To the Graduate Council:

I am submitting herewith a dissertation written by Joseph Allen Burlison entitled "Studies Directed Toward the Synthesis of Acylated Phloroglucinols." I have examined the final paper copy of this dissertation for form and content and recommend that it be accepted in partial fulfillment of the requirements for the degree of Doctor of Philosophy, with a major in Chemistry.

David G. J. Young, Major Professor

We have read this dissertation
and recommend its acceptance:

Acceptance for the Council:

Vice Chancellor and Dean of
Graduate Studies

Studies Directed Toward the Synthesis of Acylated Phloroglucinols

A Dissertation

Presented for the

Doctor of Philosophy

Degree

The University of Tennessee, Knoxville

Joseph Allen Burlison

August 2005

Thesis
2005b
.B87

Copyright © 2005 by Joseph A. Burlison
All rights reserved.

Dedication

This dissertation is to dedicated with love and admiration to
my wife, Hayley Burlison,
and to my parents, Libby and Allen Burlison.

Acknowledgments

I would like to thank the many professors and staff in the Department of Chemistry that have taken part in my experience. In particular I would like to thank Dr. Fred Schell and Dr. J. Z. Larese for their mentorship, and Dr. C. Mamantov, Dr. Jim Green and Dr. Richard Pagni for wonderful teaching experiences. For the technical aspect I would like to thank Darrell Lay, Traymon Allen, and the stockroom staff, Dr. Al Tuinman for mass spectra assistance, and Dr. Hongjun Pan for NMR assistance.

Dr. David Young's group was a great place to learn how to do research. The past members of the group, Dongxiang Zeng, Janet Gray, Michael Madigan, and Ulf Peters, created a pleasant atmosphere for work and friendship. Thanks especially to Ulf Peters for his aid in earlier projects and for his suggestions on my original research proposal. I would like to thank Dr. Young for the great research ideas and for his patience with me as an educator. I appreciate your time as my research advisor and I wish you the best of luck at the new university. Thanks for giving me the opportunity.

I can never forget my wife, Hayley Burlison, who has endured much over the past years. She has sacrificed as much (if not more) for me to pursue this dream. Thank you for always encouraging me, for your patience, and for all your love.

Likewise, I would like to thank my parents, Libby and Allen Burlison, for their encouragement to continue my education and for always being dependable friends. I am also blessed to have two brothers and sister, Josh, Alex, and Beth, that are great friends. Thanks for your support.

I am gracious for my extended family and friends that at one time or another have aided and supported us in Knoxville. In particular, I would like to thank for their encouragement and direction my grandparents, Howard and Mary Adkins, and Viola Burlison, the congregation of the First Baptist Church in Burns, TN for your support, love, and inspiration, Daryl and Karen for a wonderful friendship, and Mr. Bannockburn and his wife, Ginger, for always being there.

Abstract

The synthesis and application of α-allenyl ketones directed toward the synthesis of polycyclic polyprenylated acylphloroglucinols are described. A functionalized α-allenyl ketone was synthesized in twelve steps starting from 2-methyl-2-cyclohexenone in 24% overall yield. The α' stereocenter in the α-allenyl ketone was stereoselectively quaternized using a Tsuji allylation, Mukaiyama aldol condensation sequence to afford C-1 functionalized allenyl cyclohexanone building blocks. A survey of acetals and reaction conditions for the Mukaiyama reaction suggested that 3-*tert*-butyldiphenylsiloxypropanal dimethyl acetal could be used, and indeed this reagent in the presence of $TiCl_4 \cdot Ti[OCH(CH_3)_2]_4$ gave the aldol product in 63% yield. The furthest advanced intermediate was prepared from 2-methyl-2-cyclohexenone in sixteen steps in 6% overall yield.

Table of Contents

1. Introduction and Background 1
1.1 Polycyclic polyprenylated acylphloroglucinol natural products..... 1
1.1.1 Biological activity for selected PPAPs. 1
1.1.2 Mechanism of action for hyperforin (**2a**) and garcinol (**5**). 5
1.1.3 Biosyntheis of phloroglucinol (**1**), hyperforin (**2a**), and sampsonione A (**4**).....5
1.2 PPAP strategies and synthetic studies..... 9
1.2.1 Effenberger's double acylation approach to phloroglucinols. 9
1.2.2 Nicolaou's selenium-induced cyclization approach towards garsubellin A (**6**)... 10
1.2.3 Shibasaki's approach to garsubellin A (**6**). 10
1.2.4 Stoltz's double acylation approach towards garsubellin A (**6**). 16
1.2.5 Kraus' manganic acetate mediated cyclization methodology..... 16
1.2.6 Grossman's intramoleular aldol approach towards nemorosone (**10**). 16
1.2.7 Enantiospecific approach towards garsubellin A (**6**) by Mehta..... 19
1.2.8 Miscellaneous methodology applied to PPAP total synthesis. 19
1.3 Our strategy for the synthesis of PPAPs. 23
1.4 Allene-nitrile oxide cycloadditions..... 24
1.4.1 Intermolecular allene-nitrile oxide cycloadditions. 24
1.4.2 Allene-intramolecular nitrile oxide cycloadditions. 25
1.4.3 Trends in INOC reactivity. 28
1.5 Mukaiyama aldol condensation. 29
1.6 Hyperevolutin A (**3a**) model study by Dongxiang Zeng. 30
2. Results and Discussion 35
2.1 Assembly of allenyl ketones. 35
2.1.1 Synthesis of allenyl ketone **161**. 36
2.1.2 Studies toward the synthesis of allenyl ketone **162**. 47
2.2 Mukaiyama aldol condensation methodology studies. 55

2.2.1 3-Nitropropanal acetal studies. 57
2.2.2 3-Silyl ether propanal acetal studies. 61
2.2.3 3-Halopropanal acetal studies. 64
2.3 Further elaboration of allenyl ketone **161**. 67
2.3.1 Alkylation of allenyl ketone **161** 67
2.3.2 Mukaiyama aldol condensation of allenyl silyl enol ethers. 74
2.4 Conclusions. 79
3. Experimental Section 81
3.1 General methods. 81
3.2 Experimental procedures. 82
References 160
Appendix. ^{1}H and ^{13}C NMR for selected compounds. 173
Vita 354

List of Tables

Table 1. Results for ozonolysis of **186**..... 44
Table 2. Results for 3-nitropropanal acetal series..... 58
Table 3. Results for silyl ether series..... 62
Table 4. Results for 3-halopropanal acetals..... 65
Table 5. Attempted alkylation of allenyl ketone **161**..... 69
Table 6. Results of alkylation of allyl esters with iodide **208**..... 72
Table 7. Results for Mukaiyama aldol condensation with silyl enol ether **295**..... 77
Table 8. Results for Mukaiyama aldol condensation with silyl enol ether **296**..... 78

List of Figures

Figure 1. Phloroglucinol (**1**) and examples of polyprenylated acylphloroglucinols..... 2
Figure 2. Polyprenylated phloroglucinols..... 3
Figure 3. Berkeleydione (**13**) and berkeleytrione (**14**)..... 5
Figure 4. *p*-Ethoxyphenyl-pybox ligand for catalytic asymmetric Diels-Alder reaction. 22

List of Schemes

Scheme 1. Biosynthesis of phloroglucinol (**18**). 6
Scheme 2. Biosynthesis of acylphloroglucinol **25** towards the synthesis of **2a**. 7
Scheme 3. Hypothetical mechanism of hyperforin (**2a**) biosynthesis. 7
Scheme 4. Biosynthesis of sampsonione A (**4**) proposed by Sim. 8
Scheme 5. Preparation of phloroglucinol **36** by Effenberger. 9
Scheme 6. Nicolaou's synthesis of a functionalized garsubellin A core. 11
Scheme 7. Further elaboration of the bicyclic core of garsubellin A (**6**). 12
Scheme 8. Synthesis of bicyclic lactone **53** by Shibasaki. 12
Scheme 9. Preparation of 18-epi-8-deprenylgarsubellin A (**58**). 13
Scheme 10. Synthesis of bicyclic lactone **60**. 14
Scheme 11. Preparation of 8-deprenylgarsubellin A (**65**). 15
Scheme 12. Synthesis of phloroglucinol **72** by Stoltz. 17
Scheme 13. Preparation of hyperforin bicyclic core **77** by Kraus. 18
Scheme 14. Intramolecular aldol approach to PPAPs by Grossman. 18
Scheme 15. Enantiospecific approach to PPAPs by Mehta. 20
Scheme 16. Miesch's cyclization cascade reaction. 20
Scheme 17. Successive Michael reaction approach to bicyclo[3.3.1]nonenone cores by Ohkata. 21
Scheme 18. Example of catalytic asymmetric Diels-Alder and elaboration towards hyperforin (**2a**) by Shibasaki. 22
Scheme 19. Retrosynthetic analysis of PPAPs utilizing an allene-INOC. 23
Scheme 20. Allene-nitrile oxide cycloadditions. 24
Scheme 21. Selected allene-NOC reactions. 25
Scheme 22. Cycloaddition of allenyl sulfones and allenes. 26
Scheme 23. Intramolecular nitrone-allene cycloaddition. 26
Scheme 24. Example of an allene-INOC reaction. 27
Scheme 25. Chemoselectivity in the INOC reaction. 28
Scheme 26. Effect of olefin substitution in INOC reactions. 28

Scheme 27. Mukaiyama aldol condensation..... 29
Scheme 28. Mechanism of Mukaiyama aldol condensation..... 29
Scheme 29. Preparation of δ-alkoxy-α,β-unsaturated aldehydes. 30
Scheme 30. Exchange reaction between the acetal and isopropoxy group..... 30
Scheme 31. Retrosynthesis of hyperevolutin A (**3a**). 31
Scheme 32. Preparation of allenyl ketone **151**..... 31
Scheme 33. Mukaiyama aldol condensation in Zeng's model study. 32
Scheme 34. Allene-INOC of **156**..... 33
Scheme 35. Attempted ozonolysis of **157**..... 34
Scheme 36. Retrosynthesis of allenyl ketones. 35
Scheme 37. Preparation of enone **167**..... 36
Scheme 38. Preparation of prenyllithium (**172**)..... 37
Scheme 39. Synthesis of silyl enol ether **175** by the modified Lipshutz procedure. 37
Scheme 40. Synthesis of ketone **176**..... 38
Scheme 41. Alternative synthesis of ketone **176**. 39
Scheme 42. Synthesis of enol ether **180**. 39
Scheme 43. Alternative synthesis of **180**. 40
Scheme 44. Attempted 1,2-addition of ketone **180** with organometallic reagents. 41
Scheme 45. Cerate addition to enone **180**..... 42
Scheme 46. Dehydration of alcohol **186**. 43
Scheme 47. Ozonolysis of **186**..... 43
Scheme 48. Proposed epoxidation of **186**..... 45
Scheme 49. Epoxidation of **186**. 45
Scheme 50. Revised retrosynthetic analysis of allenyl ketone **161**. 45
Scheme 51. Reduction of aldehyde **190**..... 46
Scheme 52. Results for epoxidation of **196**. 46
Scheme 53. Preparation of allenyl ketone **161**..... 47
Scheme 54. Retrosynthesis of allenyl ketone **162**. 48
Scheme 55. Attempted alkylation of silyl enol ether **177**. 49

Scheme 56. Proposed synthesis of diene **206** via iodide **208**. 49
Scheme 57. Attempted alkylation of **177** with iodide **208**..... 49
Scheme 58. Proposed synthesis of **206** via propargyl iodide **210**..... 50
Scheme 59. Synthesis of ketone **212**..... 50
Scheme 60. Attempted cross-metathesis of enyne **211**..... 51
Scheme 61. Synthesis of ketone **205**..... 52
Scheme 62. Attempted cerate addition to ketone **205**..... 52
Scheme 63. Proposed route to α-hydroxyketone **220**..... 53
Scheme 64. Attempted Rubottom oxidation of silyl enol ether **219**..... 53
Scheme 65. Proposed synthesis of ketone **223** via oxidative rearrangement. 54
Scheme 66. Attempted oxidative rearrangement of ketone **223**..... 54
Scheme 67. Proposed synthesis of alcohol **204** via Stille coupling..... 54
Scheme 68. Various methods for preparation of acetals..... 56
Scheme 69. 1,3-Asymmetric induction by a cyclic oxonium ion described by Molander. 60
Scheme 70. Proposed mechanism of Muckaiyama aldol with 3-nitropropanal acetals... 61
Scheme 71. Attempted S_N2 reaction of iodide **265** with sodium nitrite or silver nitrite. 66
Scheme 72. Synthesis of **269**. 67
Scheme 73. Retrosynthetic analysis of isoxazoline **270**..... 68
Scheme 74. Preparation of silyl enol ether **275**. 70
Scheme 75. Alkylation of silyl enol ether **275**..... 70
Scheme 76. Proposed alkylation via Mander's strategy..... 71
Scheme 77. Acylation of **161** with cyanoformate **280**..... 72
Scheme 78. Attempted alkylation with iodide **208**..... 72
Scheme 79. Alkylation of the allyl esters with iodide **208**. 73
Scheme 80. Tsuji allylation of **161**..... 73
Scheme 81. Cross-metathesis of **287**. 73
Scheme 82. Proposed synthesis of tricycle **289**..... 74
Scheme 83. Attempted alkylation with iodide **292**..... 75

Scheme 84. Revised route to acetonide **291**. 75
Scheme 85. Aldol condensation of **161** with aldehyde **293**. 75
Scheme 86. Preparation of silyl enol ethers **295** and **296**. 76
Scheme 87. Attempted Mukaiyama aldol condensation with acetal **155**. 77
Scheme 88. Attempted hydroboration of **287**. 79

List of Abbreviations

acac	acetylacetonate
Ac	acetyl
CAN	cerium (IV) ammonium nitrate
AIBN	2,2'-azobisisobutyronitrile
Bn	benzoyl
dppf	1,1'-bis(diphenylphosphino)ferrocene
9-BBN	9-borabicyclo[3.3.1]nonane
NBS	*N*-bromosuccinimide
n-Bu or Bu	butyl
m-CPBA	3-chloroperoxybenzoic acid
ChAT	choline acetyltransferase
DNA	deoxyribonucleic acid
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCC	1,3-dicyclohexylcarbodiimide
DIBAL	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
DMPU	1,2-dimethyl-3,4,5,6-tetrahydro-2-(1*H*)-pyrimidinone
OPP	diphosphate
Et	ethyl
HMPA	hexamethylphosphoramide
HIV	human immunodeficiency virus
INOC	intramolecular nitrile oxide cycloaddition
Im	imidazole
i-Pr	*iso*-propyl
LAH	lithium aluminum hydride
LHMDS	lithium bis(trimethylsilyl)amide

LDA	lithium diisopropylamide
Mes	mesityl
Me	methyl
MOM	methoxymethyl
NMP	*N*-methyl-2-pyrrolidinone
MS	molecular sieves
NOC	nitrile oxide cycloaddition
*p*NP	*p*-nitrophenyl
Ph	phenyl
N-PSP	*N*-(phenylseleno)phthalimide
PPAP	polycyclic polyprenylated phloroglucinol
KAPA	potassium 3-aminopropylamide
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
TBAB	tetrabutylammonium bromide
TBAF	tetrabutylammonium fluoride
THF	tetrahydrofuran
TEMPO	2,2,6,6-tetramethyl-1-piperidinyloxy
TPAP	tetrapropylammonium perruthenate
TLC	thin layer chromatography
PCy_3	tricyclohexylphosphine
TES	triethylsilyl
Tf	triflate
TIPS	triisopropylsilyl
TMS	trimethylsilyl
t-Bu or ^{t}Bu	*tert*-butyl
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TBHP	*tert*-butyl hydroperoxide
p-TsOH	*p*-toluenesulfonic acid

1. Introduction and Background

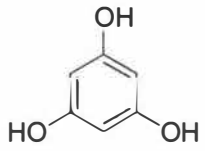
1.1 Polycyclic polyprenylated acylphloroglucinol natural products.

Phloroglucinol (**1**) is found in a variety of natural products as a substitutient or as a key structural moiety (Figure 1). In recent years, phloroglucinol based natural products isolated from *Hypericum*, *Garcinia*, and *Clusia* have attracted attention from synthetic chemists due to their medicinal properties and unique structural features. Many of the biologically active metabolites from these species are polycyclic polyprenylated acylphloroglucinol (PPAP) derivatives that are characterized by a densely substituted bicyclo[3.3.1]nonane-2,4,9-trione, that also contains prenyl or geranyl appendages. Although many groups are pursuing synthetic studies, no total synthesis has been reported for any PPAP.

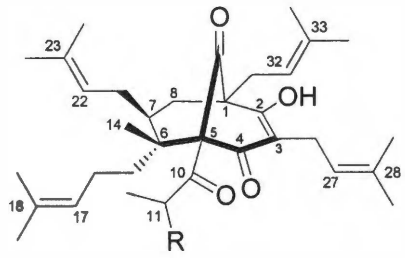
1.1.1 Biological activity for selected PPAPs.

Interest in PPAP natural products increased when hyperforin (**2a**, Figure 1) was proposed to be responsible for the medicinal effects of St. John's wort (*Hypericum perforatum*), a dietary supplement commonly used to treat mild depression.[1-3] Hyperforin displays a spectrum of antibacterial properties,[4] including against the multidrug resistant *Staphyloccoccus aureus*,[5] as well as cytostatic activity.[6] Hyperforin (**2a**) was first isolated in 1971 by Gurevich and coworkers[4] and was concluded to be a PPAP by X-ray diffraction and spectroscopic methods.[7,8] Characterization has been difficult because hyperforin is prone to oxidation in solution.

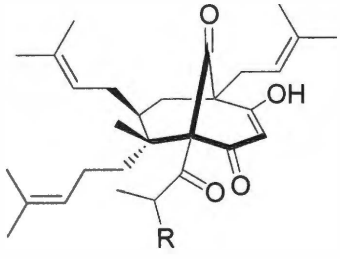
Over the past twenty years more PPAP natural products have been isolated, many of which displayed medicinal properties. The PPAPs shown in Figure 1 and Figure 2 are considered to be potential drug candidates. Some of the compounds show anticancer activity, for example, hyperevolutin A (**3a**) and B (**3b**), isolated from *Hypericum revolutum*, demonstrated growth-inhibitory activity against the Co-115 human colon carcinoma cell line.[9] Other anticancer compounds were isolated from *Hypericum*



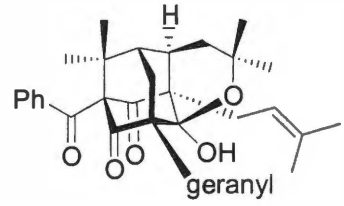
1: Phloroglucinol



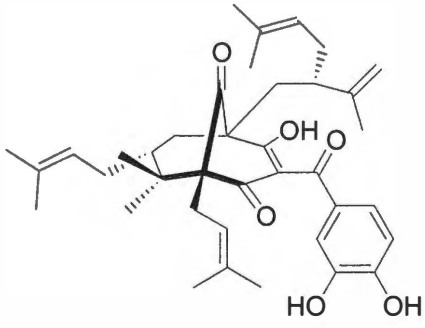
2a: R = CH_3 Hyperforin
2b: R = H Adhyperforin



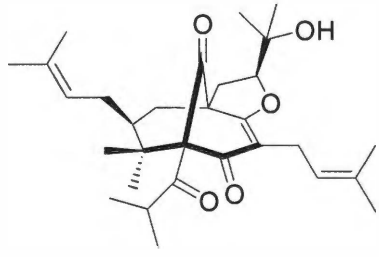
3a: R = CH_3 Hyperevolutin A
3b: R = H Hyperevolutin B



4: Sampsonione A

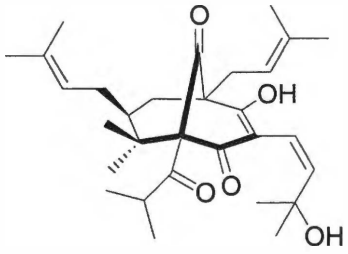


5: Garcinol

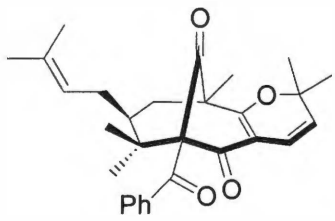


6: Garsubellin A

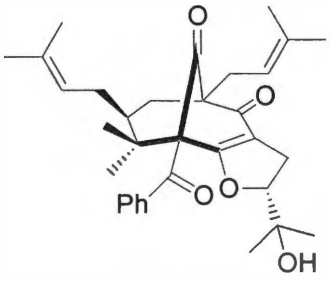
Figure 1. Phloroglucinol (**1**) and examples of polyprenylated acylphloroglucinols.



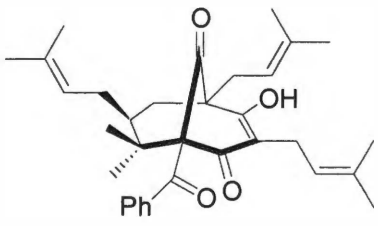
7: Garcinielliptone F



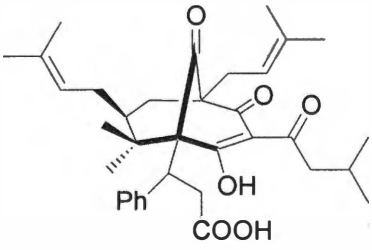
8: Papuaforin A



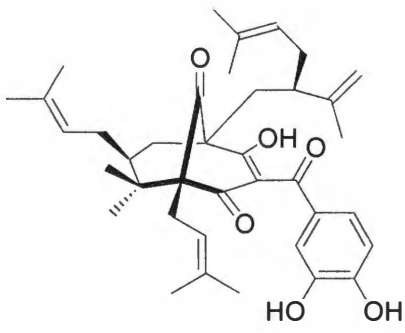
9: Hyperibone B



10: Nemorosone II



11: Laxifloranone



12: Guttiferone E

Figure 2. Polyprenylated phloroglucinols.

sampsonii, including sampsonione A (**4**) and sampsonione I (not shown), which exhibit a potent cytotoxic effect against the P388 cancer cell line (mouse lymphocytic leukemia).[10,11] Garcinol (**5**), isolated from the dried fruit rind of *Garcinia inica*,[12] induces apoptosis in human leukemia cells.[13] This compound also was recently reported to be an antioxidant[14-16] that displays antibiotic activity.[17,18]

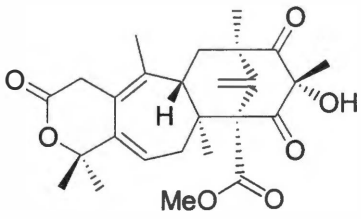
Garsubellin A (**6**), isolated from the bark and seeds of *Garcinia subelliptica*, is a potent inducer of choline acetyltransferase (ChAT), the enzyme responsible for the biosynthesis of acetylcholine. In fact, **6** is found to increase *in vitro* ChAT activity in rat septal neurons by 154% at 10 μM concentration. Since the dementia associated with neurodegenerative diseases such as Alzheimer's is partially caused by decreased levels of acetylcholine due to the atrophy of cholinergic neurons, it is postulated that **6** could be developed into a therapy.[19-21] Recent evidence suggests **6** may also have an anti-inflammatory effect.[22]

Another potential anti-inflammatory is garcinielliptone F (**7**, Figure 2), which also comes from the seeds of *Garcinia subelliptica.* This compound (**7**) was found to potently inhibit the release of β-glucuronidase and lysozyme and has an inhibitory effect on superoxide anion generation in rat neutrophils in a concentration-dependant manner. It is believed that **7** could be developed into a therapeutic treatment or a preventive measure for related peripheral diseases.[23]

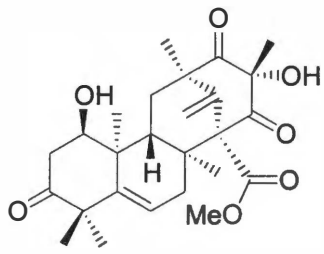
It is notable that papuaforin A (**8**, *Hypericum papuanum*),[24] hyperibone B (**9**, *Hypericum scabrum*),[25] and nemorosone II (**10**, *Clusia rosea*) display antibacterial properties.[26-28]

Other biologically active PPAPs such as laxifloranone (**11**, *Marila laxiflora*)[29] and guttiferone E (**12**, *Garcinia pyrifera*)[30] have been shown to inhibit the cytopathic effects of *in vitro* HIV infection. In addition to HIV activity, guttiferone E (**12**) also demonstrated anticancer activity via microtubule disassembly inhibition in a manner similar to the drug paclitaxel.[31]

Recently, analogues of the acylphloroglucinol core have been isolated from *Penicillium* that led to a new family of biologically active natural products. In



13: Berkeleydione



14: Berkeleytrione

Figure 3. Berkeleydione (**13**) and berkeleytrione (**14**).

berkeleydione (**13**) and berkeleytrione (**14**) the bridging carbonyl of the phloroglucinol core is replaced with an olefin (Figure 3). They both demonstrate anticancer activity.[32]

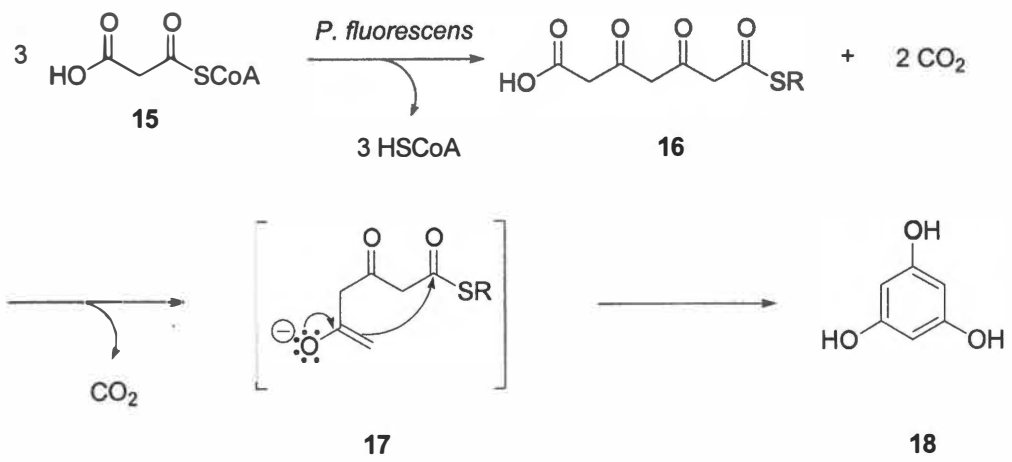
1.1.2 Mechanism of action for hyperforin (2a) and garcinol (5).

The mechanisms of action for biological activity of the PPAPs have not been the subject of study. However, the antidepressant effect observed in hyperforin (**2a**) has been attributed to inhibition of synaptosomal uptake of serotonin, dopamine, noradrenaline, and other compounds by a novel mechanism. Instead of the classical antidepressant mechanism of inhibiting monoamine transport proteins, hyperforin (**2a**) acts by changing intracellular H^+ and Na^+ concentrations.[2]

The anticancer effects of garcinol (**5**) have also been studied. It has been reported that **5** inhibits histone acetylation *in vivo* in HeLa cells in a concentration-dependant manner. Since histone acetylation is believed to directly facilitate DNA transcription, hypoacetylation of histone leads to apopthesis of the cancer cell.[33]

1.1.3 Biosyntheis of phloroglucinol (1), hyperforin (2a), and sampsonione A (4).

The biosynthesis of phloroglucinol (**1**) was recently charted by John W. Frost and coworkers (Scheme 1).[34] They identified the enzyme from *Pseudomonas fluorescens* that condenses three malonyl coenzyme A (**15**) molecules to produce activated 3,5-diketoheptanedioate **16**. The compound is decarboxylated to generate enolate **17** that

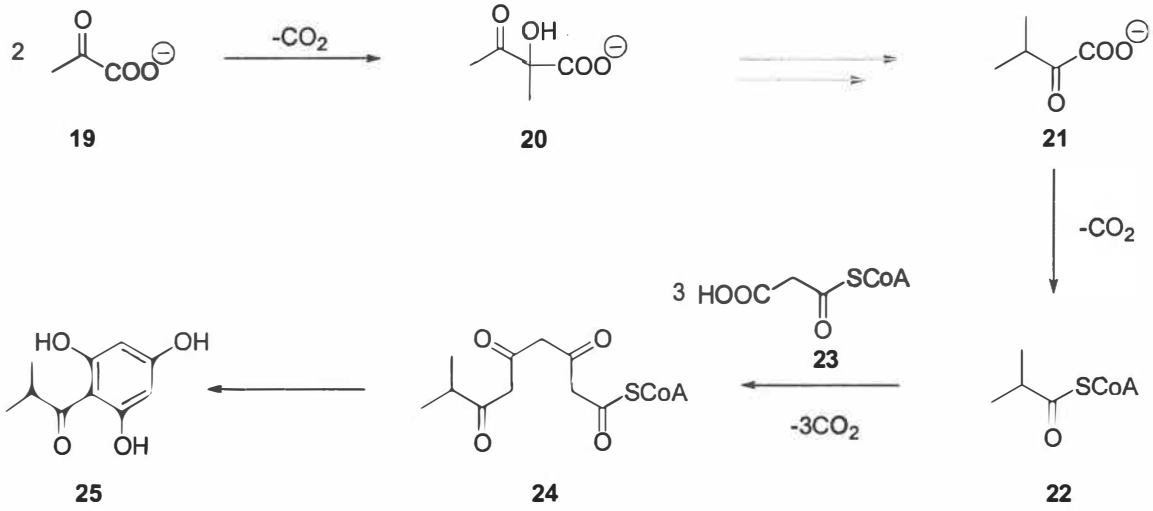


Scheme 1. Biosynthesis of phloroglucinol (**18**).

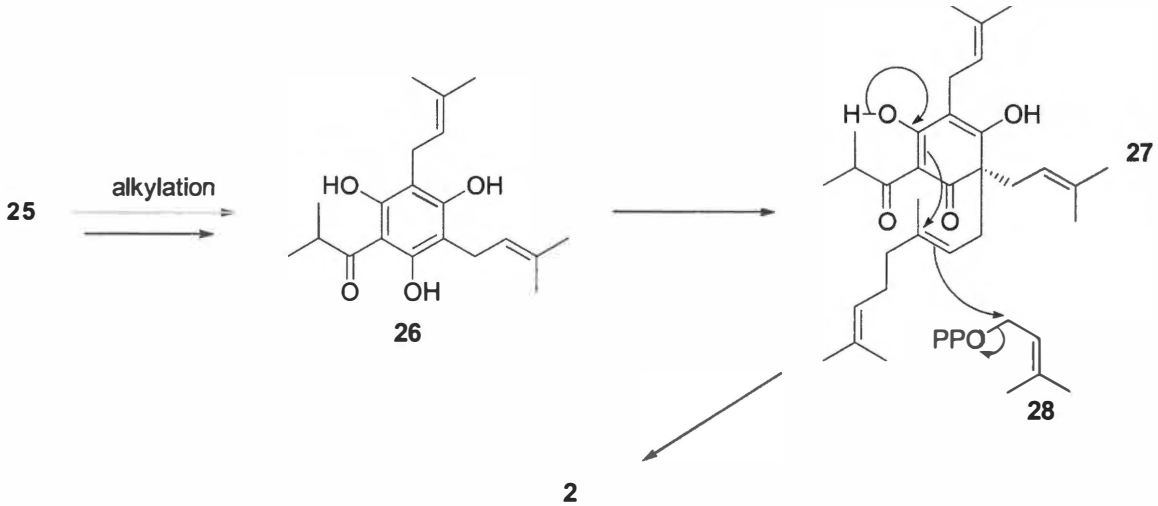
readily cyclizes to phloroglucinol (**18**). Further acetylation by enzymes can be envisioned to lead to acylphloroglucinols.

Likewise, a biosynthesis of hyperforin (**2a**) has been proposed by Wolfgang Eisenreich and coworkers.[35] They determined that the core acylphloroglucinol **25** may be prepared from pyruvate based on carbon-13 labeling experiments (Scheme 2). However, some of the intermediates could be formed from the metabolism of valine. As shown in Scheme 2, self condensation of pyruvate (**19**) is followed by decarboxylation to afford α-hydroxyketone **20** that undergoes further transformations to yield ketocarboxylate **21**. After oxidative decarboxylation, acetyl-CoA **22** is condensed with three malonyl-CoA (**23**) units to generate triketone **24**. Intramolecular cyclization ensues to produce acylphloroglucinol **25**. The biosynthesis of **2a** is postulated to follow a series of alkylations of the aromatic nucleus to yield enol **27** (Scheme 3). The synthesis of **2a** is completed by a cascade involving an enol, the 2',3' double bond of the pendant geranyl side chain, and dimethylallyl diphosphate (**28**).[36]

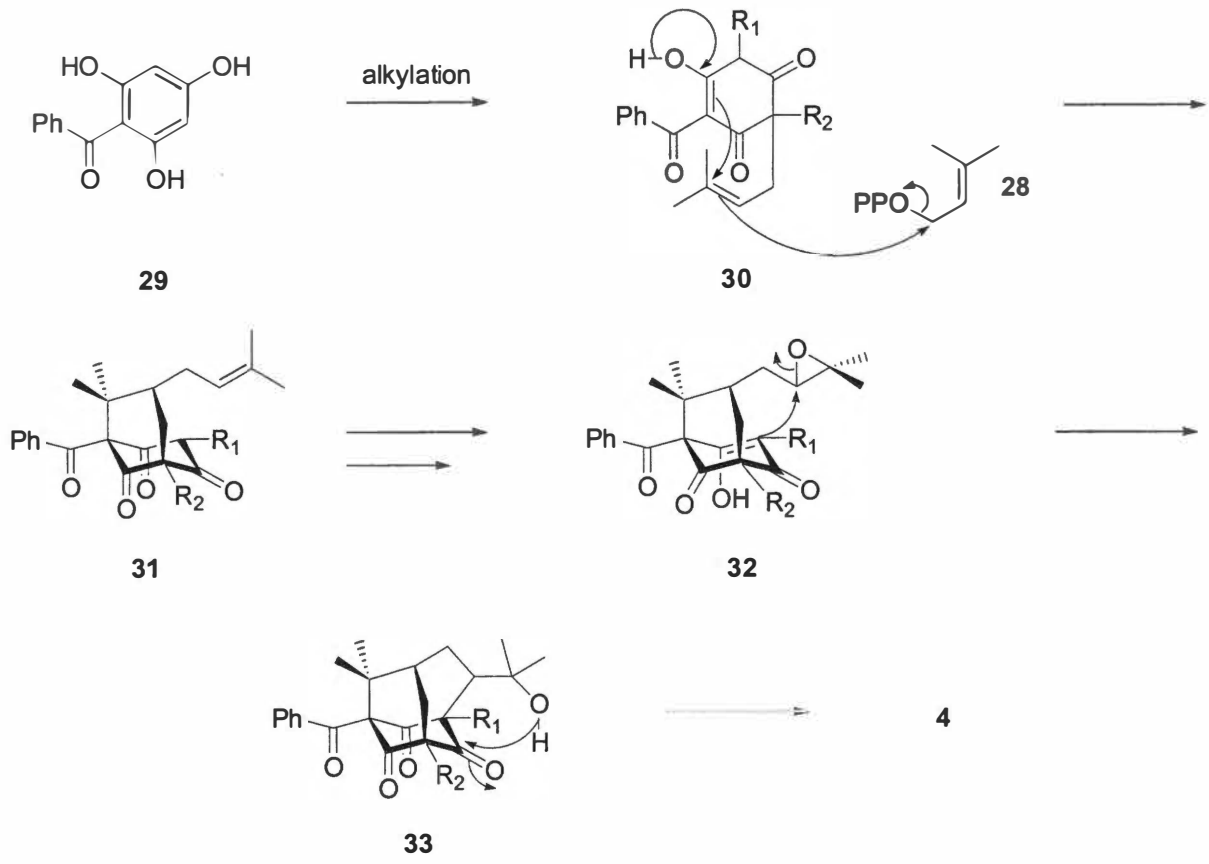
The biosynthesis of the sampsoniones from a simple benzoylphloroglucinol was proposed by Sim and Hu in 2000 (Scheme 4).[10] Presumably, a biogenetically acceptable 2,4,6-trihydoxybenzophenone is alkylated and then cyclizes to generate bicycle **31**. The double bond is epoxidized, intramolecular ring-opening by an enol generates



Scheme 2. Biosynthesis of acylphloroglucinol **25** towards the synthesis of **2a**.



Scheme 3. Hypothetical mechanism of hyperforin (**2a**) biosynthesis.



Scheme 4. Biosynthesis of sampsonione A (**4**) proposed by Sim.

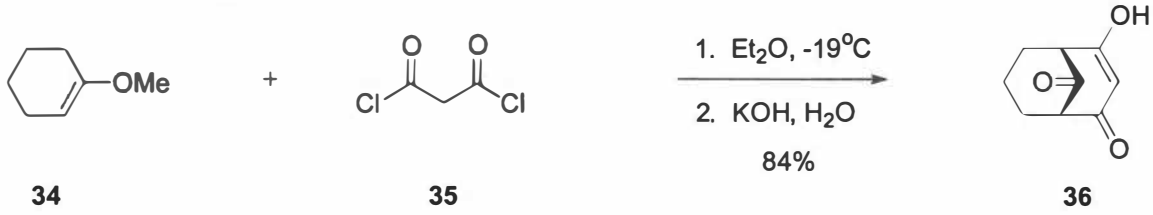
pseudoadamantane skeleton **33**. Sampsonione A (**4**) is completed by a ketalization reaction involving the free hydroxyl and the only reachable ketone.

1.2 PPAP strategies and synthetic studies.

Despite the various medicinal properties, no total synthesis has been reported for a PPAP. However, many preliminary synthetic studies have been reported. PPAPs have proven to be formidable synthetic targets because they possess asymmetric vicinal quaternary centers and a densely functionalized tetracarbonyl array which includes the bicyclo[3.3.1]nonan-9-one core. The adjacent quaternary centers in the framework make traditional annulation approaches ineffective as synthetic routes. Direct acylation of a β-diketone would also be expected to be problematic due to the preference of O-acylation. The congestion around the bridgehead and the tendency of the natural products to oxidize in air suggests that the end game must be well planned. Since the synthesis of bicyclo[3.3.1]nonanes has been reviewed,[37] the following sections will review the synthetic strategies employed by others toward the total synthesis of PPAPs.

1.2.1 Effenberger's double acylation approach to phloroglucinols.

Franz Effenberger and coworkers reported one of the first syntheses of a bicyclic phloroglucinol core in 1984 (Scheme 5).[38] Phloroglucinol core **36** was prepared by a double acylation of enol ether **34** with malonyl dichloride (**35**) in good yield. Stoltz has employed such a strategy in his approach to the garsubellins, however, the procedure is much less efficient in a more complex setting.



34 **35** **36**

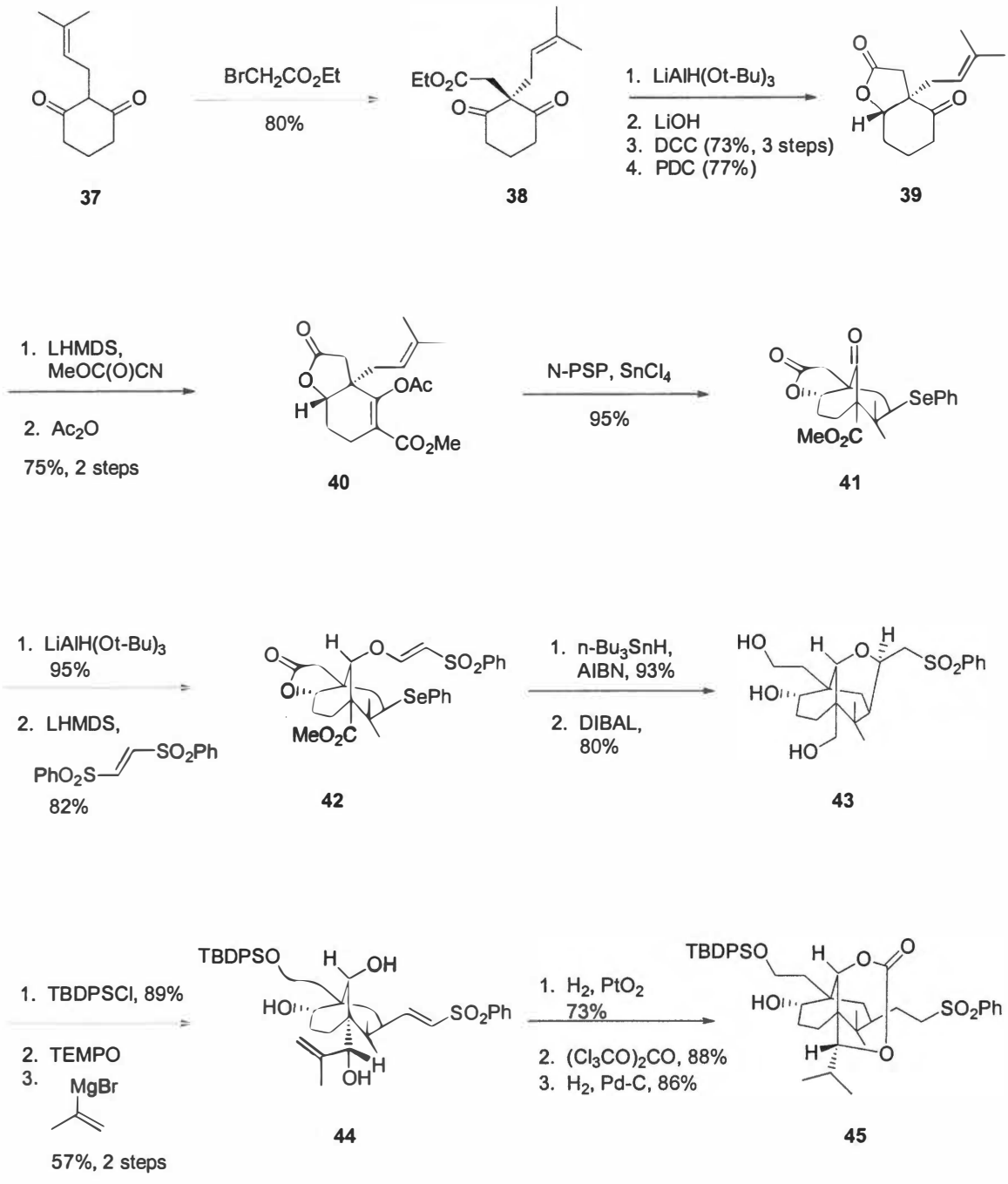
Scheme 5. Preparation of phloroglucinol **36** by Effenberger.

1.2.2 Nicolaou's selenium-induced cyclization approach towards garsubellin A (6).

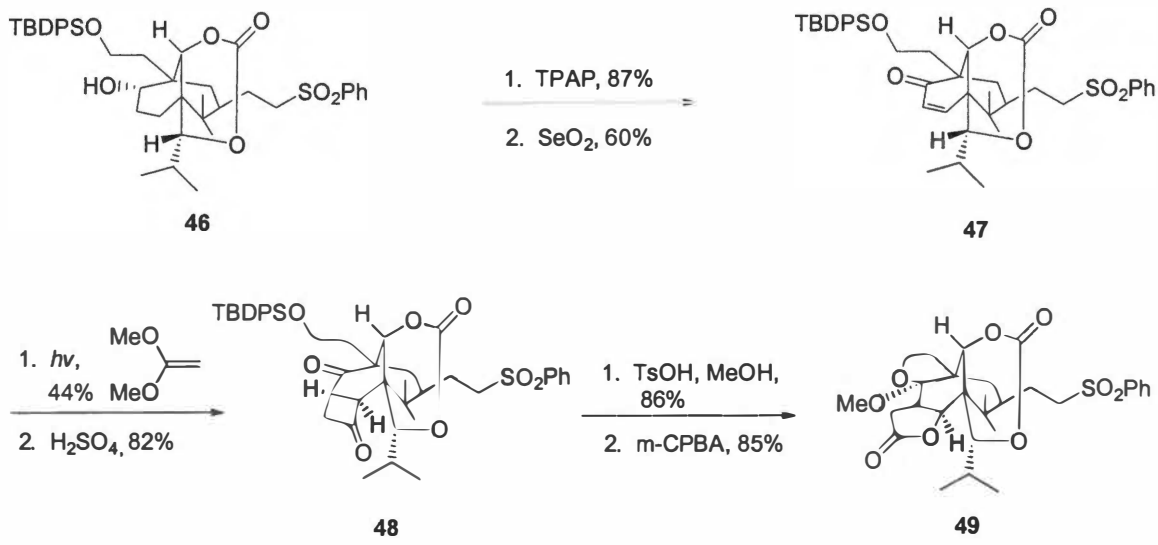
In 1999, K. C. Nicolaou and coworkers reported the synthesis of a fully functionalized [3.3.1] bicycle from readily available cyclohexanedione **37** (Scheme 6 and Scheme 7).[39] In the key step the bicyclic core **41** was prepared in 95% yield via a selenium-induced cyclization of enol ether **40** onto a pendant prenyl group in the presence of $SnCl_4$. The product contains the desired bicyclic core, the geminal dimethyl substituents, and fully functionalized bridgehead quaternary centers. Interestingly, this approach mimics the proposed biosynthesis of the phloroglucinol core and is unique because it is the only synthetic study to annulate the geminal dimethyl-containing ring onto a functionalized cyclohexanone. All other studies construct the bicyclic core via annulation of the β-dicarbonyl-containing ring onto the cyclohexanone. Sixteen additional steps were necessary from **41** to produce bicycle **49**.

1.2.3 Shibasaki's approach to garsubellin A (6).

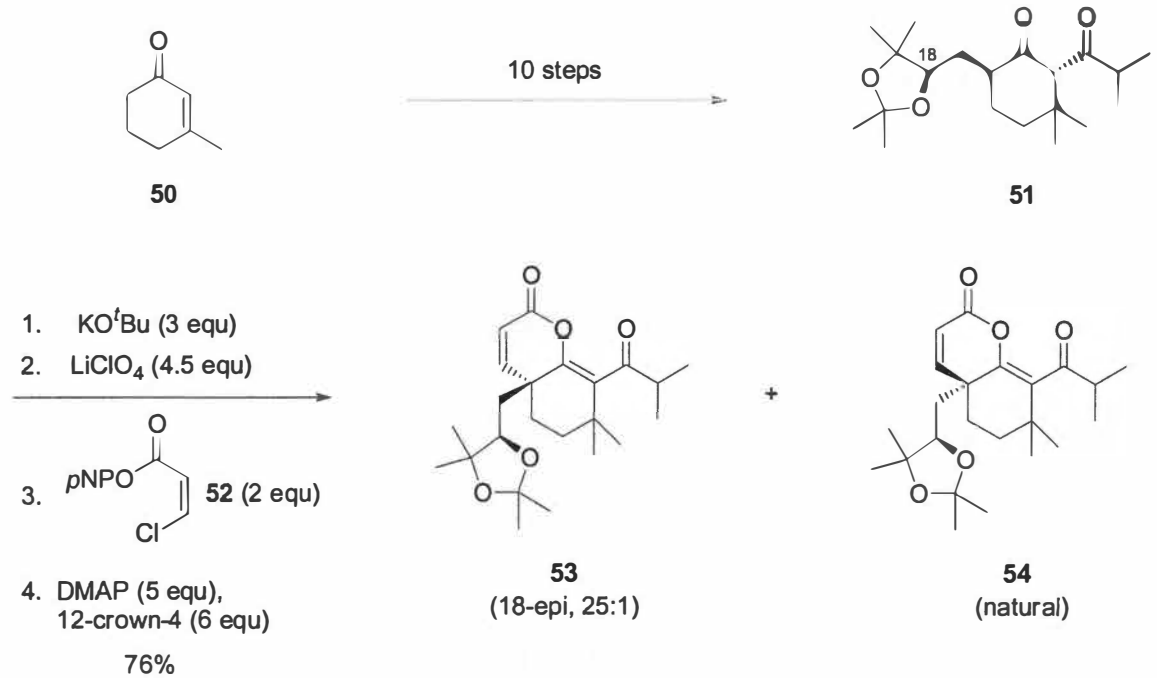
Perhaps the most advanced synthetic study toward **6** was reported by Masakatsu Shibasaki and coworkers. In the construction of the 18-epi-tricyclic core, 1,3-diketone **51** was prepared from enone **50** in ten steps (Scheme 8).[40] After surveying various conditions, bicyclic lactones **53** and **54** were made in a one-pot Michael addition–elimination reaction with electrophile **52** in 75% yield. The incorrect isomer at C-18 (epimer **53**) was favored 25:1 (**53**:**54**). Nonetheless, the synthesis continued by introducing a pentamethyldisilyl group via conjugate addition with Me_5Si_2Li that was followed by conversion of the lactone to thiol ester **55** with aluminum thiolate in excellent yield (Scheme 9). Bicyclic core **56** was completed by reducing the thiol ester under Fukuyama conditions followed by an intramolecular aldol condensation, and oxidizing the resulting aldol to the tricarbonyl. Tamao oxidiation of the silyl group and subsequent β-elimination in the same pot regenerated the α,β-unsaturated ketone. In completing the tricyclic core, the tetrahydrofuran ring was installed via a Wacker oxidation between the acetonide and the enone to generate tricycle **57** in 69% yield. 18-Epi-8-deprenylgarsubellin A (**58**) was finished by converting **57** into a vinyl iodide and



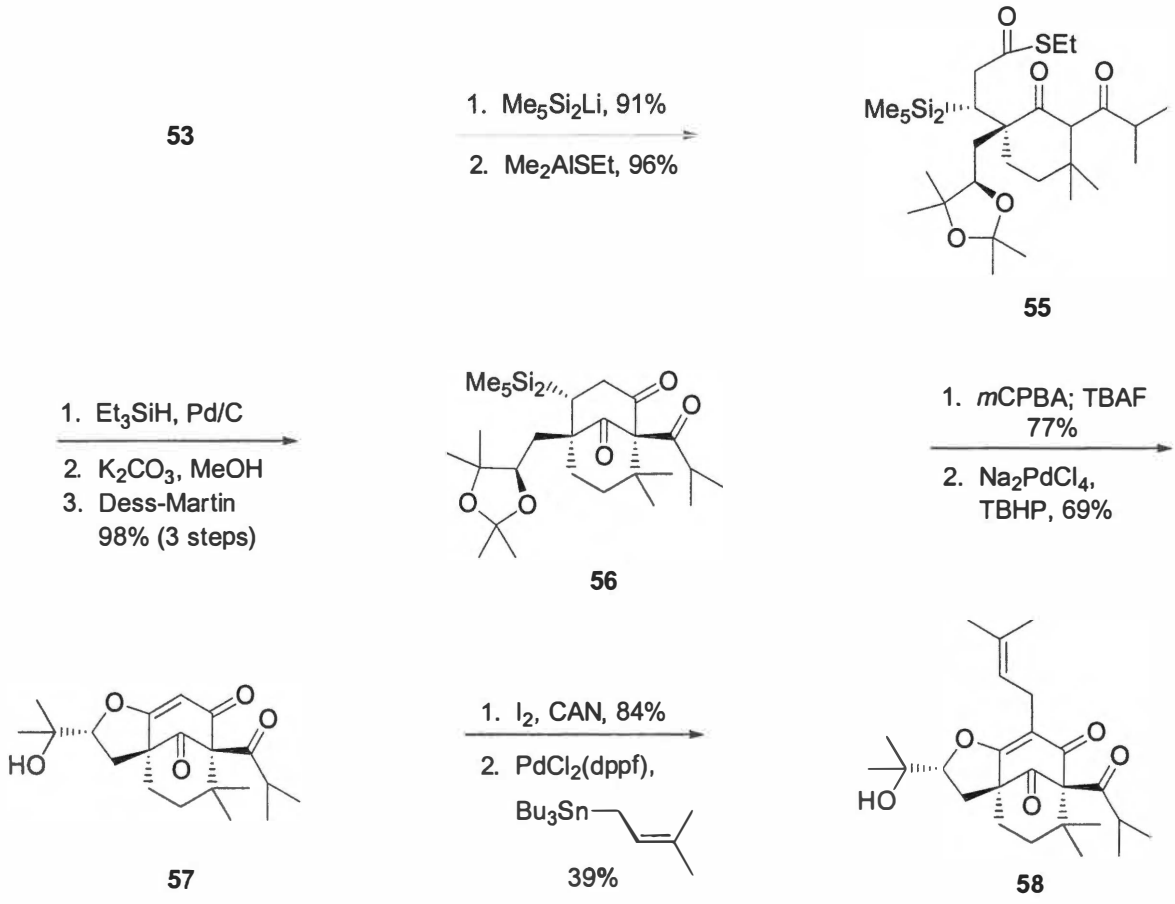
Scheme 6. Nicolaou's synthesis of a functionalized garsubellin A core.



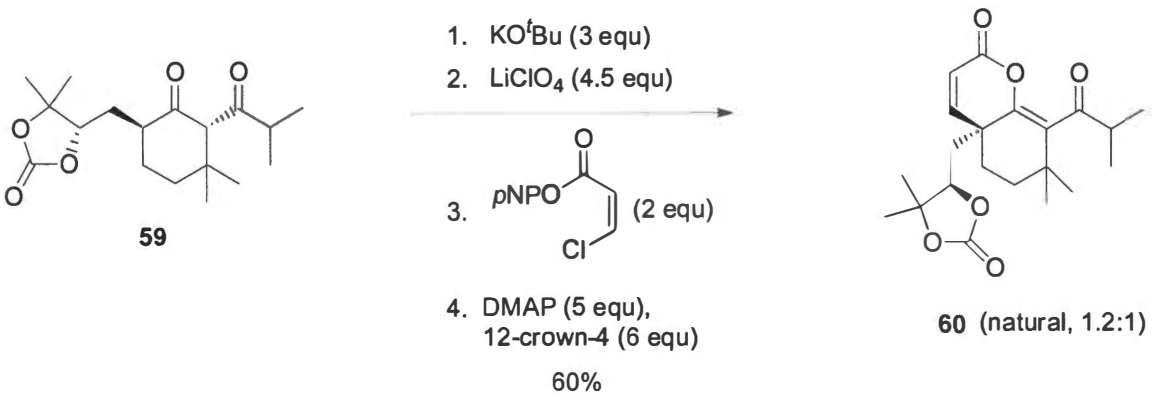
Scheme 7. Further elaboration of the bicyclic core of garsubellin A (**6**).



Scheme 8. Synthesis of bicyclic lactone **53** by Shibasaki.



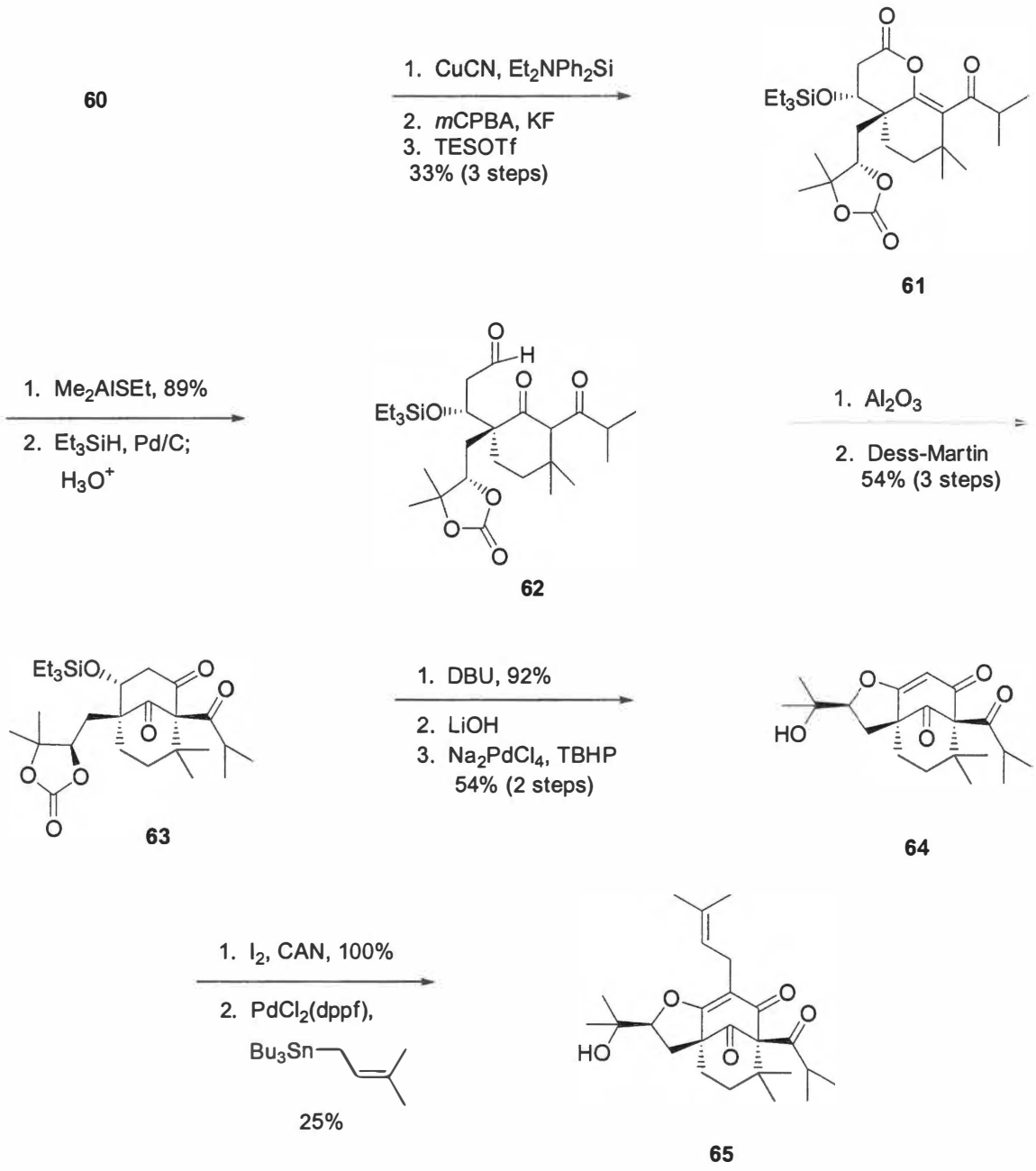
Scheme 9. Preparation of 18-epi-8-deprenylgarsubellin A (**58**).



Scheme 10. Synthesis of bicyclic lactone **60**.

then introducing a prenyl group via Stille coupling with tributylprenyltin which gave **58** in 39% yield.

In a second article, Shibasaki reported that the desired isomer could be favored in a ratio of 1.2:1 by simply changing the acetonide **51** (Scheme 8) to a carbonate **59** (Scheme 10).[41] The selectivity is attributed to chelation of the lithium enolate to the acetonide **51** that leads to the wrong isomer. However, no chelation occurs in carbonate **59** and the desired isomer is produced. The synthesis proceeded through the conversion of lactone **60** to silyl ether **61** by 1,4-addition of a silylcuprate followed by Tamao oxidation and protecting the resulting alcohol (Scheme 11). The lactone was then treated with aluminum thiolate followed by exposure to Fukuyama's conditions to give aldehyde **62**. In the key step, **62** underwent an aldol condensation in the presence of alumina. The resulting alcohol was oxidized to afford the β,β-tricarbonyl **63**. Silyl ether **63** was β-eliminated by treatment with DBU and then the carbonate was removed with lithium hydroxide. The tetrahydrofuran ring was installed via Wacker oxidation to give tricycle **64**. The product was converted to an α-iodoketone and 8-deprenylgarsubellin A (**65**) was furnished by Stille coupling with tributylprenyltin.



Scheme 11. Preparation of 8-deprenylgarsubellin A (**65**).

1.2.4 Stoltz's double acylation approach towards garsubellin A (6).

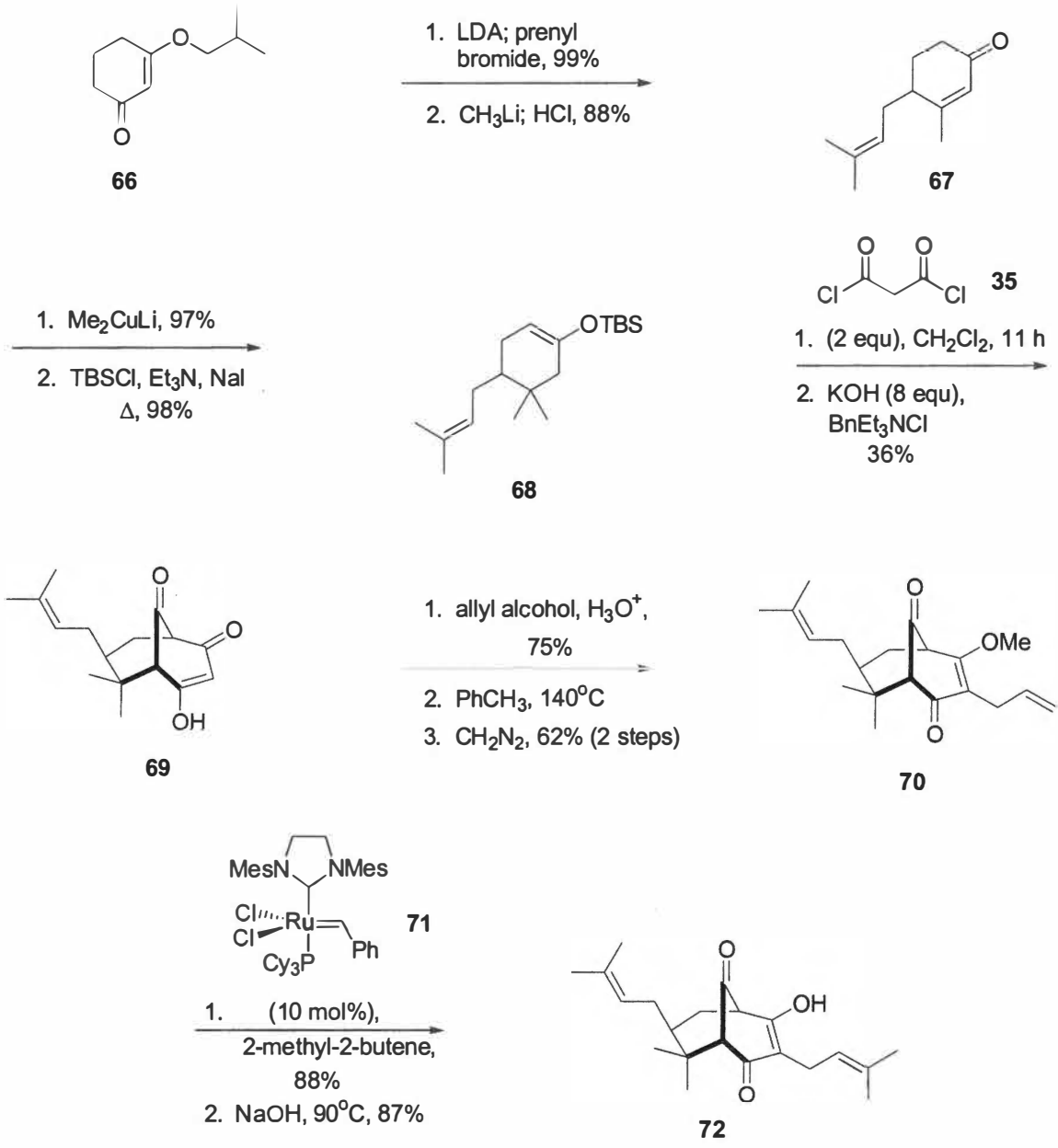
Elaborating on the double acylation method developed by Effenberger, Brian M. Stoltz and coworker applied the reaction toward the synthesis of **6** (Scheme 12).[42] Silyl enol ether **68**, prepared in four steps from readily available vinylogous ester **66**, underwent the double acylation with malonyl dichloride (**35**) to afford **69** in 36% yield. The major product was hydrolyzed silyl enol ether obtained in 59% yield. The bicyclic core was further elaborated by condensing with allyl alcohol followed by a Claisen rearrangement. The enol was converted to enol methyl ether **70** by treatment with diazomethane. In a creative way to construct a prenyl group, the allyl was converted by olefin cross-metathesis with the second generation Grubbs' ruthenium catalyst **71** in the presence with 2-methyl-2-butene at 38°C to give an 88% yield of prenyl containing material. The study was completed by saponification with sodium hydroxide, which afforded phloroglucinol **72**.

1.2.5 Kraus' manganic acetate mediated cyclization methodology.

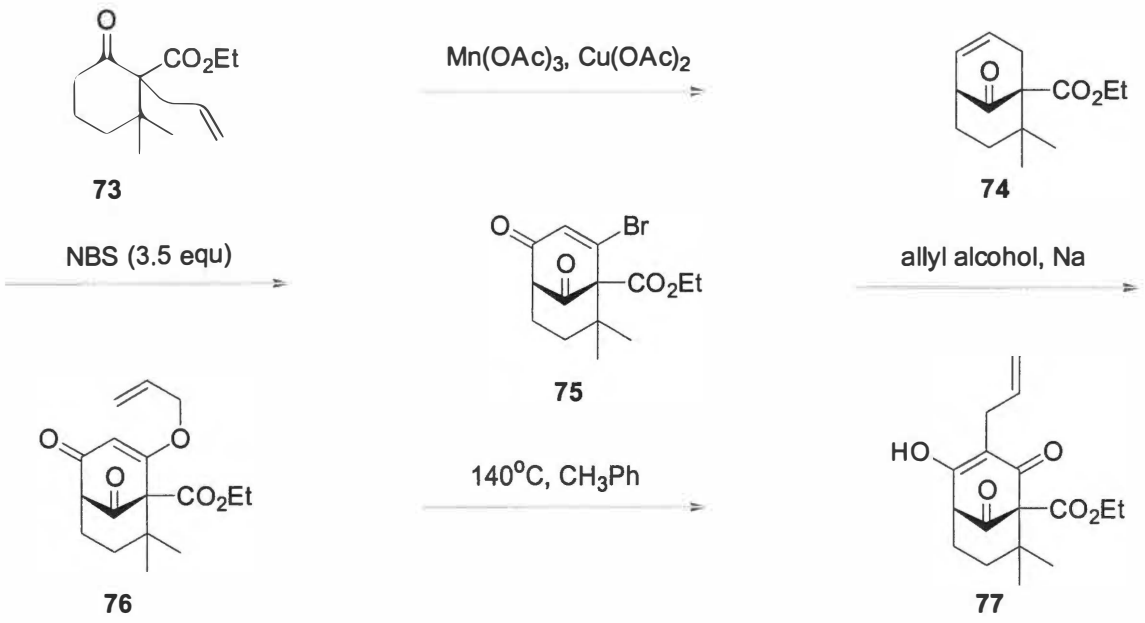
In 2003, George A. Kraus and coworkers published a series of studies utilizing a manganic-acetate mediated intramolecular cyclization approach towards the bicyclic cores of hyperforin (**2a**) and nemorosone (**10**).[43,44] In the exemplary model study, known keto ester **73** was cyclized in the presence of manganic triacetate and cupric acetate to provide **74** (Scheme 13). Olefin **74** was converted to enone **75** by bromination with 3.5 equivalents of NBS. The model was completed by reacting **75** with the sodium salt of allyl alcohol and Claisen rearrangement of the product to yield phloroglucinol **77**.

1.2.6 Grossman's intramoleular aldol approach towards nemorosone (10).

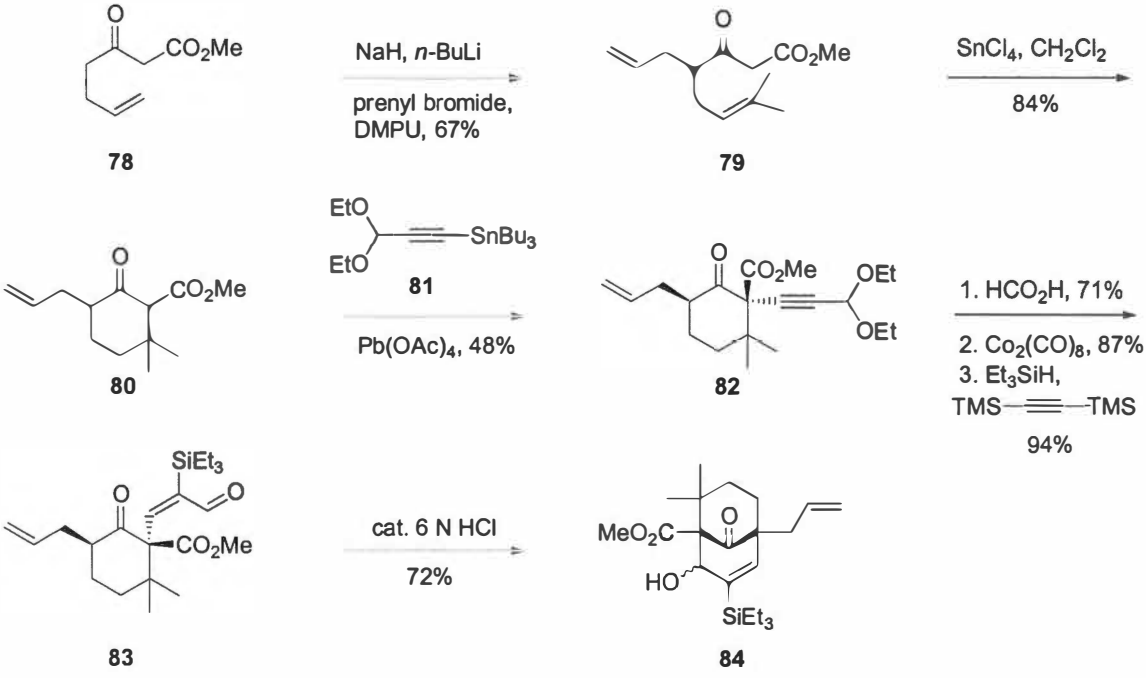
Grossman and Ciochina constructed the nemorosone skeleton using an acid catalyzed intramolecular aldol cyclization (Scheme 14).[45] The study began by alkylating known β-keto ester **78** with prenyl bromide. In the presence of tin (IV) chloride, the intramolecular cyclization proceeded smoothly to generate cyclohexanone **80**. To



Scheme 12. Synthesis of phloroglucinol **72** by Stoltz.



Scheme 13. Preparation of hyperforin bicyclic core **77** by Kraus.



Scheme 14. Intramolecular aldol approach to PPAPs by Grossman.

complete the bicyclic core, β-keto ester **80** was α-alkynylated with stannane **81** in the presence of $Pb(OAc)_4$. The resulting acetal was hydrolyzed with acid. Although Lindlar hydrogenation was unsuccessful, the triple bond was converted to a cobalt-alkyne complex with $Co_2(CO)_8$ and subsequently reduced with Et_3SiH and bis(trimethylsilyl)acetylene to yield enal **83**. Finally, an acid-catalyzed aldol condensation gave the bicyclo[3.3.1]nonanone **(84)** with the desired stereochemistry in good yield.

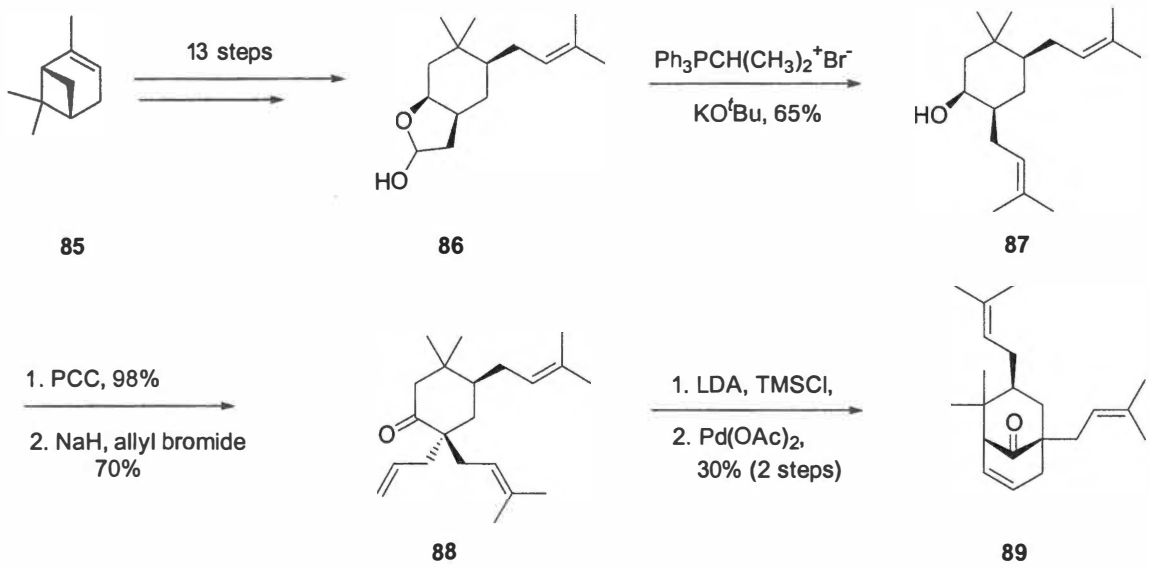
1.2.7 Enantiospecific approach towards garsubellin A (6) by Mehta.

Goverdhan Mehta and coworker reported the first enantiospecific approach to **6** (Scheme 15).[46] The chiron, α-pinene **(85)** was employed as the starting material and was transformed into lactol **86** in thirteen steps. Wittig isopropenylation of **86** was used to install the second prenyl group yielding alcohol **87**. After oxidation with PCC, the thermodynamic enolate was generated with sodium hydride and alkylation with allyl bromide furnished **88** as a single diastereomer. In the pivotal step, cyclohexanone was transformed to the silyl enol ether and then underwent Kende cyclization in the presence of palladium acetate to afford bicycle **89**.

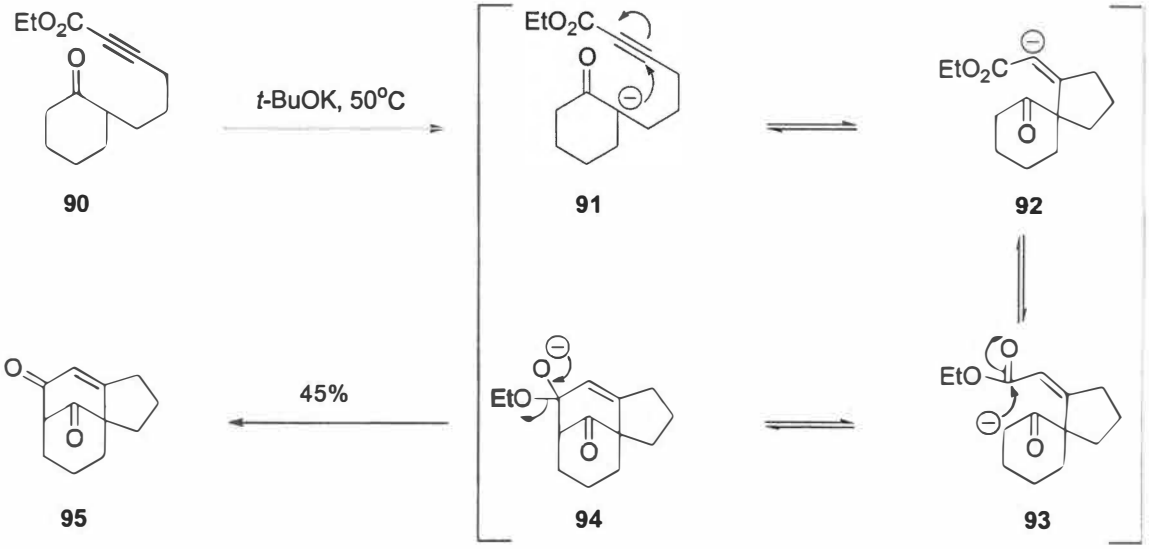
1.2.8 Miscellaneous methodology applied to PPAP total synthesis.

Over the past few years various approaches have been reported to PPAPs, albeit in the early stages. One example is the cascade reaction of acetylenic ω-ketoesters to produce substituted tricycles (Miesch and coworker, Scheme 16).[47] Thus, subjection of cyclohexanones containing an appropriate alkyne appendage (i.e. **90**) to potassium *tert*-butoxide at 50°C leads to a Michael reaction on the conjugated alkyne to afford spirocycle **93**. After an intramolecular deprotonation, Claisen condensation produces tricycle **95**.

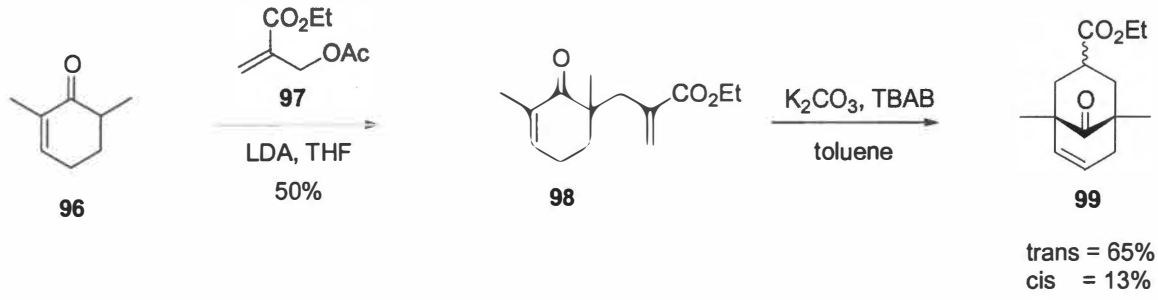
Another method for the construction of bicyclo[3.3.1]nonenones was disclosed by Katsuo Ohkata and coworkers (Scheme 17).[48] The method involves stepwise or one-pot annulation of a 2-cyclohexenone derivative by successive Michael additions. For



Scheme 15. Enantiospecific approach to PPAPs by Mehta.



Scheme 16. Miesch's cyclization cascade reaction.

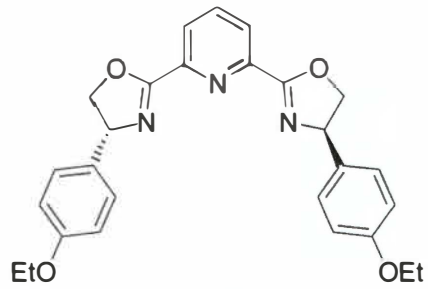


Scheme 17. Successive Michael reaction approach to bicyclo[3.3.1]nonenone cores by Ohkata.

example, cyclohexenone **96** reacts with acrylate **97** to produce **98**. The resulting α,β-unsaturated ester **98** readily undergoes another Michael addition in the presence of potassium carbonate and *tert*-butylammonium bromide to give the bicycle **99** as a mixture of isomers.

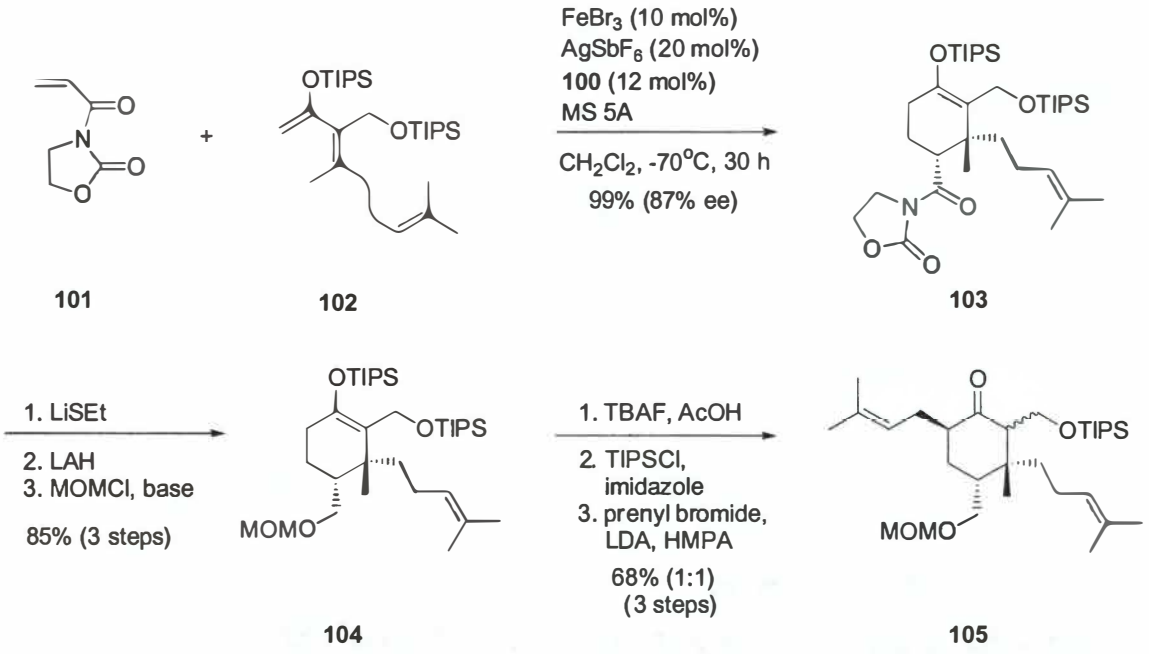
Recently, Shibasaki and coworkers published their approach towards an enantioselective synthesis of PPAPs.[49] The new method is based on synthesizing a substituted cyclohexenone via a catalytic enantioselective Diels-Alder reaction. After surveying an array of catalysts and conditions, it was found that *in situ* generation of iron (III) complexes with silver (I) salts and a modified phenyl-pybox chiral ligand **100** (Figure 4) gave satisfactory results. For example, acryloxazolidinone **101** and diene **102** underwent Diels-Alder reaction under the optimized conditions and gave cycloadduct **103** with excellent *exo* selectivity (1:>33) and high ee (87%, Scheme 18).

To illustrate how the cycloadduct could be used in total synthesis of PPAPs, alkene **103** was further elaborated. The oxazolidinone moiety was transformed to methoxymethyl ether **104** by converting to the thiol ester, reducing with LAH, and protecting the resulting alcohol with MOMCl. The silyl enol ether was hydrolyzed with TBAF to generate the ketone. Since the TIPS ether was also cleaved, the alcohol was reprotected with TIPSCl. The resulting ketone was alkylated with LDA and prenyl bromide to afford ketone **105** as a 1:1 mixture of separable diastereomers. Both diastereomers can be used in the synthesis since the stereochemistry will be relocked in during the formation of the bicyclic core.

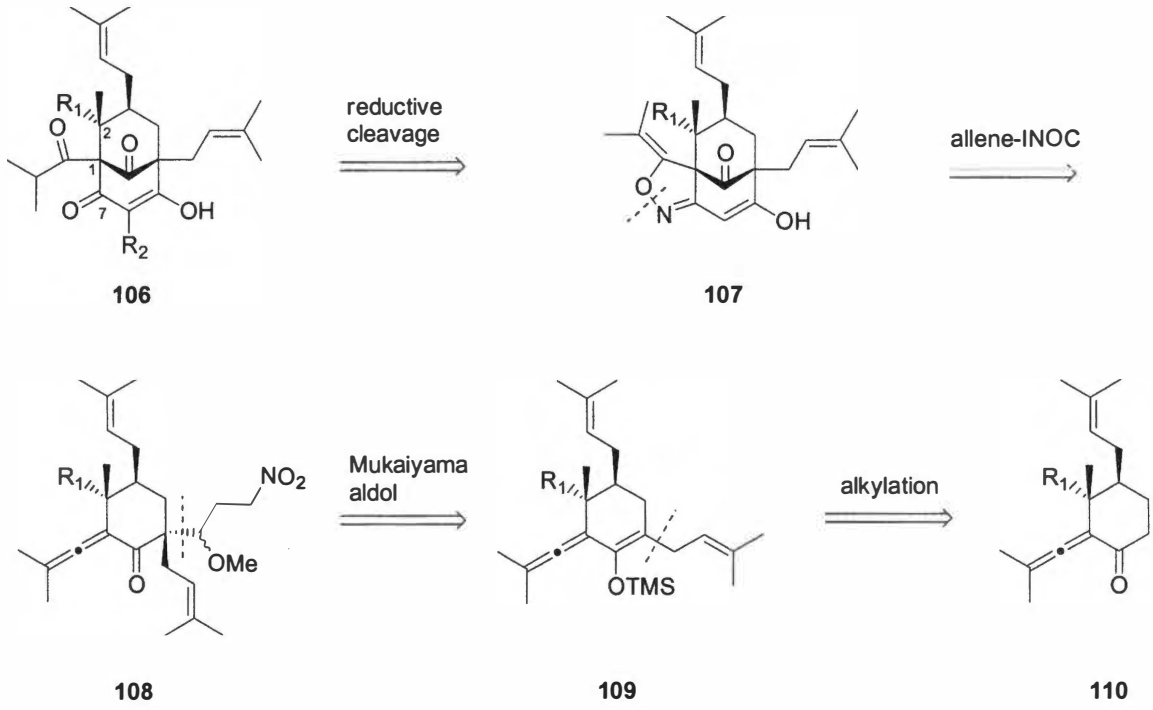


100

Figure 4. *p*-Ethoxyphenyl-pybox ligand for catalytic asymmetric Diels-Alder reaction.



Scheme 18. Example of catalytic asymmetric Diels-Alder and elaboration towards hyperforin (**2a**) by Shibasaki.

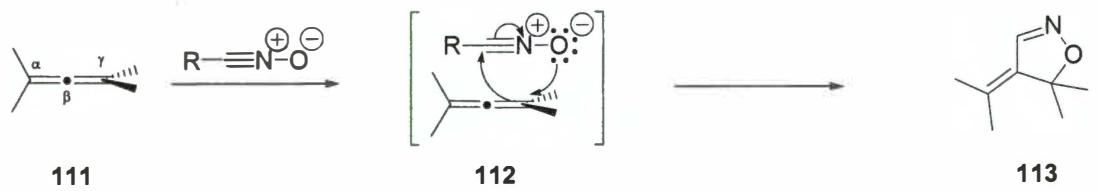


Scheme 19. Retrosynthetic analysis of PPAPs utilizing an allene-INOC.

1.3 Our strategy for the synthesis of PPAPs.

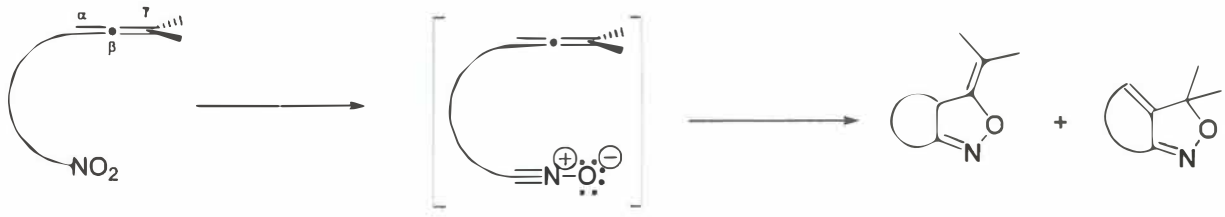
Any synthetic approach to a PPAP must address construction of the β,β-tricarbonyl and the vicinal quaternary stereocenters (such as C-1 and C-2 in **106**). We envisioned the retrosynthetic analysis in Scheme 19, where an allene-intramolecular nitrile oxide cycloaddition (allene-INOC) was to accomplish many of the synthetic objectives in one step. For example, the cycloaddition (**108** → **107**) forms the bicyclic core, introduces two latent carbonyls, and results in the direct formation of the vicinal quaternary centers. Thus, the reductive cleavage disconnection of **106** led to isoxazoline **107**, that was to be acquired from allene **108**. It was projected that the Mukaiyama aldol reaction could be used to install the nitro containing side chain in ketone **108**. Further disconnection led to allenyl ketone **110** as a synthetic intermediate. To place our studies in perspective, a review of allene-INOC reactions and Mukaiyama aldol chemistry are briefly reviewed in the following sections.

Intermolecular cycloaddition:



111 **112** **113**

Intramolecular cycloaddition:



114 **115** **116a** **116b**

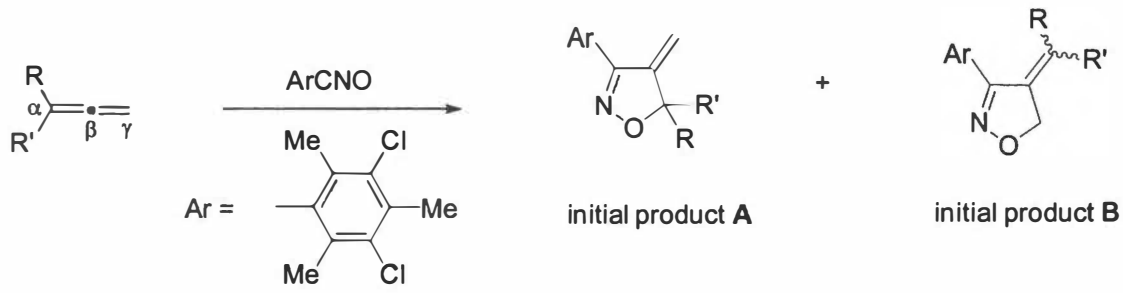
Scheme 20. Allene-nitrile oxide cycloadditions.

1.4 Allene-nitrile oxide cycloadditions.

A nitrile oxide cycloaddition (NOC) is a [3 + 2] cycloaddition involving a π bond and a nitrile oxide. The nitrile oxide is usually generated *in situ* from a nitro,[50] oxime,[51,52] or O-silylated hydroxamic acid precursor.[53] The use of an allene as a dipolarophile gives rise to site selectivity as well as regioselectivity issues, thus the INOC reactions of **114** can potentially yield either **116a** or **116b** (Scheme 20), both of which will have an ethylenic bond suitable for further transformations. Allenes used in Diels-Alder cycloadditions have been extensively reviewed[54-57] as have allenes in 1,3-dipolar cycloadditions.[57,58]

1.4.1 Intermolecular allene-nitrile oxide cycloadditions.

The 1,3-dipolar cycloaddition between nitrile oxides and allenes tends to give a mixture of products. As seen in Scheme 21, cycloaddition may occur at either or both double bonds of the allene. In addition, products may aromatize if a sufficient driving force is available. In terms of double bond selectivity, some control is achieved by



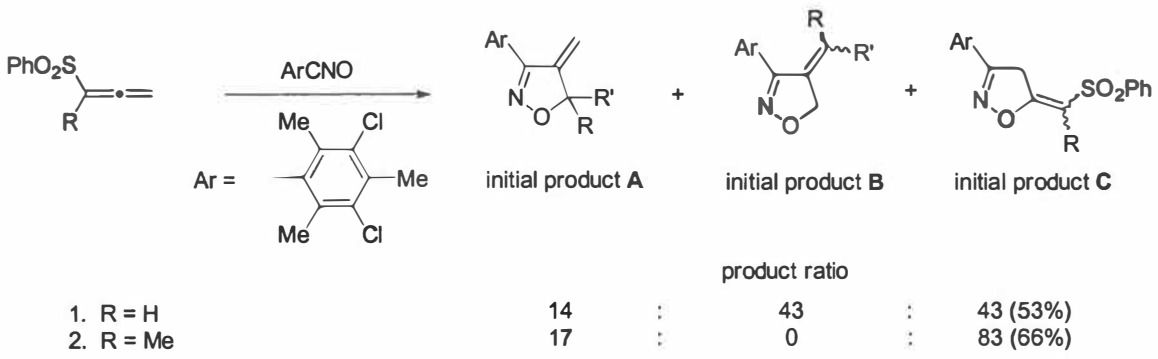
	product ratio		
1. R = Ph, R' = Ph	60	:	40 (32%)
2. R = PhO, R' = H	27	:	73 (70%)
3. R = Ph(Me)N, R' = H	100	:	0 (55%)
4. R = Ph_2N, R' = H	100	:	0 (51%)

Scheme 21. Selected allene-NOC reactions.

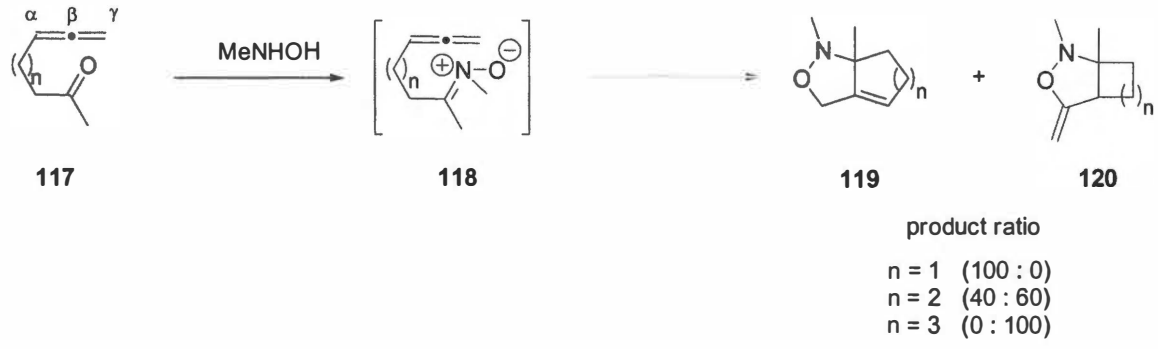
variation of the allene substituents. In entry 1 the α,β-π bond is slightly favored as the reaction site,[59,60] but when a more strongly electron-donating group is present such as the phenoxy group in entry 2, the β,γ-π bond is more reactive (Scheme 21).[61] Interestingly, an enamine-type allene reacts exclusively at the α,β-π bond (entries 3 and 4).[62,63] From the data in Scheme 21, it is evident that the carbon of the nitrile oxide generally bonds to the central carbon of the allene. However, electron-deficient allenyl sulfones demonstrate a reverse of orientation (Scheme 22).[64] This lack of selectivity hinders the application of bimolecular allene NOC reactions in synthesis.

1.4.2 Allene-intramolecular nitrile oxide cycloadditions.

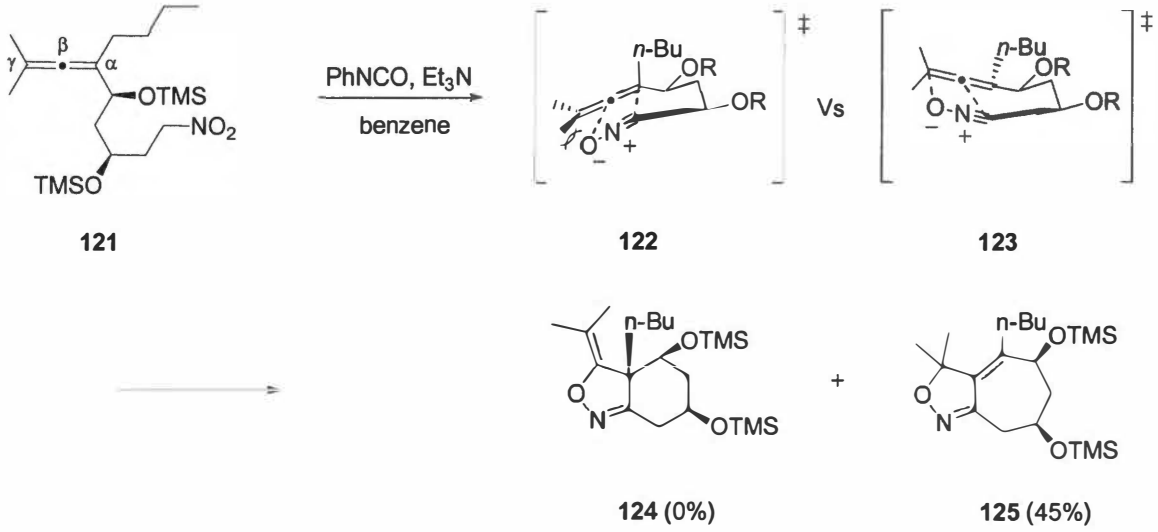
It was projected that the intramolecular allene-nitrile oxide cycloaddition (allene-INOC) would simplify selectivity issues, because the geometric constraints in the tether might outweigh substituent electronic effects. Surprisingly, there were only limited studies of intramolecular 1,3-dipolar cycloadditions with allenes. One example is the intramolecular nitrone-allene cycloaddition by Norman A. LeBel (Scheme 23).[65] According to LeBel's studies, the product distribution seemed to follow the thermodynamics of ring formation. For example, formation of five and six-membered



Scheme 22. Cycloaddition of allenyl sulfones and allenes.



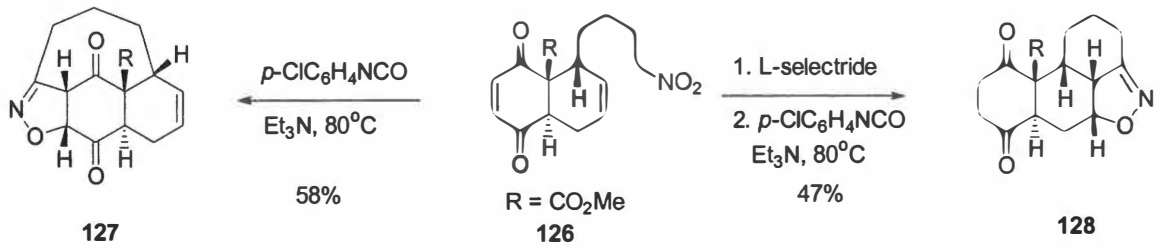
Scheme 23. Intramolecular nitrone-allene cycloaddition.



Scheme 24. Example of an allene-INOC reaction.

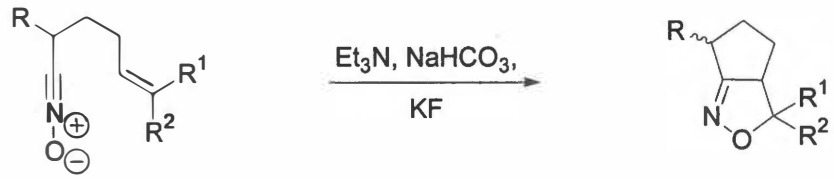
rings are favored, and formation of the four and seven-membered rings are not observed. These results also suggested the internal π-bond of the allene is more reactive in many cases.

Studies of the regiochemistry of the allene-INOC were conducted previously by our group (Scheme 24).[66,67] In contrast to the nitrone allene cycloaddition of terminal allenes presented in Scheme 23, a bulky substitutent in the α-position of the allene can make the external β,γ–π bond more reactive (compare with Scheme 23). For example, allene **121** underwent an INOC with surprising results. Instead of the thermodynamically favored six-membered ring (**124**), the only product formed was cycloheptene **125**. The results are attributed to steric interactions in the transition state, but may also be an artifact of conjugation in the product. In transition state **122**, the *n*-butyl group is pseudoaxial in the chairlike transition state, and the nitrile oxide approaches the π-bond in the same plane as the allene methyl groups. However, in favored transition state **123**, the *n*-Bu group is pseudoequatorial and the allene methyl groups are orthogonal to the approaching nitrile oxide. Clearly, transition state **123** is lower in energy and cycloheptene **125** is produced as a consequence.



127 126 128

Scheme 25. Chemoselectivity in the INOC reaction.



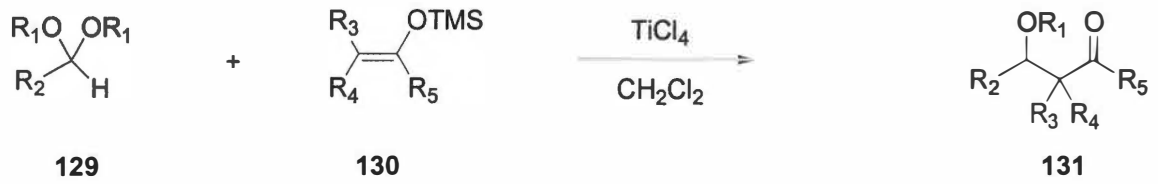
1. $R^1 = R^2 = H$ — 92%
2. $R^1 = H$, $R^2 = Ph$ — 66%
3. $R^1 = R^2 = Me$ — 8%

Scheme 26. Effect of olefin substitution in INOC reactions.

1.4.3 Trends in INOC reactivity.

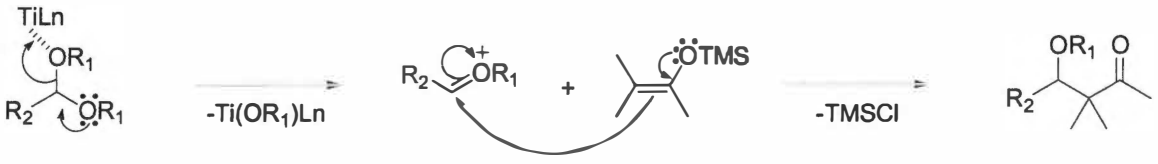
Since PPAPs contain multiple double bonds it is important to briefly discuss some of the scope and limitations of the NOC reaction. Activated double bonds preferentially react in the presence of other olefins as seen in the study conducted by B. C. Wang and coworkers (Scheme 25).[68] Under NOC conditions, a cycloaddition occurred solely at the conjugated double bond of **126** to afford tetracycle **127** in 58% yield, even though the unactivated olefin is closer in proximity. In the absence of an activated alkene, the INOC reaction generated the six-membered ring (**126 → 128**).

Another important study concerning the effect of substitution on the double bond was conducted by Hidemitsu Uno and coworkers.[69] As seen in Scheme 26, monosubstituted olefins are the most reactive and the yield rapidly decreases as substitution around the dipolarophile increases.



129 130 131

Scheme 27. Mukaiyama aldol condensation.



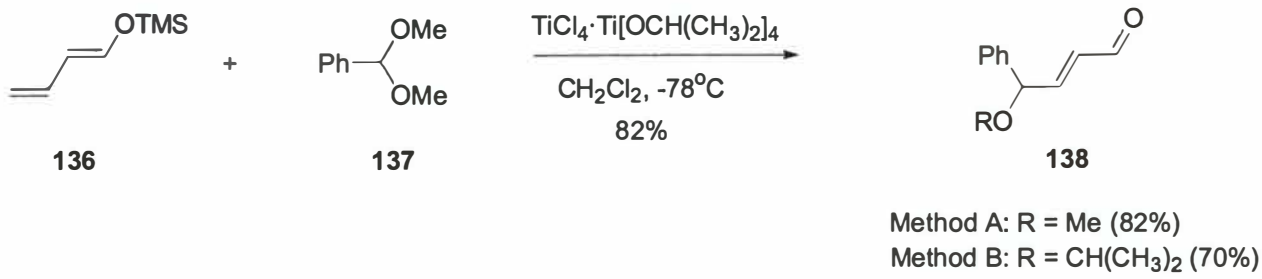
132 133 134 135

Scheme 28. Mechanism of Mukaiyama aldol condensation.

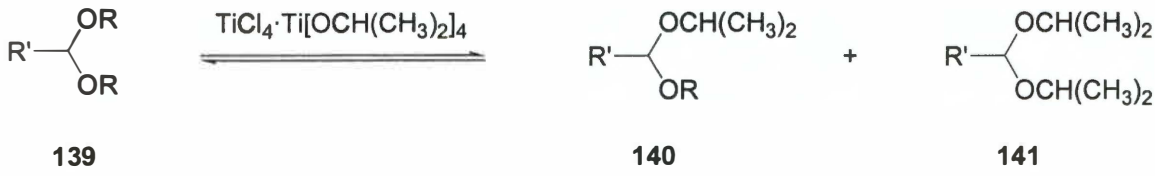
1.5 Mukaiyama aldol condensation.

The Mukaiyama aldol condensation involves the cross-coupling of an acetal (**129**) and a silyl enol ether (**130**) to afford a β-alkoxyketone (**131**, Scheme 27).[70-72] A Lewis acid such as titanium (IV) chloride is used to mediate the reaction. Mechanistically, the titanium salt first chelates to the oxygen of the acetal (**132**) resulting in the formation of oxonium ion **133** (Scheme 28). The reaction is completed when the silyl enol ether attacks the electrophile to produce a β-alkoxyketone **135**.

In the study by Mukaiyama, a 1:1 mixture of titanium (IV) chloride and titanium (IV) isoproxide was used to form a complex that is less reactive than titanium (IV) chloride itself. For example, the preparation of δ-alkoxy-α,β-unsaturated aldehydes proceeds smoothly with $TiCl_4 \cdot Ti[OCH(CH_3)_2]_4$, whereas a complex mixture is obtained with titanium (IV) chloride (Scheme 29).[73] Interestingly, the order the reagents are added influences the identity of the alkoxy group in the product. Thus, when a solution of the acetal and silyl enol ether is added to a solution of $TiCl_4 \cdot Ti[OCH(CH_3)_2]_4$ in CH_2Cl_2 at –40°C, a methoxy containing product is formed (Method A, Scheme 29). However, if the titanium reagents are added to a solution of acetal in CH_2Cl_2 at –40°C followed by addition of the silyl enol ether, the product contains an isopropoxy group (Method B,



Scheme 29. Preparation of δ-alkoxy-α,β-unsaturated aldehydes.



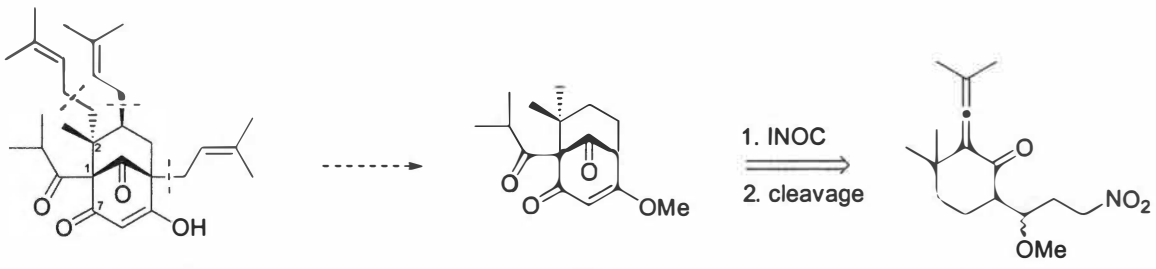
Scheme 30. Exchange reaction between the acetal and isopropoxy group.

Scheme 29). It is proposed the exchange occurs during the formation of the carbonium ion via the equilibrium shown in Scheme 30.

1.6 Hyperevolutin A (3a) model study by Dongxiang Zeng.

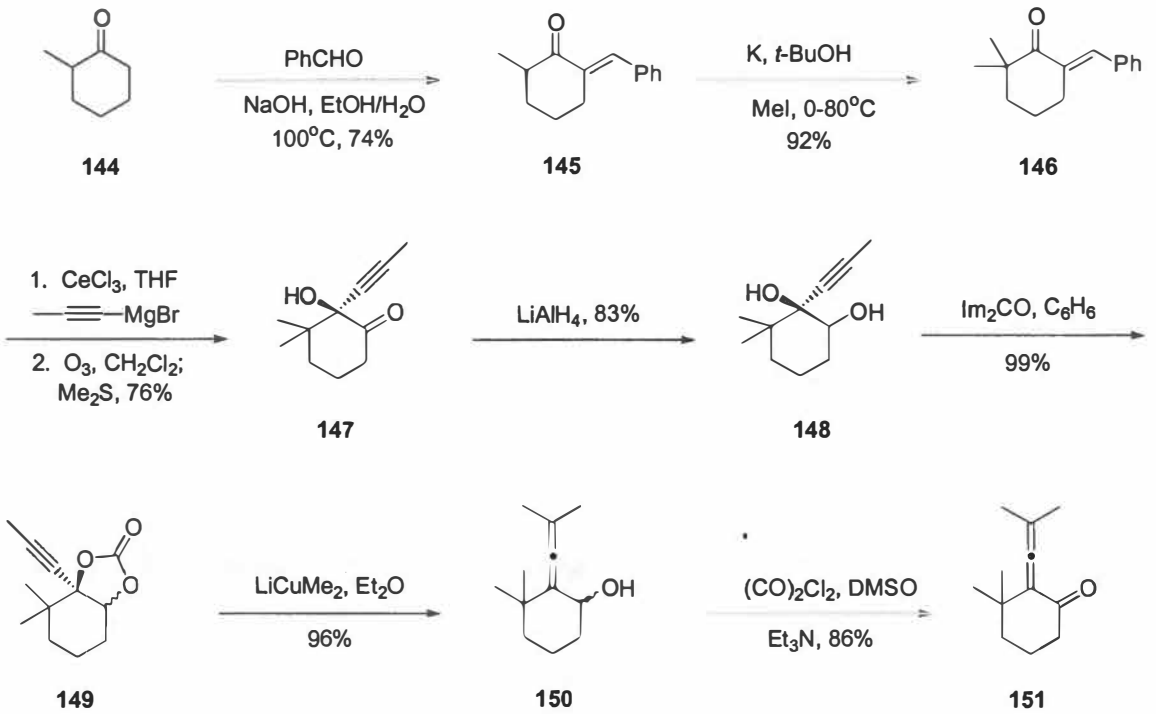
Previous studies in our group conducted by Zeng examined the feasibility of using the allene-INOC methodology to prepare the bicyclic core of PPAPs.[66,74] To simplify the target, the prenyl groups were removed in the pilot study (Scheme 31). It was projected that **142** could be prepared from allenyl ketone **143**.

As depicted in Scheme 32, allenyl ketone **151** was prepared from commercially available 2-methylcyclohexanone (**144**). The synthesis proceeded by producing ketone **146** via condensation with benzaldehyde that was followed by alkylation with methyl iodide and base. The cerate derived from 1-propynylmagnesium bromide and cerium trichloride added to the ketone in quantitative yield. The resulting alcohol was subjected to ozonolysis, which selectively cleaved the alkene to afford ketone **147**. The allene functionality was introduced by reducing the ketone with LAH and converting the



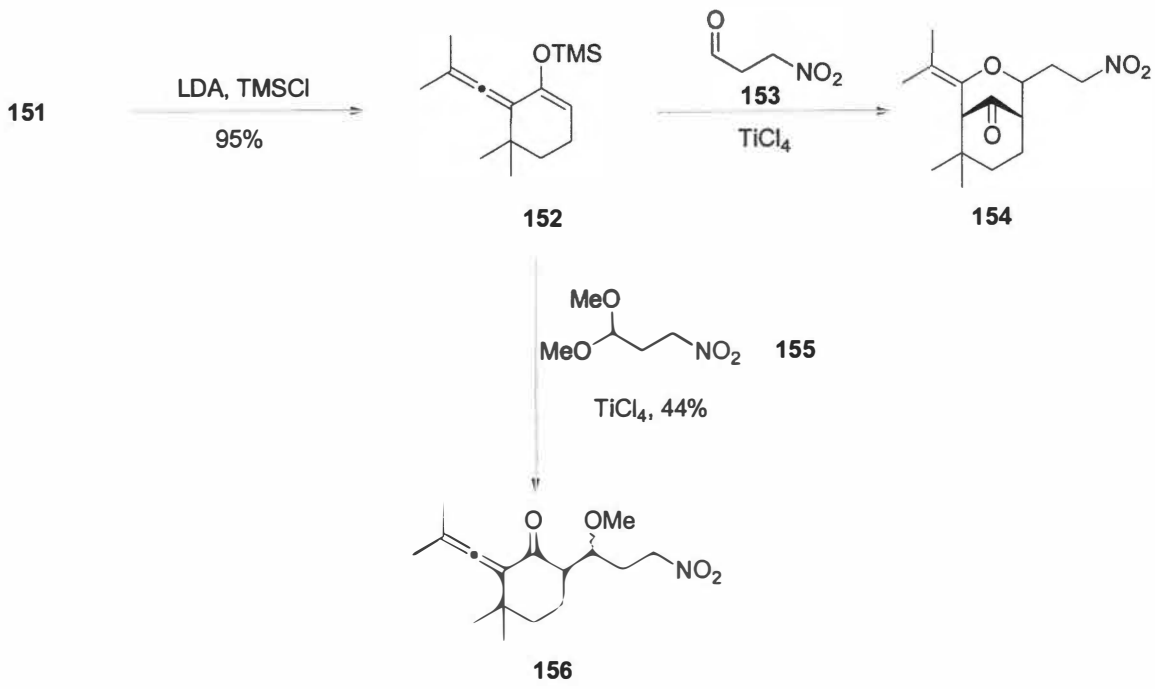
3a **142** **143**

Scheme 31. Retrosynthesis of hyperevolutin A (**3a**).



144 **145** **146** **147** **148** **149** **150** **151**

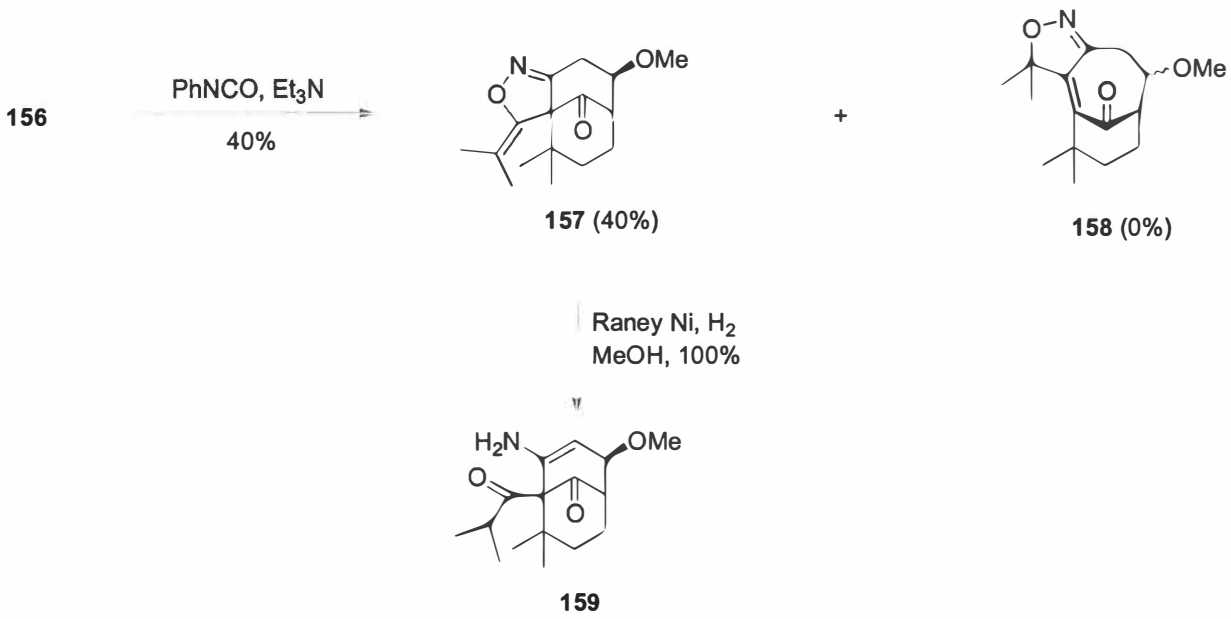
Scheme 32. Preparation of allenyl ketone **151**.



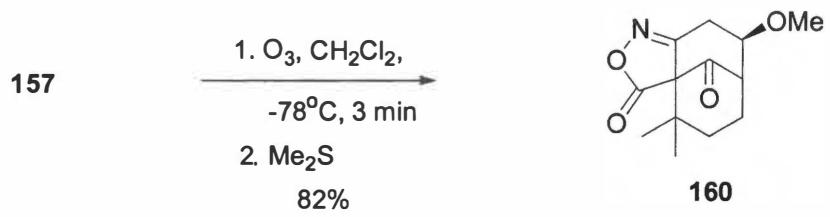
Scheme 33. Mukaiyama aldol condensation in Zeng's model study.

epimeric diols (**148**) to the derived carbonates **149** by treatment with carbonyldiimidazole. Both carbonates underwent S_N2' displacement with Gilman's reagent to yield the corresponding α-allenyl alcohols (**150**). Swern oxidation of the alcohols yielded allenyl ketone **151**.

Initially, condensation of silyl enol ether **152** with 3-nitropropanal (**153**) was explored as a method for introducing the nitro side chain (Scheme 33), but the only product isolated from this reaction was enol ether **154** formed via cyclization of the aldol intermediate. However, the intramolecular cyclization did not occur when the Mukaiyama protocol employed 3-nitropropanal dimethyl acetal **155** with **152** in the presence of titanium (IV) chloride. Using this reagent combination, diastereomers **156** were produced in 44% yield. The cycloaddition occured smoothly with phenyl isocyanate in refluxing benzene to afford cycloadduct **157** (44%) as a single diastereomer (Scheme 34). Evidently, one isomer underwent the cycloaddition in 80% yield while the other isomer was not accounted for. As expected, the six-membered ring was favored over the seven-membered ring, thus avoiding the formation of a bridgehead double bond.



Scheme 34. Allene-INOC of **156**.



Scheme 35. Attempted ozonolysis of **157**.

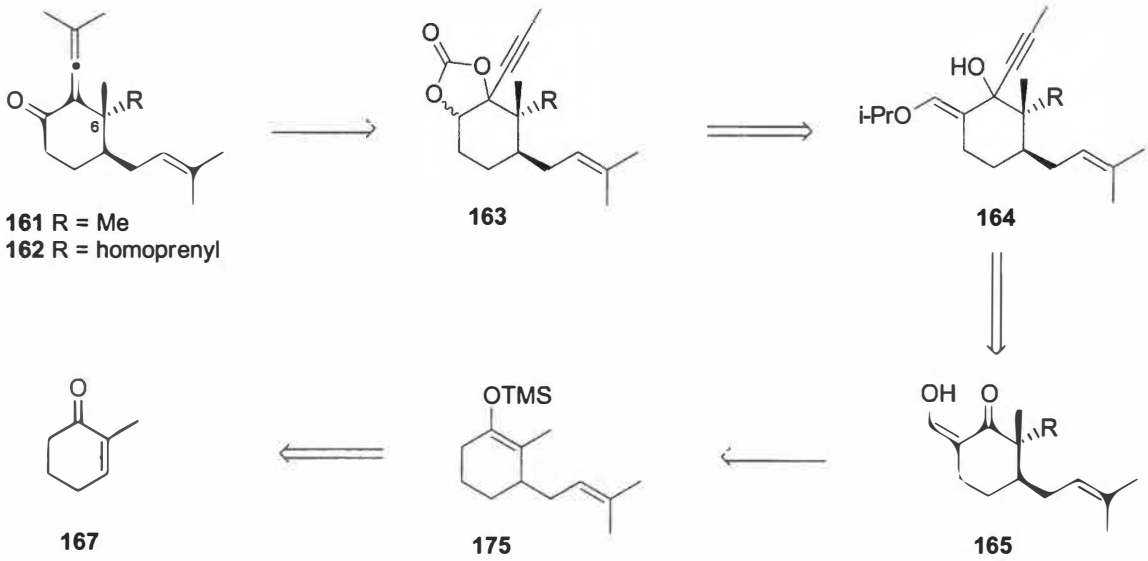
The study was completed by reducing the N-O bond of the isoxazoline with methanolic Raney nickel to produce bicyclo[3.3.1]nonanone **159** in quantitative yield.

It is notable that exploitation of the Kozikowski ozonolytic cleavage method to isoxazoline **157** only resulted in olefin oxidation (Scheme 35).[75]

2. Results and Discussion

2.1 Assembly of allenyl ketones.

Our first objective in PPAP total synthesis was to assemble an allenyl ketone that contained the correct stereochemistry and appropriate side chains (i.e. **161** and **162**, Scheme 36). Retrosynthetic analysis of allenyl ketones **161** and **162** suggested the allene functionality could be introduced by displacing a carbonate as in Zeng's model study (Scheme 32). The carbonate was to be prepared by selective ozonolysis of the enol ether double bond in **164** and protection of the diol obtained from reduction of the resulting ketone. The propynyl unit was to be introduced via 1,2-addition of an organometallic to the ketone. It was expected that alkylation of silyl enol ether **175** with an appropriate halide would afford a ketone in which the R group was *anti* to the prenyl group. In turn, silyl enol ether **175** was to be prepared by cuprate addition to enone **167** and trapping the resulting enolate with TMSCl .



Scheme 36. Retrosynthesis of allenyl ketones.



Scheme 37. Preparation of enone **167**.

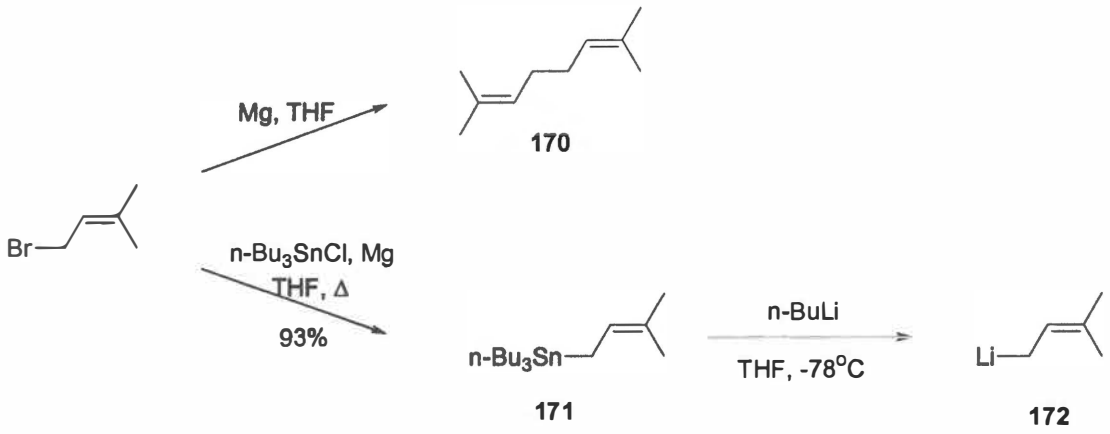
2.1.1 Synthesis of allenyl ketone 161.

Allenyl ketone **161** (Scheme 36) was projected to be a useful intermediate in the synthesis of PPAPs containing geminal dimethyl substitutents at C-6 (i.e. garsubellin A, **6**). The study towards this compound began by preparing known enone **167** by literature methods from either ketone **168** or iodide **169** in good yield (Scheme 37).[76,77]

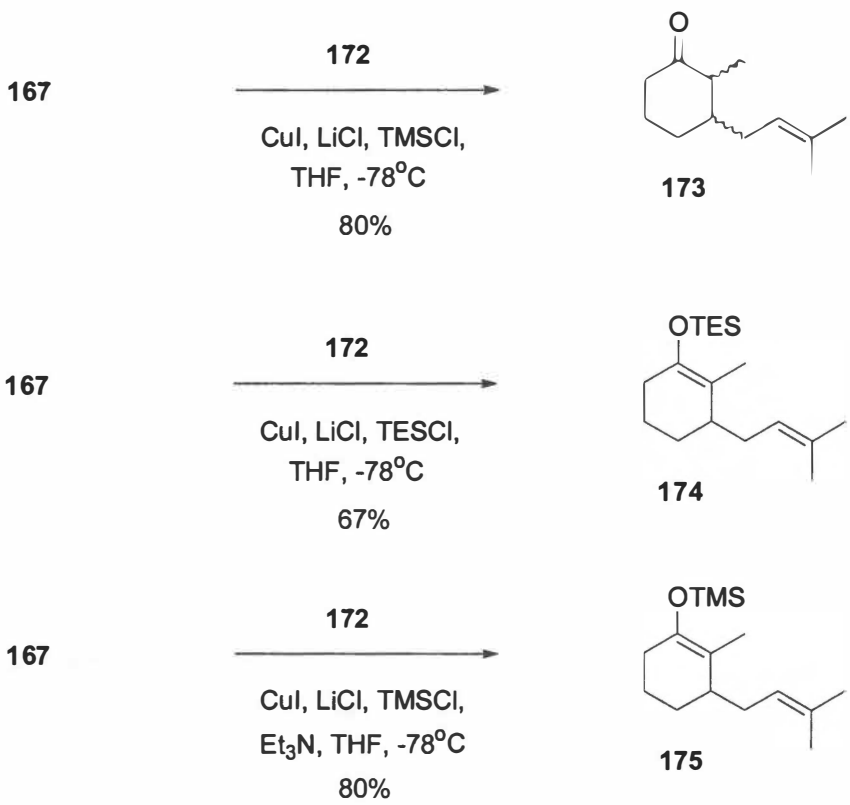
Introducing prenyl or allyl groups by copper (I)-initiated 1,4-addition to enones has historically been problematic due to significant amounts of 1,2-addition and formation of other byproducts. Recent methodologies developed by Bruce H. Lipshutz and coworkers successfully delivered the allylic group to enone **167** via conjugate addition after some modifications. Since either a Grignard or organolithium reagent was needed to prepare the cuprate, prenylmagnesium bromide was prepared according to the Lipshutz procedure,[78] but in our hands diene **170** was the only product isolated (Wurtz coupling, Scheme 38).[79] However, *in situ* preparation of prenyllithium (**172**) by transmetallation of prenylstannane **171** with *n*-BuLi was successful (Scheme 38).[80,81]

Unfortunately, more difficulties were encountered executing the conjugate addition (Scheme 39). The procedure stated the silyl enol ether was generated and workup with TBAF was necessary to isolate the ketone. In our hands, the Lipshutz conditions led to hydrolysis without TBAF. For example, TLC indicated formation of a less polar material (presumable the silyl enol ether), when enone **167** was subjected to Lipshutz's conditions, but workup afforded only ketone **173**. When TESCl was used instead of TMSCl, the more stable triethylsilyl enol ether **174** was isolated in 67% yield. Eventually it was found that by simply adding an acid scavenger such as triethylamine the reaction proceeds smoothly to give silyl enol ether **175** as the only isolable product.

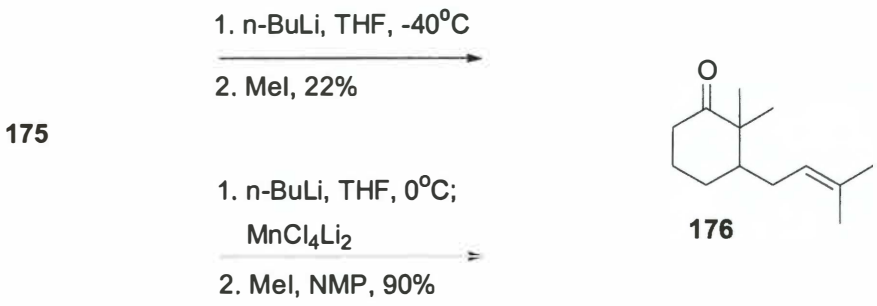
With silyl enol ether **175** in hand, methods for alkylation were explored.



Scheme 38. Preparation of prenyllithium (**172**).



Scheme 39. Synthesis of silyl enol ether **175** by the modified Lipshutz procedure.

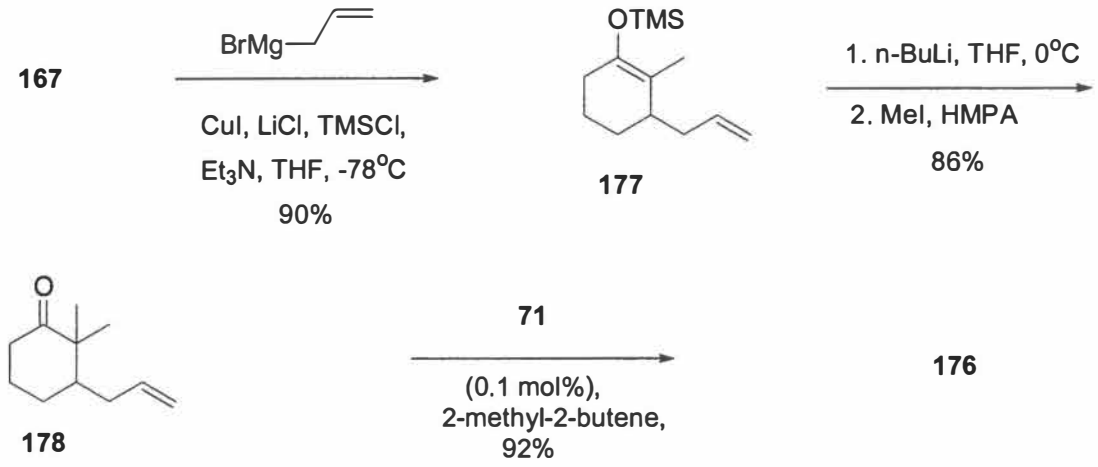


Scheme 40. Synthesis of ketone **176**.

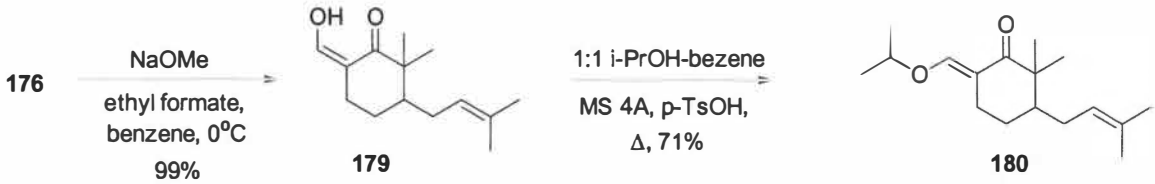
Regeneration of the lithium enolate was accomplished by treating **175** with *n*-BuLi or MeLi. Direct alkylation of the lithium enolate with methyl iodide gave a low yield of ketone **176**,[82] but if the intermediate lithium enolate was first converted to the manganese enolate and NMP was added, **176** was obtained in excellent yield (Scheme 40).[83]

A limitation of preparing silyl enol ether **175** from prenyllithium was the quantitative formation of toxic tetrabutyltin as a byproduct, which also complicated purification. An alternative procedure was therefore employed where Lipshutz conjugate addition with commercially available allylmagnesium bromide was conducted, followed by alkylation, and then the allyl was convert to a prenyl group by cross-metathesis using Grubbs' second generation catalyst (**71**). A similar process was employed by Stoltz in his PPAP model study (see section 1.2.4).[42] Silyl enol ether **177** was prepared in excellent yield by copper (I)-mediated conjugate addition of allylmagnesium bromide to enone **167** (Scheme 41).[78] Interestingly, alkylation under the same conditions as **175** led to a poor yield (14%) of the dimethyl derivative. Optimal conditions were found to involve alkylation of the lithium enolate with HMPA to afford **178** in 86% yield. Ketone **176** was furnished in excellent yield by cross-metathesis in the presence of 0.1 mol% of **71**.[84] In this manner the use of tin reagents was eliminated.

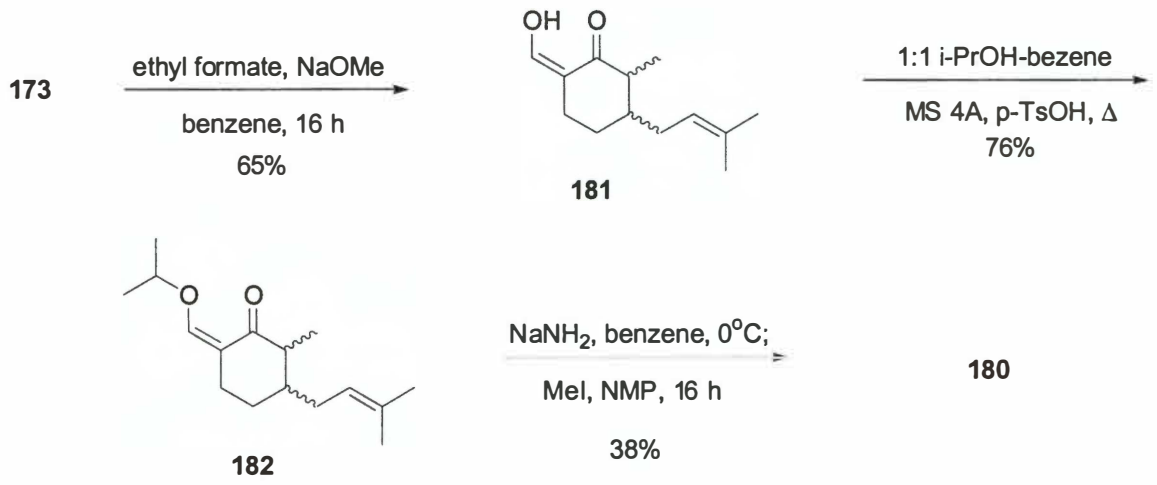
The α'-site of the ketone was subjected to a Clasien condensation with ethyl formate to furnish the hydroxymethylene compound **179** as a single isomer (Scheme 42).[85] Presumably, the stereochemistry was assigned based on the assumption of a hydrogen bond between the enol and the ketone. The enol ether **179** was converted to the



Scheme 41. Alternative synthesis of ketone **176**.



Scheme 42. Synthesis of enol ether **180**.



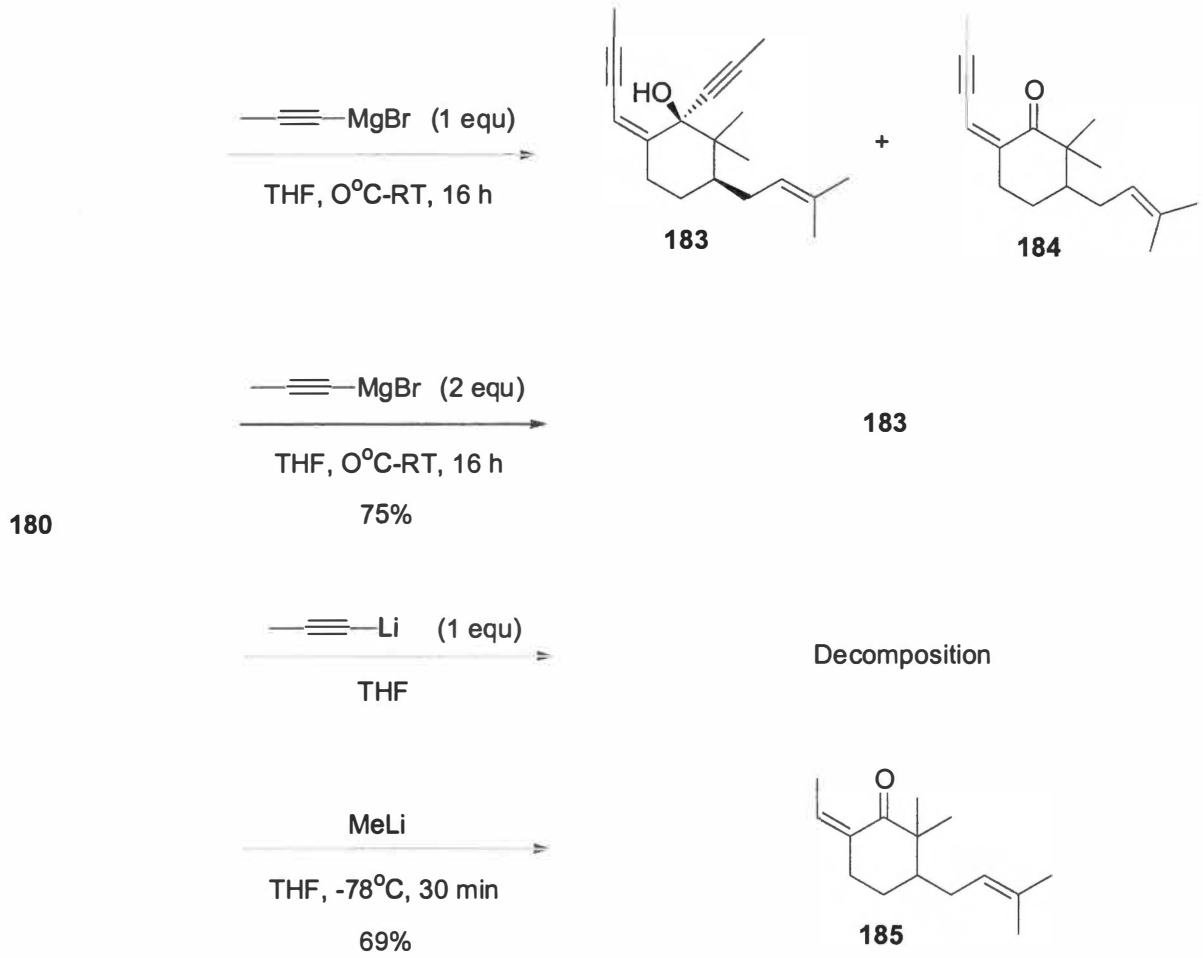
Scheme 43. Alternative synthesis of **180**.

isopropoxy derivative by conjugate addition of isopropyl alcohol followed by regeneration of the double bond to produce the vinylogous ester **180**.[86]

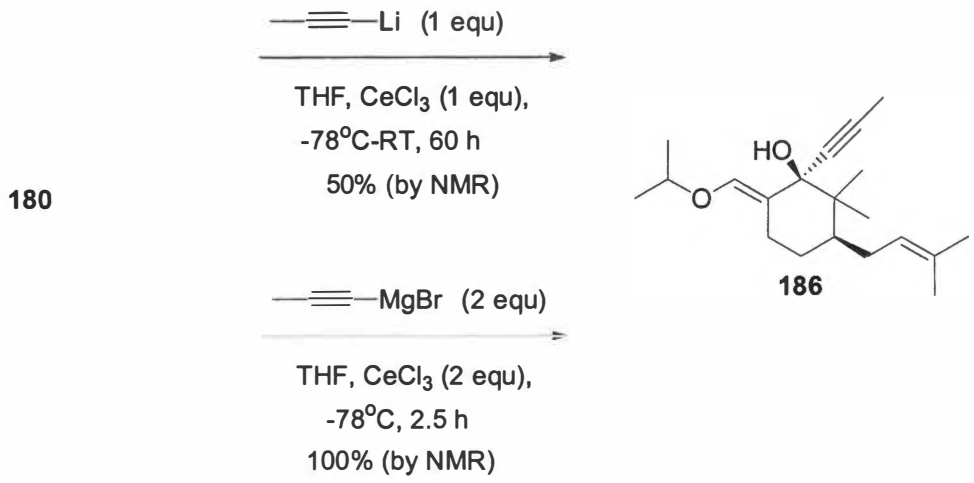
Synthesis of **180** based on alkylation of ketone **182** by using a well established procedure proceeded in poor yield (Scheme 43). The best result using this chemistry was obtained by using sodium amide in benzene with NMP as a polar additive to deliver **180** in 38% yield.[87]

The next stage of the synthetic plan was to effect 1,2-addition to ketone **180** with a 1-propynyl organometallic. Treatment of **180** with one equivalent of 1-propynylmagnesium bromide, however, produced alcohol **183** due to 1,4- followed by 1,2-addition (Scheme 44). Isolation of trace amounts of ketone **184** suggested that conjugate addition occurs first and then 1,2-addition to the ketone rapidly follows. Since organolithium reagents tend to favor 1,2-addition,[88] 1-propynyllithium was prepared *in situ* by Gribble's procedure,[89] but when added to **180** only decomposition was observed. Surprisingly, treatment of **180** with one equivalent of methyllithium resulted in the formation of **185** in 69% yield. It is suspected that steric hindrance by the *gem* dimethyl group favors conjugate addition.[88]

It was found that 1,2-addition could be effected through the use of the derived cerate (Scheme 45).[90] One equivalent of the cerate derived from 1-propynyllithium gave a 1:1 mixture of alcohol **186** and starting material (NMR). Thus, two equivalents were



Scheme 44. Attempted 1,2-addition of ketone **180** with organometallic reagents.

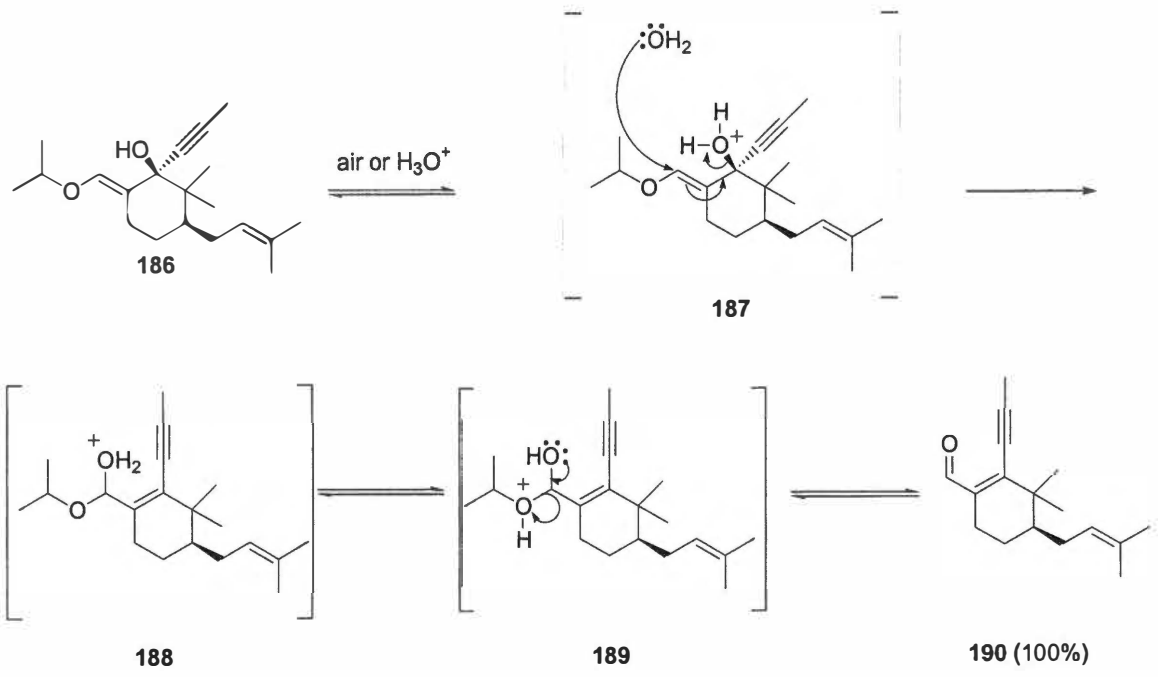


Scheme 45. Cerate addition to enone **180**.

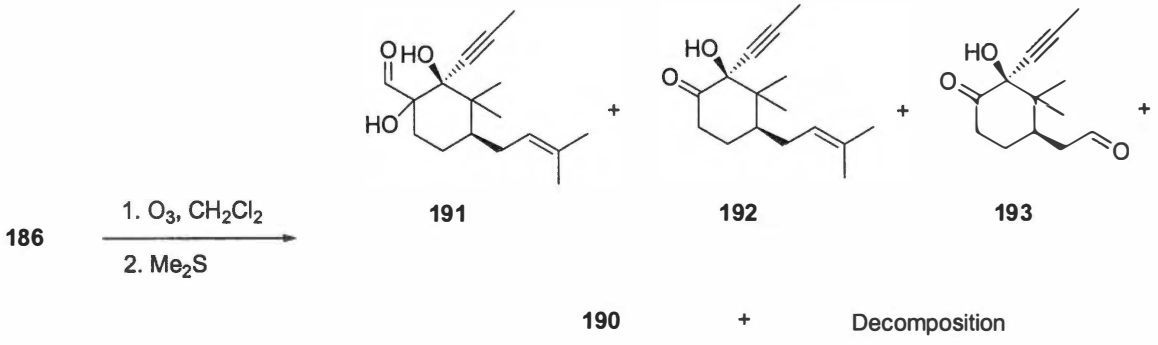
employed, and the result was quantitative conversion to **186**. The stereochemistry is tentatively assigned based on the assumption that axial attack of the nucleophile is favored, however, the need for two equivalents of cerate is not clear.

Alcohol **186** was found to be unstable when concentrated and readily eliminated water upon exposure to air or silica gel to afford aldehyde **190** (Scheme 46).[86,91] Since **186** appeared to be more stable in solution, the alcohol was generated *in situ* and further transformations were attempted. Because the next step in our synthetic plan was to assemble carbonate **163** via an oxidative cleavage, reduction, and protection sequence, selective ozonolysis of the enol ether in **186** in the presence of the prenyl and alkyne groups was attempted. Ozonolysis of electron rich double bonds is known to be generally faster than electron-deficient double bonds.[88] It was also speculated that the adjacent oxygen might have a directing effect.[92] Although selectivity of the double bond over triple bond was achieved, as seen in Scheme 47, conditions for cleavage of the enol ether in the presence of the prenyl double bond could not be identified (Table 1).

An alternative approach briefly explored was to epoxidize the enol ether in presence of the prenyl group. Since the enol ether **186** is also an allylic alcohol, it was believed the alcohol might direct the reagent to this site.[93] The resulting epoxide was



Scheme 46. Dehydration of alcohol **186**.



Scheme 47. Ozonolysis of **186**.

Table 1. Results for ozonolysis of **186**.

Entry	Equivalents of ozone	% yield for **191**	% yield for **192**	% yield for **193**	% yield for **190**
1	1	7%	9%	27% (with other aldehydes)	23%
2	2	6%	6%	15%	0%
3	4	0%	0%	16%	0%

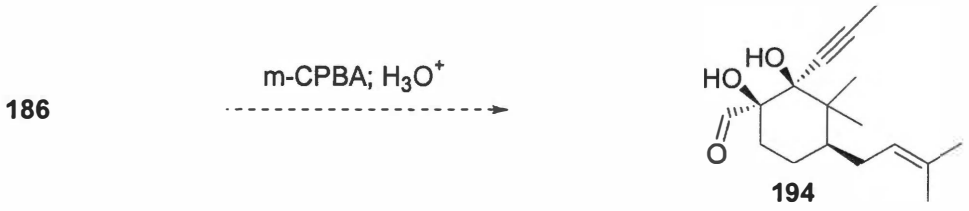
expected to ring-open in the presence of acid to produce a diol, which could potentially be protected as a carbonate that would lead to the desired allene (Scheme 48). However, attempted epoxidation with m-CPBA resulted in a complex mixture of products (Scheme 49).[94]

Given the poor results associated with functionalizing the enol ether, a synthesis of allenyl ketone **161** was devised based on aldehyde **190** (Scheme 50). It was proposed that **161** could be prepared from epoxide **195** by S_N2' cuprate addition to the alkyne. In turn, the epoxide was to be made from allyl alcohol **196** via transition metal catalyzed directed epoxidation.

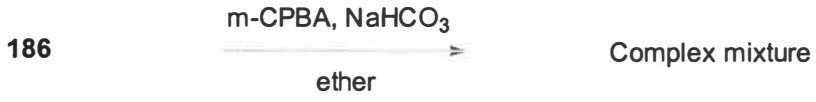
The second generation synthesis began by reducing aldehyde **190**. Luche reduction of **190** gave alcohol **196** (53%), but a significant amount of methyl acetal **197** (34%) was also generated (Scheme 51).[95] In contrast, the reduction occurred in quantitative yield when lithium aluminum hydride was employed.

Epoxidation of **196** was first attempted with m-CPBA, but once again no chemoselectivity was observed (Scheme 52).[96] Utilizing metal directed epoxidation with catalytic $V(acac)_3$ and TBHP, however, gave epoxide **195** in 72% yield.[93,97] The alcohol was subsequently protected with *tert*-butyldimethylsilyl chloride in the presence of imidazole to provide silyl enol ether **200** in excellent yield.[98]

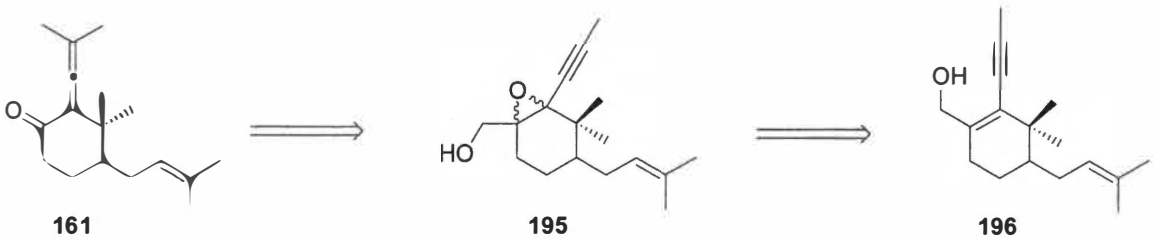
In the key step, the allene was obtained by S_N2' ring-opening of propargylic epoxide **200** with a cuprate by a modified Macdonald procedure (Scheme 53).[96,99-101] It



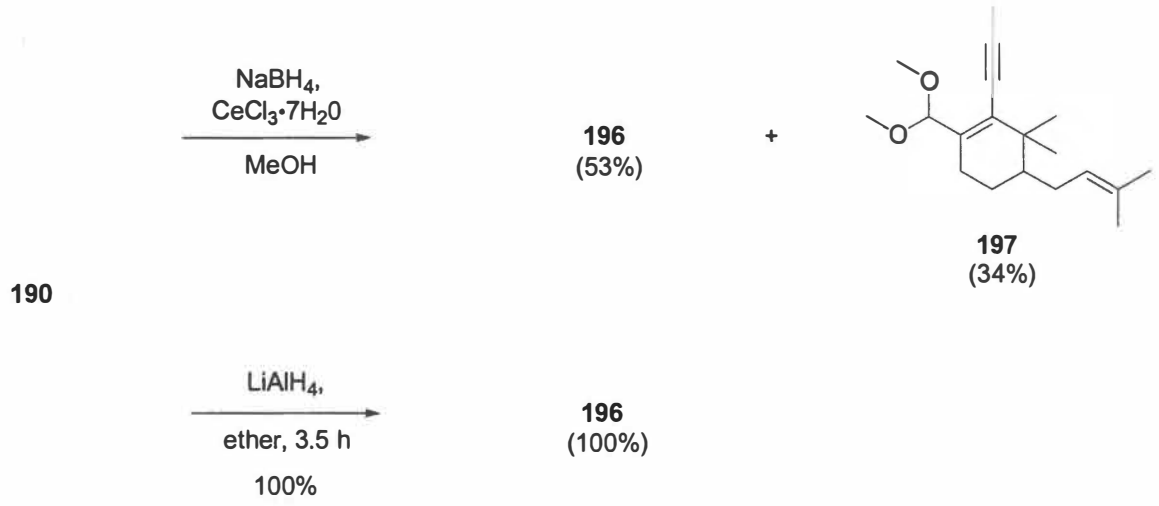
Scheme 48. Proposed epoxidation of **186**.



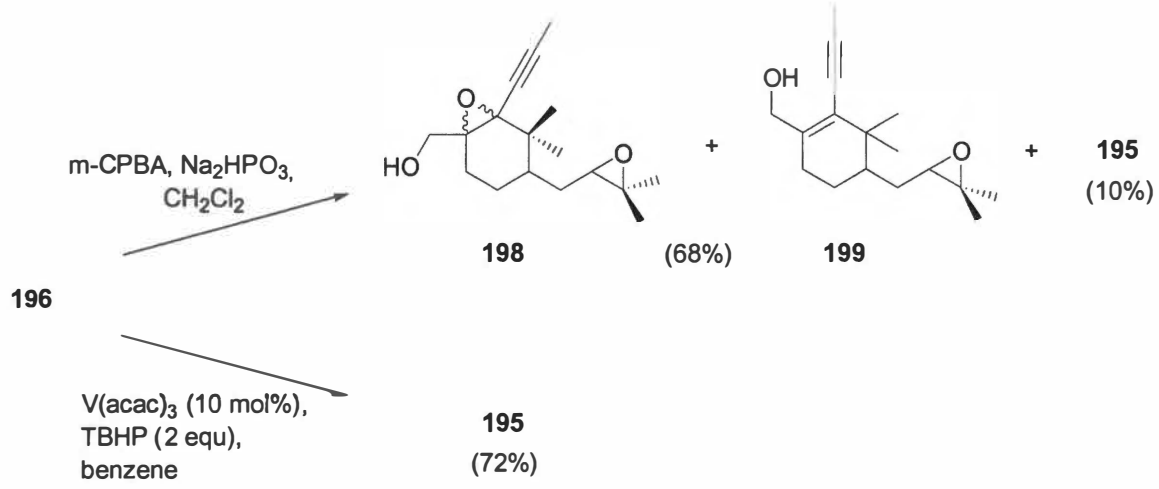
Scheme 49. Epoxidation of **186**.



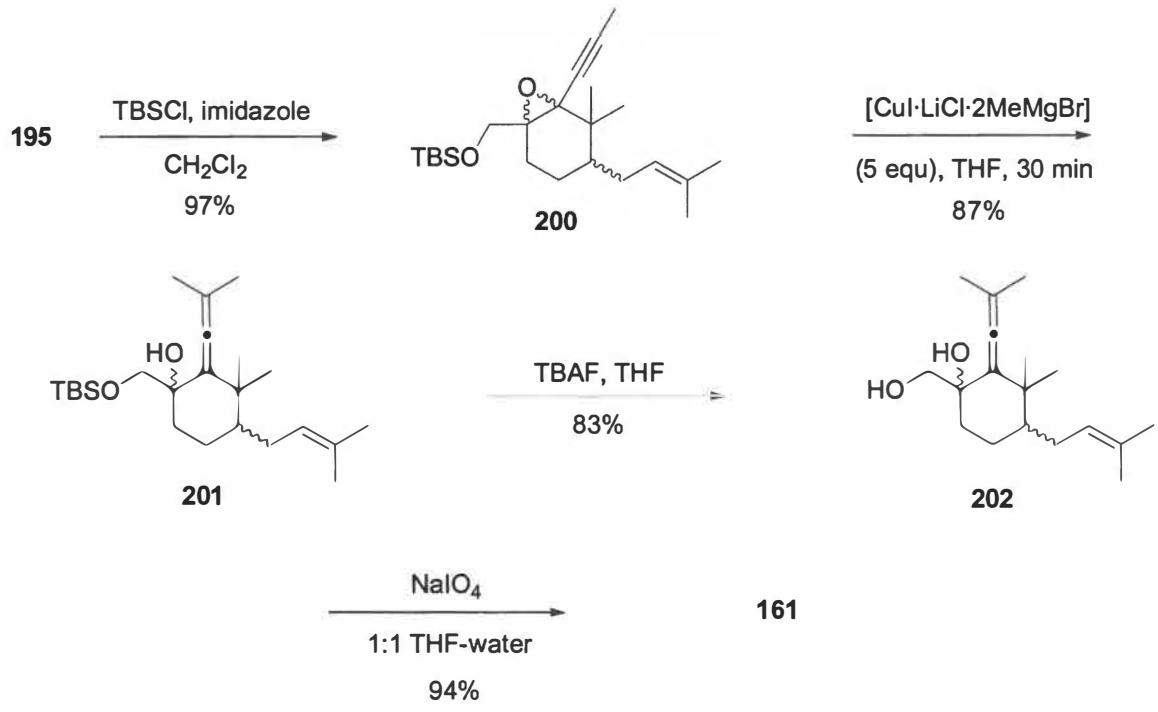
Scheme 50. Revised retrosynthetic analysis of allenyl ketone **161**.



Scheme 51. Reduction of aldehyde **190**.



Scheme 52. Results for epoxidation of **196**.



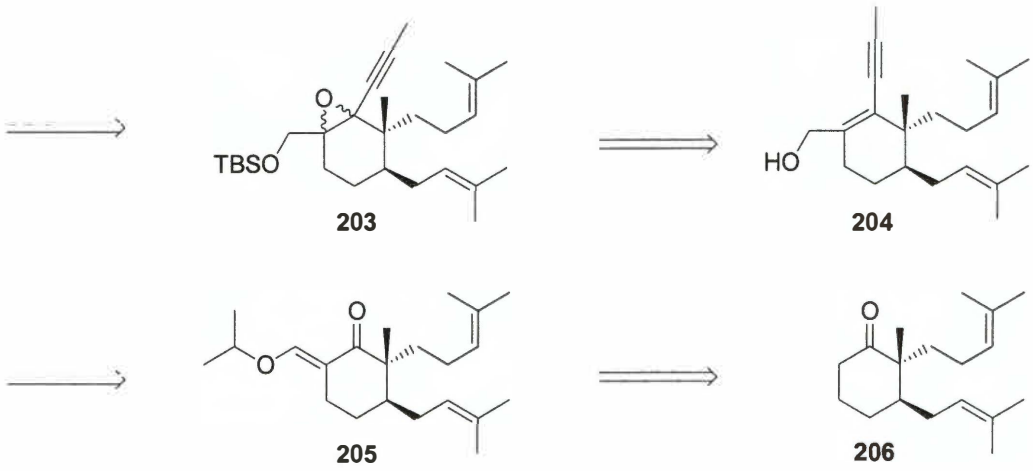
Scheme 53. Preparation of allenyl ketone **161**.

was found that five equivalents each of Gilman's reagent and lithium chloride at room temperature gave the best yields.[102]

The preparation of allenyl ketone **161** was realized by removing the silyl ether with TBAF,[98] and then generating **161** by oxidative cleavage of the resulting *vic* diol (**202**) with sodium periodate in a 1:1 mixture of THF–water (94%).[103] From enone **167**, the allenyl ketone was prepared in twelve steps with an overall yield of 24%.

2.1.2 Studies toward the synthesis of allenyl ketone 162.

In contrast to the C-6 *gem* dimethyl containing natural products, hyperforin (**2a**) and the hyperevolutins (**3**), require a homoprenyl group at C-6. To achieve this goal, the synthesis of **162** (Scheme 36) would use many of the reactions previously discussed (section 2.1.1). As shown in Scheme 54, the allene could still be introduced by a S_N2' displacement of propargylic epoxide **203** with Gilman's reagent. The epoxide could be prepared by metal directed epoxidation of allylic alcohol **204**. Further disconnections



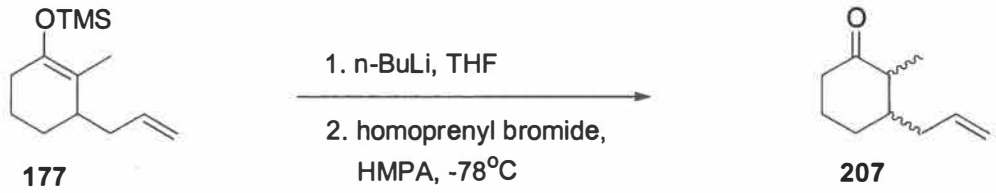
Scheme 54. Retrosynthesis of allenyl ketone **162**.

suggested that **204** could be produced via cerate addition to ketone **205** followed by elimination of the resulting alcohol. Condensation of ketone **206** with ethyl formate and subsequent protection were projected to give vinylogous ester **205**. Silyl enol ether **177** was to be used as starting material.

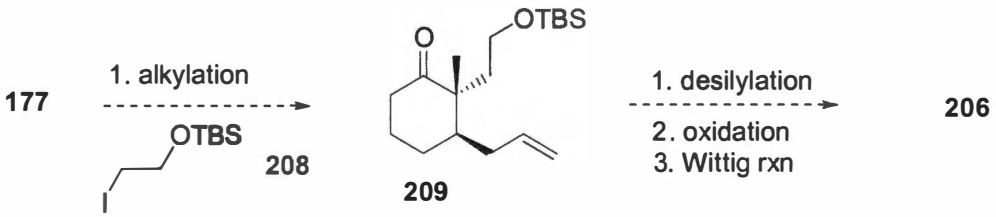
The first objective was to alkylate silyl enol ether **177** with homoprenyl bromide. The reaction was expected to generate the proper stereochemistry for steric reasons. The silyl enol ether was converted to the lithium enolate by treatment with *n*-BuLi and then attempts to alkylate with commercially available homoprenyl bromide (Scheme 55) were made.[104,105] However, hydrolyzed ketone **207** was the only product isolated.

A new strategy was envisioned in which the homoprenyl side chain was to be introduced by using a more reactive electrophile and subsquently transforming it to the homoprenyl group. For example, alkylation with iodide **208** could afford silyl ether **209** (Scheme 56). The side chain could then be converted to the desired homoprenyl group by desilylation, oxidation of the resulting alcohol, and performing a Wittig reaction on the resulting ketone to give **206**. Unfortunately, generation of the lithium enolate and alkylation with a mixture of iodide **208** and HMPA did not result in a reaction, and only hydrolyzed ketone **207** was recovered (Scheme 57).[106]

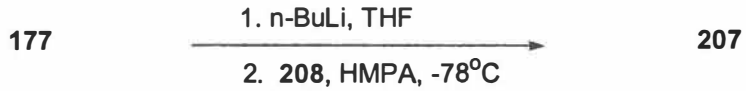
Alkylation with propargyl iodide **210** was expected to be more successful due to activation of iodide by the alkyne. After alkylation, the triple bond could be isomerized



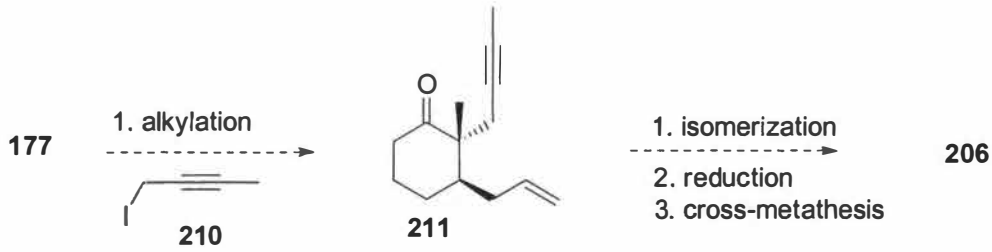
Scheme 55. Attempted alkylation of silyl enol ether **177**.



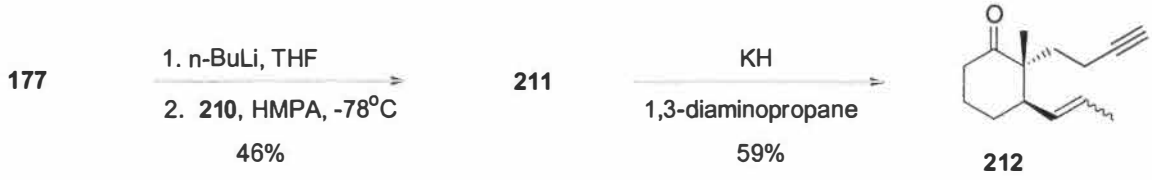
Scheme 56. Proposed synthesis of diene **206** via iodide **208**.



Scheme 57. Attempted alkylation of **177** with iodide **208**.



Scheme 58. Proposed synthesis of **206** via propargyl iodide **210**.

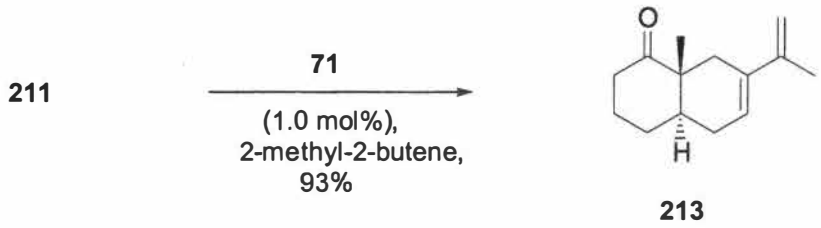


Scheme 59. Synthesis of ketone **212**.

with an appropriate base to give a terminal alkyne. Reduction using the Lindlar protocol and cross-metathesis with 2-methyl-2-butene would give diene **206** (Scheme 58).[107] In the event, generation of the lithium enolate derived from silyl enol ether **177** with *n*-BuLi followed by alkylation with a solution of iodide **210** and HMPA afforded ketone **211** as one diastereomer in 46% yield (Scheme 59). In contrast, alkylation of the manganese enolate of **177** with a solution of **210** in HMPA gave only a 14% yield.[83] Isomerization of the alkyne with potassium aminopropylamide (KAPA) was successful, but the allyl group also unexpectedly isomerized to afford the disubstitited olefin **212** in 59% yield as a 1.7 : 1 mixture of cis, trans isomers.[108]

To prevent the undesired isomerization, it was speculated that the allyl group (monosubstituted alkene) should be converted to the thermodynamically more stable prenyl group (trisubstituted alkene). Our first attempt at cross-metathesis of enyne **211** with 2-methyl-2-butene in the presence of second generation Grubbs' catalyst (**71**, 1.0 mol%, Scheme 60),[84] however, afforded ring-closing metathesis (RCM) to give exclusively bicycle **213** in 93% yield.[109] It is unclear whether the mechanism is direct enyne RCM or the combination of cross-metathesis followed by RCM.[109,110]

To remedy this problem, we successfully cross-metathesized silyl enol ether **177**



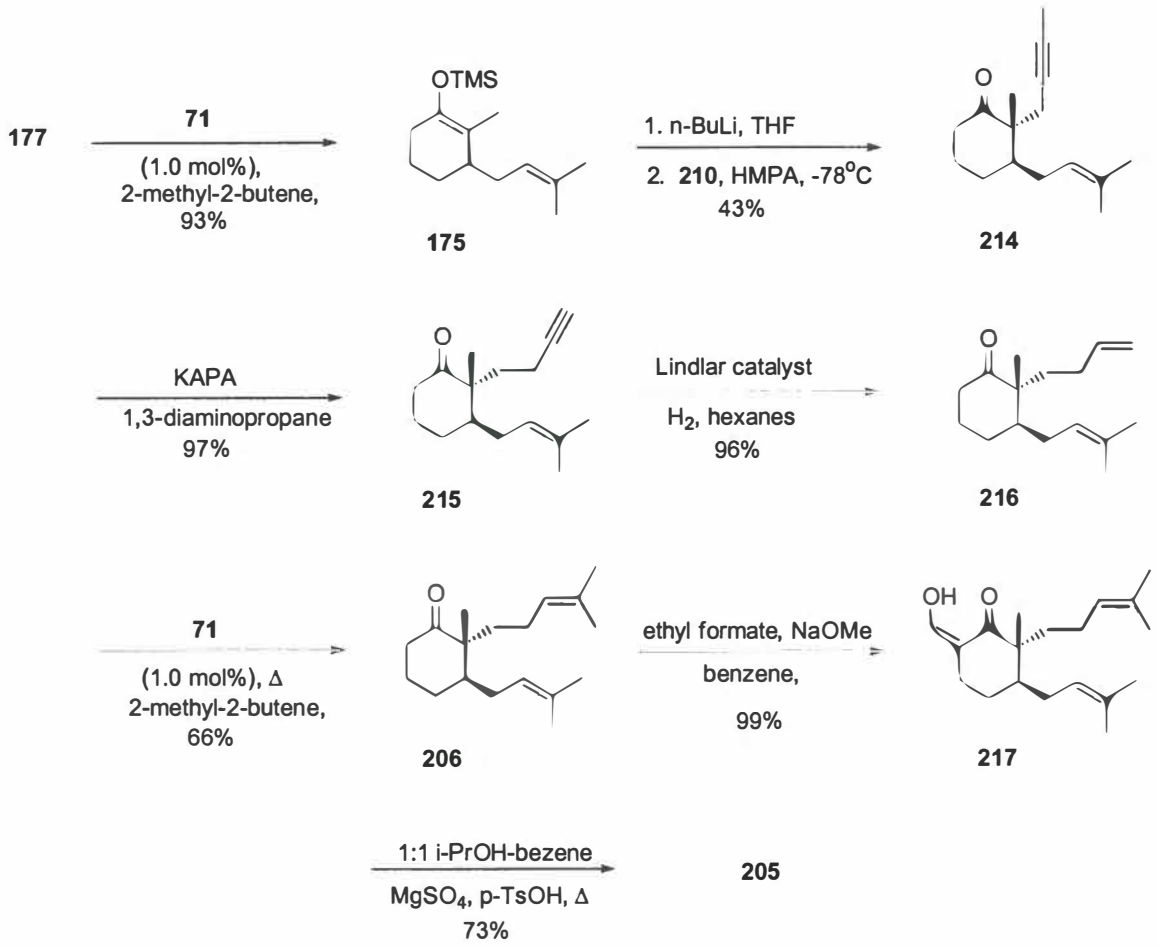
Scheme 60. Attempted cross-metathesis of enyne **211**.

with 2-methyl-2-butene using a catalytic amount of **71** to afford **175** (Scheme 61). The metathesis proceeded in the presence of the silyl enol ether, but a larger catalyst loading (1.0 mol%) was required.

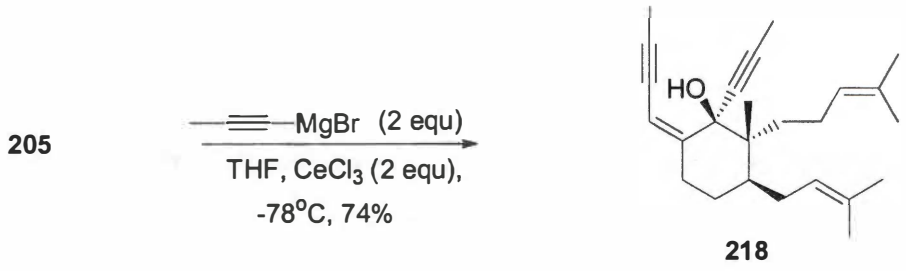
With **175** in hand, the alkylation with propargyl iodide **210** gave ketone **214** in moderate yield (43%). As predicted, the isomerization of the alkyne with KAPA did not result in migration of the double bond. The triple bond was reduced to diene **216** using Lindlar's catalyst,[111] and the resulting homoallyl side chain of **216** was converted to the homoprenyl (**206**) by cross-metathesis (1.0 mol%, 66% yield). No metathesis occurred at room temperature, and the reaction mixture turned bright violet under nitrogen. The color quickly changed back to the normal reddish brown when exposed to air. It is speculated the unique color is a consequence of diene coordination to ruthenium to form a stable intermediate. However, it was found that stirring the mixture under reflux (38°C) overnight drove the reaction to completion. As expected, no RCM product was observed.

The synthesis of vinylogous ester **205** was completed by introduction of the hydroxymethylene group via Claisen condensation of **206** with ethyl formate and freshly prepared sodium methoxide. The resulting enol (**217**) was converted to the isopropyl enol ether in good yield by an acid-catalyzed Michael addition with isopropyl alcohol (73%).[85,86]

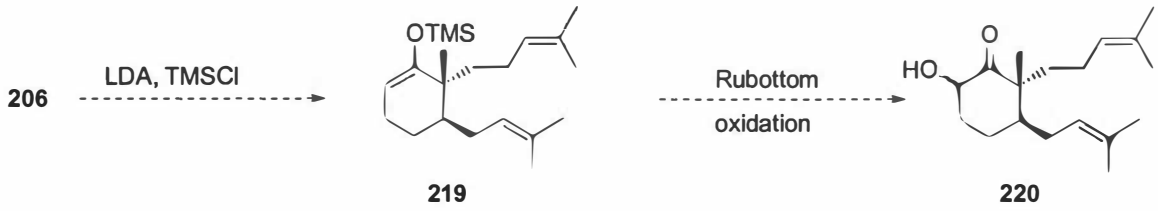
Introduction of the 1-propynyl moiety was expected to proceed under the same conditions as the geminal dimethyl model (Scheme 45). Thus, ketone **205** was reacted with two equivalents of the cerate derived from 1-propynylmagnesium bromide and anhydrous $CeCl_3$ at –78°C (Scheme 62). The only product isolated was the tandem conjugate addition-elimination followed by 1,2-addition. It is possible that the large homoprenyl group causes 1,4-addition to be favored in this case.



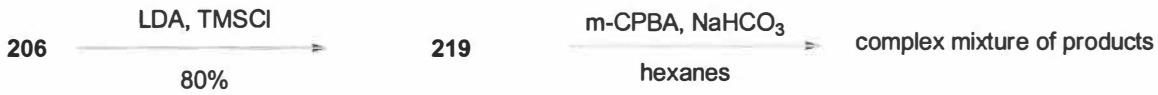
Scheme 61. Synthesis of ketone **205**.



Scheme 62. Attempted cerate addition to ketone **205**.



Scheme 63. Proposed route to α-hydroxyketone **220**.

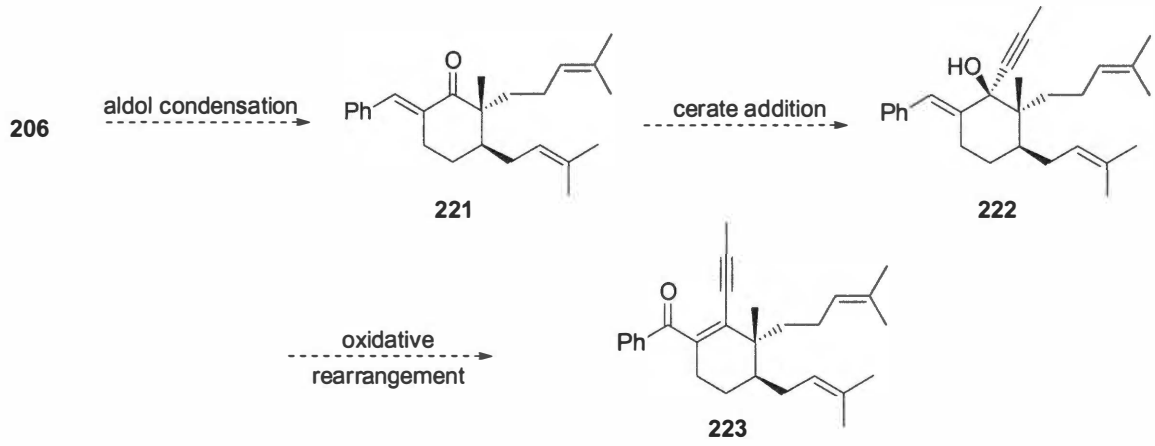


Scheme 64. Attempted Rubottom oxidation of silyl enol ether **219**.

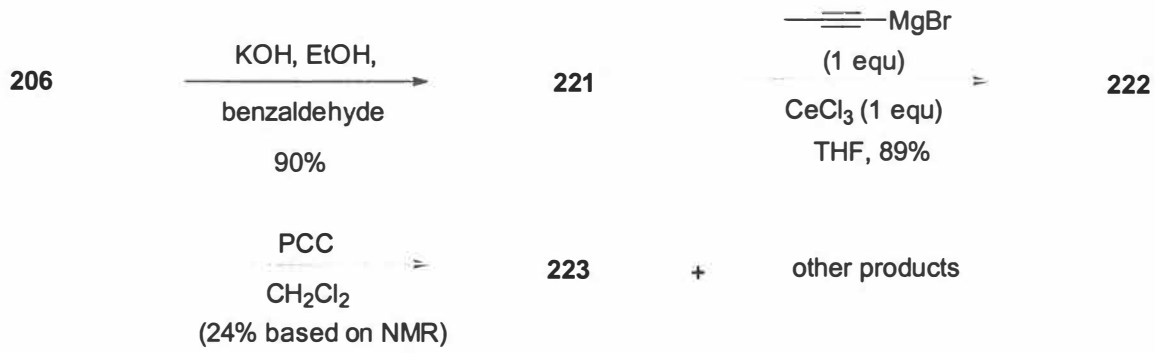
Other strategies were explored to introduce propynyl functionality in lieu of the enol ether. For example, silyl enol ether **219** was generated and oxidation of the electron rich double bond under Rubottom conditions was expected to produce an α-hydroxyketone that could be useful in a synthesis of **162** (Scheme 63). As seen in Scheme 64, the preparation of **219** with LDA and TMSCl occurred in excellent yield, but no chemoselectivity was observed in the oxidation.[112,113]

Another route was envisioned where an allylic alcohol similar to **204** could be used in a metal directed epoxidization approach. This could potentially be achieved by an aldol condensation between ketone **206** and benzaldehyde followed by β-elimination to furnish enone **221** (Scheme 65). Addition with 1-propynylmagnesium bromide in the presence of $CeCl_3$ (1 equivalent each) would afford tertiary alcohol **222**. An oxidative rearrangement by treatment with PCC should produce ketone **223**. As seen in Scheme 66, the base-catalyzed aldol condensation with benzaldehyde gave enone **221** in 90% yield. The cerate added to the ketone in 89% yield, and no 1,4-addition was observed. However, the chromium-mediated oxidative rearrangement of **222** proceeded in poor yield (24%) and the product was inseparable from byproducts.[114-116]

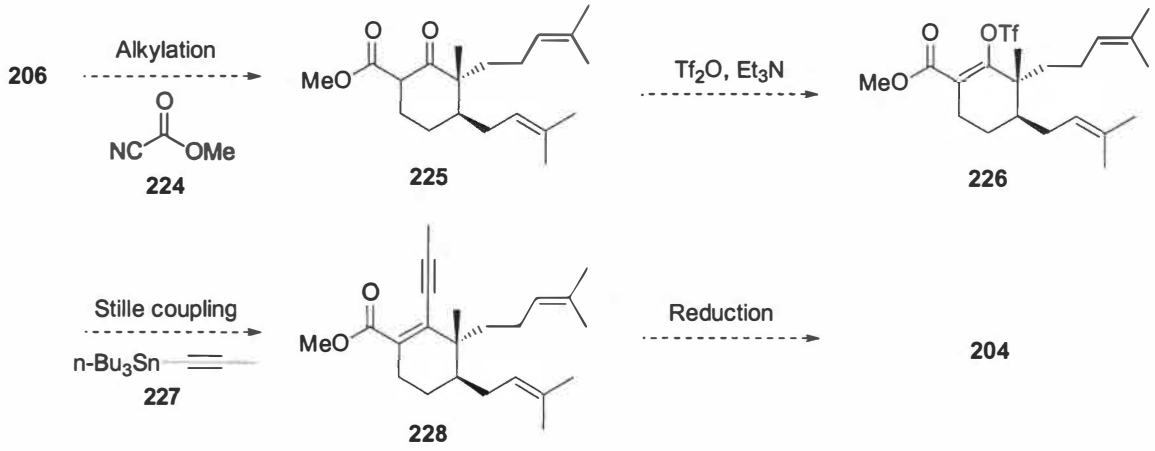
Although **204** has not been prepared as of yet, it is projected that this material should be available via the route in Scheme 67. Thus, alkylation with Mander's reagent



Scheme 65. Proposed synthesis of ketone **223** via oxidative rearrangement.



Scheme 66. Attempted oxidative rearrangement of ketone **223**.



Scheme 67. Proposed synthesis of alcohol **204** via Stille coupling.

(**224**) followed by treatment with Tf_2O would be expected to produce vinyl triflate **206**.[117,118] Palladium-catalyzed Stille coupling with stannane **227** would afford enyne **228**,[119] and reduction of the ester would produce **204**. With **204** in hand, the established route could be used to assemble the necessary allenyl ketone.

2.2 Mukaiyama aldol condensation methodology studies.

In Zeng's original study, the Mukaiyama aldol condensation of 3-nitropropanal dimethyl acetal **155** with silyl enol ether **152** in the presence of titanium (IV) chloride proceeded in 40% yield (Scheme 33). To establish the scope and limitations of the Mukaiyama aldol condensation in our advanced system, a variety of substrates and reaction conditions were examined.

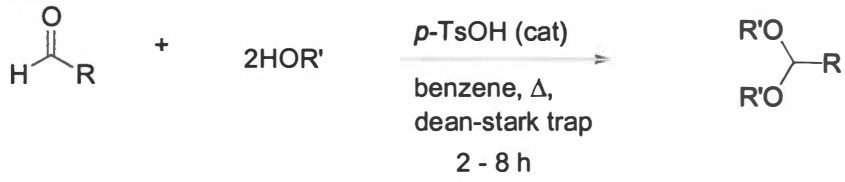
The necessary silyl enol ethers were prepared using simple reaction sequences. The majority were prepared by deprotonation with LDA to generate the kinetic enolate that was trapped by adding TMSCl. Compound **235** was prepared by the modified Lipshutz procedure,[78,81] and the preparation of silyl enol ethers **177** have previously been described (Scheme 41).

Likewise, the aldehydes 3-nitropropionaldehyde (**153**),[120] 3-(*tert*-butyldimethylsilanyloxy)propionaldehyde (**248**),[121,122] and 3-(*tert*-butyldiphenylsilanyloxy)propionaldehyde (**252**)[123,124] were prepared using literature procedures.

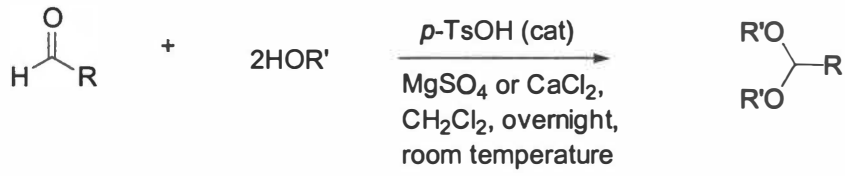
The acetals were synthesized by either an azeotropic method,[125] or by a modified Bradshaw procedure from their respected aldehydes and alcohols (Scheme 68).[126] The 3-halopropanal acetals were prepared from acrolein with TMSCl and various sodium salts by using Feringa's method.[127] 3-Nitropropanal dimethyl acetal (**155**) was prepared by a literature method (Scheme 68).[120]

Unless noted otherwise, the Mukaiyama aldol condensations were conducted by adding a solution of the silyl enol ether in CH_2Cl_2 to a stirred solution of $TiCl_4$ and acetal in CH_2Cl_2 at –78°C and stirring for 3-6 h (Method A).[70,72] Alternatively, a solution of silyl enol ether and acetal in CH_2Cl_2 was added to a 1:1 mixture of $TiCl_4$·$Ti[OCH(CH_3)_2]_4$ at –78°C and was stirred for 3-6 h (Method B).[73]

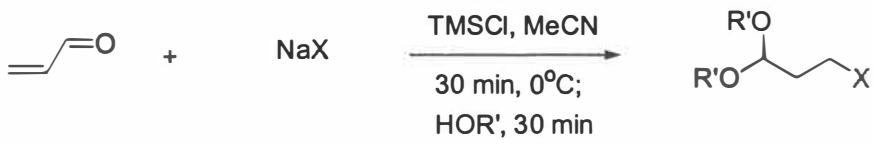
Azeotropic method:



Bradshaw procedure:



Synthesis 3-halopropanal acetals:



Scheme 68. Various methods for preparation of acetals.

2.2.1 3-Nitropropanal acetal studies.

The Mukaiyama condensation with a 3-nitropropanal acetal would be the most direct route to the appropriate nitrile oxide precursor as no further manipulation of the side chain is necessary. The study began by identifying optimal conditions for the reaction on silyl enol ether **229** and 3-nitropropanal dimethyl acetal (**155**) in the presence of titanium (IV) chloride (entry 1, Table 2, Method A). The desired aldol was formed along with a significant amount of β-elimination product (2:1 mixture, 66%). However, it was found that the reaction occurred in good yield (76%) without byproducts in the presence of $TiCl_4 \cdot Ti[OCH(CH_3)_2]_4$ (entry 2, Method B). It is speculated that the attenuated reactivity of the titanium complex facilitates the aldol condensation, but does not cause the unwanted side reactions.

Method B was found to be compatible with the condensation of silyl enol ether **229** and aldehyde **153**. As seen in entry 3, β-hydroxyketone **231** was produced in 46% yield.

Another objective of the study was to identify other acetals that could be used in the Mukaiyama procedure. In the late stages of the proposed synthesis of PPAPs, the ether produced in the aldol condensation will have to be converted to an alcohol. Given that demethylation requires vigorous conditions,[128] the formation of more easily disposed ethers was desired. An alternative previously used in the aldol condensation is the benzyl acetal,[71] which produces a benzyl ether that can be removed by hydrogenolysis.[129,130]

The use of trimethylsilyl triflate (commonly used as a Lewis acid with benzyl acetal **232**) led to decomposition as seen in entry 4,[131] but with the titanium mixture the benzyl ether **233** was isolated in 83% yield (entry 5, Method B). It was noteworthy that other Lewis acids such as catalytic trityl perchlorate,[132] tin (IV) chloride,[133] zinc (II) chloride,[134] and boron trifluoride etherate[135,136] were used with **232**, but no aldol products were observed (not shown).

Bis(2-bromoethoxy) **237** was briefly examined, but no reaction was observed as well (entry 10).

To examine the effect of steric hindrance about the silyl enol ether, the aldol condensation was conducted with **234** and the benzyl acetal. Surprisingly, only

Table 2. Results for 3-nitropropanal acetal series.

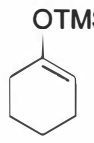
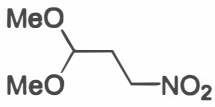
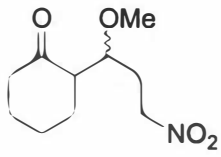
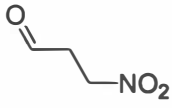
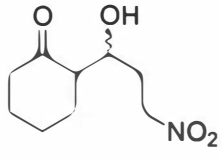
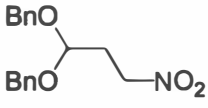
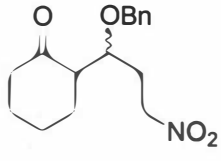
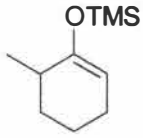
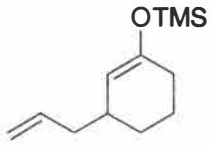
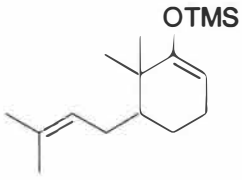
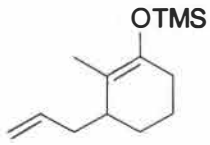
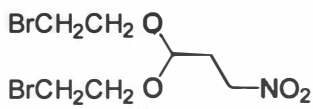
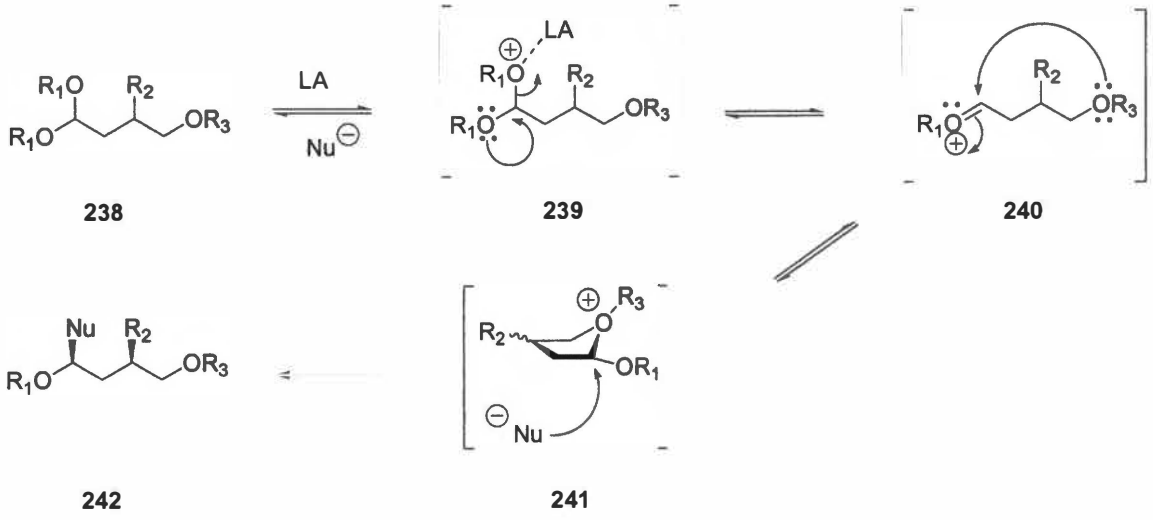
Entry	Silyl enol ether	Acetal or aldehyde	Conditions	Product	% Yield
1	 **229**	 **155**	Method A	 **230**	66%[a]
2	**229**	**155**	Method B	**230**	76%
3	**229**	 **153**	Method B	 **231**	46%
4	**229**	 **232**	TMSOTf	Decomposition	
5	**229**	**232**	Method B	 **233**	83%

Table 2. Continued.

Entry	Silyl enol ether	Acetal	Conditions	Product
6	 **234**	**232**	Method A or Method B	No Reaction
7	 **235**	**232**	Method B	No reaction
8	 **236**	**232**	Method A or Method B	No reaction
9	 **177**	**232** or **155**	Method A or Method B	No reaction
10	**229**	 **237**	Method A	No reaction

[a]2:1 inseparable mixture of β-methoxy and α,β-unsaturated ketone.



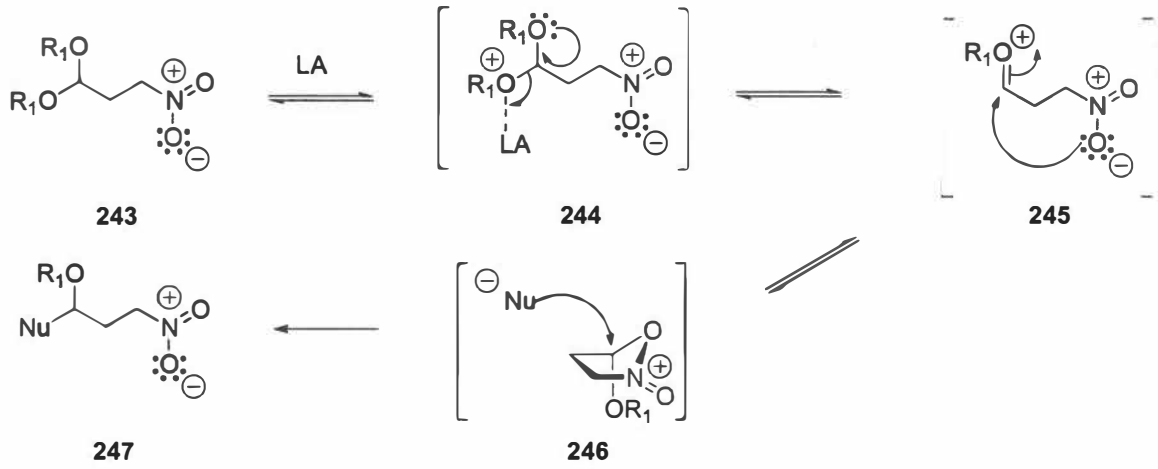
Scheme 69. 1,3-Asymmetric induction by a cyclic oxonium ion described by Molander.

hydrolyzed ketone was recovered using either method (entry 6). The degree of substitution was varied as seen in entries 7 – 9, but no reaction was observed for these cases.

A stable cyclic intermediate may be involved in these reactions. Asymmetric induction via neighboring group participation has been noted, as described in Scheme 69. For example, Gary A. Molander and coworker studied asymmetric induction by neighboring alkoxy groups such as **238**.[137] Molander speculated that upon exposure to a Lewis acid a cyclic oxonium ion **241** is formed. The conformation of **241** causes the nucleophile to attack on the face opposite of the R_2 substituent to provide **242** with *syn* stereochemistry.

Given the charge separation in the nitro group, it is proposed that a cyclic intermediate **246** forms as depicted in Scheme 70. It is possible that **246** is less reactive than the usual oxocarbenium ion **245** due to charge stabilization. If the nucleophile is not reactive enough then no reaction occurs.

Nevertheless, failure to form a quaternary center suggested the 3-nitropropanal acetals were not suitable for PPAP synthesis.



Scheme 70. Proposed mechanism of Muckaiyama aldol with 3-nitropropanal acetals.

2.2.2 3-Silyl ether propanal acetal studies.

An alternative approach would be to replace the nitro group with some other functionality that could be converted to a nitrile oxide precursor. For example, a 3-silyl ether propanal acetal could be subjected to the Mukaiyama chemistry and then be converted to an oxime.

The first compounds studied contained the *tert*-butyldimethylsilyl ether (OTBS).[98] As seen in Table 3, aldehyde **248** condensed with silyl enol ether **234** to afford β-hydroxyketone **249** in poor yield (13%, entry 1, Method B). Unfortunately, the benzyl acetal (**250**) demonstrated little improvement with Method A (23%, entry 2). A possible explanation for the low yields is that the titanium based Lewis acids led to silyl ether cleavage. In fact, some Lewis acids are known to cleave TBS ethers.[128]

The next silyl ether examined was the *tert*-butyldiphenylsilyl ether (OTBDPS),[138,139] which is about 100 times more stable to acid hydrolysis than the OTBS.[128] First, the Mukaiyama condensation was attempted with aldehyde **252** with silyl enol ether **177**, which furnished β-hydroxyketone **253** in 30% yield (entry 3, Method A). Although the yield was low, this result demonstrated that quaternary centers could be prepared with the OTBDPS compounds.

Better yields were obtained from the methyl acetal **255**. The condensation with silyl enol ether **234** provided methyl ether **256** in 70% yield (entry 5, Method B). To

Table 3. Results for silyl ether series.

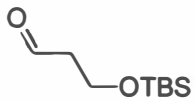
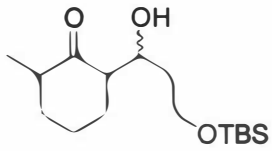
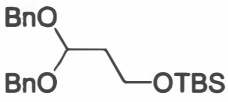
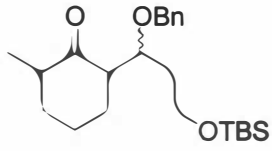
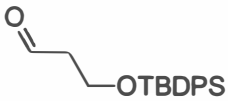
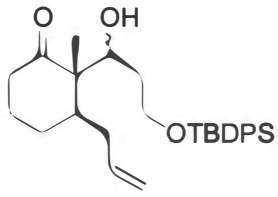
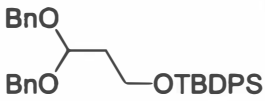
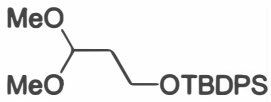
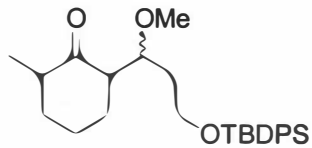
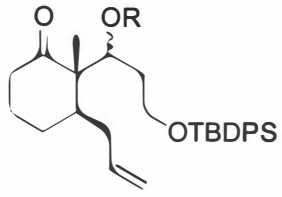
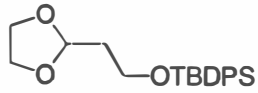
Entry	Silyl enol ether	Acetal or aldehyde	Conditions	Product	% Yield
1	**234**	 **248**	Method B	 **249**	13%
2	**234**	 **250**	Method A	 **251**	27%
3	**177**	 **252**	Method A or Method B	 **253**	30% 23%
4	**234**	 **254**	Method B	No reaction	

Table 3. Continued.

Entry	Silyl enol ether	Acetal	Conditions	Product	% Yield
5	**234**	 **255**	Method A or Method B	 **256**	62% 70%
6	**177**	**255**	Method B	 **257** R = Me **258** R = *i*-Pr	47% 29%
7	**177**	 **259**	Method B	**258**	83%

determine if the condensation could produce a quaternary center in sterically congested environment, the reaction was conducted with silyl enol ether **177** and acetal **255** (Method B). The result was a 47% yield of methyl ether **257** and 29% of *iso*-propyl ether **258** (entry 6). Apparently, the steric hindrance allowed an exchange reaction to occur between the acetal and the isopropoxy group from the titanium complex (Scheme 30). Furthermore, **258** was the sole product when dioxolane **259** was used (entry 7, 83%). Perhaps the bidentate nature of the 1,3-dioxolane promoted the exchange reaction with the isopropoxy group. It is noteworthy that benzyl acetal **254** did not react using method B (entry 4).

2.2.3 3-Halopropanal acetal studies.

Another reagent envisioned for introduction of the desired three-carbon unit was the 3-halopropanal acetal. It was projected that after the Mukaiyama aldol condensation, the halide could be converted to a nitro via S_N2 chemistry.

As seen in Table 4, the pilot study began with benzyl acetal **260**, but failed to produce an aldol product with various silyl enol ethers using Method A (entries 1 – 3). The results were independent of the halide since the bromide (**261**) and chloride (**262**) also failed to react (entries 4 and 5). However, excellent yields were obtained with methyl acetal **263** while using Method A (entry 6). It was apparent that quaternary centers could be prepared in good yield with this reagent combination as seen in entry 7.

To develop a procedure for conversion of the iodide to a nitro group, **265** was selected as a model since it resembles functionality found in the PPAP system. Initially, the direct conversion of the iodide with sodium nitrite in DMF was attempted.[140] Although the desired S_N2 reaction occurred, an intramolecular condensation followed to afford alcohol **266** (Scheme 71). Interestingly, silver nitrite as the nucleophile only yielded hemiketal **267**.[141,142]

Apparently **267** was generated by hydrolysis of the nitrite ester and the resulting alcohol underwent ketalization to form a six-membered ring. The hemiketal

Table 4. Results for 3-halopropanal acetals.

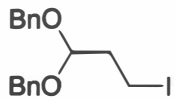
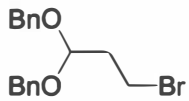
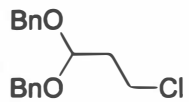
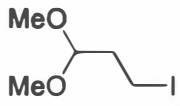
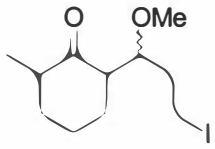
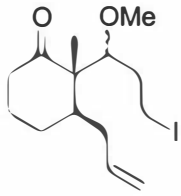
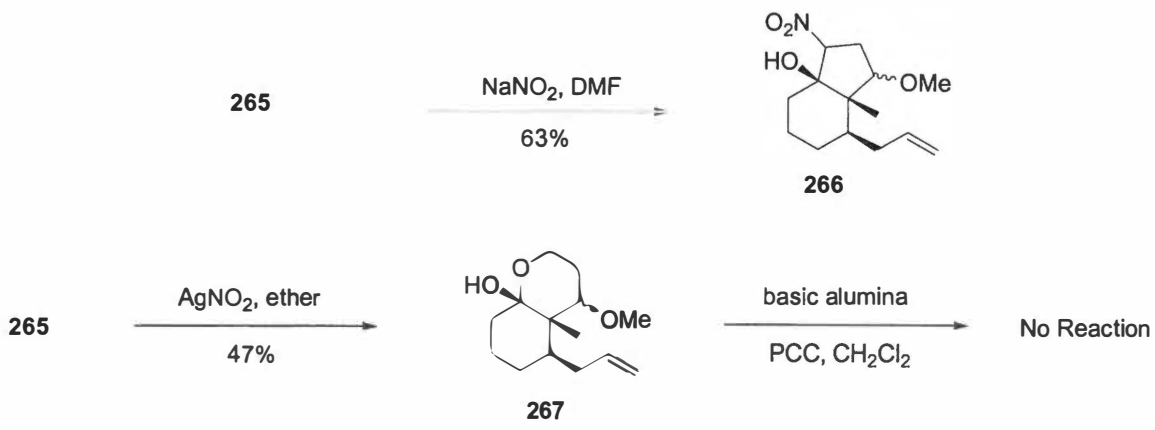
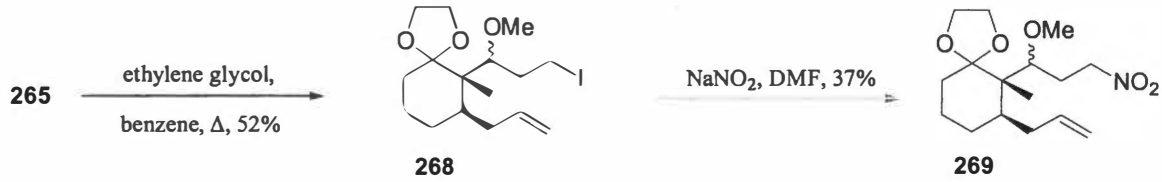
Entry	Silyl enol ether	Acetal	Conditions	Product
1	**234**	 **260**	Method A	No reaction
2	**177**	**260**	Method A	No reaction
3	**235**	**260**	Method A	No reaction
4	**234**	 **261**	Method A	No reaction
5	**235**	 **262**	Method A	No reaction

Table 4. Continued.

Entry	Silyl enol ether	Acetal	Conditions	Product	% Yield
6	**234**	 **263**	Method A	 **264**	81%
7	**177**	**263**	Method A	 **265**	74%



Scheme 71. Attempted S_N2 reaction of iodide **265** with sodium nitrite or silver nitrite.



Scheme 72. Synthesis of **269**.

demonstrated unusual stability as oxidation with PCC in the presence of basic alumina failed.[143]

To prevent the unwanted cyclization, the ketone was first protected as a 1,3-dioxolane, and then successfully converted to **269** upon treatment with sodium nitrite in DMF affording a 37% yield (50% based on recovered starting material, Scheme 72).

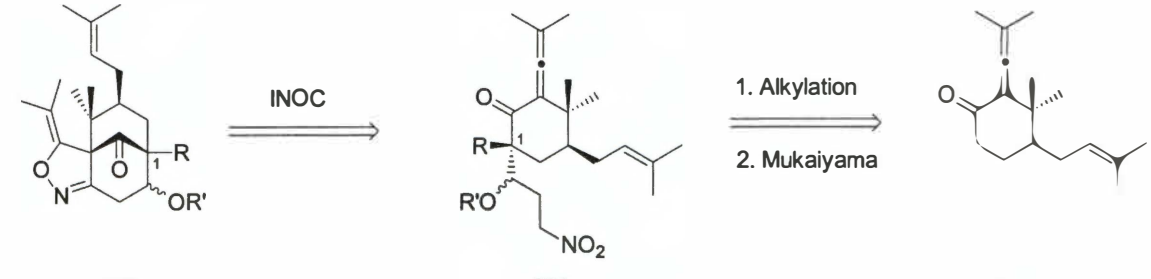
In summary, our survey of acetals and reaction conditions suggest that methyl acetal **255** or dioxolane **259** with $TiCl_4$·$Ti[OCH(CH_3)_2]_4$ from the 3-silyl ether series or methyl acetal **263** with $TiCl_4$ from the 3-halide series are the best prospects for introducing the appropriate side chain in the PPAP system.

2.3 Further elaboration of allenyl ketone 161.

The final stages of the PPAP synthetic plan required alkylation of allenyl ketone **161**, followed by a Mukaiyama aldol condensation, and an allene-INOC reaction with subsequent manipulation of the cycloadduct (Scheme 73). The following sections discuss functionalizing the α'-site of allenyl ketone **161**.

2.3.1 Alkylation of allenyl ketone 161.

Although alkylation of ketones is not always a straightforward procedure, in our plan introduction of the C-1 (hyperforin numbering scheme) side chain was to be accomplished via alkylation of allenyl ketone **161**. In some PPAP natural products this side chain is a prenyl group (i.e. hyperforin, **3a**) while in others such as garsubellin A (**6**) the side chain is oxygenated. C-1 alkylation studies were initiated by subjecting allenyl ketone **161** to LDA followed by addition of a solution of appropriate halide in THF



270 **271** **161**

Scheme 73. Retrosynthetic analysis of isoxazoline **270**.

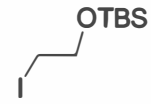
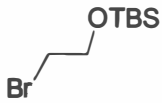
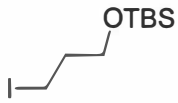
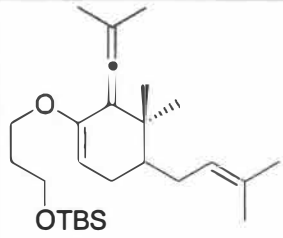
(Table 5). Unfortunately, the enolate derived from **161** did not react at temperatures ranging from –78°C to room temperature (entries 1 –3). Heating the enolate under reflux led to decomposition. When HMPA was added, O-alkylation was observed (entry 4).

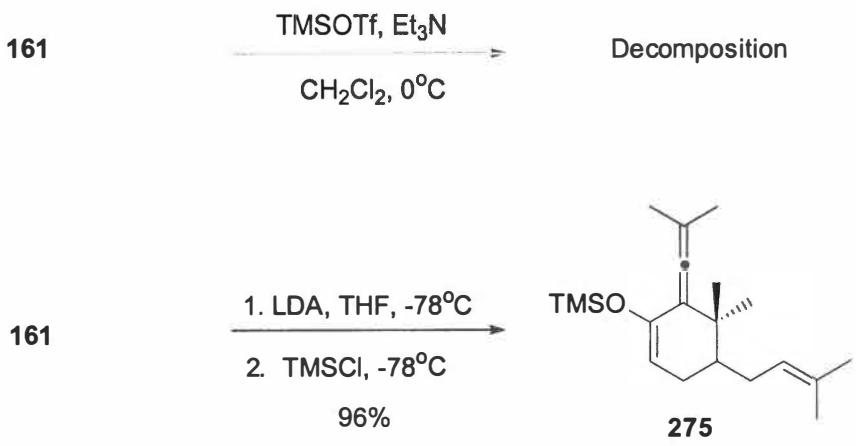
To demonstrate that the enolate was indeed formed, the ketone was converted to the silyl enol ether. Treatment of **161** with TMSOTf and triethylamine caused decomposition,[144] however, deprotonation with LDA and trapping the resulting enolate with TMSCl provided silyl enol ether **275** in excellent yield (96%, Scheme 74). Unfortunately, the lithium enolate derived from silicon oxygen bond cleavage in **275** showed the same reactivity as the enolate resulting from direct deprotonation of ketone **161** (Scheme 75). For example, alkylation with iodide **273** failed at or below room temperature while higher temperature led to decomposition.

Use of more reactive electrophiles gave mixed results. Alkylation of the lithium enolate of **275** with methyl iodide at –78°C gave an inseparable mixture of monoalkylated (**276**), dialkylated (**277**), and O-alkylated products. Likewise, using allyl bromide as the electrophile led to a mixture of products, with ketone **279** (37%) being favored when the reaction was performed in the presence of HMPA. No reaction was observed in the absence of this cosolvent.

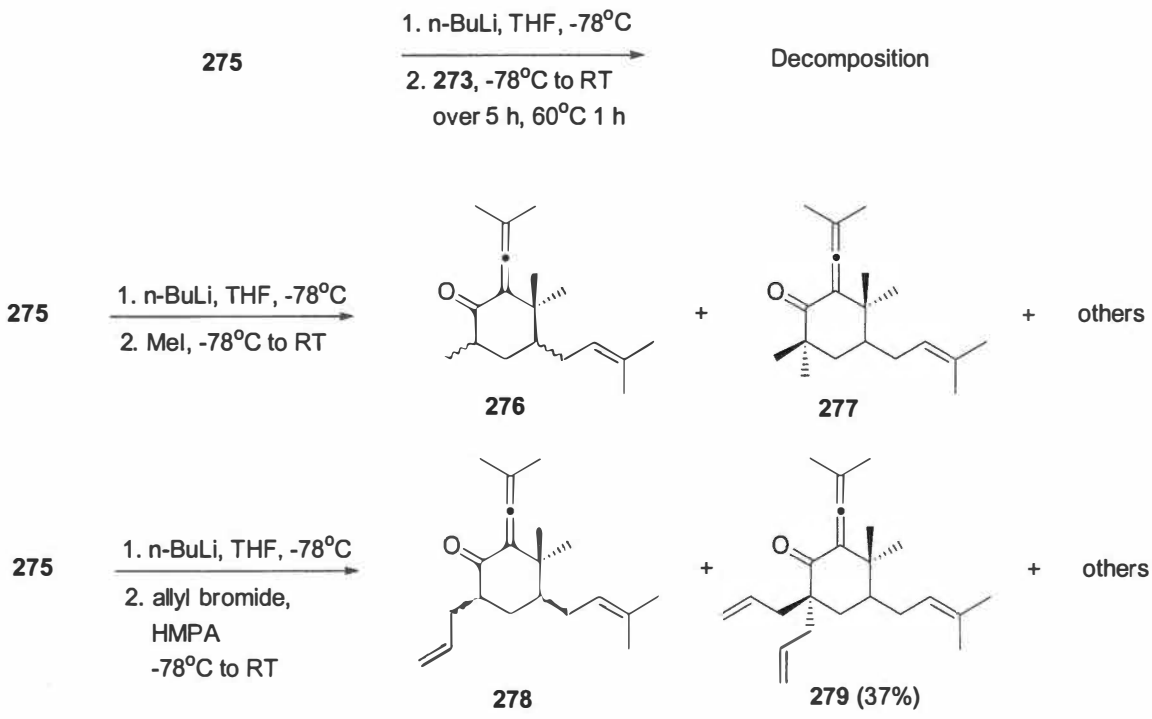
It was thought that the iodide might be more reactive if a softer nucleophile were employed. Thus, the Mander strategy was employed.[117] As depicted in Scheme 76, C-

Table 5. Attempted alkylation of allenyl ketone **161**.

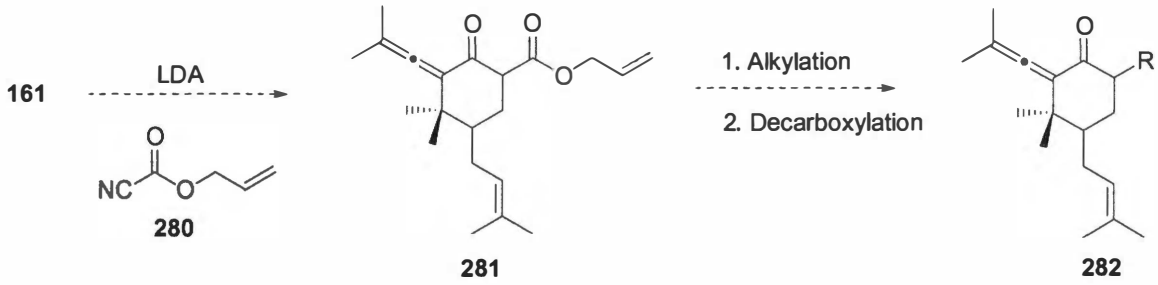
Entry	Electrophile	Conditions	Product
1	 **208**	LDA, THF; -78°C → RT	No reaction
2	 **272**	LDA, THF; NMP, -78°C → RT	No reaction
3	 **273**	LDA, THF; -78°C → RT	No reaction
4	**273**	LDA, THF; HMPA, -78°C → RT	 **274** (69%)



Scheme 74. Preparation of silyl enol ether **275**.



Scheme 75. Alkylation of silyl enol ether **275**.



Scheme 76. Proposed alkylation via Mander's strategy.

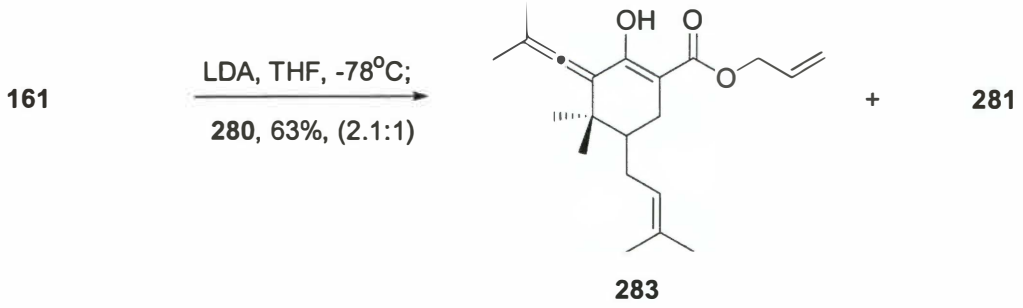
acylation with allyl cyanoformate (**280**) was expected to afford **281** that could be subjected to an alkylation, dealloxycarbonylation sequence.[145,146] In our hands acylation of the allenyl ketone with LDA and **280** provided a 2.1 : 1 mixture of enol (**283**) – keto (**281**) tautomers in 63% yield (Scheme 77).

Unfortunately, alkylation of the β-ketoesters proved to be problematic. As seen in Table 6, no reaction occurred while attempting to alkylate with iodide **208** under a variety of conditions (Scheme 78). Interestingly, prolonged heating of the allyl esters in the presence of sodium hydride and iodide **208** promoted a rearrangement to produce a structure tentatively assigned as **284** in 48% yield. Also isolated was enol ether **285** (42%) formed via O-alkylation (Scheme 79).

Tsuji allylation was subsequently explored as a strategy for installation of an allyl group at C-1.[147] Allyl enol carbonate **286** was prepared by deprotonation of **161** with LDA and O-acylating the resulting lithium enolate with allyl chloroformate (82%, Scheme 80). The palladium-catalyzed rearrangement of this substrate proceeded smoothly in the presence of dipalladium trisbenzylideneacetone chloroform complex[148] [$Pd_2(dba)_3 \cdot CHCl_3$] (10 mol%) and triphenylphosphine (40 mol%) to afford ketone **287** in 58% yield.

With **287** in hand, cross-metathesis using 1.0 mol% of Grubbs' second generation catalyst (**71**) was used to give C-1 prenylated material in excellent yield as a mixture of diastereomers (89%, Scheme 81).[84]

It was projected that the tetrahydrofuran ring in garsubellin A (**6**) could be constructed by Wacker oxidation of an appropriate acetonide as seen in Scheme 82. A



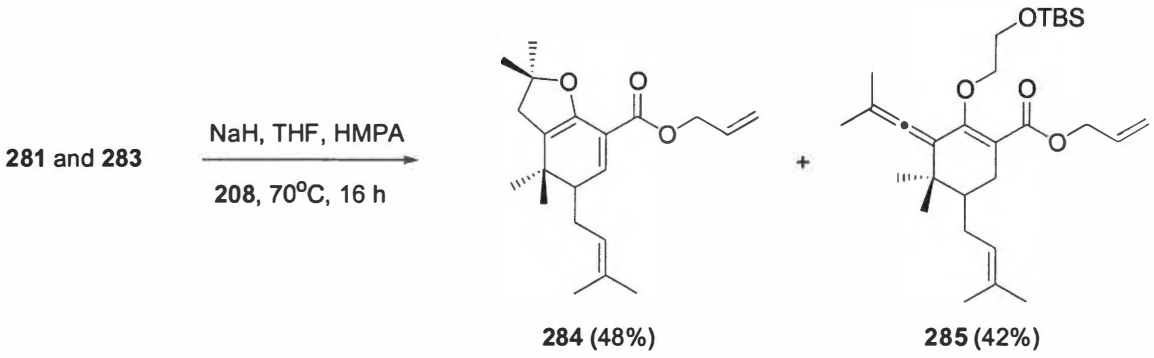
Scheme 77. Acylation of **161** with cyanoformate **280**.

Table 6. Results of alkylation of allyl esters with iodide **208**.

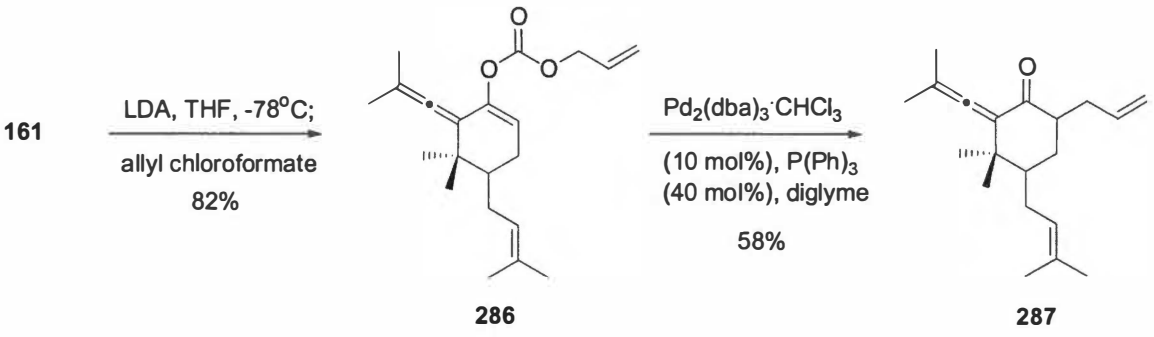
Entry	Conditions	Result
1	K_2CO_3, acetone	No reaction
2	NaH, THF, HMPA $0^o - 70^oC$, 6 h	No reaction
3	NaH, DMF, $0^o - 70^oC$, 4 h	Decomposition



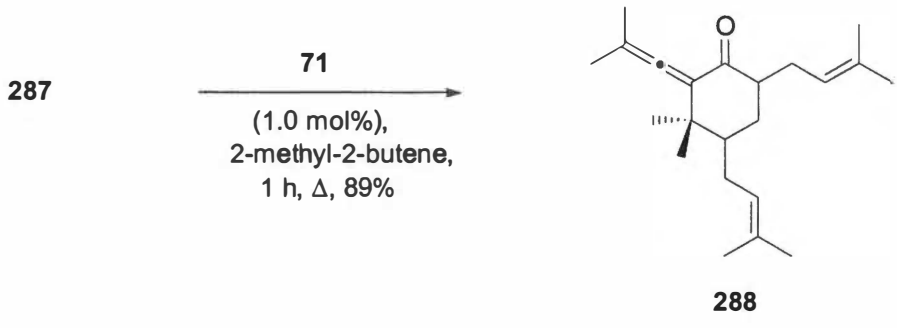
Scheme 78. Attempted alkylation with iodide **208**.



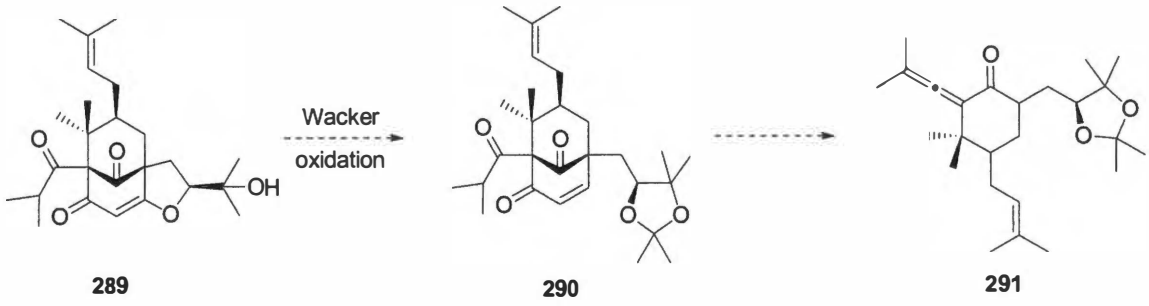
Scheme 79. Alkylation of the allyl esters with iodide **208**.



Scheme 80. Tsuji allylation of **161**.



Scheme 81. Cross-metathesis of **287**.



289 **290** **291**

Scheme 82. Proposed synthesis of tricycle **289**.

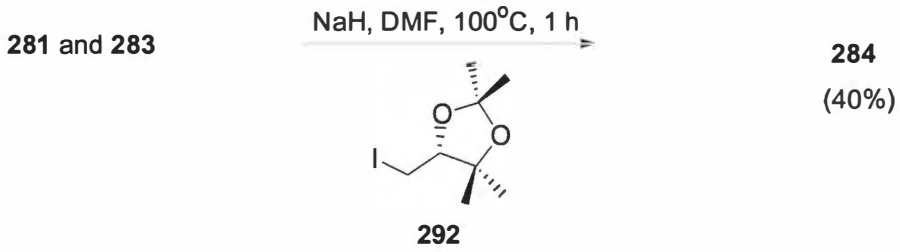
similar process was employed by Shibasaki in his PPAP model study (see section 1.2.3).[40,41] An acetonide containing side chain was also seen as valuable for the synthesis of PPAPs containing unsaturated side chains at C-1, because the acetonide could be viewed as a protected double bond, and in the event that the INOC reaction occurred on the C-1 side chain rather than the allene, a double bond surrogate would need to be employed.

It was decided to alkylate allyl ester (**281** and **283**) with iodide **292**, but no reaction occurred at room temperature and destruction of the allene occurred at higher temperature (Scheme 83).[149]

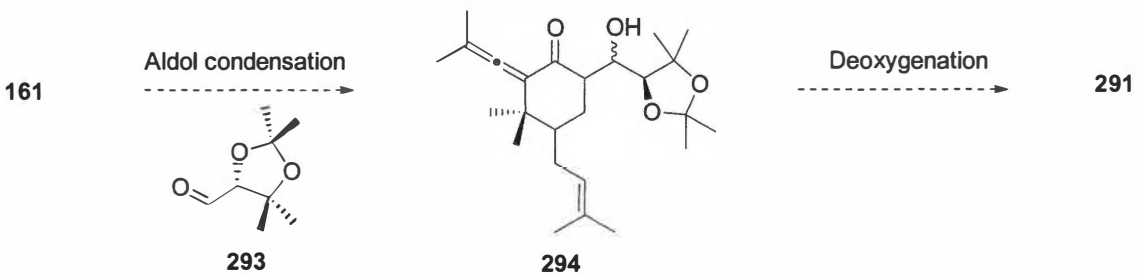
To circumvent the problematic alkylation, an aldol condensation involving the enolate derived from **161** and optically pure aldehyde **293** followed by deoxygenation was envisioned (Scheme 84).[149] As seen in Scheme 85, the condensation was successful when deprotonation was conducted with LDA at –78°C to afford β-hydroxyketone **294** as a mixture of diastereomers.[150] Dehydroxylation of **294** would yield the desired acetonide.[151,152]

2.3.2 Mukaiyama aldol condensation of allenyl silyl enol ethers.

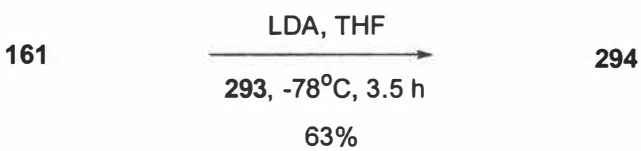
To form the appropriate quaternary center at the α'-site, allenyl ketones **287** and **288** were converted to silyl enol ethers **295** and **296** and then subjected to Mukaiyama aldol condensations with acetals developed in the methodology studies (see section 2.2).



Scheme 83. Attempted alkylation with iodide **292**.



Scheme 84. Revised route to acetonide **291**.



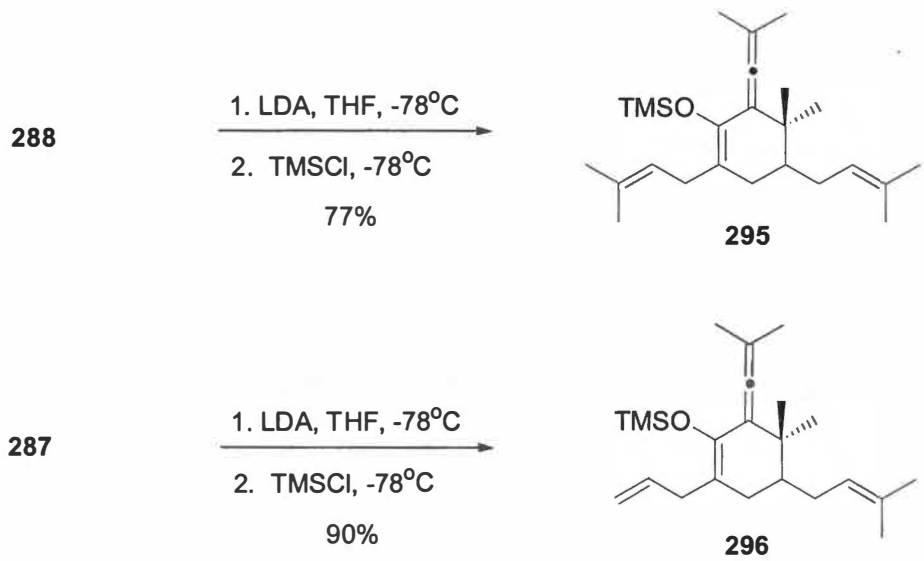
Scheme 85. Aldol condensation of **161** with aldehyde **293**.

Silyl enol ethers were prepared by treatment with LDA and trapping the resulting enolates with TMSCl (Scheme 86).

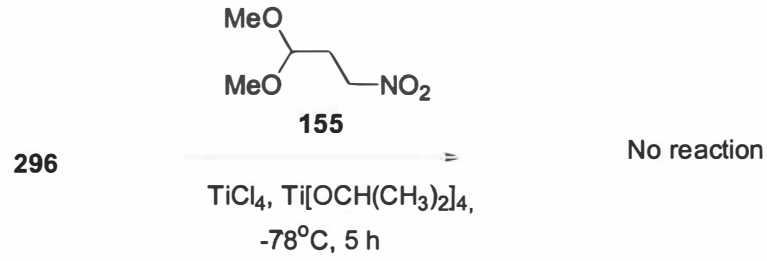
In a preliminary study, an attempt was made to condense silyl enol ether **296** with 3-nitropropanal dimethyl acetal **155**, but as predicted by the model study, acetal **155** failed to produce an aldol (Scheme 87).

The C-1 prenylated silyl enol ether **295** was subjected to the Mukaiyama aldol reaction with silyl ether **255** using $TiCl_4 \cdot Ti[OCH(CH_3)_2]_4$. As seen in Table 7, only decomposition resulted (entry 1). The use of iodide **263** provided ketone **297** in poor yield (19%, entry 2). However, iodide **263** with the titanium reagent combination gave ketone **297** as a mixture of compounds in 47% yield, although the results were capricious (entry 3).

Because silyl enol ether **295** appeared to be more stable than **296**, its Mukaiyama aldol condensation was explored next. Given the success of the cross-metathesis reaction in earlier settings, it was projected that the allyl group could be converted to prenyl group following the Mukaiyama condensation. As seen in Table 8, no condensation occurred when using either acetal **263** or **259** (entry 1 – 2). However, 3-silyl ether acetal **255** gave ketone **298** in the presence of titanium (IV) chloride primarily as two diastereomers,

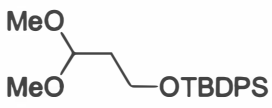
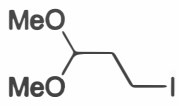
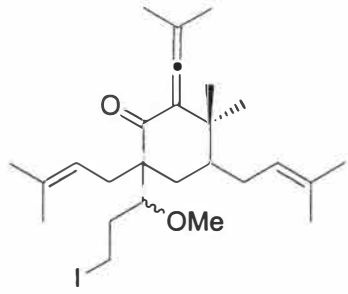


Scheme 86. Preparation of silyl enol ethers **295** and **296**.



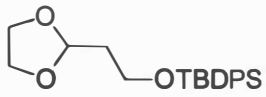
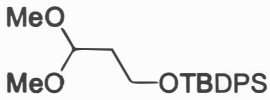
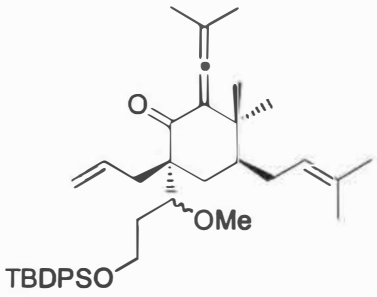
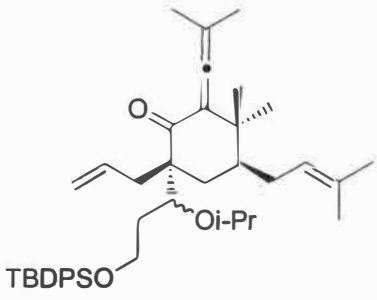
Scheme 87. Attempted Mukaiyama aldol condensation with acetal **155**.

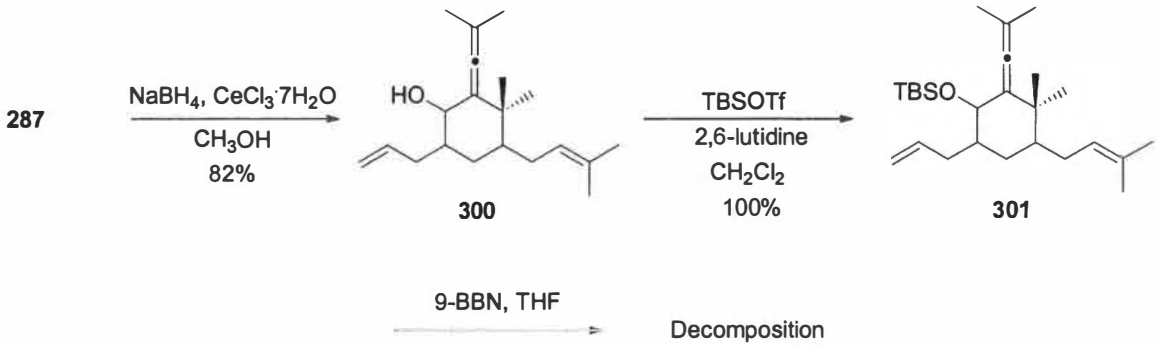
Table 7. Results for Mukaiyama aldol condensation of silyl enol ether **295**.

Entry	Acetal	Conditions	Results[a]
1	 **255**	$TiCl_4$, $Ti[OCH(CH_3)_2]_4$	Decomposition
2	 **263**	$TiCl_4$	 **297** (19%)
3	**263**	$TiCl_4$, $Ti[OCH(CH_3)_2]_4$	**297** (47%) + others

[a]percent yield based on NMR.

Table 8. Results for Mukaiyama aldol condensation with silyl enol ether **296**.

Entry	Acetal	Conditions	Results
1	**263**	$TiCl_4$	No Reaction
2	 **259**	$TiCl_4$, $Ti[OCH(CH_3)_2]_4$	Starting Material
3	 **255**	$TiCl_4$	 **298** (29%)
4	**255**	$TiCl_4$, $Ti[OCH(CH_3)_2]_4$	 **299** (63%)



Scheme 88. Attempted hydroboration of **287**.

albeit in poor yield (29%, entry 3). Much improvement was realized by using $TiCl_4 \cdot Ti[OCH(CH_3)_2]_4$ and acetal **255**. Under these conditions complete alkoxy exchange occurred affording isopropoxy ketone **299** as two diastereomers in 63% yield (entry 4).

Manipulation of the C-1 allyl group was demonstrated to be less useful. For example, it was speculated that the monosubstituted alkene might react faster than the trisubstituted olefin or the tetrasubstituted allene in various cyclohexane derivatives.[153-155] As shown in Scheme 88, ketone **287** was reduced under Luche's conditions and protected as a silyl ether **301**,[95,98] but attempts to hydroborate **301** with with 9-BBN gave a complex mixture of products.[156]

2.4 Conclusions.

Advanced intermediates toward the synthesis of PPAPs have been prepared. For example, *gem* dimethyl allenyl ketone **161** was synthesized in twelve steps with an overall yield of 24%, and vinylogous ester **205** was made in nine steps with an overall yield of 18%. Both intermediates were prepared from 2-methyl-2-cyclohexenone.

To introduce an appropriate side chain and construct the quaternary center, methodology studies on the Mukaiyama aldol condensation were conducted. Although it was determined that 3-nitropropanal acetals were not suitable for PPAP synthesis, 3-iodopropanal dimethyl acetal (**263**) and 3-silyl ether propanal dimethyl acetal (**255** and

259) were deemed to hold potential. In our systems it was found either $TiCl_4$ or $TiCl_4 \cdot Ti[OCH(CH_3)_2]_4$ were the Lewis acids of choice for the Mukaiyama reactions.

Introduction of the C-1 side chain using allenyl ketone **161** as an intermediate was problematic; however, Tsuji allylation provided a C-1 allyl derivative in good yield. In the key event, a fully functionalized cyclohexanone to be used towards the synthesis of PPAPs containing *gem* dimethyl substitution at C-6 (i.e. garsubellin A) was prepared via Mukaiyama aldol condensation of silyl enol ether **296** and acetal **255** in 63% yield.

3. Experimental Section

3.1 General methods.

All ^{1}H-NMR spectra were recorded on a Bruker AC-250 spectrometer (250 MHz) or a Varian Mercury-300 spectrometer (300 MHz) with tetramethylsilane as the internal standard. The ^{13}C-NMR spectra were recorded on a Bruker AC-250 spectrometer at 62.9 MHz or 70 MHz using the central peak of the $CDCl_3$ as the internal standard (δ 77.00). Chemical shifts were recorded as δ values in parts per million (ppm) at 20°C. Impurities present in the spectra are noted by an asterisk mark above the peak. Determination of the multiplicity of the ^{13}C NMR signals was achieved using distortionless enhancement by polarization transfer (DEPT) experiments. Multiplets are reported as follows: s, singlet; d, doublet; dd, doublet of doublets; dt, doublet of triplets; t, triplet; q, quartet; h, heptet; m, multiplet. All melting points were measured on a Thomas–Hoover capillary melting point apparatus and are uncorrected. FT-infrared (IR) spectra were obtained using potassium bromide salt plates using an Arid-zone Bomem MB100 instrument. The mass spectral analyses were obtained on a Micromass VG Quattro II electrospray instrument at the University of Tennessee using electron impact (EI) as the ionization technique. Elemental analyses were performed by Atlantic Microlab, Inc., Norcross, GA.

All commercial reagents were used without further purification unless noted otherwise. All reactions were conducted under nitrogen atmosphere in dried glassware, and yields refer to isolated yields of material unless stated otherwise. Room temperature is assumed to be 20°C.

Tetrahydrofuran and diethyl ether were distilled from sodium benzophenone ketyl. Methylene chloride, diisopropylamine, and benzene were distilled over calcium hydride. Imidazole was purchased from Aldrich and recrystallized from benzene before use. [(1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)-(tricyclohexylphosphine)ruthenium] (second generation Grubbs' catalyst) and 2-methylcyclohexanone were purchased from Aldrich and used without further purification. Acrolein and allyl chloroformate were purchased from Aldrich and were distilled prior to

use. Methyllithium, *n*-butyllithium, and methylmagnesium bromide were titrated with menthol using 1,10-phenathrolene as the indicator on a regular basis.[157]

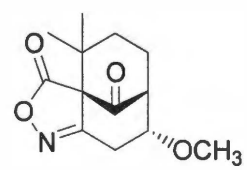
Analytical thin-layer chromatography (TLC) was conducted using Whatman K5F 150A 250 μm silica gel plates, and column chromatography was performed on Sorbent Technologies silica gel (230 x 450 mesh, 60 Å) as the stationary phase.

Allyl cyanoformate,[145] (2-bromoethoxy)-*tert*-butyldimethylsilane,[158] (3-bromoprop-oxy)-*tert*-butyldimethylsilane,[159-161] anhydrous cerium (III) chloride,[162] 1-iodobut-2-yne,[163] 2-iodo-2-cyclohexen-1-one,[164] 3-*tert*-butyldimethylsiloxy-1-propanol,[165] 3-*tert*-butyldiphenyl-siloxy-1-propanol,[166] and (4R)-2,2,5,5-tetramethyl[1.3]dioxolane-4-carbaldehyde[149] were prepared by literature methods.

Nomenclature for new compounds was generated using ChemDraw Ultra 6.0 from CambridgeSoft.com.

Abbreviations for compounds appear as follows: MeCN (acetonitrile), NH_4Cl (ammonium chloride), *n*-BuLi (*n*-Butyllithium), $CeCl_3$ (cerium (III) chloride, anhydrous), $CeCl_3 \cdot 7H_2O$ (cerium (III) chloride heptahydrate), $CDCl_3$ (chloroform-d), CuI (copper (I) iodide), DMF (N,N-dimethylformamide), HMPA (hexamethylphosphoramide), HCl (hydrochloric acid), $Fe(acac)_3$ (iron (III) acetylacetonate), LiCl (lithium chloride, anhydrous), $MgSO_4$ (magnesium sulfate, anhydrous), $MnCl_2$ (manganese (II) chloride, anhydrous), CH_2Cl_2 (methylene chloride), NMP (1-methyl-2-pyrrolidinone), $NaNH_2$ (sodium amide), $NaHCO_3$ (sodium bicarbonate), NaOH (sodium hydroxide), H_2SO_4 (sulfuric acid), THF (tetrahydrofuran).

3.2 Experimental procedures.

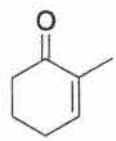


160

7-Methoxy-11,11-dimethyl-3-oxa-azatricyclo[6.3.1.$0^{1,5}$]dodec-4-ene-2,12-dione (160). A solution of 174 mg (627 μmol) of 2-isopropylidene-7-methoxy-11,11-

dimethyl-3-oxa-azatricyclo[6.3.1.$0^{1,5}$]dodec-4-ene-12-one[74] in 10 mL of CH_2Cl_2 was purged with ozone (3.6 mmol/min) until a blue color persisted (approximately three min) at –78°C. The light blue solution stirred at –78°C for 2 h and then 0.16 mL (2.19 mmol) of dimethylsulfide was added. The mixture stirred for 2 h while slowly warming to room temperature. The solvent was removed *in vacuo* and the residue was chromatographed over 2 g of silica gel (eluted with CH_2Cl_2–ether, 25:1) to afford 129 mg (82%) of **160** as a white crystalline solid: mp = 108 – 110°C; IR ($CHCl_3$) 2968 (s), 2944 (s), 2880 (m), 2836 (m), 1806 (s), 1728 (s), 1609 (m), 1239 (s), 1196 (s), 1105 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.72 – 3.56 (m, 1H, CHO), 3.33 (s, 3H, OCH_3), 3.27 (dd, J = 15.6, 7.2 Hz, 1H), 3.00 – 2.90 (m, 1H), 2.83 (dd, J = 15.5, 10.1 Hz, 1H), 2.47 – 2.25 (m, 1H), 2.12 – 1.87 (m, 2H), 1.63 – 1.36 (m, 1H), 1.22 (s, 3H, CH_3), 0.96 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 198.39 (s), 171.77 (s), 162.92 (s), 76.36 (d), 70.20 (s), 56.84 (q), 49.00 (d), 46.86 (s), 34.97 (t), 32.79 (t), 26.24 (q), 22.51 (t), 20.40 (q); exact mass calcd. for $C_{13}H_{17}NO_4$ ($M^{\cdot+}$) *m/z* 251.1158, found *m/z* 251.1166.

Anal. calcd. for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; found: C, 61.78; H, 6.87.

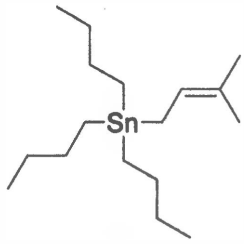


167

2-Methylcyclohex-2-enone (167).[76,167] **Method A**:[77] To a stirred solution of 6.66 g (30.0 mmol) of 2-iodo-2-cyclohexen-1-one (**169**) and 26.2 mL (26.8 g, 270 mmol) of NMP in 40 mL of THF was added 212 mg (0.60 mmol, 2 mol%) of $Fe(acac)_3$. After stirring for 5 min, the flask was placed in a room temperature water bath and then 11 mL (33.0 mmol) of a 3.0 M solution of methyllithium in THF was added to the mixture over 15 min. The reaction mixture stirred for 1 h and was quenched by slowly adding 100 mL of 1 M $HCl_{(aq)}$. After stirring for 5 min, the aqueous layer was extracted three times with 50–mL portions of ether. The combined organic layers were washed with 50 mL of saturated $NaHCO_{3(aq)}$, and then washed with 50 mL of brine, dried ($MgSO_4$), and

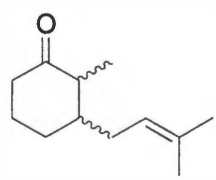
concentrated *in vacuo*. The crude material was chromatographed over 70 g of silica gel (eluted with hexanes–ethyl acetate, 10:1) to afford 1.90 g (57%) of **167** as a colorless oil.

Method B:[76] To a three-necked round bottom flask equipped with an addition funnel, a nitrogen inlet, and a hose running to a gas trap was added a solution of 16.5 mL (15.3 g, 0.136 mol) of 2-methylcyclohexanone (**168**) in 68 mL of CH_2Cl_2. The reaction vessel was placed in a room temperature water bath. To the mixture was added a solution of 12.1 mL (20.3 g, 0.150 mol) of sulfuryl chloride in 20 mL of CH_2Cl_2 via an addition funnel over 1.3 h. The reaction mixture continued to stir for 2 h and then the mixture was transferred to a separation funnel and washed twice with 20–mL portions of water, once with 20 mL of saturated $NaHCO_{3(aq)}$, and once with 20 mL of brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. To a solution of the residue in 34 mL of DMF was added 3.52 g (83.0 mmol) of anhydrous lithium chloride. The mixture was placed in a 100°C oil bath for 45 min. After cooling to room temperature the brown mixture was diluted with 136 mL of ether and treated slowly with 136 mL of 2.5 % (v/v) sulfuric acid. The mixture stirred for 1 h and then the layers were separated. The aqueous layer was extracted four times with 70–mL portions of ether. The combined organic layers were washed with 70 mL of saturated $NaHCO_{3(aq)}$, washed with 70 mL of brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 200 g of silica gel (eluted with hexanes-ethyl acetate, 10:1 → 5:1) to afford 7.055 g (47%) of **167** as a yellow oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.79 – 6.74 (m, 1H, HC=), 2.47 – 2.38 (m, 2H, CH_2), 2.38 – 2.29 (m, 2H, CH_2), 2.05 – 1.92 (m, 2H, CH_2), 1.79 – 1.75 (m, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 199.70, 145.40, 135.47, 38.13, 25.84, 23.12, 15.77.



171

Tributyl-(3-methyl-2-enyl)-stannane (171).[168,169] To a mixture of 500 mg of magnesium in 3 mL of THF was added dropwise a solution of 0.70 mL (900 mg, 6.06 mmol) of prenyl bromide and 0.82 mL (986 mg, 3.03 mmol) of tri-*n*-butylstannyl chloride in 3 mL of THF over 1 h at 0°C. The mixture was then heated under reflux for 1.5 h. After cooling to room temperature, the reaction was quenched with 10 mL of saturated $NH_4Cl_{(aq)}$. The mixture stirred for 5 min and was then filtered. The layers were separated and the aqueous layer was extracted three times with 10–mL portions of ether. The combined organic layers were washed twice with 10–mL portions of water, once with 20 mL of brine, dried ($MgSO_4$), and concentrated *in vacuo.* The residue was placed under high vacuum (0.1 torr) for 1 h to afford 1.00 g (93%) of **171** as a colorless oil: ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.30 (dt, J = 1.0, 8.5 Hz, 1H, HC=), 1.75 – 1.40 (m, 13 H), 1.39 – 1.17 (m, 7H), 0.97 – 0.74 (m, 15H).



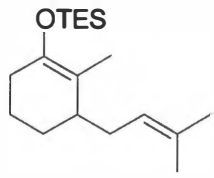
173

(±)-2-Methyl-3-(3-methylbut-2-enyl)-cyclohexanone (173). Method A: To a solution of 5.58 g (15.5 mmol) of stannane **171** in 8.5 mL of THF was added dropwise 9.7 mL (15.5 mmol) of a 1.6 M solution of *n*-butyllithium in hexanes at –78°C and the resulting solution stirred for 20 min. Concurrently, a mixture of 2.95 g (15.5 mmol) of copper (I) iodide and 0.657 mg (15.5 mmol) of lithium chloride in 13 mL of THF was prepared. The off white mixture stirred for 5 min at room temperature and then was

cooled to –78°C and stirred for 10 min. The yellow prenyllithium solution was added dropwise to the cuprous mixture to furnish a deep violet solution. Immediately, 2.8 mL (2.33 g, 15.5 mmol) of trimethylsilyl chloride was added followed by the addition of 685 mg (6.2 mmol) of enone **167**. The reaction mixture was stirred for 1 h. After warming to room temperature, the reaction was quenched by adding 45 mL of saturated $NH_4Cl_{(aq)}$. After stirring for 5 min, the layers were separated and the aqueous layer was extracted four times with 40–mL portions of ether. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over 80 g silica gel (eluted with hexanes-ethyl acetate, 100:1 → 10:1) to afford 8.12 g of tetrabutyltin and 892 mg (80%) of **173** as diastereomers that were a colorless oil.

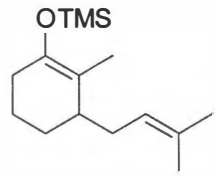
Method B: To a solution of 309 mg (2.03 mmol) of 3-allyl-2-methylcyclohexanone in 7 mL of 2-methyl-2-butene was added 1.7 mg (2.03 μmol, 0.1 mol%) of the second generation Grubbs' catalyst [(1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)-dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium] (**71**) at room temperature. After stirring for 16 h, the mixture was filtered over a 1-inch pad of silica gel (rinsed with 80 mL of hexanes–ethyl acetate, 5:1). The solvent was removed *in vacuo* to afford 343 mg (94%) of ketone **173** as diastereomers: IR (neat) 2969 (s), 2933 (s), 2867 (s), 1708 (s), 1449 (m), 913 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.20 – 5.08 (m, 1H, HC=), 5.08 – 4.97 (m, 1H, HC=), 2.69 – 2.53 (m, 1H, CH_2), 2.48 – 2.11 (m, 6H), 2.11 – 1.38 (m, 13H), 1.72 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.06 (d, J = 7.0 Hz, 3H, CH_3), 1.03 (d, J = 7.0 Hz, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 214.26 (s), (213.18) (s), (133.09) (s), 132.41 (s), 122.15 (d), (121.08) (d), (49.41) (d), 48.61 (d), (46.07) (d), 42.76 (d), (41.31) (t), 39.60 (t), (32.00) (t), (30.25) (t), 27.54 (t), 26.75 (t), (25.68) (t), 25.66 (q, 2C), 23.83 (t), 17.70 (q, 2C), 11.37 (q, 2C); exact mass calcd. for $C_{12}H_{20}O$ ($M^{\cdot+}$) *m/z* 180.1514, found *m/z* 180.1512.

Anal. calcd. for $C_{12}H_{20}O$: C, 79.94; H, 11.18; found: C, 79.62; H, 11.28.



174

Triethyl-[2-methyl-3-(3-methylbut-2-enyl)cyclohex-1-enyloxy]silane (174). To a solution of 2.08 g (5.79 mmol) of stannane **171** in 3.0 mL of THF was added dropwise 3.6 mL (5.79 mmol) of a 1.6 M solution of *n*-butyllithium in hexanes at –78°C and the resulting solution was stirred for 20 min. Concurrently, a mixture of 1.10 g (5.79 mmol) of copper (I) iodide and 245 mg (5.79 mmol) of lithium chloride in 7 mL of THF was prepared. The off white mixture stirred for 5 min at room temperature and then was cooled to –78°C and stirred for 5 min. The bright yellow prenyllithium solution was added dropwise to the cuprous mixture to furnish a deep violet solution. After stirring for 5 min, 0.97 mL (873 mg, 5.79 mmol) of triethylsilyl chloride was added dropwise, followed by the dropwise addition of 256 mg (2.32 mmol) of enone **167**. The reaction mixture stirred for 40 min. After warming to room temperature, the reaction was quenched by adding 15 mL of saturated $NH_4Cl_{(aq)}$. The layers were separated and the aqueous layer was extracted three times with 10–mL portions of ether. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over 70 g silica gel (eluted with hexanes-ethyl acetate, 100:1→ 50:1) to afford 1.95 g of tetrabutyltin and 457 mg (67%) of **174** as a colorless oil: IR (neat) 2956 (s), 2931 (s), 2878 (s), 1678 (m), 1177 (s), 736 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.09 (dt, J = 1.3, 6.6 Hz, 1H, HC=), 2.27 – 2.11 (m, 1H), 2.11 – 1.82 (m, 4H), 1.76 – 1.46 (m, 4H), 1.69 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 0.99 (t, J = 7.9 Hz, 9H, $CH_2C\underline{H}_3$), 0.66 (q, J = 7.9 Hz, 6H, $C\underline{H}_2CH_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 144.25, 131.86, 123.62, 114.62, 39.50, 31.37, 30.51, 27.16, 25.78, 20.43, 17.81, 14.31, 6.77 (3C), 5.65 (3C); exact mass calcd. for $C_{18}H_{34}OSi$ ($M^{\cdot+}$) *m/z* 294.2379, found *m/z* 294.2382.



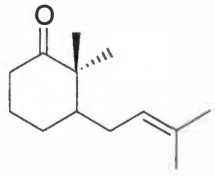
175

Trimethyl-[2-methyl-3-(3-methylbut-2-enyl)cyclohex-1-enyloxy]silane (175). **Method A**: To a solution of 18.3 g (51.0 mmol) of stannane **171** in 32.0 mL of THF was added dropwise 42.5 mL (51.0 mmol) of a 1.2 M solution of *n*-butyllithium in hexanes at –78°C and the resulting solution was stirred for 50 min. Concurrently, a mixture of 9.71 g (51.0 mmol) of copper (I) iodide and 2.16 g (51.0 mmol) of lithium chloride in 50.0 mL of THF was prepared. The off white mixture stirred for 5 min at room temperature and then was cooled to –78°C and stirred for 5 min. The bright yellow prenyllithium solution was added dropwise to the cuprous mixture to furnish a deep violet solution. After stirring for 10 min, 6.5 mL (5.5 g, 51 mmol) of trimethylsilyl chloride was added dropwise followed by the dropwise addition of 7.8 mL (5.6 g, 56 mmol) of triethylamine. After stirring for 2 min, 2.56 g (23.2 mmol) of enone **167** was added to the mixture. The reaction mixture stirred for 30 min. After warming to room temperature, the reaction was quenched by adding 130 mL of a 10% (v/v) $NH_4Cl_{(aq)}$ solution. The layers were separated and the aqueous layer was extracted three times with 100–mL portions of ether. The combined organic layers were washed with brine, dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over 240 g silica gel (eluted with hexanes → hexanes-ethyl acetate, 100:1) to afford 4.692 g (80%) of **175** as a colorless oil.

Method B: To a solution of 1.01 g (4.50 mmol) of silyl enol ether **177** in 10 mL of 2-methyl-2-butene was added 38 mg (0.045 mmol, 1.0 mol%) of the second generation Grubbs' catalyst [(1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro-(phenylmethylene)(tricyclohexylphosphine)ruthenium] (**71**) at room temperature. After stirring for 20 h, the mixture was filtered over a 1.5-inch pad of Florisil (rinsed with 120 mL of hexanes–ethyl acetate, 50:1). The solvent was removed *in vacuo* to afford 1.06 g (93%) of silyl enol ether **175** as a colorless oil: IR (neat) 2961 (m), 2929 (s), 2859 (m), 1678 (m), 1252 (s), 1177 (s), 925 (m), 844 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.13

– 5.05 (m, 1H, HC=), 2.29 – 2.12 (m, 1H, CH_2), 2.11 – 1.86 (m, 4H, CH_2), 1.82 – 1.30 (m, 4H), 1.69 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 0.17 (s, 9H, $SiCH_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 144.12 (s), 131.83 (s), 123.55 (d), 115.23 (s), 39.39 (d), 31.42 (t), 30.54 (t), 27.24 (t), 25.80 (q), 20.39 (t), 17.83 (q), 14.38 (q), 0.61 (q, 3C); exact mass calcd. for $C_{15}H_{28}OSi$ ($M^{\cdot+}$) *m/z* 252.1909, found *m/z* 252.1915.

Anal. calcd. for $C_{15}H_{28}OSi$: C, 71.36; H, 11.18; found: C, 70.97; H, 11.20.



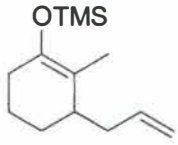
176

2,2-Dimethyl-3-(3-methylbut-2-enyl)cyclohexanone (176). Method A: To a solution of 8.11 g (32.1 mmol) of silyl enol ether **175** in 70 mL of THF was added dropwise 22.5 mL (33.7 mmol) of methyllithium as a 1.5 M solution in ether at 0°C. After the mixture stirred for 30 min at 0°C and 1 h at room temperature, a solution of $MnCl_4Li_2$ (prepared by dissolving 4.44 g (35.3 mmol) of anhydrous $MnCl_2$ and 2.99 g (70.6 mmol) of anhydrous LiCl in 84 mL of THF and stirring for 20 h) was added dropwise to the reaction mixture. The resulting light brown solution stirred for 1 h and then a solution of 8.0 mL (18 g, 0.128 mol) of methyl iodide in 18.0 mL of NMP was added dropwise. The mixture stirred for 20 h at room temperature and was then quenched with 70 mL of saturated $NH_4Cl_{(aq)}$. After stirring for 5 min, the layers were separated and the aqueous layer was extracted three times with 70–mL portions of ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 80 g of silica gel (eluted with hexanes-ether, 50:1 → 20:1) to afford 5.59 g (90%) of **176** as a colorless oil.

Method B: To a solution of 18.5 g (111 mmol) of allylketone **178** in 215 mL of 2-methyl-2-butene was added 94 mg (0.111 mmol, 0.1 mol%) of the second generation Grubbs' catalyst [(1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro-

(phenylmethylene)(tricyclohexylphosphine)ruthenium] (**71**) at room temperature. After stirring for 20 h, the mixture was filtered over a 1.5-inch pad of silica gel and washed through with 400 mL of hexanes–ethyl acetate, 10:1. The solvent was removed *in vacuo* to afford 19.85 g (92%) of ketone **176** as a colorless oil: IR (neat) 2969 (s), 2934 (s), 2864 (m), 1707 (s), 1452 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.15 – 5.02 (m, 1H, HC=), 2.61 – 2.43 (m, 1H), 2.40 – 2.23 (m, 1H), 2.22 – 2.05 (m, 1H), 2.05 – 1.75 (m, 4H), 1.70 (s, 3H CH_3), 1.60 (s, 3H, CH_3), 1.56 – 1.40 (m, 2H), 1.14 (s, 3H CH_3), 1.05 (s, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 216.10 (s), 132.38 (s), 123.26 (d), 48.87 (s), 48.51 (d), 37.96 (t), 28.29 (t), 25.96 (t), 25.72 (q), 25.12 (t), 22.81 (q), 19.87 (q), 17.74 (q); exact mass calcd. for $C_{13}H_{22}O$ ($M^{\cdot+}$) *m/z* 194.1671, found *m/z* 194.1666.

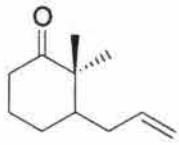
Anal. calcd. for $C_{13}H_{22}O$: C, 80.35; H, 11.41; found: C, 80.40; H, 11.62.



177

(3-Allyl-2-methylcyclohex-1-enyloxy)trimethylsilane (177).[170] A solution of 4.67 g (24.5 mmol) of copper (I) iodide and 1.04 g (24.5 mmol) of anhydrous LiCl in 55 mL of THF was prepared and stirred for 10 min at room temperature and 5 min at –78°C. To the solution was added dropwise 24.5 mL (24.5 mmol) of allylmagnesium bromide as a 1 M solution in ether. After stirring for 5 min, 3.1 mL (25 mmol) of TMSCl and 3.7 mL (25 mmol) of triethylamine were added dropwise successively. After the resulting solution stirred for 5 min, 1.23 g (11.1 mmol) of enone **167** was added and the solution continued to stir for 30 min. The reaction mixture was warmed to room temperature and quenched with 100 mL of 10% (v/v) $NH_4Cl_{(aq)}$ followed by stirring for 5 min. The solution was filtered, the layers were separated, and the aqueous phase was extracted twice with 75–mL portions of ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was taken up in 30 mL of hexanes and filtered over a 1.5-inch pad of Florisil (rinsed with 100 mL of hexanes). The

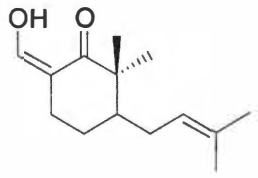
solvent was removed *in vacuo* to afford 2.24 g (90%) of silyl enol ether **177** as a colorless oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.88 – 5.62 (m, 1H, CH=), 5.02 (dd, J = 7.8, 1.0 Hz, 1H, =CH_2), 4.96 (d, J = 1.0 Hz, 1H, =CH_2), 2.45 – 2.21 (m, 1H), 2.17 – 1.87 (m, 4H), 1.82 – 1.61 (m, 2H), 1.59 (s, 3H, CH_3), 1.56 – 1.34 (m, 2H), 0.16 (s, 9H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 144.33, 137.80, 115.59, 114.81, 38.64, 37.63, 30.45, 27.05, 20.22, 14.38, 0.62 (3C).



178

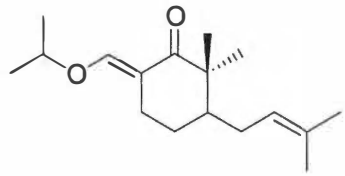
3-Allyl-2,2-dimethylcyclohexanone (178). To a solution of 13.8 g (61.7 mmol) of silyl enol ether **177** in 195 mL of THF was added dropwise 52.2 mL (67.9 mmol) of *n*-butyllithium as a 1.3 M solution in hexanes at -78°C. The yellow mixture stirred for 30 min and then a solution of 7.7 mL (17.5 g, 123 mmol) of methyl iodide in 15 mL of HMPA was added dropwise. The mixture continued to stir for 15 h while slowly warming to room temperature, and then was quenched by adding 75 mL of saturated $NH_4Cl_{(aq)}$. After stirring for 5 min, the layers were separated and the aqueous layer was extracted twice with 100–mL portions of ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was chromatographed over 70 g of silica gel (eluted with hexanes → hexanes–ether, 20:1) to afford 8.79 g (86%) of ketone **178** as a colorless oil: IR (neat) 3076 (m), 2973 (s), 2866 (s), 1707 (s), 1641 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.87 – 5.61 (m, 1H, CH=), 5.04 (d, J= 7.6 Hz, 1H, =CH_2), 4.98 (d, J= 0.6 Hz, 1H, =CH_2), 2.61 – 2.41 (m, 1H), 2.40 – 2.20 (m, 2H), 2.07 – 1.74 (m, 3H), 1.72 – 1.42 (m, 3H), 1.14 (s, 3H, CH_3), 1.04 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 215.35 (s), 137.31 (d), 115.79 (t), 48.53 (s), 47.17 (d), 37.67 (t), 34.25 (t), 25.55 (t), 24.66 (t), 22.73 (q), 19.75 (q); exact mass calcd. for $C_{11}H_{18}O$ ($M^{\cdot+}$) *m/z* 166.1358, found *m/z* 166.1365.

Anal. calcd. for $C_{11}H_{18}O$: C, 79.46; H, 10.91; found: C, 79.33; H, 10.95.



179

6-Hydroxymethylene-2,2-dimethyl-3-(3-methylbut-2-enyl)cyclohexanone (179). To a solution of 12.62 g (65.0 mmol) of ketone **176** and 13.1 mL (162 mmol) of ethyl formate in 225 mL of benzene was added 8.75 g (162 mmol) of sodium methoxide in three portions over 10 min at 0°C. The reaction mixture stirred for 16 h while slowly coming to room temperature. The reaction was quenched by adding 200 mL of saturated $NH_4Cl_{(aq)}$, and stirring for 30 min. The layers were separated and the aqueous layer was extracted with three 100–mL portions of ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford 14.24 g (99%) of **179** as a light red oil. The product was suitable for further use without further purification: IR (neat) 2972 (s), 2931 (s), 2859 (m), 1637 (s), 1586 (s), 1457 (m), 1358 (m), 1333 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 14.77 (d, J = 2.5 Hz, 1H, ȮH), 8.74 (d, J = 2.5 Hz, 1H, CHOH), 5.19 – 5.02 (m, 1H, HC=), 2.47 – 2.05 (m, 3H), 1.93 – 1.75 (m, 2H), 1.72 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.51 – 1.30 (m, 2H), 1.25 (s, 3H, CH_3), 1.09 (s, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 189.70 (s), 189.29 (d), 132.69 (s), 123.35 (d), 106.86 (s), 44.35 (d), 40.86 (s), 28.12 (t), 25.77 (q), 24.66 (q), 23.30 (t), 22.85 (t), 21.02 (q), 17.82 (q); exact mass calcd. for $C_{14}H_{22}O_2$ ($M^{\cdot+}$) *m/z* 222.1620, found *m/z* 222.1616.



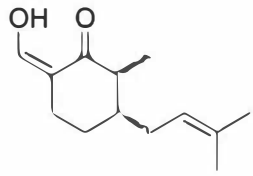
180

6-Isopropoxymethylene-2,2-dimethyl-3-(3-methylbut-2-enyl)cyclohexanone (180). Method A: A mixture of 5.42 g (24.4 mmol) of enol **179**, a catalytic amount of p-

toluene sulfonic acid, and 10 g of 4Å molecular sieves in 143 mL of a 1:1 solution of benzene-isopropyl alcohol was stirred while heating under reflux for 4.5 h. After cooling to room temperature, the mixture was filtered and the filter cake was rinsed with 50 mL of ether. The filtrate was washed with 55 mL of 1N $NaOH_{(aq)}$, and then twice with 55–mL portions of brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was recrystallized with 3.0 mL of pentane to afford 4.57 g (71%) of **180** as a white solid.

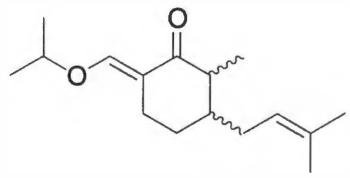
Method B: To a solution of 2.07 g (8.28 mmol) of enone **182** in 70 mL of benzene was added 484 mg (12.4 mmol) of $NaNH_2$ in one portion at 0°C. After stirring for 5 min at 0°C, the mixture stirred for 2 h at room temperature before a solution of 2.35 g (16.6 mmol) of methyl iodide in 5 mL of NMP was added dropwise. After stirring for 16 h, the reaction was quenched by slowly adding 25 mL of saturated $NH_4Cl_{(aq)}$, and stirring for 5 mins. The layers were separated and the aqueous layer was extracted twice with 25–mL portions of ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The crude product was chromatographed over 80 g of silica gel (eluted with hexanes–ethyl acetate, 10:1) to afford 830 mg (38%) of **180** as a pale yellow oil which crystallized. Recrystallization from pentane yielded a white solid: mp 43-46°C; IR (neat) 2973 (s), 2931 (s), 2868 (m), 1674 (s), 1590 (s), 1218 (s), 1110 (s), 985 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.36 (t, J = 1.9 Hz, 1H, CHO), 5.19 – 5.05 (m, 1H, HC=), 4.18 (h, J = 6.2 Hz, 1H, $CHCH_3$), 2.62 – 2.44 (m, 1H), 2.34 – 2.06 (m, 2H), 1.89 – 1.74 (m, 2H), 1.71 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.59 – 1.36 (m, 2H), 1.29 (d, J = 6.2 Hz, 6H, $CHC\underline{H}_3$), 1.18 (s, 3H, CH_3), 1.02 (s, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 205.89 (s), 155.19 (d), 132.10 (s), 123.55 (d), 113.48 (s), 77.11 (d), 46.25 (s), 45.04 (d), 28.32 (t), 25.69 (q), 24.84 (q), 22.45 (q, 2C), 22.25 (t), 21.59 (t), 20.78 (q), 17.67 (q); exact mass calcd. for $C_{17}H_{28}O_2$ ($M^{\cdot+}$) *m/z* 264.2089, found *m/z* 264.2096.

Anal. calcd. for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67; found: C, 77.11; H, 10.89.



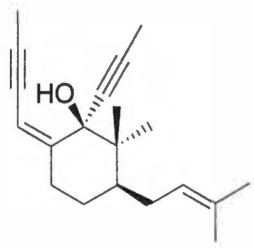
181

(±)-6-Hydroxymethylene-2-methyl-3-(3-methylbut-2-enyl)cyclohexanone (181). To a solution of 793 mg (4.40 mmol) of ketone **173** and 0.71 mL (652 mg, 8.80 mmol) of ethyl formate in 8 mL of benzene was carefully added 475 mg (8.80 mmol) of sodium methoxide at 0°C. The reaction mixture stirred overnight at room temperature and then was diluted with 15 mL of CH_2Cl_2. The reaction was quenched by adding 12 mL of saturated $NH_4Cl_{(aq)}$ and stirring for 5 min. The layers were separated and the aqueous layer was extracted with three 10–mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 80 g of silica gel (eluted with hexanes-ethyl acetate, 25:1) to afford 593 mg (65%) of **181** as a light red oil and as a mixture of diastereomers: IR (neat) 2971 (s), 2929 (s), 2859 (s), 1638 (s), 1588 (s), 1452 (m), 1376 (m), 1360 (m), 1333 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 14.59 (d, J = 2.5 Hz, OH), 14.41 (d, J = 2.5 Hz, OH), 8.76 (d, J = 2.5 Hz, C<u>H</u>OH), 8.68 (d, J = 2.5 Hz, C<u>H</u>OH), 5.26 – 5.00 (m, HC=), 2.61 – 2.06 (m), 2.06 – 1.76 (m), 1.71 (s, $2CH_3$), 1.61 (s, $2CH_3$), 1.54 – 1.30 (m), 1.26 (s, CH_3), 1.23 (s, CH_3), 1.11 (s, CH_3), 1.08 (s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 189.22 (d), 187.83 (d), 187.33 (s), 187.09 (s), 133.21 (s), 132.69 (s), 122.16 (d), 121.72 (d), 107.78 (s), 107.21 (s), 40.31 (d, 2C), 38.33 (d), 36.90 (d), 31.79 (t), 30.02 (t), 25.90 (t), 25.84 (q, 2C), 23.28 (t), 22.58 (t), 21.71 (t), 17.74 (q), 16.54 (q), 12.55 (q, 2C); exact mass calcd. for $C_{13}H_{20}O_2$ ($M^{\cdot+}$) *m/z* 208.1463, found *m/z* 208.1461.



182

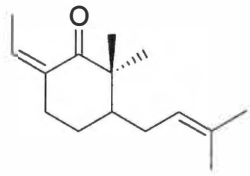
(±)-6-Isopropoxymethylene-2-methyl-3-(3-methylbut-2-enyl)cyclohexanone (182). A mixture of 467 mg (2.24 mmol) of enol **181** and a catalytic amount of p-toluene sulfonic acid in 10 mL of a 4:1 benzene–isopropyl alcohol solution was stirred for 16 h. To the resulting solution was added 2 mL of isopropyl alcohol, a catalytic amount of p-toluene sulfonic acid, and 1.0 g of 4Å molecular sieves. The reaction stirred for 1 h at room temperature and 1 h at 60°C. After cooling to room temperature, an additional 1.0 g of 4 Å molecular sieves and 1 mL of isopropyl alcohol was added and the reaction mixture was stirred at 60°C for 1 h. The cooled mixture was carefully transferred to a separatory funnel with 15 mL of ether, and was washed with 6 mL of 1 N NaOH followed by 6 mL of water. The organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over 20 g of silica gel (eluted with hexanes–ethyl acetate, 20:1) to afford 426.4 mg (76%) of **182** as a pair of inseparable diastereomers as a colorless oil: IR (neat) 2975 (m), 2929 (m), 2860 (m), 1675 (s), 1591 (s), 1217 (s), 1109 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.42 – 7.35 (m, =CHO), 5.22 – 5.03 (m, C<u>H</u>=CCH_3), 4.19 (h, J = 6.2 Hz, OC<u>H</u>CH_3), 2.65 – 2.42 (m), 2.39 – 2.13 (m), 2.12 – 1.76 (m), 1.71 (s, CH_3), 1.61 (s, CH_3), 1.60 – 1.49 (m), 1.30 (d, J = 6.2 Hz, CHC<u>H</u>$_3$), 1.20 (s, CH_3), 1.17 (s, CH_3), 1.07 (s, CH_3), 1.04 (s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ (203.83) (s), 203.14 (s), 154.73 (d, 2C), (132.82) (s), 132.25 (s), (122.48) (d), 121.79 (d), 114.27 (s), (113.76) (s), 77.16 (d, 2C), 47.46 (d), (46.16) (d), 41.40 (d), (38.61) (d), 32.33 (t), (28.97) (t), 26.00 (t), 25.70 (q, 2C), (23.57) (t), 22.44 (q, 4C), 21.45 (t), (21.11) (t), 17.71 (q), 15.32 (q, 2C), (11.99) (q); exact mass calcd. for $C_{16}H_{26}O_2$ ($M^{\cdot+}$) *m/z* 250.1933, found *m/z* 250.1931.



183

6-But-2-ynylidene-2,2-dimethyl-3-(3-methylbut-2-enyl)-1-prop-1-ynylcyclohexanol (183). To a solution of 218 mg (0.826 mmol) of vinylogous ester **180** in 4 mL of THF was added dropwise 2.0 mL (0.99 mmol) of a 0.5 M solution of 1-propynylmagnesium bromide in hexanes at 0°C. After the reaction mixture stirred for 30 min at 0°C and 17 h at room temperature, 1.0 mL (0.50 mmol) of a 0.5 M solution of 1-propynylmagnesium bromide in hexanes was added and the mixture stirred for an additional 5 h. The reaction was quenched by adding 5 mL of saturated $NH_4Cl_{(aq)}$ and stirring for 5 min. The layers were separated and the aqueous layer was extracted twice with 5–mL portions of ether. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over 20 g of silica gel (eluted with hexanes–ethyl acetate, 20:1) to afford 177 mg (75%) of **183** as a colorless oil: IR (neat) 3527 (br, m), 2972 (s), 2919 (s), 2868 (s), 2228 (w), 1669 (w), 1635 (w) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.71 – 5.63 (m, 1H, HCCC), 5.18 – 5.06 (m, 1H, $\underline{H}C{=}CCH_3$), 2.38 – 1.56 (m, 7H), 1.98 (s, 3H, CH_3), 1.84 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.15 (s, 3H, CH_3), 0.69 (s, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 152.73 (s), 131.89 (s), 124.15 (d), 101.53 (d), 89.22 (s), 82.28 (s), 80.59 (s), 76.99 (s), 76.86 (s), 44.61 (d), 44.22 (s), 28.76 (t), 28.54 (t), 27.47 (t), 25.80 (q), 22.40 (q), 17.75 (q), 14.04 (q), 4.42 (q), 3.61 (q); exact mass calcd. for $C_{20}H_{28}O$ ($M^{\cdot+}$) *m/z* 284.2140, found *m/z* 284.2145.

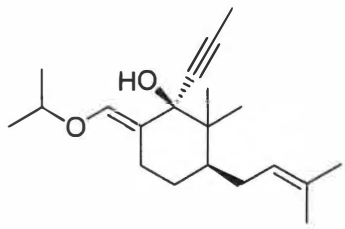
Anal. calcd. for $C_{20}H_{28}O$: C, 84.45; H, 9.92; found: C, 84.01; H, 10.11.



185

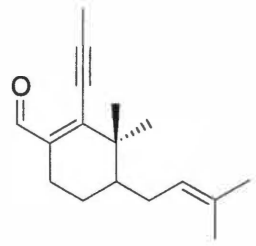
6-Ethylidene-2,2-dimethyl-3-(3-methylbut-2-enyl)cyclohexanone (185). To a solution of 138 mg (520 μmol) of vinylogous ester **180** in 4 mL of THF was added dropwise 0.35 mL (530 μmol) of methyllithium as a 1.5 M solution in ether at –78°C. The solution stirred for 30 min, was warmed to room temperature, and 5 mL of water was added. After stirring for 5 min, the layers were separated and the aqueous phase was extracted twice with 5–mL portions of ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo.* The residue was chromatographed over 20 g of silica gel (eluted with hexanes–ethyl acetate, 10:1) to afford 79.3 mg (69%) of enone **185** as a colorless oil: IR (neat) 2969 (s), 2931 (s), 2869 (m), 1684 (s), 1616 (s), 1456 (m), 1380 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.68 – 6.40 (m, 1H, =C<u>H</u>CH_3), 5.19 – 4.94 (m, 1H, HC=C), 2.68 – 2.47 (m, 1H), 2.38 – 2.03 (m, 2H), 1.99 – 1.75 (m, 2H), 1.72 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.56 – 1.38 (m, 2H), 1.18 (s, 3H, CH_3), 1.01 (s, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 206.89 (s), 136.38 (s), 133.55 (d), 132.46 (s), 123.31 (d), 47.22 (s), 45.46 (d), 28.23 (t), 25.74 (q), 24.77 (t), 24.51 (q), 23.35 (t), 20.49 (q), 17.74 (q), 13.58 (q); exact mass calcd. for $C_{15}H_{24}O$ ($M^{\cdot+}$) *m/z* 220.1827, found *m/z* 220.1819.

Anal. calcd. for $C_{15}H_{24}O$: C, 81.76; H, 10.98; found: C, 81.36; H, 11.08.



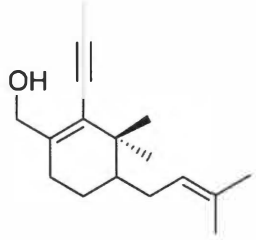
186

6-Isopropoxymethylene-2,2-dimethyl-3-(3-methylbut-2-enyl)-1-prop-1-ynyl-cyclohexanol (186). To a solution of 376 mg (1.42 mmol) of vinylogous ester **180** in 15 mL of THF was added 805 mg (3.27 mmol) of anhydrous $CeCl_3$. After the suspension stirred for 2.5 h at room temperature, the reaction was cooled to –78°C and 6.0 mL (2.98 mmol) of 1-propynylmagnesium bromide was added dropwise as a 0.5 M solution in THF. The mixture stirred for 1 h, was warmed to room temperature, and 30 mL of water was added. After stirring for 5 min, the layers were separated and the aqueous layer was extracted twice with 20–mL portions of ether (emulsions were remedied by adding several mL of CH_2Cl_2). The combined organics were washed twice with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford 446 mg of alcohol **186** (100% by NMR) as an unstable, colorless oil: IR (neat) 3451 (w), 2973 (s), 2922 (s), 2872 (m), 2247 (w), 1676 (m), 1186 (m), 1128 (s), 911 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 6.28 – 6.22 (m, 1H, =CHO), 5.19 – 5.06 (m, 1H, CH=C), 3.89 (h, J = 6.3 Hz, 1H, $CHCH_3$), 2.82 – 2.68 (m, 1H), 2.19 – 2.02 (m, 1H), 2.01 – 1.89 (m, 2H), 1.88 – 1.79 (m, 1H), 1.84 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 1.68 – 1.51 (m, 3H), 1.58 (s, 3H, CH_3), 1.21 (dd, J = 6.3, 6.3 Hz, 6H, $CHC\underline{H}_3$), 1.13 (s, 3H, CH_3), 0.75 (s, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 137.82 (d), 131.57 (s), 124.45 (d), 118.76 (s), 81.62 (s), 81.23 (s), 75.86 (s), 73.54 (d), 44.55 (d), 43.50 (s), 28.85 (t), 26.75 (t), 25.77 (q, 2C), 22.80 (t), 22.36 (q, 2C), 17.73 (q), 14.20 (q), 3.58 (q); exact mass calcd. for $C_{17}H_{24}O$ ($M^{\cdot+}$ -C_3H_8O) *m/z* 244.1827, found *m/z* 244.1833 ($M^{\cdot+}$ not observed).



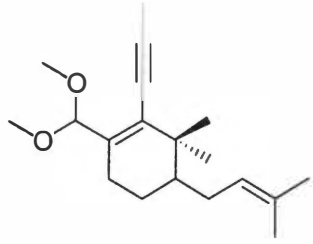
190

3,3-Dimethyl-4-(3-methylbut-2-enyl)-2-prop-1-ynylcyclohex-1-enecarb-aldehyde (190). To a suspension of 6.33 g (25.7 mmol) of anhydrous $CeCl_3$ in 140 mL of THF was added 3.09 g (11.7 mmol) of vinylogous ester **180** in one portion. After stirring for 1.5 h, the mixture was cooled to –78°C, and then 49.1 mL (24.6 mmol) of 0.5 M solution of 1-propynylmagnesium bromide in THF was added. The reaction mixture stirred at –78°C for 1.5 h, was warmed to room temperature, and was quenched with 80 mL of saturated $NH_4Cl_{(aq)}$. After stirring for 5 min, the layers were separated and the aqueous layer was extracted once with 100 mL of ether and once with 100 mL of CH_2Cl_2. The combined organic layers were treated with 200 mL of 1.4 M $H_2SO_{4(aq)}$, and stirred for 3 h. The layers were again separated and the aqueous phase was extracted two times with 100–mL portions of ether. The combined organic layers were washed with 60 mL of saturated $NaHCO_{3(aq)}$, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 60 g of silica gel (eluted with hexanes–ethyl acetate, 10:1) to afford 2.86 g (100%) of aldehyde **190** as a light red oil: IR (neat) 2971 (m), 2920 (m), 2864 (m), 2730 (w), 2253 (w), 2217 (w), 1672 (s), 1202 (m), 912 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 10.17 (s, 1H, HCO), 5.11 (t, J = 7.2 Hz, 1H, HC=), 2.49 – 2.31 (m, 1H), 2.26 – 2.11 (m, 1H), 2.08 (s, 3H, $CCCH_3$), 2.06 – 1.86 (m, 1H), 1.86 – 1.73 (m, 2H), 1.71 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.40 – 1.24 (m, 2H), 1.29 (s, 3H, CH_3), 1.08 (s, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 194.64 (d), 149.73 (s), 140.80 (s), 132.49 (s), 123.43 (d), 96.89 (s), 75.12 (s), 44.60 (d), 39.51 (s), 28.70 (t), 26.87 (q), 25.73 (q), 22.19 (t), 21.96 (q), 21.70 (t), 17.74 (q), 4.40 (q); exact mass calcd. for $C_{17}H_{24}O$ ($M^{\cdot+}$) *m/z* 244.1827, found *m/z* 244.1836.



196

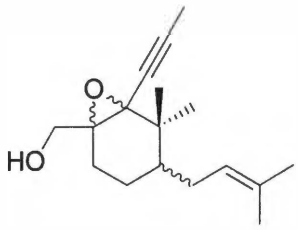
[3,3-Dimethyl-4-(3-methylbut-2-enyl)-2-prop-1-ynylcyclohex-1-enyl]-methanol (196). To a suspension of 67.3 mg (1.77 mmol) of lithium aluminum hydride in 5 mL of ether was added dropwise a solution of 289 mg (1.18 mmol) of aldehyde **190** in 5 mL of ether at 0°C. The reaction mixture stirred for 3.5 h while slowly warming to room temperature, and then was quenched by adding 2 mL of 10% $NaOH_{(aq)}$. After stirring for 5 min, the mixture was filtered, and the layers were separated. The aqueous phase was extracted once with 1 mL of ether. The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo* to afford 321 mg (100%) of alcohol **196** as a light green oil: IR (neat) 3353 (m), 2967 (s), 2919 (s), 2864 (m), 2246 (w), 1727 (m) 1245 (m), 1036 (m), 977 (m), 911 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.18 – 5.05 (m, 1H, HC=), 4.28 (d, J = 12.1 Hz, 1H, C$\underline{H_2}$OH), 4.21 (d, J = 12.1 Hz, 1H, C$\underline{H_2}$OH), 2.31 – 2.06 (m, 3H), 2.00 (s, 3H, $CCCH_3$), 1.94 (s, 1H, OH), 1.80 – 1.64 (m, 1H), 1.67 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.38 – 1.19 (m, 3H), 1.18 (s, 3H, CH_3), 0.97 (s, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 141.71 (s), 131.96 (s), 127.46 (s), 123.98 (d), 89.79 (s), 76.99 (s), 65.43 (t), 44.65 (d), 37.30 (s), 28.74 (t), 27.23 (t), 27.23 (q), 25.68 (q), 22.75 (t), 21.94 (q), 17.66 (q), 4.09 (q); exact mass calcd. for $C_{17}H_{26}O$ ($M^{\cdot+}$) *m/z* 246.1984, found *m/z* 246.1987.



197

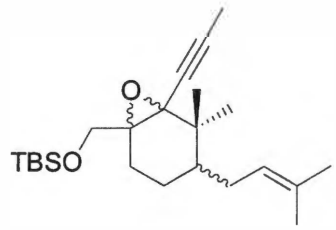
1-Dimethoxymethyl-3,3-dimethyl-4-(3-methylbut-2-enyl)-2-prop-1-ynyl-cyclohexene (197). To a solution of 553 mg (2.26 mmol) of aldehyde **190** in 15 mL of methanol was added 887 mg (2.38 mmol) $CeCl_3 \cdot 7H_2O$ in one portion. The mixture stirred for 30 min at room temperature, then was cooled to 0°C, and 90.0 mg (2.38 mmol) of sodium borohydride was added in small portions over 3 min. After stirring for 1.5 h at 0°C, another 90.0 mg (2.38 mmol) of sodium borohydride was added in small portions over 3 min. The reaction mixture stirred for 15 h while slowly warming to room temperature, and then was quenched by diluting with 30 mL of ether and adding 25 mL of saturated $NH_4Cl_{(aq)}$. The layers were separated, and the aqueous phase was extracted three times with 20–mL portions of ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 60 g of silica gel (eluted with hexanes–ethyl acetate, 10:1) to afford 350 mg (53%) of acetal **197** as a colorless oil: IR (neat) 2967 (s), 2930 (s), 2870 (m), 2828 (m), 2730 (w), 2298 (w), 2219 (w), 1675 (m), 1205 (m), 1107 (s), 1073 (s), 965 (m), 946 (m), 912 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.23 (s, 1H, CHO_2), 5.18 – 5.05 (m, 1H, HC=), 3.37 (s, 3H, OCH_3), 3.35 (s, 3H, OCH_3), 2.30 – 2.08 (m, 2H), 2.01 (s, 3H, $CCCH_3$), 1.81 – 1.64 (m, 5H), 1.60 (s, 3H CH_3), 1.34 – 1.24 (m, 3H), 1.20 (s, 3H CH_3), 0.99 (s, 3H CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 138.87 (s), 132.05 (s), 130.35 (s), 124.03 (d), 105.81 (d), 90.15 (s), 76.70 (s), 54.83 (q, 2C), 44.93 (d), 37.78 (s), 28.85 (t), 27.45 (q), 25.77 (q), 22.23 (t, 2C), 22.36 (q), 17.75 (q), 4.17 (q); exact mass calcd. for $C_{19}H_{30}O_2$ ($M^{\cdot+}$) *m/z* 290.2246, found *m/z* 290.2252.

Continued elution afforded 191 mg (34%) of alcohol **196**.



195

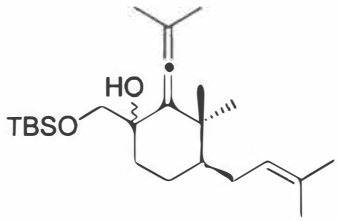
(±)-[5,5-Dimethyl-4-(3-methylbut-2-enyl)-6-prop-1-ynyl-7-oxabicyclo[4.1.0]-hept-1-yl]methanol (195). To a solution of 5.52 g (22.4 mmol) of allylic alcohol **196** in 115 mL of benzene was added 780 mg (2.24 mmol, 10 mol%) of $V(acac)_3$ in one portion and the dark green solution stirred for 15 min. To the resulting solution was added 12.8 mL of a 3.50 M solution of *tert*-butyl peroxide in toluene over 1 min. The dark red mixture stirred for 16 h, and then was quenched by adding 30 mL of 1 M sodium thiosulfate solution. The layers were separated, and the aqueous phase was extracted two times with 30–mL portions of ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 70 g of silica gel (eluted with hexanes–ethyl acetate, 5:1) to afford 4.24 g (72%) of epoxide **195** as diastereomers and as a colorless oil: IR (neat) 3426 (m), 2968 (s), 2925 (s), 2875 (m), 1706 (w), 2245 (w), 1045 (m), 901 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.12 – 4.97 (m, HC=), 3.83 (s, CH_2O), 3.75 (s, CH_2O), 2.25 – 1.97 (m), 1.87 (s, CH_3), 1.86 (s, CH_3), 1.84 – 1.72 (m), 1.67 (s, CH_3), 1.57 (s, CH_3), 1.52 – 1.28 (m), 1.21 (s, CH_3), 1.18 – 1.03 (m), 1.01 (s, CH_3), 0.97 (s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 132.05 (s), 131.78 (s), 123.78 (d), 123.62 (d), 81.80 (s, 2C), 75.84 (s), 75.76 (s), 67.82 (s), 66.75 (t), 66.68 (t), 65.72 (s), 65.33 (s), 64.12 (s), 44.83 (d), 39.15 (d), 36.70 (s), 35.68 (s), 28.50 (t), 27.42 (t), 25.79 (t, 2C), 25.52 (q, 2C), 24.05 (t, 2C), 23.38 (q), 21.34 (q), 20.18(q), 18.59 (q), 18.04 (q), 17.52 (q), 3.31 (q, 2C); exact mass calcd. for $C_{17}H_{26}O_2$ ($M^{\cdot+}$) *m/z* 262.1933, found *m/z* 262.1935.



200

(±)-*tert*-Butyl-[5,5-dimethyl-4-(3-methylbut-2-enyl)-6-prop-1-ynyl-7-oxa-bicyclo[4.1.0]hept-1-ylmethoxy]dimethylsilane (200). To a solution of 2.06 g (7.85 mmol) of alcohol **195** in 115 mL of CH_2Cl_2 was added 1.30 g (8.64 mmol) of *tert*-butyldimethylsilyl chloride and 580 mg (8.64 mmol) of imidazole. The mixture stirred for 18 h and then was filtered over a 1–inch pad of silica gel (rinsed with CH_2Cl_2). The solvent was removed *in vacuo* to afford 2.86 g (97%) of silyl ether **200** as diastereomers and as a colorless oil: IR (neat) 2956 (s), 2930 (s), 2858 (s), 2245 (w), 1705 (m), 1255 (m), 1102 (s), 839 (s), 779 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.10 – 4.95 (m, HC=), 3.89 (d, J = 10.9 Hz, CH_2O), 3.77 (d, J = 10.9 Hz, CH_2O), 3.74 (d, J = 10.9 Hz, CH_2O), 3.65 (d, J = 10.9 Hz, CH_2O), 2.20 (dd, J = 10.9, 3.5 Hz), 2.12 – 1.92 (m), 1.86 (s, CH_3), 1.85 (s, CH_3), 1.82 – 1.73 (m), 1.69 (s, CH_3), 1.67 (s, CH_3), 1.57 (s, CH_3), 1.46 – 1.24 (m), 1.20 (s, CH_3), 1.02 (d, J = 7.7 Hz, CH_3), 0.99 (d, J = 7.7 Hz, CH_3), 0.91 (s, $SiCCH_3$), 0.90 (s, $SiCCH_3$), 0.70 (s, $SiCH_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 132.18 (s), 131.87 (s), 124.15 (d), 123.97 (d), 81.47 (s, 2C), 76.49 (s, 2C), 67.84 (s), 66.90 (s), 66.72 (t), 66.33 (t), 65.93 (s), 64.42 (s), 45.15 (d), 39.54 (d), 36.91 (s), 35.90 (s), 28.84 (t, 2C), 27.67 (q), 25.78 (q, 7C), 23.84 (t, 2C), 23.60 (q, 2C), 21.68 (t), 20.41 (t), 18.77 (q), 18.20 (s, 2C), 18.11 (q, 2C), 17.74 (q), 3.59 (q, 2C), -5.35 (q, 4C); exact mass calcd. for $C_{23}H_{40}O_2Si$ ($M^{\cdot+}$) *m/z* 376.2798, found *m/z* 376.2803.

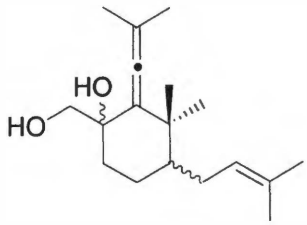
Anal. calcd. for $C_{23}H_{40}O_2Si$: C, 73.34; H, 10.70; found: C, 72.94; H, 10.81.



201

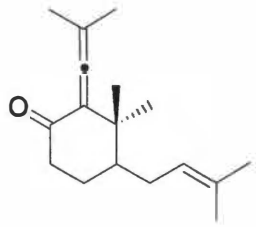
(±)-1-(*tert*-Butyldimethylsilanyloxymethyl)-3,3-dimethyl-4-(3-methylbut-2-enyl)-2-(2-methylpropenylidene)cyclohexanol (201). To a well-stirred solution of 703 mg (3.69 mmol) of copper (I) iodide and 156 mg (3.69 mmol) of lithium chloride in 10 mL of THF was added dropwise 2.5 mL (7.50 mmol) of methylmagnesium bromide as a 3.0 M solution in ether at 0°C. After stirring for 15 min, 278 mg (738 μmol) of epoxide **200** in 1 mL of THF was added and mixture stirred for 30 min. The reaction was quenched by dropwise addition of 15 mL of saturated $NH_4Cl_{(aq)}$ and stirring for 5 min. The layers were separated and the aqueous phase was extracted once with 25 mL of ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and filtered over a one-inch pad of silica gel. The solvent was removed *in vacuo* to afford 290 mg (87%) of allene **201** as diastereomers and as a colorless oil. The product was suitable for use without further purification: IR (neat) 3554 (w), 2957 (s), 2930 (s), 2859 (s), 2245 (w), 1254 (m), 1094 (s), 866 (m), 839 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.19 – 5.04 (m, HC=), 3.65 – 3.55 (m, CH_2O), 3.47 (d, J = 9.5 Hz, CH_2O), 3.29 (d, J = 9.5 Hz, CH_2O), 2.60 (s), 2.41 (s), 2.30 – 2.01 (m), 2.00 – 1.75 (m), 1.75 – 1.69 (m), 1.64 (s, CH_3), 1.61 (s, CH_3), 1.59 (s, CH_3), 1.56 – 1.23 (m), 1.21 (s, CH_3), 1.15 (s, CH_3), 1.07 – 1.01 (m), 0.93 (s, CH_3), 0.90 (s, CCH_3), 0.90 (s, CCH_3), 0.06 (s, $SiCH_3$), 0.05 (s, $SiCH_3$); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 198.15 (s), 197.30 (s), 131.72 (s), 131.59 (s), 124.45 (d), 124.25 (d), 111.45 (s), 111.26 (s), 98.45 (s), 97.05 (s), 72.45 (s), 72.37 (s), 70.57 (t), 69.98 (t), 48.37 (d), 46.20 (d), 37.81 (s, 2C), 36.45 (t), 33.07 (t), 29.87 (q, 2C), 29.19 (t), 28.47 (q, 2C), 27.83 (t), 25.94 (q, 6C), 25.44 (q), 22.92 (q), 22.65 (q), 22.64 (t, 2C), 20.77 (q, 4C), 18.36 (s), 17.78 (q, 2C), -5.40 (q, 4C); exact mass calcd. for $C_{24}H_{44}O_2Si$ ($M^{\cdot+}$) *m/z* 392.3111, found *m/z* 392.3104.

Anal. calcd. for $C_{24}H_{44}O_2Si$: C, 73.41; H, 11.29; found: C, 73.35; H, 11.41.



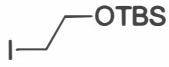
202

(±)-1-Hydroxymethyl-3,3-dimethyl-4-(3-methylbut-2-enyl)-2-(2-methylprop-enylidene)cyclohexanol (202). To a solution of 6.60 g (16.8 mmol) of silyl ether **201** in 55 mL of THF was added dropwise 20.2 mL (20.2 mmol) of tetrabutylammonium fluoride as a 1 M solution in THF. The mixture stirred for 1.5 h at room temperature and then was quenched by adding 80 mL of saturated $NH_4Cl_{(aq)}$. After stirring for 15 min, the layers were separated and the aqueous phase was extracted three times with 80–mL portions of ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 70 g of silica gel (eluted with hexanes–ethyl acetate, 2:1) to afford 3.90 g (83%) of diol **202** as a pale yellow oil and as diastereomers: IR (neat) 3399 (m), 2965 (s), 2930 (s), 2864 (s), 1960 (w), 1700 (w), 1642 (w), 1191 (m), 1092 (m), 1048 (m), 1015 (m) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.20 – 5.02 (m, HC=), 3.68 – 3.25 (m, CH_2O), 2.49 – 2.24 (m), 2.23 – 2.05 (m), 2.04 – 1.81 (m), 1.76 (s, CH_3), 1.75 (s, CH_3), 1.74 (s, CH_3), 1.70 (s, CH_3), 1.61 (s, CH_3), 1.60 (s, CH_3), 1.44 – 1.23 (m), 1.19 (s, CH_3), 1.14 (s, CH_3), 1.02 (s, CH_3), 0.94 (s, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 196.51 (s), 196.43 (s), 131.95 (s, 2C), 124.11 (d), 123.85 (d), 114.01 (s), 112.64 (s), 100.95 (s), 97.95 (s), 73.28 (s), 72.72 (s), 70.90 (t), 69.32 (t), 47.82 (d), 46.47 (d), 37.91 (s), 37.76 (s), 34.60 (t), 32.80 (t), 29.57 (q), 28.96 (t), 28.36 (q), 28.08 (t), 25.78 (q, 2C), 24.62 (q), 23.58 (q), 22.99 (t), 22.57 (t), 21.02 (q), 20.83 (q), 20.69 (q), 20.48 (q), 17.76 (q), 14.07 (q); exact mass calcd. for $C_{18}H_{30}O_2$ ($M^{\cdot+}$) *m/z* 278.2246, found *m/z* 278.2252.



161

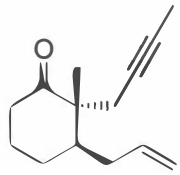
3,3-Dimethyl-4-(3-methylbut-2-enyl)-2-(2-methylpropenylidene)cyclohexanone (161). To a solution of 917 mg (3.29 mmol) of diol **202** in 14 mL of THF was added 14 mL of water and then 916 mg (4.28 mmol) of sodium periodate. The mixture stirred at room temperature for 2.5 h and then was filtered. The layers were separated and the aqueous phase was extracted twice with 15–mL portions of ether. The combined organic layers were dried ($MgSO_4$), filtered over a 1–inch pad of silica gel (rinsed with 60 mL of hexanes–ethyl acetate, 10:1), and concentrated *in vacuo* to afford 759 mg (94%) of ketone **161** as a colorless oil: IR (neat) 2965 (s), 2932 (s), 2869 (m), 1950 (m), 1682 (s) cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.22 – 5.05 (m, 1H, HC=), 2.61 – 2.40 (m, 1H), 2.39 – 2.16 (m, 2H), 2.09 – 1.84 (m, 3H), 1.80 (s, 3H, CH_3), 1.78 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.59 – 1.48 (m, 1H), 1.15 (s, 3H, CH_3), 1.01 (s, 3H, CH_3); ^{13}C NMR (62.9 MHz, $CDCl_3$) δ 204.86 (s), 201.97 (s), 132.51 (s), 123.27 (d), 114.45 (s), 100.65 (s), 44.82 (d), 38.98 (s), 38.85 (t), 28.86 (q), 28.02 (t), 25.72 (q), 24.42 (q), 23.39 (t), 19.56 (q, 2C), 17.72 (q); exact mass calcd. for $C_{17}H_{26}O$ ($M^{\cdot+}$) *m/z* 246.1984, found *m/z* 246.1988.



208

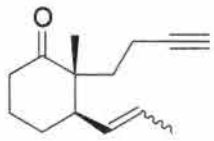
***tert*-Butyl-(2-iodoethoxy)dimethylsilane (208).**[171] To a solution of 3.60 g (15.0 mmol) of (2-bromoethoxy)-*tert*-butyldimethylsilane, in 50 mL of acetone was added 4.50 g (30.0 mmol) of sodium iodide.[158] The mixture was stirred at 55°C for 5 h, cooled to room temperature, and was concentrated *in vacuo*. The residue was diluted with 30 mL of hexanes and filtered over a 1–inch pad of Florisil (rinsed with 100 mL of hexanes).

The solvent was removed *in vacuo* to afford 3.95 g of iodide **208** as a colorless oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.83 (t, J = 7.0 Hz, 2H, CH_2), 3.19 (t, J = 7.0 Hz, 2H, CH_2), 0.91 (s, 9H, CCH_3), 0.08 (s, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 64.23, 25.83 (3C), 18.25, 6.91, -5.19 (2C).



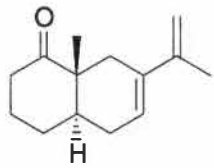
211

(±)-3-Allyl-2-but-2-ynyl-2-methylcyclohexanone (211). To a solution of 1.00 g (4.46 mmol) of silyl enol ether **177** in 25 mL of THF was added dropwise 4.1 mL of *n*-BuLi as a 1.2 M solution in hexanes at -78°C. The reaction mixture was stirred for 1 h, and then a solution of 1-iodobut-2-yne[163] **(210)** in 1 mL of HMPA was added dropwise. The solution stirred overnight while slowly coming to room temperature. The reaction was quenched with 10 mL of water. After stirring for 10 min, the layers were separated and the aqueous phase was extracted twice with 10–mL portions of ether. The combined organics were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 70 g of silica gel (eluted with hexanes-ethyl ether, 10:1) to afford 417 mg (46%) of alkyne **211** as a colorless oil: IR (neat) 3075 (w), 2936 (m), 2866 (m), 1709 (s), 1641 (w), 1460 (m), 1426 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.89 – 5.65 (m, 1H, CH=), 5.17 – 4.94 (m, 2H, CH_2=), 2.73 – 2.57 (m, 1H), 2.53 – 2.17 (m, 4H), 2.16 – 2.03 (m, 1H), 2.02 – 1.82 (m, 3H), 1.75 (t, J = 2.5 Hz, 3H, $CCCH_3$), 1.72 – 1.40 (m, 2H), 1.04 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 213.22 (s), 137.28 (d), 115.93 (t), 77.46 (s), 75.52 (s), 52.05 (s), 42.89 (d), 37.94 (t), 34.03 (t), 26.65 (t), 25.00 (t), 23.84 (t), 18.71 (q), 3.34 (q).



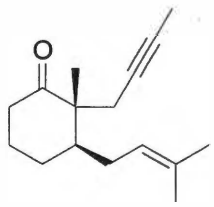
212

(±)-2-But-3-ynyl-2-methyl-3-propenylcyclohexanone (212). A solution of potassium aminopropylamide (KAPA) was prepared by slowly adding 10 mL of 1,3-diaminopropane to 866 mg (21.6 mmol) of potassium hydride and stirring for 2.5 h at room temperature. To the resulting brown mixture was added a solution of 339 mg (1.66 mmol) of alkyne **211** in 5 mL of 1,3-diaminopropane over 15 min. The solution was stirred for 2 h and then was cooled to 0°C. The reaction was quenched by carefully adding 30 mL of dilute $HCl_{(aq)}$. After stirring for 10 min, the mixture was transferred to a separatory funnel with 30 mL of ether. The layers were separated and the aqueous phase was extracted twice with 30–mL portions of ether. The combined organic fractions were washed successively with 20 mL of 1 M $HCl_{(aq)}$ and 20 mL of brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 20 g of silica gel (eluted with hexanes–ethyl acetate, 10:1) to afford 201 mg (59%) of alkyne **212** as a mixture of cis, trans isomers (1.7 : 1 ratio) as a colorless oil: IR (neat) 3305 (m), 2936 (s), 2867 (m), 2117 (w), 1704 (s), 1448 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.61 – 5.26 (m, CH=), 2.58 – 2.24 (m), 2.23 – 2.07 (m), 2.06 – 1.58 (m), 1.05 (s, CH_3), 1.02 (s, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 214.45 (s, 2C), 129.73 (d), 129.16 (d), 127.11 (d), 125.30 (d), 84.71 (s, 2C), 68.00 (d, 2C), 51.04 (s, 2C), 48.12 (d), 43.07 (d), 38.09 (t), 38.04 (t), 35.60 (t), 35.11 (t), 27.45 (t), 27.14 (t), 24.50 (t), 24.37 (t), 18.95 (q, 2C), 18.18 (q), 17.85 (q), 13.61 (t), 13.53 (t).



213

(±)-7-Isopropenyl-8a-methyl-3,4,4a,5,8,8a-hexahydro-2*H*-naphthalen-1-one (213). To a solution of 394 mg (1.93 mmol) of alkyne **211** in 6 mL of 2-methyl-2-butene was added 16 mg (0.0193 mmol, 1.0 mol%) of the second generation Grubbs' catalyst [(1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(phenylmethylene)(tricyclohexylphosphine)ruthenium] (**71**) at room temperature. After stirring for 20 h, the mixture was filtered over a 1-inch pad of Florisil. The filter cake was rinsed with 100 mL ether. Concentration of the filtrate afforded 368 mg (93%) of diene **213** as a light red oil: IR (neat) 3092 (w), 3044 (w), 2930 (s), 2867 (s), 1707 (s), 1637 (w), 1607 (m), 1449 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.74 (s, 1H, CH=), 5.07 (s, 1H, CH_2=), 4.85 (s, 1H, CH_2=), 2.76 – 2.52 (m, 1H), 2.51 – 2.33 (m, 1H), 2.32 – 2.14 (m, 3H), 2.13 – 1.96 (m, 2H), 1.88 (s, 3H, CH_3), 1.79 – 1.50 (m, 4H), 1.03 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 214.94 (s), 142.99 (s), 134.95 (s), 121.55 (d), 110.18 (t), 46.44 (s), 40.73 (d), 37.72 (t), 33.30 (t), 29.66 (t), 27.09 (t), 25.67 (t), 20.38 (q), 15.95 (q); exact mass calcd. for $C_{14}H_{20}O$ ($M^{\cdot+}$) *m/z* 204.1514, found *m/z* 204.1513.

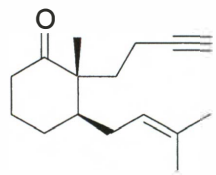


214

(±)-2-But-2-ynyl-2-methyl-3-(3-methylbut-2-enyl)cyclohexanone (214). To a solution of 1.65 g (6.54 mmol) of silyl enol ether **175** in 35 mL of THF was added dropwise 6.0 mL (7.19 mmol) of *n*-butyllithium as a 1.2 M solution in hexanes at -78°C. After the mixture stirred for 1 h at 0°C, a solution of 2.35 g (13.1 mmol) of 1-iodobut-2-

yne[163] (**210**) in 2.0 mL of HMPA was added dropwise. The mixture stirred for 20 h while slowly warming to room temperature. The reaction was quenched with 10 mL of water and stirred for 5 min. The layers were separated and the aqueous layer was extracted twice with 20–mL portions of ether. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo.* The residue was chromatographed over 70 g of silica gel (eluted with hexanes-ether, 20:1) to afford 648 mg (43%) of alkyne **214** as a colorless oil: IR (neat) 2964 (s), 2921 (s), 2864 (m), 2734 (w), 1710 (s), 1448 (m), 1379 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.23 – 5.06 (m, 1H, HC=), 2.75 – 2.55 (m), 2.54 – 1.82 (m, 9H), 1.75 (d, J = 2.3 Hz, 3H, CH_3), 1.73 (d, J = 3.0 Hz, 3H, CH_3), 1.63 (s, 3H, CH_3), 1.59 – 1.42 (m, 1H), 1.05 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 213.14 (s), 132.22 (s), 122.84 (d), 77.12 (s), 75.65 (s), 52.05 (s), 43.82 (d), 37.91 (t), 27.75 (t), 25.62 (q), 25.51 (t), 25.11 (t), 24.02 (t), 18.59 (q), 17.39 (q), 3.20 (q); exact mass calcd. for $C_{16}H_{24}O$ ($M^{\cdot+}$) *m/z* 232.1827, found *m/z* 232.1821.

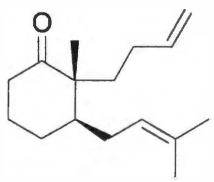
Anal. calcd. for $C_{16}H_{24}O$: C, 82.70; H, 10.41; found: C, 82.45; H, 10.41.



215

(±)-2-But-3-ynyl-2-methyl-3-(3-methylbut-2-enyl)cyclohexanone (215). A solution of potassium aminopropylamide (KAPA) was prepared by slowly adding 200 mL of 1,3-diaminopropane to 11.6 g (290 mmol) of potassium hydride and stirring for 3 h at room temperature. To the resulting brown mixture was added a solution of 5.62 g (24.2 mmol) of alkyne **214** in 60 mL of 1,3-diaminopropane over 15 min. The solution was stirred for 1 h and then was cooled to 0°C. The reaction was quenched by carefully adding 250 mL of dilute $HCl_{(aq)}$. After stirring for 10 min, the mixture was transferred to a separatory funnel with 300 mL of ether. The layers were separated and the aqueous

phase was extracted twice with 300–mL portions of ether. The combined organic fractions were washed successively with 100 mL of 1 M $HCl_{(aq)}$ and with 100 mL of brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 70 g of silica gel (eluted with hexanes–ethyl acetate, 10:1) to afford 5.44 g (97%) of alkyne **215** as a colorless oil: IR (neat) 3305 (m), 2963 (m), 2936 (m), 2867 (m), 2118 (w), 1704 (s), 1447 (m), 1380 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.14 – 5.01 (m, 1H, CH=), 2.59 – 1.73 (m, 13H), 1.70 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.58 – 1.41 (m, 1H), 1.05 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 214.42 (s), 132.44 (s), 122.82 (d), 84.54 (s), 68.10 (d), 51.67 (s), 43.77 (d), 38.19 (t), 34.32 (t), 27.66 (t), 25.62 (q), 25.08 (t), 24.23 (t), 19.00 (q), 17.68 (q), 13.62 (t); exact mass calcd. for $C_{16}H_{24}O$ ($M^{\cdot+}$) *m/z* 232.1827, found *m/z* 232.1823.

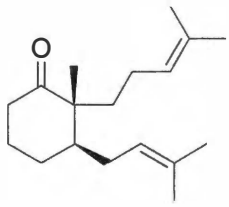


216

(±)-2-But-3-enyl-2-methyl-3-(3-methylbut-2-enyl)cyclohexanone (216). To a solution of 5.44 g (23.4 mmol) of alkyne **215** in 30 mL of hexanes was added 1.2 mL of quinoline and 117 mg of Lindlar catalyst. The reaction mixture was stirred overnight under a hydrogen atmosphere. The mixture was filtered over a 1-inch pad of silica gel (rinsed with 100 mL of hexanes–ethyl acetate, 10:1) and concentrated *in vacuo*. The residue was chromatographed over 70 g of silica gel (eluted with hexanes–ethyl acetate, 10:1) to afford 5.26 g (96%) of diene **216** as a colorless oil: IR (neat) 3076 (w), 2964 (s), 2934 (s), 2867 (m), 1706 (s), 1641 (w), 1449 (m), 1379 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.93 – 5.69 (m, 1H, C<u>H</u>=CH_2), 5.18 – 5.08 (m, 1H, CH=), 5.05 (dd, J = 17.1, 1.8 Hz, 1H, CH_2=), 4.92 (dd, J = 10.3, 1.8 Hz, 1H, CH_2=), 2.52 – 2.30 (m, 2H), 2.21 – 1.74

(m, 9H), 1.70 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.58 – 1.44 (m, 2H), 1.04 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 215.19 (s), 138.86 (d), 132.35 (s), 123.12 (d), 114.10 (t), 52.01 (s), 43.97 (d), 38.36 (t), 35.15 (t), 28.58 (t), 27.55 (t), 25.72 (q), 24.87 (t), 23.98 (t), 19.53 (q), 17.75 (q); exact mass calcd. for $C_{16}H_{26}O$ ($M^{\cdot+}$) *m/z* 234.1984, found *m/z* 234.1987.

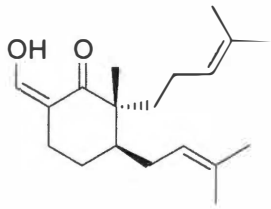
Anal. calcd. for $C_{16}H_{26}O$: C, 81.99; H, 11.18; found: C, 82.08; H, 11.24.



206

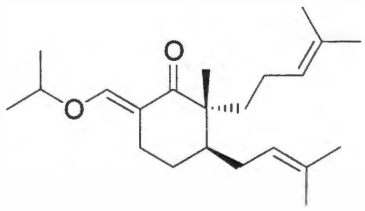
(±)-2-Methyl-3-(3-methylbut-2-enyl)-2-(4-methylpent-3-enyl)cyclohexanone (206). To a solution of 526 mg (2.24 mmol) of olefin **216** in 35 mL of 2-methyl-2-butene was added 19 mg (0.0224 mmol, 1.0 mol%) of the second generation Grubbs' catalyst [(1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro-(phenylmethylene)(tri-cyclohexylphosphine)ruthenium] (**71**) at room temperature. After stirring overnight at 38°C , the mixture was cooled to room temperature and then filtered over a 1-inch pad of silica gel (rinsed with 100 mL of hexanes–ethyl acetate, 10:1). The solvent was removed *in vacuo*, and the residue was chromatographed over 20 g silica gel (eluted with hexanes → hexanes–ethyl acetate, 25:1) to afford 387 mg (66%) of diene **206** as a colorless oil: IR (neat) 2967 (s), 2929 (s), 2864 (m), 1705 (s), 1449 (m), 1379 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.16 – 4.95 (m, 2H, HC=), 2.49 – 2.25 (m, 2H), 2.19 – 2.03 (m, 1H), 2.02 – 1.72 (m, 8H), 1.70 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.60 (s, 6H, CH_3), 1.57 – 1.41 (m, 2H), 1.03 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 215.38 (s), 132.26 (s), 131.32 (s), 124.43 (d), 123.21 (d), 52.10 (s), 44.04 (d), 38.37 (t), 36.13 (t), 27.52 (t), 25.71 (q, 2C), 24.72 (t), 23.87 (t), 22.86 (t), 19.46 (q), 17.75 (q), 17.50 (q); exact mass calcd. for $C_{18}H_{30}O$ ($M^{\cdot+}$) *m/z* 262.2297, found *m/z* 262.2293.

Anal. calcd. for $C_{18}H_{30}O$: C, 82.38; H, 11.52; found: C, 82.24; H, 11.52



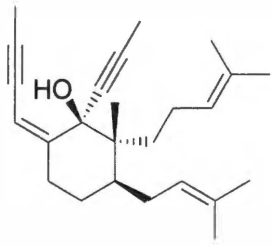
217

(±)-6-Hydroxymethylene-2-methyl-3-(3-methylbut-2-enyl)-2-(4-methylpent-3-enyl)cyclohexanone (217). To 40 mL of absolute methanol at room temperature was added 1.67 g (72.8 mmol) of sodium metal in small portions. After dissolution of sodium was complete, excess methanol was removed *in vacuo* to afford a white solid. To the solid was added 110 mL of benzene and to the resulting suspension was added 6.83 g (26.0 mmol) of ketone **206**, and 5.0 mL (4.8 g, 65 mmol) of ethyl formate. The solution was stirred overnight and then was slowly quenched with 50 mL of saturated $NH_4Cl_{(aq)}$. After stirring for 5 min, the layers were separated and the aqueous phase was extracted twice with 50–mL portions of ether. The combined organic fractions were washed with brine, dried ($MgSO_4$), and filtered over a 1-inch pad of silica gel (rinsed with 100 mL of ether). The product was concentrated *in vacuo* to afford 7.51 g (99%) of ketone **217** as a light red oil: IR (neat) 2970 (s), 2924 (s), 2857 (s), 2729 (w), 1636 (s), 1586 (s), 1450 (s), 1378 (m), 1356 (m), 1334 (m), 1311 (m), 1170 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 14.86 (d, J = 2.1 Hz, 1H, OH), 8.74 (d, J = 2.1 Hz, 1H, CHO), 5.24 – 5.08 (m, 2H, CH=), 2.45 – 1.54 (m, 10H), 1.75 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.48 – 1.26 (m, 1H), 1.10 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 189.11 (s), 188.81 (d), 132.56 (s), 131.34 (s), 124.28 (d), 123.31 (d), 108.45 (s), 44.46 (s), 38.87 (d), 35.85 (t), 27.85 (t), 25.75 (q), 25.54 (q), 23.21 (t, 3C), 21.37 (q), 17.73 (q), 17.45 (q); exact mass calcd. for $C_{19}H_{30}O_2$ ($M^{\cdot+}$) *m/z* 290.2246, found *m/z* 290.2238.



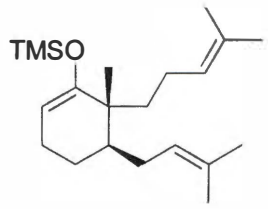
205

(±)-Isopropoxymethylene-2-methyl-3-(3-methylbut-2-enyl)-2-(4-methylpent-3-enyl)cyclohexanone (205). To a solution of 7.37 g (25.4 mmol) of ketone **217** in 120 mL of a 1:1 solution of benzene–isopropyl alcohol was added 1.45 g of p-TsOH and 7.0 g of anhydrous $MgSO_4$. The mixture was stirred at 80°C for 3 h and then was cooled to room temperature. The solution was filtered over a 0.5-inch pad of Florisil (rinsed with 100 mL of ether). The filtrate was washed successively with 50 mL of 1 M $NaOH_{(aq)}$, and 100 mL of brine. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over 70 g of silica gel (eluted with hexanes–ethyl ether, 20:1 → 5:1) to afford 6.14 g (73%) of vinylogous ester **205** as a colorless oil: IR (neat) 2972 (s), 2926 (s), 2729 (w), 1672 (s), 1588 (s), 1451 (m), 1379 (m), 1339 (m), 1217 (s), 1109 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.36 (t, J = 1.9 Hz, 1H, CHO), 5.18 – 5.02 (m, 2H, CH=), 4.18 (h, J = 6.2 Hz, 1H, CHMe), 2.59 – 2.44 (m, 1H), 2.34 – 1.74 (m, 8H), 1.72 (s, 3H, CH_3), 1.65 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.52 – 1.34 (m, 2H), 1.29 (d, J = 6.2 Hz, 6H, CH_3), 1.00 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 205.43 (s), 155.09 (d), 132.15 (s), 131.05 (s), 124.67 (d), 123.58 (d), 114.39 (s), 77.13 (d), 49.77 (s), 40.06 (d), 36.81 (t), 27.93 (t), 25.75 (q), 25.54 (q), 23.00 (t), 22.52 (q, 2C), 21.89 (t), 21.68 (t), 20.52 (q), 17.76 (q), 17.47 (q); exact mass calcd. for $C_{22}H_{36}O_2$ ($M^{\cdot+}$) *m/z* 332.2715, found *m/z* 332.2722.



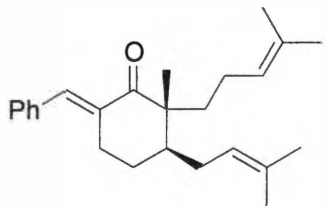
218

(±)-6-But-2-ynylidene-2-methyl-3-(3-methylbut-2-enyl)-2-(4-methylpent-3-enyl)-1-prop-1-ynylcyclohexanol (218). To a solution of 6.10 g (18.3 mmol) of vinylogous ester **205** in 165 mL of THF was added 9.96 g (40.4 mmol) of anhydrous $CeCl_3$. The resulting suspension was stirred for 1.5 h at room temperature. The mixture was cooled to –78°C and 76.9 mL (38.4 mmol) of propynylmagnesium bromide was added dropwise as a 0.5 M solution in THF. The mixture stirred overnight while slowly warming to room temperature. The reaction was slowly quenched with 100 mL of saturated $NH_4Cl_{(aq)}$. After stirring for 5 min, The layers were separated and the aqueous phase was extracted twice with 200–mL portions of CH_2Cl_2. The combined organic fractions were washed with brine, dried ($MgSO_4$), and filtered over a 1.5-inch pad of silica gel (rinsed with 100 mL of CH_2Cl_2). The solvent was removed *in vacuo* to afford 4.75 g (74%) of alkyne **218** as an orange oil: IR (neat) 3512 (m), 2967 (s), 2919 (s), 2859 (s), 2732 (w), 2245 (w), 2221 (w), 1669 (m), 1588 (m), 1442 (s), 1379 (s), 911 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.67 (d, J = 1.8 Hz, 1H, CHCC), 5.18 – 5.02 (m, 2H, CH=), 2.94 – 2.80 (m, 1H), 2.43 – 1.52 (m, 9H), 1.97 (d, J = 1.8 Hz, 3H, CH_3), 1.83 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.68 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.25 – 1.07 (m, 2H), 0.74 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 153.27 (s), 131.88 (s), 130.85 (s), 125.68 (d), 124.28 (d), 101.81 (d), 89.12 (s), 82.79 (s), 80.94 (s), 76.90 (s, 2C), 46.28 (s), 42.92 (d), 36.85 (t), 28.82 (t), 27.80 (t), 26.90 (t), 25.69 (q), 25.55 (q), 24.08 (t), 17.76 (q), 17.48 (q), 13.57 (q), 4.29 (q), 3.54 (q); exact mass calcd. for $C_{25}H_{36}O$ ($M^{\cdot+}$) *m/z* 352.2766, found *m/z* 352.2762.



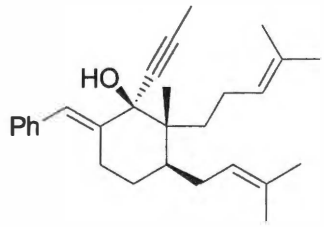
219

(±)-Trimethyl-[6-methyl-5-(3-methylbut-2-enyl)-6-(4-methylpent-3-enyl)-cyclohex-1-enyloxy]silane (219). To a solution of 350 μL (252 mg, 2.49 mmol) of N,N-diisopropylamine in 8 mL of THF was added 1.9 mL (2.29 mmol) of *n*-BuLi as a 1.2 M solution in hexanes at –78°C. The resulting solution was stirred at –78°C for 20 min, warmed to room temperature, stirred for 30 min, and recooled to –78°C. To the resulting solution was added dropwise a solution of 620 mg (2.52 mmol) of ketone **206** in 1 mL of THF. The mixture was stirred for 1.5 h followed by addition of 290 μL (249 mg, 2.29 mmol) of TMSCl. After stirring for 1 h, the mixture was warmed to room temperature and was concentrated *in vacuo*. The residue was diluted with hexanes and filtered over a 1-inch pad of Florisil (rinsed with 10 mL of pentane). The product was concentrated *in vacuo* to afford 514 mg (80%) of silyl enol ether **219** as a colorless oil: IR (neat) 3043 (m), 2965 (s), 2920 (s), 2858 (s), 2729 (w), 1659 (s), 1452 (m), 1253 (s), 1183 (s), 904 (s), 846 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.17 – 5.03 (m, 2H, C<u>H</u>=CCH_3), 4.77 – 4.66 (m, 1H, CH=C), 2.16 – 2.00 (m, 1H), 2.01 – 1.74 (m, 5H), 1.70 (s, 3H, CH_3), 1.67 (s, 3H, CH_3), 1.63 – 1.43 (m, 3H), 1.59 (s, 6H, CH_3), 1.39 – 1.08 (m, 2H), 0.88 (s, 3H, CH_3), 0.18 (s, 9H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 155.27 (s), 131.67 (d), 130.58 (d), 125.52 (s), 124.52 (s), 102.41 (d), 42.05 (s), 40.04 (d), 35.55 (t), 28.45 (t), 25.84 (q), 25.90 (q), 23.78 (t), 23.47 (t), 23.14 (t), 21.00 (q), 17.77 (q), 17.51 (q), 0.34 (q, 3C); exact mass calcd. for $C_{21}H_{38}OSi$ ($M^{\cdot+}$) *m/z* 334.2692, found *m/z* 334.2688.



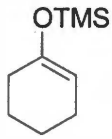
221

(±)-6-Benzylidene-2-methyl-3-(3-methylbut-2-enyl)-2-(4-methylpent-3-enyl)-cyclohexanone (221). To a solution of 472 mg (1.80 mmol) of ketone **206** in 3 mL of ethanol was added 229 mg (2.16 mmol) of benzaldehyde followed by 1 mL of a 35% (v/w) of potassium hydroxide in methanol. The resulting solution stirred for 20 h at room temperature and then was diluted with 10 mL of ether. The mixture was filtered and concentrated *in vacuo.* The residue was diluted with hexanes and the layers were separated. The aqueous phase was extracted twice with 2–mL portions of hexanes. The combined organic layers were dried ($MgSO_4$) and filtered over a 1–inch pad of Florisil (rinsed with 20 mL of ether). The solvent was removed under reduced pressure to afford 568 mg (90%) of **221** as a pale yellow oil: IR (neat) 3056 (w), 3025 (w), 2968 (s), 2925 (s), 2878 (s), 2729 (w), 1678 (s), 1594 (s), 1573 (m), 1492 (m), 1447 (s), 1376 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.49 – 7.23 (m, 6H, Ph, CHPh), 5.20 – 5.03 (m, 2H, CH=), 2.97 – 2.81 (m, 1H), 2.76 – 2.58 (m, 1H), 2.24 – 2.08 (m, 1H), 2.02 – 1.79 (m, 6H), 1.73 (s, 3H, CH_3), 1.66 (s, 3H, CH_3), 1.62 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.57 – 1.40 (m, 2H), 1.07 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 207.15 (s), 136.78 (s), 135.89 (s), 135.11 (d), 132.50 (s), 131.36 (s), 130.10 (d, 2C), 128.12 (d, 3C), 124.34 (d), 123.12 (d), 51.01 (s), 40.79 (d), 36.98 (t), 27.72 (t), 27.19 (t), 25.73 (q), 25.55 (q), 22.93 (t, 2C), 20.17 (q), 17.75 (q), 17.47 (q); exact mass calcd. for $C_{25}H_{34}O$ ($M^{\cdot+}$) *m/z* 268.1827, found *m/z* 268.1823.



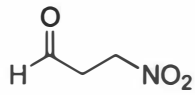
222

(±)-6-Benzylidene-2-methyl-3-(3-methylbut-2-enyl)-2-(4-methylpent-3-enyl)-1-prop-1-ynylcyclohexanol (222). To a solution of 530 mg (1.51 mmol) of ketone **221** in 13 mL of THF was added 409 mg (1.66 mmol) of anhydrous $CeCl_3$. After the suspension stirred for 2 h at room temperature, the reaction was cooled to 0°C and 3.6 mL (1.81 mmol) of 1-propynylmagnesium bromide was added dropwise as a 0.5 M solution in THF. The mixture stirred for 1 h, was warmed to room temperature, and 10 mL of saturated $NH_4Cl_{(aq)}$ was added. After stirring for 5 min, the layers were separated and the aqueous layer was extracted three times with 15–mL portions of CH_2Cl_2. The combined organics were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford 523 mg of alcohol **222** (89%) as a pale green oil: IR (neat) 3560 (w), 3505 (w), 3079 (w), 3056 (w), 3023 (w), 2968 (s), 2921 (s), 2880 (m), 2730 (w), 2247 (w), 1655 (w), 1600 (w), 1494 (w), 1446 (m), 1378 (m), 909 (s), 735 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.34 – 7.07 (m, 5H, Ph), 6.73 (s, 1H, C<u>H</u>Ph), 5.22 – 5.03 (m, 2H, CH=), 2.85 – 2.73 (m, 1H), 2.49 – 2.11 (m, 4H), 2.09 (s, 1H, OH), 1.91 – 1.62 (m, 4H), 1.86 (s, 3H, CH_3), 1.70 (s, 6H, CH_3), 1.65 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.32 – 1.05 (m, 2H), 0.84 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 143.07 (s), 138.14 (s), 131.73 (s), 130.73 (s), 128.94 (d, 2C), 127.94 (d, 2C), 126.01 (d), 125.83 (d), 124.37 (d), 121.00 (d), 82.61 (s), 81.79 (s), 77.38 (s), 46.37 (s), 42.94 (d), 37.02 (t), 29.01 (t), 27.34 (t), 25.69 (q, 2C), 24.24 (t, 2C), 17.84 (q), 17.61 (q), 13.78 (q), 3.73 (q); exact mass calcd. for $C_{28}H_{38}O$ ($M^{\cdot+}$) *m/z* 390.2923, found *m/z* 390.2923.



229

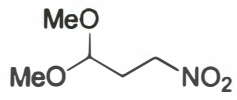
(Cyclohex-1-enyloxy)trimethylsilane (229).[172,173] To a solution of 5.4 mL (3.9 g, 38 mmol) of N,N-diisopropylamine in 95 mL of THF was added 27 mL (35 mmol) of *n*-butyllithium as a 1.3 M solution in hexanes at –78°C, and the mixture stirred for 30 min. The resulting yellow solution was warmed to 0°C and stirred for 30 min. To the solution was added 3.1 mL (2.9 g, 29 mmol) of cyclohexanone at 0°C. After the mixture stirred for 1 h, 1.5 mL (3.8 g, 35 mmol) of TMSCl was added dropwise followed by stirring for 1 h as the reaction slowly warmed to room temperature. The mixture was concentrated *in vacuo*, and the residue was diluted with 30 mL of pentane. The solution was filtered over a 1-inch pad of Florisil (rinsed with 100 mL of pentane) and the product was concentrated *in vacuo* to afford 5.0 g (100%) of silyl enol ether **229** as a colorless oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.91 – 4.81 (m, 1H, CH=), 2.09 – 1.90 (m, 4H, CH_2), 1.75 – 1.57 (m, 2H, CH_2), 1.56 – 1.42 (m, 2H, CH_2), 0.17 (s, 9H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 150.27, 104.11, 29.87, 23.77, 23.14, 22.32, 0.25 (3C).



153

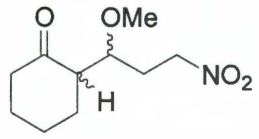
3-Nitropropionaldehyde (153).[120] To a well-stirred solution of 2.61 g (37.8 mmol) of sodium nitrite in 20 mL of a 3:2 THF–water mixture was added 1.97 mL (1.65 g, 29.1 mmol) of acrolein at 0°C in one portion followed by slow addition of 1.83 mL (1.92 g, 32.0 mmol) of concentrated acetic acid over 30 min. The reaction mixture stirred at 0°C for 3 h, was warmed to room temperature, and then diluted with 15 mL of ethyl acetate. The reaction was quenched by adding 6 mL of saturated $NaHCO_{3(aq)}$. After stirring for 5 min, the layers were separated and the aqueous phase was extracted twice with 10–mL portions of ethyl acetate. The combined organic fractions were washed

twice with 10–mL portions of brine, dried ($MgSO_4$), and concentrated *in vacuo* to afford 2.79 g (93%) of **153** as a dark yellow oil: ^1H NMR ($CDCl_3$, 250 MHz) δ 9.79 (s, 1H, CHO), 4.69 (t, J = 5.9 Hz, 2H, CH_2), 3.19 (t, J = 5.9 Hz, 2H, CH_2).



155

1,1-Dimethoxy-3-nitropropane (155).[120] To a solution of 2.71 g (26.3 mmol) of aldehyde **153** and 3.74 mL (3.63 g, 34.2 mmol) of trimethyl orthoformate in 10 mL of methanol was added 104 mg of p-TsOH at 0°C. The mixture stirred for 16 h while slowly warming to room temperature. The reaction was concentrated *in vacuo*, diluted with 5 mL of ethyl acetate, and slowly treated with 5 mL of saturated $NaHCO_{3(aq)}$. After stirring for 5 min, the phases were separated and the aqueous layer was extracted twice with 5–mL portions of ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was distilled (65°C/ 0.6 torr) to afford 2.95 g (75%) of acetal **155** as a colorless oil: ^1H NMR ($CDCl_3$, 250 MHz) δ 4.54 – 4.40 (m, 3H, CHO, CH_2), 3.36 (s, 6H, CH_3), 2.30 (m, 2H, $C\underline{H_2}CH$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 101.78, 70.97, 53.77, 30.28.

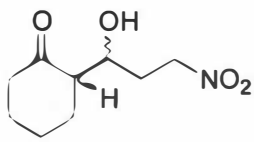


230

(±)-2-(1-Methoxy-3-nitropropyl)cyclohexanone (230). To a stirred solution of 0.67 mL (650 mg, 2.3 mmol) of titanium (IV) isopropoxide in 20 mL of CH_2Cl_2 was added dropwise 0.20 mL (340 mg, 2.3 mmol) of titanium (IV) chloride at –78°C. After the pale yellow solution stirred for 10 min, a solution of 300 mg (1.8 mmol) of silyl enol ether **229** and 290 mg (1.9 mmol) of methyl acetal **155** in 1 mL of CH_2Cl_2 was added

dropwise. The resulting light red solution stirred for 3 h and then was warmed to room temperature. The reaction was quenched with 20 mL of saturated $Na_2CO_{3(aq)}$. After stirring for 10 min, the layers were separated and the aqueous phase was extracted twice with 20–mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 20 g of silica gel (eluted with CH_2Cl_2) to afford 286 mg (76%) of ketone **230** as diastereomers (2.1 : 1.0) that were a colorless oil: IR (neat) 2940 (s), 2866 (m), 2831 (m), 1707 (s), 1553 (s), 1449 (m), 1433 (m), 1383 (s), 1126 (s), 1094 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 4.63 – 4.35 (m, CH_2NO_2), 3.81 – 3.63 (m, CHO), 3.34 (s, CH_3), 3.30 (s, CH_3), 2.85 – 2.64 (m, CH_2), 2.52 – 1.85 (m, CH_2), 1.80 – 1.43 (m, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 211.04 (s), 210.76 (s), 76.26 (d), 75.48 (d), 72.88 (t), 72.28 (t), 58.74 (q), 57.25 (q), 54.28 (d), 51.27 (d), 42.14 (t, 2C), 30.51 (t), 28.71 (t), 28.38 (t), 27.29 (t, 2C), 27.12 (t), 26.92 (t), 24.47 (t); exact mass calcd. for $C_{10}H_{18}NO_4$ ($M^{\cdot+}$ + H) *m/z* 216.1236, found *m/z* 216.1247 (No $M^{\cdot+}$ observed).

Anal. calcd. for $C_{10}H_{17}NO_4$: C, 55.80; H, 7.96; found: C, 55.94; H, 7.98.

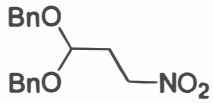


231

(±)-2-(1-Hydroxy-3-nitropropyl)cyclohexanone (231).[174] To a stirred solution of 0.90 mL (870 mg, 3.1 mmol) of titanium (IV) isopropoxide in 25 mL of CH_2Cl_2 was added dropwise 0.26 mL (460 mg, 3.1 mmol) of titanium (IV) chloride at –78°C. After the pale yellow solution stirred for 10 min, a solution of 400 mg (2.4 mmol) of silyl enol ether **229** and 270 mg (2.6 mmol) of aldehyde **153** in 2.5 mL of CH_2Cl_2 was added dropwise. The resulting light red solution stirred for 4 h and then was warmed to room temperature. The reaction was quenched with 25 mL of saturated $Na_2CO_{3(aq)}$. After stirring for 10 min, the layers were separated and the aqueous phase was extracted three times with 20–mL portions of CH_2Cl_2. The combined organic layers were washed with

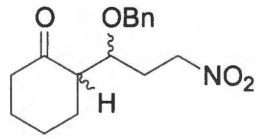
brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 20 g of silica gel (eluted with CH_2Cl_2) to afford 220 mg (47%) of β-hydroxyketone **231** as diastereomers that were a yellow oil: ^1H NMR ($CDCl_3$, 250 MHz) δ 4.75 – 4.44 (m, CH_2NO_2), 4.19 – 4.08 (m, CHOH), 3.90 – 3.76 (m, CHOH), 3.72 (d, J = 3.7 Hz, CHOH), 3.03 (d, J = 4.4 Hz, CHOH), 2.54 – 1.87 (m, CH_2), 1.81 – 1.38 (m, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 214.76, 213.62, 72.64, 72.09, 68.42, 66.04, 55.48, 54.69, 42.37, 42.13, 30.73, 30.54, 30.09, 27.36 (2C), 26.52, 24.42 (2C); exact mass calcd. for $C_9H_{16}NO_4$ ($M^{\cdot+}$ + H) *m/z* 202.1079, found *m/z* 202.1070 (No $M^{\cdot+}$ observed).

Anal. calcd. for $C_9H_{15}NO_4$: C, 53.72; H, 7.51; found: C, 53.73, H, 7.52.



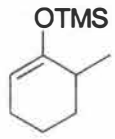
232

1,1-Dibenzyloxy-3-nitropropane (232). To a solution of 729 mg (7.08 mmol) of aldehyde **153** in 20 mL of a 1:1 benzyl alcohol–benzene solution was added a catalytic amount of p-TsOH and then the stirred mixture was heated to 55°C. After stirring for 1 h, 1 g of 4Å molecular sieves was added and the mixture was stirred for 1 h. The mixture was cooled to room temperature and then successively washed with 8 mL of saturated $NaHCO_{3(aq)}$ and 8 mL of brine. The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. The excess benzyl alcohol was removed via distillation (70-73°C/ 0.6 torr) and the residue was chromatographed over 80 g of silica gel (eluted with hexanes–ethyl acetate, 3:1) to afford 1.87 g (87%) of acetal **232** as a yellow oil: IR (neat) 3065 (w), 3032 (m), 2922 (m), 2875 (m), 1736 (w), 1688 (w), 1553 (s), 1380 (m), 1125 (s), 1043 (s), 1026 (s), 911 (m), 735 (s), 700 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.51 – 7.12 (m, 10H, CH), 4.79 (t, J = 5.2 Hz, 1H, CHO), 4.64 (d, J = 11.6 Hz, 2H, CH_2O), 4.51 (d, J = 11.6 Hz, 2H, CH_2O), 4.40 (t, J = 6.9 Hz, 2H, CH_2NO_2), 2.35 (dt, J = 6.9, 5.2 Hz, 2H CH_2CHO); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 137.33 (s, 2C), 128.42 (d, 4C), 127.79 (d, 2C), 127.68 (d, 4C), 99.05 (d), 70.91 (t), 68.55 (t, 2C), 31.13 (t); exact mass calcd. for $C_{15}H_{15}O_2$ ($M^{\cdot+} - C_2H_4O_2N$) *m/z* 227.1072, found *m/z* 227.1076 (No $M^{\cdot+}$ observed).



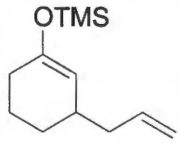
233

(±)-2-(1-Benzyloxy-3-nitropropyl)cyclohexanone (233). To a stirred solution of 0.54 mL (520 mg, 1.8 mmol) of titanium (IV) isopropoxide in 17 mL of CH_2Cl_2 was added dropwise 0.16 mL (274 mg, 1.8 mmol) of titanium (IV) chloride at –78°C. After the pale yellow solution stirred for 10 min, a solution of 240 mg (1.4 mmol) of silyl enol ether **229** and 470 mg (1.6 mmol) of benzyl acetal **232** in 1 mL of CH_2Cl_2 was added dropwise. The resulting light red solution stirred for 3 h and then was warmed to room temperature. The reaction was quenched with 18 mL of saturated $Na_2CO_{3(aq)}$. After stirring for 10 min, the layers were separated and the aqueous phase was extracted twice with 20–mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 20 g of silica gel (eluted with CH_2Cl_2) to afford 340 mg (83%) of ketone 43 as diastereomers that were a yellow oil: IR (neat) 3064 (w), 3031 (m), 2940 (s), 2865 (s), 1706 (s), 1553 (s), 1452 (s), 1432 (m), 1382 (s), 1126 (m), 1101 (s), 1064 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.52 – 7.17 (m, CH), 4.67 – 4.28 (m, CH_2NO_2, OCH_2), 4.09 – 3.90 (m, CHO), 2.81 – 2.66 (m, CH_2), 2.55 – 1.96 (m, CH_2), 1.95 – 1.80 (m, CH_2), 1.79 – 1.37 (m, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 210.93 (s), 210.83 (s), 137.84 (s), 137.72 (s), 128.23 (d, 4C), 127.63 (d, 6C), 74.33 (d), 73.36 (d), 72.89 (t), 72.82 (t), 72.20 (t), 71.66 (t), 54.55 (d), 51.81 (d), 42.16 (t), 42.06 (t), 30.78 (t), 28.75 (t), 28.52 (t), 27.28 (t), 27.09 (t), 26.95 (t), 24.57 (t), 24.51 (t); exact mass calcd. for $C_{16}H_{22}NO_4$ ($M^{\cdot+}$ + H) *m/z* 292.1549, found *m/z* 292.1568 (No $M^{\cdot+}$ observed).



234

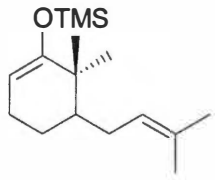
Trimethyl-(6-methylcyclohex-1-enyloxy)-silane (234).[175,176] To a solution of 3.0 mL (2.2 g, 21 mmol) of N,N-diisopropylamine in 55 mL of THF was added dropwise 12 mL (20 mmol) of *n*-butyllithium as a 1.6 M solution in hexanes at –78°C and the mixture stirred for 30 min. The mixture was warmed to 0°C and continued to stir for 30 min. To the resulting mixture was added a solution of 1.8 g (16.3 mmol) of 2-methylcyclohexanone in 1 mL of THF and the solution continued to stir for 1 h at 0°C. To the resulting solution was added 2.5 mL (2.1 g, 20 mmol) of TMSCl and the solution stirred overnight as it warmed to room temperature. The solvent was removed *in vacuo*, the residue was diluted with 30 mL of hexanes, and the mixture was filtered over a 2-inch pad of Florisil (rinsed with 100 mL of hexanes). The product was concentrated *in vacuo* to afford 2.9 g (96%) of silyl enol ether **234** as a pale-yellow oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 4.83 – 4.74 (m, 1H, HC=), 2.21 – 2.04 (m, 1H, CH, CH_2), 2.03 – 1.90 (m, 2H, CH, CH_2), 1.86 – 1.20 (m, 4H, CH, CH_2), 1.03 (d, J = 6.9 Hz, 3H, CH_3), 0.17 (s, 9H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 154.19, 103.25, 33.65, 31.67, 24.36, 20.33, 18.63, 0.25 (3C).



235

(3-Allylcyclohex-1-enyloxy)trimethylsilane (235).[78,177,178] A solution of 4.79 g (25.2 mmol) of copper (I) iodide and 1.07 g (25.2 mmol) of anhydrous LiCl in 25 mL of THF was prepared and stirred for 10 min at room temperature followed by 5 min at –78°C. To the solution was added dropwise 25.2 mL (25.2 mmol) of allylmagnesium bromide as a 1 M solution in ether. After stirring for 5 min, 3.2 mL (25 mmol) of TMSCl

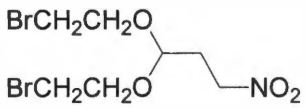
and 3.5 mL (25 mmol) of triethylamine were added dropwise successively. After the resulting solution stirred for 5 min, 1.29 g (13.4 mmol) of 2-cyclohexenone was added and the solution continued to stir for 30 min. The reaction mixture was warmed to room temperature and quenched with 50 mL of 10% (v/v) $NH_4Cl_{(aq)}$. After stirring for 5 min, the solution was filtered, the layers were separated, and the aqueous phase was extracted twice with 50–mL portions of ether. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was taken up in 30 mL of hexanes and filtered over a 1.5-inch pad of Florisil (rinsed with 70 mL of hexanes). The solvent was removed *in vacuo* to afford 2.82 g (100%) of silyl enol ether **235** as a colorless oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 5.91 – 5.66 (m, 1H, C<u>H</u>=CH_2), 5.02 (d, J = 5.3 Hz, 1H, =CH_2), 4.97 (s, 1H, =CH_2), 4.80 (s, 1H, CH=CO), 2.30 – 2.12 (m, 1H), 2.11 – 1.91 (m, 4H), 1.86 – 1.42 (m, 3H), 1.24 – 1.05 (m, 1H), 0.18 (s, 9H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 150.66, 137.22, 115.70, 108.69, 41.39, 34.50, 29.94, 28.66, 21.70, 0.28 (3C).



236

[6,6-Dimethyl-5-(3-methylbut-2-enyl)cyclohex-1-enyloxy]trimethylsilane (236). To a solution of 0.57 mL (410 mg, 4.0 mmol) of N,N-diisopropylamine in 15 mL of THF was added dropwise 3.0 mL (3.9 mmol) of *n*-butyllithium as a 1.3 M solution in hexanes at –78°C and the mixture stirred for 30 min. The mixture was warmed to 0°C and continued to stir for 30 min. To the resulting mixture was added a solution of 651 mg (3.35 mmol) of ketone **176** in 1 mL of THF. After the solution stirred for 1.5 h at 0°C, 0.51 mL (437 mg, 4.0 mmol) of TMSCl was added and the resulting solution stirred for 1.5 h while warming to room temperature. The solvent was removed *in vacuo*, the residue was diluted with 30 mL of hexanes, and was filtered over a 1-inch pad of Florisil

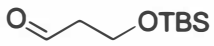
(rinsed with 100 mL of hexanes). The product was concentrated *in vacuo* to afford 815 mg (91%) of silyl enol ether **236** as a colorless oil: IR (neat) 3038 (w), 2965 (s), 2918 (s), 2860 (m), 1660 (m), 1253 (s), 1211 (s), 1175 (s), 1143 (s), 894 (s), 844 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.22 – 5.06 (m, 1H, C<u>H</u>=CCH$_3$), 4.69 (t, J = 3.9 Hz, 1H, CH=CO), 2.23 – 2.02 (m, 1H), 2.02 – 1.87 (m, 2H), 1.85 – 1.64 (m, 1H), 1.70 (s, 3H, CH_3), 1.60 (s, 3H, CH_3), 1.39 – 1.12 (m, 3H), 1.06 (s, 3H, CH_3), 0.90 (s, 3H, CH_3), 0.18 (s, 9H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 156.95 (s), 131.76 (s), 124.53 (d), 101.54 (d), 45.87 (d), 38.61 (s), 28.67 (t), 25.84 (q), 25.18 (q), 23.56 (t, 2C), 20.65 (q), 17.79 (q), 0.42 (q, 3C); exact mass calcd. for $C_{16}H_{30}OSi$ ($M^{\cdot+}$) *m/z* 266.2066, found *m/z* 266.2056.



237

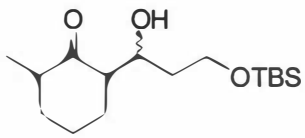
1,1-Bis-(2-bromoethoxy)-3-nitropropane (237). To a solution of 1.01 g (9.75 mmol) of aldehyde **153** in 8 mL of 2-bromoethanol was added 200 mg of anhydrous calcium chloride and 200 mg of 4Å molecular sieves. After stirring for 18 h, the mixture was diluted with 15 mL of ethyl acetate and quenched with 15 mL of saturated $NaHCO_{3(aq)}$. After stirring for 5 min, the layers were separated and the aqueous phase was extracted with 15 mL of ethyl acetate. The combined organic phases were washed with brine, dried ($MgSO_4$), filtered over 0.5-inch of silica gel (rinsed with 40 mL of ethyl acetate), and concentrated *in vacuo*. The residual alcohol was removed by distillation (35°C/ 0.6 torr) and the distillation residue was chromatographed over 20 g of silica gel (eluted with hexanes–ethyl acetate, 3:1) to afford 2.60 g (79%) of acetal **237** as a yellow oil: IR (neat) 2967 (m), 2919 (m), 2872 (m), 1554 (s), 1380 (s), 1351 (m), 1131 (s), 1088 (s), 1030 (s), 957 (m), 912 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 4.79 (t, J = 5.3 Hz, 1H, CHO), 4.54 (t, J = 6.8 Hz, 2H, CH_2NO_2), 4.10 – 3.92 (m, 2H, CH_2O), 3.91 – 3.72 (m, 2H, CH_2O), 3.50 (t, J = 5.8 Hz, 4H, CH_2Br), 2.38 (dt, J = 6.8, 5.3 Hz, 2H, C<u>H$_2$</u>CH) ; ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 100.13 (d), 70.72 (t), 66.35 (t, 2C), 30.65 (t), 30.57 (t, 2C);

exact mass calcd. for $C_7H_{12}Br_2NO_4$ ($M^{\cdot+}$ – H) *m/z* 333.9113, found *m/z* 333.9099 (No $M^{\cdot+}$ observed).



248

3-(*tert*-butyldimethylsilanyloxy)propionaldehyde (248).[121,122] To a solution of 4.00 g (21.0 mmol) of 3-*tert*-butyldimethylsiloxy-1-propanol in 80 mL of CH_2Cl_2 was added 1.38 g (16.8 mmol) of sodium acetate and 8.60 g (39.9 mmol) of PCC with rigorous stirring. The reaction mixture was stirred for 3 h and then was filtered over a 2-inch pad of silica gel (rinsed with 150 mL of hexanes–ethyl acetate, 10:1). The solvent was removed *in vacuo* to afford 3.30 g (83%) of aldehyde **248** as an orange oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.79 (s, 1H, HCO), 3.99 (t, J = 5.7 Hz, 2H, CH_2O), 2.60 (t, J = 5.7 Hz, 2H, CH_2), 0.88 (s, 9H, CCH_3), 0.068 (s, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 201.78, 57.26, 46.39, 25.66 (3C), 18.05, -5.63 (2C).

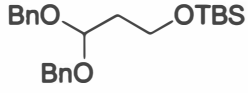


249

(±)-2-[3-(*tert*-Butyldimethylsilanyloxy)-1-hydroxypropyl]-6-methylcyclohexanone (249). To a stirred solution of 0.80 mL (780 mg, 2.7 mmol) of titanium (IV) isopropoxide in 25 mL of CH_2Cl_2 was added dropwise 0.24 mL (410 mg, 1.7 mmol) of titanium (IV) chloride at –78°C. After the pale yellow solution stirred for 10 min, a solution of 387 mg (2.10 mmol) of silyl enol ether **234** and 435 mg (2.3 mmol) of aldehyde **248** in 1.5 mL of CH_2Cl_2 was added dropwise. The resulting light yellow solution stirred for 1.5 h and then was warmed to room temperature. The reaction was slowly quenched with 20 mL of saturated $Na_2CO_{3(aq)}$. After stirring for 10 min, the layers were separated and the aqueous phase was extracted with 25 mL of CH_2Cl_2. The

combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over 70 g of silica gel (eluted with hexanes–ethyl acetate, 10:1 → 5:1) to afford 49 mg (8%) of β-hydoxyketone diastereomer **249A** and 33 mg (5%) of diastereomers **249B** as colorless oil: **Diastereomer 249A**: IR (neat) 3533 (m), 2853 (s), 2932 (s), 2859 (s), 1702 (s), 1462 (m), 1255 (s), 1094 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 4.04 – 3.90 (m, 1H, CHO), 3.82 (t, J = 6.0 Hz, 2H, CH_2O), 3.62 (d, J = 3.8 Hz, 1H, OH), 2.57 – 2.31 (m, 2H), 2.26 – 2.03 (m, 2H), 1.98 – 1.81 (m, 1H), 1.80 – 1.57 (m, 3H, CH_2), 1.57 – 1.19 (m, 2H), 1.01 (d, J = 6.4 Hz, 3H, CH_3), 0.90 (s, 9H, CCH_3), 0.07 (s, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 216.07 (s), 69.47 (d), 60.76 (t), 58.03 (d), 46.06 (d), 37.18 (t), 36.05 (t), 31.10 (t), 25.87 (q, 3C), 25.11 (t), 18.18 (s), 14.17 (q), -5.47 (q, 2C); exact mass calcd. for $C_{12}H_{23}O_3Si$ ($M^{\cdot+}$ – C_4H_9) *m/z* 243.1416, found *m/z* 243.1414 (No $M^{\cdot+}$ observed).

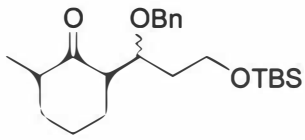
Diastereomers 249B: ^1H NMR ($CDCl_3$, 250 MHz) δ 4.26 – 4.07 (m, CHO), 3.95 – 3.74 (m, CH_2O), 3.57 (d, J = 3.2 Hz, OH), 3.50 (d, J = 3.3 Hz, OH), 2.70 – 2.36 (m), 2.17 – 1.42 (m), 1.38 – 1.22 (m), 1.12 (d, J = 7.2 Hz, CH_3), 1.09 (d, J = 7.1 Hz, CH_3), 0.90 (s, CCH_3), 0.76 (s, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 216.55 (s), 216.30 (s), 70.95 (d), 69.16 (d), 61.99 (t), 61.77 (t), 54.51 (d), 54.19 (d), 44.42 (d), 44.04 (d), 36.16 (t), 34.74 (t), 29.56 (t), 27.37 (t), 25.87 (q, 6C), 20.56 (t), 20.31 (t), 18.17 (s, 2C), 15.74 (q, 2C), -5.52 (q, 4C) (two triplets not observed).



250

(3,3-Bisbenzyloxypropoxy)-*tert*-butyldimethylsilane (250).[179] To a solution of 1.61 g (8.56 mmol) of aldehyde **248** in 50 mL of CH_2Cl_2 was added successively 2.30 g (21.4 mmol) of benzyl alcohol, 2.30 g of anhydrous $MgSO_4$, and a catalytic amount of p-TsOH. The suspension stirred overnight and then a catalytic amount of Na_2CO_3 was added. After stirring for 5 min, the solution was filtered and concentrated *in vacuo*. The

residue was chromatographed over 70 g of silica gel to afford 1.80 g (54%) of acetal **250** as a colorless oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.58 – 7.38 (m, 10H, Ph), 5.16 (t, J = 5.7 Hz, 1H, CHO), 4.87 (d, J = 11.7 Hz, 2H, CH_2O), 4.76 (d, J = 11.7 Hz, 2H, CH_2O), 4.00 – 3.87 (m, 2H, CH_2), 2.27 – 2.12 (m, 2H, CH_2), 1.09 (s, 9H, CCH_3), 0.24 (s, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 138.24 (2C), 128.28 (4C), 127.65 (4C), 127.43 (2C), 99.84, 67.45 (2C), 59.08, 38.70, 25.80 (3C), 18.14, -5.48 (2C).

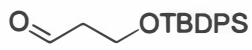


251

(±)-2-[1-Benzyloxy-3-(*tert*-butyldimethylsilanyloxy)propyl]-6-methylcyclohexanone (251). To a solution of 650 mg (1.68 mmol) of acetal **250** in 25 mL of CH_2Cl_2 was added 0.17 mL (300 mg, 1.98 mmol) of titanium tetrachloride at –78°C. After stirring for 10 min, a solution of 281 mg (1.52 mmol) of silyl enol ether **234** in 1 mL of CH_2Cl_2 was added to the mixture. The reaction was stirred for 2 h and then was warmed to room temperature. The reaction was quenched by adding 20 mL of saturated $Na_2CO_{3(aq)}$. After stirring for 5 min, the layers were separated and the aqueous phase was extracted with 30 mL of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over 20 g of silica gel (eluted with CH_2Cl_2) to afford 71 mg (12%) of **251A** as diastereomers that were a colorless oil: IR (neat) 3065 (w), 3031 (w), 2951 (s), 2951 (s), 2931 (s), 2858 (s), 1711 (s), 1456 (m), 1383 (m), 1360 (m), 1255 (m), 1097 (s), 837 (s), 777 (m), 735 (m) cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.47 – 7.18 (m, Ph), 4.66 – 4.47 (m, OCH_2Ph), 4.19 – 3.93 (m, OCH), 3.85 – 3.57 (m, OCH_2), 2.79 – 2.46 (m), 2.45 – 2.26 (m), 2.24 – 1.98 (m), 1.97 – 1.20 (m), 1.02 (d, J = 6.5 Hz, CH_3), 1.01 (d, J = 6.5 Hz, CH_3), 0.90 (s, CCH_3), 0.89 (s, CCH_3), 0.06 (d, J = 0.8 Hz, $SiCH_3$), 0.04 (d, J = 0.8 Hz, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 212.83 (s), 212.72 (s), 139.14 (s), 138.96 (s), 128.20 (d, 4C), 127.72 (d, 2C), 127.65 (d, 2C), 127.39 (d), 127.28 (d), 74.69 (d), 74.16 (d), 72.71 (t), 72.30 (t), 60.05 (t),

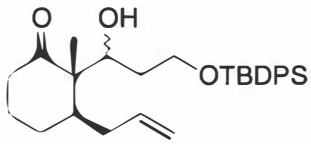
59.67 (t), 55.24 (d), 53.87 (d), 45.85 (d, 2C), 37.13 (t), 37.00 (t), 36.10 (t), 34.48 (t), 29.59 (t, 2C), 25.91 (q, 6C), 25.28 (t, 2C), 18.23 (s, 2C), 14.49 (q, 2C), -5.37 (q, 4C).

Further elution provided 87 mg (15%) of **251B** as diastereomers that were colorless oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.43 – 7.14 (m, Ph), 4.71 – 4.35 (m, OCH_2Ph), 4.21 – 3.98 (m, OCH), 3.82 – 3.63 (m, OCH_2), 2.77 – 2.59 (m), 2.58 – 2.21 (m), 2.12 – 1.34 (m), 1.13 (d, J = 6.8 Hz, CH_3), 0.99 (d, J = 6.7 Hz, CH_3), 0.91 (s, CCH_3), 0.89 (s, CCH_3), 0.06 (s, $SiCH_3$), 0.05 (s, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 214.85 (s, 2C), 140.94 (s), 138.33 (s), 128.36 (d, 2C), 128.21 (d, 2C), 127.68 (d, 2C), 127.40 (d, 2C), 126.83 (d, 2C), 75.58 (d, 2C), 71.07 (t, 2C), 61.74 (t), 59.35 (t), 53.15 (d, 2C), 43.15 (d, 2C), 35.05 (t), 34.53 (t), 31.84 (t), 31.57 (t), 28.79 (t), 27.21 (t), 25.84 (q, 6C), 22.60 (t), 20.80 (t), 18.18 (s, 2C), 15.11 (q, 2C), -5.41 (q, 4C).



252

3-(*tert*-Butyldiphenylsilanyloxy)propionaldehyde (252).[123,124] To a solution of 3.31 g (10.5 mmol) of 3-*tert*-butyldiphenylsiloxy-1-propanol in 50 mL of CH_2Cl_2 was added 691 mg (8.42 mmol) of sodium acetate and 4.30 g (20.0 mmol) of PCC with rigorous stirring. The reaction mixture was stirred for 4 h and then was filtered over a 1.5-inch pad of silica gel (rinsed with 100 mL of hexanes–ethyl acetate, 10:1). The solvent was removed *in vacuo* and the crude product was chromatographed over 70 g of silica gel (eluted with hexanes–ethyl acetate, 10:1) to afford 2.30 g (70%) of aldehyde **252** as a colorless oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 9.75 (t, J = 2.0 Hz, 1H, CHO), 7.78 – 7.54 (m, 4H, Ph), 7.47 – 7.22 (m, 6H, Ph), 4.00 (t, J = 6.0 Hz, 2H, CH_2), 2.55 (td, J = 6.0, 2.0 Hz, 2H, CH_2O), 1.05 (s, 9H, CCH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 201.36 (d), 135.38 (d, 4C), 133.10 (s, 2C), 129.68 (d, 2C), 127.64 (d, 2C), 127.50 (d, 2C), 58.16 (t), 48.19 (t), 26.66 (q, 3C), 18.99 (s).

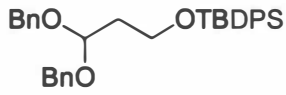


253

(±)-3-Allyl-2-[3-(*tert*-butyldiphenylsilanyloxy)-1-hydroxypropyl]-2-methyl-cyclohexanone (253). Method A: To a solution of 0.13 mL (220 mg, 1.5 mmol) of titanium (IV) chloride in 25 mL of CH_2Cl_2 was added dropwise a solution of 391 mg (1.25 mmol) of aldehyde **252** and 256 mg (1.14 mmol) of silyl enol ether **177** in 1 mL of CH_2Cl_2 at -78°C. The reaction mixture stirred for 5 h while slowly warming to room temperature, and then was quenched with 20 mL of saturated $Na_2CO_{3(aq)}$. After stirring for 5 min, the layers were separated and the aqueous phase was extracted twice with 20-mL portions of ether. The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 20 g of silica gel (eluted with hexanes-ethyl acetate, 5:1) to afford 160 mg (30%) of alcohol **253** as a colorless oil.

Method B: To a stirred solution of 390 μL (378 mg, 1.33 mmol) of titanium (IV) isopropoxide in 25 mL of CH_2Cl_2 cooled to -78°C was added dropwise 120 μL (199 mg, 1.33 mmol) of titanium (IV) chloride. After the solution stirred for 10 min, a solution of 228 mg (1.02 mmol) of silyl enol ether **177** and 349 mg (1.12 mmol) of aldehyde **252** in 1 mL of CH_2Cl_2 was added dropwise. The resulting solution stirred for 5 h and then was warmed to room temperature. The reaction was slowly quenched with 15 mL of saturated $Na_2CO_{3(aq)}$. After stirring for 10 min, the layers were separated and the aqueous phase was extracted twice with 20-mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 20 g of silica gel (eluted with hexanes-ethyl acetate, 10:1) to afford 107 mg (23%) of alcohol **253** as diastereomers (2.5 : 1) contaminated with an impurity: **Isomer 53A**: IR (neat) 3489 (m), 3072 (m), 3050 (m), 2933 (s), 2860 (s), 1702 (s), 1641 (w), 1590 (w), 1469 (m), 1428 (s), 1383 (m), 1109 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.90 – 7.54 (m, 4H, CH=), 7.43 – 7.15 (m, 6H, CH=), 5.93 – 5.56 (m, 1H, C<u>H</u>=CH_2), 5.14 – 4.88 (m, 2H, CH_2=), 4.14 (t, J = 6.0 Hz, 1H, CHO), 4.00 – 3.65 (m, 2H, CH_2O), 3.12 (d, J = 7.9

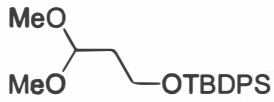
Hz, 1H, OH), 2.80 – 1.43 (m, 11H), 1.16 (s, 3H, CH_3), 1.06 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 217.13 (s), 136.98 (d), 135.46 (d, 4C), 133.46 (s, 2C), 129.61 (d, 2C), 127.62 (d, 4C), 116.21 (t), 72.27 (d), 61.84 (t), 56.11 (s), 41.70 (d), 39.31 (t), 34.48 (t), 32.75 (t), 26.78 (q, 3C), 23.98 (t), 23.24 (t), 19.05 (s), 15.17 (q).



254

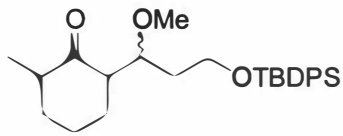
(3,3-Bisbenzyloxypropoxy)-*tert*-butyldiphenylsilane (254). To a solution of 2.30 g (7.36 mmol) of aldehyde **252** in 50 mL of CH_2Cl_2 was added successively 3.18 g (29.4 mmol) of benzyl alcohol, 2.50 g (20.8 mmol) of anhydrous $MgSO_4$, and a catalytic amount of p-TsOH. The suspension stirred overnight and then a catalytic amount of Na_2CO_3 was added to the mixture. After stirring for 5 min, the solution was filtered and concentrated *in vacuo*. The residue was chromatographed over 70 g of silica gel to afford 3.33 g (89%) of acetal **254** as a colorless oil that was crystallized at 0°C to furnish a white solid: mp 45-46°C; IR (neat) 3069 (m), 3031 (m), 2957 (m), 2931 (m), 2858 (m), 1495 (m), 1470 (m), 1428 (m), 1387 (m), 1360 (m), 1109 (s), 1025 (s), 736 (s), 701 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.74 – 7.58 (m, 4H, Ph), 7.46 – 7.18 (m, 16H, Ph), 5.07 (t, J = 5.8 Hz, 1H, CHO), 4.64 (d, J = 11.7 Hz, 2H, $PhCH_2O$), 4.54 (d, J = 11.7 Hz, 2H, $PhCH_2O$), 3.81 (t, J = 6.1 Hz, 2H, CH_2O), 2.02 (td, J = 6.1, 5.8 Hz, 2H, CH_2), 1.03 (s, 9H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 138.23 (s, 2C), 135.53 (d, 4C), 133.71 (s, 2C), 129.58 (d, 2C), 127.74 (d, 8C), 127.64 (d, 4C), 127.53 (d, 2C), 99.87 (d), 67.51 (t, 2C), 60.07 (t), 36.50 (t), 26.79 (q, 3C), 19.16 (s).

Anal. calcd. for $C_{33}H_{38}O_3Si$: C, 77.60; H, 7.50; found: C, 77.50; H, 7.49.



255

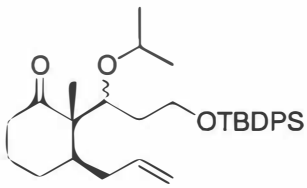
***tert*-Butyl-(3,3-dimethoxypropoxy)diphenylsilane (255).**[180] To a solution of 2.94 g (9.40 mmol) of aldehyde **252** in 50 mL of CH_2Cl_2 was added successively 1.5 g (48.3 mmol) of methanol, 2.5 g (20.8 mmol) of anhydrous $MgSO_4$, and a catalytic amount of p-TsOH. The mixture stirred overnight and then was quenched by adding a catalytic amount of Na_2CO_3. After stirring for 5 min, the mixture was filtered over a 1-inch pad of silica gel (rinsed with 50 mL of ether) and concentrated *in vacuo*. The residue was chromatographed over 70 g of silica gel (eluted with hexanes–ethyl acetate, 10:1) to afford 2.76 g (82%) of acetal **255** as a viscous colorless oil: IR (neat) 3071 (m), 3050 (m), 2957 (s), 2933 (s), 2890 (s), 2858 (s), 2831 (m), 1471 (m), 1428 (m), 1387 (m), 1363 (m), 1190 (m), 1109 (s), 967 (m), 912 (m), 823 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.77 – 7.59 (m, 4H, Ph), 7.46 – 7.26 (m, 6H, Ph), 4.65 (t, J = 5.8 Hz, 1H, CHO), 3.76 (t, J = 6.2 Hz, 1H, OCH_2), 3.29 (s, 6H, OCH_3), 1.94 – 1.78 (m, 2H, CH_2), 1.06 (s, 9H, CCH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 135.52 (d, 4C), 133.75 (s, 2C), 129.57 (d, 2C), 127.62 (d, 4C), 102.05 (d), 60.02 (t), 52.81 (q), 35.64 (t), 26.79 (q, 3C), 19.17 (s).



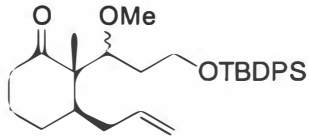
256

(±)-2-[3-(*tert*-Butyldiphenylsilanyloxy)-1-methoxypropyl]-6-methylcyclohexanone (256). To a stirred solution of 0.64 mL (630 mg, 2.2 mmol) of titanium (IV) isopropoxide in 25 mL of CH_2Cl_2 cooled to –78°C was added dropwise 0.19 mL (330 mg, 2.2 mmol) of titanium (IV) chloride. After the solution stirred for 10 min, a solution of 290 mg (1.57 mmol) of silyl enol ether **177** and 620 mg (1.73 mmol) of methyl acetal **255** in 1 mL of CH_2Cl_2 was added dropwise. The resulting solution stirred for 4 h and then was warmed to room temperature. The reaction was slowly quenched with 25 mL of

saturated $Na_2CO_{3(aq)}$. After stirring for 10 min, the layers were separated and the aqueous phase was extracted twice with 20–mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 45 g of silica gel (eluted with CH_2Cl_2) to afford 220 mg (70%) of **256** as a mixture of four isomers: IR (neat) 3071 (m), 3050 (m), 2958 (s), 2932 (s), 2859 (s), 1710 (s), 1590 (w), 1462 (m), 1428 (m), 1384 (m), 1109 (s), 823 (m), 738 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.77 – 7.60 (m, Ph), 7.48 – 7.28 (m, Ph), 3.97 – 3.63 (m, CHO, CH_2O), 3.42 – 3.19 (m, OCH_3), 2.68 – 2.15 (m), 2.14 – 1.31 (m), 1.25 – 0.98 (m, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.80 (s), 214.43 (s), 212.69 (s), 212.51 (s), 135.45 (d, 8C), 134.43 (d, 8C), 133.79 (s, 4C), 133.59 (s, 2C), 133.52 (s, 2C), 129.54 (d, 4C), 129.42 (d, 4C), 127.56 (d, 16C), 77.29 (d, 2C), 75.36 (d), 75.27 (d), 60.60 (t), 60.45 (t), 60.20 (t), 60.05 (t), 58.14 (q), 57.93 (q), 57.69 (q), 56.66 (q), 54.30 (d), 53.80 (d), 53.28 (d), 52.73 (d), 45.82 (d), 45.64 (d), 43.75 (d), 43.16 (d), 37.08 (t), 36.61 (t), 35.10 (t), 35.01 (t), 34.59 (t), 34.50 (t), 33.77 (t), 33.60 (t), 29.49 (t), 28.83 (t), 28.52 (t), 26.76 (q, 12C), 20.76 (t, 2C), 20.50 (t, 2C), 19.07 (s, 4C), 15.46 (q), 15.26 (q), 14.50 (q), 14.39 (q) (one triplet not observed).



257



258

3-Allyl-2-[3-(*tert*-butyldiphenylsilanyloxy)-1-isopropoxypropyl]-2-methyl-cyclohexanone (257). 3-Allyl-2-[3-(*tert*-butyldiphenylsilanyloxy)-1-methoxy-propyl]-2-methylcyclohexanone (258). To a stirred solution of 0.62 mL (600 mg, 2.1 mmol) of titanium (IV) isopropoxide in 25 mL of CH_2Cl_2 cooled to –78°C was added dropwise 0.18 mL (320 mg, 2.1 mmol) of titanium (IV) chloride. After the solution stirred for 10 min, a solution of 345 mg (1.54 mmol) of silyl enol ether **177** and 607 mg (1.69 mmol) of methyl acetal **255** in 1 mL of CH_2Cl_2 was added dropwise. The resulting solution stirred

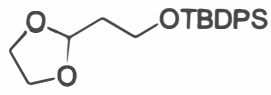
for 5 h and then was warmed to room temperature, and was quenched with 25 mL of saturated $Na_2CO_{3(aq)}$. After stirring for 10 min, the layers were separated and the aqueous phase was extracted twice with 20–mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 50 g of silica gel (eluted with hexanes–ethyl acetate, 10:1) to afford 228 mg (29%) of **257** as diastereomers that were a colorless oil: IR (neat) 3072 (m), 3050 (m), 2933 (s), 2859 (s), 1707 (s), 1641 (m), 1590 (w), 1468 (m), 1428 (m), 1384 (m), 1109 (s), 999 (m), 913 (m), 823 (m), 740 (m), 704 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.77 – 7.59 (m, Ph), 7.51 – 7.32 (m, Ph), 5.78 – 5.61 (m, CH=), 5.08 – 4.98 (m, CH_2=), 4.52 (d, J = 13.5 Hz, CHO), 4.25 (d, J = 8.7 Hz, CHO), 3.86 – 3.64 (m, CH_2O), 3.59 – 3.47 (m, OCH), 2.64 – 2.08 (m), 2.06 – 1.37 (m), 1.23 – 0.96 (m, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 215.10 (s), 215.04 (s), 137.94 (d), 137.28 (d), 135.53 (d, 4C), 135.38 (d, 4C), 133.70 (s, 2C), 133.42 (s, 2C), 129.67 (d, 2C), 129.60 (d, 2C), 127.64 (d, 4C), 127.60 (d, 4C), 115.96 (t), 115.89 (t), 75.80 (d), 73.49 (d), 71.87 (d), 70.52 (d), 61.51 (t), 60.45 (t), 59.02 (s), 57.01 (s), 41.98 (d), 41.41 (d), 39.93 (t), 38.65 (t), 35.24 (t), 34.93 (t), 33.36 (t), 32.44 (t), 26.85 (q, 6C), 23.35 (t), 23.00 (t), 22.94 (q), 22.83 (q), 22.40 (q, 2C), 22.31 (t, 2C), 19.12 (s, 2C), 14.45 (q), 13.51 (q).

Anal calcd. for $C_{32}H_{46}O_3Si$: C, 75.84; H, 9.15; found; C, 75.77; H, 9.12.

Continued elution afforded 350 mg (47%) of **258** as separable diastereomers that contained an impurity, **Diastereomer 258A:** IR (neat) 3072 (m), 3050 (m), 2961 (s), 2933 (s), 2880 (s), 1703 (s), 1641 (w), 1590 (w), 1468 (m), 1428 (m), 1382 (m), 1109 (s), 1090 (s), 737 (s), 704 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.82 – 7.59 (m, 4H, Ph), 7.48 – 7.30 (m, 6H, Ph), 5.75 – 5.57 (m, 1H, HC=), 5.08 – 4.95 (m, 2H, H_2C=), 4.08 (d, J = 8.7 Hz, 1H, HCO), 3.88 – 3.58 (m, 2H), 3.29 (s, 3H, OCH_3), 2.84 – 2.74 (m, 1H), 2.65 – 2.51 (m, 1H), 2.38 – 2.27 (m, 1H), 2.02 – 1.45 (m, 8H), 1.09 (s, 3H, CH_3), 1.06 (s, 9H, CCH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.82 (s), 137.05 (d), 135.50 (d, 2C), 134.75 (d, 2C), 133.59 (s), 133.47 (s), 129.50 (d, 2C), 127.63 (d, 2C), 127.60 (d, 2C), 116.13 (t), 80.74 (d), 61.87 (t), 61.32 (q), 60.00 (s), 41.81 (d), 38.51 (t), 34.21 (t), 32.95 (t), 26.83 (q, 3C), 23.22 (t), 22.41 (t), 19.15 (s), 14.07 (q).

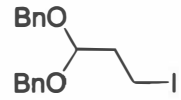
Anal. calcd. for $C_{30}H_{42}O_3Si$: C, 75.26; H, 8.84; found: C, 75.10; H, 8.87.

Diastereomer 258B: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.82 – 7.55 (m, 4H, Ph), 7.50 – 7.20 (m, 6H, Ph), 5.78 – 5.58 (m, 1H, CH=), 5.10 – 4.92 (m, 2H, CH_2=), 4.02 (t, J = 6.0 Hz, 1H, CHO), 3.98 – 3.65 (m, 2H, OCH_2), 3.57 (s, 3H, CH_3), 2.67 – 1.41 (m, 11H), 1.09 (s, 9H, CCH_3), 1.04 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.57 (s), 137.21 (d), 135.45 (d, 2C), 135.32 (d, 2C), 133.55 (s), 133.32 (s), 129.70 (d), 127.63 (d, 4C), 116.21 (t), 78.47 (d), 61.39 (q), 60.46 (t), 58.54 (s), 41.95 (d), 39.71 (t), 34.61 (t), 32.48 (t), 26.79 (q, 3C), 23.22 (t), 22.26 (t), 19.10 (s), 13.21 (q).



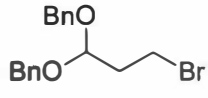
259

***tert*-Butyl-(2-[1.3]dioxolan-2-ylethoxy)diphenylsilane (259).** To a solution of 1.37 mg (4.38 mmol) of aldehyde **252** in 25 mL of benzene was added 2.50 g of ethylene glycol and a catalytic amount of p-TsOH. The mixture was stirred under reflux for 4 h in an apparatus equipped with a Dean-Stark trap. The mixture was cooled to room temperature, dried ($MgSO_4$), and filtered over a 1-inch pad of silica gel (rinsed with 100 mL of ether). The product was concentrated *in vacuo* to afford 1.21 g (78%) of **259** as a colorless oil: IR (neat) 3071 (m), 3049 (m), 2958 (m), 2932 (m), 2887 (m), 2858 (m), 1472 (m), 1428 (m), 1137 (m), 1110 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.82 – 7.57 (m, 4H, Ph), 7.50 – 7.20 (m, 6H, Ph), 5.06 (td, J = 5.0, 1.7 Hz, 1H, CH), 3.95 – 3.57 (m, 6H, CH_2O), 1.99 – 1.84 (m, 2H, CH_2), 1.06 (s, 9H, CCH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 135.52 (d, 2C), 135.34 (d, 2C), 133.78 (s, 2C), 129.54 (d, 2C), 127.61 (d, 4C), 102.26 (d), 64.66 (t, 2C), 59.92 (t), 37.04 (t), 26.84 (q, 3C), 19.17 (s).



260

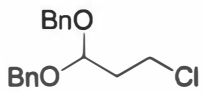
1,1-Dibenzyloxy-3-iodopropane (260). To a solution of 1.0 mL (0.84 g, 15 mmol) of acrolein and 2.70 g (18.0 mmol) of sodium iodide in 30 mL of MeCN was added dropwise 2.3 mL (2.0 g, 18 mmol) of TMSCl at 0°C. After the yellow mixture stirred for 30 min, 3.7 mL (3.9 g, 36 mmol) of anhydrous benzyl alcohol was added in one portion. The reaction mixture continued to stir for 30 min and then was poured into 40 mL of 5% saturated $NaHCO_{3(aq)}$ overlaid with 40 mL of pentane to yield three layers. The bottom aqueous phase was removed and the remaining two organic layers were washed successively with 20 mL of 0.10 M sodium thiosulfate, and twice with 20–mL portions of brine to give a single organic layer. The organic phase was dried ($MgSO_4$), and concentrated *in vacuo.* The residue was diluted with 30 mL of a 1:1 solution of CH_2Cl_2–hexanes and filtered through a 1-inch pad of Florisil (rinsed with 70 mL CH_2Cl_2–hexanes, 1:1). The solvent was removed *in vacuo* to afford 2.37 g (41%) of acetal **260** as a colorless oil: IR (neat) 3063 (m), 3030 (m), 2872 (m), 1117 (s), 1025 (s), 737 (s), 698 (s), 326 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.56 – 7.12 (m, 10H, CH), 4.81 (t, J = 5.3 Hz, 1H, CHO), 4.64 (d, J = 11.6 Hz, 2H, CH_2O), 4.53 (d, J = 11.6 Hz, 2H, CH_2O), 3.14 (t, J = 6.9 Hz, 2H, CH_2), 2.37 – 2.02 (m, 2H, CH_2I); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 137.68 (s, 2C), 128.31 (d, 4C), 127.61 (d, 6C), 102.01 (d), 68.02 (t, 2C), 37.28 (t), -0.03 (t).



261

1,1-Dibenzyloxy-3-bromopropane (261). To a solution of 1.0 mL (0.84 g, 15 mmol) of acrolein and 1.85 g (18.0 mmol) of sodium bromide in 40 mL of MeCN was added dropwise 2.3 mL (2.0 g, 18 mmol) of TMSCl at 0°C. After the yellow mixture stirred for 1 h, 3.7 mL (3.9 g, 36 mmol) of anhydrous benzyl alcohol was added in one

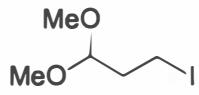
portion. The reaction mixture continued to stir for 1 h, and then was poured into 40 mL of saturated $NaHCO_{3(aq)}$ overlaid with 40 mL of pentane to produce three layers. The bottom aqueous phase was removed and the remaining two organic layers were washed with three 40–mL portions of brine to give a single organic layer. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was diluted with 30 mL of a 1:1 solution of CH_2Cl_2–hexanes and filtered through a 1–inch pad of Florisil (rinsed with 70 mL CH_2Cl_2–hexanes, 1:1). The solvent was removed *in vacuo* to afford 1.59 g (32%) of acetal **261** as a colorless oil: IR (neat) 3088 (w), 3064 (w), 3031 (m), 2873 (m), 1496 (m), 1454 (m), 1121 (s), 1052 (s), 1025 (s), 738 (s); ^{1}H NMR ($CDCl_3$, 250 MHz) δ 7.52 – 7.09 (m, 10H, CH=), 4.91 (td, J = 5.6, 2.7 Hz, 1H, CHO), 4.64 (dd, J = 11.7, 2.4 Hz, 2H, CH_2O), 4.52 (dd, J = 11.7, 2.4 Hz, 2H, CH_2O), 3.56 (td, J = 6.6, 2.1 Hz, 2H, $CH_2C\underline{H_2}Br$), 2.23 – 2.04 (m, 2H, $C\underline{H_2}CH_2Br$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 137.75 (s, 2C), 128.34 (d, 4C), 127.62 (d, 6C), 99.81 (d), 68.10 (t, 2C), 40.45 (t), 36.52 (t).



262

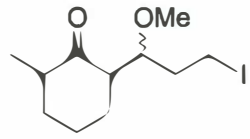
1,1-Dibenzyloxy-3-chloropropane (262). To a solution of 1.0 mL (0.84 g, 15 mmol) of acrolein and 1.05 g (18.0 mmol) of sodium chloride in 30 mL of MeCN was added dropwise 2.3 mL (2.0 g, 18 mmol) of TMSCl at 0°C. After the yellow mixture stirred for 1 h, 3.7 mL (3.9 g, 36 mmol) of anhydrous benzyl alcohol was added in one portion. The reaction mixture continued to stir for 1 h and then was poured into 20 mL of saturated $NaHCO_{3(aq)}$ overlaid with 20 mL of hexanes to produce three layers. The bottom aqueous phase was removed and the remaining two organic layers were washed with four 20–mL portions of brine to give a single organic layer. The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*. The residue was diluted with 30 mL of a 1:1 solution of CH_2Cl_2–hexanes and filtered through a 1-inch pad of Florisil (rinsed with 70 mL CH_2Cl_2–hexanes, 1:1). The solvent was removed *in vacuo* to afford 1.75 g (40%) of

acetal **262** as a colorless oil: IR (neat) 3088 (w), 3064 (m), 3031 (m), 2959 (m), 2925 (m), 2873 (m), 1121 (s), 1052 (s), 1025 (s), 737 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.50 – 7.03 (m, 10H, CH), 4.89 (t, J = 5.6 Hz, 1H, CHO), 4.60 (dd, J = 11.7, 3.0 Hz, 2H, CH_2), 4.48 (dd, J = 11.7, 3.0 Hz, 2H, CH_2), 3.51 (td, J = 6.6, 2.9 Hz, 2H, CH_2Cl), 2.20 – 1.98 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 137.65 (s, 2C), 128.19 (d, 4C), 127.48 (d, 6C), 99.67 (d), 67.93 (t, 2C), 40.33 (t), 36.38 (t).



263

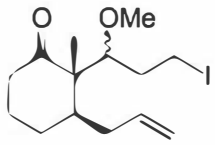
3-Iodo-1,1-dimethoxypropane (263).[127,181] To a solution of 1.2 mL (1.0 g, 18 mmol) of acrolein and 3.21 g (21.4 mmol) of sodium iodide in 45 mL of MeCN was added dropwise 2.7 mL (2.3 g, 21 mmol) of TMSCl at 0°C. After the yellow mixture stirred for 10 min, 2.39 g (42.7 mmol) of anhydrous methanol was added in one portion. The reaction mixture continued to stir for 10 min and then was poured into 40 mL of 5% saturated $NaHCO_{3(aq)}$ overlaid with 40 mL of pentane to yield three layers. The bottom aqueous phase was removed and the remaining two organic layers were washed successively with 20 mL of 0.10 M sodium thiosulfate, and twice with 20–mL portions of brine to give a single organic layer. The organic phase was dried ($MgSO_4$), and concentrated *in vacuo* to afford 1.86 g (45%) of acetal **263** as a colorless oil: ^1H NMR ($CDCl_3$, 250 MHz) δ 4.46 (t, J = 5.5 Hz, 1H, CH), 3.35 (s, 6H, CH_3), 3.17 (t, J = 7.1 Hz, 2H, CH_2I), 2.20 – 1.98 (m, 2H, CH_2); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 104.26, 53.36 (2C), 36.36, -0.21.



264

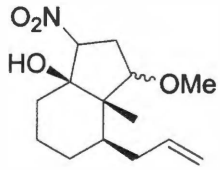
(±)-2-(3-Iodo-2-methoxypropyl)-6-methylcyclohexanone (264). To a solution of 380 mg (1.65 mmol) of acetal **263** in 20 mL of CH_2Cl_2 was added dropwise 0.14 mL (250 mg, 1.70 mmol) of titanium (IV) chloride at –78°C. After the mixture stirred for 5 min, a solution of 277 mg (1.50 mmol) of silyl enol ether **234** in 1 mL of CH_2Cl_2 was added. The reaction mixture was stirred for 2 h, warmed to room temperature, and quenched with 20 mL of saturated $Na_2CO_{3(aq)}$. After stirring for 5 min, the layers were separated and the aqueous phase was extracted twice with 20–mL portions of CH_2Cl_2. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 20 g of silica gel (eluted with CH_2Cl_2) to afford 377 mg (81%) of iodide **264** as four diastereomers and as a yellow oil, **Diastereomers 264A** (1:1): IR (neat) 2932 (m), 2867 (m), 2825 (m), 1707 (s), 1453 (m), 1375 (m), 1174 (m), 1089 (s), 331 (s), 314 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 3.78 – 3.61 (m, OCH), (3.42) (s, OCH_3), 3.38 (s, OCH_3), 3.34 – 3.19 (m), 2.75 – 2.60 (m), 2.51 – 2.32 (m), 2.31 – 2.18 (m), 2.17 – 1.62 (m), 1.52 – 1.23 (m), 1.01 (d, J = 6.4 Hz, CH_3), (1.02) (d, J = 6.4 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 212.61 (s), (212.38) (s), 79.42 (d), (78.56) (d), (59.18) (q), 58.04 (q), (54.42) (d), 52.05 (d), 45.84 (d, 2C), (37.64) (t), 36.88 (t, 2C), 35.69 (t), (29.66) (t), 28.85 (t), 25.20 (t, 2C), 14.34 (q, 2C), 2.56 (t), (2.16) (t); exact mass calcd. for $C_{11}H_{19}IO_2$ ($M^{\cdot+}$) *m/z* 310.0430, found *m/z* 310.0427.

Diastereomers 264B (3:1): ^1H NMR ($CDCl_3$, 250 MHz) δ 3.83 – 3.54 (m, OCH), (3.43) (s, OCH_3), 3.35 (s, OCH_3), 3.33 – 3.19 (m, CH_2), 2.75 – 2.40 (m), 2.18 – 1.61 (m), 1.61 – 1.42 (m), 1.10 (d, J = 6.7 Hz, CH_3), (1.08) (d, J = 6.7 Hz, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ (216.20) (s), 214.20 (s), 80.38 (d), (78.32) (d), (58.62) (q), 57.22 (q), (53.04) (d), 51.00 (d), (43.95) (d), 43.62 (d), (36.97) (t), 35.52 (t), 34.31 (t, 2C), 28.20 (t), (27.29) (t), 20.60 (t, 2C), 15.56 (q, 2C), 1.88 (t, 2C).



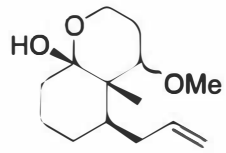
265

(±)-3-Allyl-2-(3-iodo-1-methoxypropyl)-2-methylcyclohexanone (265). To a solution of 402 mg (1.75 mmol) of methyl acetal **263** in 25 mL of CH_2Cl_2 was added dropwise 0.16 mL (280 mg, 1.90 mmol) of titanium (IV) chloride at -78°C. After the mixture stirred for 10 min, a solution of 327 mg (1.46 mmol) of silyl enol ether **177** in 1 mL of CH_2Cl_2 was added to the solution. The reaction mixture stirred for 1 h, warmed to room temperature, and was quenched with 20 mL of saturated $Na_2CO_{3(aq)}$. After stirring for 5 min, the layers were separated and the aqueous phase was extracted twice with 20-mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo.* The residue was chromatographed over 20 g of silica gel (eluted with hexanes-ethyl acetate, 10:1) to afford 377 mg (74%) of iodide **265** as a pale yellow oil: IR (neat) 3073 (w), 2938 (s), 2829 (m), 1703 (s), 1640 (m), 1458 (m), 1095 (s), 319 (s), 305 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.73 – 5.52 (m, CH=), 5.08 – 4.85 (m, CH_2=), 4.04 – 3.94 (m, CHO), 3.85 – 3.73 (m, CHO), 3.58 (s, CH_3O), 3.39 (s, CH_3O), 3.37 – 3.18 (m), 2.55 – 2.26 (m), 2.25 – 2.11 (m), 2.02 – 1.52 (m), 1.51 – 1.33 (m), 0.98 (s, CH_3), 0.93 (s, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 214.13 (s), 213.78 (s), 136.95 (d), 136.87 (d), 116.12 (t, 2C), 84.67 (d), 82.25 (d), 62.13 (q), 61.26 (q), 58.29 (s), 56.59 (s), 41.82 (d), 41.54 (d), 39.64 (t), 38.58 (t), 36.28 (t), 35.87 (t), 33.42 (t), 32.76 (t), 23.92 (t), 23.23 (t), 22.82 (t), 22.30 (t), 14.77 (q), 13.98 (q), 5.14 (t), 4.35 (t); exact mass calcd. for $C_{14}H_{23}O_2$ ($M^{\cdot+}$ – I) *m/z* 223.1698, found *m/z* 223.1698 (No $M^{\cdot+}$ observed).



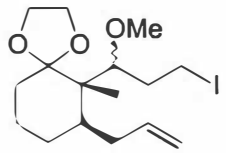
266

(±)-7-Allyl-1-methoxy-7a-methyl-3-nitrooctahydroinden-3a-ol (266). To a solution of 270 mg (0.771 mmol) of iodide **265** in 11 mL of DMF was added 96 mg (1.39 mmol) of sodium nitrite. The mixture was stirred overnight and then was poured into 80 mL of water overlaid with 20 mL of ether. The layers were separated and the aqueous phase was extracted three times with 40–mL portions of ether. The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo.* The residue was chromatographed over 20 g of silica gel (eluted with hexanes–ethyl acetate, 10:1) to afford 132 mg (63%) of **266** as a colorless oil: IR (neat) 3461 (m), 3075 (w), 2975 (m), 2939 (m), 2869 (m), 2830 (w), 1641 (m), 1553 (s), 1464 (m), 1442 (m), 1375 (m), 1339 (m), 1092 (s), 988 (m), 913 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.83 – 5.56 (m, CH=), 5.26 – 5.13 (m, $CHNO_2$), 5.07 – 4.86 (m, CH_2=), 3.83 (s, CHO), 3.70 (d, J = 5.4 Hz, CHO), 3.40 (s, CH_3O), 3.35 (s, CH_3O), 2.94 (m, OH), 2.45 – 2.27 (m), 2.24 – 1.94 (m), 1.87 – 1.62 (m), 1.58 – 1.36 (m), 1.27 – 1.09 (m), 1.07 (s, CH_3), 1.00 (s, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 138.73 (d), 137.09 (d), 116.36 (t), 115.09 (t), 88.10 (d), 88.86 (d, 2C), 85.15 (d), 84.06 (s), 82.91 (s), 58.41 (q), 57.00 (q), 53.47 (s), 50.95 (s), 39.92 (d), 37.97 (d), 36.97 (t), 36.12 (t), 30.66 (t), 29.76 (t), 29.56 (t), 28.21 (t), 26.84 (t), 25.55 (t), 21.68 (t, 2C), 11.97 (q), 8.43 (q); exact mass calcd. for $C_{14}H_{23}NO_4$ ($M^{\cdot+} - NO_2$) *m/z* 223.1698, found *m/z* 223.1671 (No $M^{\cdot+}$ observed).



267

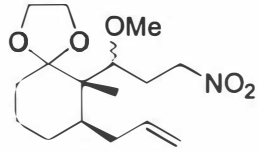
(±)-5-Allyl-4-methoxy-4a-methyloctahydrochromen-8a-ol (267). To a solution of 254 mg (0.73 mmol) of iodide **265** in 5 mL of ether was added 223 mg (1.45 mmol) of silver nitrite. After stirring for 4 days in the dark, the mixture was filtered, and then concentrated *in vacuo.* The residue was chromatographed over 20 g of silica gel (eluted with hexanes–ethyl acetate, 10:1 → ether) to afford 74.3 mg (42%) of hemiketal **267** as a yellow oil: IR (neat) 3456 (m), 3074 (w), 2937 (s), 2883 (m), 2831 (m), 1640 (m), 1555 (w), 1448 (m), 1126 (m), 1091 (m), 1058 (m), 1035 (m), 994 (m), 973 (m), 943 (m), 910 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.88 – 5.66 (m, CH=, OH), 5.08 – 4.90 (m, CH_2=), 4.18 – 3.97 (m, CHO), 3.72 – 3.49 (m, CH_2O), 3.41 (s, CH_3), 3.40 (s, CH_3), 2.23 – 1.87 (m), 1.80 – 1.18 (m), 1.08 (s, CH_3), 1.03 (s, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 138.13 (d), 137.83 (d), 115.61 (t), 115.23 (t), 99.28 (s, 2C), 81.60 (d), 79.78 (d), 57.89 (q), 56.97 (q), 54.62 (t, 2C), 43.16 (s), 42.97 (s), 38.83 (d), 35.63 (d), 34.27 (t), 33.99 (t), 33.50 (t), 32.31 (t), 26.15 (t), 25.63 (t), 23.11 (t), 22.91 (t), 21.48 (t, 2C), 15.17 (q), 13.28 (q); exact mass calcd. for $C_{13}H_{20}O_2$ ($M^{\cdot+}$ – $HOCH_3$) *m/z* 208.1463, found *m/z* 208.1472 (No $M^{\cdot+}$ observed).



268

(±)-7-Allyl-6-(3-iodo-1-methoxypropyl)-6-methyl-1,4-dioxaspiro[4.5]decane (268). To a solution of 326 mg (0.93 mmol) of iodide **265** in 10 mL of benzene was added 600 mg of ethylene glycol and a catalytic amount of p-TsOH. The mixture was stirred under reflux for 4 h in an apparatus equipped with a Dean-Stark trap. The mixture was cooled to room temperature, dried ($MgSO_4$), filtered over a 0.5-inch pad of silica gel

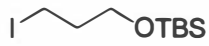
(rinsed with ether), and concentrated *in vacuo*. The residue was chromatographed over 20 g of silica gel (eluted with hexanes–ethyl acetate, 10:1) to afford 192 mg (52%) of ketal **268** as a pale-yellow oil: IR (neat) 3073 (w), 2932 (s), 2885 (s), 2829 (w), 1746 (w), 1705 (w), 1639 (w), 1443 (m), 1181 (m), 1095 (s), 1074 (s), 1047 (s), 997 (m), 951 (m), 910 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.89 – 5.63 (m, CH=), 5.11 – 4.88 (m, CH_2=), 4.19 – 3.86 (m, CH_2O), 3.52 (s, CH_3O), 3.50 (s, CH_3O), 3.49 – 3.21 (m, CHO), 2.61 – 2.29 (m), 2.06 – 1.17 (m), 1.09 (s, CH_3), 0.95 (s, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 138.96 (d), 138.01 (d), 115.02 (t), 114.91 (t), 112.94 (s), 112.76 (s), 84.15 (d), 83.67 (d), 64.24 (t), 64.05 (t), 63.78 (t), 63.60 (t), 62.63 (q), 61.02 (q), 49.38 (s), 48.91 (s), 39.41 (d), 38.87 (d), 38.58 (t), 38.16 (t), 35.82 (t), 35.60 (t), 30.81 (t), 30.24 (t), 26.34 (t), 25.45 (t), 22.34 (t), 21.34 (t), 14.13 (q), 12.85 (q), 7.44 (t), 6.59 (t); exact mass calcd. for $C_{16}H_{27}IO_3$ ($M^{\cdot+}$) *m/z* 394.1005, found *m/z* 394.1007.



269

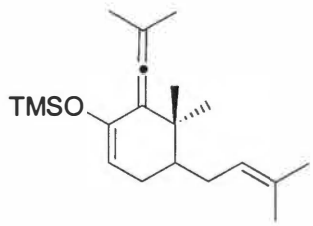
(±)-7-Allyl-6-(1-methoxy-3-nitropropyl)-6-methyl-1,4-dioxaspiro[4.5]decane (269). To a solution of 122 mg (0.31 mmol) of iodide **268** in 6 mL of DMF was added 43 mg (0.62 mmol) of sodium nitrite. After stirring for 16 h at room temperature, the solution was poured into 75 mL of water overlaid with 20 mL of ether. The layers were separated and the aqueous phase was extracted twice with 30–mL portions of ether. The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over 15 g of silica gel (eluted with hexanes–ethyl acetate, 10:1) to afford 36 mg (37%) of **269** as a colorless oil. Further elution provided 31 mg (25%) of starting material: IR (neat) 3074 (w), 2935 (s), 2868 (m), 2832 (w), 1640 (w), 1553 (s), 1441 (m), 1382 (m), 1182 (m), 1120 (m), 1087 (s), 1043 (m), 998 (m), 951 (m), 911 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.90 – 5.60 (m, CH=), 5.16 – 4.89 (m, CH_2=), 4.71 – 4.37 (m, CH_2NO_2), 4.16 – 3.72 (m, CH_2O), 3.63 – 3.24 (m, OCH_3, CHO), 2.60 – 2.30

(m), 2.29 – 2.05 (m), 2.04 – 1.13 (m), 1.09 (s, CH_3), 0.98 (s, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 138.81 (d), 137.81 (d), 115.24 (t), 115.14 (t), 112.84 (s), 112.66 (s), 81.92 (d), 81.35 (d), 74.39 (t), 73.88 (t), 64.20 (t), 64.10 (t), 63.79 (t), 63.67 (t), 62.56 (q), 60.74 (q), 49.47 (s), 48.86 (s), 39.73 (d), 38.64 (d), 35.73 (t), 35.52 (t), 33.11 (t), 32.14 (t), 30.15 (t), 29.89 (t), 26.32 (t), 25.55 (t), 22.29 (t), 21.30 (t), 13.83 (q), 12.76 (q); exact mass calcd. for $C_{16}H_{27}NO_5$ (M^{+}) *m/z* 298.1654, found *m/z* 298.1658.



273

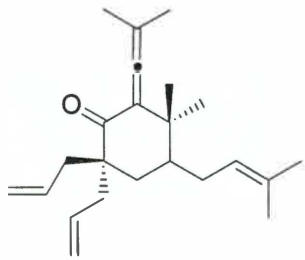
***tert*-Butyl-(3-iodopropoxy)-dimethylsilane (273).**[171,182] To a solution of 4.30 g (17.0 mmol) of (3-bromopropoxy)-*tert*-butyldimethylsilane in 60 mL of acetone was added 5.09 g (34.0 mmol) of sodium iodide.[159-161] The mixture stirred for 15 h at 40°C, was cooled to room temperature, and was concentrated *in vacuo*. The residue was chromatographed over 70 g of silica gel (eluted with hexanes–ethyl acetate, 50:1) to afford 4.83 g (95%) of iodide **273** as a colorless oil: ^{1}H NMR ($CDCl_3$, 250 MHz) δ 3.65 (t, J = 5.7 Hz, 2H, CH_2O), 3.26 (t, J = 6.7 Hz, 2H, CH_2I), 2.12 – 1.85 (m, 2H, CH_2), 0.88 (s, 9H, CH_3), 0.06 (s, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 62.29, 36.13, 25.94 (3C), 18.24, 3.56, -5.25 (2C).



275

[5,5-Dimethyl-4-(3-methylbut-2-enyl)-6-(2-methylpropenylidene)cyclohex-1-enyloxy]trimethylsilane (275). To a solution of 494 μL (356 mg, 3.52 mmol) of N,N-diisopropylamine in 12 mL of THF was added 2.52 mL (3.28 mmol) of *n*-butyllithium as

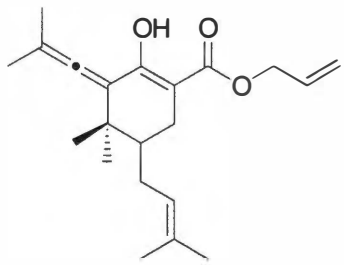
a 1.3 M solution in hexanes at –78°C. The resulting solution was stirred at –78°C for 10 min, was warmed to 0°C, stirred for 40 min, and recooled to –78°C. A solution of 620 mg (2.52 mmol) of ketone **161** in 1 mL of THF was added. The mixture was stirred for 40 min followed by addition of 420 μL (356 mg, 3.28 mmol) of TMSCl. After stirring for 1 h, the mixture was warmed to room temperature and was concentrated *in vacuo*. The residue was diluted with hexanes and filtered over a 1-inch pad of Florisil. The filter cake was rinsed with 50 mL of hexanes. The product was concentrated *in vacuo* to afford 768 mg (96%) of silyl enol ether **275** as a colorless oil: IR (neat) 3039 (w), 2964 (s), 2926 (s), 1925 (w), 1640 (m), 1250 (s), 1218 (s), 845 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.19 – 5.02 (m, 1H, HC=CMe), 4.88 (t, J = 4.3 Hz, 1H, HC=CO), 2.33 – 1.79 (m, 4H), 1.74 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.59 (s, 3H, CH_3), 1.45 – 1.24 (m, 1H), 1.08 (s, 3H, CH_3), 0.97 (s, 3H, CH_3), 0.14 (s, 9H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 199.33 (s), 144.99 (s), 131.77 (s), 124.33 (d), 110.02 (s), 105.81 (d), 99.26 (s), 43.46 (d), 37.32 (s), 27.90 (t), 25.80 (t), 25.45 (q, 2C), 24.02 (q), 20.91 (q, 2C), 17.79 (q), 0.024 (q, 3C); exact mass calcd. for $C_{20}H_{34}OSi$ ($M^{\cdot+}$) *m/z* 318.2379, found *m/z* 318.2370.



279

2,2-Diallyl-5,5-dimethyl-4-(3-methylbut-2-enyl)-6-(2-methylpropenylidene)-cyclohexanone (279). To a solution of 221 mg (0.694 mmol) of silyl enol ether **275** in 4 mL of THF was added *n*-butyllithium as a 1.3 M solution in hexanes at –78°C. The mixture stirred for 10 min, warmed to room temperature and stirred for 40 min. After the mixture was recooled to –78°C, 121 μL (168 mg, 1.39 mmol) of allyl bromide was added, and the resulting solution stirred for 3 h while slowly warming to 0°C. To the resulting

solution was added 0.50 mL of HMPA and the mixture stirred at room temperature for 16 h. The reaction was quenched by adding 4 mL of water. The aqueous layer was extracted twice with 4–mL portions of ether. The combined organic phases were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 10 g of silica gel (eluted with hexanes–ethyl acetate, 10:1) to afford 74 mg (37%) of **279** as a yellow oil: IR (neat) 3076 (w), 2966 (s), 2929 (s), 2870 (m), 1953 (w), 1684 (m), 1445 (m), 1386 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.85 – 5.55 (m, 2H, $\underline{H}C=CH_2$), 5.21 – 4.91 (m, 5H, $CH_2=$, CH=), 2.64 – 1.83 (m, 6H), 1.79 (s, 3H, CH_3), 1.75 (s, 3H, CH_3), 1.72 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.47 – 1.15 (m, 2H), 1.10 (s, 3H, CH_3), 1.06 – 0.95 (m, 1H), 0.92 (m, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 205.73 (s), 203.88 (s), 134.70 (d), 133.08 (d), 132.53 (s), 123.35 (d), 118.21 (t), 117.79 (t), 114.75 (s), 100.14 (s), 50.67 (s), 41.36 (t), 41.26 (d), 40.50 (t), 39.72 (s), 33.54 (t), 28.59 (t), 27.56 (q), 25.76 (q), 22.87 (q), 20.16 (q), 19.47 (q), 17.81 (q); exact mass calcd. for $C_{23}H_{34}O$ ($M^{\cdot+}$) *m/z* 326.2610, found *m/z* 326.2618.

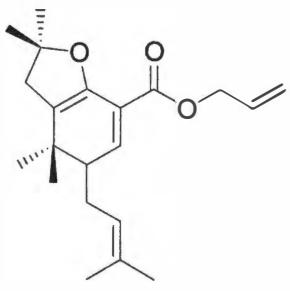


283

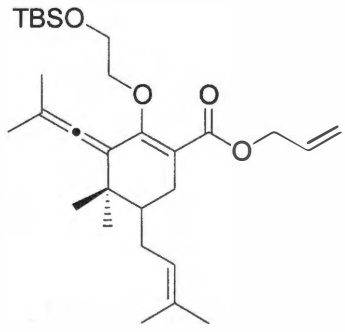
2-Hydroxy-4,4-dimethyl-5-(3-methylbut-2-enyl)-3-(2-methylpropenylidene)-cyclohex-1-ene carboxylic acid allyl ester (283). To a solution of 372 μL (268 mg, 2.65 mmol) of N,N-diisopropylamine in 10 mL of THF was added dropwise 2.0 mL (2.5 mmol) of *n*-BuLi as a 1.2 M solution in hexanes at –78°C. The solution was stirred at –78°C for 10 min, warmed to room temperature, stirred for 30 min, and recooled to –78°C. To the resulting solution was added 502 mg (2.04 mmol) of ketone **161** in 1 mL of THF. After the mixture was stirred for 1 h, 340 mg (3.06 mmol) of allyl cyanoformate (**280**) was added dropwise and the mixture stirred for 2.5 h. The reaction was quenched with 7

mL of a 10% (v/v) solution of $NH_4Cl_{(aq)}$. After stirring for 5 min, the aqueous phase was extracted twice with 10–mL portions of ether. The combined organic fractions were dried ($MgSO_4$) and concentrated *in vacuo*. The crude material was chromatographed over 40 g of silica gel (eluted with hexanes–ethyl acetate, 20:1) to afford 422 mg (63%) of a 2.1:1 mixture of enol – keto tautomers as a colorless oil. Enol **283**: IR (neat) 3085 (m), 2968 (s), 2927 (s), 2867 (m), 1952 (m), 1748 (m), 1645 (s), 1602 (s), 1447 (m), 1383 (s), 1297 (s), 1281 (s), 1252 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 12.13 (s, 1H, OH), 6.07 – 5.88 (m, 1H, C<u>H</u>=CH_2), 5.33 (d, J = 17.4 Hz, 1H, CH_2=), 5.24 (d, J = 10.5 Hz, 1H, CH_2=), 5.12 (t, J = 7.0 Hz, 1H, CH=), 4.78 – 4.57 (m, 2H, OCH_2), 2.47 (dd, J = 16.7, 4.9 Hz, 1H), 2.25 – 2.05 (m, 2H), 1.83 (s, 3H, CH_3), 1.82 (s, 3H, CH_3), 1.71 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.54 – 1.38 (m, 2H), 1.11 (s, 3H, CH_3), 0.98 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 202.32 (s), 172.03 (s), 164.21 (s), 132.28 (s), 132.16 (d), 123.47 (d), 117.41 (t), 107.45 (s), 101.15 (s), 95.95 (s), 64.59 (t), 42.96 (d), 36.82 (s), 27.63 (t), 25.72 (q), 24.30 (t), 23.66 (q), 20.12 (q), 19.99 (q), 17.65 (q), 14.01 (q); exact mass calcd. for $C_{21}H_{30}O_3$ ($M^{\cdot+}$) *m/z* 330.2195, found *m/z* 330.2202.

Anal. calcd. for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15; found: C, 76.38; H, 9.11.



284

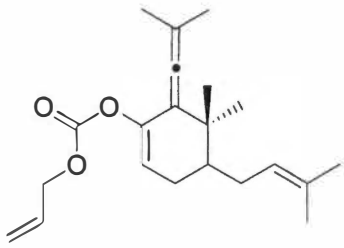


285

2,2,4,4-Tetramethyl-5-(3-methylbut-2-enyl)-2,3,4,5-tetrahydrobenzofuran-7-carboxylic acid allyl ester (284). 2-[2-(*tert*-butyldiphenylsilanyloxy)ethoxy]-4,4-dimethyl-5-(3-methylbut-2-enyl)-3-(2-methylpropenylidene)cyclohex-1-ene carboxylic acid allyl ester (285). To a solution of 74 mg (0.224 mmol) of enol **283** in 3 mL of THF was slowly added 8.1 mg (0.34 mmol) of sodium hydride in portions as a

60% dispersion in mineral oil. The reaction stirred for 1 h and then 97 mg (0.34 mmol) of iodide 29 was added. After the mixture was stirred under reflux for 4 h, 10 drops of HMPA was added. The mixture continued to stir under reflux overnight. The reaction was quenched by cooling to room temperature and adding 5 mL of water. The aqueous phase was extracted twice with 5–mL portions of ether. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed over 2 g of silica gel (eluted with hexanes–ethyl acetate, 50:1 → 10:1) to afford 41 mg (42%) of silyl ether **285** as a colorless oil: IR (neat) 3085 (w), 2958 (s), 2930 (s), 2885 (m), 2859 (m), 2736 (w), 1950 (w), 1716 (m), 1696 (m), 1648 (w), 1610 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.11 – 5.82 (m, 1H, C<u>H</u>=CH_2), 5.34 (dd, *J* = 17.2, 1.5 Hz, 1H, CH_2=), 5.22 (dd, *J* = 10.4, 1.5 Hz, 1H, CH_2=), 5.17 – 5.08 (m, 1H, CH=), 4.64 (dd, *J* = 4.5, 1.2 Hz, 2H, C=CCH_2O), 3.81 (s, 4H, CH_2O), 2.54 (dd, *J* = 17.9, 5.1 Hz, 1H), 2.16 (m, 2H), 1.77 (s, 3H, CH_3), 1.76 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.53 – 1.10 (m, 2H), 1.07 (s, 3H, CH_3), 0.96 (s, 3H, CH_3), 0.89 (s, 9H, CCH_3), 0.05 (s, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 201.90, 166.91, 157.07, 132.78, 123.45, 117.80, 112.73, 108.39, 100.21, 73.80, 64.91, 62.25, 42.92, 37.14, 27.86 (3C), 25.94 (3C), 24.58, 23.38, 20.30, 18.38, 17.87 (2C), -5.30 (2C), (one carbon was not observed); exact mass calcd. for $C_{29}H_{48}O_4Si$ ($M^{\cdot+}$) *m/z* 431.2618, found *m/z* 431.2628.

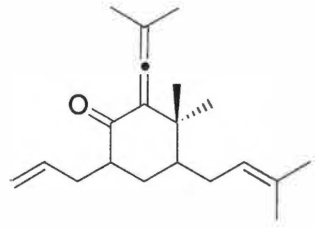
Continued elution provided 35.2 mg (48%) of material tentatively assigned the structure **284** as a colorless oil: IR (neat) 3083 (w), 2972 (m), 2031 (m), 2872 (m), 1681 (s), 1642 (s), 1624 (m), 1457 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.16 (s, 1H, CH=), 6.10 – 5.89 (m, 1H, C<u>H</u>=CH_2), 5.43 (dd, *J* = 17.2, 1.5 Hz, 1H, CH_2=), 5.20 (dd, *J* = 10.5, 1.5 Hz, 1H, CH_2=), 5.15 – 5.06 (m, 1H, CH=), 4.66 (d, *J* = 4.7 Hz, 2H, CH_2O), 2.73 – 2.50 (m, 1H), 2.24 – 2.02 (m, 2H), 1.69 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.452 (s, 3H, CH_3), 1.454 (s, 3H, CH_3), 1.19 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 0.93 – 0.79 (m, 2H); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 166.69 (s), 165.38 (s), 143.90 (s), 136.69 (d), 133.17 (d), 132.39 (s), 123.44 (d), 116.23 (t), 94.29 (s), 92.46 (s), 63.94 (t), 43.93 (d), 34.88 (s), 27.25 (t), 26.88 (q), 26.49 (q), 26.10 (q), 25.77 (q), 22.87 (q), 17.75 (q), (one triplet was not observed); exact mass calcd. for $C_{21}H_{30}O_3$ ($M^{\cdot+}$) *m/z* 330.2195, found *m/z* 330.2198.



286

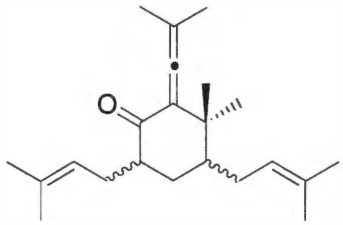
Carbonic allyl ester 5,5-dimethyl-4-(3-methylbut-2-enyl)-6-(2-methylprop-enylidene)cyclohex-1-enyl ester (286). To a solution of 332 μL (239 mg, 2.36 mmol) of N,N-diisopropylamine in 7 mL of THF was added dropwise *n*-BuLi as a 1.3 M solution in hexanes at –78°C. The solution was stirred at –78°C for 10 min, was warmed to room temperature, stirred for 30 min, and recooled to –78°C. To the resulting solution was added 415 mg (1.69 mmol) of ketone **161** in 1 mL of THF. After the mixture was stirred for 1 h, 249 μL (284 mg, 2.36 mmol) of allyl chloroformate was added dropwise and the mixture continued to stir for 1.5 h. The reaction was quenched by warming to room temperature, adding 5 mL of water, and then stirring for 5 min. The layers were separated, and the aqueous phase was extracted twice with 10–mL portions of ether. The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 20 g of silica gel (eluted with hexanes–CH_2Cl_2, 1:1) to afford 457 mg (82%) of allyl enol carbonate **286** as a colorless oil: IR (neat) 3087 (w), 2968 (m), 2922 (m), 1955 (w), 1762 (s), 1659 (w), 1449 (m), 1384 (m), 1364 (m), 1240 (s), 1191 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 6.05 – 5.81 (m, 1H, $HC{=}CH_2$), 5.47 – 5.21 (m, 3H, $C{=}CH_2$, $CH{=}CO$), 5.16 – 5.02 (m, 1H, $HC{=}CCH_3$), 4.63 (t, J = 1.3 Hz, 1H, OCH_2), 4.61 (t, J = 1.3 Hz, 1H, OCH_2), 2.32 (dt, J = 18.2, 4.7 Hz, 1H), 2.22 – 2.06 (m, 1H), 2.05 – 1.78 (m, 2H), 1.70 (s, 9H, CH_3), 1.59 (s, 3H, CH_3), 1.54 – 1.38 (m, 1H), 1.12 (s, 3H, CH_3), 1.01 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 197.42 (s), 153.24 (s), 143.17 (s), 132.32 (s), 131.62 (d), 123.67 (d), 118.52 (t), 113.94 (s), 113.3 (d), 101.74 (s), 68.37 (t), 42.94 (d), 37.36 (s), 27.72 (t), 27.34 (q), 26.09 (t), 25.76 (q), 23.38 (q), 20.47 (q, 2C), 17.75 (q); exact mass calcd. for $C_{17}H_{25}O$ ($M^{\cdot+}$ – $C_4H_5O_2$) *m/z* 245.1905, found *m/z* 245.1907 (No $M^{\cdot+}$ observed).

Anal. calcd. for $C_{21}H_{30}O_3$: C, 76.33; H, 9.15; found: C, 76.30; H, 9.08.



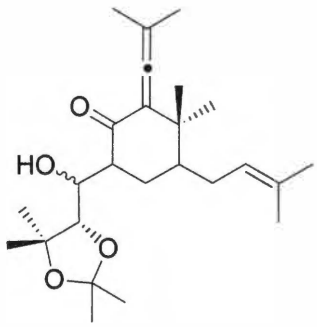
287

6-Allyl-3,3-dimethyl-4-(3-methylbut-2-enyl)-2-(2-methylpropenylidene)cyclohexanone (287). To a solution of 199 mg (602 μmol) of carbonate **286** in 4 mL of dimethoxyethane was added 62.2 mg (0.0602 μmol, 10 mol%) of dipalladium trisbenzylideneacetone chloroform complex [$Pd_2(dba)_3 \cdot CHCl_3$] in a single portion followed by 63 mg (241 μmol, 40 mol%) of triphenylphosphine. The reaction mixture was stirred for 5 h while warming to room temperature and then was filtered over a 1.5–inch pad of silica gel (rinsed with 120 mL of hexanes–CH_2Cl_2, 1:1). The filtrate was concentrated *in vacuo*, and the residue was chromatographed over 70 g of silica gel (eluted with hexanes → hexanes–ethyl acetate, 20:1) to afford 100 mg (58%) of **287** as a peach oil: IR (neat) 3076 (w), 2968 (s), 2926 (s), 2869 (s), 1954 (w), 1719 (m), 1686 (s), 1641 (w), 1445 (m), 1388 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.88 – 5.57 (m, 1H, C<u>H</u>=CH_2), 5.24 – 4.93 (m, 3H, CH=, CH_2=), 2.63 – 2.06 (m, 5H), 2.07 – 1.83 (m, 3H), 1.78 (s, 6H, CH_3), 1.71 (s, 3H, CH_3), 1.61 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 1.02 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 203.94 (s), 203.79 (s), 136.03 (d), 132.38 (s), 123.27 (d), 116.56 (t), 113.39 (s), 100.29 (s), 45.31 (d), 42.22 (d), 39.73 (s), 35.31 (t), 29.68 (q), 28.06 (t), 27.69 (t), 25.76 (q), 25.01 (q), 19.97 (q), 19.74 (q), 17.82 (q); exact mass calcd. for $C_{20}H_{30}O$ ($M^{\cdot+}$) *m/z* 286.2297, found *m/z* 286.2298.



288

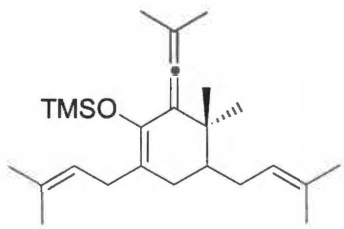
(±)-3,3-Dimethyl-4,6-bis-(3-methylbut-2-enyl)-2-(2-methylpropenylidene)-cyclohexanone (288). To a solution of 992 mg (3.46 mmol) of **287** in 50 mL of 2-methyl-2-butene was added 294 mg (0.346 mmol, 10 mol%) of the second generation Grubbs' catalyst [(1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro-(phenylmethyl-ene)(tricyclohexylphosphine)ruthenium] (**71**) at room temperature. After stirring for 1 h under reflux (38°C), the mixture was cooled to room temperature and then filtered over a 1.5-inch pad of silica gel (rinsed with 150 mL of hexanes–ethyl acetate, 10:1). The solvent was removed *in vacuo* and the residue was chromatographed over 70 g of silica gel (eluted with hexanes–ethyl acetate, 20:1) to afford 966 mg (89%) of ketone **288** as diastereomers (ratio 1.8:1) as a red oil: IR (neat) 2966 (s), 2926 (s), 2860 (m), 2728 (w), 1953 (w), 1688 (m), 1618 (w), 1449 (m), 1386 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.22 – 4.99 (m, CH=), 2.60 – 2.05 (m), 2.04 – 1.53 (m), 1.80 (s, CH_3), 1.78 (s, CH_3), 1.75 (s, CH_3), 1.72 (s, CH_3), 1.69 (s, CH_3), 1.61 (s, CH_3), 1.39 – 1.05 (m), 1.13 (s, CH_3), 1.12 (s, CH_3), 1.01 (s, CH_3), 0.94 (s, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 204.46 (s, 2C), 203.69 (s, 2C), 133.10 (s), 132.75 (s), 132.51 (s), 132.22 (s), 123.43 (d), 123.33 (d), 121.92 (d), 121.77 (d), 115.48 (s), 113.49 (s), 100.13 (s, 2C), 50.07 (d), 46.31 (d), 45.55 (d), 42.15 (d), 39.71 (s), 39.61 (s), 30.43 (t), 29.49 (q, 2C), 29.42 (t), 29.03 (t), 28.70 (t), 28.12 (t), 27.76 (t), 27.67 (q, 2C), 25.74 (q, 4C), 24.84 (q), 23.38 (q), 19.92 (q, 2C), 19.78 (q), 19.48 (q), 17.79 (q, 2C); exact mass calcd. for $C_{22}H_{34}O$ ($M^{\cdot+}$) *m/z* 314.2610, found *m/z* 314.2624.



294

6-[Hydroxy-(2,2,5,5-tetramethyl[1.3]dioxolan-4-yl)methyl]-3,3-dimethyl-4-(3-methylbut-2-enyl)-2-(2-methylpropylidene)cyclohexanone (294). To a solution of 104 μL (75 mg, 0.74 mmol) of N,N-diisopropylamine in 4 mL of THF was added dropwise 0.57 mL (0.69 mmol) of a 1.2 M solution of *n*-BuLi in hexanes at –78°C. The resulting solution was stirred at -78°C for 10 min, warmed to 0°C, stirred for 40 min, and recooled to -78°C. To the resulting solution was added a solution of 130 mg (0.53 mmol) of ketone **161** in 1 mL of THF. The mixture was stirred for 30 min at -78°C, was warmed to room temperature, stirred for 30 min, and then recooled to -78°C. To the reaction mixture was added a solution of 125 mg (0.79 mmol) of (4R)-2,2,5,5-tetramethyl[1.3]dioxolane-4-carbaldehyde[149] **(293)** in 1 mL of THF. After stirring for 3.5 h, the reaction was quenched with 5 mL of water and warmed to room temperature. The layers were separated and the aqueous phase was extracted twice with 5–mL portions of ether. The combined organic layers were dried ($MgSO_4$) and concentratrated *in vacuo.* The residue was chromatographed over 20 g of silica gel (eluted with hexanes-ethyl acetate, 10:1) to afford 134 mg (63%) of alcohol **294** as a colorless oil: IR (neat) 3450 (m), 2977 (s), 2933 (s), 2872 (m), 1950 (w), 1728 (w), 1667 (m), 1456 (m), 1375 (s), 1271 (m), 1230 (s), 1220 (s), 1196 (s), 1047 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.28 – 5.11 (m, CH=), 4.49 – 4.36 (m, CHO), 3.66 (s, CHO), 3.62 (s, CHO), 2.83 – 2.56 (m), 2.44 – 2.15 (m), 2.14 – 1.88 (m), 1.81 (s, CH_3), 1.80 (s, CH_3), 1.77 (s, CH_3), 1.75 (s, CH_3), 1.72 (s, CH_3), 1.64 (s, CH_3), 1.38 (s, CH_3), 1.37 (s, CH_3), 1.32 (s, CH_3), 1.31 (s, CH_3), 1.25 (s, CH_3), 1.16 (s, CH_3), 1.15 (s, CH_3), 1.06 (s, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 206.19 (s), 205.61 (s), 203.21 (s), 135.47 (s), 134.81 (s), 132.50 (s), 132.40 (s), 129.73 (s), 127.69 (s), 127.58 (s), 123.43 (d), 123.01 (d), 122.88 (d), 113.09 (s), 106.59 (s), 100.66 (s),

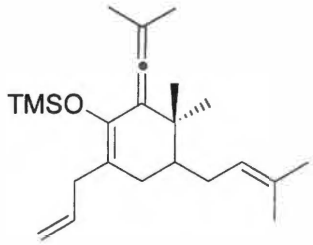
83.19 (d), 81.19 (d), 80.98 (d), 80.21 (d), 72.93 (d), 68.46 (d), 68.14 (d), 47.68 (d), 43.33 (d), 43.01 (d), 39.68 (s), 31.51 (t), 30.60 (q), 28.38 (q), 28.18 (q), 27.54 (q), 27.32 (t), 27.06 (t), 26.98 (q), 26.81 (q), 26.63 (q), 26.36 (q), 25.87 (q), 25.60 (q), 23.75 (q), 22.78 (q), 22.57 (t), 22.43 (q), 21.38 (t), 20.32 (q), 20.14 (q), 19.38 (q), 17.69 (q), 14.03 (q); exact mass calcd. for $C_{25}H_{38}O_3$ ($M^{\cdot+} - H_2O$) *m/z* 386.2821, found *m/z* 386.2816 (No $M^{\cdot+}$ observed).



295

[5,5-Dimethyl-2,4-bis-(3-methylbut-2-enyl)-6-(2-methylpropenylidene)cyclohex-1-enyloxy]trimethylsilane (295). To a solution of 110 μL (79 mg, 0.779 mmol) of N,N-diisopropylamine in 5 mL of THF was added 0.45 mL (0.723 mmol) of *n*-butyllithium as a 1.6 M solution in hexanes at –78°C. The resulting solution was stirred at –78°C for 10 min, was warmed to 0°C, stirred for 30 min, and recooled to –78°C. A solution of 175 mg (0.556 mmol) of ketone **288** in 1 mL of THF was added. The mixture was stirred for 1.5 h followed by addition of 100 μL (85 mg, 0.779 mmol) of TMSCl. After stirring for 1 h, the mixture was warmed to room temperature and was concentrated *in vacuo*. The residue was diluted with 10 mL of a 50:1 hexanes–ethyl acetate solution and filtered over a 1-inch pad of Florisil. The filter cake was rinsed with 75 mL of 50:1 hexanes–ethyl acetate. The product was concentrated *in vacuo* to afford 165 mg (77%) of silyl enol ether **295** as a colorless oil: IR (neat) 2967 (s), 2914 (s), 2729 (w), 1950 (w), 1670 (w), 1642 (m), 1249 (s), 875 (s), 844 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.17 – 4.94 (m, 2H, CH=), 2.93 – 2.64 (m, 2H), 2.38 – 1.97 (m, 2H), 1.96 – 1.55 (m, 2H), 1.74 (s, 6H, CH_3), 1.73 (s, 3H, CH_3), 1.70 (s, 3H, CH_3), 1.64 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.44 – 1.25 (m, 1H), 1.06 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.16 (s, 9H, CH_3); ^{13}C NMR

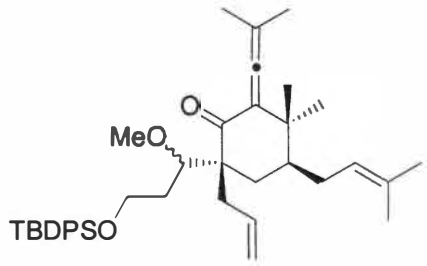
($CDCl_3$, 62.9 MHz) δ 199.46 (s), 138.89 (s), 132.10 (s), 131.82 (s), 124.49 (d), 122.40 (d), 116.85 (s), 110.89 (s), 99.54 (s), 43.52 (d), 37.80 (s), 29.90 (t, 2C), 28.21 (q), 27.98 (t), 25.78 (q, 2C), 24.43 (q), 21.32 (q), 21.08 (q), 17.83 (q, 2C), 0.40 (q, 3C); exact mass calcd. for $C_{25}H_{42}OSi$ ($M^{\cdot+}$) *m/z* 386.3005, found *m/z* 386.3011.



296

[2-Allyl-5,5-dimethyl-4-(3-methylbut-2-enyl)-6-(2-methylpropenylidene)-cyclohex-1-enyloxy]trimethylsilane (296). To a solution of 181 μL (130 mg, 1.28 mmol) of N,N-diisopropylamine in 5 mL of THF was added 0.99 mL (1.18 mmol) of *n*-butyllithium as a 1.2 M solution in hexanes at -78°C. The resulting solution was stirred at -78°C for 10 min, was warmed to 0°C, stirred for 40 min, and recooled to -78°C. A solution of 262 mg (0.91 mmol) of ketone **287** in 1 mL of THF was added. The mixture was stirred for 1 h and then 151 μL (128 mg, 1.18 mmol) of TMSCl was added dropwise. After stirring for 1 h, the mixture was warmed to room temperature and concentratrated *in vacuo*. The residue was chromatographed over 20 g of silica gel (eluted with hexanes → hexanes-ethyl acetate, 50:1) to afford 292 mg (90%) of silyl enol ether **296** as a colorless oil: IR (neat) 3077 (m), 2967 (s), 2926 (s), 2729 (w), 1950 (w), 1675 (m), 1645 (m), 1447 (m), 1384 (s), 1249 (s), 1235 (s), 843 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.81 – 5.64 (m, 1H, C<u>H</u>=CH_2), 5.15 – 4.92 (m, 3H, CH_2=, CH=), 2.86 (d, J = 6.4 Hz, 1H, CH), 2.26 – 2.00 (m, 2H), 1.93 – 1.77 (m, 2H), 1.74 (s, 3H, CH_3), 1.73 (s, 3H, CH_3), 1.69 (s, 3H, CH_3), 1.57 (s, 3H, CH_3), 1.45 – 1.22 (m, 2H), 1.06 (s, 3H, CH_3), 0.95 (s, 3H, CH_3), 0.16 (s, 9H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 199.52 (s), 139.77 (s), 136.42 (d), 131.71 (s), 124.33 (d), 115.22 (t), 115.06 (s), 110.75 (s), 99.74 (s), 43.53 (d), 37.82 (s), 35.51 (t), 29.97 (t), 28.03 (q), 27.98 (t), 25.79 (q), 24.26 (q), 21.27 (q), 21.06

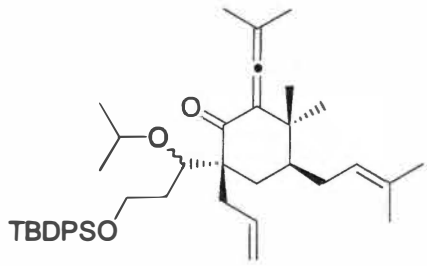
(q), 17.84 (q), 0.40 (q, 3C); exact mass calcd. for $C_{23}H_{38}OSi$ ($M^{\cdot+}$) *m/z* 358.2692, found *m/z* 358.2707.



298

2-Allyl-2-[3-(*tert*-butyldiphenylsilanyloxy)-1-methoxypropyl]-5,5-dimethyl-4-(3-methylbut-2-enyl)-6-(2-methylpropenylidene)cyclohexanone (298). To a solution of 69 mg (0.19 mmol) of methyl acetal **255** in 4 mL of CH_2Cl_2 was added dropwise 17 μL (29 mg, 0.19 mmol) of titanium (IV) chloride at -78°C. After the mixture stirred for 10 min, a solution of 53 mg (0.15 mmol) of silyl enol ether **296** in 1 mL of CH_2Cl_2 was added. The reaction mixture stirred for 2 h, was warmed to room temperature, and quenched with 3 mL of saturated $Na_2CO_{3(aq)}$. After stirring for 5 min, the layers were separated and the aqueous phase was extracted twice with 5-mL portions of ethyl acetate. The combined organic layers were washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 20 g of silica gel (eluted with hexanes-ethyl acetate, 50:1) to afford 27 mg (29%) of **298** as a colorless oil: IR (neat) 3072 (w), 2963 (s), 2932 (s), 2860 (m), 1952 (w), 1725 (w), 1682 (m), 1641 (w), 1459 (m), 1430 (m), 1387 (m), 1110 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 7.74 – 7.58 (m, Ph), 7.49 – 7.27 (m, Ph), 5.94 – 5.64 (m, C<u>H</u>=CH_2), 5.22 – 4.94 (m, CH=, CH_2=), 4.02 (t, J = 5.9 Hz, CHO), 3.96 – 3.69 (m, CH_2O), 3.64 (s, OCH_3), 3.59 (s, OCH_3), 3.21 (OCH_3), 2.68 – 2.52 (m), 2.50 – 2.12 (m), 2.11 – 1.90 (m), 1.80 (s, CH_3), 1.75 (s, CH_3), 1.73 (s, CH_3), 1.61 (s, CH_3), 1.43 – 1.21 (m), 1.12 (s, CH_3), 1.05 (s, CH_3), 1.04 (s, CH_3), 1.02 (s, CH_3), 0.97 (s, CH_3), O.94 (s, CH_3); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 203.86, 203.16, 201.74, 136.42, 135.51, 135.11, 134.77, 133.23, 130.59, 129.77, 129.56, 128.65, 128.40, 128.28, 127.73, 127.03, 126.64, 123.40, 116.33, 115.48, 100.50, 80.28, 60.69, 60.11, 58.26, 51.56, 49.82,

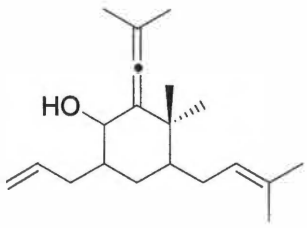
49.28, 46.34, 45.62, 42.61, 40.59, 39.67, 34.70, 33.51, 30.40, 28.73, 27.68, 26.75, 26.13, 25.81, 25.26, 23.52, 22.62, 20.63, 20.04, 19.52, 19.11, 18.30, 17.84; exact mass calcd. for $C_{40}H_{56}O_3Si$ ($M^{\cdot+}$) *m/z* 555.3294, found *m/z* 555.3293.



299

2-Allyl-2-[3-(*tert*-butyldiphenylsilanyloxy)-1-isoporpoxypropyl]-5,5-dimethyl-4-(3-methylbut-2-enyl)-6-(2-methylpropenylidene)cyclohexanone (299). To a stirred solution of 47 μL (46 mg, 0.16 mmol) of titanium (IV) isopropoxide in 2 mL of CH_2Cl_2 cooled to -78°C was added dropwise 14 μL (24 mg, 0.16 mmol) of titanium (IV) chloride. After the solution stirred for 10 min, a solution of 44 mg (0.12 mmol) of silyl enol ether **296** and 48 mg (0.14 mmol) of methyl acetal **255** in 1 mL of CH_2Cl_2 was added dropwise. The resulting solution stirred for 5 h, warmed to room temperature, and was slowly quenched with 2 mL of saturated $Na_2CO_{3(aq)}$. After stirring for 10 min, the layers were separated and the aqueous phase was extracted twice with 4-mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over 2 g of silica gel (eluted with hexanes-ethyl acetate, 50:1) to afford 53 mg (62%) of **299** as a 1:1 mixture of diastereomers that were a colorless oil: IR (neat) 3072 (m), 2964 (s), 2932 (s), 2860 (s), 2730 (w), 1954 (w), 1728 (m), 1687 (m), 1615 (w), 1463 (m), 1429 (m), 1385 (m), 1109 (s) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 7.82 – 7.53 (m, Ph), 7.52 – 7.19 (m, Ph), 5.92 – 5.61 (m, C<u>H</u>=CH_2), 5.20 – 4.92 (m, CH=, CH_2=), 4.02 (t, *J* = 6.0 Hz, HCO), 3.91 – 3.61 (m, CH_2O), 2.66 – 2.55 (m, CH_3C<u>H</u>O), 2.38 – 2.12 (m), 2.08 – 1.56 (m), 1.81 (s, CH_3), 1.70 (s, CH_3), 1.68 (s, CH_3), 1.60 (s, CH_3), 1.55 – 0.74 (m); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 204.43 (s), 203.91 (s), 201.73 (s, 2C), 135.98 (d, 2C), 135.53 (d, 8C), 133.71 (s, 2C), 132.89 (s, 2C),

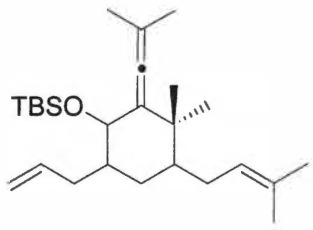
129.78 (d, 2C), 129.58(d, 2C), 127.74 (d, 4C), 127.61 (d, 4C), 123.74 (d), 123.12 (d), 119.01 (t), 117.21 (t) 116.32 (s), 115.61 (s), 99.93 (s), 99.64 (s), 77.65 (d), 75.49 (d), 71.45 (d), 69.01 (d), 60.19 (t), 58.27 (t), 55.23 (s, 2C), 46.35 (t, 2C), 40.43 (s, 2C), 40.13 (d, 2C), 36.91 (t), 35.58 (t), 32.46 (t), 31.56 (t), 30.13 (t), 29.84 (t), 26.78 (q, 6C), 25.83 (q, 2C), 24.51 (q), 23.62 (q), 22.90 (q, 2C), 22.62 (q, 2C), 19.90 (q, 2C), 19.57 (q, 2C), 19.16 (s, 2C), 17.94 (q, 2C), 14.08 (q, 2C) (two singlets not observed); exact mass calcd. for $C_{42}H_{60}O_3Si$ ($M^{\cdot+}$) *m/z* 640.4312, found *m/z* 640.4310.



300

6-Allyl-3,3-dimethyl-4-(3-methylbut-2-enyl)-2-(2-methylpropenylidene)cyclohexanol (300). To a solution of 142 mg (0.497 mmol) of ketone **287** in 3 mL of methanol was added 194 mg (0.523 mmol) of $CeCl_3 \cdot 7H_2O$ at 0°C. After stirring for 10 min, 19.8 mg (0.523 mmol) of sodium borohydride was added in portions. The reaction mixture was stirred for 1 h and then was quenched with 5 mL of water. After stirring for 5 min, the layers were separated and the aqueous phase was extracted twice with 10–mL portions of ether. The combined organic layers were dried ($MgSO_4$), and concentrated *in vacuo*. The residue was chromatographed over silica gel (eluted with hexanes–ethyl acetate, 10:1) to afford 118 mg (82%) of alcohol **300** as a pale yellow oil: IR (neat) 3539 (w), 3469 (w), 3074 (w), 2969 (s), 2929 (s), 2877 (m), 1640 (w), 1449 (m), 1383 (m), 1074 (m), 1025 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.90 – 5.61 (m, 1H, HC=CH_2), 5.16 – 4.87 (m, 3H, HC=C, H_2C=), 4.31 (t, J = 5.2 Hz, 1H, CHO), 2.34 – 2.18 (m, 1H), 2.17 – 2.01 (m, 2H), 1.94 – 1.80 (m, 3H), 1.76 (s, 6H, CH_3), 1.67 (s, 3H, CH_3), 1.58 (s, 3H, CH_3), 1.35 – 1.05 (m, 3H), 1.07 (s, 3H, CH_3), 0.98 (s, 3H, CH_3); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 192.33 (s), 137.99 (d), 131.80 (s), 123.89 (d), 115.30 (t), 113.69 (s), 103.11 (s), 68.24 (d), 41.37 (d), 40.01 (d), 38.30 (s), 29.43 (t), 28.60 (t), 28.49 (t), 27.67 (q),

25.70 (q), 21.44 (q), 21.34 (q), 21.00 (q), 17.76 (q); exact mass calcd. for $C_{20}H_{32}O$ ($M^{\cdot+}$) *m/z* 288.2453, found *m/z* 288.2453.



301

[6-Allyl-3,3-dimethyl-4-(3-methylbut-2-enyl)-2-(2-methylpropenylidene)-cyclohexyloxy]-*tert*-butyldimethylsilane (301). To a solution of 112 mg (388 μmol) of alcohol **300** in 3 mL of CH_2Cl_2 was added 90 μL (83 mg, 780 μmol) of 2,6-lutidine and 134 μL (154 mg, 582 μmol) of TBSOTf at 0°C. The reaction mixture stirred for 3 h and was quenched by adding 3 mL of water. After stirring for 5 min, the layers were separated and the aqueous phase was extracted twice with 5–mL portions of CH_2Cl_2. The combined organic layers were dried ($MgSO_4$) and concentrated *in vacuo.* The residue was chromatographed over 2 g of silica gel (eluted with hexanes) to afford 156 mg (100%) of silyl ether **301** as a colorless oil: IR (neat) 3076 (w), 2959 (s), 2930 (s), 2858 (s), 1640 (w), 1252 (m), 1126 (m), 1073 (m), 1027 (m), 1003 (m), 909 (w), 838 (s), 776 (m) cm^{-1}; ^1H NMR ($CDCl_3$, 250 MHz) δ 5.84 – 5.66 (m, 1H, C<u>H</u>=CH_2), 5.11 – 4.25 (m, 3H, CH=, CH_2=), 4.28 (d, J = 3.6 Hz, 1H, CHO), 2.37 – 2.17 (m, 1H), 2.17 – 2.00 (m, 1H), 1.99 – 1.62 (m, 4H), 1.69 (s, 6H, CH_3), 1.58 (s, 3H, CH_3), 1.42 – 1.18 (m, 2H), 1.27 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 0.93 (s, 3H, CH_3), 0.88 (s, 9H, CCH_3), 0.17 (s, 6H, $SiCH_3$); ^{13}C NMR ($CDCl_3$, 62.9 MHz) δ 197.65 (s), 138.51 (d), 131.35 (s), 124.37 (d), 114.96 (t), 110.89 (s), 96.41 (s), 71.59 (d), 42.64 (d), 40.62 (d), 37.94 (s), 31.64 (t), 28.78 (q), 28.31 (t), 27.83 (q), 25.80 (q, 3C), 22.69 (t), 21.19 (q), 20.80 (q), 18.18 (s), 17.82 (q), 14.11 (q), -4.59 (q), -5.34 (q); exact mass calcd. for $C_{22}H_{37}OSi$ ($M^{\cdot+}$ – C_4H_9) *m/z* 345.2614, found *m/z* 345.2603 (No $M^{\cdot+}$ observed).

References

(1) Butterweck, V. *CNS Drugs* **2003**, *17*, 539-562.

(2) Mennini, T.; Gobbi, M. *Life Sci.* **2004**, *75*, 1021-1027.

(3) Vollmer, J. J.; Rosenson, J. *J. Chem. Educ.* **2004**, *81*, 1450-1455.

(4) Gurevich, A. I.; Dobrynin, V. N.; Kolosov, M. N.; Popravko, S. A.; Riabova, I. D. *Antibiot.* **1971**, *16*, 510-513.

(5) Schempp, C. M.; Pelz, K.; Wittmer, A.; Schopf, E.; Simon, J. C. *Lancet* **1999**, *19*, 353.

(6) Schempp, C. M.; Kirkin, V.; Simon-Haarhaus, B.; Kersten, A.; Kiss, J.; Termeer, C. C.; Gilb, B.; Kaufmann, T.; Borner, C.; Sleeman, J. P.; Simon, J. C. *Oncogene* **2002**, *21*, 1242-1250.

(7) Bystrov, N. S.; Chernov, B. K.; Dobrynin, V. N.; Kolosov, M. N. *Tetrahedron Lett.* **1975**, 2791-2794.

(8) Brondz, I.; Greibrokk, T.; Groth, P. A.; Aasen, A. J. *Tetrahedron Lett.* **1982**, *23*, 1299-1300.

(9) Decosterd, L. A.; Stoeckli-Evans, H.; Chapuis, J. C.; Msonthi, J. D.; Sordat, B.; Hostettmann, K. *Helv. Chim. Acta* **1989**, *72*, 464-471.

(10) Hu, L. H.; Sim, K.Y. *Tetrahedron* **2000**, *56*, 1379-1386.

(11) Hu, L. H.; Sim, K. Y. *Org. Lett.* **1999**, *1*, 879-882.

(12) Krishnamurthy, N.; Ravindranath, B.; Sampathu, S. R. *Indian patent* 160753, **1987**.

(13) Matsumoto, K.; Akao, Y.; Kobayashi, E.; Ito, T.; Ohguchi, K.; Tanaka, T.; Iinuma, M.; Nozawa, Y. *Biol. Pharm. Bull.* **2003**, *26*, 569-571.

(14) Ito, C.; Itoigawa, M.; Miyamoto, Y.; Onoda, S.; Rao, K. S.; Mukainaka, T.;

Tokuda, H.; Nishino, H.; Furukawa, H. *J. Nat. Prod.* **2003**, *66*, 206-209.

(15) Pan, M. H.; Chang, W. L.; Lin-Shiau, S. Y.; Ho, C.-T.; Lin, J. K. *J. Agr. Food Chem.* **2001**, *49*, 1464-1474.

(16) Yamaguchi, F.; Ariga, T.; Yoshimura, Y.; Nakazawa, H. *J. Agr. Food Chem.* **2000**, *48*, 180-185.

(17) Bakana, P.; Claeys, M.; Totte, J.; Pieters, L. A. C.; Van Hoof, L.; Tamba, V.; Van den Berghe, D. A.; Vlietinck, A. J. *J. Ethnopharmacol.* **1987**, *21*, 75-84.

(18) Iinuma, M.; Tosa, H.; Tanaka, T.; Kanamaru, S.; Asai, F.; Kobayashi, Y.; Miyauchi, K.-i.; Shimano, R. *Biol. Pharm. Bull.* **1996**, *19*, 311-314.

(19) Fukuyama, Y.; Kuwayama, A.; Minami, H. *Chem. Pharm. Bull.* **1997**, *45*, 947-949.

(20) Fukuyama, Y.; Minami, H.; Kinoshita, M.; Takahashi, E.; Kuwayama, A.; Takahashi, H.; Kodama, M.; Yoshizawa, T. *Tennen Yuki Kagobutsu Toronkai Koen Yoshishu* **1997**, *39*, 577-582.

(21) Fukuyama, Y.; Minami, H.; Kuwayama, A. *Phytochem.* **1998**, *49*, 853-857.

(22) Weng, J. R.; Lin, C. N.; Tsao, L. T.; Wang, J. P. *Chem.-Eur. J.* **2003**, *9*, 1958-1963.

(23) Weng, J. R.; Lin, C. N.; Tsao, L. T.; Wang, J. P. *Chem.-Eur. J.* **2003**, *9*, 5520-5527.

(24) Winkelmann, K.; Heilmann, J.; Zerbe, O.; Rali, T.; Sticher, O. *J. Nat. Prod.* **2001**, *64*, 701-706.

(25) Matsuhisa, M.; Shikishima, Y.; Takaishi, Y.; Honda, G.; Ito, M.; Takeda, Y.; Shibata, H.; Higuti, T.; Kodzhimatov, O. K.; Ashurmetov, O. *J. Nat. Prod.*

2002, *65*, 290-294.

(26) De Oliveira, C. M. A.; Porto, A. M.; Bittrich, V.; Vencato, I.; Marsaioli, A. J. *Tetrahedron Lett.* **1996**, *37*, 6427-6430.

(27) De Oliveira, C. M. A.; Porto, A. L. M.; Bittrich, V.; Marsaioli, A. J. *Phytochem.* **1999**, *50*, 1073-1079.

(28) Cuesta-Rubio, O.; Frontana-Uribe, B. A.; Ramirez-Apan, T.; Cardenas, J. *Z. Naturforsch. C.* **2002**, *57*, 372-378.

(29) Bokesch, H. R.; Groweiss, A.; McKee, T. C.; Boyd, M. R. *J. Nat. Prod.* **1999**, *62*, 1197-1199.

(30) Gustafson, K. R.; Blunt, J. W.; Munro, M. H. G.; Fuller, R. W.; McKee, T. C.; Cardellina, J. H., II; McMahon, J. B.; Cragg, G. M.; Boyd, M. R. *Tetrahedron* **1992**, *48*, 10093-10102.

(31) Roux, D.; Hadi, H. A.; Thoret, S.; Guenard, D.; Thoison, O.; Paies, M.; Sevenet, T. *J. Nat. Prod.* **2000**, *63*, 1070-1076.

(32) Stierle, D. B.; Stierle, A. A.; Hobbs, J. D.; Stokken, J.; Clardy, J. *Org. Lett.* **2004**, *6*, 1049-1052.

(33) Balasubramanyam, K.; Altaf, M.; Varier, R. A.; Swaminathan, V.; Ravindran, A.; Sadhale, P. P.; Kundu, T. K. *J. Biol. Chem.* **2004**, *279*, 33716-33726.

(34) Achkar, J.; Xian, M.; Zhao, H.; Frost, J. W. *J. Am. Chem. Soc.* **2005**, *127*, 5332-5333.

(35) Adam, P.; Arigoni, D.; Bacher, A.; Eisenreich, W. *J. Med. Chem.* **2002**, *45*, 4786-4793.

(36) Eisenreich, W.; Rohdich, F.; Bacher, A. *Trends Plant Sci.* **2001**, *6*, 78-84.

(37) Butkus, E. *Synlett* **2001**, 1827-1835.

(38) Schoenwaelder, K. H.; Kollat, P.; Stezowski, J. J.; Effenberger, F. *Chem. Ber.* **1984**, *117*, 3280-3296.

(39) Nicolaou, K. C.; Pfefferkorn, J. A.; Kim, S.; Wei, H. X. *J. Am. Chem. Soc.* **1999**, *121*, 4724-4725.

(40) Usuda, H.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2002**, *4*, 859-862.

(41) Usuda, H.; Kanai, M.; Shibasaki, M. *Tetrahedron Lett.* **2002**, *43*, 3621-3624.

(42) Spessard, S. J.; Stoltz, B. M. *Org. Lett.* **2002**, *4*, 1943-1946.

(43) Kraus, G. A.; Dneprovskaia, E.; Nguyen, T. H.; Jeon, I. *Tetrahedron* **2003**, *59*, 8975-8978.

(44) Kraus, G. A.; Nguyen, T. H.; Jeon, I. *Tetrahedron Lett.* **2003**, *44*, 659-661.

(45) Ciochina, R.; Grossman, R. B. *Org. Lett.* **2003**, *5*, 4619-4621.

(46) Mehta, G.; Bera, M. K. *Tetrahedron Lett.* **2004**, *45*, 1113-1116.

(47) Klein, A.; Miesch, M. *Tetrahedron Lett.* **2003**, *44*, 4483-4485.

(48) Takagi, R.; Nerio, T.; Miwa, Y.; Matsumura, S.; Ohkata, K. *Tetrahedron Lett.* **2004**, *45*, 7401-7405.

(49) Usuda, H.; Kuramochi, A.; Kanai, M.; Shibasaki, M. *Org. Lett.* **2004**, *6*, 4387-4390.

(50) Mukaiyama, T.; Hoshino, T. *J. Am. Chem. Soc.* **1960**, *82*, 5339-5342.

(51) Ono, N. *The Nitro Group in Organic Synthesis,* Wiley-VCH, John Wiley and Sons, New York, **2001**, 258 - 301

(52) Kozikowski, A. P.; Stein, P. D. *J. Org. Chem.* **1984**, *49*, 2301-2309.

(53) Muri, D.; Bode, J. W.; Carreira, E. M. *Org. Lett.* **2000**, *2*, 539-541.

(54) Wender, P. A.; Jenkins, T. E.; Suzuki, S. *J. Am. Chem. Soc.* **1995**, *117*, 1843-1844.

(55) Himbert, G.; Diehl, K.; Schlindwein, H. J. *Chem. Ber.* **1989**, *122*, 1691-1699.

(56) Yasukouchi, T.; Kanematsu, K. *Tetrahedron Lett.* **1989**, *30*, 6559-6562.

(57) Murakami, M.; Matsuda, T. *Modern Allene Chemistry*, Wiley-VCH, John Wiley and Sons, New York, **2004**; Vol. 2, 727-815.

(58) Broggini, G.; Zecchi, G. *Gazz. Chim. Ital.* **1996**, *126*, 479-488.

(59) Beltrame, P.; Beltrame, P. L.; Filippi, A.; Zecchi, G. *J. Chem. Soc., Perkin Trans. 2* **1972**, 1914-1919.

(60) Beltrame, P.; Beltrame, P. L.; Cattania, M. G.; Zecchi, G. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1301-1303.

(61) Zecchi, G. *J. Org. Chem.* **1979**, *44*, 2796-2798.

(62) Broggini, G.; Molteni, G.; Zecchi, G. *J. Chem. Res., Synopses* **1993**, 203.

(63) Broggini, G.; Zecchi, G. *J. Chem. Soc., Perkin Trans. 1* **1991**, 1843-1846.

(64) Bruche, L.; Gelmi, M. L.; Zecchi, G. *J. Org. Chem.* **1985**, *50*, 3206-3208.

(65) LeBel, N. A.; Banucci, E. *J. Am. Chem. Soc.* **1970**, *92*, 5278-5280.

(66) Zeng, D. *Studies Toward the Synthesis of Hyperevolutin A: Nitrile Oixide-Allene Cycloaddition Approach*; M.S. Thesis, The University of Tennessee, Knoxville, **2001**.

(67) Young, D. G. J.; Zeng, D. *Heterocycles* **2004**, *62*, 121-125.

(68) Kozikowski, A. P.; Hiraga, K.; Springer, J. P.; Wang, B. C.; Xu, Z. B. *J. Am. Chem. Soc.* **1984**, *106*, 1845-1847.

(69) Uno, H.; Watanabe, N.; Fujiki, S.; Suzuki, H. *Synthesis* **1987**, 471-474.

(70) Mukaiyama, T.; Hayashi, M. *Chem. Lett.* **1974**, 15-16.

(71) Mukaiyama, T.; Murakami, M. *Synthesis* **1987**, 1043-1054.

(72) Mukaiyama, T. *Challenges in Synthetic Organic Chemistry*; Oxford University Press Inc.: New York, **1990**, 98-106.

(73) Mukaiyama, T.; Ishida, A. *Chem. Lett.* **1975**, 319-322.

(74) Young David, G. J.; Zeng, D. *J. Org. Chem.* **2002**, *67*, 3134-3137.

(75) Kozikowski, A. P.; Adamczyk, M. *Tetrahedron Lett.* **1982**, *23*, 3123-3126.

(76) Warnhoff, E. W.; Martin, D. G.; Johnson, W. S. *Org. Synth.* **1957**, *37*, 8-12.

(77) Cahiez, G.; Avedissian, H. *Synthesis* **1998**, 1199-1205.

(78) Lipshutz, B. H.; Hackmann, C. *J. Org. Chem.* **1994**, *59*, 7437-7444.

(79) Nishiyama, T.; Seshita, T.; Shodai, H.; Aoki, K.; Kameyama, H.; Komura, K. *Chem. Lett.* **1996**, 549-550.

(80) Keck, G. E.; Enholm, E. J.; Yates, J. B.; Wiley, M. R. *Tetrahedron* **1985**, *41*, 4079-4094.

(81) Lipshutz, B. H.; Ellsworth, E. L.; Dimock, S. H.; Smith, R. A. J. *J. Am. Chem. Soc.* **1990**, *112*, 4404-4410.

(82) Tanaka, M.; Sakai, K. *Tetrahedron Lett.* **1991**, *32*, 5581-5584.

(83) Cahiez, G.; Chau, K.; Clery, P. *Tetrahedron Lett.* **1994**, *35*, 3069-3072.

(84) Chatterjee, A. K.; Sanders, D. P.; Grubbs, R. H. *Org. Lett.* **2002**, *4*, 1939-1942.

(85) Johnson, W. S.; Posvic, H. *J. Am. Chem. Soc.* **1947**, *69*, 1361 - 1366.

(86) Eberbach, W.; Roser, J. *Tetrahedron* **1986**, *42*, 2221-2234.

(87) Bergmann, E. D.; Becker, A. *J. Am. Chem. Soc.* **1959**, *81*, 221-225.

(88) March, J.; Smith, M. B. *March's Advanced Organic Chemistry: reactions,*

mechanisms, and structure; 5 ed.; John Wiley and Sons, New York, **2001**.

(89) Gribble, G. W.; Joyner, H. H.; Switzer, F. L. *Synth. Commun.* **1992**, *22*, 2997-3002.

(90) Imamoto, T.; Kusumoto, T.; Tawarayama, Y.; Sugiura, Y.; Mita, T.; Hatanaka, Y.; Yokoyama, M. *J. Org. Chem.* **1984**, *49*, 3904-3912.

(91) Sondheimer, F.; Pilling, G. M. *J. Am. Chem. Soc.* **1971**, *93*, 1970-1977.

(92) Pryor, W. A.; Giamalva, D.; Church, D. F. *J. Am. Chem. Soc.* **1985**, *107*, 2793-2797.

(93) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307-1370.

(94) Siegel, C.; Gordon, P. M.; Uliss, D. B.; Handrick, G. R.; Dalzell, H. C.; Razdan, R. K. *J. Org. Chem.* **1991**, *56*, 6865-6872.

(95) Luche, J. L. *J. Am. Chem. Soc.* **1978**, *100*, 2226-2227.

(96) Marshall, J. A.; Pinney, K. G. *J. Org. Chem.* **1993**, *58*, 7180-7184.

(97) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136-6137.

(98) Corey, E. J.; Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94*, 6190-6191.

(99) Macdonald, T. L.; Reagan, D. R.; Brinkmeyer, R. S. *J. Org. Chem.* **1980**, *45*, 4740-4747.

(100) Alexakis, A.; Marek, I.; Mangeney, P.; Normant, J. F. *Tetrahedron* **1991**, *47*, 1677-1696.

(101) Schuster, H. F.; Coppola, G. M. *Allenes in Organic Synthesis*, John Wiley and Sons, New York, **1984**.

(102) Gilman, H.; Jones, R. G.; Woods, L. A. *J. Org. Chem.* **1952**, *17*, 1630-1634.

(103) Huang, H.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 2773-2779.

(104) Buchbauer, G.; Spreitzer, H.; Zechmeister-Machhart, F.; Klinsky, A.; Weiss-Greiler, P.; Wolschann, P. *Eur. J. Med. Chem.* **1998**, *33*, 463-470.

(105) Julia, M.; Julia, S.; Guegan, R. *Bull. Soc. Chim. Fr.* **1960**, 1072-1079.

(106) Doherty, G. A.; Yang, G. X.; Borges, E.; Chang, L. L.; MacCoss, M.; Tong, S.; Kidambi, U.; Egger, L. A.; McCauley, E.; Van Riper, G.; Mumford, R. A.; Schmidt, J. A.; Hagmann, W. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 1501-1505.

(107) Huang, H.; Forsyth, C. J. *J. Org. Chem.* **1995**, *60*, 5746-5747.

(108) Trost, B. M.; Doherty, G. A. *J. Am. Chem. Soc.* **2000**, *122*, 3801-3810.

(109) Diver, S. T.; Giessert, A. J. *Chem. Rev.* **2004**, *104*, 1317-1382.

(110) Hansen, E. C.; Lee, D. *J. Am. Chem. Soc.* **2004**, *126*, 15074-15080.

(111) Lindlar, H.; Dubuis, R. *Org. Synth.*, *V*, 880-883.

(112) Hodgson, D. M.; Galano, J. M.; Christlieb, M. *Chem. Commun.* **2002**, 2436-2437.

(113) Rubottom, G. M.; Gruber, J. M. *J. Org. Chem.* **1978**, *43*, 1599-1602.

(114) Babler, J. H.; Coghlan, M. J. *Synth. Commun.* **1976**, *6*, 469-474.

(115) Dauben, W. G.; Michno, D. M. *J. Org. Chem.* **1977**, *42*, 682-685.

(116) Sundararaman, P.; Herz, W. *J. Org. Chem.* **1977**, *42*, 806-813.

(117) Mander, L. N.; Sethi, S. P. *Tetrahedron Lett.* **1983**, *24*, 5425-5428.

(118) Benningshof, J. C. J.; Ijsselstijn, M.; Wallner, S. R.; Koster, A. L.; Blaauw, R. H.; van Ginkel, A. E.; Briere, J. F.; van Maarseveen, J. H.; Rutjes, F. P. J. T.; Hiemstra, H. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1701-1713.

(119) Cook, G. K.; Hornback, W. J.; Jordan, C. L.; McDonald, J. H., III; Munroe, J. E.

J. Org. Chem. **1989**, *54*, 5828-5830.

(120) Griesser, H.; Ohrlein, R.; Schwab, W.; Ehrler, R.; Jager, V. *Org. Synth.* **2000**, *77*, 236-248.

(121) Trost, B. M.; Verhoeven, T. R. *J. Am. Chem. Soc.* **1980**, *102*, 4743-4763.

(122) Wang, J.; Hsung, R. P.; Ghosh, S. K. *Org. Lett.* **2004**, *6*, 1939-1942.

(123) Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1987**, *109*, 7553-7555.

(124) Boeckman, R. K., Jr.; Charette, A. B.; Asberom, T.; Johnston, B. H. *J. Am. Chem. Soc.* **1991**, *113*, 5337-5353.

(125) Meskens, F. A. J. *Synthesis* **1981**, 501-522.

(126) Bradshaw, J. S.; Krakowiak, K. E.; LindH, G. C.; Izatt, R. M. *Tetrahedron* **1987**, *43*, 4271-4276.

(127) Feringa, B. L. *Synth. Commun.* **1985**, *15*, 87-89.

(128) Greene, T. W.; Wuts, P. G. M. *Protective Groups in Organic Synthesis. 3rd Ed*, John Wiley and Sons, New York, **1999**.

(129) Hartung, W. H.; Simonoff, R. *Org. Reactions* **1953**, *VII*, 263-326.

(130) Heathcock, C. H.; Ratcliffe, R. *J. Am. Chem. Soc.* **1971**, *93*, 1746-1757.

(131) Murata, S.; Suzuki, M.; Noyori, R. *Tetrahedron* **1988**, *44*, 4259-4275.

(132) Mukaiyama, T.; Kobayashi, S.; Murakami, M. *Chem. Lett.* **1984**, 1759-1762.

(133) Peng, S.; Qing, F. L. *J. Fluorine Chem.* **2000**, *103*, 135-137.

(134) Armstrong, A.; Critchley, T. J.; Gourdel-Martin, M. E.; Kelsey, R. D.; Mortlock, A. A. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1344-1350.

(135) Denmark, S. E.; Lee, W. *J. Org. Chem.* **1994**, *59*, 707-709.

(136) Paterson, I.; Smith, J. D.; Ward, R. A. *Tetrahedron* **1995**, *51*, 9413-9436.

(137) Molander, G. A.; Haar, J. P., Jr. *J. Am. Chem. Soc.* **1993**, *115*, 40-49.

(138) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1975**, *53*, 2975-2977.

(139) Hanessian, S.; Lavallee, P. *Can. J. Chem.* **1977**, *55*, 562-565.

(140) Kornblum, N.; Larson, H. O.; Blackwood, R. K.; Mooberry, D. D.; Oliveto, E. P.; Graham, G. E. *J. Am. Chem. Soc.* **1956**, *78*, 1497-1501.

(141) Kornblum, N.; Taub, B.; Ungnade, H. E. *J. Am. Chem. Soc.* **1954**, *76*, 3209-3211.

(142) Kornblum, N.; Smiley, R. A.; Ungnade, H. E.; White, A. M.; Taub, B.; Herbert, S. A., Jr. *J. Am. Chem. Soc.* **1955**, *77*, 5528-5533.

(143) Wrobleski, A.; Sahasrabudhe, K.; Aube, J. *J. Am. Chem. Soc.* **2004**, *126*, 5475-5481.

(144) Itoh, T.; Miyazaki, M.; Nagata, K.; Ohsawa, A. *Tetrahedron* **2000**, *56*, 4383-4395.

(145) Childs, M. E.; Weber, W. P. *J. Org. Chem.* **1976**, *41*, 3486-3487.

(146) Winkler, J. D.; Rouse, M. B.; Greaney, M. F.; Harrison, S. J.; Jeon, Y. T. *J. Am. Chem. Soc.* **2002**, *124*, 9726-9728.

(147) Tsuji, J.; Minami, I.; Shimizu, I. *Tetrahedron Lett.* **1983**, *24*, 1793-1796.

(148) Ukai, T.; Kawazura, H.; Ishii, Y.; Bonnet, J. J.; Ibers, J. A. *J. Organomet. Chem.* **1974**, *65*, 253-266.

(149) Dumont, R.; Pfander, H. *Helv. Chim. Acta* **1983**, *66*, 814-823.

(150) Hong, S. P.; Lindsay, H. A.; Yaramasu, T.; Zhang, X.; McIntosh, M. C. *J. Org. Chem.* **2002**, *67*, 2042-2055.

(151) Hartwig, W. *Tetrahedron* **1983**, *39*, 2609-2645.

(152) Dauben, W. G.; Warshawsky, A. M. *J. Org. Chem.* **1990**, *55*, 3075-3087.

(153) Zweifel, G.; Ayyangar, N. R.; Brown, H. C. *J. Am. Chem. Soc.* **1963**, *85*, 2072-2076.

(154) Zweifel, G.; Brown, H. C. *J. Am. Chem. Soc.* **1963**, *85*, 2066-2072.

(155) Brown, H. C.; Moerikofer, A. W. *J. Am. Chem. Soc.* **1963**, *85*, 2063-2065.

(156) Knights, E. F.; Brown, H. C. *J. Am. Chem. Soc.* **1968**, *90*, 5280-5281.

(157) Lin, H.-S.; Paquette, L. A. *Synth. Commun.* **1994**, *24*, 2503-2506.

(158) Vader, J.; Sengers, H.; De Groot, A. *Tetrahedron* **1989**, *45*, 2131-2142.

(159) Cossy, J.; Pete, J. P. *Bull. Soc. Chim. Fr.* **1988**, 989-994.

(160) Kuo, D. L.; Money, T. *Can. J. Chem.* **1988**, *66*, 1794-1804.

(161) Wilson, S. R.; Zucker, P. A. *J. Org. Chem.* **1988**, *53*, 4682-4693.

(162) Dimitrov, V.; Kostova, K.; Genov, M. *Tetrahedron Lett.* **1996**, *37*, 6787-6790.

(163) Rigby, J. H.; Cuisiat, S. V. *J. Org. Chem.* **1993**, *58*, 6286-6291.

(164) Zakarian, A.; Hart, D. J. *Org. Synth.* **1998**, *75*, 69-77.

(165) Wacowich-Sgarbi, S. A.; Bundle, D. R. *J. Org. Chem.* **1999**, *64*, 9080-9089.

(166) Harnden, M. R.; Jarvest, R. L. *J. Chem. Soc., Perkin Trans. 1* **1989**, 2207-2213.

(167) Girlanda-Junges, C.; Keyling-Bilger, F.; Schmitt, G.; Luu, B. *Tetrahedron* **1998**, *54*, 7735-7748.

(168) Naruta, Y.; Nishigaichi, Y.; Maruyama, K. *Org. Synth.* **1993**, *71*, 118-124.

(169) Hoffmann, R. W.; Feussner, G.; Zeiss, H. J.; Schulz, S. *J. Organomet. Chem.* **1980**, *187*, 321-329.

(170) Hayashi, M.; Mukaiyama, T. *Chem. Lett.* **1987**, 289-292.

(171) Heslin, J. C.; Moody, C. J. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1417-1423.

(172) Cambie, R. C.; Coulson, S. A.; Mackay, L. G.; Janssen, S. J.; Rutledge, P. S.; Woodgate, P. D. *J. Organomet. Chem.* **1991**, *409*, 385-409.

(173) House, H. O.; Czuba, L. J.; Gall, M.; Olmstead, H. D. *J. Org. Chem.* **1969**, *34*, 2324-2336.

(174) Young, D. G. J.; Zeng, D. *unpublished results,* **2001**.

(175) Bonafoux, D.; Bordeau, M.; Biran, C.; Cazeau, P.; Dunogues, J. *J. Org. Chem.* **1996**, *61*, 5532-5536.

(176) Stork, G.; Hudrlik, P. F. *J. Am. Chem. Soc.* **1968**, *90*, 4462-4464.

(177) Lee, P. H.; Ahn, H.; Lee, K.; Sung, S. Y.; Kim, S. *Tetrahedron Lett.* **2001**, *42*, 37-39.

(178) Mitani, M.; Osakabe, Y. *J. Chem. Soc., Chem. Commun.* **1994**, 1759-1760.

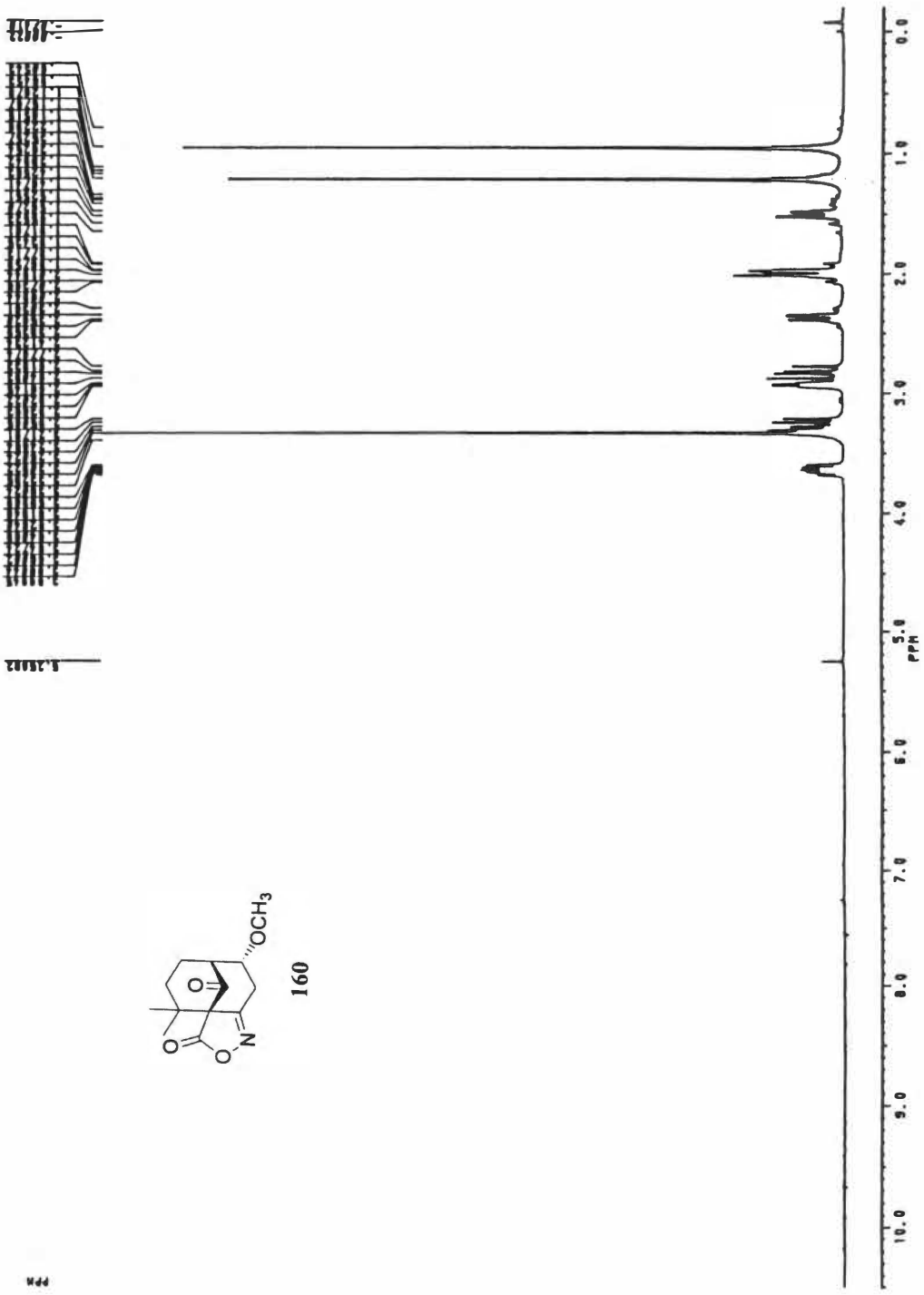
(179) Colson, P. J.; Hegedus, L. S. *J. Org. Chem.* **1994**, *59*, 4972-4976.

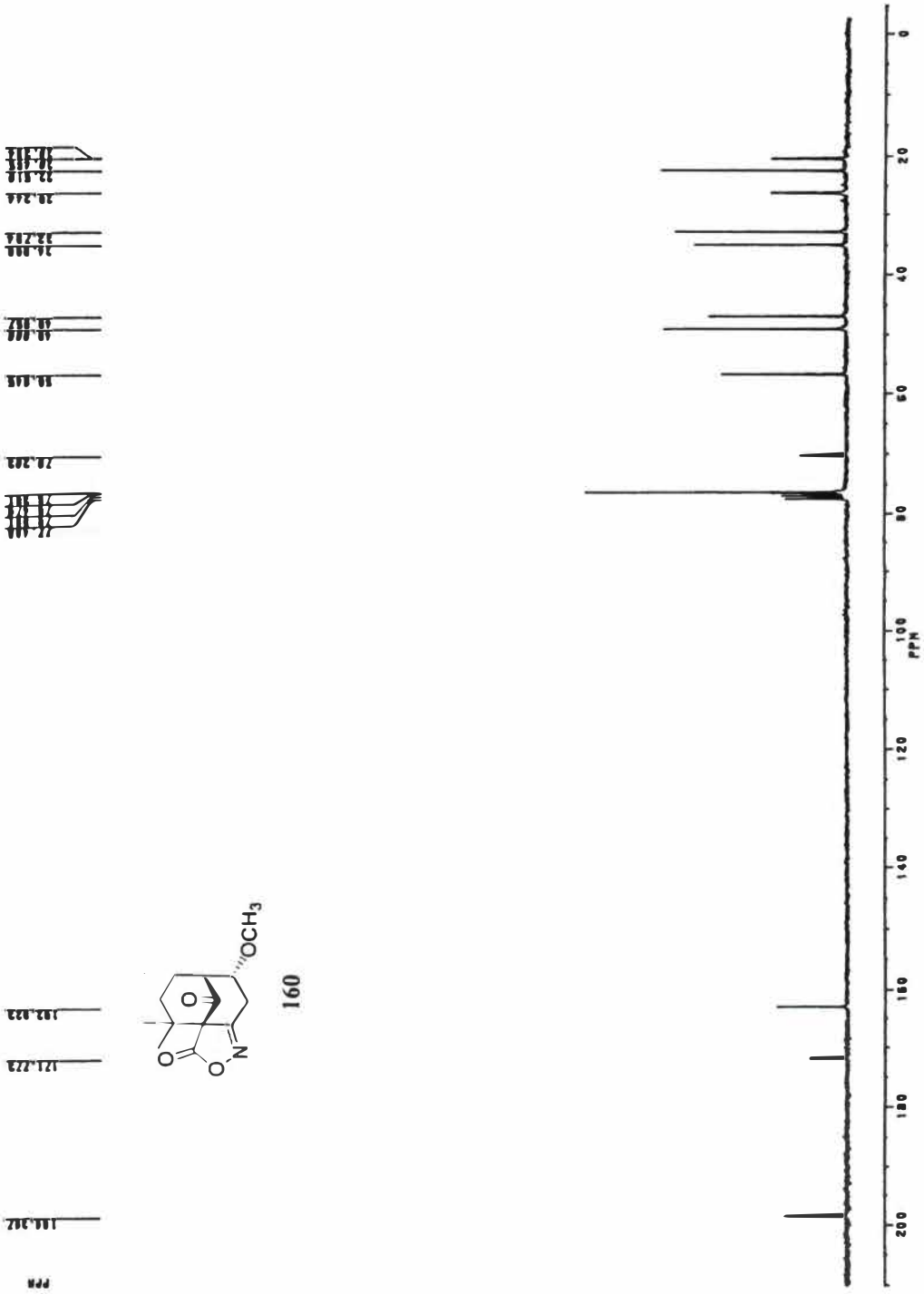
(180) Panek, J. S.; Beresis, R. T.; Celatka, C. A. *J. Org. Chem.* **1996**, *61*, 6494-6495.

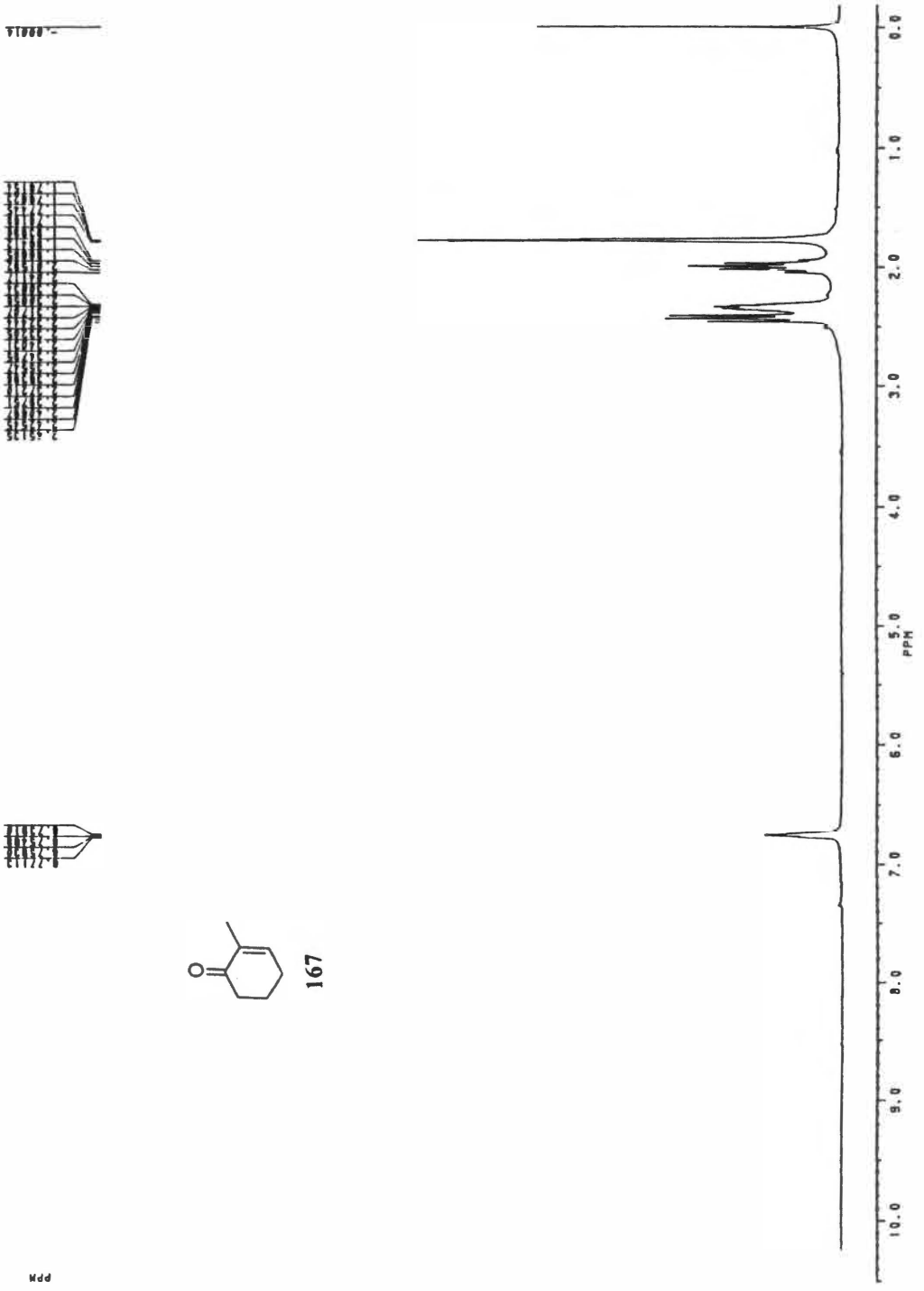
(181) Clive, D. L. J.; Paul, C. C.; Wang, Z. *J. Org. Chem.* **1997**, *62*, 7028-7032.

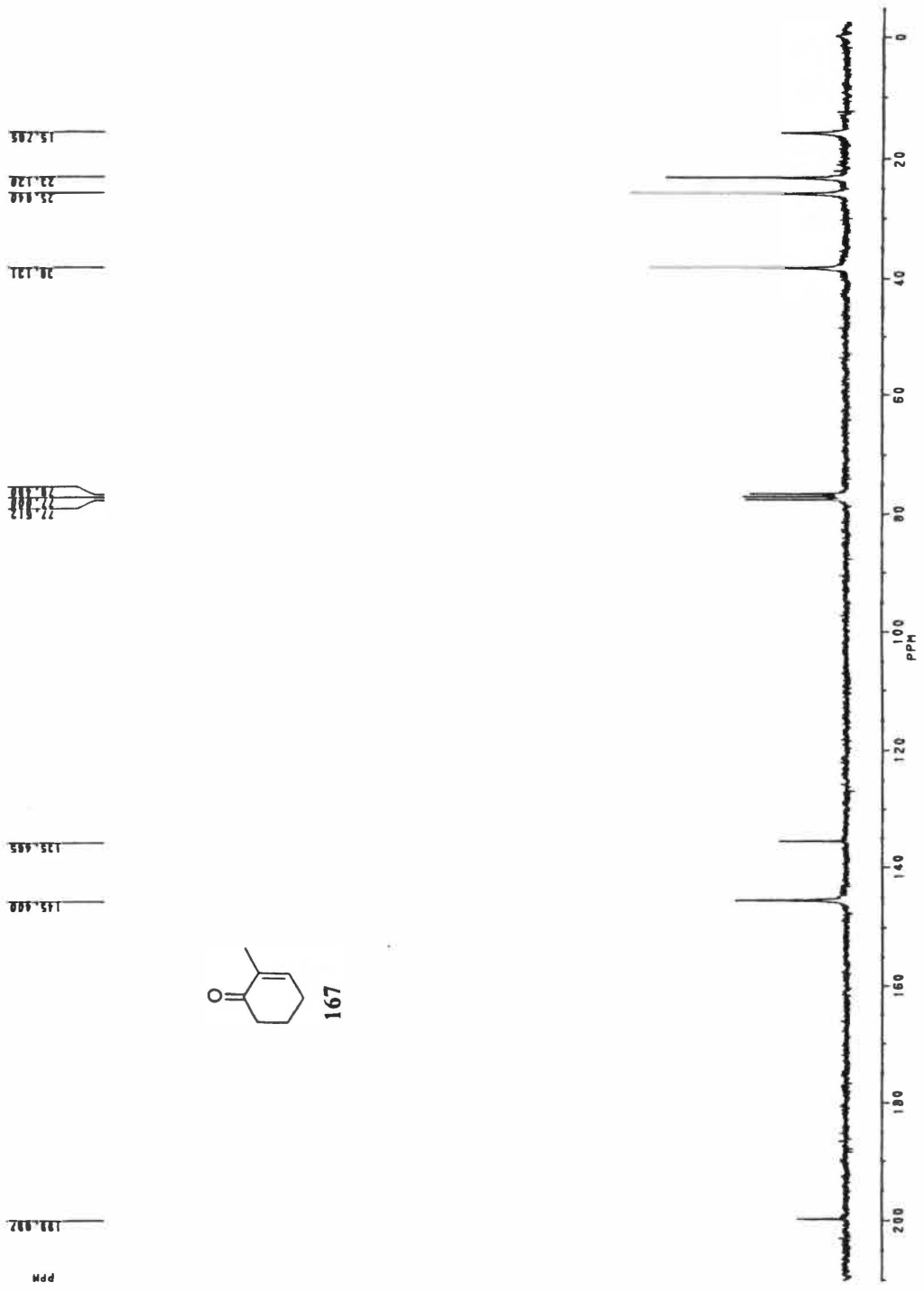
(182) Nicolaou, K. C.; Papahatjis, D. P.; Claremon, D. A.; Magolda, R. L.; Dolle, R. E. *J. Org. Chem.* **1985**, *50*, 1440-1456.

Appendix 1. ^{1}H and ^{13}C NMR for selected compounds.

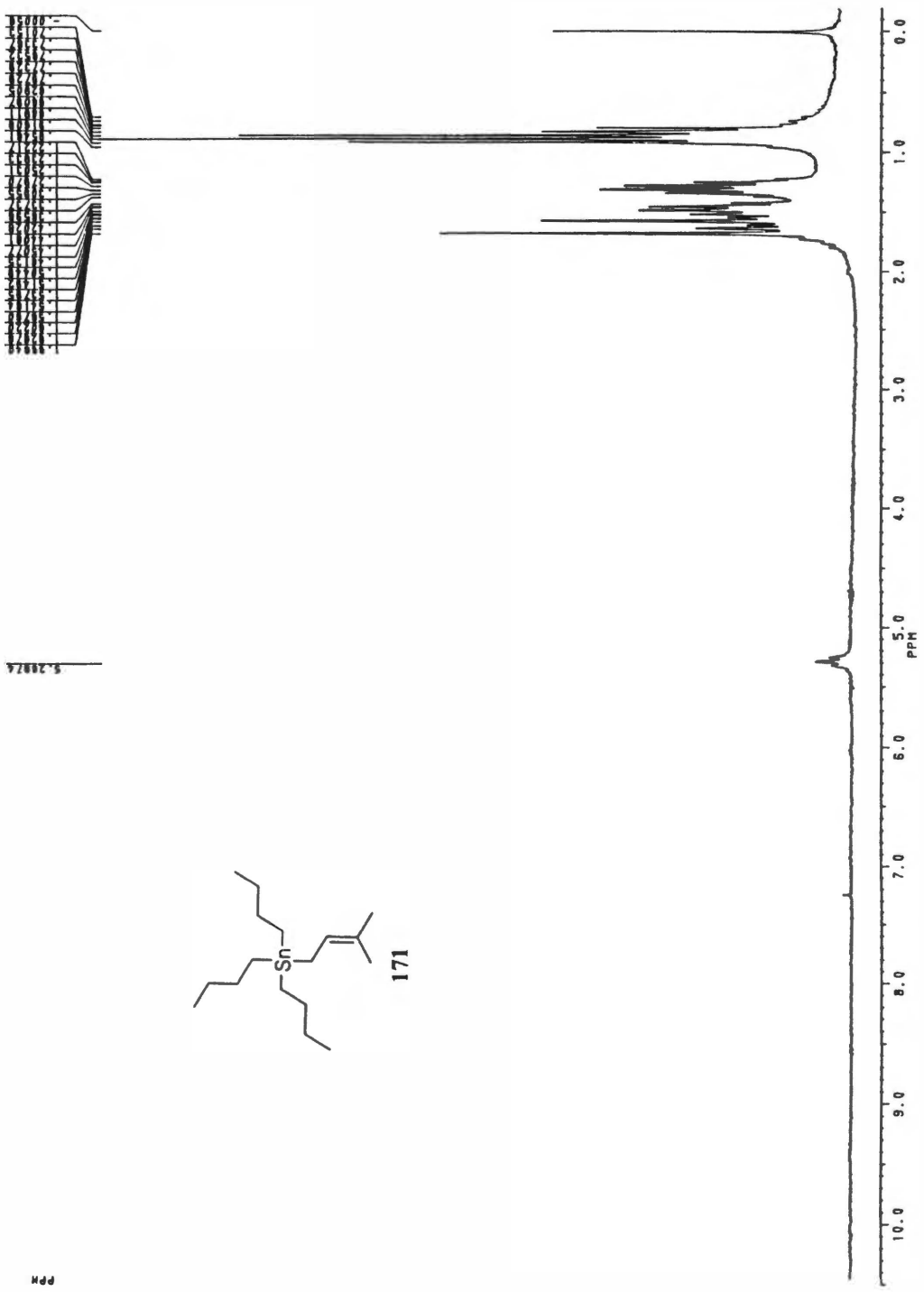

OCH3
O
N
O
O
160
PPM

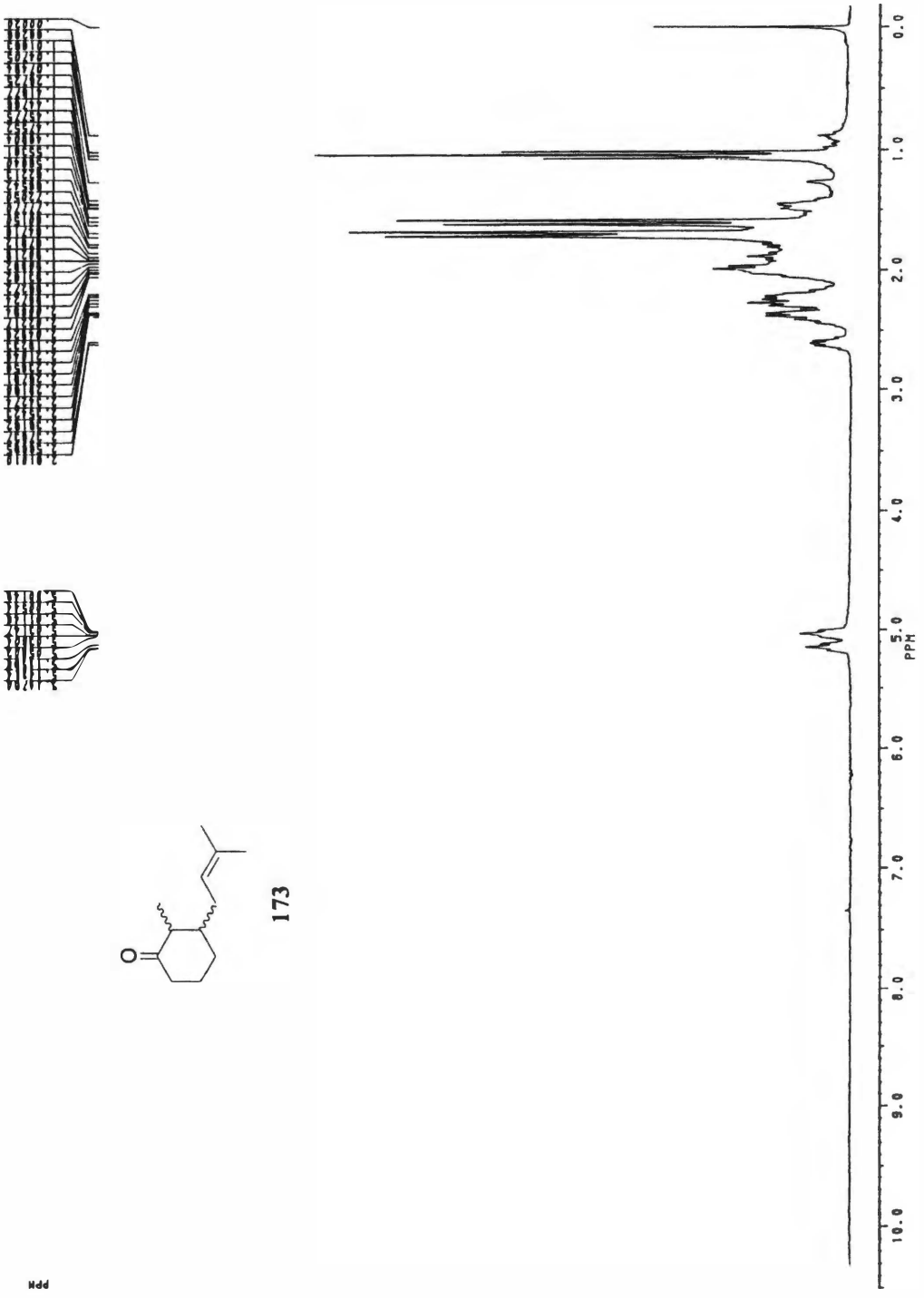

OCH3
O
O
N
O
160
PPM


167
PPM

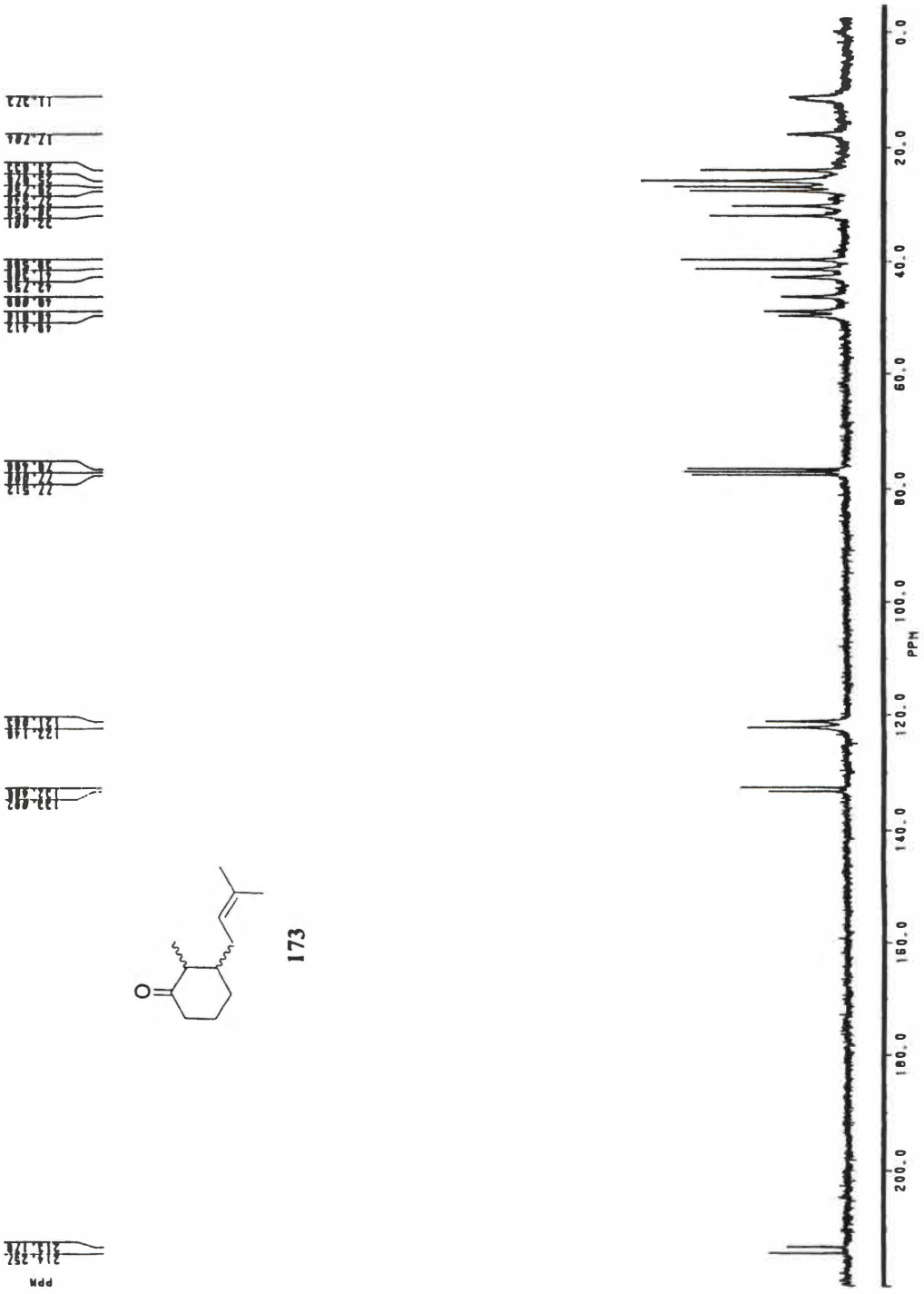


167

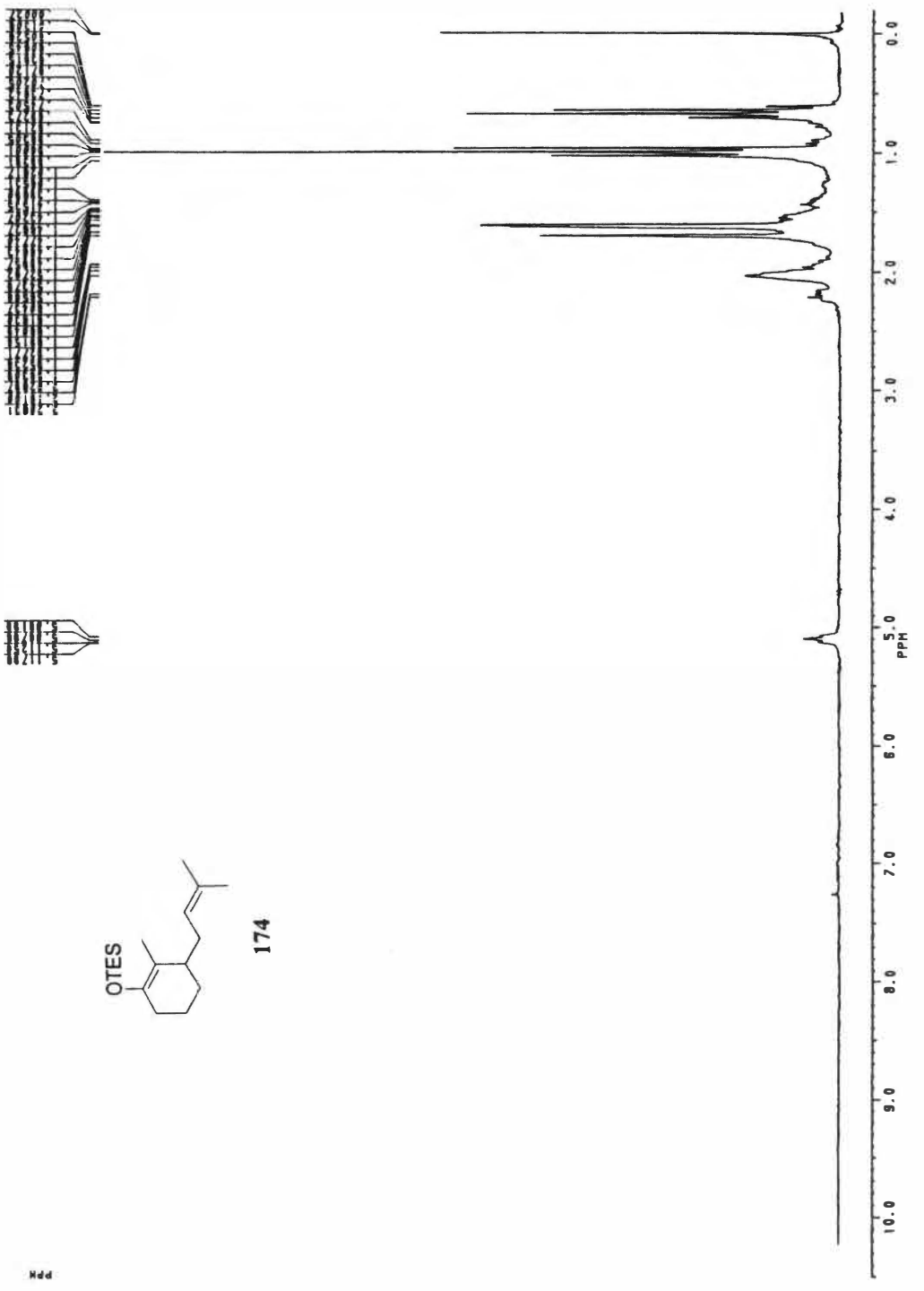

Sn
171
PPM

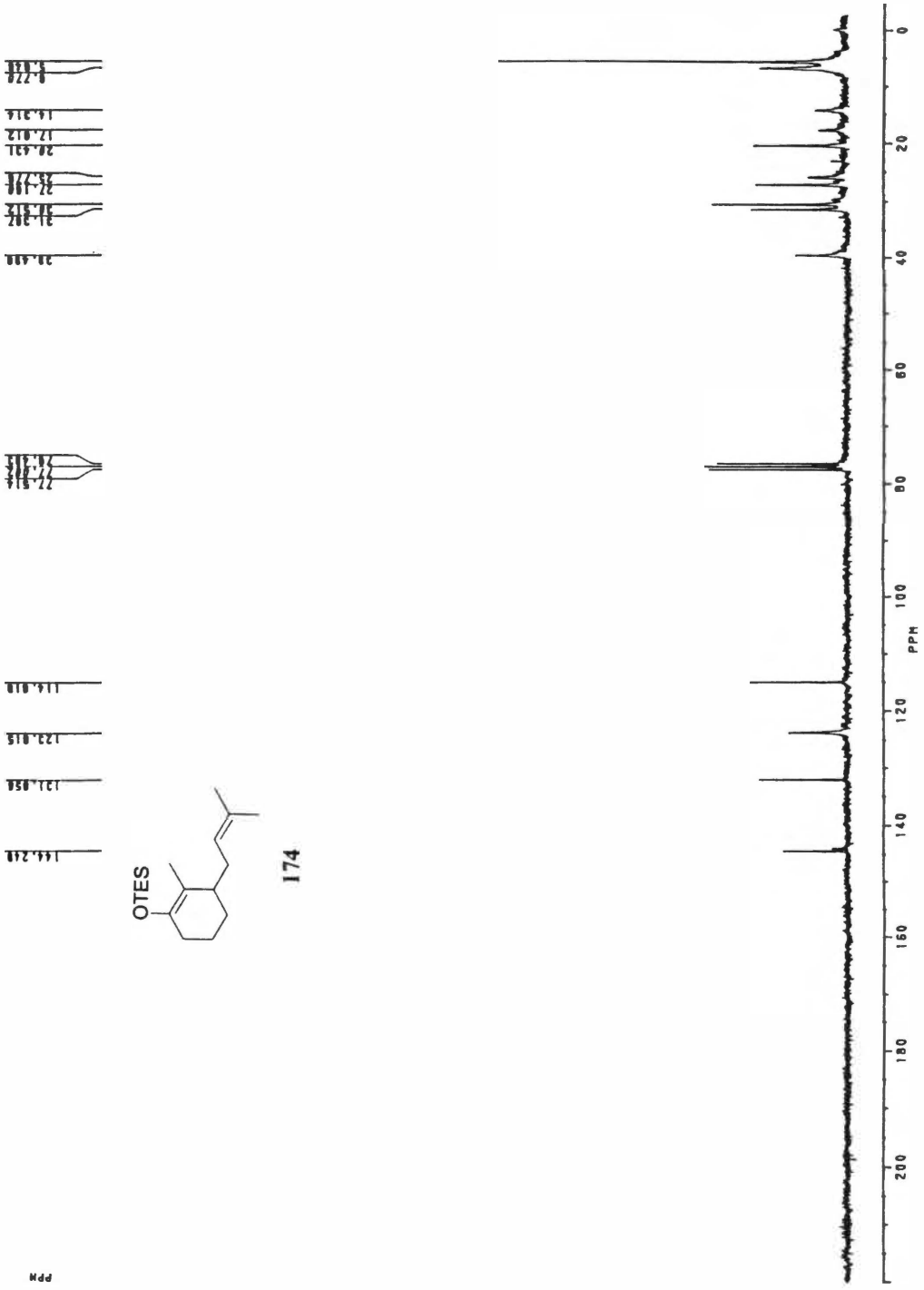


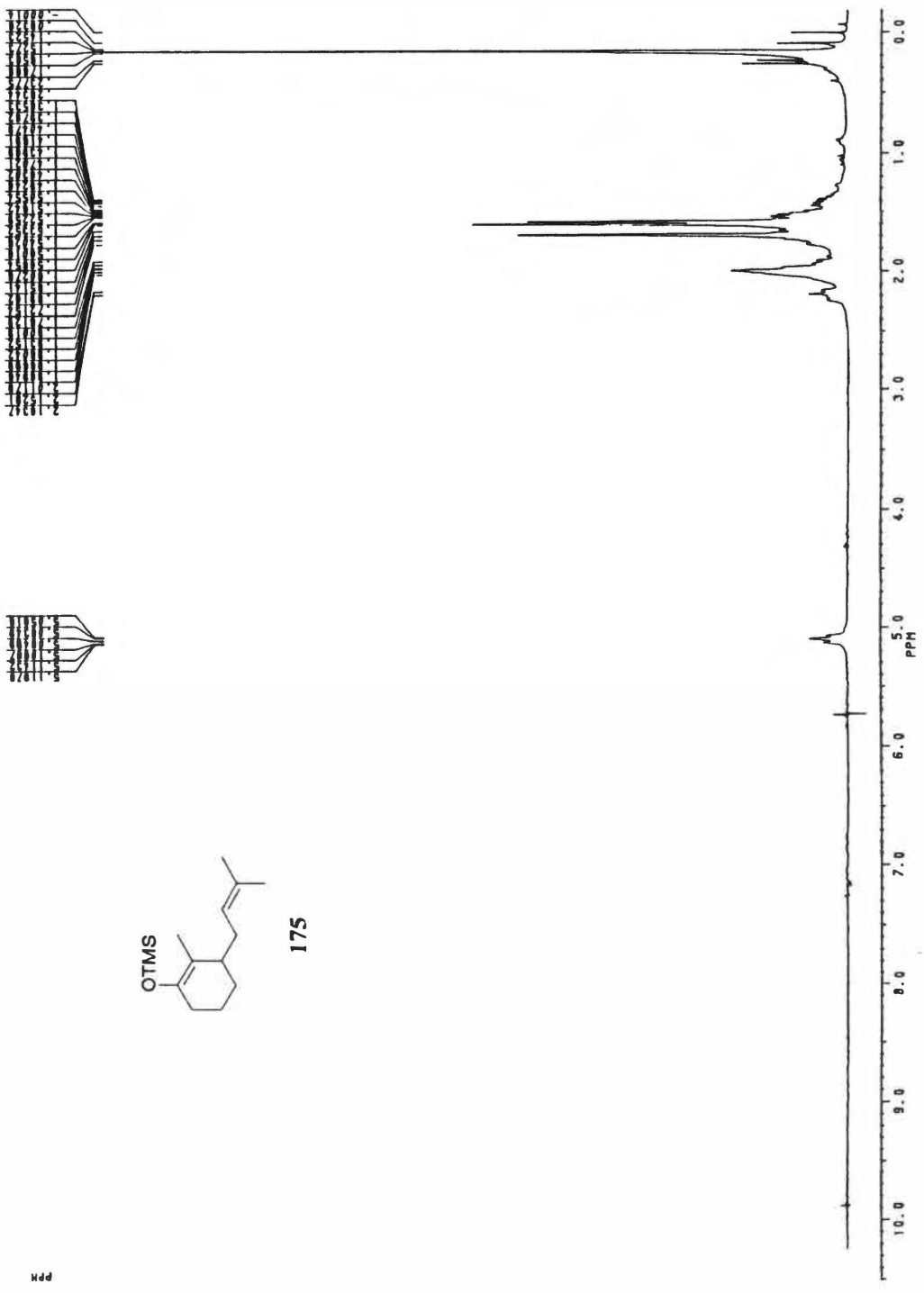
173

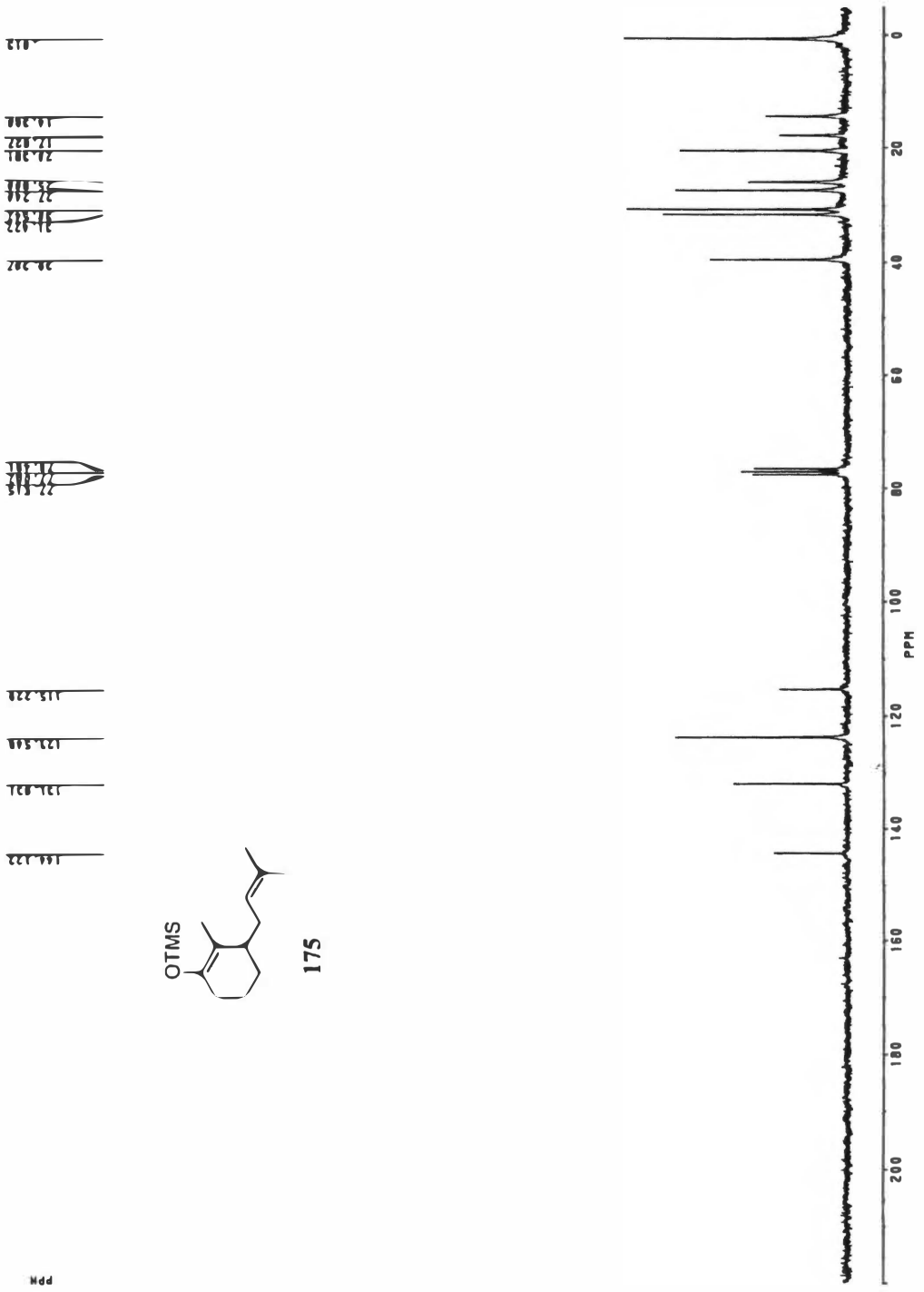


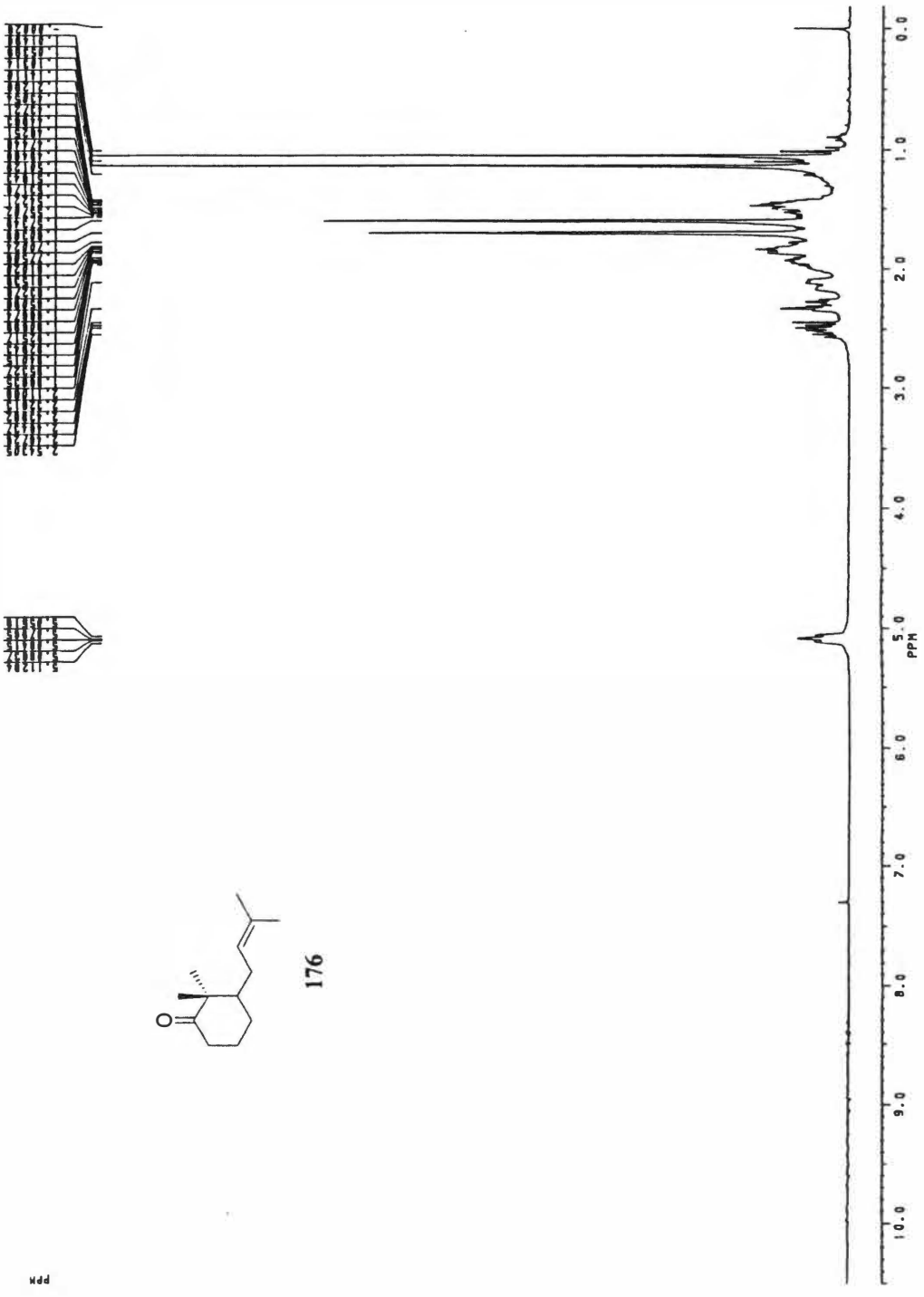
173


OTES
174
PPM

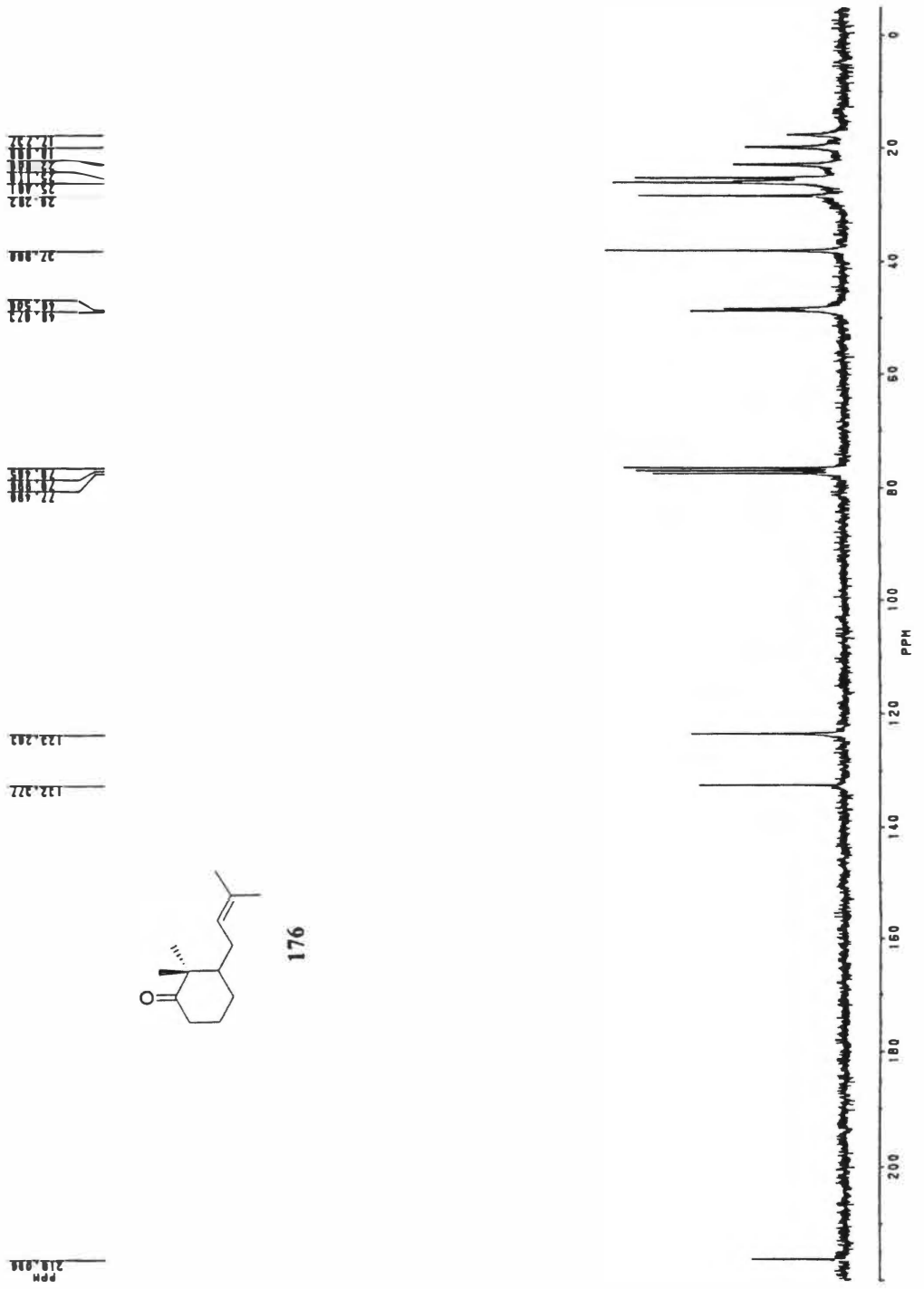

OTES
174
PPM


OTMS
175
PPM
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
PPM

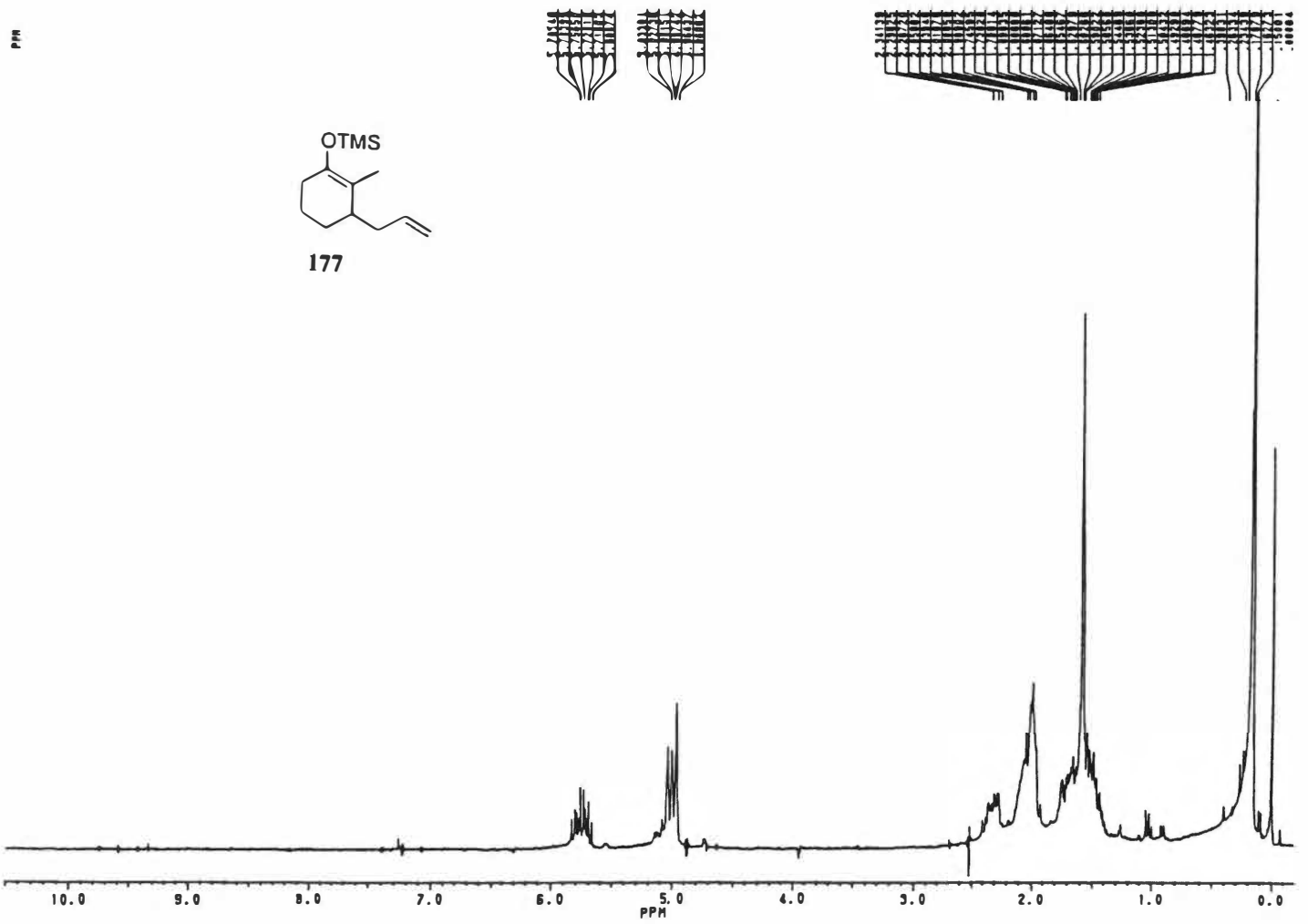

OTMS
175
PPM

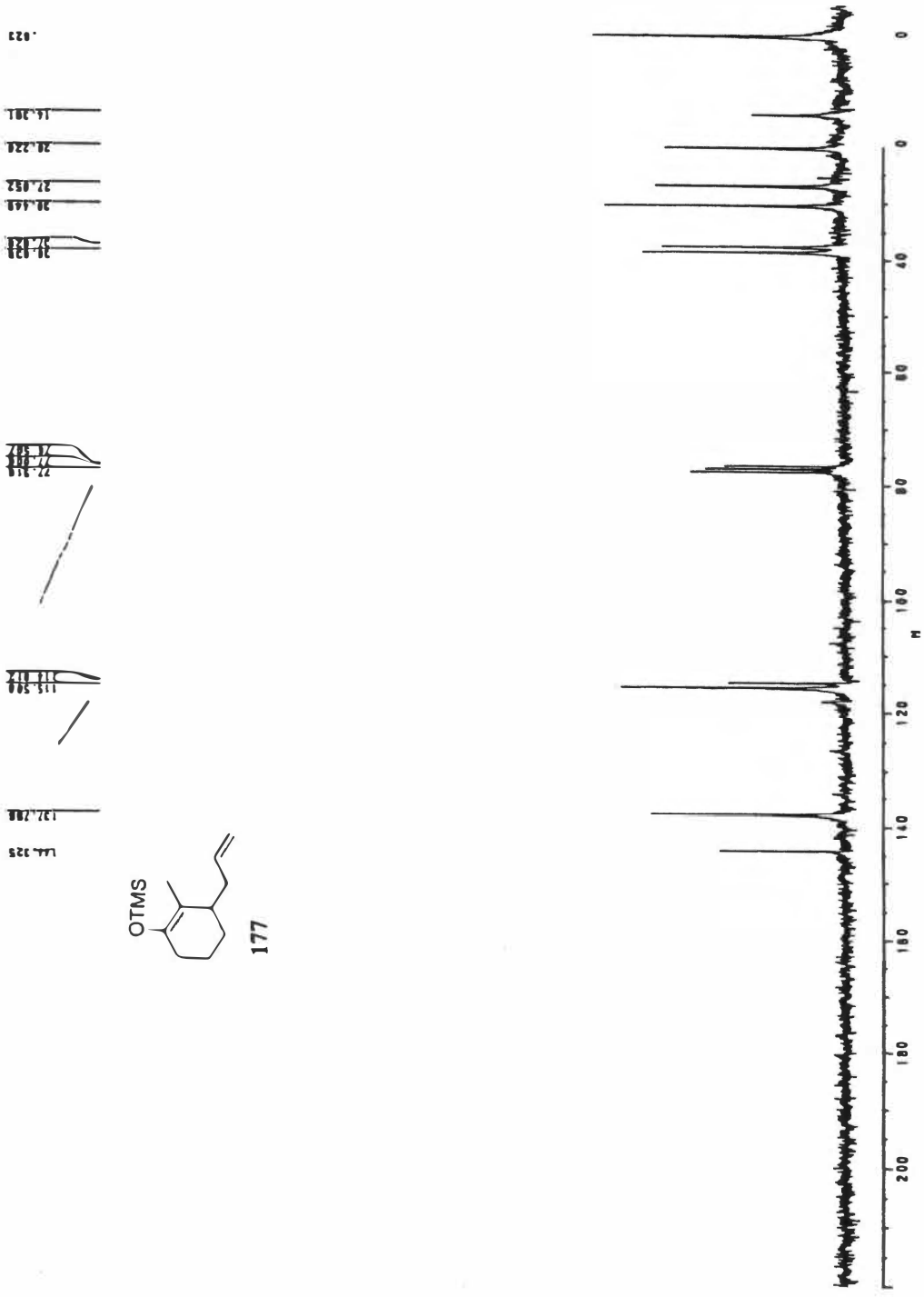


176

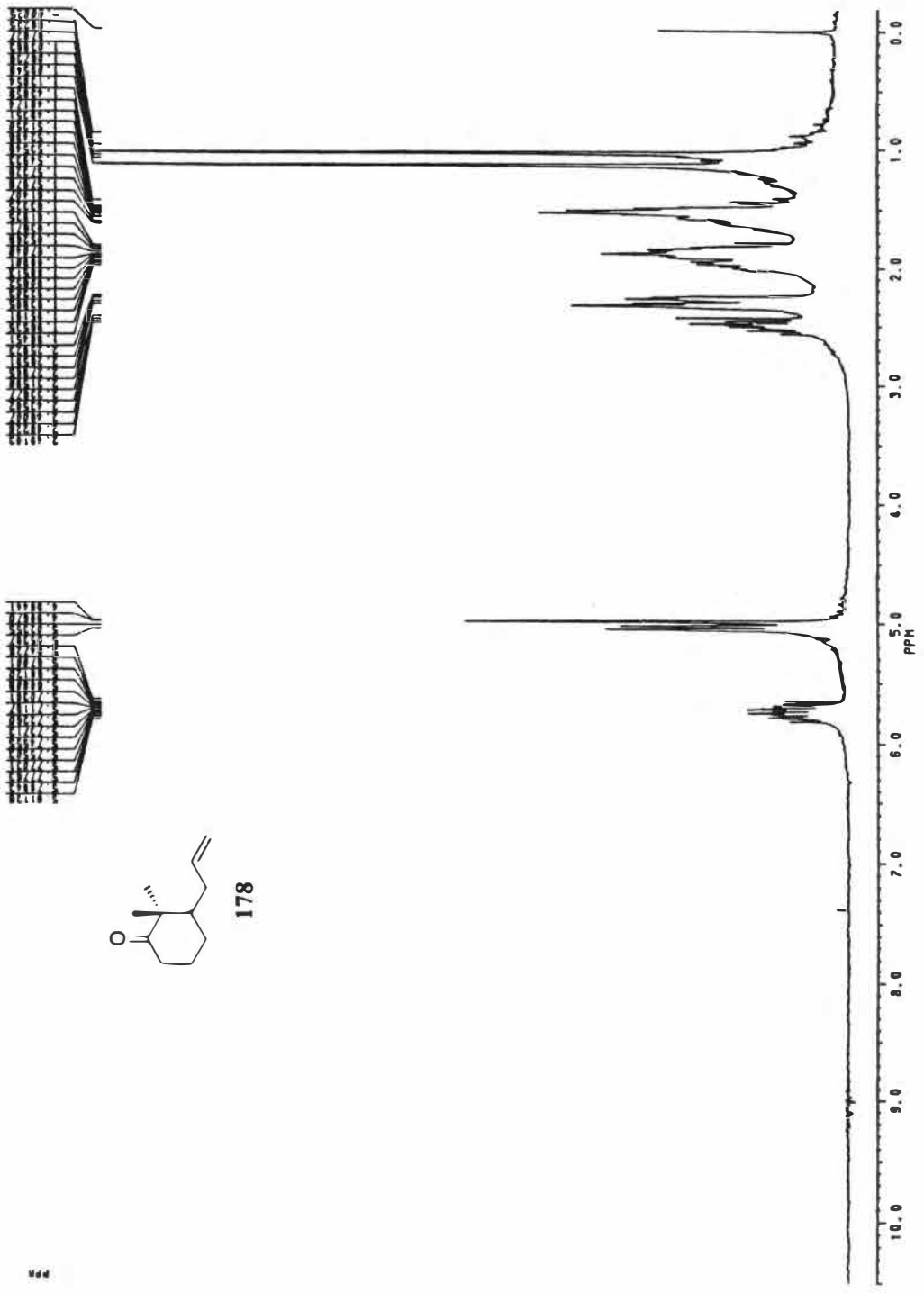


176

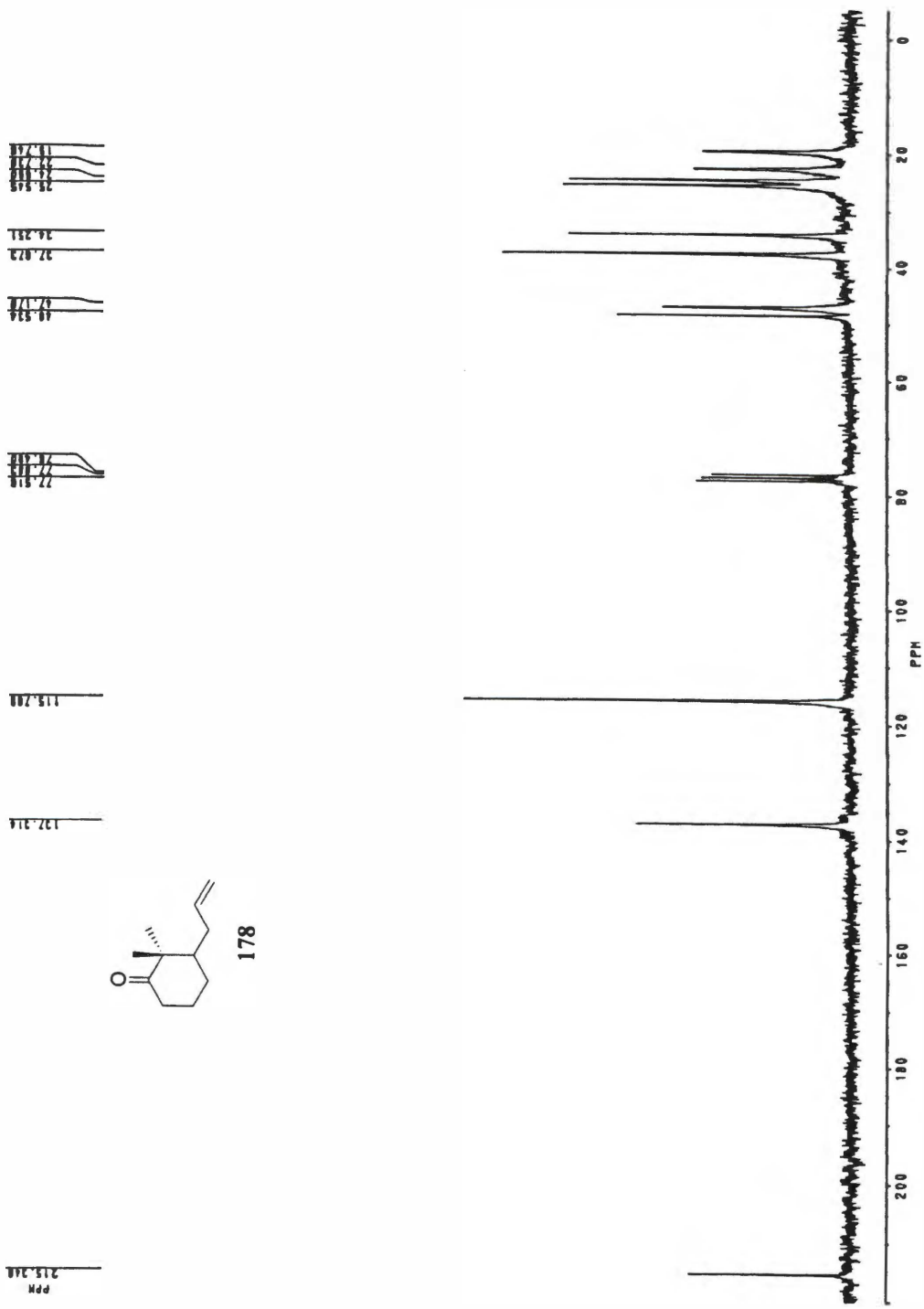

OTMS
177
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM



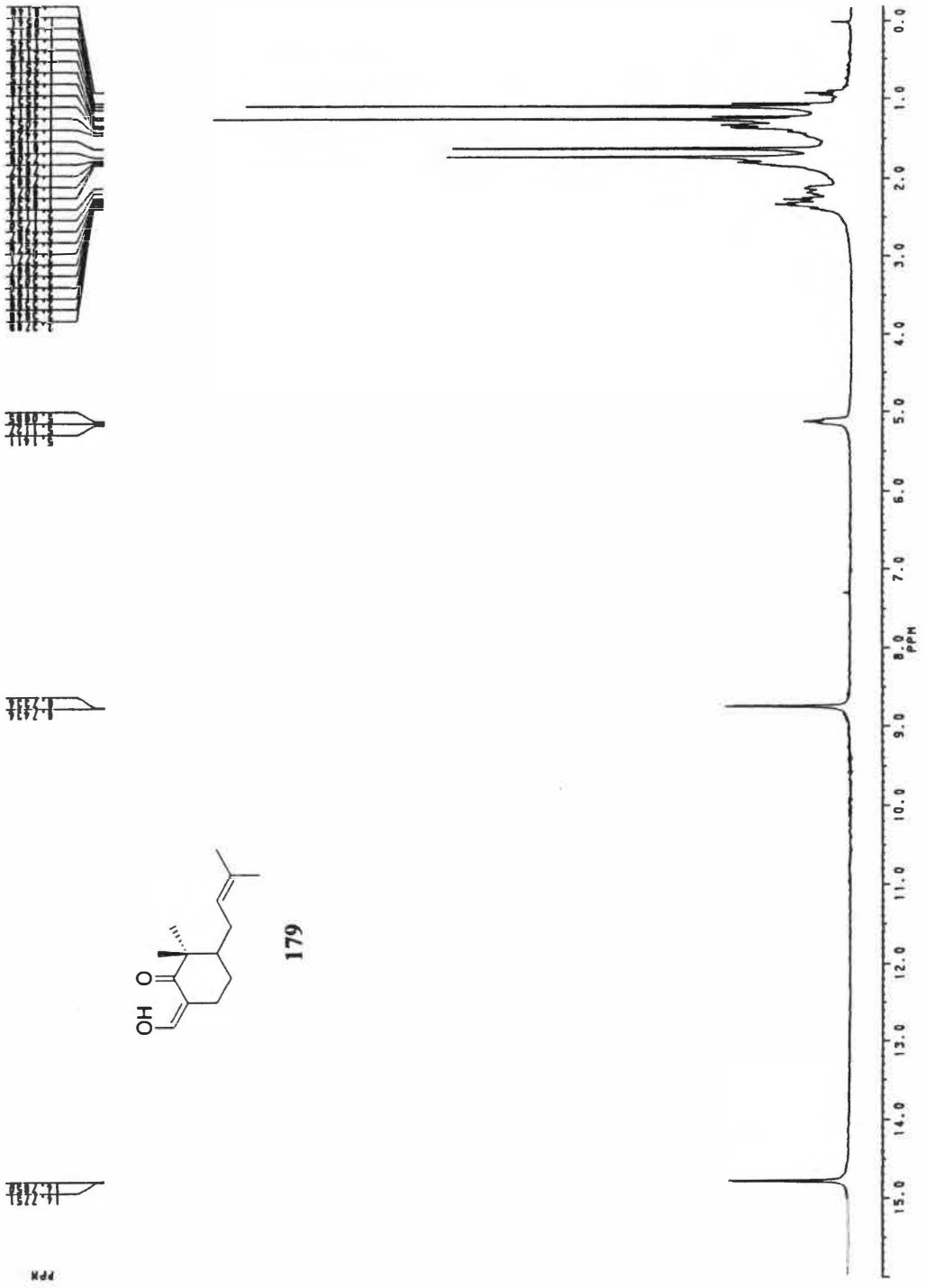
177

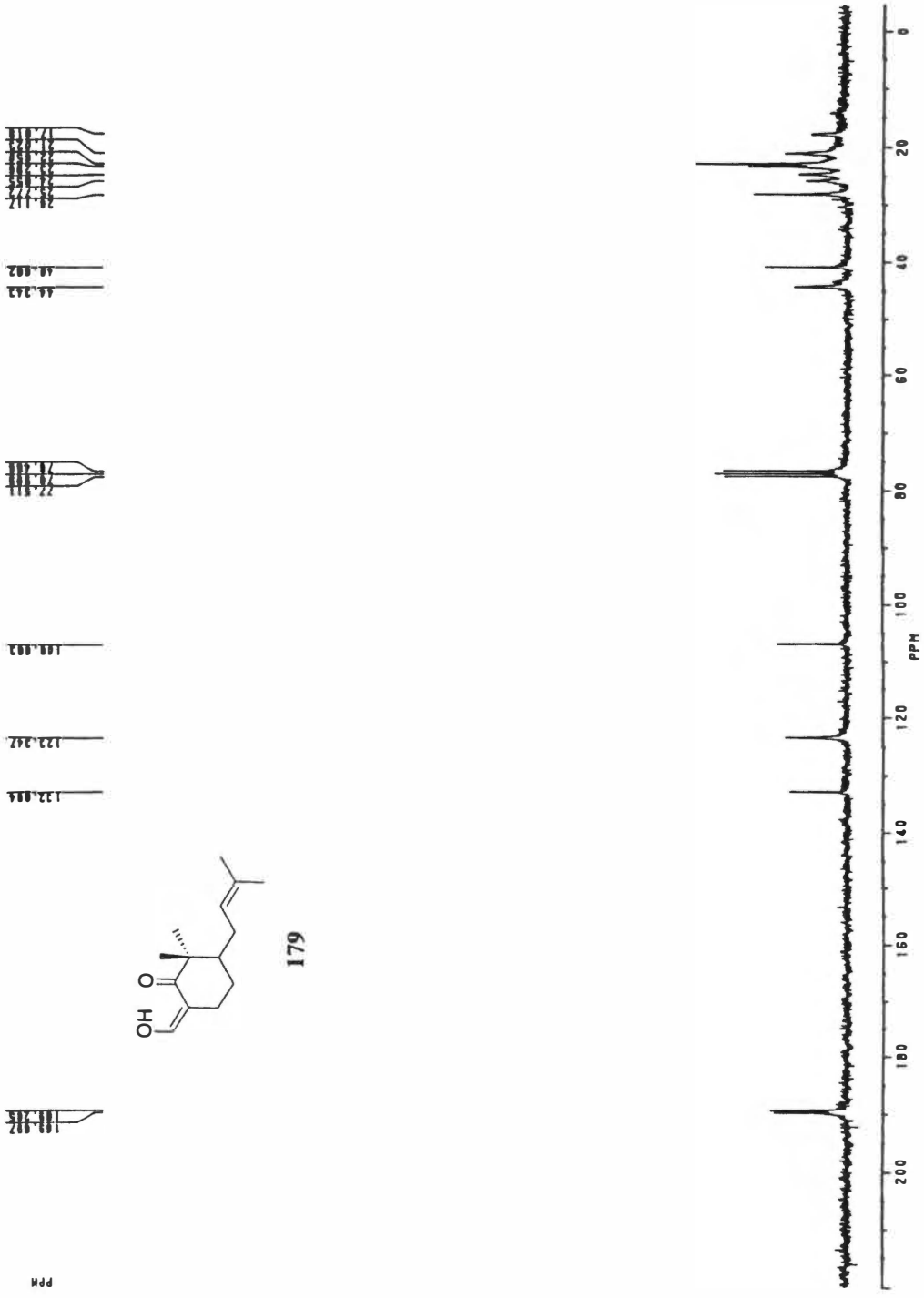


178

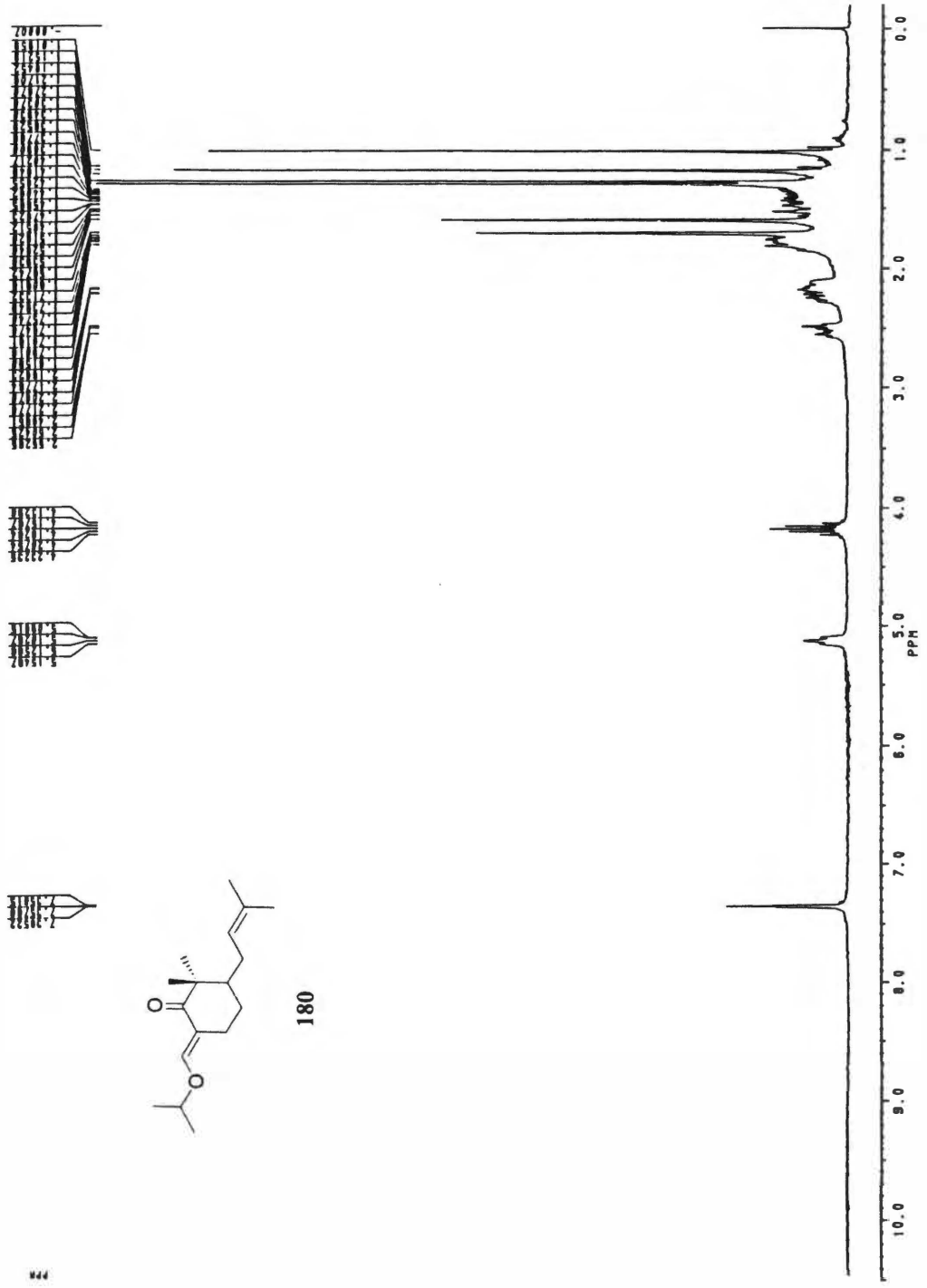


178

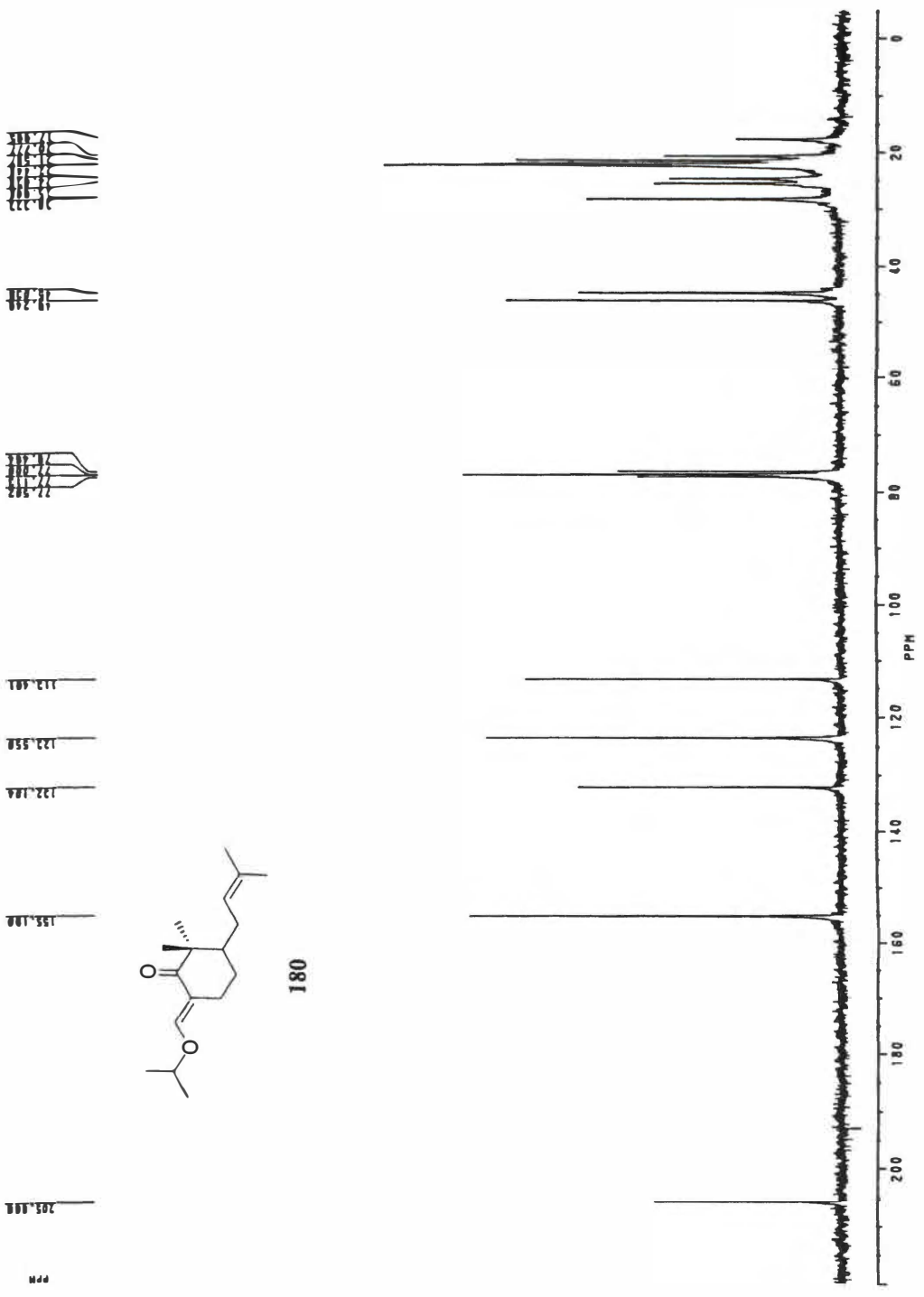

OH
O
179
PPM
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
11.0
12.0
13.0
14.0
15.0



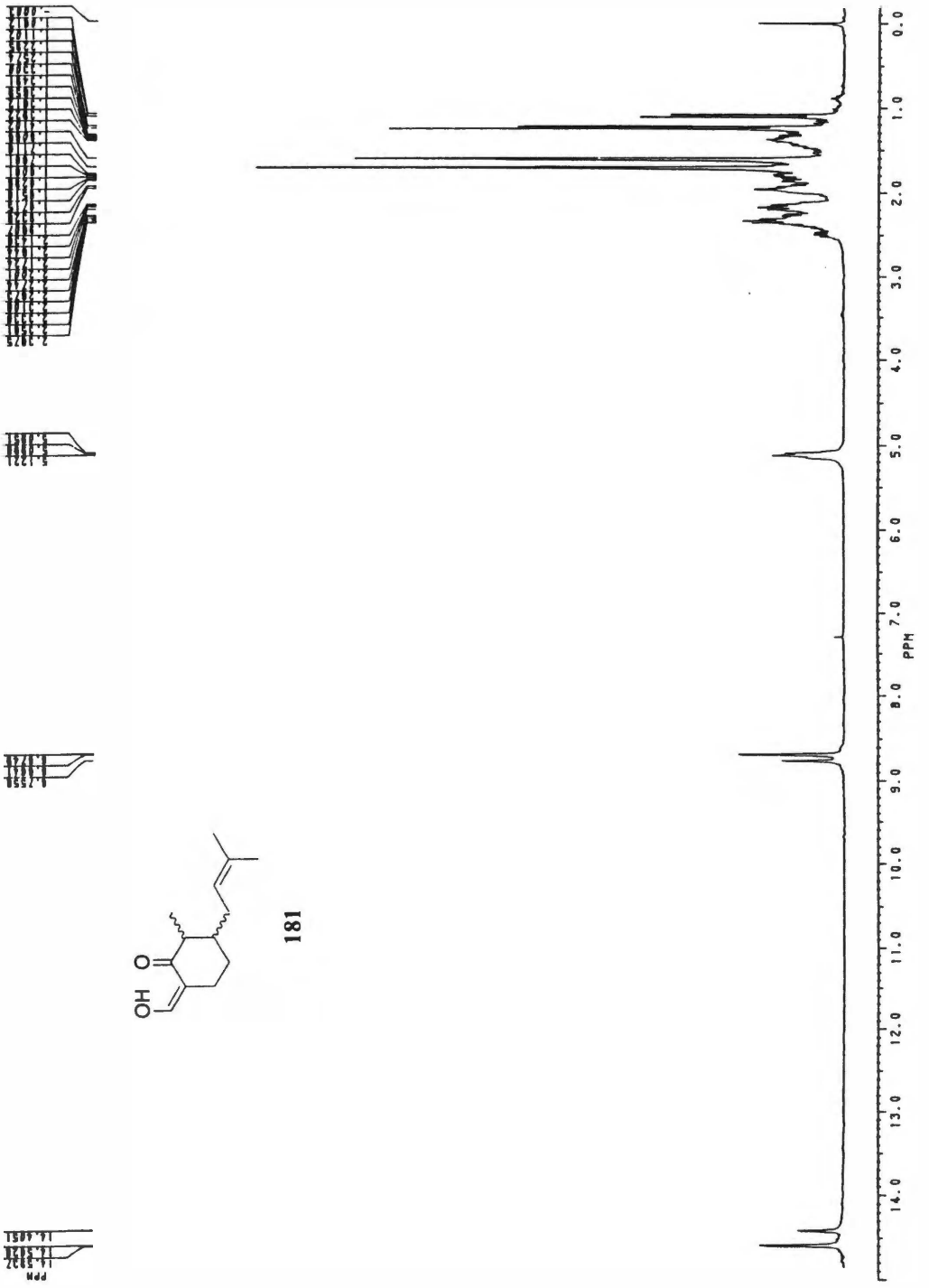
179



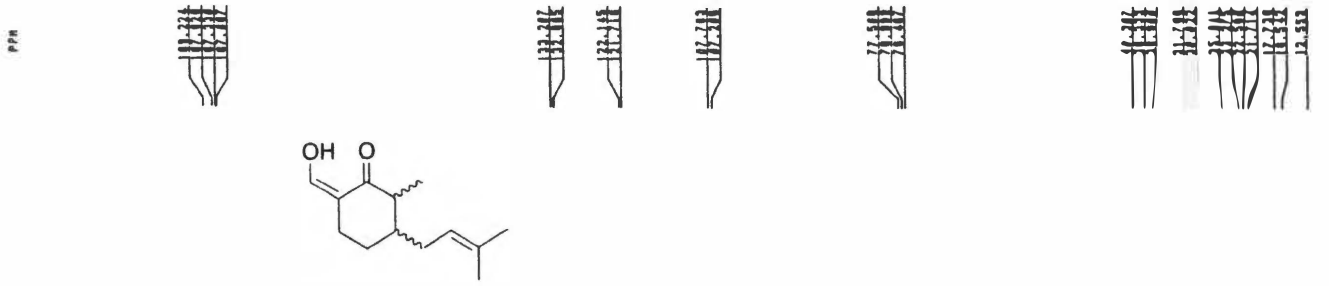
180



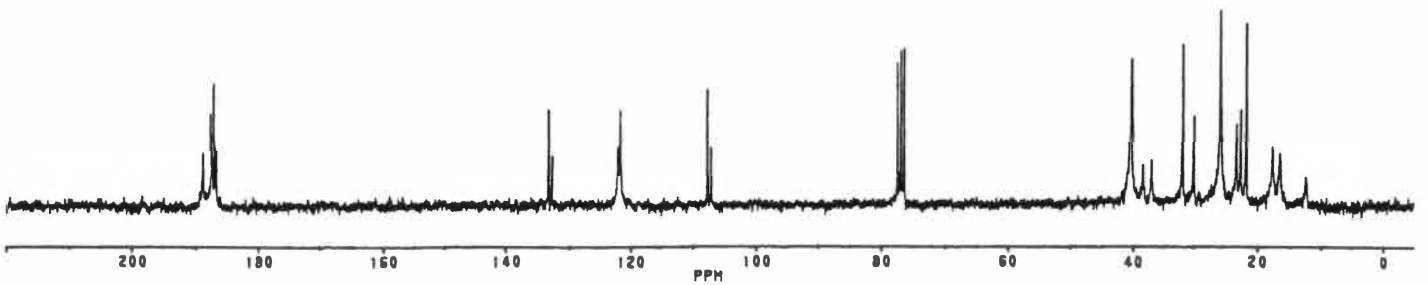
180

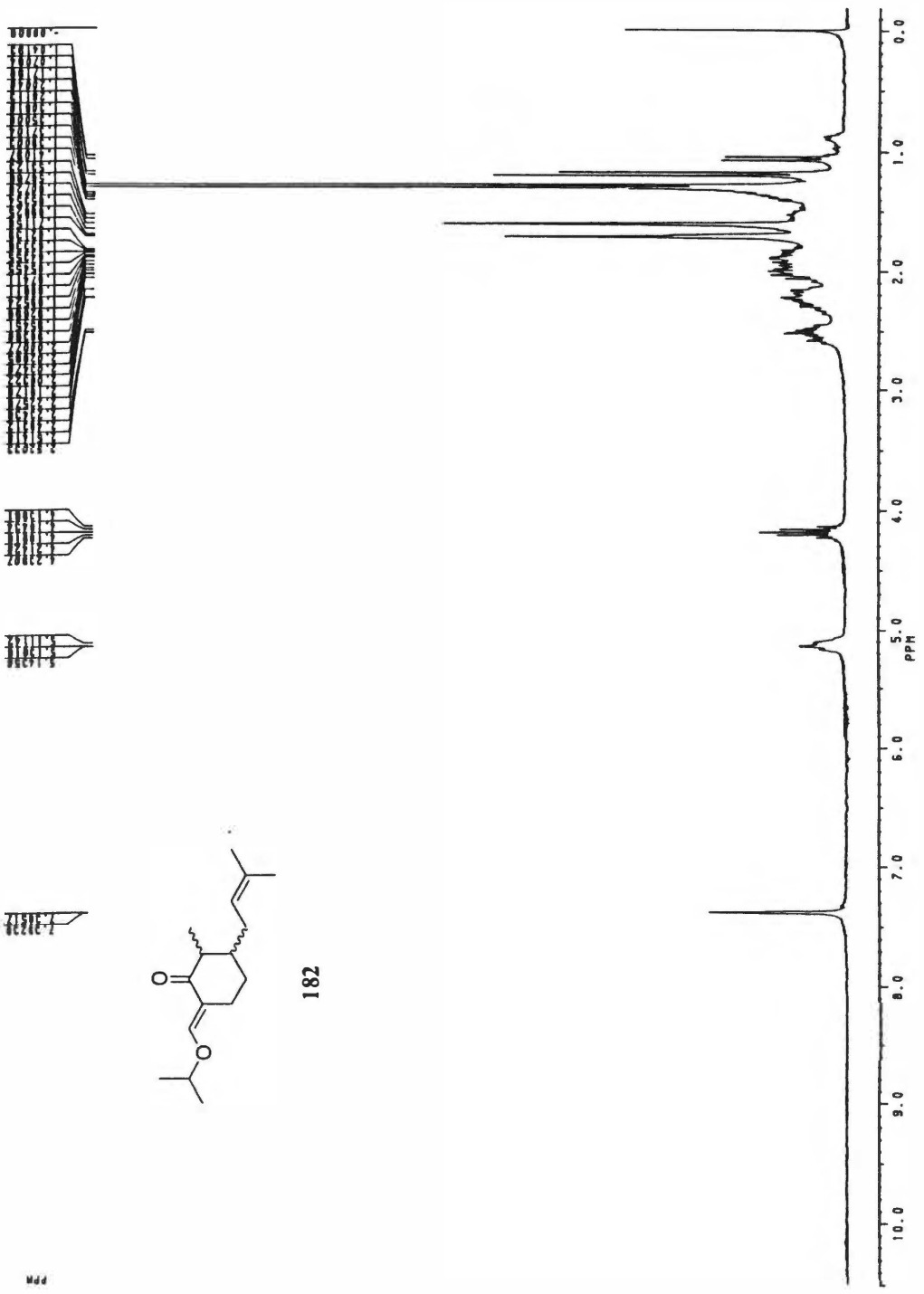


181

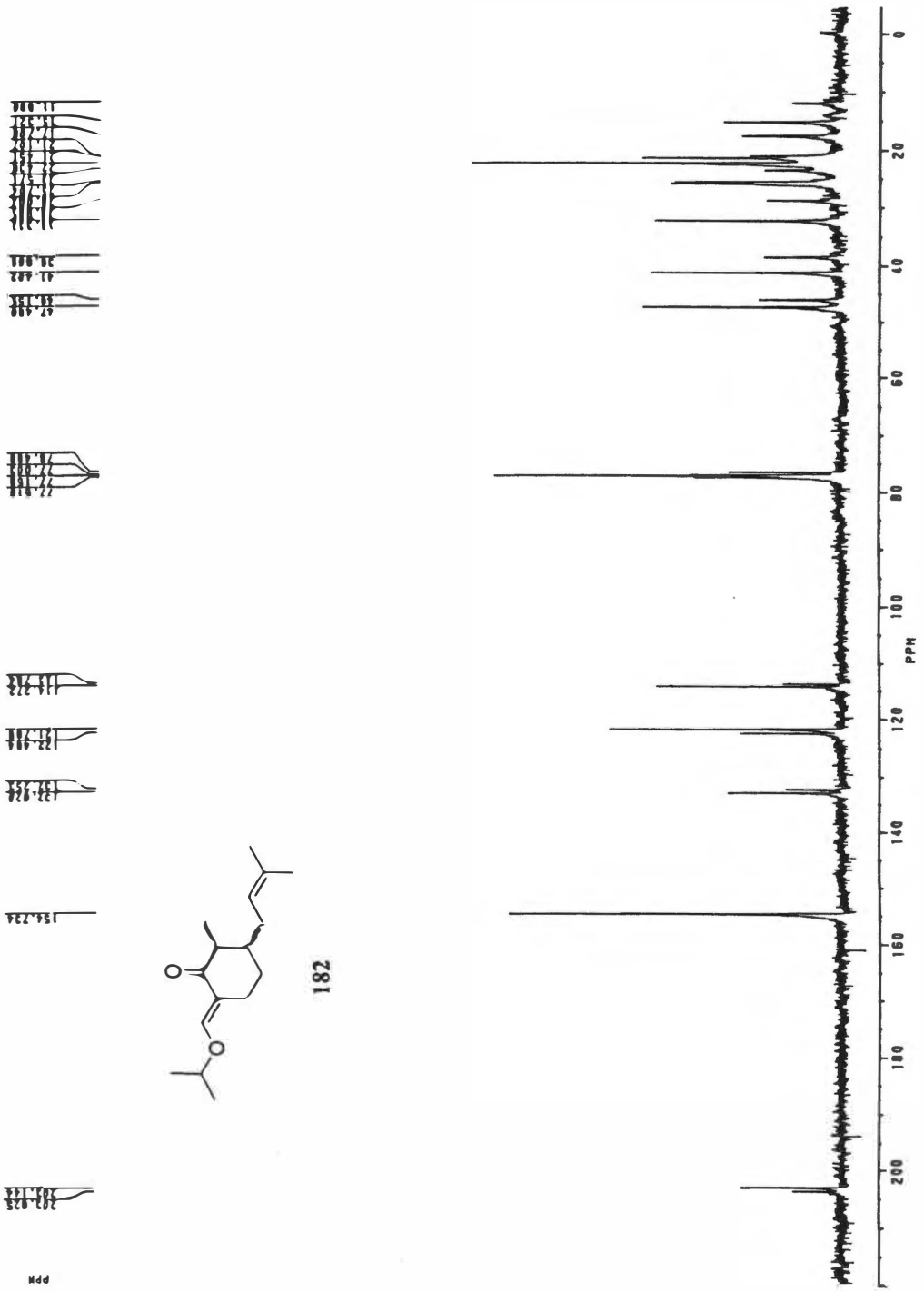


181

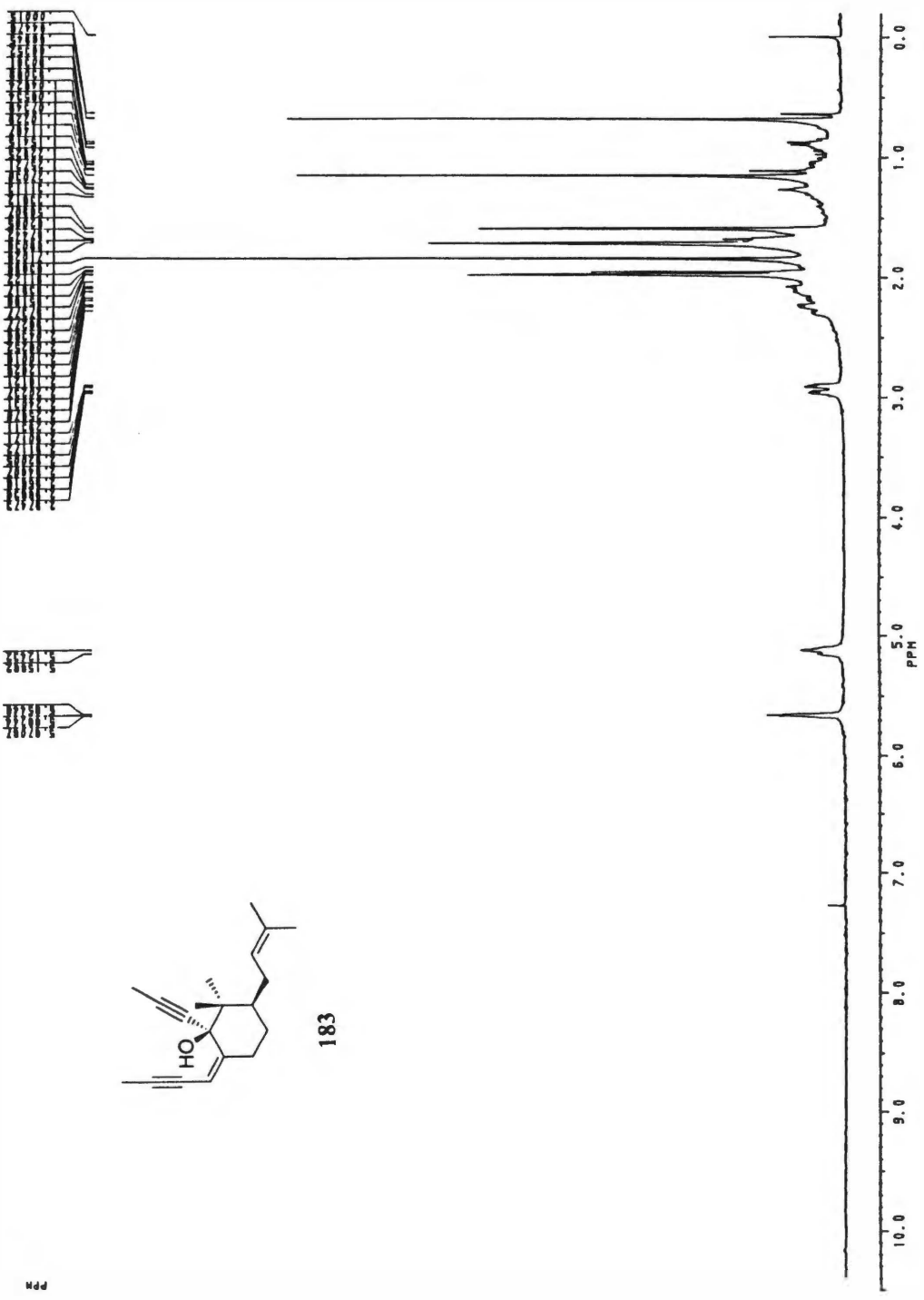


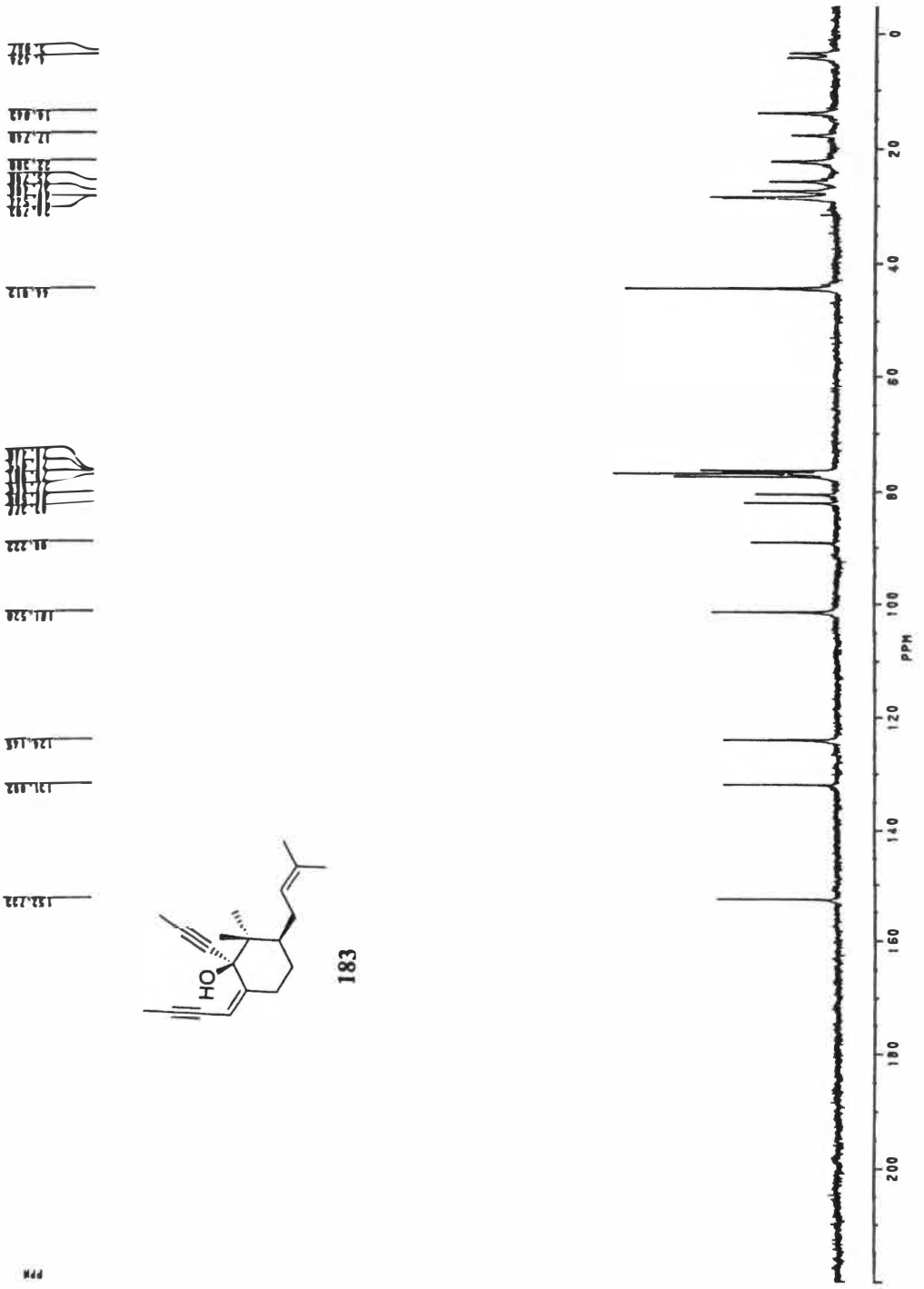


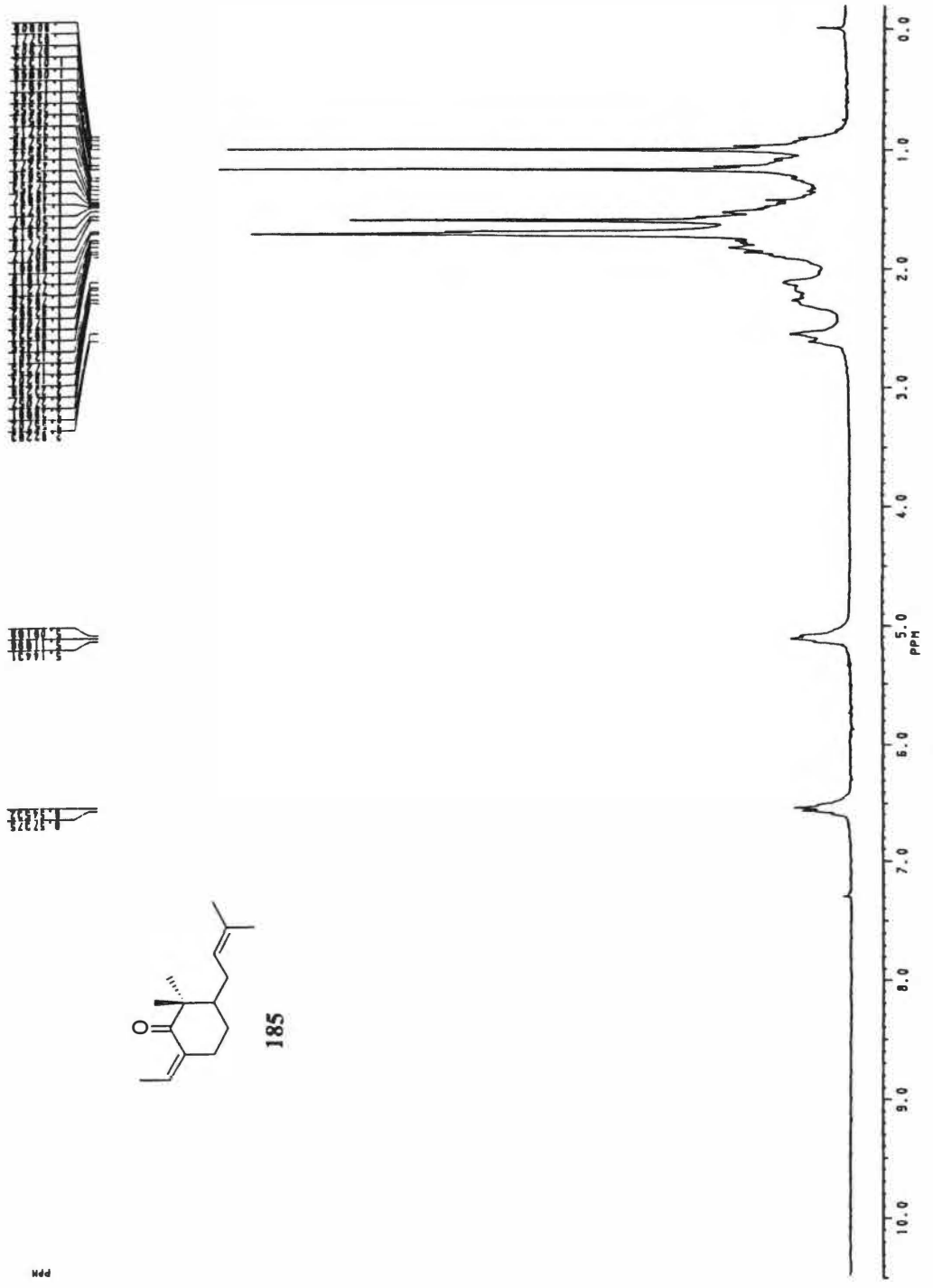
182

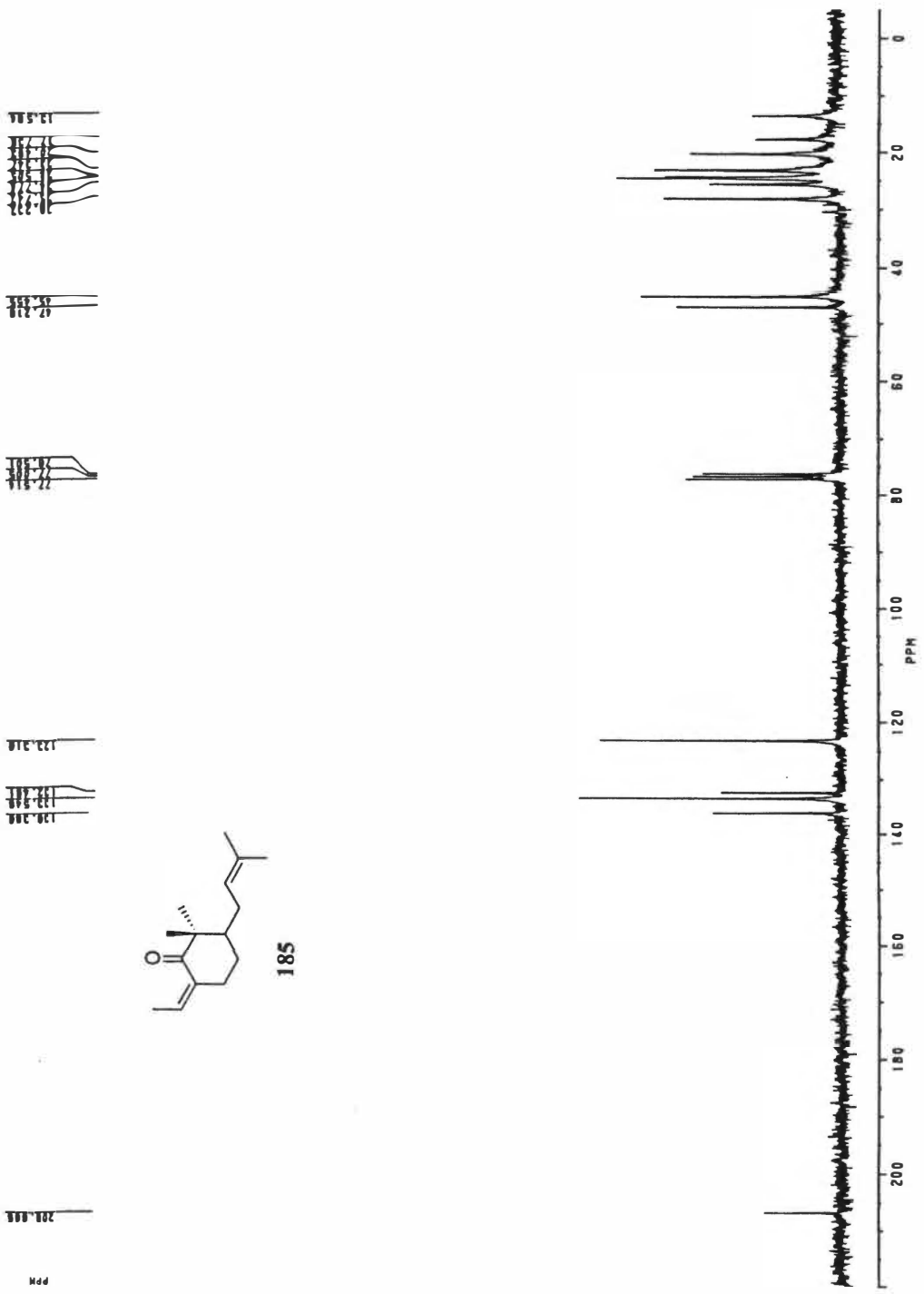


182

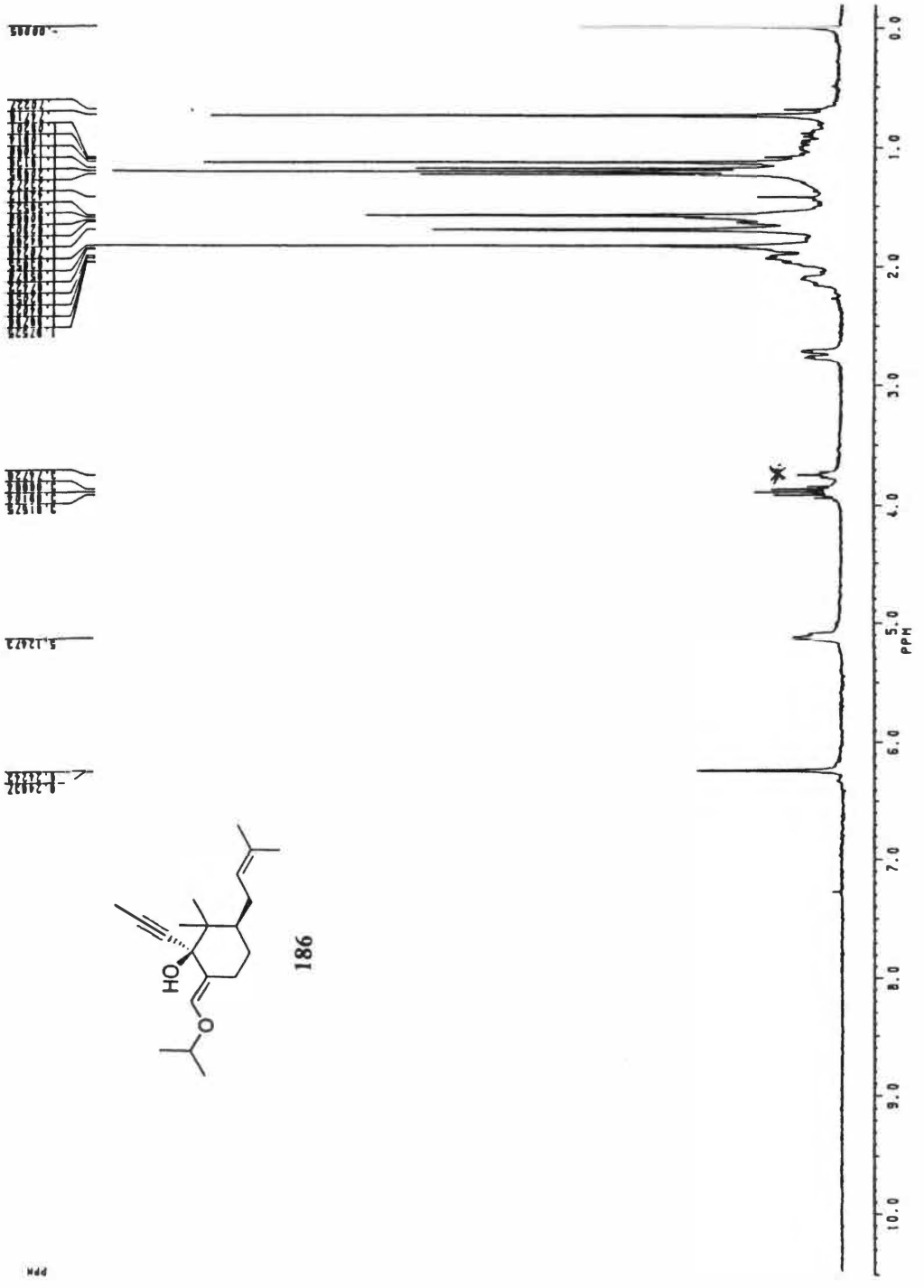

HO
183
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

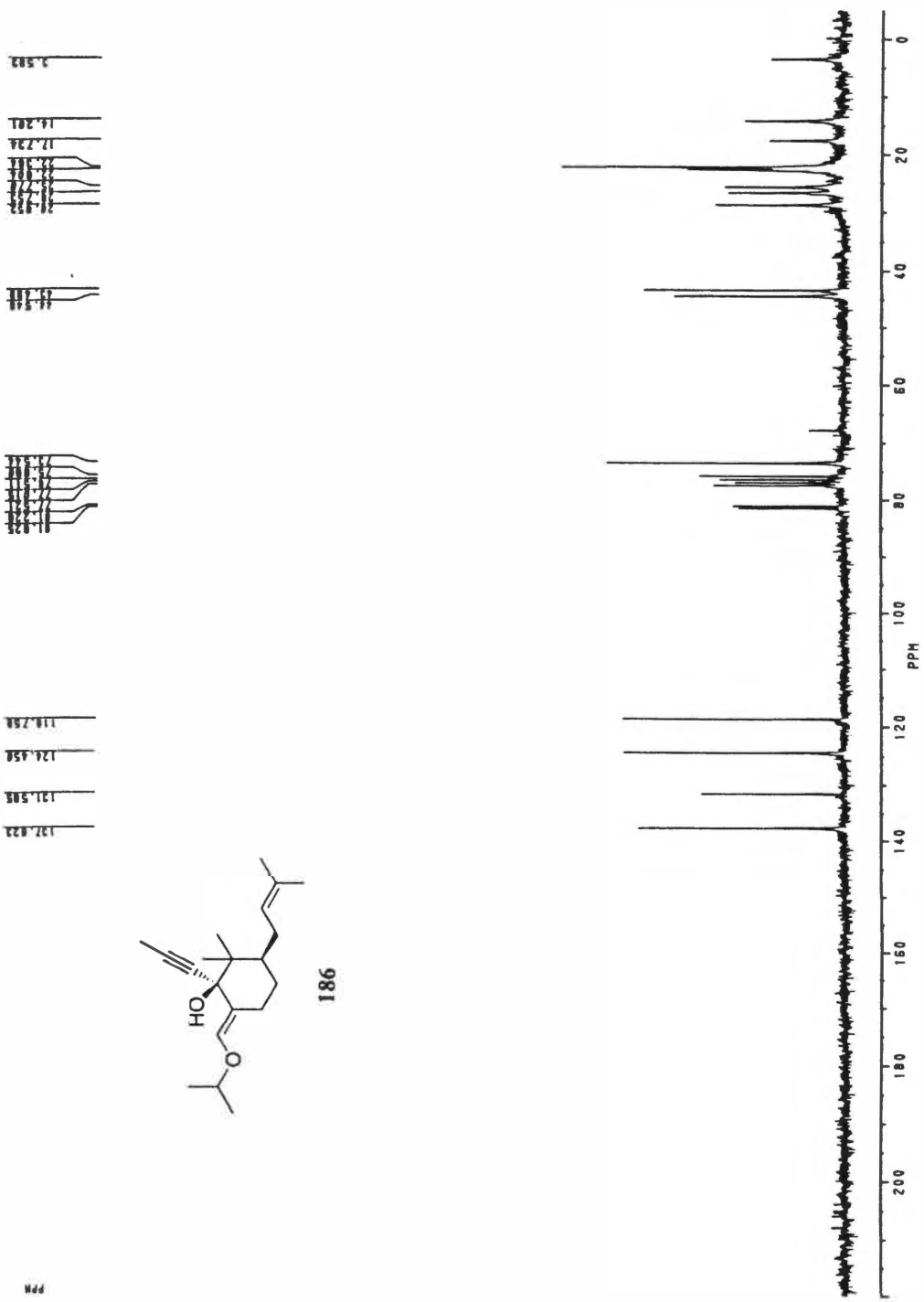

HO
183
PPM
0
20
40
60
80
100
120
140
160
180
200


185
PPM

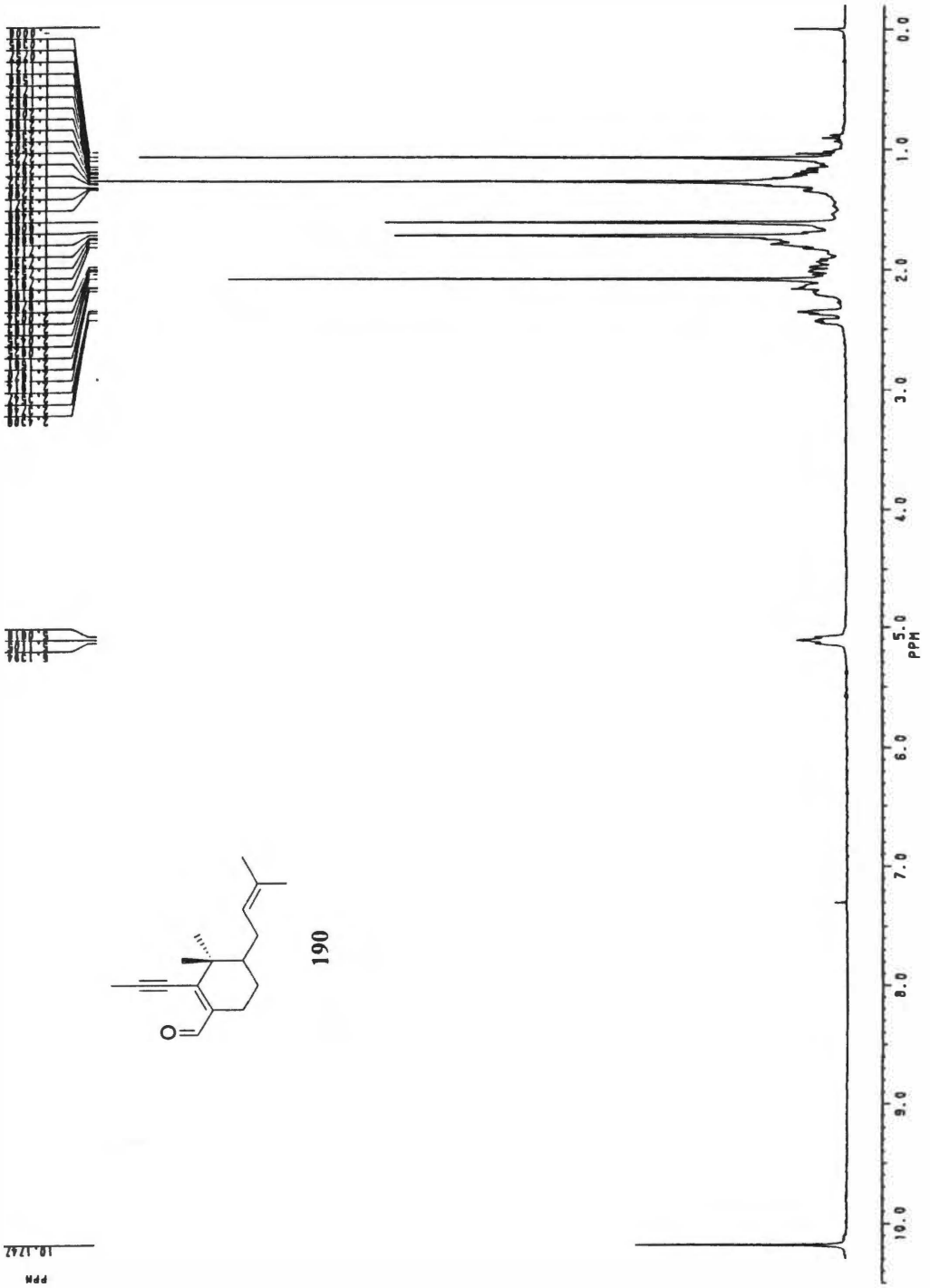


185


HO
O
186
PPM

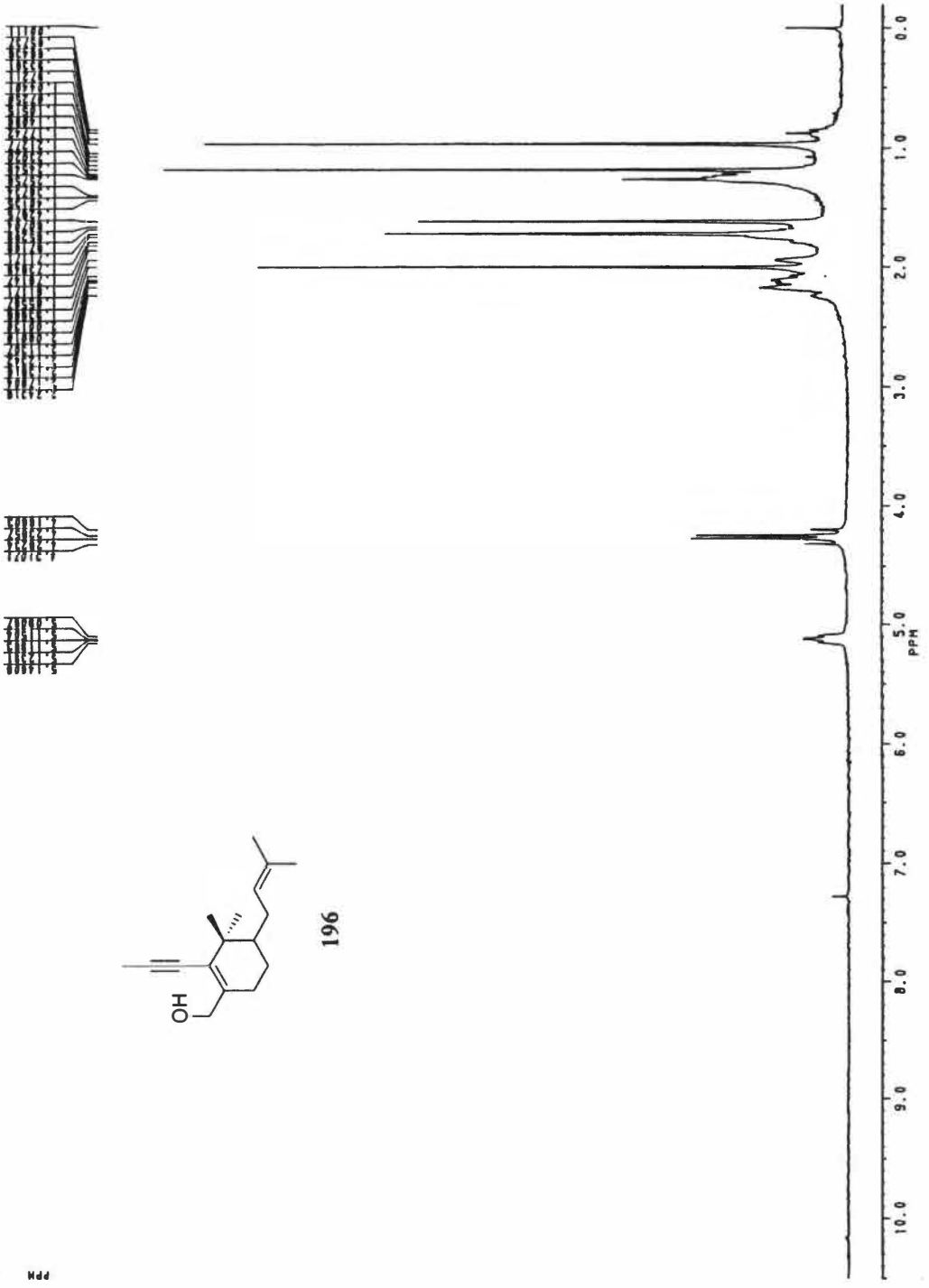


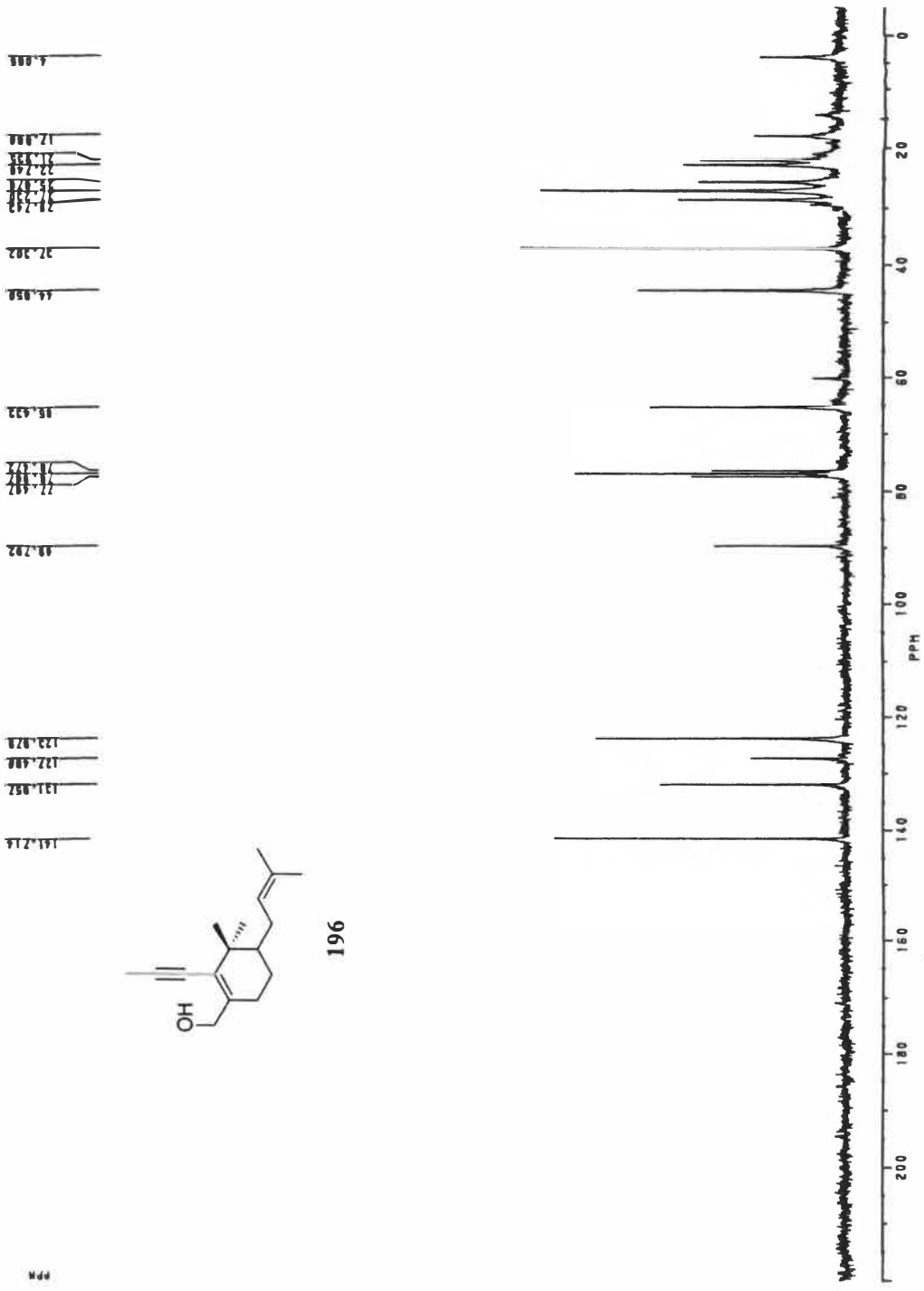
186



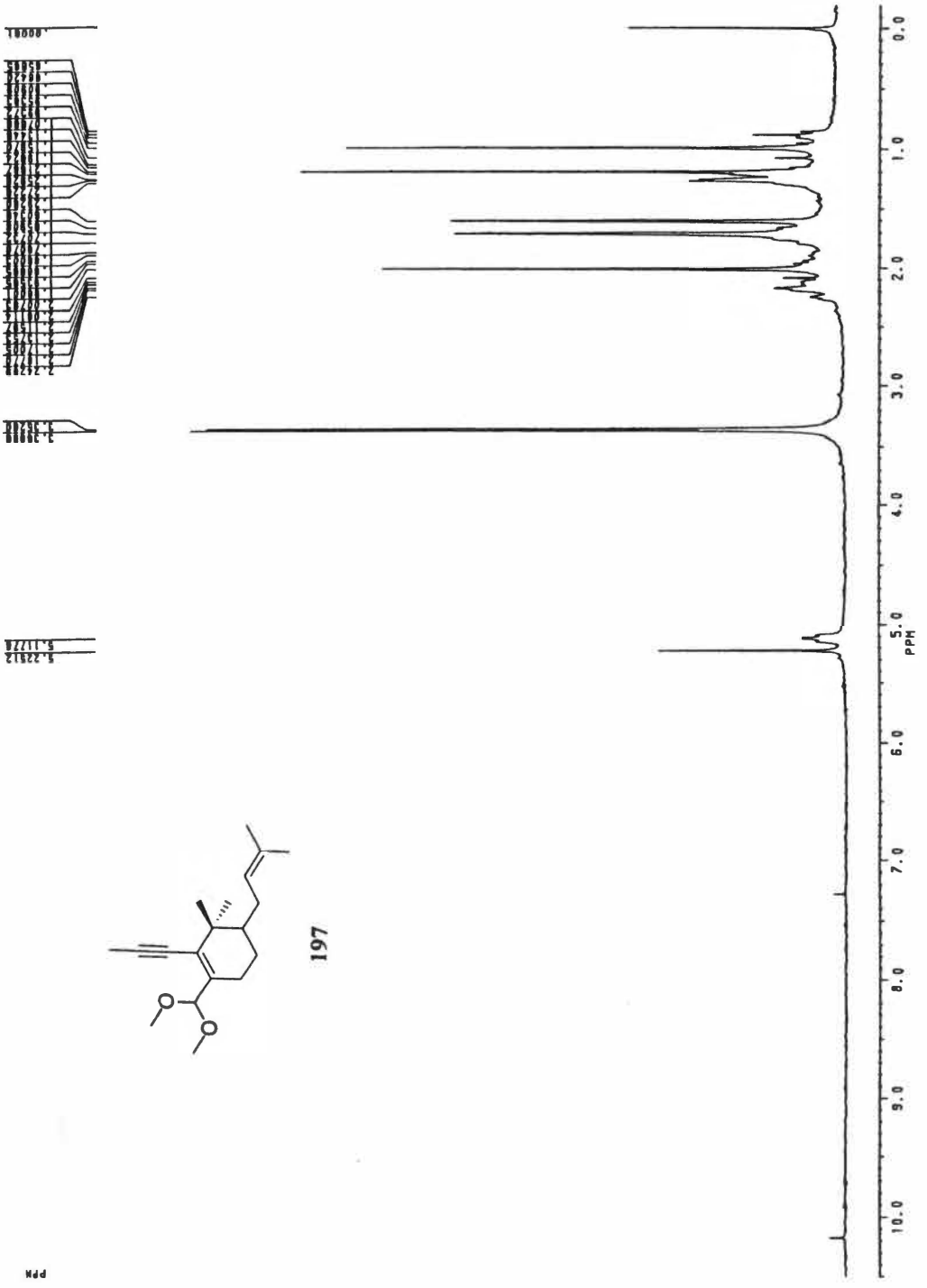
190

190

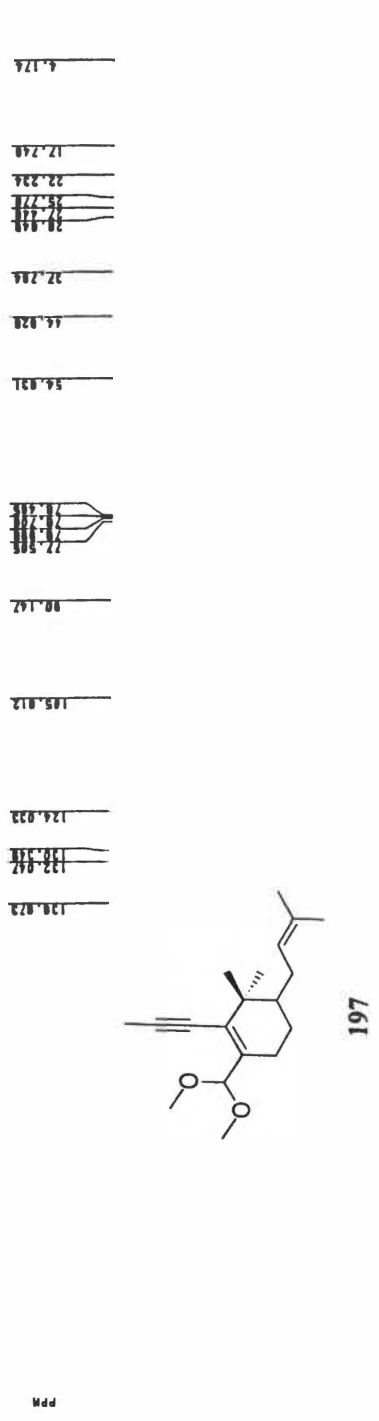

OH
196
PPM
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
PPM



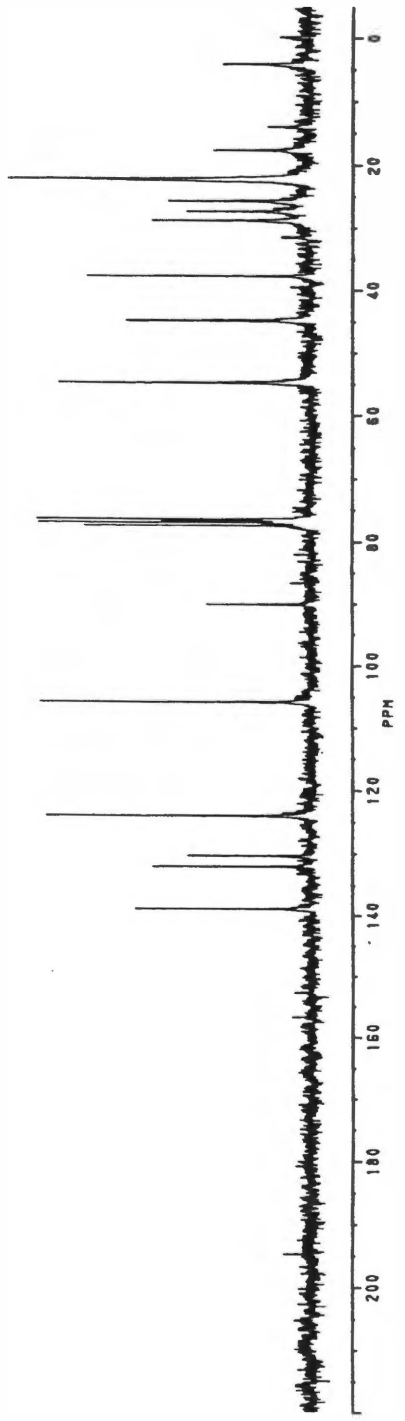
196

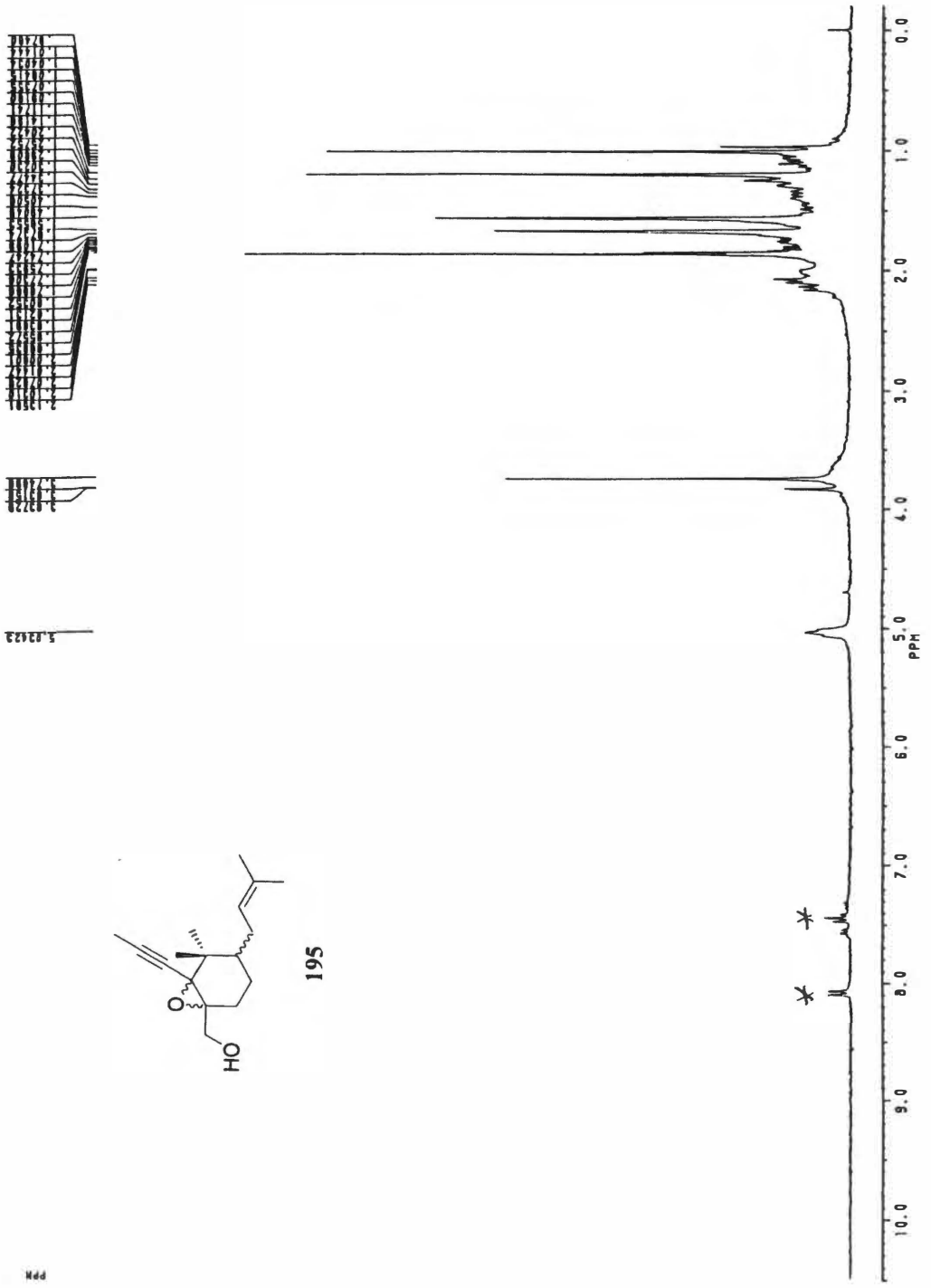


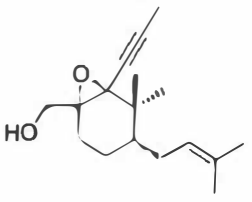
197



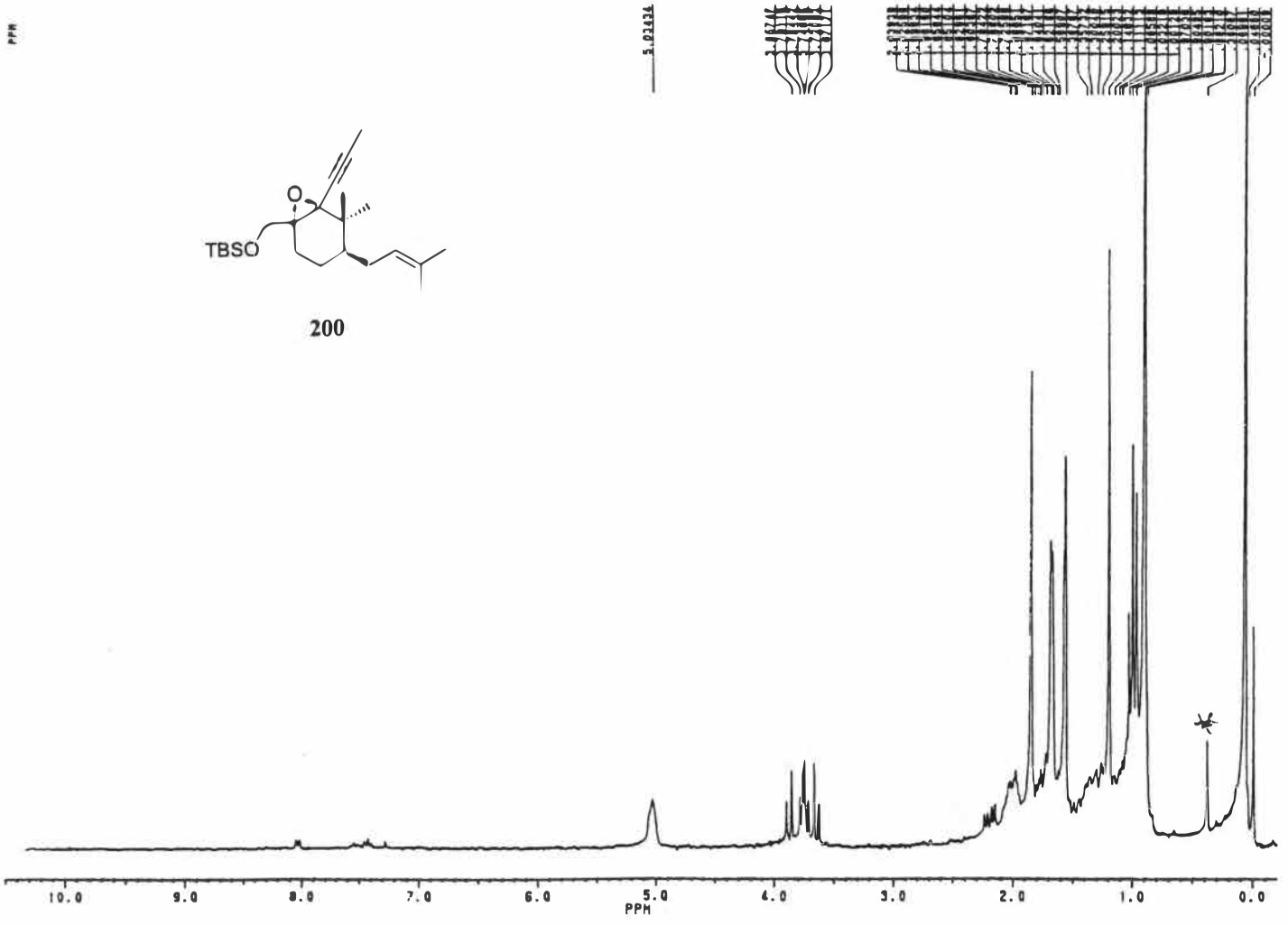
197



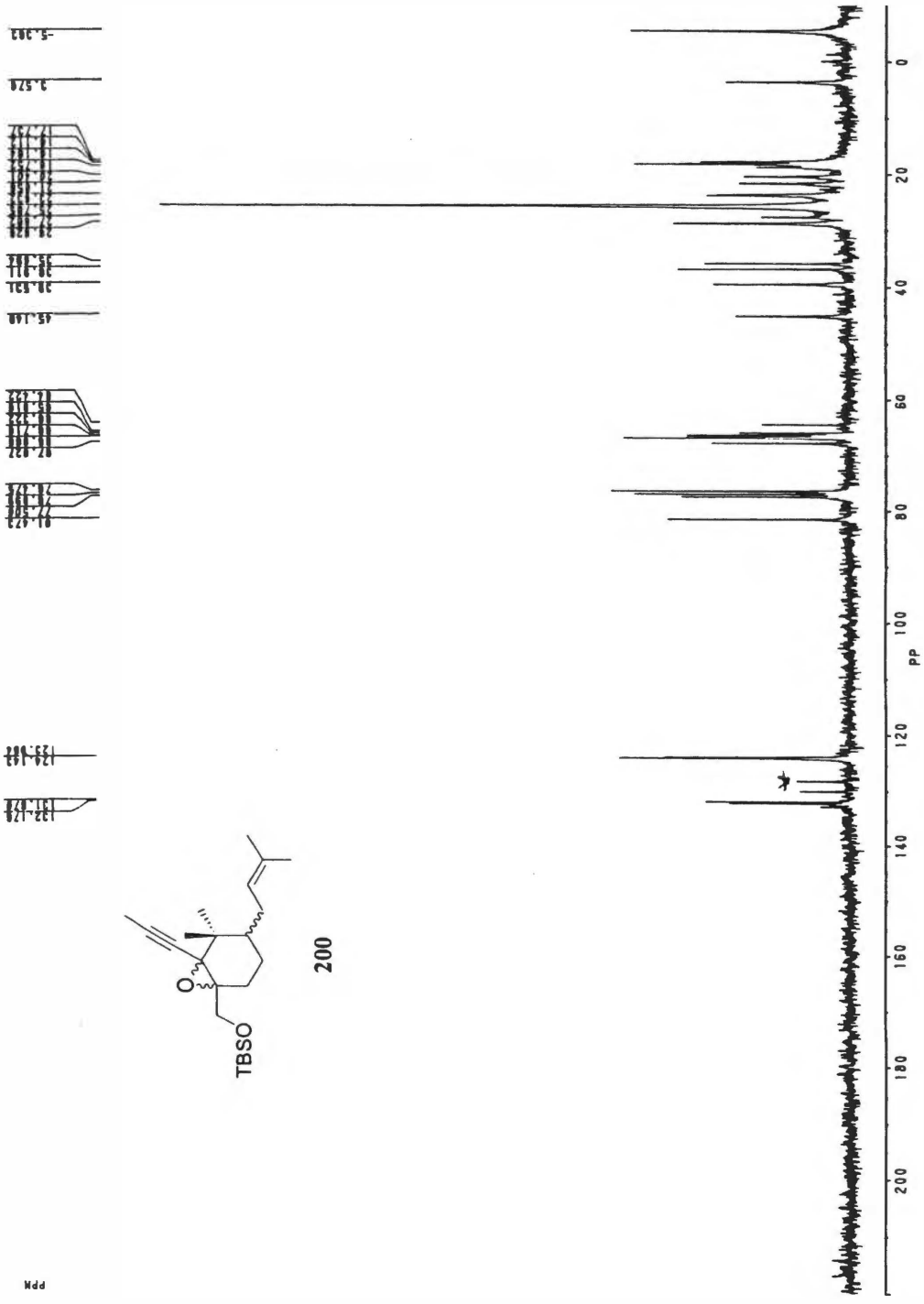

OH
O
195
PPM

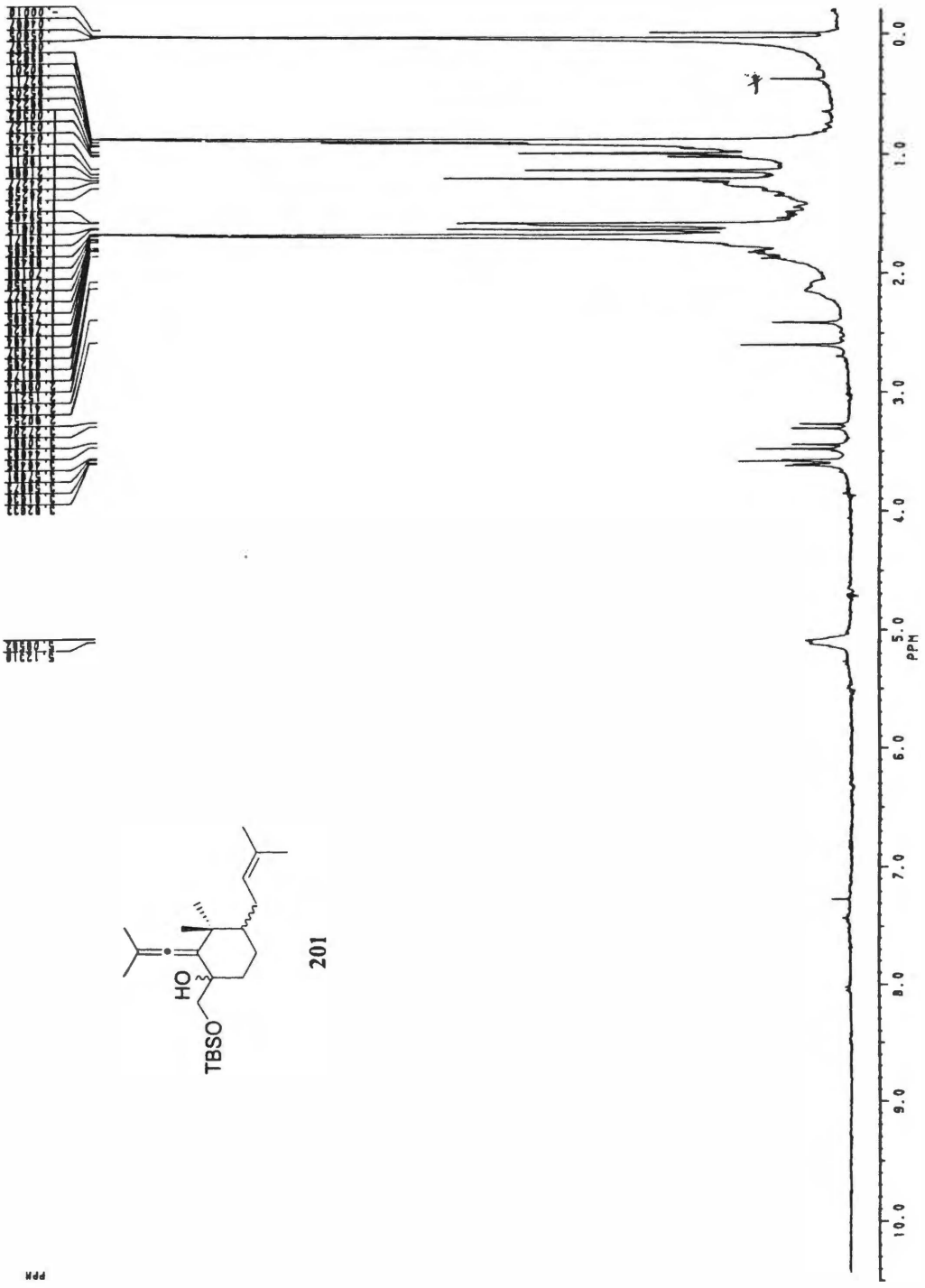


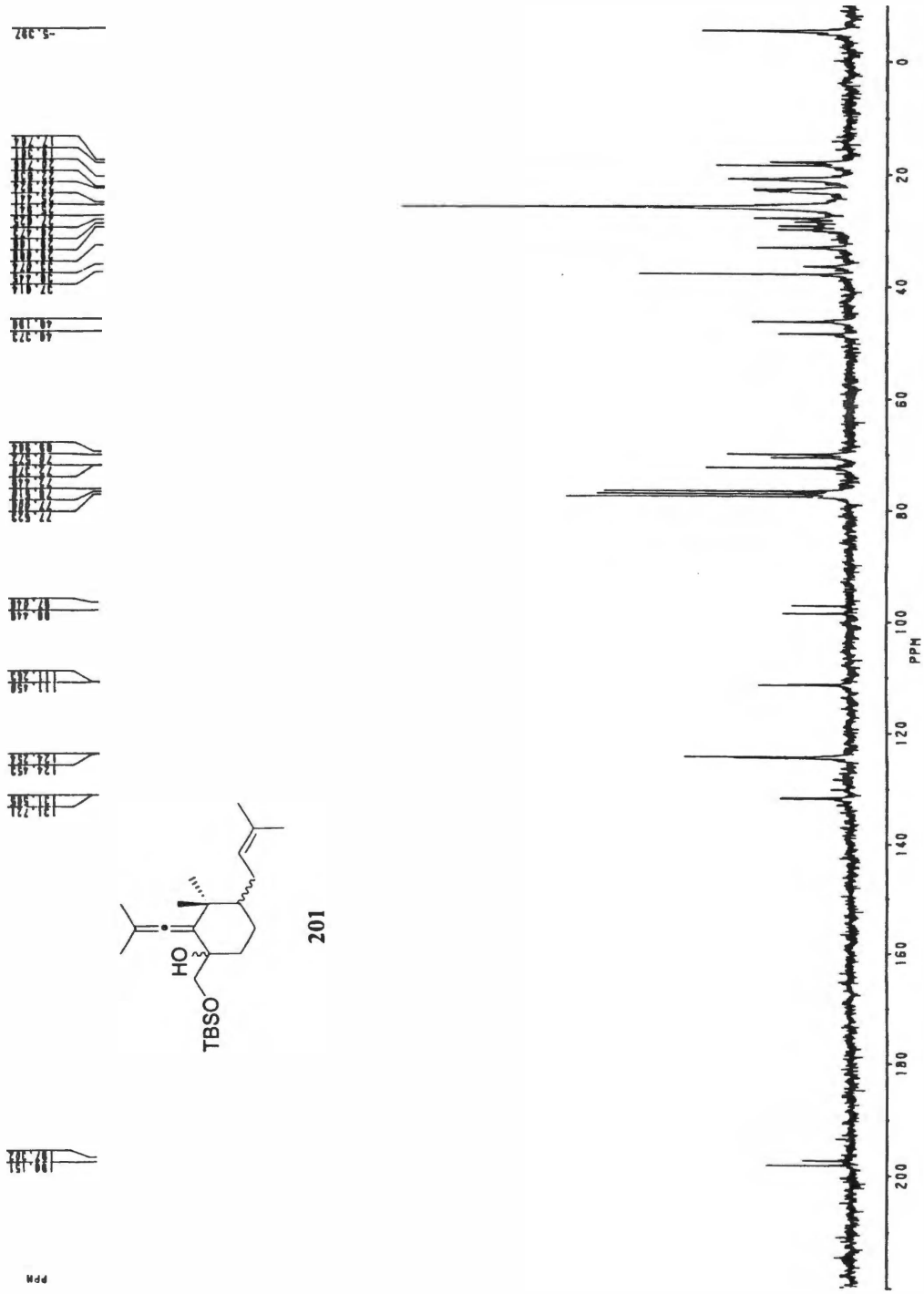
195

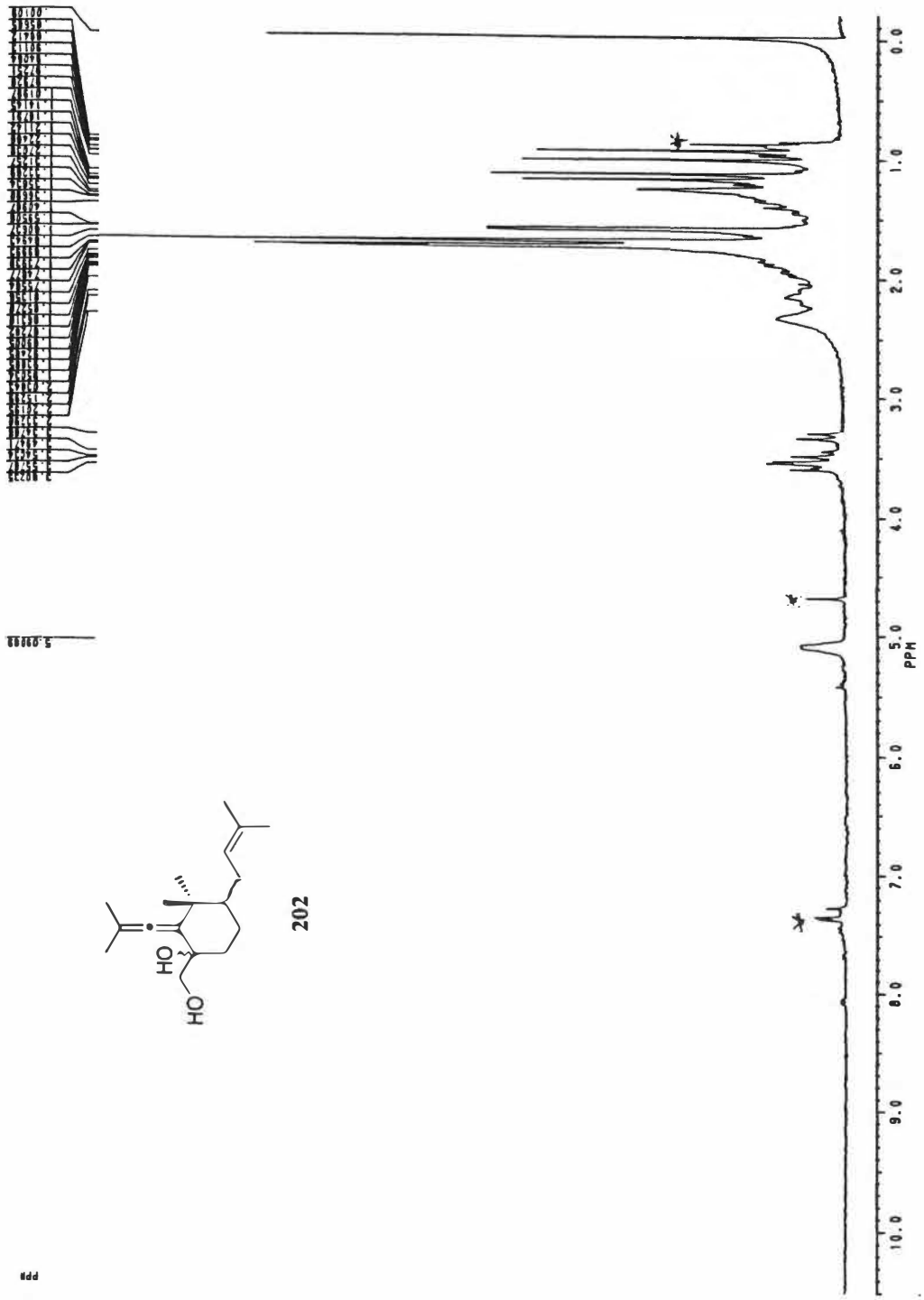


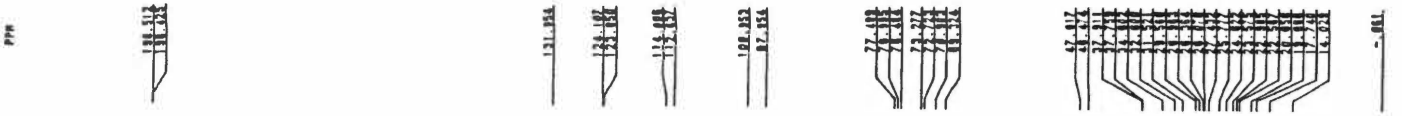
200

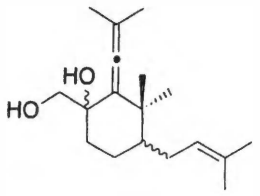

TBSO
O
200
PPM
PP


HO
TBSO
201
PPM

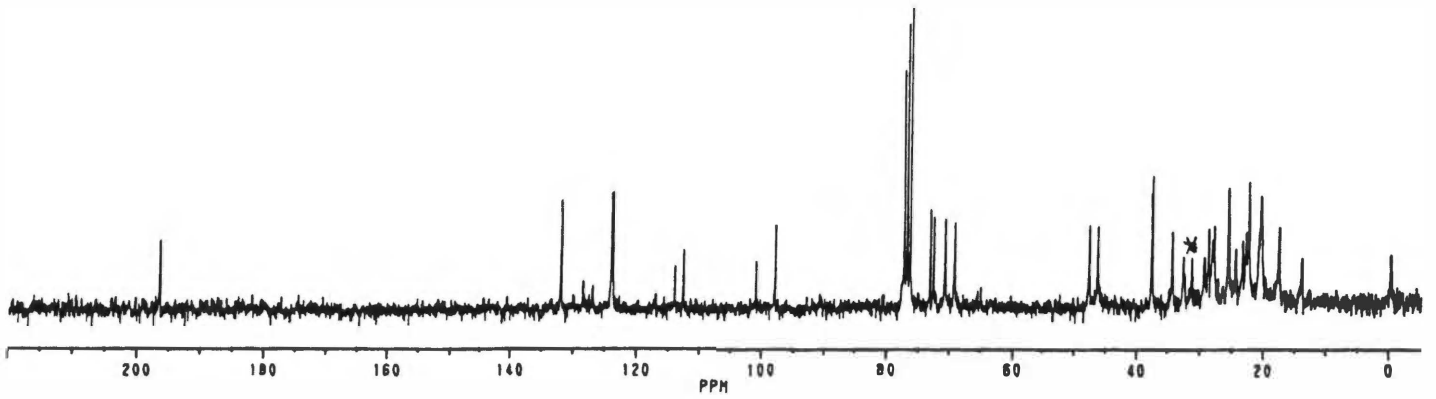

HO
TBSO
201
PPM

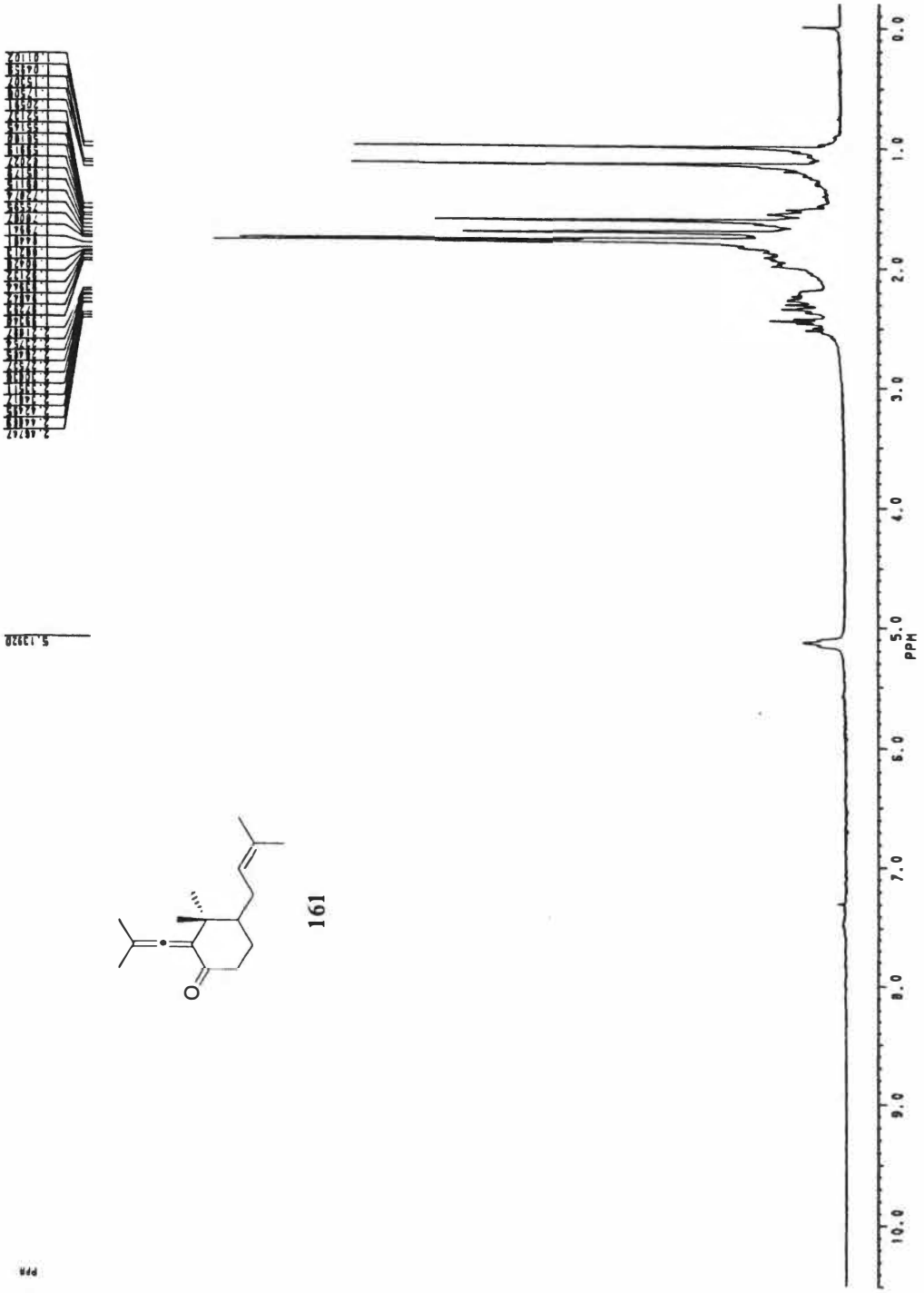

HO
HO
202
PPM



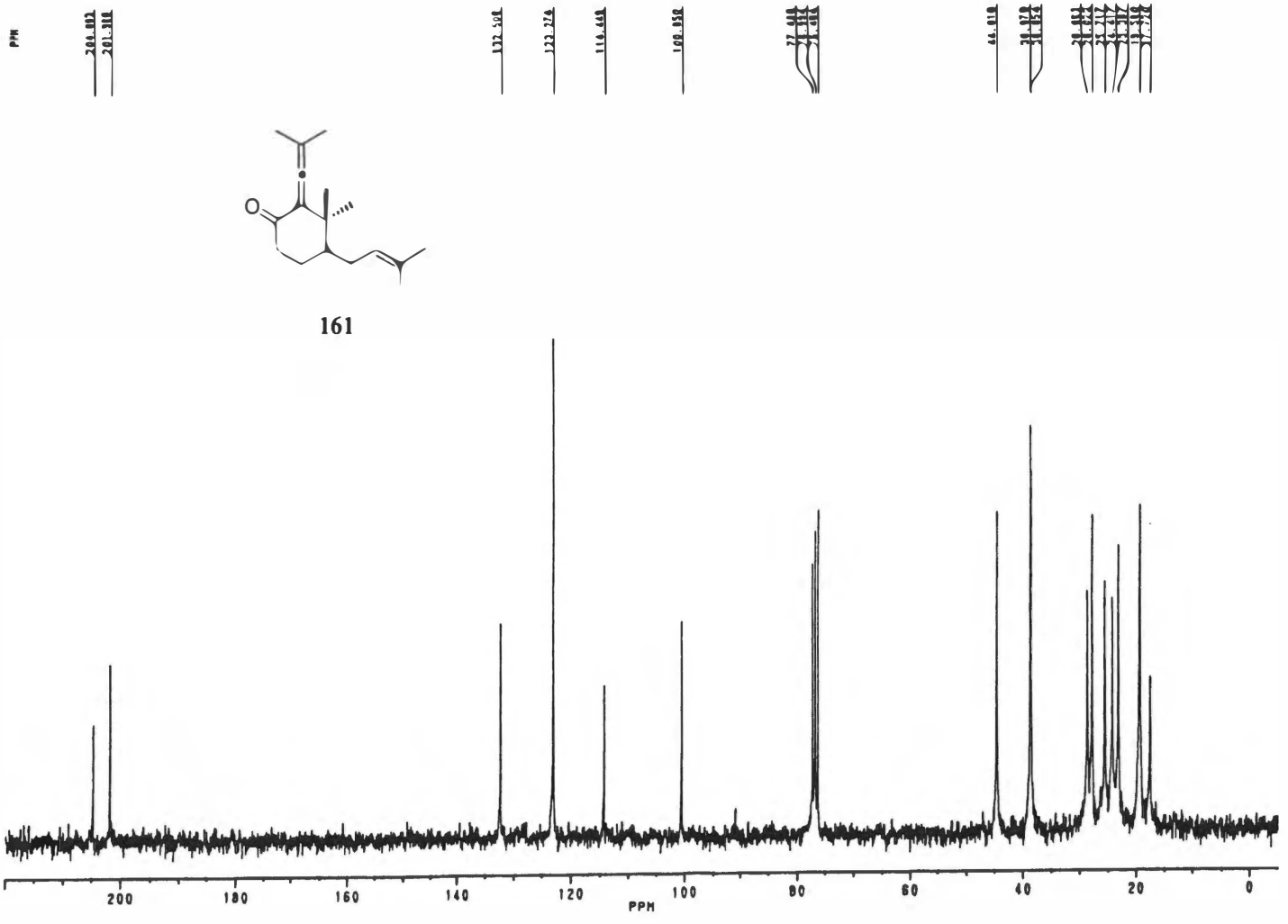


202

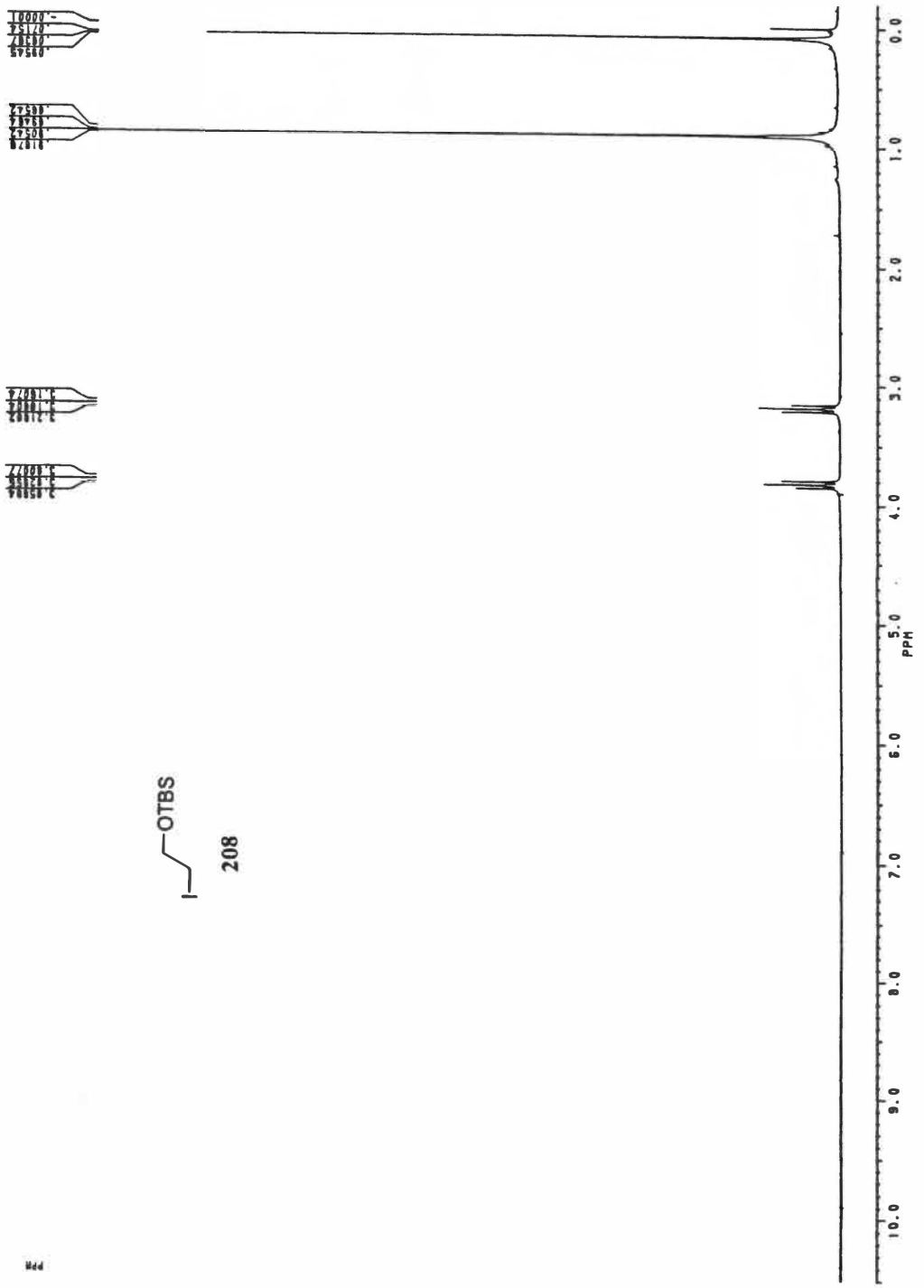


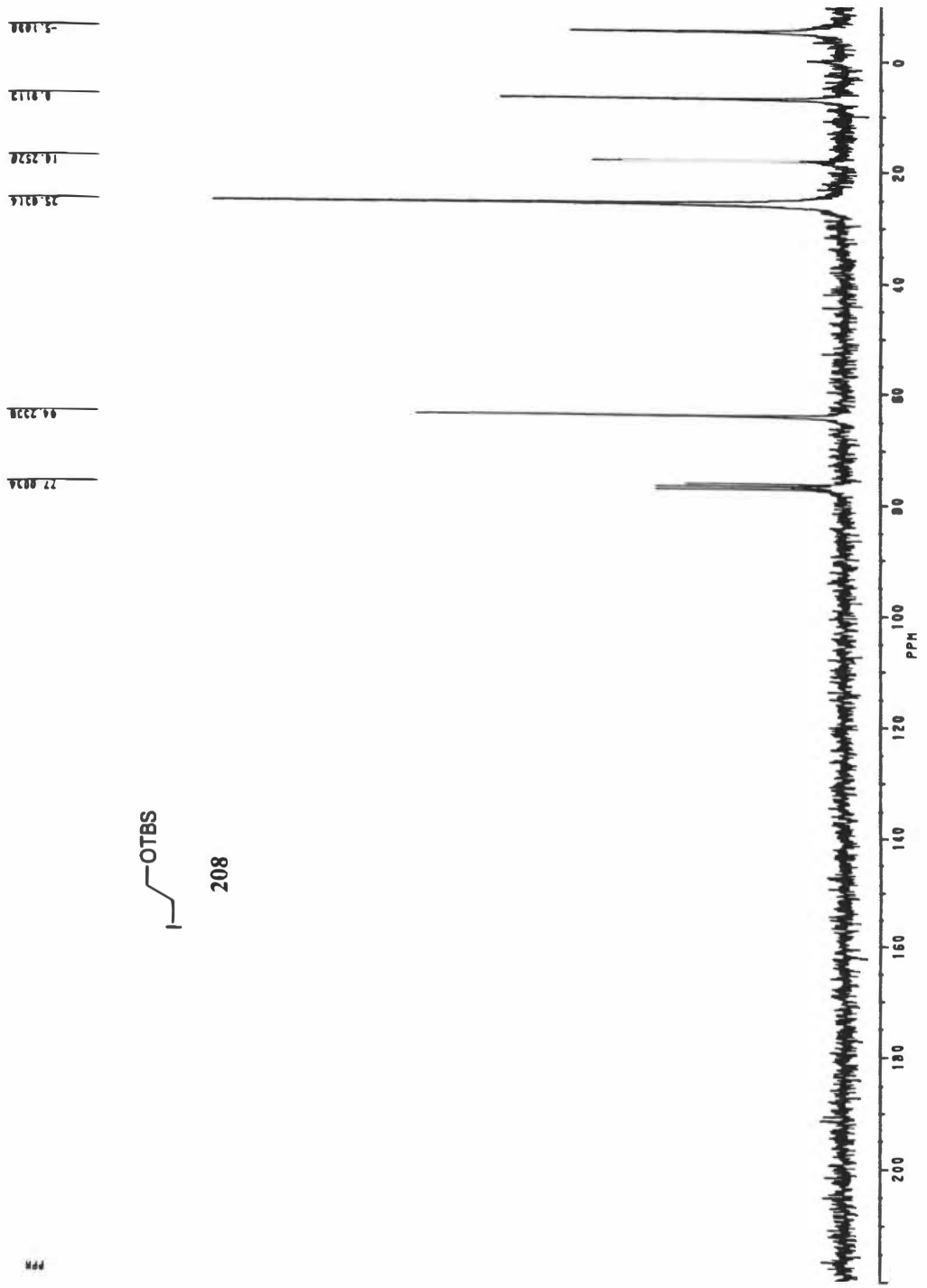


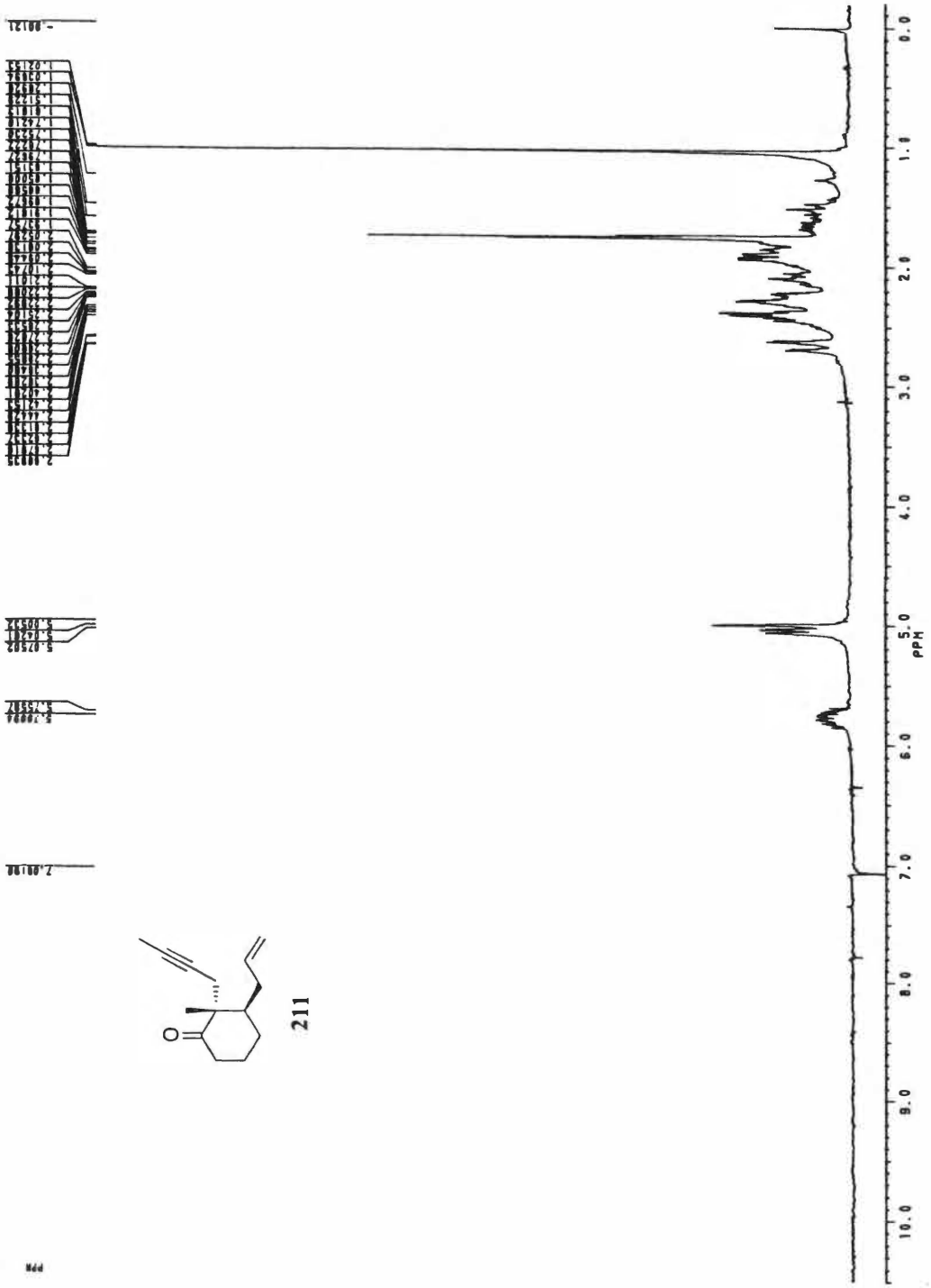
161

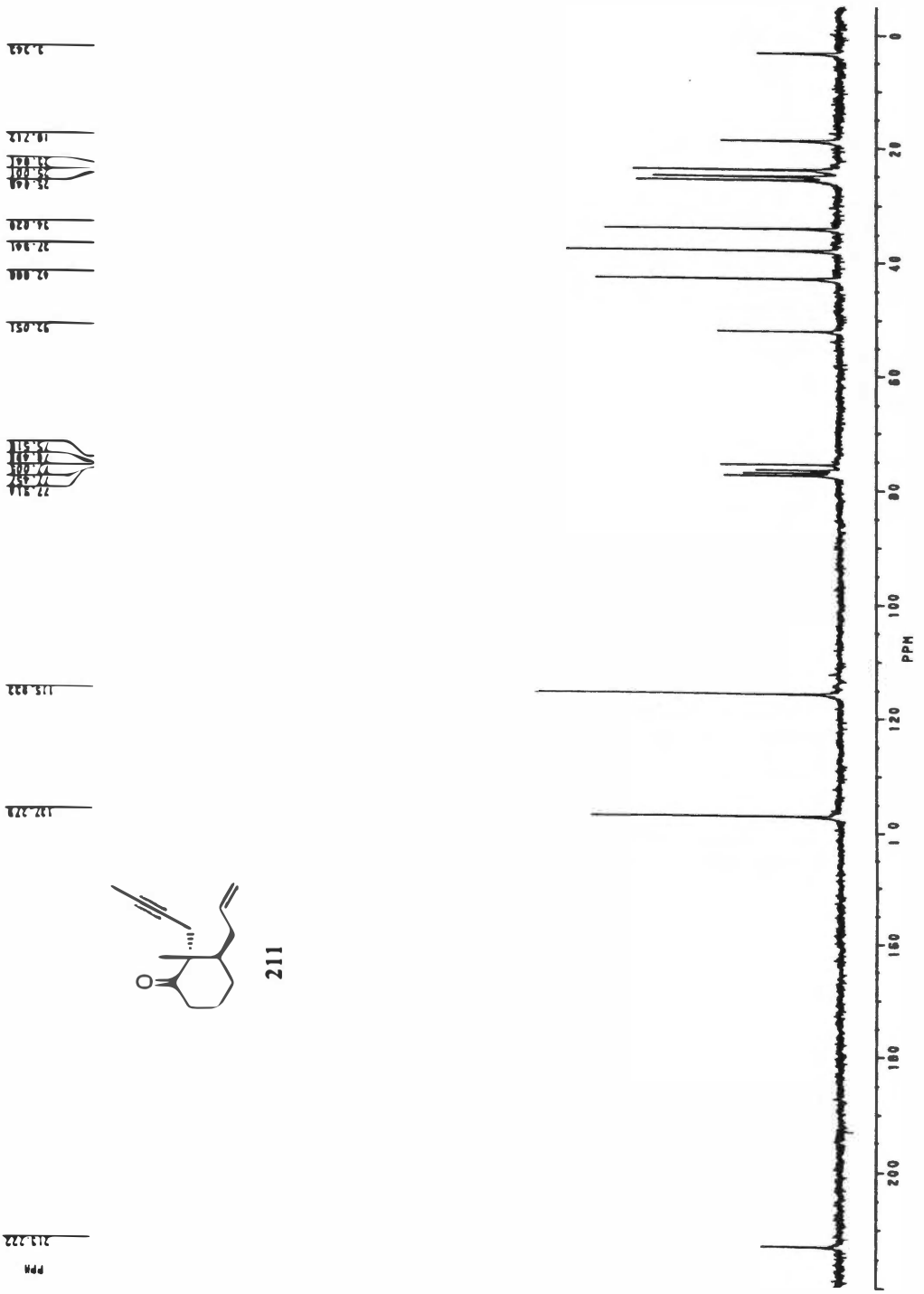

PPM
200.803
201.388
132.508
122.274
110.449
100.858
44.818
31.173
31.042
27.448
27.317
27.186
25.317
25.186
17.724
200
180
160
140
120
100
80
60
40
20
0
PPM

161

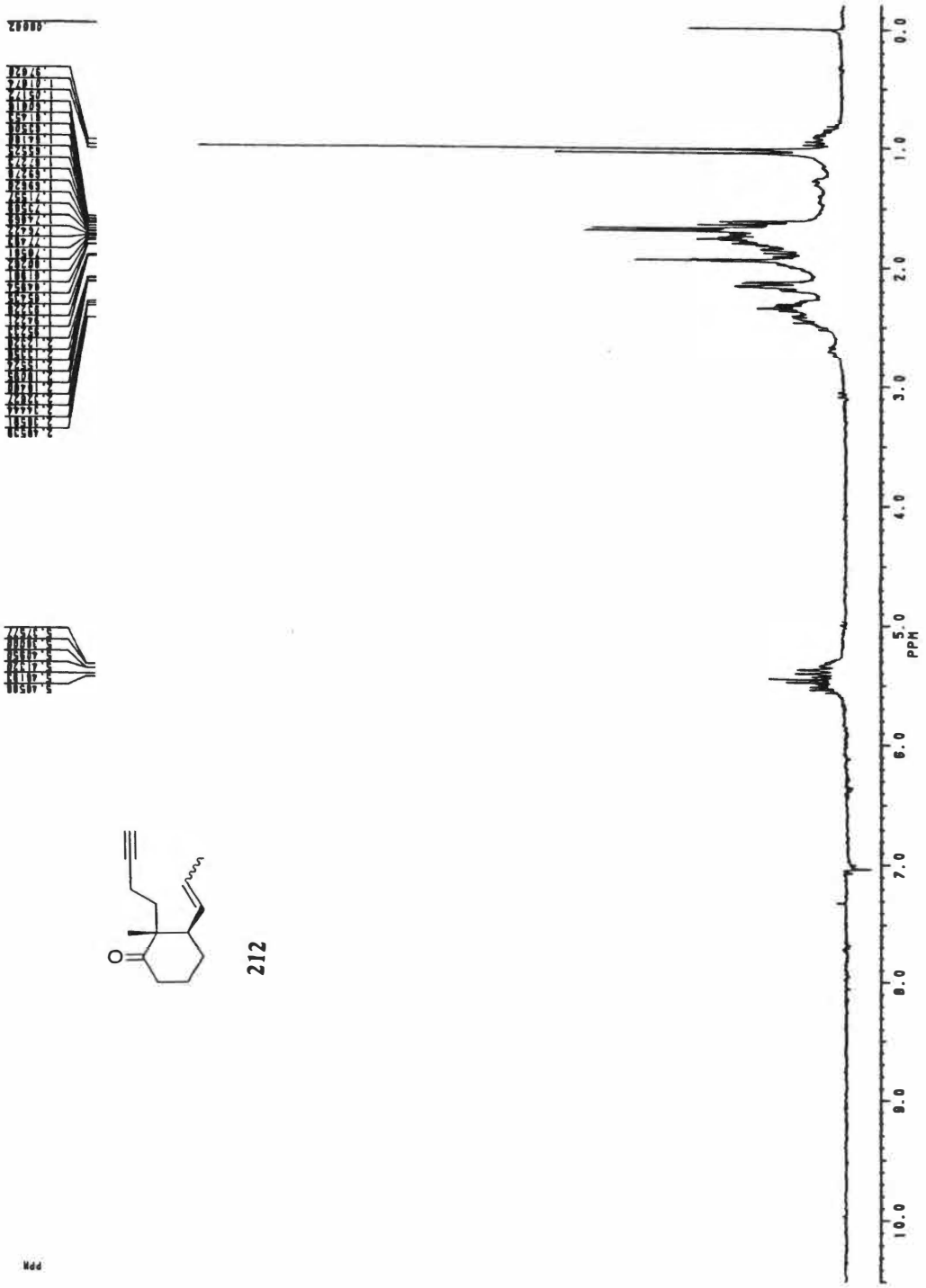

OTBS
208
PPM

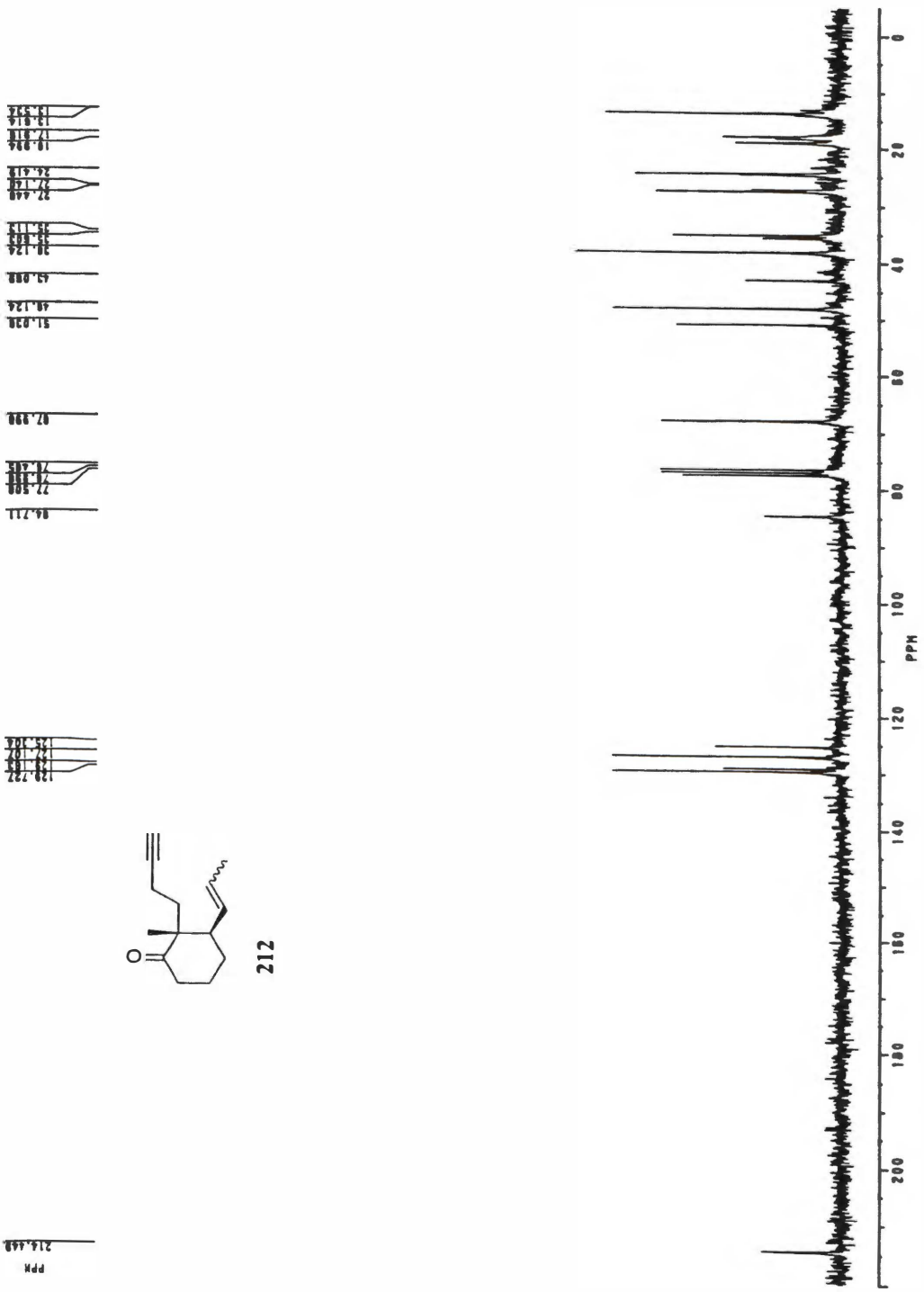

OTBS
208
PPM


O
211
PPM

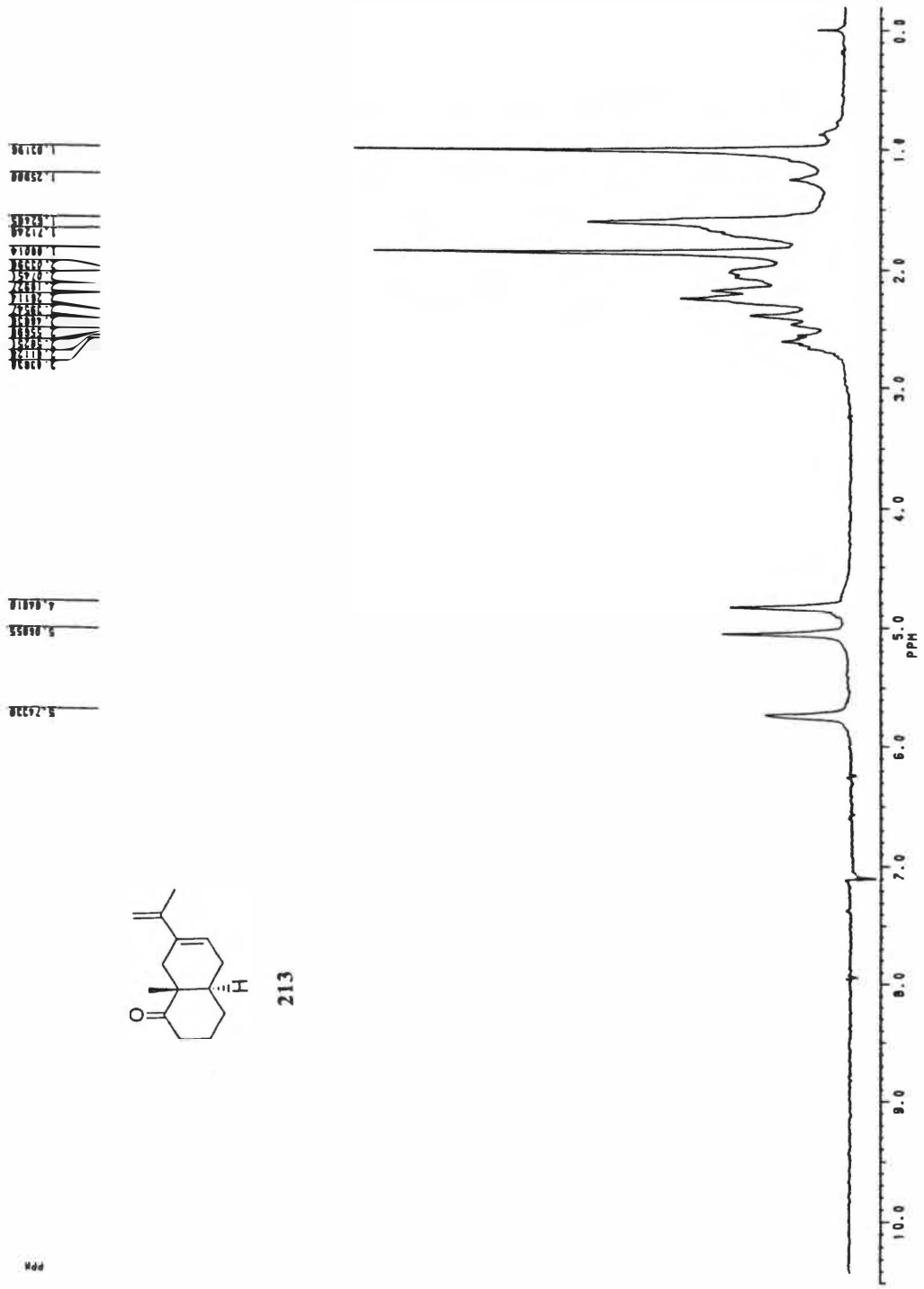


211

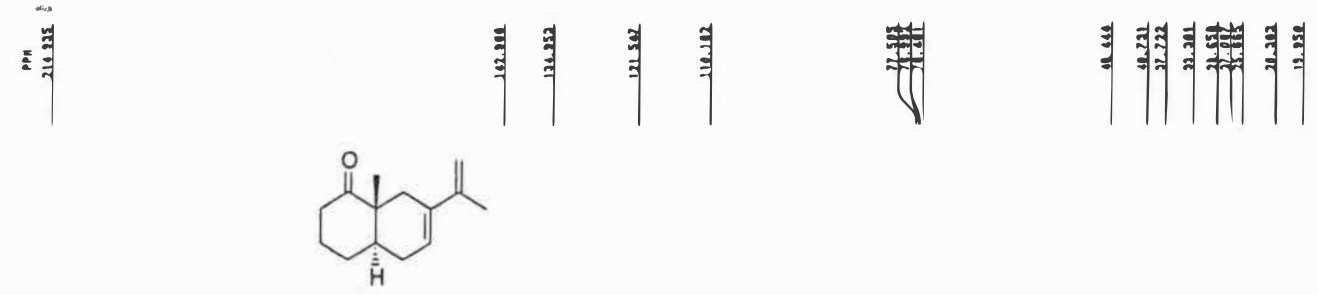

O
212
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0



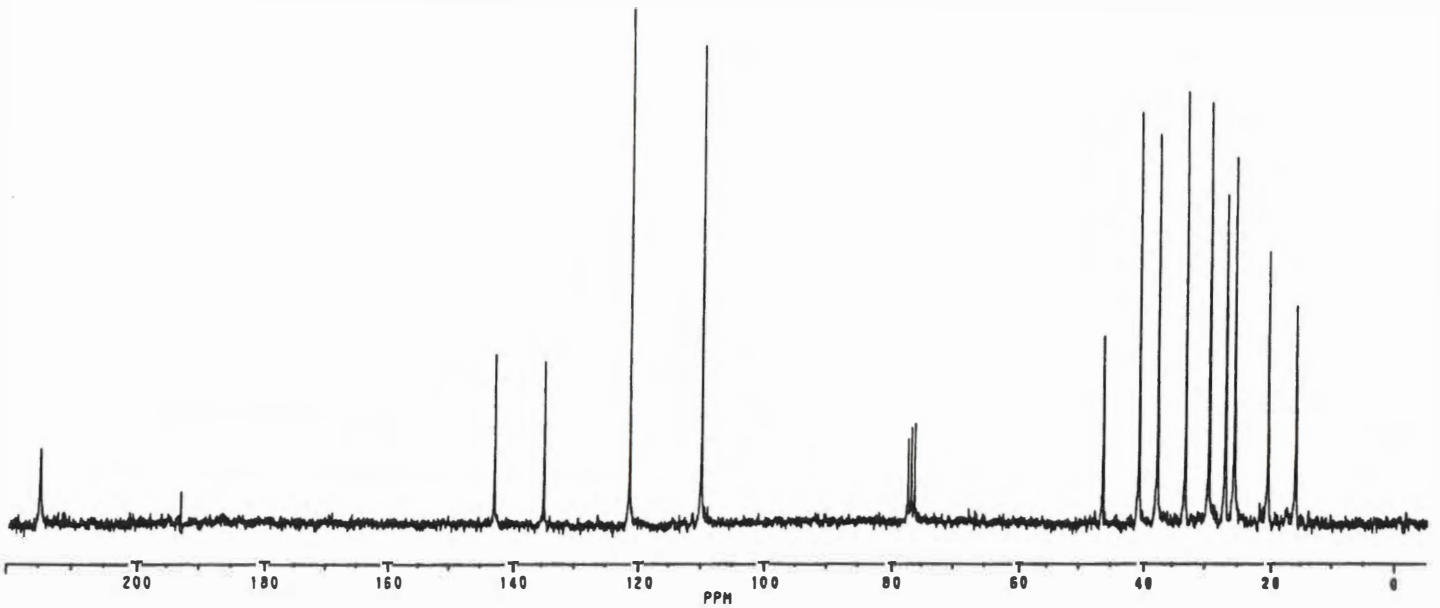
212

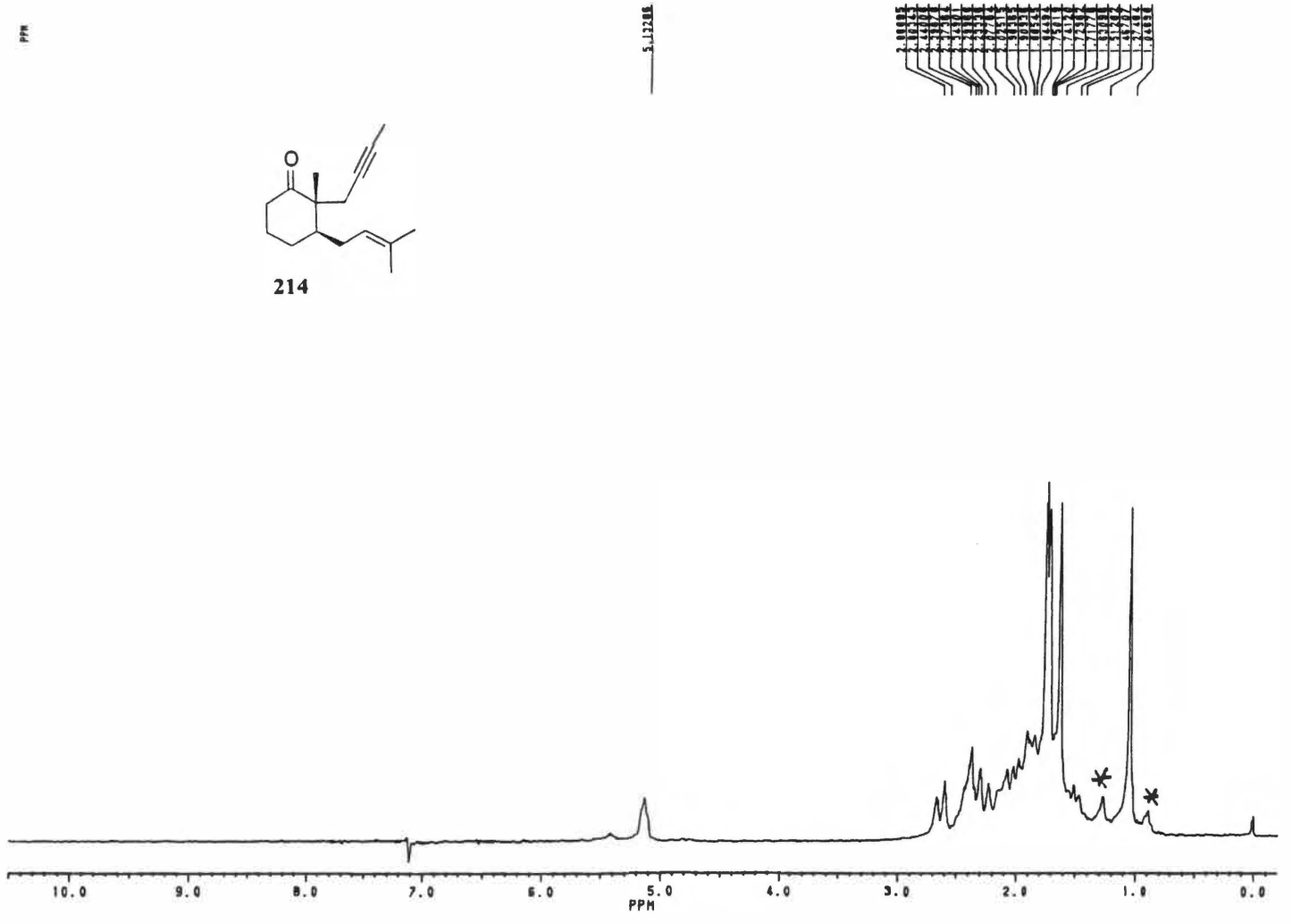


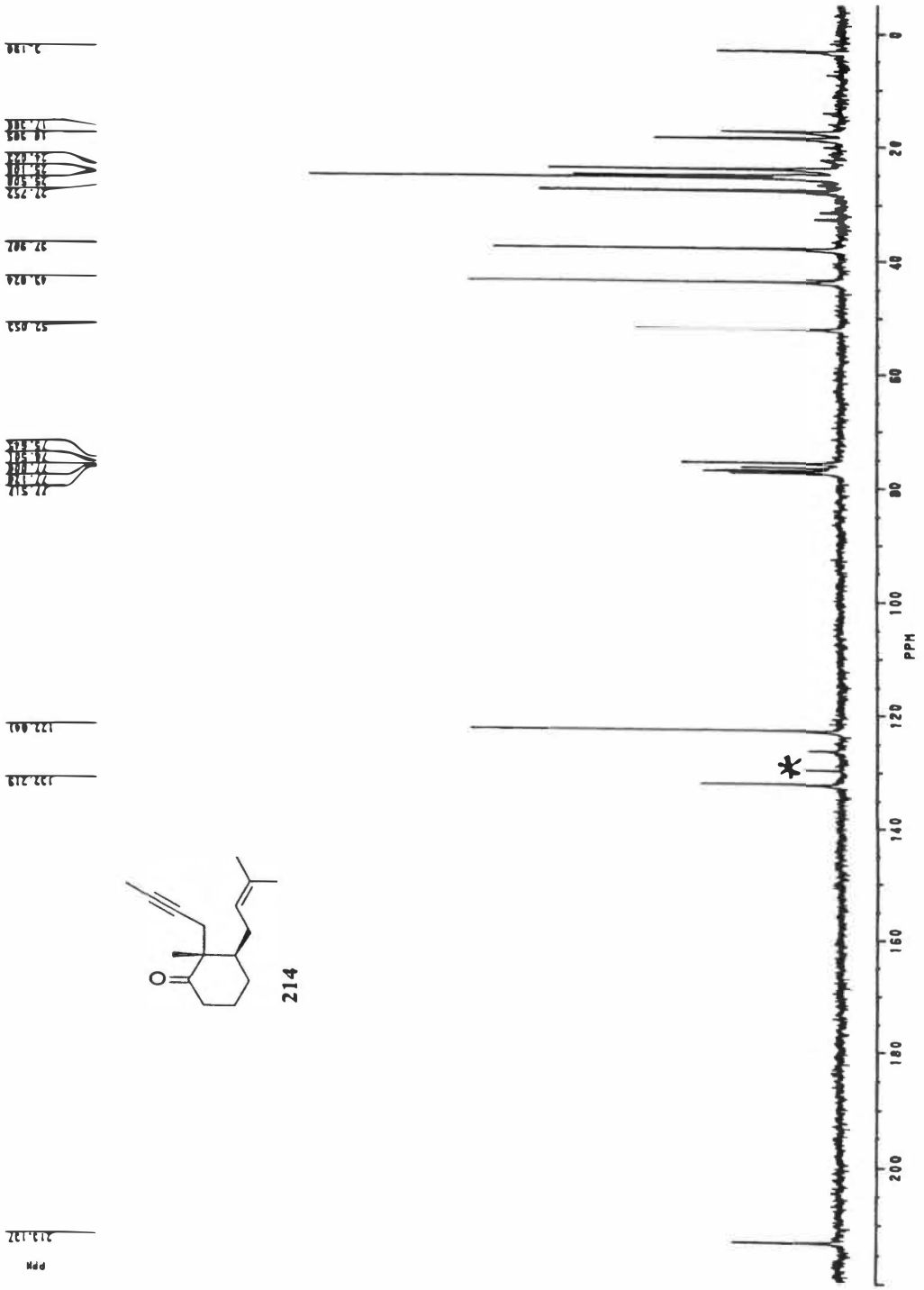
213

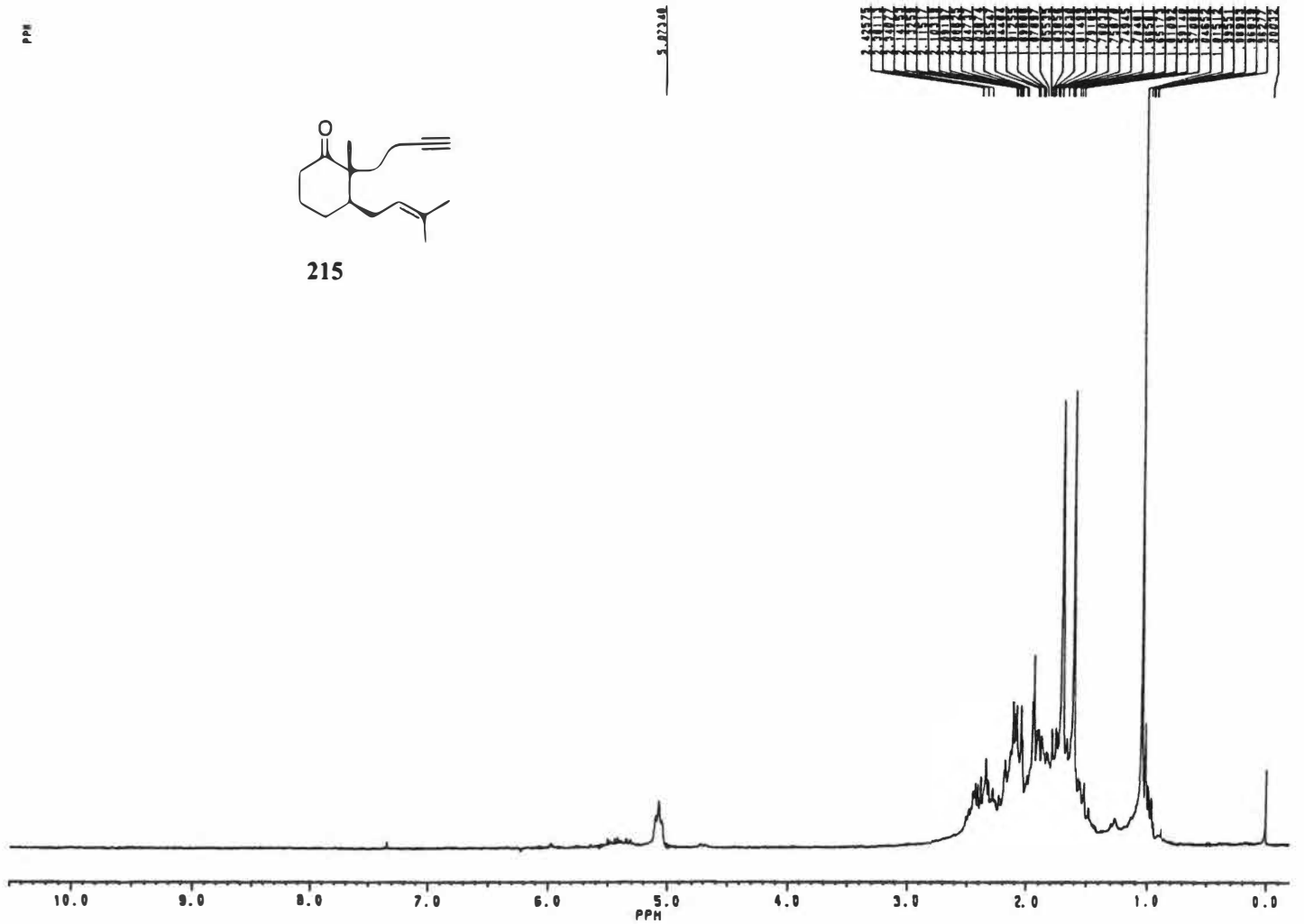


213



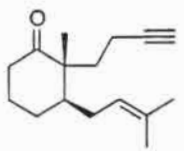

O
214
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM


O
214
*
PPM

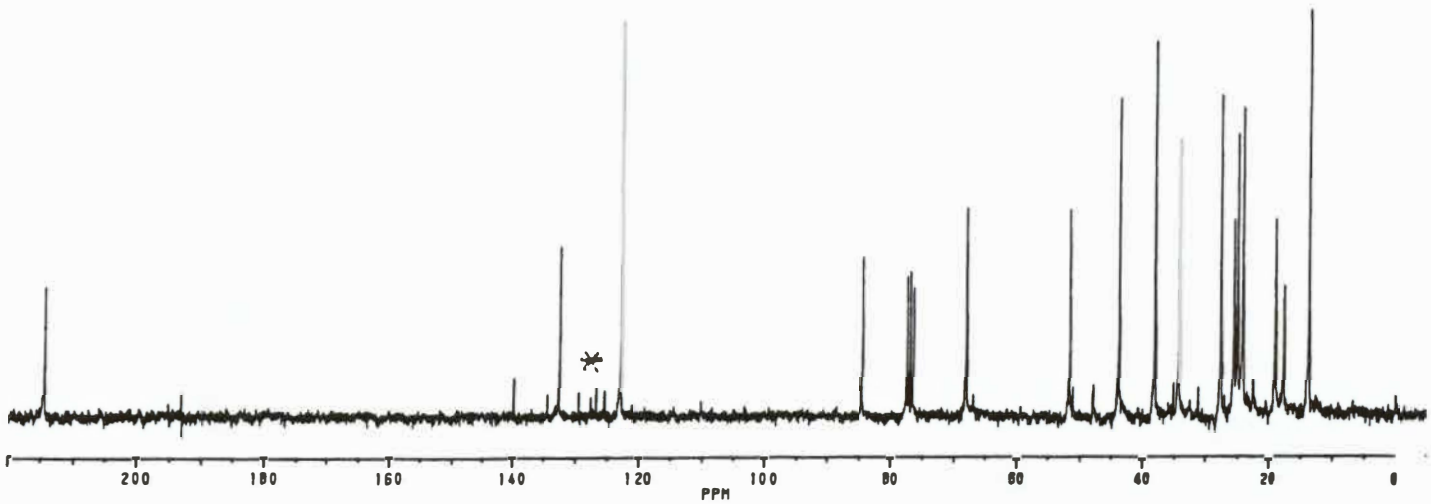


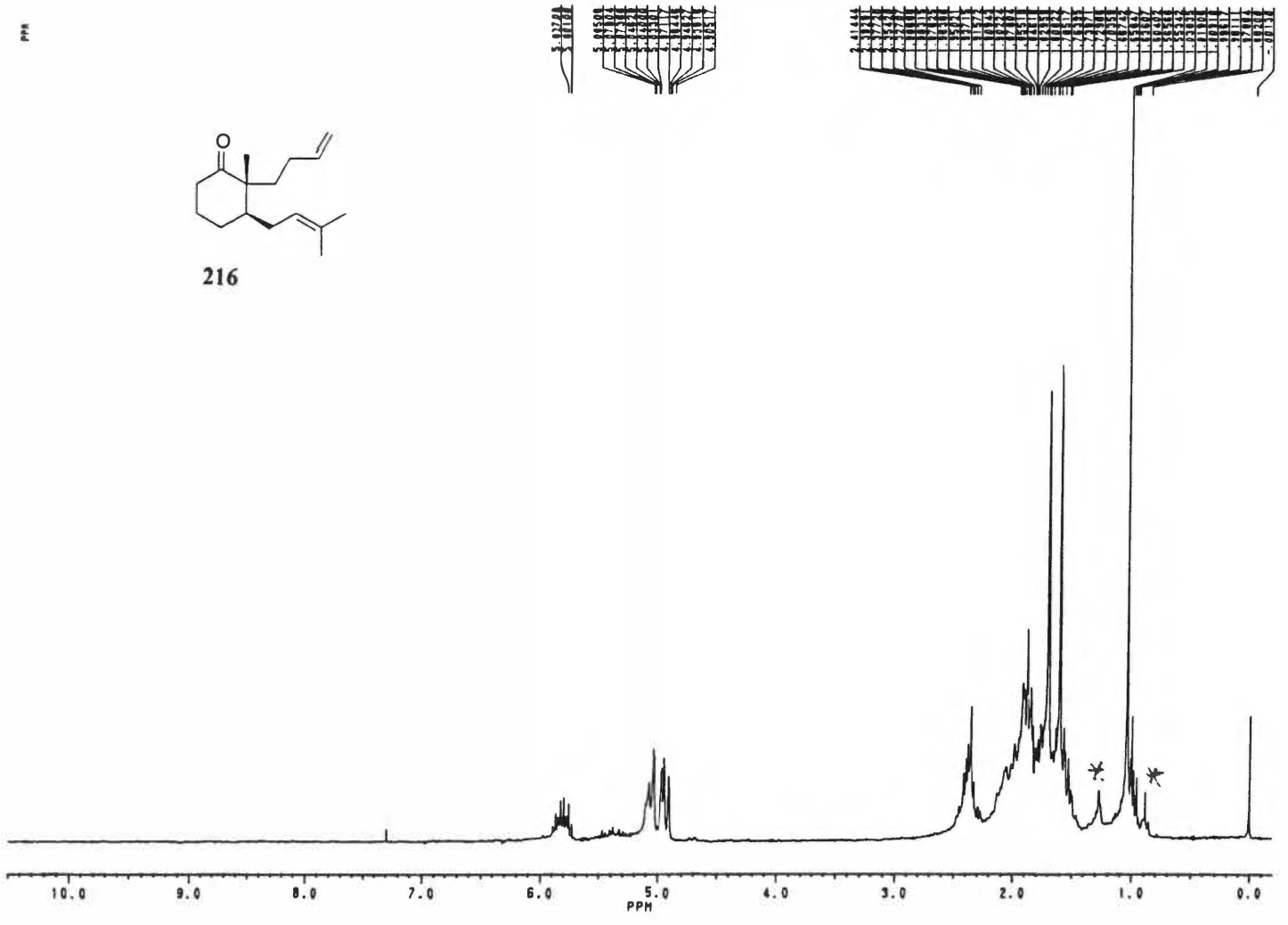
215





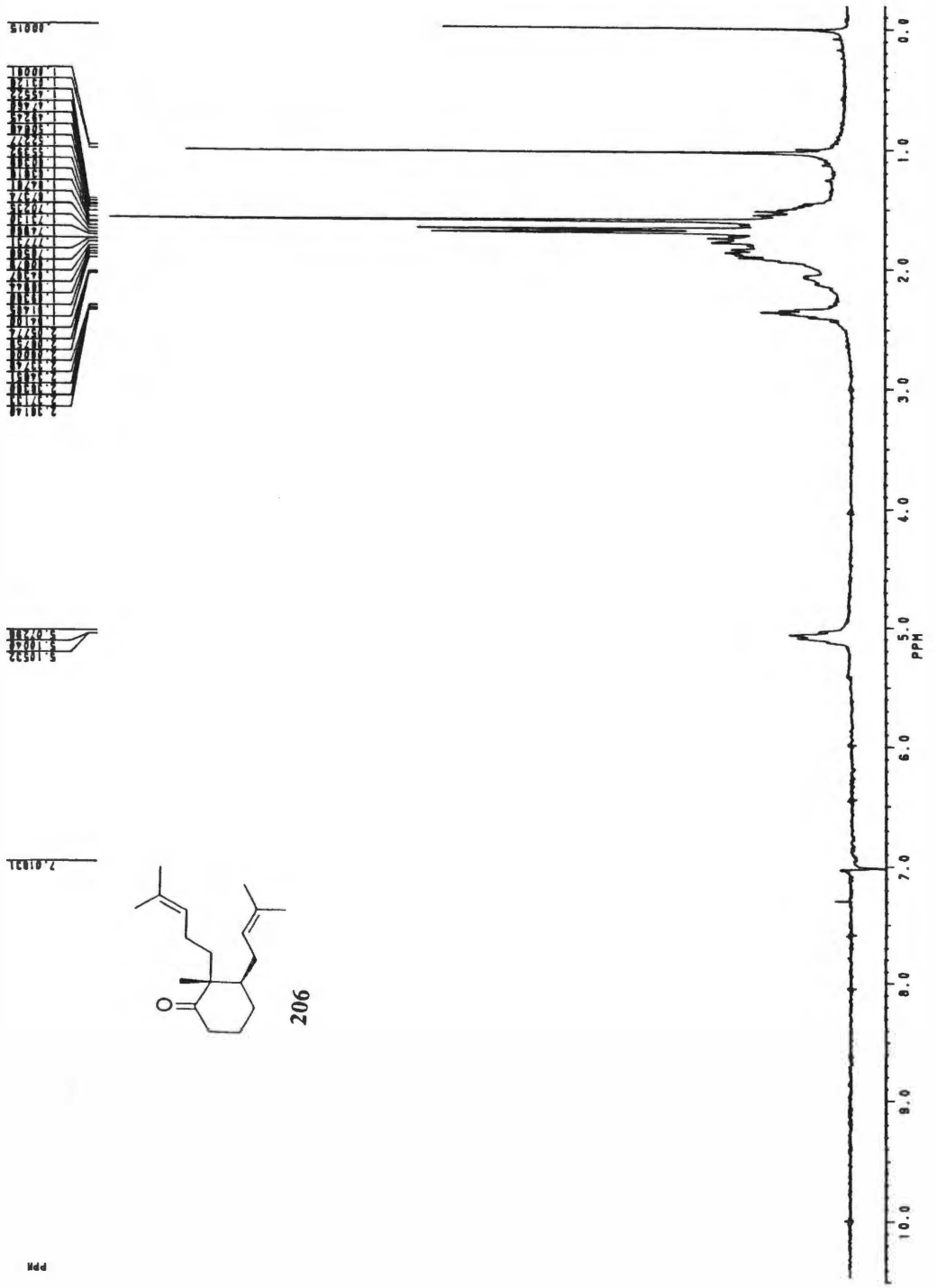
215

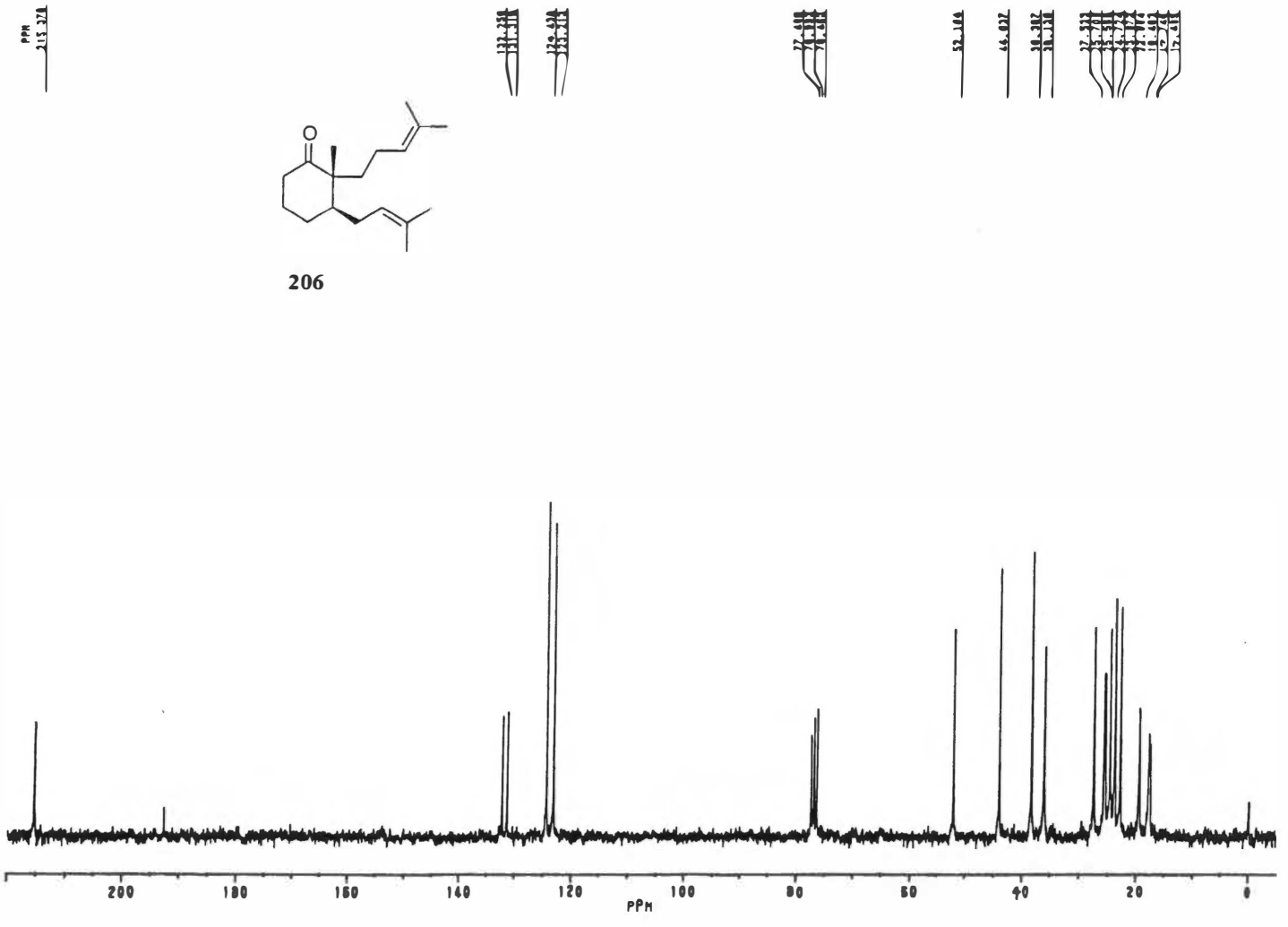




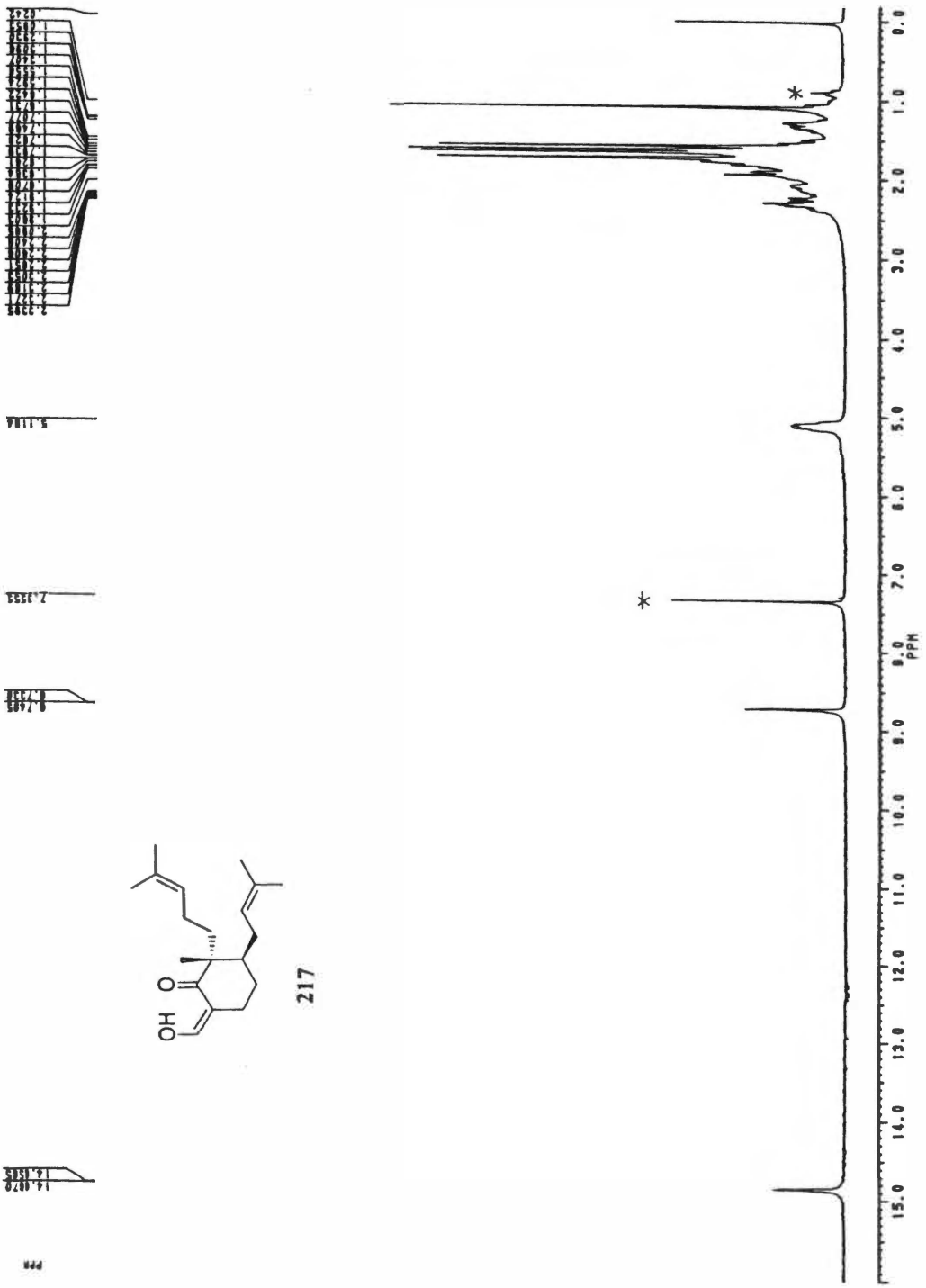
216

216

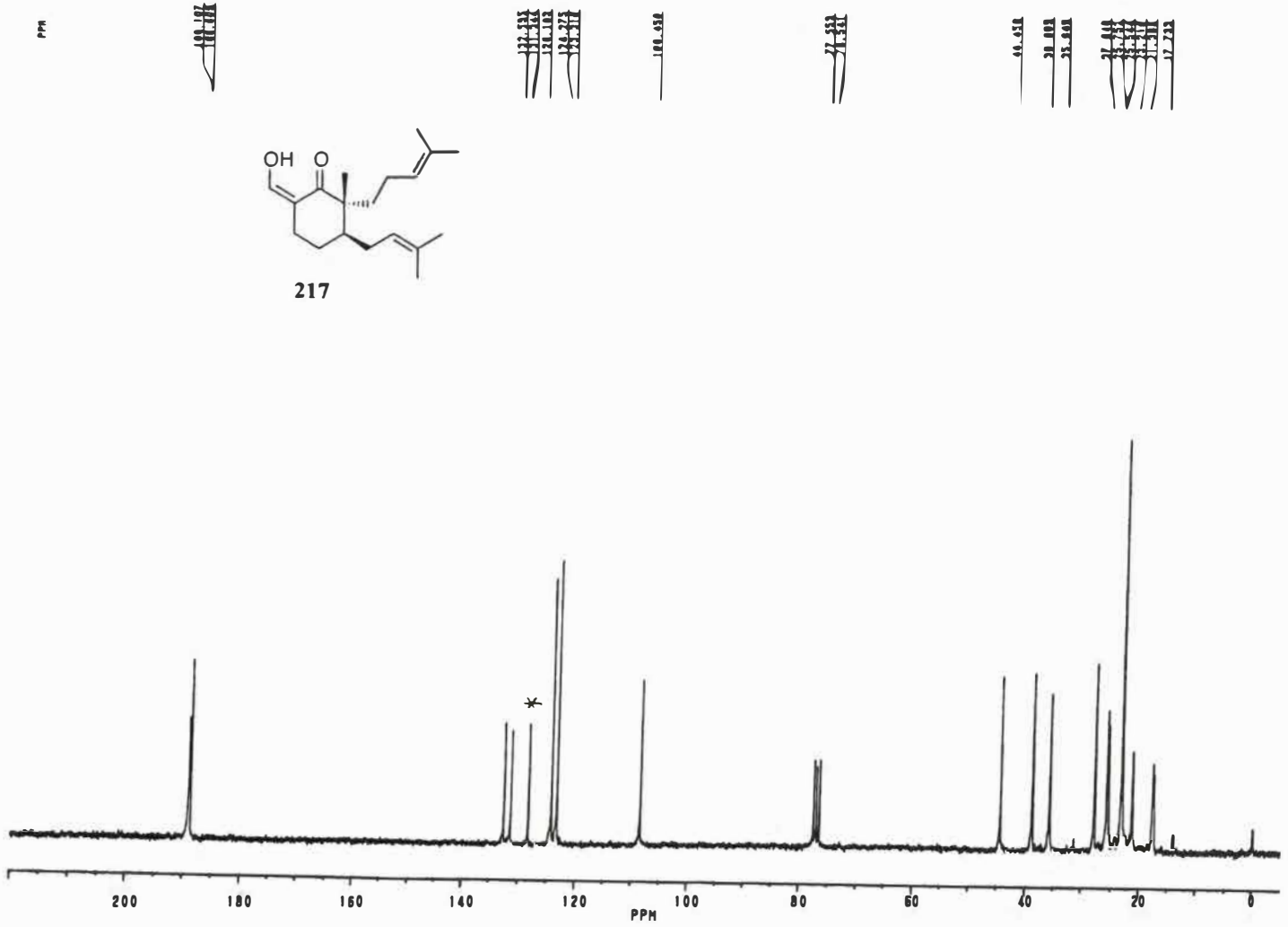

PPM
206



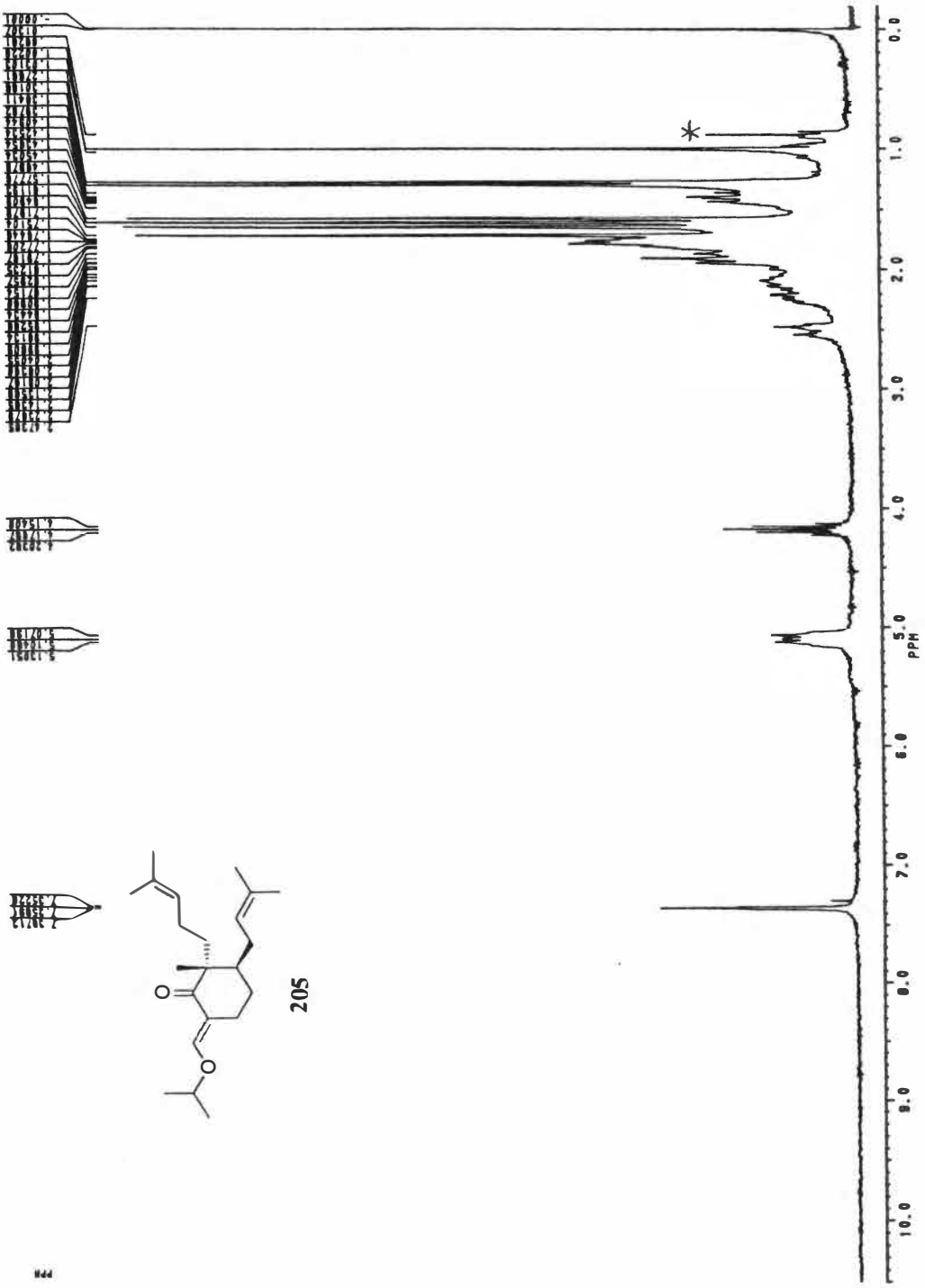
206



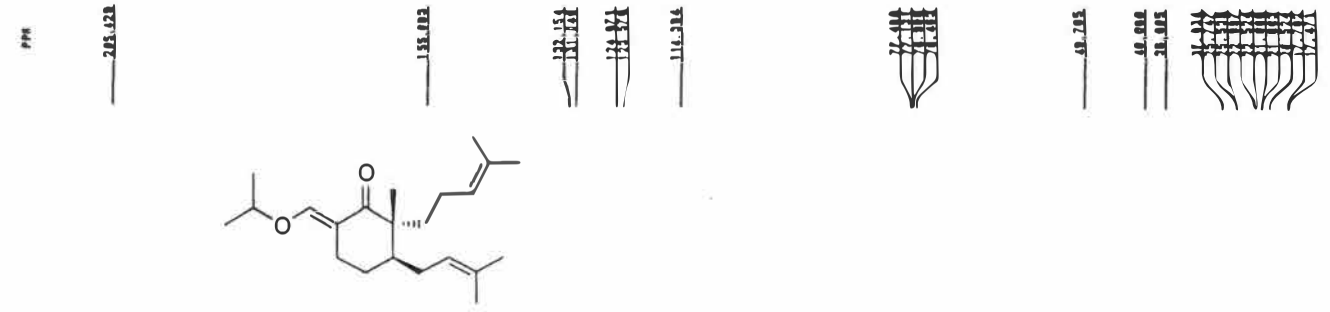
217



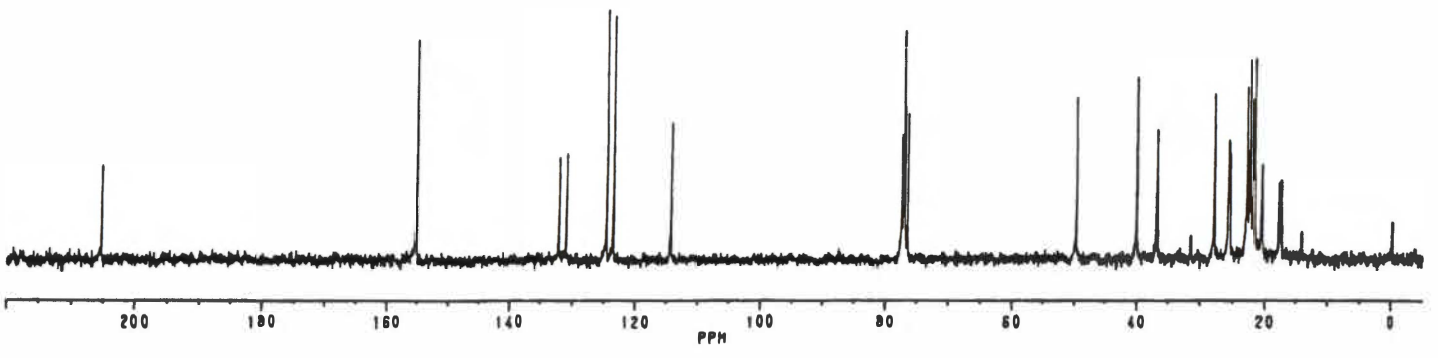
217

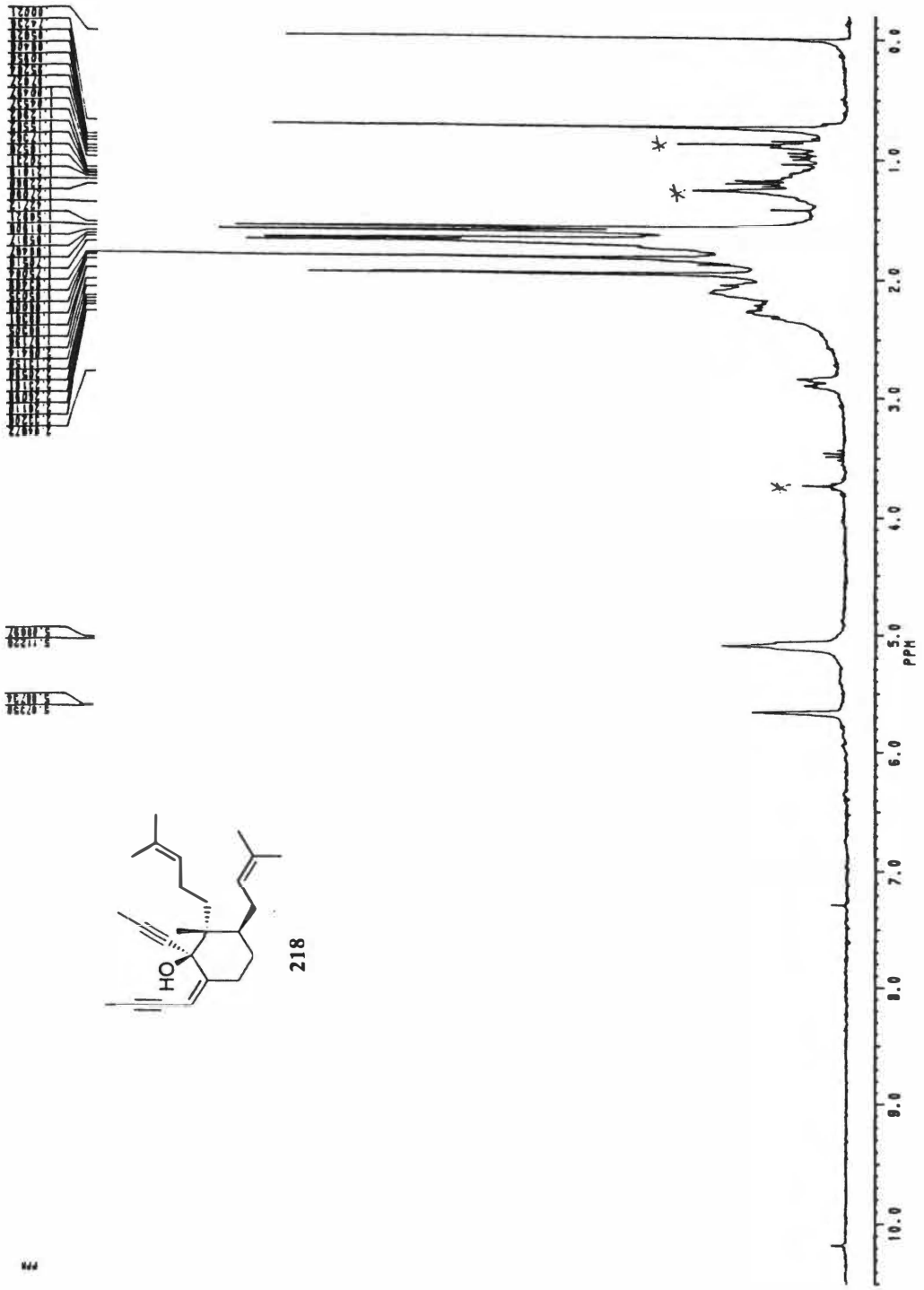


205

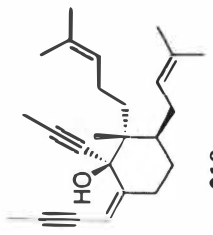


205

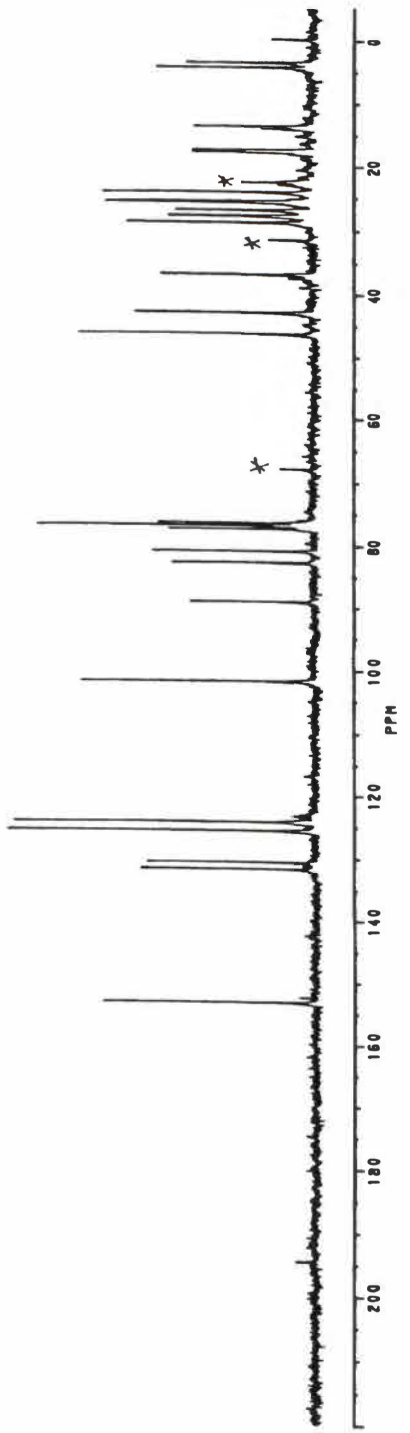


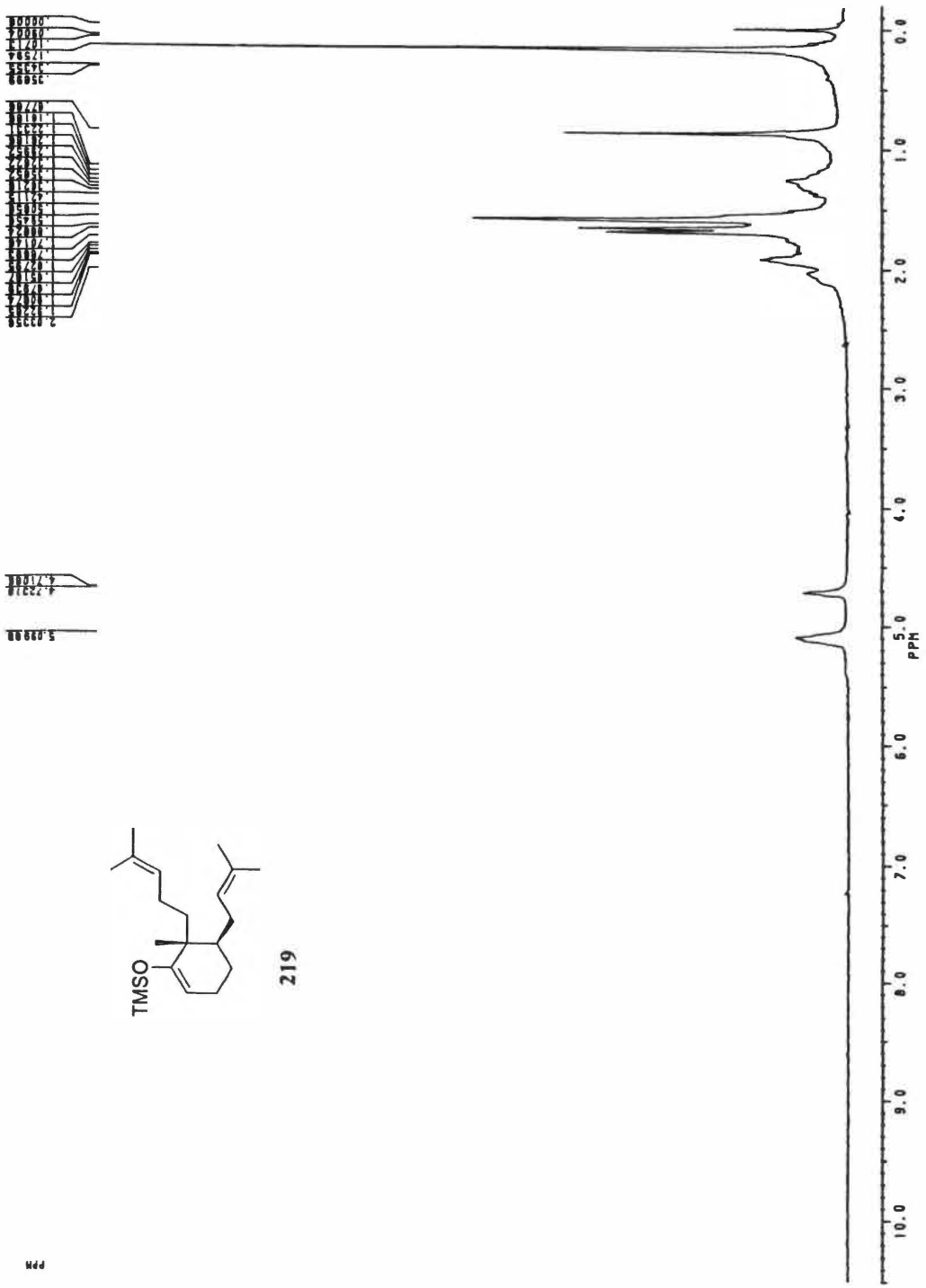

HO
218
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

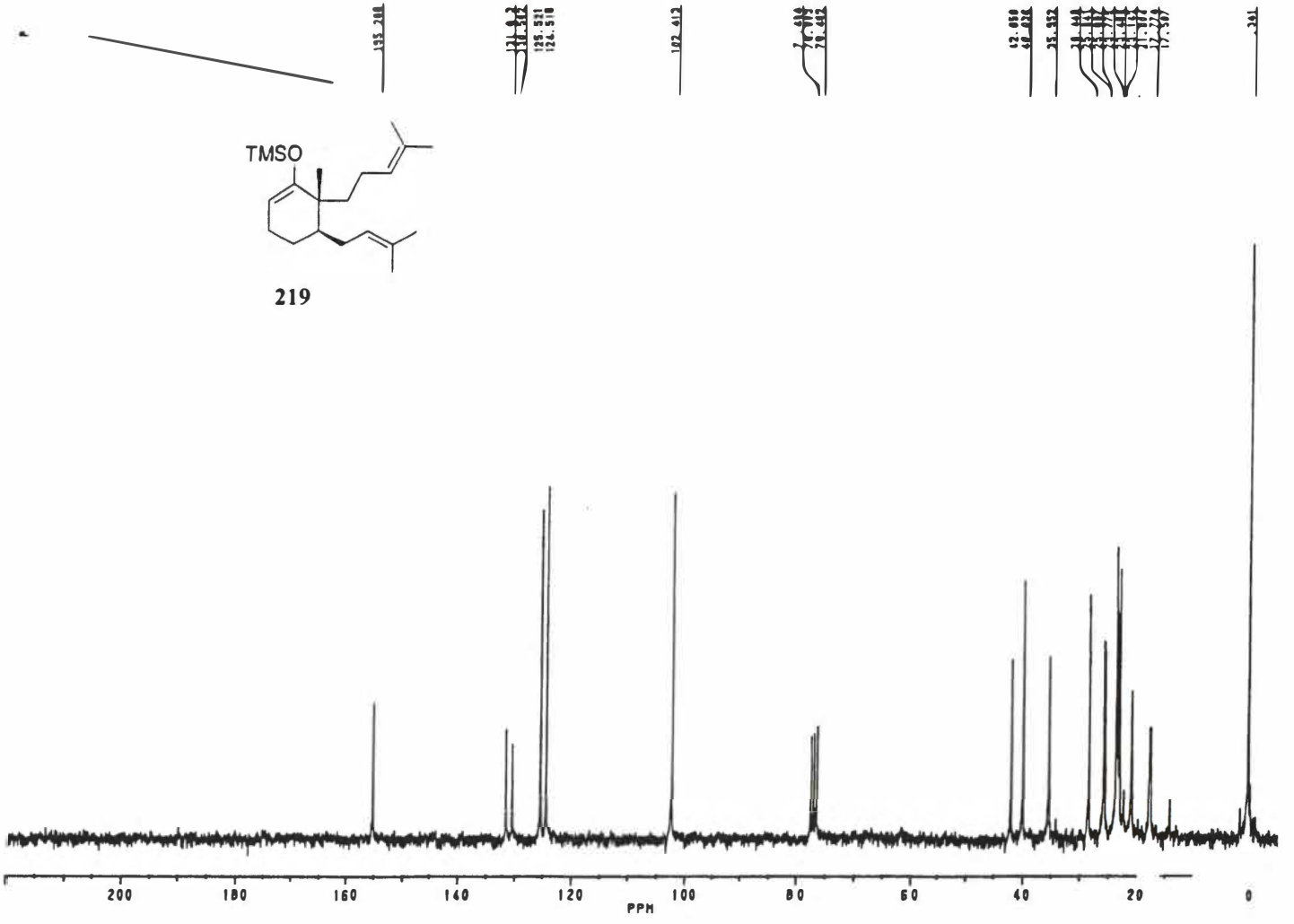




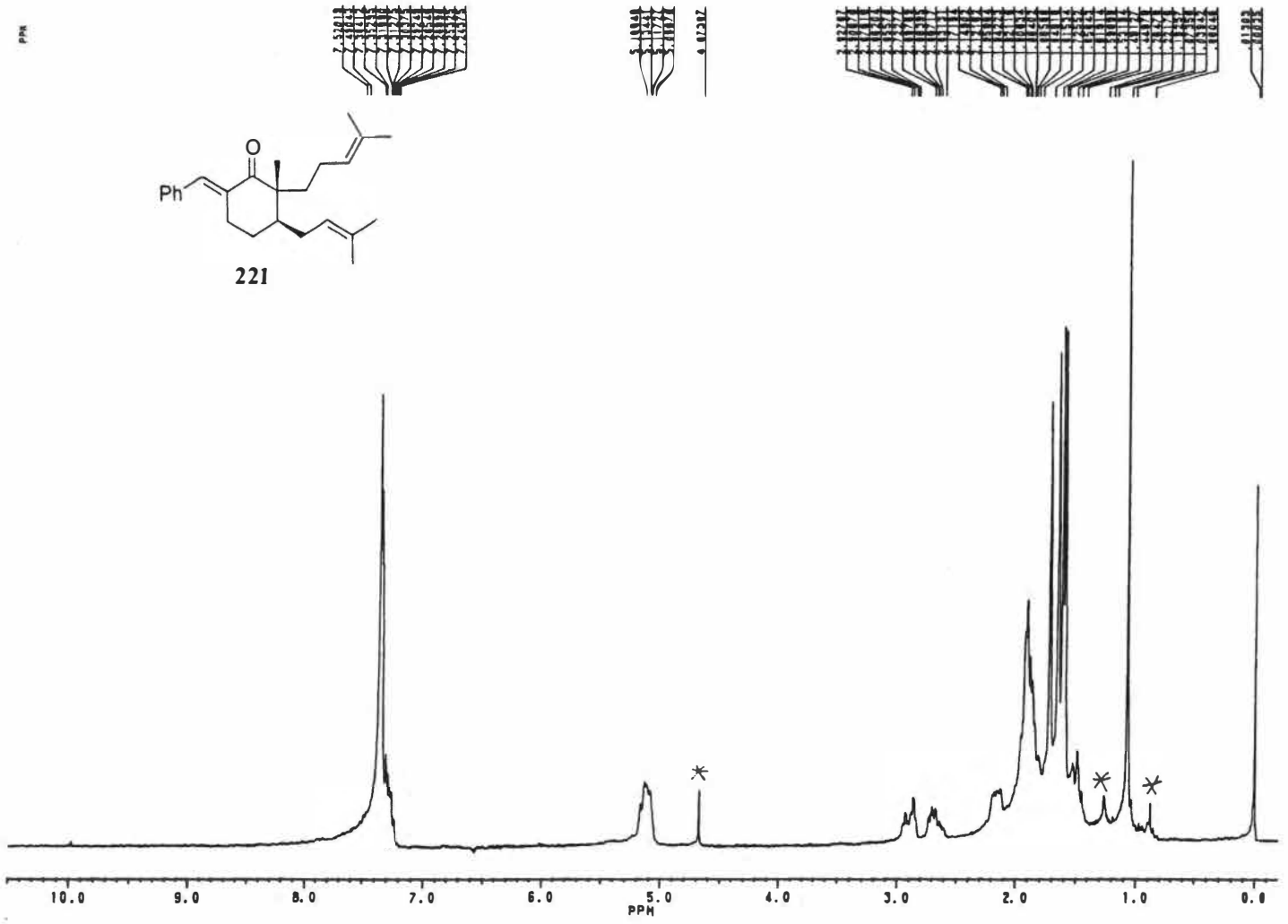
218



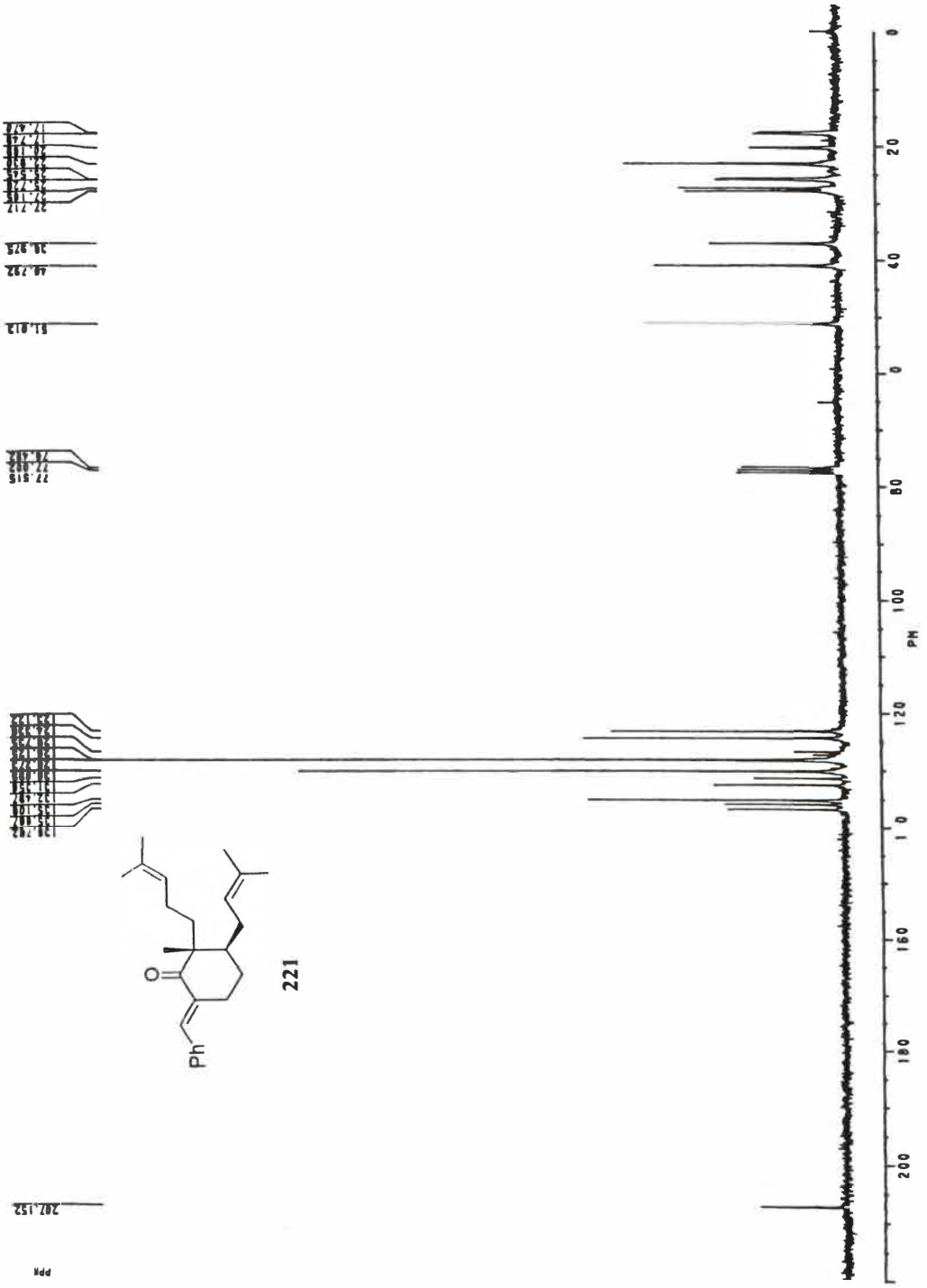

TMSO
219
PPM

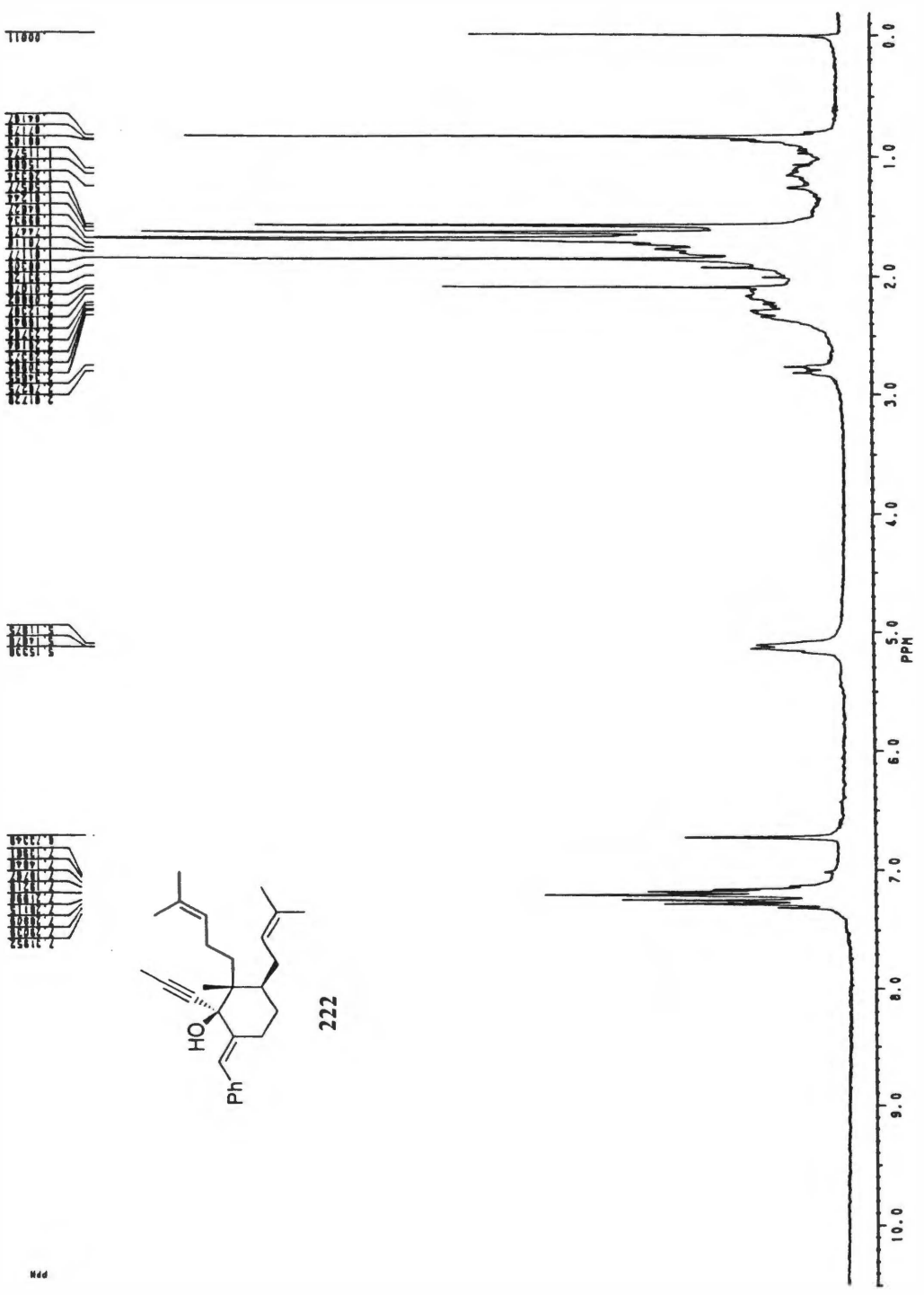


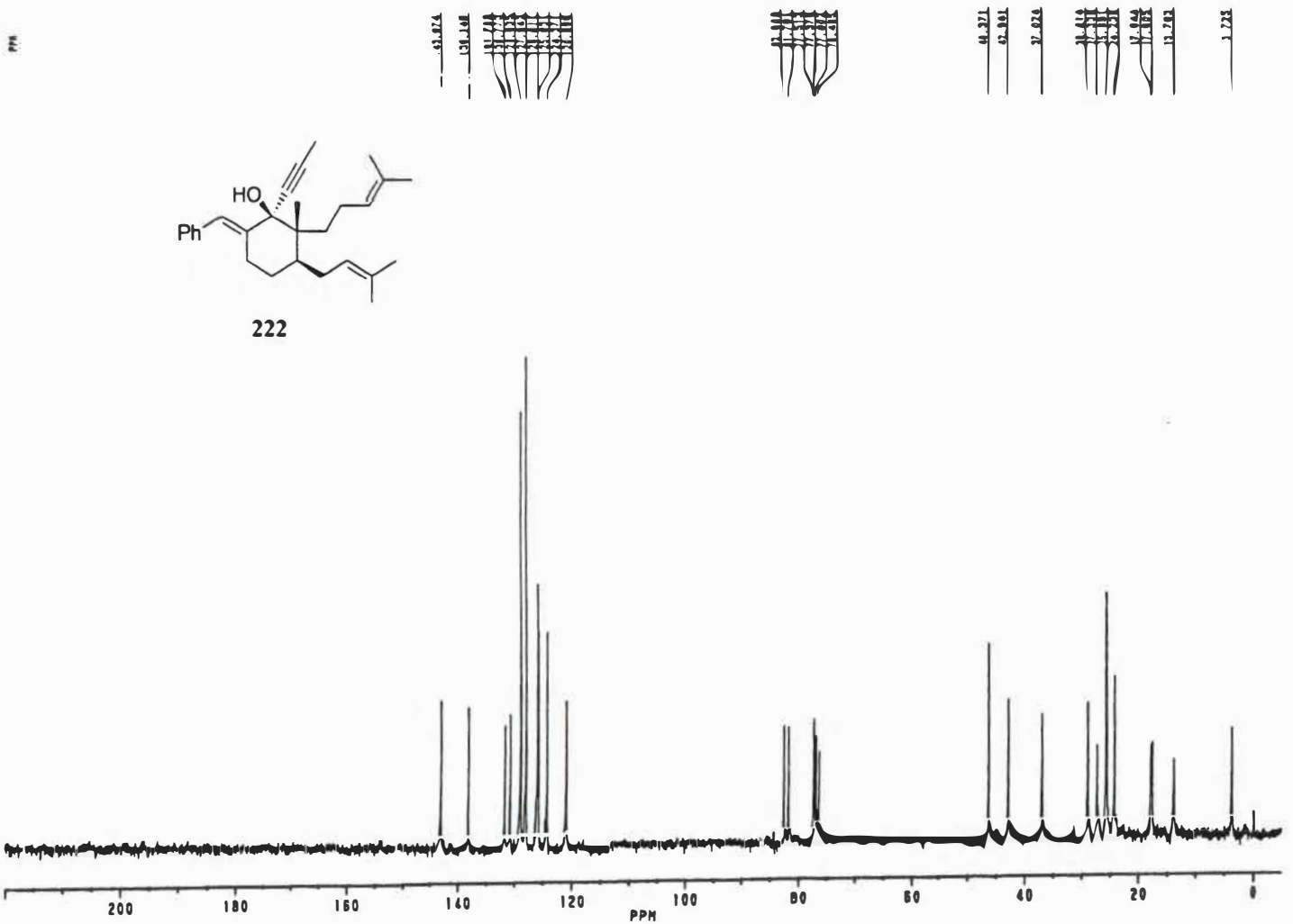
219



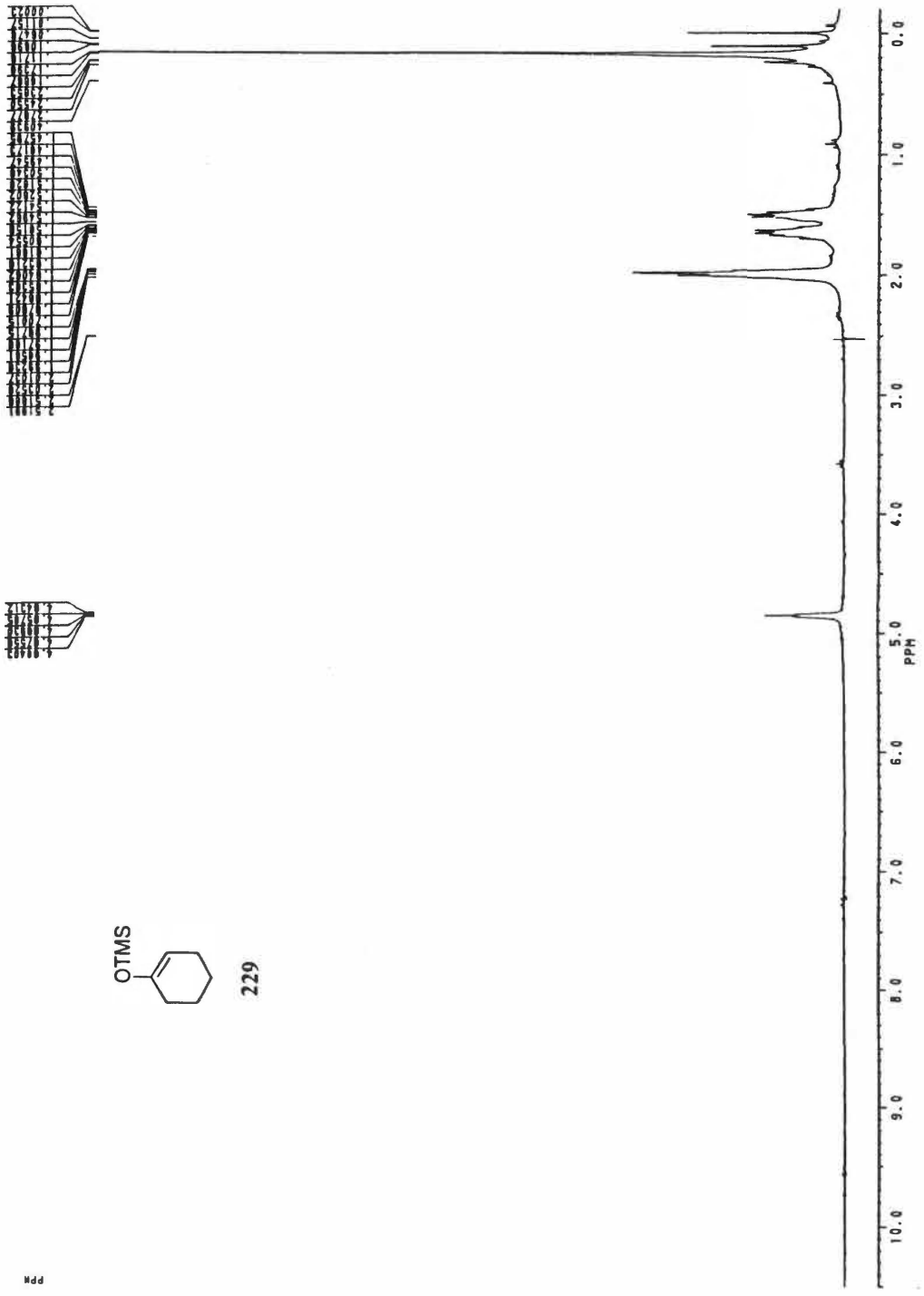
221

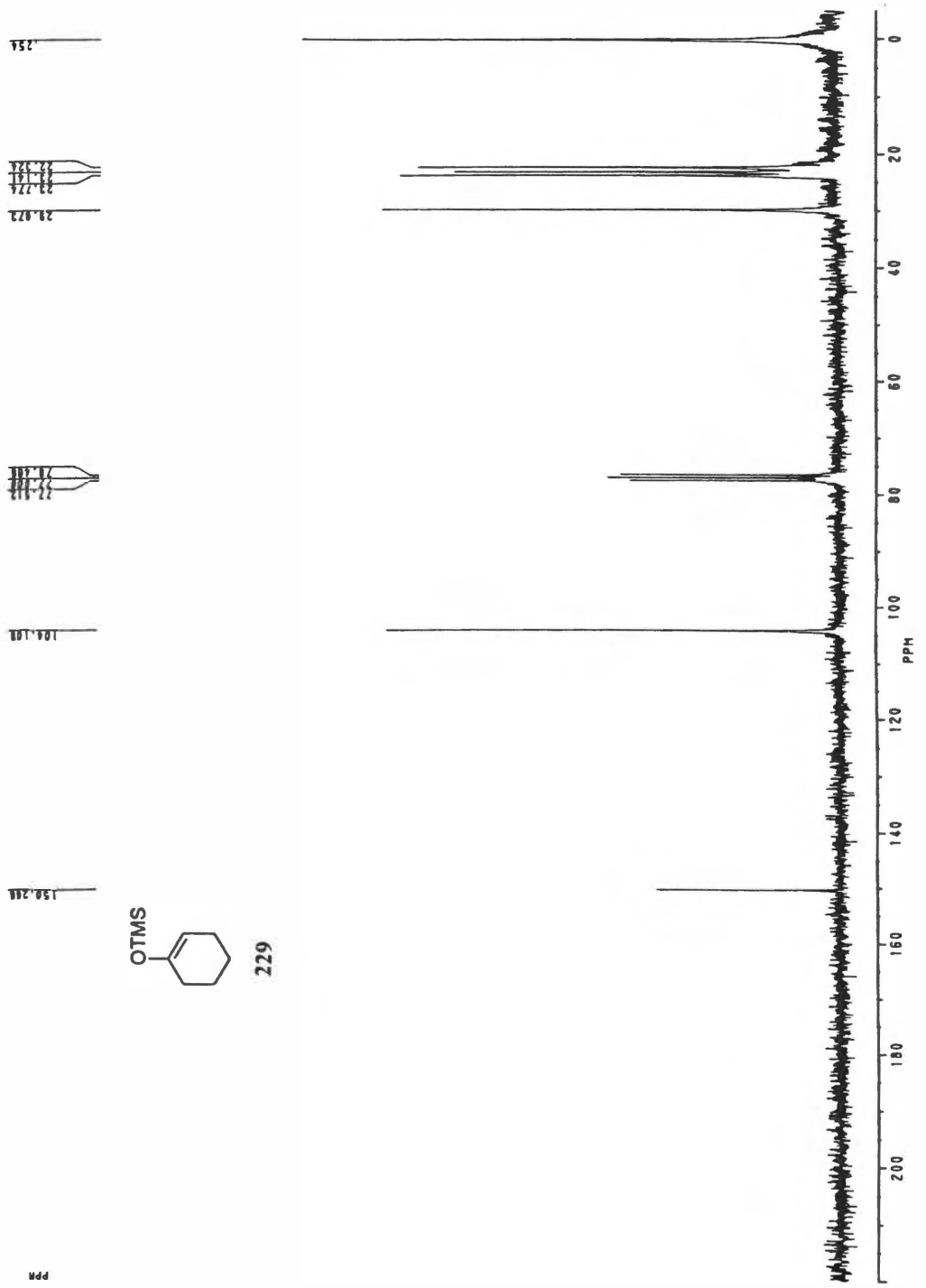

Ph
O
221
PPM

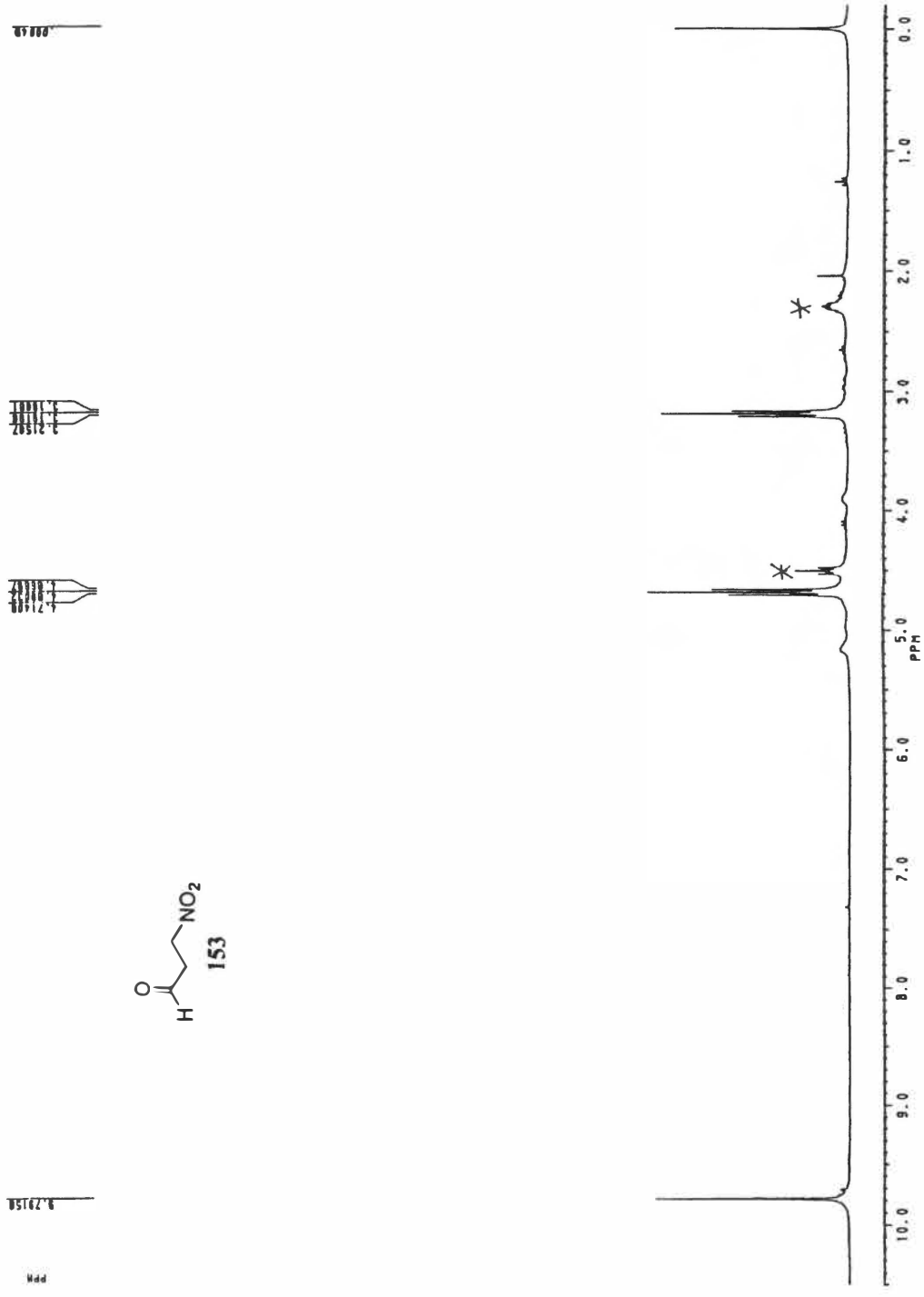

HO
Ph
222
PPM

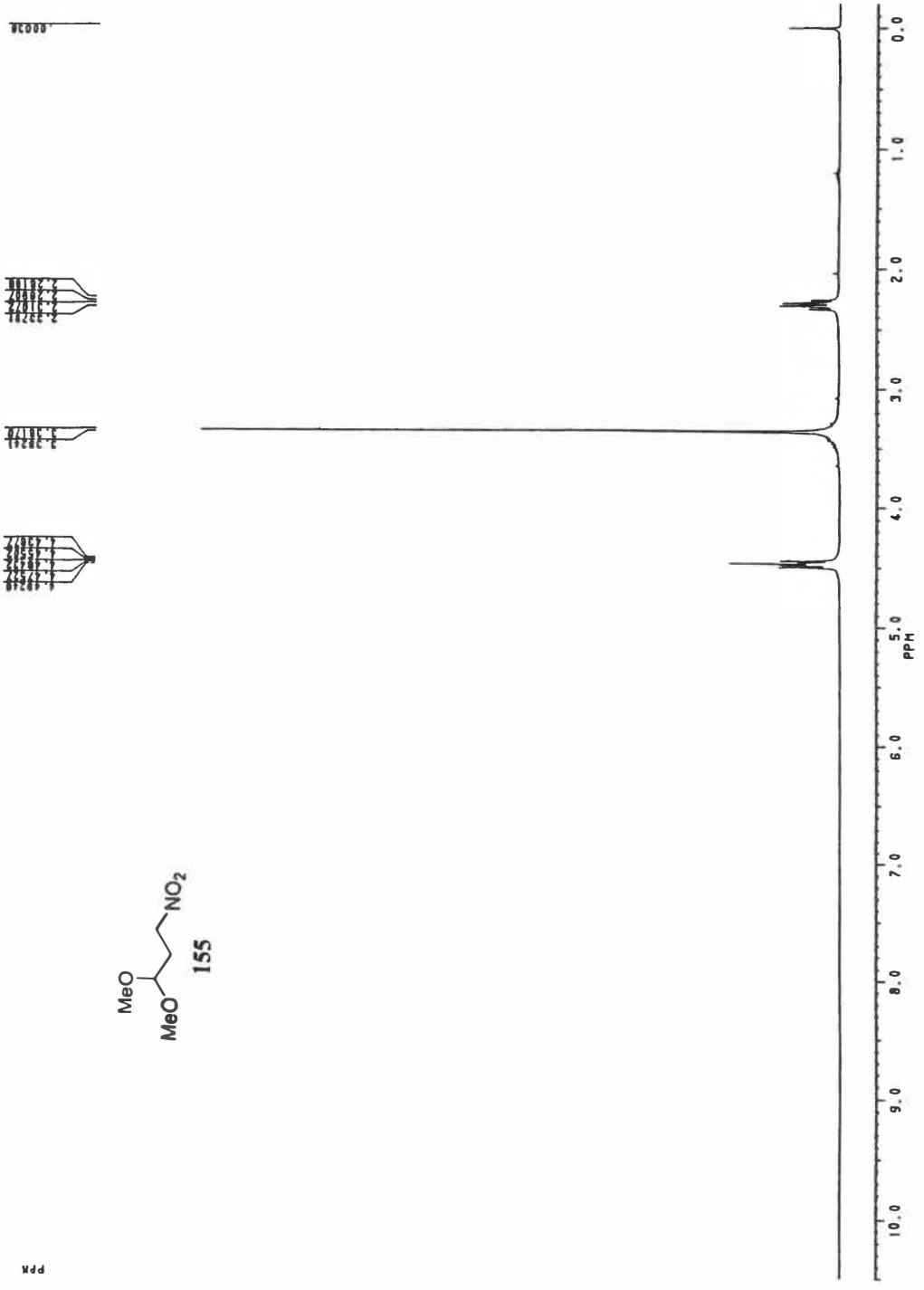


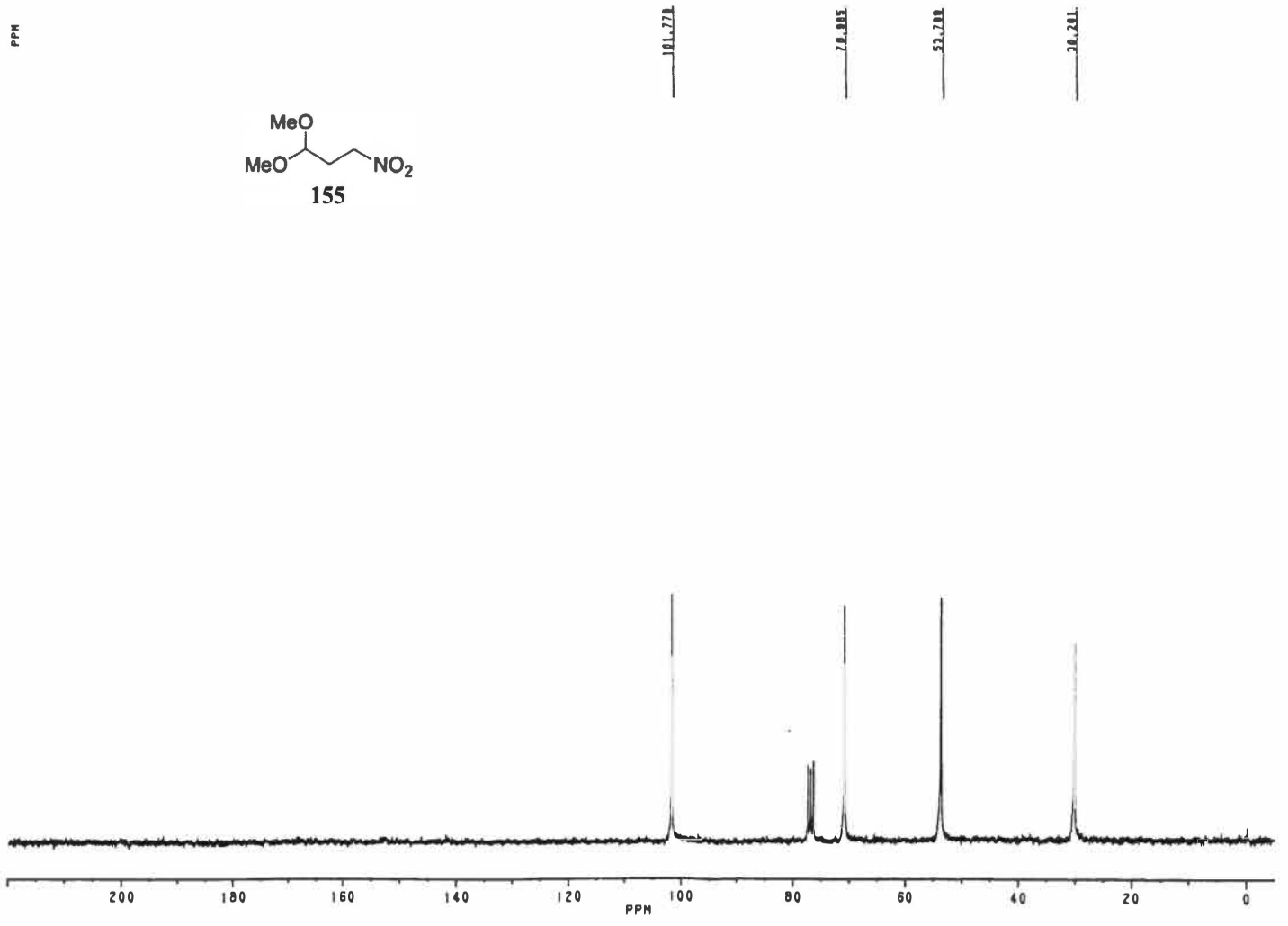
222

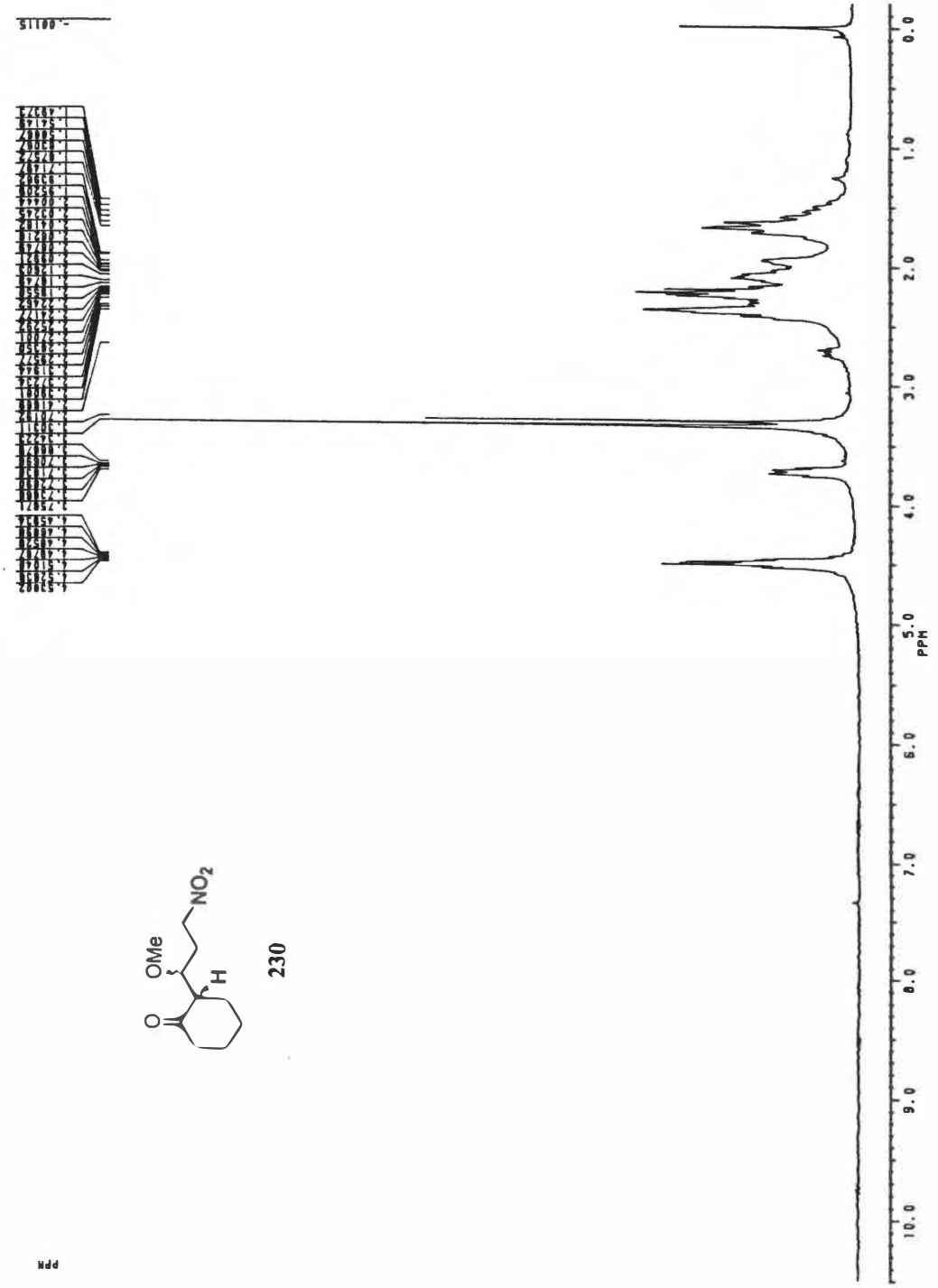

OTMS
229
PPM

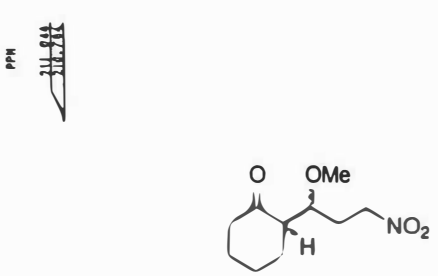

OTMS
229
PPM


O
H
NO2
153
PPM

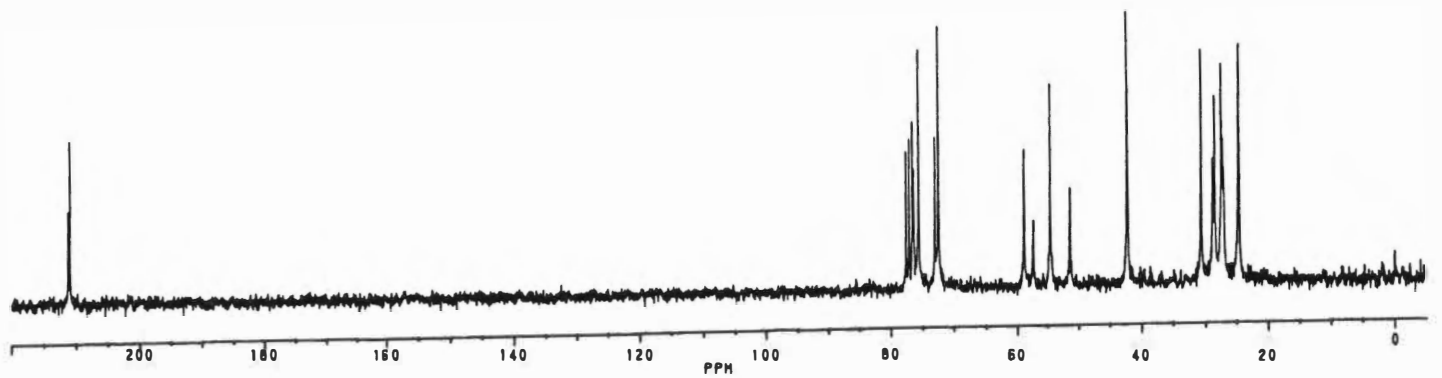

MeO
MeO
NO2
155
PPM

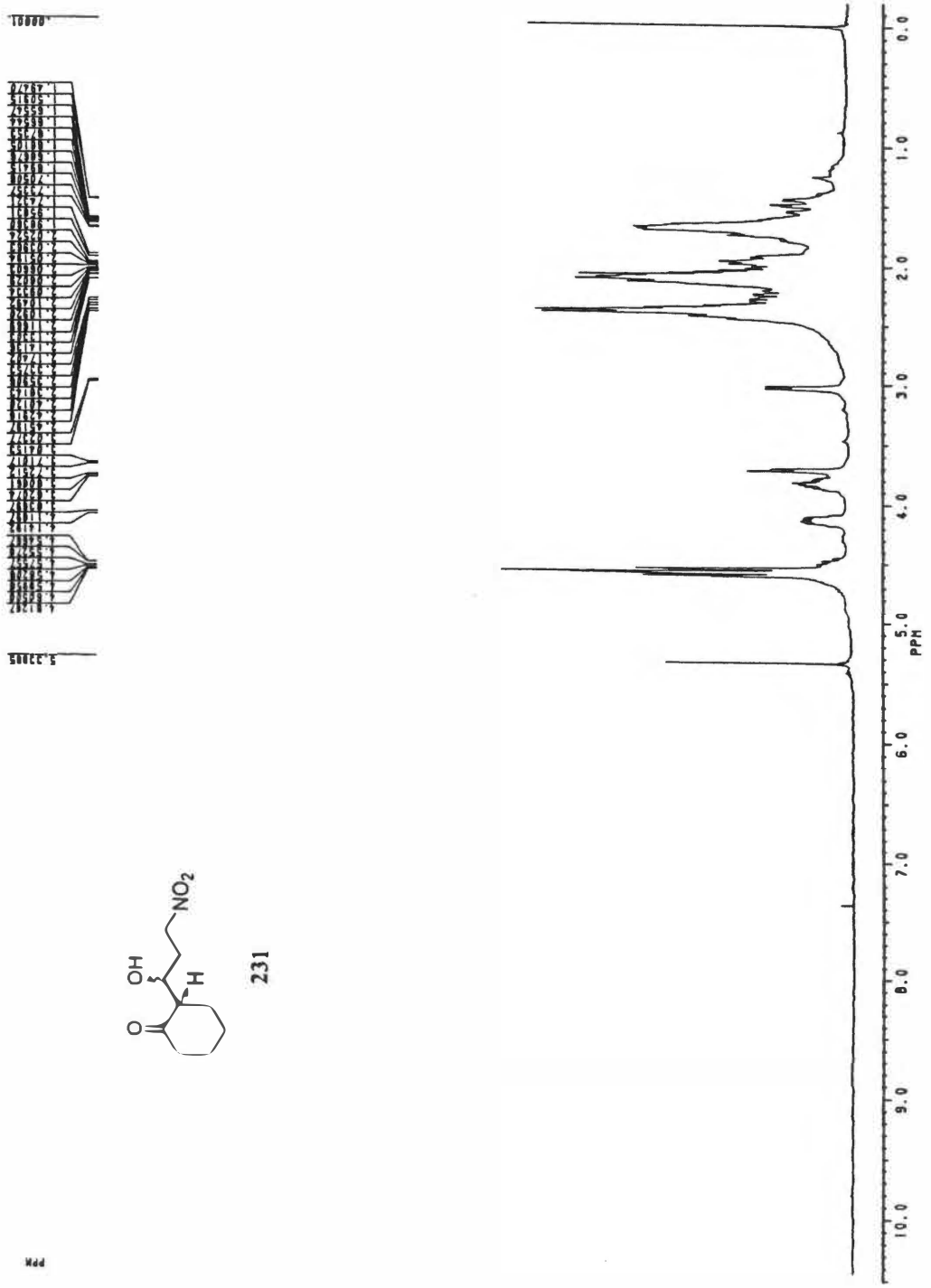

PPM
101.778
78.865
53.788
30.281
MeO
MeO
NO2
155
200
180
160
140
120
100
80
60
40
20
0
PPM


OMe
NO2
H
O
230
PPM

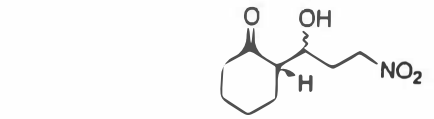


230

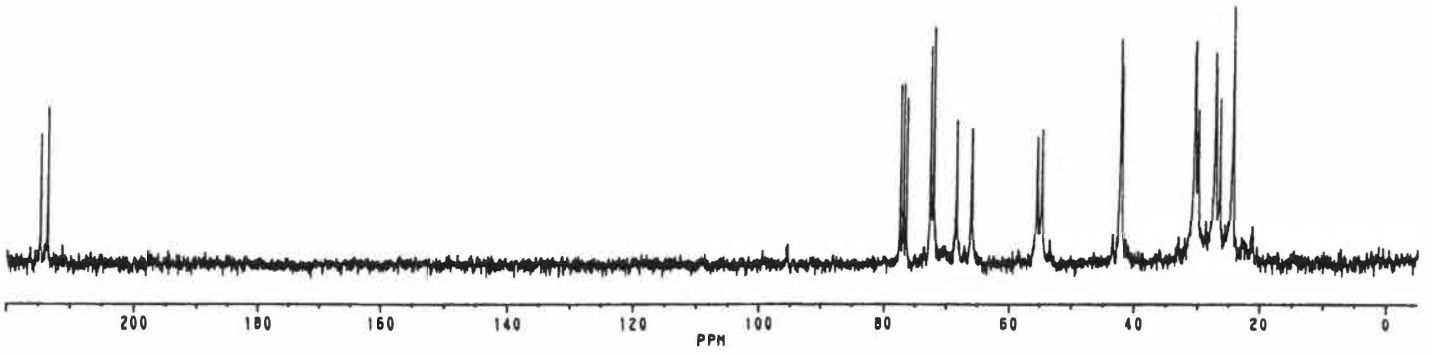


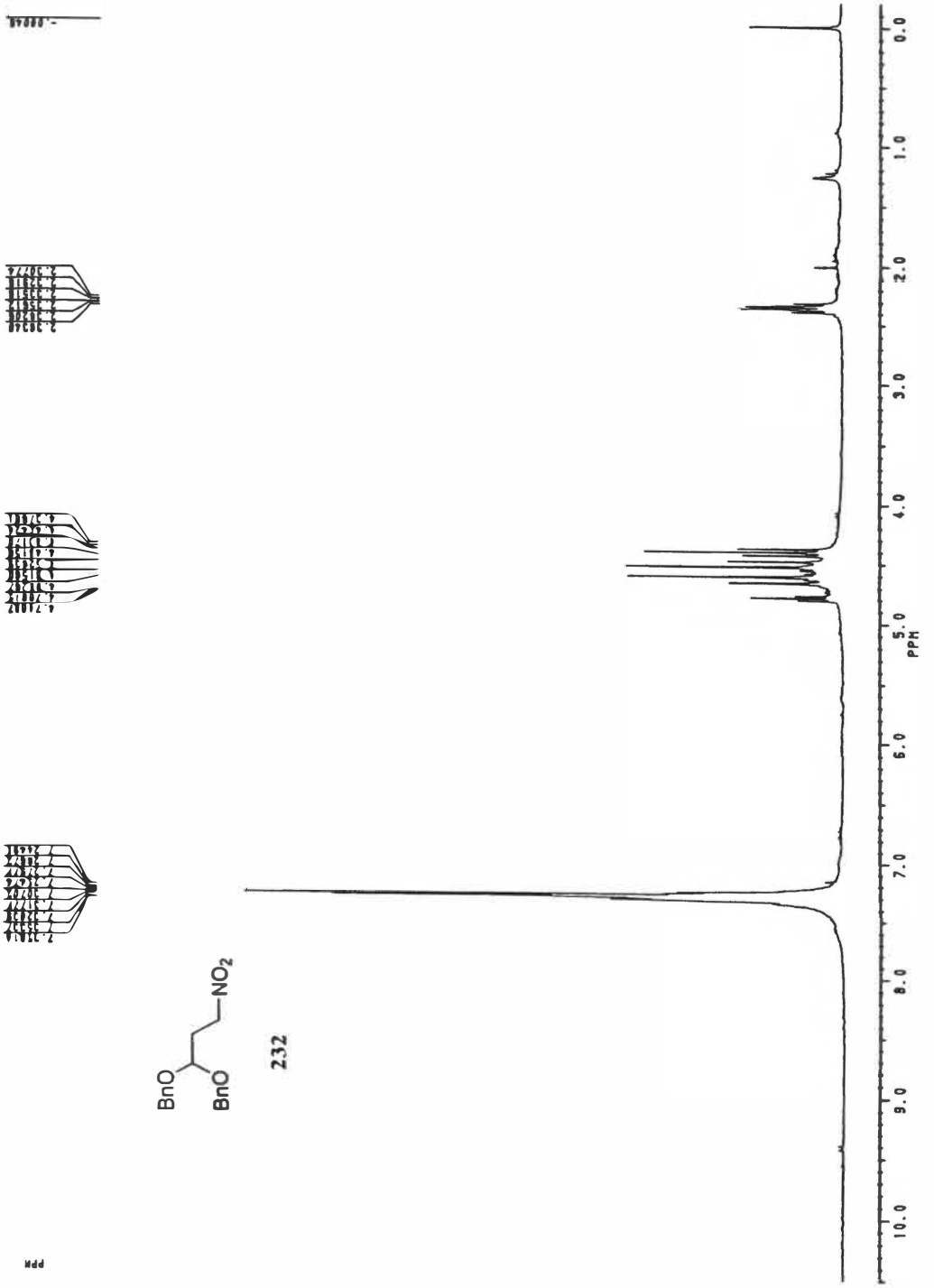


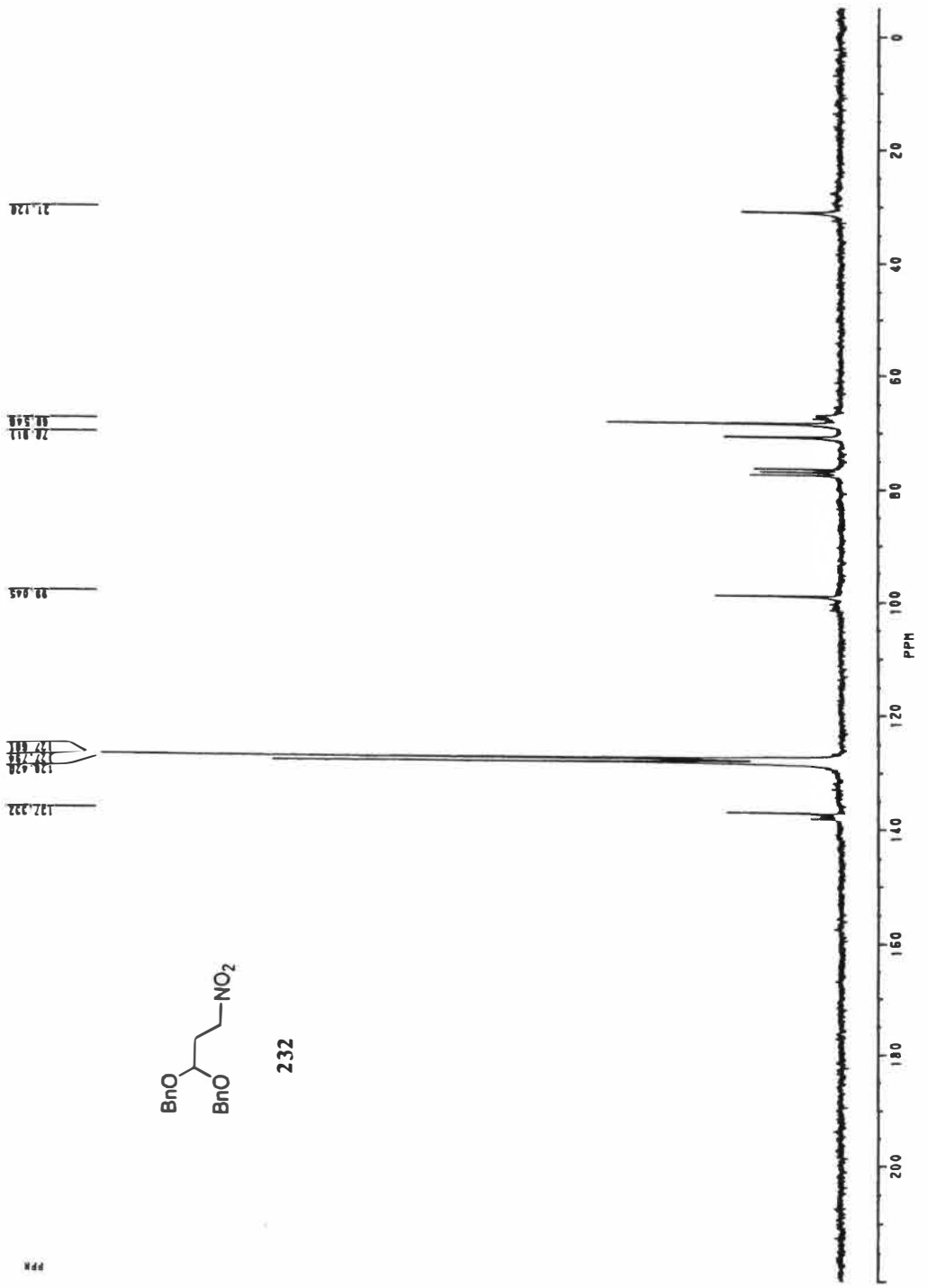
231

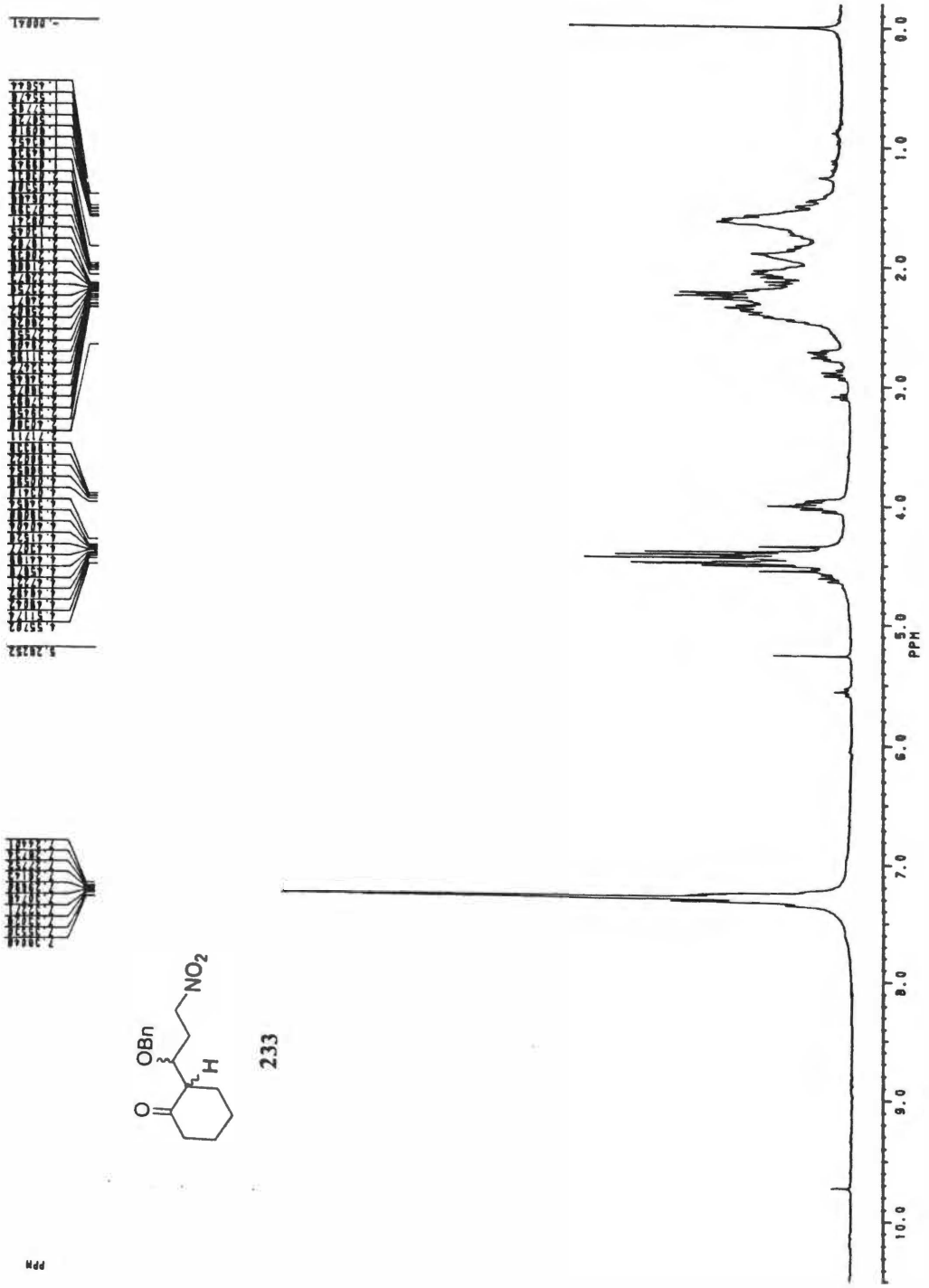


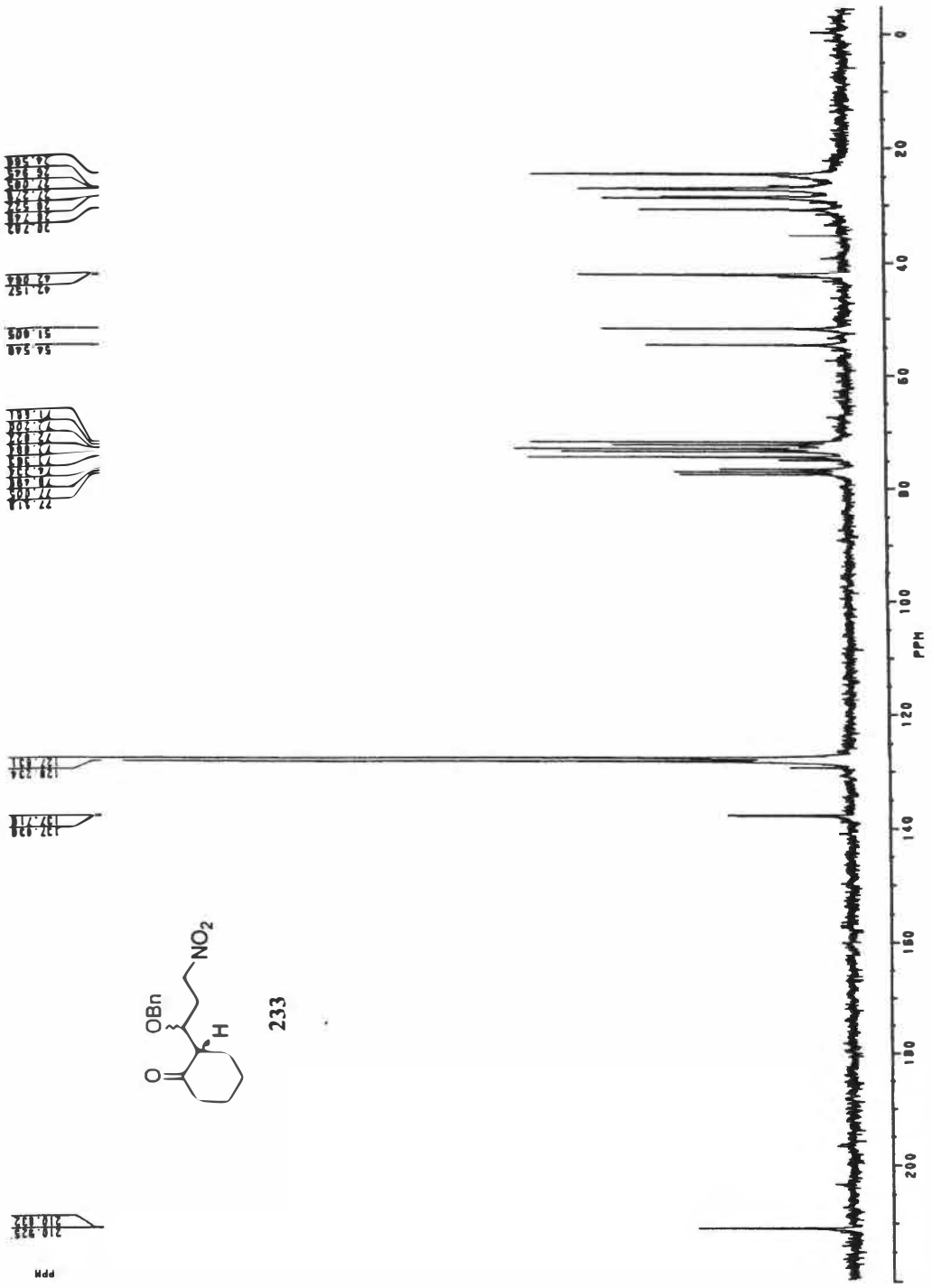
231

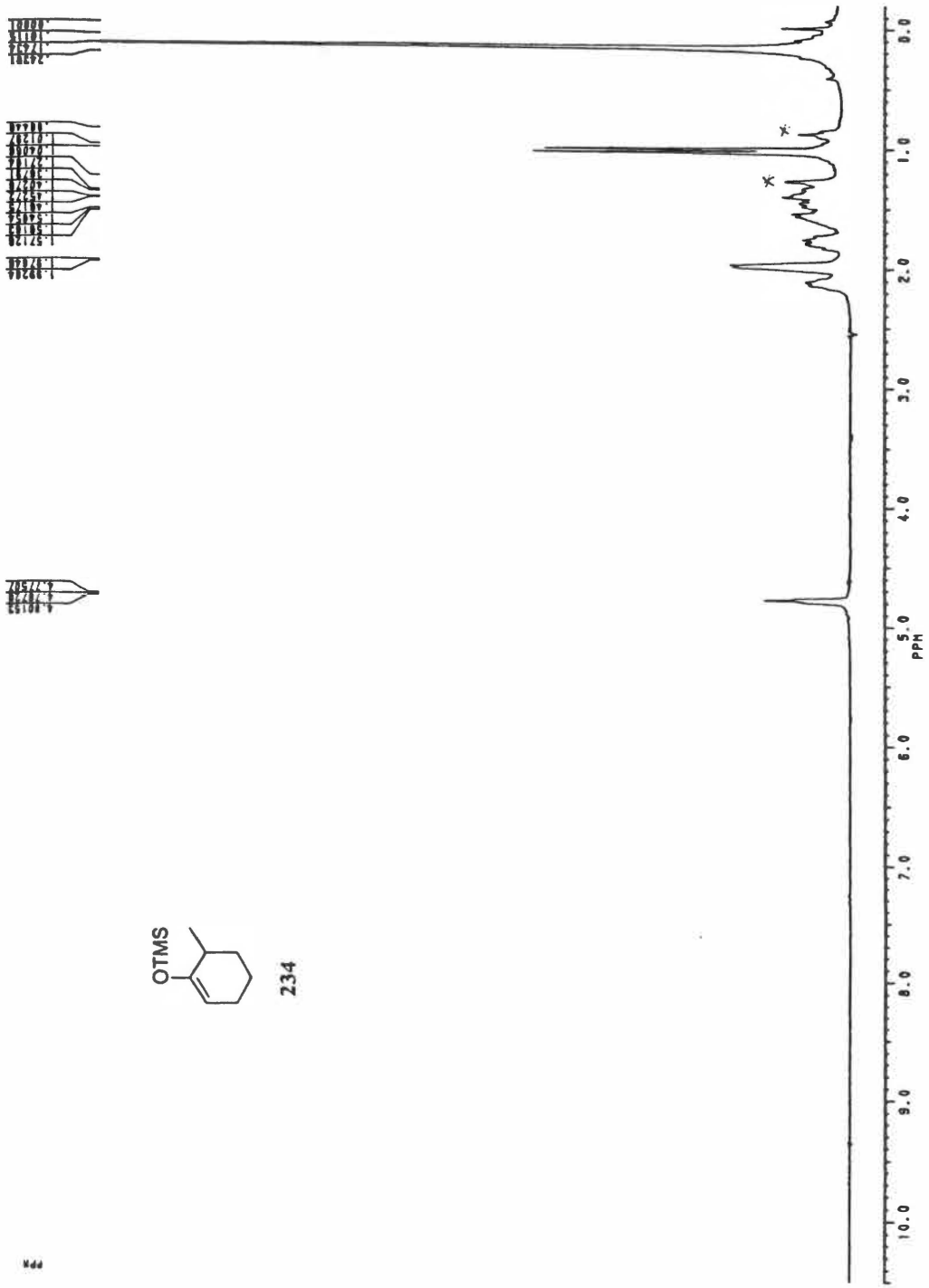


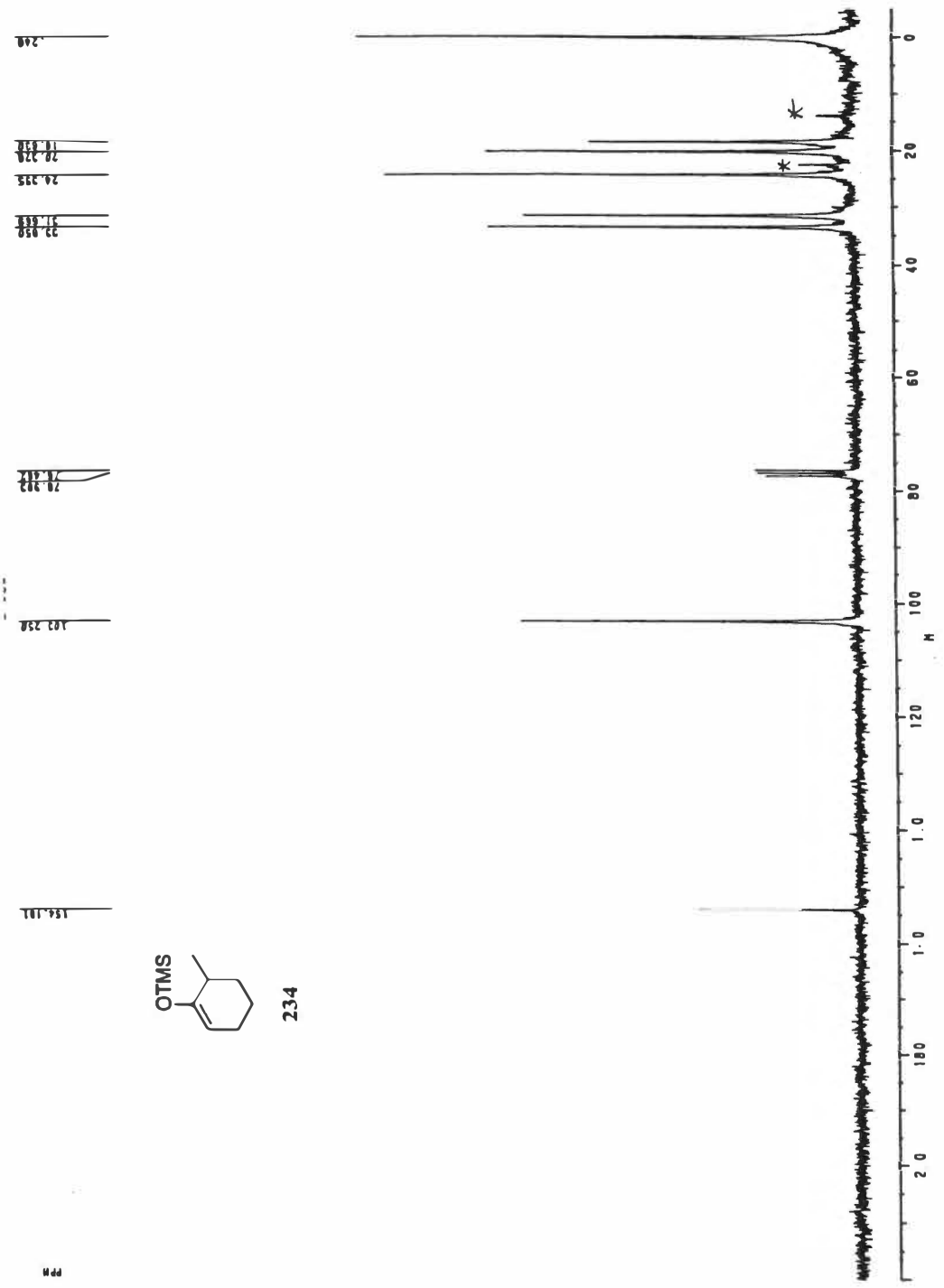

BnO
BnO
NO2
232
PPM

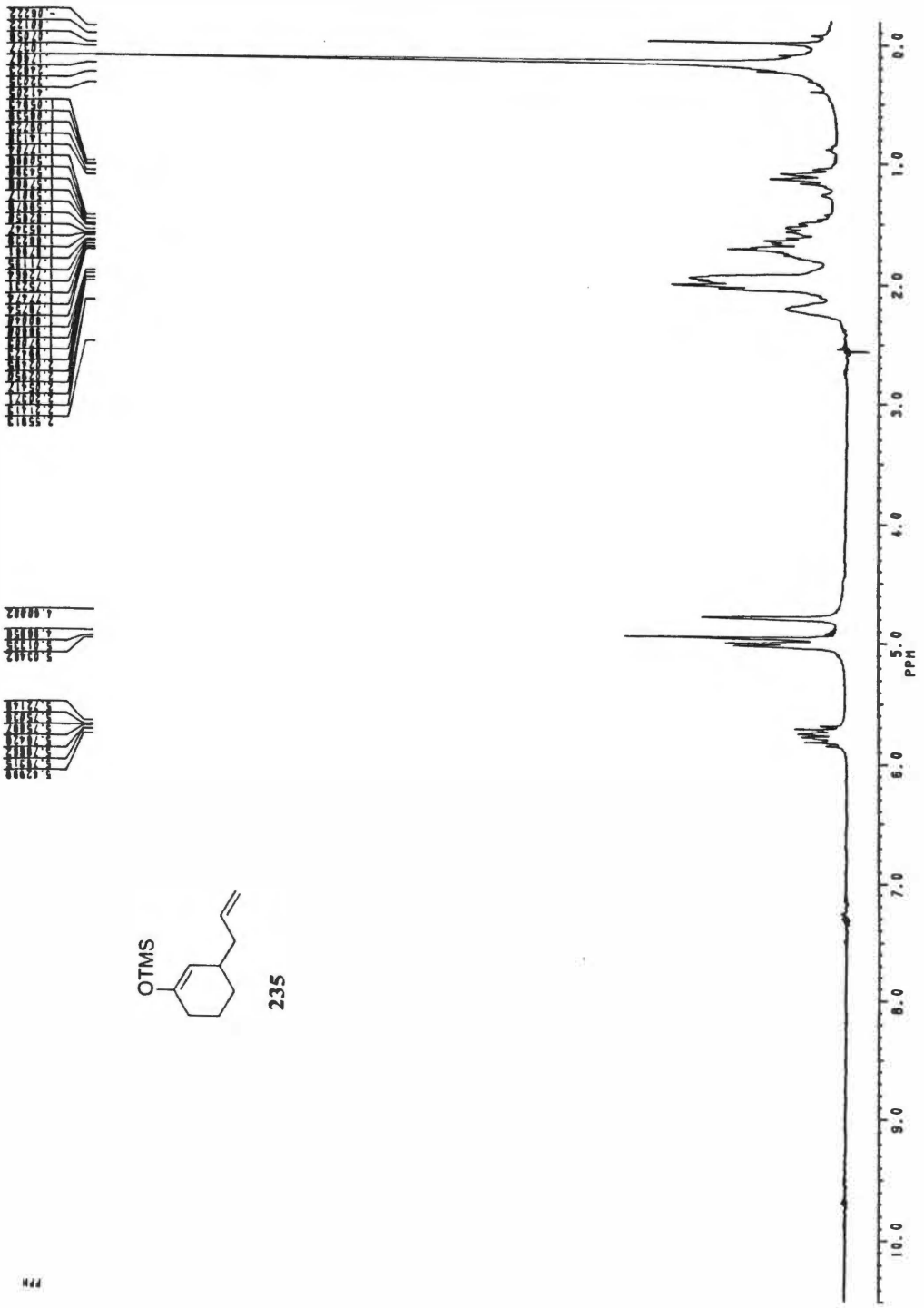

BnO
BnO
NO2
232
PPM

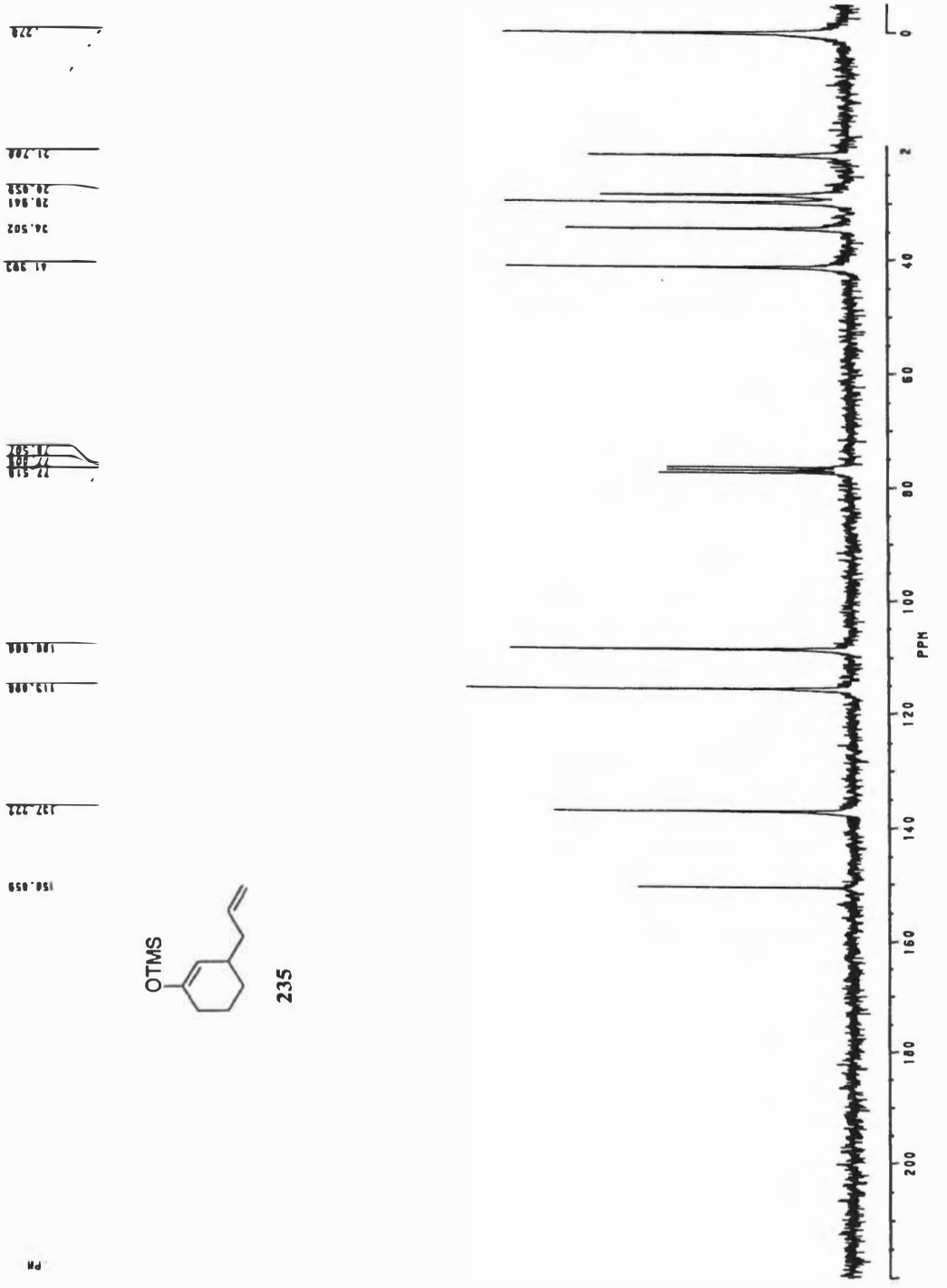

OBn
NO2
H
O
233
PPM

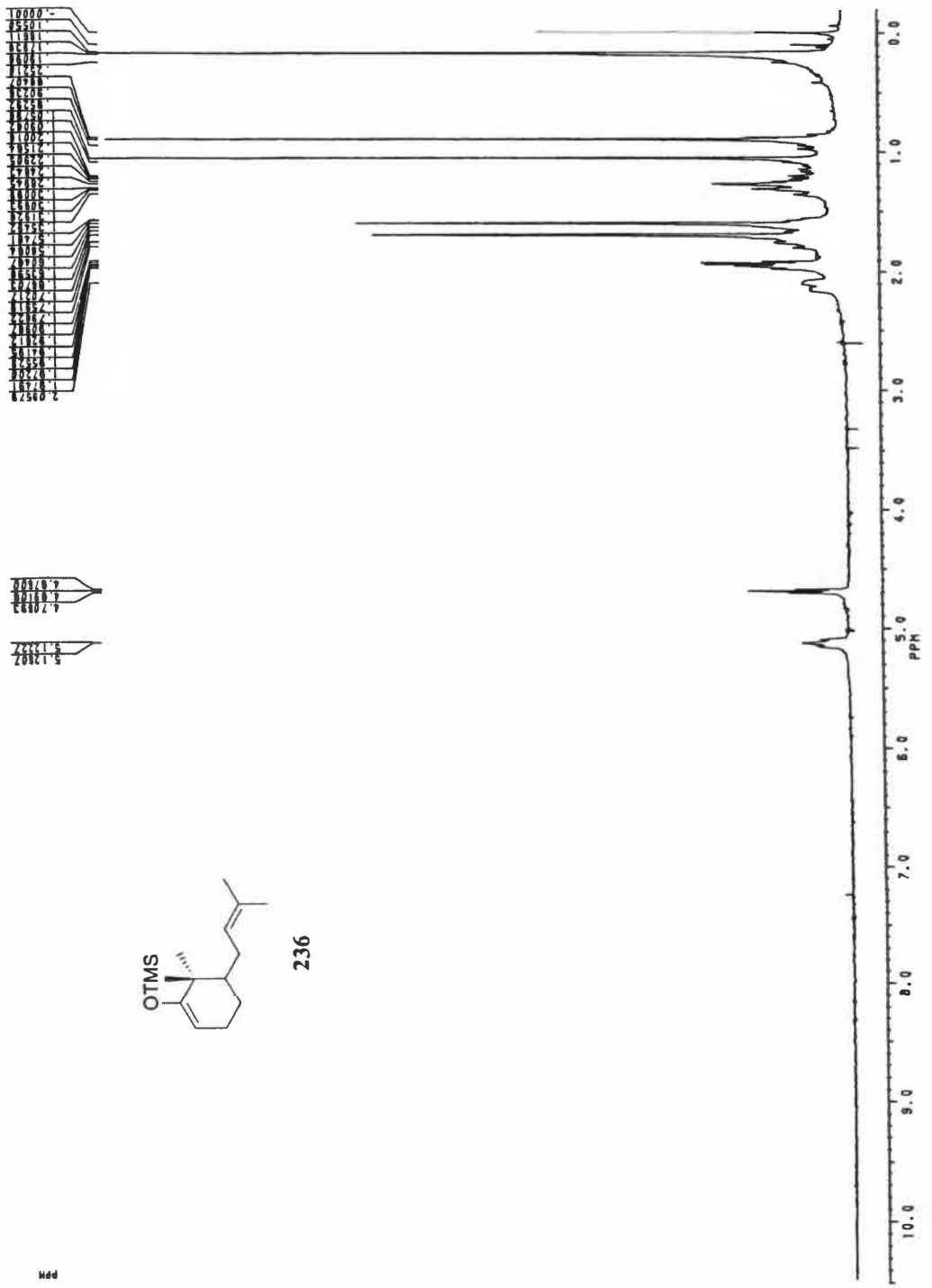

NO2
OBn
O
H
233
PPM

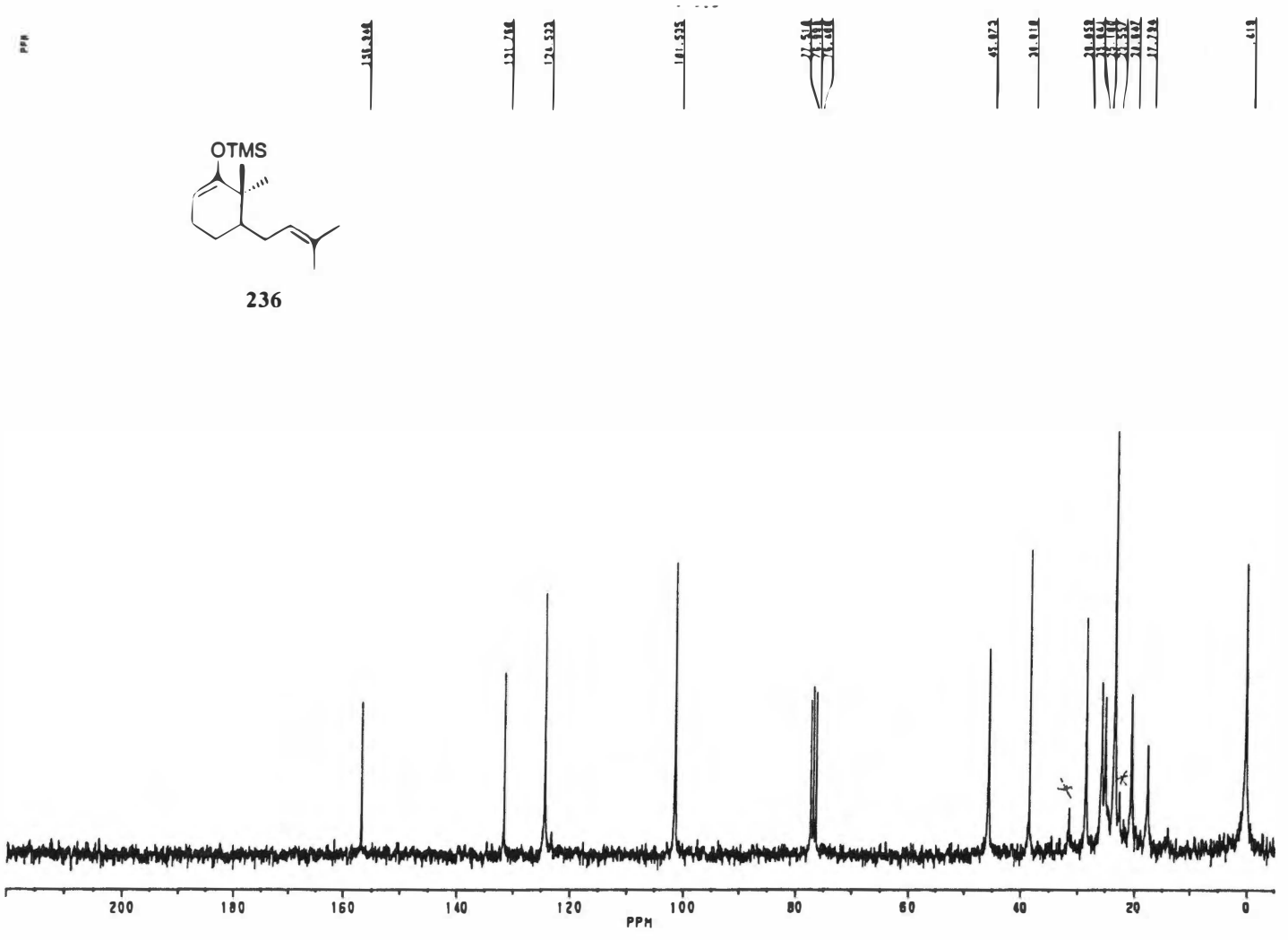

OTMS
234
PPM


OTMS
234

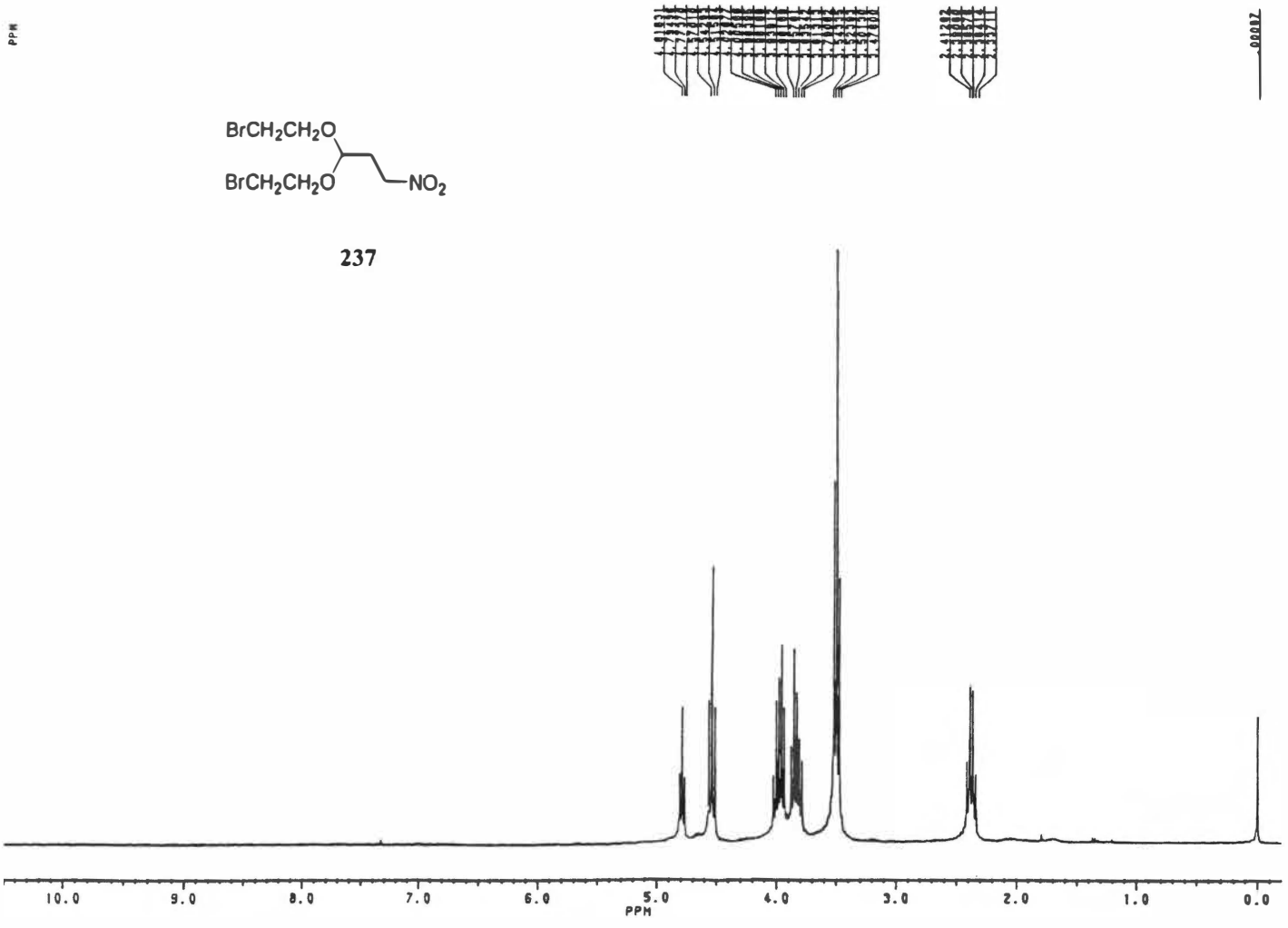

OTMS
235
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM


OTMS
235
PPM

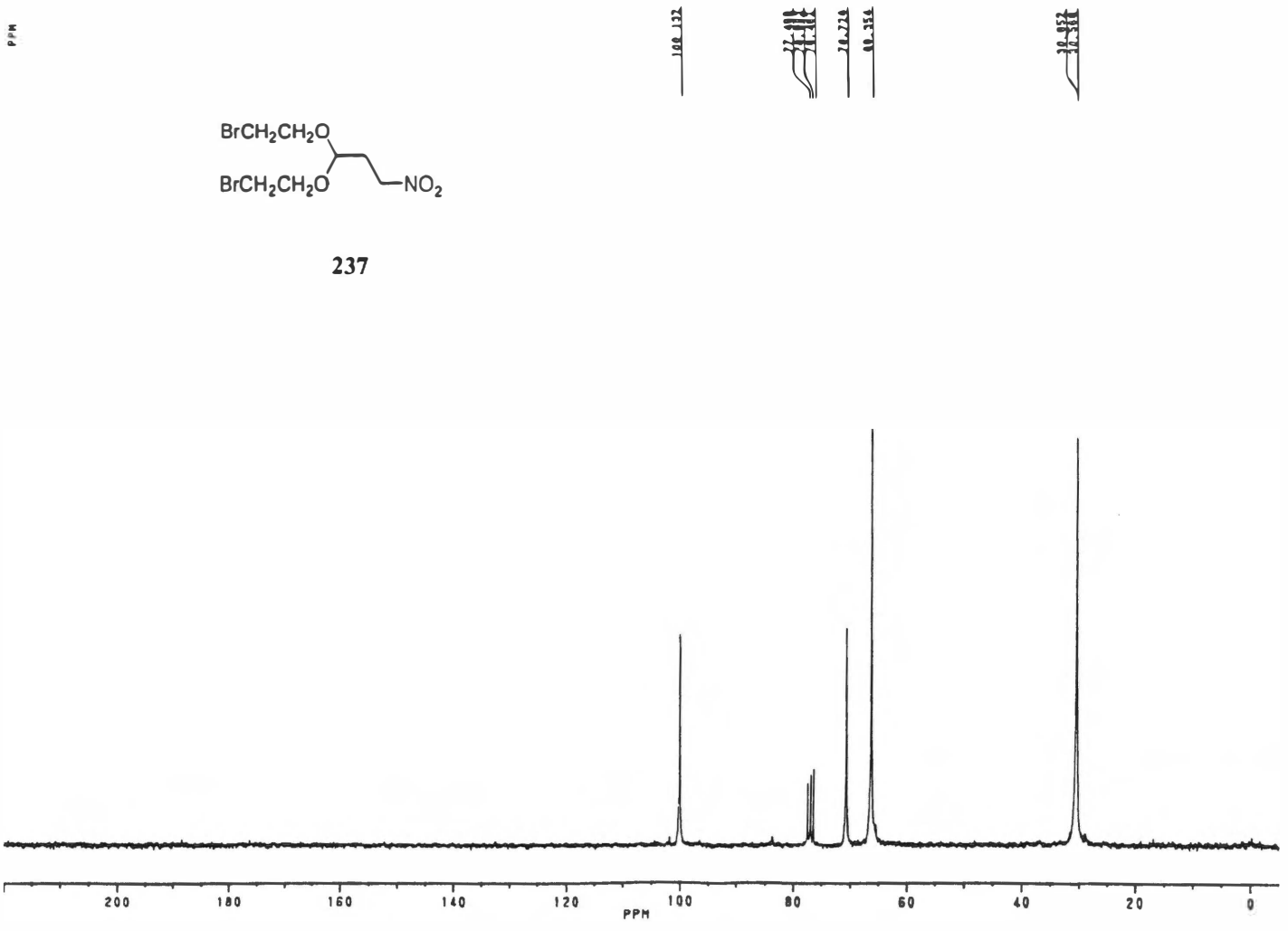

OTMS
236
PPM



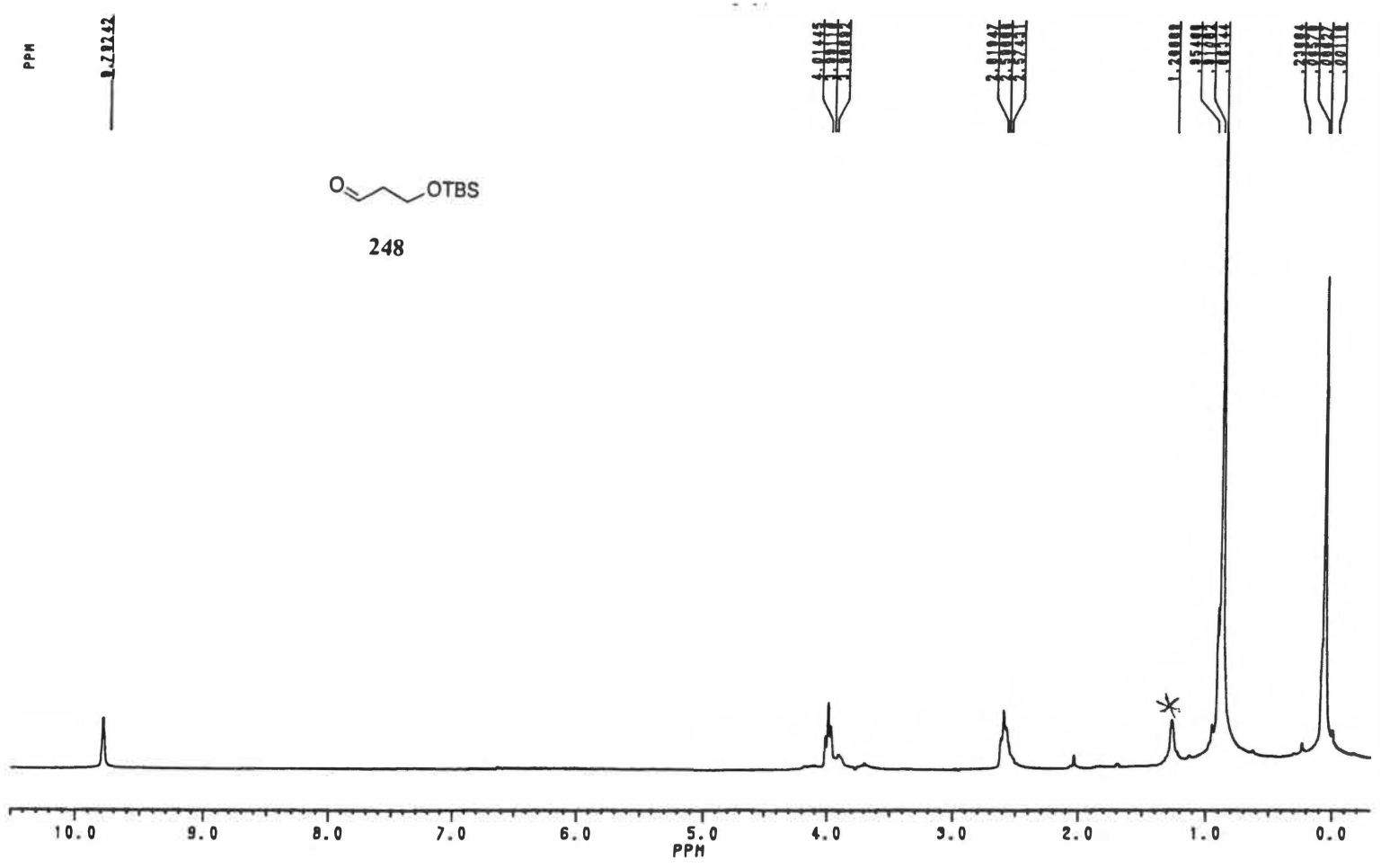
236


PPM
BrCH2CH2O
BrCH2CH2O
NO2
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

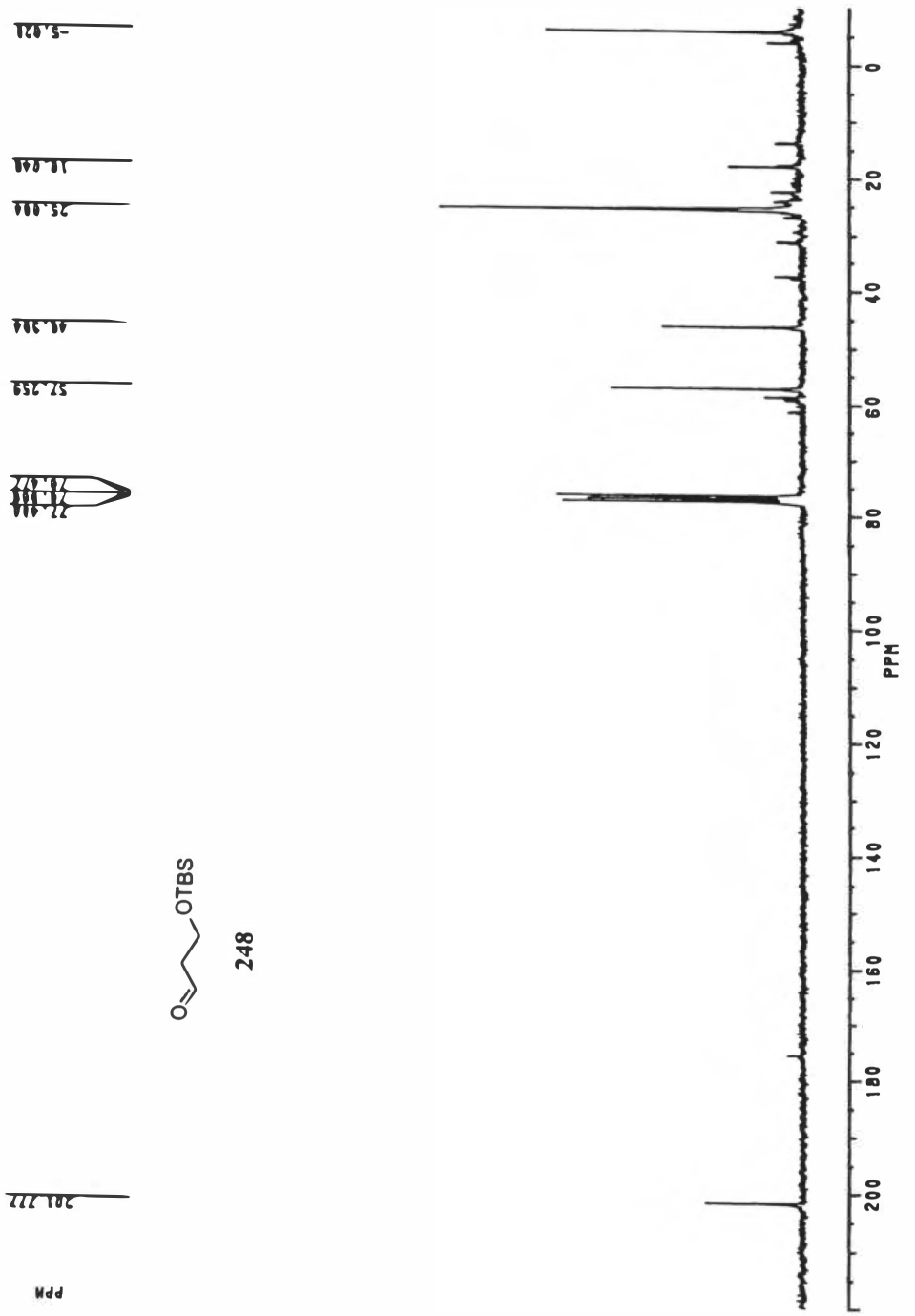
237

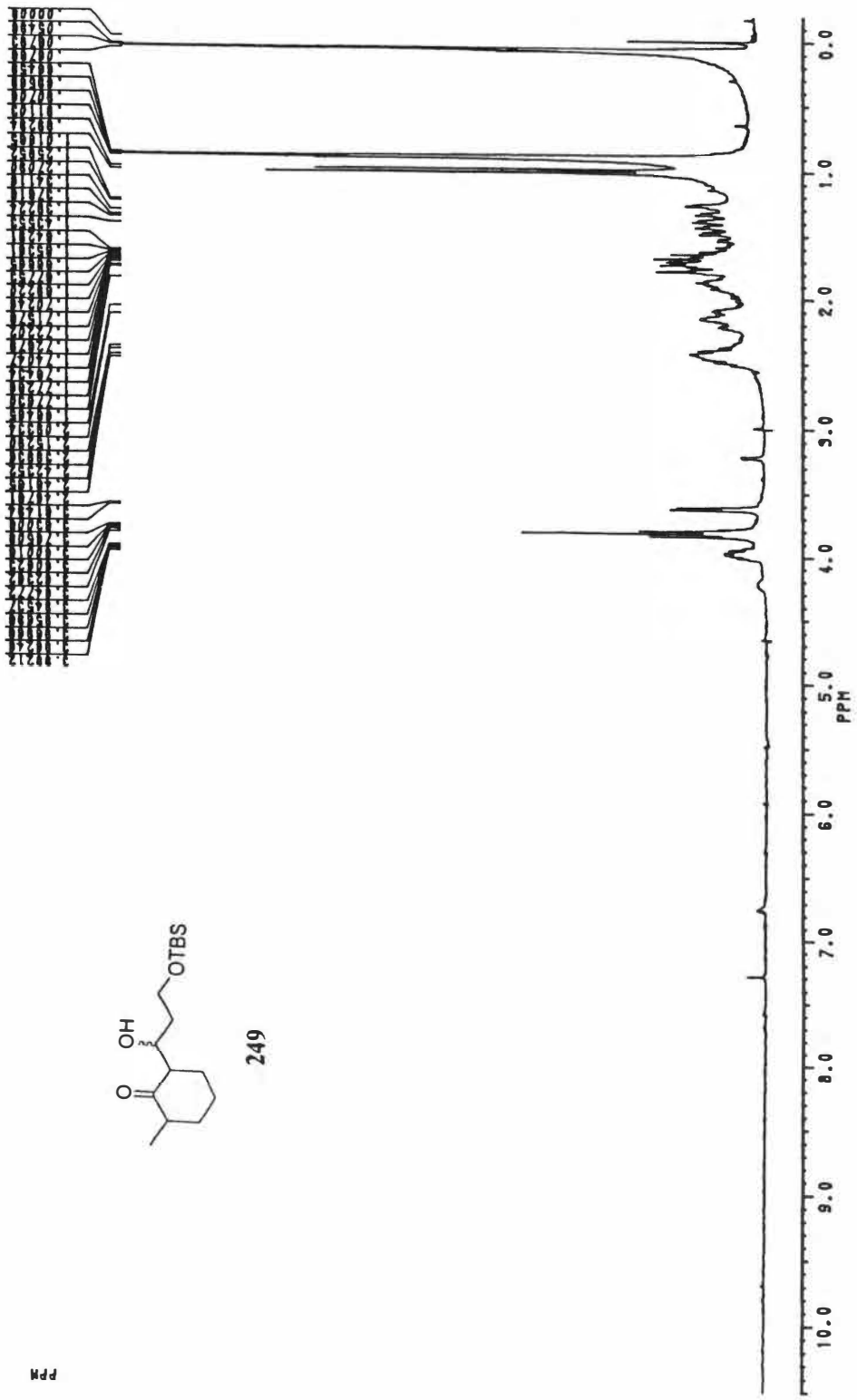

PPM
100.132
70.729
69.354
30.952
BrCH2CH2O
BrCH2CH2O
NO2
200
180
160
140
120
100
80
60
40
20
0
PPM

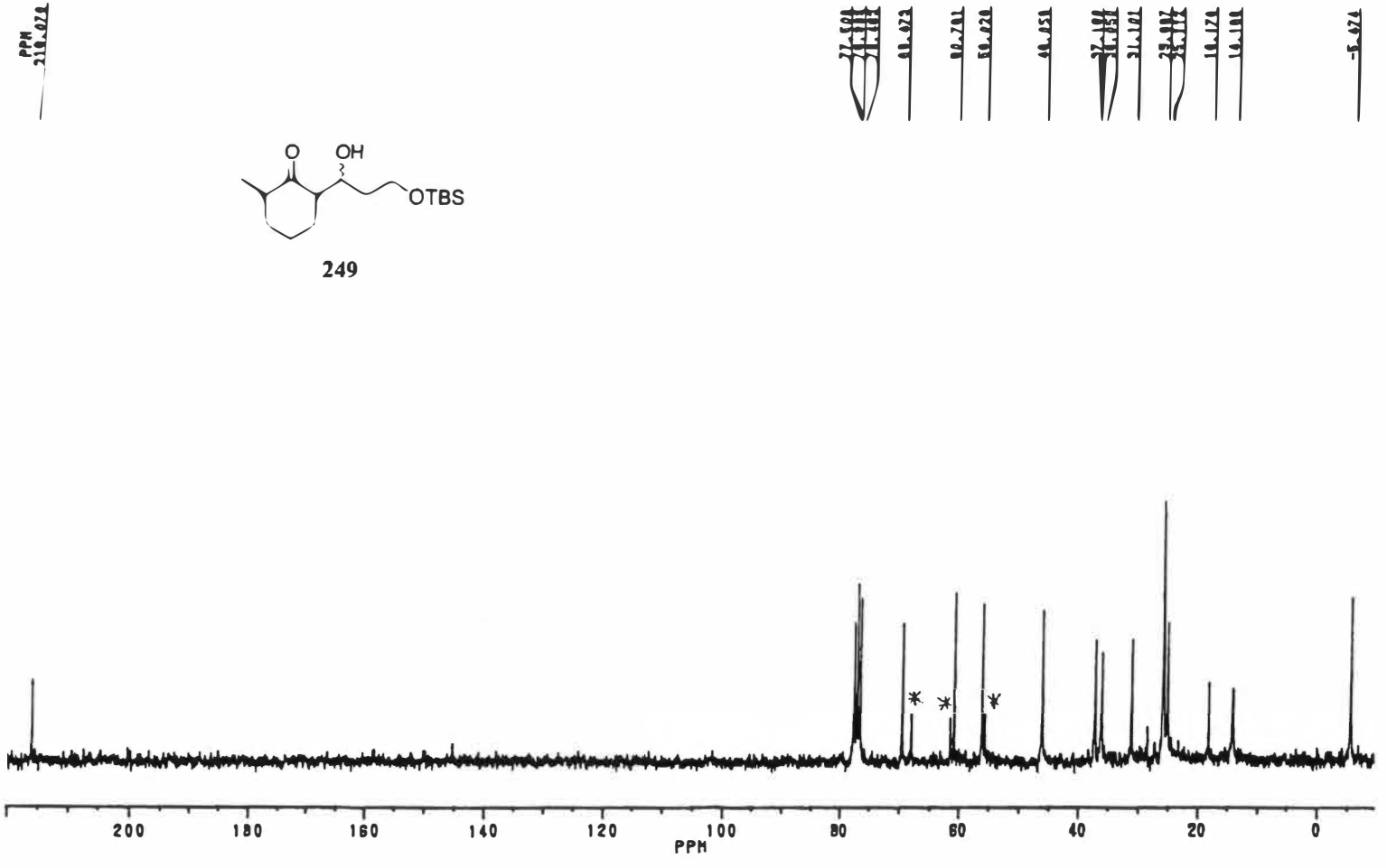
237


PPM
9.782
1.000
1.154
1.154
2.111
2.111
3.000
1.200
1.154
1.154
1.154
2.308
2.111
2.111
2.111
3.000
O
OTBS
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

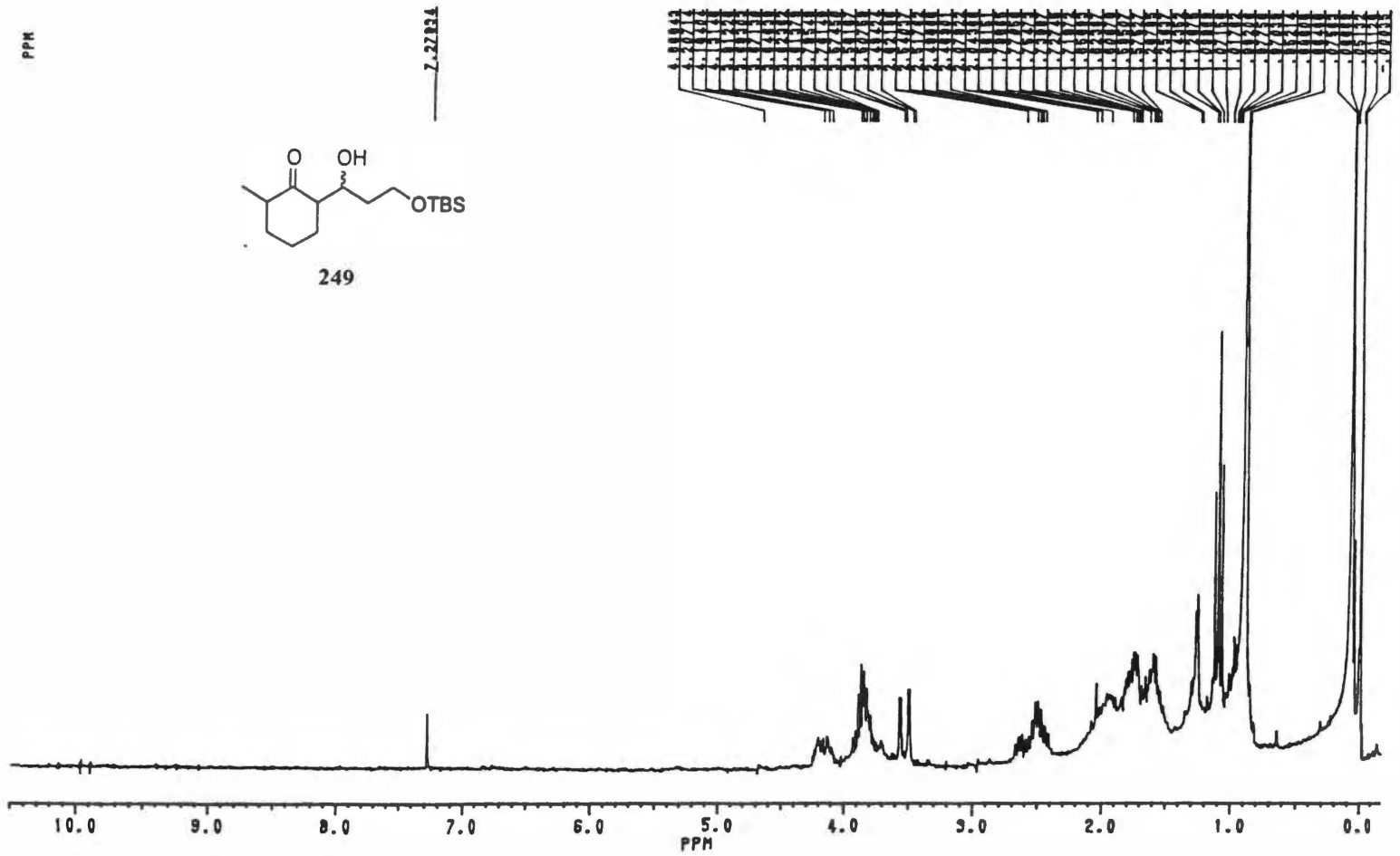
248

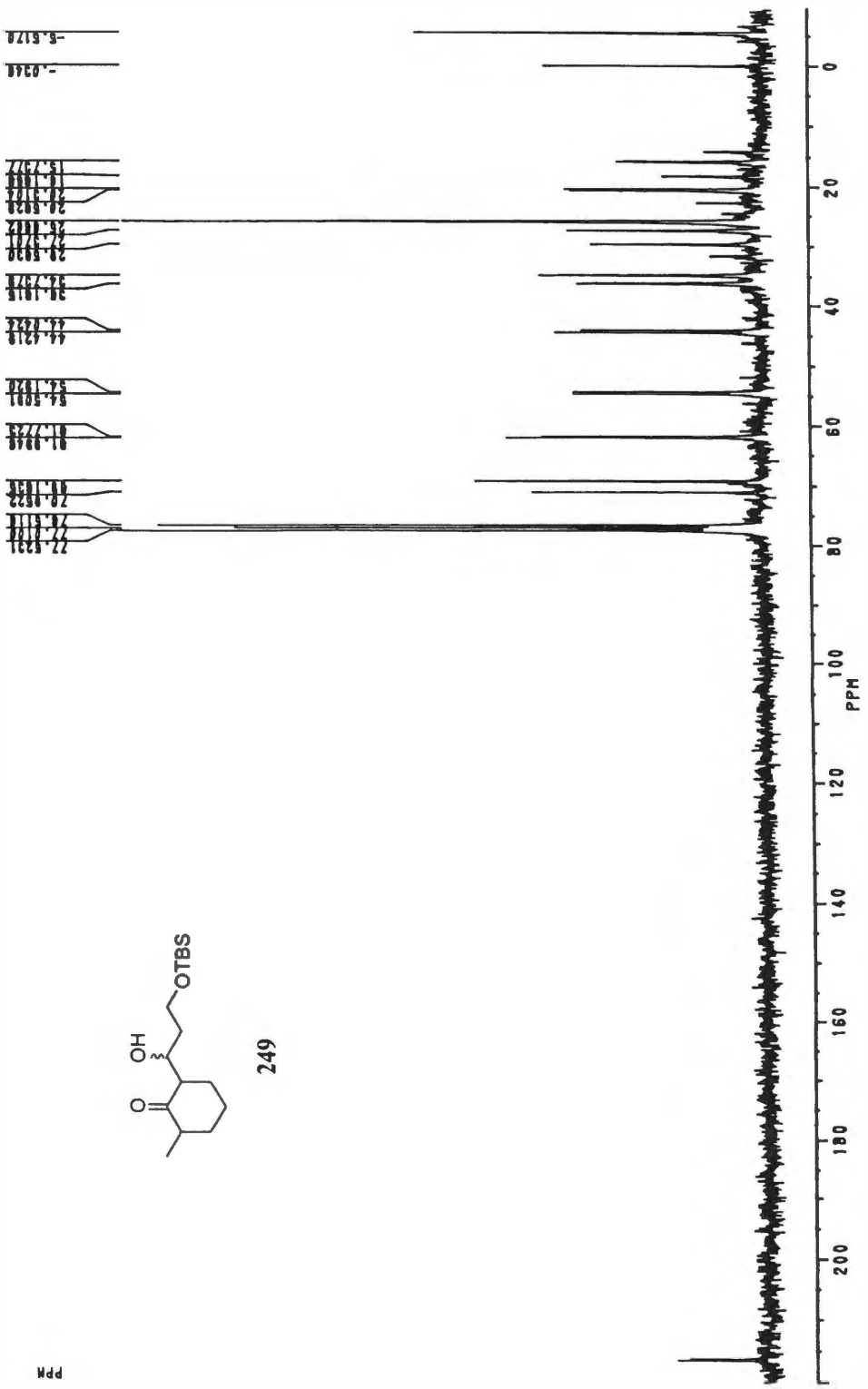

OTBS
O
248
PPM
0
20
40
60
80
100
120
140
160
180
200

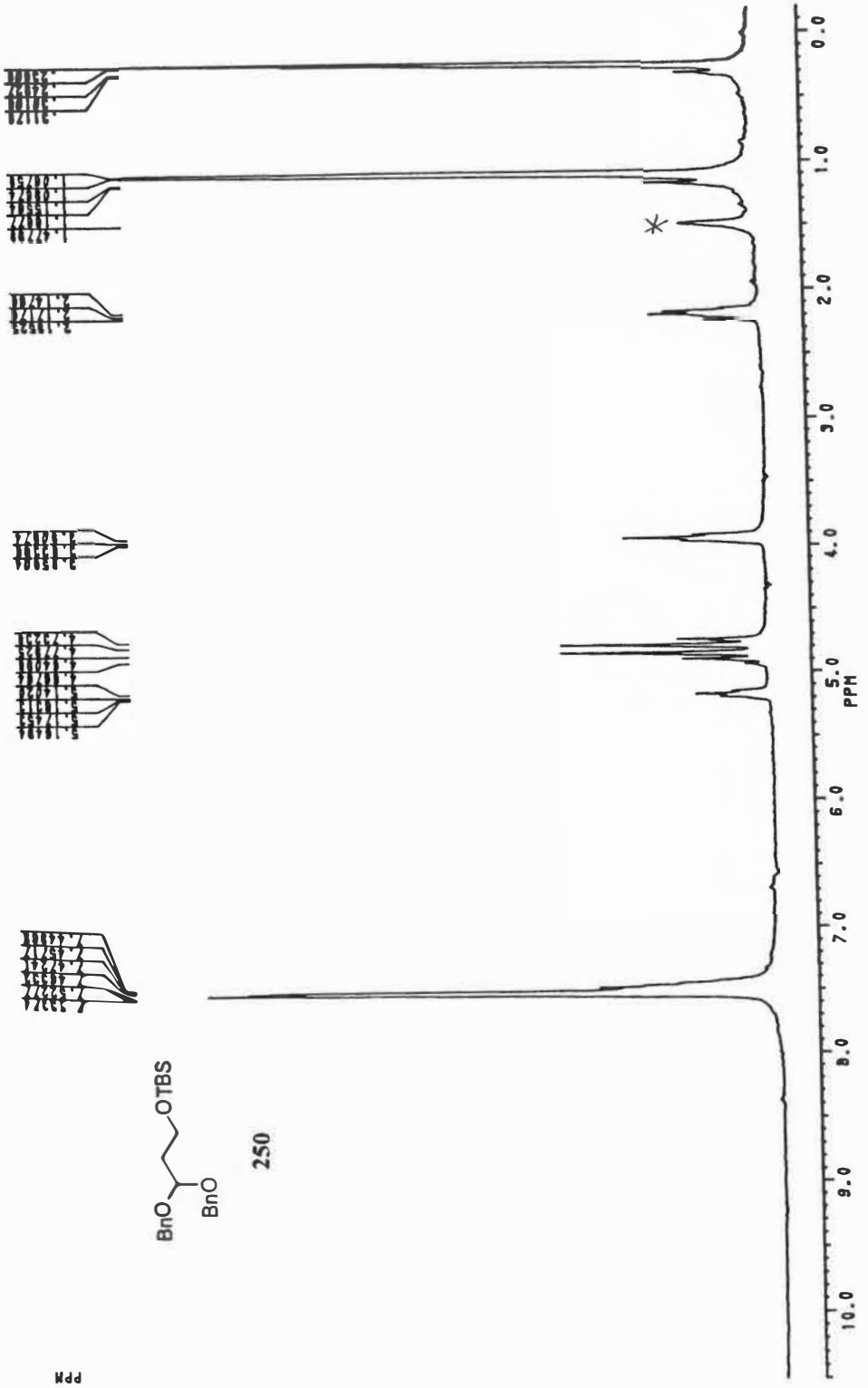

OTBS
OH
O
249
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

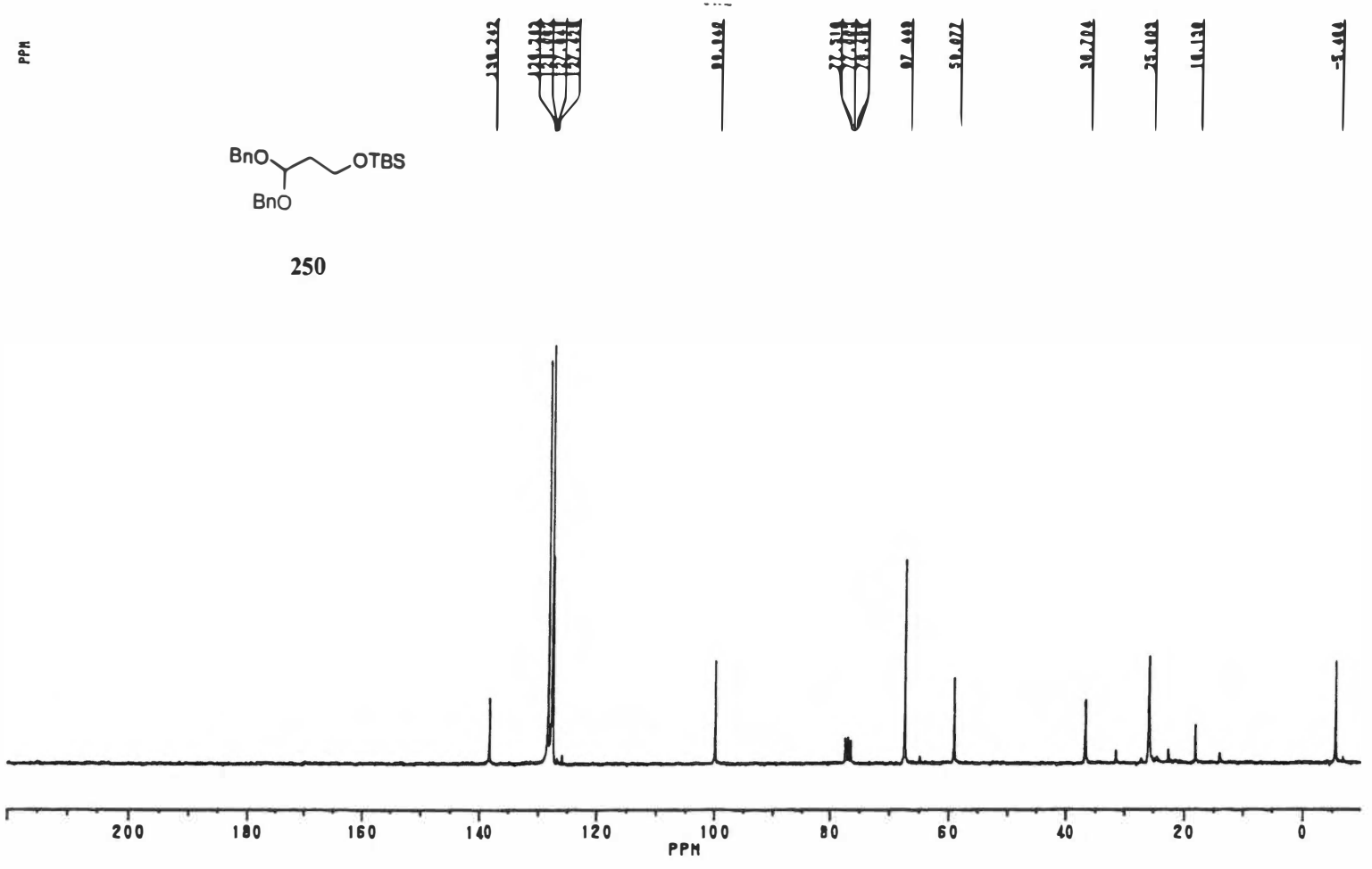


249

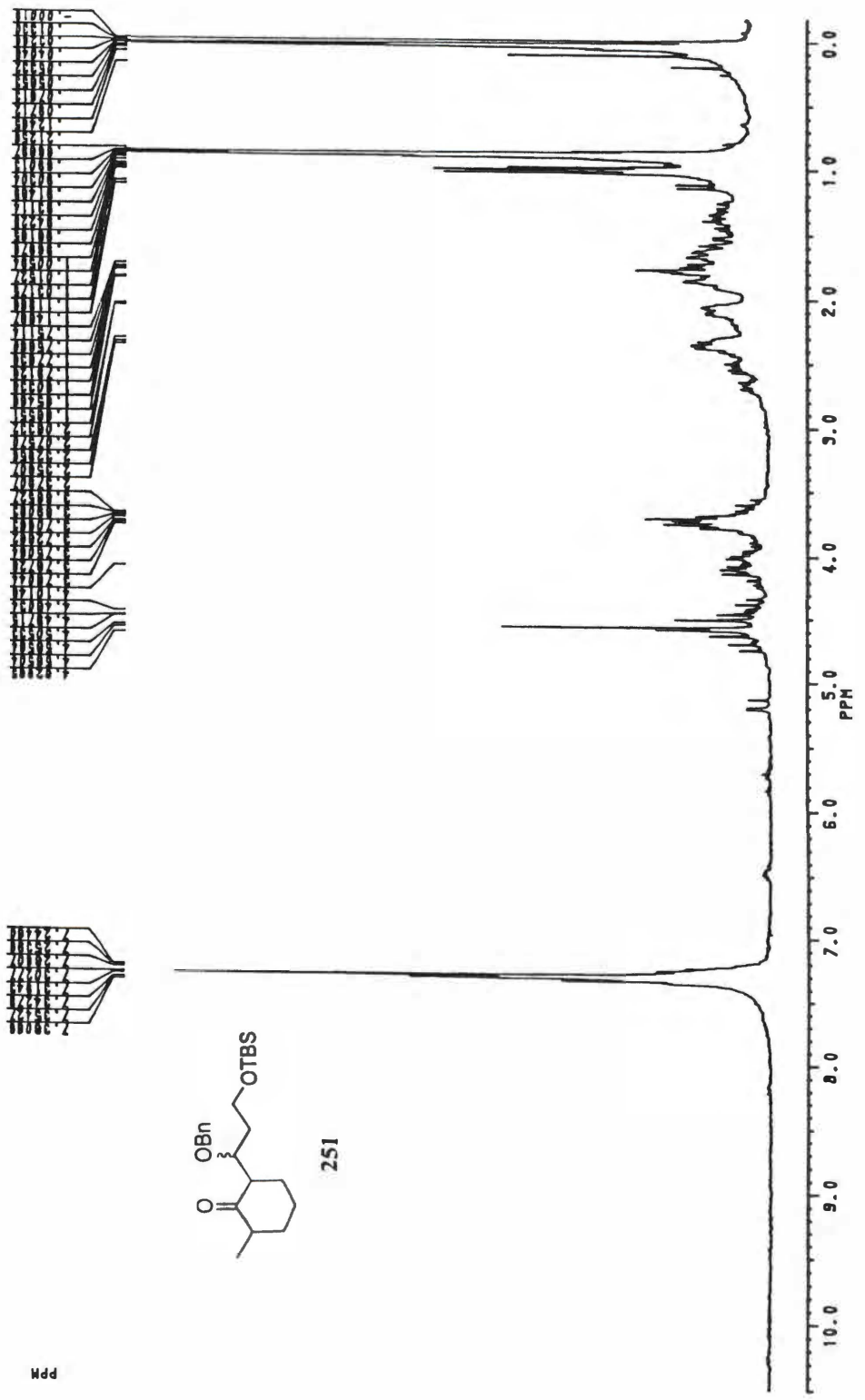

PPM
O
OH
OTBS
249
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

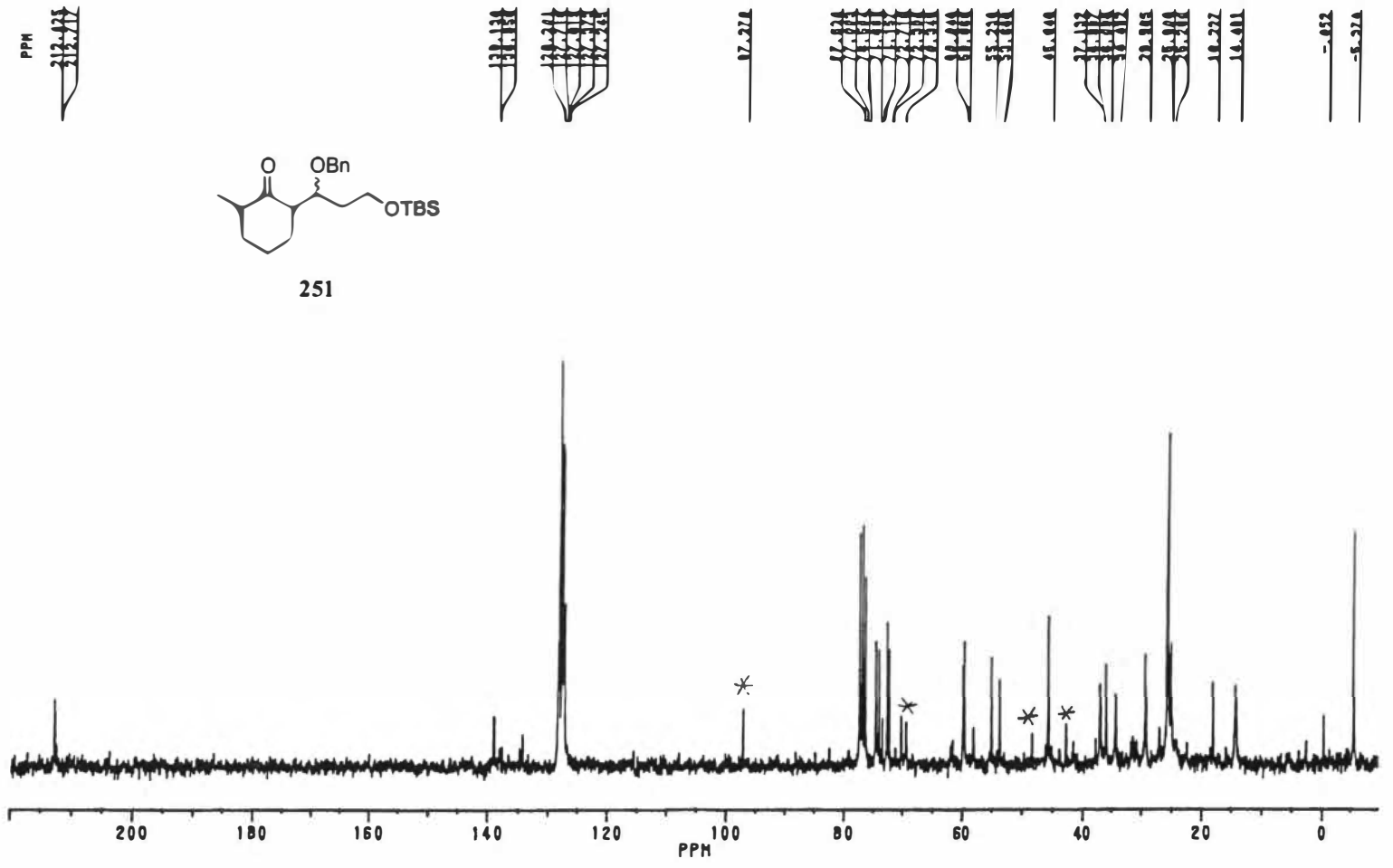

OTBS
OH
O
249
PPM


BnO
BnO
OTBS
250
PPM
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0

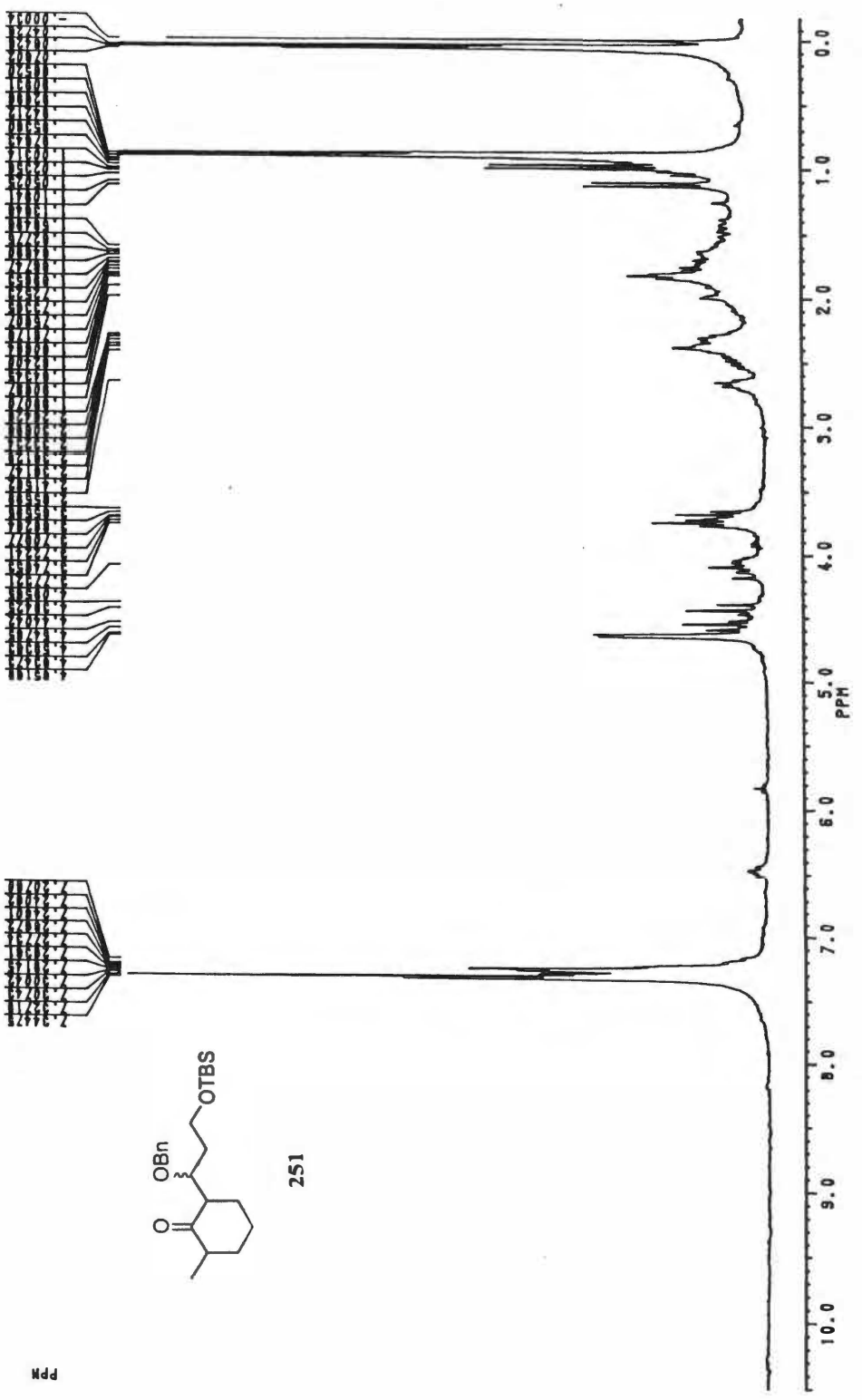


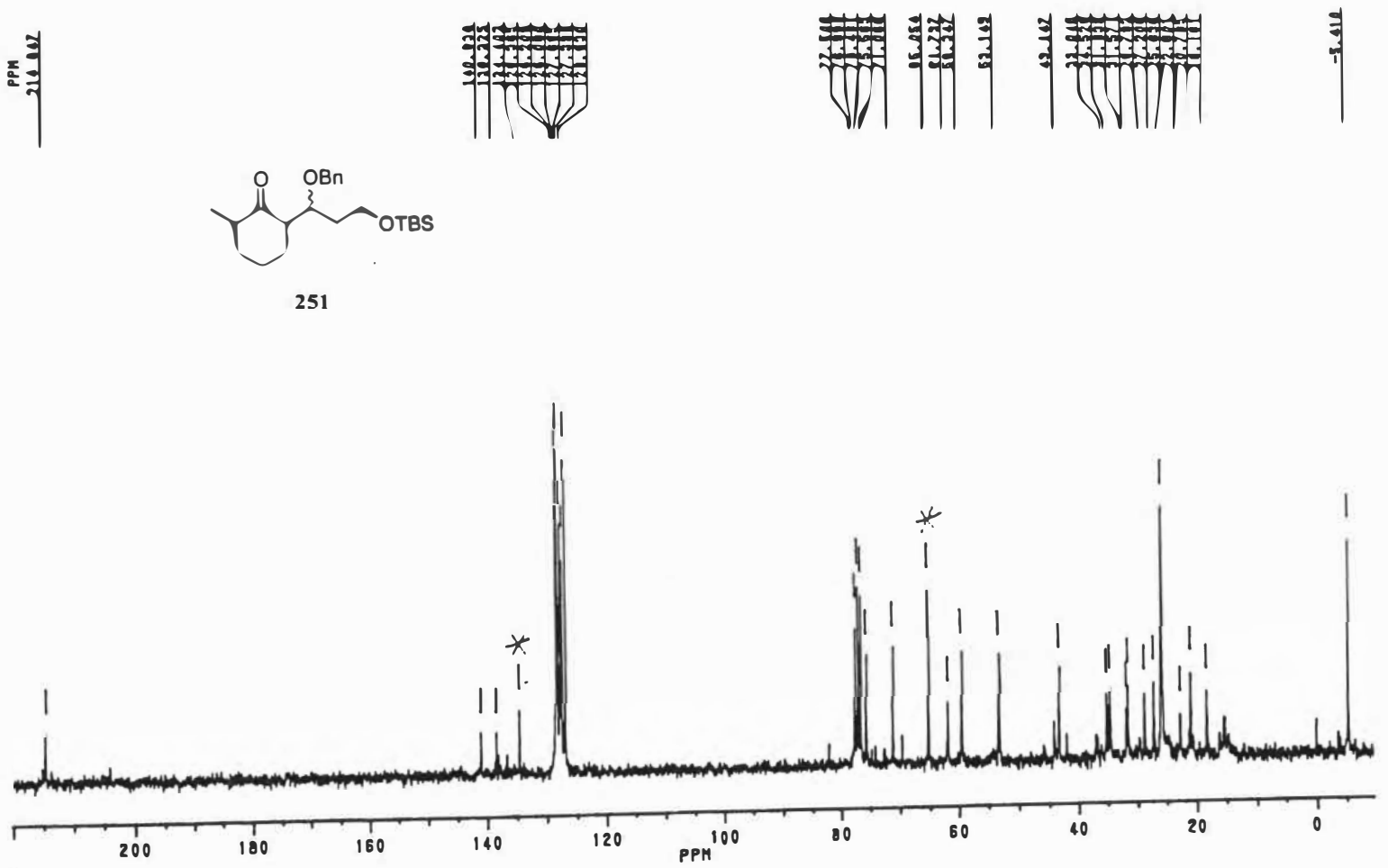
250


OBn
OTBS
O
251
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

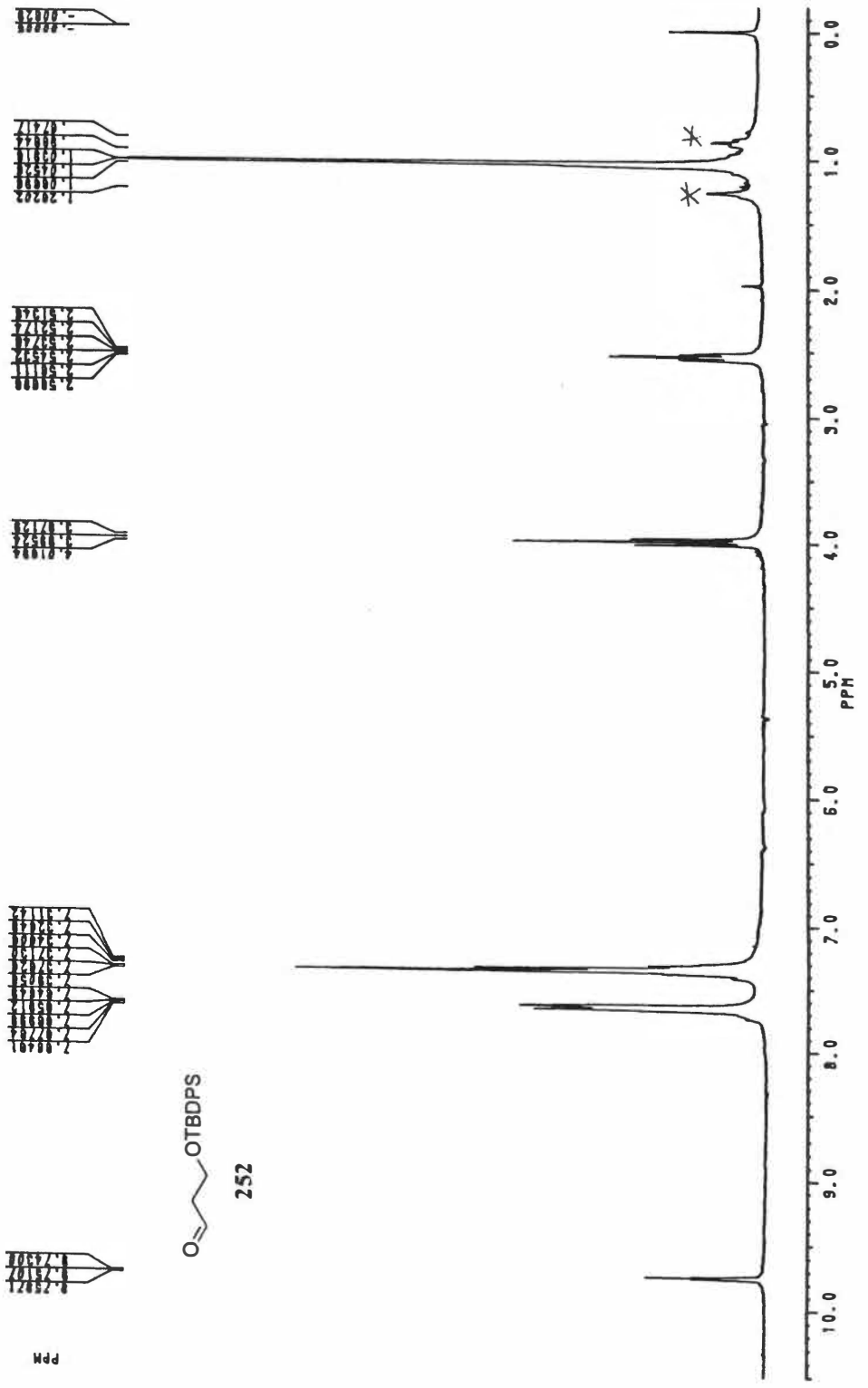


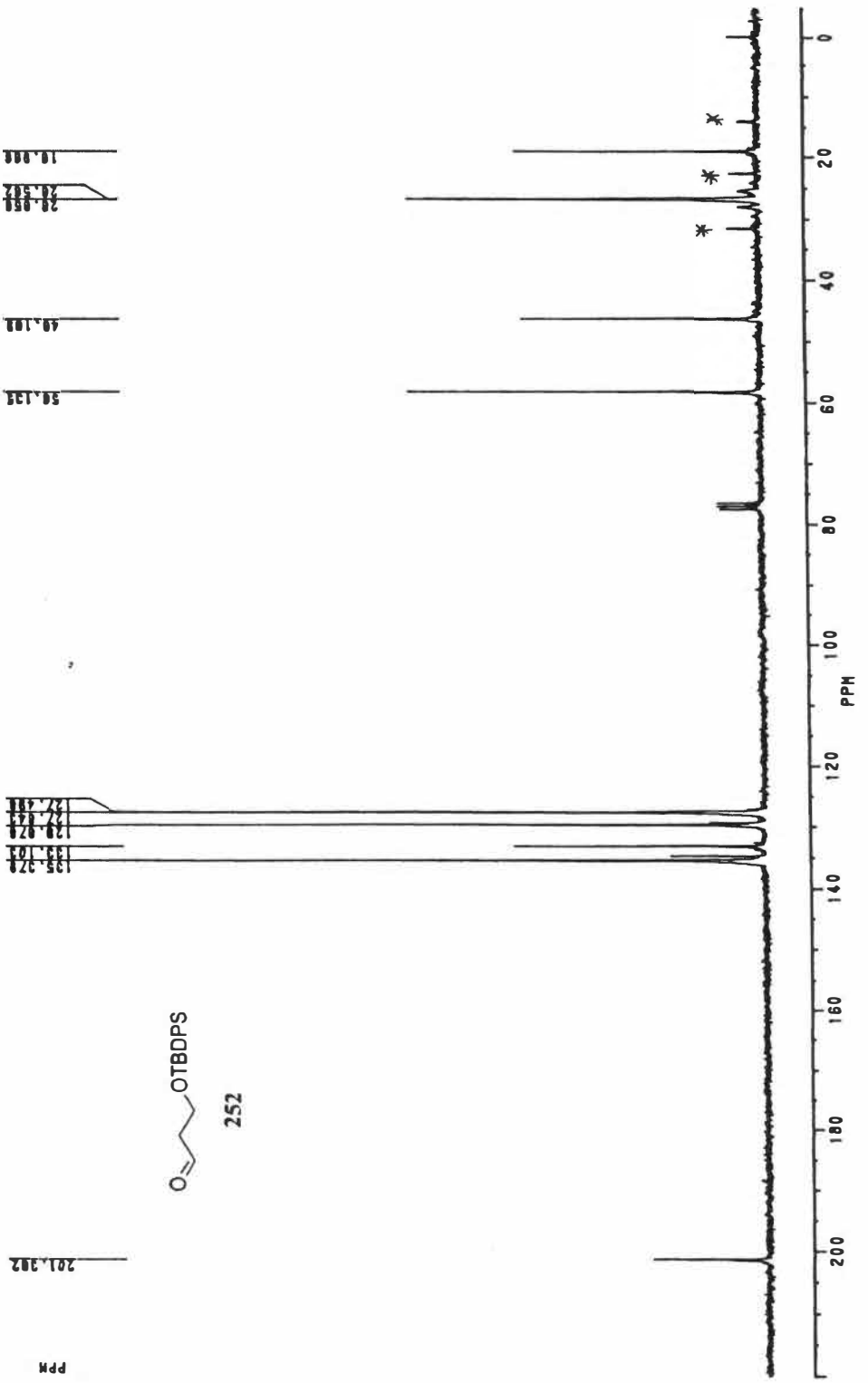
251

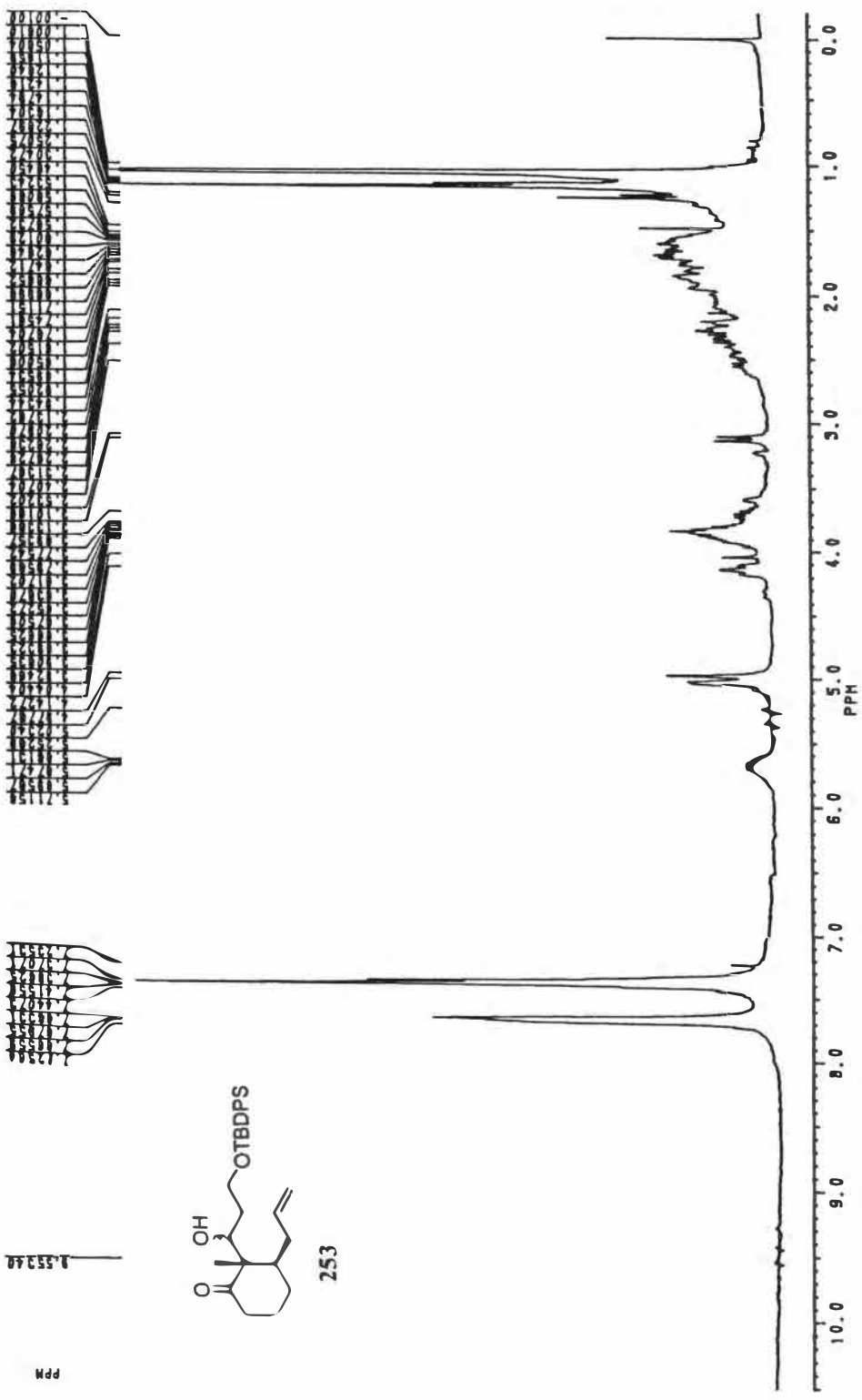

OBn
OTBS
O
251
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

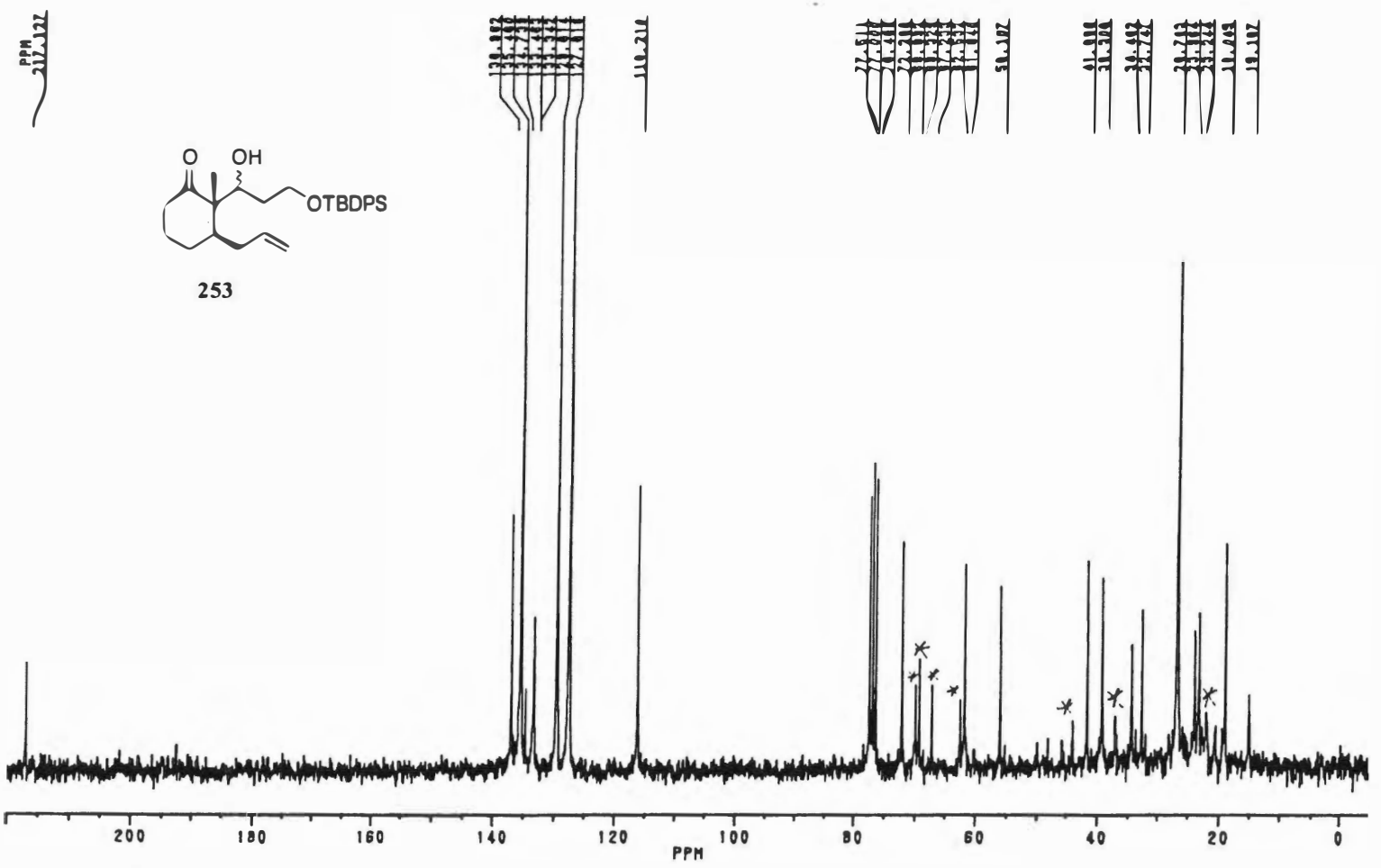


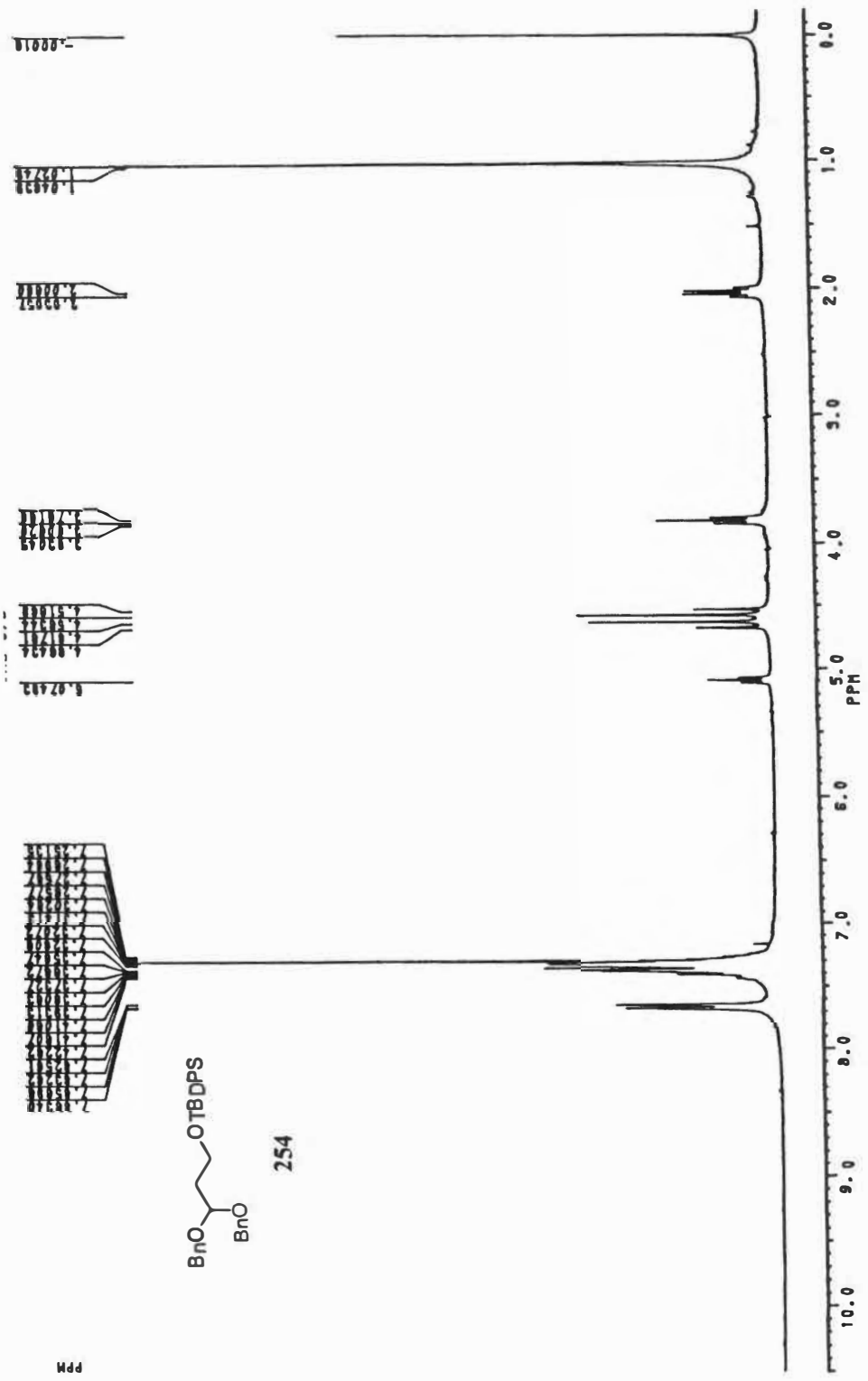
251

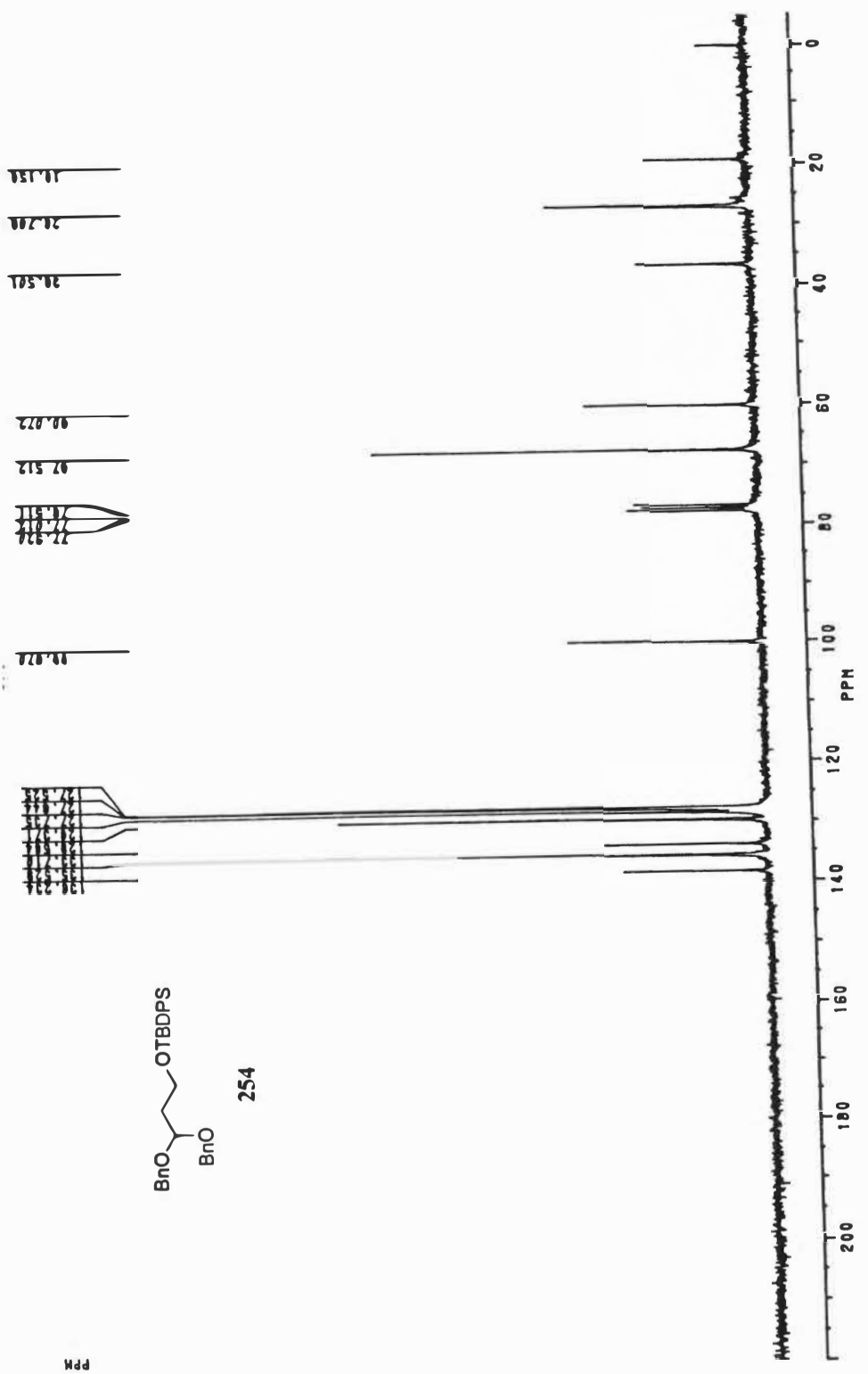

OTBDPS
252
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

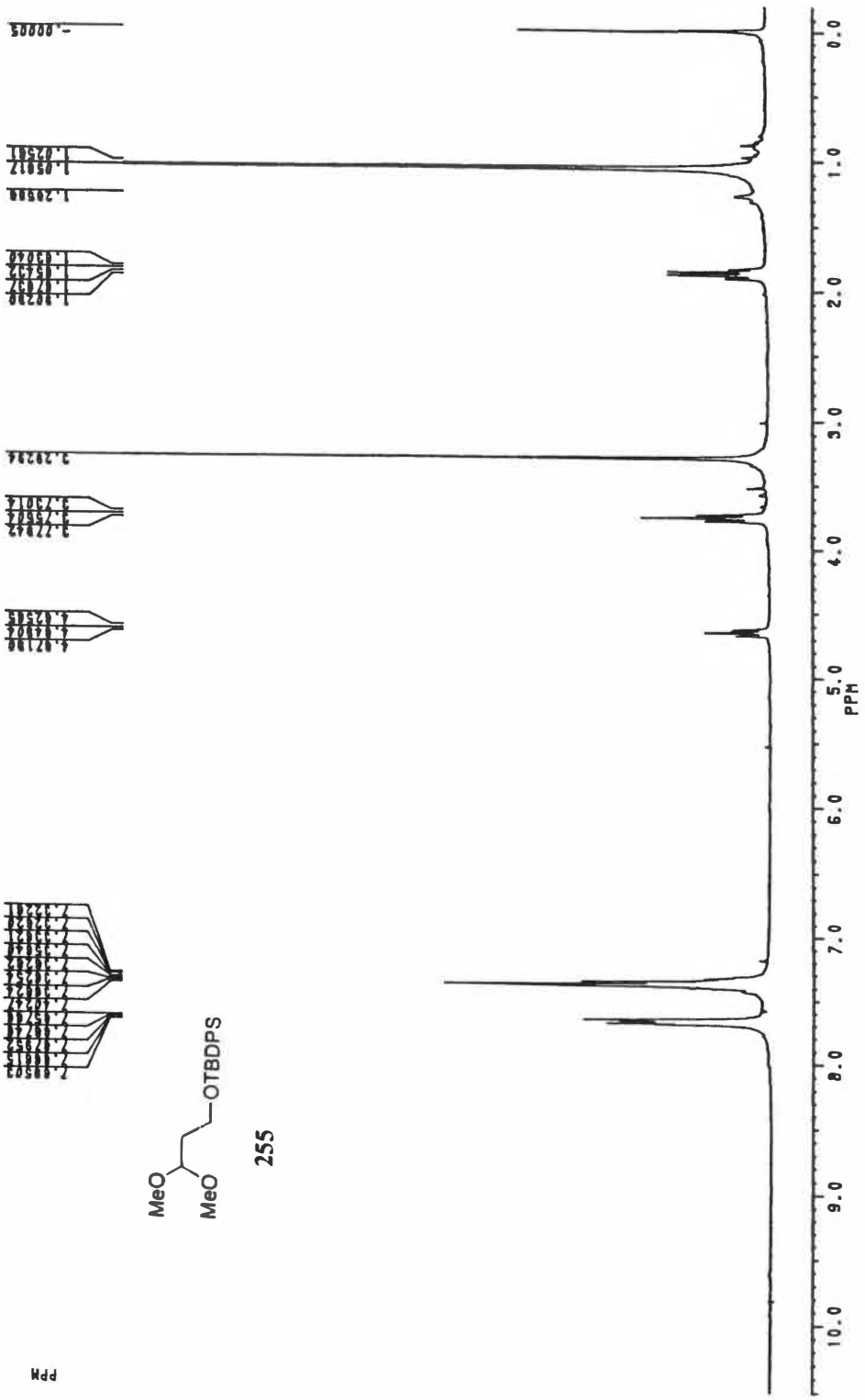

OTBDPS
252
PPM

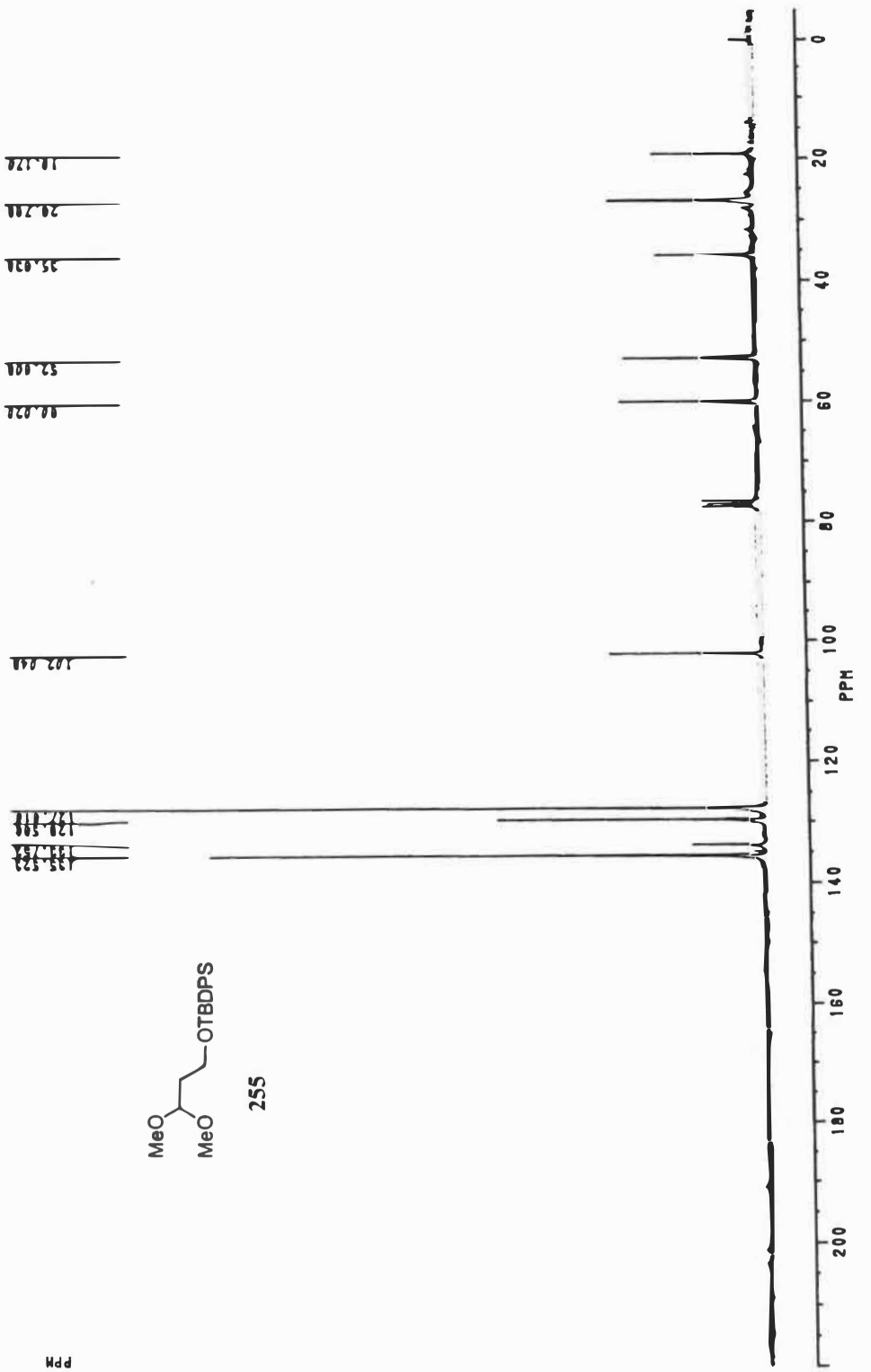

OTBDPS
OH
O
253
PPM
PPM

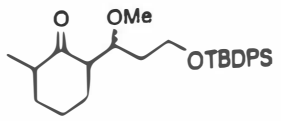

O
OH
OTBDPS
253
200
180
160
140
120
100
80
60
40
20
0
PPM


OTBDPS
BnO
BnO
254
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

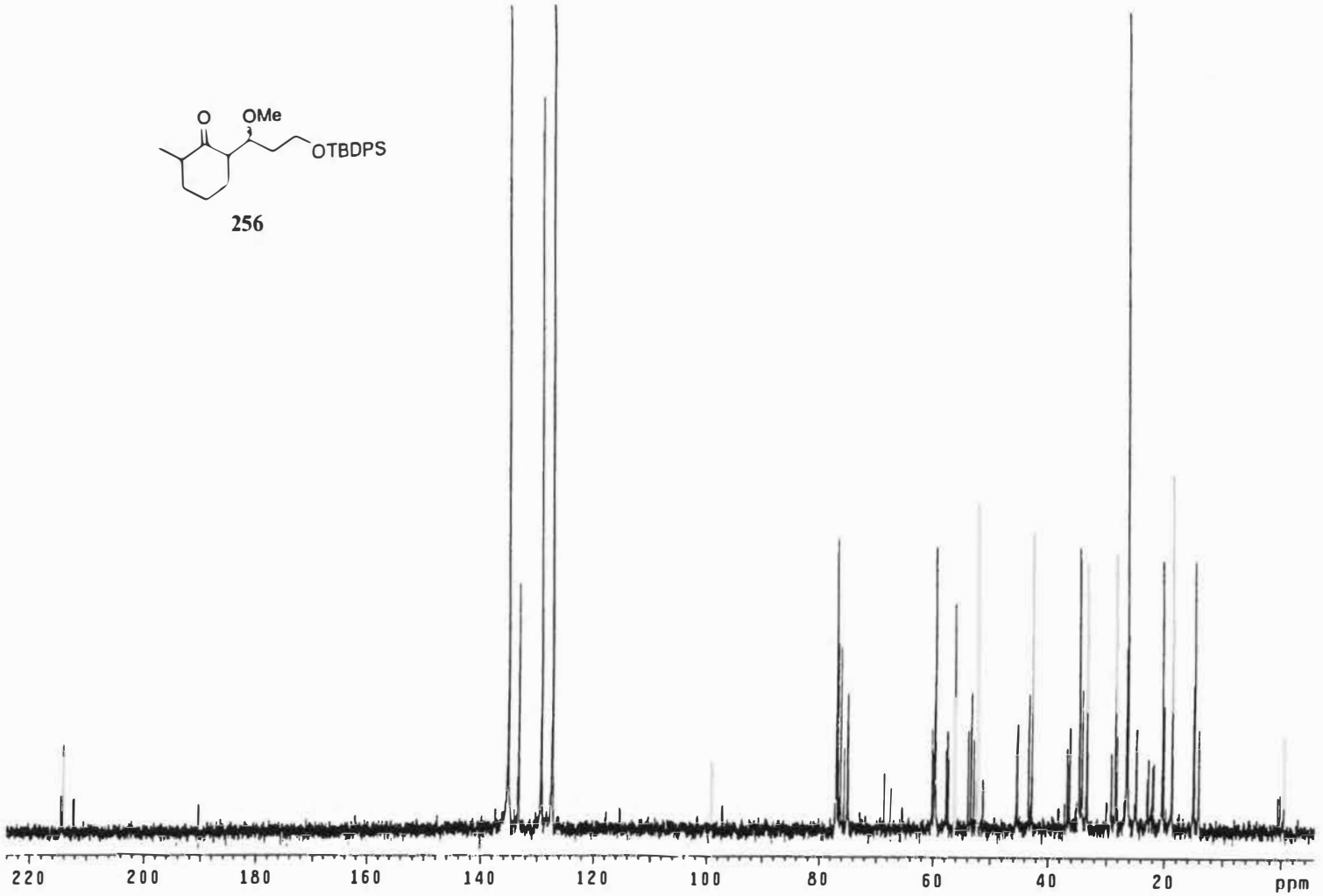

OTBDPS
BnO
BnO
254
PPM


OTBDPS
MeO
MeO
255
PPM

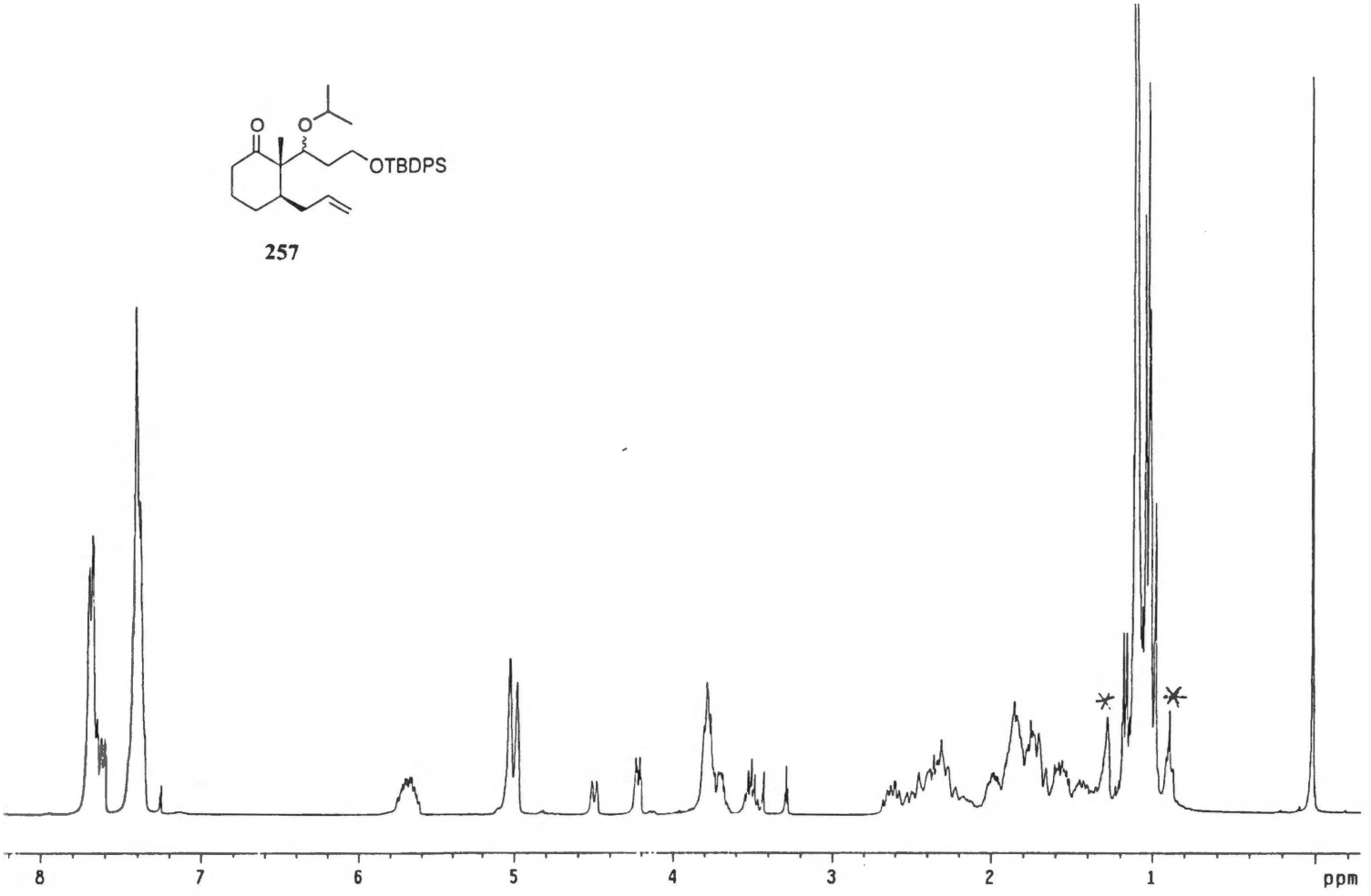

OTBDPS
MeO
MeO
255
PPM



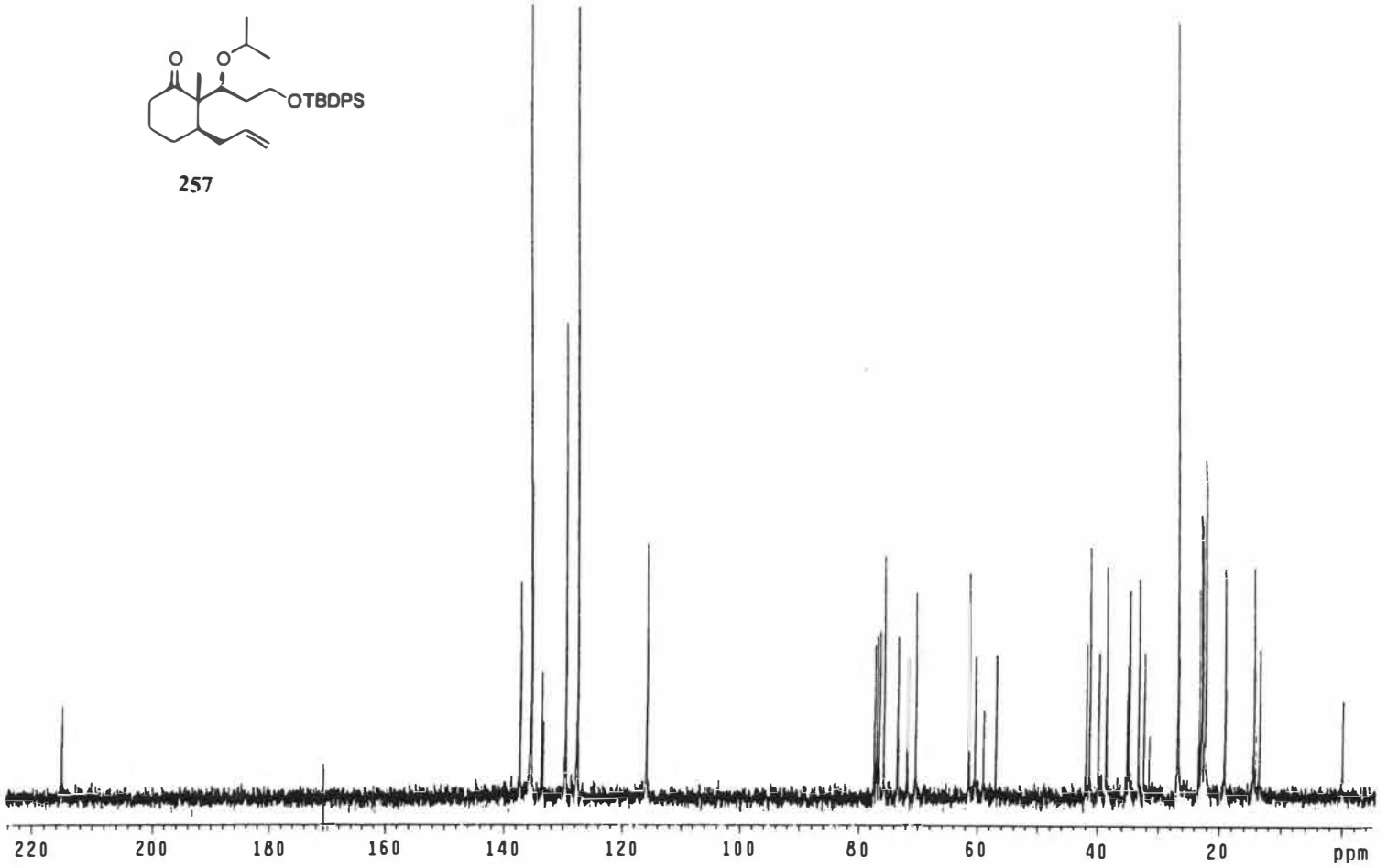
256



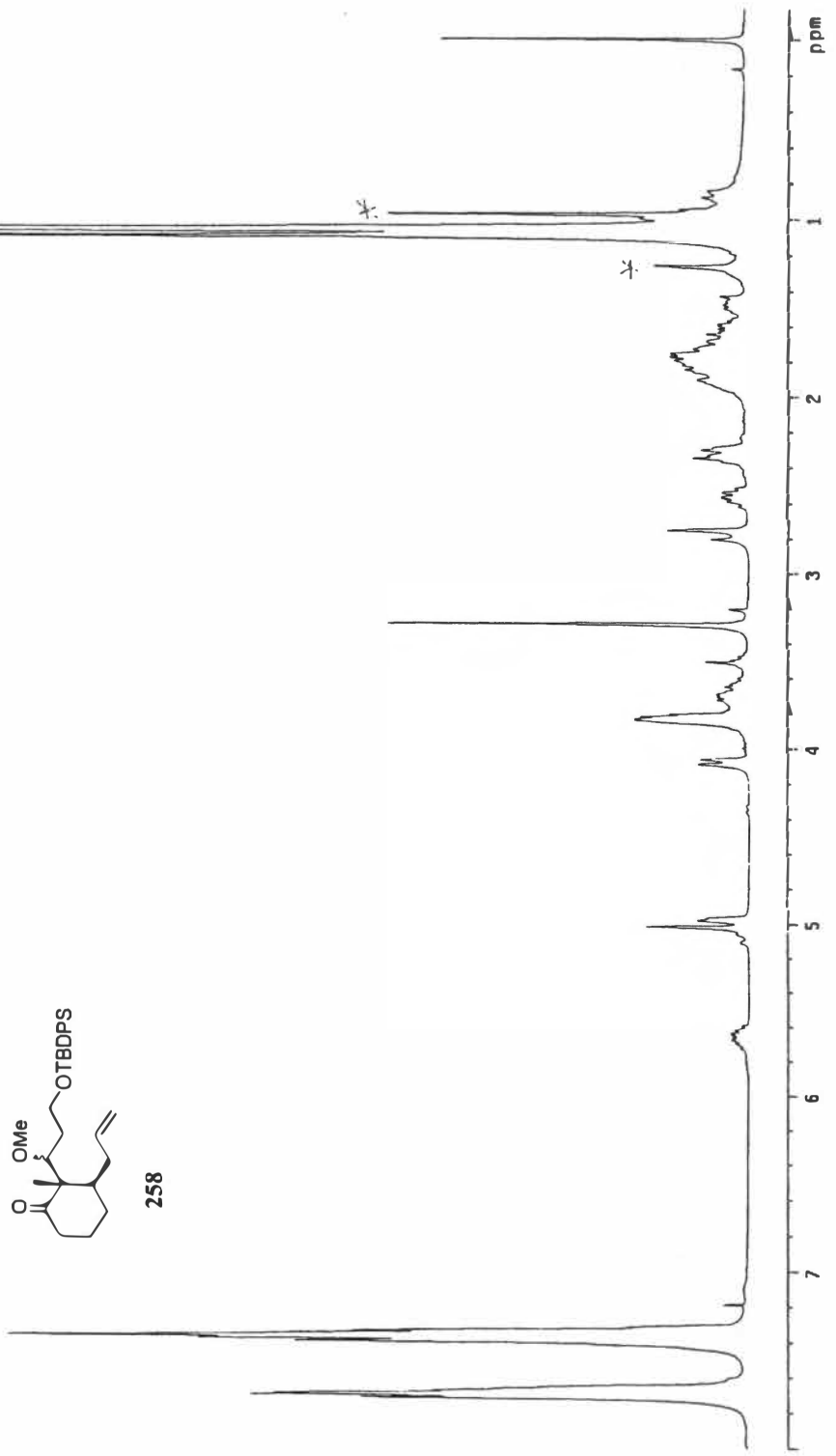
256

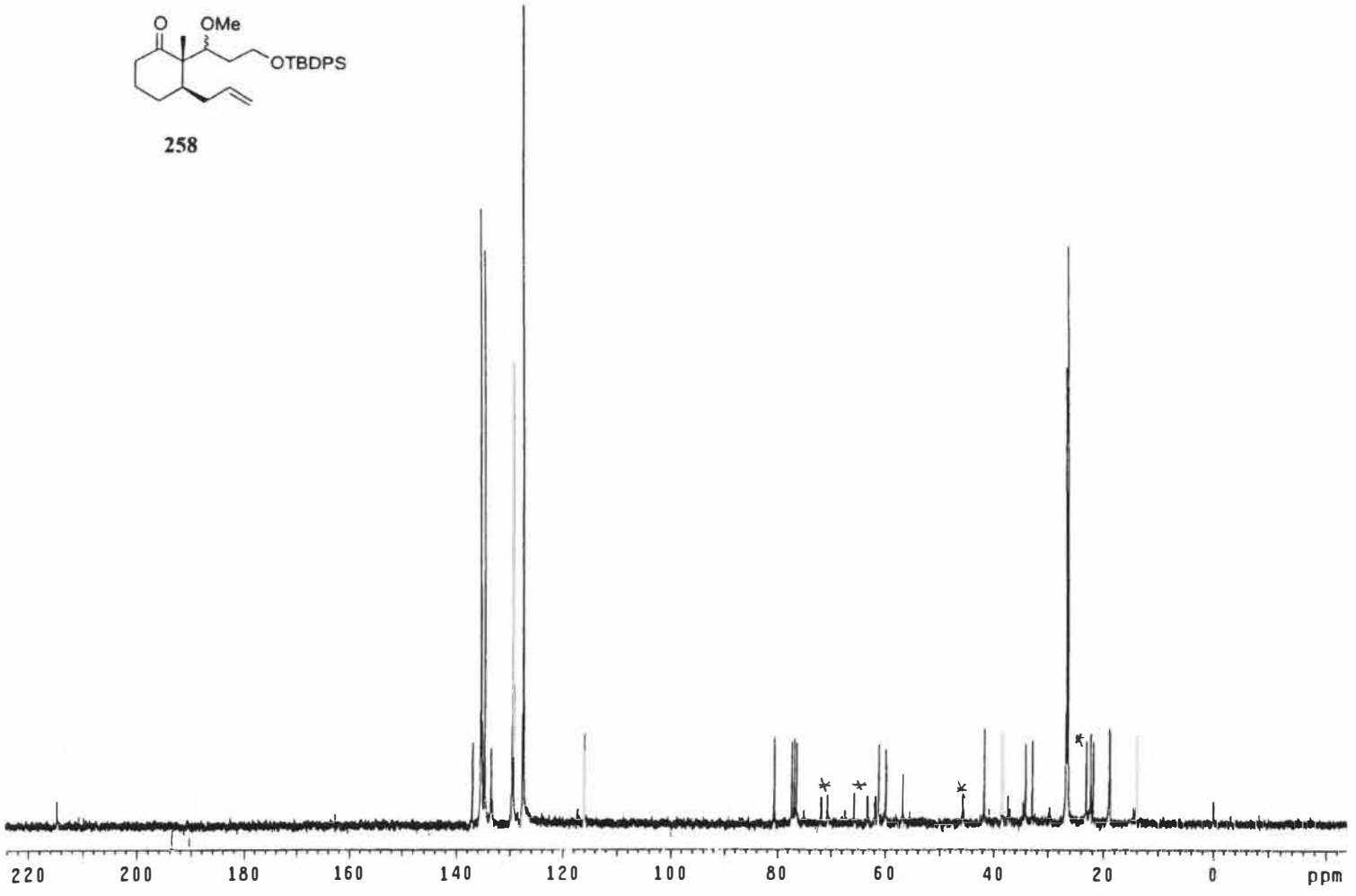


257

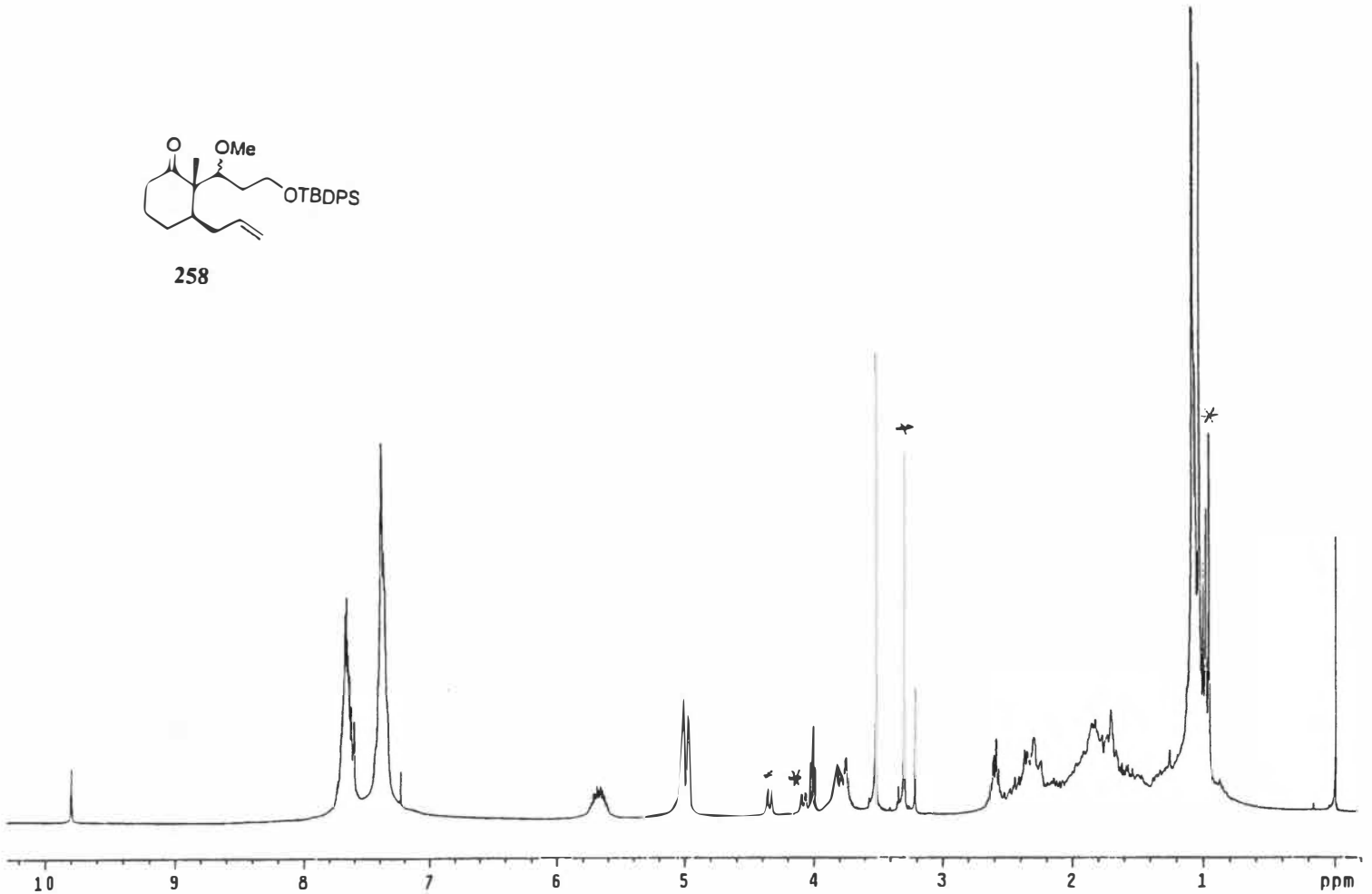


257

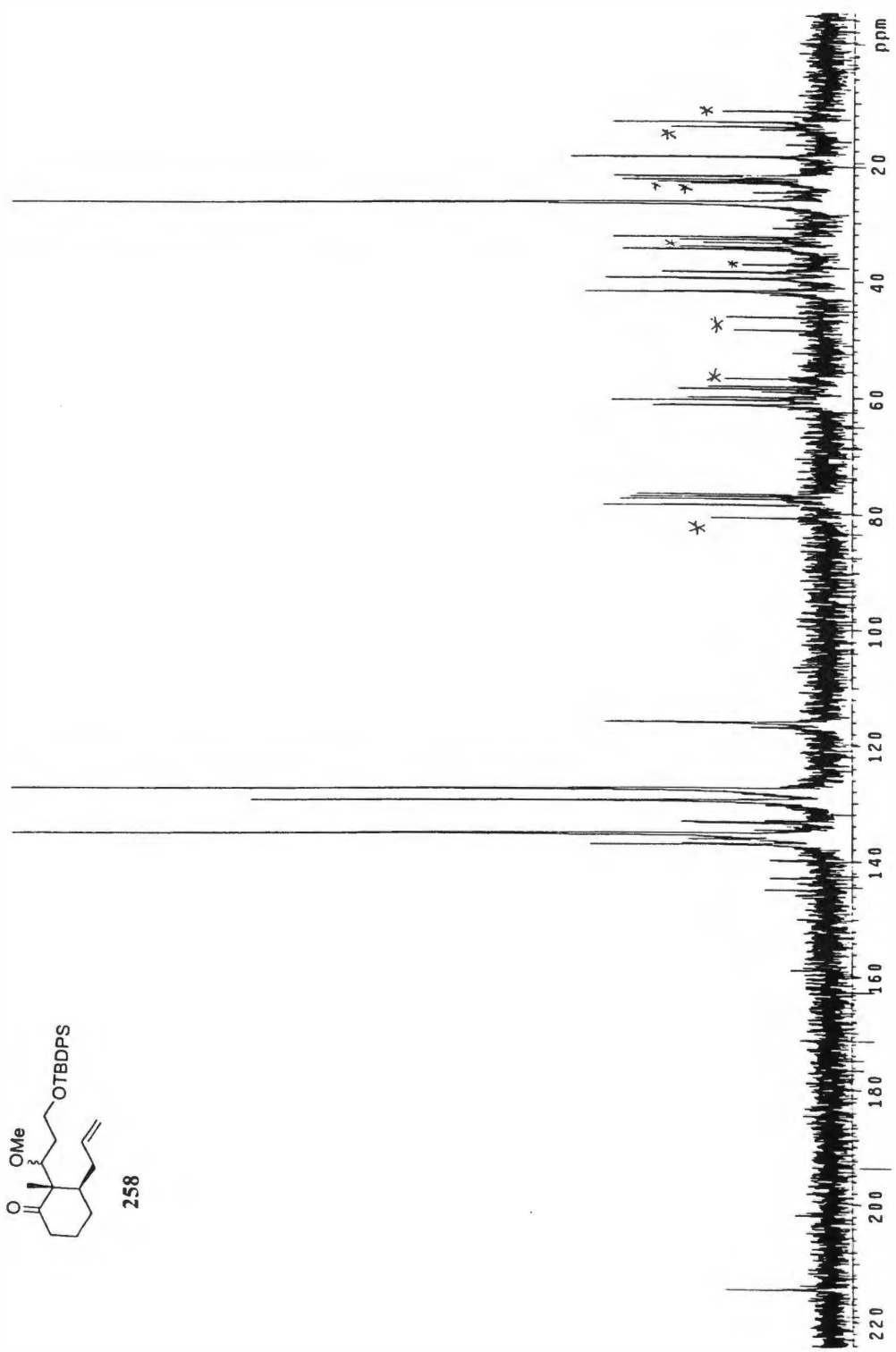

OMe
OTBDPS
O
258
ppm
1
2
3
4
5
6
7



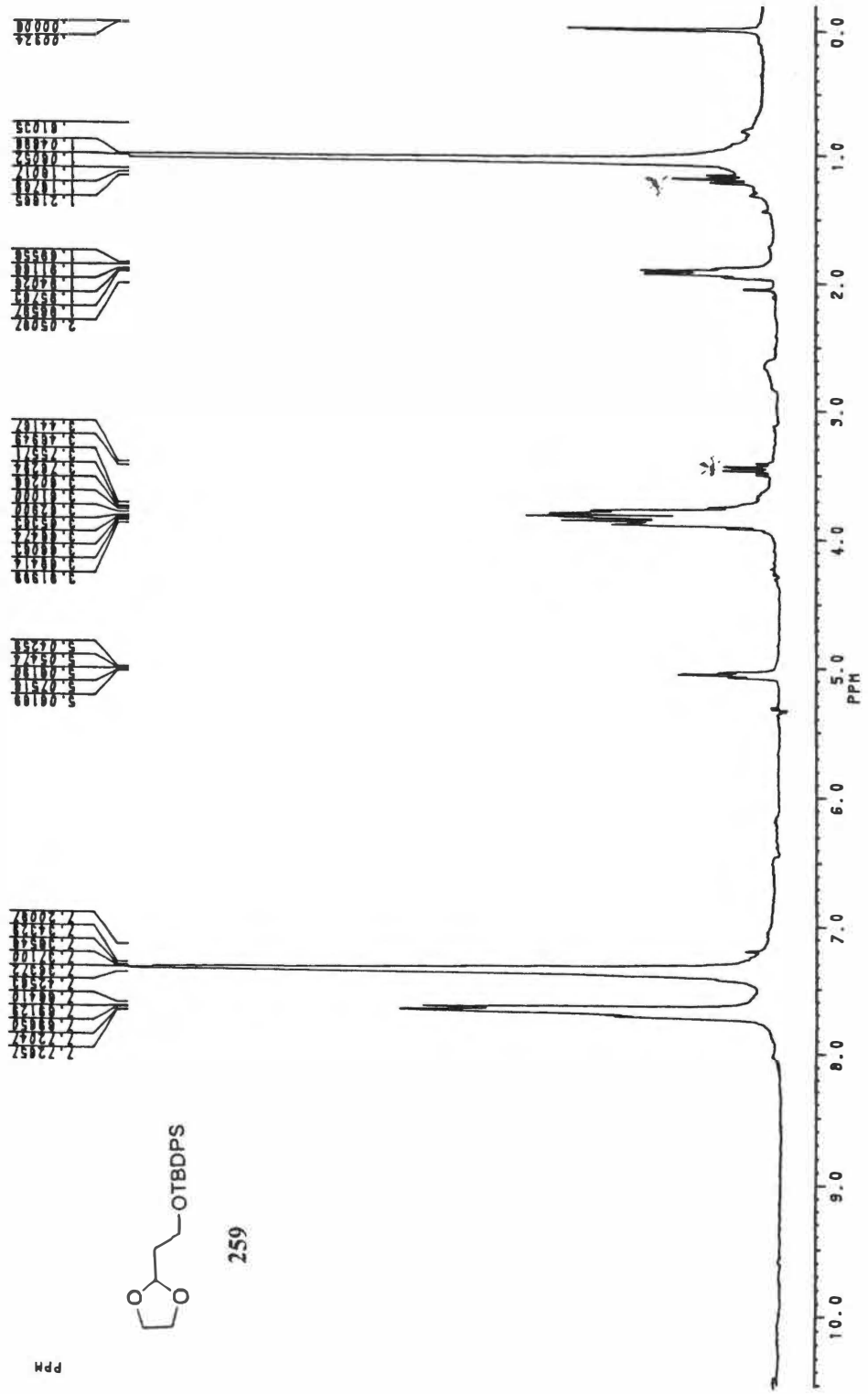
258

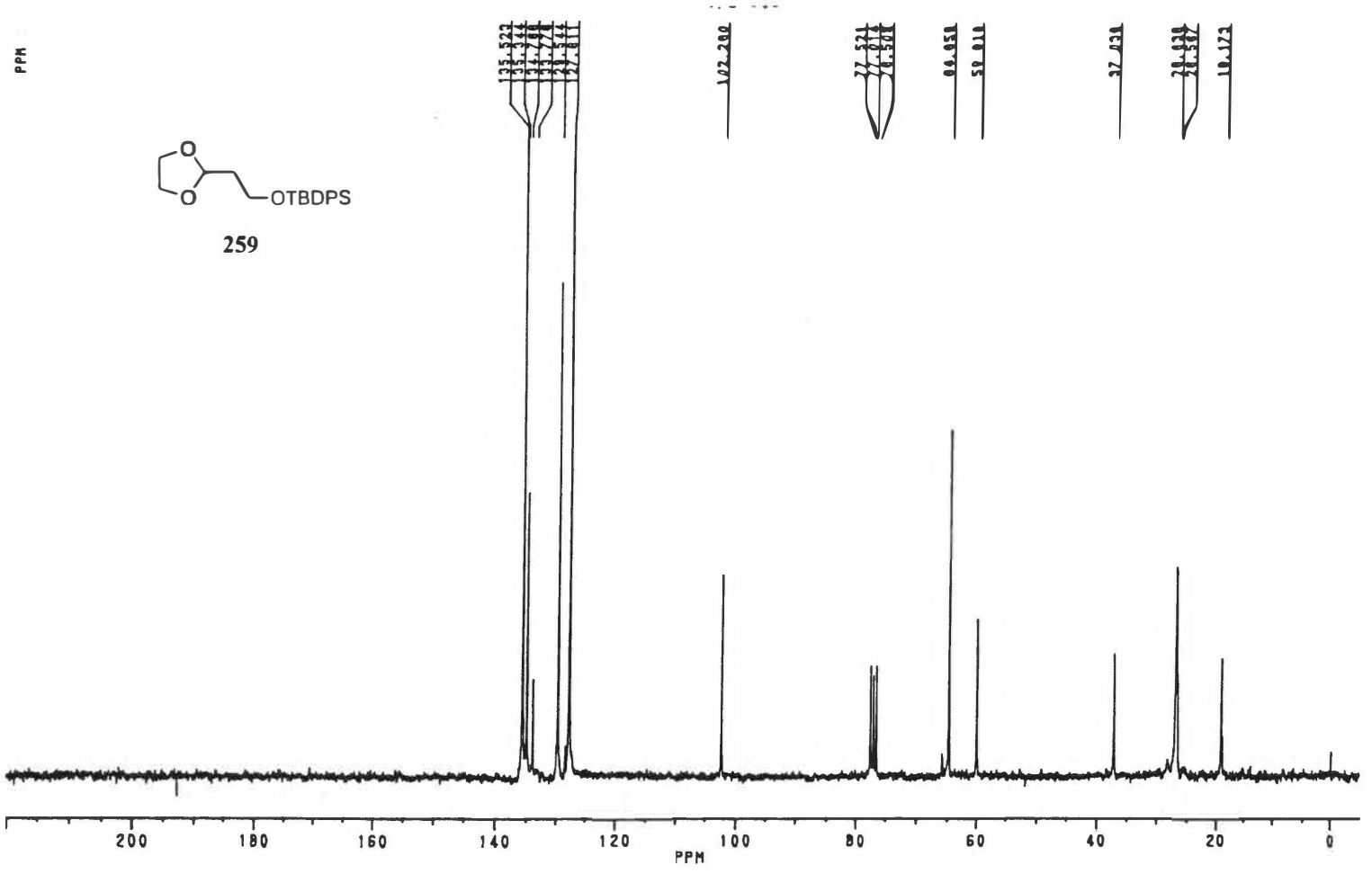


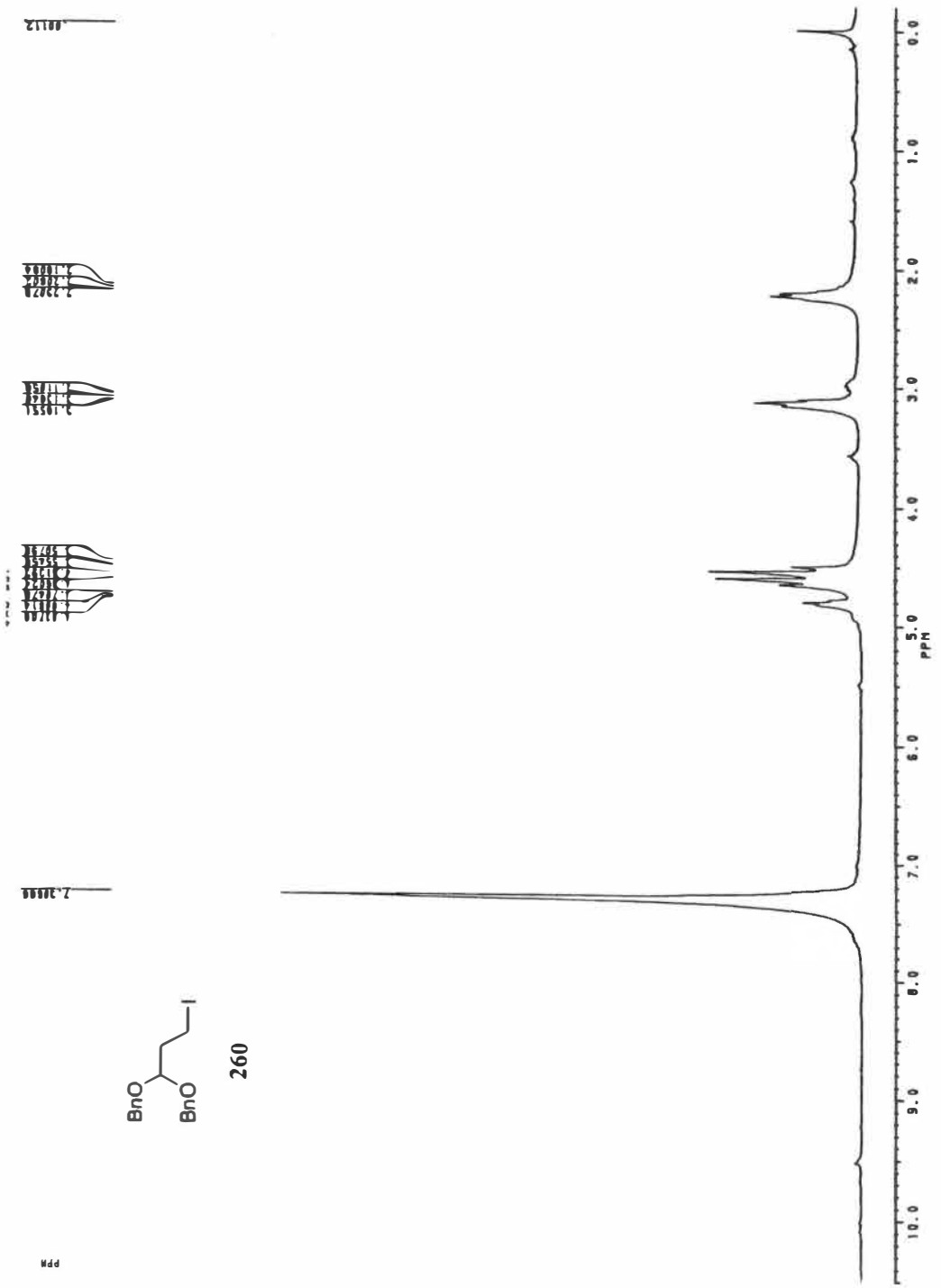
258

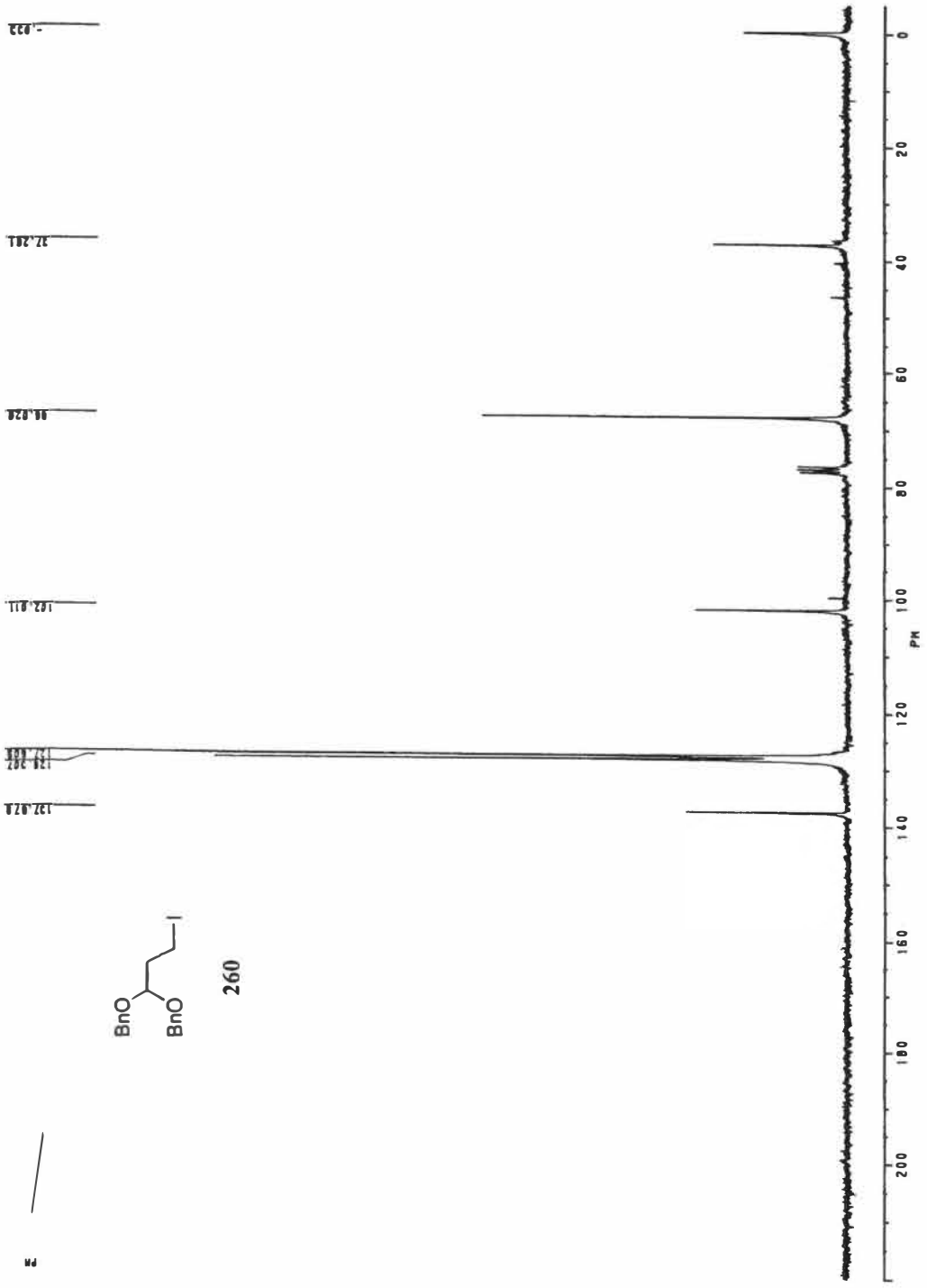


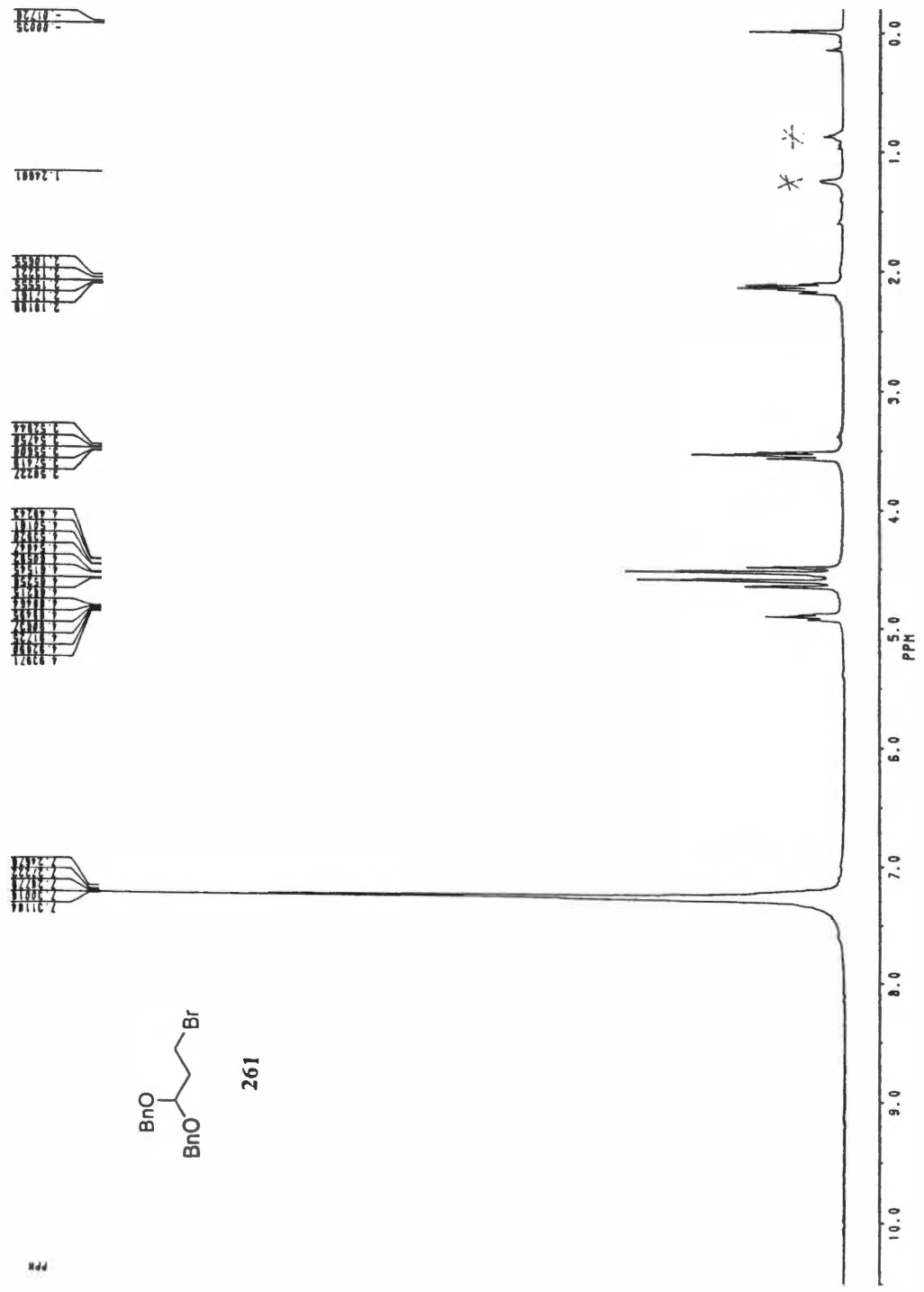
258

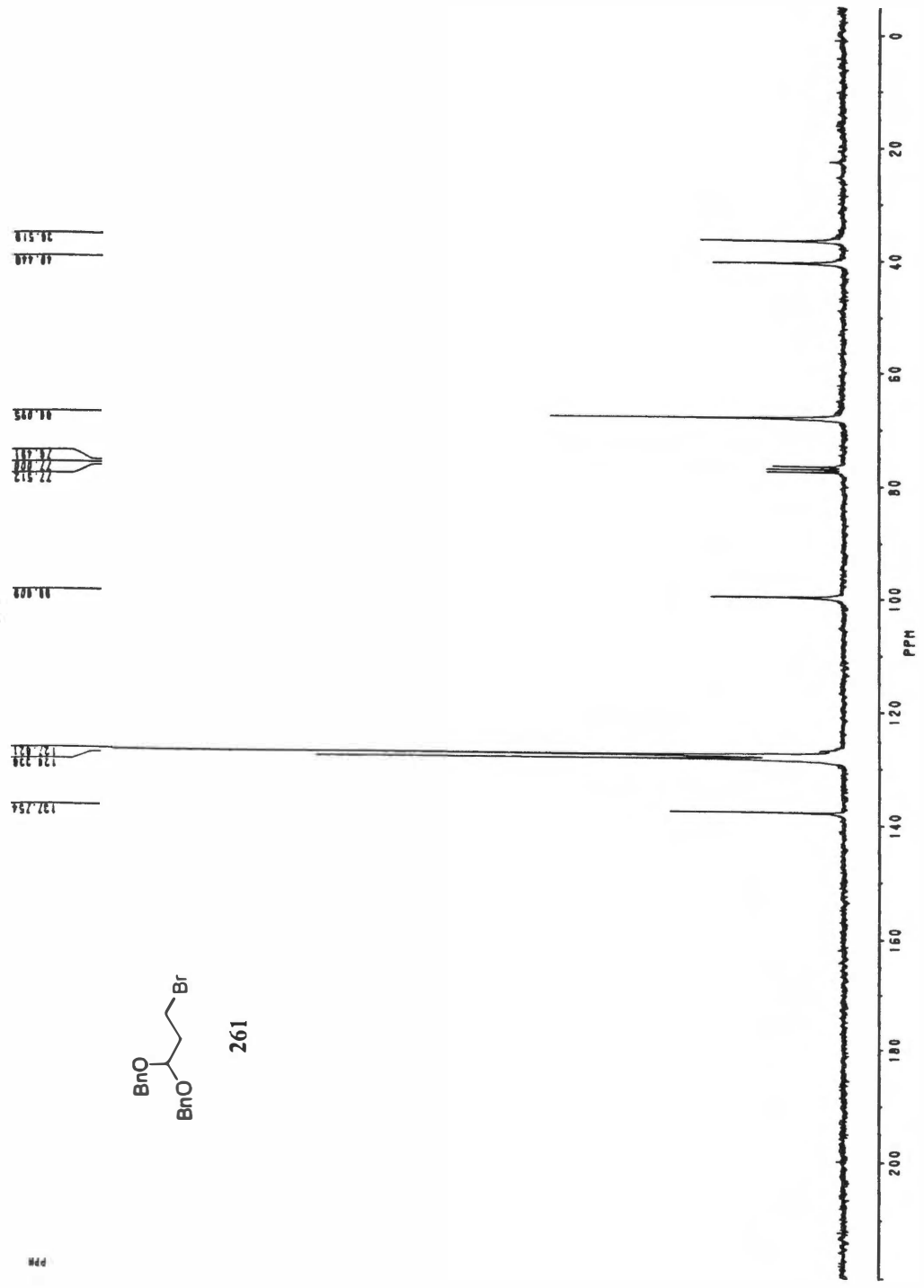

OTBDPS
259
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

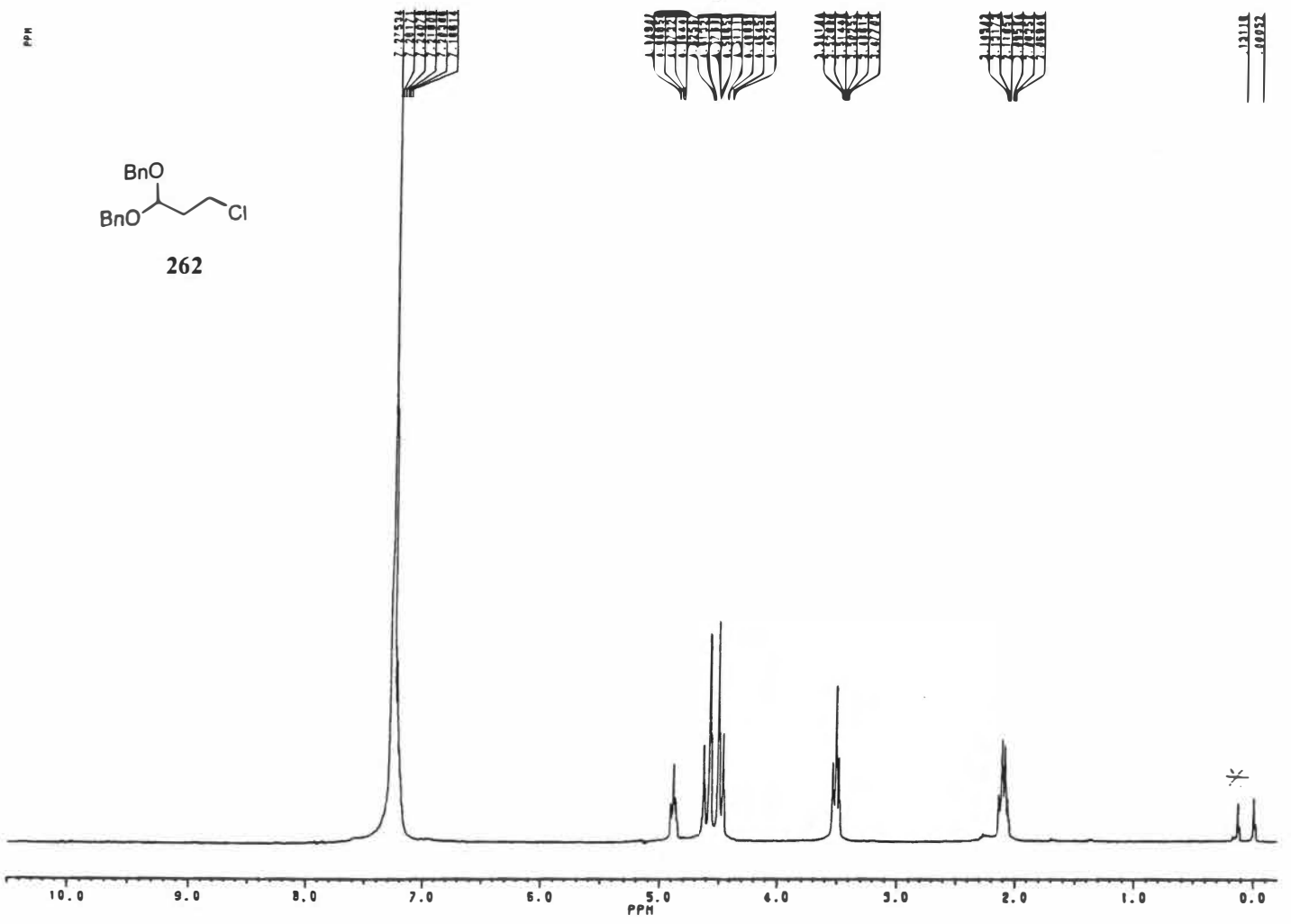

PPM
OTBDPS
259
200
180
160
140
120
100
80
60
40
20
0
PPM

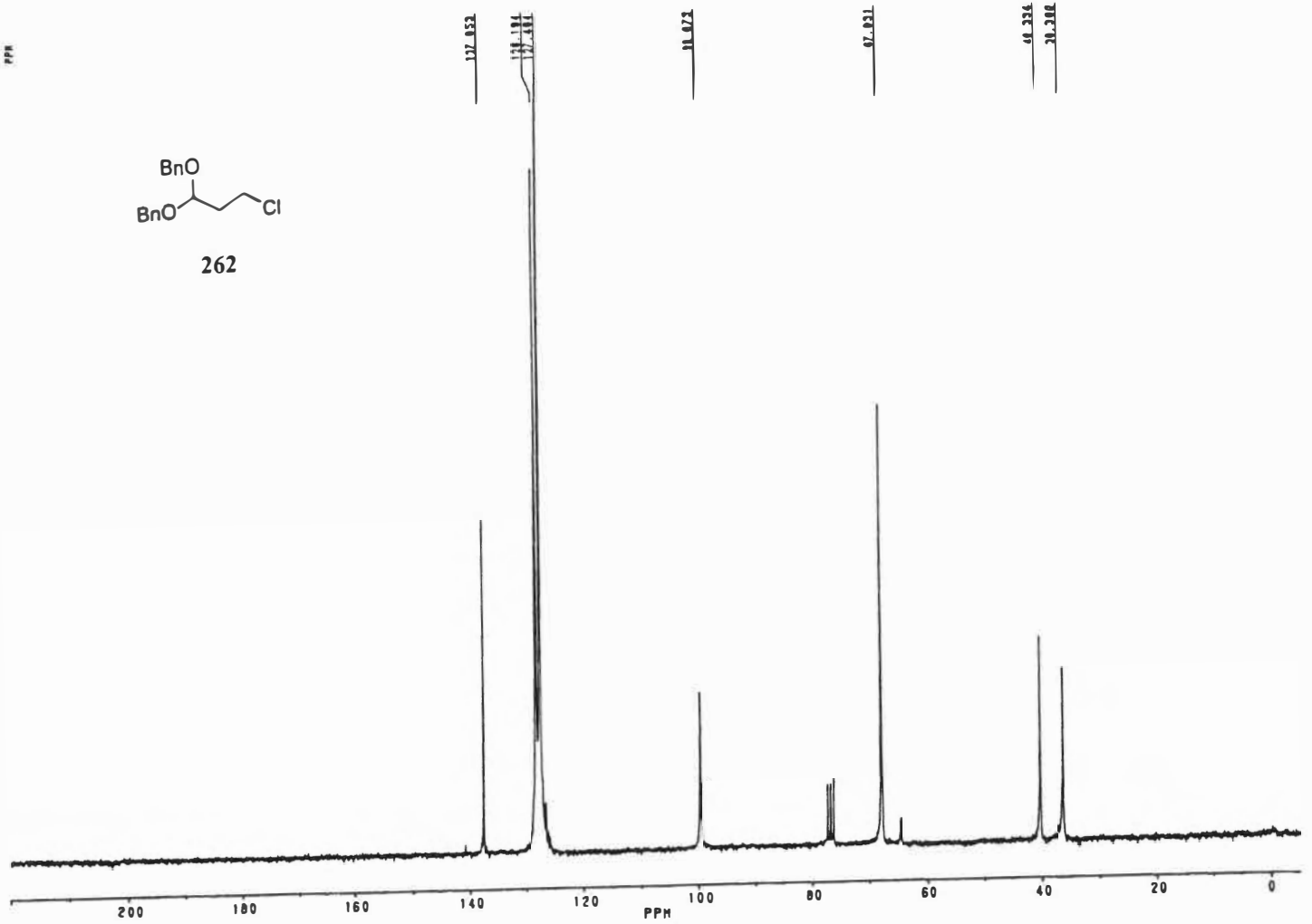

BnO
BnO
I
260
PPM

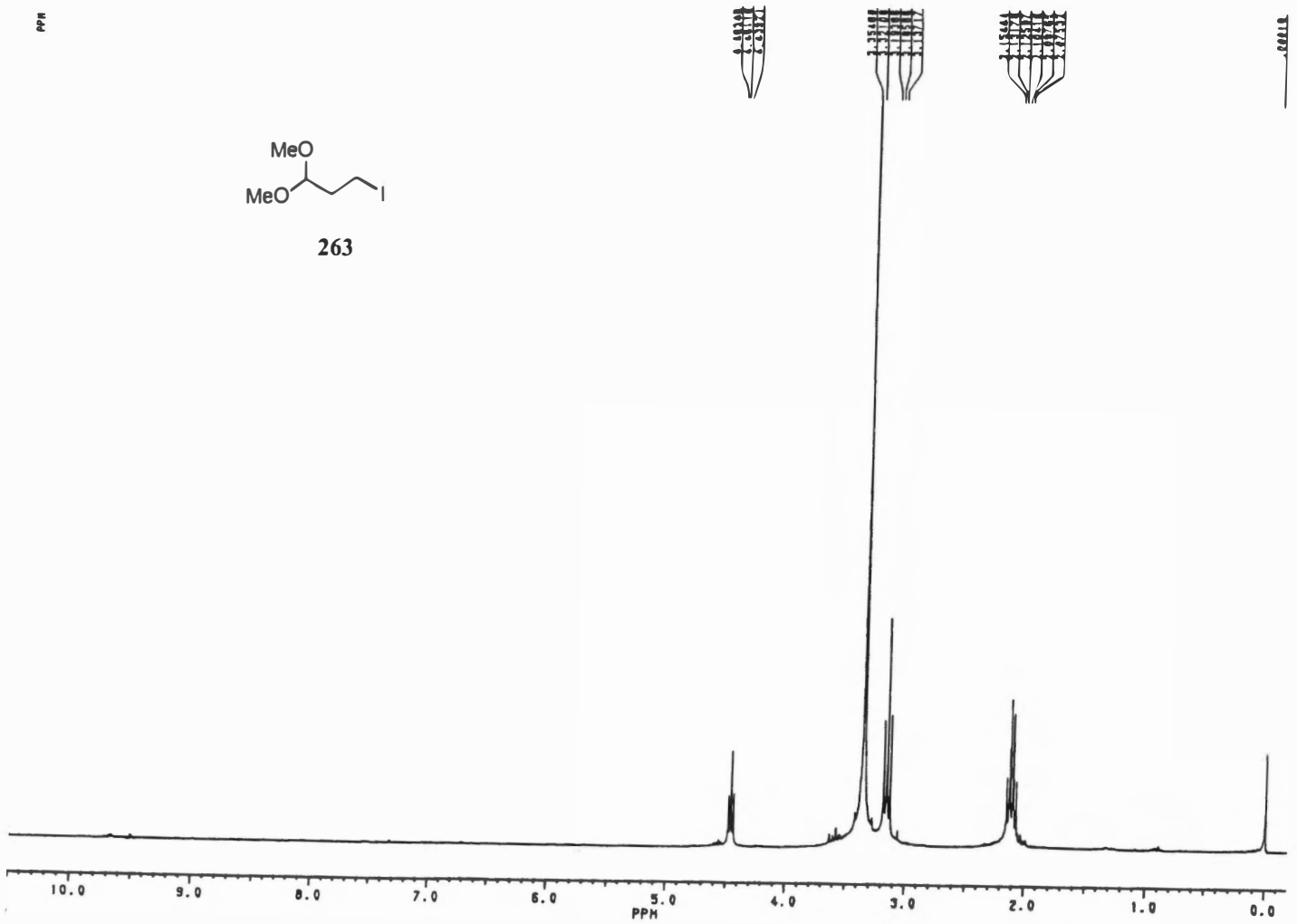

BnO
BnO
I
260
PPM


BnO
BnO
Br
261
PPM

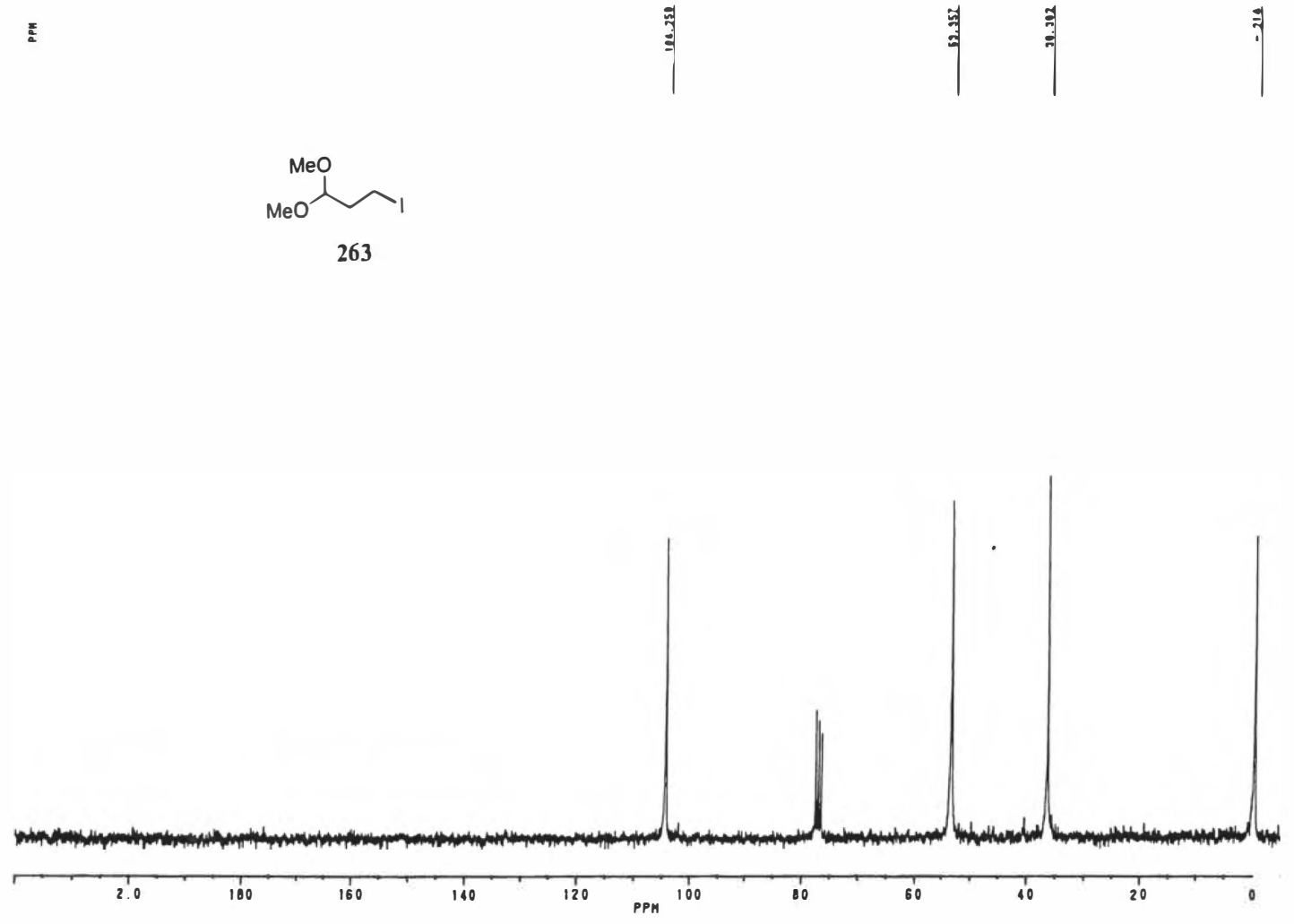

BnO
BnO
Br
261
PPM

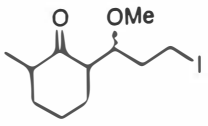

BnO
BnO
Cl
262
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM


BnO
BnO
Cl
262
200
180
160
140
120
100
80
60
40
20
0
PPM



263

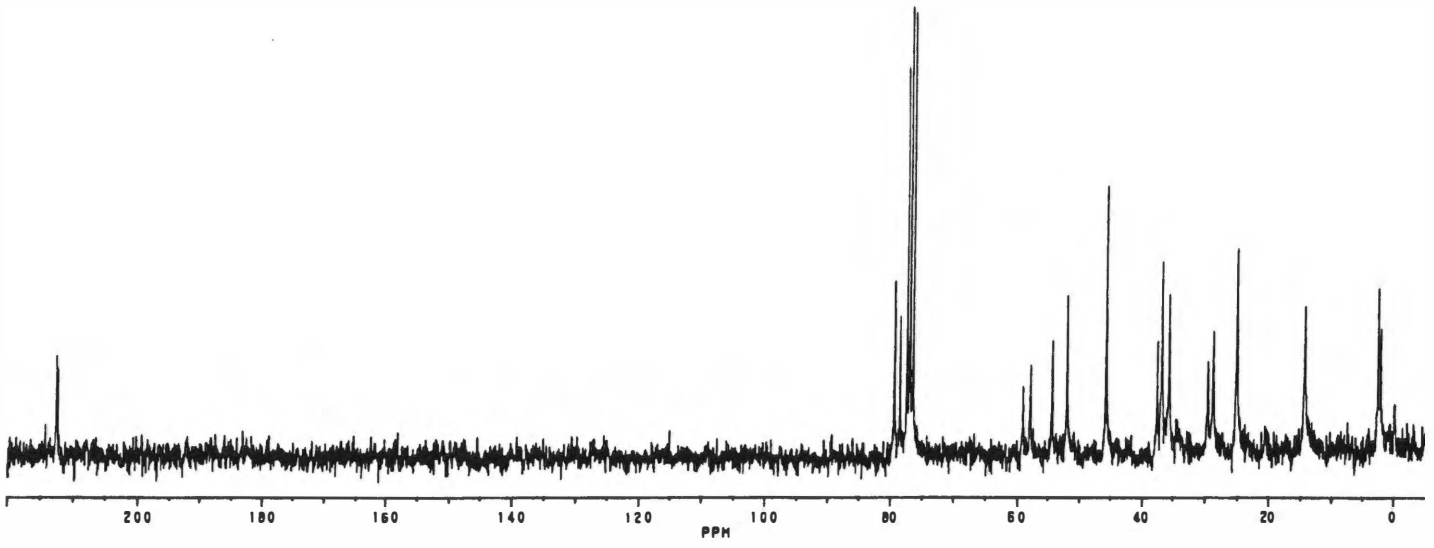

PPM
MeO
MeO
I
263
2.0
180
160
140
120
PPM
100
80
60
40
20
0

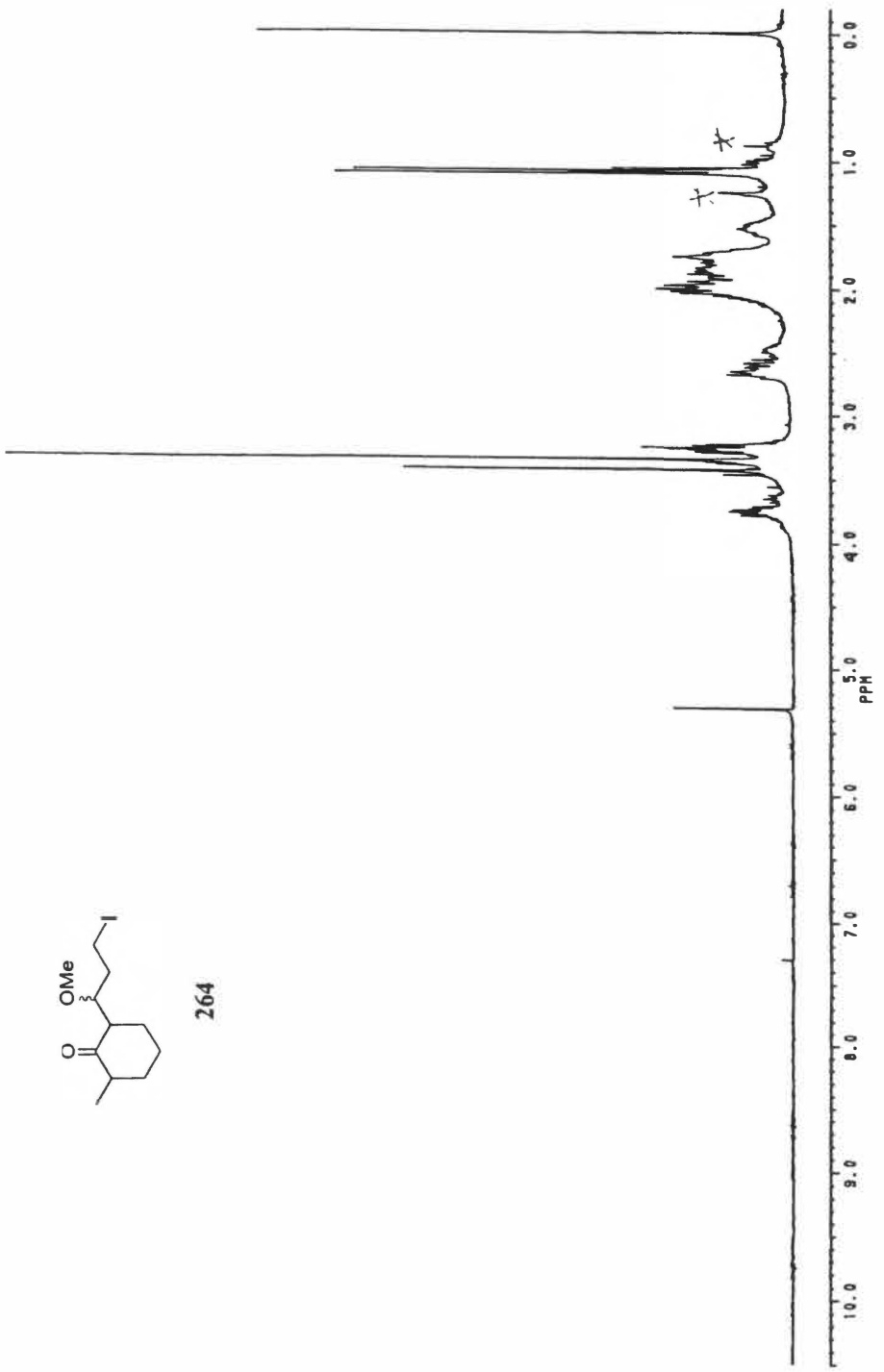


264



264

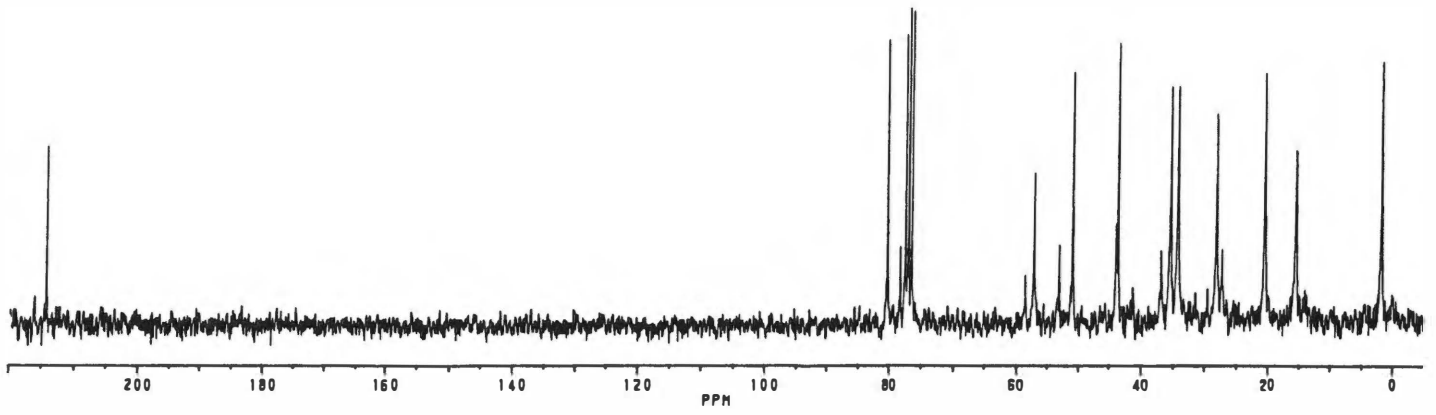


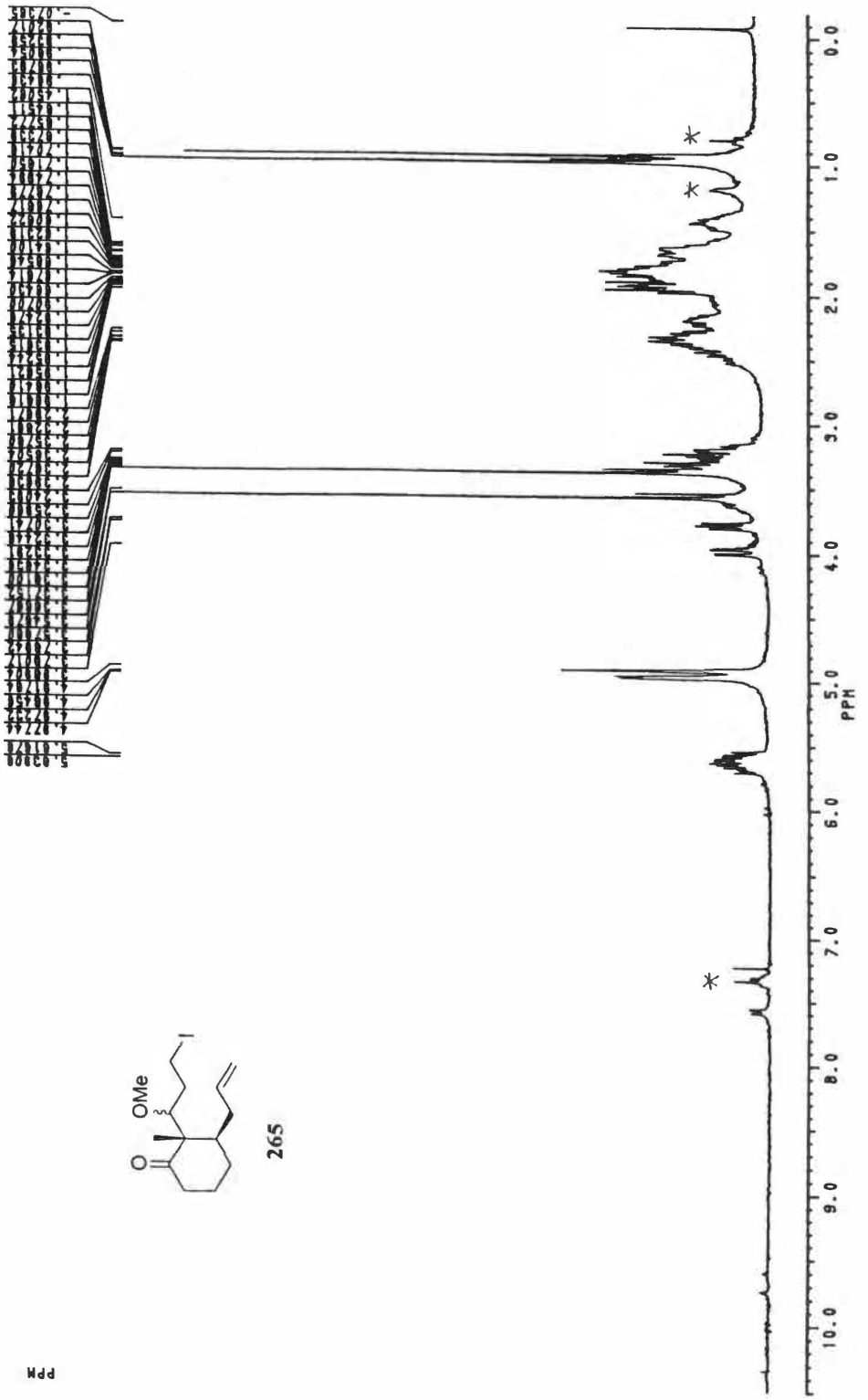


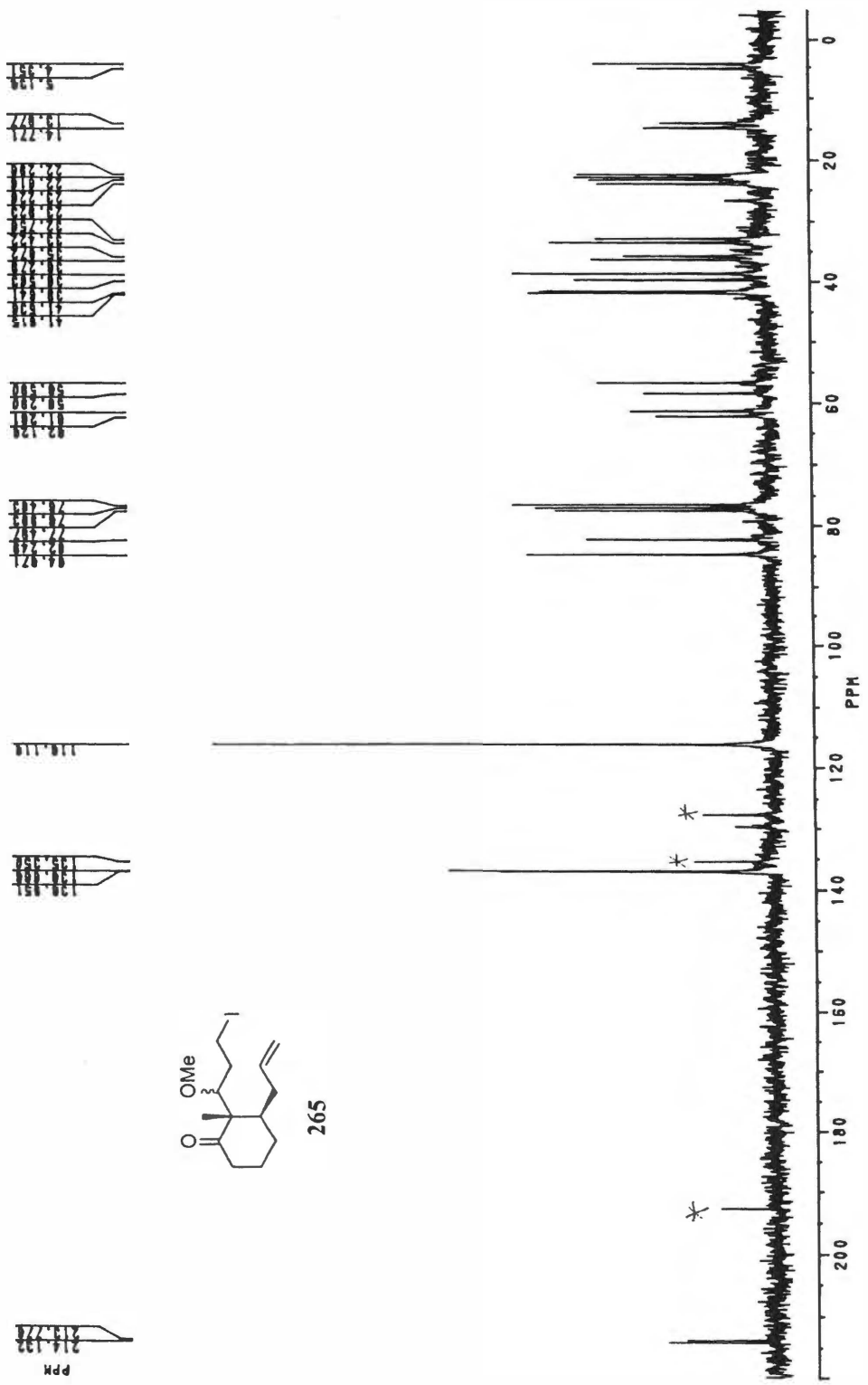
264



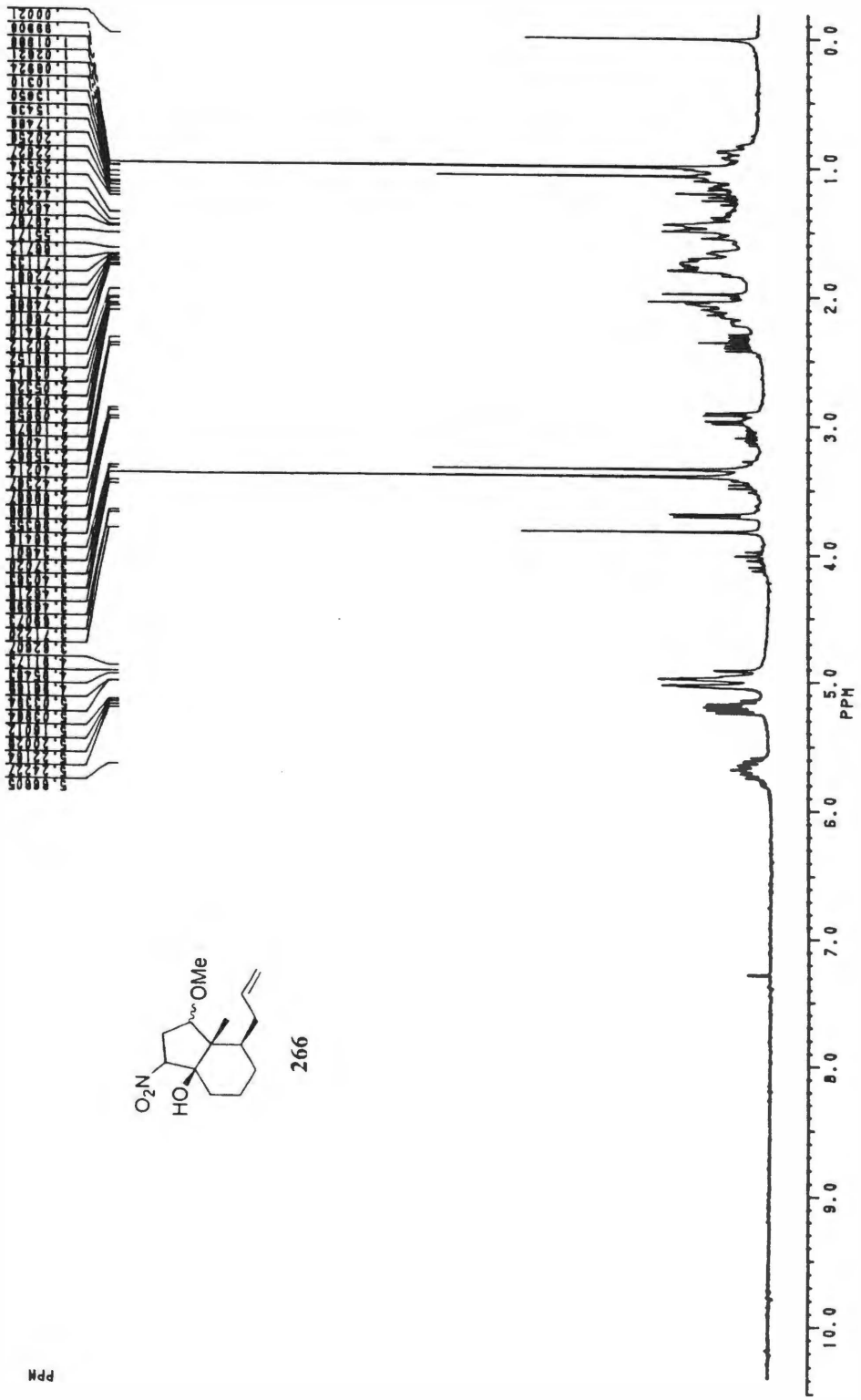
264

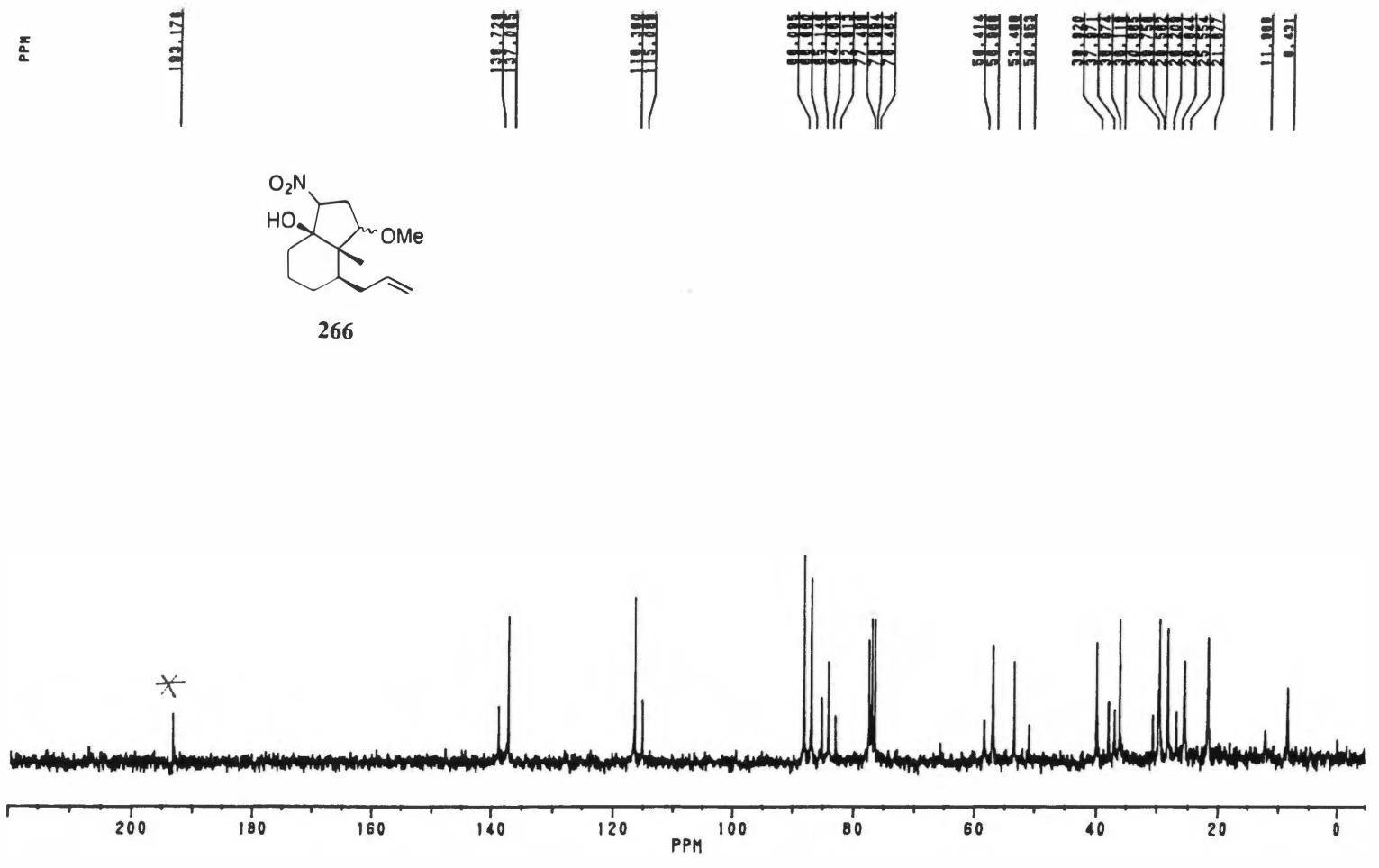



OMe
I
O
265
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

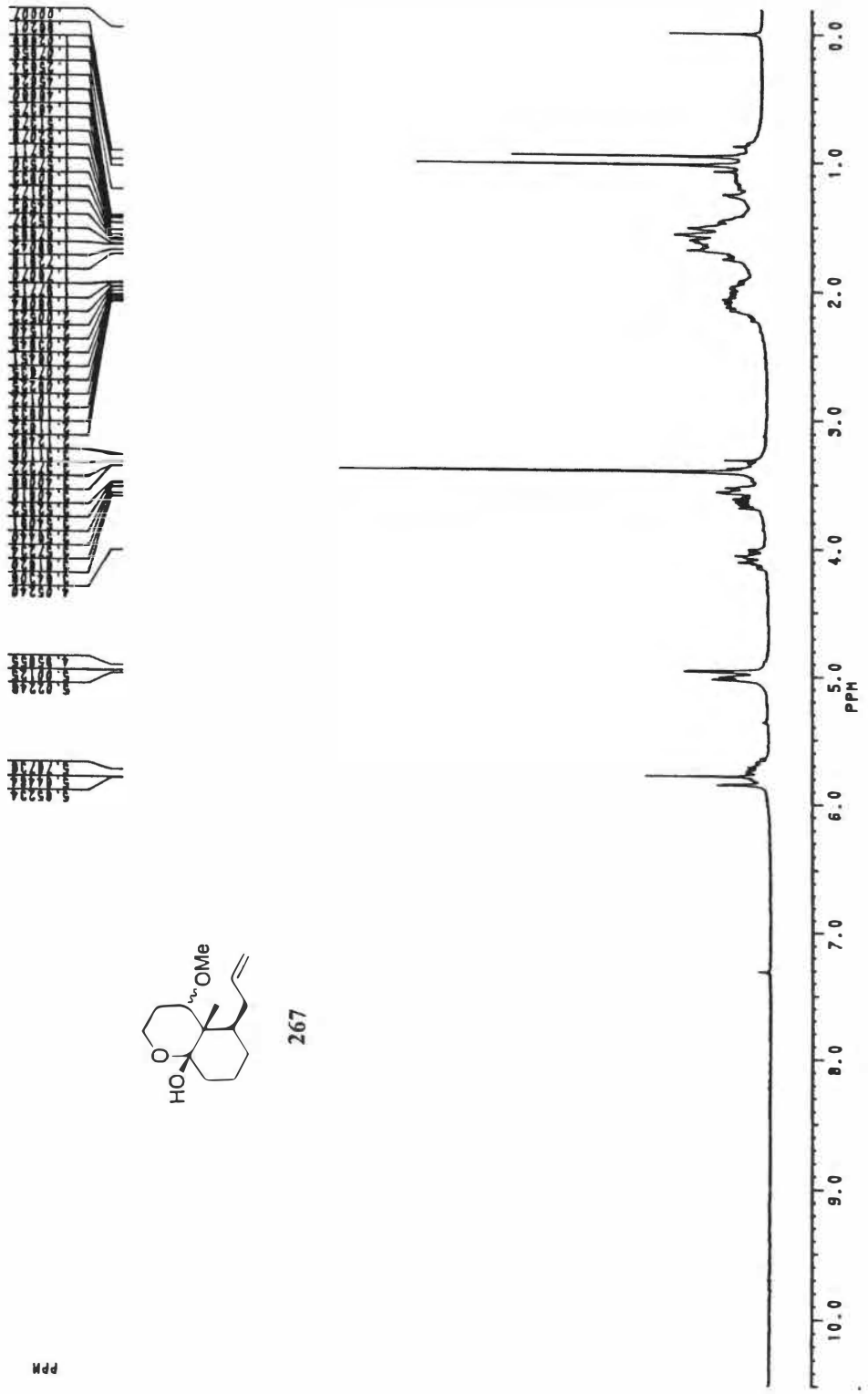


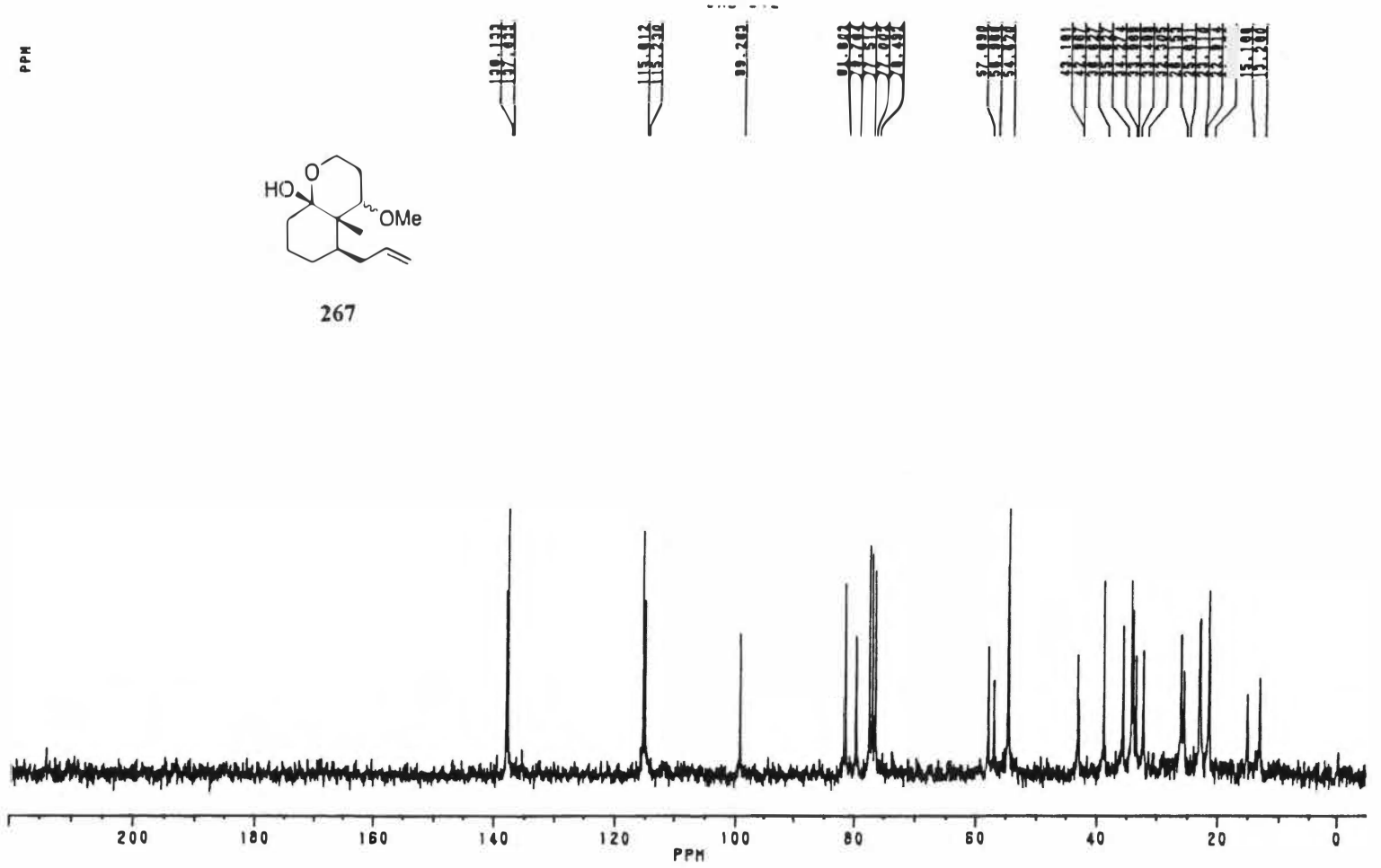
265


OMe
O_2N
HO
266
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

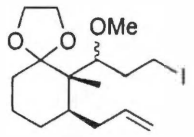

PPM
183.174
138.723
137.005
119.388
115.081
88.085
83.143
83.003
82.911
77.681
77.264
76.847
58.414
58.108
53.488
50.853
39.128
37.197
36.972
36.117
31.345
31.142
29.302
29.201
28.144
25.554
21.877
11.888
9.421
O2N
HO
OMe
200
180
160
140
120
100
80
60
40
20
0
PPM

266

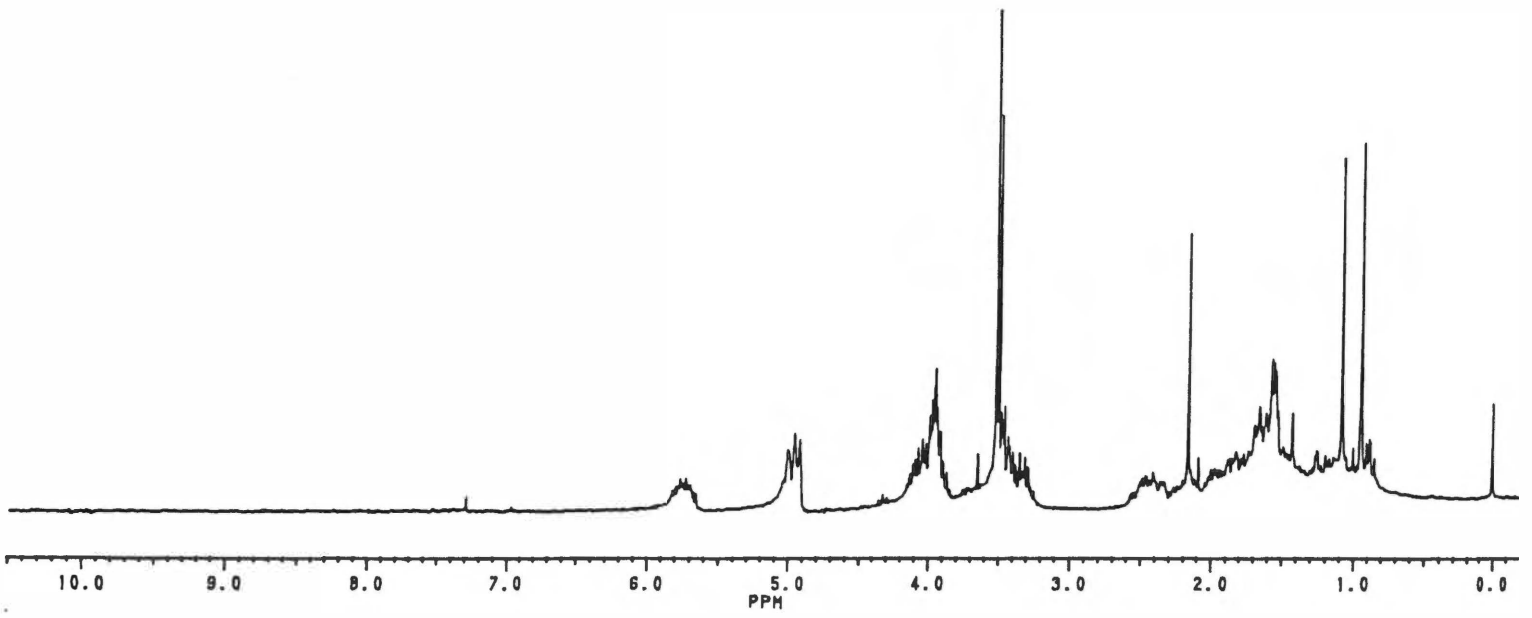

OMe
HO
O
267
PPM
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

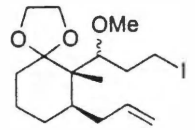


267

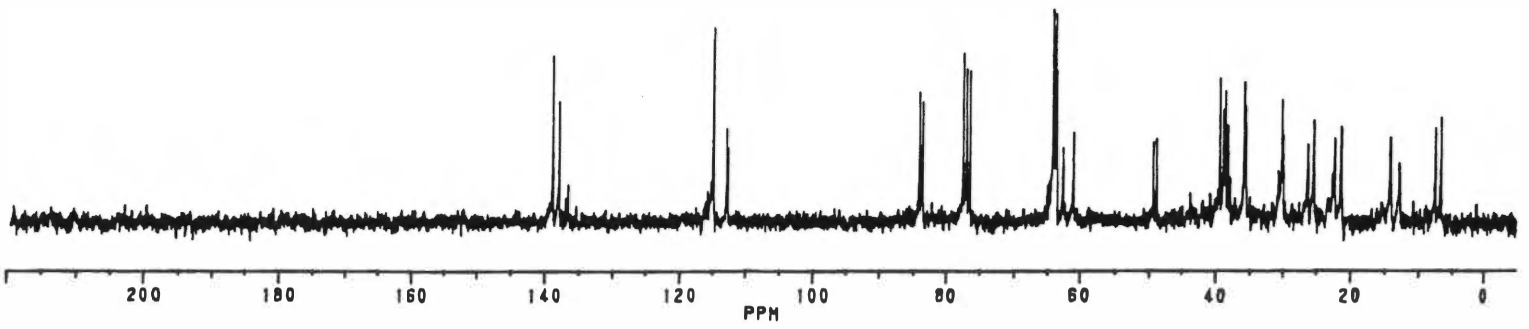


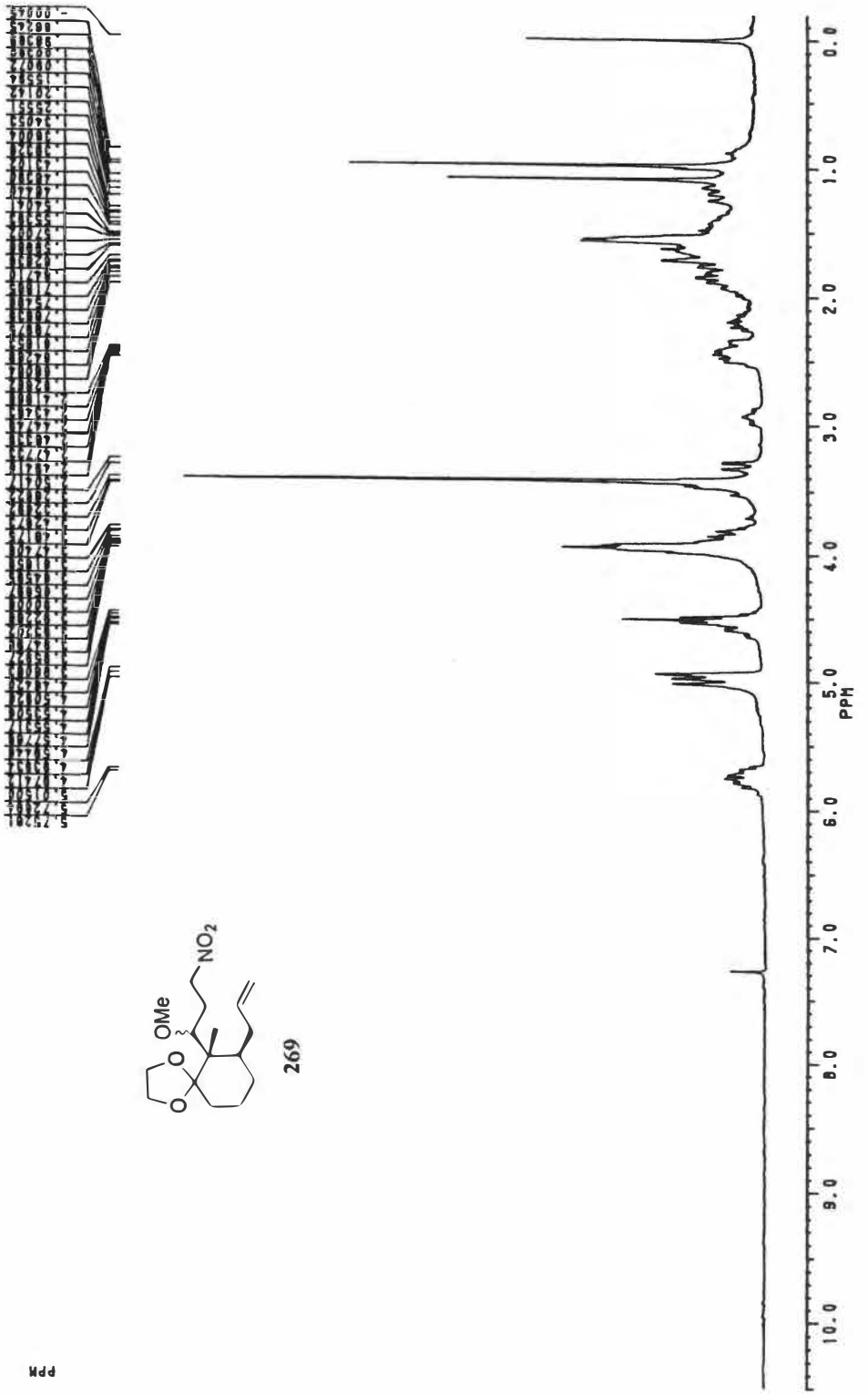
268

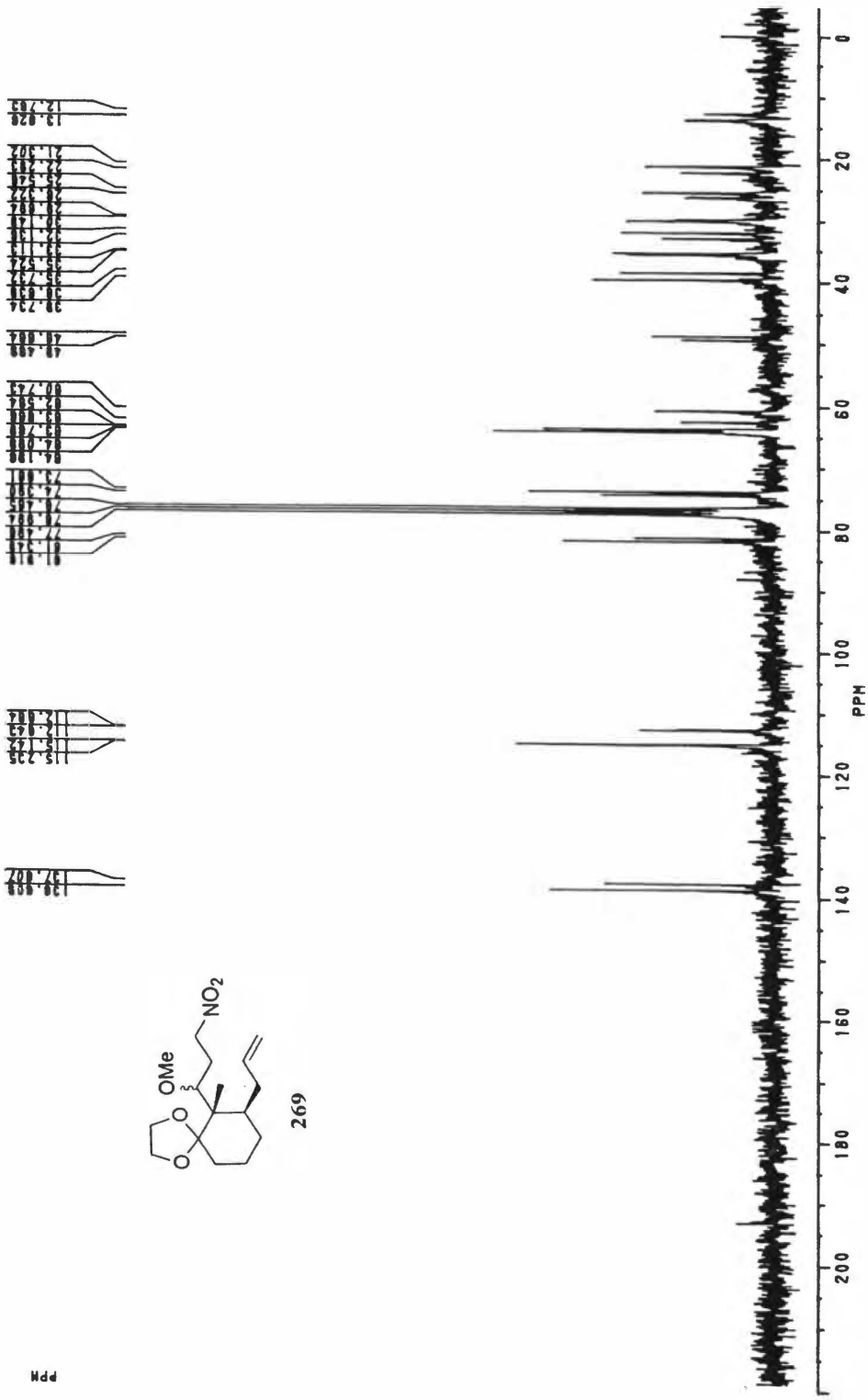


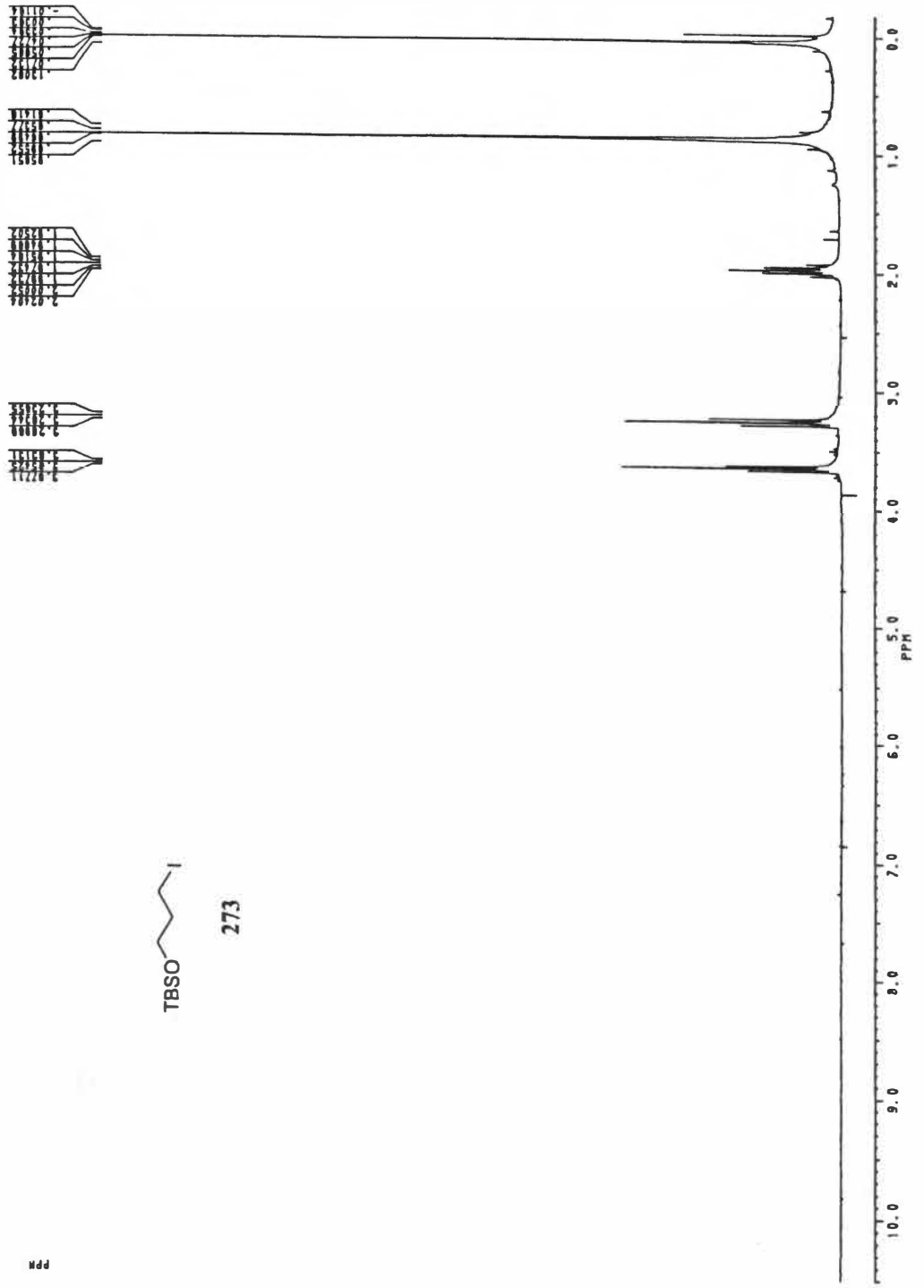


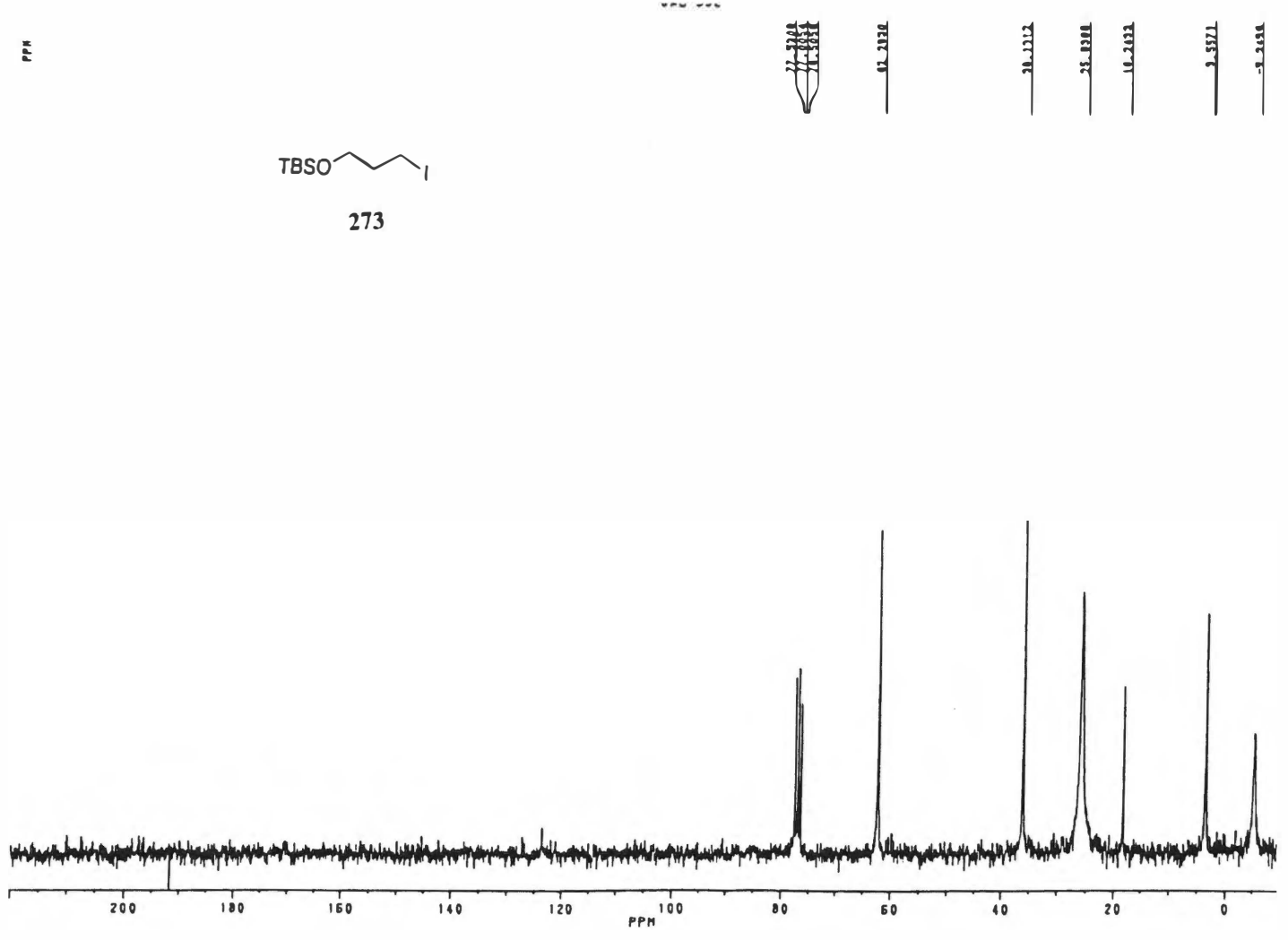
268

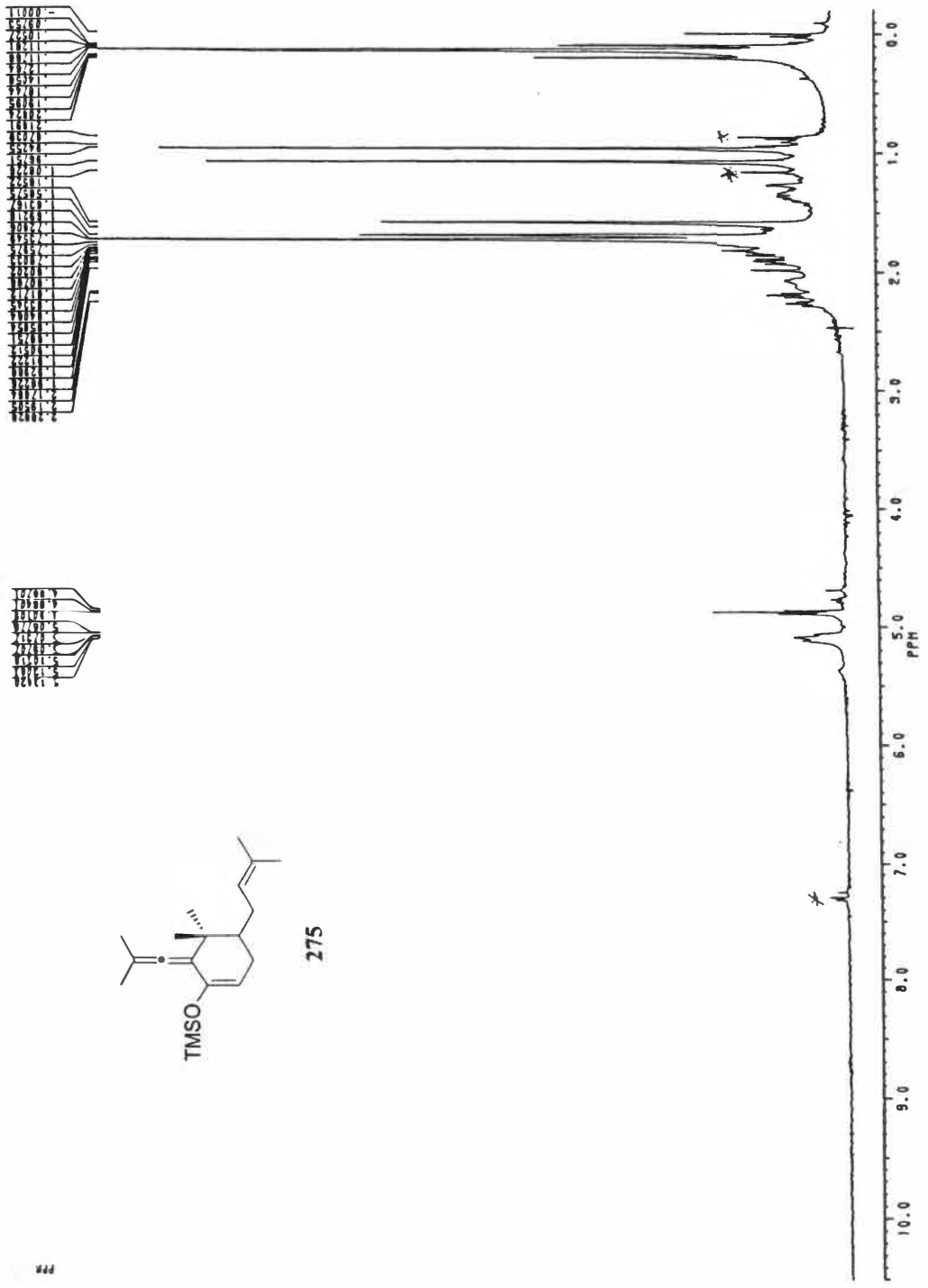


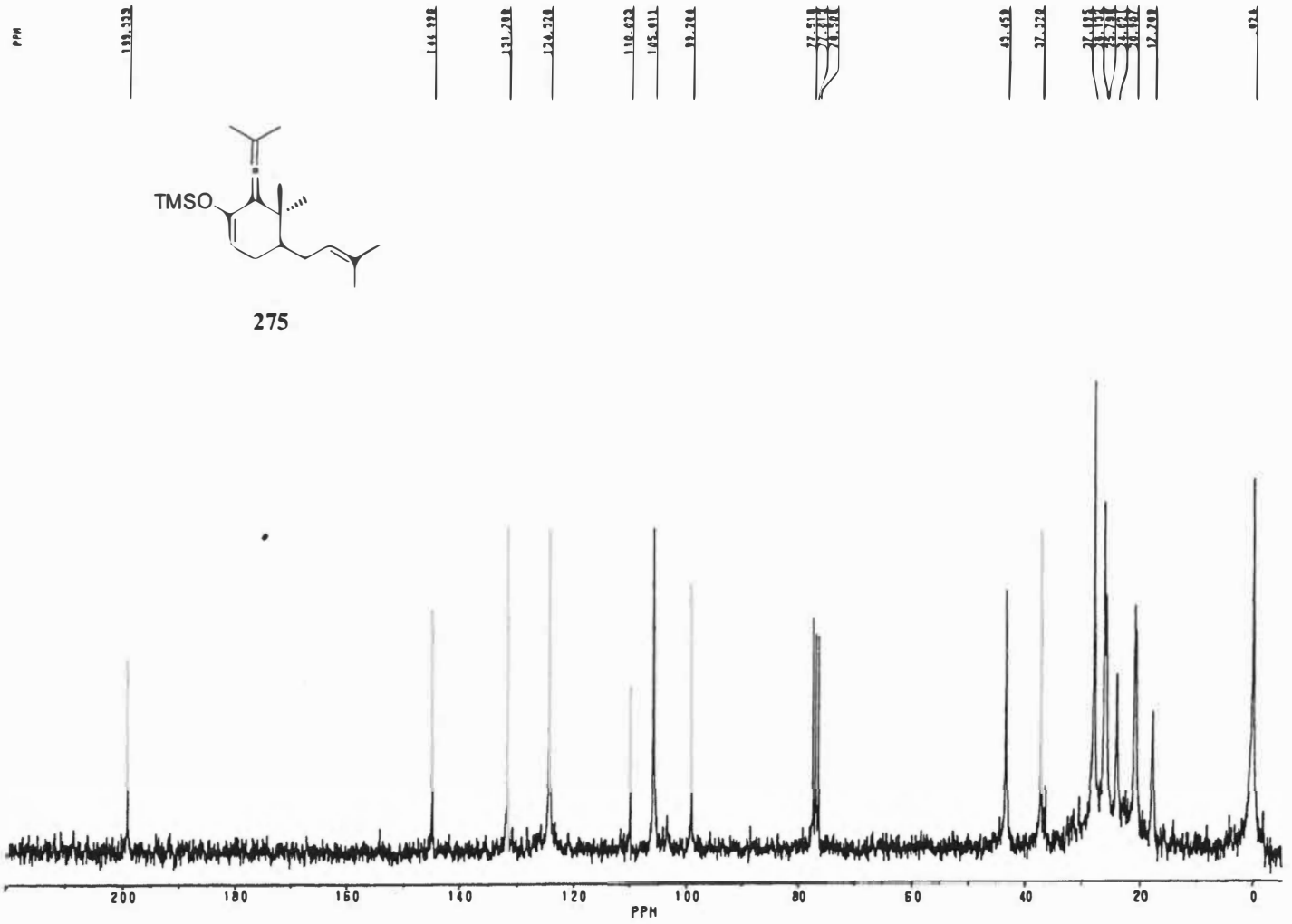

OMe
NO2
O
O
O
269
PPM
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM


OMe
NO2
O
O
O
269
PPM
0
20
40
60
80
100
120
140
160
180
200

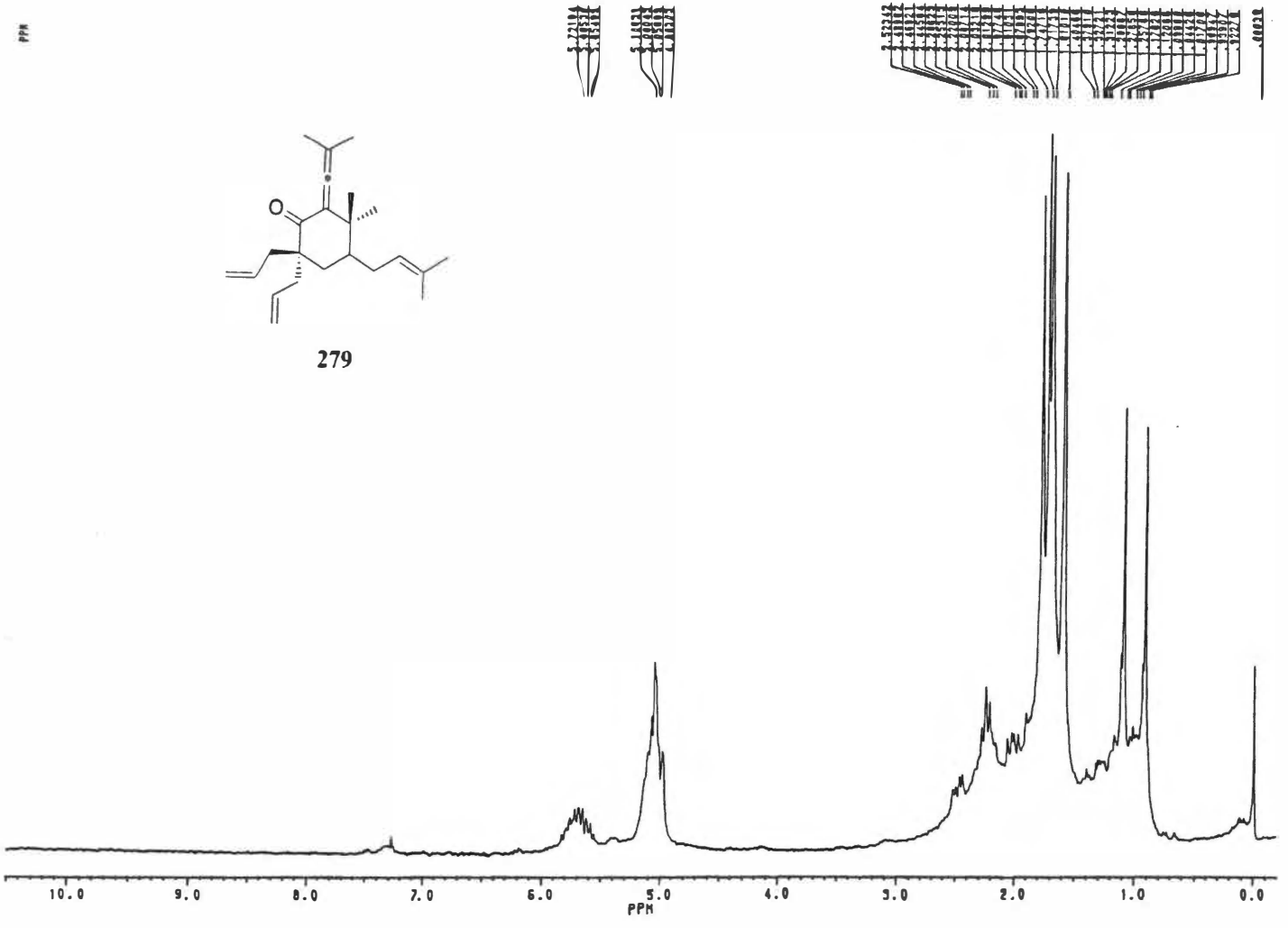

TBSO
I
273
PPM
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0
PPM


TBSO
I
273
200
180
160
140
120
100
80
60
40
20
0
PPM

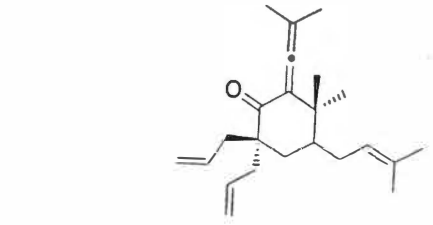

TMSO
275
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM



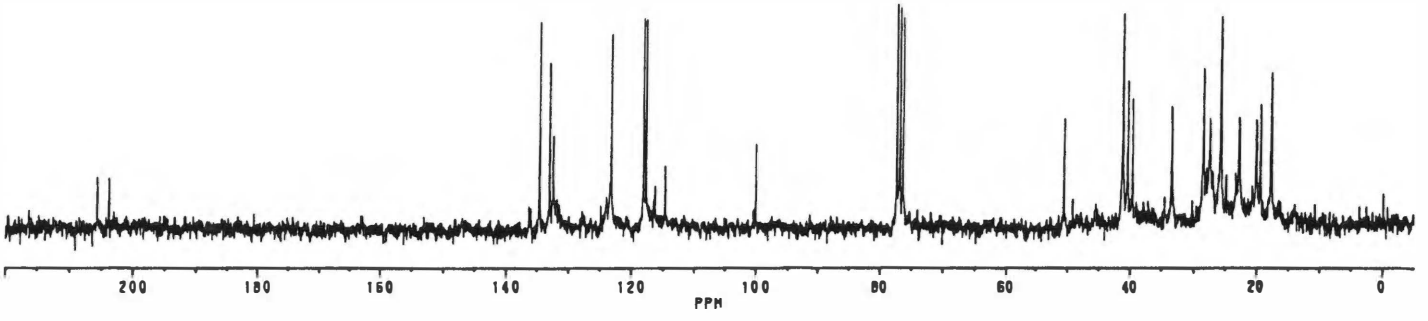
275

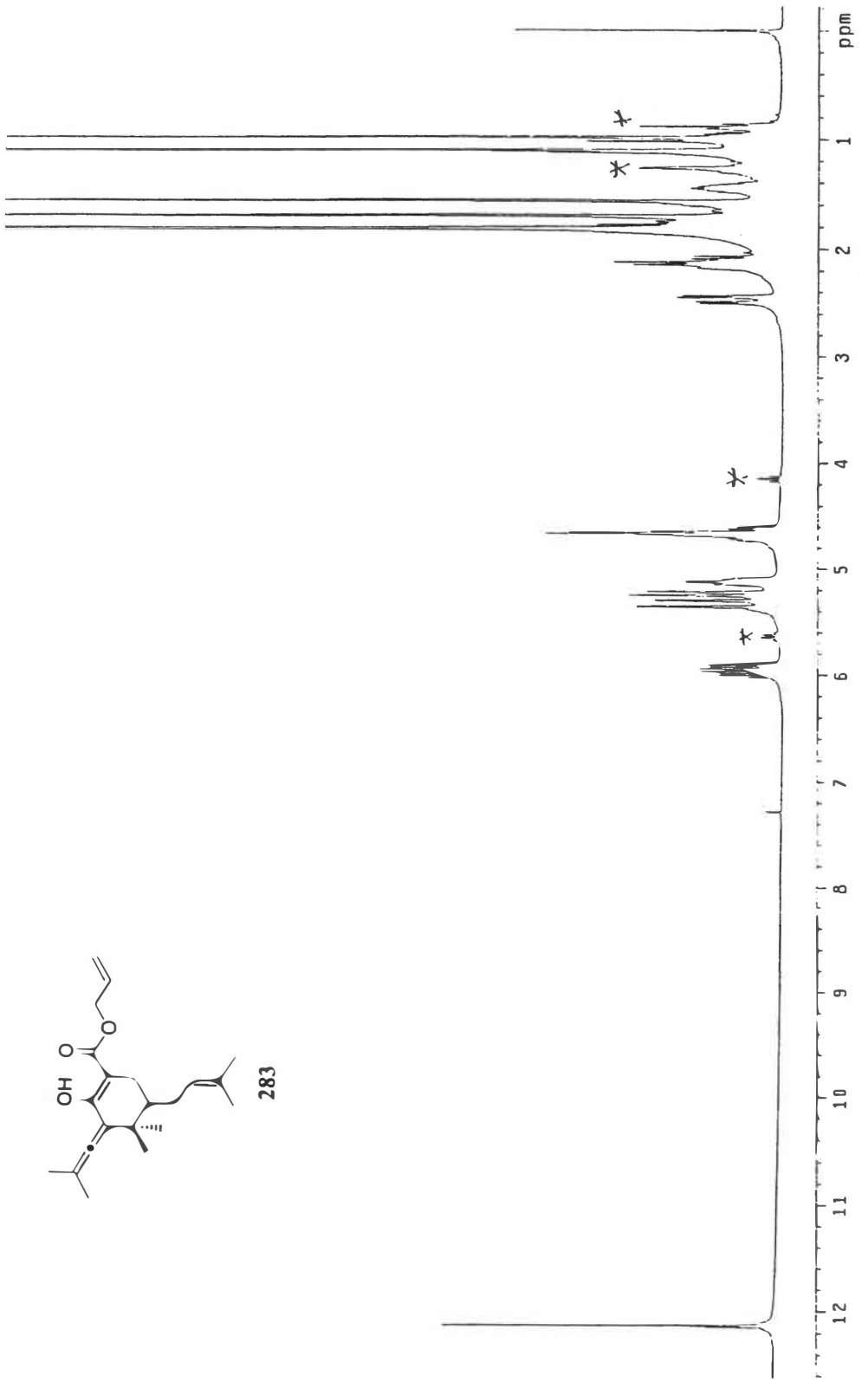


279

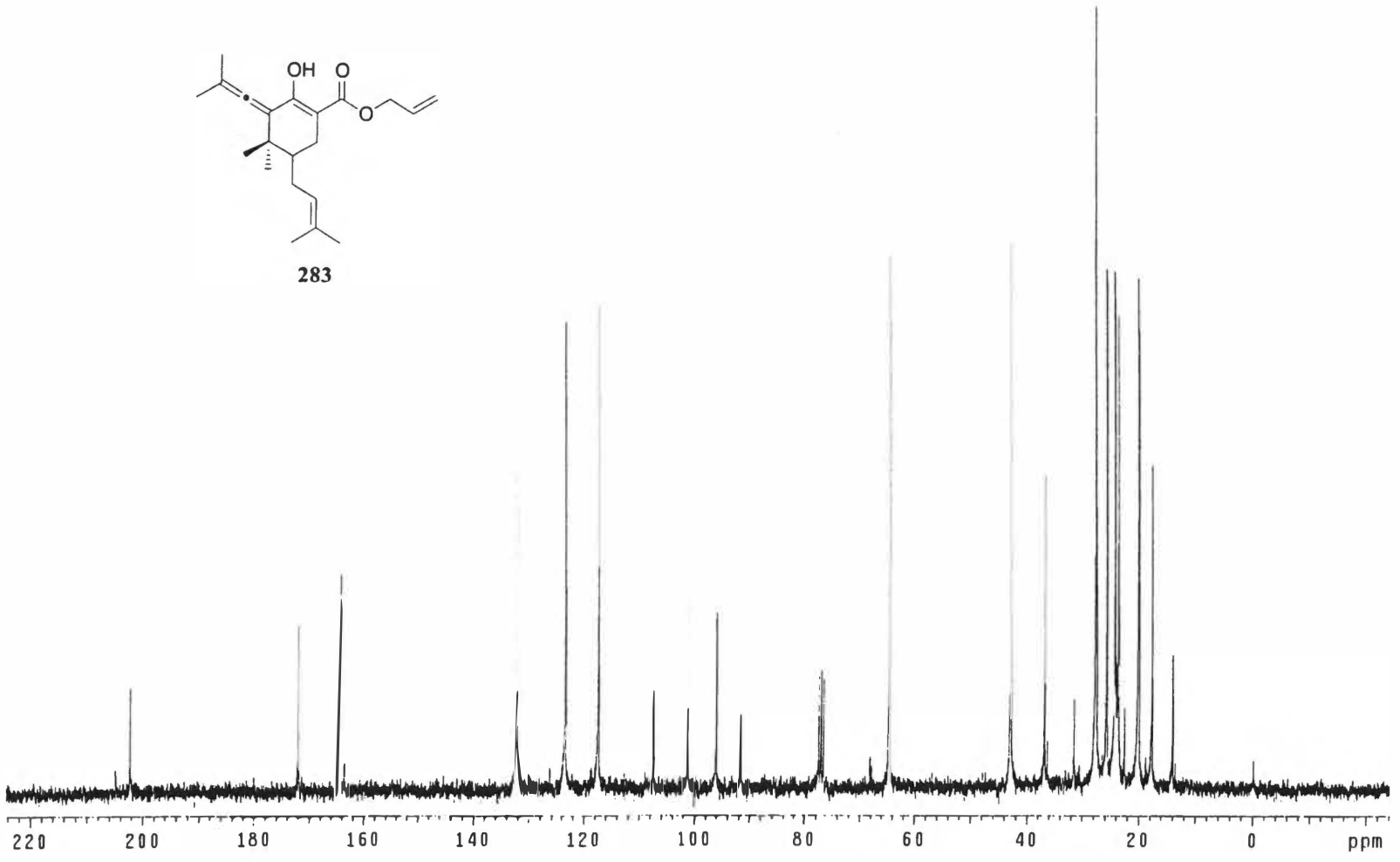


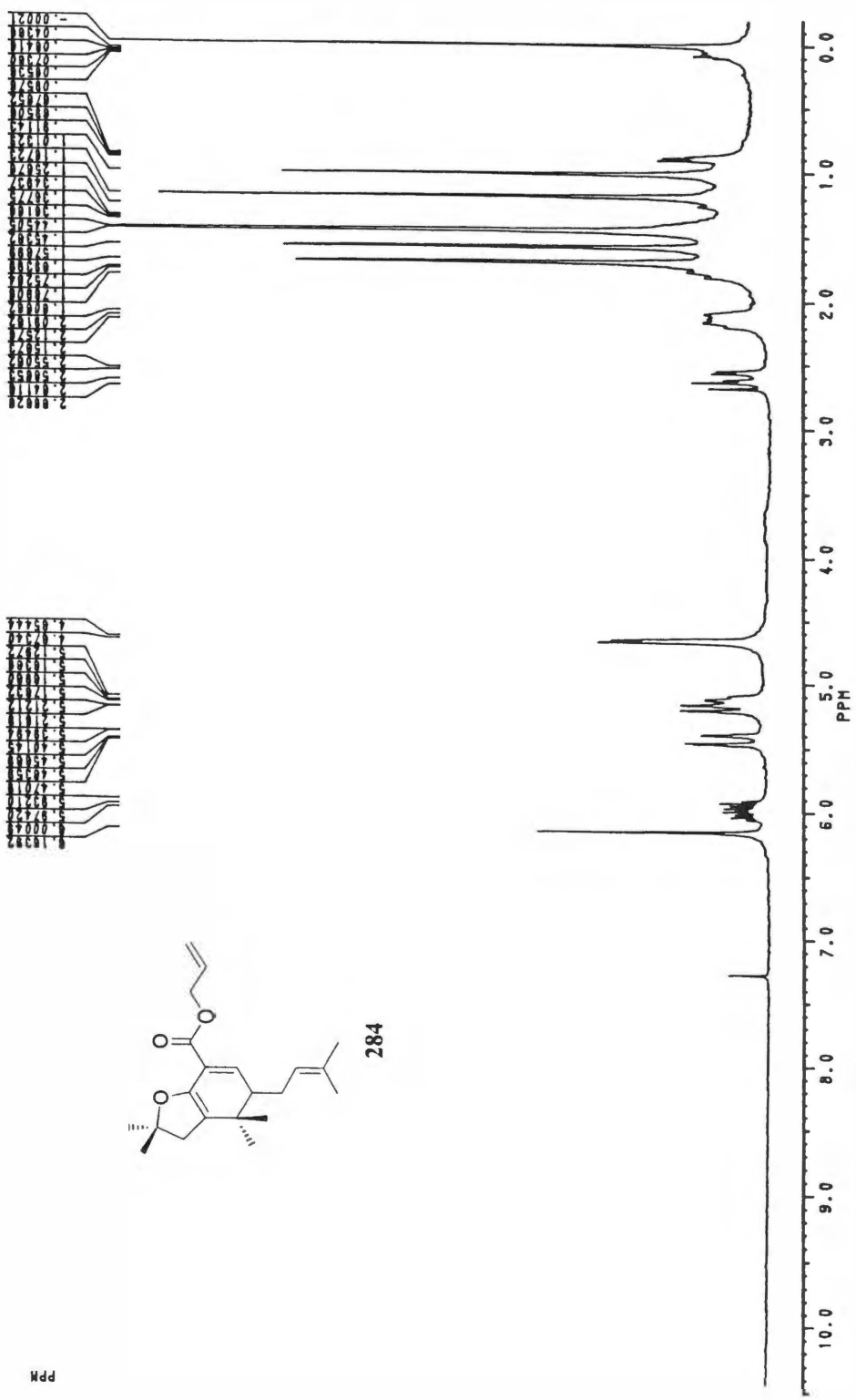
279



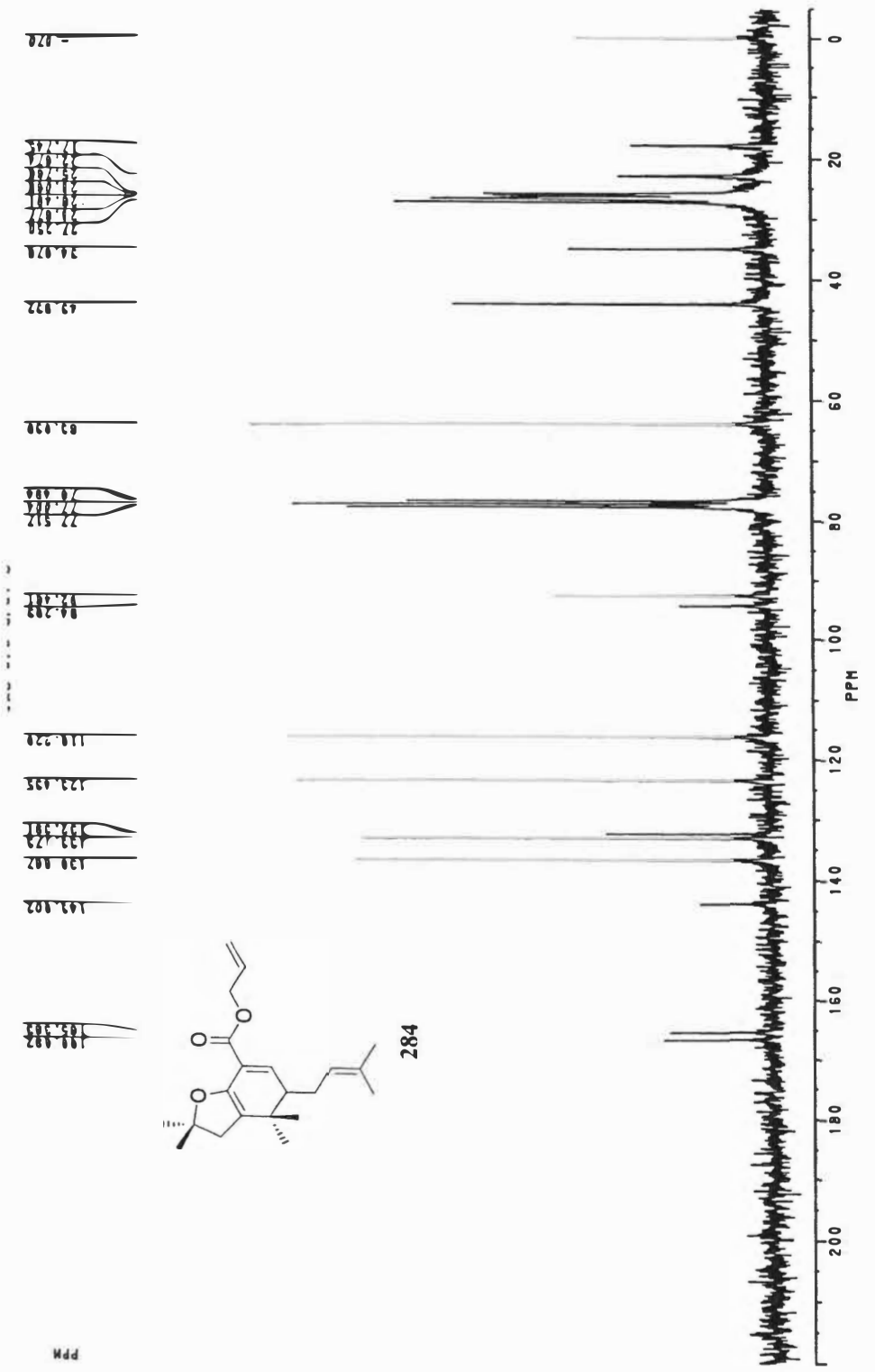


283

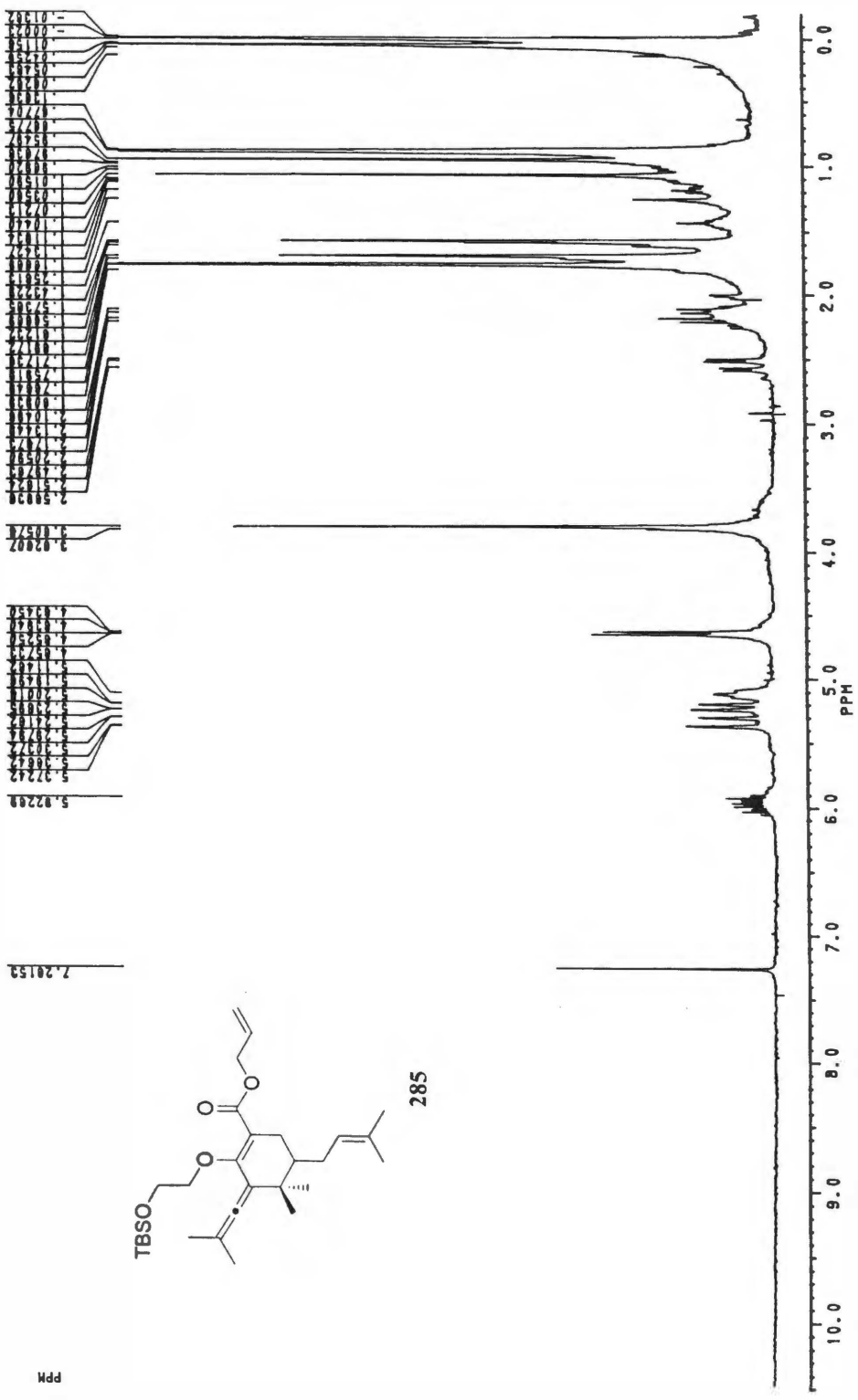

OH
O
O
283
220
200
180
160
140
120
100
80
60
40
20
0
ppm

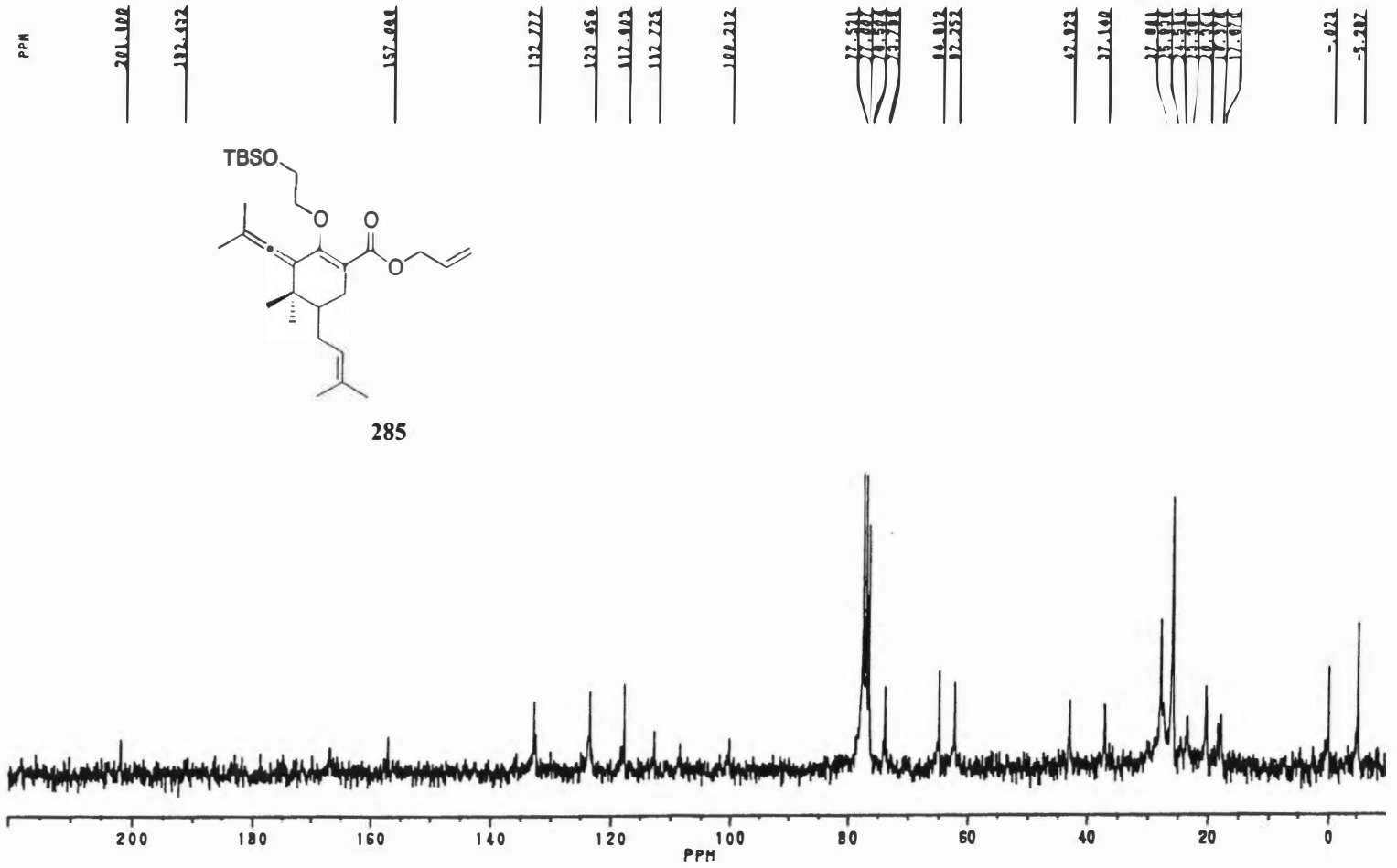


284

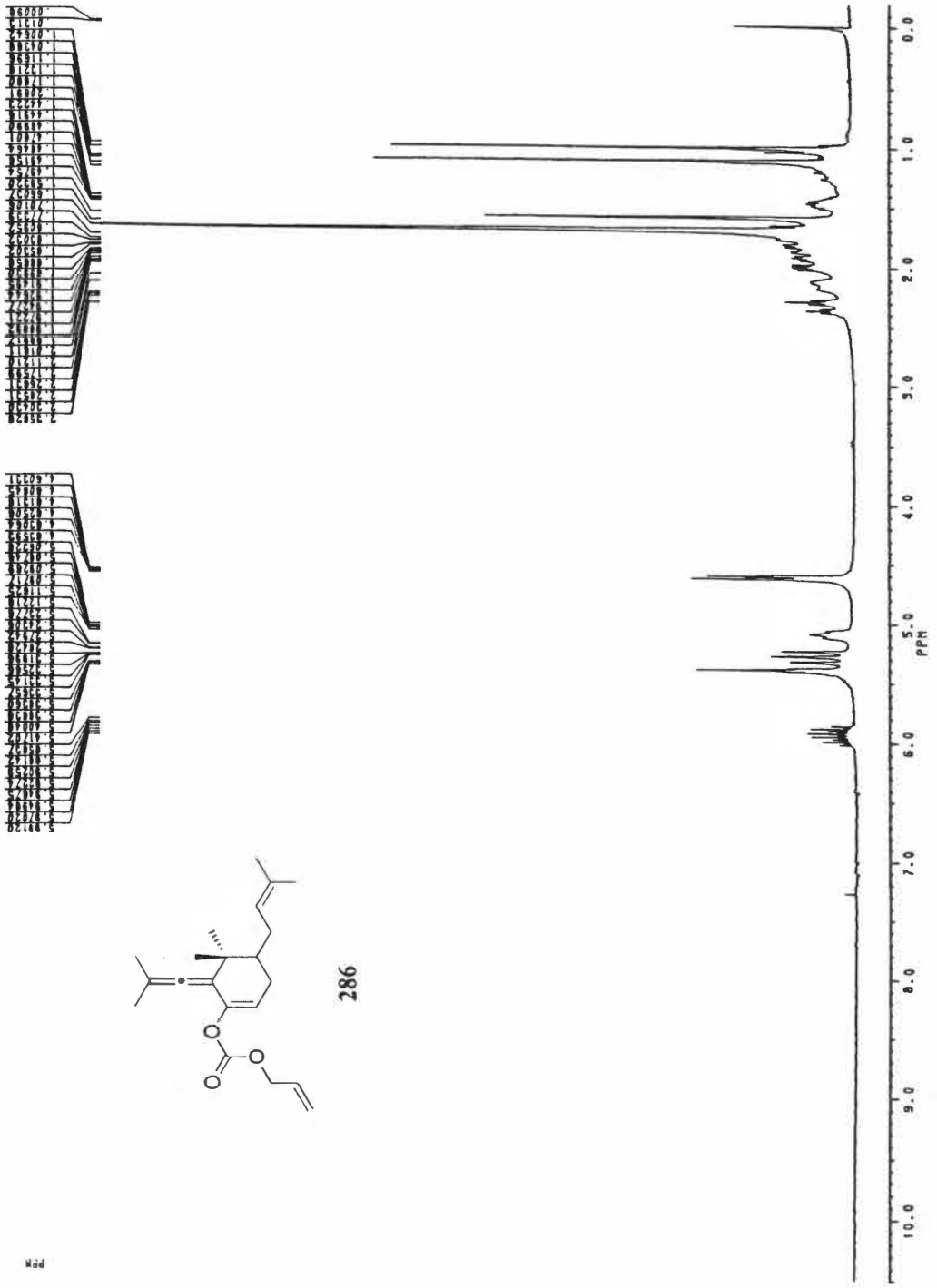


284

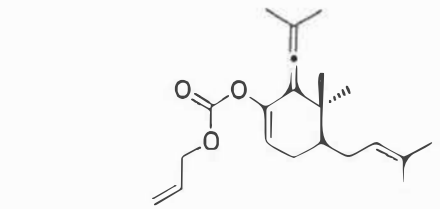

TBSO
285
PPM



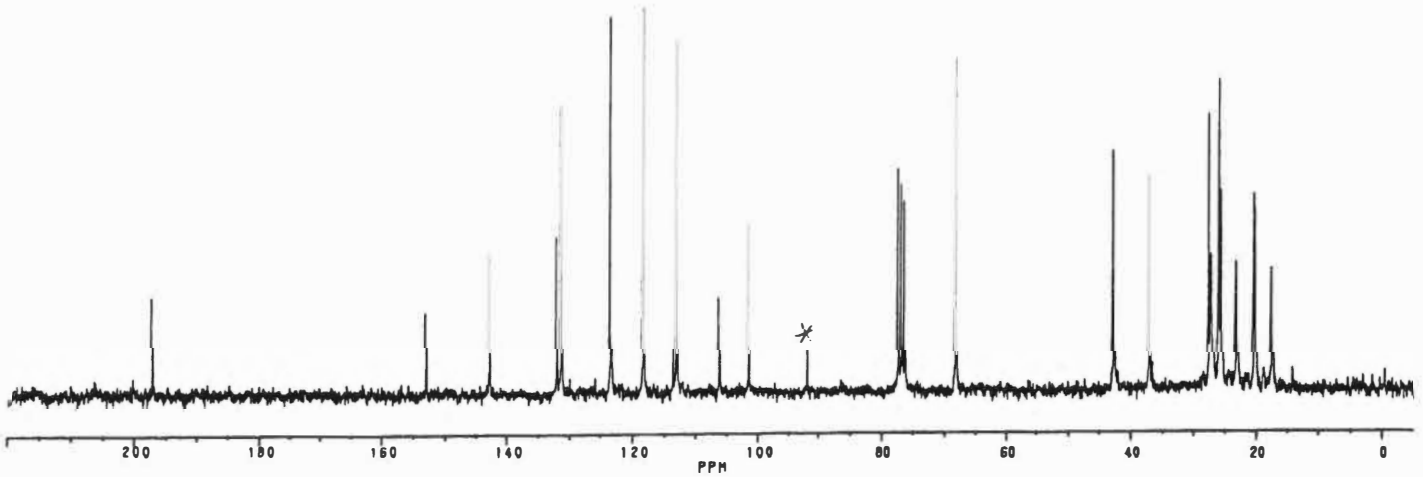
285

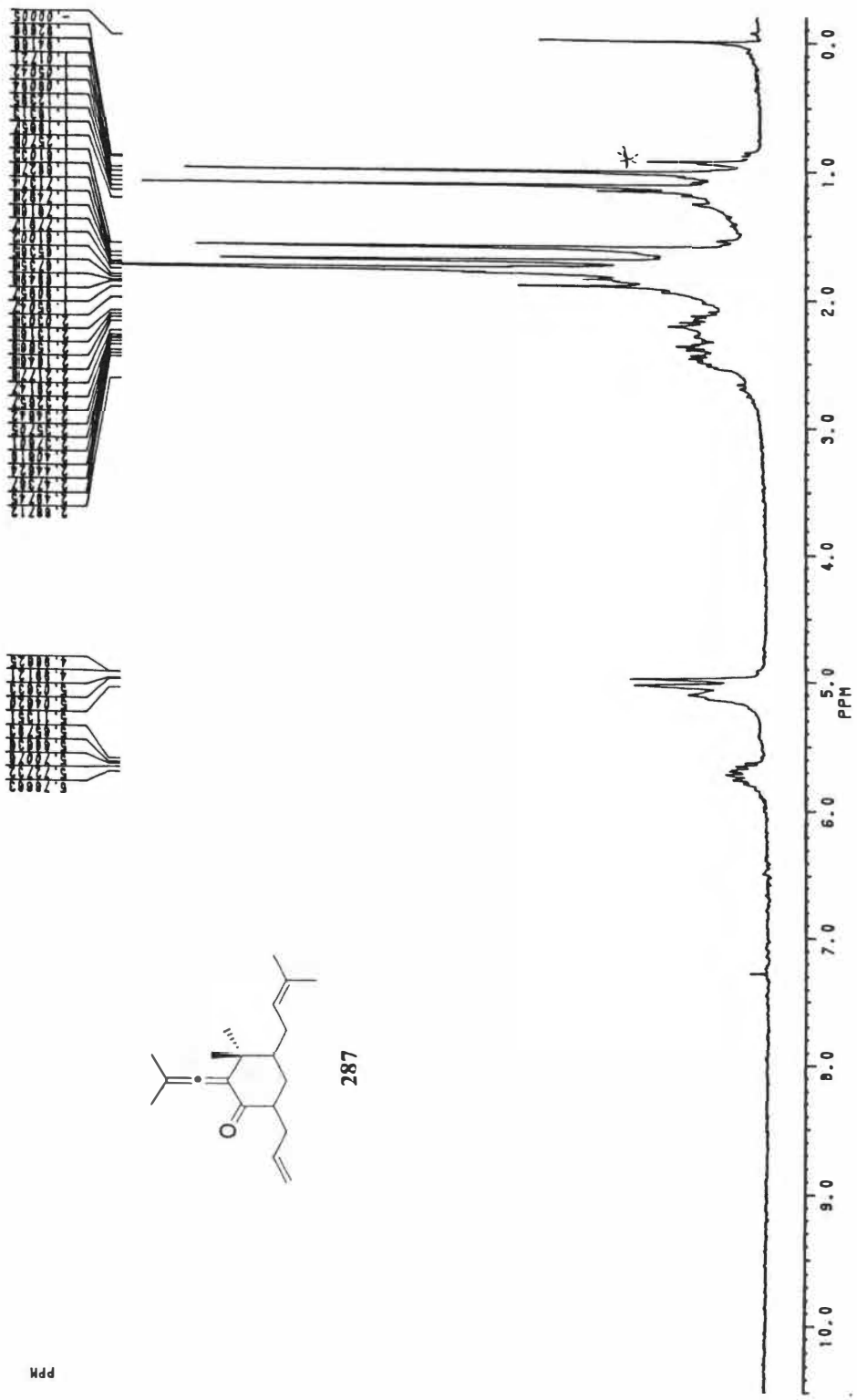


286

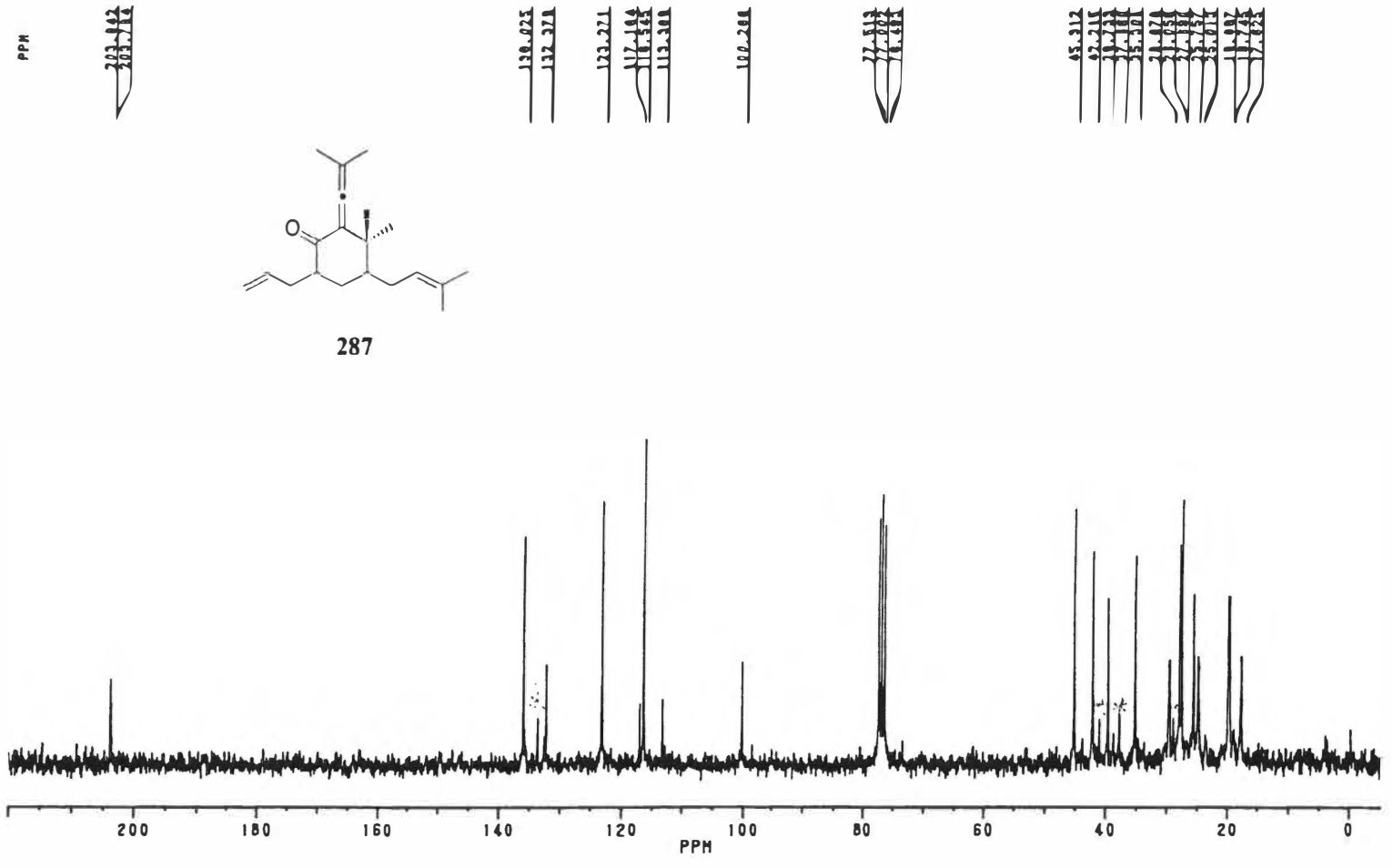


286

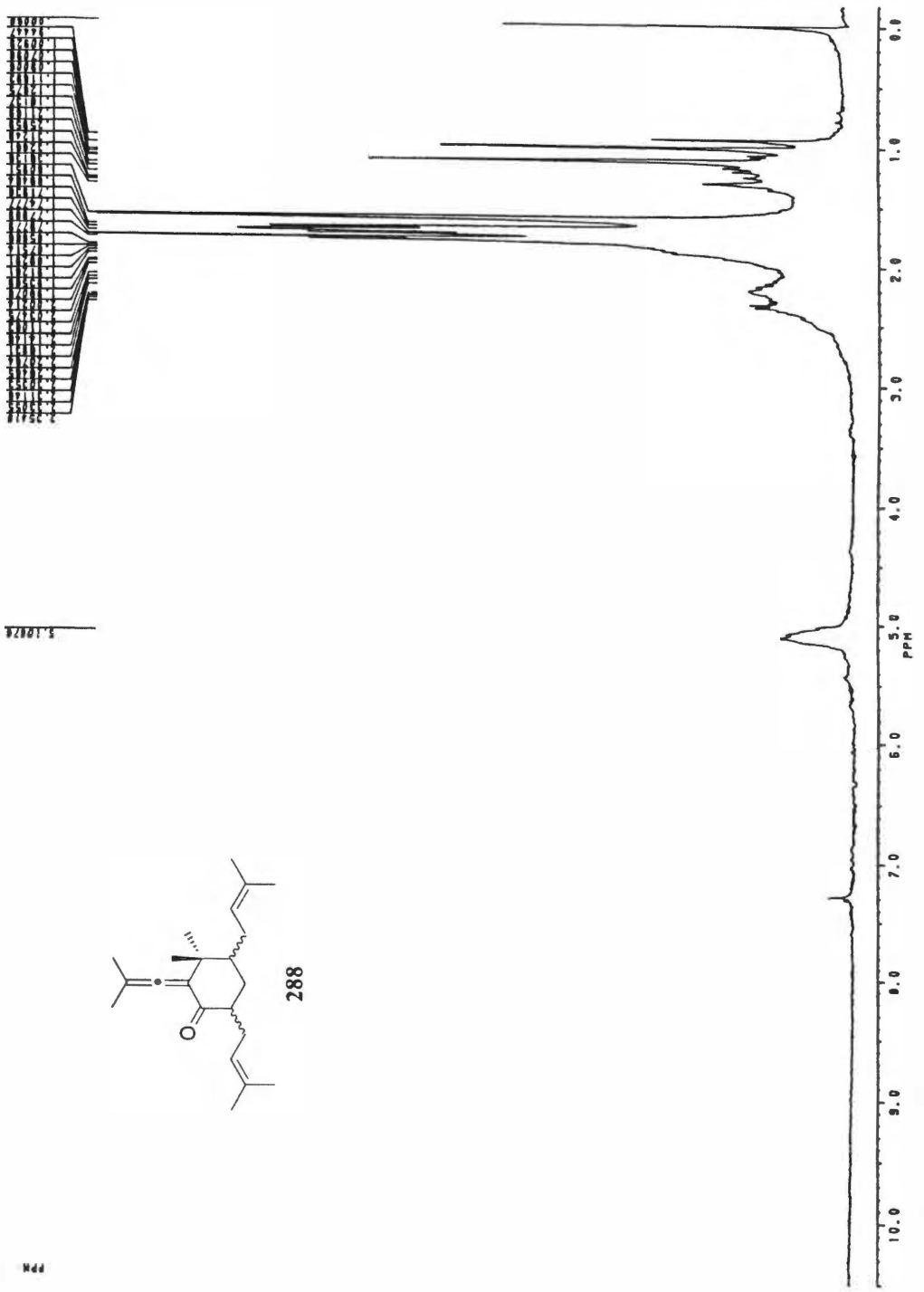




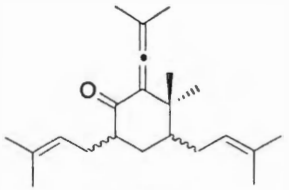
287



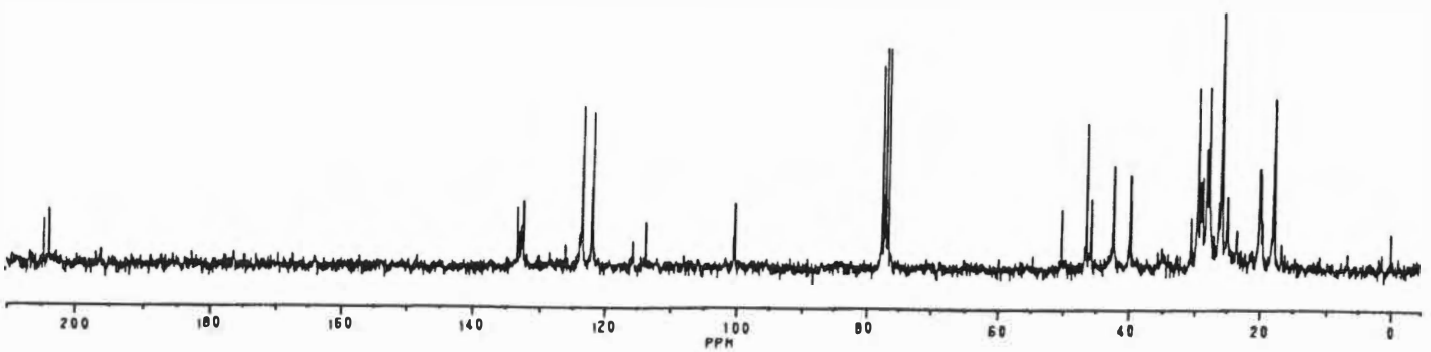
287

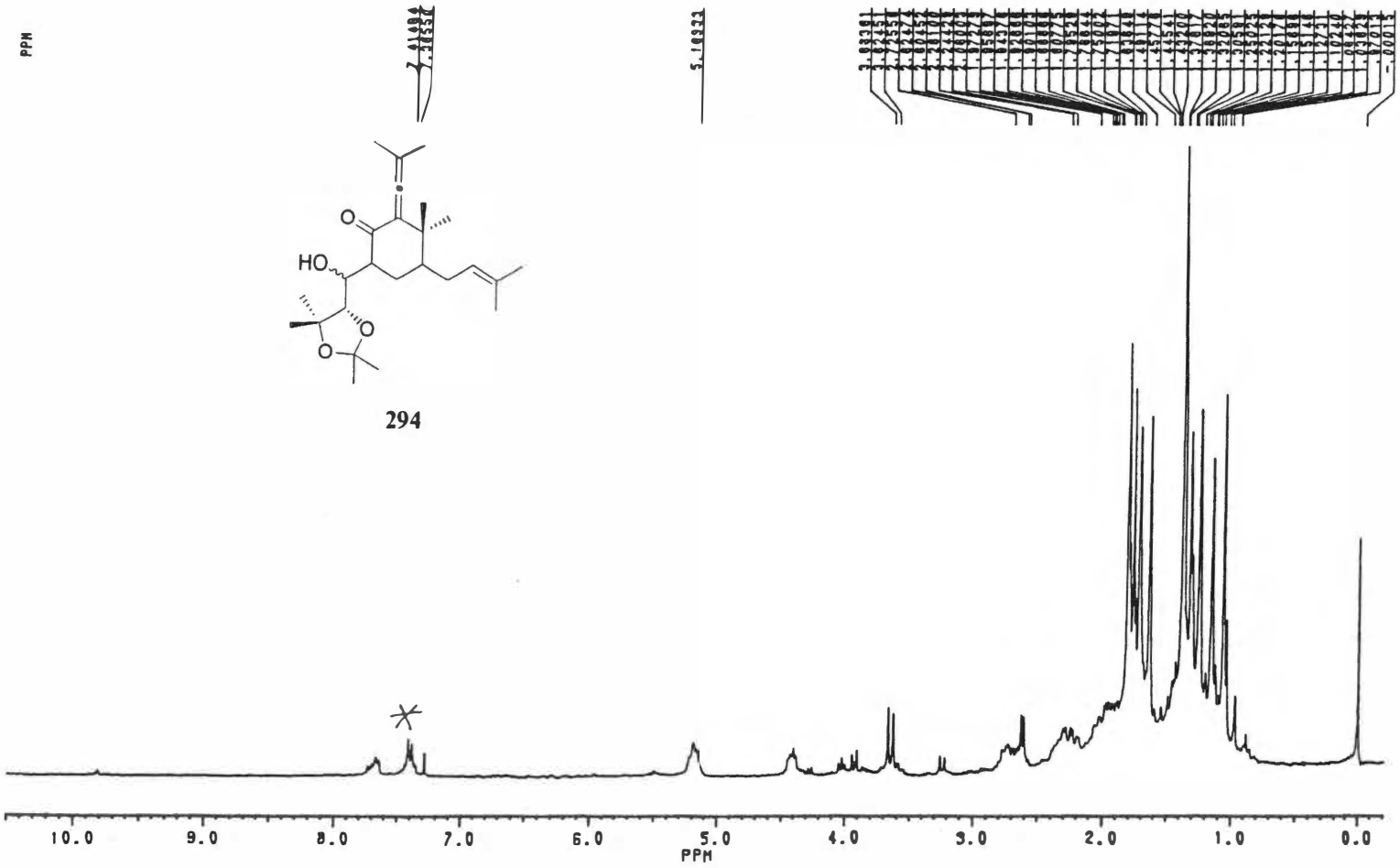


288

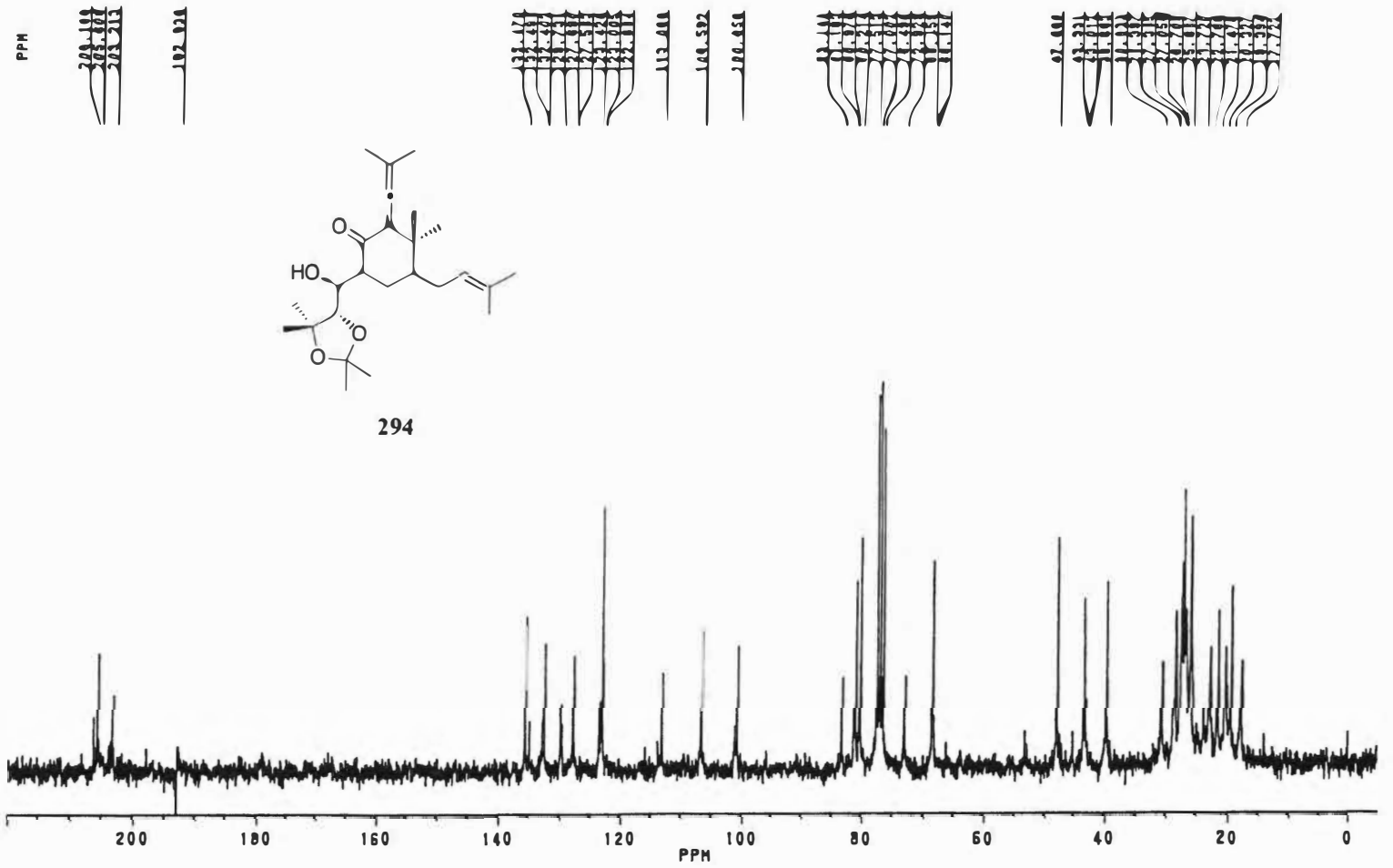


288

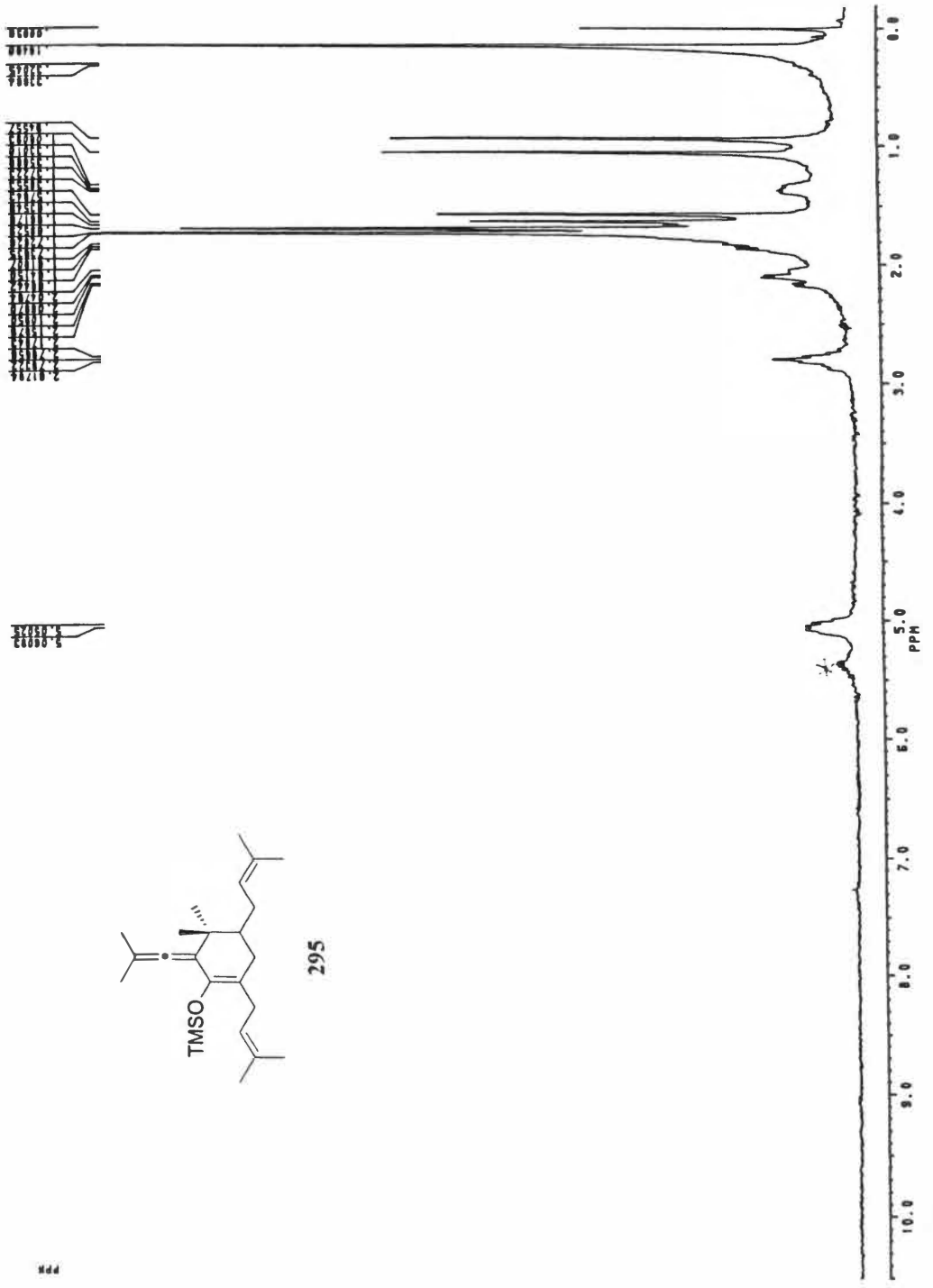


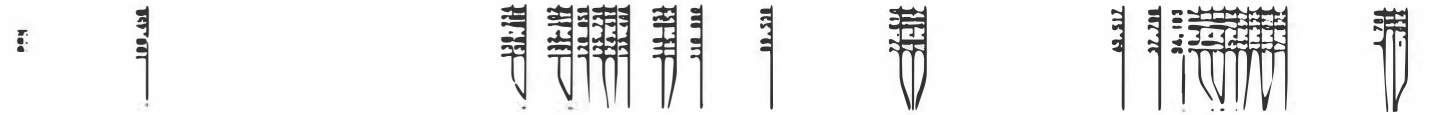


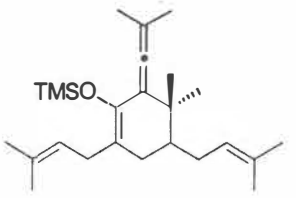
294



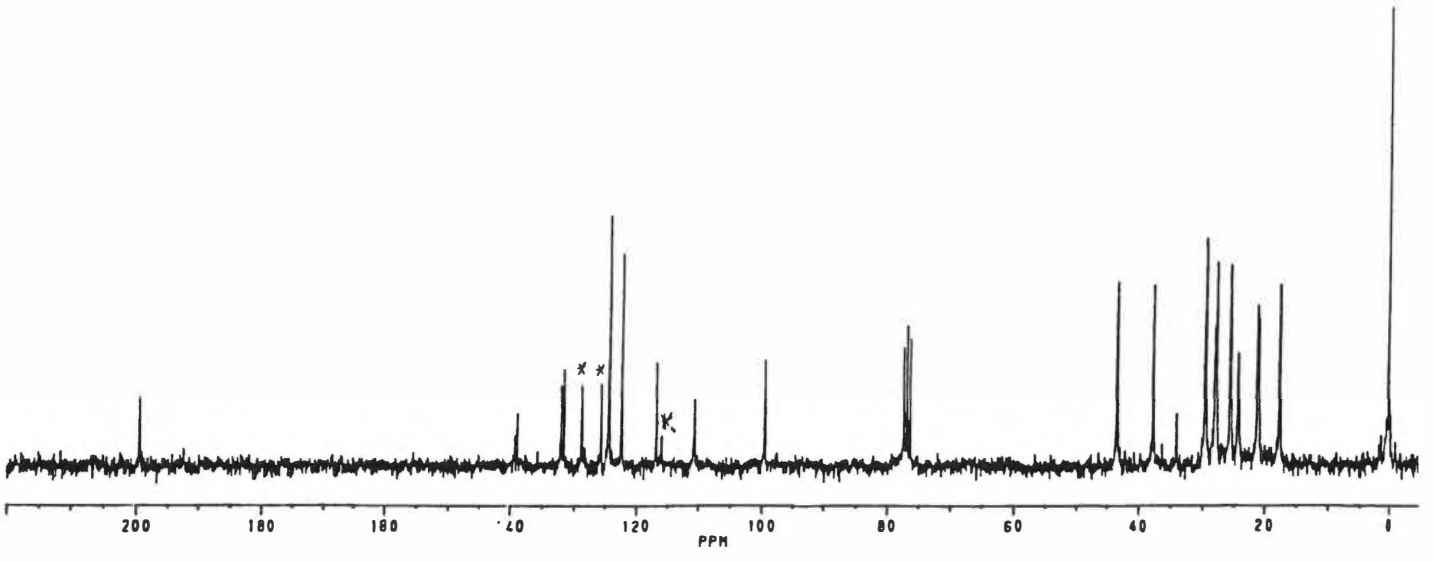
294

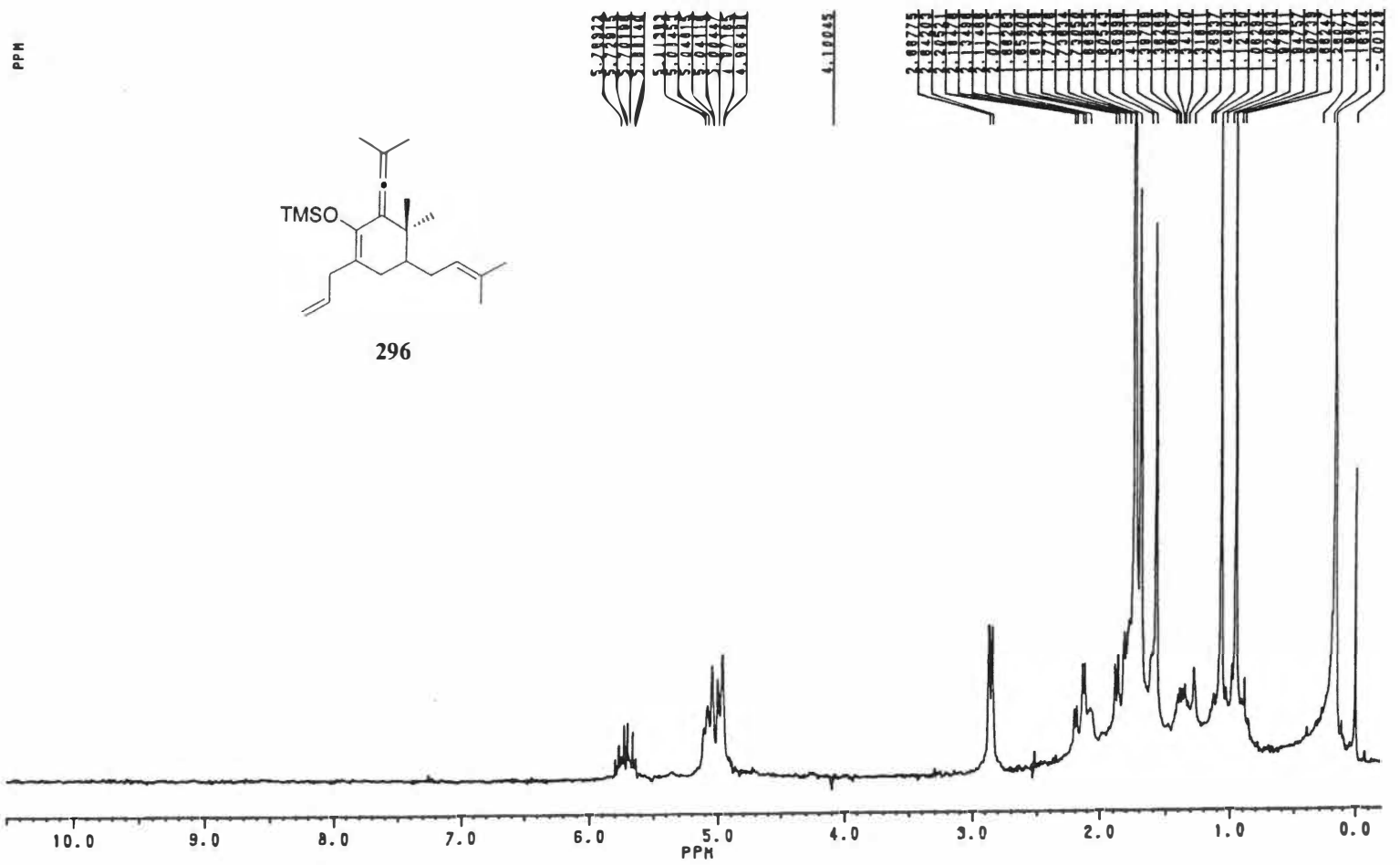

TMSO
295
PPM



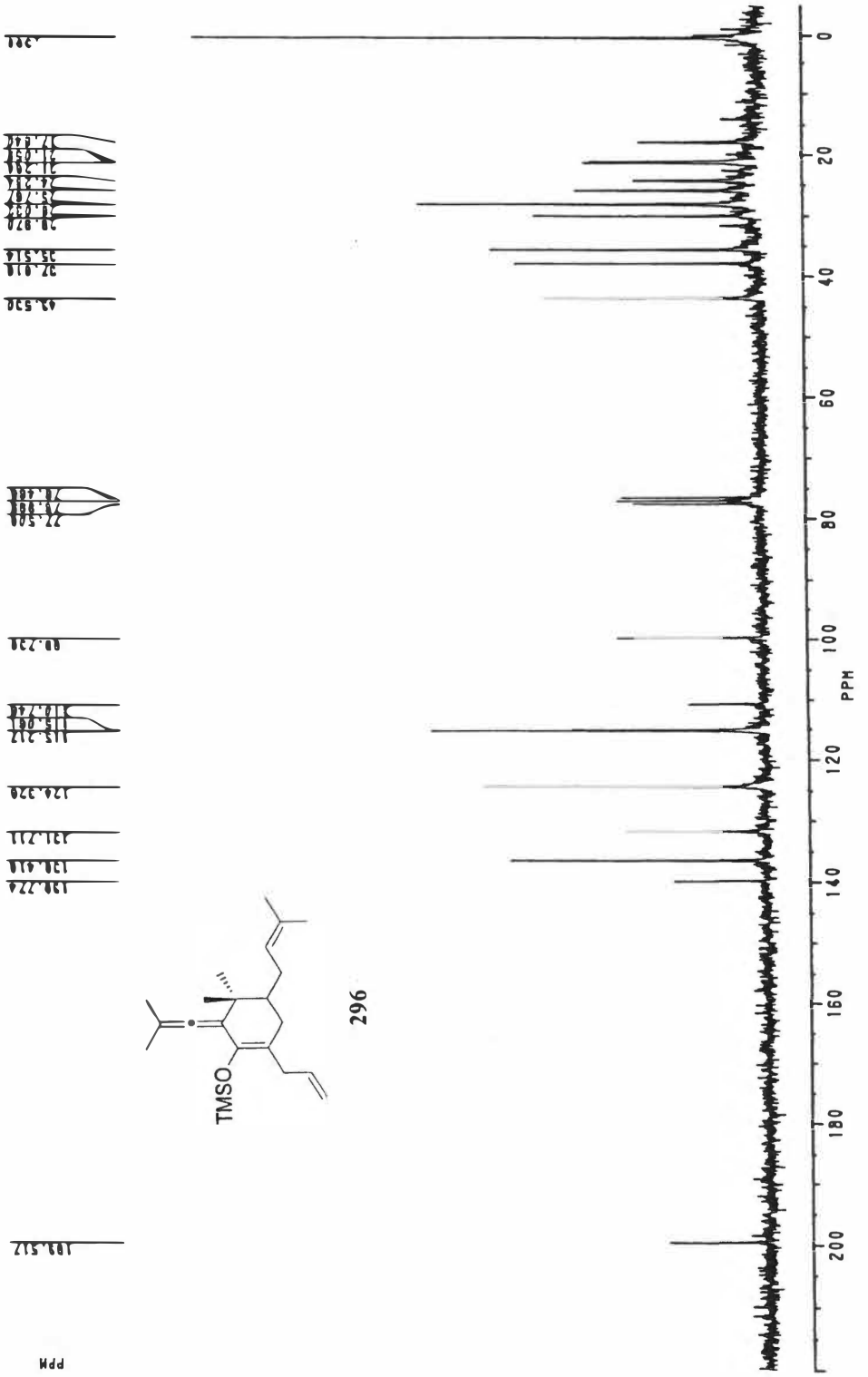


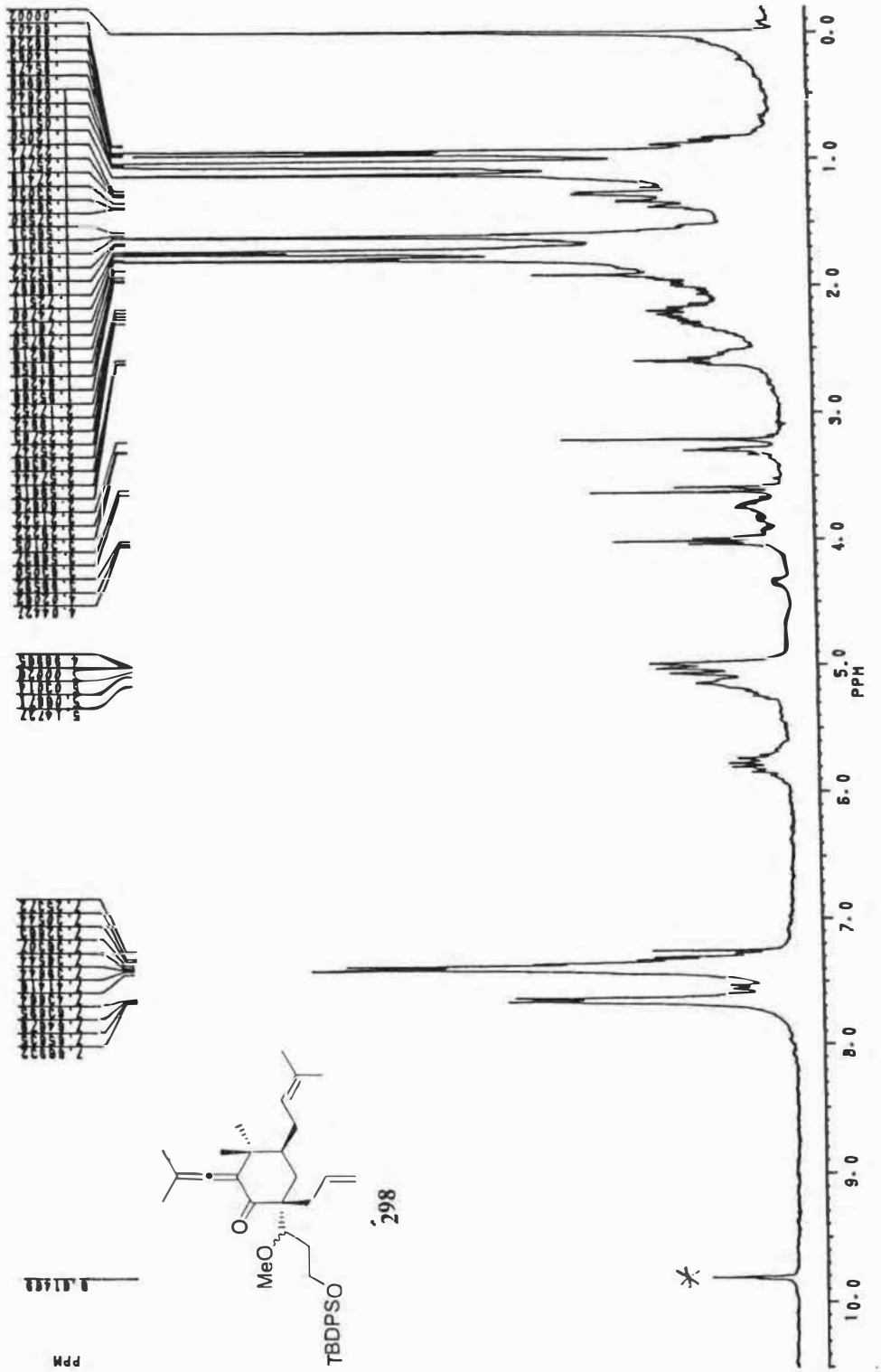
295

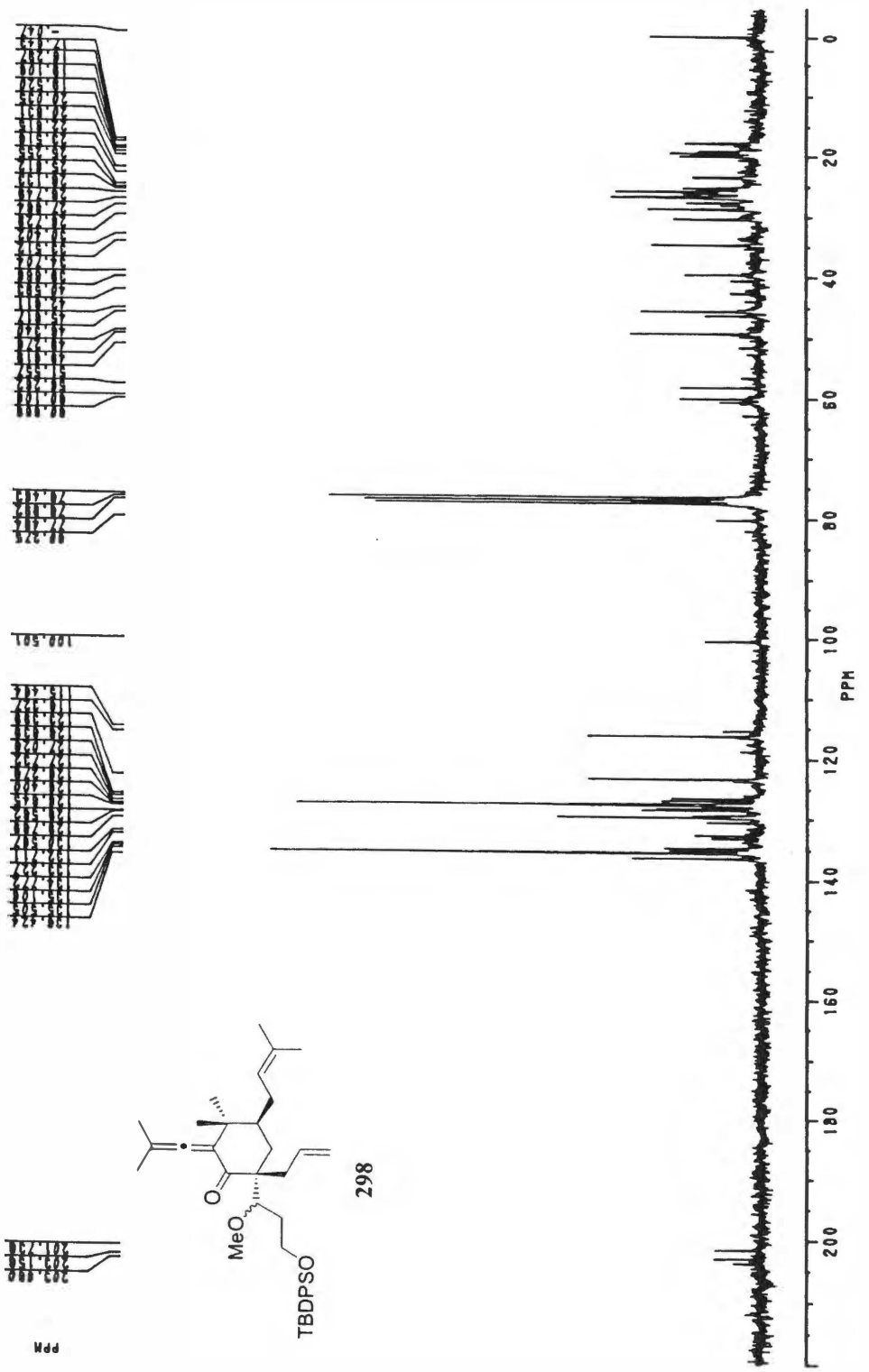


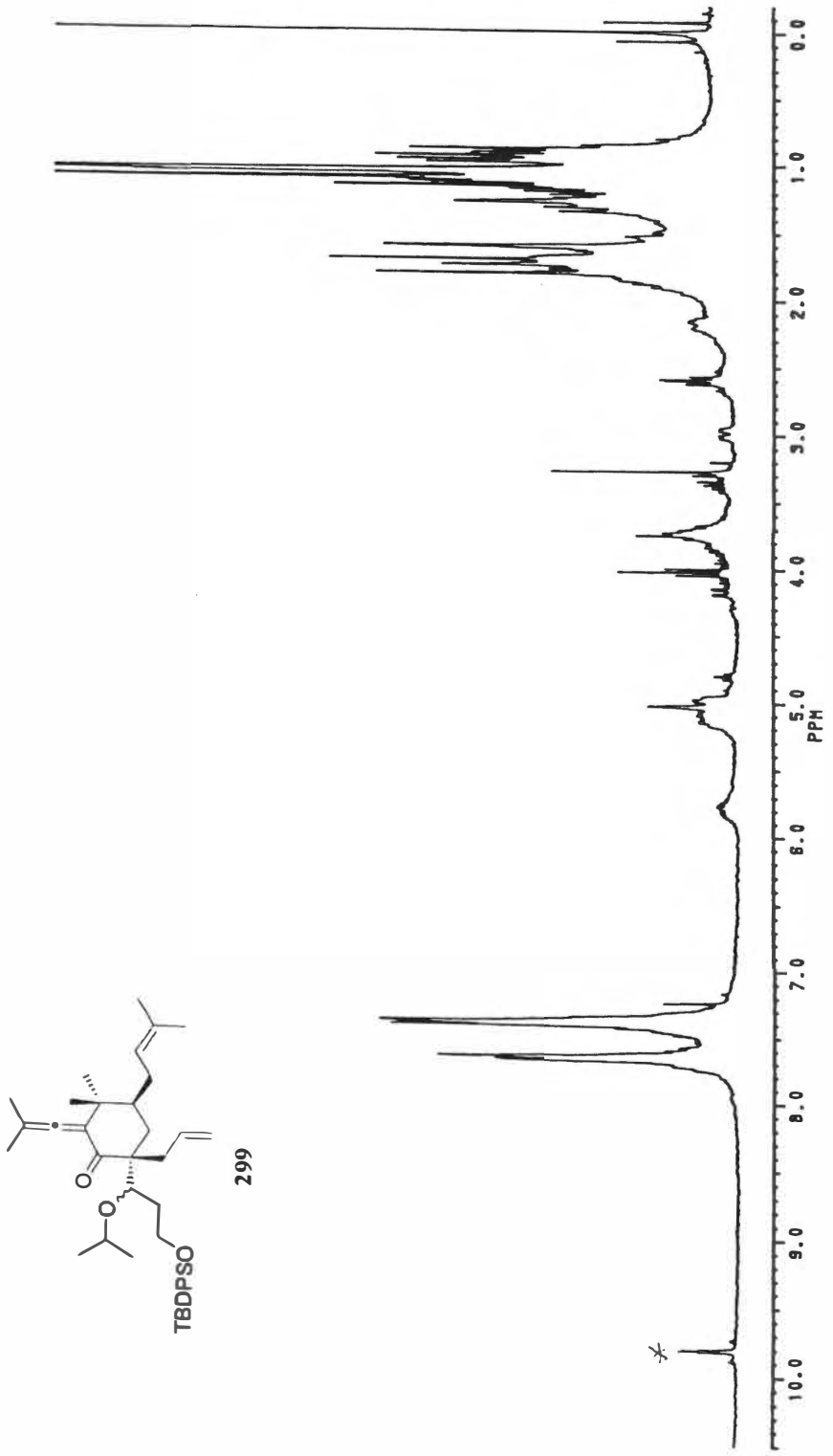


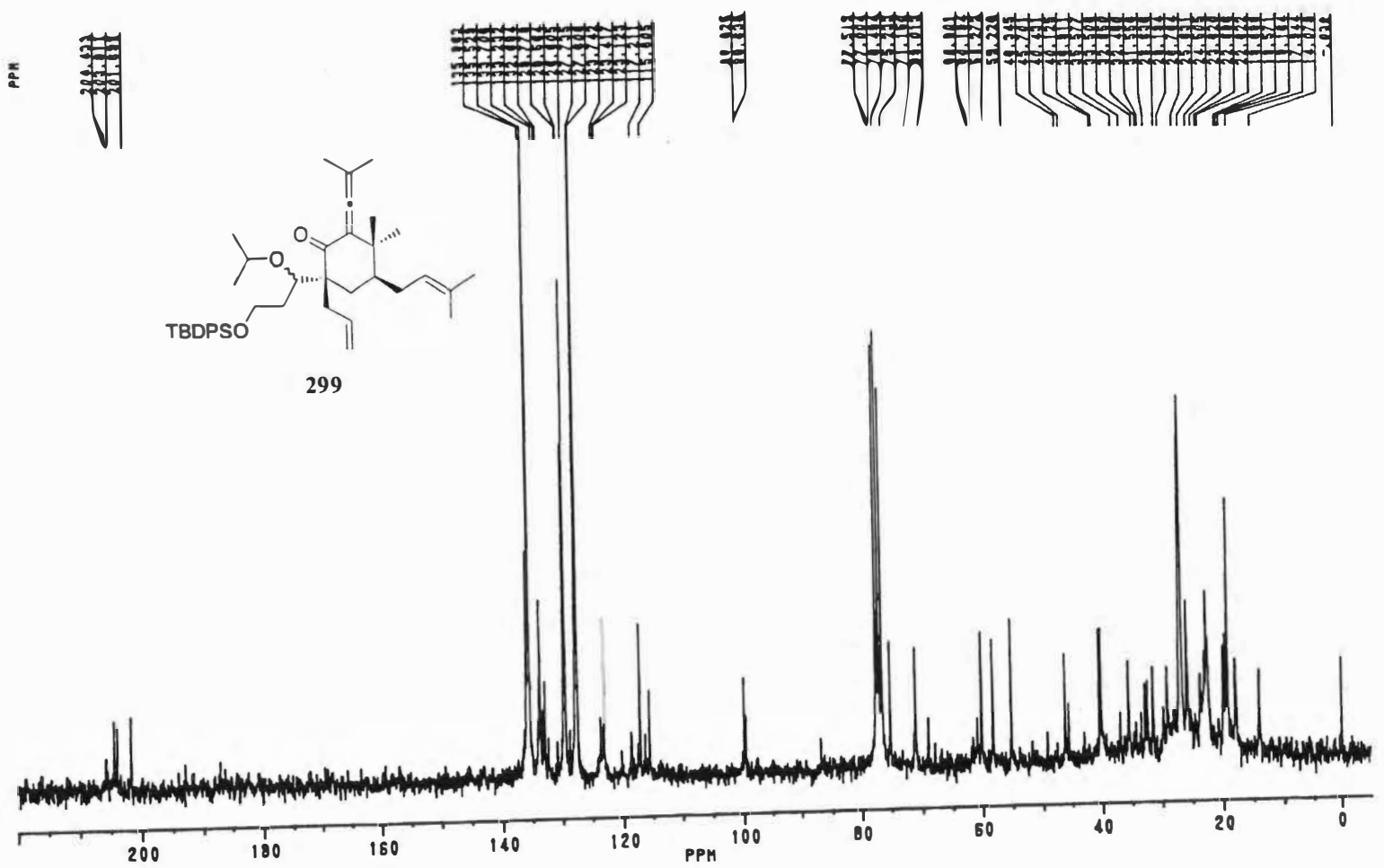
296

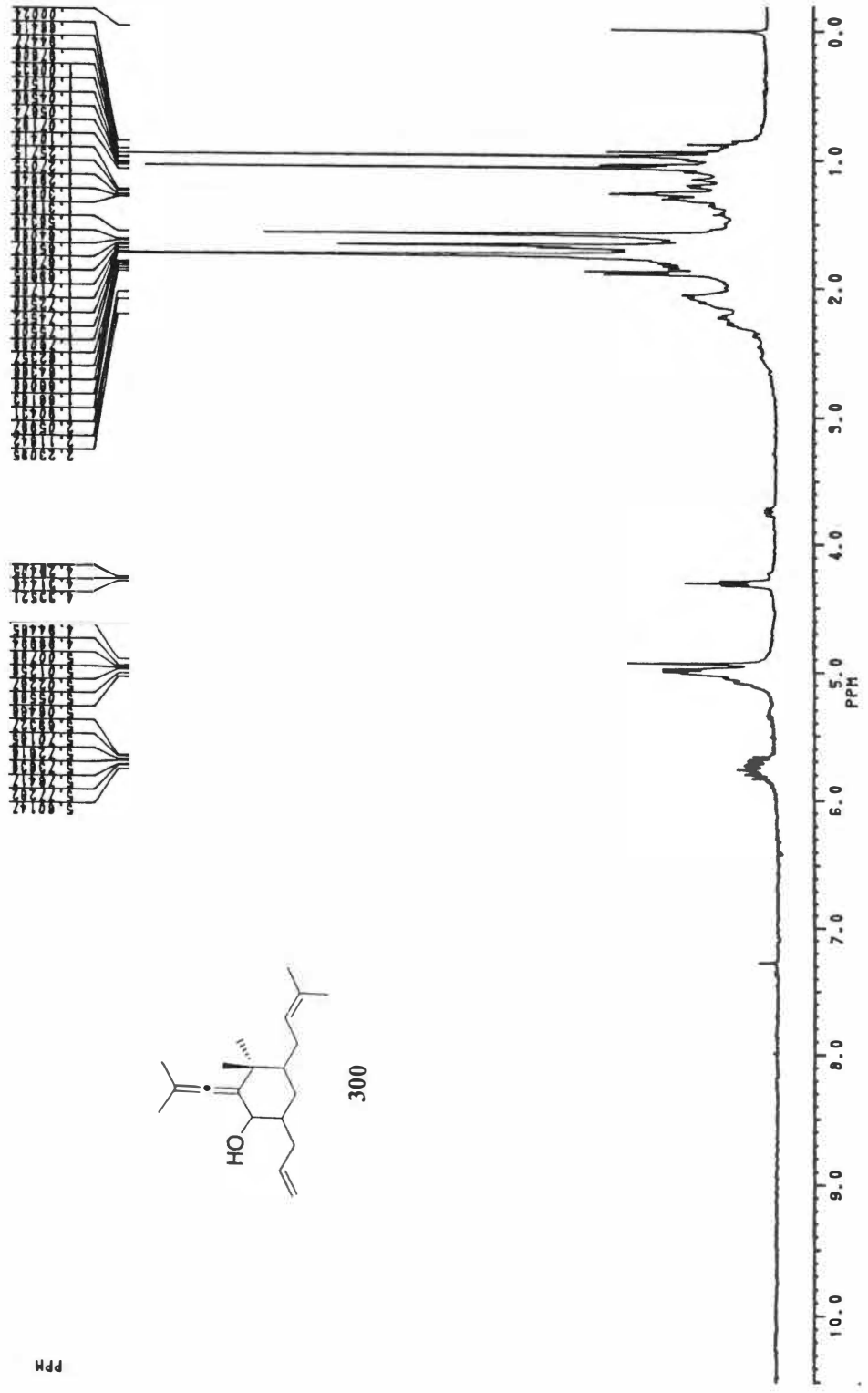

TMSO
296
PPM

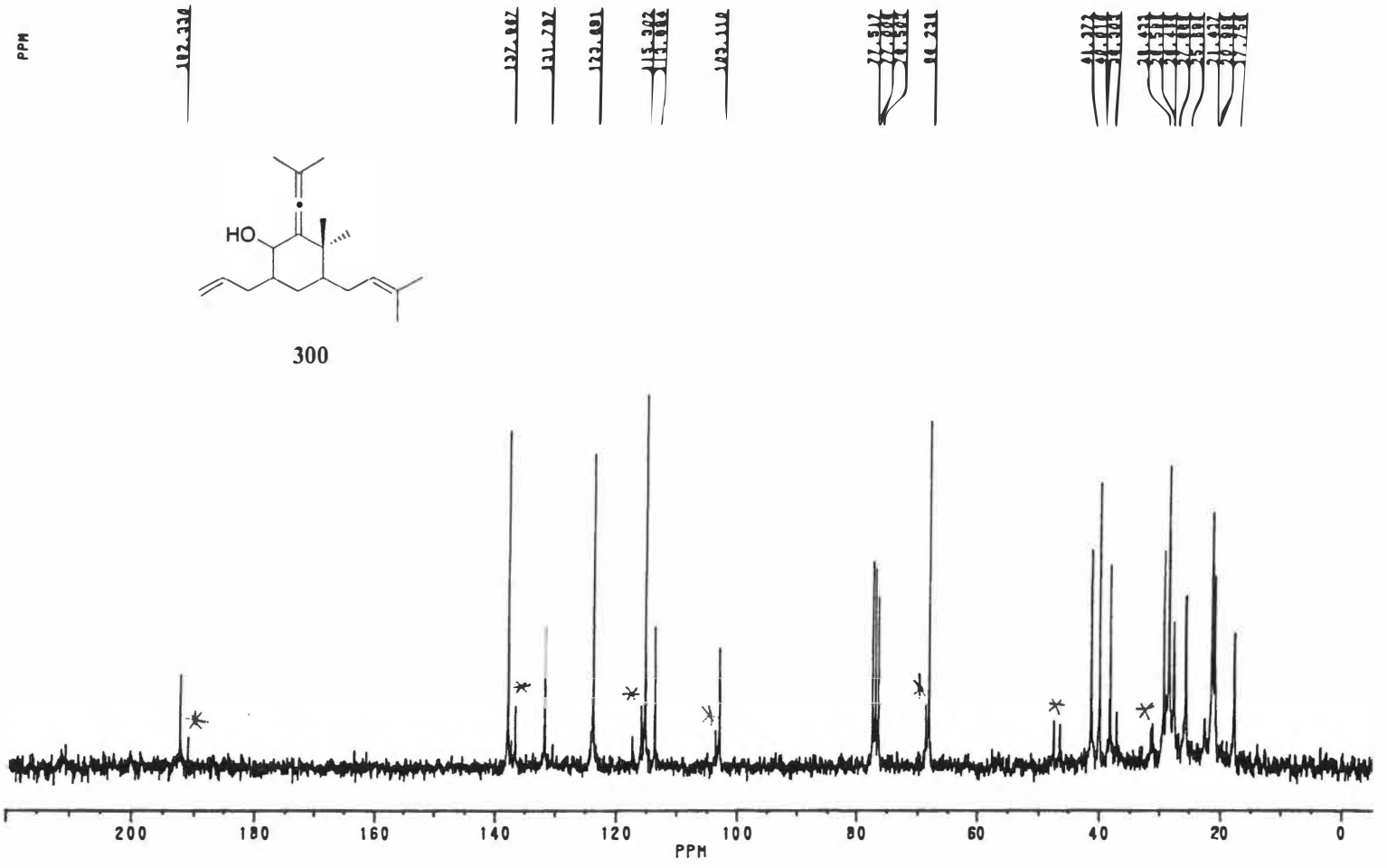

PPM
MeO
TBDPSO
O
298
*
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM

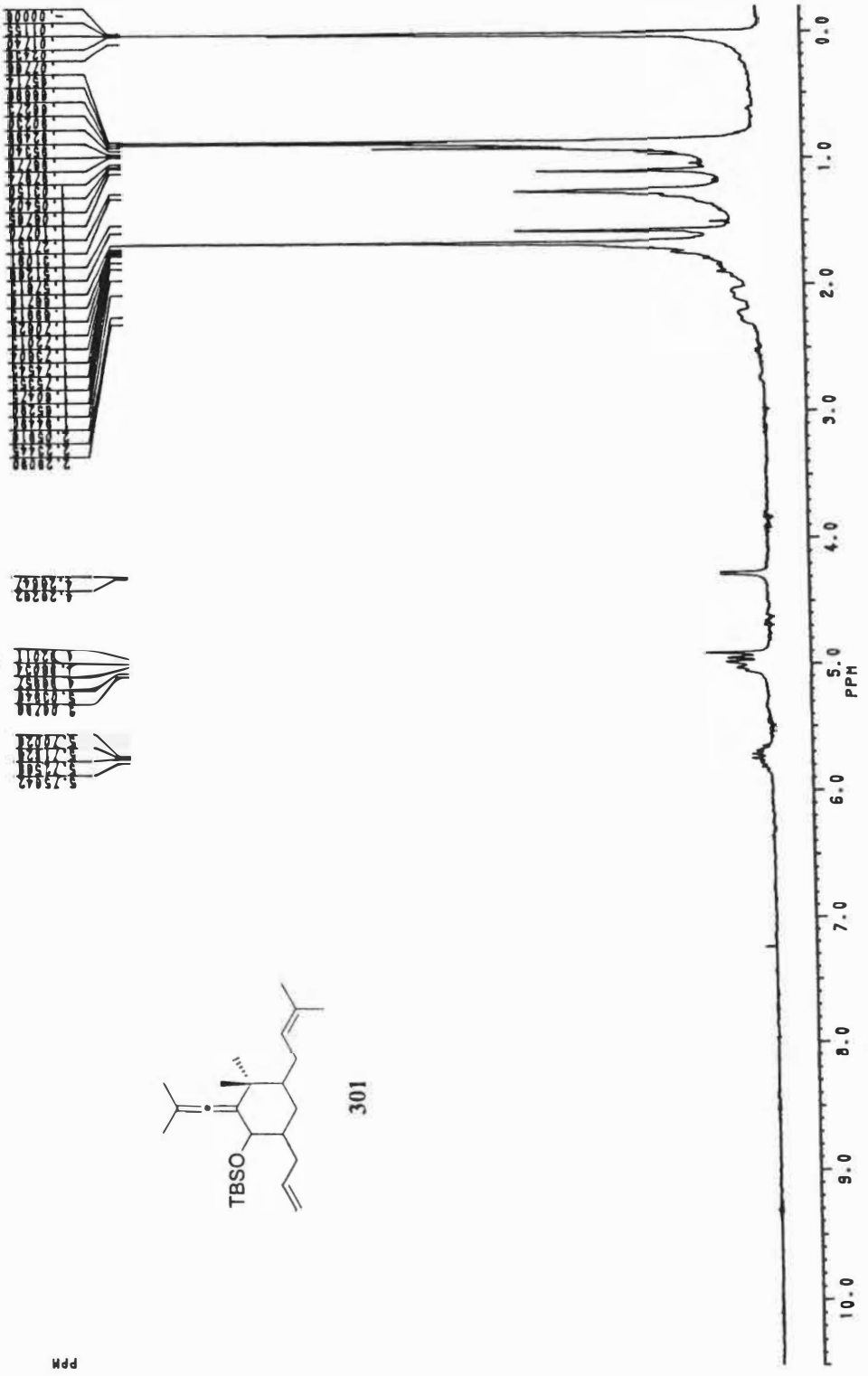

PPM
MeO
TBDPSO
O
298
PPM

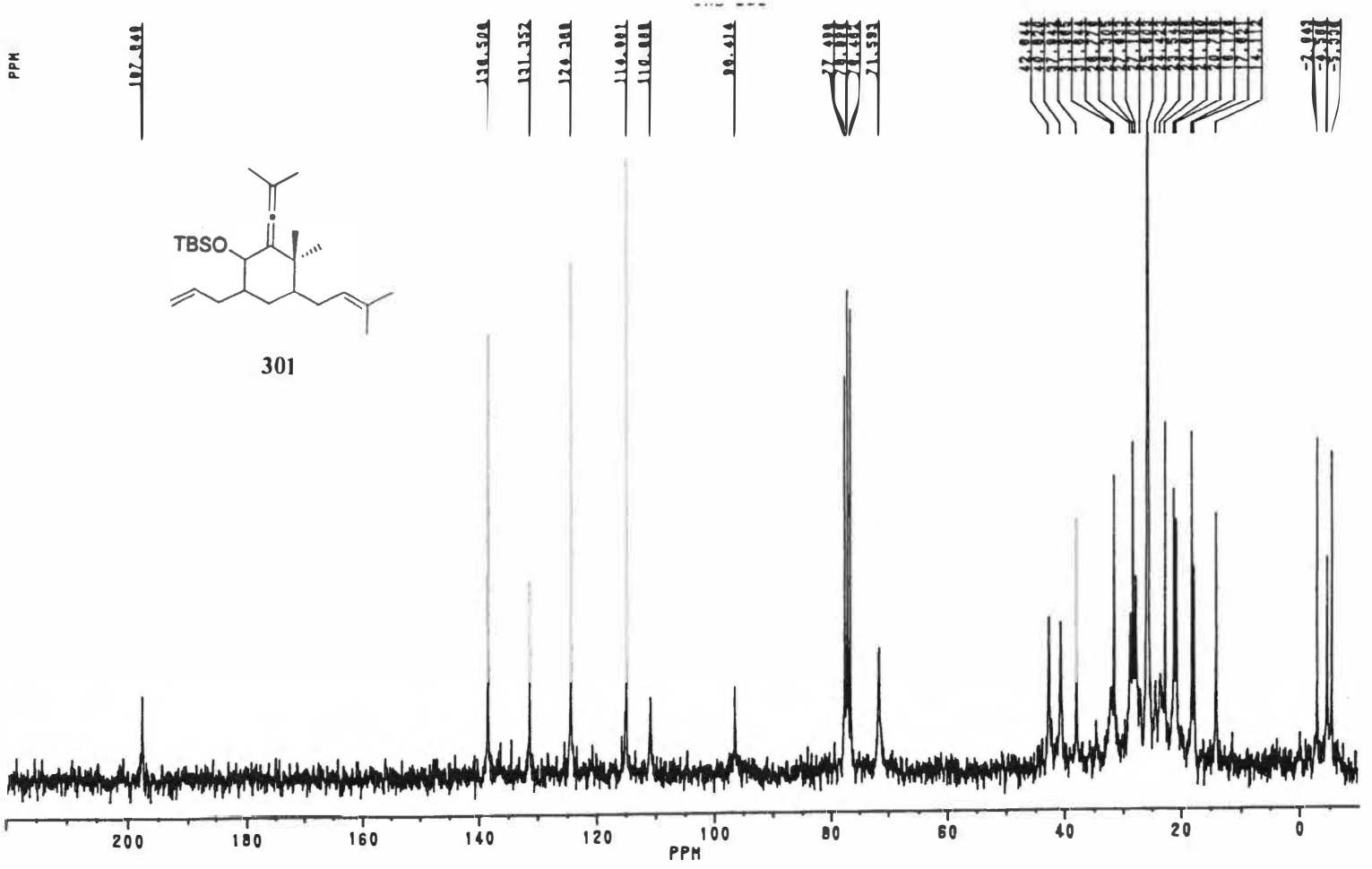

TBDPSO
299
*
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
PPM


TBDPSO
O
O
299
200
180
160
140
120
100
80
60
40
20
0
PPM


HO
300
PPM
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0


HO
300
PPM
200
180
160
140
120
100
80
60
40
20
0
PPM


TBSO
301
PPM
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
10.0


TBSO
301
PPM
200
180
160
140
120
100
80
60
40
20
0

Vita

Joseph Allen Burlison was born in Nashville, TN on August 9, 1977. He was raised in Dickson, TN and then in Fairview, TN. He graduated from Fairview High School in 1995. The same year he attended Belmont University in Nashville, TN and received a B.S. in professional chemistry in 1999. From there, he went to the University of Tennessee, Knoxville and earned a M.S. in 2002 and his Ph.D. in organic chemistry under the direction of Dr. David G. J. Young in 2005. He won the C. W. Keenan Outstanding Graduate Teaching Award in 2003 and a Research Merit Award in 2005.

Joe is currently a postdoctoral research associate at the University of Kansas, Lawrence under the direction of Dr. Brian S. Blagg. He plans to pursue a career in drug design.

4535 0545 8
11/09/05 MAB