To the Graduate Council:
I am submitting herewith a dissertation written by Sarah A. Headrick entitled "Synthetic Studies on Anti-cancer and Anti-HIV Compounds." 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 C. Baker

David C. Baker, Major Professor

We have read this dissertation
and recommend its acceptance:

David D. J. Young

Mark D. Drew

Accepted for the Council:

~~Vice Provost and Dean of~~
Graduate Studies

Synthetic Studies on Anti-cancer and Anti-HIV Compounds

A Dissertation
Presented for the
Doctor of Philosophy
Degree
The University of Tennessee, Knoxville

Sarah Autumn Headrick
August 2003

Thesis
2003b
.H437

DEDICATION

This dissertation is dedicated in loving memory to my mother, Barbara Sanzenbacher and my grandmother, Dolores Sanzenbacher. I would also like to dedicate this to my father, John, my step-mother, Debra, my brothers, Scott and Jeremy, my sister, Kristi, and last but not least, my husband Jeremy.

ACKNOWLEDGEMENTS

I would first like to thank Dr. Baker for the opportunity to work in his group and for all his encouragement and support. I would also like to thank Drs. Dadmun, Young, and Roberts for agreeing to serve on my committee.

I would like to thank all the present and past members of the Baker group for inspiration and encouragement, particularly Riyam Kafri, Karen Welch, Qiang (Jay) Yang, Sean Hamilton, Jeremy Clark and Conrad Kaczmarek. I would also like to thank the Chemistry Department at the University of Tennessee and the NCI for financial support.

I would like to thank my step-mother, father, brothers, sister and grandparents who have listened and encouraged me over my many years here. Without the encouragement of my family, I know I would never have made it. I would also like to thank my husband Jeremy for the love and support he provided through difficult times. Lastly, I would like to thank God.

ABSTRACT

The research discussed in this dissertation focuses on the synthesis and biological evaluation of two families of therapeutic agents.

In 1999 a group of scientists at the National Cancer Institute reported that during a screening of their database they had found an active non-nucleoside reverse transcriptase inhibitor. This compound (NSC-108406) was substantially more potent than the other inhibitors identified during their screening with an IC_{50} of 0.5 ± 0.3 μM. During a cell-based antiviral screen, it was found to provide an EC_{50} of 1.5 ± 1.0 μM. In an effort to increase the potency of the lead, a set of analogs of NSC-108406 was synthesized in our laboratories, providing a compound with an EC_{50} of 0.036 μM.

Hydramycin is a naturally occurring pluramycinone that is a potent antimicrobial and antitumor agent and whose biological activity has created an interest in its synthesis. Our work began with a model study that established a strategy by which the pyranone system and associated functionality could be realized. The route makes use of a novel alkyne and a fluoride-induced ring closure that provided a molecule consisting of a chromenone with the essential moieties analogous to those of hydramycin. The protocol was applied to a compound containing the hydramycin anthraquinone system via a 2-formyl-1-hydroxy anthraquinone that was coupled with an alkyne.

TABLE OF CONTENTS

PART ONE. SYNTHESIS OF SULTAM ANALOGS.

I. Introduction..... 2

A. Overview..... 2

B. Reverse Transcriptase Inhibitors..... 5

C. NSC-108406..... 8

II. Statement of the Problem..... 8

A. Objectives..... 8

B. Research Plan..... 10

C. Significance..... 13

III. Discussion..... 13

IV. Conclusions..... 26

V. Experimental..... 27

A. General Methods..... 27

B. Synthesis of Sultams..... 28

PART TWO. SYNTHESIS OF HYDRAMYCIN ANALOGS

I. Introduction..... 36

A. Anthraquinone History: Example of Alizarin..... 36

B. Anthraquinones and Anticancer Activity..... 40

II. Statement of the Problem..... 45

A. Objectives..... 45

B. Research Plan and Retrosynthesis..... 46

C. Significance..... 46

III. Discussion..... 48

A. Model Compound Synthesis..... 48

1. Initial attempt using a coupling of a methyl ketone derivative and an aldehyde..... 48

2. Second and third model attempts utilizing a coupling of a methyl ketone and an aldehyde..... 53

a. Aldehyde synthesis..... 53

b. Methyl ketone synthesis..... 57

3. Fourth attempt requiring the coupling of 2-(*tert*-butyldimethylsilyloxy)benzaldehyde and an alkyne..... 59

a. Synthesis of the alkyne..... 59

b. Preparation of 2-(*tert*-butyldimethylsilyloxy)benzaldehyde, coupling and further reactions..... 59

4. Fifth attempt using the coupling of *o*-anisaldehyde and alkyne 2.15..... 63

5. Sixth attempt using the coupling of 2-(methoxymethoxy)benzaldehyde and alkyne 2.15..... 65

6. Synthesis of the model compound using the coupling of 2-(methoxymethoxy)benzaldehyde and a new alkyne..... 68
a. Alkyne synthesis..... 68
b. Coupling and further reactions..... 68
7. Synthesis of the model compound using the coupling of 2-*(tert*-butyldimethylsilyloxy)benzaldehyde and alkyne 2.31..... 71
B. Synthesis of the Hydramycin Analog..... 71
1. Attempts to synthesis anthraquinone aldehydes..... 71
2. Successful syntheses of anthraquinone and anthracene aldehydes..... 76
a. Alizarin method..... 76
b. Preparation of 1,8-dimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde..... 79
c. Synthesis of 1-methoxymethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde..... 82
d. Preparation of 1-methoxymethoxy-2-

carbaldehyde..... 84

e. Preparation of 1-hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde using compound 2.56..... 84

3. Initial attempt at analog synthesis using the coupling of aldehyde 2.54 and alkyne 2.15..... 86

4. Second attempt at analog synthesis using the coupling of aldehyde 2.59 and alkyne 2.15..... 86

5. Attempted analog synthesis using the coupling of aldehyde 2.62 and alkyne 2.31..... 90

6. Hydramycin analog synthesis using the coupling of aldehyde 2.60 and 3-methyl-1-penten-4-yn-3-ol..... 90

IV. Conclusions..... 92

V. Proposed Future Work..... 94

VI. Experimental..... 100

A. General Methods..... 100

B. Model Compound Synthesis..... 100

1. Initial attempt using the coupling of a methyl ketone derivative and an aldehyde..... 100

2. Second attempt using the coupling of a methyl ketone and an aldehyde..... 102

a. Aldehyde synthesis..... 102

b. Methyl ketone synthesis..... 106

c. Coupling of the methyl ketone and the aldehyde..... 107

3. Attempted synthesis requiring the coupling of 2-*(tert*-butyldimethylsilyloxy)benzaldehyde and an alkyne..... 108

a. Synthesis of the alkyne..... 108

b. Synthesis of 2-(*tert*-butyldimethylsilyloxy)-benzaldehyde, coupling and further reactions..... 110

4. Attempted synthesis using the coupling of *o*-anisaldehyde and alkyne 2.15..... 113

5. Attempted synthesis using the coupling of 2-(methoxymethoxy)benzaldehyde and alkyne 2.15..... 114

6. Synthesis of the model compound using the the coupling of 2-methoxymethoxybenzaldehyde and a new alkyne..... 118

a. Alkyne synthesis..... 118

b. Coupling and further reactions..... 121

7. Synthesis of the model compound using the coupling

of 2-(*tert*-butyldimethylsilyloxy)benzaldehyde and alkyne 2.31 125

C. Synthesis of Hydramycin Analog 129

1. Attempts to synthesize anthraquinone aldehydes 129

2. Syntheses of anthraquinone and anthracene aldehydes 130

a. Alizarin method 130

b. Synthesis of 1,8-dimethoxy-9,10-dioxo-9,10-dihyroanthracene-2-carbaldehyde 134

c. Preparation of 1-methoxymethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde 138

d. Preparation of 1-methoxymethoxyanthracene-2-carbaldehyde 142

e. Preparation of 1-hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde using compound 2.56 1434

3. Initial attempt at analog synthesis using the the coupling of 1,8-dimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde and alkyne 2.15 145

4. Attempted analog synthesis using the coupling of aldehyde **2.62** and alkyne **2.31**..... 147

5. Analog synthesis using the coupling of aldehyde **2.47** and 3-methyl-1-penten-4-yn-3-ol..... 148

REFERENCES..... 152

APPENDICES..... 159

Appendix A. ^{1}H and ^{13}C NMR Spectra of Sultam Analogs....160

Appendix B. ^{1}H and ^{13}C NMR Spectra of Hydramycin Analogs..... 185

VITA..... 324

LIST OF FIGURES

Figure 1.1. Replication of an HIV Capsule..... 4

Figure 1.2. Some NRTI's..... 6

Figure 1.3. Some NNRTI's..... 7

Figure 1.4. NSC-108406..... 9

Figure 1.5. NSC-108406 (with A, B, and C rings labeled)..... 12

Figure 2.1. The Anthraquinone Skeleton..... 37

Figure 2.2. Anthracycline Skeleton..... 41

Figure 2.3. Adriamycin..... 41

Figure 2.4. Pyranoanthraquinone Skeleton..... 41

Figure 2.5. Pluramycin A..... 42

Figure 2.6. Kidamycin..... 42

Figure 2.7. Hedamycin..... 42

Figure 2.8. Hydramycin..... 44

Figure 2.9. Kapuramycin A_3..... 44

Figure 2.10. Aldehyde complex with TMEDA and BuLi..... 97

LIST OF SCHEMES

Scheme 1.1. Retrosynthesis of Sultam Analogs..... 11

Scheme 1.2. Synthesis of Sultam Analogs..... 14

Scheme 2.1. Alizarin Synthesis..... 39

Scheme 2.2. Retrosynthesis of Hydramycin Analogs..... 47

Scheme 2.3. First Model Compound Retrosynthesis..... 49

Scheme 2.4. First Model Compound Attempt..... 50

Scheme 2.5. Second Model Compoound Retrosynthesis..... 52

Scheme 2.6. Second Model Compound Attempt..... 54

Scheme 2.7. Third Model Compound Retrosynthesis..... 55

Scheme 2.8. Synthesis of Aldehyde **2.9**..... 56

Scheme 2.9. Third Model Compound Attempt..... 57

Scheme 2.10. Final Model Compound Retrosynthesis..... 60

Scheme 2.11. Synthesis of Alkyne **2.15**..... 61

Scheme 2.12. Fourth Model Compound Attempt..... 62

Scheme 2.13. Fifth Model Compound Attempt..... 64

Scheme 2.14. Sixth Model Compound Attempt..... 66

Scheme 2.15. Synthesis of Alkyne **2.31**..... 67

Scheme 2.16. First Model Compound Synthesis..... 70

Scheme 2.17. Second Model Compound Synthesis..... 72

Scheme 2.18. Attempted Synthesis of Anthraquinone Aldehydes by Formylation Reactions..... 73

Scheme 2.19. Attempted Synthesis of Anthraquinone Aldehydes Using Formaldehyde..... 73

Scheme 2.20. Attempt to Synthesize Anthraquinone Aldehydes Using a Claisen Rearrangement..... 74

Scheme 2.21. Attempt to Synthesize Anthraquinone Aldehydes by the Stille Reaction..... 77

Scheme 2.22. Preparation of Aldehyde **2.47** by the Alizarin Method..... 78

Scheme 2.23. Attempt to Synthesize TBS protected Anthraquinone Aldehydes..... 80

Scheme 2.24. Preparation of Aldehyde **2.54**..... 81

Scheme 2.25. Preparation of Aldehyde **2.59**..... 83

Scheme 2.26. Preparation of Aldehyde **2.62**..... 85

Scheme 2.27. Preparation of Aldehyde **2.47** using Compound **2.56**..... 87

Scheme 2.28. First Hydramycin Analog Attempt..... 88

Scheme 2.29. Second Hydramycin Analog Attempt..... 89

Scheme 2.30. Third Hydramycin Analog Attempt..... 91

Scheme 2.31. Synthesis of the Hydramycin Analog..... 93

Scheme 2.32. Proposed Synthesis of Amide **2.78**..... 96

Scheme 2.33. Proposed Syntheses of 1,8-Dihydroxyanthraquinone Analogs..... 99

Scheme 2.34. Proposed Syntheses of Anthrarufin Analogs..... 99

LIST OF TABLES

Table 1.1. Biological Data for Sultams **1.4a–g** Synthesized by the Author..15

Table 1.2. Biological Data for Sultams Synthesized in the Group.....16

Table 1.3. Experimental Data for Carbinol Sulfonamides **1.3a–g** Synthesized by the Author..... 30

Table 1.4. NMR Data for Carbinol Sulfonamides **1.3a,b** and **f** Synthesized by the Author..... 31

Table 1.5. Experimental Data for Sultams **1.4a–g** Synthesized by the Author.....32

LIST OF ABBREVIATIONS

AIDS	Acquired Immunodeficiency Syndrome
Bn	Benzyl
BPSP	Bis(pyridine) silver permanganate
n-BuLi	*n*-Butyllithium
CNS	Central nervous system
m-CPBA	3-Chloroperbenzoic acid
DIPEA	*N, N*-Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DNA	Deoxyribonucleic acid
EC_{50}	50% Effective concentration
EtOAc	Ethyl acetate
EtOH	Ethanol
HIV	Human immunodeficiency virus
IC_{50}	50% Inhibitory concentration
iPrOH	Isopropanol
LDA	Lithium diisopropylamide
MeMgBr	Methylmagnesium bromide
MeOH	Methanol
MOM	Methoxymethyl

MOMCl	Chloromethyl methyl ether
NaOEt	Sodium ethoxide
NaOMe	Sodium methoxide
NBS	*N*-Bromosuccinimide
NCI	National Cancer Institute
NMR	Nuclear magnetic resonance
NNRTI	Non-nucleoside reverse transcriptase inhibitor
NRTI	Nucleoside reverse transcriptase inhibitor
PivCl	Trimethylacetyl chloride
RNA	Ribonucleic acid
RT	Reverse transcriptase
Ru(cot)Cl	Ruthenium(II) chloride 1,5-cyclooctatriene complex
TEA	Triethylamine
Tf	Trifluoromethanesulfonic
Tf_2O	Trifluoromethanesulfonic anhydride
TBS	*tert*-Butyldimethylsilyl
TBSCl	*tert*-Butyldimethylsilyl chloride
THF	Tetrahydrofuran
TLC	Thin-layer chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine
TMS	Trimethylsilyl
TMSI	Trimethylsilyl iodide

UV	Ultraviolet

PART ONE

SYNTHESIS OF SULTAM ANALOGS

I. Introduction

A. Overview

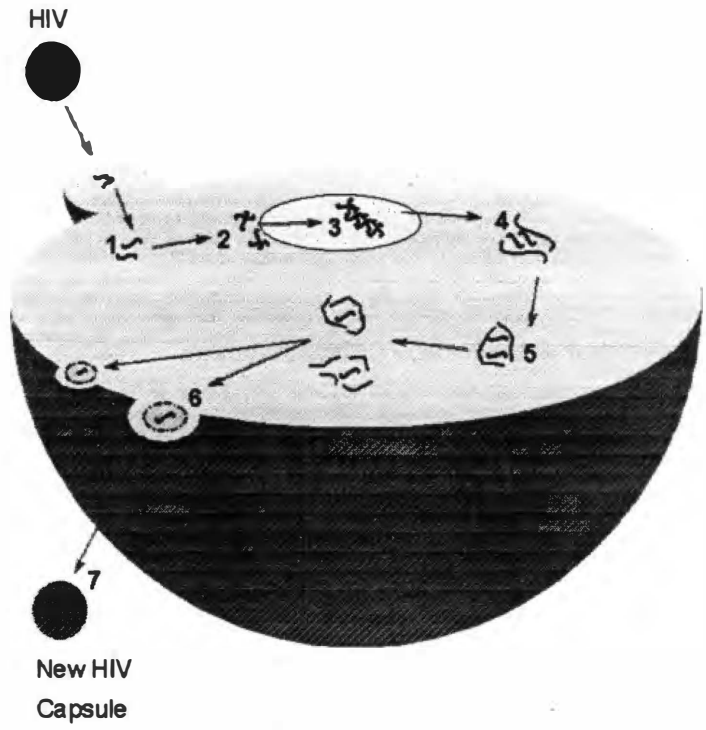
Today, close to 70 million people are infected with and more than 20 million are dead from the sinister disease that we call AIDS.[1] AIDS was first identified in 1981 as an immunodeficiency condition among very sexually active, young gay men.[2] The emergence of AIDS of course brought about the question of cause. The answer to that question came in the form of results from two separate laboratories, those of Luc Montagnier, who was at the Pasteur Institute in France and Robert Gallo of the National Cancer Institute (Maryland).[2-4] Montagnier was the first to report the discovery of HIV, the virus that is the cause of AIDS. Soon thereafter, Gallo's group proved that the virus reported by Montagnier was the cause of AIDS. Finally, Gallo's group developed a blood test for detecting HIV, a discovery of great importance as it prevented the transfusion of tainted blood[2]. Remarkably, it had only been 2.5 years since the identification of the disease when the cause of AIDS was determined and only two years after that, blood tests had become commercially available.[3]

The first drug to combat HIV called AZT was introduced in 1987. To date, sixteen antiretroviral drugs have been approved by the U.S. FDA for the treatment of HIV.[5] All of these drugs serve to either inhibit the protease or reverse transcriptase enzymes, both of which are key enzymes in the HIV replication cycle. Initial studies have shown that a cocktail treatment that

combined the use of a protease inhibitor and two different kinds of reverse transcriptase inhibitors appeared to stop the effects of HIV.[5,6] However, in time, resistance to the drugs developed, and the HIV resistant strains were being rapidly transmitted from partner to partner.[5] The emergence of these resistant strains resulted in the need for more drugs of this nature that could be used in cocktail therapy. Also, drugs that were active against the resistant strains were necessary. This dissertation presents one synthesis of a family of novel compounds that have proved to be active against HIV reverse transcriptase.

Before one can understand the methods by which anti-HIV drugs work, one must understand the process involved in the replication of an HIV capsule. This process is outlined in Figure 1.1.[7] First of all, HIV is an RNA virus, that is, it essentially is made up of a single strand of RNA that is encapsulated in a protein cover. This HIV capsule will attach itself to the host cell and release its genetic material (RNA) into that cell. Next, the enzyme HIV-RT will convert the viral RNA by reverse transcription into complementary DNA. The integrase enzyme will next splice the new viral DNA into the chromosomes of the host cell. This cell will now act as a virus factory, producing more viral RNA and other viral constituents. The protease enzyme will then cut the viral proteins and these proteins will fold together to form a new HIV capsule that is released into the body. This capsule will then serve to attack other host cells.

At this point, the only enzymes targeted by drugs on the market are reverse transcriptase and protease. There are 12 more drugs that are



1. **HIV attaches to receptors on host cell, releasing its genetic material as RNA.**

2. **An enzyme called reverse transcriptase (RT) makes use of the HIV RNA to create a complementary strand of DNA. Drugs called RT inhibitors can interrupt this process.**

3. **An enzyme called integrase splices the viral DNA into the host cell's chromosomes. Scientists hope to develop a new class of drugs called integrase inhibitors, which will add another obstacle.**

4. **The infected cell produces new viral RNA, which generates proteins and other virus constituents.**

5. **The protease enzyme cuts the viral proteins into shorter pieces. Protease inhibitors foil replication by neutralizing the enzyme. They are even therapeutically more effective when combined with RT inhibitors.**

6. **The newly milled proteins fold together to form new HIV capsules.**

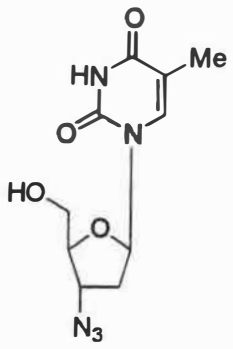
Figure 1.1. Replication of an HIV Capsule

presently in clinical trials, some which target reverse transcriptase or protease, but there are others that target the integrase enzyme and receptors that allow the HIV capsule entry into a host cell.[5] These drugs help to provide hope that the increase of drugs available will result in fewer HIV-related deaths.

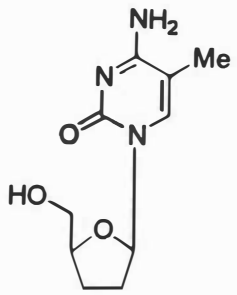
B. Reverse Transcriptase Inhibitors

Presently, twelve of the sixteen drugs on the market are reverse transcriptase inhibitors.[5] Of these, there are two different kinds of inhibitors, nucleoside reverse trancriptase inhibitors (NRTI) and non-nucleoside reverse transcriptase inhibitors (NNRTI). These two classes of compounds work in different ways to debilitate the enzyme. The NRTI's are a class of compounds which bind directly to the catalytic site of the enzyme. These compounds are competitive inhibitors and they will incorporate into the growing DNA chain that is being generated by the enzyme. Once incorporated, they will stop the growth of the chain.[8] Figure 1.2 depicts some NRTI compounds presently on the market.[5]

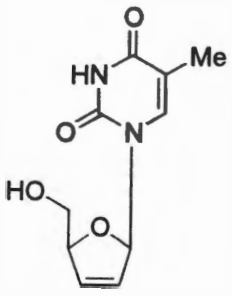
NNRTI's bind to a hydrophobic pocket in the enzyme that is in close proximity to the catalytic site. X-ray crystallography has shown that these compounds all tend to maintain a similar "butterfly-like" conformation when they are in the binding pocket. They appear to serve as π-donors to the aromatic side-chains which surround the binding pocket.[6] This site will then have an influence on the catalytic site.[8] See Figure 1.3 for



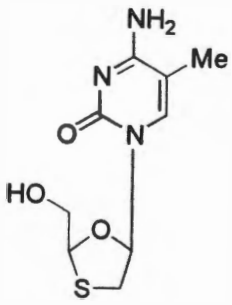
AZT



ddC

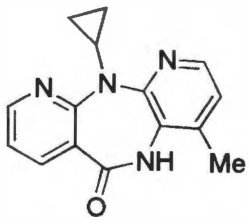


d4T

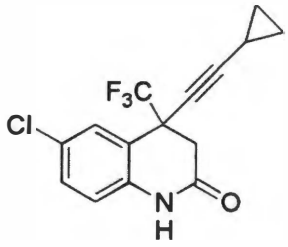


3TC

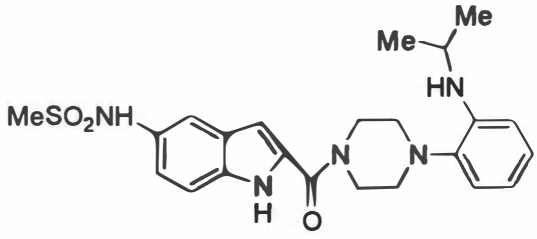
Figure 1.2. Some NRTI's



Nevirapine



Efavirenz



Delavirdine

Figure 1.3. Some NNRTI's

structures of some NNRTI's that are being administered today.[5]

C. NSC-108406

In 1996, a paper was published detailing a molecular model of nevirapine in the NNRTI pocket of HIV-1 RT.[9] This model provided a set of pharmacophore points that would be necessary for optimum binding of a substrate to the HIV-1 neviripine–binding pocket. This information was then used in 1999 by a group of scientists at the National Cancer Institute to search the NCI database for other potential NNRTI's. Two such searches were carried out. The first search resulted in 30 possible active compounds. These were tested for inhibition of HIV-1 RT and three compounds showed clear activity. The second search resulted in the testing of 195 compounds. These were also submitted for testing and only three compounds of this group had an IC_{50} value of less than 10 μM.[10]

One compound (NSC-108406) of the six identified was found to be substantially more potent than the other inhibitors identified during their screening with an IC_{50} of 0.5 ± 0.3 μM (Figure 1.4). During a cell-based antiviral screen, it was found to provide an EC_{50} of 1.5 ± 1.0 μM. The need for synthesis of this and similar compounds was apparent.

II. Statement of the Problem

A. Objectives

As can be seen from the information provided in the introduction section of Part One, there is a constant need for the synthesis of new anti-HIV

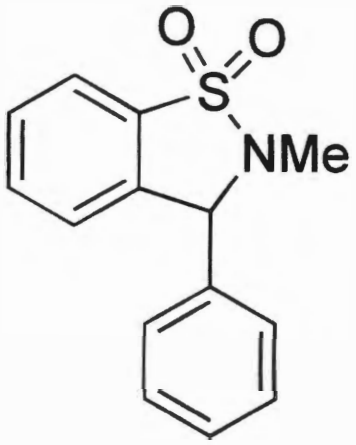


Figure 1.4. NSC-108406

compounds to provide compounds to replace those to which HIV develops a resistance. Since NSC-108406 proved to be a very viable lead compound, the synthesis of its analogs was necessary. The objectives of this chapter are as follows:

•To synthesize novel NSC-108406 derivatives.

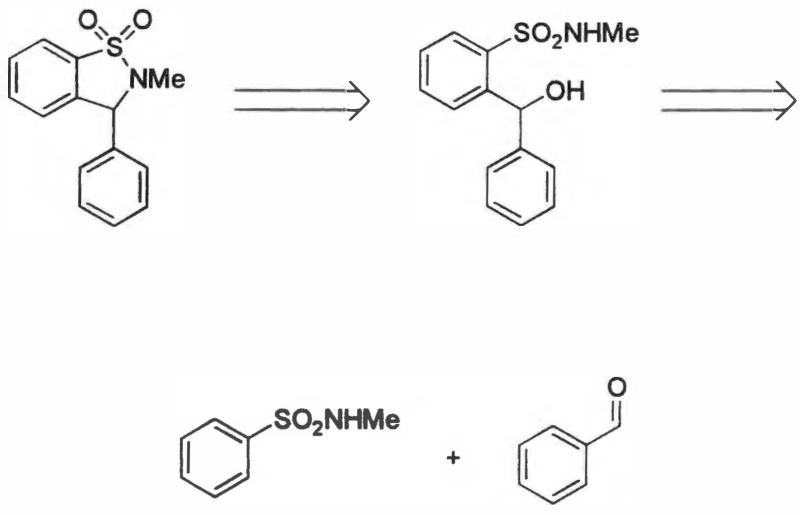
•To test the compounds for biological activity against HIV-1 and use this information to develop structure–activity relationship.

•To determine what variations of the lead compound will provide the greatest increase in activity against HIV.

B. Research Plan

The retrosynthesis for the sultam compounds is given in Scheme 1.1. It is essentially the method used by Watanabe for the synthesis of the lead compound.[11] The compounds can be made in racemic form in three very simple steps.

In modifying the lead compound, there were a number of choices available. The lead compound shown in Figure 1.5 contained three rings, two phenyl rings (the A and C rings) and a heterocyclic 5-membered ring (the B ring). This allows for a host of modifications. The initial modifications were done on the A-ring as this was suggested to our group by the molecular modeling staff at the NCI. (Note that these modifications were done previous to the author's participation in the project). Subsequently, substitution on the B and C rings was



Scheme 1.1. Retrosynthesis of Sultam Analogs

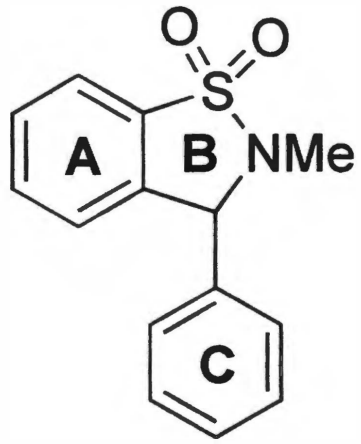


Figure 1.5. NSC-108406 (with A, B and C rings labeled)

explored.

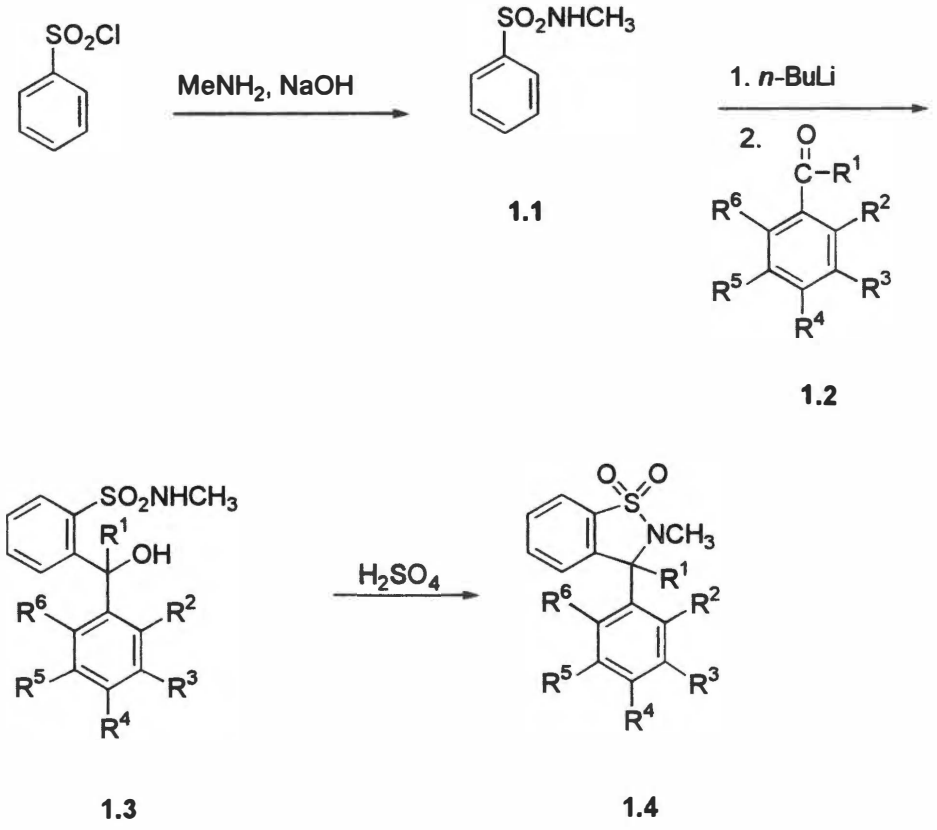
C. Significance

This project would serve to not only provide novel, potent anti-HIV drugs, but it should also serve to determine what kind of variations on the lead compound would give active compounds. This information could be vital in the ongoing effort to develop new anti-HIV drugs.

III. Discussion

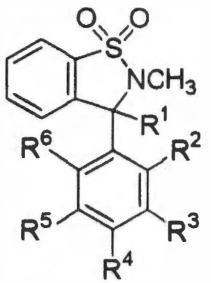
Synthesis of the racemic sultam compounds began as commercially available benzenesulfonyl chloride was reacted with sodium hydroxide and methylamine to produce *N*-methylbenzenesulfonamide (Scheme 1.2). The sulfonamide could then be ortho-lithiated using *n*-BuLi and condensed with various benzaldehydes producing carbinol sulfonamides **1.3a–g**. Yields for this reaction varied from 38% to 80%. An acid catalyzed ring closure of the carbinol sulfonamides with concd H_2SO_4 served to provide the racemic sultams **1.4a–g** in yields ranging from 54% to 91%.

There were seven sultams that were synthesized by the author. These compounds and their activities are depicted in Table 1.1. Table 1.2 lists all of the other sultams synthesized in our laboratories. The results give a very general view of what kind of variations on the original sultam resulted in more active compounds. The molecular modeling staff at the NCI initially supported modification on the A-ring of the compound to increase activity. However, these



Scheme 1.2. Synthesis of Sultam Analogs

Table 1.1. Biological Data for Sultams 1.4a–g Synthesized by the Author



Cmpd	R^1	R^2	R^3	R^4	R^5	R	EC_{50} (μM)	IC_{50} (μM)	TI_{50}	% Yield
1.4a	CH_3	H	H	H	H	H	4.52	117	25.9	69
1.4b	H	H	H	Br	H	H	11.02	36.8	3.34	91
1.4c	H	H	F	H	H	H	0.173	66.7	385	69
1.4d	H	H	CH_3	H	H	H	0.036	>200	>556	48
1.4e	CH_3	H	Cl	H	H	H	0.198	32.4	164	74
1.4f	H	H	CF_3	H	H	H	0.653	48	73.5	71
1.4g	H	F	F	F	F	F	40.2	>198	4.93	54

Table 1.2. Biological Data for Sultams Synthesized in the Group

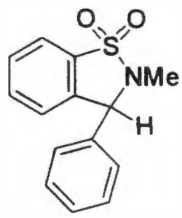
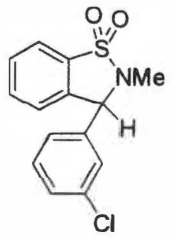
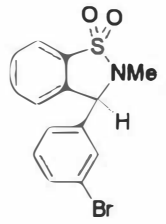
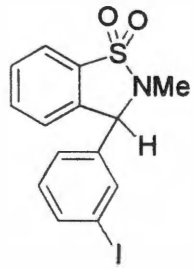
Cmpd #	Structure	EC_{50} (μM)	IC_{50} (μM)	Activity
1.5				
	±	1.5	0.5	A
	(S)	0.471	>316	A
1.6				
	±	0.38	113	A
	(S)	0.086	>2	A
	(R)	5.28	26.8	M
1.7				
	±	0.781	45.6	A
	(S)	0.074	101	A
1.8				
	±	38.7	>30	A

Table1.2 continued

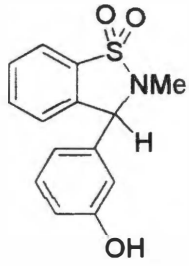
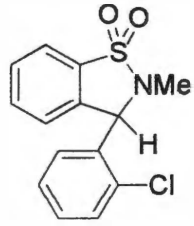
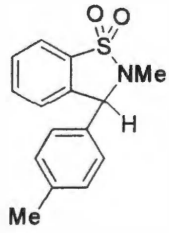
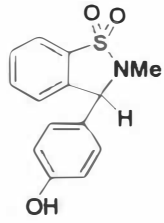
Cmpd #	Structure	EC_{50} (μM)	IC_{50} (μM)	Activity
1.9				
	±	38.7	>30	M
1.10				
	±	0.093	>11	A
1.11				
	(S)	153	138	A
	(R)	-	-	I
1.12				
	±	-	>200	I
	(S)	-	>200	I
	(R)	-	>200	I

Table 1.2 continued

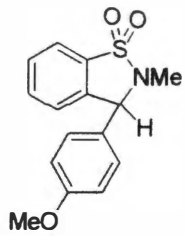
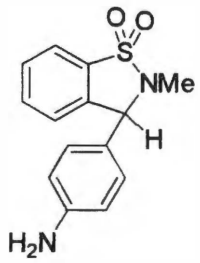
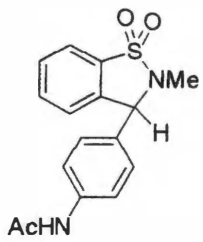
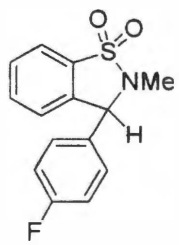
Cmpd #	Structure	EC_{50}(μM)	IC_{50}(μM)	Activity
1.13				
	(S)	-	>200	I
	(R)	-	>200	I
1.14				
	±	65	>200	I
1.15				
	±	-	>200	I
1.16				
	±	37.5	161	M

Table 1.2 Continued

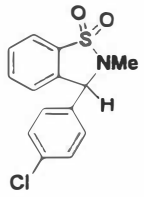
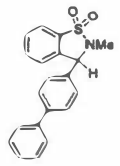
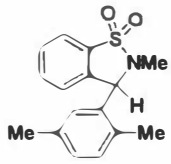
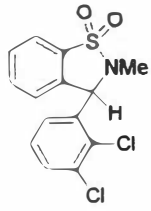
Cmpd #	Structure	EC_{50}(μM)	IC_{50}(μM)	Activity
1.17				
	±	19.6	29	I
1.18				
	±	-	>200	I
1.19				
	±	0.512	>200	I
1.20				
	±	0.039	>200	A

Table1.2 continued

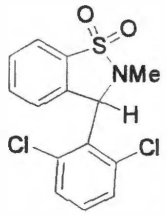
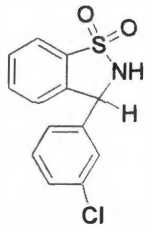
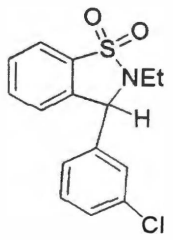
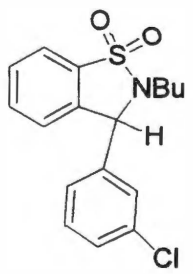
Cmpd #	Structure	$EC_{50}(\mu M)$	$IC_{50}(\mu M)$	Activity
1.21				
	±	5.09	10.9	M
1.22				
	±	33.8	427	M
1.23				
	±	0.167	39.7	A
1.24				
	±	1.35	18.2	M

Table 1.2 continued

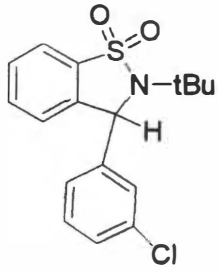
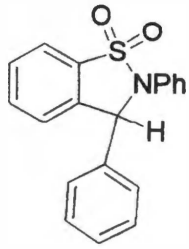
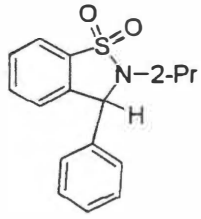
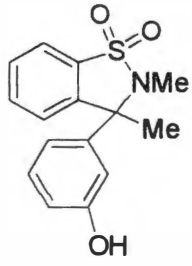
Cmpd #	Structure	EC_{50}(μM)	IC_{50}(μM)	Activity
1.25				
	±	-	>200	I
1.26				
	±	-	>200	I
1.27				
	±	0.198	32.4	A
1.28				
	±	30.7	>200	M

Table 1.2 continued

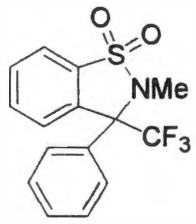
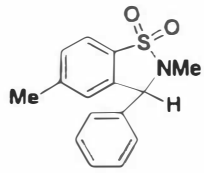
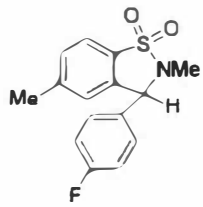
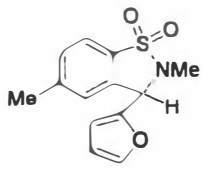
Cmpd #	Structure	EC_{50}(μM)	IC_{50}(μM)	Activity
1.29				
	±	0.46	31.8	A
1.30				
	±	31	156	M
1.31				
	±	-	76.9	I
1.32				
	±	-	>200	I

Table 1.2 continued

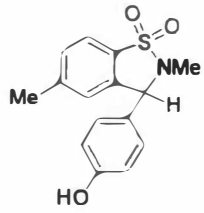
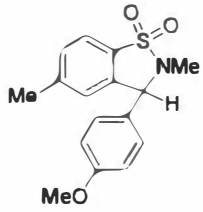
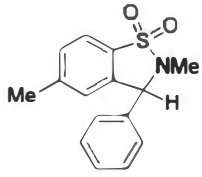
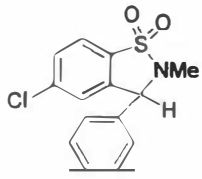
Cmpd #	Structure	$EC_{50}(\mu M)$	$IC_{50}(\mu M)$	Activity
1.33				
	±	-	>140	I
1.34				
	±	-	>200	I
1.35				
	±	-	107	I
1.36				
	±	26.1	>147	M

Table 1.2 continued

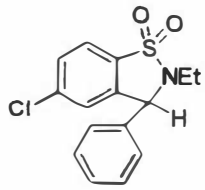
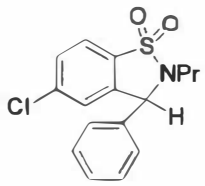
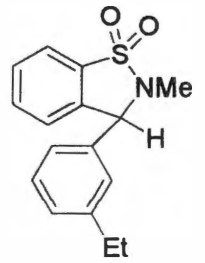
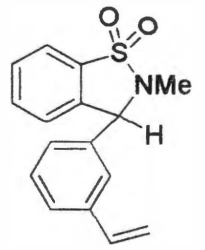
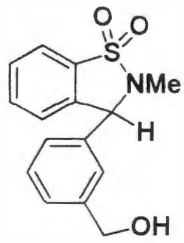
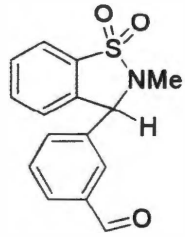
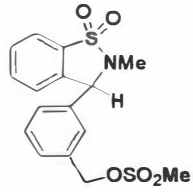
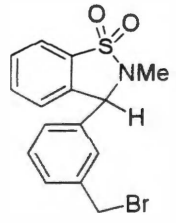
Cmpd #	Structure	$EC_{50}(\mu M)$	$IC_{50}(\mu M)$	Activity
1.37				
	±	19.3	60.6	M
1.38				
	±	-	365	I
1.39				
	(S)	0.12	25	A
1.40				
	(S)	0.86	4.28	A

Table 1.2 continued

Cmpd #	Structure	$EC_{50}(\mu M)$	$IC_{50}(\mu M)$	Activity
1.41	 (S)	6.04	>200	A
1.42	 (S)	1.41	31.55	A
1.43	 (S)	1.92	72	A
1.44	 (S)	0.9	3.07	A

*A = Active, I = Inactive, M = Moderately Active

modifications did not produce a positive result. A-ring modification was found to generally lower activity. Substitution of the B-ring provided some positive results at times as compounds **1.4a** and **1.4e** were both found to have moderate activity. C-ring substitution gave varying results. Compound **1.4b** contained a bromo-group in the para position of the sultam and was found to be moderately active. However, movement of the bromo-group to the meta position in compound **1.7** yielded a very active compound with an EC_{50} of 0.074 μM. This gave some insight into structure–activity relationships. Obviously, the most active position on the C-ring was the meta-position. The meta-position was thoroughly investigated, and it was found that while the meta-hydroxyl compound **1.9** gave moderate activity, the most active compounds resulted from less polar groups. Compounds containing halogens in the meta-position all proved active as can be seen from compounds **1.4c**, **1.6**, **1.7**, and **1.8**. It is interesting to note from the information provided by compound **1.44** that a larger group containing a halogen decreases activity. The most active sultam was the meta-methyl compound **1.4d** that provided an EC_{50} value of 0.036 μM. Once again, by comparison with sultam **1.39**, it is clear that larger meta-substituents with the same general polarity and electronegativity tend to result in lowered activity.

IV. Conclusions

There were nine novel sultams provided by the author. Of these nine, compounds **1.4c**,**1.4d**, **1.4e** and **1.4f** all proved to be more active than the lead

compound and **1.4d** proved to be the most active compound of the series. As a general rule, it was learned that sultams containing relatively small, nonpolar substituents in the meta-position of the C-ring provided the most activity. The meta-methyl sultam **1.4d** was the most active sultam with an EC_{50} of 0.036 μM.

V. Experimental

A. General Methods.

Melting points were determined by the capillary method and are uncorrected. Analytical TLC was performed on aluminum-backed plates coated with E. Merck Silica Gel-60 F-254. The developed plates were air-dried and detection was with UV light (254 nm). Column chromatography was performed on Silica Gel-60 (40–63 mesh). ^{1}H NMR and ^{13}C NMR spectra were acquired at 250.13 MHz and 62.89 MHz, respectively, on a Bruker AC 250 instrument or at 300.087 MHz and 75.464 MHz on a Varian MERCURY 300 instrument. ^{1}H NMR chemical shifts are reported as δ (ppm) downfield from tetramethylsilane (TMS), which was used as an internal standard. ^{13}C NMR chemical shifts are reported as δ (ppm) relative to the solvent ($CDCl_3$, 77.0 ppm). Elemental analyses were carried out by Atlantic Microlab, Inc. of Atlanta, GA. Chemicals were of reagent grade and used directly. THF was dried using sodium and benzophenone as an indicator, CH_2Cl_2 was dried over CaH_2.

B. Synthesis of Sultams

Preparation of *N*-methylbenzenesulfonamide (1.1).

To a solution containing 6.5 mL of *N*-methylamine in 60–65 mL of water was added 3.22 g (80.5 mmol) of NaOH, and the solution was cooled to 0 °C. Benzenesulfonyl chloride (10.3 mL, 80.7 mmol) was added over a period of 2 to 3 min, and the solution was stirred for 3 h. The solution was then warmed to RT and extracted with EtOAc. The organic layer was washed with brine, dried with $MgSO_4$ and concentrated. The crude product was purified by column chromatography using 3:1 hexanes–EtOAc as an eluent to yield 7.46 g (55%) of *N*-methylbenzenesulfonamide **1.1**. ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H), 5.17 (br s, 1H), 7.50 (m, 3H), 7.83 (d, J = 6.9 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 29.50, 127.39, 129.38, 132.98, 138.76. The NMR data matched that reported.[12]

Condensations of *N*-methylbenzenesulfonamide with Ketones 1.2a–gand Aldehydes to form Carbinol Sulfonamides.

To a solution of sulfonamide **1.1** (1 g, 5.84 mmol) dissolved in 23 mL of THF and cooled to 0 °C was added 5.8 mL of a 2.5 M solution (14.5 mmol) of *n*-BuLi. The reaction was stirred for 25 min at 0 °C. To the solution was added 9.35 mmol of the ketone or aldehyde **1.2a–g** dissolved in 9.4 mL of THF. The reaction was stirred for 45 min and quenched with 5% HCl . Upon warming to RT, the layers were separated and the aqueous layer was extracted with ether. The combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated. The resulting product was subjected to silica gel chromatography using 3:1

hexanes–EtOAc. Specific reaction conditions and yields are presented in Table 1.3. NMR data for compounds **1.3a**, **1.3b** and **1.3f** are listed in Table 1.4.

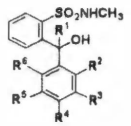
Cyclodehydrations of Carbinol Sulfonamides to Form Sultams 1.4a–g. The carbinol sulfonamide **1.3a–g** (200 mg) was dissolved in 2 mL of concd H_2SO_4 and stirred at room temperature. After 2 h, the solution was poured over ice. The solution was then extracted three times with CH_2Cl_2 (25 mL), and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated. Specific reaction conditions and yields are listed in table 1.5.

2,3-Dimethyl-3-phenyl-2,3-dihydrobenzo[d]isothiazole 1,1-dioxide (1.4a). mp: 170 °C. ^{1}H NMR ($CDCl_3$) δ 1.67 (s, 3H), 2.58 (s, 3H), 6.99 (m, 1H), 7.27 (m, 6H), 7.411 (m, 2H), 7.75 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 23.08, 67.35, 121.00, 124.13, 126.82, 128.26, 128.80, 128.92, 132.96, 133.04, 140.17. Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.90; H, 5.53; N, 5.12; S, 11.73. Found: C, 65.84; H, 5.59; N, 5.02; S, 11.61.

3-(4-Bromophenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (1.4b). ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 5.15 (s, 1H), 7.02 (m, 1H), 7.23 (d, 2H), 7.54 (d, 4H), 7.85 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 27.43, 66.33, 121.16, 123.28, 124.66, 129.53, 129.74, 131.94, 132.37, 133.04, 134.01, 134.89, 135.80, 137.71. Anal. Calcd for $C_{14}H_{12}BrNO_2S$: C, 49.72; H, 3.58; N, 4.14; S, 9.48. Found: C, 49.52; H, 3.60; N, 4.26; S, 9.52.

3-(3-Fluorophenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (1.4c). mp: 127 °C. ^{1}H NMR ($CDCl_3$) δ 2.79 (s, 3H), 5.20 (s, 1H), 7.07 (m, 3H),

Table 1.3. Experimental Data for Carbinol Sulfonamides 1.3a–g Synthesized by the Author

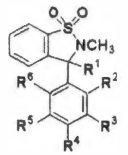


Cmpd	R^1	R^2	R^3	R^4	R^5	R^6	Amt. of 1.1 Used (mmol)	Yield (mmol)	% Yield
1.3a	CH_3	H	H	H	H	H	1.0 g (5.84)	0.83 g (2.85)	49
1.3b	H	H	H	Br	H	H	1.0 g (5.84)	1.35 g (3.80)	65
1.3c	H	H	F	H	H	H	0.5 g (2.92)	0.60 g (2.03)	70
1.3d	H	H	CH_3	H	H	H	0.5 g (2.92)	0.58 g (1.99)	68
1.3e	CH_3	H	Cl	H	H	H	1.0 g (5.84)	0.72 g (2.21)	38
1.3f	H	H	CF_3	H	H	H	1.0 g (5.84)	1.61 g (4.67)	80
1.3g	H	F	F	F	F	F	1.0 g (5.84)	1.29 g (3.51)	60

Table 1.4. NMR Data for Carbinol Sulfonamides 1.3a, b, and f Synthesized by the Author

Cmpd	NMR Data
1.3a	**^{1}H NMR ($CDCl_3$)** δ 1.95 (s, 3H), 2.16 (d, *J* = 5.3 Hz, 3H), 2.95 (broad s, 1H), 5.76 (s, 1H), 7.31 (m, 5H), 7.46 (t, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.5 Hz, 1H), 7.75 (d, *J* = 7.8 Hz, 1H), 8.11 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR ($CDCl_3$)** δ 29.42, 32.86, 125.70, 127.46, 127.80, 128.41, 129.58, 132.80, 136.07, 145.90, 148.17.
1.3b	**^{1}H NMR ($CDCl_3$)** δ 2.54 (d, *J* = 5.2 Hz, 3H), 3.60 (d, *J* = 4.3 Hz, 1H), 4.93 (d, *J* = 5, 1H), 6.66 (d, *J*= 4 Hz, 1H), 7.23 (d, *J* = 8.0 Hz, 3H), 7.45 (m, 4H), 7.97 (d, *J* = 7.5 Hz, 1H). **^{13}C NMR ($CDCl_3$)** δ 29.36, 71.09, 121.77, 128.12, 128.59, 130.04, 130.53, 130.61, 133.11, 136.50, 140.83, 141.4.
1.3f	**^{1}H NMR ($CDCl_3$)** δ2.56 (d, *J* = 5.4 Hz, 3H), 3.91 (d, *J* = 4.8 Hz, 1H), 5.15 (d, *J* = 5.1 Hz, 1H), 6.76 (d, *J* = 4.2 Hz, 1H), 7.13 (dd, *J* = 1.2 and 6.6 Hz, 1H), 7.52 (m, 6H), 7.95 (dd, *J* = 1.8 and 5.7 Hz, 1H). **^{13}C NMR ($CDCl_3$)** δ29.56, 71.02, 124.18 (q, *J* = 3.47 Hz, 1H), 128.51, 129.18, 130.16, 130.55, 130.76, 130.89, 131.19, 133.53

Table 1.5. Experimental Data for Sultams 1.4a–g Synthesized by the Author



Cmpd	R^1	R^2	R^3	R^4	R^5	R^6	Amt. of 1.3 used (mmol)	Yield (mmol)	% Yield
1.4a	CH_3	H	H	H	H	H	0.20 g (0.69)	0.13 g (0.48)	69
1.4b	H	H	H	Br	H	H	0.10 g (0.28)	0.086 g (0.26)	91
1.4c	H	H	F	H	H	H	0.10 g (0.34)	0.065 g (0.23)	69
1.4d	H	H	CH_3	H	H	H	0.20 g (0.69)	0.09 g (0.33)	48
1.4e	CH_3	H	Cl	H	H	H	0.39 g (1.24)	0.27 g (0.91)	74
1.4f	H	H	CF_3	H	H	H	0.42 g (1.21)	0.52 g (1.49)	71
1.4g	H	F	F	F	F	F	1.00 g (2.72)	0.59 g (1.99)	54

7.19 (m, 1H), 7.41 (m, 1H), 7.56 (m, 2H), 7.87 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 27.51, 66.36, 114.86 (d, J = 21.6 Hz), 116.25 (d, J = 21.3 Hz), 121.16, 123.80 (d, J = 2.6 Hz), 124.85, 129.53, 130.77 (d, J = 8.0 Hz), 133.07, 133.95, 139.30 (d, J = 6.4 Hz), 163.20 (d, J = 248.6 Hz). Anal. Calcd for $C_{14}H_{12}FNO_2S$: C, 60.64; H, 4.36; N, 5.05; S, 11.54. Found: C, 60.37; H, 4.43; N, 4.95; S, 11.50.

2-Methyl-3-*m*-tolyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (1.4d). mp: 103 °C. ^1H NMR ($CDCl_3$) δ 2.35 (s, 3H), 2.77 (s, 3H), 5.14 (s, 1H), 7.18 (m, 5H), 7.51 (m, 2H), 7.65 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 21.36, 27.40, 67.00, 121.06, 125.00, 125.34, 128.55, 128.97, 129.25, 129.93, 132.92, 134.04, 136.53, 138.49, 139.05. Anal. Calcd for $C_{15}H_{15}NO_2S$: C, 65.90; H, 5.53; N, 5.12; S, 11.73. Found: C, 66.03; H, 5.63; N, 5.05; S, 11.60.

3-(3-Chlorophenyl)-2,3-dimethyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (1.4e). mp:118-120 °C ^1H NMR ($CDCl_3$) δ 1.93 (s, 3H), 2.68 (s, 3H), 7.06 (m, 1H), 7.29 (m, 3H), 7.42 (m, 1H), 7.54 (m, 2H), 7.85 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 23.02, 23.34, 66.93, 121.28, 124.07, 125.25, 127.04, 128.63, 129.28, 130.22, 132.98, 133.25, 134.95, 142.59, 143.44. Anal. Calcd for $C_{14}H_{12}ClNO_2S$: C, 58.53; H, 4.58; N, 4.55; S, 10.42. Found: C, 58.41; H, 4.57; N, 4.46; S, 10.43.

2-Methyl-3-(3-trifluoromethylphenyl)-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (1.4f). ^1H NMR ($CDCl_3$) δ 2.77 (d, 3H), 5.24 (s, 1H), 7.12 (m, 1H), 7.51 (m,4H), 7.64 (m, 2H), 7.84 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 27.09, 27.95, 28.75, 65.59, 66.12, 67.33, 120.90, 122.14, 122.65, 124.16, 124.84, 125.42, 125.78, 126.05, 126.68, 127.37, 129.06, 129.27, 130.01, 130.21, 130.91, 131.12,

131.63, 132.06, 132.62, 133.49, 134.20, 134.42, 137.59, 137.64, 137.70, 138.22, 138.25. Anal. Calcd for $C_{15}H_{12}F_3NO_2S$: C, 55.04; H, 3.70; N, 4.28 . Found: C, 55.04; H, 3.74; N, 4.21.

2-Methyl-3-pentafluorophenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (1.4g). ^{1}H NMR ($CDCl_3$) δ 2.85 (s, 3H), 5.69 (s, 1H), 7.16 (dd, *J* = 3.4 and 1.9 Hz, 1H), 7.63 (m, 2H), 7.91 (dd, *J* = 3.3 and 2.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 28.25, 56.60, 110.54 (m, 1H), 121.77, 123.70, 130.16, 133.47, 134.38, 134.54, 135.74 (m, 1H), 139.80 (m,1H), 144.04 (m, 1H), 147.91 (m, 1H). Anal. Calcd for $C_{14}H_8F_5NO_2S$: C, 48.14; H, 2.31; N, 4.01; S, 9.18. Found: C, 48.23; H, 2.26; N, 3.97; S, 9.25.

PART TWO

SYNTHESIS OF HYDRAMYCIN ANALOGS

I. Introduction

A. Anthraquinone History: Example of Alizarin

Anthraquinones are a class of compounds commonly found in plants. They contain a fused, three-ring system of the structure shown in Figure 2.1 and tend to be brilliantly colored compounds. The color associated with anthraquinones renders them valuable chemicals for the dye industry. One of the most well-known examples of such a compound is alizarin.

Alizarin was used as a starting material in one of the syntheses to follow and can be found in madder root, a plant that is indigenous to western Asia.[1] The bones of animals who feed on madder become purplish-red as alizarin bonds with calcifying tissue. This fact led to its later use in studies on bone formation.[2]

The madder root was widely used in Holland during the sixteenth century as a dyestuff for textiles. The textile shades of this compound could range from pink to red to purple and black. It was not originally known what was the cause of the colors produced from the madder root; however, in 1827, two frenchmen, Colin and Robiquet discovered a method of producing a concentrated form of the madder called garancine. The process involved heating ground madder with various acids and potash. This resulted in a yellow vapor that crystallized to needles of bright red. The two men named the compound alizarin, from the Levantine term for madder, which was alizari.[1]

The madder root consists of only about one percent alizarin, and chemists

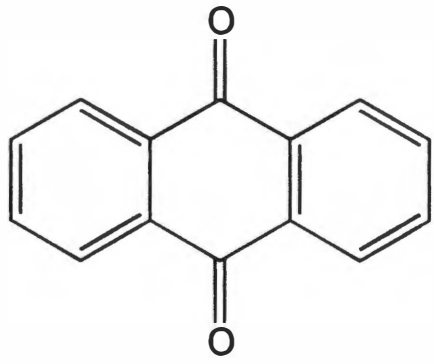
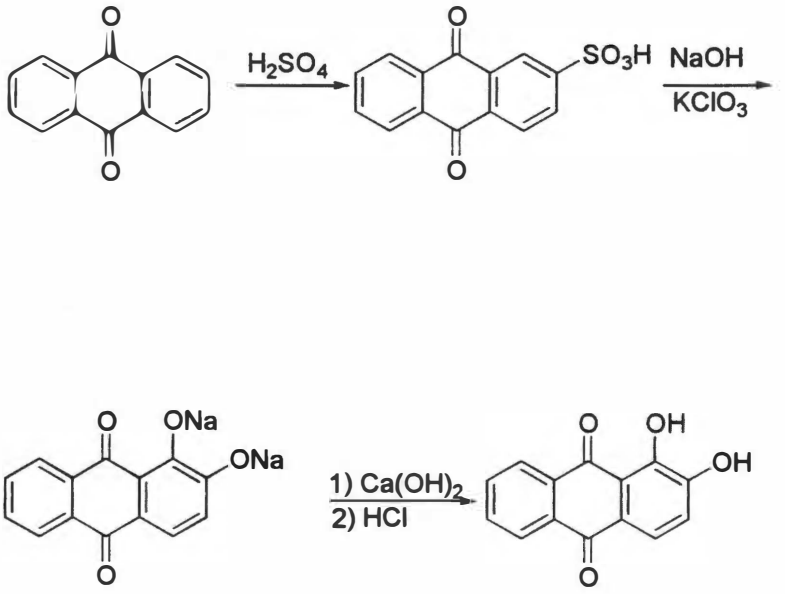


Figure 2.1. The Anthraquinone Skeleton

realized that by learning the correct structure of the substance, they could obtain it more efficiently and in greater purity. A calico printer named Henry Edward Schunck began work with alizarin. He analyzed the material to be $C_{14}H_{10}O_4$, remarkably close to the $C_{14}H_8O_4$ we know it to be today. Schunck oxidized alizarin to give "alizarinic acid," which was later found to be phthalic acid. He knew that this acid was the product obtained through the oxidation of naphthalene and therefore determined naphthalene to be the parent hydrocarbon of alizarin. Work continued along these lines for eighteen years. However, in 1868 two other chemists, Carl Graebe and Carl Liebermann proved that alizarin did not have the naphthalene skeleton, but that of anthracene. They also developed the first synthesis, one in which anthraquinone was first brominated and then hydrolyzed to alizarin. The synthesis required the use of bromine, which was expensive and also prohibited the synthesis from being useful on large scale. (Details are provided from the book, "Mauve" by Simon Garfield[1]).

The search for a new synthesis began. In 1869, Liebermann, Graebe and Heinrich Caro submitted a patent detailing a new method of obtaining alizarin. Just a day later, another patent was filed by William Perkin using a similar synthetic method. The method (Scheme 2.1) began with anthraquinone, which was sulfonated in the 2-position with fuming sulfuric acid. Next, heating the substance with sodium hydroxide and potassium chlorate yielded the disodium salt of alizarin. Finally, calcium hydroxide served to precipitate the compound as



Scheme 2.1. Alizarin Synthesis

its calcium salt, and treatment with hydrochloric acid provided the pure compound.[1,3]

B. Anthraquinones and Anticancer Activity

Anthraquinone compounds are often associated with anticancer activity. These compounds can be of varying structures. Anthracycline compounds (Figure 2.2) contain the anthraquinone system, but also contain a cyclohexane ring at the end of the fused-ring system. One of the most famous anticancer compounds of this type is doxorubicin, also known as adriamycin (Figure 2.3). Adriamycin is currently used for the treatment of various types of cancer. Anthracyclines of this type are known to bind intercalatively to the double helical DNA. The major disadvantage involved with the use of adriamycin is its cardiotoxicity. The drug can result in side effects ranging from delayed cardiomyopathy to irreversible heart failure.[4]

Other anticancer anthraquinone compounds include those of the pluramycin group. Pluramycins are compounds that contain a pyranoanthraquinone structure shown in Figure 2.4 along with one or more *C*-glycosidic groups on the A-ring.[5] This class of compounds includes pluramycin A, kidamycin and hedamycin (Figures 2.5–2.7), all of which are active against cancer.[6] This type of compound has been shown to also bind intercalatively with DNA like the anthracyclines. However, when an epoxide group is present, they also serve to alkylate DNA on N-7 of guanine.[7]

Another anthraquinone compound that is active against cancer was

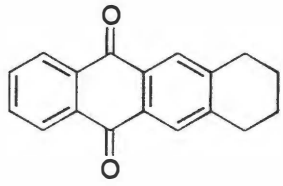


Figure 2.2. Anthracycline Skeleton

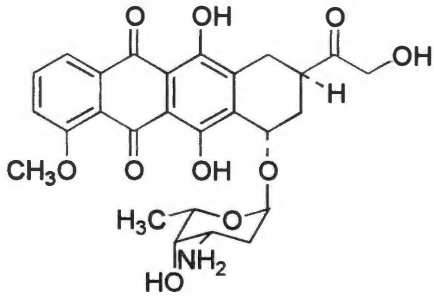


Figure 2.3. Adriamycin

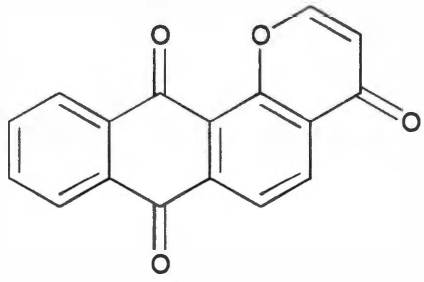


Figure 2.4. Pyranoanthraquinone Skeleton

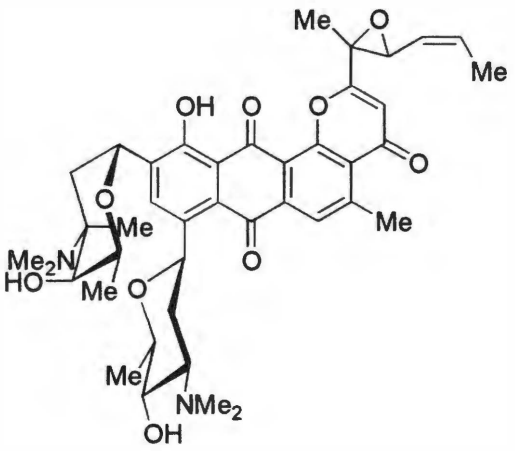


Figure 2.5. Pluramycin A

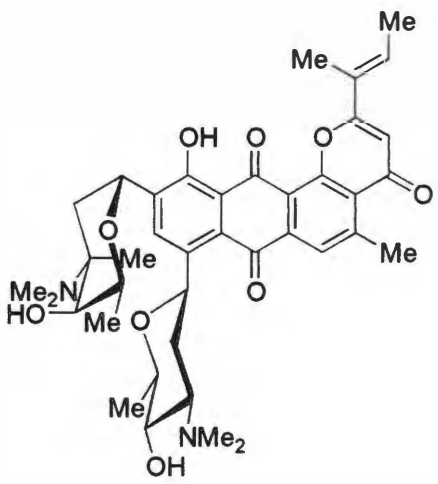


Figure 2.6. Kidamycin

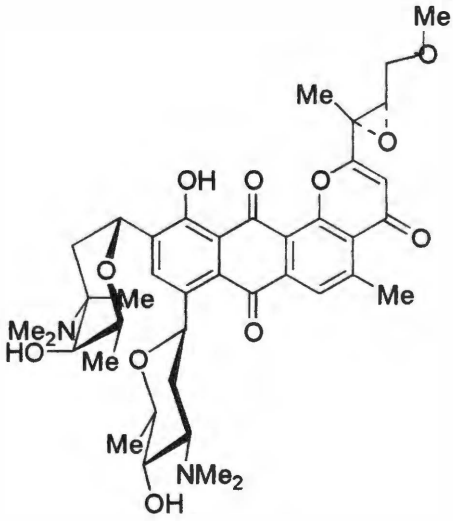


Figure 2.7. Hedamycin

isolated from the fermentation broth of *Streptomyces violaceus* P950-4 in 1991.[8] The compound, hydramycin (Figure 2.8), is a complex structure containing the pyranoanthraquinone skeleton mentioned above. Ring systems of this type that do not contain glycoside substituents are referred to as pluramycinones.[5,9] Vital to the molecule, and probably related to the activity associated with the compound is an epoxide ring located as part of a substituent on the pyranone ring.

Hydramycin is most closely related in structure to a compound called kapurimycin A_3 (Figure 2.9), which was isolated from *Streptomyces sp.* DO-115 and is also an anticancer agent. This compound is also known to alkylate DNA through attack of the epoxide ring of Kapurimycin A_3 by the N-7 on guanine. This forms a kapurimycin–DNA adduct, and from the selectivity associated with the alkylation of guanine at N-7 one can infer that the epoxide is placed in the major groove of DNA and aligned with N-7 of guanine through precovalent intercalation of the aromatic system.[10] The similarities between hydramycin and kapurimycin A_3 reveal the possibility that the anticancer activity of hydramycin may also result from this kind of interaction.

Hydramycin was analyzed by hollow fiber assay, an in vivo evaluation technique for determining the potential anticancer activity of compounds that have been identified as active by the large scale in vitro cell-based screen. The test agent is assayed against a standard panel of 12 human tumor cell line and is evaluated on a point system. Generally, a score of 20 points or more deems a

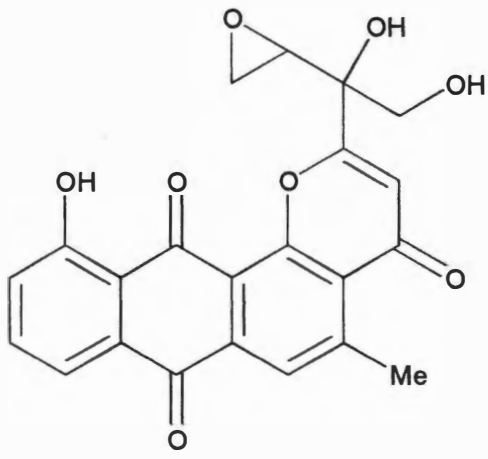


Figure 2.8. Hydramycin

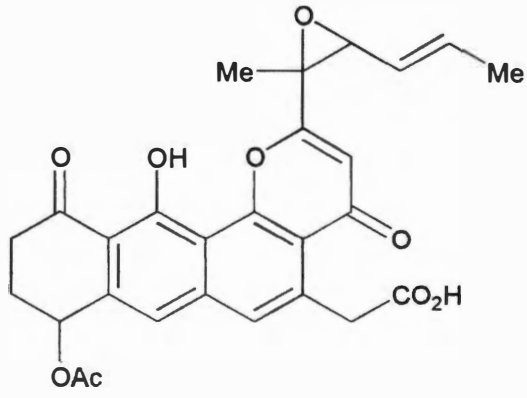


Figure 2.9. Kapurimycin A_3

compound to be one of interest. Also, if a compound exhibits net cell kill against any of the cell lines, it is considered active.[11] Hydramycin received a score of 24 and resulted in cell kill in a prostate line, a lung line, and a CNS line.

Anthraquinone compounds are a class of compounds rich in history. Not only have they been extremely useful in the area of the dye chemistry, they also have many applications in the pharmaceutical industry. Hydramycin has been shown to be a very active anticancer agent, especially in the area of prostate cancer. This activity implies the urgent need for a synthetic route to hydramycin.

II. Statement of the Problem

A. Objectives

Examination of hydramycin revealed that there were two main synthetic challenges provided by this compound. The first challenge involved the anthraquinone system. Although various synthetic strategies have been used in the past to generate such compounds, an approach that could serve to incorporate the anthraquinone into this particular compound was needed. The second challenge was to determine the most efficient route to the pyranone system and its substituents. The main objectives of this dissertation are as follows:

• To provide a model compound of hydramycin containing only a single benzene ring with the presumed active epoxide attached.

•To determine a viable synthesis to hydramycin itself.

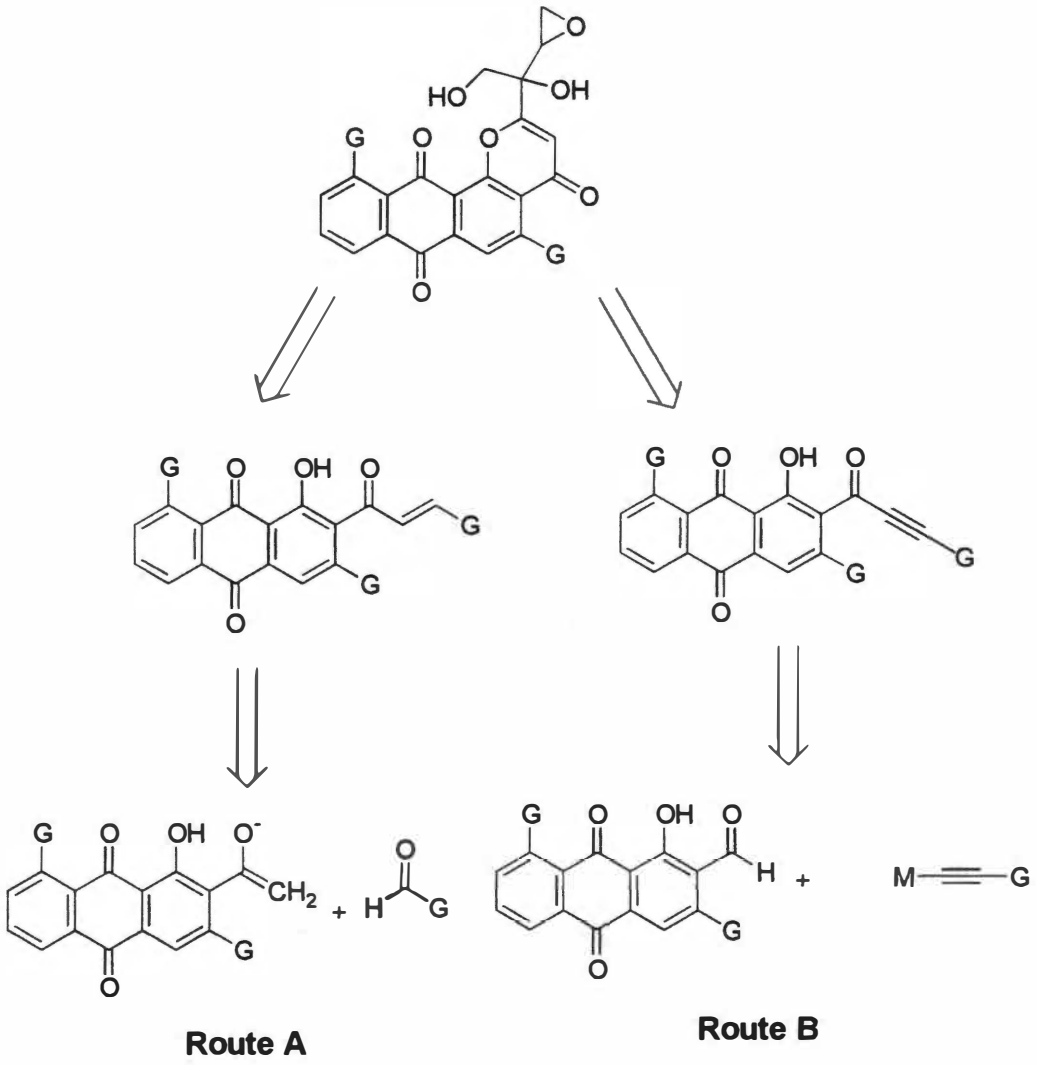
•To provide a simplified analog of hydramycin that contains both the anthraquinone system and the chromenone ring system with related moieties.

B. Research Plan and Retrosynthesis

Upon retrosynthetic analysis of the pyranone system and its moieties, two general strategies were envisioned. The first (Scheme 2.2, route A) was contingent upon a coupling between an enolate ion and an aldehyde to provide an α,β-unsaturated ketone. The ketone could undergo ring closure to provide the pyranone ring, and further manipulations would provide the hydramycin core. A second synthetic plan (Scheme 2.2, route B) required the coupling of an aldehyde and an alkynyl anion. This would provide a secondary alcohol that could be oxidized to give an acetylenic ketone. Again, a ring closure followed by additional simple chemistry would provide the hydramycin system. The second strategy proved to be most successful.

C. Significance

This work is of great importance to the synthesis of pluramycinone systems. Only a few syntheses of such compounds exist in the literature today and they entail complicated and arduous efforts. For example, Hauser and Rhee[6] designed an anthracene derivative of an anthraquinone in which the system is generated piecewise from a compound containing only a single benzene ring. Uno et al.[12] developed pluramycinone systems through first the development of *o*-alkynoylnaphthols, ring closure, and then providing the anthraquinones. Our route employs commercially available (and relatively



Scheme 2.2. Retrosynthesis of Hydramycin Analogs

inexpensive) anthraquinones that can be derivatized. Also, the element of convergence in this synthesis allows not only for the two building blocks to be generated simultaneously, but it also provides the ability to easily alter substituents on one of the building blocks and provide novel compounds.

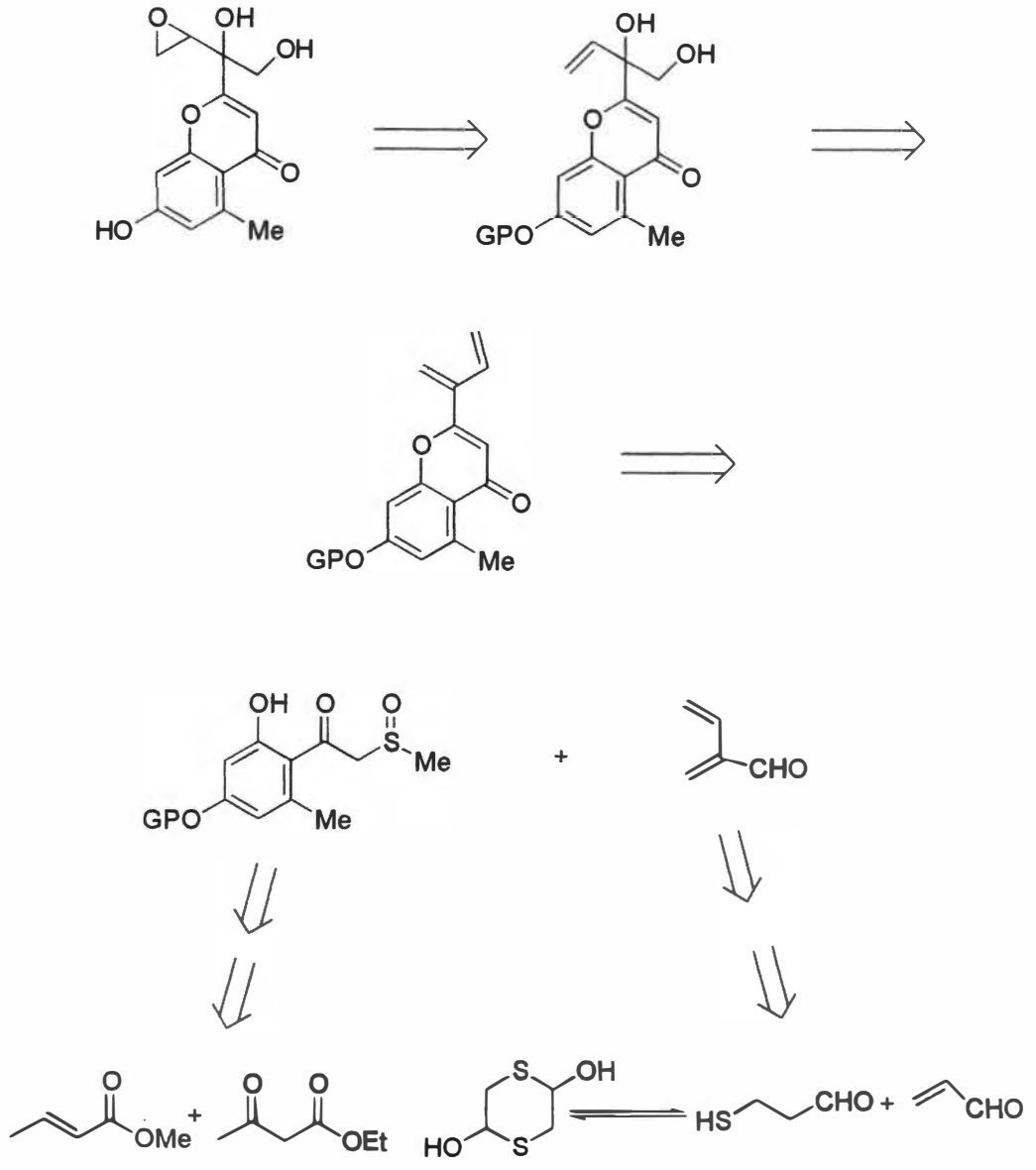
II. Discussion

A. Model Compound Synthesis

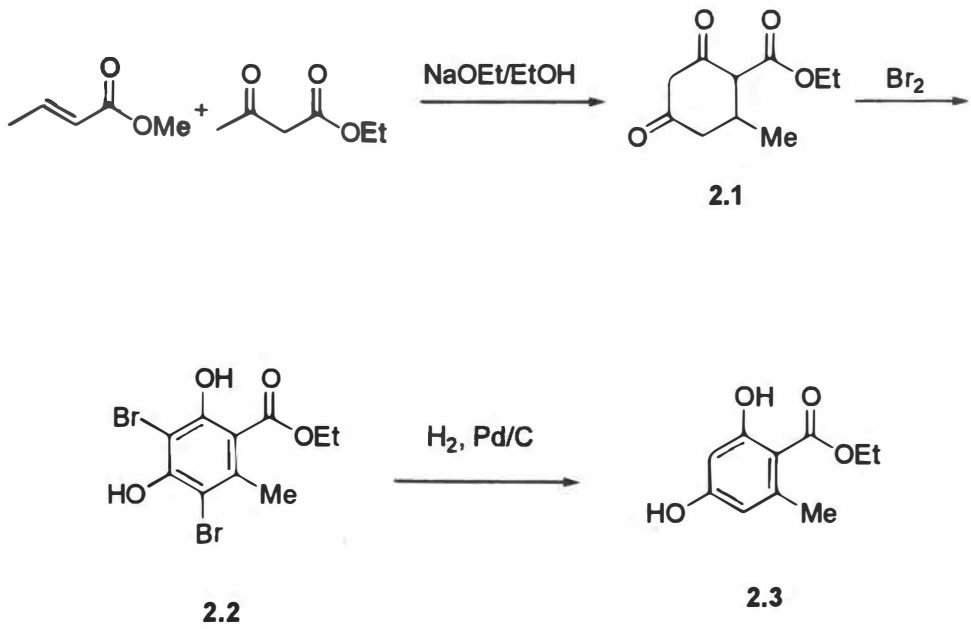
1. Initial attempt using a coupling of a methyl ketone derivative and an aldehyde.

The proposed method for providing the model compound is outlined in Scheme 2.3.[13] The key step in this synthesis would be formation of the chromenone ring system from a coupling between a methylsulfinyl acetophenone and an aldehyde. The methylsulfinyl acetophenone could be formed from a Claisen condensation between ethyl acetoacetate and methyl crotonate and further manipulations. Generation of the aldehyde could occur through some simple chemistry with the dimer of 2-mercaptoethanol and acrolein as the starting materials.

Model compound preparation began as methyl crotonate and ethyl acetoacetate underwent a Claisen condensation using NaOEt in EtOH to provide the cyclohexadione derivative **2.1** (Scheme 2.4). Although the literature claimed that the product could be crystallized from boiling water, this never occurred in my hands. Also, the NMR spectra of this compound were indecipherable due to



Scheme 2.3. First Model Compound Retrosynthesis

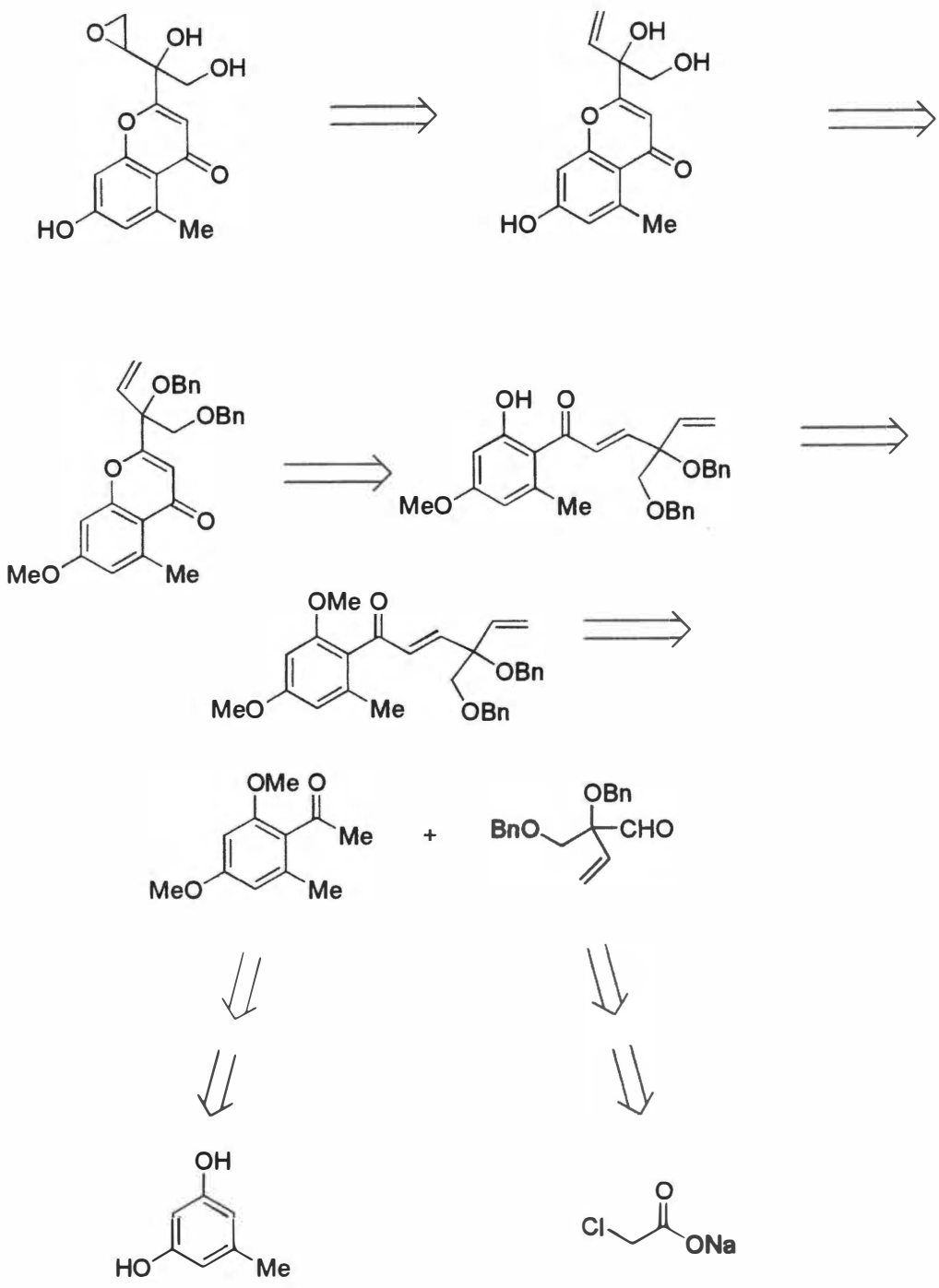


Scheme 2.4. First Model Compound Attempt

the presence of tautomers. Both of these aspects contributed to the use of this compound in the following step without purification. Cyclohexadione **2.1** was aromatized with bromine in acetic acid to give compound **2.2**. Cleavage of the bromine atoms was achieved via hydrogenation using 10% palladium-on-carbon in 2 N NaOH. The next step served to selectively protect the phenolic group that was not involved in hydrogen bonding; however, purification of the product was problematic. A need for a more efficient, convergent synthesis became apparent, and this approach was discontinued.

2. Second and third model attempts utilizing the coupling of a methyl ketone and an aldehyde.

A new retrosynthesis was designed (Scheme 2.5) which would incorporate the coupling between an enolate of a methyl ketone and an aldehyde. The resulting α,β-unsaturated ketone could react with SeO_2[6] to provide the chromenone ring system. Generation of the methyl ketone would involve a Houben–Hoesch reaction of orcinol,[14] followed by protection of the phenolic groups. The aldehyde synthesis would begin from the sodium salt of chloroacetic acid and entail some simple chemistry involving the attack of a Weinreb amide.[15]

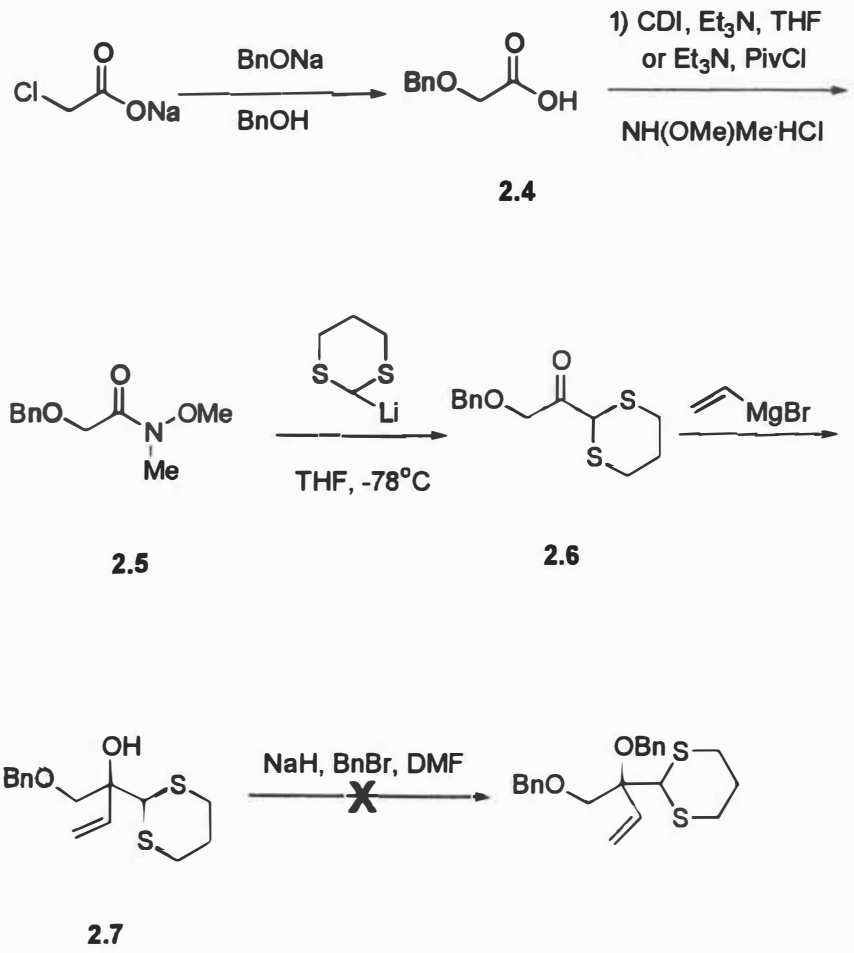


Scheme 2.5. Second Model Compound Retrosynthesis

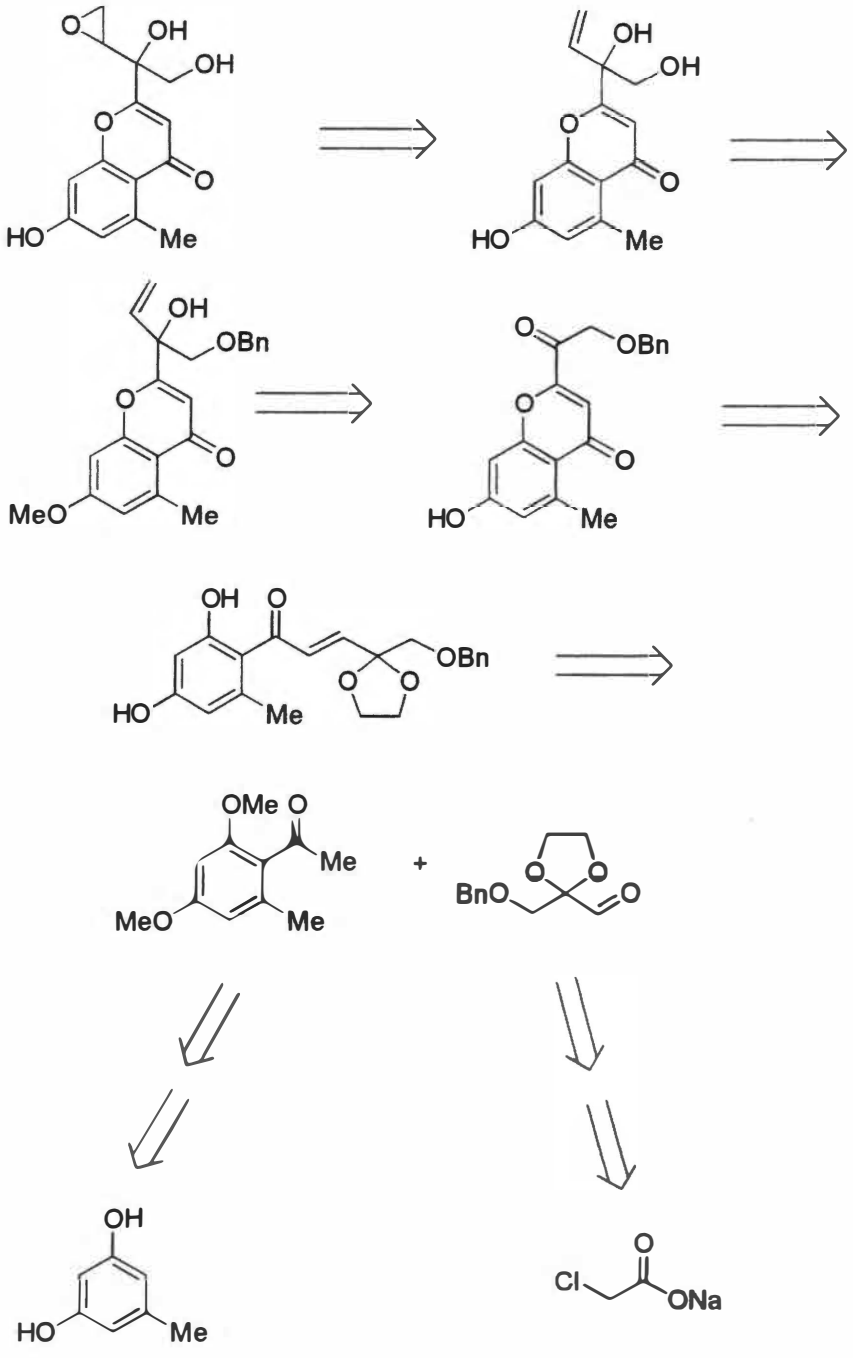
a. Aldehyde synthesis.

This strategy would entail the development of a complicated aldehyde that would serve as a "side chain" to the methyl ketone described above. The synthesis of the aldehyde began as the sodium salt of chloroacetic adic reacted with sodium benzyloxide in benzyl alcohol yielding acid **2.4** (Scheme 2.6). The acid was initially converted to its Weinreb amide **2.5** with carbonyldiimidazole and *N,O*-dimethylhydroxylamine hydrochloride in THF; however, a much less costly method was applied later utilizing triethylamine, pivaloyl chloride and *N,O*-dimethylhydroxylamine hydrochloride.[16] Attack of the lithium adduct of 1,3-dithiane on the amide **2.5** in THF provided the dithianyl ketone **2.6**, which reacted with vinylmagnesium bromide to give the tertiary alcohol **2.7**. Protection of the tertiary alcohol with a benzyl group was attempted on several occasions; however, the desired product was never produced. The synthesis of the aldehyde was thus deemed to be in need of revision.

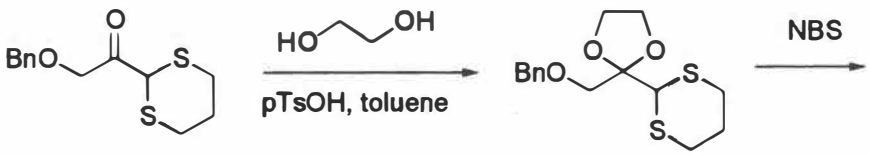
Since problems were occurring after the formation of the tertiary alcohol, possibly the aldehyde could contain a protected ketone that would later be deprotected and reacted to give the appropriate tertiary alcohol structure. A new retrosynthesis is shown in Scheme 2.7. Ketone **2.6** was protected as the acetal using ethylene glycol and catalytic *p*-toluenesulfonic acid in toluene (Scheme 2.8). This method smoothly provided protected ketone **2.8** that was converted to aldehyde **2.9** with *N*-bromosuccinimide. The aldehyde was now ready to be coupled.



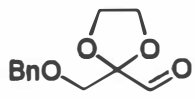
Scheme 2.6. Second Model Compound Attempt



Scheme 2.7. Third Model Compound Retrosynthesis



2.6 **2.8**



2.9

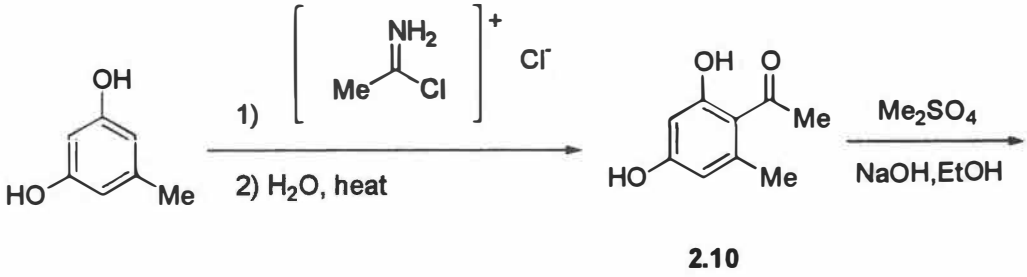
Scheme 2.8. Synthesis of the Aldehyde 2.9

b. Methyl ketone synthesis.

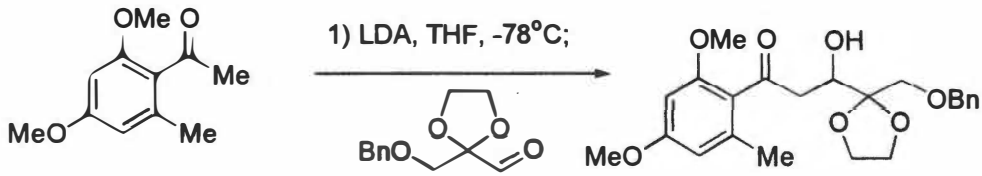
This method first required the generation of a methyl ketone to couple. Synthesis of the methyl ketone began when orcinol was reacted with zinc chloride and acetonitrile in ether in Houben–Hoesch fashion (Scheme 2.9).

The resulting intermediate ketimine hydrochloride was refluxed in water to yield the methyl ketone **2.10**. Protection of the phenolic groups was achieved with dimethyl sulfate and aq NaOH in EtOH, followed by purification via steam distillation.

The coupling began as ketone **2.11** was converted to its enolate with LDA, then reacted with aldehyde **2.9**. Initially, it was assumed that the alcohol that was formed would dehydrate to its α,β-unsaturated ketone upon workup. It did not. A small amount of the α,β-unsaturated ketone was formed, but the main product was β-hydroxy ketone **2.12**. At this point, the synthesis was terminated. This was partially due to the fact that the coupling provided a low yield. This low yield could be attributed to the fact that the aldehyde contained an α-oxygen, resulting in a compound (the gem diol), which rendered the material highly hygroscopic.[17] General ease of the method was also a factor as the Houben–Hoesch reaction was difficult to carry out and took six days to complete. Such a reaction was not suitable if the synthesis was to be efficient.



2.10



2.11

2.9

2.12

Scheme 2.9. Third Model Compound Attempt

3. Fourth attempt requiring the coupling of a 2-*(tert*-butyldimethylsilyloxy)benzaldehyde and an alkyne.

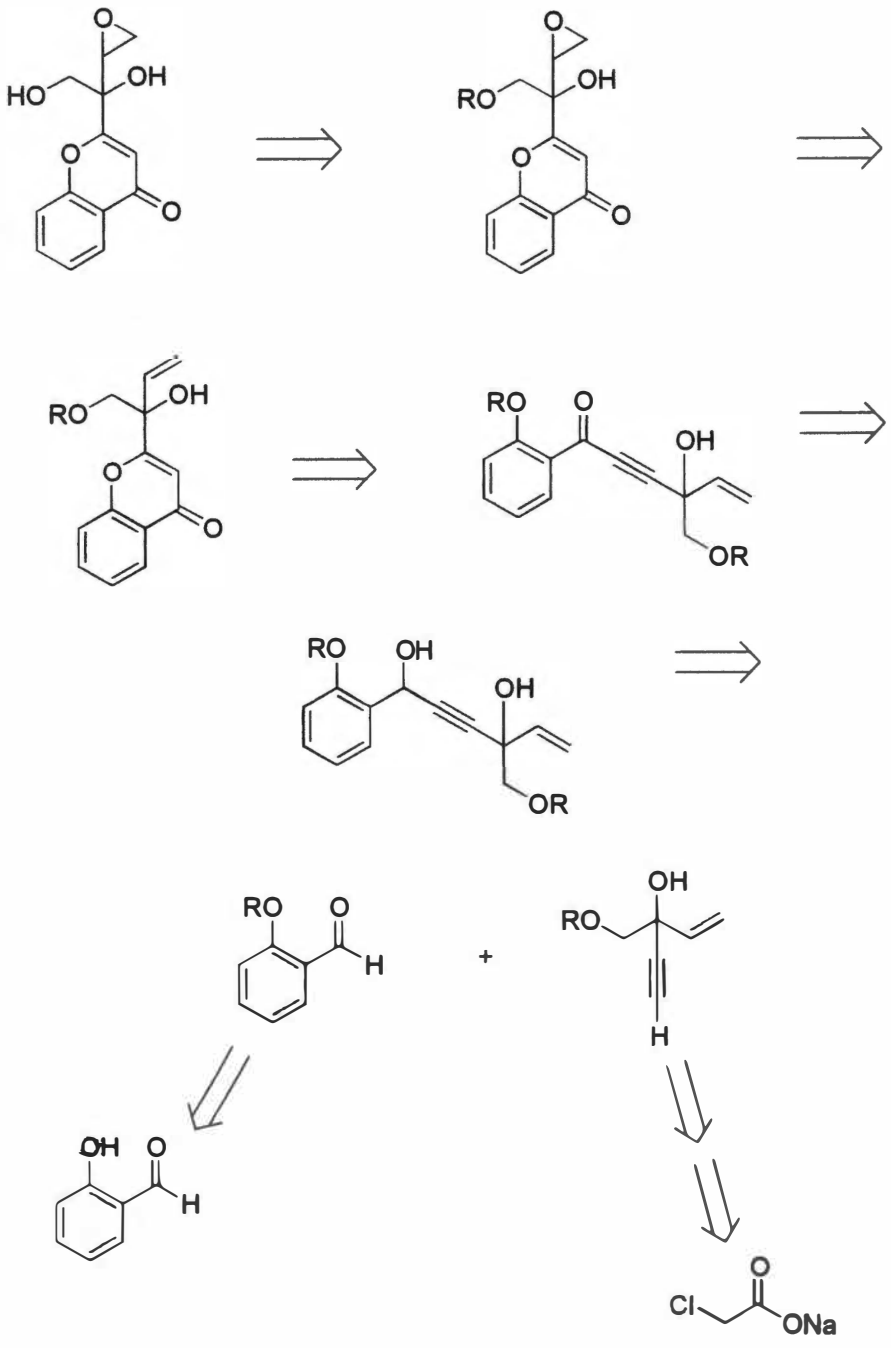
A new retrosynthesis of the pyranone ring was envisioned (Scheme 2.10) employing a coupling between an aldehyde and an alkynyl magnesium bromide compound. In this situation, the aldehyde would now contain the benzene ring, and the alkynyl compound would consist of the "side chain".

a. Synthesis of alkyne 2.15.

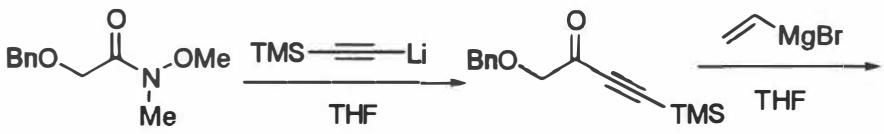
The first order of business was synthesis of the alkyne (Scheme 2.11). Luckily, chemistry that was used to generate the aldehyde for the previous synthetic scheme could be recycled and applied to the development of the alkyne. Weinreb amide **2.5** was reacted with lithium trimethylsilylacetylide to yield acetylenic ketone **2.13**. The ketone was subsequently attacked by vinylmagnesium bromide in THF to yield tertiary alcohol **2.14,** and deprotection of the silyl group was accomplished with NaOMe in MeOH to give the final alkyne **2.15**.

b. Preparation of the 2-*(tert*-butyldimethylsilyloxy)benzaldehyde, coupling with alkyne 2.15 and further reactions.

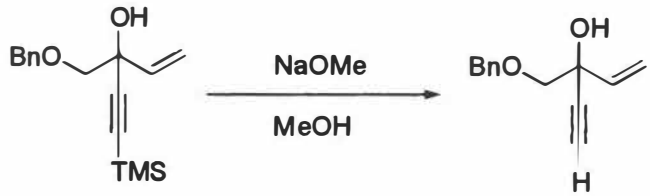
Salicylaldehyde was protected with TBSCl, imidazole and DMAP in DMF, yielding aldehyde **2.16** (Scheme 2.12). The magnesium bromide salt of alkyne **2.15** was generated by reaction with two equivalents of MeMgBr in THF. After stirring for 3 h at 60 °C, aldehyde **2.16** was added. The secondary alcohol **2.17**



Scheme 2.10. Final Model Compound Retrosynthesis

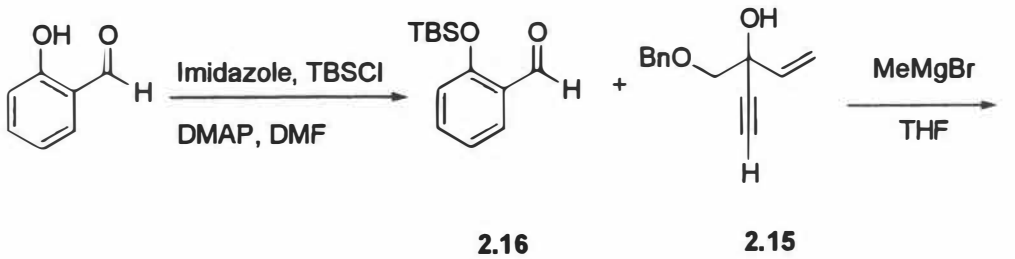


2.5 **2.13**

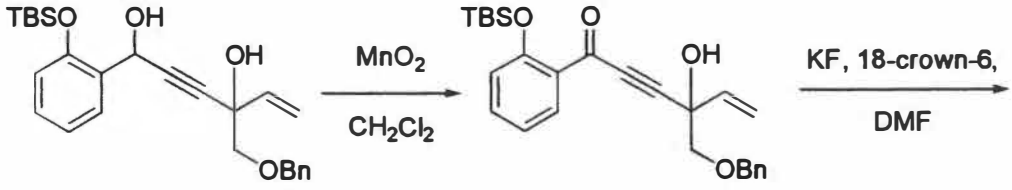


2.14 **2.15**

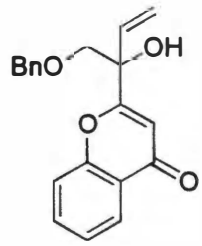
Scheme 2.11. Synthesis of Alkyne 2.15



2.16 **2.15**



2.17 **2.18**



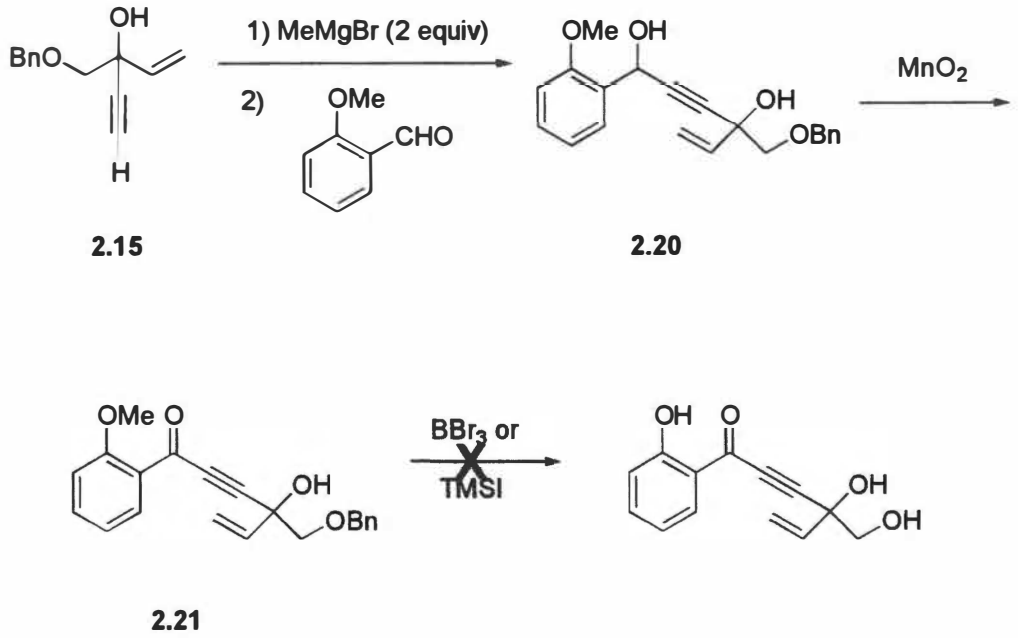
2.19

Scheme 2.12. Fourth Model Compound Attempt

provided by this reaction was oxidized to ketone **2.18** with MnO_2. Initially, this reaction was run at room temperature, but this resulted in a low yield. The optimum yield was achieved by refluxing the reaction mixture, although the starting material was never completely consumed. Ketone **2.18** was subjected to reaction with potassium fluoride and 18-crown-6 in DMF to simultaneously remove the silyl group and effect ring closure.[18] Although the synthesis of the model compound was successful up to this point, other factors contributed to discontinuation of this method. Protection of a 1,8-dihydroxyanthraquinone with the *tert*-butyldimethylsilyl group had been attempted on several occasions with little success. The model compound synthesis was adjusted to employ a protective group that could be applied to the anthraquinone system.

4. Fifth attempt using the coupling of o-anisaldehyde and alkyne 2.15.

Literature reports[19,20] had shown that the hydroxyanthraquinones were often protected using the methyl protective group, and this protective group was chosen for the synthesis of the hydramycin analog. Therefore, this protective group was attempted on the model compound. Also, *o*-anisaldehyde was commercially available and this would shorten the synthesis. First, alkyne **2.15** was reacted with two equivalents of MeMgBr for 3 h (Scheme 2.13), and then *o*-anisaldehyde was added to give alcohol **2.20**. Alcohol **2.20** was oxidized via MnO_2. Deprotection of both the methyl and benzyl protective groups was attempted on several occasions with TMSI[21,22], BBr_3[23] and several other



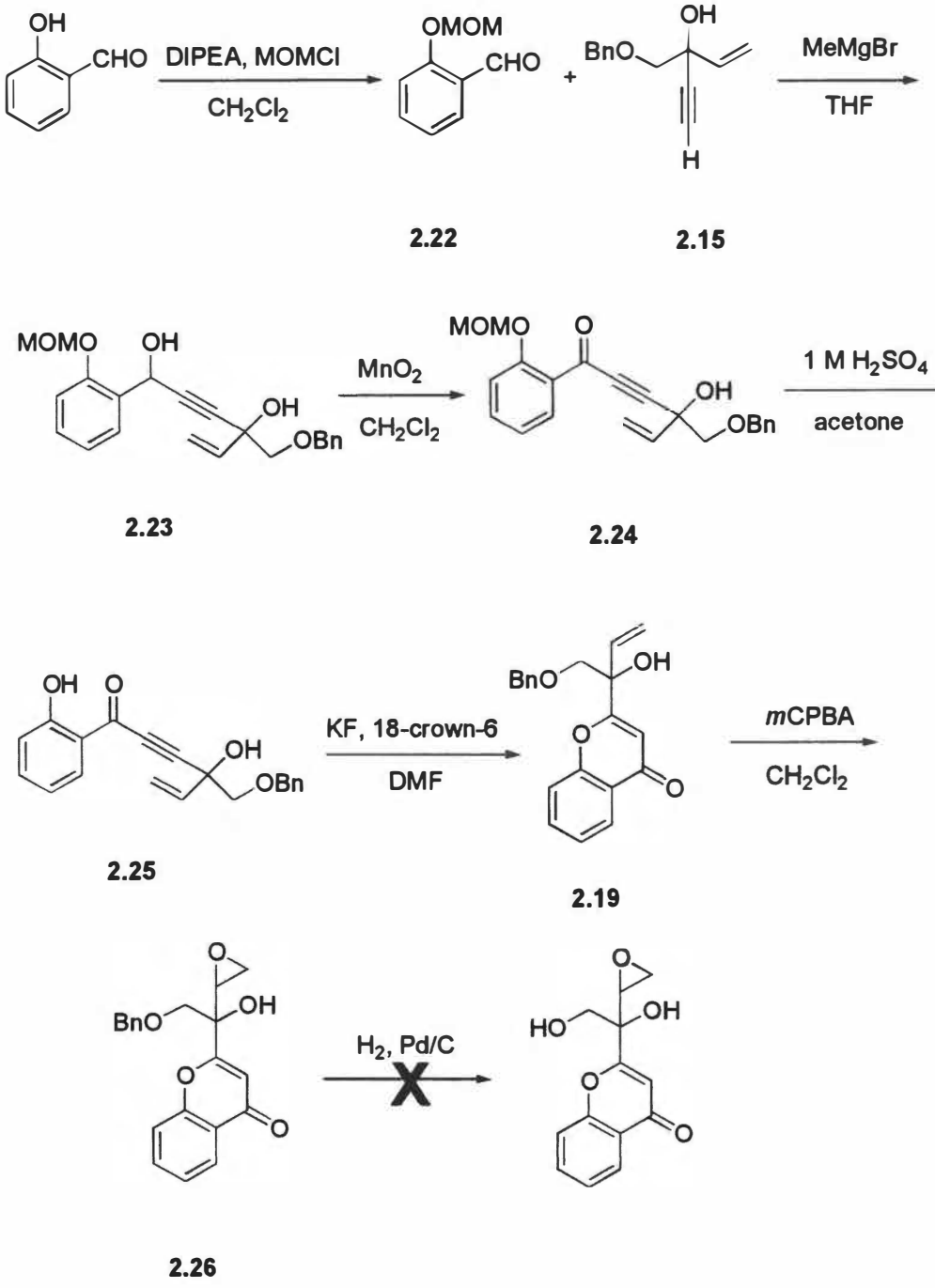
2.15 **2.20** **2.21**

Scheme 2.13. Fifth Model Compound Attempt

reagents. However, it appeared that the sensitive groups introduced with the alkyne could not withstand these harsh conditions. Therefore, a new protective group was chosen, the methoxymethyl (MOM) protective group.

5. Sixth attempt using the coupling of 2-(methoxymethoxy)benzaldehyde and alkyne 2.15.

The new model compound synthesis began with the protection of salicylaldehyde using Hünig's base and chloromethyl methyl ether (Scheme 2.14) to produce aldehyde **2.22**. This aldehyde was coupled with alkyne **2.15** in the same fashion as mentioned earlier. Next, MnO_2 oxidized secondary alcohol **2.23** to ketone **2.24**. The deprotection of the MOM group was the next step. First, deprotection was attempted with 1 M HCl, a reagent that had been used for these kind of deprotections in the past.[24] However, HCl could also add across the vinyl group that was present in the molecule. Since 1 M HCl should have been sufficient to remove the group, by analogy 1 M H_2SO_4 should also provide the required acidity. However, H_2SO_4 provides a conjugate base (HSO_4^-) that is not as nucleophilic as the one (Cl^-) from HCl. The reaction yielded the expected phenol **2.25**, although it required longer reaction times than the HCl reaction should have (approximately 24 h). Next, the ring-closure reaction was run as before with KF and 18-crown-6. The literature reports on this reaction claimed that without the presence of the TBS protective group, a small amount of the 5-membered ring product would also form.[25] Concerns arose about the



Scheme 2.14. Sixth Model Compound Attempt

possibility that these products could be inseparable by chromatography. However, after a simple chromatographic purification of the reaction mixture, 73% of chromenone **2.19** was obtained. Next, the epoxidation reaction was run using *m*-CPBA. This reaction served to provide epoxide compound **2.26** that contained a second chiral center. This second chiral center was contiguous with the tertiary alcohol chiral center already present in the molecule. This meant the reaction provided a set of diastereomers that had to be separated in order to characterize them both, a difficult task as they ran very closely on TLC. Finally, chromatography on silica gel, eluting with 2:1 petroleum ether–EtOAc (500 mL), followed by 500 mL of 1:1 petroleum ether–EtOAc, provided the clean diastereomers. The final debenzylation reaction was attempted with H_2 using 10% Pd/C as a catalyst; however, this reaction also served to reduce the double bond present in the chromenone ring. Although a literature report[26] had supported the debenzylation under these conditions, these reactions had been run on systems in which a double bond of the chromenone ring system was conjugated with a benzene ring. Obviously, this could provide a double bond of greater stability which would be much less susceptible to hydrogenation than one that is not conjugated.

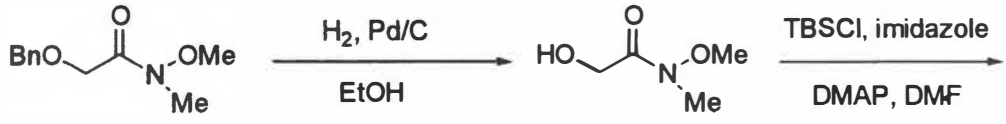
6. Synthesis of the model compound using the coupling of 2-(methoxymethoxy)benzaldehyde and a new alkyne.

a. Alkyne synthesis.

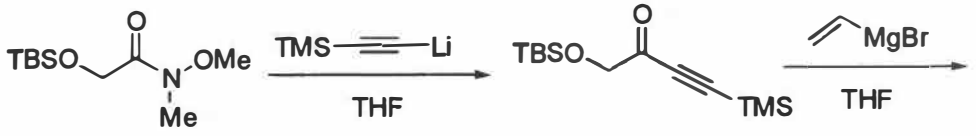
Synthesis of the new alkyne began from Weinreb amide **2.5** that was used in the previous alkyne synthesis (Scheme 2.15). The benzyl group of the amide was deprotected via hydrogenation with a Pd/C catalyst in ethanol to give alcohol **2.27**. Amide **2.28** resulted from reprotection with TBSCl, imidazole and DMAP. The TBS protective group was chosen because is could be simultaneously deprotected with the MOM group in a later step. As before, the Weinreb amide **2.28** was reacted with lithium trimethylsilylacetylide, and acetylenic ketone **2.29** was produced. Attack of the ketone by vinylmagnesium bromide yielded tertiary alcohol **2.30**, and K_2CO_3 provided deprotected alkyne **2.31**.

b. Coupling and further reactions.

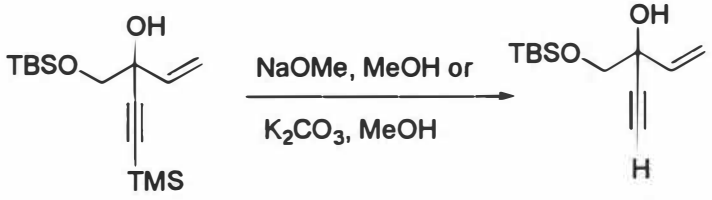
Once again, the alkyne was coupled with aldehyde **2.22** as described previously (Scheme 2.16). This time, however, the alkyne was deprotonated with 2 equivalents of *n*-BuLi. It had been found during the synthesis of the alkyne that the TBS protective group was somewhat susceptible to attack by Grignard reagents. The alcohol **2.32** that resulted from the coupling was oxidized with MnO_2. As described previously, the deprotection of the MOM and TBS groups were accomplished with 1 M H_2SO_4. The ring closure of phenol **2.34** was run with KF and 18-crown-6. Chromenone **2.35** was converted to the



2.5 **2.27**

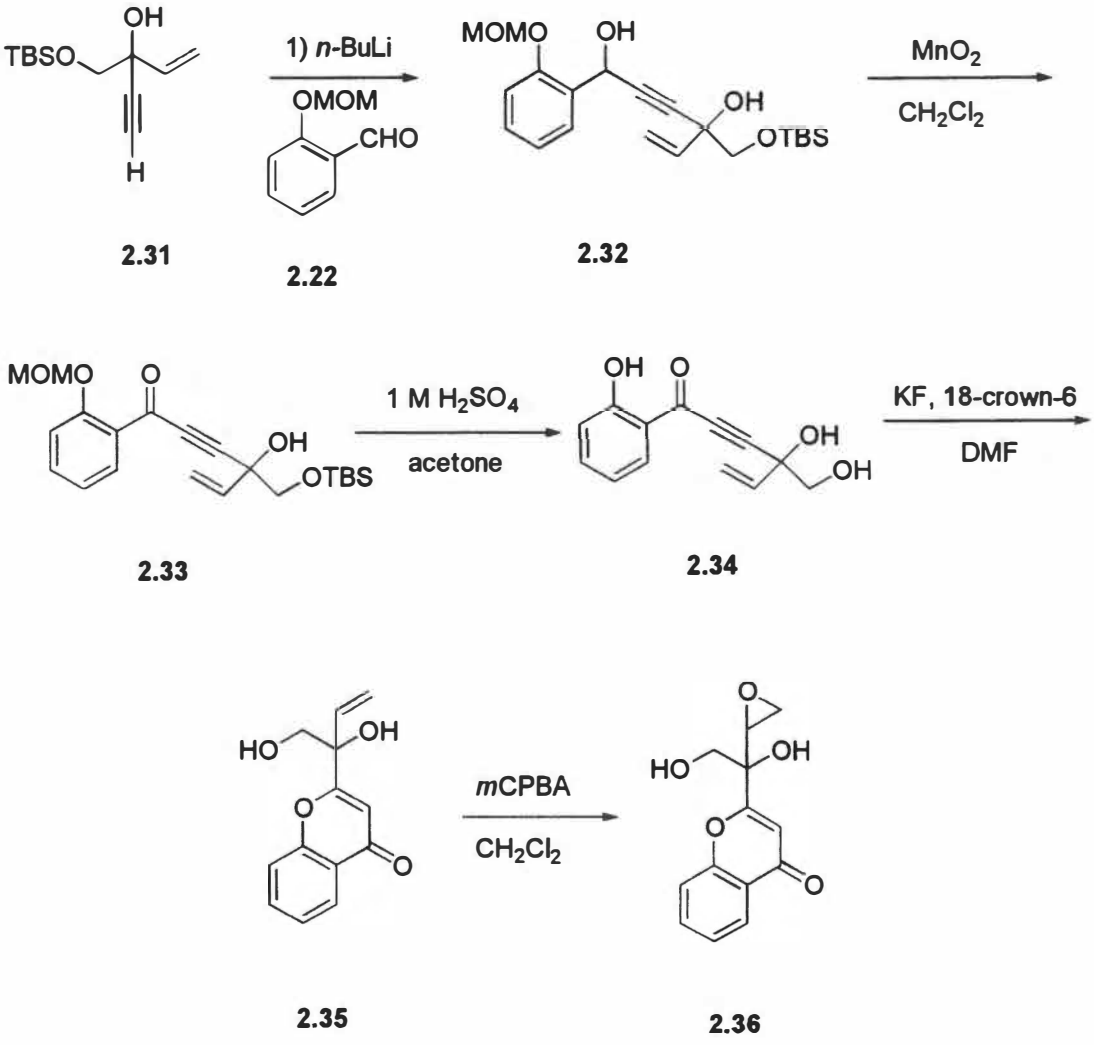


2.28 **2.29**



2.30 **2.31**

Scheme 2.15. Synthesis of Alkyne 2.31



2.31 2.22 2.32 2.33 2.34 2.35 2.36

Scheme 2.16. First Model Compound Synthesis

epoxy compound **2.36** with *m*-CPBA.

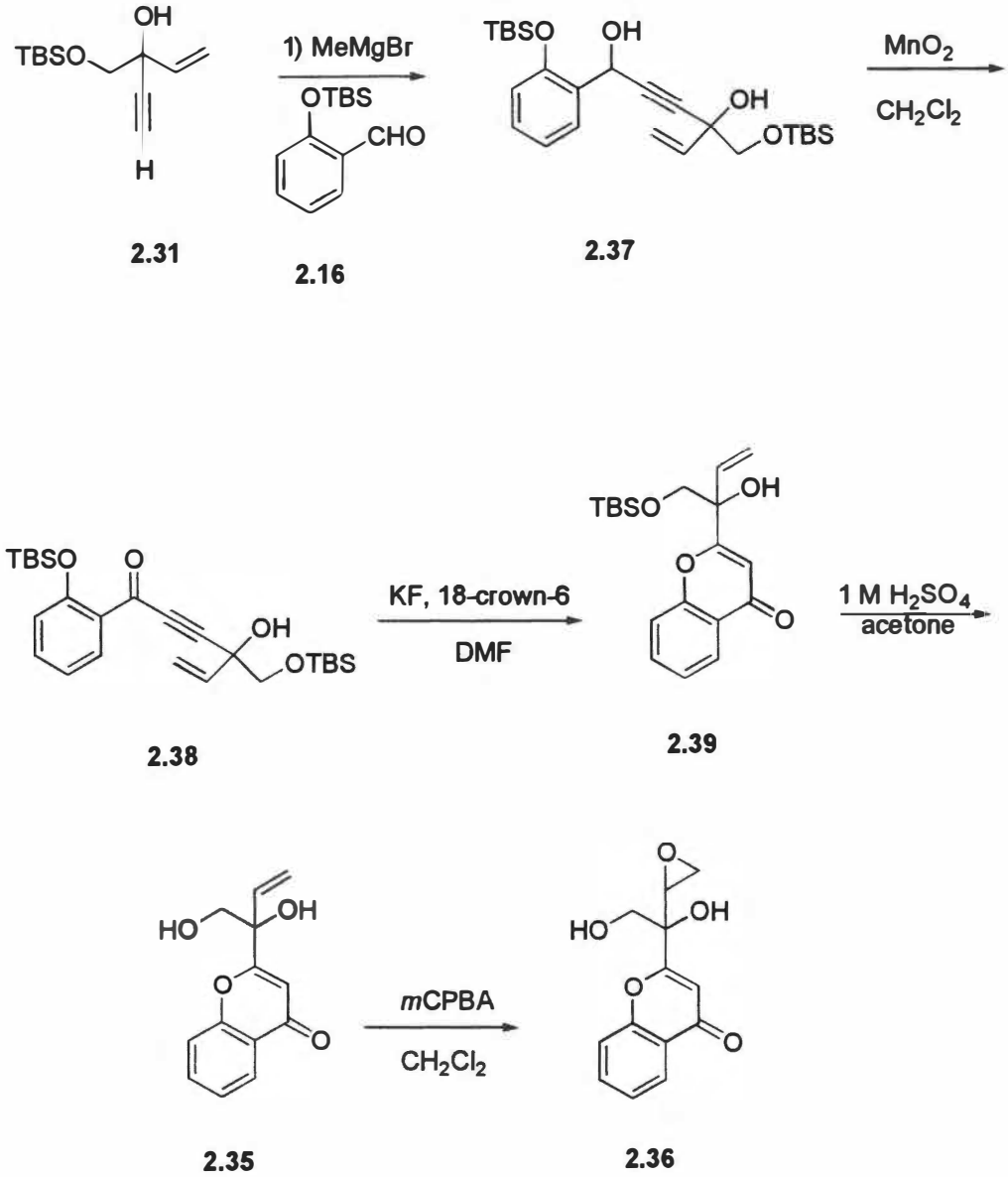
7. Synthesis of the model compound using the coupling of 2-(*tert*-butyldimethylsilyloxy)benzaldehyde and alkyne 2.31.

Model compound synthesis was attempted with aldehyde **2.16** and alkyne **2.31** in an effort to improve the yield of the model compound. The synthesis began with the coupling reaction that gave **2.37** (Scheme 2.17). Alkyne **2.31** was deprotonated with *n*-BuLi and reacted with aldehyde **2.16**. Next, oxidation was again achieved via MnO_2 to give ketone **2.38**. The ring closing reaction was accomplished as before with KF and 18-crown-6 providing chromenone **2.39**. It was strange that despite the fact that 4 molar equivalents of the KF and 18-crown-6 to the substrate was used, the primary TBS group was not deprotected. The deprotection was accomplished with 1 M H_2SO_4 as before to give compound **2.35**. Finally, *m*-CPBA was used to produce the final model compound **2.36**. The new method did not shorten the synthesis as hoped, but it did serve to improve the yields, and the reactions were often cleaner than in the initial method.

B. Synthesis of the Hydramycin Analog.

1. Attempts to synthesize anthraquinone aldehydes.

Once a route to form the pyranone ring had been established, formation of an anthraquinone containing 1-hydroxy and 2-carbaldehyde moieties was imperative. Many attempts were made to attain such a molecule. Since molten



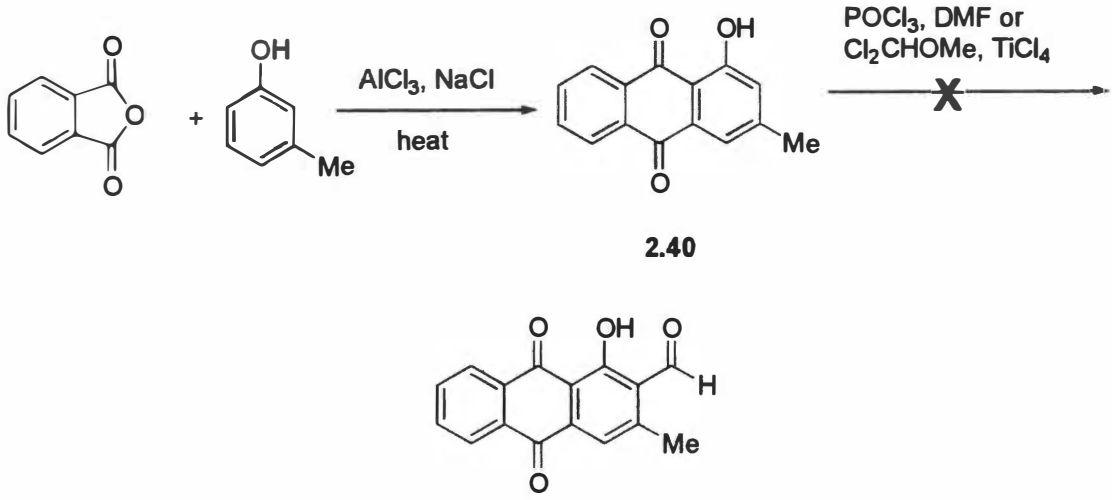
2.31 2.16 2.37 2.38 2.39 2.35 2.36

Scheme 2.17. Second Model Compound Synthesis

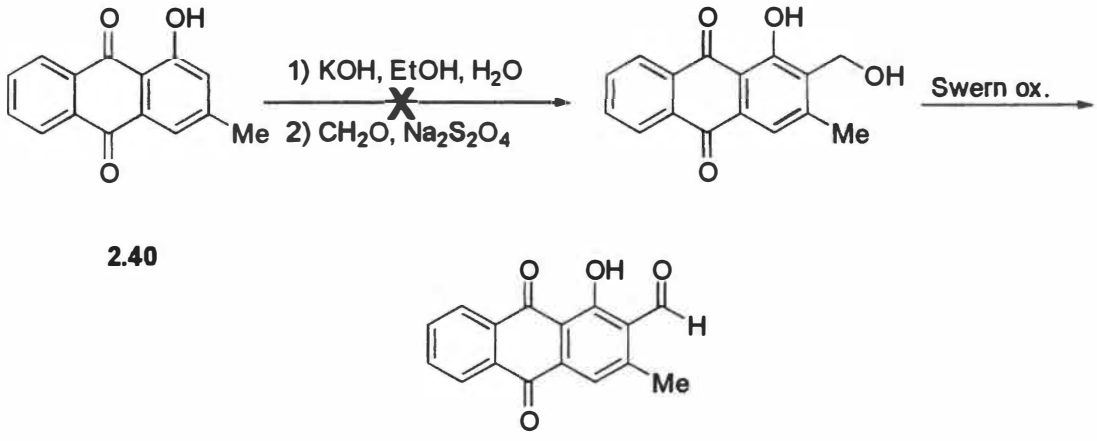
salt chemistry was the method of choice for acquiring anthraquinones[27-30], many molten salt couplings were attempted between phthalic anhydride and various phenols. Some compounds that did not couple are the following: 2-hydroxymethyl-3-methylphenol, 2-methoxymethyl-3-methylphenol, 2-hydroxy-6-methylbenzaldehyde and 3-methyl-2-vinylphenol. A molten salt coupling that was run with *m*-cresol provided anthraquinone **2.40** (Scheme 2.18) giving hope that this method could be used. Installation of the 2-formyl moiety was attempted using phosphorus oxychloride and DMF[31]. This reaction proved unsuccessful, and a similar reaction was attempted with dichloromethoxymethane and $TiCl_4$[32], which were also unsuccessful.

Since formylation reactions did not appear to be the answer, other strategies were explored. A reaction was found in the literature in which 1-hydroxyanthraquinone could be converted to 1-hydroxy-2-hydroxymethylanthraquinone. This reaction was attempted with anthraquinone **2.40** as it was dissolved in aq NaOH and ethanol then reacted with formaldehyde (Scheme 2.19).[33] However, this method was discontinued when it was discovered that these same conditions had also been used to install a 2-methyl substituent.[34]

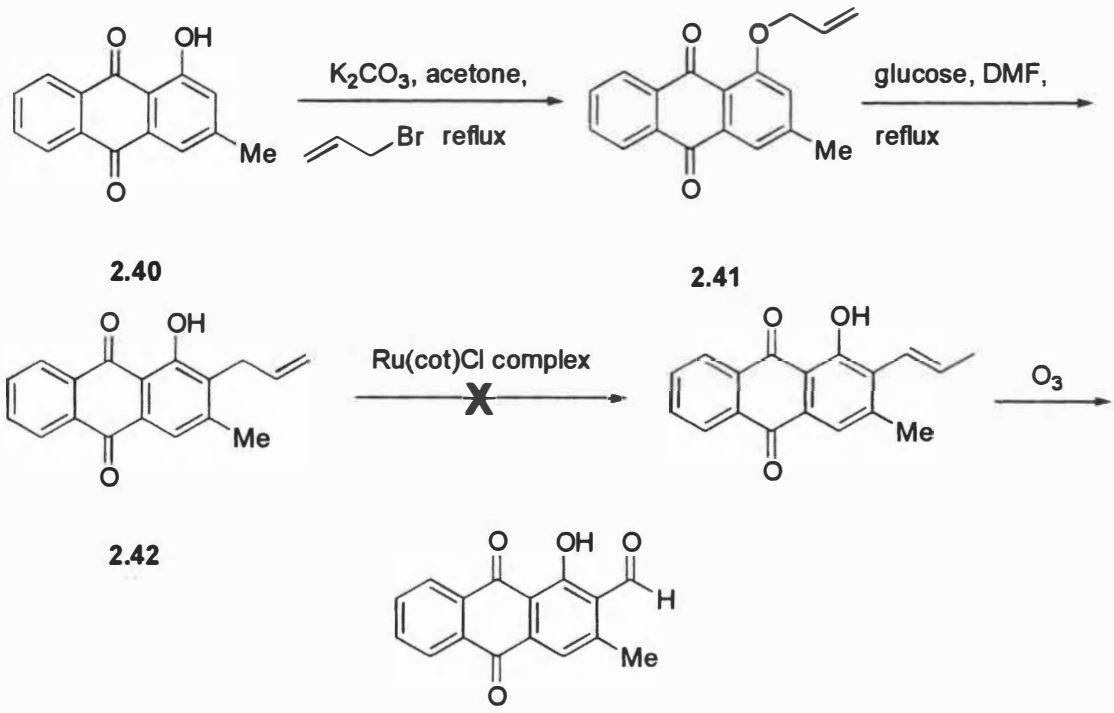
Despite unsuccessful attempts to generate a 2-formyl moiety, a new strategy to develop the correct aldehyde using anthraquinone **2.40** began (Scheme 2.20). First, an allyl protection reaction was run with NaH and allyl bromide in THF. The 1-allyloxyanthraquinone **2.41** underwent a glucose-



Scheme 2.18. Attempted Synthesis of Anthraquinone Aldehydes by Formylation Reactions



Scheme 2.19. Attempted Synthesis of Anthraquinone Aldehydes using Formaldehyde.



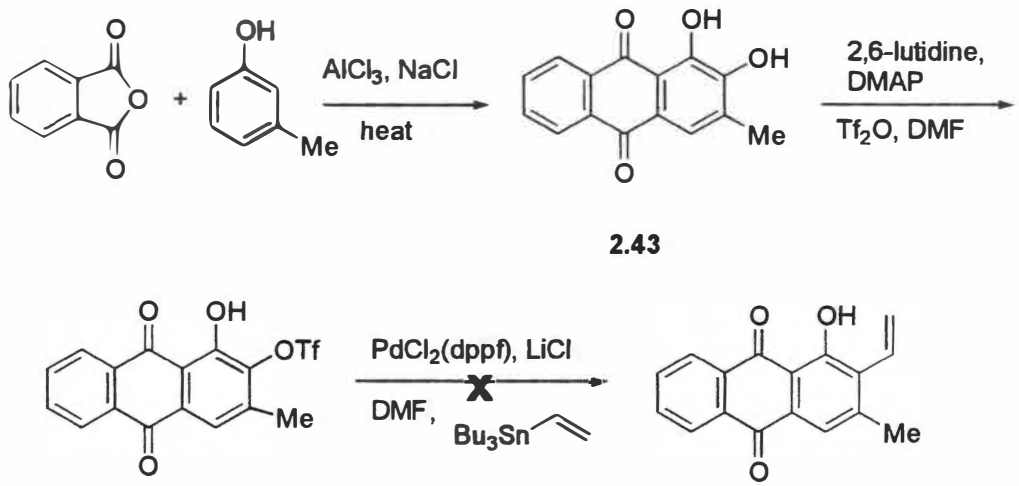
Scheme 2.20. Attempt to Synthesize Anthraquinone Aldehydes using a Claisen Rearrangement

promoted Claisen rearrangement in DMF[35] to yield the 2-allylanthraquinone **2.42**. Isomerization of the double bond was attempted with Ru(cot)Cl,[36] but proved to be unsuccessful. This method was abandoned as a shorter synthesis had been found.

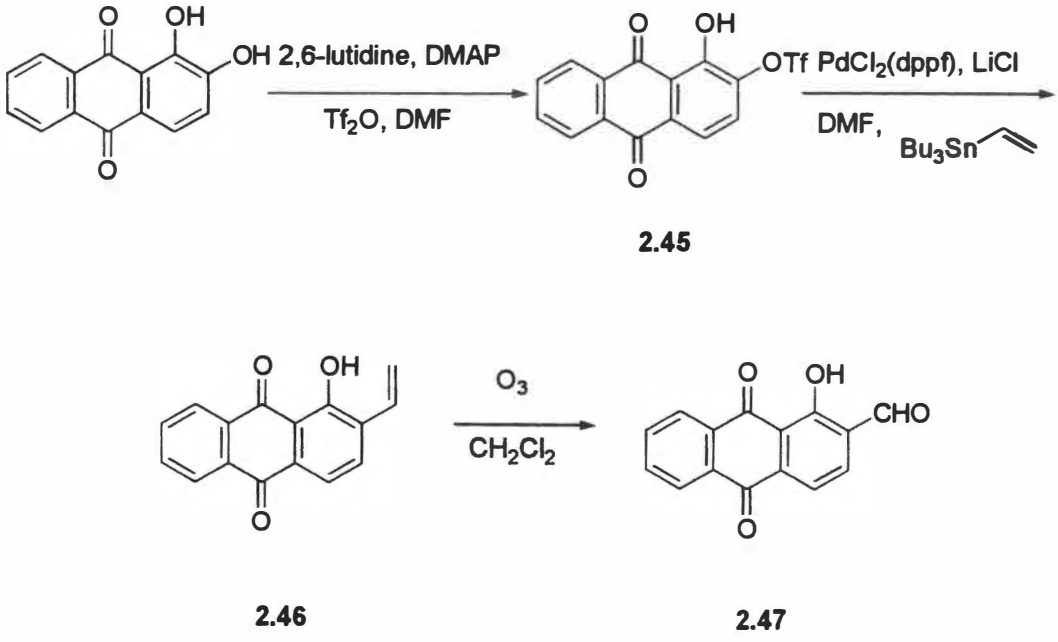
2. Successful syntheses of anthraquinone and anthracene aldehydes

a. Alizarin method.

The new synthesis of the aldehyde began with a molten salt coupling between phthalic anhydride and 3-methylcatechol (Scheme 2.21). This reaction proved successful, and anthraquinone **2.43** was reacted with a 1.1 molar equivalent of 2,6-lutidine and trifluoromethanesulfonic anhydride with DMAP to give selective protection of the 2-hydroxyl group, as the 1-hydroxyl group was hydrogen bonded to the ketone of the anthraquinone. Triflate **2.44** was reacted in a Stille fashion with tributylvinylstannane in the presence of LiCl and bis(diphenylphosphino)dichloropalladium complex with CH_2Cl_2. The reaction did not work. Since a literature article[37] had claimed to run the reaction on triflate **2.45**, the reaction was attempted on the exact same compound (Scheme 2.22). Triflate **2.45** could be generated by the reaction of 2,6-lutidine, DMAP and trifluoromethanesulfonic anhydride with alizarin. Alizarin is an inexpensive, commercially available compound. The first few attempts at the reaction were still ineffective. It became obvious that moisture in the system was preventing the reaction from taking place. The reaction was repeated using sublimed LiCl



Scheme 2.21. Attempt to Synthesize Anthraquinone Aldehydes using the Stille Reaction



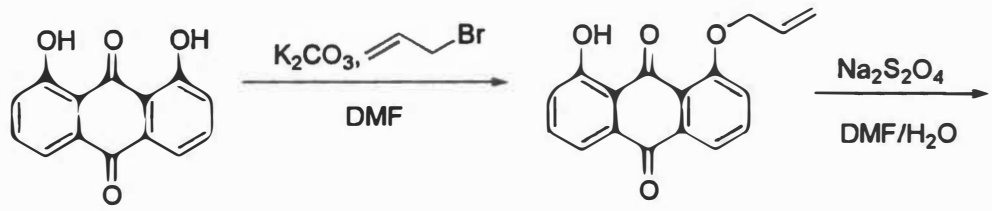
Scheme 2.22. Preparation of Aldehyde 2.47

and freshly distilled DMF kept over 4 Å sieves. The solid materials were also weighed out in a dry box to prevent the highly hygroscopic LiCl from absorbing moisture. The reaction finally worked, and ozonolysis of alkene **2.46** produced the necessary aldehyde **2.47**. However, the analogous reaction with triflate **2.44** using these conditions still failed.

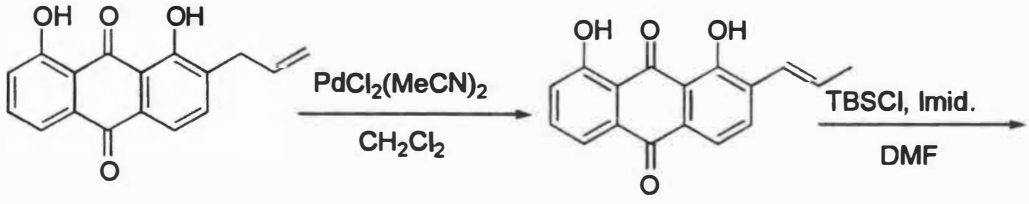
b. Preparation of 1,8-dimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde.

A new, simpler method of generating anthraquinone aldehydes was investigated (Scheme 2.23). The synthesis began when 1,8-dihydroxyanthraquinone was reacted with K_2CO_3 and allyl bromide in DMF to give the monoprotected compound **2.48**. Next, a reductive Claisen reaction[19] was run with $Na_2S_2O_4$ in a 1:1 DMF–H_2O solution yielding phenol **2.49**. The double bond was isomerized with bis(acetonitrile)dichloropalladium(II),[19] and protection of the compound with TBSCl, DMAP and imidazole was attempted, but appeared troublesome. The reaction did not produce a good yield, and a different protective group was then employed.

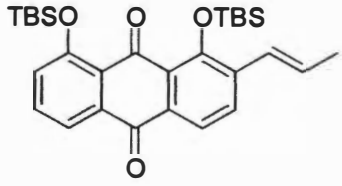
The new method began as allyl compound **2.49** was protected with dimethyl sulfate and K_2CO_3 in acetone (Scheme 2.24). Isomerization of the double bond was now achieved with NaOH in MeOH.[19] Lastly, the propenyl compound **2.53** underwent ozonolysis to yield aldehyde **2.54**. Inability to deprotect the methyl protective groups as is mentioned later led to the synthesis of a new aldehyde.



2.48

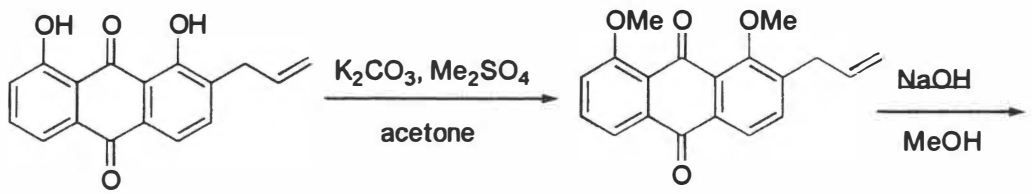


2.49 **2.50**

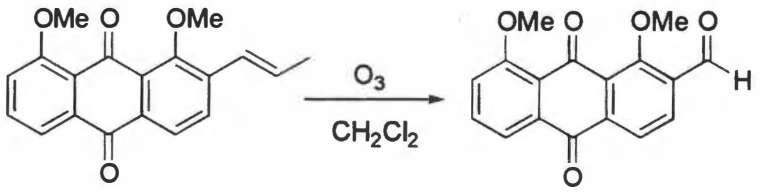


2.51

Scheme 2.23. Attempt to Synthesize TBS-protected Anthraquinone Aldehydes



2.49 **2.52**

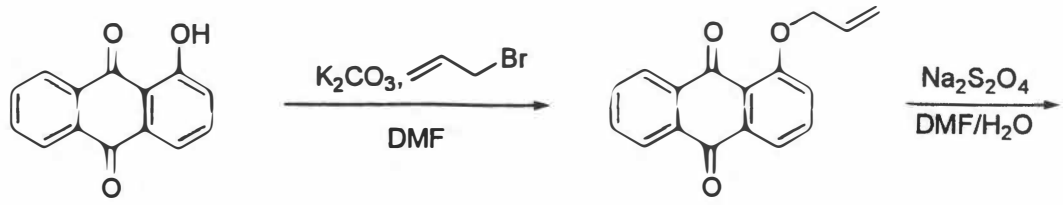


2.53 **2.54**

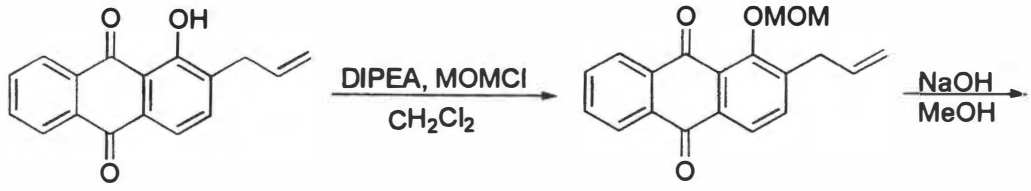
Scheme 2.24. Preparation of Aldehyde 2.54

c. Preparation of 1-methoxymethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde.

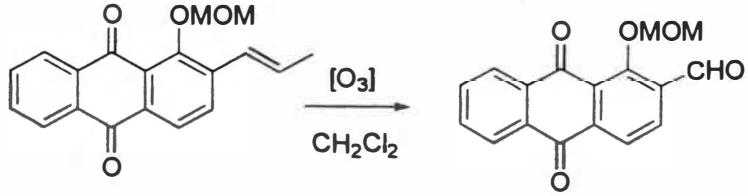
Once the model compound synthesis had proved that the MOM protective group could be deprotected in the presence of the moieties provided by the alkyne, synthesis toward the MOM-protected anthraquinone aldehyde **2.59** began (Scheme 2.25). For this synthesis, 1-hydroxyanthraquinone was used. The reason for this was two-fold. The initial allyl protection of just one hydroxyl group on the 1,8-dihydroxyanthraquinone was a low-yielding reaction and required a frustrating separation of the starting material, desired product and the diprotected product. Also, deprotection of the two hydroxyl groups later in the synthesis could prove to be somewhat confusing in determining which was the fully deprotected compound. Therefore, in the interest of both higher yields and ease of reactions, 1-hydroxyanthraquinone became the starting material of choice. The allyl protection could now be run with K_2CO_3, KI and allyl bromide in DMF to give allyloxy compound **2.55**. Phenol **2.56** resulted from the reductive Claisen rearrangement described earlier. The MOM protection could be achieved with Hünig's base and chloromethyl methyl ether, and finally isomerization to the propenyl compound **2.58** resulted from the reaction of compound **2.57** with NaOH in MeOH for 30 min. Ozonolysis yielded aldehyde **2.59**.



2.55



2.56 **2.57**



2.58 **2.59**

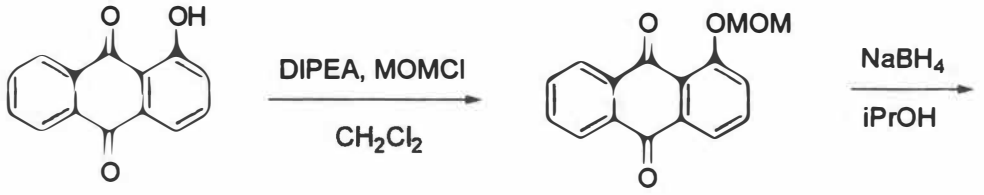
Scheme 2.25. Preparation of Aldehyde 2.59

d. Preparation of 1-methoxymethoxyanthracene-2-carbaldehyde.

Aldehyde **2.59** did not prove to be a good option for this synthesis; therefore, a new synthesis began. Problems were occurring due to the reactions of the anthraquinone ketone groups with nucleophiles, and eliminating the presence of these ketones might alleviate such problems. Also, there was evidence that the anthraquinone functionality could be later regenerated. The new synthesis began as 1-hydroxyanthraquinone was reacted with MOMCl and DIPEA to give the methoxymethoxyanthraquinone **2.60** (Scheme 2.26). The compound was easily reduced to anthracene **2.61** with $NaBH_4$ in refluxing 2-propanol.[38] The presence of the MOM protective group now provided a unique opportunity to install an aldehydic moiety in the ortho position. Through reaction with TMEDA and *n*-BuLi, the ortho anion was generated and could be subsequently quenched with DMF to give aldehyde **2.62.**[39] Complications discussed later required the synthesis of yet another aldehyde.

e. Preparation of 1-hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde using compound 2.56.

There became a need for synthesis of aldehyde **2.47**. Although it had been synthesized earlier, the use of the reductive Claisen method was much easier chemistry to deal with on a large scale than the chemistry shown in Scheme 2.21. The synthesis of this compound now begain as isopropenyl compound **2.63** was generated through the reaction of anthraquinone **2.56** with



2.60



2.61 **2.62**

Scheme 2.26. Preparation of Aldehyde 2.62

bis(acetonitrile)dichloropalladium(II) (Scheme 2.27). Ozonolysis of the double bond yielded aldehyde **2.47**.

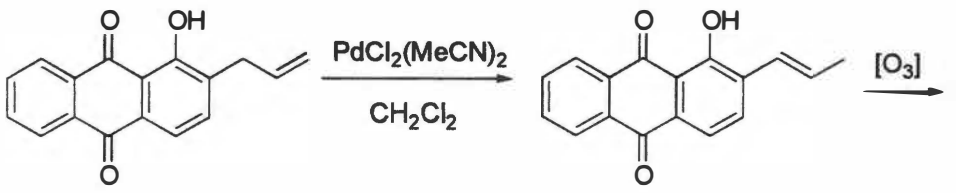
3. Initial attempt at analog synthesis using the coupling of aldehyde 2.54 and alkyne 2.15.

Once synthesis of the building blocks was completed, alkyne **2.15** and aldehyde **2.54** were coupled (Scheme 2.28). Alcohol **2.64** that had been formed was oxidized with MnO_2. Removal of all protective groups was attempted next with TMSI and BBr_3, but neither worked. A new synthetic scheme was needed.

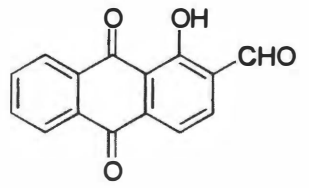
4. Second attempt at analog synthesis using the coupling of aldehyde 2.59 and alkyne 2.15.

A new protective group was needed, one that could withstand both basic and oxidative reactions, but could be removed relatively easily with mild acid. The literature was consulted and the MOM protective group was found to be consistent with these demands. The reactions up to the deprotection of the MOM protective group were first run on the model compound.

The coupling reaction between alkyne **2.15** and anthraquinone aldehyde **2.59** was next attempted; however, the reaction provided numerous compounds (Scheme 2.29). The problems most likely arose due to the chelating interactions between the MOM group and the Grignard reagent, which could draw the alkyne

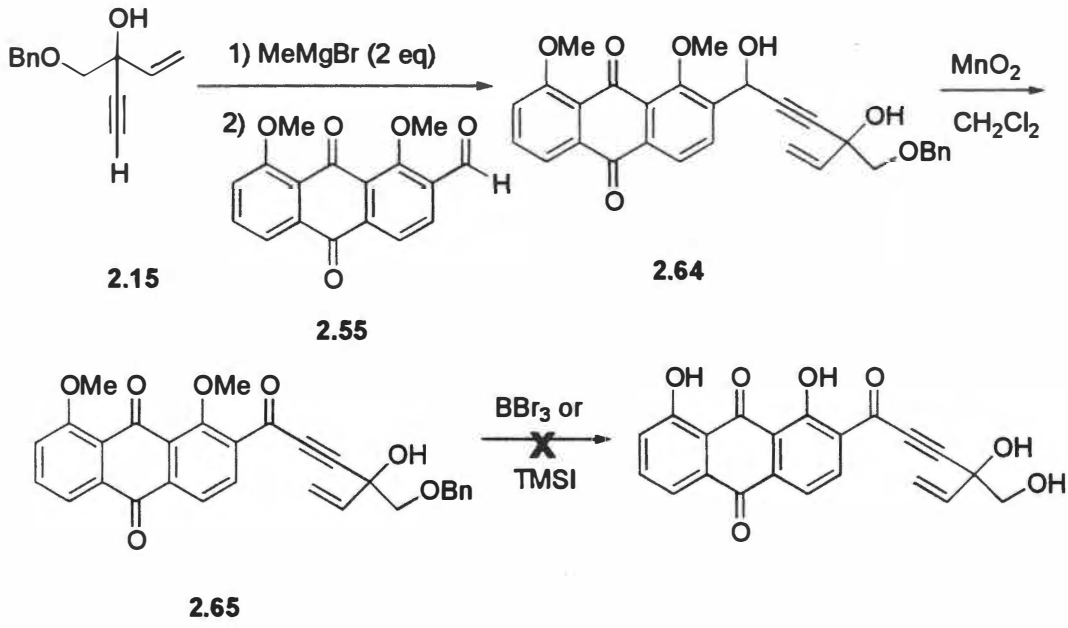


2.56 **2.63**

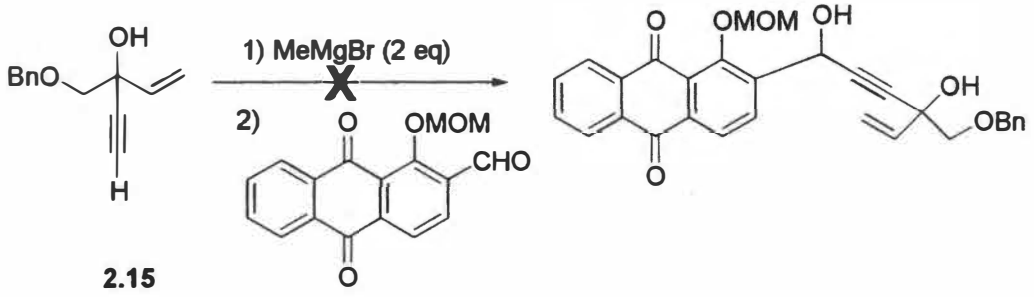


2.47

Scheme 2.27. Preparation of Aldehyde 2.47 Using Compound 2.56



Scheme 2.28. First Hydramycin Analog Attempt



Scheme 2.29. Second Hydramycin Analog Attempt

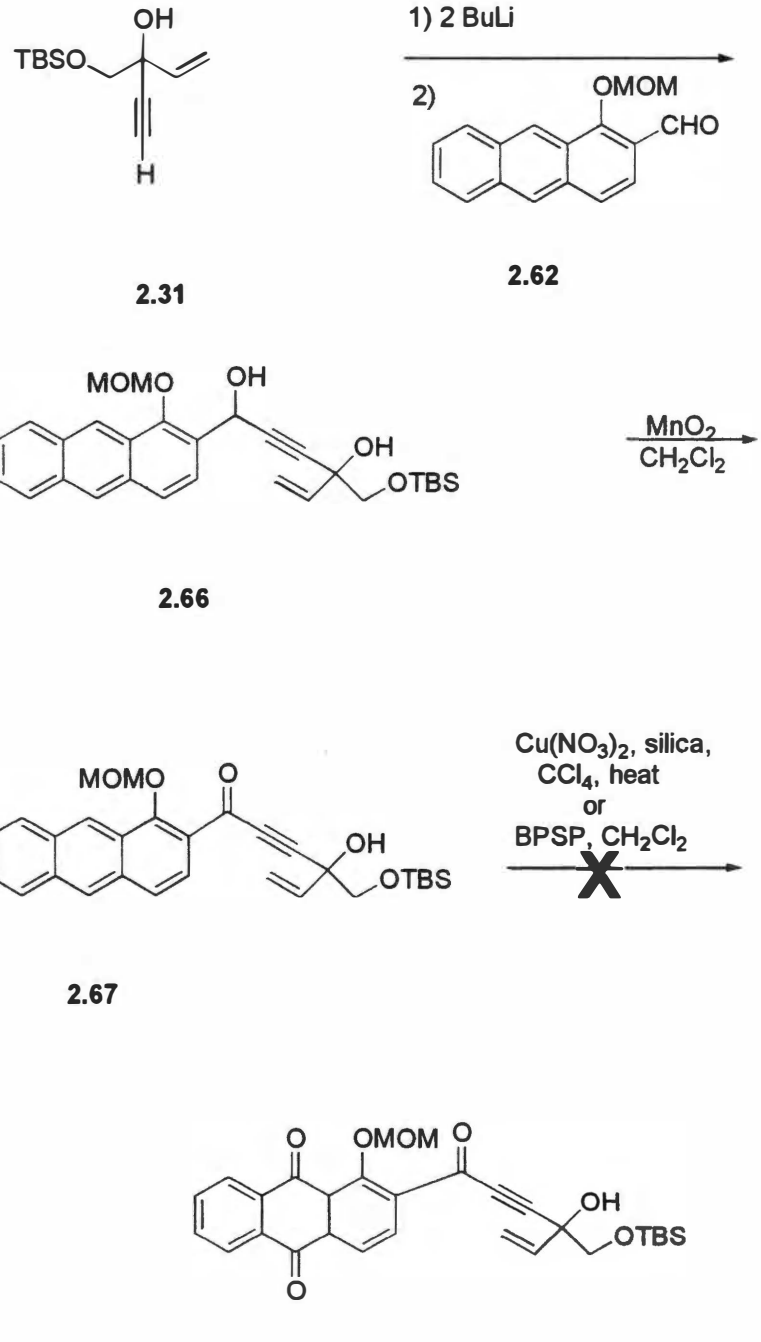
in to react with the anthraquinone carbonyls[38]. Alternative avenues were then explored.

5. Attempted analog synthesis using the coupling of aldehyde 2.62 and alkyne 2.31.

The carbonyl groups on the anthraquinone would either need to be reduced and protected or completely reduced to the anthracene. Complete reduction was the chosen method, as it was found that an aldehydic moiety could be easily added to the methoxymethoxyanthracene **2.61** (Scheme 2.26). Once the aldehyde had been generated, alkyne **2.31** was reacted with 2 equivalents of *n*-BuLi for 3 h, then with anthracene aldehyde **2.62** (Scheme 2.30). The alcohol **2.66** was oxidized with MnO_2 to give ketone **2.67**. Although literature had shown the oxidation of the anthracene to the anthraquinone could be straightforward when using bis(pyridine)silver permanganate on silica gel[38], the reaction failed to produce the desired product. The oxidation was also attempted with $Cu(NO_3)_2$ on silica gel[40], but this also did not give the desired product.

6. Hydramycin analog synthesis using the coupling of aldehyde 2.60 and 3-methyl-1-penten-4-yn-3-ol.

Precedent found in the literature[41] that implied that the protection of 1-hydroxyl groups on anthraquinones could be detrimental in a reaction of a carbonyl attached to the anthraquinone with organometallic reagents. However,



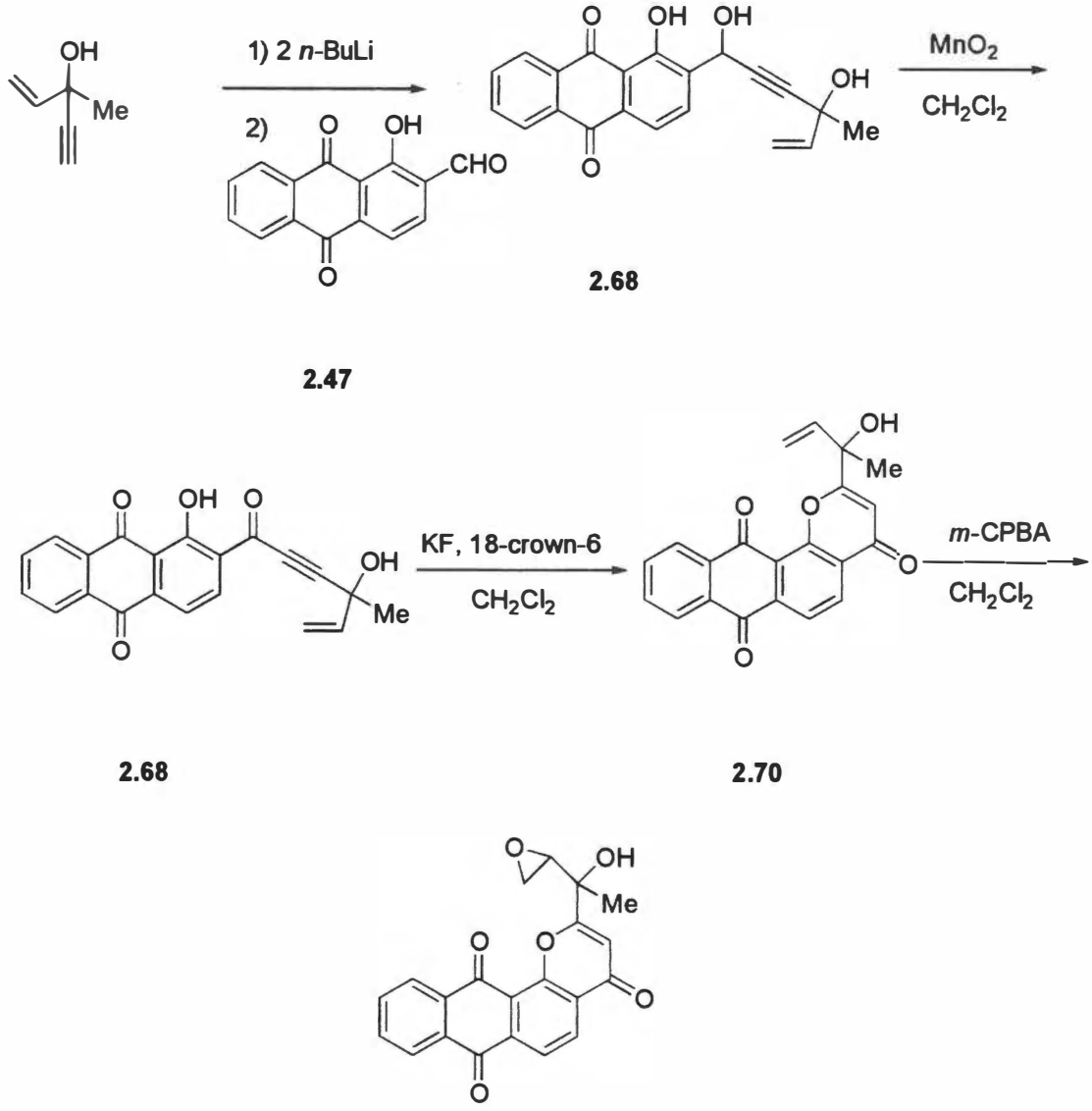
2.31 **2.62** **2.66** **2.67**

Scheme 2.30. Third Hydramycin Analog Attempt

two equivalents of the attacking specimen could be used, one to deprotect the hydroxyl group and one to attack the carbonyl. Side reactions would occur with protected hydroxyanthraquinones that would not occur with their unprotected counterparts. Therefore, aldehyde **2.47** had been generated for use (Scheme 2.27). The final synthesis of the analog is shown in Scheme 2.31. The aldehyde and alkyne were coupled as described previously with BuLi serving to deprotonate the alkyne. This reaction was closely monitored by TLC and terminated upon disappearance of the starting material as longer reaction times would result in addition to the anthraquinone carbonyls. The alcohol **2.68** was oxidized with MnO_2. This reaction was also tricky as longer reaction times caused the formation of compound **2.70** and its 5-membered ring counterpart, but not in the desired product ratio. Therefore, the ring-closure was afforded with KF and 18-crown-6 in DMF to give chromenone compound **2.70**. Finally, hydramycin analog **2.71** was produced as a set of diastereomers through the reaction of chromenone **2.70** with *m*-CPBA. The structure of the final analog **2.71** was established by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis.

IV. Conclusions

As can be concluded from the spectrum of work provided, anthraquinone compounds can be very unpredictable. The model compound synthesis did provide valuable insight into the synthesis of the hydramycin analog; however, it



Scheme 2.31. Synthesis of the Hydramycin Analog

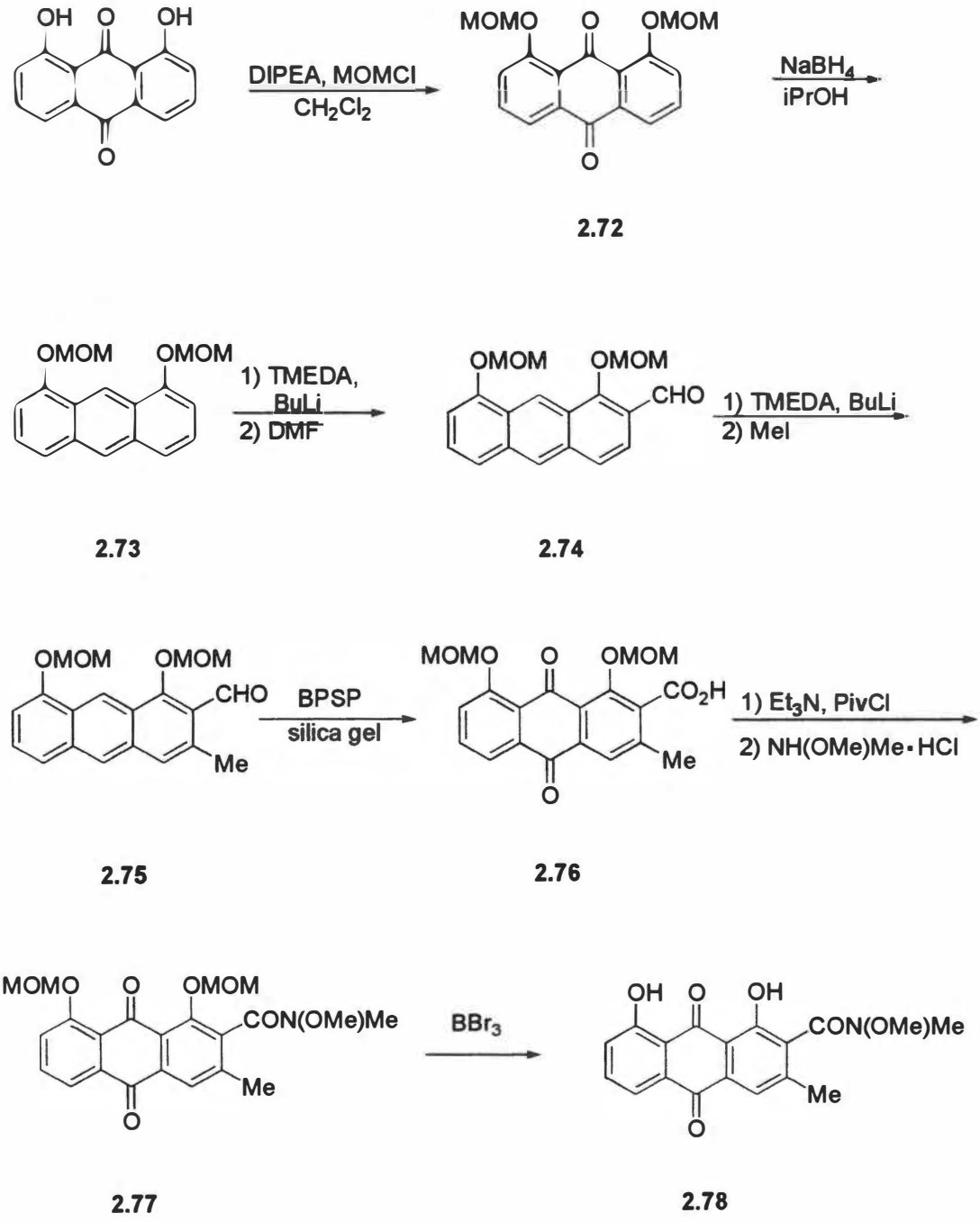
did not provide insight into the most valuable reaction, the coupling of the anthraquinone aldehyde with the alkyne. This coupling was the most challenging step in the synthesis of the analog. The valuable lesson to be learned is that the anthraquinone system does not act analogously to the anthracene system. The conjugation in the anthraquinone appears to be much less stable. Also, it is important to take note of the varied effects displayed by the 1-hydroxyl position. The MOM and Me protective groups are often used interchangeably, but their usages brought about very different results in this situation.

Despite difficulties which were faced during the syntheses depicted in this dissertation, the final results proved to be very promising. The hydramycin analog was elegantly prepared in just 8 steps in contrast to the arduous route to these systems by Hauser.[6] The overall result is one of versatility, as numerous aldehydes and alkynes can be employed in analogous syntheses. This would serve to provide a large number of analogs and might be adaptable to combinatorial or parallel synthetic methods. Also, the novel alkyne **2.31** can be eventually used in the synthesis of hydramycin.

V. Proposed Future Work

The information provided in this dissertation opens up many new avenues to be investigated in the ongoing effort of providing hydramycin and its analogs.

The first and most obvious work to be done is to generate the anthraquinone compound necessary for the synthesis of hydramycin itself. This synthesis could begin with the use of some methods provided in Scheme 2.32. The synthesis would begin as 1,8-dihydroxyanthraquinone would converted to diprotected anthraquinone **2.72** using Hünig's base and MOMCl. Next, reduction with $NaBH_4$ in refluxing isopropanol would give compound **2.73**. The aldehydic moiety would then be installed as described for aldehyde **2.62** with TMEDA and BuLi, followed by quenching with DMF. This should provide addition of just a single aldehydic group as suggested by Marcus Tius' addition reaction between such an anion and methyl chloroformate[38]. Next, aldehyde **2.74** would be reacted with TMEDA and BuLi to give a complex as shown in Figure 2.10 [42]. Although these same conditions had been used to lithiate ortho to the methoxymethoxy group earlier, the aldehyde should be much more reactive to this set of reagents than the open ortho position to the methoxymethoxy group. If there were such a problem, however, 1,8-dihydroxyanthraquinone could be monoprotected with an alternative protective group, such as the methyl protective group. The remaining unprotected phenol would then be protected with the MOM protective group, yielding only a single carbon on the anthraquinone that would be reactive to the ortho-lithiation conditions. The complex shown in Figure 2.10 could be reacted with MeI, and workup should result in regeneration of the aldehyde to give anthracene **2.75**. Finally, bis(pyridine)silver permanganate will serve to oxidize the anthracene to the



Scheme 2.32. Proposed Synthesis of Amide 2.78

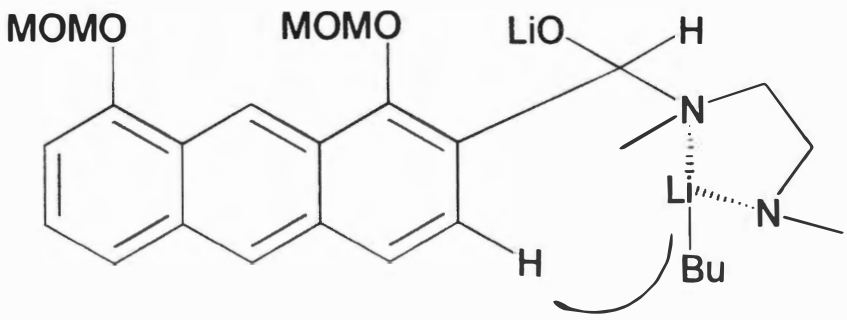
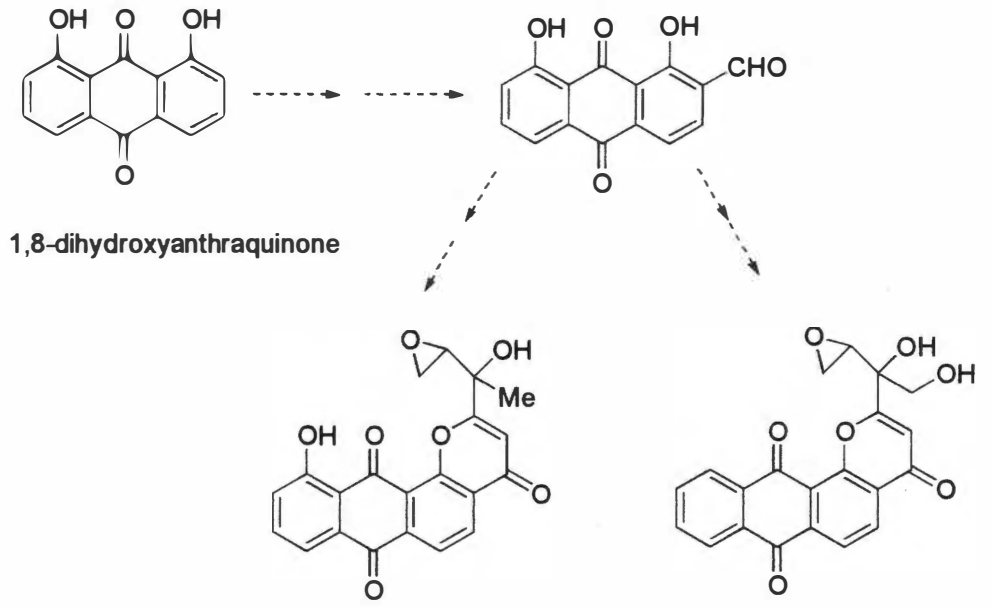


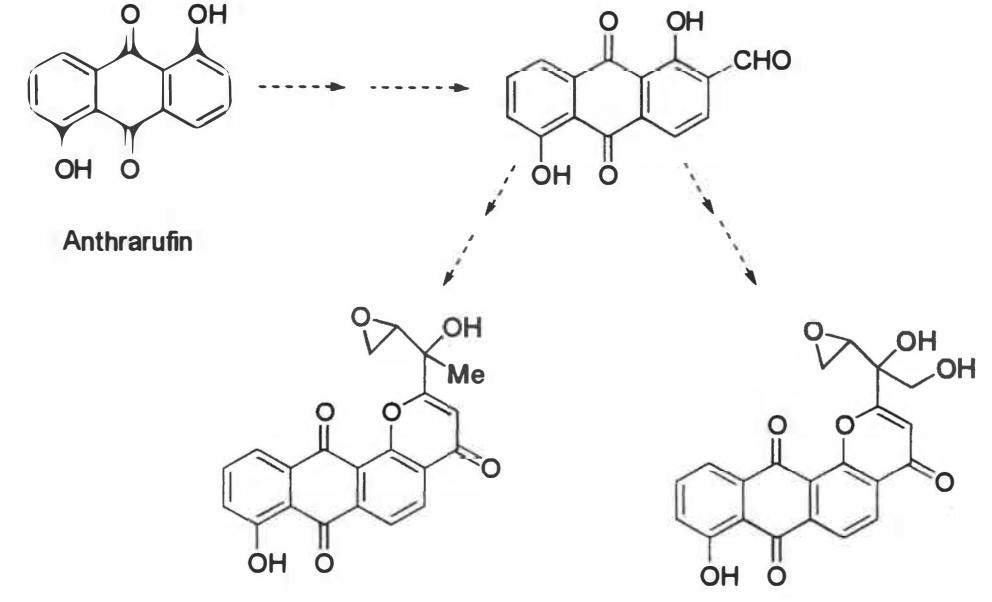
Figure 2.10. Aldehyde Complex with TMEDA and BuLi

anthraquinone. This reagent will most likely also oxidize the aldehyde to its carboxylic acid, which would not be a problem as the acid could then be converted to its Weinreb amide using TEA, pivaloyl chloride and *N,O*-dimethylhydroxylamine hydrochloride. This amide would now be the species that is attacked during the coupling reaction with an alkyne. This method would provide a shorter synthesis after the coupling as the oxidation step with MnO_2 could now be eliminated.

This work also provides many other analogs that could be made. For example, both 1,8-dihydroxyanthraquinone and anthrarufin could be used to make aldehydes and subsequently, new hydramycin analogs. Since these aldehydes could react with both the commercially available 3-methyl-1-penten-4-yn-3-ol and alkyne **2.31**, these two starting materials could provide a total of four novel analogs. (Schemes 2.33 and 2.34).



Scheme 2.33. Proposed Syntheses of 1,8-Dihydroxyanthraquinone Analogs



Scheme 2.34. Proposed Syntheses of Anthrarufin Analogs

VI. Experimental

A. General Methods

Melting points were determined by the capillary method and are uncorrected. Analytical TLC was performed on aluminum-backed plates coated with E. Merck Silica Gel-60 F-254. The developed plates were air-dried and detection was irradiated with UV light at 254 nm. Column chromatography was performed on Silica Gel-60 (40–63 mesh). ^{1}H NMR and ^{13}C NMR spectra were acquired at 250.13 MHz and 62.89 MHz, respectively, on a Bruker AC 250 instrument or at 300.087 MHz and 75.464 MHz on a Varian MERCURY 300 instrument. ^{1}H NMR chemical shifts are reported as δ (ppm) downfield from tetramethylsilane (TMS), which was used as the internal standard. ^{13}C NMR chemical shifts are reported as δ (ppm) relative to the solvent ($CDCl_3$: 77.0 ppm). Elemental analyses were carried out by Atlantic Microlab, Inc. of Atlanta, GA. Chemicals were of reagent grade and used directly. THF was dried using sodium and benzophenone as an indicator; CH_2Cl_2 was dried over CaH_2.

B. Model Compound Synthesis

1. Initial attempt using the coupling of a methyl ketone derivative and an aldehyde.

Preparation of 2-methyl-4,6-dioxocyclohexanecarboxylic acid ethyl ester (2.1).

Sodium (6.9 g, 0.30 mol) was dissolved in 100 mL of ethanol. To the solution was added 41.1 mL (42 g, 0.32 mol) of ethyl acetoacetate and 37 mL (34.8 g,

0.35 mol) of methyl crotonate. The reaction was heated at 90 °C for two hours. A thick mixture of sodium salts separated and the crude product was precipitated with dilute aqueous sulfuric acid. The material was filtered. The product precipitated with water to yield 4.3 g (0.22 mol, 69%). Due to the presence of tautomers, the NMRs were too complex to decipher.

Preparation of 3,5-dibromo-2,4-dihydroxy-6-methyl-benzoic acid ethyl ester (2.2).

To a solution of 4-methyl-2,6-dioxocyclohexanecarboxylic acid ethyl ester (0.24 g, 1.2 mmol) dissolved in 1 mL of glacial acetic acid was added 0.5 mL (1 mmol) of bromine in 1 mL of glacial acetic acid. The reaction was stirred for 1 h and then allowed to stand overnight at room temperature. The solution was concentrated and purified on a silica gel column with 9:1 hexanes–EtOAc to give 0.12 g (0.33 mmol, 28%) of the white solid. ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 3H, J = 7 Hz), 2.66 (s, 3H), 4.45 (q, 2H, J = 7 Hz), 6.47 (s,1H), 12.27 (s,1H). ^{13}C NMR ($CDCl_3$) δ 14.37, 23.56, 62.72, 96.58, 105.69, 108.16, 140.76, 154.00, 159.71, 171.02. The NMR data matched that reported.[13]

Preparation of 2,4-dihydroxy-6-methylbenzoic acid ethyl ester (2.3).

To a solution of 3,5-dibromo-2,4-dihydroxy-6-methylbenzoic acid ethyl ester (0.13 g, 0.37 mmol) dissolved in 2 mL of 2 N sodium hydroxide solution cooled to 0 °C was added 10% palladium-on-carbon (0.05 g), and hydrogen gas was

passed through at atmospheric pressure overnight. The catalyst was filtered over Celite into ice-cold concentrated hydrochloric acid. The precipitate that formed was collected and dried with $MgSO_4$ yielding 0.05 g (0.25 mmol, 68%) of the white solid. ^1H NMR ($CDCl_3$) δ 1.35 (t, J = 7.5 Hz, 3H), 2.43 (s, 3H), 4.33 (q, J = 6.9 Hz, 2H), 5.28 (s, 1H), 6.15 (d, J = 2.7 Hz, 1H), 6.21 (d, J = 2.4 Hz, 1H), 11.79 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 13.21, 23.36, 60.31, 100.26, 104.77, 110.27, 143.05, 159.10, 164.32, 170.70.[13]

2. Second attempt utilizing the coupling of a methyl ketone and an aldehyde.

a. Aldehyde synthesis.

Preparation of benzyloxyacetic acid (2.4).

Sodium metal (5.4 g, 0.23 mol) was added to 108 mL of benzyl alcohol in five portions at 90–110 °C. After all of the sodium had reacted, 24.7 g (212 mmol) of the sodium salt of chloroacetic acid were added slowly to the solution. The reaction was heated to 165 °C and stirred for 48 h. The benzyl alcohol was distilled off at 0.25 mm Hg and 40 °C. (It is important to note here that 80 mL ± 5 mL of the benzyl alcohol had to be removed. If not, the remaining benzyl alcohol would react with the benzyloxyacetic acid to give the unwanted ester.) Water was added to the sticky residue, and the resulting solution was extracted with ether. The aqueous layer was brought to pH 2, and was again extracted with

ether. The combined ether extracts were dried over $MgSO_4$ and concentrated. The pale-yellow residue was distilled at 0.1 mm Hg and 120 °C (Lit.[43] 135–140 °C at 0.24 mm Hg), yielding 27.74 g (0.17 mol, 79%) of product as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 4.09 (s, 2H), 4.58 (s, 2H), 7.18-7.31 (m, 5H), 10.68 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 66.57, 73.41, 128.17, 128.22, 128.59, 136.66, 175.51.

Preparation of 2-benzyloxy-*N*-methoxy-*N*-methylacetamide (2.5).

A solution of benzyloxyacetic acid (11.5 g, 69.2 mmol) and 11.8 g (72.8 mmol) 1,1-carbonyldiimidazole dissolved in 360 mL of dry THF was stirred until no more CO_2 evolved. Next, 7.10 g (72.8 mmol) of *N,O*-dimethylhydroxylamine hydrochloride were added, and the reaction was stirred at room temperature for 48 h. The solution was filtered, and the filtrate diluted with ether, then washed with 1 N HCl and brine. The organic layer was dried over $MgSO_4$ and concentrated. Distillation at 0.1 mm Hg and 110–115 °C (Lit.[44] 132 °C at 0.2 mm Hg) yielded 10.8 g (51.6 mmol, 74% yield) of product as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 3.13 (s, 3H), 3.52 (s, 3H), 4.21 (s, 2H), 4.63 (s, 2H), 7.22 (m, 5H). ^{13}C NMR: δ 61.37, 67.31, 73.21, 127.82, 128.03, 128.42, 128.51, 137.45, 221.43.

Synthesis of 2-benzyloxy-1-[1,3]dithian-2-ylethanone (2.6).

A solution of 1,3-dithiane (3.6 g, 30 mmol dissolved in 60 mL of dry THF was cooled to -40 °C. To the solution was added 13.2 mL of 2.5 M butyllithium (33 mmol). The solution was stirred at -40 °C for 2 h. The solution was further

cooled to -78 °C, and 6 g (29 mmol) of 2-benzyloxy-N-methoxy-N-methylacetamide were added. The reaction was warmed to room temperature and stirred overnight. A satd aq NH_4Cl solution was added, and the mixture was extracted with ether. The organic layer was dried with $MgSO_4$ and concentrated to yield a yellow oil that was purified on a silica gel column (25:1 petroleum ether–EtOAc) to give 4.72 g (17 mmol, 61.4%) of the pure white crystals. ^1H NMR ($CDCl_3$) δ 2.05 (m, 2H), 2.53 (m, 2H), 3.29 (m, 2H), 4.26 (s, 2H), 4.46 (s, 1H), 4.60 (s, 2H), 7.34 (m, 5H). ^{13}C NMR δ 25.02, 25.36, 40.52, 72.24, 73.49, 127.85, 128.01, 128.46, 136.91.

Synthesis of 1-benzyloxy-2-[1,3]dithian-2-ylbut-3-en-2-ol (2.7).

A solution of 18.7 mL (18.7 mmol) of 1.0 M vinylmagnesium bromide in THF was cooled to 0 °C, and a solution of 2.0 g (7.5 mmol) of 2-benzyloxy-1-[1,3]-dithian-2-yl-ethanone in 10 mL of THF was added. The reaction was warmed to room temperature and stirred for 2 h. Water was added dropwise to quench the reaction mixture, and the mixture was then poured into a 5% aq NH_4Cl solution. The organic layer was separated and washed with satd aq $NaHCO_3$ and water, then dried over $MgSO_4$ and concentrated. The crude material was purified via silica gel chromatography (3:1 petroleum ether–EtOAc) to give 0.85 g (2.9 mmol, 39%) of the pure product. ^1H NMR (CDCl3) δ 1.85 (m, 1H), 2.09 (m, 1H), 2.66 (m, 5H), 3.52 (d, J = 11.5 Hz, 1H), 3.72 (d, J = 11.4 Hz, 1H), 4.45 (s, 1H), 4.59 (s, 2H), 5.32 (d, J = 12.9 Hz, 1H), 5.55 (d, J = 21 Hz, 1H), 6.03 (dd, J = 13.0 and

20 Hz, 1H), 7.33 (m, 5H).

Synthesis of 2-benzyloxymethyl-2-[1,3]dithian-2-yl[1,3]dioxolane (2.8).

A solution of 2-benzyloxy-1-[1,3]dithian-2-ylethanone (3.0 g, 11 mmol), 2.8 mL (3.1 g, 51 mmol) of ethylene glycol and 0.15 g (0.79 mmol) of *p*-toluenesulfonic acid monohydrate dissolved in 45 mL of dry toluene was refluxed overnight while fitted with a Dean-Stark trap. The solution was then cooled, diluted with 1:1 petroleum ether–CH_2Cl_2, washed with 0.5 M aq $NaHCO_3$, water and brine, then dried over $MgSO_4$. The solution was concentrated and the crude material was purified on a silica gel column (9:1 petroleum ether–EtOAc) to yield 2.46 g (7.87 mmol, 70.4%) of a pale-yellow oil. ^{1}H NMR ($CDCl_3$) δ 1.91 (m, 2H), 2.63 (m, 2H), 2.90 (m, 2H), 3.61 (s, 2H), 3.97 (m, 2H), 4.08 (m, 2H), 4.23 (s, 1H), 4.51 (s, 2H), 7.22 (m, 5H). 13C NMR (CDCl3) δ 25.36, 28.26, 28.42, 49.40, 64.87, 66.28, 70.81, 73.42, 76.48, 76.99, 77.50, 111.09, 126.64, 127.31, 127.37, 127.80, 128.04, 128.19, 137.86.

Synthesis of 2-benzyloxymethyl[1,3]dioxolane-2-carbaldehyde (2.9).

To a solution of 3.4 g of NBS (19 mmol) dissolved in 30 mL of aq 80% acetonitrile solution at 15 °C was added 2-benxyloxymethyl-[1,3]-dithian-2-yl-[1,3]-dioxolane (1.0 g, 3.2 mmol) dissolved in 4 mL of acetonitrile. The reaction was stirred at 15 °C for 10 min, then shaken with a mixture of satd sodium sulfite solution and 1:1 petroleum ether–CH_2Cl_2. The organic layer was washed with

1.0 M aq $NaHCO_3$, brine and water, dried with $MgSO_4$ and concentrated. The reaction yielded 1.32 g (5.94 mmol, 75.7%) of an orange oil that was used without further purification.

b. Methyl ketone synthesis

Preparation of 1-(2,4-dihydroxy-6-methylphenyl)ethanone (2.10).

Anhydrous acetonitrile (1.8 mL, 34 mmol) and 1.1 g (8.3 mmol) of zinc chloride were placed in 10 mL of dry ethyl ether at 0 °C. Dry HCl gas was passed into the solution for 45 min at 0 °C. The reaction stood for 3 h. Next, 3.1 g (25 mmol) of orcinol was added, and the reaction was allowed to stand at -6 °C for 6 days. The reaction material was filtered, the precipitate was dissolved in 38 mL of water, and this solution was refluxed for 1.5 h. The reaction was cooled to room temperature and the precipitate was filtered to give 1.1 g (6.6 mmol, 26.5%) of the ketone. ^{1}H NMR (DMSO) δ 2.15 (s, 3H), 2.40 (s, 3H), 6.08 (d, J = 2.1, 1H), 6.15 (d, J = 2.4, 1H), 9.77 (br s, 1H), 10.60 (br s, 1H). ^{13}C NMR (DMSO) δ 21.00, 32.40, 100.31, 109.67, 119.01, 139.09, 159.10, 159.92, 203.10. The NMR data matched that reported.[45]

Synthesis of 1-(2,4-dimethoxy-6-methylphenyl)ethanone (2.11).

A solution of 1-(2,4-dihydroxy-6-methylphenyl)ethanone (1.6 g, 9.6 mmol) in 7.3 mL of ethanol was heated until the solid dissolved. The heat was removed, and

to the hot solution was added 1.0 g (25 mmol) of NaOH in 2.5 mL of water and 2.93 g (23.0 mmol) of dimethyl sulfate, followed by another 0.20 g (5.0 mmol) of NaOH in 0.5 mL of water. The solution was refluxed for 3 h. The ethanol was removed under reduced pressure, and the resulting residue was steam-distilled to yield 1.25 g (6.4 mmol, 66.8%) of a white crystal. ^{1}H NMR ($CDCl_3$) δ 2.25 (s, 3H), 2.46 (s, 3H), 3.80 (s, 6H), 6.30 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 20.25, 32.66, 55.57, 55.76, 96.16, 107.40, 124.31, 138.15, 158.67, 161.33, 204.86. The NMR data matched that reported.[46]

c. Coupling of the methyl ketone and the aldehyde.

Synthesis of 3-(2-benzyloxymethyl[1,3]dioxan-2-yl)-1-(2,4-dimethoxy-6-methylphenyl)-3-hydroxypropan-1-one (2.12).

To a solution of 1-(2,4-dimethoxy-6-methylphenyl)ethanone (104 mg, 0.535 mmol) in 1 mL of anhydrous THF at -78 °C, was added 0.5 mL (1.0 mmol) of 2.0 M LDA in THF–heptane–ethylbenzene and 2-benzyloxy[1,3]dioxolane-2-carbaldehyde (0.31 g, 1.4 mmol) in 3 mL of THF. The reaction was stirred overnight, then quenched with satd aq NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and water, dried with $MgSO_4$ and concentrated. The crude oil was purified on a silica gel column (3:1 petroleum ether–EtOAc) to yield 0.11 g (0.54 mmol, 49%) of the yellow oil. ^{1}H NMR ($CDCl_3$) δ 2.26 (s, 3H), 2.94 (dd, 1H, J = 9.9 and17.1 Hz), 3.16 (dd, 1H, J = 3

and 17.1 Hz), 3.57 (d, 1H, *J* = 10.5 Hz), 3.65 (d, 1H, *J* = 10.5 Hz), 3.75 (s, 3H), 3.81 (s, 3H), 4.01 (m, 4H), 4.41 (dd, 1H, *J* = 2.4 and 9.9 Hz), 4.61 (s, 2H), 6.29 (d, 1H, *J* = 1.8), 6.32 (d, 1H, *J* = 1.8), 7.30 (m, 5H). ^{13}C NMR δ 45.59, 55.35, 55.56, 65.78, 66.14, 70.20, 70.44, 73.76, 95.99, 107.41, 109.30, 127.58, 128.35, 161.33, 206.53.

3. Attempted synthesis requiring the coupling of 2-(*tert*-butyldimethylsilyloxy)benzaldehyde and an alkyne.

a. Synthesis of the alkyne.

Synthesis of 1-benzyloxy-4-trimethylsilyl-but-3-yn-2-one (2.13).

To a solution of ethynyltrimethylsilane (0.30 g 3.0 mmol) in 30 mL of anhydrous THF cooled to -78 °C was added 1.8 mL (3.0 mmol) of a 1.6 M solution of butyllithium. The reaction was stirred for 30 min. A solution of 0.31 g (1.5 mmol) of 2-benzyloxy-*N*-methoxy-*N*-methylacetamide in 5 mL of THF was added and the reaction was warmed to -10 °C over 1 h. The solution was kept at -10 °C for 1 h. Upon cooling to -78 °C, the reaction was quenched with 1 mL of glacial acetic acid. The solution was slowly warmed to 0 °C, and 20 mL of brine and 20 mL of ethyl ether were added. The aqueous layer was washed with ether. The combined organic layers were washed with brine and satd aq $NaHCO_3$, dried over $MgSO_4$ and concentrated to yield 0.31 g (1.3 mmol, 87%) of a brown oil that was used without further purification. ^1H NMR ($CDCl_3$) δ 0.24 (s, 9H), 4.23 (s,

2H), 4.64 (s, 2H), 7.37 (m, 5H). ^{13}C NMR ($CDCl_3$) δ -0.88, 73.34, 75.71, 99.71, 101.27, 127.92, 128.02, 128.47, 137.01, 184.66.

Synthesis of 3-benzyloxymethyl-5-trimethylsilylpent-1-en-4-yn-3-ol (2.14).

A 1.0 M solution of vinylmagnesium bromide in THF (4.1 mL, 4.1 mmol) was cooled to 0 °C. To the solution was added 0.31 g (1.25 mmol) of 1-benzyloxy-4-trimethylsilanylbut-3-yn-2-one dissolved in 2 mL of THF. The solution was stirred at room temperature overnight. The reaction was quenched with satd aq NH_4Cl. The aqueous layer was washed with ether, and the combined organic layers were washed with brine, dried over $MgSO_4$ and concentrated to give 0.38 g (1.4 mmol, 90.9%) of a brown oil that was used without further purification. ^1H NMR ($CDCl_3$) δ 0.19 (s, 9H), 2.92 (br s, 1H), 3.49 (d, J = 9.3 Hz, 1H), 3.58 (d, J = 9.3 Hz, 1H), 4.68 (s, 2H), 5.27 (d, J = 10.2, 1H), 5.63 (d, J = 17.1 Hz, 1H), 5.91 (dd, J = 17.0 and 10.0 Hz, 1H), 7.35 (m, 5H). ^{13}C NMR ($CDCl_3$) δ -0.15, 71.09, 73.55, 76.42, 90.56, 104.54, 116.69, 127.60, 127.75, 128.40, 137.30, 137.76.

Synthesis of 3-benzyloxymethylpent-1-ene-4-yn-3-ol (2.15).

A solution containing 0.38 g (1.4 mmol) of 3-benzyloxymethyl-5-trimethylsilylpent-1-en-4-yn-3-ol dissolved in 40 mL of anhyd methanol was cooled to 0 °C. To the solution was added 0.5 mL of 25% sodium methoxide by weight in methanol. The reaction was allowed to stir at room temperature for 3 h. The reaction was quenched with satd aq NH_4Cl, and the aqueous layer was

extracted with ether. The combined organic layers were washed with water and brine, dried with $MgSO_4$ and concentrated to yield 0.2 g (0.98 mmol, 71.3%) of a colorless oil. ^1H NMR ($CDCl_3$) δ 2.59 (s, 1H), 2.98 (br s, 1H), 3.49 (d, *J* = 9.3 Hz, 1H), 3.59 (d, *J* = 9.3 Hz, 1H), 4.68 (s, 2H), 5.29 (d, *J* = 10.5 Hz, 1H), 5.64 (d, *J* = 16.8 Hz, 1H), 5.91 (dd, *J* = 17.1 and 10.5, 1H), 7.34 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 70.67, 73.71, 73.86, 76.36, 83.29, 117.02, 127.72, 127.86, 128.45, 136.92, 137.49.

b. Preparation of 2-(*tert*-butyldimethylsilyloxy)benzaldehyde, coupling and further reactions.

Preparation of 2-(*tert*-butyldimethylsilyloxy)benzaldehyde (2.16).

A solution containing 5.0 mL (47 mmol) of 2-hydroxybenzaldehyde, 6.4 g (94 mmol) of imidazole, 9.2 g (61 mmol) of *tert*-butyldimethylchlorosilane and a catalytic amount of DMAP in 250 mL of DMF was stirred for 4 h at room temperature. The reaction was quenched with satd aq NH_4Cl and extracted with EtOAc. The organic layers were dried with $MgSO_4$ and concentrated. The crude material was purified via silica gel chromatography with 9:1 petroleum ether–EtOAc to give 8.1 g (34 mmol, 73%) of the colorless oil. ^1H NMR ($CDCl_3$) δ 0.28 (s, 6H), 1.01 (s, 9H), 6.88 (d, *J* = 7.8 Hz, 1H), 7.04 (t, *J* = 8.1 Hz, 1H), 7.47 (t, *J* = 7.2 Hz, 1H), 7.81 (d, *J* = 7.8 Hz, 1H), 10.47 (s, 1H). ^{13}C NMR ($CDCl_3$) δ -4.33, 18.32, 25.62, 120.17, 121.44, 127.16, 128.28, 135.73, 158.91, 190.22.

The NMR data matched that reported.[18]

Synthesis of 4-benzyloxymethyl-1-[2-*tert*-butyldimethylsilyloxy)-phenyl]hex-5-en-2-yne-1,4-diol (2.17).

A 3.0 M solution of MeMgBr in diethyl ether (0.84 mL, 2.5 mmol) was placed in 20 mL of THF under N_2. To the solution was added 254 mg (1.26 mmol) of 3-benzyloxymethylpent-1-en-4-yn-3-ol in 3 mL of THF. The reaction stirred at 50 °C. After 3 h, 240 mg (1.00 mmol) of 2-(*tert*-butyldimethylsilyloxy)-benzaldehyde were added and the reaction was stirred overnight. The reaction was quenched with satd aq NH_4Cl and extracted with EtOAc. The organic layer was washed with brine and water, dried with $MgSO_4$ and concentrated. The product was purified on a silica gel column (6:1 petroleum ether–EtOAc) to yield 318 mg (0.73 mmol, 71%) of a yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.256 (s, 3H), 0.281 (s, 3H), 1.02 (s, 9H), 2.80 (d, J = 3.6, 1H), 3.02 (d, J = 3, 1H), 3.56 (m, 2H), 4.64 (s, 2H), 5.26 (d, J = 10.5, 1H), 5.62 (d, J = 16.8, 1H), 5.81 (d, J = 4.2, 1H), 5.92 (dd, J = 10.5 and 16.5, 1H), 6.82 (d, J = 8.1, 1H), 6.96 (t, J = 6.6, 1H), 7.20 (t, J = 7.5, 1H), 7.31 (s, 5H), 7.61 (d, J = 7.5, 1H).

Synthesis of 4 -benzyloxymethyl-1-[2-(*tert*-butyldimethylsilyloxy)phenyl]-4-hydroxyhex-5-en-2-yn-1-one (2.18).

A solution of 4-benzyloxymethyl-1-[2-*tert*-butyldimethylsilyloxy)phenyl]hex-5-en-2-yne-1,4-diol (318 mg, 0.725 mmol) and manganese dioxide (950 mg, 10.9

mmol) in 6 mL of anhyd CH_2Cl_2 was refluxed overnight. The solid MnO_2 was filtered over Celite, and the solution was concentrated. The product was purified on a silica gel column (6:1 petroleum ether–EtOAc) to yield 105 mg (0.240 mmol, 31%) of a yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.229 (s, 6H), 1.01 (s, 9H), 3.12 (s, 1H), 3.56 (d, *J* = 9.5, 1H), 3.68 (d, *J* = 9.3, 1H), 4.68 (s, 2H), 5.34 (d, *J* = 10.3, 1H), 5.68 (d, *J* = 17, 1H), 5.92 (dd, *J* = 10.3 and 17, 1H), 6.88 (d, *J* = 8, 1H), 7.01 (t, *J* = 7.8, 1H), 7.33 (m, 6H), 8.01 (d, *J* = 7.5, 1H).

Synthesis of 2-(1-benzyloxymethyl-1-hydroxyallyl)chromene-4-one (2.19). To a solution of 4 -benzyloxymethyl-1-[2-(*tert*-butyldimethylsilyloxy)phenyl]hex-5-en-2-yne-1,4-diol (138 mg, 0.316 mmol) dissolved in 6.3 mL of DMF was added spray-dried KF (36 mg, 0.62 mmol) and 18-crown-6 (0.17 g, 0.64 mmol), and the reaction was stirred for 2 h. The reaction was quenched with satd aq NH_4Cl, extracted with EtOAc and the organic layer was washed with brine and water. The solution was dried with $MgSO_4$ and concentrated. The crude product was purified on a silica gel column (3:1 petroleum ether–EtOAc) to yield 60 mg (0.19 mmol, 59%) of the white solid. ^{1}H NMR ($CDCl_3$) δ 3.33 (s, 1H), 3.57 (d, *J* = 9.6, 1H), 4.02 (d, *J*= 9.3), 4.50 (d, *J* = 12.3, 1H), 4.61 (d, *J* = 12.3, 1H), 5.32 (d, *J* = 10.5, 1H), 5.57(d, *J* = 16.5, 1H), 6.05 (dd, *J* = 10.5 and 17.1, 1H), 6.69 (s, 1H), 7.29 (m, 7H), 7.65 (m, 1H), 8.20 (dd, *J* = 1.2 and 6.3, 1H). ^{13}C NMR ($CDCl_3$) δ 73.34, 73.55, 73.65, 108.79, 109.11, 118.05, 118.23, 124.08, 125.37, 125.92,

126.22, 127.77, 128.04, 128.60, 133.79, 135.70, 137.30, 156.29, 169.48, 178.63.

4. Attempted synthesis using the coupling of o-anisaldehyde and an alkyne 2.15.

Synthesis of 4-benzyloxymethyl-1-(2-methoxyphenyl)hex-5-en-2-yne-1,4-diol (2.20).

To a solution containing 5.4 mL (16 mmol) of 3.0 M MeMgBr was added 1.63 g (8.06 mmol) of 3-Benzyloxymethylpent-1-en-4-yn-3-ol in 10 mL of THF. The mixture was stirred for 3.5 h at 60 °C. The reaction mixture was cooled to room temperature and a solution of 1.0 g (7.3 mmol) of *o*-anisaldehyde in 10 mL of THF was added. The reaction was stirred for an additional 2 h. Satd aq NH_4Cl was added to quench the reaction. The solution was then extracted with EtOAc, dried over $MgSO_4$ and concentrated. The crude material was subjected to silica gel chromatography (3:1 petroleum ether–EtOAc) to give 2.07 g (6.1 mmol, 83%) of the oil. ^1H NMR ($CDCl_3$) δ 2.96 (m, 2H), 3.52 (d, J = 9.6 Hz, 1H), 3.61 (d, J = 9.3 Hz, 1H), 3.87 (s, 3H), 4.66 (s, 2H), 5.27 (d, J = 11.7 Hz, 1H), 5.62 (d, J = 17.1 Hz, 1H), 5.76 (d, J = 6.6 Hz, 1H), 5.95 (dd, J = 10.2 and 17.1 Hz, 1H), 6.92 (m, 2H), 7.32 (m, 6H), 7.48 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 55.46, 60.84, 70.86, 73.56, 85.23, 110.71, 116.73, 116.75, 120.77, 127.66, 127.70, 127.94, 128.36, 128.43, 129.62, 137.29, 137.31, 137.62, 156.66.

Synthesis of 4-benzyloxymethyl-4-hydroxy-1-(2-methoxyphenyl)hex-5-en-2-yn-1-one (2.21).

To a solution containing 0.92 g (2.7 mmol) of 4-benzyloxymethyl-1-(2-methoxyphenyl)hex-5-en-2-yne-1,4-diol in 7.5 mL of CH_2Cl_2 is added MnO_2 (3.55 g, 40.8 mmol). The reaction is stirred at 35 °C for 30 min. The mixture was filtered over Celite and concentrated to give 0.27 g (0.80 mmol, 30%) of a yellow oil. ^1H NMR ($CDCl_3$) δ 3.17 (s, 1H), 3.49 (d, J = 9.6 Hz, 1H), 3.60 (d, J = 9.6 Hz), 3.80 (s, 3H), 4.61 (s, 2H), 5.26 (d, J = 10.5 Hz, 1H), 5.63 (d, J = 17.1 Hz, 1H), 5.87 (dd, J = 10.5 and 17.1 Hz, 1H), 6.91 (m, 2H), 7.25 (m, 5H), 7.45 (m, 1H), 7.95 (m, 1H).

5. Attempted synthesis using the coupling of 2-(methoxymethoxy)benzaldehyde and alkyne 2.15.

Preparation of 2-(methoxymethoxy)benzaldehyde (2.22).

To a solution containing 3.0 g (25 mmol) of salicylaldehyde and 22 mL (4.2 g, 33 mmol) of diisopropylethylamine in 30 mL of anhydrous CH_2Cl_2 was added 5.7 mL (6.0 g, 75 mmol) of chloromethyl methyl ether. The reaction was refluxed overnight and quenched with satd aq NH_4Cl. The layers were separated, and the organic layer was washed with brine, dried with $MgSO_4$ and concentrated. The crude material was purified on silica gel (3:1 petroleum ether–EtOAc) to

give 3.10 g (18.7 mmol, 77%) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ 3.53 (s, 3H), 5.31 (s, 2H), 7.08 (t, *J* = 7.2 Hz, 1H), 7.14 (d, *J* = 7.8 Hz), 7.53 (t, *J* = 7.5 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 10.51 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 56.47, 94.56, 114.98, 121.83, 125.42, 128.33, 135.83, 159.63, 189.73. The NMR data matched that reported.[47]

Synthesis of 4-benzyloxymethyl-1-(2-methoxymethoxyphenyl)hex-5-en-2-yne-1,4-diol (2.23).

A solution of 0.67 g (3.3 mmol) of 3-benzyloxymethylpent-1-ene-4-yn-3-ol in 10 mL of THF was added to 2.2 mL of a 3.0 M MeMgBr solution in diethyl ether (6.6 mmol) that had been cooled to 0 °C. The solution was then stirred at 50 °C for 5 h. The reaction was cooled to room temperature and a solution containing 0.5 g (3.0 mmol) of 2-methoxymethoxybenzaldehyde in 10 mL of THF was added. The reaction mixture was stirred at RT overnight and then quenched with satd aq NH_4Cl. The layers were separated, and the organic layer was washed with brine, dried with $MgSO_4$ and concentrated. The crude oil was purified via silica gel chromatography (3:1 petroleum ether–EtOAc) to give 0.84 g (2.3 mmol, 76%) of a pale-yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.14 (br s, 2H), 3.37 (s, 3H), 3.46 (m, 2H), 4.55 (s, 2H), 5.14 (m, 3H), 5.52 (d, *J* = 15 Hz, 1H), 5.70 (br s, 1H), 5.83 (dd, *J* = 10.5 and 6.6 Hz, 1H), 6.91 (t, *J* = 7.5 Hz, 1H), 7.02 (dd, *J* = 8.1 and 1.2 Hz, 1H), 7.19 (m, 6H), 7.49 (dd, 7.5 and 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 56.24, 60.62, 70.80, 73.56, 76.49, 85.17, 85.34, 94.62, 114.53, 116.62, 122.05, 127.64, 127.72, 127.93, 128.36, 129.41, 129.60, 137.34, 137.57, 154.38. Anal. Calcd

for $C_{22}H_{24}O_5 \cdot 0.035H_2O$: C, 71.11; H, 6.61. Found: C, 71.10; H, 6.72.

Synthesis of 4-benzyloxymethyl-4-hydroxy-1-(2-methoxymethoxyphenyl)hex-5-en-2-yn-1-one (2.24).

To a solution containing 0.74 g (2.0 mmol) of 4-benzyloxymethyl-1-(2-methoxymethoxyphenyl)hex-5-en-2-yne-1,4-diol in 10 mL of CH_2Cl_2 was added 2.86 g (40.3 mmol) of MnO_2. The reaction was heated to 35 °C for 30 min. The solution was filtered over Celite and concentrated. The crude oil was purified by silica gel chromatography (3:1 petroleum ether–EtOAc) to give 0.44 g (1.2 mmol, 59%) of the yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.32 (br s, 1H), 3.39 (s, 3H), 3.48 (d, *J* = 9.6, 1H), 3.59 (d, *J* = 9.3 Hz, 1H), 4.59 (s, 2H), 5.15 (s, 2H), 5.25 (d, *J* = 10.5 Hz, 1H), 5.61 (d, *J* = 17.4 Hz, 1H), 5.87 (dd, *J* = 10.5 and 17.4 Hz, 1H), 6.96 (t, *J* =7.2 Hz, 1H), 7.11 (d, *J* = 7.5 Hz, 1H), 7.24 (m, 5H), 7.40 (t, *J* = 7.2 Hz, 1H), 7.9 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 56.49, 71.04, 73.70, 76.03, 85.05, 91.57, 94.77, 115.90, 117.59, 121.54, 127.14, 127.74, 127.87, 128.42, 132.17, 134.91, 136.05, 137.28, 157.31, 176.09. Anal. Calcd for $C_{22}H_{22}O_5 \cdot 0.037H_2O$: C, 71.47; H, 6.10. Found: C, 71.51; H, 6.12.

Synthesis of 4-benzyloxymethyl-4-hydroxy-1-(2-hydroxyphenyl)hex-5-en-2-yn-1-one (2.25).

A solution containing 0.35 g (0.96 mmol) of 4-benzyloxymethyl-4-hydroxy-1-(2-methoxymethoxyphenyl)-hex-5-en -2-yn-1-one and 1 mL of 1 M H_2SO_4 in 4

mL of acetone was stirred at room temperature overnight. The reaction was quenched with satd aq $NaHCO_3$ and extracted with EtOAc. The organic layer was separated, dried over $MgSO_4$ and concentrated. The crude oil was subjected to chromatography (4:1 petroleum ether–EtOAc on silica gel) to give 0.21 g (0.66 mmol, 69%) of a pure yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.40 (s, 1H), 3.52 (d, *J* = 9.3 Hz, 1H), 3.62 (d, *J* = 9.0 Hz, 1H), 4.61 (s, 2H), 5.31 (d, *J* = 10.5 Hz, 1H), 5.62 (d, *J* = 17.1 Hz, 1H), 5.87 (dd, *J* = 10.5 and 17.1 Hz, 1H), 6.84 (m, 2H), 7.26 (m, 5H), 7.42 (m, 1H), 7.94 (m, 1H), 11.50 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 71.20, 73.80, 75.97, 81.29, 95.91, 117.99, 118.15, 119.48, 120.54, 127.79, 128.03, 128.54, 133.27, 135.41, 137.12, 137.32, 162.69, 181.81.

Synthesis of 2-(1-benzyloxymethyl-1-hydroxyallyl)chromen-4-one (2.19). The reaction was run as before, but using 4-benzyloxymethyl-4-hydroxy-1-(2-hydroxy-phenyl)-hex-5-en-2-yn-1-one (0.62 g, 1.9 mmol) as the starting material. The reaction was run with 18-crown-6 (1.0 g, 3.9 mmol) and 0.22 g (3.8 mmol) of spray-dried KF in 39 mL of DMF to provide 0.6 g (1.9 mmol, 73%) of a pale-yellow oil.

Synthesis of 2-(2-benzyloxy-1-hydroxy-1-oxiranylethyl)chromen-4-one (2.26).

A solution containing 0.52 g (1.6 mmol) of 2-(1-benzyloxymethyl-1-hydroxyallyl)-chromene-4-one and 0.54 g (3.1 mmol) of *m*-CPBA in 10 mL of CH_2Cl_2 was

stirred under N_2 overnight. The reaction was quenched with satd aq NH_4Cl, and the layers were separated. The organic layer was washed with brine, dried with $MgSO_4$ and concentrated. The crude material was purified on silica gel using 500 mL of 2:1 petroleum ether–EtOAc and 500 mL of 1:1 petroleum ether–EtOAc successively. Diastereomer A: ^{1}H NMR ($CDCl_3$) δ 2.77 (m, 1H), 2.89 (m, 1H), 3.10 (br s, 1H), 3.46 (m, 1H), 3.72 (d, *J* = 9.6 Hz, 1H), 3.85 (d, *J* = 9.6 Hz, 1H), 4.45 (d, *J* = 12.3 Hz, 1H), 4.54 (d, *J* = 12.3 Hz, 1H), 6.64 (1H), 7.15 (m, 5H), 7.32 (m, 2H), 7.59 (m, 1H), 8.13 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 43.54, 53.20, 71.49, 73.55, 73.63, 109.81, 117.93, 125.30, 125.81, 127.62, 127.92, 128.42, 133.71, 137.08, 156.05, 167.75, 178.16.

Diastereomer B: ^{1}H NMR ($CDCl_3$) δ 2.66 (m, 1H), 2.83 (m, 1H), 3.05 (br s, 1H), 3.36 (m, 1H), 3.79 (d, *J* = 9.6 Hz, 1H), 3.94 (d, *J* = 9.6 Hz, 1H), 4.48 (d, *J* = 12.3 Hz, 1H), 4.57 (d, *J* = 12.3 Hz, 1H), 6.61 (s, 1H), 7.16 (m, 5H), 7.33 (m, 2H), 7.60 (m, 1H), 8.14 (m, 1H).

6. Synthesis of model compound using the coupling of 2-(methoxymethoxy)benzaldehyde and a new alkyne.

a. Alkyne synthesis

Synthesis of 2-hydroxy-*N*-methoxy-*N*-methylacetamide (2.27).

A solution containing 10.5 g (50.4 mmol) of 2-benzyloxy-*N*-methoxy-*N*-methylacetamide and 1.05 g of 10% Pd/C in 200 mL of absolute ethanol was

reacted with H_2 gas at 40 psi for 20 h. The reaction material was filtered over celite. The solid Pd/C was washed with CH_2Cl_2, and the filtrate was concentrated yielding 5.89 g (49.4 mmol, 98%) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ 3.24 (s, 3H), 3.69 (s, 3H), 4.29 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 31.95, 59.35, 61.00, 172.80.

Synthesis of 2-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*-methylacetamide (2.28).

A solution containing 4.7 g (40 mmol) of 2-hydroxy-*N*-methoxy-*N*-methylacetamide, 6.35 g (42.1 mmol) of TBSCl and 5.61 g (82.4 mmol) of imidazole and a catalytic amount of DMAP in 20 mL of DMF was stirred overnight. The solution was diluted with 100 mL of water and extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified via silica gel chromatography (2:1 petroleum ether–EtOAc) yielding 8.05 g (34.5 mmol, 87%) of a pale-yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.12 (s, 6H), 0.92 (s, 9H), 3.18 (s, 3H), 3.68 (s, 3H), 4.43 (s, 2H). ^{13}C NMR ($CDCl_3$) δ -5.63, 18.23, 25.57, 32.18, 61.10, 61.52, 172.18.

Synthesis of 1-(*tert*-butyldimethylsilyloxy)-4-trimethylsilylbut-3-yn-2-one (2.29).

To a solution containing 7.5 mL (53 mmol) of trimethylsilylacetylene in 170 mL of THF cooled to -78 °C was added 12.4 mL of a 2.5 M solution of BuLi in hexane.

The reaction was stirred at -78 °C for 30 min. Next, a solution containing 6.0 g (2.6 mmol) of 2-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*-methylacetamide in 20 mL of THF was added. The reaction was allowed to warm to -10 °C over a period of 1 h. The temperature was kept at -10 °C for an additional hour. The reaction was cooled to -78 °C, and 2 mL of glacial acetic acid were added. After the reaction was slowly allowed to warm to -5 °C, brine and ethyl ether were added. The layers were separated, and the aqueous layer was extracted with ethyl ether. The organic layer was dried over $MgSO_4$ and concentrated to give 6.2 g (2.3 mmol, 90%) of a yellow oil that was used without further purification. ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 6H), 0.24 (s, 9H), 0.93 (s, 9H), 4.32 (s, 2H). ^{13}C NMR ($CDCl_3$) δ -5.39, -0.83, 18.38, 25.75, 70.27, 99.90, 101.19, 186.62.

Synthesis of 3-(tert-butyldimethylsilyloxymethyl)-5-trimethylsilylpent-1-en-4-yn-3-ol (2.30).

To a solution containing1.0 g (3.7 mmol) of 1-(*tert*-butyldimethylsilyloxy)-4-trimethylsilylbut-3-yn-2-one in 5 mL of THF was added 4.4 mL (4.4 mmol) of 1.0 M vinylmagnesium bromide in THF, and the solution was stirred for 20 min. The reaction was quenched with satd aq NH_4Cl and extracted with EtOAc. The aqueous layer was dried over $MgSO_4$ and concentrated to give 0.97 g (3.2 mmol, 86%) of a product that was used without further purification. ^{1}H NMR ($CDCl_3$) δ 0.12 (m, 12H), 0.89 (s, 9H), 3.14 (br s, 1H), 3.59 (m, 2H), 5.24 (d, J = 8.7 Hz,

1H), 5.60 (d, J = 16.8 Hz, 1H), 5.85 (m, 1H). ^{13}C NMR ($CDCl_3$) δ -5.39, -5.34, -0.16, 18.34, 25.78, 70.21, 71.82, 89.81, 104.99,. 116.74, 137.13.

Synthesis of 3-(*tert*-butyldimethylsilyloxymethyl)pent-1-en-4-yn-3-ol (2.31). To a solution containing 0.97 g (3.2 mmol) of 1-(*tert*-butyldimethylsilyloxy)-4-trimethylsilylbut-3-yn-2-one is added 1 mL of 25% by weight NaOMe in MeOH. The reaction was stirred for 30 min. Satd aq NH_4Cl was added, and the mixture was extracted with EtOAc. The organic extracts were dried over $MgSO_4$ and concentrated. The crude material was purified via silica gel chromatography (25:1 petroleum ether–EtOAc) to give 0.32 g (0.14 mmol, 43%) of a pale-yellow oil. ^1H NMR ($CDCl_3$) δ 0.075 (s, 3H), 0.086 (s, 3H), 0.886 (s, 6H), 0.895 (s, 3H), 2.49 (s, 1H), 3.16 (s, 1H), 3.55 (d, J = 9.6 Hz, 1H), 3.66 (d, J = 9.3 Hz, 1H), 5.25 (d, J = 10.2 Hz, 1H), 5.61 (d, J = 17.1 Hz, 1H), 5.85 (dd, J = 10.2 and 17.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ -5.45, -5.38, 18.30, 25.75, 70.11, 71.36, 73.41, 83.51, 116.88, 136.93. Anal. Calcd for $C_{12}H_{22}O_2Si$: C, 63.66; H, 9.74. Found: C, 63.27; H, 9.74.

b. Coupling and further reactions.

Synthesis of 4-(*tert*-butyldimethylsilyloxymethyl)-1-(2-methoxymethoxyphenyl)hex-5-en-2-yne-1,4-diol (2.32). A solution containing 0.36 g (1.6 mmol) of 3-(*tert*-

butyldimethylsilyloxymethyl)pent-1-en-4-yn-3-ol in 7 mL of THF was cooled to -78 °C and 1.3 mL (3.25 mmol) of 2.5 M *n*-BuLi were added. The reaction mixture was allowed to warm slowly for 3 h. The reaction mixture was again cooled to -78 °C, 0.32 g (1.9 mmol) of 2-methoxymethoxybenzaldehyde were added, and the solution was stirred overnight. Satd aq NH_4Cl was added to quench the reaction and the solution was extracted with EtOAc. The aqueous layer was dried over $MgSO_4$ and concentrated. The crude product was subjected to silica gel chromatography (4:1 petroleum ether–EtOAc) to give 0.27 g (0.69 mmol, 36%) of a pale-yellow oil. ^1H NMR ($CDCl_3$) δ 0.06 (s, 6H), 0.89 (s, 9H), 3.29 (m, 2H), 3.48 (s, 3H), 3.58 (d, *J* = 9.6 Hz, 1H), 3.69 (d, *J* = 9.3 Hz, 1H), 5.23 (m, 3H), 5.59 (d, *J* = 17.1 Hz, 1H), 5.76 (s, 1H), 5.89 (dd, *J* = 10.2 and 17.1 Hz, 1H), 7.05 (m, 2H), 7.27 (m, 1H), 7.57 (m, 1H). ^{13}C NMR ($CDCl_3$) δ -5.55, -5.48, 18.20, 25.68, 56.15, 60.44, 70.09, 71.41, 84.95, 85.20, 94.47, 114.35, 116.47, 121.92, 127.88, 129.40, 129.46, 137.33, 154.25, 171.13.

Synthesis of 4-(*tert*-butyldimethylsilyloxymethyl)-4-hydroxy-1-(2-methoxymethoxyphenyl)hex-5-en-2-yn-1-one (2.33).

To a solution of 0.25 g (0.64 mmol) of 4-(*tert*-butyldimethylsilyloxymethyl)-1-(2-methoxymethoxyphenyl)hex-5-en-2-yne-1,4-diol in 5 mL of CH_2Cl_2 was added 2.5 g of MnO_2. The reaction mixture was stirred for 20 min. The mixture was filtered over Celite and concentrated. The crude product was purified via silica gel chromatography (6:1 petroleum ether–EtOAc) to give 0.16 g (0.40 mmol,

63%) of a pale-yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.09, 0.87(s, 1H), 3.39 (s, 1H), 3.50 (s, 1H), 3.63 (d, *J* = 9.6 Hz, 1H), 3.78 (d, *J* = 9.9 Hz, 1H), 5.26 (s, 1H), 5.33 (d, *J* = 10.2, 1H), 5.67 (d, *J* = 18.0 Hz, 1H), 5.90 (dd, *J* = 10.5 and 17.4 Hz, 1H), 7.05 (t, *J* = 7.8 Hz, 1H), 7.19 (d, *J* = 7.5 Hz, 1H), 7.48 (m, 1H), 7.98 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ -5.49, -5.40, 18.25, 25.69, 56.45, 69.88, 71.85, 84.70, 91.88, 94.67, 115.88, 117.65, 121.47, 127.08, 132.34, 134.85, 135.94, 157.24, 176.09.

Synthesis of 4-hydroxy-4-hydroxymethyl-1-(2-hydroxyphenyl)hex-5-en-2-yn-1-one (2.34).

A solution containing 0.15 g (0.38 mmol) 4-(*tert*-butyldimethylsilyloxymethyl)-4-hydroxy-1-(2-methoxymethoxyphenyl)hex-5-en-2-yn-1-one in 2 mL of acetone and 0.5 mL of 1 M H_2SO_4 was stirred overnight. The reaction was diluted with water and extracted with EtOAc. The aqueous layer was dried over $MgSO_4$ and concentrated. The crude material was purified via silica gel chromatography (4:1 CH_2Cl_2–EtOAc) to give 0.046 mg (0.20 mmol, 52%) of a pale-yellow oil. ^{1}H NMR ($CDCl_3$) δ 3.04 (br s, 1H), 3.70 (m, 2H), 3.86 (d, *J* = 11.1 Hz, 1H), 5.42 (d, *J* = 10.5 Hz, 1H), 5.71 (d, *J* = 17.4 Hz, 1H), 5.97 (dd, *J* = 10.2 and 16.8 Hz, 1H), 6.93 (m, 2H), 7.51 (m, 1H), 7.97 (m, 1H), 11.43 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 69.32, 72.49, 81.90, 95.59, 118.09, 118.51, 119.67, 120.25, 133.18, 135.29, 137.69, 162.74, 181.84.

Synthesis of 2-(1-hydroxy-1-hydroxymethylallyl)chromen-4-one (2.35).

To a solution containing 46 mg (0.20 mmol) of 4-hydroxy-4-hydroxymethyl-1-(2-hydroxyphenyl)hex-5-en-2-yn-1-one and 0.10 g (0.39 mmol) of 18-crown-6 in 2 mL of DMF was added 22 mg (0.38 mmol) of KF. The reaction was stirred for 4 h at RT. The reaction mixture was quenched with satd NH_4Cl and was extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated. The crude material was purified via silica gel chromatography (1:2 CH_2Cl_2–EtOAc) to give 11 mg (0.047 mmol, 24%) of the product. ^1H NMR ($CDCl_3$) δ 3.54 (br s, 1H), 3.73 (dd, *J* = 6.0 and 5.1 Hz, 1H), 3.87 (br s, 1H), 4.23 (dd, *J* = 6.3 and 5.1 Hz, 1H), 5.38 (d, *J* = 11.4 Hz, 1H), 5.62 (d, *J* = 18 Hz, 1H), 6.14 (dd, *J* = 10.8 and 17.1 Hz, 1H), 7.25 (m, 1H), 7.43 (d, *J* = 8.7 Hz, 1H), 7.61 (m, 1H), 7.90 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 67.38, 108.77, 117.57, 117.88, 123.17, 125.26, 125.31, 133.85, 135.33, 156.12, 170.31, 179.07. Anal. Calcd for $C_{13}H_{12}O_4$: C, 67.23; H, 5.21. Found: C, 67.41; H, 5.24.

Synthesis of 2-(1,2-dihydroxy-1-oxiranylethyl)chromen-4-one (2.36).

To a solution containing 0.51 g (2.2 mmol) of 2-(1-hydroxy-1-hydroxymethylallyl)chromen-4-one in 35 mL of CH_2Cl_2 was added 0.75 g (2.5–3.7 mmol) of 57-86% *m*-CPBA. An additional 0.35 g (1.2–1.7 mmol) of 57–86% *m*-CPBA was added after 6 h. The reaction mixture was stirred overnight at room temperature. The reaction was then quenched with satd $Na_2S_2O_3$ and satd $NaHCO_3$. The layers were separated, and the organic layer

was washed with $NaHCO_3$ and brine, dried over $MgSO_4$ and concentrated. The crude material was purified via silica gel chromatography, first with 300 mL of 1:2 petroleum ether–EtOAc, then with 1:4 petroleum ether–EtOAc to give 0.087 g (0.35 mmol, 16%) of the final compound.

Diastereomer A: R_f = 0.26 in 1:4 petroleum ether–EtOAc. ^{1}H NMR ($CDCl_3$) δ 2.76 (m, 1H), 2.88 (m, 1H), 2.98 (br s, 1H), 3.23 (br s, 1H), 3.50 (m, 1H), 4.05 (d, J = 11.7 Hz, 1H), 4.21 (d, J = 11.4 Hz, 1H), 6.64 (s, 1H), 7.36 (m, 2H), 7.66 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 42.70, 53.19, 66.58, 73.17, 109.36, 117.89, 123.69, 125.48, 125.72, 133.92, 156.08, 167.48, 178.33. HREIMS–ZAB (m/z): $[M + H]^+$ calcd for $C_{13}H_{12}O_5$, 249.0719; found, 249.0791.

Diastereomer B: R_f = 0.16 in 1:4 petroleum ether–EtOAc. ^{1}H NMR ($CDCl_3$) δ 2.96 (m, 1H), 3.03 (m, 1H), 3.26 (br s, 1H), 3.59 (m, 2H), 3.90 (d, J = 11.7 Hz, 1H), 4.10 (d, J = 9.0 Hz, 1H), 6.66 (s, 1H), 7.3 (m, 2H), 7.44 (m, 1H), 8.02 (m, 1H). ^{13}C NMR ($CDCl_3$) δ 43.83, 53.12, 65.07, 74.11, 109.73, 117.91, 123.50, 125.42, 125.64, 133.95, 137.72, 156.13, 168.34, 178.50. HREIMS–ZAB (m/z): $[M + H]^+$ calcd for $C_{13}H_{12}O_5$, 249.0719; found, 249.0733.

7. Synthesis of the model compound using the coupling of 2-(*tert*-butydimethylsilyloxy)benzaldehyde and alkyne 2.31.

Synthesis of 4-(*tert*-butyldimethylsilyloxymethyl)-1-[2-(*tert*-butyldimethylsilyloxy)phenyl]hex-5-en-2-yne-1,4-diol (2.37).

To a solution containing 1.05 g (4.64 mmol) of 3-(*tert*-butyldimethylsilyloxymethyl)-pent-1-en-4-yn-3-ol in 10 mL of THF cooled to -78 °C was added 3.7 mL (9.3 mmol) of 2.5 M *n*-BuLi in hexanes. The solution was allowed to slowly warm to room temperature as it stirred for 3 h. The solution was next cooled to 0 °C, and a solution containing 1.10 g (4.65 mmol) of 2-*tert*-butylsilyloxybenzaldehyde in 10 mL of THF was added. The reaction mixture was stirred for 10 min. The reaction was quenched with satd aq NH_4Cl, and the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified via silica gel chromatography using 19:1 petroleum ether–EtOAc to give 1.09 g (2.36 mmol, 47%) of a pale-yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.01, (s, 6H), 0.20 (s, 3H), 0.22 (s, 3H), 0.83 (s, 9H), 0.86 (s, 9H), 2.70 (d, *J* = 5.4 Hz, 1H), 3.08 (d, *J* = 2.1 Hz, 1H), 3.52 (d, *J* = 9.6 Hz, 1H), 3.64 (dd, *J* = 3.3 and 9.9 Hz, 1H), 5.19, (d, *J* = 10.2 Hz, 1H), 5.54 (d, *J* = 17.4 Hz, 1H), 5.78 (m, 2H), 6.75 (d, *J* = 8.4 Hz, 1H), 6.90 (t, *J* = 7.8 Hz, 1H), 7.12 (t, *J* = 7.8 Hz, 1H), 7.53 (m, 1H). ^{13}C NMR ($CDCl_3$) δ -5.48, -5.40, -4.27, -4.16, 18.13, 18.28, 25.72, 25.74, 60.37, 70.12, 71.45, 84.81, 85.52, 116.67, 118.31, 121.33, 128.14, 129.32, 130.72, 137.20, 152.84. Anal. Calcd for $C_{25}H_{42}O_4Si_2$: C, 64.88; H, 9.15. Found: C, 65.02; H, 9.21.

Synthesis of 4-(*tert*-butyldimethylsilyloxymethyl)-1-[2-(*tert*-butyldimethylsilyloxy)phenyl]-4-hydroxyhex-5-en-2-yn-1-one (2.38).

To a solution containing 0.38 g (0.82 mmol) of 3-(*tert*-

butyldimethylsilyloxymethyl)-pent-1-en-4-yn-3-ol in 7 mL CH_2Cl_2 is added 2.0 g (mmol) of MnO_2. The reaction mixture was stirred for 1 h at room temperature. The mixture was filtered over Celite and concentrated. The crude material was purified via silica gel chromatography with 19:1 petroleum ether–EtOAc to give 0.17 g (0.37 mmol, 45%) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.21 (s, 6H), 0.90 (s, 9H), 1.00 (s, 9H), 3.30 (s, 1H), 3.63 (d, *J* = 9.6 Hz, 1H), 3.78 (d, *J* = 9.9 Hz, 1H), 5.33 (d, *J* = 10.2 Hz, 1H), 5.67 (d, *J* =17.4 Hz, 1H), 5.89 (dd, *J* = 10.2 and 17.1 Hz, 1H), 6.87 (d, *J* = 8.4 Hz, 1H), 7.01 (t, *J* = 7.5 Hz, 1H), 7.40 (t, *J* = 7.5 Hz, 1H), 8.01 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ -5.45, -5.38, -4.31, 18.28, 18.37, 25.74, 69.93, 71.84, 83.93, 91.36, 117.84, 120.85, 121.61, 128.62, 133.49, 134.39, 135.74, 155.77, 176.61. Anal. Calcd for $C_{25}H_{40}O_4Si_2$: C, 65.17; H, 8.75. Found: C, 65.05; H, 8.69.

Synthesis of 2-[1-(*tert*-butyldimethylsilyloxymethyl)-1-hydroxyallyl]chromen-4-one (2.39).

To a solution containing 0.35 g (0.76 mmol) of 4-(*tert*-butyldimethylsilyloxymethyl)-1-[2-(*tert*-butyldimethylsilyloxy)phenyl]-4-hydroxyhex-5-en-2-yn-1-one and 0.80 g (3.0 mmol) of 18-crown-6 in 2 mL of DMF is added 0.177 (3.04 mmol) of KF. The reaction was stirred for 3 h and then quenched with satd aq NH_4Cl. The mixture was extracted with EtOAc, and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified via silica gel chromatography with 5:1 petroleum ether–EtOAc to give 0.11 g (0.32 mmol, 42%) of a yellow oil. ^{1}H NMR ($CDCl_3$) δ

-0.07 (s, 3H), 0.01 (s, 3H), 0.78 (s, 9H), 3.37 (s, 1H), 3.67 (d, *J* = 9.6 Hz, 1H), 4.19 (d, *J* = 9.6 Hz, 1H), 5.34 (d, *J* = 10.8 Hz, 1H), 5.58 (d, *J* = 17.4 Hz, 1H), 6.07 (dd, *J* = 10.8 and 17.4 Hz, 1H), 6.69 (s, 1H), 7.41 (m, 2H), 7.66 (m, 1H), 8.20 (d, *J* = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ -5.62, -5.53, 18.13, 25.60, 67.45, 108.99, 117.46, 117.70, 123.76, 125.18, 125.88, 133.65, 135.08, 156.02, 169.58, 178.29. Anal. Calcd for $C_{19}H_{26}O_4Si$: C, 65.86; H, 7.56. Found: C, 65.76; H, 7.73.

Synthesis of 2-(1-hydroxy-1-hydroxymethylallyl)-chromen-4-one (2.36).

A solution containing 0.11 g (0.32 mmol) of 2-[1-(*tert*-Butyldimethylsilyloxymethyl)-1-hydroxyallyl]chromen-4-one and 0.5 mL of 1 M H_2SO_4 in 2 mL of acetone was stirred for 2.5 h at room temperature. Water was added, and the reaction mixture was extracted with EtOAc. The organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified as mentioned earlier to give 0.062 g (0.27 mmol, 84%) of the white solid. Spectral data and analysis were given earlier.

C. Synthesis of the Hydramycin Analog.

1. Attempts to synthesize anthraquinone aldehydes.

Preparation of 1-hydroxy-3-methylanthraquinone (2.40).

Aluminum chloride (29 g, 0.22 mol) and NaCl (4.8 g, 0.082 mmol) were heated under N_2 in a three-neck flask fitted with a drying tube. At 140 °C, the salts melted to form a gray solution. To the solution was added 1.6 g (10 mmol) of phthalic anhydride. Once the anhydride had dissolved, 1.0 mL (8.9 mmol) of *m*-cresol was added. The reaction was stirred for 7 min. The heat was removed, and the reaction mixture was allowed to continue stirring for about 10 min. Ice and concd HCl were slowly added to the reaction material. Once the mixture had reached room temperature, the mixture was filtered. The remaining solid was chromatographed on silica gel with CH_2Cl_2. The material was crystallized in CH_2Cl_2–MeOH to yield 0.44 g (1.8 mmol, 20%) of bright-yellow needles: mp 170–171 °C (lit.[33] 178–180 °C); ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H), 7.10 (s, 1H), 7.64 (s, 1H), 7.80 (m, 2H), 8.29 (m, 2H), 12.57 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 22.26, 114.06, 120.81, 124.12, 126.78, 127.36, 133.10, 133.29, 133.59, 134.11, 134.42, 148.64, 162.74, 188.05.

Synthesis of 1-allyloxy-3-methylanthraquinone (2.41).

A solution containing 1-hydroxy-3-methylanthraquinone (0.10 g, 0.42 mmol), 0.28 g (2.0 mmol) of potassium carbonate, and 0.15 mL (1.7 mmol) of allyl

bromide was refluxed overnight. The reaction material was concentrated, then dissolved in water and extracted with CH_2Cl_2. The organic layer was dried and concentrated to give 0.090 g (0.32 mmol, 76%) of a yellow solid. ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H), 4.67 (d, *J* = 4.8 Hz, 2H), 5.32 (dd, *J* = 1.5 and 9 Hz, 1H), 5.62 (dd, *J* = 4.8 and 18.9 Hz, 1H), 6.07 (m, 1H), 7.03 (s, 1H), 7.66 (m, 3H), 8.17 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 22.52, 70.15, 118.36, 119.76, 120.18, 120.98, 126.73, 127.41, 132.43, 132.72, 133.24, 134.40, 135.31, 135.68, 146.46, 159.74, 182.16, 183.99.

Synthesis of 2-allyl-1-hydroxy-3-methylanthraquinone (2.42).

A solution containing 0.65 g (0.36 mmol) of glucose and 0.33 g (1.2 mmol) of 1-allyloxy-3-methylanthraquinone in 40 mL of DMF was refluxed for 8 h at 125 °C. The reaction material was poured into 400 mL of water, and the resulting mixture was extracted with EtOAc. The crude product was chromatographed on silica gel (5:1 petroleum ether–CH_2Cl_2) to give 0.057 g (0.20 mmol, 17% yield) of the final product. ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 3.55 (d, *J* = 6 Hz, 2H), 5.02 (m, 2H), 5.96 (m, 1H), 7.65 (s, 1H), 7.79 (m, 2H), 8.29 (m, 2H).

2. Syntheses of anthraquinone aldehydes.

a. Alizarin method

Preparation of 1,2-dihydroxy-3-methylanthraquinone (2.43).

Aluminum chloride (44 g, 0.33 mol) and NaCl (7.1 g, 0.12 mol) were heated under N_2 in a three-neck flask fitted with a drying tube. At 140 °C, the salts melted to give a gray solution. To the solution was added 2.47 g (16.7 mmol) of phthalic anhydride. Upon dissolution of the anhydride, 1.74 g (14.0 mmol) of 3-methylcatechol was added. The reaction was allowed to stir for 7 min. The heat was removed, and the reaction mixture was allowed to continue stirring for about 10 min. Ice and concd HCl were slowly added to the reaction material. Upon complete cooling, the mixture was filtered. The remaining solid was chromatographed on silica gel with CH_2Cl_2. The material was crystallized in CH_2Cl_2–MeOH to yield 0.22 g (0.87 mmol, 6%) of an orange crystal. ^{1}H NMR ($CDCl_3$) δ 2.4 (s, 3H), 6.28 (s, 1H), 7.77 (m, 3 H), 8.30 (m, 2H), 12.76 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 16.20, 123.13, 124.41, 126.66, 127.46, 131.43, 133.12, 133.64, 134.17, 134.75, 138.72, 148.56, 148.69, 181.65, 188.87. The NMR data matched that reported.[28]

Synthesis of trifluoromethanesulfonic acid 1-hydroxy-3-methyl-9,10-dioxo-9,10-dihydroanthracen-2-yl ester (2.44).

A solution containing 0.11 g (0.43 mol) of 1,2-dihydroxy-3-methylanthraquinone, 0.06 mL (0.5 mmol) of 2,6-lutidine and 0.14 mL (0.83 mmol) of trifluoromethanesulfonic anhydride in 20 mL of CH_2Cl_2 was stirred overnight at room temperature. The reaction mixture was quenched with satd aq NH_4Cl. The organic layer was separated, washed with brine and water, dried with

$MgSO_4$, and concentrated. The crude material was crystallized with EtOAc–petroleum ether to yield 0.14 g (0.36 mmol, 84%) of orange crystals: mp 206 °C; ^1H NMR ($CDCl_3$) δ 2.54 (s, 3H), 7.82 (m, 3H), 8.32 (m, 2H), 13.00 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 17.83, 76.57, 116.31, 116.66, 121.75, 127.38, 127.95, 131.70, 133.15, 133.52, 134.80, 135.46, 141.16, 154.76, 181.66, 188.29. Anal. calcd. for $C_{16}H_9F_3O_6S$: C, 49.75; H, 2.35; S, 8.30. Found: C, 49.75; H, 2.46; S, 8.35.

Preparation of trifluoromethanesulfonic acid 1-hydroxy-9,10-dioxo-9,10-dihydroanthracen-2-yl ester (2.45).

Alizarin (0.50 g, 2.1 mmol) was dissolved in 40 mL of anhyd CH_2Cl_2 under N_2. To the reaction was added 0.27 mL (2.3 mmol) of 2,6-lutidine, and the reaction mixture was stirred for 5 min. Next, 0.39 mL (2.3 mmol) of trifluoromethanesulfonic anhydride was added, and the reaction mixture was stirred overnight. The reaction was quenched with satd aq NH_4Cl. The organic layer was separated, washed with brine and water, dried with $MgSO_4$ and concentrated. The crude material was crystallized with EtOAc–petroleum ether to yield 0.62 g (1.7 mmol, 81%) of yellow crystals: mp 187–189 °C ^1H NMR ($CDCl_3$) δ 7.65 (d, J = 8.4 Hz, 1H), 7.86 (m, 3H), 8.33 (m, 2H), 12.93 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 118.64 (q, 1C), 119.28, 127.25, 127.76, 129.06, 132.58, 132.76, 133.27, 134.62, 135.45, 141.80, 154.37, 181.06, 188.45.

Preparation of 1-hydroxy-2-vinylanthraquinone (2.46)

Trifluoromethanesulfonic acid 1-hydroxy-9,10-dioxo-9,10-dihydroanthracen-2-yl ester (1.5 g, 4.1 mmol) was weighed out in a dry box along with LiCl (0.54 g, 13 mmol) and 0.34 g (0.42 mmol) of [1,1'-bis(diphenylphosphino)-ferrocene]dichloropalladium(II), complex with CH_2Cl_2 (1:1). To the dry reagents was added 140 mL of DMF and 1.5 g (4.9 mmol) of tributylvinylstannane, and the solution was refluxed. After 45 min, an additional 0.24 g (0.76 mmol) of the stannane was added. Another 0.12 g (0.38 mmol) of the stannane were added after 1.5 h had passed. The reaction was refluxed overnight. After cooling to room temperature, the reaction was diluted with ethyl ether and filtered over Celite. The solution was next washed with 0.1 M HCl, water and brine. The solution was dried with $MgSO_4$, concentrated and purified on a silica gel column (22:1 petroleum ether–EtOAc) to yield 0.21 g (20%, 0.84 mmol) of an orange solid. ^{1}H NMR ($CDCl_3$) δ 5.47 (d, J = 11.7 Hz, 1H), 5.95 (d, J = 17.1 Hz, 1H), 7.08 (dd, J = 11.1, 18 Hz, 1H), 7.77 (m, 4H), 8.25 (m, 2H), 13.14 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 116.04, 118.51, 119.33, 126.95, 127.35, 129.74, 132.20, 132.88, 133.13, 133.20, 133.67, 134.08, 134.71, 160.11, 182.11, 189.00.

Preparation of 1-hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde (2.47).

A solution of 1-hydroxy-2-vinylanthraquinone (0.21 g, 0.84 mmol) dissolved in 7 mL of CH_2Cl_2 was cooled to -78 °C. Ozone was passed into the solution until it

turned blue. N_2 gas was bubbled through the solution to ensure removal of residual ozone (as could be seen by the disappearance of the blue color) and 3 mL of methyl sulfide was added with stirring. The solution was concentrated, and the product was purified on a silica gel column using a 19:1 petroleum ether–EtOAc solution to yield 70 mg (0.28 mmol, 33%) of a yellow-orange solid: mp 179 °C (lit.[48] 176°C; ^{1}H NMR ($CDCl_3$) δ 7.81 (m, 3H), 8.23 (m, 3H), 10.56 (s, 1H), 13.2 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 117.40, 118.66, 127.14, 127.69, 128.32, 132.85, 133.26, 134.67, 135.26, 135.41, 137.16, 164.47, 181.81, 187.98, 188.87.

b. Synthesis of 1,8-dimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde.

Preparation of 1-allyloxy-8-hydroxyanthraquinone (2.48).

A solution containing 6.6 g (27 mmol) of 1,8-dihydroxyanthraquinone, 3.2 mL (37 mmol) of allyl bromide and 16 g (116 mmol) of potassium carbonate in DMF was heated at 70 °C. After 8 h, the mixture was filtered, and the solid material was washed with acetone until the washings ran clear. The filtrate was concentrated under reduced pressure, and the crude product was applied to a silica gel column. The column was treated first with 19:1 petroleum ether–EtOAc until all of the starting material eluted. The product was then eluted with 9:1 petroleum ether–EtOAc. The yellow solid was crystallized with CH_2Cl_2– MeOH to give 2.17 g (7.58 mmol, 28.2%) of product. ^{1}H NMR ($CDCl_3$) δ 4.75 (d, J = 4.8 Hz, 2H),

5.39 (d, J = 7.8 Hz, 1H), 5.66 (d, J = 18 Hz, 1H), 6.11 (m, 1H), 7.26 (m, 2H), 7.64 (m, 3H), 7.89 (dd, J = 1.2 and 7.8 Hz, 1H), 12.99, (s, 1H). ^{13}C NMR ($CDCl_3$) δ 70.21, 117.21, 118.58, 119.00, 119.68, 120.44, 121.09, 124.93, 132.06, 132.82, 135.83, 135.88, 136.02, 159.98, 162.63, 182.86, 188.86. The NMR data matched that reported.[49]

Preparation of 2-allyl-1,8-dihydroxyanthraquinone (2.49).

A solution containing 0.50 g (2.9 mmol) of $Na_2S_2O_4$ in 200 mL of 3:1 H_2O–DMF was heated to 90 °C. To this was added a solution of 0.50 g (1.8 mmol) of 1-allyloxy-8-hydroxyanthraquinone in 100 mL of DMF. The reaction was then refluxed for 7 h. After cooling to room temperature, 100 mL of water was added and the mixture was cooled in a refrigerator for 2 h. The mixture was filtered to yield 0.475 g (1.69 mmol, 95%) of an orange solid: mp 127–128 °C (lit.[50] 131–132 °C; ^1H NMR ($CDCl_3$) δ 3.43 (d, J = 6.9 Hz, 2H), 5.09 (m, 2H), 5.94 (m, 1H), 7.20 (d, J = 9.6 Hz, 1H), 7.47 (d, J = 8.1 Hz, 1H), 7.66 (m, 3H), 11.99 (s, 1H), 12.35 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 33.81, 115.18, 115.89, 117.22, 119.80, 119.88, 124.45, 131.71, 133.71, 134.67, 136.83, 136.96, 137.15, 160.51, 162.46.

Synthesis of 1,8-dihydroxy-2-propenylanthraquinone. (2.50).

A solution of CH_2Cl_2 containing 0.10 g (0.36 mmol) of 2-allyl-1,8-

dihydroxyanthraquinone and 0.01 g (0.04 mmol) of bis(acetonitrile)dichloropalladium(II) was refluxed for 9 h. The reaction material was then cooled to room temperature and allowed to stand overnight. Upon completion, the reaction was diluted with more CH_2Cl_2, washed with H_2O and concentrated to give 0.091 g (91%) of a red solid. ^1H NMR ($CDCl_3$) δ 1.98 (d, *J* = 6.3 Hz, 3H), 6.52 (m, 1H), 6.80 (d, *J* = 15.9 Hz, 1H), 7.28 (d, *J* = 9 Hz, 1H), 7.73 (m, 4 H), 12.02 (s, 1H), 12.30 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.55, 110.00, 115.84, 116.17, 120.13, 120.26, 124.06, 124.66, 131.81, 133.08, 134.03, 134.22, 137.47, 159.73, 162.73, 181.64, 193.62.

Synthesis of 1,8-bis-(*tert*-butyldimethylsilanyloxy)-2-propenylanthraquinone (2.51).

A solution containing 0.12 g (0.43 mmol) of 1,8-dihydroxy-2-propenylanthraquinone, 0.18 g (2.6 mmol) of imidazole and 0.19 g (1.3 mmol) of *tert*-butyldimethylsilyl chloride in 1 mL of DMF was stirred at 70 °C overnight. The reaction was quenched with satd aq NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. The crude material was purified via silica gel chromatography (25:1 petroleum ether–EtOAc) to give 0.017 g, (0.033 mmol, 7.8%) of an orange solid. ^1H NMR ($CDCl_3$) δ 0.10 (s, 6H), 0.33 (s, 6H), 1.07 (s, 18H), 1.93 (d, *J* = 6.3 Hz, 3H), 6.28 (m, 1H) 6.82 (d, *J* = 15.9 Hz, 1H), 7.19 (d, *J* = 8.1 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.70 (d, *J* = 15.6 Hz, 1H), 7.85 (d, *J* = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ -4.08, -3.86, 18.61,

18.73, 18.95, 26.00, 26.08, 119.94, 120.51, 125.57, 126.64, 127.66, 127.91, 129.34, 129.77, 132.64, 133.27, 135.22, 138.41, 151.52, 155.56, 183.07, 183.66.

Preparation of 2-allyl-1,8-dimethoxyanthraquinone (2.52).

Potassium carbonate (3.5 g, 25 mmol) and dimethyl sulfate (1.2 mL, 12 mmol) were added to a solution of 2-allyl-1,8-dihydroxyanthraquinone (0.35 g,1.2 mmol) in acetone. The reaction mixture was refluxed overnight and concentrated upon cooling. The solid was then dissolved in EtOAc and washed with water. The organic layer was dried and concentrated to yield 0.375 g (1.20 mmol, 100%) of an orange solid. ^{1}H NMR ($CDCl_3$) δ 3.44 (d, J = 5.4 Hz, 2H), 3.86 (s, 3H), 3.90 (s, 3H), 5.02 (m, 2H), 5.87 (m, 1H), 7.19 (d, J =9.3 Hz, 1H), 7.42 (d, J = 8.1 Hz, 1H), 7.54 (t, J = 7.5 Hz, 1H), 7.70 (d, 7.5 Hz, 1H), 7.83 (d, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 34.40, 56.80, 62.67, 117.25, 118.09, 119.16, 122.76, 123.99, 128.23, 133.31, 134.35, 134.93, 135.14, 135.99, 142.50, 158.20, 159.63, 183.33, 183.68. The NMR data matched that reported.[50]

Synthesis of 1,8-dimethoxy-2-propenylanthraquinone (2.53).

A solution of NaOH (1.7 g, 43 mmol) in 64 mL of hot MeOH was added to a solution of 2-allyl-1,8-dimethoxyanthraquinone (0.79 g, 2.6 mmol) in 85 mL of hot MeOH. The reaction mixture was refluxed for 30 min, and the solution was poured over ice. The mixture was then extracted with CH_2Cl_2. The organic layer

was dried with $MgSO_4$ and concentrated to give 0.77 g (97%) of a red solid: 155–156 °C; ^{1}H NMR ($CDCl_3$) δ 1.88 (d, *J* = 6.6 Hz, 3H), 3.87 (s, 3H), 3.92 (s, 3H), 6.35 (m, 1H), 6.73 (d, *J* = 15.9 Hz, 1H), 7.20 (d, *J* = 3.3 Hz, 1H), 7.54 (d, *J* = 8.7 Hz, 1H), 7.67 (d, *J* = 8.1, 1H), 7.73 (d, 7.8 Hz, 1H), 7.85 (d, *J* = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.39, 56.78, 62.62, 118.00, 119.15, 122.93, 123.99, 124.79, 128.87, 130.46, 131.29, 132.90, 134.33, 135.23, 139.66, 156.70, 159.66, 183.25, 183.49.

Preparation of 1,8-dimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde (2.54).

A solution of 0.98 g (3.2 mmol) of 1,8-dimethoxy-2-propenylanthraquinone in 50 mL of CH_2Cl_2 was cooled to -78 °C. Ozone was passed through the solution until the solution appeared green (45 min). Upon completion, N_2 gas was passed through the solution for 0.5 h. Dimethyl sulfide (1 mL) was added, and the solution was washed with water and concentrated, yielding 0.95 g (3.2 mmol, 100%) of a bright-yellow solid. The product was used in the next step without further purification.

c. Preparation of 1-Methoxymethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde.

Preparation of 1-allyloxyanthraquinone (2.55).

To a solution containing 2.5 g (11 mmol) of 1-hydroxyanthraquinone, 0.92 g (5.5

mmol) of KI and 15.6 g (114 mmol) of K_2CO_3 in 350 mL of DMF was added 3.0 mL (34.8 mmol) of allyl bromide. The reaction was heated to 70 °C for 2 h. Upon completion, the mixture was filtered, and the solid K_2CO_3 was washed several times with acetone. The solution was concentrated, and the crude material was chromatographed via silica gel chromatography (9:1 petroleum ether–EtOAc). Upon elution of the starting material, the product was eluted with CH_2Cl_2: mp 142 °C (lit.[51] 141–142 °C) ^{1}H NMR ($CDCl_3$) δ 4.76 (d, J = 4.8 Hz, 2H), 5.38 (d, J = 10.8 Hz, 1H), 5.67 (d, J = 16.8 Hz, 1H), 6.13 (m, 1H), 7.30 (m, 1H), 7.71 (m, 3H), 7.94 (m, 1H), 8.23 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 70.21, 118.47, 119.69, 120.19, 122.01, 126.77, 127.46, 132.35, 132.67, 133.41, 134.46, 135.04, 135.25, 135.95, 159.55, 182.44, 183.68.

Preparation of 1-hydroxy-2-allylanthraquinone (2.56).

A solution containing 0.50 g (2.9 mmol) of $Na_2S_2O_4$ in 150 mL of water and 50 mL of DMF was heated to 90–110 °C. To this was added a solution containing 0.50 g (1.9 mmol) of 1-allyloxyanthraquinone in 100 mL of DMF. The reaction refluxed for 2 h. Upon cooling, 250 mL of water was added, and the flask was placed in a refrigerator overnight or until the flask was no longer warm to the touch. The precipitate was filtered and dried in vacuo to give 0.47 g (1.8 mmol, 94%) of a yellow solid. ^{1}H NMR ($CDCl_3$) δ 3.52 (d, J = 6.9 Hz, 2H), 5.16 (d, J = 13.2 Hz, 2H), 6.02 (m, 1H), 7.54 (d, J = 8.1 Hz, 1H), 7.79 (m, 3H), 8.29 (m, 2H), 13.00 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 33.81, 115.47, 117.08, 119.32, 126.87,

127.30, 131.60, 133.24, 133.70, 134.01, 134.57, 134.84, 136.47, 136.57, 160.57, 182.33, 188.92. The NMR data matched that reported.[52]

Preparation of 2-allyl-1-methoxymethoxyanthraquinone (2.57).

A solution containing 2.77 g (10.5 mmol) of 2-allyl-1-hydroxyanthraquinone in 90 mL of CH_2Cl_2 was stirred with 18.8 mL (107.9 mmol) of diisopropylethylamine for 5 min. Chloromethyl methyl ether (5.8 mL, 76.3 mmol) was added, and the solution was refluxed overnight. The reaction was quenched with saturated NH_4Cl, and the layers were separated. The organic layer was washed with brine, 1 M HCl, dried over $MgSO_4$ and concentrated. The resulting yellow solid was crystallized with CH_2Cl_2 and MeOH to give 2.9 g (9.4 mmol, 90%) of the product: mp 123 °C (Lit.[53] 120–120.5 °C; ^{1}H NMR ($CDCl_3$) δ 3.65 (m, 5H), 5.13 (m, 2H), 5.15 (s, 2H), 6.0 (m, 1H), 7.63 (d, J = 8.1 Hz, 1H), 7.76 (m, 2H), 8.10 (d, J = 8.1 Hz, 1H), 8.24 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 35.05, 57.94, 102.31, 117.48, 124.02, 125.25, 126.92, 127.44, 132.93, 133.88, 134.26, 134.40, 134.98, 135.74, 135.79, 142.96, 156.66. 183.07, 183.18.

Preparation of 1-methoxymethoxy-2-propenylanthraquinone (2.58).

To a heated solution of 2-allyl-1-methoxymethoxyanthraquinone (2.5 g, 8.1 mmol) in 206 mL of MeOH was added a solution of 5.44 g NaOH in 268 mL of MeOH. The reaction was refluxed for 0.5 h, and the reaction solution was poured over ice-water. The precipitate was filtered and chromatographed on

silica gel (7:1 petroleum ether: CH_2Cl_2) to give 1.09 g (3.54 mmol, 44%) of an orange solid: mp 185 °C; ^{1}H NMR ($CDCl_3$) δ 1.92 (d, *J* = 6.3 Hz, 3H), 3.58 (s, 3H), 5.11 (s, 2H), 6.37 (m, 1H), 6.97 (d, *J* = 15.9 Hz, 1H), 7.70 (m, 2H), 7.80 (d, *J* = 8.4 Hz, 1H), 8.04 (d, *J* = 7.8 Hz, 1H), 8.18 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 19.17, 57.96, 101.66, 123.83, 125.26, 125.70, 126.65, 127.17, 131.14, 132.72, 133.61, 133.75, 134.09, 134.79, 139.88, 154.60, 182.79, 182.86. Anal. Calcd for $C_{19}H_{16}O_4$: C, 74.01; H, 5.23. Found: C, 74.22; H, 5.16.

Preparation of 1-methoxymethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde (2.59).

A solution containing 1.00 g (2.71 mmol) of 1-methoxymethoxy-2-propenylanthraquinone was cooled to -78 °C, and ozone was passed through the solution. Upon the appearance of a dark blue color (indicating excess ozone), the ozone source was removed and the system was flushed with N_2. Methyl sulfide (1 mL) was added, and the solution was concentrated to yield 0.81 g (2.3 mmol, 85%) of a yellow solid that was used without further purification. ^{1}H NMR ($CDCl_3$) δ 3.57 (s, 3H), 5.25 (s, 2H), 7.76 (m, 2H), 8.20 (m, 4H), 10.51 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 58.24, 102.70, 123.79, 126.14, 127.03, 127.35, 132.41, 133.09, 134.14, 134.42, 134.73, 160.84, 182.34, 189.84, 189.86.

d. Preparation of 1-Methoxymethoxyanthracene-2-carbaldehyde.

Preparation of 1-methoxymethoxyanthraquinone (2.60).

A solution containing 3.0 g (13 mmol) of 1-hydroxyanthraquinone, 43.0 mL (247 mmol) of DIPEA and 3.10 mL (40.8 mmol) of MOMCl in 150 mL of CH_2Cl_2 was refluxed overnight. The reaction was quenched with water and extracted with CH_2Cl_2. The organic layer was washed with 0.2 M HCl, dried over $MgSO_4$ and concentrated. The crude material was purified over a short plug of silica with CH_2Cl_2, then crystallized from CH_2Cl_2 and MeOH to give 3.38 g (12.6 mmol, 94%) of bright-yellow needles. ^{1}H NMR ($CDCl_3$) δ 3.58 (s, 3H), 5.41 (s, 2H), 7.58 (d, J = 8.4 Hz, 1H), 7.73 (m, 3H), 8.03 (d, J = 7.5 Hz, 1H), 8.25 (m, 2H). ^{13}C NMR ($CDCl_3$) δ 56.65, 95.22, 121.22, 122.44, 126.63, 127.19, 132.49, 133.35, 134.26, 134.80, 134.95, 135.60, 157.83, 182.45, 183.30. The NMR data matched that reported.[38]

Preparation of 1-methoxymethoxyanthracene (2.61).

A solution containing 5.0 g (19 mmol) of 1-methoxymethoxyanthraquinone and 21.5 g (0.568 mol) of $NaBH_4$ in 300 mL of 2-propanol was refluxed overnight. The reaction material was then poured over ice-water and treated slowly with 6 M HCl until the pH of the mixture was 4–6. The mixture was then extracted with CH_2Cl_2, and the organic layer was dried with $MgSO_4$. The extracts were concentrated, and the crude material was subjected to flash chromatography on silica (8:1 petroleum ether–CH_2Cl_2) to give 2.2 g (9.2 mmol, 49%) of a pale-

yellow solid. ^{1}H NMR ($CDCl_3$) δ 3.63 (s, 3H), 5.51 (s, 2H), 7.06 (d, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.51 (m, 2H), 7.68 (d, *J* = 8.7 Hz, 1H), 8.06 (m, 2H), 8.41 (s, 1H), 8.92 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 56.32, 94.65, 105.51, 120.88, 121.54, 125.11, 125.19, 125.22, 125.61, 125.79, 127.90, 128.67, 131.24, 131.84, 132.59, 152.76. The NMR data matched that reported.[38]

Preparation of 1-methoxymethoxyanthracene-2-carbaldehyde (2.62).

A solution containing 0.20 g (0.84 mmol) of 1-methoxymethoxyanthracene and 1.7 mL (11 mmol) of TMEDA in 5 mL of dry ether was cooled to -18 °C on an ice and salt bath. To the solution was added 0.4 mL (1.0 mmol) of 2.5 M *n*-BuLi in hexanes. The reaction was stirred at -18 °C for 1 h. To the reaction mixture was added 0.13 mL (1.7 mmol) of DMF, and the reaction mixture was stirred for another 2 h at -18 °C. The reaction was quenched with water, extracted with CH_2Cl_2, and dried over $MgSO_4$. The crude material was dissolved in a minimum amount of ether and stirred with a 0.5 M $NaHSO_3$ solution for 20 min. The layers were separated, and the aqueous layer was taken to pH 11 and extracted again with ether. The combined organic layer was dried over $MgSO_4$ and concentrated. The resulting solid was purified via silica gel chromatography (2:1 petroleum ether–CH_2Cl_2) to give 0.17 g (0.67 mmol, 75%) of a pale-yellow solid: mp 105–106 °C (Lit.[39] 108 °C); ^{1}H NMR ($CDCl_3$) δ 3.72 (s, 3H), 5.39 (s, 2H), 7.56 (m, 2H), 7.81 (m, 2H), 8.05 (m, 2H), 8.41 (s, 1H), 8.81 (s, 1H), 10.57 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 58.29, 101.92, 121.09, 123.58, 124.61, 125.27, 126.29,

126.41, 126.90, 127.28, 128.03, 128.93, 131.83, 133.57, 134.59, 160.62, 190.17.

e. Preparation of 1-Hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde using 2-Allyl-1-hydroxyanthraquinone.

Preparation of 1-hydroxy-2-propenylanthraquinone (2.63).

A solution containing 2.0 g (7.6 mmol) of 2-allyl-1-hydroxyanthraquinone and 0.20 g (0.77 mmol) of bis(acetonitrile)dichloropalladium(II) in 150 mL of CH_2Cl_2 was refluxed for 9 h. The reaction mixture was cooled and allowed to stand at room temperature overnight. The solution was next diluted with CH_2Cl_2 to dissolve any precipitate. The mixture was then washed with water, dried over $MgSO_4$ and concentrated to give 1.95 g (7.38 mmol, 98%) of pure orange solid. ^1H NMR ($CDCl_3$) δ 1.98 (d, J = 6.6 Hz, 3H), 6.54 (m, 1H), 6.82 (d, J = 16.2 Hz, 1H), 7.78 (m, 4H), 8.29 (m, 2H), 13.19 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.26, 115.90, 119.52, 124.03, 126.88, 127.27, 131.25, 131.29, 132.43, 133.24, 133.73, 133.76, 133.94, 134.61, 159.60, 182.09, 189.05.

Preparation of 1-hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde (2.47).

The ozonolysis reaction for this compound was run as described earlier; however, this time 1-hydroxy-2-propenylanthraquinone (**2.63**) was used as the

starting material in place of 1-hydroxy-2-vinylanthraquinone (**2.46**). The reaction was run with 2.29 g (8.67 mmol) of 1-hydroxy-2-propenylanthraquinone in 150 mL of CH_2Cl_2 yielding 2.26 g (8.96 mmol, 103%) of the crude material that was used without further purification. (Spectral data is given earlier).

3. Initial attempt at analog synthesis using the coupling of 1,8-Dimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde and alkyne 2.15.

Synthesis of 2-(4-benzyloxymethyl-1,4-dihydroxyhex-5-en-2-ynyl)-1,8-dimethoxyanthraquinone (2.64).

To a solution of 2.7 mL of 3.0 M methylmagnesium bromide in THF (8.1 mmol) was added a solution of 3-benzyloxymethylpent-1-en-4-yn-3-ol in 5 mL of THF. The reaction was heated to 60 °C for 3 h. The solution was cooled to room temperature and a solution containing 0.95 g (3.2 mmol) of 1,8-dimethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde in 15 mL of THF was added. The reaction was stirred overnight. A satd solution of NH_4Cl was added, and the reaction material was extracted with CH_2Cl_2. The remaining oil was purified by column chromatography on silica gel (3:1 petroleum ether–EtOAc) to yield 0.54 g (1.1 mmol, 34%) of the product. ^1H NMR ($CDCl_3$) δ 2.97 (broad s, 2H), 3.47 (m, 2H), 3.96 (s, 3H), 3.97 (s, 2H), 4.55 (s, 2H), 5.20 (dd, J = 1.2 and 10.5 Hz,

1H), 5.52 (dd, J = 0.9 and 16.2, 1H), 5.83 (m, 1H), 7.24 (m, 5H), 7.77 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 56.88, 60.61, 63.66, 73.93, 76.67, 85.04, 86.57, 117.19, 118.31, 119.41, 120.46, 123.17, 123.87, 127.96, 128.17, 128.71, 132.61, 134.67, 134.91, 135.07, 137.24, 137.65, 141.77, 158.00, 159.78, 182.91, 183.46.

Synthesis of 2-(4-benzyloxymethyl-4-hydroxyhex-5-en-2-ynoyl)-1,8-dimethoxyanthraquinone (2.65).

A solution containing 0.2 g (0.4 mmol) of 2-(4-benzyloxymethyl-1,4-dihydroxyhex-5-en-2-ynyl)-1,8- dimethoxyanthraquinone in 5 mL of CH_2Cl_2 and 0.53 g (6.1 mmol) of MnO_2 was heated to 35 °C for 2 h. Upon completion, the reaction material was filtered over Celite and the remaining MnO_2 is washed with CH_2Cl_2. The solution was then concentrated to yield 0.16 g (0.32 mmol, 80%) of a yellow solid. ^1H NMR ($CDCl_3$) δ 3.55 (dd, J = 9.3 and 33.9 Hz, 2H), 3.94 (s, 3H), 3.97 (s, 3H), 4.59 (s, 2H), 5.28 (d, J = 10.5 Hz, 1H), 5.62 (d, J = 17.4 Hz, 1H), 5.85 (dd, J = 10.2 and 17.1 Hz, 1H), 7.24 (m, 5H), 7.59 (t, J = 7.8 Hz, 1H), 7.74 (d, J = 7.2 Hz, 1H), 7.91 (d, J = 8.1 Hz, 1H), 8.03 (d, J = 7.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 56.89, 64.59, 71.41, 74.06, 76.22, 76.74, 84.87, 93.86, 118.32, 118.55, 119.45, 122.26, 123.94, 127.93, 128.07, 128.26, 128.77, 129.44, 134.79, 134.84, 134.95, 135.31, 135.83, 137.43, 137.49, 137.74, 159.73, 160.67, 176.24, 183.22.

4. Attempted analog synthesis using the coupling of aldehyde 2.62 and alkyne 2.31.

Synthesis of 4-(*tert*-butyldimethylsilanyloxymethyl)-1-(1-methoxymethoxyanthracen-2-yl)-hex-5-en-2-yne-1,4-diol (2.66).

To a solution containing 0.39 g (1.7 mmol) of 3-(*tert*-butyldimethylsilyloxymethyl)- pent-1-en-4-yn-3-ol in 3 mL of THF cooled to -78 °C was added 1.5 mL (3.6 mmol) of 2.5 M BuLi in hexanes. The reaction mixture was stirred at -78 °C for 1.5 h. A solution of 1-methoxymethoxyanthracene-2-carbaldehyde (0.37 g, 1.4 mmol) in THF was added, and the reaction mixture was allowed to slowly cool to 0 °C at which point the reaction was quenched with water. The reaction mixture was extracted with CH_2Cl_2, and the organic layer was washed with brine, dried over $MgSO_4$ and concentrated. The crude material was purified via silica gel chromatography (4:1 petroleum ether–EtOAc) to give 0.40 g (0.82 mmol, 59%) of the desired product as a white solid. ^{1}H NMR ($CDCl_3$) δ 0.09 (s, 6H), 0.90 (s, 9H), 3.20 (br s, 1H), 3.53 (br s, 1H), 3.53–3.78 (m, 5H), 5.17 (d, J = 6.3 Hz, 1H), 5.28 (m, 1H), 5.38 (d, J = 6.0 Hz, 1H), 5.68 (m, 1H), 5.94 (dd, J = 9.9 and 17.4 Hz, 1H), 6.14 (s, 1H), 7.50 (m, 2H), 7.84 (m, 2H), 8.02 (m, 2H), 8.42 (s, 1H), 8.57 (m, 1H). ^{13}C NMR ($CDCl_3$) δ -5.47, -5.40, 18.27, 25.74, 57.77, 59.35, 70.17, 71.54, 84.86, 85.95, 100.06, 116.69, 121.31, 124.79, 125.64, 125.72, 125.90, 126.37, 126.58, 127.94, 128.45, 128.69, 131.67, 131.92, 132.80, 137.29, 150.35.

Synthesis of 4-(*tert*-butyldimethylsilyloxymethyl)-4-hydroxy-1-(1-methoxymethoxyanthracen-2- yl)hex-5-en-2-yn-1-one (2.67).

To a solution containing 0.30 g (0.61 mmol) of 4-(*tert*-butyldimethylsilyloxymethyl)-1-(1-methoxymethoxyanthracen-2-yl)-hex-5-en-2-yne-1,4-diol in 5 mL of CH_2Cl_2 is added 2.4 g MnO_2. The reaction mixture was stirred at room temperature for 1 h. The solid MnO_2 was removed by filtration over Celite, and the solid was thoroughly washed with CH_2Cl_2. The solution was concentrated, and the crude material was purified via silica gel chromatography (4:1 petroleum ether–EtOAc) to give 0.24 g (0.49 mmol, 80%) of a bright-yellow oil. ^{1}H NMR ($CDCl_3$) δ 0.11 (s, 6H), 0.92 (s, 9H), 3.51 (s, 1H), 3.69 (m, 4H), 3.85 (d, J = 9.6 Hz, 1H), 5.40 (m, 3H), 5.75 (d, J = 16.2 Hz, 1H), 5.97 (dd, J = 10.2 and 16.8 Hz, 1H), 7.56 (m, 2H), 7.77 (d, J = 9.3 Hz, 1H), 8.05 (m, 3H), 8.39 (s, 1H), 9.04 (s, 1H).

5. Analog synthesis using the coupling of aldehyde 2.47 and 3-methyl-1-penten-4-yn-3-ol.

Synthesis of 2-(1,4-dihydroxy-4-methylhex-5-en-2-ynyl)-1-hydroxyanthraquinone (2.68).

A solution containing 0.65 mL (6.0 mmol) of 3-methyl-1-penten-4-yn-3-ol in 5 mL of THF was cooled to -78 °C. To the solution was added 4.8 mL (12 mmol) of a

2.5 M solution of *n*-BuLi in hexanes. The reaction was allowed to slowly warm over 3 h. The solution was again cooled to -78°C and 0.65 g (2.6 mmol) of 1-hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde were added. The bath was removed immediately and the reaction was stirred at room temperature until the disappearance of the aldehyde on TLC (15–20 min). The reaction was then quenched with satd NH_4Cl and the mixture was extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. The crude material was purified via silica gel chromatography (4:1 CH_2Cl_2–EtOAc) to give 0.492 g (1.41 mmol, 54%) of a bright-yellow solid: mp 180 °C; ^{1}H NMR ($CDCl_3$) δ 1.61 (s, 3H), 2.12 (s, 1H), 3.09 (d, *J* = 5.7 Hz, 1H), 5.16 (d, *J* = 10.2 Hz, 1H), 5.53 (d, *J* = 17.1 Hz, 1H), 5.91 (d, *J* = 6 Hz, 1H), 6.00 (dd, *J* = 10.5 and 17.1 Hz, 1H), 7.91 (m, 4H), 8.33 (m, 2H), 13.25 (s, 1H). Anal. Calcd for $C_{21}H_{16}O_5$: C, 72.41; H, 4.63. Found: C, 72.34; H, 4.67.

Synthesis of 1-hydroxy-2-(4-hydroxy-4-methylhex-5-en-2-ynoyl)anthraquinone (2.69).

To a solution containing 0.11 g (0.32 mmol) of 2-(1,4-dihydroxy-4-methylhex-5-en-2-ynyl)-1-hydroxyanthraquinone in 25 mL of CH_2Cl_2 was added 0.40 g (4.6 mmol) of MnO_2. The reaction was stirred for 20 min. The mixture was filtered over Celite and concentrated to give 0.078 g (0.23 mmol, 71%) of a bright-yellow solid: mp 141–142 °C; ^{1}H NMR ($CDCl_3$) δ 1.64 (s, 1H), 2.36 (s, 1H), 5.20 (d, *J* = 10.2 Hz, 1H), 5.57 (d, *J* = 17.1 Hz, 1H), 5.97 (dd, *J* = 10.2 and 17.1

Hz, 1H), 7.75 (m, 3H), 8.25 (m, 3H), 13.62 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 29.29, 68.47, 83.60, 96.12, 115.17, 117.25, 118.15, 127.19, 127.52, 129.83, 132.89, 133.00, 134.71, 135.14, 136.69, 139.15, 140.17, 162.84, 174.83, 181.72, 188.41. Anal. Calcd for $C_{21}H_{14}O_5$: C, 72.83; H, 4.07. Found: C, 72.83; H, 4.04.

Synthesis of 2-(1-Hydroxy-1-methylallyl)-1-oxabenzo[a]anthracene-4,7,12-trione (2.70).

To a solution containing 0.078 g (0.23 mmol) of 1-hydroxy-2-(4-hydroxy-4-methylhex-5-en-2-ynoyl)anthraquinone and 0.12 g (0.45 mmol) of 18-crown-6 in 5 mL of DMF was added 0.025 g (0.43 mmol) of KF. The reaction was stirred for 3 h. Upon completion, the reaction was quenched with satd NH_4Cl and extracted with CH_2Cl_2. The organic layer was dried over $MgSO_4$ and concentrated. The crude material was purified via silica gel chromatography (4:1 CH_2Cl_2–EtOAc) to give 0.063 g (0.18 mmol, 81%) of a pale-yellow solid: mp 255–256 °C; ^1H NMR ($CDCl_3$) δ 1.84 (s, 1H), 5.34 (d, J = 10.8 Hz, 1H), 5.59 (d, J = 17.4 Hz, 1H), 6.34 (dd, J = 10.8 and 17.1 Hz, 1H), 6.65 (s, 1H), 7.85 (m, 2H), 8.34 (m, 3H), 8.61 (d, J = 8.4 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 26.57, 29.69, 74.07, 107.65, 115.36, 123.19, 127.18, 127.38, 131.94, 132.16, 134.21, 134.85, 137.65, 140.25, 172.41, 177.08, 181.24, 182.10. Anal. Calcd for $C_{21}H_{14}O_5$: C, 72.83; H, 4.07. Found: C, 72.56; H, 4.06.

Synthesis of 2-(1-hydroxy-1-oxiranylethyl)-1-oxabenzo[a]anthracene -4,7,12-trione (2.71).

A solution containing 50 mg (0.14 mmol) of 2-(1-hydroxy-1-methylallyl)-1-oxabenzo[a]anthracene-4,7,12-trione, 0.10 g (0.33–0.50 mmol) of 57–86% *m*-CPBA and 0.10 g (0.70 mmol) of Na_2HPO_4 in 10 mL of CH_2Cl_2 was stirred at room temperature. After 18 h, an additional 0.10 g (0.33–0.50 mmol) of *m*-CPBA was added. An additional 0.10 g (0.33–0.50 mmol) was added after 24 h. The reaction mixture was stirred overnight. The reaction mixture was quenched with satd $Na_2S_2O_3$ and satd $NaHCO_3$. The mixture was extracted with CH_2Cl_2, dried over $MgSO_4$ and concentrated. The crude material was purified via silica gel chromatography (4:1 CH_2Cl_2–EtOAc) to give 29 mg (0.08 mmol, 55%) of a pale-yellow solid: mp 243 °C; Anal. Calcd for $C_{21}H_{14}O_6$ (analysis was on a mixture of the two diastereomers): C, 69.61; H, 3.89. Found: C, 69.46; H, 4.17.

Diastereomer A: ^{1}H NMR ($CDCl_3$) δ 1.91 (s, 3H), 2.61 (s, 1H),2.82 (m, 1H), 2.94 (m, 1H), 3.79 (m, 1H), 6.72 (s, 1H), 7.86 (m, 2H), 8.35 (m, 3H), 8.63 (d, J = 6.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 25.69, 44.14, 56.09, 70.71, 108.18, 122.39, 123.28, 127.18,127.32, 128.08, 132.00, 132.14, 134.14, 134.22, 134.88, 137.65, 154.24, 170.99, 176.80, 181.15, 182.23.

Diastereomer B: ^{1}H NMR ($CDCl_3$) δ 1.77 (s, 3H), 2.80 (s, 1H), 2.98 (m, 1H), 3.04 (m, 1H), 4.00 (m, 1H), 6.75 (s, 1H), 7.85 (m, 2H), 8.35 (m, 3H), 8.63 (d, J = 8.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 23.11, 43.76, 55.47, 70.84, 108.38, 122.39, 123.29, 127.20, 127.29,127.99, 132.03, 132.15, 134.14, 134.21, 134.84, 137.69, 154.28, 172.58, 176.84, 181.20, 182.22.

REFERENCES

REFERENCES FOR PART ONE

(1) Gallo, R.C.; Montagnier, L. *Science* **2002**, *298*, 1730-1731.

(2) Prusiner, S.B. *Science* **2002**, *298*, 1726-1727.

(3) Montagnier, L. *Science* **2002**, *298*, 1727-1728.

(4) Gallo, R.C. *Science* **2002**, *298*, 1728-1730.

(5) Cohen, J. *Science* **2002**, *298*, 2320-2324.

(6) Pederson, O.S.; Pederson, E.B. *Antiviral Chem. Chemother.* **1999**, *10*, 285-314.

(7) Cowley, J. *Newsweek*, **1996**, 68-69.

(8) Mayasundari, A. Synthetic and Structural Studies on Anti-HIV Agents. In *Chemistry*; University of Tennessee: Knoxville, 1998; pp 264.

(9) Gussio, R.; Pattabiraman, N.; Zaharevitz, D.W.; Kellogg, G.E.; Topol, I.A.; Rice, W.G.; Schaeffer, C.A.; Erickson, J.W.; Burt, S.K. *J. Med. Chem.* **1996**, *39*, 1645-1650.

(10) Zaharevitz, D.W.; Gussio, R.; Wiegand, A.; Jalluri, R.; Pattabiraman, N.; Kellogg, G.E.; Pallansch, L.A.: Yang, S.S.; Buckheit, Jr., R.W. *Med. Chem. Res.* **1999**, *9*, 551-564.

(11) Watanabe, H.; Gay, R.L.; Hauser, C.R. *J. Org. Chem.* **1968**, *33*, 900.

(12) Wrobel, J.; Dietrich, A. *Heterocycles* **1994**, *38*, 1823-1838.

REFERENCES FOR PART TWO

(1) Garfield, S. *Mauve;* W.W. Norton & Company, Inc.: New York, **2001**, pp 89-99.

(2) Thomson, R.H. *Naturally Occurring Quinones III, Recent Advances*; University Press: Cambridge, **1987**; pp 358-359.

(3) Brown, T.M.; Cooksey, C.J.; Dronsfield, A.T. *Education in Chemistry* **1999**, *36*, 20-22.

(4) Lown, J.W. *Pharmacol. Ther.* **1993**, *60*, 185-214.

(5) Hansen, M.R.; Hurley, L.H. *Biochemistry* **1993**, *32*, 8068-8074.

(6) Hauser, F.M.; Rhee, R.P. *J. Org. Chem.* **1980**, *45*, 3061-3068.

(7) Sun, D.; Hansen, M.; Clement, J.J.; Hurley, L.H. *Biochemistry* **1993**, *32*, 8068-8074.

(8) Hanada, M.; Kaneta, K.; Nishiyama, Y.; Hoshino, Y.; Konishi, M. et al. *J. Antibiot.* **1991**, *44*, 824-831.

(9) Biabani, M.A.F.; Laatsch, H.; Helmke, E.; Weyland, H. *J. Antibiot.* **1997**, *50*, 874-877.

(10) Chan, K.L.; Sugiyama, H.; Saito, I.; Hara, M. *Tetrahedron Lett.* **1991**, *32*, 7719-7722.

(11) Plowman, J.; Dykes, D.J.; Hollingshead, M.; Simpson-Herren, L; Ally, M.C. Human Tumor Xenograft Models in NCI Drug

Development. *Anticancer Drug Development Guide: Preclinical Screening, Clinical Trials, and Approval*; Humana Press, Inc.: Totowa, NJ, **1997**.

(12) Uno, H.; Sakamoto, K.; Honda, E.; Fukuhara, K.; Ono, N.; Tanaka, J.; Masahiro, S. *J. Chem. Soc, Perkin Trans. 1* **2001**, *3*, 229-238.

(13) Gramatica, P.; Gianotti, M.P.; Speranza, G.; Manitto, P. *Heterocycles* **1986**, *24*, 743-750.

(14) Zil'berman, E.N.; Rybakova, N.A.*; Zh. Obshch. Khim.* **1960**, *30*, 1992-1996.

(15) Guanti, G.; Banfi, L.; Narisano, E. *Tetrahedron Lett.* **1986**, *27*, 3547-3550.

(16) Raghuram, T.; Vijaysaradhi, S.; Singh, I.; Singh, J. *Synth. Commun.* **1999**, *29*, 3215-3219.

(17) Wade, L.G. *Organic Chemistry;* Second ed.; Paramount Communications Company: Englewood Cliffs, 1991; 1233.

(18) Nakatani, K.; Okamoto, A.; Saito, I. *Tetrahedron* **1996**, *52*, 9427-9446.

(19) Bercich, M.D.; Cambie, R.C.; Rutledge, P.S.; *Aust. J. Chem.* **1999**, *52*, 241-257.

(20) Pausler, M.G.; Rutledge, P.S. *Aust. J. Chem.* **1994**, *47*, 2135-2147.

(21) Jung, M.E.; Lyster, M.A. *J. Org. Chem.* **1977**, *42*, 3761-3764.

(22) Olah, G.A.; Narang, S.C.; Gupta, B.G.B.; Malhotra, R. *J. Org.*

Chem. **1979**, *44*, 1247-1251.

(23) Matsumoto, T.; Jona, H.; Miyoko, K.; Suzuki, K. *Tetrahedron Lett.* **1991**, *32*, 5103-5106.

(24) Townsend, C.A.; Isomura, Y.; Davis, S.G.; Hodge, J.A. *Tetrahedron* **1989**, *45*, 2263-2276.

(25) Nakatani, K., Okamoto, A.; Yamanuki, M.; Saito, I. *J. Org. Chem.* **1994**, *59*, 4360-4361.

(26) Kumuzawa, T.; Kimura, T.; Matsuba, S.; Sato, S.; Onodera, J. *Carbohydrate Res.* **2001**, *334*, 183-194.

(27) Sardessai, M.S.; Abramson, H.N.; Wormser, H.C. *Synth. Commun.* **1993**, *23*, 3223-3229.

(28) Zhang, X.; Fox, B.W.; Hadfield, J.A. *Synth. Commun.* **1996**, *26*, 49-62.

(29) Gaddil, D.D.; Rama Rao, A.V. *Tetrahedron Lett.* **1968**, *18*, 2223-2227.

(30) Rama Rao, A.V.; Deshpande, V.H.; Reddy, N.L. *Tetrahedron Lett.* **1980**, *21*, 2661-2664.

(31) Xie, L.; Takeuchi, Y.; Cosentino, L.M.; McPhail, A.T.; Lee, K.H. *J. Med. Chem.* **2001**, *44*, 664-671.

(32) Pulgarin, C.; Tabacchi, R.; *Helv. Chim. Acta* **1988**, *71*, 876-880.

(33) Krohn, K.; Klimars, M.; Koehle, H.J.; Ebeling, E. *Tetrahedron* **1984**, *40*, 3677-3694.

(34) Zembower, D.E.; Kam, C.M.; Powers, J.C.; Zalkow, L.H. *J. Med. Chem.* **1992**, 1597-1605.

(35) Murty, K.; Pal, R.; Datta, K.; Mal, D. *Synth. Commun.* **1994**, *24*, 1287-1292.

(36) Sato, T.; Komine, N.; Hirano, M.; Komiya, S. *Chem. Lett.* **1999**, 441-442.

(37) Tamayo, N.; Echavarren, A.M.; Paredes, M.C.; Farina, F.; Noheda, P. *Tetrahedron Lett.* **1990**, *31*, 5189-5192.

(38) Tius, M.A.; Gomez-Galeno, J.; Xue-qin, G.; Zaidi, J.H. *J. Am. Chem. Soc.* **1991**, *113*, 5775-5683.

(39) Harvey, R.G.; Cortez, C.; Ananthanarayan, T.P.; Schmolka, S. *J. Org. Chem.* **1988**, *53*, 3936-3943.

(40) Anastasia, M.; Allevi, P.; Bettini, C.; Fiecchi, A.; Sanvito, A.M. *Synthesis* **1990**, 1083-1084.

(41) Krohn, K.; Baltus, W. *Tetrahedron* **1988**, *44*, 49-54.

(42) Comins, D.L.; Brown, J.D. *J. Org. Chem.* **2000**, *65*, 2813-2815.

(43) Benington, F.; Morin, R.D. *J. Org. Chem.* **1961**, *26*, 194-197.

(44) Williams, R.M.; Ehrlich, P.P.; Zhai, W.; Hendrix, J. *J. Org. Chem.* **1987**, *52*, 2615-2617.

(45) Yu, T.W.; Shen, Y.; McDaniel, R.; Floss, H.G.; Khosla, C.; Hopwood, D.A.; Moore, B.S. *J. Am. Chem. Soc.* **1998**, *120*, 7749-7759.

(46) Bruun, T. *Acta Chem. Scand.* **1965**, *19*, 1677-1693.

(47) Aardt, T.G.; Rensburg, H.; Ferreira, D. *Tetrahedron* **1999**, *55*, 11773-11786.

(48) Bredereck, K.; Kimmich, H.; Sigmund, G. *Justus Liebigs Ann. Chem.* **1977**, 184-188.

(49) Shargi, H.; Aghapour, G. *J. Org. Chem.* **2000**, *65*, 2813-2815.

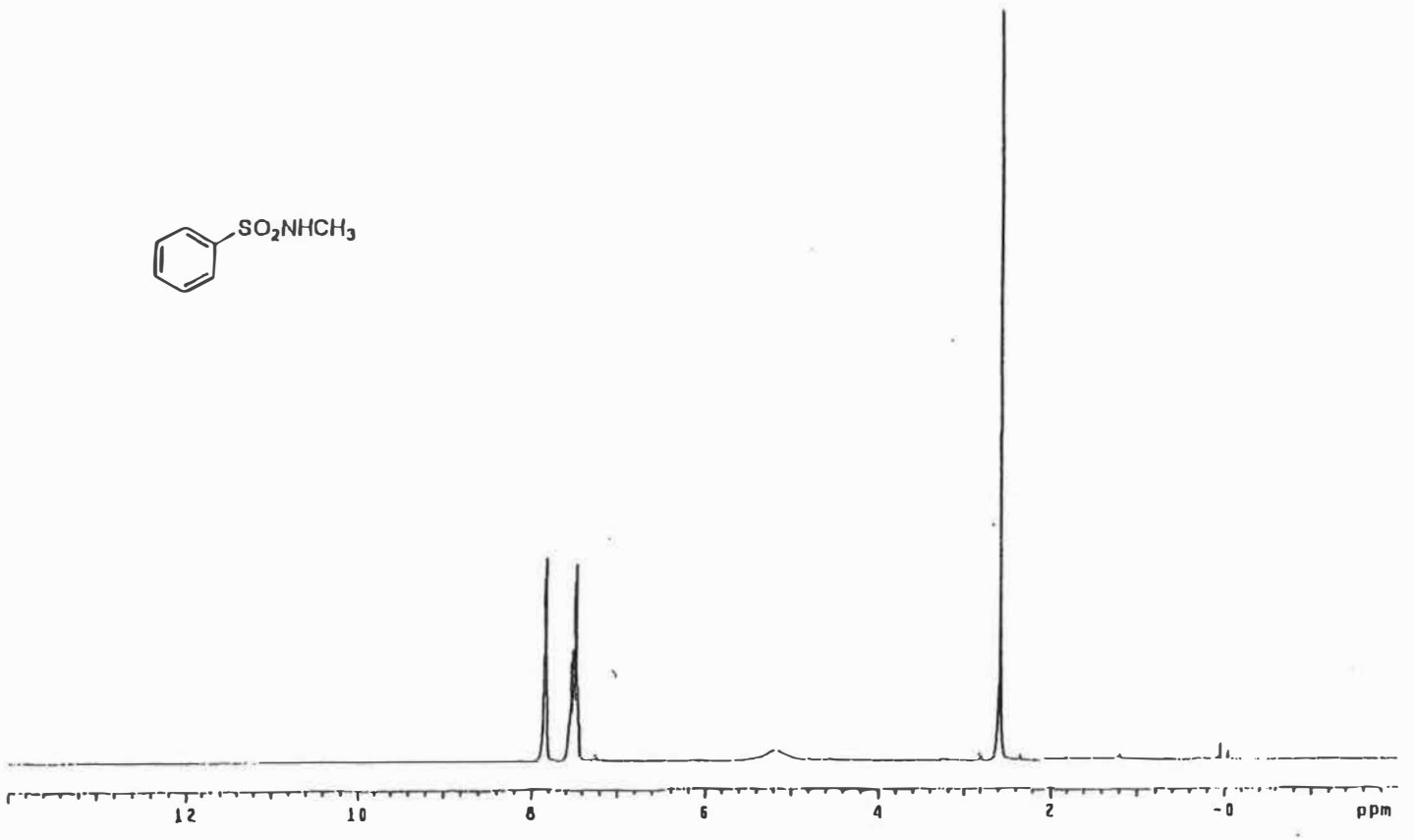
(50) Zembower, D.E.; Kam, C.M.; Powers, J.C.; Zalkow, L.H.; *J. Med. Chem.* **1992**, *35*, 1597-1605.

(51) Fang, J.P.; Lu, T.; Kim, H.; Delgado, I.; Geoffrey, P.; Atwood, J.L.; Gokel, G.W. *J. Org. Chem.* **1991**, *56*, 7059-7065.

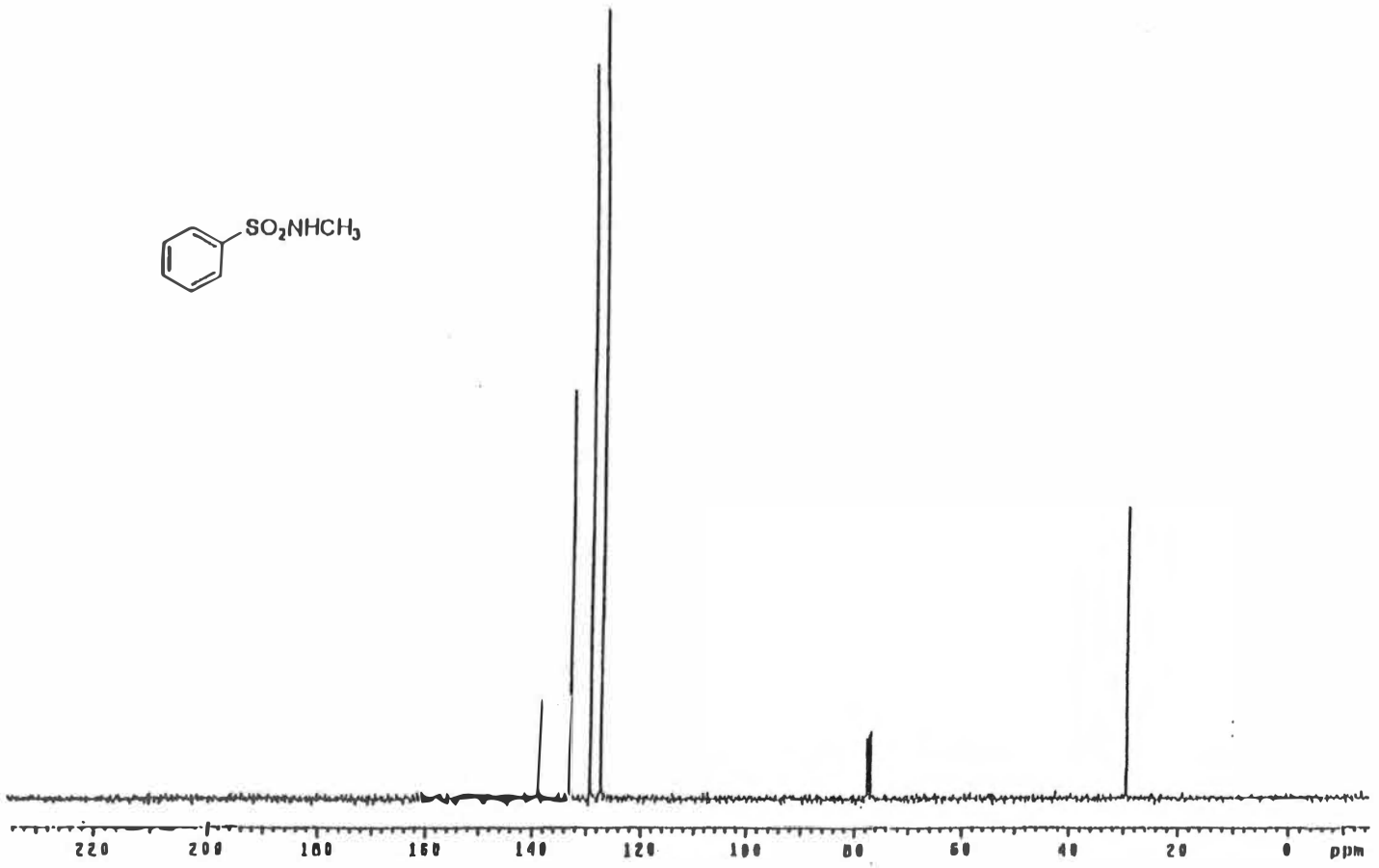
(52) Boddy, I.K.; Boniface, P.J.; Cambie, R.C.; Craw, P.A.; Huang, Z.D.; Larsen, D.S.; McDonald, H.; Rutledge, P.S.; Woodgate, P.D. *Aust. J. Chem.* **1984**, *37*, 1511-1529.

APPENDICES

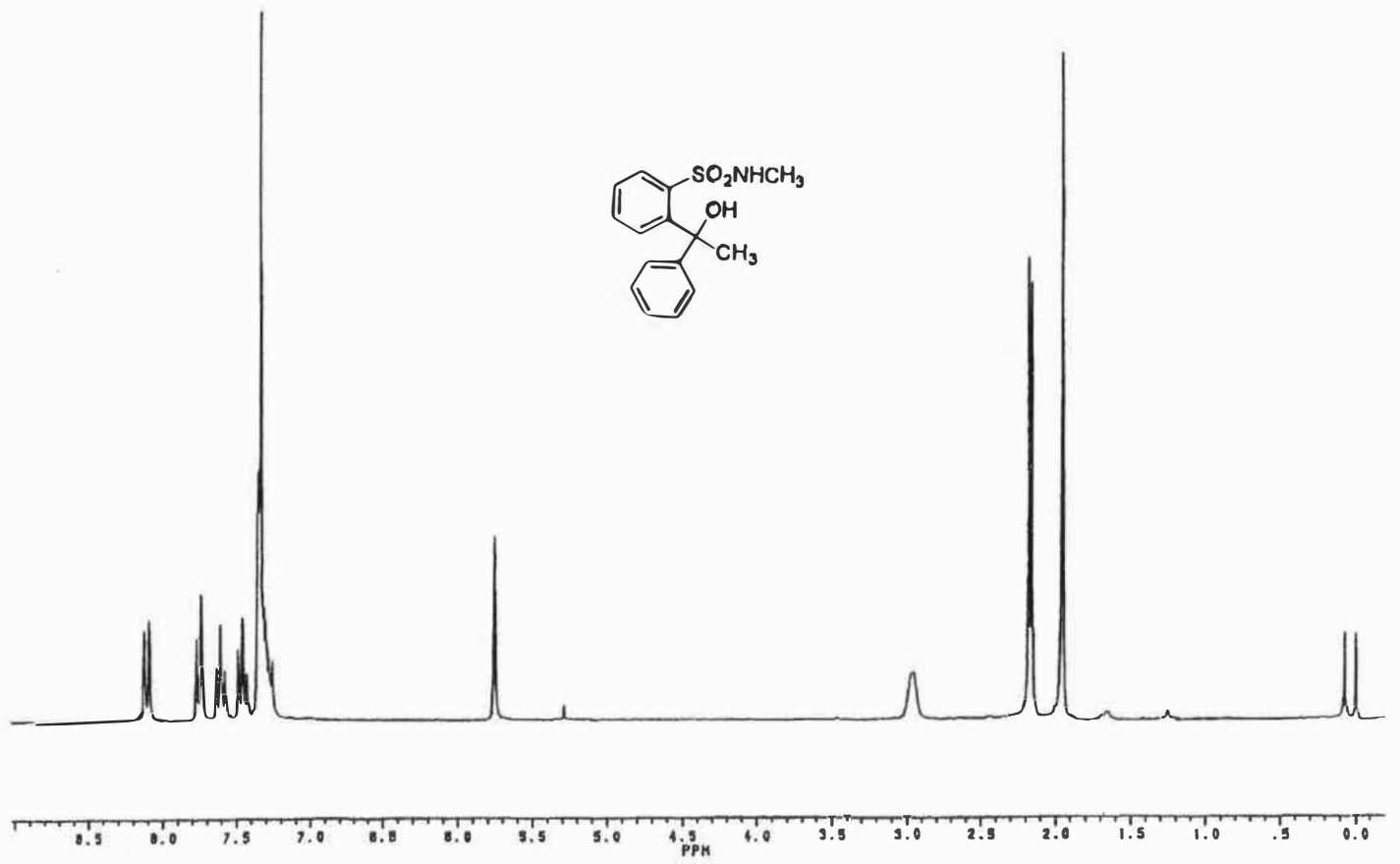
APPENDIX A. ^{1}H and ^{13}C NMR Spectra for Sultam Analogs



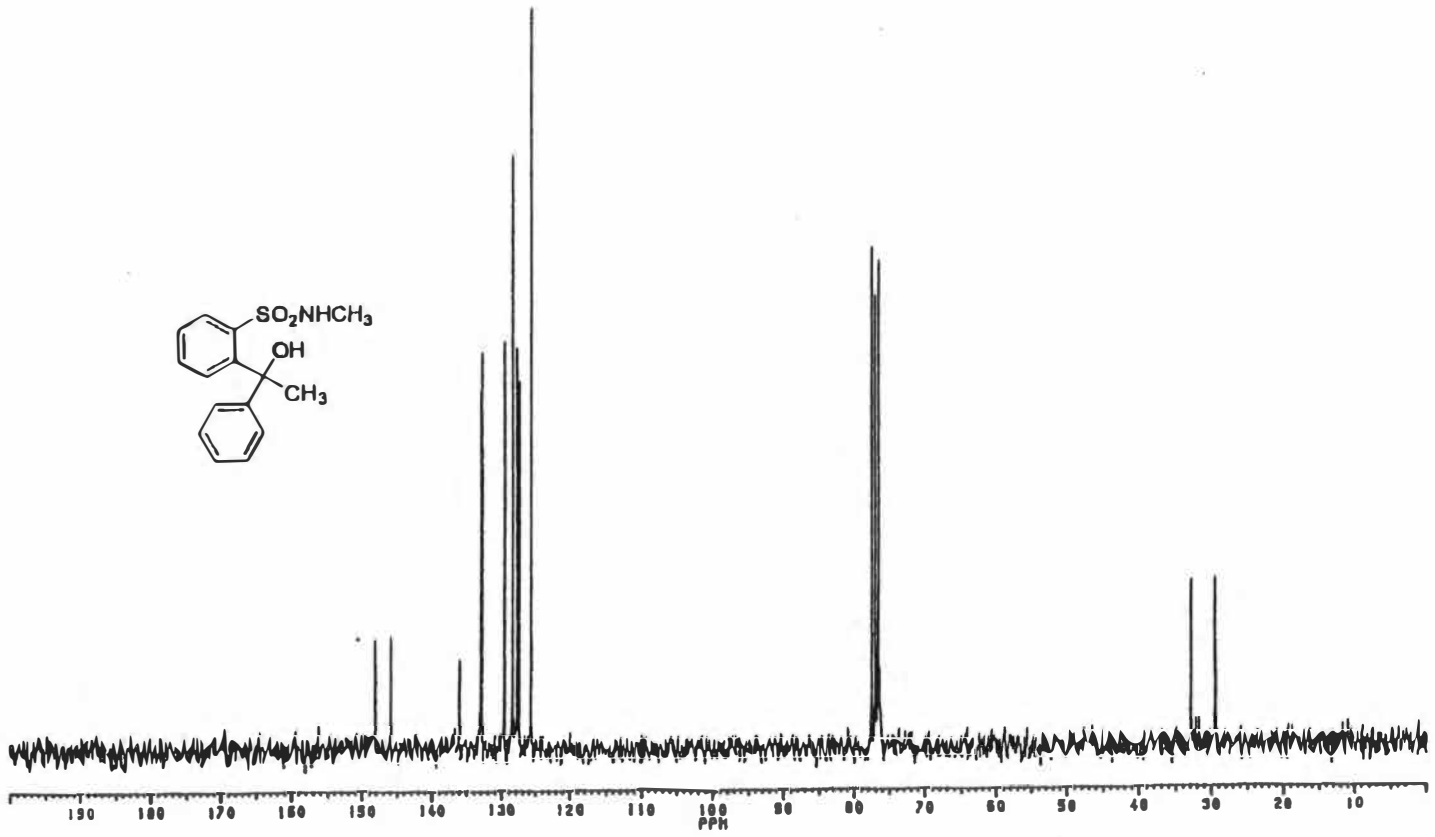
^{1}H NMR spectrum of Benzenesulfonyl chloride (**1.1**).



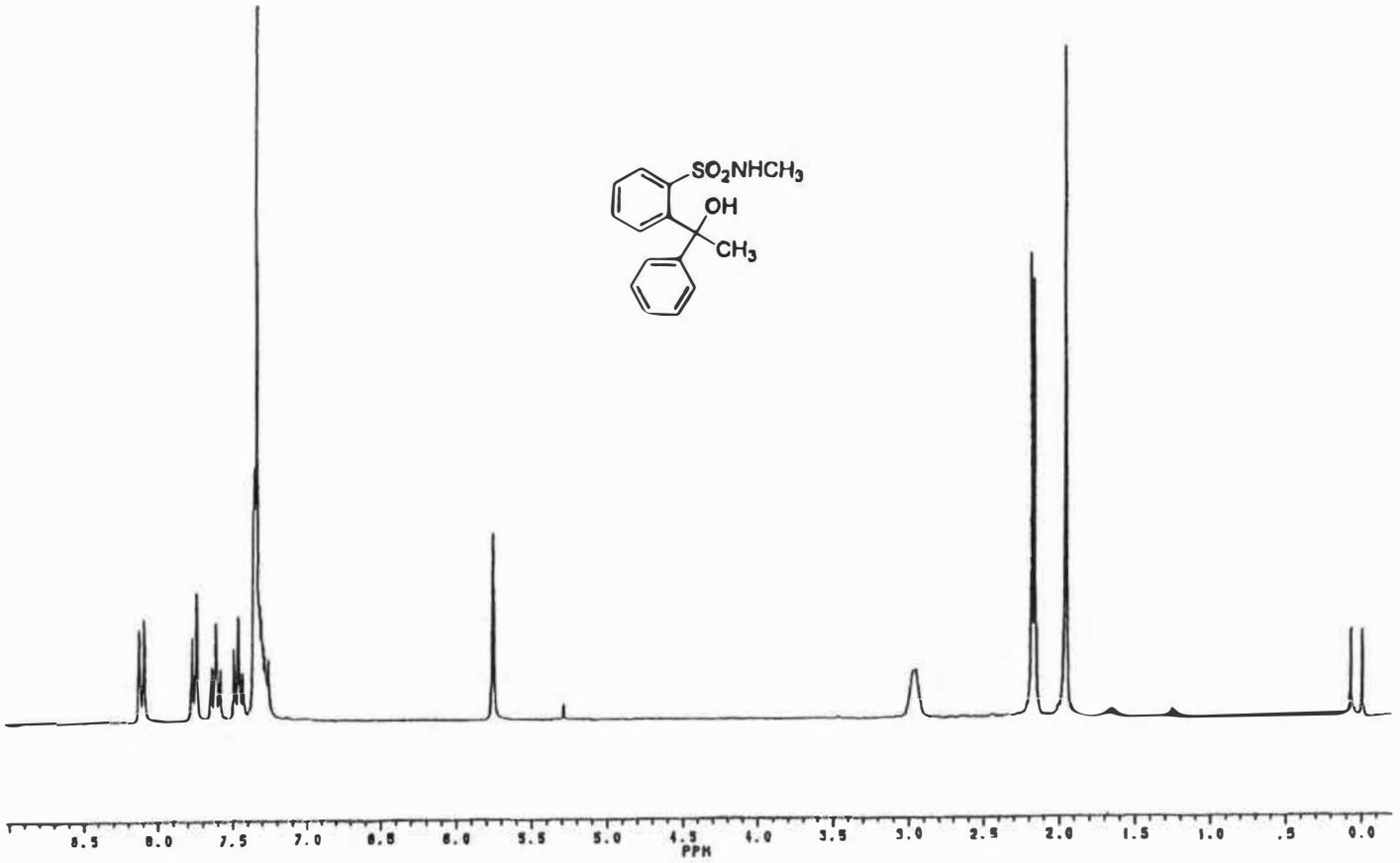
^{13}C NMR spectrum of Benzenesulfonyl chloride (**1.1**)



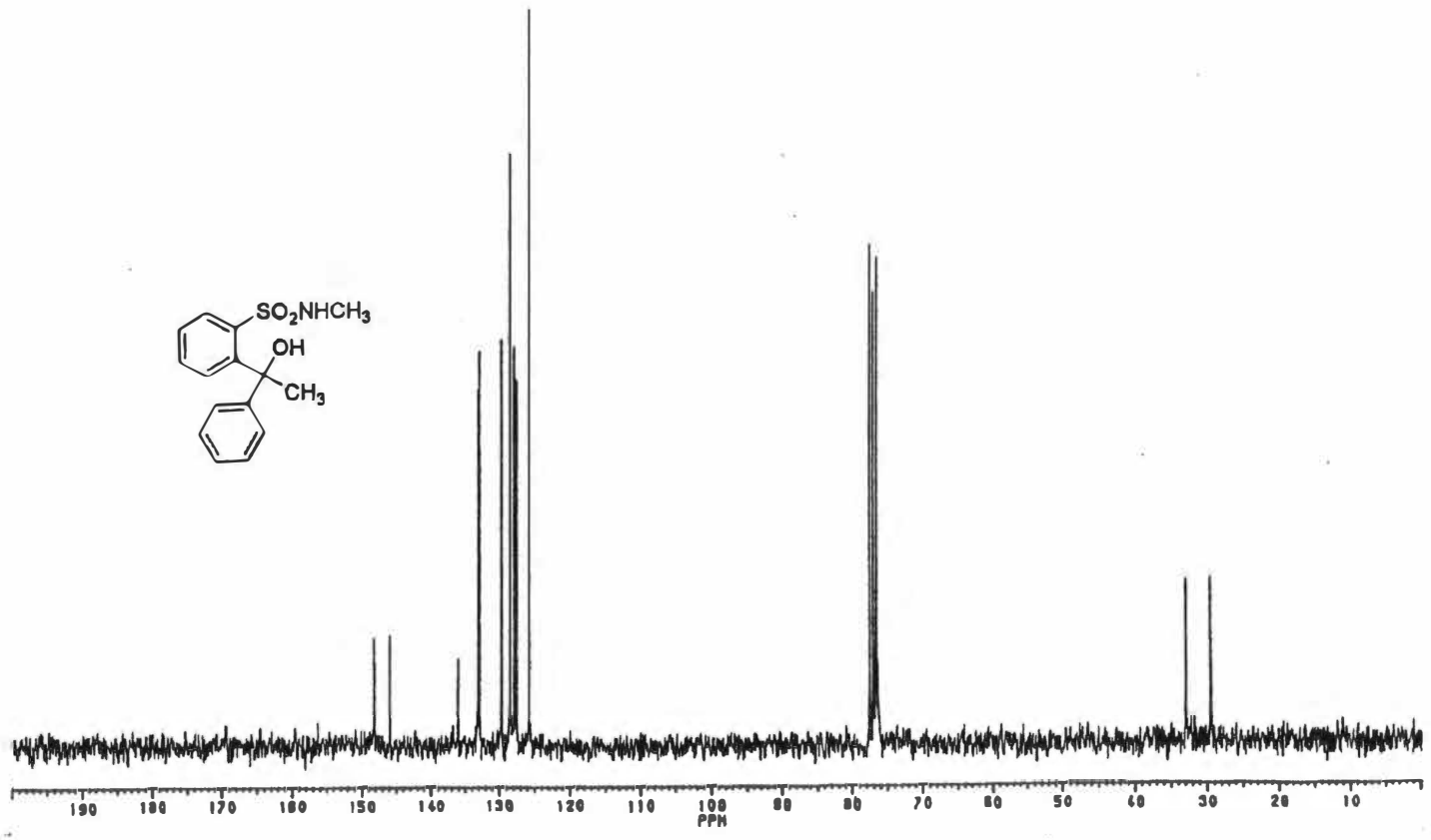
^{1}H NMR spectrum of 2-(1-Hydroxy-1-phenylethyl)-*N*-methylbenzenesulfonamide (**1.3a**)



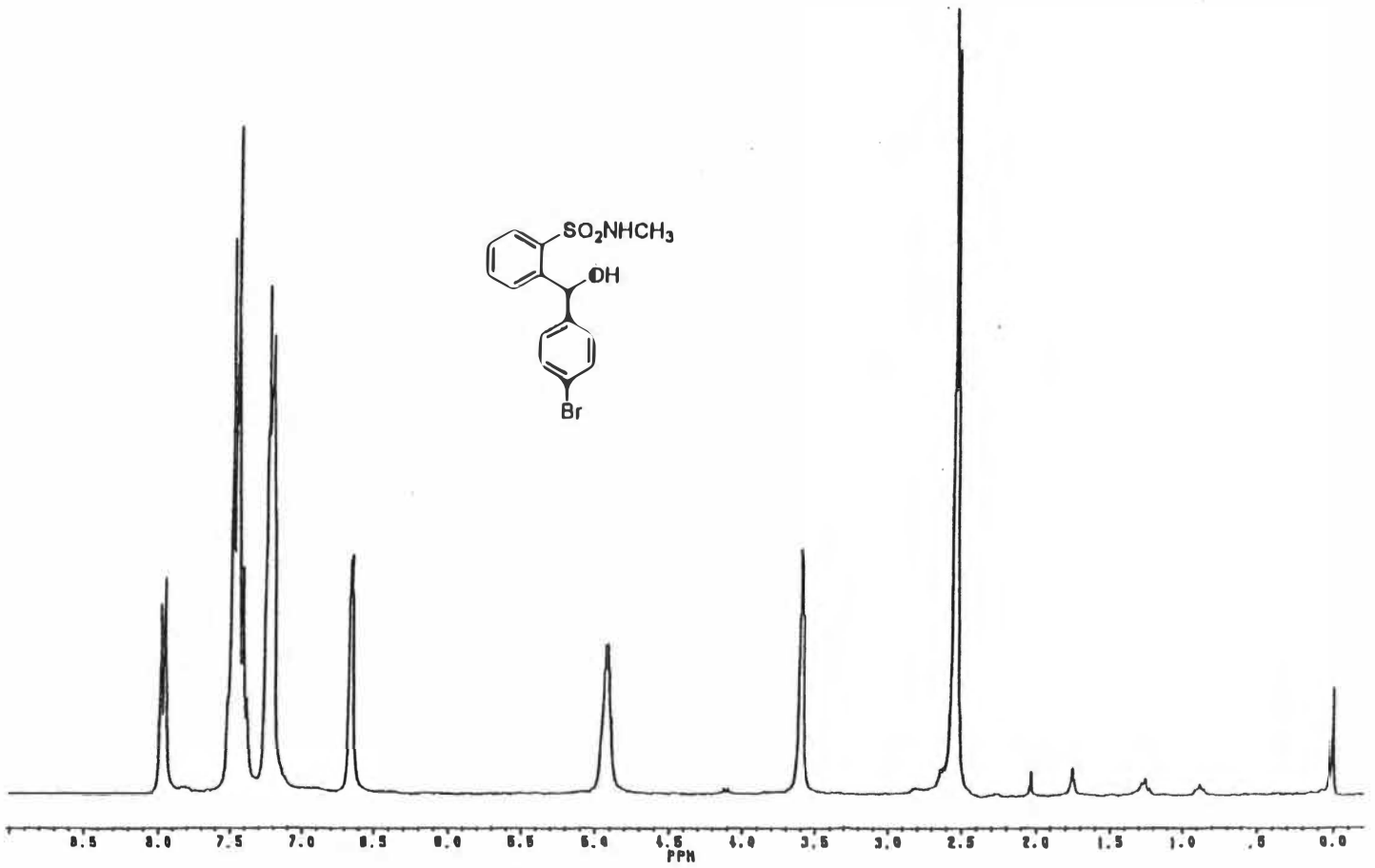
^{13}C NMR spectrum of 2-(1-Hydroxy-1-phenylethyl)-*N*-methylbenzenesulfonamide (**1.3a**).



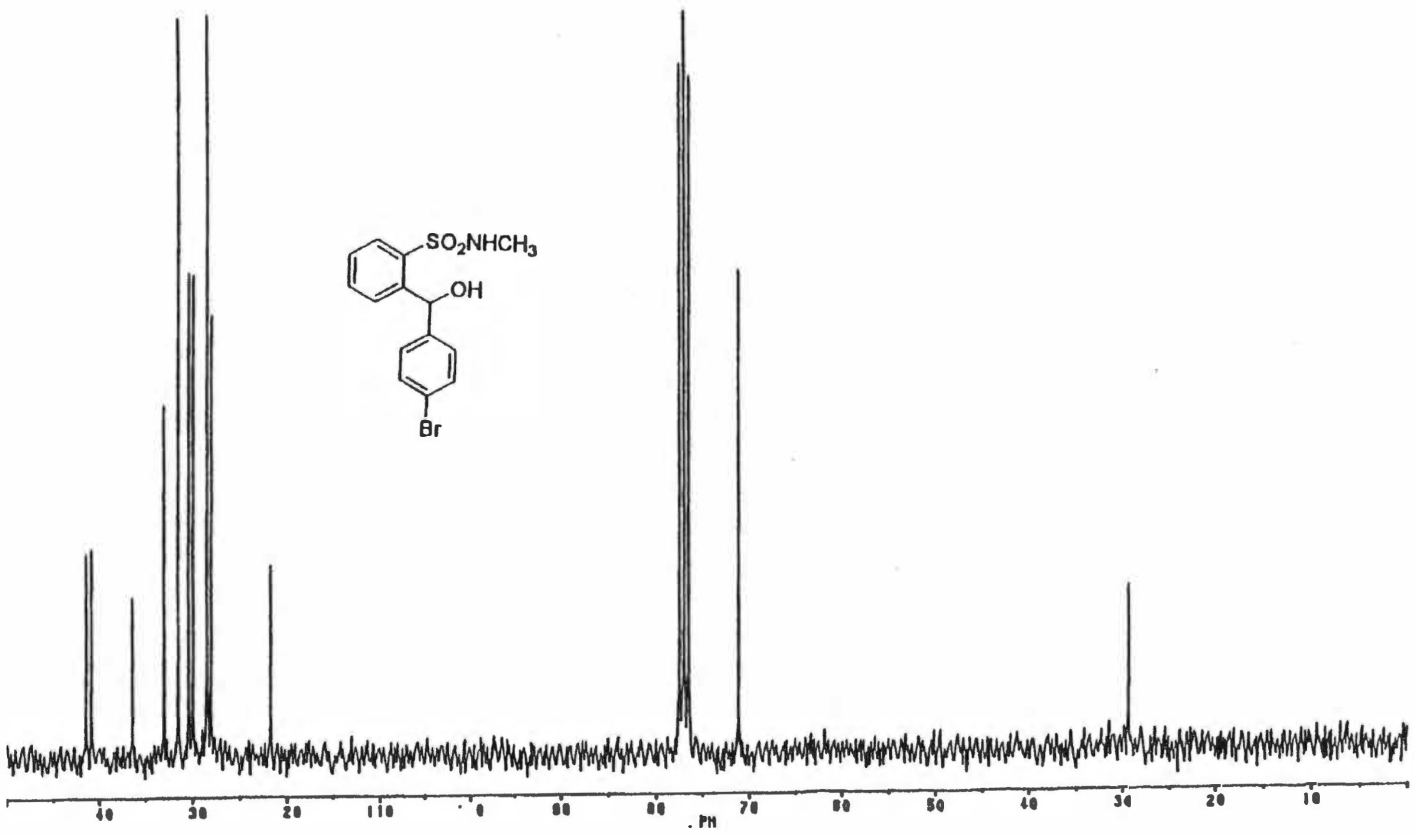
^{1}H NMR spectrum of 2-(1-Hydroxy-1-phenylethyl)-*N*-methylbenzenesulfonamide (**1.3a**)



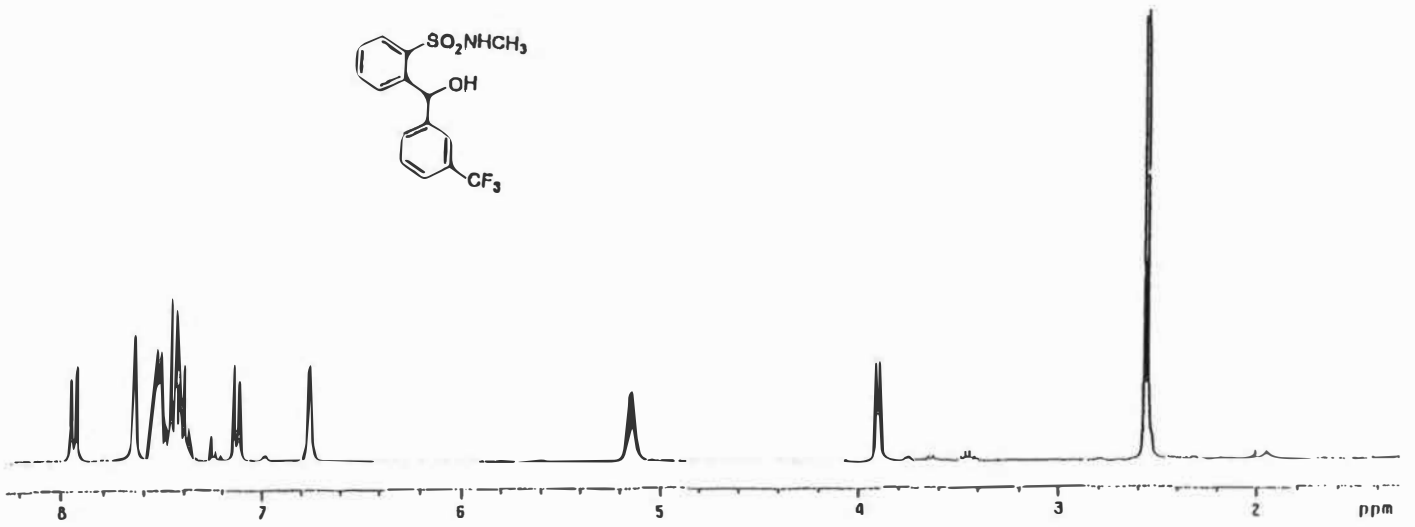
^{13}C NMR spectrum of 2-(1-Hydroxy-1-phenylethyl)-*N*-methylbenzenesulfonamide (**1.3a**).



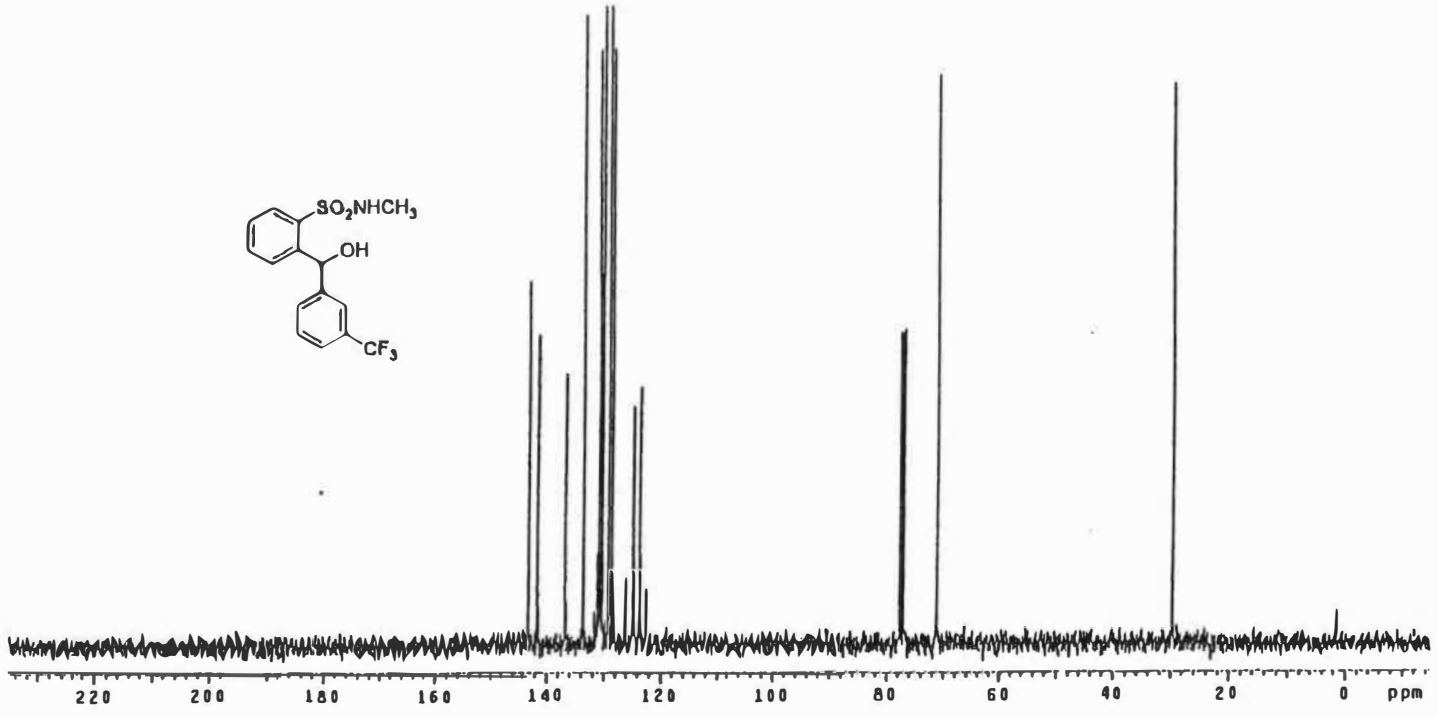
^{1}H NMR spectrum of 2-[(4-Bromophenyl)-hydroxymethyl]-*N*-methylbenzenesulfonamide (**1.3b**).



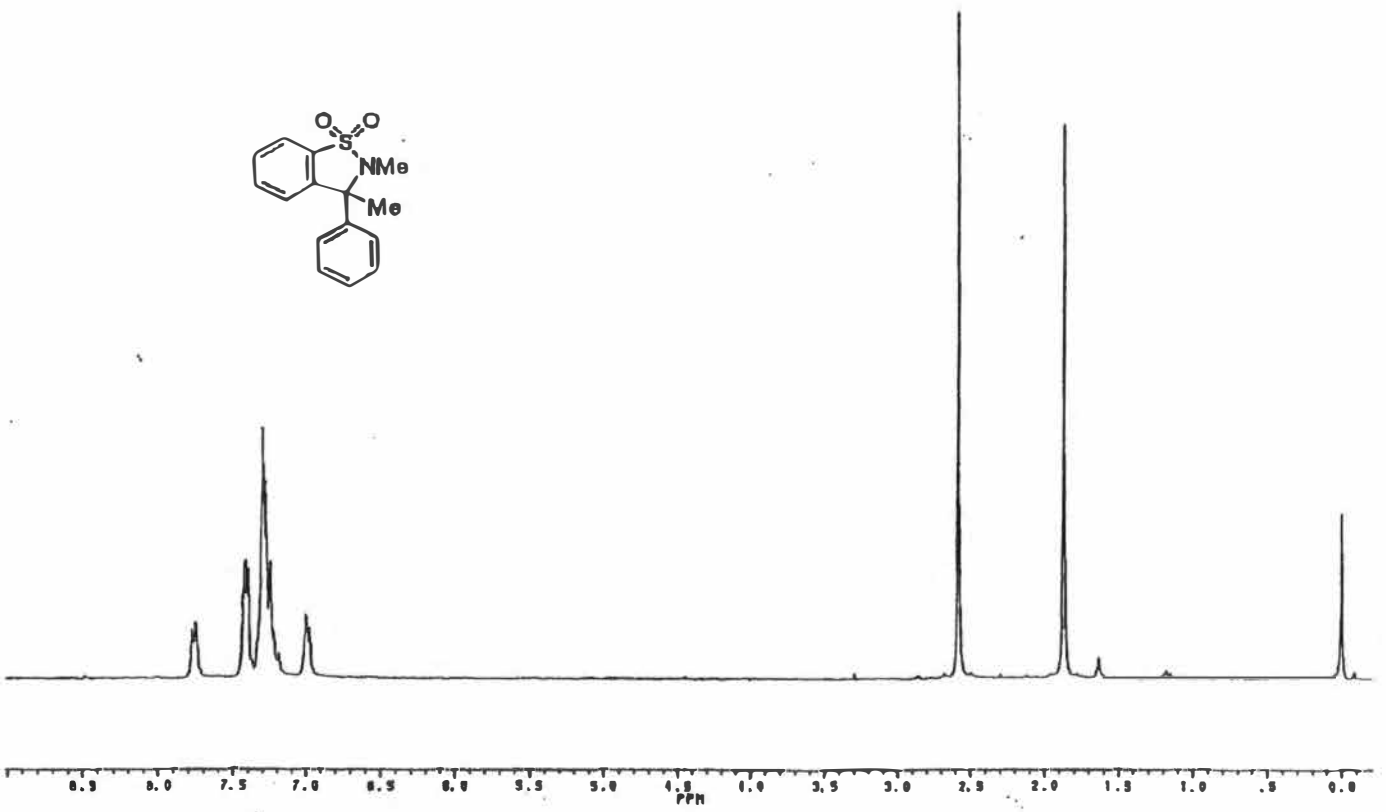
^{13}C NMR spectrum of 2-[(4-Bromophenyl)-hydroxymethyl]-*N*-methylbenzenesulfonamide (**1.3b**).



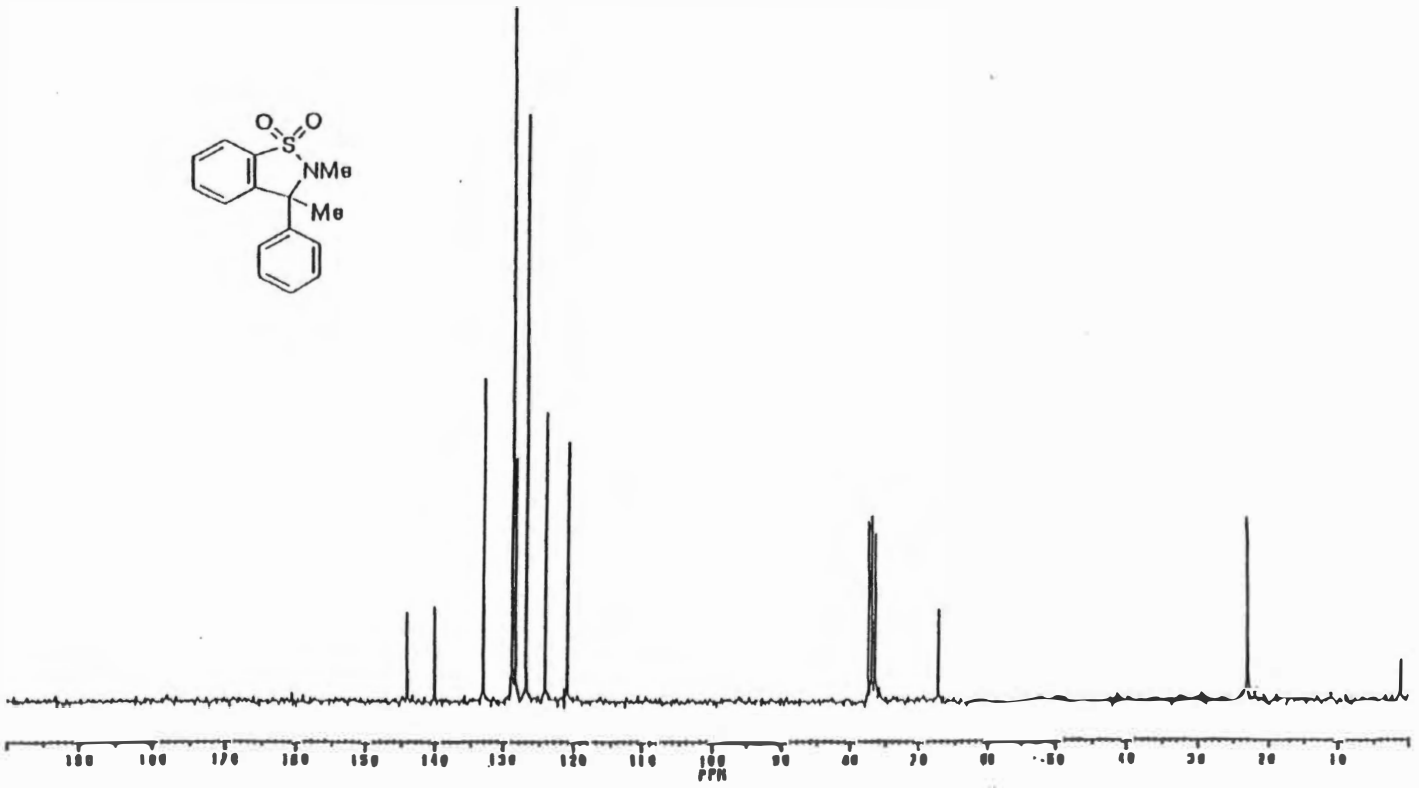
^{1}H NMR spectrum of 2-[Hydroxy-(3-trifluoromethylphenyl)-methyl]-*N*-methylbenzenesulfonamide (**1.3f**).



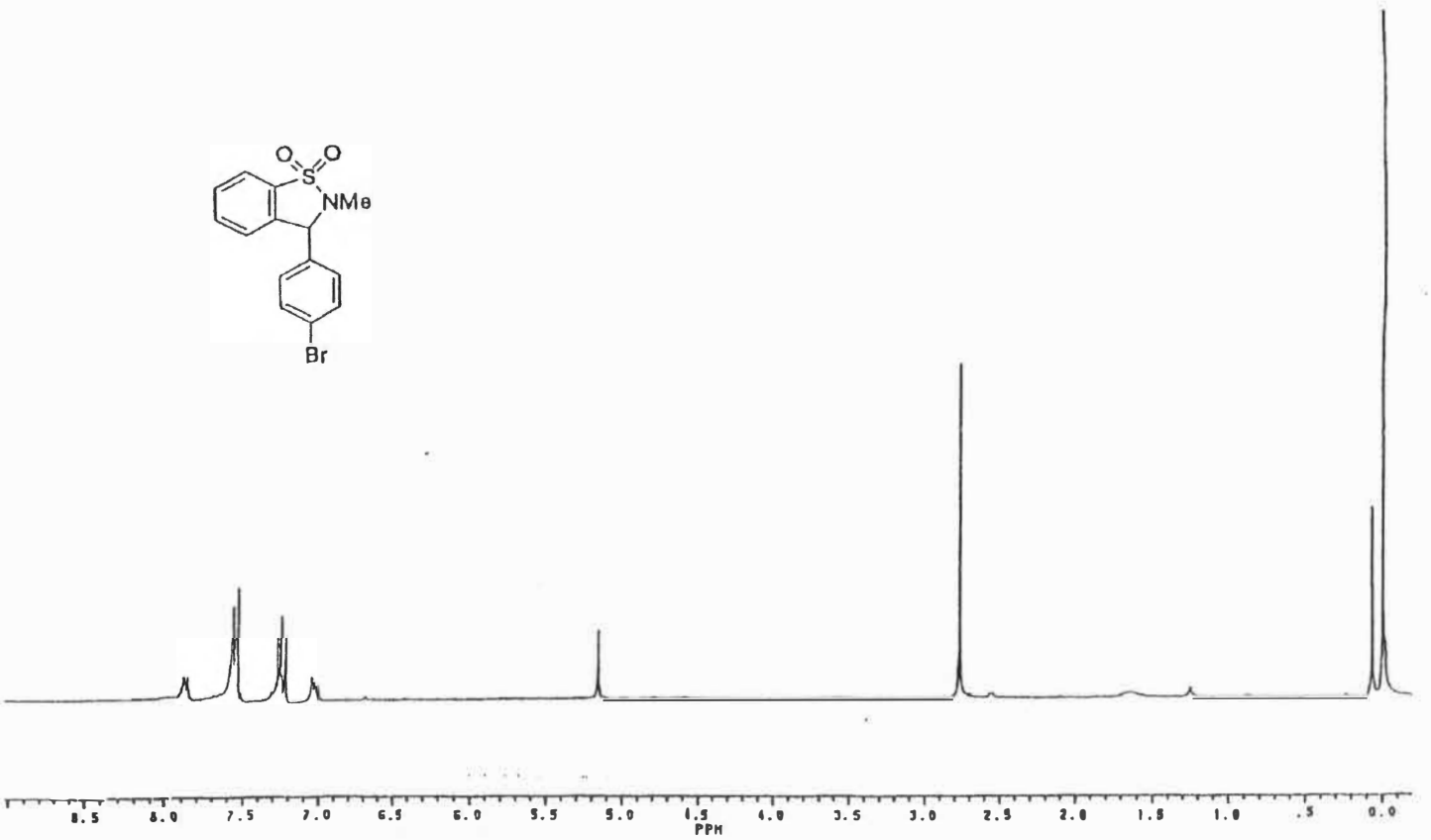
^{13}C NMR spectrum of 2-[Hydroxy-(3-trifluoromethylphenyl)-methyl]-*N*-methylbenzenesulfonamide (**1.3f**).



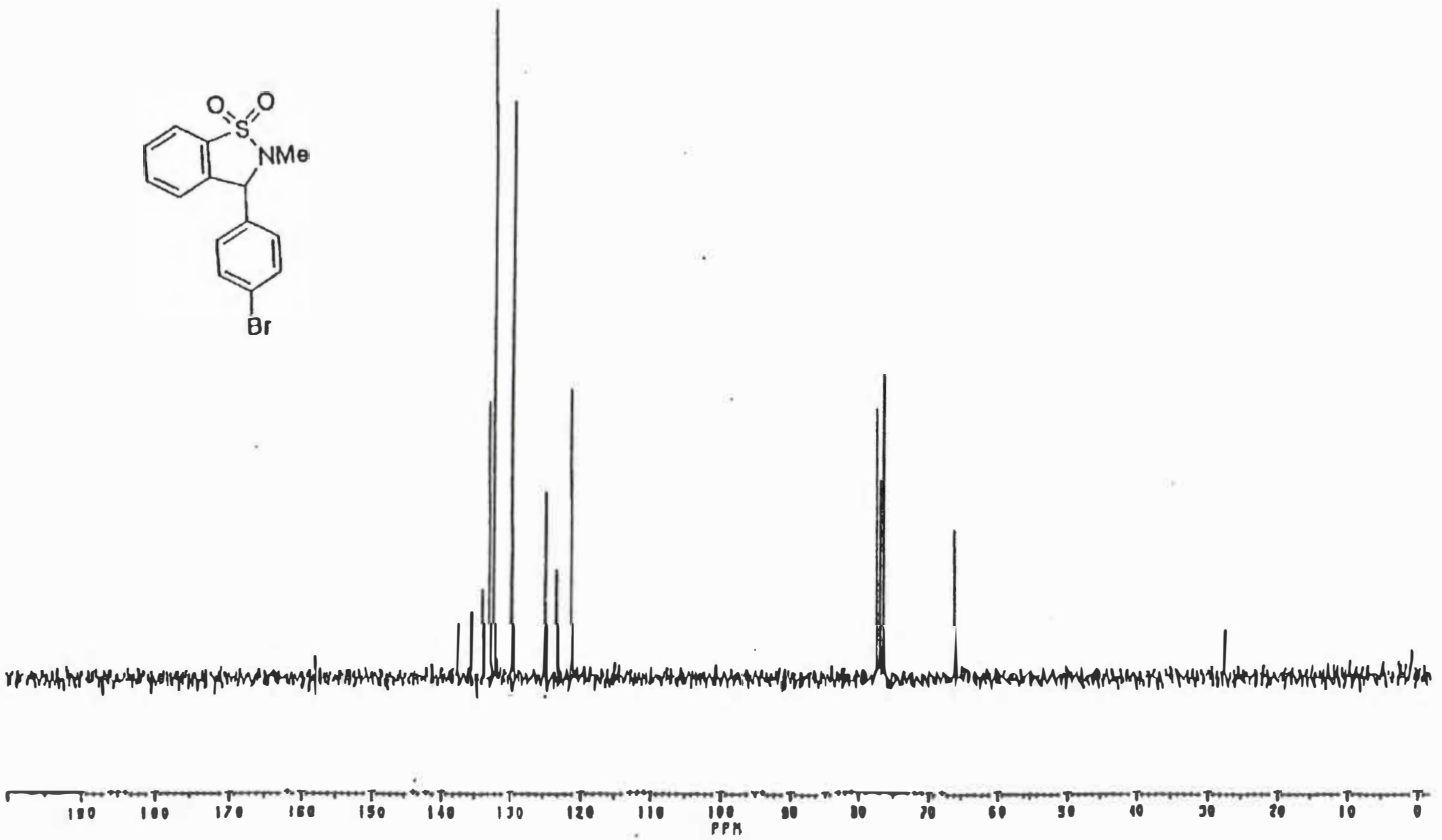
^{1}H NMR spectrum of 2,3-Dimethyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**1.4a**).



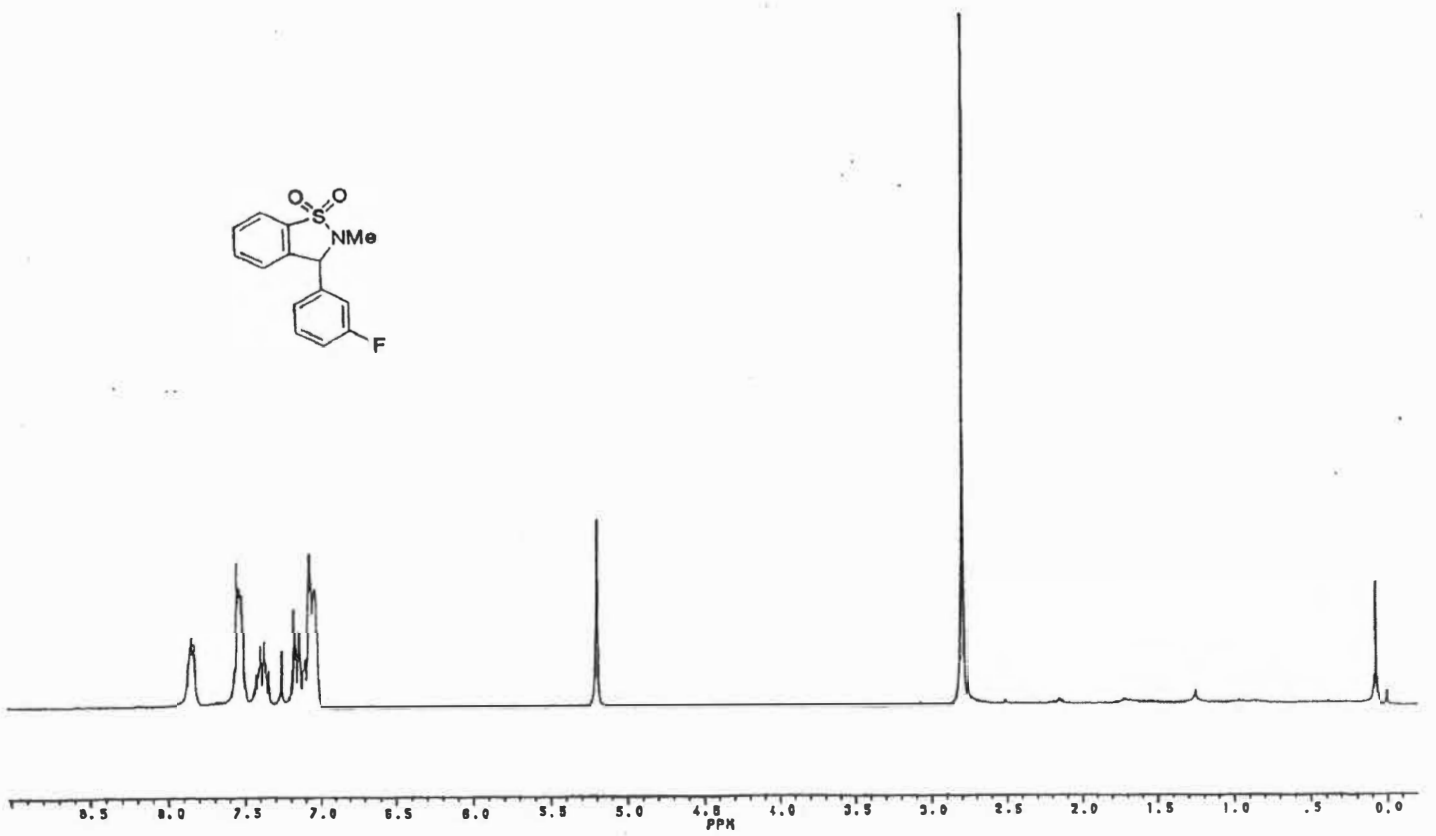
^{13}C NMR spectrum of 2,3-Dimethyl-3-phenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**1.4a**).



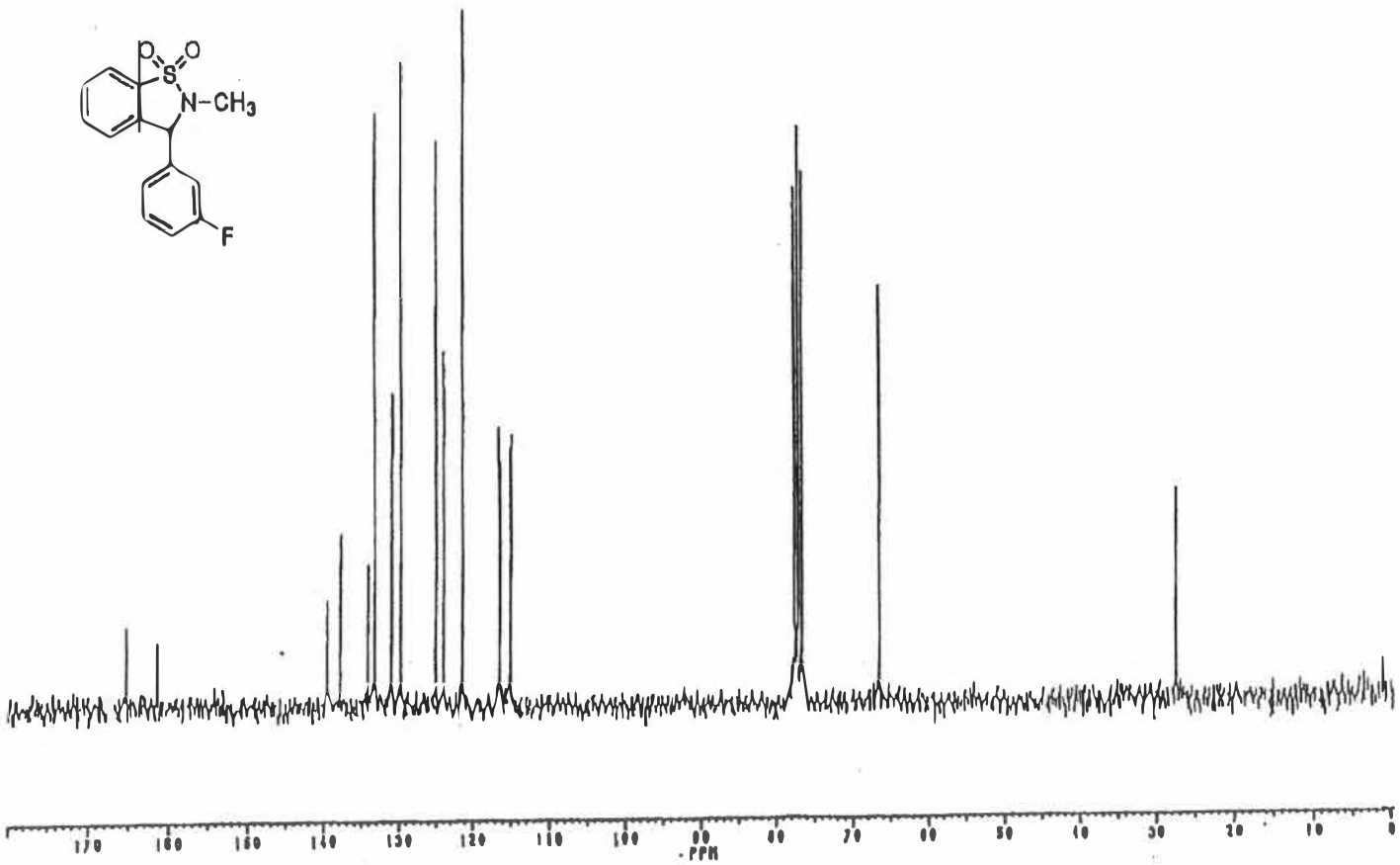
^{1}H NMR spectrum of 3-(4-Bromophenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**1.4b**).



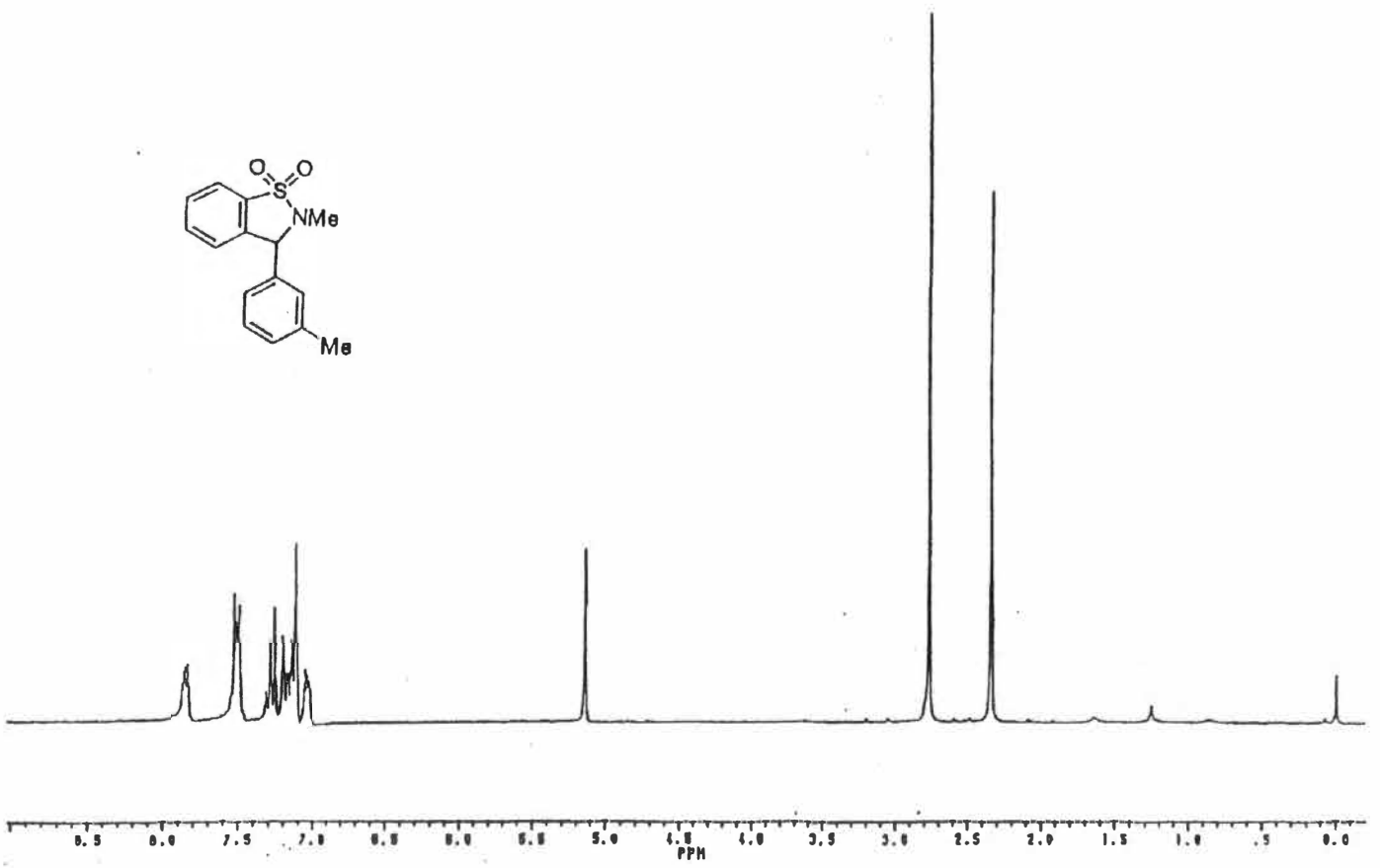
^{13}C NMR spectrum of 3-(4-Bromophenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**1.4b**).



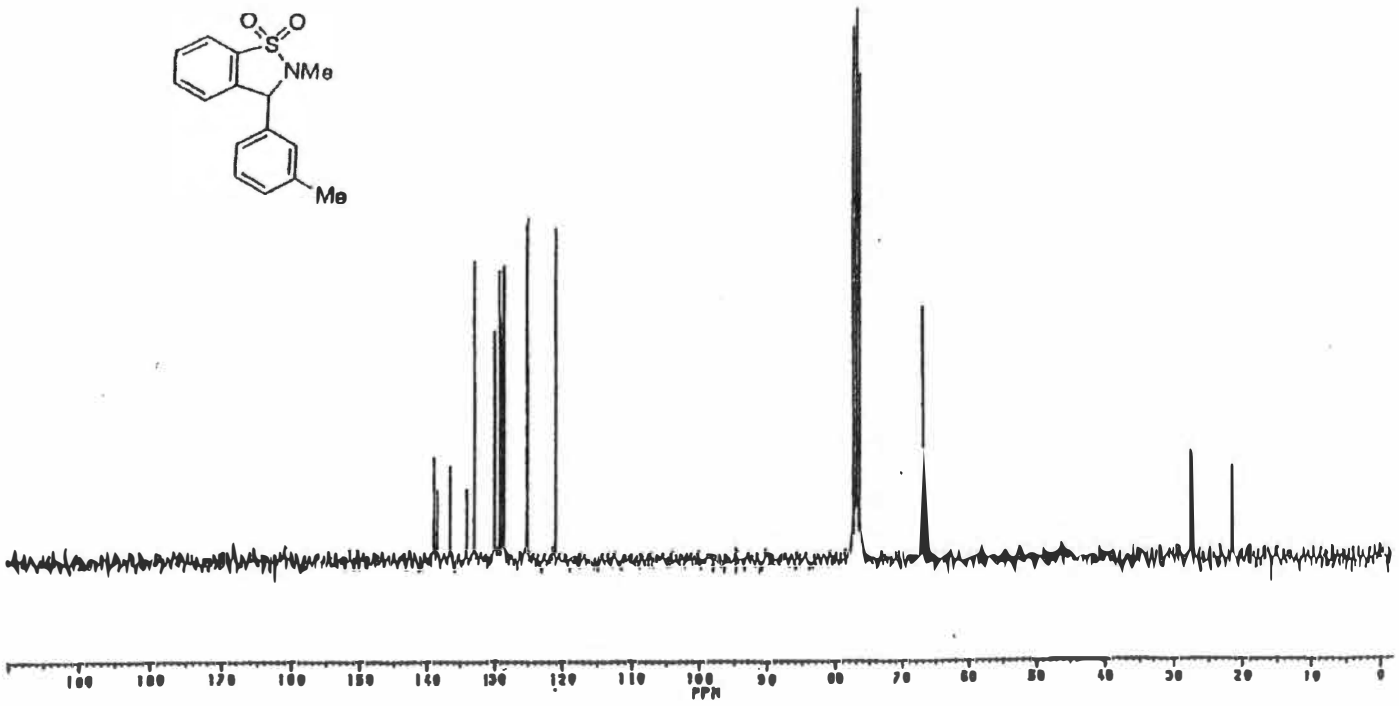
^{1}H NMR spectrum of 3-(3-Fluorophenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**1.4c**).



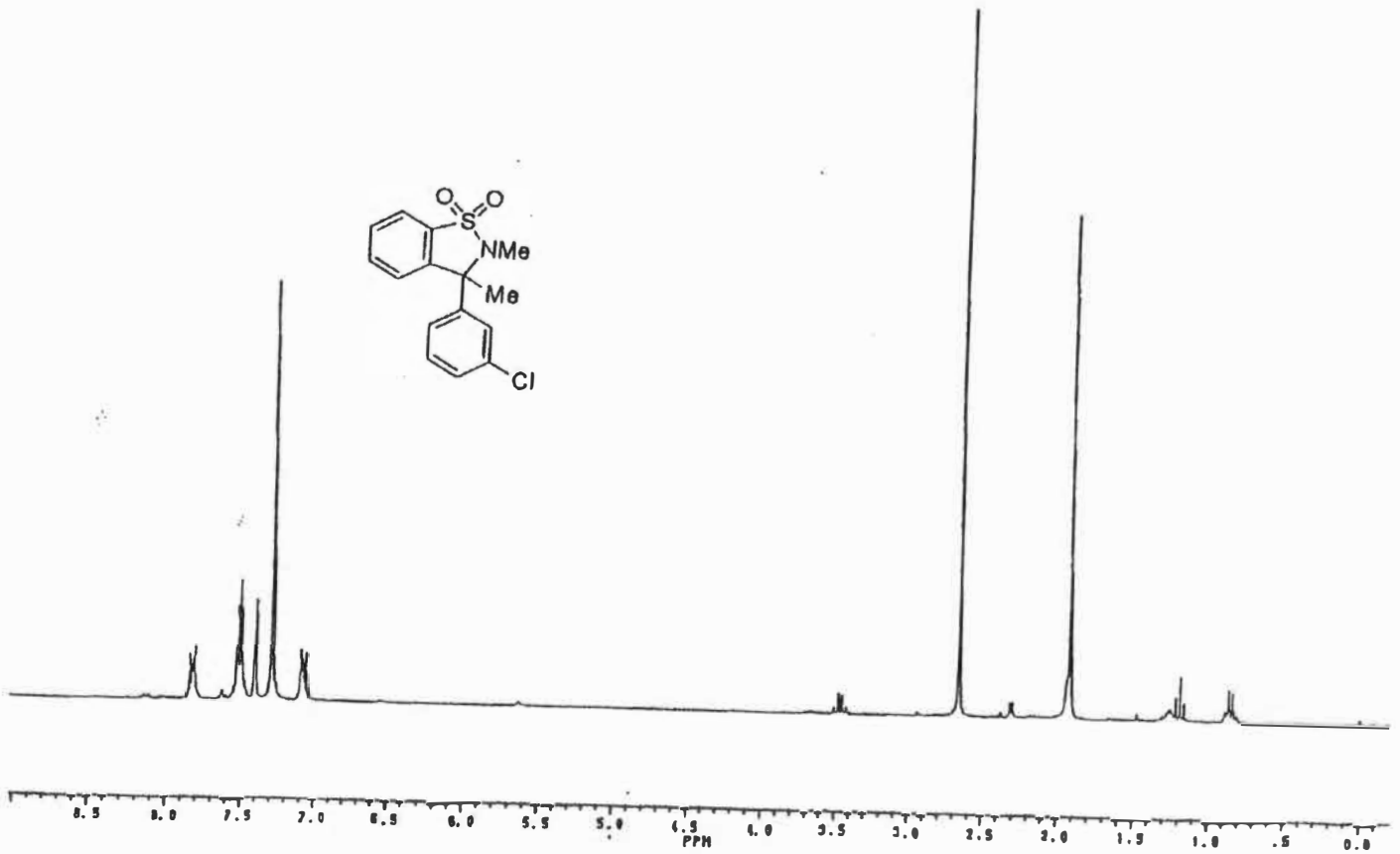
^{13}C NMR spectrum of 3-(3-Fluorophenyl)-2-methyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**1.4c**).



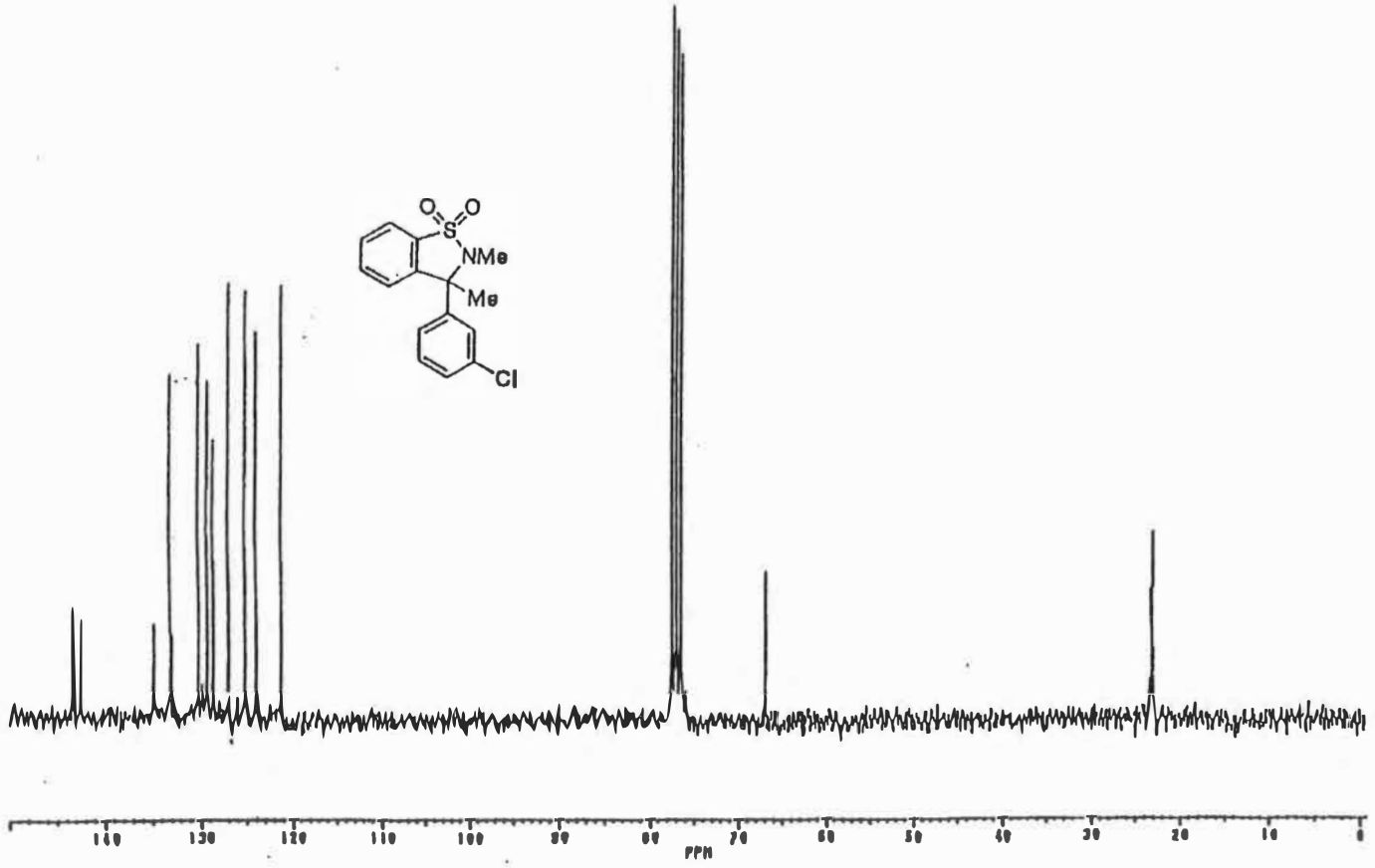
^{1}H NMR spectrum of 2-Methyl-3-*m*-tolyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**1.4d**).



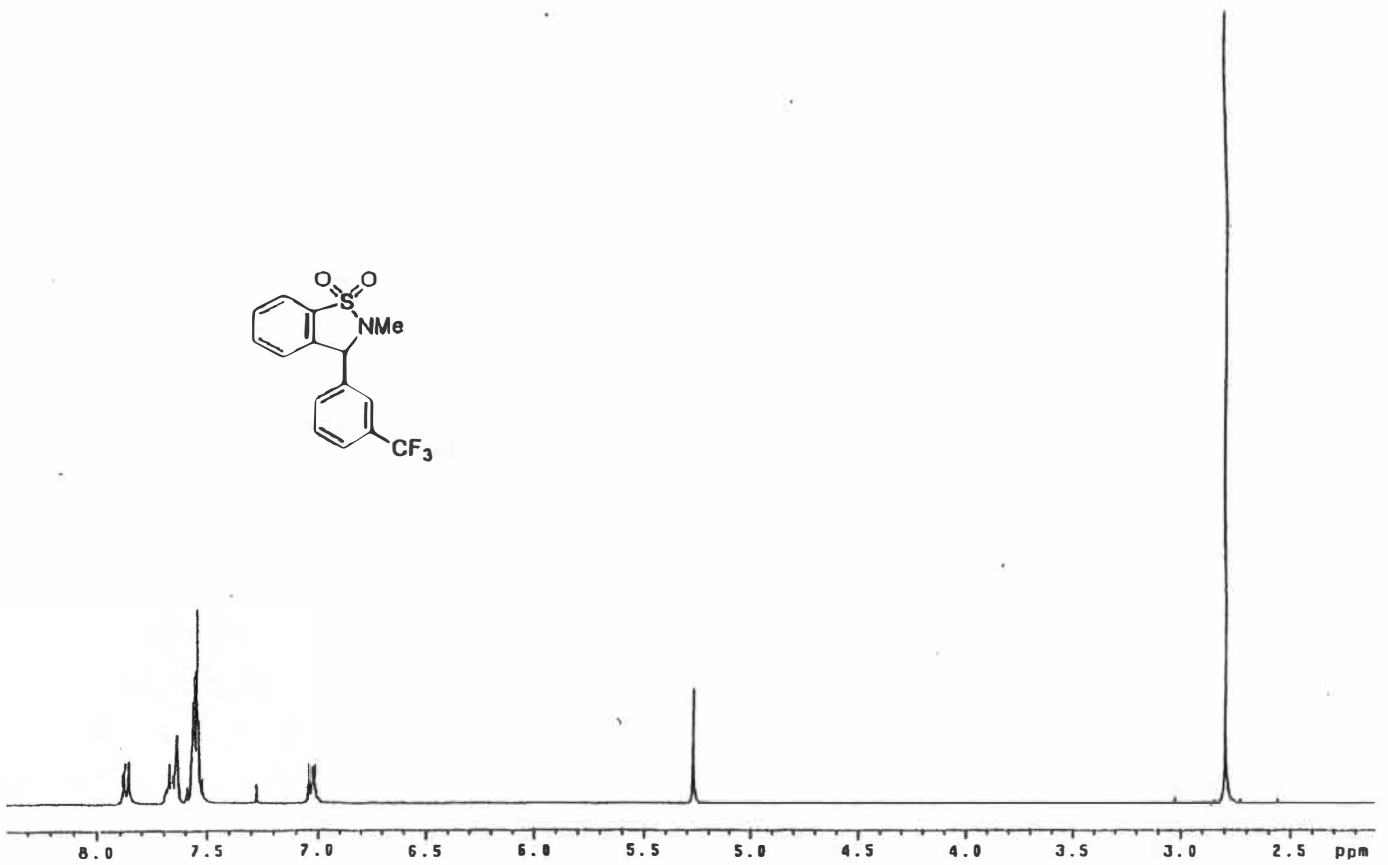
^{13}C NMR spectrum of 2-Methyl-3-*m*-tolyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**1.4d**).



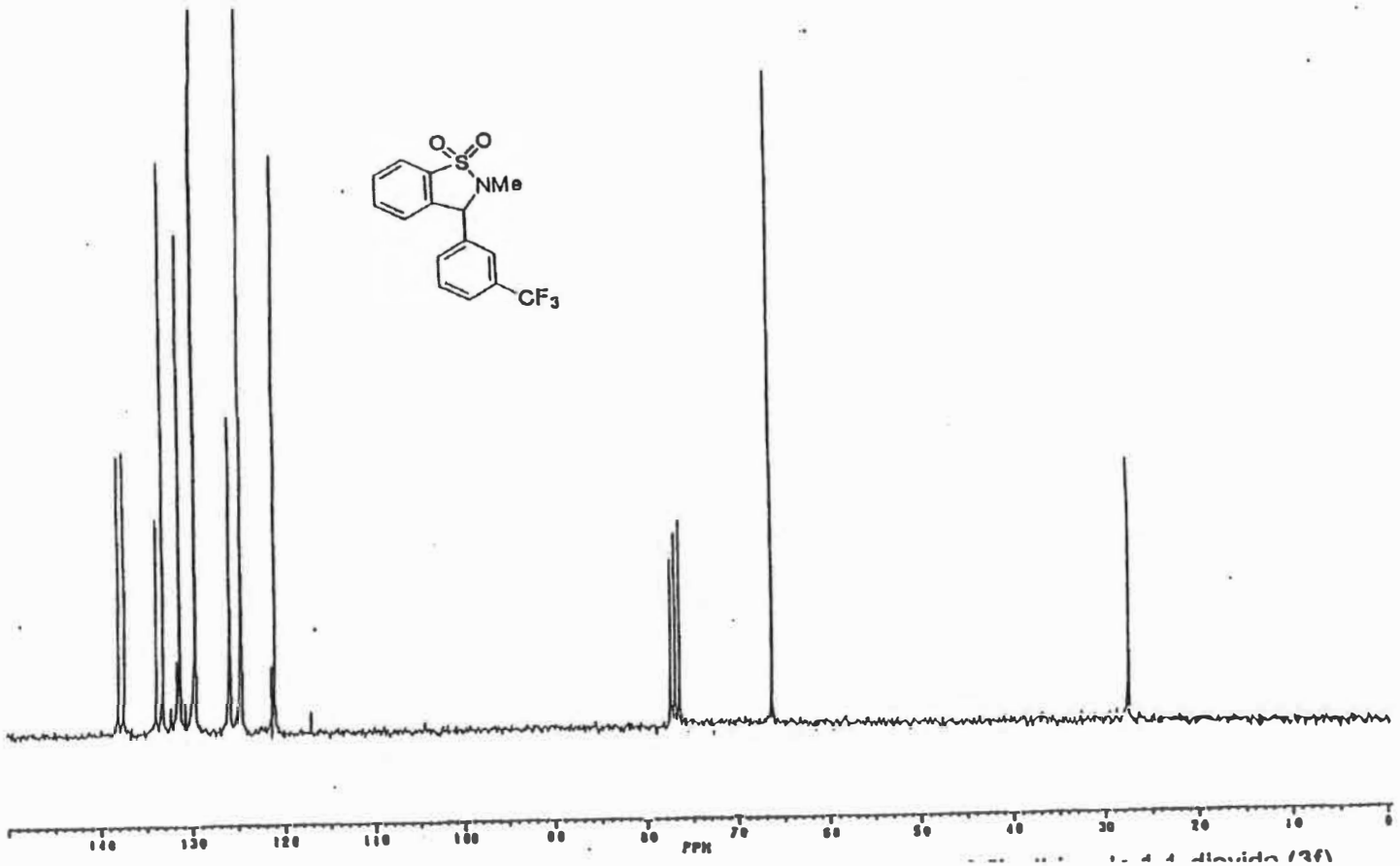
^{1}H NMR spectrum of 3-(3-Chlorophenyl)-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**1.4e**).



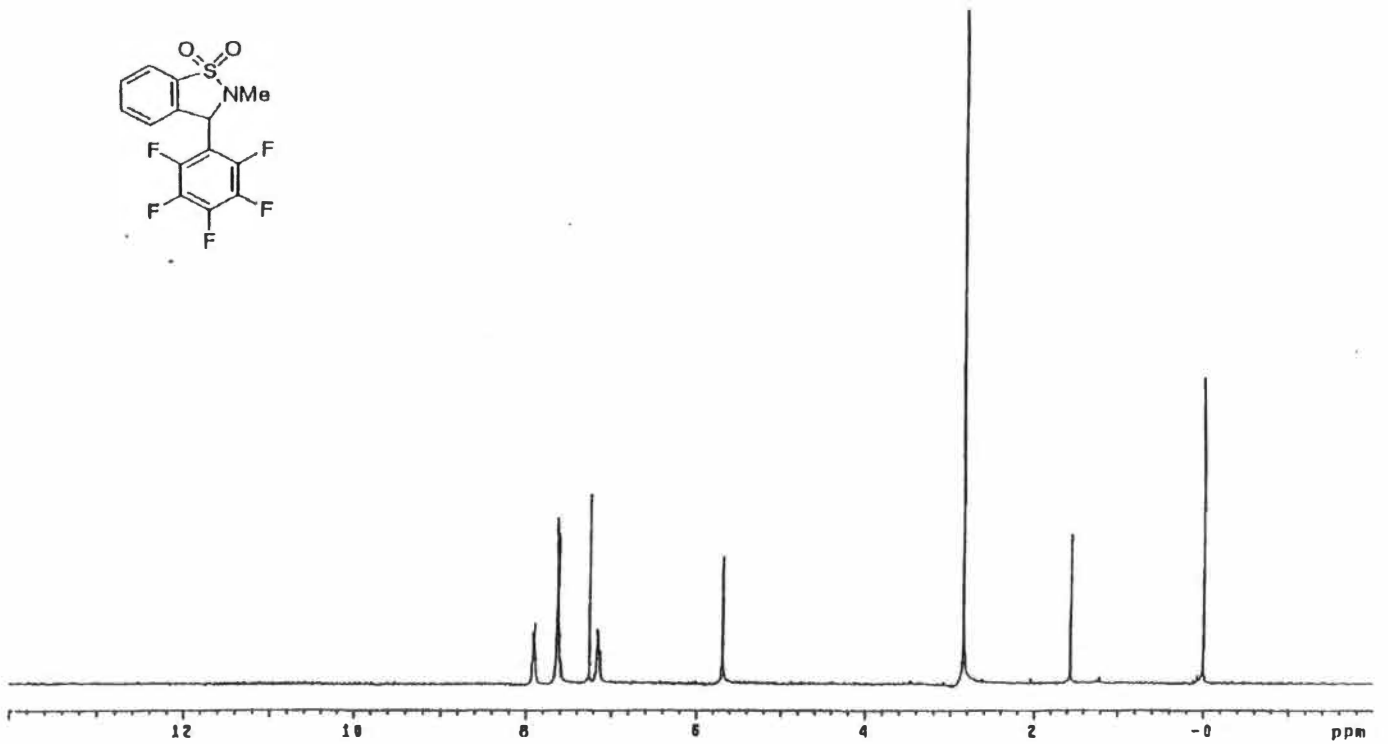
^{13}C NMR spectrum of 3-(3-Chlorophenyl)-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**1.4e**).



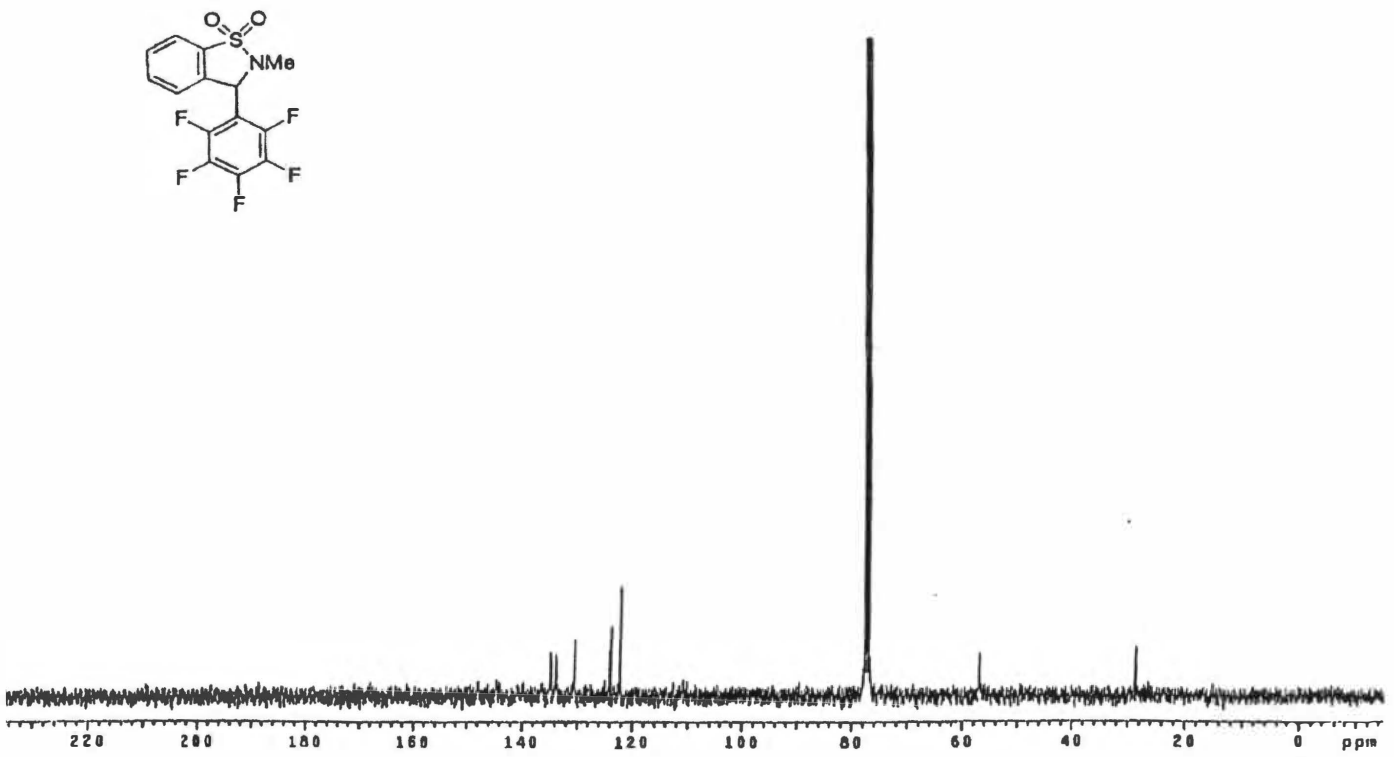
^{1}H NMR spectrum of 2-Methyl-3-(3-trifluoromethylphenyl)-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**1.4f**).



^{13}C NMR spectrum of 2-Methyl-3-(3-trifluoromethylphenyl)-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**1.4f**).

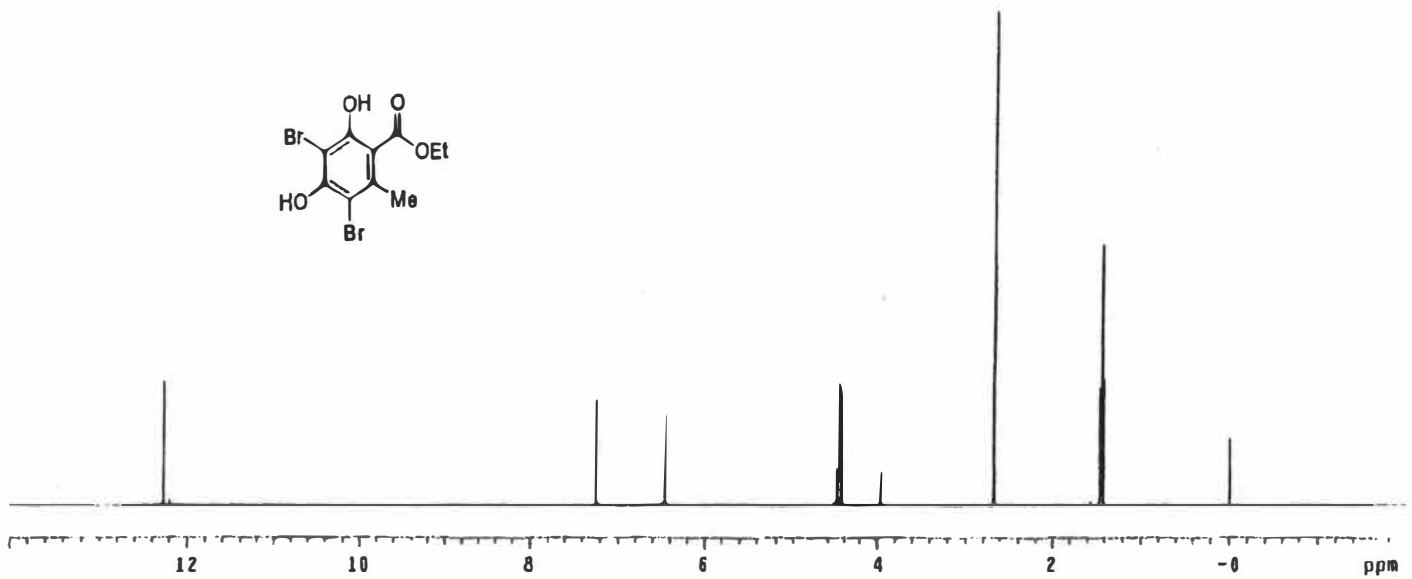


^{1}H NMR spectrum of 2-Methyl-3-pentafluorophenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**1.4g**).

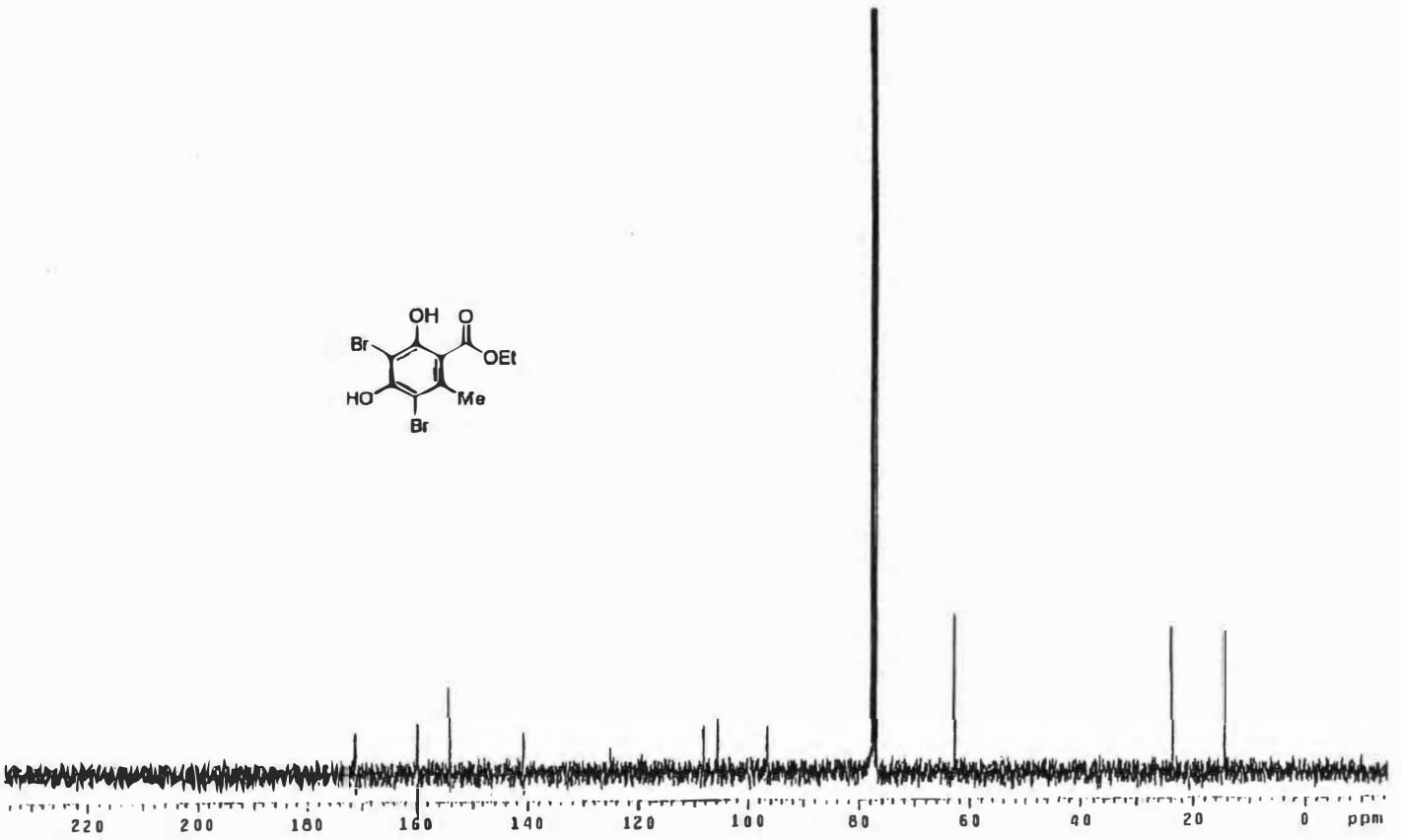


^{13}C NMR spectrum of 2-Methyl-3-pentafluorophenyl-2,3-dihydrobenzo[*d*]isothiazole 1,1-dioxide (**1.4g**).

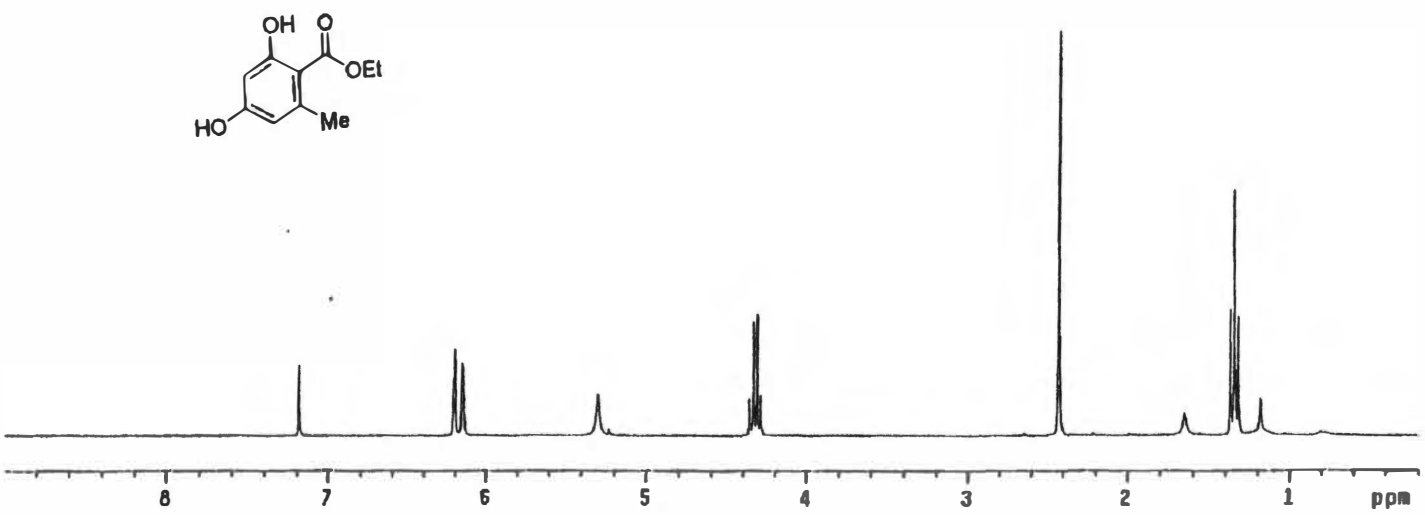
APPENDIX B. ^{1}H and ^{13}C NMR Spectra for Hydramycin Analogs



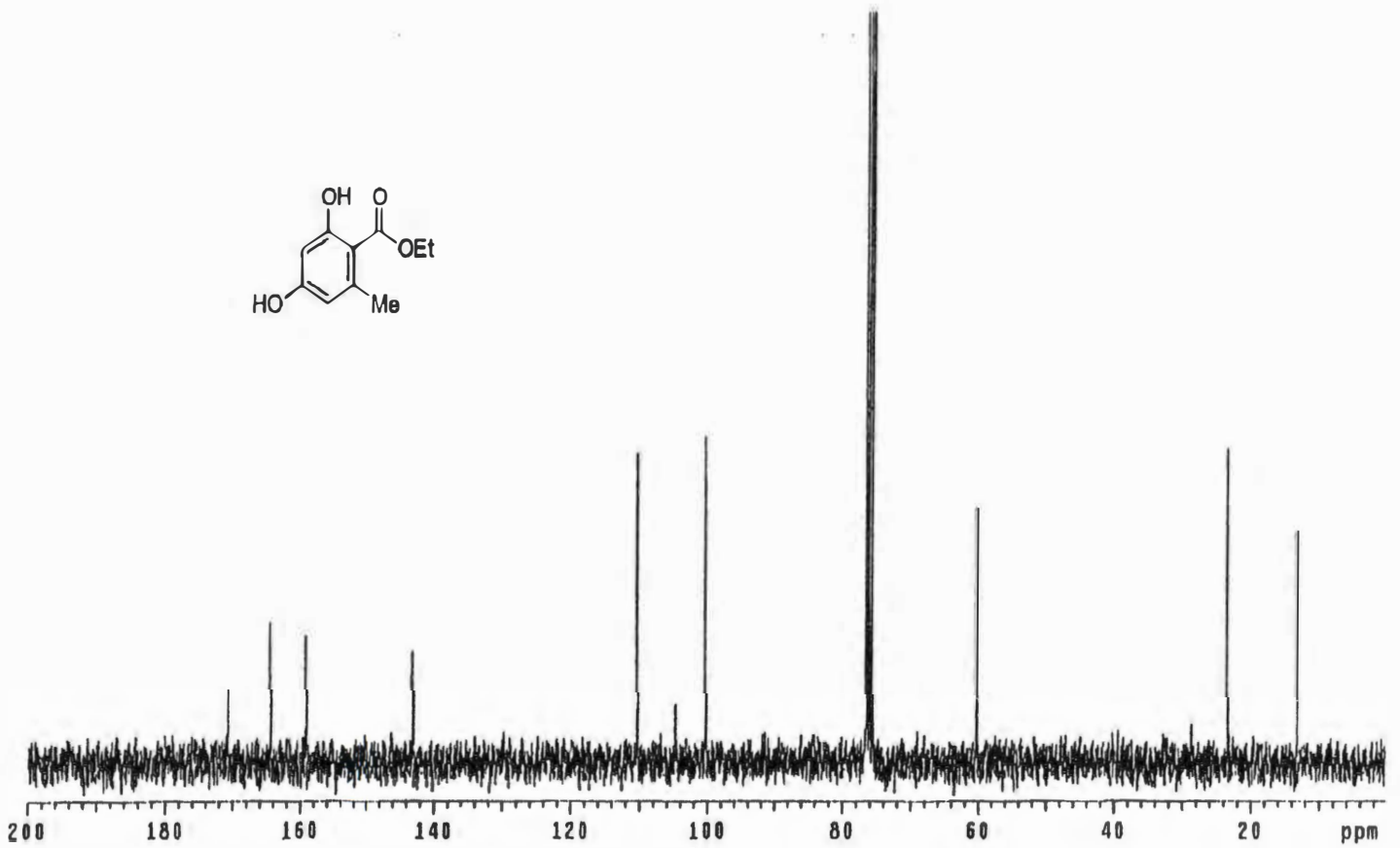
^{1}H NMR spectrum of 3,5-Dibromo-2,4-dihydroxy-6-methylbenzoic acid ethyl ester (**2.2**).



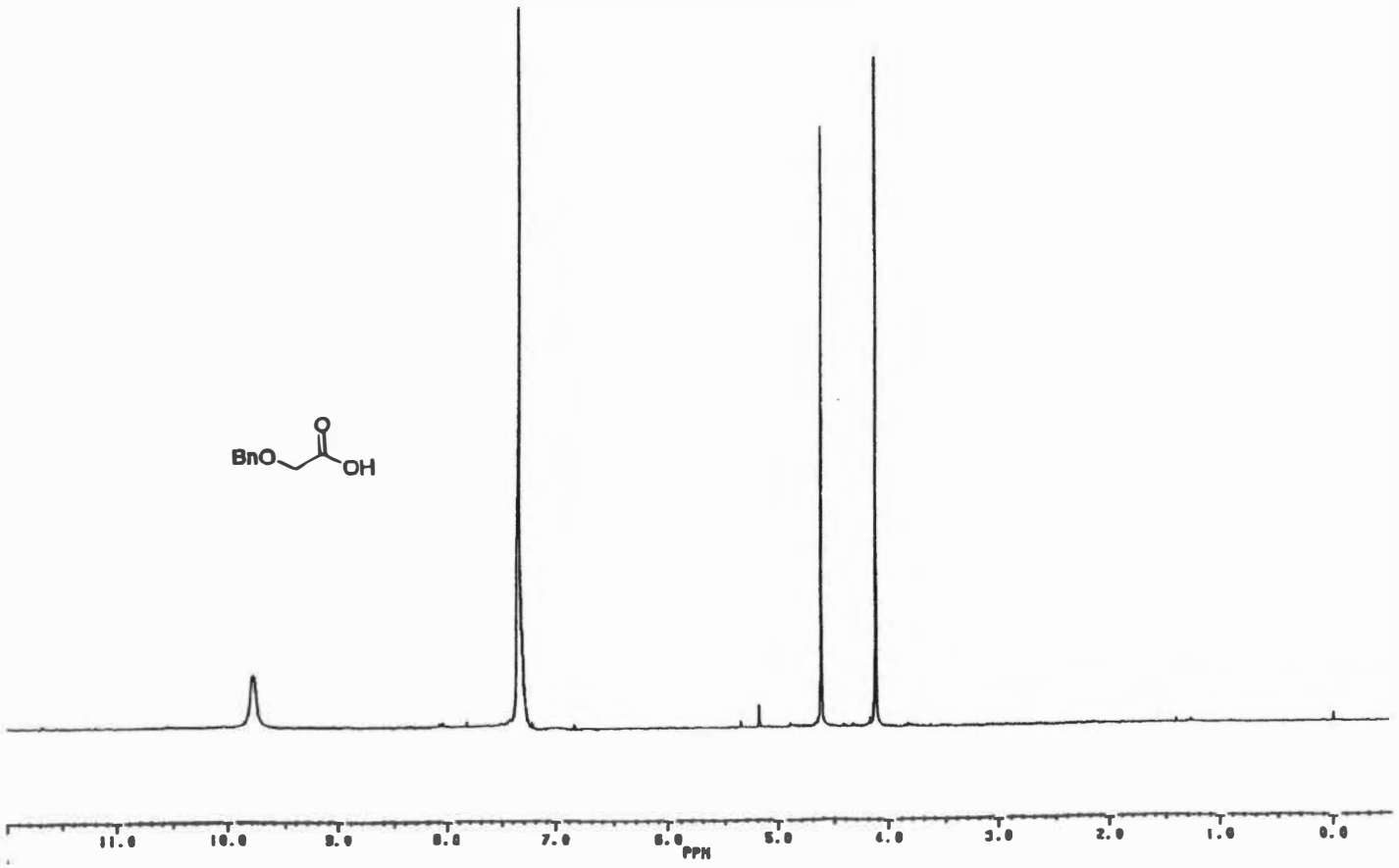
^{13}C NMR spectrum of 3,5-Dibromo-2,4-dihydroxy-6-methylbenzoic acid ethyl ester (**2.2**).



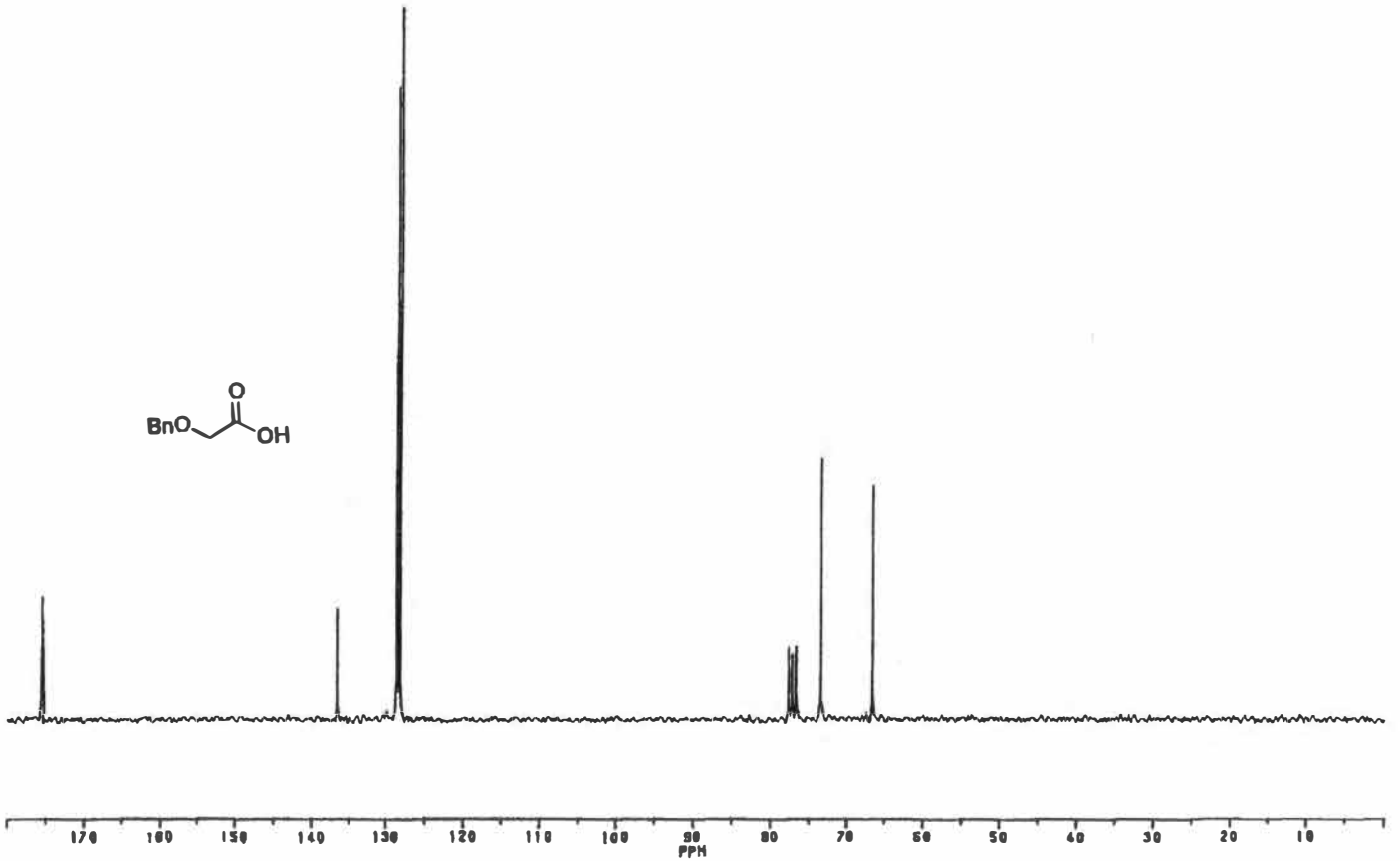
^{1}H NMR spectrum of 2,4-Dihydroxy-6-methylbenzoic acid ethyl ester (**2.3**).



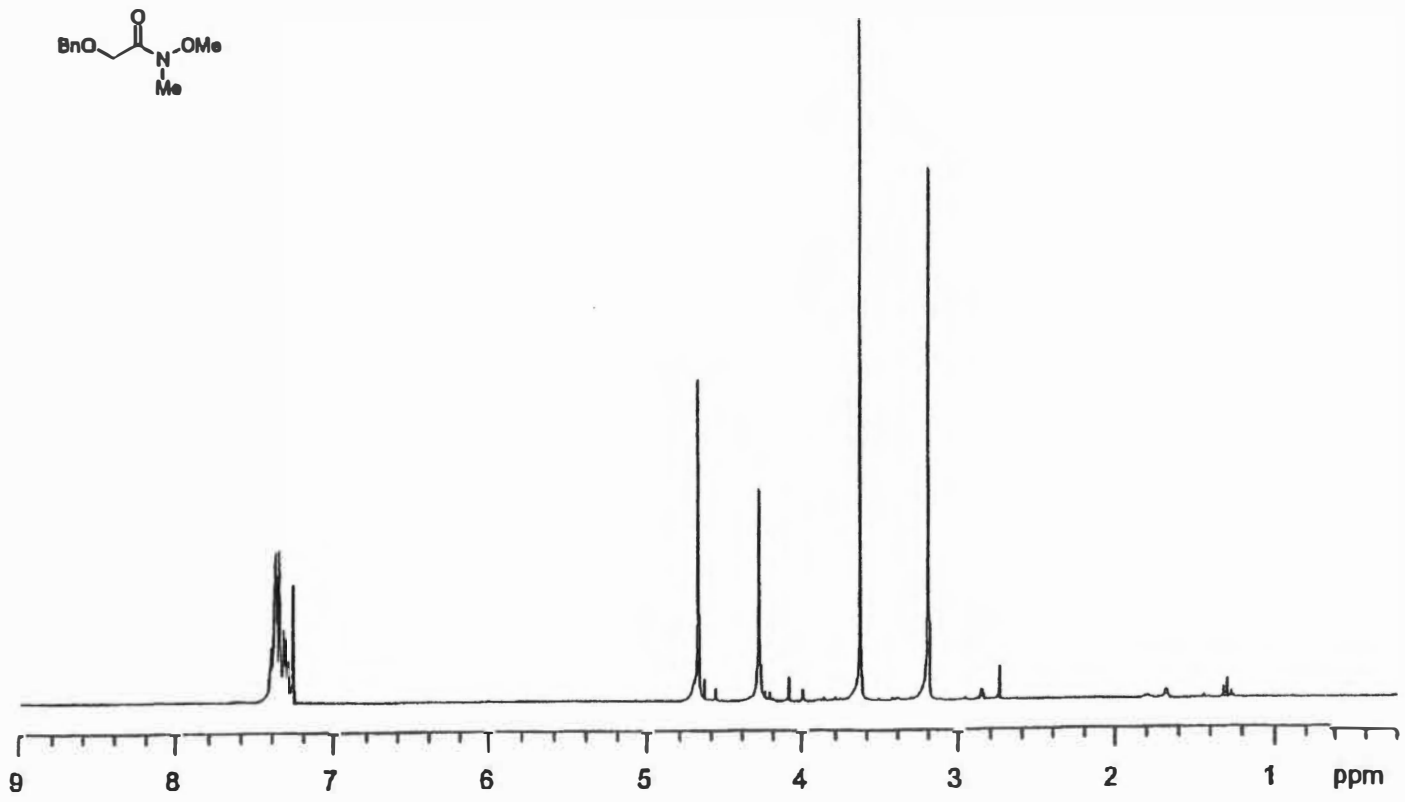
^{13}C NMR spectrum of 2,4-Dihydroxy-6-methylbenzoic acid ethyl ester (**2.3**).



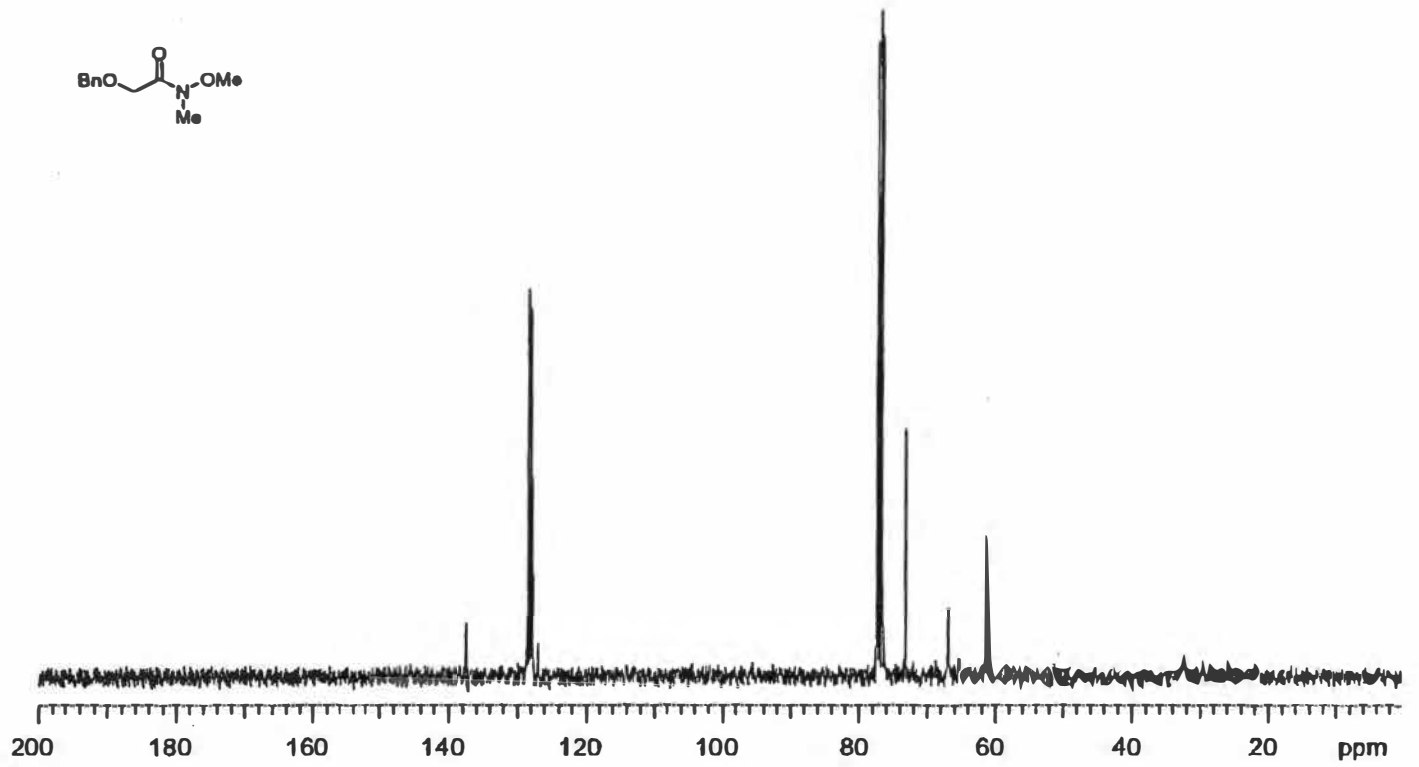
^{1}H NMR spectrum of Benzyloxyacetic acid (**2.4**).



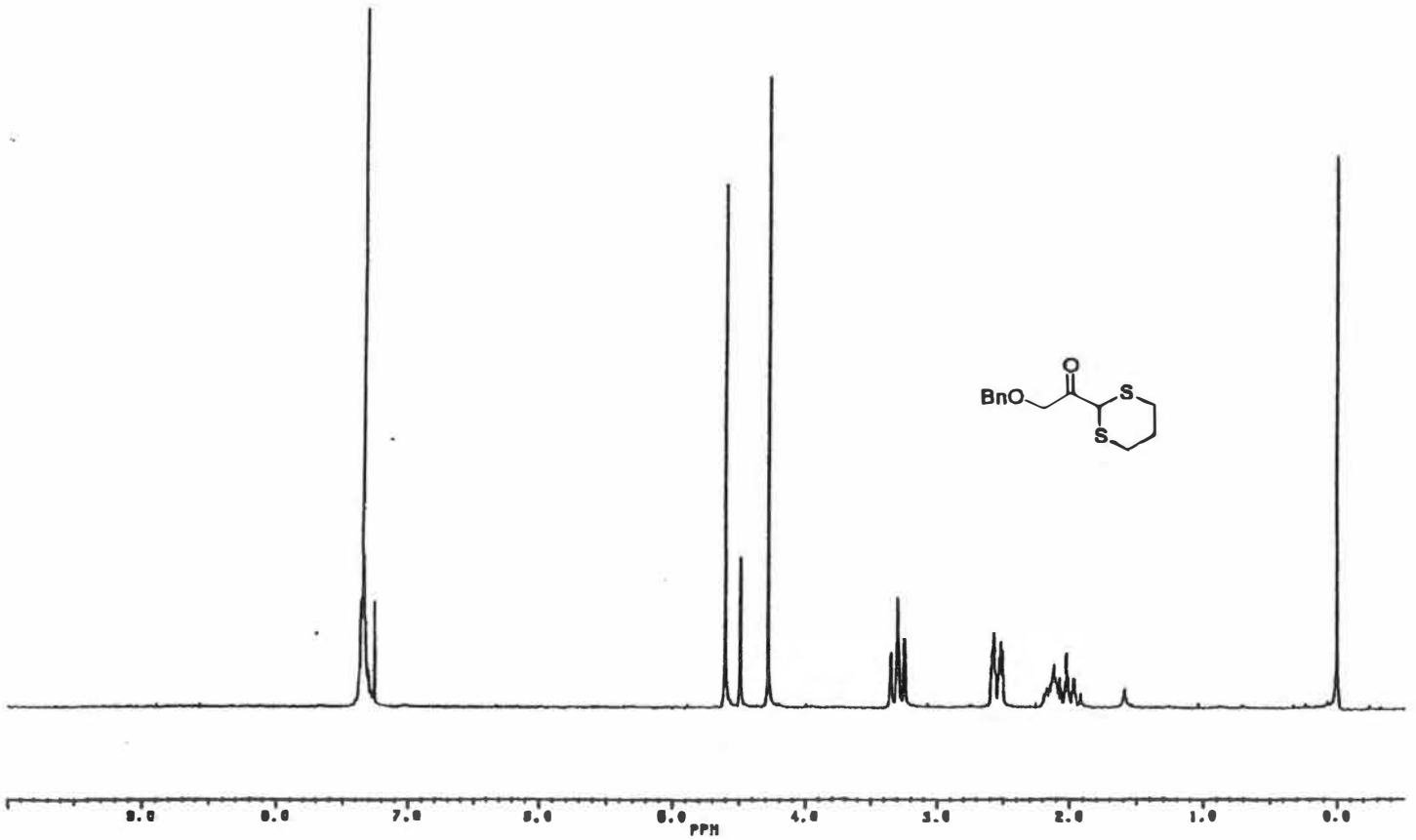
^{13}C NMR spectrum of Benzyloxyacetic acid (**2.4**).



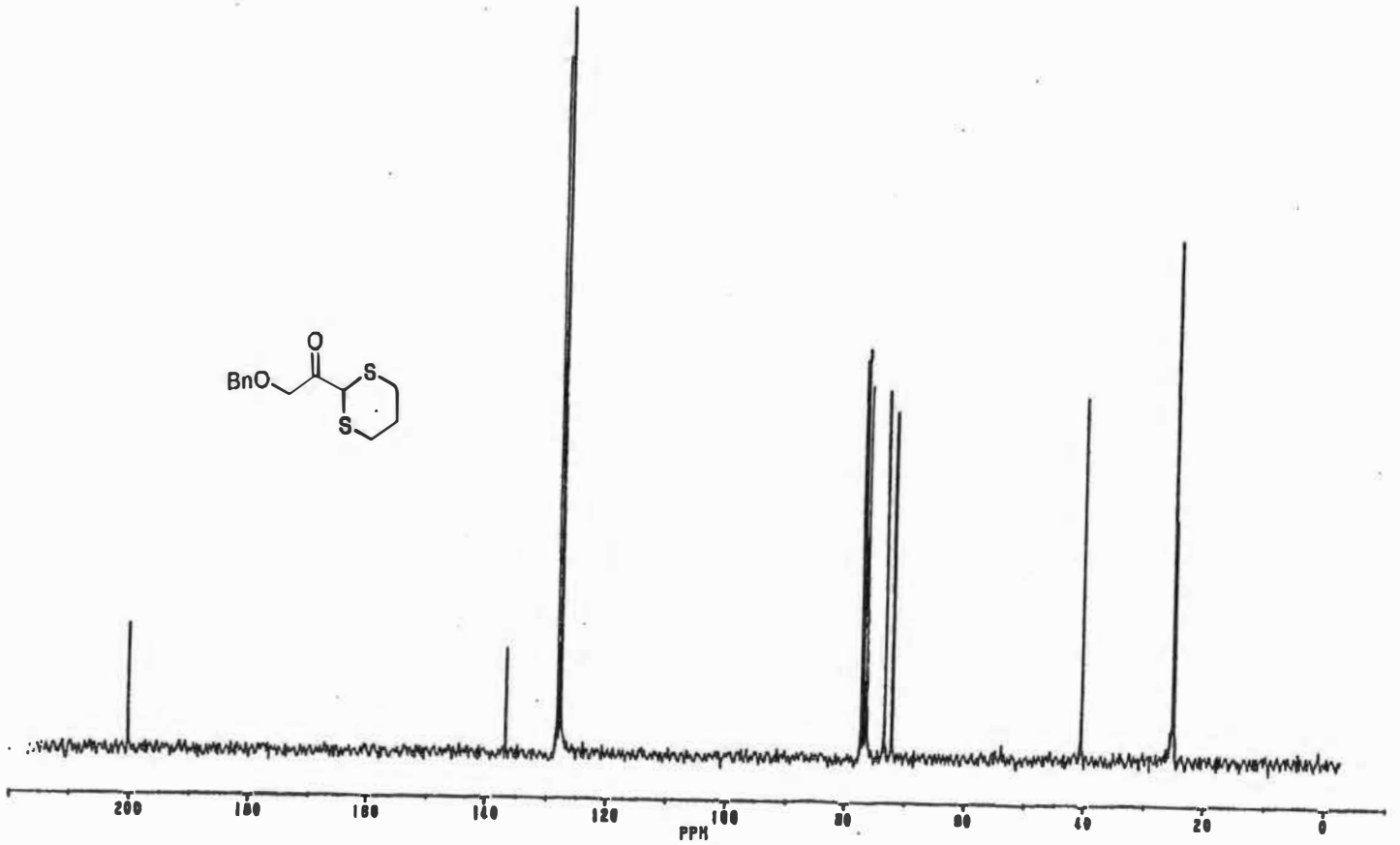
^{1}H NMR spectrum of 2-Benzyloxy-*N*-methoxy-*N*-methylacetamide (**2.5**).



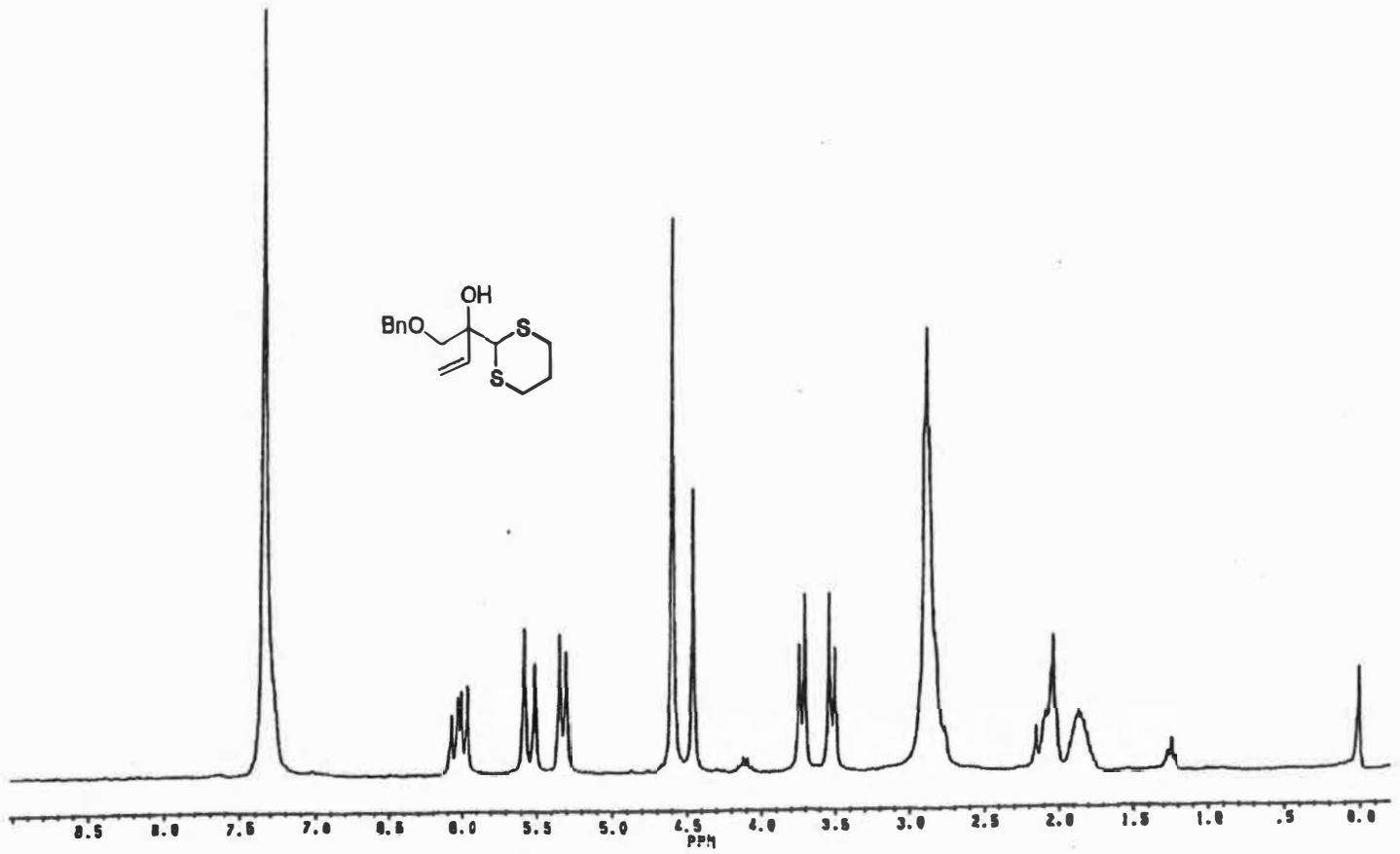
^{13}C NMR spectrum of 2-Benzyloxy-*N*-methoxy-*N*-methylacetamide (**2.5**).



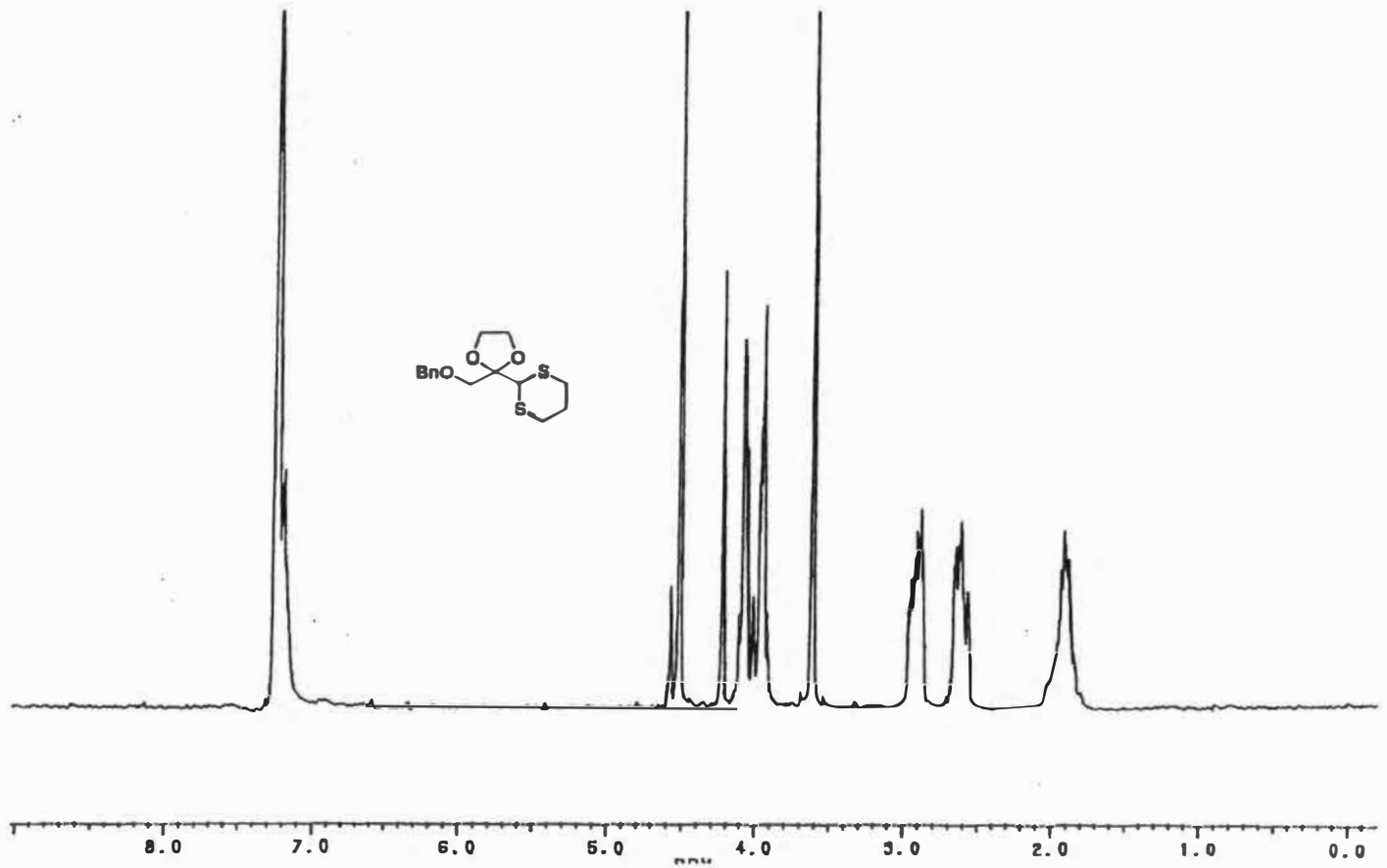
^{1}H NMR spectrum of 2-Benzyloxy-1-[1,3]dithian-2-ylethanone (**2.6**).



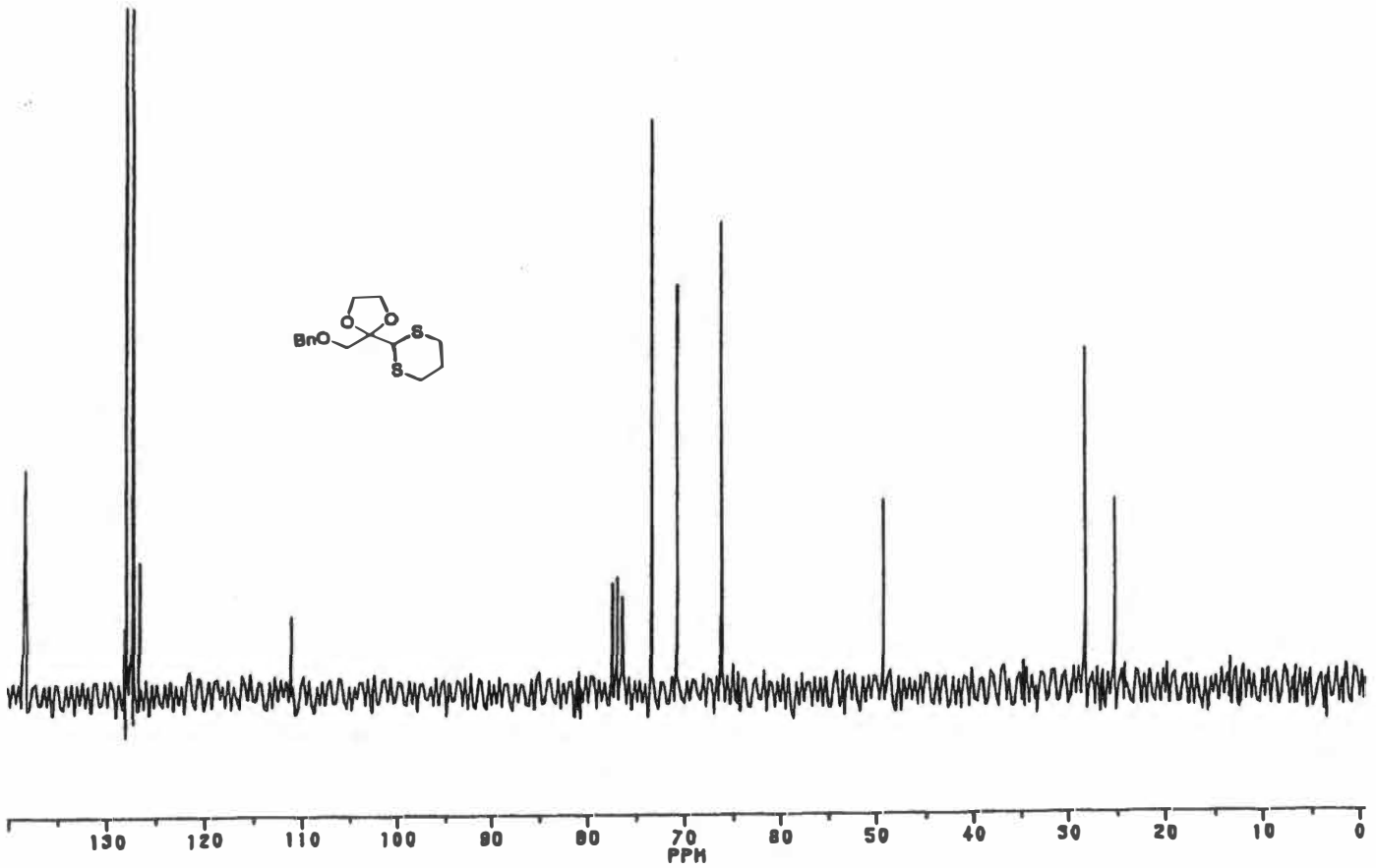
^{13}C NMR spectrum of 2-Benzyloxy-1-[1,3]dithian-2-ylethanone (**2.6**).



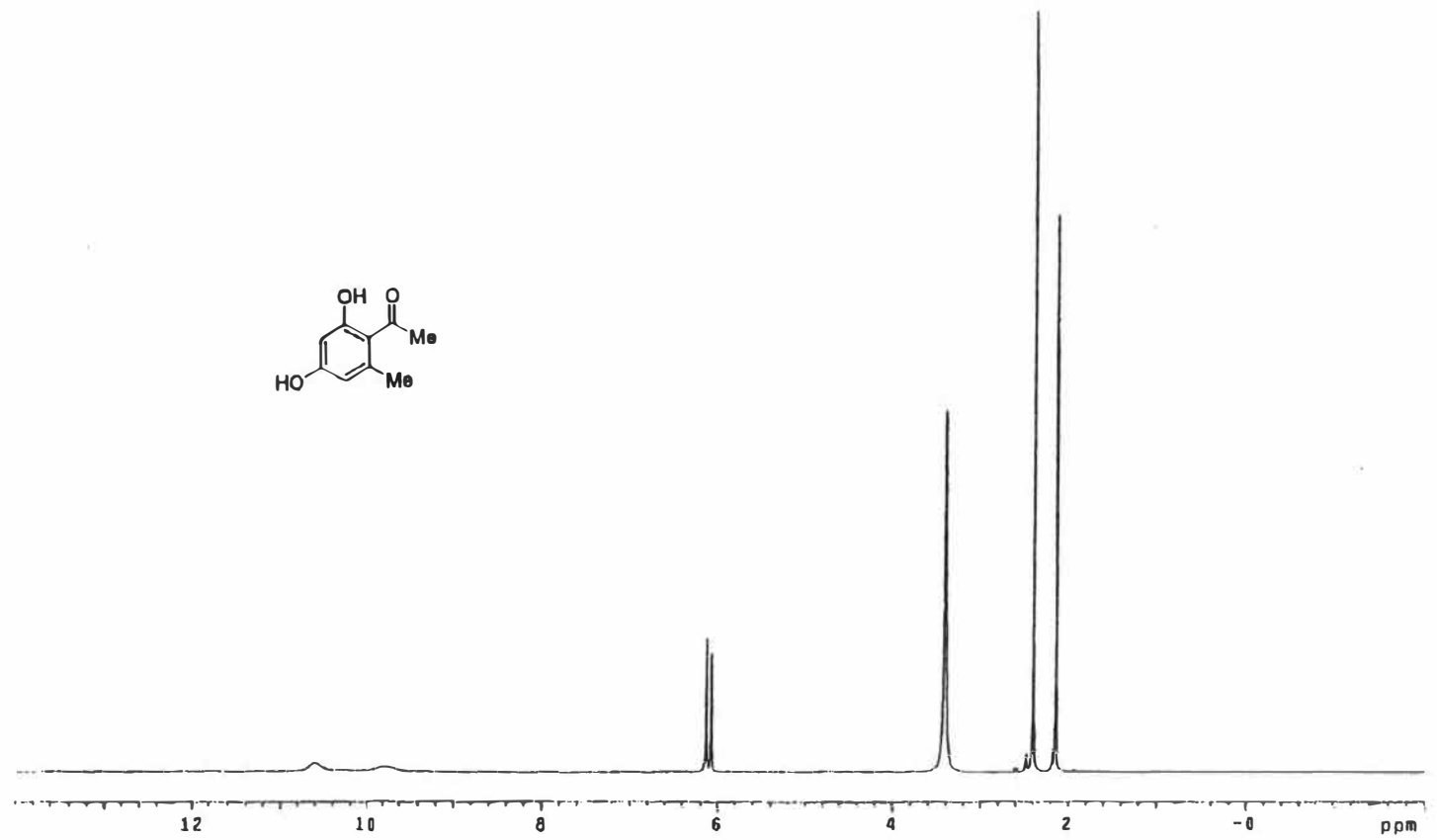
^{1}H NMR spectrum of 2-Benzyloxy-2-[1,3]dithian-2-ylbut-3-en-2-ol (**2.7**).



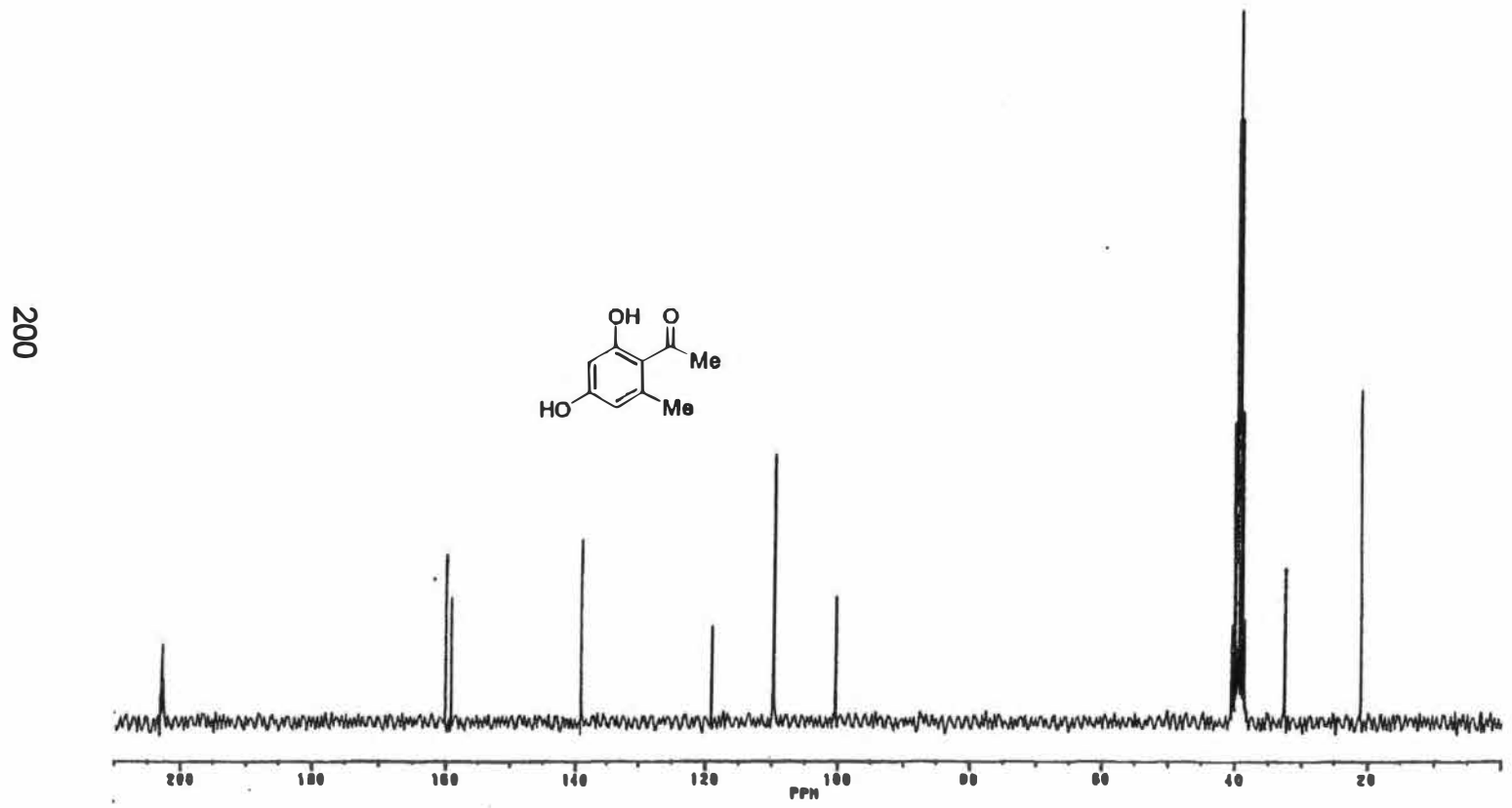
^{1}H NMR spectrum of 2-Benzyloxymethyl-2-[1,3]dithian-2-yl[1,3]dioxolane (**2.8**).



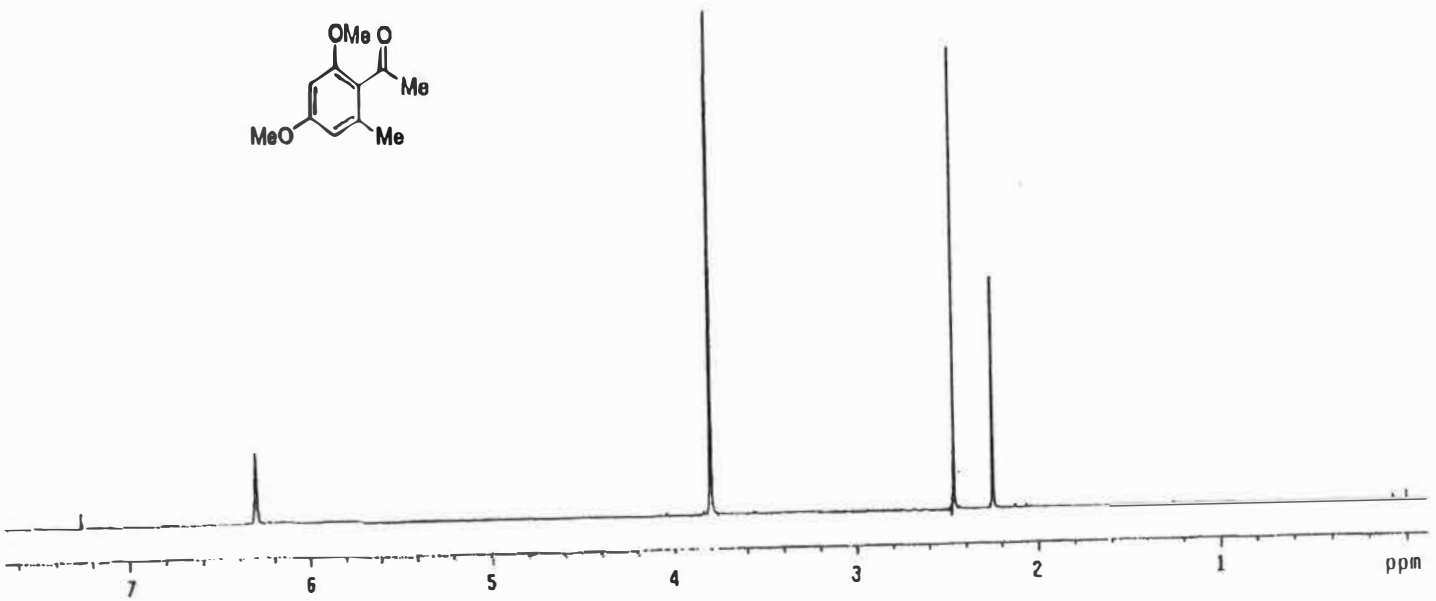
^{13}C NMR spectrum of 2-Benzyloxymethyl-2-[1,3]dioxolane (**2.8**).



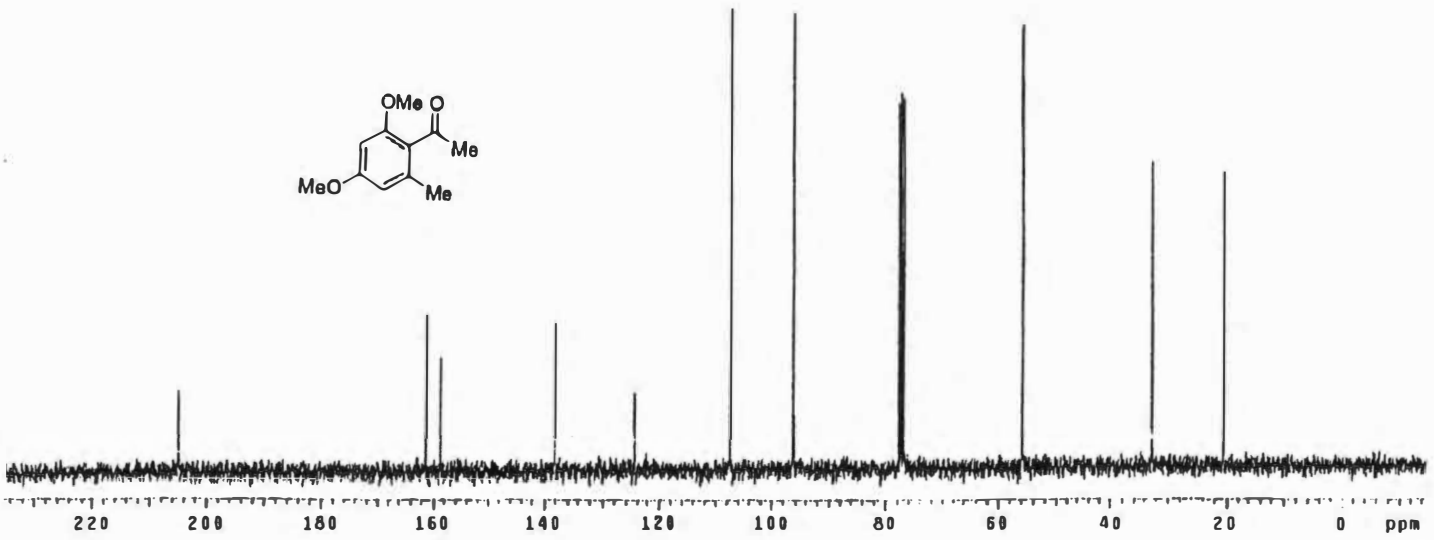
^{1}H NMR spectrum of 1-(2,4-Dihydroxy-6-methylphenyl)ethanone (**2.10**).



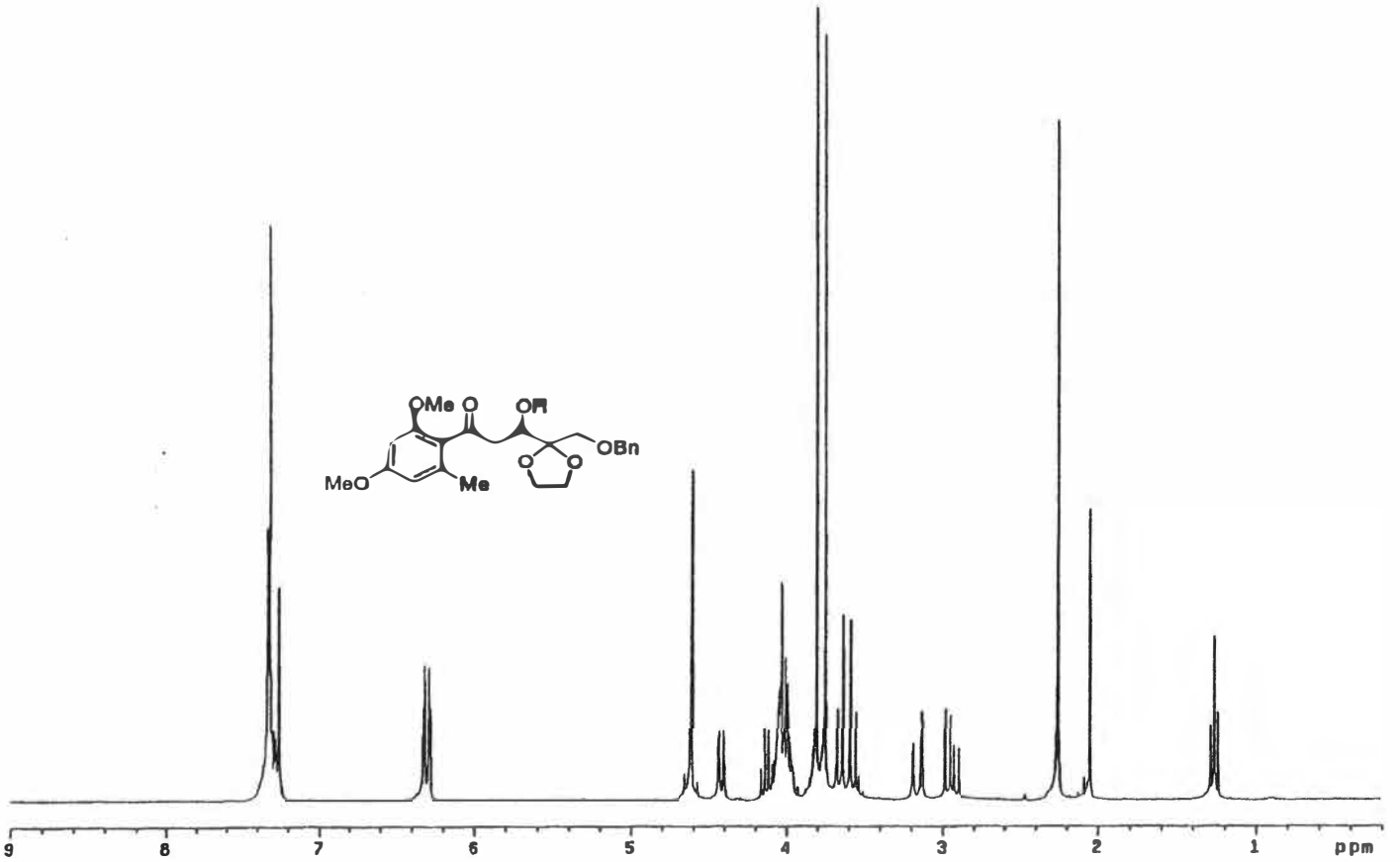
^{13}C NMR spectrum of 1-(2,4-Dihydroxy-6-methylphenyl)ethanone (**2.10**).



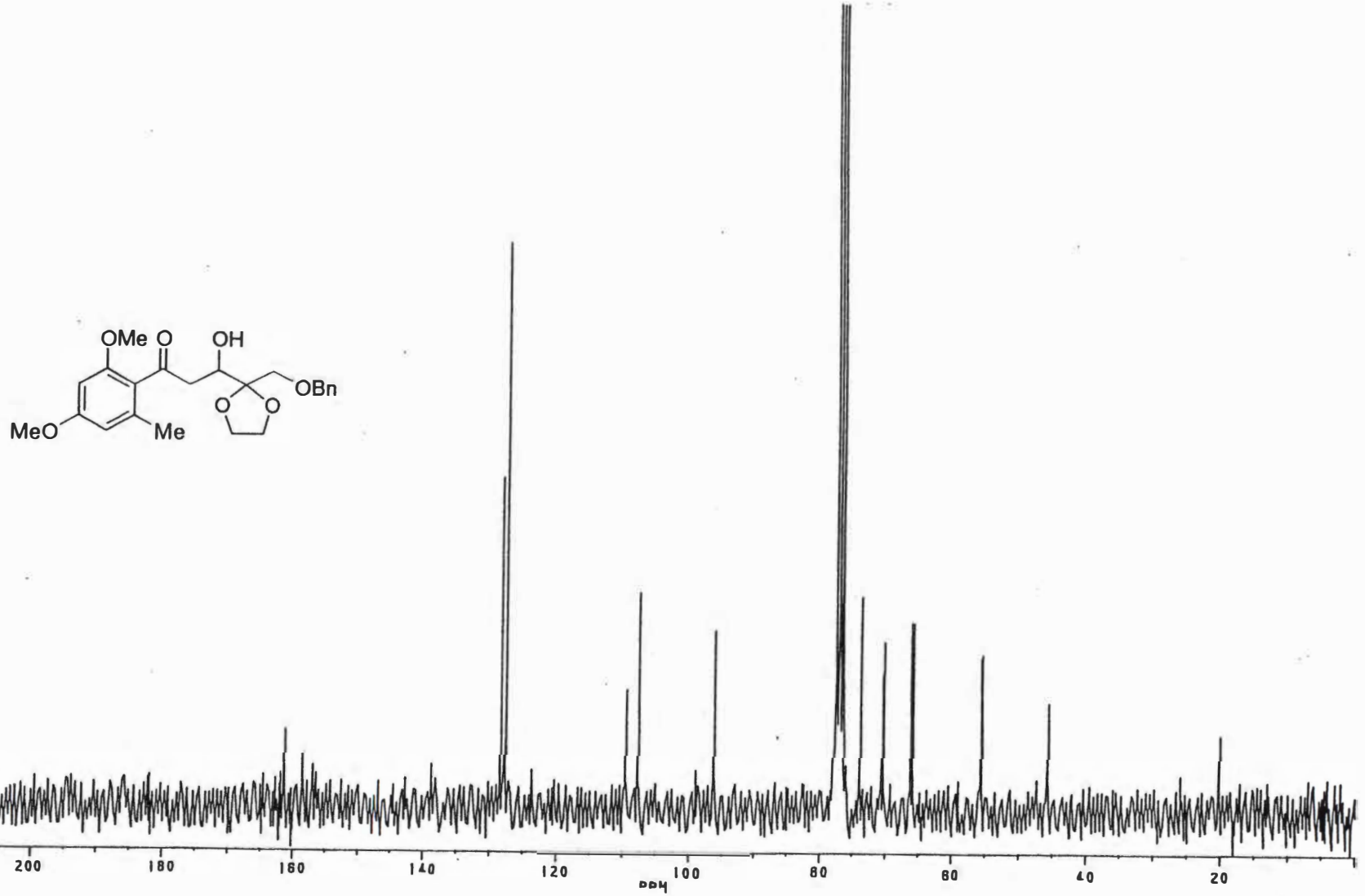
^{1}H NMR spectrum of 1-(2,4-Dimethoxy-6-methylphenyl)ethanone (**2.11**).



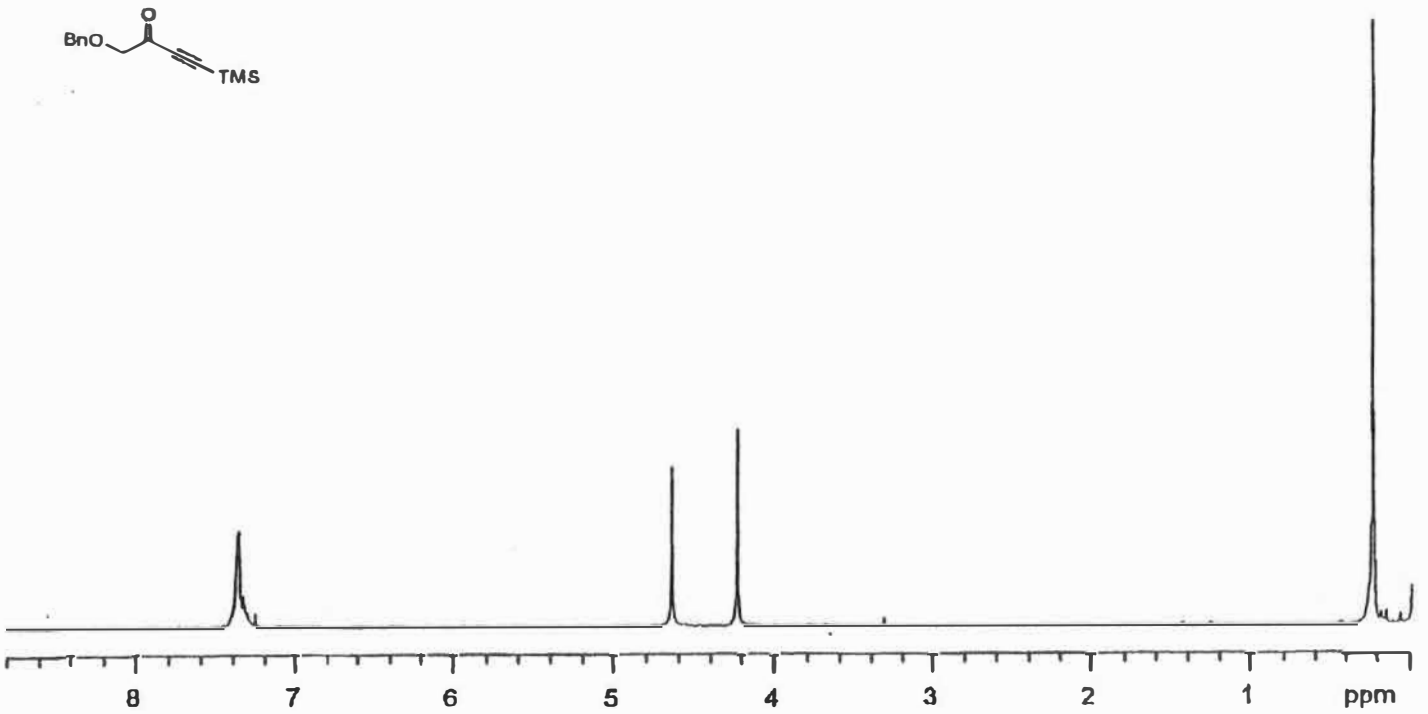
^{13}C NMR spectrum of 1-(2,4-Dimethoxy-6-methylphenyl)ethanone (**2.11**).



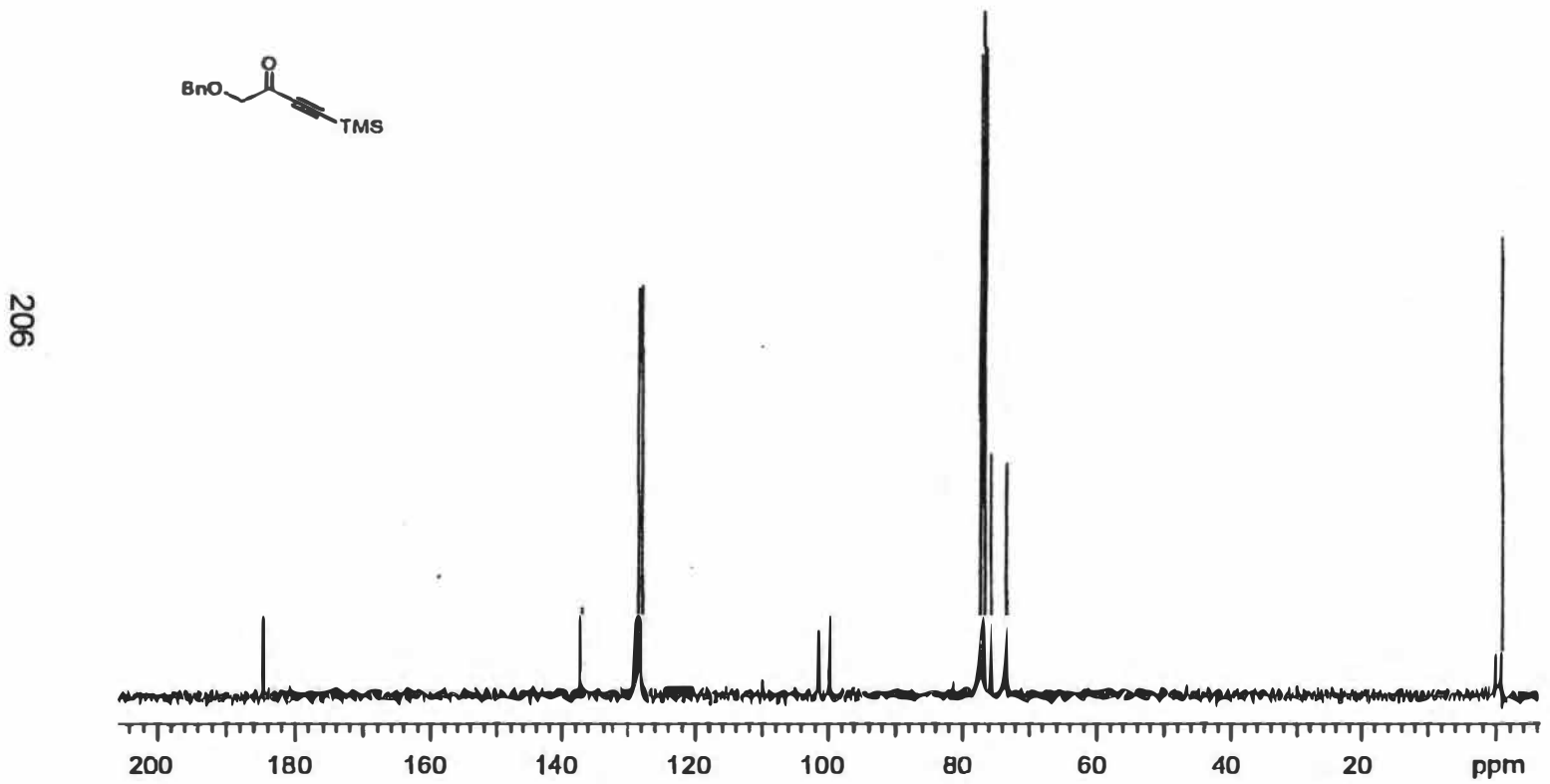
^{1}H NMR spectrum of 3-(2-Benzyloxymethyl[1,3]dioxan-2-yl)-1-(2,4-dimethoxy-6-methylphenyl)-3-hydroxypropan-1-one (**2.12**).



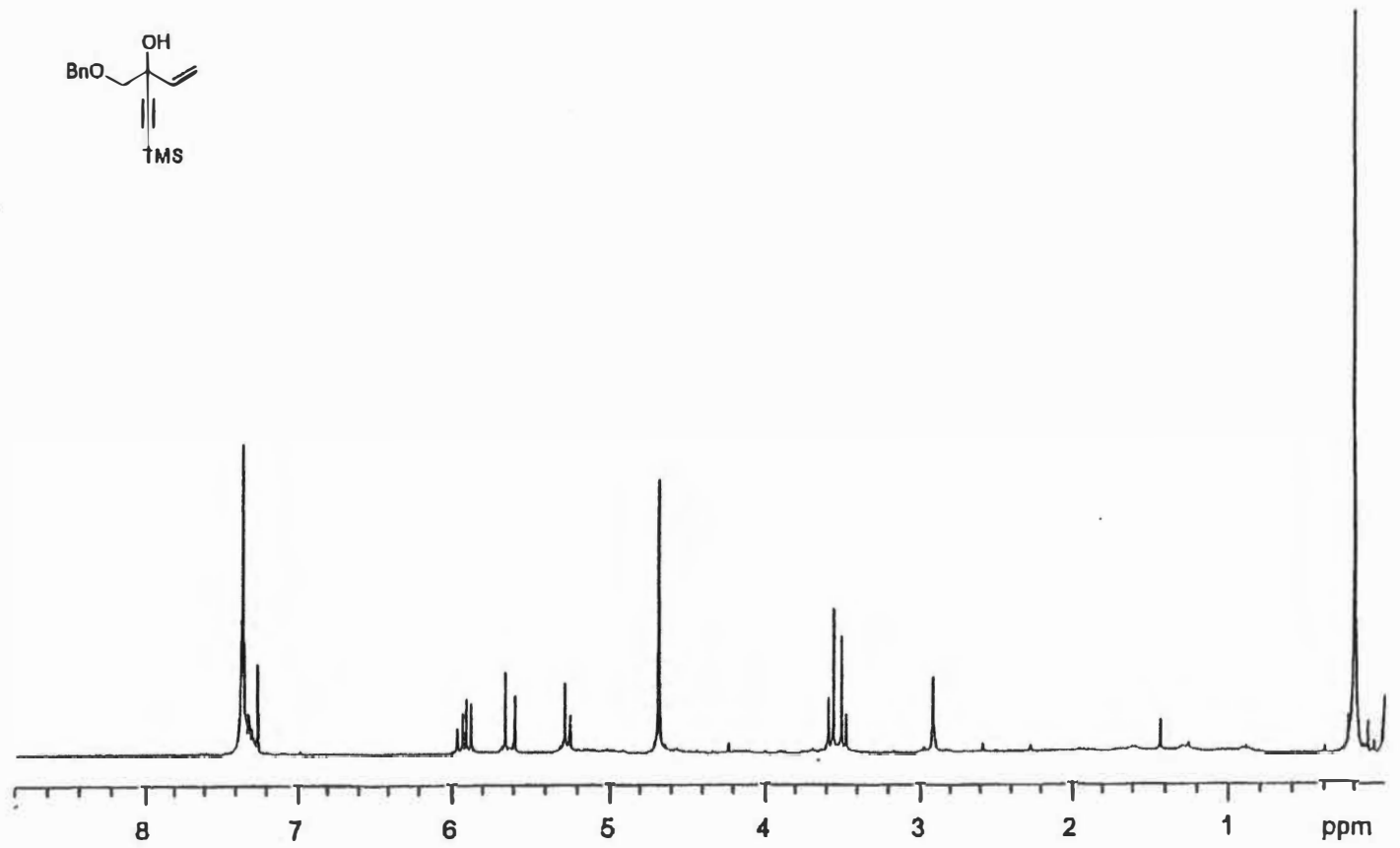
^{13}C NMR spectrum of 3-(2-Benzyloxymethyl[1,3]dioxan-2-yl)-1-(2,4-dimethoxy-6-methylphenyl)-3-hydroxypropan-1-one (**2.12**).



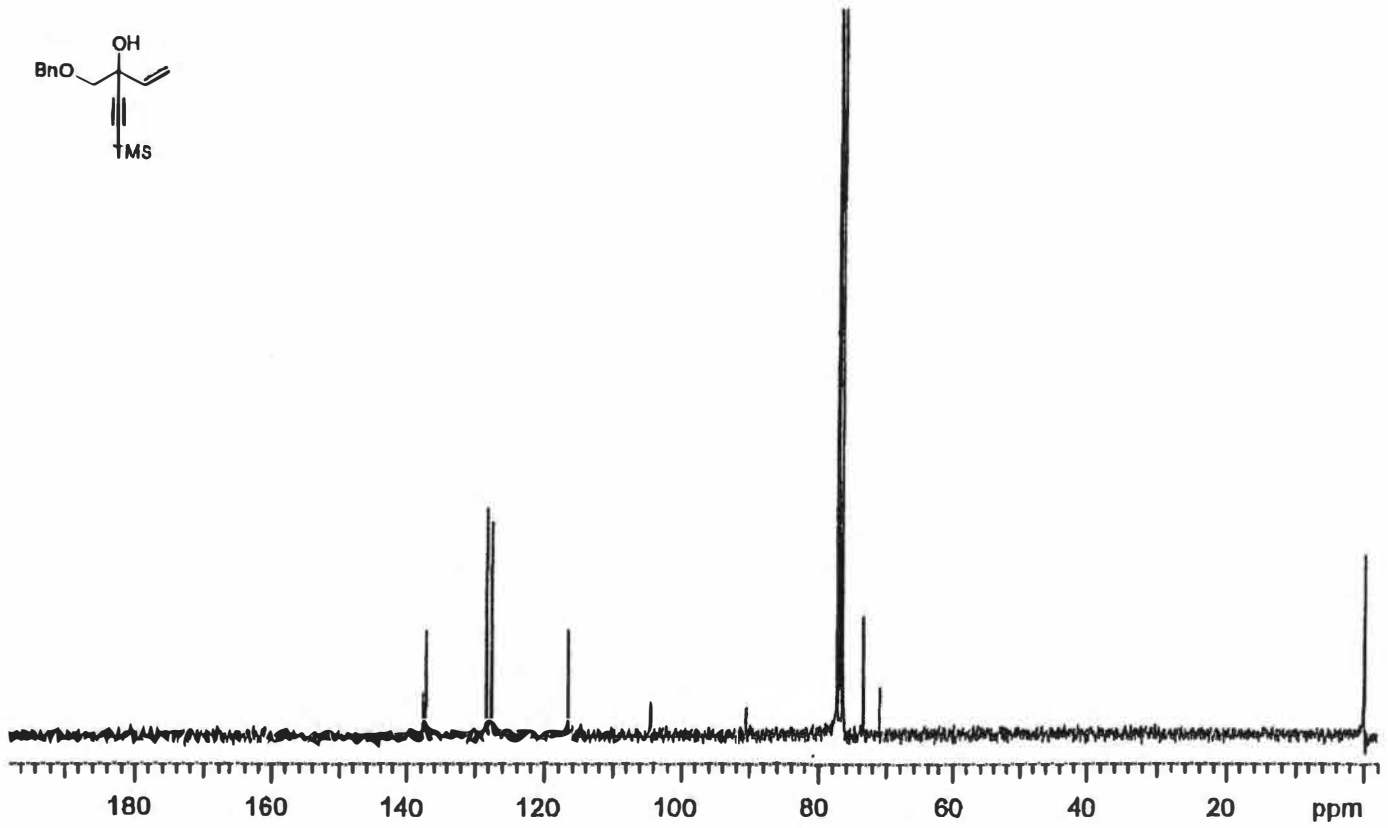
^{1}H NMR spectrum of 1-Benzyloxy-4-trimethylsilylbut-3-yn-2-one (**2.13**).



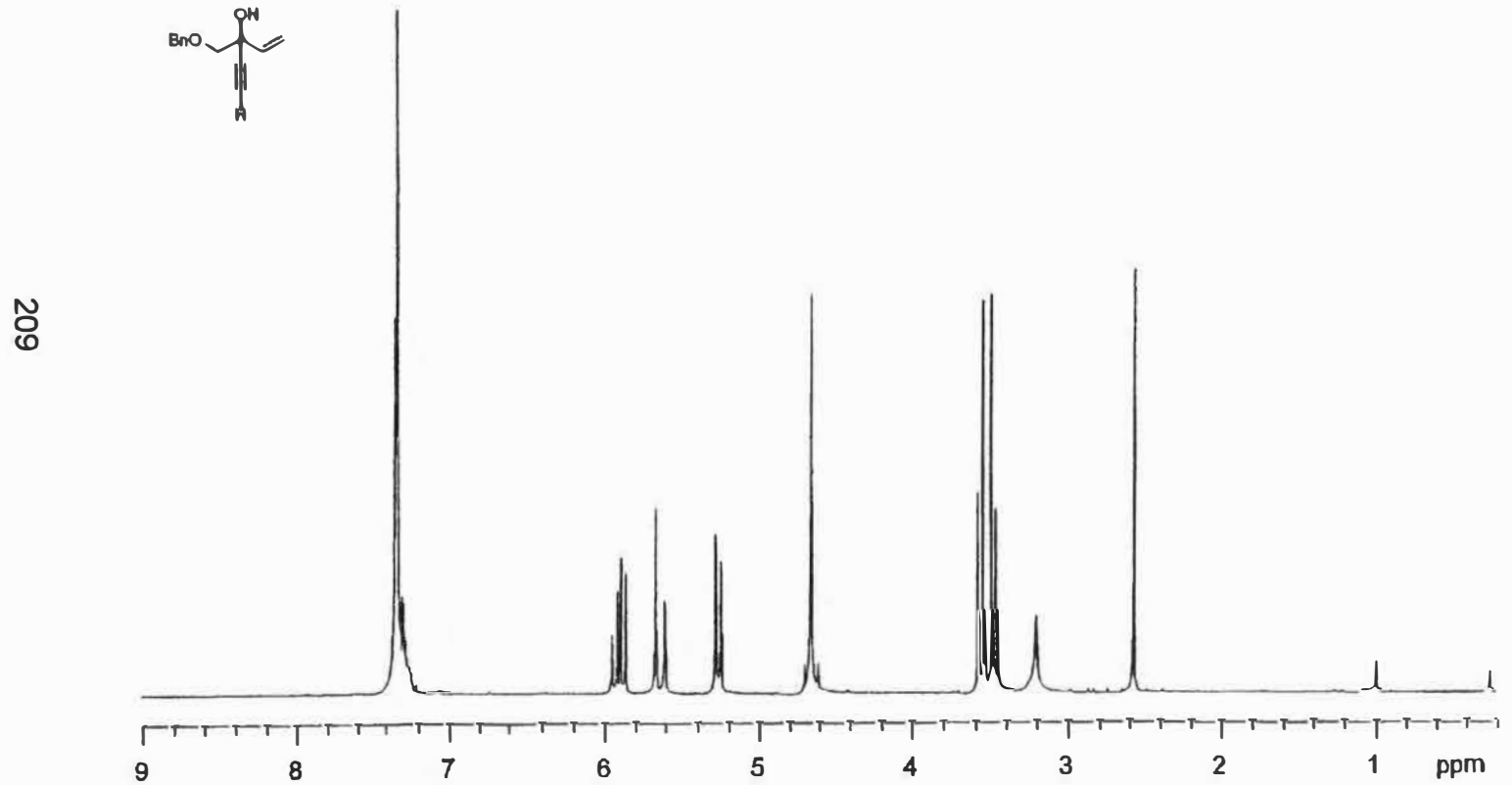
^{13}C NMR spectrum of 1-Benzyloxy-4-trimethylsilylbut-3-yn-2-one (**2.13**).



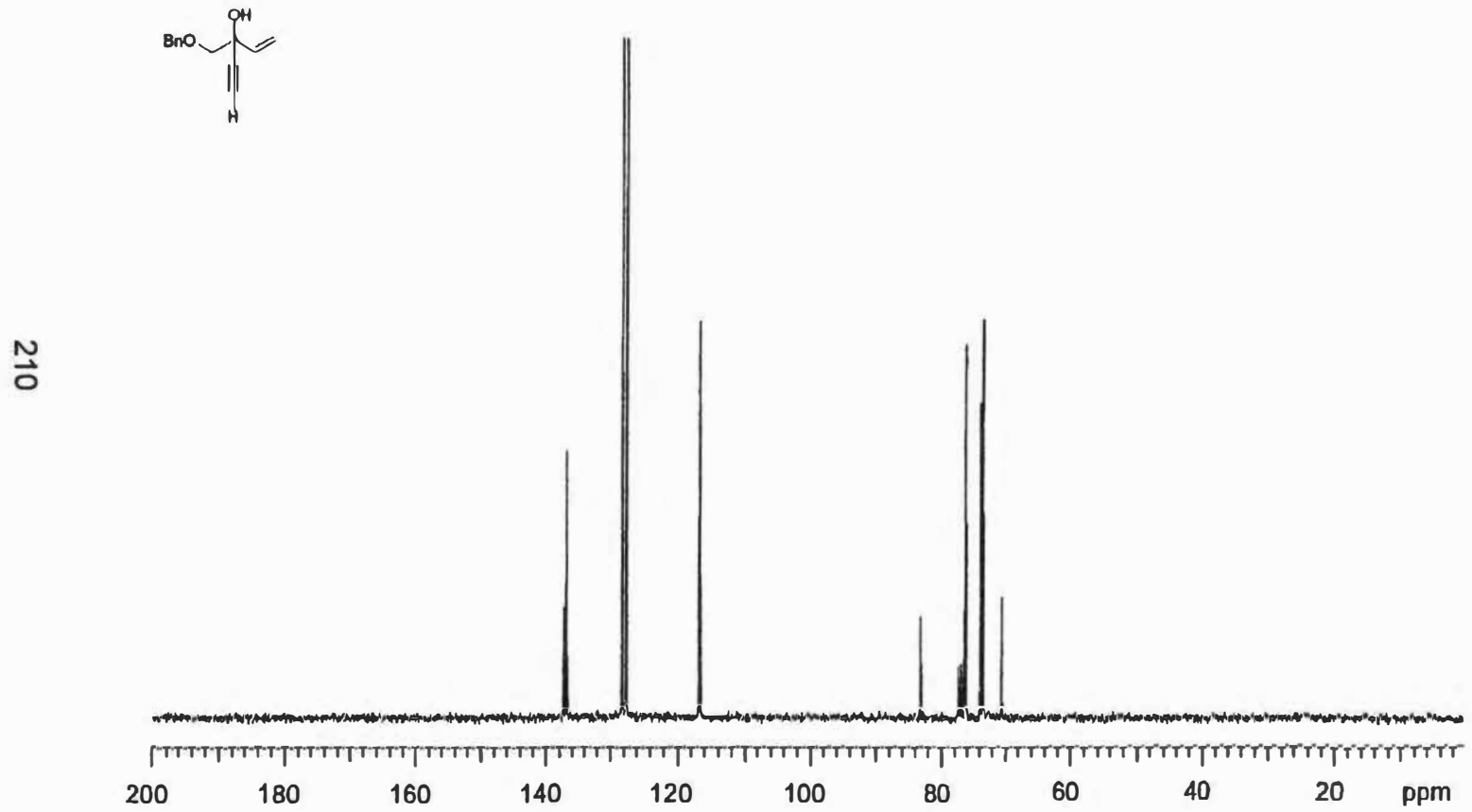
^{1}H NMR spectrum of 1-Benzyloxymethyl-5-trimethylsilylpent-1-en-4-yn-3-ol (**2.14**).



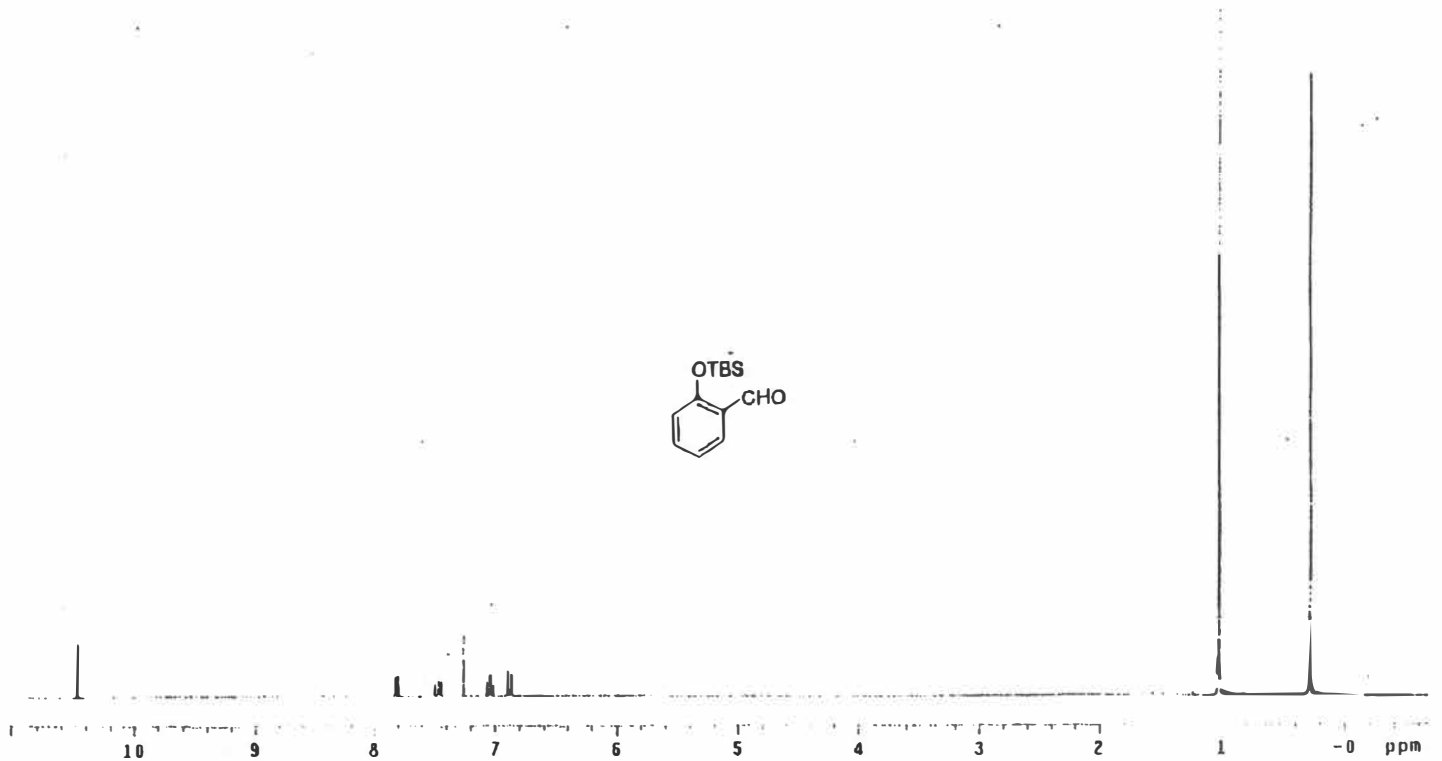
^{13}C NMR spectrum of 1-Benzyloxymethyl-5-trimethylsilylpent-1-en-4-yn-3-ol (**2.14**).



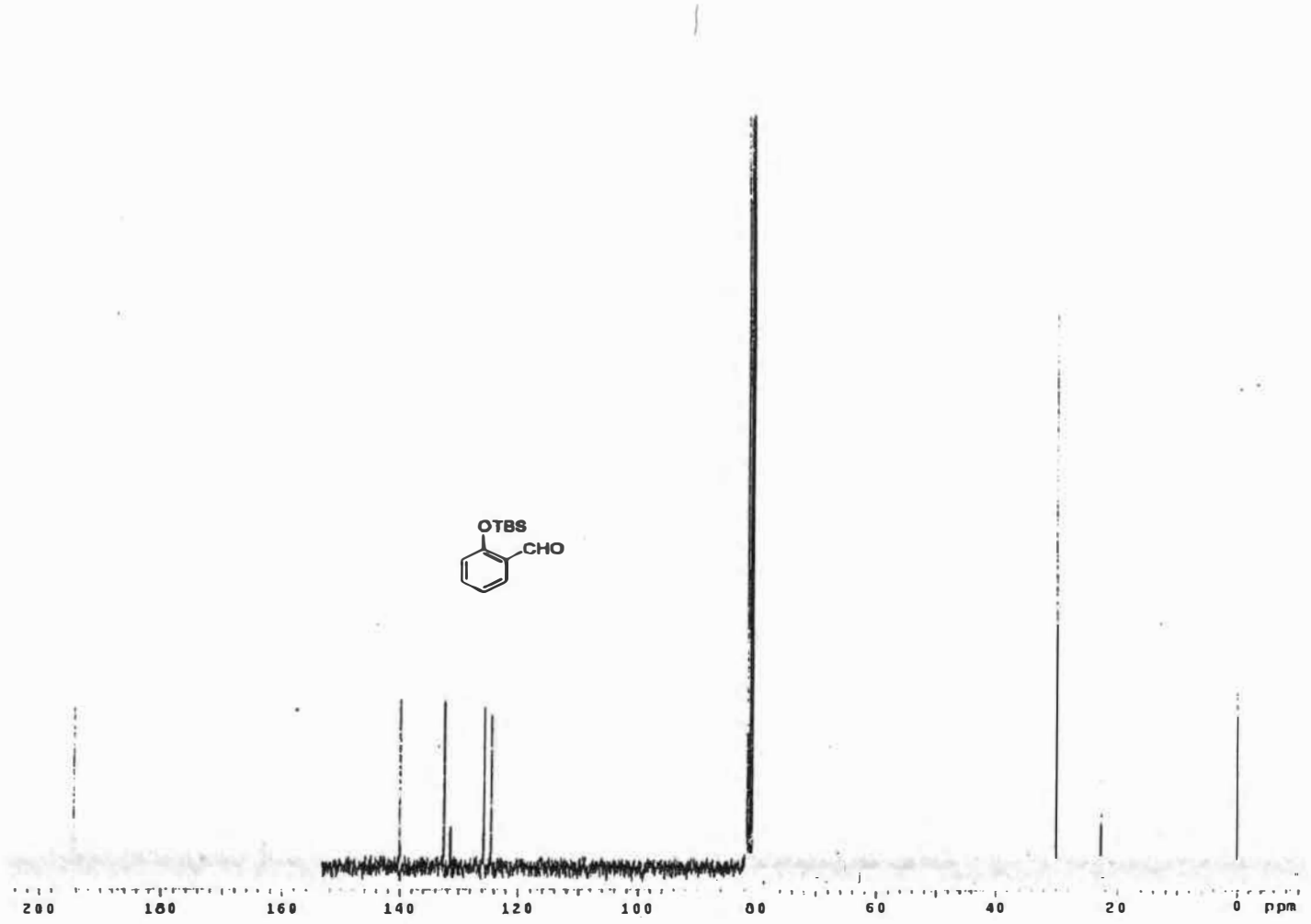
^{1}H NMR spectrum of 3-Benzyloxymethylpent-1-ene-4-yn-3-ol (**2.15**).



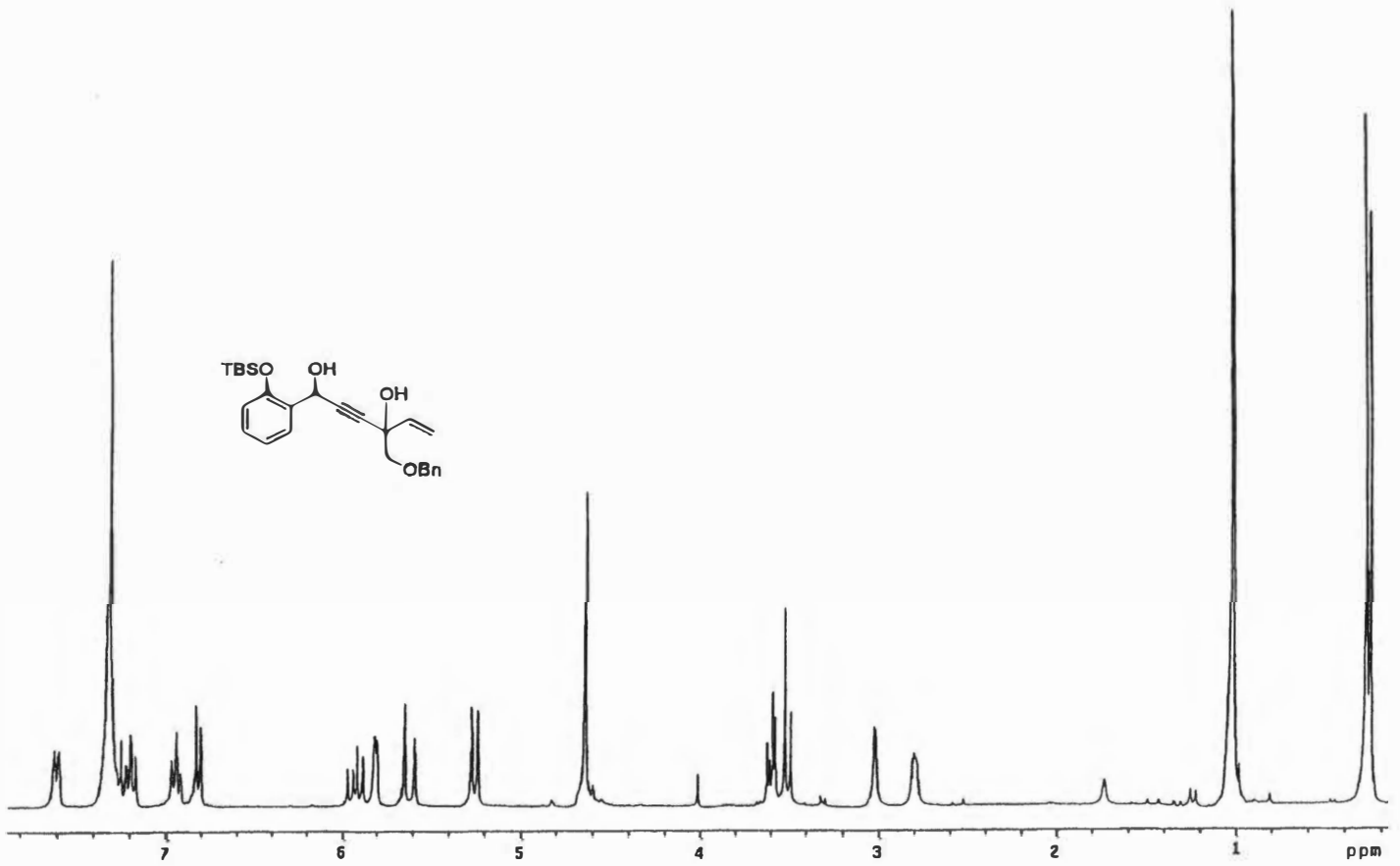
^{13}C NMR spectrum of 3-Benzyloxymethylpent-1-ene-4-yn-3-ol (**2.15**).



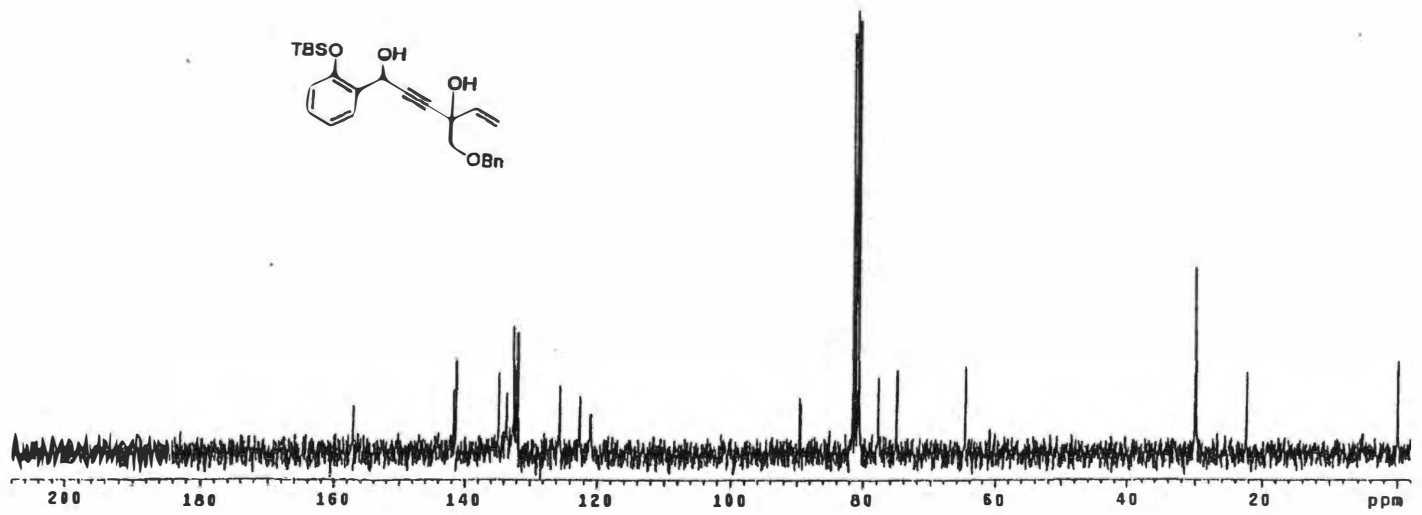
^{1}H NMR spectrum of 2-(*tert*-Butyldimethylsilyloxy)benzaldehyde (**2.16**).



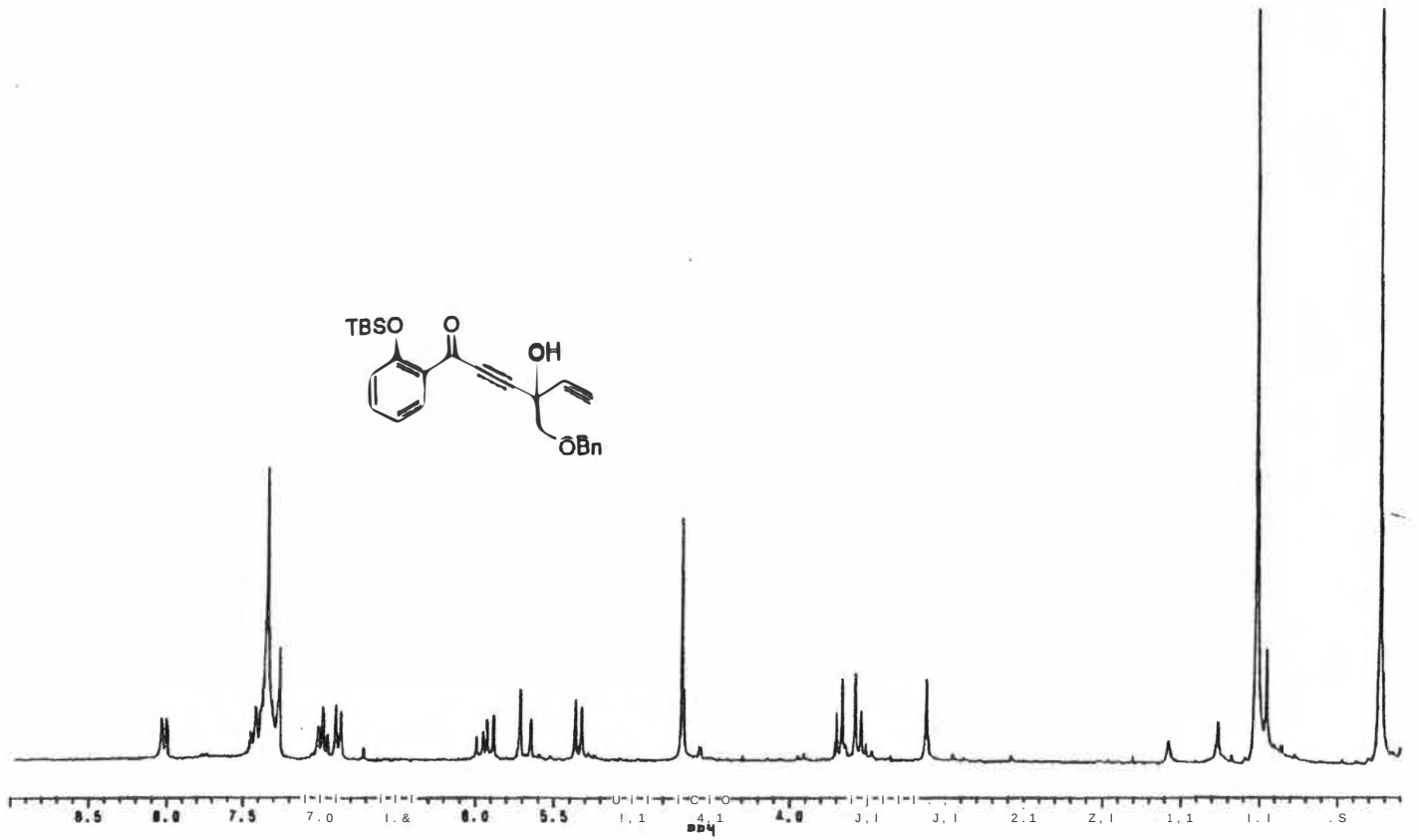
^{13}C NMR spectrum of 2-(*tert*-Butyldimethylsilyloxy)benzaldehyde (**2.16**).



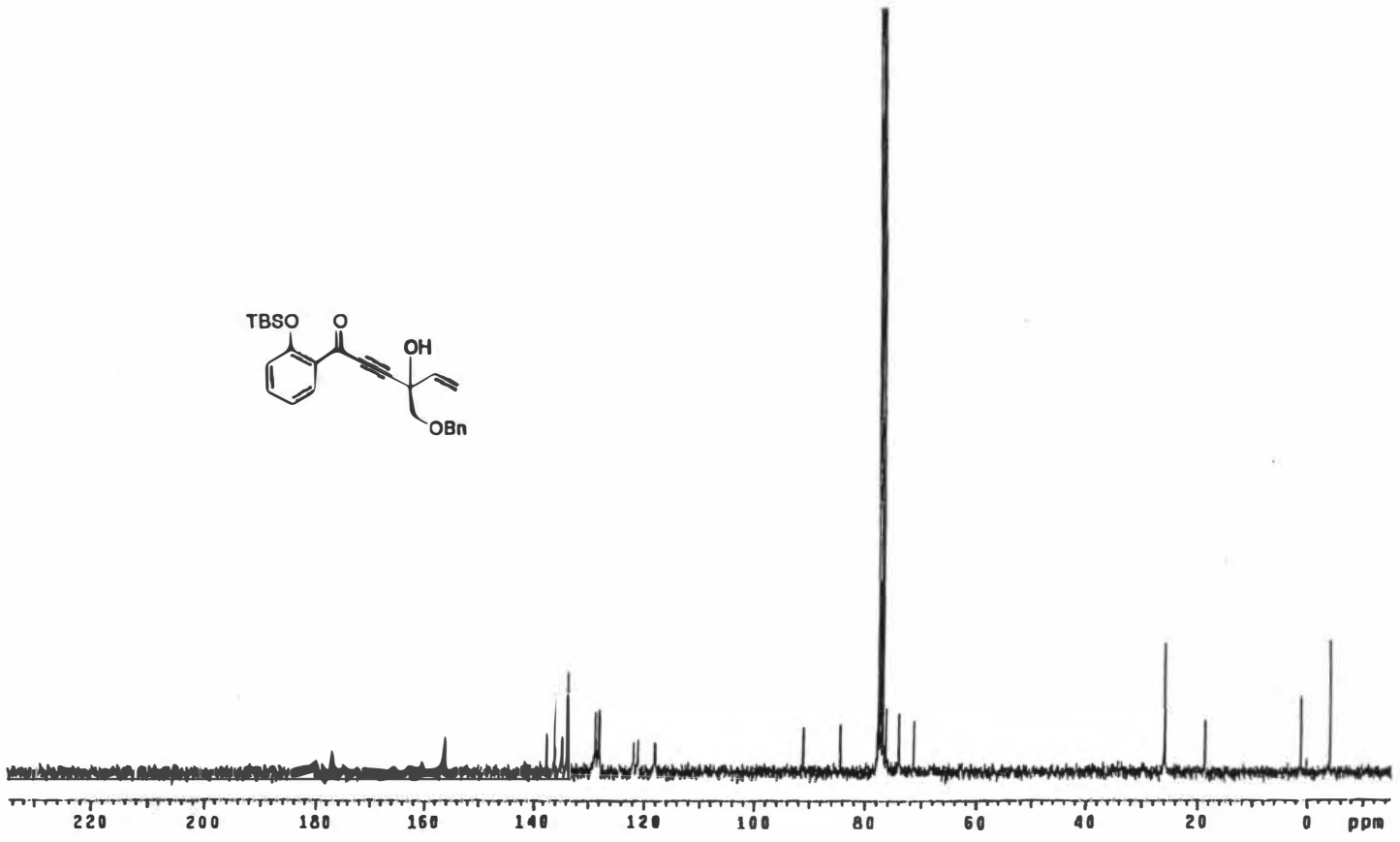
^{1}H NMR spectrum of 4-Benzyloxymethyl-1-[2-*tert*-butyldimethylsilyloxy)phenyl]hex-5-en-2-yne 1,4 diol (**2.17**).



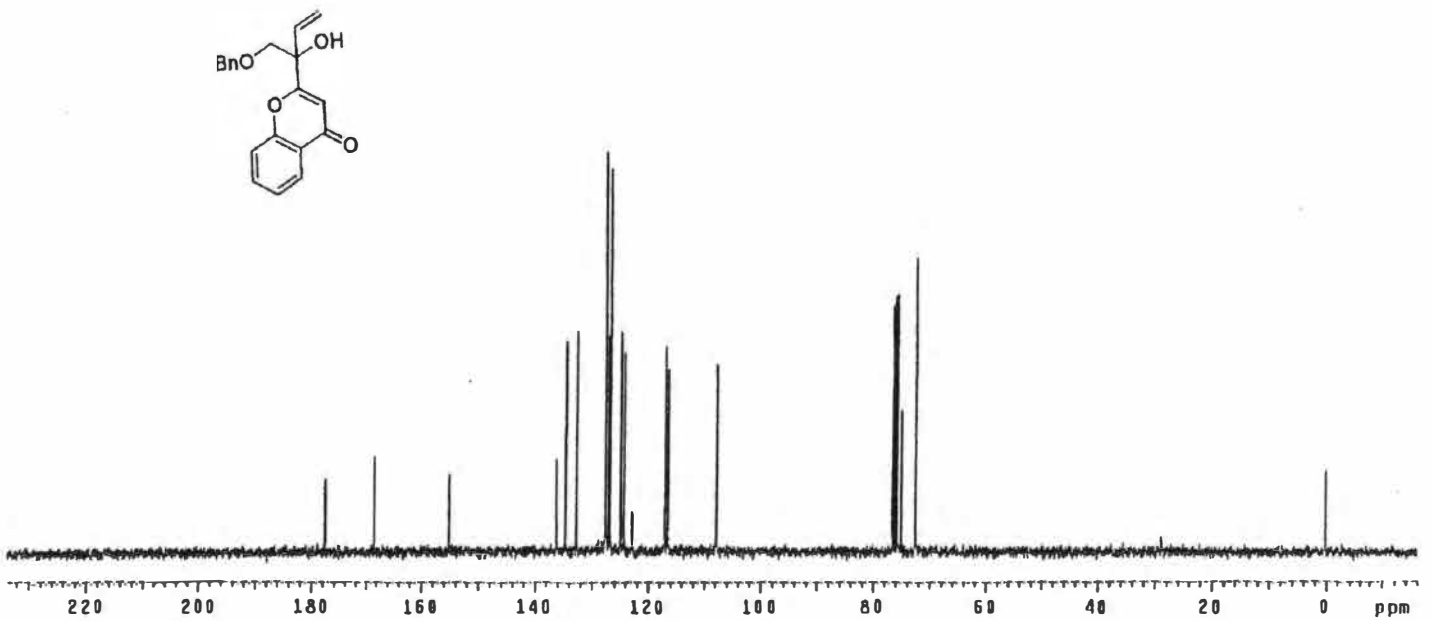
^{13}C NMR spectrum of 4-Benzyloxymethyl-1-[2-*tert*-butyldimethylsilyloxy)phenyl]hex-5-en-2-yne 1,4 diol (**2.17**).



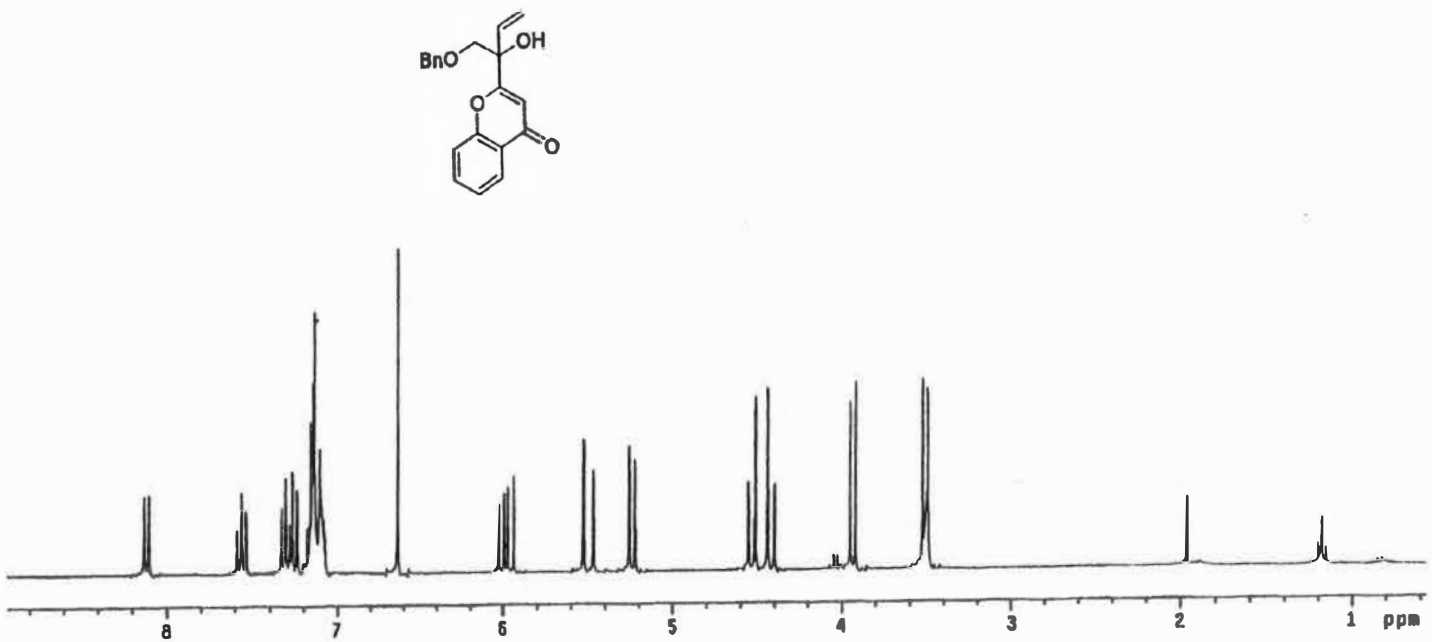
^{1}H NMR spectrum of 4-Benzyloxymethyl-1-[2-(*tert*-butyldimethylsilyloxy)phenyl]-4-hydroxyhex-5-en-2-yn-1-one (**2.18**).



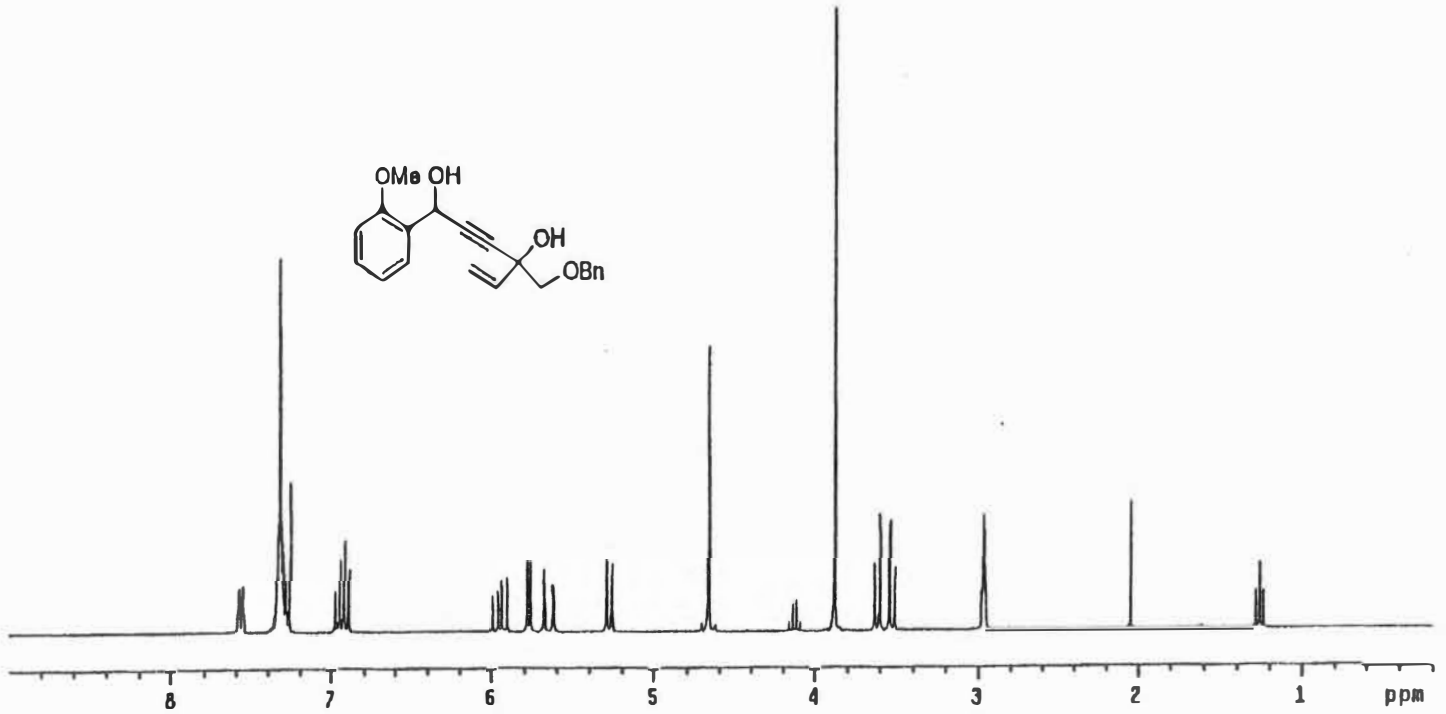
^{13}C NMR spectrum of 4-Benzyloxymethyl-1-[2-(*tert*-butyldimethylsilyloxy)phenyl]-4-hydroxyhex-5-en-2-yn-1-one (**2.18**).



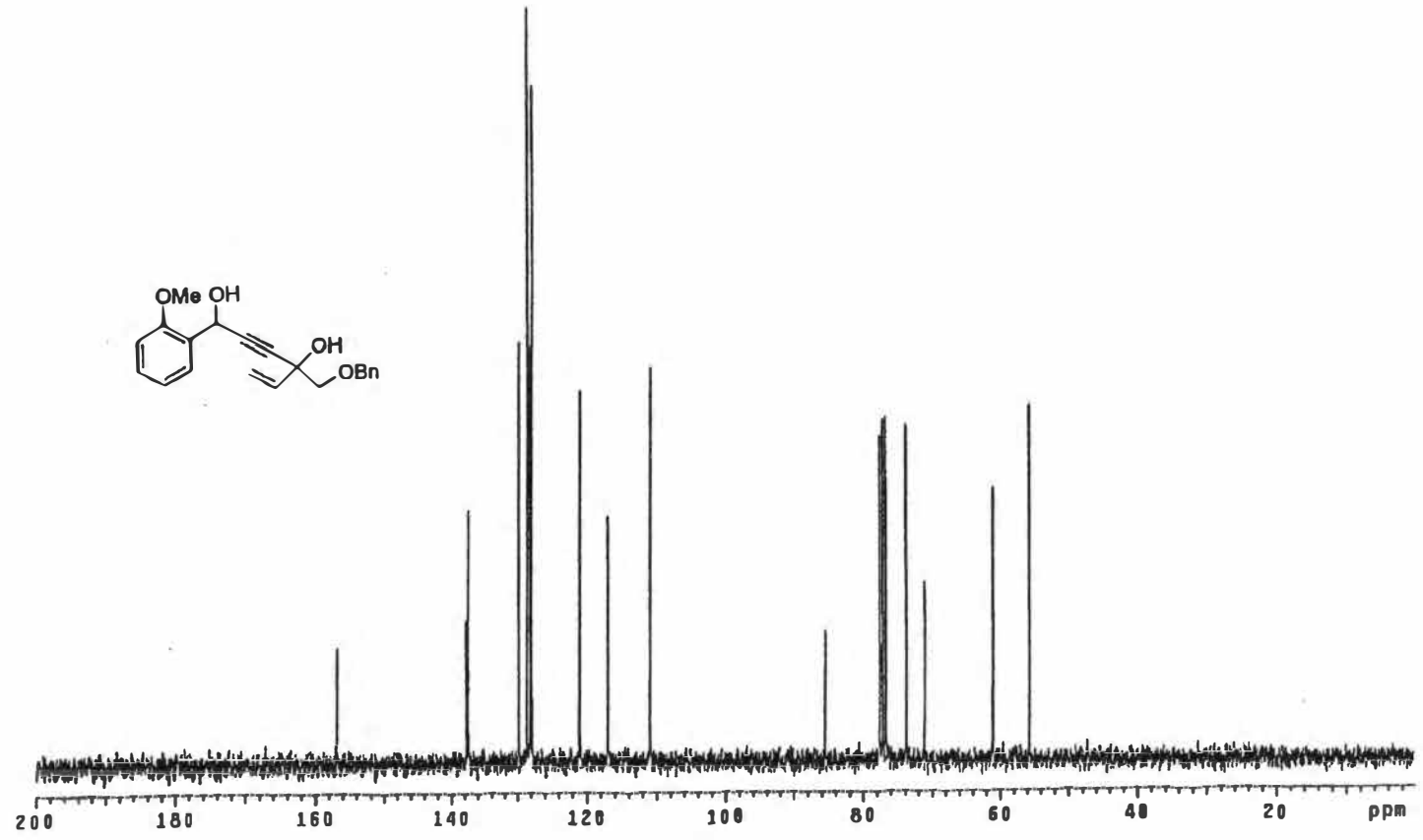
^{13}C NMR spectrum of 2-(1-Benzyloxymethyl-1-hydroxyallyl)chromen-4-one (**2.19**).



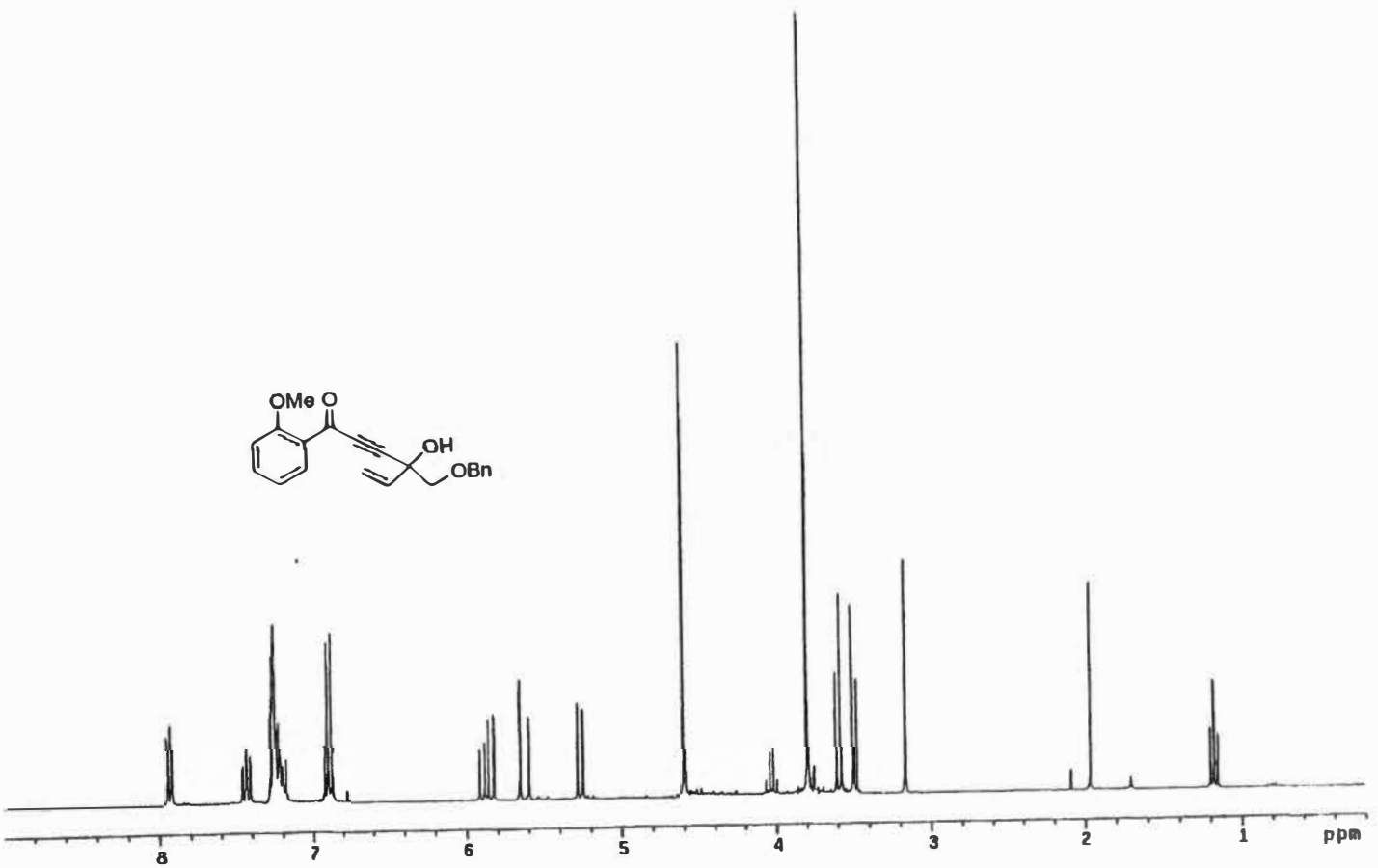
^{1}H NMR spectrum of 2-(1-Benzyloxymethyl-1-hydroxyallyl)chromen-4-one (**2.19**).



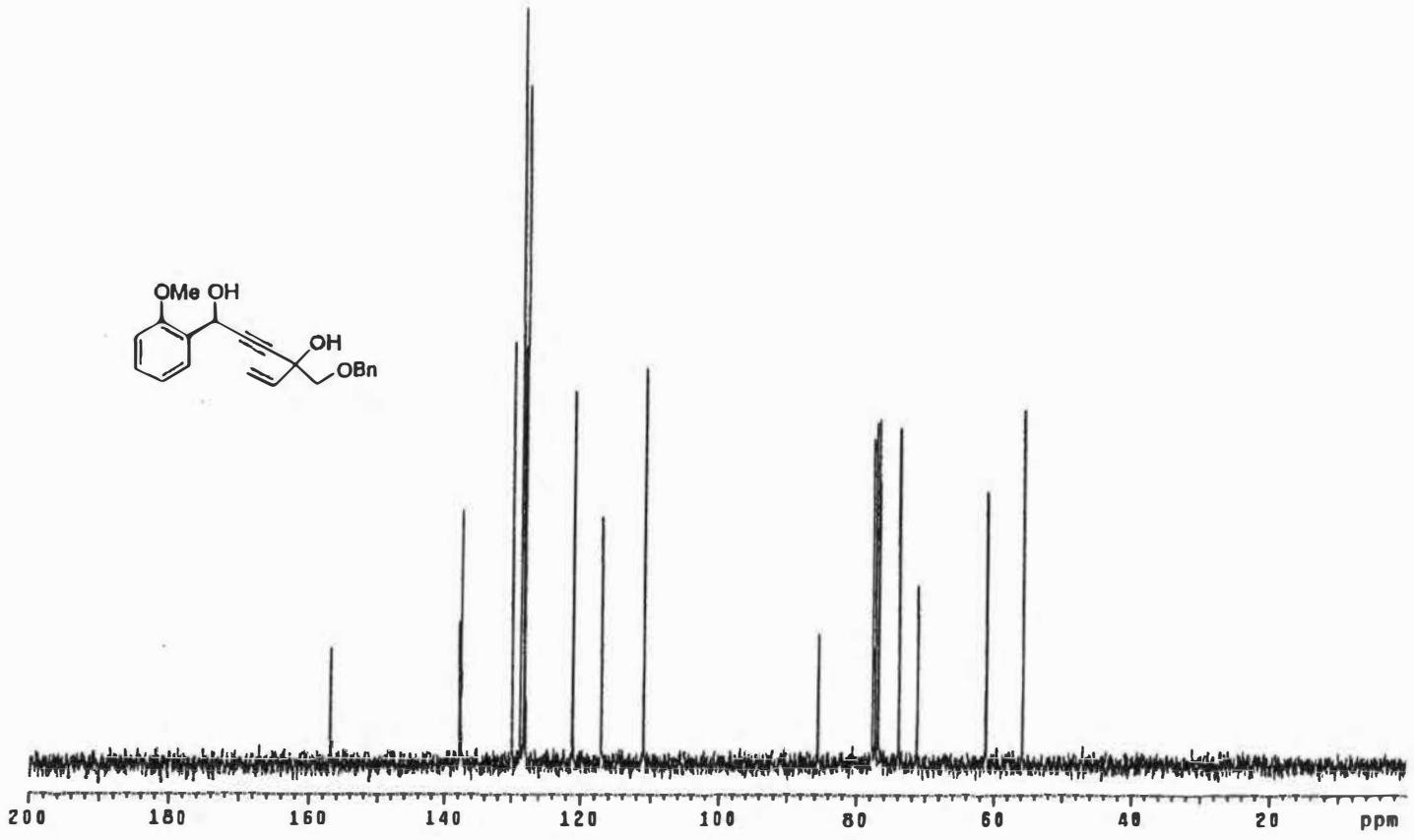
^{1}H NMR spectrum of 4-Benzyloxymethyl-1-(2-methoxyphenyl)hex-5-en-2-yne 1,4-diol (**2.20**).



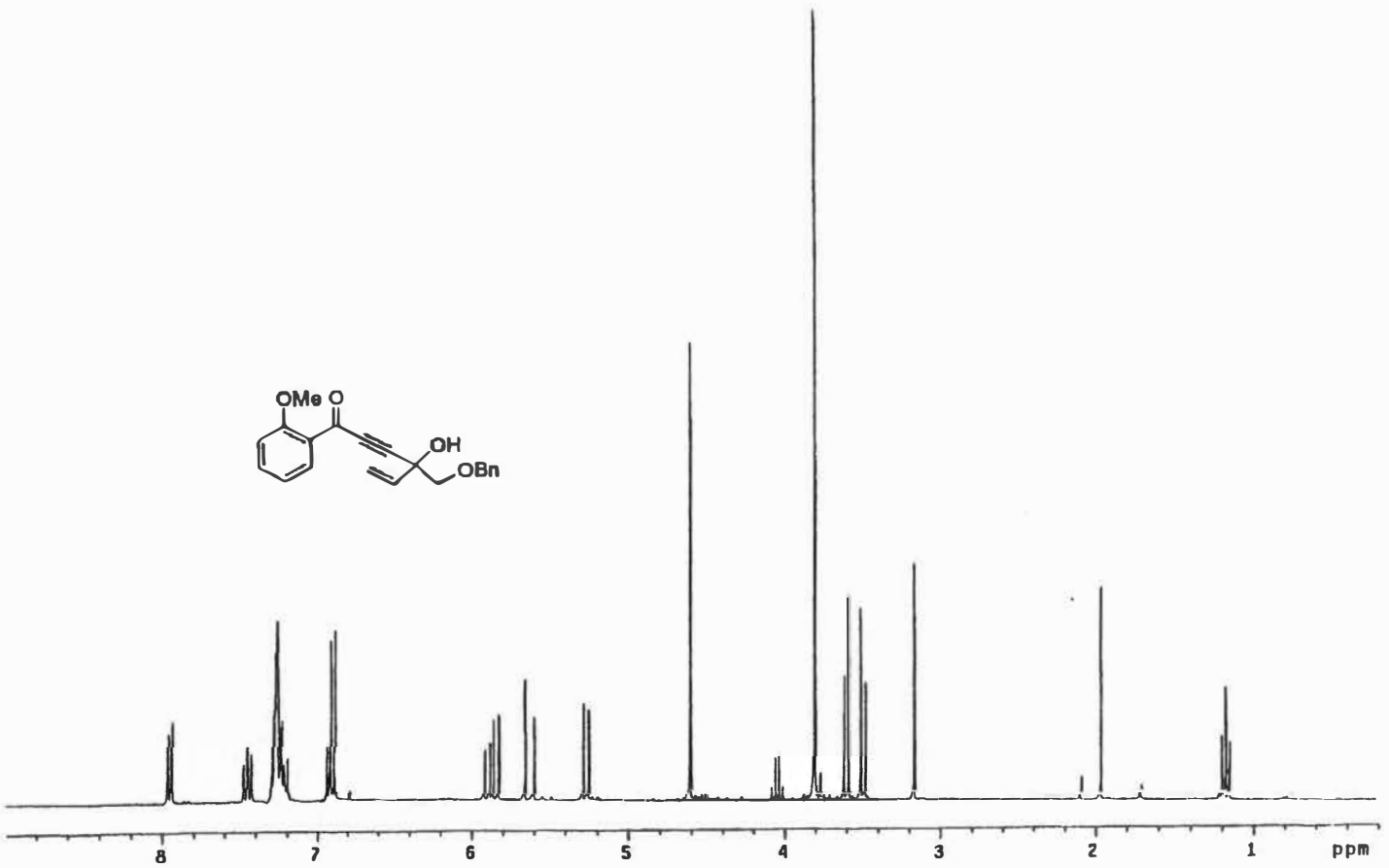
^{13}C NMR spectrum of 4-Benzyloxymethyl-1-(2-methoxyphenyl)hex-5-en-2-yne 1,4-diol (**2.20**).



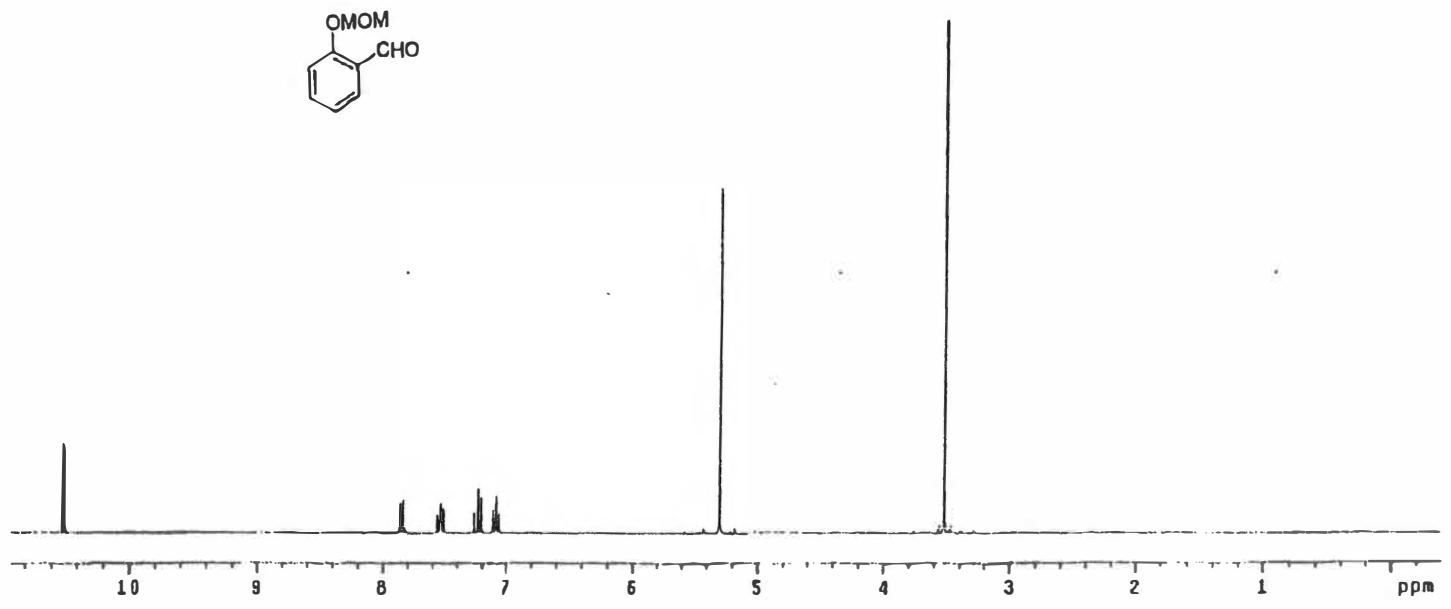
^{1}H NMR spectrum of 4-Benzyloxymethyl-4-hydroxy-1-(2-methoxyphenyl)hex-5-en-2-yn-1-one (**2.21**).



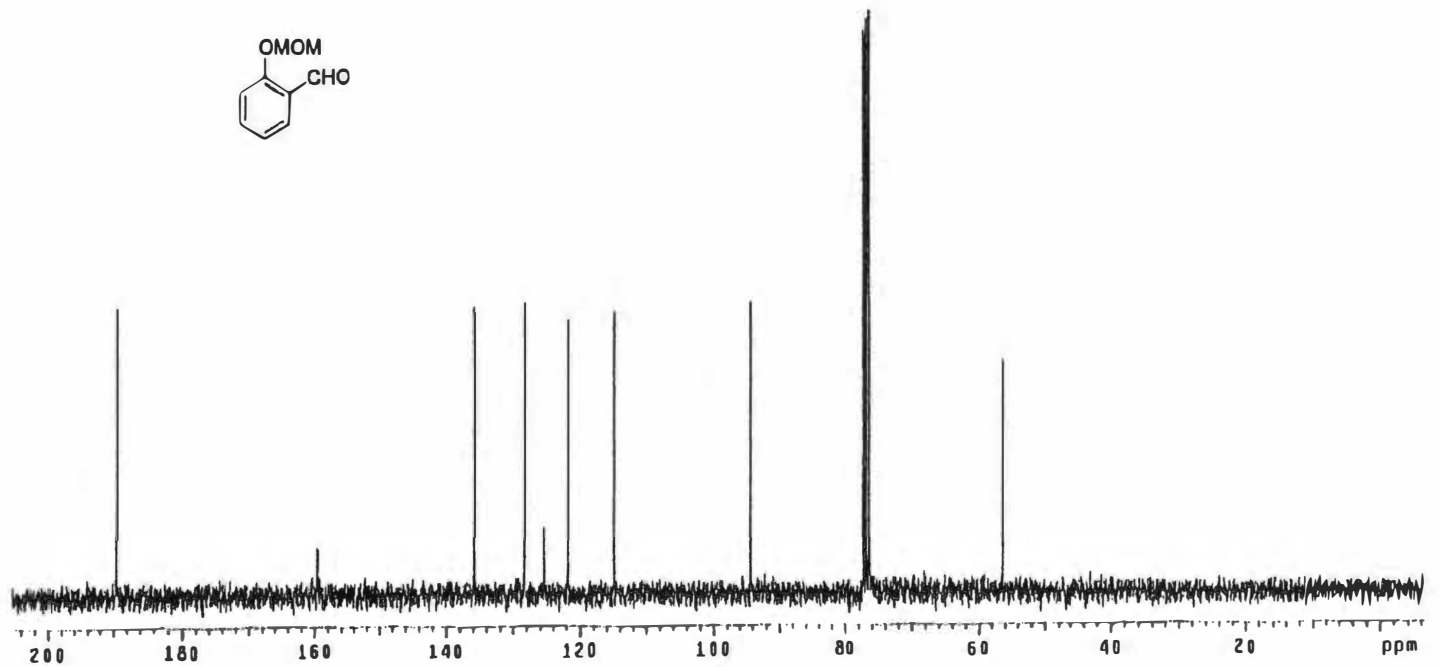
^{13}C NMR spectrum of 4-Benzyloxymethyl-1-(2-methoxyphenyl)hex-5-en-2-yne 1,4-diol (**2.20**).



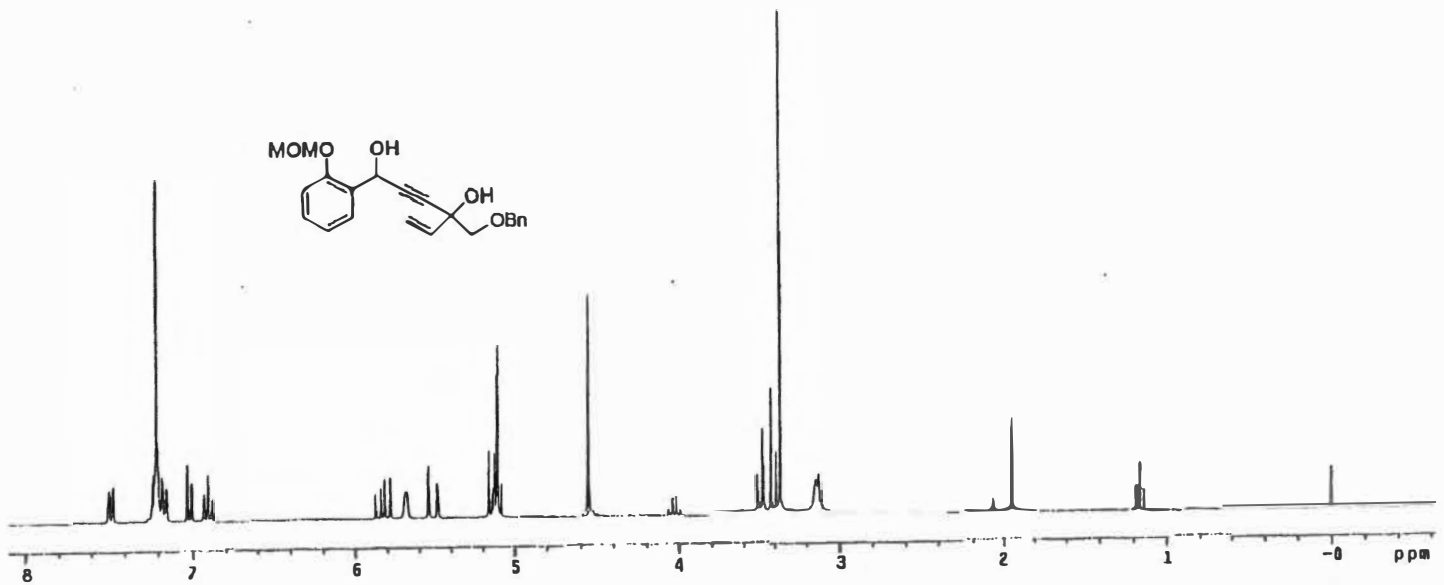
^{1}H NMR spectrum of 4-Benzyloxymethyl-4-hydroxy-1-(2-methoxyphenyl)hex-5-en-2-yn-1-one (**2.21**).



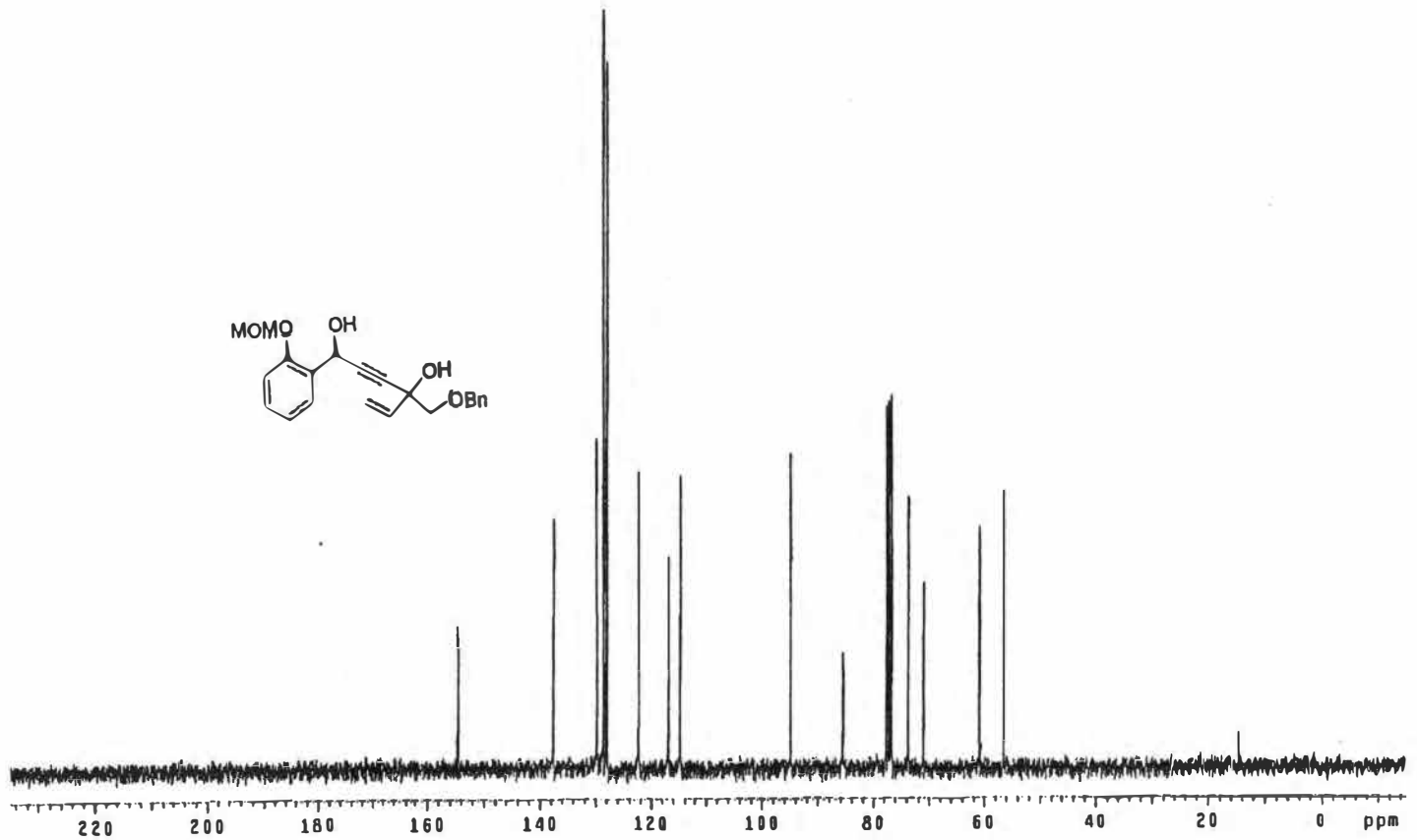
^{1}H NMR spectrum of 2-Methoxymethoxybenzaldehyde (**2.22**).



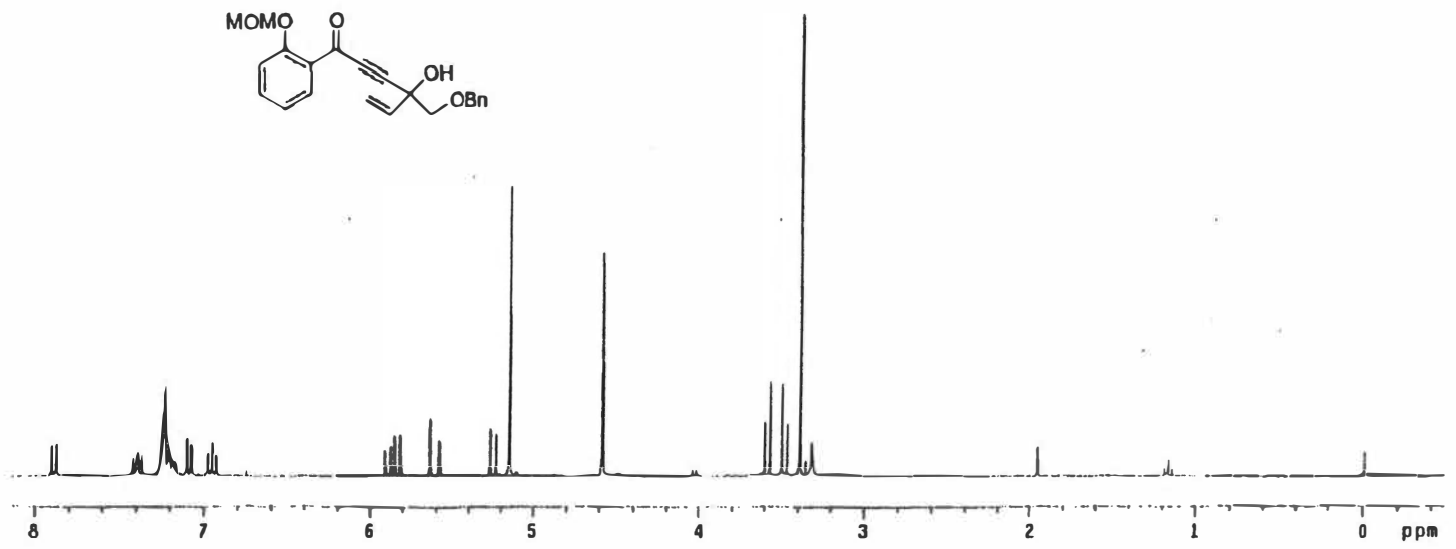
^{1}H NMR spectrum of 2-Methoxymethoxybenzaldehyde (**2.22**).



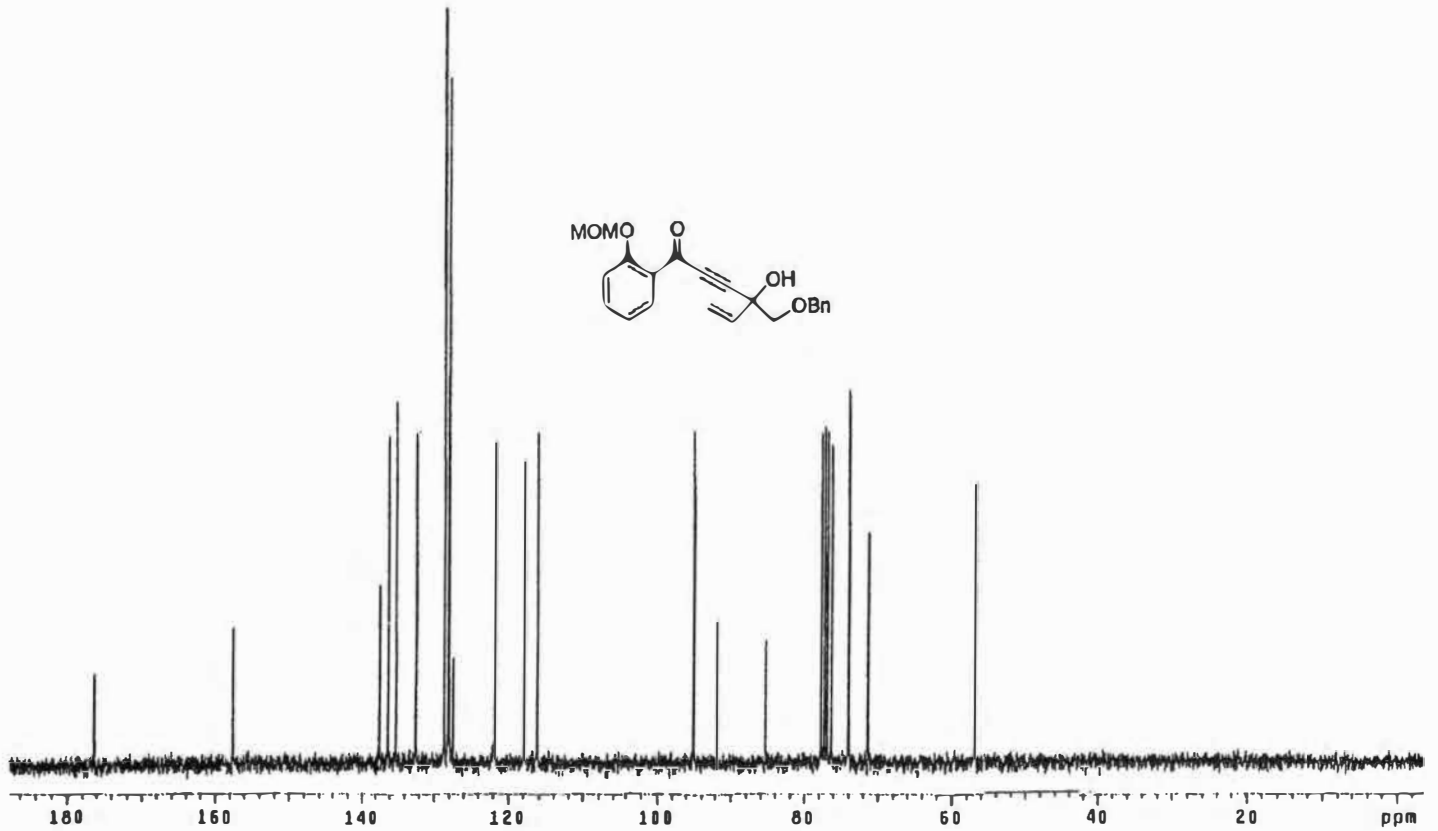
^{1}H NMR spectrum of 4-Benzyloxymethyl-1-(2-methoxymethoxyphenyl)hex-5-en-2-yne 1,4-diol (**2.23**).



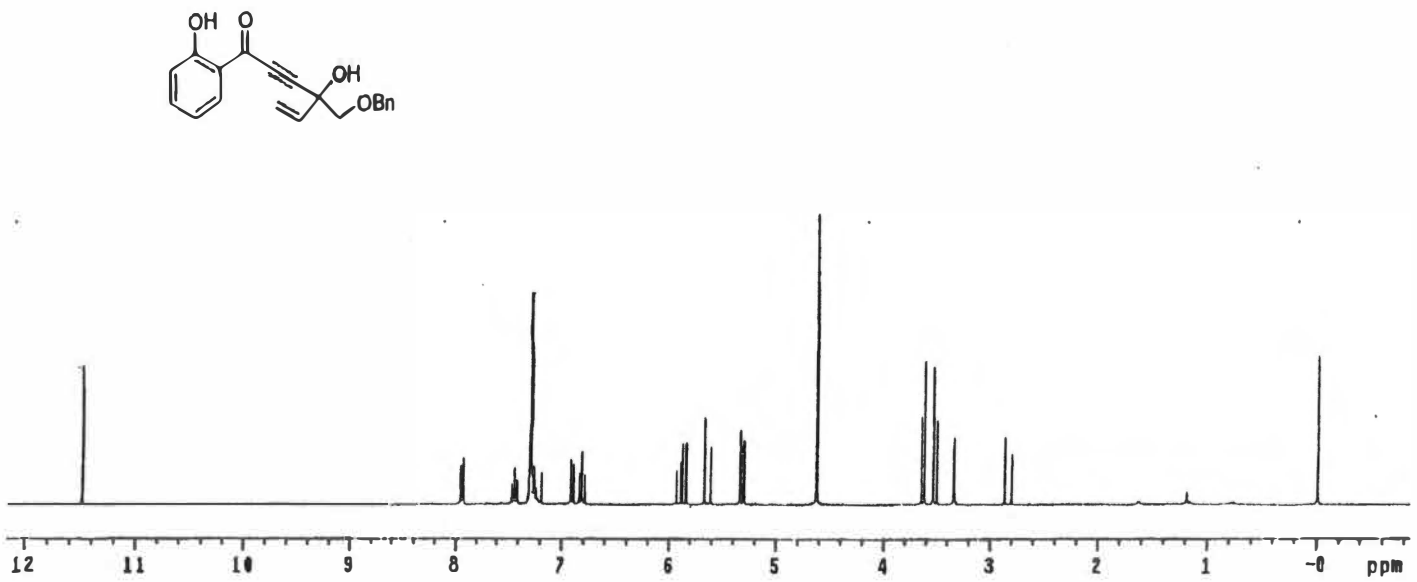
^{13}C NMR spectrum of 4-Benzyloxymethyl-1-(2-methoxymethoxyphenyl)hex-5-en-2-yne 1,4-diol (**2.23**).



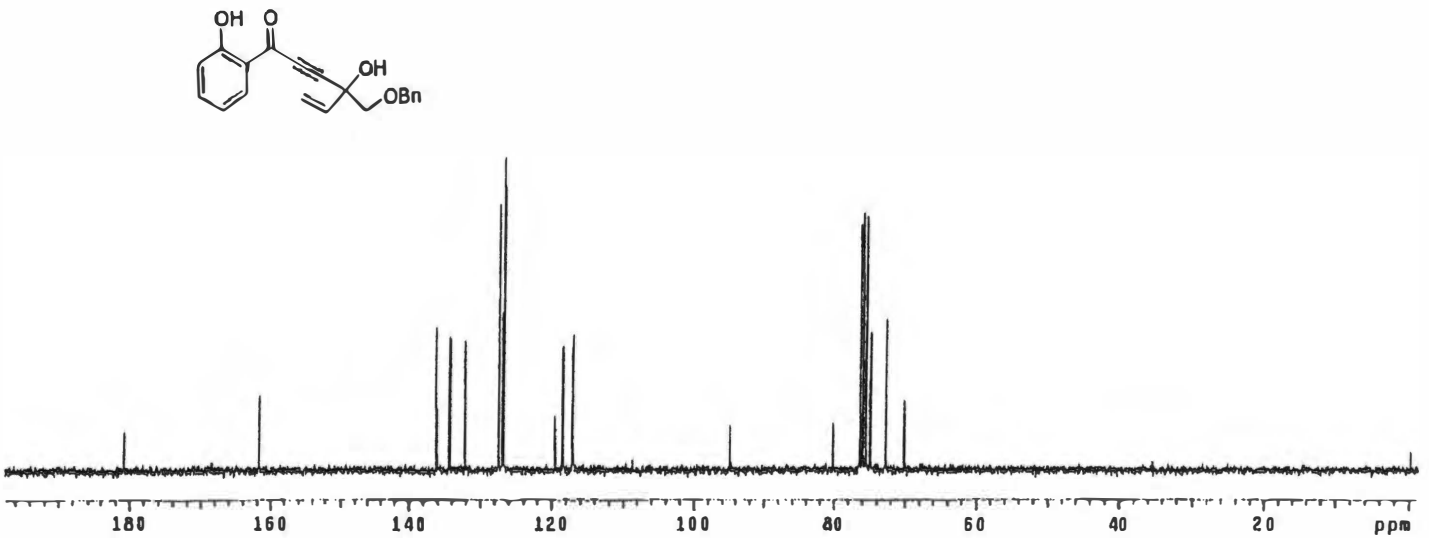
^{1}H NMR spectrum of 4-Benzyloxymethyl-4-hydroxy-1-(2-methoxymethoxyphenyl)hex-5-en-2-yn-1-one (**2.24**).



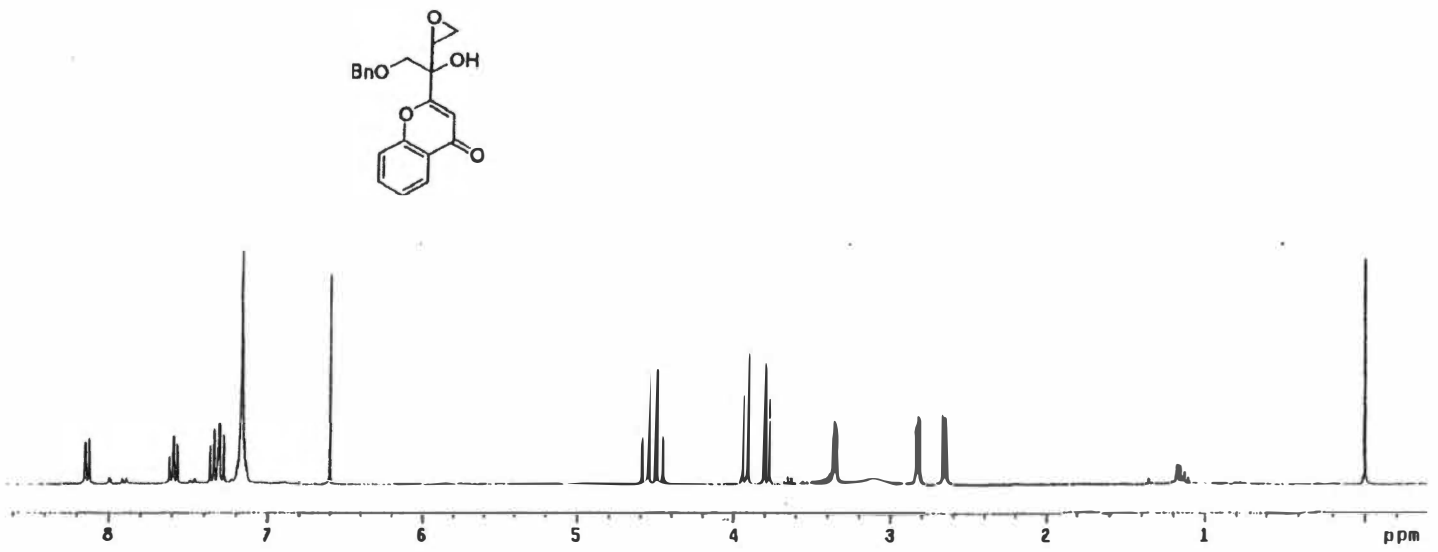
^{13}C NMR spectrum of 4-Benzyloxymethyl-4-hydroxy-1-(2-methoxymethoxyphenyl)hex-5-en-2-yn-1-one (**2.24**).



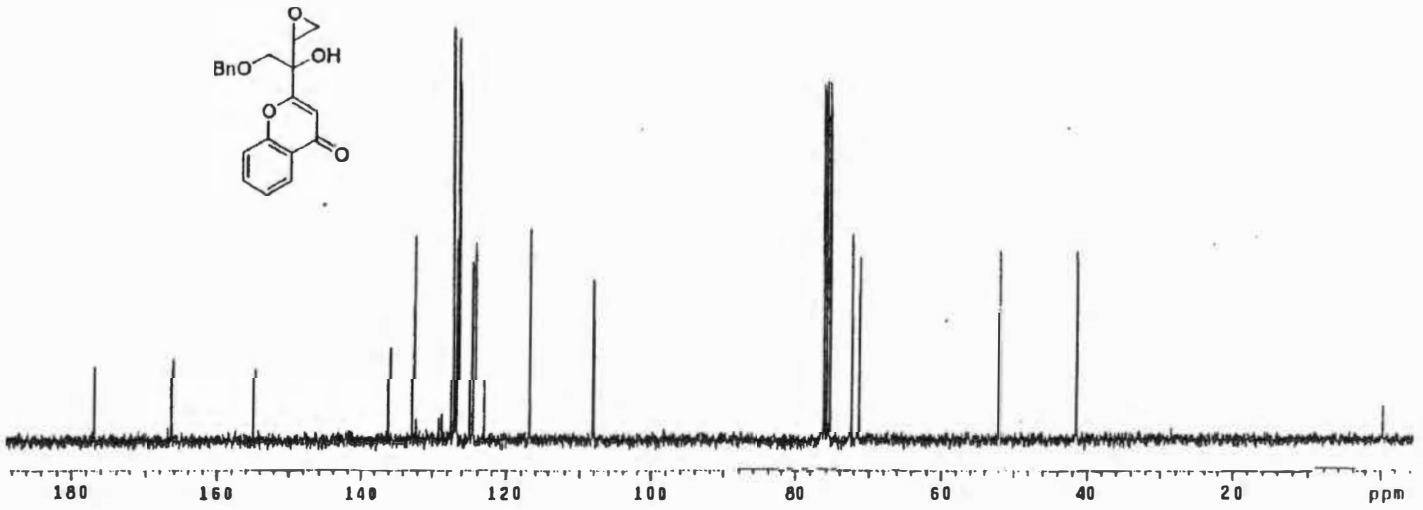
^{1}H NMR spectrum of 4-Benzyloxymethyl-4-hydroxy-1-(2-hydroxyphenyl)hex-5-en-2-yn-1-one (**2.25**).



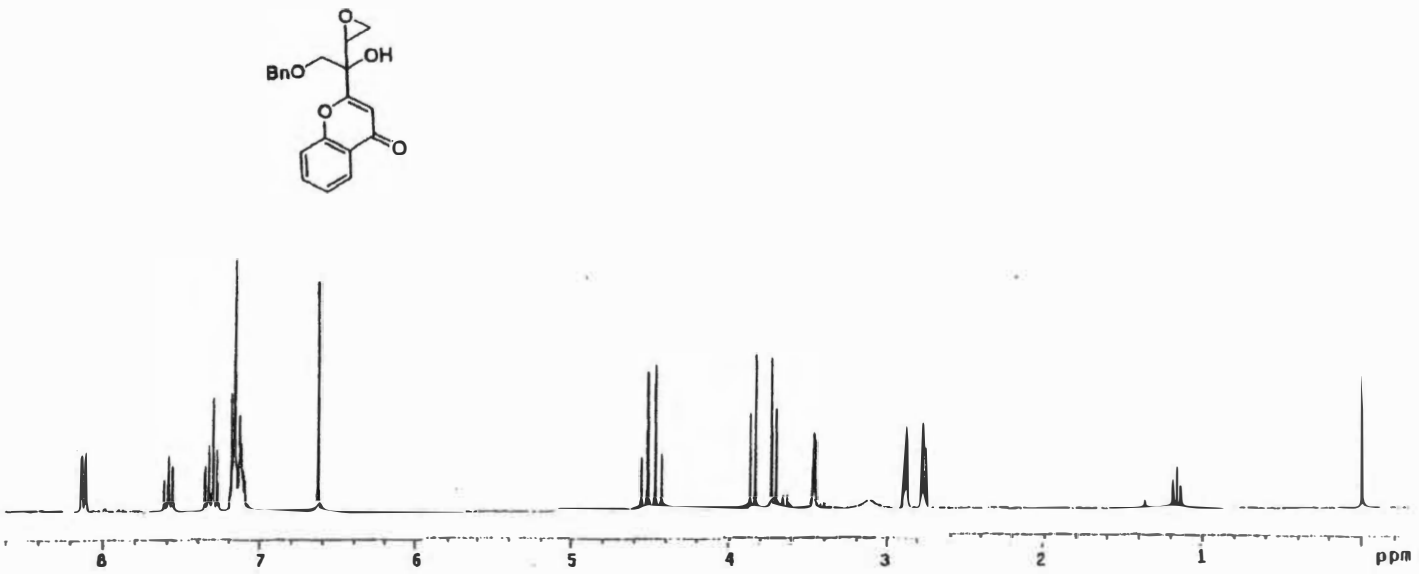
^{13}C NMR spectrum of 4-Benzyloxymethyl-4-hydroxy-1-(2-hydroxyphenyl)hex-5-en-2-yn-1-one (**2.25**).



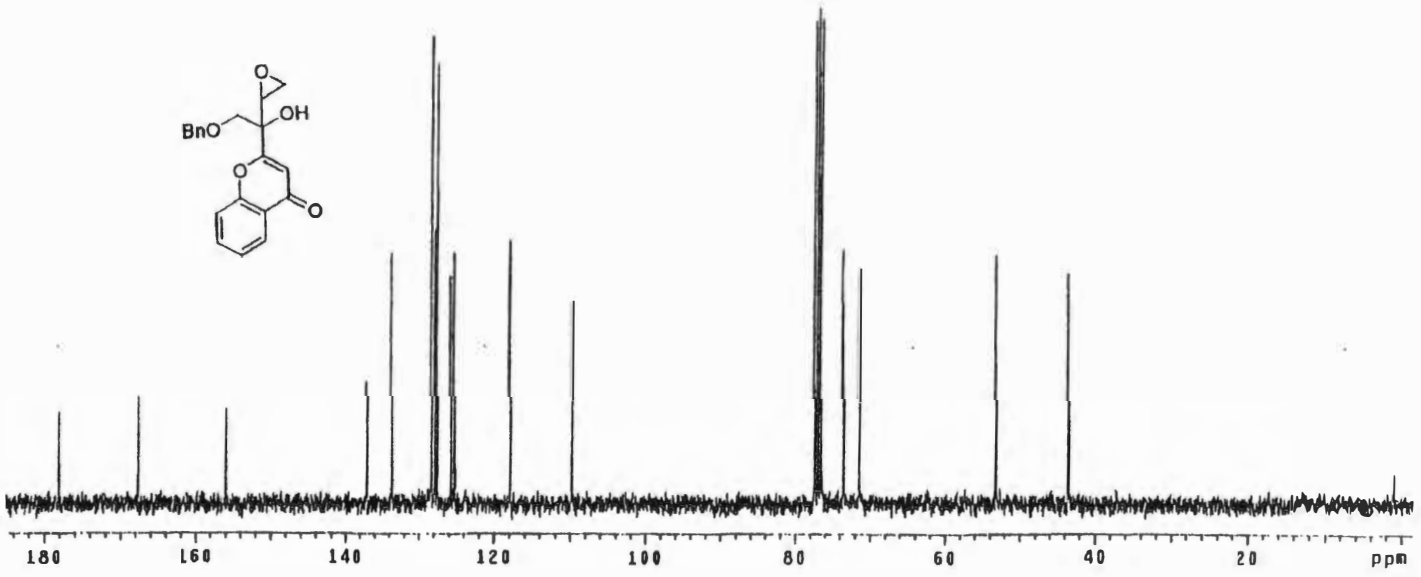
^{1}H NMR spectrum of 2-Benzyloxy-1-hydroxy-1-oxiranylethyl)chromen-4-one, Diastereomer A (**2.26**).



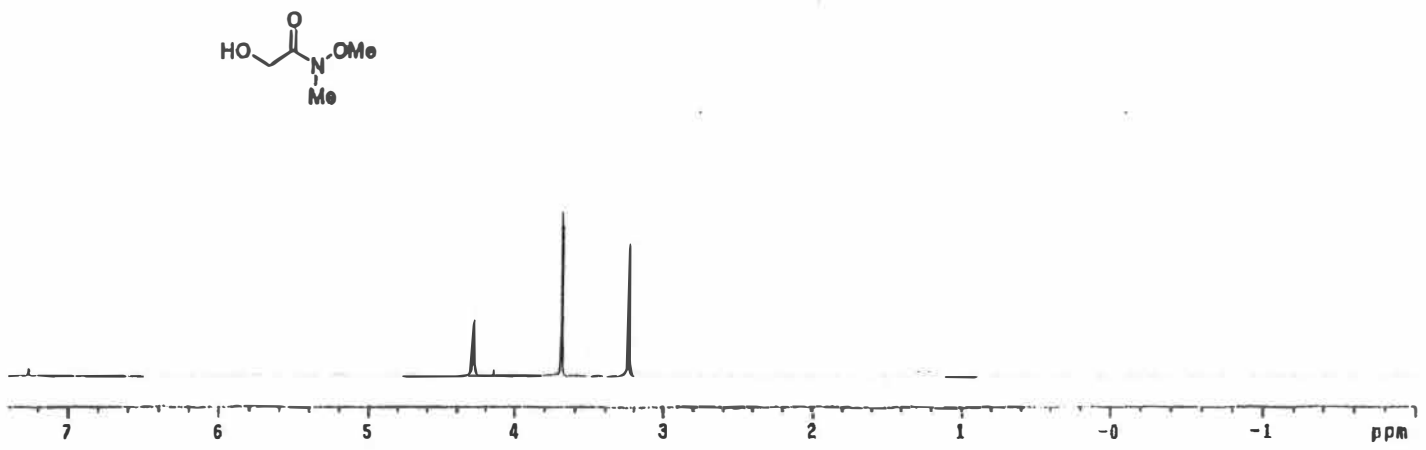
^{13}C NMR spectrum of 2-Benzyloxy-1-hydroxy-1-oxiranylethyl)chromen-4-one, Diastereomer A (**2.26**).



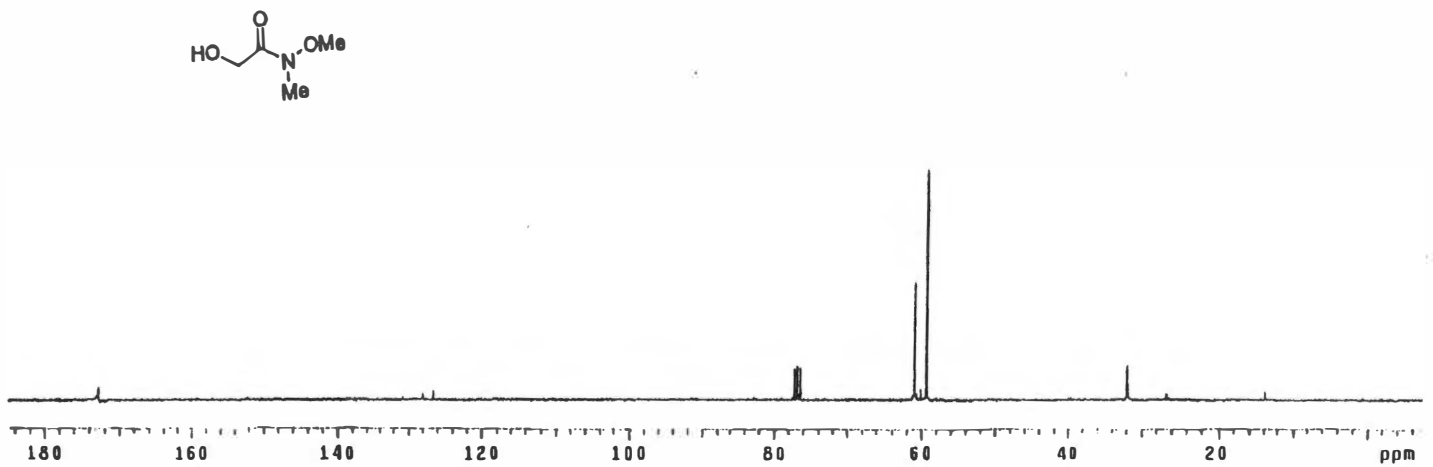
^{1}H NMR spectrum of 2-Benzyloxy-1-hydroxy-1-oxiranylethyl)chromen-4-one, Diastereomer B (**2.26**).



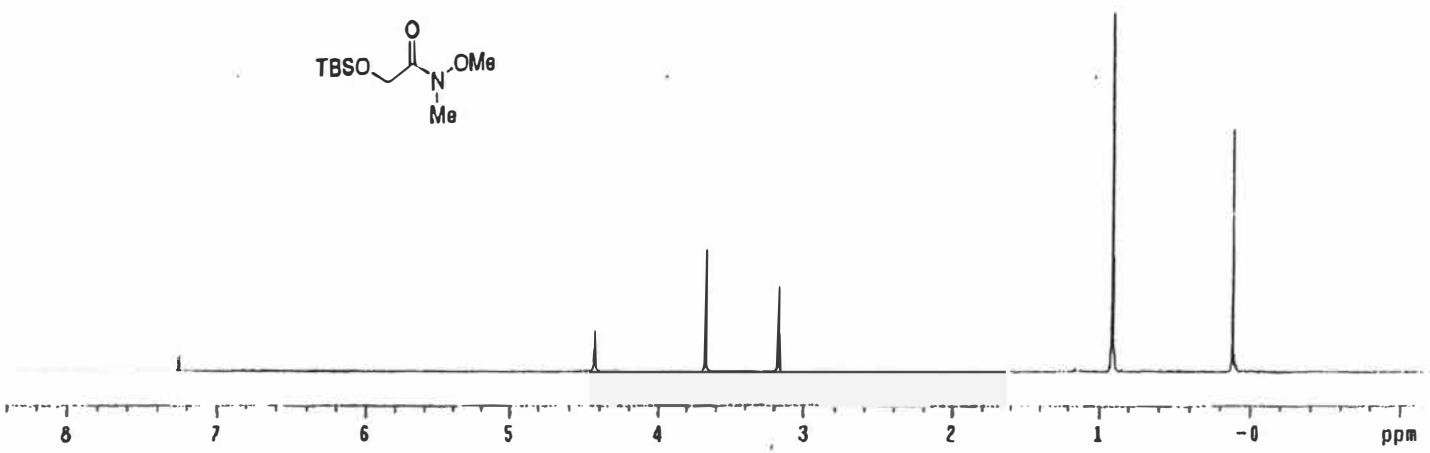
^{13}C NMR spectrum of 2-Benzyloxy-1-hydroxy-1-oxiranylethyl)chromen-4-one, Diastereomer B (**2.26**).



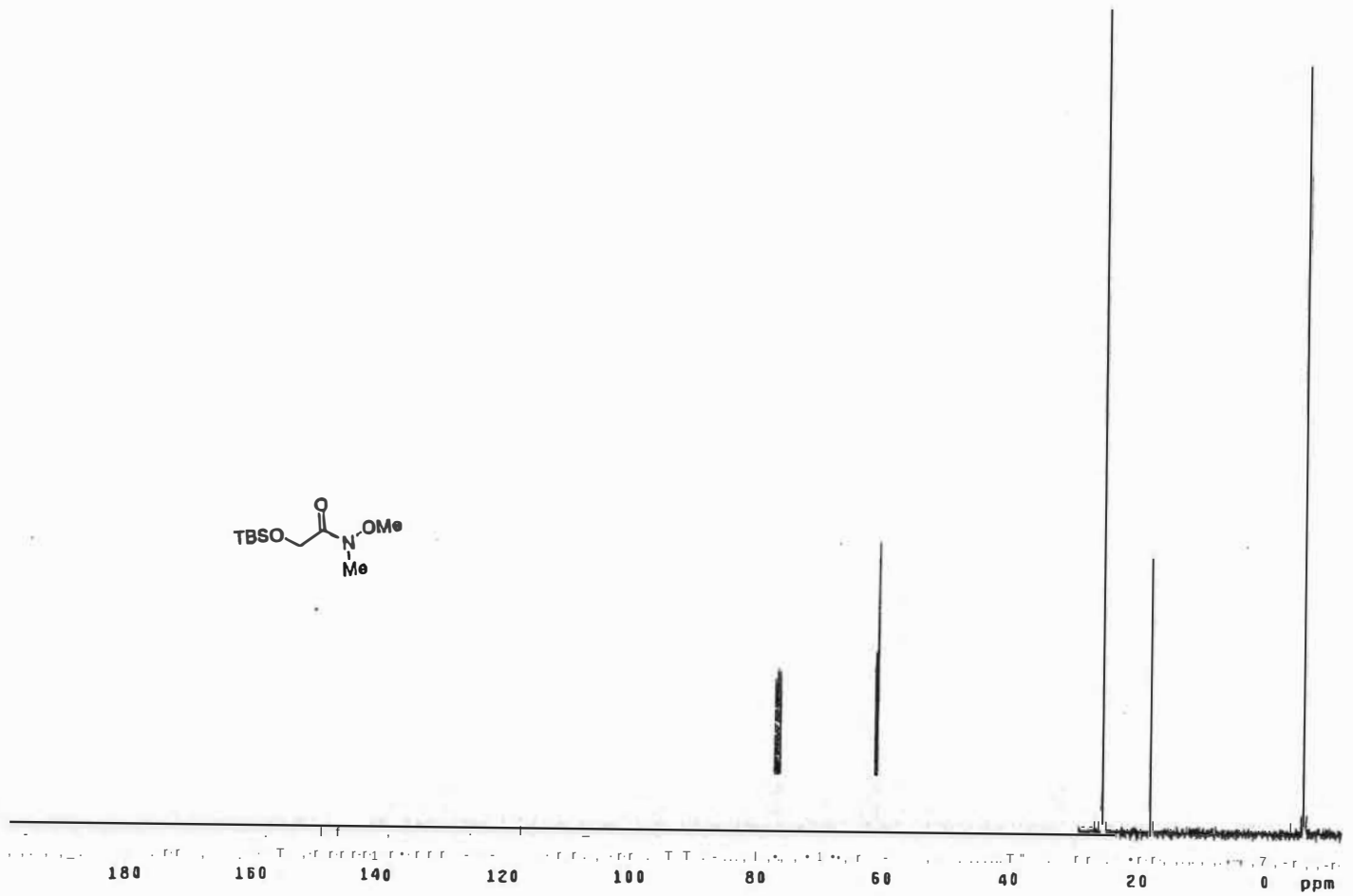
^{1}H NMR spectrum of 2-Hydroxy-*N*-methoxy-*N*-methylacetamide (**2.27**).



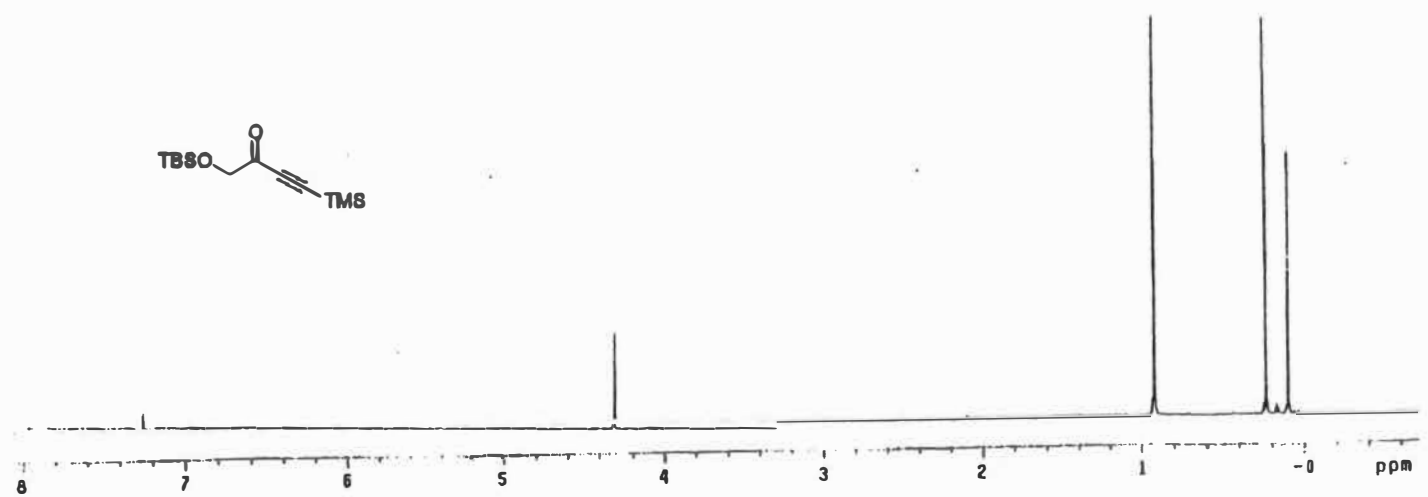
^{13}C NMR spectrum of 2-Hydroxy-*N*-methoxy-*N*-methylacetamide (**2.27**).



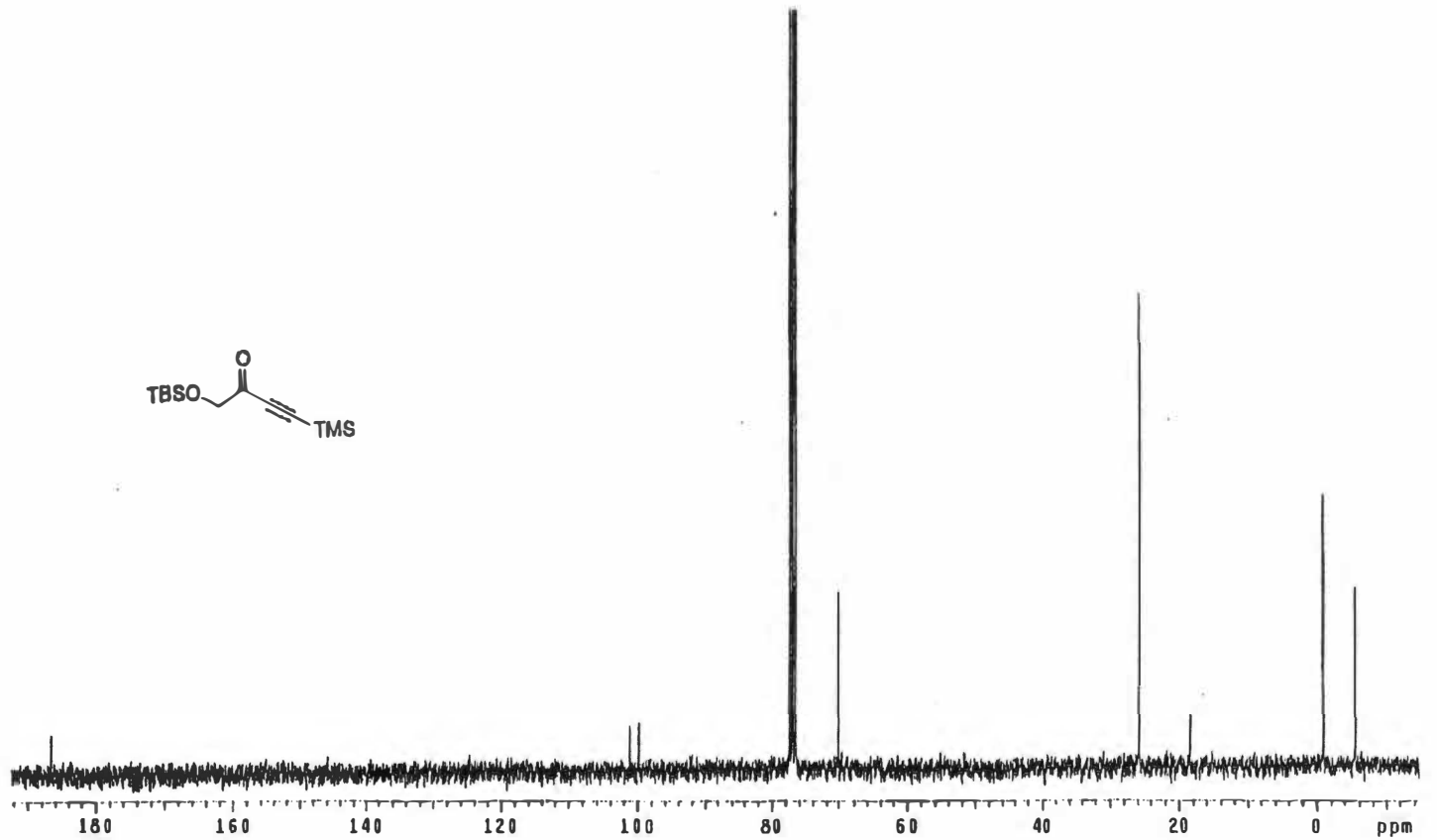
^{1}H NMR spectrum of 2-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*-methylacetamide (**2.28**).



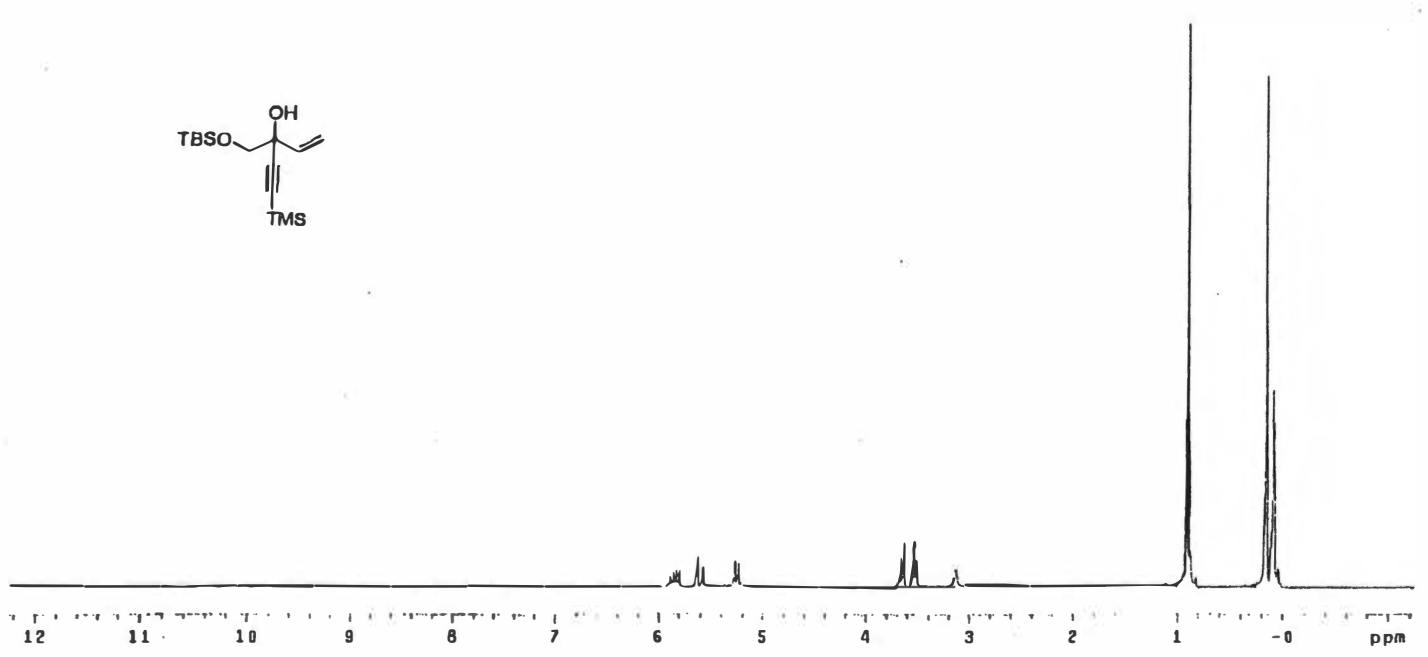
^{13}C NMR spectrum of 2-(*tert*-butyldimethylsilyloxy)-*N*-methoxy-*N*-methylacetamide (**2.28**).



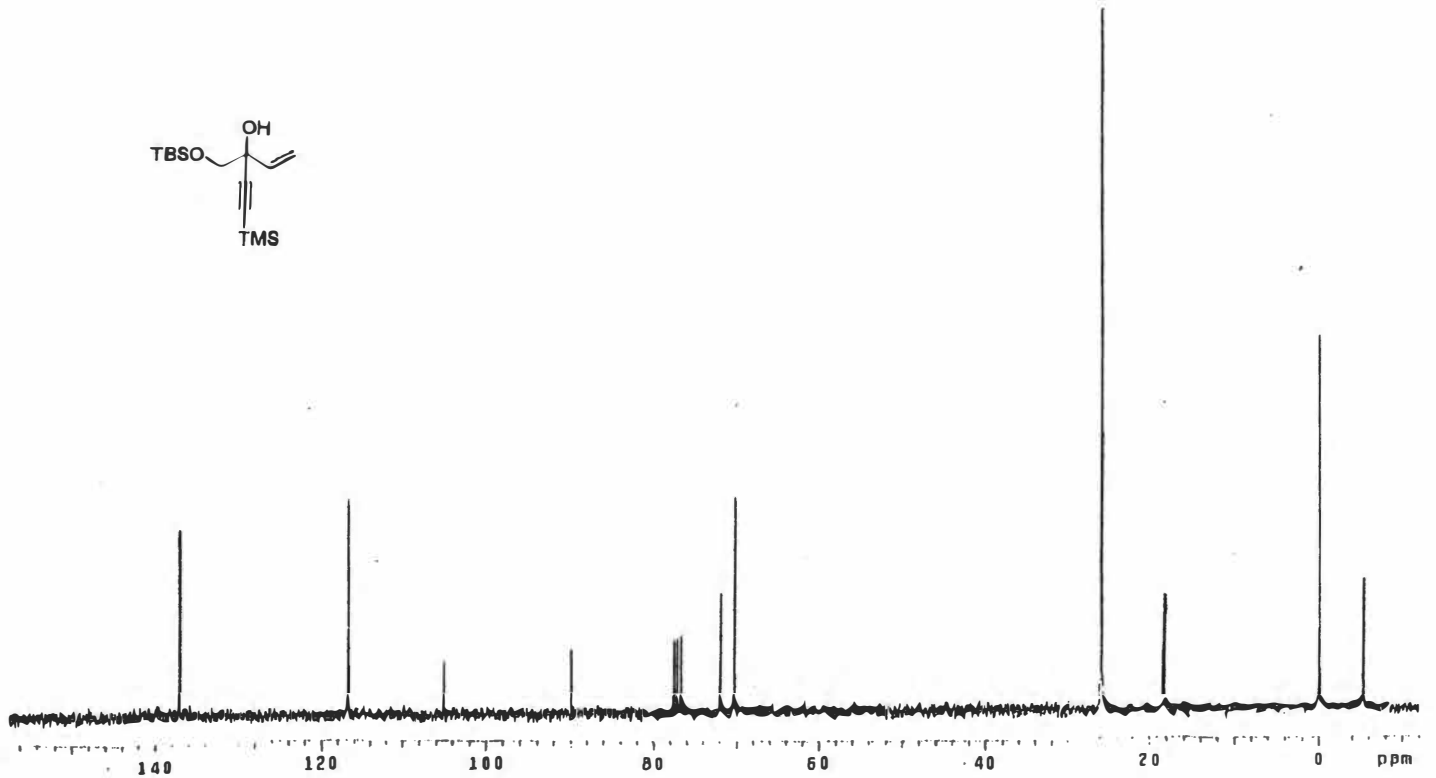
^{1}H NMR spectrum of 1-(*tert*-Butyldimethylsilyloxy)-4-trimethylsilylbut-3-yn-2-one (**2.29**).



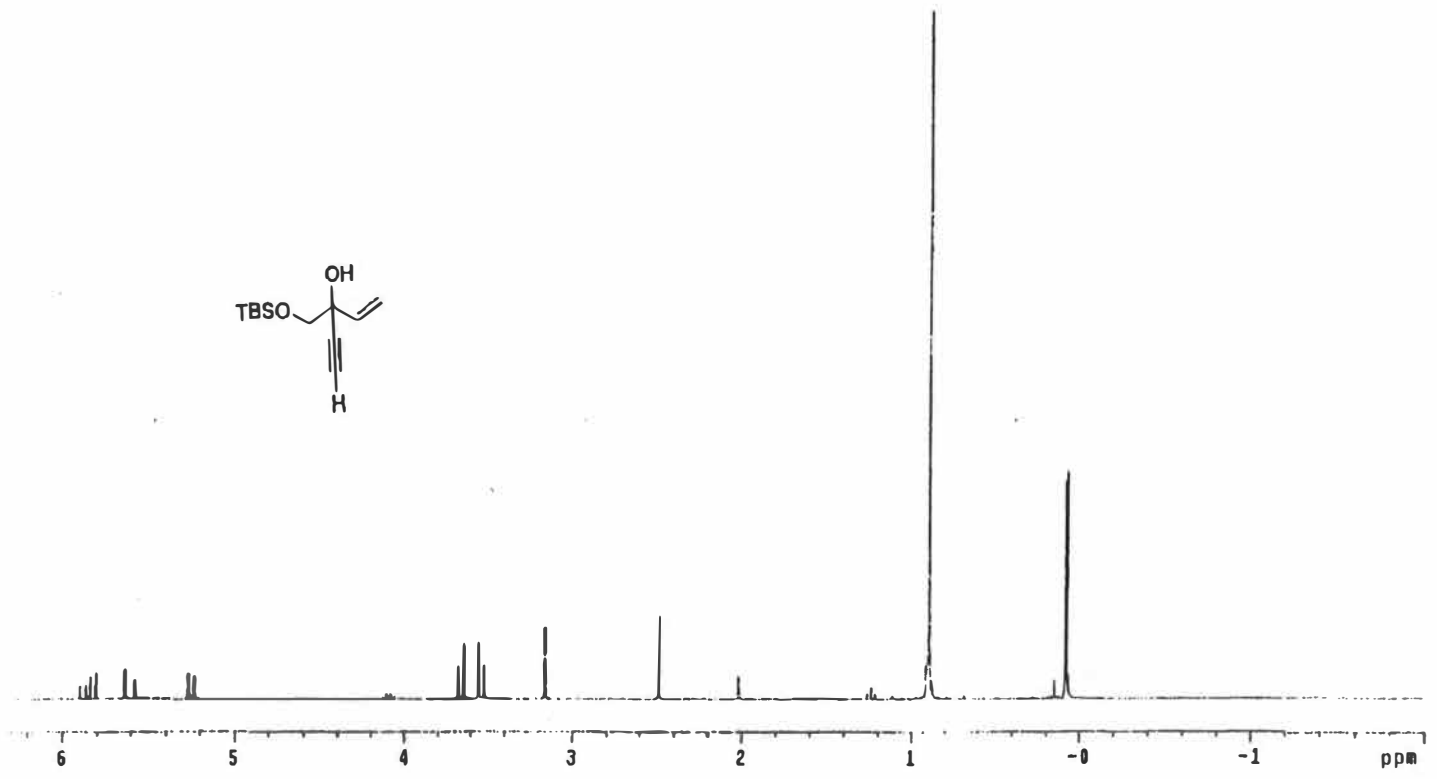
^{13}C NMR spectrum of 1-(*tert*-Butyldimethylsilyloxy)-4-trimethylsilylbut-3-yn-2-one (**2.29**).



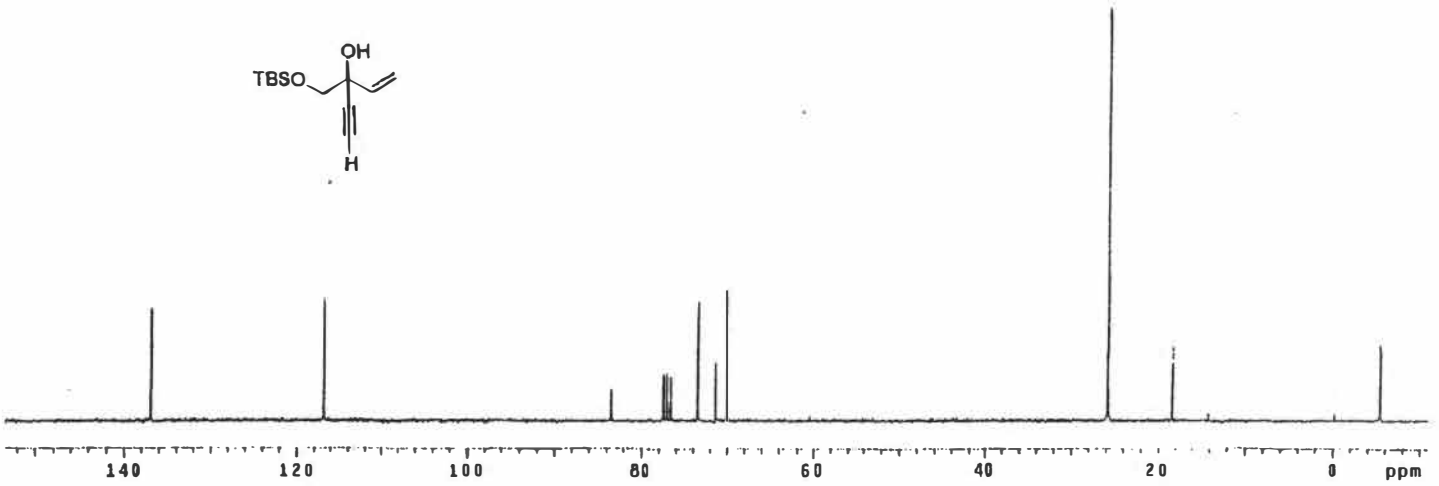
^{1}H NMR spectrum of 3-(*tert*-butyldimethylsilyloxymethyl)-5-trimethylsilylpent-1-en-4-yn-3-ol (**2.30**).



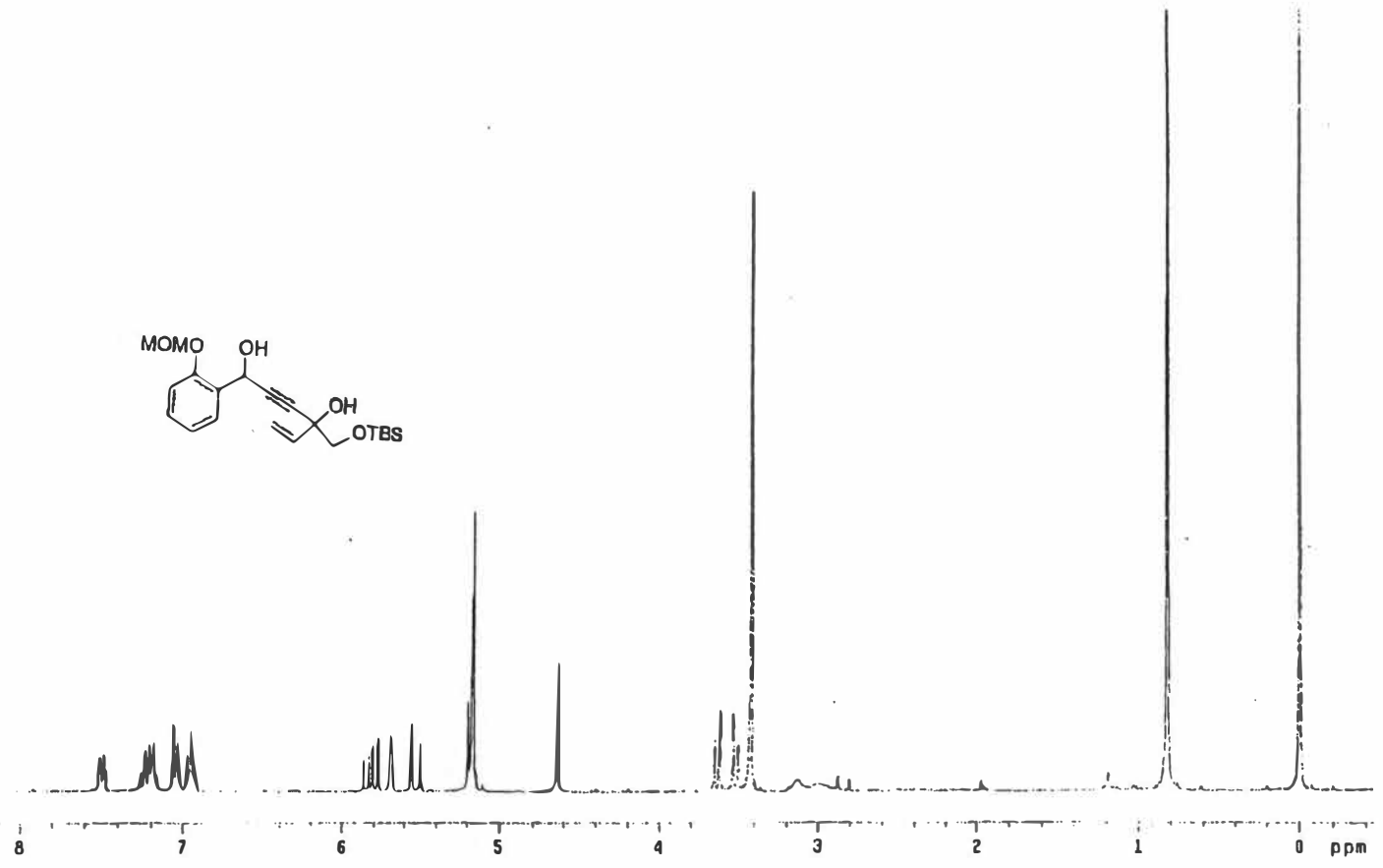
^{13}C NMR spectrum of 3-(*tert*-butyldimethylsilyloxymethyl)-5-trimethylsilylpent-1-en-4-yn-3-ol (**2.30**).



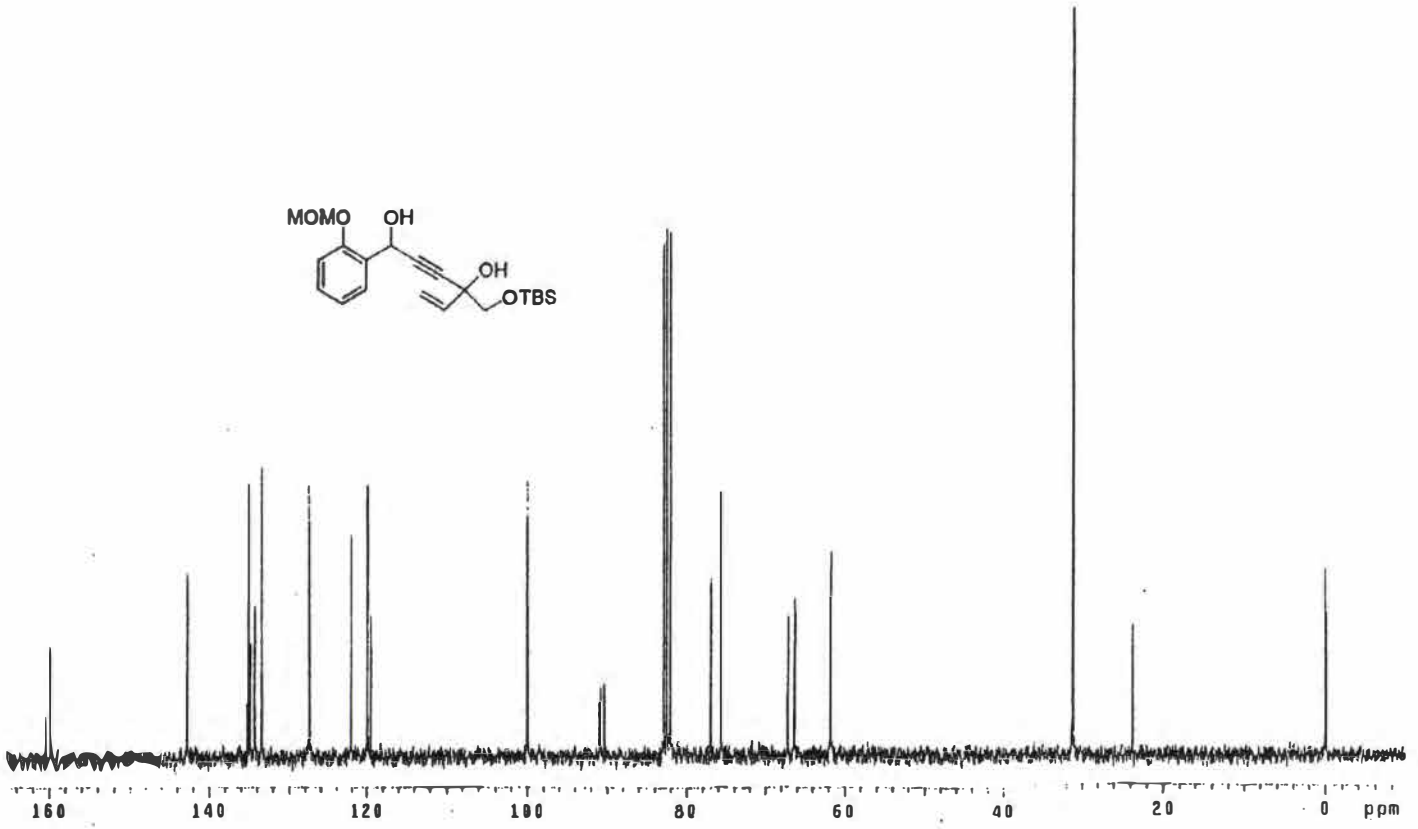
^{1}H NMR spectrum of 3-(*tert*-Butyldimethylsilyloxymethyl)pent-1-en-4-yn-3-ol (**2.31**).



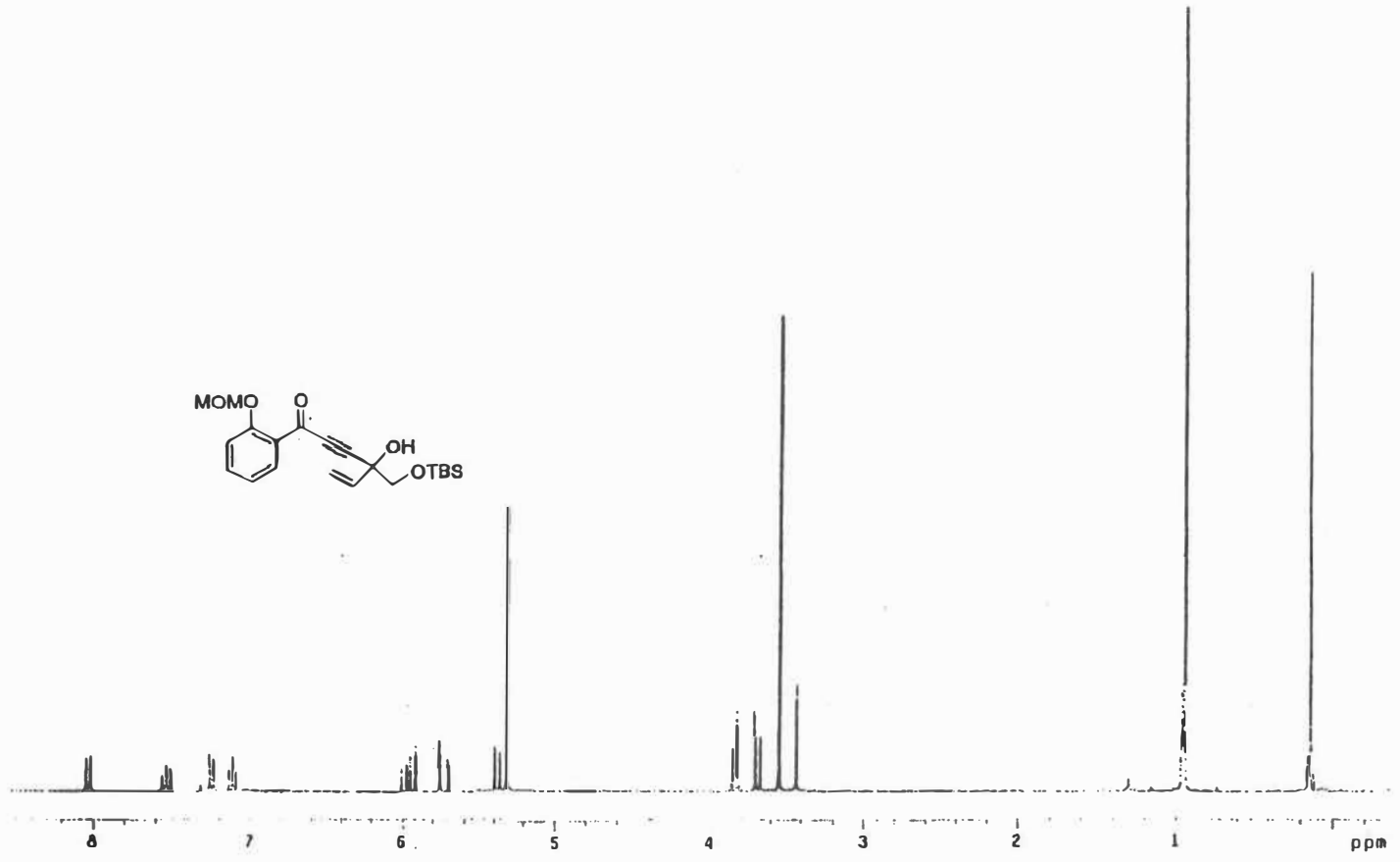
^{13}C NMR spectrum of 3-(*tert*-Butyldimethylsilyloxymethyl)pent-1-en-4-yn-3-ol (**2.31**).



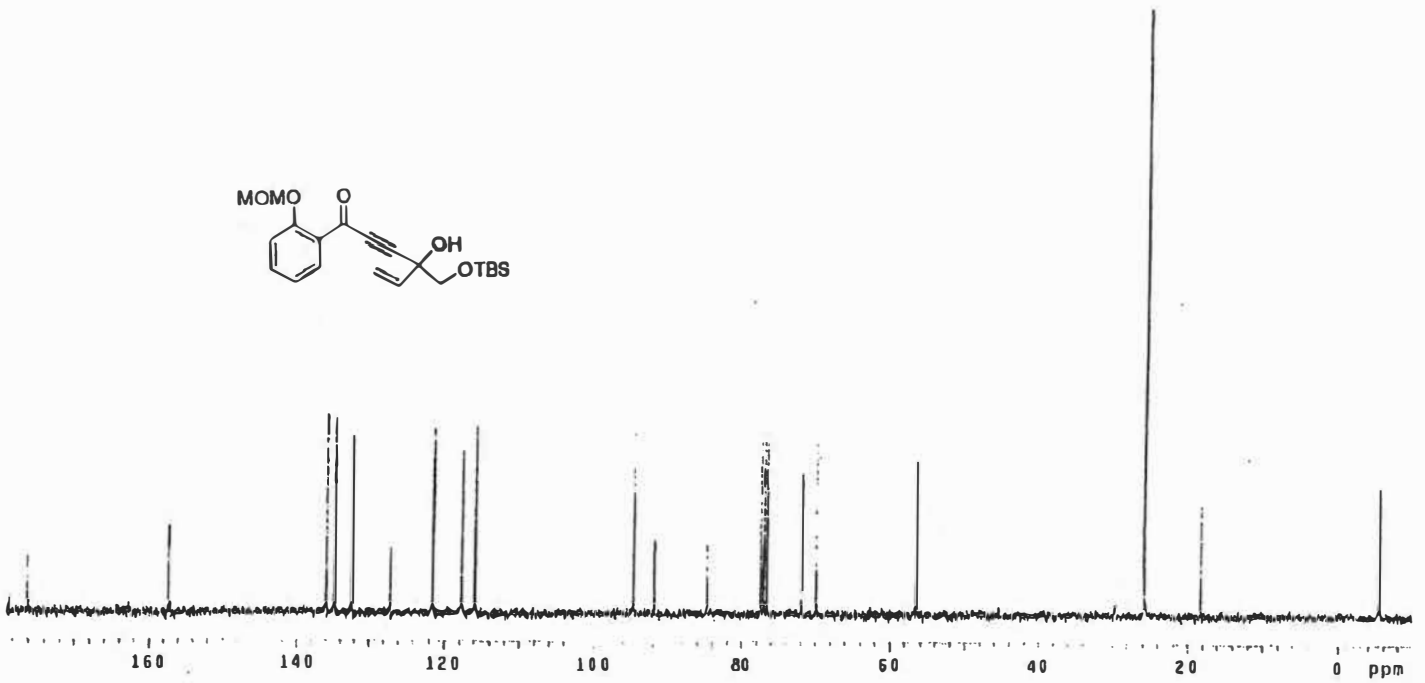
^{1}H NMR spectrum of 4-(*tert*-Butyldimethylsilyloxymethyl)-1-(2-methoxymethoxyphenyl)hex-5-en-2-yne 1,4-diol (**2.32**).



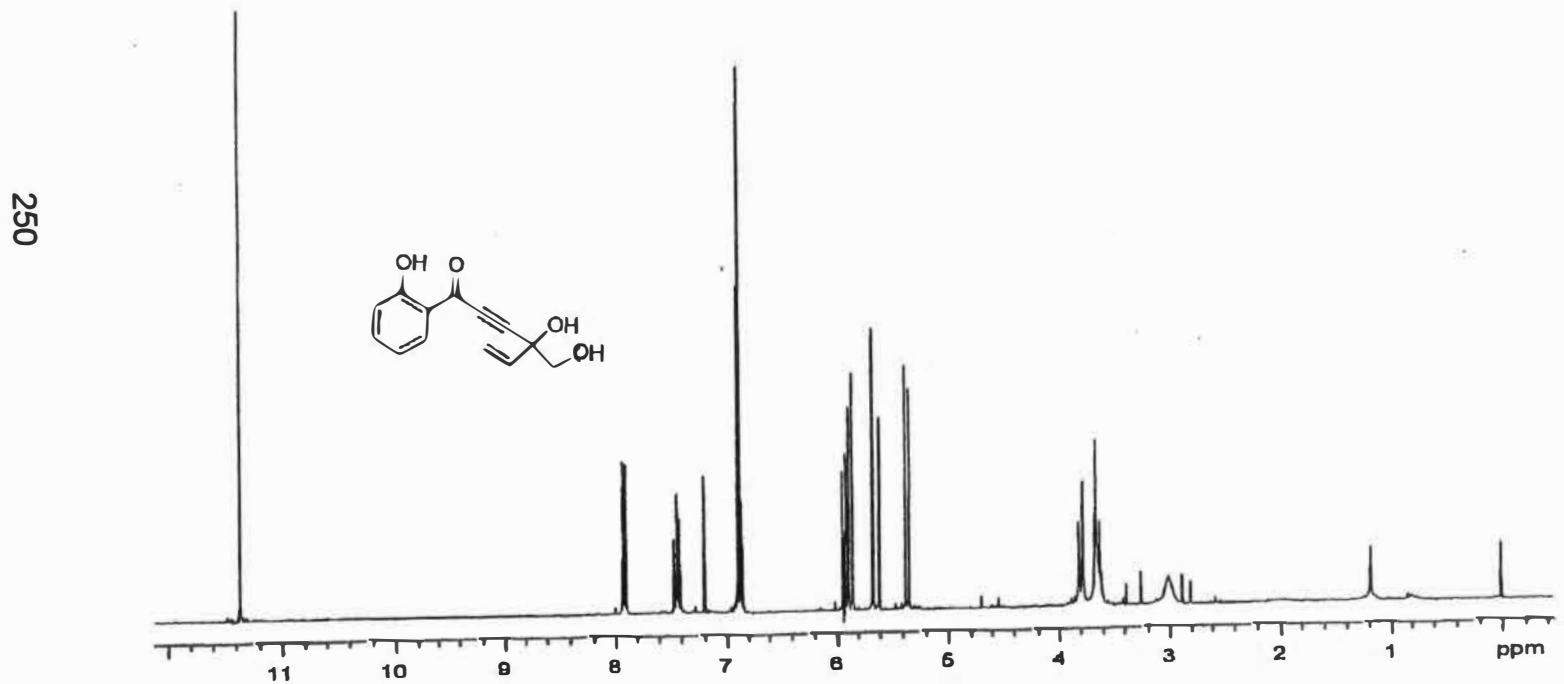
^{13}C NMR spectrum of 4-(*tert*-Butyldimethylsilyloxymethyl)-1-(2-methoxymethoxyphenyl)hex-5-en-2-yne 1,4-diol (**2.32**).



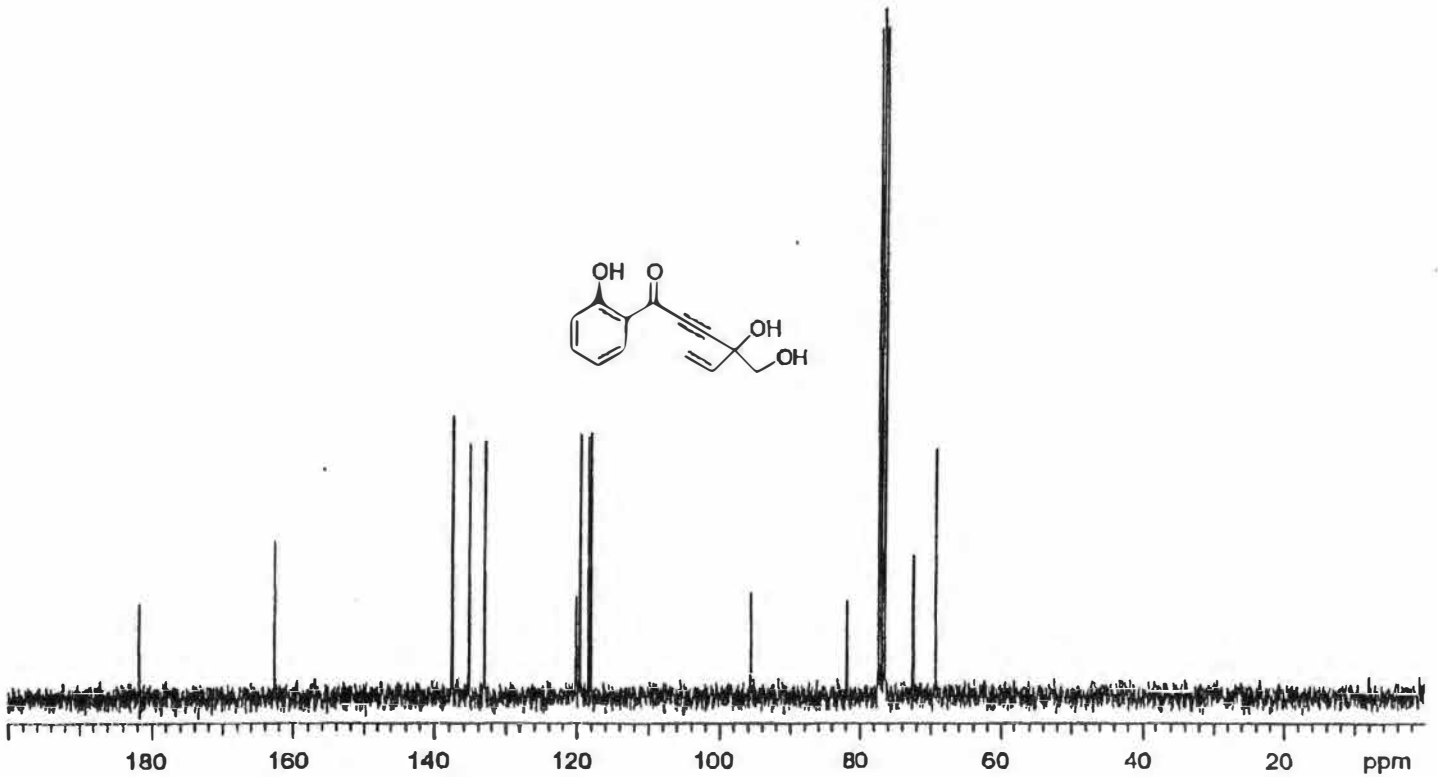
^{1}H NMR spectrum of 4-(*tert*-Butyldimethylsilyloxymethyl)-4-hydroxy-1-(2-methoxymethoxyphenyl)hex-5-en-2-yn-one (**2.33**).



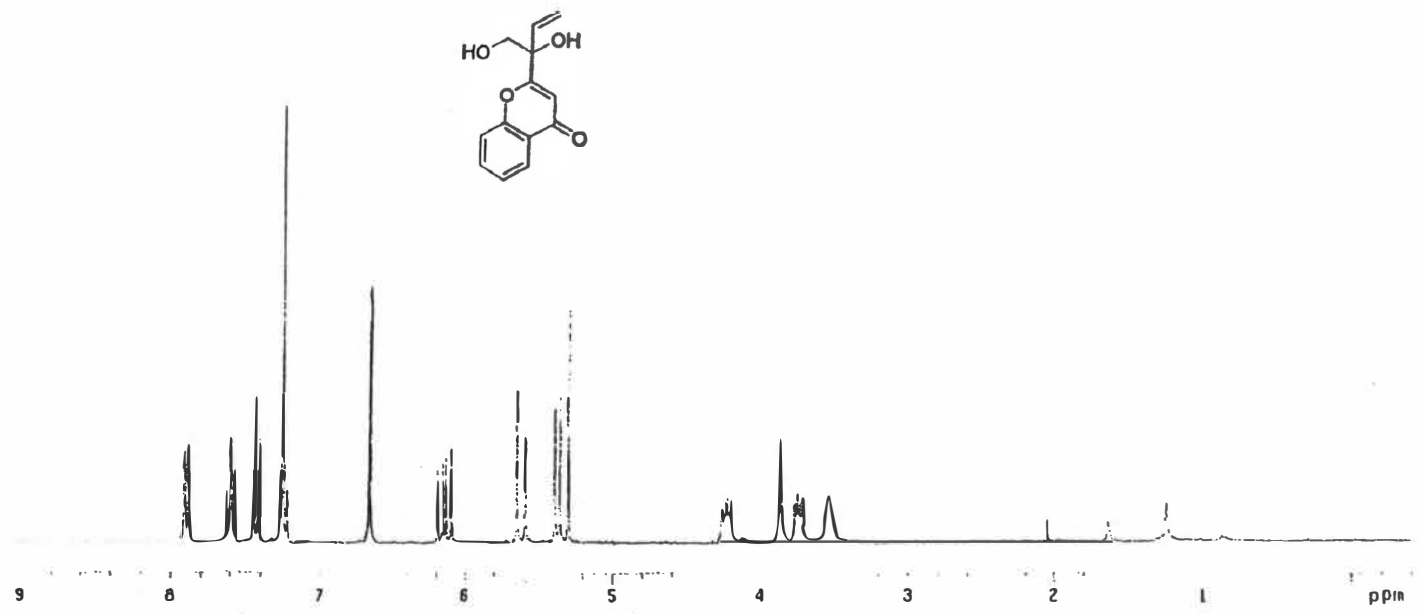
^{13}C NMR spectrum of 4-(*tert*-Butyldimethylsilyloxymethyl)-4-hydroxy-1-(2-methoxymethoxyphenyl)hex-5-en-2-yn-one (**2.33**).



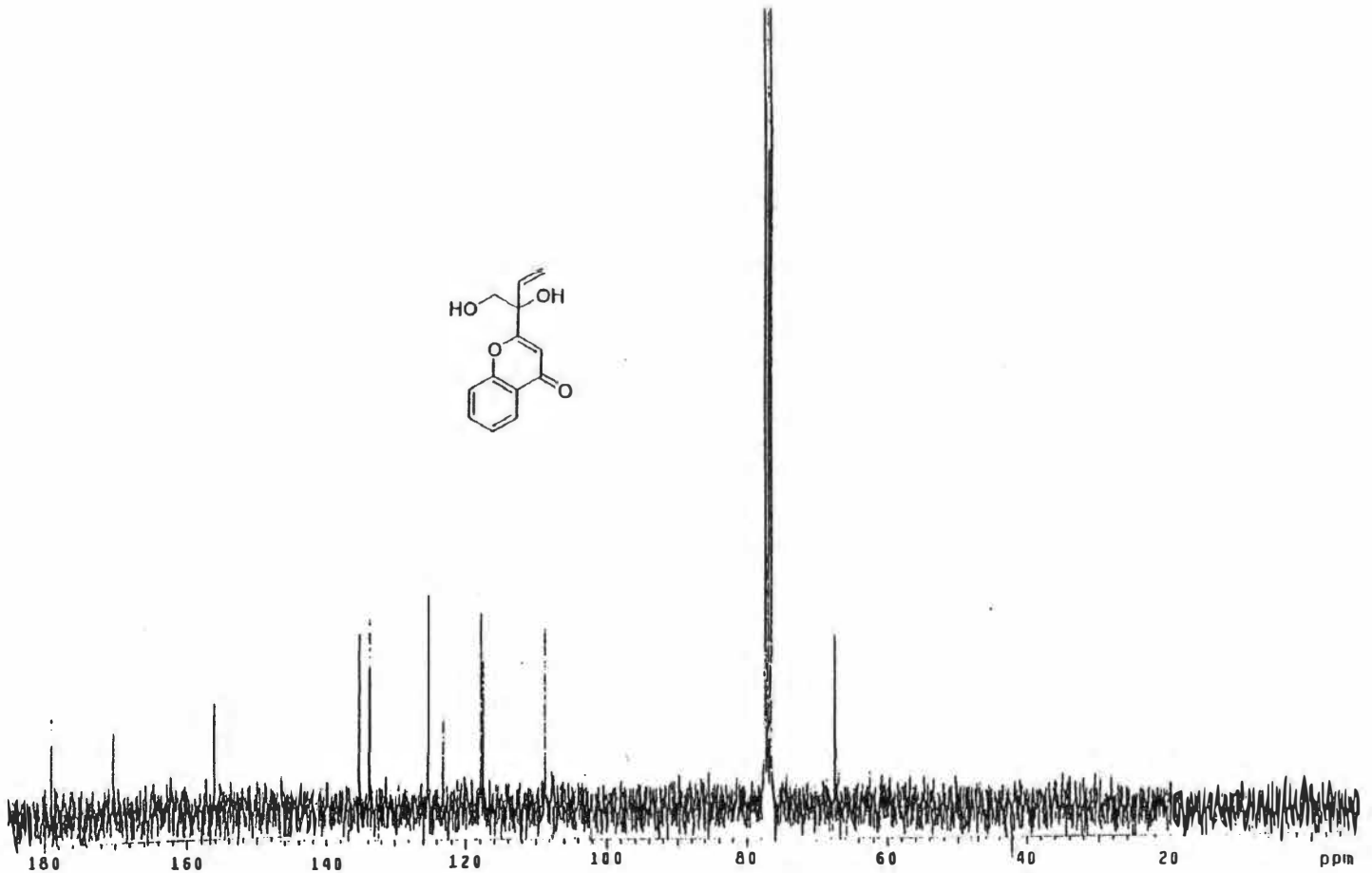
^{1}H NMR spectrum of 4-Hydroxy-4-hydroxymethyl-1-(2-hydroxyphenyl)hex-5-en-2-yn-1-one (**2.34**).



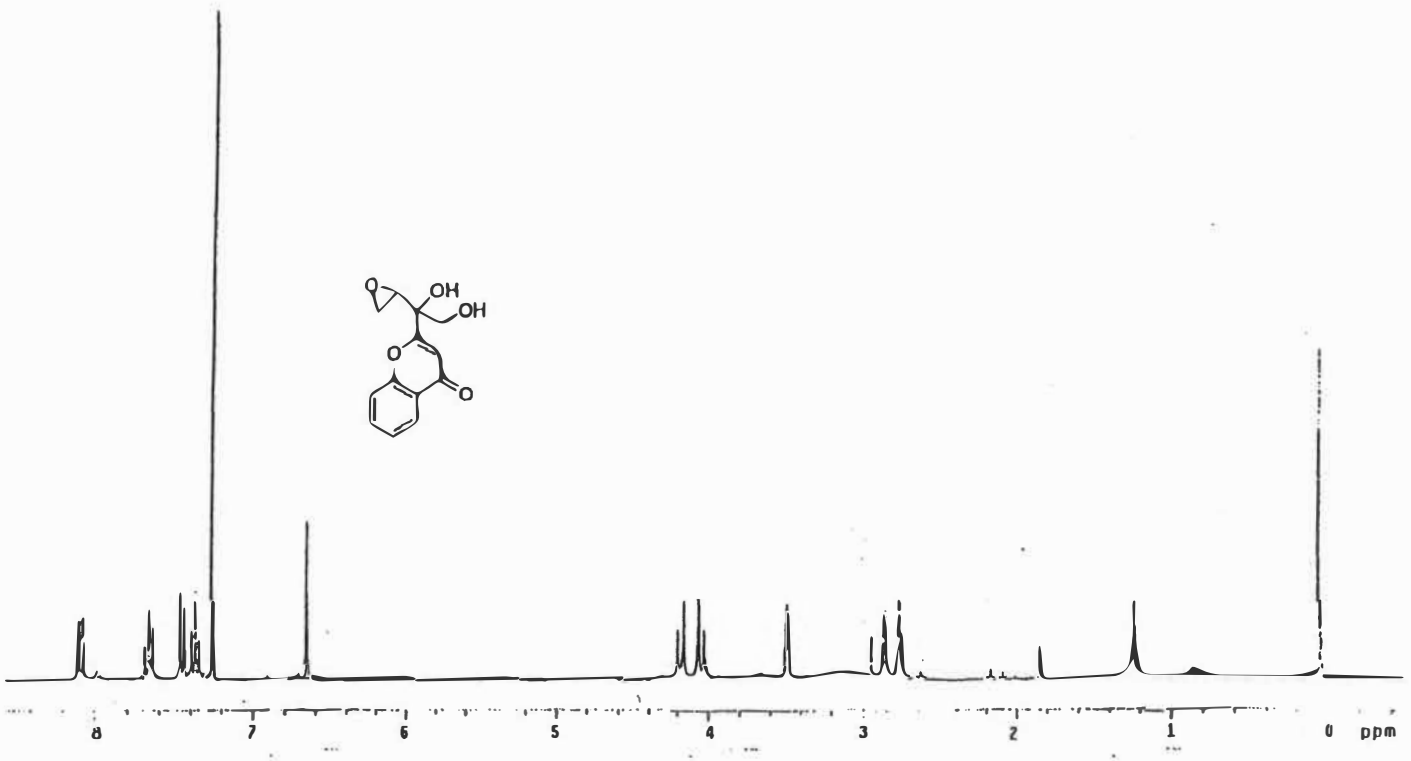
^{13}C NMR spectrum of 4-Hydroxy-4-hydroxymethyl-1-(2-hydroxyphenyl)hex-5-en-2-yn-1-one (**2.34**).



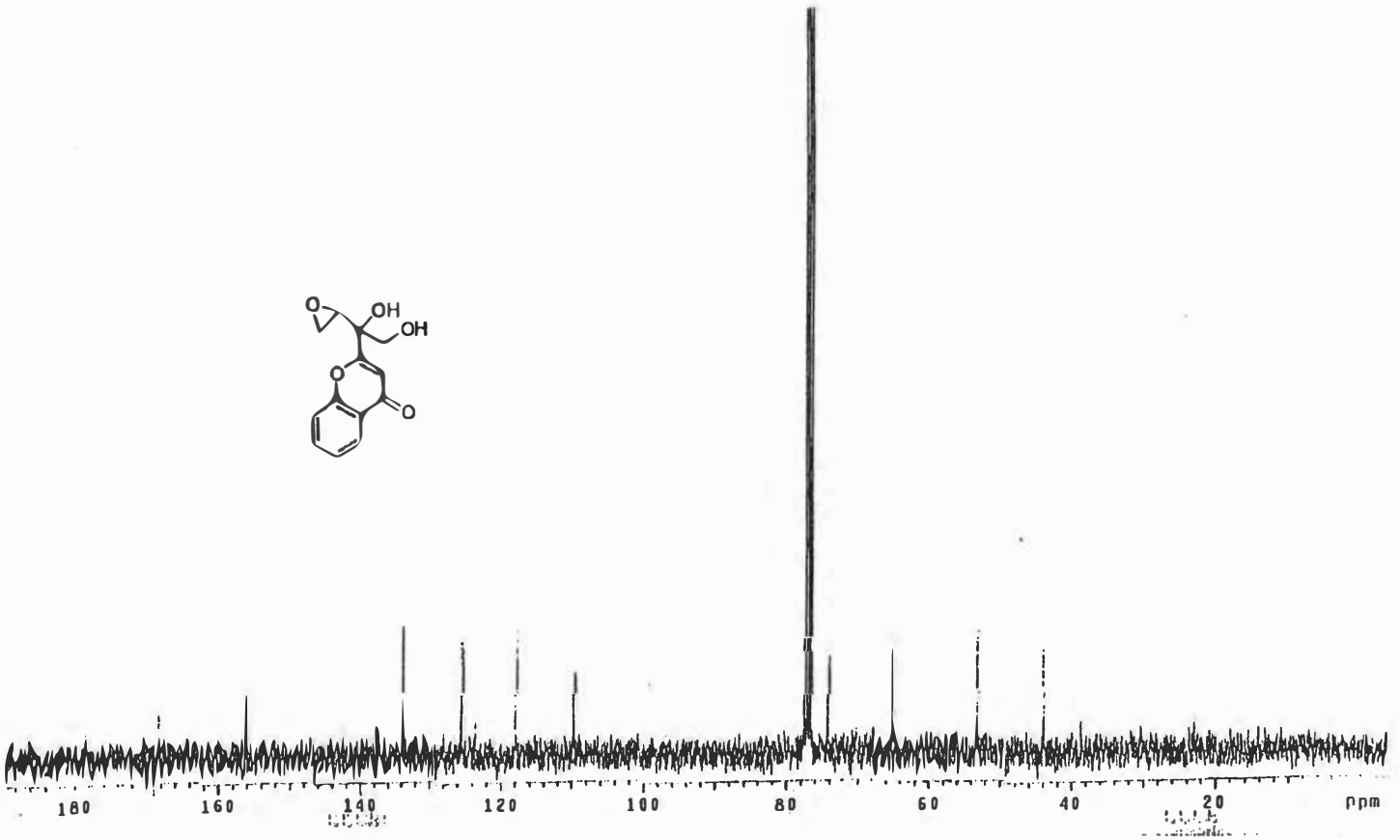
^{1}H NMR spectrum of 2-(1-Hydroxy-1-hydroxymethylallyl)chromen-4-one (**2.35**).



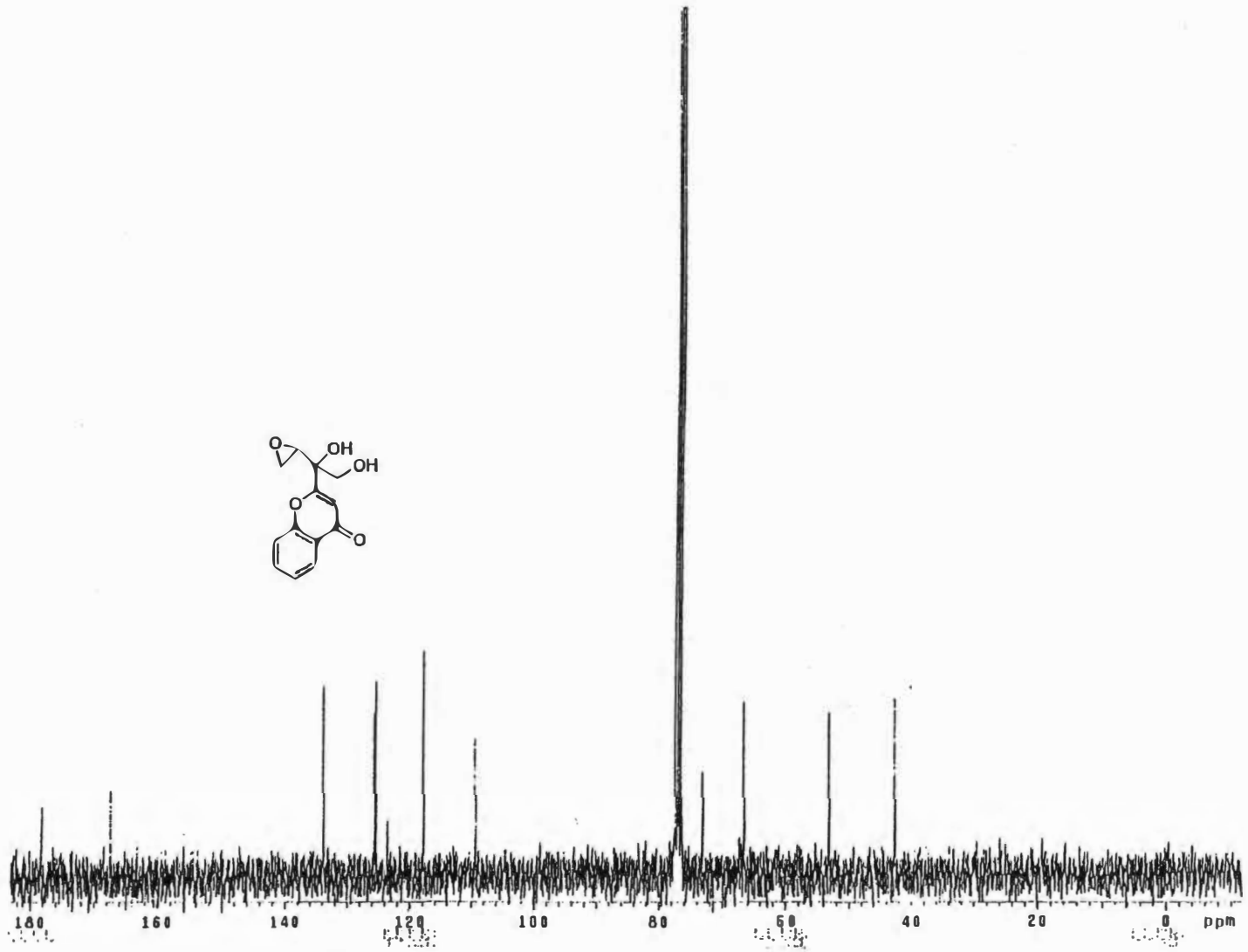
^{13}C NMR spectrum of 2-(1-Hydroxy-1-hydroxymethylallyl)chromen-4-one (**2.35**).



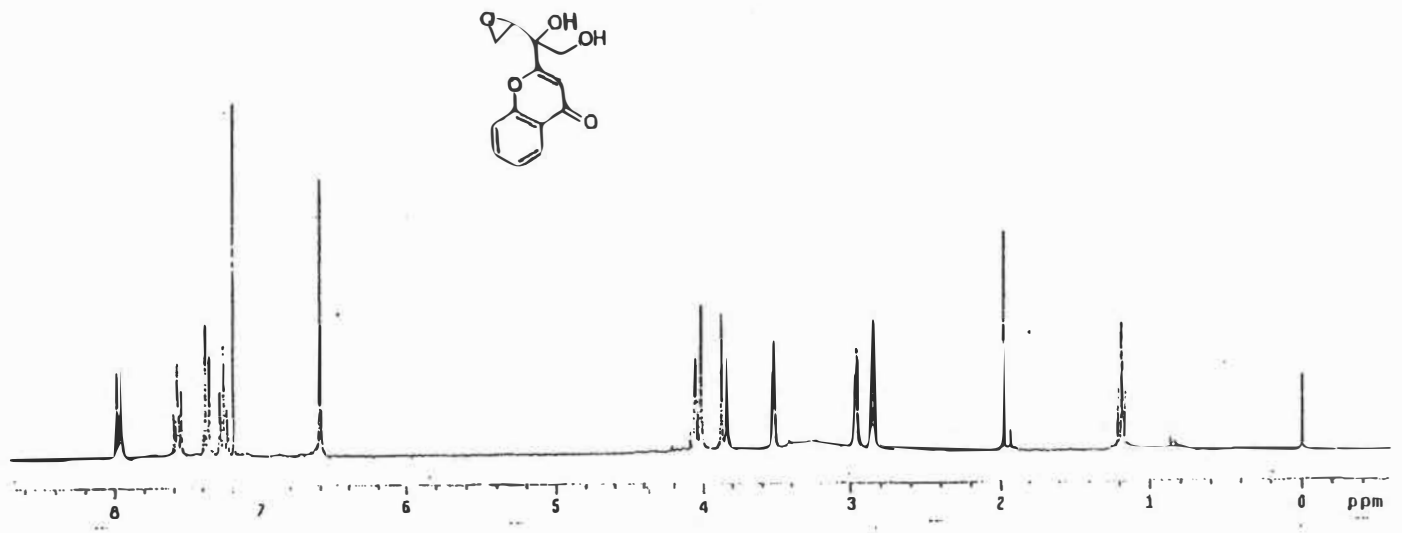
^{1}H NMR spectrum of 2-(1,2-Dihydroxy-1-oxiranylethyl)-chromen-4-one, Diastereomer A (**2.36**).



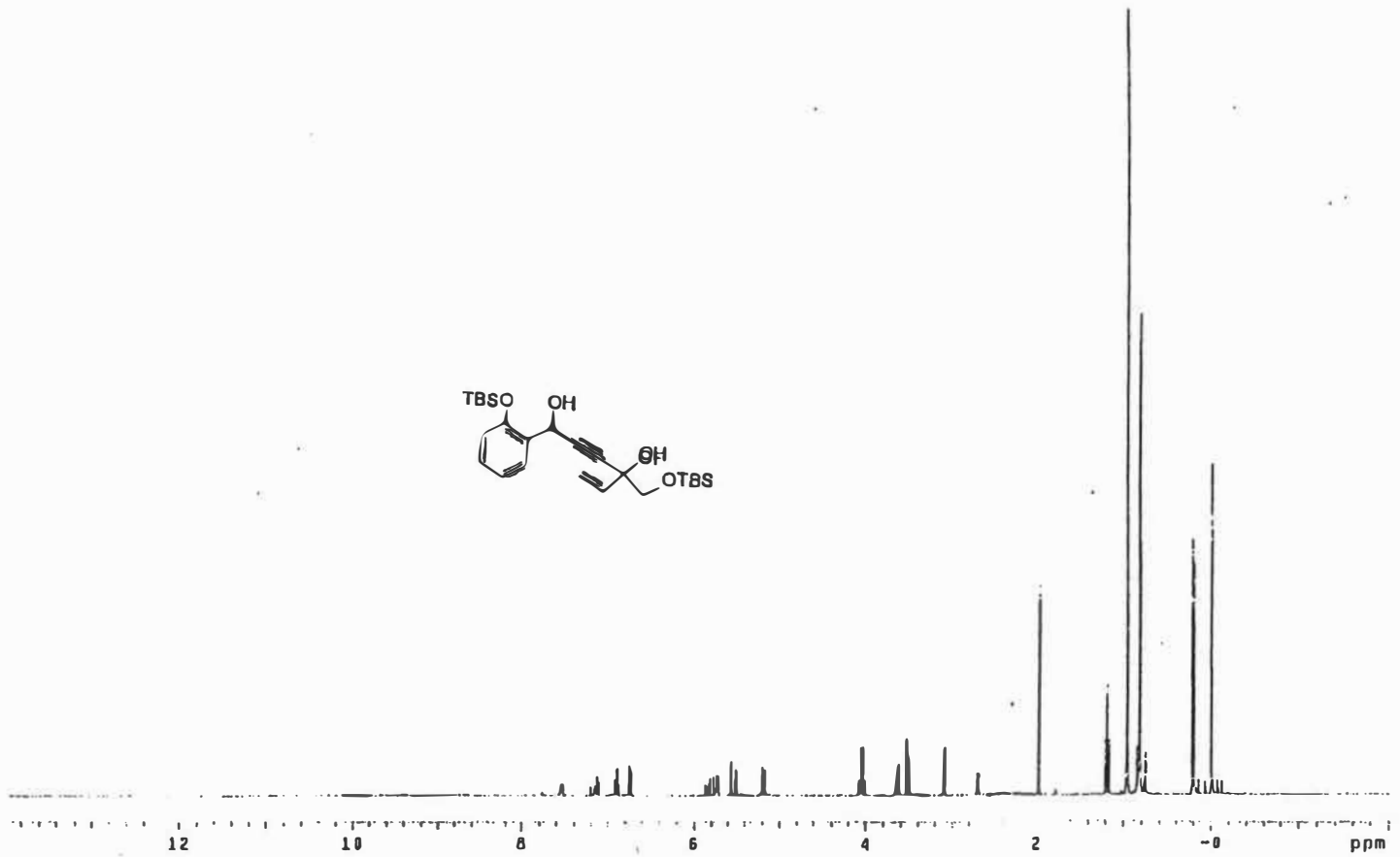
^{13}C NMR spectrum of 2-(1,2-Dihydroxy-1-oxiranylethyl)-chromen-4-one, Diastereomer A (**2.36**).



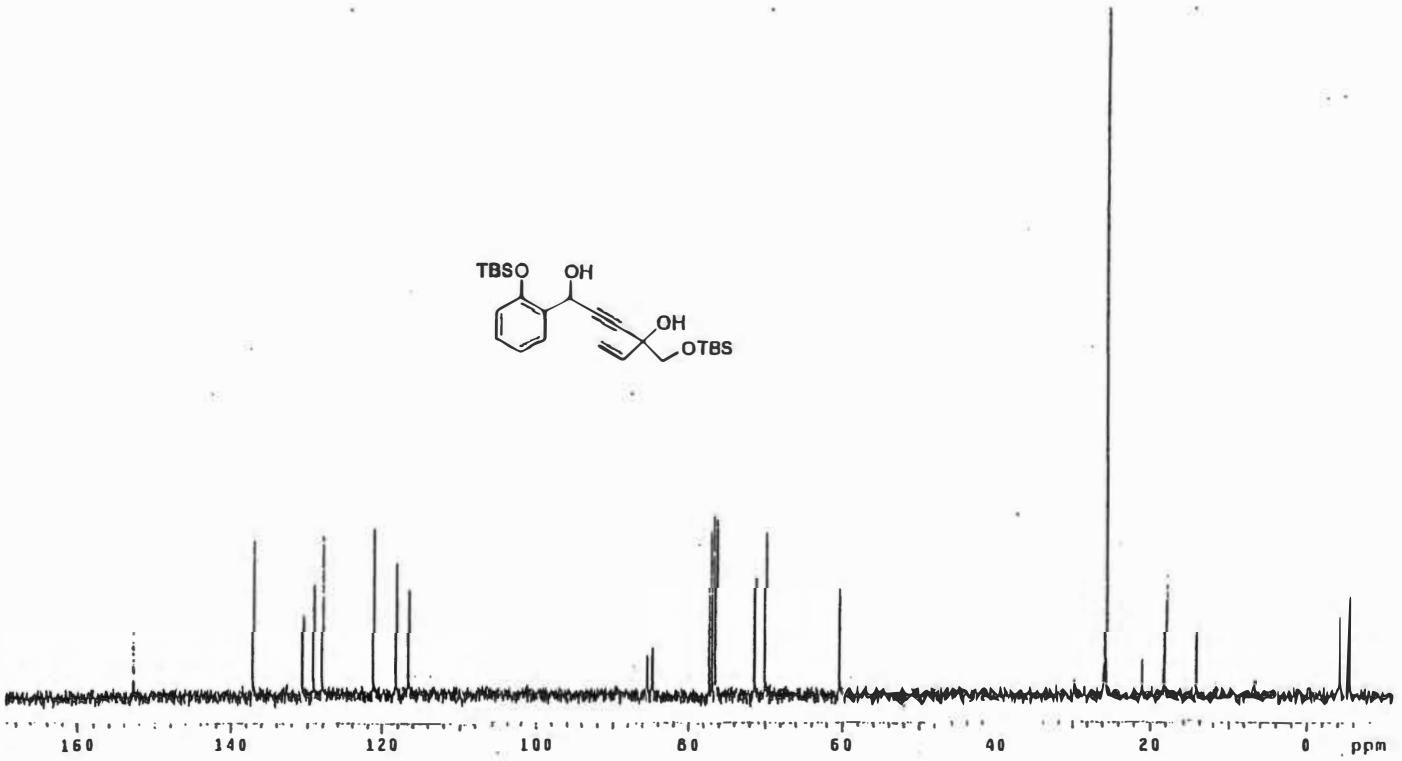
^{13}C NMR spectrum of 2-(1,2-Dihydroxy-1-oxiranylethyl)-chromen-4-one, Diastereomer B (**2.36**).



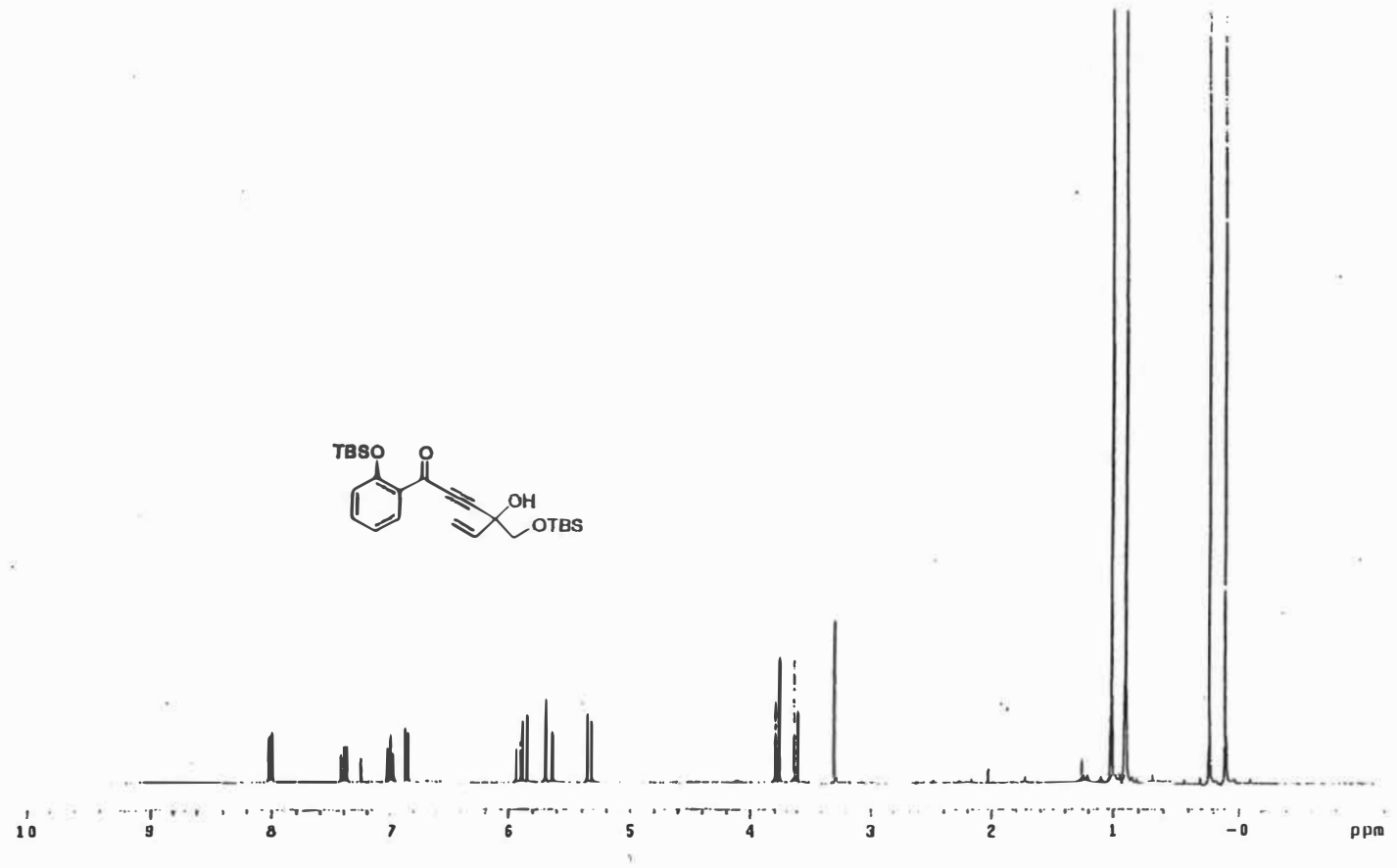
^{1}H NMR spectrum of 2-(1,2-Dihydroxy-1-oxiranylethyl)-chromen-4-one, Diastereomer B (**2.36**).



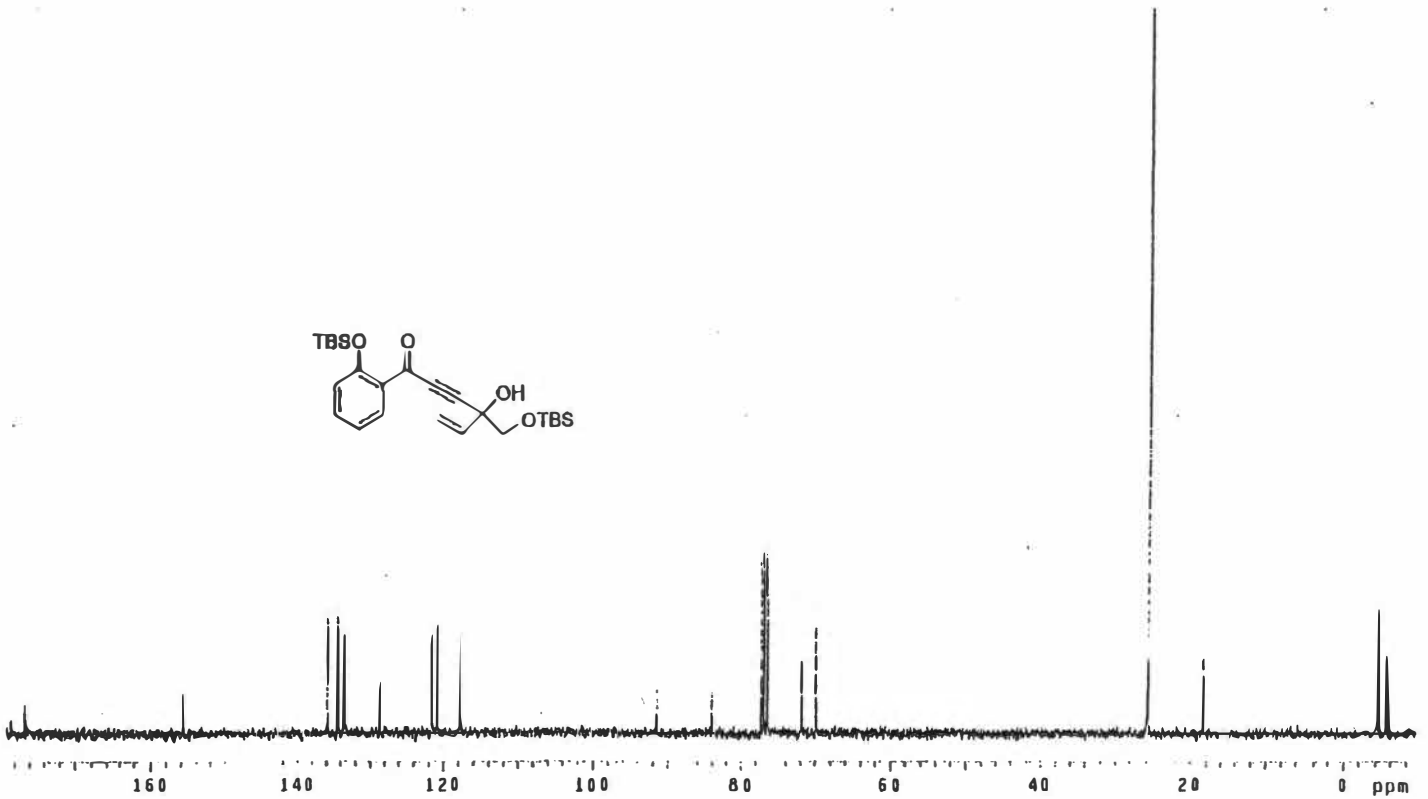
^{1}H NMR spectrum of 4-(*tert*-Butyldimethylsilyloxymethyl)-1-[2-(*tert*-butyldimethylsilyloxy)phenyl]hex-5-en-2-yne 1,4-diol (**2.37**).



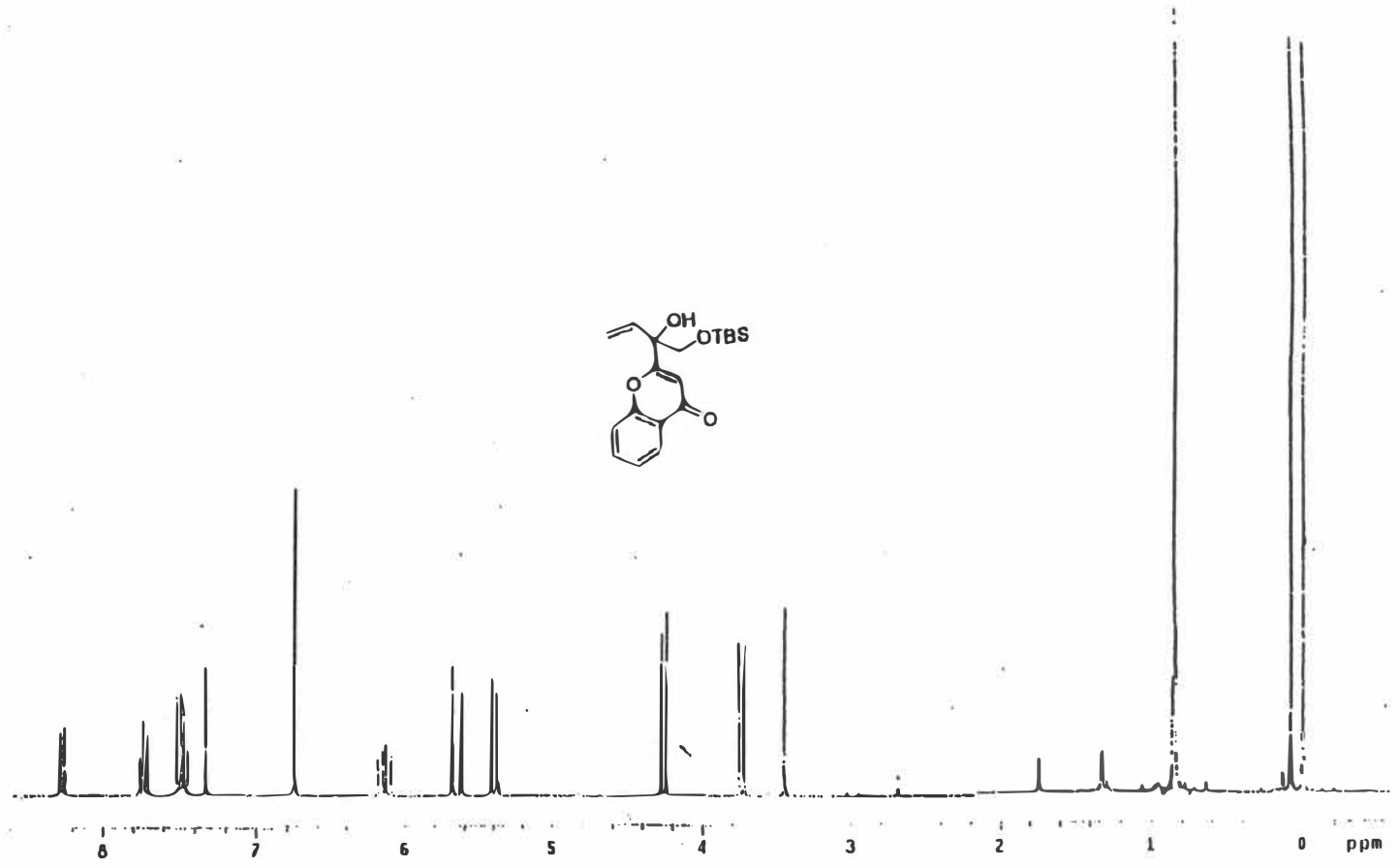
^{13}C NMR spectrum of 4-(*tert*-Butyldimethylsilyloxymethyl)-1-[2-(*tert*-butyldimethylsilyloxy)phenyl]hex-5-en-2-yne 1,4-diol (**2.37**).



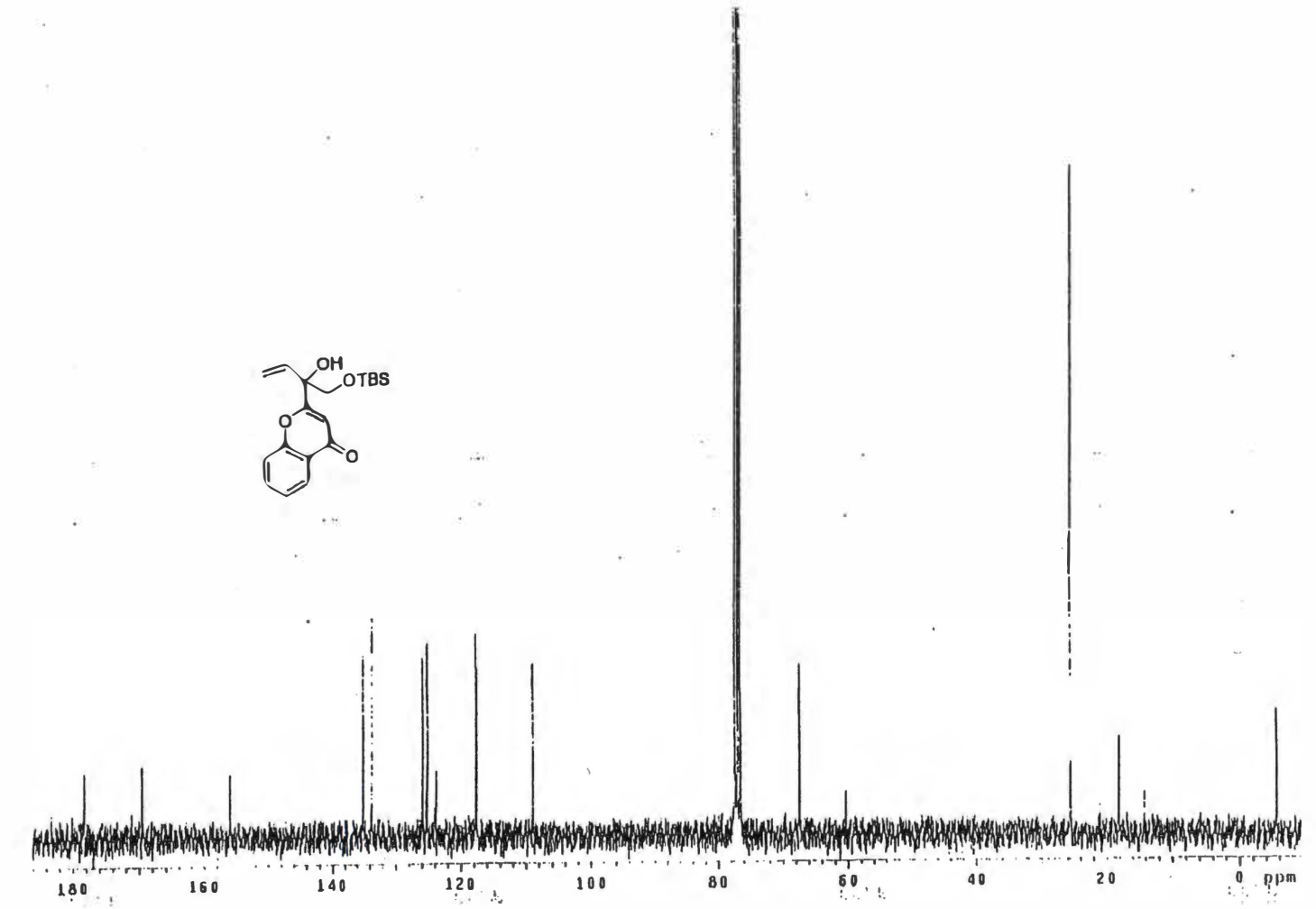
^{1}H NMR spectrum of 4-(*tert*-Butyldimethylsilyloxymethyl)-1-[2-(*tert*-butyldimethylsilyloxy)phenyl]-4-hydroxyhex-5-en-2-yn-1-one (**2.38**).



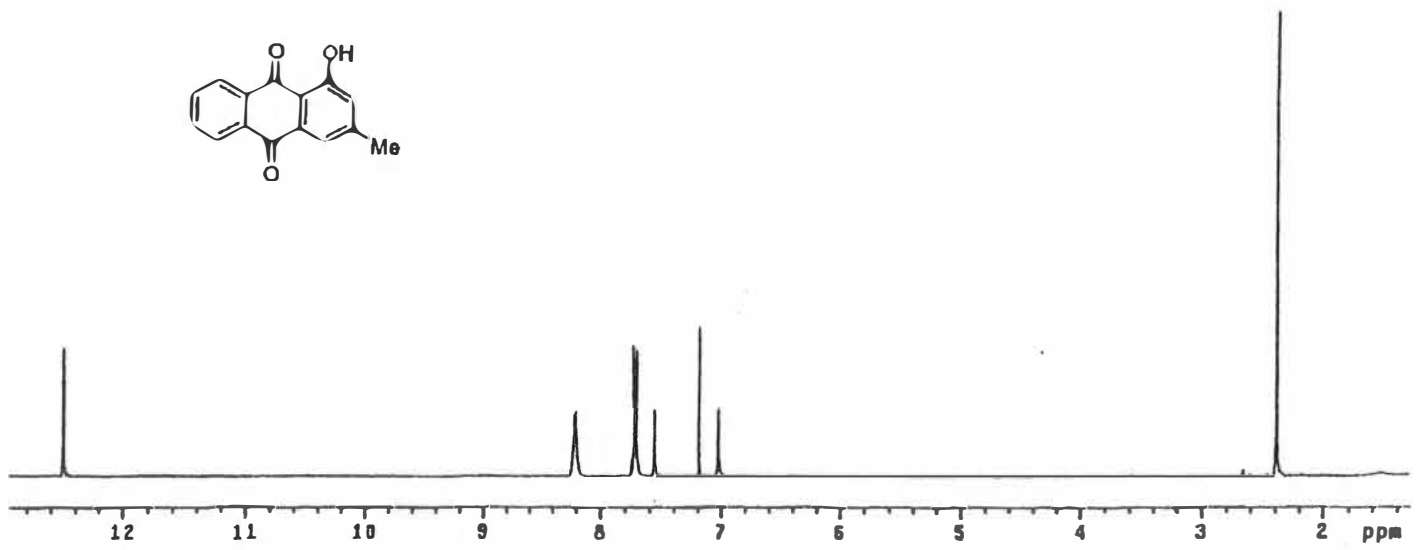
^{13}C NMR spectrum of 4-(*tert*-Butyldimethylsilyloxymethyl)-1-[2-(*tert*-butyldimethylsilyloxy)phenyl]-4-hydroxyhex-5-en-2-yn-1-one (**2.38**).



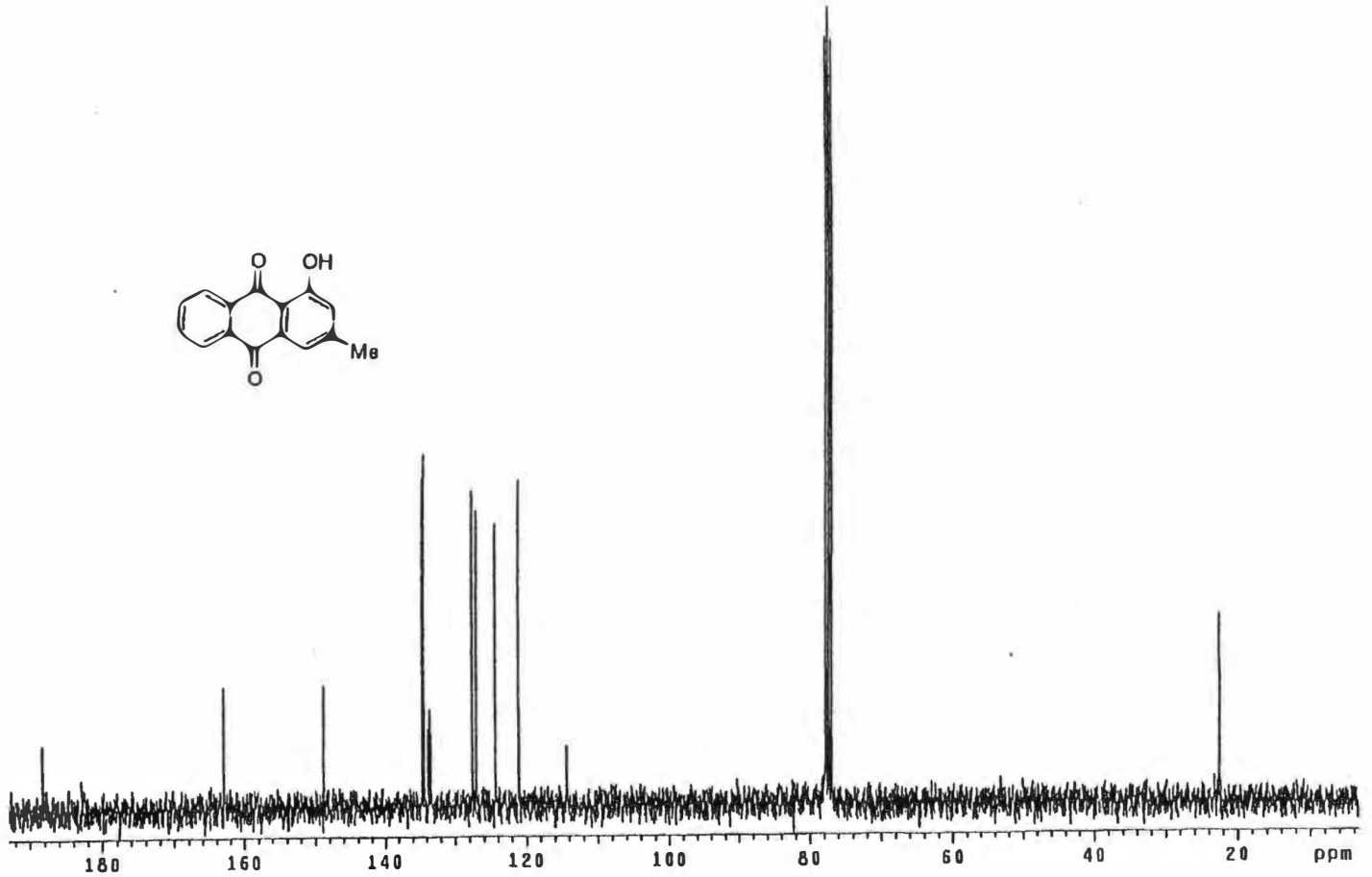
^{1}H NMR spectrum of 2-[1-(*tert*-Butyldimethylsilyloxymethyl)-1-hydroxyallyl]chromen-4-one (**2.39**).



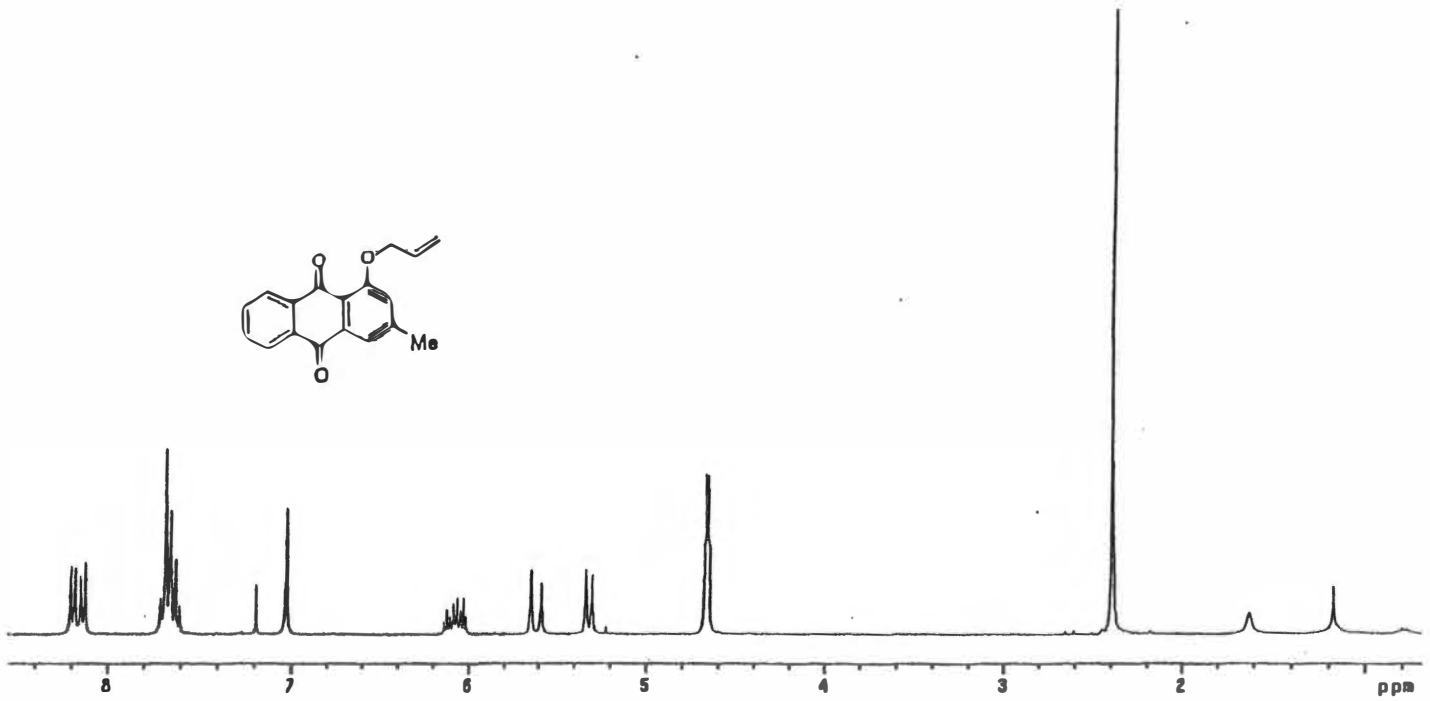
^{13}C NMR spectrum of 2-[1-(*tert*-Butyldimethylsilyloxymethyl)-1-hydroxyallyl]chromen-4-one (**2.39**).



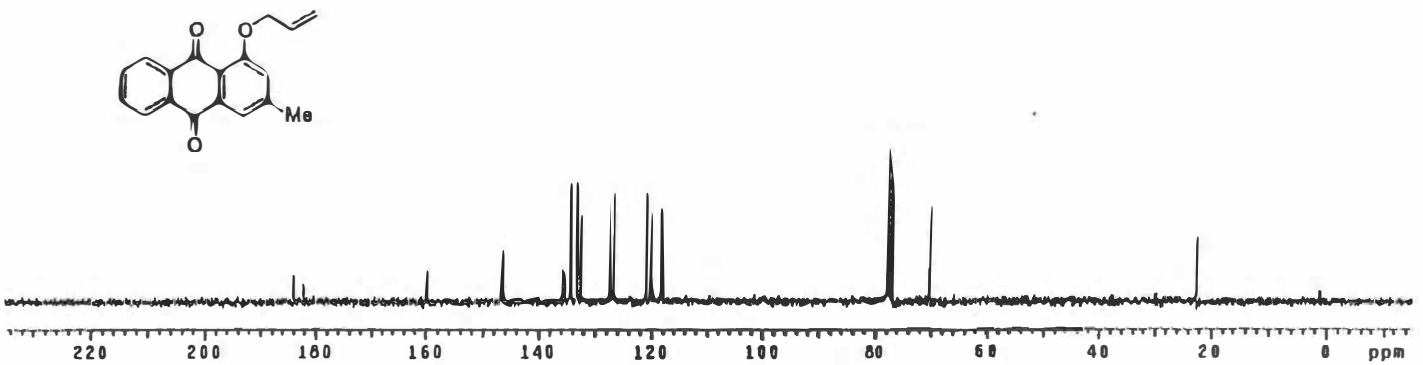
^{1}H NMR spectrum of 1-Hydroxy-3-methylanthraquinone (**2.40**).



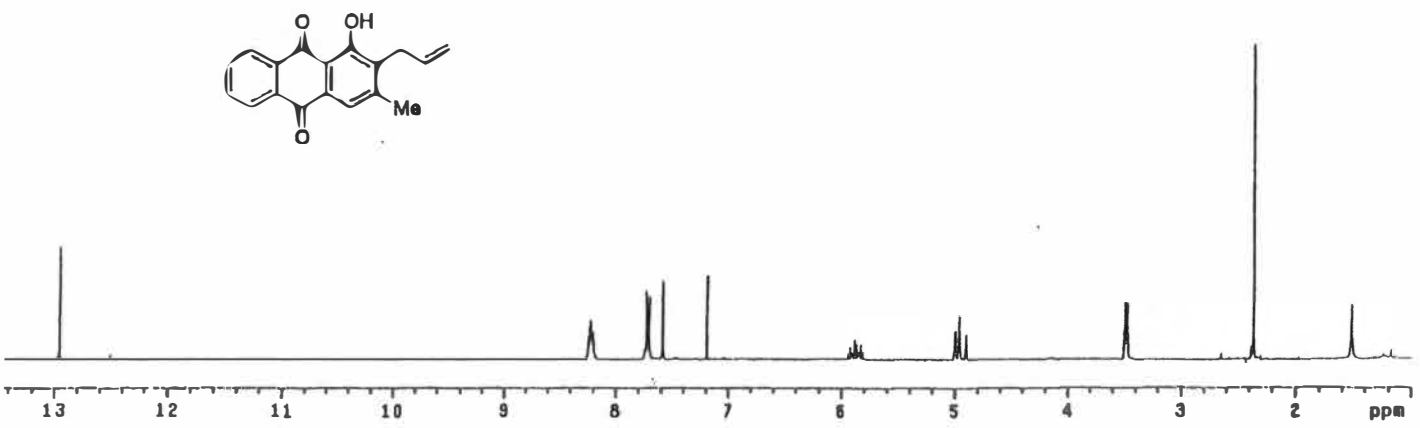
^{13}C NMR spectrum of 1-Hydroxy-3-methylanthraquinone (**2.40**).



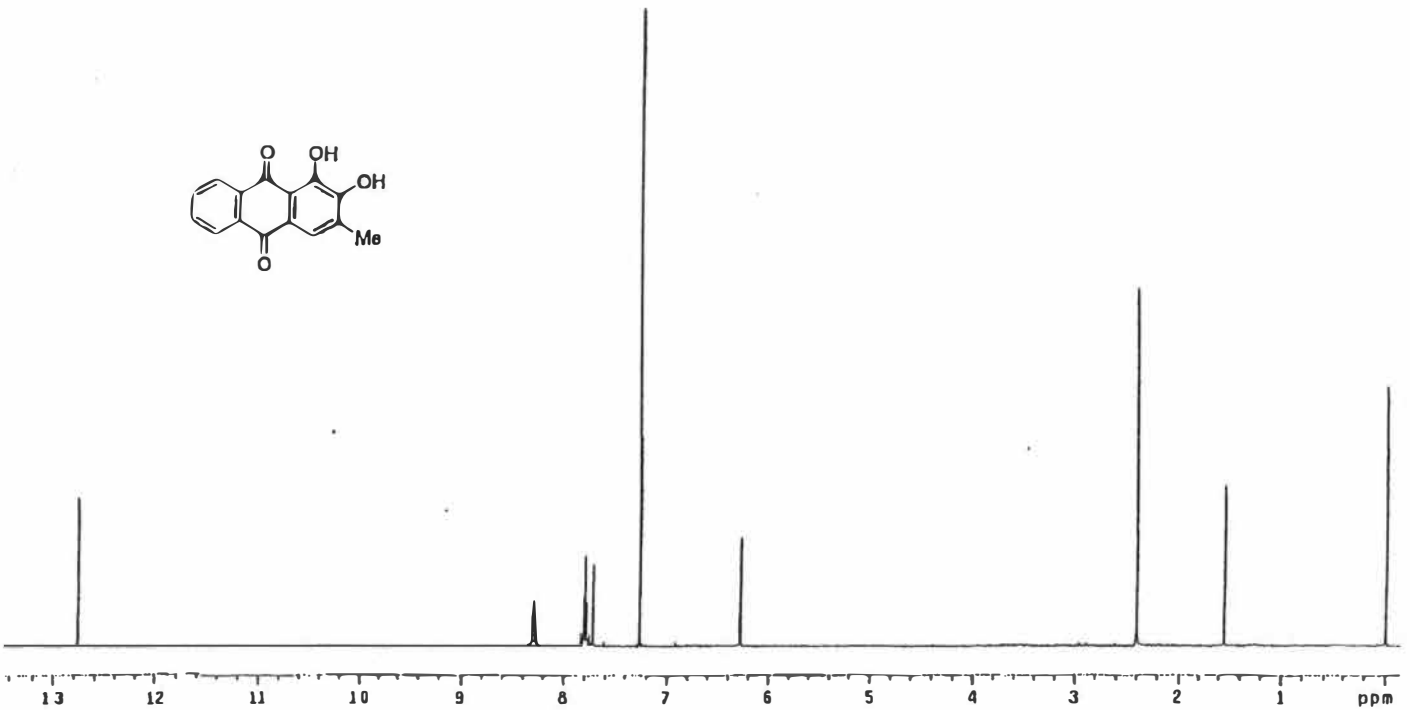
^{1}H NMR spectrum of 1-Allyloxy-3-methylanthraquinone (**2.41**).



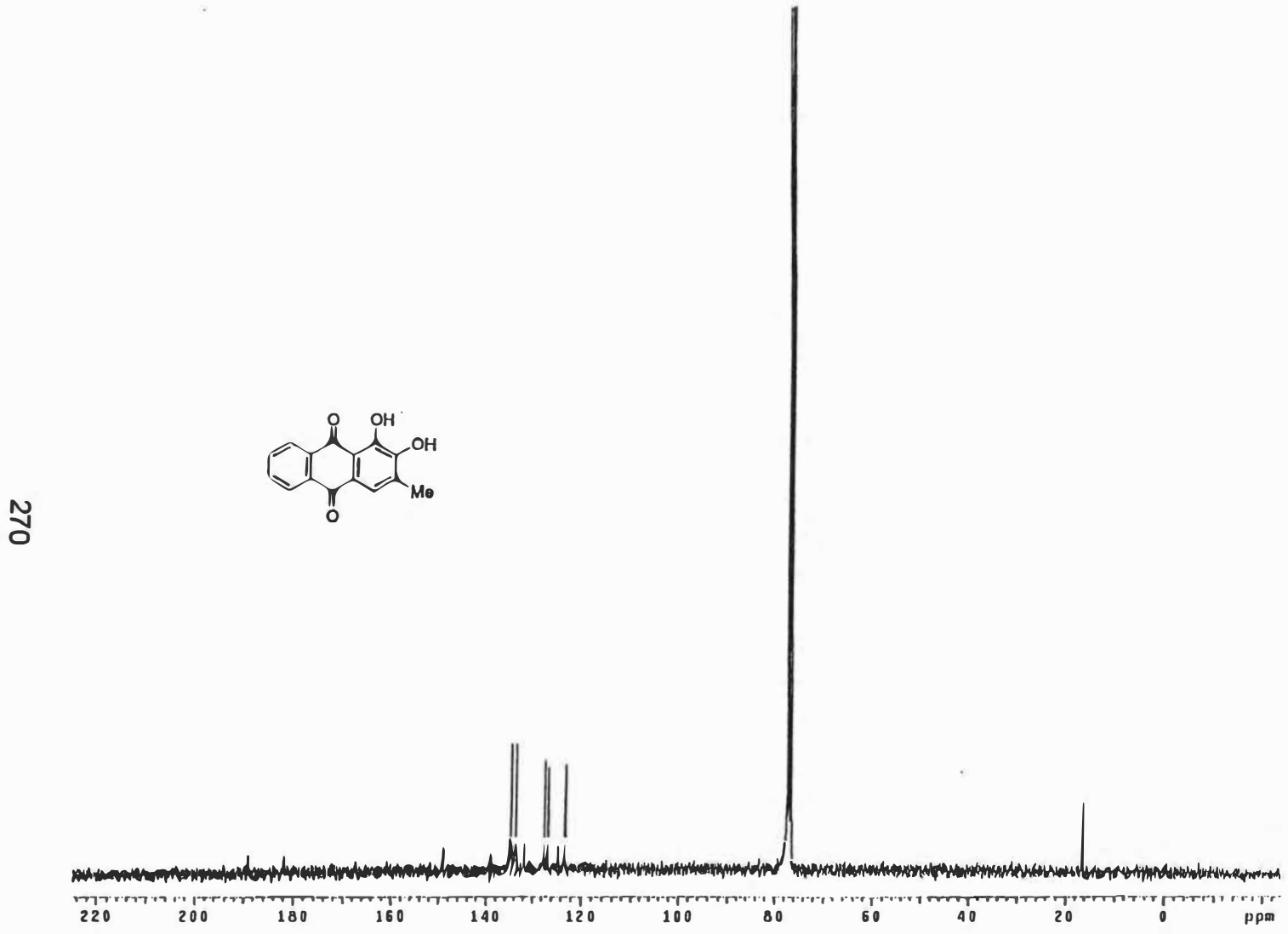
^{13}C NMR spectrum of 1-Allyloxy-3-methylanthraquinone (**2.41**).



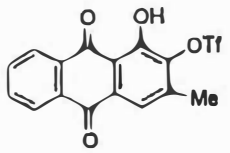
^{1}H NMR spectrum of 2-Allyloxy-1-hydroxy-3-methylanthraquinone (**2.42**).

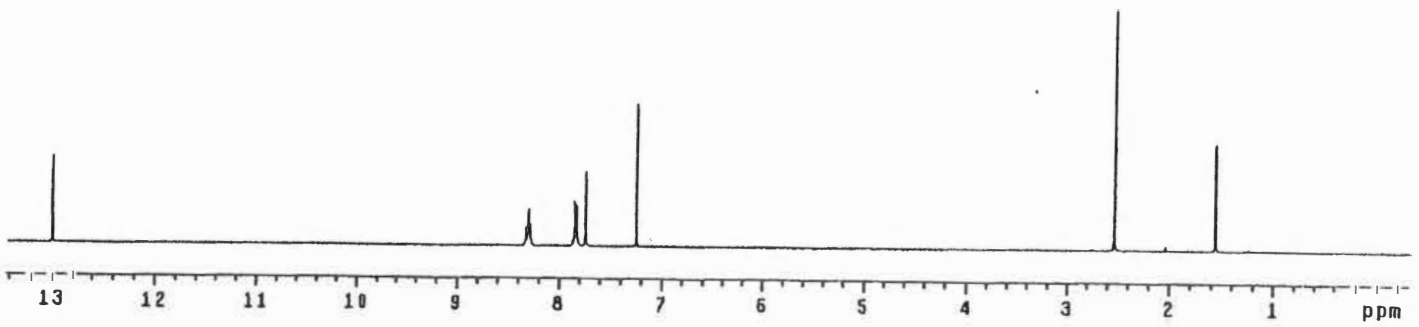


^{1}H NMR spectrum of 1,2-Dihydroxy-3-methylanthraquinone (**2.43**).

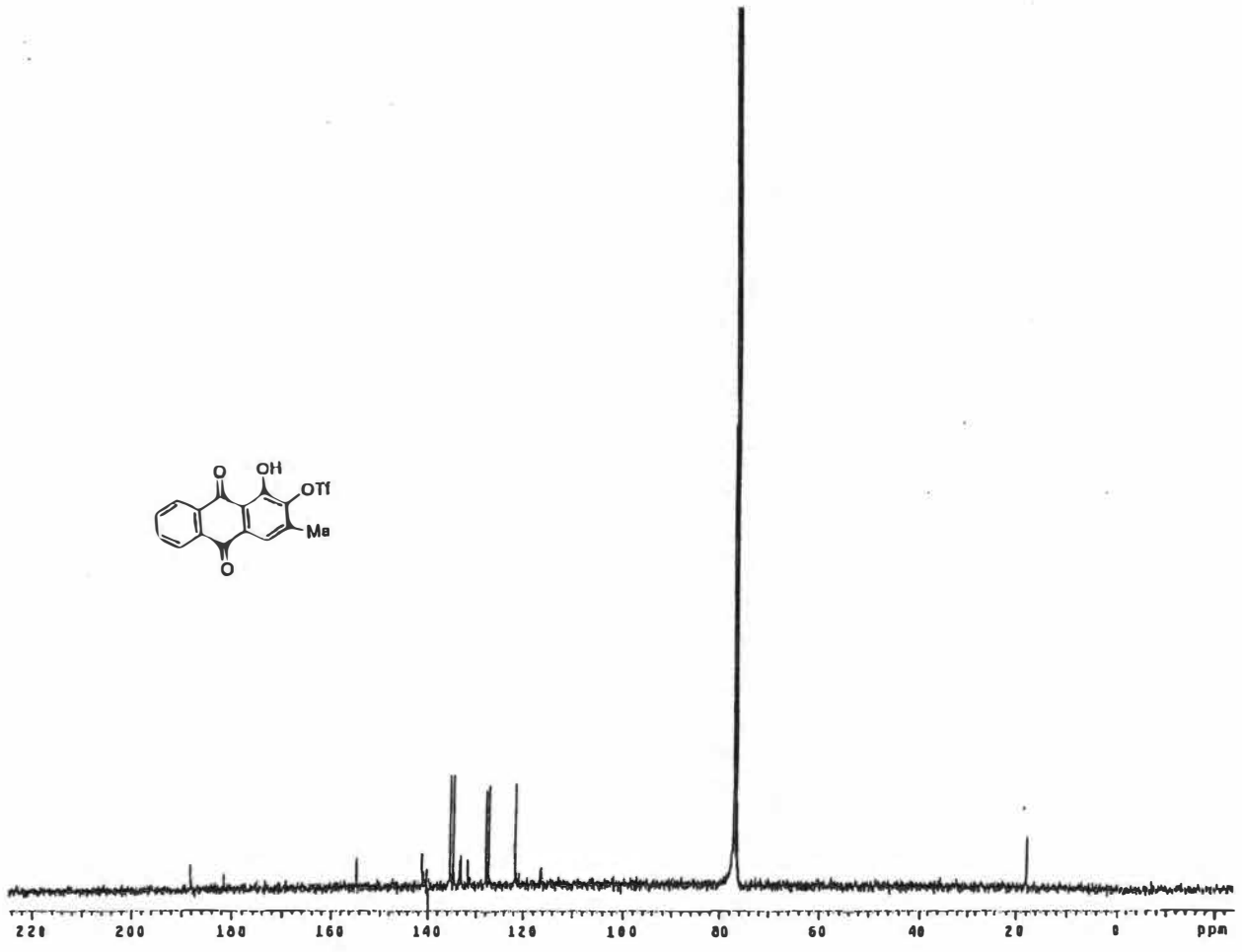


^{13}C NMR spectrum of 1,2-Dihydroxy-3-methylanthraquinone (**2.43**).

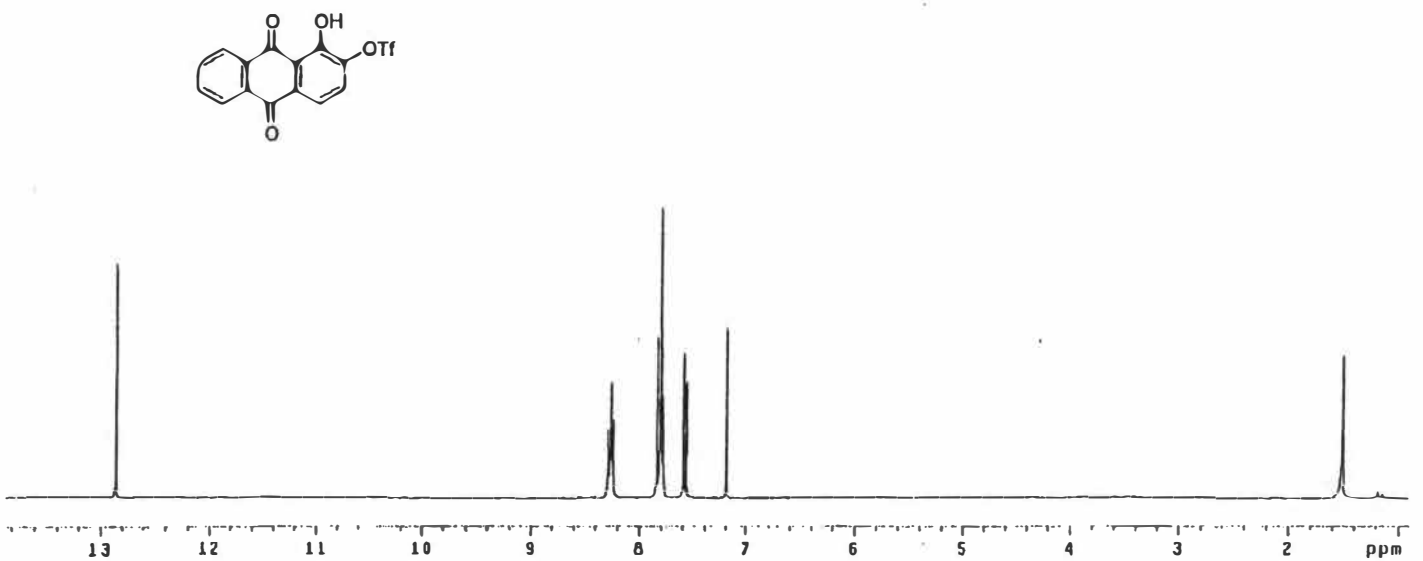




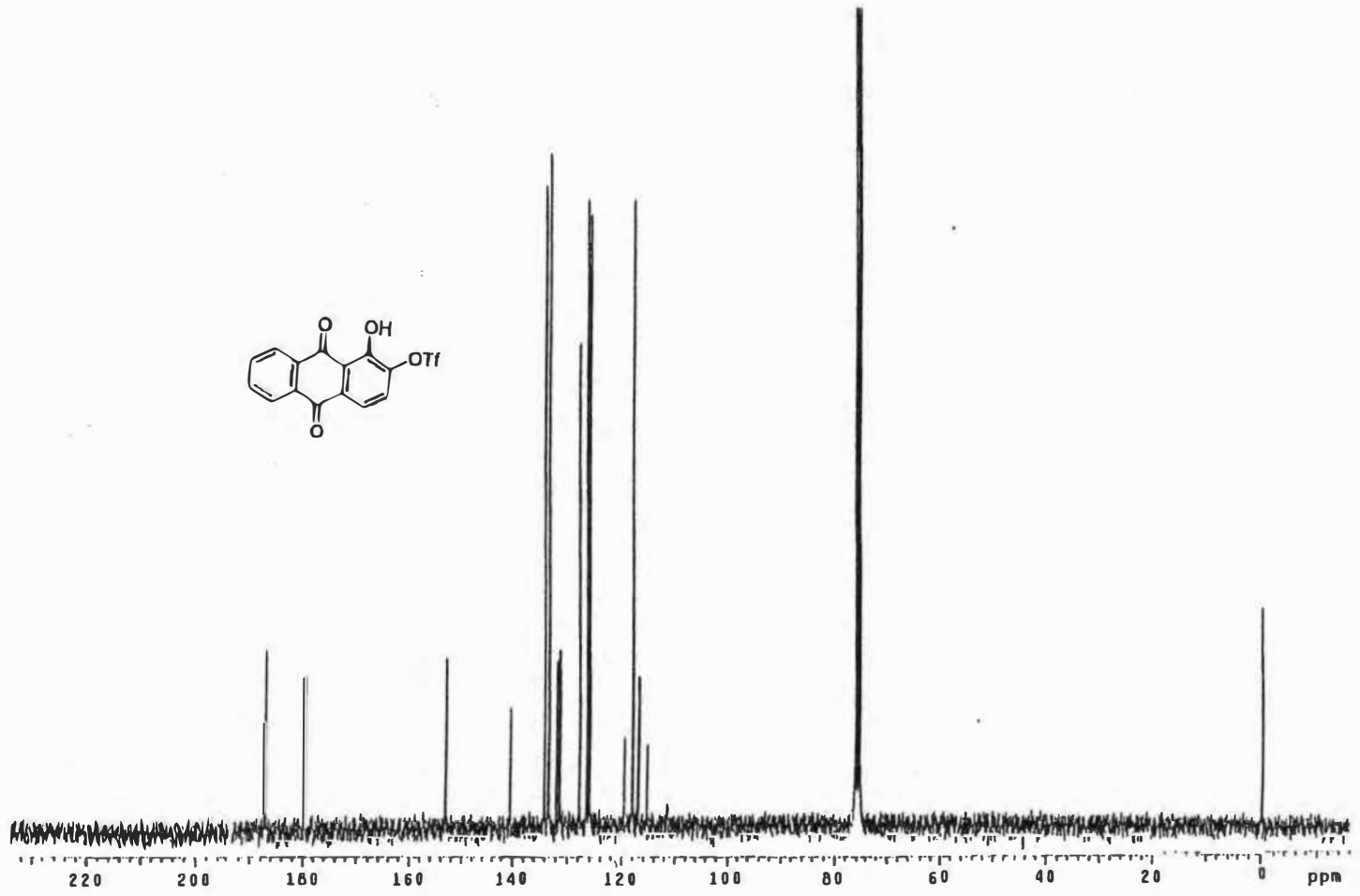
^{1}H NMR spectrum of Trifluoromethanesulfonic acid 1-hydroxy-3-methyl-9,10-dioxo-9,10-dihydroanthracen-2-yester(**2.44**).



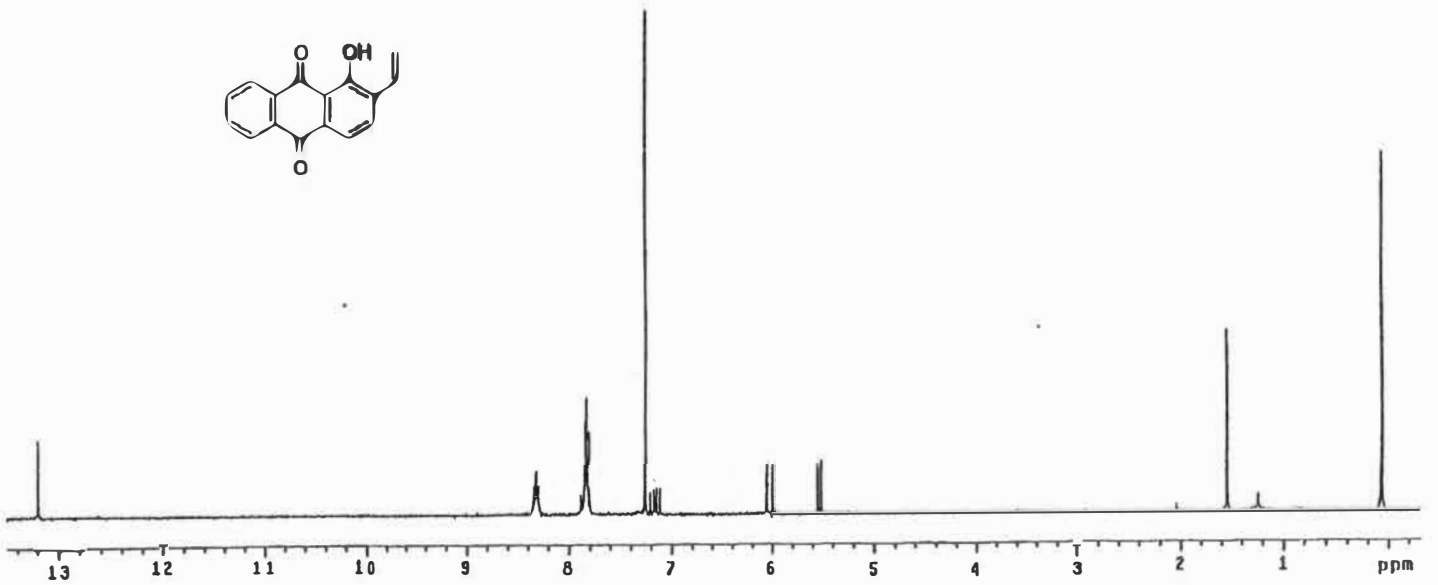
^{13}C NMR spectrum of Trifluoromethanesulfonic acid 1-hydroxy-3-methyl-9,10-dioxo-9,10-dihydroanthracen-2-yl ester (**2.44**).



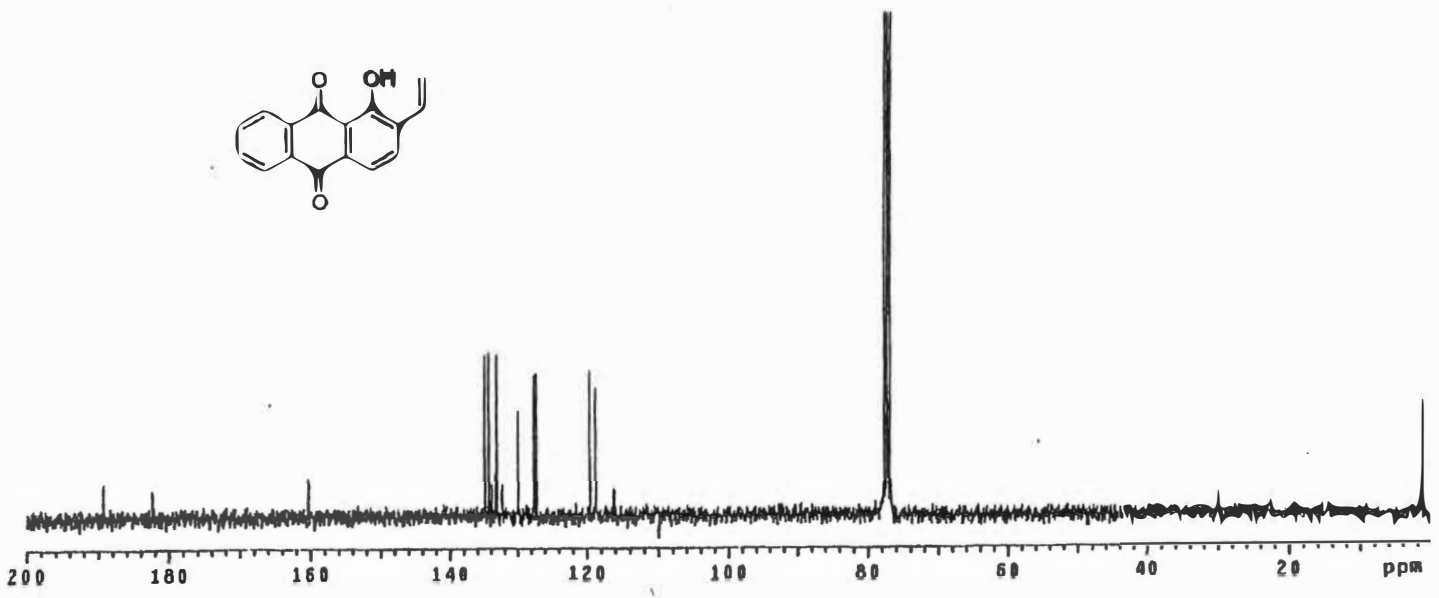
^{1}H NMR spectrum of Trifluoromethanesulfonic acid 1-hydroxy-9,10-dioxo-9,10-dihydroanthracen-2-yl ester (**2.45**).



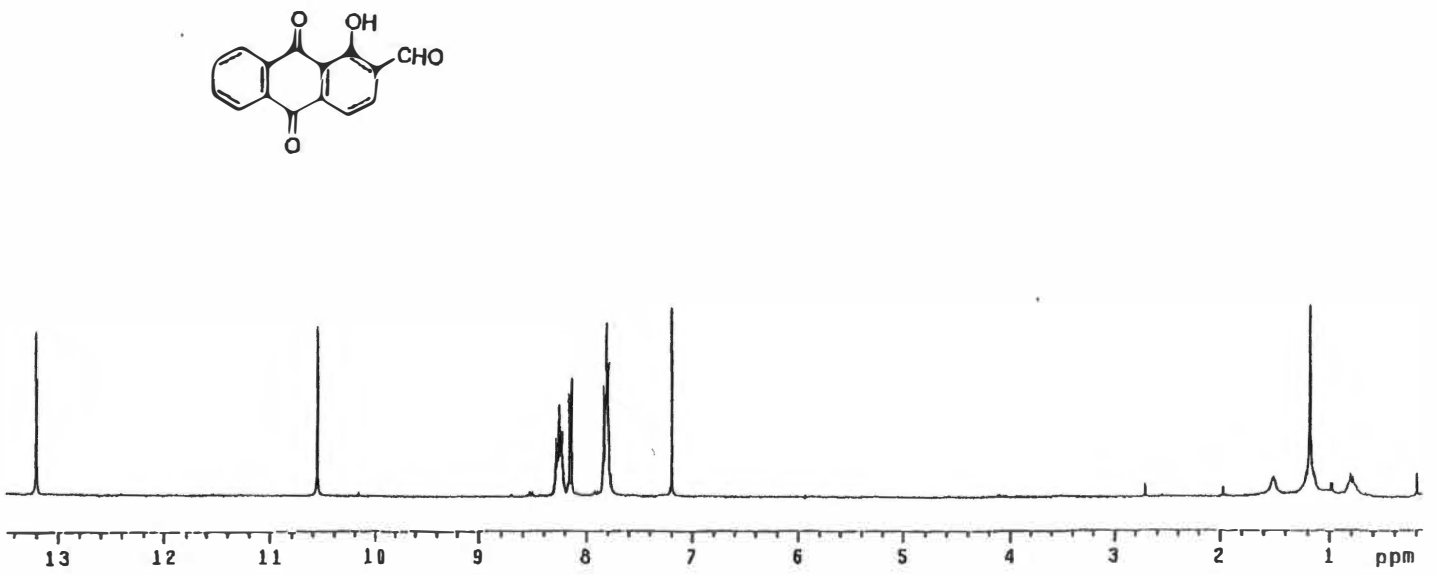
^{13}C NMR spectrum of Trifluoromethanesulfonic acid 1-hydroxy-9,10-dioxo-9,10-dihydroanthracen-2-yl ester (**2.45**).



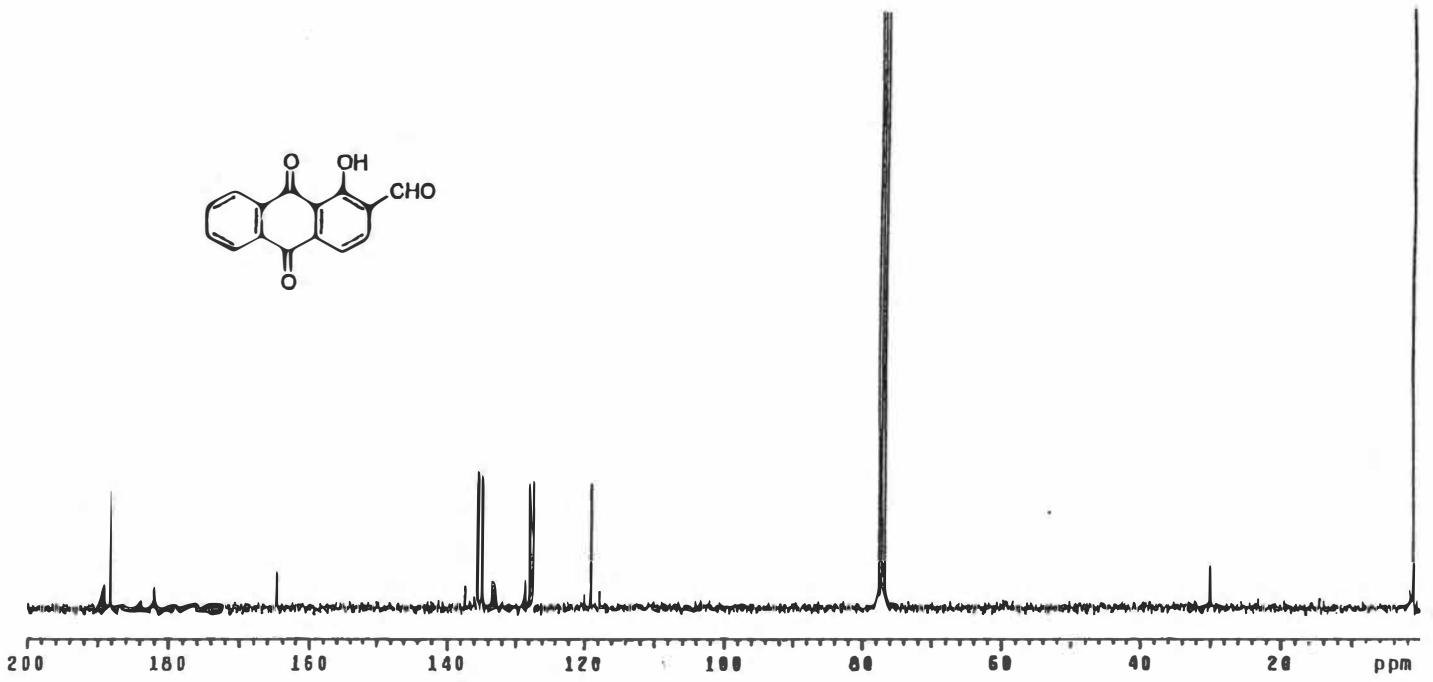
^{1}H NMR spectrum of 1-Hydroxy-2-vinylanthraquinone (**2.46**).



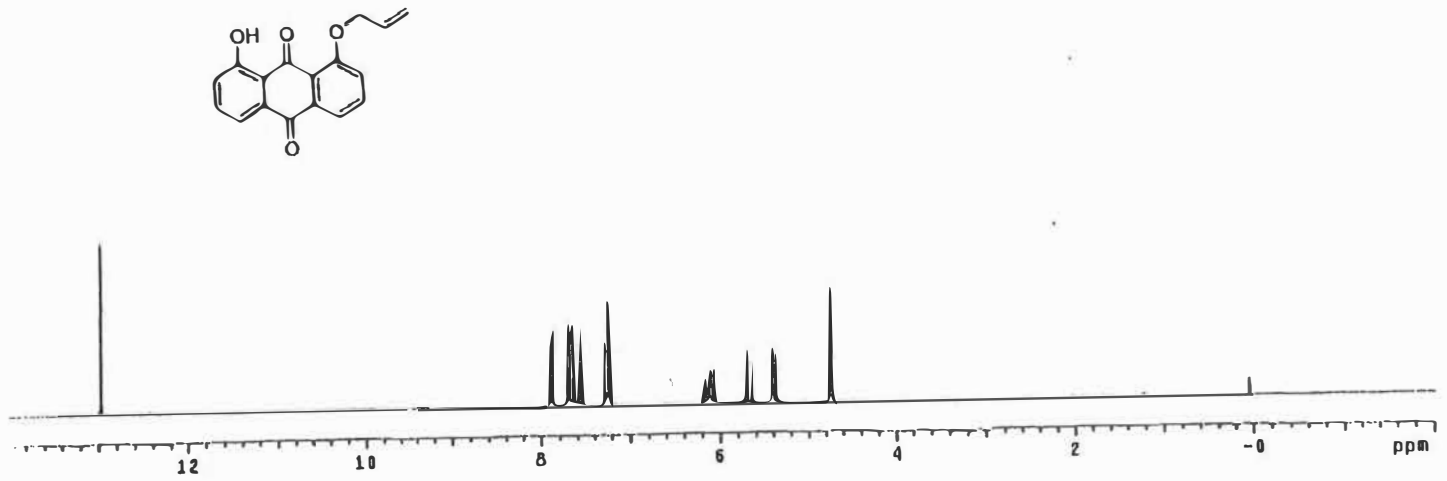
^{13}C NMR spectrum of 1-Hydroxy-2-vinylanthraquinone (**2.46**).



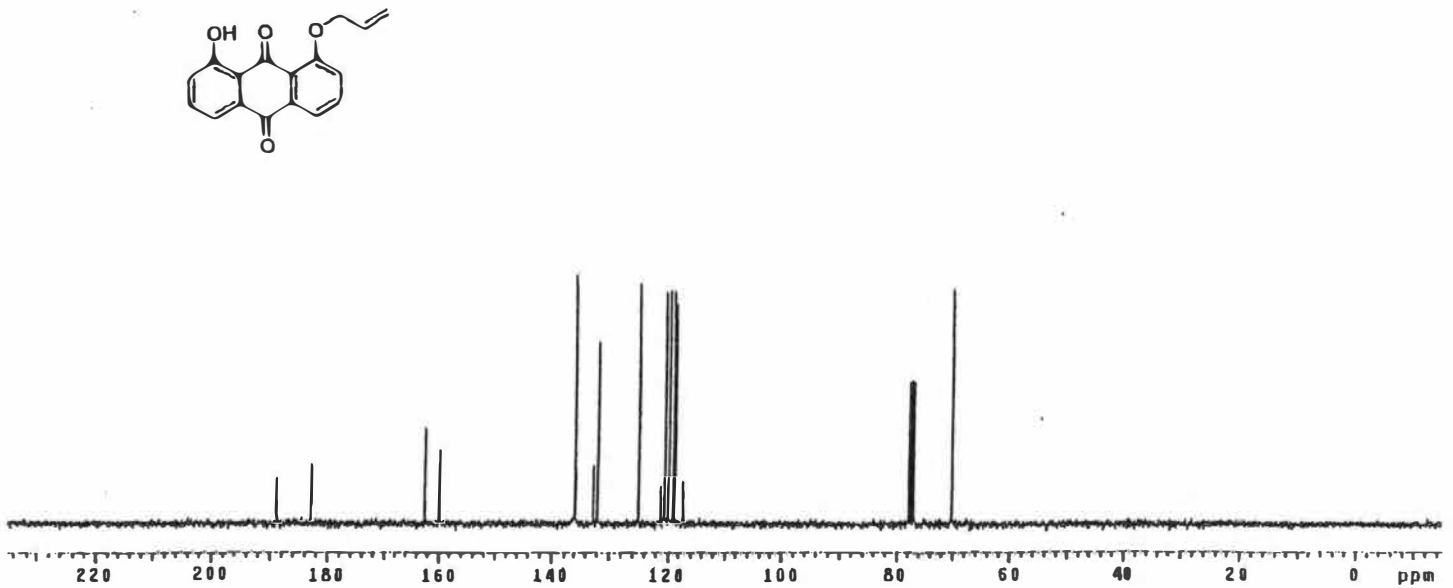
^{1}H NMR spectrum of 1-Hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde (**2.47**).



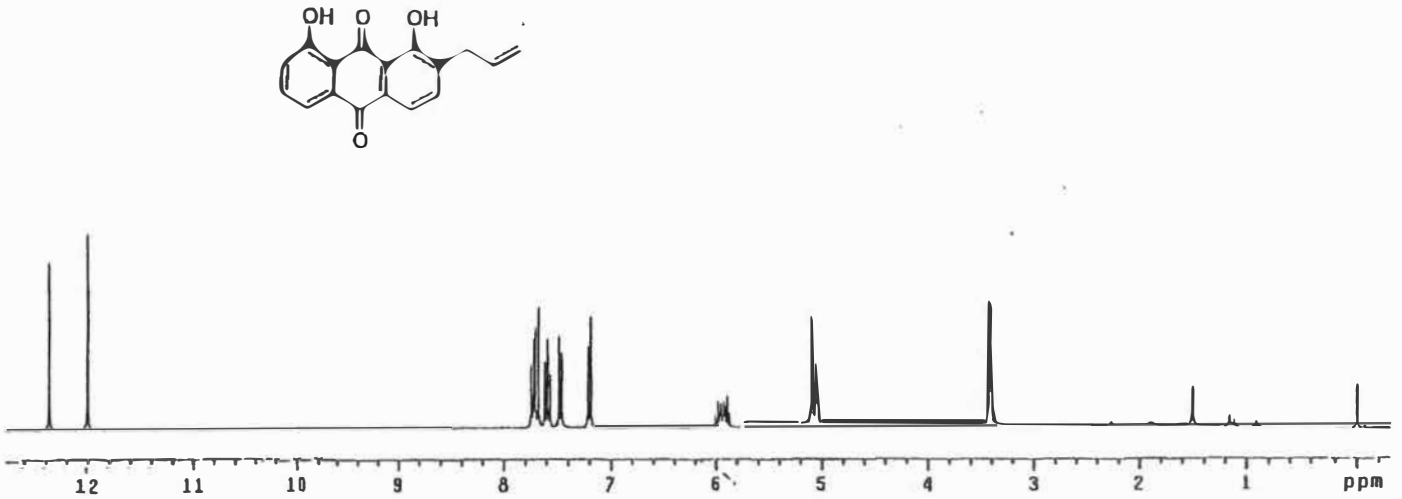
^{13}C NMR spectrum of 1-Hydroxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde (**2.47**).



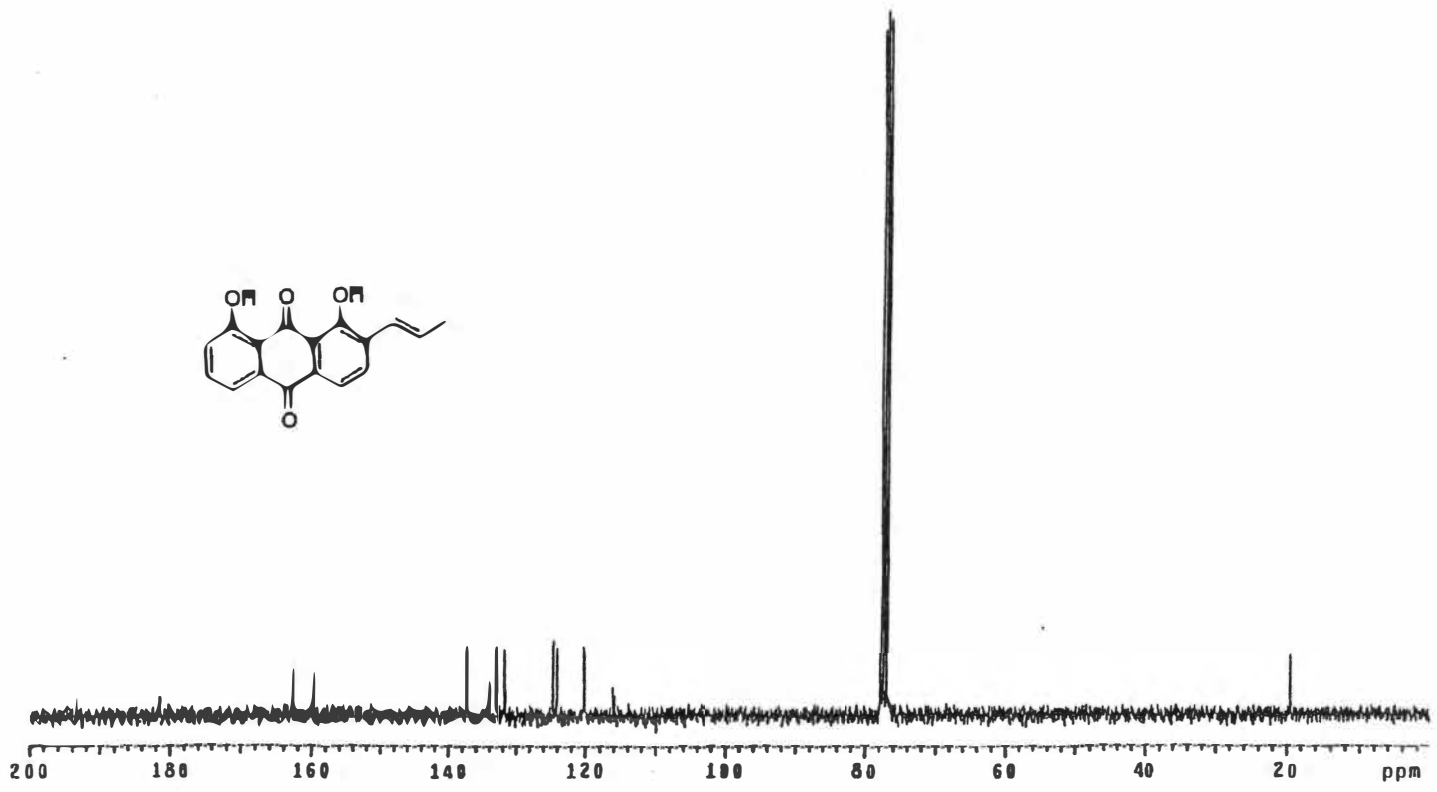
^{1}H NMR spectrum of 1-Allyloxy-8-hydroxyanthraquinone (**2.48**).



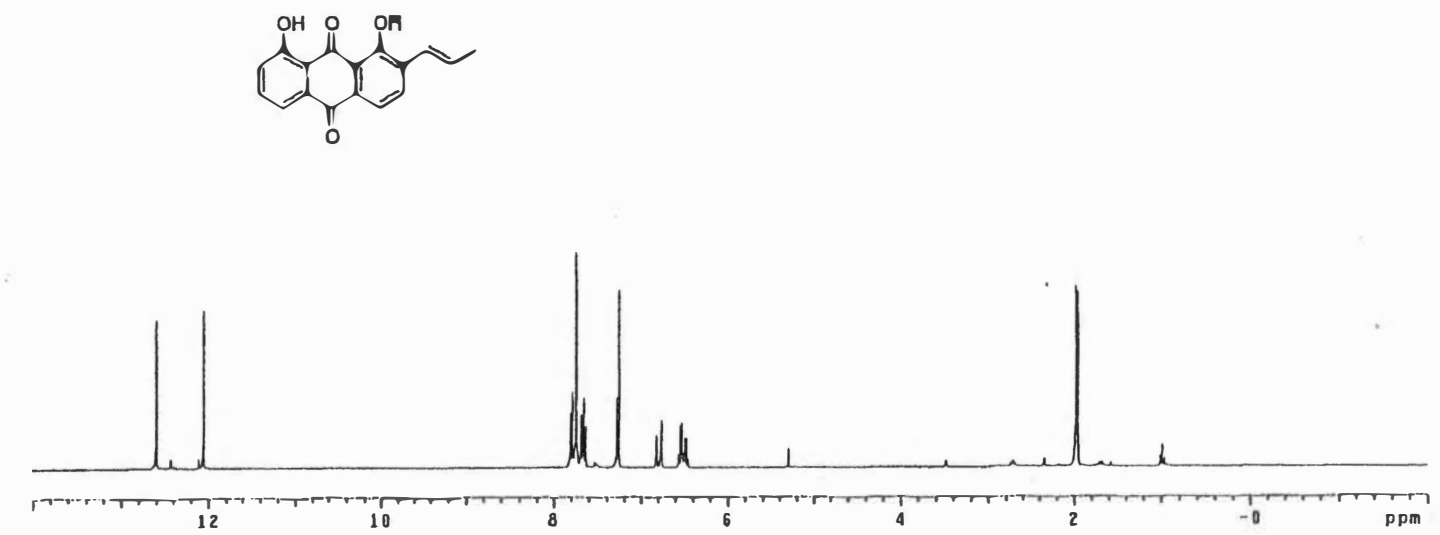
^{13}C NMR spectrum of 1-Allyloxy-8-hydroxyanthraquinone (**2.48**).



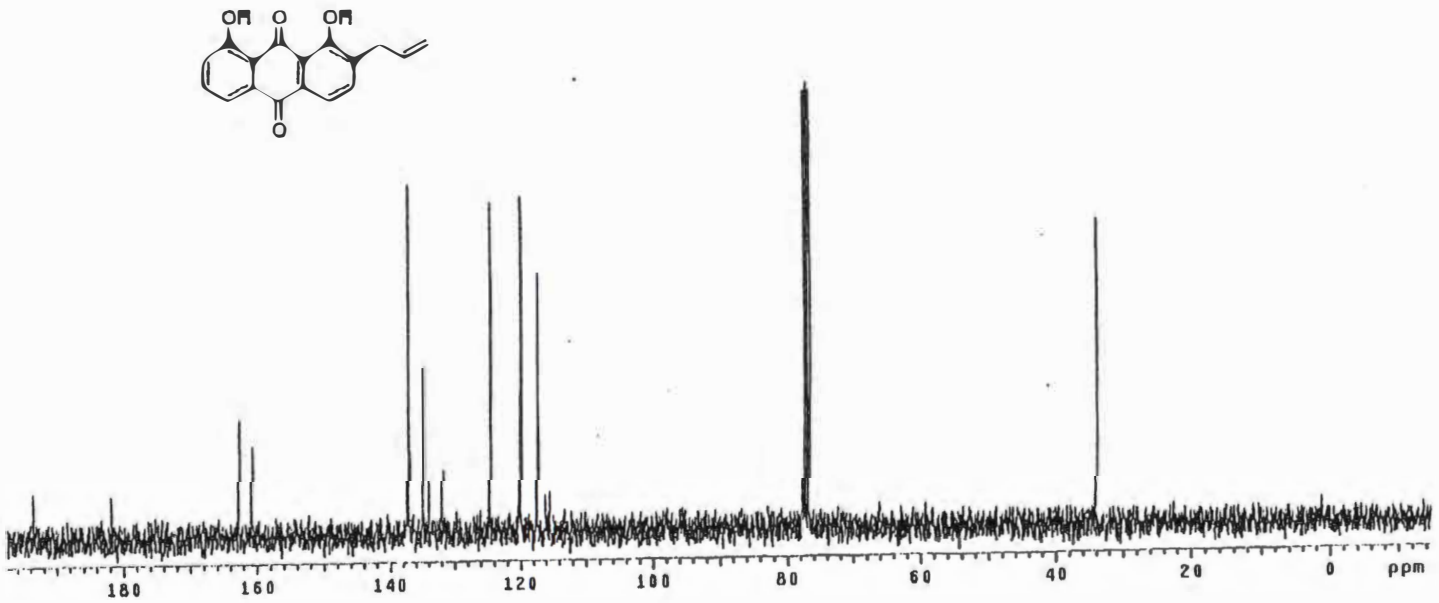
^{1}H NMR spectrum of 2-Allyl-1,8-dihydroxyanthraquinone (**2.49**).



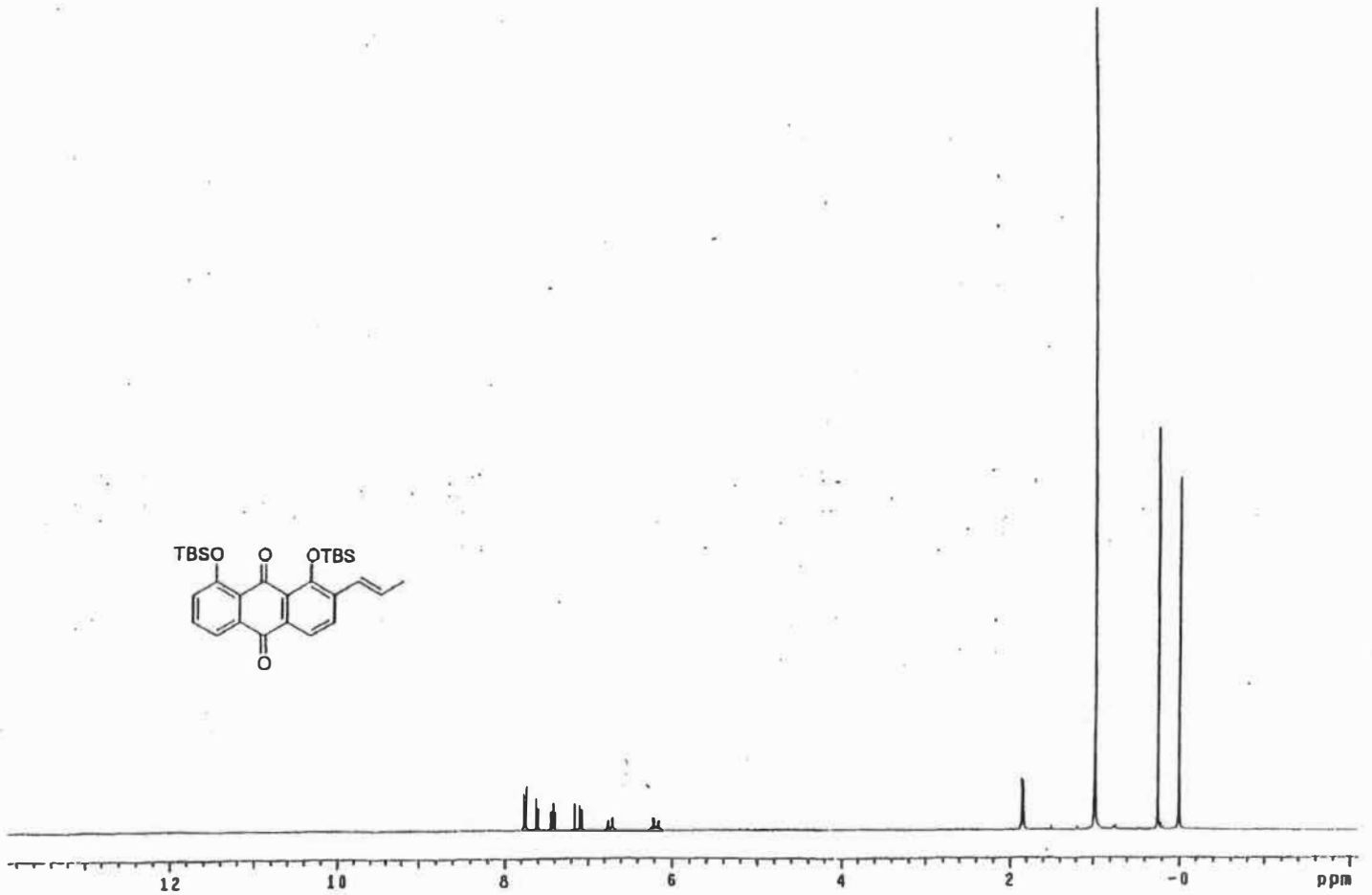
^{13}C NMR spectrum of 1,8-Dihydroxy-2-propenylanthraquinone (**2.50**).



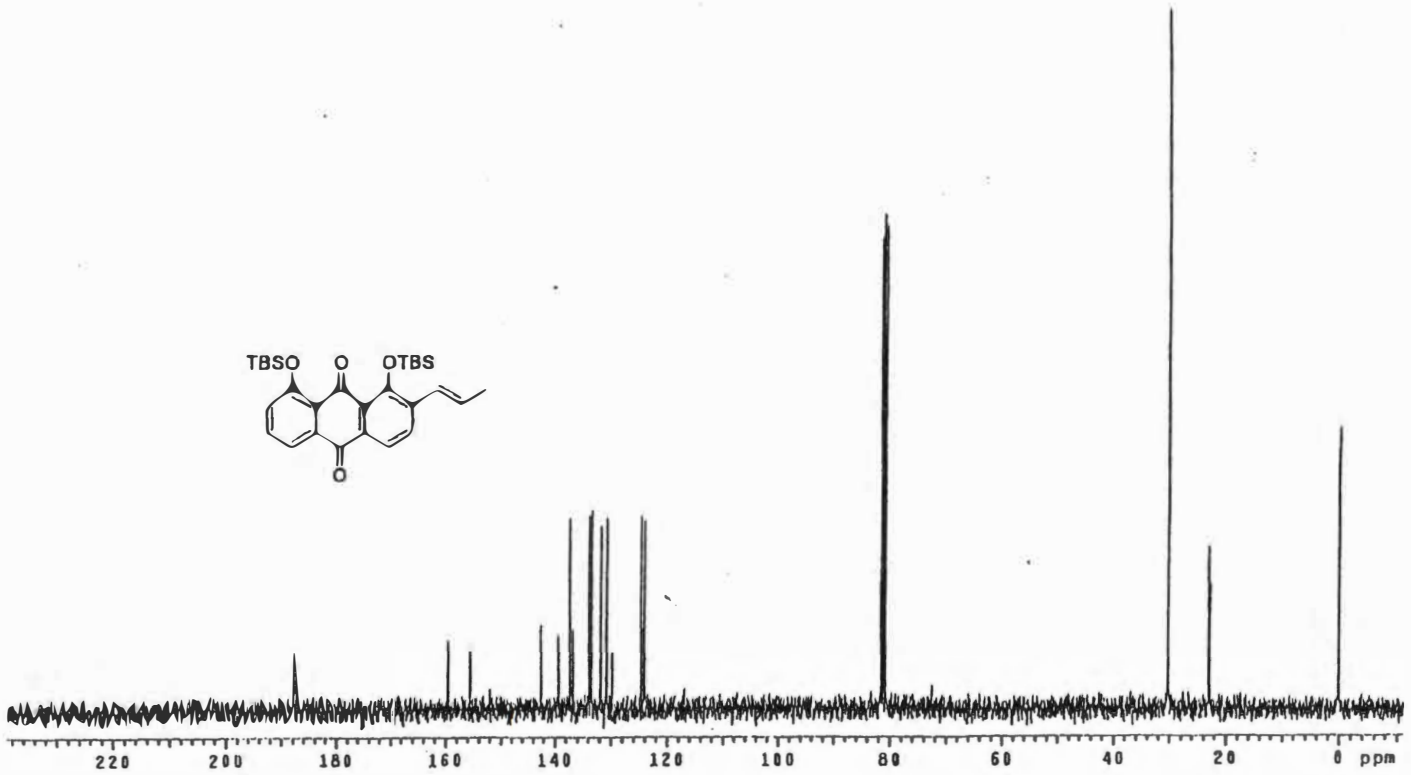
^{1}H NMR spectrum of 1,8-Dihydroxy-2-propenylanthraquinone (**2.50**).



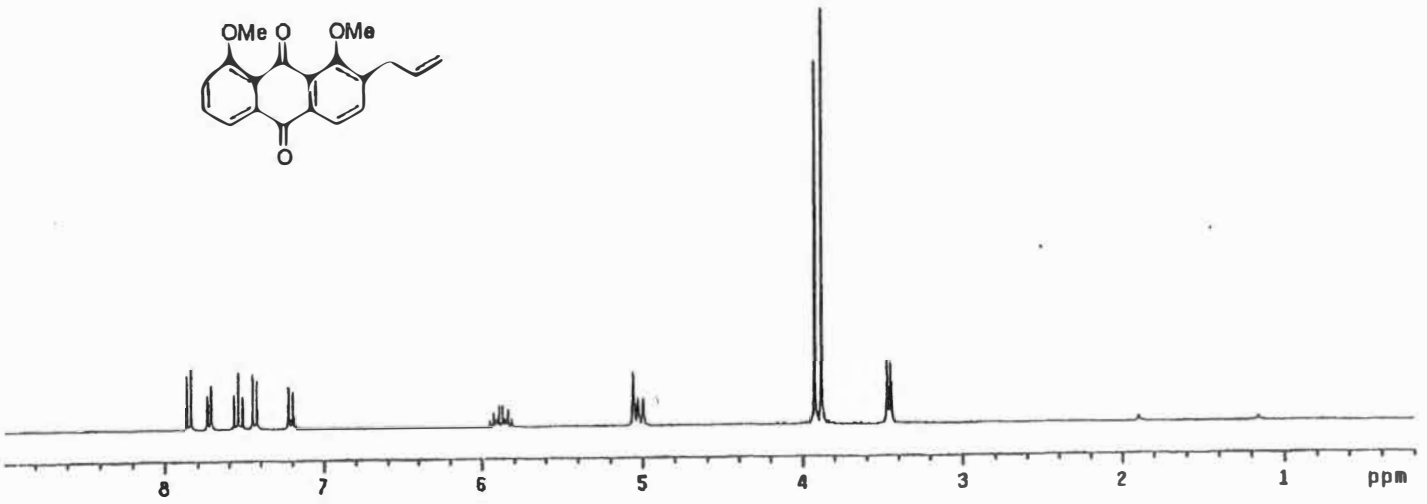
^{13}C NMR spectrum of 2-Allyl-1,8-dihydroxyanthraquinone (**2.49**).



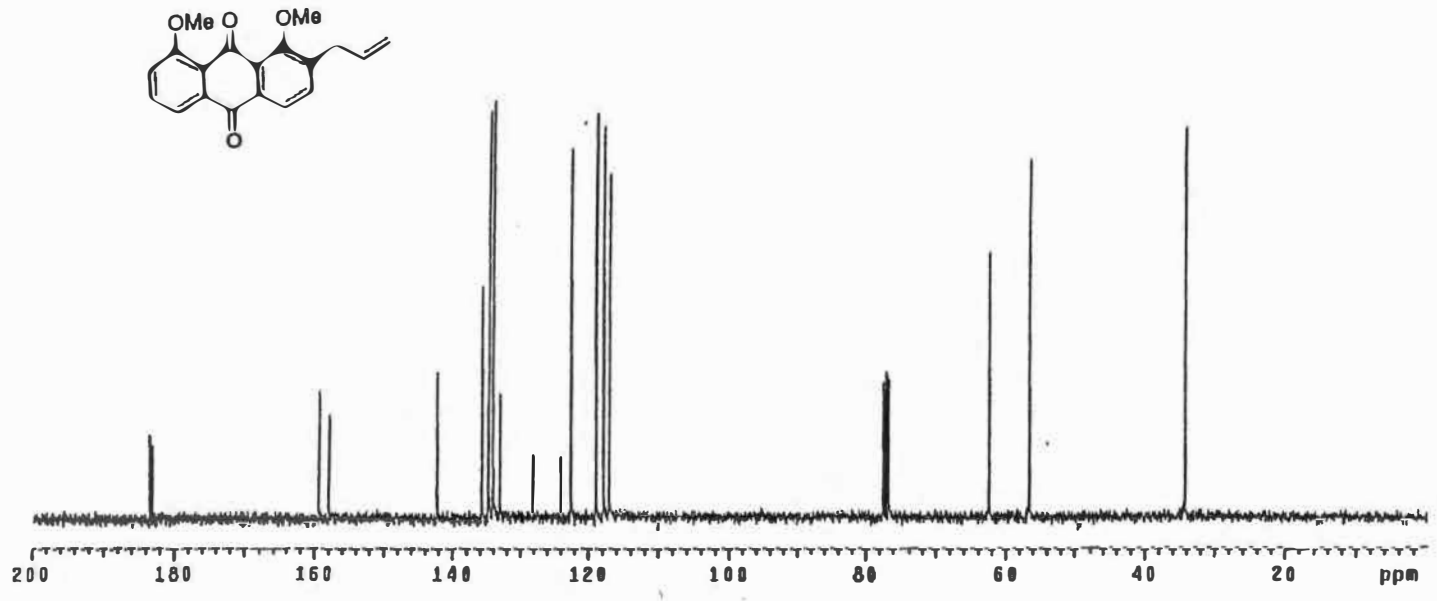
^{1}H NMR spectrum of 1,8-Bis(*tert*-butydimethylsilyloxy)-2-propenylanthraquinone (**2.51**).



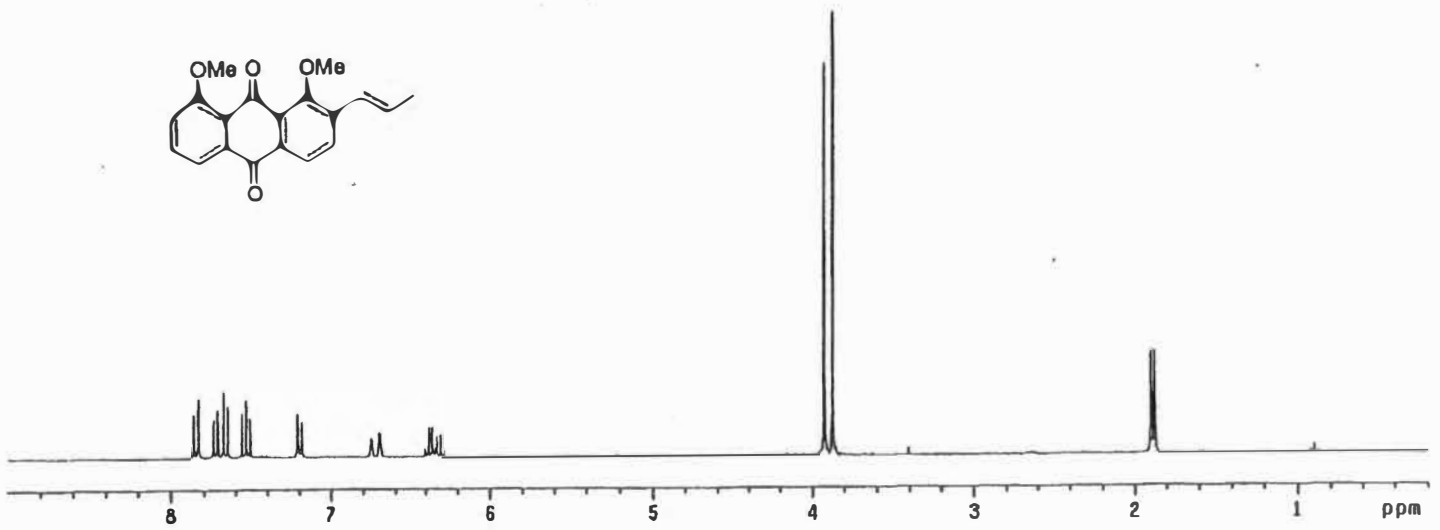
^{13}C NMR spectrum of 1,8-Bis(*tert*-butydimethylsilyloxy)-2-propenylanthraquinone (**2.51**).



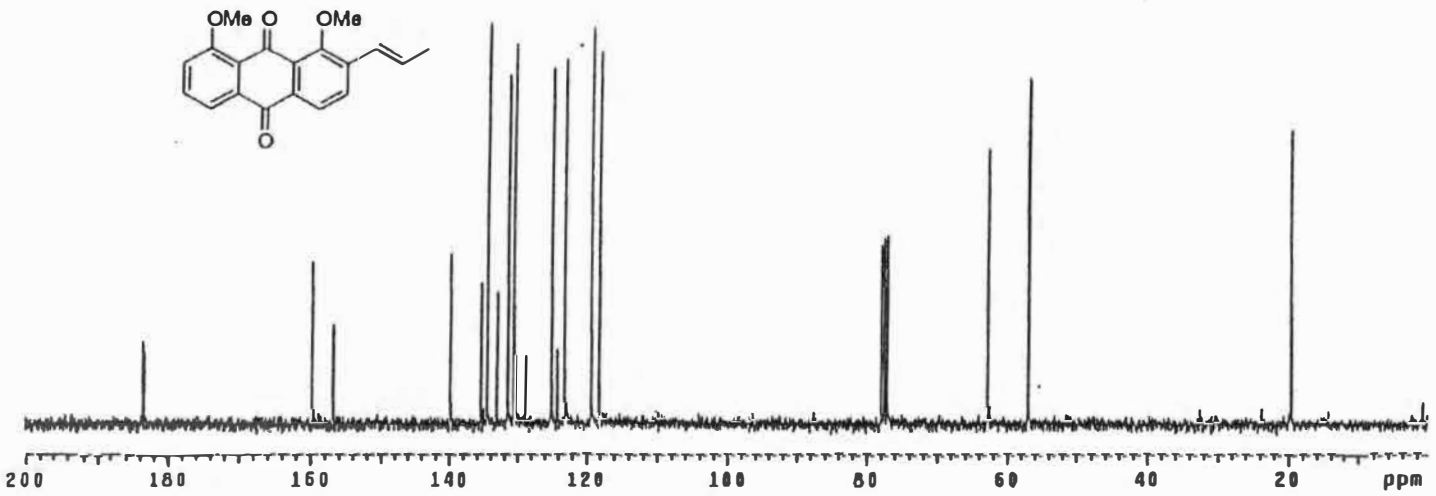
^{1}H NMR spectrum of 2-Allyl-1,8-dimethoxyanthraquinone (**2.52**).



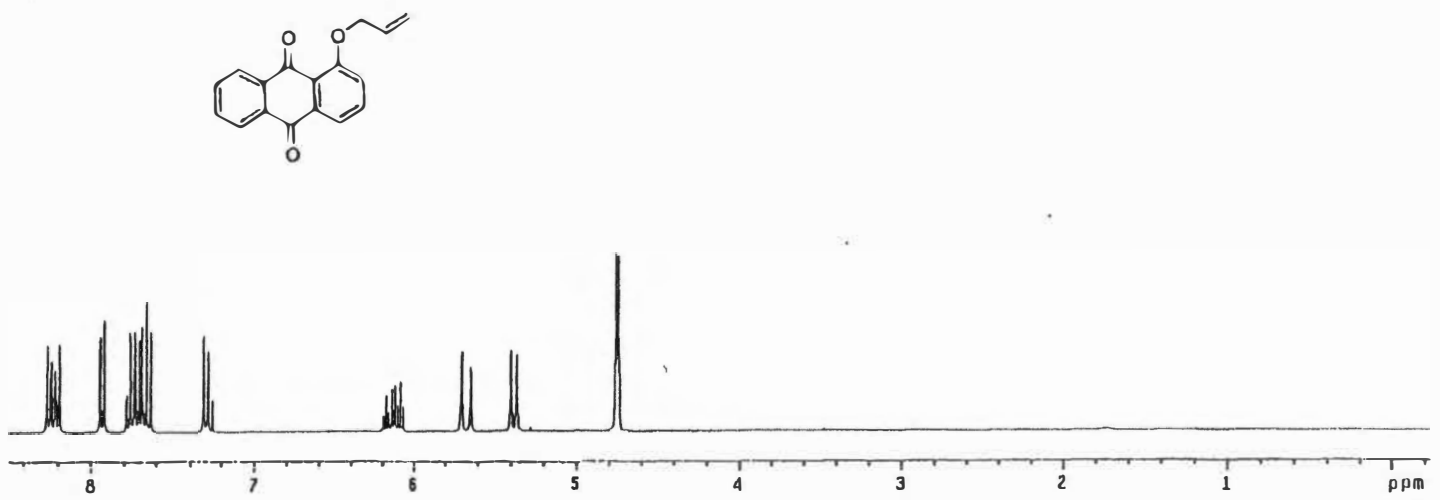
^{13}C NMR spectrum of 2-Allyl-1,8-dimethoxyanthraquinone (**2.52**).



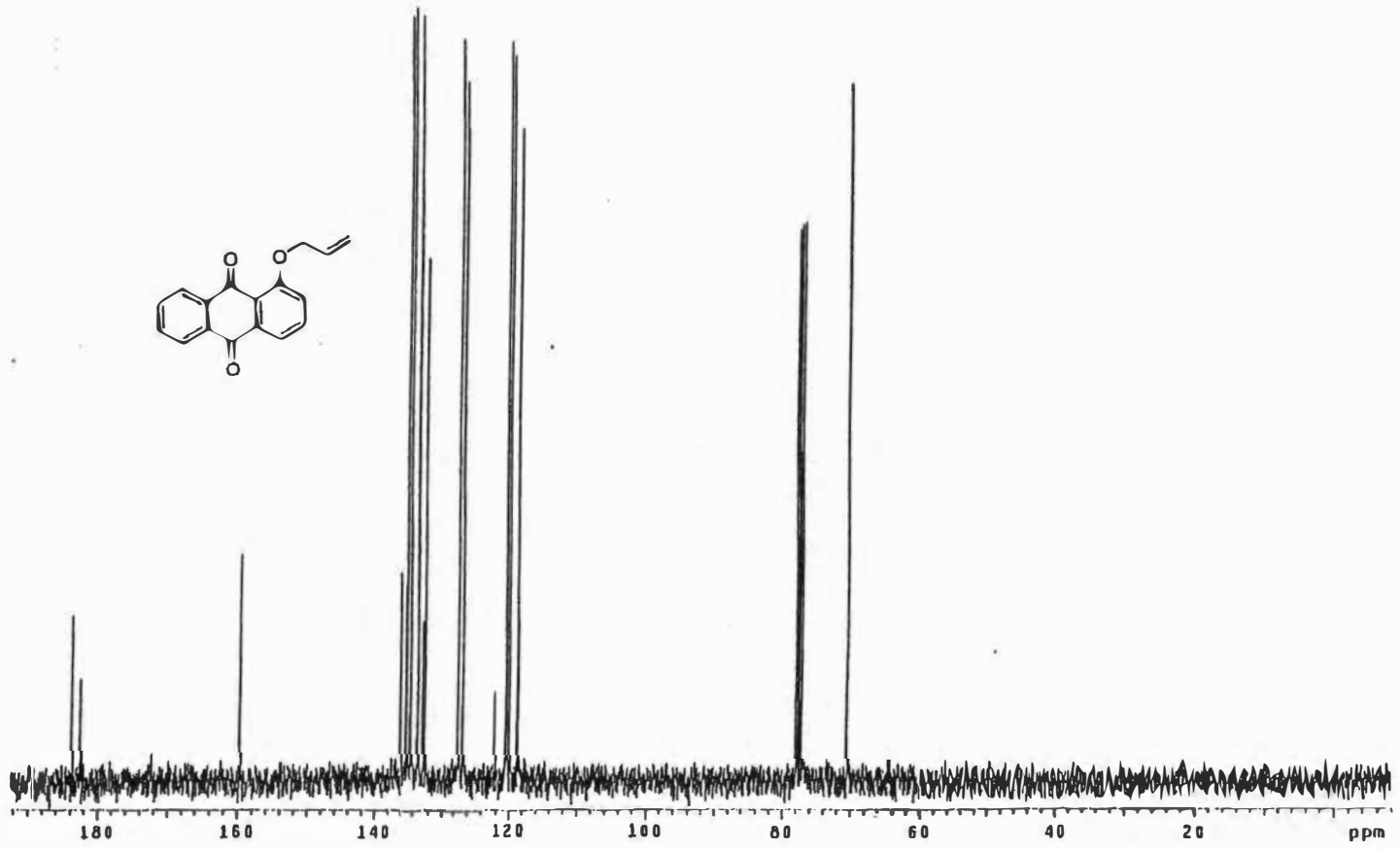
^{1}H NMR spectrum of 1,8-dimethoxy-2-propenylanthraquinone (**2.53**).



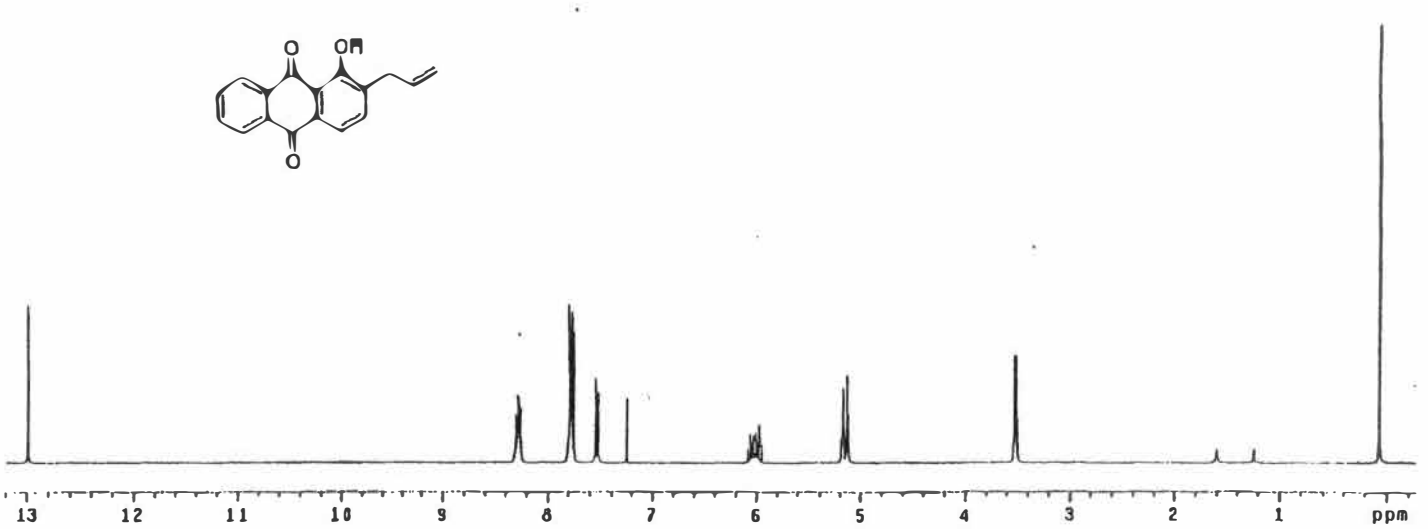
^{13}C NMR spectrum of 1,8-dimethoxy-2-propenylanthraquinone (**2.53**).



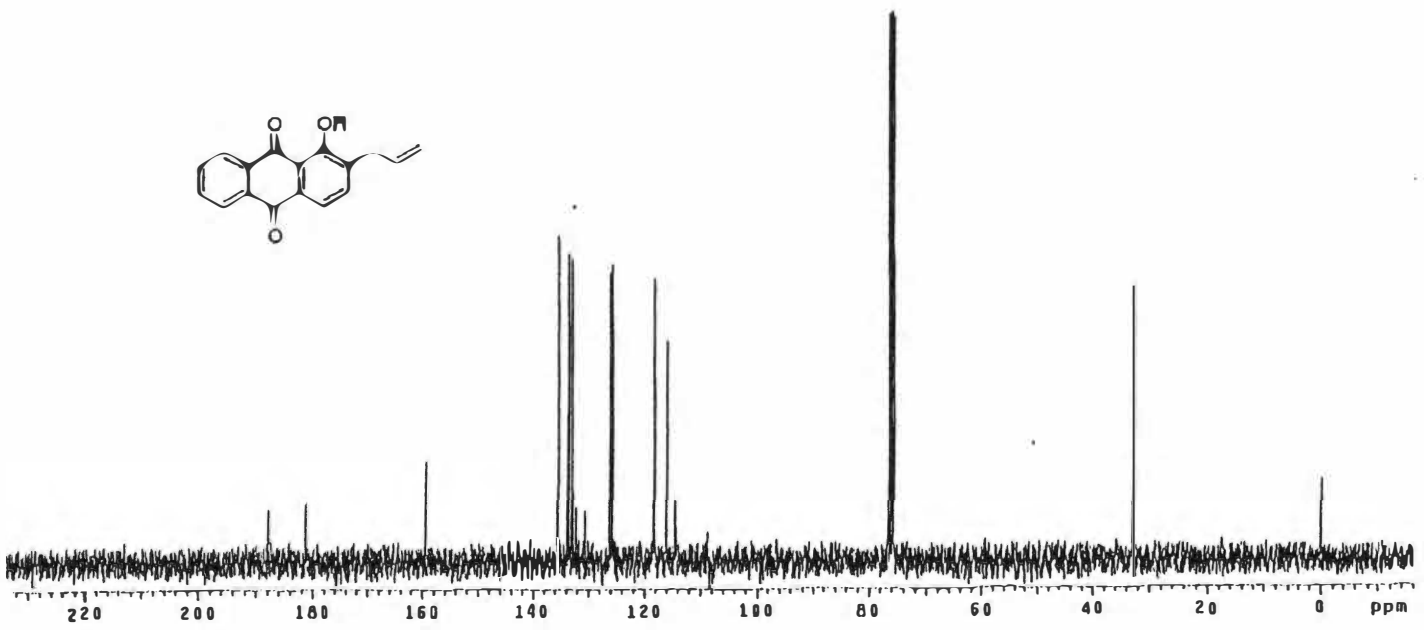
^{1}H NMR spectrum of 1-Allyloxyanthraquinone (**2.55**).



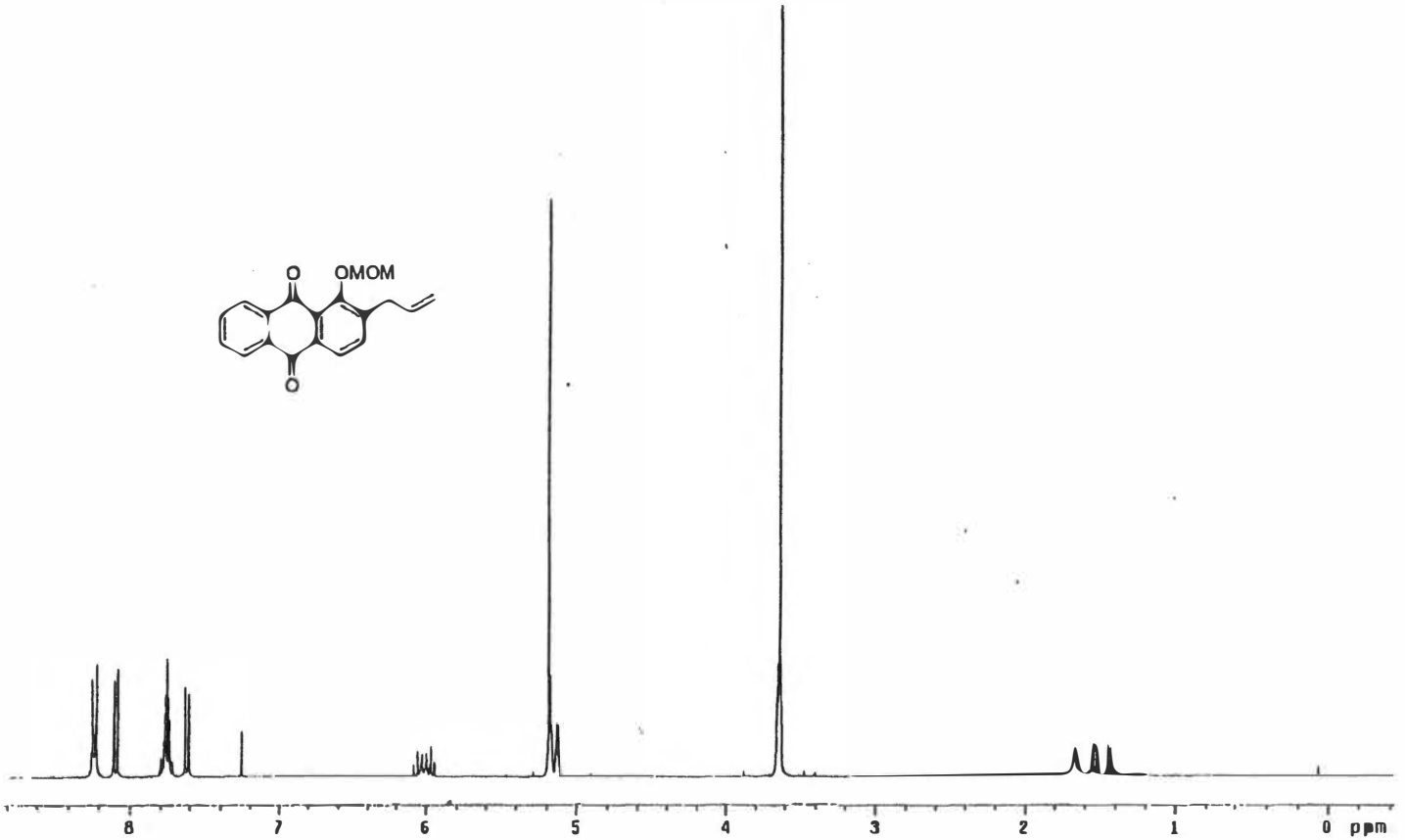
^{13}C NMR spectrum of 1-Allyloxyanthraquinone (**2.55**).



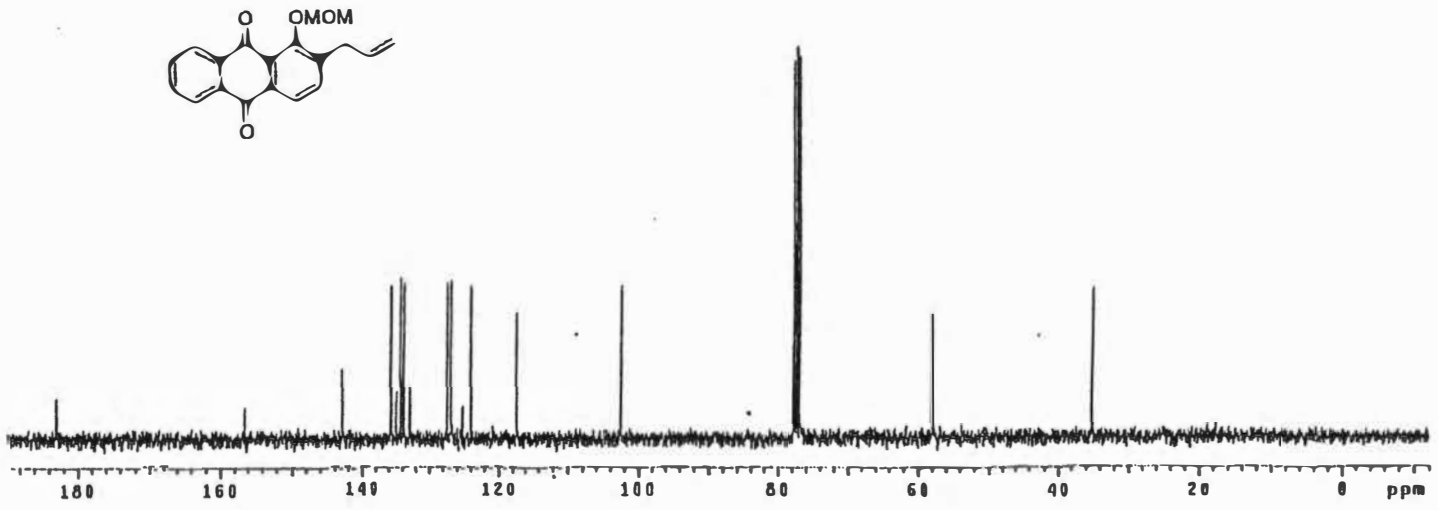
^{1}H NMR spectrum of 1-Hydroxy-2-allylanthraquinone (**2.56**).



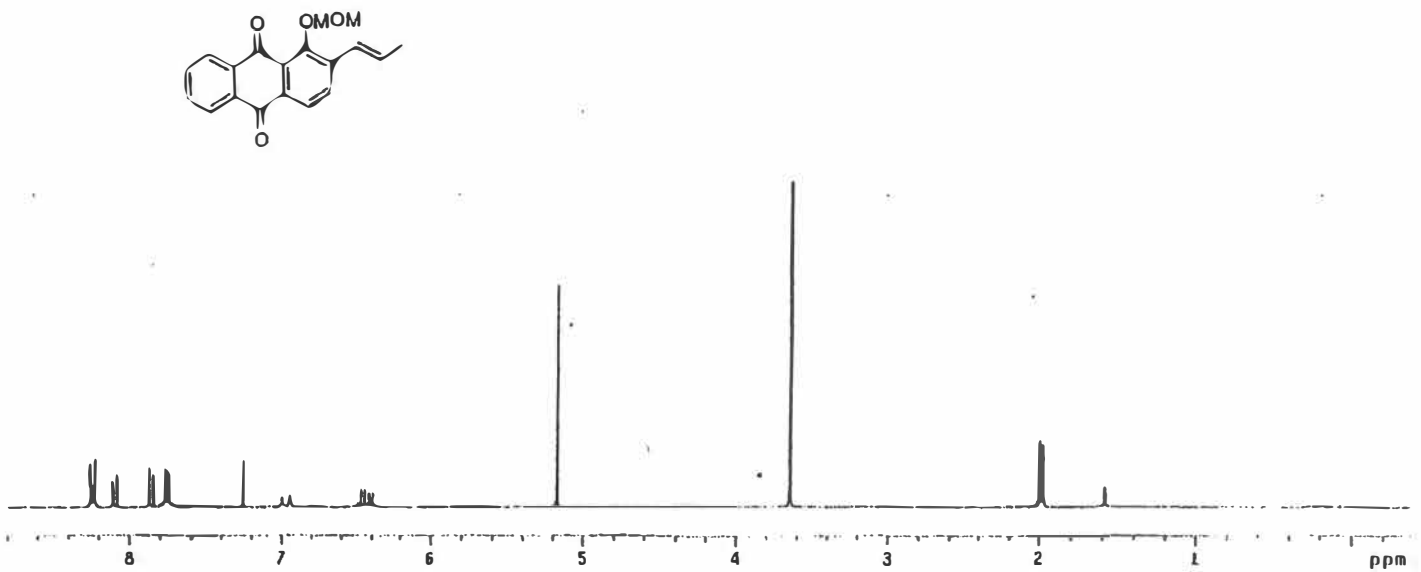
^{13}C NMR spectrum of 1-Hydroxy-2-allylanthraquinone (**2.56**).



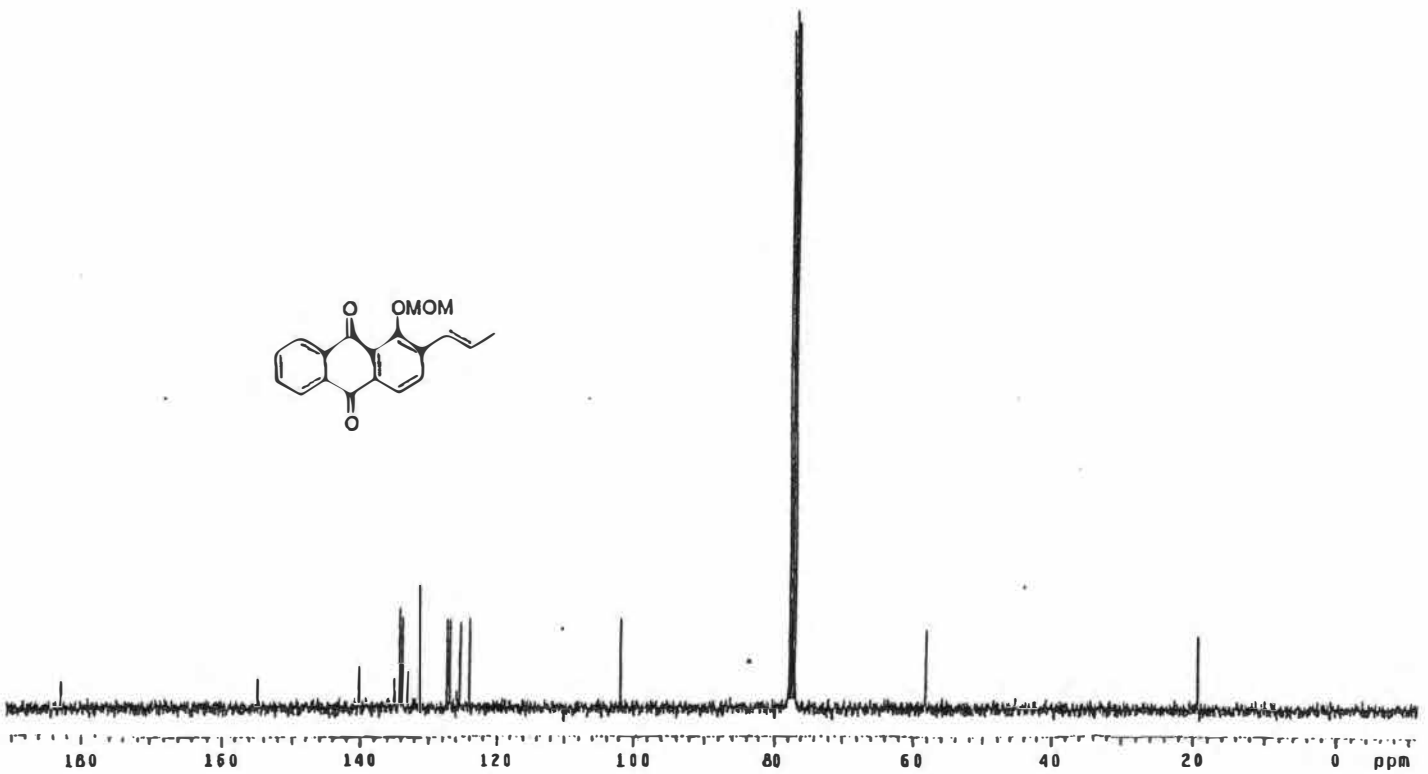
^{1}H NMR spectrum of 2-Allyl-1-methoxymethoxyanthraquinone (**2.57**).



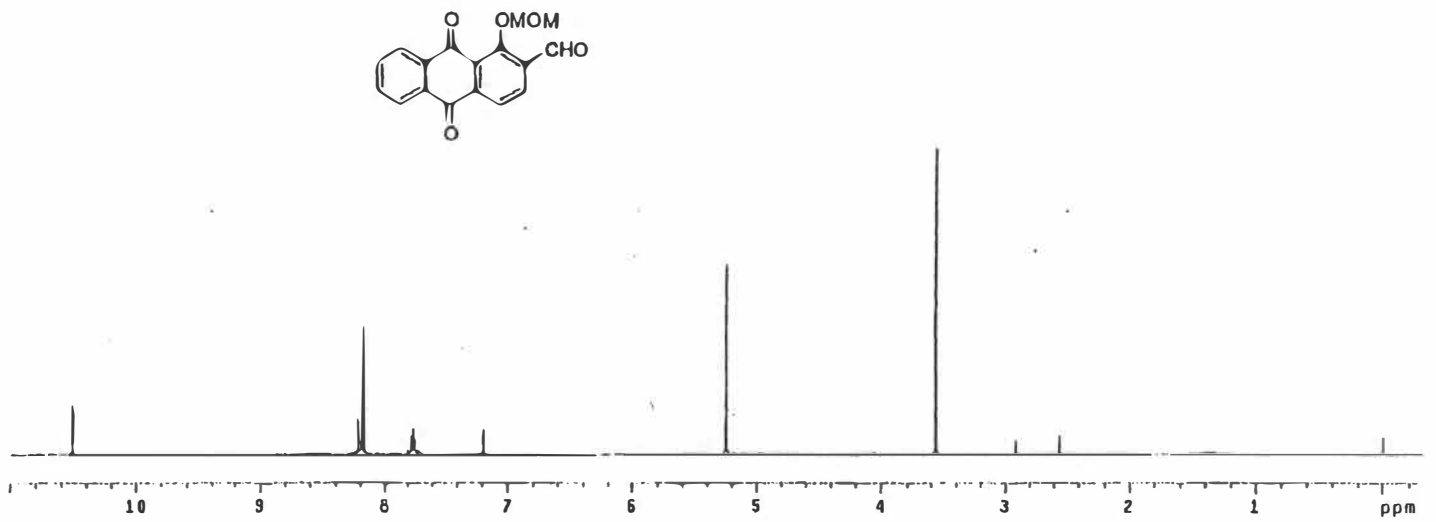
^{13}C NMR spectrum of 2-Allyl-1-methoxymethoxyanthraquinone (**2.57**).



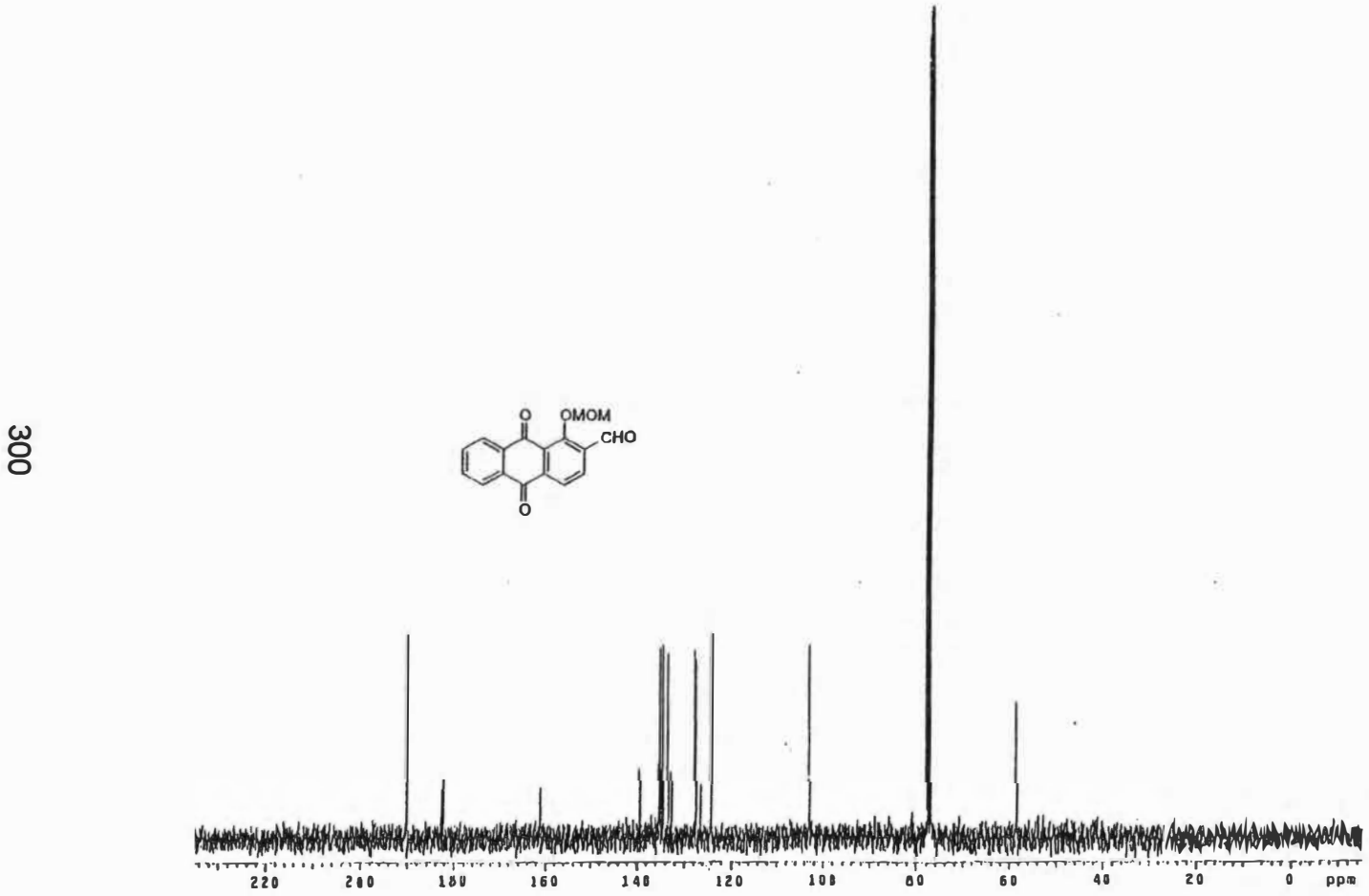
^{1}H NMR spectrum of 1-Methoxymethoxy-2-propenylanthraquinone (**2.58**).



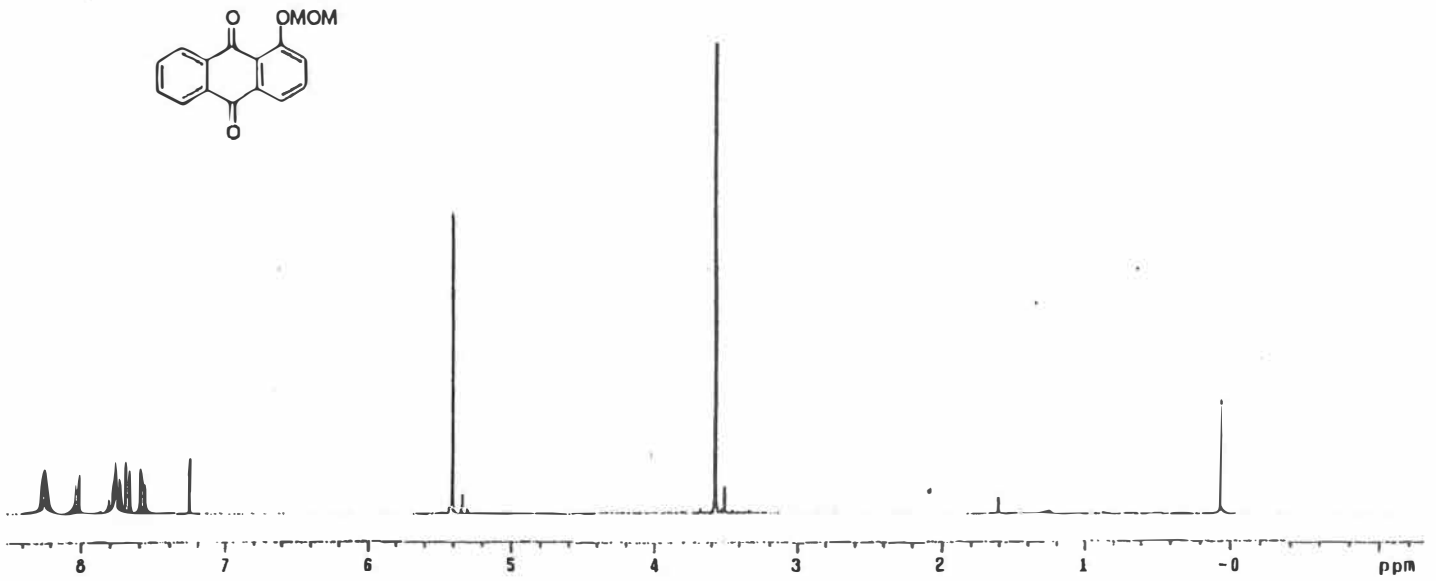
^{13}C NMR spectrum of 1-Methoxymethoxy-2-propenylanthraquinone (**2.58**).



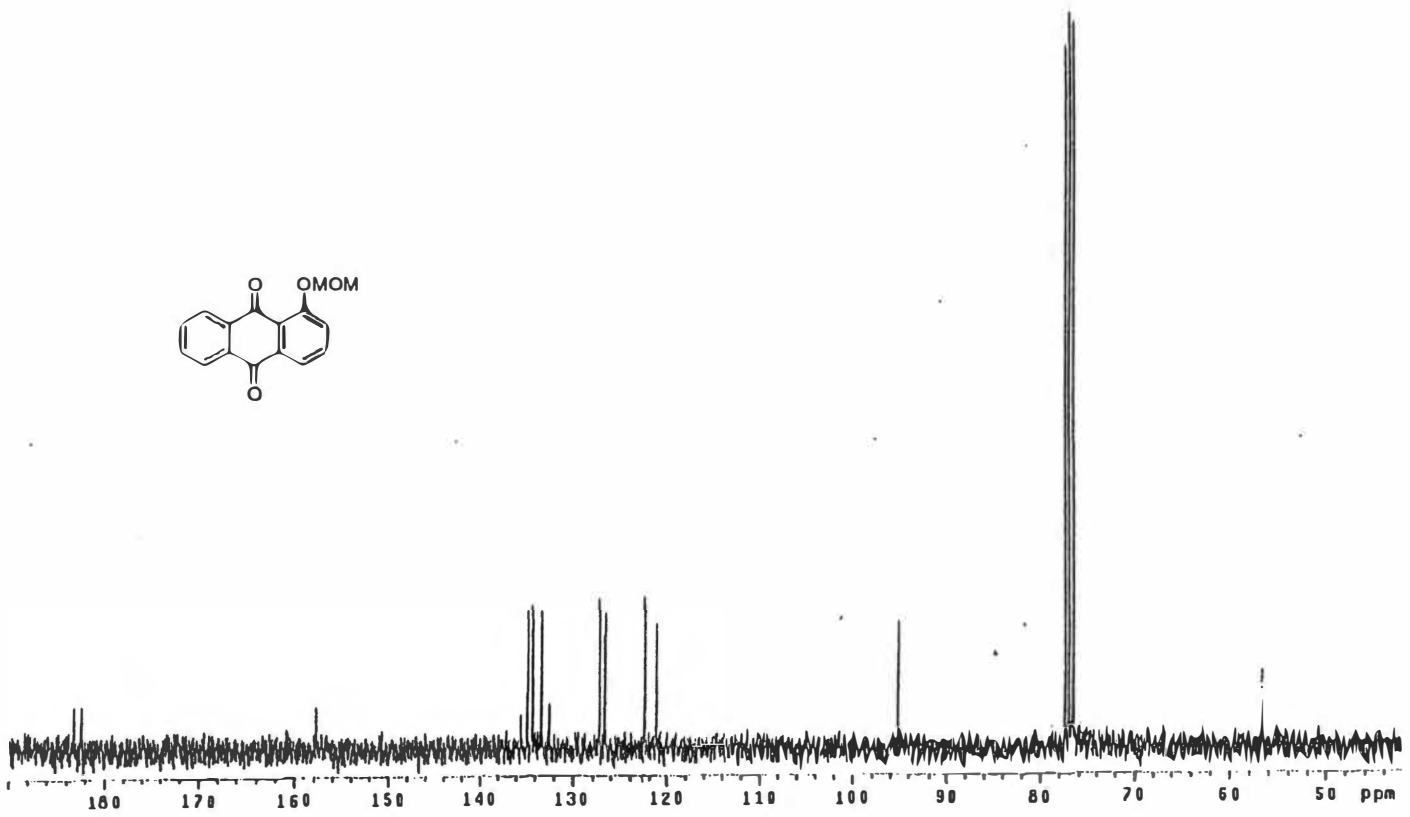
^{1}H NMR spectrum of 1-Methoxymethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde (**2.59**).



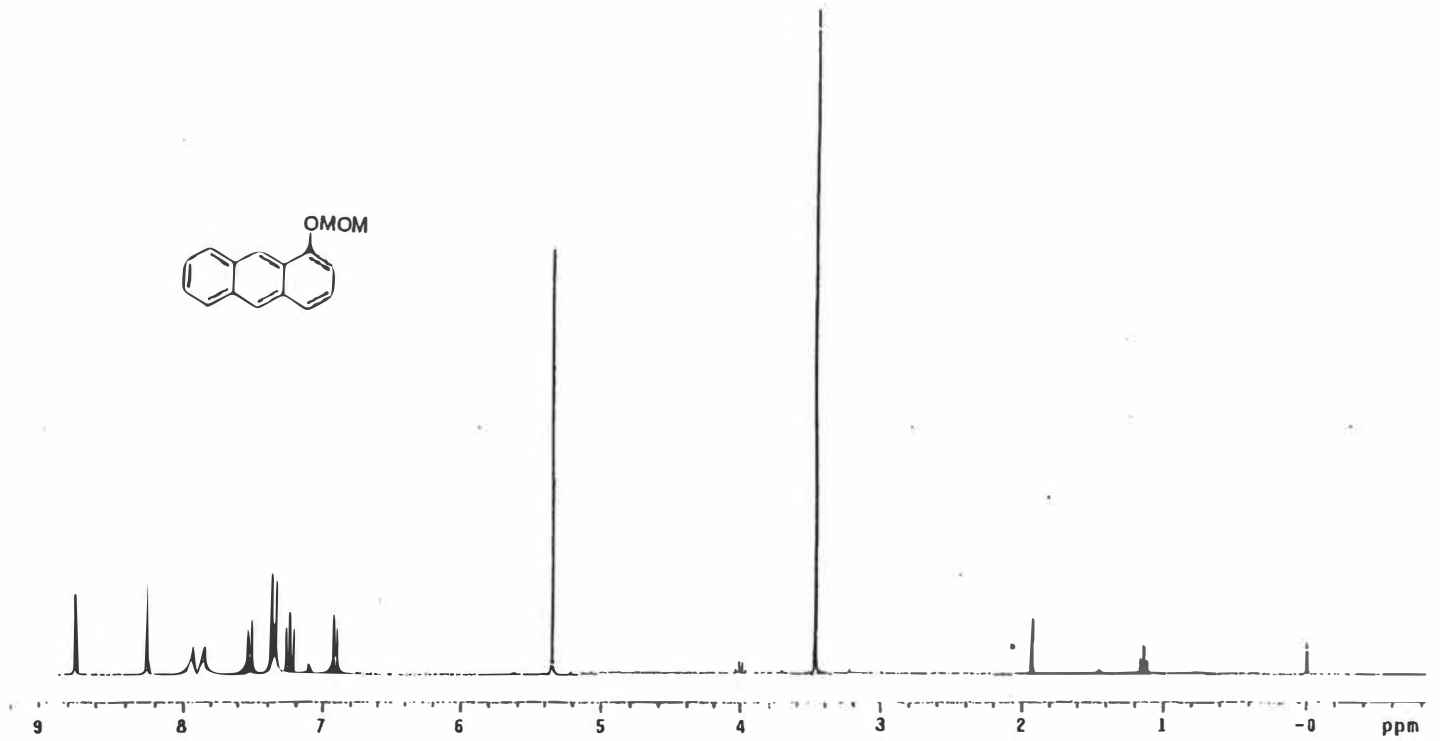
^{13}C NMR spectrum of 1-Methoxymethoxy-9,10-dioxo-9,10-dihydroanthracene-2-carbaldehyde (**2.59**).



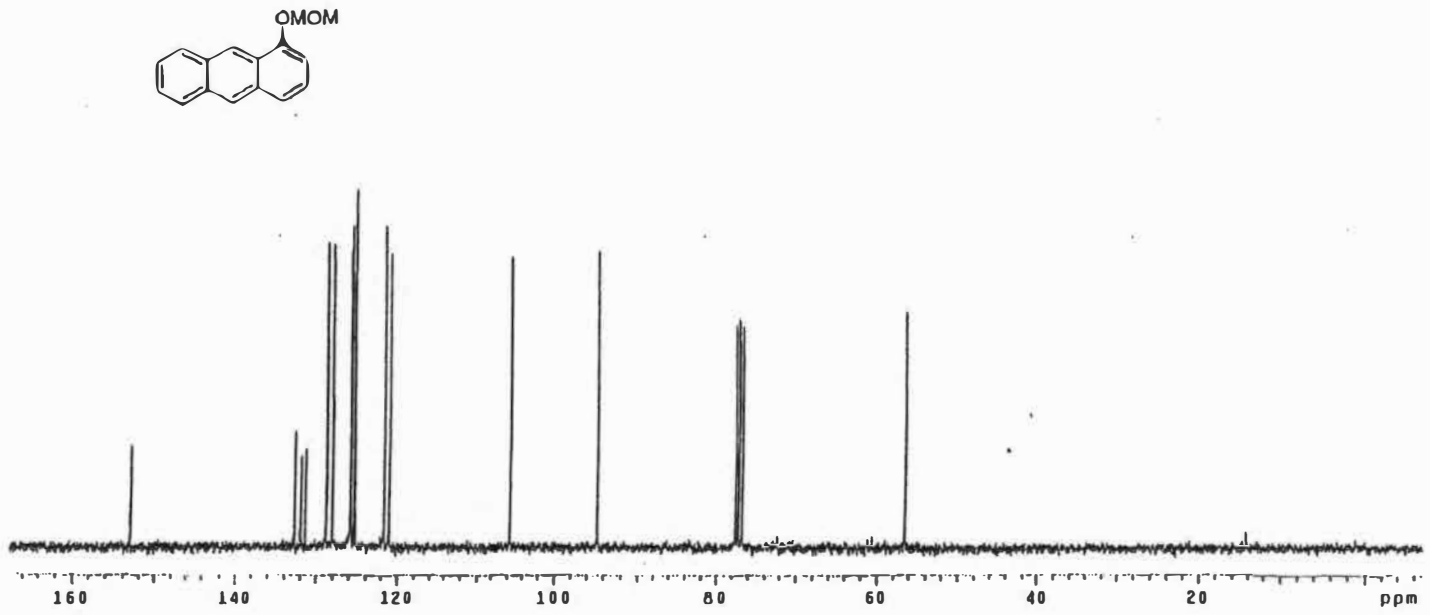
^{1}H NMR spectrum of 1-Methoxymethoxyanthraquinone (**2.60**).



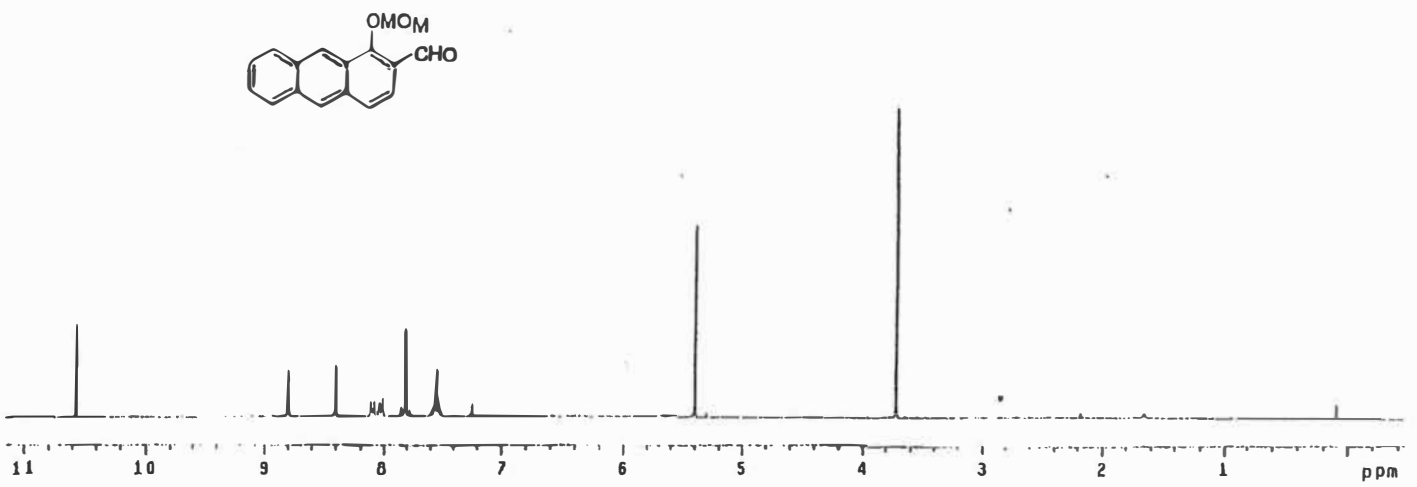
^{13}C NMR spectrum of 1-Methoxymethoxyanthraquinone (**2.60**).



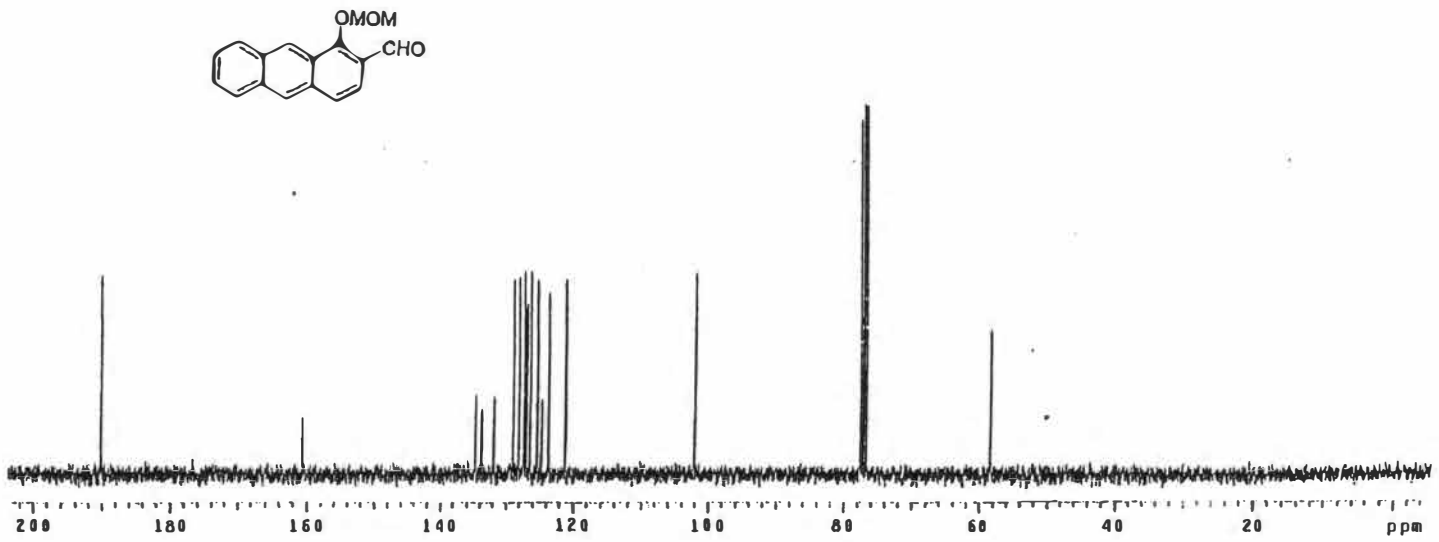
^{1}H NMR spectrum of 1-Methoxymethoxyanthracene (**2.61**).



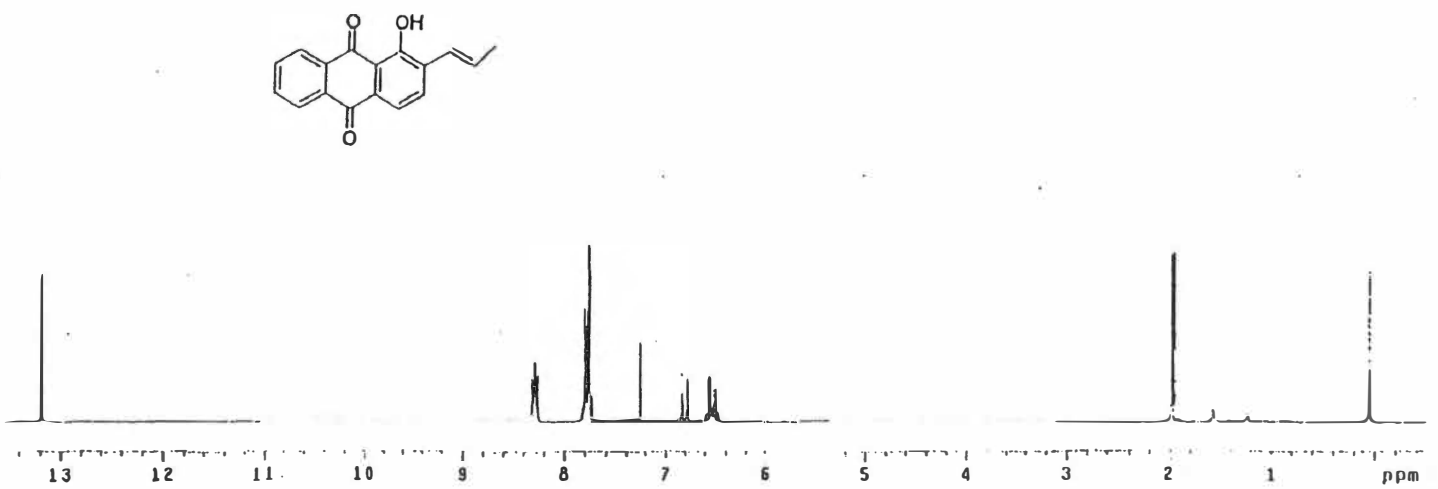
^{13}C NMR spectrum of 1-Methoxymethoxyanthracene (**2.61**).



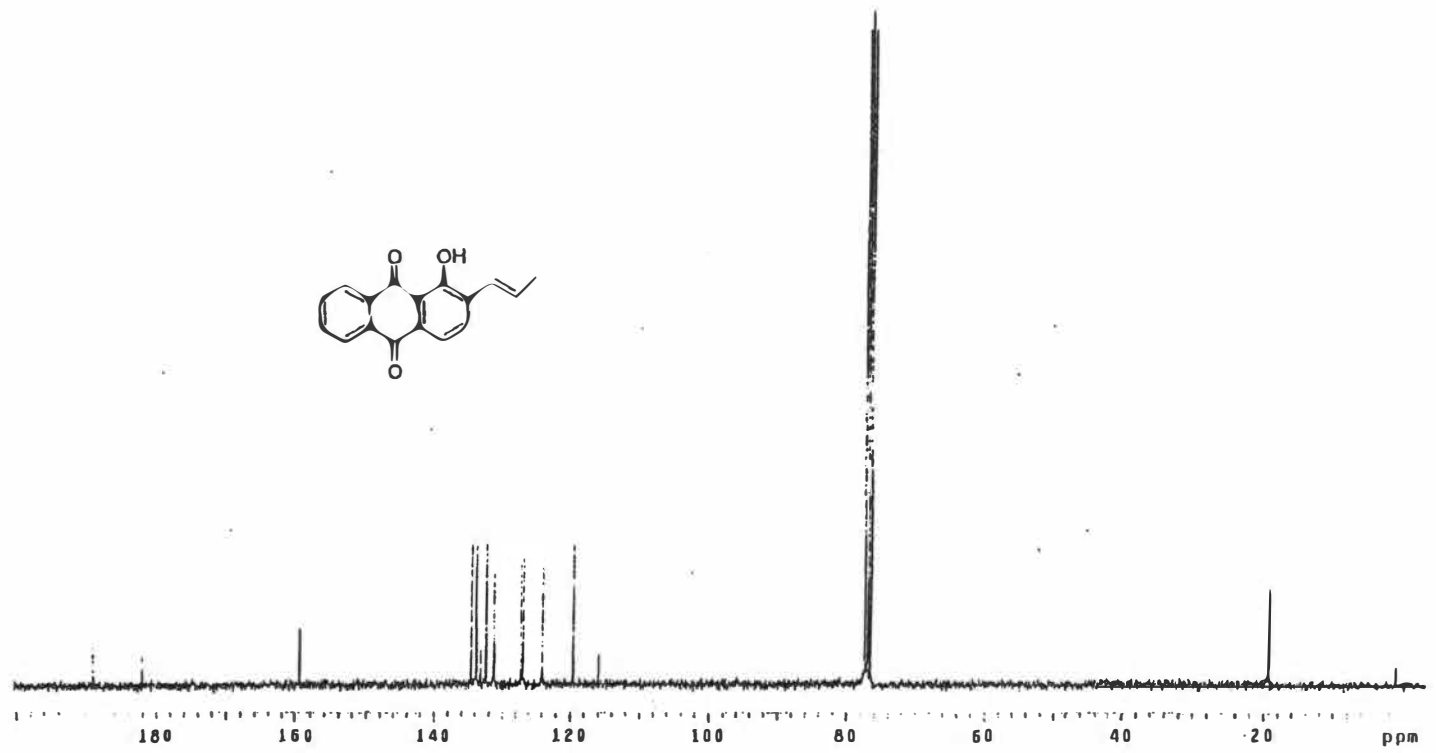
^{1}H NMR spectrum of 1-Methoxymethoxyanthracene-2-carbaldehyde (**2.62**).



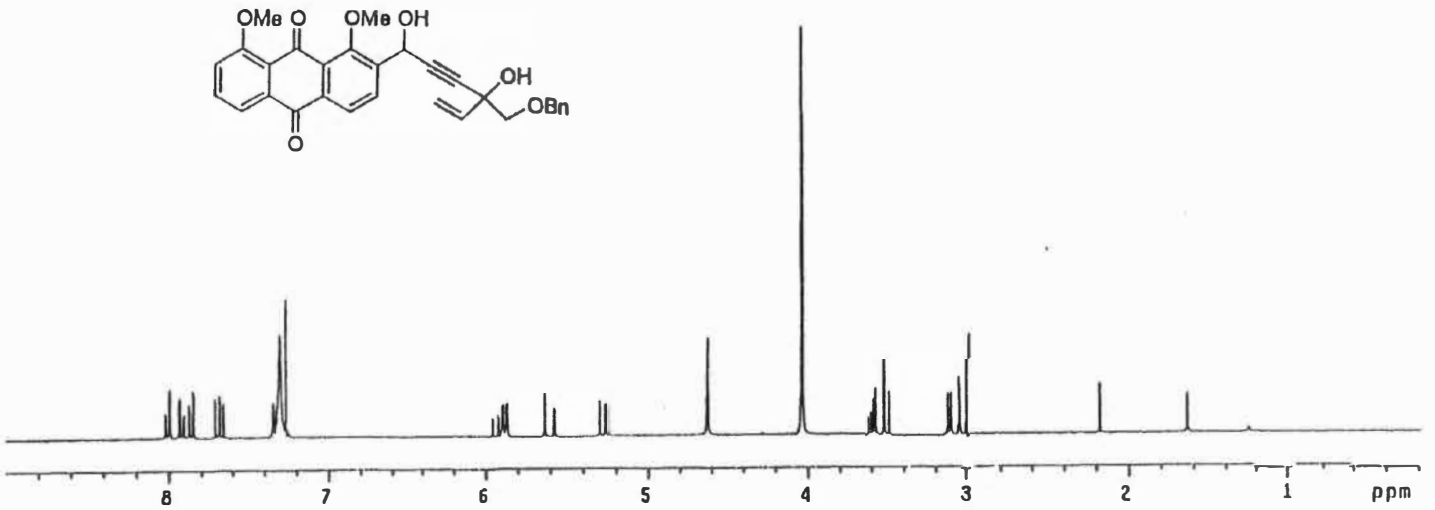
^{13}C NMR spectrum of 1-Methoxymethoxyanthracene-2-carbaldehyde (**2.62**).



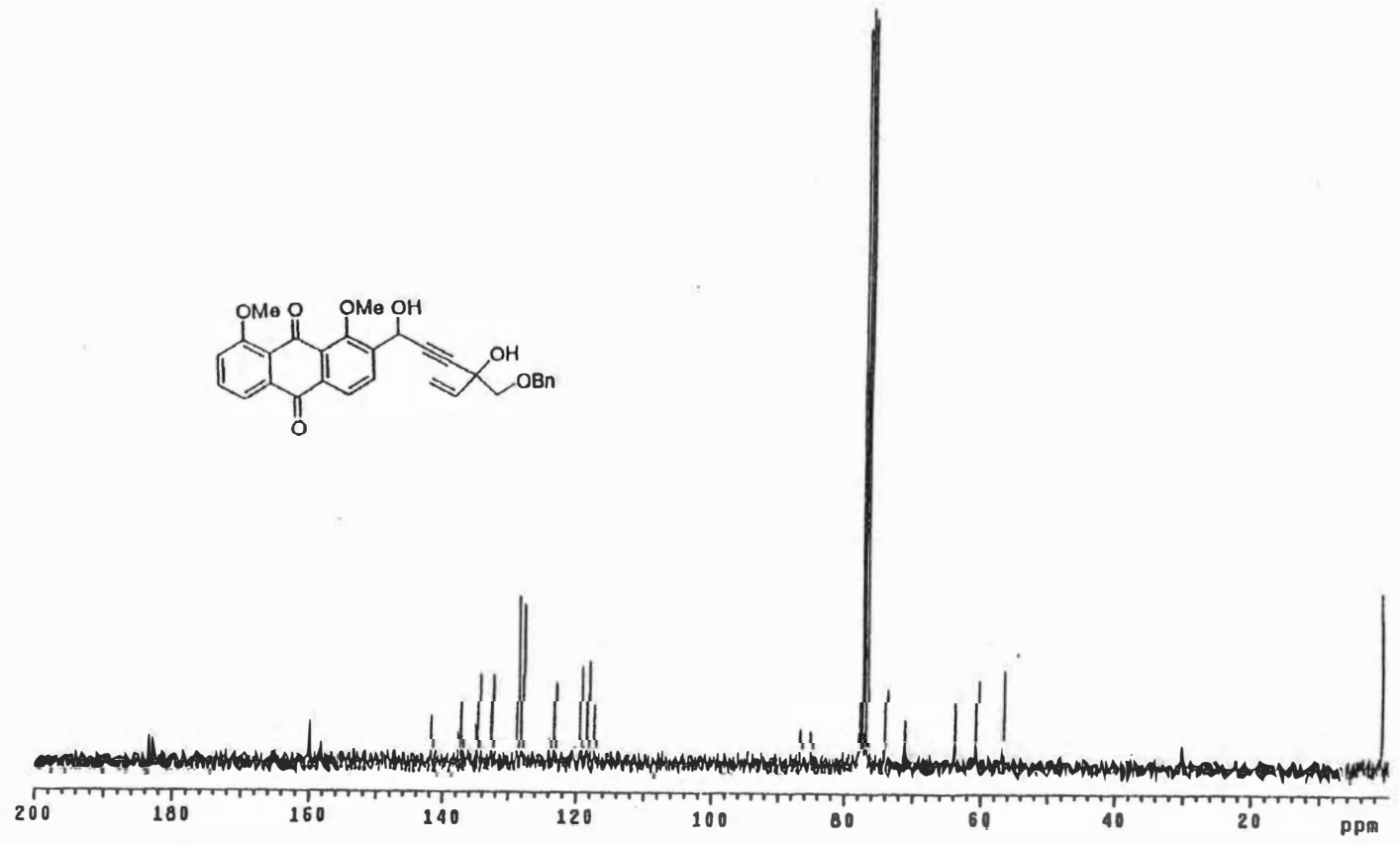
^{1}H NMR spectrum of 1-Hydroxy-2-propenylanthraquinone (**2.63**).



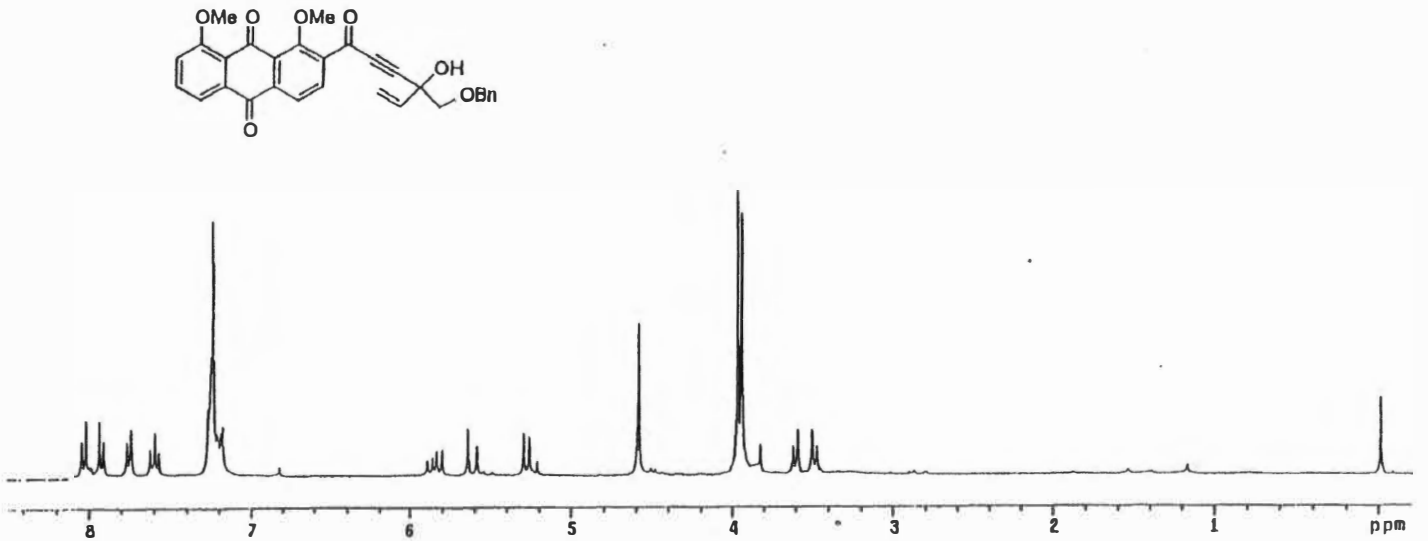
^{13}C NMR spectrum of 1-Hydroxy-2-propenylanthraquinone (**2.63**).



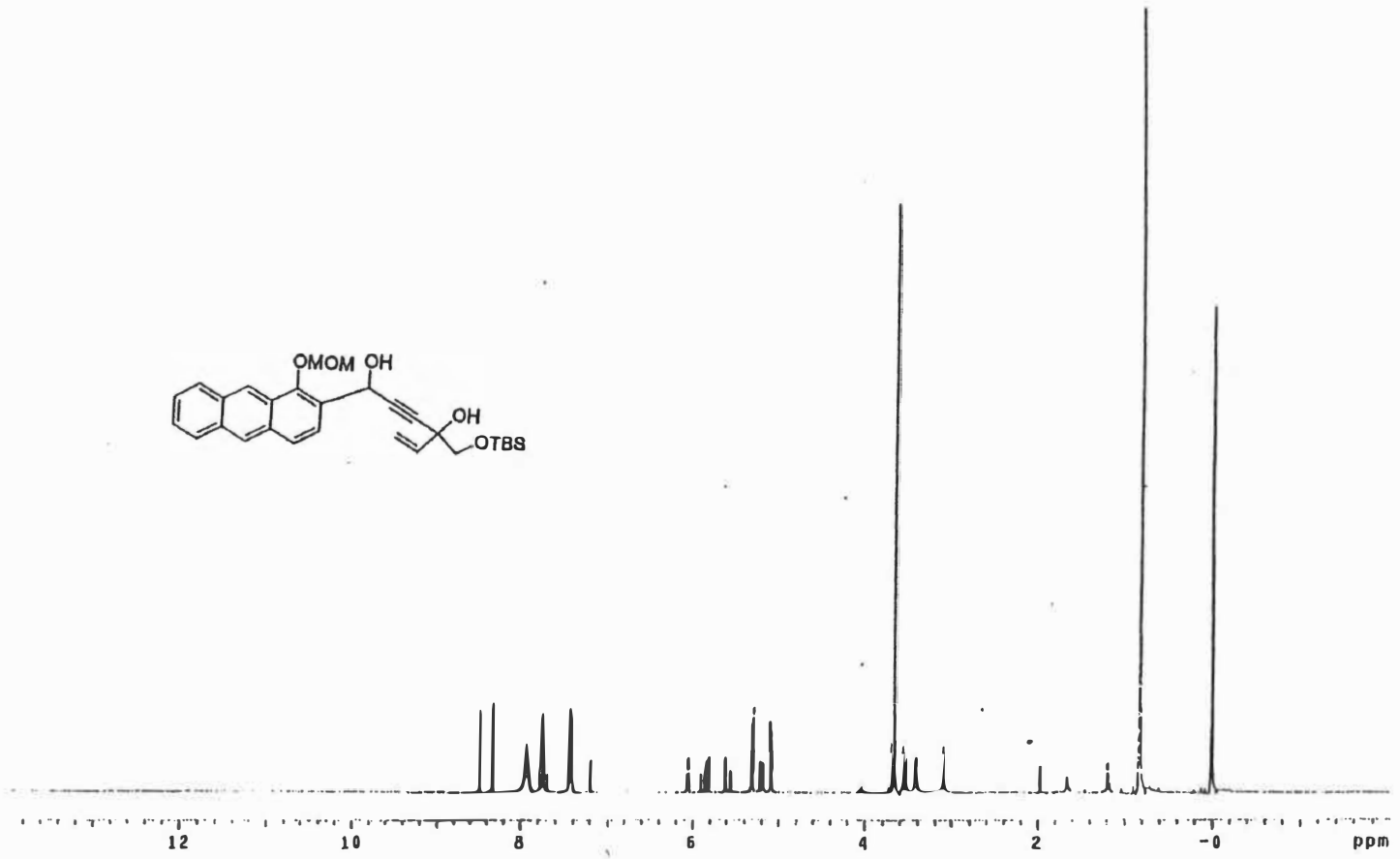
^{1}H NMR spectrum of 2-(4-Benzyloxymethyl-1,4-dihydroxyhex-5-en-2-ynyl)-1,8-dimethoxyanthraquinone (**2.64**).



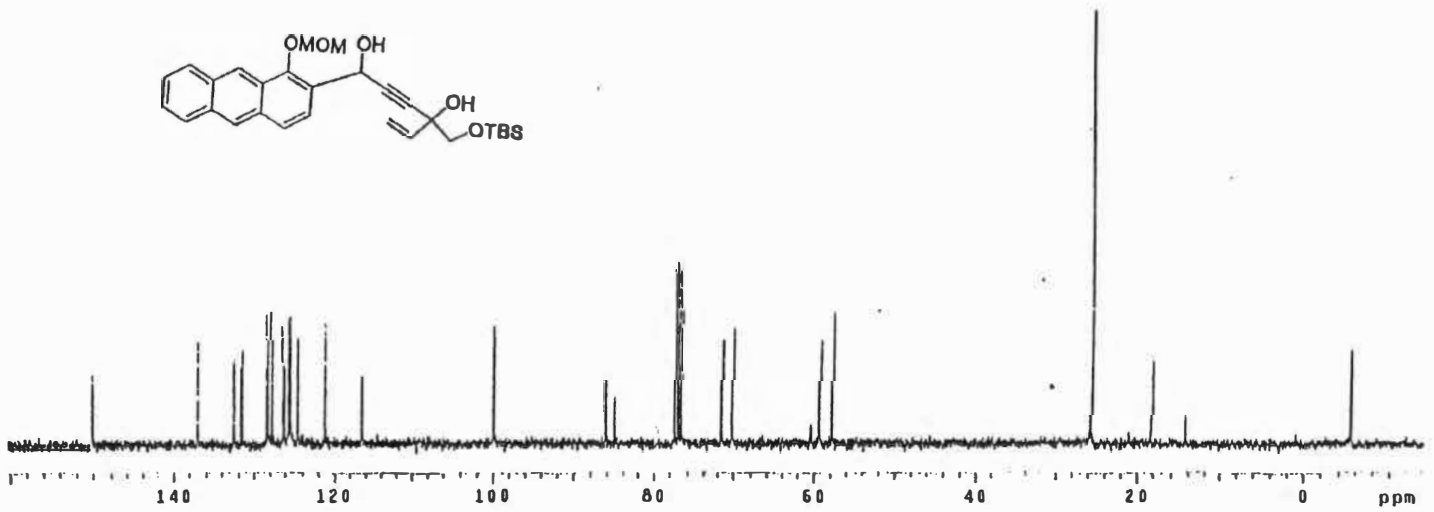
^{13}C NMR spectrum of 2-(4-Benzyloxymethyl-1,4-dihydroxyhex-5-en-2-ynyl)-1,8-dimethoxyanthraquinone (**2.64**).



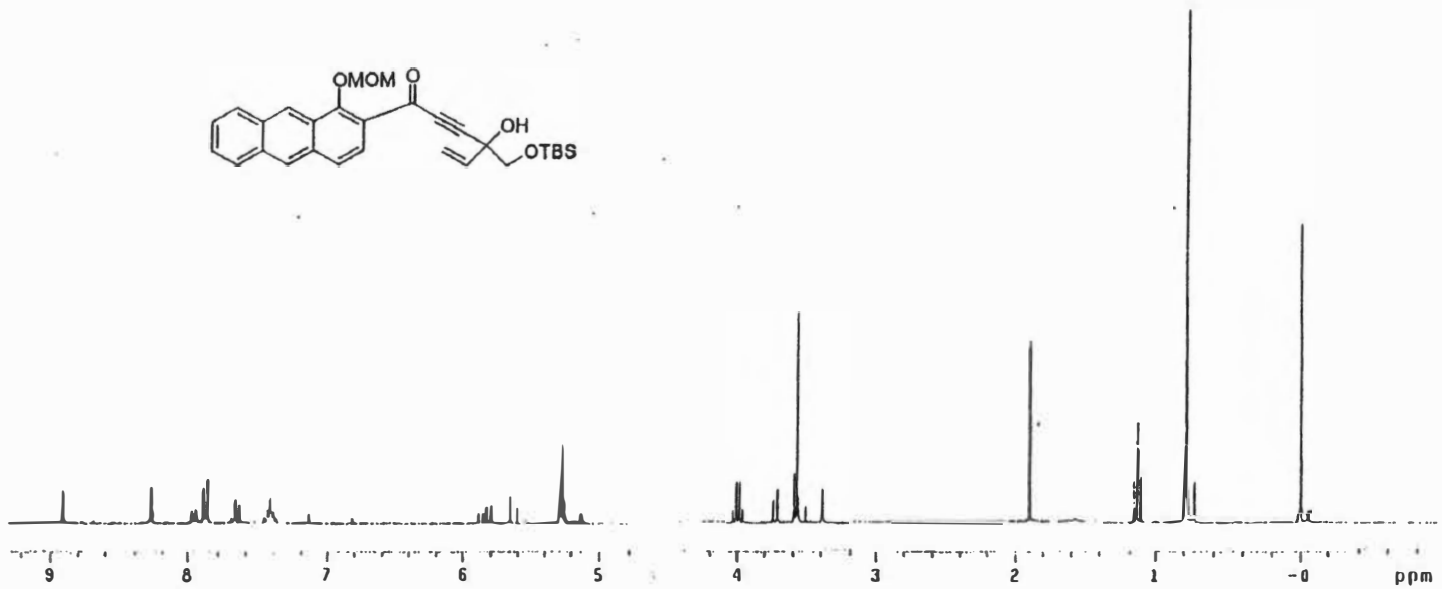
^{1}H NMR spectrum of 2-(4-Benzyloxymethyl-4-hydroxyhex-5-en-2-ynoyl)-1,8-dimethoxyanthraquinone (**2.65**).



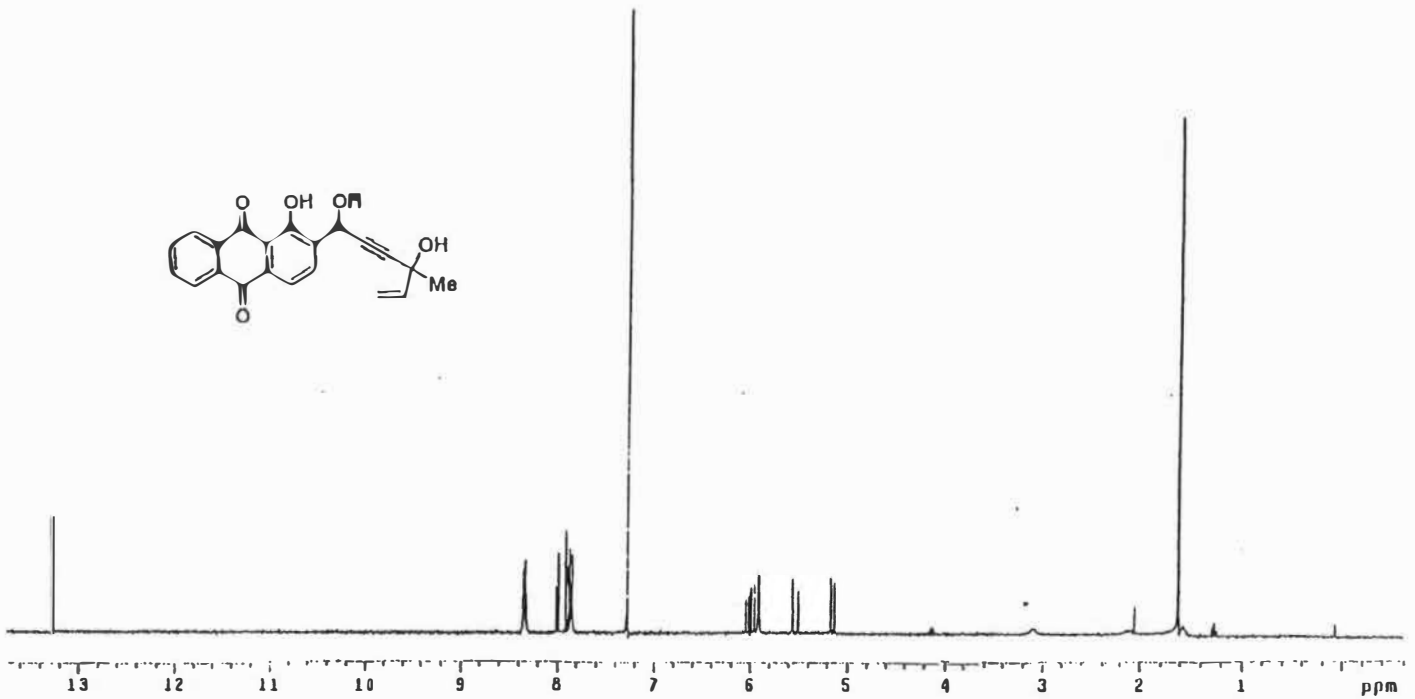
^{1}H NMR spectrum of 4-(*tert*-Butyldimethylsilyloxymethyl)-1-(1-methoxymethoxyanthracen-2-yl)hex-5-en-2-yne 1,4-diol (**2.66**).



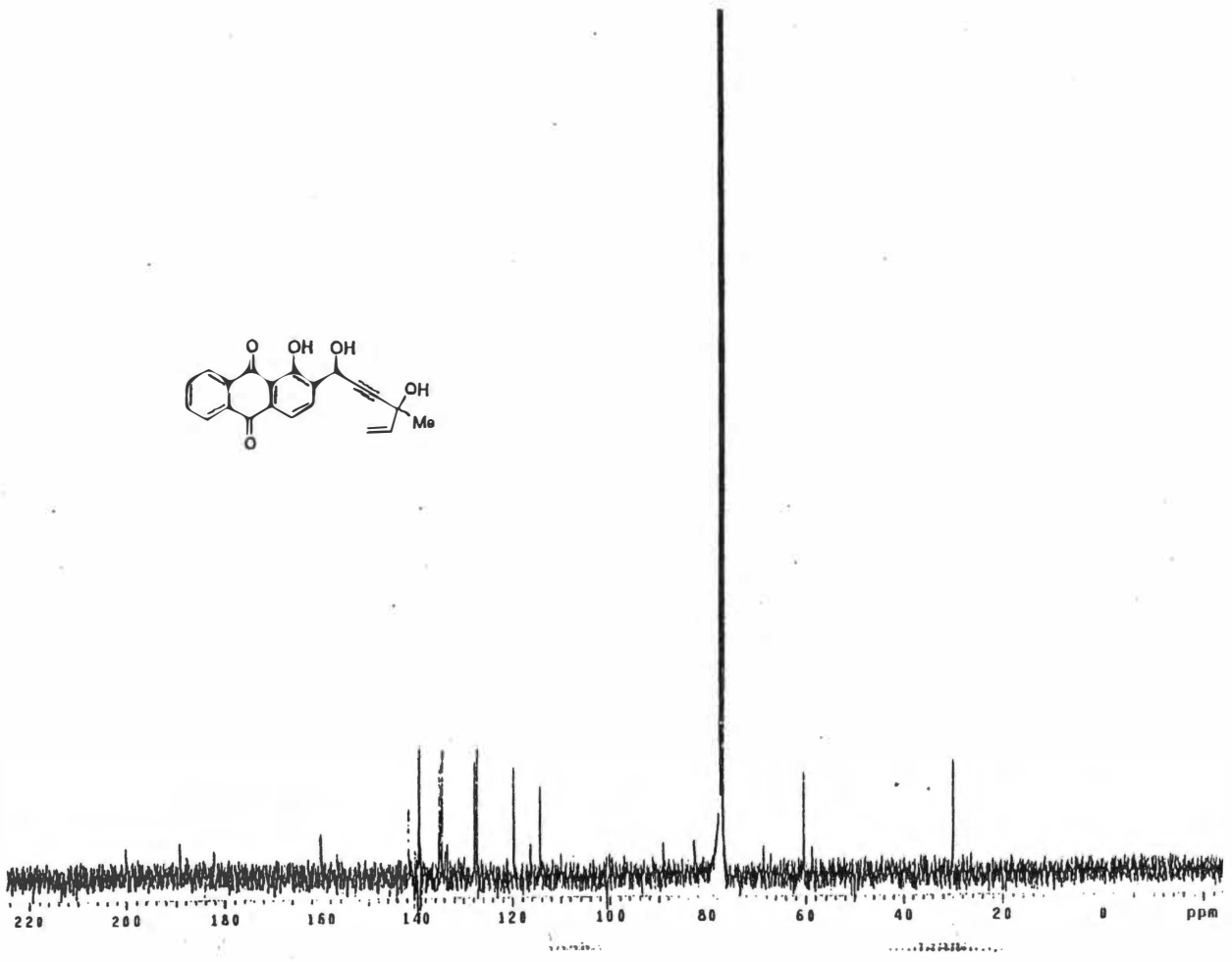
^{13}C NMR spectrum of 4-(*tert*-Butyldimethylsilyloxymethyl)-1-(1-methoxymethoxyanthracen-2-yl)hex-5-en-2-yne 1,4-diol (**2.66**).



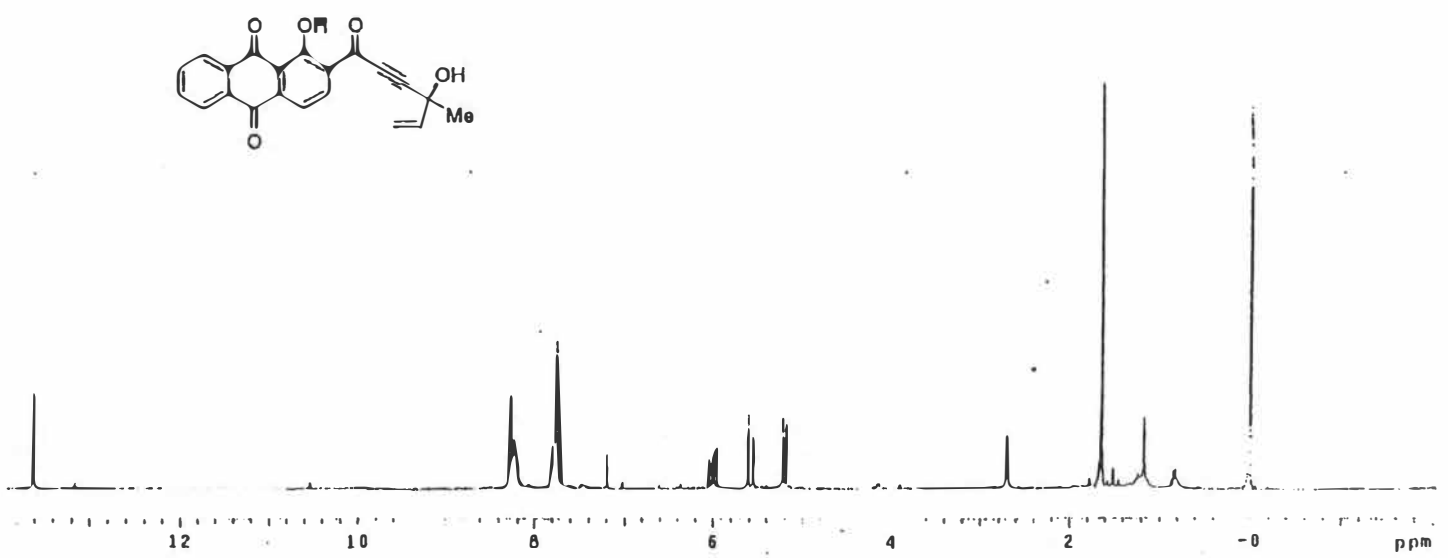
^{1}H NMR spectrum of 4-(*tert*-Butyldimethylsilyloxymethyl)-4-hydroxy-1-(1-methoxymethoxyanthracen-2-yl)hex-5-en-2-yn-1-one (**2.67**).



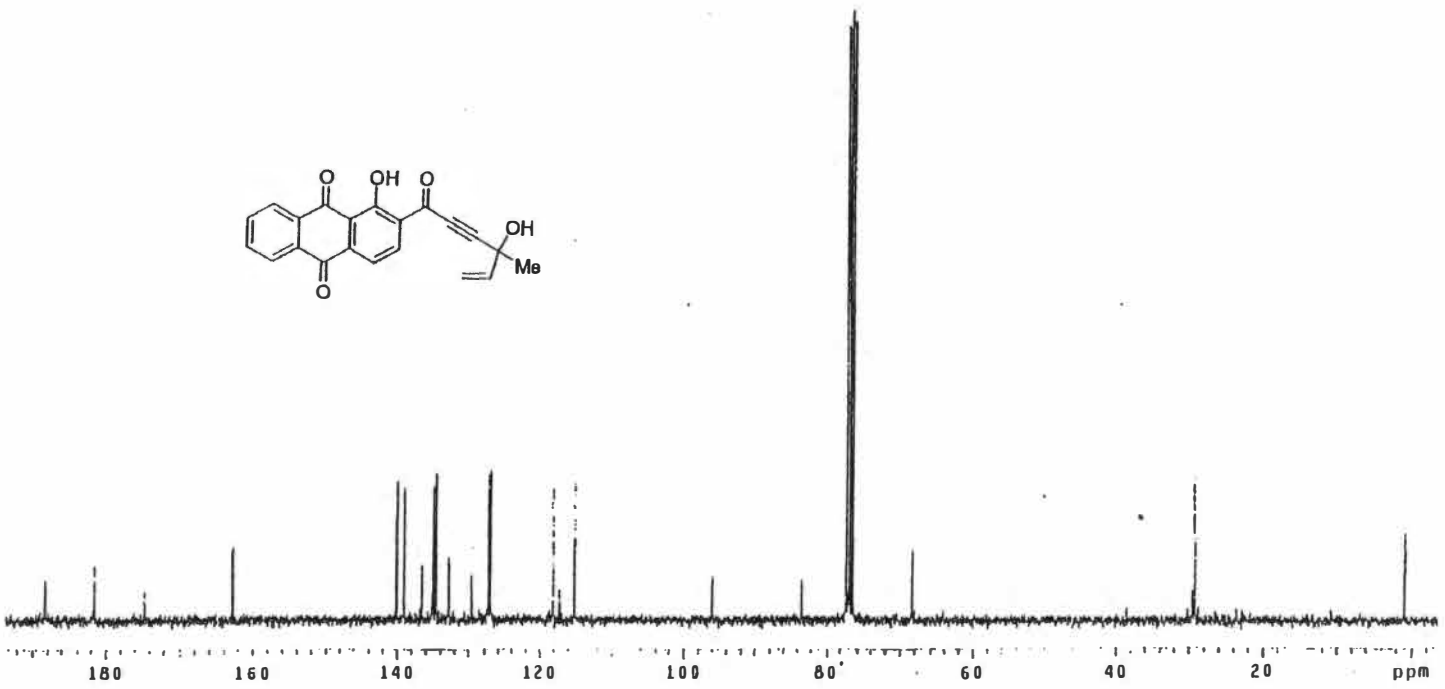
^{1}H NMR spectrum of 2-(1,4-Dihydroxy-4-methylhex-5-en-2-ynyl)-1-hydroxyanthraquinone (**2.68**).



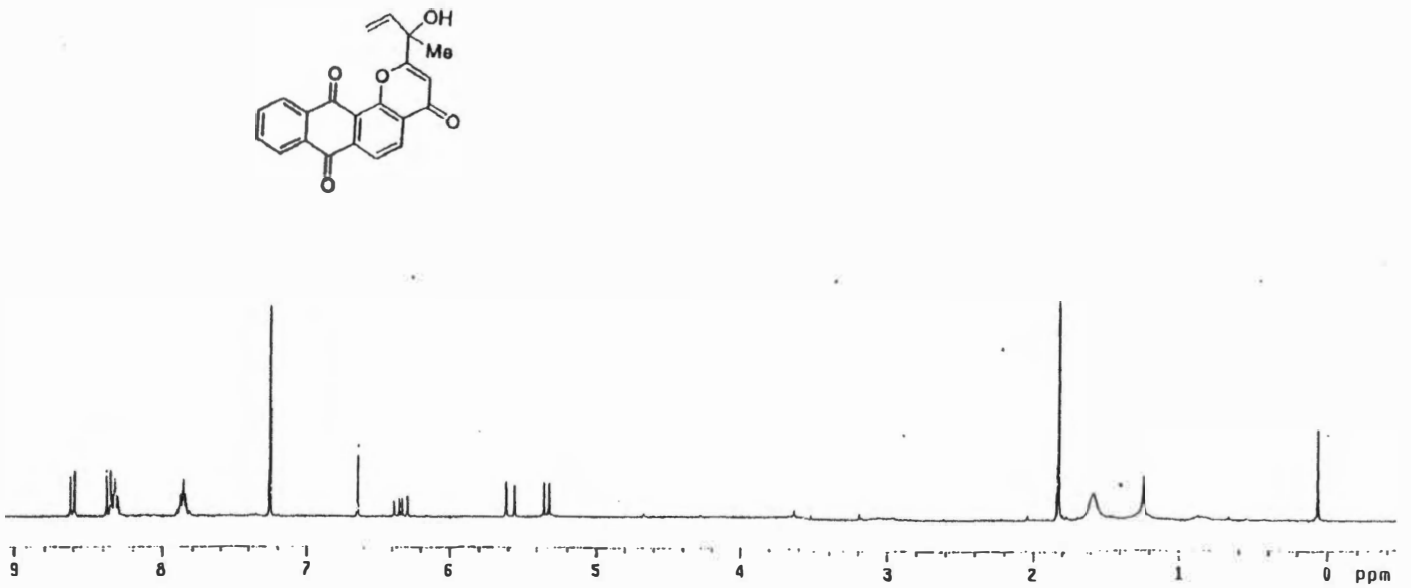
^{1}H NMR spectrum of 2-(1,4-Dihydroxy-4-methylhex-5-en-2-ynyl)-1-hydroxyanthraquinone (**2.68**).



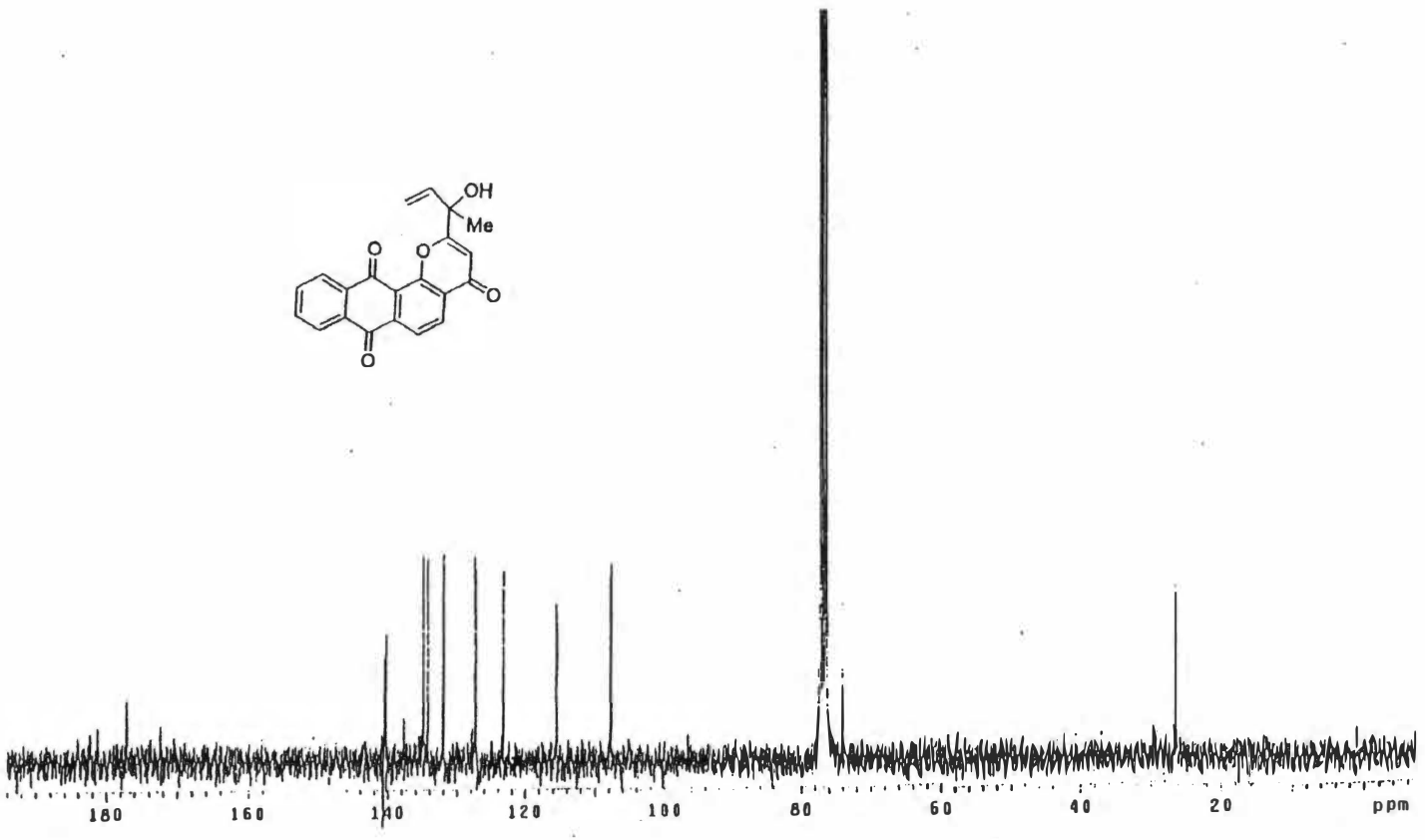
^{1}H NMR spectrum of 1-Hydroxy-2-(4-hydroxy-4-methylhex-5-en-2-ynoyll)anthraquinone (**2.69**).



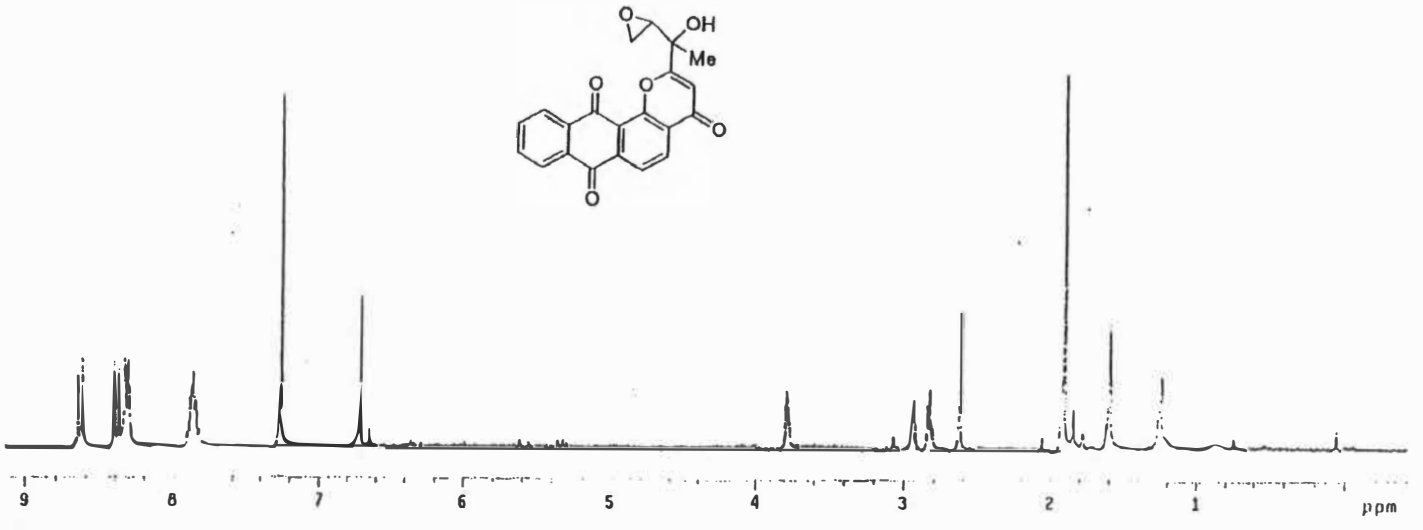
^{13}C NMR spectrum of 1-Hydroxy-2-(4-hydroxy-4-methylhex-5-en-2-ynoyl)anthraquinone (**2.69**).



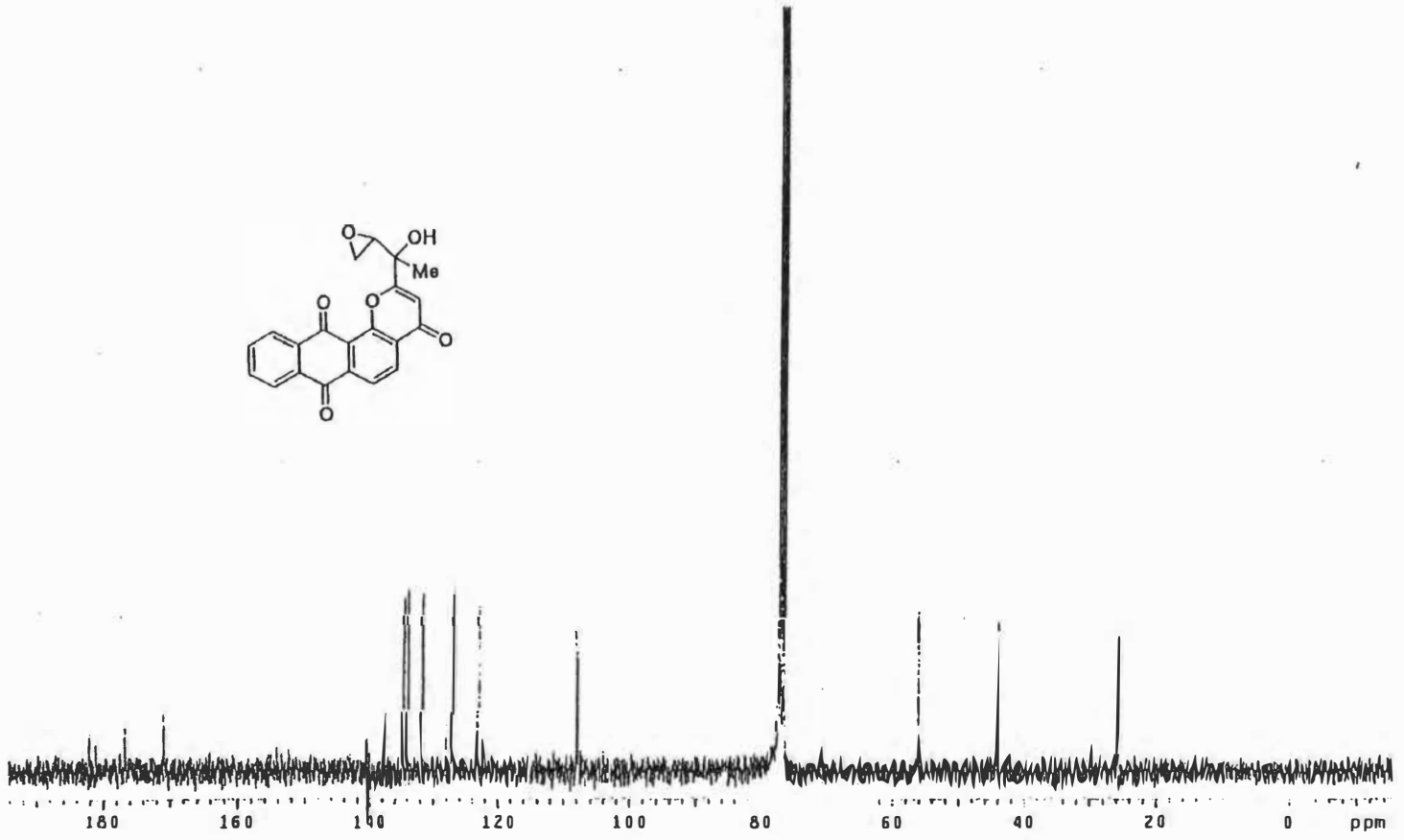
^{1}H NMR spectrum of 2-(1-Hydroxy-1-methylallyl)-1-oxabenzo[*a*]anthracene-4,7,12-trione (**2.70**).



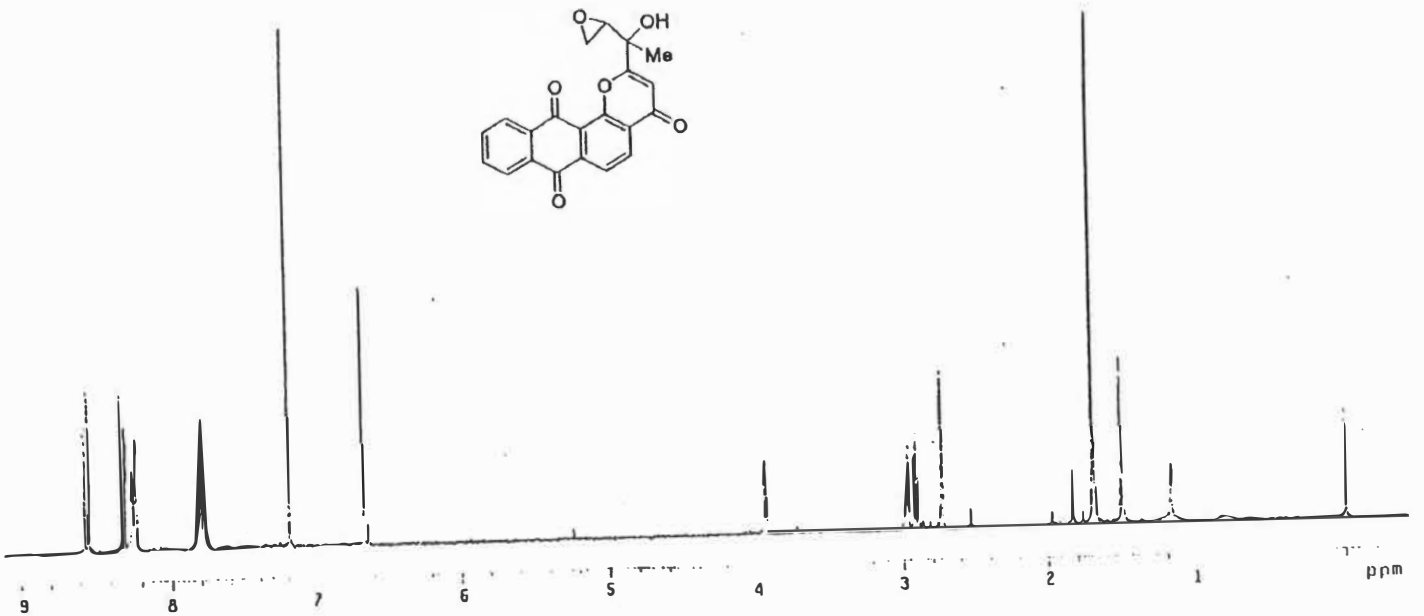
^{13}C NMR spectrum of 2-(1-Hydroxy-1-methylallyl)-1-oxabenzo[*a*]anthracene-4,7,12-trione (**2.70**).



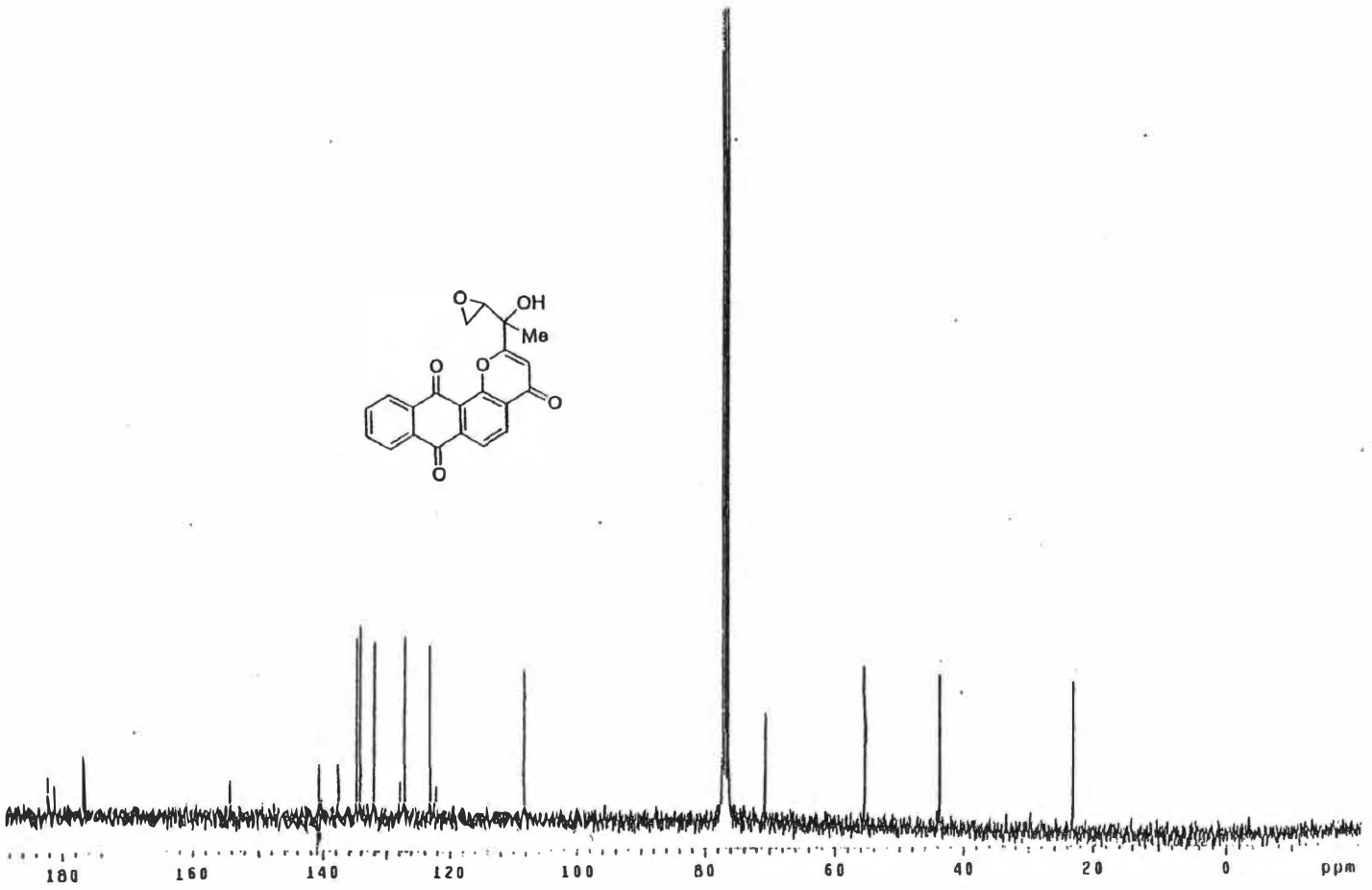
^{1}H NMR spectrum of 2-(1-Hydroxy-1-oxiranylethyl)-1-oxabenzo[*a*]anthracene-4,7,12-trione, Diastereomer A (**2.71**).



^{13}C NMR spectrum of 2-(1-Hydroxy-1-oxiranylethyl)-1-oxabenzo[*a*]anthracene-4,7,12-trione, Diastereomer A (**2.71**).



^{1}H NMR spectrum of 2-(1-Hydroxy-1-oxiranylethyl)-1-oxabenzo[*a*]anthracene-4,7,12-trione, Diastereomer B (**2.71**).



^{13}C NMR spectrum of 2-(1-Hydroxy-1-oxiranylethyl)-1-oxabenzo[*a*]anthracene-4,7,12-trione, Diastereomer B (**2.71**).

VITA

Sarah Autumn Headrick was born on August 6, 1974 to John A. Sanzenbacher, Jr. and Barbara J. Sanzenbacher in Bowling Green, Ohio. The family later moved to Maumee, Ohio where she graduated from Maumee High School in 1993. She then enjoyed four years at Bluffton College of Bluffton, Ohio while playing for the college soccer team and receiving her B.A. degree in Chemistry .

In the summer of 1993, Sarah began her work with Dr. David C. Baker at the University of Tennessee as a undergraduate researcher. Her work continued in the fall of 1993 when she began her graduate studies under Dr. Baker. The focus of her studies was on synthetic studies of anti-cancer and anti-HIV agents and upon completion of her PhD in spring 2003, she has accepted a position at ATK Thiokol in Promontory, Utah.