# DEVELOPMENT OF INTRAMOLECULAR *AZA*-[3 + 3] ANNULATION REACTION AND ITS APPLICATIONS IN NATURAL PRODUCT SYNTHESIS

by

Aleksey Igorevich Gerasyuto

A dissertation submitted in partial fulfillment of

the requirements for the degree of

Doctor of Philosophy

(Pharmaceutical Sciences)

at the

UNIVERSITY OF WISCONSIN-MADISON

2007

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# A dissertation entitled

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**Date of Final Oral Examination:** April 13, 2007

Month & Year Degree to be awarded: **December** **May** 2007 **August**

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# DEVELOPMENT OF INTRAMOLECULAR *AZA*-[3 + 3] ANNULATION REACTION AND ITS APPLICATIONS IN NATURAL PRODUCT SYNTHESIS

Aleksey Igorevich Gerasyuto

Under the supervision of Professor Richard P. Hsung

At the University of Wisconsin-Madison

Evolution of intramolecular *aza*-[3 + 3] annulation reaction from its discovery to applications in natural product synthesis is described.

Part 1 of this thesis concentrates on development of enantioselective version of the cycloaddition reaction promoted by chiral secondary amine salts. The dependence of enantioselectivity on the structural features of these catalysts has been thoroughly investigated. A very interesting reversal of the stereochemistry in the respective annulation products obtained using $C_1$- and $C_2$-symmetric amine salts was found. On the basis of these experimental results and semi-empirical calculations, a unified mechanistic model was proposed. Developed methodology was also successfully applied for total synthesis of enantioenriched *R*-(+)-Deplancheine.

Part 2 describes application of the intramolecular *aza*-[3 + 3] annulation reaction to total synthesis of *Coccinellidae* defensive alkaloids. All five members of this family: precoccinelline, hippodamine, coccinelline, convergine, and myrrhine were successfully synthesized from the same common intermediate which was derived from a stereoselective *aza*-[3 + 3] annulation reaction. Stereoselectivity of the cycloaddition reaction was rationalized on basis of semi-empirical calculations. This work provided a *de novo* stereoselective approach toward 2-methyl-perhydro-9b-azaphenalene family of alkaloids.

Part 3 focuses on expanding the scope of intramolecular *aza*-[3 + 3] annulation to vinylogous amides tethered with α,β-unsaturated ketones. Quest for suitable conditions for this transformation as well as current progress toward synthesis of propyleine alkaloid featuring discovered reaction are described in the third part of the thesis.

*Dedicated to my parents with love and deep gratitude for all support and endless encouragement they have given me*

# Acknowledgement

My very exciting and rewarding adventure in the Graduate School would never be possible without a large number of people who played important role at different stages of my life. Herein I want to give my deepest gratitude to them.

First and foremost I would like to thank my parents Tatyana Tyutyunnikova and Igor Gerasyuto and my younger brother Sergey Gerasyuto for all their love and care that always surrounded and supported me through out my life journey even when I was thousands and thousands of miles away from Home. I especially grateful to them for guiding me and being with me in my decisions.

I express my deepest gratitude and sincere appreciation to my graduate research advisor Professor Richard P. Hsung. We first met in summer 1999 when he kindly invited me to his research group as a summer student. Despite my expectations to be making starting materials for a graduate student, I got my own independent project which later grew into the topic for my graduate research studies! I so much enjoyed three consecutive summers I spent in Minnesota working in Richard Hsung's lab that I didn't need to think for a second where I want to pursue my Graduate studies. I'm extremely thankful to Richard for his guidance, help, encouragement throughout my thesis research. Knowing my keen interest in biochemistry and chemical biology he was supportive in taking several elective classes in those disciplines even though they kept me off the lab for some time. I will never forget the greatest research environment in Richard's research group to grow and develop as independent scientist. I'm also very grateful to him for giving a great opportunity to attend various scientific meetings as well as to have a great time off from work. I will always remember Richard as the greatest teacher, excellent mentor and also a good friend.

That is where I want to thank all current and former Hsung group members I have been working with over last five years. It was a great pleasure to do research in such friendly and supportive environment. My special thanks go to Mike McLaughlin, Kevin Cole and Aleksey Kurdyumov for being great friends, for valuable discussions and suggestions and also for taking the hit of my bad mood on those days when nothing worked out in the lab.

I have my very special thanks to my best friend Nadiya Sydorenko for her care, help, endless patience, support and simply for being in my life over these years. She always stood behind me especially when times were unbearably difficult. I also very much enjoyed great skiing and camping trips which with took together and that were important and essential part of my Graduate career.

I express my deep gratitude to Dr. Lev Lis of University of Minnesota for being my "American father" and also for great advices he has given over the years which have been and will always be very valuable to me.

I also want to specially thank my first Chemistry teacher in the high school Alexander Kristinin for making me interested in this science and allowing me to do some crazy experiments in his small school laboratory. I will always remember his endless patience when he came into the lab where we with my friend were trying to make ZnS by heating Zn powder with elemental sulfur... He stepped in right on time when we got this reaction to go, or at least we thought we did. The whistling sound, splash and cloud of something sky-rocketing to the ceiling with distinct smell of $H_2S$ just made him smile – be more careful, kids, he said. I'm also grateful to him and my parents for encouraging me to go to Moscow Chemical Lyceum for my last three years in the high school where I met a lot of great people and most of my best friends.

I cordially would like to acknowledge Sergey Semenov, the Director of the Moscow Chemical Lyceum, who played the key role in my journey of becoming a Scientist. He was a absolutely great teacher with enormous amount of enthusiasm and patience. I still remember his unusual but very efficient lecturing style. Me and my classmates always had a feeling that Sergey Semenov never knew exactly what he will be talking about in class before he had a piece of chalk in his hands. He could have spent the whole lecture talking about just one mechanism, taking arrow pushing to perfection, or we could fly over ten different topics. Over three years of his enjoyable and exciting lectures I imperceptibly gained a great fundamental knowledge and what I call a “feel” for Chemistry. Sergey Semenov also “opened a door” to actual synthetic organic laboratory where I did my first experiment by mixing anisaldehyde and two equivalents of bromine in refluxing $CCl_4$ to give 3-bromo-4-methoxybenzoic acid!

I’m really thankful to my undergraduate research advisor Professor Sergey Zlotin who was a great teacher and excellent supervisor. He was always helpful when I needed and advice but he also provided me with freedom in solving research problems myself. I’m especially grateful to him for teaching me how to write a scientific paper, how to make good slides and how to give a research presentation.

Thanks are also due to all chemistry teachers and professors in Higher Chemical College and institutions of Russian Academy of Sciences whom I met over 5 years in college and especially Professor Leonid Kovalenko, Professor William Smit, Professor Nataliya Tarasova and Professor Semen Ioffe who had the great impact on my education.

Finally I want to say thanks to all my friends and relatives who were around me over these years with their support and criticism, with their help and advices which I greatly appreciate.

# Table of Contents

# Abbreviations

| | |
|---|---|
| Å | angstrom |
| Ac | acetate |
| $Ac_2O$ | acetic anhydride |
| AcOH | acetic acid |
| AIBN | azobisisobutyronitrile |
| anhyd | anhydrous |
| aq | aqueous |
| atm | atmospheres |
| APCI | atmospheric pressure chemical ionization |
| 9-BBN | 9-borabicyclo[3.3.1]nonane |
| Bn | benzyl |
| Boc | *tert*-butoxycarbonyl |
| BINAP | 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl |
| $Boc_2O$ | di-*tert*-butyl dicarbonate |
| BORSM | based on recovered starting material |
| brs | broad singlet |
| B3LYP | Becke 3-Parameter, Lee, Yang, Parr density functional method |

| | |
|---|---|
| brd | broad doublet |
| Bu | butyl |
| C | Celsius |
| calcd | calculated |
| conc | concentrated |
| COSY | correlation spectroscopy |
| CSA | camphorsufonic acid |
| CSP-HPLC | chiral solid phase high pressure chromatography |
| Cy | cyclohexyl |
| $\delta$ | chemical shift in ppm |
| d | doublet |
| DBU | 1,8-Diazabicyclo[5.4.0]undec-7-ene |
| dd | doublet of doublets |
| ddd | doublet of doublets of doublets |
| dddd | doublet of doublets of doublets of doublets |
| DDQ | dichlorodicynoquinone |
| decomp | decomposition |
| DIAD | diisopropyl azodicarboxylate |

| | |
|---|---|
| DIBAL-H | diisobutyl aluminum hydride |
| DIPEA | N,N'-diisopropylethylamine |
| DMAP | 4-dimethyl aminopyridine |
| DMF | *N,N*-dimethylformamide |
| DME | 1,2-dimethoxy ethane |
| DMP | Dess-Martin periodinane |
| DMS | dimethyl sulfide |
| DMSO | dimethyl sulfoxide |
| *dr* | diastereomeric ratio |
| dt | doublet of triplets |
| EDTA | ethylenediaminetetraacetic acid |
| *ee* | enantiomeric excess |
| EI | electronic ionization |
| equiv | equivalent |
| *er* | enantiomeric ratio |
| Et | ethyl |
| $Et_2O$ | diethyl ether |
| EtOH | ethanol |

| | |
|---|---|
| EtOAc | ethyl acetate |
| g | gram |
| GCMS | gas chromatography mass spectrometry |
| h | hour |
| HRMS | high resolution mass spectrometry |
| Hz | hertz |
| *i*-Bu | *iso*-butyl |
| imid | imidazole |
| IPA | *iso*-propyl alcohol |
| *i*-Pr | *iso*-propyl |
| IR | infrared absorption spectroscopy |
| *J* | spin-spin coupling constant |
| Kcal | kilocalorie |
| KHMDS | potassium-hexamethyldisilazane |
| L | liter |
| LAH | lithium aluminum hydride |
| LCMS | liquid chromatography mass spectrometry |
| LDA | lithium diisopropylamine |

| | |
|---|---|
| m | multiplet |
| *M* | molar |
| mmHg | millimeters of mercury |
| mp | melting point |
| μ | mikro |
| *m*CPBA | *meta*-chloroperbenzoic acid |
| *m*/*e* | mass to charge ratio |
| Me | methyl |
| mg | miligram |
| MHz | mega Hertz |
| min | minute |
| mL | milliliter |
| mmol | millimole |
| Ms | mesityl |
| MS | molecular seives |
| mp | melting point |
| MTBE | methyl *tert*-butyl ether |
| *n*Bu | *normal*-butyl |

| | |
|---|---|
| NCS | *N*-chlorosuccimide |
| $Ni(acac)_2$ | nickel(II) acetylacetonate |
| NMO | 4-methyl morpholine *N*-oxide |
| NMR | nuclear magnetic resonance |
| nOe | nuclear Overhauser effect |
| OAc | acetate |
| OMe | methoxy |
| OTBS | *tert*-butyldimethylsiloxy |
| PCC | pyridinium chlorochromate |
| PDC | pyridinium dichromate |
| Pd/C | palladium on carbon |
| $Pd(OH)_2/C$ | palladium hydroxide on carbon |
| pipH | piperidine |
| Ph | phenyl |
| PM3 | parameterized model 3 |
| $PPh_3$ | triphenylphosphine |
| ppm | parts per million |
| PPTS | pyridinium *para*-toluenesulfonate |

| | |
|---|---|
| Pr | *normal*-propyl |
| *psi* | pounds per squire inch |
| *p*-TSA | *para*-toluenesulfonic acid |
| pyr | pyridine |
| quint | quintet |
| $R_f$ | retention factor |
| rt | room temperature |
| s | singlet |
| sat | saturated |
| t | triplet |
| TBAF | tetra-*n*-butyl ammonium fluoride |
| TBDPS | *tert*-butyldiphenyl silyl |
| TBS | *tert*-butyldimethyl silyl |
| *t*-Bu | *tert*-butyl |
| td | triplet of doublets |
| TEAF | tetraethyl ammonium fluoride |
| TEMPO | 2,2,6,6-tetramethyl-piperidine-1-oxyl radical |
| Tf | triflate |

| | |
|---|---|
| TFA | triflouroacetic acid |
| THF | tetrahydrofurane |
| THP | tetrahydropyranyl |
| TLC | thin layer chromatography |
| TMS | trimethylsilyl |
| TPAP | tetra-*n*-propylammonium perruthenate |
| TS | transition state |
| Ts | tosyl |
| TsOH | 4-toluene sulfonyl acid |
| tt | triplet of triplets |

# List of Figures, Schemes and Tables

# Part 1

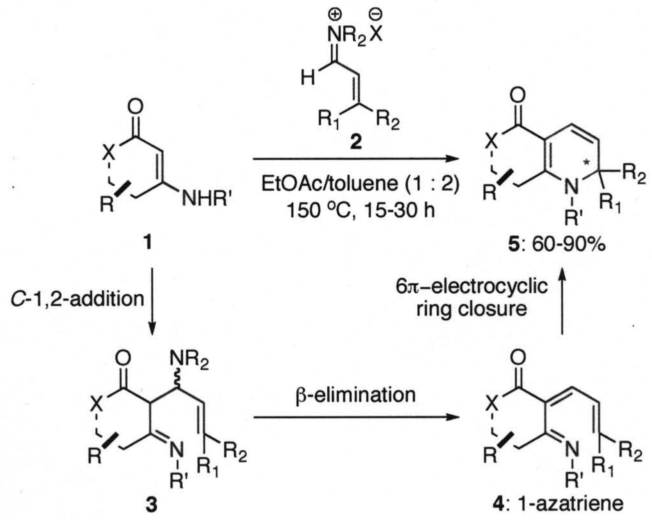
# Development of Enantioselective Intramolecular *Aza*-[3 + 3] Annulation

## 1.1. Introduction.

### 1.1.1 Intermolecular *Aza*-[3 + 3] Annulation.

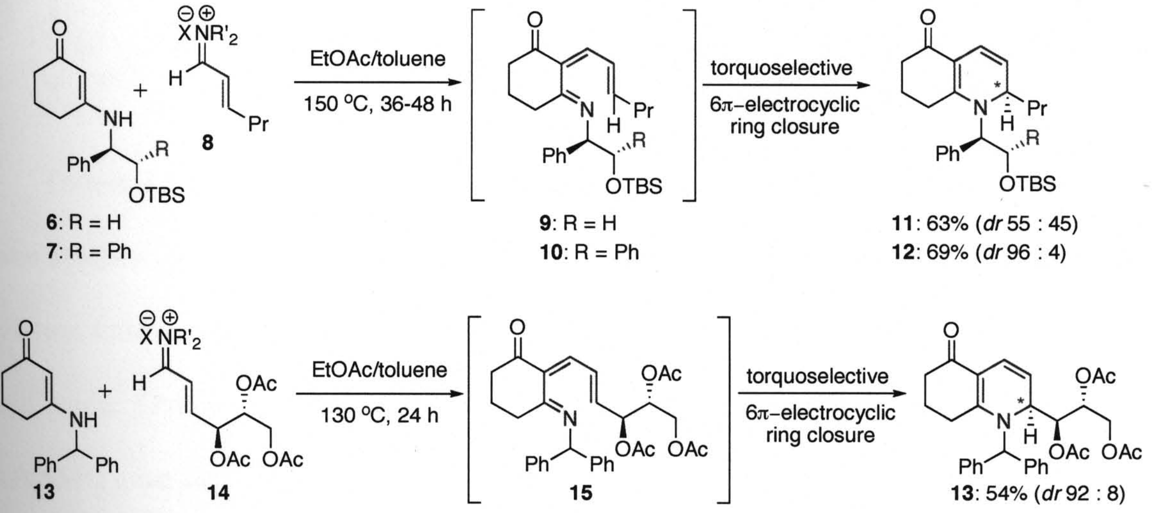
The *aza*-[3 + 3] annulation reaction of vinylogous amides with α,β-unsaturated iminium salts is being intensively studied in our group.[1] Specifically, this annulation provides a powerful synthetic strategy to nitrogen heterocycles such as dihydropyridines **5** (**Figure 1-1**).[2-4] It represents a formal *aza*-[3 + 3] cycloaddition[5,6] with two of the five carbons along with nitrogen atom coming from the vinylogous amide **1**, and the remaining three carbons coming from the α,β-unsaturated iminium salt **2**. The net result is the formation of two new σ-bonds and a stereocenter adjacent to the nitrogen atom. Mechanistically this intermolecular process [**1** + **2** → **5**] constitutes a tandem Knoevenagel condensation–6π-electron electrocyclic ring-closure involving an 1-azatriene intermediate **4**.[7-9]

**Figure 1-1.** Intermolecular *aza*-[3 + 3] annulation.



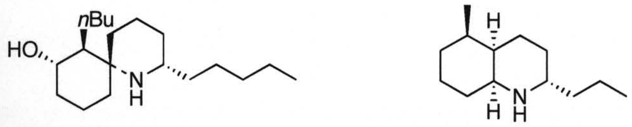
The latter part of this tandem sequence, the pericyclic ring-closure, can be rendered highly stereoselective when driven by a chiral auxiliary on the nitrogen atom or on the *C*-terminus of the azatriene (**Scheme 1-1**). Thus, increase in the bulk of the chiral auxiliary on the nitrogen atom of vinylogous amide led to higher diastereoselectivity of the annulation reaction (**6** + **8** → **11** versus **7** + **8** → **12**) via torquoselective pericyclic ring-closure of chiral azatriene intermediates **9** and **10**.[4c-e] Also, torquoselective ring-closure of the azatriene **15** with chirality on the *C*-terminus could be rendered by utilizing sterically encumbered vinylogous amide **13** and chiral enal **14** in the *aza*-[3 + 3] annulation reaction providing cycloadduct **16** with high degree of diastereoselectivity.[4a]

**Scheme 1-1.** Stereoselective intermolecular *aza*-[3 + 3] annulation.



The developed intermolecular *aza*-[3 + 3] annulation methodology was recently applied to the syntheses of several natural products such as (±)-2-*epi*-perhydrohistrionicotoxin[4d] and (-)-4a-8a-*diepi*-pumiliotoxin C[4c] (**Figure 1-2**).

**Figure 1-2.** Natural products prepared via intermolecular *aza*-[3 + 3] annulation.

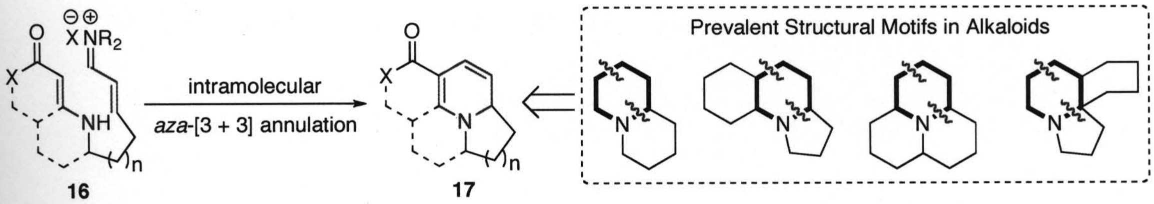


**14**: 2-*epi*-perhydrohistrionicotoxin **15**: (-)-4a-8a-*diepi*-pumiliotoxin C

### 1.1.2 Intramolecular *Aza*-[3 + 3] Annulation.

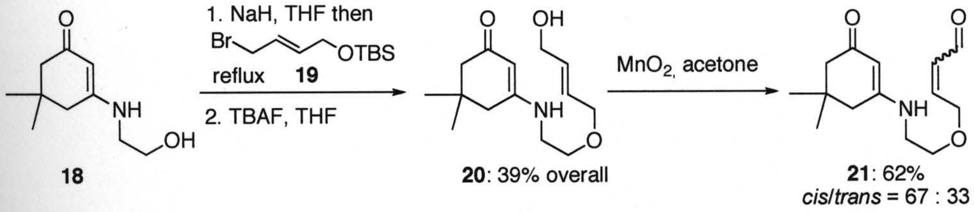
Our work on intermolecular annulation has also allowed to propose an intramolecular version of this reaction (**Figure 1-3**). It was suggested that vinylogous amide **16** bearing the iminium salt tether could cyclize in a fashion similar to the intermolecular case, producing fused heterocycles **17**, which could be useful intermediates in alkaloid syntheses.

**Figure 1-3.** Intramolecular *aza*-[3 + 3] annulation.



To test the concept of the intramolecular *aza*-[3 + 3] annulation, cycloaddition precursor **21** was synthesized from commercially available alcohol **18** and bromide **19** (**Scheme 1-2**). *O*-Alkylation followed by removal of the TBS group using TBAF gave allylic alcohol **20** in 36% overall yield. Oxidation of alcohol **20** with a variety of oxidants such as PDC, PCC and TPAP/NMO gave aldehyde **21** with low yields.

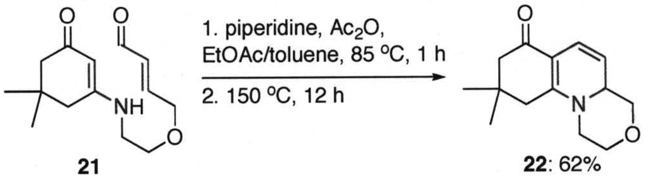
**Scheme 1-2.** Synthesis of the precursor **21**.



Dess-Martin oxidation of **11** produced the desired aldehyde with good yield according to the $^1$H NMR spectrum of the crude material, but the product could not be separated from the periodinane by-products due to its very polar nature. Finally, oxidation of **20** to **21** was successfully accomplished by use of activated $MnO_2$ (**Scheme 1-2**). The main advantage of using this protocol is that the product can be isolated by simple filtration of $MnO_2$ and evaporation of the solvent.

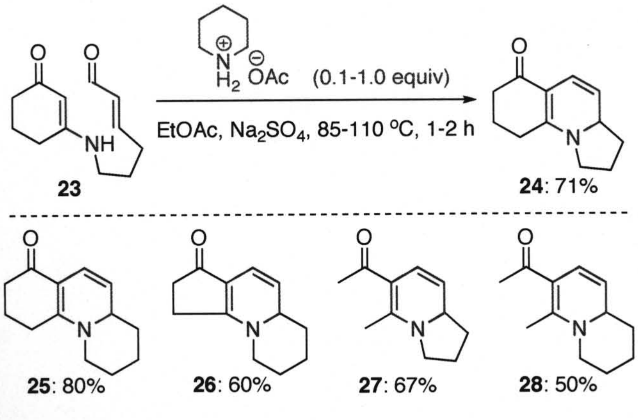
Vinylogous amide **21** was subjected to the reaction conditions generally used for our intermolecular [3 + 3] annulations reactions. Reaction of amide **21** with piperidine and acetic anhydride at 80 °C for 1 h followed by heating at 150 °C for 12 h in a sealed tube produced the desired quinolizidine **22** in 62% yield (**Scheme 1-3**).

**Scheme 1-3.** The first example of intramolecular *aza*-[3 + 3] annulation.



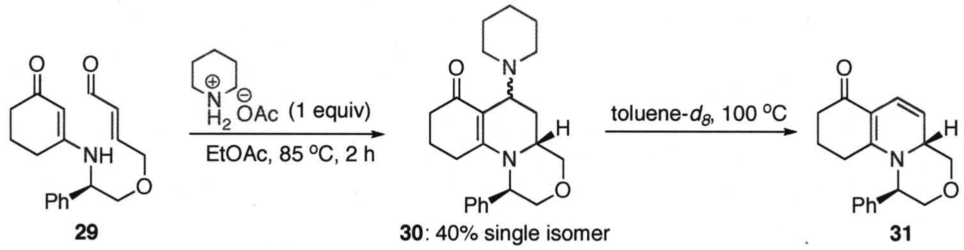
It was later found that the discovered reaction could be promoted by the salts of secondary amines such as piperidinium acetate (pipH·AcOH).[10] These conditions have allowed for the reaction to be run at a lower temperature (85-100 °C) and with sub-stoichiometric amount of pipH·AcOH (**Scheme 1-4**). This protocol was suitable for the synthesis of a variety of different azadecalines **24-28** which could be difficult to access through the original procedure.

**Scheme 1-4.** Optimized conditions.



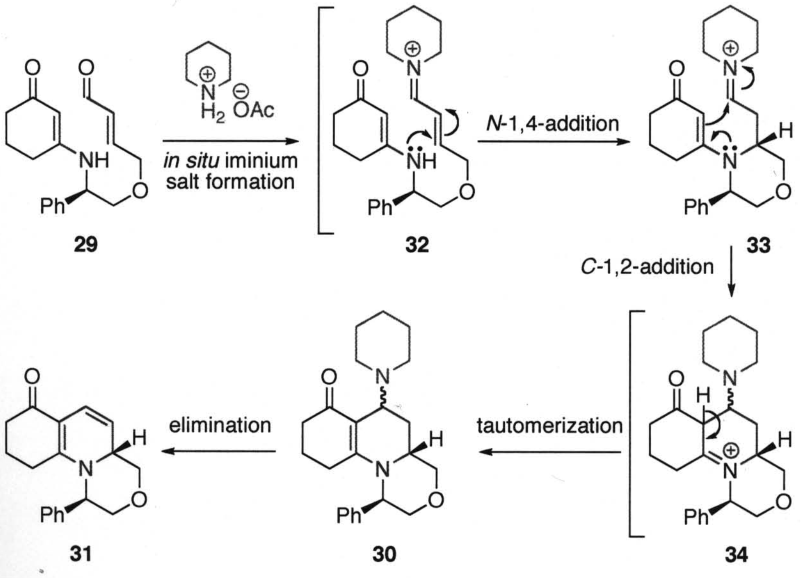
During optimization of the reaction conditions for the intramolecular [3 + 3] cycloaddition reaction, we also isolated the intermediate **30** of the cycloaddition reaction as a single diastereomer after heating vinylogous amide **29** with 1 equiv of pipH·AcOH in ethyl acetate at 85 °C for 2 h (**Scheme 1-5**).[4c] It is noteworthy that heating of the isolated intermediate **30** in deuterated toluene in a sealed NMR tube at 100 °C for 2 h led cleanly to product **31**.

**Scheme 1-5.** Intermediate of intramolecular annulation.



This discovery suggested the following mechanism for intramolecular *aza*-[3 + 3] annulation that differs from the intermolecular case (**Scheme 1-6**).

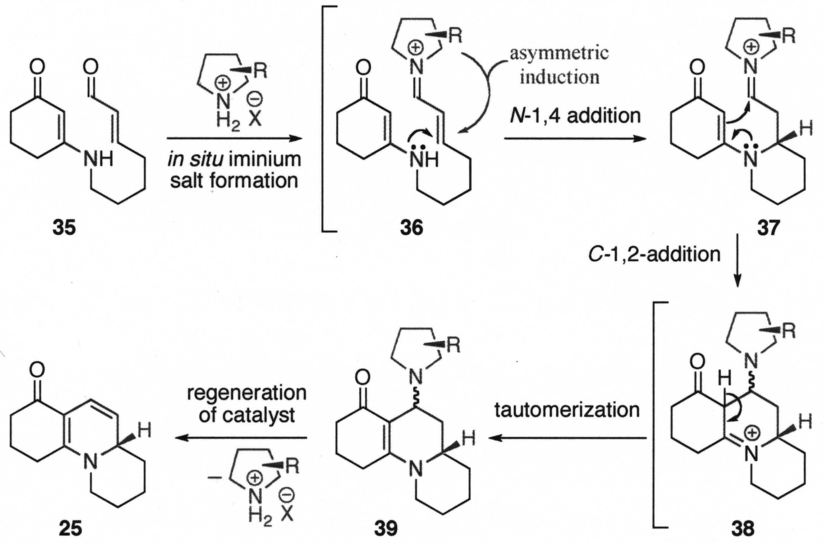
**Scheme 1-6.** Mechanism of intramolecular annulation.



α,β-Unsaturated iminium salt **32**, generated *in situ* from vinylogous amide **29** undergoes a *N*-1,4-addition, followed by *C*-1,2-addition to the iminium salt, that gives the intermediate **30** after tautomerization of **34**. Subsequent elimination of piperidine furnishes the formation of the cycloadduct **31**. In this case the stereochemistry of the chiral center adjacent to nitrogen atom formed during 1,4-addition is controlled by the existing phenyl-substituted chiral center.

Consequently, the proposed mechanism has allowed us to envision the possibility of chiral induction during the *N*-1,4-addition step by use of the chiral amine salts as the catalysts for intramolecular [3 + 3] reaction (**35** → **25**, **Scheme 1-7**).

**Scheme 1-7.** Proposed scheme of asymmetric induction.



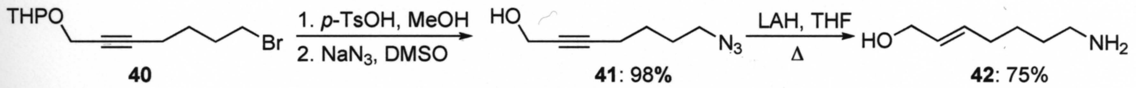
Since this process involves regeneration of the catalyst step (**39** → **25**, **Scheme 1-7**) it could be rendered both enantioselectively and catalytically. Also given that organocatalysis has attracted much attention recently,[11-15] investigations on intramolecular *aza*-[3 + 3] annulation could represent an unique opportunity to explore organocatalysis in a tandem process.

## 1.2. Results and Discussions

### 1.2.1. Synthetic Feasibility

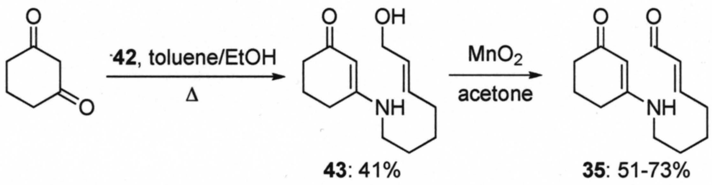
To explore the feasibility of an enantioselective formal *aza*-[3 + 3] cycloaddition, vinylogous amide **35** was chosen as a model system. It was prepared in 5 operational steps from known THP-protected alkynyl bromide **40**[16a] (**Scheme 1-8**). Removal of the THP-protecting group by treatment with TsOH in MeOH, followed by conversion of bromide to azide by reaction with $NaN_3$ in DMSO led to azido alcohol **41** in nearly quantitative yield. Reduction of **41** with excess LAH under reflux conditions afforded amino alcohol **42** in 75% yield.

**Scheme 1-8.** Synthesis of amino alcohol **42**.



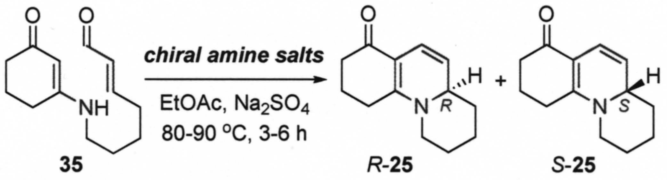
Condensation of the amino alcohol **42** with 1,3-cyclohexanedione led to formation of vinylogous amide **43** in moderated yield. Activated $MnO_2$ oxidation protocol worked well on this system generally giving 59-73% yield of desired enal **35** (**Scheme 1-9**).

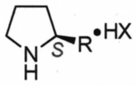
**Scheme 1-9.** Synthesis of the annulation precursor **35**.

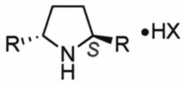


With compound **35** in hands its intramolecular *aza*-[3 + 3] annulation reaction was first examined using a series of *L*-proline based amine salts **44a-e**, which are $C_1$-symmetric, and various pyrrolidine based amine salts **45a-c**, which are $C_2$-symmetric. The obtained results are summarized in **Table 1-1**.

**Table 1-1.** Chiral pyrrolidines catalyzed annulation.







**44a:** R = COOH
**44b:** R = COOMe, X = Cl
**44c:** R = $CH_2OH$, X = OAc
**44d:** R = $CH_2OTBDPS$, X = OAc
**44e:** R = $C(Ph)_2OH$, X = OAc

**45a:** R = $CH_2OMe$, X = Cl
**45b:** R = COOMe, X = Cl
**45c:** R = $CH_2OTBDPS$, X = OAc

| entry | catalyst | mol% | yield (%) | *er* (*R* : *S*) |
|---|---|---|---|---|
| 1 | **44a** | 40 | 26 | 56 : 44 |
| 2 | **44b** | 30 | 68 | 52 : 48 |
| 3 | **44b** | 100 | 68 | 52 : 48 |
| 4 | **44c** | 100 | 52 | 50 : 50 |
| 5 | **44d** | 100 | 56 | 55 : 45 |
| **6** | **44e** | **40** | **60** | **81 : 19** |
| 7 | **44e** | 100 | 63 | 80 : 20 |
| 8 | **45a**[16b] | 40 | 57 | 50 : 50 |
| 9 | *ent*-**45b** | 100 | 67 | 60 : 40 |
| **10** | **45c** | **40** | **46** | **27 : 73** |

It can be seen that in all cases the reaction proceeded well to give the annulation product **25** in moderate to good yields. The use of 30-40 mol% of the chiral catalyst was sufficient to promote the cycloaddition [entries 1, 2, 6, 8, and 10], while increasing the amount of the catalyst did not necessarily lead to an improved enantioselectivity [entries 3-5, 7 and 9].

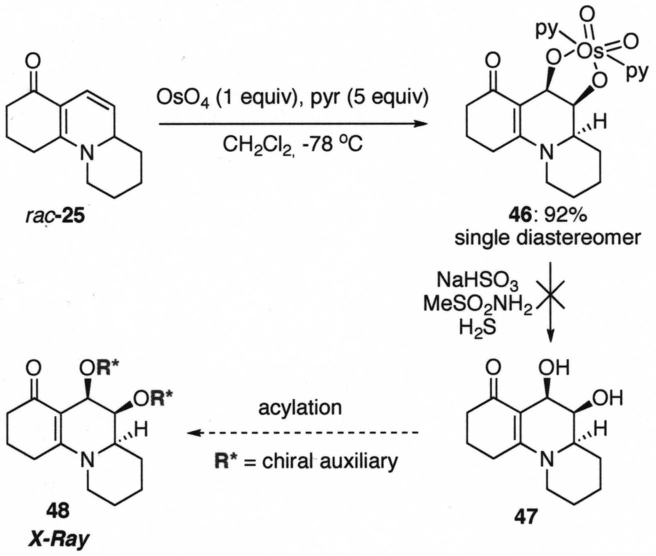
More importantly, three features of the annulation captured our attention. First, $C_2$-symmetric pyrrolidine based catalysts gave higher enantiomeric ratios than those obtained from using L-proline based derivatives [entries 2 and 5 versus 9 and 10, respectively]. Secondly, the enantioselectivity could be modestly enhanced using sterically more bulky catalysts such as **44e** [entry 6] and **45c** [entry 10] but appear to have reached the maximum. Thirdly, it was found that

$C_1$ and $C_2$-symmetric catalysts provided cycloadduct **25** with enrichment for the opposite enantiomer [entry 6 versus 10].

### 1.2.2. Absolute Configuration Assignment.

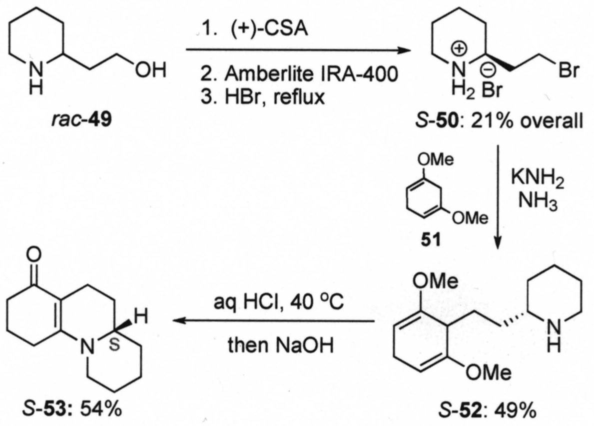
In order to assess the origin of observed enantioselectivity, the absolute configuration of major enantiomer was first determined. We initially tried to functionalize annulation product **25** with hopes to obtain X-Ray quality crystals from derivative containing pre-existing stereogenic center like **48** (**Scheme 1-10**). Toward this goal tricycle **25** was treated with 1 equiv of $OsO_4$ in presence of 5 equiv of pyridine at -78 °C. Removal of the solvent led to isolation of osmate ester **46** as very stable brown solid in 92% yield. It is noteworthy that **46** was stable to silica gel and could be purified by column chromatography. Unfortunately numerous attempts to cleave osmate ester **46** and convert it to the diol **47** have all failed.

**Scheme 1-10.** Synthesis of osmate ester **46**.



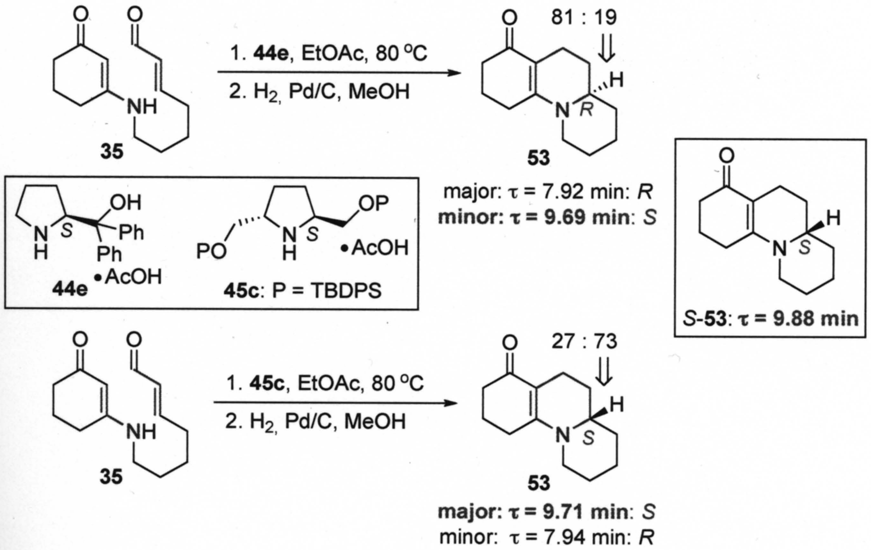
At this point we decide to synthesize enantiomerically pure *S*-**53** independently as shown in **Scheme 1-11**,[17] featuring a resolution of racemic piperidine **49** with (+)-CSA using a procedure developed by Toy.[18] Amino alcohol was then converted to bromide **50** by treatment with conc aqueous HBr. Alkylation of diene **51** with bromide **50** afforded compound **52** in 49% yield. Finally, cleavage of both methyl enol ethers followed by spontaneous cyclization finished the formation of desired tricycle **53** as *S*-enantiomer.

**Scheme 1-11.** Independent synthesis of *S*-**53**.



The absolute configuration of annulation product **25** was determined based on CSP-HPLC comparison between the scalemic **53** obtained via hydrogenation of the formal cycloadduct **25** and the enantiomerically pure *S*-**53** (**Figure 1-4**).

**Figure 1-4.** Determination of absolute configuration.

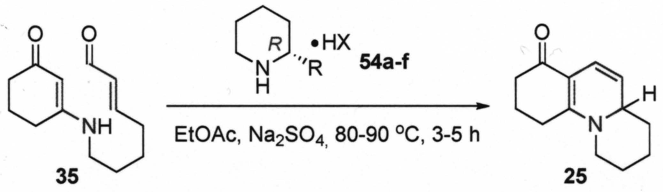


Interestingly, when the *S*-enantiomer of $C_1$-symmetric catalyst such as **44e** was used, the cycloaddition favored the *R*-enantiomer, while the 2*S*,5*S*-enantiomer of $C_2$-symmetric catalyst **45c** gave predominantly *S*-enantiomer.

### 1.2.3. Catalyst Screening.

In the search for an amine catalyst that can provide improved asymmetric induction, chiral piperidines **54a-f** were screened (**Table 1-2**). The first observation was that the nature of counter-anion in the catalyst did not appear to have any impact on the enantioselectivity. For instance, using the L-tartrate salt of pipecolic acid **54b** did not lead to any improvement in the enantiomeric ratio when compared to the acetate salt **54a** [entry 2 versus 1]. Most disappointingly, none of the chiral piperidines provided any meaningful enantioselectivity.

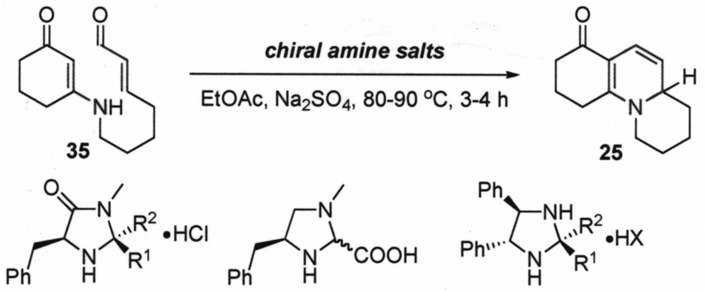
**Table 1-2.** Chiral piperidines as catalysts.



| entry | piperidine catalyst | mol% | yield (%) | *er* (*R* : *S*) |
|---|---|---|---|---|
| 1 | **54a:**[19a] R = COOH<br>X = OAc | 40 | 45 | 48 : 52 |
| 2 | **54b:**[19a] R = COOH<br>X = L-tartrate | 40 | 53 | 47 : 53 |
| 3 | **54c:**[19a,b] R = COOMe<br>X = Cl | 50 | 65 | 48 : 52 |
| 4 | **54d:** R = $CH_2OTBDPS$<br>X = OAc | 100 | 42 | 47 : 53 |
| 5 | **54e:**[19b] R = $C(Ph)_2OH$<br>X = Cl | 40 | *ca* 15<br>(130 °C) | 49 : 51 |
| 6 | **54f:** R = $C(Ph)_2OH$<br>X = $O_2CCF_3$ | 40 | 62 | 48 : 52 |

Moreover, treatment of vinylogous amide **35** with the amine salt **54e** bearing a diphenylhydroxymethyl substituent did not lead to the desired dihydropyridine **25** under standard reaction conditions [entry 5]. Instead, the reaction had to be heated at an elevated temperature (130 °C) for 14 h in a sealed tube in which severe decomposition occurred with only *ca* 50% conversion. Although we were able to isolate some **35**, it was racemic. The reaction temperature could be lowered to 80 °C when using the more active trifluoroacetate salt **54f** (see **Section 1.2.3** below for details). In this case, the cycloaddition of **35** went to completion in 2 h and **25** was isolated in good yield [entry 6]. However, the product remained racemic. These results suggest that chiral piperidines are even less useful as chiral catalysts than chiral pyrrolidines for this particular reaction.

**Table 1-3.** MacMillan's and Jørgensen's amine salts.



**55a:** $R^1 = R^2 = Me$
**55b:** $R^1 = t\text{-Bu}, R^2 = H$
**55c:** $R^1 = H, R^2 = t\text{-Bu}$

**56**

**57a:** $R^1 = COOH, R^2 = H$
**57b:** $R^1 = R^2 = CH_3$, X = OAc
**57c:** $R^1 = Ph, R^2 = H$, X = OAc

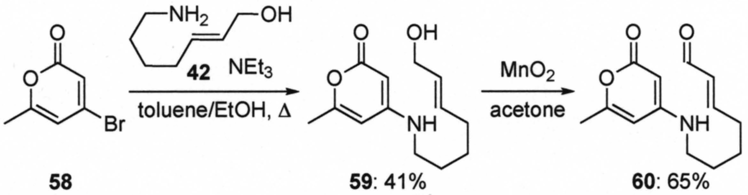
| entry | catalyst | mol% | yield (%) | *er* (*R* : *S*) |
|---|---|---|---|---|
| 1 | **55a**[12i] | 50 | 16 | 50 : 50 |
| 2 | **55b**[12d] | 50 | 27(rt) | 50 : 50 |
| 3 | **55c**[12d] | 50 | 22 (rt) | 58 : 42 |
| 4 | **56**[14g] | 100 | 57 | 60 : 40 |
| 5 | **57a**[14g] | 100 | 53 | 63 : 37 |
| 6 | **57b**[14g] | 100 | 48 | 62 : 38 |
| 7 | **57c**[14g] | 100 | 63 | 50 : 50 |

To continue our efforts, we turned to MacMillan's chiral amine salts **55a-c**[12d,i] (**Table 1-3**) as well as those developed by Jørgensen [**56** and **57a-c**].[14g] These amines are known to catalyze a variety of organic transformations in a highly enantioselective manner.[11-15] As summarized in **Table 1-3**, the desired cycloadduct **25** was isolated in all cases, but the highest enantiomeric ratio was only 63 : 37 when using $C_2$-symmetric catalyst **57a** [entry 5]. In addition, for reactions catalyzed with **55a-c**, a significant amount of decomposition occurred, thereby leading to lower yields [entries 1-3].

### 1.2.4. Synthetic Scope.

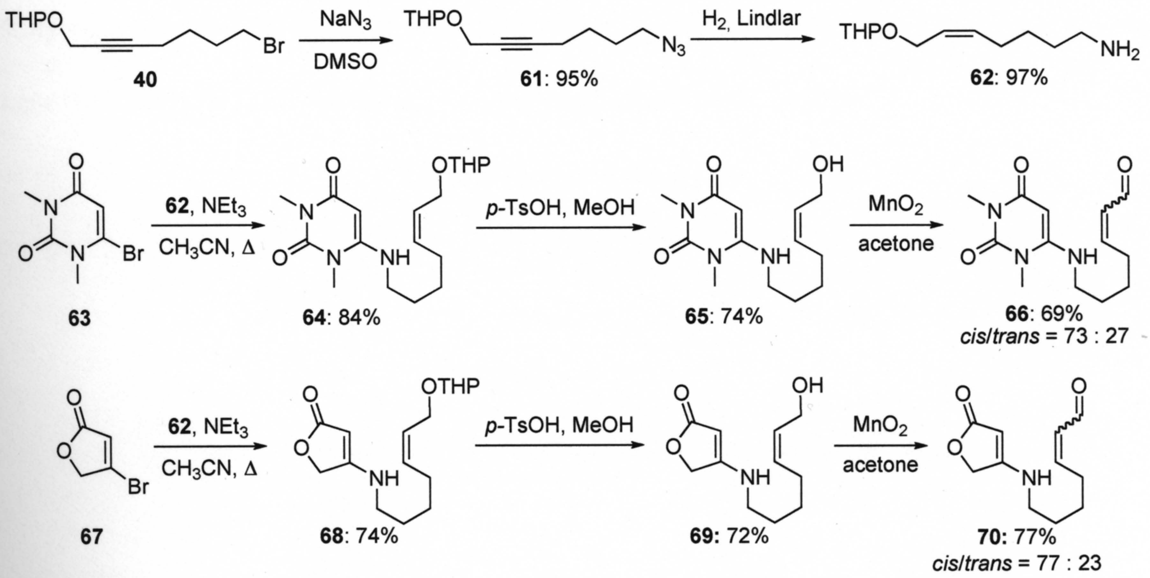
Based on these results, the acetate salt of α,α-diphenyl-2-pyrrolidinemethanol **44e** appears to be the most efficient catalyst to promote a modestly enantioselective intramolecular *aza*-[3 + 3] annulation of vinylogous amide **25**. Thus, to explore the synthetic scope of the developed methodology various other vinylogous amides were prepared. Pyrone containing annulation precursor **60** was prepared by condensation of bromide **58**[20] with amino alcohol **42** followed by $MnO_2$ oxidation (**Scheme 1-12**).

**Scheme 1-12.** Pyrone containing vinylogous amide **60**.



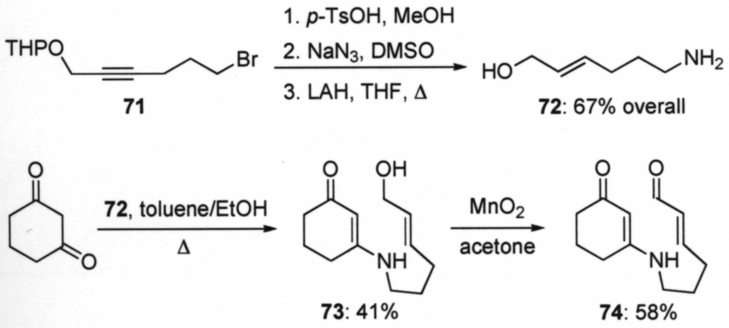
To prepare cycloaddition precursors **66** and **70** *cis*-THP-protected amino alcohol **62** was synthesized (**Scheme 1-13**). Bromide **40** was converted to azide **61** by treatment with sodium azide. *Cis*-amine **62** was obtained in excellent yield upon hydrogenation of **61** over Lindlar's catalyst. Condensation of amine **62** with bromide **63**[20] in $CH_3CN$ afforded corresponding vinylogous amide **64** in good yield. THP-protecting group was removed under acidic conditions and allyl alcohol **65** was subjected to $MnO_2$ oxidation conditions. Reaction proceeded smoothly with good yield but with partial isomerization of the double bond to give enal **66** as *cis*/*trans* mixture of isomers. The same protocol was utilized to prepare annulation precursor **70** from corresponding bromide **67**[20] (**Scheme 1-13**).

**Scheme 1-13.** Annulation precursor syntheses.



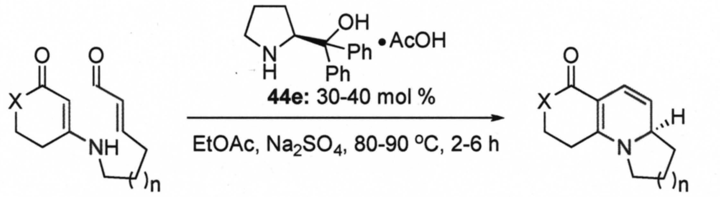
Vinylogous amide containing 3-carbon tether **74** was prepared starting from known bromide **71**[21a] by 3 steps protocol used for synthesis of amino alcohol **42** (**Scheme 1-8**). Subsequent condensation of amine **72** with 1,3-cyclohexanedione followed by $MnO_2$ oxidation of allyl alcohol **73** afforded vinylogous amide **74** in modest yield (**Scheme 1-14**).

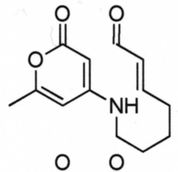
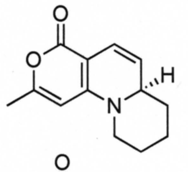
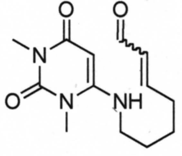
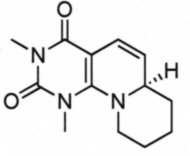
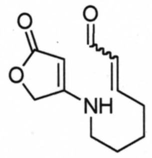
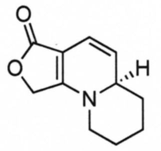
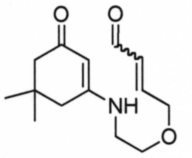
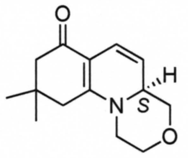
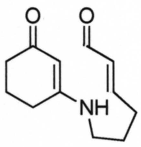
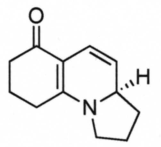
**Scheme 1-14.** Vinylogous amide bearing 3-carbon tether.



With annulation precursors in hands they were employed in the intramolecular *aza*-[3 + 3] annulation reaction catalyzed by amine salt **44e**. As illustrated in **Table 1-4**, all reactions proceeded to give the respective cycloadducts **75-78** and **22** in modest to good yields and comparable enantioselectivity (*er* ~80 : 20) with the exception of vinylogous amide **74**, bearing a 3-carbon tether, which gave only 20% *ee* [entry 5]. Lower enantioselectivity in this case could probably be explained on basis of less rigid transition state structure for *N*-1,4-addition step in this case (see **Section 1.2.5** for details on proposed mechanistic model).

**Table 1-4.** Synthetic scope.

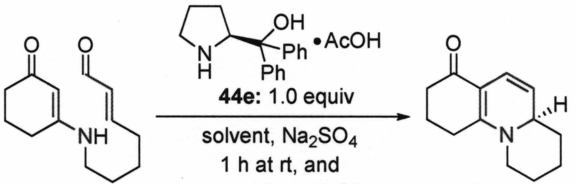


| entry | starting amide | | cycloadduct | | yield (%) | *er* (*R* : *S*) |
|---|---|---|---|---|---|---|
| 1 |  | **60** |  | **75** | 56 | 75 : 25 |
| 2 |  | **66** |  | **76** | 65 | 80 : 20 |
| 3 |  | **70** |  | **77** | 41 | 74 : 26 |
| 4 |  | **21** |  | **22** | 61 | 27 : 73 |
| 5 |  | **74** |  | **78** | 44 | 60 : 40 |

### 1.2.5. Solvent, Counter-Anion, and Temperature Effects.

*Solvent Effect.* We subsequently pursued a series of studies to investigate what other factors could effect or improve the enantioselectivity of this annulation reaction. Toward this goal, the reaction of vinylogous amide **35** was carried out in different solvents in the presence of 1.0 equiv of the amine salt **44e** (**Table 1-5**). The reaction was kept at rt for 1 h, and was then heated to 80 °C for 2 h. At this point complete consumption of **35** was observed by TLC. Only in the case of acetic acid [entry 6], no formation of the desired cycloadduct **25** was detected besides decomposition of starting material. Under these conditions, it appears to be no significant dependence of the enantioselectivity on solvent. The observed enantiomeric ratio remained at about 80 : 20, which was initially found for reactions carried out in EtOAc [entry 1]. Only a slight increase in selectivity was detected when acetone was used [entry 4].

**Table 1-5.** Solvent effect.



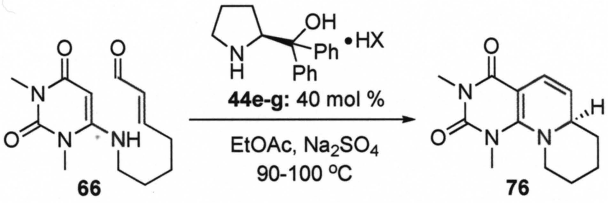
**35** **25**

| entry | solvent | yield$^a$ (%) | *er* (*R* : *S*) |
|---|---|---|---|
| 1 | EtOAc | 60 | 81 : 19 |
| 2 | $CHCl_3$ | 57 | 76 : 24 |
| 3 | EtOH | 42 | 81 : 19 |
| **4** | **acetone** | 53 | **84 : 16** |
| 5 | THF | 48 | 83 : 17 |
| 6 | AcOH | NA | decomp |

**a)** Based on $^1H$ NMR

*Counter-Anion Effect.* We then examined the possibility of a counter-anion effect in the case of the most effective amine, α,α-diphenyl-2-pyrrolidinemethanol. Therefore, vinylogous amide **66** was allowed to react with three different amine salts **44e-g** under standard reaction conditions (**Table 1-6**).

**Table 1-6.** Counter-anion effect.



| entry | catalyst | time (h) | yield (%) | *er* (*R* : *S*) |
|---|---|---|---|---|
| 1 | **44e:** X = OAc | 1.5 | 61 | 80 : 20 |
| 2 | **44f:** X = $O_2CCF_3$ | 1 | 58 | 79 : 21 |
| 3 | **44g:** X = Cl[21b] | 12 | 66 | 76 : 24 |

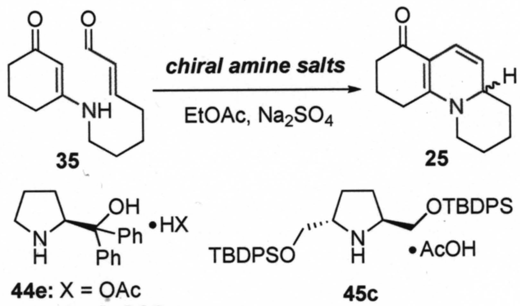
In all cases, the desired cycloadduct **76** was isolated in good yield, but there was again no significant dependence of enantioselectivity of the reaction on the nature of the counter-anion. However, there was a noticeable difference in reaction rate between the three catalysts. It turned out that the trifluoroacetate salt **44f** was the most active and provided complete conversion of **66** to **76** in 1 h [entry 2]. The reaction with the acetate salt **44e** took longer time to complete [entry 1], while the chloride salt **44g** was found to be the least active [entry 3].

The observed difference in reactivity can be rationalized in two possible ways. First, the chloride salt **44g** is not as soluble in EtOAc as the acetate salt **44e** or the trifluoroacetate salt **44f**. Secondly, a more important possibility would be that the difference in reactivity is related to the dissociation capacity of the respective amine salts.

Since both "free amine" and "free acid" are needed in a synergistic manner to generate an α,β-unsaturated iminium salt from the corresponding aldehyde, the ability of the amine salt to dissociate to its "free amine" and "free acid" can exert an impact on the rate of the iminium salt formation. The low reactivity of the chloride salt **44g** can be attributed to its higher resistance toward dissociation, in the other words **44g** is simply a tighter ion-pair comparing to the acetate salt **44e** and the trifluoroacetate **44f.** At the same time, the formation of α,β-unsaturated iminium salt from the aldehyde and the "free amine" is also promoted by protonation of the carbonyl group via the "free acid." Consequently, increased reactivity of the trifluoroacetate salt **44f** from the acetate salt **44e** can be attributed to a higher acidity of trifluoroacetic acid.

*Temperature Effect.* Finally, we examined the temperature effect as shown in **Table 1-7.** Vinylogous amide **35** was reacted with chiral amine salt **45c** and reactive trifluoroacetate **44f** at rt, and the resulting enantiomeric ratios were compared with reactions carried out at 80 °C. The reaction took much longer at rt and led to lower yields of **25** [entries 1 and 3], and no significant increase in enantioselectivity was observed in either case.

**Table 1-7.** Temperature effect.



**44e:** X = OAc
**44f:** X = $O_2CCF_3$
**45c**

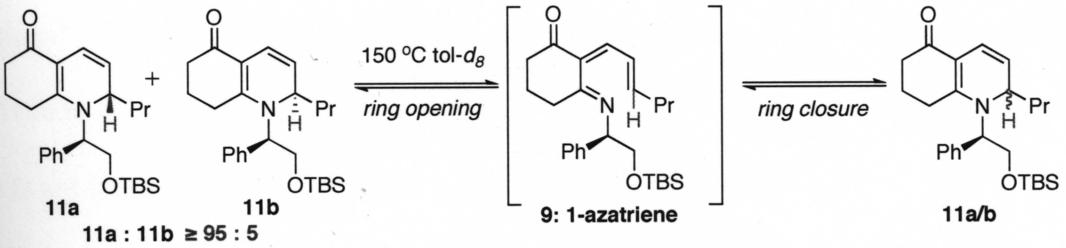
| entry | cat (mol %) | temp (°C) | time (h) | yield (%) | *er* (*R* : *S*) |
|---|---|---|---|---|---|
| 1 | **44f** (40) | rt | 10 | 43 | 75 : 25 |
| 2 | **44e** (50) | 80 | 6 | 60 | 81 : 19 |
| 3 | **45c** (40) | rt | 14 | 16 | 23 : 77 |
| 4 | **45c** (40) | 80 | 3 | 46 | 27 : 73 |

### 1.2.6. Racemization Possibility and Enal-Geometry.

As was discussed in the introduction, the intermolecular *aza*-[3 + 3] cycloaddition undergoes a pericyclic ring-closure of 1-azatriene intermediates *en route* to the formation of 1,2-

dihydropyridines (**Scheme 1**).[4c] Also reversibility of the pericyclic ring-closure was confirmed by the following experiment. From 1 : 1 mixture of cycloadducts **11**, prepared as shown in **Scheme 1-1**, pure sample of one diastereomer **11a** was isolated and then heated in toluene-$d_8$ at 150 °C for 60 h. The reaction was monitored by $^1$H NMR, and observed diastereomeric ratios of **11a/11b** as a function of time are shown in **Table 1-8**. Although the rate of equilibration through a sequence of ring-opening of **11** to 1-azatriene **9** with subsequent ring-closure of **9** appeared to be slow, it is unambiguous that the ring closure is reversible and ultimately led to **11a/b** with a ratio [entry 6] matching the original ratio (55 : 45) obtained from annulation reaction (**Scheme 1**).[4c]

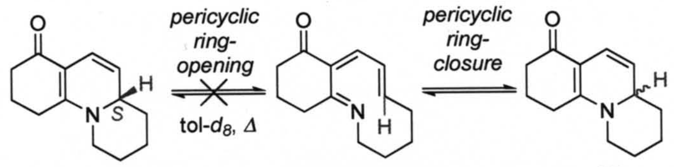
**Table 1-8.** Reversibility of 6π-electrocyclic ring-closure.



| entry | time (h) | *dr* (**11a** : **11b**) |
|---|---|---|
| 1 | 0 | ≥ 95 : 5 |
| 2 | 1.5 | 93 : 7 |
| 3 | 12 | 82 : 18 |
| 4 | 20 | 77 : 23 |
| 5 | 36 | 66 : 34 |
| 6 | 60 | **60 : 40** |
| ratio from the reaction | | **55 : 45** |

Although intramolecular reactions proceed through a different mechanism,[4c,10] we still questioned if the modest enantioselectivity obtained from these chiral amine catalyzed cycloadditions could be a result of racemization of the final cycloadduct via the same 6π-electron electrocyclic ring-opening and ring-closure through the 1-azatriene intermediate **79** (**Table 1-9**).

**Table 1-9.** Racemization via pericyclic ring-opening.



*enriched-S*-**25**

**79:** 1-azatriene
$\Delta E$ = + 31 kcal/mol
(*Spartan'02:* B3LYP/6-31G*)

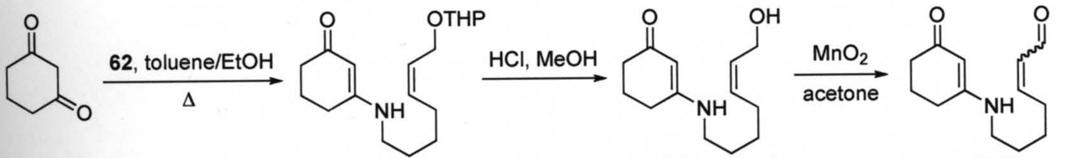
*rac*-**25**

| entry | time (h) | temp (°C) | *er* (*R* : *S*) |
|---|---|---|---|
| 1 | 0 | rt | 27 : 73 |
| 2 | 3 | 85 | 26 : 74 |
| 3 | 12 | 130 | 27 : 73 |

To test this possibility, an enantiomerically enriched sample of cycloadduct **25** was heated in toluene-$d_8$. After 3 h at 85 °C, no loss of *ee* was detected [entry 2]. More significantly, even after **25** was heated at 130 °C for 12 h, no racemization had occurred [entry 3]. *Ab initio* calculations[22] indicate that 1-azatriene **79** is destabilized relative to **25** by ~ 31 kcal/mol. Since the activation barrier would be even higher, we believe that 6π-electrocyclic ring-opening process is not thermally accessible under our standard reaction conditions.

To examine the influence of the enal-geometry on enantioselectivity, vinylogous amide **35** was prepared as mixture of *cis*/*trans* isomers in three steps from 1,3-cyclohexanedione and amine **62** (**Scheme 1-15**).

**Scheme 1-15.** *Cis*-annulation precursor **35**.



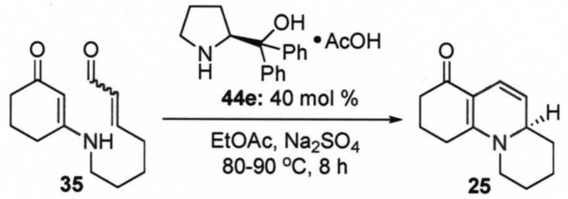
**80**

**81**: 53% (2 steps)

**35**: 56%
*cis*/*trans* = 73 : 27

Then it was submitted to standard reaction conditions using **44e** (**Table 1-10**). The product **35** was isolated in comparable yield and its enantiomeric purity [entry 2] was virtually the same as in the reaction of pure *trans*-isomer [entry 1]. We believe that a facile isomerization of *cis*-enal to the more stable *trans*-isomer takes place under the reaction conditions, thereby rendering the enal-geometry irrelevant to the asymmetric induction.

**Table 1-10.** Impact of enal-geometry.

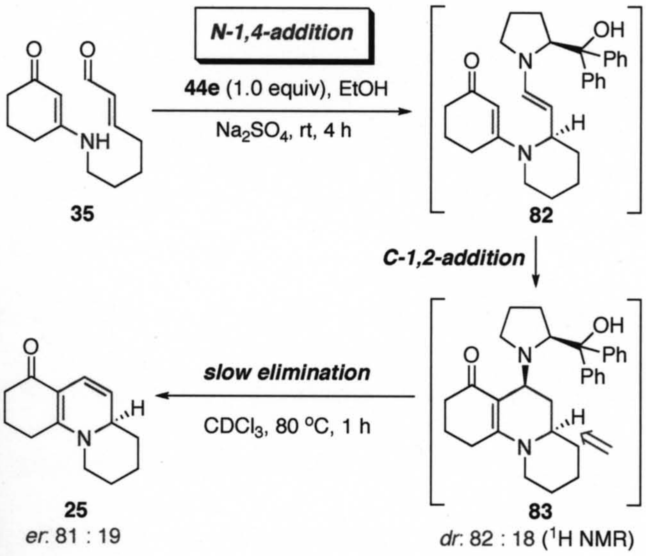


| entry | *E* : *Z* | yield (%) | *er* (R : S) |
|---|---|---|---|
| 1 | 100 : 0 | 60 | 81 : 19 |
| 2 | 27 : 73 | 58 | 77 : 23 |

### 1.2.7. Detection of the Key Intermediate.

When vinylogous amide **35** was reacted with 1.0 equiv of the amine salt **44e** at rt in EtOH, the formation of the intermediate **83** was detected by $^1$H NMR and mass spectroscopy (**Scheme 1-16**).

**Scheme 1-16.** Detection of the key intermediate.

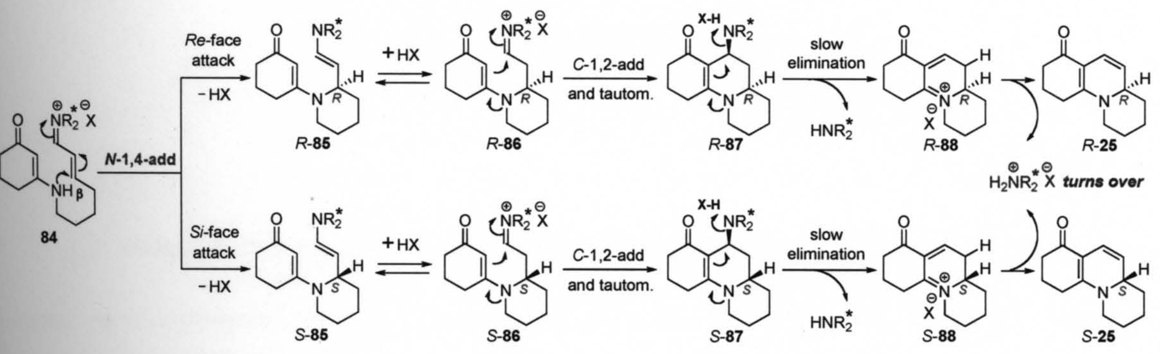


Interestingly, only two of the four possible diastereomers were seen with a ratio of 82 : 18, and heating of the intermediate **83** at 80 °C led to the formation of **25** with an enantiomeric ratio of 81 : 19. This experimental outcome suggests that the stereochemical induction most likely occurs during the *N*-1,4-addition step.

### 1.2.8 A Proposed Mechanism.

With all of the above experimental findings, we propose the following mechanism for our enantioselective intramolecular *aza*-[3 + 3] annulation reaction (**Figure 1-5**). The initial chiral iminium salt **84** can undergo *N*-1,4-addition in either a *Re*- or *Si*-facial approach toward the β-carbon, leading to two diastereomeric enamines *R*-**85** and *S*-**85**. At this stage, the enantiomeric induction is already determined. Protonation of these two enamines should give the respective iminium salts *R*-**86** and *S*-**86**, and a subsequent *C*-1,2-addition should furnish the second bond in this annulation sequence, leading to tricyclic intermediates *R*-**87** and *S*-**87**.

**Figure 1-5.** A proposed mechanism for the enantioselective *aza*-[3 + 3] annulation.

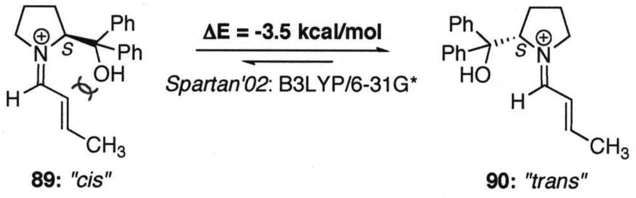


Finally, given the fact that we were able to detect the diastereomeric mixture (see **83** in **Scheme 1-16**) related to *R*-**87** and *S*-**87**, regeneration of the chiral amine via elimination is likely to be slow. This makes intuitive sense, as generation of vinyl iminium salts *R*-**88** and *S*-**88** could be uphill energetically. Subsequent tautomerization of *R*-**88** and *S*-**88** should lead to the enantiomeric 1,2-dihydropyridines *R*-**25** and *S*-**25** concomitant with the chiral amine salt turning over.

### 1.2.9. Computational Study.

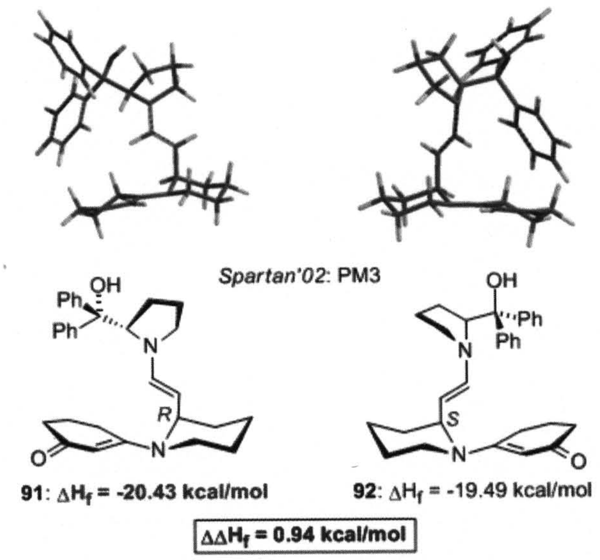
To further probe the origin of the observed enantioselectivity as well as the difference in the stereochemical outcomes from cycloaddition reactions carried out with $C_1$ and $C_2$-symmetric amine salts, computational studies were performed. Foremost, when an iminium salt such as **84** (see **Figure 1-5**) is generated with a $C_1$-symmetric catalyst such as **44e**, two geometric isomers can be formed. *Ab initio* calculations[22] using a simplified model system (crotonaldehyde) suggest that the formation of "*cis*"-isomer **89** is disfavored by 3.5 kcal/mol relative to "*trans*"-isomer **90**, presumably due to allylic strain present in **89** (**Figure 1-6**). Therefore, to simplify the computational analysis, we assumed the exclusive formation of the "*trans*"-isomer of the iminium salt.

**Figure 1-6.** Iminium salt stereoisomers.



In order to understand the preferred formation of *R*-enantiomer of **25** when using the *S*-isomer of $C_1$-symmetric amine salt **44e**, we calculated the stabilities of the two diastereomeric enamines **91** and **92** (**Figure 1-7**), which are products after the initial *N*-1,4-addition step (see **Figure 5**). Using a *Monte-Carlo* simulation in *Spartan'02* program,[23] we found that enamine **91** which would give *R*-**25** is ~ 1 kcal/mol more stable than corresponding diastereomer **92** leading to the *S*-enantiomer.

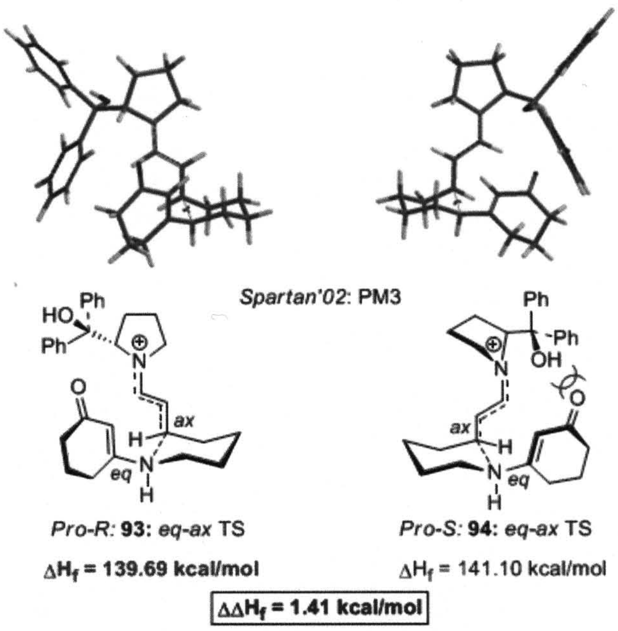
**Figure 1-7.** $C_1$-Symmetric amine salts: Enamine stability and conformation.



Based on this product stability analysis and the preferred conformations shown for **91** and **92**, the corresponding transition states [TS$^{‡}$] **93** and **94** for the *N*-1,4-addition step of the reaction were identified. It is noteworthy that the localization of the transition state structures was proven by the presence of one negative eigenvalue and corresponding imaginary frequency, which reflect formation of the N-C bond. Models and their respective energies are shown in **Figure 1-8.**

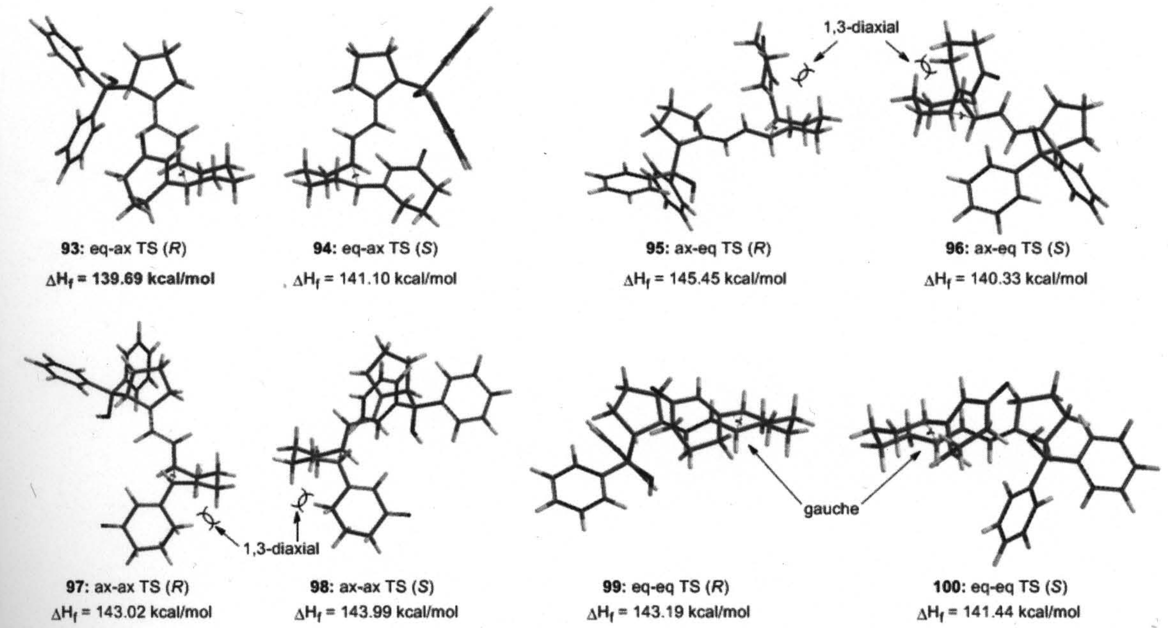
Both transition state structures represent a *chair* conformation with nitrogen substituent being *equatorial* and the enal moiety being *axial.* Calculations indicate that *Pro-R* TS$^{‡}$–**93** is more stable relative to the corresponding diastereomeric *Pro-S* TS$^{‡}$–**94** by ~ 1.41 kcal/mol. This is consistent with calculations obtained for the respective enamines **91** and **92**. This energy difference can be rationalized by the steric interaction between the bulky diphenylhydroxymethyl substituent on the pyrrolidine ring and the cyclohexenone moiety in *Pro-S* TS$^{‡}$–**94** (**Figure 1-8**).

**Figure 1-8.** $C_1$-Symmetric amine salts: Relevant transition states.



To be cautious, we looked at all six other possible *chair* transition states that differ in the relative localized positions of the nitrogen substituent and the enal functionality. Structures for four pairs of diastereomeric TS$^‡$–**[93-100]** along with their energies are shown in **Figure 1-9.** None of the other transition states are lower in energy than *Pro-R* TS$^‡$–**93**. In particular, TS$^‡$–**95** and TS$^‡$–**96** having the nitrogen substituent *axial* are destabilized in comparison with *Pro-R* TS$^‡$–**93** due to more severe 1,3-diaxial interactions. A similar interpretation can be made in the case of TS$^‡$–**97** and TS$^‡$–**98** where both side chains are *axial.* Finally, placing both substituents *equatorial* as shown in TS$^‡$–**99** and TS$^‡$–**100** leads to destabilization of the transition state structures due to the gauche interaction. Based on these computational results, it can be postulated that the asymmetric intramolecular *aza*-[3 + 3] annulations promoted with $C_1$-symmetrical catalysts such as **44e** proceed predominantly through *Pro-R* TS$^‡$–**93** giving rise to *R*-**25** as the major enantiomer.

**Figure 1-9.** $C_1$-Symmetrical amine salts: All possible transition states.



**93:** eq-ax TS (*R*) $\Delta H_f$ = 139.69 kcal/mol

**94:** eq-ax TS (*S*) $\Delta H_f$ = 141.10 kcal/mol

**95:** ax-eq TS (*R*) $\Delta H_f$ = 145.45 kcal/mol

**96:** ax-eq TS (*S*) $\Delta H_f$ = 140.33 kcal/mol

**97:** ax-ax TS (*R*) $\Delta H_f$ = 143.02 kcal/mol

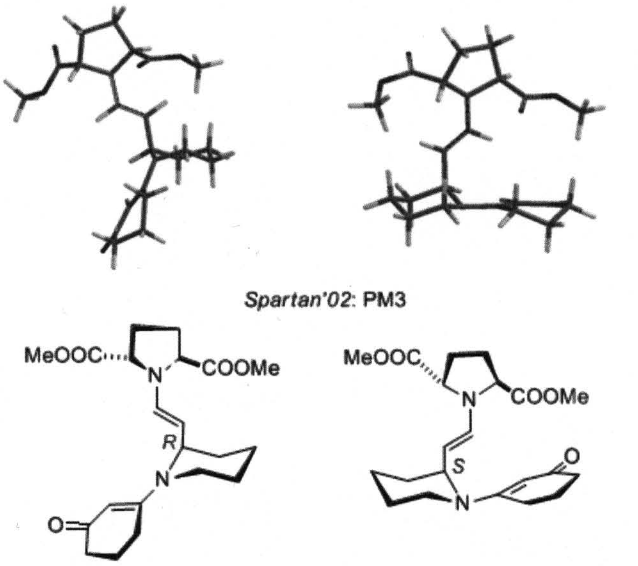
**98:** ax-ax TS (*S*) $\Delta H_f$ = 143.99 kcal/mol

**99:** eq-eq TS (*R*) $\Delta H_f$ = 143.19 kcal/mol

**100:** eq-eq TS (*S*) $\Delta H_f$ = 141.44 kcal/mol

A similar approach was used to rationalize the observed formation of *S*-enantiomer of **25** when $C_2$-symmetric amine salts are employed. To reduce the computational time, all calculations were performed with **45b** bearing two methyl ester substituents. It should be noted that in this case only one geometric isomer of the iminium salt exists due to $C_2$-symmetric nature of **45b**. Stabilities and conformations for the two diastereomeric enamines **101** and **102** were again found through *Monte-Carlo* simulation in *Spartan'02* (**Figure 1-10**). The relative stability of conformers is now reversed comparing to the $C_1$-symmetric case. Specifically, enamine **102**, which would yield the *S*-**25** is ~ 1 kcal/mol more stable than **101**, which would lead to the *R*-enantiomer.

**Figure 1-10.** $C_2$-Symmetric amine salts: Enamine stability and conformation.



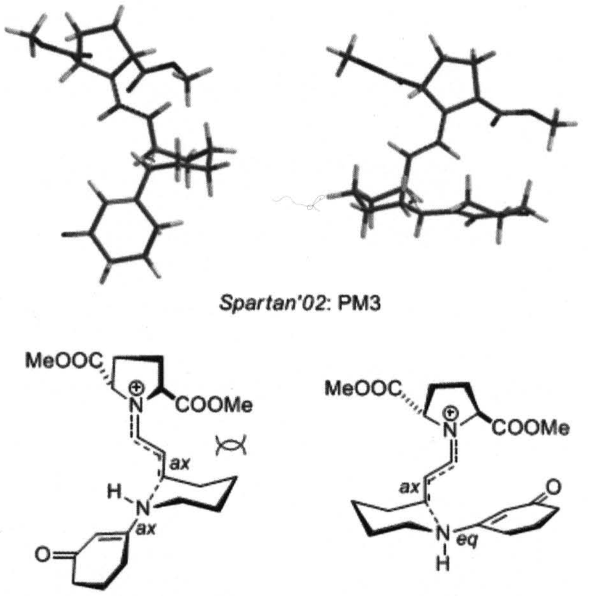
**101**: $\Delta H_f$ = -194.70 kcal/mol **102**: $\Delta H_f$ = -195.75 kcal/mol

$\boxed{\Delta\Delta H_f = 1.05 \text{ kcal/mol}}$

When the corresponding TS‡–**103** and TS‡–**104** were localized, the same trend in relative stabilities was observed. *Pro-S* TS‡–**104**, which has the nitrogen substituent *equatorial* and the enal functionality *axial*, is lower in energy than *Pro-R* TS‡–**103** where now both side chains are *axial* (**Figure 1-11**). Six other chair-like transition states were also modeled but none of them show greater stability than *Pro-S* TS‡–**104**.

Most likely the steric interaction between one of the ester groups on **44b** and the piperidine ring is responsible for destabilization of *Pro-R* TS‡–**103** in comparison with *Pro-S* TS‡–**104** (**Figure 1-11**). An increase in the substituent size as shown in then amine salt **44e** would further disfavor *Pro-R* TS‡–**103**, thereby leading to enhanced enantioselectivity in favor of *S*-**25**. It can be suggested that this particular steric interaction, which does not exist in $C_1$-symmetric amine salts, is responsible for the opposite stereochemical outcome.

**Figure 1-11.** $C_2$-Symmetric amine salts: Relevant transition states.



*Pro-R:* **103:** ax-ax TS
$\Delta H_f$ = -24.69 kcal/mol

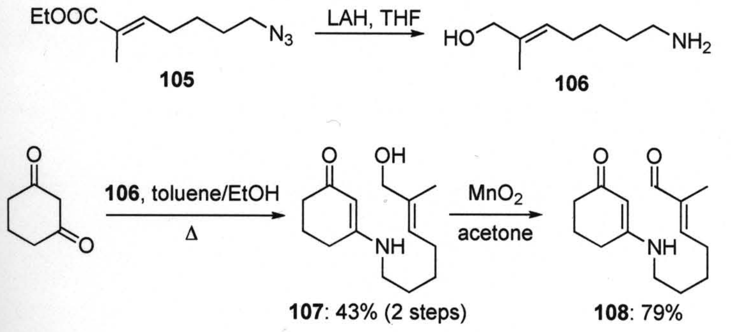
*Pro-S:* **104:** eq-ax TS
$\Delta H_f$ = -25.05 kcal/mol

$\boxed{\Delta\Delta H_f = 0.36 \text{ kcal/mol}}$

### 1.2.10. Effect of α-Methyl Substituent.

One of the key assumptions in our mechanistic model is the exclusive formation of the "*trans*"-isomer of the iminium salt **90** (**Figure 1-6**) for the case of $C_1$-symmetric amine salts. To validate this assumption, vinylogous amide **108** containing a methyl substituent at the α-position was synthesized (**Scheme 1-17**).

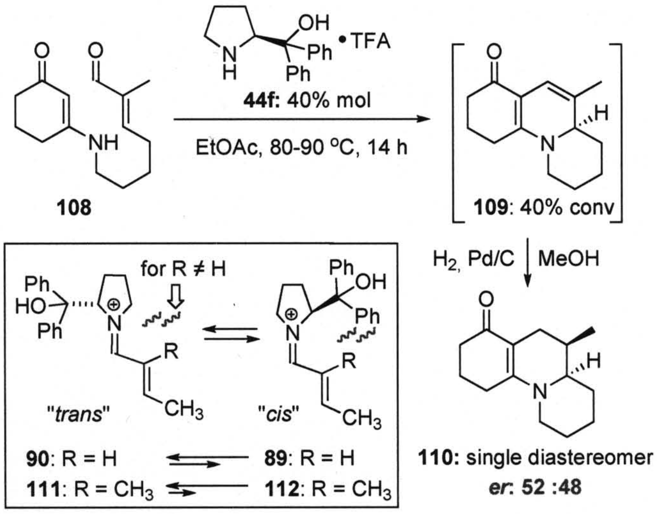
**Scheme 1-17.** Synthesis of α-methyl substituted annulation precursor **108**.



Amino alcohol **106** obtained by LAH reduction of azide **105**[24] was submitted to condensation reaction with 1,3-cyclohexanedione to afford allyl alcohol **107**. Oxidation of **107** with $MnO_2$ led to desired annulation precursor **108** in 79% yield.

Since the formation of the "*cis*"-isomer of iminium salt **112** (see the box in **Scheme 1-18**) intuitively should be further disfavored in this case compared to **89**, the enantioselectivity of the cycloaddition should stay the same if not improve.

**Scheme 1-18.** The effect of the α-methyl substituent.



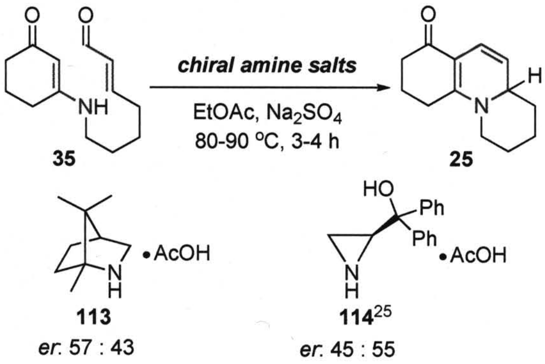
It was found that vinylogous amide **108** would undergo intramolecular annulation only if the most active trifluoroacetate salt **44f** was used (**Scheme 1-18**). No product formation was detected after running the reaction overnight with chloride salt **44g** or acetate salt **44e**. In the case of **44f**, only 40% conversion was observed after 14 h at 80 °C, and after hydrogenation of initial cycloadduct **109**, quinolizidine **110** was isolated as a single isomer. Relative "*trans*"-stereochemistry was assigned based on the coupling constants analysis as well as nOe data. But to our surprise, CSP-HPLC revealed that quinolizidine **110** was nearly racemic.

Due to the low yielding and sluggish nature of this reaction, it is not clear what caused the drop in the enantioselectivity and we did not follow up in this pursuit. It could be that the background reaction gained momentum given that formation of the iminium salt is now more difficult with severe allylic strain present in both **111** and **112**.

### 1.2.11. Rigid amine salts.

We also tried to use more rigid chiral amine salts, presuming that the conformational flexibility of pyrrolidine-based amine salts might have compromised the enantioselectivity. To that end, amine salts **113** and **114**[25] were tested in the cycloaddition of **35** but neither was useful (**Scheme 1-19**). It is nonetheless noteworthy that both amine salts were efficient in promoting the reaction.

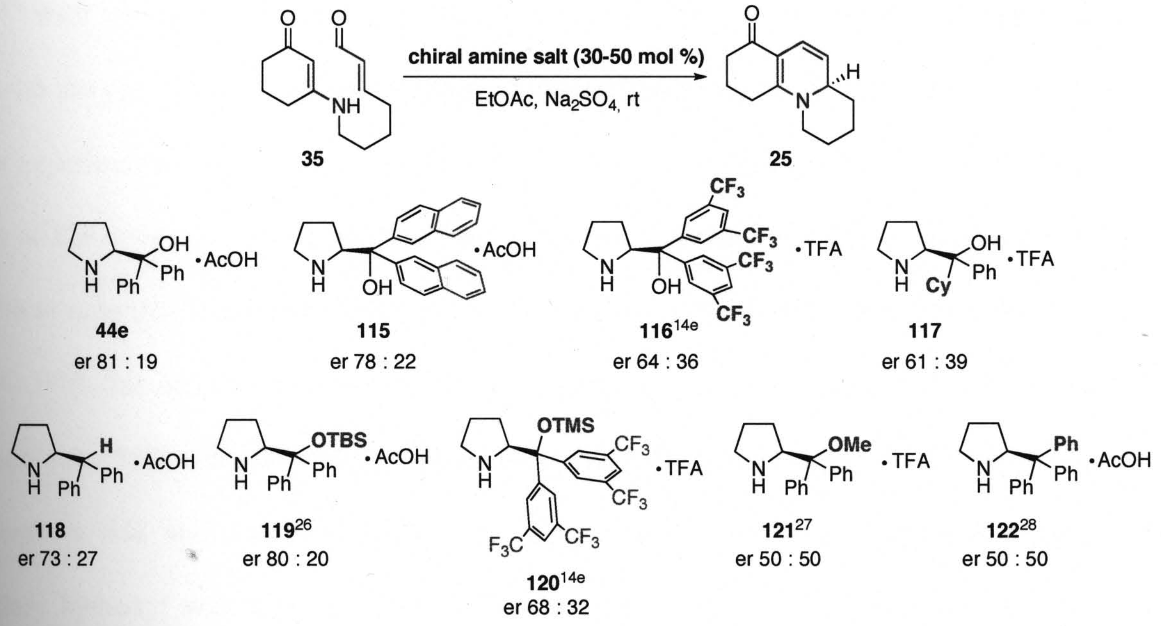
**Scheme 1-19.** Rigid amine salts.



### 1.2.12. SER – Structure and Enantioselectivity Relationship.

Finally substituent with most efficient chiral amine salt **44e** in hands that promotes intramolecular *aza*-[3 + 3] annulation with highest degree of enantioselectivity we decided to modify the structure of this catalyst in rational manner. There are two structural features in this chiral amine salt which could be tweaked. First is the size of the aryl substituents at the quaternary center. Our proposed mechanistic model (see **Section 1.2.8**) suggests that pyrrolidine catalyst with more bulky substituent should lead to higher enantioselectivity of the reaction. With this in mind, chiral amine salts **115-117** were employed in the annulation reaction of vinylogous amide **35** (**Scheme 1-20**).

**Scheme 1-20.** Structure and enantioselectivity relationship (SER).



It was found that the use of the amine salt **115**, which has a more extensive naphthyl-substituents relative to **44e**, did not lead to any improvement in the enantioselectivity. Interestingly enough, further increase of the size of the substituent by introducing sterically demanding trifluoromethyl group[14e] into the aromatic system (amine salt **116**) or by hydrogenation of one phenyl ring to cyclohexyl (amine salt **117**) actually led to decrease in enantioselectivity of the annulation reaction. It is noteworthy that the reactions with amines **116** and **117** were even performed at room temperature since the active trifluoroacetate salts were employed.

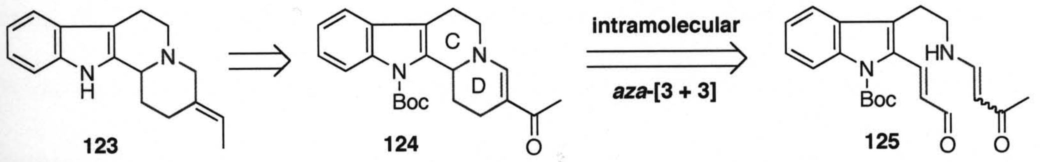
Second structural feature of the amine salt catalyst **44e** which captured our attention is free tertiary hydroxyl group. To test the importance of this functional group for enantioselectivity of the annulation reaction series of chiral amine salts **118-122** were prepared and used in the annulation reaction (**Scheme 1-20**). Simple removal of hydroxyl group as in amine salt **118** led to decrease in enantioselectivity of the process. Interestingly, utilizing the amine salts **119**[26] and **120**[14e] with tertiary hydroxyls being protected as silyl ether in the reaction afforded cycloadduct **25** with the same degree of enantioselectivity as corresponding unprotected analogs **44e** and **116**. This experimental finding puzzled us for a while until it was found that TMS-protecting group in case of **120** does not survive reaction conditions and is cleaved rapidly in the reaction mixture. It worth to note that amine salt **120** is stable by itself in EtOAc solution even in presence of excess TFA. With this observation we believe that enantiomeric ratios of the annulations obtained with amine salts **119** and **120** simply reflect the ratios from reactions promoted with unprotected precursors **44e** and **116** correspondingly. To overcome protecting group cleavage problem tertiary hydroxyl was capped as a methyl ether (amine salt **121**[27]). Unexpectedly, running the annulation reaction with this catalyst afforded cycloadduct **25** as racemate. When trifluoroacetate of triphenylmethyl pyrrolidine **122**[28] was used to promote the *aza*-[3 + 3] annulation reaction tricycle **25** was isolated as racemate as well.

There are two take-home messages that could be drawn from these structure and enantioselectivity relationship studies. First, further increase of the bulk of the substituent on the pyrrolidine ring of the catalyst in comparison with **44e** leads to decrease in enantioselectivity. Also it appears that unprotected tertiary hydroxyl group also plays an important role in controlling the enantioselectivity of intramolecular *aza*-[3 + 3] annulation reaction.

### 1.2.13. Synthesis of Enantiomerically Enriched *R*-(+)-Deplancheine.[29,33]

At the time we have developed enantioselective intramolecular *aza*-[3 + 3] annulation methodology we also have been working on total synthesis of Deplancheine alkaloid[30-32] **(Figure 1-12)** utilizing intramolecular cycloaddition in a key step. Retrosynthetically it was envisioned to come from tetracyclic precursor **124** where both C and D rings could be constructed simulteneously via intramolecular *aza*-[3 + 3] annulation reaction of vinylogous amide **125**.

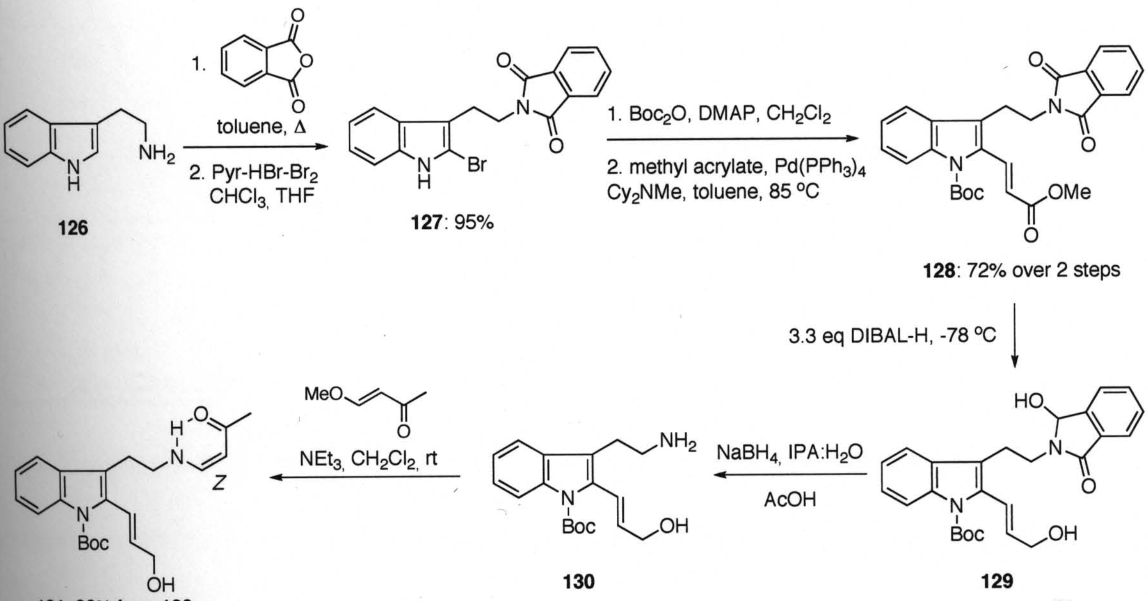
**Figure 1-12.** Retrosynthesis of Deplancheine featuring *aza*-[3 + 3] annulation.



123
(±)-Deplancheine
124
125

Synthetic approach to cycloaddition precursor **125** was developed earlier[33] and is outlined in **Schemes 1-21, 1-22.**

**Scheme 1-21.** Annulation precursor synthesis.

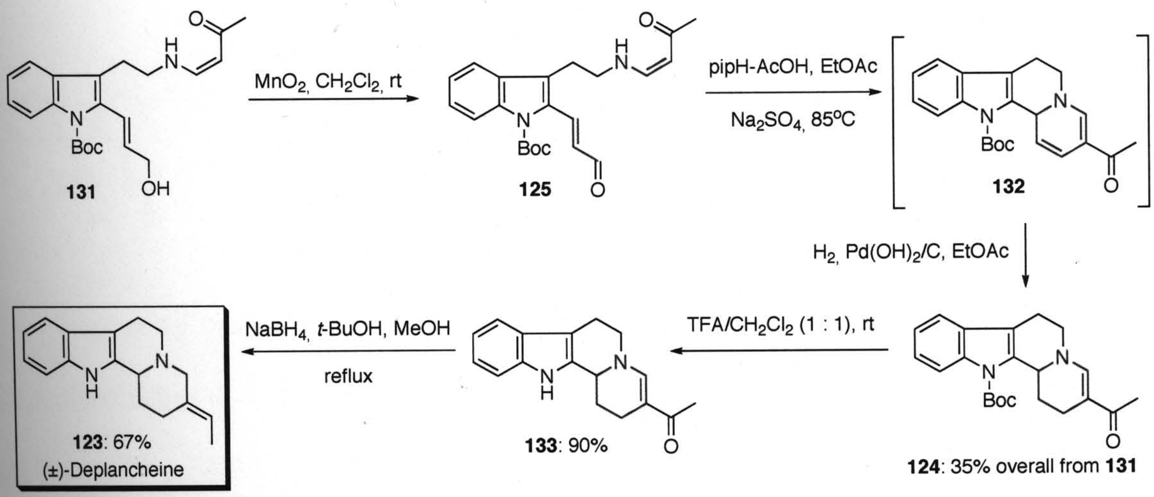


126
127: 95%
128: 72% over 2 steps
129
130
131: 26% from 128

Protected bromo-tryptamine **127** was prepared in 2 steps from tryptamine **126**. Protection of indole nitrogen with Boc-group followed by Heck coupling with methylacrylate gave phthalimido ester **128** in 72% yield. Phthalimide protecting group was removed by 2 steps reduction sequence involving treatment of **128** with DIBAL-H and $NaBH_4$ followed by quenching the reaction mixture with AcOH to yield aminoalcohol **130**. Crude amino alcohol **130** was condensed with 4-methoxy-3-buten-2-one to afford allyl **131** in 28% overall yield from phthalimido ester **128**. It is noteworthy that vinylogous amide geometry in **131** had *Z*-configuration presumably due to strong intramolecular hydrogen bonding.

Oxidation of allyl alcohol **131** with $MnO_2$ provided the annulation precursor **125** which was submitted directly to standard intramolecular *aza*-[3 + 3] cycloaddition conditions (**Scheme 1-22**).

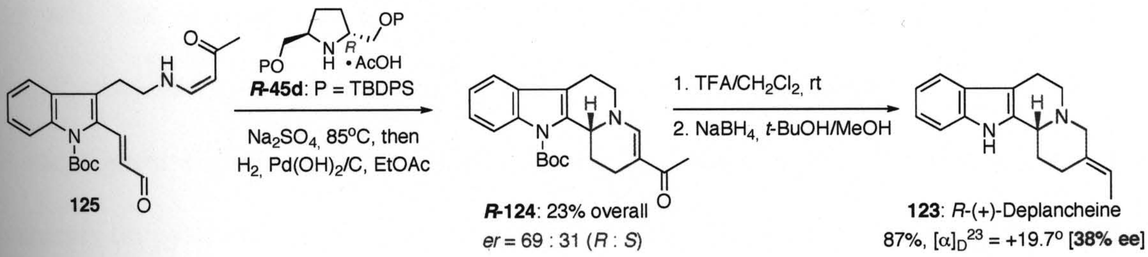
**Scheme 1-22.** (±)-Deplancheine end-game.



Compound **125** was treated with piperidinium acetate salt in EtOAc at 85 °C. After complete consumption of starting material disubstituted double bond in cycloadduct **132** was hydrogenated *in situ* over $Pd(OH)_2/C$. Tetracycle **124** was obtained in 35% overall yield from allyl alcohol **131**. Boc-protecting group in **124** was removed under acidic conditions to give known tetracycle **133**[31f] in excellent yield, thereby formal synthesis of Deplancheine was completed.[33] To finish the total synthesis of racemic Deplancheine, indoloquinolizidine **133** was treated with $NaBH_4$ in *t*-BuOH/MeOH mixture.[31b] Reduction of vinylogous amide functionality followed by *in situ* dehydration led to Deplancheine in 67% yield.[29]

At this point we realized that utilizing chiral amine salt as a catalyst for the key intramolecular *aza*-[3 + 3] annulation (**Scheme 1-22**) could allow us to access Deplancheine alkaloid in enantiomerically enriched form. To test this proposal and demonstrate the usefulness of the developed enantioselective *aza*-[3 + 3] annulation methodology enal **125** was treated with chiral amine salt ***R*-45d**[34] (**Scheme 1-23**). Reaction proceeded smoothly and after *in situ* hydrogenation tetracycle **124** was isolated in 23% yield in enantimerically enriched form favoring *R*-isomer.

**Scheme 1-23.** *R*-(+)-Deplancheine synthesis.

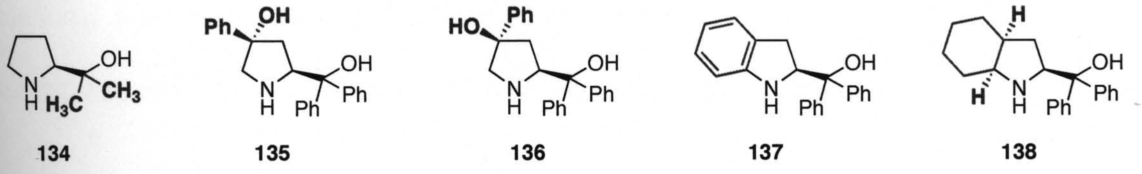


Employing the same two step sequence used in racemic synthesis (see **Scheme 1-22**) indoloquinolizidine ***R*-124** was converted to enantioenriched Deplancheine **123** in 87% overall yield.[29] Natural product was isolated with 38% *ee* enantiopurity which was determined on basis of specific rotation.[32] This experimental result was in perfect agreement with ratio of enantiomers of tetracycle **124** derived from enantioselective intramolecular *aza*-[3 + 3] annulation reaction.

## 1.3. Future work.

The most recent findings in our structure and enantioselectivity relationship studies (SER) (see **Section 1.2.12**) will motivate us to continue the quest for a better catalyst which would give higher than 62% *ee* in the intramolecular *aza*-[3 + 3] annulation reaction. Achieving this goal would allow us to better understand the mechanistic origin of the selectivity in this tandem process. With take-home messages from SER studies in mind we are planning to try several amine salts which are structurally related to our "the best" catalyst **44e** (**Scheme 1-24**).

**Scheme 1-24.** Future catalyst designs.



Firstly, we intend to test whether decreasing the size of the substituents at the quaternary center will lead to increase in enantioselectivity (amine salt **134**). Also pyrrolidine with diphenylhyroxymethyl substituent (amine salt **44e** promoted the *aza*-[3 + 3] annulation reaction with the highest degree of enantioselectivity so far. We also plan to test if placing other substituents on pyrrolidine ring while retaining diphenylhyroxymethyl group (amine salts **135-138**) will give any advantages in catalyzing the cycloaddition reaction with higher enantioselectivity.

## 1.4. Conclusion.

In conclusion, we have developed an enantioselective version of intramolecular *aza*-[3 + 3] annulation promoted by chiral secondary amine salts. The dependence of enantioselectivity on the structural feature of these chiral amines has been thoroughly investigated, and we found a very interesting reversal of the stereochemistry in the respective formal cycloadducts obtained using $C_1$- and $C_2$-symmetric amine salts. Effects of solvents, counter-anions, and temperatures on the enantioselectivity were also investigated and appear to have no real impact. On the basis of these experimental results and some semi-empirical calculations, a unified mechanistic model was proposed. Also developed methodology was successfully applied for total synthesis of enantioenriched *R*-(+)-Deplancheine.

# Part 2

# Application of Intramolecular *Aza*-[3 + 3] Annulation to Syntheses of *Coccinellidae* Defensive Alkaloids

## 2.1. Introduction.

### 2.1.1 Applications of Intramolecular *Aza*-[3 + 3] Annulation in Natural Product Synthesis.

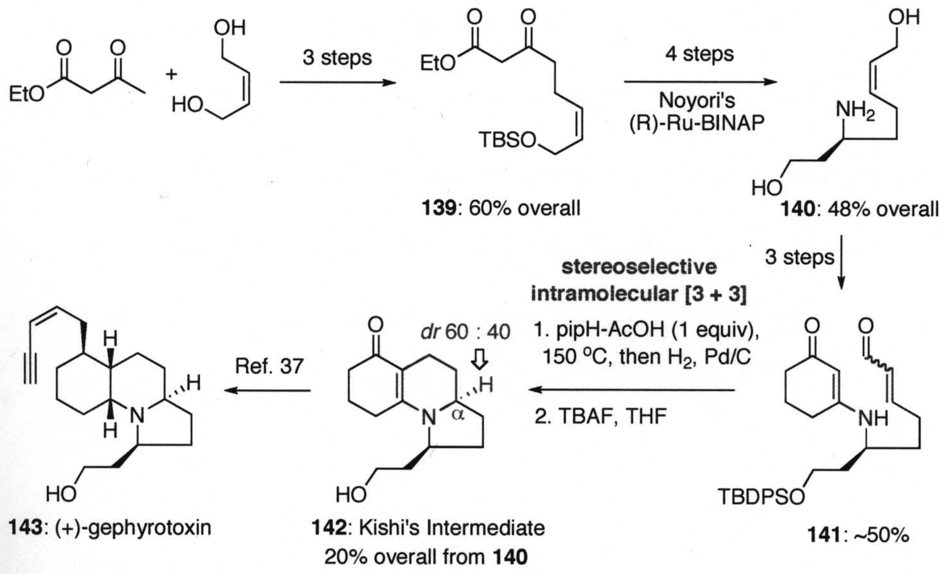
With well-established intramolecular *aza*-[3 + 3] annulation methodology we have been recently applying it in our research group to total syntheses of various natural products and alkaloids. Historically, the first formal synthesis of Gephyrotoxin alkaloid utilizing this annulation reaction in a key step was accomplished in 2002 by Dr. Lin-Li Wei.

### (+)-Gephyrotoxin.[10]

Gephyrotoxin (**143**) was originally isolated from *Dendrobates histrionicus*[35a] and belongs to a class of alkaloids derived from the skins of tropical frogs of the genus *Dendrobates*.[35b] There are three known total syntheses of (±)-Gephyrotoxin.[36] Kishi's synthesis involves the tricyclic intermediate **142** *en route* to this natural product (**Scheme 2-1**). The only enantioselective synthesis of (+)-Gephyrotoxin, which was reported by Kishi and Fujimoto, also utilized the optically active **142**, which was prepared in 18 steps.[37] We envisioned to intercept Kishi's intermediate by constructing B and C rings simultaneously via diastereoselective intramolecular *aza*-[3 + 3] annulation reaction of chiral vinylogous amide **141** (**Scheme 2-1**).[10]

Synthesis of **141** commenced with preparation of β-keto ester **139** in 3 steps from cheap commercially available starting materials. Compound **139** was converted to the amino diol **140** in 4 steps with good overall yield featuring Noyori asymmetric hydrogenation. Finally, condensation of amino diol **140** with 1,3-cyclohexanedione followed by selective oxidation of allylic alcohol with $MnO_2$ and protection of primary hydroxyl group as TBDPS-silyl ether led to desired *aza*-[3 + 3] annulation precursor **141**.

**Scheme 2-1.** Formal total synthesis of Gephyrotoxin via intramolecular *aza*-[3 + 3].

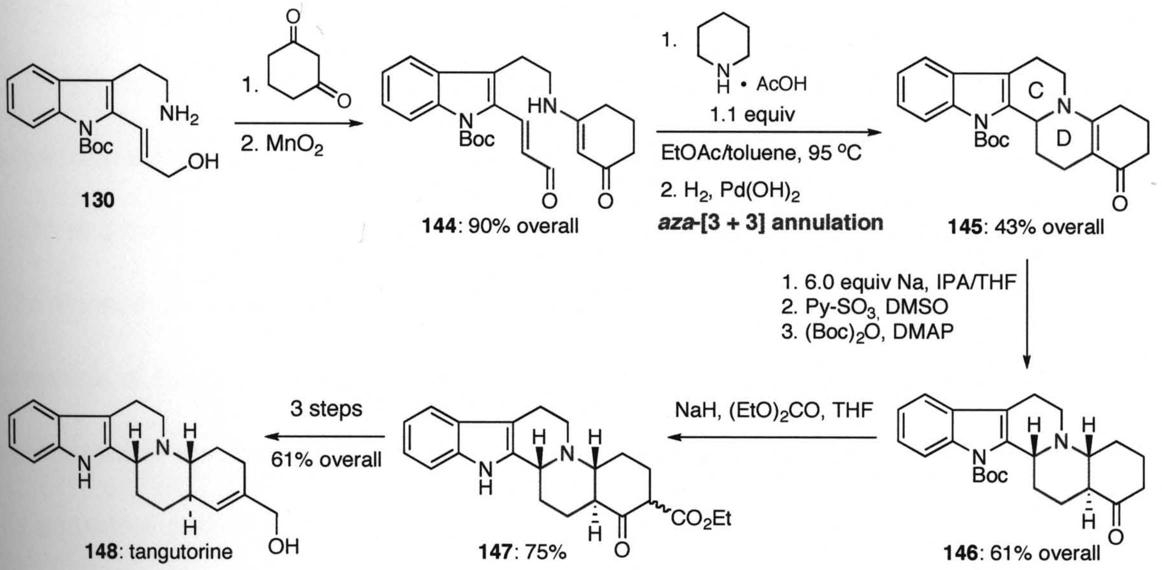


Heating of enal **141** with piperidinium acetate salt at 150 °C followed by *in situ* hydrogenation over Pd/C and removal of the TBDPS protecting group furnished the formation of Kishi's intermediate **142** as mixture of two diastereomers (α : β = 60 : 40), favoring the desired α-isomer. It is noteworthy, that observed diastereomeric ratio of **142** actually rises from intramolecular *aza*-[3 + 3] annulation, and TBDPS-protecting group plays an important role in controlling the selectivity of this transformation. If unprotected **141** is used in the annulation only undesired β-isomer is formed. Although the stereoselectivity of the *aza*-[3 + 3] annulation reaction should be improved to pursue a potential total synthesis of gephyrotoxin, the overall sequence to Kishi's intermediate **142** is short, and demonstrates the synthetic potential of this intramolecular annulation in the synthesis of natural products.

### (±)-Tangutorine.[38]

Tangutorine (**149**) was first isolated by Che from the leaves of *Nitraria tangutorum* in 1999.[39] There was one total synthesis of tangutorine by Jokela and co-workers[40] at the time when we became interested in this alkaloid. Pictet-Spengler cyclization was utilized as a key transformation for C-ring construction of the natural product. Synthesis of this alkaloid was also completed in 2004 by Zhai[41a] and by Ho group in 2006.[41b] In our retrosynthestic plan we envisioned that Tangutorine (**149**) alkaloid should be attainable from pentacycle **145** (**Scheme 2-2**). At the same time, construction of C-D rings in **145** could be achieved via an intramolecular *aza*-[3 + 3] annulation of vinylogous amide with α,β-unsaturated aldehyde tether **144**.[38]

**Scheme 2-2.** Total synthesis of Tangutorine via intramolecular *aza*-[3 + 3] annulation.

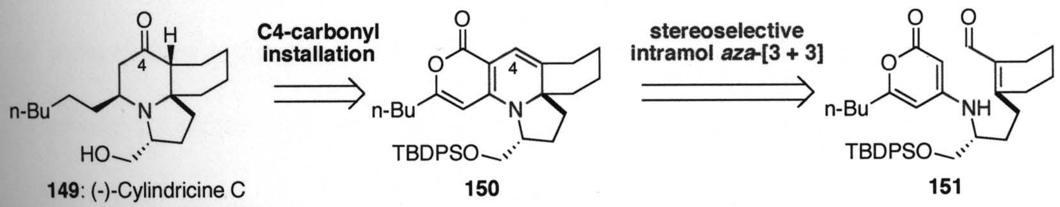


Annulation precursor **144** was prepared in 2 steps from amino alcohol **130** which was also used in our synthesis of Deplancheine alkaloid[29,33] (see **Section 1.2.13** for details). Condensation of **130** with 1,3-cyclohexanedione followed by $MnO_2$ oxidation of allylic alcohol afforded enal **144** in 90% yield. Under standard intramolecular *aza*-[3 + 3] annulation conditions, the desired pentacycle **145** was isolated in 43% overall yield after hydrogenation of the endocyclic olefin.[38] Compound **145** was reduced using the dissolving metal protocol reported by Palmieri for the reduction of vinylogous amides.[42] Unfortunately significant reduction of the carbonyl group as well as partial removal the Boc-protecting group were also observed. Thus, Doering re-oxidation as well as re-protection of the indole nitrogen atom with Boc-anhydride, were necessary to obtain to pentacycle **146** as a single diastereomer in 61% overall yield. Refluxing of pentacycle **146** in THF in the presence of NaH and diethyl carbonate led to regioselective carboxymethylation and formation of known β-keto ester **147**[40] as a mixture of two diastereomers in a good yield. Jokola's three steps protocol[40] was utilized to convert pentacycle **147** to tangutorine alkaloid (**148**) in 61% overall yield.[38]

### (-)-Cylindricine C.[43]

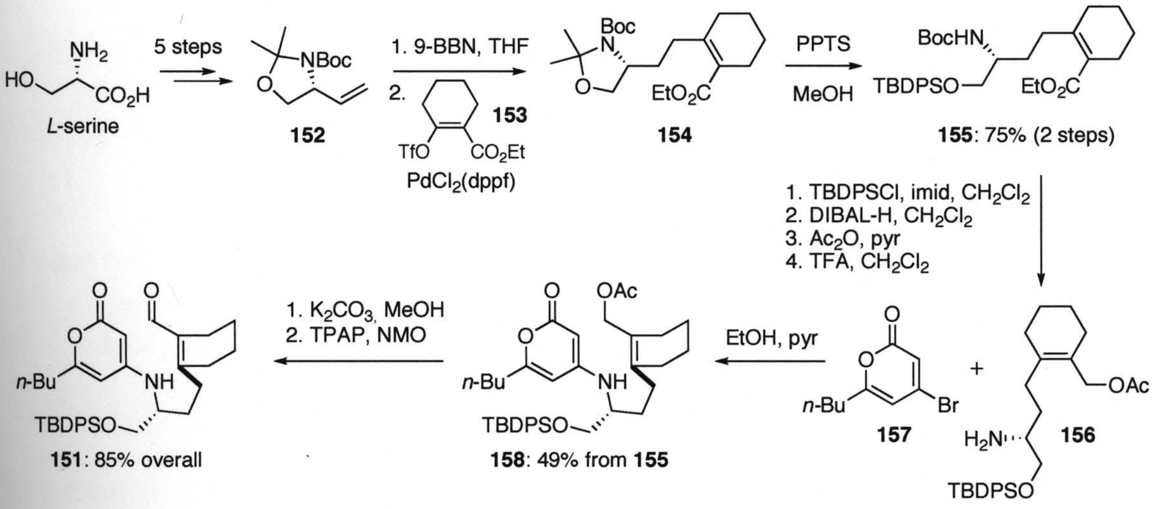
Cylindricine C (**149**) is a member of a big family of cylindricine alkaloids that were first isolated from marine ascidians *Clavelina Cylindrica* by Blackman in 1993.[44] Due to their unique tricyclic structural motif cylindricines attracted a lot of attention from synthetic community.[45-46] We envisioned possibility to use our stereoselective *aza*-[3 + 3] annulation methodology for construction of the tricyclic core of the Cylindricine C (**Figure 2-1**). Annulation of the readily accessible chiral vinylogous amide **151** should give the key intermediate **150**. which could be easily converted to the natural product upon installation of C4-carbonyl group.

**Figure 2-1.** Retrosynthesis of Cylindricine C.



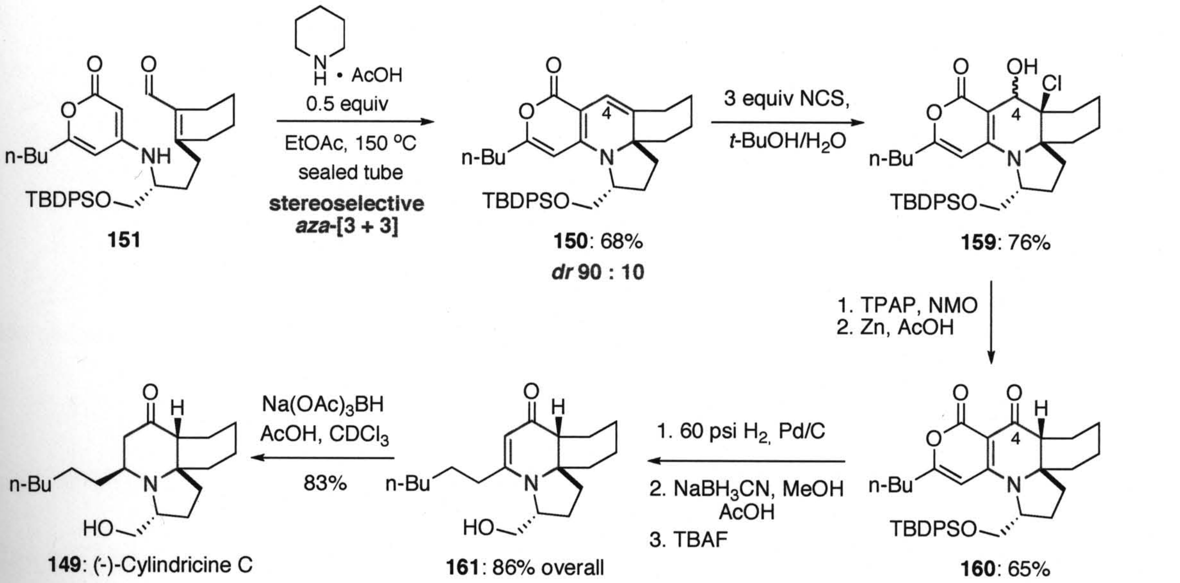
Synthesis of annulation precursor **151** started with hydroboration of vinyl oxazoline **152** followed by Suzuki-Miyara coupling to give ester **154** (**Scheme 2-3**) Protecting group manipulations and reduction of an ester group in **155** with DIBAL-H afforded orthogonally protected amino diol **156** in 5 steps. Condensation of amine **156** with bromo pyrone **157** provided vinylogous amide **158** in 49% overall yield from ester **155**. Finally, removal of an acetate with subsequent TPAP/NMO oxidation led to formation of desired annulation precursor **151** in excellent yield.[43]

**Scheme 2-3.** Synthesis of the annulation precursor.



Annulation precursor **151** was heated with piperidinium acetate salt in EtOAc in a sealed tube at 150 °C for 12 h. Under these conditions intramolecular *aza*-[3 + 3] annulation proceeded stereoselectively to provide cycloadduct **150** in 68% isolated yield mainly as desired disatereomer (**Scheme 2-4**). To install C4-carbonyl group elegant three steps protocol was used which involved intermediate formation of chlorohydrin **159** followed by oxidation of hydroxyl group and reduction of tertiary chloride with Zn in AcOH. Tetracycle **160** was obtained as single diastereomer and its stereochemistry was unambiguously confirmed by X-ray analysis.[43] At this point masked hexyl group was unraveled by reductive cleavage of α-pyrone accompanied by spontaneous decarboxylation to afford tricycle **161** in 86% overall yield upon removal of TBDPS-protecting group.

**Scheme 2-4.** (-)-Cylindricine C end-game.

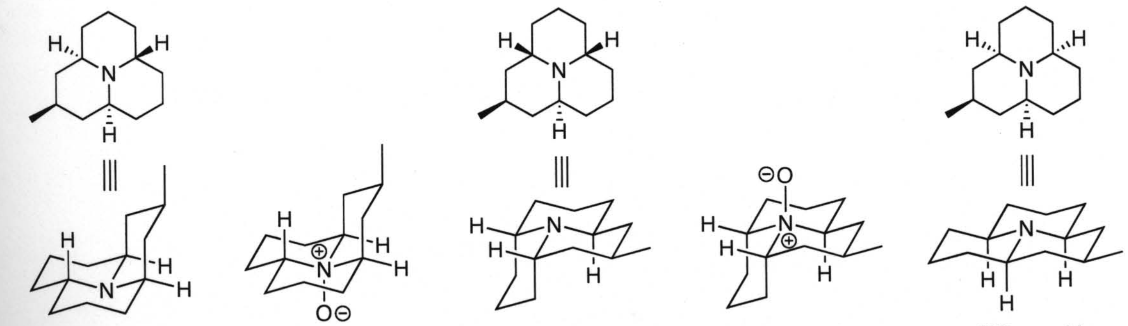


Finally, $Na(OAc)_3BH$ reduction of vinylogous amide **161** in presence of catalytic AcOH led to formation of Cylindricine C (**149**) as single isomer in 83% yield, thereby enantioselective synthesis of this alkaloid was completed.[43]

### 2.1.2. *Coccinellidae* Defensive Alkaloids.

To advance our quest in demonstrating the utility of our intramolecular *aza*-[3 + 3] annulation methodology as a unified strategy to access different *N*-heterocyclic structure manifolds known in natural alkaloids, we recently became interested in the family of *Coccinellidae* defensive alkaloids **162-166** (**Figure 2-2**). Ladybird beetles (*Coccinellidae*) play an important role in controlling populations of agricultural pests such as aphids, mealy bugs and scale insects. To protect themselves from their natural predators such as ants and quails, they utilize *reflex bleeding* mechanism[47a] in which when being pressed into a defensive mode, they release orange fluid from their joints which contains a mixture of alkaloids.[47]

**Figure 2-2.** *Coccinellidae* defensive alkaloids.



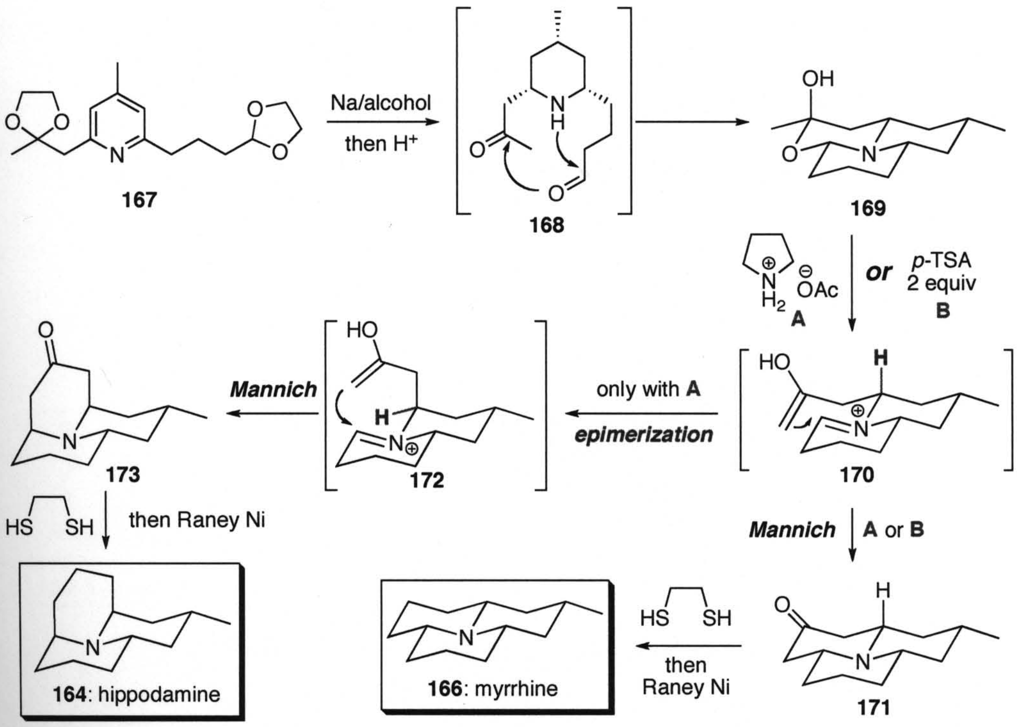
**162**: precoccinelline **163**: coccinelline **164**: hippodamine **165**: convergine **166**: myrrhine

In 1971, Tursch and co-workers reported their isolation of a crystalline substance coccinelline (**163**) along with its free base precoccinelline (**162**) from this fluid.[48a] The proposed structure of (**163**) was confirmed by a single crystal X-ray analysis.[48b] Other stereoisomers of the 2-methyl-perhydro-9b-azaphenalene system with the methyl group occupying an equatorial position were later isolated and characterized as hippodamine (**164**),[48c,d] its *N*-oxide convergine (**165**),[48c,d] and the thermodynamically most stable all-*syn* myrrhine (**166**).[48e] Interestingly, *N*-oxide of myrrhine (**166**) is not known to occur in nature.

The unique structural feature of these alkaloids has attracted a lot of attention in the last 30 years. There are 5 syntheses of precoccinelline **(162)**, 3 of hippodamine **(164)**, 2 of 2-*epi*-hippodamine and 2 of myrrhine **(166)** known up to date. The first total syntheses of the whole family of alkaloids **162-166** was reported by Ayer in 1976.[49a,50a]

In his syntheses of hippodamine and myrrhine Ayer started with dissolving metal reduction of trisubstituted pyridine **167** which led to thermodynamically most stable all-*syn* isomer **168** as the major product (**Scheme 2-5**). Purification and treatment with an acid yielded hemiketal **169** via intramolecular cyclization of ketoaldehyde **168**. Heating of **169** with *p*-TSA in toluene led to formation of ketone **171** as the only product via intramolecular Mannich cyclization of iminium salt **170**. Two steps deoxygenation of **171** finished the synthesis myrrhine **(166)**.[49a]

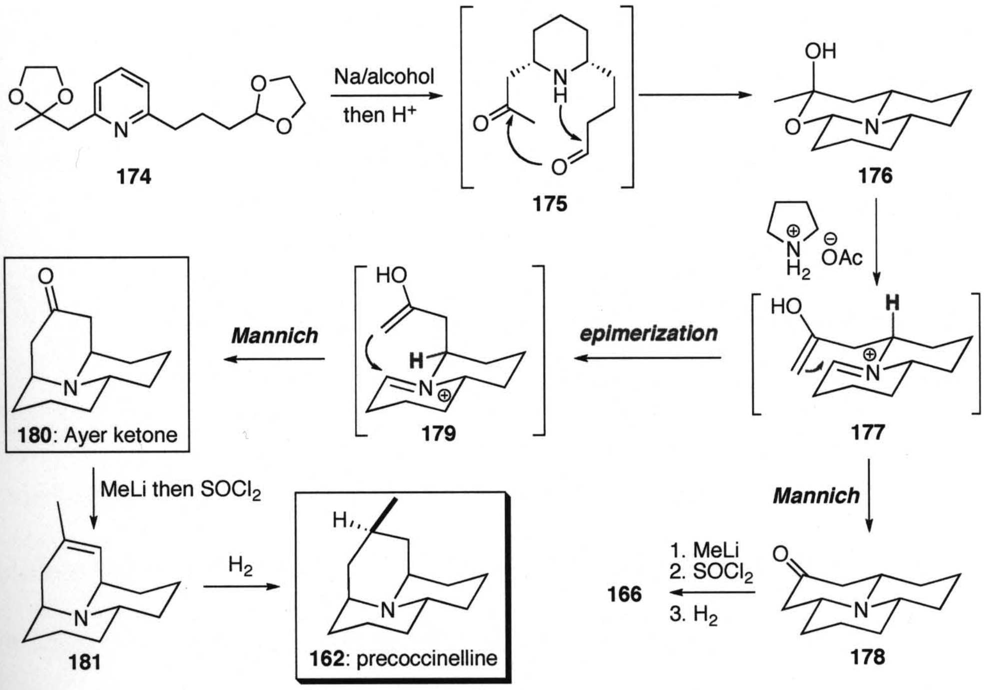
**Scheme 2-5.** Ayer syntheses of hippodamine and myrrhine.



Interestingly, treatment of hemiketal **169** with pyrrolidine acetate salt afforded isomeric mixture of ketones **171** and **173**. Ayer rationalized formation of ketone **173** by epimerization at carbon center adjacent to nitrogen atom (in blue, **Scheme 2-5**) of iminium salt **170**. Intramolecular Mannich cyclization of iminium salt **172** led to formation of ketone **173**. Finally, conversion of the crude mixture of ketones **171** and **173** to corresponding thioacetals followed by desulfurization afforded ~1 : 1 mixture of hippodamine and myrrhine which were readily separable by column chromatography. Hippodamine **(164)** was converted to its *N*-oxide convergine **(165)** by *m*CPBA oxidation.[49a]

Ayer and Feruichi took similar approach to synthesize precoccinelline **(162)** and coccinelline **(163)** alkaloids.[50a] In this case they envisioned to introduce methyl group of the natural products later in the synthesis. Thus, disubstituted pyridine **174** was converted to the corresponding hemiketal **176** via two steps protocol used in Ayer's synthesis of hippodamine and myrrhine (**Scheme 2-6**).[49a] Treatment of tricycle **176** with pyrrolidine acetate afforded 1 : 1 mixture of ketones **178** and **180** which were separated by column chromatography.

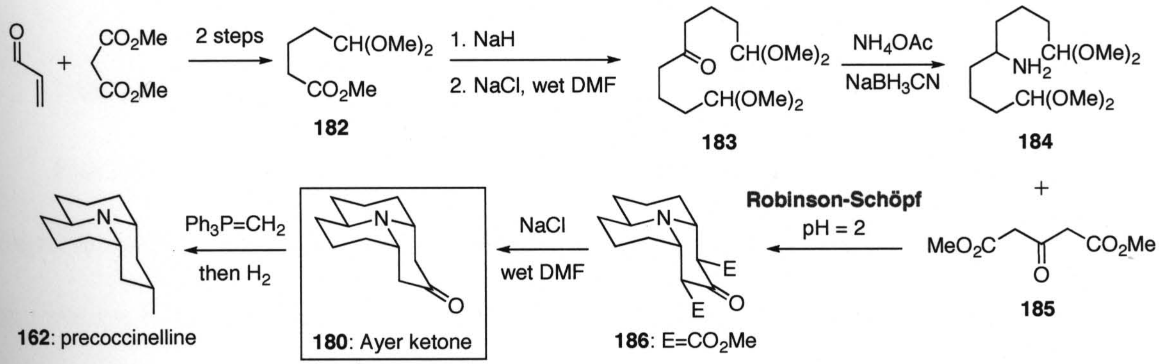
**Scheme 2-6.** Ayer- Feruichi synthesis of precoccinelline.



Stereoselective MeLi addition to ketone **180** followed by dehydration provided alkene **181**. Stereoselective hydrogenation of the double bond in **181** led to formation of precoccinelline **(162)**.[50a] It is noteworthy, that Ayer ketone **180** was intercepted as a key intermediate in all subsequent syntheses of precoccinelline **(162)** alkaloid. Coccinelline **(163)** was easily prepared by *m*CPBA oxidation of precoccinelline. Ketone **178** was also shown to be useful in synthesis of myrrhine **(166)** by the same three steps protocol which was used for conversion of **180** to precoccinelline (**Scheme 2-6**).

In 1979 Stevens and Lee reported their approach to precoccinelline (**162**) utilizing Robinson-Schöpf annulation to build the azaphenalene core of the natural product.[50d] Amino diacetal annulation precursor **184** was prepared starting from dimethyl malonate and acrolein. Dimerization of ester **182** followed by decarboxylation afforded ketone **183**. Reductive amination of ketone **183** furnished the amine **184** (**Scheme 2-7**).

**Scheme 2-7.** Stevens-Lee synthesis of precoccinelline.

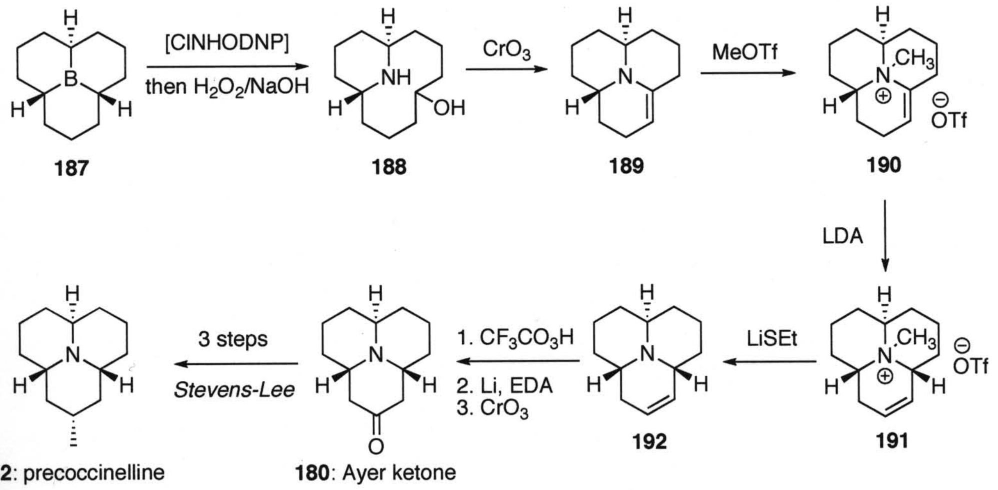


Condensation of amino diacetal **184** with dimethyl acetonedicarboxylate **(185)** under acidic conditions afforded tricyclic ketone **186** as the only isomer. Hydrolysis of both ester groups with subsequent decarboxylation led to formation of known Ayer ketone **180**.[50a] Methyl group of the natural product was installed by Wittig olefination-hydrogenation sequence to finish the synthesis of precoccinelline **(162)** (**Scheme 2-7**).[50d]

Mueller and co-workers in series of papers[49b,50b,c] reported their approach to azaphenalene alkaloids with perhydroboraphenalene **187** as the starting point.

In synthesis of precoccinelline[50b,c] perhydroboraphenalene **187** was submitted to oxidation conditions with *N*-chloro-*O*-(2,4-dinitrophenyl)hydroxylamine and $H_2O_2$ to give amino alcohol **188** which was converted without purification to enamine **189** by treatment with Jones reagent (**Scheme 2-8**).

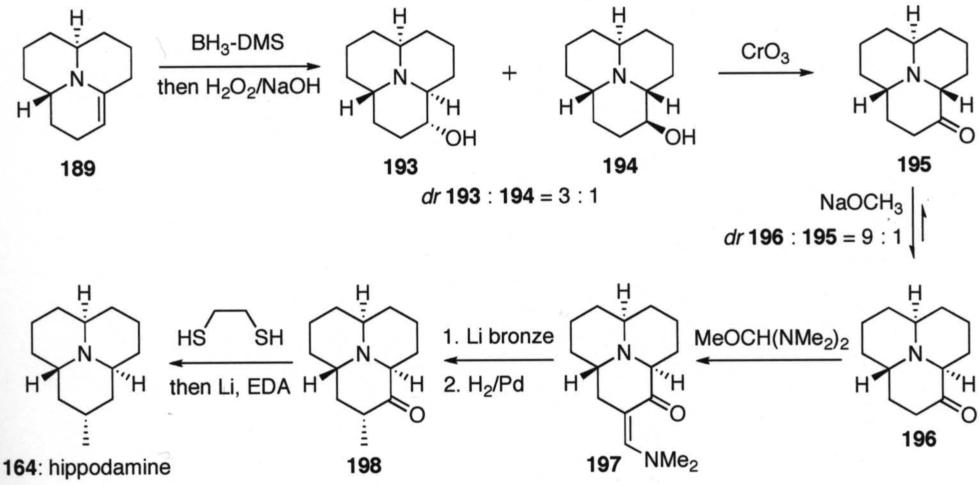
**Scheme 2-8.** Mueller synthesis of precoccinelline.



Enamine **189** was then isomerized to tricyclic alkene **192** in three steps involving nitrogen quaternization with methyl triflate to give salt **190**, followed by LDA promoted isomerization to endocyclic olefin **191** and demethylation with lithium thioethylate (**Scheme 2-8**). By epoxidation of the double bond in **192** with peroxytrifluoroacetic acid and regioselective reduction of intermediate epoxide with subsequent oxidation of the secondary hydroxyl group Mueller and co-workers intercepted the known ketone **180**.[50a] They used Stevens-Lee three steps protocol[50d] to access precoccinelline **(162)** from Ayer ketone **180** (**Scheme 2-7**).

To synthesize hippodamine alkaloid **(164)** Mueller and co-workers[49b,50c] started with hydroboration of the enamine **189** used in their synthesis of precoccinelline **(162)**. Two diastereomeric alcohols **193** and **194** were obtained in 3 : 1 ratio favoring the desired one **193** (**Scheme 2-9**). This mixture was taken forward into the oxidation with Jones reagent to give separable mixture of corresponding isomeric ketones **195** and **196**. Moreover, it was found that the minor isomer **195** could be readily equilibrated to the desired one **196** under action of sodium methoxide.

**Scheme 2-9.** Mueller synthesis of hippodamine.

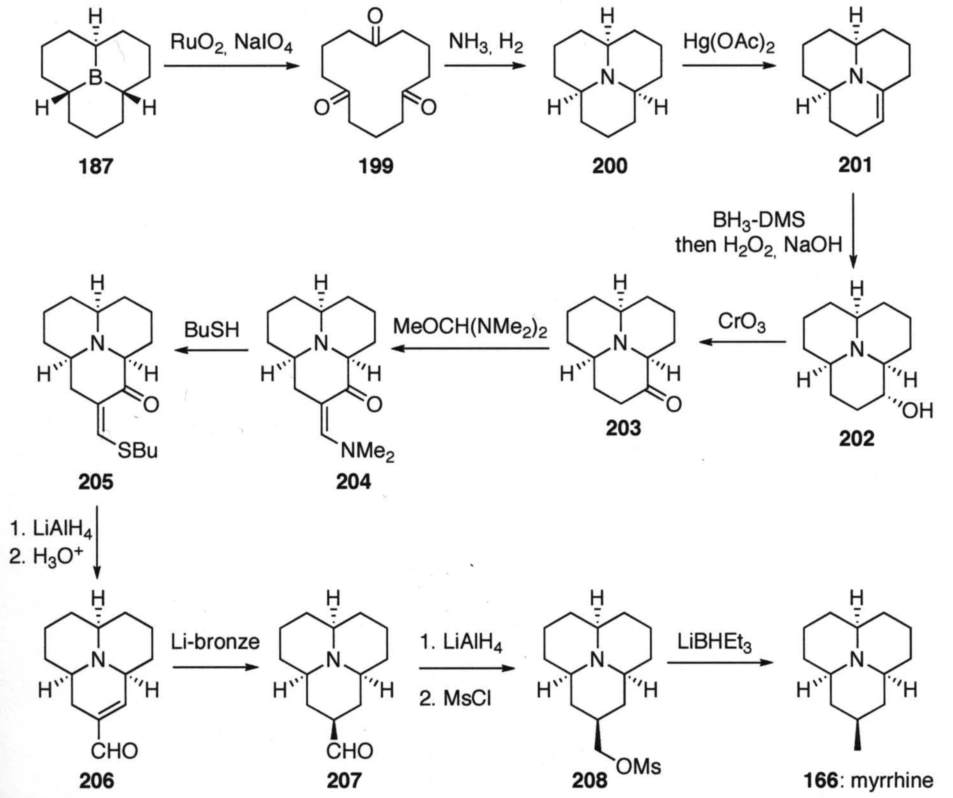


Equatorial methyl group of the natural product was installed by treatment of ketone **196** with Bredereck reagent[51] that afforded vinylogous amide **197**. Reduction of amide **197** with Li-bronze followed by catalytic hydrogenation of intermediate β-amino ketone led to formation of methyl ketone **198** as the only isomer. Finally, hippodamine **(164)** was obtained after deoxygenation of ketone **198** **(Scheme 2-9)**.

Mueller and co-workers also synthesized myrrhine **(166)** starting from perhydroboraphenalene **187**.[50c] In this case desired all-*syn* strereochemistry at the ring junctions was obtained by oxidation of **187** to triketone **199** and subsequent reductive amination to give tertiary amine **200** (**Scheme 2-10**). Tricycle **200** was converted to enamine **201** by oxidation with mercury acetate. Stereoselective hydroboration of enamine **201** followed by Jones oxidation of alcohol **202** gave ketone **203**.

Installation of the equatorial methyl group required a lot of effort. Thus, treatment of ketone **203** with Bredereck reagent gave vinylogous amide **204** which was converted to corresponding vinylogous thioester **205** by reaction with BuSH (**Scheme 2-10**).

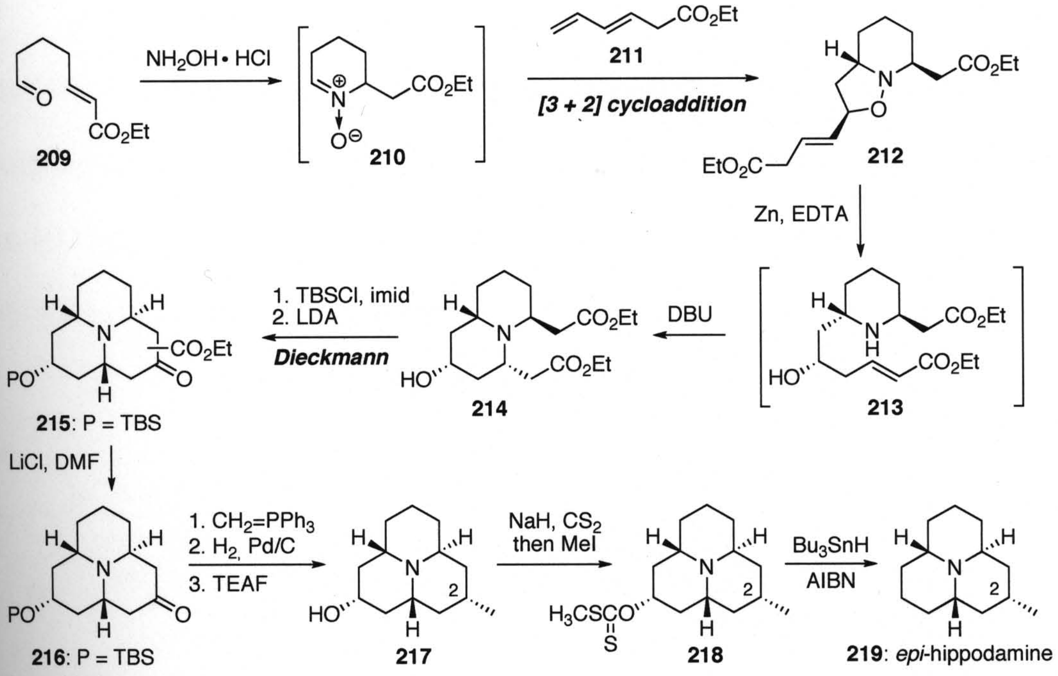
**Scheme 2-10.** Mueller synthesis of myrrhine.



Regioselective 1,2-reduction of **205** with lithium aluminum hydride followed by acidic work-up afforded enal **206** as the only product. Conjugated reduction of enal **206** with Li-bronze gave predominantly equatorial aldehyde **207**. Aldehyde **207** was converted to mesylate **208** by $LiAlH_4$ reduction and treatment of intermediate alcohol with MsCl. Finally, reduction of the mesylate **208** with $LiBHEt_3$ finished the synthesis of myrrhine alkaloid **(166)**.

The next landmark in syntheses of azaphenalene alkaloids was Adams' synthesis of 2-*epi*-hippodamine accomplished in 1991[49c]. He started with 1,3-dipolar cycloaddition between diene **211** and nitrone **210** generated *in situ* from ester **209** and hydroxyl amine (**Scheme 2-11**). Isoxazoline **212** was obtained predominantly as one diastereomer. Reduction of N-O bond in **212** followed by intramolecular Michael addition led to diester **214**. To finish the formation of tricyclic azaphenalene core, secondary hydroxyl group was first protected as TBS silyl ether and resulting product was treated with LDA to give ketoester **215** as mixture of regioisomers. Ester hydrolysis and decarboxylation yielded ketone **216**.

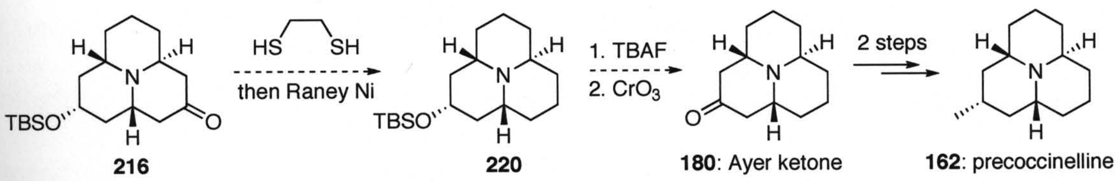
**Scheme 2-11.** Adams synthesis of 2-*epi*-hippodamine.



At this point Adams and co-workers installed methyl group required for the natural product by the Wittig olefination of ketone **216** followed by hydrogenation of exo-cyclic double bond. It turned out that facial selectivity of the hydrogenation was exactly opposite of what was expected and tricycle **217** was obtained with *epi*-stereochemistry at C2-position with respect to the hippodamine alkaloid **(164)** (**Scheme 2-11**). Nonetheless, amino alcohol **217** was taken forward into the deoxygenation reaction via xanthate ester **218** to accomplish the synthesis of 2-*epi*-hippodamine **(219)**.[49c]

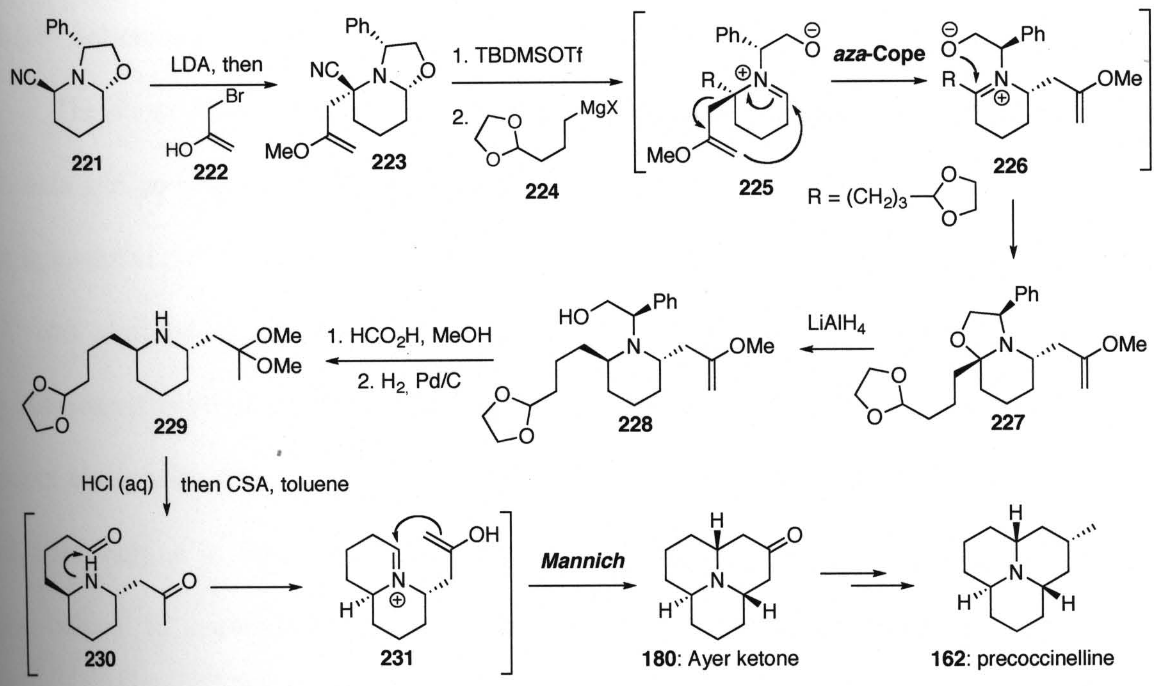
Interestingly, Adams and co-workers have never pursued, what appears to be obvious, transformation of their intermediate **216** to the known Ayer ketone **180**[50a] (**Figure 2-3**). This would have allowed them to synthesize precoccinelline natural product **(162)**.

**Figure 2-3.** Possible route to precoccinelline.



In 1994 Royer and co-workers accomplished the forth synthesis of the precoccinelline[50e] by intercepting Ayer ketone **180** which was prepared from *trans*-2,6-disubstituted piperidine **227** (**Scheme 2-12**). It is noteworthy, that similar *cis*-ketoaldehyde **175** was the key intermediate in Ayer's synthesis of precoccinelline (**Scheme 2-6**).[50a]

**Scheme 2-12.** Royer synthesis of precoccinelline.



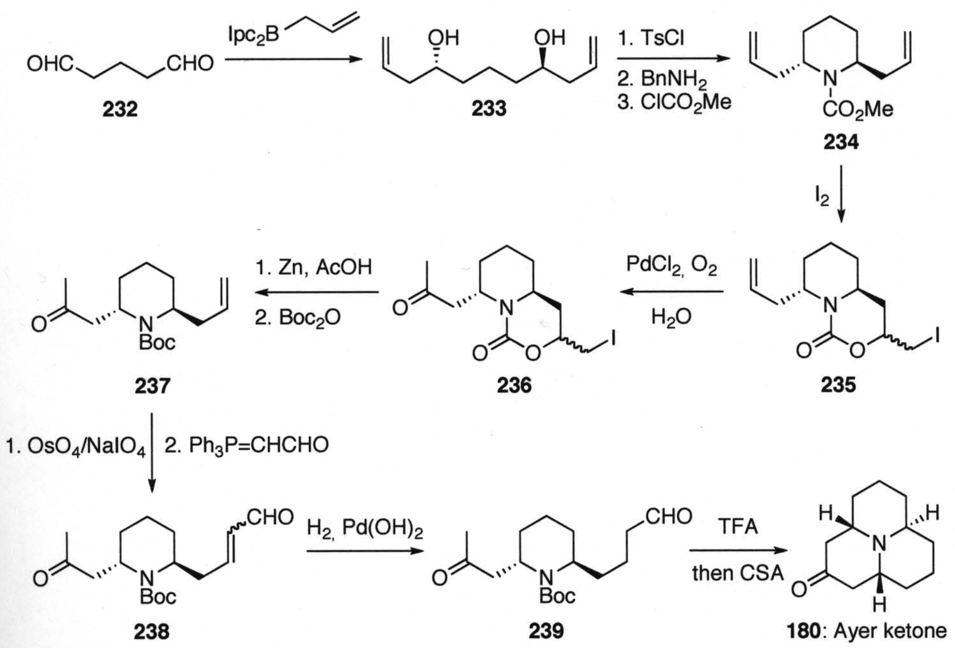
To construct piperidine **227** Royer utilized his "CN(R,S)" methodology which allows to synthesize 2,6-*trans* or 2,6-*cis*-disubstituted piperidines stereoselectively.[52] Thus, stereoselective alkylation of oxazolopiperidine **221** with bromide **222** yielded the precursor **223** for tandem alkylation/*aza*-Cope sequence. Upon *in situ* generation of the iminium salt from cyanide **223** and

TBDMSOTf it was reacted with Grignard reagent **224** to give zwitterionic intermediate **225**. *Aza*-Cope rearrangement of iminium salt **225** with subsequent cyclization afforded oxazolopiperidine **227**. Lithium aluminum hydride reduction of **227** provided exclusively 2,6-*cis*-piperidine **228** which was converted to diacetal **229** by treatment with formic acid in methanol followed by cleavage of benzyl protecting group of the nitrogen atom by hydrogenation.

Under acidic conditions piperidine **229** underwent tandem cyclization to give tricyclic Ayer ketone **180**.[50e] Conversion of **180** to precoccinelline **(162)** was first accomplished by Ayer[50a] (see **Scheme 2-6**) and then reported by Stevens[50d] and Mueller[50b,c] in their syntheses of **162** (see **Schemes 2-8**, **2-9**).

The most recent formal total synthesis of precoccinelline **(162)** was a published by Takahata and co-workers in 2002.[50f] As in all preceding syntheses of this natural product they also intercepted the Ayer ketone **180** in their synthetic route. The key 2,6-*trans*-diallyl piperidine **234** was derived in 3 steps from allylboration reaction of dialdehyde **232** with *B*-allyldiisocamphenylborane (**Scheme 2-13**). $C_2$-Symmetric diol **233** was obtained as major product along with some *meso*-isomer. Diol **233** was converted to ditosylate and then treated with benzylamine to form piperidine ring. Finally, changing protecting group on the nitrogen from benzyl to carbamate furnished Takahata's key building block **234**. Intramolecular iodocarbamation reaction of **234** served as elegant way to temporarily protect one of the double bonds while second allyl group was converted to methyl ketone **236** using Wacker oxidation protocol. At this point masked double bond was liberated by treatment of oxazolidinone **236** with Zn in acetic acid. Protection of the nitrogen as Boc-carbamate provided ketone **237**.

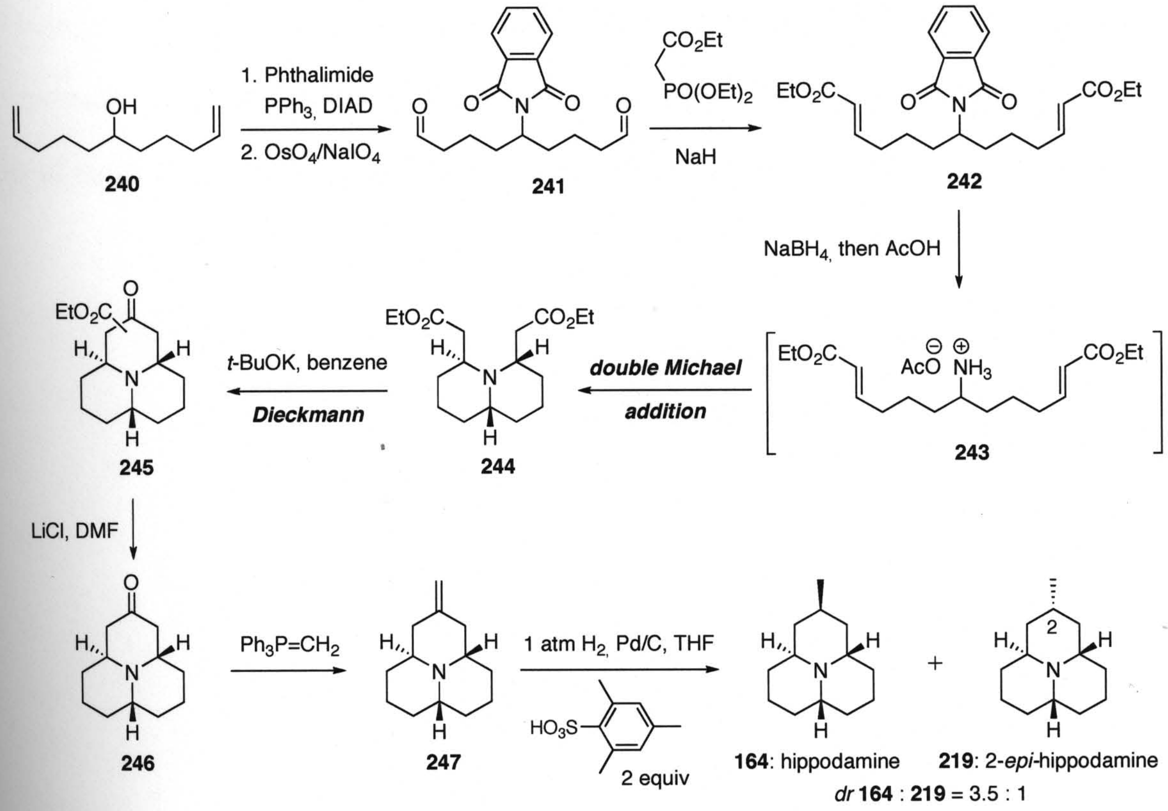
**Scheme 2-13.** Takahata synthesis of precoccinelline.



Oxidative cleavage of terminal double bond with subsequent Wittig olefination of the intermediate aldehyde gave enal **238** as mixture of geometrical isomers. This mixture was taken forward into the hydrogenation reaction over $Pd(OH)_2$ catalyst to yield ketoaldehyde **239**. Removal of the Boc-protecting group with TFA led to *in situ* formation of ketoaldehyde **230** (see **Scheme 2-12**) which spontaneously cyclized to known Ayer ketone **180**[50a] upon heating with CSA. Thereby the formal total synthesis of precoccinelline alkaloid **(162)** was accomplished.

The latest reported synthesis of azaphenalene alkaloids was Stockman's approach to hippodamine natural product published in 2005.[49d] As a key strategy for construction of the azaphenalene core Stockman and co-workers utilized tandem intramolecular double-Michael addition – Dieckmann condensation sequence (**Scheme 2-14**). The precursor **242** for this transformation was prepared from alcohol **240** by Mitsunobu reaction to install phthalimide moiety followed by oxidative cleavage of both terminal alkenes and subsequent Horner-Wadsworth-Emmons olefination.

**Scheme 2-14.** Stockman synthesis of hippodamine and 2-*epi*-hippodamine.



Phthalimide protecting group in diester **242** was cleaved under reductive conditions and upon acidic work-up intermediate amine salt **243** underwent sponteneous double-Michael addition to give quinolizidine **244** as single diastereomer. To finish the formation of azaphenalene framework bicycle **244** was submitted to Dieckmann condensation reaction with *t*-BuOK. Resulting mixture of diastereomeric ketoesters **245** was treated with LiCl in wet DMF to provide ketone **246**. Exo-cyclic olefin **247** was obtained by Wittig reaction of ketone **246**. It is noteworthy, that similar approach was also used earlier in 1991 by Adams[49c] in his synthesis of *epi*-hippodamine **(219)** (see **214** → **216** in **Scheme 2-11**). At this point Stockman and co-workers ran into the same problem Adams experienced in his synthesis – facial selectivity of the hydrogenation reaction. Thus, hydrogenation of the exo-cyclic olefin under standard conditions

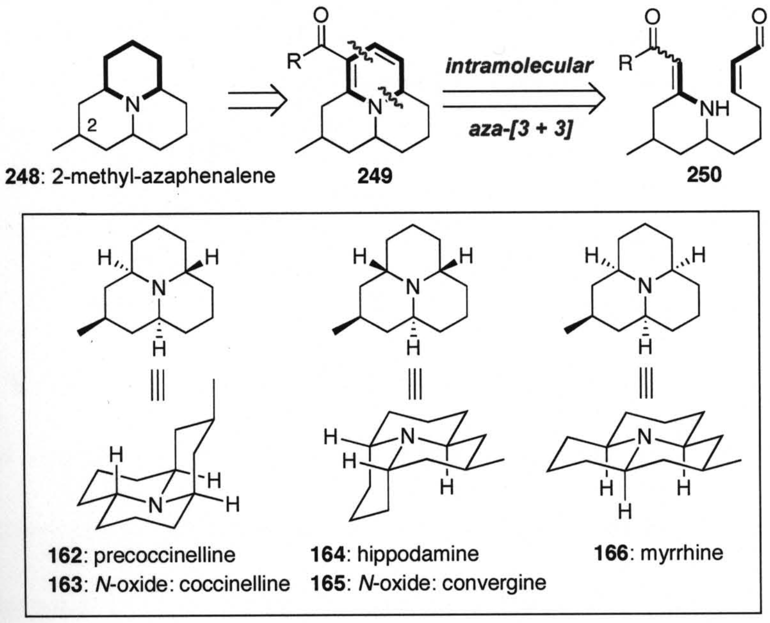
(1 atm $H_2$, Pd/C) afforded the mixture of hippodamine **(164)** and 2-*epi*-hippodamine **(219)** with **219** being a major product. After extensive screening of reaction conditions such as temperature, solvent nature and various additives they found that running the hydrogenation in THF with 2 equiv of mesitylenesulfonic acid allowed them to obtain hippodamine **(162)** as a major product.

## 2.2 Results and discussion

### 2.2.1 Intramolecular *Aza*-[3 + 3] Annulation Approach to Azaphenalene Alkaloids.

In all known syntheses of *Coccinellidae* defensive alkaloids **162-166** generally distinct synthetic strategies are used to access different members of this family of natural products. Also in all syntheses with the exception of one,[49a] the equatorial methyl group is being introduced in the latter steps of the synthetic sequence. We envisioned accessing the entire family of *Coccinellidae* alkaloids featuring the construction of their azaphenalene core (**Figure 2-4**) from a common *aza*-tricycle **249** attained via an intramolecular *aza*-[3 + 3] annulation of vinylogous amide **250.**

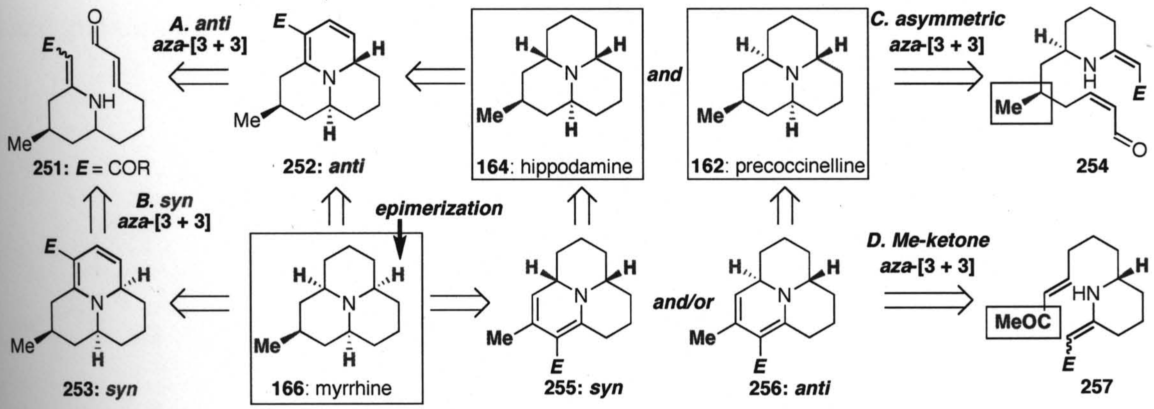
**Figure 2-4.** An *aza*-[3 + 3] annulation approach to azaphenalenes.



### 2.2.2. Retrosynthetic Plan.

Due to the symmetric nature of precoccinelline **(162)**, hippodamine **(164)**, and myrrhine **(166)**, retrosynthetically, they could be derived via four distinct pathways depending upon the stereochemical outcome of intramolecular *aza*-[3 + 3] annulation and the location of the methyl substituent (**Figure 2-5**). If the *aza*-[3 + 3] annulation of vinylogous amide **251** proceeds selectively to favor the *anti* [defined by the angular hydrogen atoms in blue] annulation product **252** as shown in pathway **A**, we could then quickly access both precoccinelline **162** and hippodamine **164**, as **252** would match three of the four stereocenters in **162** and **164**. However, an appropriate epimerization of **252** would be required to access myrrhine **166**. A more direct synthesis of **166** would be to employ the *syn* [defined by the angular hydrogen atoms in red] *aza*-tricycle **253** via a *syn*-selective annulation of **251** [pathway **B**].

**Figure 2-5.** Retrosynthetic analysis.

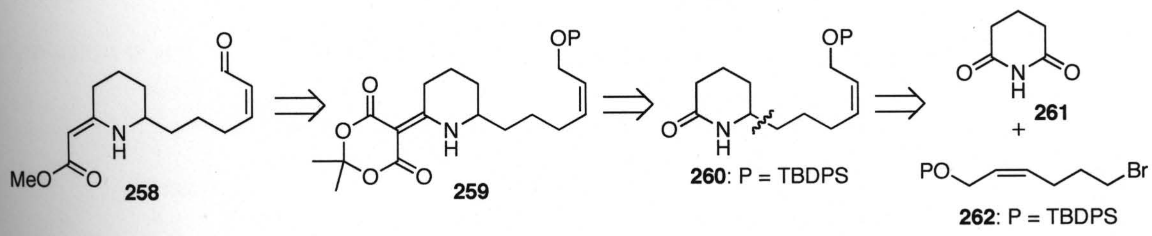


In pathway **C**, the methyl group required for these natural products is envisioned to be on the carbon tether of vinylogous amide **254**, and if **254** could be accessed in an optically enriched manner, it would constitute an enantioselective total synthesis of **164** (**162** and **166** are achiral or *meso*). Finally, these alkaloids could also be derived from **255** and/or **256** that can be attained through an intramolecular *aza*-[3 + 3] annulation reaction of vinylogous amide **257**, which would require an enone annulation (see pathway **D** in **Figure 2-5**). We focused on pathways **A** and **B** because it is not trivial to prepare **254** in an optically enriched manner and we have not yet developed a useful enone version of *aza*-[3 + 3] annulation reaction at that time (see **Part 3** for disscusion).

### 2.2.3. Model Study.

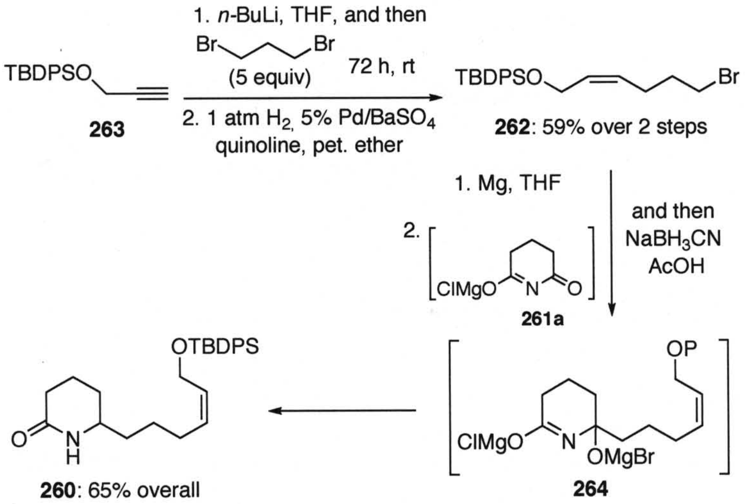
Based on our retrosynthetic analysis, a foremost critical question that needs to be addressed would be the stereochemical outcome of the strategic *aza*-[3 + 3] annulation reaction. To explore the feasibility and stereoselectivity of this key transformation, we commenced our efforts with a model system involving the annulation precursor **258** (**Figure 2-6**), which should be accessible from Meldrum's acid derivative **259** prepared from lactam **260** along with bromide **262** and glutarimide **261**.

**Figure 2-6.** Retrosynthesis of the annulation precursor.



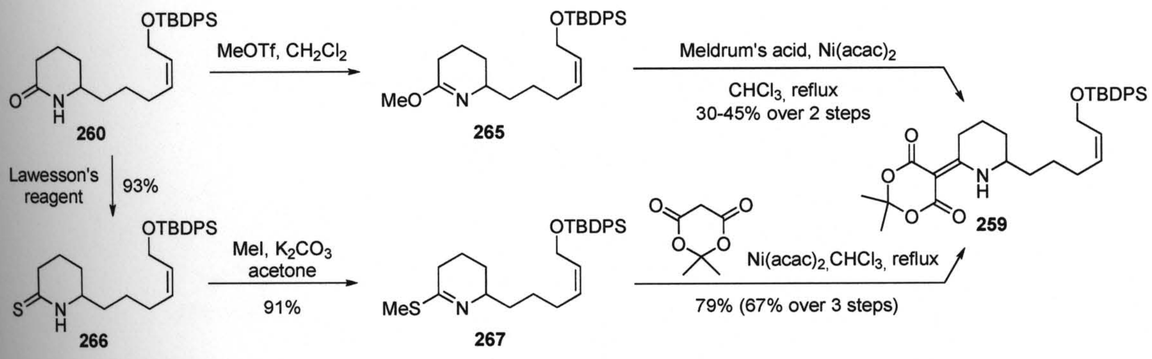
To prepare vinylogous urethane **258**, alkylation of TBDPS-protected propargyl alcohol **263**[53] employing excess 1,3-dibomopropane followed by Lindlar hydrogenation led to bromide **262** in 59% overall yield (**Scheme 2-15**). Lactam **260** was prepared via reductive alkylation[54] of glutarimide **261**. The Grignard reagent generated from bromide **262** was added to the Mg-salt **261a** formed *in situ* from glutarimide **261** and 1.0 equiv of $CH_3MgCl$. Subsequent reduction of the hemi-aminal intermediate **264** with $NaBH_3CN$ and AcOH gave lactam **260** in 65% yield over three steps.

**Scheme 2-15.** Reductive alkylation.



After an extensive screening of various methylating conditions, *O*-methyl imidate **265** was prepared in nearly quantitative yield via treatment of lactam **260** with freshly distilled MeOTf in $CH_2Cl_2$ (**Scheme 2-16**).[55] Without further purification, it was submitted for the condensation reaction with Meldrum's acid in the presence of $Ni(acac)_2$ catalyst.[56]

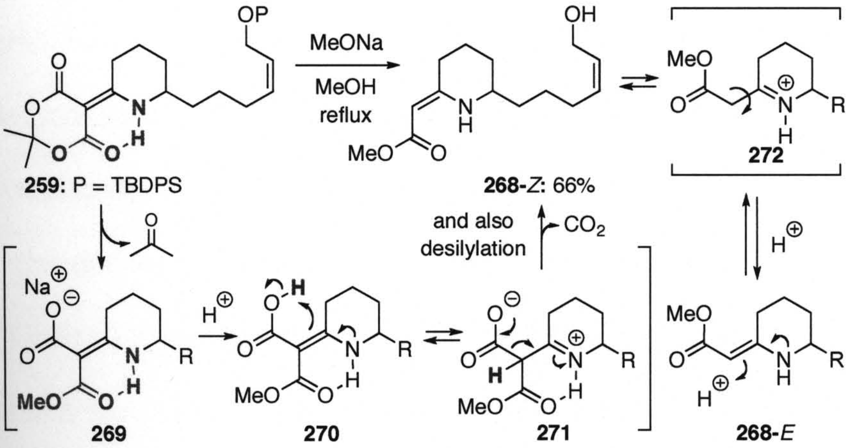
**Scheme 2-16.** Synthesis of Meldrum's acid derivative.



The two-step sequence led to piperidine **259** in 30-45% overall yield. Alternatively, piperidine **259** was prepared in three steps with a higher yield from lactam **260**: 1) Lawesson's reagent,[57] 2) methylation, and 3) $Ni(acac)_2$ catalyzed condensation with Meldrum's acid.

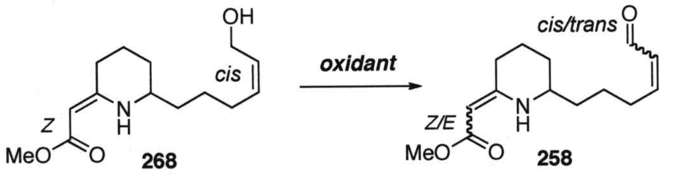
Treatment of piperidine **259** with an excess of MeONa in refluxing MeOH led to the formation of vinylogous urethane **268-*Z*** in 66% yield exclusively as a *Z*-isomer (**Scheme 2-17**),[56] and the TBDPS group was also cleaved under the reaction conditions. Mechanistically, the intriguing selectivity for the *Z*-isomer could be rationalized via a regioselective addition of methoxide anion to the carbonyl group [in red] in **259** that is activated by intramolecular hydrogen bonding to give sodium carboxylate **269**. Upon protonation of **269** during the work up, a neutral vinylogous carbamic acid **270** could be attained. However, this carbamic acid could also exist in equilibrium with the zwitterion **271** as shown through the arrow pushing [although proton could come from external sources]. The zwitterion **271** would represent the most suitable intermediate to undergo a facile decarboxylation, leading to *Z*-urethane **268-*Z***. Alternatively, if decarboxylation of **271** would give enamine **268-*E***, it could still be converted to the *Z*-isomer via the iminium intermediate **272** upon protonation of **268-*E***. Rotation around C-C bond in intermediate **272** followed by deprotonation will lead to the thermodynamically more stable **268-*Z***.

**Scheme 2-17.** Proposed mechanism for derboxylation.



Various oxidation protocols were evaluated to efficiently convert allyl alcohol **268-*Z*** to the corresponding enal **258** (**Scheme 2-18**). $MnO_2$ oxidation was relatively slow giving only 49% yield of the desired enal **258** [entry 1], but under these conditions, a mixture of both *cis* and *trans* enals was obtained. The Swern oxidation conditions[58a] allowed us to access enal **258** in quantitative yield [entry 2] exclusively as *cis* isomer, but the *Z* geometry in the vinylogous urethane fragment was completely scrambled. Finally, the Doering-Parikh oxidation protocol[58b,c] provided **258** in excellent yield with retention of the *Z* geometry in the vinylogous urethane moiety [entry 3].

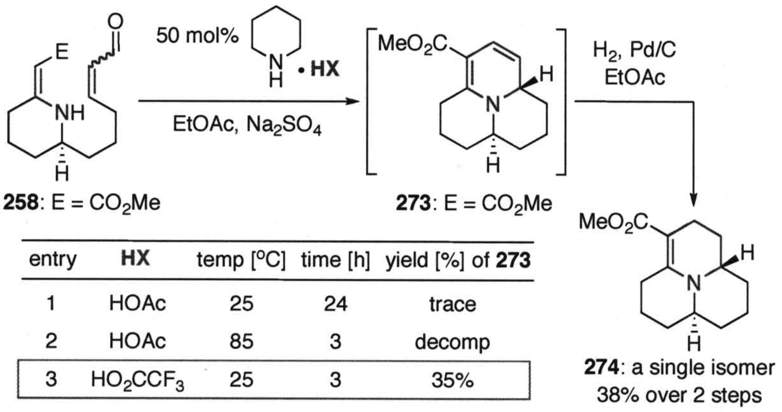
**Scheme 2-18.** Screening of oxidation protocols.



| entry | *oxidants* | yield [%] | enal and amide ratios |
|---|---|---|---|
| 1 | $MnO_2$ | 49 | *cis* : *trans* = 3 : 1 (enal) |
| 2 | $(COCl)_2$/DMSO | 100 | *Z* : *E* = 1 : 1 (amide) |
| 3 | Pyr-$SO_3$/DMSO | 87 | *cis* : *trans* = 7 : 1 (enal) |

Enal **258** (*cis* : *trans* = 7 : 1) was subjected to the *aza*-[3 + 3] annulation conditions employing piperidinium acetate salts in EtOAc (**Scheme 2-19**). After 24 h at rt, only a trace amount of the desired *aza*-tricycle **273** was detected by $^1$H NMR [entry 1]. Subsequent heating of the reaction mixture to 85 °C for 3 h led to the decomposition of **258** [entry 2]. Upon using the more reactive piperidinium trifluoroacetate salt [entry 3], complete consumption of **258** was observed at 25 °C after 3 h, and the desired *aza*-tricycle **273** was isolated in 35% yield as a single diastereomer. Its *anti* stereochemistry at the ring junctions was established via nOe experiments. Because of the precarious nature of **273**, we found it more convenient to hydrogenate the reaction mixture over Pd-C after the annulation.[10] This one-pot protocol allowed us to access the more stable *aza*-tricyclic **274** in 38% overall yield.

**Scheme 2-19.** Intramolecular *aza*-[3 + 3] annulation.



**258**: E = $CO_2Me$

**273**: E = $CO_2Me$

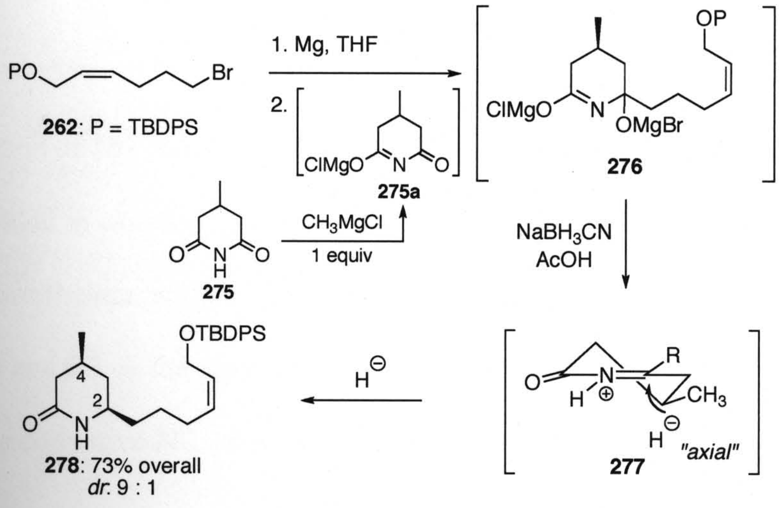
| entry | HX | temp [°C] | time [h] | yield [%] of **273** |
|---|---|---|---|---|
| 1 | HOAc | 25 | 24 | trace |
| 2 | HOAc | 85 | 3 | decomp |
| 3 | $HO_2CCF_3$ | 25 | 3 | 35% |

**274**: a single isomer
38% over 2 steps

## 2.2.4 An Approach to Precoccinelline, Hippodamine, Coccinelline and Convergine.

Having succeeded in the model study, we turned our attention to the actual total syntheses of alkaloids **162-166** via the same route developed above for the des-methyl model. Toward this end, lactam **278** was prepared similarly to des-methyl case via reductive alkylation[54] of 4-methyl glutarimide **275**[59] (**Scheme 2-20**).

**Scheme 2-20.** Stereoselective reductive alkylation.



**262**: P = TBDPS

**275a**

**275**

**276**

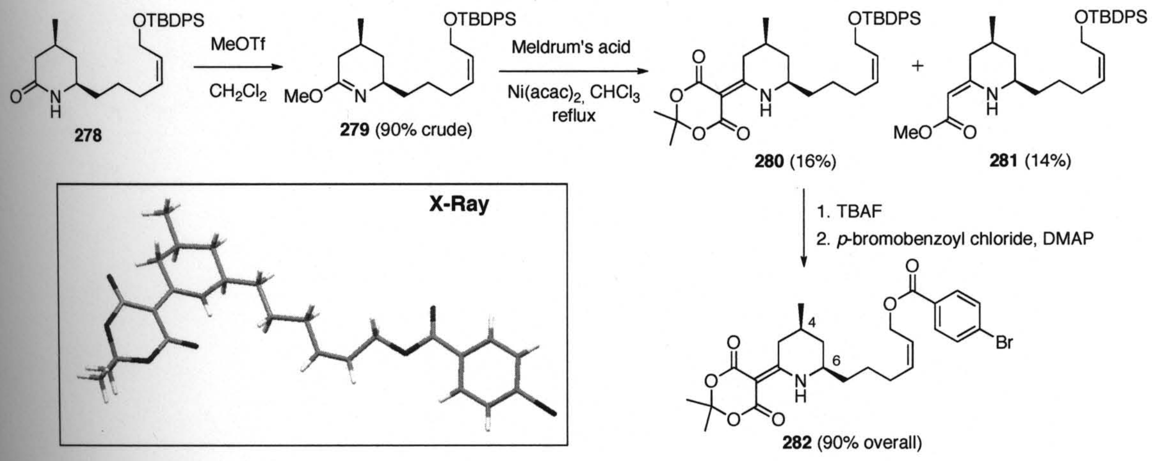
**277**

**278**: 73% overall
*dr.* 9 : 1

The Grignard reagent generated from bromide **262** was added to the Mg-salt **275a** formed *in situ* from glutarimide **275** and 1.0 equiv of $CH_3MgCl$, and after stirring overnight at rt, $NaBH_3CN$ and AcOH were added to reduce the intermediate hemi-aminal **276**. The reduction proceeded stereoselectively and afforded lactam **278** in 73% overall yield exclusively as the 2,4-*syn* isomer. This is likely a result of *axial* approach of hydride to the conformation shown for *N*-acyliminium ion **277**.

After converting lactam **278** to methyl imidate **279** using fresh MeOTf in $CH_2Cl_2$, lactim ether **279** was subjected to the condensation reaction with Meldrum's acid in the presence of $Ni(acac)_2$ catalyst (**Scheme 2-21**).[56] However, in this case, the desired piperidine **280** was isolated only in 16% yield over two steps along with 14% of vinylogous urethane **281**.

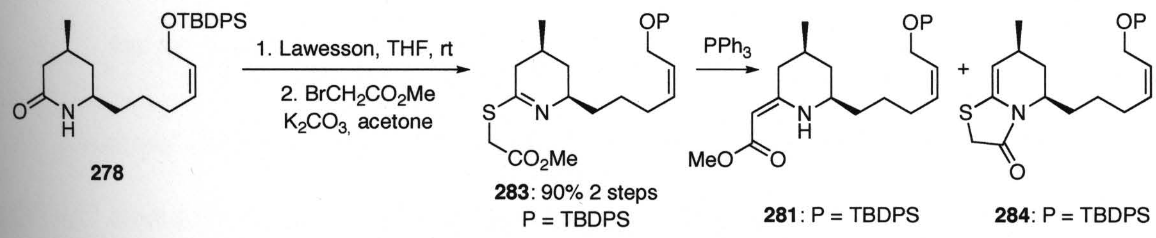
**Scheme 2-21.** Assignment of relative stereochemistry.



The formation of **281** was likely a result of ring-opening of the 1,3-dioxanone ring in **280** with MeOH generated *in situ* during the condensation reaction followed by decarboxylation (see **Scheme 2-17**). Nevertheless, we were able to unambiguously assign the relative stereochemistry with respect to C4 and C6 on the piperidine ring as *syn* based on the single crystal X-ray analysis of bromo-benzoate derivative **282** prepared in two steps from **280**.

To access vinylogous urethane **281** more effectively, we investigated an alternative approach that would feature Eschenmoser sulfide contraction reaction.[60a,b] As shown in **Scheme 2-22**, thiol imidate **283** was prepared in two steps from the lactam **278**, and was subsequently treated with $PPh_3$ in the presence of $NEt_3$ in $CH_3CN$. After 72 h at rt, no formation of the desired vinylogous urethane **281** was observed [entry 1]. After addition of DBU and refluxing in $CH_3CN$ for 48 h, vinylogous urethane **281** was isolated in 69% yield along with an interesting by-product thiazolidinone **284** [entry 2]. There are literature precedents[60c] for the formation of this by-product in the Eschenmoser sulfide contraction reaction when using strong base such as DBU. After tuning both the base and the solvent for the reaction, an excellent yield of the desired vinylogous urethane **281** could be achieved [entry 4].

**Scheme 2-22.** Eschenmoser sulfide contraction.



**278**

**283**: 90% 2 steps
P = TBDPS

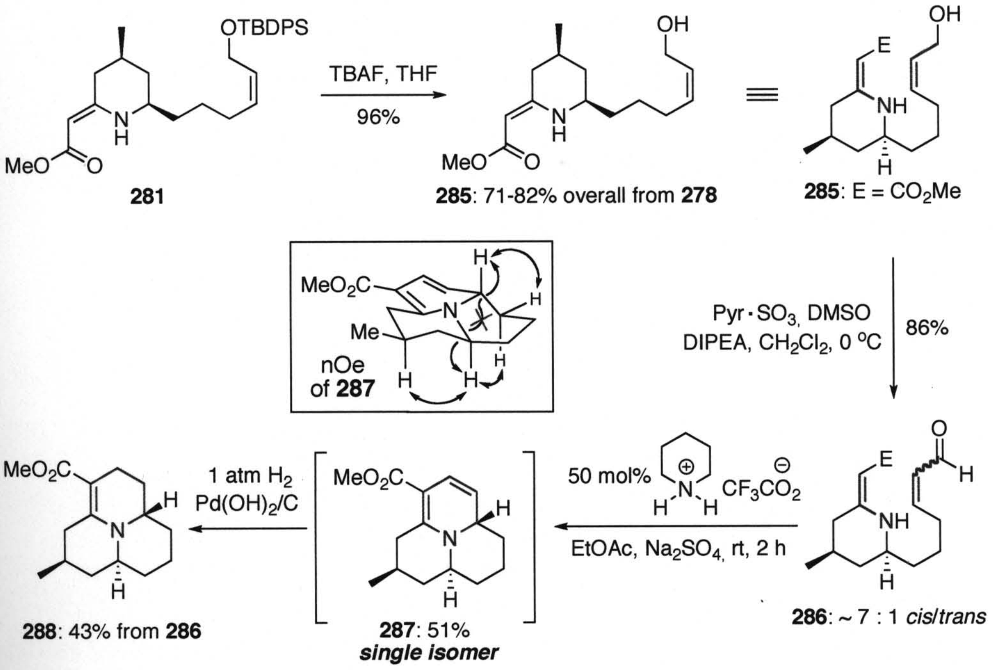
**281**: P = TBDPS

**284**: P = TBDPS

| entry | base | solvent | temp [°C] | time [h] | yield [%]: **281** | **284** |
|---|---|---|---|---|---|---|
| 1 | $NEt_3$ | $CH_3CN$ | 25 | 72 | no rxn | no rxn |
| 2 | $NEt_3$/DBU | $CH_3CN$ | 80 | 48 | 69% | 5-10% |
| 3 | DIPEA | toluene | 100 | 96 | 60% | trace |
| 4 | DIPEA | $CH_3CN$ | 100 | 48 | 82-95 | trace |

Cleavage of the TBDPS-protecting group with TBAF furnished allyl alcohol **285** (**Scheme 2-23**). It is noteworthy that the described sequence was suitable for multi-gram scale synthesis of alcohol **285** with a 71-82% overall yield starting from lactam **278**. Subsequent pyr•$SO_3$ oxidation of allyl alcohol **285** led to the corresponding enal **286** as a 7 : 1 *cis/trans* isomeric mixture. Enal **286** was subjected to the *aza*-[3 + 3] annulation conditions employing piperidinium trifluoroacetate in EtOAc. The desired cycloadduct **287** was obtained as a single diastereomer in 51% yield, and its *anti* relative stereochemistry at the ring junction was established using nOe [see the box] and by X-ray of a later intermediate.

**Scheme 2-23.** The key intramolecular *aza*-[3 + 3] annulation.



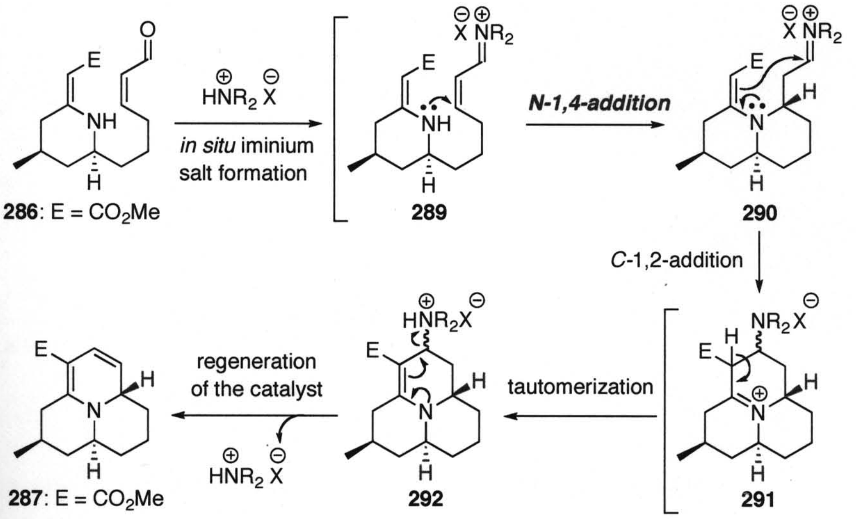
A one-pot protocol involving *in situ* hydrogenation of the disubstituted double bond over $Pd(OH)_2/C$ after the annulation afforded *aza*-tricycle **288** in a reproducible 43% yield over two steps. We chose $Pd(OH)_2/C$ here because it is less prone to amine poisoning than Pd/C that was previously used for the hydrogenation of **273** (see **Scheme 2-19**), and we did not go back and repeat this work using $Pd(OH)_2/C$. It is noteworthy that *aza*-tricycle **288** contains three of the four stereocenters required for precoccinelline **(162)** and hippodamine **(164)**.

### 2.2.5 Mechanistic and Computational Studies.

To rationalize the exclusive formation of *anti* stereochemistry at the ring junction observed for the annulation product **287** (**Figure 2-7**), transition state structures for the key *N*-

1,4-addition step of the reaction where the new stereogenic center is being set were located. Calculations were carried out on the simplified iminium salt derived from enal **286** and dimethyl amine using the Spartan'02 program at PM3 level of theory.[22,23]

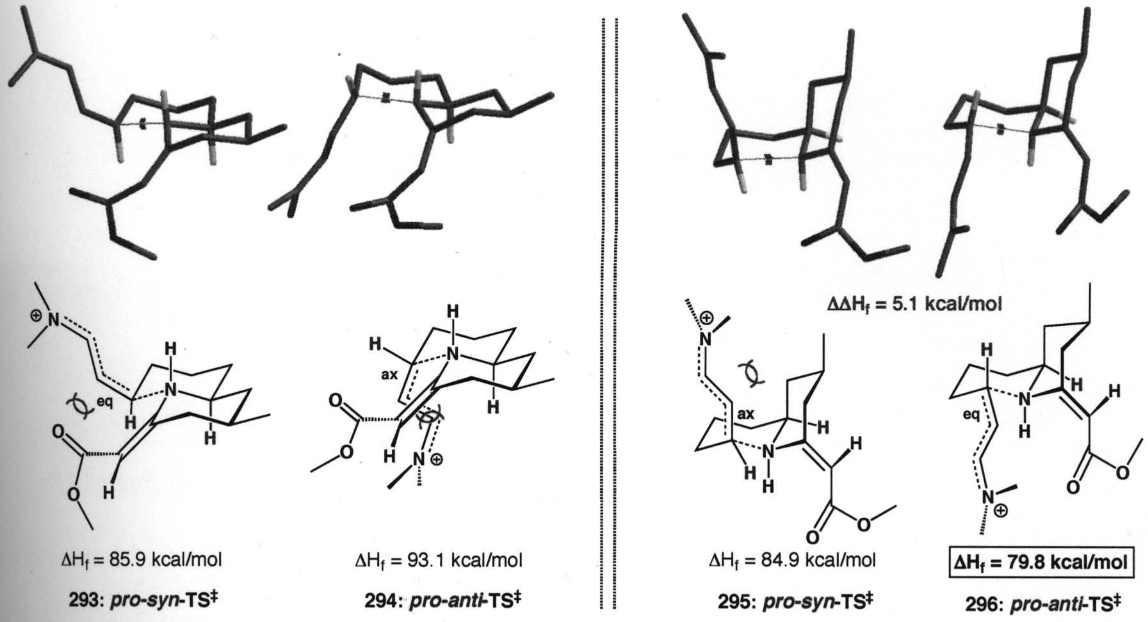
**Figure 2-7.** Mechanism of the intramolecular *aza*-[3 + 3] annulation.



Location of transition state structures was confirmed by the presence of one negative eigenvalue and corresponding imaginary frequency, which reflects formation of the N-C bond for the N-1,4 addition step of the reaction. Models and their respective energies are shown in **Figure 2-8**.

There are two possible *pro-syn* and *pro-anti* transition states **293/294** and **295/296**, which differ in the chair flip of the piperidine ring. In **293/294**, the lone pair on the nitrogen atom occupies the pseudo-equatorial position whereas in **295/296** it is pseudo-axial making it more nucleophilic. It turned out that both *pro-syn*-**TS-293** and *pro-anti*-**TS-294** (left side in **Figure 2-8**) are energetically disfavored in comparison with *pro-syn*-**TS-295** and *pro-anti*-**TS-296** (right side). Because of the *Z*-geometry of the vinylogous urethane, the methoxy carbonyl group in both **293** and **294** appear to be bumping into the iminium ion fragment during formation of N-C bond, thereby destabilizing both transition states.

**Figure 2-8.** Transition states for the initial *N*-1,4-addition.



ΔH$_f$ = 85.9 kcal/mol
**293:** ***pro-syn*-TS‡**

ΔH$_f$ = 93.1 kcal/mol
**294:** ***pro-anti*-TS‡**

ΔH$_f$ = 84.9 kcal/mol
**295:** ***pro-syn*-TS‡**

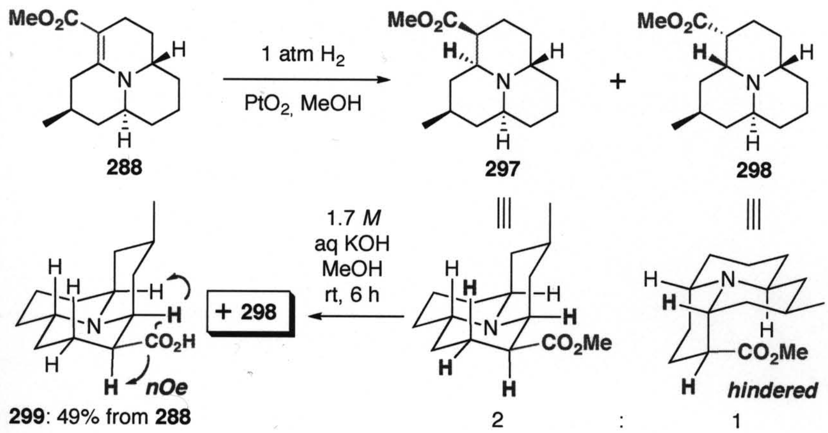
**ΔH$_f$ = 79.8 kcal/mol**
**296:** ***pro-anti*-TS‡**

On the other hand, this interaction is minimized in *pro-syn*-**TS-295** and *pro-anti*-**TS-296**, as shown in the models (right side in **Figure 2-8**). Within these two possible transitions states, *pro-anti*-**TS-296** was estimated to be 5.1 kcal/mol more stable than *pro-syn*-**TS-295**, which is likely due to the severe 1,3-diaxial interaction in **295**. According to computational results, the annulation reaction should be favored to proceed via *pro-anti*-**TS-296,** leading to the observed *anti*-isomer **287**.

### 2.2.6. Syntheses of Precoccinelline, Hippodamine, Coccinelline and Convergine.

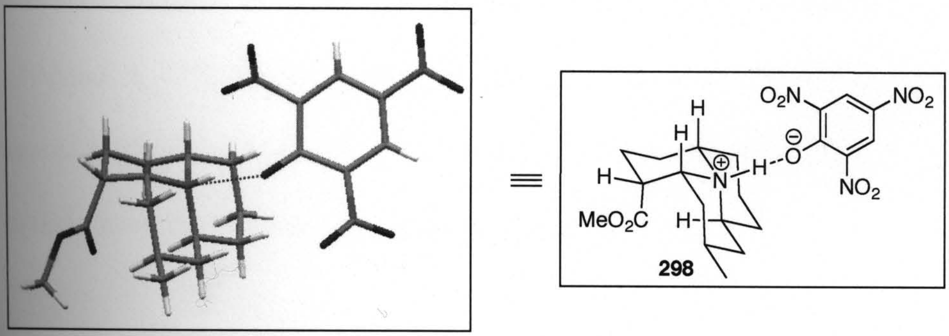
With *aza*-tricycle **288** in hand, we hydrogenated the internal double bond employing Adam's catalyst[61] (**Scheme 2-24**). To our advantage, hydrogenation occurred in a stereodivergent manner, leading to both isomers **297** and **298** with a ratio of 2 : 1. It is noteworthy that major isomer **297** resembles the *aza*-tricyclic manifold in precoccinelline **(162)**, whereas **298** has the framework of hippodamine **(164)**.

**Scheme 2-24.** A stereodivergent hydrogenation.



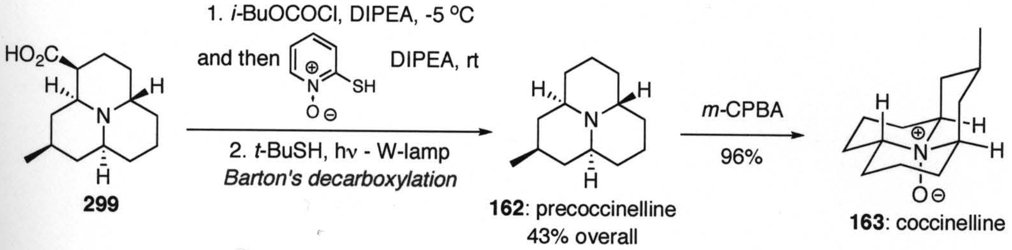
Although esters **297/298** could be separated by tedious alumina gel column, it was found that they could be readily resolved via a selective alkaline hydrolysis of the equatorial ester **297** (**Scheme 2-24**). Upon treatment of the crude hydrogenation mixture with 1.7 *M* aq KOH, unreacted axial ester **298** was recovered by simple extraction in 36% overall yield from **288**. Upon acidification of the aqueous phase, acid **299** was isolated in 49% yield with its assigned relative stereochemistry being supported by nOe. Structure of **298** was unambiguously assigned by X-ray analysis of its corresponding picrate salt (**Figure 2-9**).

**Figure 2-9.** X-ray structure of picrate salt of **298**.



To complete the total synthesis of precoccinelline **(162)**, acid **299** was subjected to Barton's decarboxylation conditions[62] (**Scheme 2-25**). The desired alkaloid was isolated in 43% overall yield with all physical data matching the reported literature data.[50c,63] Subsequent oxidation of precoccinelline employing *m*-CPBA provided coccinelline **(163)** in excellent yield.

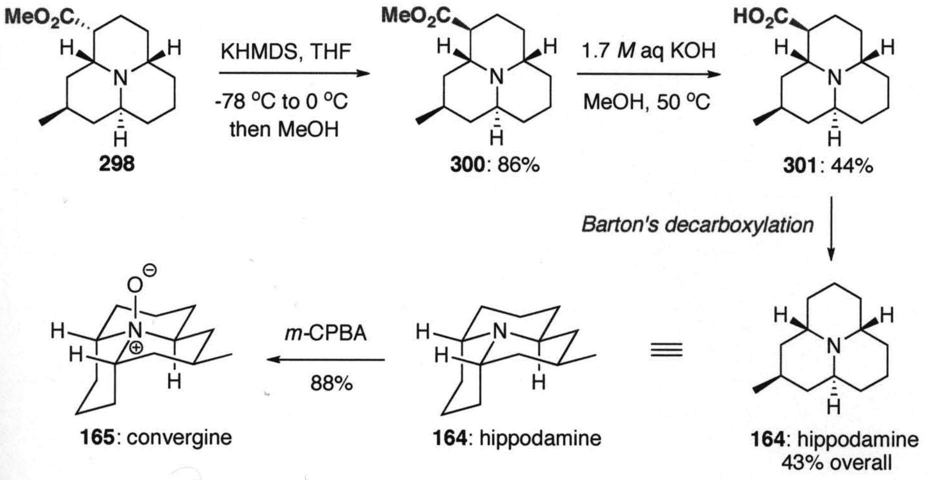
**Scheme 2-25.** Completion of total syntheses of precoccinelline and coccinelline.



The synthesis of hippodamine **(164)** turned out to be more challenging, as all attempts to directly hydrolyze of ester **298** failed. This can be attributed to the inaccessibility of the hindered axial ester group in **298**. We attempted to epimerize the axial ester to the more stable equatorial one using $K_2CO_3$/MeOH and DBU/toluene protocols, but neither condition was suitable with complete recovery of the starting material.

Ultimately, we found that treatment of ester **298** with KHMDS[64] at -78 °C with subsequent quenching of the reaction mixture with MeOH at 0 °C led to the desired equatorial ester **300** with 86% yield (**Scheme 2-26**). Hydrolysis of the **300** was successful using 1.7 *M* aq KOH at 50 °C, leading to carboxylic acid **301** in 44% yield. Subsequently, hippodamine **(164)** was obtained in 43% overall yield after decarboxylation of **301** under Barton's conditions.[62] Successive oxidation of **164** with *m*-CPBA afforded convergine **(165)** in 88% yield. Both natural products matched the literature spectroscopic data.[49d,63]

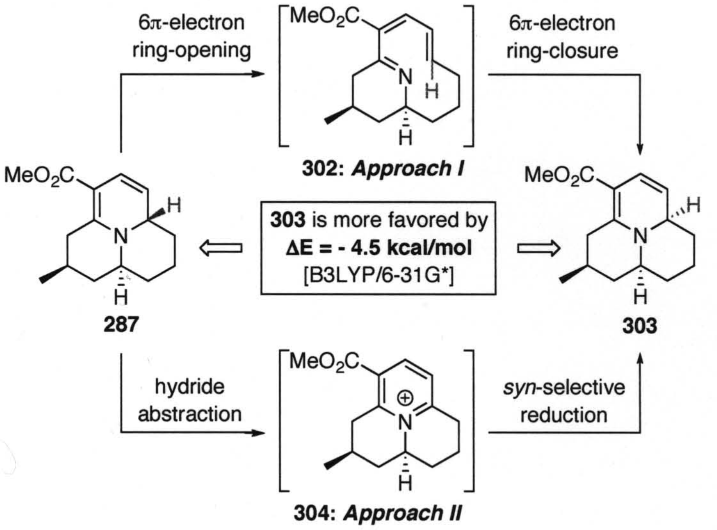
**Scheme 2-26.** Hippodamine and convergine end-game.



## 2.2.7. Total Synthesis of Myrrhine.

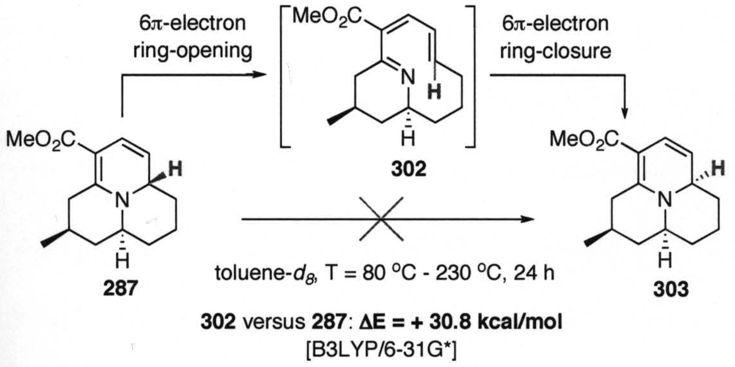
After successful conversions of *aza*-tricycle **287** to precoccinelline **(162)**, hippodamine **(164)**, and their corresponding *N*-oxides, we were poised to achieve a total synthesis of myrrhine **166**, the final member of *Coccinellidae* family of defensive alkaloids, also from the same common intermediate **287**. However, the challenge in this endeavor was to achieve an appropriate epimerization at the stereocenter shown in red in *aza*-tricycle **287** (**Figure 2-10**). Toward this end, we envisioned two possible approaches for this transformation. The first one involves a 6π-electrocyclic ring-opening of *anti*-tricycle **287** under thermal conditions *en route* to 1-azatriene **302**, which upon 6π-electrocyclic ring-closure, could lead to the thermodynamically more stable *syn aza*-tricycle **303**. The second approach consists of an aromatization of the dihydropyridine ring in **287** via hydride abstraction followed by *syn*-selective reduction of the pyridinium salt **304** to furnish all-*syn* stereochemistry at the ring junction required for myrrhine **166**.

**Figure 2-10.** Possible epimerization approaches.



To probe the feasibility of shuttling the *anti aza*-tricycle **287** to the more stable *syn*-**303** through 1-azatriene **302**, compound **287** was heated at 80 °C for 6 h in toluene-$d_8$ (**Scheme 2-27**). However, no formation of desired isomer **303** was observed under these conditions. Heating of **287** at higher temperatures for longer time [150 °C, 12 h, then 230 °C 2 h] was pursued but only led to decomposition of the starting material.

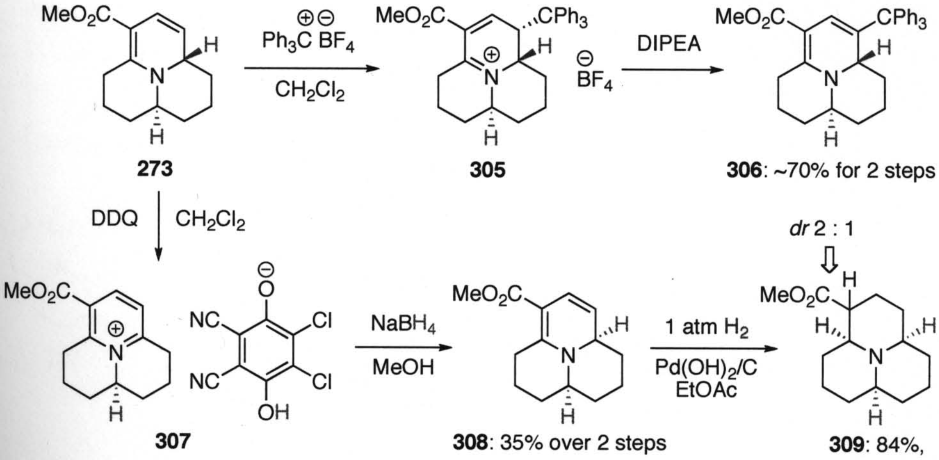
**Scheme 2-27.** Failed isomerization attempts.



*Ab initio* calculations (B3LYP/6-31G*)[22,23] indicated that 1-azatriene **302** is relatively destabilized in comparison with *aza*-tricycle **287** [by ~ 31 kcal/mol]. Since the activation barrier would be even higher, we believed that 6π-electrocyclic ring-opening approach is not a thermally feasible option for our purpose. This experimental data is also in accord with our earlier findings (see **Section 1.2.6**).[10b]

After failure of isomerization approach we then investigated the aromatization-reduction route. Des-methyl tricycle **273** served as a model system for this study. It was first treated with triphenylcarbonium tetrafluoroborate in $CH_2Cl_2$ (**Scheme 2-28**). Interestingly, instead of the hydride abstraction triphenylcarbonium cation added across electron rich azadiene to give tetrafluoroborate **305** in nearly quantitative yield.

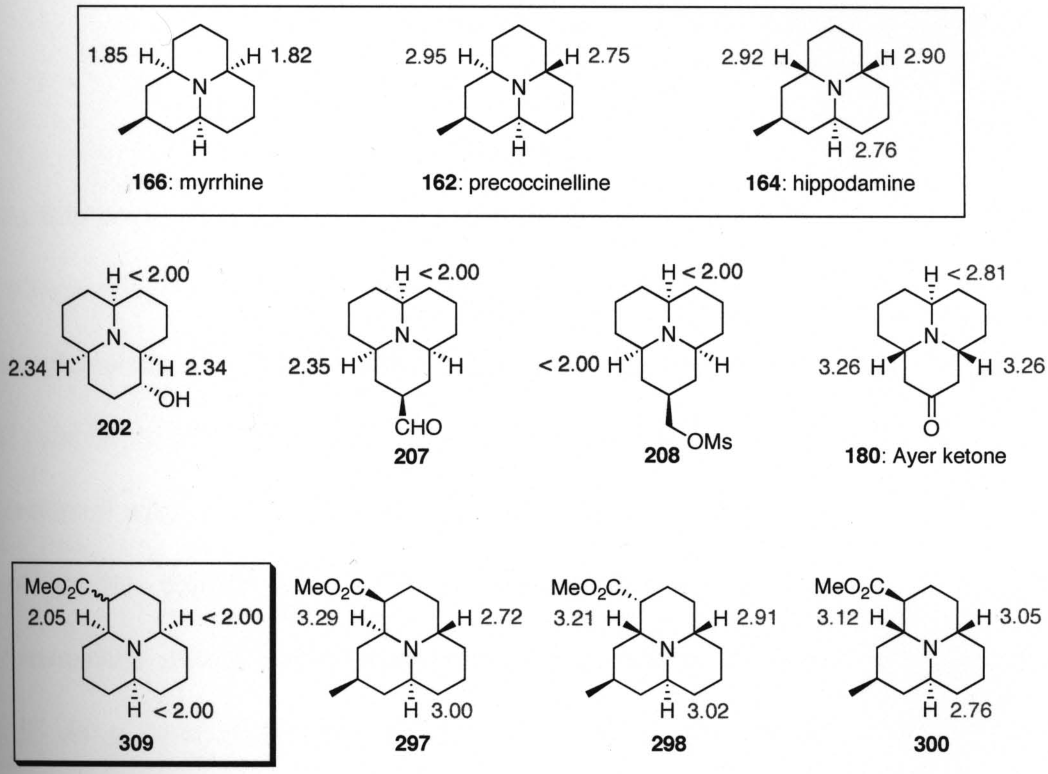
**Scheme 2-28.** Aromatization-reduction approach.



Subsequent treatment of the salt **305** with Hunig's base regenerated dihydropyridine motif to form tricycle **306** but it was a "dead-end" for synthesis of a myrrhine alkaloid. Oxidation of the tricycle **273** with DDQ in $CH_2Cl_2$[65] led to isolation of the pyridinium salt **307** which was directly reduced with sodium borohydride in MeOH. Luckily, hydride addition occurred stereoselectively leading to the desired *syn*-tricycle **308** in 35% over 2 steps. To our surprise, both double bonds in *syn*-tricycle **308** can be reduced simultaneously by hydrogenation using $Pd(OH)_2/C$ catalyst and 1 atm of $H_2$. It is noteworthy that in case of *anti*-tricycles **273** and **287** only disubstituted double bond was hydrogenated under these conditions (see **Schemes 2-19,**

**2-23**). This result could most likely be attributed to better accessibility of the internal double bond in flatter *syn*-tricycle **308**. All-*syn* azaphenalene **309** was obtained in 84% yield as mixture of two ester diastereomers. All-*syn* relative stereochemistry of **309** was assigned based on the chemical shifts analysis of hydrogens adjacent to the nitrogen atom which are known to be shielded in all-*syn* azaphenalenes [shown in blue] comparing to *anti-syn* tricycles [in red] by about 1 ppm on average (**Figure 2-11**).

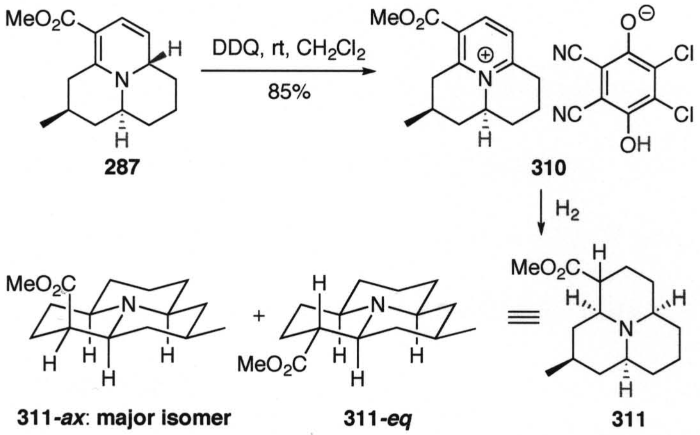
**Figure 2-11.** Chemical shifts of α-hydrogens in azaphenalene systems.



It is very consistent trend in azaphenalene alkaloids [**166** versus **162**, **164**] as well as in various synthetic intermediates prepared by different groups[50a,c] [**202**, **207**, **208** versus **180**] and by us *en route* to precoccinelline and hippodamine natural products [**309** versus **297**, **298**, **300**].

Employing the epimerization protocol developed for our model system **273**, pyridinium salt **310** was prepared in 85% yield from *aza*-tricycle **287** and DDQ in $CH_2Cl_2$ (**Scheme 2-29**).

**Scheme 2-29.** Hydrogenation of a pyridinium salt.

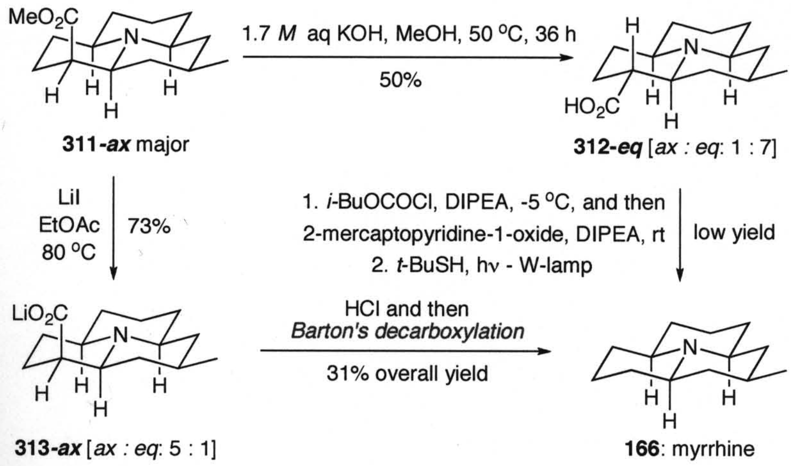


| entry | catalyst | $H_2$ [psi] | solvent | yield [%] | *dr*: **ax : eq** |
|---|---|---|---|---|---|
| 1 | $PtO_2$ | 60 | MeOH | 61 | 2 : 1 |
| 2 | $Pd(OH)_2/C$ | 14 | MeOH | 44 | 5 : 1 |
| 3 | $PtO_2$ | 60 | AcOH | 63 | 2 : 1 |

At this point we discovered that pyridinium salt **310** could be directly converted to the desired all-*syn* tricycle **311** by hydrogenation avoiding intermediate $NaBH_4$ reduction to *syn*-dihydroazaphenalene like **308** (**Scheme 2-28**). Thus, hydrogenation of the salt **310** over $PtO_2$ [Adams' catalyst] in MeOH afforded 61% yield of the all-*syn aza*-tricycle **311** as a 2 : 1 mixture of diastereomers with respect to the stereochemistry at the ester group [entry 1]. This is likely a result of partial epimerization of the initially formed axial isomer **311-*ax*** to the thermodynamically more stable equatorial **311-*eq*** under the reaction conditions. Using $Pd(OH)_2/C$ as a catalyst for the hydrogenation led to the formation of **311** with some epimerization but also a lower yield [entry 2]. The cleanest reaction with the highest isolated yield was obtained when the hydrogenation was carried out over Adams' catalyst in AcOH [entry 3].[61] The all-*syn* stereochemistry at the ring junctions was confirmed by the presence of strong Bohlmann bands[66] in IR spectra [2793, 2734, 2619 $cm^{-1}$] of the **311** as well as by chemical shift analysis similar to des-methyl system **309** (**Figure 2-11**).

Saponification of a mixture of ester **311-*ax*** and **311-*eq*** [***ax* : *eq*** = 3 : 1] with aqueous KOH in MeOH at 50 °C for 36 h led to predominantly the formation of equatorial acid **312-*eq*** (**Scheme 2-30**), thereby suggesting that significant epimerization of the axial isomer to the more stable equatorial one had occurred. However, subjecting this mixture to Barton's decarboxylation conditions[62] led to myrrhine **166** in a very low yield with almost complete recovery of the equatorial acid **312-*eq***. This result suggested that the axial acid **312-*ax*** is more reactive in the decarboxylation reaction than **312-*eq***.

**Scheme 2-30.** Myrrhine end-game.



To explore this hypothesis, ester **311** [5 : 1 isomer ratio in favor of **311-*ax***] was saponified by treatment with LiI in EtOAc at 80 °C. Under this condition, no epimerization was observed and the diastereomeric ratio of the isolated lithium carboxylate remained at ~ 5 : 1 in favor of **313-*ax***. Finally, acidification of this mixture and subjecting the resulting free acid **312-*ax*** to the Barton's decarboxylation conditions afforded myrrhine **166** in 31% yield over 4 operational steps. Our synthetic sample matched the literature spectroscopic data for the natural myrrhine **166**.[50c,63]

## 2.3. Conclusion.

We have accomplished total syntheses of *Coccinellidae* defensive alkaloids featuring an intramolecular *aza*-[3 + 3] annulation reaction as the key transformation. All five members of this family, precoccinelline, coccinelline, hippodamine, convergine, and myrrhine have been prepared from the same common intermediate derived from a stereoselective *aza*-[3 + 3] annulation reaction. A mechanistic model for the observed *anti* stereoselectivity in the annulation step based on semi-empirical calculations was also established. This work provides a *de novo* stereoselective approach toward 2-methyl-perhydro-9b-azaphenalene family of alkaloids.

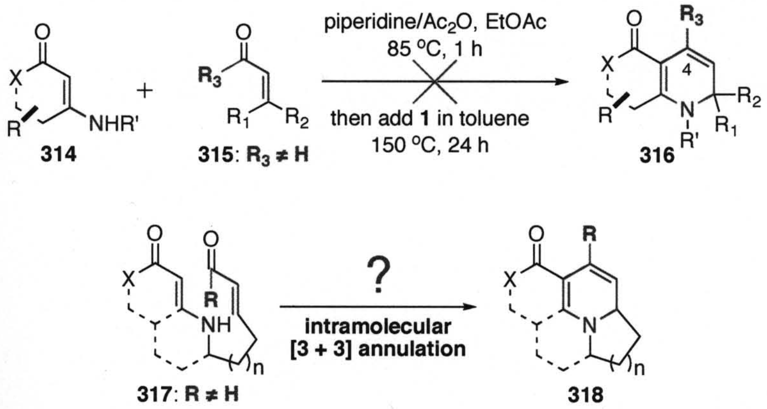
# Part 3

## Enone Version of Intramolecular *Aza*-[3 + 3] Annulation Reaction

## 3.1. Introduction.

One of the significant limitations of our *aza*-[3 + 3] annulation methodology was inability to employ α,β-unsaturated ketones in this transformation. No formation of desired C4-substituted azadecalines **316** was observed in intermolecular [3 + 3] annulations between vinylogous amides **314** and enones **315** under standard reaction conditions (**Figure 3-1**). Moreover, we were also unsuccessful in finding any other suitable conditions for this transformation so far. Generally, reactions were messy and formation of the complex mixture of products was observed.

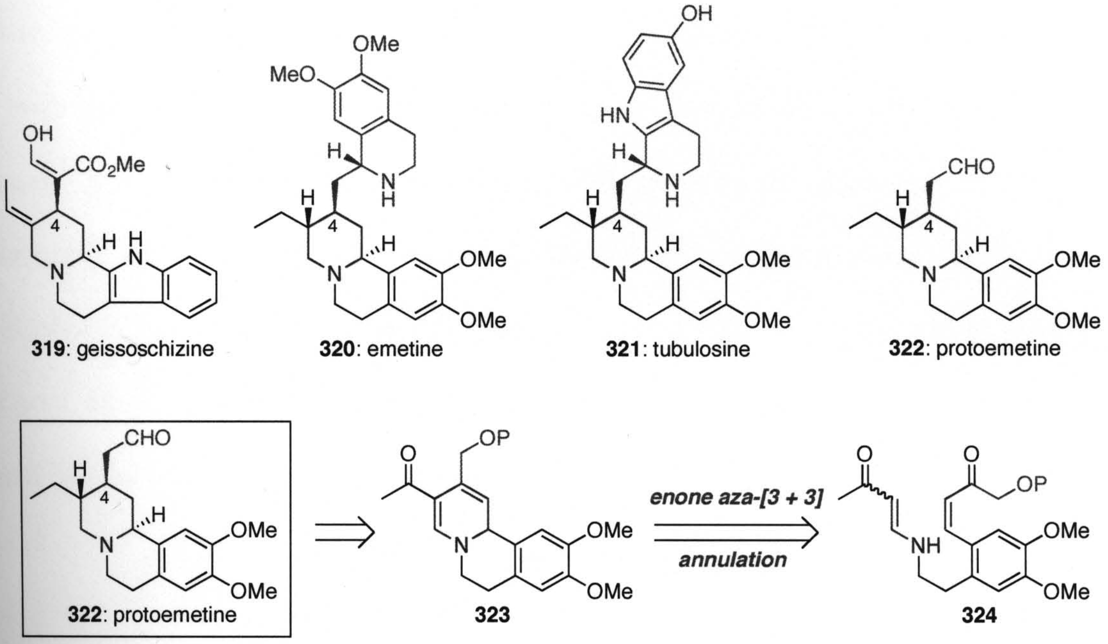
**Figure 3-1.** Limitation of *aza*-[3 + 3] annulation methodology.



On the other hand, as described earlier (see **Parts 1, 2**), intramolecular *aza*-[3 + 3] annulations of vinylogous amides tethered with α,β-unsaturated aldehydes require less harsh conditions and in some cases proceed readily at temperatures as low as 25 °C. Therefore, we thought we might have more success with development of the enone version of intramolecular *aza*-[3 + 3] cycloaddition reaction (**317 → 318**, **Figure 3-1**).

Expanding scope of our intramolecular annulation methodology in such a way will open a new horizons in syntheses of various natural products. Such natural products as geissoschizine (**319**),[67] emetine (**320**) and its related alkaloids (**321-322**)[68] having the substituent at C4-position of piperidine ring (shown in red, **Figure 3-2**) should be readily accessible using enone version of intramolecular annulation.

**Figure 3-2.** Possible targets for enone version of *aza*-[3 + 3] annulation.

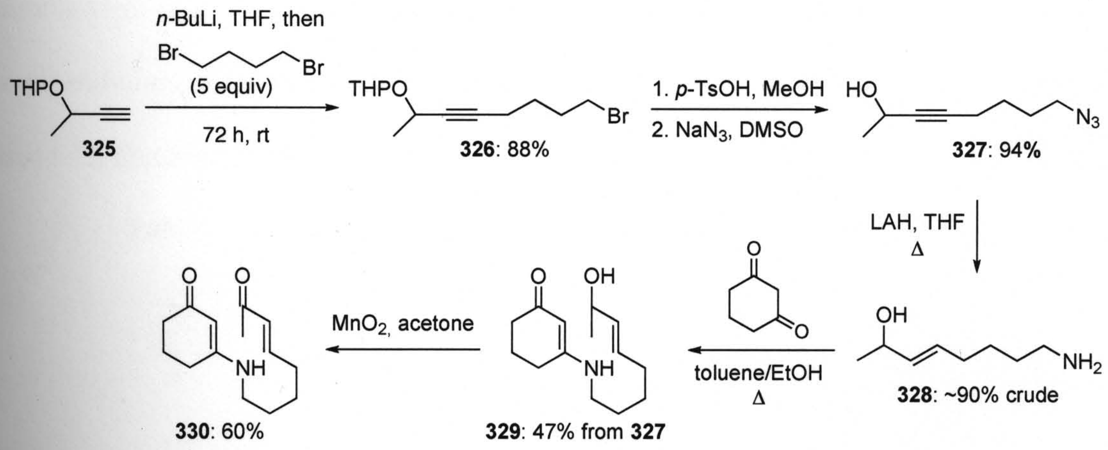


## 3.2. Results and discussion.

### 3.2.1. Synthetic Feasibility.

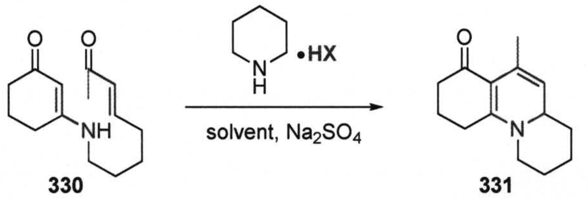
To test the feasibility of enone version of intramolecular *aza*-[3 + 3] annulation precursor **330** was synthesized in several steps starting with alkylation of THP-protected 1-butyne-3-ol **325**[69] with excess of dibromobutane to give bromide **326** in 88% yield. Cleavage of THP-protecting group under acidic conditions with subsequent treatment of intermediate bromoalcohol with $NaN_3$ afforded azide **327** in 94% overall yield. After LAH reduction of azidoalcohol **327** crude amino alcohol **328** was condensed with 1,3-cyclohexanedione to provide vinylogous amide **329** in 47% yield over two steps. Finally, annulation precursor **330** was prepared by $MnO_2$ oxidation of allyl alcohol **329**.

**Scheme 3-1.** Synthesis of enone **330**.



With enone **330** in hands we investigated the feasibility of intramolecular annulation using piperidinium acetate and trifluoacetate salts. When vinylogous amide **330** was heated with piperidinium acetate salt in EtOAc at 85 °C overnight no desired cycloadduct **331** was formed, only minor decomposition of starting material was observed [entry 1]. We were excited to find that annulation of the enone **333** could be successfully promoted simply by switching to more reactive piperidinium trifluoroacetate salt [entry 2]. Unfortunately, under these conditions reaction stopped at ~60% conversion and longer heating did not lead to any improvement in product/starting material ratio. The desired cycloadduct **331** was isolated in ~60% BORSM yield. Nonetheless, we were interested in why did this annulation reaction stop at certain point and never went to completion. We realized that one of the possible side reactions is amidation of the solvent (EtOAc) with piperidinium salt catalyst, to give corresponding *N*-acetylpiperidine. This will eventually lead to quenching of the amine salt catalyst therefore shutting down the annulation reaction. To test this proposal enone **330** was heated at 120 °C in toluene with 1 equiv of the piperidinium trifluoroacetate [entry 3]. Indeed, after 5 h complete consumption of starting material **330** was observed and desired annulation product **331** was isolated in 52% yield. It is noteworthy that annulation reaction could be carried out at lower temperature (85 °C) with comparable yield (50%) using toluene as the solvent [entry 4]. We also tried to lower the loading of the piperidinium trifluoroacetate salt catalyst to 50 mol% but in this case product **331** was obtained with much lower yield [entry 5].

**Table 3-1.** Enone version of intramolecular *aza*-[3 + 3] annulation.



**330** **331**

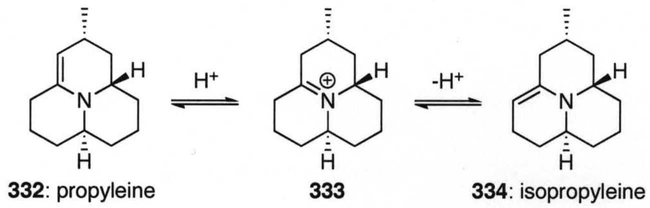
| entry | HX (mol %) | solvent | time (h) | temp | conversion | yield (%) |
|---|---|---|---|---|---|---|
| 1 | HOAc (100) | EtOAc | 12 | 85 | no rxn | N/A |
| 2 | $HO_2CCF_3$ (100) | EtOAc | 12 | 85 | 60 | ~60 |
| 3 | $HO_2CCF_3$ (100) | toluene | 5 | 120 | 100 | 52 |
| 4 | $HO_2CCF_3$ (100) | toluene | 5 | 85 | 100 | 50 |
| 5 | $HO_2CCF_3$ (50) | toluene | 7 | 100 | 100 | 23 |
| 6 | $HO_2CCF_3$ (100) | EtOAc/toluene | 1 | microwave | 100 | 54 |

It is well-known that microwave irradiation may have advantage over conventional heating for reactions that require harsh conditions.[70] There is also a recent report in the literature by Beifuss and co-workers on microwave-assisted intermolecular *oxa*-[3 + 3] annulations.[70b] They found that microwave assisted reactions generally require less time to go to completion and sometimes are higher yielding when compared to reactions performed with conventional heating. With this in mind, enone **330** was microwaved in EtOAc/toluene mixture in a sealed tube with 1 equiv of piperidinium trifluoroacetate salt [entry 6]. After one hour (4 × 15 min) complete consumption of the starting material was observed and the desired cycloadduct **331** was isolated in 54% yield. Indeed, there was a noticeable rate acceleration for the annulation reaction performed under microwave irradiation conditions comparing to reaction performed with conventional heating but isolated yields of the product **331** were comparable [entry 6 versus 3, 4].

### 3.2.2. Studies Toward Propyleine.

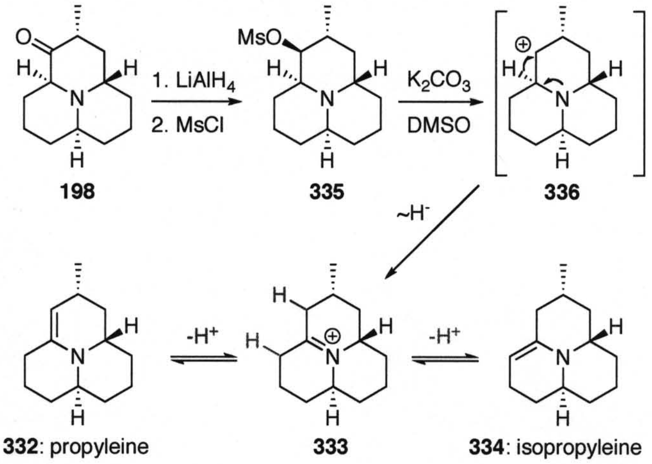
After establishing the feasibility of enone version of intramolecular *aza*-[3 + 3] annulation we turned our attention to propyleine alkaloid **(332)** as a possible synthetic target utilizing the developed methodology (**Figure 3-3**). Propyleine was isolated in 1972 from *Propylaea quatuordecimpunctata* as a continued efforts by Tursch and co-workers[71] in their isolation of azaphenalene family of defensive alkaloids from various ladybug beetles (See **Section 2.1.2**).[48] Mueller and Thompson in 1980 found it interesting that isomeric enamine named isopropyleine **(334)** was not reported in original paper[71] taking into the account isolation conditions (acid-base extraction). It is conceivable that propyleine **(332)** and isopropyleine **(334)** could be interconvertable under acidic conditions via intermediate iminium salt **333**.

**Figure 3-3.** Tentative propyleine-isopropeleine interconversion.



To investigate this matter Mueller and Thompson carried out the first and the only synthesis of propyleine known up to date (**Scheme 3-2**).[72] They started with reduction of methyl ketone **198** which was the key intermediate in their earlier synthesis of hippodamine **(164)**[49b] (see **Scheme 2-9**). Subsequent treatment of intermediate alcohol with MsCl afforded mesylate **335** as single diastereomer.

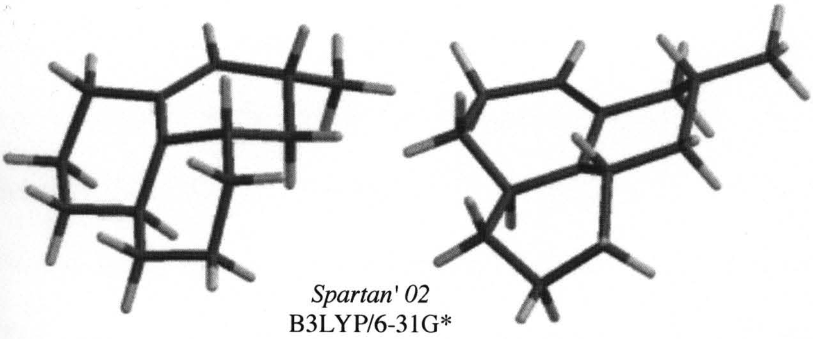
**Scheme 3-2.** Mueller synthesis of propyleine.



Mesylate **335** was ionized under conditions favoring E1 elimination to give intermediate cation **336** which upon 1,2-hydride shift presumably led to formation of iminium salt **333**. Finally, deprotonation of **333** afforded mixture of propyleine and isopropyleine with 1 : 3 ratio as determined by $^1$H NMR. After addition of TFA to this mixture two sets of signals in proton spectra collapsed into one set of resonances for the corresponding iminium salt **333**, therefore suggesting that propyleine **(332)** and isopropyleine **(334)** could equilibrate under acidic conditions. Based on observed ratio of **332** and **334** authors claimed that isopropyleine is thermodynamically more stable than propyleine.[72] With all this experimental findings Mueller and Thompson concluded that alkaloid isolated from *Propylaea quatuordecimpunctata* by Tursch and co-workers[71] was actually a mixture of **332** and **334** which are readily interconvertable.

We found that controversy in isolation and total synthesis papers is interesting and deserves further investigation. To begin with we performed *ab initio* calculations on regioisomeric enamines **332** and **334** to get better insight on their relative thermodynamic stability. Models of most stable conformers and their corresponding energies are shown in **Figure 3-4**. To our surprise, it turned out that propyleine is 2.59 kcal/mol more stable than isopropyleine which is opposite with what was postulated by Mueller.[72]

**Figure 3-4.** Relative thermodynamic stabilities of propyleine an isopropyleine.



**332**: propyleine
**E = -562.7870479 a.u.**

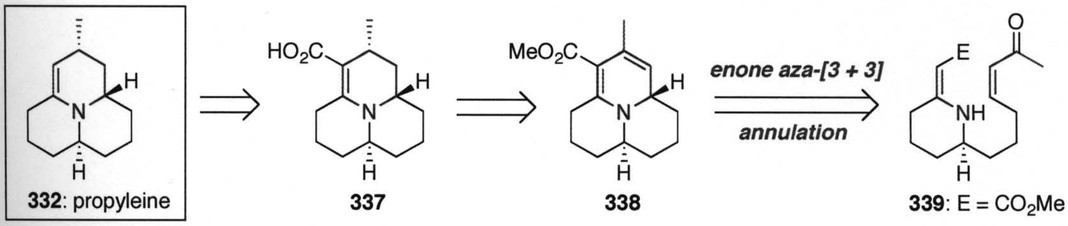
**334**: isopropyleine
E = -562.7829256 a.u.

**ΔE = 2.59 kcal/mol**

With our computational results it is apparent that ratio of enamines **332** and **334** obtained from elimination reaction in Mueller's synthesis of propyleine (**Scheme 3-2**) was determined by kinetics of the deprotonation of iminium salt **333**, not by thermodynamics as originally proposed. At this point we thought that additional studies on possible interconversion of propyleine (**332**) and isopropyleine **(334)** are necessary to resolve controversy existing in the literature. Toward this end, it would be desirable to synthesize these alkaloids as individual entities.

In our approach we envisioned propyleine **(332)** to come from decarboxylation reaction of vinylogous carbamic acid **337** which could be derived from stereoselective hydrogenation of endocyclic olefin in tricycle **338** (**Figure 3-5**). Vinylogous urethane **338** should be accessible via our intramolecular *aza*-[3 + 3] annulation of enone **339**.

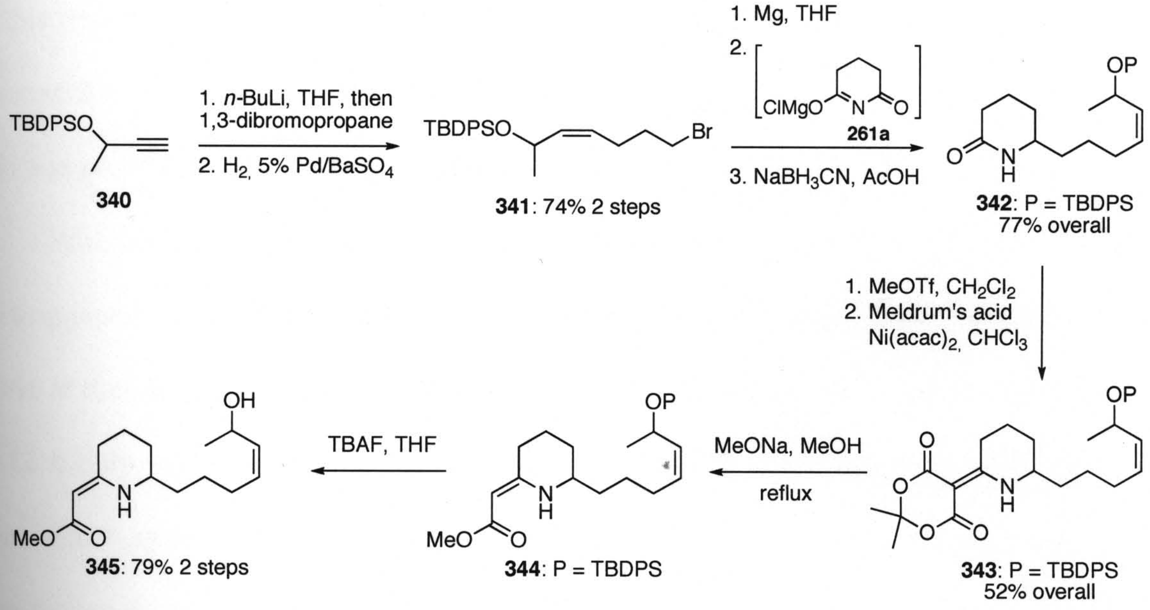
**Figure 3-5.** Retrosynthesis of propyleine.



**332**: propyleine  **337**  **338**  **339**: E = $CO_2Me$

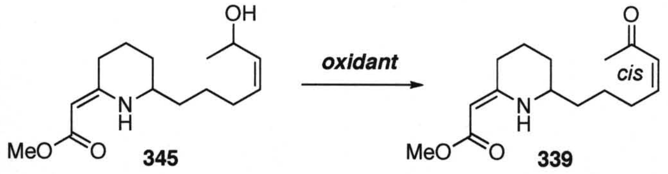
In forward direction to prepare annulation precursor **339** we used the approach developed in our model study for synthesis precoccinelline, hippodamine and myrrhine alkaloids (see **Section 2.2.3**). Thus, TBDPS-protected 1-butyne-3-ol **340** was converted to bromoalkene **341** in 2 steps involving alkylation with excess of dibromopropane and subsequent Lindlar's hydrogenation (**Scheme 3-3**). Reductive alkylation[54] of glutarimide salt **261a** with Grignard reagent prepared from bromide **341** afforded lactam **342** as inseparable 1 : 1 mixture of 2 diastereomers in 77% overall yield. Piperidine **343** was prepared by *O*-methylation of lactam **342** with freshly distilled MeOTf followed by condensation with Meldrum's acid in presence of $Ni(acac)_2$ catalyst. Treatment of compound **343** with MeONa in MeOH under refluxing conditions gave vinylogous urethane **344**. Cleavage of TBDPS-protecting group of the secondary hydroxyl with TBAF provided allyl alcohol **345** in 79% from **343**.

**Scheme 3-3.** Synthesis of allyl alcohol **345**.



To our surprise, submission of allyl alcohol **345** to standard $MnO_2$ oxidation procedure did not lead to formation of desired enone **339** and only starting material was recovered (**Table 3-2**).

**Table 3-2.** Synthesis of annulation precursor **339**.

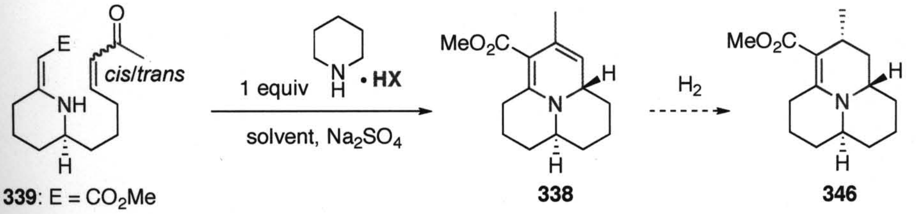


| entry | ***oxidants*** | solvent | yield [%] |
|---|---|---|---|
| 1 | $MnO_2$ | $CH_2Cl_2$ | no rxn (rt) |
| 2 | $MnO_2$ | $CH_2Cl_2$ | decomp (40 °C) |
| 3 | $BaMnO_4$ | $CH_2Cl_2$ | no rxn |
| 4 | DMP | $CH_2Cl_2$ | slow decomp |
| 5 | PCC | $CH_2Cl_2$ | decomp |
| 6 | TEMPO/oxone | toluene | no rxn |
| 7 | TPAP/NMO | $CH_2Cl_2$ | decomp |
| 8 | Pyr-$SO_3$/DMSO | $CH_2Cl_2$ | 72% |

After extensive screening of various oxidation protocols we were successful in carrying out this transformation only under Doering-Parikh conditions.[58] Allyl alcohol **345** was oxidized to enone **339** using $SO_3$pyr/DMSO with good 72% yield. In addition geometry of *cis*-double bond was preserved under these conditions.

With enone **339** in hands we studied its intramolecular *aza*-[3 + 3] annulation reaction utilizing piperidinium salts (**Table 3-3**). When compound **339** was treated with acetate salt in EtOAc at rt no reaction was observed after 18 h [entry 1]. Heating this reaction mixture at 85 °C for 12 h only led to slow isomerization of *cis*-enone **339** to thermodynamically more stable *trans*-isomer again with no formation of desired cycloadduct **338** [entry 2]. Inefficiency of piperidinium acetate salt in intramolecular *aza*-[3 + 3] annulation of enones was consistent with our previous findings (see **Table 3-1**).

**Table 3-3.** Intramolecular *aza*-[3 + 3] annulation.



| entry | HX | solvent | temp [°C] | time [h] | yield [%] |
|---|---|---|---|---|---|
| 1 | HOAc | EtOAc | 25 | 18 | no rxn |
| 2 | HOAc | EtOAc | 85 | 12 | *trans*-**339** |
| 3 | $HO_2CCF_3$ | EtOAc | 55 | 12 | *trans*-**339** |
| 4 | $HO_2CCF_3$ | EtOAc | 130 | 12 | *trans*-**339**/decomp |
| 5 | $HO_2CCF_3$ | toluene | 100 | 5 | ~20 (NMR) |

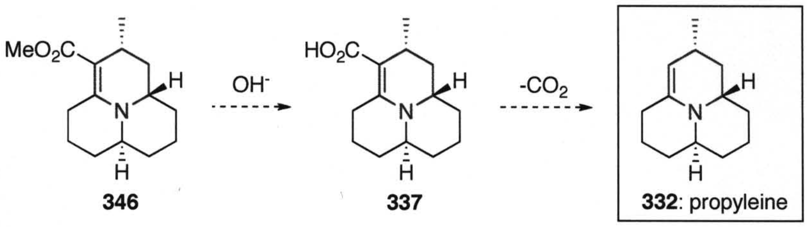
We were also not successful in converting enone **339** to desired tricycle **338** by switching to more reactive trifluoroacetate salt. In this case also only isomerization to *trans*-enone was detected [entry 3]. Heating this reaction to 130 °C led to eventual decomposition of starting material [entry 4]. Interestingly, when enone was heated with trifluoroacetate salt at 100 °C in toluene complete consumption of starting material was observed after 5 h [entry 5]. Even though reaction was relatively messy formation of desired cycloadduct **338** was confirmed by presence of characteristic signals in $^1$H NMR spectra of the crude mixture. Unfortunately, attempts to isolate annulation product in pure form were not successful probably due to high instability of electron-rich dihydropyridine moiety in **338**. Based on our previous experience with precarious annulation products it is possible that *in situ* hydrogenation of endocyclic olefin in **338** might help to overcome product instability problem.

It is clear that additional studies are desirable to find conditions suitable for synthesis of tricycles **338** or **346** with acceptable yield. But our preliminary results are encouraging and show proof of principle for possible application of enone version of intramolecular *aza*-[3 + 3] annulation reaction to synthesis of natural products such as propyleine (**332**).

## 3.3. Future Work.

After finding optimal conditions for the key transformation (see **339** → **346**, **Table 3-3**) in our propyleine synthesis we will be only two steps away from the natural product. Saponification of the ester **346** with subsequent decarboxylation of vinylogous urethane **337** should lead to the desired alkaloid (**Figure 3-6**).

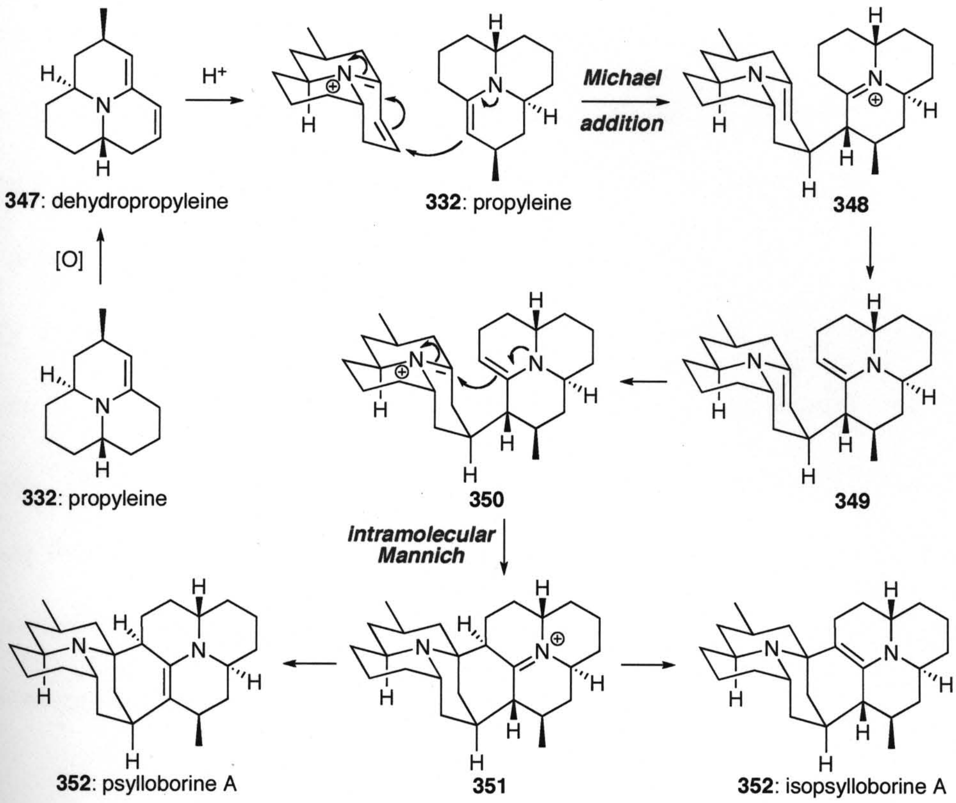
**Figure 3-6.** Proposed propyleine end-game.



Recently Schröder and Lebrun reported isolation of interesting dimeric azaphenalene alkaloids named psylloborine A[73a] and isopsylloborine A[73b] from ladybird beetles. We believe that biomimetically they might derive from monomeric dehydroazaphenalenes such as propyleine (**332**) via acid-catalyzed Michael addition/intramolecular Mannich cascade (**Figure 3-7**).

Presumably, propyleine is first oxidized (**332**) to dehydropropyleine **347** under biological conditions. Subsequent protonation of enamine **347** will lead to α,β-unsaturated iminium salt **348** which can react with second molecule of propyleine to give dimer **349**. After isomerization of **348** to **351** via dienamine **349** intramolecular Mannich condensation will furnish the formation of six-member ring to give heptacycle **351**. Finally, deprotonation of iminium salt **351** could lead to both regioisometric enamines psylloborine (**352**) and isopsylloborine (**353**).

**Figure 3-7.** Proposed biomimetic synthesis of psylloborine A and isopsylloborine A.



Accomplishing synthesis of propyleine via our key intramolecular aza-[3 + 3] annulation will allow us to test this proposed biomimetic transformation to form dimeric azaphenalene alkaloids.

## 3.3. Conclusion.

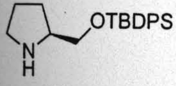
Enone version of intramolecular *aza*-[3 + 3] annulation reaction has been developed. Use of piperidinium trifluoroacetate salt and toluene as a solvent were shown to be critical for successful transformation. We also demonstrated for the first time that microwave irradiation can accelerate *aza*-[3 + 3] annulation reactions. Expanding the scope of our cycloaddition methodology in such a way has allowed us to envision the access to propyleine alkaloid with a title reaction in a key step. Synthesis of enone annulation precursor was successfully accomplished, and its cycloaddition revealed encouraging preliminary results. Future investigations should culminate in finishing the synthesis of propyleine alkaloid, which could be further converted to interesting dimeric alkaloids such as psylloborine and isopsylloborine via proposed biomimetic pathway.

# Experimental Procedures

# PART 1.

## PREPARATION OF CHIRAL AMINE SALTS.

### Amine 44d.

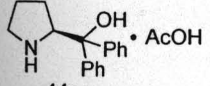


**44d**

To a solution of (*S*)-prolinol (553.0 mg, 5.47 mmol) in $CH_2Cl_2$ (18 mL) were imidazole (445.0 mg, 6.54 mmol), DMAP (20.0 mg), and TBDPSCl (1.70 mL, 6.54 mmol) dropwise at 0 °C. The reaction mixture was allowed to warm up to rt and stirred overnight before $CH_2Cl_2$ (15 mL) and water (20 mL) were added. The aqueous layer was extracted with $CH_2Cl_2$ (3 × 30 mL), the combined organic fractions were washed with sat aq NaCl (30 mL) and dried over $Na_2SO_4$. Removal of the solvent under reduced pressure provided amine **44d** (1.662 g, 89%) as colorless oil, which solidified upon addition of hexane (5 mL).

**44d:** $R_f = 0.32$ [$CH_2Cl_2 : CH_3OH = 7 : 1$]; mp = 145–150 °C; $[\alpha]_D^{20} = -4.4$ ° [c = 1, $CHCl_3$]; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.09 (s, 9 H), 1.65 – 1.87 (m, 1 H), 1.90 – 2.08 (m, 3 H), 3.49 (dd, 2 H, *J* = 7.5, 6.3 Hz), 3.71 – 3.79 (m, 1 H), 3.84 (dd, 1H, *J* = 11.1, 5.2 Hz), 3.94 (dd, 1 H, *J* = 11.1, 4.8 Hz), 7.37 – 7.43 (m, 6 H), 7.67 – 7.73 (m, 4 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 19.4, 23.9, 27.1, 45.8, 60.2, 63.0, 128.1, 130.1, 130.2, 132.5, 132.7, 135.8, 135.9 (two carbons missing due to overlap); IR (film) cm$^{-1}$ 3071m, 3048m, 2954-2857s, 2741m, 2482m, 1589m, 1428m, 1113s; mass spectrum [EI] *m/e* (% relative intensity) 339 (1) $M^+$, 324 (1), 282 (70), 204 (14), 181 (11), 70 (100); *m/e* calcd for $C_{21}H_{30}NOSi$ 340.2097 ($M^+ + H$), found 340.2093.

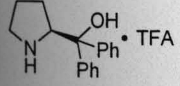
### Acetate 44e.


**44e**

To a solution of (*S*)-α,α-diphenyl-2-pyrrolidinemethanol (726.0 mg, 2.87 mmol) in MeOH (10 mL) was added glacial AcOH (0.80 mL, 14.00 mmol). The reaction mixture was kept at rt for 15 min before MeOH was evaporated under reduced pressure. To the glass-looking solid residue was added $Et_2O$ (10 mL) and the mixture was stirred until formation of white flakes was complete. The precipitate was filtered and the filter cake was washed with $Et_2O$ (2 x 5 mL) to give **44e** (0.813 g, 90%) as white solid.

**44e:** mp = 182–185 °C; $[\alpha]_D^{20}$ = +37.2 ° [c = 1, $CH_3OH$]; $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.49 – 1.55 (m, 1 H), 1.68 – 1.77 (m, 1 H), 1.83 – 1.86 (m, 1 H), 1.88 (s, 3 H), 1.90 – 2.01 (m, 1 H), 2.83 (ddd, 1 H, *J* = 16.5, 9.5, 6.2 Hz), 3.02 (ddd, 1 H, *J* = 10.5, 7.0, 4.5 Hz), 7.05 (brs, 2 H, NH), 7.15 (t, 1 H, *J* = 7.5 Hz), 7.19 – 7.28 (m, 5 H), 7.41 (d, 2 H, *J* = 7.5 Hz), 7.54 (d, 2 H, *J* = 7.5 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 23.9, 25.9, 26.9, 46.8, 64.9, 77.7, 125.5, 126.3, 126.9, 127.4, 128.3, 128.8, 144.9, 145.6, 178.5; IR (film) $cm^{-1}$ 3365brs, 3058w, 2978s, 1576s, 1418m.

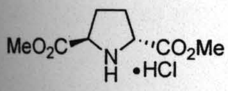
### Trifluoroacetate 44f.


**44f**

Trifluoroacetate **44f** (272.0 mg, 94%) was prepared using the similar procedure as described above for **44e** starting from (*S*)-α,α-diphenyl-2-pyrrolidinemethanol (0.20 g, 0.79 mmol) and trifluoroacetic acid (0.20 mL, 2.60 mmol).

**44f:** mp = 221–225 °C (decomp); $[\alpha]_D^{20}$ = –119.0 ° [c = 1, $CDCl_3$]; $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.54 – 1.60 (m, 1 H), 1.70 – 1.80 (m, 1 H), 1.86 – 1.91 (m, 1 H), 1.96 – 2.04 (m, 1 H), 2.69 (dd, 1 H, *J* = 16.5, 9.5 Hz), 2.81 – 2.84 (m, 1 H), 4.64 (dd, 1 H, *J* = 8.0, 7.5 Hz), 5.15 (brs, 1 H, OH), 7.09 – 7.14 (m, 2 H), 7.18 – 7.21 (m, 4 H), 7.34 (d, 2 H, *J* = 7.5 Hz), 7.44 (d, 2 H, *J* = 7.5 Hz), 8.31 (brs, 1 H, NH), 9.92 (brs, 1 H, NH); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 25.0, 26.6, 47.1, 65.9, 77.5, 125.3, 125.8, 127.4, 127.8, 128.6, 129.0, 143.8, 144.1; $^{19}F$ NMR ($CDCl_3$) δ -76.1; IR (film) $cm^{-1}$ 3389m, 3220m, 2997s, 2790m, 2577m, 1683s, 1655s, 1637m.

**Hydrochloride 45b.**

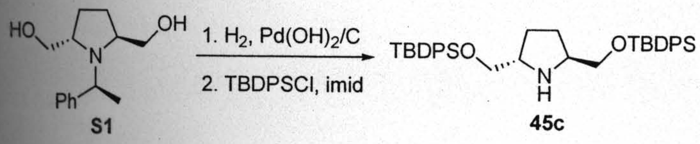


**45b**

Dry HCl was bubbled through a solution of (2*R*,5*R*)-dimethyl-pyrrolidine-2,5-dicarboxylate[16b] (83.7 mg, 0.45 mmol) in $Et_2O$ (7 mL). The precipitate **45b** (72.4 mg, 72%) was collected by filtration.

**45b:** mp = 160–162 °C; $[\alpha]_D^{20}$ = +33.0 ° [c = 0.6, $CD_3OD$]; $^1H$ NMR (300 MHz, $CD_3OD$) δ 2.15 – 2.30 (m, 2 H), 2.44 (m, 2 H), 3.87 (s, 6 H), 4.53 – 4.59 (m, 2 H); $^{13}C$ NMR (75 MHz,$CDCl_3$) δ 28.9, 54.2, 61.2, 170.2; IR (film) $cm^{-1}$ 2944w, 2882m, 1746s, 1260m.

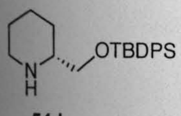
**Amine 45c.**



A solution of diol **S1**[16b] (183.0 mg, 0.78 mmol) in MeOH (6 mL) was subjected to hydrogenation conditions in a Paar apparatus at 40–50 *psi* $H_2$ over 20% $Pd(OH)_2/C$ (0.12 g) for 3 h. The reaction mixture was filtered through Celite and the filter cake was washed with MeOH (5 mL). After evaporation of the solvent under reduced pressure, the crude residue was dissolved in $CH_2Cl_2$ (7 mL), and to this solution were successively added imidazole (0.14 g, 2.06 mmol), DMAP (20.0 mg), and TBDPSCl (0.53 mL, 2.04 mmol). The reaction mixture was stirred overnight before $CH_2Cl_2$ (15 mL) and water (20 mL) were added. The organic layer was separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic fractions were washed with sat aq NaCl (30 mL) and dried over $Na_2SO_4$. Evaporation of the solvent under reduced pressure gave amine **45c** (430.0 mg, 91% overall) as colorless oil.

**45c:** $R_f = 0.57$ [$CH_2Cl_2 : CH_3OH = 11 : 1$], $R_f = 0.61$ [EtOAc : hexanes = 1 : 1]; $[\alpha]_D^{20} = -1.5°$ [c = 2.12, $CHCl_3$], (lit.[34] $[\alpha]_D^{20} = +1.5$ ° for (2*R*,5*R*)-isomer); $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.08 (s, 18 H), 1.41 – 1.48 (m, 2 H), 1.78 – 1.86 (m, 2 H), 3.38 (quint, 2 H, $J = 6.0$ Hz), 3.56 (d, 4 H, $J = 6.0$ Hz), 7.37 – 7.45 (m, 8 H), 7.68 – 7.71 (m, 12 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 19.5, 27.1, 27.4, 58.9, 67.5, 127.9, 129.8, 133.9, 134.0, 135.8, 135.9 (two carbons missing due to overlap); IR (film) $cm^{-1}$ 3070m, 3049m, 2958-2857s, 1589w, 1428m, 1112s; *m*/*e* calcd for $C_{38}H_{50}NO_2Si_2$ 608.3380 ($M^+ + H$), found 608.3392.

**Amine 54d.**



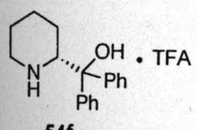
**54d**

To a suspension of LAH (0.32 g, 8.42 mmol) in THF (15 mL) was added in portions the powdered (*R*)-methylpipecolate hydrochloride[19a,b] **(54c)** (0.50 g, 2.78 mmol) at 0 °C. The reaction mixture was heated to reflux for 3 h. After which, the excess LAH was quenched upon cooling to rt via addition of sat aq $Na_2SO_4$ (*ca.* 3 mL). The resulting white precipitate was filtered and washed with *t*-butyl methyl ether [MTBE] (2 × 20 mL). The filtrate was dried over $Na_2SO_4$ and concentrated under reduced pressure to yield (2*R*)-piperidinylmethanol (235.0 mg, 75%) as colorless oil.

To a solution of the amino alcohol obtained above in $CH_2Cl_2$ (7 mL) were added successively imidazole (0.152 g, 2.23 mmol), DMAP (20.0 mg), and TBDPSCl (0.58 mL, 2.23 mmol). The reaction mixture was stirred overnight before $CH_2Cl_2$ (10 mL) and water (15 mL) were added. The organic layer was separated and the aqueous phase was extracted with $CH_2Cl_2$ (3 × 20 mL). The combined organic fractions were washed with sat aq NaCl (25 mL) and dried over $Na_2SO_4$. Evaporation of the solvent under reduced pressure afforded amine **54d** (0.46 g, 64%) as a colorless oil.

**54d:** $R_f = 0.28$ [$CH_2Cl_2$ : $CH_3OH$ = 7 : 1]; $[\alpha]_D^{20} = -7.6$ ° [c = 1, $CDCl_3$]; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.84 – 1.13 (m, 1 H), 1.06 (s, 9 H), 1.24 – 1.39 (m, 1 H), 1.42 (dd, 1 H, *J* = 7.8, 4.0 Hz), 1.49 (dd, 1 H, *J* = 7.8, 4.0 Hz), 1.57 – 1.63 (m, 1 H), 1.73 – 1.78 (m, 1 H), 2.31 (brs, 1 H, NH), 2.63 (dd, 1 H, *J* = 11.7, 2.7 Hz), 2.66 – 2.73 (m, 1 H), 3.10 (ddd, 1 H, *J* = 13.5, 3.8, 2.7 Hz), 3.51 (dd, 1 H, *J* = 9.8, 8.0 Hz), 3.57 (dd, 1 H, *J* = 9.8, 4.1 Hz), 7.34 – 7.42 (m, 6 H), 7.64 – 7.69 (m, 4 H); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 19.4, 24.5, 26.6, 27.0, 28.6, 46.8, 58.4, 68.6, 127.6, 127.7, 129.6, 133.5, 133.7, 135.5, 135.6 (one carbon missing due to overlap); IR (film) $cm^{-1}$ 3069m, 3048m, 2930s, 2856s, 2799m, 1428m, 1112s; mass spectrum [EI] *m/e* (% relative intensity) 353 (1) $M^+$, 338 (1), 218(10), 199 (8), 181 (8), 84 (100); *m/e* calcd for $C_{22}H_{32}NOSi$ 354.2253 ($M^+$ + H), found 354.2249.

**Trifluoroacetate 54f.**

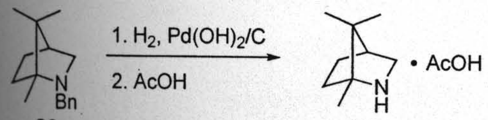


**54f**

Trifluoroacetate **54f** (0.202 g, 62%) was prepared using the similar procedure as described above for **44e** starting from (*R*)-pipradrol[19] (230.0 mg, 0.86 mmol) and trifluoroacetic acid (0.15 mL, 1.95 mmol).

**44f:** mp = 195–198 °C (decomp); $[\alpha]_D^{20}$ = +38.7 ° [c = 1.05, $CHCl_3$]; $^1H$ NMR (300 MHz, $CDCl_3$) δ 1.40 – 1.48 (m, 1 H), 1.61 (d, 1 H, *J* = 13.5 Hz), 1.66 (d, 1 H, *J* = 13.5 Hz), 1.77 (d, 1 H, *J* = 13.5 Hz), 1.82 – 1.91 (m, 2 H), 2.81 (dd, 1 H, *J* = 12.5, 12.0 Hz), 2.97 (d, 1 H, *J* = 12.0 Hz), 3.78 (brs, 1 H, OH), 3.98 (d, 1 H, *J* =11.0 Hz), 7.19 (d, 1 H, *J* = 8.0 Hz), 7.22 (d, 1 H, *J* = 8.0 Hz), 7.26 – 7.33 (m, 4 H), 7.43 (d, 2 H, *J* = 8.0 Hz), 7.53 (d, 2 H, *J* = 8.0 Hz), 7.84 (brs, 1 H, NH) 8.73 (brs, 1 H, NH); $^{13}C$ NMR (75 MHz, $CDCl_3$) δ 22.5, 22.7, 23.9, 46.3, 63.5, 78.3, 125.5, 125.8, 127.5, 128.2, 128.7, 129.2, 142.7, 142.8; $^{19}F$ NMR ($CDCl_3$) δ -75.9; IR (film) $cm^{-1}$ 3324brs, 3062m, 3027m, 2949s, 2870m, 1671s, 1201s.

**Acetate 113.**



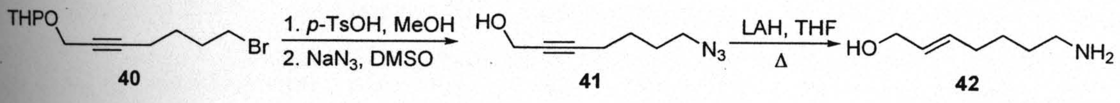
**S2** **113**

A solution of amine **S2**[74] (322.0 mg, 1.40 mmol) in EtOAc (10 mL) was subjected to hydrogenation conditions in a Paar-shaker apparatus at 50–60 *psi* $H_2$ over 20% $Pd(OH)_2/C$ (0.12 g) for 6 h. The reaction mixture was filtered through Celite and washed with MeOH (5 mL). Solution was concentrated very carefully under reduced pressure at rt (product is volatile) and the residue was dissolved in $Et_2O$ (5 mL). To this solution was added glacial AcOH (0.20 mL, 3.49 mmol) and the mixture was placed to the freezer for 48 h. The resulting precipitate was filtered and washed with $Et_2O$ (2 × 3 mL) to give **58** (0.162 g, 58%) as colorless needles.

**113:** mp = 73–74 °C; $[\alpha]_D^{20} = -13.8$ ° [c = 1, $CDCl_3$]; $^1$H NMR (300 MHz, $CDCl_3$) δ 0.92 (s, 3 H), 1.03 (s, 3 H), 1.24 (s, 3 H), 1.46 (ddd, 1 H, $J$ = 13.0, 9.0, 4.0 Hz), 1.65 (ddd, 1 H, $J$ = 13.8, 9.0, 4.0 Hz), 1.77 – 1.88 (m, 1 H), 1.93 (s, 3 H), 1.94 – 2.07 (m, 2 H), 2.90 (d, 1 H, $J$ = 10.8 Hz), 3.24 (dt, 1 H, $J$ = 11.1, 3.6 Hz), 9.98 (brs, 2 H, NH); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 13.1, 17.9, 19.1, 23.2, 26.3, 32.4, 44.6, 47.9, 48.7, 69.6, 177.5; IR (film) cm$^{-1}$ 2965m, 1715m, 1567s, 1399s, 1261m.

## PREPARATION OF THE ANNULATION PRECURSORS.

### Amino alcohol 42.



To a solution of bromide **40**[16a] (6.83 g, 24.8 mmol) in MeOH (70 mL) was added *p*-TsOH (0.25 g, 1.3 mmol). After stirring at rt for 2 h, the starting material disappeared as observed using TLC analysis [10% EtOAc in petroleum ether]. The acid was neutralized by addition of solid $NaHCO_3$ (0.40 g), and the excess solid was filtered off and MeOH was evaporated under reduced pressure.

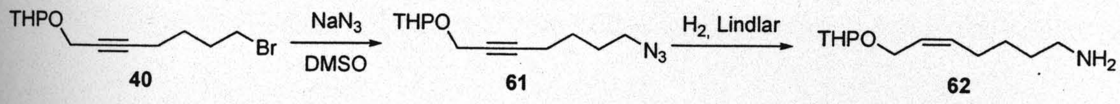
To a solution of the above crude residue in DMSO (60 mL) was added $NaN_3$ (2.02 g, 31.1 mmol). The reaction mixture was stirred for 2 h at rt before water (200 mL) was added. The aqueous layer was extracted with MTBE (4 × 80 mL), and the combined organic fractions were washed with sat aq NaCl (70 mL) and dried over $MgSO_4$. Removal of the solvent under reduced pressure provided azide **41** (3.75 g, 98%) as colorless oil, which was used for the next step without further purification. Product could be purified by filtration through short silica gel column with MTBE as isocratic eluent.

**41:** $R_f = 0.60$ [MTBE]; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.53 – 1.64 (m, 2 H), 1.65 – 1.76 (m, 2 H), 2.03 (brs, 1 H, OH), 2.27 (tt, 2 H, $J = 6.6, 2.1$ Hz), 3.30 (t, 2 H, $J = 6.6$ Hz), 4.23 (t, 2 H, $J = 6.0, 2.1$ Hz); mass spectrum [EI] *m/e* (% relative intensity) 153 (67) $M^+$, 125 (88), 108 (29), 96 (55), 84 (100).

To a suspension of LAH (3.11 g, 81.9 mmol) in THF (150 mL) was added slowly dropwise a solution of **41** (2.51 g, 16.4 mmol) in THF (50 mL) while keeping the temperature below 30 °C. When the reaction slowed down, the mixture was heated to reflux for 24 h. The excess LAH was quenched by addition of sat aq $Na_2SO_4$ (ca. 5 mL). The resulting white precipitate was filtered off and the filter cake was washed with MTBE (2 × 30 mL). The filtrate was dried over $Na_2SO_4$ and concentrated under reduced pressure to yield amino alcohol **42** (1.57 g, 75%) as pale yellow oil.

**42:** $^1$H NMR (300 MHz, $CDCl_3$) δ 1.36 – 1.56 (m, 4H), 1.81 (brs, 3H, $NH_2$ + OH), 2.08 (dd, 2 H, $J = 3.9, 6.9$ Hz), 2.70 (t, 2 H, $J = 6.9$ Hz), 4.07 (d, 2 H, $J = 2.7$ Hz), 5.57 – 5.63 (m, 2 H); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 26.5, 32.1, 33.2, 42.1, 63.7, 129.7, 132.9; IR (film) $cm^{-1}$ 3333brs, 2931s, 2859s, 1573m, 1488s, 1323m; mass spectrum [EI] *m/e* (% relative intensity) 128 (1) $M^+ - 1$, 112 (44), 94 (19), 86 (23), 79 (49), 56 (100); *m/e* calcd for $C_7H_{16}NO$ ($M^+$ + H) 130.1232, found 130.1236.

**Amine 62.**



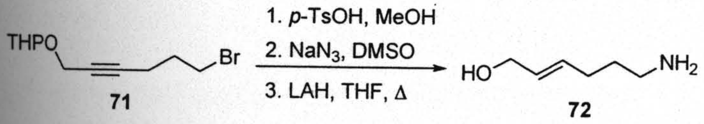
To a solution of bromide **40**[16a] (5.00 g, 18.2 mmol) in DMSO (35 mL) was added NaN$_3$ (1.75 g, 26.9 mmol). The reaction mixture was stirred for 2 h at rt before water (70 mL) was added. The aqueous layer was extracted with MTBE (4 × 50 mL), and the combined organic fractions were washed with sat aq NaCl (40 mL) and dried over Na$_2$SO$_4$. Removal of the solvent under reduced pressure provided azide **61** (4.10 g, 95%) as colorless oil, which was used for the next step without further purification.

**61:** $R_f = 0.59$ [EtOAc : hexanes = 1 : 9]; $^1$H NMR (500 MHz, CDCl$_3$) δ 1.51 – 1.56 (m, 2 H), 1.59 – 1.66 (m, 4 H), 1.67 – 1.74 (m, 3 H), 1.81 – 1.87 (m, 1 H), 2.28 (tt, 2 H, $J$ = 7.0, 2.5 Hz), 3.30 (t, 2 H, $J$ = 7.0 Hz), 3.53 (dtd, 1 H, $J$ = 10.0, 4.5, 2.0 Hz), 3.84 (ddd, 1 H, $J$ = 11.0, 9.0, 3.5 Hz), 4.19 (dt, 1 H, $J$ = 13.0, 2.0 Hz), 4.29 (dt, 1 H, $J$ = 13.0, 2.0 Hz), 4.80 (t, 1 H, $J$ = 3.5 Hz); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 19.5, 20.2, 22.7, 25.6, 29.9, 30.6, 46.4, 60.2, 62.3, 98.2, 115.5, 132.6; IR (film) cm$^{-1}$ 2926s, 2854m, 2096m, 1719m, 1702m, 1024s; mass spectrum (APCI): *m/e* (% relative intensity) 238 (5) M$^+$ + 1, 154 (100), 138 (5), 128 (5), 108 (30); *m/e* calcd for $C_{12}H_{20}N_3O_2$ (M$^+$ + H) 238.1570, found 238.1556.

A solution of azide **61** (4.10 g, 17.3 mmol) in MeOH (100 mL) was subjected to hydrogenation conditions at 1 atm H$_2$ over Lindlar's catalyst (1.10 g). The reaction was monitored using TLC analysis [20% EtOAc in hexanes], and a complete conversion of starting material was observed in 6 h. The Pd catalyst was filtered off through Celite and removal of solvent under reduced pressure gave the desired amine **62** (3.57 g, 97%) as pale yellow oil, which was used for the next step without further purification.

**62:** $R_f$ = 0.19 [$CH_2Cl_2$ : $CH_3OH$ = 7 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.38 – 1.49 (m, 4 H), 1.52 – 1.56 (m, 2 H), 1.58 – 1.62 (m, 2 H), 1.70 – 1.75 (m, 1 H), 1.80 – 1.86 (m, 1 H), 2.10 (q, 2 H, *J* = 7.0 Hz), 2.69 (t, 2 H, *J* = 7.0 Hz), 3.51 (dd, 1 H, *J* = 11.0, 4.5 Hz), 3.89 (ddd, 1 H, *J* = 11.5, 8.0, 3.0 Hz), 4.08 (dd, 1 H, *J* = 12.0, 6.0 Hz), 4.25 (dd, 1 H, *J* = 12.0, 5.0 Hz), 4.64 (dd, 1 H, *J* = 4.0, 3.5 Hz), 5.58 (ddd, 2 H, *J* = 14.5, 9.5, 5.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.6, 25.6, 26.2, 27.4, 30.7, 33.5, 42.2, 62.3, 62.8, 98.0, 126.2, 133.5; IR (film) cm$^{-1}$ 3234brs, 3017m, 2943s, 2867s, 2097s, 1665m; mass spectrum (APCI): *m/e* (% relative intensity) 212 (35) $M^+$ - 1, 154 (60), 138 (5), 128 (100), 110(42); *m/e* calcd for $C_{12}H_{24}NO_2$ ($M^+$ + H) 214.1807, found 214.1791.

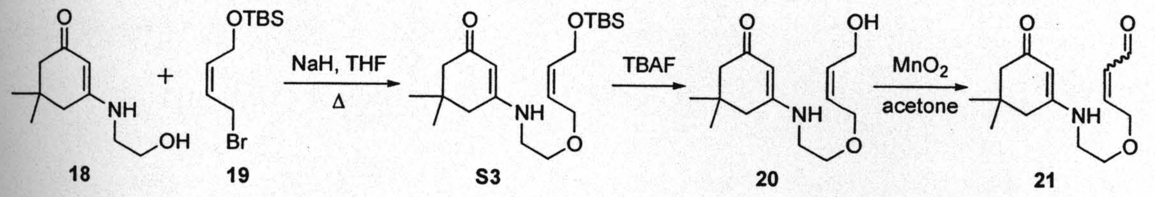
**Amino alcohol 72.**



Amino alcohol **72** (2.45 g, 67% overall) was synthesized using the similar procedure as described above for **42** starting from the corresponding THP-protected bromide **71**[75] (8.26 g, 31.6 mmol).

**72:** $^1$H NMR (500 MHz, $CDCl_3$) δ 1.54 (quint, 2 H, *J* = 7.5 Hz), 1.82 (brs, 3 H, $NH_2$+OH), 2.09 (q, 2 H, *J* = 8.0 Hz), 2.70 (t, 2 H, *J* = 7.5 Hz), 4.07 (d, 2 H, *J* = 4.5 Hz), 5.62 – 5.71 (m, 2 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 29.8, 32.2, 41.8, 63.6, 129.8, 132.3; IR (film) cm$^{-1}$ 3333brs, 2932s, 2859s, 1572m, 1486s, 1322m; mass spectrum [EI] *m/e* (% relative intensity) 114 (2) $M^+$ – 1, 98 (100), 84 (21), 70 (19), 67 (37), 56 (66); *m/e* calcd for $C_6H_{14}NO$ ($M^+$ + H) 116.1075, found 116.1070.

**Aldehyde 21.**



NaH (60%, 0.42 g, 10.5 mmol) was washed with pentane and suspended in THF (25 mL). To this suspension was added 3-(2-Hydroxyethylamino)-5,5-dimethylcyclohex-2-enone **18** (1.40 g, 7.64 mmol) in one portion and the mixture was stirred at rt for 1 h. After which, a solution of bromide **19**[76] (2.20 g, 8.28 mmol) in THF (20 mL) was added to the reaction and the mixture was heated to reflux for 12 h. The precipitate was filtered and washed thoroughly with EtOAc (2 × 25 mL). The solvents were removed under reduced pressure and the residue was purified via silica gel flash column chromatography [gradient eluent: EtOAc to EtOAc/MeOH (7 : 1)] to give TBS-protected alcohol **S3** (1.00 g, 42%) as a colorless oil.

**S3:** $R_f = 0.44$ [acetone : EtOAc = 3 : 1]; $^1$H NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 6 H), 0.91 (s, 9 H), 1.07 (s, 6 H), 2.19 (s, 4 H), 3.25 (q, 2 H, $J = 5.2$ Hz), 3.61 (t, 2 H, $J = 5.2$ Hz) 4.09 (dd, 2 H, $J = 6.4, 1.0$ Hz), 4.24 (dd, 2 H, $J = 5.8, 1.0$ Hz), 4.72 (brs, 1 H, NH), 5.10 (s, 1 H), 5.57 (dtt, 1 H, $J = 11.4, 6.4, 1.0$ Hz), 5.73 (dtt, 1 H, $J = 11.4, 5.8, 1.0$ Hz); $^{13}$C NMR (50 MHz, $CDCl_3$) δ -5.2, 18.3, 25.9, 28.3, 32.8, 42.4, 43.5, 50.3, 59.5, 66.8, 67.3, 95.8, 126.3, 133.1, 162.5, 196.9; IR (film) cm$^{-1}$ 3258brs, 2955m, 1548s, 1253s, 1151s; mass spectrum [EI] *m/e* (% relative intensity) 367 (2) M$^+$, 352 (2), 310 (100), 240 (19), 184 (44), 127 (49).

To a stirred solution of the above TBS-protected alcohol **S3** (1.00 g, 2.72 mmol) in THF (12 mL), was added TBAF (1.0 *M* in THF, 3.00 mL, 3.00 mmol). The reaction mixture was stirred at rt for 1 h and then the solvent was evaporated. The residue was filtered through a short silica gel column with acetone/EtOAc (3 : 1) as isocratic eluent to afford alcohol **20** (0.63 g, 92%) as a pale yellow oil.

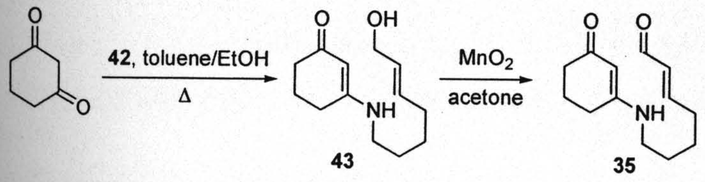
**20:** $R_f$ = 0.13 [acetone : EtOAc = 3 : 1]; $R_f$ = 0.26 [$CH_2Cl_2$ : MeOH = 7 : 1]; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.07 (s, 6 H), 2.17 (s, 2 H), 2.19 (s, 2 H), 3.00 (brs, 1 H, OH), 3.26 (q, 2 H, $J$ = 5.1 Hz), 3.61 (t, 2 H, $J$ = 5.1 Hz), 4.09 (dd, 2 H, $J$ = 6.3, 1.0 Hz), 4.21 (d, 2 H, $J$ = 6.3 Hz), 5.08 (s 1 H), 5.16 (brs, 1 H, OH), 5.65 (dtt, 1 H, $J$ = 11.4, 6.3, 1.0 Hz), 5.84 (dtt, 1 H, $J$ = 11.4, 6.3, 1.0 Hz); $^{13}$C NMR (50 MHz, $CDCl_3$) δ 28.3, 32.8, 42.5, 43.3, 50.1, 58.2, 66.5, 67.2, 95.2, 127.3, 133.2, 163.6, 197.2; IR (film) cm$^{-1}$ 3264brs, 2955m, 1548s, 1273s; mass spectrum [EI] *m/e* (% relative intensity) 253 (4) M$^+$, 238 (30), 221 (92), 207 (30), 182 (39), 152 (42), 83 (100).

According to the general procedure, oxidation of alcohol **20** (221.4 mg, 0.87 mmol) with activated $MnO_2$ (88%, 1.75 g, 17.7 mmol) in acetone (9 mL) afforded aldehyde **21** (136.0 mg, 62%, *cis* : *trans* = 67 : 33) as yellow oily solid.

**21:** *Major Product: cis aldehyde:* $R_f$ = 0.39 [$CH_2Cl_2$ : MeOH = 7 : 1]; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.04 (s, 6 H), 2.15 (s, 2 H), 2.19 (s, 2 H), 3.29 (q, 2 H, $J$ = 5.1 Hz), 3.67 (t, 2 H, $J$ = 5.1 Hz), 4.51 (dd, 1 H $J$ = 5.4, 1.8 Hz), 5.07 (s, 1 H), 5.11 (brs, 1 H, NH), 6.06 (ddt, 1 H, $J$ = 11.7, 6.0, 1.8 Hz), 6.83 (dt, 1 H, $J$ = 11.7, 5.4 Hz), 9.99 (d, 1 H, $J$ = 6.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 28.4, 33.0, 42.6, 43.6, 50.4, 68.2, 69.7, 95.8, 129.7, 146.9, 163.1, 191.3, 197.2.

**21**: *Minor Product: trans aldehyde:* $R_f$ = 0.35 [$CH_2Cl_2$ : MeOH = 7 : 1]; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.03 (s, 6 H), 2.13 (s, 2 H), 2.20 (s, 2 H), 3.29 (q, 2 H, $J$ = 5.1 Hz), 3.67 (t, 2 H, $J$ = 5.1 Hz), 4.27 (dd, 1 H $J$ = 4.2, 2.1 Hz), 5.06 (s, 1 H), 5.11 (brs, 1 H, NH), 6.31 (ddt, 1 H, $J$ = 15.6, 7.8, 2.1 Hz), 6.83 (dt, 1 H, $J$ = 15.6, 4.2 Hz), 9.99 (d, 1 H, $J$ = 6.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 28.5, 32.9, 42.6, 43.6, 50.4, 68.3, 68.4, 95.8, 131.9, 152.3, 163.1, 193.2, 197.2; IR (film) cm$^{-1}$ 3262 brs, 3073m, 2956s, 1684s, 1557s, 1471w, 1367w, 1272m, 1119m; mass spectrum (APCI): *m/e* (% relative intensity) 252 (100) $M^+ + 1$, 234 (148), 184 (52), 166 (32), 152 (20); *m/e* calcd for $C_{14}H_{22}NO_3$ ($M^+ + H$) 252.1600, found 252.1602.

**Aldehyde 35 (*trans*).**



A solution of amino alcohol **42** (2.05 g, 15.87 mmol) and 1,3-cyclohexanedione (1.70 g, 15.16 mmol) in toluene (70 mL) and EtOH (5 mL) was heated at 100 °C for 6 h. The solvents were removed under reduced pressure, and the residue was purified via silica gel flash column chromatography [gradient eluent: $CH_2Cl_2$ to $CH_2Cl_2$/MeOH (6 : 1)] to give amide **43** (1.37 g, 41%) as a yellow solid.

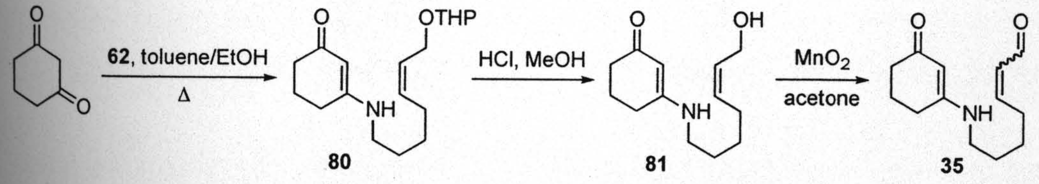
**43:** $R_f = 0.23$ [$CH_2Cl_2$ : $CH_3OH$ = 7 : 1]; mp = 54–58 °C; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.45 (quint, 2 H, $J = 7.2$ Hz), 1.61 (quint, 1 H, $J = 7.5$ Hz) 1.96 (quint, 2 H, $J = 6.3$ Hz), 2.09 (q, 2 H, $J = 6.9$ Hz), 2.29 – 2.35 (m, 4 H), 3.08 (q, 2 H, $J = 6.9$ Hz), 4.11 (d, 2 H, $J = 4.2$ Hz), 4.67 (brs, 1 H, NH), 5.14 (s, 1 H), 5.59 – 5.73 (m, 2 H); mass spectrum [EI] *m/e* (% relative intensity) 223 (33) $M^+$, 206 (30), 194 (14), 178 (16), 164 (22), 152 (49), 138 (60), 125 (100).

**General Procedure for the $MnO_2$ Oxidation.**

To a 0.1 *M* solution of amide **43** (45-250 mg, 0.20-1.12 mmol) in acetone was added activated $MnO_2$ (88%, 20 equiv). The reaction mixture was stirred for 2 h and monitored through TLC analysis [$CH_2Cl_2$/MeOH (7 : 1)]. After which, the solid was filtered off and the filter cake was washed with acetone. The filtrate was concentrated under reduced pressure to provide aldehyde **35** in 51-73% yield range as yellow oil, which was pure enough to be submitted to the formal *aza*-[3 + 3] cycloaddition reaction. The product could be further purified by filtration through short silica gel column with EtOAc/MeOH (7 : 1) as isocratic eluent.

**35:** $R_f$ = 0.35 [$CH_2Cl_2$ : $CH_3OH$ = 7 : 1]; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.50 – 1.67 (m, 4 H), 1.87 – 1.96 (m, 2 H), 2.24 – 2.38 (m, 6 H), 3.07 (q, 2 H, *J* = 6.5 Hz), 4.68 (brs, 1 H, NH), 5.11 (s, 1 H), 6.08 (ddt, 1 H, *J* = 15.7, 7.8, 1.5 Hz), 6.81 (dt, 1 H, *J* = 15.7, 6.8 Hz), 9.51 (d, 1 H, *J* = 7.8 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 22.0, 25.2, 27.9, 29.7, 32.2, 36.4, 42.5, 96.5, 133.2, 157.7, 164.7, 194.0, 197.2; IR (film) cm$^{-1}$ 3266brm, 2937m, 1688s, 1541s, 1456w, 1372m, 1258m; mass spectrum [EI] *m/e* (% relative intensity) 221 (2) M$^+$, 165 (100), 143 (50); *m/e* calcd for $C_{13}H_{19}NO_2Na$ (M$^+$ + Na) 244.1313, found 244.1309.

**Aldehyde 35 (*cis*/*trans* mixture).**



A mixture of crude amine **62** (2.62g, 12.29 mmol) and 1,3-cyclohexanedione (1.40 g, 12.28 mmol) in toluene (40 mL) and EtOH (2 mL) was heated at 100 °C for 6 h. The solvents were removed under reduced pressure to give the desired amide **80** (3.77 g) as yellow oil, which was used for the next step without further purification.

**80:** $R_f$ = 0.49 [$CH_2Cl_2$ : $CH_3OH$ = 10 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.42 (quint, 2 H, *J* = 7.0 Hz), 1.54 – 1.62 (m, 7 H), 1.70 – 1.85 (m, 2 H), 1.97 (quint, 2 H, *J* = 6.5 Hz), 2.14 (quint, 2 H, *J* = 6.5 Hz), 2.32 (quint, 2 H, *J* = 6.5 Hz), 3.08 (dd, 2 H, *J* = 13.0, 7.0 Hz), 3.51 (dd, 1 H, *J* = 10.5, 5.5 Hz), 3.88 (ddd, 1 H, *J* = 10.5, 8.0, 4.0 Hz), 4.07 (dd, 1 H, *J* = 12.0, 6.0 Hz), 4.24 (dd, 1

H, $J$ = 12.0, 6.0 Hz), 4.64 (dd, 2 H, $J$ = 4.5, 3.0 Hz), 5.12 (s, 1 H), 5.57 (dd, 1 H, $J$ = 11.5, 6.0 Hz), 5.59 (dd, 1 H, $J$ = 11.5, 6.0 Hz).

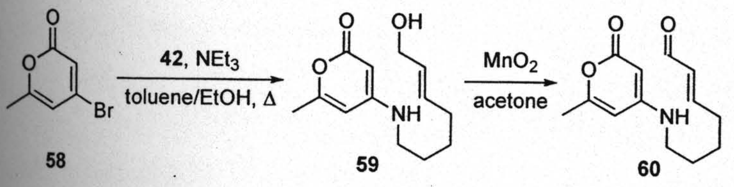
Conc aq HCl (37%, 12 mL, 1.25 mmol) was added to the solution of amide **81** (3.77 g, 12.28 mmol) in MeOH (70 mL). After stirring at rt for 36 h, the starting material disappeared as observed through TLC analysis [$CH_2Cl_2$ : $CH_3OH$ = 10 : 1]. At which time, MeOH was evaporated under reduced pressure. The crude residue was dissolved in $CH_2Cl_2$ (50 mL), and the resulting solution was washed with sat aq $NaHCO_3$ (3 × 10 mL) and sat aq NaCl (10 mL). The organic layer was dried over $Na_2SO_4$, and removal of the solvent under reduced pressure provided a crude residue that was purified via silica gel flash column chromatography [isocratic eluent: $CH_2Cl_2$ : $CH_3OH$ = 10 : 1] to afford amide **82** (1.45 g, 53 % over 2 steps) as yellow oil.

**81:** $R_f$ = 0.34 [$CH_2Cl_2$ : $CH_3OH$ = 10 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.43 (quint, 2 H, $J$ = 7.5 Hz), 1.60 (quint, 2 H, $J$ = 7.5 Hz), 1.95 (quint, 2 H, $J$ = 6.5 Hz), 2.11 (q, 2 H, $J$ = 7.5 Hz), 2.30 (t, 2 H, $J$ = 6.5 Hz), 2.36 (t, 2 H, $J$ = 6.5 Hz), 3.08 (dd, 2 H, $J$ = 13.5, 7.0 Hz), 3.47 (brs, 1 H, OH), 4.19 (d, 2 H, $J$ = 6.0 Hz), 5.09 (s, 1 H), 5.31 (brs, 1 H, NH), 5.45 (ddd, 1 H, $J$ = 11.0, 6.5, 3.0 Hz), 5.64 (ddd, 1 H, $J$ = 11.0, 6.5, 3.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 22.1, 26.8, 26.9, 27.7, 29.6, 36.4, 42.7, 58.1, 95.8, 130.0, 131.1, 165.8, 197.4; IR (film) cm$^{-1}$ 3428brs, 3054s, 2986m, 2943m, 2855m, 1609m, 1584s, 1265s; mass spectrum (APCI): *m/e* (% relative intensity) 224 (15) $M^+$ + 1, 223 (5) $M^+$, 205 (100), 110 (60); *m/e* calcd for $C_{13}H_{21}NO_2Na$ ($M^+$ + Na) 246.1470, found 246.1458.

According to the general procedure, oxidation of alcohol **81** (191.0 mg, 0.86 mmol) with activated $MnO_2$ (88%, 1.68 g, 17.11 mmol) in acetone (4 mL) afforded aldehyde **35** (107.0 mg, 56%, *cis* : *trans* = 73 : 27) as yellow oil.

**35**: *Major Product: cis-aldehyde*: $R_f = 0.29$ [$CH_2Cl_2$ : $CH_3OH$ = 7 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.53 (quint, 2 H, *J* = 7.5 Hz), 1.64 (quint, 2 H, *J* = 7.5 Hz), 1.92 (quint, 2 H, *J* = 6.5 Hz), 2.26 (t, 2 H, *J* = 6.5 Hz), 2.32 (t, 2 H, *J* = 6.5 Hz), 2.61 (q, 2 H, *J* = 7.5 Hz), 3.08 (dd, 2 H, *J* = 13.5, 7.0 Hz), 5.06 (s, 1 H), 5.45 (brs, 1 H, NH), 5.95 (dd, 1 H, *J* = 11.0, 9.5 Hz), 6.56 (dt, 1 H, *J* = 11.0, 7.5 Hz), 10.01 (d, 1 H, *J* = 7.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 22.1, 26.7, 27.7, 29.7, 32.7, 36.5, 42.6, 96.5, 130.5, 152.3, 165.8, 190.9, 197.3; IR (film) cm$^{-1}$ 3243brm, 3009w, 2948m, 1688s, 1549s, 1260m; mass spectrum (APCI): *m/e* (% relative intensity) 221 (2) M$^+$, 165 (100), 143 (50); *m/e* calcd for $C_{13}H_{19}NO_2Na$ (M$^+$ + Na) 244.1313, found 244.1316.

**Aldehyde 60.**



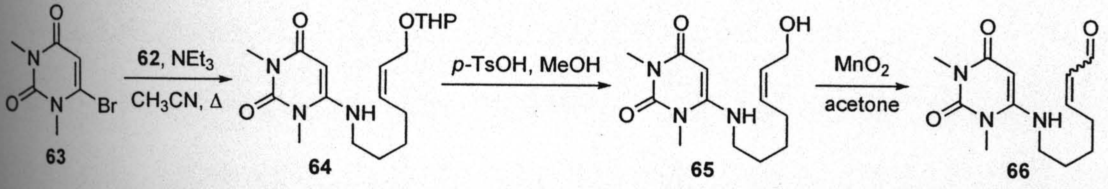
A mixture of amino alcohol **42** (0.70 g, 5.42 mmol), $NEt_3$ (0.60 mL, 4.18 mmol), and 4-bromo-6-methyl-2H-pyran-2-one[20] **58** (0.79 g, 4.30 mmol) in toluene (15 mL) and EtOH (4 mL) was heated at 80 °C for 4 h. After which, the solvent and excess of reagents were evaporated under reduced pressure, and the crude residue was purified via silica gel flash column chromatography [gradient eluent: $CH_2Cl_2$ to $CH_2Cl_2$/MeOH (12 : 1)] to yield amide **59** (355.0 mg, 41% based on recovered starting material) as orange-yellow solid.

**59:** $R_f = 0.32$ [$CH_2Cl_2$ : $CH_3OH$ = 7 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.46 (quint, 2 H, *J* = 7.0 Hz), 1.62 (quint, 2 H, *J* = 7.5 Hz), 1.97 (brs, 1 H, OH), 2.07 – 2.11 (m, 2 H), 2.14 (s, 3 H), 3.11 (q, 2 H, *J* = 6.5 Hz), 4.11 (s, 2 H), 4.95 (brs, 1 H, NH), 4.97 (d, 1 H, *J* = 2.0 Hz), 5.56 (s, 1 H), 5.62 – 5.70 (m, 2 H); mass spectrum [EI] *m/e* (% relative intensity) 237 (20) M$^+$, 220 (16), 208 (11), 194 (20), 166 (36), 152 (67), 139 (100), 110 (43).

According to the general procedure, oxidation of alcohol **59** (354.9 mg, 1.50 mmol) with activated $MnO_2$ (88%, 3.00 g, 30.37 mmol) in acetone (11 mL) afforded aldehyde **60** (227.9 mg, 65%) as yellow oil.

**60:** $R_f$ = 0.46 [$CH_2Cl_2$ : $CH_3OH$ = 7 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.57 – 1.63 (m, 2H), 1.64 – 1.69 (m, 2H), 2.12 (s, 3H), 2.37 (qd, 2H, *J* = 7.5, 1.5 Hz), 3.13 (q, 2H, *J* = 6.5 Hz), 4.98 (d, 1H *J* = 2.1 Hz), 5.48 (brs, 1H, NH), 5.62 (s, 1H), 6.10 (ddt, 1H, *J* = 15.5, 7.5, 1.5 Hz), 6.83 (dt, 1H, *J* = 15.5, 7.5 Hz), 9.48 (d, 1H, *J* = 7.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 20.0, 25.3, 28.1, 32.4, 42.4, 80.1, 99.4, 133.4, 157.8, 158.3, 160.9, 165.7, 194.1; IR (film) cm$^{-1}$ 3281brs, 3105m, 2938m, 1683s, 1557s, 1471w, 1291m, 1158m; mass spectrum (APCI): *m/e* (% relative intensity) 236 (35) M$^+$ + 1, 218 (100), 208 (5), 190 (11), 125 (10); *m/e* calcd for $C_{13}H_{17}NO_2Na$ (M$^+$ + Na) 258.1106, found 258.1091.

**Aldehyde 66.**



A mixture of crude amine **62** (1.14 g, 5.32 mmol), $NEt_3$ (0.91 mL, 6.54 mmol), and 6-bromo-1,3-dimethyluracil[20] **63** (1.30 g, 5.94 mmol) in $CH_3CN$ (40 mL) was heated to 80 °C for 4 h. After which, the solution was concentrated under reduced pressure, and the crude residue was purified via silica gel flash column chromatography [gradient eluent: $CH_2Cl_2$ to $CH_2Cl_2$/MeOH (7 : 1)] to give amide **64** (1.57 g, 84 %) as orange-yellow oil.

**64:** $R_f$ = 0.58 [$CH_2Cl_2$ : $CH_3OH$ = 7 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.45 (q, 2 H, $J$ = 7.0 Hz), 1.48 – 1.60 (m, 4 H), 1.64 – 1.85 (m, 4 H), 2.10 – 2.18 (m, 2 H), 3.11 (dd, 1 H, $J$ = 13.0, 7.0 Hz), 3.32 (s, 1 H), 3.33 (s, 3 H), 3.40 (s, 3 H), 3.49 – 3.53 (m, 1 H), 3.88 (td, 1 H, $J$ = 7.5, 3.5 Hz), 4.09 (dd, 1 H, $J$ = 12.0, 6.5 Hz), 4.25 (dd, 1 H, $J$ = 12.0, 6.5 Hz), 4.49 (dd, 1 H, $J$ = 4.0, 2.5 Hz), 4.66 (dd, 1 H, $J$ = 4.0, 3.0 Hz), 4.86 (s, 1 H), 5.54 – 5.63 (m, 2 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.6, 25.6, 26.7, 27.0, 28.7, 30.9, 36.8, 43.0, 62.2, 62.5, 74.9, 77.7, 105.9, 126.7, 132.5, 151.9, 153.2, 163.0.

To a solution of amide **64** (1.57 g, 4.45 mmol) in MeOH (50 mL) was added *p*-TsOH (100.0 mg, 0.53 mmol). After stirring at rt for 6 h, the starting material disappeared as observed by TLC [$CH_2Cl_2$ : $CH_3OH$ = 8 : 2]. The acid was neutralized by addition of $NaHCO_3$ (0.10 g) to the reaction mixture, and the solid was then filtered off and MeOH was evaporated under reduced pressure. The crude product was purified via silica gel flash column chromatography [isocratic eluent: $CH_2Cl_2$ : $CH_3OH$ = 7 : 1] to afford alcohol **65** (0.95 g, 74 %) as yellow oil.

**65:** $R_f$ = 0.28 [$CH_2Cl_2$ : $CH_3OH$ = 10 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.24 (quint, 2 H, $J$ = 7.5 Hz), 1.45 (quint, 2 H, $J$ = 7.5 Hz), 1.90 (q, 2 H, $J$ = 7.5 Hz), 2.92 (dd, 2 H, $J$ = 12.5, 7.5 Hz), 3.06 (s, 3 H), 3.20 (s, 3 H), 3.47 (brs, 1 H, OH), 3.97 (d, 2 H, $J$ = 6.0 Hz), 4.60 (s, 1 H), 5.25 (dt, 1 H, $J$ = 10.5, 7.5 Hz), 5.41 (dt, 1 H, $J$ = 10.5, 7.5 Hz), 6.07 (dd, 1 H, $J$ = 5.5, 5.0 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 26.3, 27.2, 27.4, 28.9, 42.6, 49.7, 57.7, 74.1, 129.5, 130.9, 151.8, 153.5, 163.4; IR (film) cm$^{-1}$ 3455brs, 3057s, 2988 – 2940m, 1692m, 1638s, 1611m, 1266s; mass spectrum (APCI): *m/e* (% relative intensity) 268 (15) $M^+$ + 1, 267 (45) $M^+$, 259 (100), 154 (15), 113 (50); *m/e* calcd for $C_{13}H_{21}N_3O_3Na$ ($M^+$ + Na) 290.1481, found 290.1469.

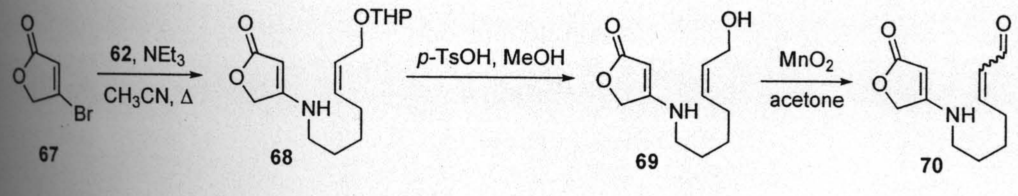
According to the general procedure, oxidation of alcohol **65** (353.0 mg, 1.32 mmol) with activated $MnO_2$ (88%, 2.66 g, 26.9 mmol) in acetone (8 mL) afforded aldehyde **66** (243.0 mg, 69%, *cis* : *trans* = 77 : 23) as yellow oil.

**66:** *Major Product: cis aldehyde*: $R_f$ = 0.39 [$CH_2Cl_2$ : $CH_3OH$ = 10 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.61 (quint, 2 H, *J* = 7.5 Hz), 1.72 (quint, 2 H, *J* = 7.5 Hz), 2.68 (q, 2 H, *J* = 7.5 Hz), 3.15 (ddd, 2 H, *J* = 12.0, 7.5, 4.5 Hz), 3.32 (s, 3 H), 3.40 (s, 3H), 4.45 (brs, 1 H, NH), 4.87(s, 1 H), 6.03 (dd, 1 H, *J* = 11.0, 7.5 Hz), 6.58 (dt, 1 H, *J* = 11.0, 7.5 Hz), 10.05 (d, 1 H, *J* = 7.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 26.5, 28.0, 28.1, 28.8, 32.3, 43.1, 75.7, 130.6, 151.8, 153.1, 157.3, 163.2, 190.8.

**66:** *Minor Product: trans aldehyde*: $R_f$ = 0.36 [$CH_2Cl_2$ : $CH_3OH$ = 10 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.61 (quint, 2 H, *J* = 7.5 Hz), 1.72 (quint, 2 H, *J* = 7.5 Hz), 2.41 (q, 2 H, *J* = 7.5 Hz), 3.15 (ddd, 2 H, *J* = 12.0, 7.5, 4.5 Hz), 3.32 (s, 3 H), 3.40 (s, 3 H), 4.39 (brs, 1 H, NH), 4.87(s, 1 H), 6.13 (dd, 1 H, *J* = 15.5, 7.5 Hz), 6.83 (dt, 1 H, *J* = 15.5, 7.5 Hz), 9.52 (d, 1 H, *J* = 7.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 25.3, 27.8, 28.0, 28.2, 32.3, 43.2, 75.7, 133.6, 152.1, 153.1, 157.3, 163.2, 194.0.

IR (film) cm$^{-1}$ 3350brm, 3011m, 2987s, 2939s, 2788s, 1710s, 1620s, 1570m; mass spectrum (APCI): *m/e* (% relative intensity) 267 (10) $M^+$ + 1, 266 (5) $M^+$, 154 (100), 113 (10); *m/e* calcd for $C_{13}H_{19}N_3O_3Na$ ($M^+$ + Na) 288.1324, found 288.1326.

**Aldehyde 70.**



Amide **68** (0.73 g, 74 %) was synthesized using the procedure described above for **64** starting from 4-bromo-5H-furan-2-one[20] **67** (0.60 g, 3.70 mmol), amine **62** (0.71 g, 3.33 mmol), and $NEt_3$ (0.56 mL, 4.11 mmol) in $CH_3CN$ (40 mL).

**68:** $R_f$ = 0.45 [$CH_2Cl_2$ : $CH_3OH$ = 10 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.45 (quint, 2 H, $J$ = 7.5 Hz), 1.52– 1.64 (m, 5 H), 1.70 – 1.75 (m, 1 H), 1.80 – 1.85 (m, 1 H), 2.10 – 2.18 (m, 3 H), 3.12 (dd, 2 H, $J$ = 12.0, 7.0 Hz), 3.46 (s, 1 H), 3.50 (ddd, 1 H, $J$ = 12.0, 10.0, 4.5 Hz), 3.88 (ddd, 1 H, $J$ = 12.0, 8.0, 3.0 Hz), 4.07 (dd, 1 H, $J$ = 12.0, 5.5 Hz), 4.24 (dd, 1 H, $J$ = 12.0, 4.5 Hz), 4.61– 4.63 (m, 1 H), 4.67 (s, 2 H), 5.56(dd, 1 H, $J$ = 11.0, 6.0 Hz), 5.60 (dd, 1 H, $J$ = 11.0, 6.0 Hz), 6.98 (s, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.6, 25.5, 26.7, 26.9, 27.0, 30.8, 44.9, 62.4, 63.7, 67.8, 80.1, 98.0, 126.5, 132.9, 168.6, 176.6; IR (film) cm$^{-1}$ 3290brs, 3082w, 3017w, 2953s, 2858s, 1758m, 1716s, 1618s.

Amide **69** (375.0 mg, 72 %) was prepared using the similar procedure as described above for **65** starting from THP–protected alcohol **68** (730.0 mg, 2.47 mmol) and *p*-TsOH (40.0 mg, 0.21 mmol) in $CH_3OH$ (30 mL).

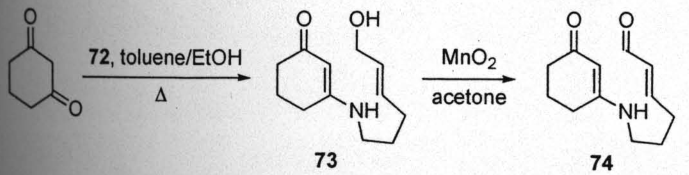
**69:** $R_f$ = 0.40 [$CH_2Cl_2$ : $CH_3OH$ = 7 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.47 (quint, 2 H, $J$ = 7.5 Hz), 1.66 (quint, 2 H, $J$ = 7.5 Hz), 2.01 (q, 2 H, $J$ = 7.5 Hz), 3.17 (q, 2 H, $J$ = 6.5 Hz), 3.65 (brs, 1 H), 4.14(d, 2 H, $J$ = 6.5 Hz), 4.56 (s, 1 H), 4.66 (s, 2 H), 5.43 (ddd, 1 H, $J$ = 18.0, 12.0, 7.0 Hz), 5.59 (ddd, 1 H, $J$ = 18.0, 12.0, 7.0 Hz), 6.75 (s, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 26.5, 27.6, 29.8, 44.6, 57.7, 67.6, 78.9, 129.4, 130.9, 168.9, 176.7; IR (film) cm$^{-1}$ 3291brs, 3075 – 3012m, 2934s, 2860s, 1713s, 1614s; mass spectrum (APCI): *m/e* (% relative intensity) 212 (30) $M^+ + 1$, 211 (5) $M^+$, 193 (100), 101 (15), 56 (50); *m/e* calcd for $C_{11}H_{17}NO_3Na$ ($M^+$ + Na) 234.1106, found 234.1111.

According to the general procedure, oxidation of alcohol **69** (132.0 mg, 0.63 mmol) with activated $MnO_2$ (88%, 1.23 g, 15.21 mmol) in acetone (4 mL) afforded aldehyde **70** (101.0 mg, 77%, *cis* : *trans* = 73 : 27) as yellow oil.

**70:** *Major Product: cis aldehyde:* $R_f$ = 0.35 [$CH_2Cl_2$ : $CH_3OH$ = 7 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.63 (quint, 2 H, *J* = 7.0 Hz), 1.69 (quint, 2 H, *J* = 7.0 Hz), 2.68 (q, 2 H, *J* = 7.5 Hz), 3.16 (q, 2 H, *J* = 6.5 Hz), 4.58 (s, 1 H), 4.71 (s, 2 H), 5.99 (dd, 1 H, *J* = 11.0, 8.0 Hz), 6.80 (dd, 1 H, *J* = 5.5, 4.5 Hz), 6.64 (dt, 1 H, *J* = 11.0, 8.0 Hz), 10.07 (d, 1 H, *J* = 8.0 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 26.5, 27.8, 32.3, 44.8, 68.0, 79.9, 133.3, 152.7, 169.0, 176.8, 191.0.

**70:** *Minor Product: trans aldehyde:* $R_f$ = 0.47 [$CH_2Cl_2$ : $CH_3OH$ = 7 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.63 (quint, 2 H, *J* = 7.0 Hz), 1.69 (quint, 2 H, *J* = 7.0 Hz), 2.40 (q, 2 H, *J* = 7.0 Hz), 3.16 (q, 2 H, *J* = 6.5 Hz), 4.57 (s, 1 H), 4.70 (s, 2 H), 6.11 (dd, 1 H, *J* = 16.0, 8.0 Hz), 6.80 (dd, 1 H, *J* = 5.5, 4.5 Hz), 6.89 (dt, 1 H, *J* = 16.0, 7.5 Hz), 9.49 (d, 1 H, *J* = 7.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 24.9, 27.9, 32.2, 44.7, 67.9, 79.3, 133.1, 158.4, 169.2, 176.9, 194.2. IR (film) cm$^{-1}$ 3412brm, 3011m, 2927s, 2855s, 1717m, 1617s, 1559m; mass spectrum (APCI): *m/e* (% relative intensity) 210 (3) M$^+$ + 1, 208 (5), 191 (100), 101 (45); *m/e* calcd for $C_{11}H_{15}NO_3Na$ (M$^+$ + Na) 232.0950, found 232.0950.

**Aldehyde 74.**



A mixture of amino alcohol **72** (318.0 mg, 2.76 mmol) and 1,3-cyclohexanedione (310.0 mg, 2.76 mmol) in toluene (15 mL) and EtOH (1 mL) was heated at 100 °C for 6 h. The solvents were removed under reduced pressure, and crude the residue was purified via silica gel flash column chromatography [gradient eluent: $CH_2Cl_2$ to $CH_2Cl_2$/MeOH (6 : 1)] to give amide **73** (462.0 mg, 41%) as a yellow solid.

**73:** $R_f = 0.18$ [$CH_2Cl_2$ : MeOH = 7 : 1]; mp = 48–51°C; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.68 (quint, 2 H, $J = 7.5$ Hz), 1.95 (quint, 2 H, $J = 6.9$ Hz), 2.09 – 2.12 (m, 2 H), 2.30 (t, 2 H, $J = 6.9$ Hz), 2.33 (t, 2 H, $J = 6.9$ Hz), 2.70 (brs, 1 H, OH), 3.09 (q, 2 H, $J = 6.5$ Hz), 4.09 (s, 2 H), 5.05 (brs, 1 H, NH), 5.11 (s, 1 H), 5.62 – 5.70 (m, 2 H); mass spectrum *m/e* (% relative intensity) 209 (32) $M^+$, 192 (13), 178 (12), 150 (20), 138 (48), 125 (67), 97 (100).

According to the general procedure, oxidation of alcohol **73** (233.4 mg, 1.12 mmol) with activated $MnO_2$ (88%, 2.20 g, 22.27 mmol) in acetone (10 mL) afforded aldehyde **74** (133.6 mg, 58%) as yellow solid.

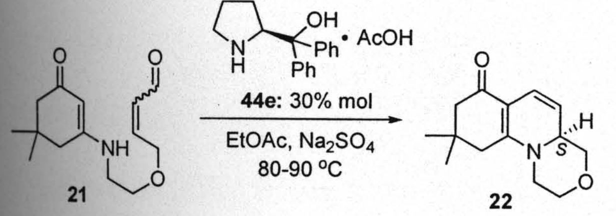
**74:** $R_f = 0.29$ [$CH_2Cl_2$ : MeOH = 7 : 1]; mp = 86–89°C; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.82 (quint, 2 H, $J = 7.0$ Hz), 1.97 (quint, 2 H, $J = 6.9$ Hz), 2.32 (t, 2 H, $J = 6.9$ Hz), 2.33 (t, 2 H, $J = 6.9$ Hz), 2.41 (qd, 2 H, $J = 7.0, 1.5$ Hz), 3.15 (q, 2 H, $J = 7.0$ Hz), 4.75 (brs, 1 H, NH), 5.12 (s, 1 H), 6.14 (ddt, 1 H, $J = 16.0, 7.5, 1.5$ Hz), 6.83 (dt, 1 H, $J = 16.0, 7.0$ Hz), 9.51 (d, 1 H, $J = 7.5$ Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 21.9, 26.3, 29.3, 30.1, 36.4, 42.0, 95.8, 133.2, 157.4, 165.6, 193.9, 197.1; IR (film) cm$^{-1}$ 3250brm, 3066w, 2942m, 1686s, 1541s, 1457w, 1255m, 1190m; mass spectrum [EI] *m/e* (% relative intensity) 207 (1) $M^+$, 188 (100), 172 (13), 158 (22), 132 (21); *m/e* calcd for $C_{12}H_{18}NO_2$ ($M^+$ + H) 208.1338, found 208.1324.

## PREPARATION OF THE AZA [3 + 3] ANNULATION PRODUCTS.

***General Procedure.*** To a 0.05 – 0.08 *M* solution of freshly prepared aldehyde (0.20–0.60 mmol) in EtOAc (4 – 12 mL) in a flame-dried round bottom flask were added solid $Na_2SO_4$

(0.10 – 0.30 g) and an appropriate amount of chiral amine salt. In cases where *in situ* generation of the catalyst was noted, free amine and 1 equiv of AcOH were premixed in EtOAc followed by successive addition of $Na_2SO_4$ and starting aldehyde. The reaction flask was then sealed under nitrogen with a new rubber septum and heated to desired temperature (usually 80–90 °C). For the reaction performed at 100 °C and above, a proper sealed tube was used instead of a round-bottom flask. The course of the reaction was monitored using TLC analysis (in all cases cycloadducts show lower polarity and higher $R_f$ values). Upon completion, $Na_2SO_4$ solid was filtered, and the filter cake was washed with excess EtOAc. The organic solvent was removed under reduced pressure to give a crude residue that was purified via silica gel flash column chromatography. All cycloadducts were not very stable and decomposed relatively fast if stored in air at rt. However, if they were kept under nitrogen in the freezer, no noticeable decomposition was observed.

**Cycloadduct 22.**

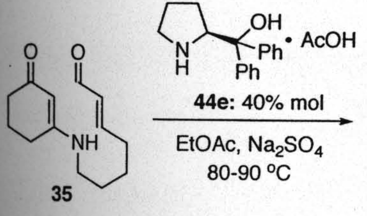


According to the general procedure, the annulation reaction of amide **21** (113.6 mg, 0.55 mmol) through treatment with amine salt **44e** (42.0 mg, 0.13 mmol) in EtOAc (12 mL) afforded cycloadduct **22** (64.2 mg, 61%) as yellow oil upon purification on silica gel column [isocratic eluent: EtOAc].

**22:** $R_f = 0.45$ [$CH_2Cl_2$ : MeOH = 7 : 1], $R_f = 0.75$ [EtOAc : MeOH : hexanes = 1 :1 : 1]; $^1$H NMR (300 MHz, $CDCl_3$) δ 1.05 (s, 3 H), 1.07 (s, 3 H), 2.17 (s, 2 H), 2.22 (d, 2 H, $J = 2.7$ Hz), 3.08

(ddd, 1 H, $J$ = 13.5, 12.0, 3.3 Hz), 3.58 – 3.62 (m, 3 H), 3.71 (d, 1 H, $J$ = 14.1 Hz), 3.90 (dd, 1 H, $J$ = 11.4, 2.1 Hz), 4.50 (m, 1 H), 4.83 (dd, 1 H, $J$ = 10.2, 2.7 Hz), 6.45 (dd, 1 H, $J$ = 10.2, 1.8 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 28.8, 29.5, 31.9, 39.6, 47.3, 49.0, 59.6, 67.8, 71.2, 105.0, 109.6, 122.5, 158.1,191.2; IR (film) cm$^{-1}$ 2960s, 2929s, 1659s, 1543s, 1423m; mass spectrum [EI] *m/e* (% relative intensity) 233 (6) M$^+$, 218 (16), 203 (5), 188 (100), 175 (10), 160 (14), 119 (32); *m/e* calcd for $C_{14}H_{19}NO_2Na$ (M$^+$ + Na) 256.1313, found 256.1300; CSP-HPLC (Chiralcel OD column, IPA/hexane [20 : 80], 0.75 mL/min) τ = 18.0 min (27%, *R*), τ = 20.1 min (73%, *S*).

**Cycloadduct 25.**

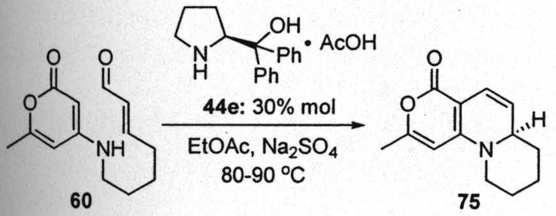


As in the general procedure, the annulation reaction of amide **35** (61.1 mg, 0.28 mmol) through treatment with amine salt **44e** (33.2 mg, 0.11 mmol) in EtOAc (5 mL) afforded cycloadduct **25** (34.1 mg, 61%) as yellow solid upon purification on silica gel column [gradient eluent: $CH_2Cl_2$ to $CH_2Cl_2$/MeOH (10 : 1)].

**25:** $R_f$ = 0.46 [$CH_2Cl_2$ : MeOH = 7 : 1]; mp = >90 °C (decomp); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.50 – 1.63 (m, 4 H), 1.72 – 1.79 (m, 2 H), 1.93 – 2.00 (m, 2 H), 2.21 – 2.33 (m, 2 H), 2.41 – 2.51 (m, 2 H), 2.78 (td, 1 H, $J$ = 12.3, 2.4 Hz), 3.96 (d, 1 H, $J$ = 13.5 Hz), 4.22 (d, 1 H, $J$ = 11.1 Hz), 5.00 (dd, 1 H, $J$ = 10.2, 3.9 Hz), 6.60 (d, 1 H, $J$ = 10.2 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 21.0, 25.1, 25.9, 26.9, 34.6, 35.0, 48.5, 61.0, 105.2, 114.7, 119.7, 159.8, 191.1; IR (film) cm$^{-1}$ 2932m, 2856w, 1626s, 1526s, 1462s, 1360m, 1319m, 1268m, 1195w, 1146w; mass spectrum

[EI] *m/e* (% relative intensity) 203 (90) $M^+$, 174 (62), 161 (45), 146 (58), 119 (100), 91 (27); *m/e* calcd for $C_{13}H_{17}NONa$ ($M^+$ + Na) 226.1208, found 226.1199; CSP-HPLC (Chiralcel OD column, IPA/hexane [30 : 70], 0.75 mL/min) $\tau$ = 11.0 min (81%, *R*), $\tau$ = 12.1 min (19%, *S*).

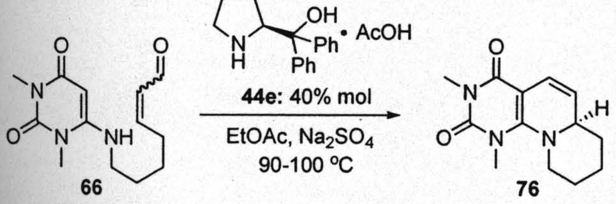
**Cycloadduct 75.**



According to the general procedure, the annulation reaction of amide **60** (153.7 mg, 0.65 mmol) through treatment with amine salt **44e** (60.9 mg, 0.19 mmol) in EtOAc (12 mL) afforded cycloadduct **75** (78.8 mg, 56%) as yellow solid upon purification on silica gel column [isocratic eluent: EtOAc].

**75:** $R_f$ = 0.34 [EtOAc]; mp = >90 °C (decomp); $^1$H NMR (300 MHz, $CDCl_3$) δ 1.51 – 1.63 (m, 3 H), 1.93 – 1.98 (m, 1 H), 1.93 – 2.00 (m, 2 H), 2.20 (s, 3 H), 2.79 (td, 1 H, *J* = 12.6, 3.0 Hz), 3.90 (dd, 1 H, *J* = 15.3, 3.0 Hz), 4.24 (dt, 1 H, *J* = 11.1 1.5 Hz), 5.13 (dd, 1 H, *J* = 10.2, 3.9 Hz), 5.80 (s, 1 H), 6.45 (d, 1 H, *J* = 10.2 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 20.9, 24.8, 26.3, 34.3, 47.7, 60.0, 91.6, 94.6, 117.5, 120.1, 152.5, 161.9, 162.4; IR (film) cm$^{-1}$ 2928m, 2854m, 1675s, 1522s, 1329m; mass spectrum [EI] *m/e* (% relative intensity) 216 (100) $M^+$ – 1, 187 (32), 160 (39), 146 (20), 119 (24); *m/e* calcd for $C_{13}H_{16}NO_2$ ($M^+$ + H) 218.1181, found 218.1186; CSP-HPLC (Chiralcel OD column, IPA/hexane [30 : 70], 0.75 mL/min) $\tau$ = 12.3 min (25%, *S*), $\tau$ = 14.8 min (75%, *R*).

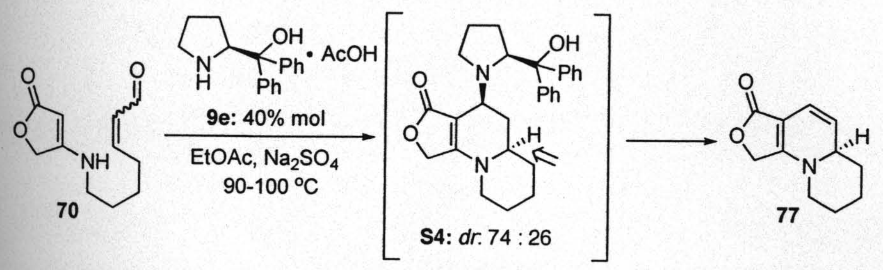
**Cycloadduct 76.**



According to the general procedure, the annulation reaction of amide **66** (219.0 mg, 0.83 mmol) through treatment with amine salt **44e** (104.0 mg, 0.33 mmol) in EtOAc (12 mL) afforded cycloadduct **76** (56.4 mg, 68%) as yellow solid upon purification on silica gel column [isocratic eluent: EtOAc].

**76:** $R_f$ = 0.42 [$CH_2Cl_2$ : $CH_3OH$ = 10 : 1], $R_f$ = 0.21 [EtOAc : hexane = 2 : 3]; mp = 108–110 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.39 (dddd, 1 H, *J* = 24.0, 13.5, 4.5, 3.5 Hz), 1.52 (dddd, 1 H, *J* = 24.0, 13.5, 4.5, 3.5 Hz), 1.61(ddd, 1 H, *J* = 13.0, 3.0, 2.5 Hz), 1.70 (ddd, 1 H, *J* = 13.0, 3.0, 2.5 Hz), 1.91 – 1.96 (m, 2 H), 2.51 – 2.60 (m, 2 H), 3.38 (s, 3 H), 3.45 (s, 3 H), 3.69 (ddd, 1 H, *J* = 7.5, 4.5, 3.0 Hz), 5.29 (dd, 1 H, *J* = 9.0, 3.0 Hz), 6.68 (dd, 1 H, *J* = 9.0, 3.0 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.9, 24.0, 28.1, 28.4, 30.9, 42.6, 54.0, 101.0, 119.3, 131.6, 152.1, 155.6, 161.5; IR (film) cm$^{-1}$ 3044w, 2978s, 2855s, 1703s, 1211m; mass spectrum (APCI): *m/e* (% relative intensity) 192 (100) $M^+$ + 1, 191 (40) $M^+$, 156 (30), 81 (10) ; *m/e* calcd for $C_{13}H_{17}N_3O_2Na$ ($M^+$ + Na) 270.1218, found 270.1195; CSP-HPLC (Chiralcel OD column, IPA/hexane [1.5 : 98.5], 0.75 mL/min) τ = 58.4 min (20%, *S*), τ = 66.7 min (80%, *R*).

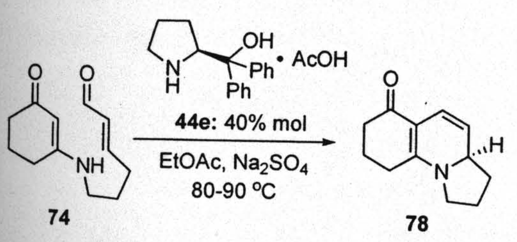
**Cycloadduct 77.**



According to the general procedure, the annulation reaction of amide **70** (101.1 mg, 0.48 mmol) through treatment with amine salt **44e** (60.9 mg, 0.19 mmol) in EtOAc (6 mL) afforded cycloadduct **77** (37.6 mg, 41 %) as yellow solid upon purification on silica gel column [isocratic eluent: EtOAc]. Enantiomers of the product were found to be inseparable on CSP-HPLC. Enantiomeric ratio was determined based on the ratio of diastereomeric intermediates **S4** in the reaction sample upon 1 h of heating as determined by LC/MS analysis.

**77:** $R_f$ = 0.42 [$CH_2Cl_2$ : $CH_3OH$ = 10 : 1]; mp = >100 °C (decomp); $^1$H NMR (500 MHz, $CDCl_3$) δ 1.52 – 1.65 (m, 3 H), 1.73 – 1.79 (m, 1 H), 1.80 – 1.86 (m, 1 H), 1.95 – 2.01 (m, 1 H), 2.96 (dt, 1 H, *J* = 13.0, 3.0 Hz), 3.23 (dt, 1 H, *J* = 13.0, 2.0 Hz), 4.40 (dq, 1 H, *J* = 11.5, 2.5 Hz), 4.64 (s, 2 H), 4.96 (dd, 1 H, *J* = 10.0, 3.0 Hz), 6.07 (dd, 1 H, *J* = 10.0, 2.0 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 24.4, 26.2, 33.9, 48.6, 60.8, 64.5, 91.6, 117.2, 117.9, 164.7, 171.5; IR (film) cm$^{-1}$ 3057s, 2988s, 2864s, 1632s, 1265m; mass spectrum (APCI): *m/e* (% relative intensity) 192 (100) M$^+$ + 1, 191 (40) M$^+$, 156 (30), 81 (10) ; *m/e* calcd for $C_{11}H_{13}NO_2Na$ (M$^+$ + Na) 214.0844, found 214.0835; LC/MS for intermediates **S4** (ZORBAX Eclipse XDB-C8 column, 5 min $H_2O$/AcCN [95 : 5], 0.70 mL/min, then 10 min $H_2O$/AcCN [5 : 95], 0.70 mL/min) τ = 8.75 min (74%), *m/e* 445 (M$^+$ + 1), τ = 9.42 min (26%), *m/e* 445 (M$^+$ + 1).

**Cycloadduct 78.**

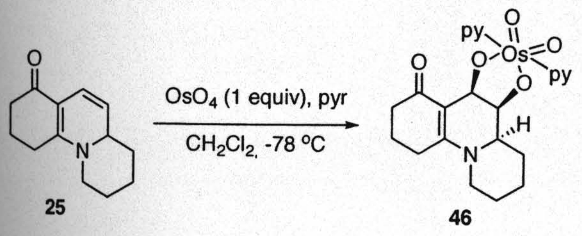


According to the general procedure, the annulation reaction of amide **74** (128.5 mg, 0.62 mmol) through treatment with amine salt **44e** (78.0 mg, 0.25 mmol) in EtOAc (8 mL) afforded cycloadduct **78** (52.1 mg, 44%) upon purification on silica gel column [gradient eluent: $CH_2Cl_2$ to $CH_2Cl_2$/MeOH (9 : 1)].

**78:** $R_f$ = 0.40 [$CH_2Cl_2$ : MeOH = 7 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.78 – 2.01 (m, 5 H), 2.20 – 2.25 (m, 1 H), 2.27 – 2.36 (m, 2 H), 2.38 – 2.51 (m, 2 H), 3.42 (ddd, 1 H, *J* = 13.0, 11.0, 3.5 Hz), 3.60 (dt, 1 H, *J* = 11.0, 8.5 Hz), 4.38 – 4.42 (m, 1 H), 5.07 (dd, 1 H, *J* = 10.0, 1.5 Hz), 6.62 (dd, 1 H, *J* = 10.0, 2.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 21.1, 22.3, 27.1, 32.6, 35.6, 47.0, 60.1, 107.3, 111.7, 121.7, 160.6, 190.8; IR (film) cm$^{-1}$ 2942s, 2872w, 1606s, 1525s, 1465s, 1420m, 1289m, 1186m; mass spectrum [EI] *m/e* (% relative intensity) 189 (59) M$^+$, 188 (100) M$^+$ – 1, 172 (13), 161 (11), 132 (20); *m/e* calcd for $C_{12}H_{16}NO$ (M$^+$ + H) 190.1232, found 190.1222; CSP-HPLC (Chiralcel OD column, IPA/hexane [30 : 70], 0.75 mL/min) τ = 11.4 min (60%, *R*), τ = 12.7 min (40%, *S*).

## ABSOLUTE CONFIGURATION ASSIGNMENT.

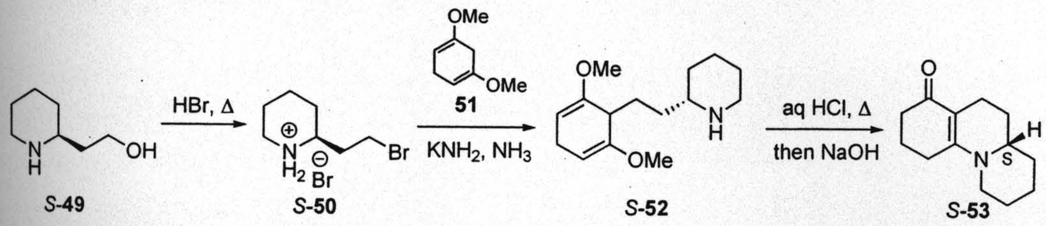
**Osmate ester 46.**



To a solution of cycloadduct **25** (0.105 g, 0.52 mmol) in $CH_2Cl_2$ (6 mL) at -78 °C a solution of $OsO_4$ (0.131g, 0.52 mmol) and pyridine (0.20 mL, 2.45 mmol) in $CH_2Cl_2$ (2 mL) was added dropwise. Immediate color change from pale yellow to dark brown occurred. Reaction mixture was allowed to warm up to rt and stirred at this temperature for 1 h. Solvent was evaporated under reduced pressure to yield osmate ester **46** (0.30 g) as brown solid in nearly quantitative yield. Product may be further purified by silica gel column chromatography ($CH_2Cl_2$ : MeOH = 7 : 1)

**46:** $R_f$ = 0.50 (brown spot) [$CH_2Cl_2$ : MeOH = 7 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.39 (qd, 1 H, $J$ = 13.5, 3.5 Hz), 1.45 – 1.57 (m, 2 H), 1.77 (dd, 1 H, $J$ = 13.5, 2.0 Hz), 1.89 (brd, 1 H, $J$ = 13.5 Hz), 1.94 – 2.08 (m, 2 H), 2.33 – 2.41 (m, 3 H), 2.52 – 2.62 (m, 2 H), 2.77 (td, 1 H, $J$ = 13.0, 2.0 Hz), 3.57 (td, 1 H, $J$ = 10.5, 2.5 Hz), 3.67 (dd, 1 H, $J$ = 10.5, 4.5 Hz), 3.95 (d, 1 H, $J$ = 13.0 Hz), 5.74 (d, 1 H, $J$ = 4.5 Hz), 7.45 (brs, 4 H), 7.82 (brs, 2 H), 8.84 (brs, 4 H); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 22.2, 23.7, 26.2, 27.8, 30.5, 36.4, 47.1, 54.7, 82.3, 86.9, 106.9, 125.4, 140.3, 149.6 and 150.3, 162.2, 195.3.

## SYNTHESIS OF *S*-53



### Hydrobromide *S*-50.[17]

A mixture of (2*S*)-(2-bromoethyl)-piperidine[18] *S*-**49** (5.00 g, 38.7 mmol) and conc aq HBr (48%, 15 mL) was heated to reflux for 1 h. After which, an additional 10 mL of conc aq HBr was added and the solution was refluxed for 6 h. Excess of the acid was evaporated under reduced pressure. The residue was washed with EtOAc (2 × 10 mL) and recrystallized from EtOH to give *S*-**50** (5.50 g, 52%) as colorless needles.

**50:** mp = 195–197 °C; $[\alpha]_D^{20}$ = +5.8 ° [c = 2, $CHCl_3$]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.48 – 1.56 (m, 1 H), 1.74 – 1.83 (m, 1 H), 1.88 (d, 1 H, *J* = 14.5 Hz), 1.94 – 2.04 (m, 3 H), 2.32 (sextet, 1 H, *J* = 7.0 Hz) 2.69 (sextet, 1 H, *J* = 7.0 Hz), 2.88 (brs, 1 H), 3.33 (brs, 1 H), 3.50 – 3.55 (m, 2 H), 3.70 (dt, 1 H, *J* = 10.5, 6.5 Hz), 8.99 (brs, 1 H, NH), 9.21 (brs, 1 H, NH); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 22.1, 22.4, 27.9, 28.3, 35.8, 45.1, 56.4; IR (film) cm$^{-1}$ 2939s, 2830m, 2797s, 2721m, 1577w, 1453w; *m*/*e* calcd for $C_7H_{15}BrN$ 192.0388, 194.0367 ($M^+$ + H), found 192.0378, 194.0360.

### Compound *S*-52.[17]

To a mixture of $KNH_2$ (prepared from 0.40 g (10.3 mmol) of K metal) in liquid $NH_3$ (35 mL) was added 2,5-dihydro-1,3-dimethoxybenzene **51** (1.00 g, 7.13 mmol). The resulting red solution was stirred for 20 min before **13** (1.23 g, 4.51 mmol) was added in portions over 30 min to discharge the color. After most of liquid $NH_3$ was evaporated, $H_2O$ (15 mL) was added. The aqueous mixture was extracted with $Et_2O$ (3 × 20 mL), and the combined organic fractions were washed with sat aq NaCl (20 mL) and dried over $Na_2SO_4$. Removal of the solvent under reduced pressure to provide the crude **52** that was purified by distillation (bp = 140–145 °C at 3 mmHg) giving compound *S*-**52** (0.56 g, 49%) as colorless oil.

**52:** $[\alpha]_D^{20} = -1.5$ ° [c = 2, $CHCl_3$]; $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.00 (m, 1 H), 1.14 – 1.19 (m, 2 H), 1.29 (ddt, 1 H, 25.0, 13.0, 4.0 Hz), 1.31 – 1.37 (m, 1 H), 1.38 (ddt, 1 H, *J* = 25.0, 13.0, 4.0 Hz), 1.55 (dm, 1 H, *J* = 12.5 Hz), 1.63 (dm, 1 H, *J* = 13.5 Hz), 1.70 – 1.77 (m, 3 H), 2.35 (ddd, 1 H, *J* = 17.0, 7.5, 2.5 Hz), 2.59 (td, 1 H, *J* = 11.5, 3.0 Hz), 2.74 (dq, 1 H, *J* = 21.0, 4.0 Hz), 2.81 (dq, 1 H, *J* = 21.0, 3.0 Hz), 2.95 (tt, 1 H, *J* = 6.0, 4.5 Hz), 3.00 (dm, 1 H, *J* = 11.5 Hz), 3.52 (s, 3 H), 3.53 (s, 3 H), 4.70 (dd, 2 H, *J* = 7.5, 3.5 Hz); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 24.7, 25.2, 26.1, 26.9, 32.1, 33.2, 40.8, 47.5, 54.5, 57.4, 91.9, 154.4; *m*/*e* calcd for $C_{15}H_{26}NO_2$ 252.1964 ($M^+$ + H), found 252.1964.

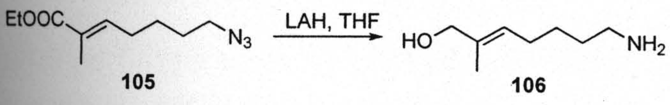
### Tricycle *S*-53.[17]

A solution of **52** (0.56 g, 2.23 mmol) in aq HCl (2 *M*, 4 mL) was heated to 40 °C for 30 min. After being cooled to rt, it was neutralized with 10% aq NaOH. The reaction mixture was extracted with $Et_2O$ (4 × 15 mL), and the combined organic fractions were washed with sat aq NaCl (20 mL) and dried over $Na_2SO_4$. After removal of the solvent under reduced pressure, the residue was purified by silica gel flash column chromatography [isocratic eluent: EtOAc : MeOH = 7 : 1] to afford tricycle *S*-**53** (0.25 g, 54%) as white solid.

**53:** $R_f = 0.32$ [EtOAc : MeOH = 7 : 1]; mp = 74–77 °C; $[\alpha]_D^{20} = +4.1$ ° [c = 2, $CDCl_3$]; $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.37 – 1.44 (m, 2 H), 1.51 (ddt, 1 H, *J* = 25.5, 13.0, 4.0 Hz), 1.58 – 1.63 (m, 2 H), 1.66 – 1.70 (m, 1 H), 1.84 – 1.89 (m, 2 H), 1.90 – 1.96 (m, 2 H), 2.27 – 2.32 (m, 3 H), 2.34 – 2.40 (m, 3 H), 2.78 (td, 1 H, *J* = 13.5, 2.5 Hz), 3.05 – 3.08 (m, 1 H), 3.87 (dd, 1 H, *J* = 13.5, 1.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 17.8, 22.2, 24.7, 26.6, 27.3, 28.1, 32.4, 35.8, 48.2, 57.1, 108.1, 159.4, 194.5; IR (film) cm$^{-1}$ 2934m, 2853w, 1616m, 1560s, 1437m, 1186w; mass spectrum [EI] *m/e* (% relative intensity) 205 (88) M$^+$, 190 (100), 176 (30), 162 (12), 149 (51), 134 (18), 120 (15); *m/e* calcd for $C_{13}H_{19}NONa$ 228.1364 (M$^+$ + Na), found 228.1355; CSP-HPLC (Chiralcel OD column, IPA/hexane [30 : 70], 0.75 mL/min) τ = 9.9 min (99% *ee*, *S*), for *R*-isomer τ = 7.9 min (determined from scalemic sample of **53** obtained by hydrogenation of cycloadduct **25**).

## SYNTHESIS OF 110. THE EFFECT OF α-METHYL SUBSTITUENT.

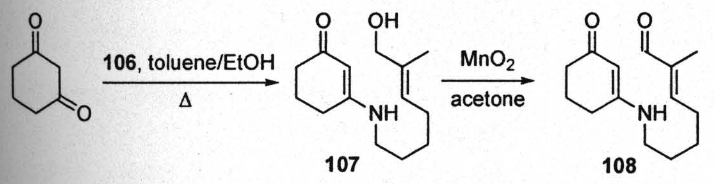
### Amino alcohol 106.



To a suspension of LAH (0.33 g, 8.70 mmol) in THF (15 mL) was added slowly dropwise a solution of azido ester **105**[24] (0.614 g, 2.91 mmol) in THF (10 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 30 min before it was allowed to warm up to rt and was kept at this temperature for an additional 3 h. The excess LAH was quenched by addition of sat aq $Na_2SO_4$ (ca. 2 mL). The resulting white precipitate was filtered off and the filter cake was washed with MTBE (2 × 10 mL). The filtrate was dried over $Na_2SO_4$ and concentrated under reduced pressure to yield amino alcohol **106** (335.0 mg) as colorless oil that was used for the next step without further purification.

**106:** $^1$H NMR (300 MHz, $CDCl_3$) δ 1.30 – 1.51 (m, 7 H), 1.67 (s, 3 H), 2.06 (q, 2 H, $J$ = 6.9 Hz), 2.69 (t, 2 H, $J$ = 6.9 Hz), 4.00 (s, 2 H), 5.41 (td, 1 H, $J$ = 6.9, 1.2 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 13.9, 26.9, 27.4, 33.0, 42.0, 68.7, 125.7, 135.4; IR (film) cm$^{-1}$ 3286brs, 2928s, 2856s, 1582w, 1456m, 1017m; mass spectrum [EI] *m/e* (% relative intensity) 142 (1) M$^+$ – 1, 126 (23), 110 (65), 93 (66), 82 (18), 67 (29), 56 (100).

**Amide 108.**



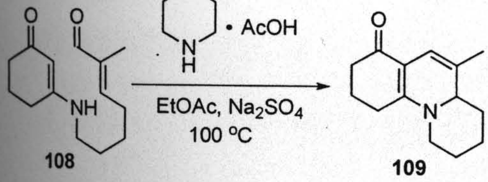
A mixture of crude amino alcohol **106** (0.335 g, 2.34 mmol) and 1,3-cyclohexanedione (0.26 g, 2.32 mmol) in toluene (8 mL) and EtOH (2 mL) was heated at 80 °C overnight. After which, the solvent were removed under reduced pressure, and the crude residue was purified via silica gel flash column chromatography [gradient eluent: $CH_2Cl_2$ to $CH_2Cl_2$/MeOH (11 : 1)] to give amide **107** (296.0 mg, 43% over two steps) as a yellow oil.

**107:** $R_f$ = 0.18 [$CH_2Cl_2$ : MeOH = 10 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.42 (quint, 2 H, $J$ = 7.5 Hz), 1.60 (quint, 2 H, $J$ = 7.5 Hz), 1.65 (s, 3 H), 1.94 (quint, 2 H, $J$ = 6.5 Hz), 2.06 (q, 2 H, $J$ = 7.5 Hz), 2.29 (t, 2 H, $J$ = 6.5 Hz), 2.32 (t, 2 H, $J$ = 6.5 Hz), 2.58 (brs, 1 H, OH), 3.05 (dd, 2 H, $J$ = 13.0, 7.5 Hz), 3.99 (s, 2 H), 5.01 (brs, 1 H, NH), 5.10 (s, 1 H), 5.38 (td, 1 H, $J$ = 7.5, 1.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 13.9, 22.2, 26.8, 27.0, 27.9, 29.9, 36.5, 42.9, 68.6, 96.7, 124.9, 135.9, 164.9, 197.6; mass spectrum [EI] *m/e* (% relative intensity) 237 (34) M$^+$, 220 (25), 208 (13), 176 (14), 164 (19), 152 (43), 138 (62), 125 (100).

According to the general procedure, oxidation of alcohol **107** (295.6 mg, 1.25 mmol) with activated $MnO_2$ (88%, 2.50 g, 25.30 mmol) in acetone (9 mL) afforded aldehyde **108** (231.8 mg, 79%) as a yellow oil.

**108:** $R_f$ = 0.31 [$CH_2Cl_2$: MeOH = 10 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.49 – 1.56 (m, 2 H), 1.59 – 1.65 (m, 2 H), 1.68 (s, 3 H), 1.90 (quint, 2 H, *J* = 6.5 Hz), 2.24 (t, 2 H, *J* = 7.5 Hz), 2.32 (t, 2 H, *J* = 6.5 Hz), 2.35 (t, 2 H, *J* = 6.5 Hz), 3.06 (dd, 2 H, *J* = 13.5, 6.5 Hz), 5.03 (s, 1 H), 5.64 (brs, 1 H, NH), 6.42 (td, 1 H, *J* = 7.5, 1.0 Hz), 9.3 (s, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 9.3, 22.1, 25.9, 28.2, 28.6, 29.7, 36.5, 42.7, 96.3, 139.8, 153.9, 165.1, 195.2, 197.2; IR (film) cm$^{-1}$ 3258brm, 3073w, 2928s, 2857m, 1683m, 1557s, 1256m, 1190m; mass spectrum [EI] *m/e* (% relative intensity) 235 (39) M$^+$, 218 (5), 204 (32), 192 (6), 178 (18), 164 (23), 152 (100), 138 (41), 124 (71); *m/e* calcd for $C_{14}H_{22}NO_2$ (M$^+$ + H) 236.1651, found 236.1626.

**Cycloadduct 109.**

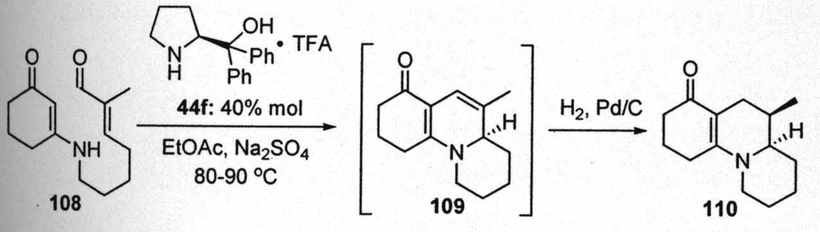


As in the general procedure, the cycloaddition of **108** (133.3 mg, 0.57 mmol) via treatment with piperidinium acetate (82.3 mg, 0.57 mmol) in EtOAc (10 mL) at 100 °C overnight to afford **109** (55.6 mg, 45%) as yellow oil upon purification on silica gel column [gradient eluent: $CH_2Cl_2$ to $CH_2Cl_2$/MeOH (11 : 1)].

109: $R_f$ = 0.40 [$CH_2Cl_2$ : MeOH = 10 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.47 – 1.62 (m, 3 H), 1.67 (s, 3 H), 1.69 – 1.72 (m, 1 H), 1.77 – 1.80 (m, 1 H), 1.91 – 1.98 (m, 3 H), 2.26 (ddd, 1 H, *J* = 17.0, 7.5, 6.0 Hz), 2.31 (ddd, 1 H, *J* = 17.0, 7.5, 6.0 Hz), 2.41 (dt, 1 H, *J* = 16.5, 6.5 Hz), 2.48

(dt, 1 H, $J$ = 16.5, 6.5 Hz), 2.78 (td, 1 H, $J$ = 14.0, 2.5 Hz), 3.95 – 3.98 (m, 2 H), 6.36 (s, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.8, 21.3, 25.5, 25.7, 26.5, 30.1, 35.3, 48.8, 65.3, 106.0, 115.6, 121.8, 157.7, 191.2.

**Tricycle 110.**

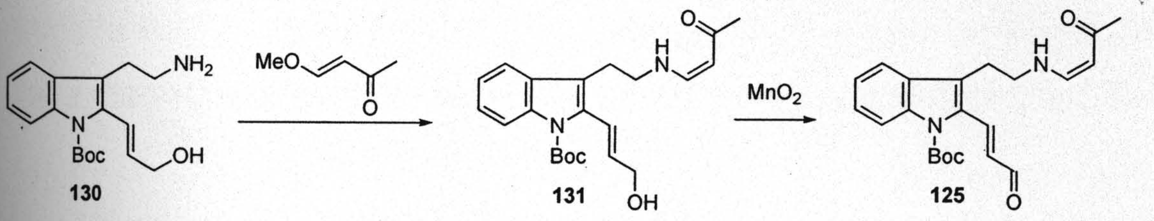


A mixture of amide **108** (69.7 mg, 0.30 mmol), amine salt **44f** (43.3 mg, 0.12 mmol), and $Na_2SO_4$ (ca. 50.0 mg) in EtOAc (6 mL) was heated at 100 °C overnight. About 40% conversion of the starting material to the desired cycloadduct **109** was observed via $^1$H NMR. The cycloadduct was isolated by purification on silica gel column [gradient eluent: $CH_2Cl_2$ to $CH_2Cl_2$/MeOH (11 : 1)] and subjected to hydrogenation conditions at 1 atm $H_2$ over 10% Pd/C (80 mg) in MeOH (4 mL). After 14 h, the Pd catalyst was filtered off using Celite, and MeOH was evaporated under reduced pressure to give a crude residue that was purified by silica gel flash column chromatography [isocratic eluent: EtOAc : MeOH (8 : 1)], providing tricycle **110** as a single diastereomer (17.3 mg, 67% over 2 steps based on 40% conversion).

**110:** $R_f$ = 0.42 [EtOAc : MeOH = 7 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 0.98 (d, 3 H, $J$ = 6.5 Hz ), 1.27 (ddd, 1 H, $J$ = 25.0, 12.5, 3.5 Hz), 1.38 (ddt, 1 H, $J$ = 26.0, 12.5, 4.0 Hz) 1.51 – 1.66 (m, 3 H), 1.87 – 2.00 (m, 5 H), 2.27 – 2.38 (m, 3 H), 2.47 (dt, 1 H, $J$ = 16.5, 5.0 Hz), 2.53 (dd, 1 H, $J$ = 16.0, 4.0 Hz), 2.93 (td, 1 H, $J$ = 14.0, 2.5 Hz), 3.10 (dt, 1 H, $J$ = 11.5, 2.0 Hz), 3.90 (dt, 1 H, $J$ = 14.0, 2.0 Hz); $^{13}$C NMR (75 MHz, $CDCl_3$) δ 17.4, 22.0, 24.6, 25.0, 25.1, 26.7, 27.0, 29.7, 35.7, 49.6, 62.4, 107.4, 158.4, 194.4; IR (film) cm$^{-1}$ 2942s, 2853m, 1606m, 1557s, 1432m, 1178w; mass spectrum [EI] *m/e* (% relative intensity) 219 (38) M$^+$, 204 (100), 190 (38), 176 (9), 162 (8), 148 (12),; *m/e* calcd for $C_{14}H_{22}NO$ 220.1701 (M$^+$ + H), found 220.1694; CSP-HPLC (Chiralcel OD column, IPA/hexane [10 : 90], 0.75 mL/min) $\tau$ = 14.7 min (48%), $\tau$ = 17.6 min (52%).

## SYNTHESIS OF ENANTIOMERICALLY ENRICHED *R*-(+)-DEPLANCHEINE.

### Aldehyde 125.

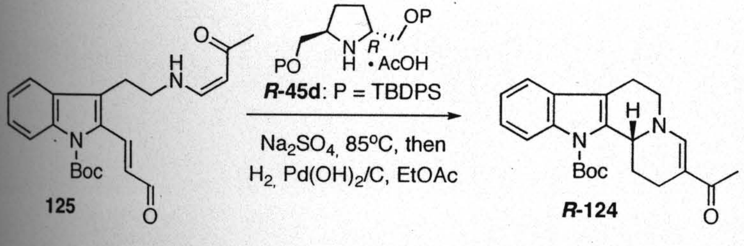


Crude amino alcohol **130**[29,33] (500.0 mg, 1.58 mmol) was dissolved in $CH_2Cl_2$ (5 mL). Triethylamine (0.35 mL, 2.50 mmol) was added followed by addition of 4-methoxy-3-buten-2-one (0.20 mL, 1.80 mmol), and the reaction mixture was allowed to stir at rt for 20 h. Purification of the concentrated mixture by silica gel column chromatography afforded vinylogous amide **131** as a yellow oil (200.0 mg, 33%).

**131**: $R_f$ = 0.21 (EtOAc : hexane = 4 : 1); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$ 1.61 (s, 9 H), 1.95 (s, 3 H), 2. 96 (t, 2 H, *J* = 6.5 Hz), 3.34 (q, 2 H, *J* = 6.5 Hz), 3.98 (brs, 1 H, OH), 4.23 (dd, 2 H, *J* = 5.5, 1.5 Hz), 4.77 (d, 1 H, *J* = 7.5 Hz), 5.89 (dt, 1 H, *J* = 16.0, 5.5 Hz), 6.20 (dd, 1 H, *J* = 13.5, 7.5 Hz), 6.58 (d, 1 H, *J* = 16.0 Hz), 7.15 (t, 1 H, *J* = 7.5 Hz), 7.21 (t, 1 H, *J* = 7.5 Hz), 7.34 (d, 1 H, *J* = 7.5 Hz), 8.04 (d, 1 H, *J* = 7.5 Hz), 9.82 (brs, 1 H, NH); $^{13}$C NMR (125 MHz, $CDCl_3$) $\delta$ 25.8, 28.3, 28.9, 49.4, 63.2, 84.1, 93.7, 115.6, 115.7, 118.2, 122.2, 122.8, 124.7, 129.4, 133.0, 135.8, 135.9, 150.4, 153.3, 197.7; IR (thin film) cm$^{-1}$ 3440brs, 3109s, 2970s, 2863s, 1725s, 1622s; mass spectrum (APCI): m/e (% relative intensity) 385 (1) M+H$^+$, 367 (10), 311 (45), 267 (100), 182 (80), 170 (30); HRMS: m/e calcd for $C_{22}H_{28}N_2O_4Na$ 407.1947 (M$^+$+Na), found 407.1921.

A solution of alcohol **131** (200.0 mg, 0.52 mmol) in acetone (3 mL) was stirred with $MnO_2$ (1.02 g, 10.4 mmol, 20 equiv) at rt for 6 h. Filtration through Celite and removal of the solvent under reduced pressure afforded the pure aldehyde **125** (133.0 mg, 67 %) as a yellow oil. **125:** $R_f$ = 0.33 (EtOAc : hexane = 4 : 1); $^1$H NMR (500 MHz, $CDCl_3$) δ 1.67 (s, 9 H), 2.01 (s, 3 H), 3.07 (t, 2 H, *J* = 6.5 Hz), 3.45 (q, 2 H, *J* = 6.5 Hz), 4.92 (d, 1 H, *J* = 12.0 Hz), 6.33 (dd, 1 H, *J* = 16.0, 7.5 Hz), 6.42 (dd, 1 H, *J* = 12.0, 7.5 Hz), 7.28 (td, 1 H, *J* = 7.5, 1.0 Hz), 7.40 (td, 1 H, *J* = 7.5, 1.0 Hz), 7.53 (d, 1 H, *J* = 7.5 Hz), 7.88 (d, 1 H, *J* = 16.0 Hz), 8.11 (d, 1 H, *J* = 7.5 Hz), 9.68 (d, 1 H, *J* = 7.5 Hz), 9.83 (brs, 1 H, NH); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 27.4, 28.4, 29.2, 48.9, 85.4, 94.7, 116.0, 119.7, 121.7, 123.6, 126.8, 129.3, 130.2, 132.4, 137.0, 143.6, 150.4, 152.1, 193.7, 197.8; IR (thin film) cm$^{-1}$ 3452brs, 3024s, 2970s, 2844m, 1731s, 1683s, 1652s; mass spectrum (APCI): m/e (% relative intensity) 383 (5) M+H$^+$, 283 (75), 263 (30), 198 (100), 180 (40), 170 (50); HRMS: m/e calcd for $C_{22}H_{26}N_2O_4Na$ 405.1790 (M$^+$+Na), found 405.1802.

**Tetracycle *R*-124.**

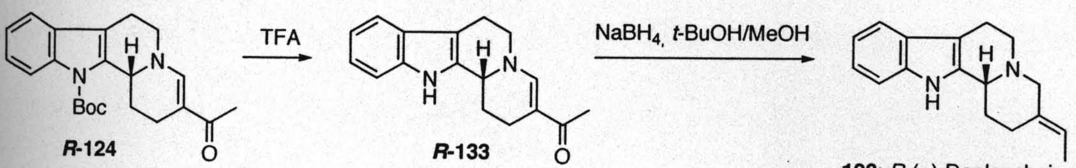


To a solution of aldehyde **125** (27.4 mg, 0.072 mmol) in EtOAc (3 mL) were added $Na_2SO_4$ (~100 mg), amine salt ***R*-45d**[34] (20.0 mg, 0.033 mmol) and AcOH (2 μL, 0.035 mmol).

The mixture was sealed under nitrogen and heated in an 85°C oil bath for 2 h. After cooling the mixture, Pd/C (25 mol%) was added and the mixture was stirred under 1 atm of $H_2$ for 12 h. Filtration through Celite, removal of solvent under reduced pressure, and purification of the crude residue via silica gel column chromatography [EtOAc : hexanes = 2 : 3] afforded the cycloadduct **124** (6.0 mg, 23 %).

***R*-124**: $R_f = 0.16$ (EtOAc); $[\alpha]_D^{20} = +44.8°$ [c = 0.50, $CHCl_3$]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.31 (ddd, 1 H, *J* = 24.0, 13.0, 5.5 Hz), 1.59 (s, 9 H), 2.05 (s, 3 H), 2.24 – 2.30 (m, 1 H), 2.53 (dd, 1 H, *J* = 13.0, 5.5, 4.5, 2.5 Hz), 2.67 (dd, 1 H, *J* = 16.5, 2.5 Hz), 2.73 (ddd, 1 H, *J* = 15.5, 2.5, 2.0 Hz), 2.78 (ddd, 1 H, *J* = 10.0, 5.5, 2.5 Hz), 3.57 (ddd, 1 H, *J* = 13.0, 5.5, 1.5 Hz), 3.63 (dd, 1 H, *J* = 13.0, 3.5 Hz), 4.76 (dd, 1 H, *J* = 10.0, 1.5 Hz), 7.19 (td, 1 H, *J* = 7.5, 1.0 Hz), 7.25 (td, 1 H, *J* = 7.5, 1.0 Hz), 7.36 (d, 1 H, *J* = 7.5 Hz), 7.37 (s, 1H), 8.08 (d, 1 H, *J* = 7.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 21.2, 22.8, 24.2, 28.4, 29.5, 51.0, 54.3, 86.4, 115.9, 116.5, 118.2, 123.2, 124.9, 128.6, 134.5, 137.0, 148.2, 150.1, 179.5, 193.7; IR (thin film) cm$^{-1}$ 2974m, 2924m, 1728s, 1660m, 1588s, 1456m, 1402m; mass spectrum (APCI): m/e (% relative intensity) 367 (1) M+H$^+$, 311 (100) M$^+$-Boc, 267 (45), 261 (10), 170 (20), 144 (15); HRMS: m/e calcd for $C_{22}H_{26}N_2O_3Na$ 389.1841 (M$^+$+Na), found 389.1830; CSP-HPLC (Chiralcel OD column, IPA/hexane [10 : 90], 0.75 mL/min) τ = 20.2 min (31 %, *S*), τ = 24.3 min (69 %, *R*); 38% *ee*.

### *R*-(+)-Deplancheine 123.



123: *R*-(+)-Deplancheine

A solution of annulation product ***R*-124** (6.20 mg, 0.017 mmol) in $CH_2Cl_2$ : TFA (1 : 1, 0.5 mL) was stirred at rt for 20 h. The reaction mixture was diluted with $CH_2Cl_2$ (2 mL) and 10% aq $NH_4OH$ (2 mL). The layers were separated and aqueous layer was extracted with $CH_2Cl_2$ (3 x 2 mL). The combined organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure to give desired ***R*-133** (4.5 mg, 95%) as a yellow oil which was used for the next step without further purification.

***R*-133**: $R_f$ = 0.12 (EtOAc : hexanes = 4 : 1); $[\alpha]_D^{20}$ = +18.0 ° [c = 0.1, $CHCl_3$]; $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.75 (ddd, 1H, *J* = 24.0, 12.5, 5.0 Hz), 2.22 (s, 3H), 2.34 (ddd, 1 H, *J* = 17.0, 16.5, 5.0 Hz), 2.45 – 2.50 (m, 1 H), 2.76 (ddd, 1 H, *J* = 16.5, 5.0, 2.5 Hz), 2.85 (dddd, 1 H, *J* = 16.5, 4.0, 2.5, 1.0 Hz), 2.94 – 3.01 (m, 1 H), 3.68 (ddd, 2 H, *J* = 24.0, 12.5, 5.0 Hz), 4.54 (brd, 1 H, *J* = 11.0 Hz), 7.14 (td, 1 H, *J* = 7.5, 1.0 Hz), 7.21 (td, 1 H, *J* = 7.5, 1.0 Hz), 7.37 (d, 1 H, *J* = 8.0 Hz), 7.45 (s, 1 H), 7.51 (d, 1 H, *J* = 8.0 Hz), 8.17 (brs, 1 H, NH); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 20.0, 22.2, 24.1, 28.6, 51.7, 52.4, 81.4, 108.4, 111.3, 118.4, 120.1, 122.4, 127.0, 132.9, 139.5, 148.5, 193.8; IR (neat) $cm^{-1}$ 3228m, 2960m, 1574s, 1440m, 1402m; mass spectrum (APCI): m/e (% relative intensity) 267 (100) $M+H^+$, 263 (10), 238 (5), 223 (5), 196 (5), 170 (70), 144 (35); HRMS: m/e calcd for $C_{17}H_{19}N_2O$ 267.1497 ($M^+$+H), found 267.1526.

Amide ***R*-133** (4.50 mg, 0.017 mmol) was dissolved in *t*-BuOH (1 mL) and $NaBH_4$ (7.00 mg, 0.18 mmol) was added then. Reaction mixture was refluxed with occasional addition of MeOH (0.10 mL) in portions for 6 h. When most of the starting material was consumed as indicated by TLC analysis (eluent EtOAc : hexanes = 4 : 1), the reaction mixture was cooled down to room temperature, water (1.5 mL) was added and excess of *t*-BuOH was removed in vacuo. The residue (containing *E*- and *Z*-deplancheine as 9 : 1 mixture) was purified by preparative silica gel TLC plate [eluent EtOAc : hexanes = 2 : 1] to yield enantiomerically enriched *R*-(+)-deplancheine **(123)** (1.50 mg, 87 % BORSM) as yellowish gummy solid. The spectral data of **123** was in accordance with those reported in literature.[32]

***R*-123**: $R_f$ = 0.20 (EtOAc : hexanes = 4 : 1); $[\alpha]_D^{20}$ = +19.7 ° [c = 0.2, $CHCl_3$]; 38.0 % ee (31 % *S*, 69 % *R*). Lit.[32b] $[\alpha]_D^{20}$ = +52.0 ° [c = 1, $CHCl_3$]; $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.55 – 1.61 (m, 1 H), 1.64 (d, 3 H, *J* = 7.0 Hz), 2.01 (br t, 1 H, *J* = 10.0 Hz), 2.18 – 2.20 (m, 1 H), 2.62 – 2.69 (m, 1 H), 2.72 – 2.76 (m, 1 H), 2.80 – 2.85 (m, 1 H), 3.01 – 3.13 (m, 3 H), 3.36 (d, 1 H, *J* = 12.5 Hz), 3.42 – 3.45 (m, 1 H), 5.45 (q, 1 H, *J* = 7.0 Hz), 7.09 (td, 1 H, *J* = 7.5, 1.0 Hz), 7.14 (td, 1 H, *J* = 7.5, 1.0 Hz), 7.32 (d, 1 H, *J* = 8.0 Hz), 7.48 (d, 1 H, *J* = 8.0 Hz), 7.73 (brs, 1 H, NH); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 12.9, 21.8, 26.1, 30.5, 53.1, 60.4, 63.6, 108.4, 110.9, 118.4, 119.6, 119.7, 121.6, 127.7, 134.1, 134.8, 136.4; IR (neat) $cm^{-1}$ 3415s, 3123m, 2867s, 2790m, 1436m; mass spectrum (GC/MS, EI): m/e (% relative intensity) 252 (90) $M^+$, 251 (100), 237 (20), 223 (25), 169 (50), 156 (30); HRMS: m/e calcd for $C_{17}H_{21}N_2$ 253.1705 ($M^+$+H), found 253.1678.

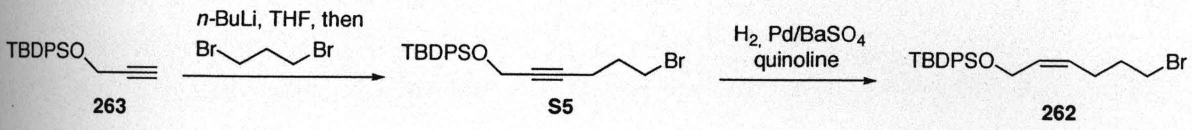
## DEPLANCHEINE COMPARISON NMR TABLE.

| NMR Data for the Synthetic Deplancheine | | Reported Data for Deplancheine[32a] | |
|---|---|---|---|
| $^{1}$H NMR, δ, *J* | $^{13}$C NMR, δ (Δδ with lit. data) | $^{1}$H NMR, δ | $^{13}$C NMR, δ |
| 1.55 – 1.61 | 12.9 (0.2) | 1.52 – 1.60 | 12.7 |
| 1.64 (0.01) | 21.8 (0.2) | 1.63 | 21.6 |
| 2.01 | 26.1 (0.2) | 1.95 – 2.02 | 25.9 |
| 2.18 – 2.20 | 30.5 (0.2) | 2.15 – 2.20 | 30.3 |
| 2.62 – 2.69 | 53.1 (0.2) | 2.61 – 2.75 | 52.9 |
| 2.72 – 2.76 | 60.4 (0.2) | | 60.2 |
| 2.80 – 2.85 | 63.6 (0.1) | 2.80 – 2.84 | 63.5 |
| 3.01 – 3.13 | 108.4 (0.0) | 2.98 – 3.11 | 108.4 |
| 3.36 | 110.9 (0.2) | 3.32 – 3.35 | 110.7 |
| 3.42 – 3.45 | 118.4 (0.2) | 3.38 – 3.41 | 118.2 |
| 5.45 | 119.6 (0.2) | 5.43 | 119.4 |
| 7.09 | 119.7 (0.3) | 7.06 – 7.15 | 119.4 |
| 7.14 | 121.6 (0.3) | | 121.3 |
| 7.32 | 127.7 (0.3) | 7.30 – 7.33 | 127.4 |
| 7.48 | 134.1 (0.1) | 7.46 – 7.48 | 134.0 |
| 7.73 | 134.8 (0.2) | 7.76 | 134.6 |
| | 136.4 (0.4) | | 136.0 |

## PART 2.

## MODEL STUDY.

### Bromide 262.

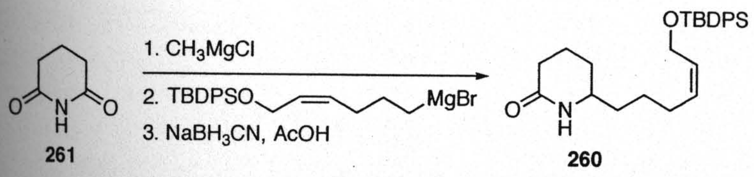


To a solution of TBDPS-protected propargyl alcohol[53] (49.4 g, 0.168 mol) in THF (200 mL) was added *n*-BuLi (2.5 *M* in hexanes, 84.0 mL, 0.210 mol) at -78 °C. The reaction was stirred at this temperature for 20 min before 1,3-dibromopropane (87.0 mL, 0.853 mol) was added in one portion. The resulting mixture was allowed to warm up to rt and was stirred for 72 h before it was quenched with $H_2O$ (100 mL). Aqueous layer was back-extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic layers were washed with sat aq NaCl (100 mL) and dried over $Na_2SO_4$. Solvents and excess of 1,3-dibromopropane were removed under reduced pressure and the crude residue was purified via Kugelrohr distillation. Bromide **S5** (46.1 g, 66%) was collected at 170-180 °C (0.1 mmHg) as pale yellow oil.

S5: $R_f = 0.52$ [10% EtOAc in hexanes]; $^1$H NMR (300 MHz, $CDCl_3$): δ 1.05 (s, 9 H), 1.95 (quint, 2 H, $J = 6.6$ Hz), 2.34 (tt, 2 H, $J = 6.6, 2.1$ Hz), 3.44 (t, 2 H, $J = 6.6$ Hz), 4.31 (t, 2 H, $J = 2.1$ Hz), 7.38 – 7.42 (m, 6 H), 7.72 (d, 4 H, $J = 7.5$ Hz).

A suspension of 5% Pd/$BaSO_4$ catalyst (0.660 g) in petroleum ether (110 mL) was pre-reduced via hydrogenation until the color changed from complete brown to black (within ~ 20-30 min). After which, quinoline (0.700 mL) was added to the above suspension and the resulting mixture was stirred for 15 min before a solution of bromide **S1** (24.2 g, 58.3 mmol) in petroleum ether (110 mL) was added. The reaction mixture was hydrogenated with an $H_2$-balloon for 9 h until complete consumption of the starting material was observed through $^1$H NMR. The excess solvent was removed under reduced pressure and the crude residue was purified via Kugelrohr distillation. Bromide **262** (21.7 g, 89%) was collected at 160-165 °C (0.1 mmHg) as a yellow oil. **262:** $R_f$ = 0.47 [10% EtOAc in hexanes]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9 H), 1.81 (quint, 2 H, $J$ = 7.0 Hz), 2.00 (q, 2 H, $J$ = 7.5 Hz), 3.29 (t, 2 H, $J$ = 7.0 Hz), 4.26 (d, 2 H, $J$ = 6.5 Hz), 5.32 – 5.37 (m, 1 H), 5.64 – 5.68 (m, 1 H), 7.37 – 7.44 (m, 6 H), 7.68 (dd, 4 H, $J$ = 7.5, 1.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.3, 26.2, 27.0, 32.6, 33.2, 60.4, 127.9, 128.9, 129.8, 130.9, 133.9, 135.8; IR (Film) cm$^{-1}$ 2932s, 2853s, 1473m, 1429s, 1109s, 701s; mass spectrum (TOF ES): m/e (% relative intensity) 439 (100) $M^+$ + Na, 441 (100) $M^+$ + Na, 359 (40), 250 (25), 227 (90).

**Lactam 260.**

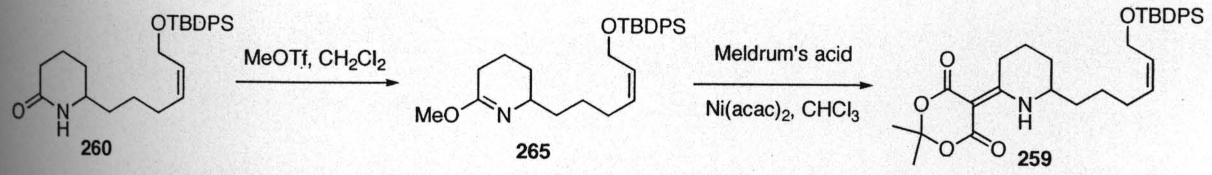


To a solution of glutarimide **261** (2.40 g, 21.2 mmol) in THF (100 mL) was added $CH_3MgCl$ (3 *M* in THF, 7.50 mL, 22.5 mmol) dropwise at 0 °C. The reaction mixture was allowed to warm up to rt and was stirred for 30 min and then cooled back down to 0 °C. A warm solution of Grignard reagent (35-40 °C to prevent precipitation) in THF (30 mL) prepared from bromide **262** (13.2 g, 31.7 mmol) and Mg (0.850 g, 35.0 mmol) through activation using dibromoethane (0.150 mL, 1.74 mmol) was added *via* a cannula. The resulting reaction mixture was stirred for 12 h at rt before $NaBH_3CN$ (1.37 g, 23.4 mmol) and HOAc (4.5 mL) were added successively. After stirring at ambient temperature for 45 min, reaction was quenched with sat aq

$NaHCO_3$ solution (65 mL). After layer separation, the organic phase was washed with an additional portion of $NaHCO_3$ solution (65 mL). Aqueous washes were back-extracted with EtOAc (3 × 70 mL). The combined organic layers were washed with sat aq NaCl (2 × 50 mL) and dried over $Na_2SO_4$. After solvent removal under reduced pressure, the crude residue was purified through two silica gel columns (1st: 0%-50% acetone in EtOAc; 2nd: 7%-10% MeOH in $CH_2Cl_2$) to afford lactam **260** (5.96 g, 65%) as thick colorless oil.

**260:** $R_f = 0.43$ [EtOAc : acetone = 1 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.05 (s, 9 H), 1.25 – 1.32 (m, 3 H), 1.34 – 1.38 (m, 2 H), 1.60 – 1.68 (m, 1 H), 1.82 – 1.89 (m, 4 H), 2.25 (ddd, 1 H, $J$ = 17.0, 11.0, 6.0 Hz), 2.36 (brd, 1 H, $J$ = 17.0 Hz), 3.26 – 3.30 (m, 1 H), 4.23 (d, 2 H, $J$ = 6.0 Hz), 5.36 (dt, 1 H, $J$ = 11.0, 7.5 Hz), 5.63 (dt, 1 H, $J$ = 11.0, 6.0 Hz), 5.90 (brs, 1 H), 7.37 – 7.44 (m, 6 H), 7.68 (dd, 4 H, $J$ = 7.5, 1.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.3, 19.9, 25.3, 27.0, 27.4, 28.4, 31.5, 36.5, 53.2, 60.4, 127.8, 129.8, 130.1, 130.2, 134.0, 135.8, 172.7; IR (Film) cm$^{-1}$ 3219m, 3072m, 2932s, 2858s, 1666s, 1428m, 1111s, 1083s; mass spectrum (APCI): m/e (% relative intensity) 436 (10) M$^+$ + H, 358 (100); *m/e* calcd for $C_{27}H_{37}NO_2SiNa$ (M$^+$ + Na) 458.2491, found 458.2489.

**Meldrum's Acid Derivative 259. Route A.**



To a solution of lactam **260** (2.32 g, 5.33 mmol) in $CH_2Cl_2$ (20 mL) was added freshly distilled MeOTf (0.750 mL, 6.62 mmol). The reaction mixture was stirred at ambient temperature for 10 h before the excess solvent was evaporated under reduced pressure. The oily residue was treated with cold 5% aq $Na_2CO_3$ (40 mL), and the resulting mixture was extracted with $CH_2Cl_2$ (3 × 30 mL), washed with sat aq NaCl (2 × 40 mL), and dried over $Na_2SO_4$. Removal of the excess solvent gave lactim ether **265** (2.07 g) as colorless oil, which was used for the next step without further purification.

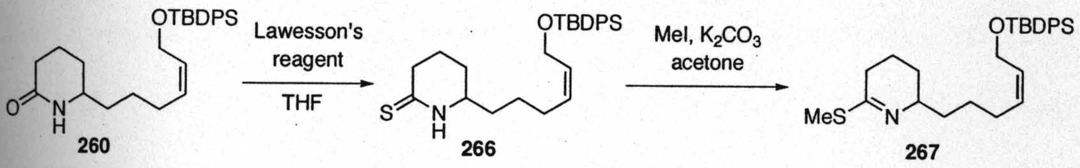
**265:** $R_f$ = 0.66 [30% EtOAc in hexanes]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 9 H), 1.06 – 1.13 (m, 1 H), 1.29 – 1.50 (m, 4 H), 1.53 – 1.60 (m, 1 H), 1.67 (ddd, 1 H, *J* = 13.0, 8.0, 4.0 Hz), 1.74 – 1.80 (m, 1 H), 1.90 (q, 2 H, *J* = 7.0 Hz), 2.05 (dddd, 1 H, *J* = 17.5, 9.0, 7.0, 2.0 Hz), 2.12 (ddd, 1 H, *J* = 17.5, 7.0, 4.0 Hz), 3.26 (brs, 1 H), 3.58 (s, 3 H), 4.26 (d, 2 H, *J* = 6.5 Hz), 5.44 (dt, 1 H, *J* = 11.0, 7.0 Hz), 5.60 (dt, 1 H, *J* = 11.0, 6.5 Hz), 7.37 – 7.43 (m, 6 H), 7.69 (dd, 4 H, *J* = 7.5, 1.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.4, 19.6, 25.8, 26.4, 27.0, 27.9, 28.1, 37.9, 51.8, 55.9, 60.5, 127.8, 129.3, 129.7, 131.4, 134.2, 135.8, 161.9; IR (Film) cm$^{-1}$ 2928s, 2856s, 1680s, 1428m, 1231s, 1110s 1086s; *m/e* calcd for $C_{28}H_{40}NO_2Si$ ($M^+$ + H) 450.2828, found 450.2831.

To a solution of the above lactim ether **265** (2.07 g, 4.60 mmol) in $CHCl_3$ (30 mL) were successively added Meldrum's acid (0.720 g, 5.27 mmol) and $Ni(acac)_2$ catalyst (*ca.* 50.0 mg). The reaction mixture was refluxed for 18 h under $N_2$ atmosphere. Upon solvent removal under reduced pressure, the crude residue was purified by silica gel flash column chromatography (20%-50% EtOAc in hexanes) to give Meldrum's acid derivative **259** (1.14 g, 38% over 2 steps) as colorless oil.

**259:** $R_f$ = 0.53 [50% EtOAc in hexanes]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 9 H), 1.33 – 1.42 (m, 2 H), 1.43 – 1.58 (m, 3 H), 1.61 – 1.65 (m, 1 H), 1.67 (s, 3 H), 1.68 (s, 3 H), 1.89 – 1.94 (m, 4 H), 2.96 (ddd, 1 H, *J* = 19.5, 10.0, 6.0 Hz), 3.33 (brd, 1 H, *J* = 19.5 Hz), 3.36 – 3.42 (m, 1 H), 4.23 (d, 2 H, *J* = 6.0 Hz), 5.39 (dt, 1 H, *J* = 11.0, 7.0 Hz), 5.65 (dt, 1 H, *J* = 11.0, 6.0 Hz), 7.37 – 7.44 (m, 6 H), 7.69 (dd, 4 H, *J* = 7.5, 1.5 Hz), 11.66 (brs, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ

18.2, 19.3, 25.4, 26.3, 26.9, 27.0, 27.1, 27.2, 29.4, 35.8, 53.4, 60.4, 83.1, 102.6, 127.8, 129.8, 130.0, 130.2, 134.0, 135.7, 163.2, 167.8, 174.0; IR (Film) cm$^{-1}$ 3071w, 2928s, 2858s, 1713s; 1657s, 1599s, 1391s, 1331s, 1206m, 1110m; mass spectrum (APCI): m/e (% relative intensity) 518 (20) $M^+ - CO_2 + H$, 492 (30), 458 (45), 434 (55), 426 (100); *m/e* calcd for $C_{33}H_{43}NO_5SiNa$ ($M^+ + Na$) 584.2808, found 584.2830.

**Thioimidate 267.**



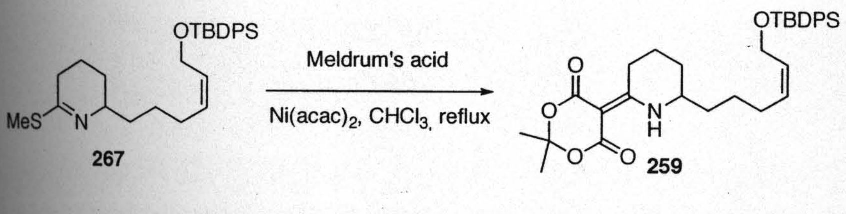
To a solution of lactam **260** (0.668 g, 1.53 mmol) in THF (10 mL) was added Lawesson's reagent (0.470 g, 1.16 mmol), and the resulting mixture was stirred at rt for 1 h. After removal of the excess solvent under reduced pressure, the pure thiolactam **266** (0.647 g, 93%) was isolated by silica gel column chromatography (25% EtOAc in hexanes) as thick pale yellow oil.

**266:** $R_f = 0.46$ [40% EtOAc in hexanes]; $^1$H NMR (500 MHz, CDCl$_3$) δ 1.04 (s, 9 H), 1.30 – 1.36 (m, 3 H), 1.38 – 1.46 (m, 2 H), 1.58 – 1.67 (m, 2 H), 1.80 (dddd, 1 H, $J$ = 15.0, 7.5, 6.0, 4.0 Hz), 1.88 (q, 2 H, $J$ = 6.0 Hz), 2.74 (ddd, 1 H, $J$ = 19.0, 10.5, 6.0 Hz), 2.98 (dt, 1 H, $J$ = 19.0, 4.5 Hz), 3.24 – 3.30 (m, 1 H), 4.23 (d, 2 H, $J$ = 6.0 Hz), 5.37 (dtt, 1 H, $J$ = 11.0, 7.5, 1.5 Hz), 5.65 (dtt, 1 H, $J$ = 11.0, 6.0, 1.5 Hz), 7.37 – 7.45 (m, 6 H), 7.68 (dd, 4 H, $J$ = 8.0, 1.5 Hz), 7.94 (brs, 1 H); $^{13}$C NMR (125 MHz, CDCl$_3$) δ 19.4, 19.8, 25.2, 27.0, 27.2, 27.3, 35.6, 39.3, 56.0, 60.4, 127.9, 129.8, 129.9, 130.4, 134.0, 135.8, 203.5; IR (Film) cm$^{-1}$ 3176m, 3047m, 2930s, 2856s, 1646m, 1554s, 1460m, 1109s 1080s; mass spectrum (APCI): m/e (% relative intensity) 452 (80) $M^+ + H$, 420 (15), 374 (100), 358 (15), 196 (25).

To a solution of the above thiolactam **266** (1.47 g, 3.26 mmol) in acetone (25 mL) were successively added powdered $K_2CO_3$ (0.900 g, 6.52 mmol) and $CH_3I$ (0.400 mL, 6.42 mmol). The reaction mixture was stirred at rt for 6 h and then solids were filtered. After solvent removal under reduced pressure, 10% EtOAc in hexanes (20 mL) was added to the crude residue. Precipitate (KI) was filtered off using Celite$^{TM}$ and washed with 10% EtOAc in hexanes (20 mL). Upon concentration of the mother liquor under reduced pressure, thiol ether **267** (1.38 g, 91%) was obtained as pale yellow oil.

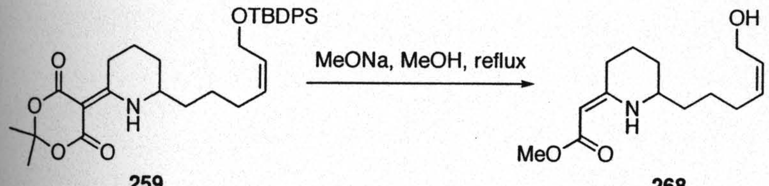
**267:** $R_f$ = 0.68 [40% EtOAc in hexanes]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 9 H), 1.12 – 1.20 (m, 1 H), 1.34 – 1.49 (m, 3 H), 1.51 – 1.64 (m, 2 H), 1.70 – 1.78 (m, 2 H), 1.92 (q, 2 H, $J$ = 7.0 Hz), 2.21 – 2.26 (m, 2 H), 2.24 (s, 3 H), 3.28 – 3.34 (m, 1 H), 4.26 (d, 2 H, $J$ = 6.0 Hz), 5.44 (dt, 1 H, $J$ = 11.5, 7.0 Hz), 5.61 (dt, 1 H, $J$ = 11.5, 6.0 Hz), 7.36 – 7.44 (m, 6 H), 7.69 (dd, 4 H, $J$ = 7.5, 1.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 11.9, 19.4, 19.8, 26.4, 27.0, 27.9, 28.6, 31.6, 37.6, 59.3, 60.5, 127.8, 129.4, 129.8, 131.4, 134.2, 135.8, 163.9; IR (Film) cm$^{-1}$ 3070w, 2931s, 2857s, 1631s, 1472m, 1427m, 1109s 1071s; mass spectrum (APCI): m/e (% relative intensity) 464 (100) $M^+$ – H, 372 (20).

**Meldrum's acid derivative 259. Route B.**



To a solution of the above thiol ether **267** (1.08 g, 2.31 mmol) in $CHCl_3$ (20 mL) were successively added Meldrum's acid (0.350 g, 2.42 mmol) and Ni(acac)$_2$ catalyst (*ca.* 25.0 mg). The reaction mixture was refluxed for 6 h under $N_2$ atmosphere. Upon solvent removal under reduced pressure, the crude residue was purified by silica gel flash column chromatography (40%-50% EtOAc in hexanes) to give Meldrum's acid derivative **259** (1.02 g, 79%) as colorless oil.

**Alcohol 268.**



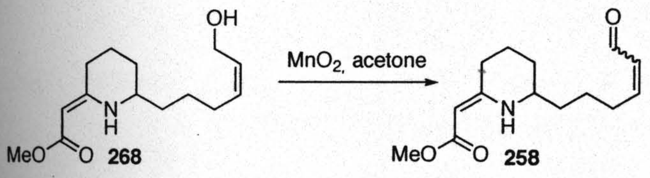
**259** **268**

To a solution of MeONa prepared by dissolving Na metal (0.420 g, 18.3 mmol) in anhyd MeOH (15 mL) was added a solution of compound **259** (1.45 g, 2.58 mmol) in MeOH (10 mL). The reaction mixture was heated to reflux until complete ring-opening and desilylation was observed by TLC analysis (~12 h) as indicated by disappearance of the $KMnO_4$-active spot with $R_f$ = 0.80 in 50% EtOAc in hexanes (TBDPS-protected alcohol **268**). After cooling the reaction mixture to rt, MeOH was evaporated and $H_2O$ (20 mL) was added to the crude residue, and subsequently, aq HCl (3 *M*) was also added dropwise to adjust pH to 5-6. The resulting mixture was extracted with $CHCl_3$ (3 × 25 mL), the combined organic layers were washed with sat aq NaCl (2 × 25 mL) and dried over $Na_2SO_4$. Upon removal of excess solvents under reduced pressure, the crude residue was purified via silica gel flash column chromatorgraphy (20%-60% EtOAc in hexanes). Alcohol **268** (0.430 g, 66%) was isolated as colorless oil.

**268:** $R_f$ = 0.34 [50% EtOAc in hexanes]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.37 (dddd, 1 H, *J* = 13.0, 11.5, 10.0, 3.5 Hz), 1.47 – 1.63 (m, 5 H), 1.70 (brs, 1 H, OH), 1.75 – 1.81 (m, 1 H), 1.90 (ddd, 1 H, *J* = 13.0, 8.5, 4.5 Hz), 2.06 – 2.20 (m, 2 H), 2.33 (q, 2 H, *J* = 4.5 Hz), 3.24 (sextet, 1 H, *J* = 5.0 Hz), 3.62 (s, 3 H), 4.14 – 4.24 (m, 2 H), 4.37 (s, 1 H), 5.55 (dt, 1 H, *J* = 11.0, 7.5

Hz), 5.65 (dtt, 1 H, $J$ = 11.0, 7.0, 1.5 Hz), 8.86 (brs, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.7, 25.7, 27.2, 29.4, 29.5, 36.7, 50.1, 51.8, 58.6, 79.9, 129.5, 132.2, 163.1, 171.4; IR (Film) cm$^{-1}$ 3442s, 2924s, 2860s, 1649s; 1604s, 1338m, 1271s, 1241s, 1168s, 1064m; mass spectrum (APCI): m/e (% relative intensity) 254 (100) $M^+ + H$, 236 (15), 222 (15), 196 (50); *m/e* calcd for $C_{14}H_{24}NO_3$ ($M^+ + H$) 254.1756, found 254.1754.

**Aldehyde 258.**

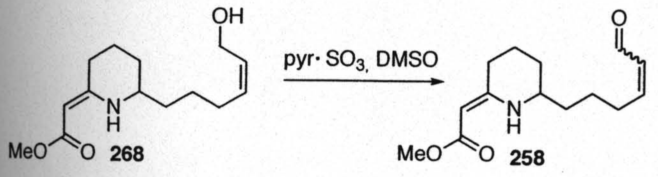


To a solution of alcohol **268** (44.4 mg, 0.180 mmol) in acetone (4 mL) was added activated $MnO_2$ (*Acros*, 88%, 0.350 g, 3.54 mmol). The reaction mixture was stirred at rt before another portion of $MnO_2$ (0.350 g, 3.54 mmol) was added. After which, the reaction mixture was stirred until complete conversion to an aldehyde was observed via TLC analysis. $MnO_2$ was filtered off and the filter cake was washed with acetone (2 × 5 mL). Concentration of the filtrate under reduced pressure provided aldehyde **258** (21.6 mg, 49%) as a yellow oil as inseparable mixture (*cis*/*trans* = 3 : 1) of isomers.

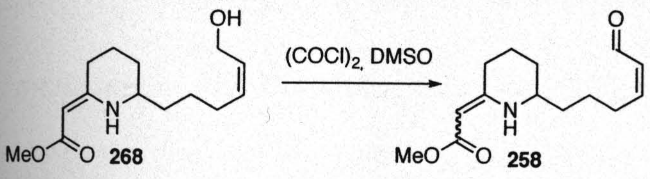
$R_f$ = 0.52 [50% EtOAc in hexanes];

**258 *cis***: $^1$H NMR (500 MHz, $CDCl_3$) δ 1.38 (dddd, 1 H, $J$ = 16.5, 14.5, 12.5, 4.5 Hz), 1.49 – 1.65 (m, 4 H), 1.67 – 1.74 (m, 1 H), 1.76 – 1.84 (m, 1 H), 1.91 (ddd, 1 H, $J$ = 16.5, 10.5, 5.5 Hz), 2.32 – 2.35 (m, 2 H), 2.67 (qd, 2 H, $J$ = 9.0, 1.5 Hz), 3.29 (sextet, 1 H, $J$ = 6.0 Hz), 3.62 (s, 3 H), 4.39 (s, 1 H), 5.99 (ddt, 1 H, $J$ = 13.5, 10.0, 1.5 Hz), 6.62 (dt, 1 H, $J$ = 13.5, 10.0 Hz), 8.85 (brs, 1 H), 10.07 (d, 1 H, $J$ = 10.0 Hz).

**258 *trans***: $^1$H NMR (500 MHz, $CDCl_3$) δ 1.38 (dddd, 1 H, $J$ = 16.5, 14.5, 12.5, 4.5 Hz), 1.49 – 1.65 (m, 4 H), 1.67 – 1.74 (m, 1 H), 1.76 – 1.84 (m, 1 H), 1.91 (ddd, 1 H, $J$ = 16.5, 10.5, 5.5 Hz), 2.32 – 2.35 (m, 2 H), 2.67 (qd, 2 H, $J$ = 9.0, 1.5 Hz), 3.29 (sextet, 1 H, $J$ = 6.0 Hz), 3.62 (s, 3 H), 4.39 (s, 1 H), 6.14 (ddt, 1 H, $J$ = 19.5, 9.5, 2.0 Hz), 6.85 (dt, 1 H, $J$ = 19.5, 9.0 Hz), 8.85 (brs, 1 H), 9.53 (d, 1 H, $J$ = 9.5 Hz); mass spectrum (APCI): m/e (% relative intensity) 252 (100) $M^+$ + H, 234 (10), 220 (10), 194 (15).

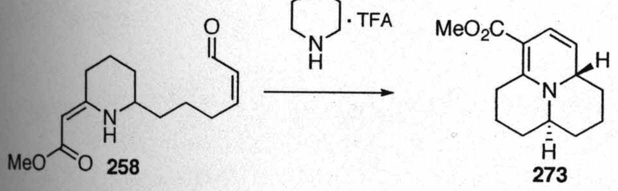


To the pyr•$SO_3$ complex (0.310 g, 1.95 mmol) were added pyridine (0.160 mL, 2.00 mmol) and DMSO (0.350 mL, 4.93 mmol) successively at rt. The resulting suspension was stirred at rt for 15 min, and after which, $CH_2Cl_2$ (2 mL) was added and the mixture was cooled to 0 °C. A pre-cooled solution of alcohol **268** (0.244 g, 0.970 mmol), diisopropylethylamine (0.560 mL, 3.39 mmol), and DMSO (0.350 mL, 4.93 mmol) in $CH_2Cl_2$ (5 mL) was added to the suspension over 2 min. The reaction mixture was stirred at 0 °C for 40 min before $H_2O$ (5 mL) was added. After layers were separated, the organic phase was washed once with $H_2O$ (5 mL). The combined aqueous washes were back-extracted with $CH_2Cl_2$ (2 × 7 mL). The combined organic phases were washed with 1.5% aq HCl (2 × 7 mL), aq $NaHCO_3$ (5 mL), sat aq NaCl (10 mL) and dried over $Na_2SO_4$. Removal of the excess solvent gave aldehyde **258** (210.3 mg, 87%) as yellow oil and as an inseparable mixture (*cis*/*trans* = 7 : 1) of isomers. It was used for the next step without further purification.



To a solution of DMSO (100.0 mL, 1.41 mmol) in $CH_2Cl_2$ (2 mL) was added an oxalyl chloride solution (2 *M* in $CH_2Cl_2$, 0.350 mL, 0.70 mmol) carefully dropwise at -78 °C. The reaction mixture was stirred for 20 min before a solution of alcohol **268** (0.103 g, 0.410 mmol) in $CH_2Cl_2$ (2 mL) was added dropwise over 10 min. The resulting mixture was stirred for 45 min at -78 °C, and after which, diisopropylethylamine (0.340 mL, 2.06 mmol) was added. The mixture was kept at this temperature for 15 min before being warmed up to 0 °C and quenched by addition of $H_2O$ (6 mL). The aqueous layers were extracted with $CH_2Cl_2$ (2 × 7 mL). The combined organic layers were washed successively with 1% aq HCl (6 mL), aq $NaHCO_3$ (6 mL), sat aq NaCl (6 mL), and then dried over $Na_2SO_4$. Evaporation of the excess solvent afforded *cis* aldehyde **258** (0.102 g, ~ 100%) as a mixture of isomers with respect to the vinylogous amide double bond (*E*/*Z* = ~ 1 : 1).

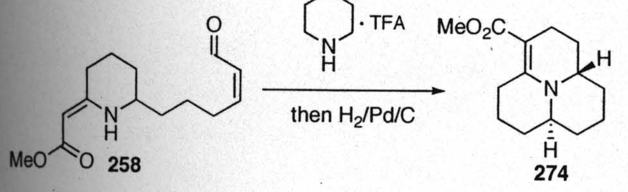
**Cycloadduct 273.**



To a solution of freshly prepared aldehyde **258** (77.0 mg, 0.310 mmol) in freshly distilled EtOAc (10 mL) under $N_2$ atmosphere were added powdered $Na_2SO_4$ (~ 100.0 mg) and piperidinium trifluoroacetate (30.0 mg, 0.150 mmol). The reaction mixture was stirred at rt for 3 h before the excess solvent was evaporated under reduced pressure [Note: Be sure the evaporation temperature is at rt]. The crude residue was submitted to flash column chromatography using silica gel deactivated with $NEt_3$ (2% in EtOAc : hexanes = 9 : 1) eluted with 10% EtOAc in hexanes). Cycloadduct **273** (25.6 mg, 35%) was obtained as very air-sensitive yellow oil.

**273:** $R_f = 0.28$ [10% EtOAc in hexanes, neutral $Al_2O_3$]; $^1$H NMR (400 MHz, $CDCl_3$) δ 1.49 – 1.59 (m, 1 H), 1.63 – 1.74 (m, 6 H), 1.78 – 1.92 (m, 2 H), 1.95 – 2.06 (m, 1 H), 2.79 (dt, 1 H, $J$ = 16.8, 6.8 Hz), 3.35 (dt, 1 H, $J$ = 16.8, 6.4 Hz), 3.41 – 3.48 (m, 1 H), 3.66 (s, 3 H), 4.01 (ddt, 1 H, $J$ = 12.0, 4.0, 2.0 Hz), 4.64 (dd, 1 H, $J$ = 9.2, 2.0 Hz), 6.48 (dd, 1 H, $J$ = 9.2, 2.0 Hz); $^{13}$C NMR (125 MHz, $CD_2Cl_2$) δ 19.1, 19.5, 27.5, 29.9, 30.1, 30.5, 50.5, 52.4, 54.2, 97.8, 110.6, 125.6, 161.4, 167.7; IR (Film) cm$^{-1}$ 2942m, 2864m, 1676s; 1643s, 1526s, 1499s, 1277s, 1162s, 1110s, 1091s, 1070s; mass spectrum (APCI): m/e (% relative intensity) 234 (100) $M^+$ + H, 226 (20), 202 (20); *m/e* calcd for $C_{14}H_{20}NO_2$ ($M^+$ + H) 234.1494, found 234.1486.

**Tricycle 274.**

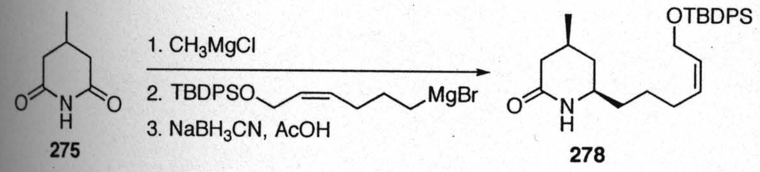


To a solution of aldehyde **258** (56.0 mg, 0.220 mmol) in freshly distilled EtOAc (10 mL) under $N_2$ atmosphere were added powdered $Na_2SO_4$ (~ 100.0 mg) followed by piperidinium trifluoroacetate (30.0 mg, 0.150 mmol). The reaction mixture was stirred at rt and monitored by TLC ($Al_2O_3$). After complete consumption of starting material (~ 2 h), 10% Pd/C (20.0 mg) was added and the resulting mixture was hydrogenated with an $H_2$-balloon for 3 h until the intermediate cycloadduct **273** was not detected via TLC analysis ($Al_2O_3$). After filtering off the catalyst and $Na_2SO_4$, the EtOAc filtrate was evaporated under reduced pressure and the crude residue was purified using silica gel flash column chromatography deactivated with $NEt_3$ (2% in EtOAc : hexanes = 9 : 1) (eluent: 10% EtOAc in hexanes) to afford tricycle **274** (20.0 mg, 38%) as yellow oil.

**274:** $R_f = 0.37$ [10% EtOAc in hexanes, neutral $Al_2O_3$]; $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.40 – 1.82 (m, 12 H), 2.21 (dddd, 1 H, $J$ = 16.0, 13.0, 7.0, 1.5 Hz), 2.49 (dd, 1 H, $J$ = 16.0, 5.5 Hz), 2.68 (tt, 1 H, $J$ = 10.5, 4.5 Hz), 3.07 – 3.16 (m, 3 H), 3.64 (s, 3 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ 19.0, 21.5, 25.4, 27.5, 29.1, 29.5, 31.9, 32.1, 50.6, 53.7, 54.6, 97.8, 159.1, 170.2; IR (Film) $cm^{-1}$ 2940s, 2863m, 1674s; 1538s, 1433m, 1266s, 1244s, 1222s, 1116s, 1087s; mass spectrum (APCI): m/e (% relative intensity) 236 (100) $M^+$ + H, 204 (10); *m/e* calcd for $C_{14}H_{22}NO_2$ ($M^+$ + H) 236.1651, found 236.1642.

## PRECOCCINELLINE, HIPPODAMINE, COCCINELLINE, AND CONVERGINE.

**Lactam 278.**

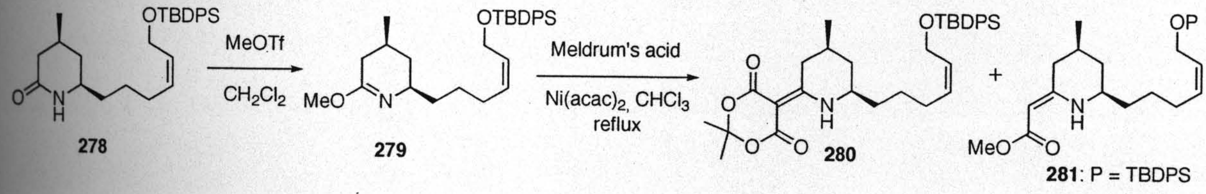


To a solution of 4-methylglutarimide[59] **275** (2.90 g, 22.8 mmol) in THF (100 mL) was added $CH_3MgCl$ (3 *M* in THF, 8.00 mL, 24.0 mmol) dropwise at 0 °C. The mixture was allowed to warm up to rt and stirred for 30 min before being cooled back down to 0 °C. A warm solution of Grignard reagent (35-40 °C to prevent precipitation) in THF (30 mL) prepared from bromide **262** (14.3 g, 34.4 mmol) and Mg (0.920 g, 37.8 mmol) activated with 1,2-dibromoethane (0.150 mL, 1.74 mmol) was added *via* a cannula. The mixture was stirred at rt for 12 h before

$NaBH_3CN$ (1.60 g, 25.5 mmol) and HOAc (4.5 mL) were added successively. After stirring at ambient temperature for 45 min, it was quenched with sat aq $NaHCO_3$ (65 mL). After layers were separated, the organic phase was washed with additional portions of sat aq $NaHCO_3$ solution (65 mL). The combined aqueous washes were back-extracted with EtOAc (3 × 70 mL), and the combined organic layers were washed with sat aq NaCl (2 × 50 mL) and dried over $Na_2SO_4$. After removal of excess solvents under reduced pressure, the crude residue was purified via two silica gel columns (1$^{st}$: 0%-50% acetone in EtOAc; 2$^{nd}$: 7%-10% MeOH in $CH_2Cl_2$) to afford lactam **278** (7.44 g, 73%) as thick colorless oil.

**278:** $R_f$ = 0.40 [EtOAc : acetone = 2 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 0.97 – 1.01 (m, 1 H), 0.99 (d, 3 H, $J$ = 5.5 Hz), 1.05 (s, 9 H), 1.28 – 1.38 (m, 4 H), 1.78 (brd, 1 H, $J$ = 13.0 Hz), 1.85 – 1.89 (m, 4 H), 2.40 (dd, 1 H, $J$ = 22.0, 11.0 Hz), 3.27 – 3.32 (m, 1 H), 4.24 (d, 2 H, $J$ = 6.5 Hz), 5.34 – 5.40 (m, 1 H), 5.61 – 5.66 (m, 1 H), 6.10 (brs, 1 H) 7.38 – 7.45 (m, 6 H), 7.69 (d, 4 H, $J$ = 7.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.3, 21.7, 25.1, 27.0, 27.4, 27.6, 36.6, 37.4, 39.8, 53.1, 60.4, 127.8, 129.8, 130.1, 130.2, 134.0, 135.8, 173.0; IR (Film) cm$^{-1}$ 3219m, 2929s, 2856m, 1656s, 1458m, 1241s, 1108s; mass spectrum (APCI): m/e (% relative intensity) 448 (25) $M^+ - H$, 370 (100); *m/e* calcd for $C_{28}H_{39}NO_2SiNa$ ($M^+ + Na$) 472.2648, found 472.2650.

**Meldrum's Acid Derivative 280.**



To a solution of lactam **278** (3.23 g, 7.18 mmol) in $CH_2Cl_2$ (28 mL) was added freshly distilled MeOTf (1.00 mL, 8.84 mmol). The mixture was stirred at rt for 8 h before the excess solvent was evaporated under reduced pressure. The oily crude residue was treated with cold 5% aq $Na_2CO_3$ (50 mL), and the resulting mixture was extracted with $CH_2Cl_2$ (3 × 40 mL), washed with sat aq NaCl (2 × 50 mL), and dried over $MgSO_4$. Removal of the excess solvent under reduced pressure gave lactim ether **279** (2.96 g, 89% crude) as colorless oil, which was used for the next step without further purification.

**279:** $R_f = 0.73$ [30% EtOAc in hexanes]; $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.70 (q, 1 H, $J$ = 12.0 Hz), 0.96 (d, 3 H, $J$ = 6.0 Hz), 1.05 (s, 9 H), 1.26 – 1.52 (m, 4 H), 1.57 – 1.77 (m, 3 H), 1.91 (q, 2 H, $J$ = 6.9 Hz), 2.21 (dd, 1 H, $J$ = 16.5, 5.1 Hz), 3.27 (brs, 1 H), 3.60 (s, 3 H), 4.26 (d, 2 H, $J$ = 6.3 Hz), 5.45 (dtt, 1 H, $J$ = 11.1, 7.2, 1.5 Hz), 5.61 (dtt, 1 H, $J$ = 11.1, 6.3, 1.5 Hz), 7.37 – 7.44 (m, 6 H), 7.70 (dd, 4 H, $J$ = 7.5, 2.1 Hz).

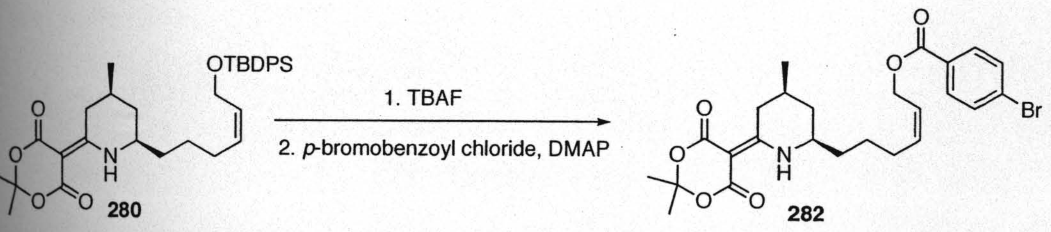
To a solution of the above lactim ether **279** (2.96 g, 6.38 mmol) in $CHCl_3$ (45 mL, freshly distilled over $CaH_2$ to remove any traces of EtOH stabilizer) were added Meldrum's acid (0.920 g, 6.38 mmol) and $Ni(acac)_2$ catalyst (*ca.* 50.0 mg). The mixture was refluxed for 24 h under $N_2$ atmosphere. After removal of the excess solvent under reduced pressure, the crude residue was purified by silica gel flash column chromatography (20-60% EtOAc in hexanes) to give Meldrum's acid derivative **280** (0.600 g, 16%) and urethane **281** (0.440 g, 14%) as colorless oils.

**280:** $R_f = 0.57$ [50% EtOAc in hexanes]; $^1H$ NMR (500 MHz, $CDCl_3$) δ 1.02 (q, 1 H, $J$ = 12.5 Hz), 1.04 (s, 9 H), 1.07 (d, 3 H, $J$ = 6.5 Hz), 1.34 – 1.42 (m, 1 H), 1.46 – 1.53 (m, 3 H), 1.67 (s, 3 H), 1.68 (s, 3 H), 1.74 – 1.81 (m, 1 H), 1.87 (brd, 1 H, $J$ = 13.0 Hz), 1.92 (q, 2 H, $J$ = 6.5 Hz), 2.42 (dd, 1 H, $J$ = 19.5, 12.0 Hz), 3.42 (sextet, 1 H, $J$ = 5.5 Hz), 3.55 (dd, 1 H, $J$ = 19.5, 3.5 Hz), 4.24 (d, 2 H, $J$ = 5.5 Hz), 5.39 (dt, 1 H, $J$ = 11.0, 7.5 Hz), 5.65 (dt, 1 H, $J$ = 11.0, 5.5 Hz), 7.36 – 7.44 (m, 6 H), 7.69 (dd, 4 H, $J$ = 7.5, 1.5 Hz), 11.66 (brs, 1 H); $^{13}C$ NMR (125 MHz, $CDCl_3$) δ

19.3, 21.8, 25.1, 26.0, 27.0, 27.1, 27.2, 35.8, 36.0, 37.4, 54.3, 60.3, 82.9, 102.5, 127.8, 129.8, 130.0, 130.2, 134.0, 135.7, 163.0, 167.8, 173.5.

**281:** $R_f = 0.50$ [20% EtOAc in hexanes]; $^1$H NMR (500 MHz, $CDCl_3$) δ 0.95 (q, 1 H, $J = 11.5$ Hz), 0.96 (d, 3 H, $J = 6.5$ Hz), 1.04 (s, 9 H), 1.34 – 1.46 (m, 4 H), 1.67 – 1.75 (m, 1 H), 1.78 (brd, 1 H, $J = 13.0$ Hz), 1.89 (q, 2 H, $J = 6.5$ Hz) 1.96 (dd, 1 H, $J = 16.5, 12.0$ Hz), 2.27 (ddd, 1 H, $J = 16.5, 4.5, 2.5$ Hz), 3.17 – 3.23 (m, 1 H), 3.61 (s, 3 H), 4.24 (d, 2 H, $J = 5.5$ Hz), 4.35 (s, 1 H), 5.37 – 5.42 (m, 1 H), 5.60 – 5.65 (m, 1 H), 7.36 – 7.42 (m, 6 H), 7.68 (dd, 4 H, $J = 8.0, 1.5$ Hz), 8.72 (brs, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.4, 22.0, 25.4, 27.0, 27.2, 27.5, 36.9, 38.0, 38.4, 50.1, 52.9, 60.4, 79.9, 127.8, 129.8, 129.9, 130.5, 134.1, 135.8, 162.6, 171.3; IR (Film) $cm^{-1}$ 2927s, 2855s, 1649s; 1602s, 1427m, 1239s, 1168s, 1109s; mass spectrum (APCI): m/e (% relative intensity) 506 (10) $M^+$ + H, 504 (15) M – H, 279 (100), 184 (60); *m/e* calcd for $C_{31}H_{43}NO_3SiNa$ ($M^+$ + Na) 528.2910, found 528.2926.

**Bromobenzoate 282.**

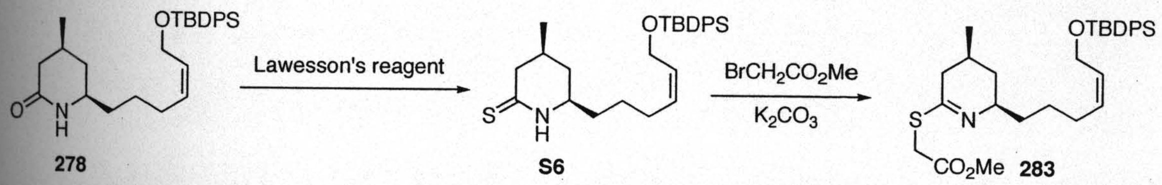


To a solution of compound **280** (118.6 mg, 0.210 mmol) in $CH_2Cl_2$ (3 mL) was added TBAF (1 *M* in THF, 0.500 mL, 0.500 mmol), and the resulting mixture was stirred at rt for 2 h. After which, the excess solvent was removed under reduced pressure and the crude residue was purified on short silica gel column (EtOAc). The resulting allyl alcohol (0.0630 g, 0.190 mmol) was quickly dissolved in $CH_2Cl_2$ (2 mL) and treated with DMAP (28.0 mg, 0.230 mmol) and *p*-

bromonenzoyl chloride (50.0 mg, 0.230 mmol). The reaction mixture was stirred at rt overnight, and after which, the excess solvent was removed under reduced pressure, and the crude residue was purified by silica gel column chromatography (60% EtOAc in hexanes) to yield bromobenzoate **282** (94.0 mg, 90% over two steps) as colorless solid.

**282:** $R_f$ = 0.39 [50% EtOAc in hexanes]; mp = 79 – 82 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.07 (q, 1 H, *J* = 12.0 Hz), 1.08 (d, 3 H, *J* = 6.5 Hz), 1.50 – 1.58 (m, 1 H), 1.62 – 1.66 (m, 3 H), 1.67 (s, 3 H), 1.69 (s, 3 H), 1.79 – 1.85 (m, 1 H), 1.92 (brd, 1 H, *J* = 11.5 Hz), 2.25 (q, 2 H, *J* = 6.5 Hz), 2.43 (dd, 1 H, *J* = 19.5, 6.0 Hz), 3.48 – 3.55 (m, 1 H), 3.57 (ddd, 1 H, *J* = 19.5, 5.0, 1.5 Hz), 4.86 (d, 2 H, *J* = 6.0 Hz), 5.66 – 5.74 (m, 2 H), 7.58 (d, 2 H, *J* = 8.5 Hz), 7.90 (d, 2 H, *J* = 8.5 Hz), 11.73 (brs, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 21.9, 25.2, 26.08, 26.12, 27.2, 27.4, 36.0, 36.1, 37.5, 54.3, 61.1, 83.0, 102.6, 124.4, 128.3, 129.3, 131.4, 132.0, 134.8, 163.1, 166.0, 167.9, 173.7; mass spectrum (APCI): m/e (% relative intensity) 520 (100), 518 (100) $M^+$ – H, 418 (10), 416 (10).

### Thiol Ether 283.



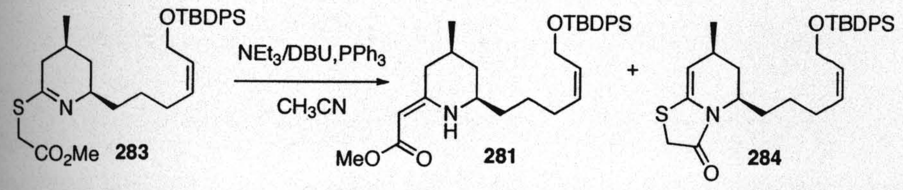
Lawesson's reagent (5.30 g, 13.1 mmol) was added to a solution of lactam **278** (7.82 g, 17.4 mmol) in THF (100 mL), and the resulting mixture was stirred at rt for 1 h. After removal of the excess solvent under reduced pressure, the pure thiolactam **S6** (7.26 g, 90%) was obtained via silica gel flash column chromatography (30% EtOAc in hexanes) as thick pale yellow oil.

**S6:** $R_f$ = 0.24 [20% EtOAc in hexanes]; $^1$H NMR (500 MHz, $CDCl_3$) δ 0.98 (d, 3 H, $J$ = 6.5 Hz), 0.98 – 1.02 (m, 1 H), 1.05 (s, 9 H), 1.30 – 1.36 (m, 2 H), 1.39 – 1.46 (m, 2 H), 1.81 – 1.92 (m, 4 H), 2.29 (dd, 1 H, $J$ = 18.5, 12.0 Hz), 3.09 (ddd, 1 H, $J$ = 18.5, 4.5, 2.5 Hz), 3.29 – 3.34 (m, 1 H), 4.24 (d, 2 H, $J$ = 6.5 Hz), 5.34 – 5.39 (m, 1 H), 5.63 – 5.68 (m, 1 H), 7.38 – 7.44 (m, 6 H), 7.69 (dd, 4 H, $J$ = 8.0, 1.5 Hz), 7.92 (brs, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.4, 21.2, 25.0, 26.0, 27.3, 27.4, 35.7, 36.1, 47.7, 56.6, 60.4, 127.9, 129.8, 129.9, 130.4, 134.0, 135.8, 203.1; mass spectrum (APCI): m/e (% relative intensity) 466 (95) $M^+$ + H, 388 (100), 210 (30).

To a solution of the above thiolactam **S6** (7.26 g, 15.6 mmol) in acetone (100 mL) were successively added powdered $K_2CO_3$ (4.30 g, 31.1 mmol) and methyl a-bromo acetate (1.70 mL, 18.4 mmol). The reaction mixture was stirred at rt for 12 h, and after which, the solids were filtered off. After removal of the excess solvent under reduced pressure, thiol ether **283** (8.27 g, 100%) was obtained as yellow oil.

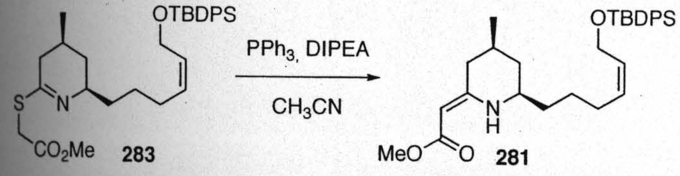
**283:** $R_f$ = 0.44 [20% EtOAc in hexanes]; $^1$H NMR (500 MHz, $CDCl_3$) δ 0.77 (q, 1 H, $J$ = 12.0 Hz), 0.92 (d, 3 H, $J$ = 6.5 Hz), 1.06 (s, 9 H), 1.33 – 1.41 (m, 3 H), 1.51 – 1.59 (m, 1 H), 1.67 (brd, 1 H, $J$ = 12.5 Hz), 1.72 – 1.79 (m, 1 H), 1.83 (ddd, 1 H, $J$ = 17.0, 11.5, 3.0 Hz), 1.91 (q, 2 H, $J$ = 6.5 Hz), 2.33 (dd, 1 H, $J$ = 17.0, 10.0 Hz), 3.26 (brs, 1 H), 3.62 (d, 1 H, $J$ = 16.0 Hz), 3.65 (s, 3 H), 3.71 (d, 1 H, $J$ = 16.0 Hz), 4.26 (d, 2 H, $J$ = 5.5 Hz), 5.41 – 5.46 (m, 1 H), 5.59 – 5.64 (m, 1 H), 7.36 – 7.43 (m, 6 H), 7.69 (dd, 4 H, $J$ = 8.0, 1.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.3, 21.9, 26.0, 27.0, 27.4, 27.7, 31.4, 37.6, 37.9, 39.6, 52.4, 60.5, 60.6, 127.8, 129.3, 129.7, 131.3, 134.1, 135.7, 161.4, 170.6; IR (Film) cm$^{-1}$ 2928s, 2856s, 1741s; 1637s, 1423m, 1293s, 1109s 1059s; mass spectrum (APCI): m/e (% relative intensity) 538 (100) $M^+$ + H, 506 (10), 372 (15); *m/e* calcd for $C_{31}H_{44}NO_3SSi$ ($M^+$ + H) 538.2811, found 538.2807.

**Urethane 281.**



A mixture of thiol ether **283** (0.983 g, 1.82 mmol), $PPh_3$ (600.0 mg, 2.29 mmol), triethylamine (50.0 mL, 0.360 mmol), and DBU (0.100 mL, 0.660 mmol) in $CH_3CN$ (5 mL) was refluxed for 48 h. After removal of the excess solvent under reduced pressure, a solvent mixture of EtOAc/hexanes (1 : 1, 5 mL) was added to the crude residue and the resulting precipitate ($S=PPh_3$) was filtered off. After concentration of the filtrate under reduced pressure, the crude residue was subjected to silica gel column chromatography (5-20% EtOAc in hexanes) to give urethane **281** (0.640 g, 69%) and thiazolidinone **284** (~ 70.0 mg, 7%) as colorless oils.

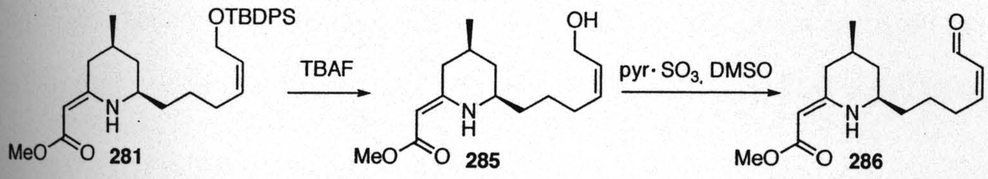
**284**: $R_f = 0.32$ [20% EtOAc in hexanes]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.04 (s, 9 H), 1.09 (d, 3 H, $J = 7.5$ Hz), 1.26 – 1.42 (m, 3 H), 1.50 – 1.58 (m, 1 H), 1.71 (brd, 1 H, $J = 15.0$ Hz), 1.82 – 1.91 (m, 3 H), 2.38 – 2.44 (m, 1 H) 3.64 (d, 1 H, $J = 16.0$ Hz), 3.70 (d, 1 H, $J = 16.0$ Hz), 4.13 – 4.18 (m, 1 H), 4.23 (d, 2 H, $J = 6.5$ Hz), 4.81 (d, 1 H, $J = 5.0$ Hz), 5.39 (dtt, 1 H, $J = 11.0, 7.5, 1.5$ Hz), 5.61 (dt, 1 H, $J = 11.0, 6.5$ Hz), 7.36 – 7.44 (m, 6 H), 7.69 (dd, 4 H, $J = 8.0, 1.5$ Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.3, 22.8, 26.4, 27.0, 27.41, 27.43, 30.0, 32.1, 32.3, 51.9, 60.4, 104.1, 127.9, 129.8, 130.0, 130.6, 133.6, 134.1, 135.9, 169.9.



A mixture of thiol ether **283** (8.37 g, 15.6 mmol), $PPh_3$ (5.30 g, 20.2 mmol), and diisopropylethylamine (1.00 mL, 6.06 mmol) in $CH_3CN$ (85 mL) was heated in a sealed tube at

100 °C for 60 h. After evaporating the excess solvent under reduced pressure, a solvent mixture of EtOAc/hexanes (1 : 1, 50 mL) was added to the crude residue and the resulting precipitate (S=PPh$_3$) was filtered off. After concentration of the filtrate under reduced pressure, the crude residue was subjected to silica gel flash column chromatography (5-10% EtOAc in hexanes) to give urethane **281** (7.50 g, 95%) as colorless oil.

**Aldehyde 286.**



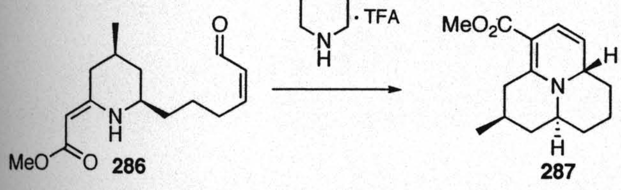
To a solution of urethane **281** (7.50 g, 14.8 mmol) in THF (80 mL) TBAF (1 *M* in THF, 20.0 mL, 20.0 mmol) was added, and the resulting mixture was stirred at ambient temperature for 1 h. After which, the excess solvent was removed under reduced pressure and the crude residue was purified on a short silica gel column (20-60% EtOAc in hexanes). Alcohol **285** (3.79 g, 96%) was isolated as colorless oil.

**285:** $R_f$ = 0.44 [60% EtOAc in hexanes]; $^1$H NMR (500 MHz, CDCl$_3$) δ 0.98 (d, 3 H, *J* = 6.5 Hz), 1.02 (q, 1 H, *J* = 12.5 Hz), 1.48 – 1.53 (m, 3 H), 1.54 – 1.60 (m, 1 H), 1.65 (t, OH, *J* = 6.0 Hz), 1.73 – 1.79 (m, 1 H), 1.84 (brd, 1 H, *J* = 13.0 Hz) 1.99 (dd, 1 H, *J* = 16.0, 12.0 Hz), 2.08 – 2.18 (m, 2 H), 2.30 (ddd, 1 H, *J* = 16.0, 4.5, 2.0 Hz), 3.27 – 3.31 (m, 1 H), 3.62 (s, 3 H), 4.14 – 4.24 (m, 2 H), 4.36 (s, 1 H), 5.52 – 5.57 (m, 1 H), 5.62 – 5.68 (m, 1 H), 8.84 (brs, 1 H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 22.0, 25.6, 27.2, 27.3, 36.8, 37.9, 38.5, 50.2, 52.7, 58.6, 80.0, 129.4, 132.3, 162.8, 171.5; IR (Film) cm$^{-1}$ 3394s, 2924m, 2854m, 1635s; 1597s, 1457m, 1297s, 1239s, 1168s, 1043s; mass spectrum (APCI): m/e (% relative intensity) 268 (100) $M^+$ + H, 236 (10), 210 (40); *m/e* calcd for $C_{15}H_{25}NO_3Na$ ($M^+$ + Na) 290.1732, found 290.1715.

To the pyr•$SO_3$ complex (4.50 g, 28.3 mmol) were added pyridine (2.30 mL, 28.7 mmol) and DMSO (5.00 mL, 70.4 mmol) successively at rt. The resulting suspension was stirred at rt for 15 min, and after which, $CH_2Cl_2$ (20 mL) was added and mixture was cooled down to 0 °C. A pre-cooled solution of alcohol **285** (3.74 g, 14.0 mmol), diisopropylethylamine (8.00 mL, 48.5 mmol), and DMSO (5.00 mL, 70.4 mmol) in $CH_2Cl_2$ (80 mL) was added to suspension over 10 min. The reaction mixture was stirred at 0 °C for 40 min before $H_2O$ (50 mL) was added. After separating the layers, the organic phase was washed once with $H_2O$ (50 mL). The combined aqueous layers were back-extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic phases were washed with 1.5% aq HCl (1 × 100 mL, 1 × 50 mL), sat aq $NaHCO_3$ (50 mL), sat aq NaCl (100 mL) and dried over $Na_2SO_4$. Removal of the excess solvent under reduced pressure gave aldehyde **286** (3.19 g, 86%) as yellow oil, which was used for the next step without further purification.

**286:** $R_f$ = 0.56 [60% EtOAc in hexanes]; $^1H$ NMR (500 MHz, $CDCl_3$) δ 0.99 (d, 3 H, $J$ = 6.5 Hz), 1.03 (q, 1 H, $J$ = 12.5 Hz), 1.53 – 1.65 (m, 3 H), 1.69 – 1.79 (m, 2 H), 1.85 (dd, 1 H, $J$ = 13.0, 2.5 Hz) 1.99 (dd, 1 H, $J$ = 16.5, 12.0 Hz), 2.30 (ddd, 1 H, $J$ = 16.5, 4.5, 2.0 Hz), 2.66 (qd, 2 H, $J$ = 7.5, 1.5 Hz), 3.31 – 3.35 (m, 1 H), 3.62 (s, 3 H), 4.38 (s, 1 H), 5.99 (ddd, 1 H, $J$ = 11.0, 8.0, 1.5 Hz), 6.61 (dt, 1 H, $J$ = 11.0, 7.5 Hz), 8.83 (brs, 1 H), 10.07 (d, 1 H, $J$ = 8.0 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 22.0, 25.1, 27.2, 28.1, 36.8, 37.9, 38.3, 50.2, 52.7, 80.3, 130.7, 152.3, 162.6, 171.4, 190.9; IR (Film) $cm^{-1}$ 2947m, 2854m, 1679s; 1644s, 1598s, 1499m, 1297s, 1238s, 1158s, 1044s; mass spectrum (APCI): m/e (% relative intensity) 266 (100) $M^+$ + H, 248 (10), 234 (15), 208 (5); *m/e* calcd for $C_{15}H_{24}NO_3$ ($M^+$ + H) 266.1756, found 266.1753.

**Cycloadduct 287.**



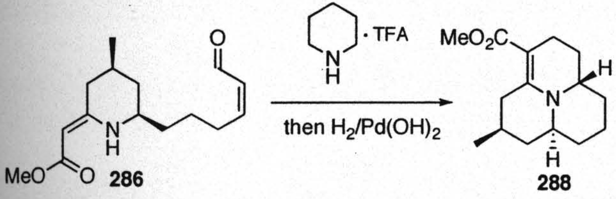
286

287

To a solution of aldehyde **286** (95.7 mg, 0.360 mmol) in freshly distilled EtOAc (10 mL) under $N_2$ atmosphere were added powdered $Na_2SO_4$ (~ 100.0 mg) and piperidinium trifluoroacetate (38.0 mg, 0.190 mmol). The mixture was stirred at rt for 3 h before the excess solvent was removed under reduced pressure [Note: Be sure the evaporation temperature is at rt]. The crude residue was submitted to flash silica gel column chromatography with $NEt_3$-deactivated (2% in EtOAc : hexanes = 9 : 1) silica gel (eluent: 10% EtOAc in hexanes). Cycloadduct **287** (45.6 mg, 51%) was obtained as air-sensitive yellow oil, which slowly solidifies upon keeping under a high vacuum.

**287:** $R_f$ = 0.38 [10% EtOAc in hexanes, neutral $Al_2O_3$]; mp = 48 – 50 °C; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.00 (d, 3 H, *J* = 7.0 Hz), 1.17 (q, 1 H, *J* = 12.0 Hz), 1.58 – 1.78 (m, 5 H), 1.83 (dtd, 1 H, *J* = 13.0, 4.0, 2.5 Hz), 1.88 – 1.94 (m, 1 H), 2.02 – 2.11 (m, 1 H), 2.46 (dd, 1 H, *J* = 17.0, 6.0, Hz), 3.25 (ddd, 1 H, *J* = 17.0, 4.5, 2.5 Hz), 3.37 (tt, 1 H, *J* = 11.0, 3.5 Hz), 3.67 (s, 3 H), 4.01 (ddt, 1 H, *J* = 11.5, 3.5, 2.0 Hz), 4.61 (dd, 1 H, *J* = 9.0, 2.0 Hz), 6.51 (dd, 1 H, *J* = 9.0, 2.0 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 18.6, 22.4, 26.6, 29.5, 30.3, 36.3, 39.7, 50.5, 53.0, 54.0, 98.6, 109.9, 125.7, 159.7, 167.7; IR (Film) cm$^{-1}$ 2945m, 1671s; 1638s, 1494s, 1277s, 1238s, 1126s, 1081s, 1041s; mass spectrum (APCI): m/e (% relative intensity) 248 (100) $M^+$ + H, 216 (20); *m/e* calcd for $C_{15}H_{22}NO_2$ ($M^+$ + H) 248.1651, found 248.1643.

**Tricycle 288.**

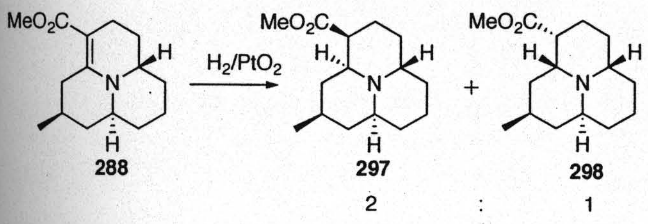


To solution of aldehyde **286** (2.77 g, 10.4 mmol) in freshly distilled EtOAc (240 mL) under $N_2$ atmosphere were added powdered $Na_2SO_4$ (~ 1.00 g) and piperidinium trifluoroacetate (1.00 g, 5.02 mmol). The reaction mixture was stirred at rt and monitored by TLC ($Al_2O_3$). After complete consumption of the starting material with ~ 2 h, 20% $Pd(OH)_2/C$ (1.50 g) was added and the resulting mixture was hydrogenated with a $H_2$-balloon for 3 h until the intermediate cycloadduct **287** was no longer detectable by TLC analysis ($Al_2O_3$). After filtering off the catalyst and $Na_2SO_4$, the EtOAc filtrate was concentrated under reduced pressure, and the crude residue was purified via flash column chromatography using $NEt_3$ deactivated (2% in EtOAc : hexanes = 9 : 1) silica gel (eluent: 10% EtOAc in hexanes) to afford tricycle **288** (1.10 g, 43%) as yellow oil.

**288:** $R_f$ = 0.49 [10% EtOAc in hexanes, neutral $Al_2O_3$]; $^1$H NMR (500 MHz, $CDCl_3$) δ 0.96 (d, 3 H, $J$ = 6.5 Hz), 1.12 (q, 1 H, $J$ = 12.0 Hz), 1.43 (ddd, 1 H, $J$ = 24.0, 11.5, 6.5 Hz), 1.49 – 1.67 (m, 5 H), 1.69 – 1.85 (m, 4 H), 2.02 (t, 1 H, $J$ = 15.5 Hz), 2.20 (dddd, 1 H, $J$ = 16.5, 12.5, 7.5, 2.5 Hz), 2.51 (dd, 1 H, $J$ = 16.5, 5.5, Hz), 3.01 – 3.09 (m, 2 H), 3.37 (ddd, 1 H, $J$ = 15.5, 4.0, 2.5 Hz), 3.65 (s, 3 H); $^1$H NMR (400 MHz, toluene-$d_8$) δ 0.83 (d, 3 H, $J$ = 6.4 Hz), 0.88 (q, 1 H, $J$ = 12.0 Hz), 1.04 – 1.52 (m, 10 H), 2.06 (tt, 1 H, $J$ = 14.8, 2.4 Hz), 2.28 (dddd, 1 H, $J$ = 16.8, 12.8, 7.6, 2.4 Hz), 2.54 (tt, 1 H, $J$ = 11.2, 3.2 Hz), 2.71 (dd, 1 H, $J$ = 16.8, 5.6 Hz), 2.75 – 2.79 (m, 1 H), 3.59 (s, 3 H), 3.77 (ddd, 1 H, $J$ = 14.8, 4.4, 2.4 Hz);$^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.1, 22.5, 25.8, 27.0, 28.9, 29.6, 32.4, 37.7, 41.1, 50.7, 54.3, 54.8, 98.9, 158.4, 170.2; IR (Film) cm$^{-1}$

2939m, 1672s; 1533s, 1430m, 1230s, 1179s, 1122s, 1084s; mass spectrum (APCI): m/e (% relative intensity) 250 (100) $M^+$ + H, 218 (10); *m/e* calcd for $C_{15}H_{23}NO_2Na$ ($M^+$ + Na) 272.1626, found 272.1617.

**Esters 297 and 298. Hydrogenation of 288.**



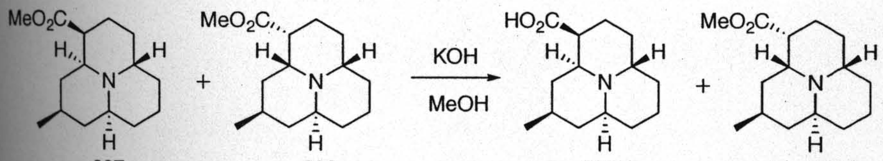
Adams catalyst (0.4 g) was hydrogenated in MeOH (10 mL) until formation of black sponge was completed (~30 min). Solution of urethane **288** (0.95 g, 3.81 mmol) in MeOH (30 mL) was added via canula. Mixture was hydrogenated with $H_2$ balloon until complete consumption of starting material (~3 h). Catalyst was filtered, washed with MeOH (10 mL) and mother liquor was concentrated to afford diastereomeric mixture of esters **297** and **298** (0.934 g, 98%, *dr*: 2 : 1 = **297** : **298**) as pale yellow oil .

**297**: $R_f$ = 0.29 [2 × 10% EtOAc in hexanes, neutral $Al_2O_3$]; $^1H$ NMR (500 MHz, $CDCl_3$): δ 0.90 – 0.92 (m, 1 H), 1.05 (d, 3 H, *J* = 6.5 Hz), 1.05 (brd, 1 H, *J* = 13.5 Hz), 1.10 – 1.21 (m, 2 H), 1.33 (q, 1 H, *J* =12.5 Hz), 1.47 – 1.54 (m, 3 H), 1.56 – 1.68 (m, 5 H), 1.70 – 1.77 (m, 1 H), 1.81 – 1.88 (m, 1 H), 2.72 (t, 1 H, *J* =11.0 Hz), 2.86 (dt, 1 H, *J* = 12.5, 4.5 Hz), 3.00 (brd, 1 H, *J* = 12.0 Hz), 3.29 (ddd, 1 H, *J* = 12.5, 4.5, 2.5 Hz) 3.67 (s, 3 H); $^{13}C$ NMR (125 MHz, $CDCl_3$): 19.8, 21.5, 22.8, 27.2, 31.2, 31.4, 32.4, 33.6, 34.5, 46.4, 47.7, 51.8, 58.5, 59.7, 174.5; IR (Film, $cm^{-1}$): 2944s, 2864m, 2574m, 1726s, 1456m, 1377m, 1218s, 1197s, 1181s, 1044m; mass spectrum (APCI): m/z (% rel intensity) 252 (100) $M^+$ + H.

**298**: $R_f$ = 0.40 [2 × 10% EtOAc in hexanes, neutral $Al_2O_3$]; $R_f$ = 0.37 [0.5% $CH_2Cl_2$ in MeOH, neutral $Al_2O_3$]; $^1$H NMR (500 MHz, $CDCl_3$): δ 0.71 (q, 1 H, $J$ =12.0 Hz), 0.77 (d, 3 H, $J$ = 6.5 Hz), 0.89 – 0.98 (m, 2 H), 1.22 – 1.32 (m, 1 H), 1.41 – 1.50 (m, 5 H), 1.52 (dt, 1 H, $J$ = 11.0, 1.5 Hz), 1.65 (tdd 1 H, $J$ = 13.5, 5.5, 4.5 Hz), 1.74 (tt, 1 H, $J$ = 13.5, 5.5 Hz), 1.81 (ddt, 1 H, $J$ = 13.5, 4.0, 2.0 Hz), 2.03 (brd, 1 H, $J$ = 13.5 Hz), 2.23 (t, 1 H, $J$ = 5.5 Hz), 2.46 (qd, 1 H, $J$ = 13.5, 3.5 Hz), 2.91 (dd, 1 H, $J$ = 13.5, 5.5 Hz), 3.02 (tt, 1 H, $J$ = 11.0, 2.5 Hz), 3.21 (t, 1 H, $J$ = 5.5 Hz), 3.58 (s, 3 H); $^{13}$C NMR (125 MHz, $CDCl_3$): 19.9, 20.1, 22.8, 26.0, 29.0, 32.0, 35.0, 37.9, 40.9, 43.1, 48.7, 51.6, 58.4, 59.1, 178.8; IR (Film) cm$^{-1}$ 2923s, 2861m, 1730s, 1445m, 1381m, 1195ss, 1156s, 1086s; mass spectrum (APCI): m/z (% rel intensity) 252 (100) $M^+$ + H; *m/e* calcd for $C_{15}H_{26}NO_2$ ($M^+$ + H) 252.1964, found 252.1964.

**The picrate salt of 298**: mp = 163 – 165 °C; $^1$H NMR (400 MHz, $CDCl_3$): 0.92 (d, 3 H, $J$ = 6.4 Hz), 1.43 – 1.49 (m, 1 H), 1.52 (dd, 1 H, $J$ = 13.2, 3.2 Hz), 1.65 – 1.90 (m, 9 H), 1.94 (dd, 1 H, $J$ = 13.2, 4.4 Hz), 2.02 – 2.10 (m, 1 H), 2.13 (brd, 1 H, $J$ = 14.4 Hz), 2.74 (qd, 1 H, $J$ = 13.2, 3.6 Hz), 2.85 (t, 1 H, $J$ = 6.0 Hz), 3.70 (brd, 1 H, $J$ = 16.4 Hz), 3.75 (s, 3 H), 3.86 – 3.90 (m, 1 H), 3.94 (t, 1 H, $J$ = 6.0 Hz), 8.90 (s, 2 H), 9.71 (brs, 1 H).

**Acid 299. Selective Hydrolysis.**



**297** **298** **299** **298**

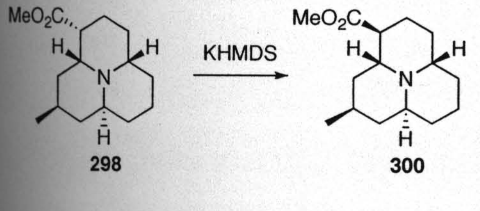
2 : 1

A crude mixture of esters **297** and **298** (0.183 g, 0.73 mmol) was dissolved in MeOH (10 mL) and KOH (1.7 *M* in $H_2O$, 4 mL, 6.80 mmol) was added. Reaction was stirred at ambient temperature and monitored by TLC ($Al_2O_3$). After complete disappearance of equatorial ester

**297** (~6 h) MeOH was evaporated and $H_2O$ (4 mL) was added. The unreacted axial ester **298** was extracted with $CH_2Cl_2$ (3 × 7 mL), and the combined organics were washed with sat aq NaCl (8 mL) and dried over $Na_2SO_4$. To isolate acid **299**, the aqueous phase was acidified with 1 *M* HCl until pH = 3 - 4, and after which, it was saturated with solid NaCl. Product was extracted with $CHCl_3$ (5 × 15 mL), and the combined organics were washed with sat aq NaCl (15 mL) and dried over $Na_2SO_4$. Removal of the solvent under reduced pressure afforded acid **299** (0.0851 g, 49%) as colorless solid along with the recovered ester **298** (0.0626 g, 39%) as pale yellow oily solid, which could be further purified by column chromatography on neutral alumina gel (1% MeOH in $CH_2Cl_2$).

**299**: mp = >250 °C; $^1$H NMR (500 MHz, $CD_3OD$): δ 1.07 (d, 3 H, *J* = 5.5 Hz), 1.52 – 2.00 (m, 14 H), 2.07 (tt, 1 H, *J* = 14.0, 5.0 Hz), 3.09 (dt, 1 H, *J* = 13.0, 4.0 Hz), 3.61 – 3.65 (m, 1 H), 3.70 (tt, 1 H, *J* =12.0, 3.0 Hz), 3.84 (tt, 1 H, *J* =13.0, 4.0 Hz); $^{13}$C NMR (125 MHz, $CD_3OD$): 18.6, 20.8, 21.6, 28.3, 29.9, 31.2, 31.6, 32.1, 32.4, 45.2, 52.6, 62.1, 62.3, 173.4; IR (Film, cm$^{-1}$): 2923s, 2866m, 2574m, 1735s, 1443m, 1366m, 1237m 1172s, 1132s; mass spectrum (APCI): m/z (% rel intensity) 237 (100) $M^+$ + H; *m/e* calcd for $C_{14}H_{24}NO_2$ ($M^+$ + H) 238.1807, found 238.1809.

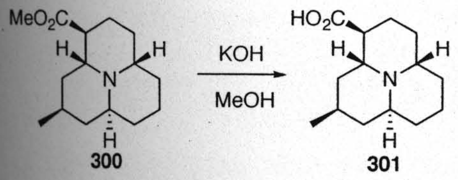
**Ester 300.**



To solution of ester **298** (0.1665 g, 0.66 mmol) in THF (10 mL) at -78 °C was added KHMDS (0.5 *M* in toluene, 4.00 mL, 2.00 mmol). Reaction was stirred at this temperature for 15 min and was allowed to warm up to 0 °C and stirred for another 2 h until complete conversion was observed by TLC. The reaction was quenched by addition of MeOH (1.5 mL). Solvents were removed under reduced pressure, and $H_2O$ (7 mL) was added and product was extracted with $CH_2Cl_2$ (3 × 8 mL). Combined organics were washed with sat aq NaCl (6 mL) and dried over $Na_2SO_4$. Removal of the solvent afforded ester **300** (0.142 g, 86%) as pale yellow oil, which was used for the next step without further purification.

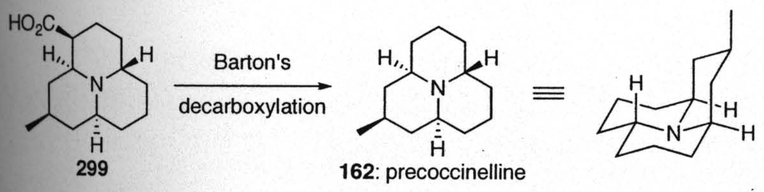
**300**: $R_f = 0.49$ [0.5% $CH_2Cl_2$ in MeOH, neutral $Al_2O_3$]; $^1$H NMR (400 MHz, $CDCl_3$): δ 0.83 (q, 1 H, $J$ = 11.2 Hz), 0.84 (d, 3 H, $J$ = 6.4 Hz), 1.05 – 1.19 (m, 2 H), 1.32 – 1.60 (m, 7 H), 1.64 – 1.72 (m, 1 H), 1.75 – 1.88 (m, 2 H), 1.92 (qd, 1 H, $J$ = 12.8, 3.6 Hz), 2.04 (ddd, 1 H, $J$ = 11.6, 6.4, 3.6 Hz), 2.76 (tt, 1 H, $J$ = 11.2, 2.8 Hz), 2.88 (td, 1 H, $J$ = 11.2, 3.6 Hz), 3.03 – 3.07 (m, 1 H), 3.12 (ddd, 1 H, $J$ =11.2, 6.0, 2.0 Hz), 3.67 (s, 3 H); $^{13}$C NMR (100 MHz, $CDCl_3$): 19.7, 21.3, 22.6, 25.7, 29.7, 31.2, 34.8, 37.5, 38.5, 43.3, 48.8, 51.6, 57.8, 60.7, 176.5; IR (Film) cm$^{-1}$ 2926s, 2865m, 1730s, 1455m, 1366m, 1320s, 1253m, 1161s, 1108s; mass spectrum (APCI): m/z (% rel intensity) 252 (100) $M^+$ + H, 219 (20); *m/e* calcd for $C_{15}H_{26}NO_2$ ($M^+$ + H) 252.1964, found 252.1975.

**Acid 301.**



To solution of ester **300** (0.131 g, 0.52 mmol) in MeOH (7 mL) was added KOH (1.7 *M* in $H_2O$, 3 mL, 5.10 mmol). Reaction was heated at 50 °C for 18 h and monitored by TLC ($Al_2O_3$). After complete consumption of starting material, the reaction mixture was cooled down to room temperature, and MeOH was evaporated under reduced pressure, and $H_2O$ (7 mL) was added subsequently. Aqueous phase was extracted with $CH_2Cl_2$ (2 × 7 mL) to remove impurities, and then acidified with 1 *M* HCl until pH = 3 - 4 before being saturated with solid NaCl. Product was extracted with $CHCl_3$ (5 × 15 mL) and the combined organics were dried over $Na_2SO_4$. Removal of the solvents under reduced pressure afforded acid **301** (0.062 g, 44%) as an HCl salt. **301**: mp = 179 – 184 °C; $^1$H NMR (400 MHz, $CD_3OD$): δ 1.03 (d, 3 H, *J* = 6.0 Hz), 1.26 (q, 1 H, *J* = 12.4 Hz), 1.54 – 2.15 (m, 12 H), 2.27 – 2.32 (m, 1 H), 2.36 (qd, 1 H, *J* = 13.6, 4.0 Hz), 3.27 (td, 1 H, *J* = 12.4, 4.0 Hz), 3.63 – 3.70 (m, 2 H) 3.82 (t, 1 H, *J* = 12.4 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$): 17.8, 21.5, 22.5, 24.3, 27.4, 28.4, 31.3, 34.5, 39.4, 40.0, 52.9, 59.5, 60.7, 173.3; IR (Film) cm$^{-1}$: 3063s, 2949s, 1715s, 1438s, 1198s, 1038s; *m/e* calcd for $C_{14}H_{22}NO_2$ ($M^+$ – H) 236.1651, found 236.1657.

**Precoccinelline (162).**

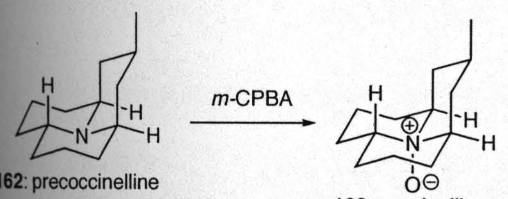


299
162: precoccinelline

To suspension of acid **299** (0.053 g, 0.22 mmol) in THF (4 mL) was added diisopropylethylamine (0.075 ml, 0.45 mmol) and the resulting mixture was cooled down to -10 $^0$C. *i*-BuOCOCl (0.05 ml, 0.38 mmol) was then added and the mixture was stirred at -10 $^0$C for 15 min before being allowed to warm up to room temperature. After 2 h at rt, the mixture was cooled back down to -10 $^0$C and a solution of 2-mercaptopyridine-*N*-oxide (0.057 g, 0.45 mmol) and diisopropylethylamine (0.075 ml, 0.45 mmol) in THF (2 mL) was added. Reaction was stirred at this temperature for 2 h shielded from light. Then *t*-BuSH (0.4 ml, 3.55 mmol) was added and the mixture was irradiated with W-lamp (200 W), while being cooled with water bath. Solvent and excess of *t*-BuSH were removed under reduced pressure and $NaHCO_3$ (5% in $H_2O$, 7 mL) was added. Aqueous phase was extracted with $CH_2Cl_2$ (4 × 5 mL), and the combined organics were washed with sat aq NaCl (5 mL) and dried over $MgSO_4$. After solvent removal under reduced pressure, the crude residue was purified by column chromatography on neutral alumina gel (0.5%-1% MeOH in $CH_2Cl_2$) to yield precoccinelline **(162)** (0.0184 g, 43%) as colorless oil.

**162**: $R_f = 0.29$ [$Et_2O$, neutral $Al_2O_3$]; $^1H$ NMR (400 MHz, $CDCl_3$): δ 0.93 (d, 3 H, $J = 6.8$ Hz), 1.01 (brd, 2 H, $J = 12.8$ Hz), 1.11 – 1.21 (m, 2 H), 1.46 – 1.55 (m, 10 H), 1.57 – 1.66 (m, 1 H), 1.82 – 1.91 (m, 2 H), 2.71 (tt, 1 H, $J = 11.2, 2.4$ Hz), 2.94 (brd, 2 H, $J = 12.0$ Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$): 20.0, 22.9, 31.3, 31.4, 32.8, 34.9, 48.4, 58.3; IR (Film) $cm^{-1}$ 2931s, 2865m, 1730s, 1456s, 1282m, 1196m, 1099s; mass spectrum (APCI): m/z (% rel intensity) 194 (100) $M^+ + H$; *m*/*e* calcd for $C_{13}H_{24}N$ ($M^+ + H$) 194.1909, found 194.1917.

**Coccinelline (163).**



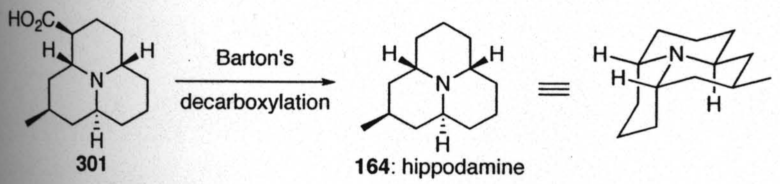
**162**: precoccinelline

**163**: coccinelline

To solution of precoccinelline (0.017 g, 0.09 mmol) in $CH_2Cl_2$ (2 mL) at 0 °C was added *m*-CPBA (88%, 0.030 g, 1.5 mmol). The resulting mixture was stirred at this temperature for 3 h. After which, solvent was removed under reduced pressure, and the crude residue was purified by column chromatography on neutral alumina gel (2% MeOH in $CH_2Cl_2$) to afford coccinelline **(163)** (0.0177 g, 96%) as light tan solid.

**163**: $R_f$ = 0.48 [$CH_2Cl_2$ : MeOH = 10 : 1, neutral $Al_2O_3$]; mp = >200 °C (decomp), lit.[4] mp = >205 °C (decomp); $^1H$ NMR (400 MHz, $CDCl_3$): δ 0.94 (d, 3 H, *J* = 6.0 Hz), 1.22 (br t, 4 H, *J* = 12.4 Hz), 1.44 – 1.51 (m, 4 H), 1.54 (brd, 2 H, *J* = 14.4 Hz), 1.73 (q, 2 H, *J* = 13.6 Hz), 1.80 – 1.88 (m, 1 H), 2.02 – 2.13 (m, 2 H), 2.77 – 2.86 (m, 2 H), 3.24 (brd, 2 H, *J* = 12.0 Hz), 3.36 (tt, 1 H, *J* = 11.6, 2.8 Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$): 18.3, 21.6, 25.7, 27.6, 30.7, 36.0, 58.9, 73.9; IR (Film) $cm^{-1}$ 2925s, 2869s, 1444s, 1374s, 1299s, 1208m, 1044s; mass spectrum (APCI): m/z (% rel intensity) 210 (50) $M^+$ + H, 194 (100); *m/e* calcd for $C_{13}H_{24}NO$ ($M^+$ + H) 210.1858, found 210.1856.

**Hippodamine (164).**



**301**

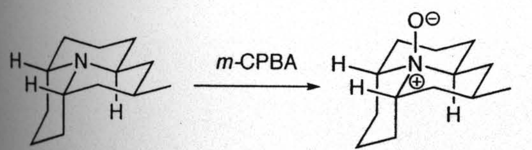
**164**: hippodamine

To suspension of the HCl salt of acid **301** (0.0561 g, 0.20 mmol) in THF (4 mL) was added diisopropylethylamine (0.085 ml, 0.51 mmol), and the resulting mixture was cooled down to -10 °C. After which, *i*-BuOCOCl (0.045 ml, 0.34 mmol) was added and reaction was stirred at -10 °C for 15 min and allowed to warm up to room temperature. After 2 h, the mixture was cooled down to -15 °C and a solution of 2-mercaptopyridine-*N*-oxide (0.052 g, 0.40 mmol) and diisopropylethylamine (0.075 ml, 0.45 mmol) in THF (2 mL) was added. The reaction mixture was stirred at this temperature for 2 h while being shielded from light. Subsequently, *t*-BuSH (0.35 ml, 3.11 mmol) was added and the mixture was irradiated with W-lamp (200 W) while being cooled with water bath. Solvent and excess of *t*-BuSH were removed under reduced pressure and $NaHCO_3$ (5% in $H_2O$, 7 mL) was added. Aqueous phase was extracted with $CH_2Cl_2$

(4 × 6 mL), and the combined organics were washed with sat aq NaCl (6 mL) and dried over $Na_2SO_4$. After solvent removal residue was purified by column chromatography on neutral alumina gel (0.5%-1% MeOH in $CH_2Cl_2$) to yield hippodamine **(164)** (0.0171 g, 43%) as colorless oil.

**164**: $R_f = 0.27$ [$Et_2O$, neutral $Al_2O_3$]; $^1H$ NMR (400 MHz, $CDCl_3$): δ 0.83 (q, 1 H, $J$ = 12.4 Hz), 0.85 (d, 3 H, $J$ = 6.4 Hz), 0.94 – 1.03 (m, 2 H), 1.09 – 1.20 (m, 1 H), 1.44 – 1.58 (m, 8 H), 1.60 – 1.71 (m, 1 H), 1.77 – 1.92 (m, 4 H), 2.83 (tt, 1 H, $J$ = 11.2, 2.8 Hz), 2.95 – 3.01 (m, 2 H); $^{13}C$ NMR (100 MHz, $CDCl_3$): 19.9, 22.5, 22.7, 23.3, 25.9, 26.3, 31.5, 34.8, 40.2, 43.6, 48.1, 58.3, 59.0; IR (Film) $cm^{-1}$ 2924s, 2863m, 1444s, 1364m, 1295m, 1132s, 1081m; mass spectrum (APCI): m/z (% rel intensity) 194 (100) $M^+ + H$; *m/e* calcd for $C_{13}H_{24}N$ ($M^+ + H$) 194.1909, found 194.1918.

**Convergine (165).**



**164**: hippodamine

**165**: convergine

To solution of hippodamine (0.0162 g, 0.08 mmol) in $CH_2Cl_2$ (2 mL) at 0 °C was added *m*-CPBA (88%, 0.030 g, 1.5 mmol). Reaction was stirred at this temperature for 3 h. Then it was washed with KOH (10% in $H_2O$, 5 mL) and aqueous phase was back-extracted with $CH_2Cl_2$ (4 × 6 mL). Combined organics were washed with sat aq NaCl (4 mL) and dried over $Na_2SO_4$. Removal of the solvent gave convergine **(165)** (0.0154 g, 88%) as light tan solid.

165: $R_f = 0.65$ [$CH_2Cl_2$ : MeOH = 7 : 1, neutral $Al_2O_3$]; mp (**165•**HCl)= 234 -239 °C (decomp), lit.[49a] mp = 225 - 230 °C (decomp); $^1H$ NMR (400 MHz, $CDCl_3$): δ 0.92 (d, 3 H, $J$ = 6.4 Hz), 1.26 – 1.33 (m, 4 H), 1.51 – 1.58 (m, 2 H), 1.61 – 1.69 (m, 3 H), 1.73 – 1.83 (m, 1 H), 1.85 (q, 1 H, $J$ = 12.4 Hz), 1.86 – 1.91 (m, 1 H), 2.00 – 2.20 (m, 3 H), 2.58 (td, 1 H, $J$ = 13.2, 5.2 Hz), 2.85 – 2.95 (m, 1 H), 3.34 (brs, 2 H), 3.49 (tt, 1 H, $J$ = 11.6, 2.8 Hz); $^{13}$C NMR (100 MHz, $CDCl_3$): 18.3, 21.7, 23.8, 24.8, 25.8, 27.5, 27.6, 28.3, 34.2, 36.1, 58.8, 74.0, 74.7; IR (Film) cm$^{-1}$ 2927s, 2870m, 1448s, 1371m, 1273m, 1211m, 1124m, 1034m; mass spectrum (APCI): m/z (% rel intensity) 210 (40) M$^+$ + H, 194 (100); *m/e* calcd for $C_{13}H_{24}NO$ (M$^+$ + H) 210.1858, found 210.1851.

## PRECOCCINELLINE COMPARISON NMR TABLE.

| **Data for the Synthetic Precoccinelline**<br>$^{1}$H NMR with TMS reference set at δ = 0.00<br>$^{13}$C NMR with CDCl$_3$ reference set at δ = 77.1 | | **Reported Data for Precoccinelline**[63]<br>$^{1}$H NMR with TMS reference set at δ = 0.00<br>$^{13}$C NMR with CDCl$_3$ reference set at δ = 77.1 | |
|---|---|---|---|
| $^{1}$H NMR, δ (Δδ with lit. data) | $^{13}$C NMR, δ (Δδ with lit. data) | $^{1}$H NMR, δ | $^{13}$C NMR, δ |
| 0.93 (0.01) | 19.9 (0.1) | 0.94 | 19.8 |
| 1.01 (0.02) | 22.8 (0.1) | 1.02 | 22.7 |
| 1.16 (0.02) | 31.2 (0.1) | 1.18 | 31.1 |
| 1.46 – 1.55 | 31.3 (0.1) | 1.50 – 1.56 | 31.2 |
| 1.62 (0.00) | 32.7 (0.1) | 1.62 | 32.6 |
| 1.87 (0.01) | 34.7 (0.1) | 1.88 | 34.6 |
| 2.71 (0.03) | 48.3 (0.0) | 2.74 | 48.3 |
| 2.94 (0.01) | 58.2 (0.1) | 2.95 | 58.1 |

## COCCINELLINE COMPARISON NMR TABLE.

| **NMR Data for the Synthetic Coccinelline**<br>$^1$H NMR with TMS reference set at $\delta = 0.00$<br>$^{13}$C NMR with CDCl$_3$ reference set at $\delta = 77.1$ | | **Reported Data for Coccinelline**[50c]<br>$^1$H NMR with TMS reference set at $\delta = 0.00$<br>$^{13}$C NMR with CDCl$_3$ reference set at $\delta = 77.1$ | |
|---|---|---|---|
| $^1$H NMR, δ (Δδ with lit. data) | $^{13}$C NMR, δ (Δδ with lit. data) | $^1$H NMR, δ | $^{13}$C NMR, δ |
| 0.94 (0.07) | 18.1 (0.3) | 1.01 | 17.8 |
| 2.08 (0.08) | 21.4 (0.3) | 2.16 | 21.1 |
| 2.82 (0.09) | 25.5 (0.3) | 2.91 | 25.2 |
| 3.24 (0.05) | 27.4 (0.3) | 3.29 | 27.1 |
| 3.36 (0.08) | 30.5 (0.2) | 3.44 | 30.3 |
| | 35.8 (0.3) | | 35.5 |
| | 58.6 (0.4) | | 58.2 |
| | 73.6 (0.2) | | 73.4 |

## HIPPODAMINE COMPARISON NMR TABLE.

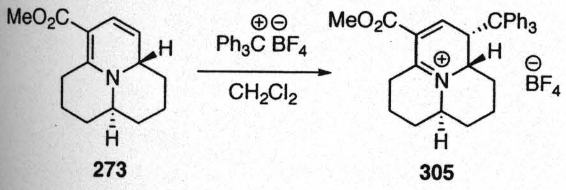
| **NMR Data for the Synthetic Hippodamine**<br>$^{1}$H NMR with TMS reference set at δ = 0.00<br>$^{13}$C NMR with CDCl$_3$ reference set at δ = 77.1 | | **Reported Data for Hippodamine**<br>$^{1}$H NMR with TMS reference at δ = 0.00[49d]<br>$^{13}$C NMR with CDCl$_3$ reference at δ = 77.1[63] | |
|---|---|---|---|
| $^{1}$H NMR, δ, *J*<br>(Δδ with lit. data) | $^{13}$C NMR, δ<br>(Δδ with lit. data) | $^{1}$H NMR, δ | $^{13}$C NMR, δ |
| 0.83 (0.05) | 19.8 (0.1) | 0.78 – 0.87 | 19.7 |
| 0.85 (0.07) | 22.4 (0.1) | 0.78 | 22.3 |
| 1.94 – 1.03 | 22.6 (0.2) | 0.94 – 1.04 | 22.4 |
| 1.09 – 1.20 | 23.2 (0.2) | 1.12 – 1.21 | 23.0 |
| 1.44 – 1.58 | 25.8 (0.2) | 1.44 – 1.59 | 25.6 |
| 1.60 – 1.71 | 26.2 (0.2) | 1.63 – 1.70 | 26.0 |
| 1.77 – 1.92 | 31.4 (0.1) | 1.77 – 1.93 | 31.3 |
| 2.83 (0.00) | 34.7 (0.2) | 2.83 | 34.5 |
| 2.95 – 3.01 | 40.1 (0.2) | 2.95 – 3.00 | 39.9 |
| 3.36 (0.08) | 43.5 (0.2) | 3.44 | 43.3 |
| | 48.0 (0.1) | | 47.9 |
| | 58.2 (0.2) | | 58.0 |
| | 58.9 (0.1) | | 58.8 |

## CONVERGINE COMPARISON NMR TABLE.

| **NMR Data for the Synthetic Convergine**<br>$^1$H NMR with TMS reference set at $\delta = 0.00$<br>$^{13}$C NMR with $CDCl_3$ reference set at $\delta = 77.1$ | | **Reported Data for Convergine**[63]<br>$^1$H NMR with TMS reference set at $\delta = 0.00$<br>$^{13}$C NMR with $CDCl_3$ reference set at $\delta = 77.1$ | |
|---|---|---|---|
| $^1$H NMR, δ, (Δδ with lit. data) | $^{13}$C NMR, δ (Δδ with lit. data) | $^1$H NMR, δ | $^{13}$C NMR, δ |
| 0.92 (0.01) | 18.2 (0.2) | 0.91 | 18.0 |
| 1.26 – 1.33 | 21.6 (0.1) | 1.31 – 1.34 | 21.5 |
| 1.55 (0.01) | 23.7 (0.2) | 1.56 | 23.5 |
| 1.61 – 1.69 | 24.6 (0.1) | 1.65 – 1.68 | 24.5 |
| 1.78 (0.00) | 25.7 (0.1) | 1.78 | 25.6 |
| 1.85 (0.03) | 27.41 (0.12) | 1.82 | 27.29 |
| 1.88 (0.03) | 27.47 (0.14) | 1.85 | 27.33 |
| 2.00 – 2.20 | 28.1 (0.10) | 2.02 – 2.13 | 28.0 |
| 2.58 (0.04) | 34.1 (0.2) | 2.54 | 33.9 |
| 2.90 (0.1) | 35.9 (0.1) | 2.78 | 35.8 |
| 3.34 | 58.6 (0.1) | 3.39 – 3.42 | 58.7 |
| 3.49 (0.04) | 73.9 (0.2) | 3.53 | 73.7 |
| | 74.5 (0.2) | | 74.3 |

## SYNTHESIS OF MYRRHINE.

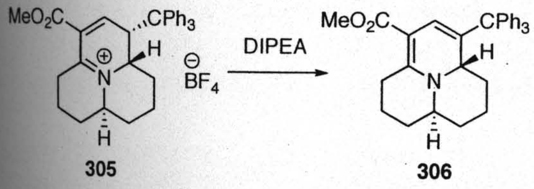
### Tetrafluoroborate salt 305.



To a solution of tricycle **273** (19.3 mg, 82.83 μmol) in $CH_2Cl_2$ (2 mL) was added a triphenylcarbonium tetrafluoroborate (34.0 mg, 102.99 μmol) in one portion at rt. The reaction mixture was stirred for 1 h at rt and then solvent was removed under reduced pressure. Tetrafluoroborate **305** (52.3 mg, ~100%) was obtained as pale yellow solid.

**305:** $^1$H NMR (500 MHz, $CDCl_3$) δ 1.15 – 1.24 (m, 1 H), 1.30 – 1.41 (m, 2 H), 1.73 – 2.00 (m, 5 H), 2.09 – 2.23 (m, 2 H), 2.95 (br t, 1 H, $J$ = 14.0 Hz), 3.02 (brd, 1 H, $J$ = 21.5 Hz), 3.26 – 3.33 (m, 1 H), 3.74 (s, 3 H), 4.47 (brs, 1 H), 5.51 (d, 1 H, $J$ = 15.5 Hz), 7.26 – 7.35 (m, 15 H), 8.00 (d, 1 H, $J$ = 1.5 Hz).

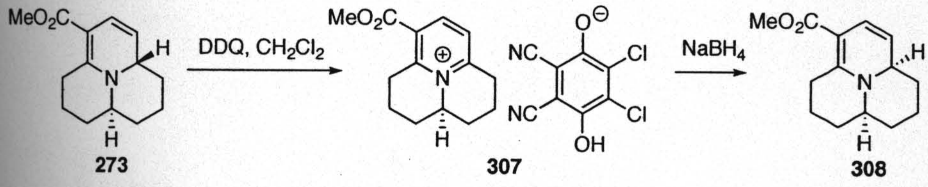
### Tricycle 306.



To a solution of tetrafluoroborate **305** (52.3 mg, 92.89 μmol) in $CDCl_3$ (1 mL) was added diisopropylethylamine (20.0 μL, 122.08 μmol). The reaction mixture was kept for 15 min at rt and solvent was removed under reduced pressure. Tricycle **306** was isolated in ~70% yield via silica gel column chromatography (50% EtOAc in hexanes) as pale yellow solid.

**306:** $^1$H NMR (500 MHz, $CDCl_3$) δ 1.01 – 1.09 (m, 2 H), 1.26 – 1.29 (m, 2 H), 1.33 – 1.45 (m, 2 H), 1.47 – 1.51 (m, 1 H), 1.58 – 1.78 (m, 3 H), 2.59 – 2.68 (m, 1 H), 2.96 – 2.99 (m, 1 H), 3.57 – 3.61 (m, 1 H), 3.59 (s, 3 H), 3.68 (brd, 1 H, *J* = 21.0 Hz), 6.40 (s, 1 H), 7.24 – 7.33 (m, 15 H).

**Tricycle 308.**



To a solution of tricycle **273** (0.086 g, 0.37 mmol) in $CH_2Cl_2$ (7 mL) was added a DDQ (0.092 g, 0.41 mmol) in one portion at 0 °C. An immediate color change from yellow to dark brown was observed. The reaction mixture was stirred vigorously for 1 h at rt and the formation of dark brown oil on the bottom of the flask occurred, at which time, the stirring was stopped. The reaction mixture was cooled down to 0 °C, and $CH_2Cl_2$ was carefully decanted, leaving behind the precipitated brown oil that solidified upon placing the flask on the high vacuum. The brown solid was pulverized, washed with $Et_2O$ (7 mL), and dried on high vacuum to give pyridinium salt **307** (0.155 g, 87%) as brown solid.

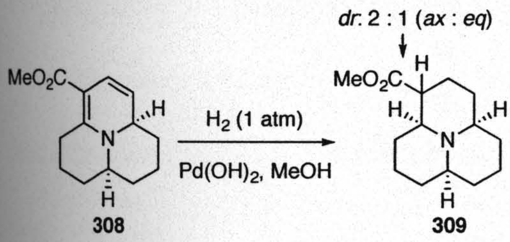
**307:** $^1$H NMR (500 MHz, $CD_3OD$) δ 1.87 – 1.95 (m, 4 H), 2.08 – 2.15 (m, 2 H), 2.42 – 2.46 (m, 2 H), 3.26 – 3.42 (m, 3 H), 3.86 (dt, 1 H, *J* = 18.0, 6.5 Hz), 4.02 (s, 3 H), 4.56 (septet, 1 H, *J* = 5.0 Hz), 7.88 (d, 1 H, *J* = 8.5 Hz), 8.72 (d, 1 H, *J* = 8.5 Hz).

To a stirring solution of pyridinium salt **307** (29.0 mg, 0.0637 mmol) in MeOH (1 mL) was added a $NaBH_4$ (~10.0 mg, 0.27 mmol) at rt. The reaction mixture was stirred at rt and then solvent was evaporated. Residue was submitted to flash column chromatography using $NEt_3$

deactivated (2% in EtOAc : hexanes = 9 : 1) silica gel (eluent: 10% EtOAc in hexanes). Tricycle **308** (6.0 mg, 41%) was obtained as yellow oil.

**308:** $^1$H NMR (400 MHz, $CDCl_3$) δ 1.43 (brd, 1 H, *J* = 12.8 Hz), 1.57 – 2.34 (m, 9 H), 2.92 – 2.99 (m, 2 H), 3.21 (tt, 1 H, *J* = 18.8, 5.2 Hz), 3.62 (s, 3 H), 4.18 (brd, 1 H, *J* = 11.2 Hz), 4.77 (dd, 1 H, *J* = 10.0, 3.6 Hz), 6.38 (dd, 1 H, *J* = 10.0, 1.2 Hz).

**Hydrogenation of tricycle 308.**

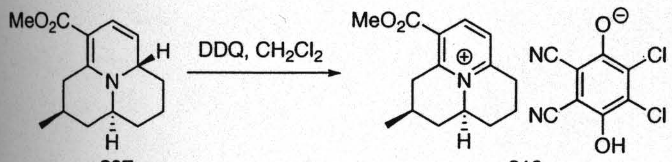


A solution of tricycle salt **308** (6.0 mg, 25.8 mmol) in glacial MeOH (1 mL) was hydrogenated over $Pd(OH)_2/C$ (5.0 mg) at 1 atm of $H_2$ overnight. After filtering off the catalyst, MeOH was evaporated under reduced pressure and the crude product was purified by filtration through short column chromatography using $NEt_3$ deactivated (2% in EtOAc : hexanes = 9 : 1) silica gel (eluent: 10% EtOAc in hexanes) to afford the all-*syn* tricycle **309** (5.1 mg, 84%) as an inseparable 2 : 1 mixture of axial and equatorial esters.

**309-*ax*:** $^1$H NMR (400 MHz, $CDCl_3$) δ 1.26 – 1.39 (m, 4 H), 1.28 – 1.80 (m, 12 H), 1.88 – 1.98 (m, 2 H), 2.07 (ddd, 1 H, *J* = 11.2, 3.6, 2.8 Hz), 2.51 – 2.55 (m, 1 H), 3.65 (s, 3 H).

**309-*eq*:** $^1$H NMR (400 MHz, $CDCl_3$) δ 1.26 – 1.39 (m, 4 H), 1.28 – 1.80 (m, 12 H), 1.88 – 1.98 (m, 2 H), 2.15 (t, 1 H, *J* = 10.0 Hz), 2.38 (ddd, 1 H, *J* = 12.0, 10.0, 3.6 Hz), 3.66 (s, 3 H).

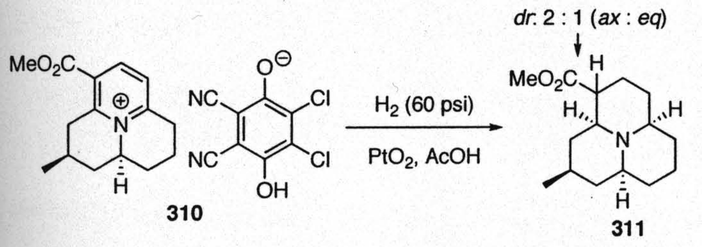
**Pyridinium salt 310.**



To a solution of tricycle **287** (0.253 g, 1.02 mmol) in $CH_2Cl_2$ (7 mL) was added a warm solution of DDQ (0.270 g, 1.19 mmol) in $CH_2Cl_2$ (20 mL). An immediate color change from yellow to dark brown was observed. The reaction mixture was stirred vigorously for 1 h at rt and the formation of dark brown oil on the bottom of the flask occurred, at which time, the stirring was stopped. The reaction mixture was cooled down to 0 °C, and $CH_2Cl_2$ was carefully decanted, leaving behind the precipitated brown oil that solidified upon placing the flask on the high vacuum. The brown solid was pulverized, washed with $Et_2O$ (7 mL), and dried on high vacuum to give pyridinium salt **310** (0.414 g, 85%) as orange solid.

**310:** mp = 125 – 130 °C (decomp); $^1$H NMR (400 MHz, $CD_3OD$) δ 1.14 (d, 3 H, *J* = 6.4 Hz), 1.55 (q, 1 H, *J* = 12.4 Hz), 1.70 – 1.90 (m, 2 H), 2.11 – 2.25 (m, 2 H), 2.38 – 2.44 (m, 2 H), 2.49 – 2.59 (m, 1 H), 3.18 – 3.36 (m, 2 H), 3.62 (ddd, 1 H, *J* = 18.8, 5.2, 2.4 Hz), 3.97 (s, 3 H), 4.54 (tt, 1 H, *J* = 11.2, 4.4 Hz), 7.84 (d, 1 H, *J* = 8.4 Hz), 8.66 (d, 1 H, *J* = 8.4 Hz); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 17.3, 21.6, 25.17, 25.25, 30.0, 37.9, 54.1, 55.0, 64.0, 100.6, 116.4, 126.9, 129.9, 131.5, 145.5, 154.3, 159.1, 161.9, 165.1; IR (Film) cm$^{-1}$ 2956m, 2226s, 1734s; 1618s, 1564m, 1437s, 1278s, 1207s, 1135s, 1079s.

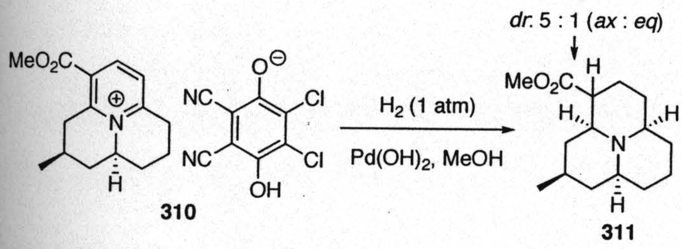
**Hydrogenation of Pyridinium Salt 310.**



A solution of pyridinium salt **310** (40.0 mg, 90.0 mmol) in glacial AcOH (2 mL) was hydrogenated over pre-reduced Adams' catalyst $PtO_2$ (10.0 mg) in a Parr apparatus at 60 psi of $H_2$ overnight. After filtering off the catalyst, AcOH was evaporated under reduced pressure, and aq NaOH (1 *M*, 0.5 mL) and $H_2O$ (1 mL) were added to the highly colored residue. The resulting mixture was extracted with $Et_2O$ (5 × 4 mL), and the combined organic layers were washed with sat aq NaCl (5 mL) and dried over $MgSO_4$. After removal of excess solvents under reduced pressure, the crude product was purified by flash column chromatography using $NEt_3$ deactivated (2% in EtOAc : hexanes = 9 : 1) silica gel (eluent: 30% EtOAc in hexanes) to afford the all-*syn* tricycle **311** (13.3 mg, 63%) as an inseparable 2 : 1 mixture of axial and equatorial esters.

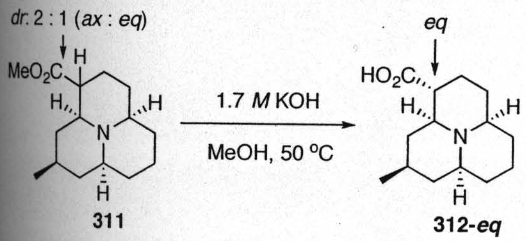
**311-*ax*:** $R_f = 0.29$ [10% EtOAc in hexanes, neutral $Al_2O_3$]; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.86 (d, 3 H, *J* = 6.4 Hz), 1.00 (q, 1 H, *J* = 11.6 Hz), 1.17 (q, 1 H, *J* = 11.6 Hz), 1.26 – 1.59 (m, 10 H), 1.61 – 1.66 (m, 1 H), 1.71 – 1.79 (m, 2 H), 1.87 – 1.95 (m, 2 H), 2.09 (ddd, 1 H, *J* = 11.6, 4.0, 2.4 Hz), 2.54 (ddt, 1 H, *J* = 6.8, 4.0, 1.6 Hz), 3.66 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 22.2, 24.5, 27.0, 29.9, 31.0, 34.0, 34.2, 40.5, 42.5, 45.2, 51.2, 62.9, 63.2, 63.4, 174.3.

**311-*eq*:** $R_f = 0.29$ [10% EtOAc in hexanes, neutral $Al_2O_3$]; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.85 (d, 3 H, *J* = 6.4 Hz), 0.89 – 1.06 (m, 2 H), 1.26 – 1.59 (m, 10 H), 1.61 – 1.66 (m, 1 H), 1.71 – 1.79 (m, 2 H), 1.87 – 1.95 (m, 2 H), 2.18 (td, 1 H, *J* = 10.8, 2.0 Hz), 2.37 (ddd, 1 H, *J* = 12.4, 10.8, 4.0 Hz), 3.67 (s, 3 H); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 22.1, 24.2, 28.4, 30.1, 32.8, 34.3, 34.4, 40.1, 42.6, 49.9, 51.7, 61.8, 62.2, 62.9, 175.9; IR (Film) cm$^{-1}$ 2925s, 2862s, 2793m, 2734m, 2619m, 1737s, 1445m, 1374m, 1152s; mass spectrum (APCI): m/e (% relative intensity) 252 (100) $M^+ + H$.



A solution of pyridinium salt **310** (0.131 g, 0.280 mmol) in MeOH (2 mL) was hydrogenated over $Pd(OH)_2/C$ (10.0 mg) with $H_2$-balloon for 8 h. After filtering off the catalyst, MeOH was evaporated under reduced pressure, and aq NaOH (1 *M*, 0.5 mL) and $H_2O$ (1 mL) were added to the highly colored residue. The resulting mixture was extracted with $Et_2O$ (5 × 4 mL), and the combined organic layers were washed with sat aq NaCl (5 mL) and dried over $MgSO_4$. After solvent removal under reduced pressure, the crude product was purified by flash column chromatography using $NEt_3$ deactivated (2% in EtOAc : hexanes = 9 : 1) silica gel (eluent: 30% EtOAc in hexanes) to afford the all-*syn* tricycle **311** (30.0 mg, 44%) as an inseparable 5 : 1 mixture of axial and equatorial esters.

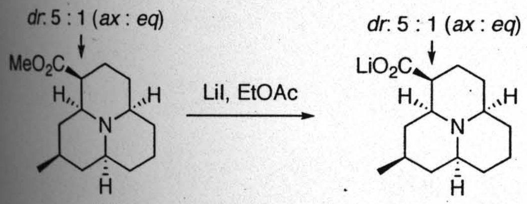
**KOH-Hydrolysis of Ester 311.**



To a solution of esters **311** (20.8 mg, 80.0 mmol) in MeOH (1.5 mL) was added KOH (1.7 *M* in $H_2O$, 500.0 mL, 8.50 mmol). The reaction mixture was heated at 50 °C for 36 h and monitored by TLC ($Al_2O_3$). After complete consumption of the starting material, the mixture was cooled to rt, and after which, MeOH was evaporated under reduced pressure and $H_2O$ (2 mL) was added. The aqueous phase was extracted with $CH_2Cl_2$ (1 × 2 mL) to remove impurities, and then acidified with 1 *M* HCl until pH = 3 - 4 before being saturated with solid NaCl. The crude product was extracted with $CHCl_3$ (6 × 5 mL) and the combined organic layers were dried over $Na_2SO_4$. Removal of $CHCl_3$ under reduced pressure afforded acid 56-*eq* (9.80 mg, 50%) as colorless solid.

**312-*eq*:** $^1$H NMR (500 MHz, $CDCl_3$) δ 0.96 (d, 3 H, $J$ = 6.0 Hz), 1.54 (qt, 1 H, $J$ = 13.5, 3.5 Hz), 1.63 – 1.91 (m, 9 H), 1.98 (brd, 1 H, $J$ = 13.5 Hz), 2.13 – 2.23 (m, 3 H), 2.30 (q, 1 H, $J$ = 13.0 Hz), 2.80 (t, 1 H, $J$ = 12.0 Hz), 2.87 (t, 1 H, $J$ = 12.0 Hz), 3.09 (t, 1 H, $J$ = 11.5 Hz), 3.25 (td, 1 H, $J$ = 11.5, 3.5 Hz), 11.15 (brs, 1 H).

### LiI-Hydrolysis of Ester 311.

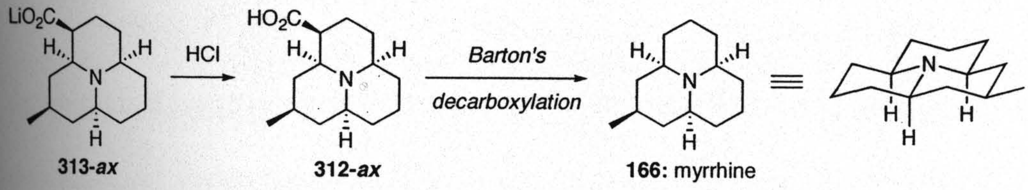


**311** **313-*ax***

A solution of ester **311** (29.9 mg, 0.120 mmol) and LiI (65.0 mg, 0.490 mmol) in EtOAc (1.5 mL) was heated at 80 °C in a sealed tube overnight shielded from light with Al-foil. The reaction mixture was cooled down to rt, and the precipitate was filtered off, and the filter cake was washed with EtOAc (1 mL) and $Et_2O$ (1 mL), and dried on high vacuum to afford Li-carboxylate **313-*ax*** (21.0 mg, 73%) as slightly brown solid.

**313-*ax***: mp = > 200 °C; $^1$H NMR (400 MHz, $CD_3OD$) δ 0.96 (d, 3 H, *J* = 6.0 Hz), 1.25 (q, 1 H, *J* = 12.0 Hz), 1.55 – 1.70 (m, 4 H), 1.77 – 2.02 (m, 10 H), 2.59 (brs, 1 H), 3.07 (tt, 1 H, *J* = 12.0, 2.4 Hz), 3.10 – 3.18 (m, 1 H), 3.21 (dd, 1 H, *J* = 11.6, 2.4 Hz); $^{13}$C NMR (100 MHz, $CD_3OD$) δ 21.6, 23.3, 24.3, 26.9, 29.3, 29.7, 33.1, 33.6, 38.9, 40.7, 64.8, 65.5, 65.8, 180.4; IR (Film) cm$^{-1}$: 2931s, 2871s, 2730m, 2652m, 1573s, 1425s, 1415s, 1187m, 1047m.

### Synthesis of Myrrhine (166).



Li-carboxylate **313-*ax*** (11.8 mg, 50.0 mmol) was dissolved in $H_2O$ and acidified with 1% aq HCl until pH = 3–4 before being saturated with solid NaCl. The mixture was extracted with $CHCl_3$ (5 × 5 mL) and the combined organic layers were dried over $Na_2SO_4$. Removal of $CHCl_3$ under reduced pressure afforded acid **312-*ax*** (3.80 mg) as colorless solid.

**312-*ax***: $^1$H NMR (500 MHz, $CDCl_3$) δ 0.91 (d, 3 H, *J* = 6.5 Hz), 1.17 (q, 1 H, *J* = 11.5 Hz), 1.40 – 1.50 (m, 3 H), 1.53 – 1.60 (m, 1 H), 1.64 (brd, 1 H, *J* = 14.0 Hz), 1.68 – 1.79 (m, 8 H), 2.06 – 2.09 (m, 1 H), 2.24 (t, 1 H, *J* = 11.5, 2.4 Hz), 2.32 (t, 1 H, *J* = 10.5 Hz), 2.44 (d, 1 H, *J* = 11.0 Hz), 2.61 (brs, 1 H); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 21.6, 23.6, 27.0, 29.4, 29.7, 33.3, 33.7, 39.2, 40.8, 46.9, 62.7, 62.9, 63.2, 176.5; mass spectrum (APCI): m/e (% relative intensity) 238 (100) M$^+$ + H.

To a suspension of above acid **312-*ax*** (3.80 mg, 16.0 mmol) in THF (0.5 mL) was added diisopropylethylamine (8.00 mL, 48.0 mmol) and the resulting mixture was cooled down to -10 °C. *i*-BuOCOCl (4.00 mL, 31.0 mmol) was then added and the mixture was stirred at -10 °C for 15 min before being allowed to warm up to rt. After 2 h at rt, the mixture was cooled back down to -10 °C and a solution of 2-mercaptopyridine-*N*-oxide (40.0 mg, 31.0 mmol) and diisopropylethylamine (6.00 mL, 36.0 mmol) in THF (0.5 mL) was added. The reaction mixture was stirred at this temperature for 2 h while being shielded from light. After which, *t*-BuSH (30.0 mL, 0.270 mmol) was added and the mixture was irradiated with W-lamp (200 W), while being cooled in a water bath. Excess of solvent and *t*-BuSH were removed under reduced pressure and 5% aq $NaHCO_3$ (2 mL) was added. The aqueous phase was extracted with $Et_2O$ (5 × 3 mL), and the combined organic layers were washed with sat aq NaCl (2 mL) and dried over $MgSO_4$. After concentration under reduced pressure, the crude residue was filtered through a short plug of deactivated silica gel (2% $NEt_3$ in 10% EtOAc in hexanes) with 20% EtOAc in hexanes. Solvent removal under reduced pressure afforded myrrhine **166** (*ca.* 2.90 mg, 75%) as colorless oil.

**166:** $R_f = 0.60$ [10% EtOAc in hexanes, neutral $Al_2O_3$]; $^1H$ NMR (400 MHz, $CDCl_3$) δ 0.86 (d, 3 H, $J = 6.4$ Hz), 1.04 (q, 2 H, $J = 12.0$ Hz), 1.30 – 1.38 (m, 6 H), 1.44 – 1.50 (m, 1 H), 1.52 – 1.57 (m, 6 H), 1.64 – 1.67 (m, 2 H), 1.79 – 1.84 (m, 1 H), 1.86 (brt, 2 H, $J = 10.0$ Hz); $^{13}C$ NMR (100 MHz, $CDCl_3$) δ 22.1, 24.3, 30.4, 34.0, 34.1, 42.6, 62.3, 62.5; IR (Film) $cm^{-1}$ 2924s, 2852s, 2730m, 1464s, 1426m, 1377m, 1315m; mass spectrum (APCI): m/e (% relative intensity) 194 (100) $M^+ + H$; *m/e* calcd for $C_{13}H_{24}N$ ($M^+ + H$) 194.1909, found 194.1915.

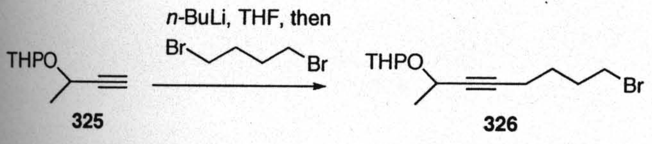
## MYRRHINE COMPARISON NMR TABLE.

| **NMR Data for the Synthetic Myrrhine**<br>$^1$H NMR with TMS reference set at δ = 0.00<br>$^{13}$C NMR with CDCl$_3$ reference set at δ = 77.1 | | **Reported Data for Myrrhine**[63]<br>$^1$H NMR with TMS reference set at δ = 0.00<br>$^{13}$C NMR with CDCl$_3$ reference set at δ = 77.1 | |
|---|---|---|---|
| $^1$H NMR, δ (Δδ with lit. data) | $^{13}$C NMR, δ (Δδ with lit. data) | $^1$H NMR, δ | $^{13}$C NMR, δ |
| 0.86 (0.00) | 22.1 (0.1) | 0.86 | 22.0 |
| 1.04 (0.00) | 24.3 (0.0) | 1.04 | 24.3 |
| 1.30 – 1.38 | 30.4 (0.1) | 1.34, 1.38 | 30.3 |
| 1.44 – 1.50 | 34.0 (0.0) | 1.47 | 34.0 |
| 1.52 – 1.57 | 34.1 (0.1) | 1.54, 1.56 | 34.0 |
| 1.64 – 1.67 | 42.6 (0.0) | 1.65 | 42.6 |
| 1.79 – 1.84 (0.01) | 62.3 (0.1) | 1.82 | 62.2 |
| 1.86 (0.01) | 62.5 (0.3) | 1.85 | 62.2 |

## PART 3.

## ENONE VERSION OF INTRAMOLECULAR *AZA*-[3 + 3] ANNULATION.

### Bromide 326.



To a solution of THP-protected propargyl alcohol[69] **325** (8.08 g, 52.40 mmol) in THF (65 mL) was added *n*-BuLi (2.5 *M* in hexanes, 26.0 mL, 65.0 mol) at -78 °C. The reaction was stirred at this temperature for 40 min before 1,3-dibromobutane (31.0 mL, 261.0 mmol) was added in one portion. The resulting mixture was allowed to warm up to rt and was stirred for 72 h before it was quenched with $H_2O$ (2 mL). Reaction mixture was concentrated under reduced pressure and then diluted with $H_2O$ (60 mL) Aqueous layer was back-extracted with $CH_2Cl_2$ (3 × 50 mL). The combined organic layers were washed with sat aq NaCl (100 mL) and dried over $Na_2SO_4$. Solvents and excess of 1,3-dibromobutane were removed under reduced pressure and the crude residue was purified via Kugelrohr distillation. Bromide **326** (13.40 g, 88%) was collected at 130-140 °C (0.15 mmHg) as inseparable 4.5 : 1 mixture of two diastereomers.

326: $R_f = 0.45$ [15% EtOAc in petroleum ether];

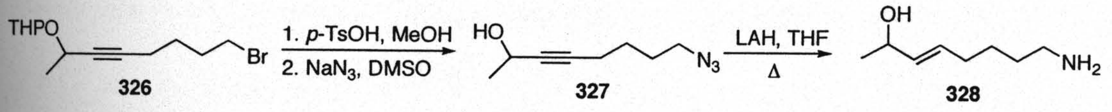
***major isomer:*** $^1$H NMR (500 MHz, $CDCl_3$): δ 1.43 (d, 3 H, $J = 7.0$ Hz), 1.53 – 1.62 (m, 4 H), 1.66 (quint, 2 H, $J = 7.5$ Hz), 1.72 – 1.78 (m, 1 H), 1.81 – 1.86 (m, 1 H), 1.77 (quint, 2 H, $J = 7.5$ Hz), 2.26 (td, 2 H, $J = 7.0, 2.0$ Hz), 3.43 (t, 2 H, $J = 6.5$ Hz), 3.50 – 3.54 (m, 1 H), 3.82 (ddd, 1 H, $J = 11.5, 8.0, 3.5$ Hz), 4.53 (qd, 1 H, $J = 7.0, 2.0$ Hz), 4.92 (t, 1 H, $J = 3.0$ Hz).

***minor isomer:*** $^1$H NMR (500 MHz, $CDCl_3$): δ 1.41 (d, 3 H, $J = 6.5$ Hz), 1.53 – 1.62 (m, 4 H), 1.63 – 1.71 (m, 2 H), 1.72-1.78 (m, 1 H), 1.81 – 1.86 (m, 1 H), 1.92 (quint, 2 H, $J = 7.5$ Hz), 2.27

(td, 2 H, $J = 7.0, 2.0$ Hz), 3.43 (t, 2 H, $J = 6.5$ Hz), 3.50 – 3.54 (m, 1 H), 3.98 (ddd, 1 H, $J = 11.5, 8.0, 3.0$ Hz), 4.46 (qd, 1 H, $J = 6.5, 2.0$ Hz), 4.75 (t, 1 H, $J = 3.5$ Hz).

IR (film) cm$^{-1}$ 2941s, 2868s, 2362w, 2212m, 1728s, 1712s, 1676s, 1440s, 1116s.

**Amino alcohol 328.**



To a solution of bromide **326** (5.27 g, 18.2 mmol) in MeOH (50 mL) was added *p*-TsOH (0.30 g, 1.6 mmol). After stirring at rt for 1.5 h, the starting material disappeared as observed using TLC analysis [$R_f = 0.14$, 15% EtOAc in petroleum ether]. The acid was neutralized by addition of solid $NaHCO_3$ (0.40 g), and the excess solid was filtered off and MeOH was evaporated under reduced pressure.

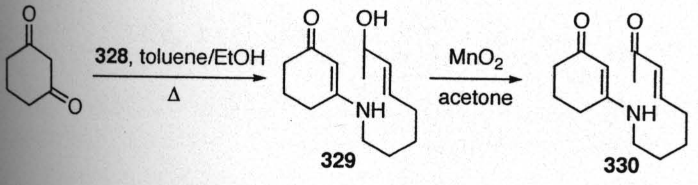
To a solution of the above crude residue in DMSO (60 mL) was added $NaN_3$ (2.32 g, 31.1 mmol). The reaction mixture was stirred for 2 h at rt before water (100 mL) was added. The aqueous layer was extracted with MTBE (4 × 70 mL), and the combined organic fractions were washed with sat aq NaCl (70 mL) and dried over $Na_2SO_4$. Removal of the solvent under reduced pressure provided azide **327** (2.85 g, 94% over two steps) as colorless oil, which was used for the next step without further purification. Product could be purified by filtration through short silica gel column with MTBE as isocratic eluent.

**327**: $^1$H NMR (300 MHz, $CDCl_3$) δ 1.19 (s, 1 H, OH), 1.43 (d, 3 H, $J = 6.6$ Hz), 1.54 – 1.65 (m, 2 H), 1.67 – 1.77 (m, 2 H), 2.27 (td, 2 H, $J = 6.9, 2.1$ Hz), 3.31 (t, 2 H, $J = 6.6$ Hz), 4.47 – 4.57 (m, 1 H).

To a suspension of LAH (3.90 g, 102.77 mmol) in THF (150 mL) was added slowly dropwise a solution of azido alcohol **327** (2.85 g, 17.04 mmol) in THF (50 mL) while keeping the temperature below 30 °C. When the reaction slowed down, the mixture was heated to reflux for 36 h. The excess LAH was quenched by addition of sat aq $Na_2SO_4$ (ca. 10 mL). The resulting white precipitate was filtered off and the filter cake was washed with MTBE (2 × 30 mL). The filtrate was dried over $Na_2SO_4$ and concentrated under reduced pressure to yield amino alcohol **328** (2.20 g, 90%) as pale yellow oil.

**328**: $^1$H NMR (300 MHz, $CDCl_3$) δ 1.25 (d, 3 H, *J* = 6.3 Hz), 1.41 – 1.63 (br m, 7 H), 2.04 (q, 2 H, *J* = 6.3 Hz), 2.69 (t, 2 H, *J* = 6.9 Hz), 4.26 (quint, 1 H, *J* = 6.3 Hz), 5.48 – 5.68 (m, 2 H).

**Enone 330.**



A solution of amino alcohol **328** (2.20 g, 15.36 mmol) and 1,3-cyclohexanedione (1.72 g, 15.34 mmol) in toluene (50 mL) and EtOH (5 mL) was heated at 80 °C for 6 h. The solvents were removed under reduced pressure, and the residue was purified via silica gel flash column chromatography [gradient eluent: $CH_2Cl_2$/MeOH (10 : 1) to $CH_2Cl_2$/MeOH (7 : 1)] to give amide **329** (1.91 g, 47%) as a yellow solid.

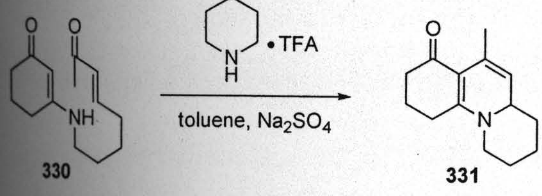
**329:** $R_f$ = 0.34 [$CH_2Cl_2$ : $CH_3OH$ = 7 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.26 (d, 3 H, *J* = 6.5 Hz), 1.45 (quint, 2H, *J* = 7.5 Hz), 1.57 – 1.63 (m, 2 H), 1.97 (quint, 2 H, *J* = 7.0 Hz), 2.07 (q, 2 H, *J* = 7.0 Hz), 2.32 (t, 2 H, *J* = 6.5 Hz), 2.33 (t, 2 H, *J* = 6.5 Hz), 3.08 (q, 2 H, *J* = 6.5 Hz), 4.28 (quint, 1 H, *J* = 6.5 Hz), 4.52 (brs, 1 H, NH), 5.13 (s, 1 H), 5.55 (dd, 1 H, *J* = 15.5, 6.0 Hz), 5.55

(dt, 1 H, $J$ = 15.5, 6.0 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) □ 22.1, 23.7, 26.5, 27.8, 29.9, 31.6, 36.5, 42.8, 68.6, 96.6, 129.7, 135.5, 164.9, 197.4; IR (film) cm$^{-1}$ 3256brm, 3073m, 2934m, 1534s, 1454m, 1368m, 1255s; mass spectrum (APCI): m/e (% relative intensity) 238 (85) M$^+$ + H, 220 (100), 192 (10).

To a solution of allyl alcohol **329** (0.6556 g, 2.76 mmol) in acetone (30 mL) was added activated $MnO_2$ (5.5 g, 88% *Acros*, 71.89 mmol). The reaction mixture was stirred for 2 h and monitored through TLC analysis [$CH_2Cl_2$/MeOH (7 : 1)]. After which, the solid was filtered off and the filter cake was washed with acetone. The filtrate was concentrated under reduced pressure and crude product was purified by filtration through short silica gel column with EtOAc/MeOH (7 : 1) as isocratic eluent. Enone **330** (0.3868, 60%) was obtained as yellow oil.

**330:** $R_f$ = 0.45 [$CH_2Cl_2$ : $CH_3OH$ = 7 : 1]; $^1$H NMR (500 MHz, $CDCl_3$) δ 1.51 – 1.58 (m, 2 H), 1.60 – 1.66 (m, 2 H), 1.98 (quint, 2 H, $J$ = 6.5 Hz), 2.25 (s, 3 H), 2.26 (qd, 2 H, $J$ = 7.0, 1.5 Hz), 2.32 (t, 4 H, $J$ = 6.5 Hz), 3.10 (q, 2 H, $J$ = 6.5 Hz), 4.42 (brs, 1 H, NH), 5.12 (s, 1 H), 6.09 (dt, 1 H, $J$ = 15.5, 1.5 Hz), 6.77 (dt, 1 H, $J$ = 15.5, 7.0 Hz), 9.51 (d, 1H, $J$ = 7.8 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 22.1, 25.6, 27.1, 28.1, 29.8, 32.1, 36.6, 42.7, 96.6, 131.7, 147.4, 164.9, 194.3, 198.7; IR (film) cm$^{-1}$ 3254brm, 3073m, 2942m, 1673s, 1538s, 1470m, 1364m, 1254s, 1190s; mass spectrum [APCI] *m/e* (% relative intensity) 236 (100) M$^+$ + H, 218 (15).

**Cycloadduct 331.**



*Procedure with conventional heating.*

To solution of an enone **330** (0.0324 g, 0.138 mmol) in toluene (4 mL) were added powdered $Na_2SO_4$ (~0.10 g) and piperidinium trifluoroacetate salt (0.0274 g, 0.138 mmol). Reaction was heated under $N_2$ atmosphere at 85 °C for 5 hours until complete consumption of the starting material was observed by TLC analysis. After cooling the reaction to rt it was diluted with EtOAc (4 mL) and successively washed with $H_2O$ (3 mL) and sat aq $NaHCO_3$ (4 mL). Aqueous washes were back-extracted with EtOAc (4 mL). Combined organic phase were washed with brine (6 mL) and dried over $Na_2SO_4$. Evaporation of the solvent afforded tricycle **331** (0.015 g, 50%) as yellow oil which slowly solidified upon keeping on high vacuum. Product could also be further purified by silica gel column chromatography [gradient eluent: $CH_2Cl_2$ to $CH_2Cl_2$/MeOH (10 : 1)].

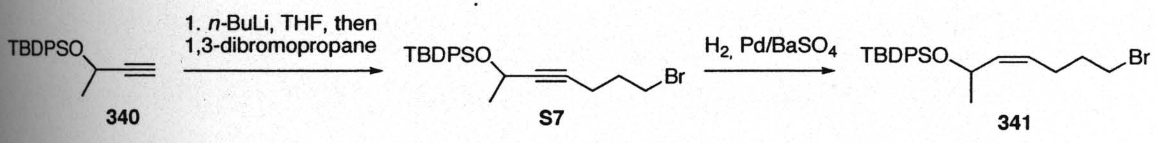
**331:** $^1$H NMR (500 MHz, $CDCl_3$) δ 1.46 (brd, 1 H, $J$ = 12.5 Hz), 1.50 – 1.61 (m, 2 H), 1.67 – 1.75 (m, 2 H), 1.87 – 1.93 (m, 3 H), 2.12 (s, 3 H), 2.27 (t, 2 H, $J$ = 7.5 Hz), 2.38 (ddd, 1H, $J$ = 17.0, 8.0, 5.5 Hz), 2.51 (dt, 1 H, $J$ = 17.0, 6.0 Hz), 2.77 (td, 1 H, $J$ = 12.5, 2.5 Hz), 3.96 – 4.02 (m, 2 H), 4.73 (dd, 1 H, $J$ = 3.5, 1.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 20.8, 22.6, 25.1, 26.9, 27.1, 33.7, 37.3, 48.7, 60.4, 107.9, 113.9, 132.2, 160.7, 192.8.

*Procedure with microwave irradiation.*

Mixture of an enone **330** (0.0759 g, 0.322 mmol), piperidinium trifluoroacetate salt (0.019 g, 0.095 mmol, 30 mol%) and powdered $Na_2SO_4$ (~0.10 g) in EtOAc (3 mL) and toluene (4.5 mL) was microwaved on high (2 × 15 min) in a sealed tube. Additional portion of piperidinium trifluoroacetate (0.037 g, 0.186 mmol, 60 mol%) was added to reaction mixture and microwave irradiation continued for another 3 × 20 min. After cooling the reaction to rt it was diluted with EtOAc (4 mL) and washed with $H_2O$ (2 × 10 mL). Aqueous washes were back-extracted with EtOAc (10 mL). Combined organic phase were washed with brine (10 mL) and dried over $Na_2SO_4$. Evaporation of the solvent afforded tricycle **331** (0.048 g, 68%) as dark yellow oil. Product was purified by silica gel column chromatography [gradient eluent: $CH_2Cl_2$ to $CH_2Cl_2$/MeOH (10 : 1)] to afford pure cycloadduct **331** (0.0337 g, 54%) as yellow oil which slowly solidified upon keeping on high vacuum.

## STUDIES TOWARD PROPYLEINE.

### Bromide 341.



To a solution of 1-butyne-3-ol (16.5 mL, 0.210 mol) and imidazole (12.85 g, 0.188 mol) in THF (80 mL) was added solution of TBDPSCl (51.87 g, 0.188 mol) in THF (50 mL) dropwise over 15-20 min. Reaction was allowed to stir at rt for 3 h before $H_2O$ (100 mL) was added. Layers were separated and aqueous phase was back-extracted with $CH_2Cl_2$ (2 × 50 mL). The combined organic layers were washed with sat aq NaCl (100 mL) and dried over $Na_2SO_4$. Solvents were removed under reduced pressure and the crude residue was purified by vacuum distillation. Alkyne **340** (48.37 g, 83%) was collected at 130-135 $^{o}$C (0.3 mmHg) as colorless oil. **340**: $^1$H NMR (500 MHz, $CDCl_3$): δ 1.08 (s, 9 H), 1.39 (d, 3 H, *J* = 6.5 Hz), 2.33 (d, 2 H, *J* = 2.0 Hz), 4.45 (qd, 1 H, *J* = 6.5, 2.0 Hz), 7.36 – 7.40 (m, 4 H), 7.41 – 7.45 (m, 2 H), 7.68 (dd, 2 H, *J* = 7.5, 1.5 Hz), 7.75 (dd, 2 H, *J* = 8.0, 1.5 Hz).

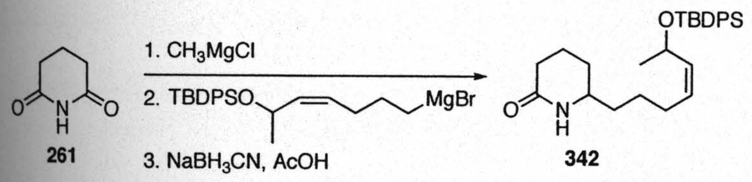
To a solution of alkyne **340** (48.37 g, 0.157 mol) in THF (200 mL) was added *n*-BuLi (2.5 *M* in hexanes, 80.0 mL, 0.200 mol) at -78 °C. The reaction was stirred at this temperature for 20 min before 1,3-dibromopropane (80.0 mL, 0.785 mol) was added in one portion. The resulting mixture was allowed to warm up to rt and was stirred for 72 h before it was quenched with $H_2O$ (100 mL). Aqueous layer was back-extracted with MTBE (2 × 50 mL). The combined organic layers were washed with sat aq NaCl (100 mL) and dried over $Na_2SO_4$. Solvents and excess of 1,3-dibromopropane were removed under reduced pressure and the crude residue was purified via Kugelrohr distillation. Bromide **S7** (59.63 g, 88%) was collected at 190-195 °C (0.3 mmHg) as pale yellow oil.

**S7**: $^1$H NMR (500 MHz, $CDCl_3$): δ 1.06 (s, 9 H), 1.39 (d, 3 H, $J$ = 6.5 Hz), 1.87 (quint, 2 H, $J$ = 7.0 Hz), 2.25 (td, 2 H, $J$ = 7.0, 2.0 Hz), 3.36 (t, 2 H, $J$ = 6.5 Hz), 4.47 (qt, 1 H, $J$ = 6.5, 2.0 Hz), 7.36 – 7.44 (m, 6 H), 7.69 (dd, 2 H, $J$ = 7.5, 1.5 Hz), 7.74 (dd, 2 H, $J$ = 8.0, 1.5 Hz); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 17.6, 19.4, 25.6, 27.1, 31.5, 32.6, 60.3, 82.2, 84.0, 127.6, 127.8, 129.8, 129.9, 134.1, 134.2, 136.0, 136.2.

A suspension of 5% $Pd/BaSO_4$ catalyst (2.04 g) in petroleum ether (120 mL) was pre-reduced via hydrogenation until the color changed from complete brown to black (within ~ 20-30 min). After which, quinoline (2.0 mL) was added to the above suspension and the resulting mixture was stirred for 15 min before a solution of bromide **S7** (24.2 g, 56.35 mmol) in petroleum ether (120 mL) was added. The reaction mixture was hydrogenated with a $H_2$-balloon for 5 h until complete consumption of the starting material was observed through $^1$H NMR. The excess solvent was removed under reduced pressure and the crude residue was purified via Kugelrohr distillation. Bromide **341** (23.0 g, 95%) was collected at 165-170 °C (0.1 mmHg) as a pale yellow oil.

**341:** $^1$H NMR (300 MHz, CDCl$_3$) δ 1.04 (s, 9 H), 1.18 (d, 3 H, $J$ = 6.3 Hz), 1.59 – 1.86 (m, 4 H), 3.17 (t, 2 H, $J$ = 6.6 Hz), 4.57 (quint, 1 H, $J$ = 6.6 Hz), 5.10 (dt, 1 H, $J$ = 11.1, 6.6 Hz), 5.55 (dd, 1 H, $J$ = 11.1, 8.7 Hz), 7.32 – 7.45 (m, 6 H), 7.65 – 7.70 (m, 4 H); $^{13}$C NMR (75 MHz, CDCl$_3$) δ 19.4, 24.9, 26.1, 27.1, 32.6, 33.3, 66.0, 126.3, 127.6, 127.7, 129.68, 129.73, 134.4, 134.7, 136.0, 136.1, 136.3.

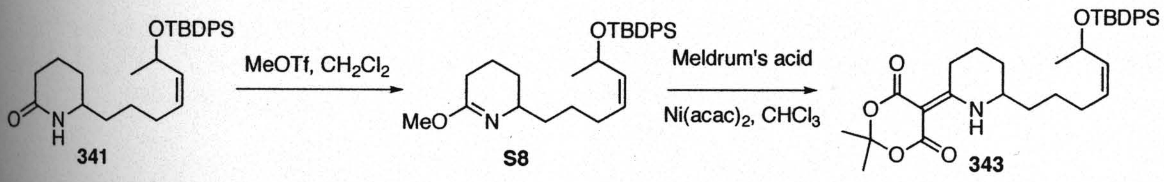
**Lactam 342.**



To a solution of glutarimide (2.85 g, 25.20 mmol) in THF (80 mL) was added CH$_3$MgCl (3 *M* in THF, 9.0 mL, 27.0 mmol) dropwise at 0 °C. The reaction mixture was allowed to warm up to rt and was stirred for 30 min and then cooled back down to 0 °C. A warm solution of Grignard reagent (35-40 °C to prevent precipitation) in THF (30 mL) prepared from bromide **341** (16.23 g, 37.60 mmol) and Mg (1.04 g, 43.33 mmol) through activation using dibromoethane (0.50 mL, 5.80 mmol) was added *via* a cannula. The resulting reaction mixture was stirred for 12 h at rt before NaBH$_3$CN (1.74 g, 27.69 mmol) and HOAc (7.5 mL) were added successively. After stirring at ambient temperature for 45 min, reaction was quenched with sat aq NaHCO$_3$ solution (80 mL). After layer separation, the organic phase was washed with an additional portion of NaHCO$_3$ solution (80 mL). Aqueous washes were back-extracted with EtOAc (3 × 80 mL). The combined organic layers were washed with sat aq NaCl (2 × 50 mL) and dried over Na$_2$SO$_4$. After solvent removal under reduced pressure, the crude residue was purified through two silica gel columns (1st: 0%-50% acetone in EtOAc; 2nd: 7%-10% MeOH in $CH_2Cl_2$) to afford lactam **342** (8.70 g, 77%) as thick colorless oil.

**342:** $^1H$ NMR (300 MHz, $CDCl_3$) δ 0.95 – 1.09 (m, 1 H), 1.07 (s, 9 H), 1.13 – 1.27 (m, 6 H), 1.17 (d, 3 H, *J* = 6.0 Hz), 1.57 – 1.71 (m, 3 H), 1.78 – 1.89 (m, 2 H), 2.22 (td, 1 H, *J* = 6.0, 3.0 Hz), 2.31 – 2.62 (m, 1 H), 3.18 – 3.26 (m, 1 H), 4.54 (quint, 1 H, *J* = 6.3 Hz), 5.12 (dt, 1 H, *J* = 12.0, 7.2 Hz), 5.53 (dd, 1 H, *J* = 12.0, 8.4 Hz), 5.66 (brs, 1 H, NH), 7.33 – 7.46 (m, 6 H), 7.63 – 7.71 (m, 4 H).

### Meldrum's Acid Derivative 343.



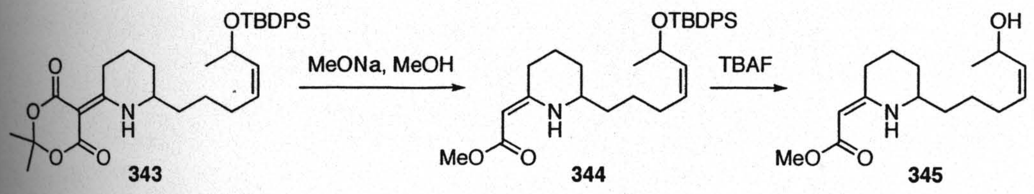
To a solution of lactam **341** (1.10 g, 2.45 mmol) in $CH_2Cl_2$ (15 mL) was added freshly distilled MeOTf (0.35 mL, 3.09 mmol). The reaction mixture was stirred at ambient temperature for 8 h before reaction mixture was treated with cold 5% aq $Na_2CO_3$ (20 mL). After layers separation aqueous phase was extracted with $CH_2Cl_2$ (2 × 10 mL). Combined organics were washed with sat aq NaCl (15 mL), and dried over $Na_2SO_4$. Removal of the excess solvent gave lactim ether **S8** as colorless oil, which was used for the next step without further purification.

To a solution of the above lactim ether **S8** in $CHCl_3$ (15 mL) were successively added Meldrum's acid (0.350 g, 2.43 mmol) and $Ni(acac)_2$ catalyst (*ca.* 25.0 mg). The reaction mixture was heated in sealed tube at 70-80 °C for 18 h under $N_2$ atmosphere. Upon solvent removal under reduced pressure, the crude residue was purified by silica gel flash column chromatography

(20%-50% EtOAc in hexanes) to give Meldrum's acid derivative **343** (0.74 g, 52% over 2 steps) as colorless oil.

**343:** $^1$H NMR (500 MHz, $CDCl_3$) δ 1.03 (s, 9 H), 1.17 (d, 3 H, *J* = 6.0 Hz), 1.22 – 1.41 (m, 5 H), 1.60 – 1.71 (m, 3 H), 1.67 (s, 3 H), 1.68 (s, 3 H), 1.86 – 1.91 (m, 2 H), 2.92 – 2.99 (m, 1 H), 3.31 – 3.36 (m, 2 H), 4.52 – 4.58 (m, 1 H), 5.15 (dt, 1 H, *J* = 11.0, 7.0 Hz), 5.54 (t, 1 H, *J* = 11.0 Hz), 7.33 – 7.44 (m, 6 H), 7.65 – 7.69 (m, 4 H), 11.62 (brs, 1 H, NH).

**Alcohol 345.**

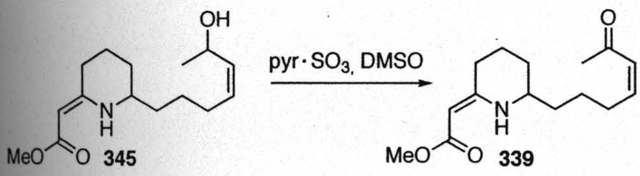


To a solution of MeONa prepared by dissolving Na metal (0.640 g, 27.82 mmol) in anhyd MeOH (35 mL) was added a solution of compound **343** (3.22 g, 5.59 mmol) in MeOH (35 mL). The reaction mixture was heated to reflux overnight. After cooling the reaction mixture to rt, MeOH was evaporated and $H_2O$ (60 mL) was added to the crude residue, and subsequently, aq HCl (1 *M*) was also added dropwise to adjust pH to 5-6. The resulting mixture was extracted with $CH_2Cl_3$ (3 × 70 mL), the combined organic layers were washed with sat aq NaCl (2 × 25 mL) and dried over $Na_2SO_4$. Upon removal of excess solvents under reduced pressure, the crude vinylogous urethane **344** was submitted to the next step without further purification.

To a solution of crude vinylogous urethane **344** in THF (30 mL) was added TBAF solution (1 *M* in THF, 6.4 mL, 6.4 mmol). Reaction mixture was stirred at rt for 2 h before another portion of TBAF solution (5.0 mL, 5.0 mmol) was added. After complete consumption of starting material as observed by TLC analysis THF was removed under reduced pressure and the residue was purified by silica gel column chromatography (50% EtOAc in hexanes) to yield allyl alcohol **345** (1.18 g, 79% over 2 steps) as colorless oil. $^{13}$C NMR spectra confirmed presence of two diatereomers in 1 : 1 ratio.

**345:** $^1$H NMR (500 MHz, $CDCl_3$) δ 1.25 (d, 3 H, *J* = 6.0 Hz), 1.36 (qd, 1 H, *J* = 10.5, 3.5 Hz), 1.46 – 1.66 (m, 5 H), 1.75 – 1.81 (m, 1 H), 1.87 – 1.94 (m, 1 H), 2.03 – 2.14 (m, 1 H), 2.16 – 2.26 (m, 1 H), 2.31 – 2.35 (m, 2 H), 3.27 (brs, 1 H), 3.61 (s, 3 H), 4.37 (s, 1 H), 4.64 (brs, 1 H), 5.40 – 5.48 (m, 2 H), 8.85 (brs, 1 H, NH) 8.89 (brs, 1 H, NH); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.7, 23.7, 23.8, 25.76, 25.84, 27.1, 27.6, 29.4, 29.5, 29.6, 36.5, 36.8, 50.1, 50.2, 51.6, 52.0, 63.7, 63.9, 79.88, 79.92, 130.2, 130.4, 134.8, 134.9, 163.0, 163.1, 171.4.

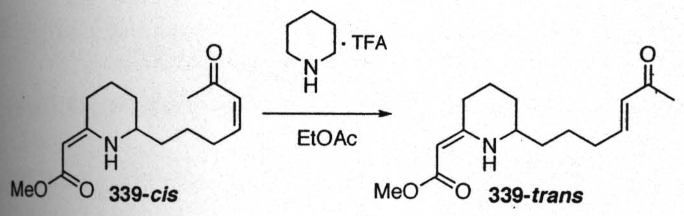
**Enone 339.**



To the pyr•$SO_3$ complex (0.273 g, 1.72 mmol) were added pyridine (0.14 mL, 1.75 mmol) and DMSO (0.30 mL, 4.22 mmol) successively at rt. The resulting suspension was stirred at rt for 15 min before $CH_2Cl_2$ (2 mL) was added, and then the mixture was cooled to 0 °C. A pre-cooled solution of alcohol **345** (0.2293 g, 0.86 mmol), diisopropylethylamine (0.50 mL, 3.01 mmol), and DMSO (0.30 mL, 4.22 mmol) in $CH_2Cl_2$ (5 mL) was added to the suspension dropwise. The reaction mixture was stirred at 0 °C for 1 h before $H_2O$ (6 mL) was added. After layers were separated, the organic phase was washed once with $H_2O$ (6 mL). The combined aqueous washes were back-extracted with $CH_2Cl_2$ (2 × 6 mL). The combined organic phases were washed with 1.0% aq HCl (2 × 7 mL), aq $NaHCO_3$ (6 mL), sat aq NaCl (6 mL) and dried over $Na_2SO_4$. Removal of the excess solvent gave enone **339** (0.1938 g, 85%) as yellow oil. It was used for the annulation reaction without further purification.

**339-*cis***: $^1$H NMR (500 MHz, $CDCl_3$) δ 1.36 (dddd, 1 H, *J* = 13.5, 11.5, 10.0, 3.5 Hz), 1.49 – 1.63 (m, 5 H), 1.75 – 1.80 (m, 1 H), 1.88 – 1.93 (m, 1 H), 2.21 (s, 3 H), 2.32 (q, 2 H, *J* = 5.5 Hz), 2.65 (qd, 2 H, *J* = 7.0, 1.0 Hz), 3.25 – 3.29 (m, 1 H), 3.62 (s, 3 H), 4.36 (s, 1 H), 6.06 (dt, 1 H, *J* = 11.5, 7.5 Hz), 6.16 (brd, 1 H, *J* = 11.5 Hz), 8.81 (brs, 1 H, NH); $^{13}$C NMR (125 MHz, $CDCl_3$) δ 19.7, 25.2, 29.2, 29.38, 29.40, 31.8, 36.9, 50.0, 51.9, 79.9, 127.6, 147.8, 163.0, 171.2, 199.4.

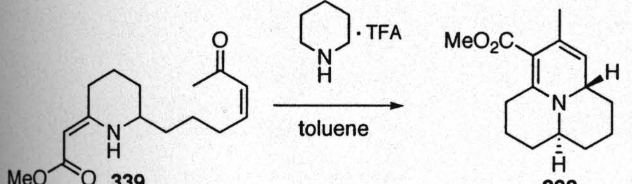
**Enone 339 isomerization.**



To a solution of freshly prepared enone **339** (30.8 mg, 0.116 mmol) in freshly distilled EtOAc (4 mL) under $N_2$ atmosphere were added powdered $Na_2SO_4$ (~ 100.0 mg) and piperidinium trifluoroacetate (23.0 mg, 0.115 mmol). The reaction mixture was heated at 55 °C until complete consumption of strating material (~12-14 h) as indicated by TLC analysis (**339-*trans*** has lower $R_f$-value). Then the excess solvent was evaporated under reduced pressure. The crude residue was submitted to silica gel flash column chromatography (50% EtOAc in hexanes). Enone **339-*trans*** (25.0 mg, 85%) was obtained as yellow oil.

**339-*trans***: $^1$H NMR (400 MHz, $CDCl_3$) δ 1.34 – 1.40 (m, 1 H), 1.49 – 1.70 (m, 5 H), 1.75 – 1.83 (m, 1 H), 1.89 – 1.93 (m, 1 H), 2.25 – 2.29 (m, 2 H), 2.25 (s, 3 H), 2.30 – 2.35 (m, 2 H), 3.27 (sextet, 1 H, *J* = 5.6 Hz), 3.62 (s, 3 H), 4.38 (s, 1 H), 6.09 (dt, 1 H, *J* = 16.0, 1.6 Hz), 6.78 (dt, 1 H, *J* = 16.0, 6.8 Hz), 8.84 (brs, 1 H, NH).

**Cycloadduct 338.**



**339**

**338**

To a solution of freshly prepared enone **339** (193.8 mg, 0.730 mmol) in dry degassed toluene (7 mL) under $N_2$ atmosphere were added powdered $Na_2SO_4$ (~ 100.0 mg) and piperidinium trifluoroacetate (150.0 mg, 0.750 mmol). The reaction mixture was heated at 100 °C for 5 h before the excess solvent was evaporated under reduced pressure. The crude residue was submitted to flash column chromatography using silica gel deactivated with $NEt_3$ (2% in EtOAc : hexanes = 9 : 1) eluted with 10% EtOAc in hexanes). Cycloadduct **338** (60.3 mg) was obtained as very air-sensitive yellow oil with significant contamination according to $^1H$ NMR analysis.

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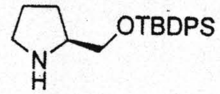
# Appendix

# Selected $^1$H and $^{13}$C NMR Spectra



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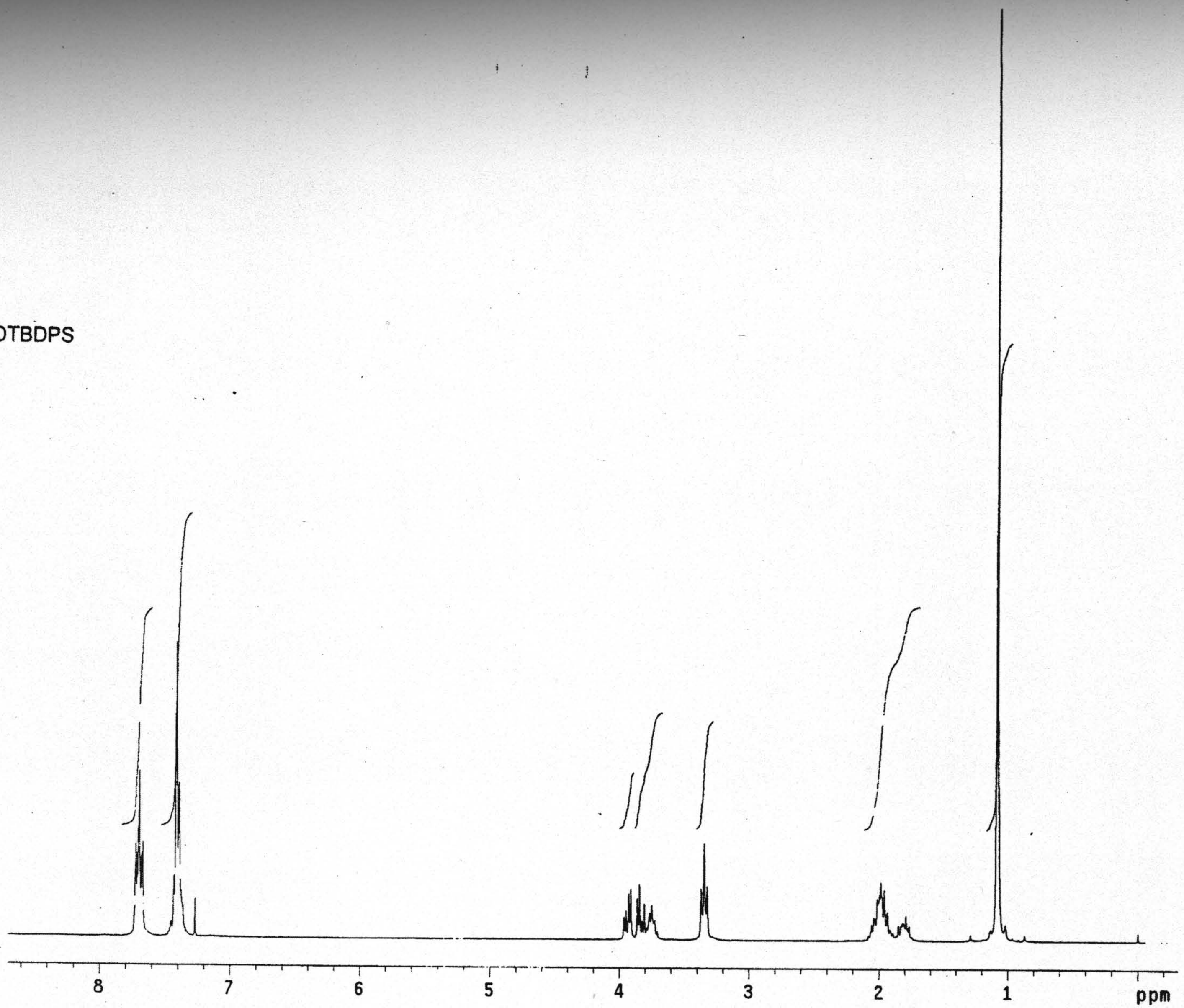

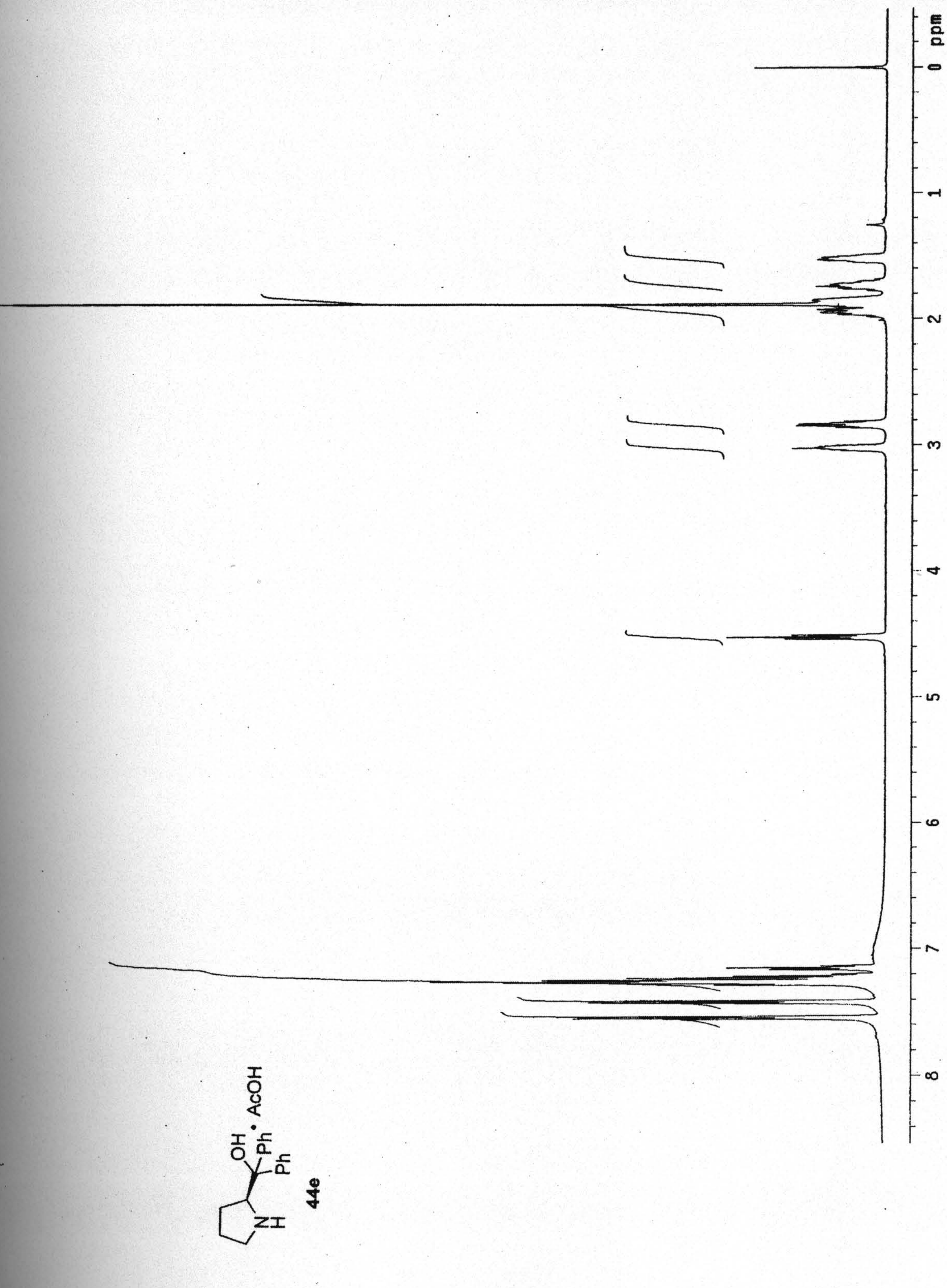

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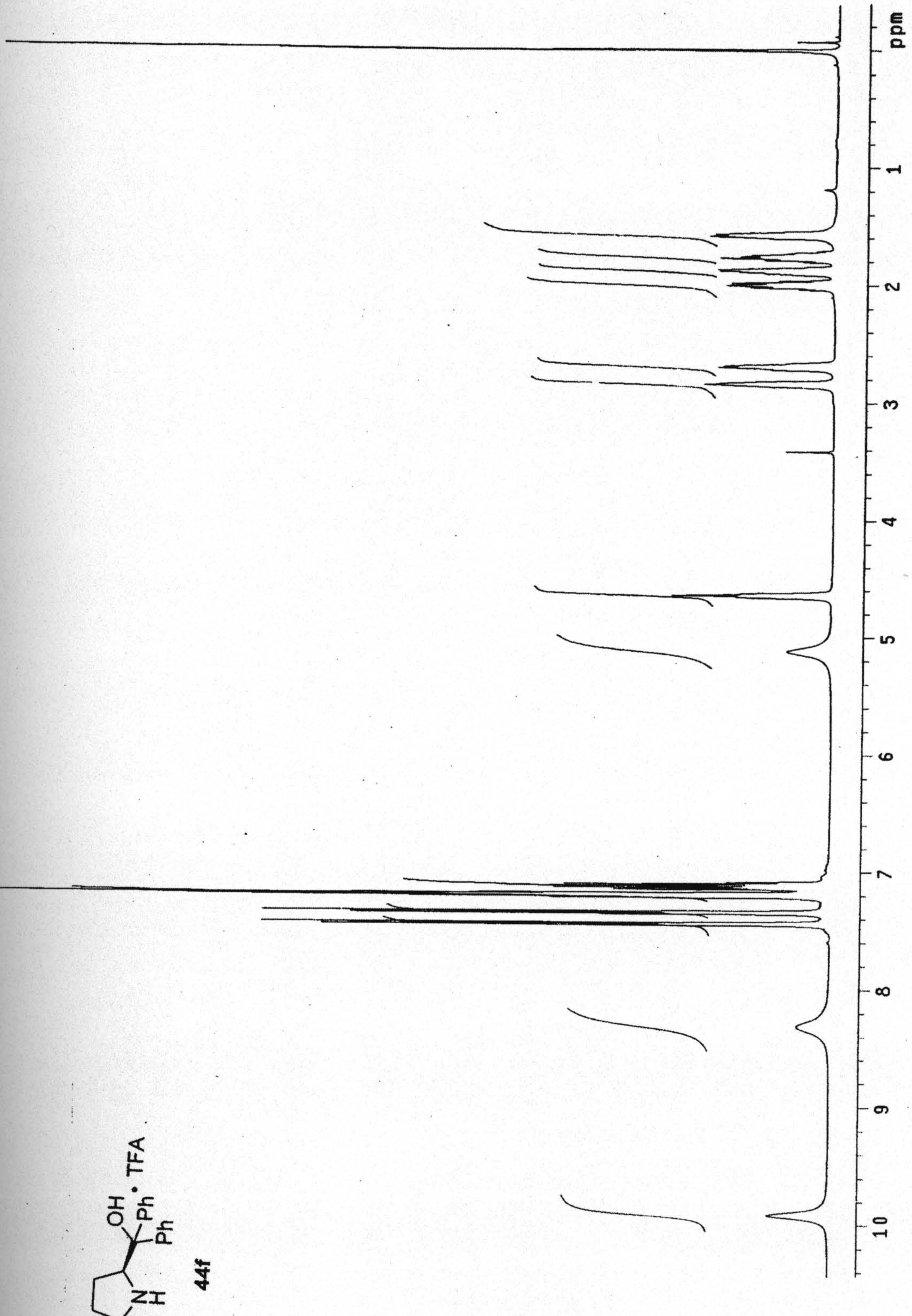

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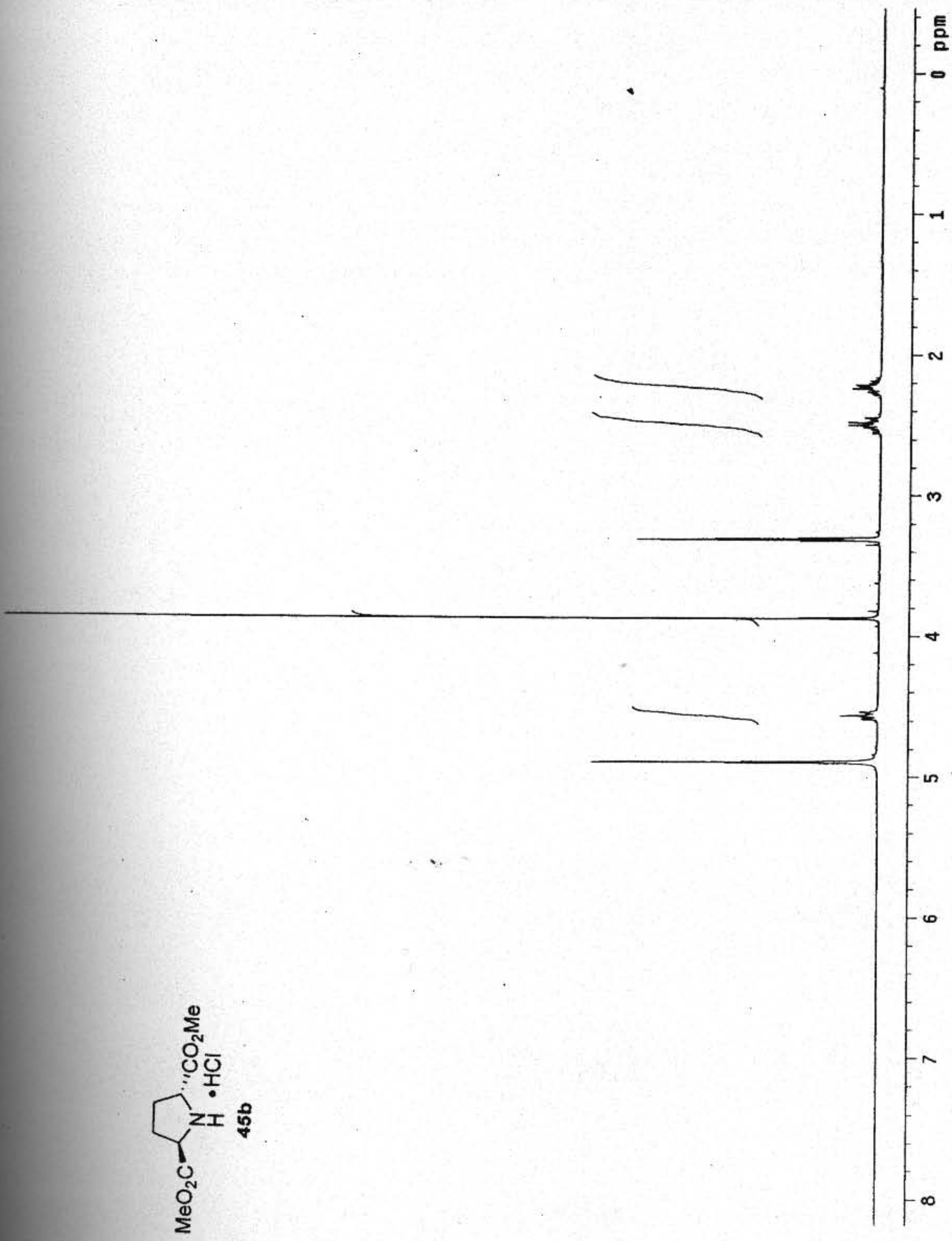

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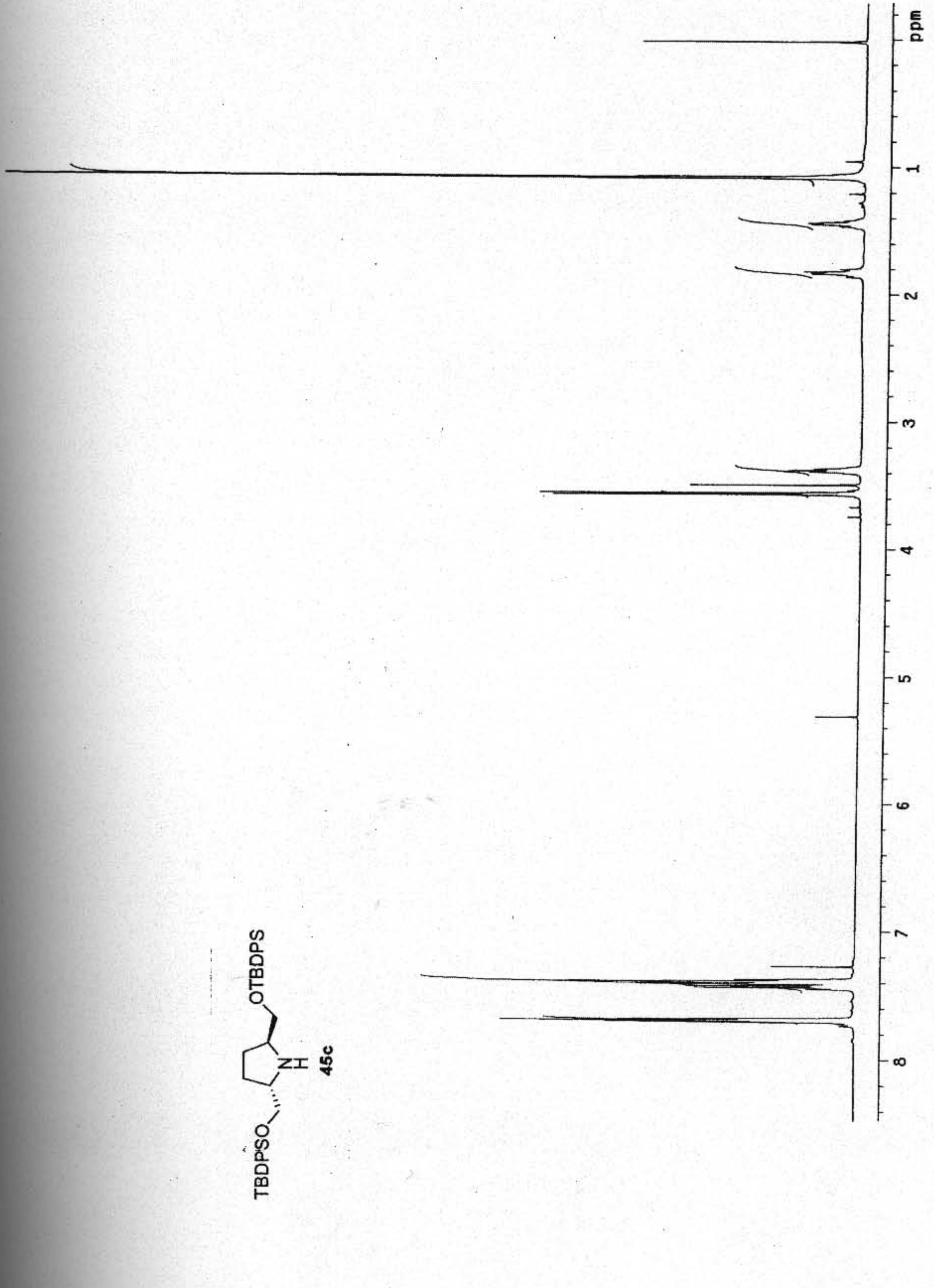

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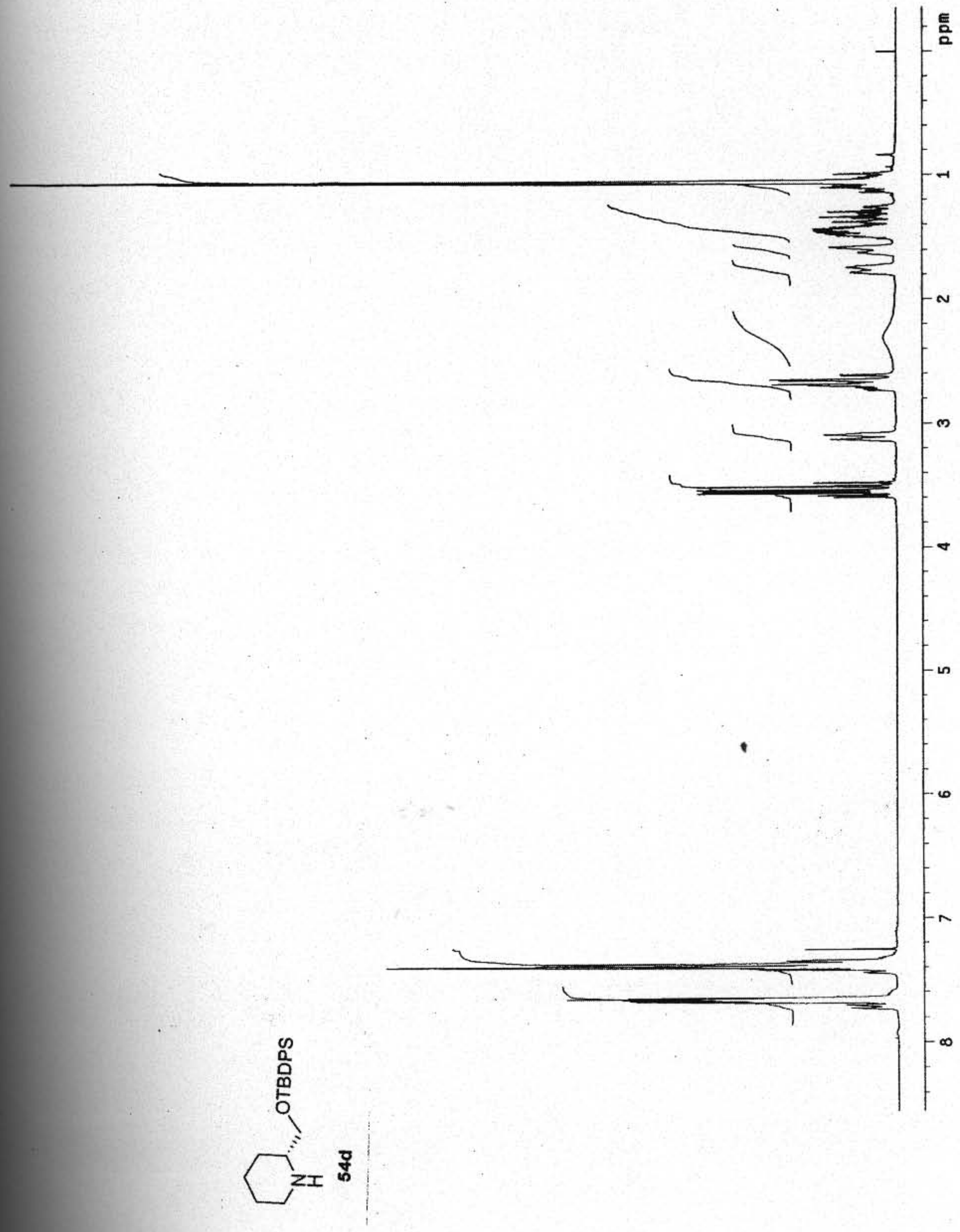

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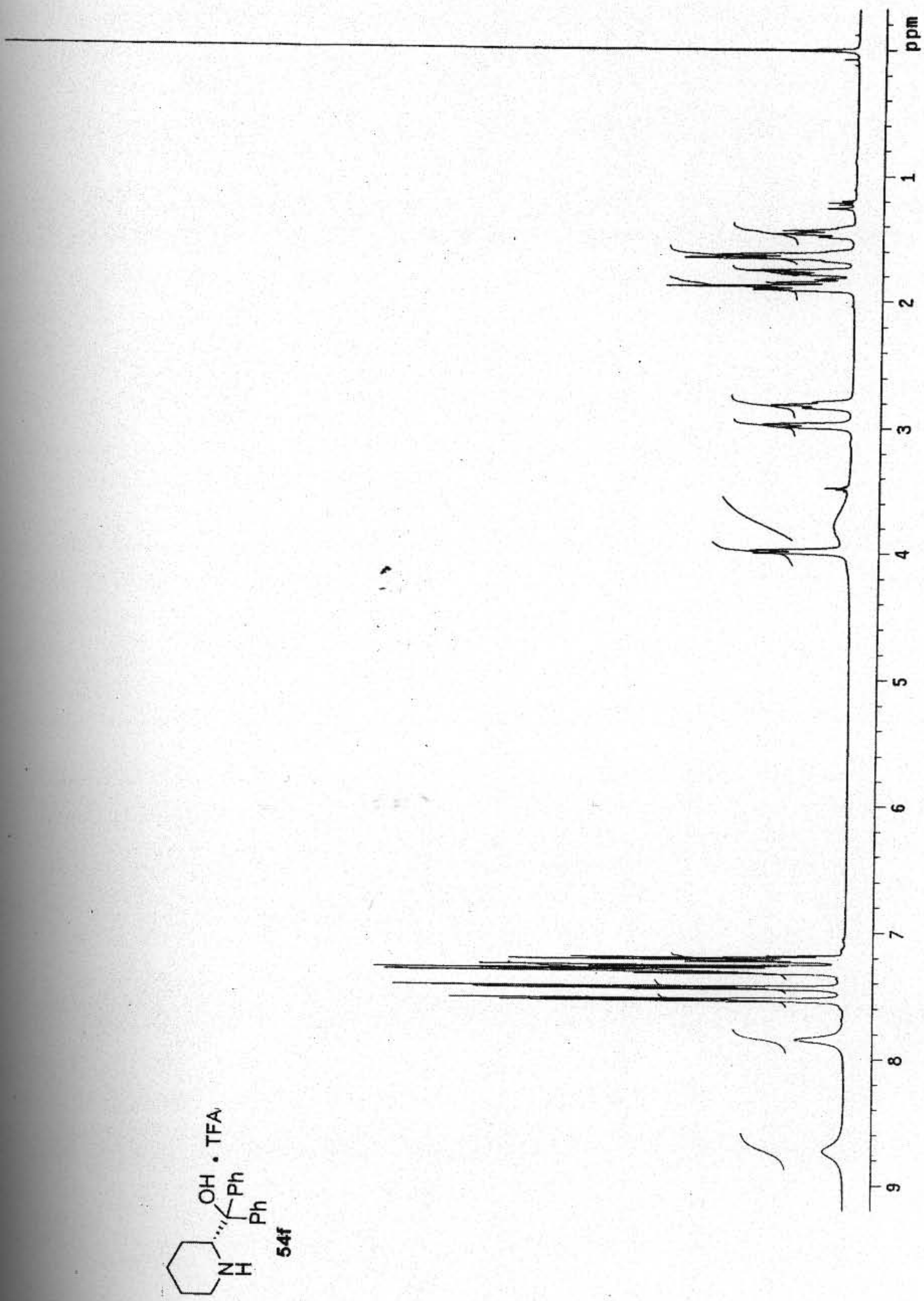

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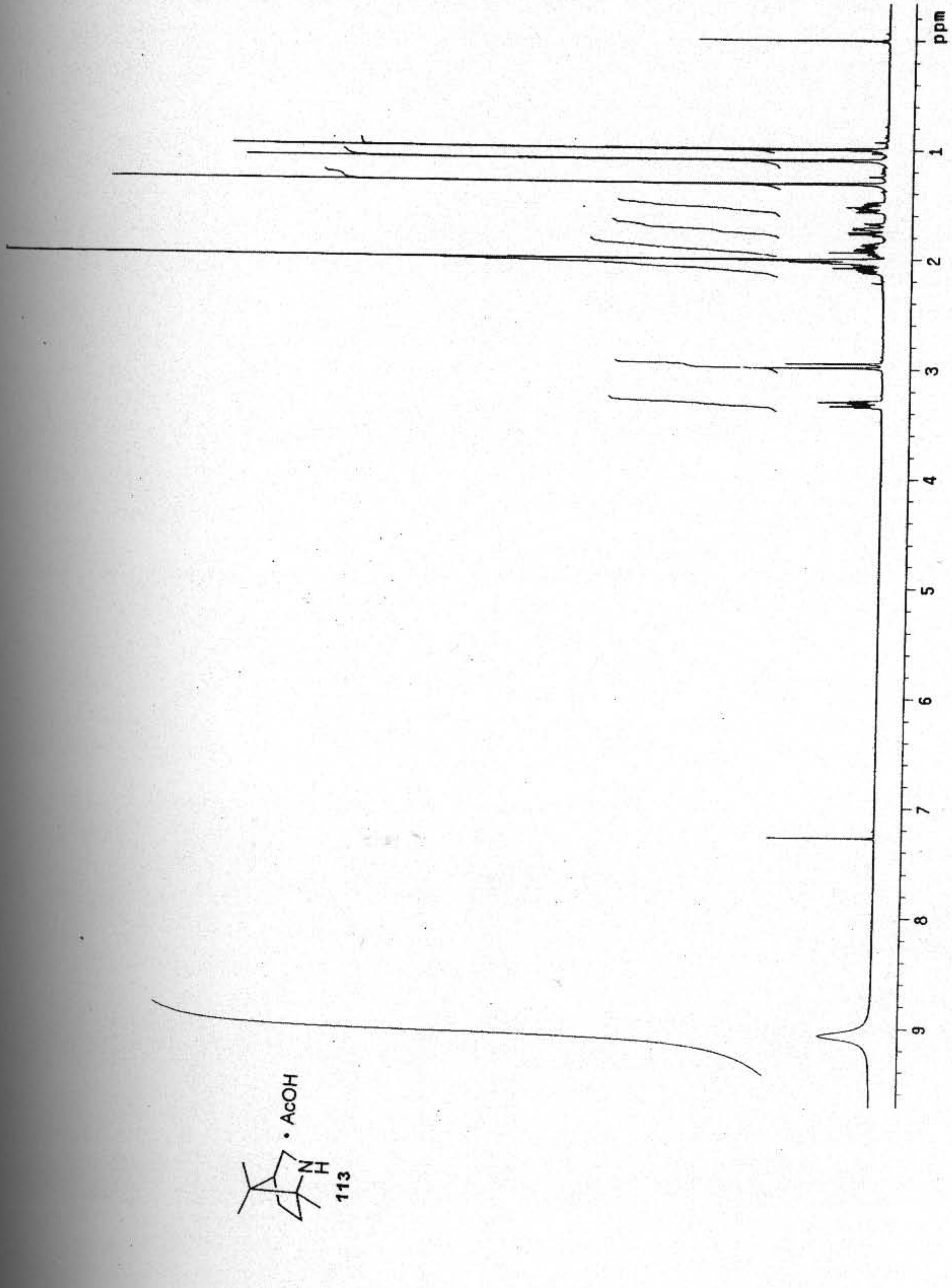
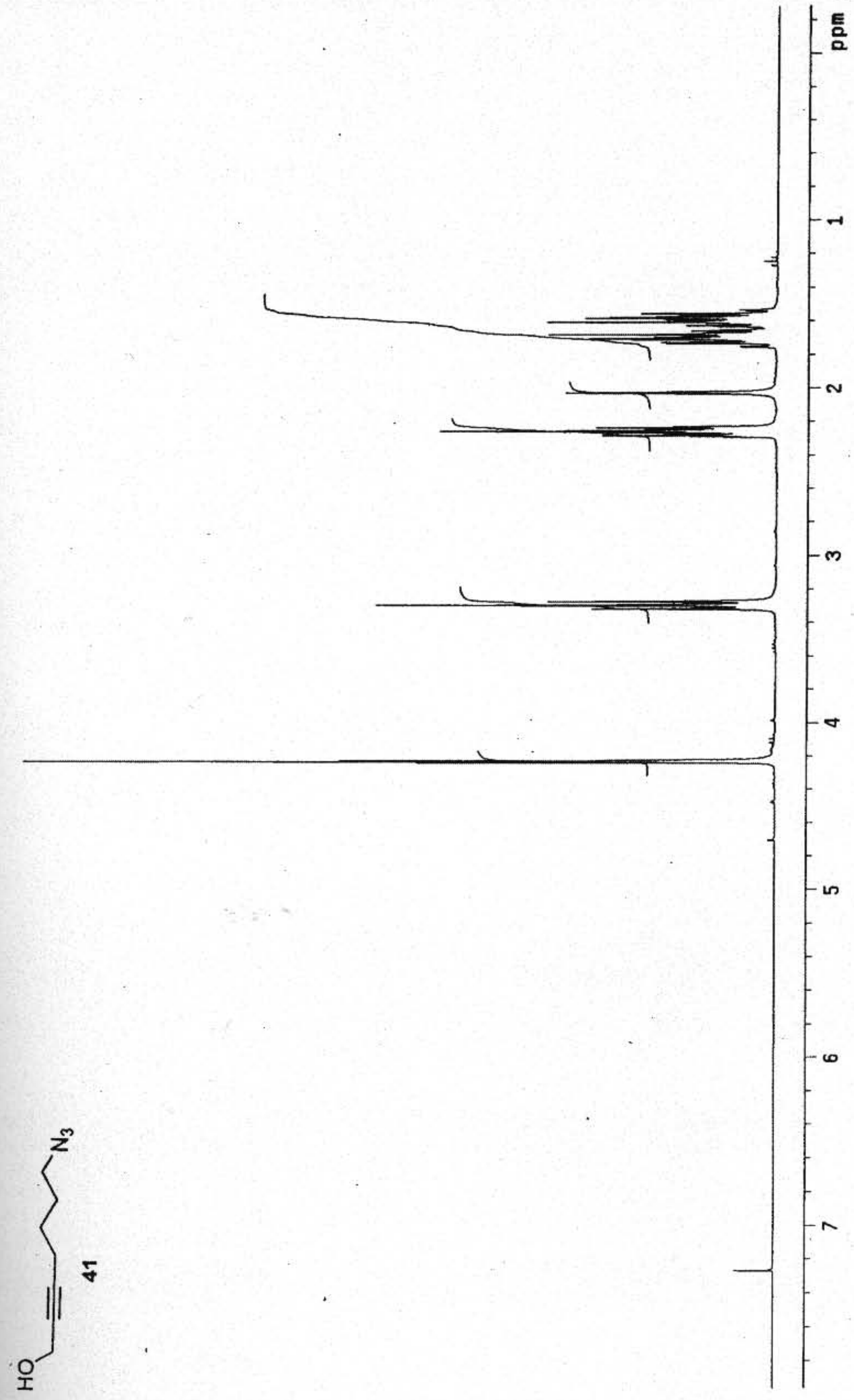
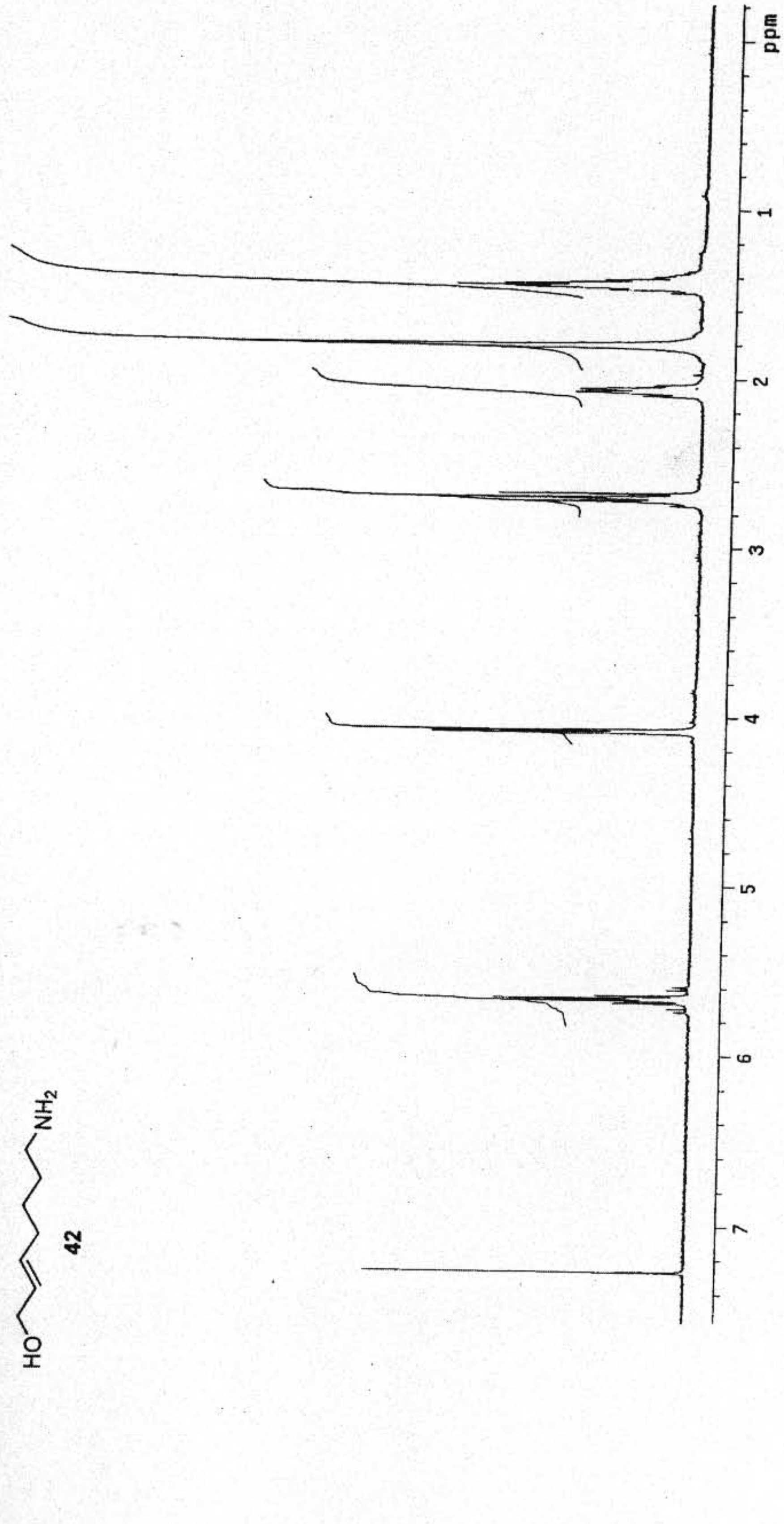


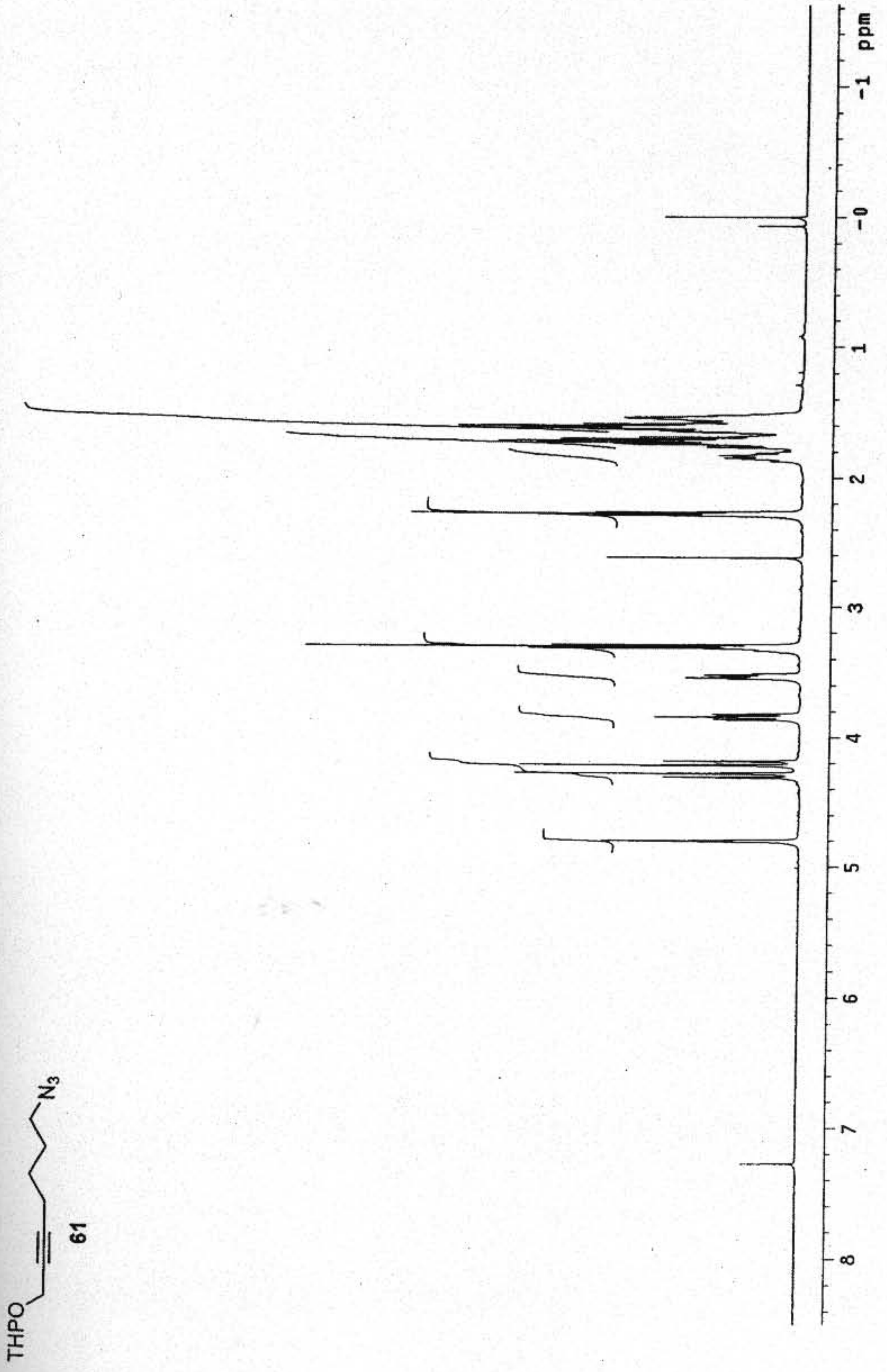
113



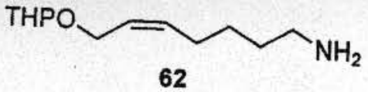
41



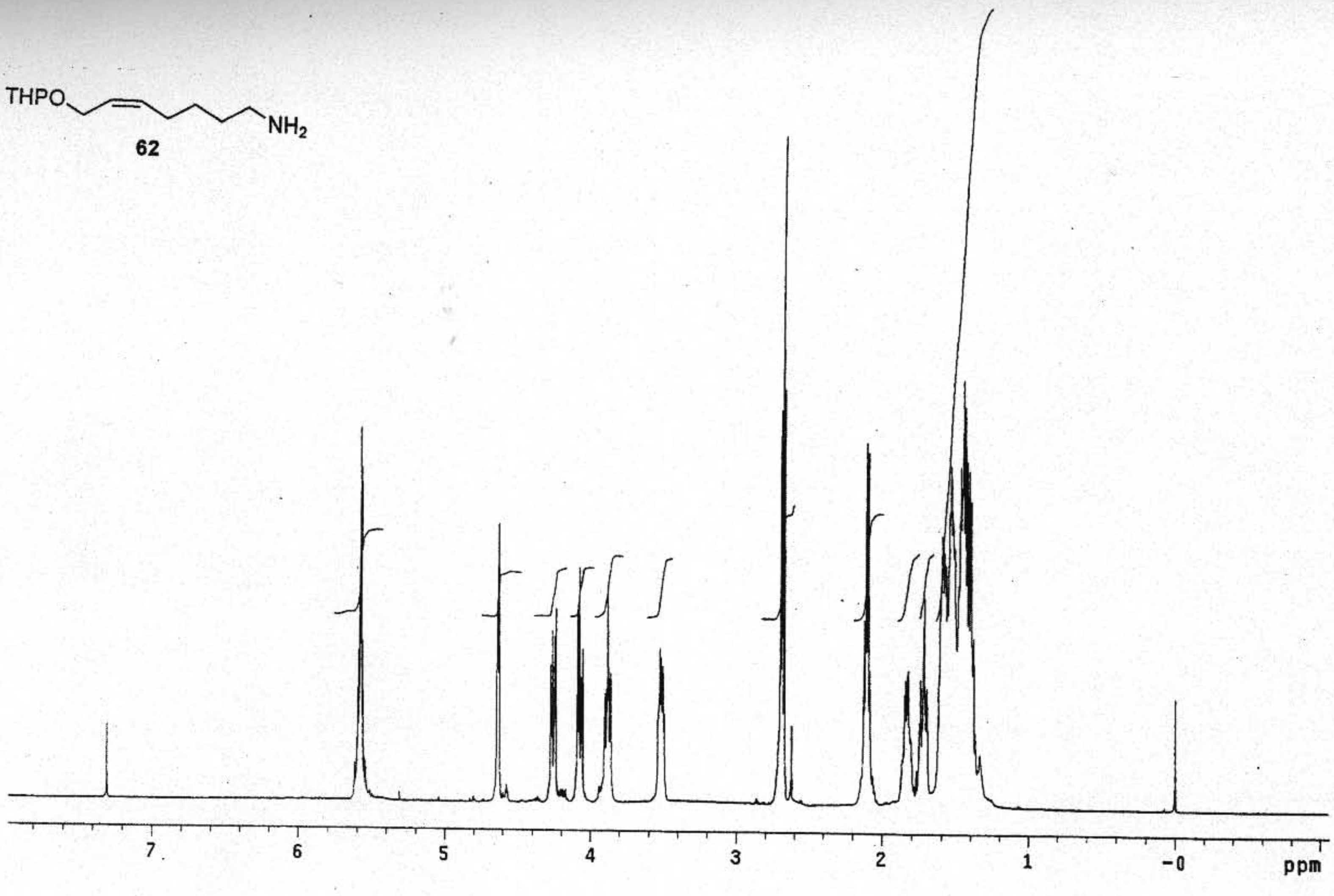
**42**

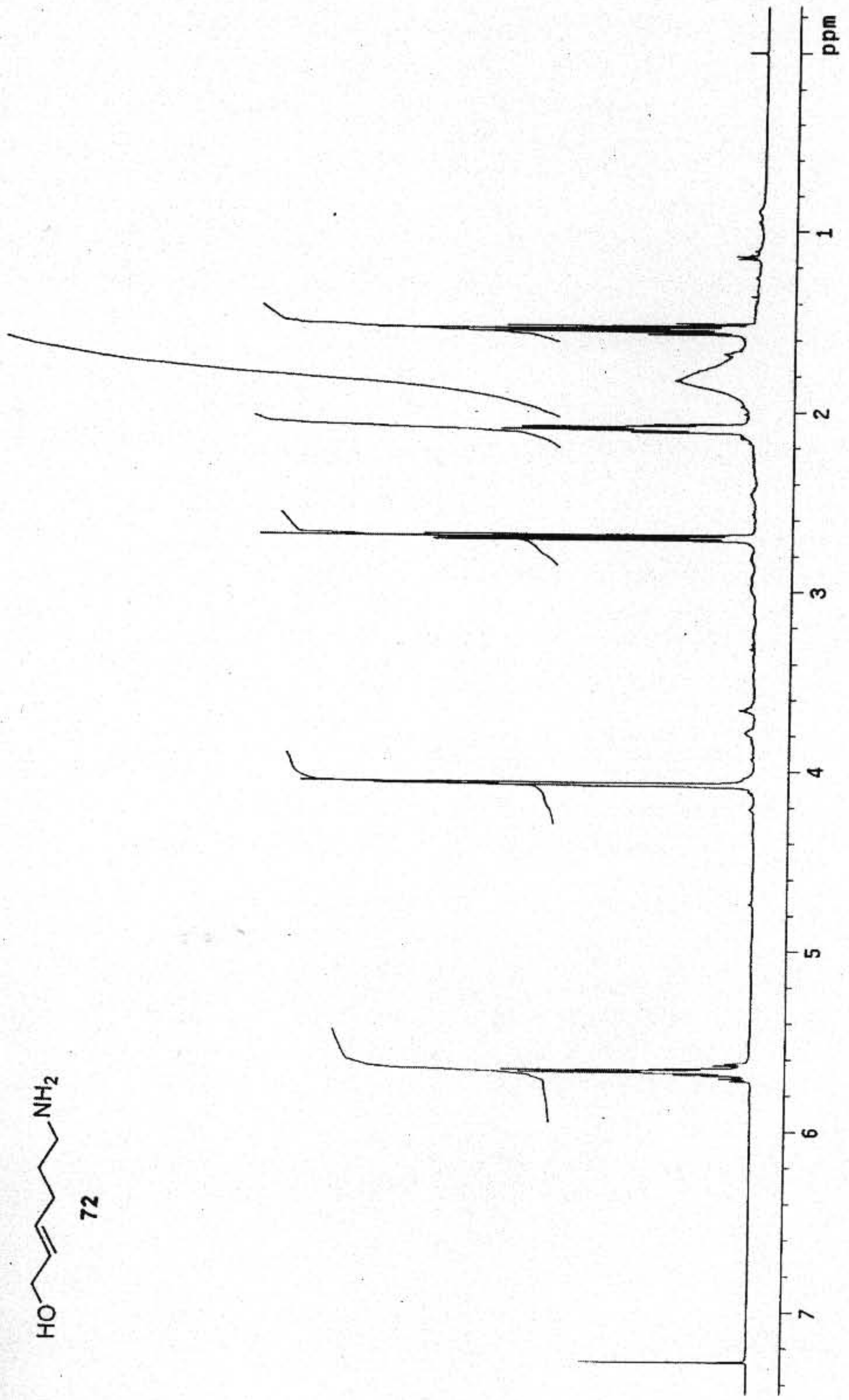


61

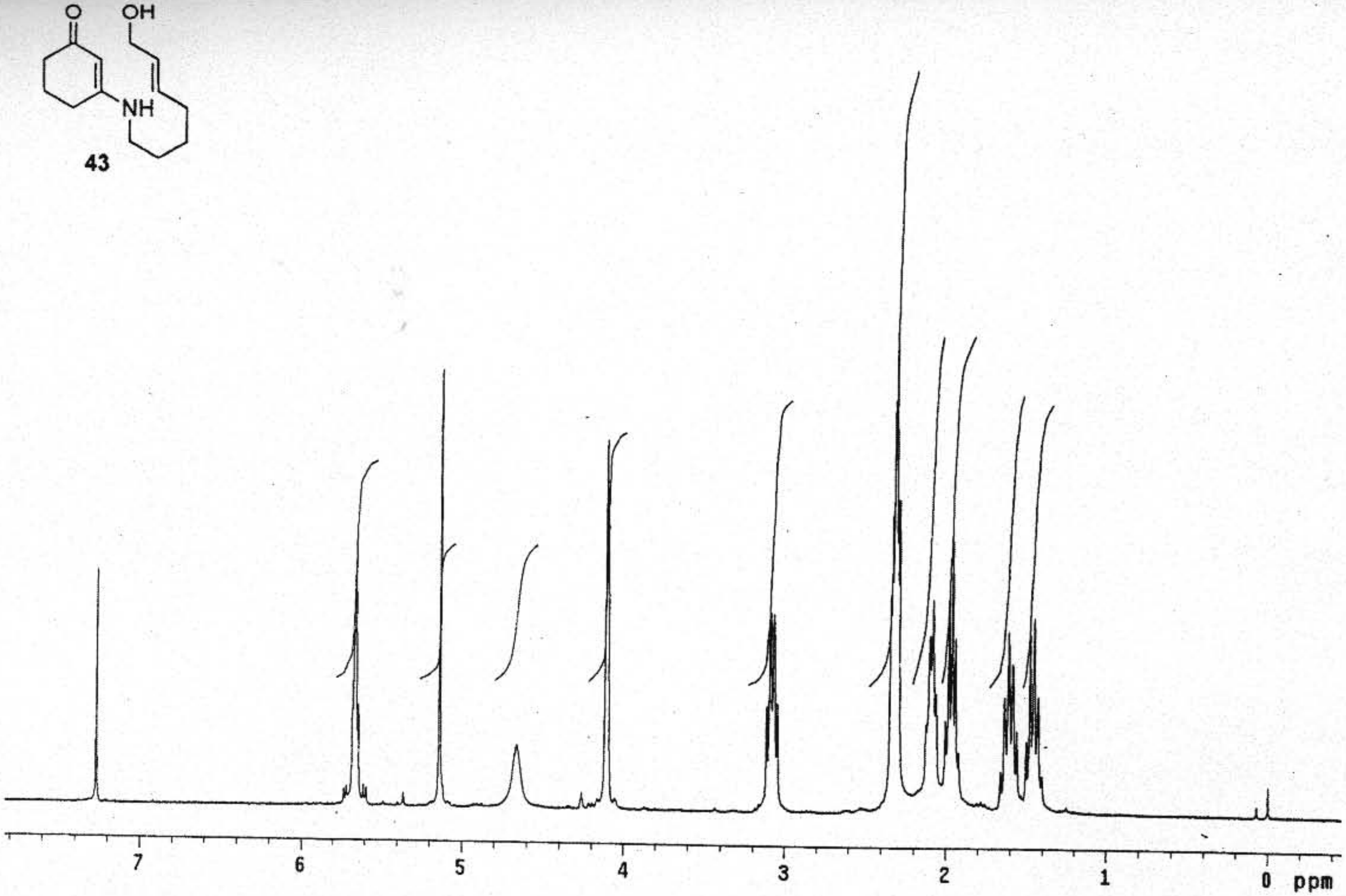


**62**





**72**



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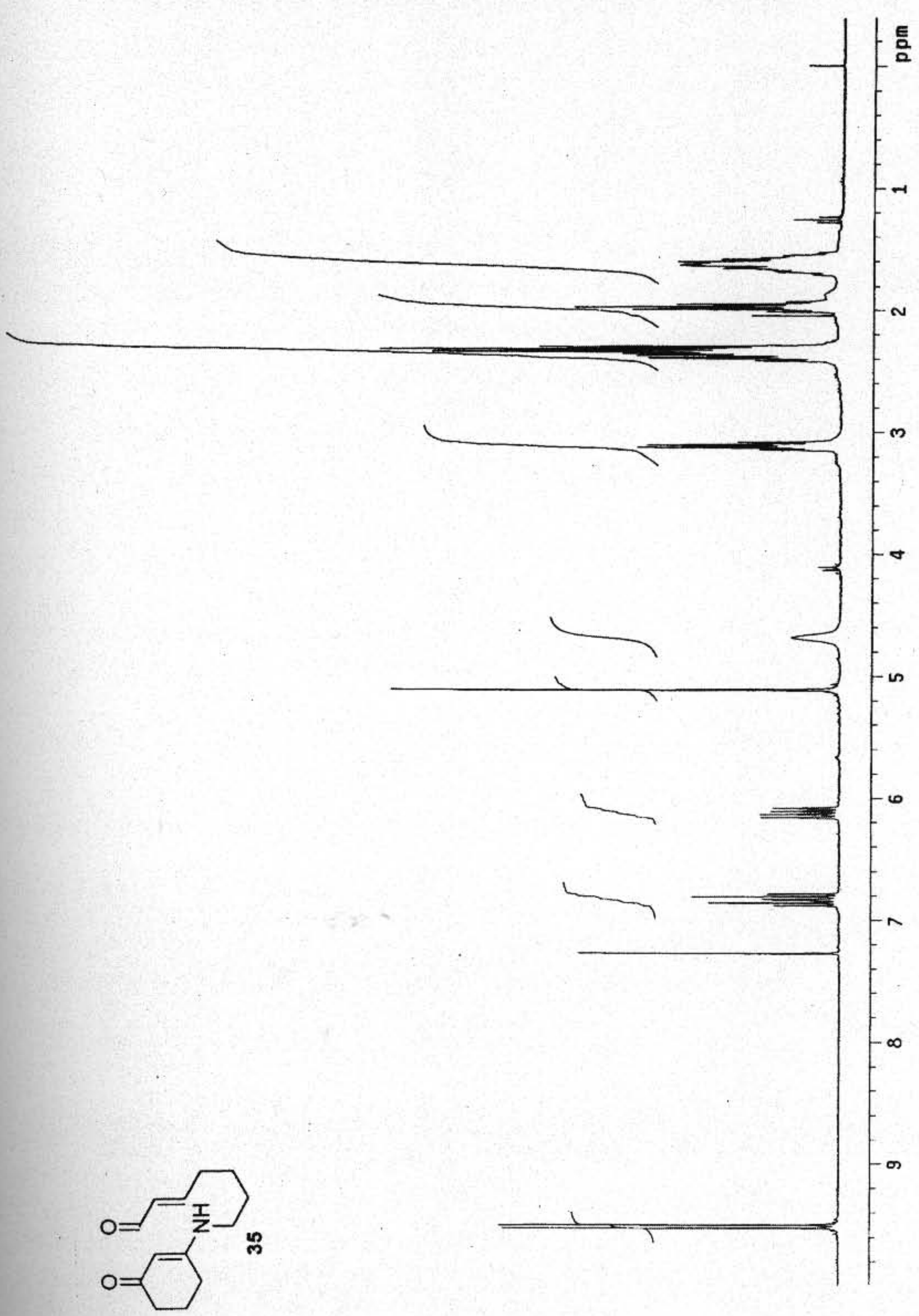

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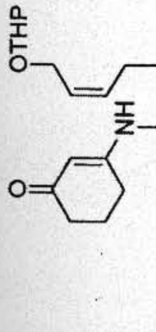
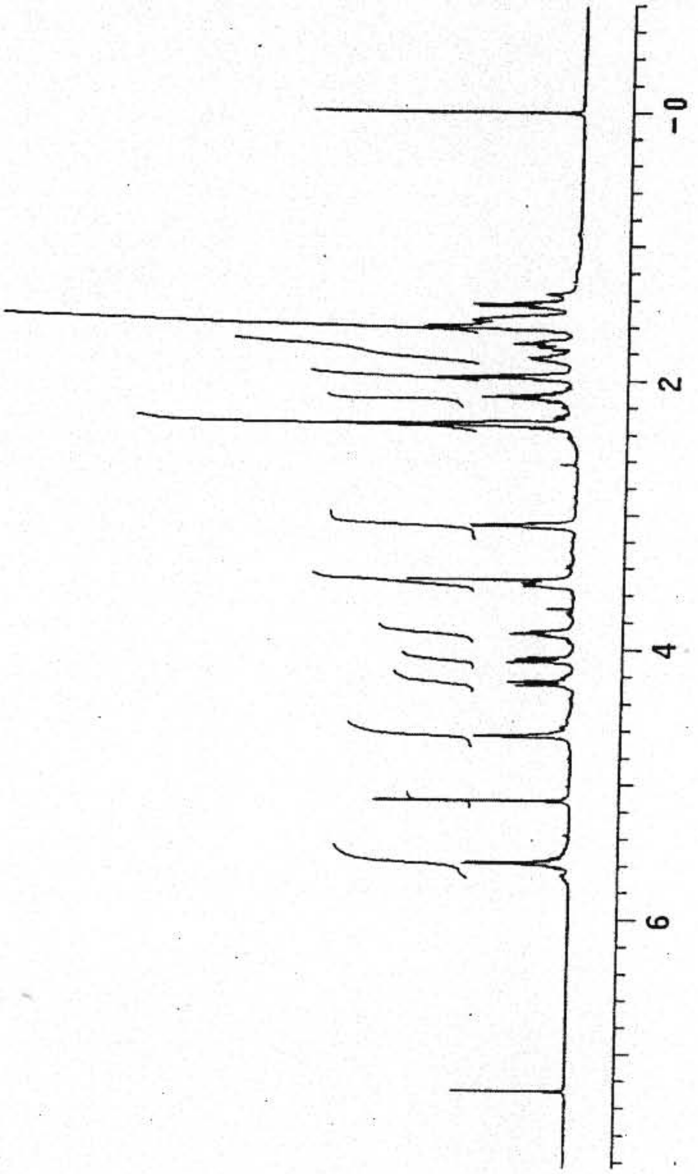
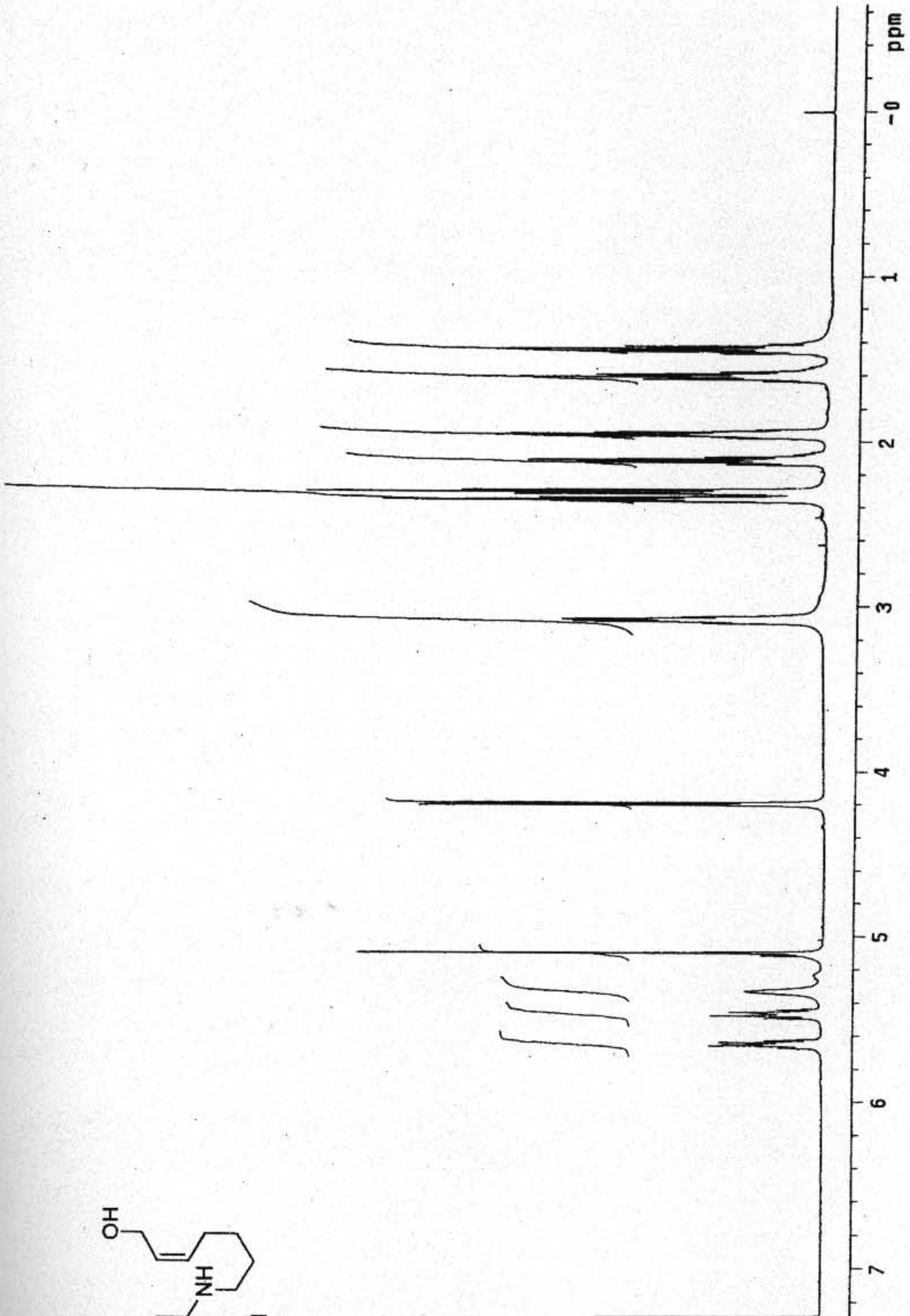


80





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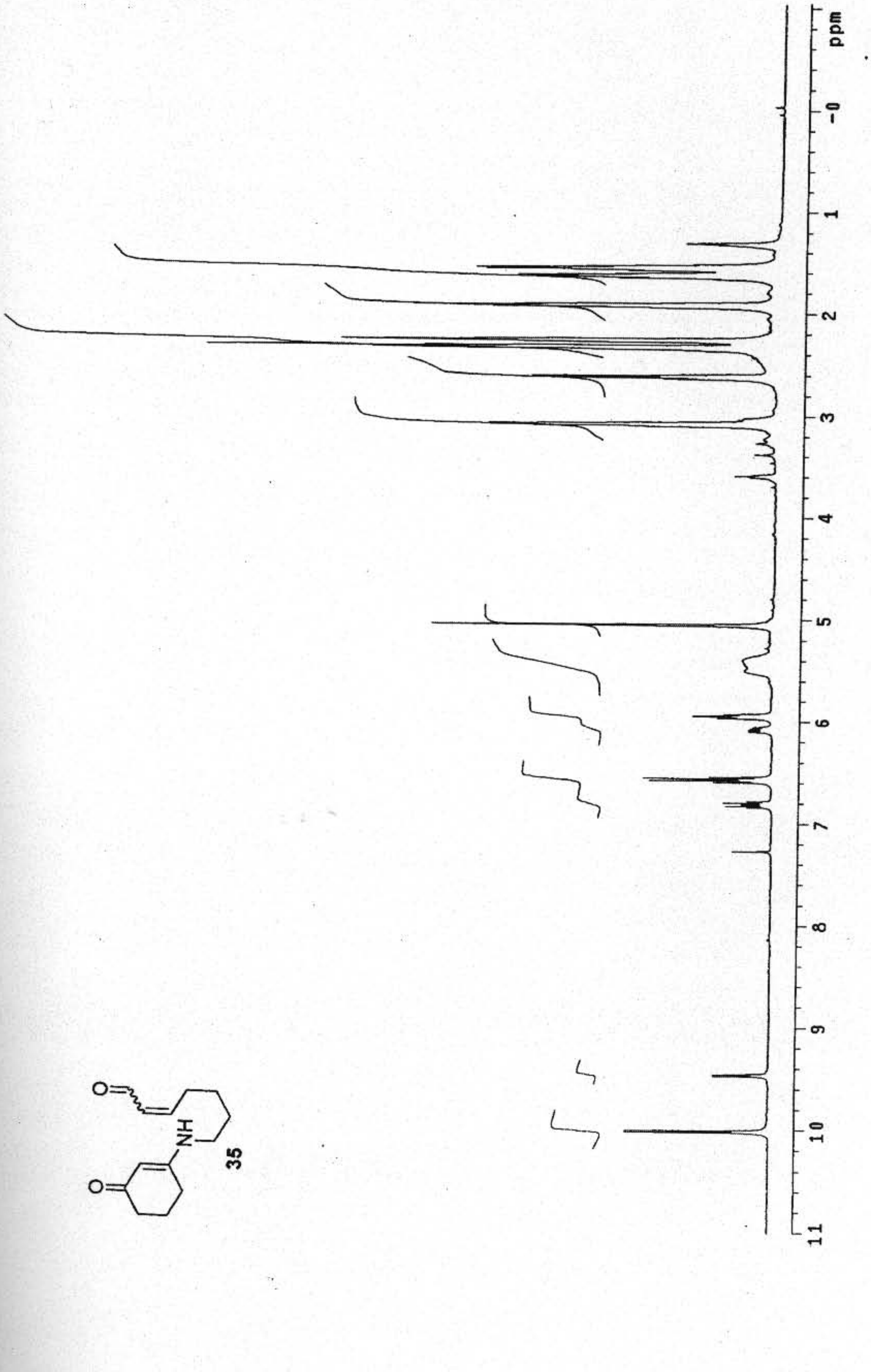

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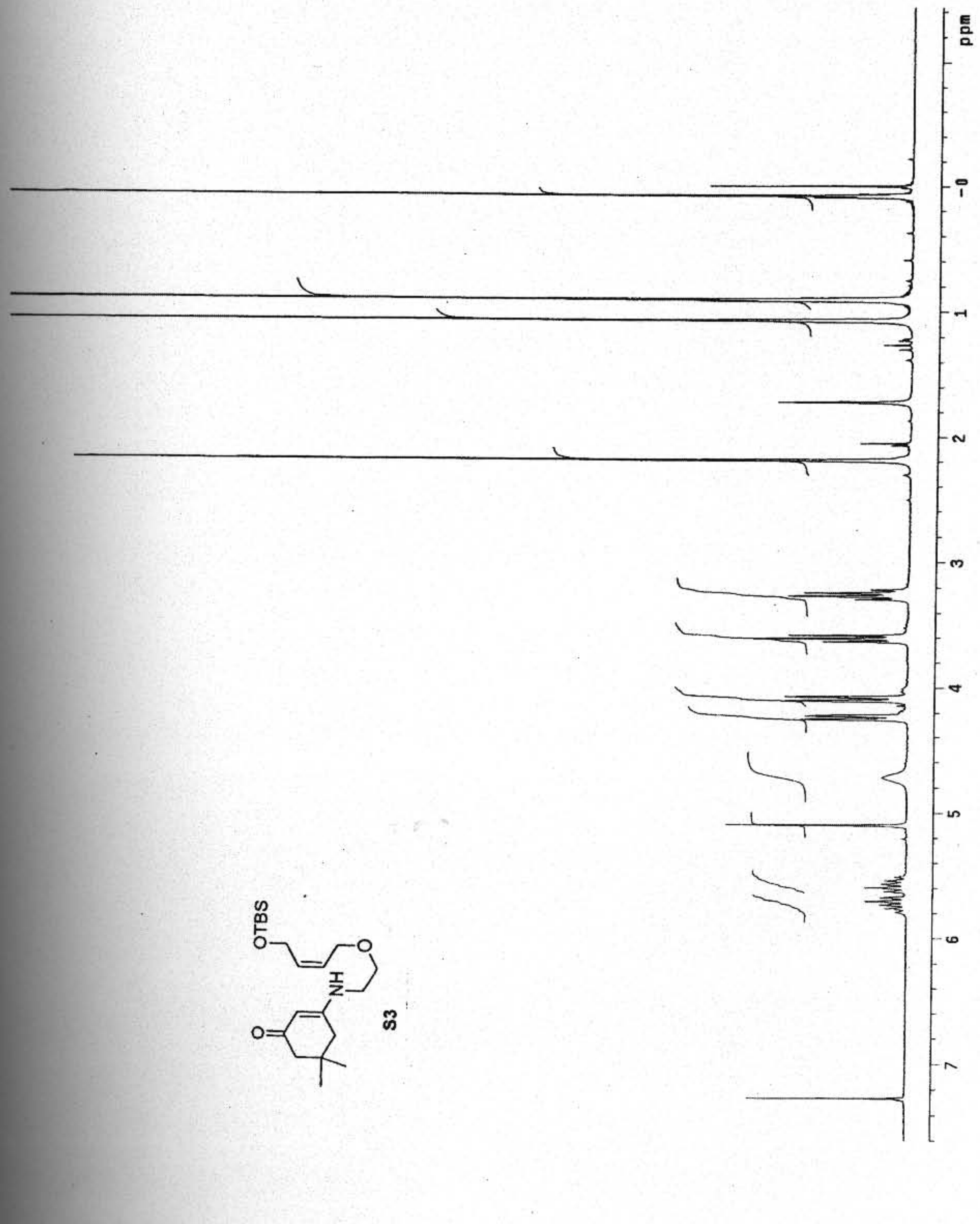
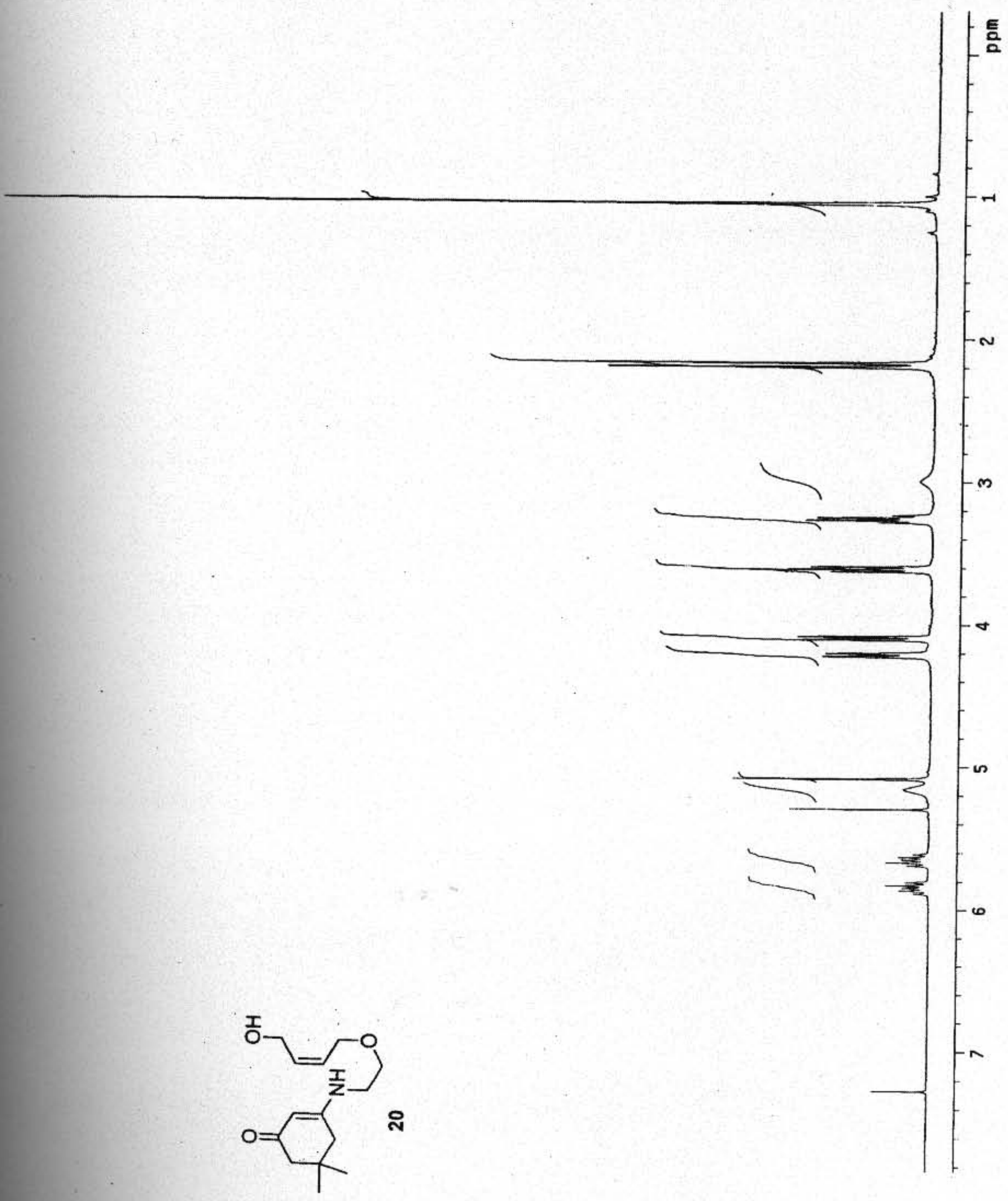
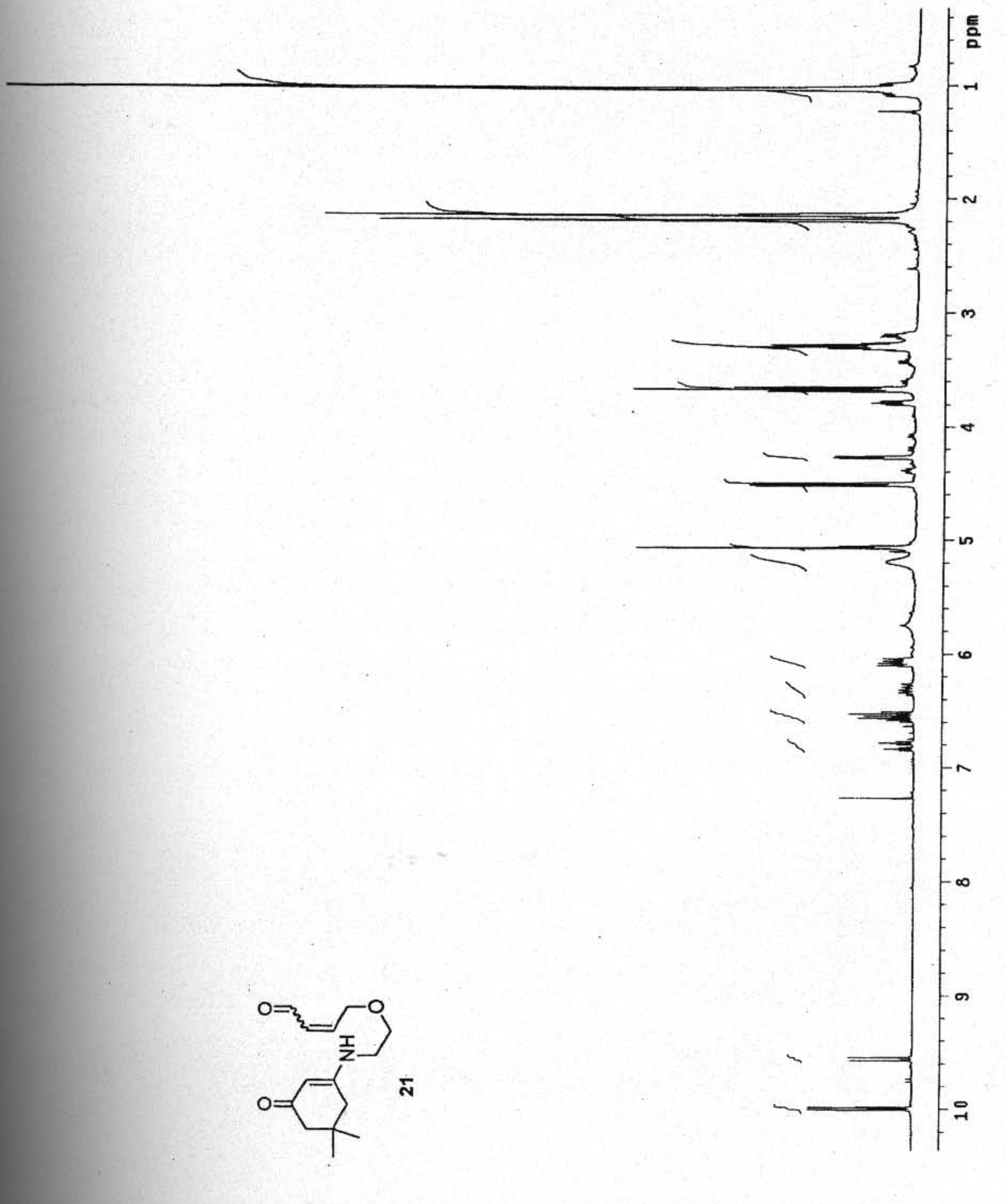


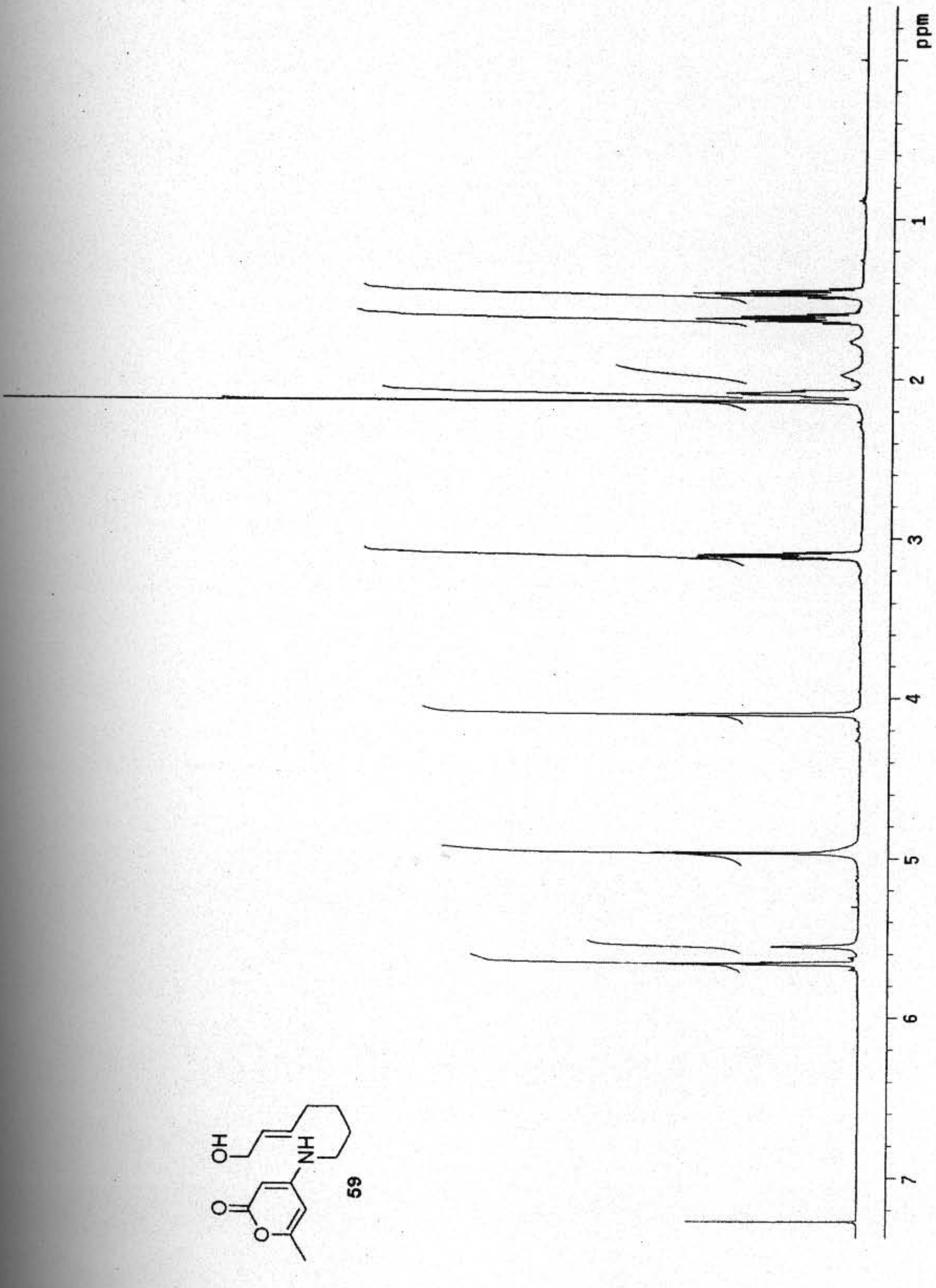
**S3**



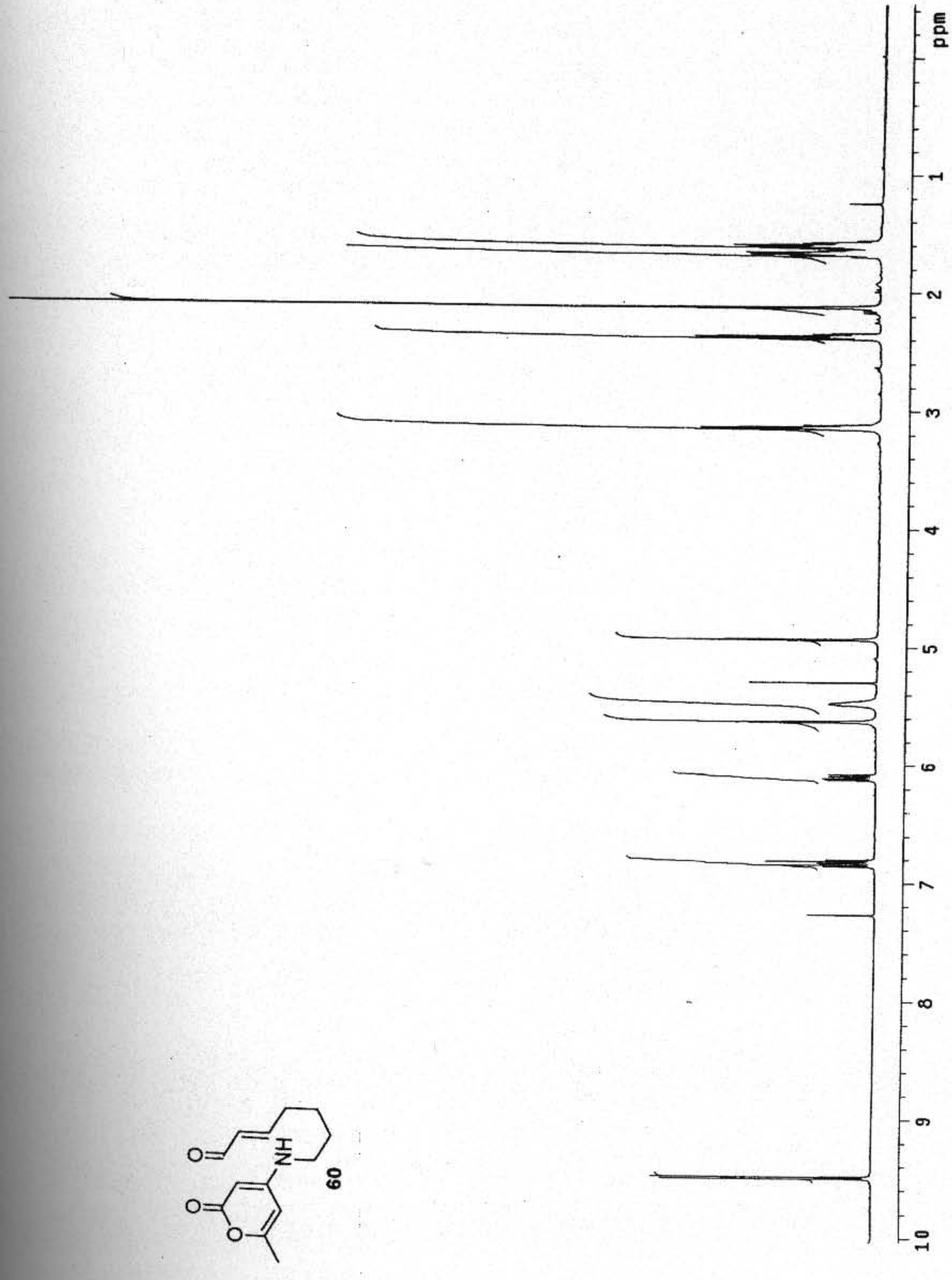
20



21



59



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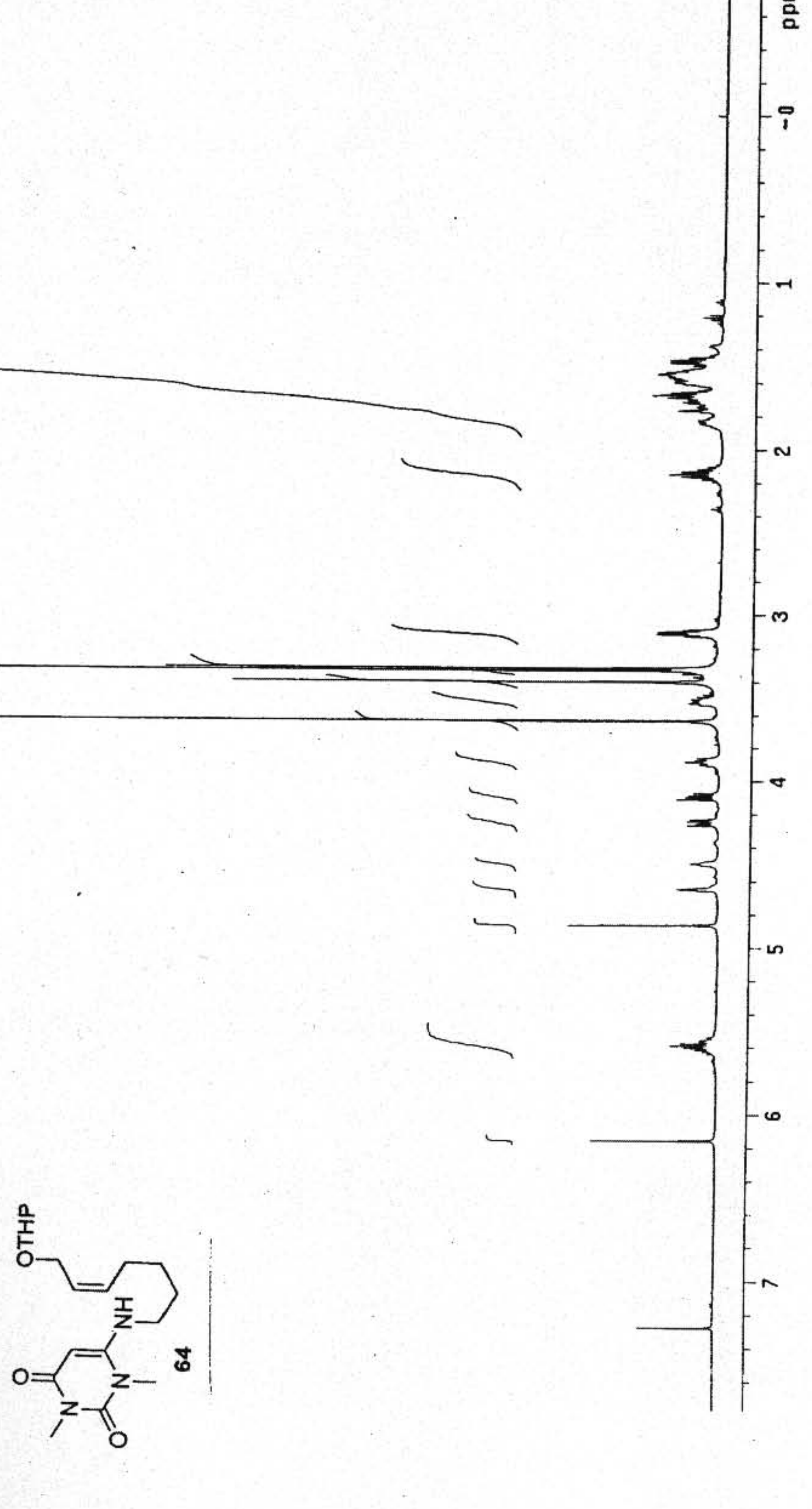
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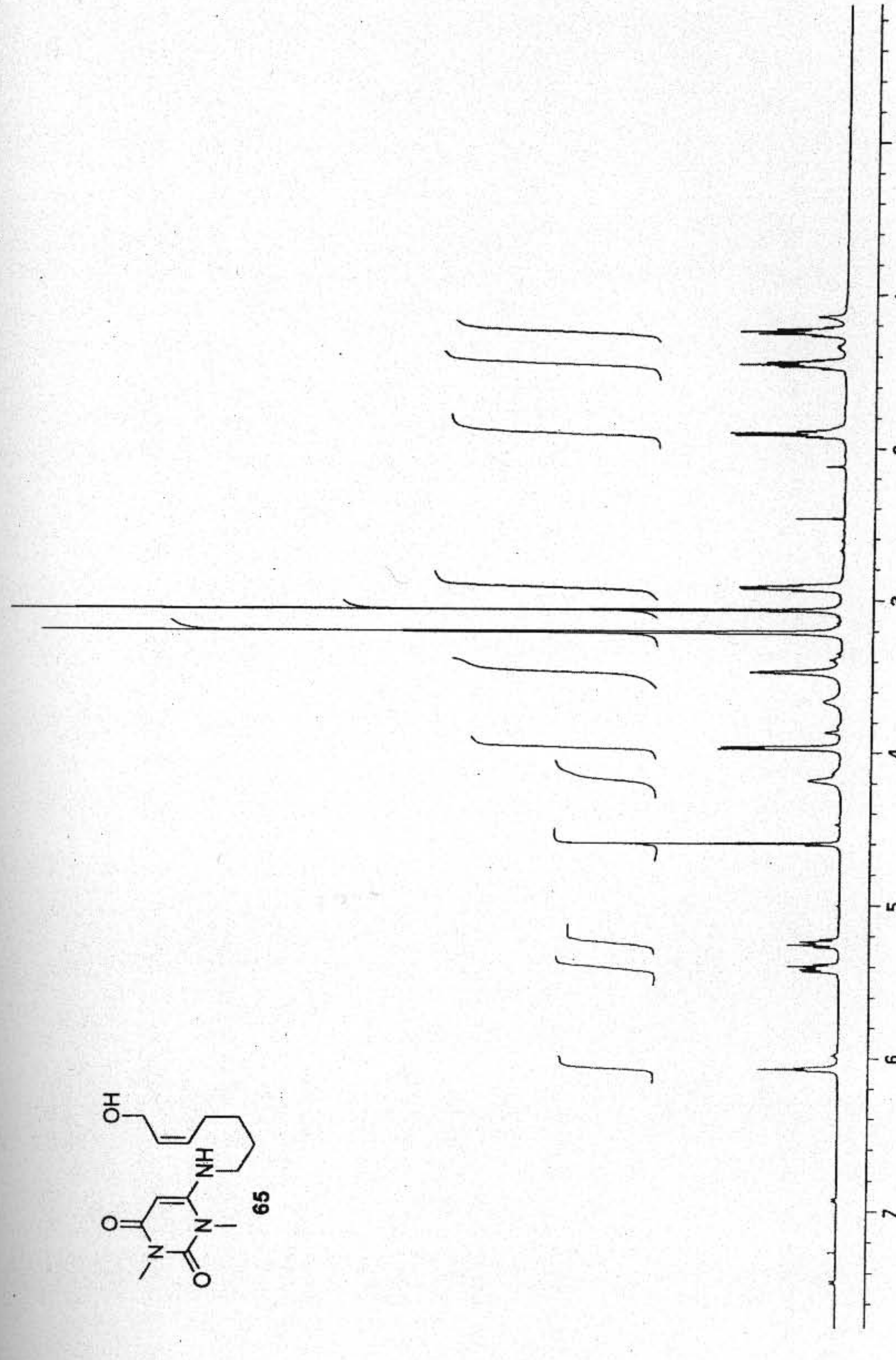
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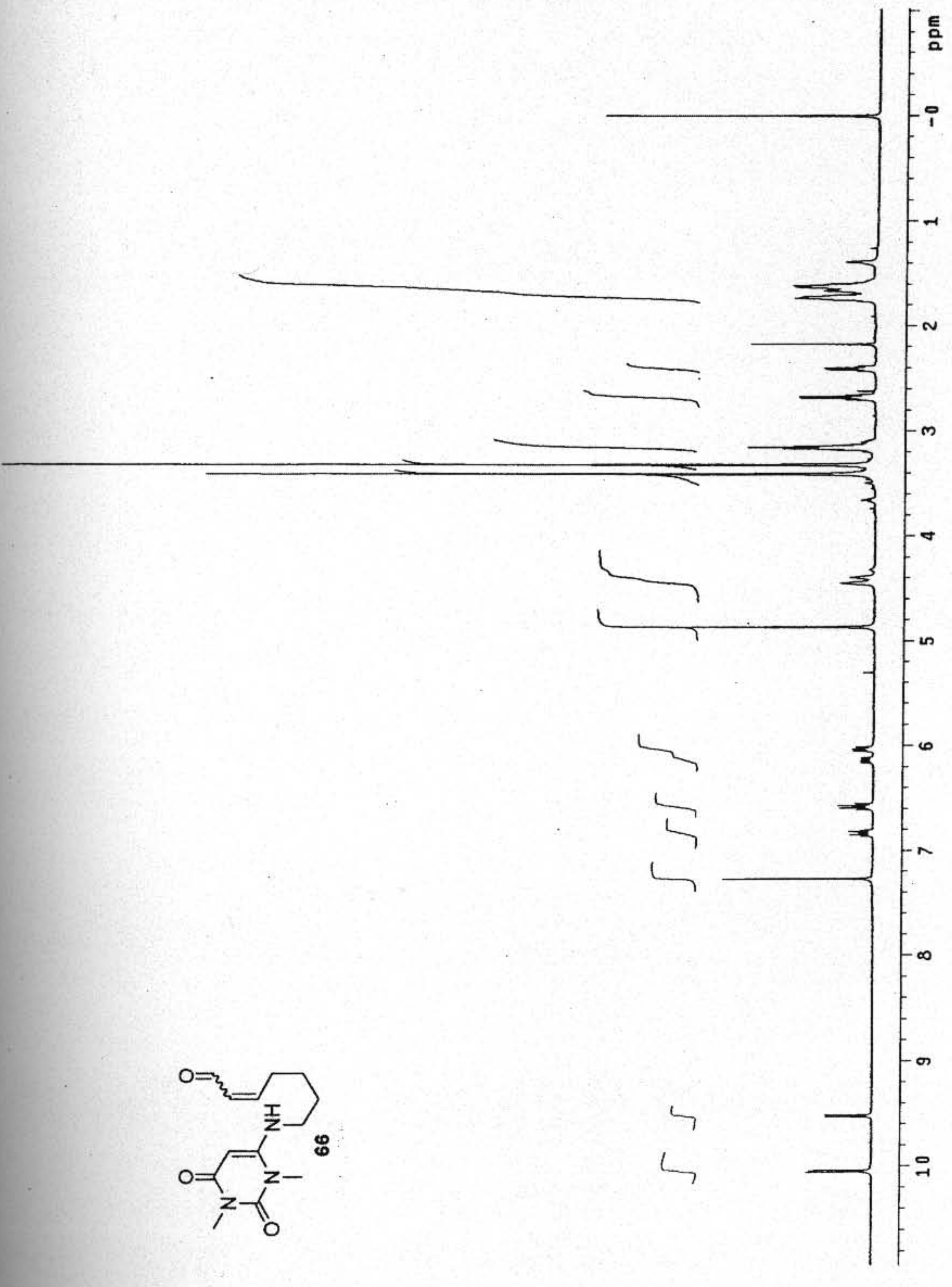
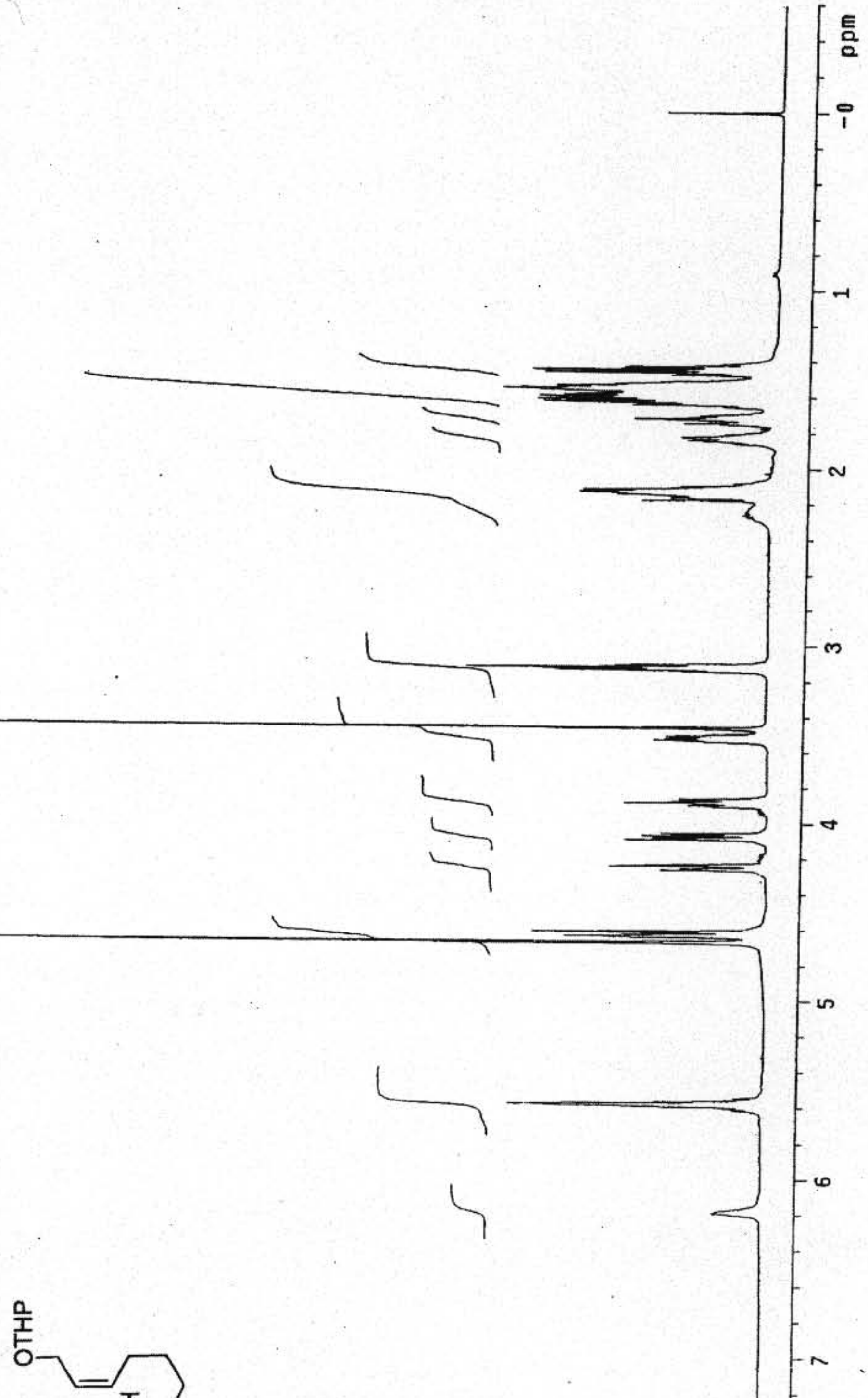
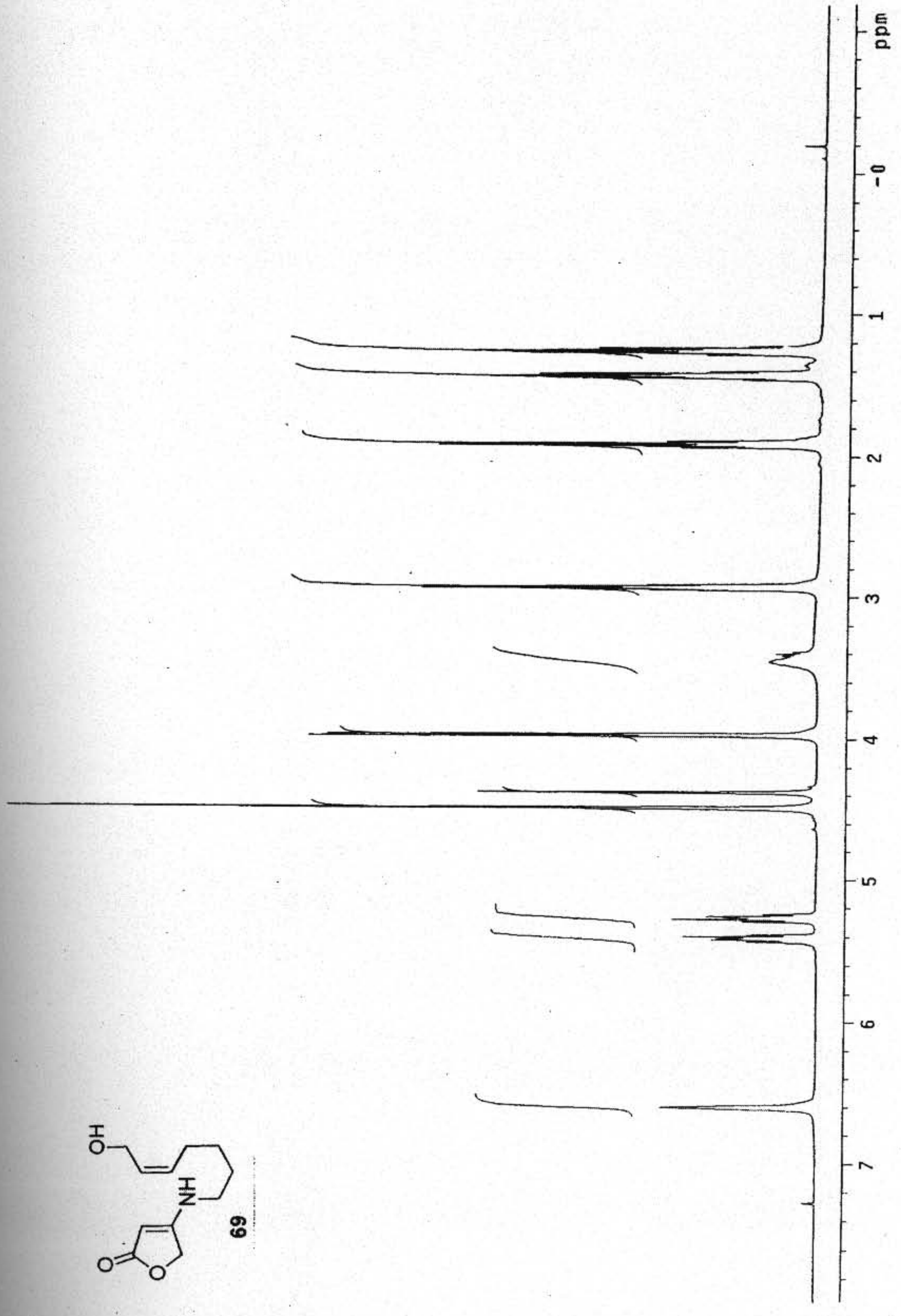


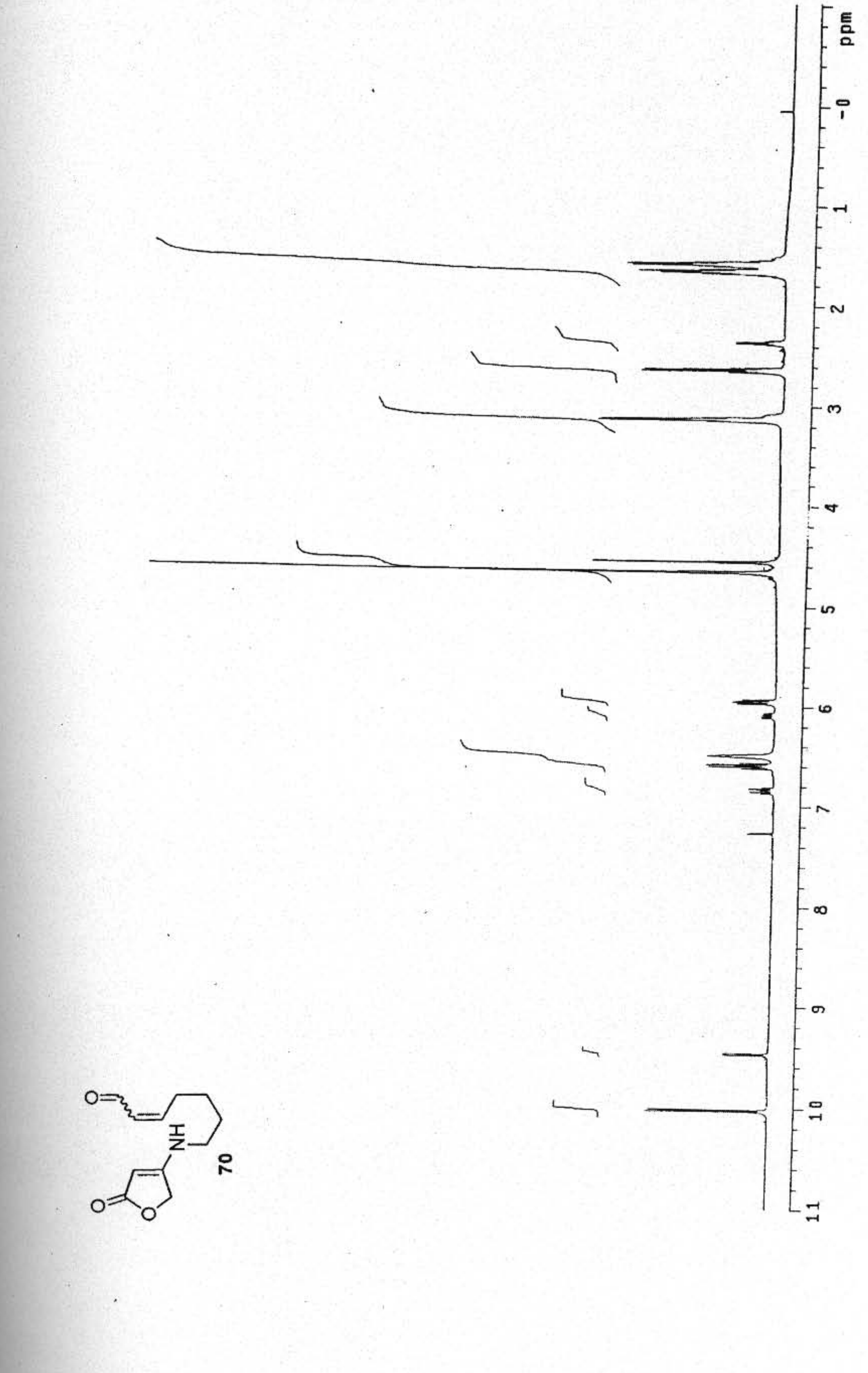
66



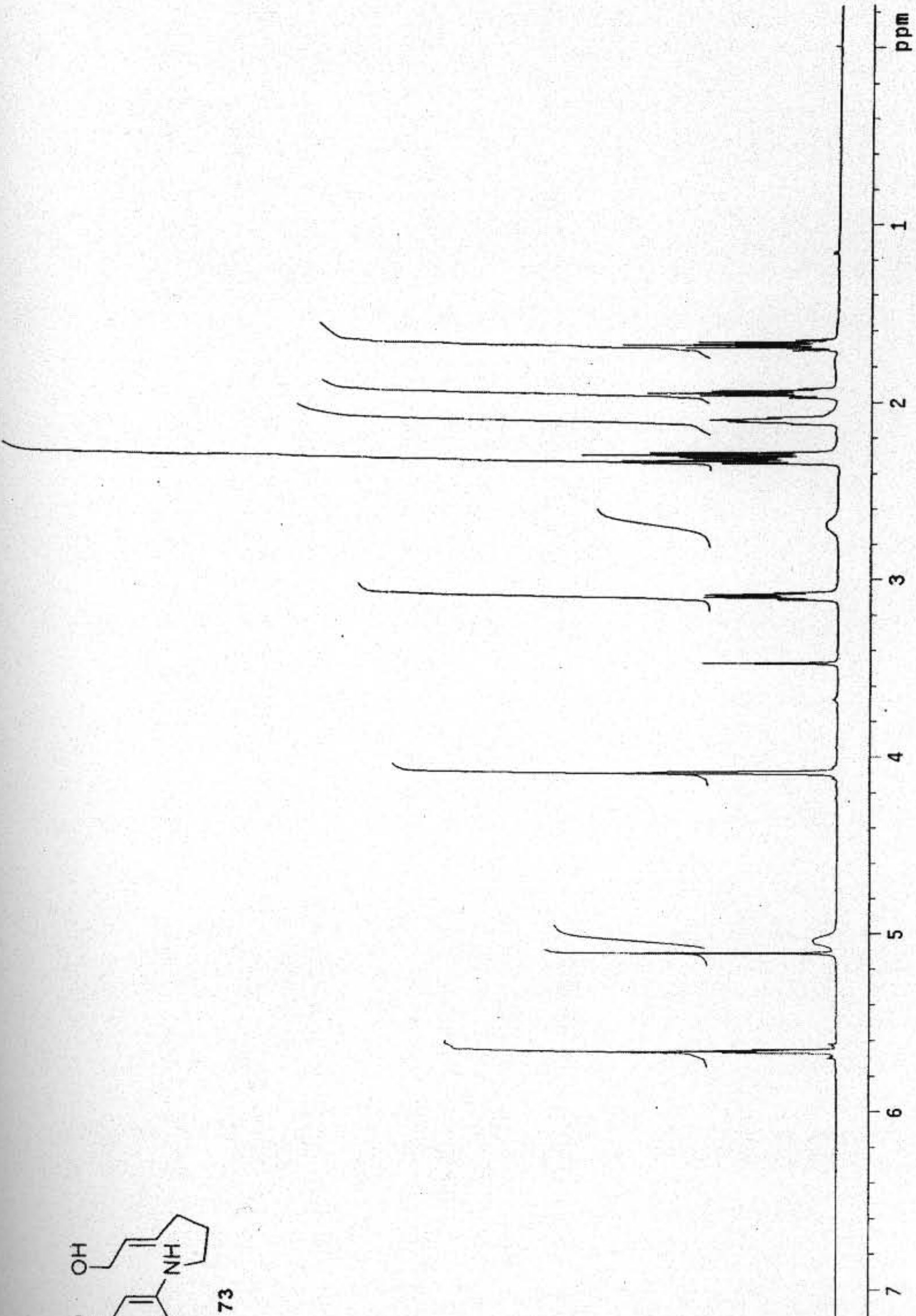
68



69



70



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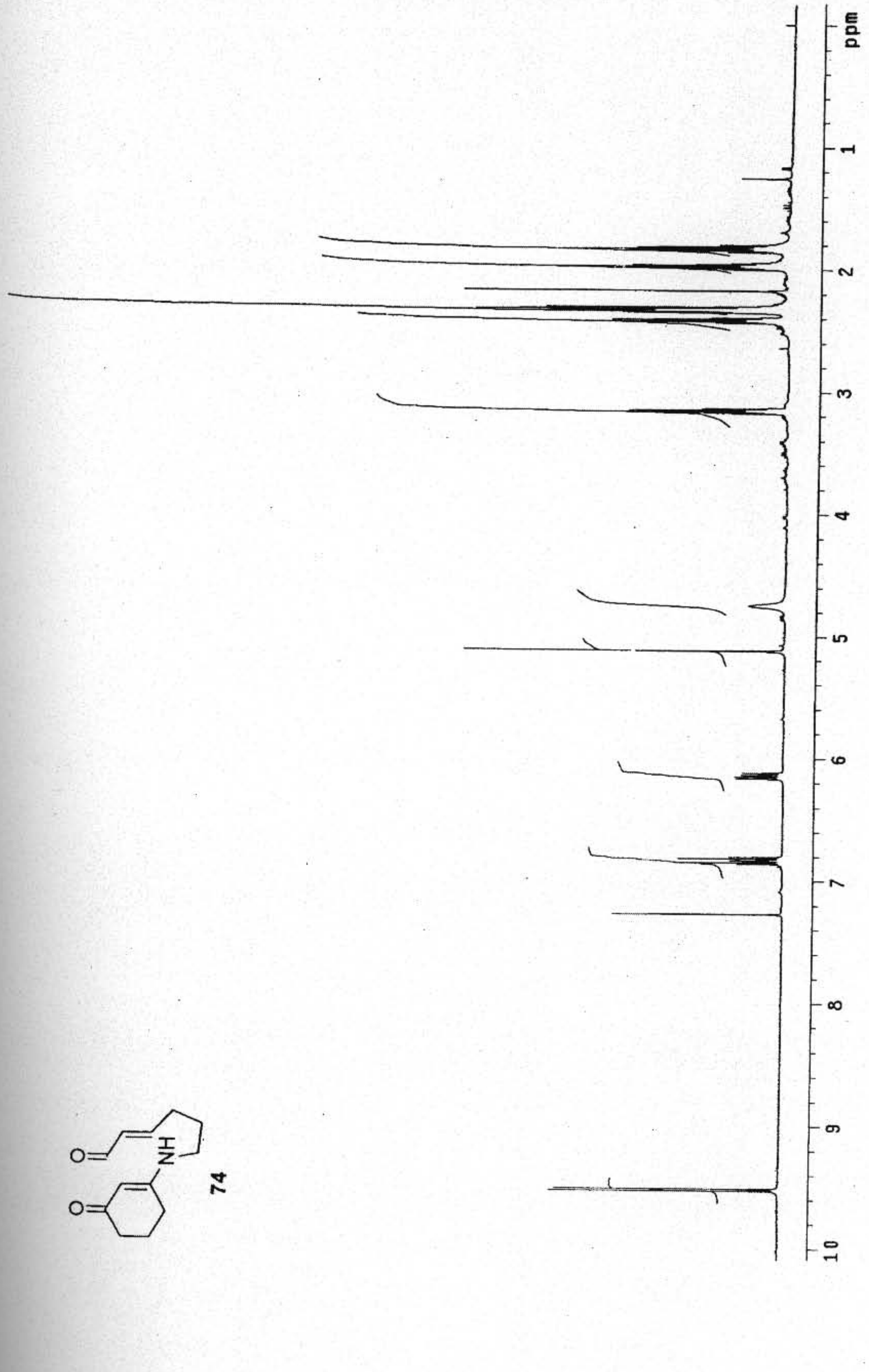
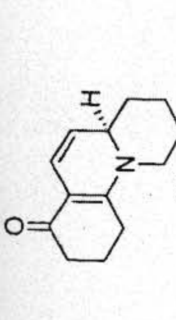


74



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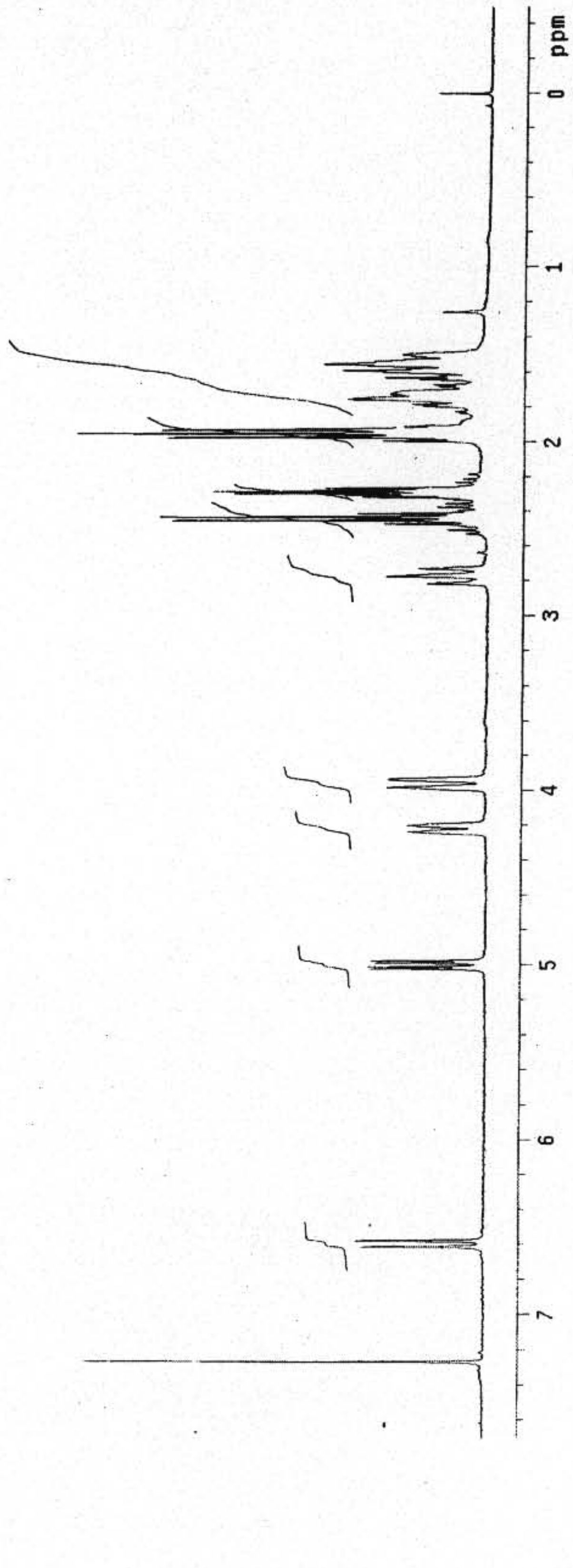

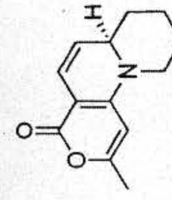

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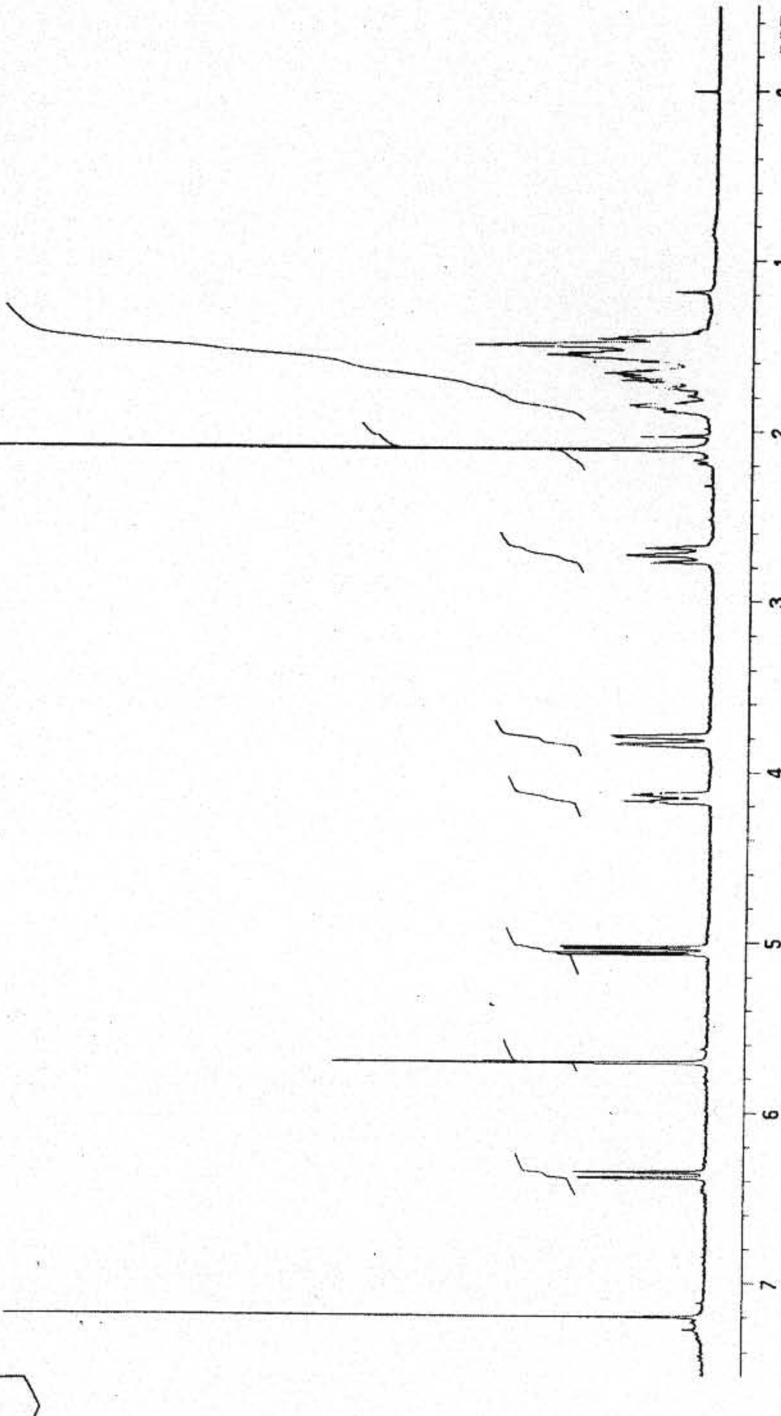
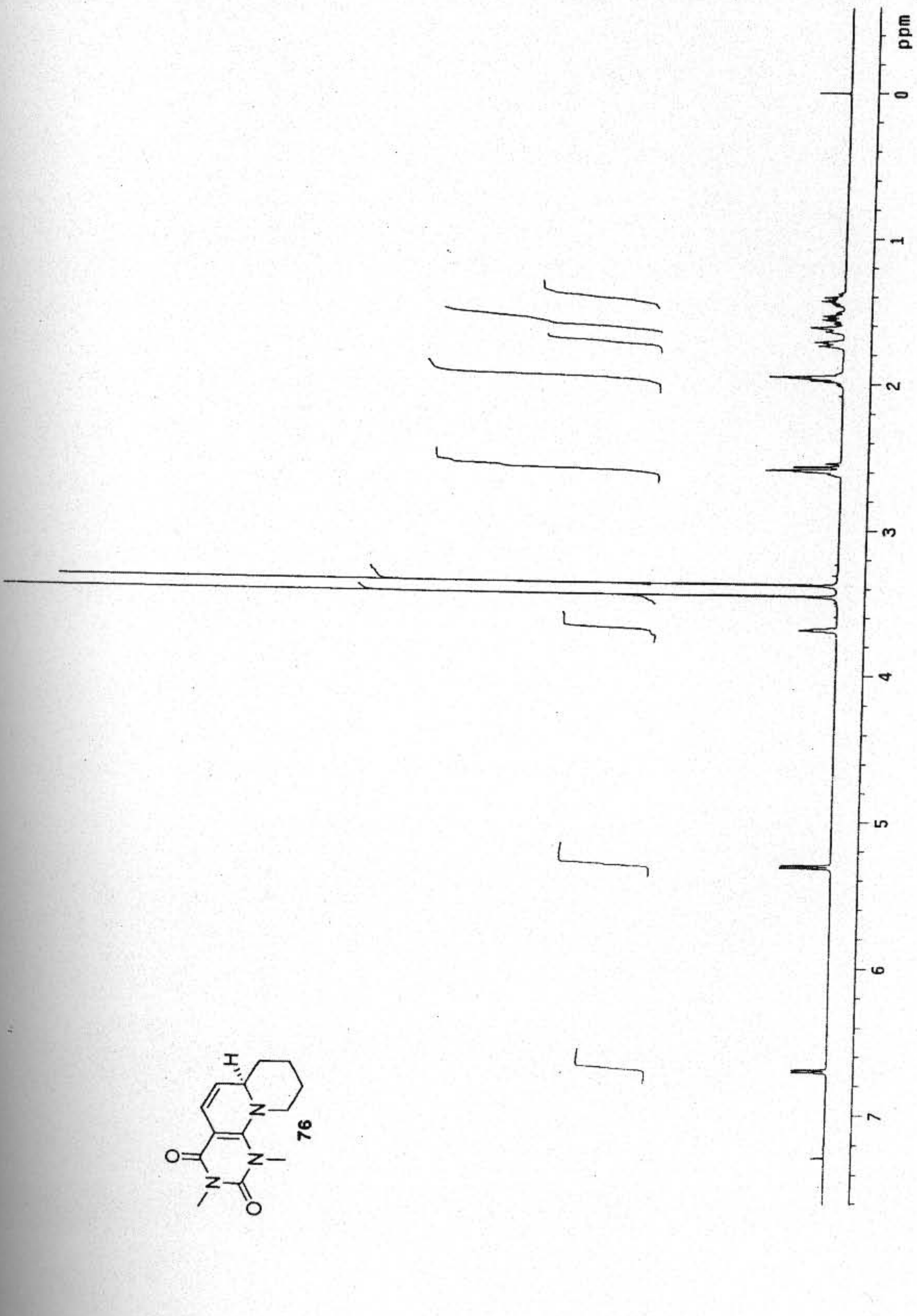
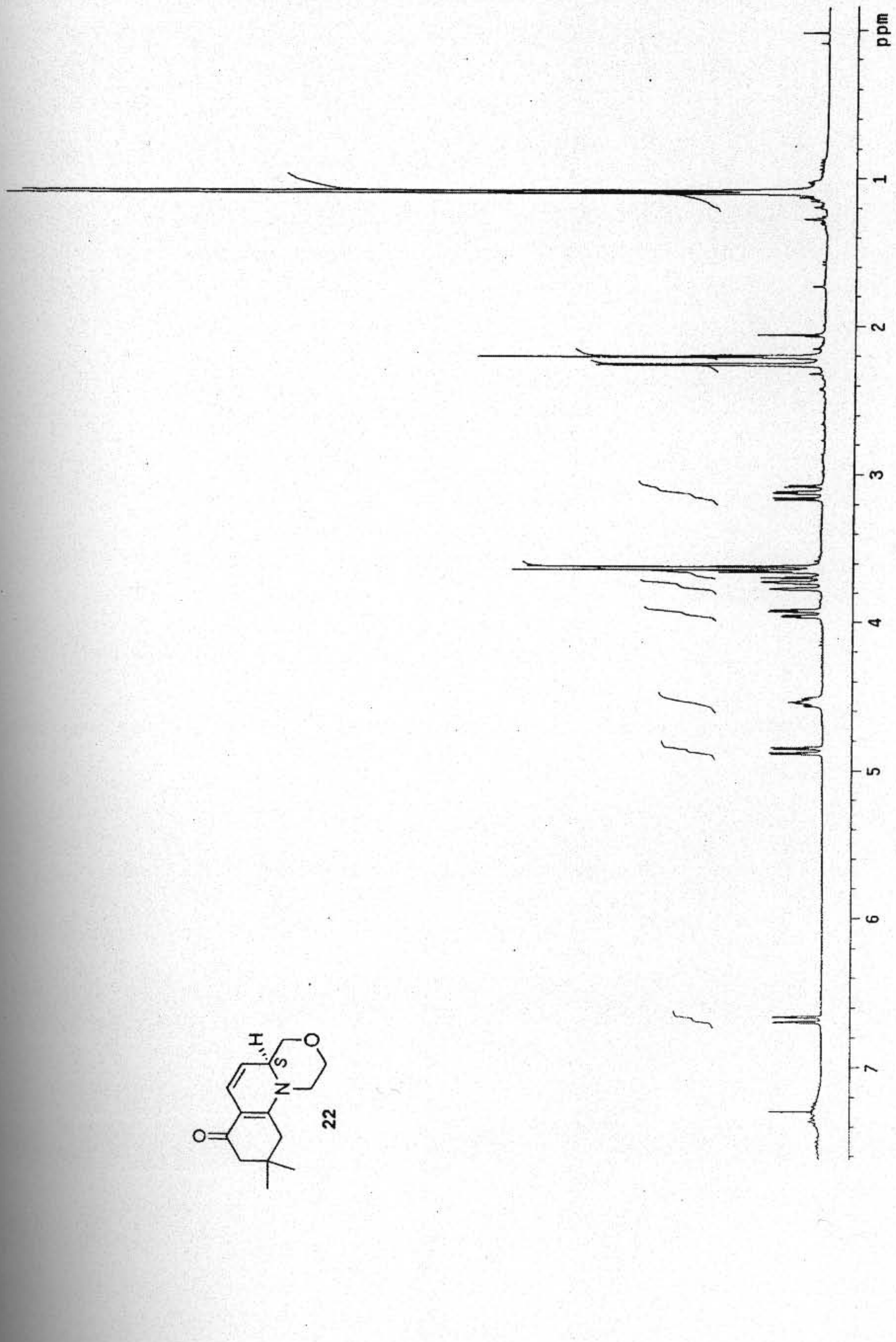
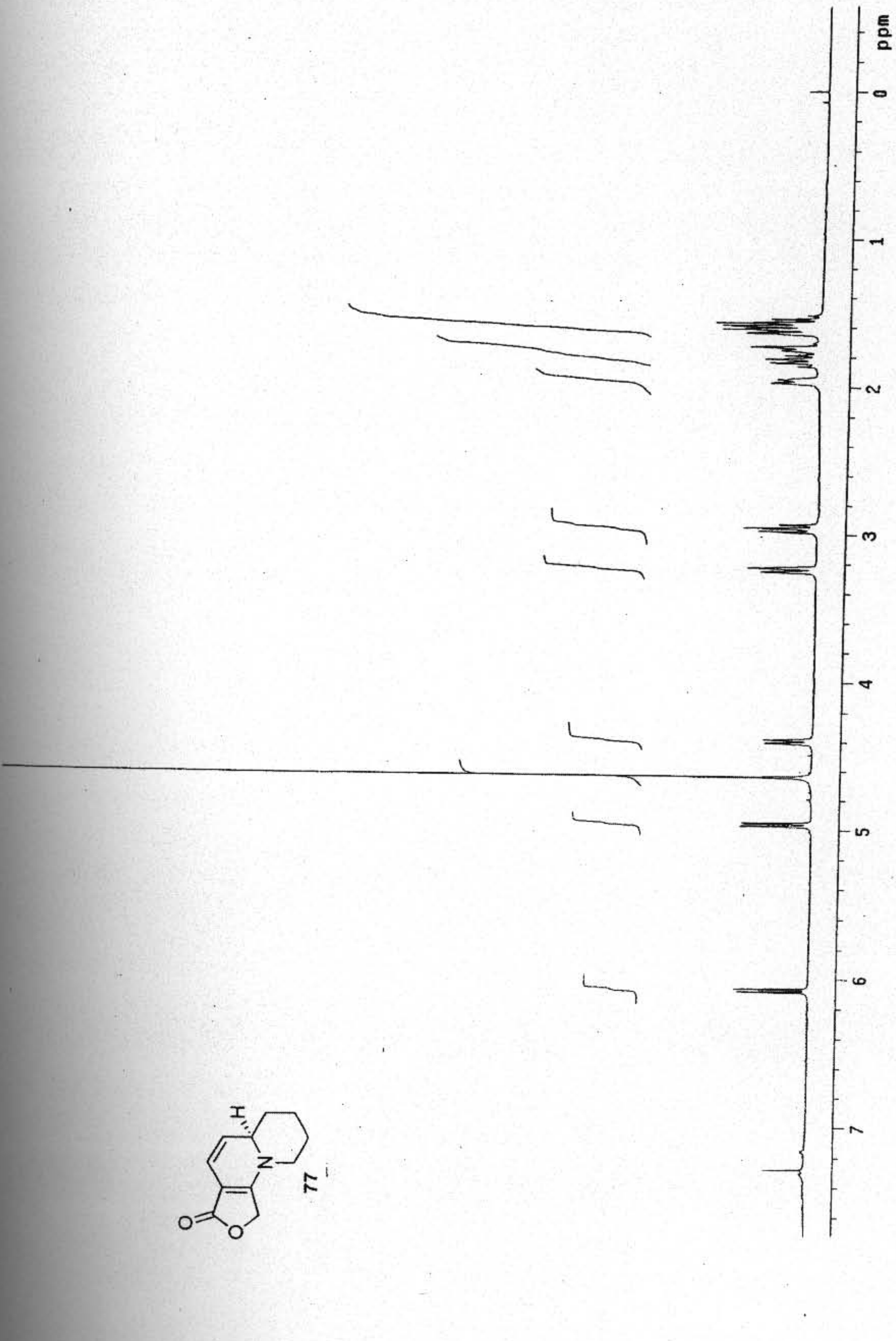




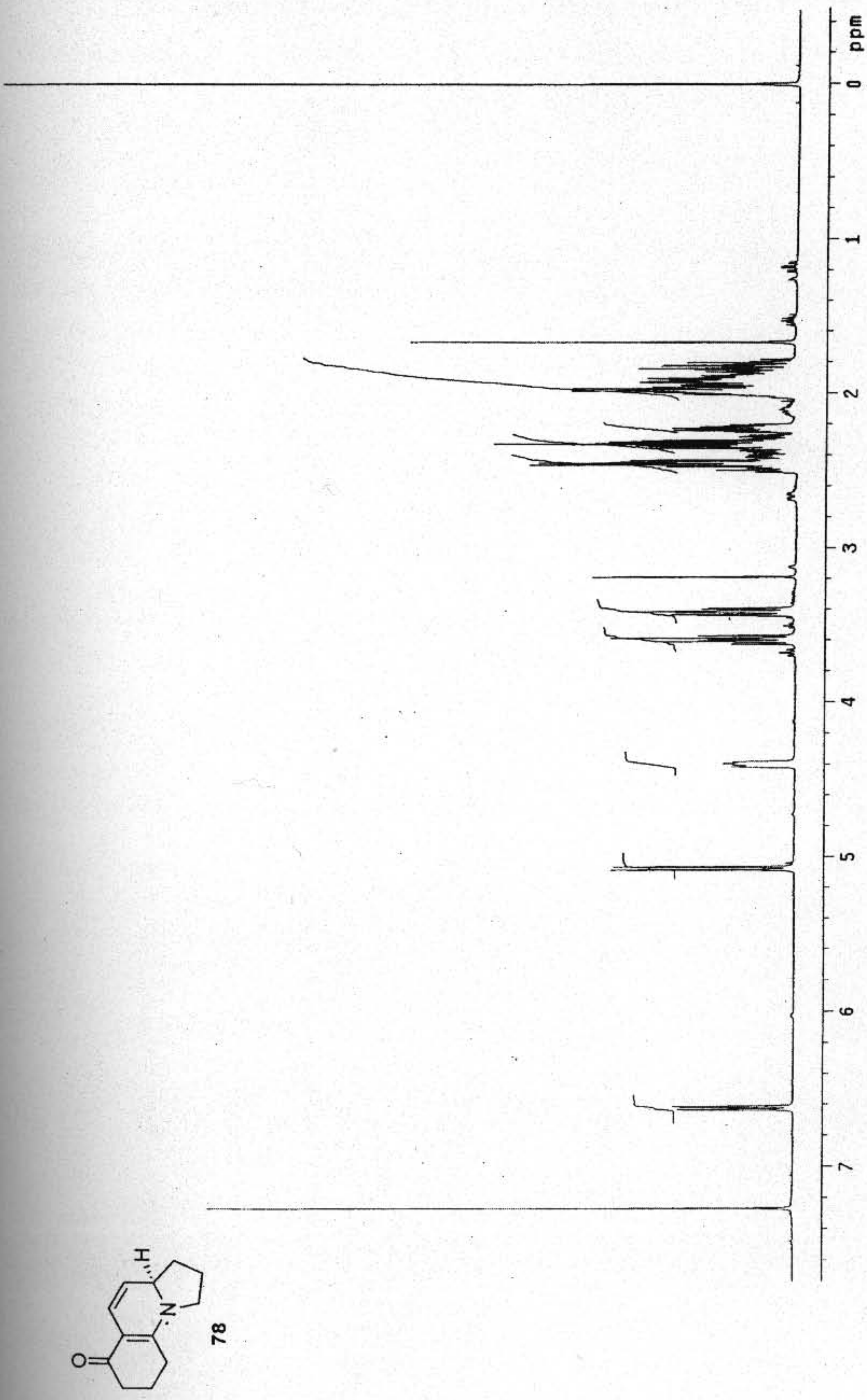
76

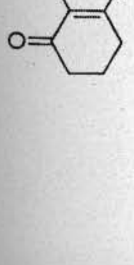


22



77





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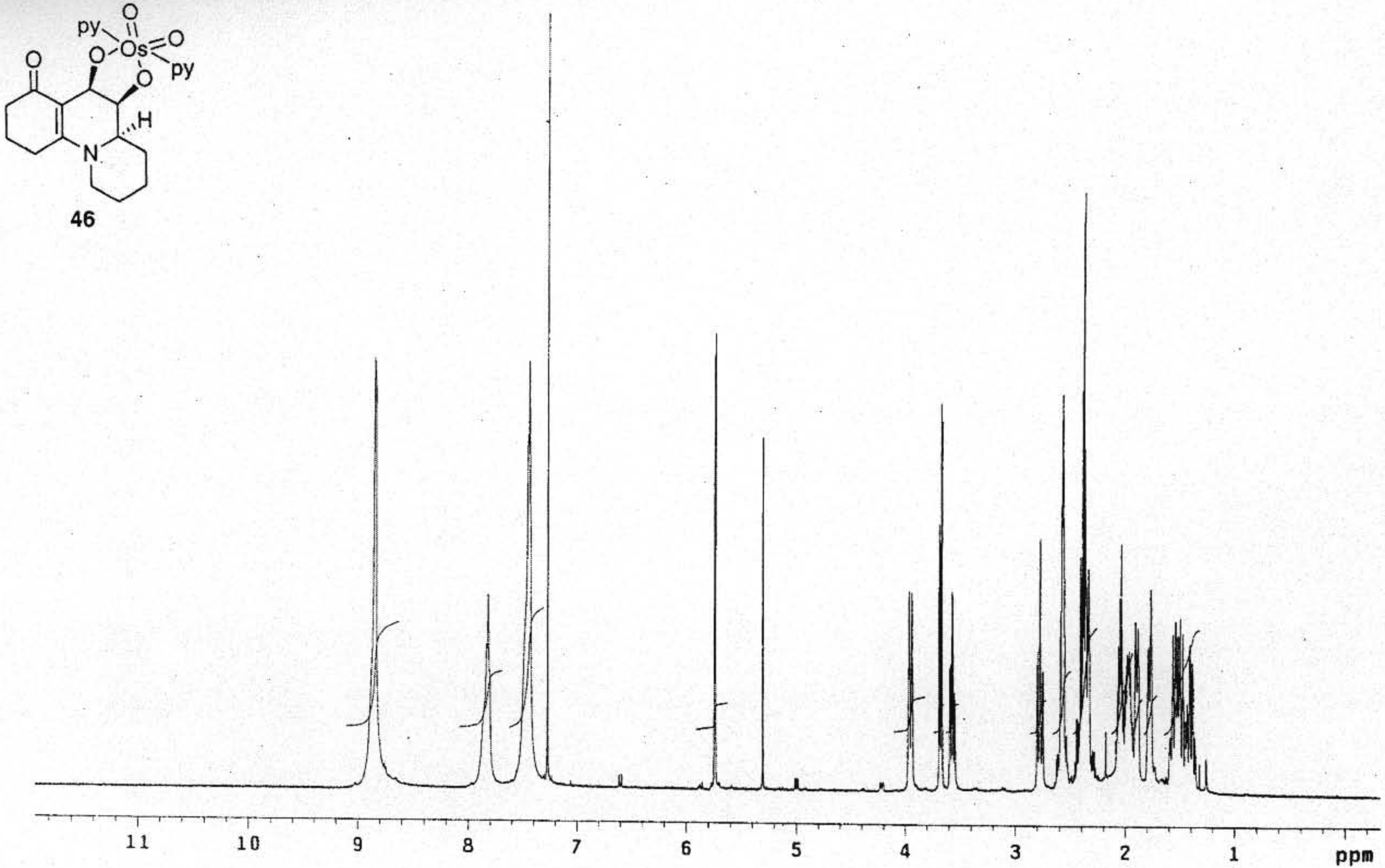
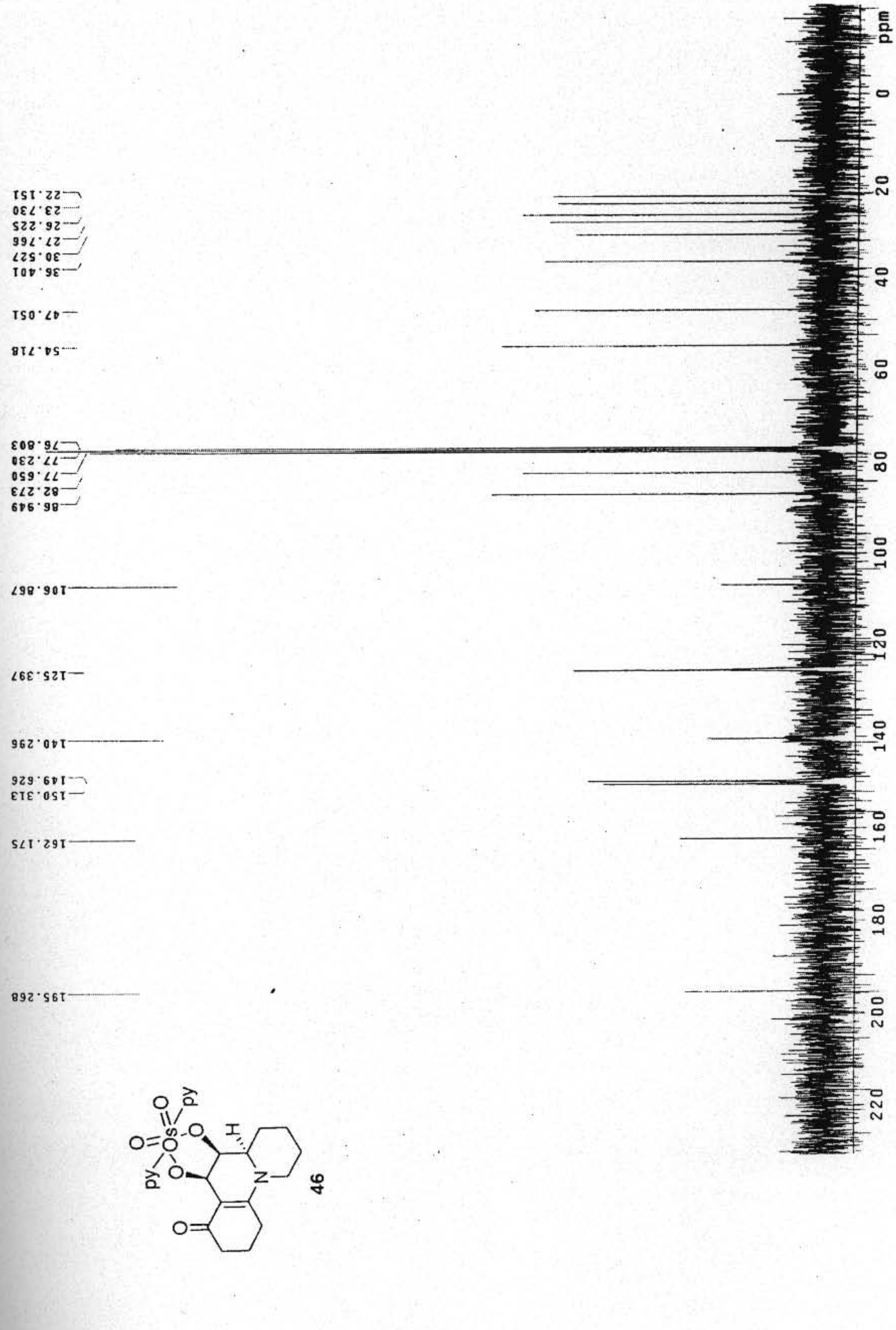
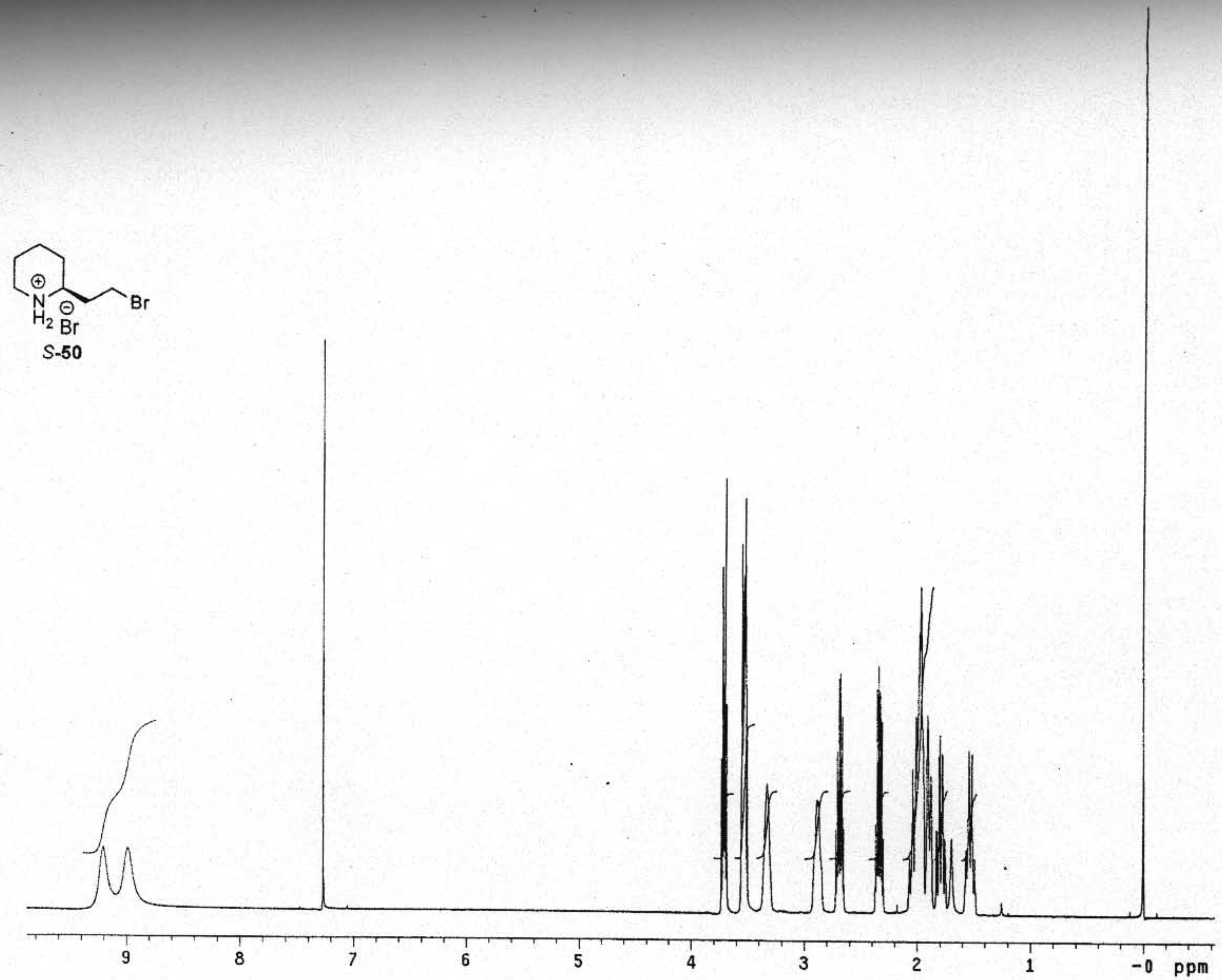


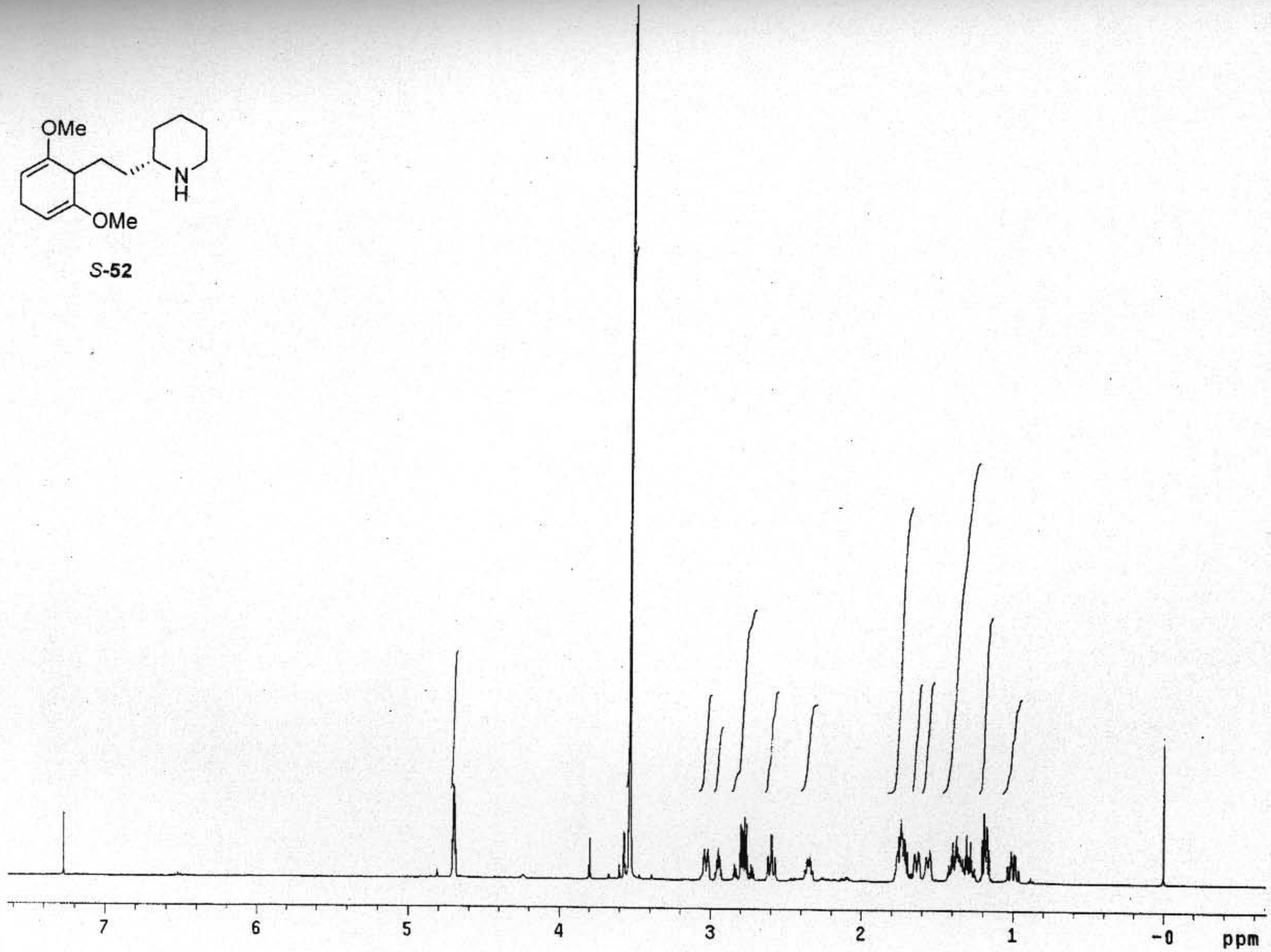
46


22.151
23.730
26.225
27.766
30.527
36.401
47.051
54.718
76.803
77.230
77.650
82.273
86.949
106.867
125.397
140.296
149.626
150.313
162.175
195.268
ppm
0
20
40
60
80
100
120
140
160
180
200
220
py
O
Os
O
O
O
py
H
N
O

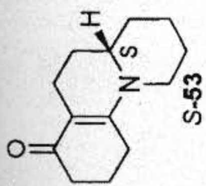
46



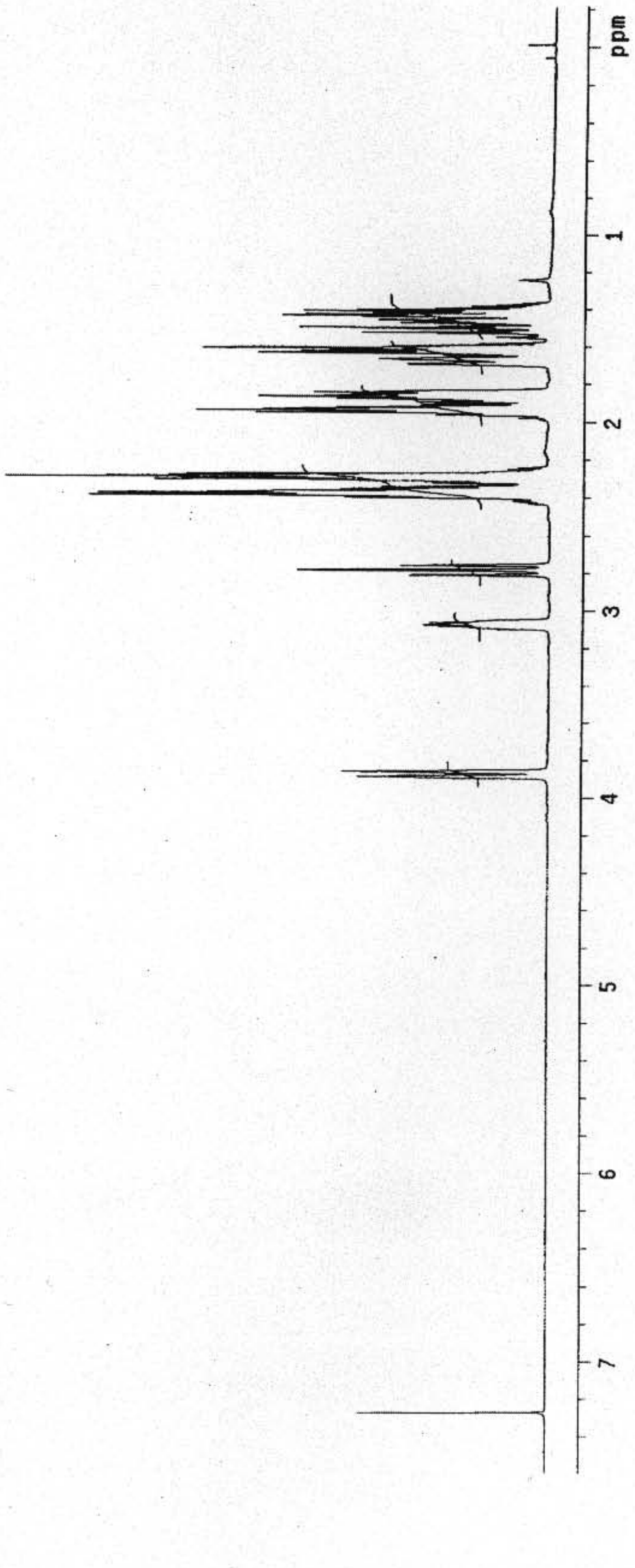
S-50

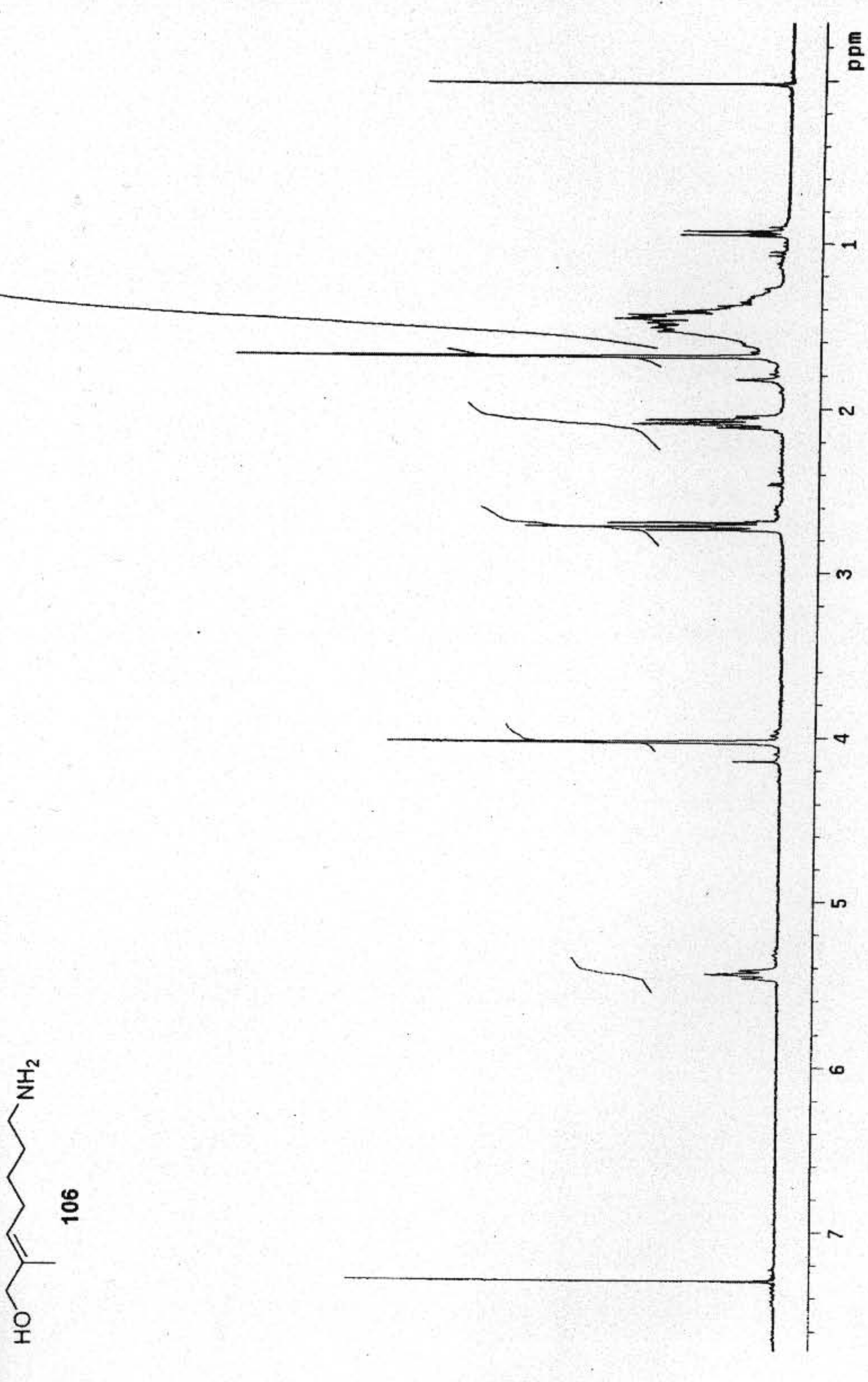


S-52

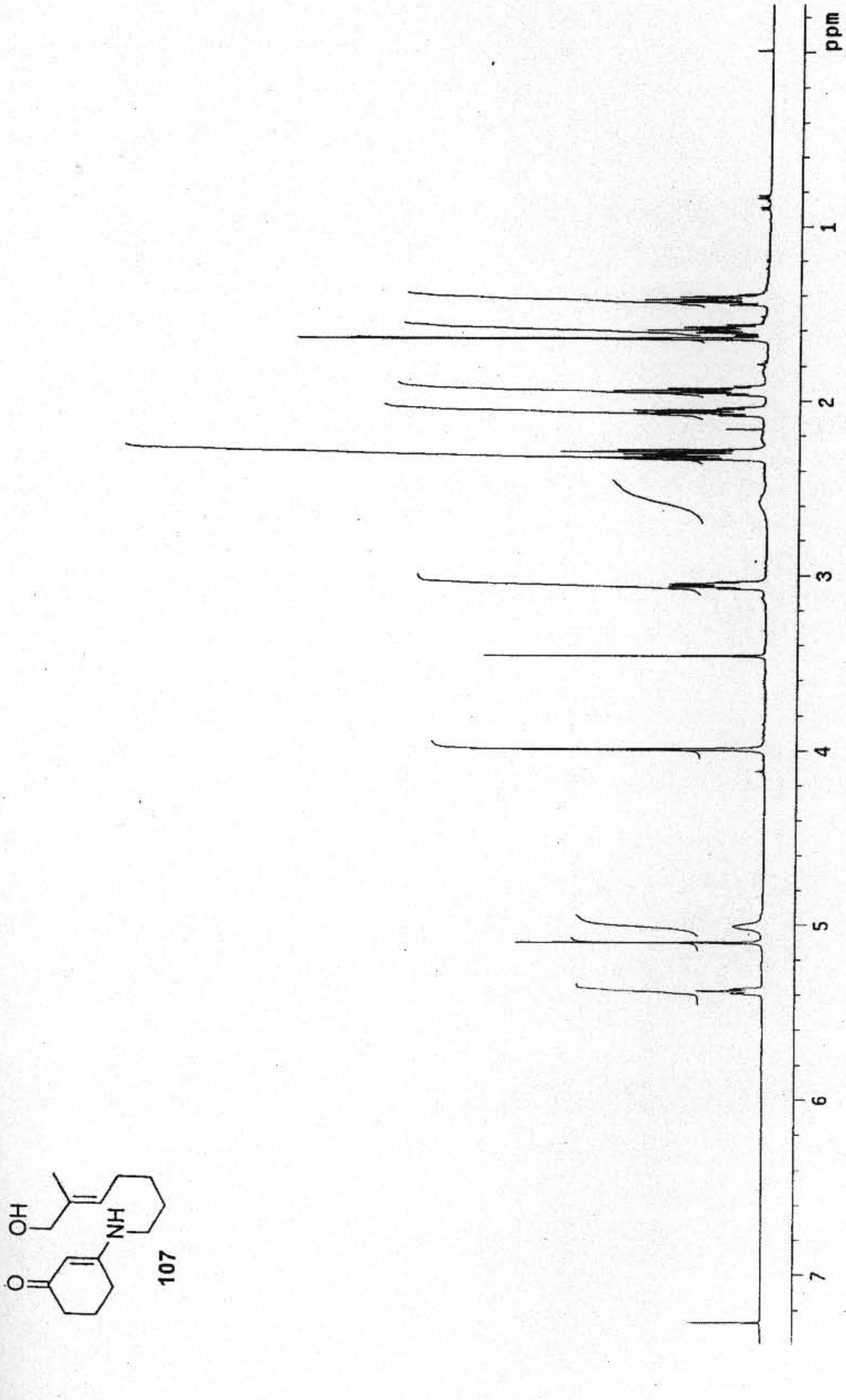


S-53

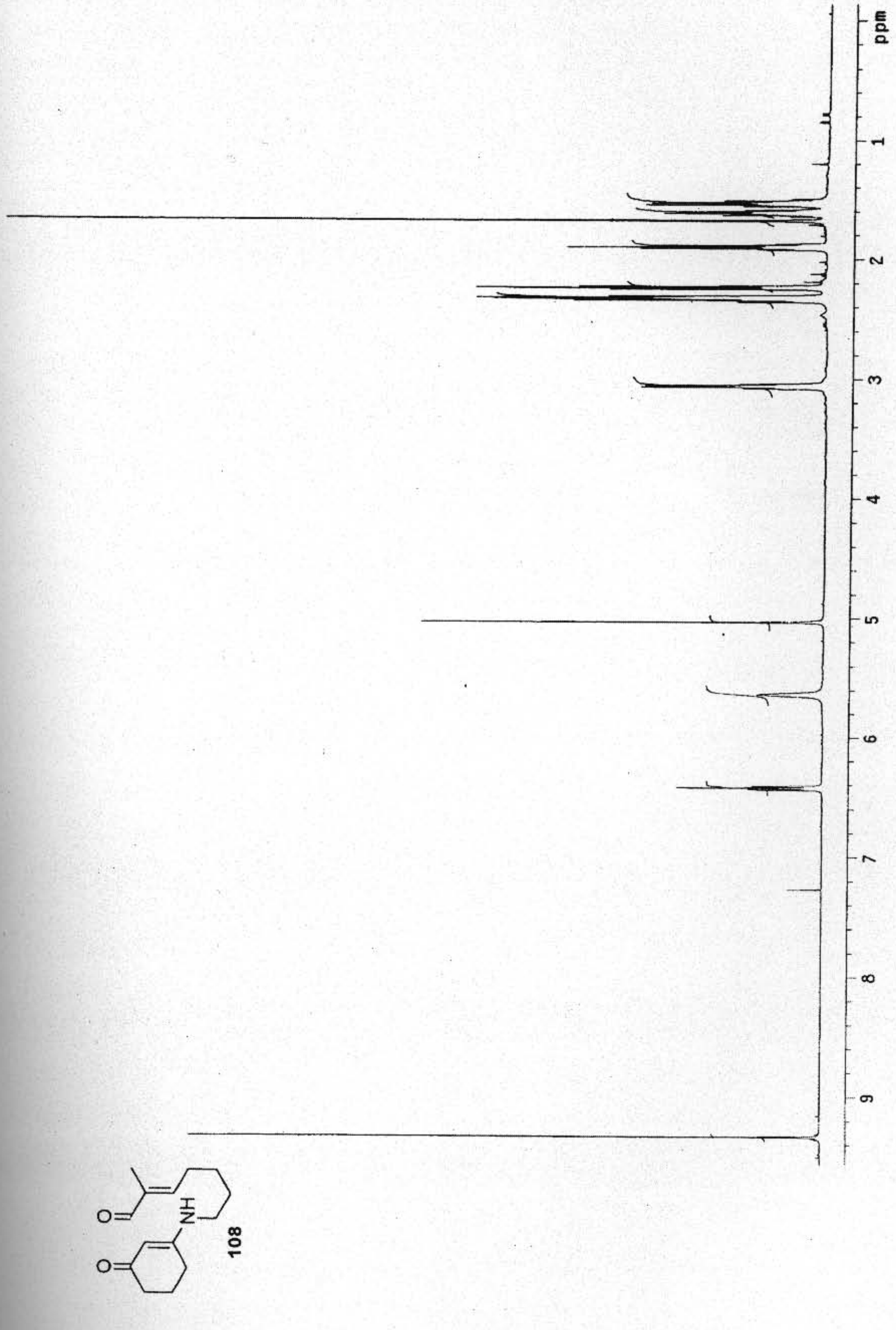




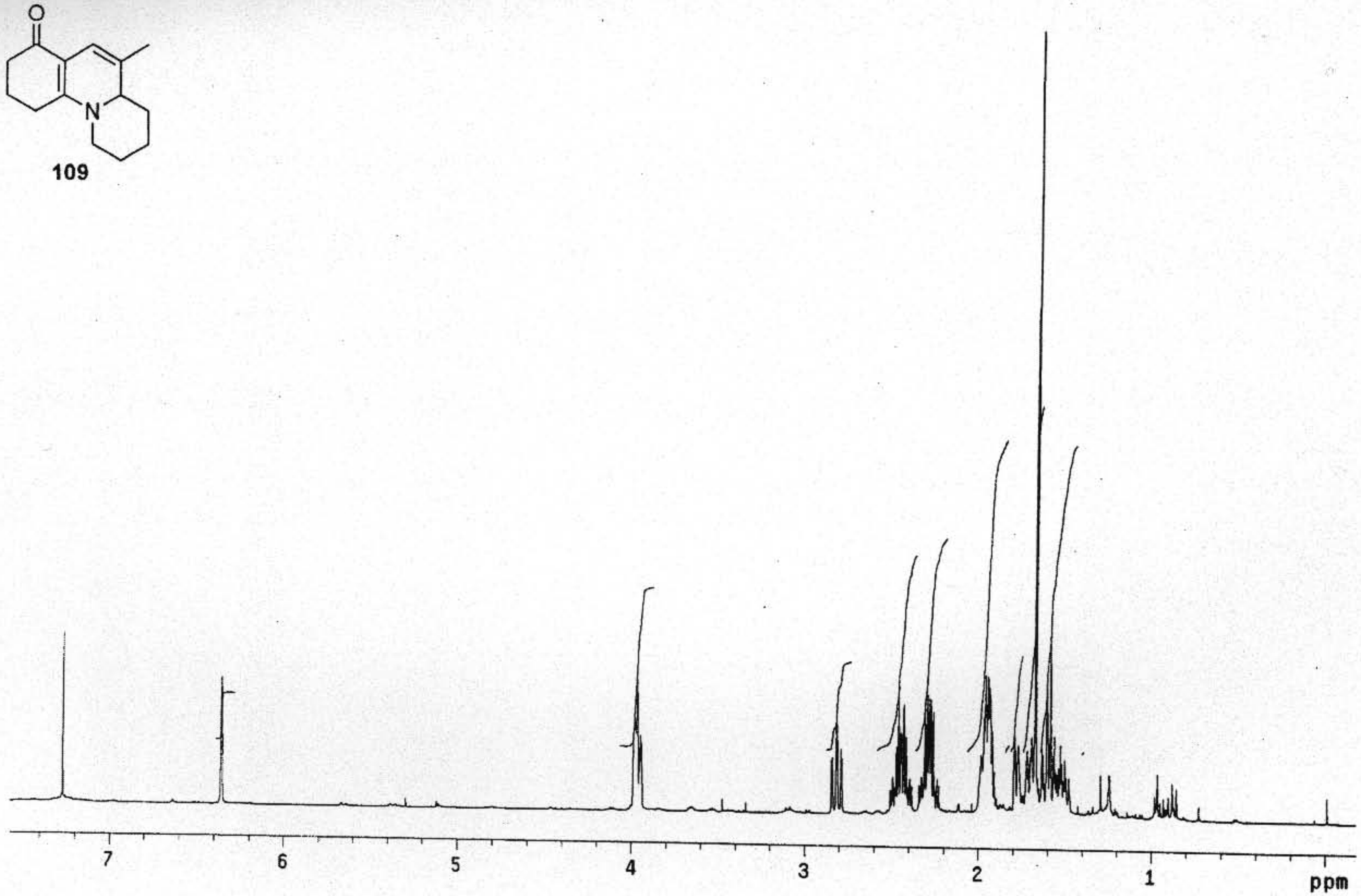
106



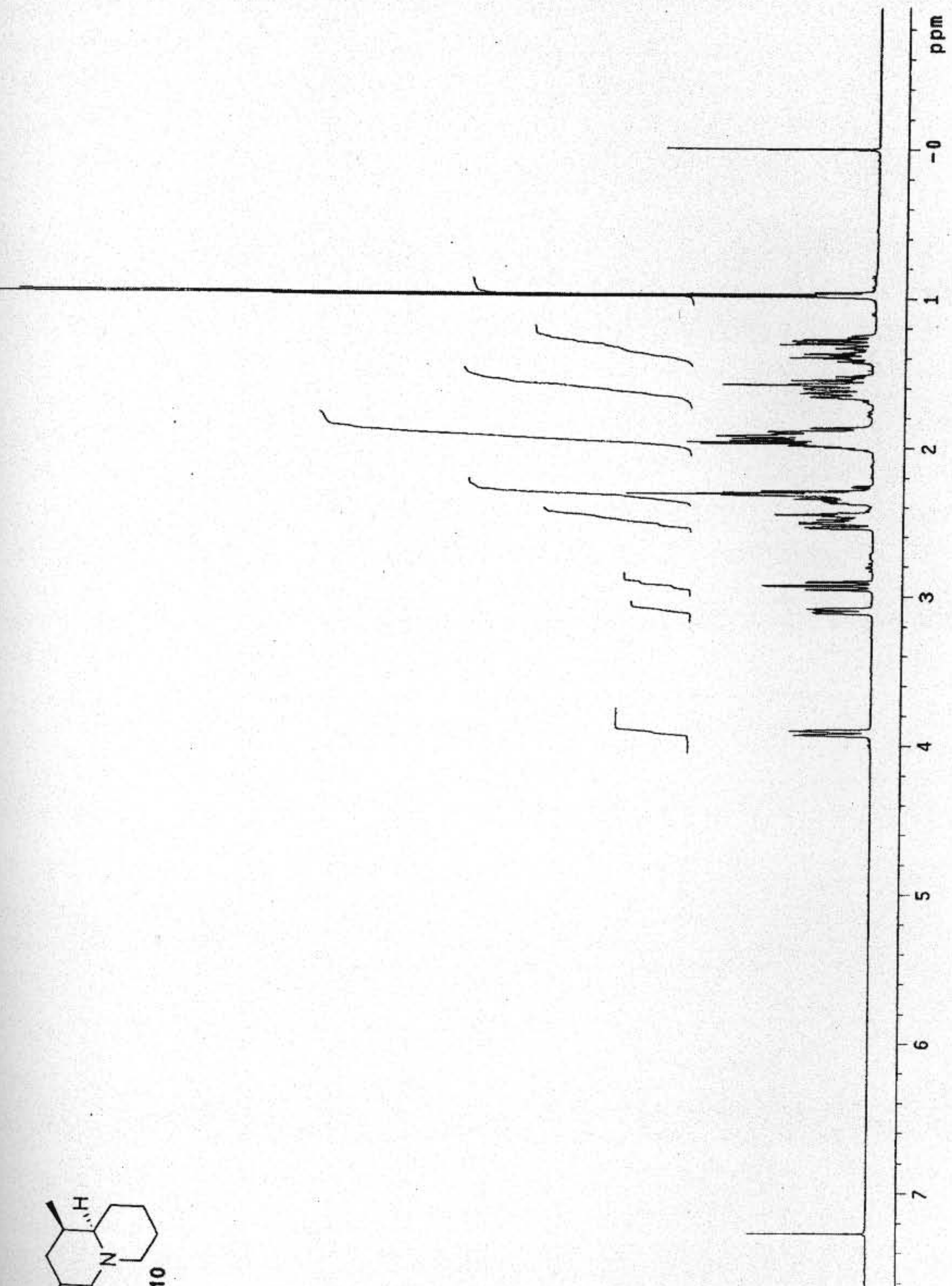
**107**



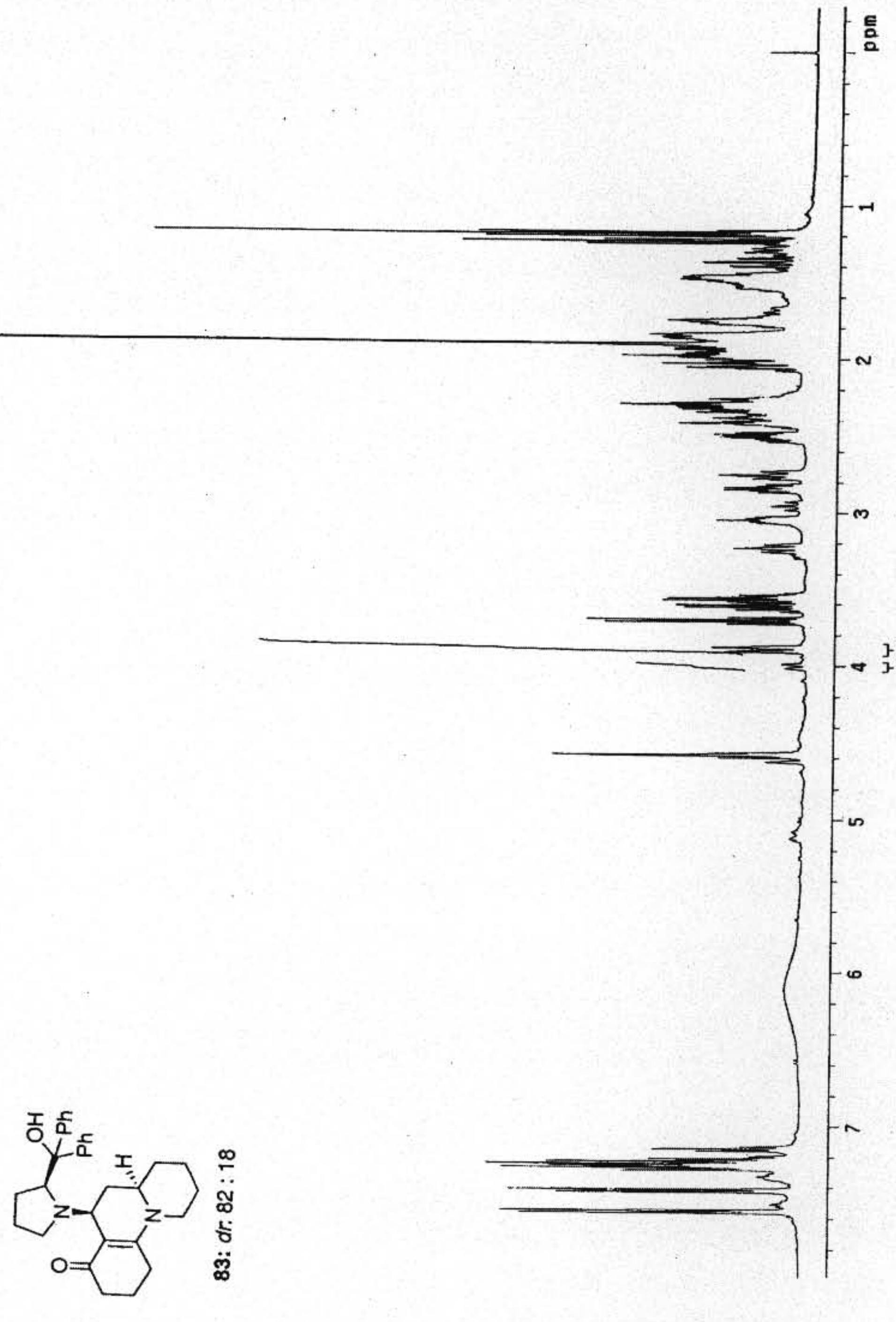
108



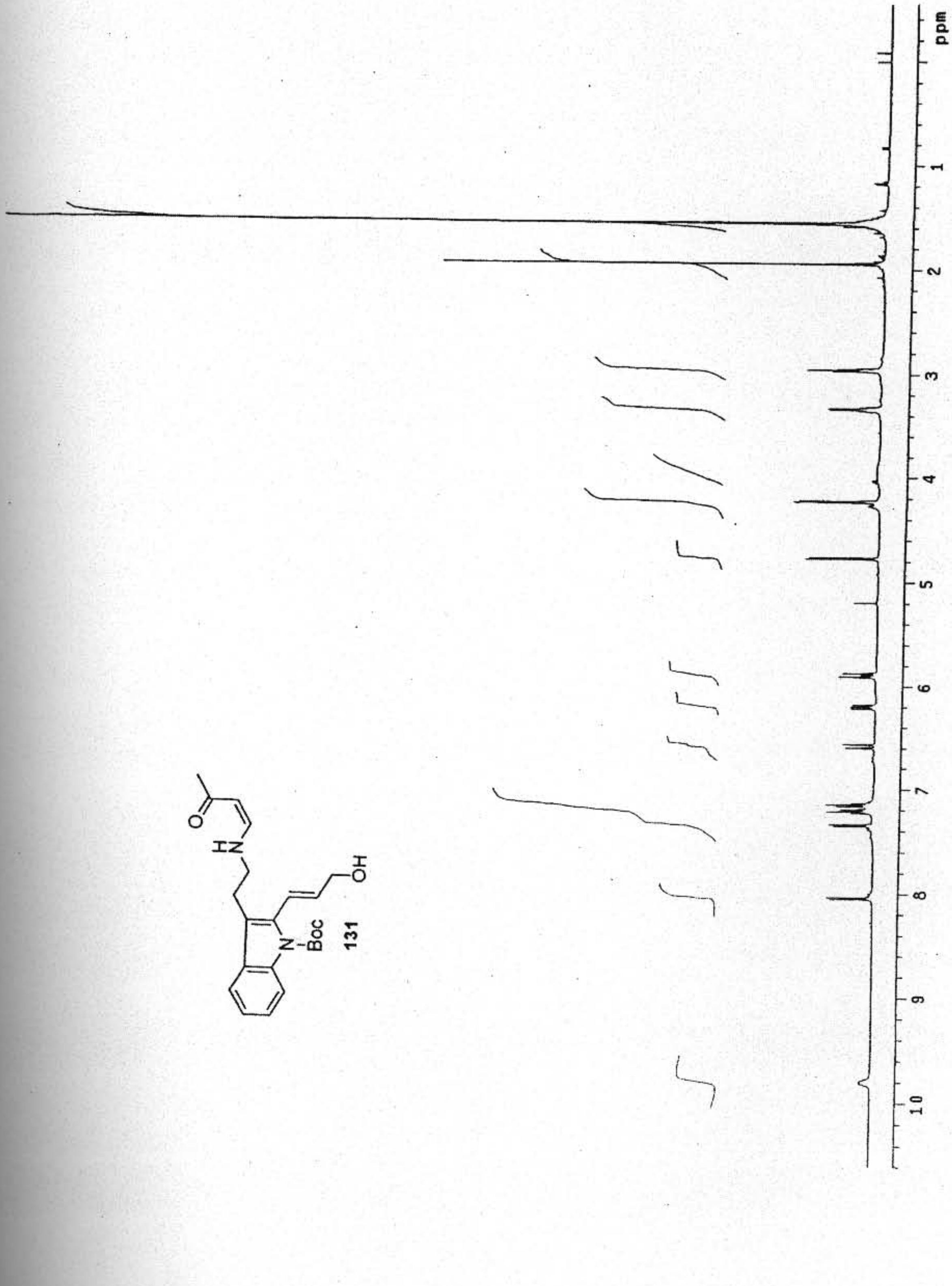
**109**



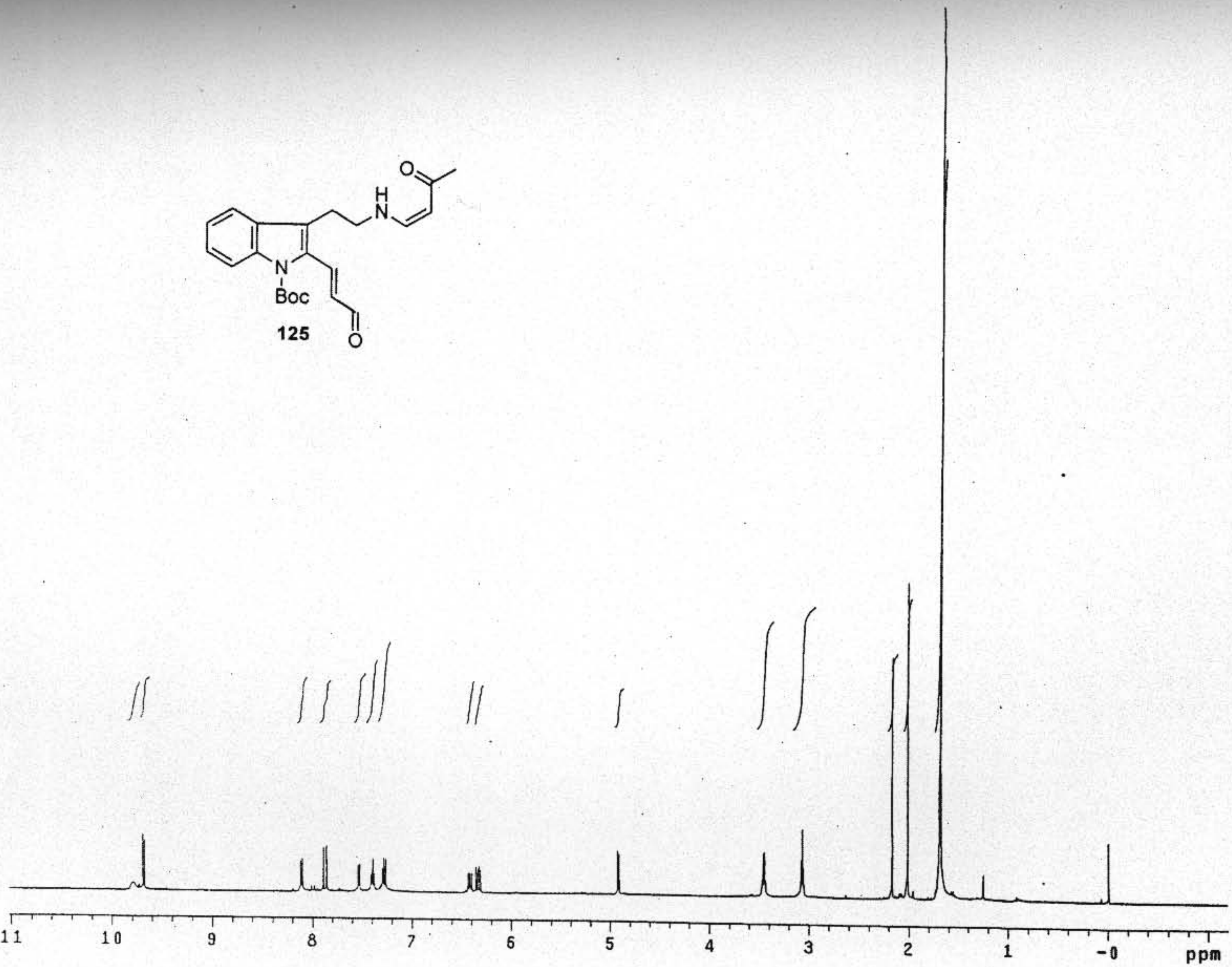
110



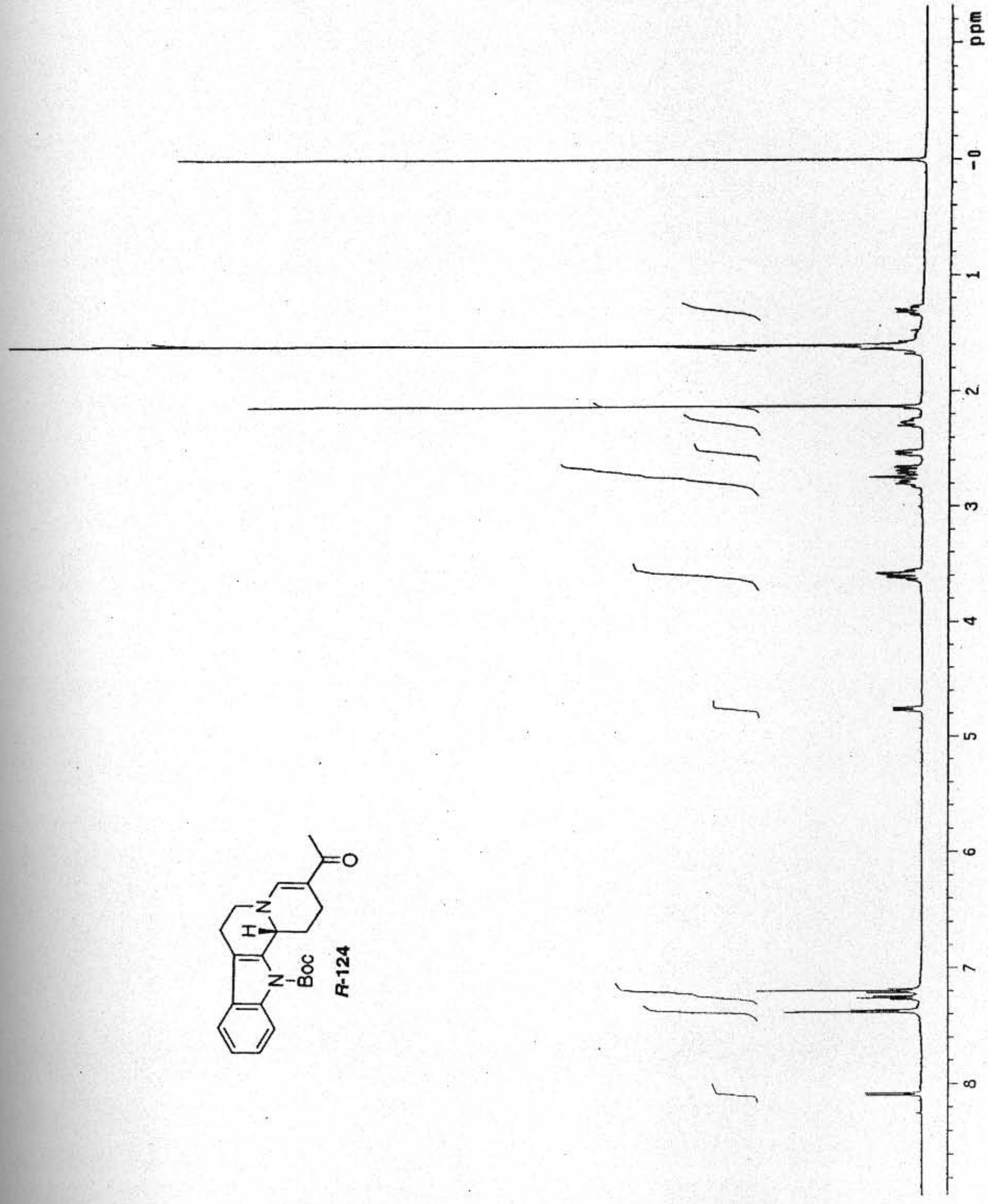
83: *dr.* 82 : 18



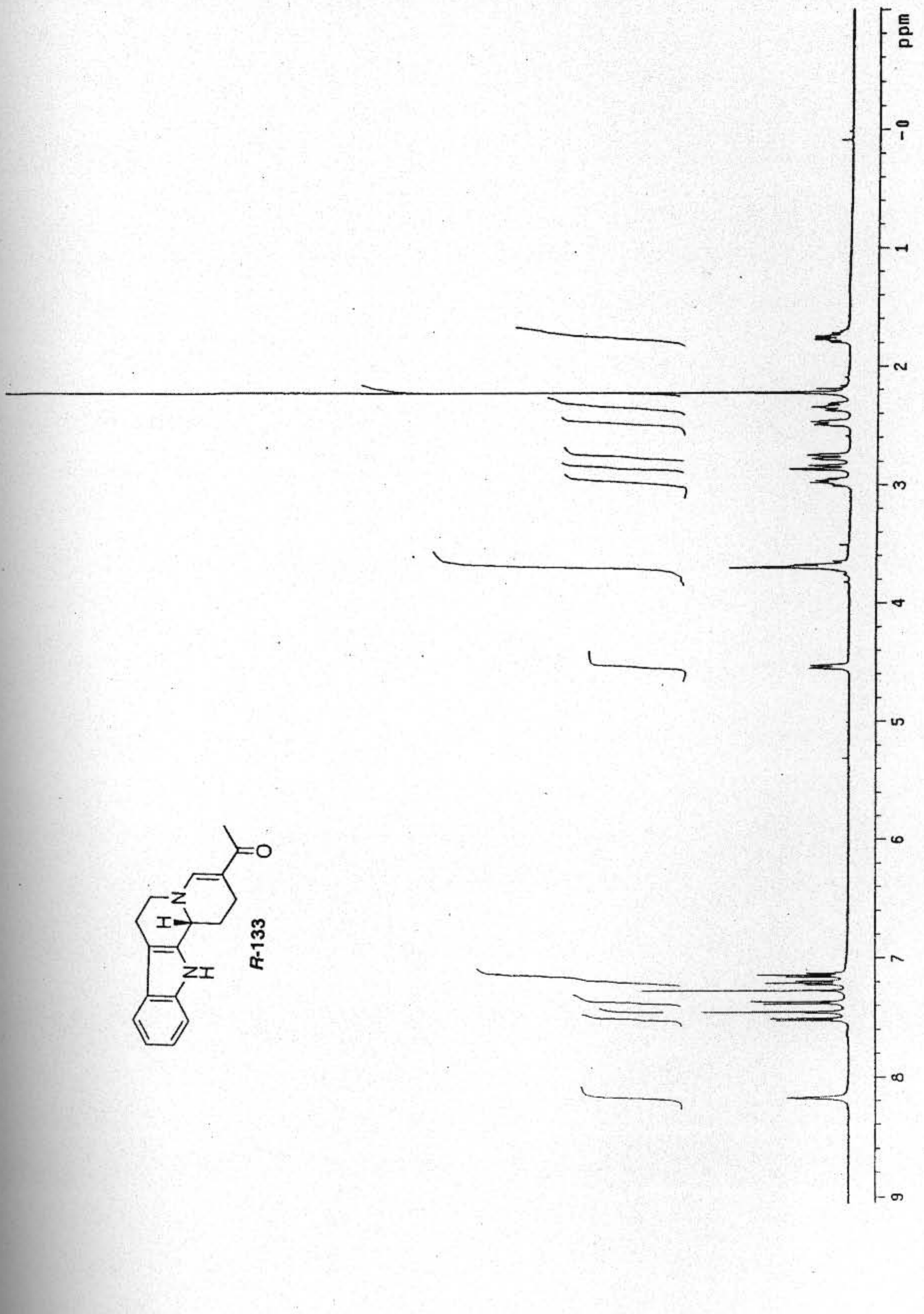
131



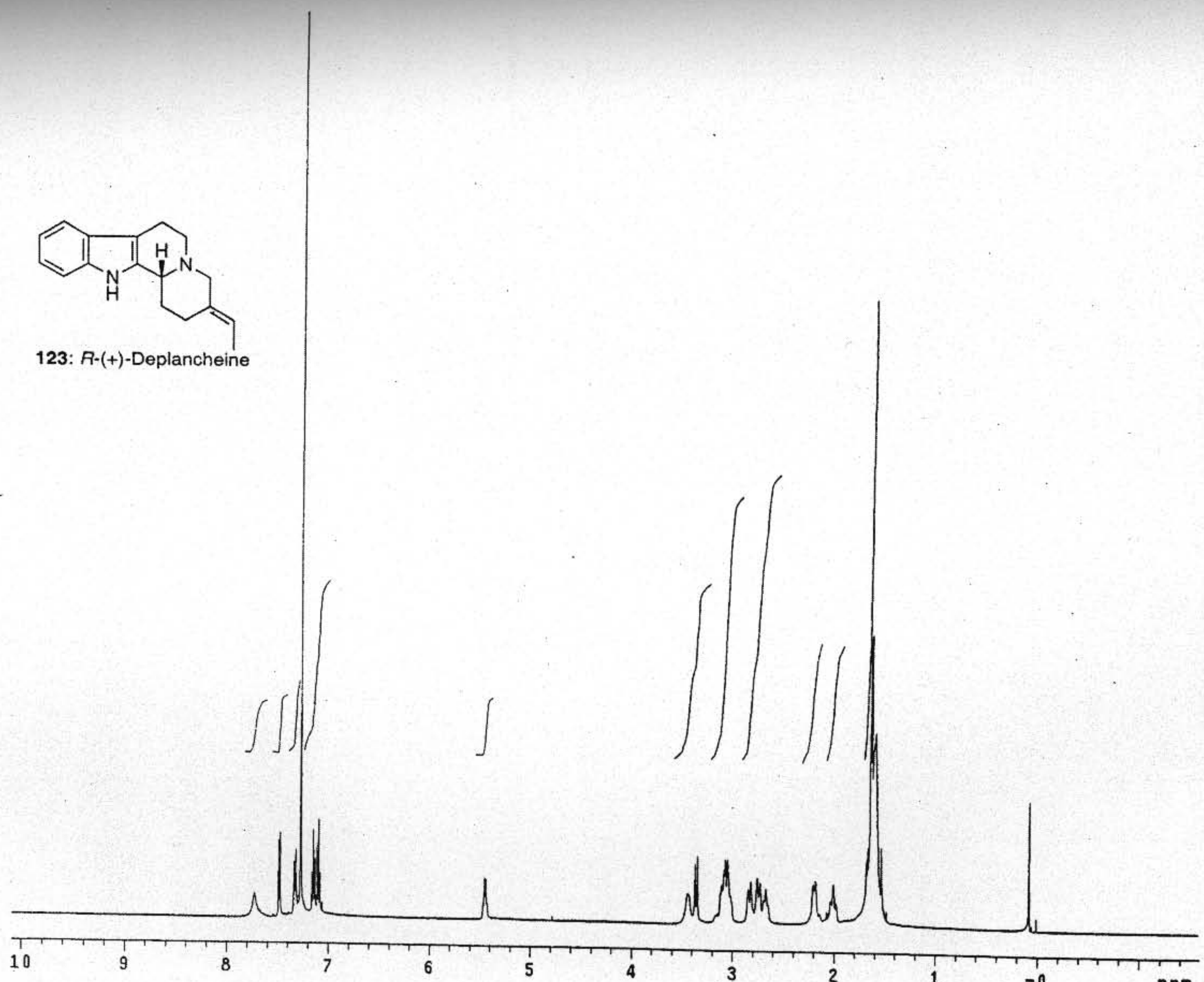
125



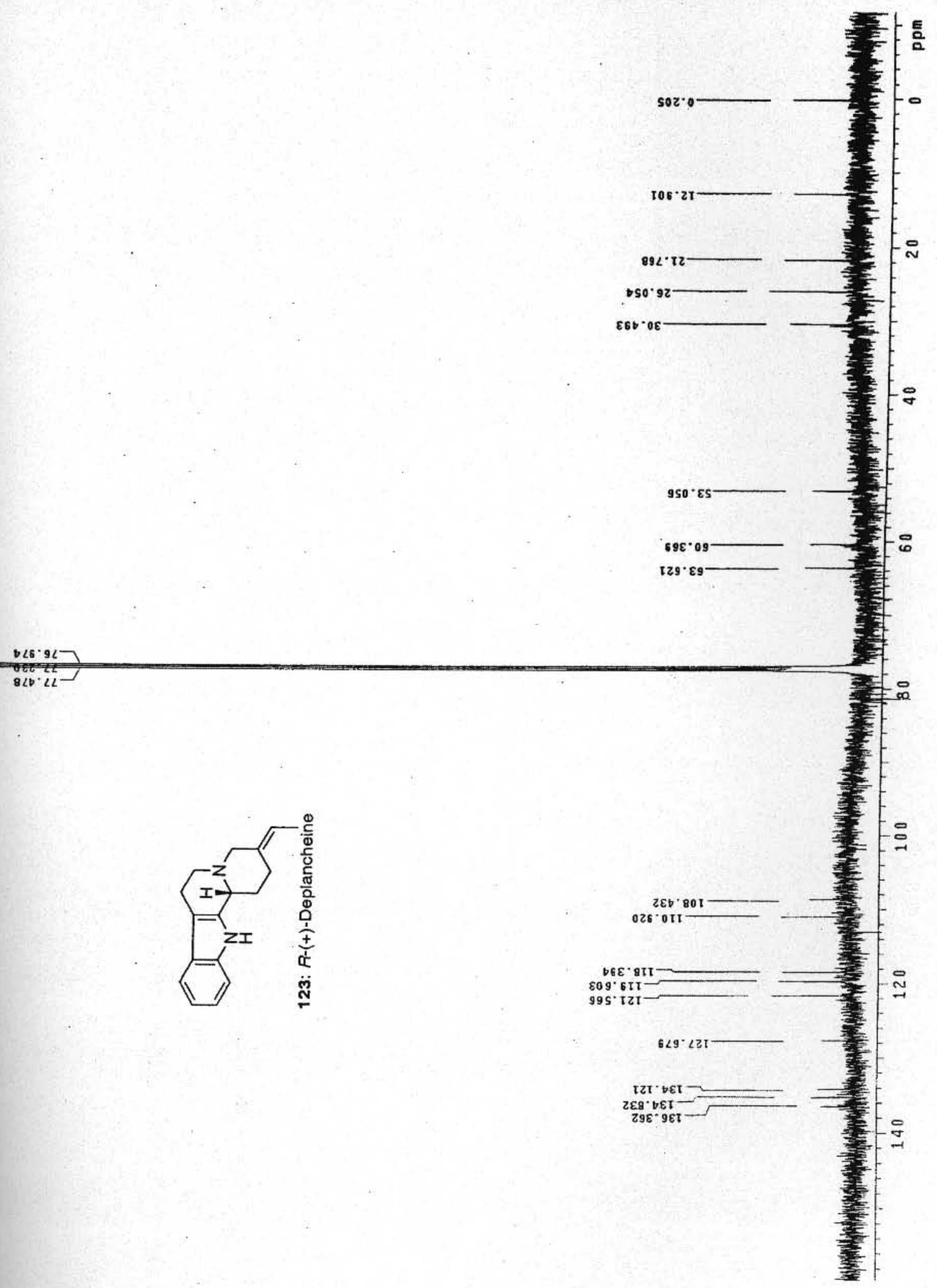
***R*-124**

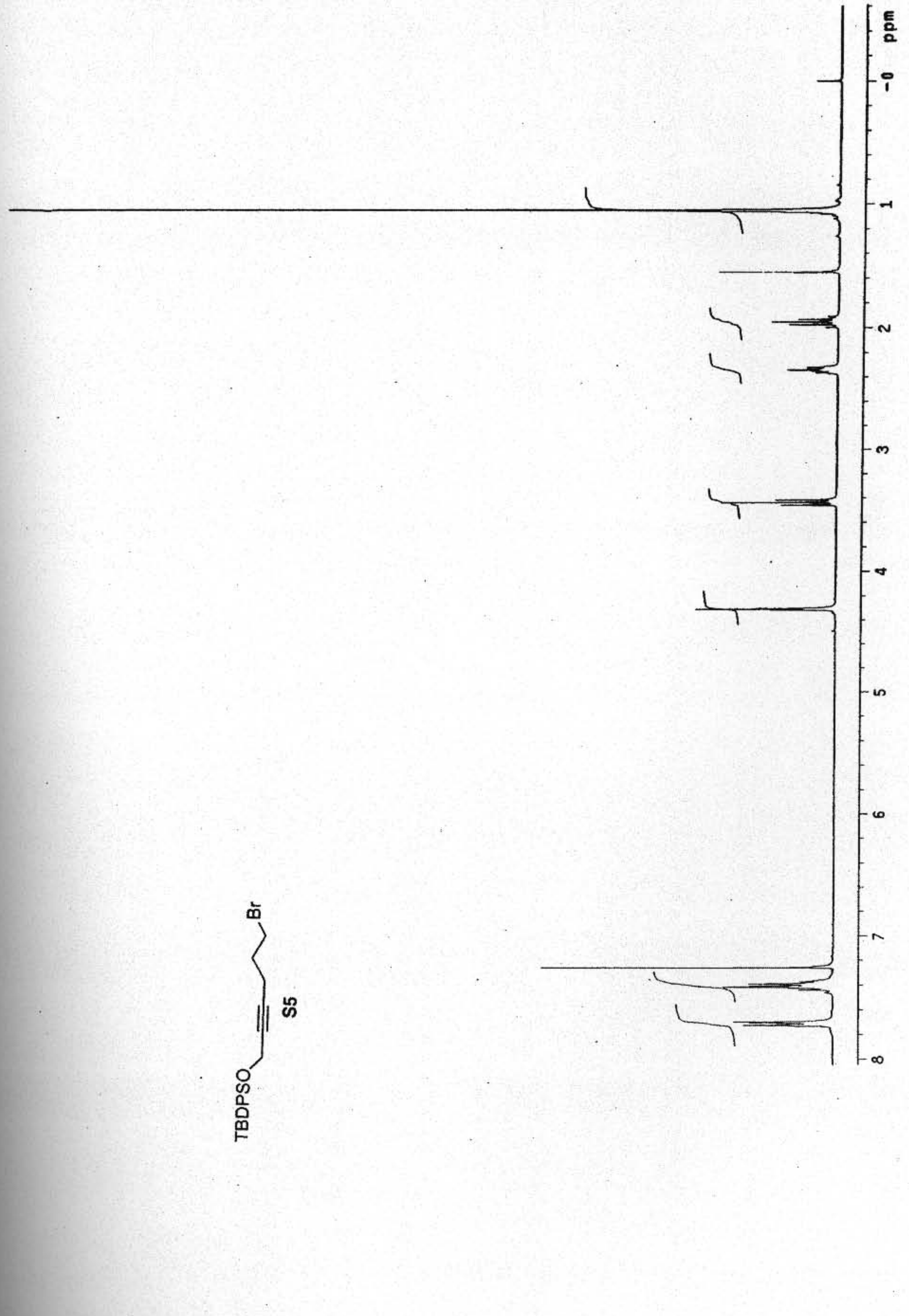


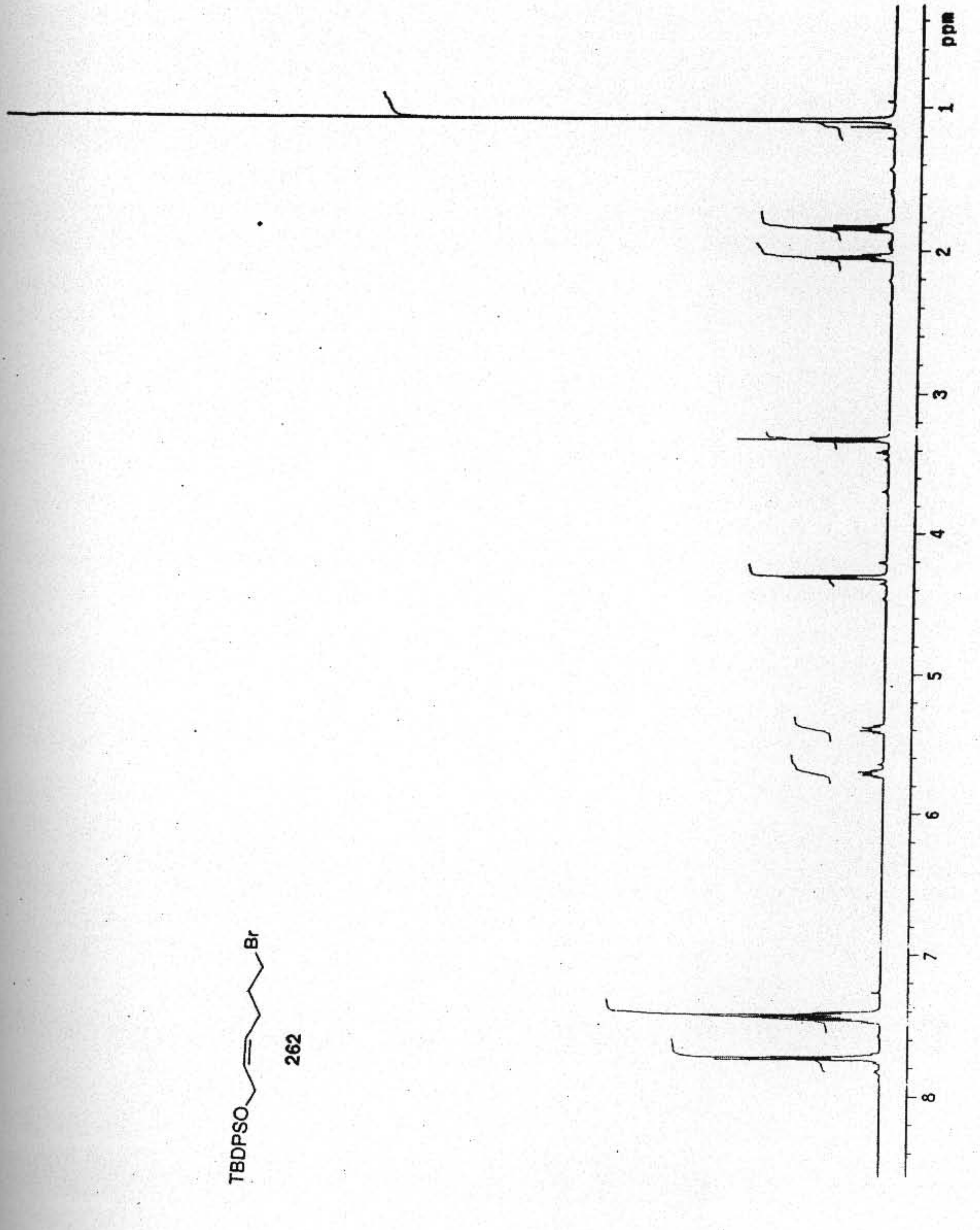
R-133



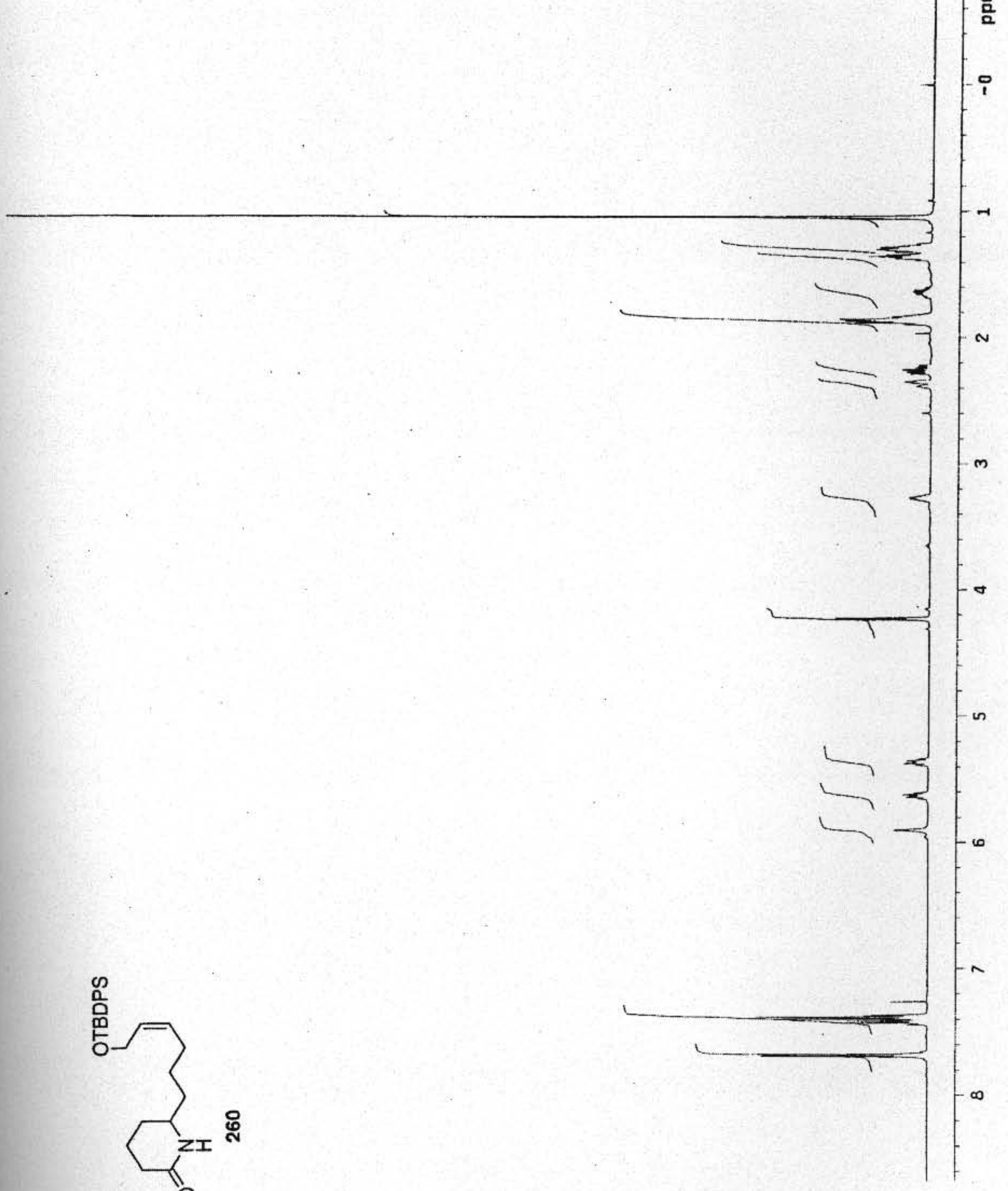
**123**: *R*-(+)-Deplancheine


123: *R*-(+)-Deplancheine

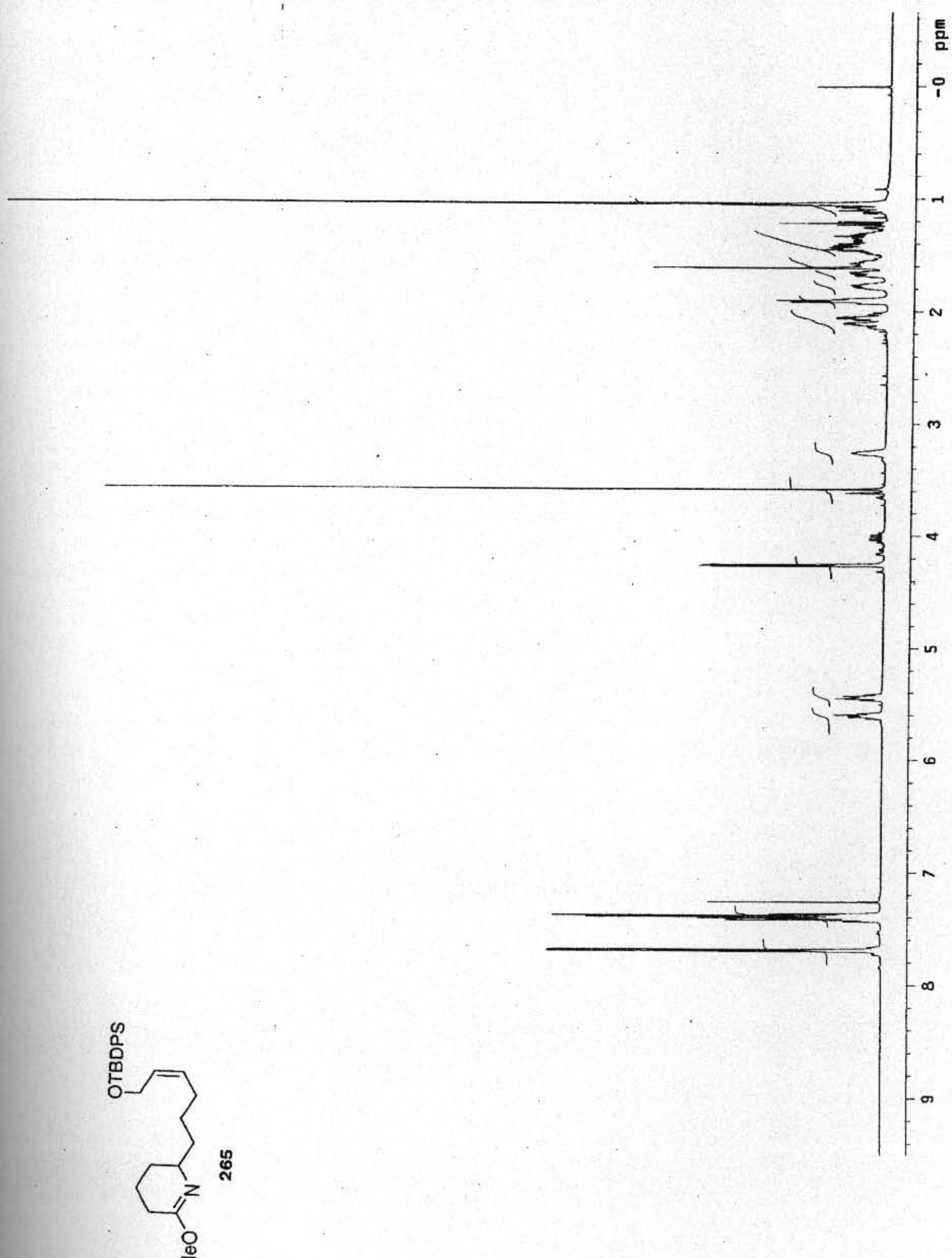

TBDPSO
Br
S5
ppm
8
7
6
5
4
3
2
1
-0



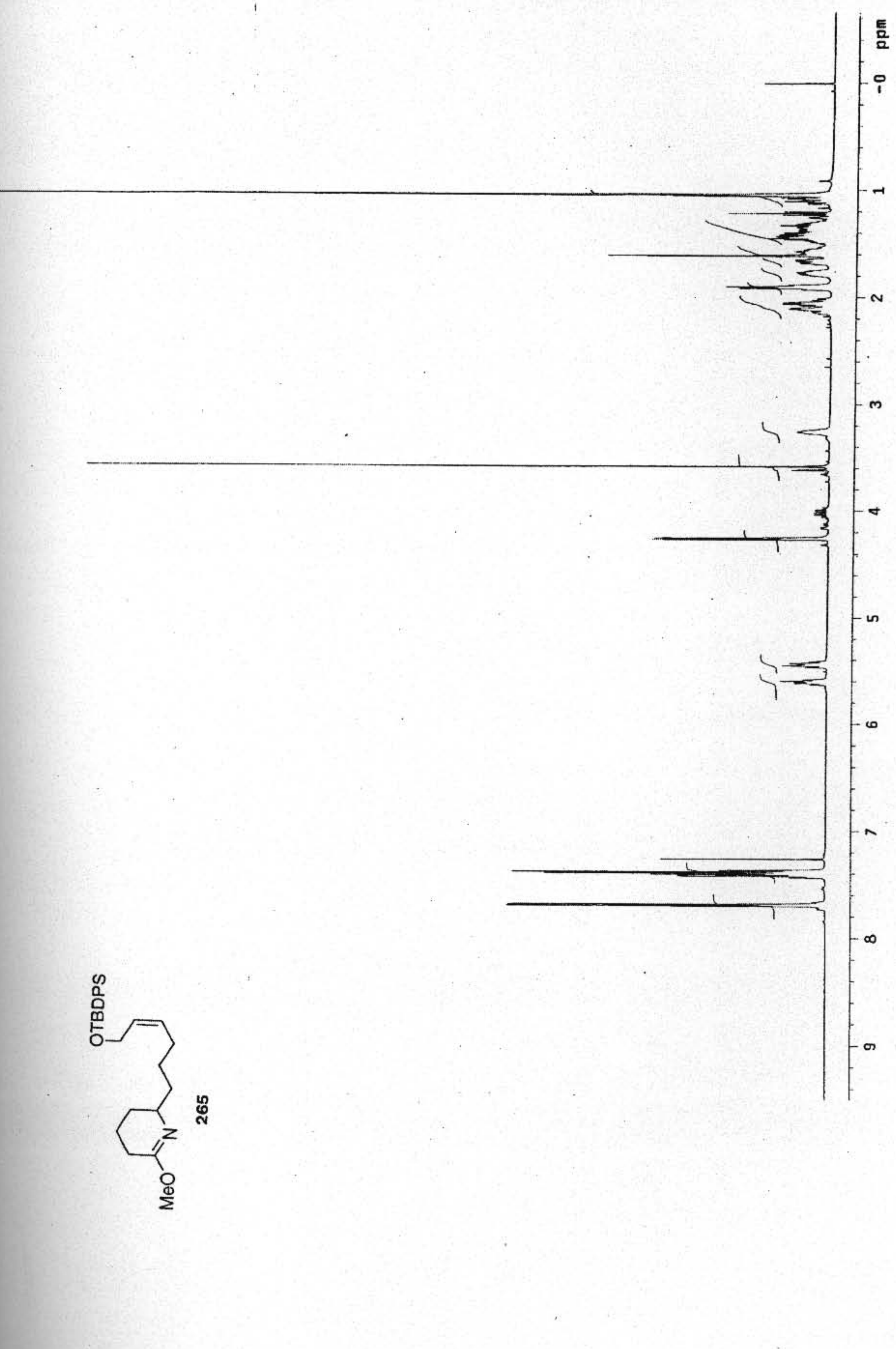
262



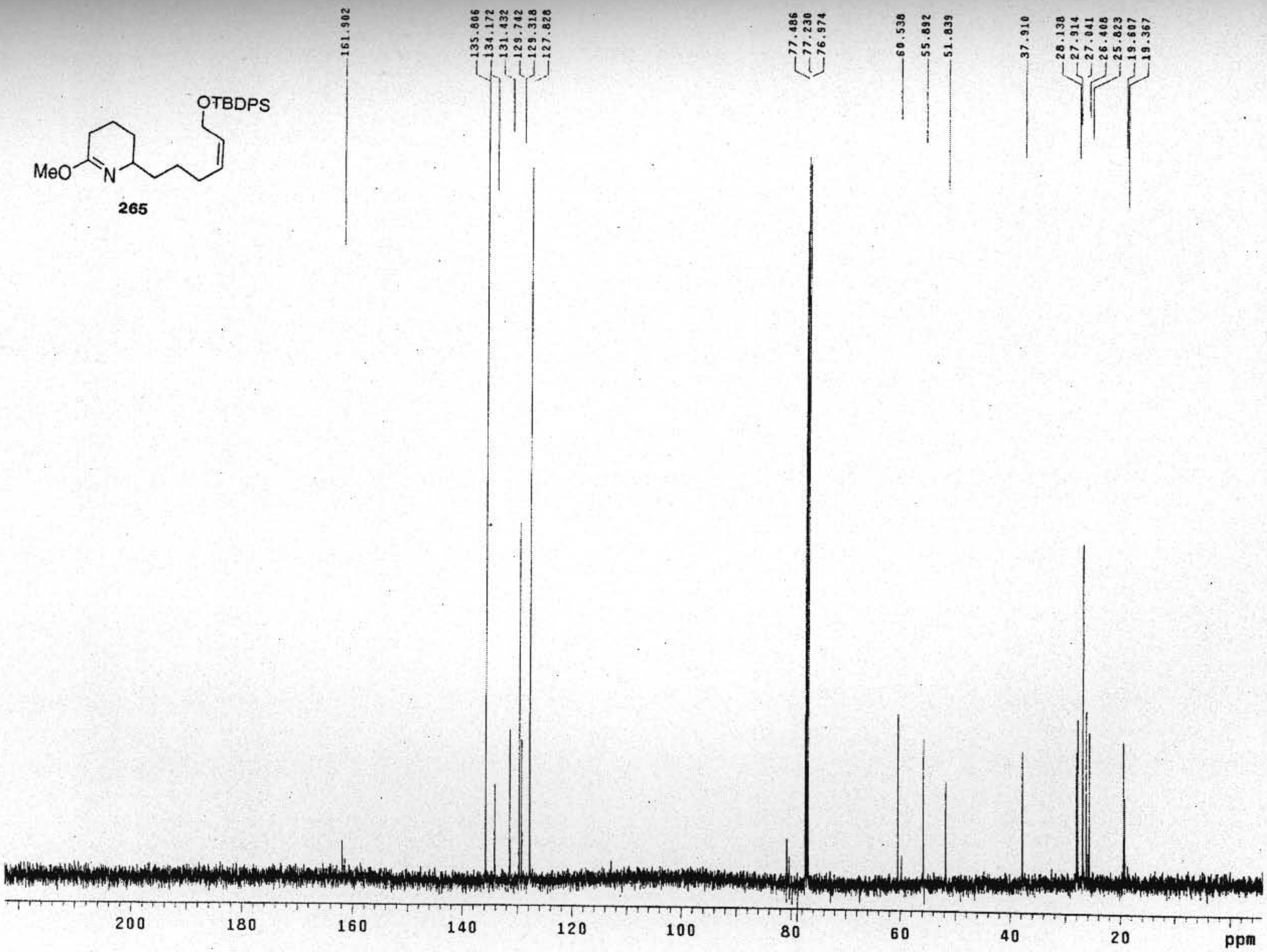
260



265

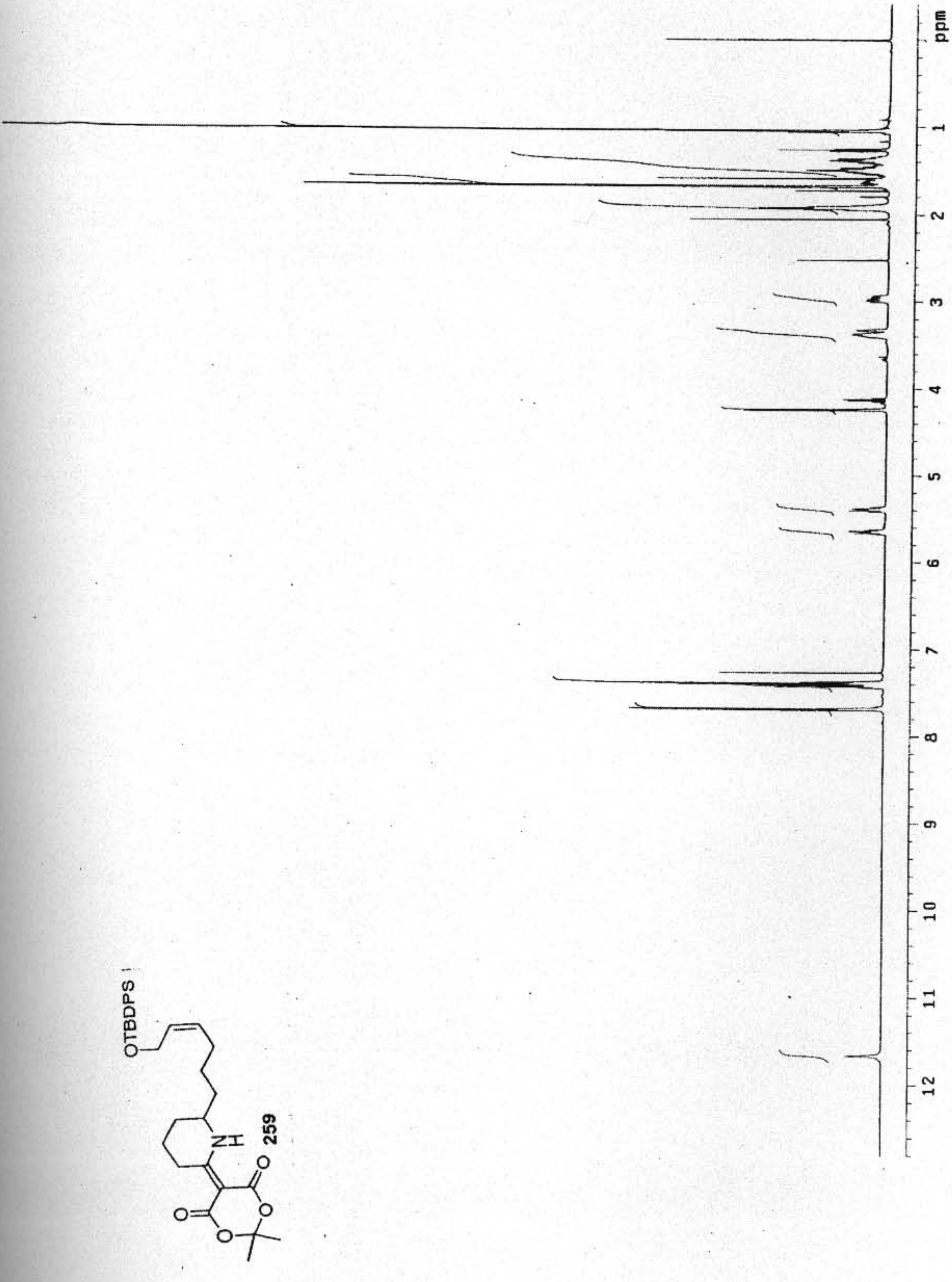


265

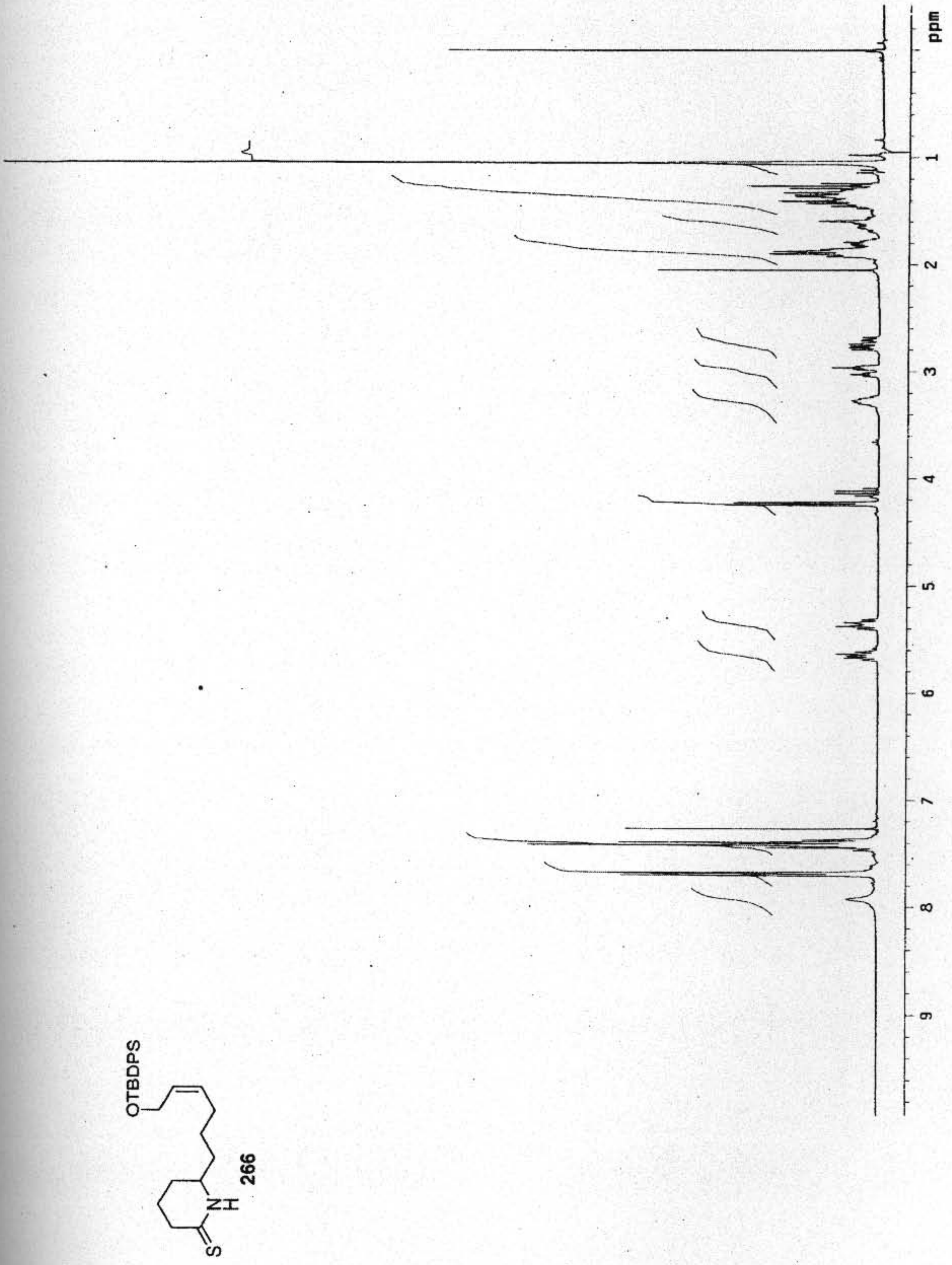


265

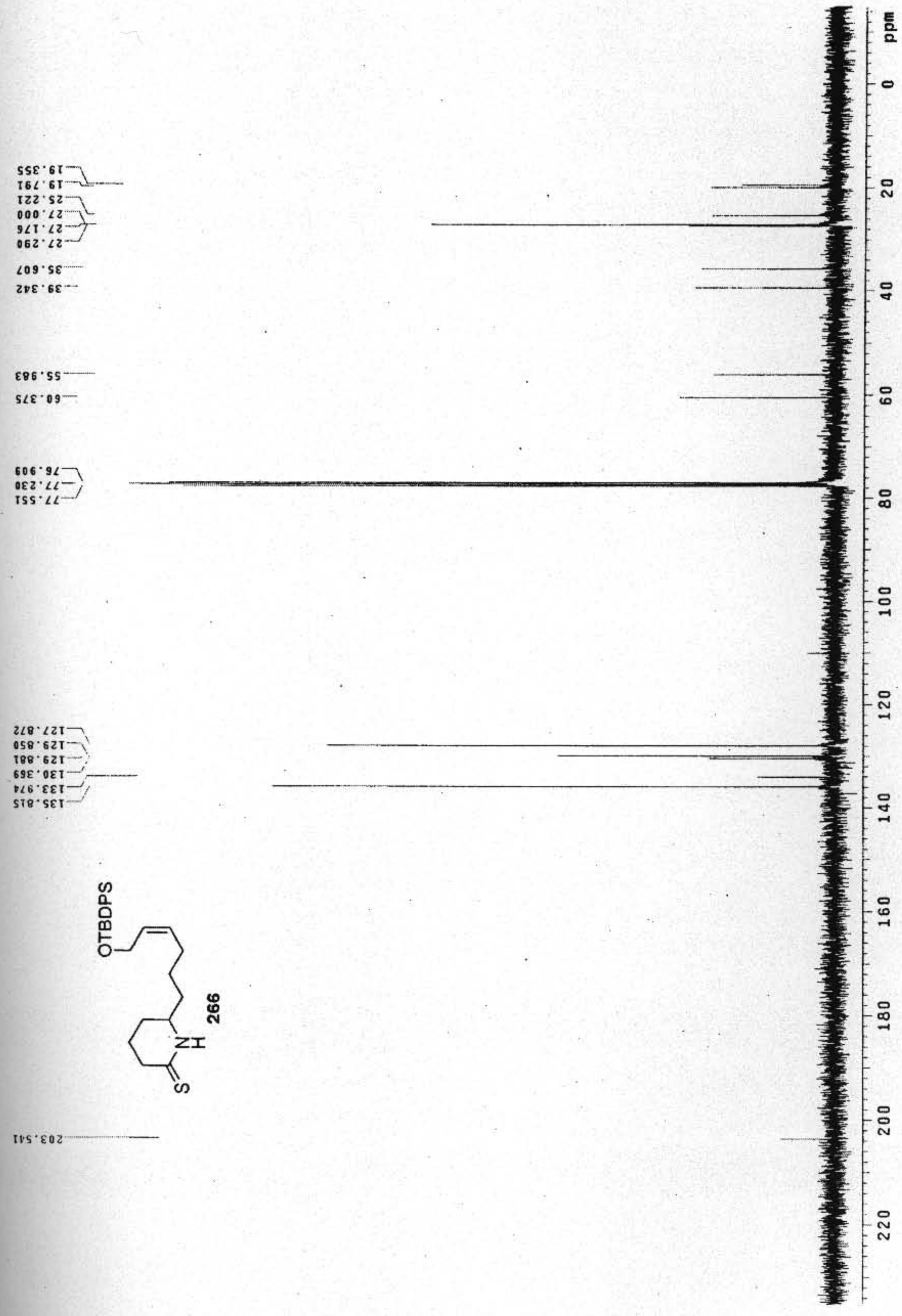
MeO
N
OTBDPS
161.902
135.806
134.172
131.432
129.742
129.318
127.828
77.486
77.230
76.974
60.538
55.892
51.839
37.910
28.138
27.914
27.041
26.408
25.823
19.607
19.367
200
180
160
140
120
100
80
60
40
20
ppm

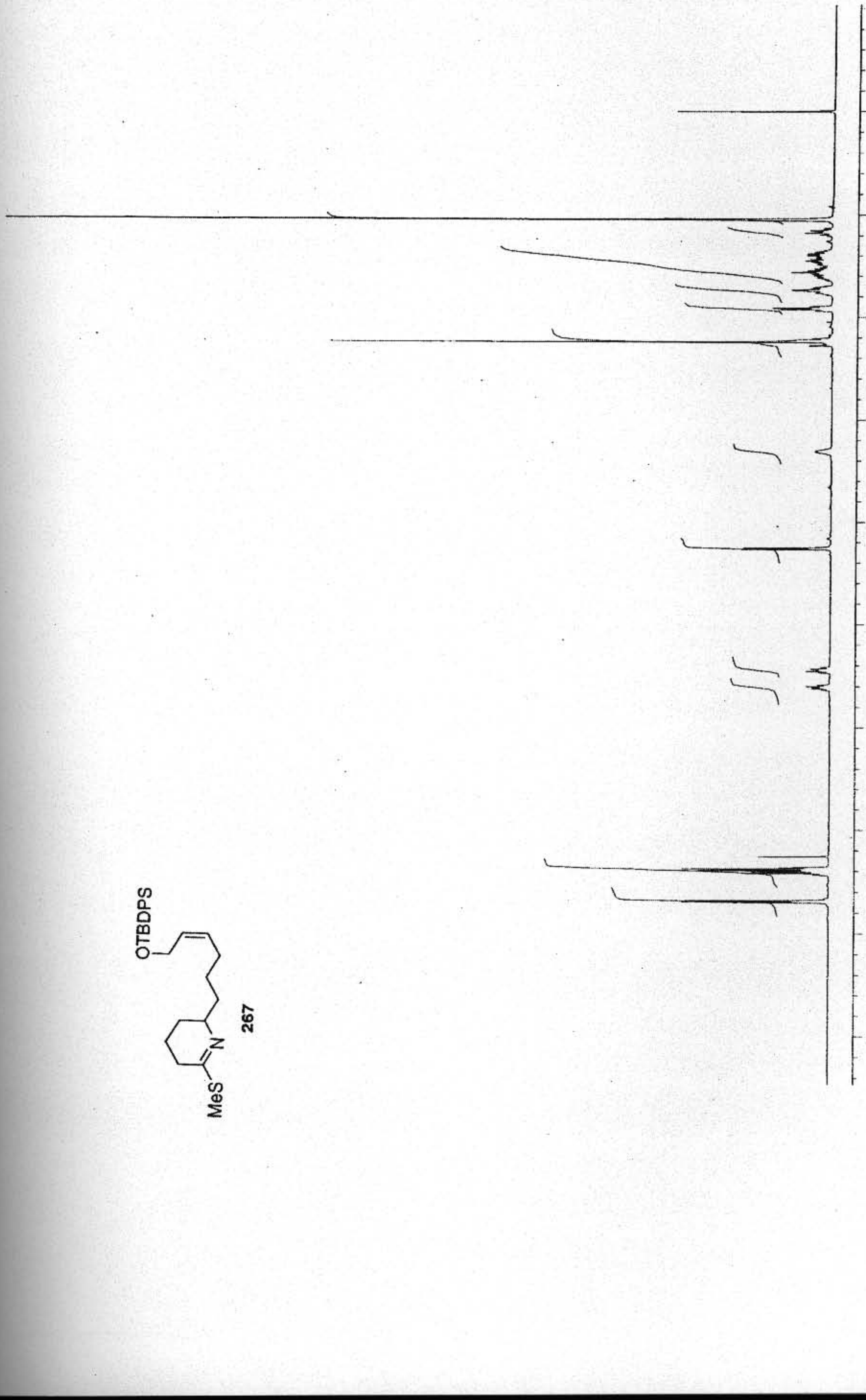


259

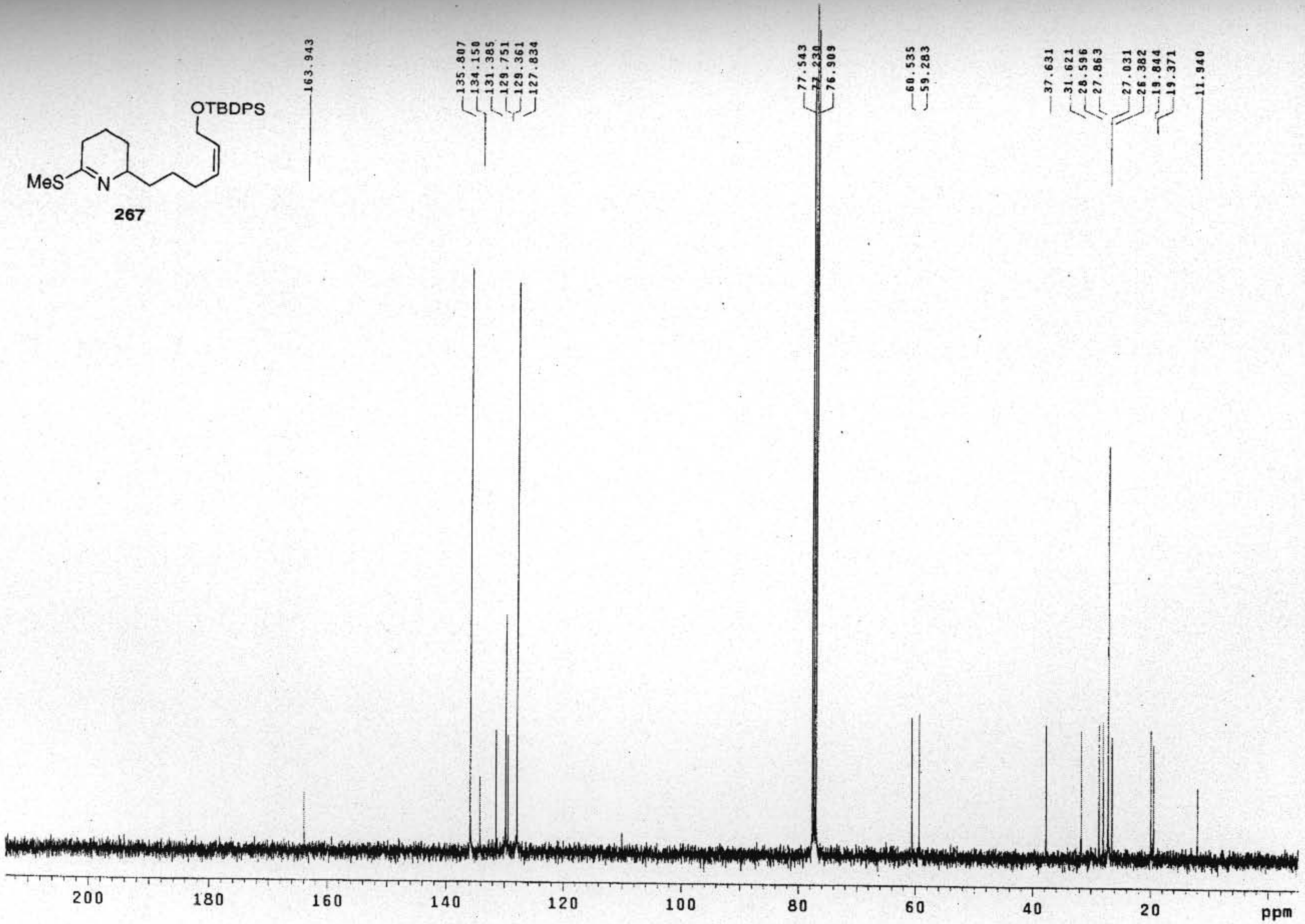


**266**


19.355
19.791
25.221
27.000
27.176
27.290
35.607
39.342
55.983
60.375
76.909
77.230
77.551
127.872
129.850
129.881
130.369
133.974
135.815
203.541
OTBDPS
S
N
H
266
ppm
0
20
40
60
80
100
120
140
160
180
200
220



267



267

MeS
N
OTBDPS
163.943
135.807
134.150
131.385
129.751
129.361
127.834
77.543
77.230
76.909
60.535
59.283
37.631
31.621
28.596
27.863
27.031
26.382
19.844
19.371
11.940
200
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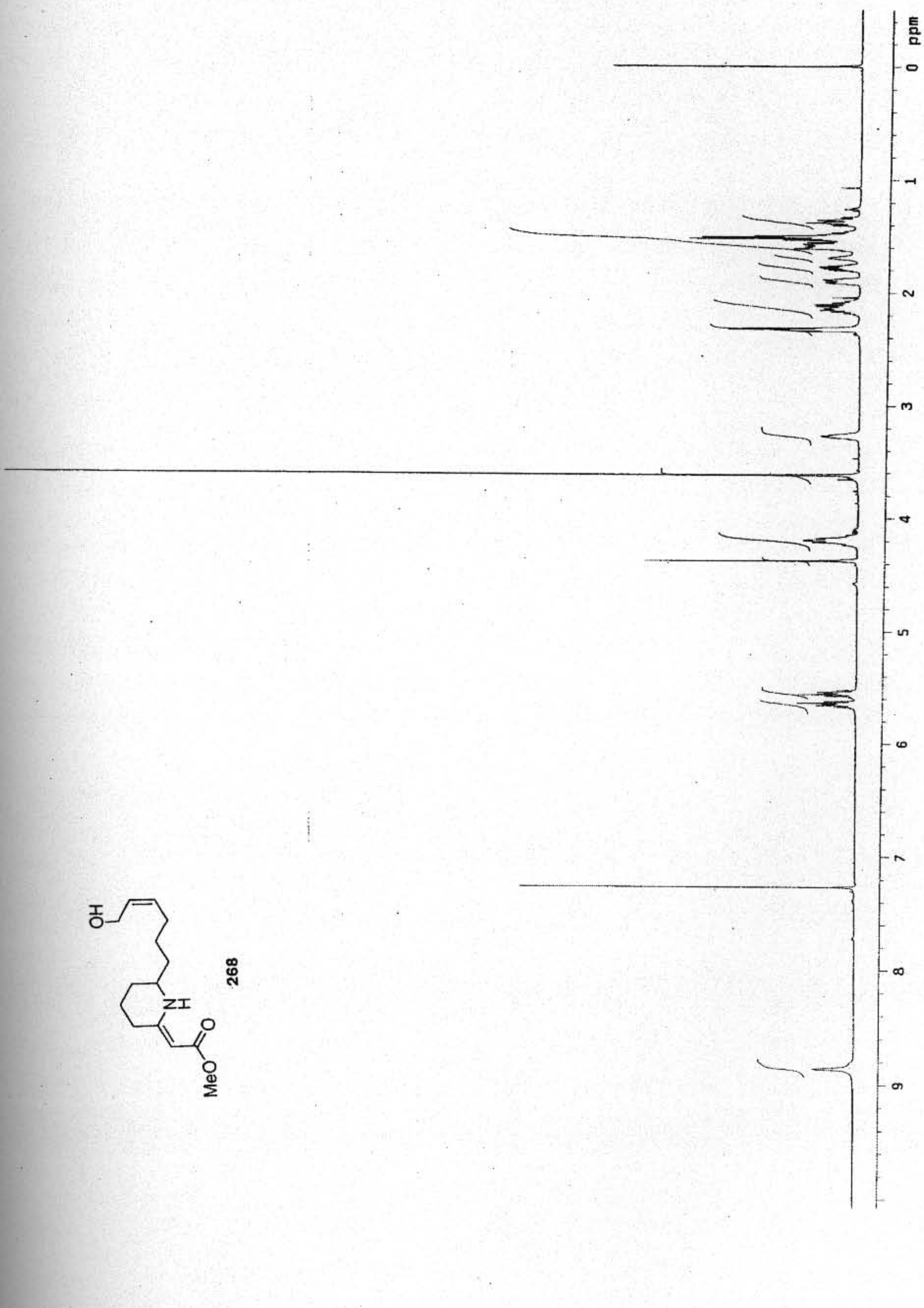
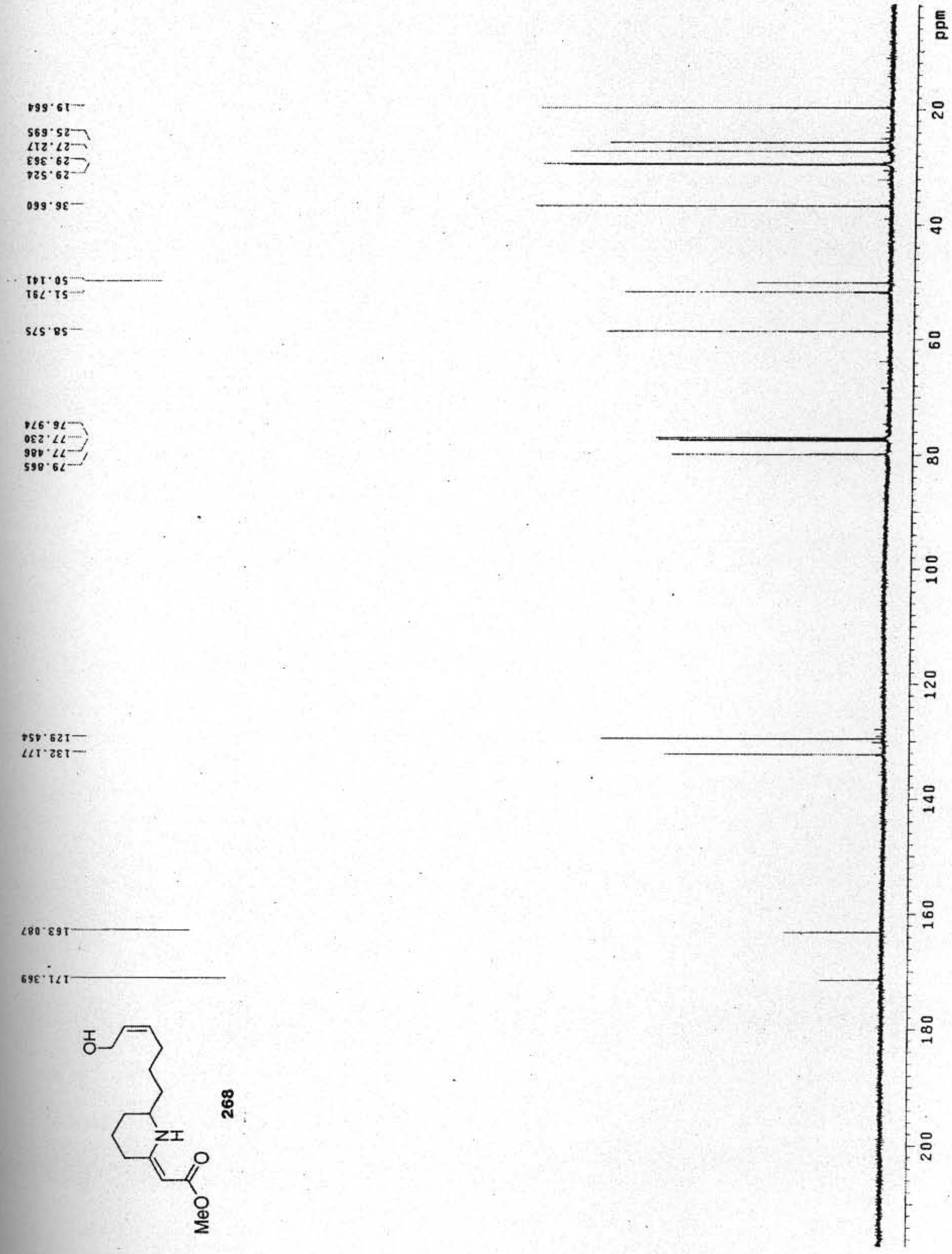
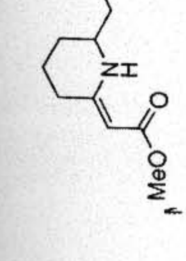
100
80
60
40
20
ppm



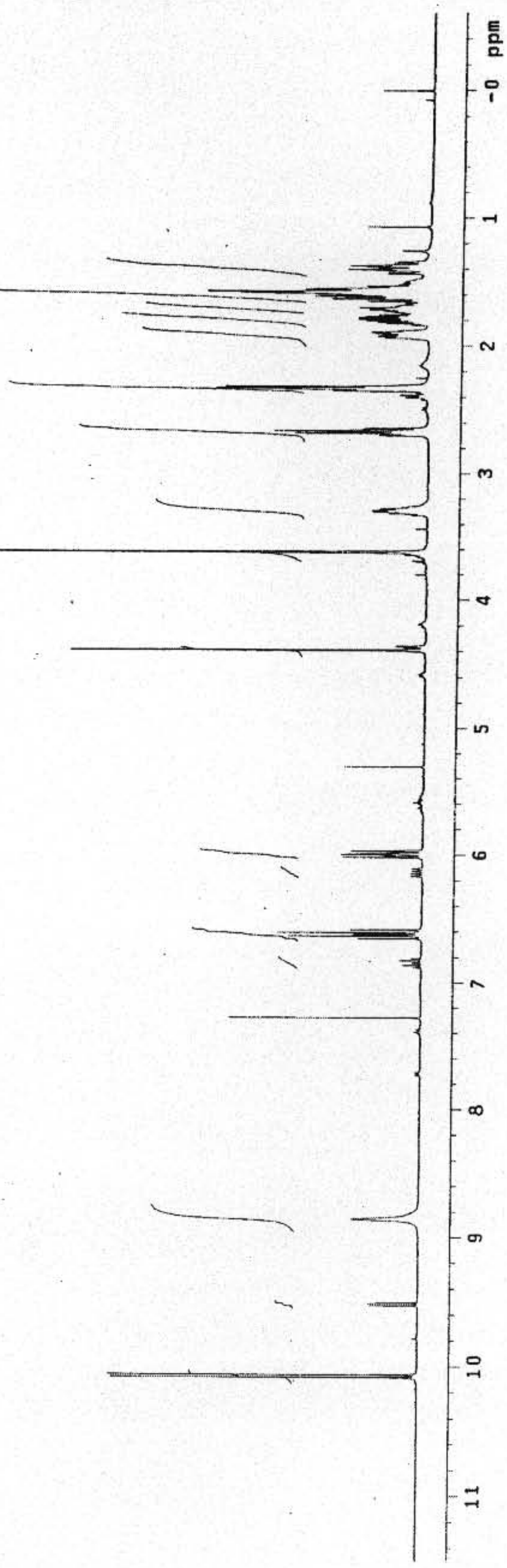
**268**

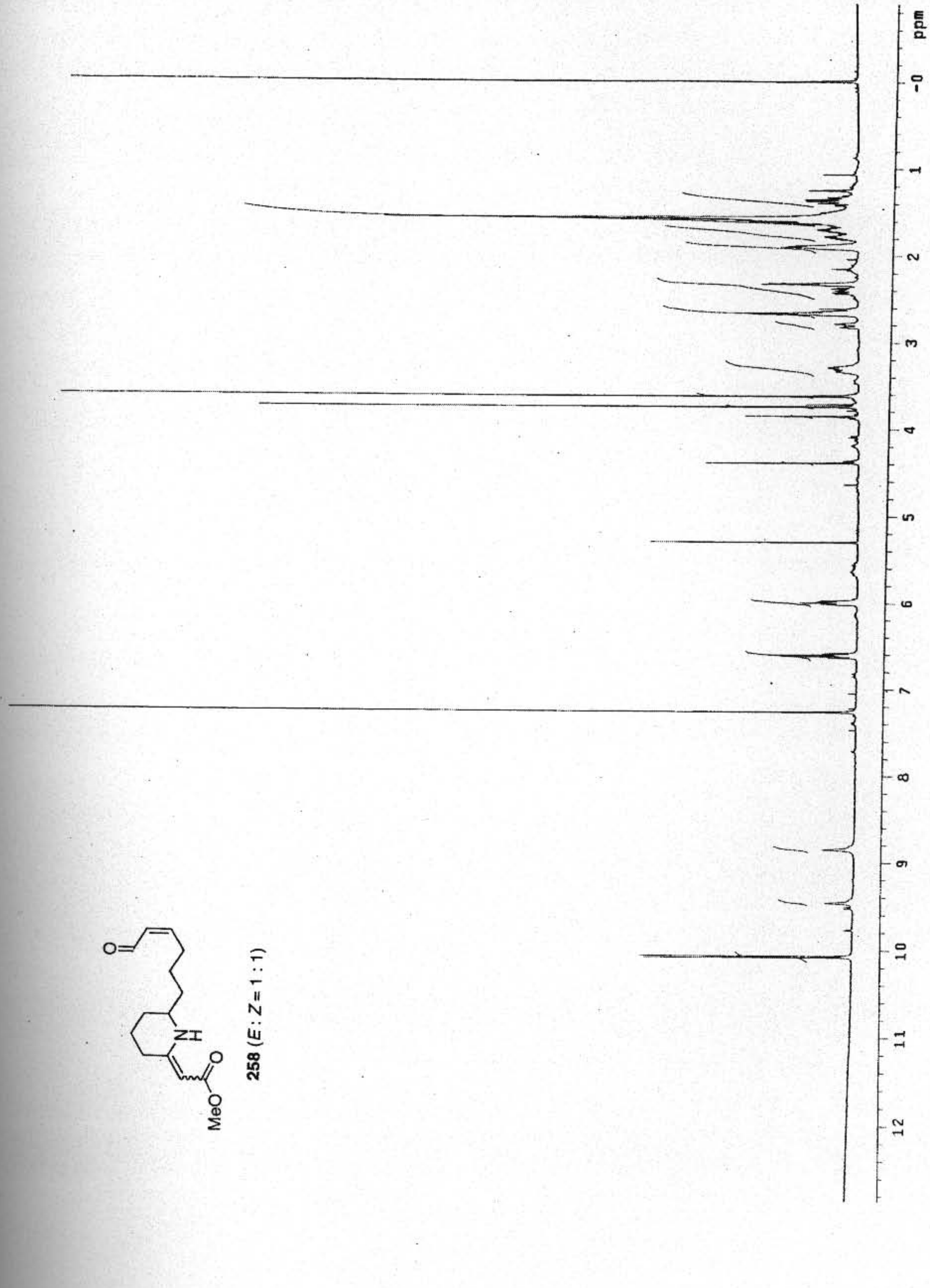

19.664
25.695
27.217
29.363
29.524
36.660
50.141
51.791
58.575
76.974
77.230
77.486
79.865
129.454
132.177
163.087
171.369
MeO
O
NH
OH
ppm
20
40
60
80
100
120
140
160
180
200

268

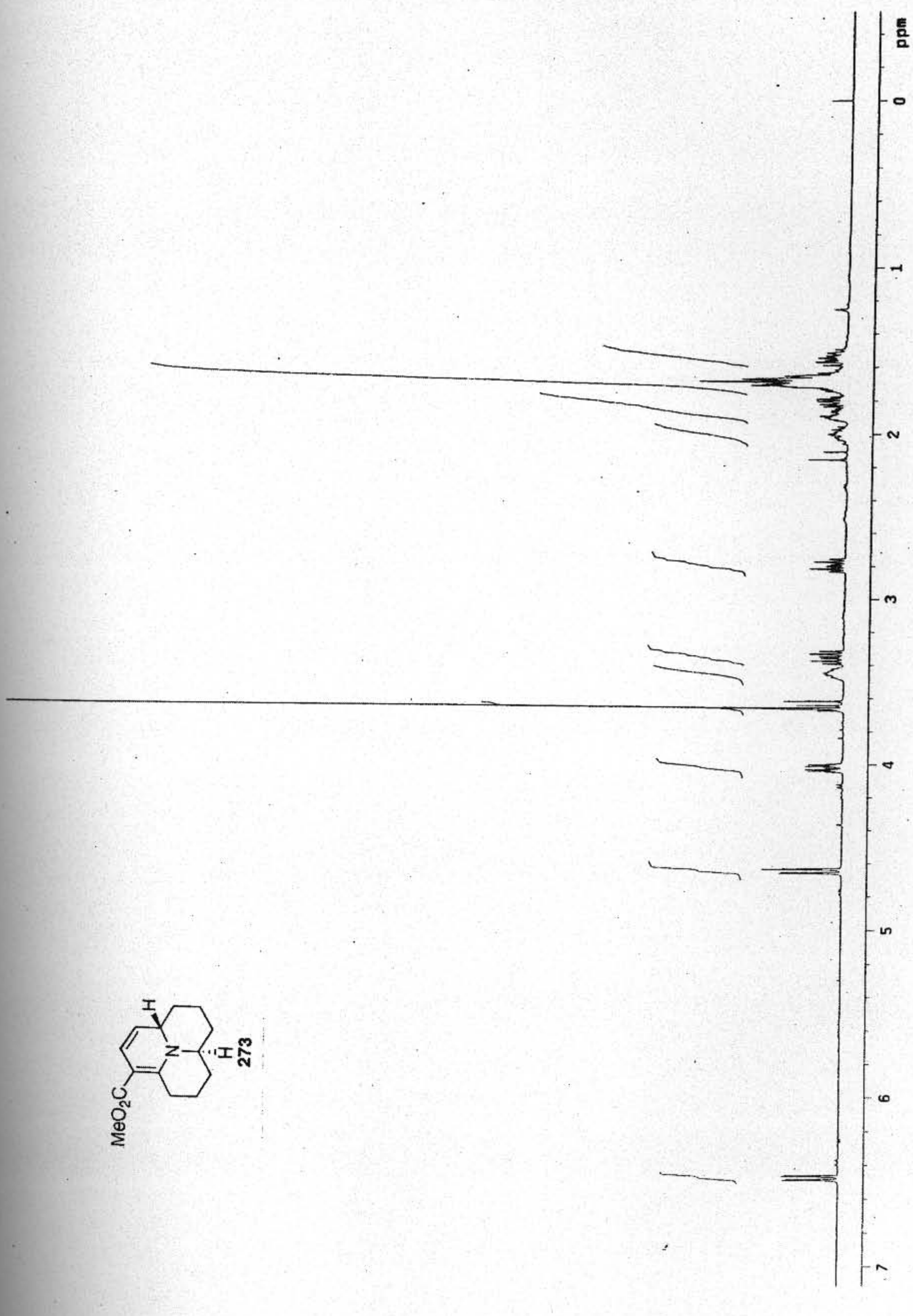


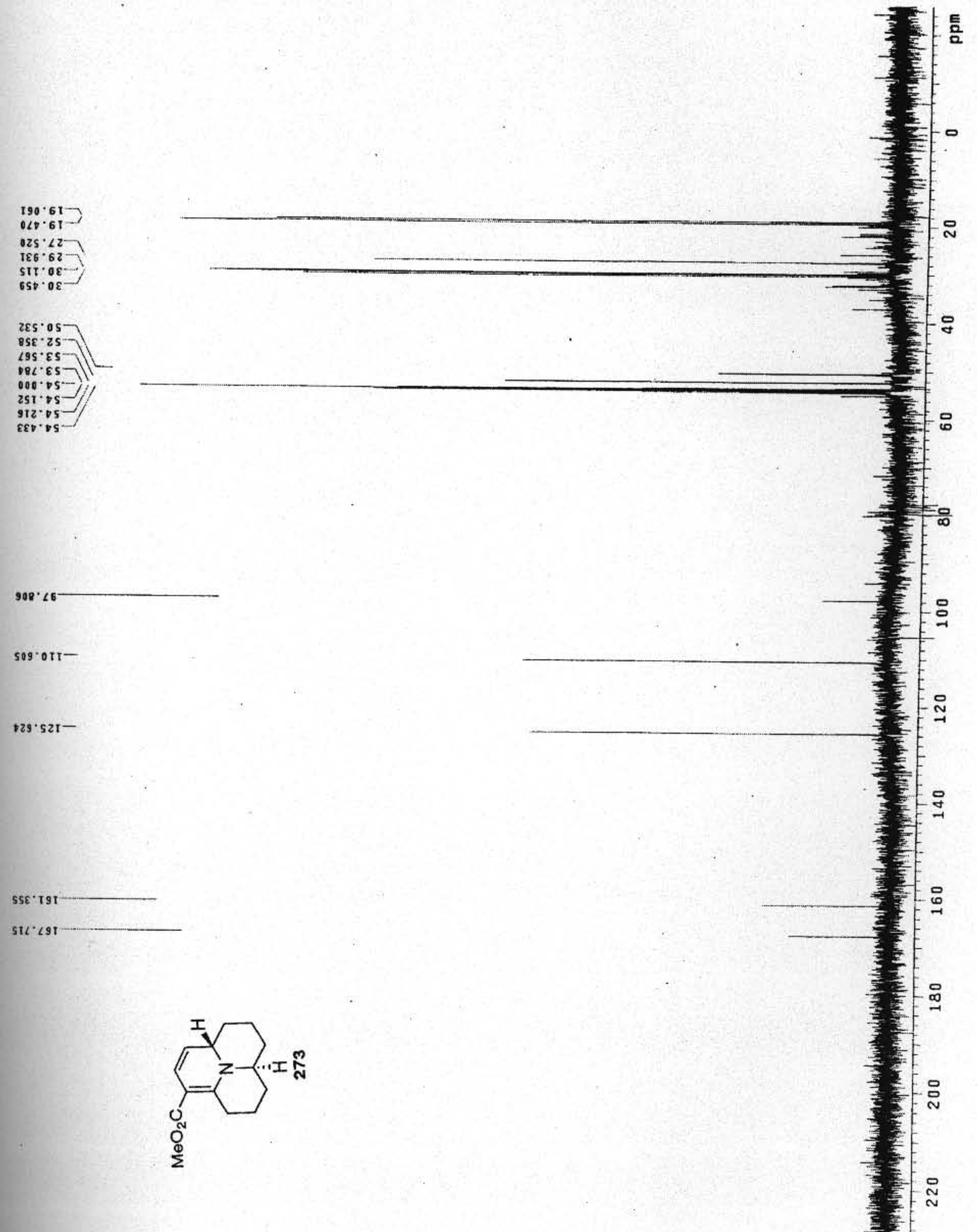
**258** (*cis* : *trans* = 7 : 1)





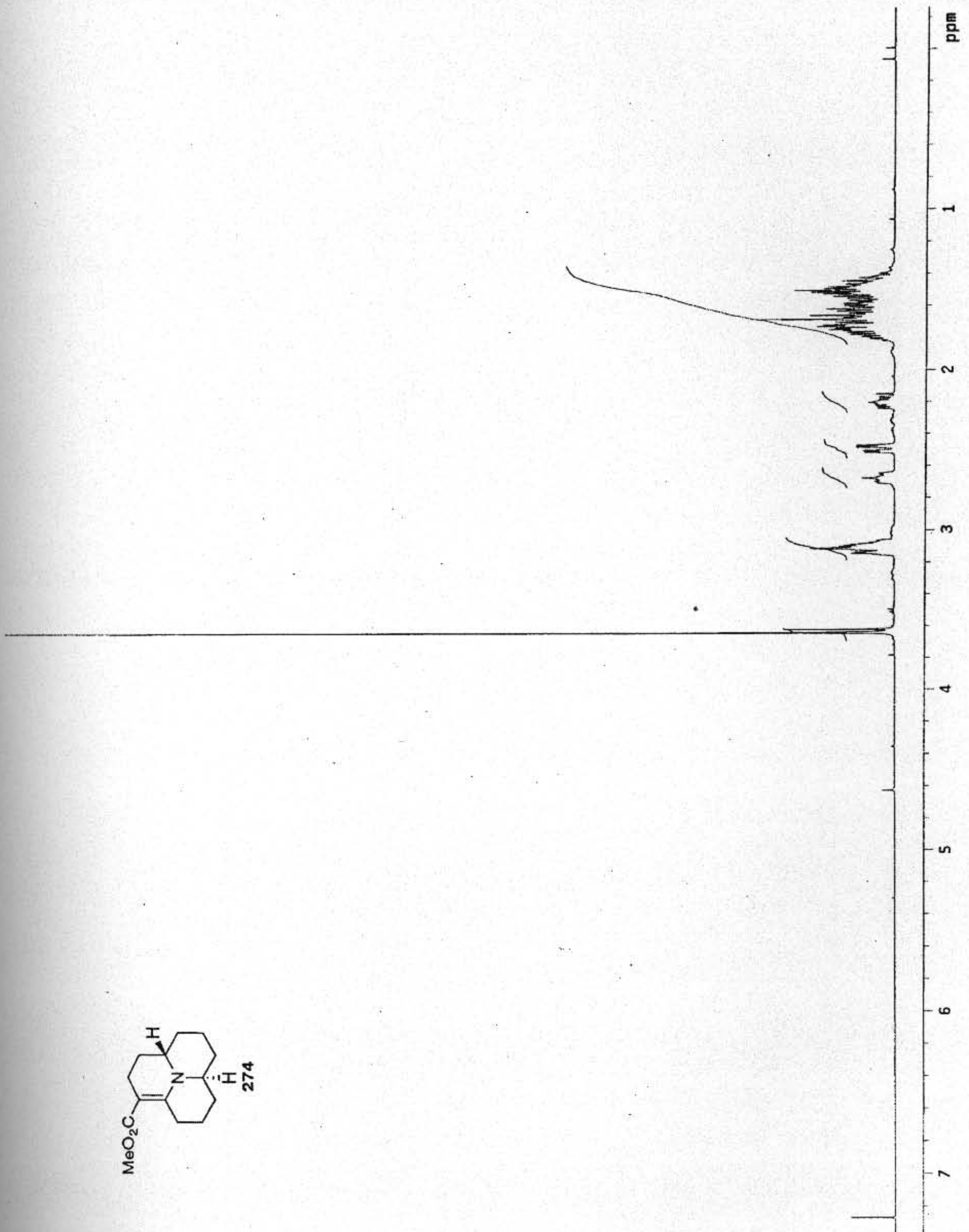
**258** (*E* : *Z* = 1 : 1)


MeO2C
N
H
H
273
7
6
5
4
3
2
1
0
ppm

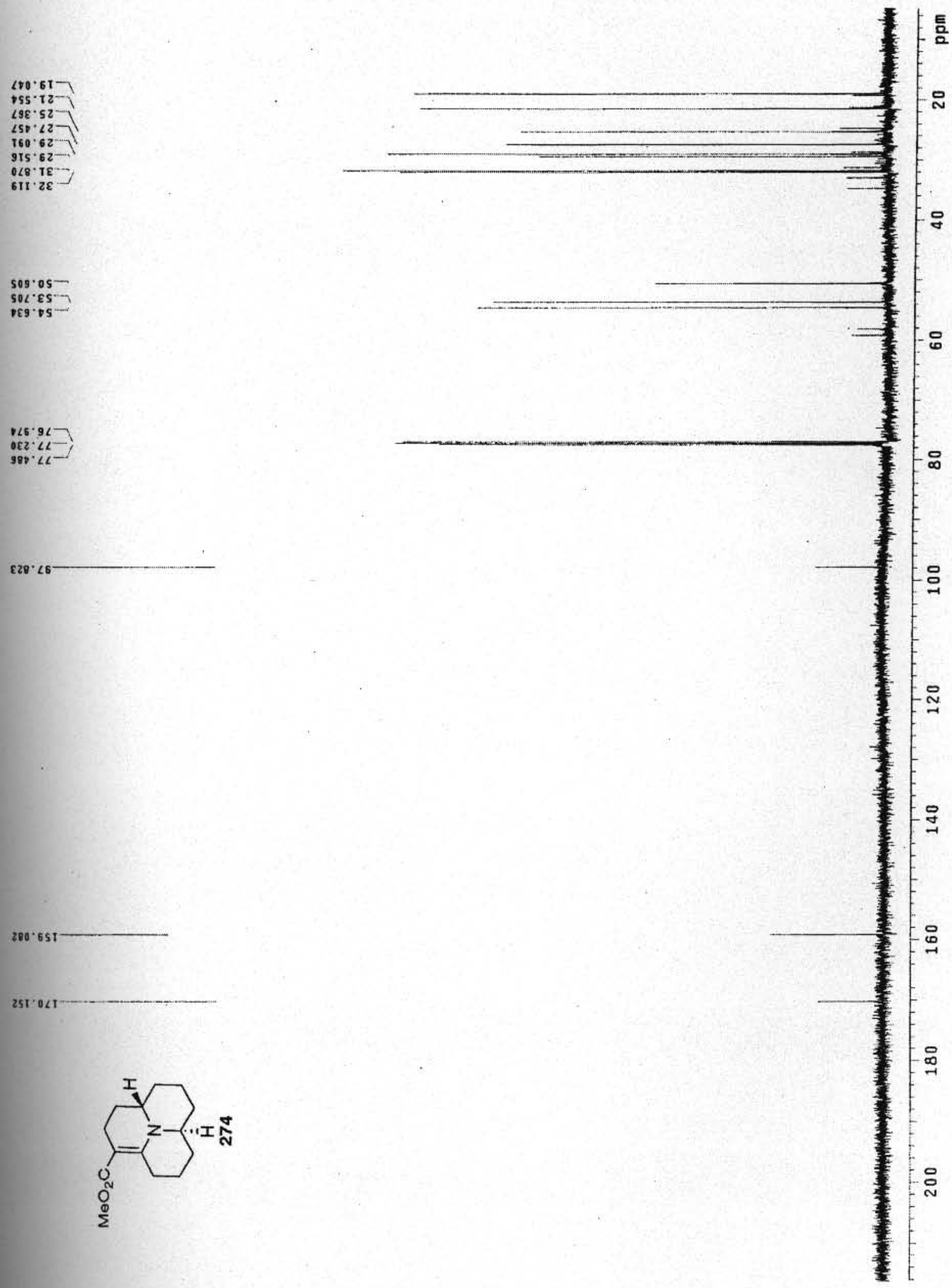


273

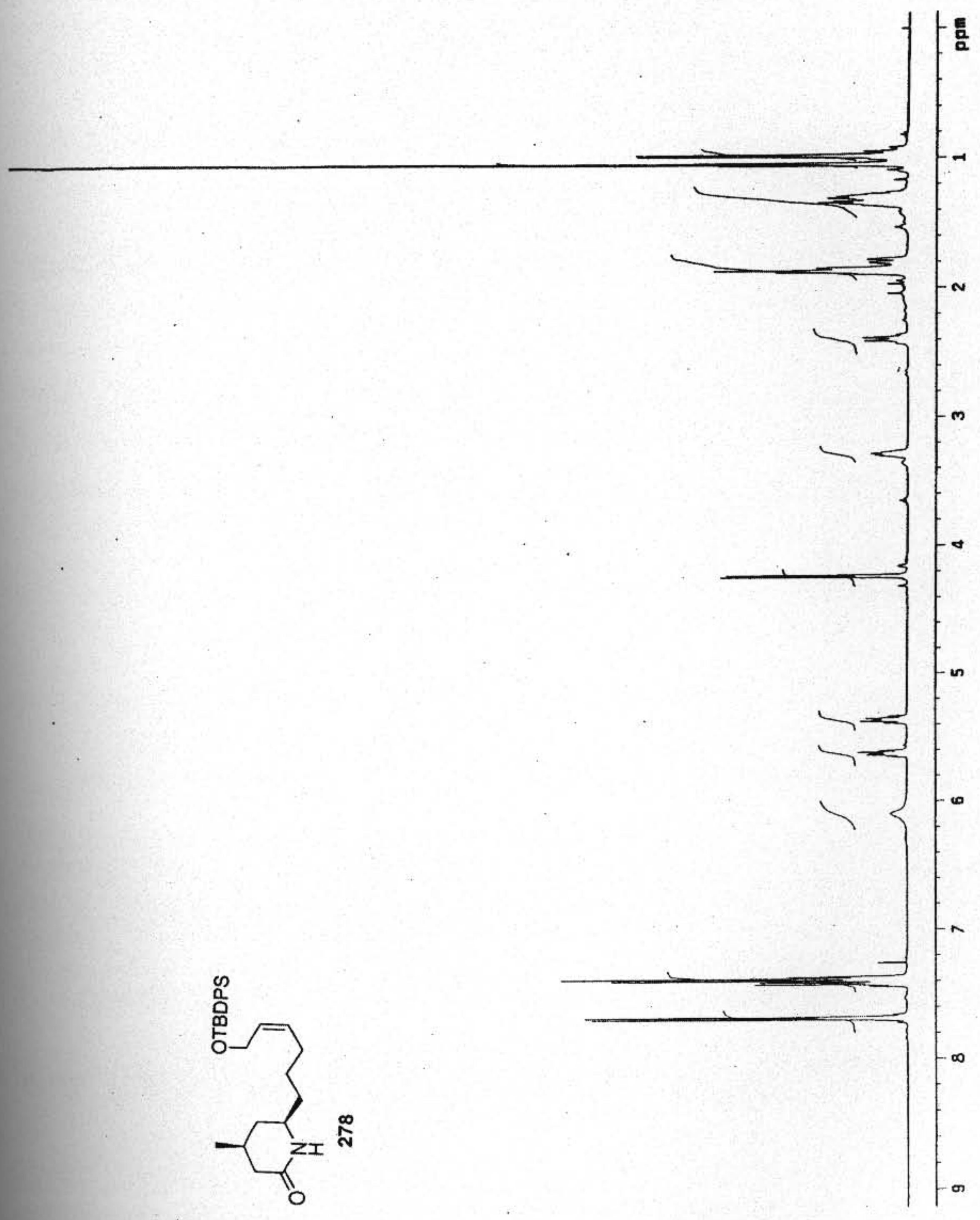
19.061
19.470
27.520
29.931
30.115
30.459
50.532
52.358
53.567
53.784
54.000
54.152
54.216
54.433
97.806
110.605
125.624
161.355
167.715
ppm
0
20
40
60
80
100
120
140
160
180
200
220
MeO2C
N
H
H

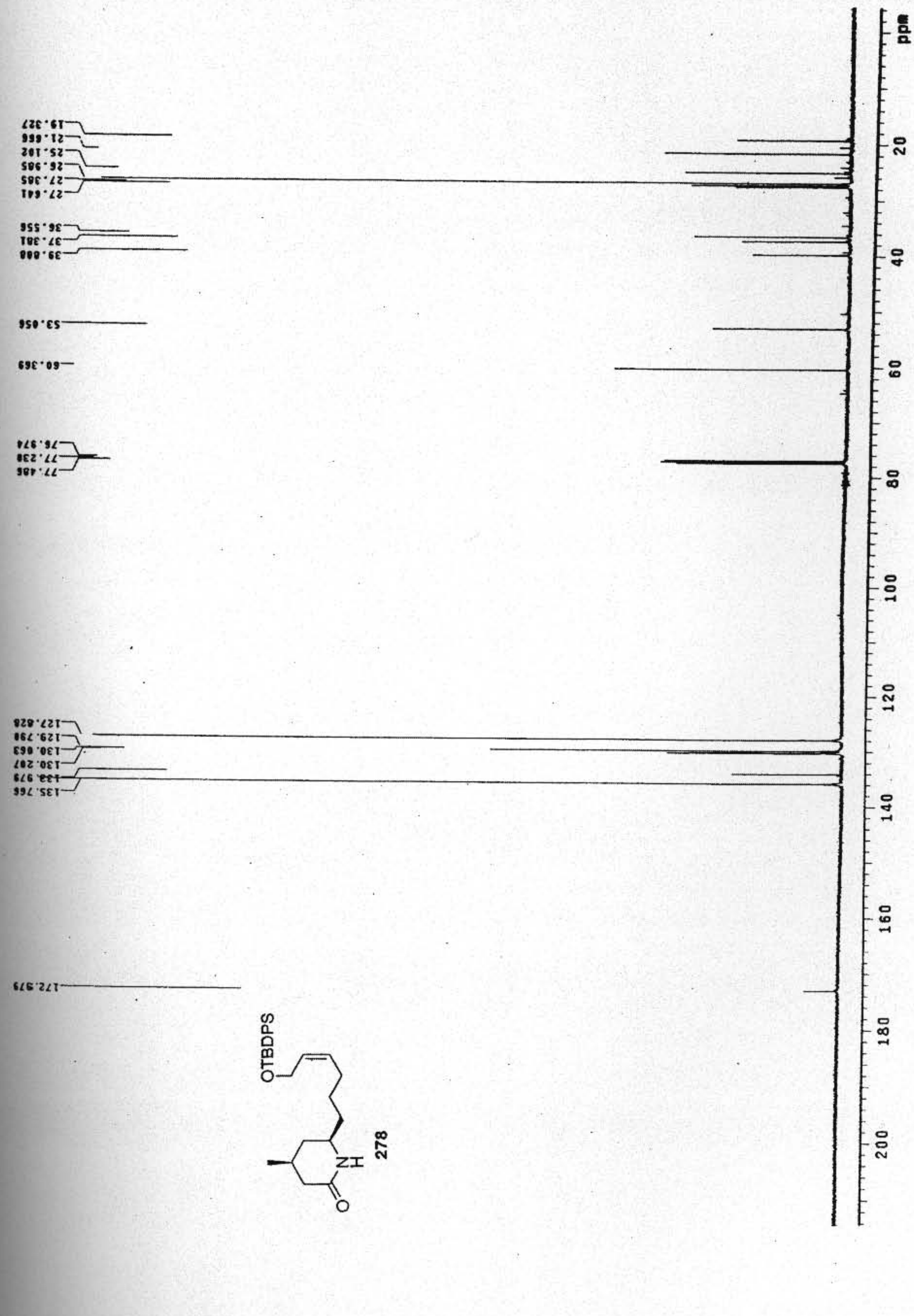


274

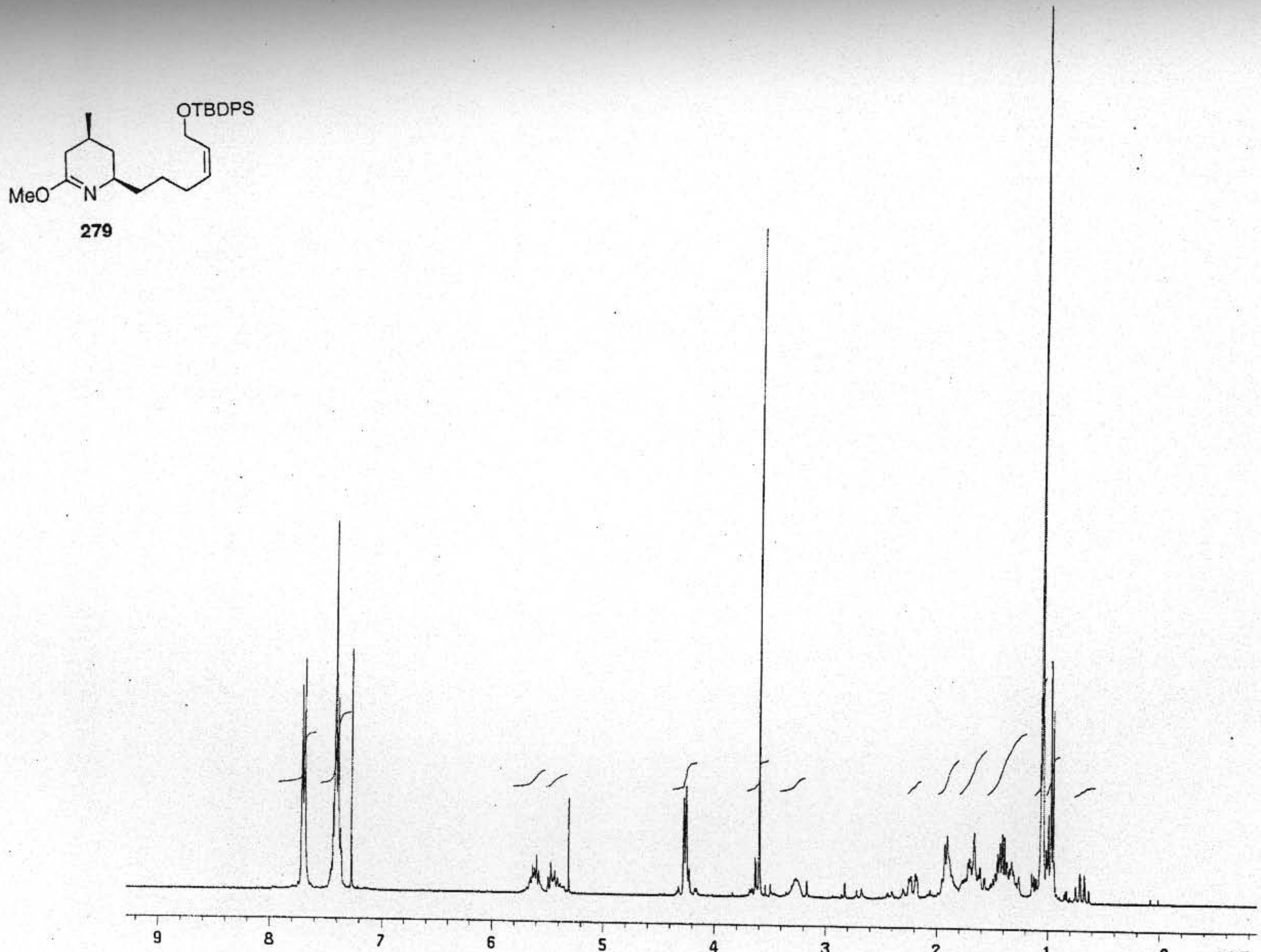

274

19.047
21.554
25.367
27.457
29.091
29.516
31.870
32.119
50.605
53.705
54.634
76.974
77.230
77.486
97.823
159.082
170.152
ppm
20
40
60
80
100
120
140
160
180
200
MeO2C
N
H
H

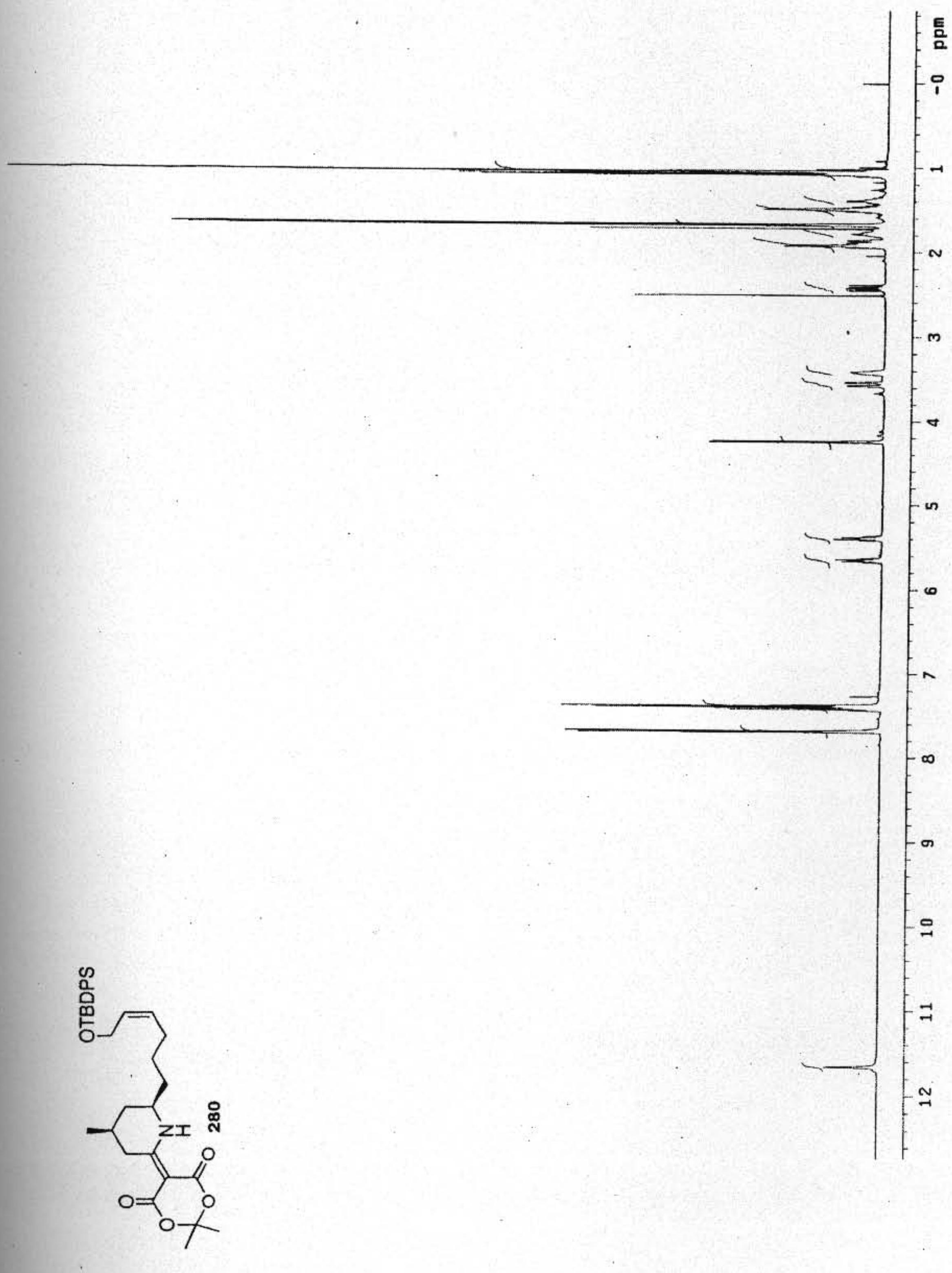

OTBDPS
O
N
H
278
ppm
9
8
7
6
5
4
3
2
1


19.327
21.666
25.102
26.985
27.385
27.641
36.556
37.381
39.088
53.056
60.369
76.974
77.230
77.486
127.828
129.798
130.063
130.207
133.979
135.766
172.979
OTBDPS
O
NH
ppm
20
40
60
80
100
120
140
160
180
200

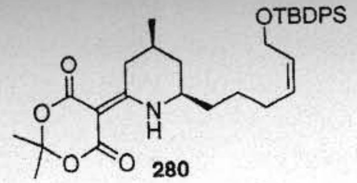
278



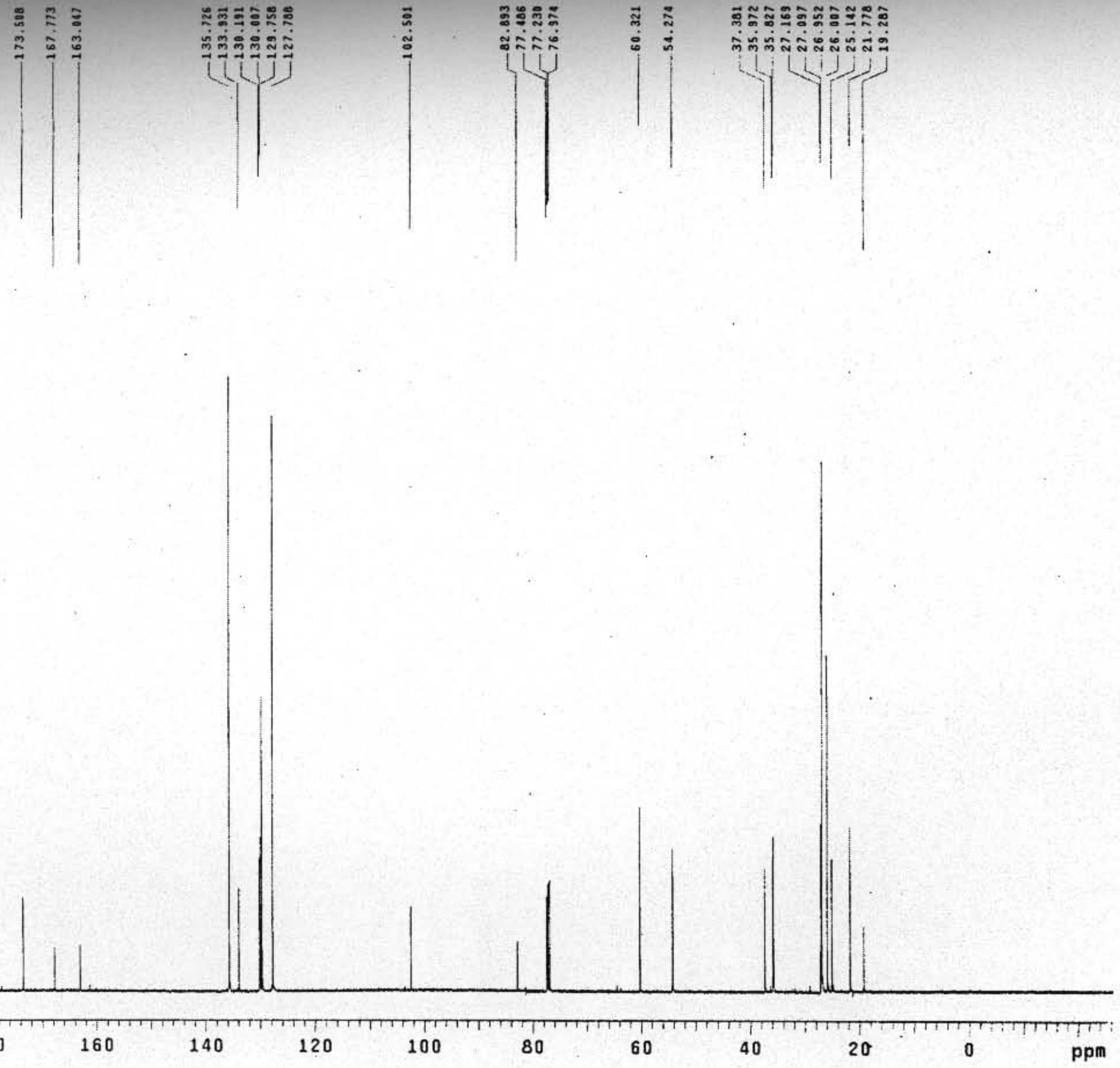
**279**

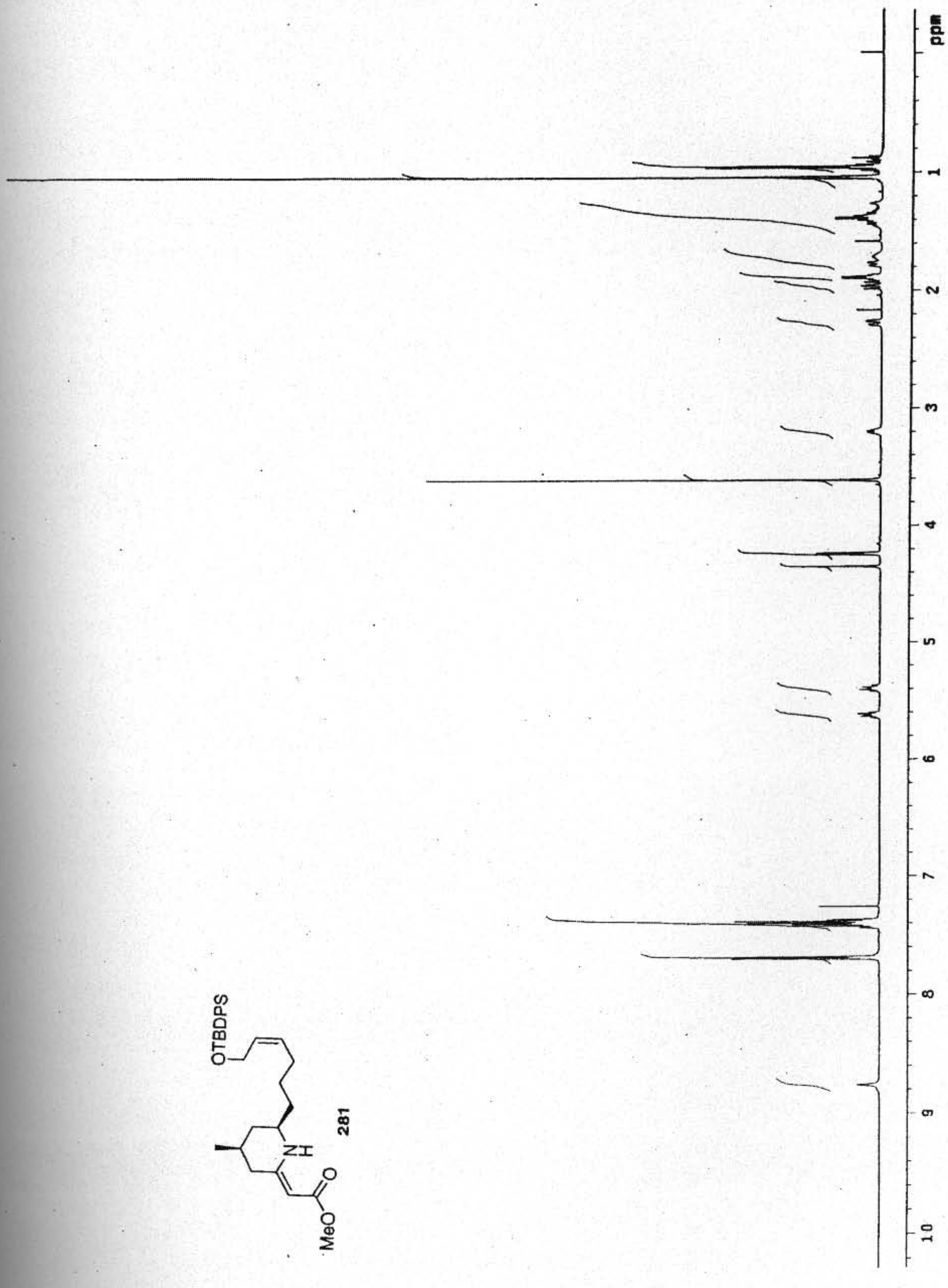


280

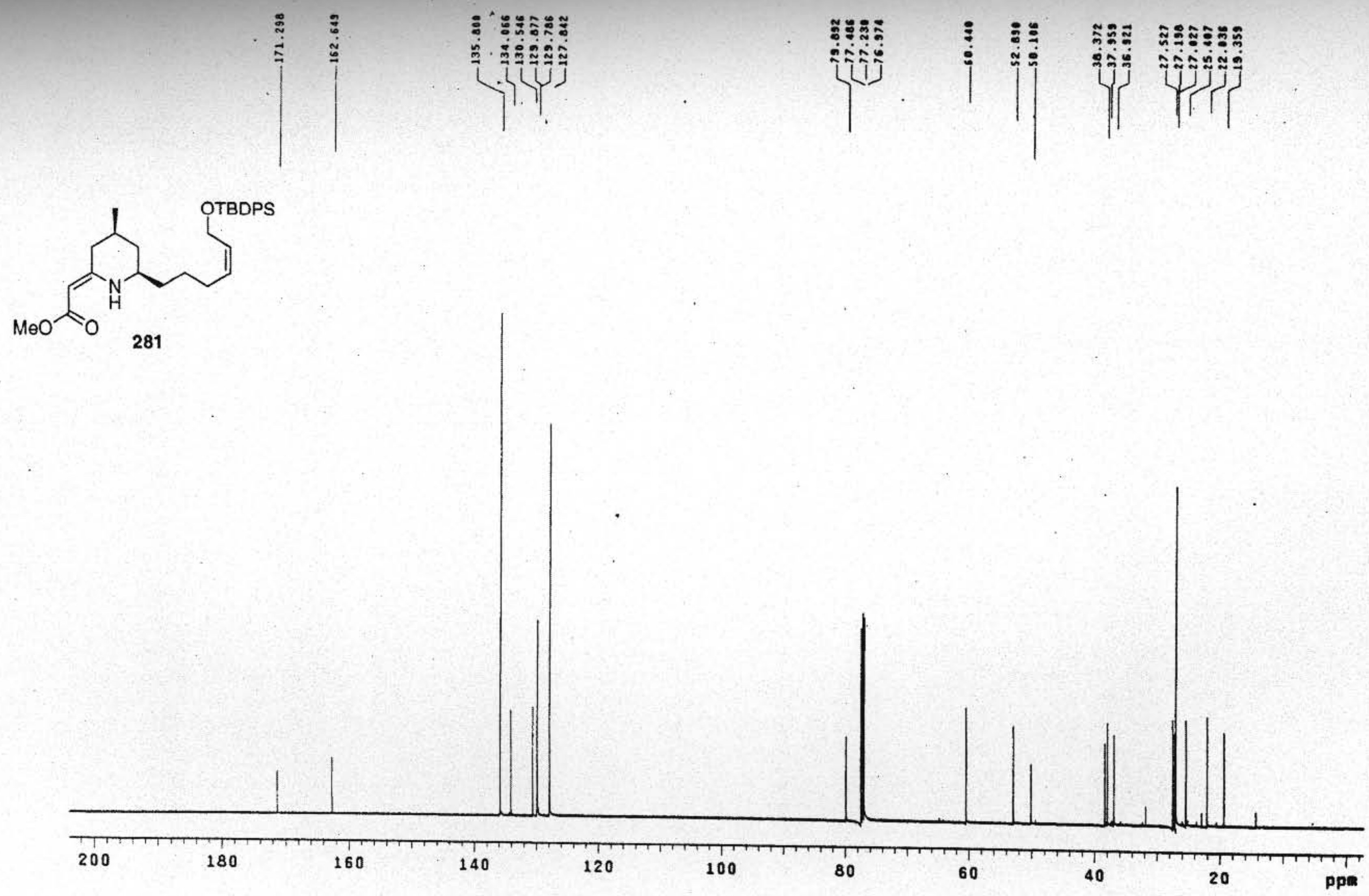


280

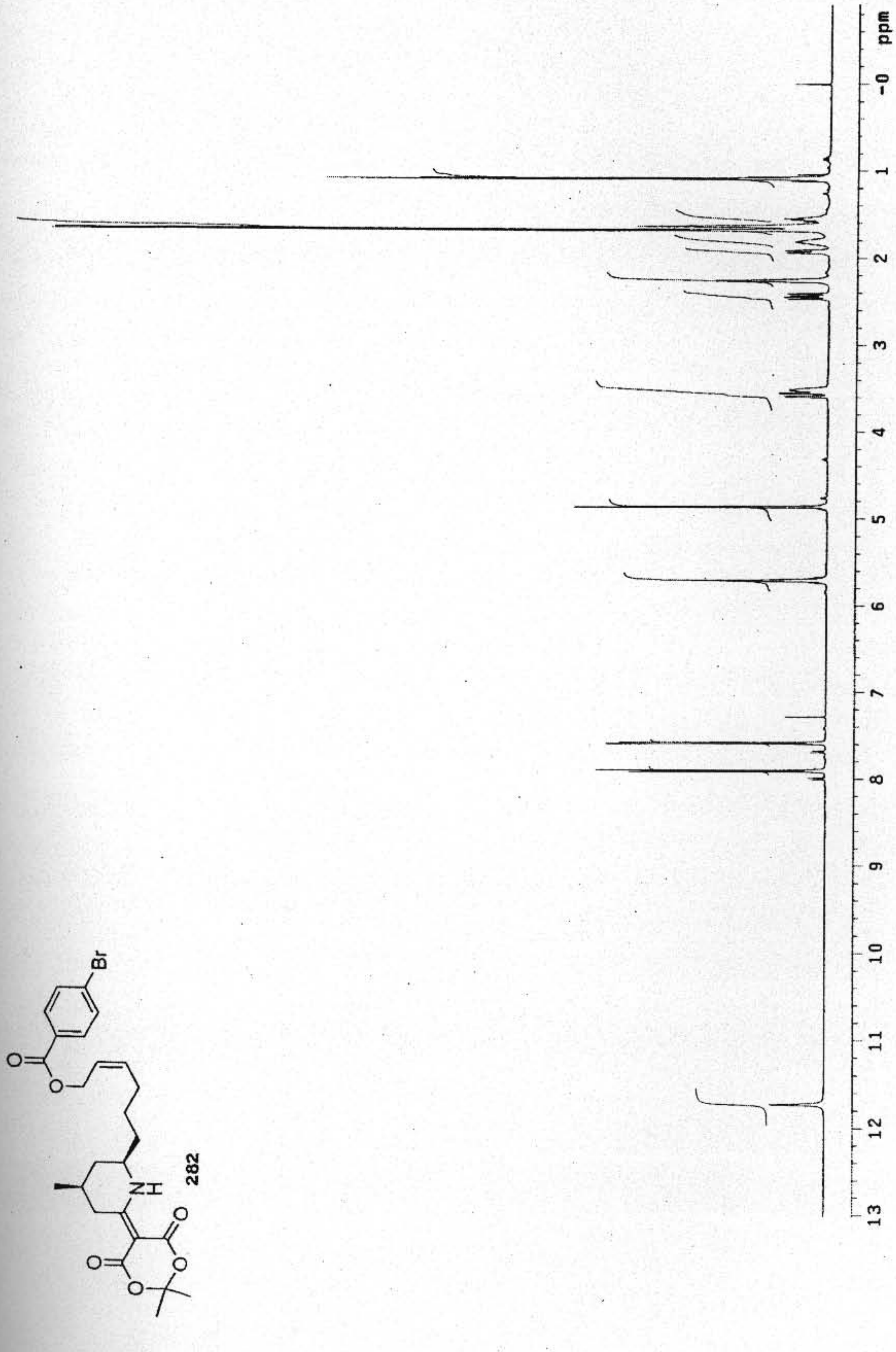

173.508
167.773
163.047
135.726
133.931
130.191
130.007
129.758
127.788
102.501
82.893
77.486
77.230
76.974
60.321
54.274
37.381
35.972
35.827
27.169
27.097
26.952
26.007
25.142
21.778
19.287
220
200
180
160
140
120
100
80
60
40
20
0
ppm



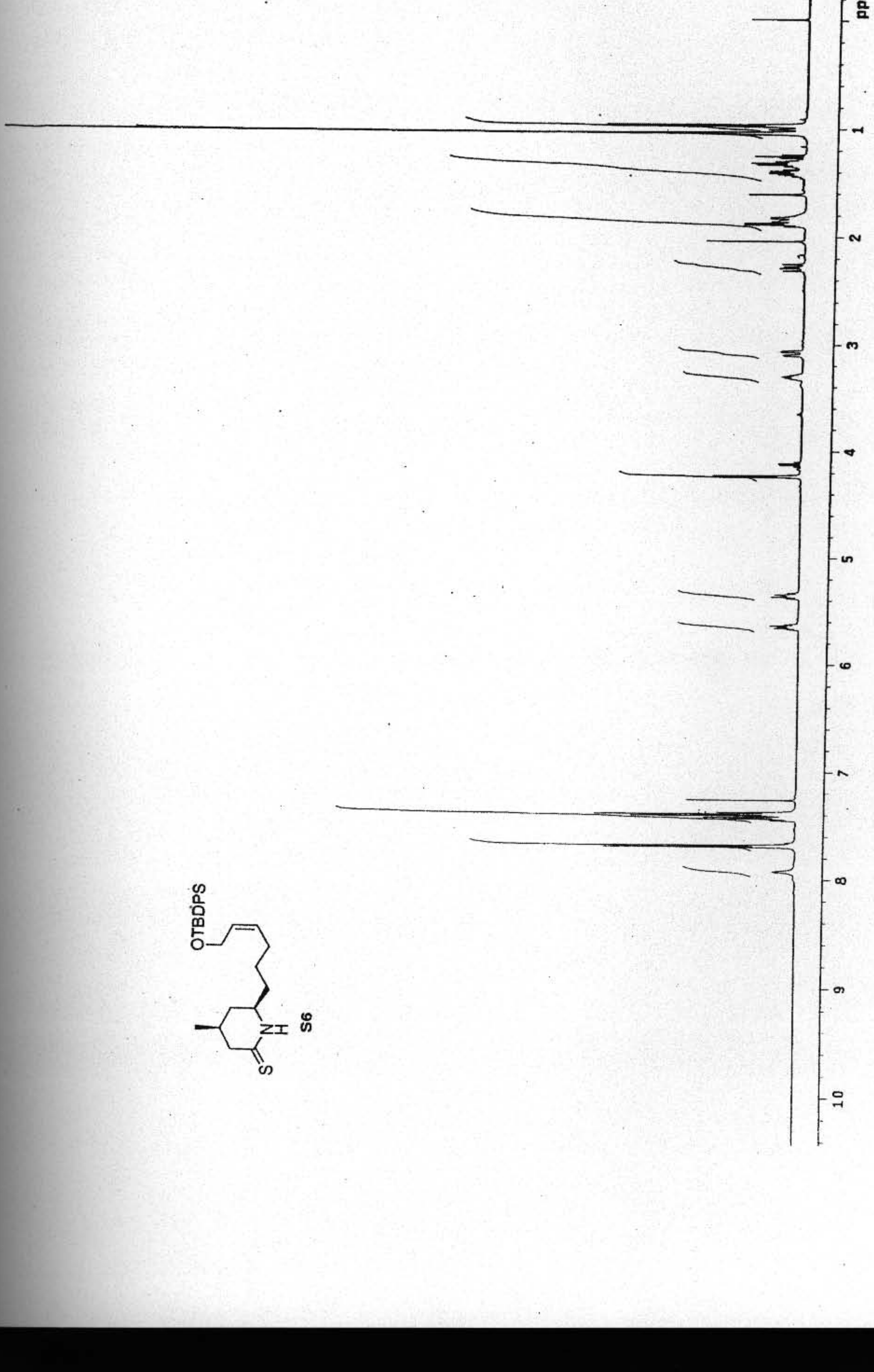
281


281

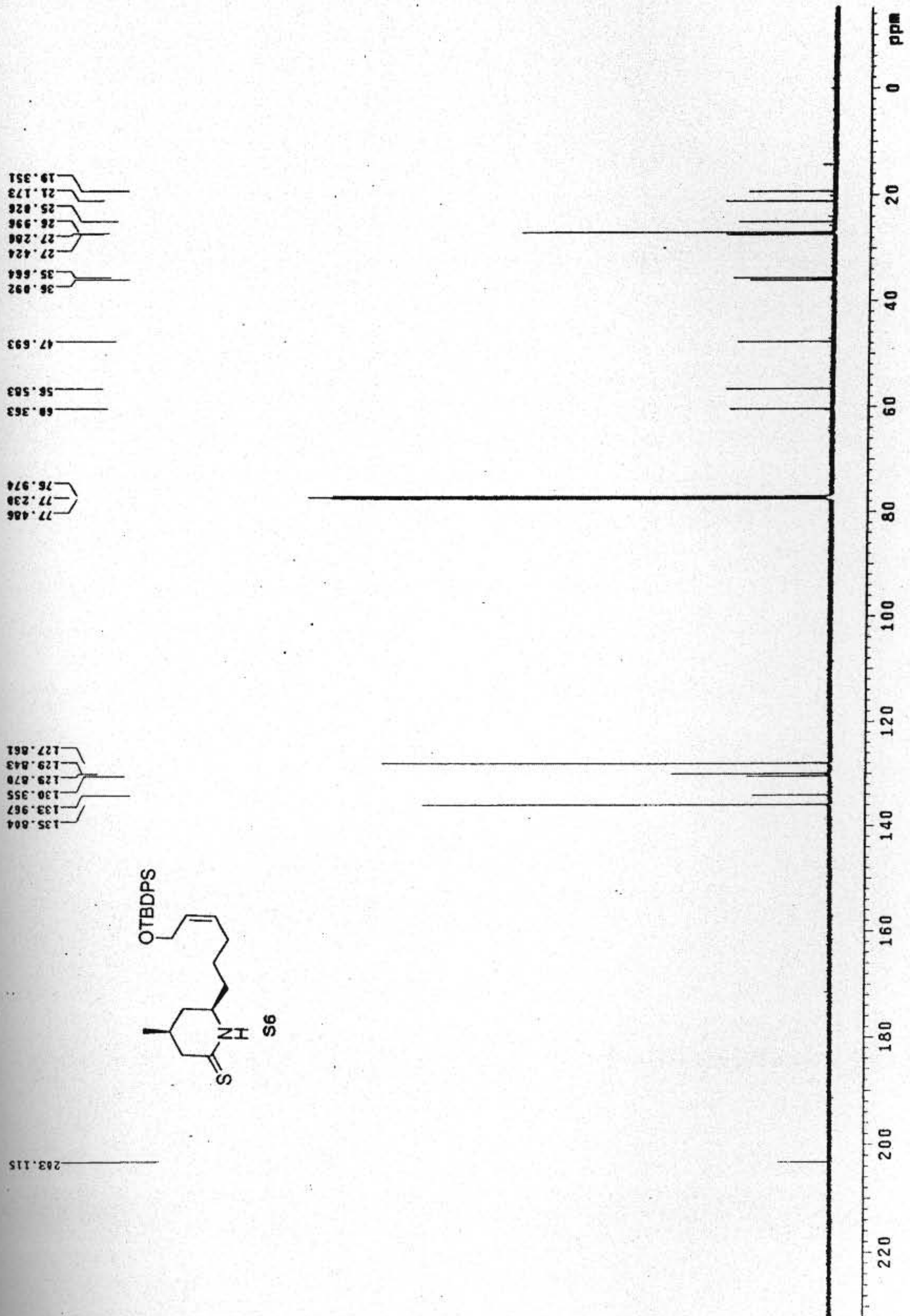
OTBDPS
MeO
O
N
H
171.298
162.649
135.808
134.066
130.546
129.877
129.786
127.842
79.892
77.486
77.230
76.974
60.440
52.890
50.106
38.372
37.959
36.921
27.527
27.196
27.027
25.407
22.036
19.359
200
180
160
140
120
100
80
60
40
20
ppm

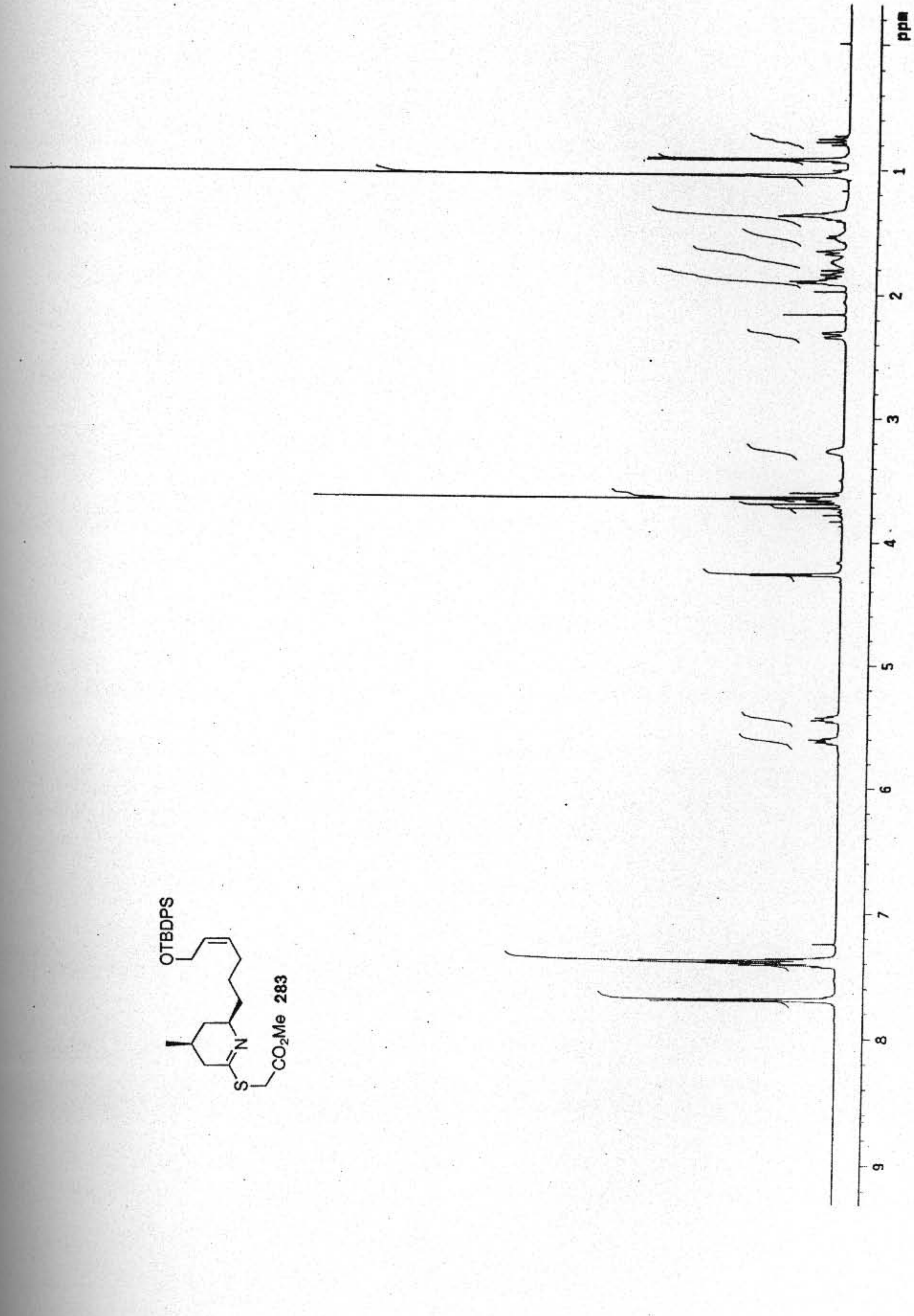


282

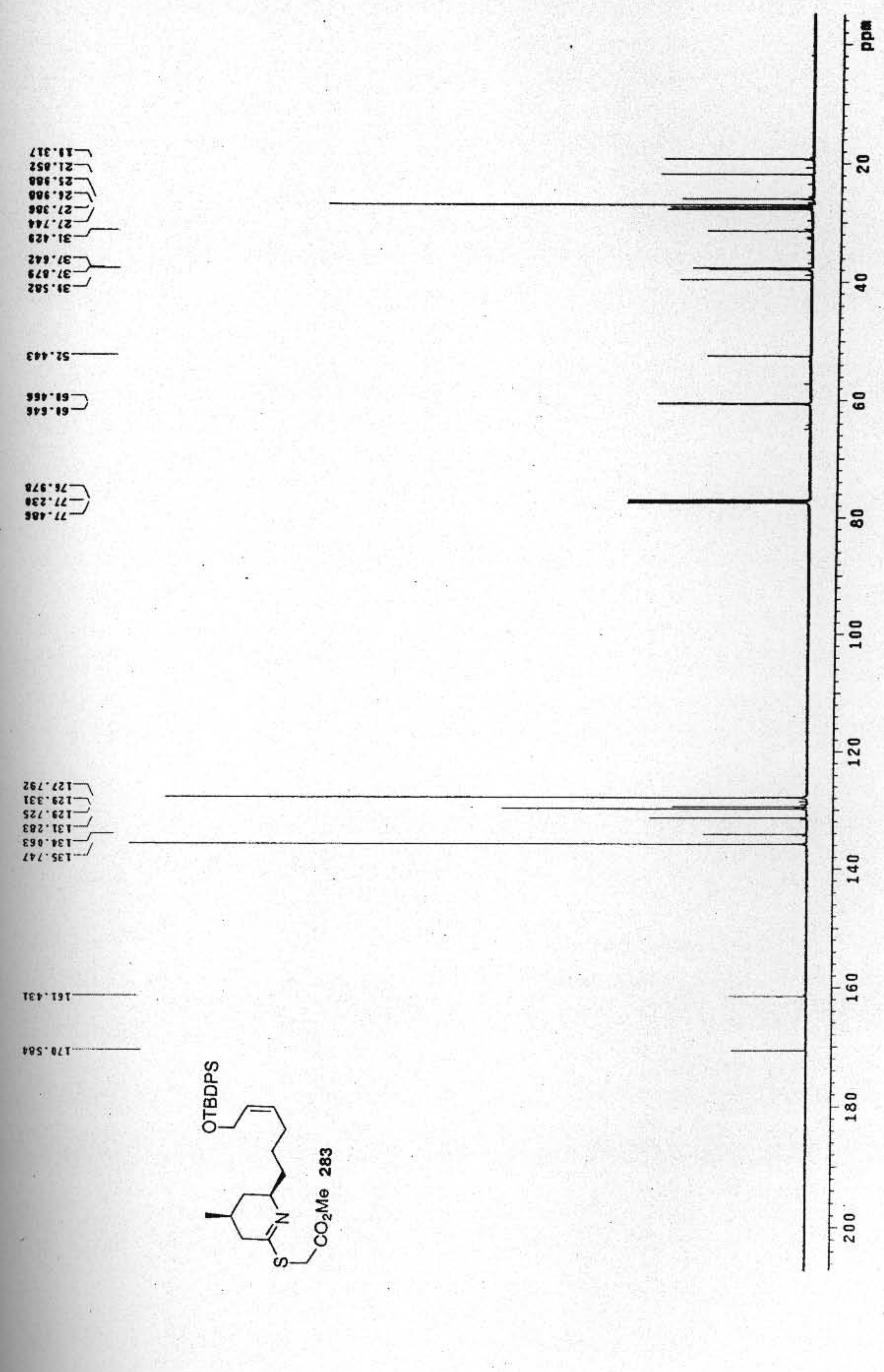


S6

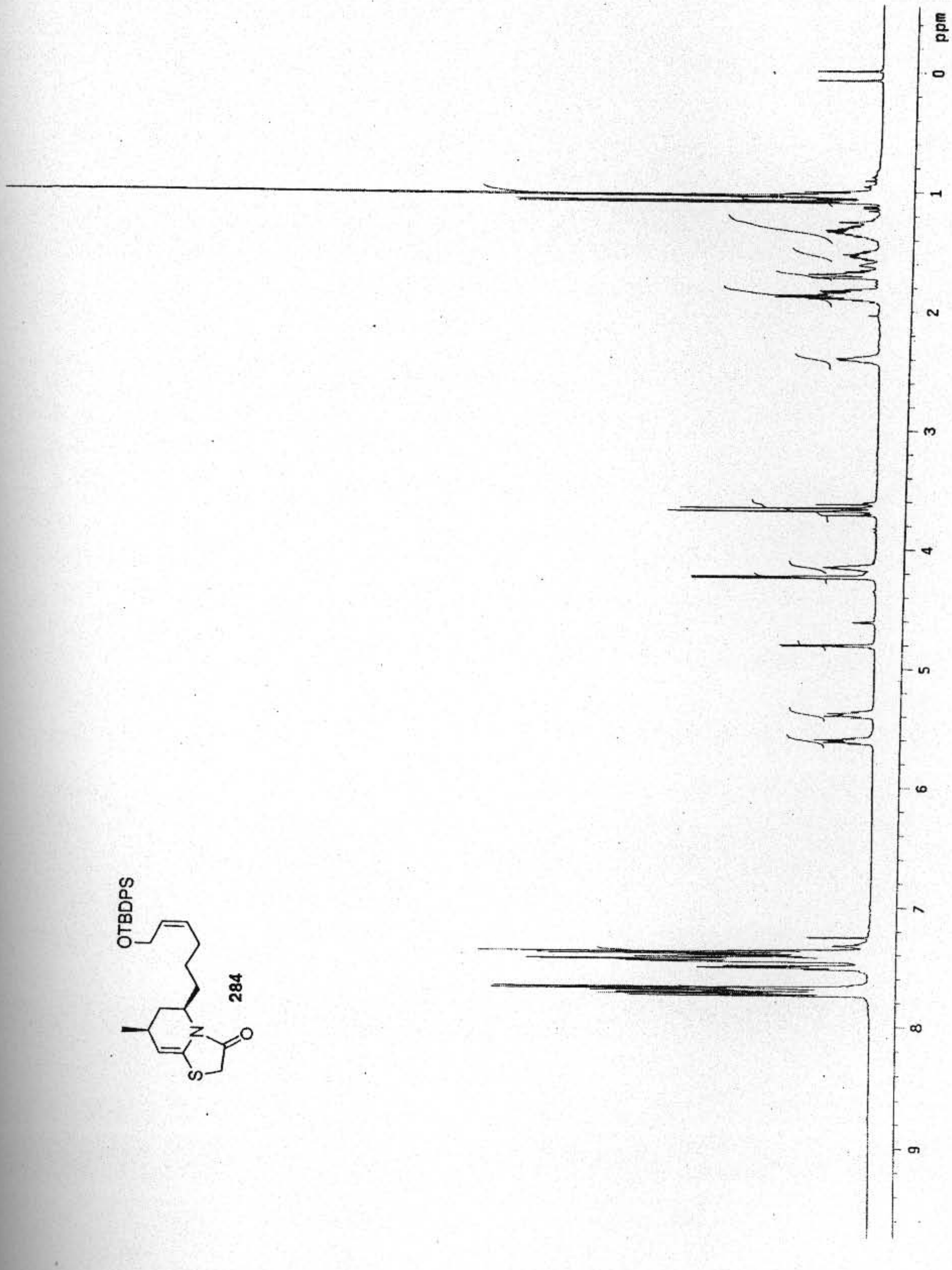

19.351
21.173
25.828
26.996
27.206
27.424
35.664
36.092
47.693
56.583
60.363
76.974
77.230
77.486
127.861
129.843
129.870
130.355
133.967
135.604
203.115
OTBDPS
S
NH
S6
ppm
0
20
40
60
80
100
120
140
160
180
200
220



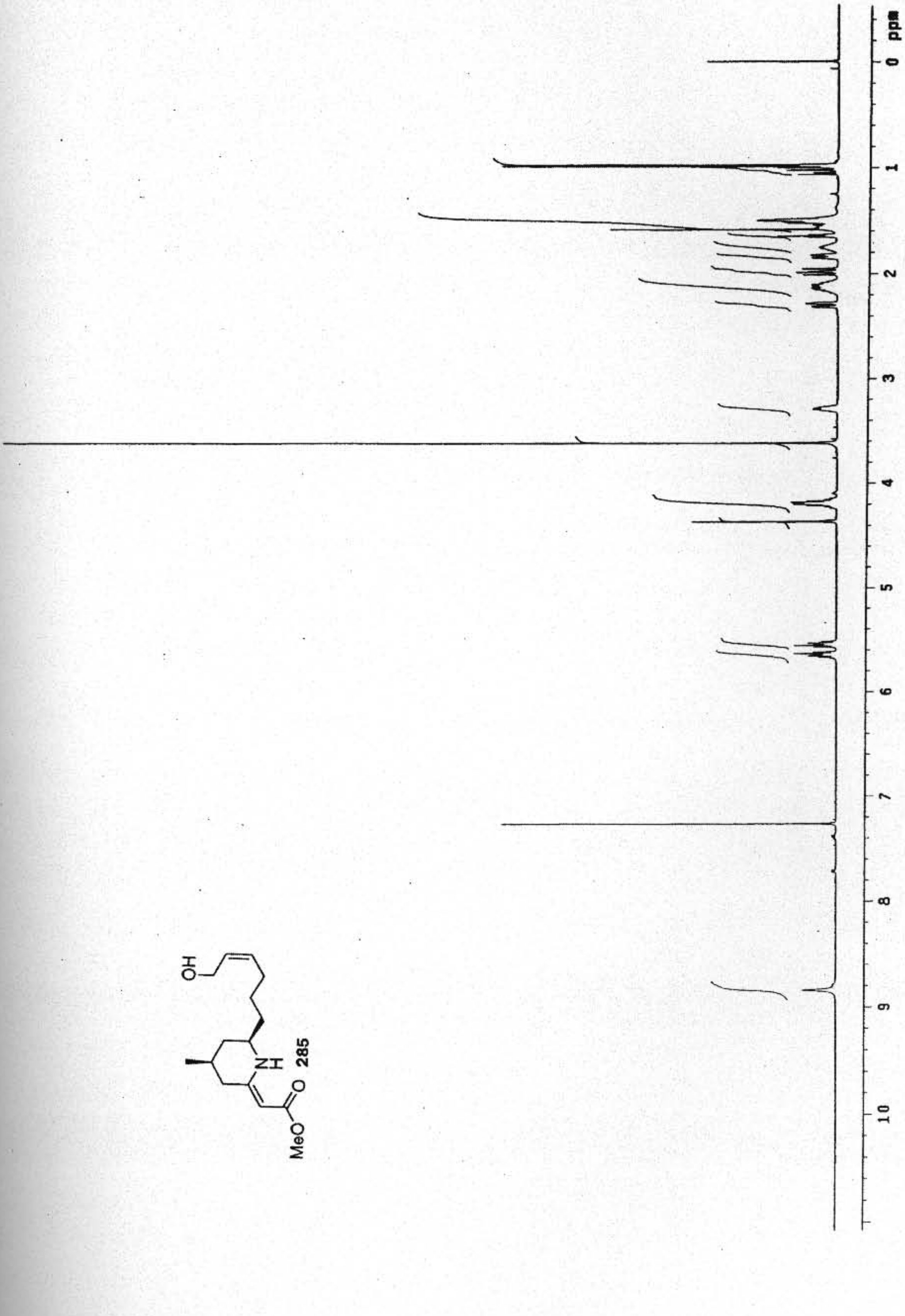
**283**


283

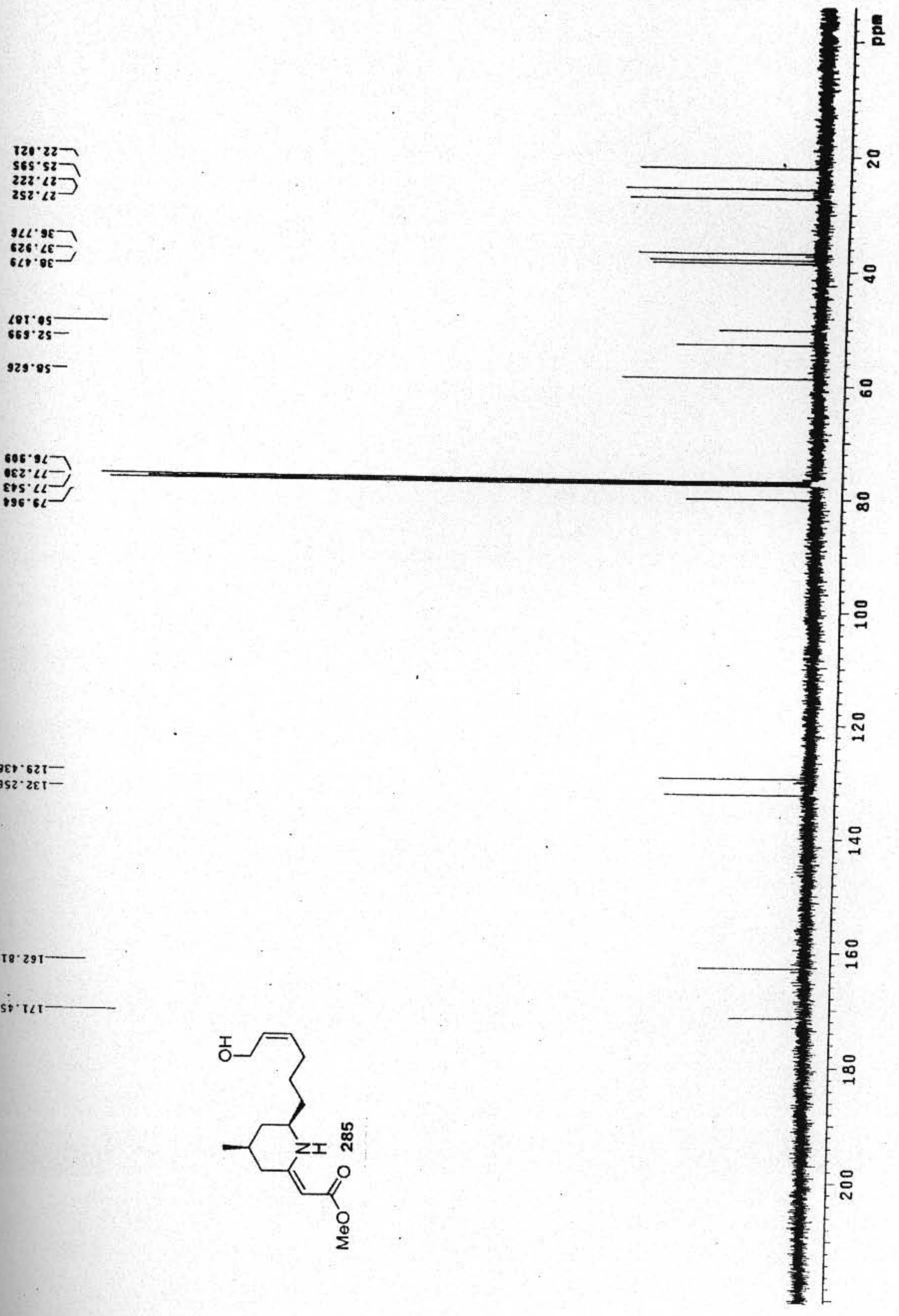
OTBDPS
S
N
CO2Me
19.317
21.852
25.988
26.988
27.386
27.744
31.429
37.642
37.879
39.582
52.443
61.466
61.646
76.978
77.230
77.486
127.792
129.331
129.725
131.283
134.063
135.747
161.431
170.584
ppm
20
40
60
80
100
120
140
160
180
200



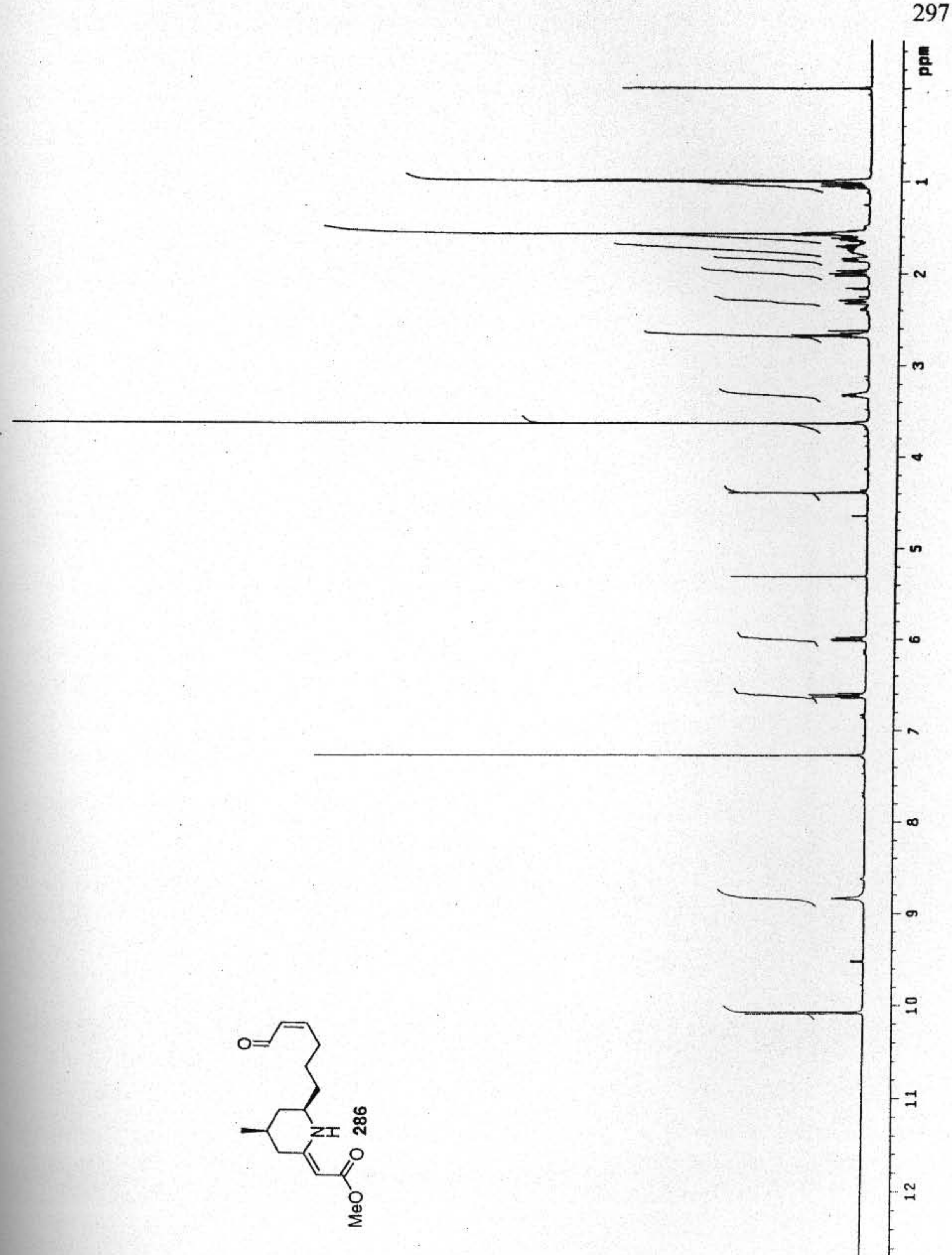
284



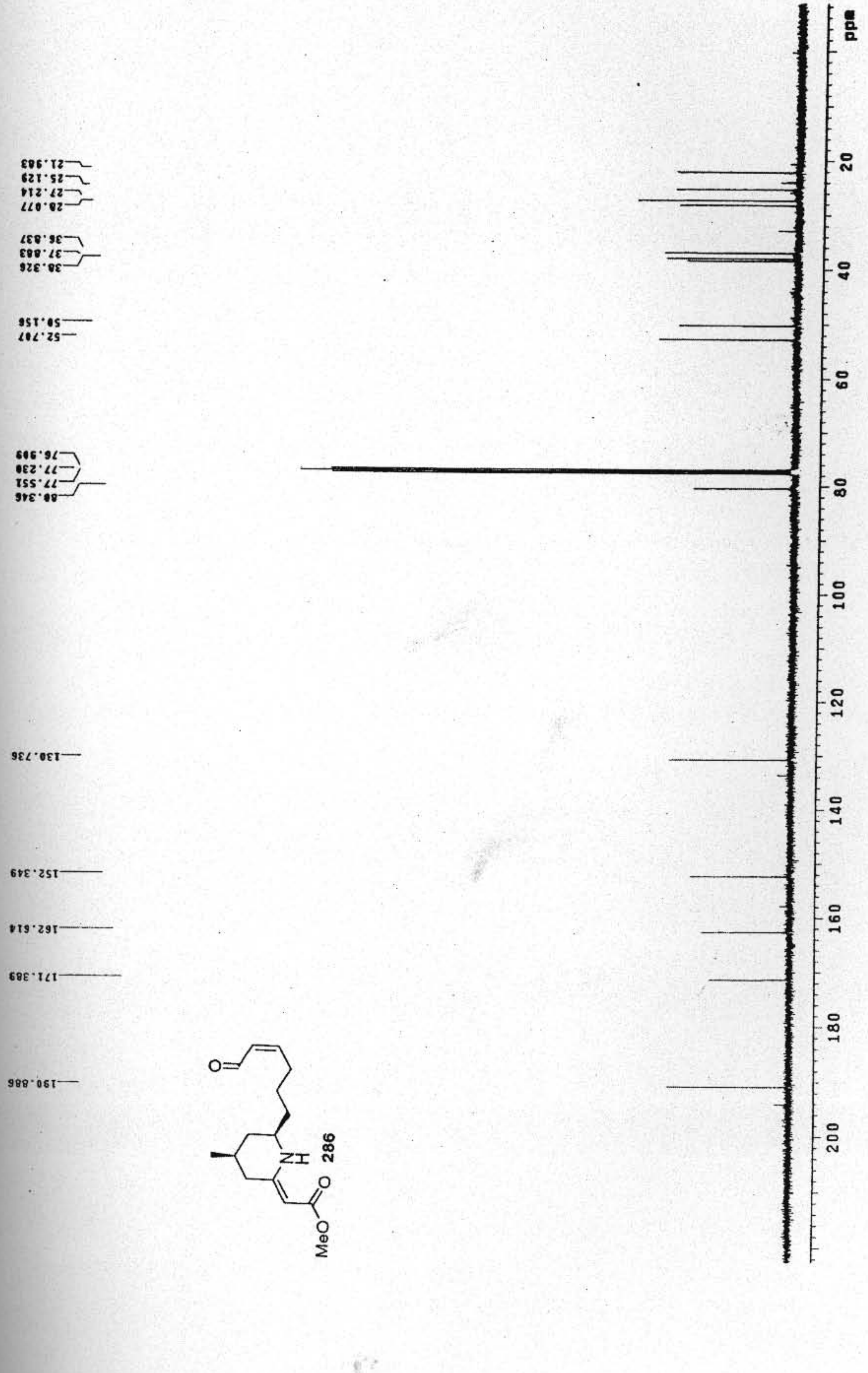
285


22.021
25.595
27.222
27.252
36.776
37.929
38.479
50.187
52.699
58.626
76.909
77.230
77.543
79.964
129.438
132.256
162.812
171.458
ppm
20
40
60
80
100
120
140
160
180
200
MeO
O
N
H
OH

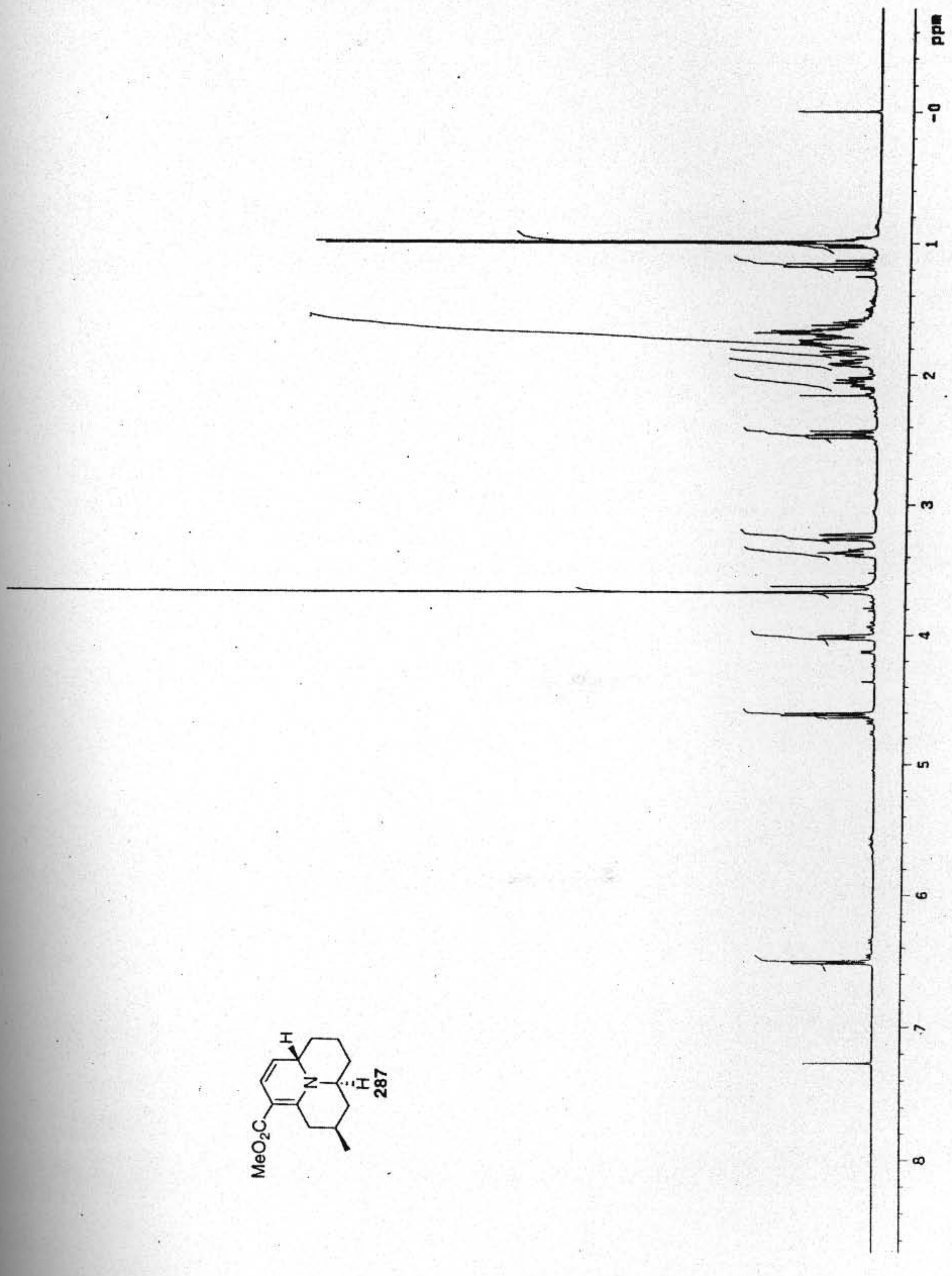
285



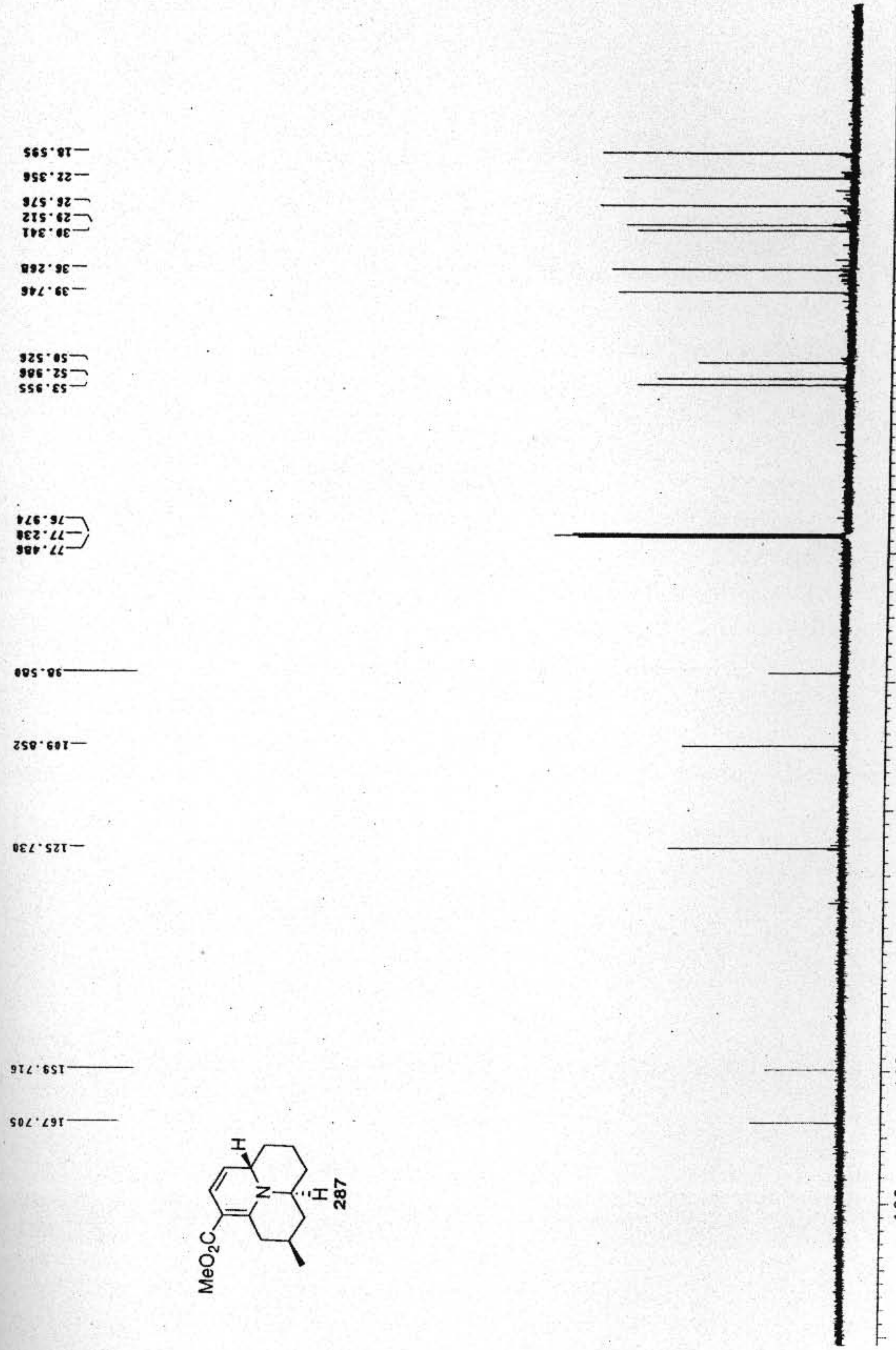
**286**


21.983
25.129
27.214
28.077
36.837
37.883
38.326
50.156
52.707
76.999
77.230
77.551
80.346
130.736
152.349
162.614
171.389
190.886
ppm
20
40
60
80
100
120
140
160
180
200
MeO
O
NH
O

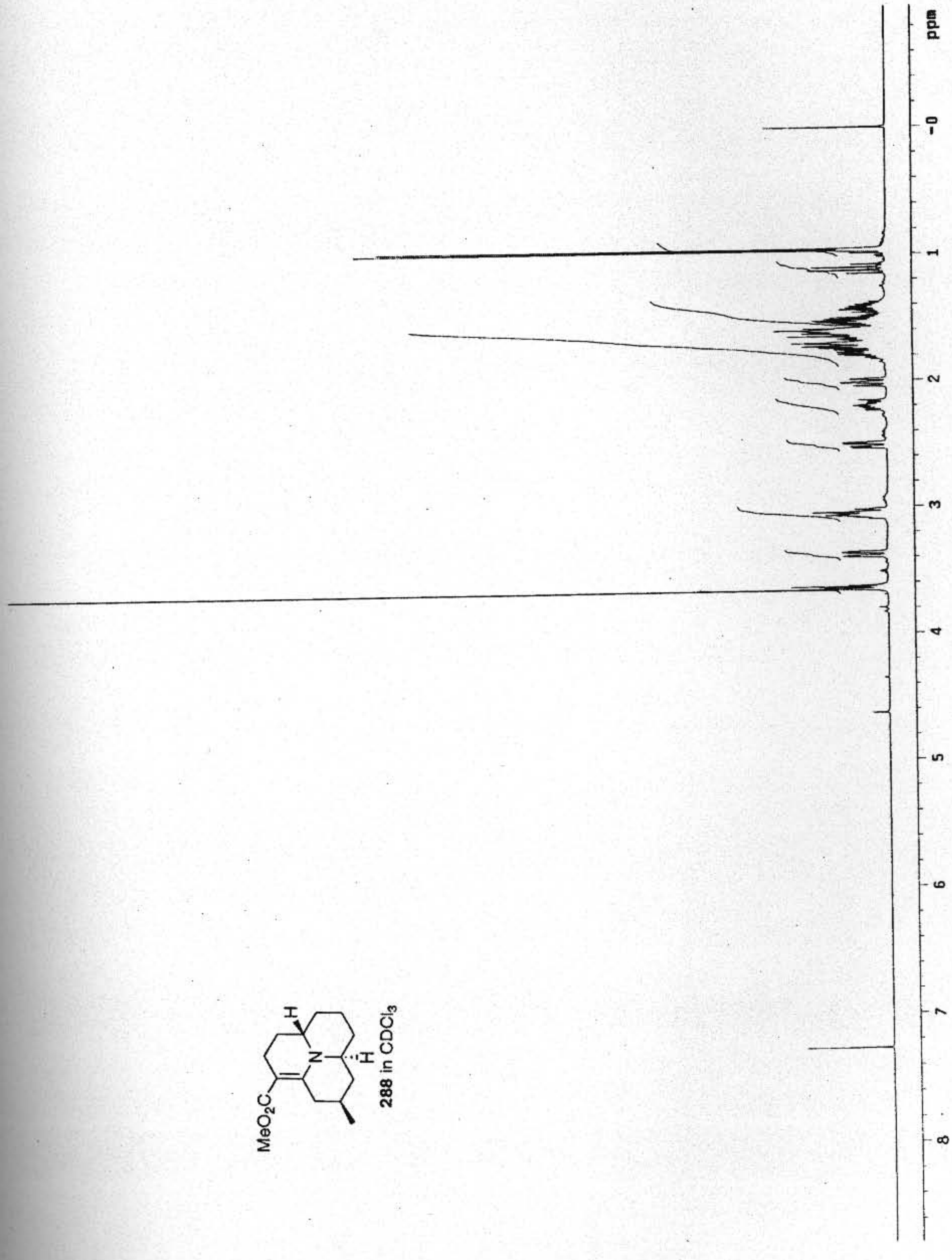
286



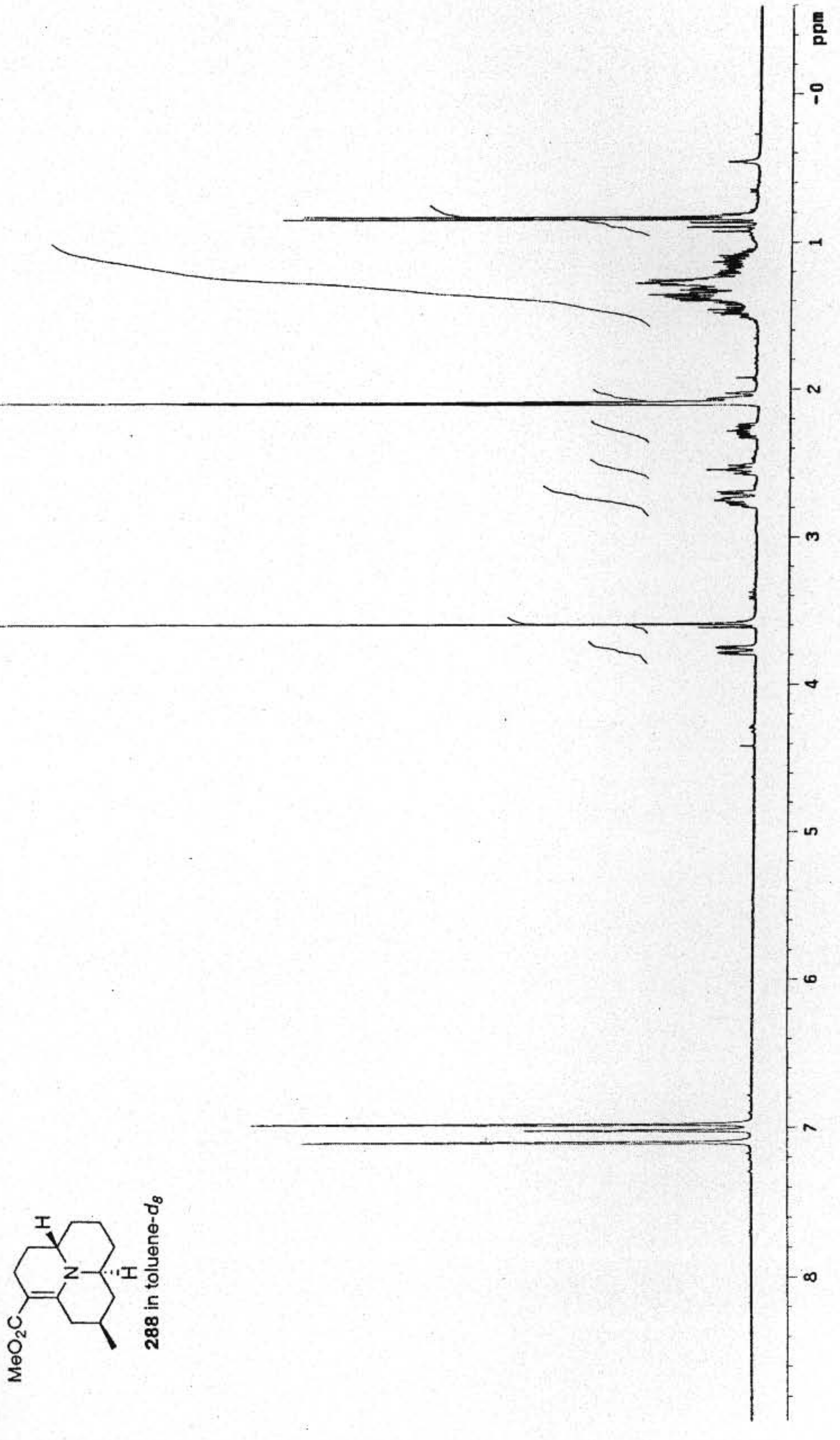
287


18.595
22.356
26.576
29.512
30.341
36.268
39.746
50.526
52.986
53.955
76.974
77.238
77.486
98.588
109.852
125.730
159.716
167.705
MeO$_2$C
N
H
H
ppm
20
40
60
80
100
120
140
160
180

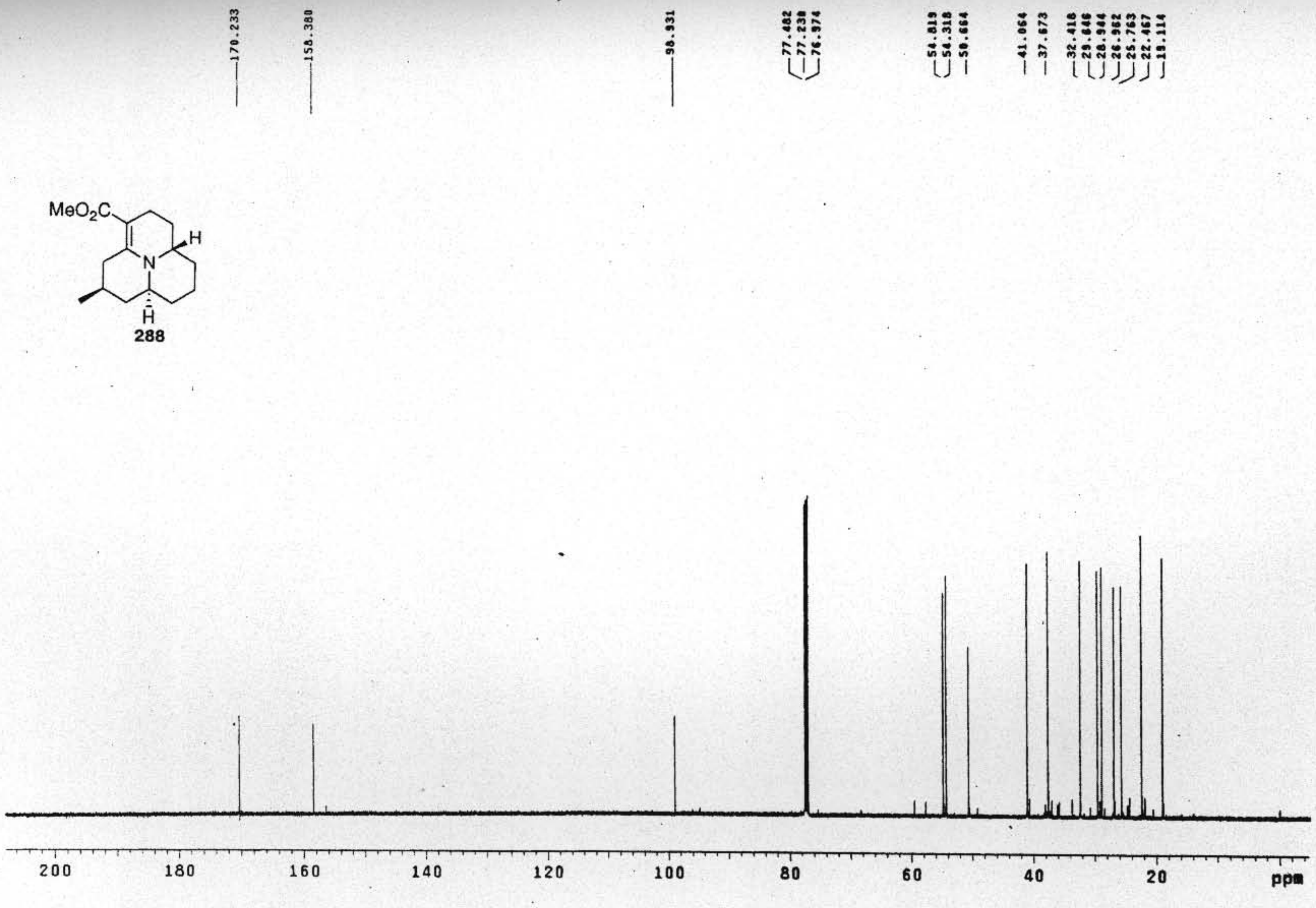
287



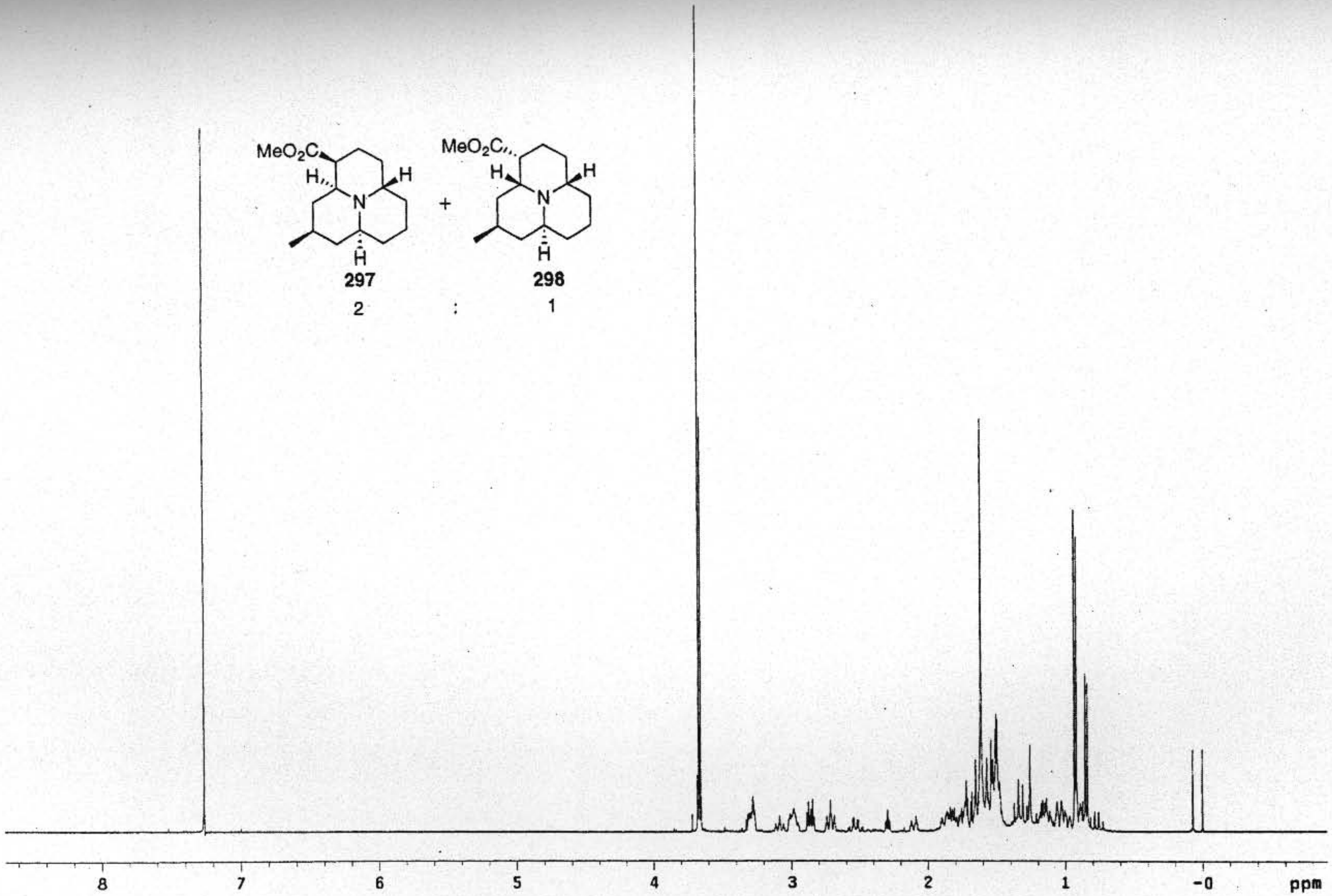
288 in CDCl$_3$



**288** in toluene-$d_8$

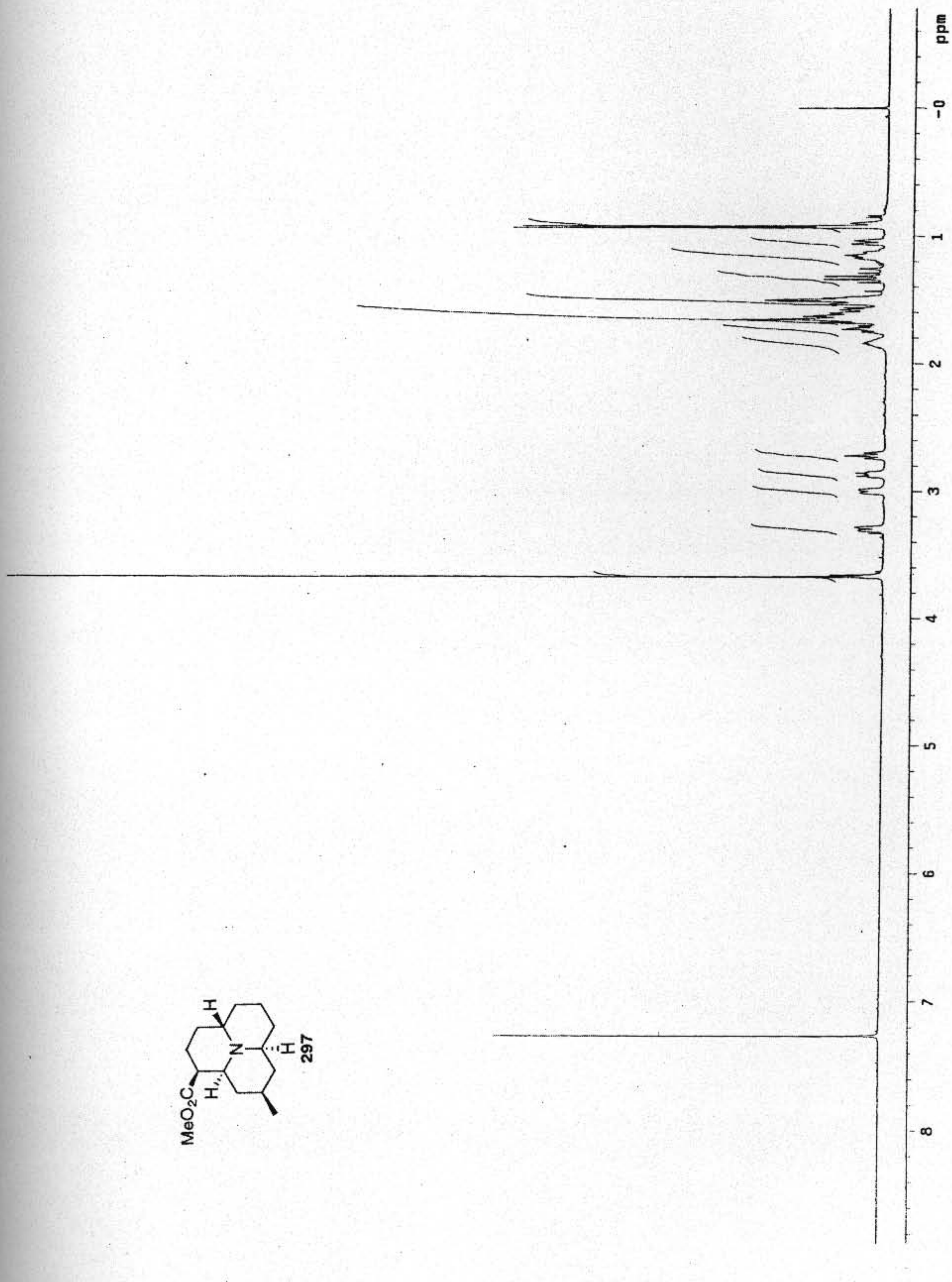

170.233
158.380
98.931
77.482
77.238
76.974
54.819
54.318
50.664
41.064
37.673
32.418
29.646
28.944
26.962
25.763
22.467
19.114
MeO2C
N
H
H
200
180
160
140
120
100
80
60
40
20
ppm

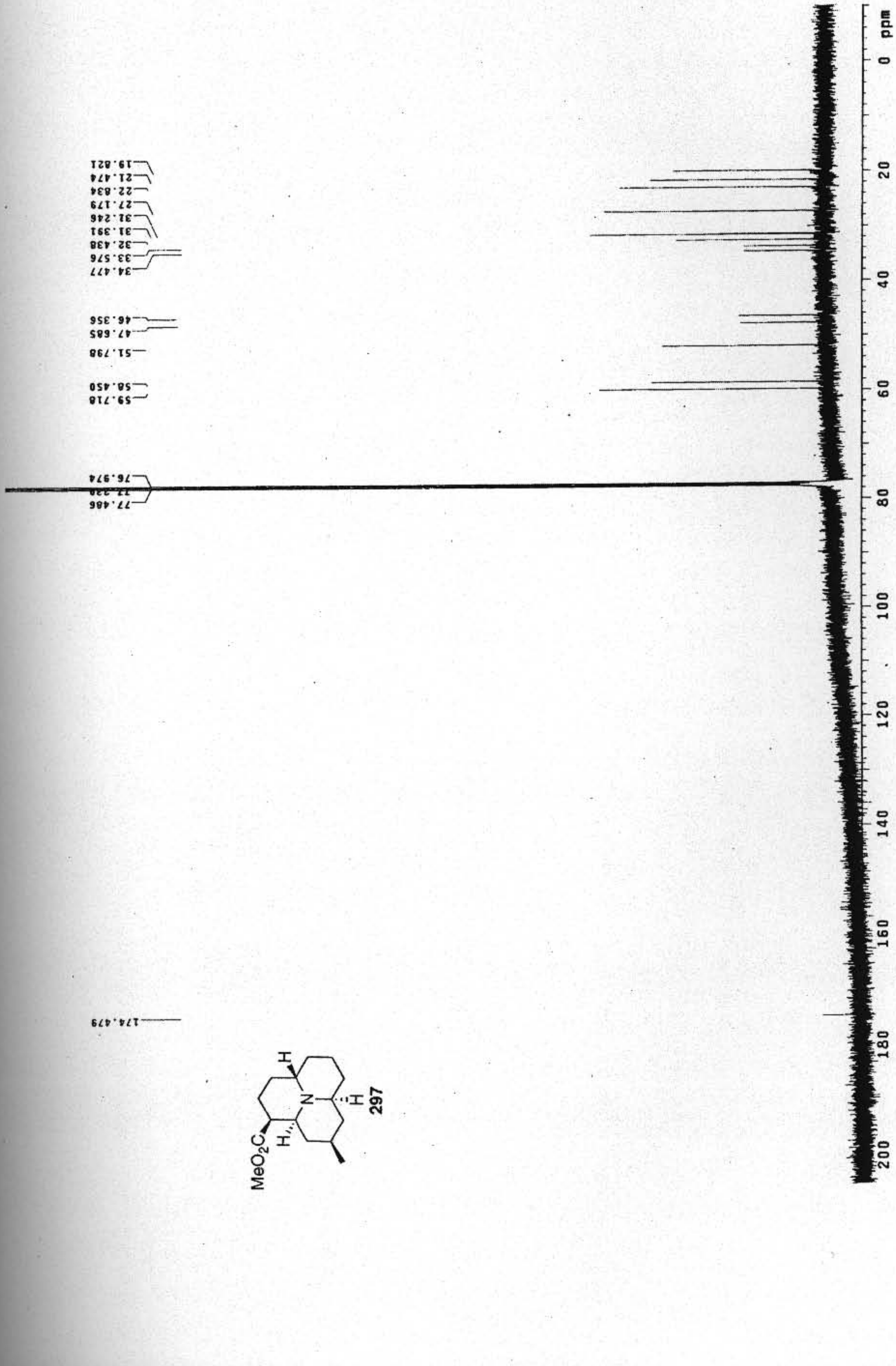
288



297 + 298

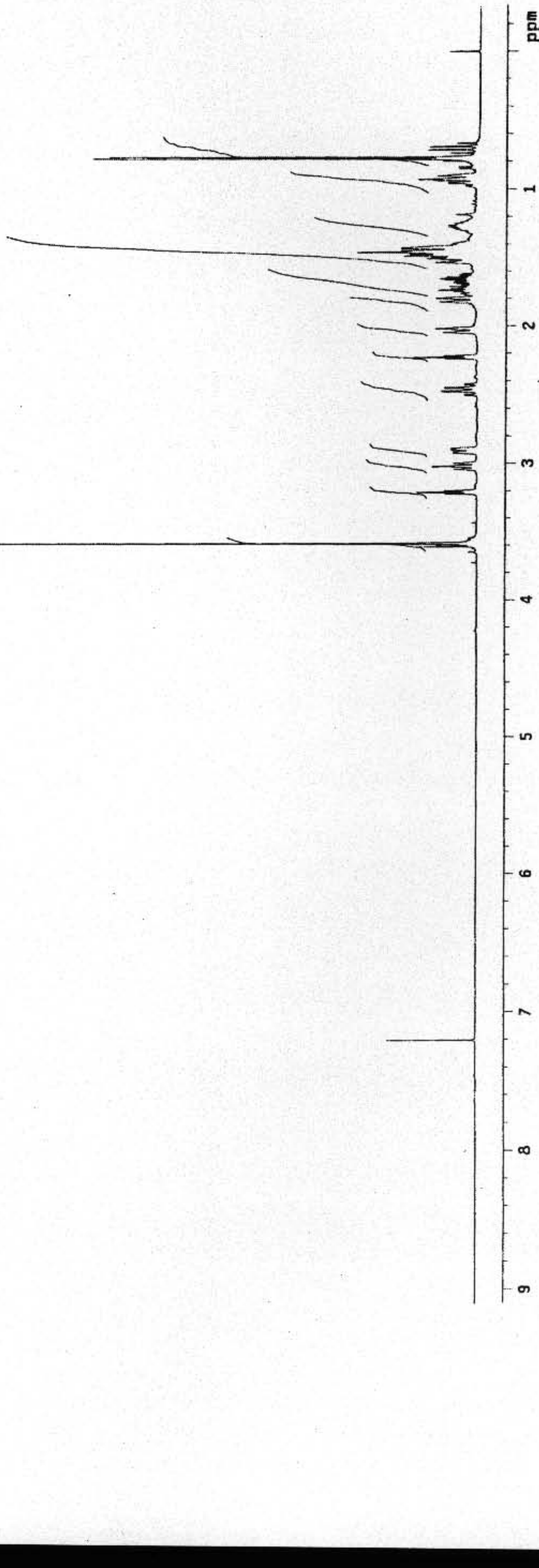
2 : 1

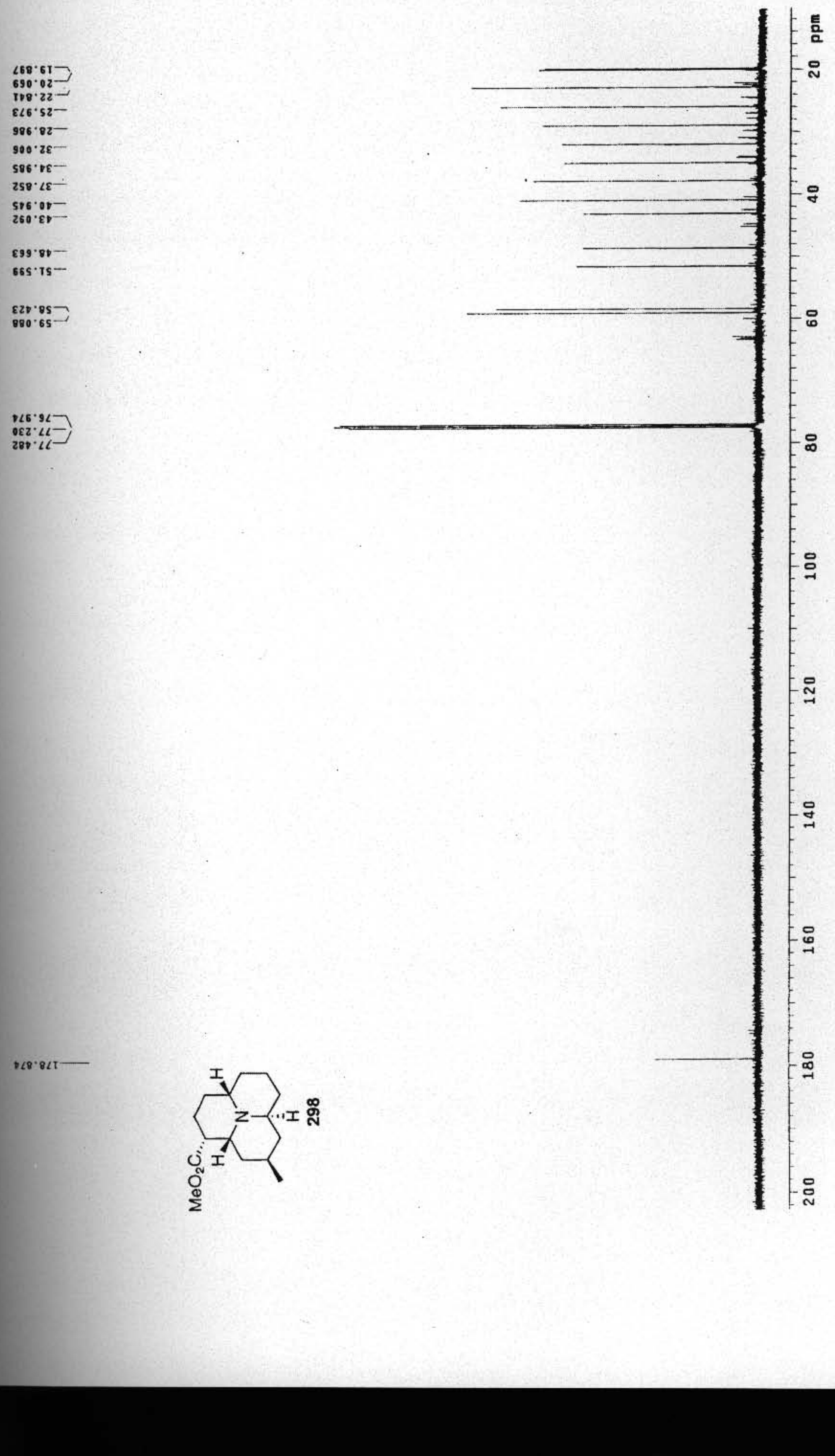

297


19.821
21.474
22.834
27.179
31.246
31.391
32.438
33.576
34.477
46.356
47.685
51.798
58.450
59.718
76.974
77.230
77.486
174.479
MeO2C
H
N
H
H
ppm
0
20
40
60
80
100
120
140
160
180
200

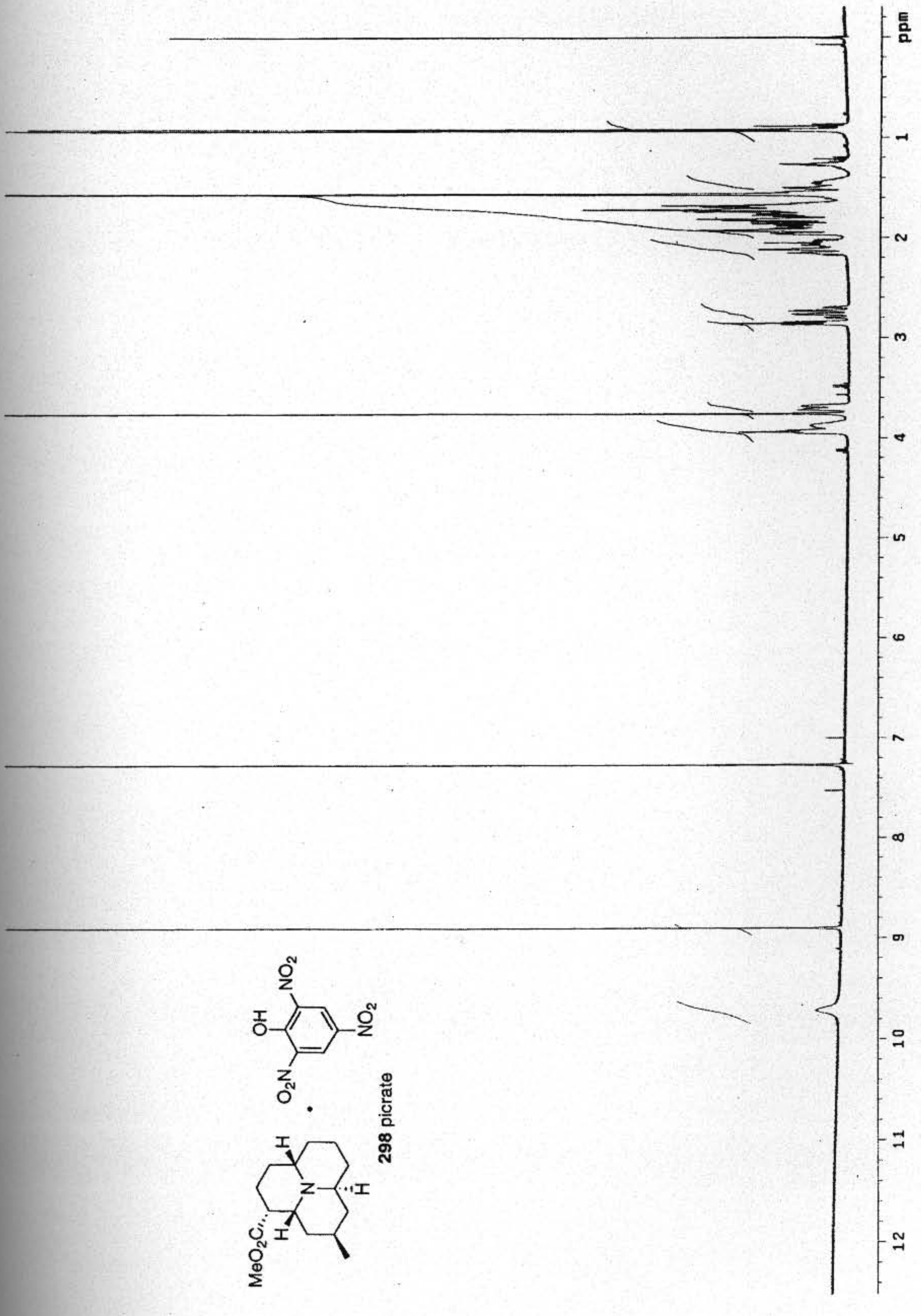
297

298

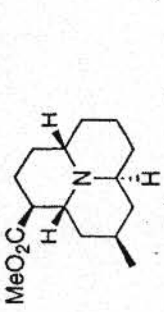



19.897
20.069
22.841
25.973
28.986
32.006
34.985
37.852
40.945
43.092
48.663
51.599
58.423
59.086
76.974
77.230
77.482
178.874
MeO2C
H
N
H
H
ppm
20
40
60
80
100
120
140
160
180
200

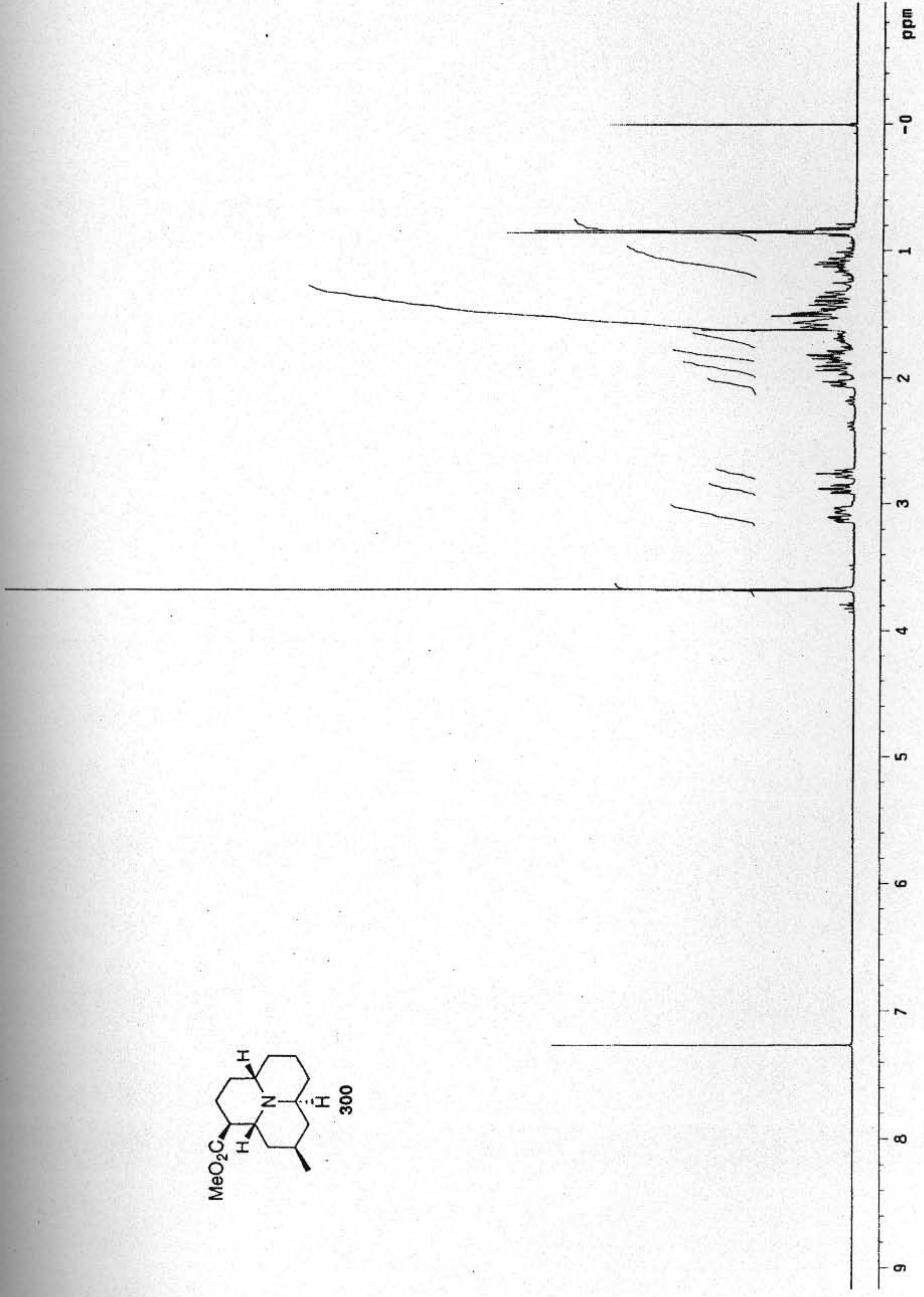
298

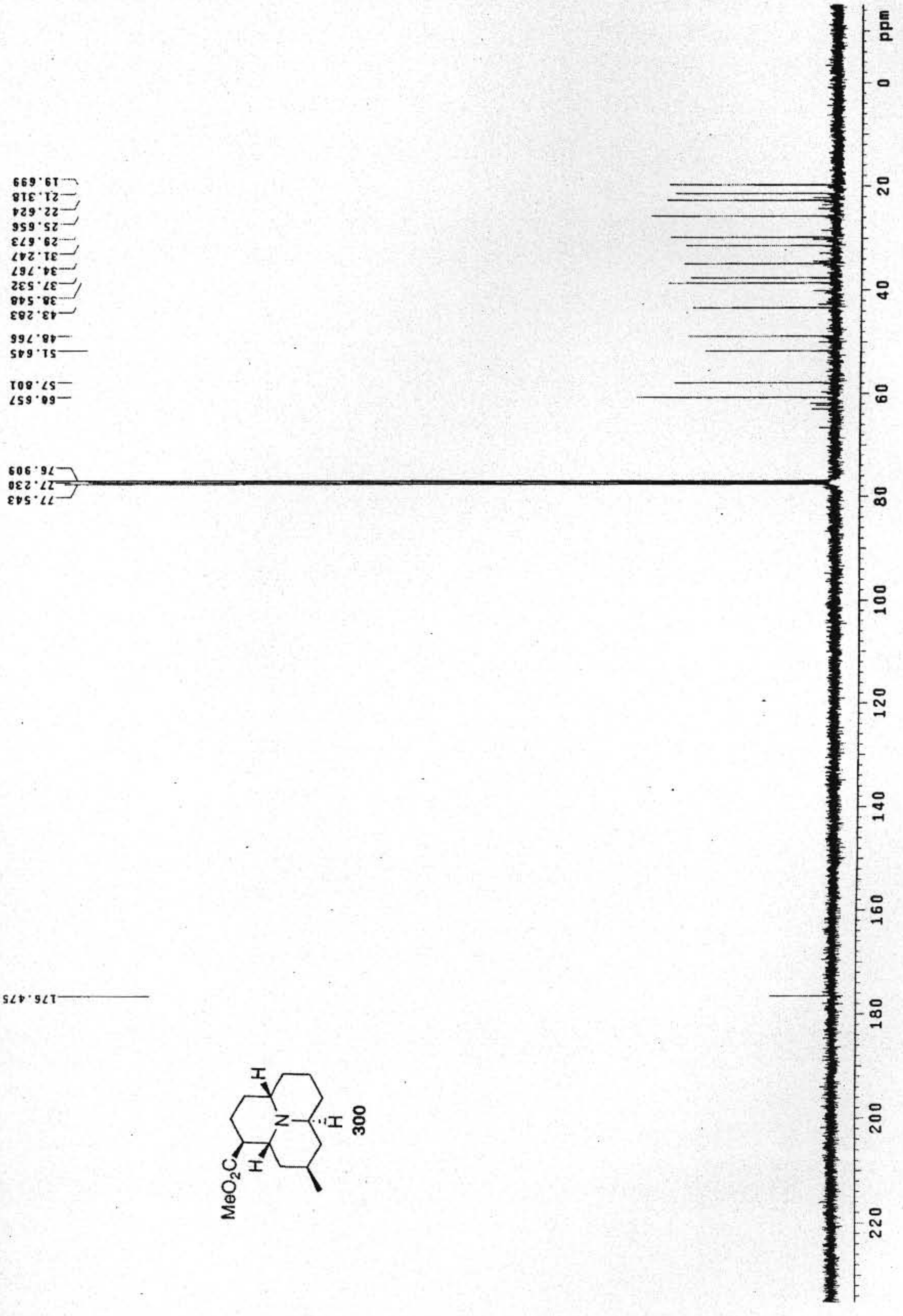


**298** picrate

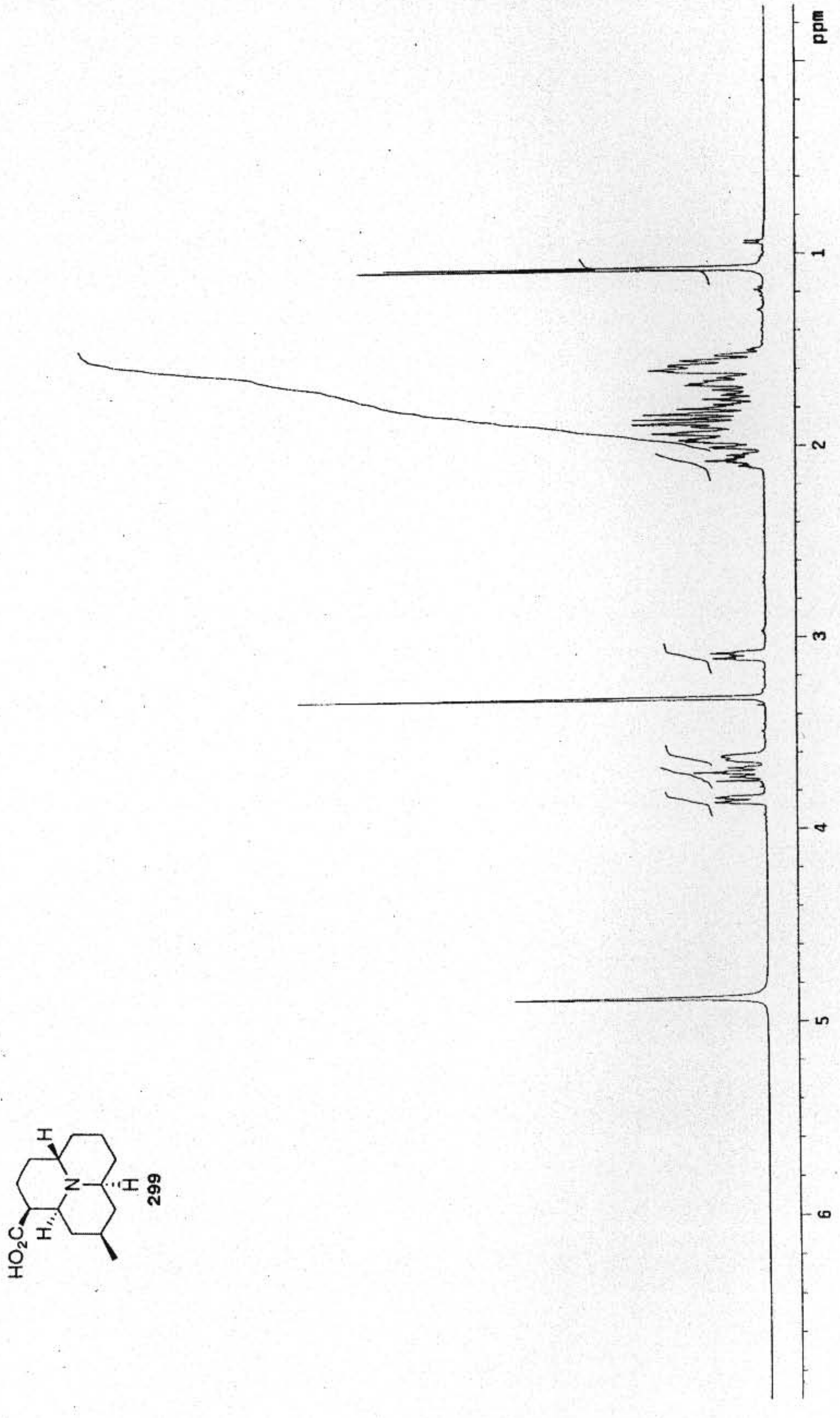


300

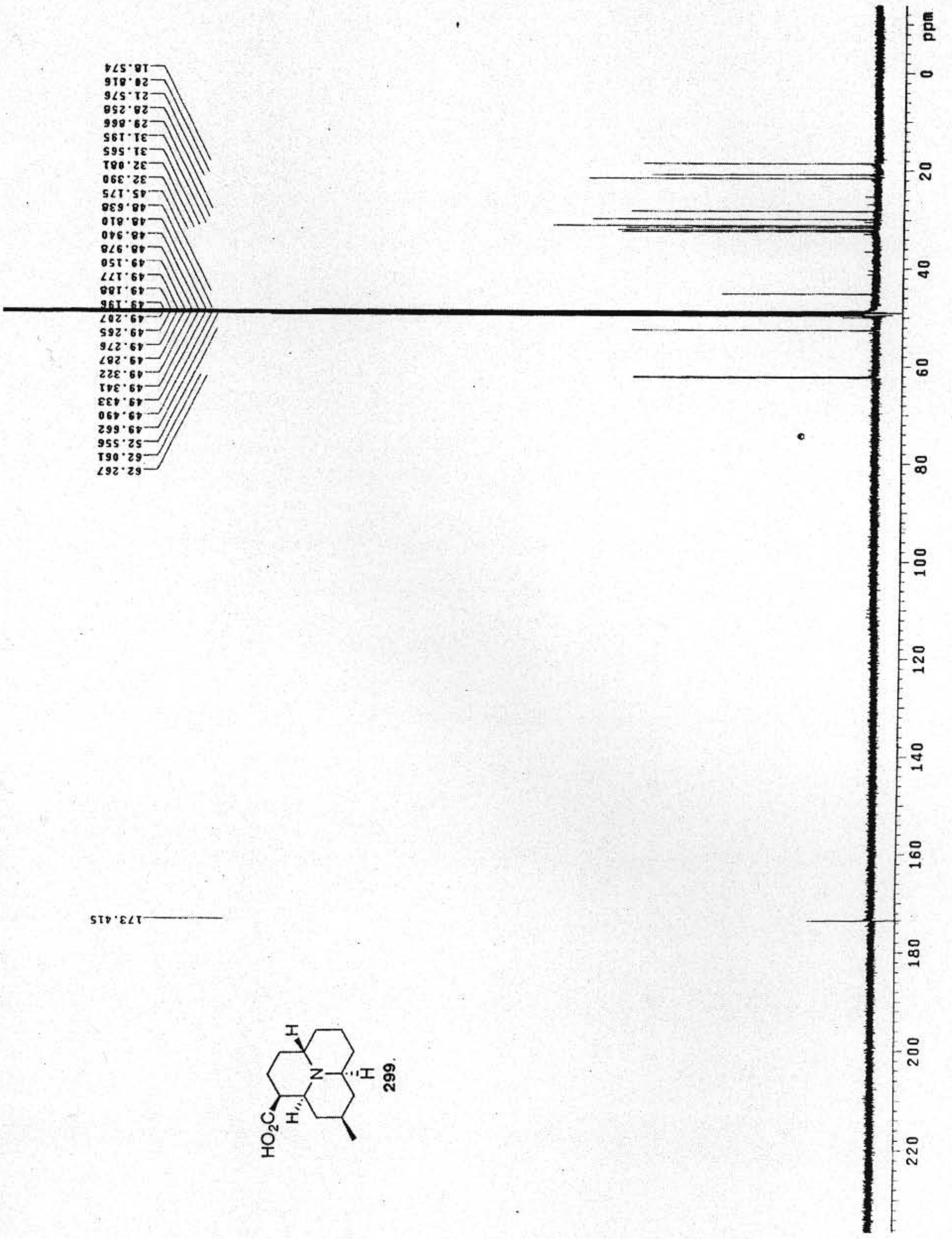



19.699
21.318
22.624
25.656
29.673
31.247
34.767
37.532
38.548
43.283
48.766
51.645
57.801
60.657
76.909
77.230
77.543
176.475
ppm
0
20
40
60
80
100
120
140
160
180
200
220
MeO$_2$C
H
N
H
H

300

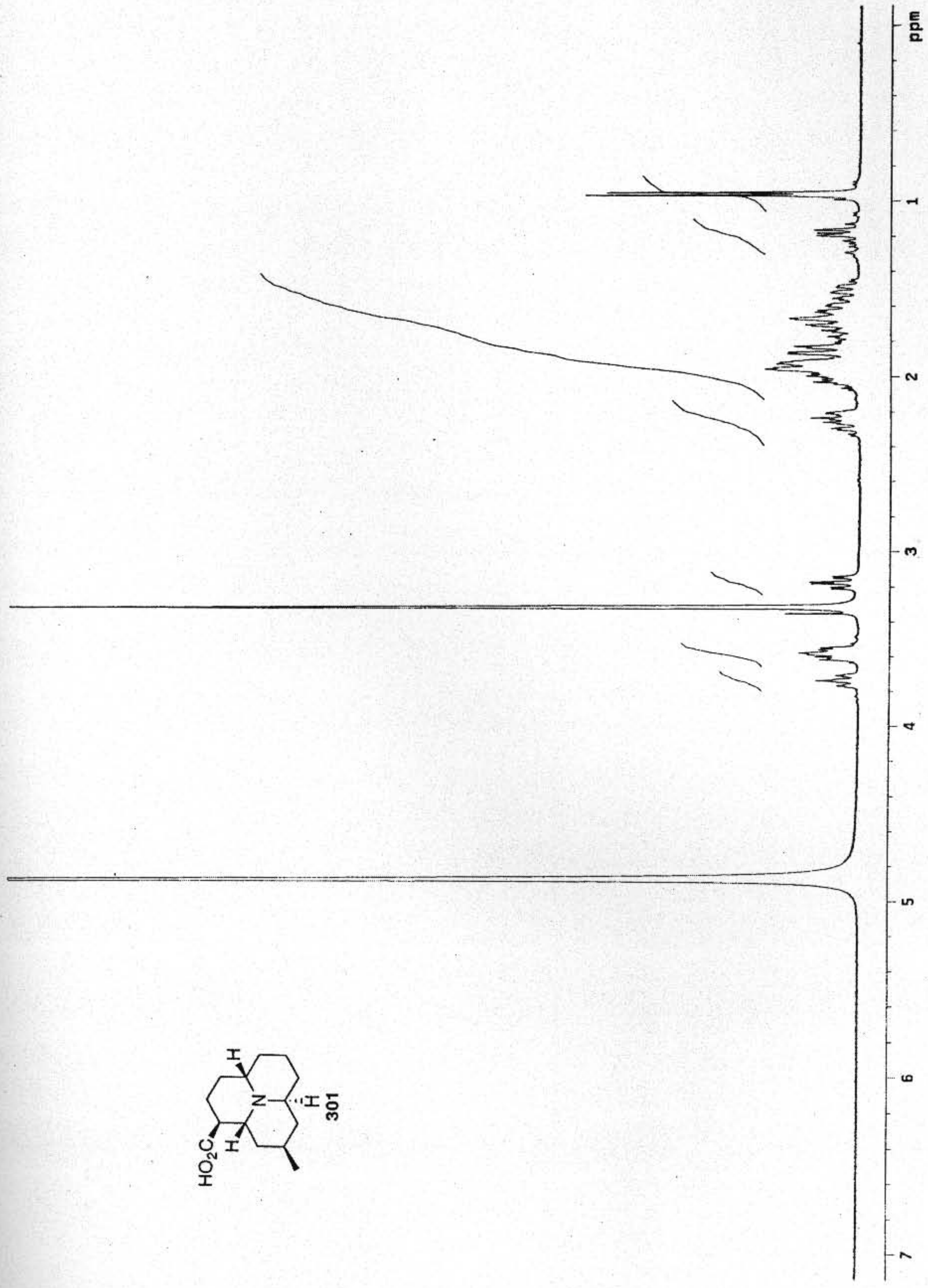


299

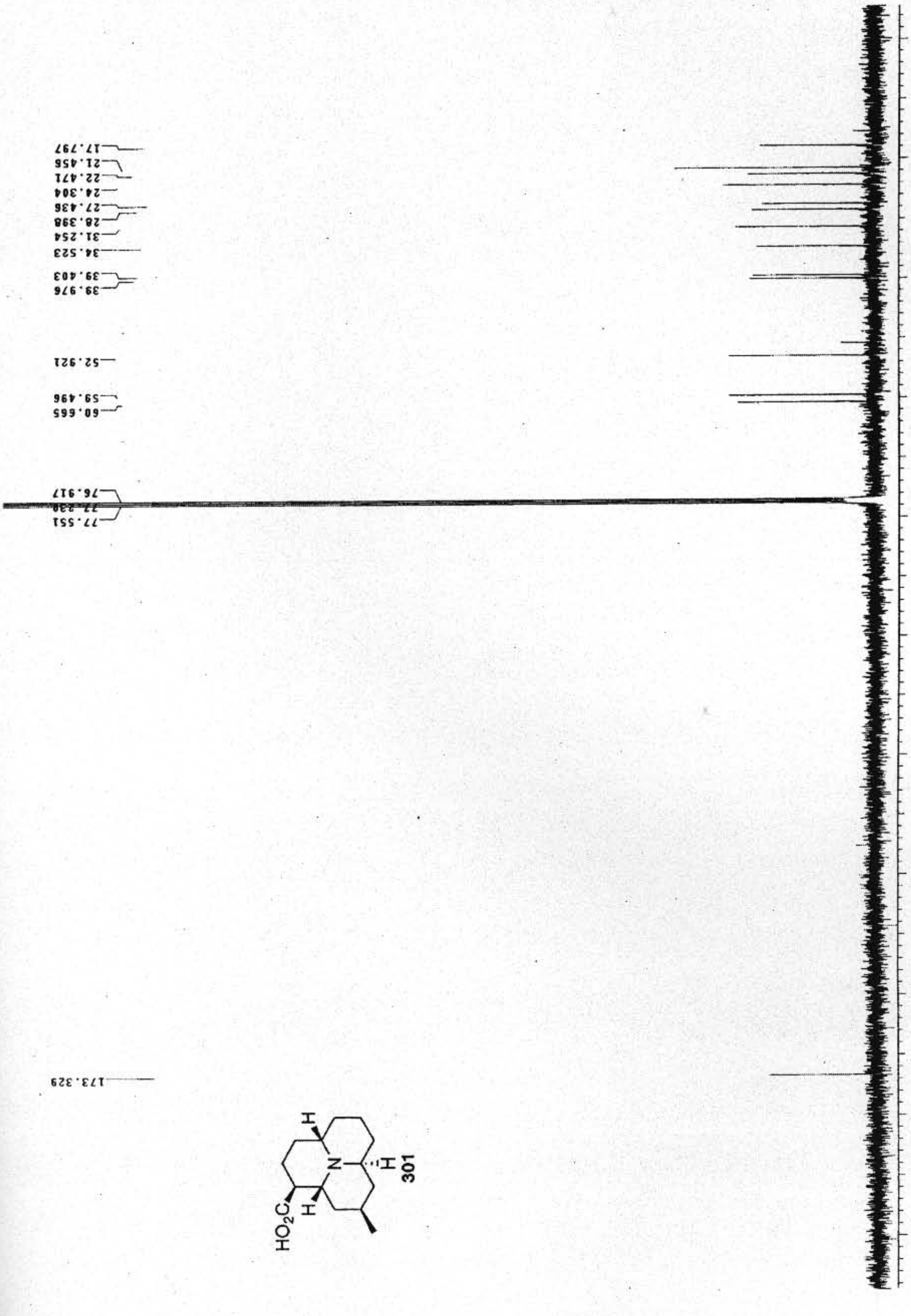


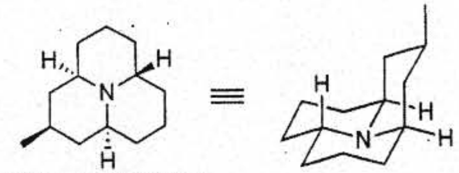
18.574
20.816
21.576
28.258
29.866
31.195
31.565
32.081
32.390
45.175
48.638
48.810
48.940
48.978
49.150
49.177
49.188
49.196
49.207
49.265
49.276
49.287
49.322
49.341
49.433
49.490
49.662
52.556
62.061
62.267
173.415
HO2C
H
N
H
H
ppm
0
20
40
60
80
100
120
140
160
180
200
220

299.

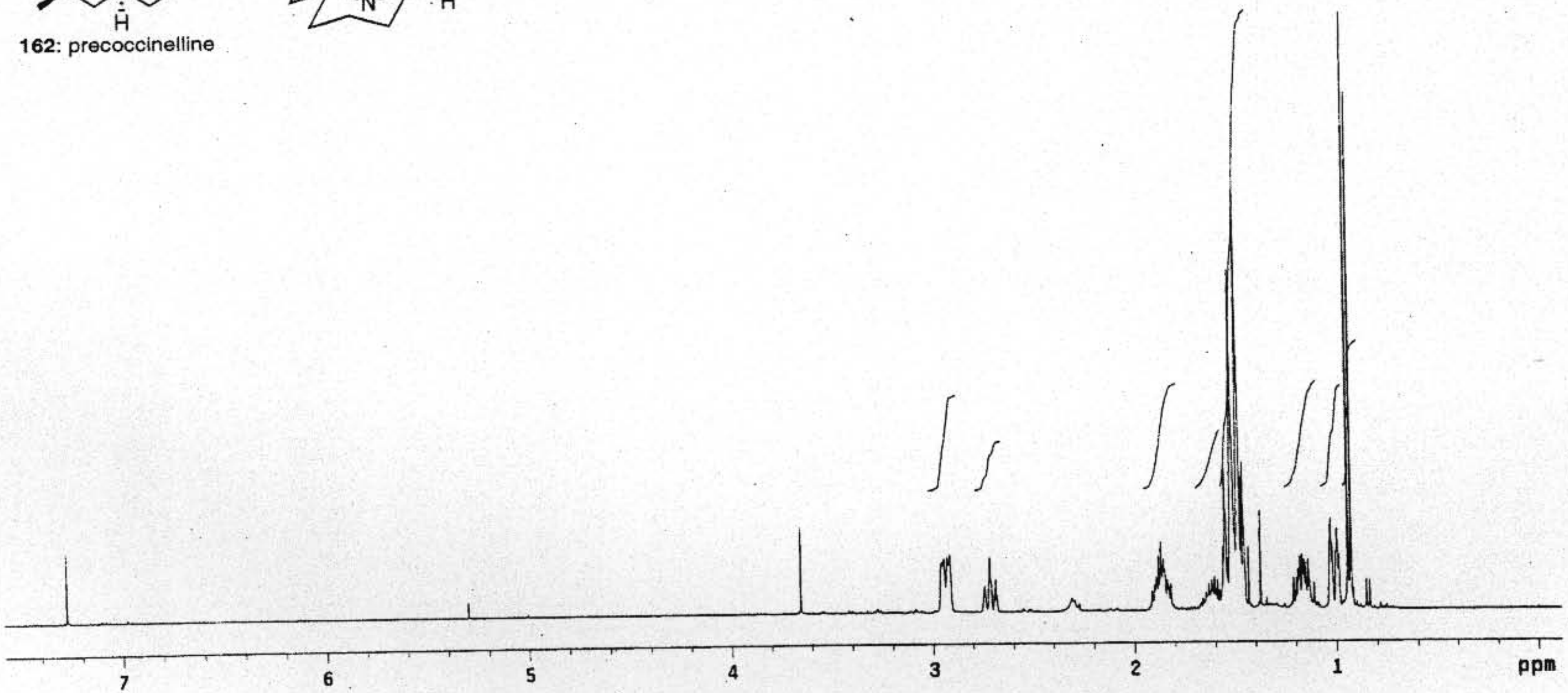


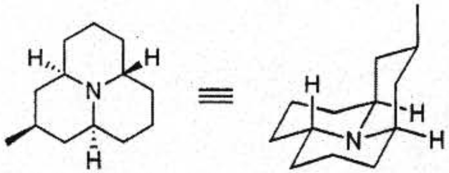
301


17.797
21.456
22.471
24.304
27.436
28.398
31.254
34.523
39.403
39.976
52.921
59.496
60.665
76.917
77.238
77.551
173.329
ppm
20
40
60
80
100
120
140
160
180
200
HO2C
H
N
H
H
301

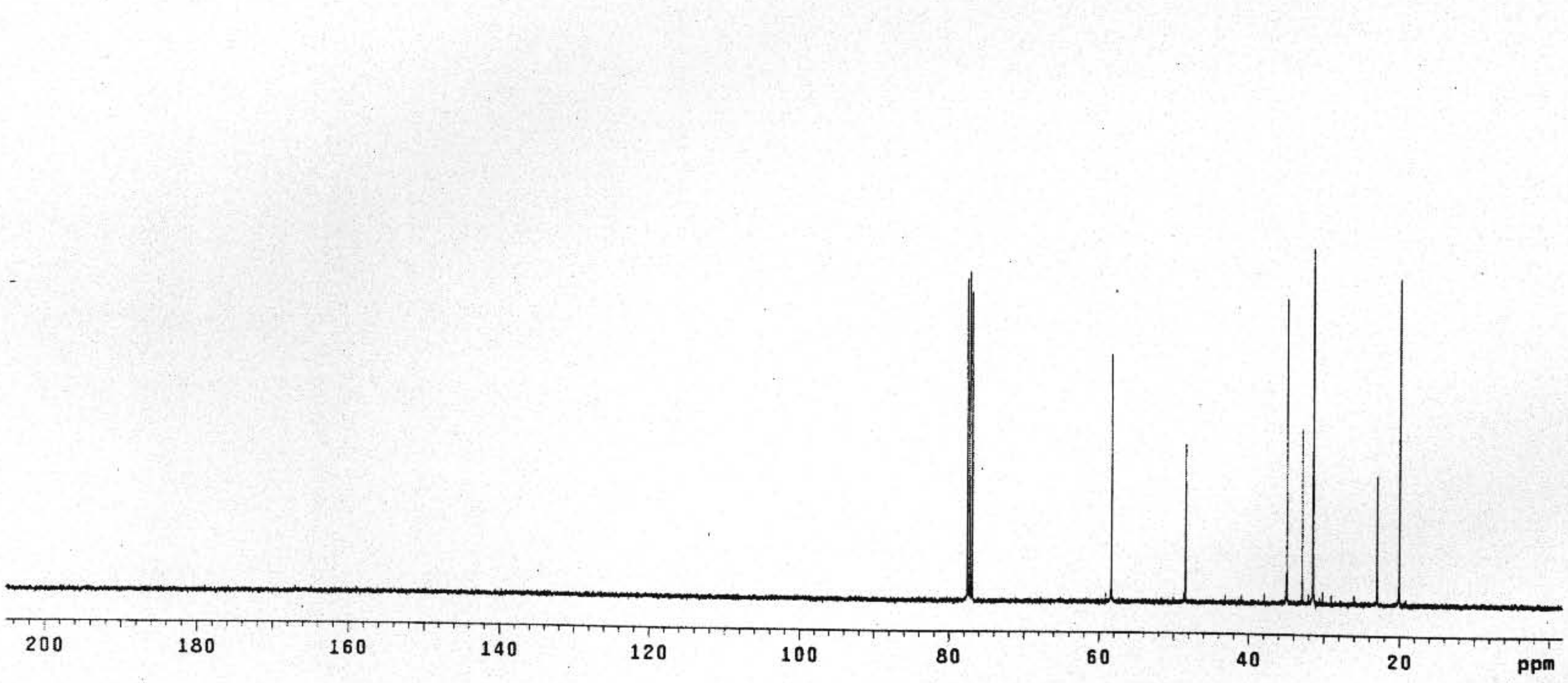


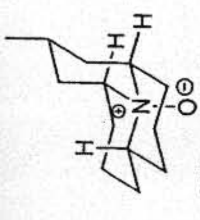
**162**: precoccinelline



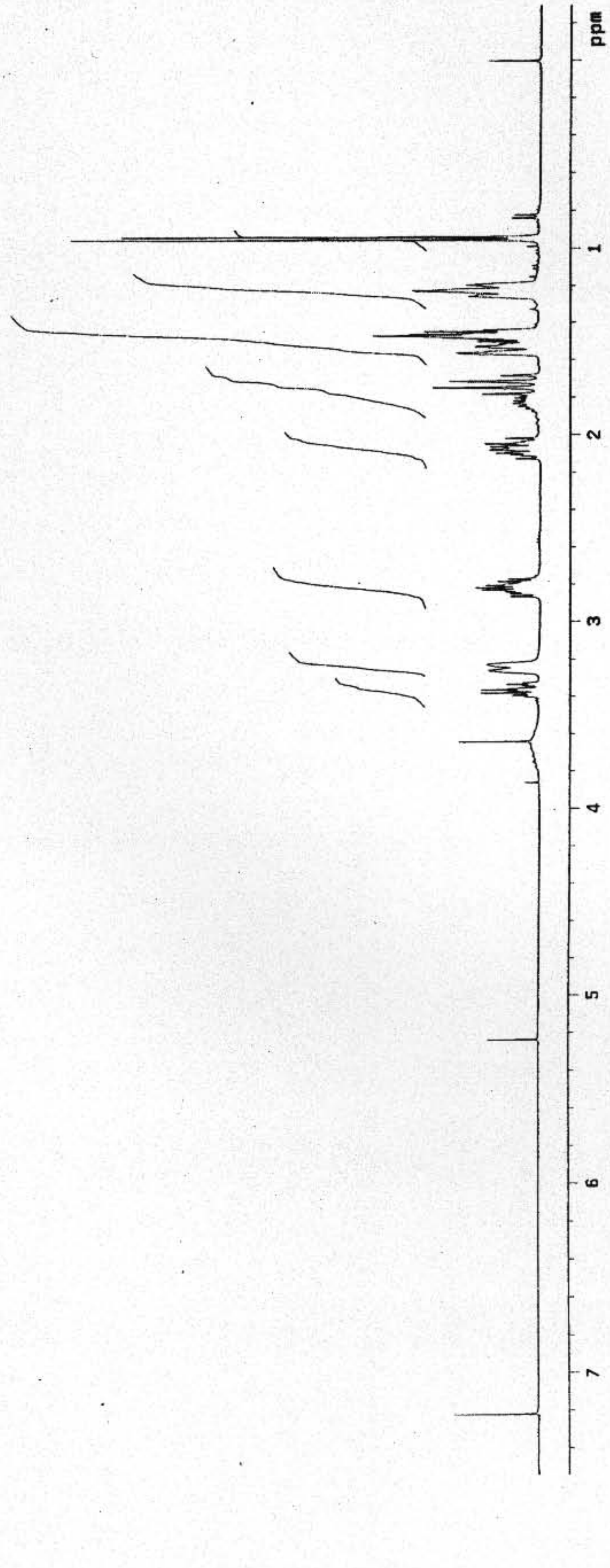


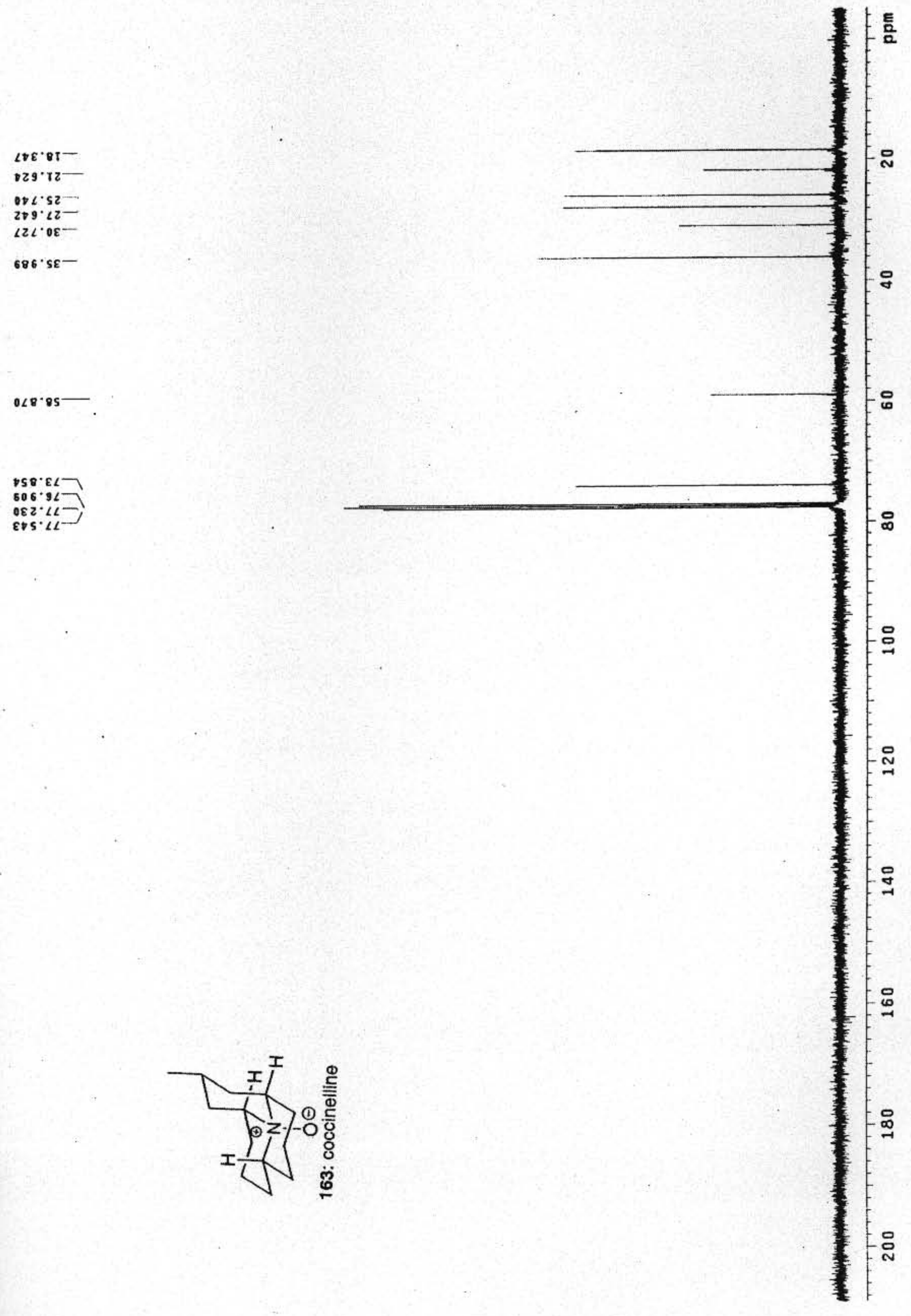
**162**: precoccinelline



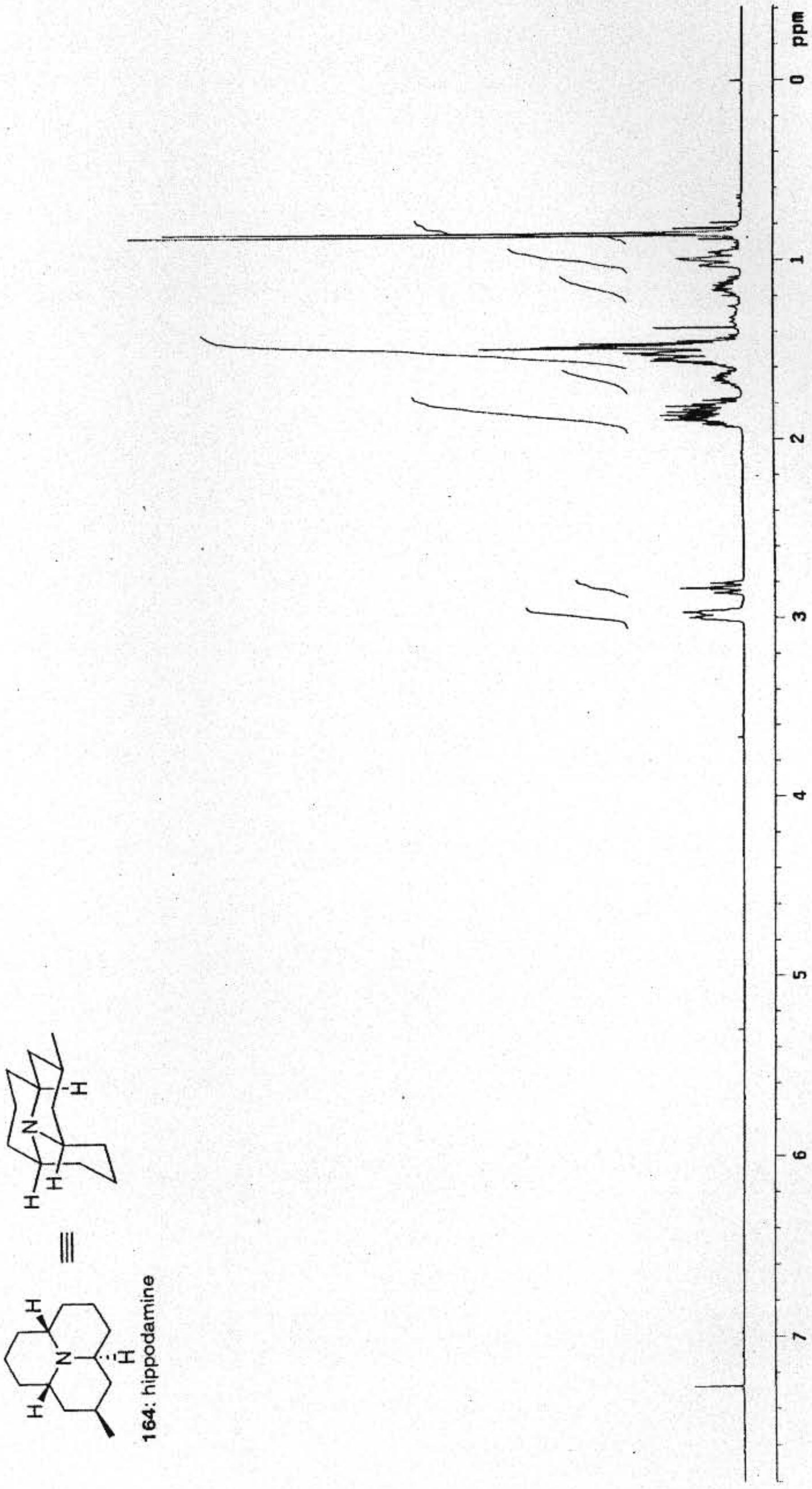


**163**: coccinelline

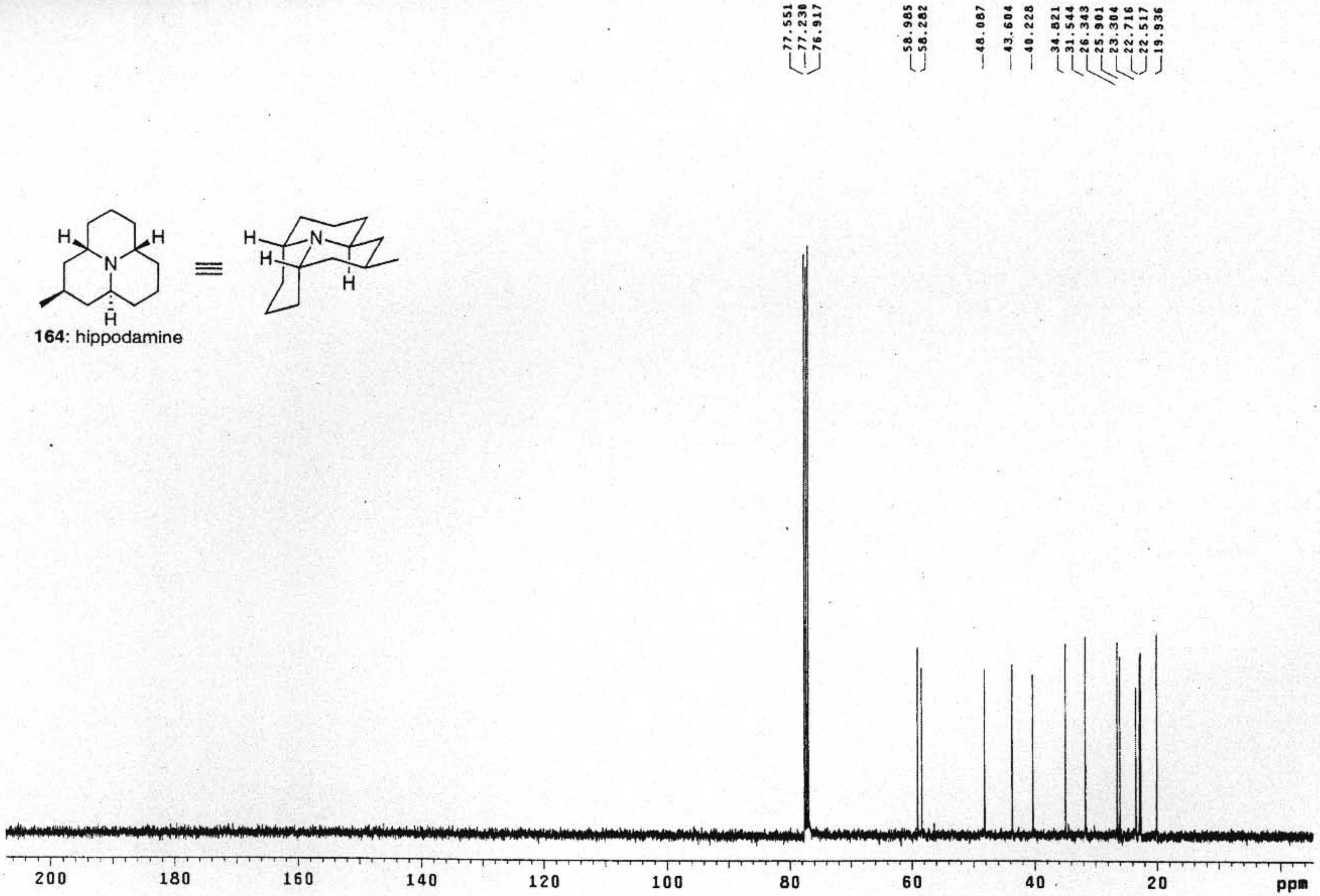




163: coccinelline

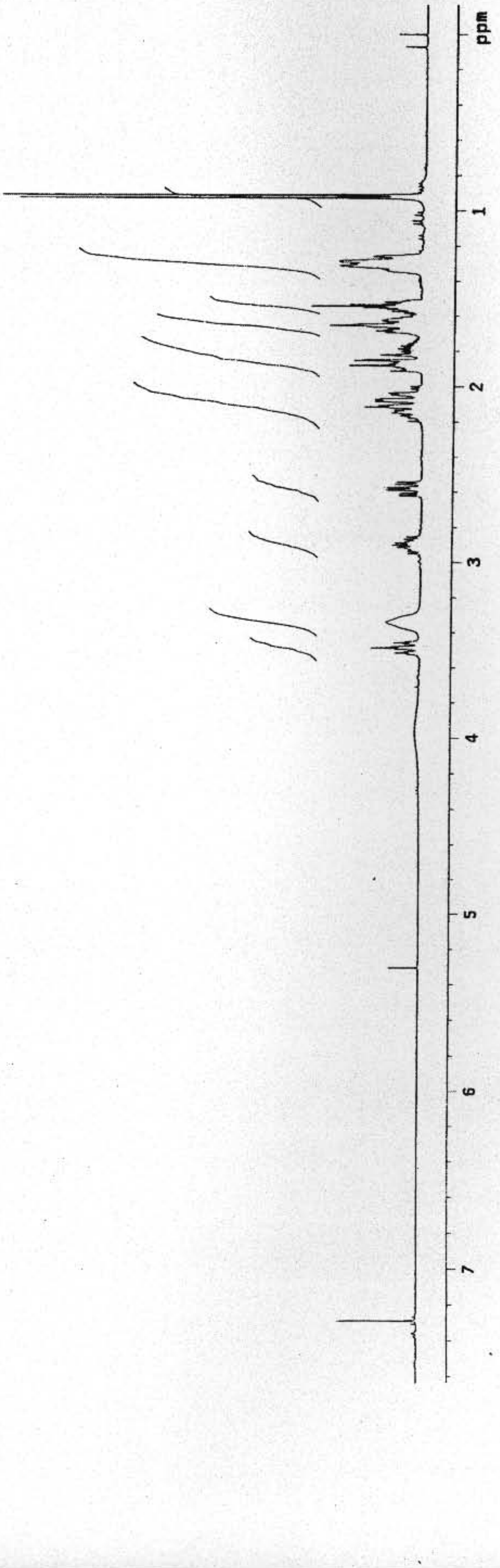


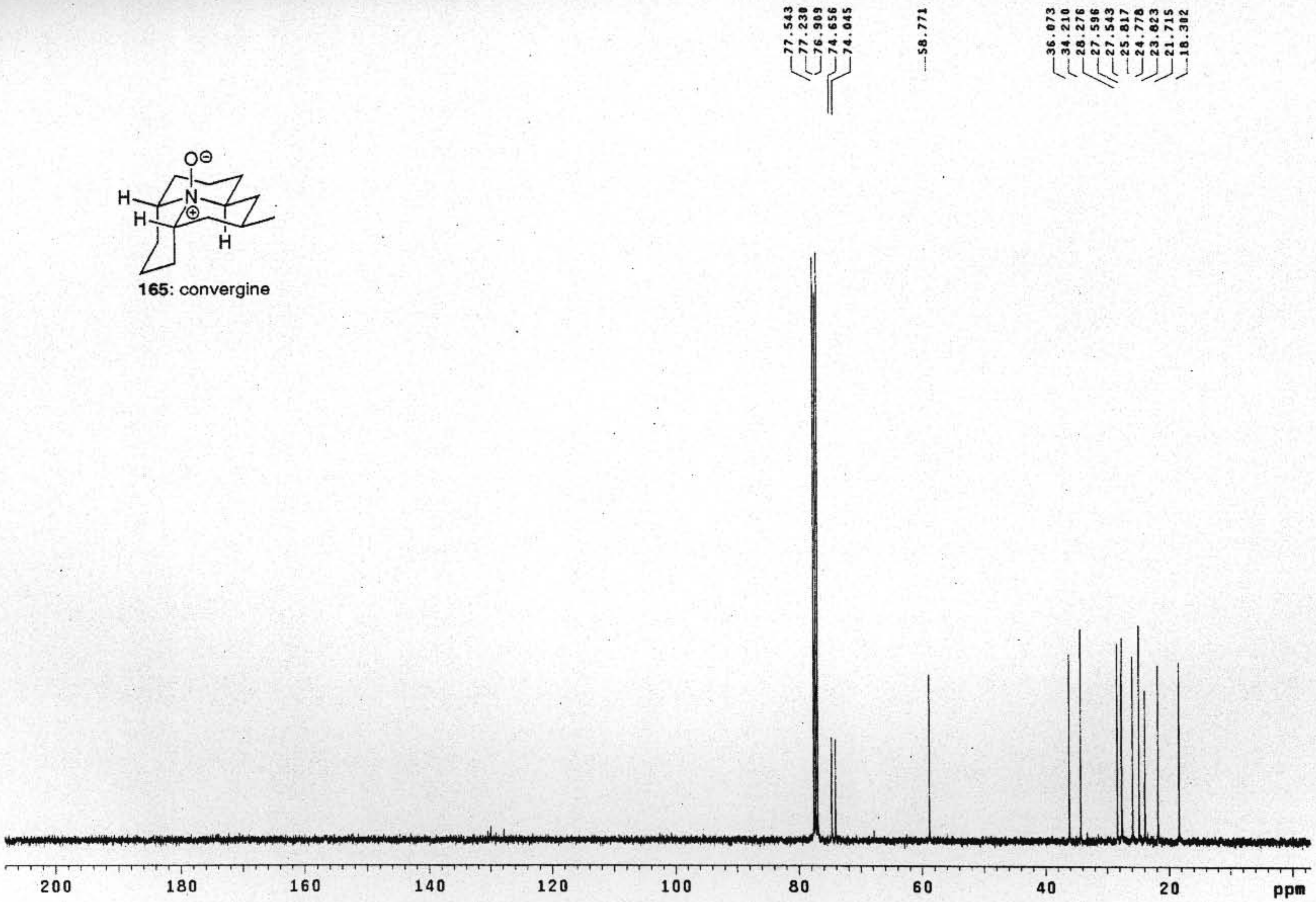
164: hippodamine



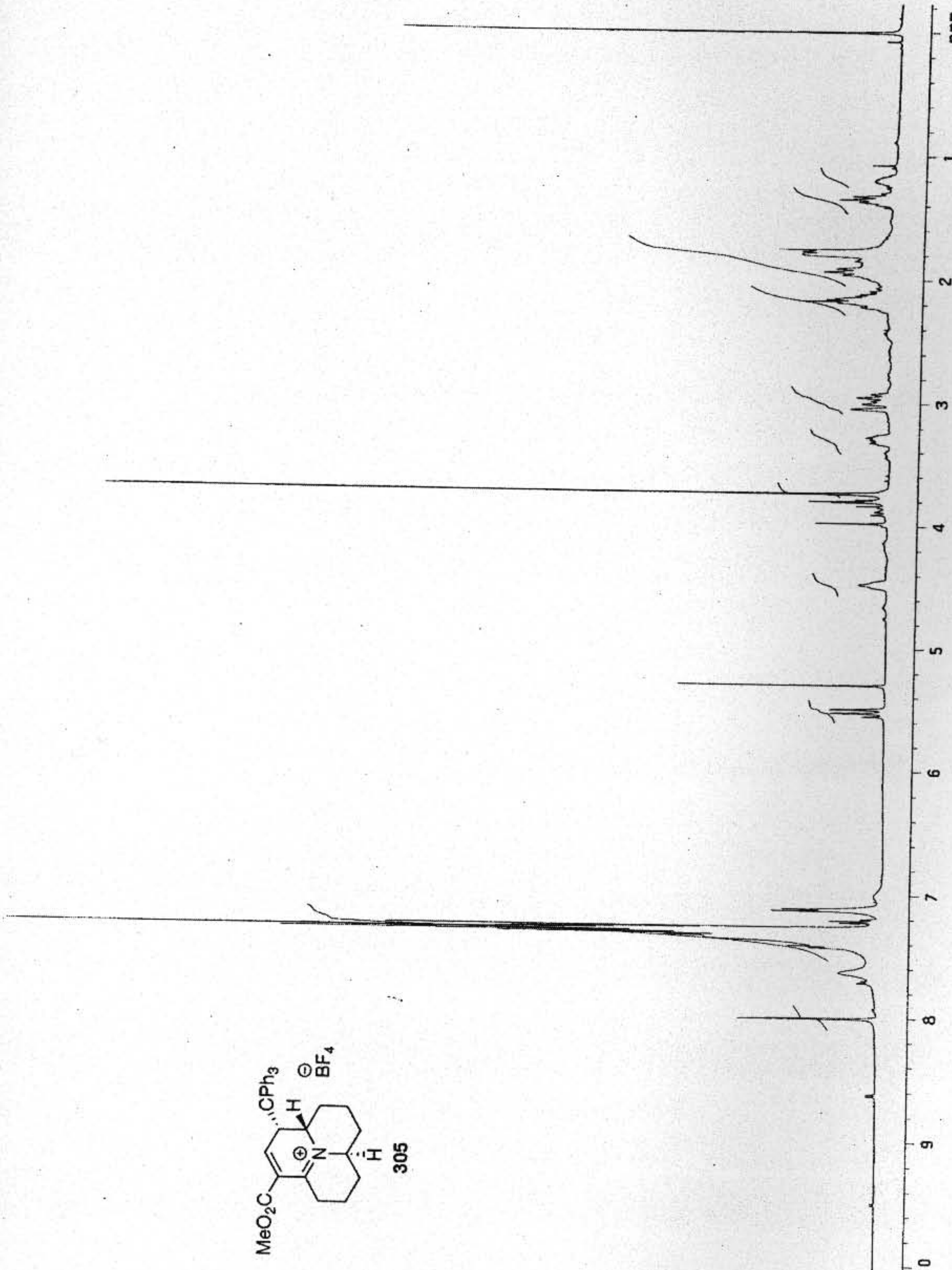
**164**: hippodamine

**165**: convergine

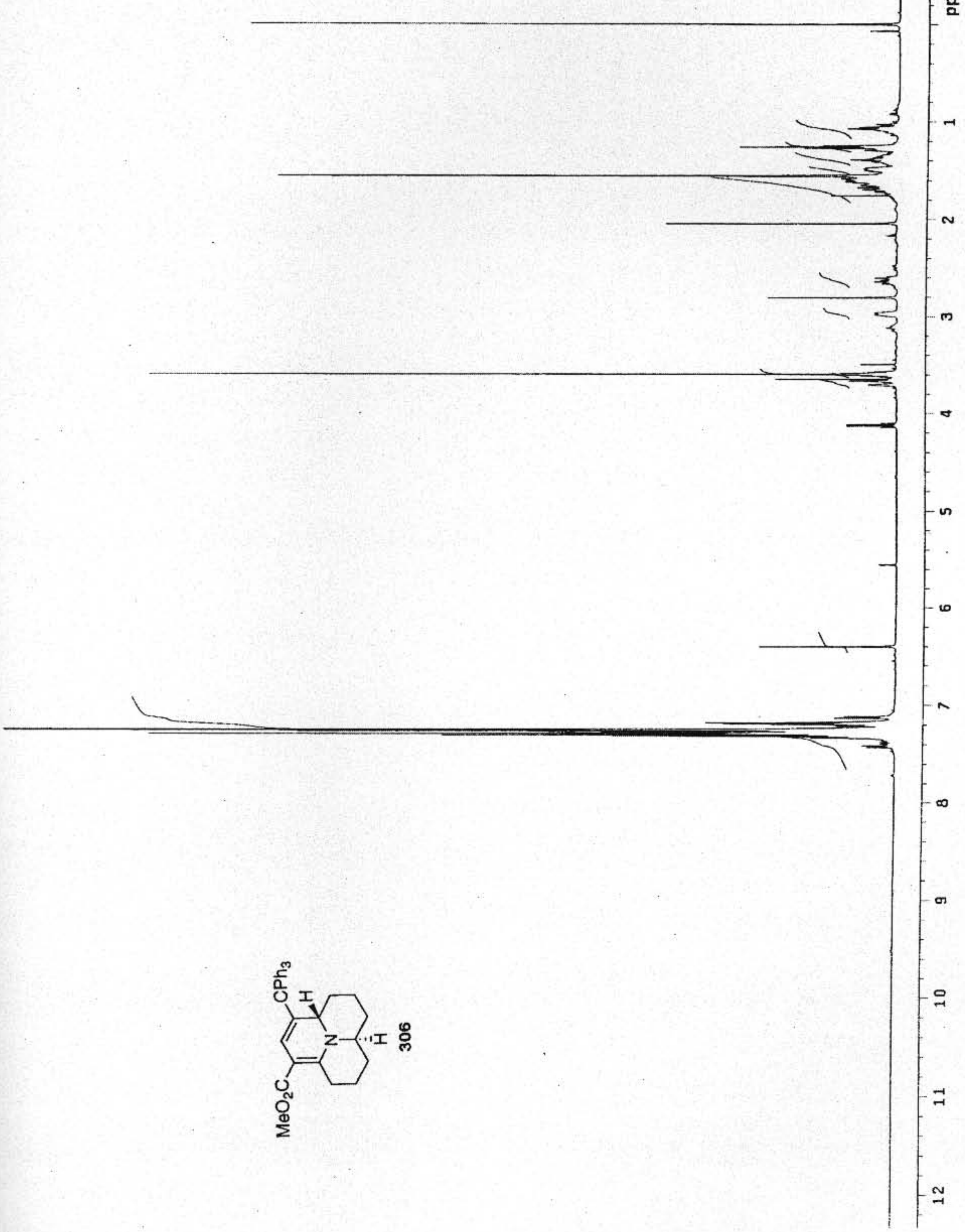


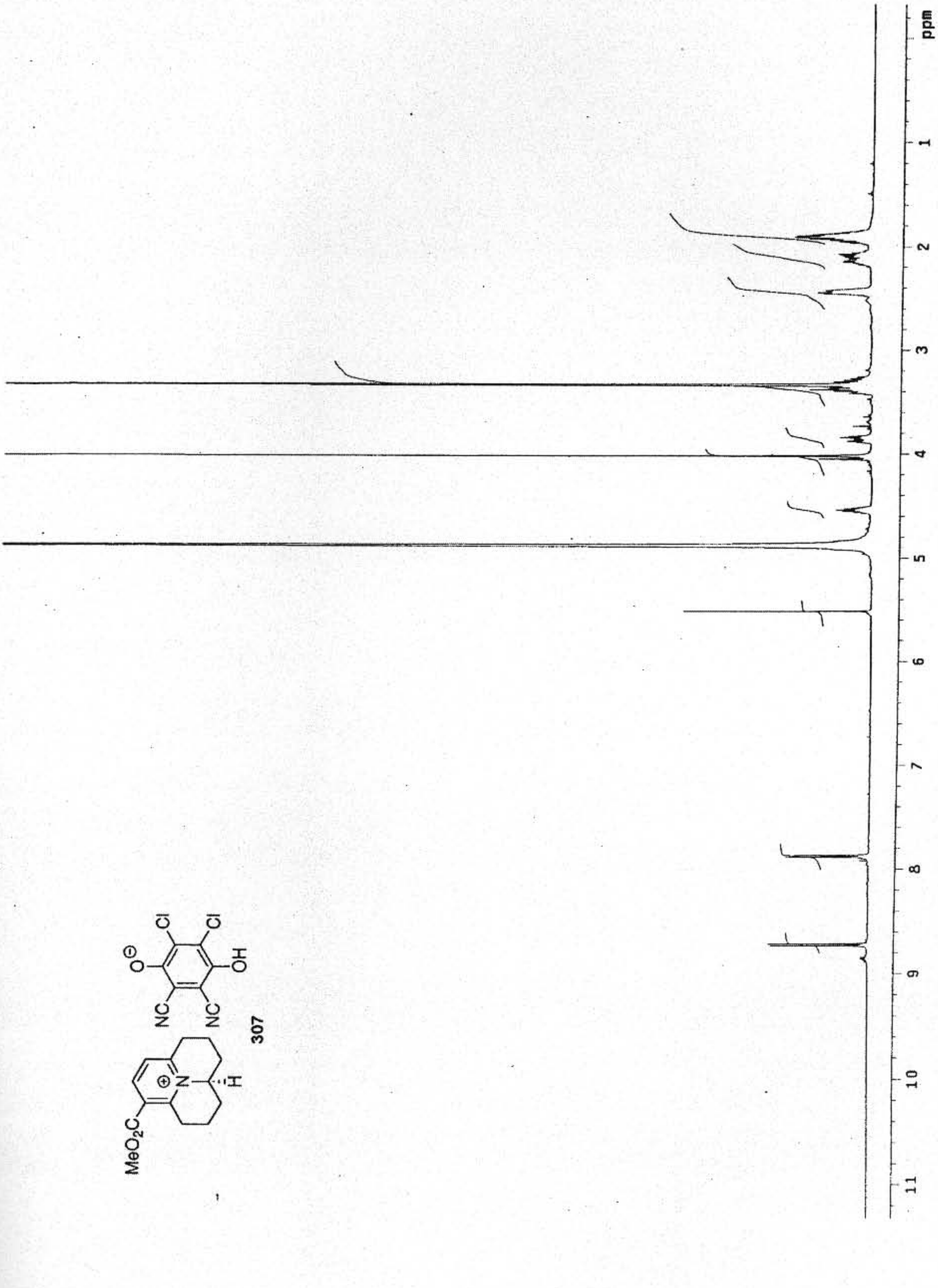


**165**: convergine

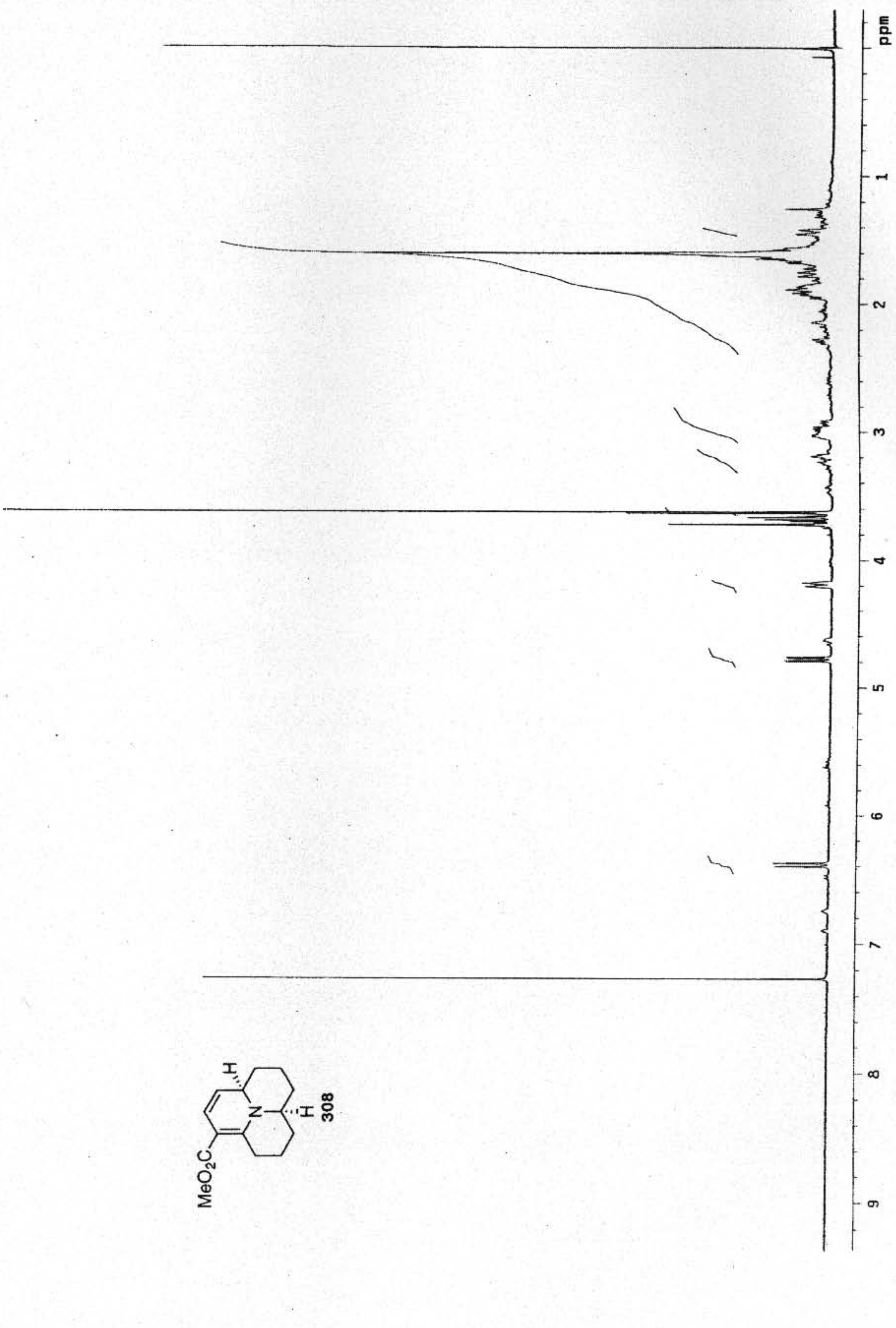


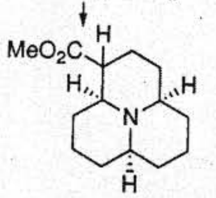
305


MeO2C
CPh3
H
N
H
306
ppm
12
11
10
9
8
7
6
5
4
3
2
1

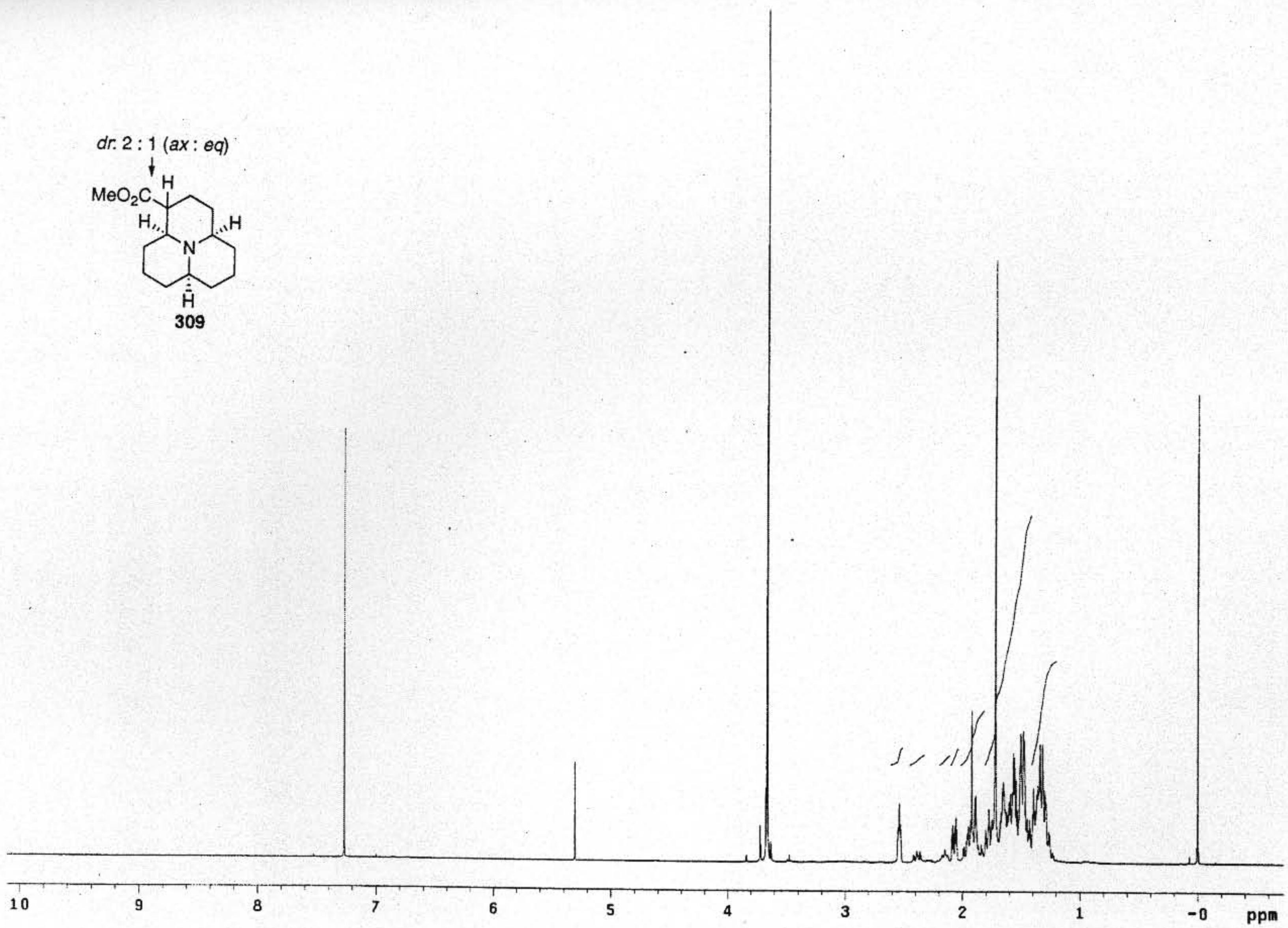


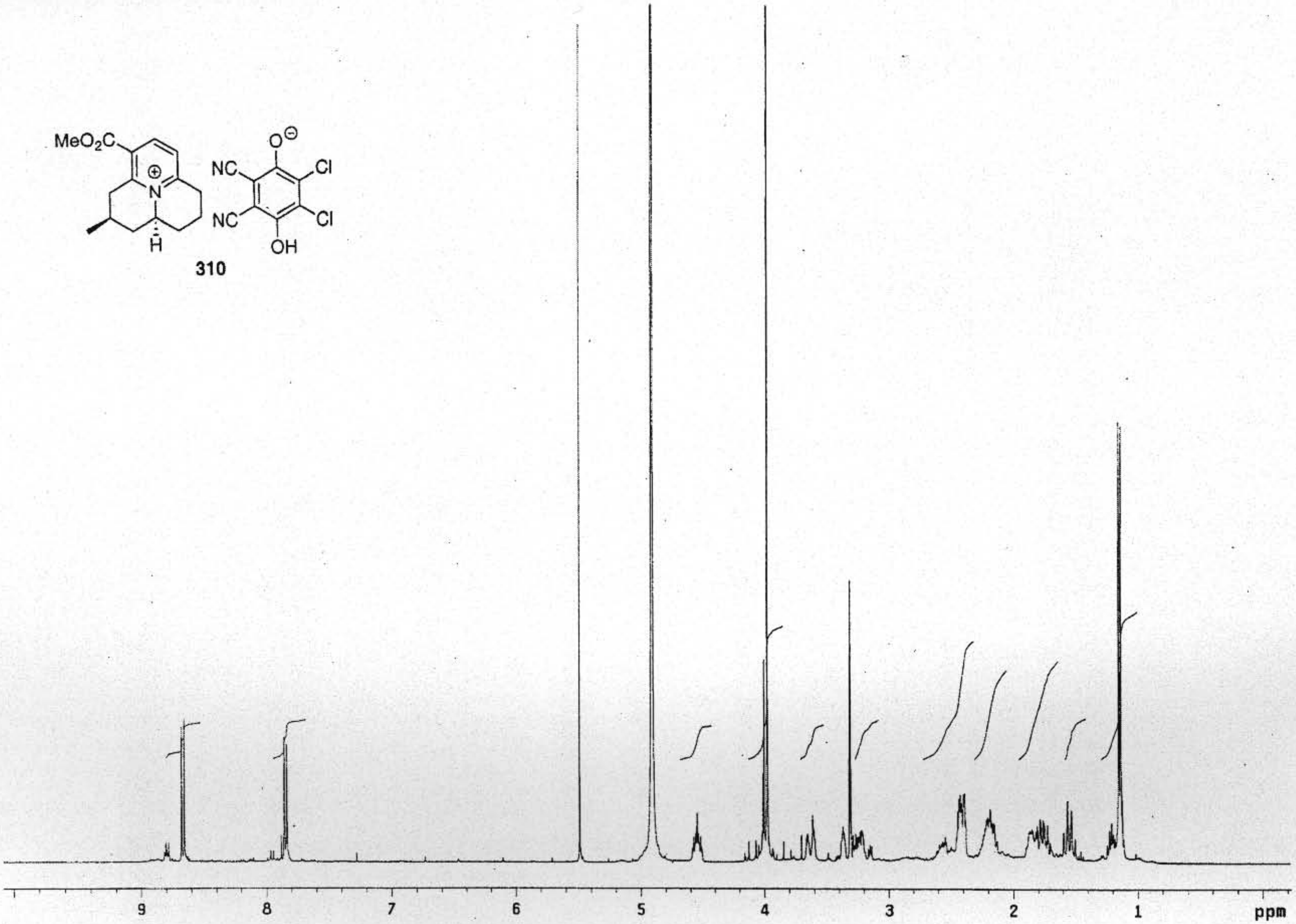
307

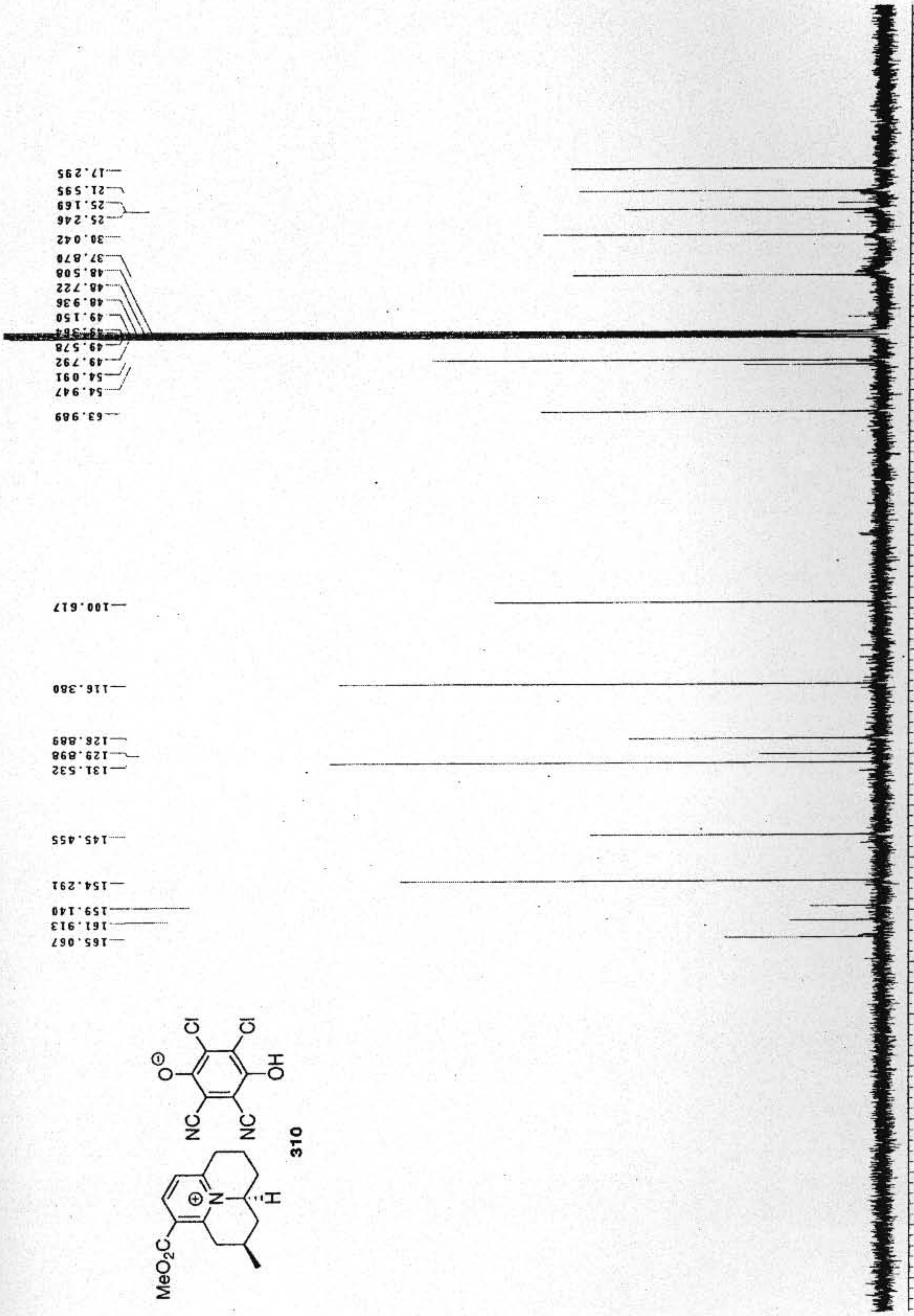

308



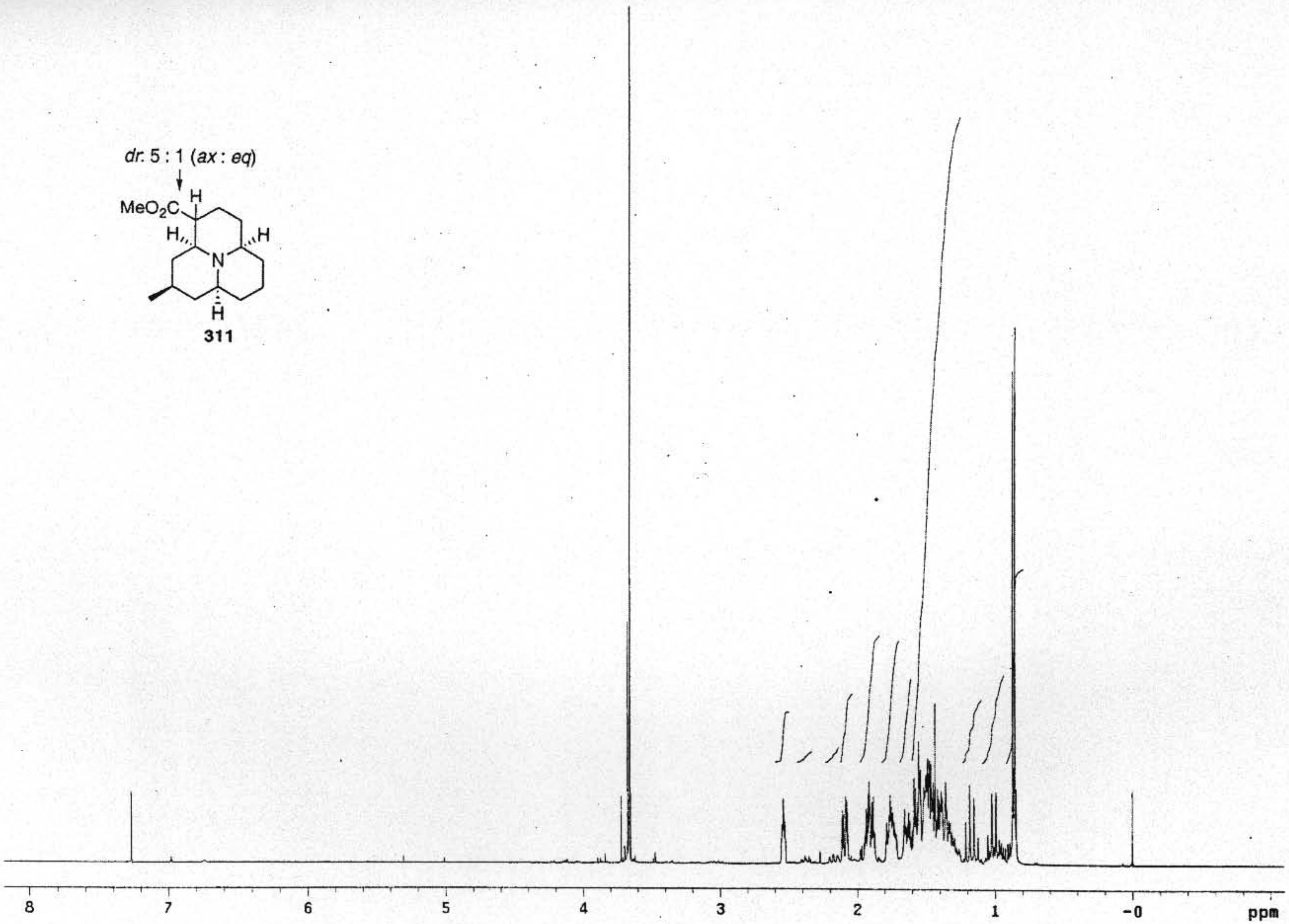
**309**




310


17.295
21.595
25.169
25.246
30.042
37.870
48.508
48.722
48.936
49.150
49.364
49.578
49.792
54.091
54.947
63.989
100.617
116.380
128.889
129.898
131.532
145.455
154.291
159.140
161.913
165.067
MeO2C
N
H
NC
NC
O
Cl
Cl
OH
ppm
0
20
40
60
80
100
120
140
160
180
200
220

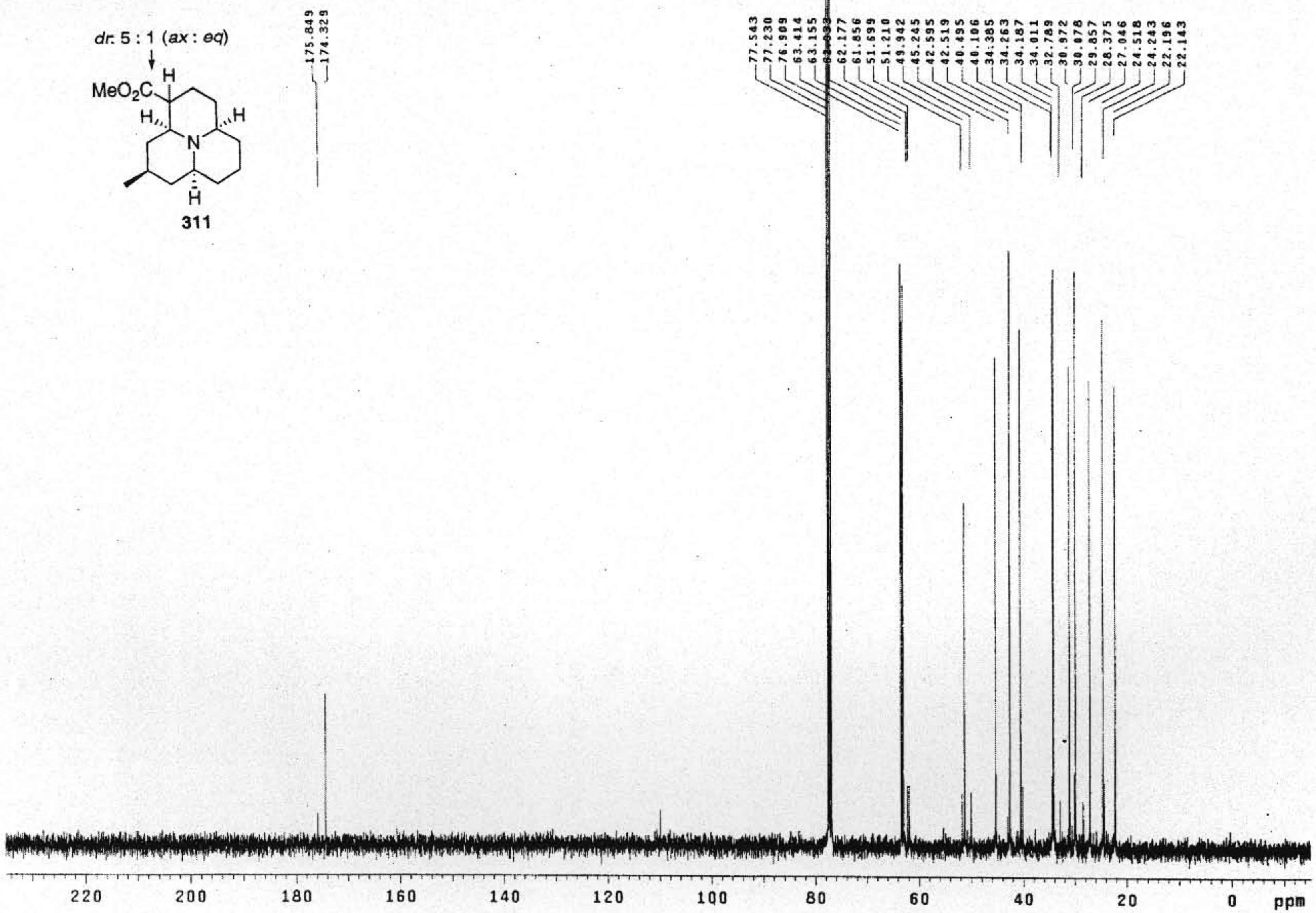
310

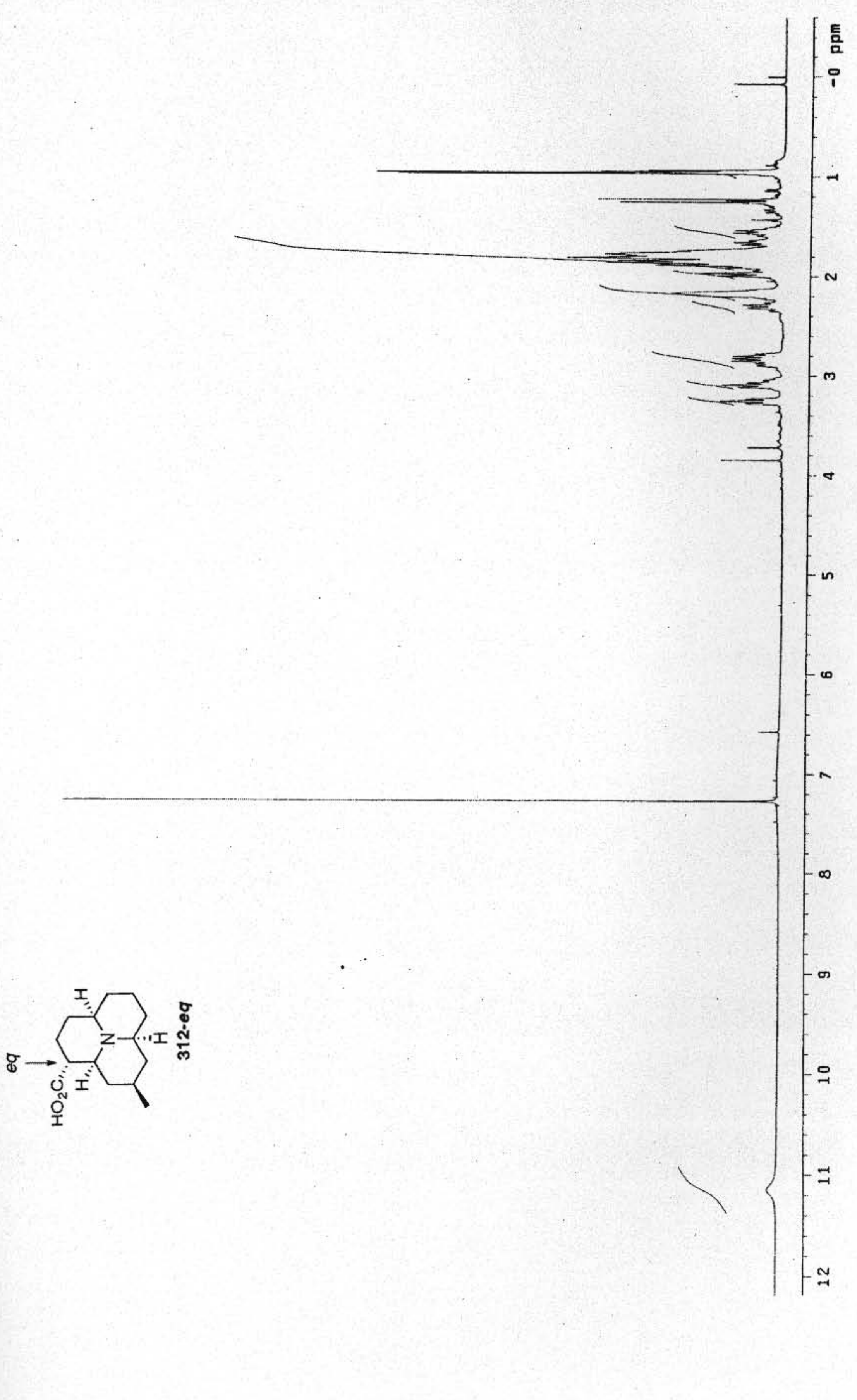


dr. 5 : 1 (ax : eq)
MeO2C
H
H
H
N
H
311
8
7
6
5
4
3
2
1
-0
ppm

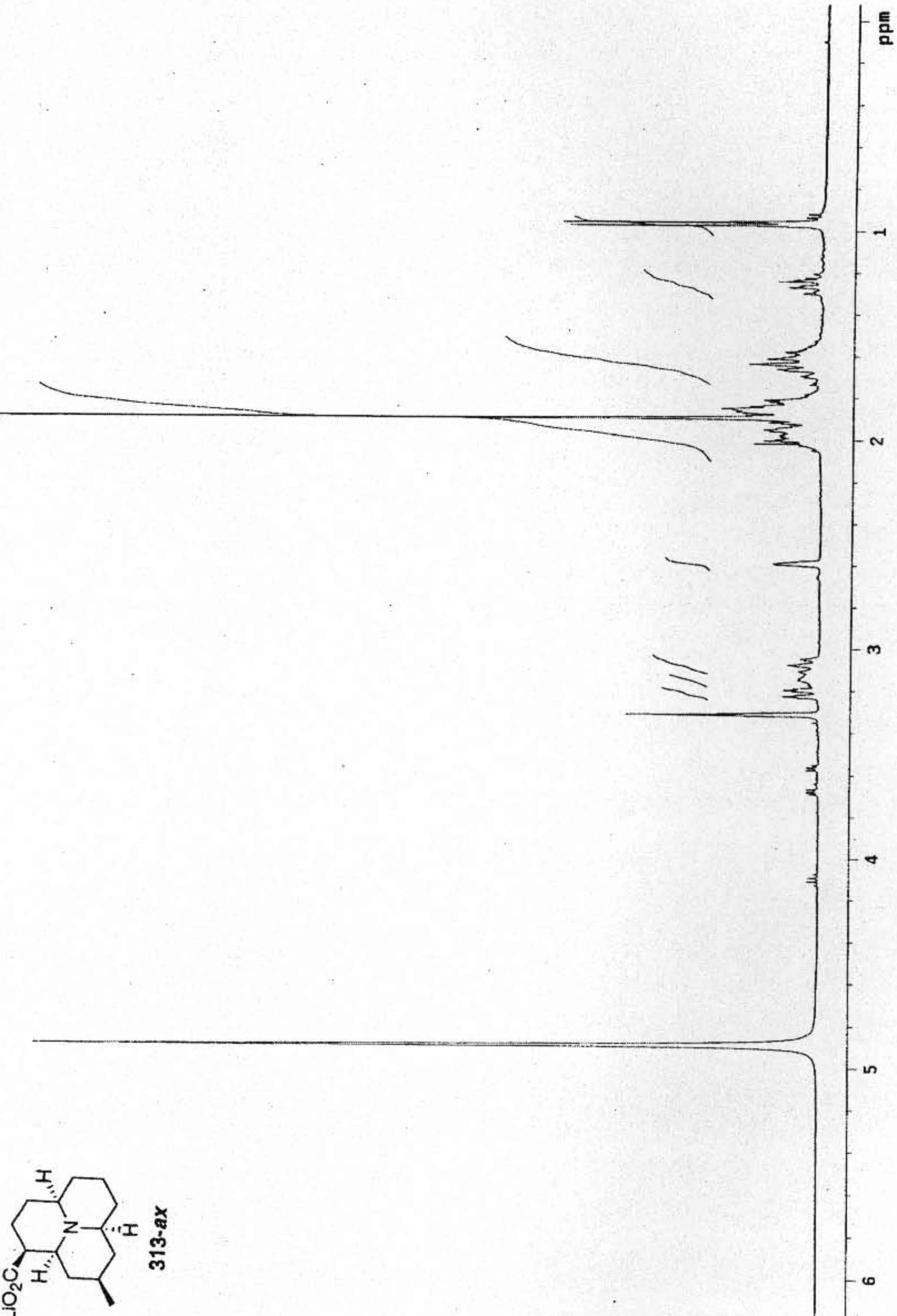
*dr.* 5 : 1 (*ax* : *eq*)

**311**

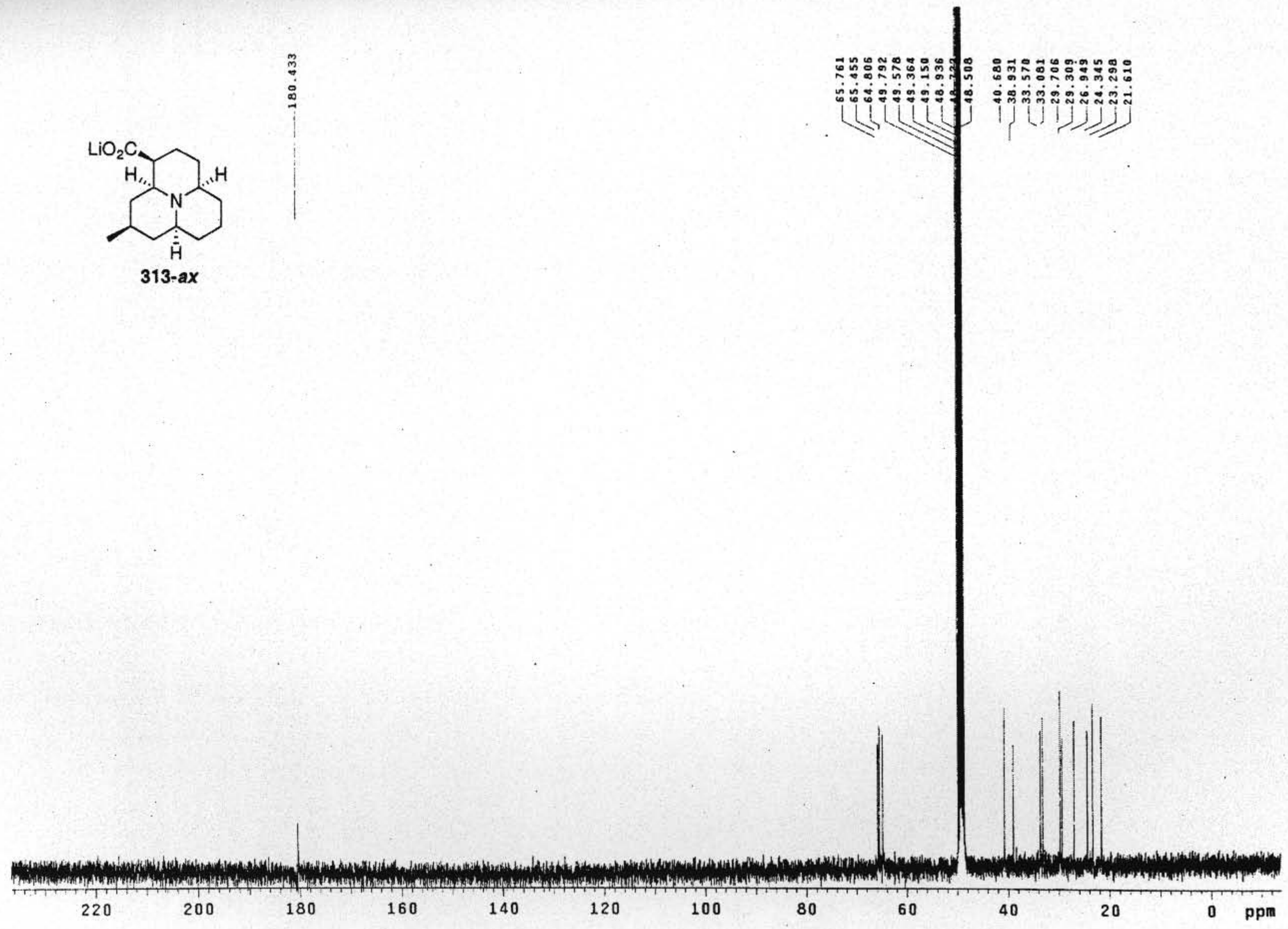




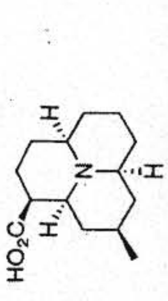
**312-eq**



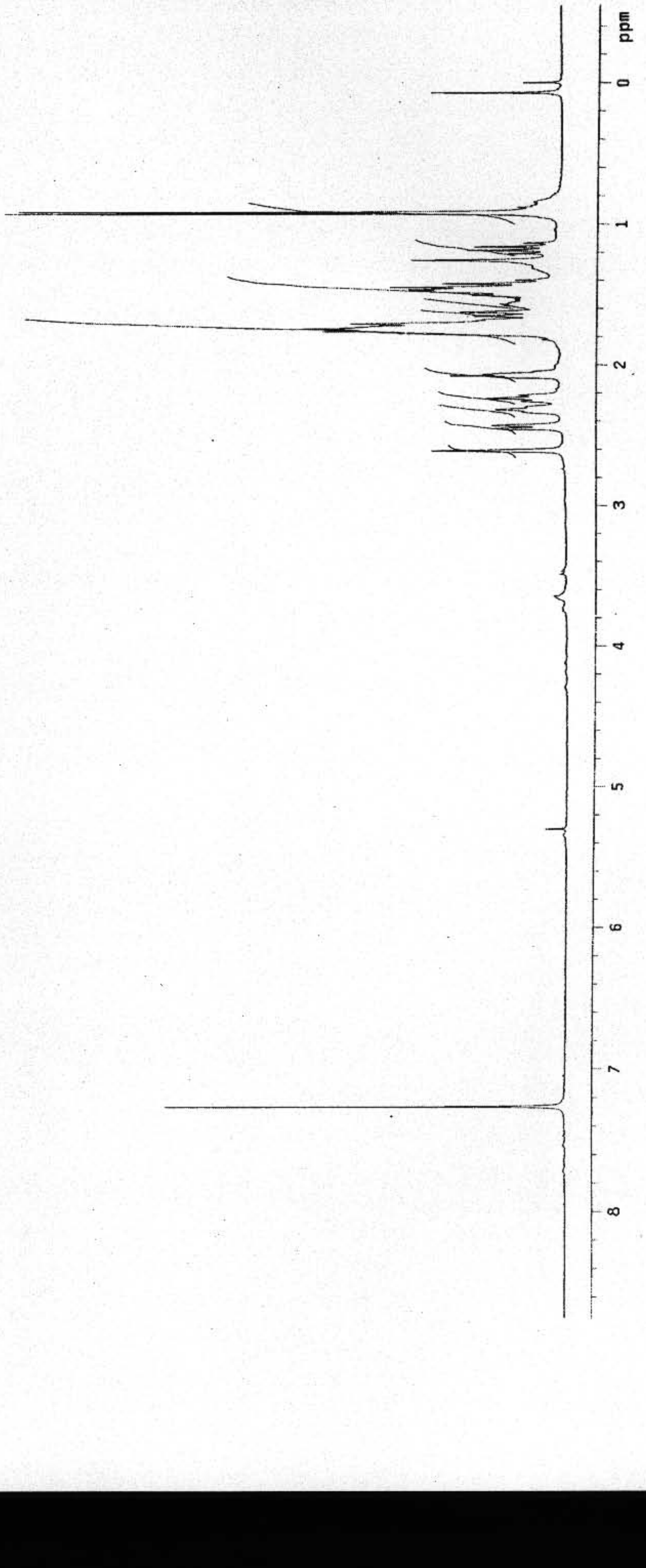
313-ax

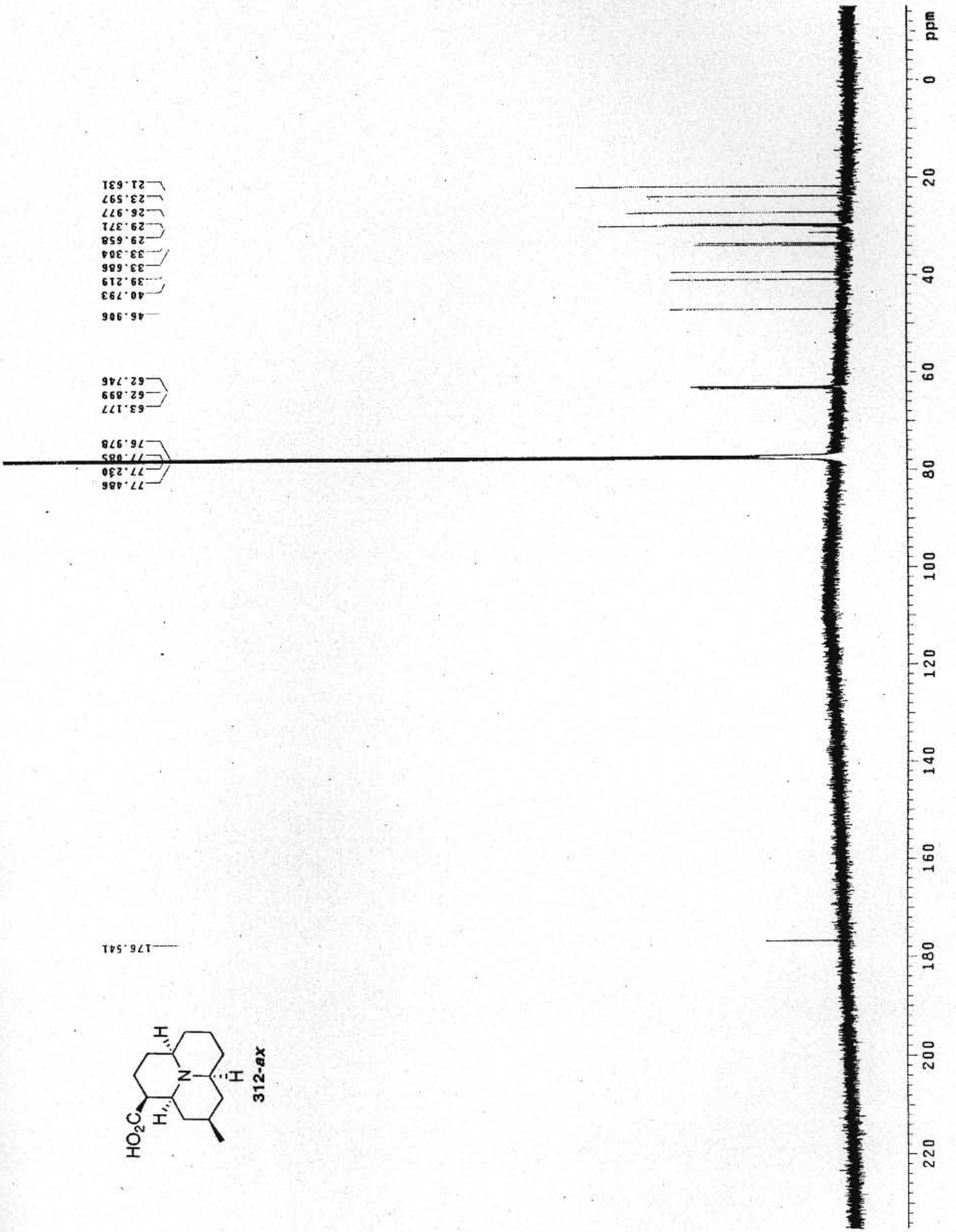

313-*ax*

LiO2C
H
N
H
H
180.433
65.761
65.455
64.806
49.792
49.578
49.364
49.150
48.936
48.722
48.508
40.680
38.931
33.570
33.081
29.706
29.309
26.949
24.345
23.298
21.610
220
200
180
160
140
120
100
80
60
40
20
0
ppm

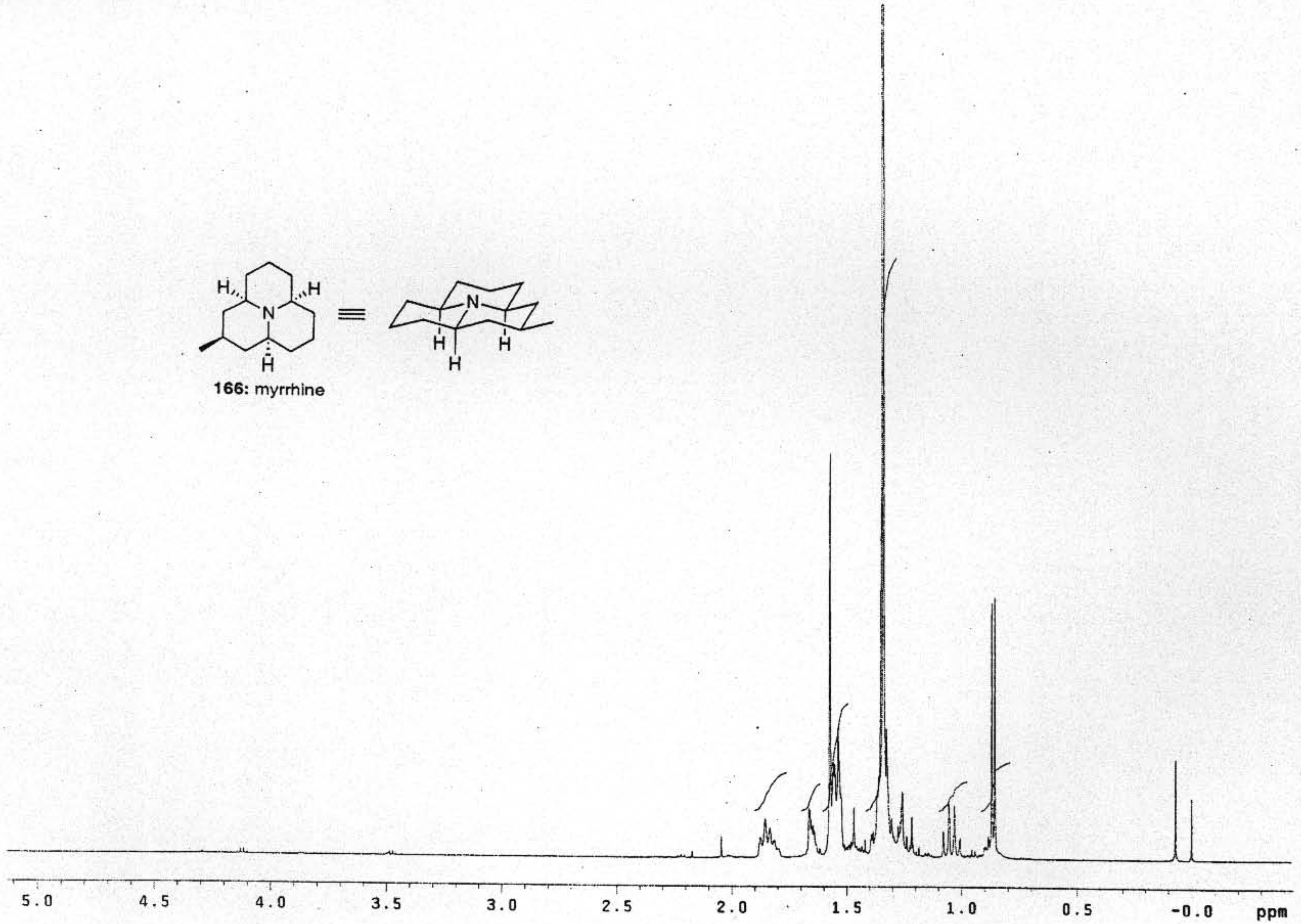


**312-ax**

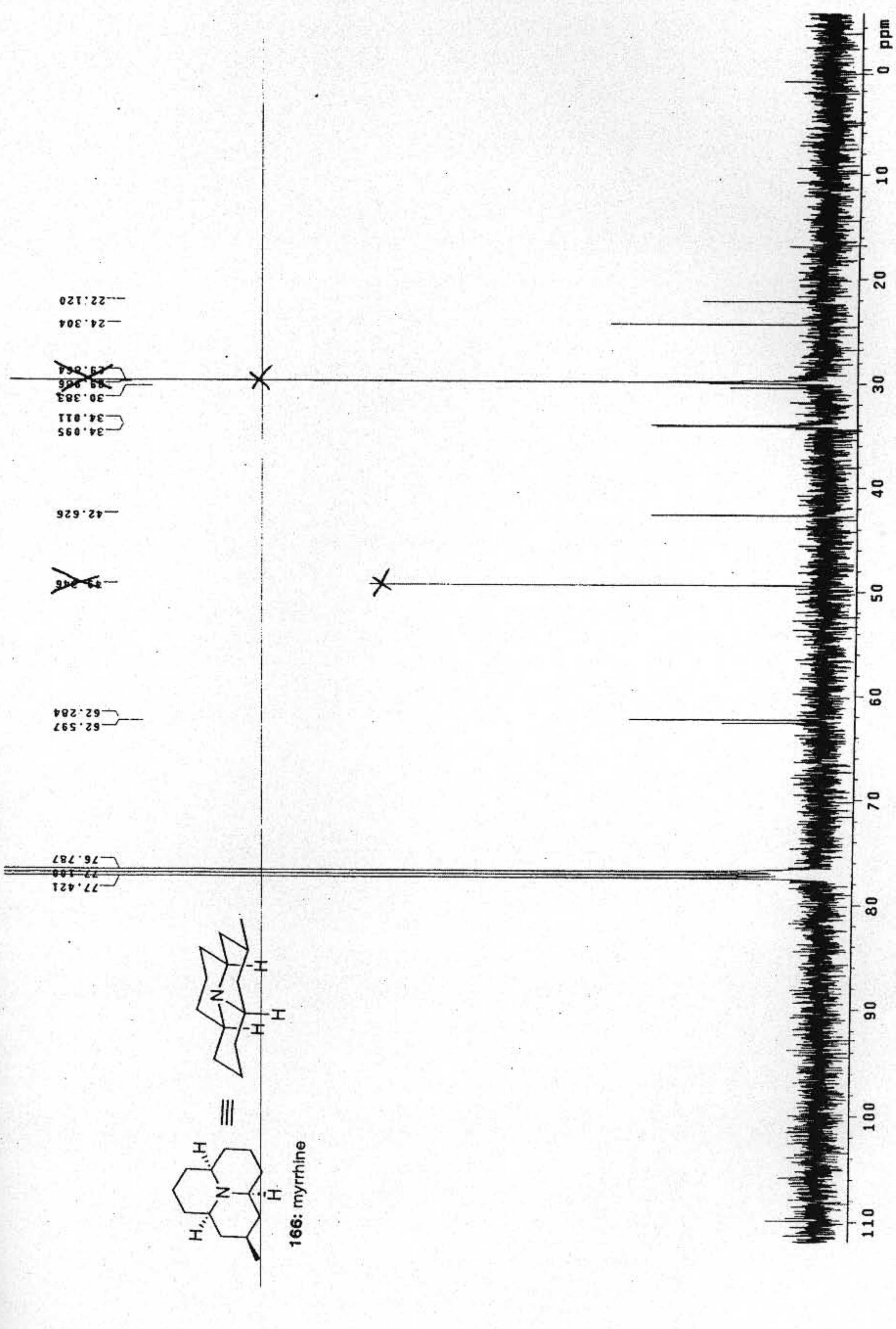



21.631
23.597
26.977
29.371
29.658
33.304
33.686
39.219
40.793
46.906
62.746
62.899
63.177
76.978
77.085
77.230
77.486
176.541
HO2C
H
H
N
H
ppm
0
20
40
60
80
100
120
140
160
180
200
220

312-ax

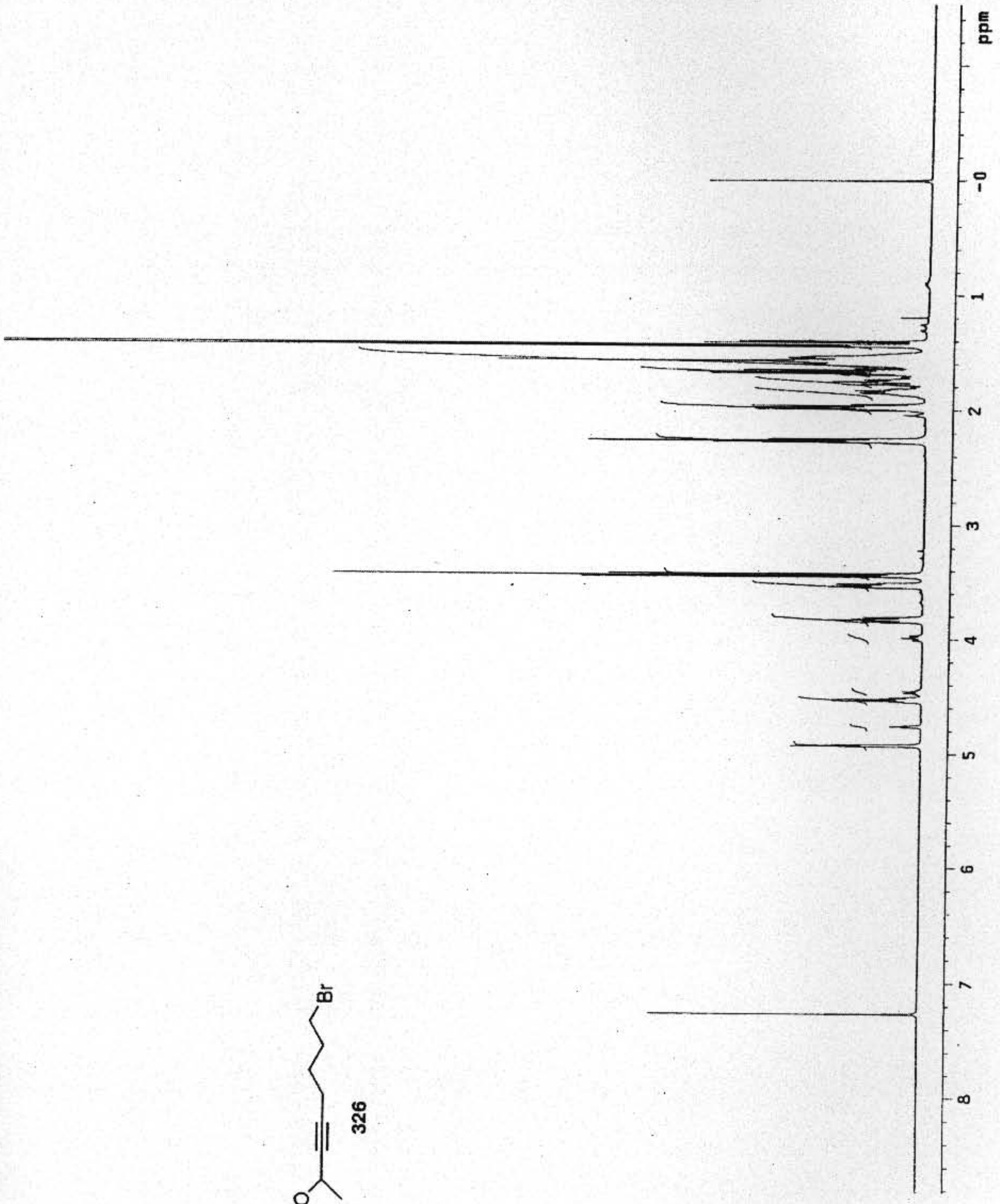


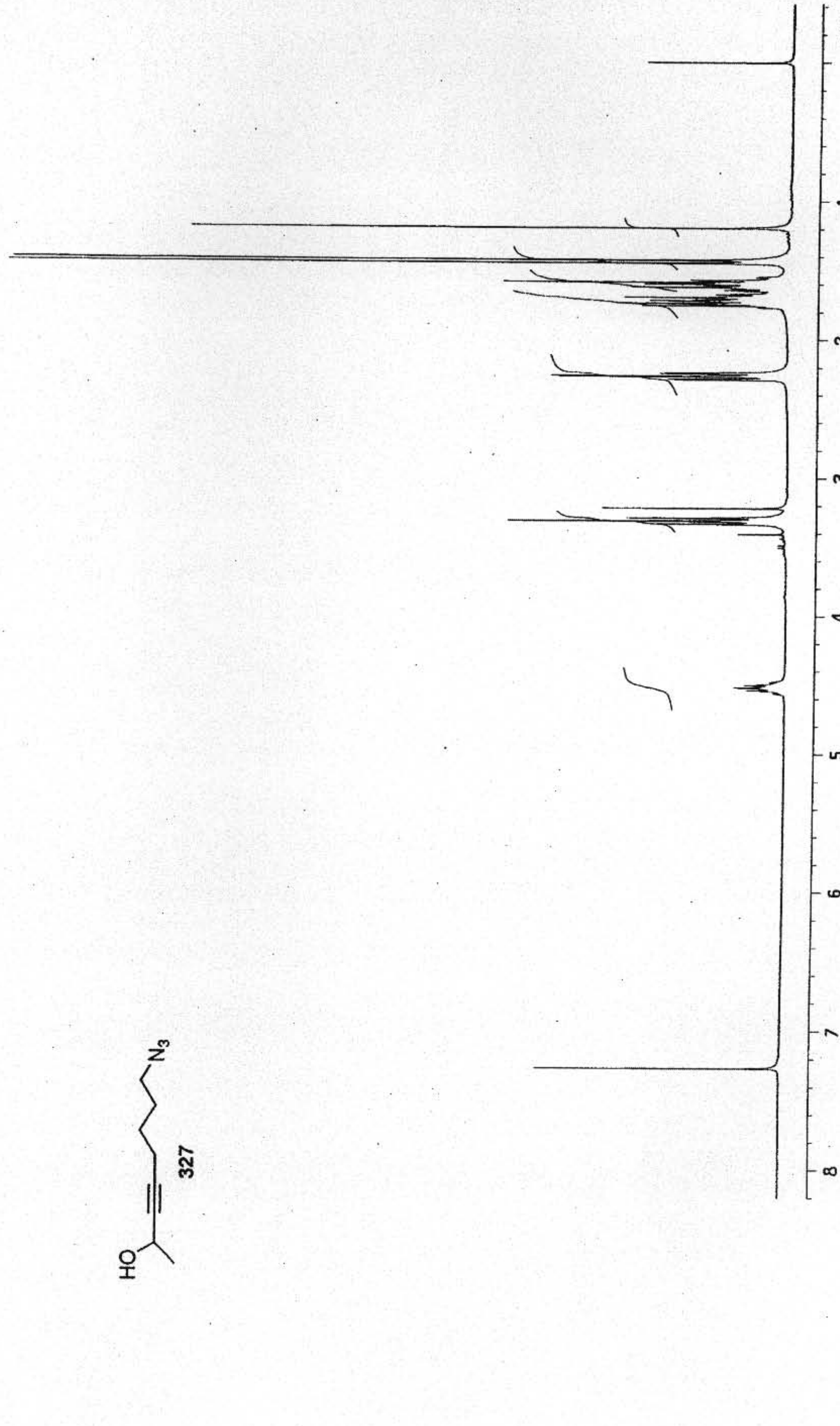
**166**: myrrhine



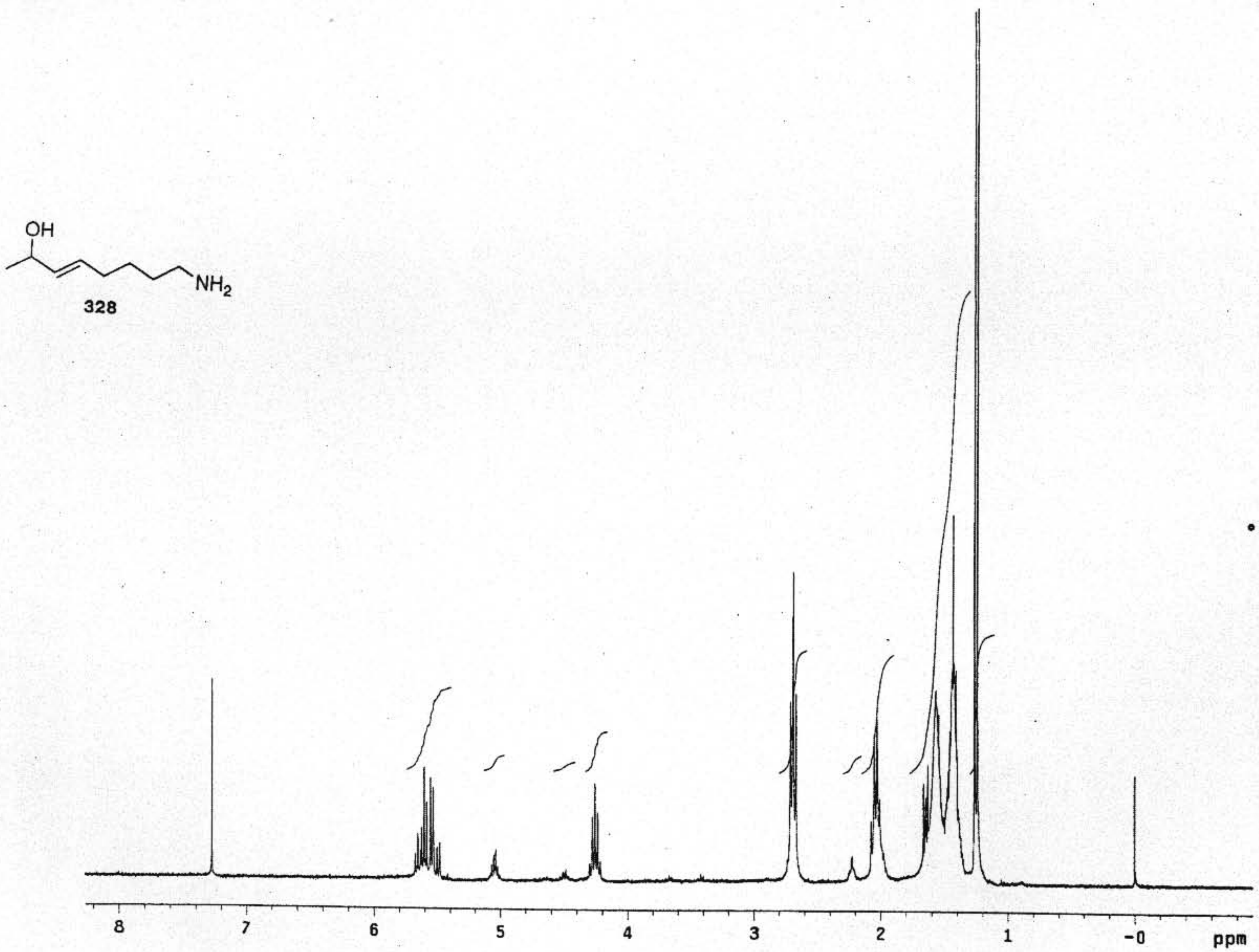
166: myrrhine

**326**

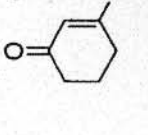




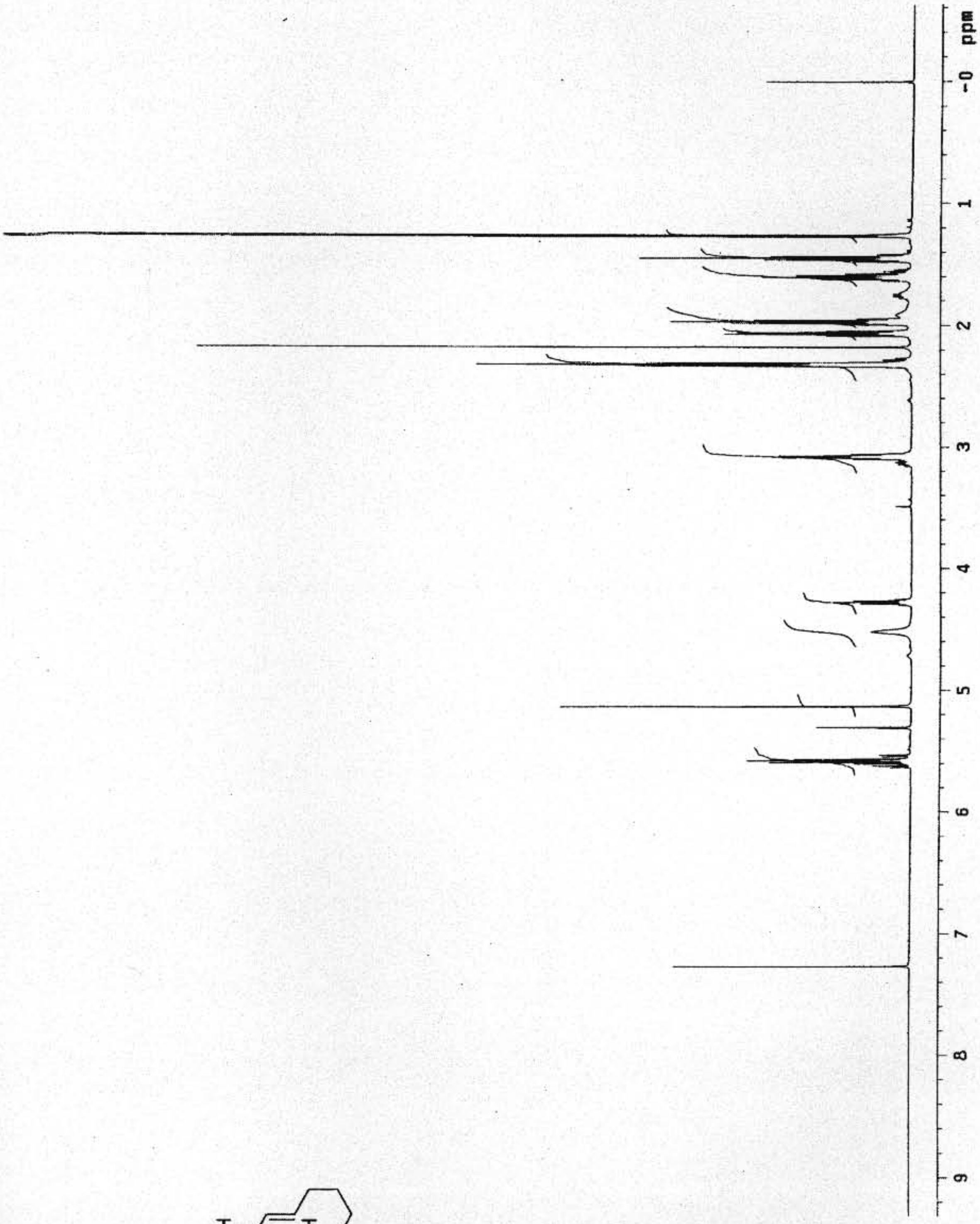
**327**

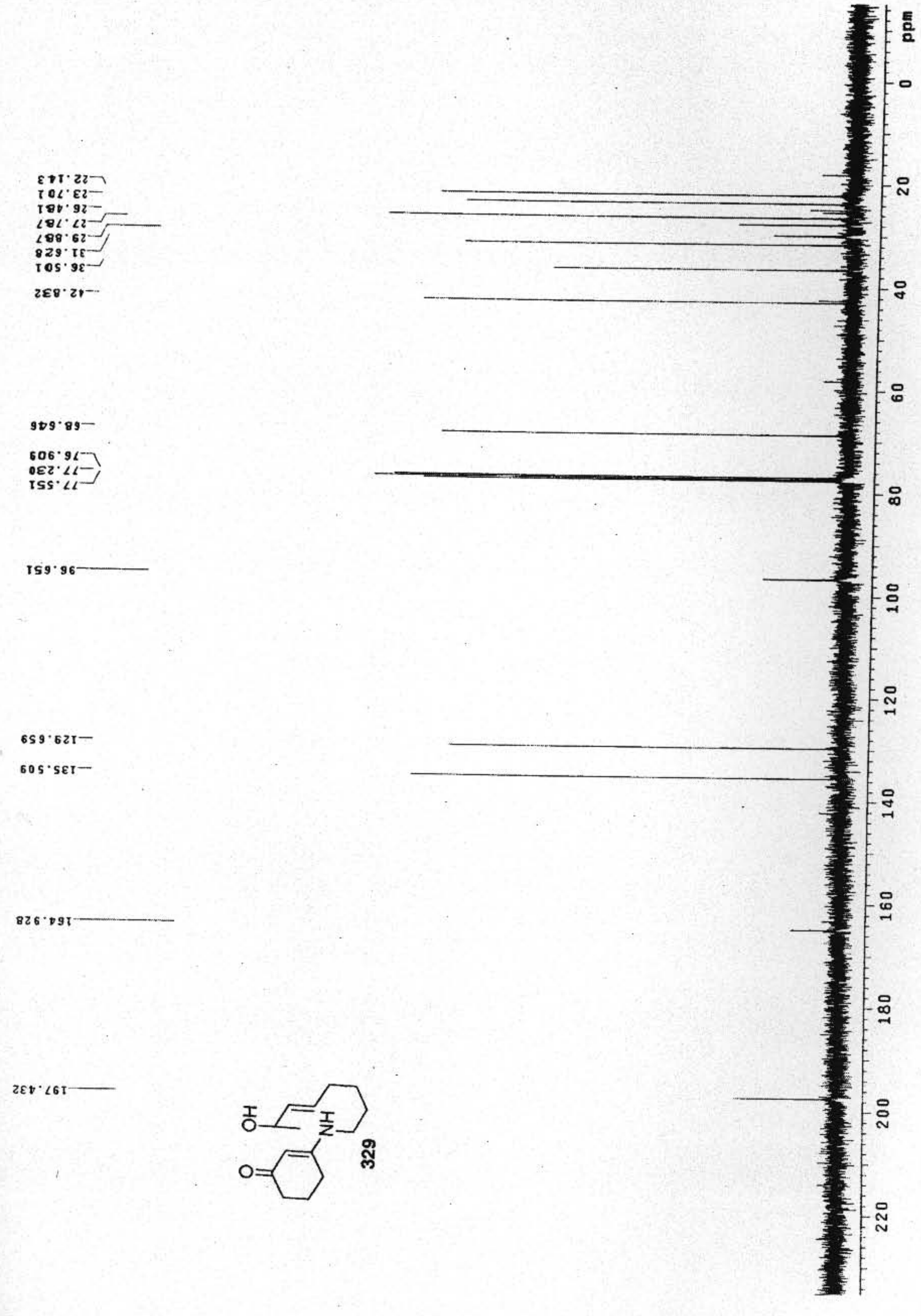


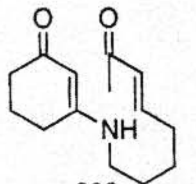
**328**



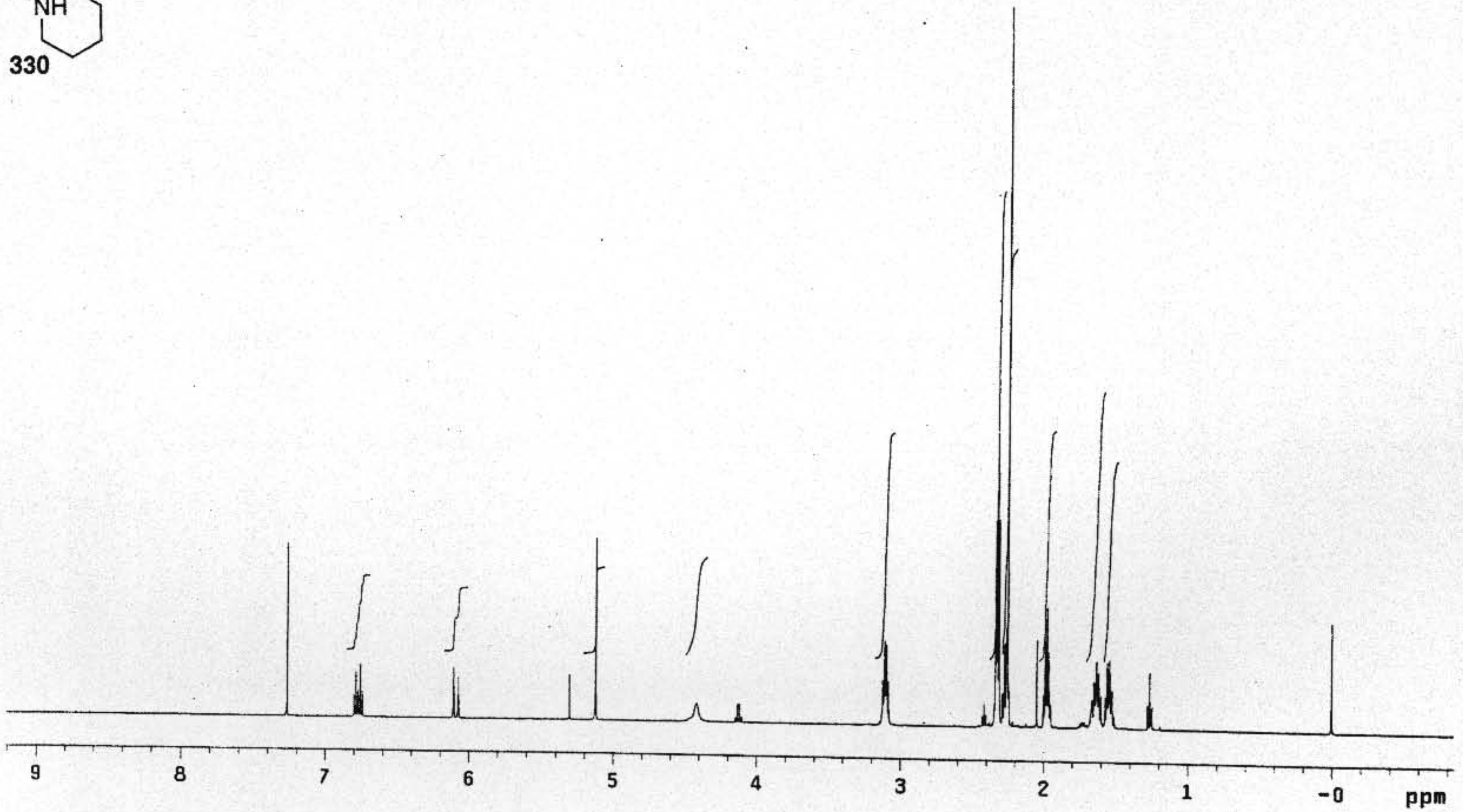
329

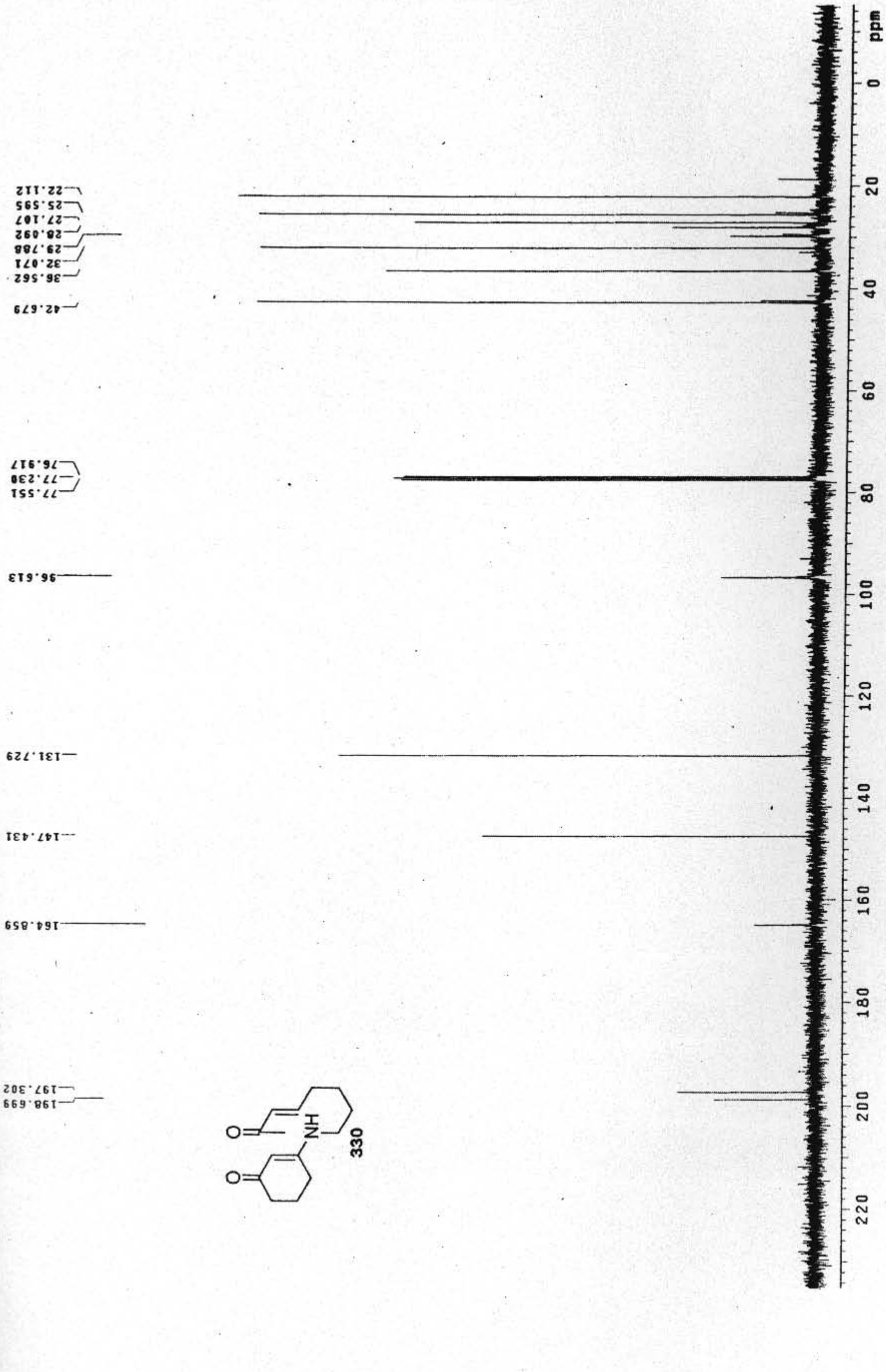



329
22.143
23.701
26.481
27.787
29.887
31.628
36.501
42.832
68.646
76.909
77.230
77.551
96.651
129.659
135.509
164.928
197.432
O
NH
OH
ppm
0
20
40
60
80
100
120
140
160
180
200
220



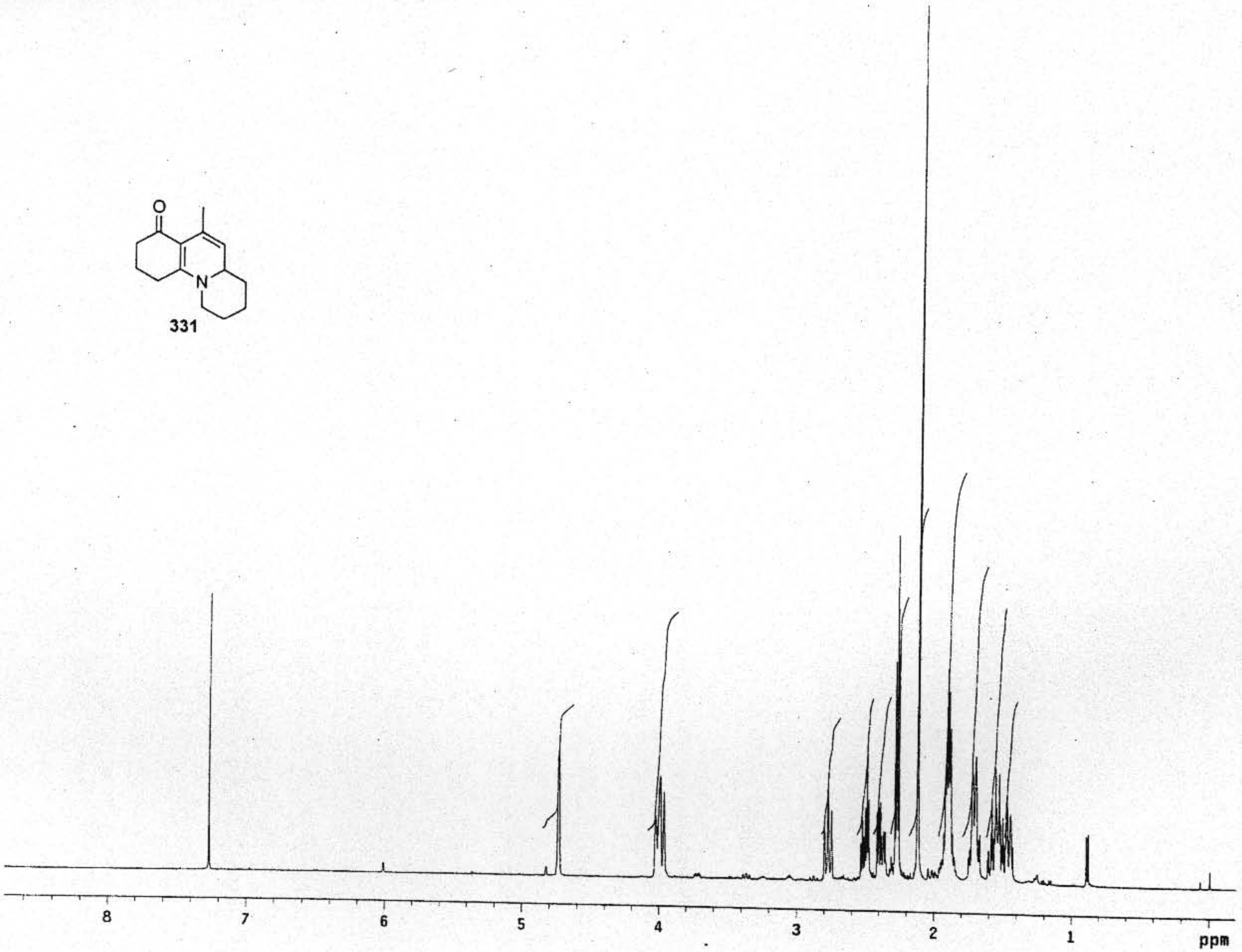
**330**



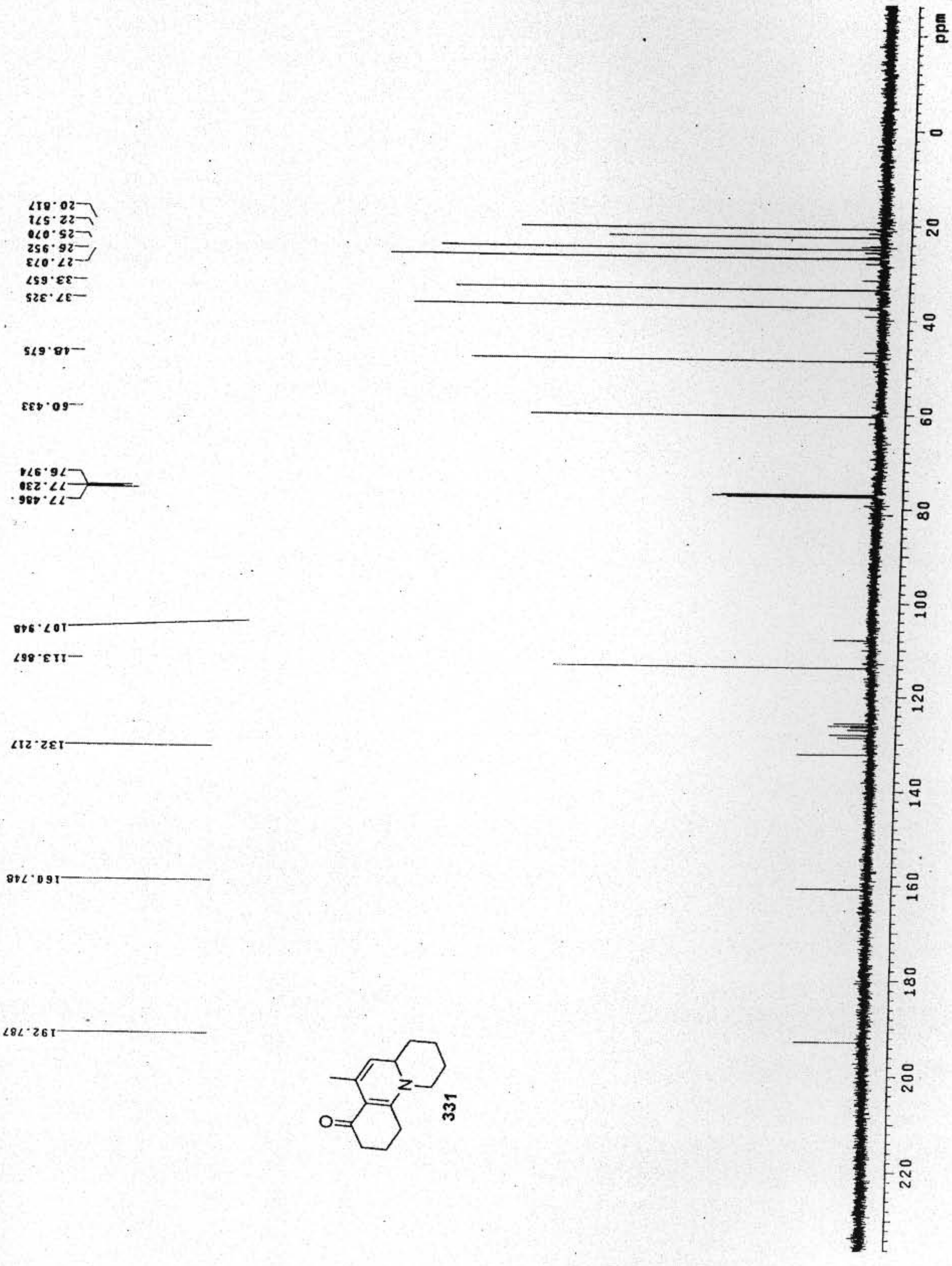


330

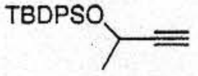
22.112
25.595
27.107
28.092
29.788
32.071
36.562
42.679
76.917
77.230
77.551
96.613
131.729
147.431
164.859
197.302
198.699
NH
O
O
ppm
0
20
40
60
80
100
120
140
160
180
200
220



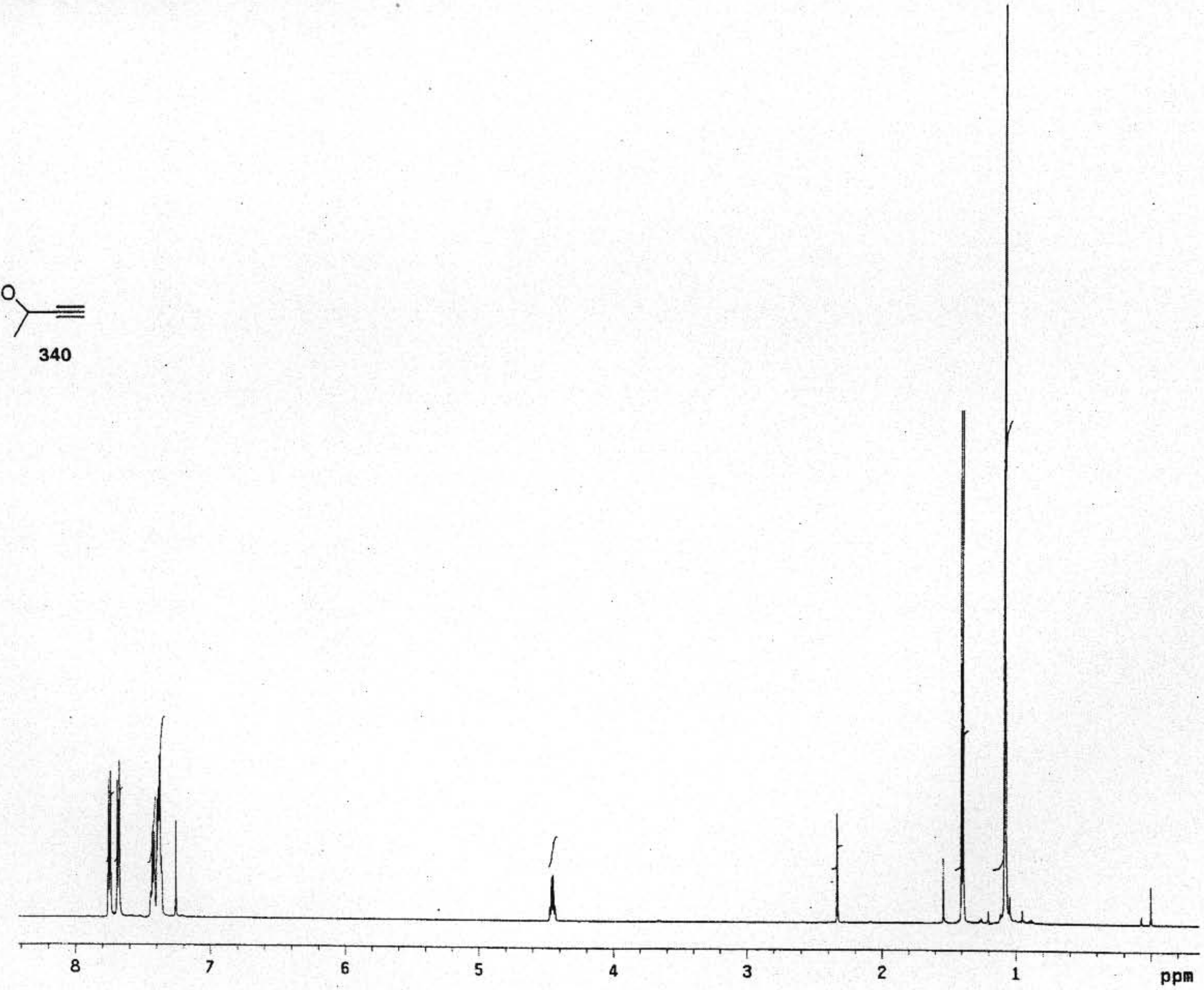
331

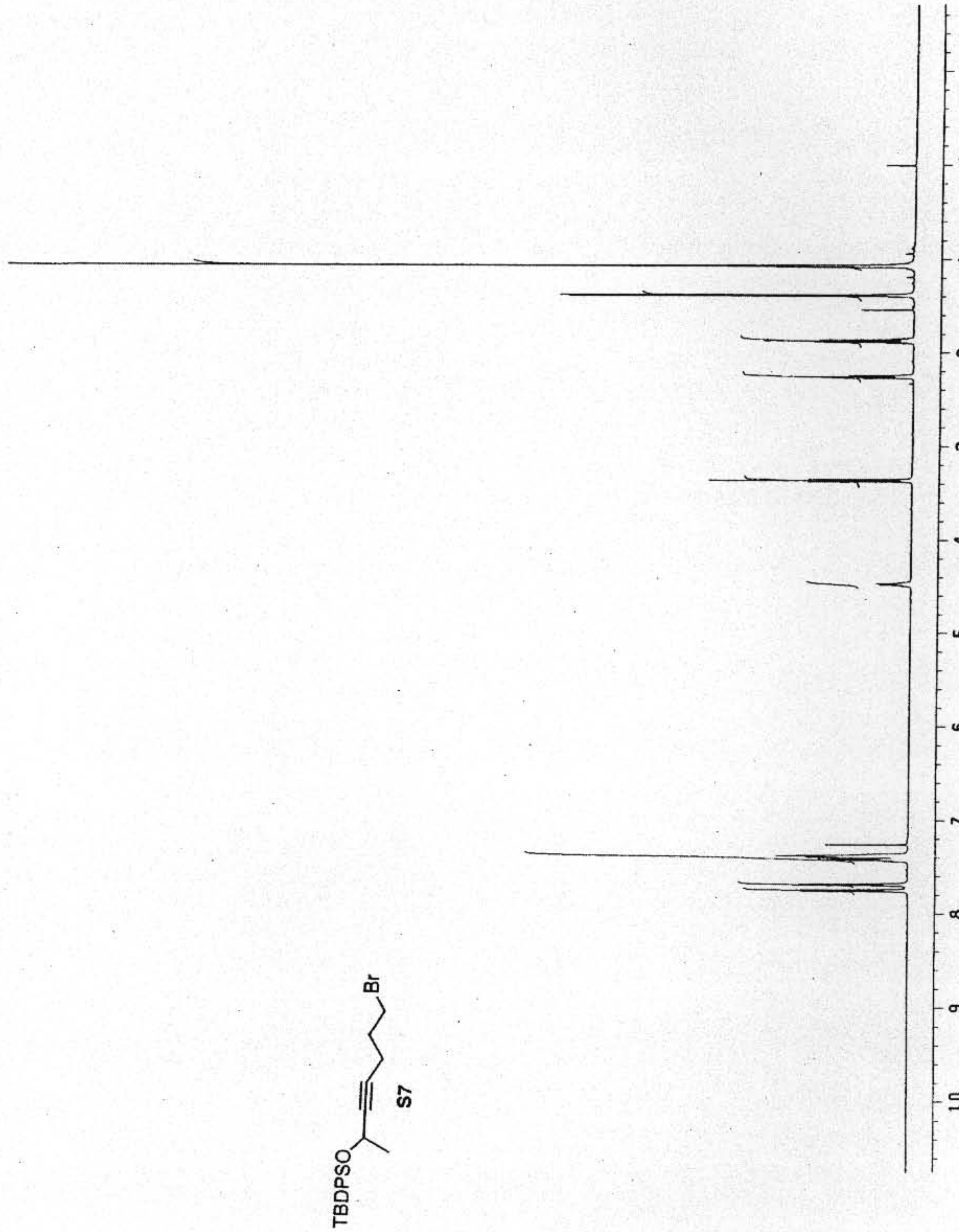

20.817
22.571
25.070
26.952
27.073
33.657
37.325
48.675
60.433
76.974
77.230
77.486
107.948
113.867
132.217
160.748
192.787
ppm
0
20
40
60
80
100
120
140
160
180
200
220
O
N

331

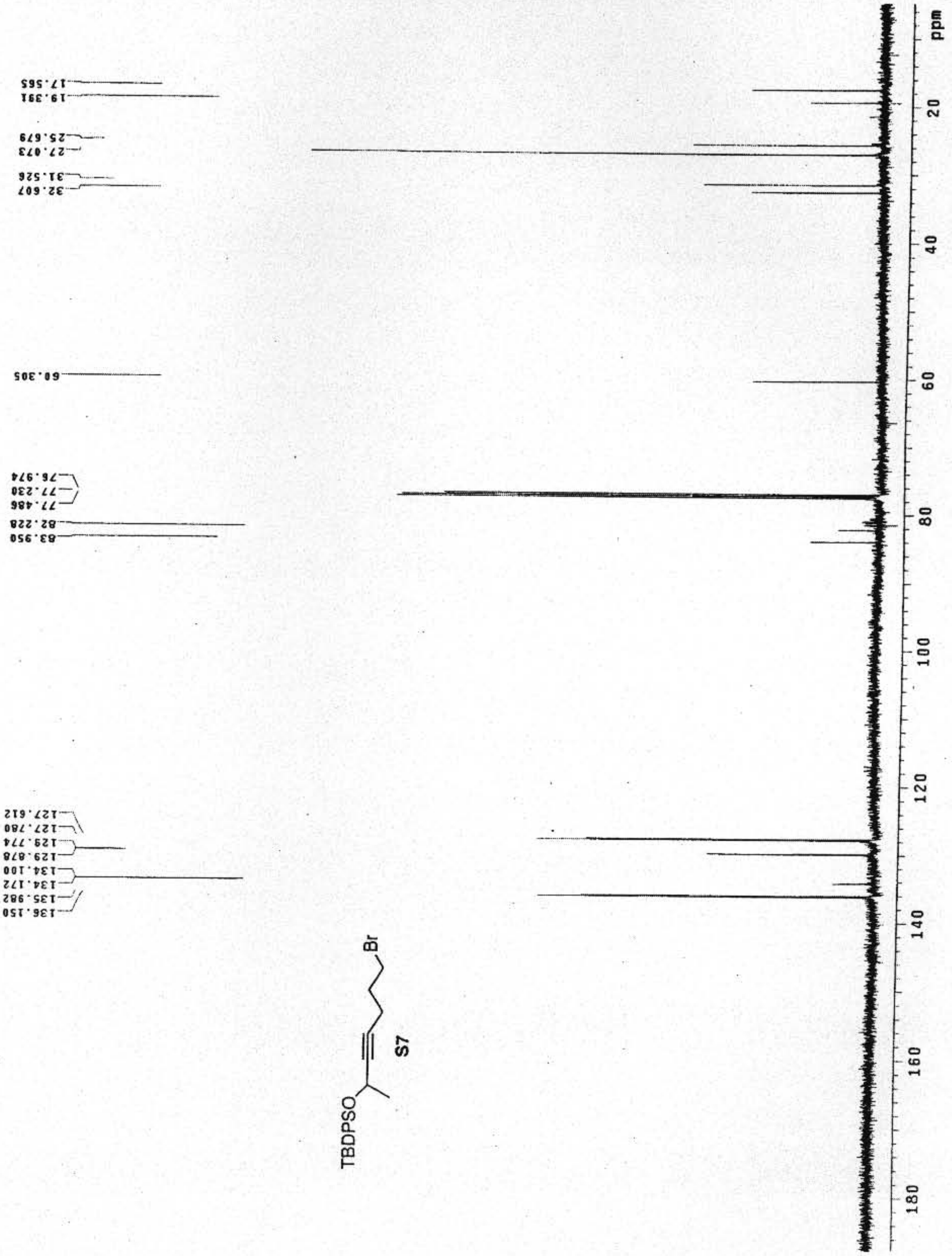


**340**

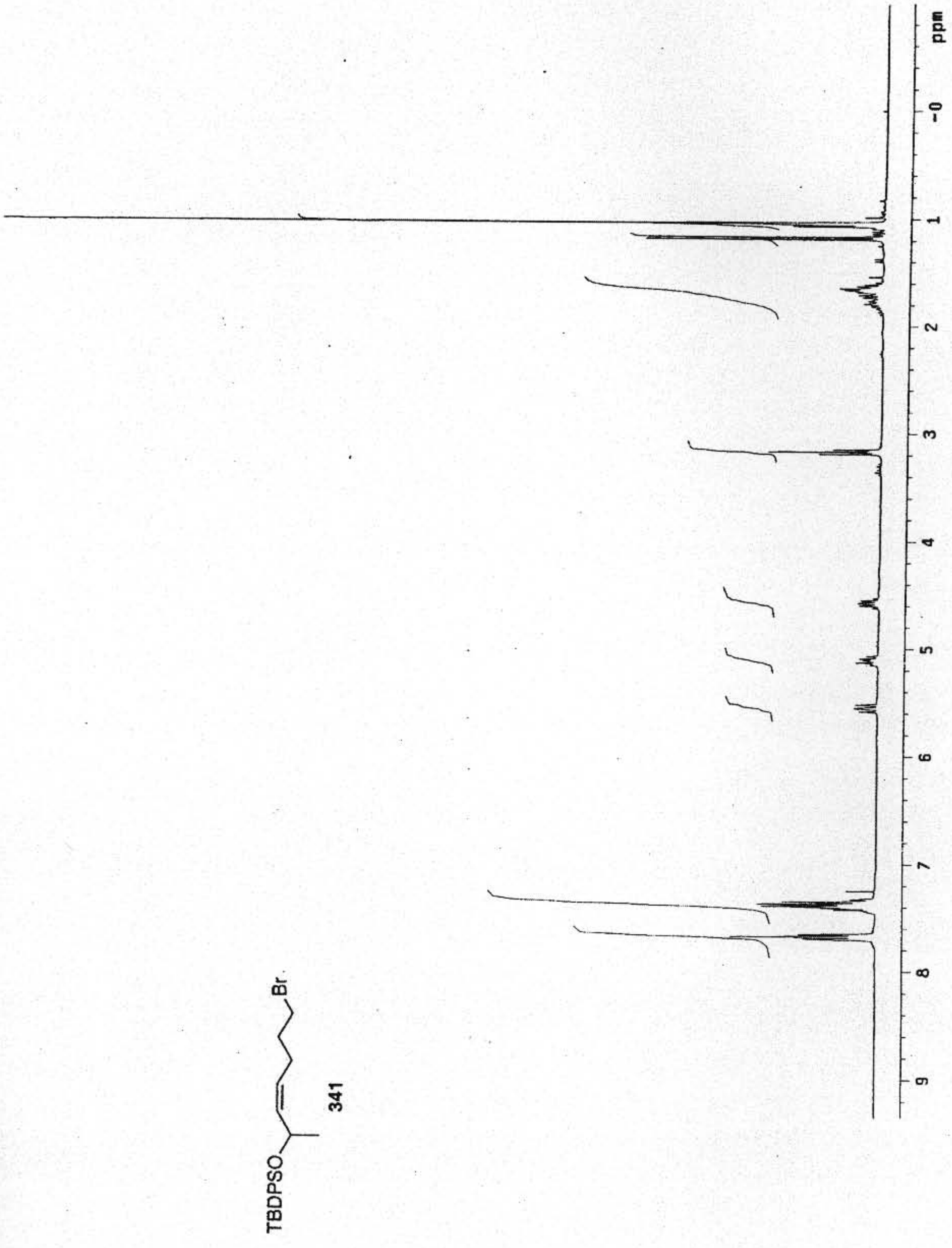




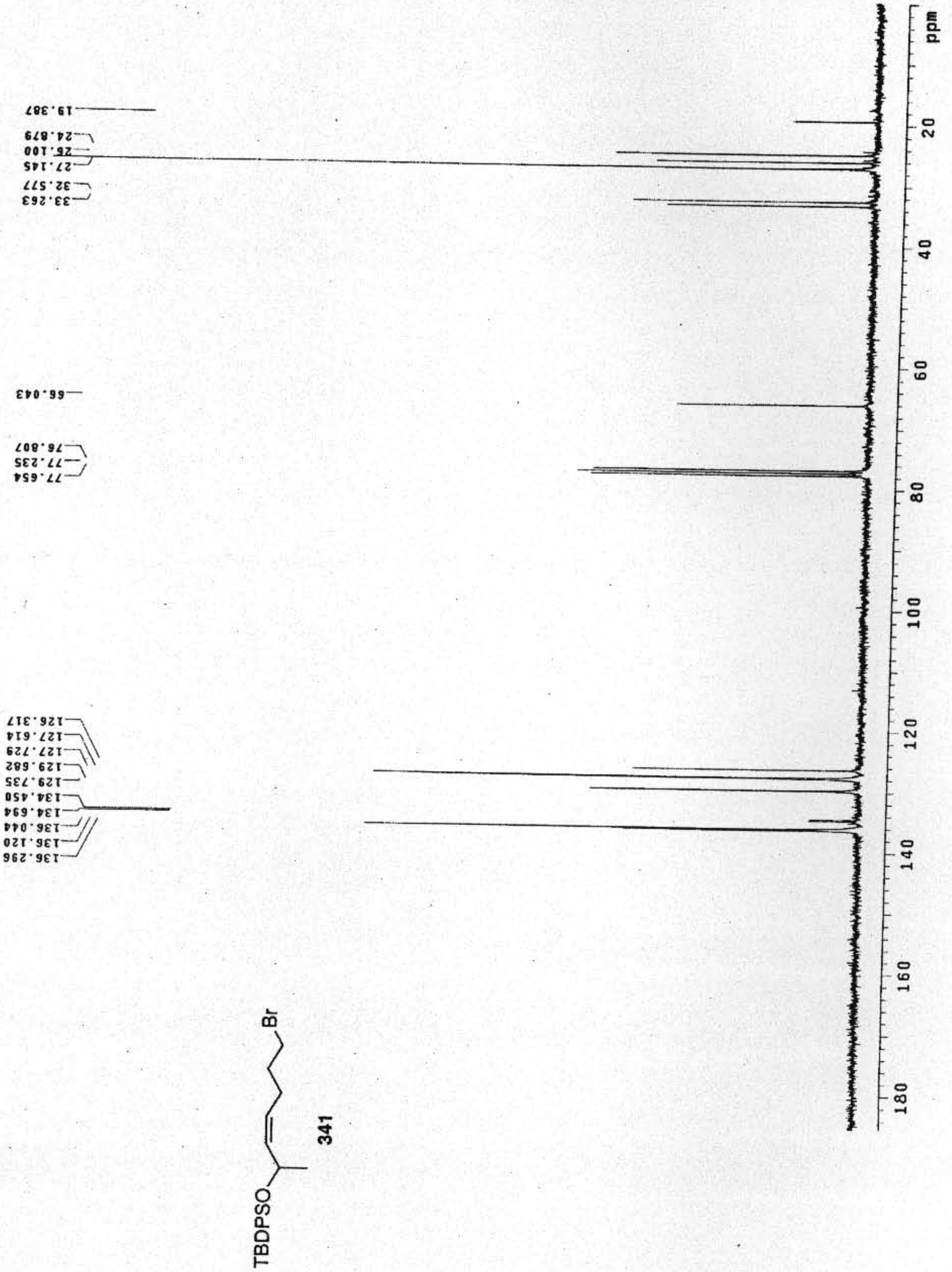
S7


17.565
19.391
25.679
27.073
31.526
32.607
60.305
76.974
77.230
77.486
82.228
83.950
127.612
127.780
129.774
129.878
134.100
134.172
135.982
136.150
TBDPSO
Br
ppm
20
40
60
80
100
120
140
160
180

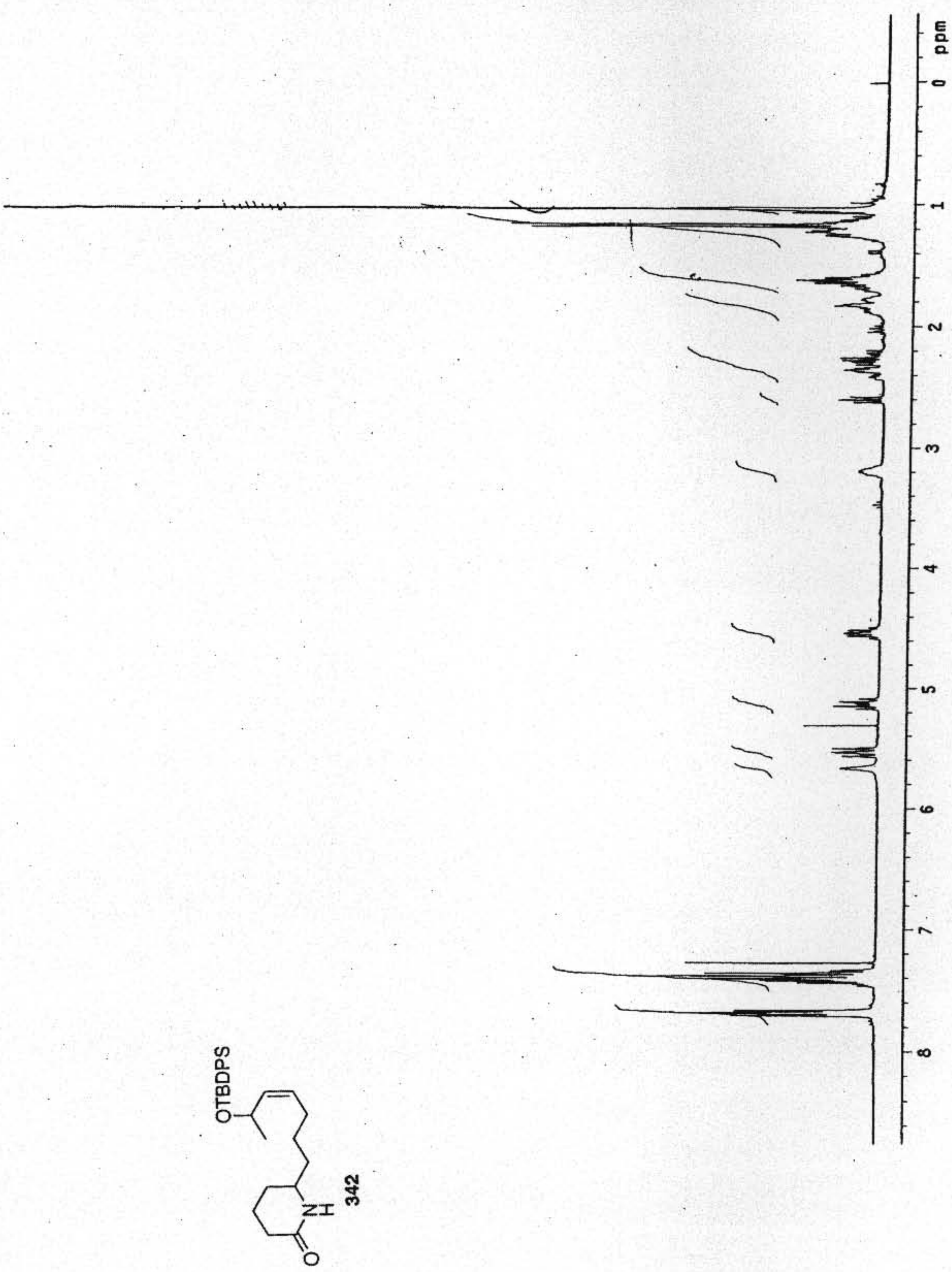
S7



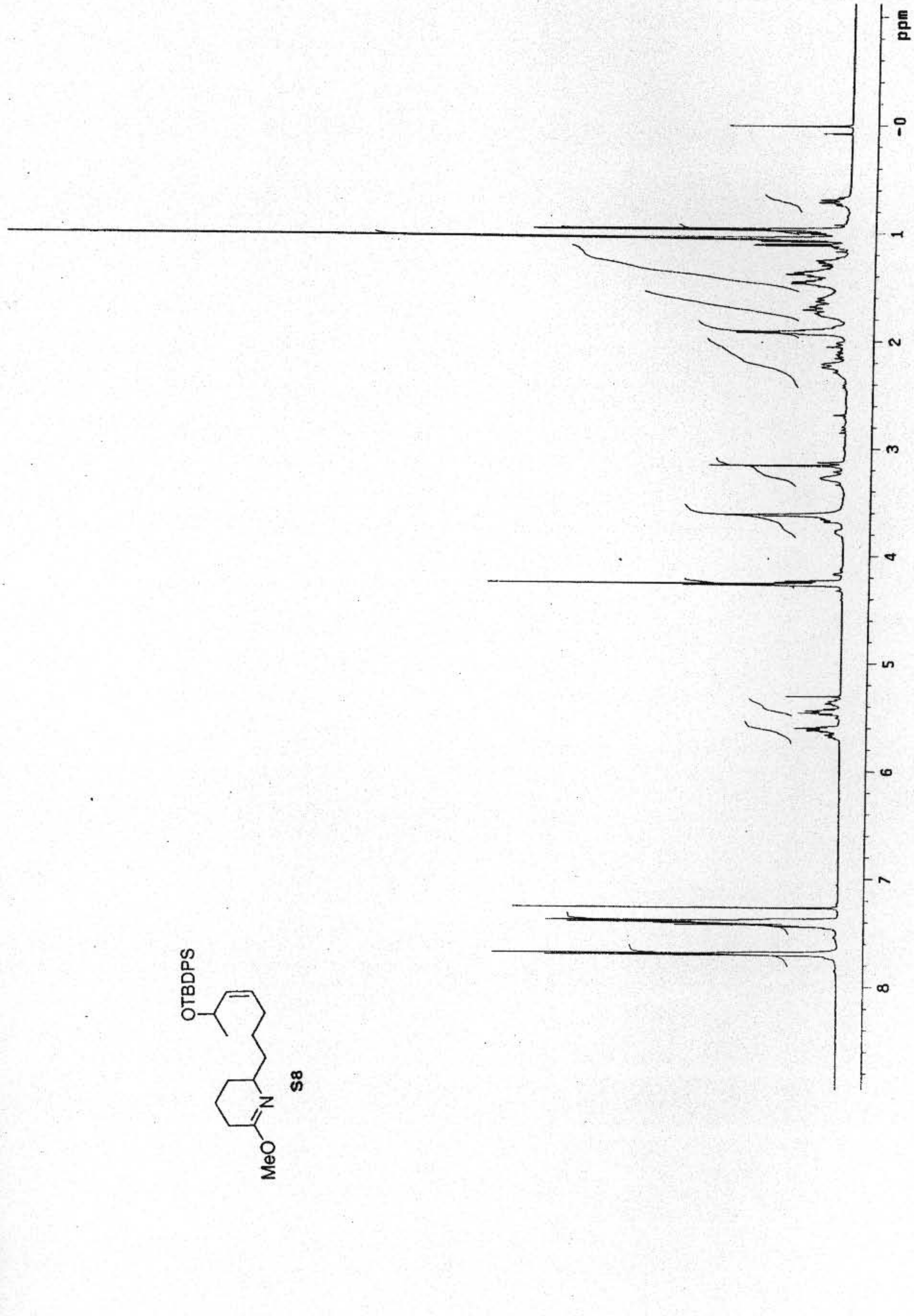
341


19.387
24.879
26.100
27.145
32.577
33.263
66.043
76.807
77.235
77.654
126.317
127.614
127.729
129.682
129.735
134.450
134.694
136.044
136.120
136.296
ppm
20
40
60
80
100
120
140
160
180
TBDPSO
Br

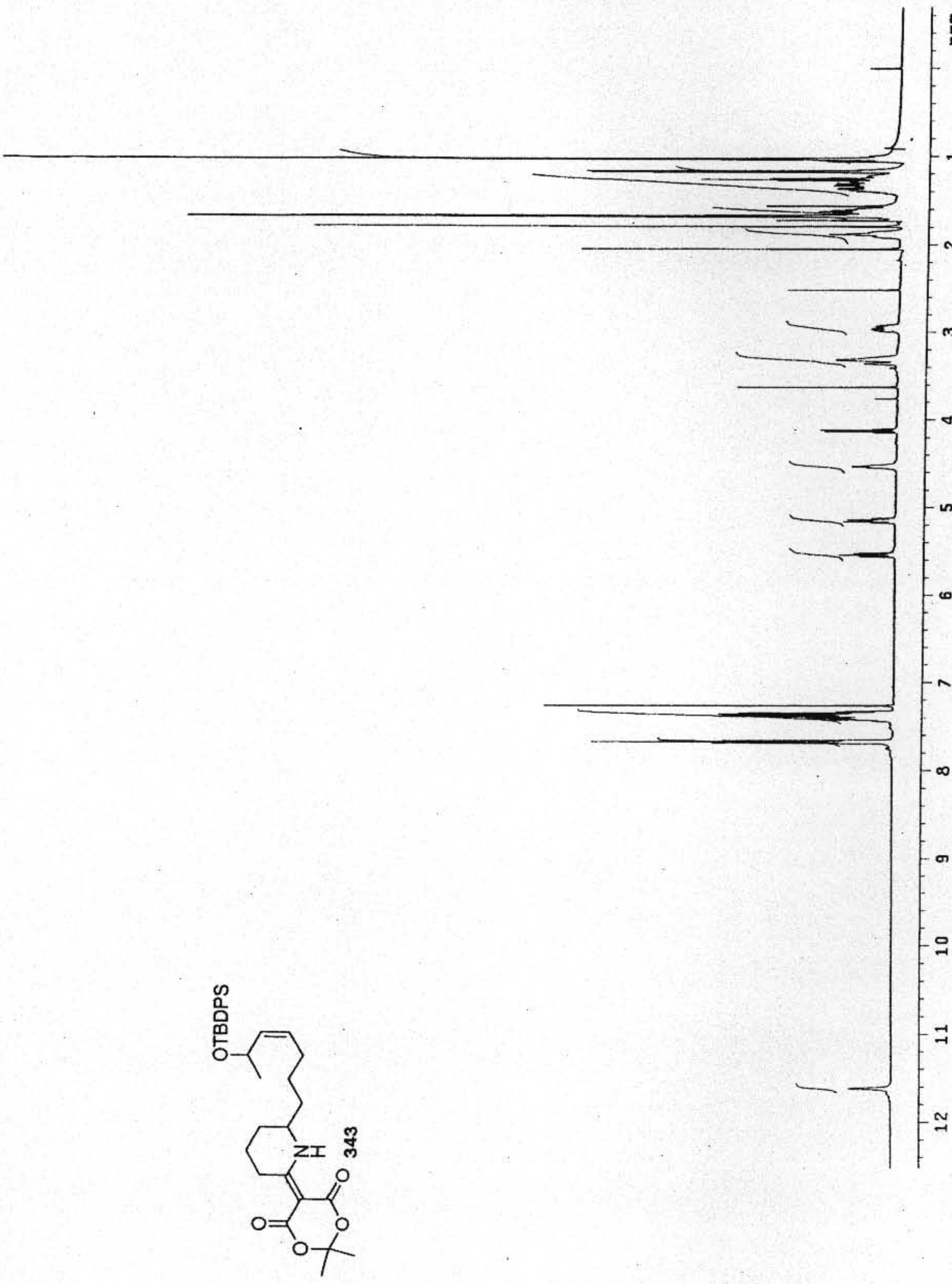
**341**



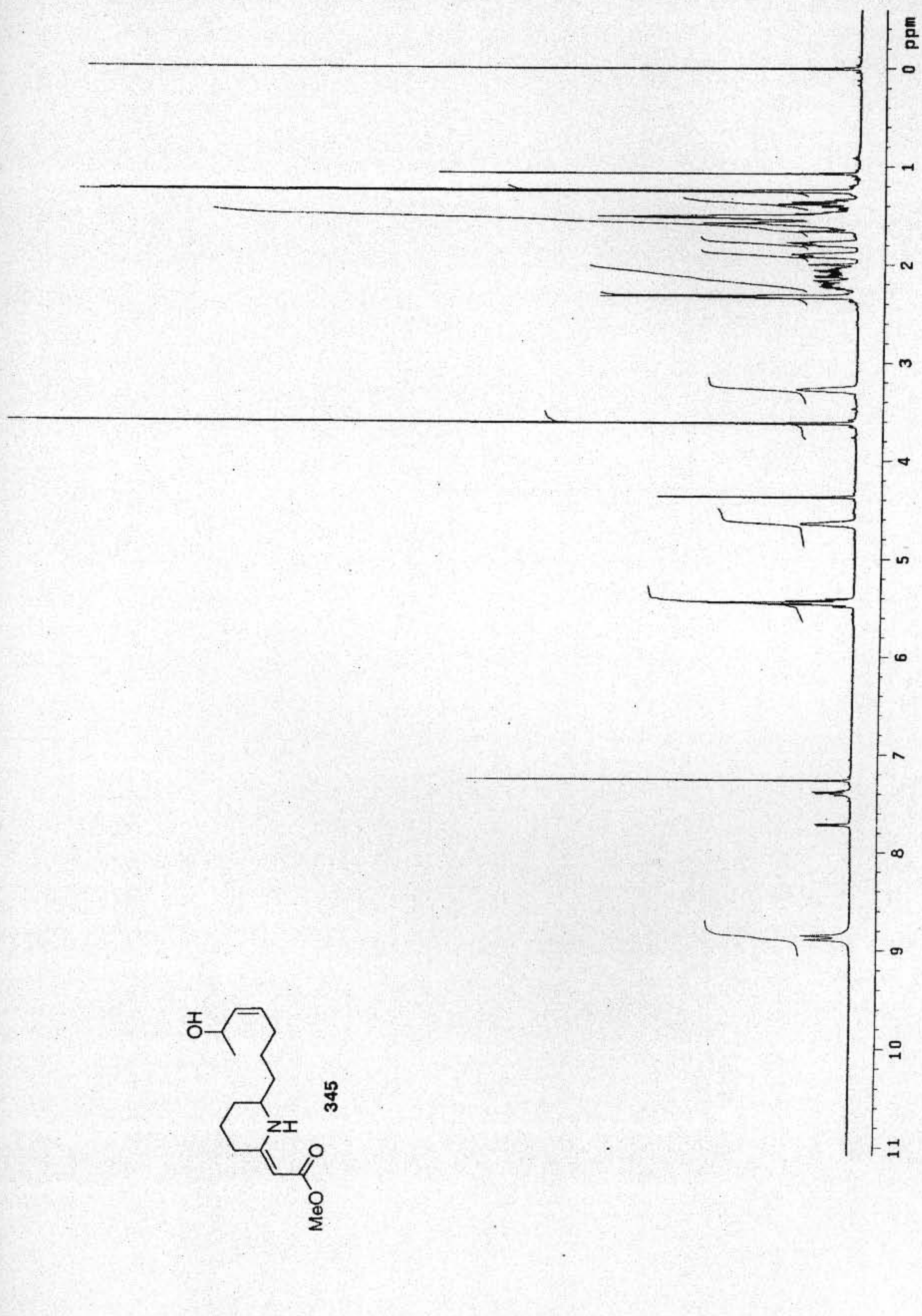
**342**



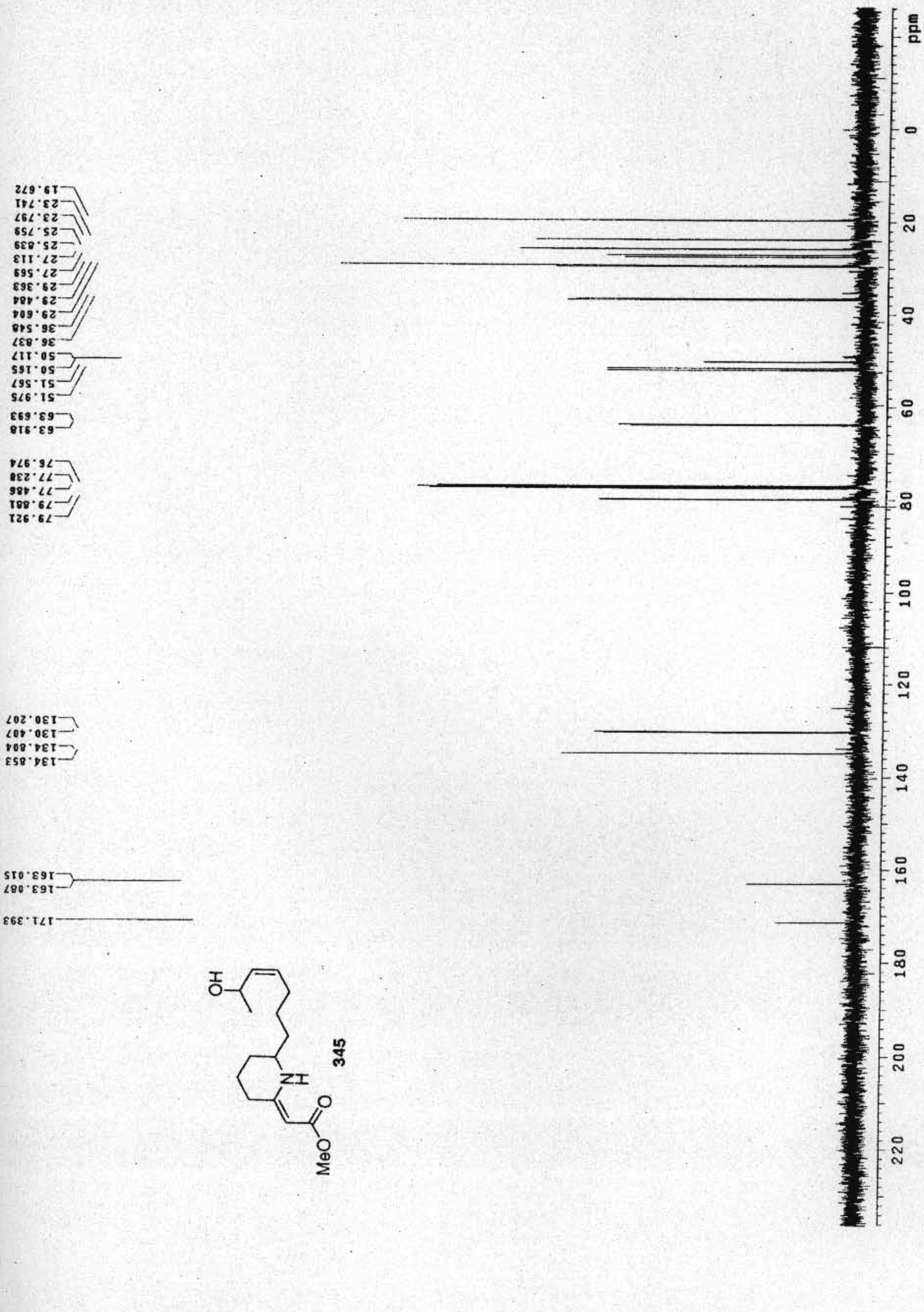
S8

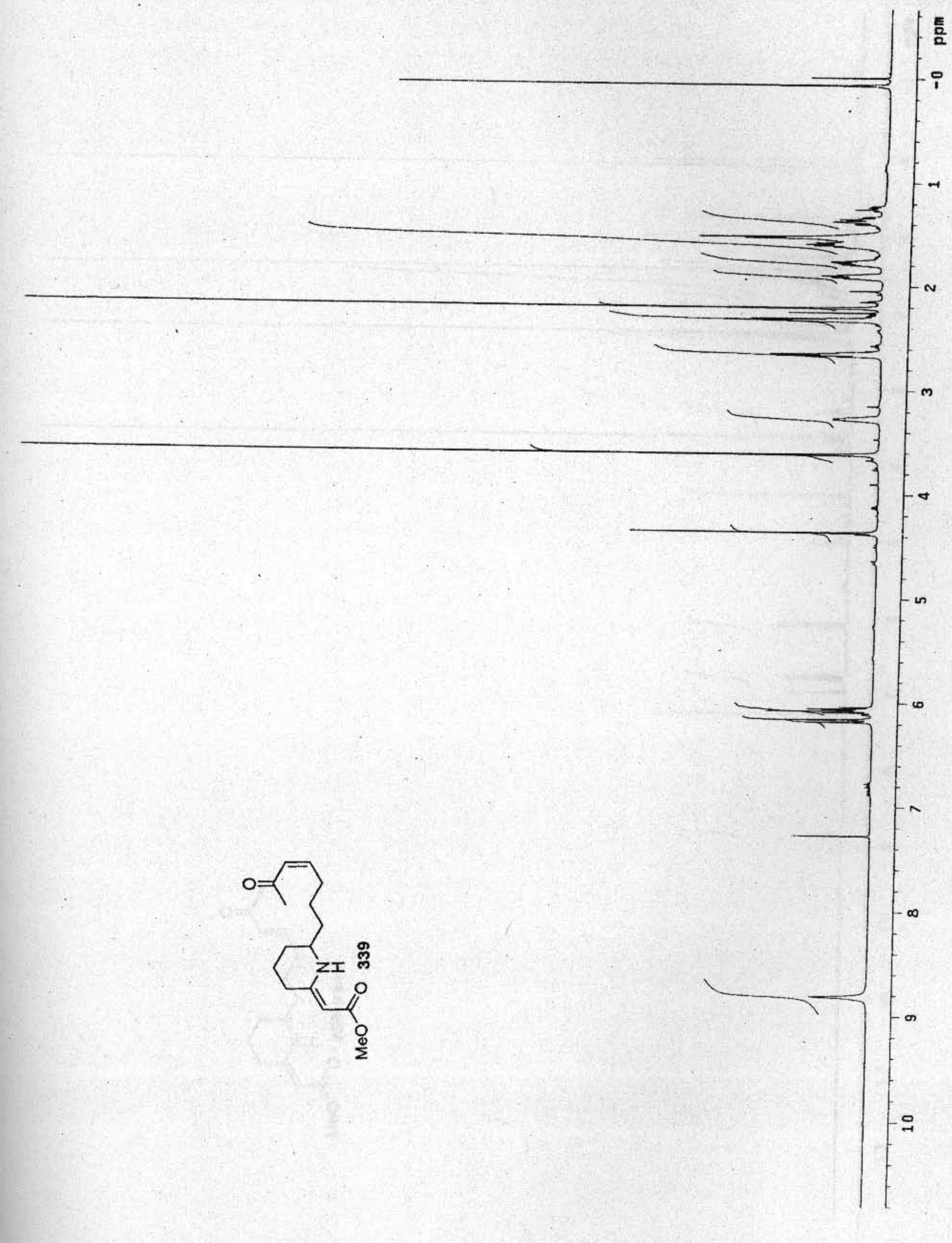


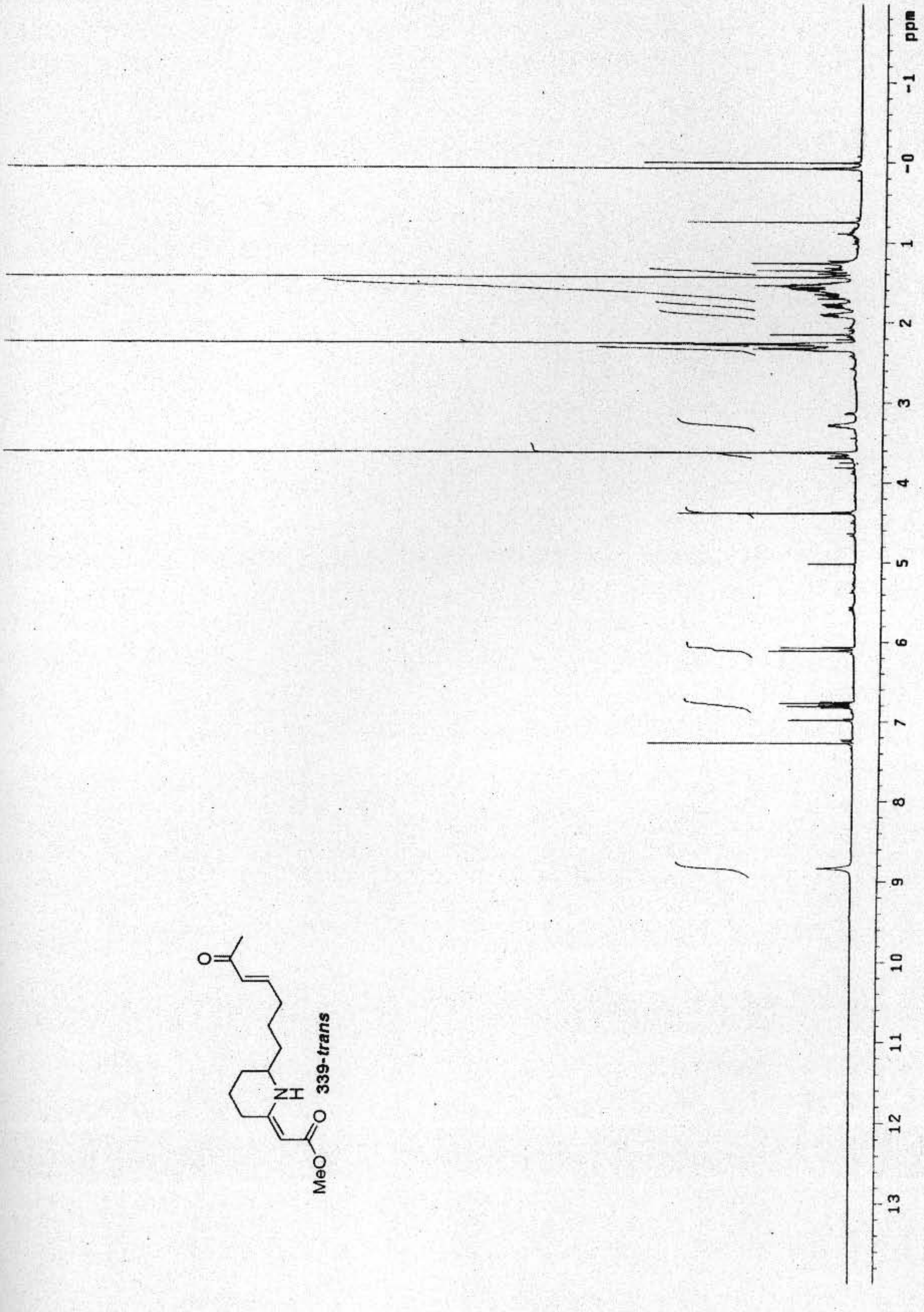
343



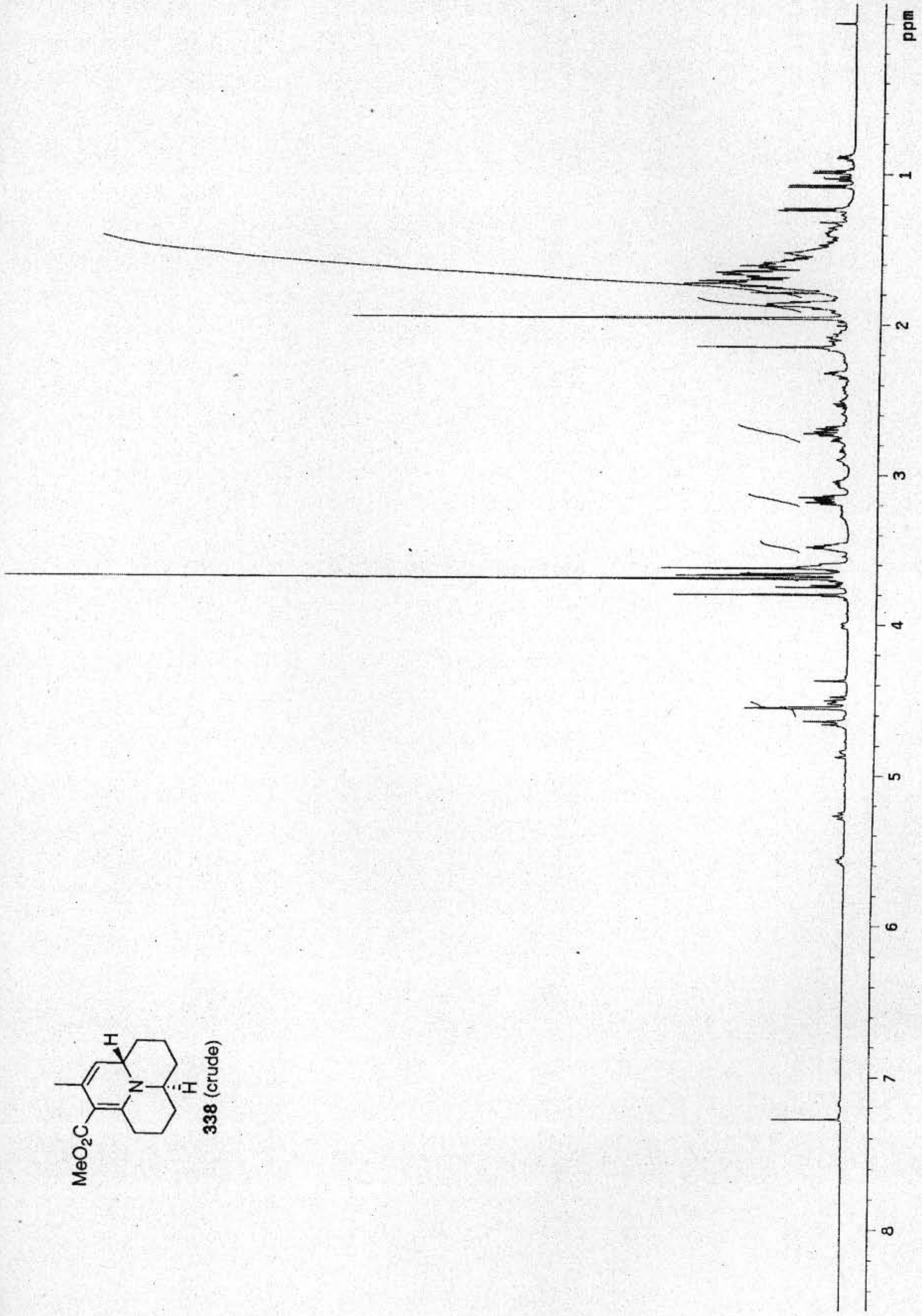
345


19.672
23.741
23.797
25.759
25.839
27.113
27.569
29.363
29.484
29.604
36.548
36.837
50.117
50.165
51.567
51.975
63.693
63.918
76.974
77.238
77.486
79.881
79.921
130.207
130.407
134.804
134.853
163.015
163.087
171.393
HO
NH
MeO
O
345
ppm
0
20
40
60
80
100
120
140
160
180
200
220


339

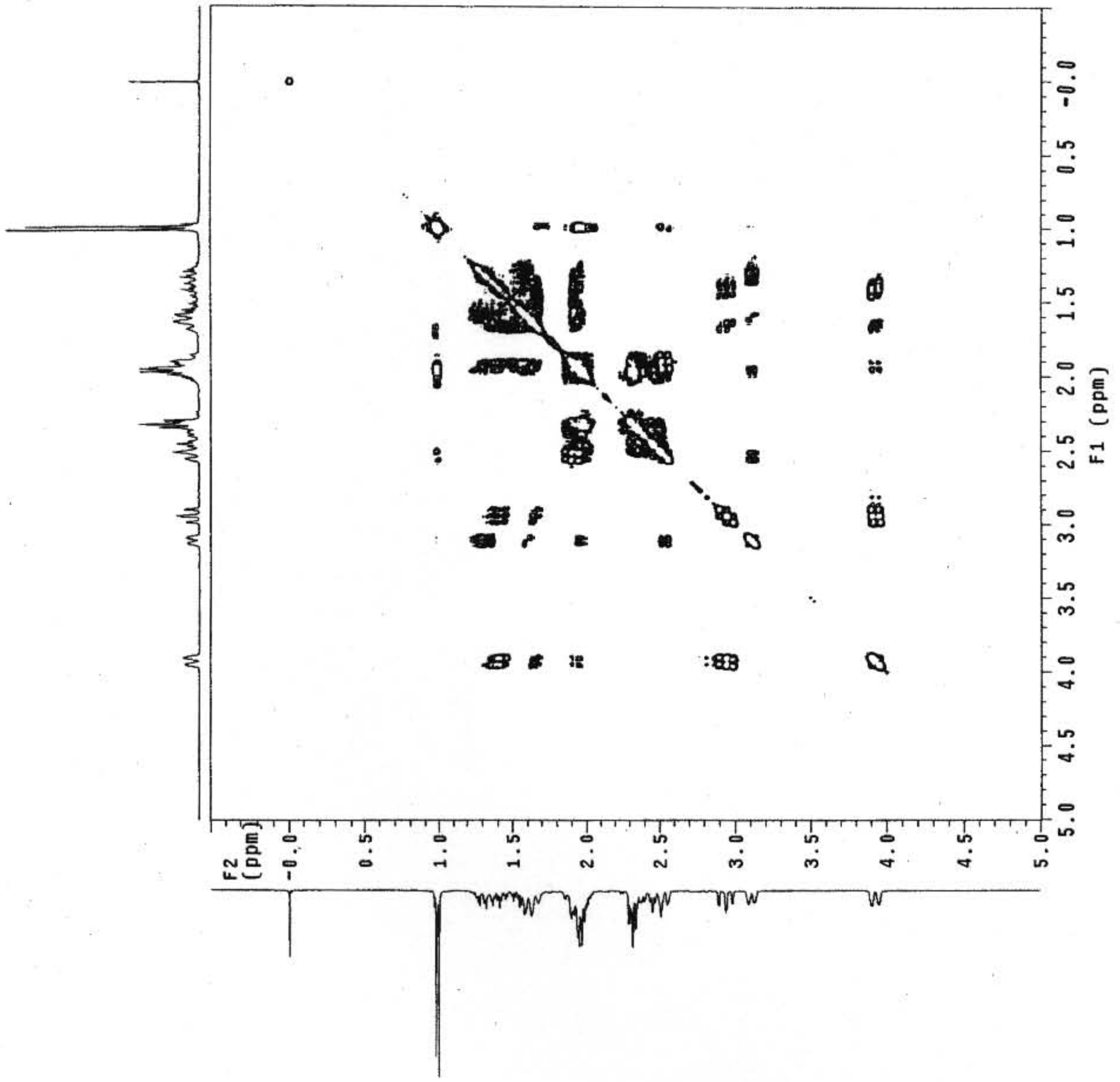


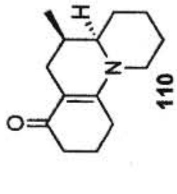
**339-*trans***



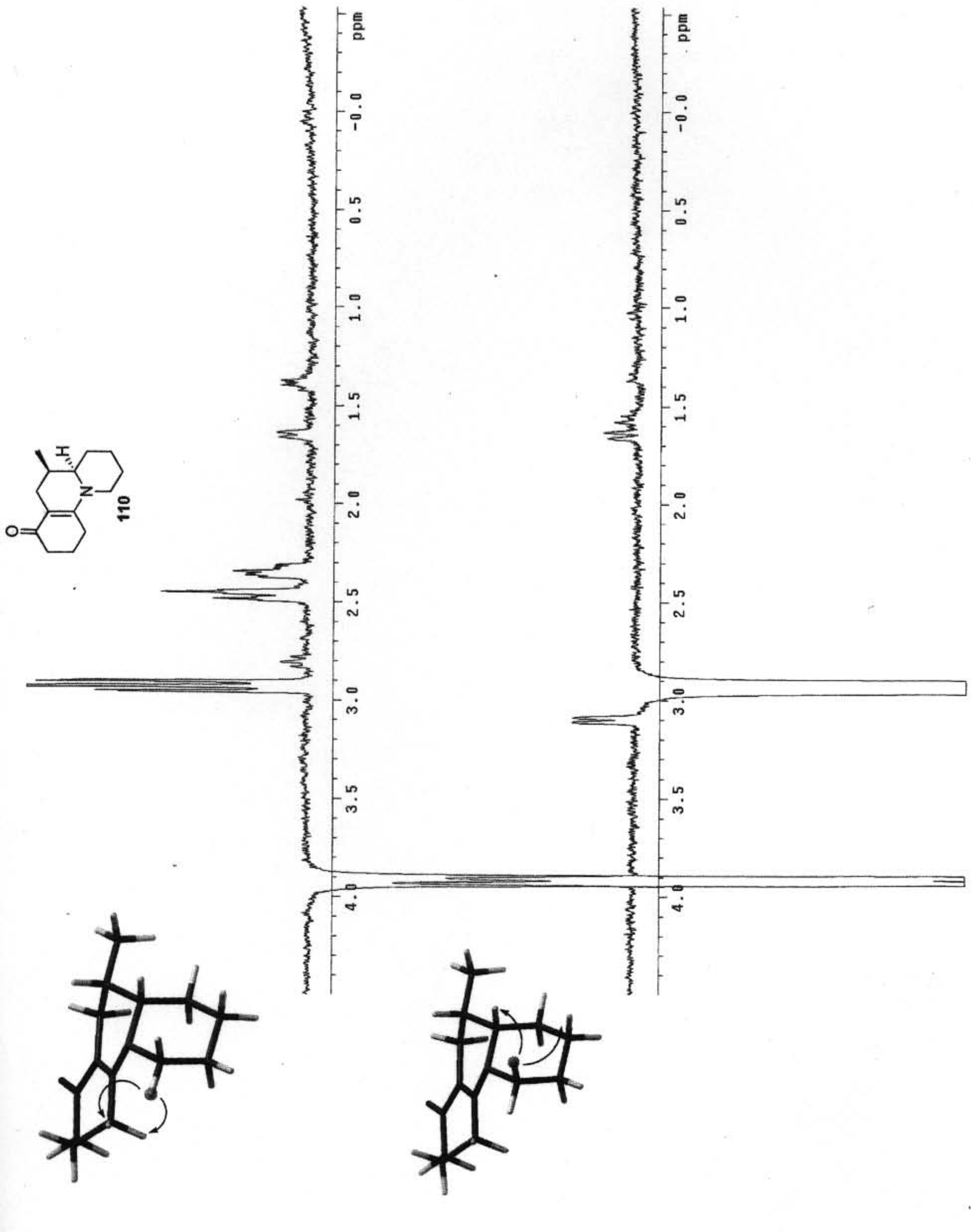
**338** (crude)

# NOE Experiments

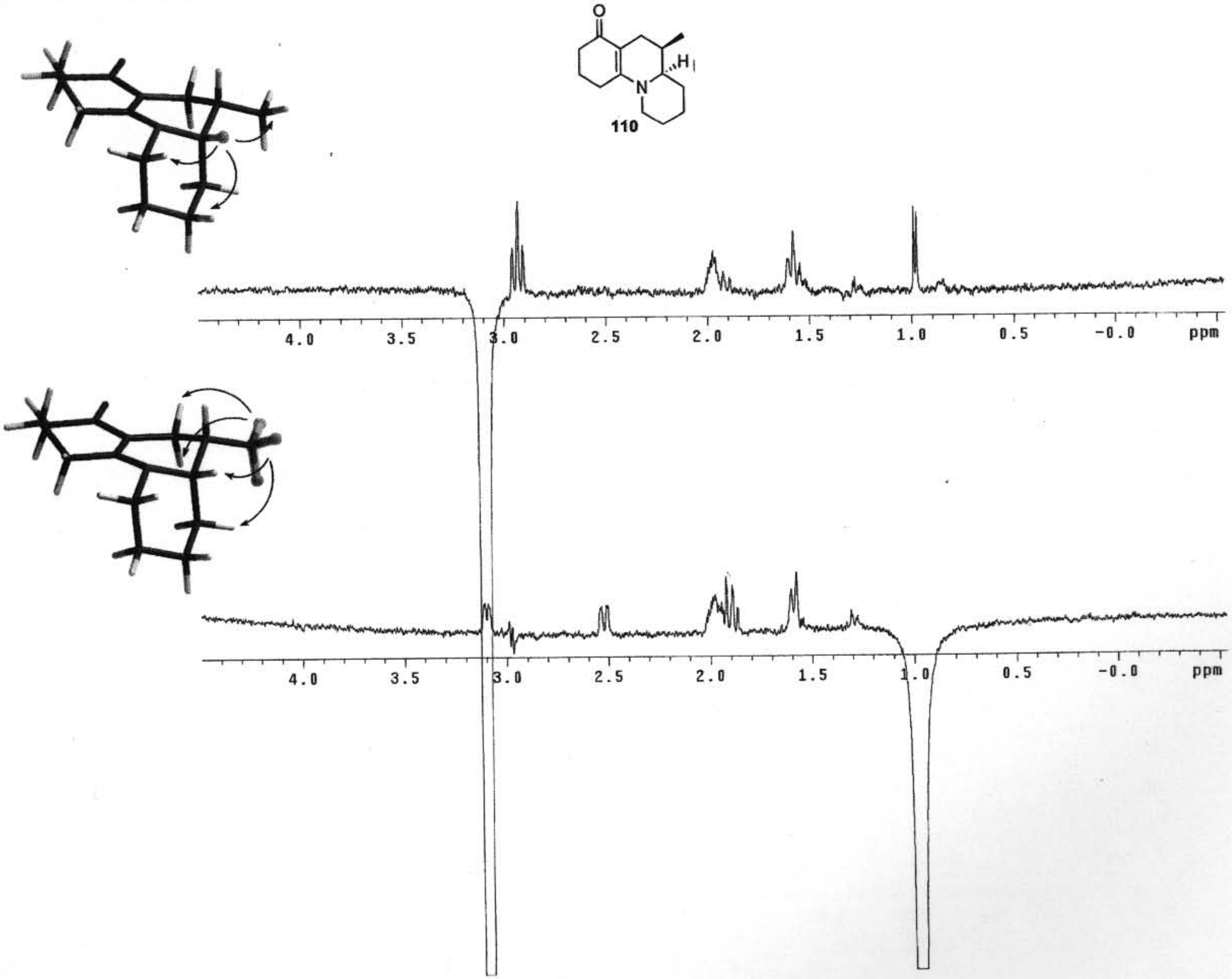




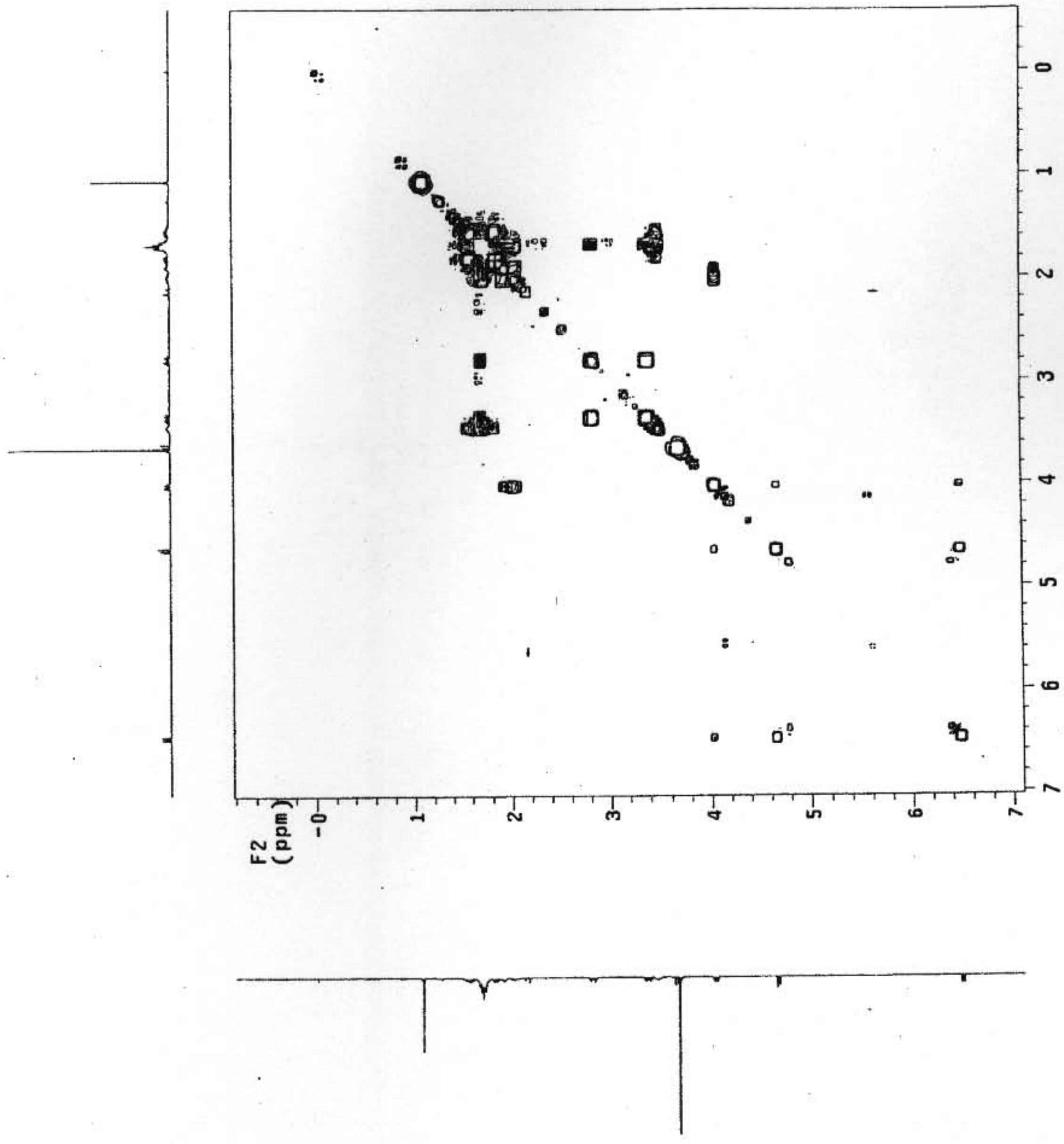
**110**

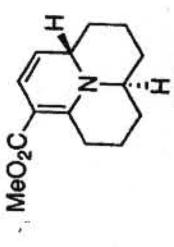


110

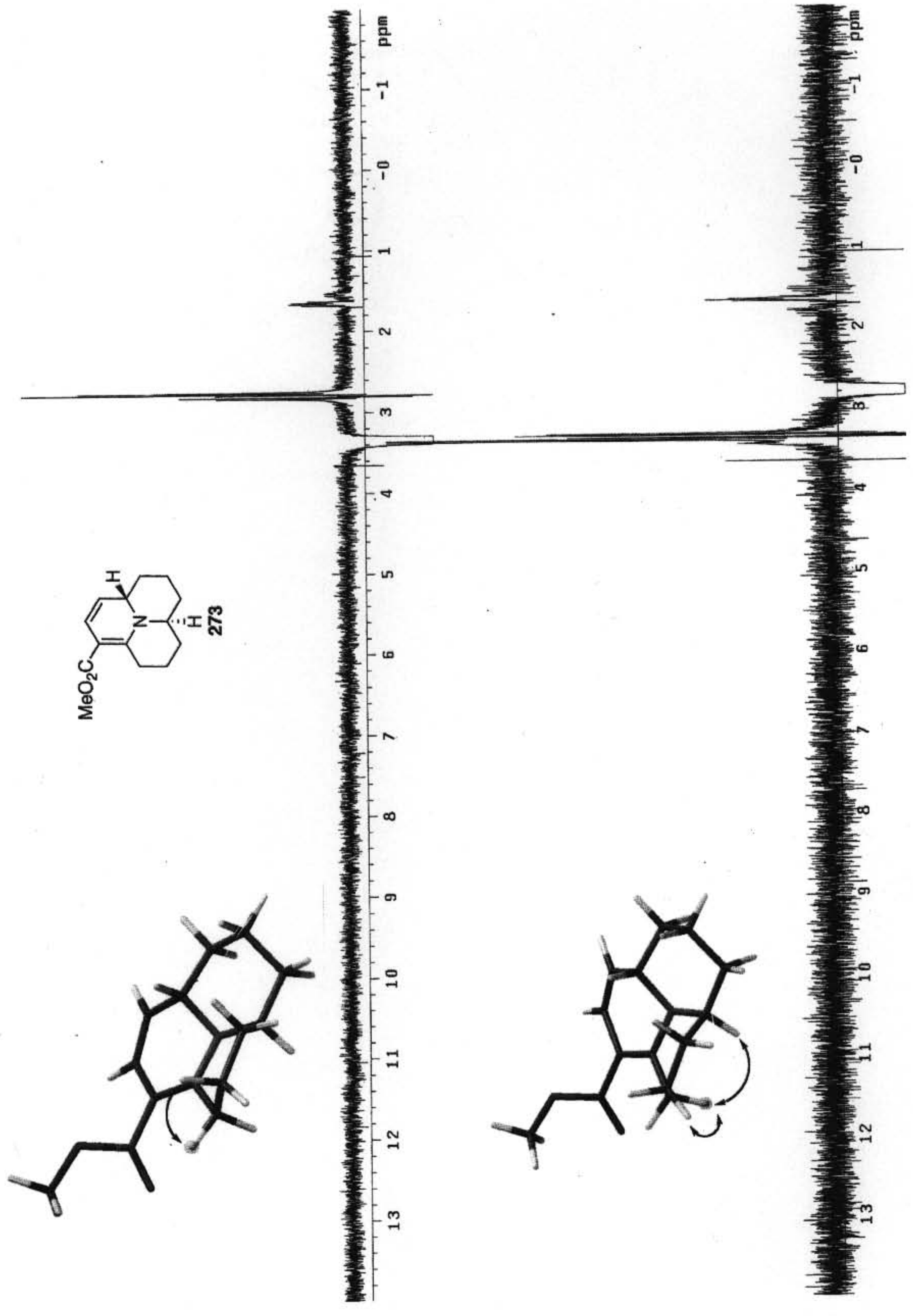


110

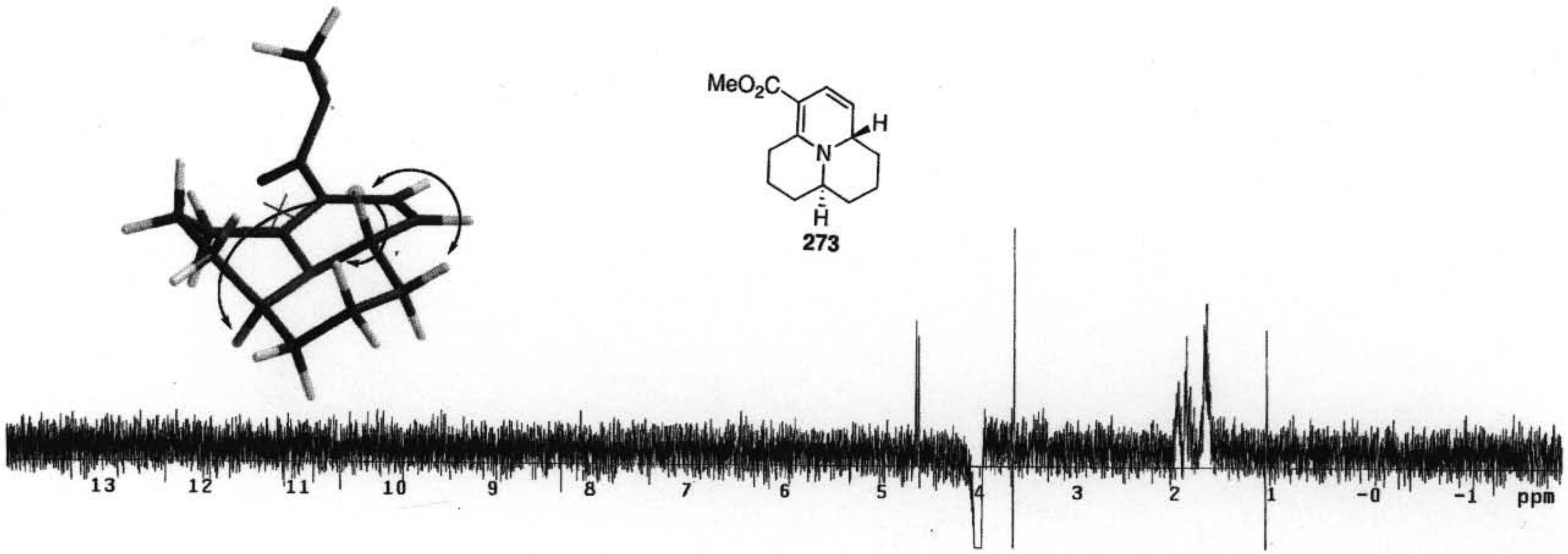




273

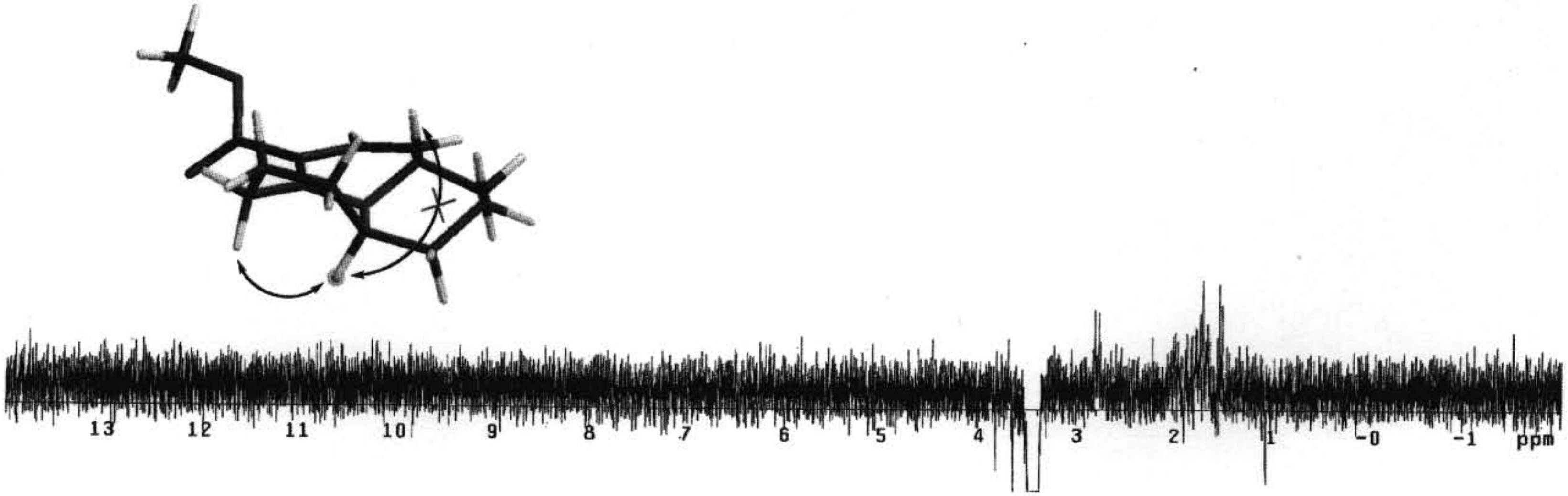


273

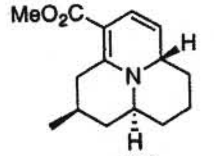


273

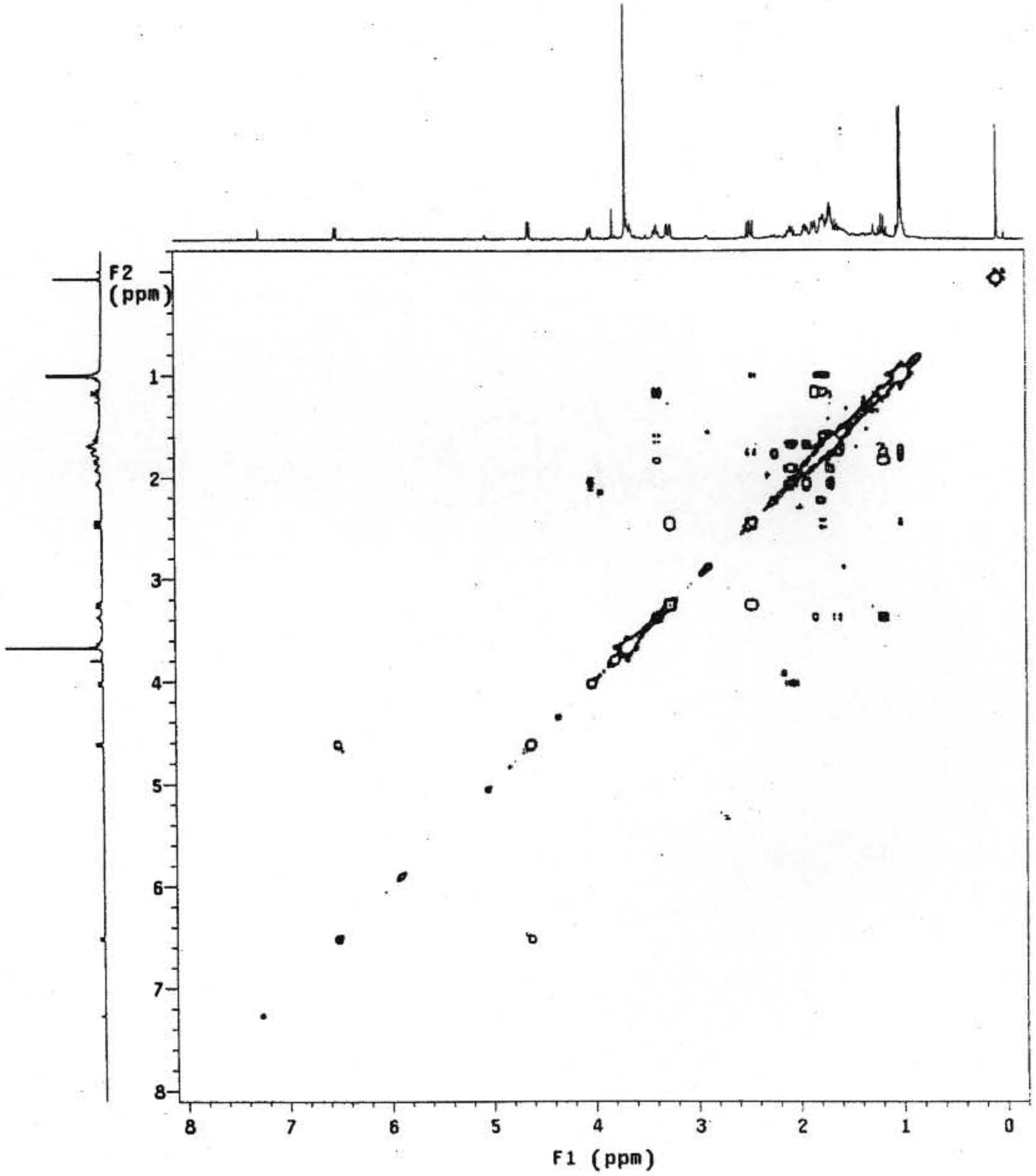
MeO2C
N
H
H
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm

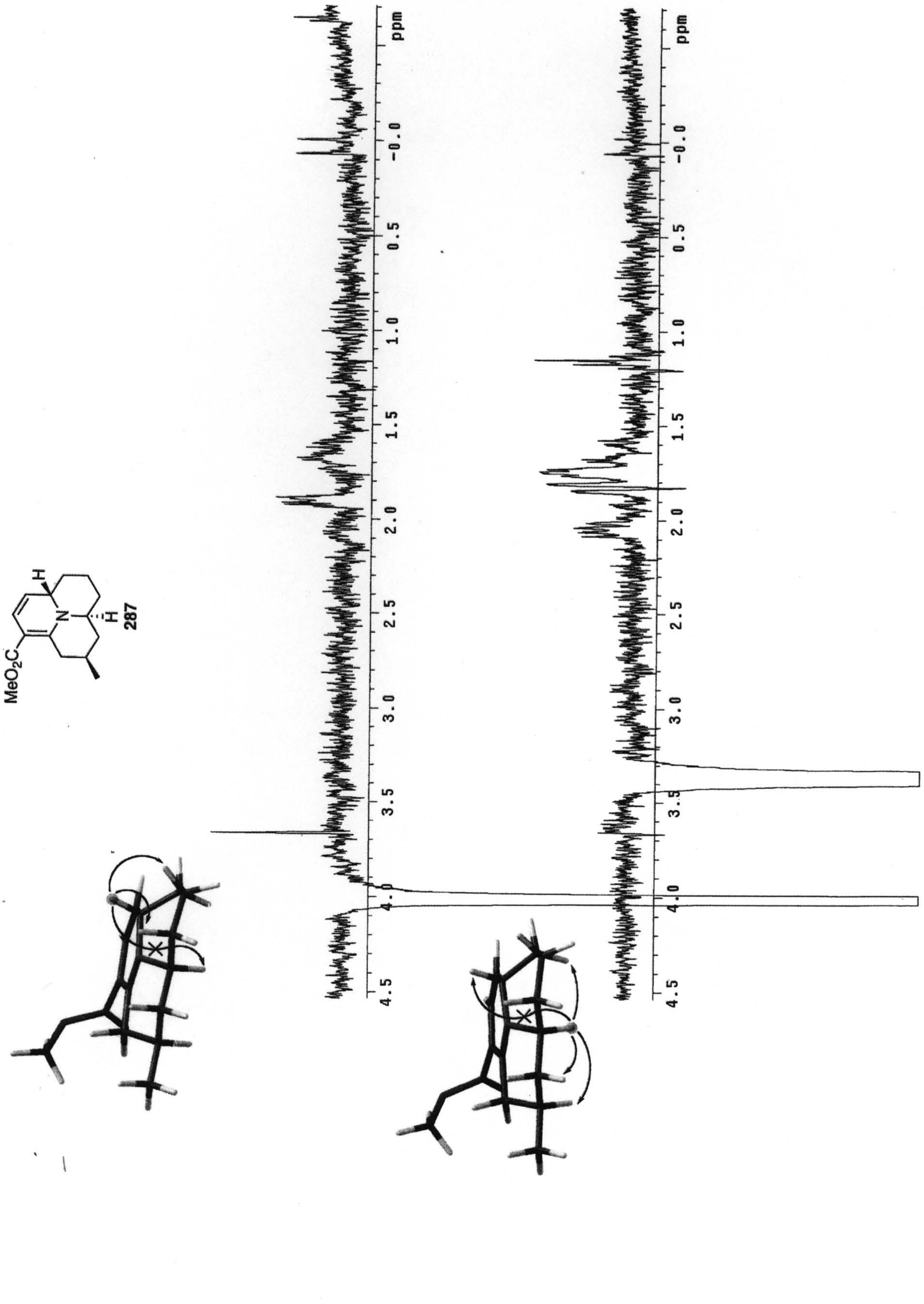


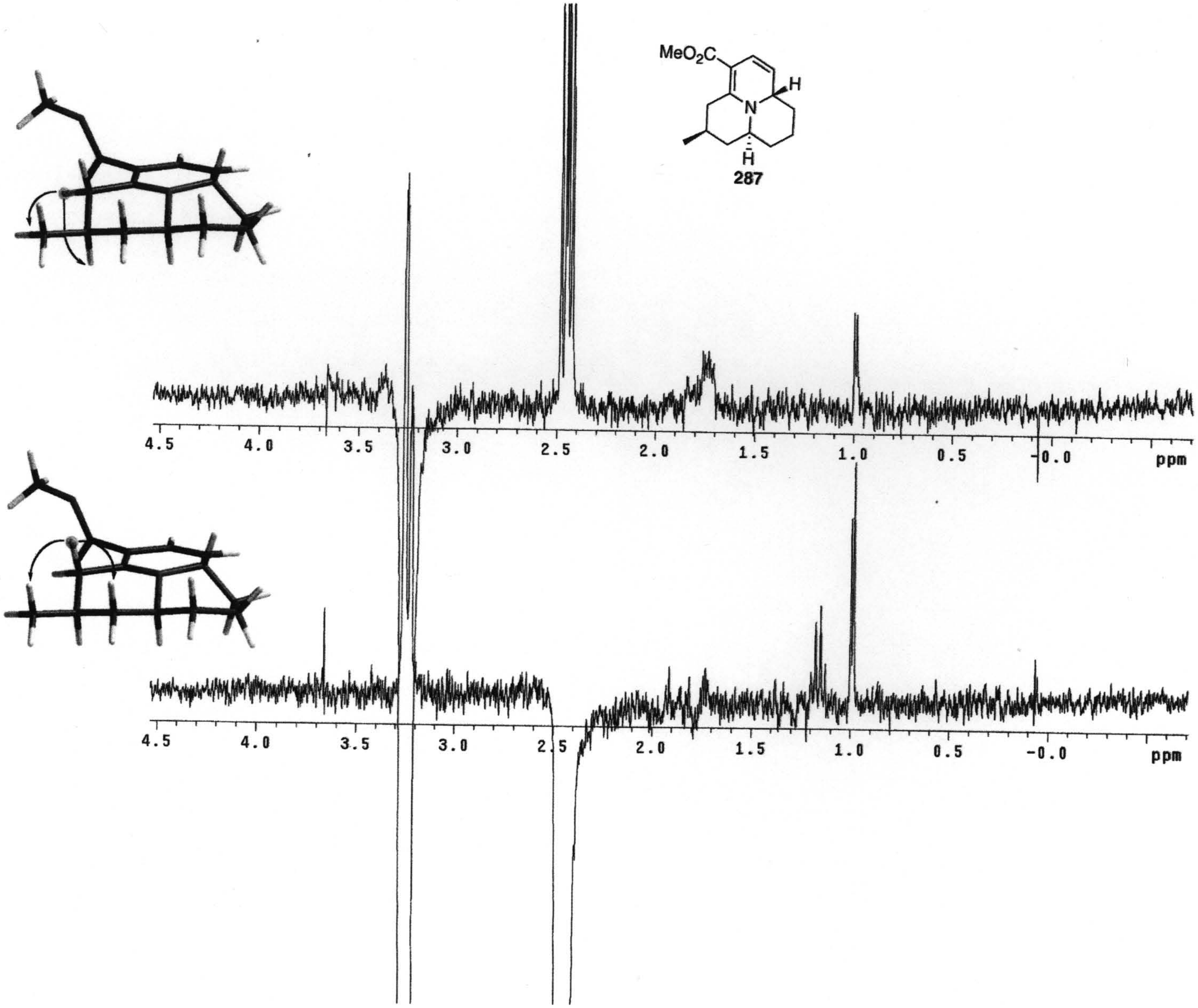
13
12
11
10
9
8
7
6
5
4
3
2
1
-0
-1
ppm



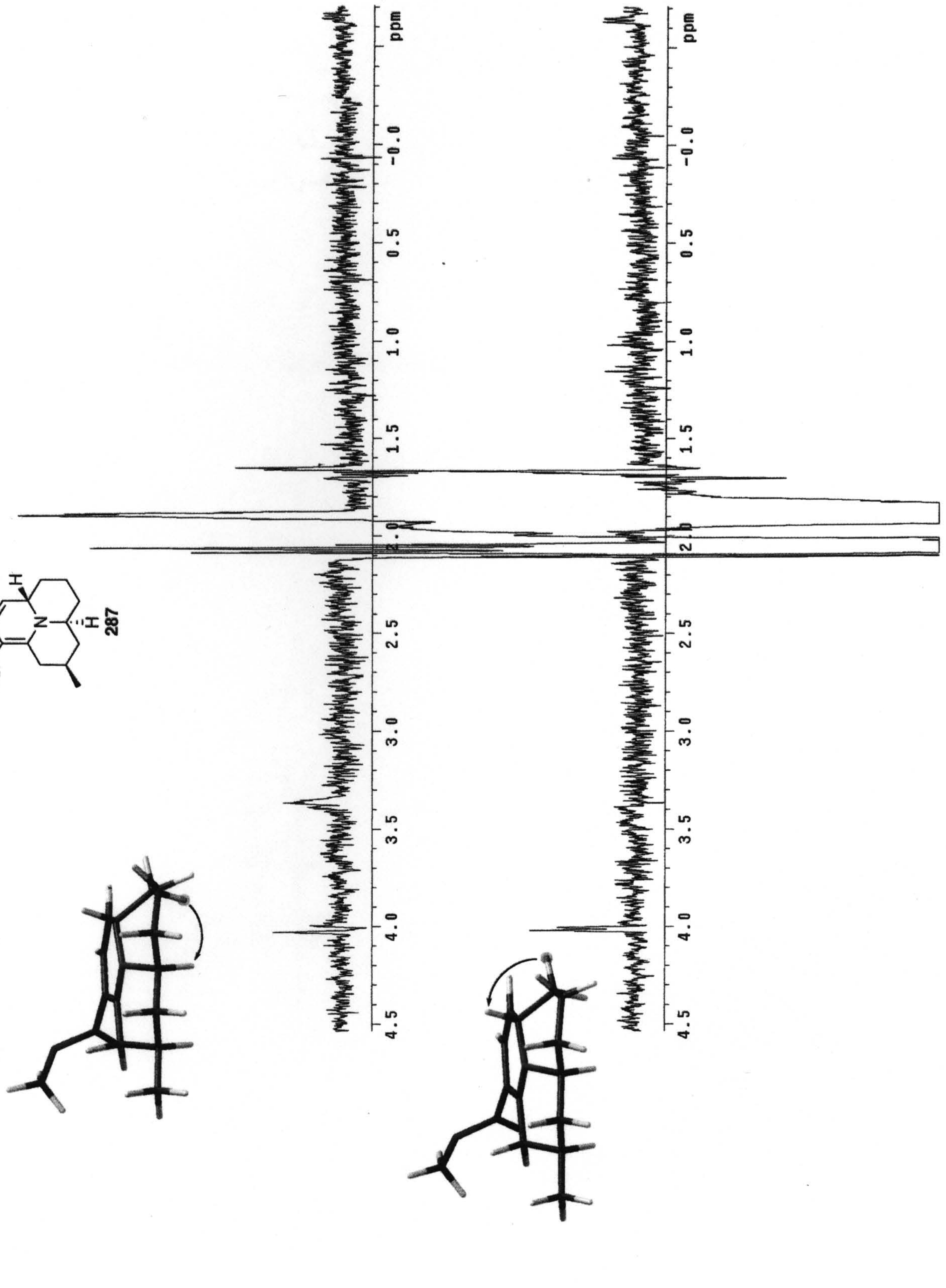
**287**

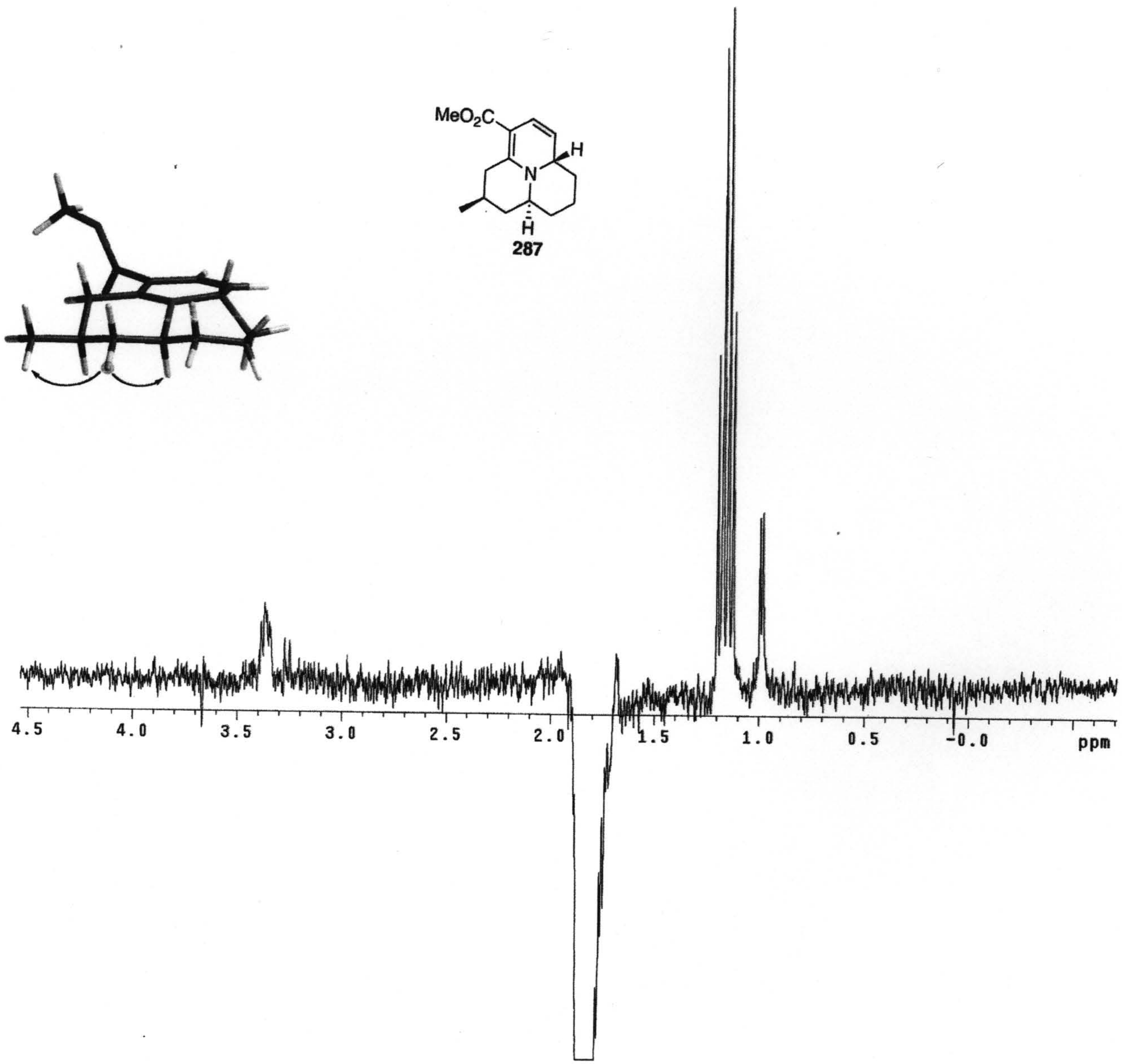


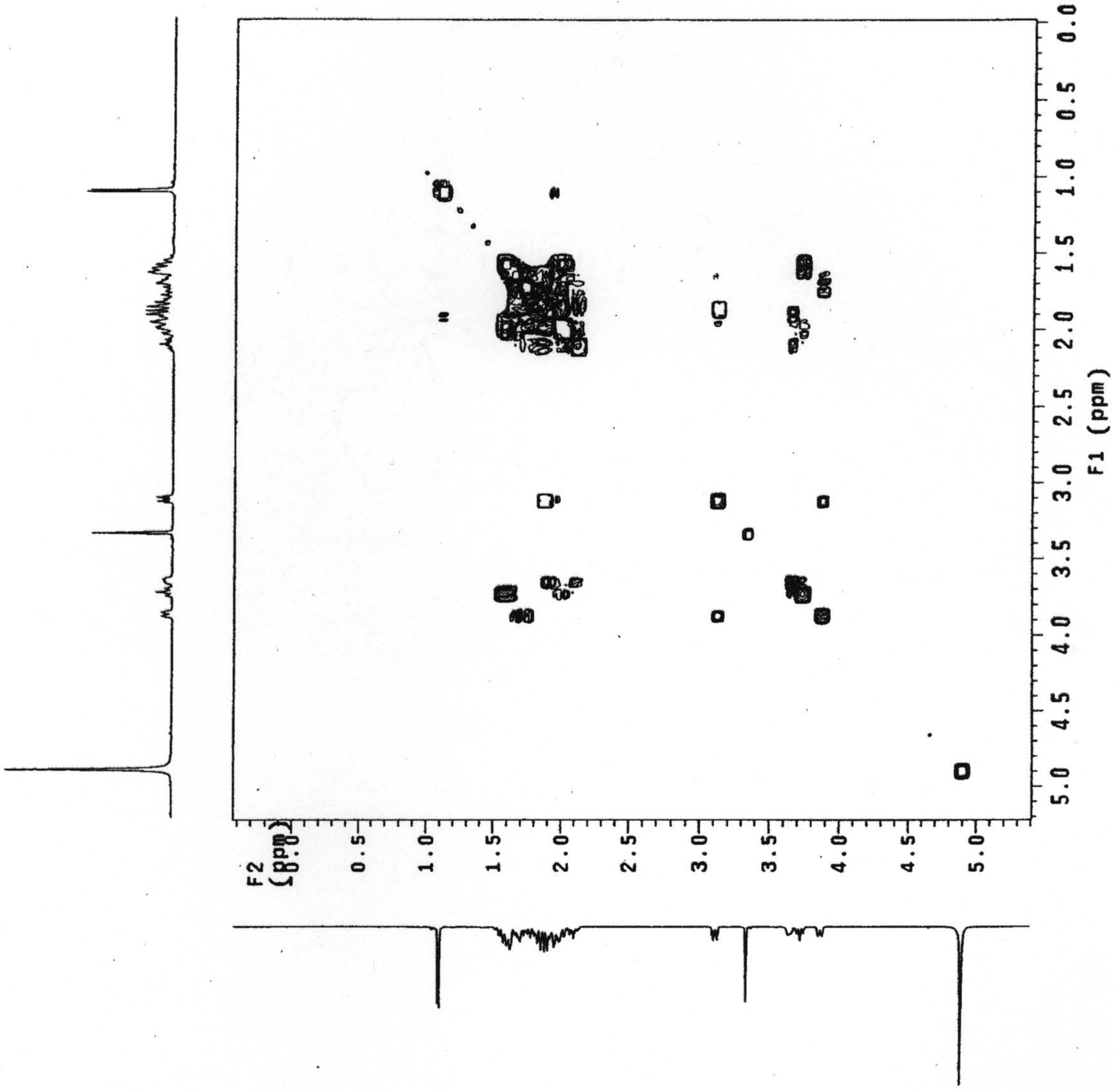

287

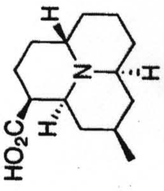


**287**

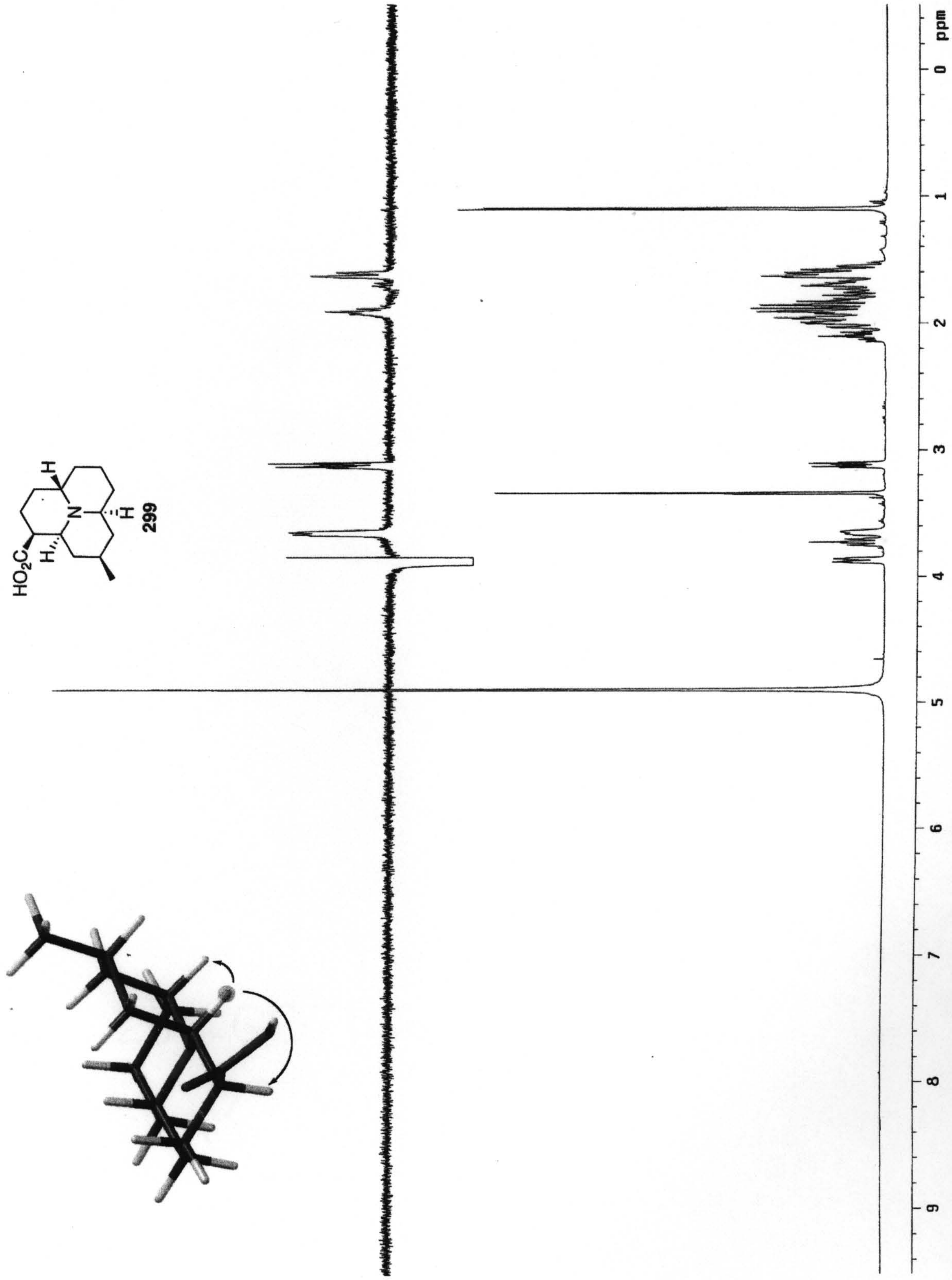

MeO2C
H
N
H
287
ppm
-0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
ppm
-0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5


287

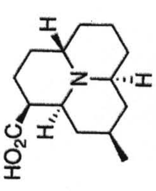

F1 (ppm)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
F2 (ppm)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0


HO$_2$C
H
N
H
H

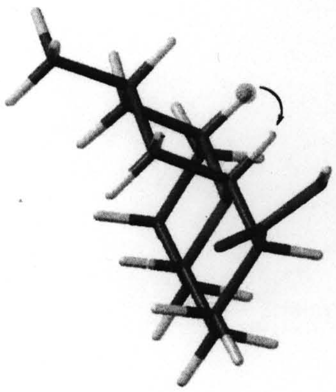
299

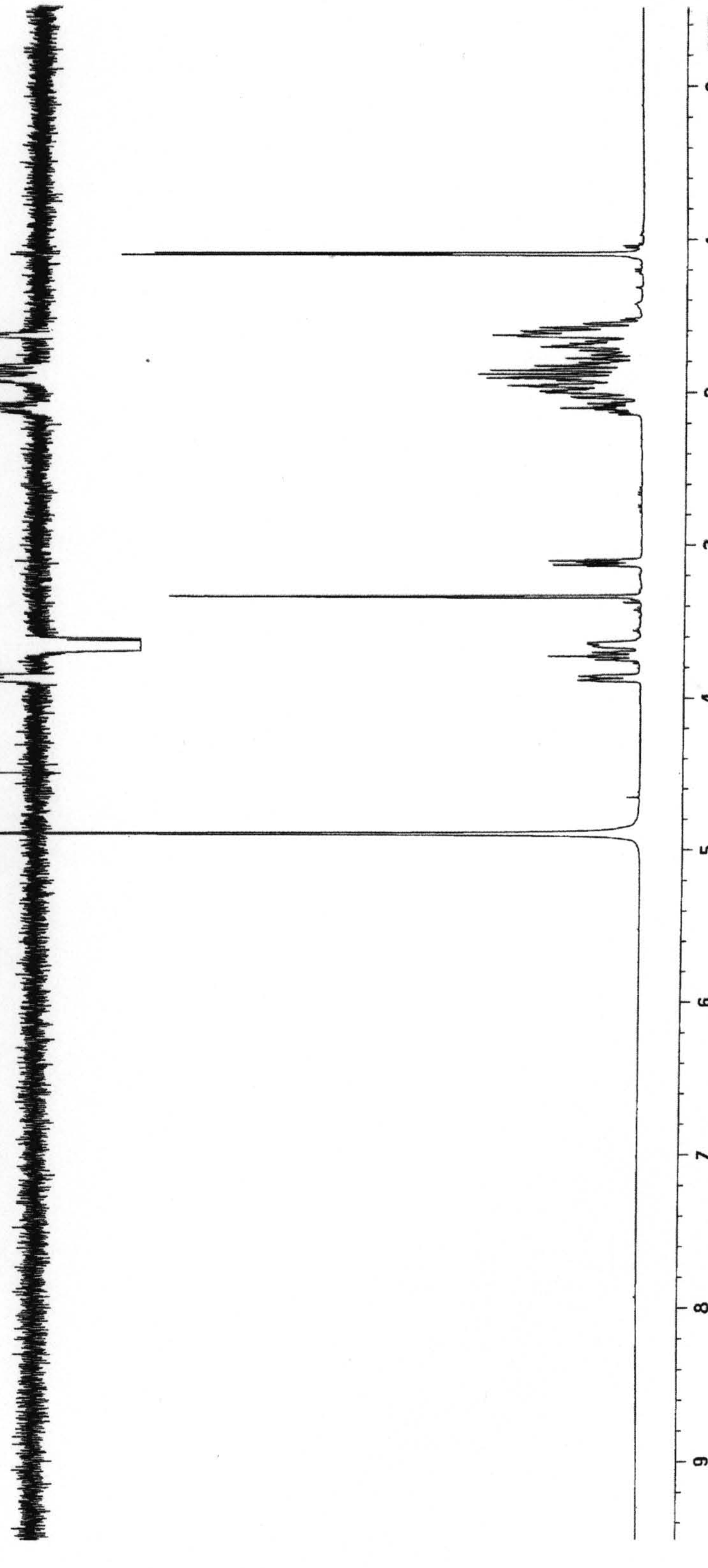


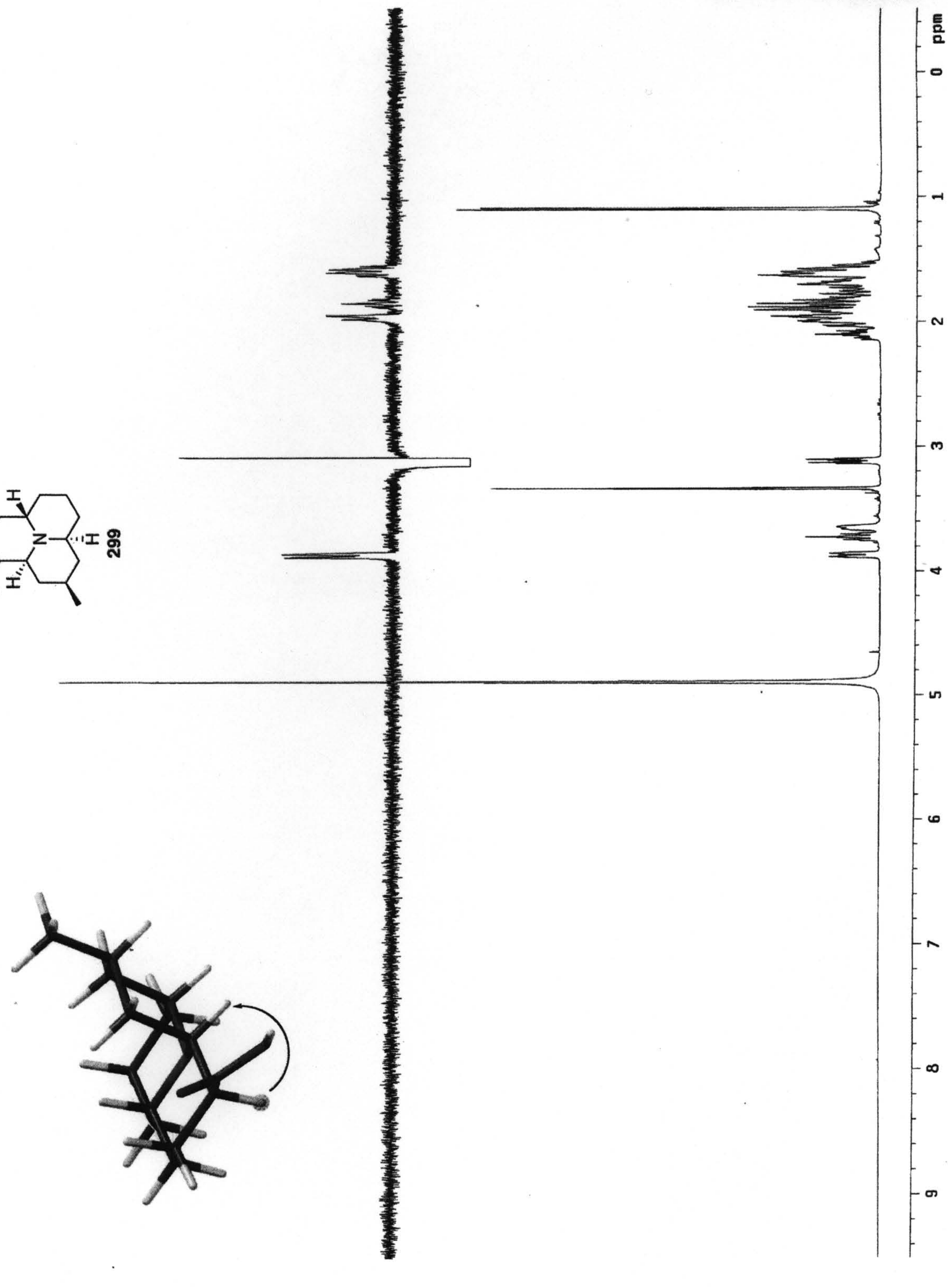
299



**299**







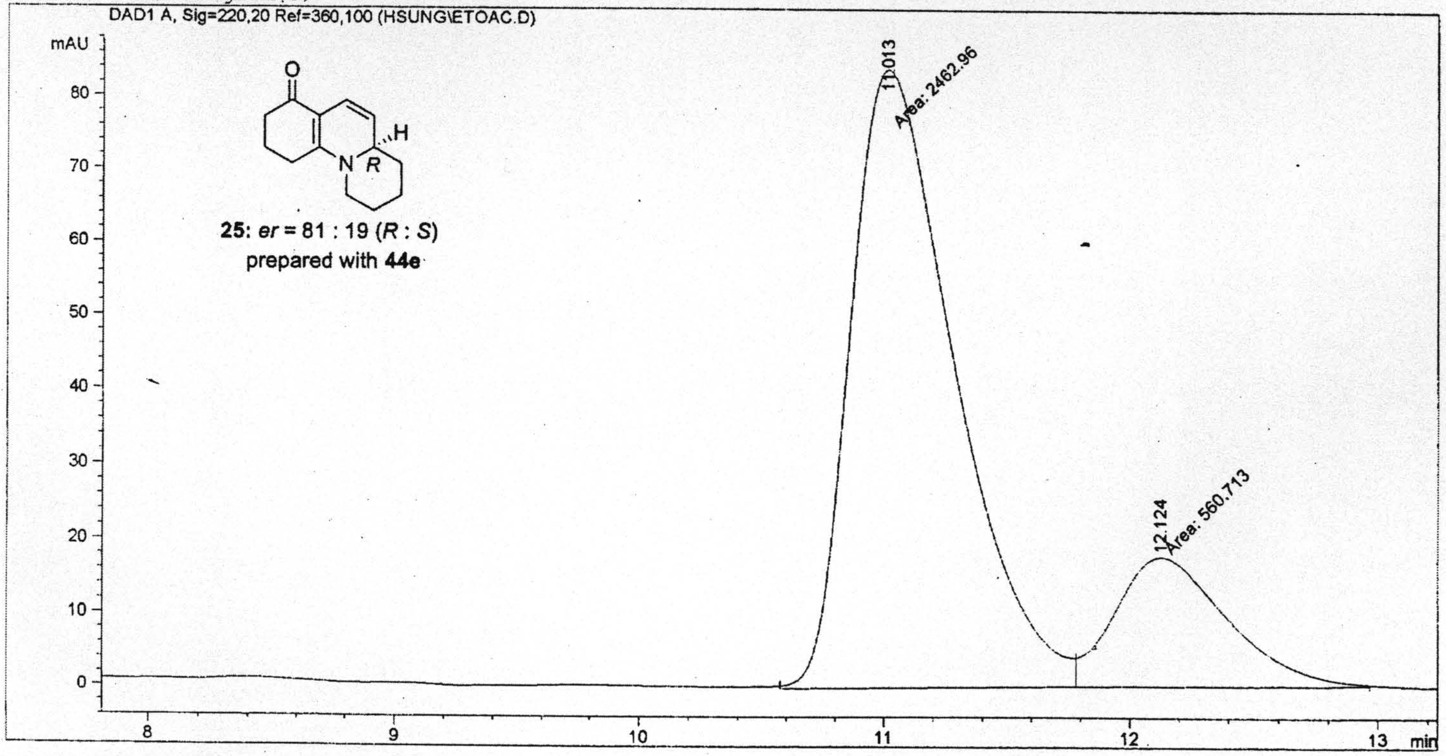
299

# CSP-HPLC Traces

```
Print of window 38: Current Chromatogram(s)
solvent study EtOAc

=====================================================================
Injection Date  : 01/02/2004 6:53:23 AM
Sample Name     : EtOAc                       Location : Vial 1
Acq. Operator   : Aleksey
                                            Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\1\METHODS\CHIRAL.M
Last changed    : 01/02/2004 3:33:48 AM by Aleksey
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\CHIRAL.M
Last changed    : 12/13/2004 2:06:15 AM by hj
                  (modified after loading)
d method
```

Current Chromatogram(s)



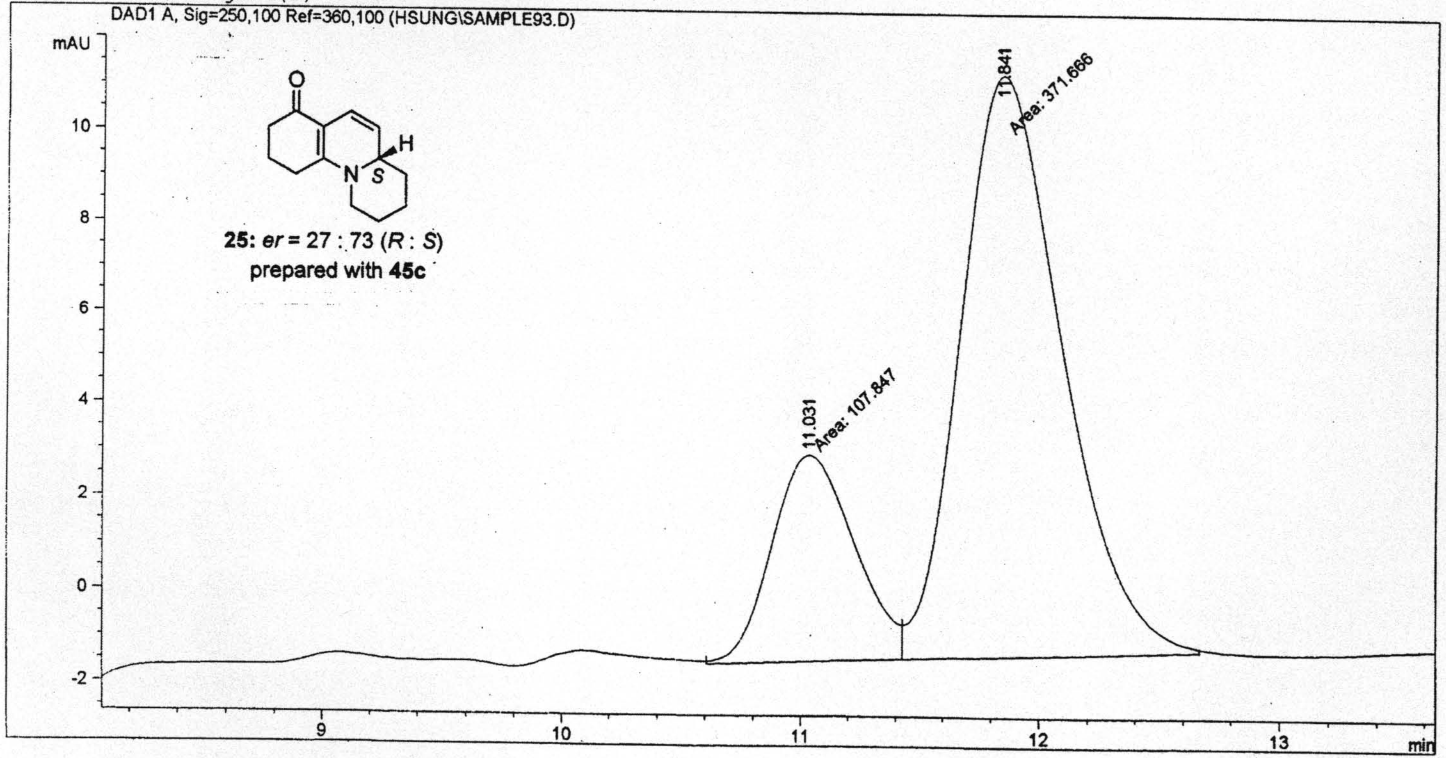
**25:** *er* = 81 : 19 (*R* : *S*)
prepared with **44e**

```
Instrument 1 12/27/2004 11:21:46 PM hj                                Page 1 of 1
```

```
Print of window 38: Current Chromatogram(s)
TBDPS 2 before hydrogenation after heat

=====================================================================
Injection Date  : 06/15/2003 11:28:37 AM
Sample Name     :                                 Location : Vial 41
Acq. Operator   : aleksey
                                                Inj Volume : 5 µl
Acq. Method     : C:\HPCHEM\1\METHODS\CHIRAL.M
Last changed    : 06/15/2003 10:56:35 AM by aleksey
                  (modified after loading)
Analysis Method : C:\HPCHEM\1\METHODS\CHIRAL.M
Last changed    : 12/13/2004 2:06:15 AM by hj
                  (modified after loading)
d method
```

Current Chromatogram(s)



**25:** *er* = 27 : 73 (*R* : *S*)
prepared with **45c**

```
Instrument 1 12/27/2004 11:15:05 PM hj                              Page 1 of 1
```

# X-Ray Cover Pages

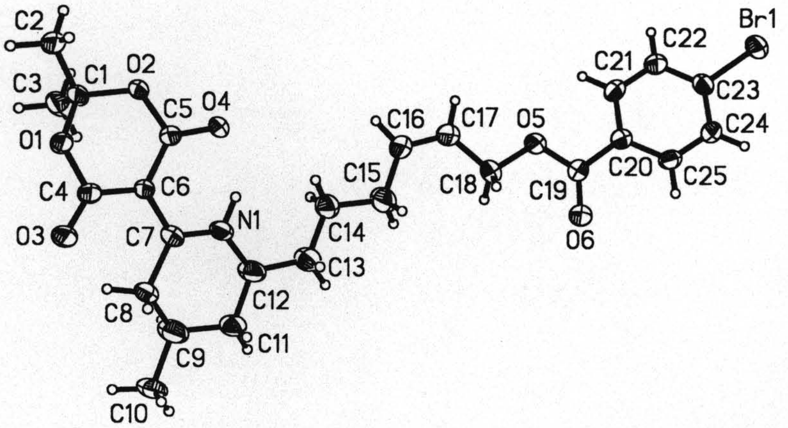
REFERENCE NUMBER: 06092a

# CRYSTAL STRUCTURE REPORT for compound **282**

$C_{25}H_{30}BrNO_6$

Report prepared for:
Aleksey Gerasyuto
Prof. Richard Hsung

April 12, 2006



Victor G. Young, Jr.
X-Ray Crystallographic Laboratory
Department of Chemistry
University of Minnesota
207 Pleasant St. S.E.
Minneapolis, MN 55455

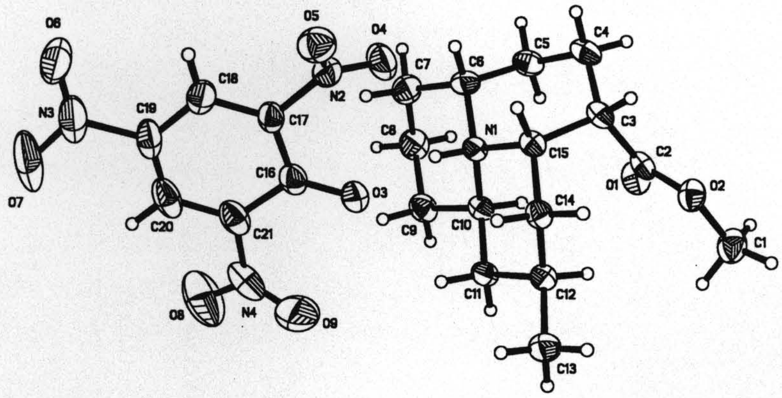
REFERENCE NUMBER: 06196

# CRYSTAL STRUCTURE REPORT for picrate salt of compound **298**

$[C_{15} H_{26} N O_2][C_6 H_2 N_3 O_7]$

Report prepared for:
Aleksey Gerasyuto
Prof. Richard Hsung

July 30, 2006



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