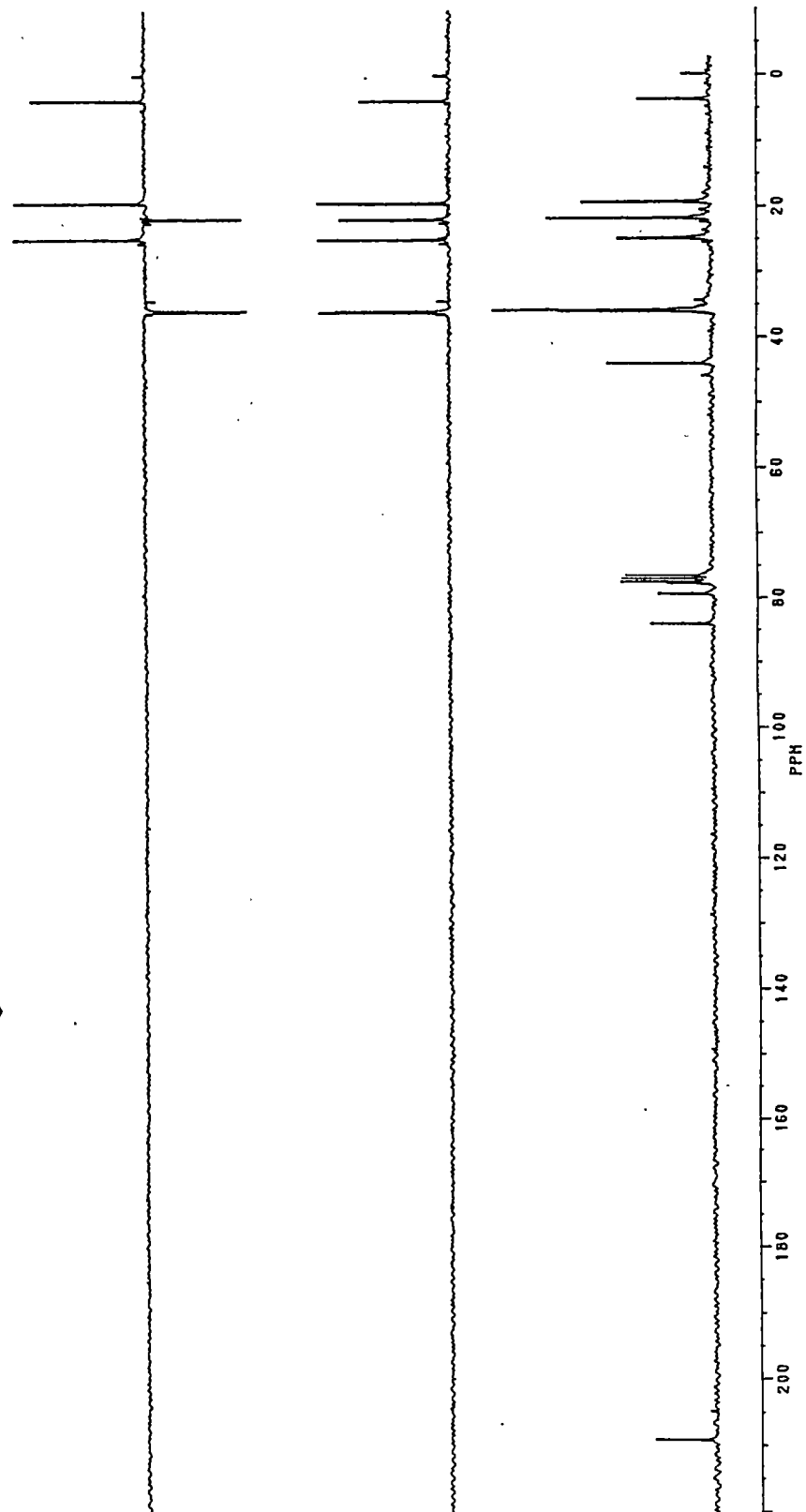
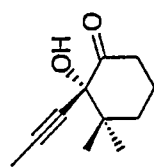


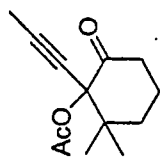
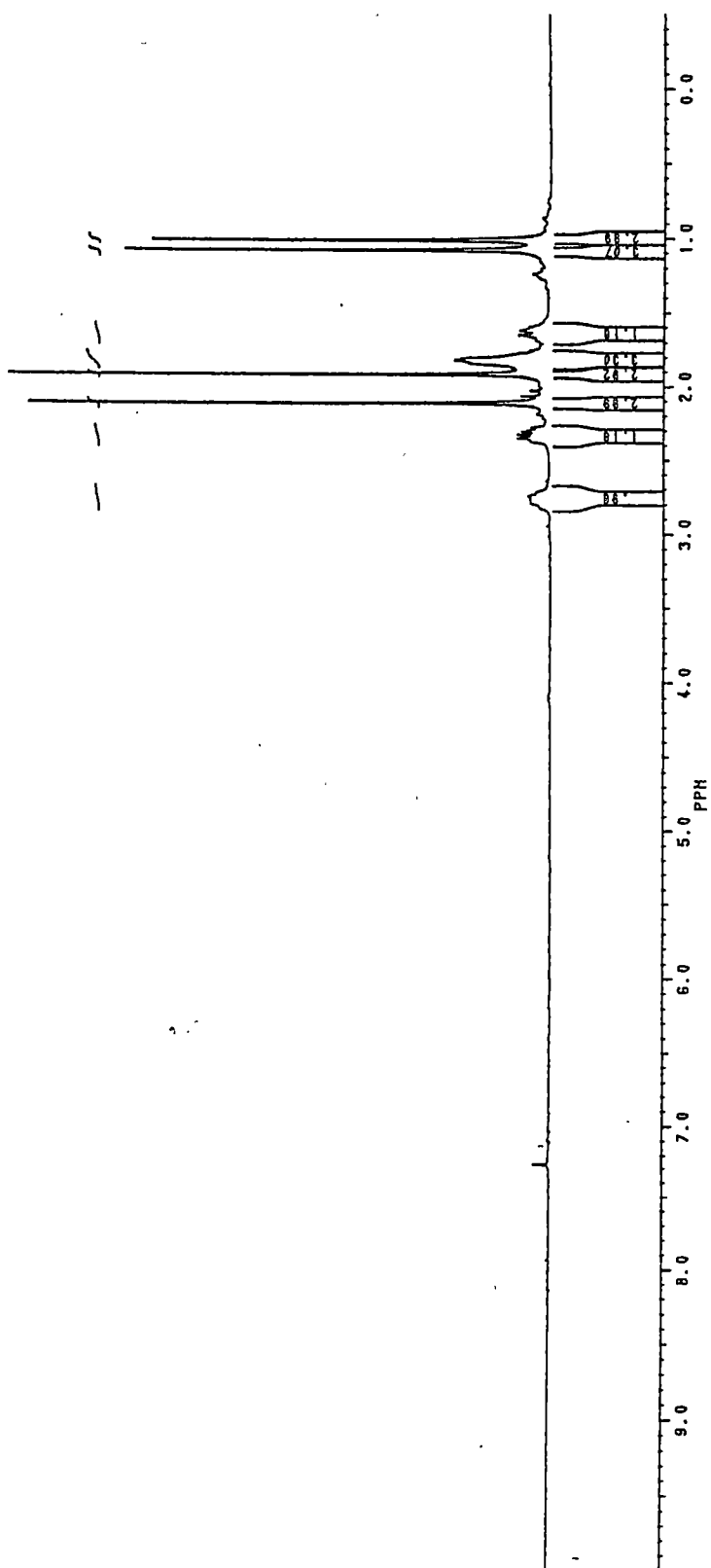


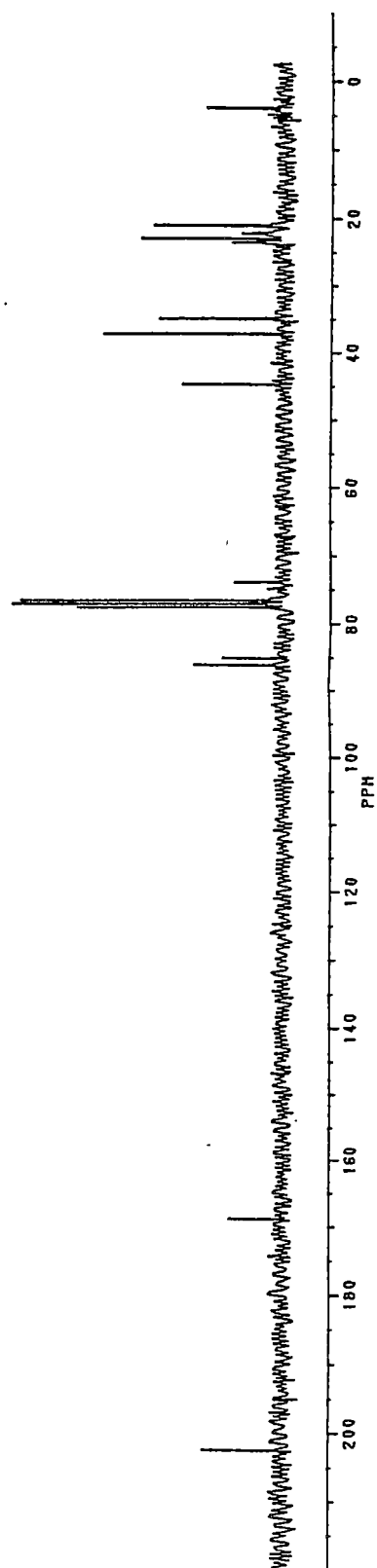
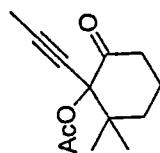


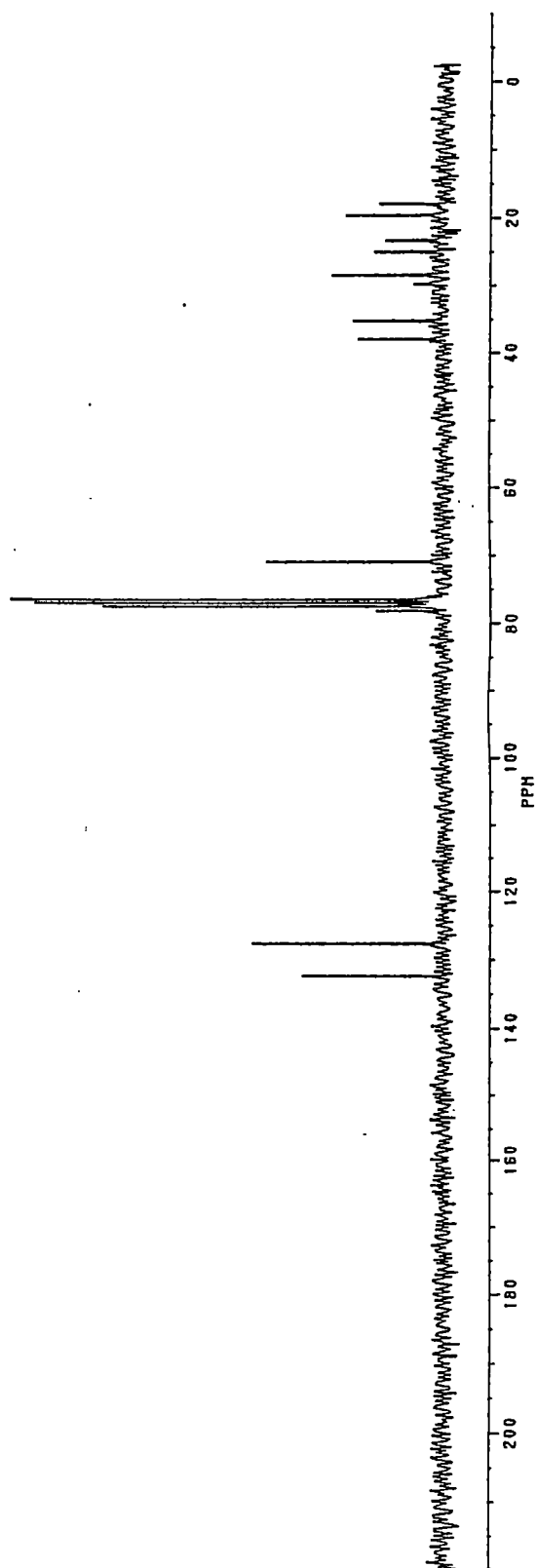
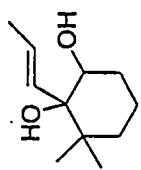


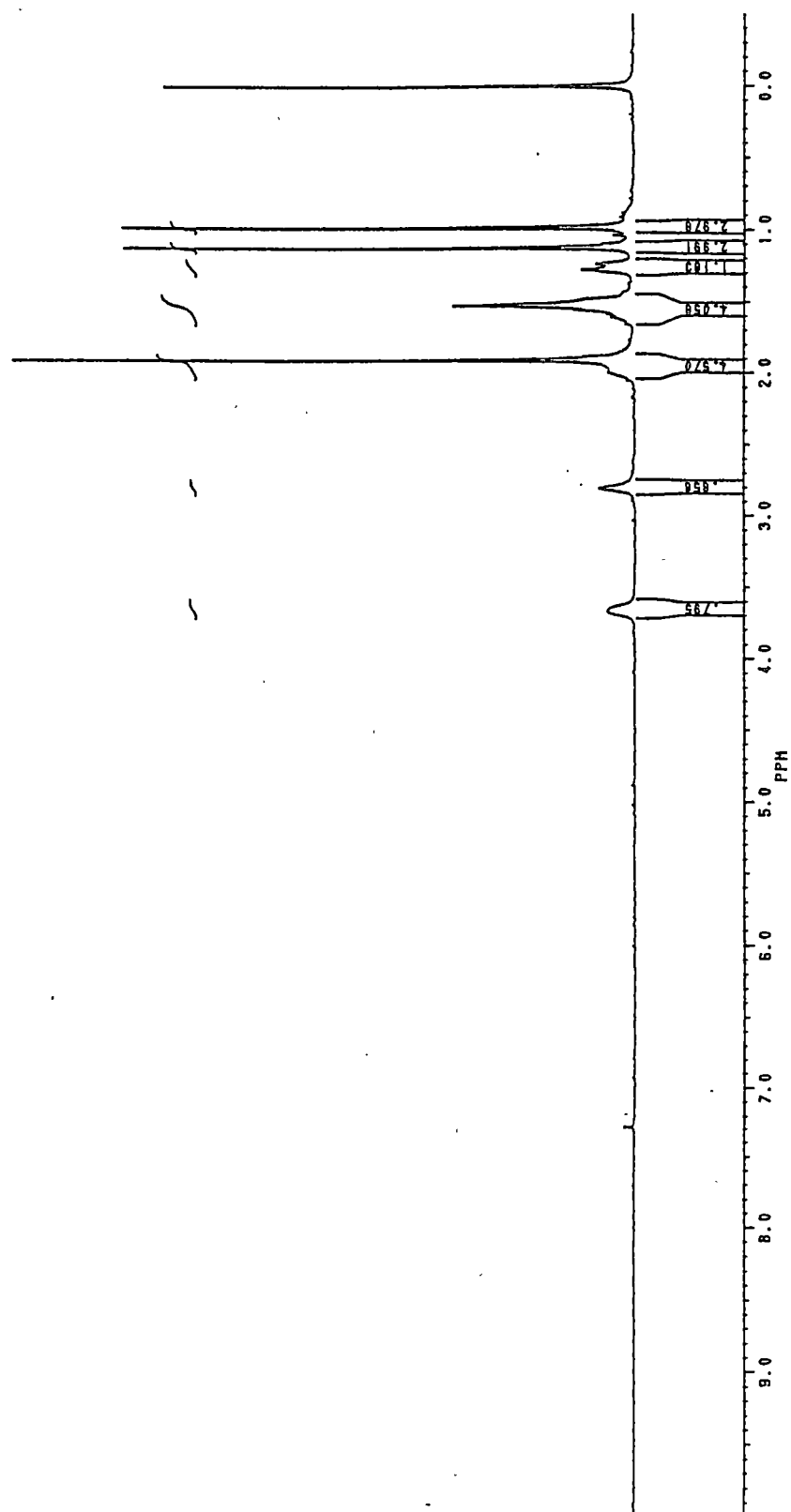
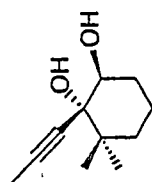


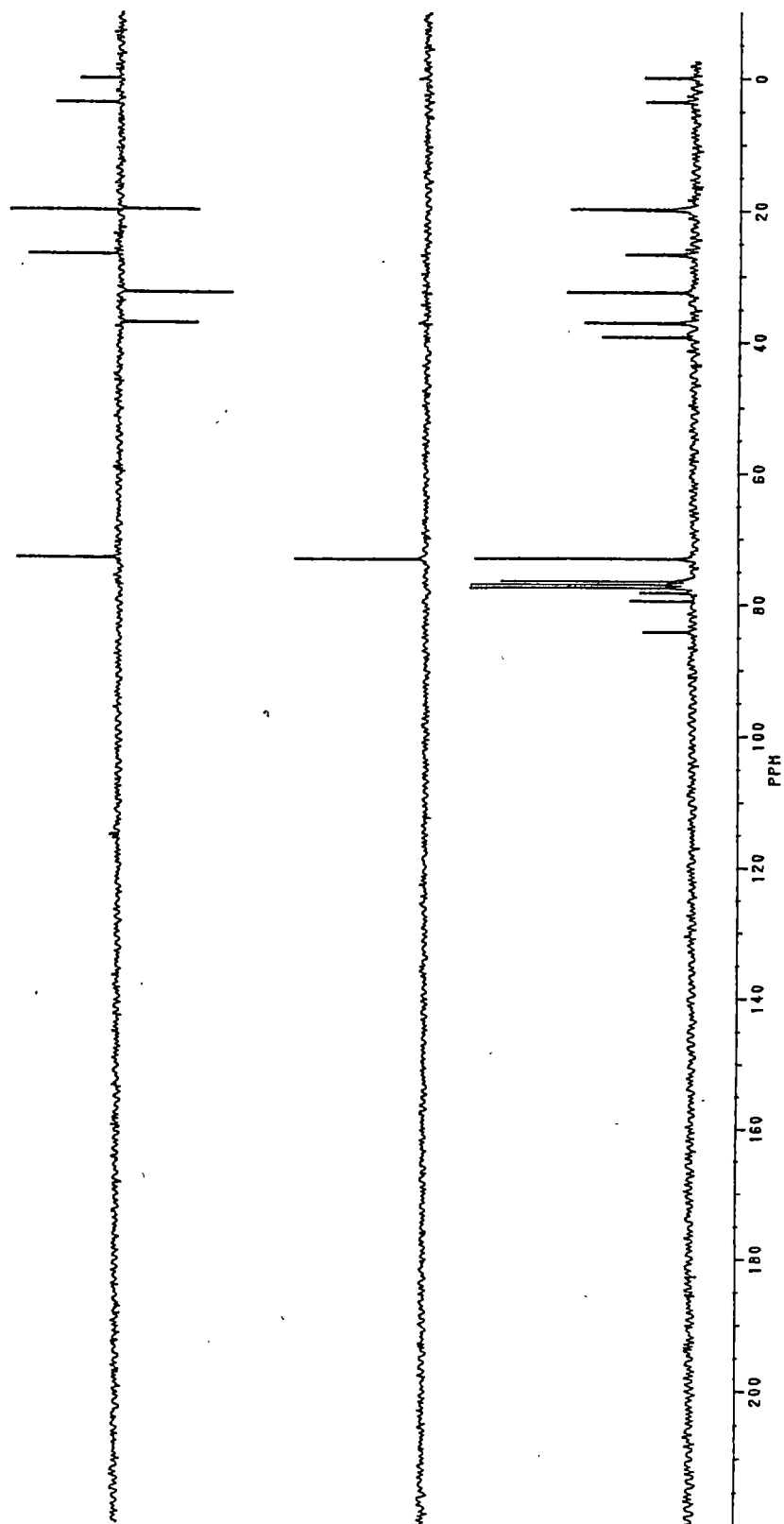
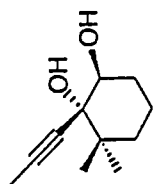


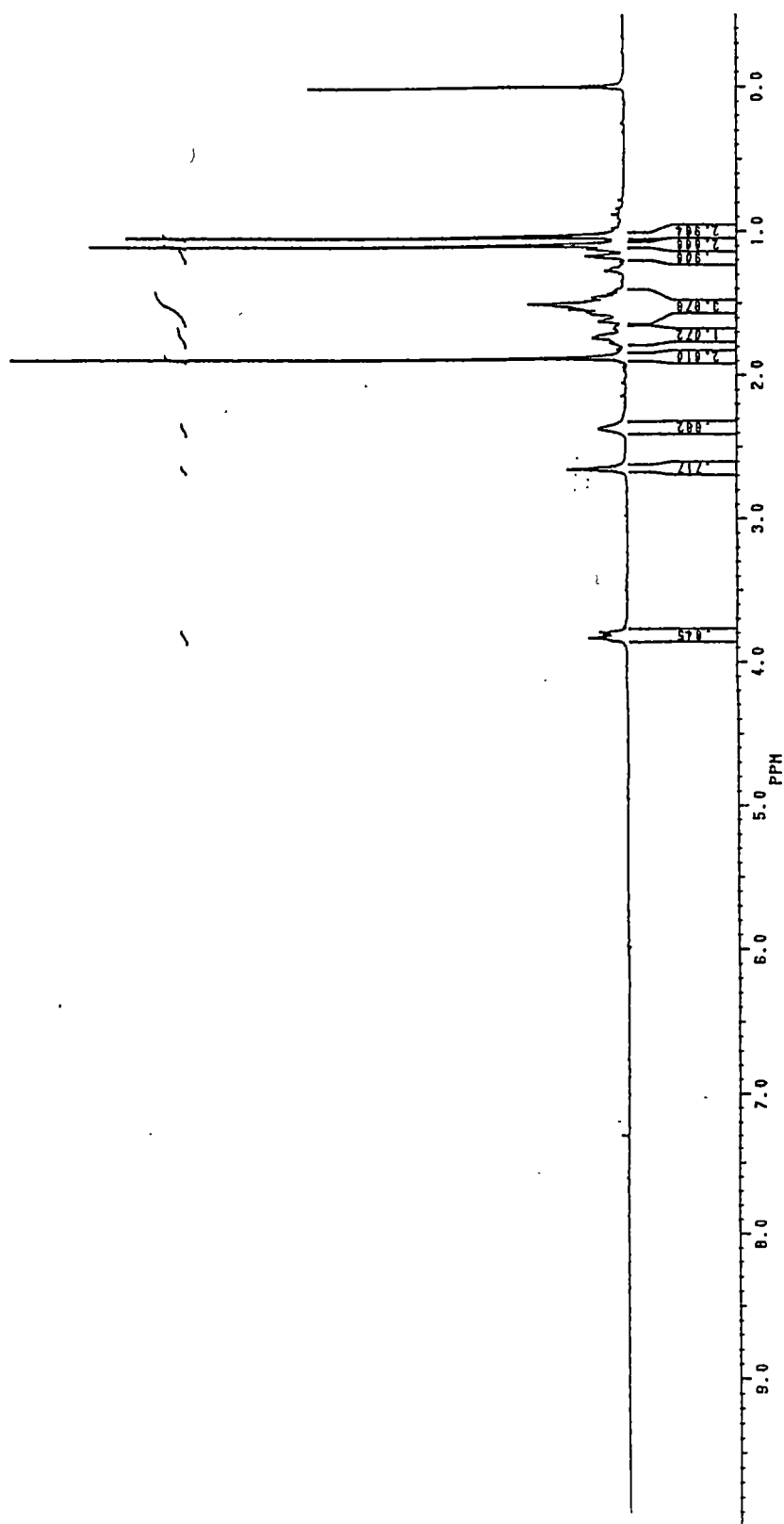
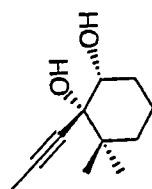


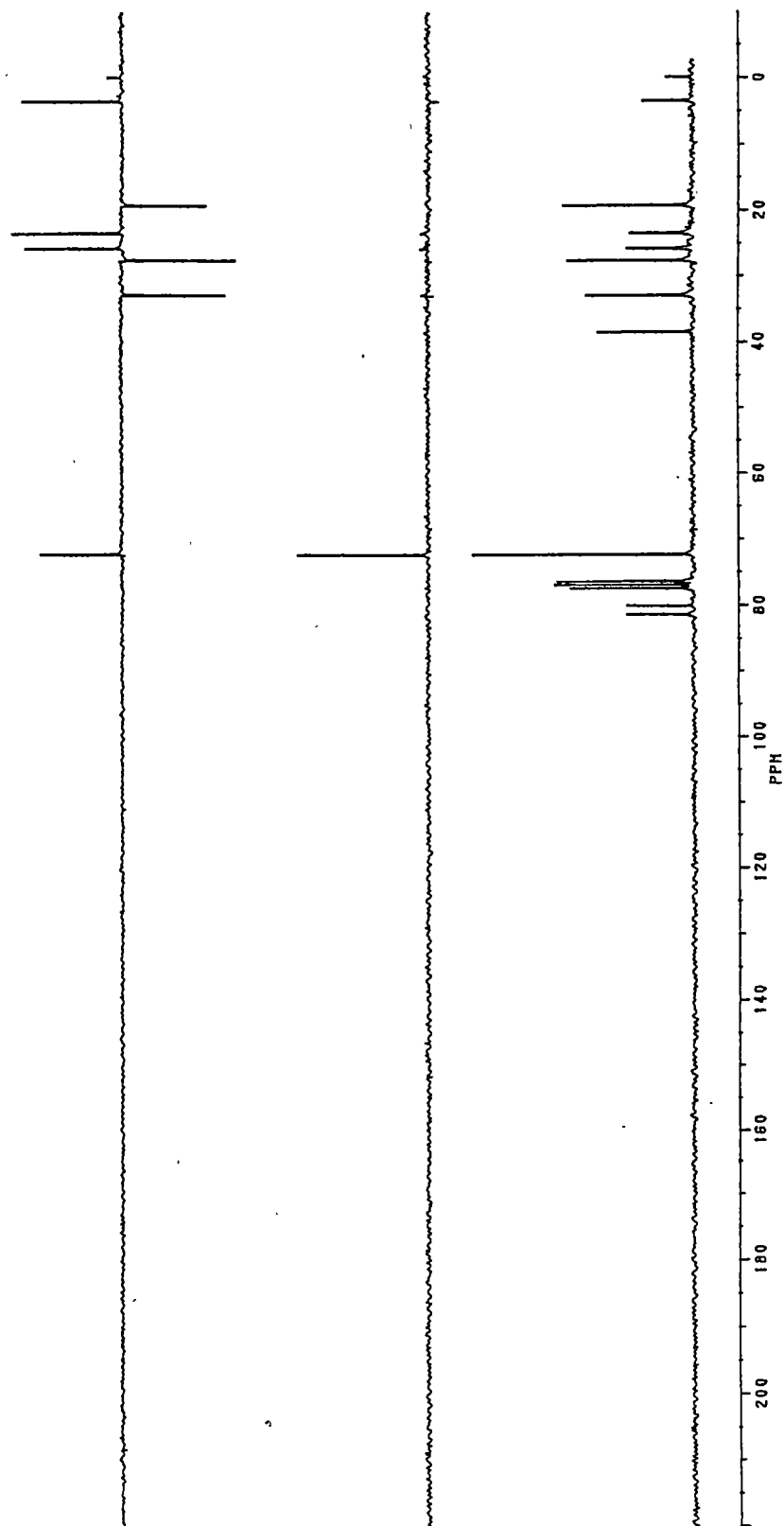
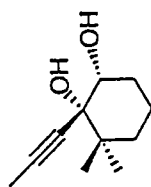


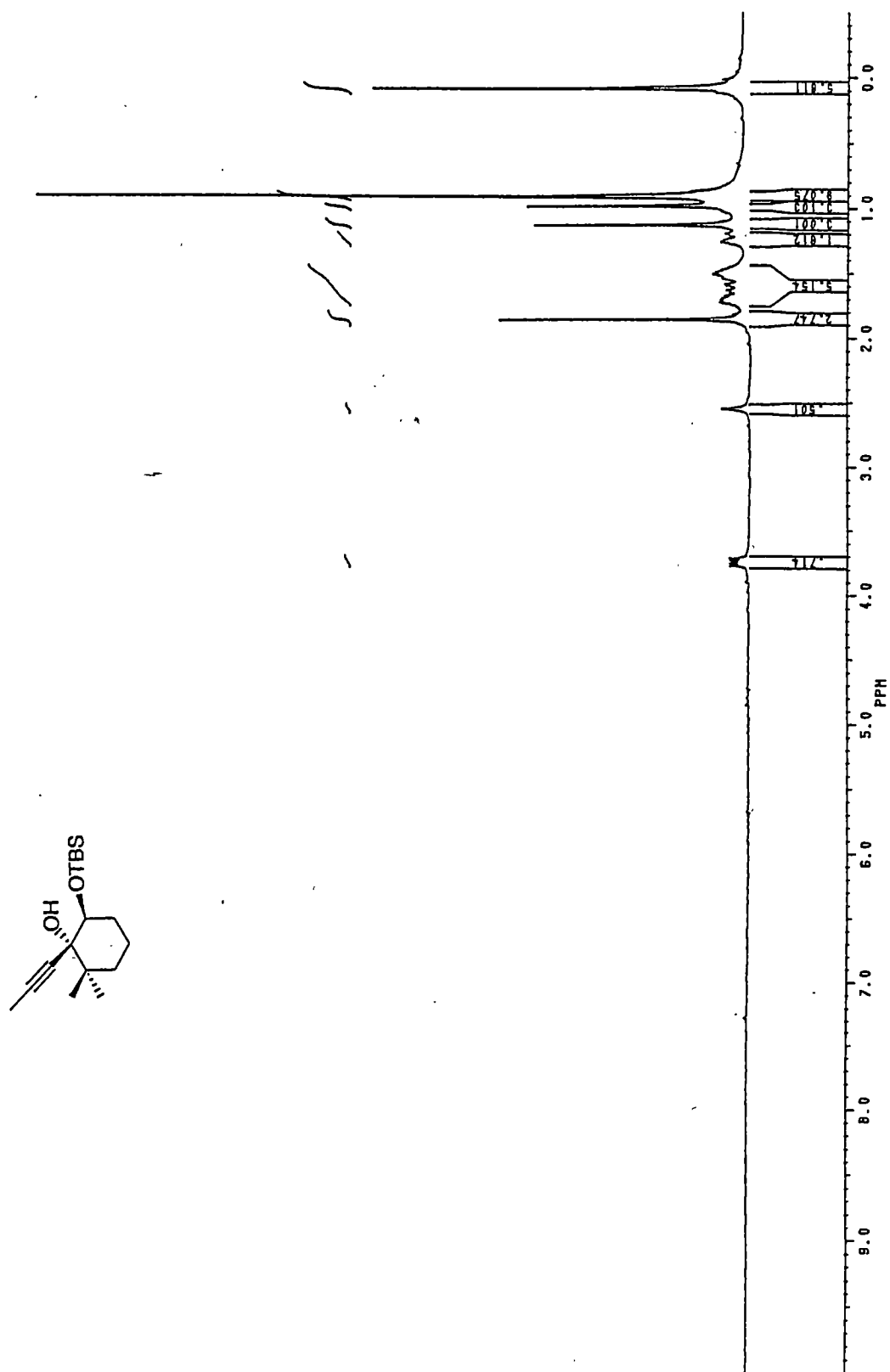


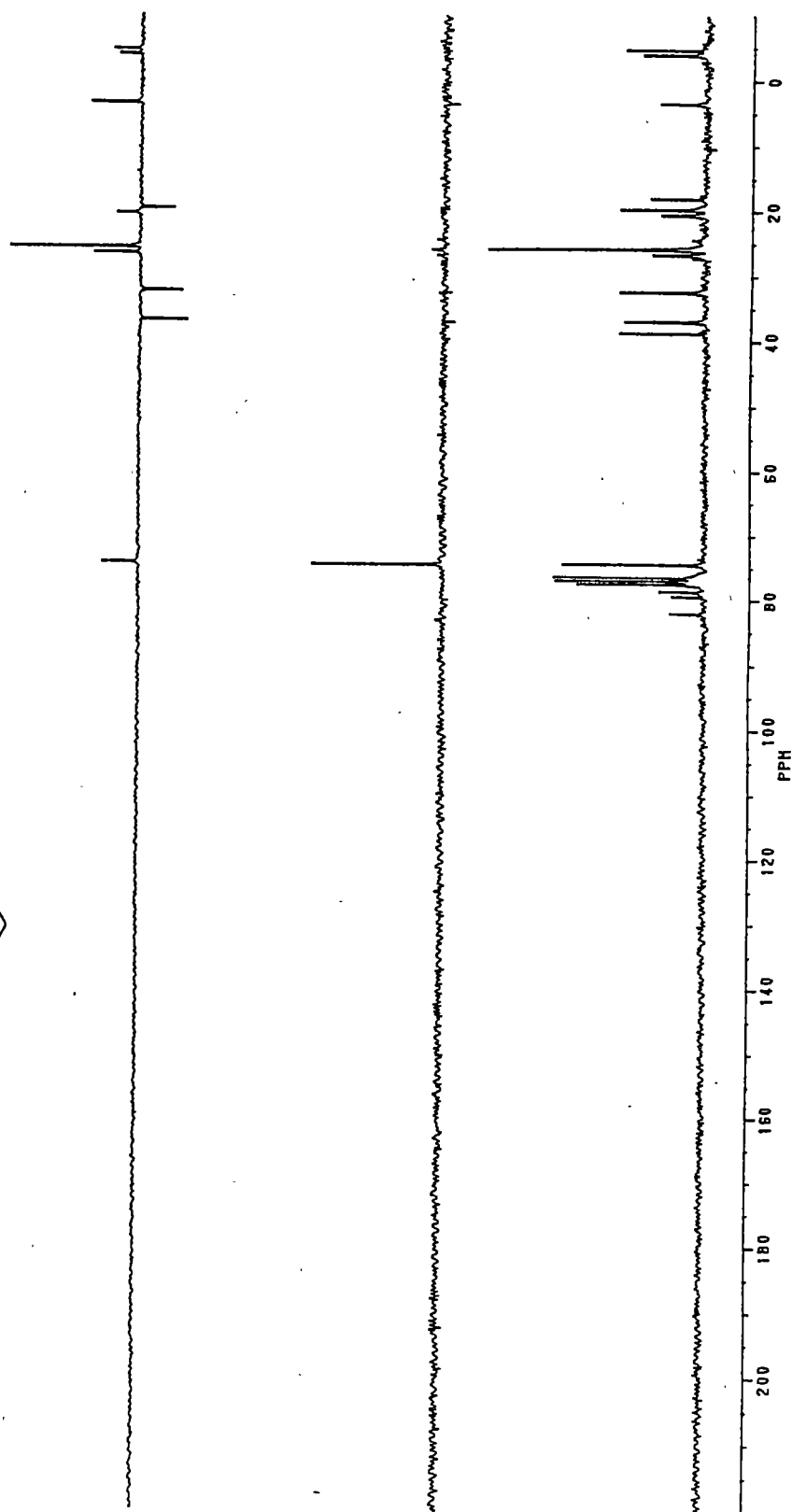
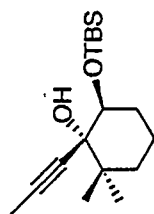


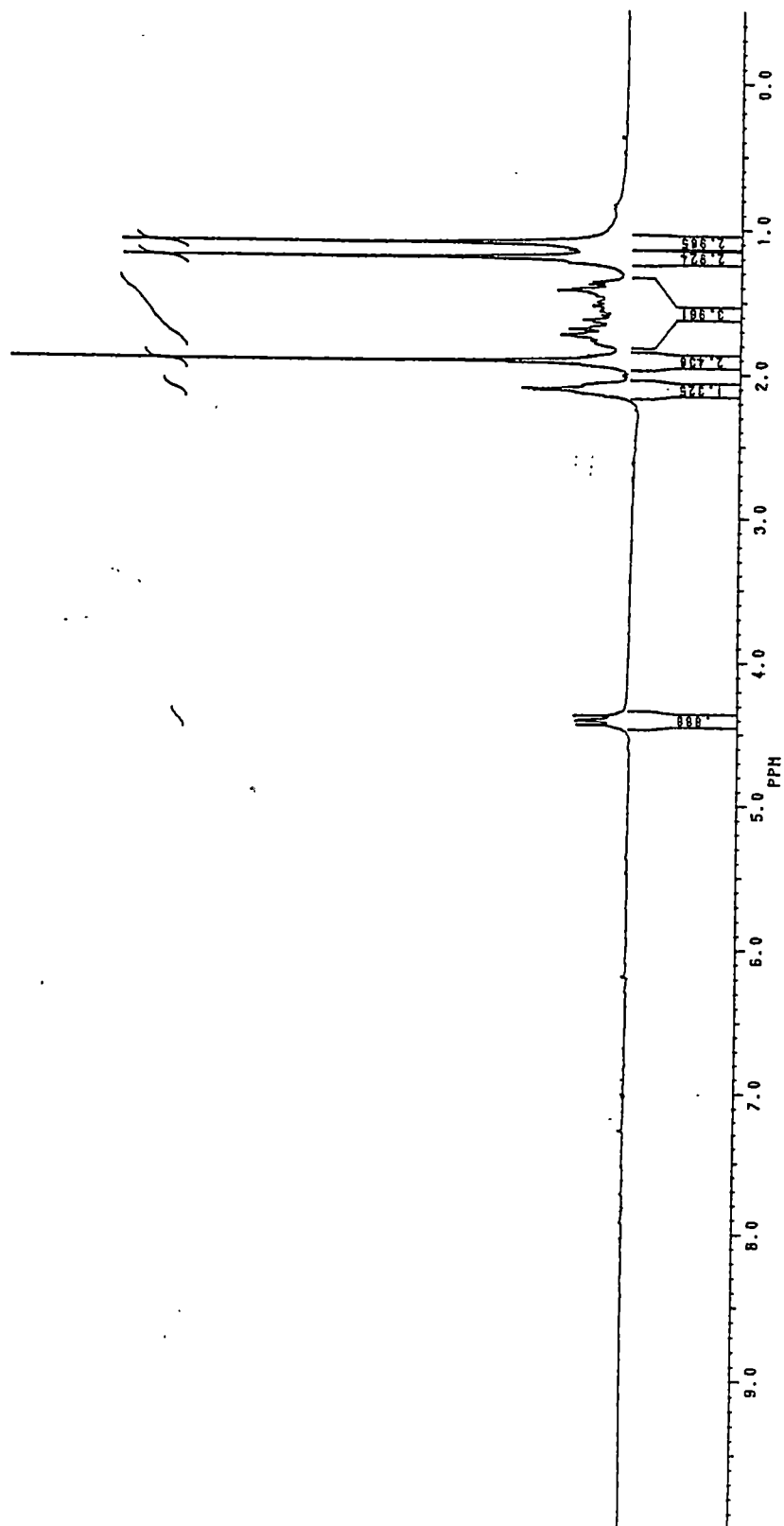
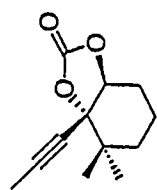


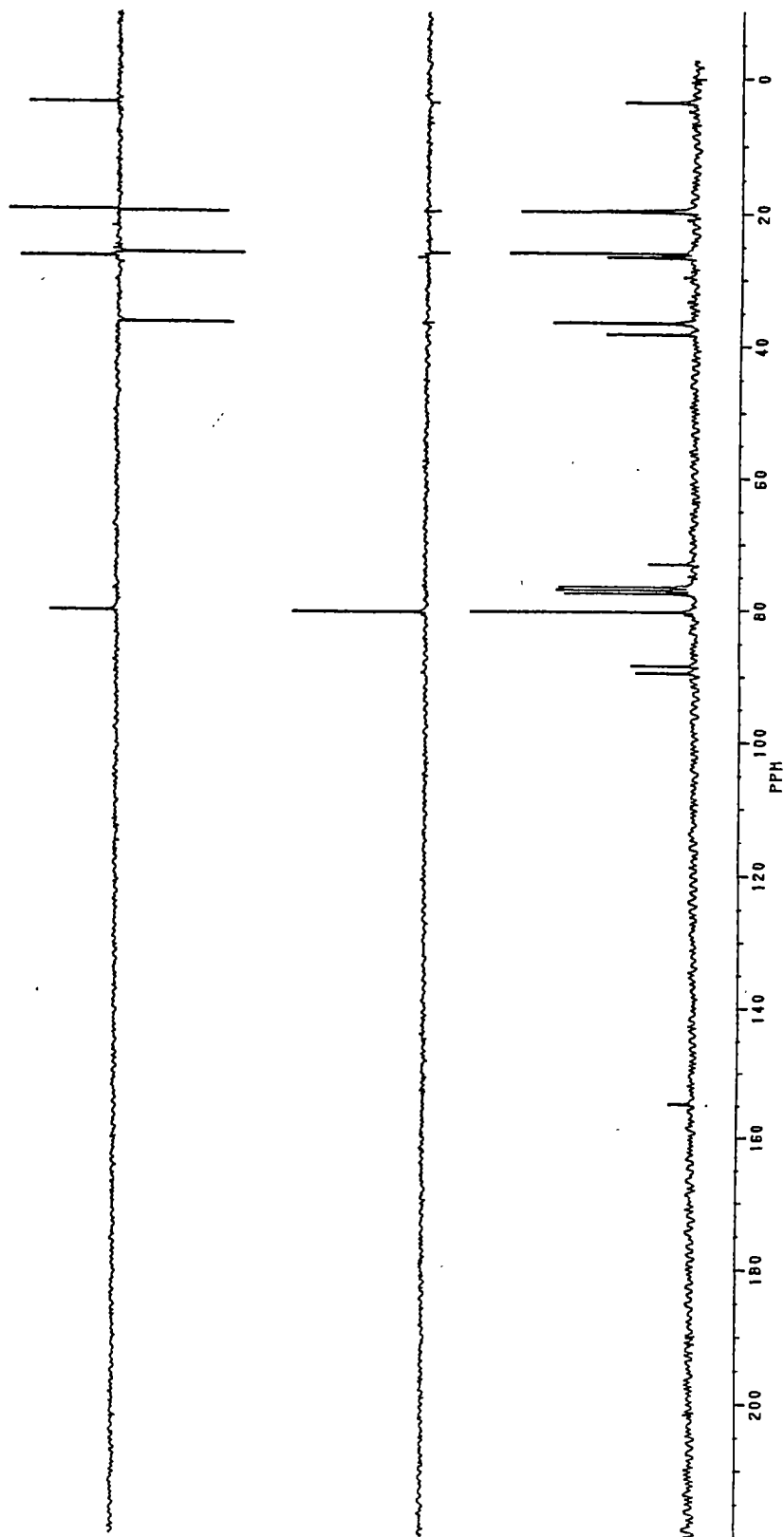
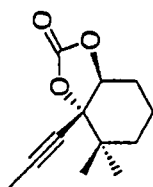


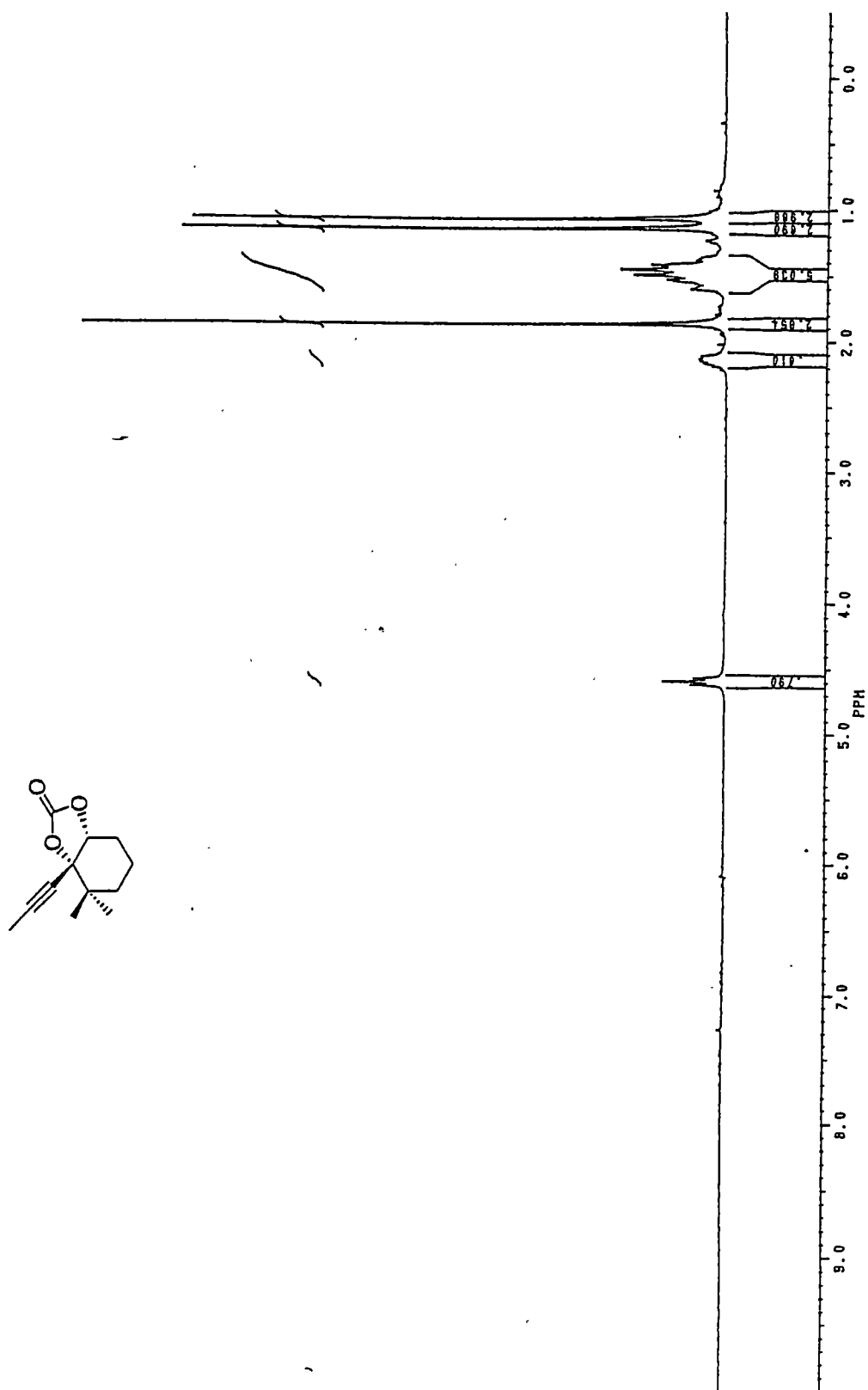


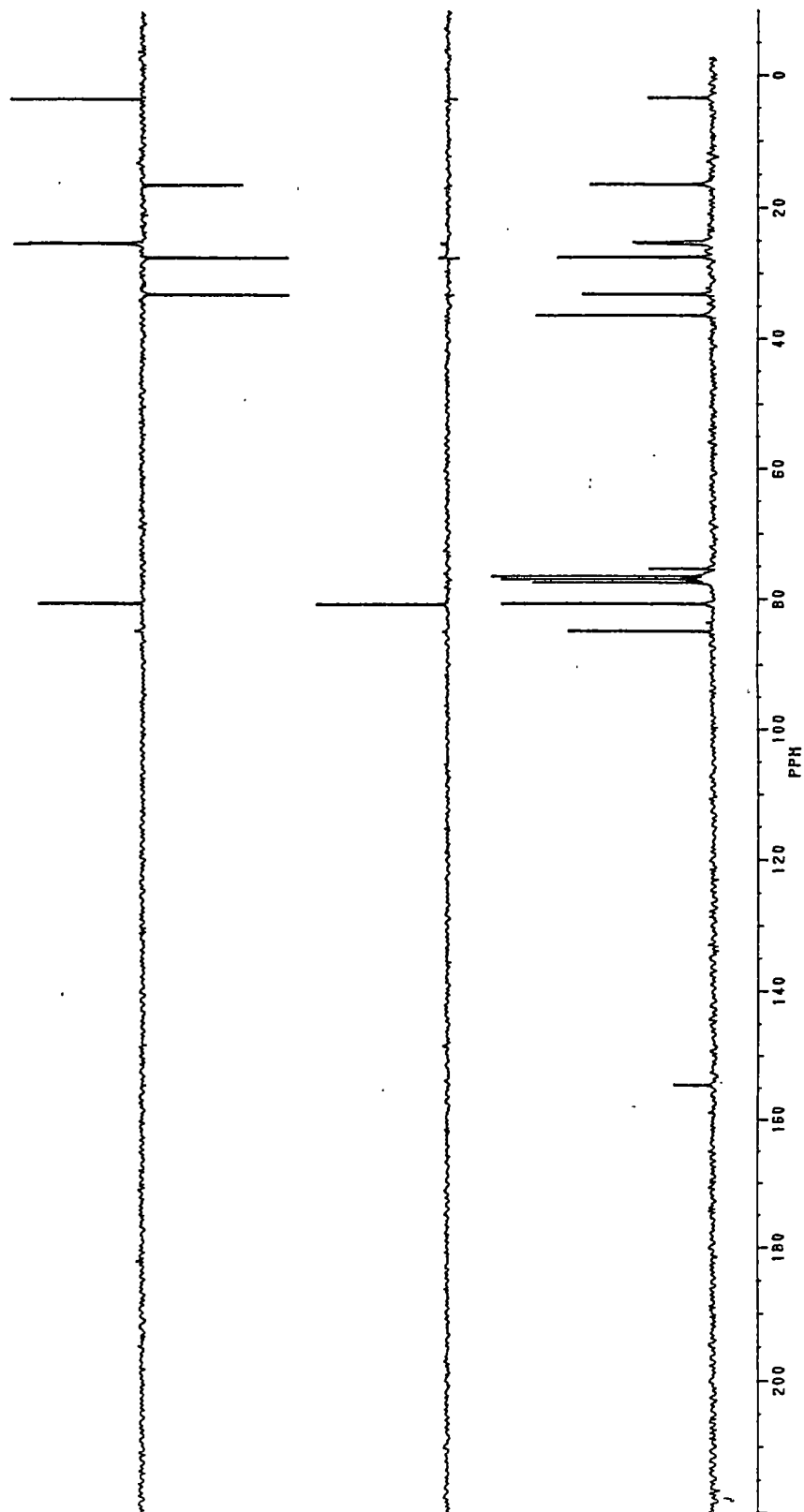
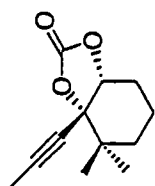


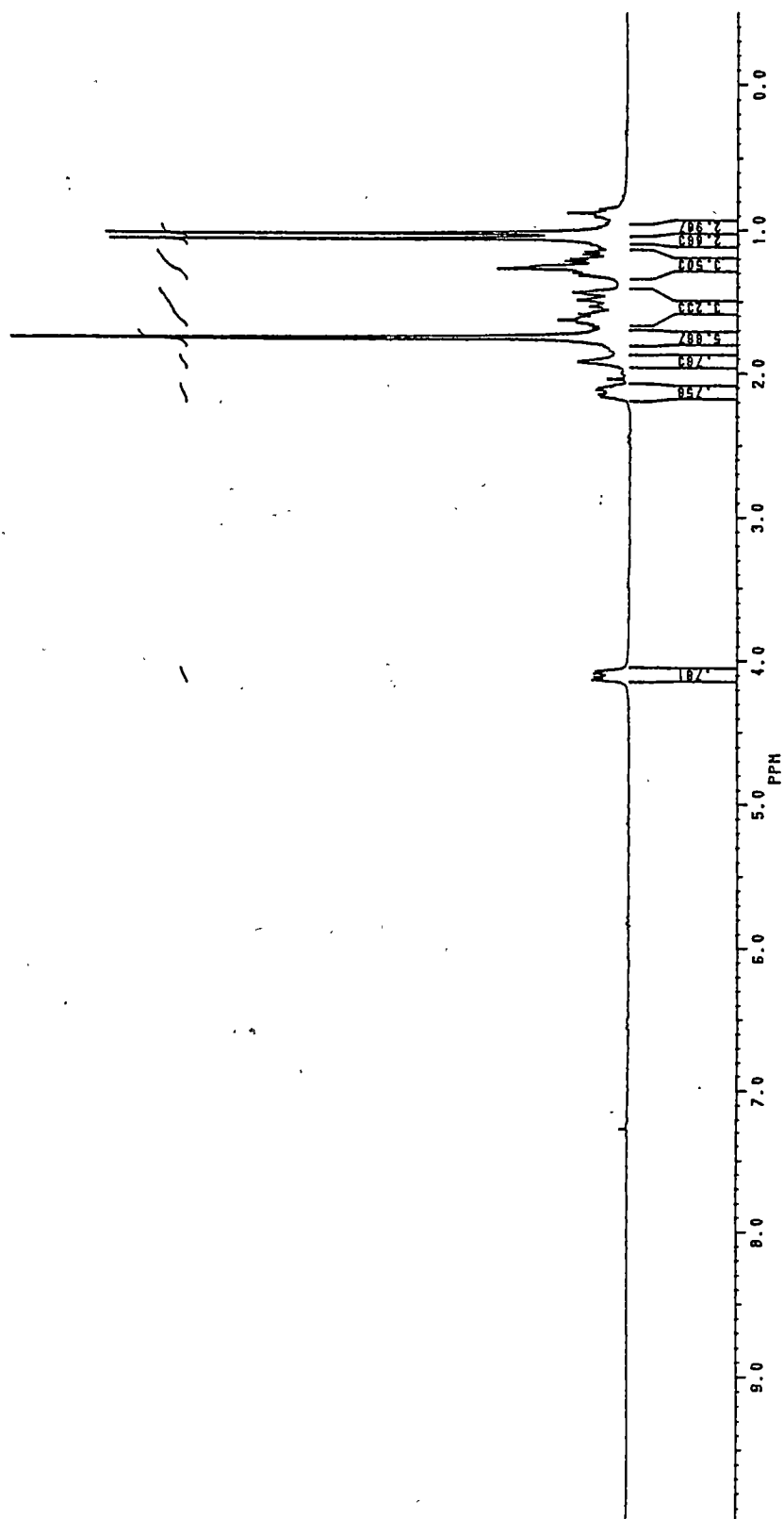
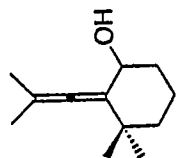


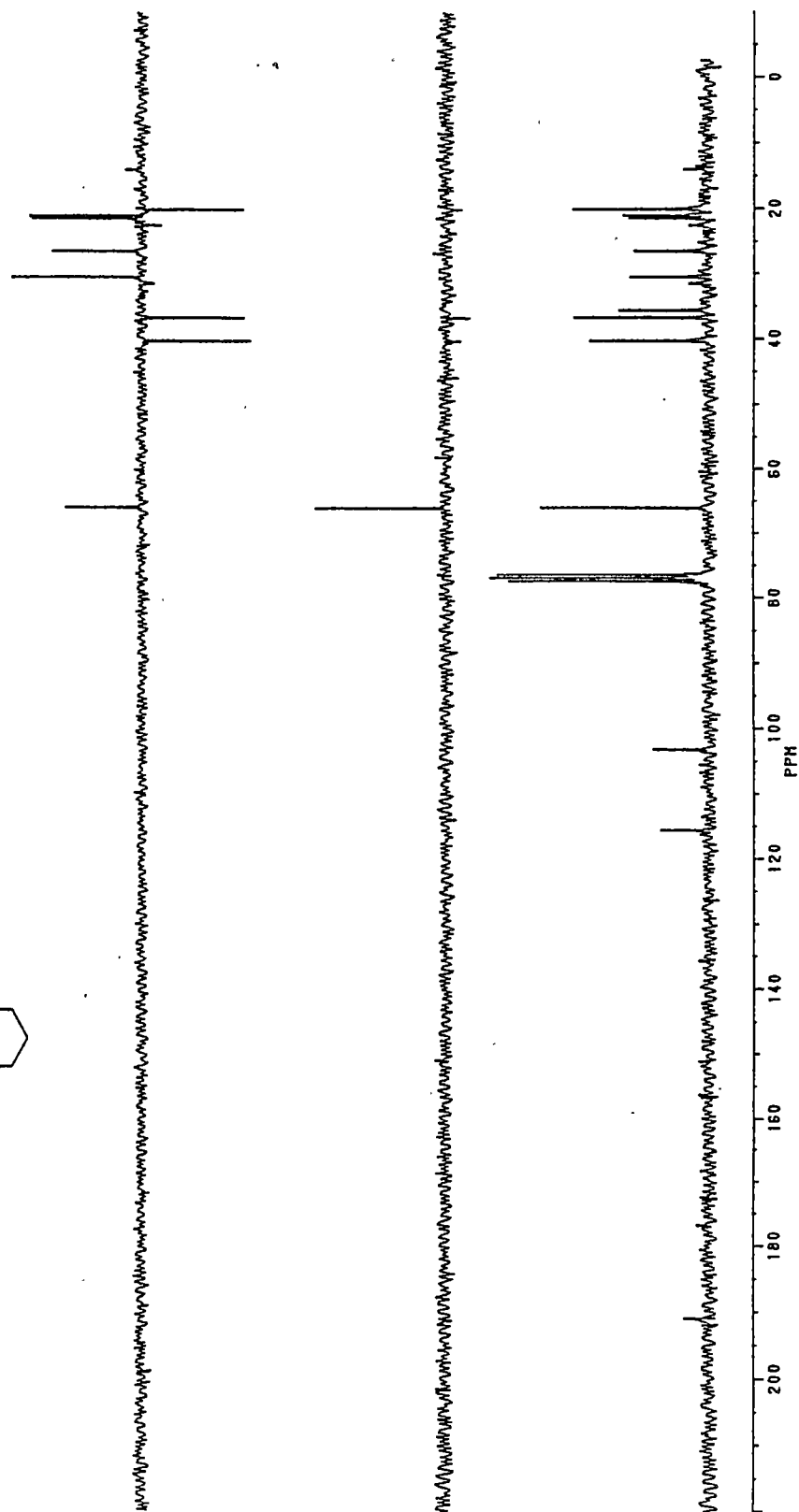
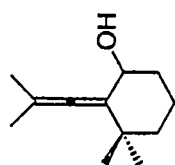


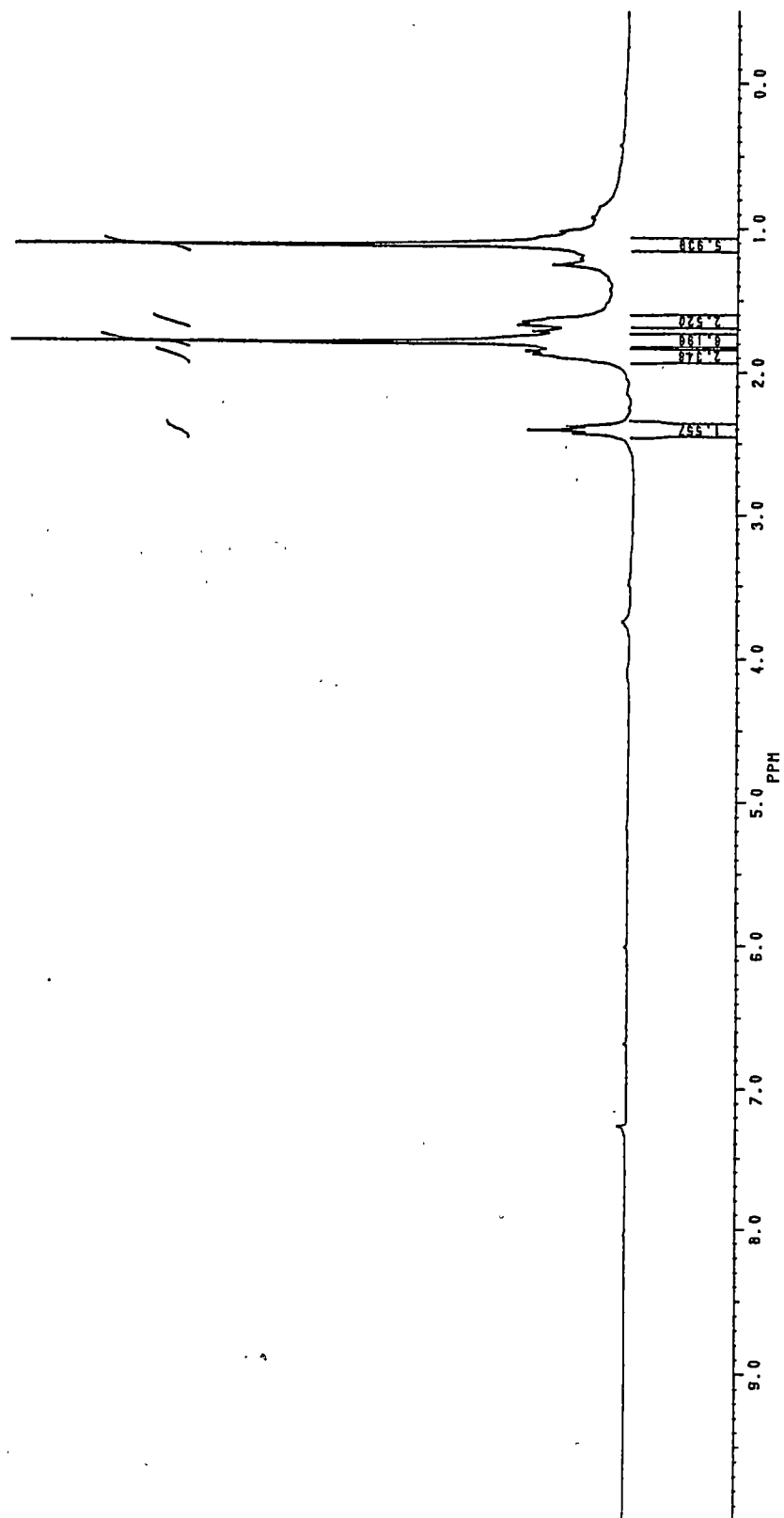
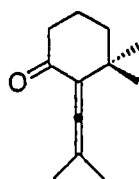


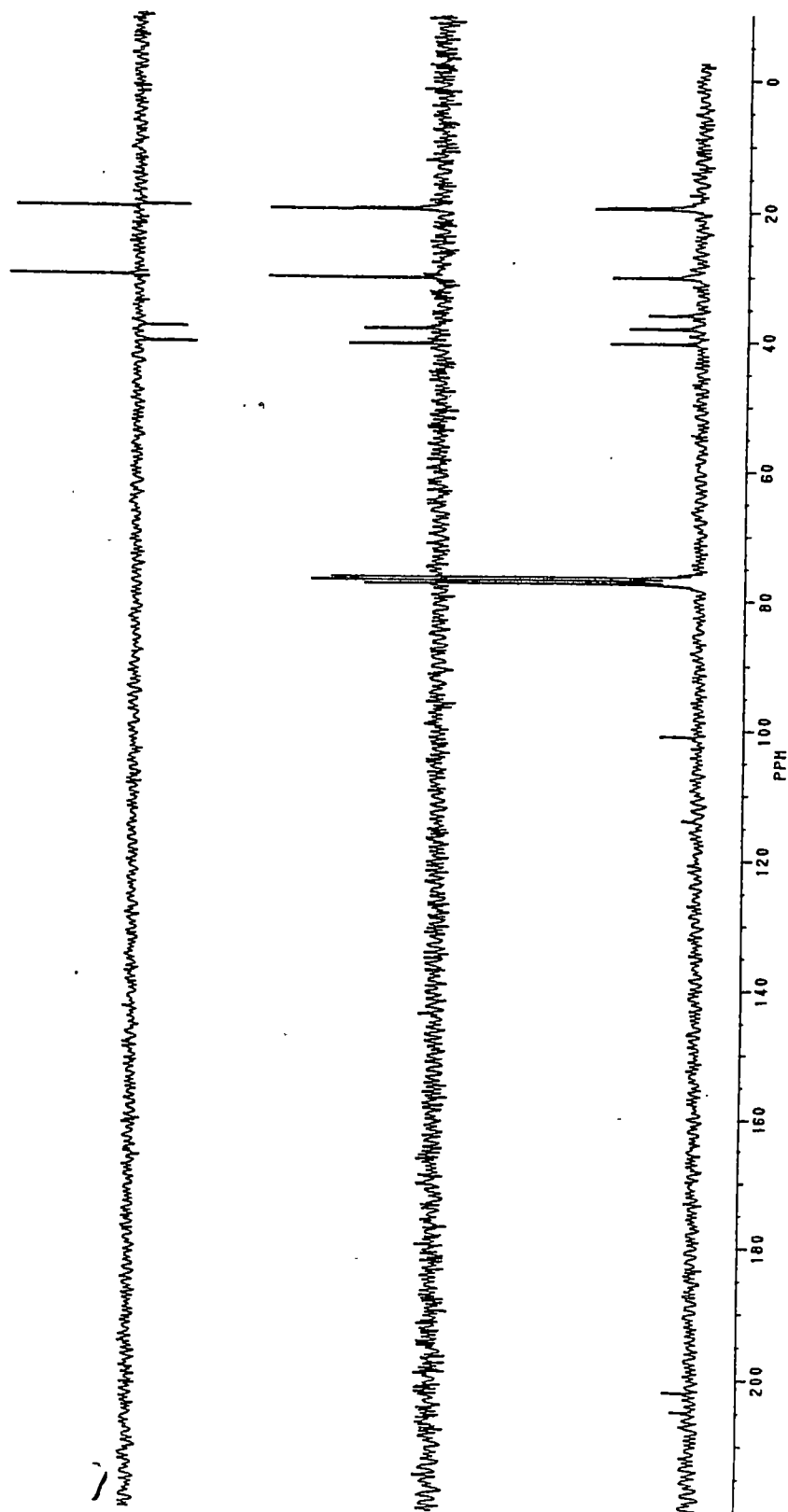
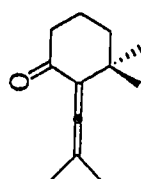


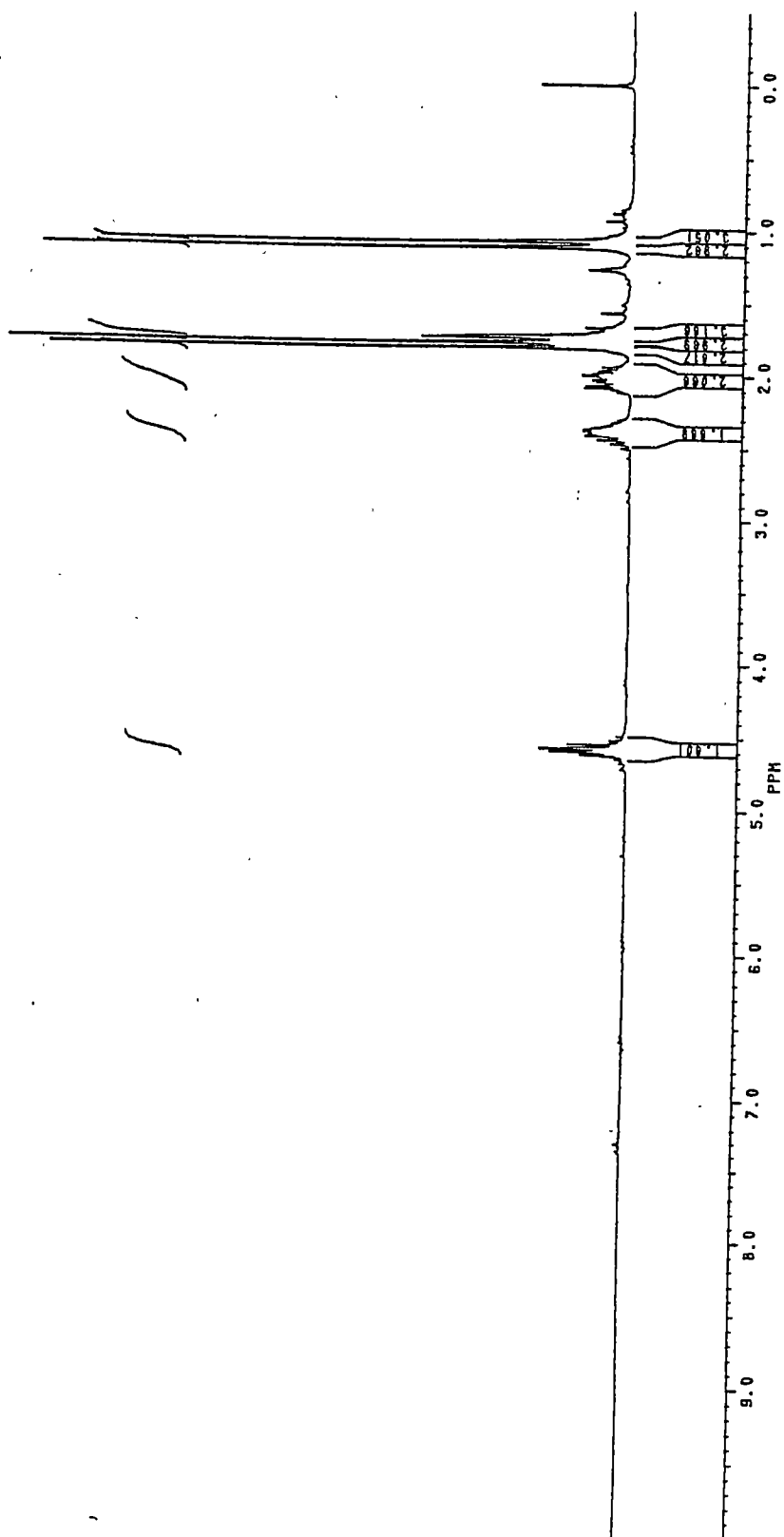
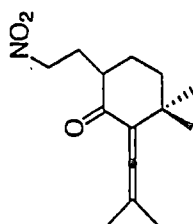


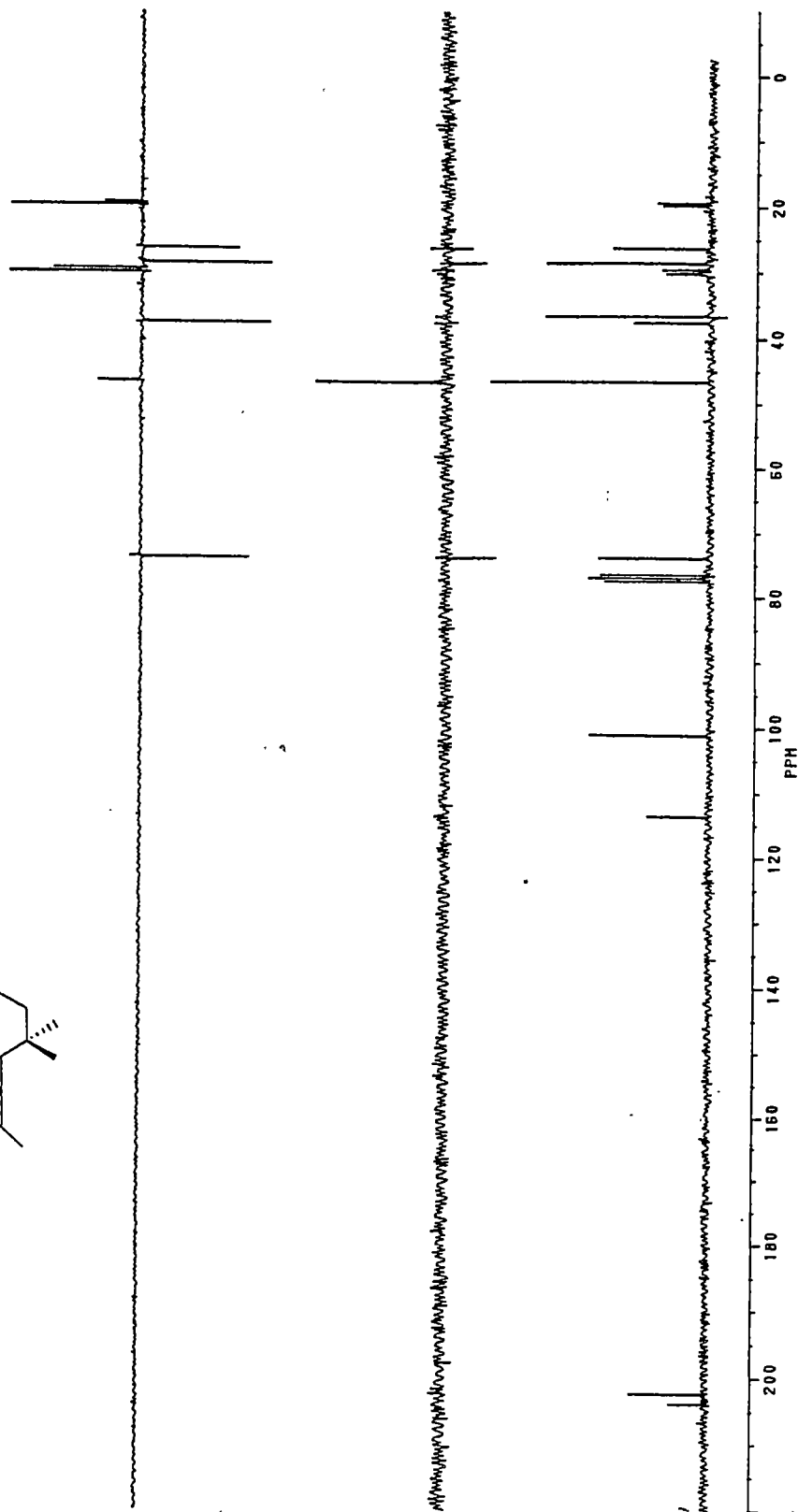
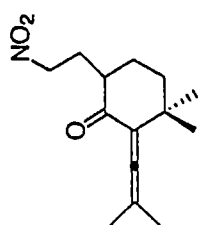


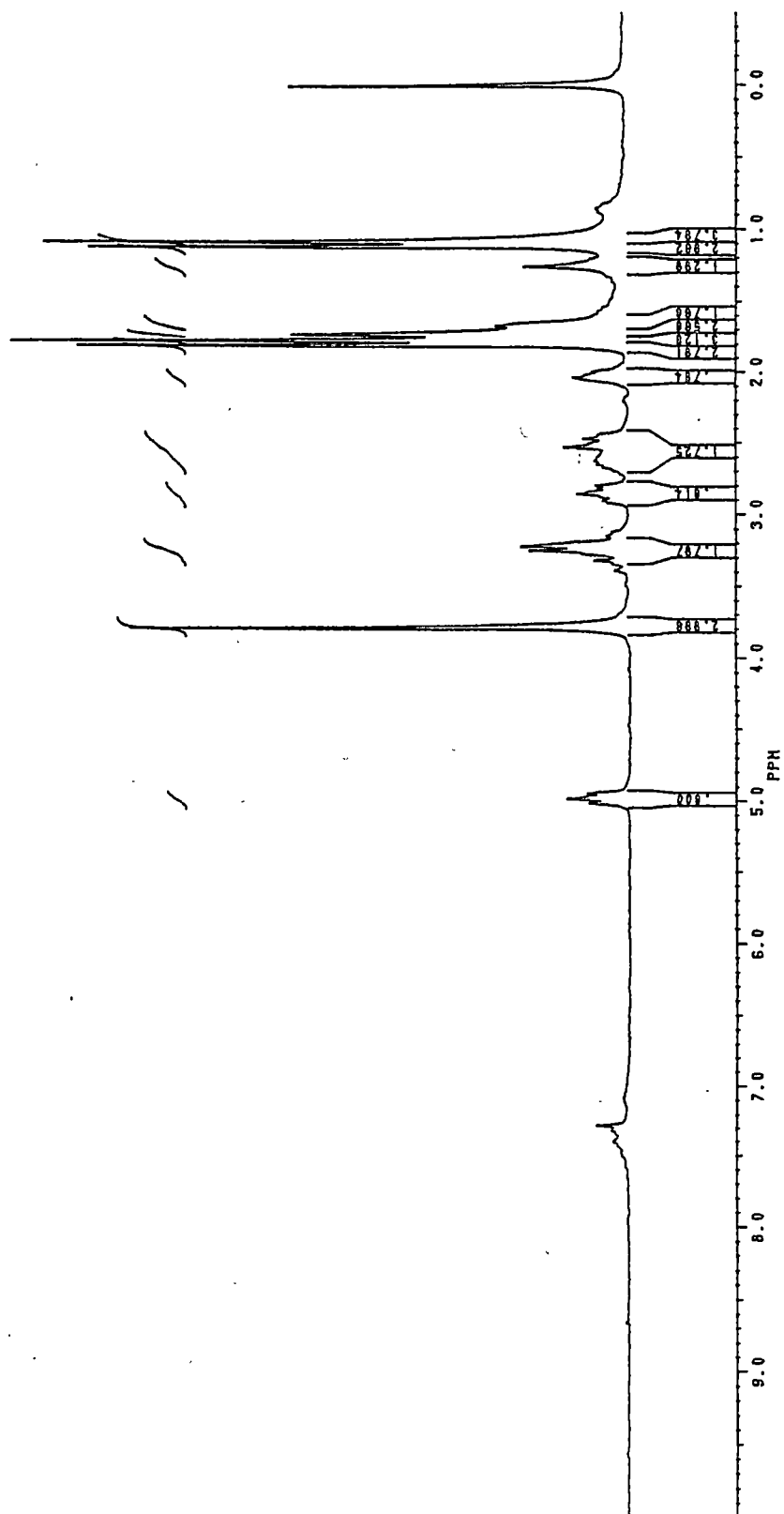
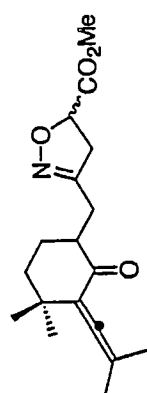


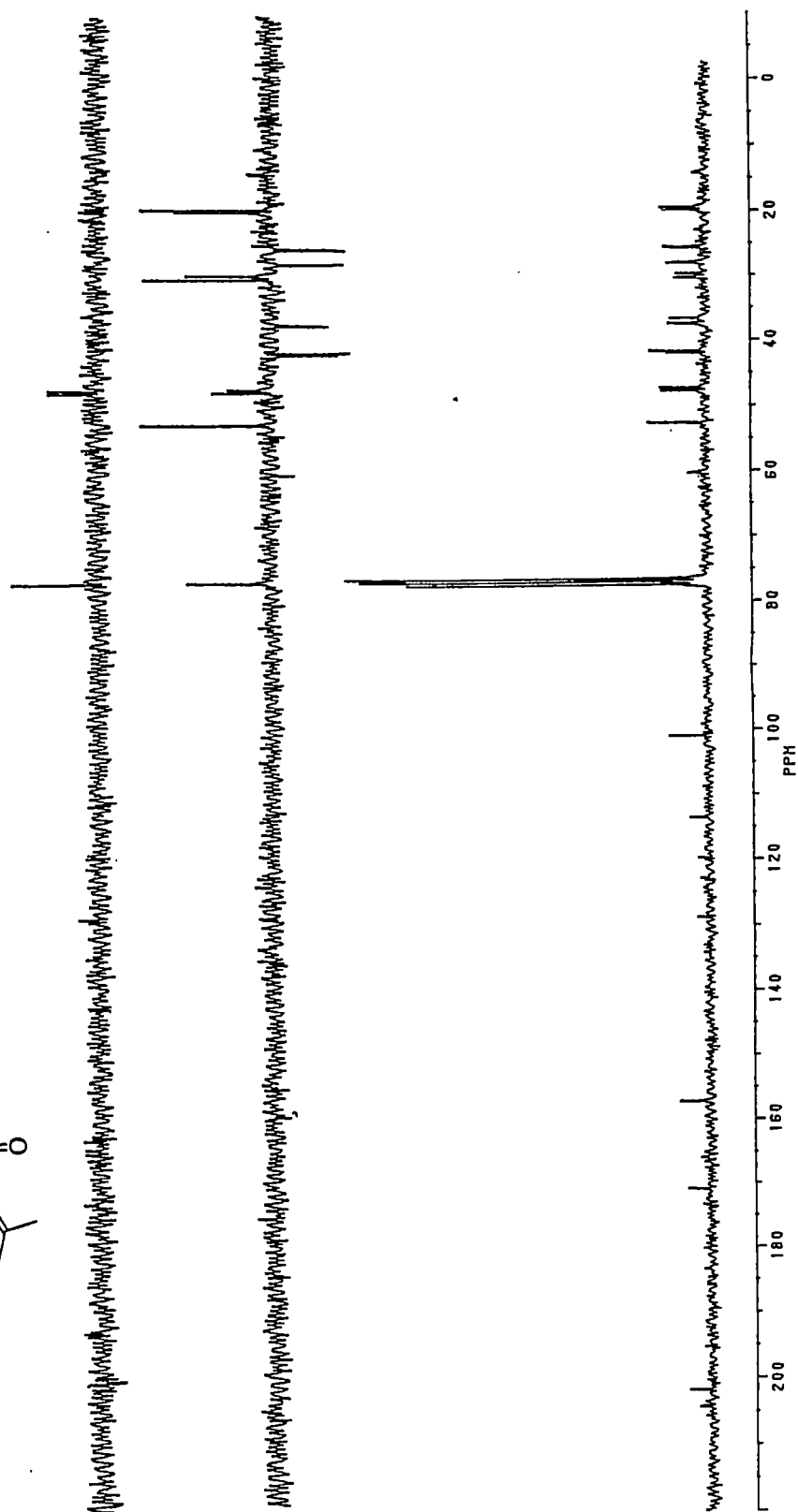
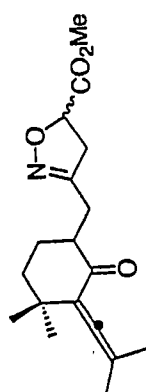


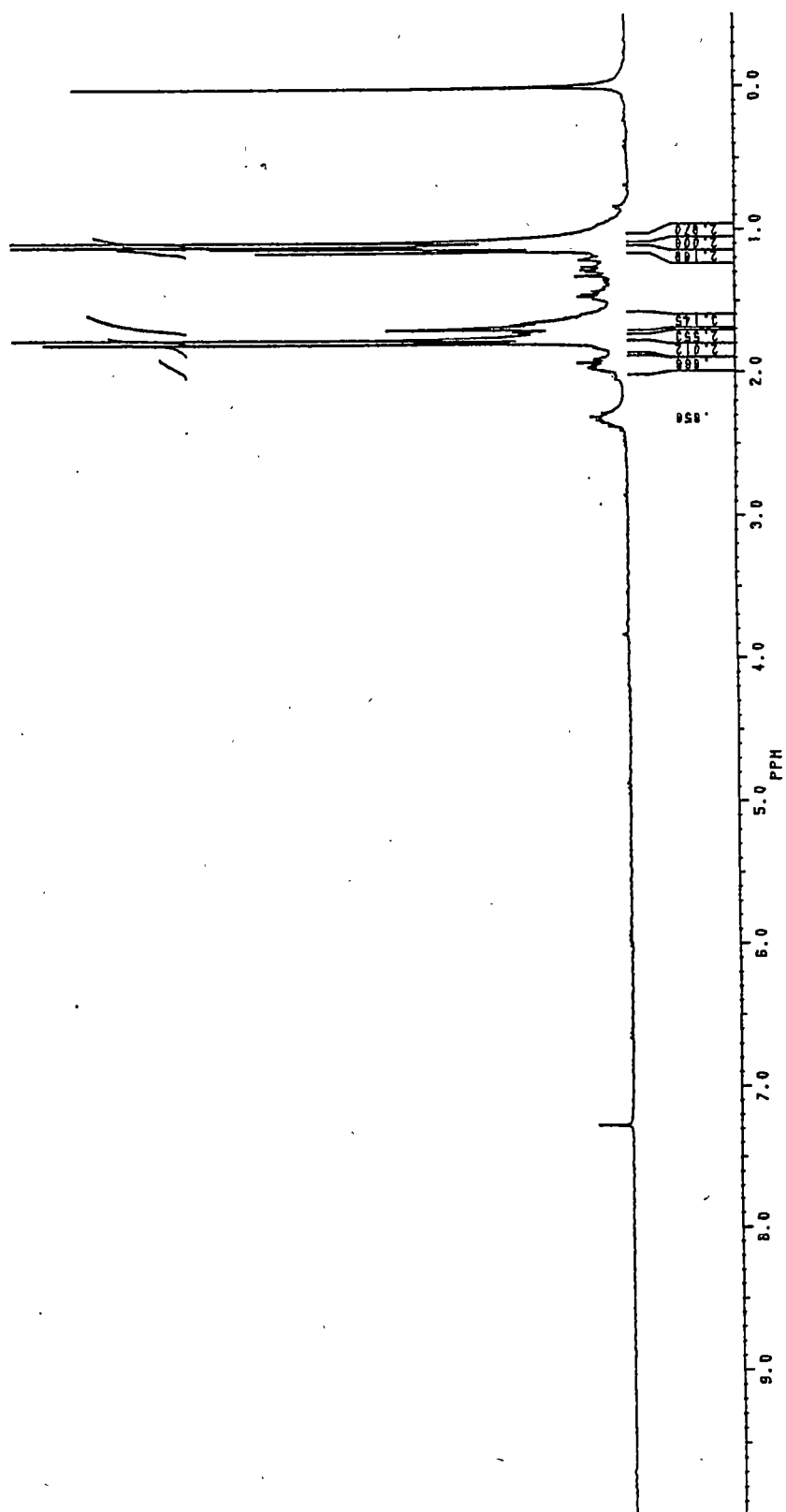
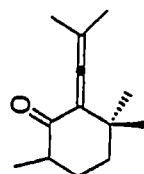


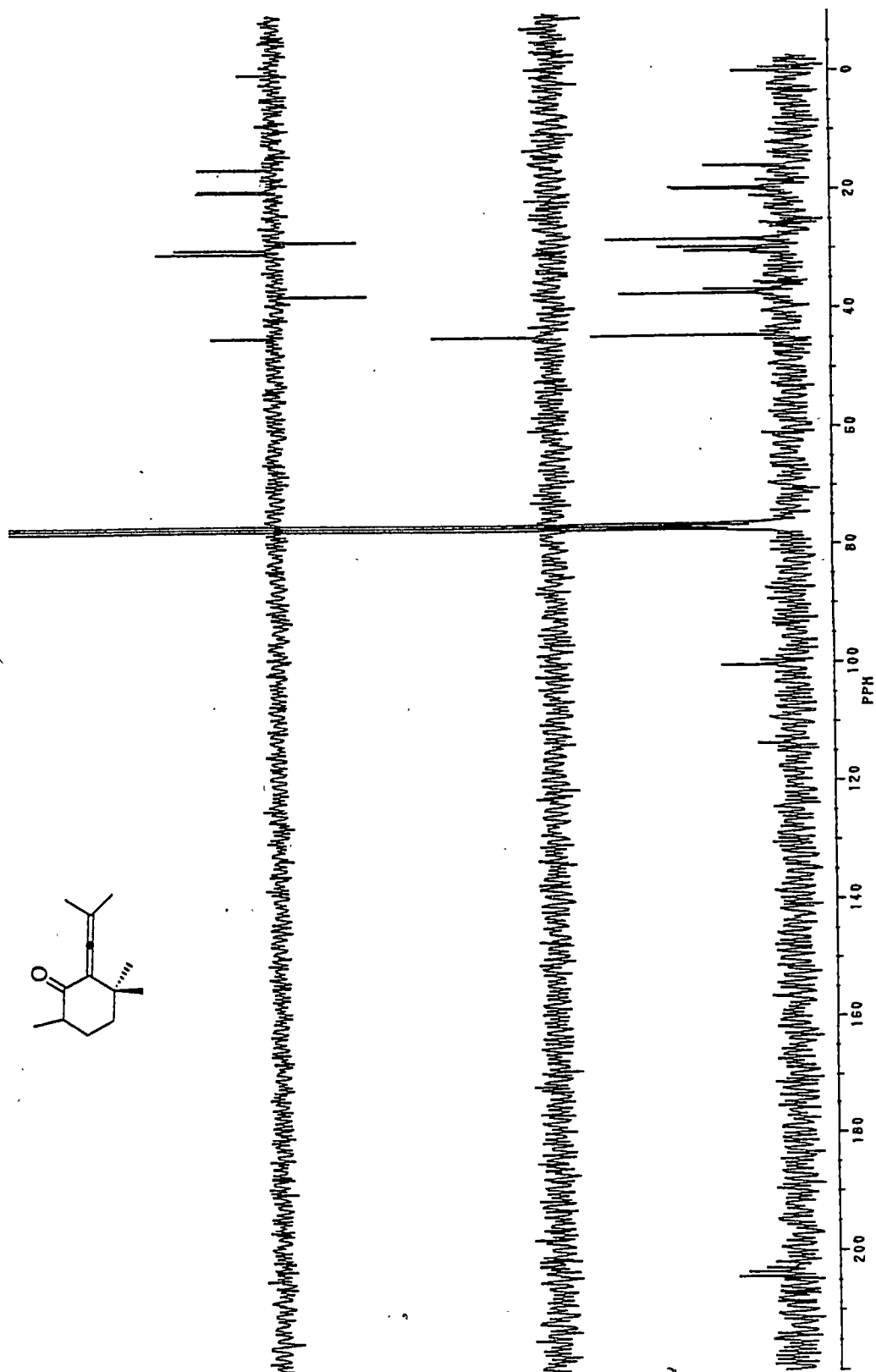


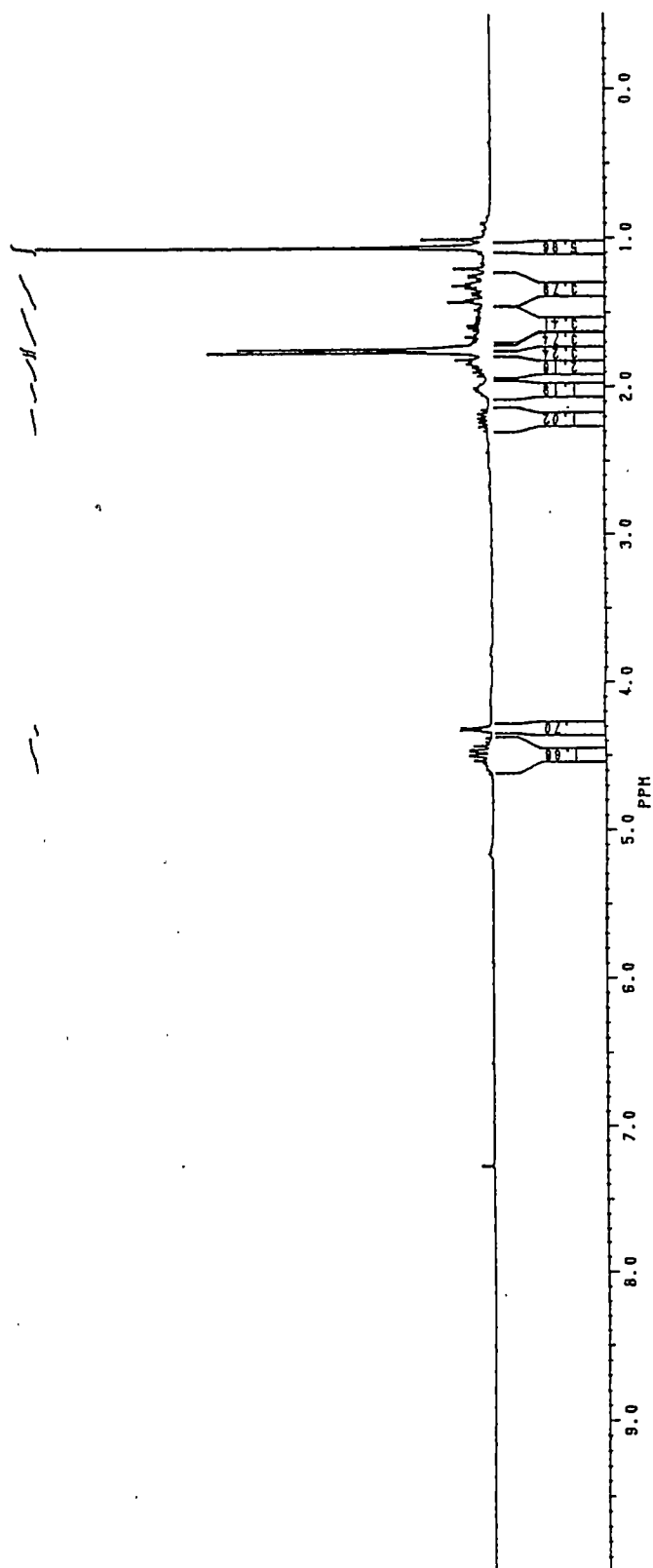
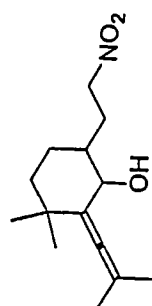


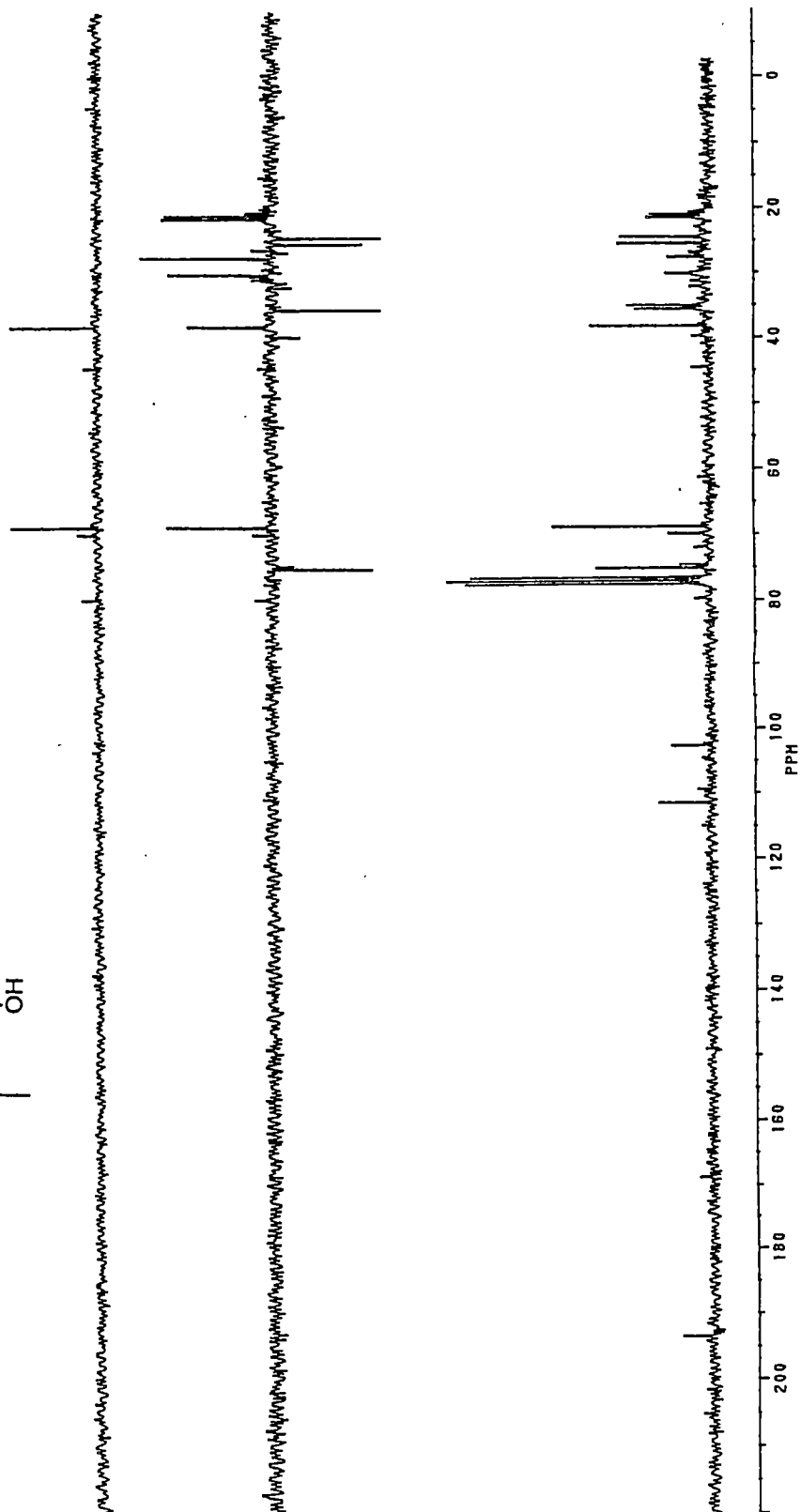
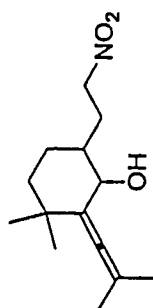


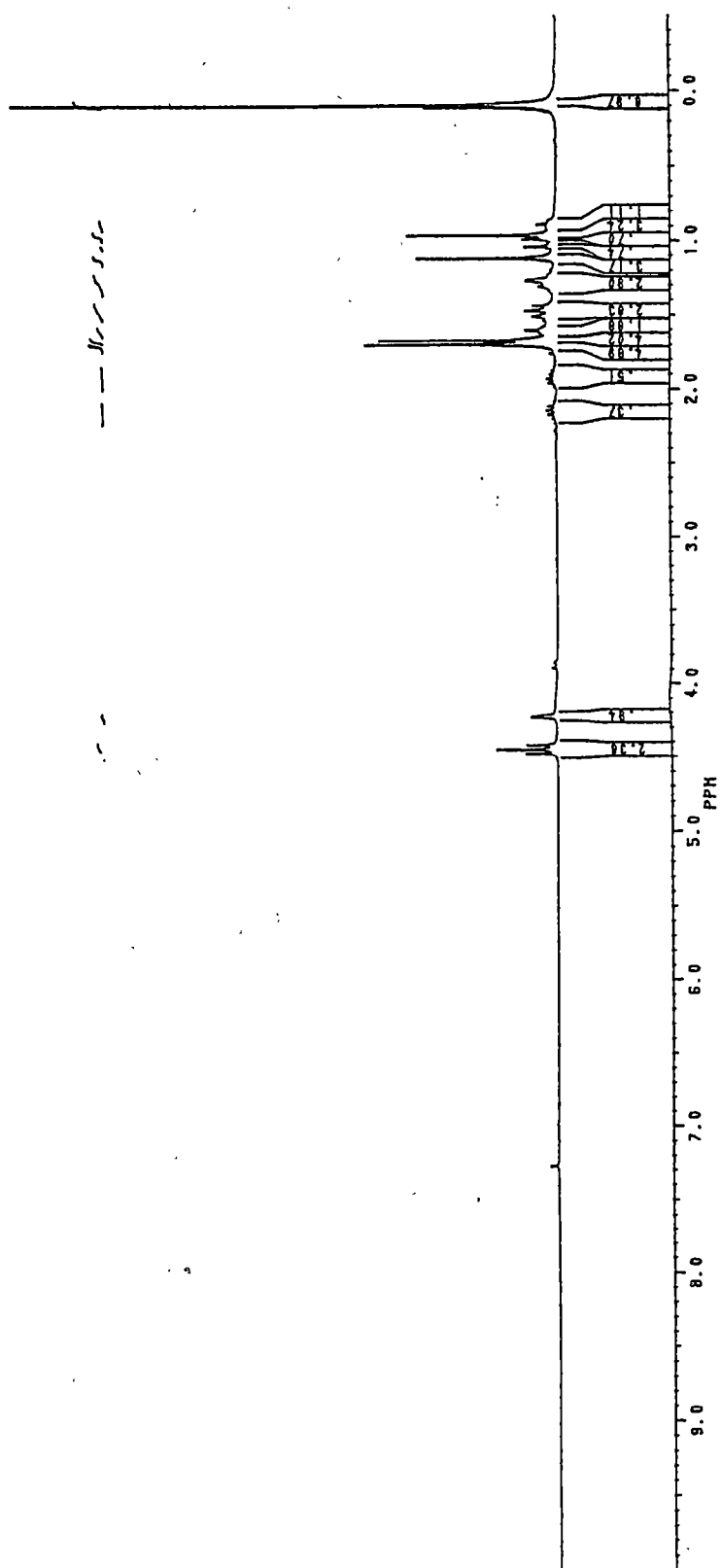
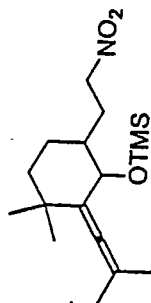


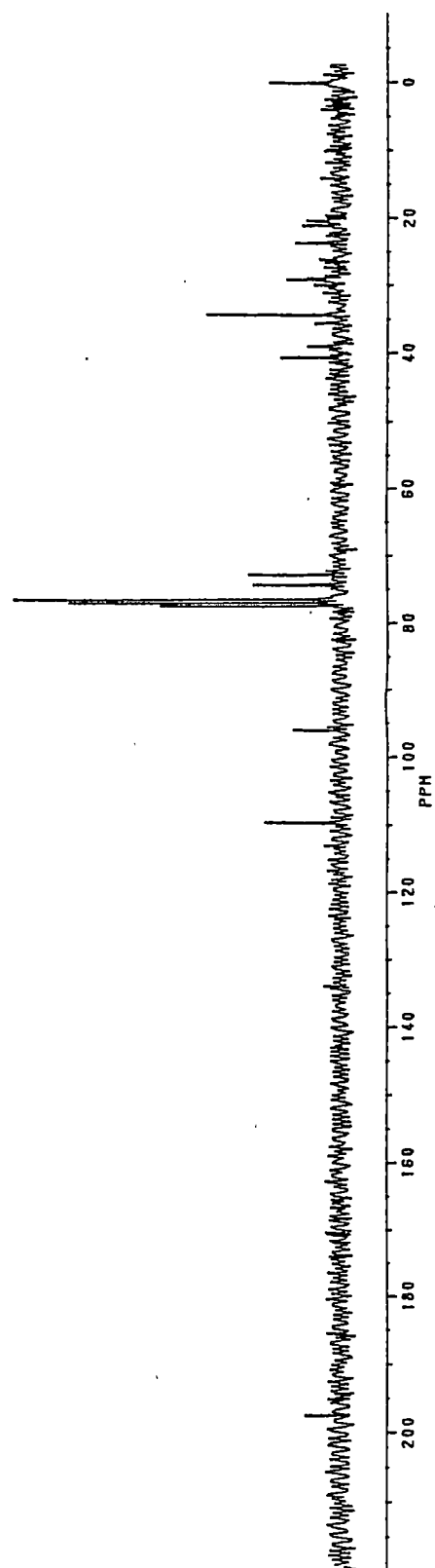
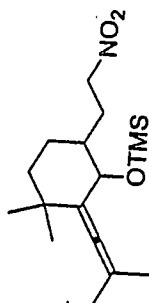


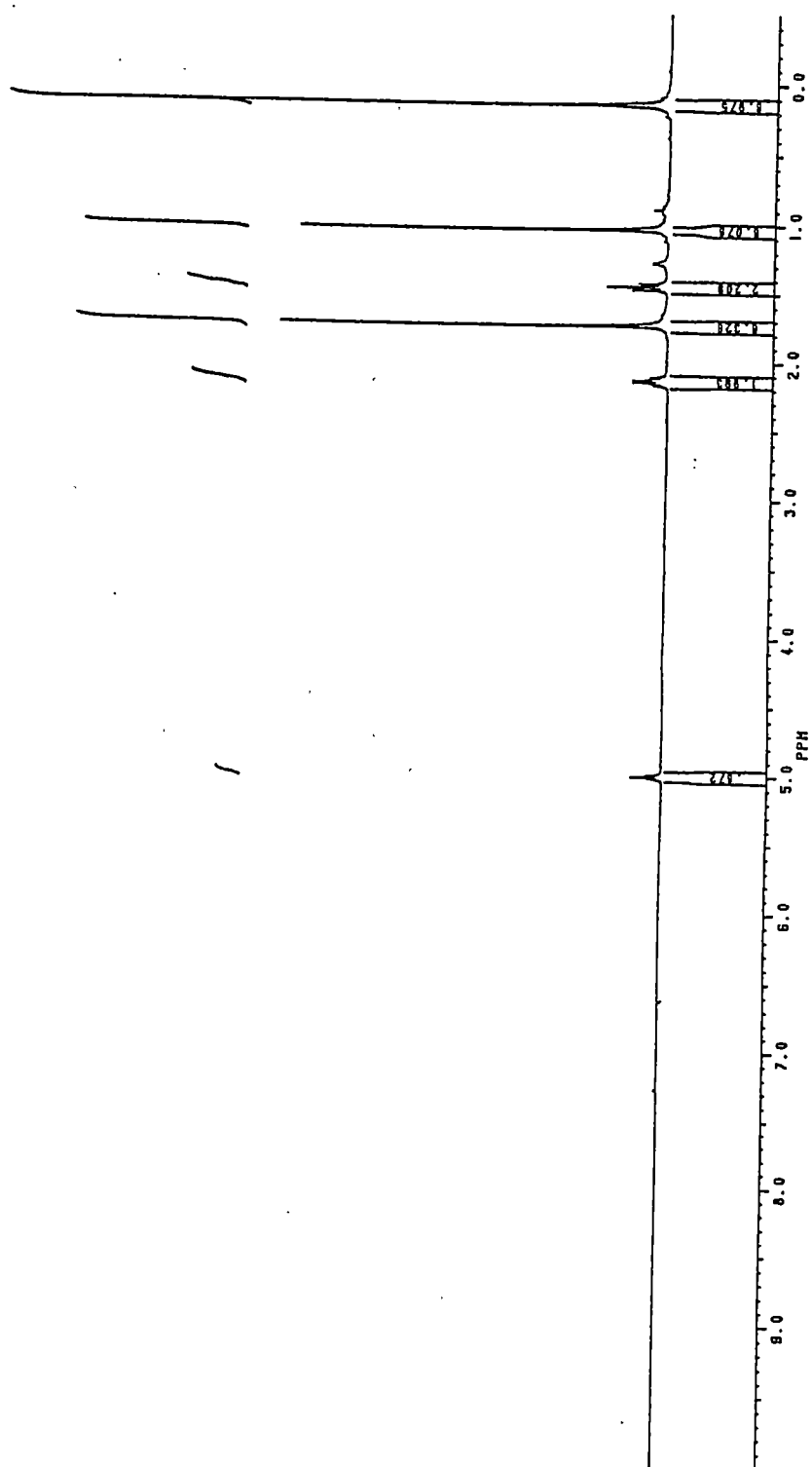
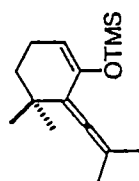


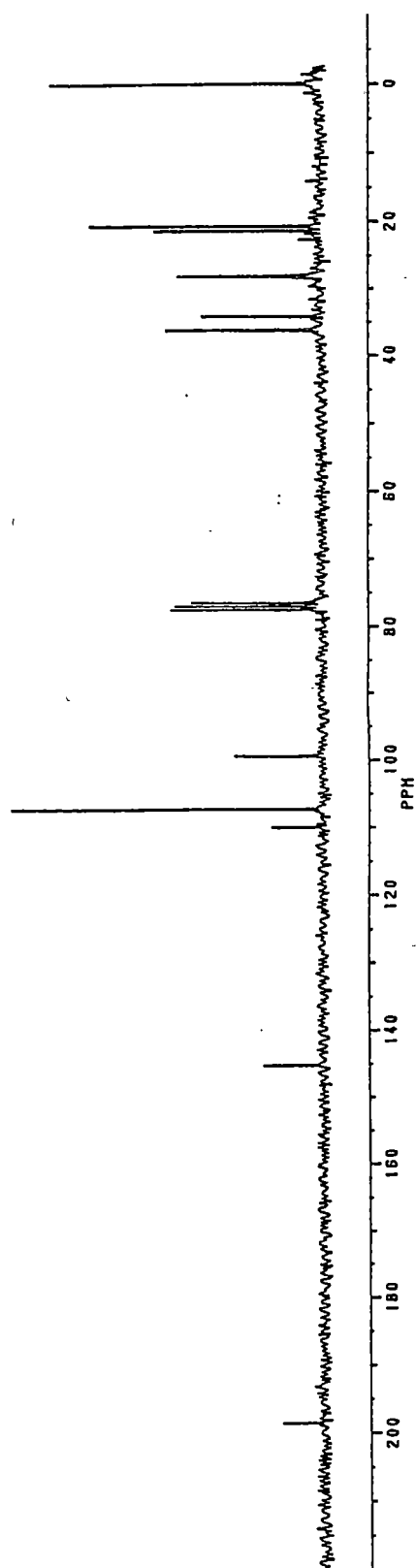
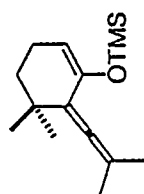


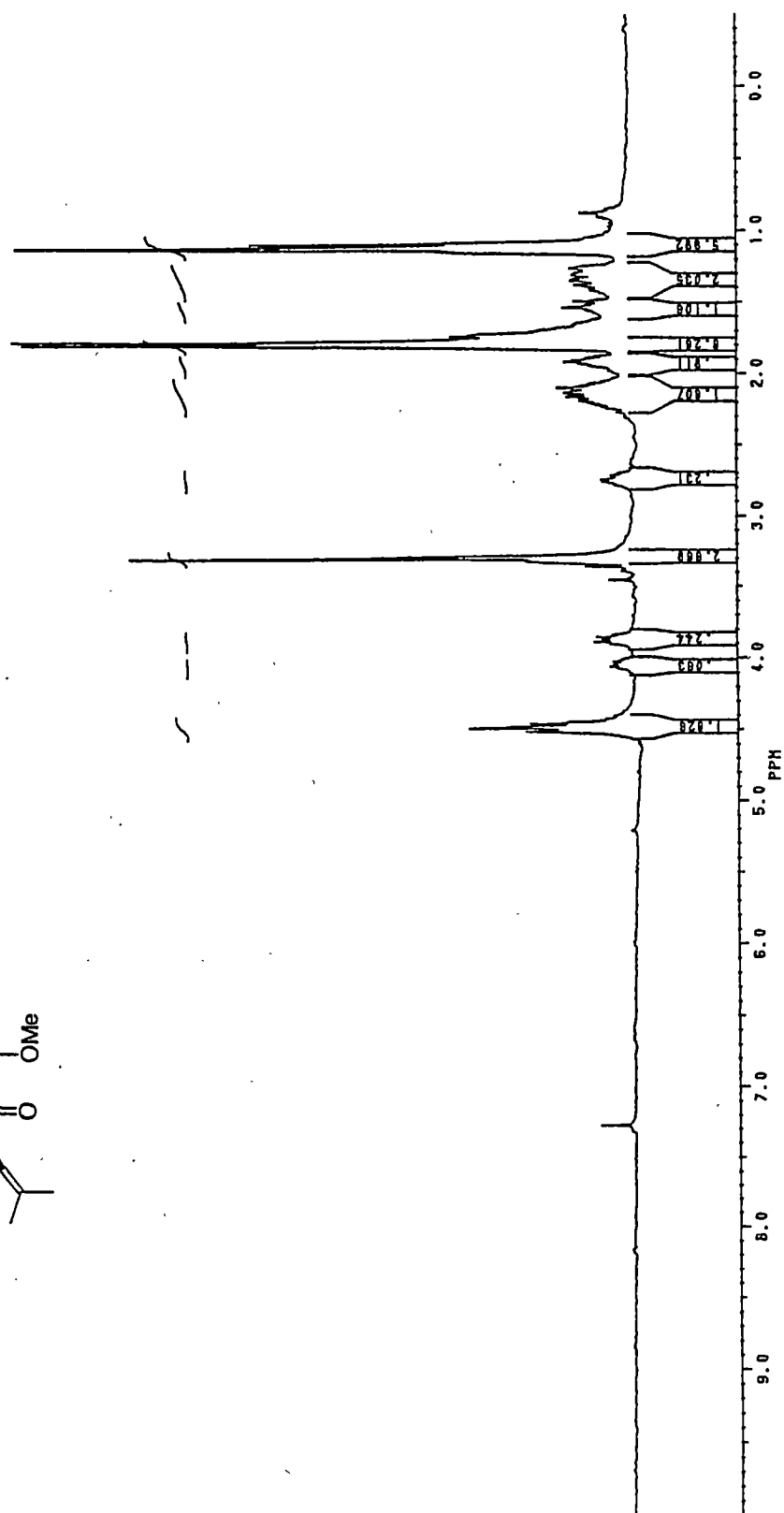
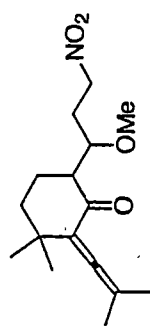


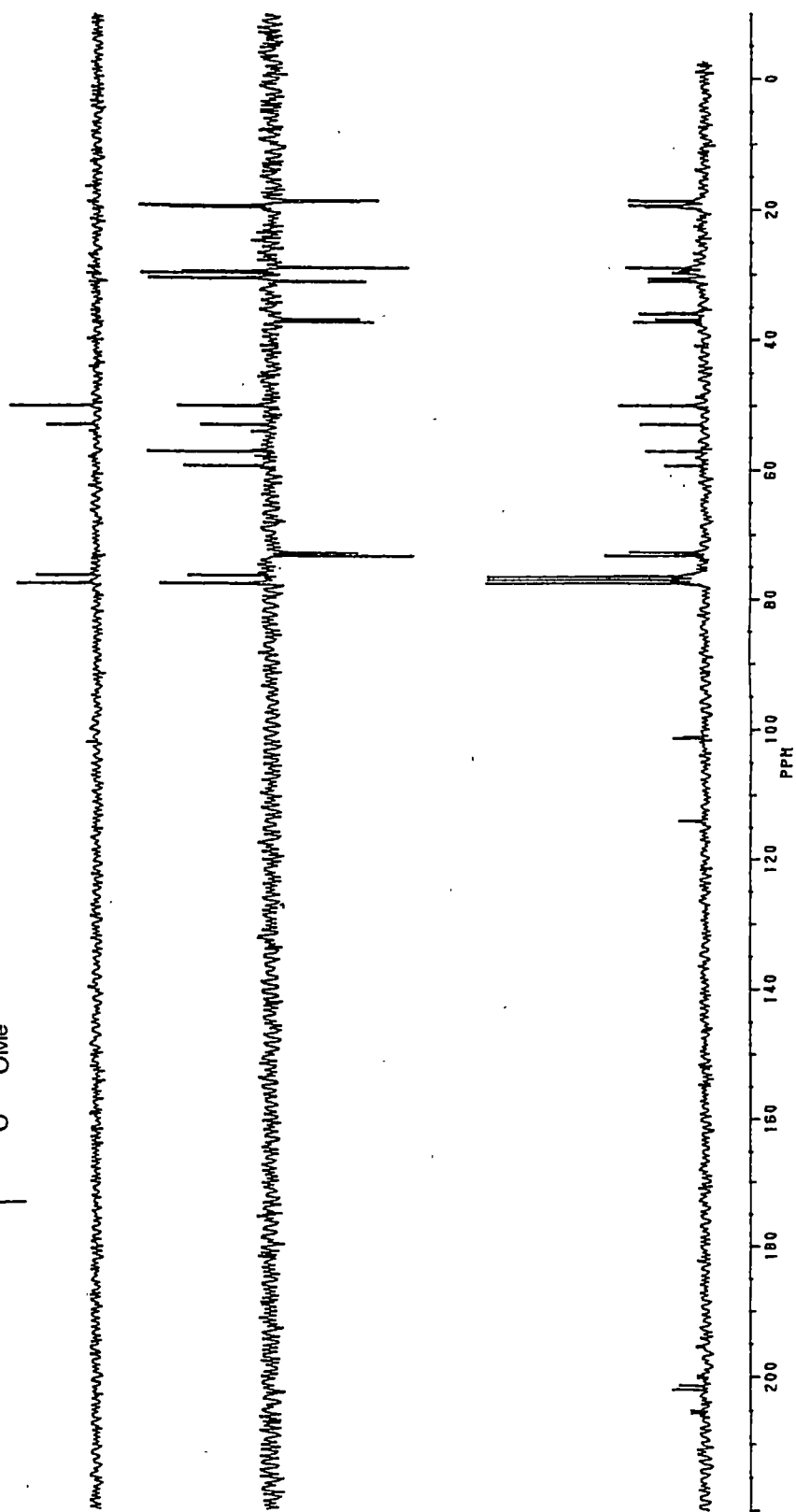
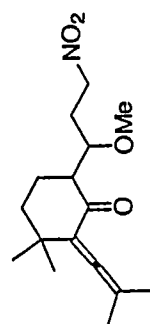


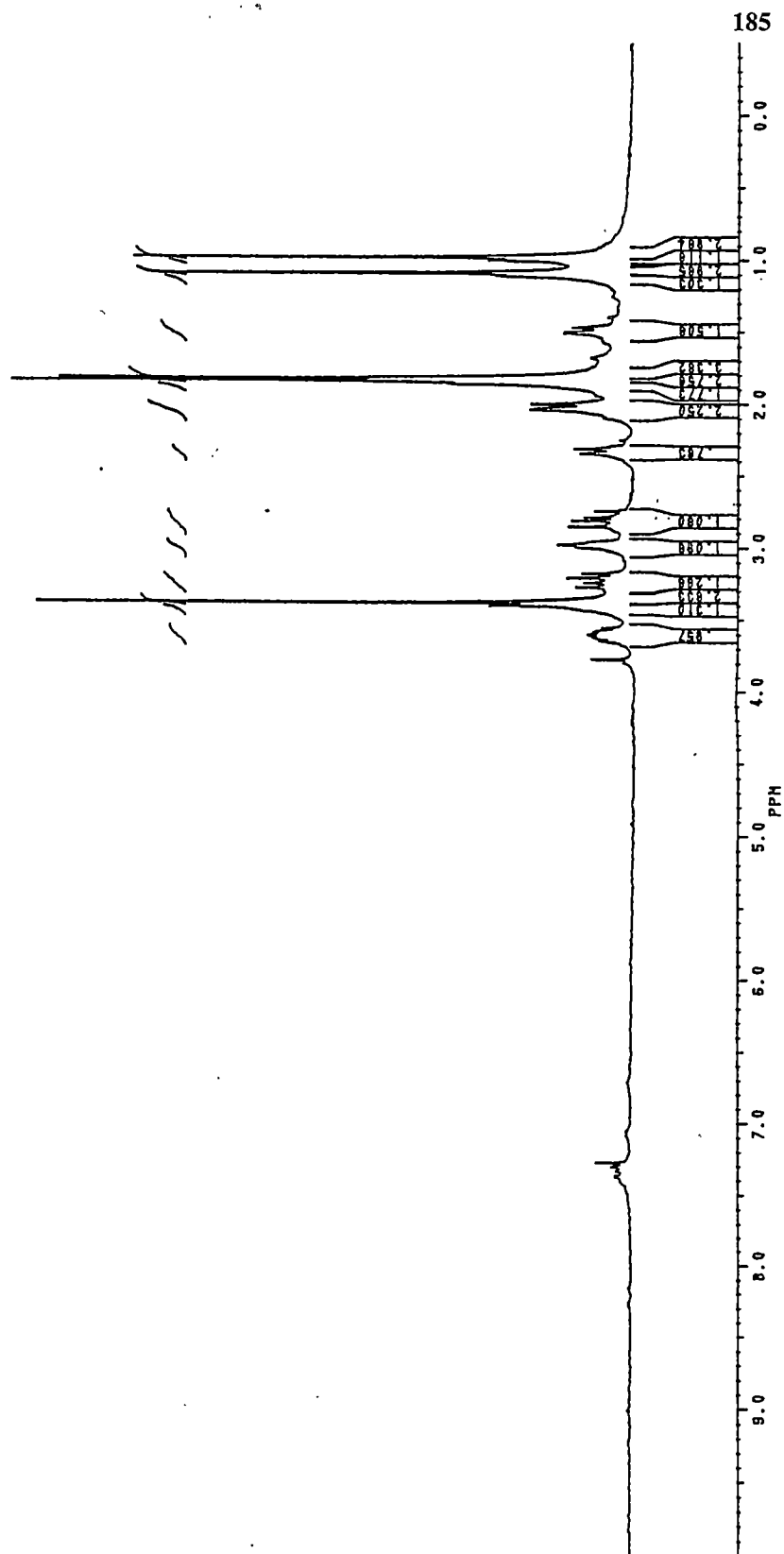
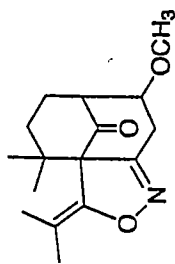


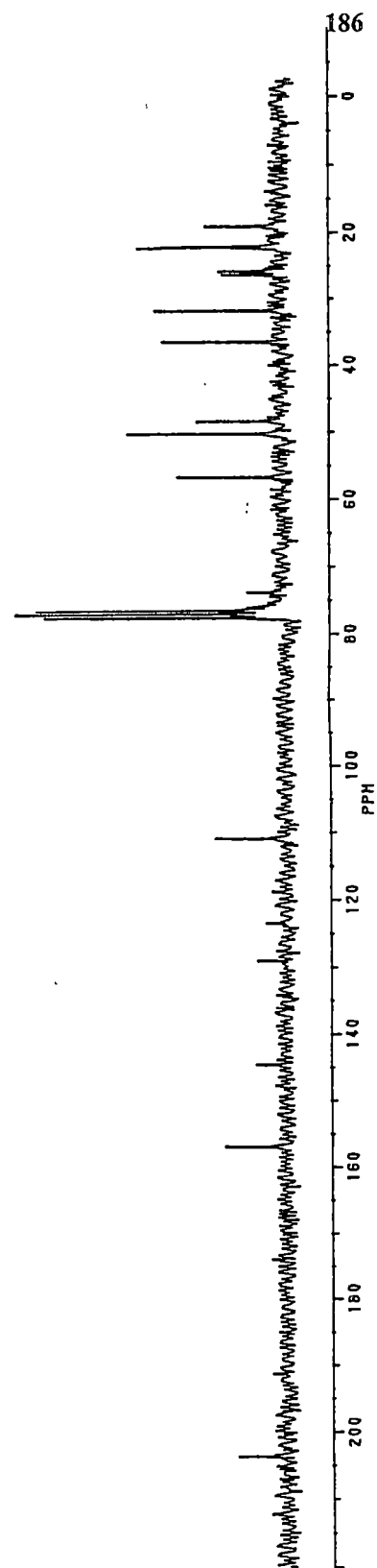
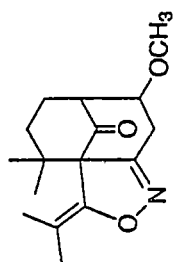


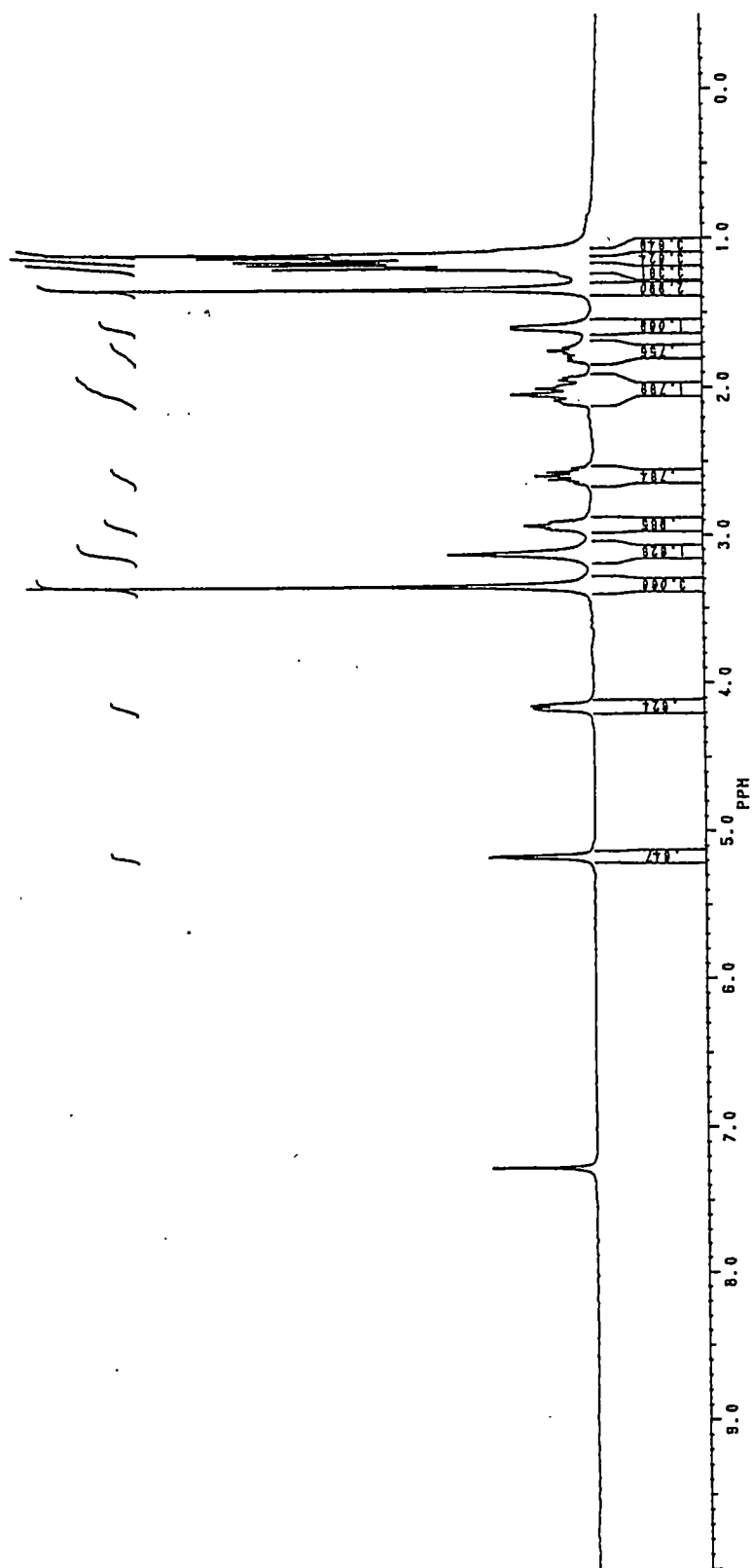
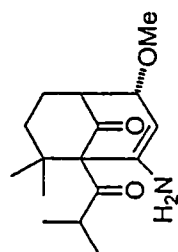


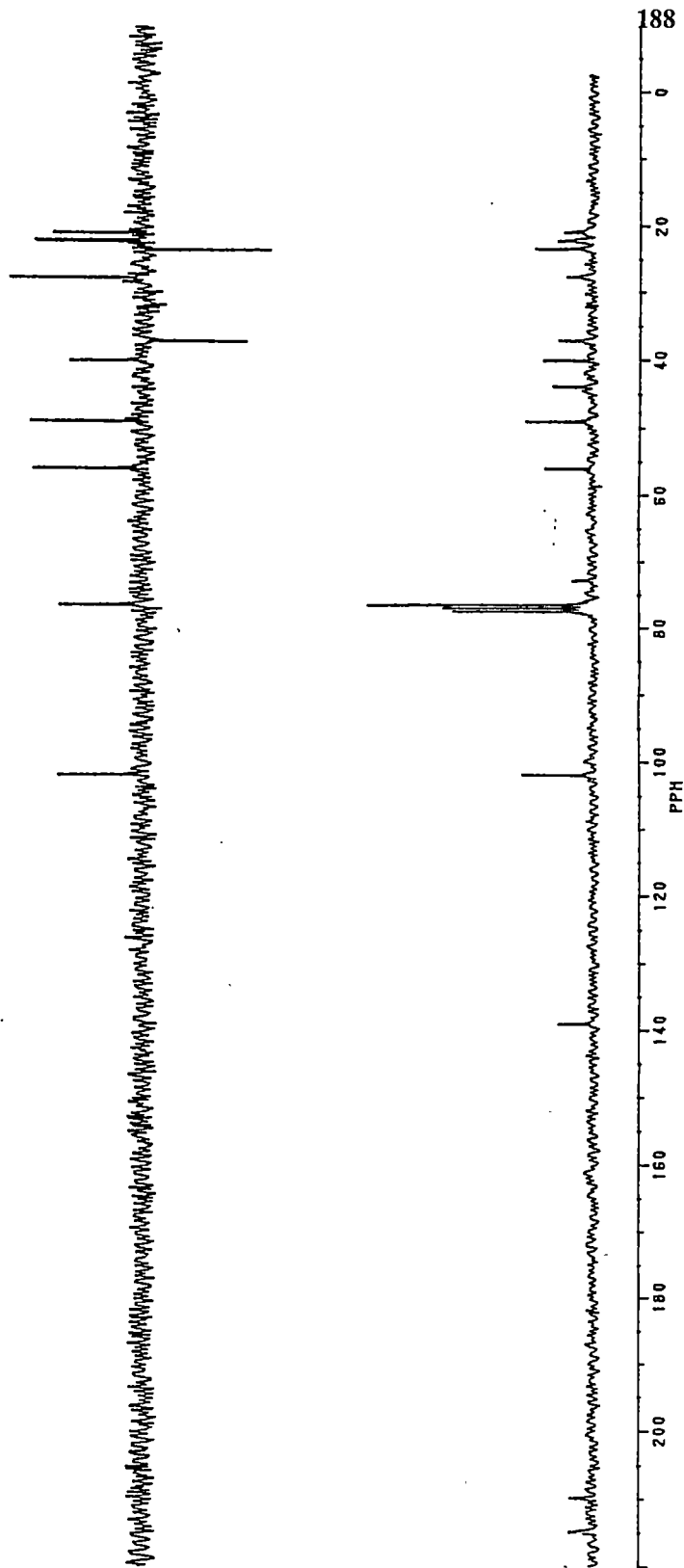
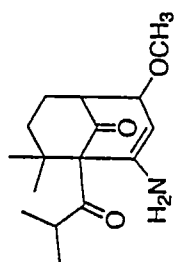


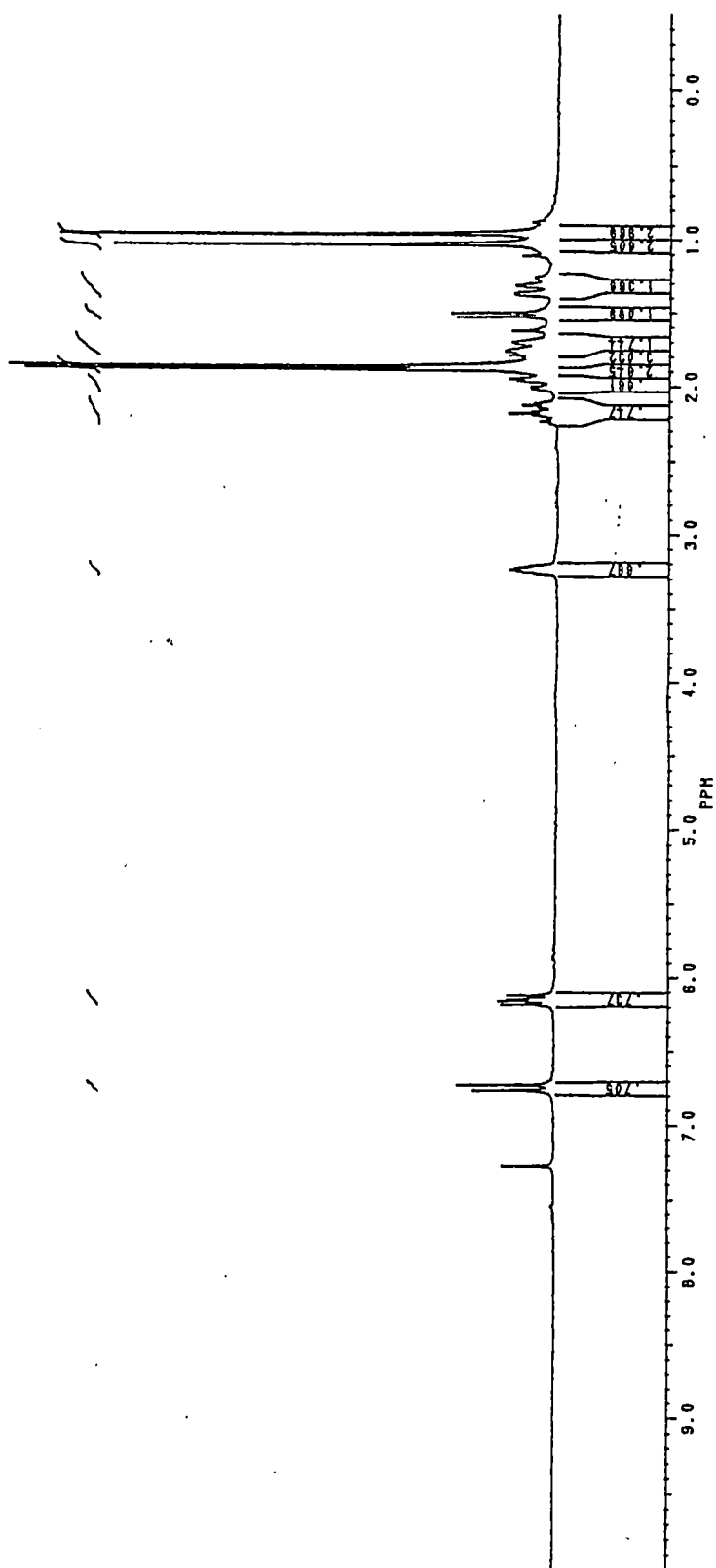
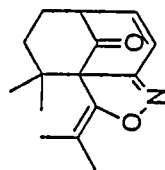


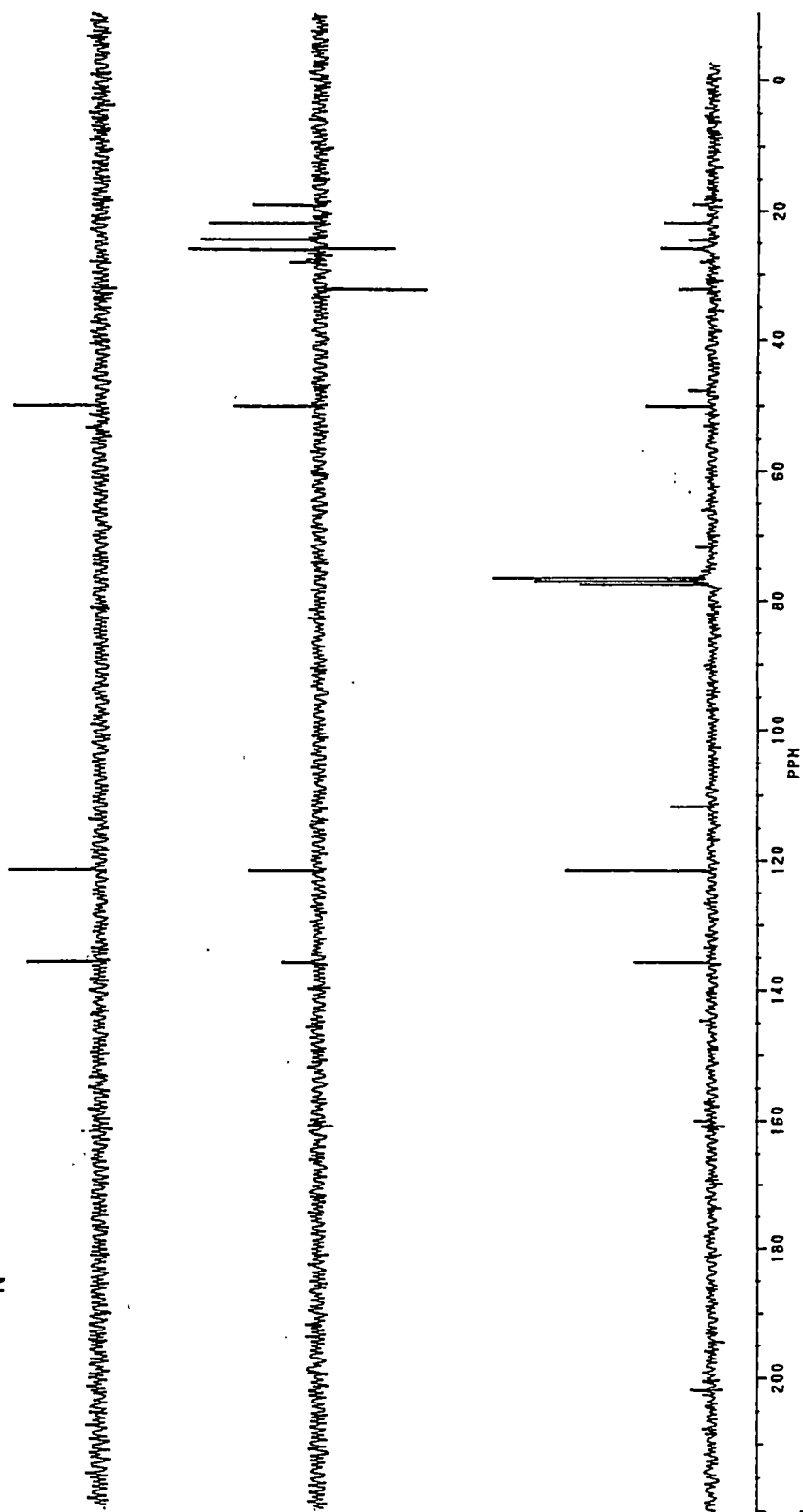
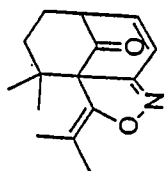












Appendix II. X-ray diffraction data for 162 and 178.

Table A-1. Crystal data and structure refinement for 162.

Identification code	162	
Empirical formula	C ₁₂ H ₁₆ O ₃	
Formula weight	208.25	
Temperature	294(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 7.8887(9) Å	$\alpha = 90^\circ$.
	b = 11.5644(13) Å	$\beta = 97.221(2)^\circ$.
	c = 12.6545(14) Å	$\gamma = 90^\circ$.
Volume	1145.3(2) Å ³	
Z	4	
Density (calculated)	1.208 Mg/m ³	
Absorption coefficient	0.086 mm ⁻¹	
F(000)	448	
Crystal size	0.21 x 0.20 x 0.19 mm ³	
Theta range for data collection	2.39 to 26.41°.	
Index ranges	-9 ≤ h ≤ 9, -14 ≤ k ≤ 14, -15 ≤ l ≤ 15	
Reflections collected	8888	
Independent reflections	2341 [R(int) = 0.0303]	
Completeness to theta = 26.41°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9839 and 0.9822	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	2341 / 0 / 139	
Goodness-of-fit on F ²	1.036	
Final R indices [I > 2sigma(I)]	R1 = 0.0545, wR2 = 0.1328	
R indices (all data)	R1 = 0.0792, wR2 = 0.1503	
Largest diff. peak and hole	0.129 and -0.216 e.Å ⁻³	

Table A-2. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **162**. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	7879(2)	10460(1)	3449(1)	59(1)
C(1)	7611(2)	9413(1)	2787(1)	44(1)
C(8)	7680(2)	9793(2)	1686(2)	54(1)
C(9)	7636(3)	10140(2)	805(2)	62(1)
O(2)	5082(2)	10305(1)	3005(1)	74(1)
C(2)	8945(2)	8482(2)	3165(2)	55(1)
C(6)	5770(2)	9147(2)	2971(2)	54(1)
C(3)	8590(3)	7988(2)	4242(2)	69(1)
C(5)	5576(3)	8553(2)	4014(2)	73(1)
C(4)	6782(3)	7557(2)	4236(2)	73(1)
O(3)	6178(3)	11974(1)	3652(2)	114(1)
C(7)	6362(3)	11001(2)	3391(2)	73(1)
C(11)	8820(3)	7523(2)	2324(2)	81(1)
C(10)	7573(4)	10555(2)	-296(2)	90(1)
C(12)	10735(3)	9014(3)	3271(2)	94(1)

Table A-3. Bond lengths [$\text{\AA}$] and angles [$^\circ$] for **162**.

O(1)-C(7)	1.344(3)	O(1)-C(1)	1.4714(19)
C(1)-C(8)	1.469(2)	C(1)-C(6)	1.531(2)
C(1)-C(2)	1.539(2)	C(8)-C(9)	1.181(3)
C(9)-C(10)	1.468(3)	O(2)-C(7)	1.335(3)
O(2)-C(6)	1.448(2)	C(2)-C(11)	1.531(3)
C(2)-C(12)	1.531(3)	C(2)-C(3)	1.536(3)
C(6)-C(5)	1.513(3)	C(3)-C(4)	1.510(3)
C(5)-C(4)	1.498(3)	O(3)-C(7)	1.187(2)
C(7)-O(1)-C(1)	106.79(14)	C(8)-C(1)-C(6)	110.66(14)
C(8)-C(1)-O(1)	105.93(13)	C(8)-C(1)-C(2)	113.46(15)
O(1)-C(1)-C(6)	98.65(13)	C(6)-C(1)-C(2)	115.89(14)
O(1)-C(1)-C(2)	110.83(13)	C(8)-C(9)-C(10)	179.2(2)
C(9)-C(8)-C(1)	175.5(2)	C(11)-C(2)-C(12)	109.28(19)
C(7)-O(2)-C(6)	107.43(15)	C(12)-C(2)-C(3)	109.91(16)
C(11)-C(2)-C(3)	110.17(18)	C(12)-C(2)-C(1)	109.44(17)
C(11)-C(2)-C(1)	108.03(15)	O(2)-C(6)-C(5)	108.32(17)
C(3)-C(2)-C(1)	109.98(15)	C(5)-C(6)-C(1)	115.19(15)
O(2)-C(6)-C(1)	100.63(14)	C(4)-C(5)-C(6)	112.40(18)
C(4)-C(3)-C(2)	113.30(16)	O(3)-C(7)-O(2)	124.1(2)
C(5)-C(4)-C(3)	108.96(17)	O(2)-C(7)-O(1)	111.50(16)
O(3)-C(7)-O(1)	124.4(3)		

Table A-4. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **162**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	76(1)	46(1)	54(1)	-8(1)	5(1)	-6(1)
C(1)	52(1)	39(1)	41(1)	-3(1)	1(1)	0(1)
C(8)	64(1)	48(1)	49(1)	0(1)	2(1)	1(1)
C(9)	78(1)	53(1)	53(1)	5(1)	1(1)	-3(1)
O(2)	67(1)	64(1)	92(1)	13(1)	14(1)	24(1)
C(2)	50(1)	62(1)	53(1)	3(1)	2(1)	13(1)
C(6)	50(1)	47(1)	63(1)	7(1)	0(1)	5(1)
C(3)	72(1)	74(1)	56(1)	16(1)	-4(1)	23(1)
C(5)	62(1)	79(1)	79(2)	22(1)	18(1)	1(1)
C(4)	90(2)	63(1)	67(1)	22(1)	9(1)	2(1)
O(3)	183(2)	51(1)	114(2)	-8(1)	41(1)	30(1)
C(7)	101(2)	49(1)	70(1)	3(1)	24(1)	20(1)
C(11)	104(2)	62(1)	77(2)	-3(1)	16(1)	32(1)
C(10)	133(2)	80(2)	54(1)	20(1)	-2(1)	-15(2)
C(12)	49(1)	131(2)	99(2)	12(2)	1(1)	9(1)

Table A-5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **162**.

	x	y	z	U(eq)
H(6)	5178	8712	2369	65
H(3A)	9374	7355	4437	82
H(3B)	8811	8584	4782	82
H(5A)	5781	9110	4589	87
H(5B)	4412	8275	3995	87
H(4A)	6536	6969	3692	88
H(4B)	6646	7216	4921	88
H(11A)	9526	6884	2587	121
H(11B)	9201	7814	1684	121
H(11C)	7655	7271	2175	121
H(10A)	8622	10364	-565	136
H(10B)	7419	11378	-312	136
H(10C)	6635	10193	-730	136
H(12A)	11571	8425	3475	140
H(12B)	10822	9609	3804	140
H(12C)	10935	9341	2600	140

Table A-6. Crystal data and structure refinement for 178.

Identification code	178	
Empirical formula	C ₁₆ H ₂₃ N O ₃	
Formula weight	277.35	
Temperature	295(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 9.8412(13) Å	$\alpha = 90^\circ$.
	b = 12.8152(18) Å	$\beta = 101.421(2)^\circ$.
	c = 12.1972(17) Å	$\gamma = 90^\circ$.
Volume	1507.8(4) Å ³	
Z	4	
Density (calculated)	1.222 Mg/m ³	
Absorption coefficient	0.084 mm ⁻¹	
F(000)	600	
Crystal size	0.51 x 0.39 x 0.32 mm ³	
Theta range for data collection	2.11 to 26.49°.	
Index ranges	-12 ≤ h ≤ 12, -16 ≤ k ≤ 15, -15 ≤ l ≤ 15	
Reflections collected	14686	
Independent reflections	3123 [R(int) = 0.0216]	
Completeness to theta = 26.49°	99.6 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9737 and 0.9586	
Refinement method	Full-matrix least-squares on F ²	
Data / restraints / parameters	3123 / 0 / 186	
Goodness-of-fit on F ²	1.056	
Final R indices [I > 2sigma(I)]	R1 = 0.0519, wR2 = 0.1482	
R indices (all data)	R1 = 0.0728, wR2 = 0.1722	
Largest diff. peak and hole	0.433 and -0.336 e.Å ⁻³	

Table A-7. Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 178. $U(\text{eq})$ is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	$U(\text{eq})$
O(1)	9796(2)	10622(1)	1335(1)	63(1)
C(1)	9895(2)	9779(2)	1786(2)	48(1)
O(2)	7258(2)	9744(1)	3436(1)	68(1)
C(2)	8728(2)	9243(1)	2231(2)	46(1)
C(3)	9303(2)	9050(2)	3469(2)	53(1)
C(9)	8377(2)	8164(2)	1576(2)	51(1)
C(12)	7481(2)	9899(2)	2334(2)	54(1)
C(8)	9697(2)	7502(2)	1681(2)	58(1)
C(6)	11215(2)	9153(2)	2004(2)	56(1)
N	8484(2)	9327(2)	4106(1)	65(1)
O(3)	13010(2)	8548(2)	3507(2)	92(1)
C(5)	11760(2)	9125(2)	3279(2)	61(1)
C(7)	10960(2)	8080(2)	1434(2)	62(1)
C(13)	6633(2)	10561(2)	1690(2)	62(1)
C(10)	7777(2)	8377(2)	344(2)	62(1)
C(4)	10728(2)	8657(2)	3926(2)	61(1)
C(11)	7299(3)	7567(2)	2076(2)	74(1)
C(14)	6702(3)	10862(2)	520(2)	71(1)
C(15)	5500(3)	11104(3)	2145(3)	88(1)
C(16)	14071(4)	8943(4)	4127(6)	203(3)

Table A-8. Bond lengths [Å] and angles [°] for 178.

O(1)-C(1)	1.207(2)	C(1)-C(6)	1.505(3)
C(1)-C(2)	1.528(2)	O(2)-C(12)	1.418(2)
O(2)-N	1.421(3)	C(2)-C(12)	1.513(3)
C(2)-C(3)	1.524(3)	C(2)-C(9)	1.601(3)
C(3)-N	1.276(3)	C(3)-C(4)	1.491(3)
C(9)-C(10)	1.527(3)	C(9)-C(11)	1.529(3)
C(9)-C(8)	1.535(3)	C(12)-C(13)	1.331(3)
C(8)-C(7)	1.527(3)	C(6)-C(5)	1.541(3)
C(6)-C(7)	1.538(3)	O(3)-C(16)	1.267(4)
O(3)-C(5)	1.415(3)	C(5)-C(4)	1.527(3)
C(13)-C(14)	1.492(3)	C(13)-C(15)	1.511(3)
		O(1)-C(1)-C(6)	123.18(18)
O(1)-C(1)-C(2)	124.41(18)	C(6)-C(1)-C(2)	112.39(16)
C(12)-O(2)-N	108.95(14)	C(12)-C(2)-C(3)	99.02(15)
C(12)-C(2)-C(1)	117.35(15)	C(3)-C(2)-C(1)	105.51(15)
C(12)-C(2)-C(9)	115.03(16)	C(3)-C(2)-C(9)	110.80(15)
C(1)-C(2)-C(9)	108.29(14)	N-C(3)-C(4)	121.83(19)
N-C(3)-C(2)	113.73(19)	C(4)-C(3)-C(2)	124.27(17)
C(10)-C(9)-C(11)	108.60(18)	C(10)-C(9)-C(8)	109.68(17)
C(11)-C(9)-C(8)	109.42(18)	C(10)-C(9)-C(2)	109.89(16)
C(11)-C(9)-C(2)	109.36(16)	C(8)-C(9)-C(2)	109.88(16)
C(13)-C(12)-O(2)	116.87(18)	C(13)-C(12)-C(2)	136.79(19)
O(2)-C(12)-C(2)	106.31(16)	C(7)-C(8)-C(9)	115.07(17)
C(1)-C(6)-C(5)	107.88(17)	C(1)-C(6)-C(7)	109.76(17)
C(5)-C(6)-C(7)	115.35(18)	C(3)-N-O(2)	108.74(17)
C(16)-O(3)-C(5)	119.4(3)	O(3)-C(5)-C(4)	109.5(2)
O(3)-C(5)-C(6)	109.06(18)	C(4)-C(5)-C(6)	113.36(17)
C(8)-C(7)-C(6)	114.25(17)	C(12)-C(13)-C(14)	125.9(2)
C(12)-C(13)-C(15)	119.9(2)	C(14)-C(13)-C(15)	114.2(2)
C(3)-C(4)-C(5)	110.27(18)		

Table A-9. Anisotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for **178**. The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U^{11} + \dots + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	74(1)	47(1)	71(1)	8(1)	24(1)	-6(1)
C(1)	59(1)	42(1)	47(1)	-3(1)	17(1)	-5(1)
O(2)	70(1)	86(1)	56(1)	-1(1)	30(1)	6(1)
C(2)	55(1)	44(1)	42(1)	0(1)	16(1)	-4(1)
C(3)	68(1)	49(1)	44(1)	-1(1)	16(1)	-7(1)
C(9)	64(1)	45(1)	46(1)	-3(1)	18(1)	-10(1)
C(12)	59(1)	56(1)	51(1)	-3(1)	22(1)	-4(1)
C(8)	81(1)	42(1)	52(1)	-5(1)	14(1)	0(1)
C(6)	56(1)	53(1)	61(1)	0(1)	20(1)	-5(1)
N	79(1)	72(1)	48(1)	-3(1)	23(1)	-2(1)
O(3)	64(1)	82(1)	117(2)	-27(1)	-13(1)	11(1)
C(5)	60(1)	52(1)	70(1)	-9(1)	7(1)	0(1)
C(7)	66(1)	61(1)	60(1)	-9(1)	17(1)	9(1)
C(13)	59(1)	61(1)	68(1)	-3(1)	19(1)	3(1)
C(10)	73(1)	63(1)	50(1)	-7(1)	11(1)	-5(1)
C(4)	76(1)	60(1)	46(1)	-3(1)	7(1)	0(1)
C(11)	91(2)	64(1)	74(2)	-7(1)	34(1)	-29(1)
C(14)	72(1)	68(2)	74(2)	12(1)	15(1)	5(1)
C(15)	75(2)	97(2)	95(2)	1(2)	28(1)	24(2)
C(16)	77(2)	115(3)	374(9)	-54(4)	-60(4)	1(2)

Table A-10. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($\text{\AA}^2 \times 10^3$) for 178.

	x	y	z	U(eq)
H(8A)	9928	7225	2436	70
H(8B)	9501	6915	1174	70
H(6)	11899	9524	1665	67
H(5)	11962	9842	3539	74
H(7A)	10842	8175	632	74
H(7B)	11774	7650	1675	74
H(10A)	7583	7727	-47	93
H(10B)	8436	8766	23	93
H(10C)	6936	8772	279	93
H(4A)	10741	7902	3870	74
H(4B)	10994	8844	4710	74
H(11A)	6476	7982	2015	111
H(11B)	7668	7420	2849	111
H(11C)	7077	6924	1677	111
H(14A)	7464	10508	298	107
H(14B)	6834	11602	482	107
H(14C)	5853	10669	27	107
H(15A)	4622	10792	1831	132
H(15B)	5482	11830	1951	132
H(15C)	5674	11033	2945	132
H(16A)	13865	9642	4327	305
H(16B)	14823	8957	3731	305
H(16C)	14330	8530	4793	305

Vita

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