I. STEREOSELECTIVE EXCHANGE OF KETONE α-PROTONS IN TRIFLUOROACETIC ACID-*d*

II. SYNTHESIS OF ESTROGENIC STEROID HOMOLOGS

By

MIKE DOUGLAS CAGLE

Bachelor of Science
Hardin-Simmons University
Abilene, Texas
1987

Master of Science
Oklahoma State University
Stillwater, Oklahoma
1990

Submitted to the Faculty of the
Graduate College of the
Oklahoma State University
in Partial fulfillment of
the requirements for
the Degree of
DOCTOR OF PHILOSOPHY
July, 1993

I. STEREOSELECTIVE EXCHANGE OF KETONE α-PROTONS IN TRIFLUOROACETIC ACID-*d*

II. SYNTHESIS OF ESTROGENIC STEROID HOMOLOGS

Thesis Approved:

E. J. Eisenbraun
Thesis Adviser

Richard A. Bunce

H. A. Mottola

Andrew Mort

Thomas C. Collins
Dean of the Graduate College

ACKNOWLEDGMENTS

I am deeply indebted to my research adviser, Dr. E. J. Eisenbraun, for his encouragement, friendship, guidance, and patience throughout the course of my graduate studies. I also wish to extend my appreciation to my committee members, Dr. H. A. Mottola, R. A. Bunce, and A. J. Mort for their help and guidance. I would also like to thank E. M. Holt for her x-ray analysis.

I would especially like to thank Dr. G. J. Mains for his assistance, encouragement, and advice in the uses of MOPAC and interpretation of the resulting data.

I wish to thank the faculty, staff, and my fellow graduate students for their help, suggestions, and friendship over the years. I particularly wish to thank S. Shankar, Kirk Payne, Juan Zhang, and Dr. Firsan, who have listened to my complaints, problems, and ideas for three years without failing to provide encouragement and friendship.

I would also like to recognize my parents, Mr. and Mrs. Melvin D. Cagle, for their constant support, understanding, and love provided throughout the years.

TABLE OF CONTENTS

Chapter Page

LIST OF TABLES

LIST OF FIGURES

LIST OF SPECTRA

SYMBOLS AND ABBREVIATIONS

°C	degree Centigrade
cm	centimeter
FT	Fourier transform
g	gram
GC	gas chromatography
h	hour
HPLC	high performance liquid chromatography
Hz	Hertz
IR	infrared
L	liter
LDA	lithium diisopropylamide
M	molar
m	multiplet
mL	milliliter
mm	millimeter
mmol	millimole
d	doublet
mol	mole
mp	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
p	page
pp	pages
ppm	parts per million
q	quartet
RT	room temperature
s	singlet
t	triplet
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TMS	tetramethylsilane

CHAPTER I

INTRODUCTION AND HISTORICAL

The labeling of compounds with deuterium or tritium has become important in elucidating reaction mechanisms (by isotope effects, and/or product tracing),[1-5] determining mass spectral fragmentation pathways,[6-9] tracing metabolic pathways,[10a,11] and assigning NMR spectra.[12,13] The C-D bond is considerably stronger than the C-H bond which gives rise to isotope effects.[14a] Therefore, deuterium-labeled analogs of drugs have potential as medicinal agents since the expected isotope effect can favorably influence the rate of metabolism.[15]

The usefulness of these deuterated products has prompted extensive research into the labeling of organic compounds. Some of the methods that have been used to incorporate deuterium into organic compounds are catalytic deuteration of olefins,[10b,14b] reduction of aldehydes, ketones, and halides with lithium aluminum deuteride or sodium borodeuteride,[10c,14c] exchange of hydrogen atoms attached at benzylic and aromatic positions with strong deuterio-mineral acids (DCl, D_2SO_4), D_2O with BF_3, and D_2O with rhodium(III) chloride or platinum,[14d] and reacting organometallic compounds with deuterium containing acids (D_2O, D_2SO_4, DCl).[14e] Ketones with α-protons have become a major source of labeled organic compounds through exchange of the α-hydrogens with deuterium.[16] Efficient procedures have been developed for the large-scale (kilogram or larger) production of α-deuterated ketones.[17] The majority of laboratory-scale, α-hydrogen-deuterium exchange

reactions of ketones are base catalyzed with alkali-metal carbonate, alkoxide, or deuteroxide.[16] These exchange procedures usually require multiple-exchange steps with a large excess of deuterated solvents and a solvent extraction to isolate the labeled material. These multiple steps and extraction processes can result in loss of the product, introduction of side reactions, and back exchange. To avoid the extraction step, acetyl chloride has been used to neutralize sodium ethoxide by aspirating AcOEt/EtOD/EtOH in a base-catalyzed exchange.[18] Exchange utilizing deuteroxide, triethylamine, and dioxane followed by fractional distillation has also been used to avoid extraction.[1] Acid-catalyzed exchange has been used with DCl or DCl mixed with other acids ($DCl/D_3PO_4/D_2O$).[16] Other methods include the deuteration of ketones through enamines.[19] These acid-catalyzed procedures also require a solvent extraction to isolate the labeled material.

Recently in our laboratory, the use of neat trifluoroacetic acid-*d* (TFA-*d*) as a deuterium exchange solvent for preparing gram-quantity samples of α-deuterated ketones was investigated.[20,21] This procedure proved to be a highly effective method of obtaining α-deuterated ketones requiring less deuterated solvent, no extraction, and fewer overall manipulations. A single flask served for both the exchange and, after the spent mixture of TFA-*d*/TFA had been pumped from the flask, distillation of the final product.[20] At room temperature, the exchange is comparatively free of acid-catalyzed side reactions, and deuteration occurs exclusively at the α-position for simple ketones.[20] The versatility of this exchange is quickly realized from examination of the structures previously investigated.[20]

These ketones are shown in Tables I, II, and III and their structures are given in the glossary: 2-heptanone (**1**), 2-octanone (**2**), 3-heptanone (**3**), cyclopentanone (**4**), 2-methylcyclopentanone (**5**), cyclohexanone (**6**), 2-*t*-

butylcyclohexanone (**7**), 3-*t*-butylcyclohexanone (**8**), 4-*t*-butylcyclohexanone (**9**), cis-2,6-dibenzyl-4-*t*-butylcyclohexanone (**10**), 1-phenyl-2-propanone (**11**), 1-phenyl-1-propanone (**12**), 4-acetyl-6-*t*-butyl-1,1-dimethylindan (**13**), 1-(8'-methyl-1',2',3',4'-tetrahydronapthyl)-1-ethanone (**14**), 4'-methyl-1-acetonapthone (**15**), 2-acetonapthone (**16**), 1-(2-naphthyl)-1-hexanone (**17**), 1-(5',6',7',8'-tetrahydro-2-naphthyl)-1-hexanone (**18**), 1,2-diphenyl-1-ethanone (**19**), 1,3-diphenyl-1-propanone (**20**), 1-(2-naphthyl)-3-phenyl-1-propanone (**21**), 1-indanone (**22**), 1-tetralone (**23**), 2,5,8-trimethyl-1-tetralone (**24**), 3,5,8-trimethyl-1-tetralone (**25**), 6-methoxy-1-tetralone (**26**), 7-methoxy-1-tetralone (**27**), 3-*t*-butyl-1-tetralone (**28**), 1,3-diphenyl-1,3-propane-dione (**29**), 2-phenyl-1,3-indandione (**30**), and dibenzocycloheptadienone (dibenzosuberone) (**31**), 2-benzylidene-1-tetralone (**32**), 2-(3,4-dihydro-1-naphthyl)-3,4-dihydro-1-(2*H*)-naphthalenone (**33**), 2,5-dibenzylindene-3-methylcyclopentanone (**34**), cholestenone (**35**), β-ionone (**36**), camphor (**37**), and androsterone (**38**).

Table I. Conditions for α-Hydrogen/Deuterium Exchange of Ketones (25 °C for 20 hours)

ketone	mole ratio of TFA-*d*	number of cycles	% exchanged	number exchanged
1	1 : 8	5	>95	5
2	1 : 4	7	>97	5
3	1 : 8	5	>95	4
4	1 : 8	4	>95	4
5	1 : 8	4	>95	3

Table II. Conditions for α-Hydrogen/Deuterium Exchange of Ketones

(25 °C for 20 hours)

ketone	mole ratio of TFA-*d*	number of cycles	% exchanged	number exchanged
6	1 : 8	4	>95	4
7	1 : 8	4	>90	3
8	1 : 8	4	>90	4
9	1 : 8	4	>90	4
10	1 : 8	3	>95	2
11	1 : 8	1	85	(CH_2)
			30	(CH_3)
	1 : 8	9	>95	5
12	1 : 8	4	>95	2
13	1 : 4	5	>90	3
14	1 : 8	4	75	(CH_3)
			10	(CH)
15	1 : 8	4	>95	3
16	1 : 4	5	>95	3
17	1 : 8	4	>95	2
18	1 : 8	4	>95	2
19	1 : 8	1	>95	2
20	1 : 8	3	>95	2
21	1 : 8	3	>95	2
22	1 : 4	4	>95	2
23	1 : 4	4	>90	2
24	1 : 4	4	>95	1

Table III. Conditions for α-Hydrogen/Deuterium Exchange of Ketones

(25 °C for 20 hours)

ketone	mole ratio of TFA-*d*	number of cycles	% exchanged	number exchanged
25	1 : 15	4	>90	2
26	1 : 8	4	>95	2
27	1 : 8	4	>95	2
28	1 : 8	4	>95	2
29	1 : 8[a]	1	>95	2
30	1 : 8	1	>95	1
31[b]	1 : 8	8[c]	0	
32	1 : 8	8[c]	0	
33	1 : 8	1	>95 (α,γ)	
34[b]	1 : 8	3[d]	0	
35	1 : 12	4	21	2
			42	3
			34	4
			3	5
36[e]	1 : 4	3		
37[b]	1 : 4	3[c]	>90	2
38[f]	1 : 77	6	>90	1

[a]50 % $CDCl_3$. [b]Heated at reflux instead of 25 °C. [c]168 h per cycle. [d]68 h per cycle. [e]Product decomposed. [f]The hydroxyl group of the product became esterified.

The exchange process can be monitored by withdrawing samples and directly acquiring ^{1}H and ^{13}C NMR spectra without the addition of other solvents.[20,21,22] This is a significant advantage over other exchange methods in which the product must be isolated before an NMR spectrum can be obtained to determine the extent of incorporation. The use of TFA-*d* also allows a small sample of ketone to be used to determine its stability to the exchange conditions before a larger amount of material is committed.[20] For ^{1}H NMR spectra using TFA-*d*, downfield shifts are observed for hydrogens at the α-position of the ketone carbonyl.[22]

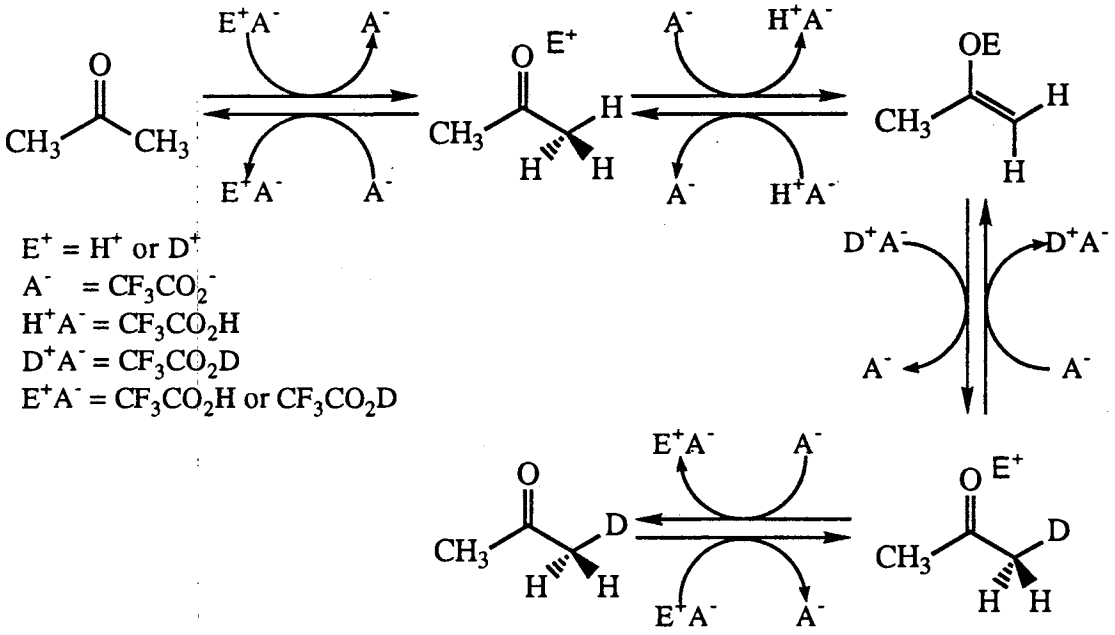


Figure 1. Mechanism for the TFA-*d* catalyzed deuterium exchange of acetone.

While the mechanism for the TFA-*d* catalyzed deuterium exchange of ketones has not been delineated, the likely mechanism is acid-catalyzed

enolization followed by acid-catalyzed ketonization.[20] This process can be visualized for acetone as shown in Figure 1. The expected free energy-coordinate profile of the reaction pathway is shown in Figure 2.[23]

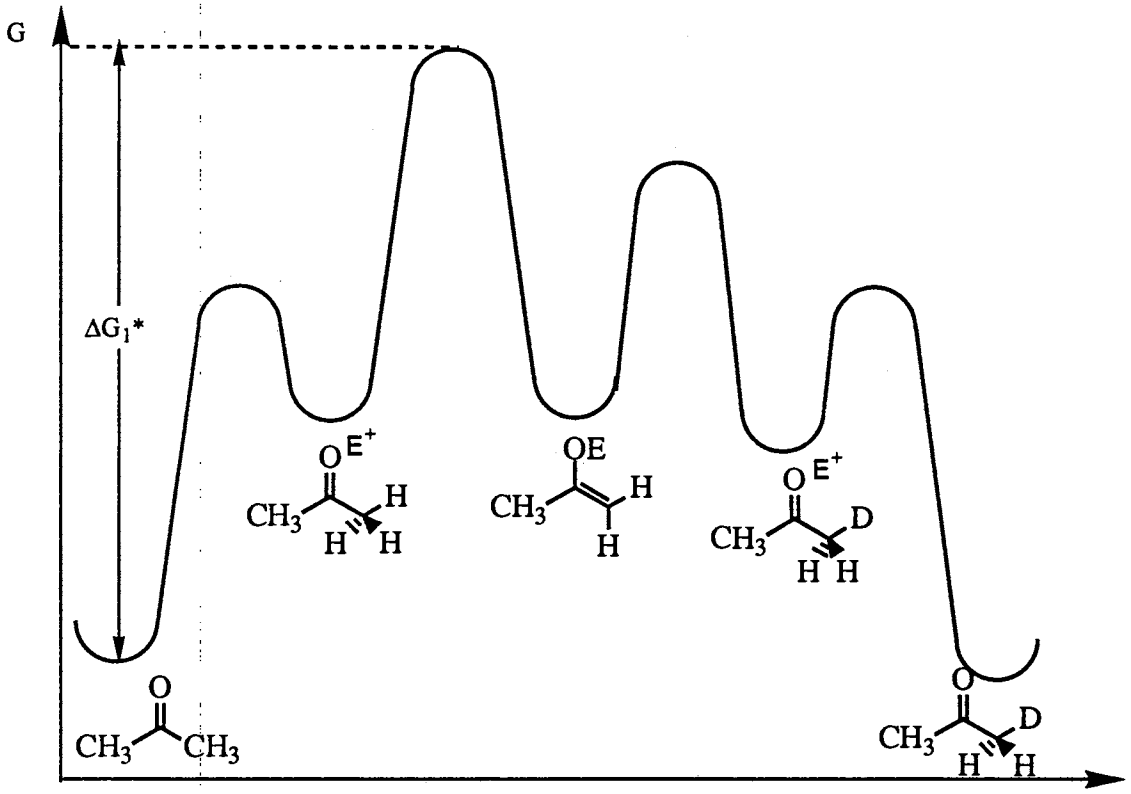


Figure 2. Free energy-coordinate profile for the TFA-*d* catalyzed deuterium exchange of acetone.

Specific acid catalysis is the generally accepted mechanism for the enolization of ketones.[24] In this mechanism, the abstraction of the α-proton from the O-protonated ketone is expected to be the rate determining step[24] due to the weakly basic nature of the trifluoroacetic anion. It was demonstrated by

Swain and Rosenberg that even in strongly acidic medium (94% H_2SO_4) a base was always necessary for enolization.[25]

This mechanism of O-protonation followed by abstraction of the α-proton implies that this enolization is a bimolecular reaction with the initial rate being given by the following equation where D^+ = deuterium ion, DA = acid, and A^- = conjugate base ion:[23]

$$\text{rate} = k\,[\text{ketone}][DA][A^-]$$

Since $pKa = -\log([D^+][A^-]/[DA])$, this rate equation implies a dependence of the enolization rate on the pKa of the acid. Such relationships have been found for the enolization of cyclohexanone by various carboxylic acids, however there were some exceptions.[26] The mechanism of acid-catalyzed ketonization of the enol is expected to be the reverse of enolization.[23] This rate equation does not take into account the isotope effects on the pKa of the acid, solvent isotope effects, or the possible secondary isotope effects that may be present once the ketone has undergone partial deuterium-hydrogen exchange.[14g] Therefore, this rate equation is expected to be valid only for the initial part of the exchange.

In contrast to TFA-*d*, tetradeuteroacetic acid is ineffective as an exchange reagent for catalyzing α-deuterium/hydrogen exchange in ketones.[20] For ^1H NMR spectra using tetradeuteroacetic acid, no downfield shifts are observed for hydrogens at the α-position of the ketone carbonyl.[20]

CHAPTER II

RESULTS AND DISCUSSION

Synthesis Problems and Studies

The successful use of TFA-*d* in yielding preparative samples (81-97% isolated yields) of α-labeled ketones with a high incorporation of the deuterium label[20] (Table I) prompted a more extensive study. The difference in rates of deuterium/hydrogen exchange of ketones due to steric inhibition or ease of enolization is known.[6,12,27,28,29] For example, the rate of deuteration of the methylene group of 2-butanone is more than twice the deuteration rate of the methine group of 3-methyl-2-butanone.[27] Therefore, ketones which required abnormally long reaction times, different conditions, more rigorous conditions, or underwent side reactions were selected for further investigation.[20]

The ketone 2,5,8-Trimethyl-1-tetralone (**24**) readily undergoes exchange[21] and therefore it was selected to establish a standard exchange which would avoid secondary isotope effects.[14a] The exchange of **24** was carried out in an NMR tube and the progress of the exchange was followed by taking spectra at specific intervals. The exchange initially proceeded rapidly and appeared almost complete within 34 h. This exchange can be followed in two ways; the decreasing area of the proton signal at 2.80 ppm due to the proton alpha to the carbonyl group or the increasing area of the proton signal at 11.6 ppm due to the trifluoroacetic acid proton. This change in area of these two proton signal are shown in Figure 3. From these data, it appears that the

number of treatment cycles is not as critical as the time needed for the exchange. However, the exchange seems to asymptotically approach a limit which is probably the result of an equilibration of the reaction components. To achieve a greater incorporation of deuterium, the spent TFA-*d*/TFA needs to be aspirated and a fresh charge of TFA-*d* added to the ketone.

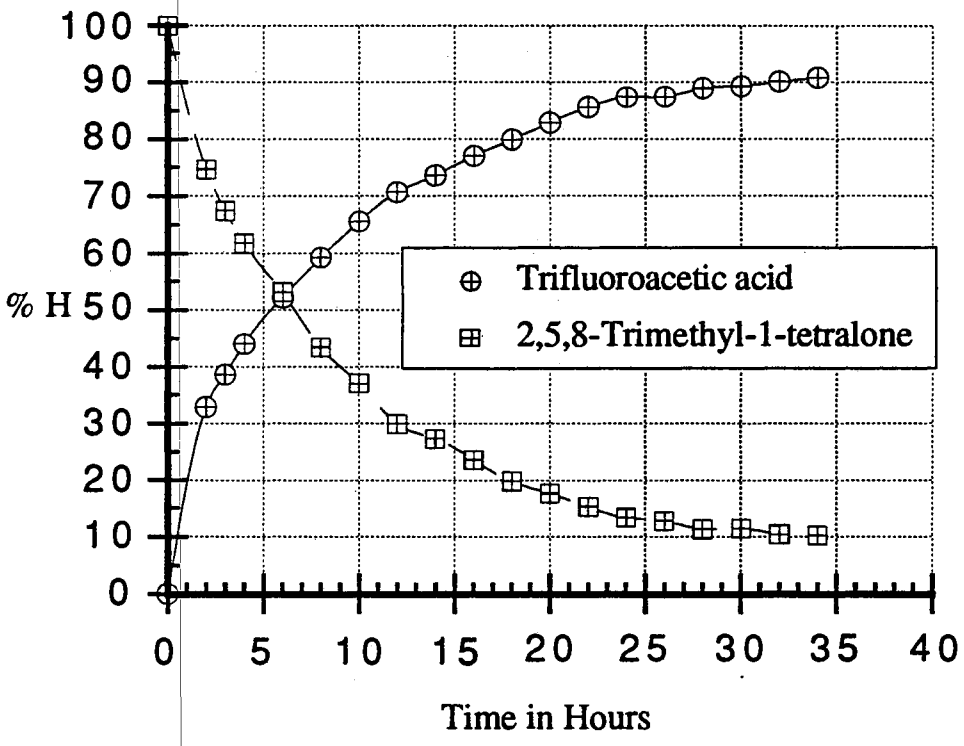


Figure 3. Graph showing % α-hydrogen of 2,5,8-trimethyl-1-tetralone (**24**), and % hydrogen of TFA-*d* vs. time as determined through ^{1}H NMR studies.

The next system studied was 1-phenyl-2-propanone (**11**). In the original study, the deuterium-hydrogen exchange was carried out with a mole ratio of 1:8 (**11** : TFA-*d*).[20] This required nine cycles to effect complete deuterium-

hydrogen exchange of the protons alpha to the carbonyl group.[20] For the ^1H NMR study of this deuterium-hydrogen exchange as shown in Figure 4, a single treatment with a mole ratio of 1:10 (**11** : TFA-*d*) was used.[20]

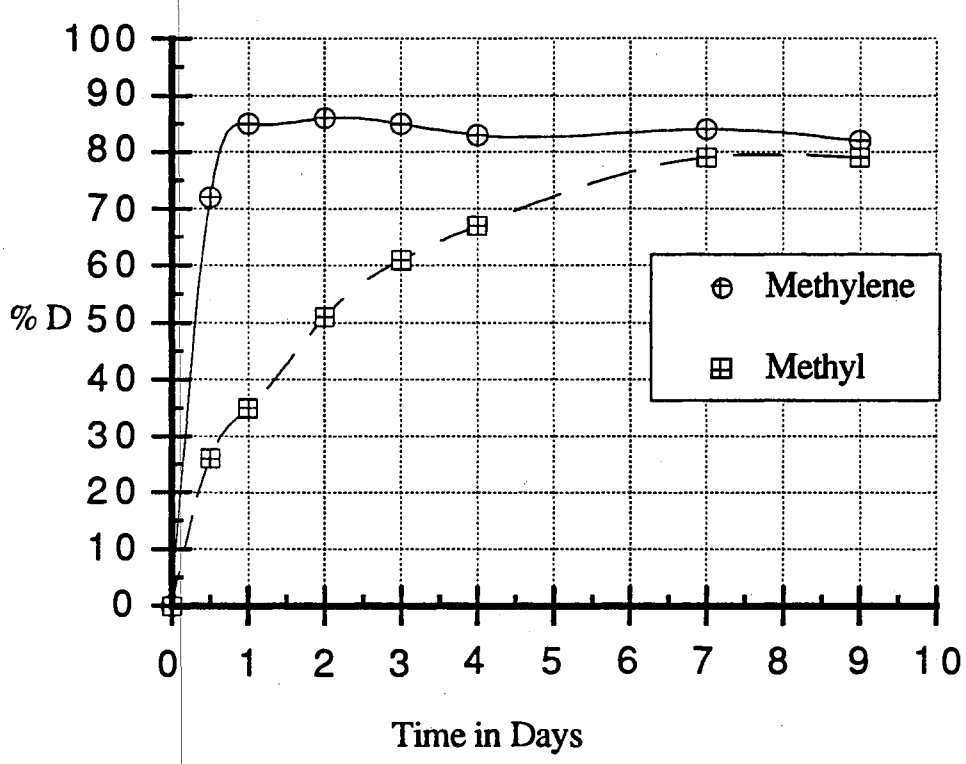
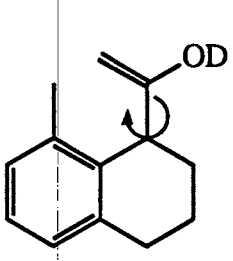


Figure 4. Graph showing % deuterium-hydrogen exchange of the methylene and methyl groups of 1-phenyl-2-propanone vs. time as determined by ^1H NMR exchange study.

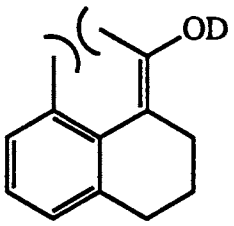
This latter study indicates that the disparity in the rate of exchange of these two groups allows preferential deuterium incorporation at the benzylic position alpha to the carbonyl group.[20] The maximum extent of benzylic (methylene) proton exchange occurred within 24 h, and was followed by a slight decrease probably due to back exchange of these protons.[20] The incorporation

of deuterium at the methyl position steadily increased to a maximum at 80%.[20] Since deuterium incorporation at the benzylic position had decreased to approximately this amount, this may represent equilibration of the various labeled products of **11**, TFA-*d*, and TFA. The observance of this equilibration indicates that the exchange is reversible which is consistent with the proposed exchange mechanism previously shown in Figures 1 and 2. This confirms a need for multiple treatment cycles to achieve maximum incorporation of the deuterium label.

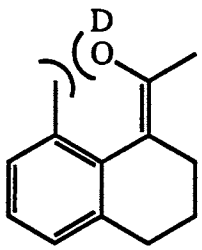
Ketone **14** provided an example wherein preferential deuterium incorporation did not readily occur at the benzylic (methine) position alpha to the carbonyl group. Further investigation revealed that even after 10 treatment cycles, only 30% of the protons at this position exchanged with deuterium.[20] The methyl protons of **14** completely exchanged within 7 treatment cycles at room temperature[20] as expected from the results obtained for ketone **11**. The slow exchange rate at the benzylic position of **14** can be rationalized in terms of unfavorable steric interactions in the enolization step. In the enolization at the benzylic position, either the methyl group or the deuteroxy group is forced into closer proximity with the 8-methyl group resulting in a strained system.[20] Therefore, enolization occurs preferentially at the α-methyl group. This is demonstrated by comparing the three possible enolates (**14 E1**, **14 E2**, **14 E3**) with **14 E2** and **14 E3** shown as planar systems while **14 E1** is considered to undergo free rotation or possibly libration.



14 E1



14 E2



14 E3

A varied response was found for α,β-unsaturated ketones and other olefinic ketones. A study of the α,β-unsaturated ketone cholestenone (**35**) was made as the initial attempts to exchange it appeared to show only partial exchange.[20] Further attempts to exchange this material resulted in decomposition of the ketone to a red oil which would not crystallize. The ^{1}H NMR spectra indicated that rearrangement and isomerization of the double bond had occurred. Investigation of the literature revealed that TFA is capable of causing hydrogenation/deuteration of olefinic sites through generation of cations and subsequent capture of hydride ion.[30]

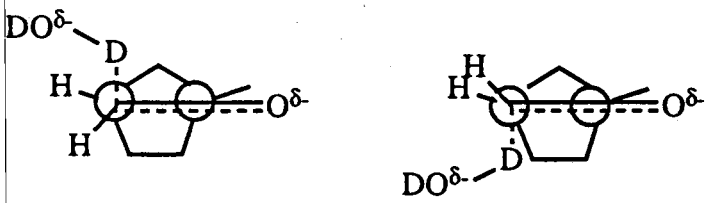
Careful treatment of **33** over a limited time (3 h) allowed exchange of α and γ protons with a 90% yield although longer treatment resulted in decomposition.[20] From these studies, it was determined that this method of exchange is generally unsuitable for compounds containing olefinic functional groups. There are exceptions (such as **34**)[20] which withstand these reaction conditions.

Camphor (**37**) provided a known example in which TFA-*d* was used to effect deuterium-hydrogen exchange.[7,16,31] To effect this deuterium-hydrogen exchange, a solution of **37**, TFA-*d*, and deuterium oxide (in a ratio of 1:10:50) was heated at 130 °C in a sealed tube for 9 days.[7] To obtain the final product, this reaction mixture was neutralized, extracted, and sublimed.[7] This procedure

was originally developed by Djerassi to obtain camphor-d_2 since a base-catalyzed procedure produced only a monodeuterated product.[7,29] Utilizing the neat TFA-*d* procedure at RT showed no detectable deuterium-hydrogen exchange of **37** by ^{1}H NMR or MS analysis.[20] Treatment of **37** with refluxing TFA-*d* however readily gave the dideuterio product[20] (>95% d_2 incorporation, 90+ % isolated yield after sublimation). This procedure has several advantages over the sealed-tube procedure. This earlier method requires a sealed tube, more of the deuterated solvents, a neutralization and extraction step, and finally must be worked-up before determining the extent of deuterium incorporation.[7] Treatment with neat TFA-*d* allows the exchange to be followed by ^{1}H NMR. After exchange is complete, TFA-*d* is aspirated from the sample, and the exchanged product is sublimed from the reaction flask thus avoiding the possibility of back exchange.

Attempts were made to find an intermediate temperature at which only the exo-hydrogen of **37** would undergo exchange. This study was prompted by the report[29] that the base-catalyzed method of exchange (NaOD in a 50/50 solution of dioxane/D_2O) at 25-90 °C gave exclusively the exo-monodeuterated isomer of **37** as determined by ^{1}H NMR (MS analysis 85% d_1). The dideuterio isomerof **37** can be obtained with base catalysis, if high pressures and temperatures are used.[16] It should be noted that back exchange has been found in similar compounds during quenching of these reactions.[32] Although the ^{1}H NMR indicated that the exo-hydrogen was exchanging faster at 40 °C, the exchange did not occur exclusively at the exo-position. The rate of exchange at this temperature was prohibitively slow detracting from its use as a method for obtaining the monodeuterated exo isomer of **37**. This is not the intuitive result since the most likely mechanisms for both TFA-*d* catalyzed exchange and the base-catalyzed exchange involve enolization to the α-

carbon. The explanation of these results lie in the detailed mechanism of base-catalyzed enolization. In contrast to the proposed acid-catalyzed mechanism, base-catalyzed exchange is considered to proceed by α-proton abstraction by the deuteroxide anion.[14g] The oxygen group of the enolate anion may then abstract a deuterium atom to form the enol intermediate which subsequently tautomerizes.[14f,14g] For exchange to occur, the enol intermediate is not required as in acid catalysis[14f,14g] and deuteration can occur by the carbanion abstracting a deuterium from deuterium oxide.[14g] This changes the rate determining step of the reaction significantly so that the angle strain and torsional strain become the determining factor rather than steric approach of the exchange reagents.[16] This is apparent from the two possible transition states shown in Figure 5.[16] The first transition state shows an ideally skewed bond arrangement while the second gives eclipsing between the bridgehead hydrogen and the α-hydrogen of the carbonyl group.[16]

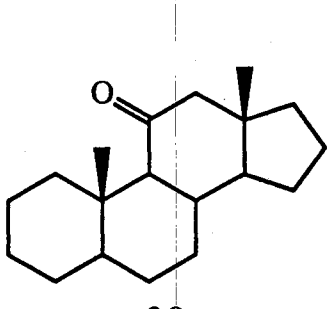


37 I1 37 I2

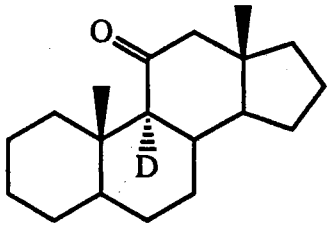
Figure 5. Possible transition states for the base-catalyzed, deuterium-hydrogen exchange of camphor (Newman projections as viewed from the enolate edge).

The steroid system is known to undergo stereospecific deuterium incorporation when subjected to various methods of exchange.[10d] For

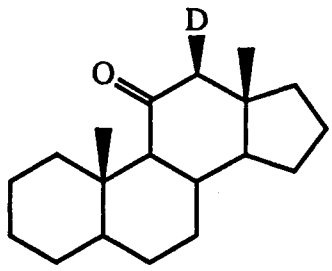
example, extensive work has been done with 5α-androstan-11-one (**39**) in which, depending on conditions used, the following products were isolated as shown below ; 9α-deuterio-5α-androstan-11-one (**40**), 12β-deuterio-5α-androstan-11-one (**41**), 9α,12α-dideutero-5α-androstan-11-one (**42**), and 9α,12,12-trideuterio-5α-androstan-11-one (**43**).[6,10d,12,16] In these studies, the extent of stereoelectronic control decreased with increasing acid strength.[10d]



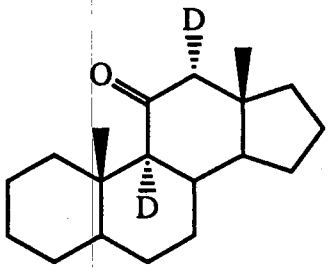
39



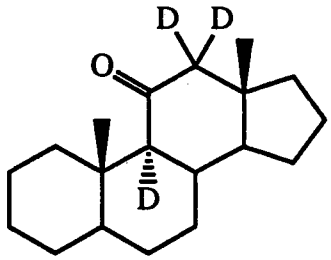
40



41



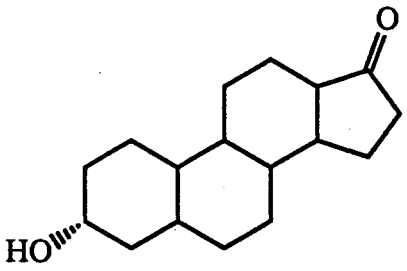
42



43

To examine the possibility of a deuterium-hydrogen exchange in which the steric approach of the exchange reagents determined the stereoselectivity, the reaction of epiandrosterone (**38**), shown below, was investigated further. Since **38** undergoes exchange of one hydrogen with TFA-*d* and two hydrogens exchange under base-catalyzed conditions,[8,34] attempts were made to exchange the second α-hydrogen by stirring with TFA-*d* for longer periods of

time and increasing the number of treatment cycles.[20] The second α-hydrogen remained resistant to complete exchange. Refluxing TFA-*d* resulted in partial elimination of the acylated 3-α-hydroxyl group, indicated by the appearance of olefinic peaks in the ^{13}C NMR spectrum and complication of the ^{1}H NMR spectrum.[33] The ^{1}H NMR spectrum also indicated that the second α-hydrogen had undergone exchange.[33]

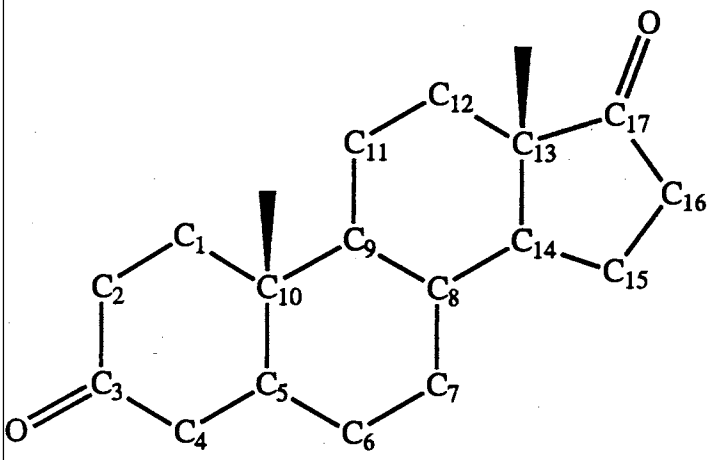


38

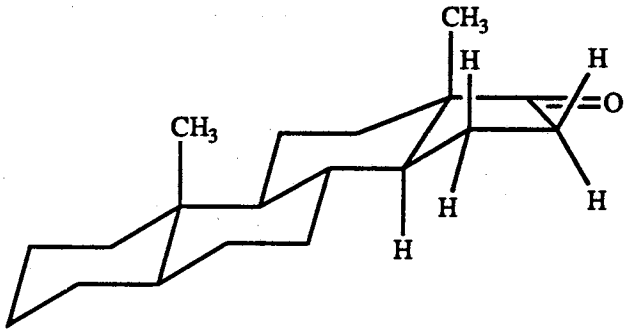
To further investigate this phenomenon and the application of the TFA-*d* exchange process, androstan-3, 17-dione (**44**) was treated with TFA-*d* for 9 treatment cycles at RT.[20] This resulted in the exchange of all hydrogens at C-2 and C-4 positions and exchange of one of the hydrogens at C-16.[20] The number scheme for steroids is indicated below using **44** as an example. An exchange ratio of d_5:d_6 (3:1) was estimated from mass spectral data of the product, however the INCORP program has a limit of calculating the exchange of 5 hydrogens. Thus exact calculations of deuterium incorporation were not possible. [20]

The hydrogen that resisted exchange by TFA-*d* at RT, was found to be the 16β-hydrogen. The assignment of α orientation for deuterium at C-16 is

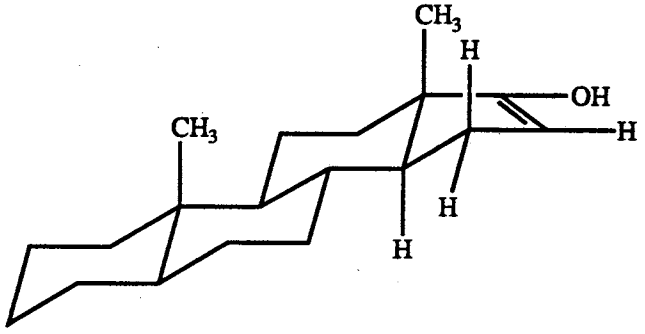
based on the assumption that stereoelectronic effects are negligible at C-17 since the carbonyl group bisects the angle between the α and β hydrogens.



44



45



46

Thus stereoselectivity would be dictated by steric hindrance from the presence of the methyl group at C-13.[10d] The difference in steric hindrance to α approach vs. β approach in both the ketone and enolate can be appreciated from the stereochemical drawing shown above for androstan-17-one (**45**) and the corresponding enol (**46**). For this reaction to be stereo-selective, both the abstraction of the hydrogen by TFA anion and deuteration of the resulting enol must occur from the same side. The signal lost (2.0-2.2 ppm) in the ^{1}H NMR spectra of the exchanged product from **45** corresponds to the signal of α–hydrogens in 17-keto steroids which were determined by more elaborate labeling procedures.[13,28] This also is in agreement with tritium back exchange experiments where the radioactive label was lost approximately 5 times faster from 16α labeled 17-keto-steroids as compared to the 16β labeled 17-keto-steroids in acid-catalyzed enolization.[10d,28] The exchange media used for this latter acid-catalyzed enolization study were AcOH/H_2O/H_2SO_4 (44/5/1) at 38 °C, dioxane/H_2SO_4 (1/1) at RT, and ethanol/H_2O/H_2SO_4 (25/21/4) at RT.[10d,28]

The two ketones, 5-α-androstan-3-one (**47**) and 5-α-androstan-17-one (**45**), were prepared to separately model the two ketone functional groups of androstan-3,17-dione (**44**). These ketones were used to compare the outcome of the previous enolization studies using mineral acids[10d,28] to the TFA-*d* studies and to verify that the 16β-hydrogens of androsterone (**38**) and **44** were the hydrogens resisting exchange. Ketone (**47**) was treated once with TFA-*d* at RT. The ^{1}H NMR signals indicated considerable exchange of all of the hydrogens adjacent to the carbonyl of **47** (MS analysis: 19% d_3, 71% d_4) after 7 days. Since all of the α-hydrogens of ketone **47** were affected in the exchange, this supports the concept that the hydrogen resistant to exchange in **38** and **44** is attached to C-16.

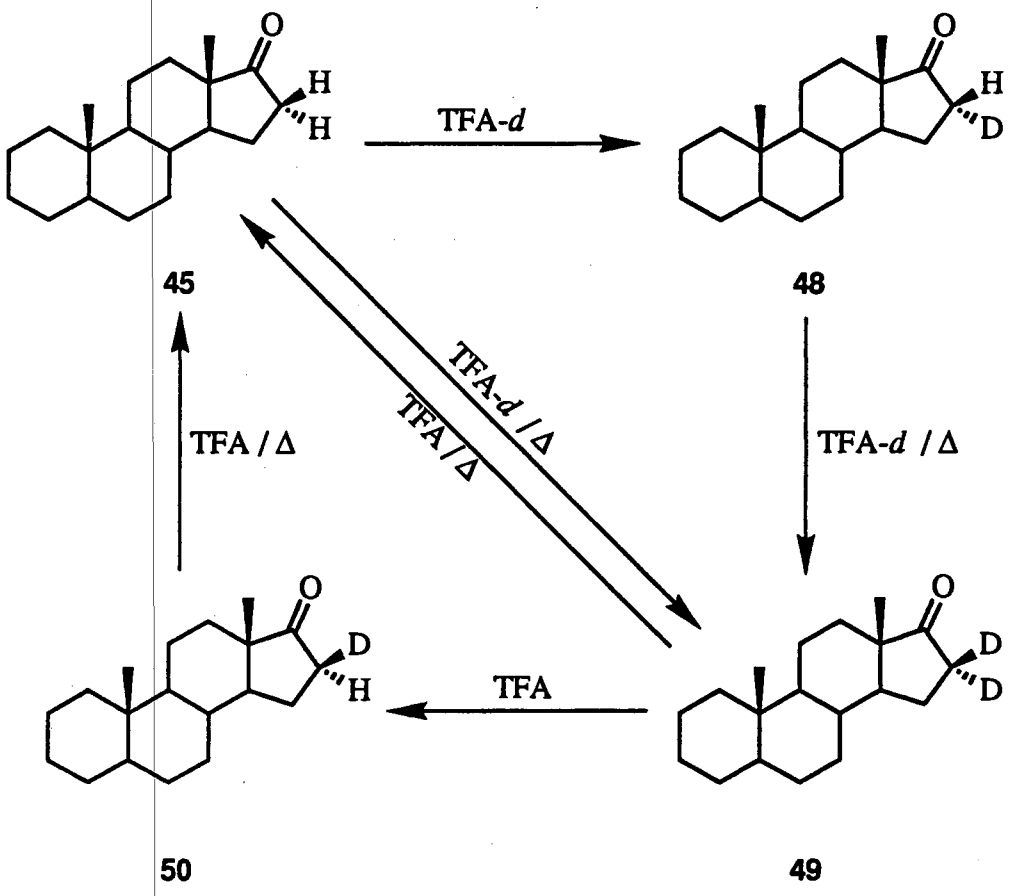


Figure 6. Summary of experiments to obtain all possible α-exchanged products of **45** and to demonstrate the versatility of the neat TFA-*d* exchange process.

A series of exchange experiments was devised to obtain the various possible α-exchanged products of **45** and to test the versatility and stereoselectivity of TFA-*d* as an exchange reagent. This series of experiments is summarized in Figure 6. Deuterium /hydrogen exchange of **45** with TFA-*d* at RT mainly resulted in incorporating a single deuterium atom at the α position as indicated by the disappearance of the signal at 2.0-2.2 ppm (MS analysis: 80% d_1, 16% d_2). Treatment of this product (**48**) or **45** with refluxing TFA-*d* resulted

in incorporation of deuterium at C-16 in both the α and β positions to give the doubly labeled ketone (**49**) (MS analysis: 6%d_1, 94%d_2). This was confirmed by the loss of both ^{1}H NMR signals (2.0-2.2 ppm and 2.3-2.5 ppm) corresponding to the hydrogens attached to C-16 (as determined by a HETCOR NMR experiment). These results correlate to the data reported for base-catalyzed exchange (11% d_1, 89% d_2).[8] The subsequent treatment of **49** with TFA at RT resulted in back exchange. Due to the unfavorable isotope effect, the back exchange was slow and exhibited limited stereoselectivity which prevented isolation of **50**. The hydrogen/deuterium exchange of **49** utilizing refluxing TFA resulted in rapid regeneration of the original unlabeled ketone (^{1}H and ^{13}C NMR identical to original sample of **45**). The ^{1}H NMR spectra for these reactions are included in Appendix B.

Other examples investigated involve the metacyclophane system 5,14-dimethoxy[3.3]metacyclophane-1,10-dione (**51**). From Dreiding models of **51**, the enolization during the hydrogen/deuterium exchange was expected to introduce strain into this system. The hydrogen/deuterium exchange also may be influenced by steric hindrance due to the interaction of the two aromatic rings and their substituents, particularly the hydrogens attached to C-9 and C-18. Attempts to exchange the α-hydrogens of **51** utilizing neat TFA-*d* for 7 days at RT resulted in no detectable exchange as shown by the ^{1}H NMR spectrum or from MS analysis. Treatment with TFA-*d* at reflux resulted in some decomposition accompanied by exchange of the aromatic and benzylic positions in addition to exchange at the α-positions. No stereoselectivity was observed for this latter exchange. Base-catalyzed exchange of **51** (MeOD, D_2O, NaOD in a mole ratio of 24:22:1) resulted in exchange of the α-hydrogens, with no apparent stereo-selectivity. The ^{1}H NMR spectra are shown in

Appendix B and the MS spectra are shown in Appendix C. The MS fragmentation mechanism is shown for **51** in Figure 7.[35]

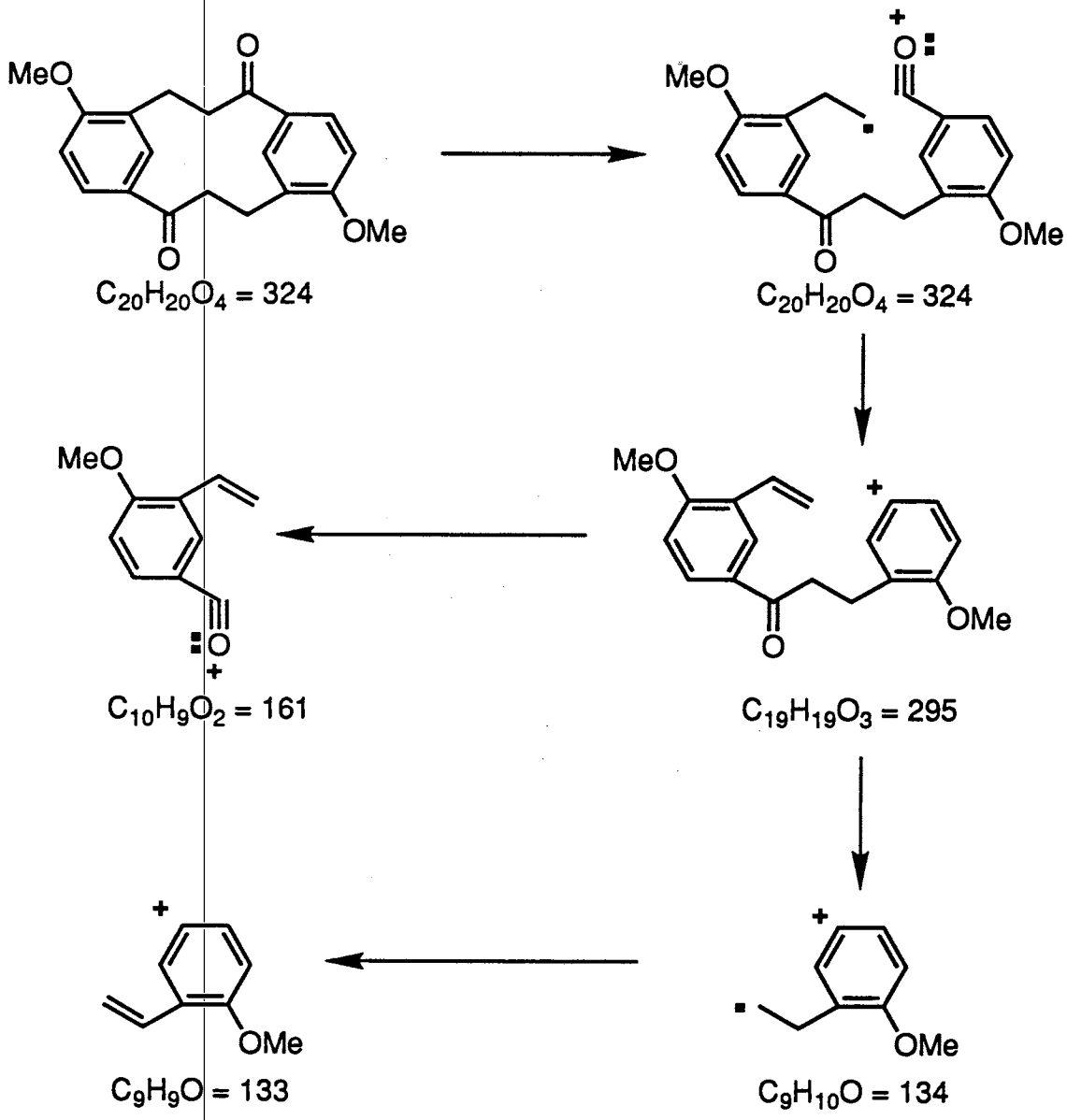


Figure 7. Fragmentation observed in MS spectrum.

The hydrogen/deuterium exchange was extremely slow for both the TFA-*d* catalyzed exchange and base-catalyzed exchange of **51**. This suggests the formation of the enolate is hindered by angle strain, torsional strain, steric hindrance, or a combination of these effects. This result was investigated further using MOPAC calculations and X-ray analysis.

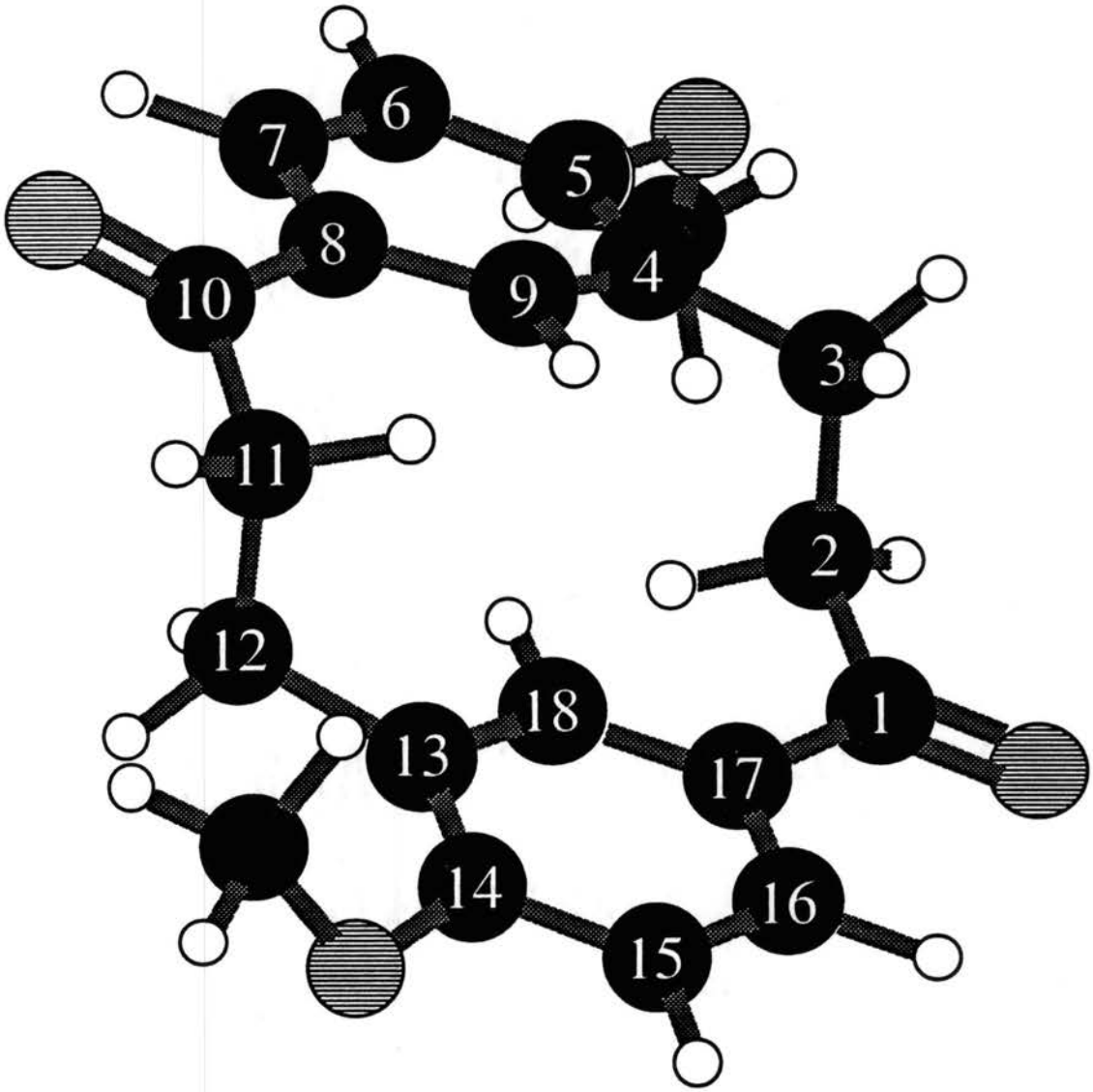


Figure 8. Final geometry of the MOPAC PM3 optimized *anti*-conformation of **51** (ΔH_f = -99.013 Kcal/mole)

The [3.3]metacyclophane system is known to exist in *syn* and *anti* forms.[36-42] MOPAC calculations using PM3 Hamiltonians for **51** resulted in the *anti*-form (ΔH_f = -99.013 Kcal/mole) to be thermodynamically favored over the *syn*-form (ΔH_f = -38.847 Kcal/mole). The final geometry of the MOPAC optimized *anti* and *syn* forms are shown in Figures 8 and 9 respectively.

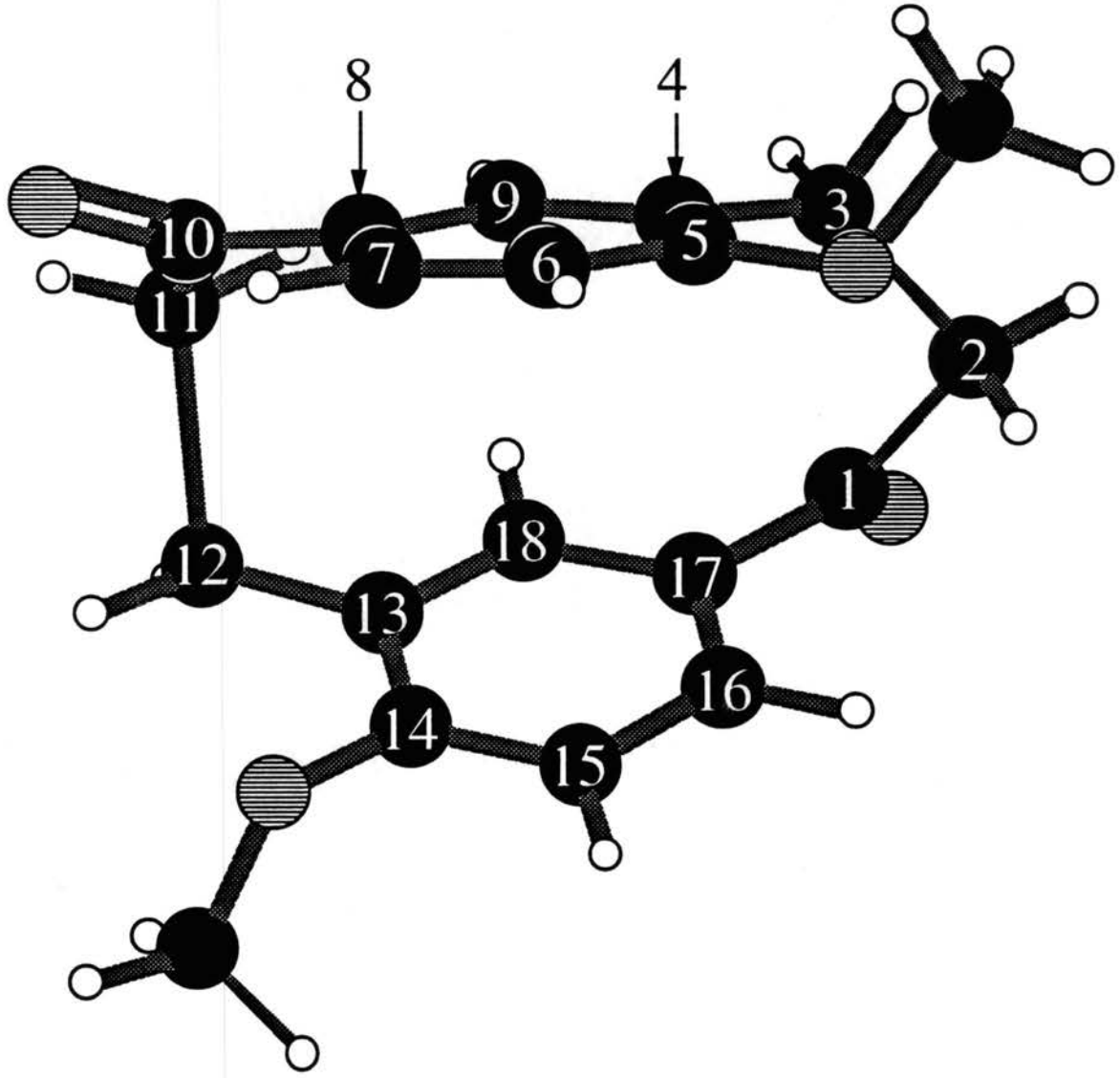


Figure 9. Final geometry of the MOPAC PM3 optimized *syn*-conformation of **51**(ΔH_f = -38.847 Kcal/mole)

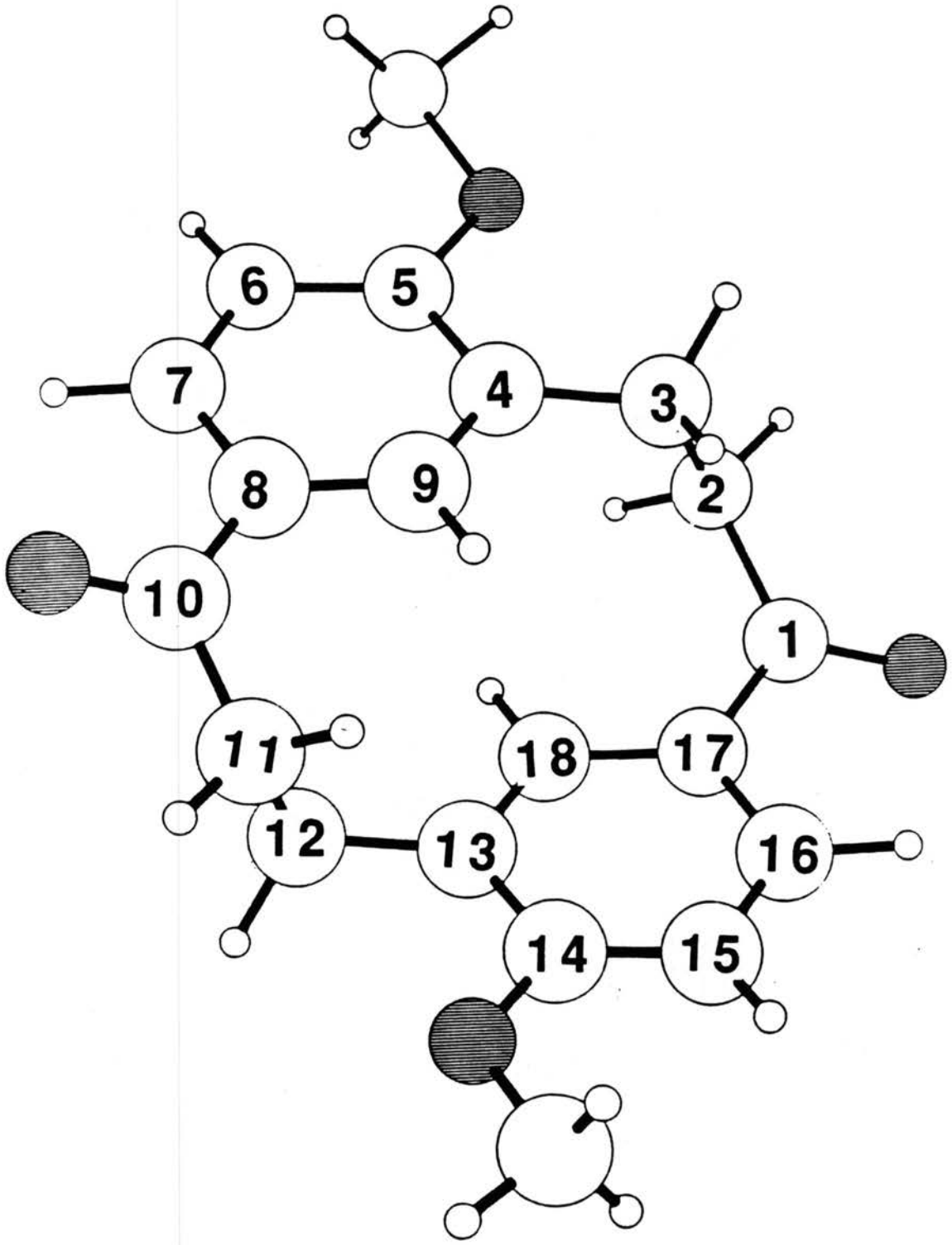


Figure 10. Structure of **51** as determined by single crystal X-ray analysis.

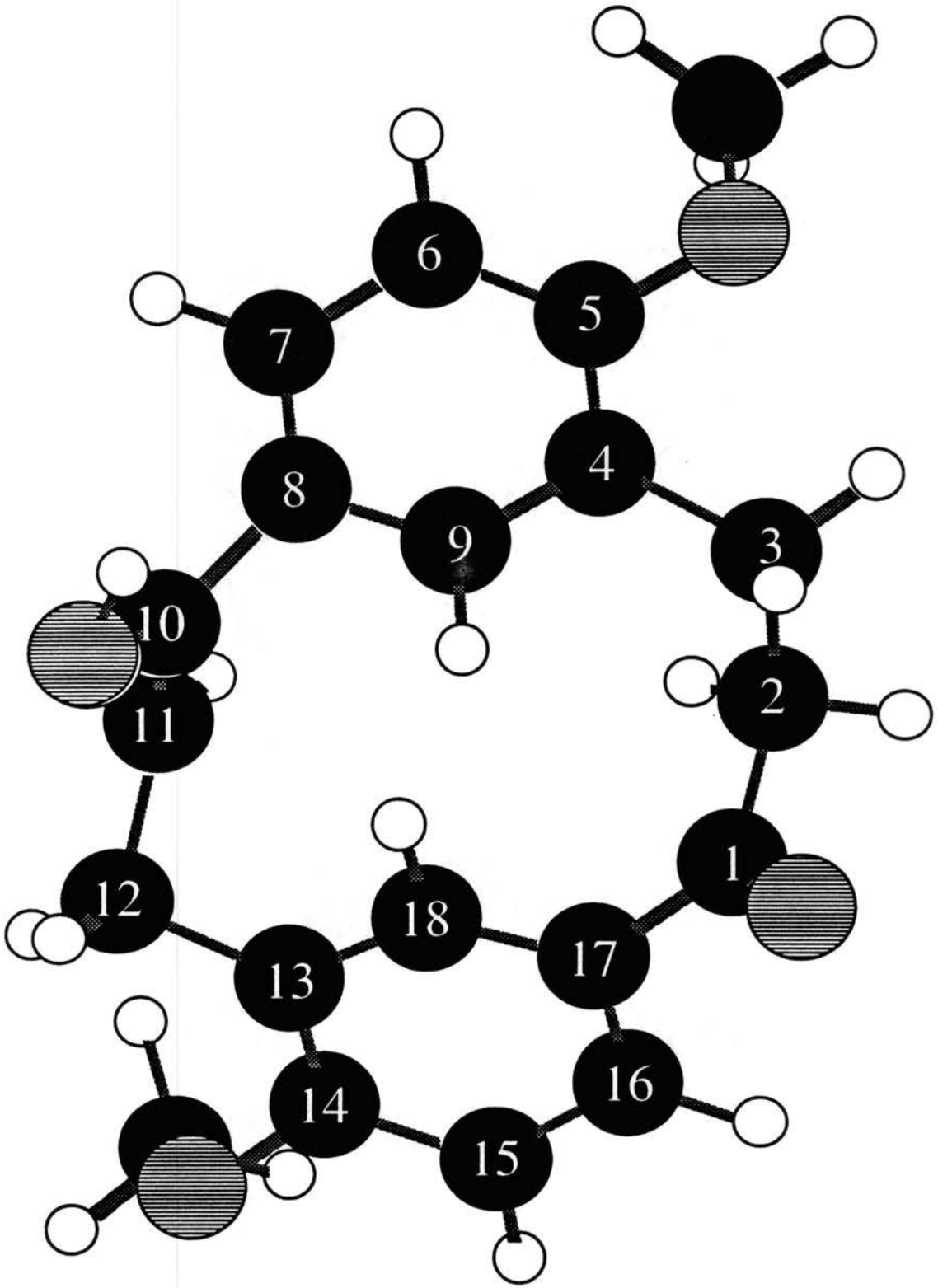


Figure 11. Final geometry of the MOPAC PM3 optimized mono-enolate of **51** (ΔH_f = -78.310 Kcal/mole)

This result is in accord with the X-ray analysis of a single crystal of **51** which was found to consist of the *anti* form as shown in Figure 10 (detailed data for the X-ray analysis is included in Appendix D). The MOPAC calculation of the mon0-`enol of **51** (ΔH_f = -78.310 Kcal) suggests that the enolate is not in favorable equilibrium with the ketone as can be deduced from the geometry of the optimized enolate shown in Figure 11. All MOPAC calculations are summarized in Appendix E. Since there was no detectable exchange, this unfavorable equilibrium combined with the relatively high energy barrier to the transition state (ΔG_1^*, shown Figure 2) must be sufficient for the acid-catalyzed deuterium/hydrogen exchange to be inhibited at room temperature.

CHAPTER III

EXPERIMENTAL

General Information. NMR spectral data were recorded on a Varian XL-300 spectrometer with ^{1}H and ^{13}C data being taken at 299.99 Hz and 75.4 Hz with reference to TMS in δ values or ppm respectively; J values are reported in Hz. Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. Mass spectra were obtained on a VG Tritech TS-250 trisector mass spectrometer equipped with a VG 11-250J data system. Sampling and ionization were by direct probe insertion and 70 eV ionization. The program INCORP written for IBM by J. P. Freeman gave the extent of deuterium exchange in each compound. This program compares the molecular ion cluster peaks of the mass spectrum of the undeuterated species to those of the deuterated species and, by successive approximations, calculates the percentage incorporation of deuterium required to give the peak distribution observed in the spectrum of the deuterated sample. INCORP makes the fundamental assumption that the extent of fragmentation observed will be identical with species d_0-d_5. The exact masses of certain compounds were obtained from the mass spectral laboratory with a VG-analytical ZAB 2-SE high resolution, reversed-geometry mass spectrometer.

Preparation of Trifluoroacetic Acid-*d*. TFA-*d* was prepared as needed in 50-mL, round-bottomed, long-neck flask containing a Teflon-coated magnetic stirring bar and equipped with a pressure-equalizing dropping funnel and argon inlet. The apparatus was equipped with a Teflon stopcock, Teflon-

faced glass joints, and Teflon stopper. All glassware was treated with D_2O and baked at 165 °C overnight, assemble hot, and flushed with argon. Deuterium oxide (1.28 mL, 1.42 g, 70.7 mmol) was added to the cooled flask and trifluoroacetic anhydride (10.0 mL, 14.9 g, 70.8 mmol) was added dropwise using a dropping funnel since the reaction is exothermic. Both trifluoroacetic anhydride and TFA-*d* are corrosive, toxic, and have a high vapor pressure. Therefore, all reactions with these reactants should be conducted in a well-ventilated hood, with gloves, and face shield.

^{1}H NMR Study of 2,5,8-Trimethyl-1-tetralone (24). Ketone **24** (3 mg, 0.6 mmol) was dissolved in TFA-*d* (0.6 mL, 900 mg, 8 mmol) and transferred to an NMR tube. The set up of the experiment took approximately 1 h. The NMR instrument was set up to record a spectrum and store the resulting spectrum in an array at given intervals. The initial point was assumed to start with no exchange and does not represent an actual measurement. All data points were normalized by comparison to non-exchanging hydrogens (the three methyl groups). The results of this experiment are depicted in Figure 3.

General Exchange Procedure for Other Ketones. The dropping funnel was removed from the apparatus used to prepare the TFA-*d* and a water cooled condenser fitted with a drying tube (molecular sieves) was added. The ketone (14 mmol) was added to the reaction flask and stirred at RT or heated at the indicated temperature. These deuterium-hydrogen exchanges were monitored by ^{1}H NMR to determine the optimum time needed for each exchange. These experiments were then repeated without the removal of NMR samples. The reaction mixture was then freed of spent TFA-*d* by vacuum aspiration. MeOD (0.5 mL) was added to assist the removal of the last traces of TFA-*d* and TFA. The MeOD and remaining solvent was removed under

vacuum. A sample was sent for MS analysis and the remainder was used in NMR studies.

Controlled Temperature Experiments: Ketones **37** and **51** were treated with TFA-*d* and TFA at a controlled temperature. This was done by adding a condenser to the reaction flask and surrounding the flask with refluxing solvents. The solvents used were:

Solvent	bp
diethyl ether	34.6 °C
dichloromethane	40 °C
cyclopentane	50 °C
acetone	56 °C
hexanes	68-69 °C

Androstan-17-one (45). A 250 mL Erlenmeyer flask was charged with epiandrosterone (**28**) (5.00 g, 17.22 mmol), and pyridine (75.0 mL). This solution was placed in the refrigerator until the temperature was below -10 °C. *p*-Toluenesulfonyl chloride (19.0 g) in pyridine (50.0 mL) was added and the mixture was allowed to warm to RT for 2 days. The mixture was poured into ice water. The tosylate was filtered, dissolved in chloroform, washed with 10% HCl and saturated NaCl, dried ($MgSO_4$), filtered, and concentrated to a yellow solid. This material was dissolved in THF (40 mL), and added dropwise to a slurry of $LiAlH_4$ (7.00 g, 185 mmol) in THF (40 mL). This solution was heated at reflux for 12 h. The excess $LiAlH_4$ was quenched with H_2O (7.0 mL), and NaOH (3 M, 7.0 mL), followed by a second addition of H_2O (21.0 mL). This mixture was filtered through Dicalite with toluene (100 mL). The resulting alcohol was oxidized using excess Jones reagent.[43] The excess reagent was consumed

with 2-propanol. The solution was filtered through Dicalite and concentrated to a solid. The product was dissolved in toluene (500 mL), washed with 10% HCl (20 mL), saturated $NaHCO_3$ (100 mL), and saturared NaCl (100 mL), dried ($MgSO_4$), filtered, and concentrated to a yellow solid. This material was recrystallized from ethanol to give **45** as a white solid (mp 117-119.5 °C), ^{13}C NMR ($CDCl_3$) 221.59, 54.86, 51.58, 47.84, 47.04, 38.65, 36.43, 35.88, 35.09, 31.63, 31.01, 28.99, 28.76, 26.75, 22.13, 21.77, 20.08, 13.87, 12.23 ppm.

Androstan-3-one (47). A 1-L, round-bottomed flask equipped with a heating mantle, magnetic stirring bar, Dean-Stark trap, and condenser, was charged with epiandrosterone (**28**) (5.00 g, 17.22 mmol), toluene (700 mL), *p*-toluenesulfonylhydrazine (7.45 g, 40.0 mmol), and Amberlyst-15 resin (7.5 g). The resulting mixture was heated at reflux for 1 h and water was removed using a Dean-Stark trap. The reaction mixture was filtered, concentrated, and crystallized from methanol to give 2.00 g of a white solid. This material was dissolved in methanol (40 mL) and a solution of sodium cyanoborohydride and $ZnCl_2$ [$NaBH_3CN$ (0.60 g, 9.50 mmol), $ZnCl_2$ (0.65 g, 4.75 mmol) in methanol (20 mL)] was added. This reaction mixture[43] was heated at reflux for 3 h, taken up in 1 M NaOH (500 mL), and extracted with toluene (3 X 100 mL). The combined extracts were washed with H_2O (100 mL), 10% HCl (10 mL), saturated $NaHCO_3$ (100 mL), saturated NaCl (100 mL), dried ($MgSO_4$), and concentrated. The resulting solid was dissolved in acetone, oxidized with Jones reagent,[44] filtered, and concentrated to a solid. Recrystallization of this material from acetone gave **47** as a white fluffy solid (mp 98.0- 99.5 °C). ^{13}C NMR ($CDCl_3$) 212.19, 54.35, 54.07, 46.74, 44.74, 40.83, 40.37, 38.78, 38.66, 38.21, 35.75, 32.08, 29.00, 25.52, 21.47, 20.50, 17.51, 11.50 ppm.

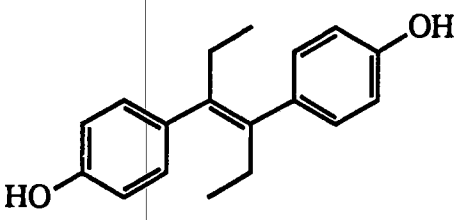
CHAPTER IV

RESULTS AND DISCUSSION

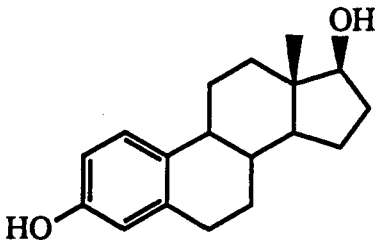
Introduction and Historical

Antifertility agents have been of synthetic and biological interest. Some of these antifertility drugs exhibit undesired estrogenic side effects.[45] Although estrogenicity generally parallels antifertility activity, these effects have been separated with some success.[46] Diethylstilbestrol (**52**) has been shown to bind to the same uterine receptor as 17β-estradiol (**53**) in the cytosol, nucleus, and nonhistone chromatin protein preparations.[47,48] Both of these compounds and structurally related compounds have been used in the treatment of pseudopregnancy, uterine inertia, and to prevent conception in animals. [49]

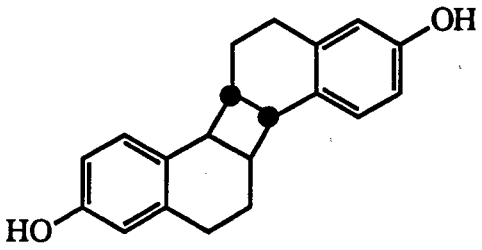
The diphenol, 3,9-Dihydroxy-5,6,6aα,6bβ,11,12,12aβ,12bα-octahydrodibenzo [a,g]biphenylene (**54**), can be structurally compared to **52** and **53** as shown below.[50] The successful synthesis and anti-fertility activity of **54**[50] prompted the synthesis of a potentially more effective antifertility agent which would include some of these structural features.



52



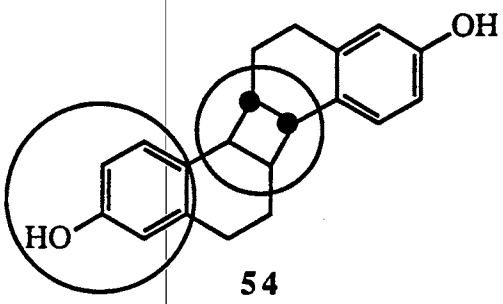
53



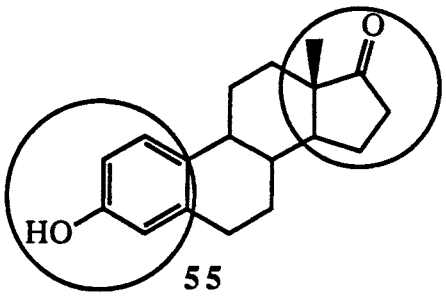
54

Synthesis Problems and Studies

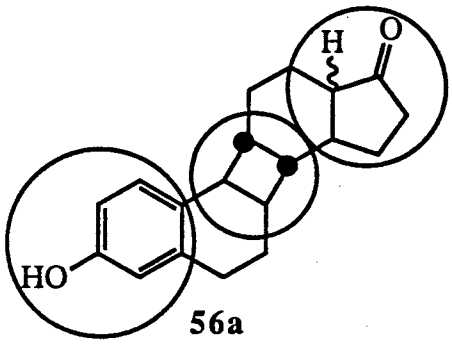
To improve on this earlier work, a target molecule was chosen which incorporated structural features of both 3,9-dihydroxy-5,6,6aα,6bβ,11,12,12aβ, 12bαoctahydrodibenzo[a,g]biphenylene (**54**) and estrone (**55**). Both of these molecules have a phenolic functional group so the features selected were a phenolic group, a four-membered ring in the center of the molecule, and a cyclopentanone ring, common to steroid ketones, opposite the phenolic group. The target molecule chosen, 1,2,3aα,4,5,5aα,5bβ,10,11,11aβ,11bα,11cβ-dodecahydro-8-hydroxy-3*H*-benzo[*a*]cyclo-penta[*g*]biphenylen-3-one (**56a**), along with **54** and **55** is shown below. The targeted functional groups are indicated below within the circled areas.



54



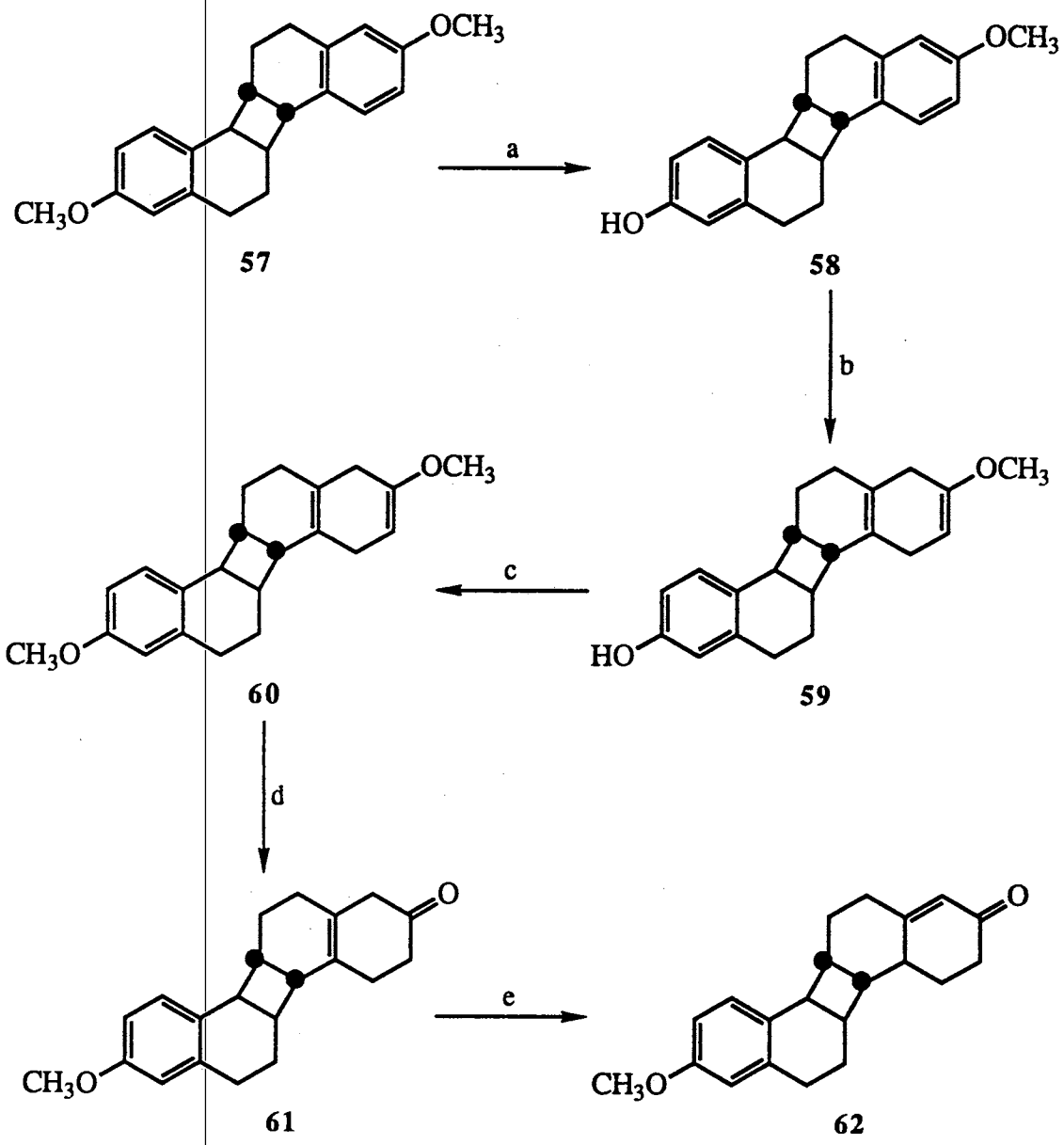
55



56a

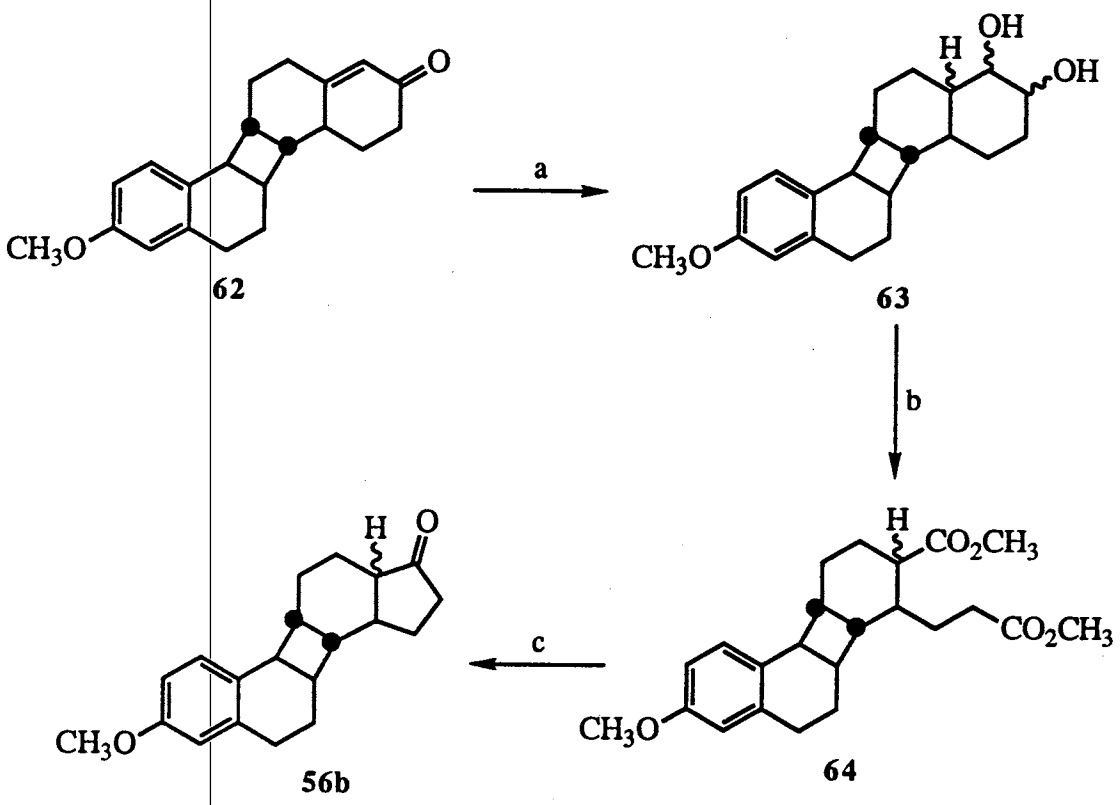
The reaction scheme shown in Figures 12 and 13 was designed to obtain this product, as the methyl ether **56b**, utilizing 3,9-dimethoxy-5,6, 6aα,6bβ,11,12,12aβ,12bα-octahydrodibenzo-[*a,g*]biphenylene (**57**), obtained from earlier studies[50] as starting material.

Since the synthesis target, steroid homolog **56b,** was intended to resemble the steroid **55**, the structures in this thesis were drawn accordingly. Unfortunately, Chemical Abstracts Services consider **56b** to be a derivative of biphenylene and accordingly use a different numbering system from that of the steroid nucleus. This results in an apparent reversal of α and β. This is illustrated by considering **56b** shown drawn as **A**, which is similar to that of steroids, and drawn as **B**, which is used for biphenylene derivatives.



[a]BBr_3, CH_2Cl_2. [b]Li, NH_3, THF, $(CH_3)_3COH$. [c]NaOH, CH_3I. [d]Oxalic Acid, 2-propanol, THF, H_2O, Δ. [e]TFA, CH_3CO_2H.

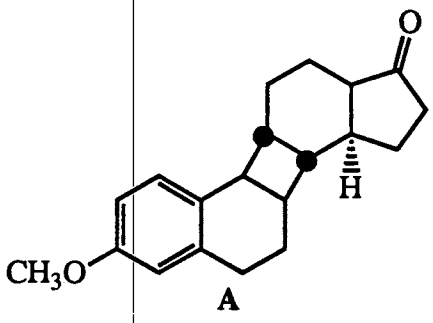
Figure 12. Synthesis scheme for ketone **62**.



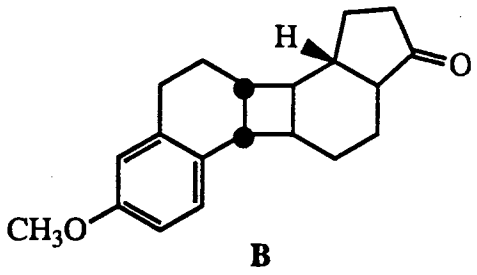
[a]BH_3-THF, THF; H_2O_2, NaOH. [b]$NaIO_4$, $KMnO_4$, $(CH_3)_3COH$; CH_2N_2, diethyl ether. [c]Toluene, $(CH_3)_3COK$, Δ; Diethylene glycol, H_2O, Δ.

Figure 13. Synthesis scheme for ketone **56b**.

Hydrogens represented by heavy dots or solid wedges are considered to be β in steriod notation. In viewing **A** and other biphenylene derivatives drawn to resemble a steroid these hydrogens are α as shown drawn in **B**. The biphenylene derivatives shown in Appendix A and the body of the thesis are drawn to resemble steroids, but are named to follow Chemical Abstracts Services nomenclature as shown drawn in **B**.



A



B

The reaction for the cleavage[51] of the methyl ether of **57** proceeded smoothly. Initially, separation of the unreacted starting material **57**, the monophenol [3-hydroxy-9-methoxy-5,6,6aα,6bβ,11,12,12aβ,12bα-octahydro-dibenzo[*a,g*]biphenylene (**58**)], and the diphenol **54** proved difficult. Attempts to separate these compounds by chromatography resulted in a significant loss of material. Further attempts to extract the phenolic material from the unreacted starting material resulted in soapy emulsions.

It was finally discovered that extracting an ether solution with 10% NaOH, saturated with NaCl, allowed separation of these three components. The monophenol **58** formed as a soapy solid at the ether-water interface. This was collected by filtration through Dicalite. During filtration, a fresh filtering surface was acquired by scraping the surface since the suspended material quickly plugged the filter. The filtrate separated into layers allowing the isolation of **57** and **58**. To recover the monophenol **58**, the Dicalite cake was transferred to a separatory funnel, and ether was added. The ether and Dicalite mixture were shaken until the cake was converted to a foamy mush. A 10% HCl solution was then added and the mixture was shaken until there was no foaming and the material was extracted from the Dicalite particles. The Dicalite was removed with the water layer and the ether layer was washed with additional 10% HCl,

saturated $NaHCO_3$, saturated NaCl, and dried with $MgSO_4$. The ^1H ,^{13}C, and COSY NMR are consistent with the structure of **58**. These spectra are shown as 5a-5c in Appendix B.

The Birch reduction of the monoether **58** was carried out without difficulty. This reacttion did not reduce the phenolic ring. Attempts to isolate the phenolic product **59**, resulted only in isolating the phenolic ketone, 1,2,4,5,6,6aα,6bβ,11,12,12aβ,12bα-decahydro-9-hydroxydibenzo[*a,g*]biphenylen-3(2*H*)-one (**65**) shown in Appendix A. The spectra of **65** are shown as 7a-7b. To successfully isolate the enol ether 5,6,6aα,6bβ,7,10,11,12,12aβ,12bα-decahydro-3,9-dimethoxy-dibenzo[*a,g*]biphenylene (**60**), the phenolic enol-ether **59** was methylated and then repeatedly crystallized from methanol. The NMR spectra (6a-6b, Appendix B) are consistent with structure of **60**.

Conversion of the enol ether **60** to the β,γ-unsaturated ketone 1,2,4,5,6,6aα,6bβ,11,12,12aβ,12bα-decahydro-9-methoxydibenzo[*a,g*]biphenylen-3(2*H*)-one (**61**) was done under acidic conditions using oxalic acid. The NMR spectra (8a-8d, Appendix B) were consistent with the structure of the expected product **61**.

The acid-catalyzed isomerization of the β,γ-unsaturated ketone **61** to the α,β-unsaturated ketone 1,5,6,6aα,6bβ,11,12,12aβ,12bα,12cβ-decahydro-9-methoxy-dibenzo[*a,g*]biphenlen-3(2*H*)-one (**62**) was expected to proceed without difficulty. However, TLC analysis of the product indicated that there was a significant amount of unreacted starting material. Separation of these components was accomplished using a Waters Prep-LC 500. The ^1H NMR spectrum of the chromatogram peak corresponding to starting material was identical to that of **61**. The spectra (9a-9b, Appendix B) of the α,β-unsaturated ketone indicated that two isomers of **62** were present although TLC analysis indicated only one product. Several attempts to separate these compounds

were unsuccessful. Finally separation was achieved using two HPLC semiprep, reverse-phase columns connected in series and eluted with methanol. Both the HPLC chromatogram and the ^{1}H NMR spectrum indicate that these isomers formed in approximately equal amounts. The later eluting peak represented material which crystallized and allowed the isolation of a significant quantity by seeding a saturated solution of the mixture. The ^{1}H, ^{13}C, and HETCOR NMR spectra for this isomer are shown as 10a-10c (Appendix B).

Oxidation of **62** to 5,6,6aα,6bβ,6cα,7,8,9,10,10aβ,11,12,12aβ,12bα-dodeca-hydro-9α,10β-dihydroxy-3-methoxydibenzo[*a,g*]biphenylene (**63**) using THF-borane followed by basic hydrogen peroxide did not proceed stereo-specifically and no attempts were made to separate these isomers.

Oxidation of the diol mixture **63** using $NaIO_4$ and $KMnO_4$ resulted in a diacid (see diester **64**).[52] To isolate the major isomer for NMR analysis, the product was esterified using diazomethane and the diester, methyl 5,6,6aα,6bβ,7,8,9,10,10aβ,10bα-decahydro-3-methoxy-8-(methoxycarbonyl)-benzo[*a*]biphenylene-7-propionate (**64**), was purified by preparative TLC. The NMR spectra of the major isomer isolated are shown as spectra 11a-11b (Appendix B).

The target molecule (**56b**) was prepared by a Dieckmann cyclization[53] of **64** followed by demethylation and decarboxylation of the resulting keto-ester to methoxyketone **56b**. This product was purified by eluting with dichloromethane on a preparative TLC plate. The corresponding ^{1}H and ^{13}C NMR spectra (12a-12b) are also shown in Appendix B.

CHAPTER V

EXPERIMENTAL

General Information. NMR spectral data were recorded on a Varian XL-300 spectrometer with ^{1}H and ^{13}C data being taken at 299.99 Hz and 75.4 Hz with reference to TMS in δ values or ppm respectively; J values are reported in Hz. Melting points were determined with a Thomas-Hoover Unimelt apparatus and are uncorrected. Mass spectra were obtained on a VG Tritech, TS-250 trisector mass spectrometer equipped with a VG 11-250J data system. Sampling and ionization were by direct probe insertion and 70 eV ionization. The exact masses were obtained from the OSU mass spectral laboratory with a VG-analytical ZAB 2-SE-high resolution, reversed-geometry mass spectrometer. Analytical TLC plates were Silica Gel 60 F_{254} precoated onto aluminum with a layer thickness of 0.2 mm. These were purchased from EM Science. Preparative TLC plates, purchased from Analtech, were Tapered Preparative Uniplate T™* precoated with silica gel GF. Reverse phase HPLC, analytical and semi-preparative, was performed using a Waters M6000A solvent delivery system with recycle, equipped with a Waters U6k injector, two Whatman Partisil 10 ODS M9 columns (particle size 10.0 um, length 500 mm, o.d.: 12.80 mm, i.d.: 9.40 mm), connected in series, and a Waters M440 absorbance detector, set at λ = 254 nm and at λ = 280 nm.

1,2,3aα,4,5,5aα,5bβ,10,11,11aβ,11bα,11cβ-Dodecahydro-8-methoxy-3*H*-benzo[*a*]cyclopenta[*g*]biphenylen-3-one (56b). A 10 mL, round-bottomed flask equipped with a Teflon-encapsulated magnetic stirring

bar, reflux condenser, argon inlet/outlet, and dropping funnel was charged with potassium *tert*-butoxide (50 mg) and toluene (3 mL). A solution of diester **64** (5 mg), dissolved in toluene (3 mL), was added and the reaction mixture was heated at reflux for 4 h. The reaction mixture was allowed to cool overnight, neutralized with 10% acetic acid (1 ml), and extracted with toluene (3 X 5 mL). The toluene layers were combined, washed with saturated NaCl (2 X 5 mL), dried ($MgSO_4$), filtered, and concentrated to a tan oil. The oil was dissolved in diethylene glycol (1 mL). Water (0.2 mL) was added to this solution which was then heated at reflux for 30 min under argon. The water was allowed to distill out and the temperature of the solution reached 180 °C. Water (3 mL) was added and the product was extracted with toluene (3 X 5 mL). The toluene layer was dried ($MgSO_4$), filtered, and concentrated. The resulting thick brown oil was dissolved in dichloromethane and developed on a preparative TLC plate using dichloromethane. The main fraction was collected, extracted with ether using a Soxhlet, and concentrated to solid **56b** (3 mg, mp 137-140 °C); ^{1}H NMR ($CDCl_3$) δ 6.99 (d, 1, J = 6.94), 6.75 (d, 1, J = 6.94), 6.68 (s, 1), 3.80 (s, 3), 3.06 (dd, 1, J = 6.0), 2.76-2.88 (m, 1), 2.68 (dt, 1, J = 12, J = 4.5), 2.52-2.62 (m, 1), 2.36-2.46 (m, 1), 2.22 (t, 2, J = 6.0), 2.09-2.18 (m, 1), 1.89-2.01 (m, 3), 1.80-1.89 (m, 1), 1.58-1.80 (m, 3), 1.40-1.58 (m, 2), 1.18-1.30 (m, 1); ^{13}C ($CDCl_3$), 228.7, 157.4, 138.3, 132.4, 129.5, 113.5, 112.5, 55.3, 47.4, 40.0, 39.9, 37.2, 36.9, 36.7, 35.1, 27.6, 26.4, 26.0, 25.1, 20.7 ppm.

3-Hydroxy-9-methoxy-5,6,6aα,6bβ,11,12,12aβ,12bα-octahydrodibenzo[*a,g*]biphenylene (58). The starting material (**57**) was a crude mixture of products. To purify this material, it was recrystallized from ethanol and dichloromethane to give a fluffy white powder. A typical run using this purified material follows:

A 1L, round-bottomed flask equipped with a drying tube and a magnetic stirring bar was charged with a solution of the diether **57** (8.00 g, 25.0 mmol) in dichloromethane (240 mL). Boron tribromide (3.13 g, 12.49 mmol) in 5 mL of dichloromethane was added dropwise. After 30 minutes, the solvent was removed by rotary evaporation. Ether (500 mL) was added and the solution was transferred to a separatory funnel. This solution was extracted with 10% NaOH saturated with NaCl. The starting material was then isolated from the ether layer (1.78 g)- this material was used in the next run. From the basic layer, diphenol **54** was isolated (1.50 g)-this material was dissolved in alkali and treated with dimethyl sulfate to convert it back to starting material **57**. The desired product **58** formed as an insoluble mass which was separated by filtration. This material was dissolved by shaking in a separatory funnel with ether and 10% HCl. The ether layer was washed with saturated $NaHCO_3$ (100 mL), and saturated NaCl (100 mL). The solution was then dried ($MgSO_4$), filtered, and concentrated to give **58** as light tan solid (3.00 g, mp 170-172 °C); ^{1}H NMR ($CDCl_3$) δ 7.00 (d, 1, J = 9.11), 6.95 (d, 1, J = 10.15), 6.74-6.78 (m, 2), 6.65-6.69 (m, 2), 4.71 (s-broad, 1), 3.81 (s, 3), 3.17-3.22 (m, 2), 2.90-3.02 (m, 2), 2.72 (tt, 2, J = 15.2, 4.6), 2.48-2.54 (m, 2), 1.88-1.98 (m, 2), 1.66-1.78 (m, 2); ^{13}C ($CDCl_3$), 157.4, 153.2, 139.3, 139.0, 133.2, 133.1, 129.2, 129.0, 115.1, 113.7, 113.4, 112.2, 55.3, 41.1, 37.1, 29.7, 27.6, 27.4, 26.2, 26.2 ppm.

5,6,6aα,6bβ,7,10,11,12,12aβ,12bα-Decahydro-3,9-dimethoxy-dibenzo[*a,g*]biphenylene (60). Birch reduction of the monophenol **58**, was done in 2.00 g (6.57 mmol) quantities. The monophenol was dissolved in THF (50 mL), and *t*-butyl alcohol (50 mL). The resulting solution was added to a 500 round-bottomed flask equipped with an NH_3 inlet/outlet, a dry-ice/2-propanol condenser, and a dry-ice/2-propanol cooling bath. Approximately 100 mL of NH_3(g) was condensed and lithium metal (1.00 g, 144 mmol) was added during

a 1 h period. This reaction mixture was stirred overnight and NH_3 was allowed to evaporate. Methanol (100 mL) was added to the resulting solution, and the mixture was neutrallized with concentrated HCl (11.5 mL). This solution was transferred to a separatory funnel, saturated NaCl (750 mL) was added, and the product was extracted with diethyl ether (2 X 500 mL). The combined ether layers were washed with saturated $NaHCO_3$ (500 mL), and saturated NaCl (200 mL), and concentrated to an oil. This oil was dissolved in chloroform, dried ($MgSO_4$), filtered, and concentrated to a solid. A 500-mL, round-bottomed flask was used to dissolve the combined products from several Birch reductions (10.75 g, 35.1 mmol) into a basic methanol solution (4.4 g of NaOH in 150 mL of methanol). Methyl iodide was added (12.0 g, 84.5 mmol) and the solution was heated on a steam bath. This solution was stored over night, during which time a precipitate formed. This material was filtered off, methyl iodide was added to the reaction mixture, and the process was repeated. The addition of methyl iodide was repeated for two additional days. The material collected was combined and recrystallized from methanol to give a solid with a broad melting point. This material was recrystallization twice, with considerable loss of material, to give 10 mg of **60** as a white solid mp 112- 116°C; ^{1}H NMR ($CDCl_3$) δ 6.99 (d, 1, J = 6.9), 6.75 (d, 1, J = 6.9), 6.68 (s, 1), 4.68 (s, 1), 3.80 (s, 3), 3.56 (s, 3), 3.14 (t, 1, J = 7.7), 2.55-2.88 (m, 6), 2.40-2.55 (m, 1), 2.20-2.40 (m, 2), 1.95 (d, 1, J = 12), 1.70-1.90 (m, 3), 1.50-1.70 (m, 2); ^{13}C ($CDCl_3$) 157.3, 153.0, 139.3, 133.4, 128.6, 128.4, 124.7, 113.7, 111.9, 90.7, 55.2, 53.8, 40.7, 40.1, 38.5, 36.1, 34.3, 29.3, 28.6, 27.8, 26.2, 23.5 ppm.

1,2,4,5,6,6aα,6bβ,11,12,12aβ,12bα-Decahydro-9-methoxy-dibenzo[*a,g*]biphenylen-3(2*H*)-one (61). The crude material from the recrystallization of the enol **60** (approx. 8.5 g) was dissolved in a mixture of 2-propanol (150 mL), THF (50 mL), and water (10 mL), containing oxalic acid (0.3

g). The reaction mixture was heated on a steam bath for 1 h and water was added until the solution became turbid. After chilling in the refrigerator, a solid was collected by filtration. This material was recrystallized from methanol to give 8.5 g of **61** as a white solid mp 121-124 °C; ^{1}H NMR ($CDCl_3$) δ 6.93 (d, 1, J = 7.9), 6.71 (d, 1, J = 7.9), 6.69 (s, 1), 3.77 (s, 3), 3.14 (t, 1, J = 7.9), 2.86 (d, 2, 8.8), 2.73 (dt, 2, J = 22.6, 6.4), 2.40-2.58 (m, 4), 2.25-2.40 (m, 4), 1.96 (s- broad, 1), 1.80-1.90 (m, 2), 1.72-1.81 (m, 1), 1.48-1.63 (m, 1); ^{13}C ($CDCl_3$) 211.0, 157.4, 139.0, 132.8, 131.3, 128.6, 125.7, 113.7, 112.0, 55.2, 44.9, 40.5, 40.0, 39.3, 39.1, 35.9, 28.6, 28.6, 27.7, 26.4, 23.2 ppm.

1,5,6,6aα,6bβ,11,12,12aβ,12bα,12c-Decahydro-9-methoxy-dibenzo[*a,g*]biphenlen-3(2*H*)-one (62) mixture. A 500-mL, round-bottomed flask was charged with the β,γ-unsaturated ketone **61**(8.50 g, 27.6 mmol), acetic acid (68 mL), and trifluoroacetic acid (17 mL). The resulting solution was stirred overnight, then poured into a saturated $NaHCO_3$ solution and extracted with dichloromethane. The organic layer was washed with saturated NaCl, dried ($MgSO_4$), filtered, and concentrated to a solid. The α,β-unsaturated ketone **62** was separated from the β,γ-unsaturated ketone **61** by HPLC using a Waters Prep-LC 500 fitted with two silica cartriges in series after recycling twice. Dichloromethane was used as the eluting solvent. After the solvent was distilled and the product was vacuum aspirated overnight, a white solid was isolated. This represented the retained peak (3.90 g). ^{1}H NMR revealed that this material consisted of two isomers of **62**.

1,5,6,6aα,6bβ,11,12,12aβ,12bα,12cβ-Decahydro-9-methoxy-dibenzo[*a,g*]biphenylen-3(2*H*)-one (62). The 12cβ isomer of ketone **62** was separated from the 12cα isomer using reversed phase HPLC and elution with methanol. The maximum injection size was 50 mg. Attempts to modify the solvent system (H_2O, THF, acetonitrile) resulted in poorer resolution. Isopropyl

alcohol gave a better baseline but due to viscosity problems, the maximum flow rate that could be used was 1.0 mL/min. This resulted in prohibitively long separation times. A saturated solution of the isomer mixture, was treated with a crystal of purified material to preferentially crystallize out the 12cβ isomer of ketone **62** (mp 150-153 °C); ^{1}H NMR ($CDCl_3$) δ 6.95 (d, 1, J = 8.3), 6.75 (dd, 1, J = 8.3, 2.6), 6.69 (d, 1, J = 2.6), 6.03 (s, 1), 3.79 (s, 3), 3.12 (dd, 1, J = 9.2, 3.2), 2.84-2.96 (m, 2), 2.70 (t, 1, J = 4.0), 2.65 (t, 1, J = 4.0), 2.50-2.59 (m, 2), 2.47 (t, 1, J = 3.8), 2.40-2.44 (m, 1), 2.28-2.40 (m, 2), 1.72-1.90 (m, 4), 1.59-1.65 (m, 2); ^{13}C ($CDCl_3$) 199.2, 167.9, 157.4, 138.3, 132.5, 129.3, 127.3, 113.5, 112.6, 55.2, 40.2, 37.7, 37.6, 36.9, 36.2, 33.4, 28.4, 26.8, 26.7, 25.9, 24.5 ppm.

5,6,6aα,6bβ,6cα,7,8,9,10,10aβ,11,12,12aβ,12bα-Dodecahydro-9α,10β-dihydroxy-3-methoxydibenzo[*a,g*]biphenylene (63). A dried, 3-necked, round-bottomed flask equipped with a magnetic stirring bar, condenser, septum, argon inlet/outlet, and heating mantle was charged with the α,β-unsaturated ketone **62** (2.80 g, 9.08 mmol) in THF (200 mL). THF-borane (1M in THF, 40 mL) was added by syringe. After the addition was complete, the resulting solution was heated to reflux for 1 h, then cooled to RT during which time a thick white precipitate formed. Water was added until the precipitate dissolved. A solution of NaOH (2.40 g, 60 mmol in 20 mL H_2O) was added, followed by the dropwise addition of 30% hydrogen peroxide (11 mL). Ether (200 mL) and dichloromethane (200 mL) were used to extract this solution. The organic layer was washed with saturated $NaHCO_3$ (100 mL), saturated NaCl (100 mL), dried ($MgSO_4$), filtered, and concentrated to a dark tan solid. The solid was recrystallized from methanol to give 2.00 g of **63** (6.09 mmol, 67% yield) as a white solid, mp 193-196 °C. ^{1}H NMR ($CDCl_3$) δ 6.93 (d, 1, J = 7.9), 6.71 (d, 1, J = 7.9), 6.69 (s, 1), 3.75 (s, 3), 3.36-3.57 (m, 1), 3.22-3.35 (m, 1), 2.97-3.21 (m, 1), 2.52-2.73 (m, 2), 2.21-2.52 (m, 3), 2.07-2.21 (m, 2), 1.91-2.06

(m, 2), 1.69-1.91 (m, 3), 1.40-1.69 (m, 5), 0.94-1.11 (m, 2); ^{13}C ($CDCl_3$) 143.4, 130.0, 128.1, 113.9, 112.0, 111.9, 55.2, 45.5, 44.1, 42.1, 40.8, 40.4, 38.8, 36.4, 29.7, 29.4, 27.4, 27.3, 27.1, 25.5, 25.3 ppm. Elemental analysis calculated for $C_{21}H_{23}O_3$: C, 76.79; H, 8.59. Found: C, 76.66; H, 8.74.

Methyl 5,6,6aα,6bβ,7,8,9,10,10aβ,10bα-decahydro-3-methoxy-8-(methoxycarbonyl)-benzo[*a*]biphenylene-7-propionate (64). A 1-L round-bottomed flask equipped with a magnetic stirring bar was charged with *tert*-butyl alcohol (500 mL), diol **63** (2.00 g, 6.09 mmol), potassium carbonate (2.0 g), meta-sodium periodate (6.20 g) dissolved in water (80 mL) , and potassium permanganate (200 mg). This mixture was stirred for 20 h, then poured into water (1L). Sulfuric acid was added to the solution until a pH of 4 was achieved and sodium bisulfite was added until the solution became colorless. The resulting solution was extracted with ether (3 X 1L). The combined ether extracts were concentrated to 1 L and extracted with 5% NaOH (3 X 250 mL). The water layer was neutralized with 10% hydrochloric acid and extracted into ether (1 L). The ether layer was washed with saturated NaCl (500 mL), dried ($MgSO_4$), and filtered. An ether solution of diazomethane was added to this solution until a light yellow color persisted and gas evolution ceased. This solution was concentrated to a tan solid (6 mg, 0.015 mmol). The product was purified by preparative TLC and recrystallization from methanol to give **64** as an off white solid, (m p 117-118 °C). ^1H NMR ($CDCl_3$) δ 6.93 (d, 1, J = 7.9), 6.69 (d, 1, J = 7.9), 6.66 (s, 1), 3.78 (s, 3), 3.72 (s, 3), 3.68 (s, 3), 3.26-3.39 (m, 1), 2.57-2.74 (m, 2), 2.42-2.52 (m, 1), 2.24-2.40 (m, 2), 2.13-2.24 (m, 1), 1.99-2.08 (m, 1), 1.90-1.99 (m, 2), 1.73-1.90 (m, 4), 1.58-1.66 (m, 2), 1.42-1.56 (m, 2); ^{13}C ($CDCl_3$) 176.9, 174.0, 157.5, 138.9, 132.5, 128.1, 113.8, 112.0, 55.2, 51.6, 47.0, 41.1, 40.5, 40.3, 39.1, 35.8, 31.2, 30.2, 29.2, 26.6, 26.3, 25.4 ppm.

Elemental Analysis calculated for $C_{23}H_{30}O_5$: C, 71.48; H, 7.82. Found: C, 71.64; H, 7.93.

1,2,4,5,6,6aα,6bβ,11,12,12aβ,12bα-Decahydro-9-hydroxy-dibenzo[*a,g*]biphenylen-3(2*H*)-one (65). This material was isolated by prep TLC (CH_2Cl_2, saturated with NH_3) from a methanol recrystallization of a Birch reduction product. (see preparatation of **60**). The ^1H and ^{13}C NMR spectra for **65** are shown as 7a and 7b in Appendix B. Elemental analysis calculated for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.42; H, 7.43.

BIBLIOGRAPHY

(1) Montgomery, L. K.; Applegate L. E. *J. Am. Chem. Soc.* **1967**, *89*, 2952-2960.

(2) Shiner, V. J. ; Dowd, W. *J. Am. Chem. Soc.* **1971**, *93,* 1029-1030.

(3) Shiner, V. J.; Fisher, R. D. *J. Am. Chem. Soc.* **1971**, *93*, 2553-2554.

(4) Shiner, V. J.; Neumann, T. E.; Fisher, R. D. *J. Am. Chem. Soc.* **1982**, *104*, 354-355.

(5) Ribi, M.; Sin-Ren, C. A.; Kung, H. P; Eugster, C. H. *Helv. Chim. Acta.* **1969**, *52*, 1685-1729

(6) Williams, D. H.; Wilson, J. M.; Budzikiewicz, H.; Djerassi, C. *J. Am. Chem. Soc.* **1963**, *85*, 2091-2104.

(7) Weinberg, D. S., Djerassi, C. *J. Org. Chem.* **1966** ,*31* ,115-119.

(8) Tokes, L.; LaLonde, R. T.; Djerassi, C. *J. Org. Chem.* **1967**, *32*, 1012-1019.

(9) Benfenati, E.; Icardi, G.; Chen, S.; Fanelli, R. *J. Label. Compd. Radiopharm.* **1989**, *28*, 411-419.

(10) *Organic Reactions in Steroid Chemistry*; Fried, J.; Edwards, J. A., Eds; Van Nostrand Reinhold Company: New York, Litton Educational Publishing, Inc. ; 1972; Vol. 1, (a) pp. 145-148. (b) pp. 183-184. (c) pp.160-179. (d) pp. 149-156.

(

11) Bloch, K.; Rittenberg, D. *J. Biol. Chem.* **1943**, *149*, 505.

(12) Williams, D. H.; Bhacca, N. S.; Djerassi, C. *J. Am. Chem. Soc.* **1963**, *85*, 2810-2813.

(13) Fishman, J. *J. Am. Chem. Soc.* **1965**, *87,* 3455-3460.

(14) March, J. *Advanced Organic Chemistry* 4th ed. John Wiley & Sons: New York,**1992**, (a) pp. 226-230. (b) pp. 776-777. (c) p. 439. (d) pp. 521-522. (e) p. 610. (f) pp. 584-587 and references cited therein. (g) pp. 266-230, 584-587, 608-609, 741-742 and references cited therein.

(15) Najar ,S. E.; Blake, M. I.; Benoit, P. A.; Lu, M. C. *J. Med. Chem.* **1978**, *21*, 557.

(16) Thomas, A.F. *Deuterium Labelling in Organic Chemistry;* Appleton-Century-Crofts, Educational Division/Meredith Corp., **1971**, pp.167-229, and references cited therein.

(17) Rosatzin, H. *J. Label .Compd.* **1968**, *4*, 219.

(18) Watson, J. M.; Tanner, A. R.; Roberts, R. M. *J. Org. Chem.* **1972**, *37*, 3743.

(19) Schaefer, J. P.; Weinberg, D. S.; *Tetrahedron Lett.* **1965**, *23*, 1801-1804.

(20) Dewprashad, B. Ph.D. Thesis, Oklahoma State University, July, **1989.**

(21) Eisenbraun, E. J.; Dewprashad, B. ; Geno, P. W.; Taylor, A. R. *J. Label Compd. Radiopharm.* **1990**, *29*, 25-28.

(22) Peterson, P. E. *J. Org. Chem.* **1966**, *31*, 439-442.

(23) Lamaty, G. in *Isotopes in Hydrogen Transfer Processes;* Buncel, E.; Lee, C. C. Eds.; Elsevier: Amsterdam, **1976**, Vol. 2, Chapter 2.

(24) Lowry, T. H.; Richardson, K. S. *Mechanism and Theory in Organic Chemistry;* Harper and Row: N. Y., **1981**, pp. 661-662.

(25) Swain, C. G.; Rosenberg, A. S. *J. Am. Chem. Soc.* **1961**, *83*, 2154.

(26) Lienhard, G. E.; Wang, T. C. *J. Am. Chem. Soc.* **1969**, *91*, 1146.

(27) Rappe, C.; Sachs, W. H. *J. Org. Chem.* **1967**, *32*, 4127.

(28) Fishman, J. *J. Org. Chem.* **1966**, *31*, 520-523.

(29) Thomas, A. F.; Willhelm, B. *Tetrahedron Lett.* **1965**, *18*, 1309-1311.

(30) Andersen, N. H.; Syrdal, D. D.; Graham, C. *Tetrahedron Lett.* **1972**, *10*, 903-904.

(31) Thomas, A. F.; Schneider, R. A.; Meinwald, *J. Am. Chem. Soc.* **1967**, *89*, 68.

(32) Lightner, D. A.; Gawronski, J. K.; Bouman, T. D. *J. Am. Chem. Soc.* **1980**, *102*, 1983-1990.

(33) Private communication from B. Dewprashad.

(34) Block, J. H.; Djerassi, C. *Steroids* **1973**, *22*, 591-596.

(35) Silverstein, R. M.; Bassler, G. C.; Morrill, T. C. *Spectrometric Identification of Organic Compounds*, 4th ed.; John Wiley & Sons: New York, **1981**, pp. 3-94.

(36) Staab, H. A.; Herz, C. P; Dohling, A. *Chem. Ber.* **1980**, *113*, 233-240.

(37) Mitchell, R. H.; Weerawarna, K. S.; Bushnell, G. W. *Tetrahedron Lett.* **1984**, *25*, 907-910.

(38) Krois, D.; Lehner, H. *J. Chem. Soc. Perkin I*, **1982**, 477-481.

(39) Blall, S. E. *J. Chem. Ed.* **1990**, *67*, 1038-1039.

(40) Bresciani-Pahor, N.; Calligaris, M.; Randaccio, L. *Acta. Cryst.* **1980**, *B36*, 632-638.

(41) Staab, H. A.; Dohling, A. *Tetrahedron Lett.* **1979**, *22*, 2019-2022.

(42) Semmelhack, M. F.; Harrison, J. J.; Young, D. C.; Gutierrez, A.; Raffin, S.; Clardy, J. *J. Am. Chem. Soc.* **1985**, *107*, 7508-7514.

(43) Hutchins, R. O.; Milewski, C. A.; Maryanoff, B. E. *J. Am. Chem. Soc.* **1973**, *95*, 3662-3668.

(44) Rangarajan, R.; Eisenbraun, E. J. *J. Org. Chem.* **1985**, *50*, 2435-2438.

(45) Edgren, R. A. *Contraception: The Chemical Control of Fertility*, Lednicer, D. Ed., Marcel Dekker, New York: **1969**, pp. 23-38.

(46) Bennett, J. P.; Kendie, K. E.; Vallance, D. K.; Vickery, B. H. *Acta. Endocrinol.* **1966**, *53*, 443.

(47) Hospital, M.; Busetta, B.; Bucort, R.; Weintraub, H.; Baulieu, E. E. *Mol. Pharmacol.* **1972**, *8*, 438-445.

(48) Laumas, K. R.; Uniyal, J. P.; Krishnan, A. R.; Murugesan, K.; Koshti, G. S. *Res. Steroids*, **1970**, *4*, 145-152.

(49) The Merck Index (8th Ed.), Stecher, P. G.ed.: Merck & Co., Inc. : **1968**, pp. 360-361, 372, 442-424, 665.

(50) Ruehle, P. H.; Browne, C. E.; Vickery, E. H.; Beller, N. R.; Eisenbraun, E. J.; Loghry, R. A.; van der Helm, D. *J. Med. Chem.* **1980**, *23*, 1410-1414.

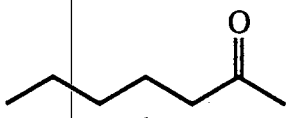
(51) Jardon, P. W.; Vickery, E. H.; Pahler, L. F.; Pourahmady, N.; Mains, G. J.; Eisenbraun, E. J. *J. Org. Chem.* **1984**, *49*, 2130-2135.

(52) Edward, J. T.; Holder, P.; Lumm, W. H.; Puskas, I. *Can J. Chem.* **1961**, *39*, 599.

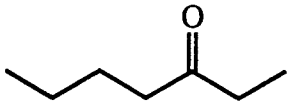
(53) Meyer, W. L.; Cameron, D. D.; Johnson, W. S. *J. Org. Chem.* **1962**, *27*, 1130.

APPENDIX A

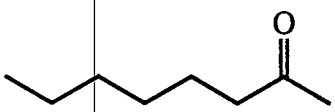
GLOSSARY OF STRUCTURES



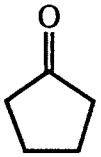
1



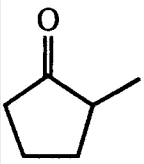
2



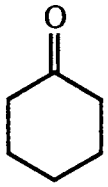
3



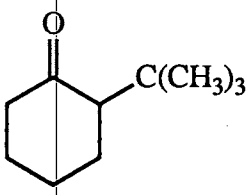
4



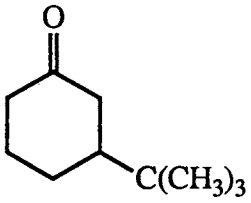
5



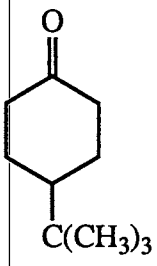
6



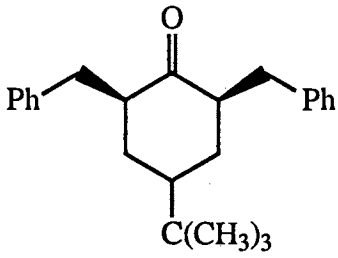
7



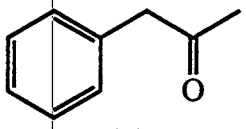
8



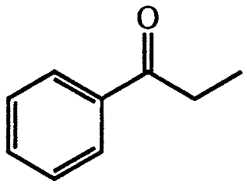
9



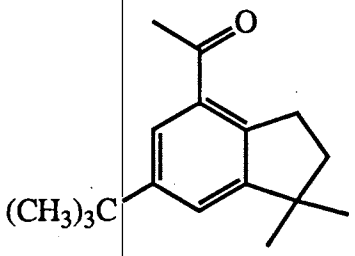
10



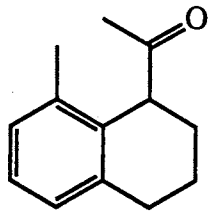
11



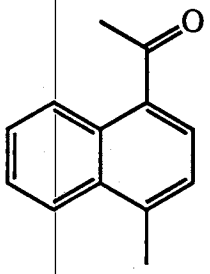
12



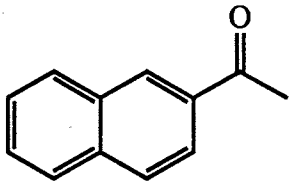
13



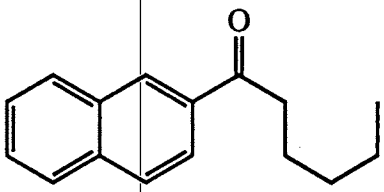
14



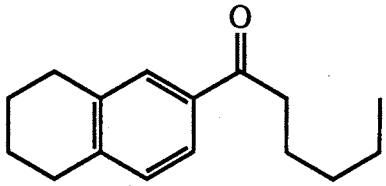
15



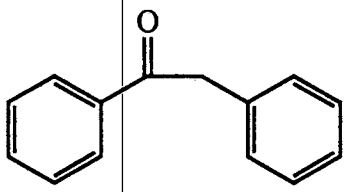
16



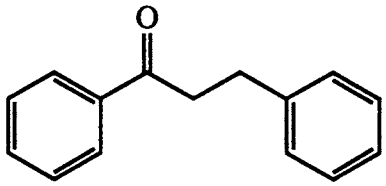
17



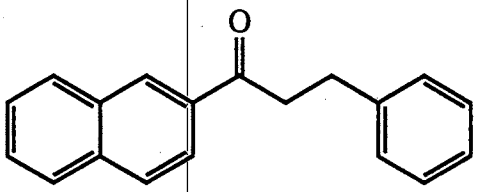
18



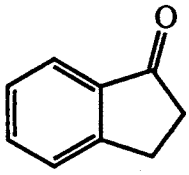
19



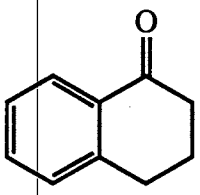
20



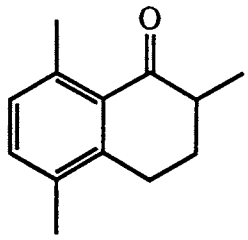
21



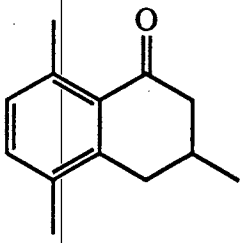
22



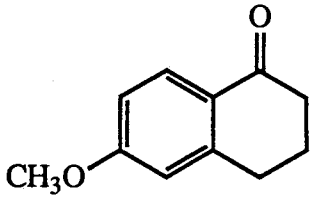
23



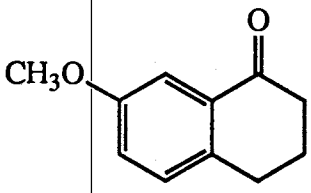
24



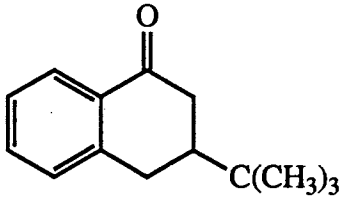
25



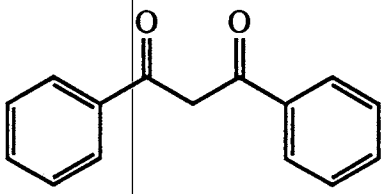
26



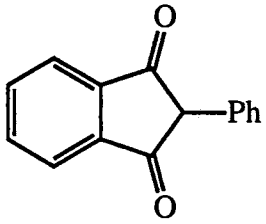
27



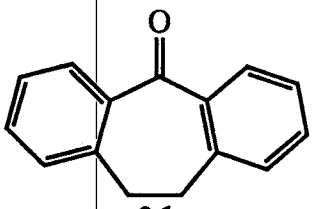
28



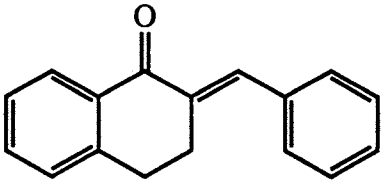
29



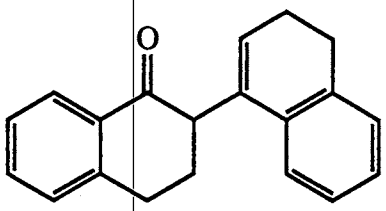
30



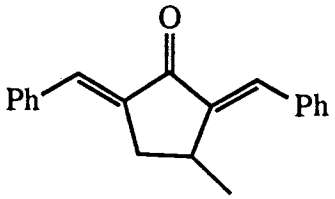
31



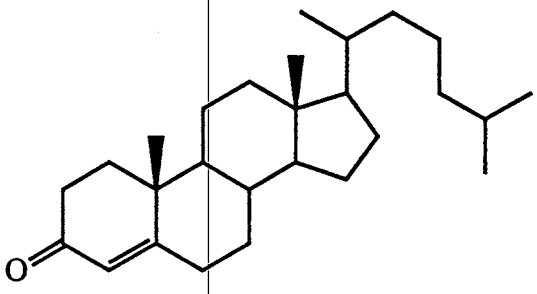
32



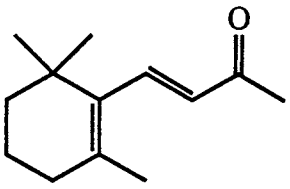
33



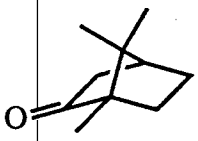
34



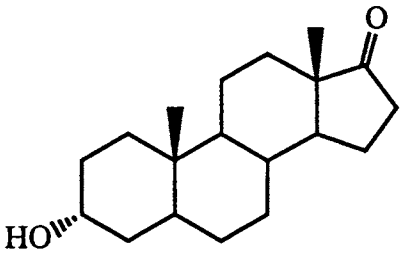
35



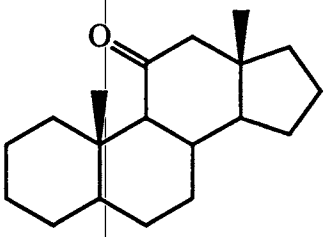
36



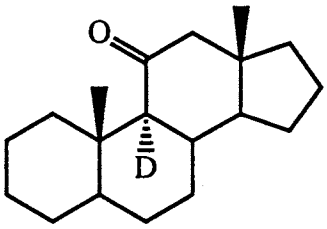
37



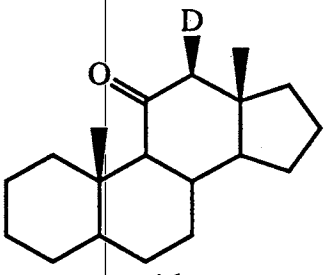
38



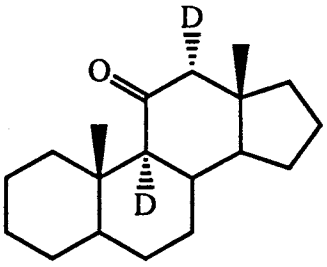
39



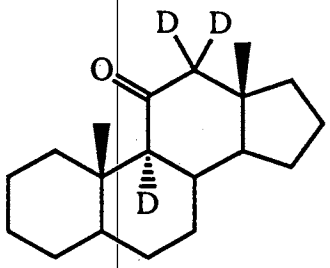
40



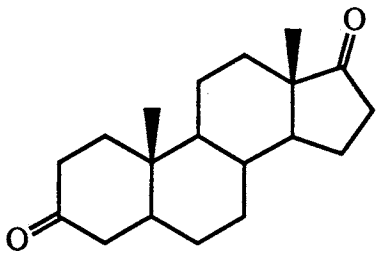
41



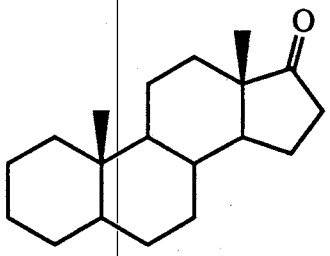
42



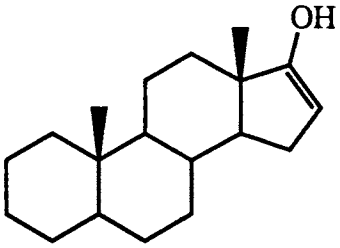
43



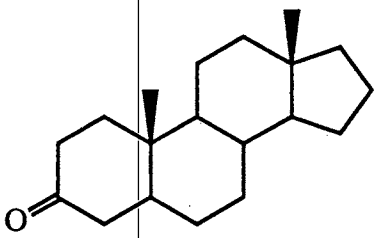
44



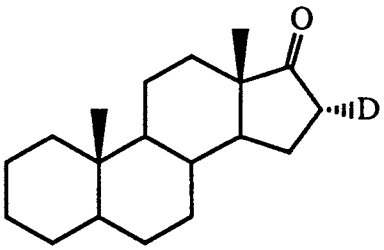
45



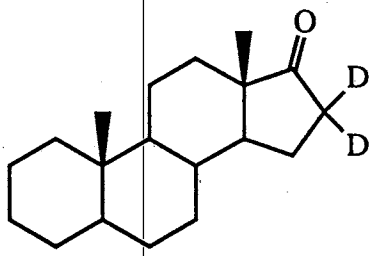
46



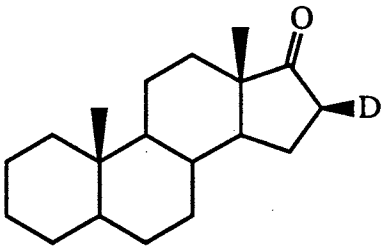
47



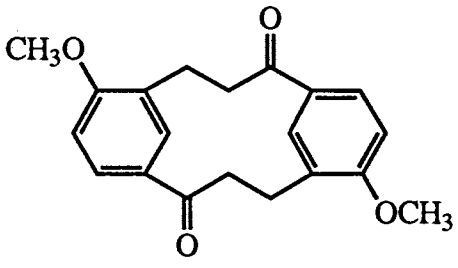
48



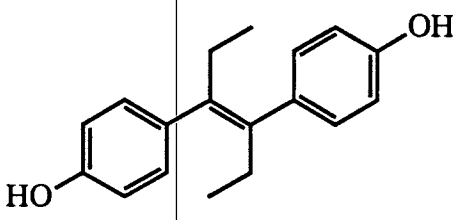
49



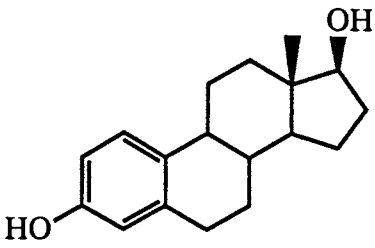
50



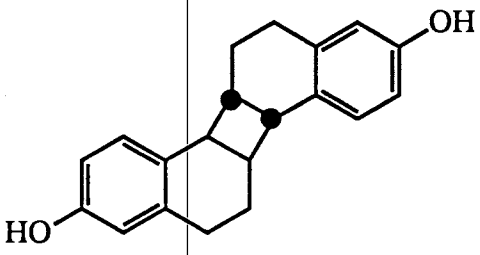
51



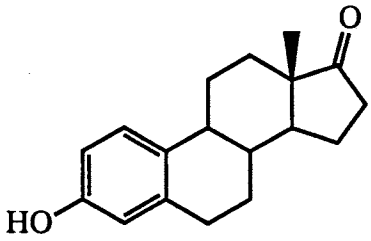
52



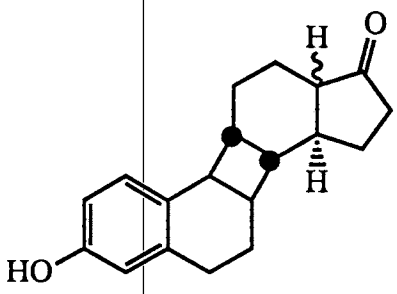
53



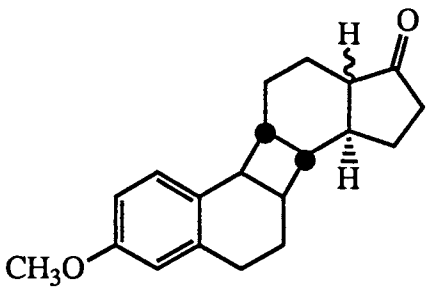
54



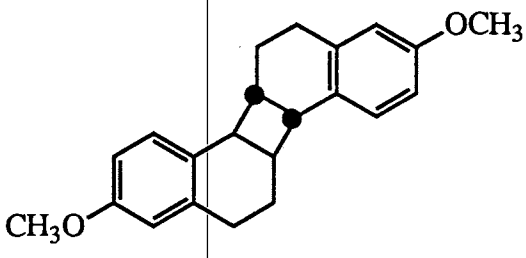
55



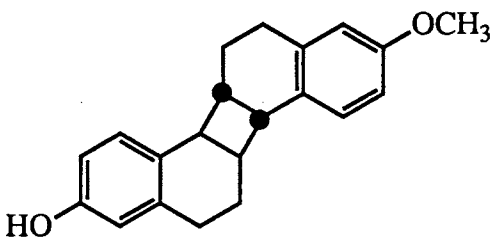
56a



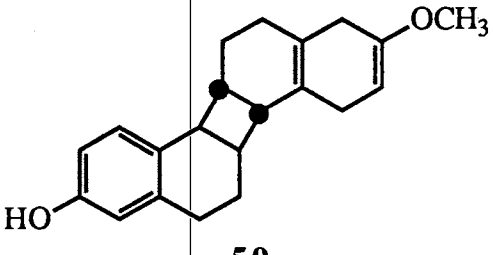
56b



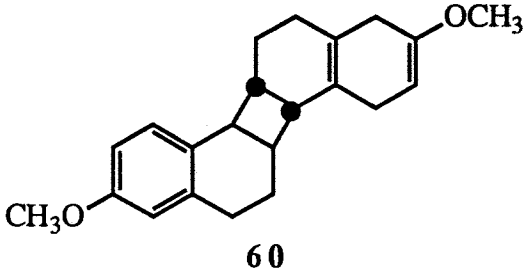
57



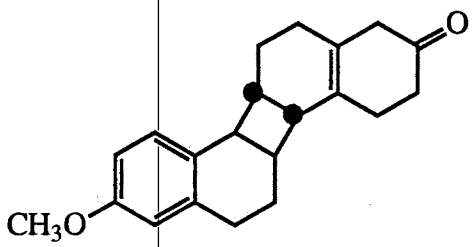
58



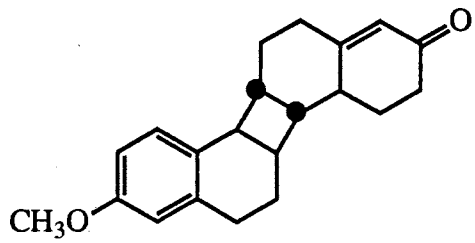
59



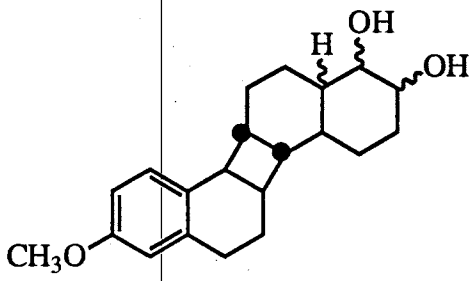
60



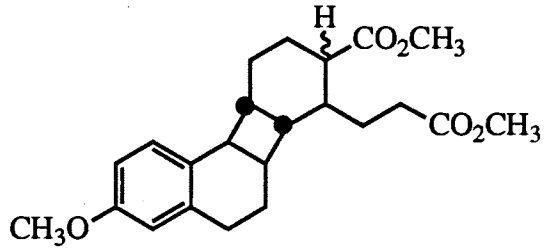
61



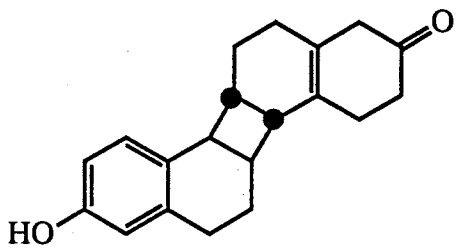
62



63



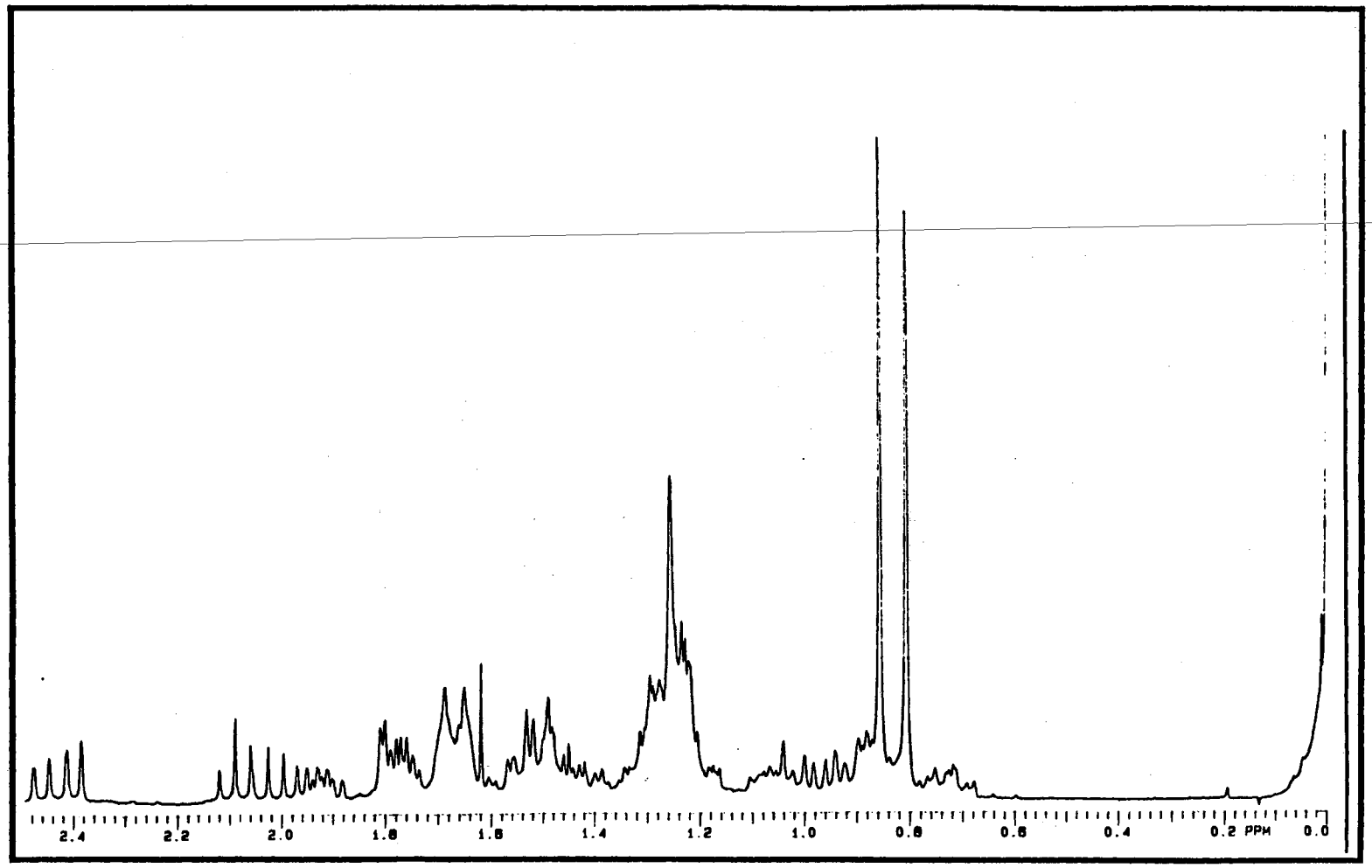
64



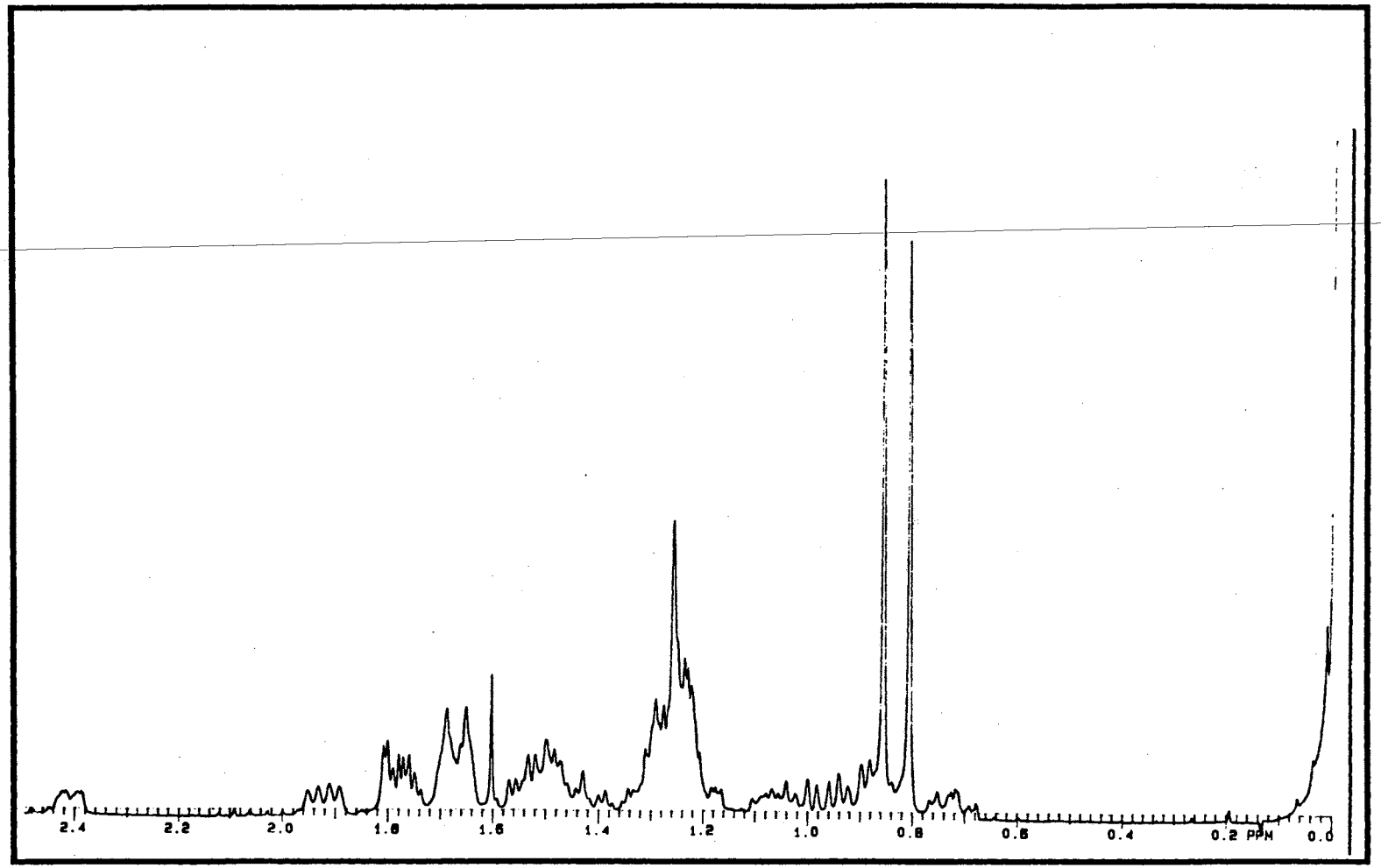
65

APPENDIX B

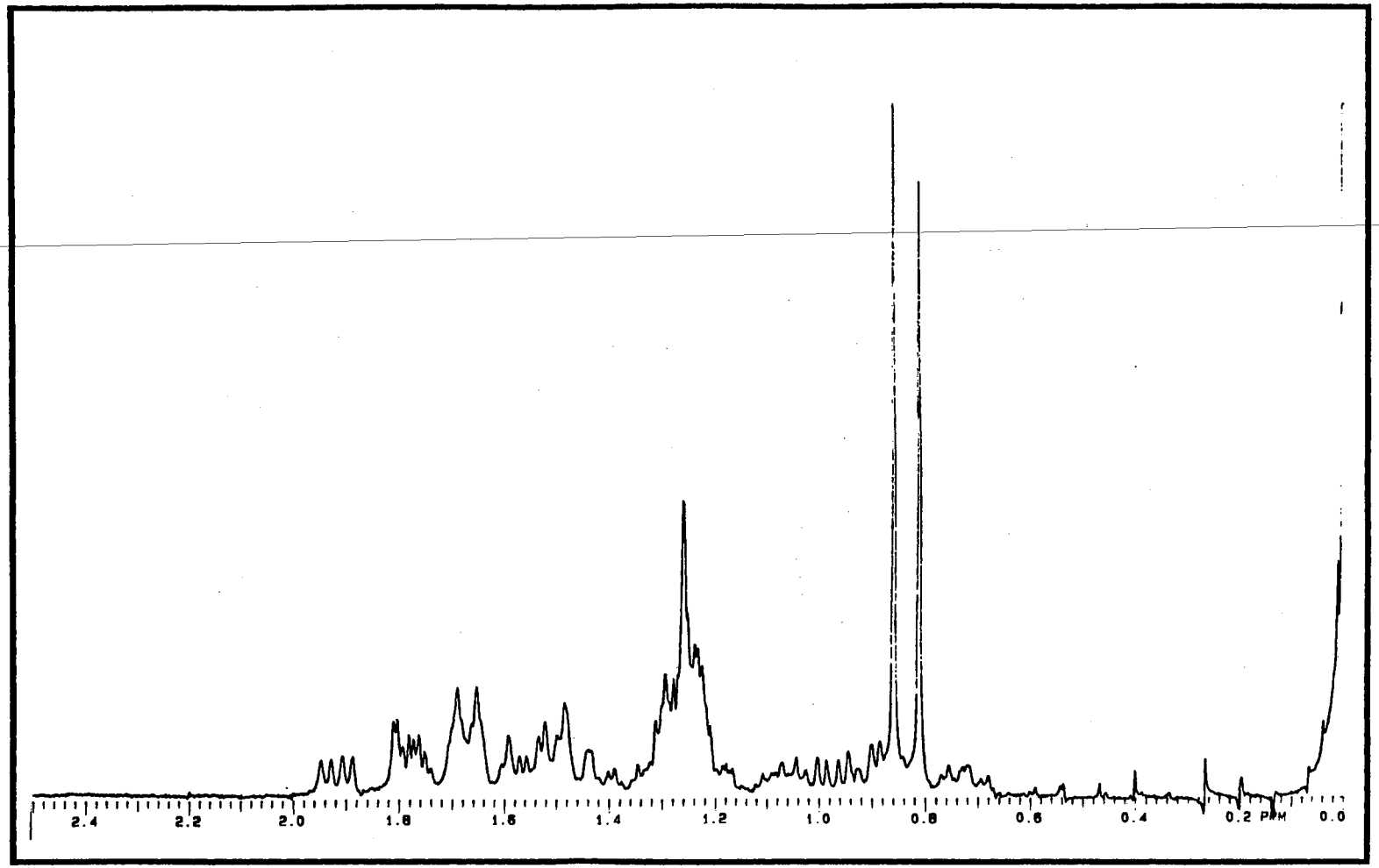
SELECTED ^{1}H AND ^{13}C NMR SPECTRA



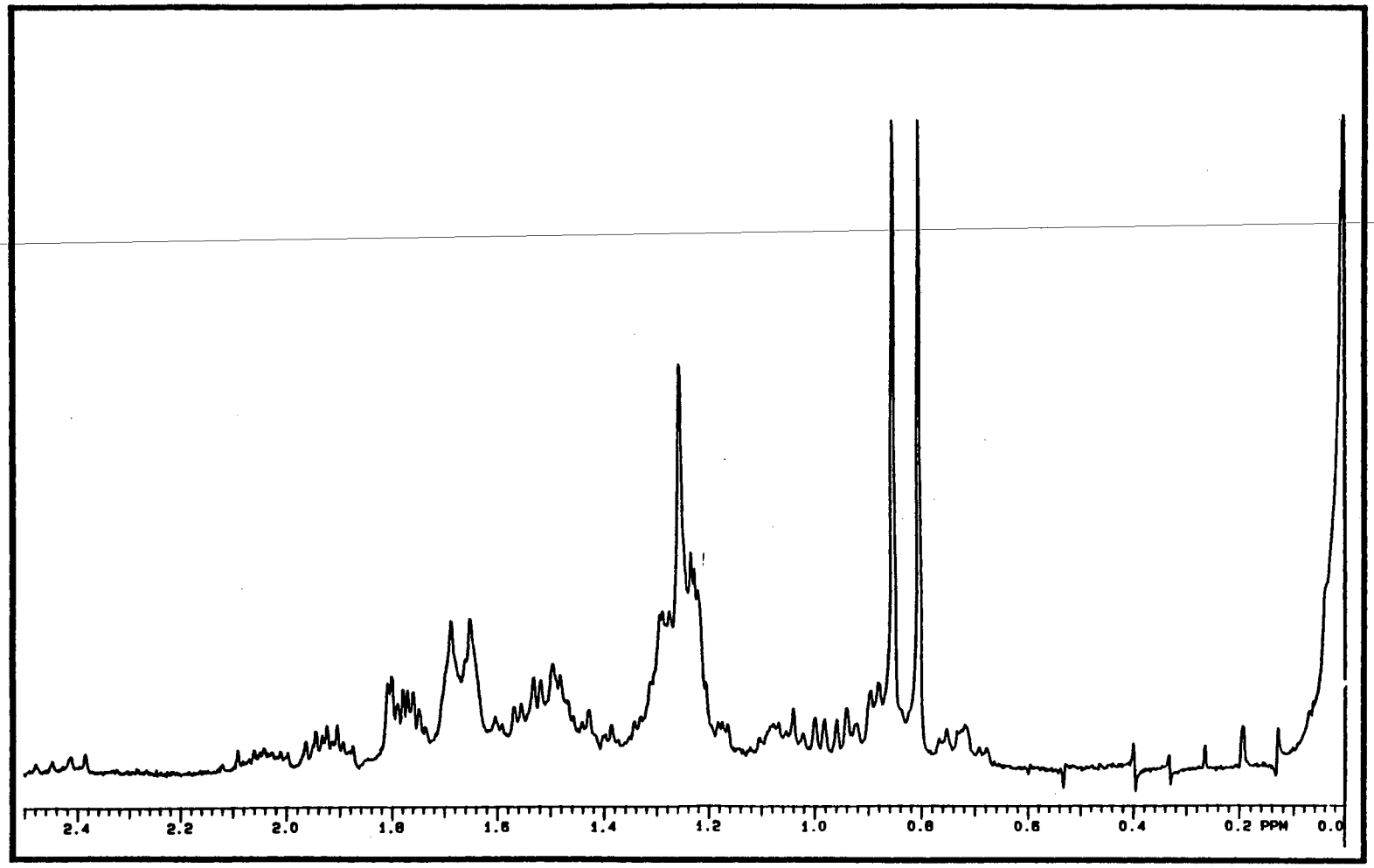
Spectrum 1a. ^{1}H NMR of 5α-androstan-17-one (**45**).



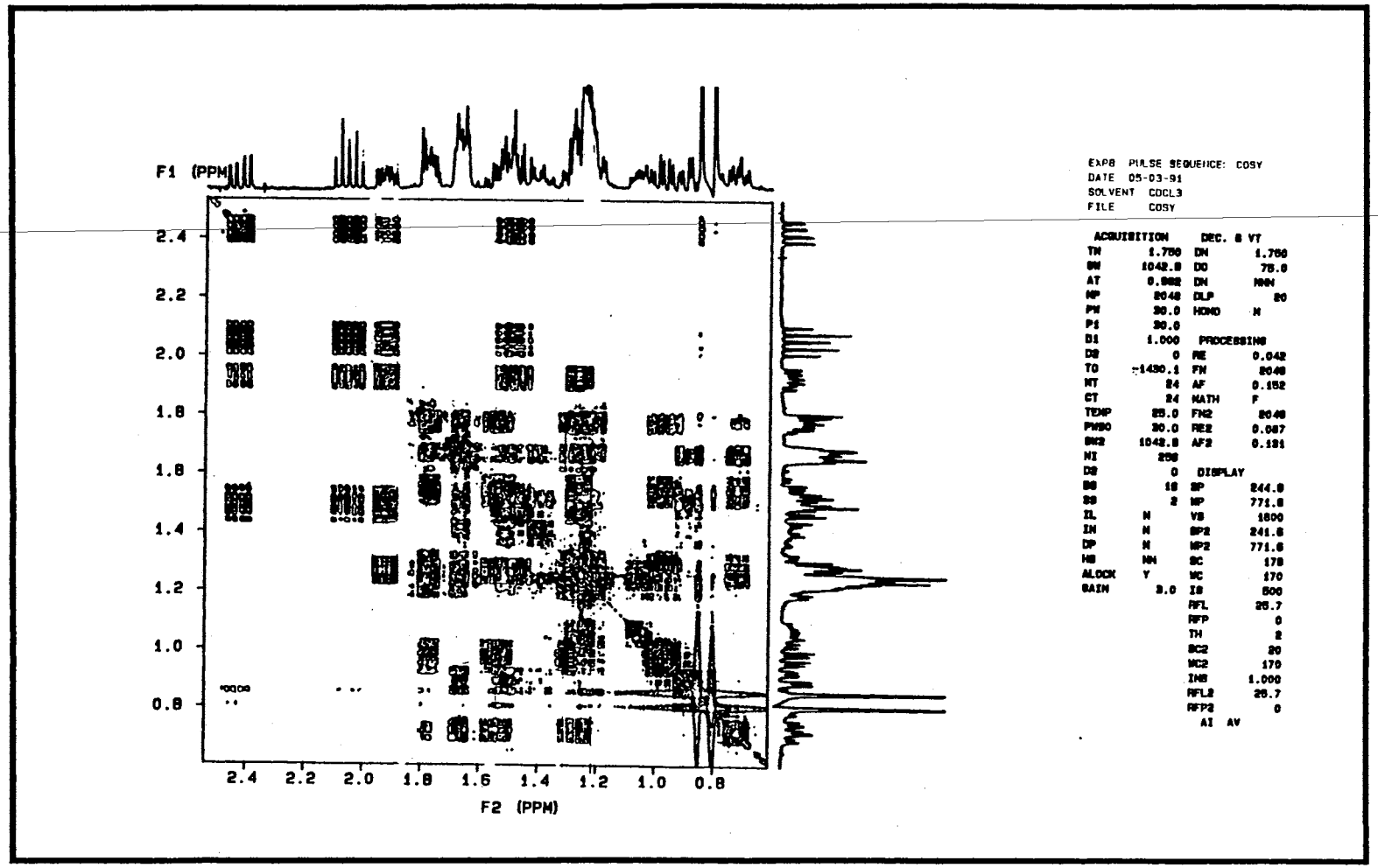
Spectrum 1b. ^{1}H NMR of 16α-deutero-5α-androstan-17-one (**48**).



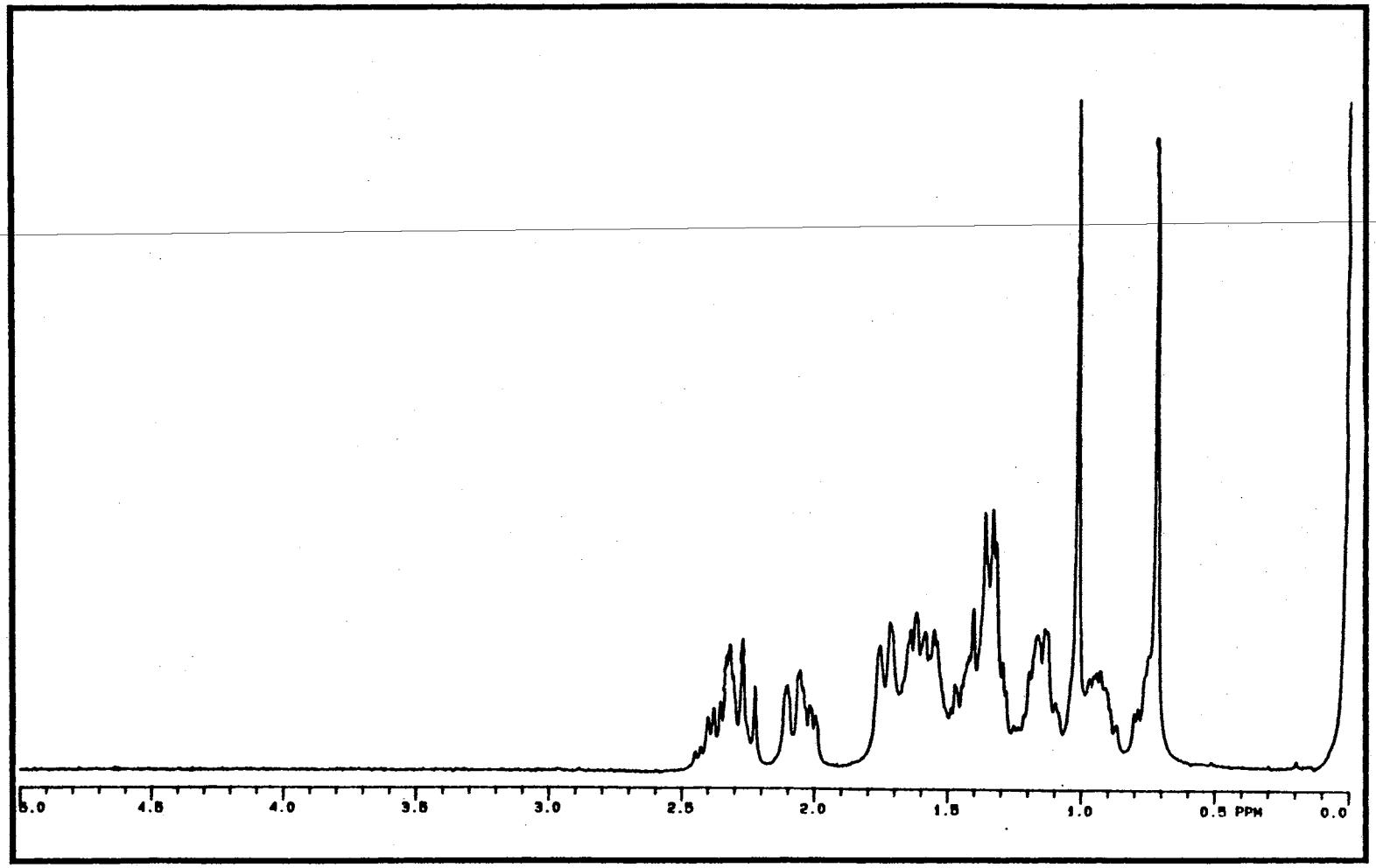
Spectrum 1c. ^{1}H NMR of 16,16-dideutero-5α-androstan-17-one (**49**).



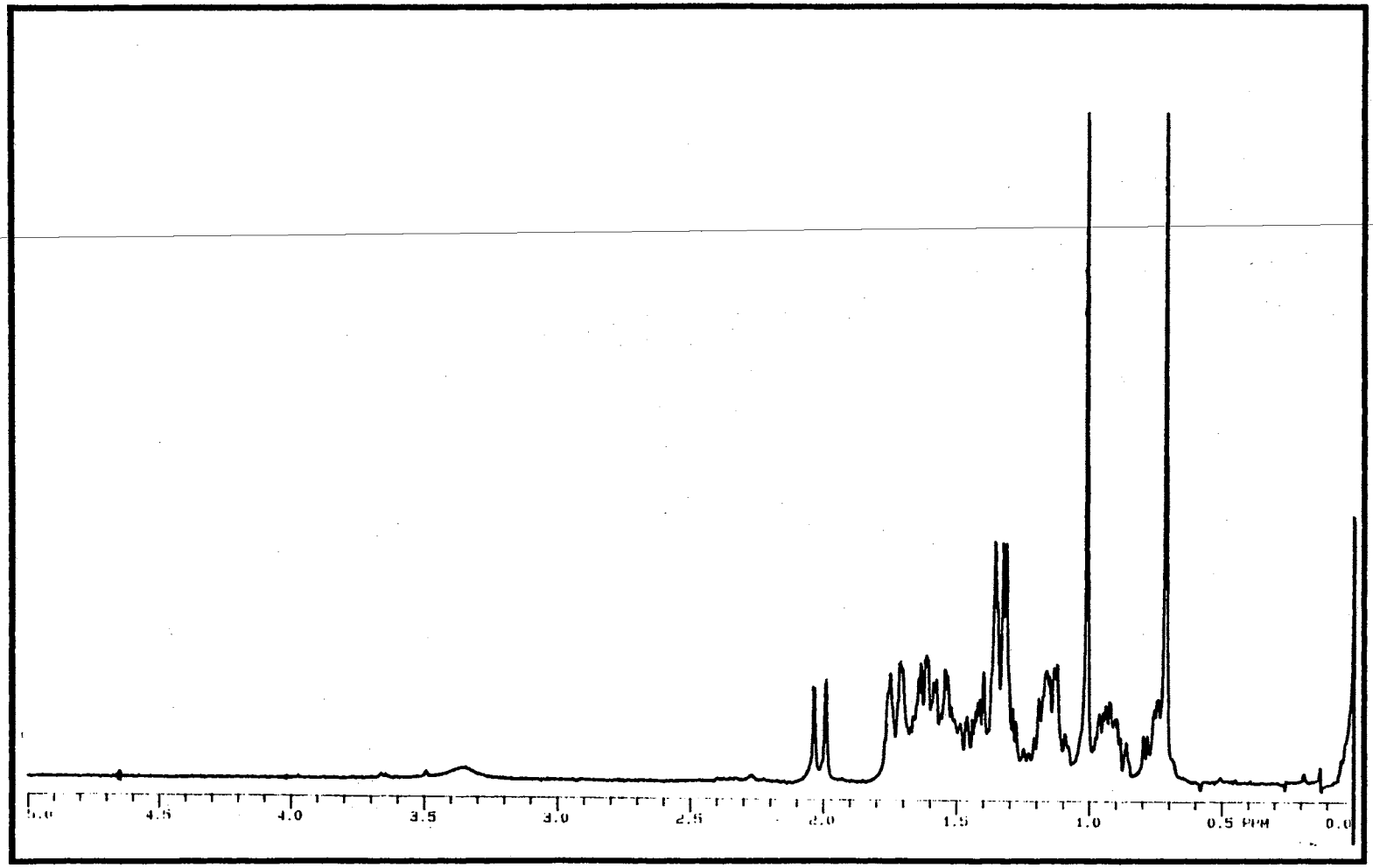
Spectrum 1d. ^{1}H NMR of 16,16-dideutero-5α-androstan-17-one (**49**) treated with neat TFA at RT.



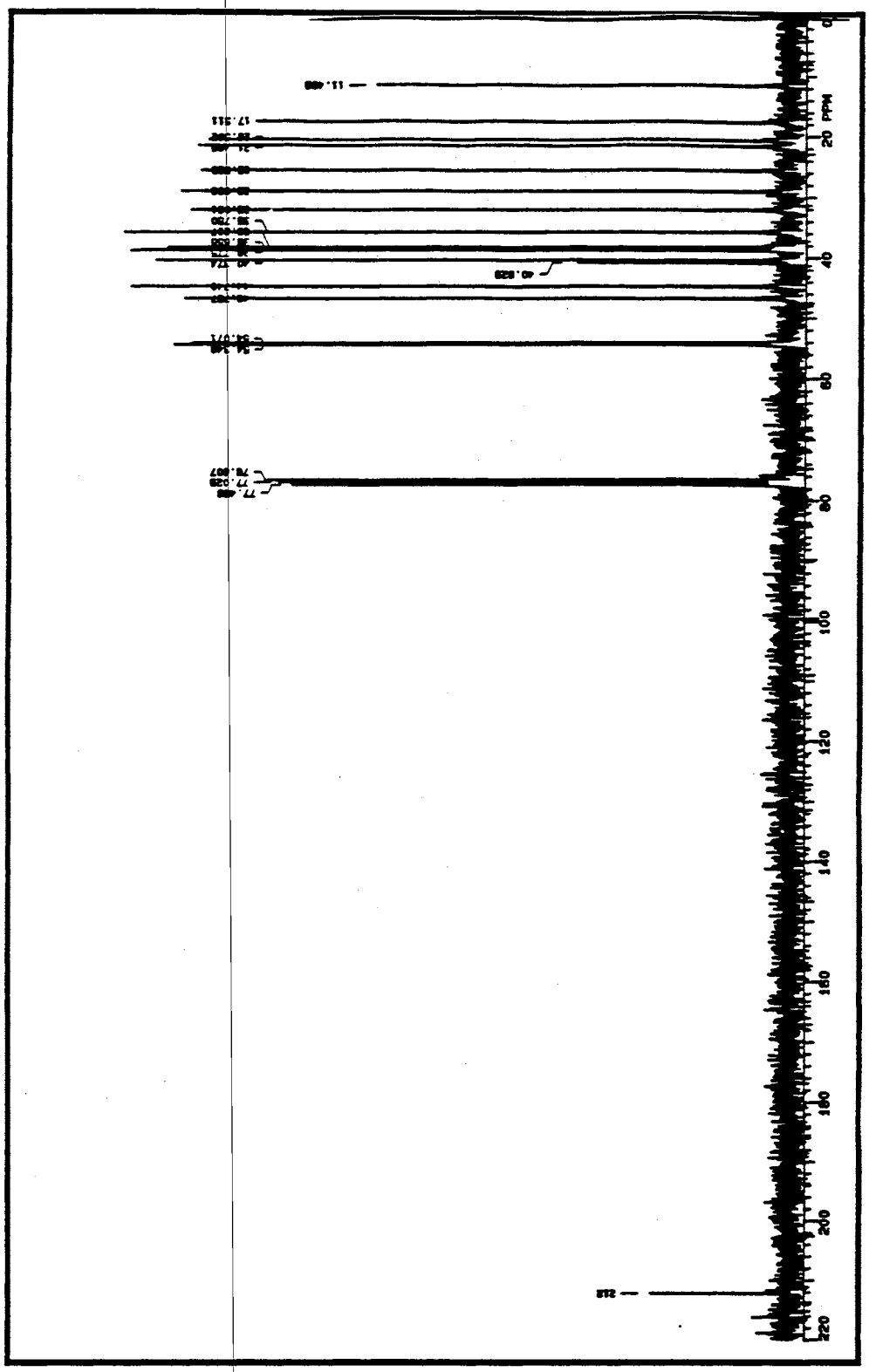
Spectrum 1e. COSY NMR of 5α-androstan-17-one (**45**).



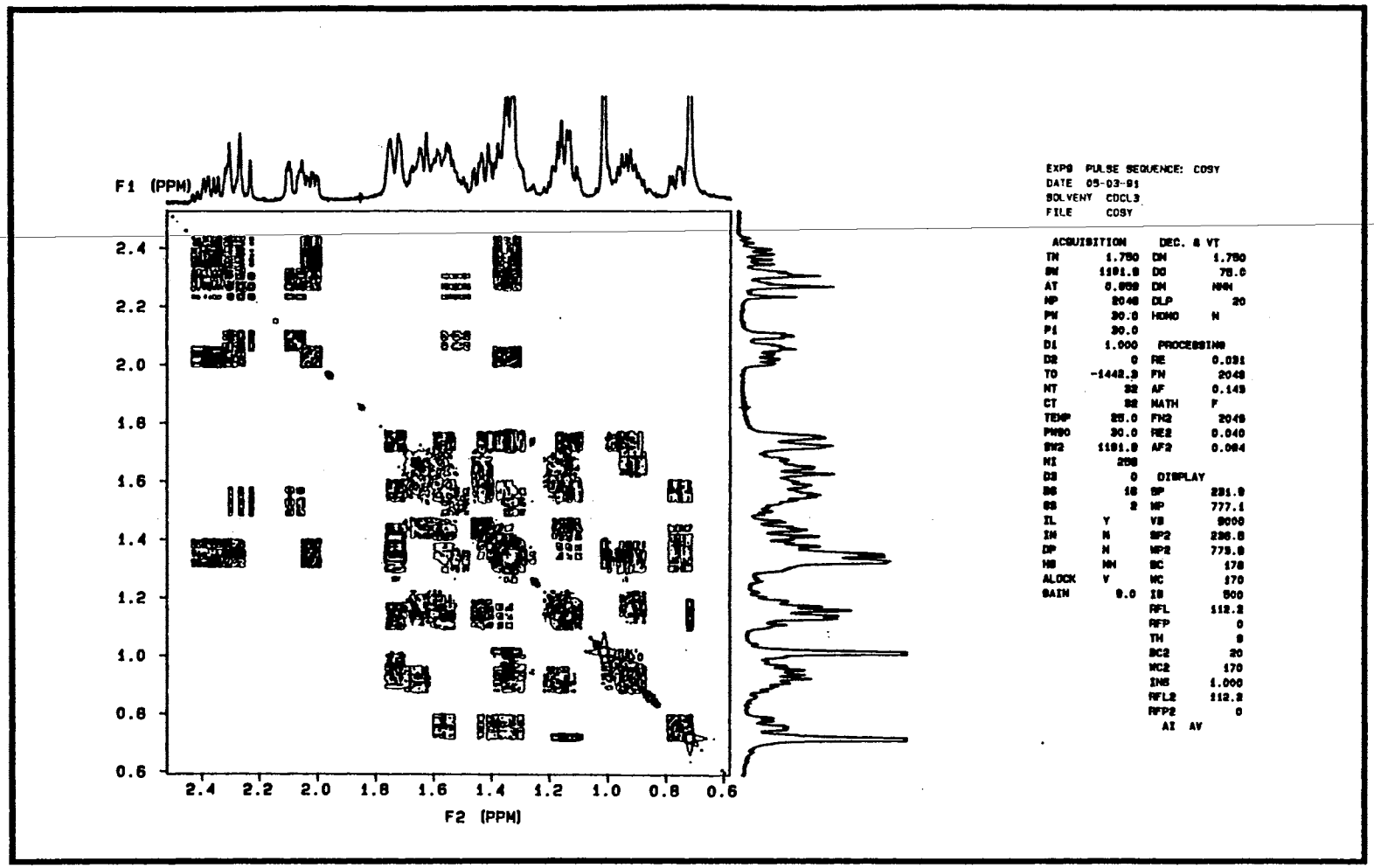
Spectrum 2a. ^{1}H NMR of 5α-androstan-3-one (**47**).



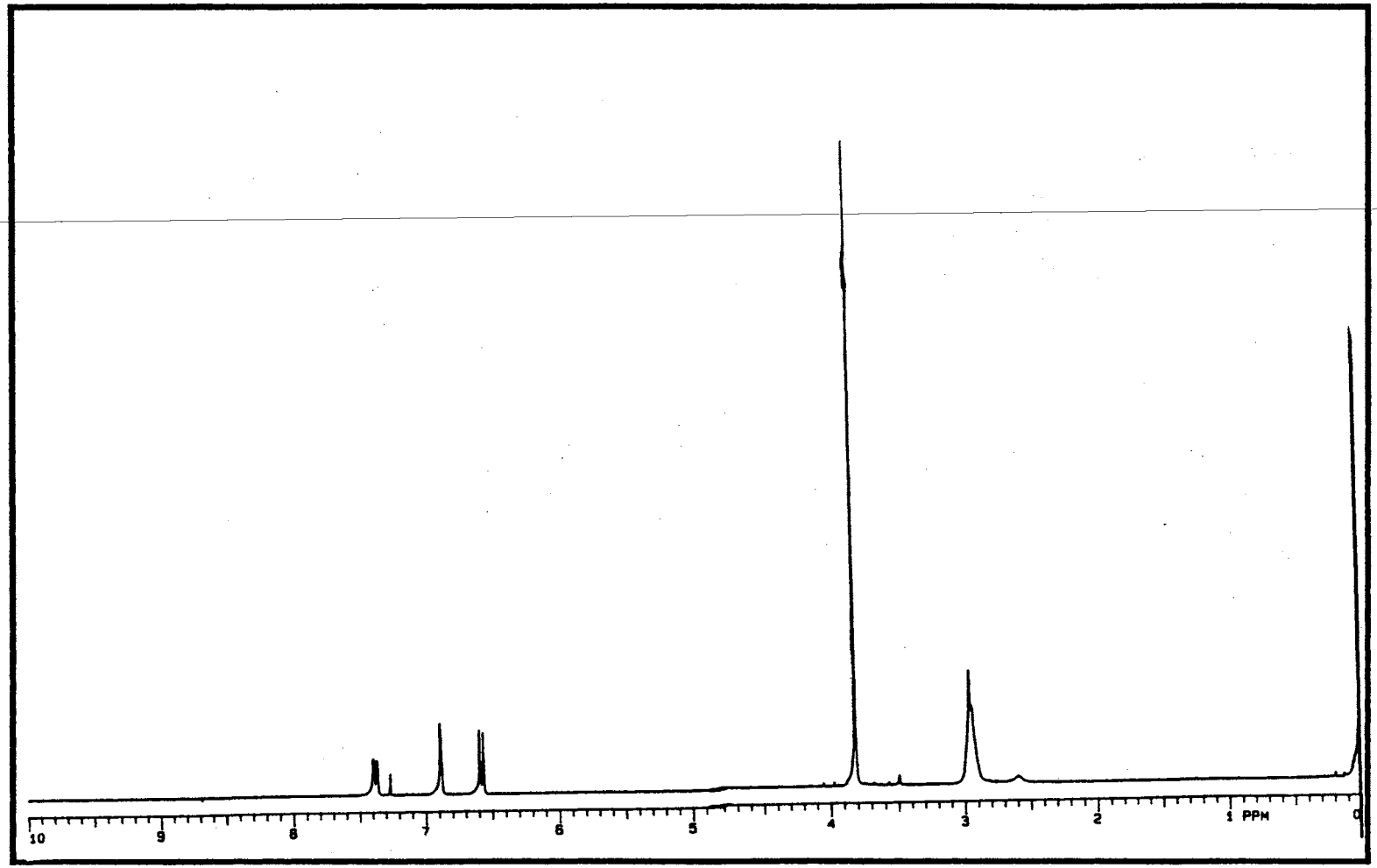
Spectrum 2b. ^{1}H NMR of 2,2,4,4-tetradeutero-5α-androstan-3-one (**47**).



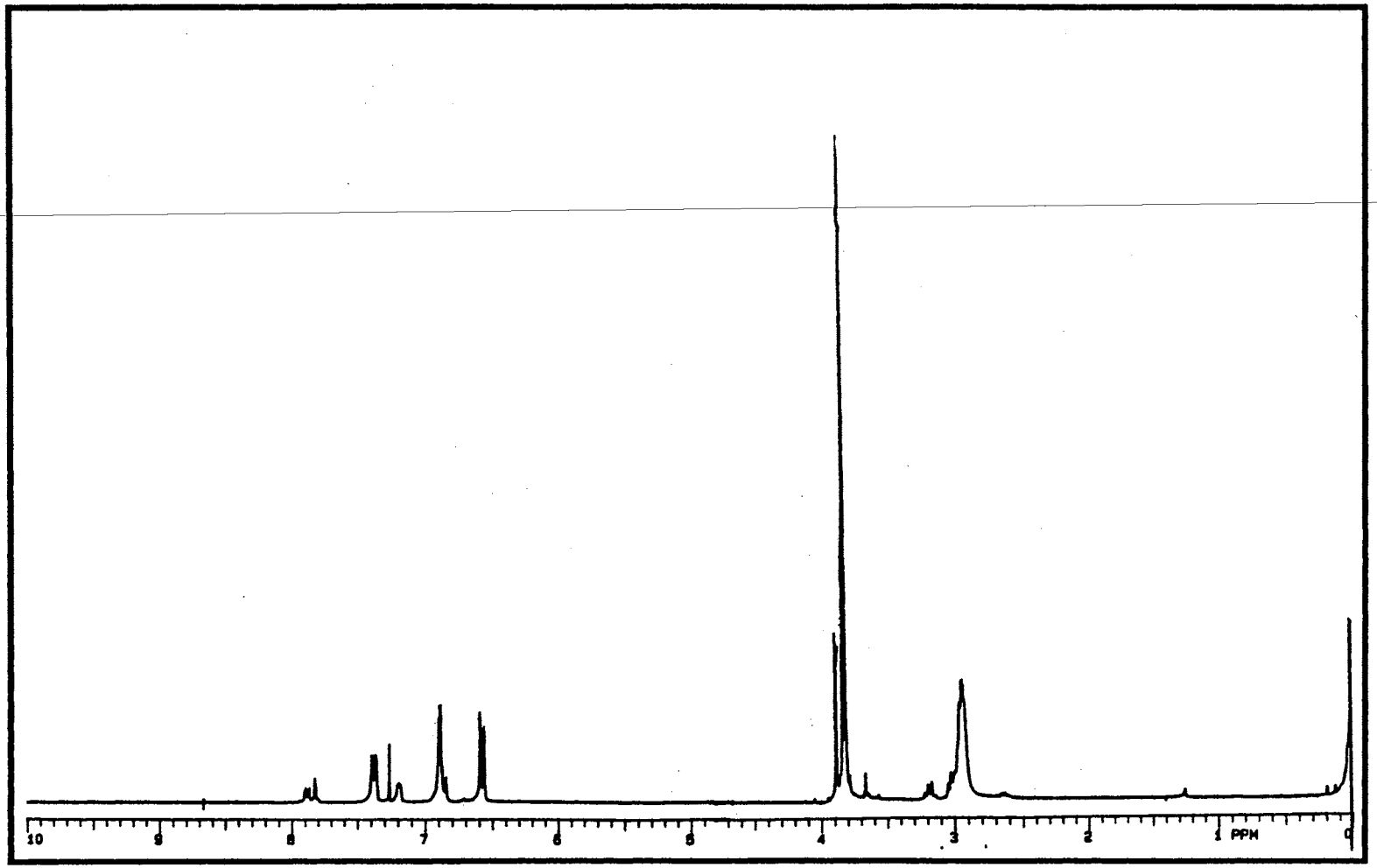
Spectrum 2c. ^{13}C NMR of 5α-androstan-3-one (47).



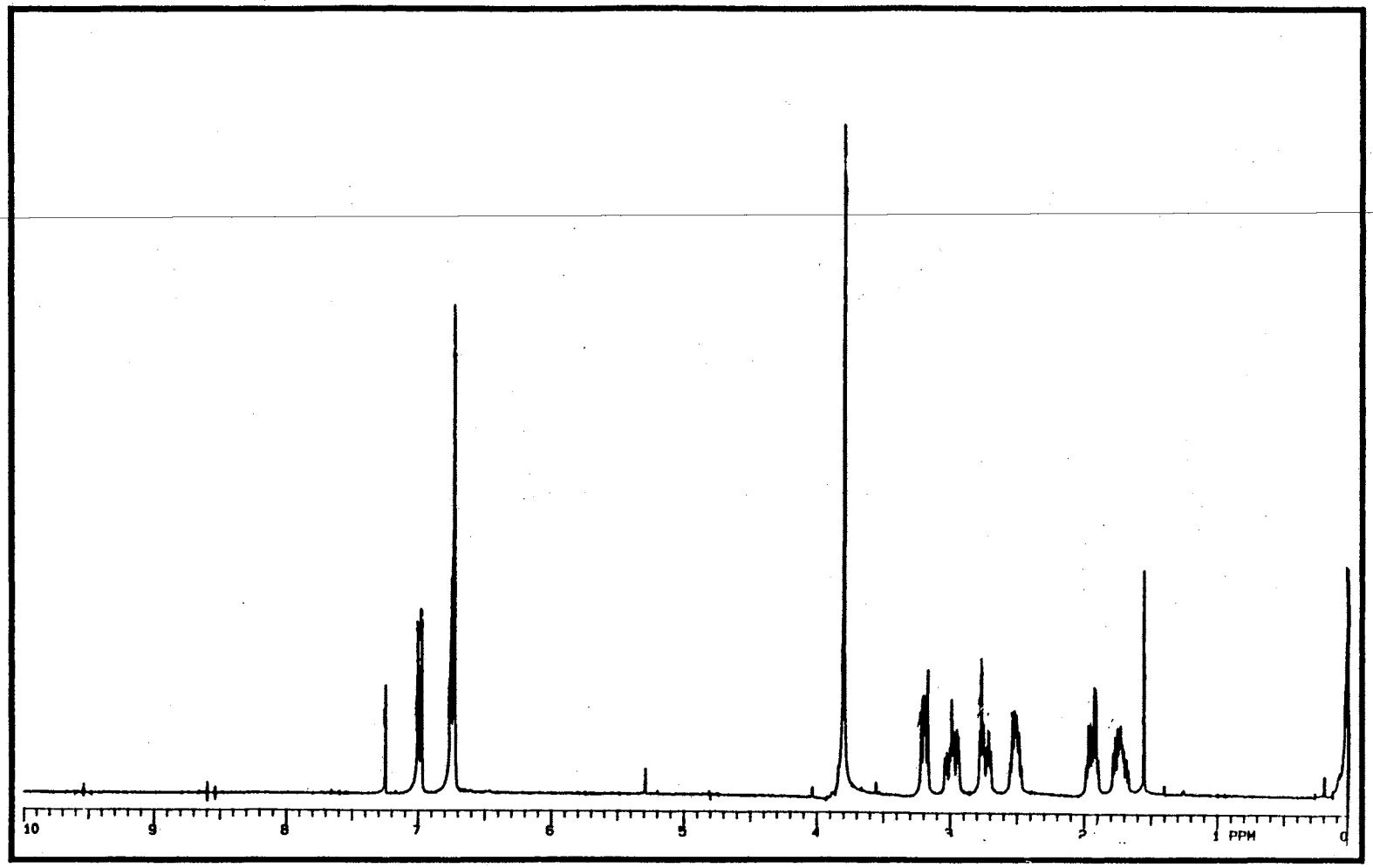
Spectrum 2d. COSY NMR of 5α-androstan-3-one (**47**).



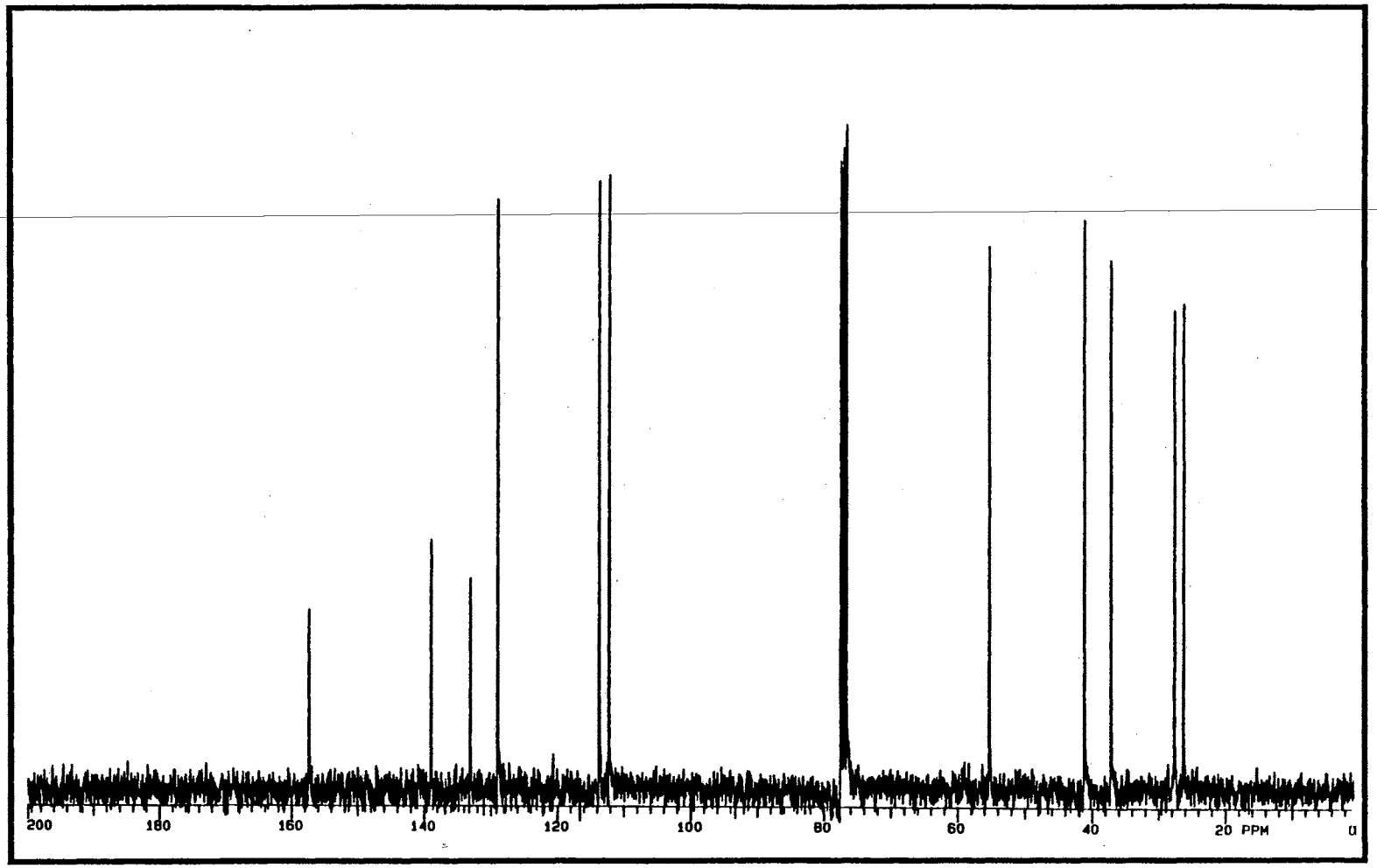
Spectrum 3a. ^{1}H NMR 5,14-dimethoxy[3,3]metacyclophane (**51**).



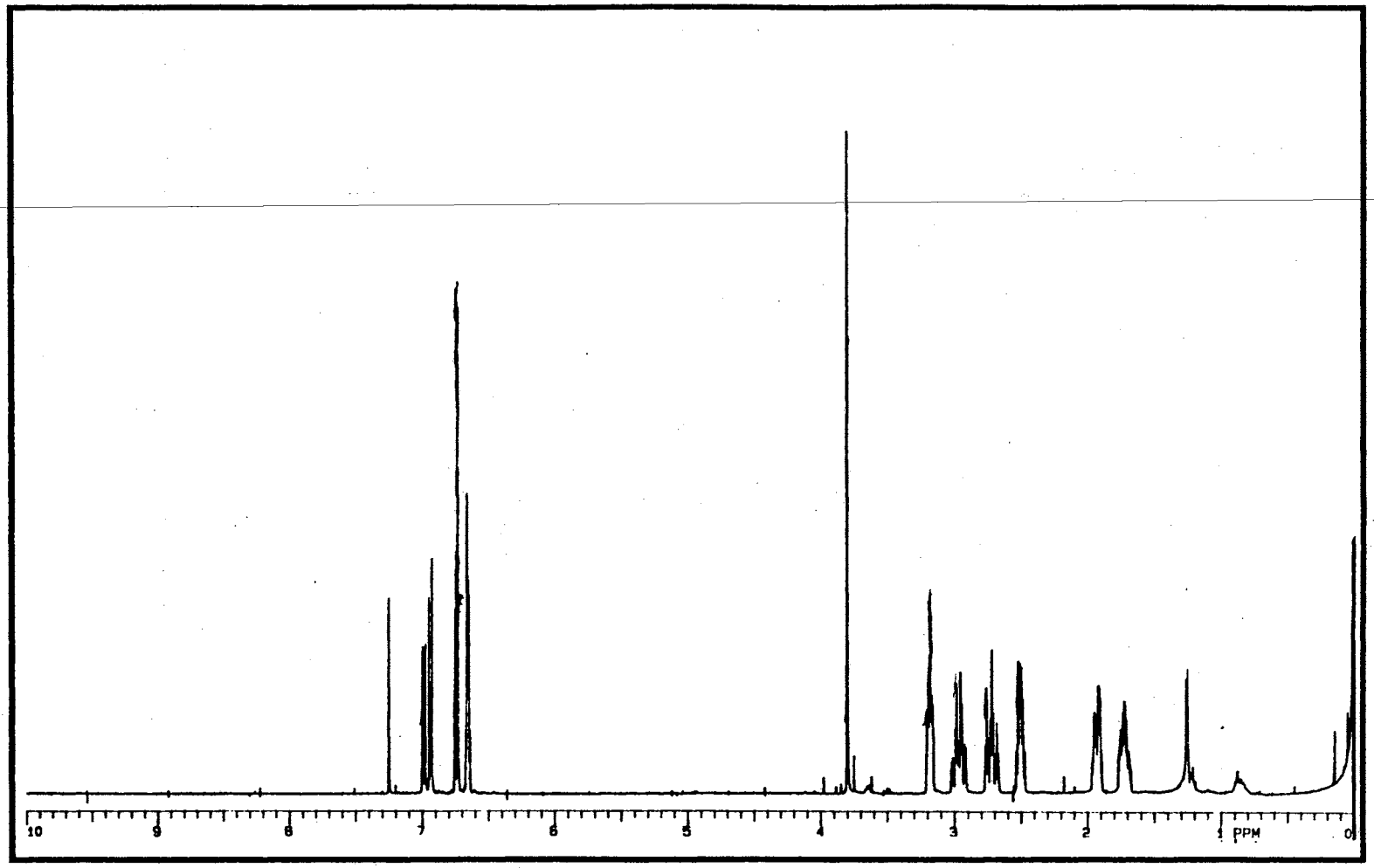
Spectrum 3b. ^{1}H NMR 5,14-dimethoxy[3,3]metacyclophane (**51**).



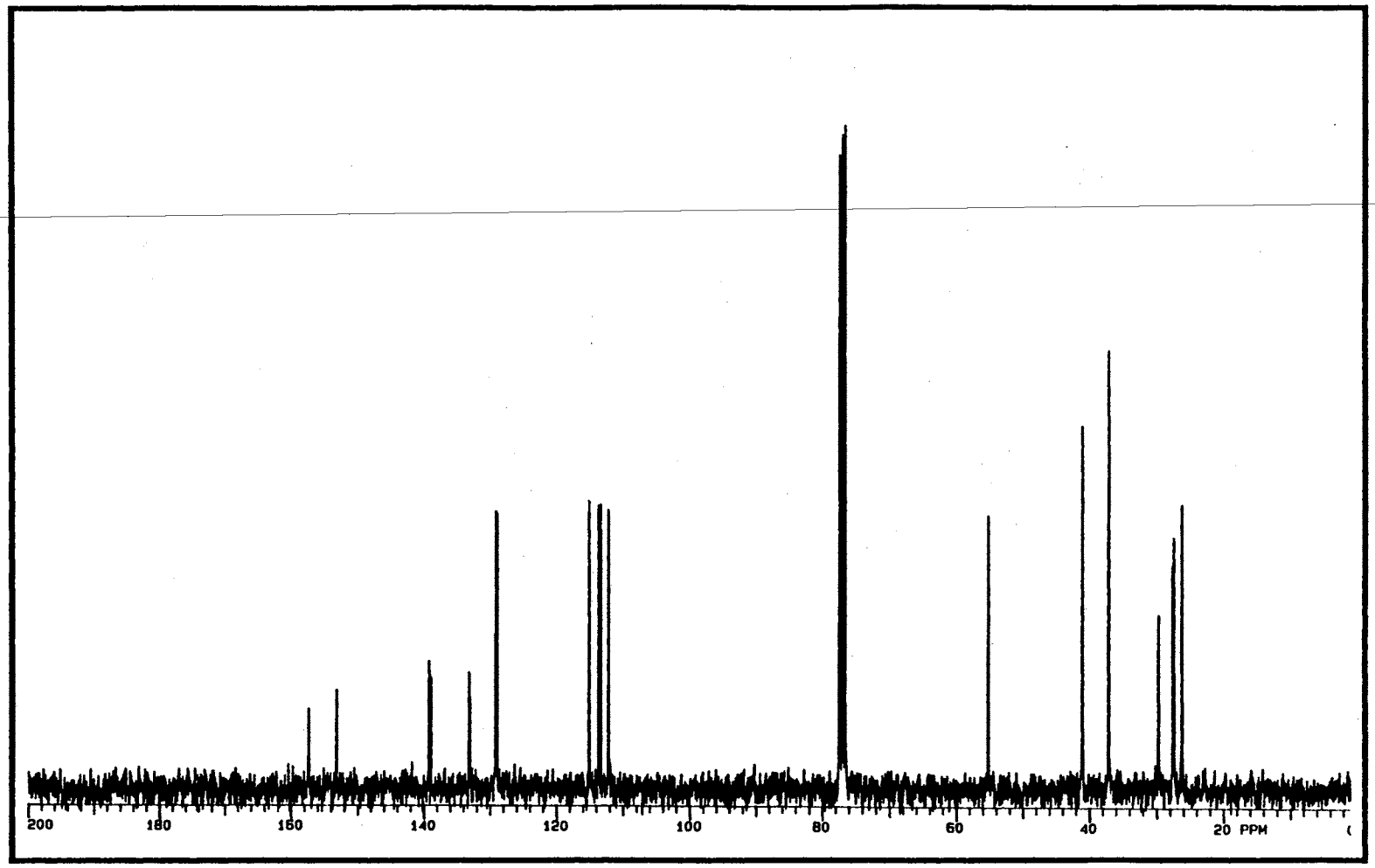
Spectrum 4a. ^{1}H NMR of 3,9-dimethoxy-5,6,6aα,6bβ,11,12,12aβ,12bα-octahydrodibenzo[*a,g*]biphenylene (**57**).



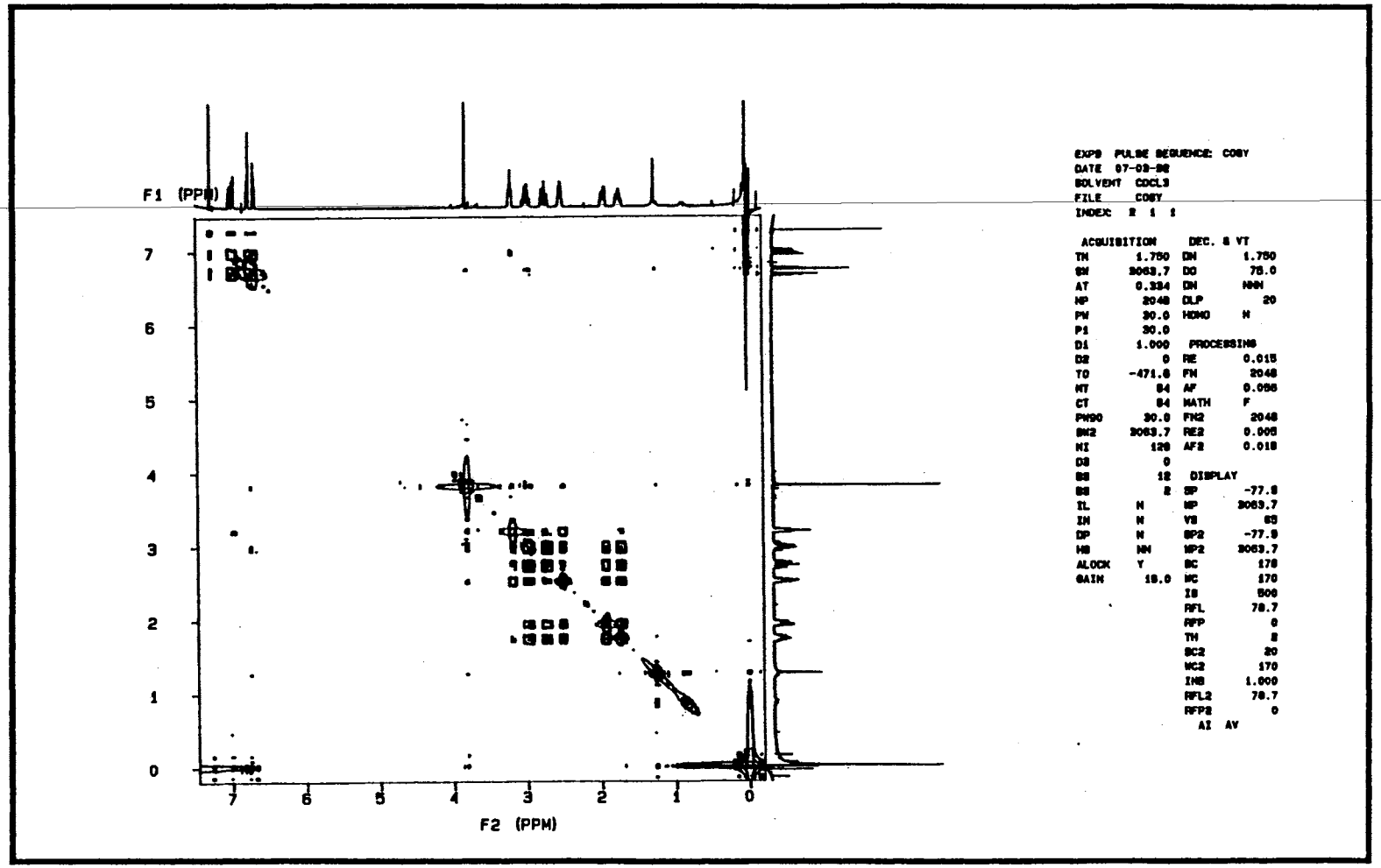
Spectrum 4b. ^{13}C NMR of 3,9-dimethoxy-5,6,6aα,6bβ,11,12,12aβ,12bα-octahydrodibenzo[*a,g*]biphenylene (**57**).



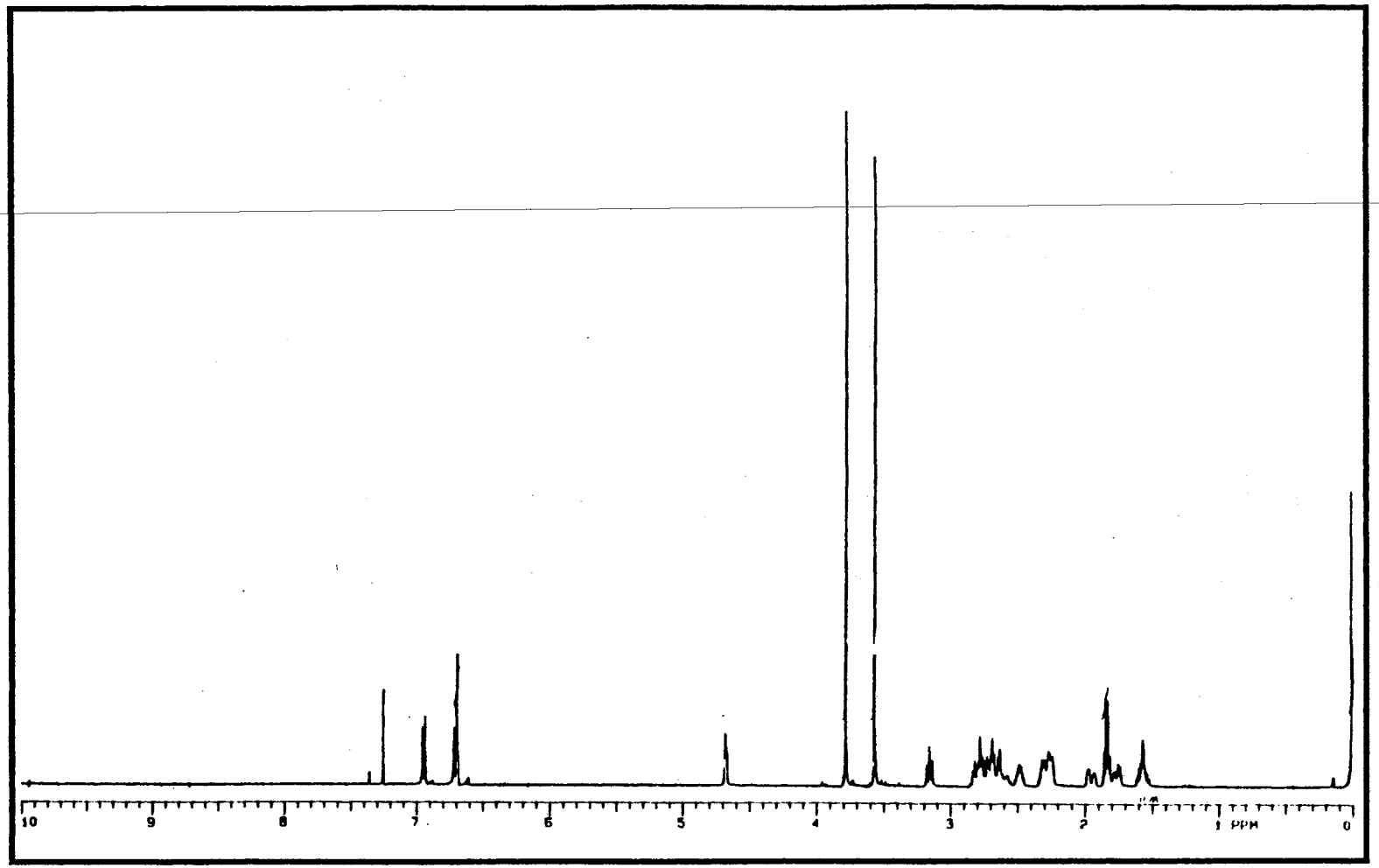
Spectrum 5a. ^{1}H NMR of 3-hydroxy-9-methoxy-5,6,6aα,6bβ,11,12,12aβ,12bα-octahydrodibenzo[*a,g*]biphenylene (**58**).



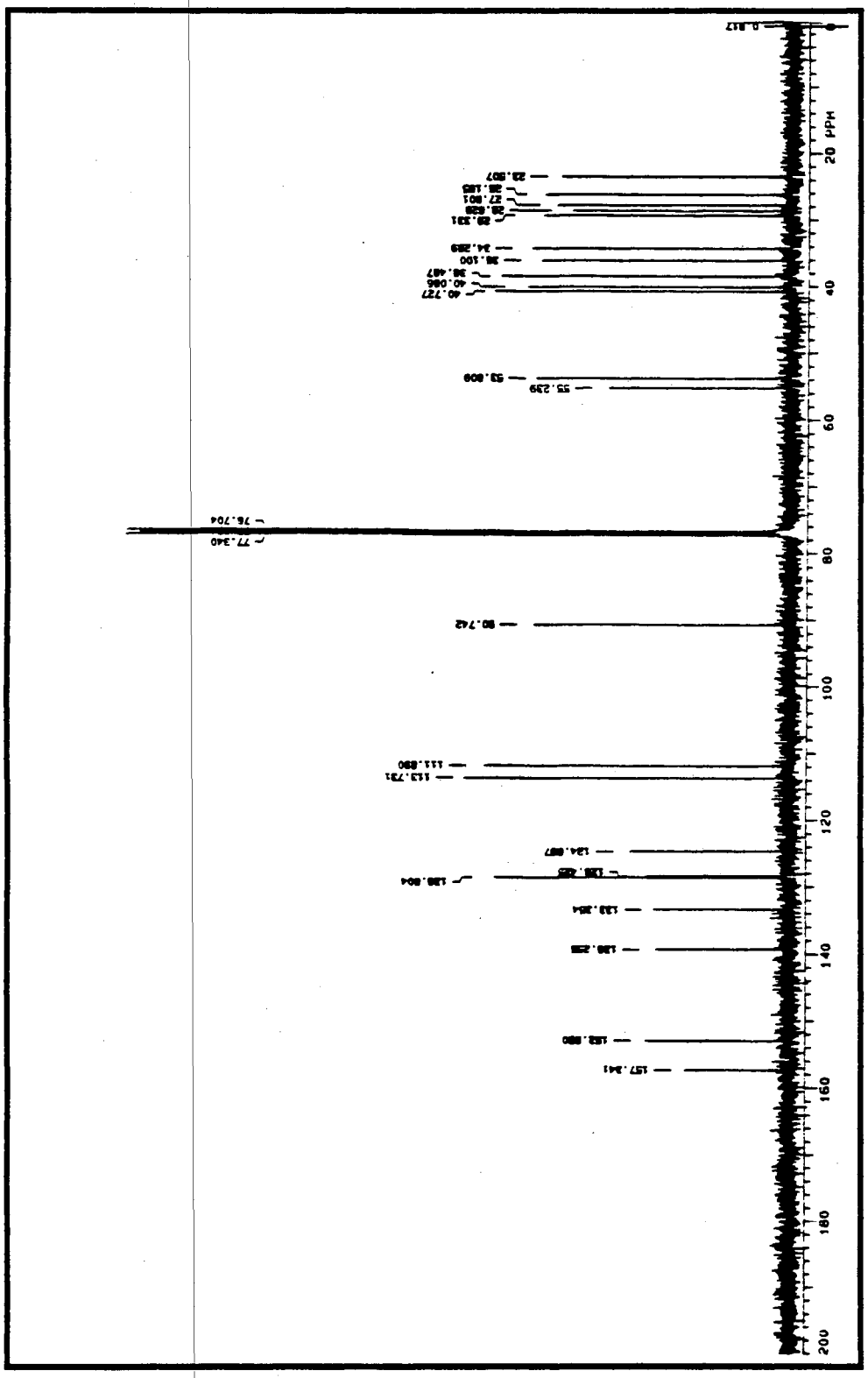
Spectrum 5b. ^{13}C NMR of 3-hydroxy-9-methoxy-5,6,6aα,6bβ,11,12,12aβ,12bα-octahydrodibenzo[*a*,*g*]biphenylene (**58**).



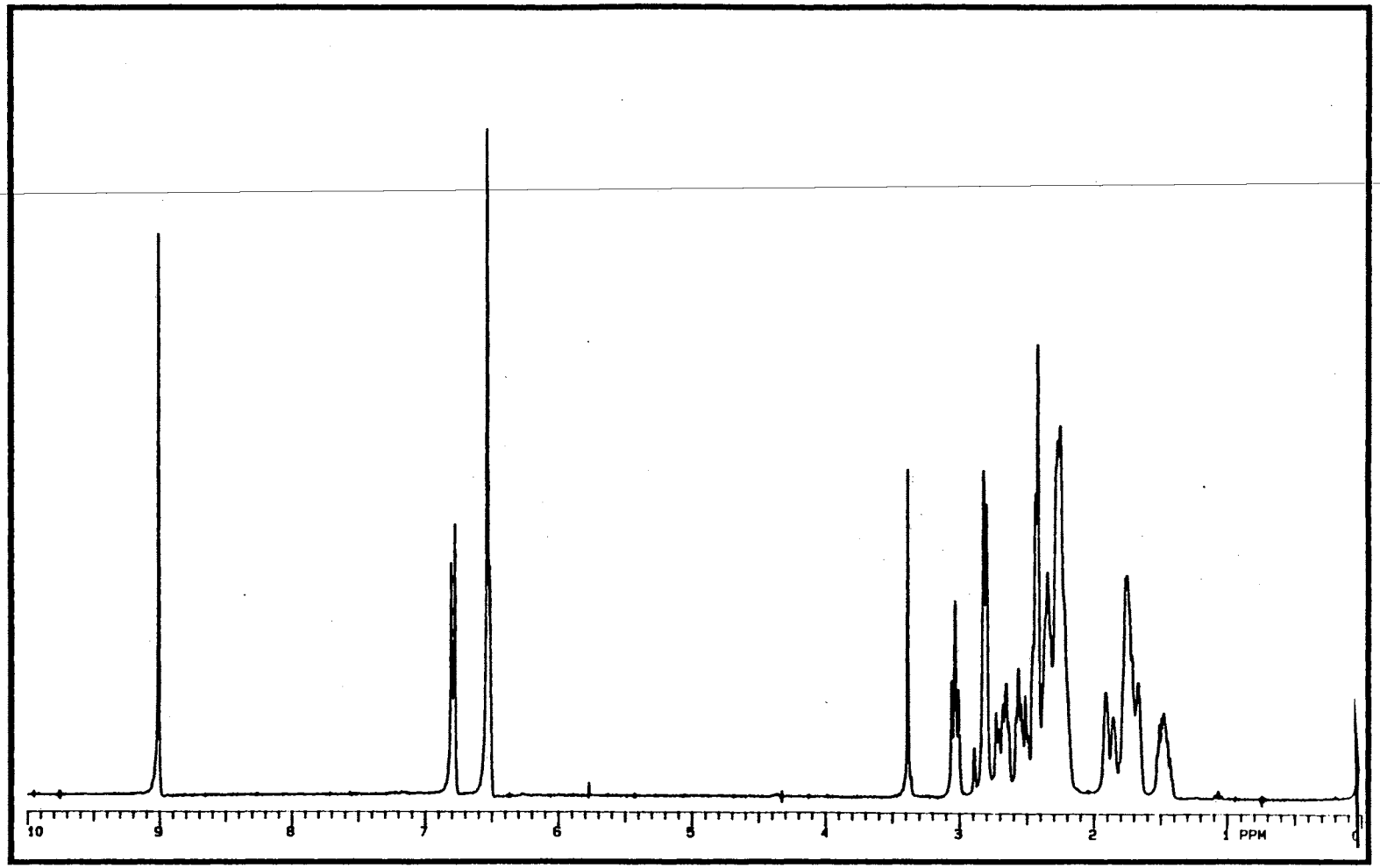
Spectrum 5c. COSY NMR of 3-hydroxy-9-methoxy-5,6,6aα,6bβ,11,12,12aβ,12bα-octahydrodibenzo[*a,g*]biphenylene (**58**).



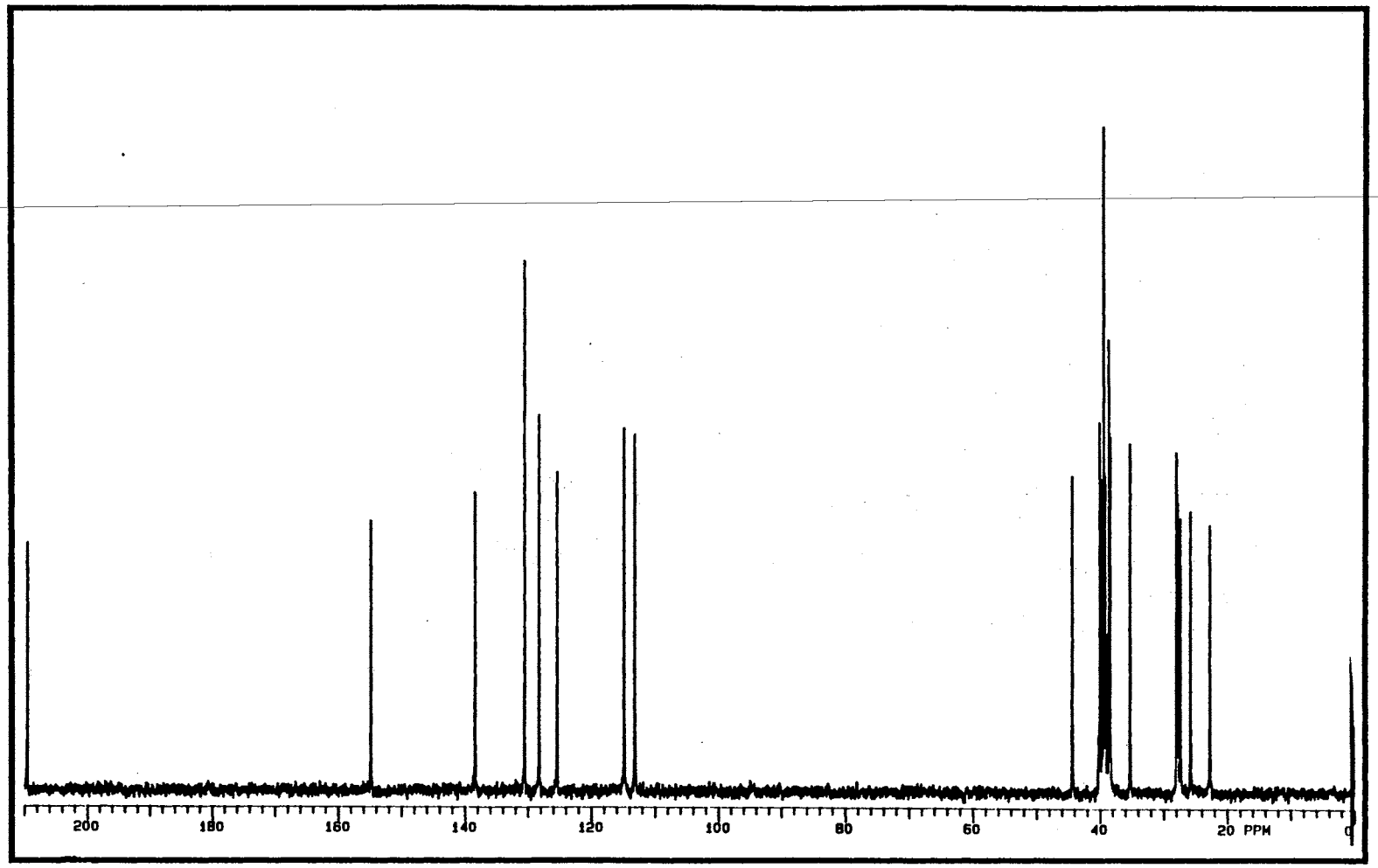
Spectrum 6a. ^{1}H NMR of 5,6,6aα,6bβ,7,10,11,12,12aβ,12bα-decahydro-3,9-dimethoxy-dibenzo[*a,g*]biphenylene (**60**).



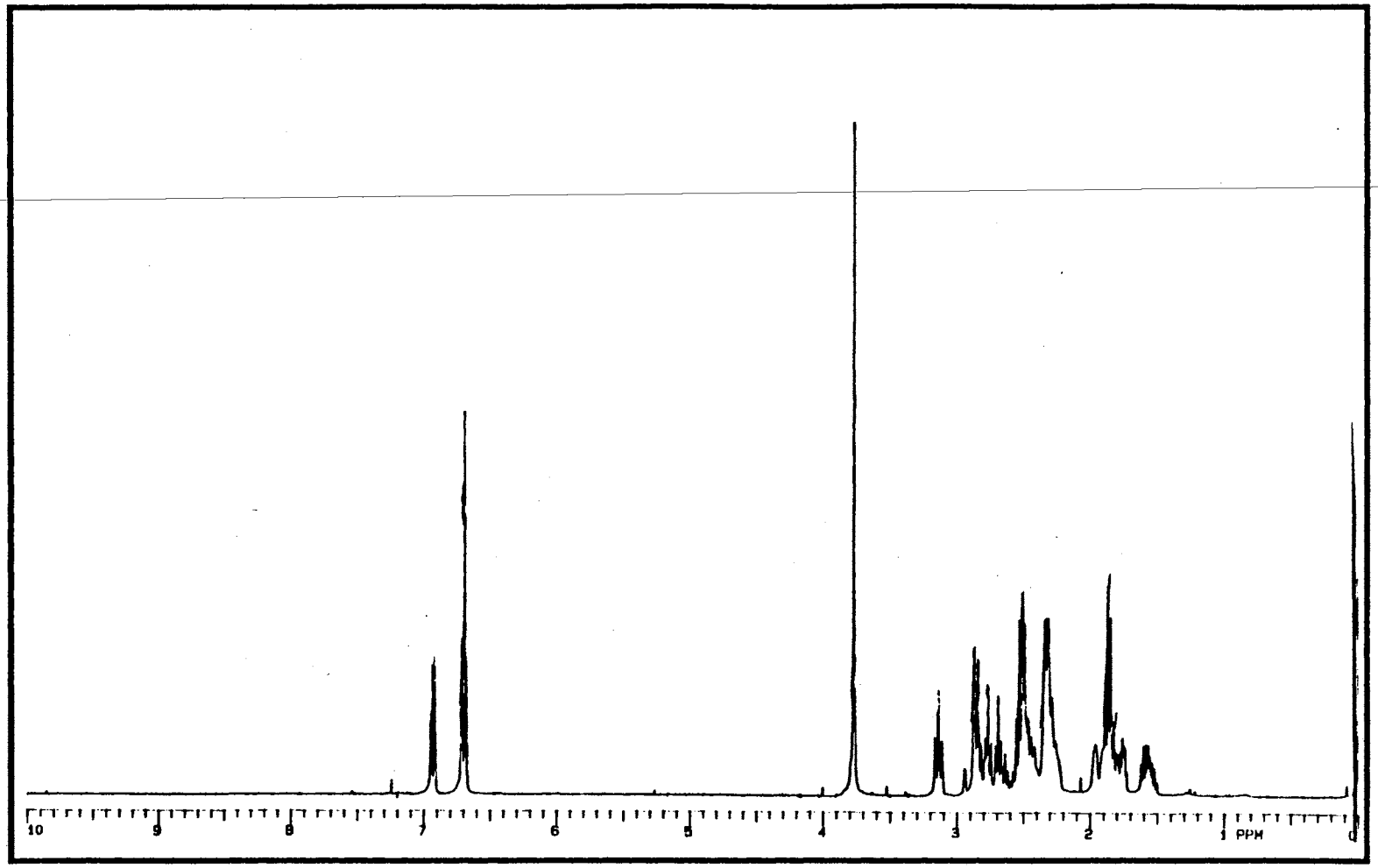
Spectrum 6b. ^{13}C NMR of 5,6,6aα,6bβ,7,10,11,12,12aβ,12bα-decahydro-3,9-dimethoxy-dibenzo[*a*,*g*]biphenylene (**60**).



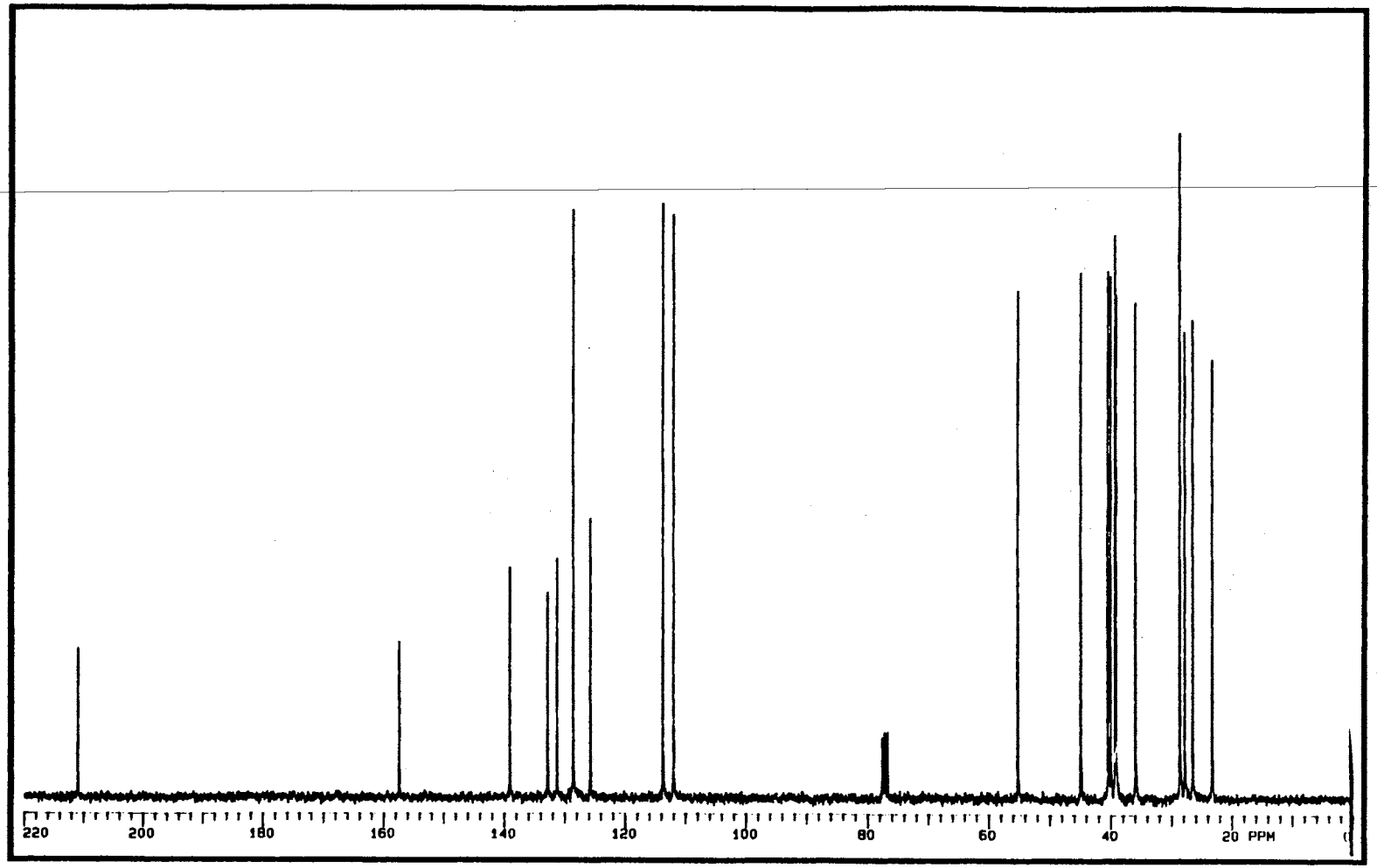
Spectrum 7a. ^{1}H NMR of 1,2,4,5,6,6aα,6bβ,11,12,12aβ,12bα-decahydro-9-hydroxydibenzo[*a,g*]biphenylen-3(2*H*)-one (**65**).



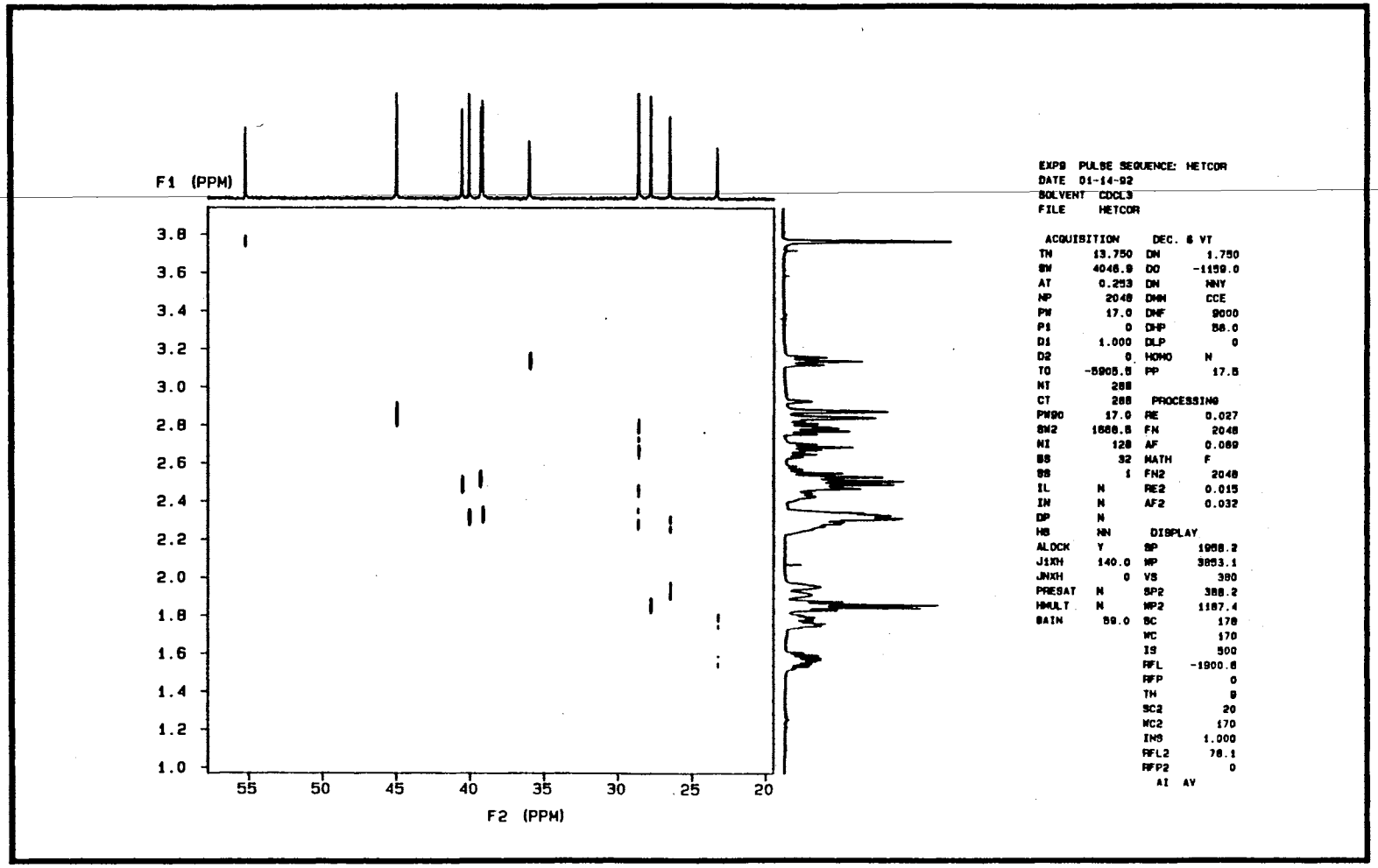
Spectrum 7b. ^{13}C NMR of 1,2,4,5,6,6aα,6bβ,11,12,12aβ,12bα-decahydro-9-hydroxydibenzo[*a,g*]biphenylen-3(2*H*)-one (**65**).



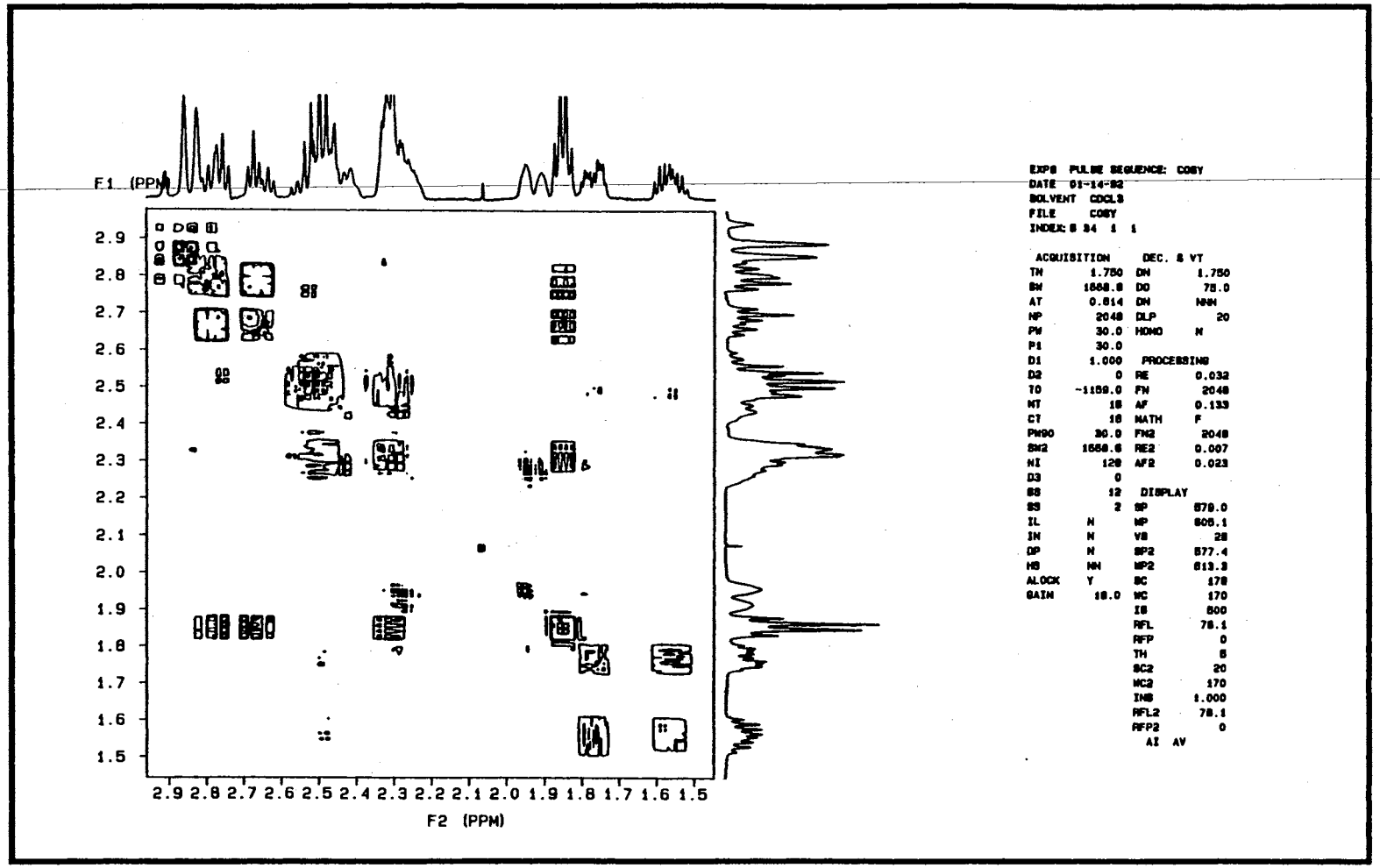
Spectrum 8a. ^{1}H NMR of 1,2,4,5,6,6aα,6bβ,11,12,12aβ,12bα-decahydro-9-methoxydibenzo[*a,g*]biphenylen-3(2*H*)-one (**61**).



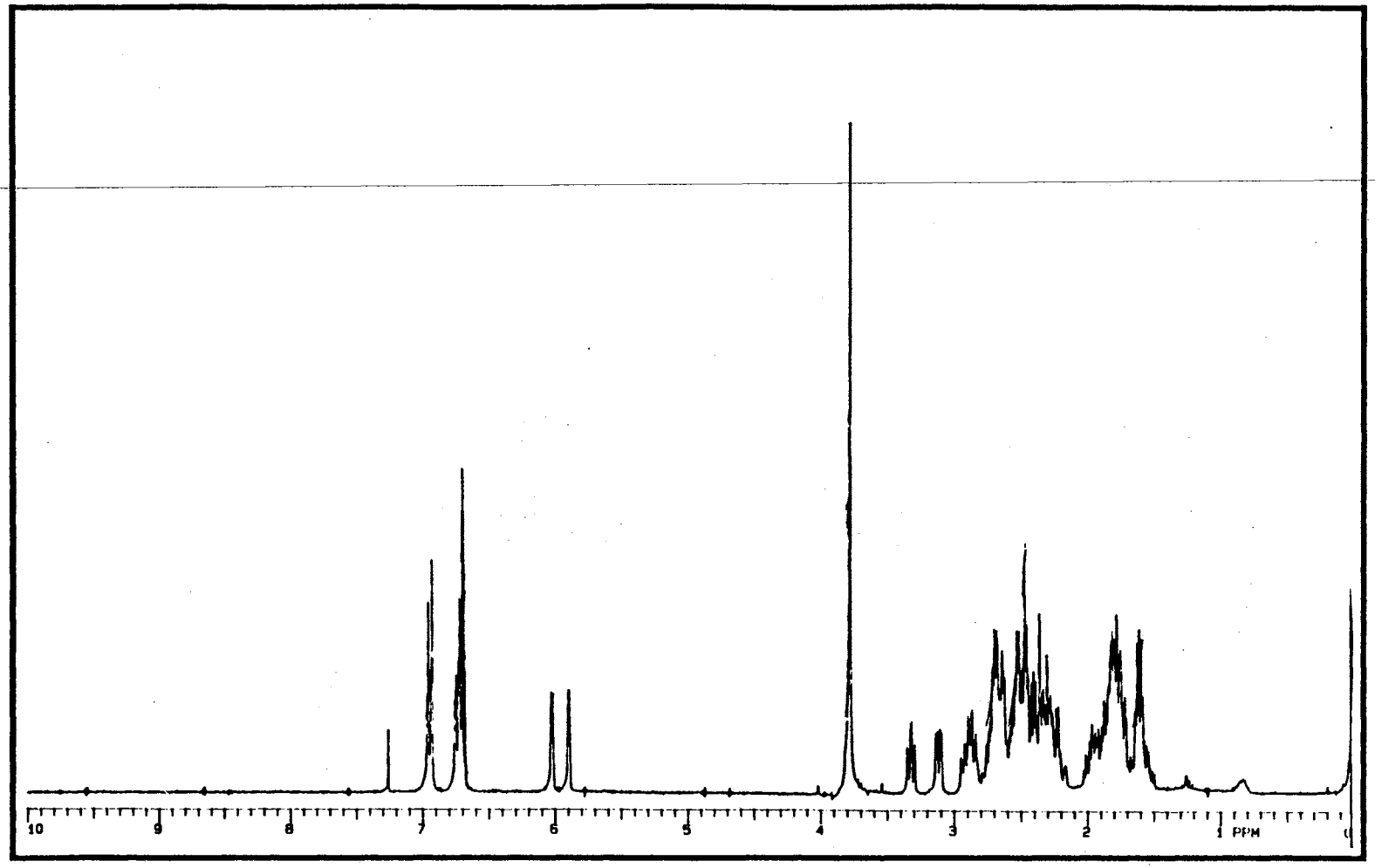
Spectrum 8b. ^{13}C NMR of 1,2,4,5,6,6aα,6bβ,11,12,12aβ,12bα-decahydro-9-methoxydibenzo[*a*,*g*]biphenylen-3(2*H*)-one (**61**).



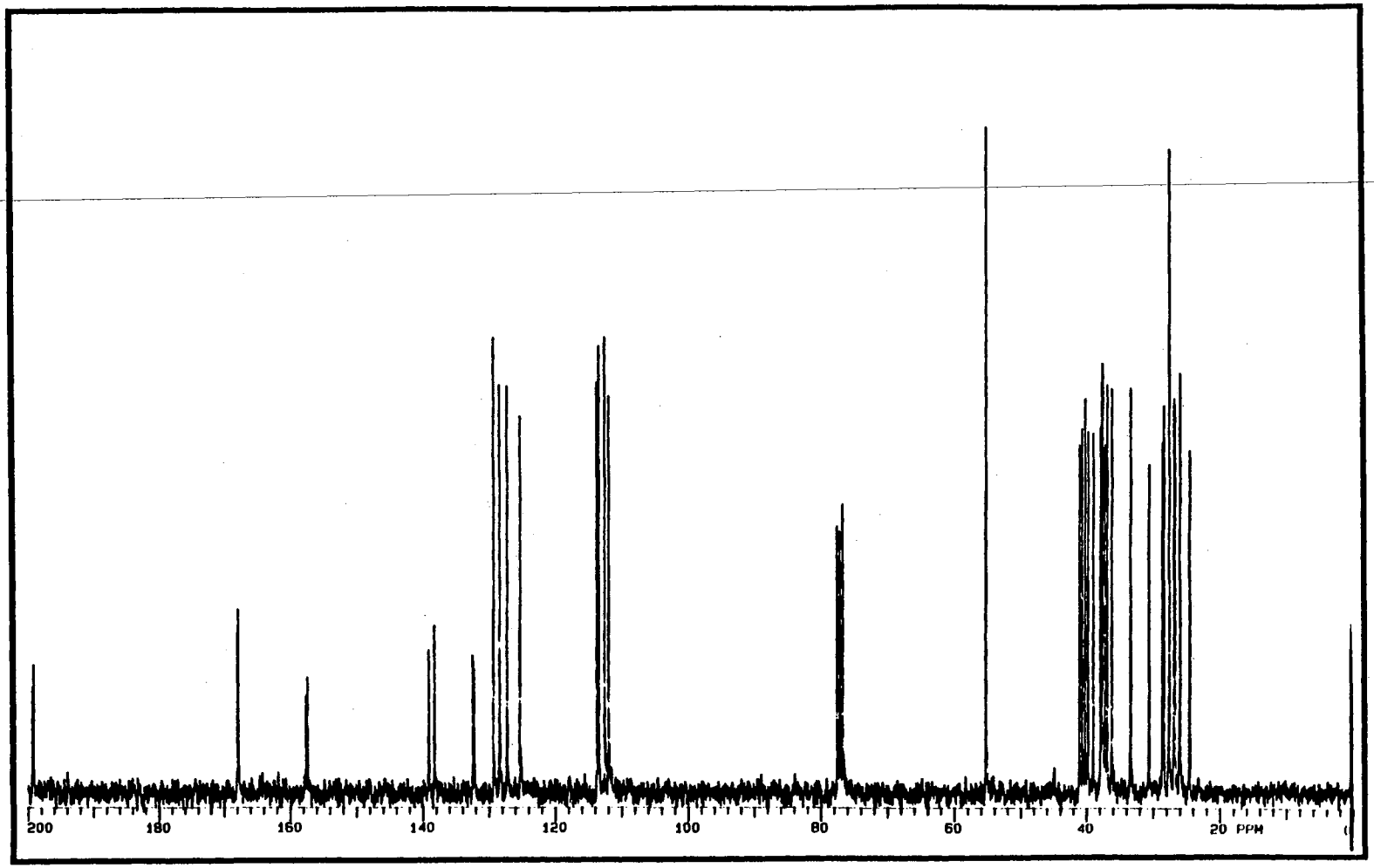
Spectrum 8c. HETCOR NMR of 1,2,4,5,6,6aα,6bβ,11,12,12aβ,12bα-decahydro-9-methoxydibenzo[*a*,*g*]biphenylen-3(2*H*)-one (**61**).



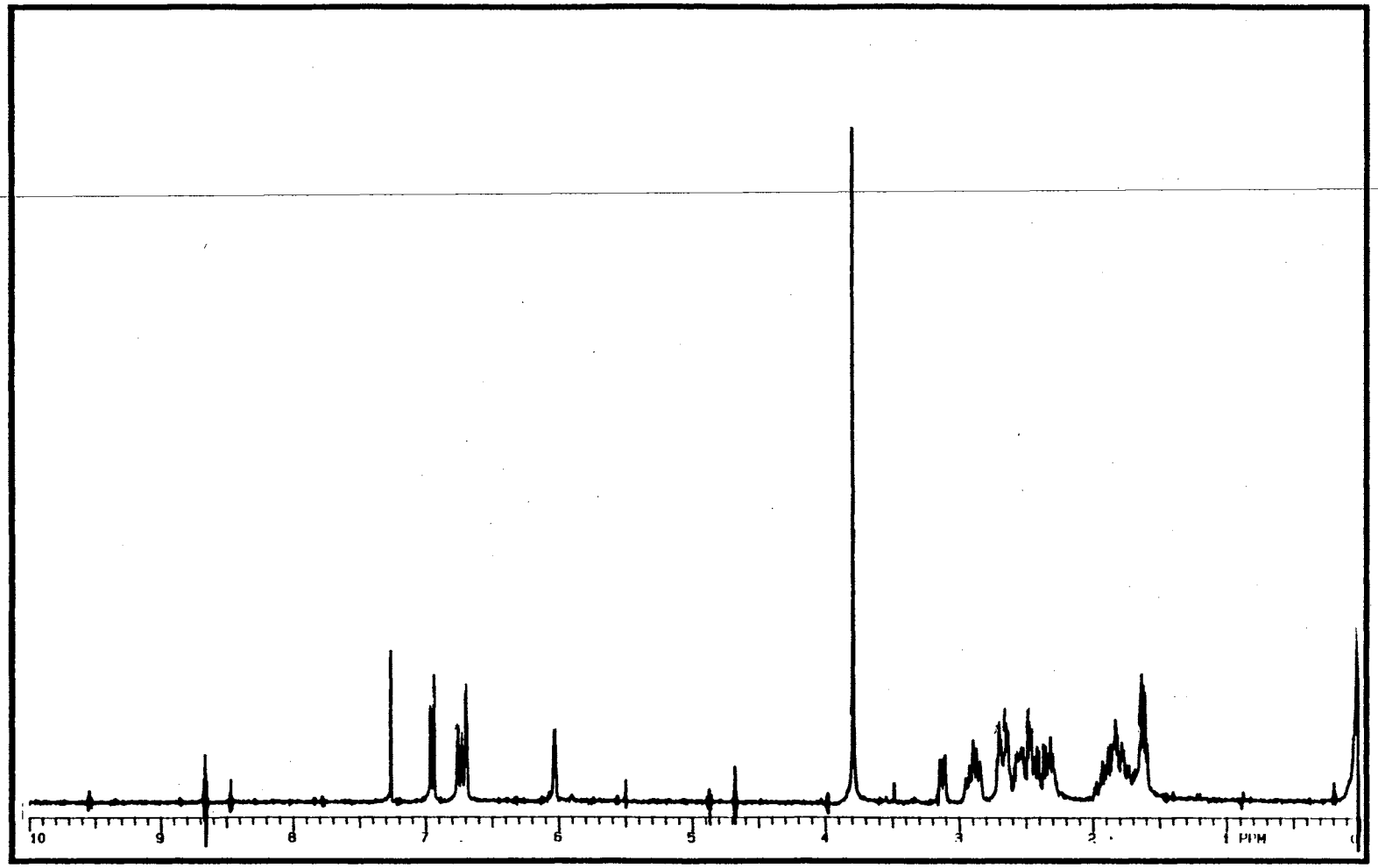
Spectrum 8d. COSY NMR of 1,2,4,5,6,6aα,6bβ,11,12,12aβ,12bα-decahydro-9-methoxydibenzo[*a*,*g*]biphenylen-3(2*H*)-one (**61**).



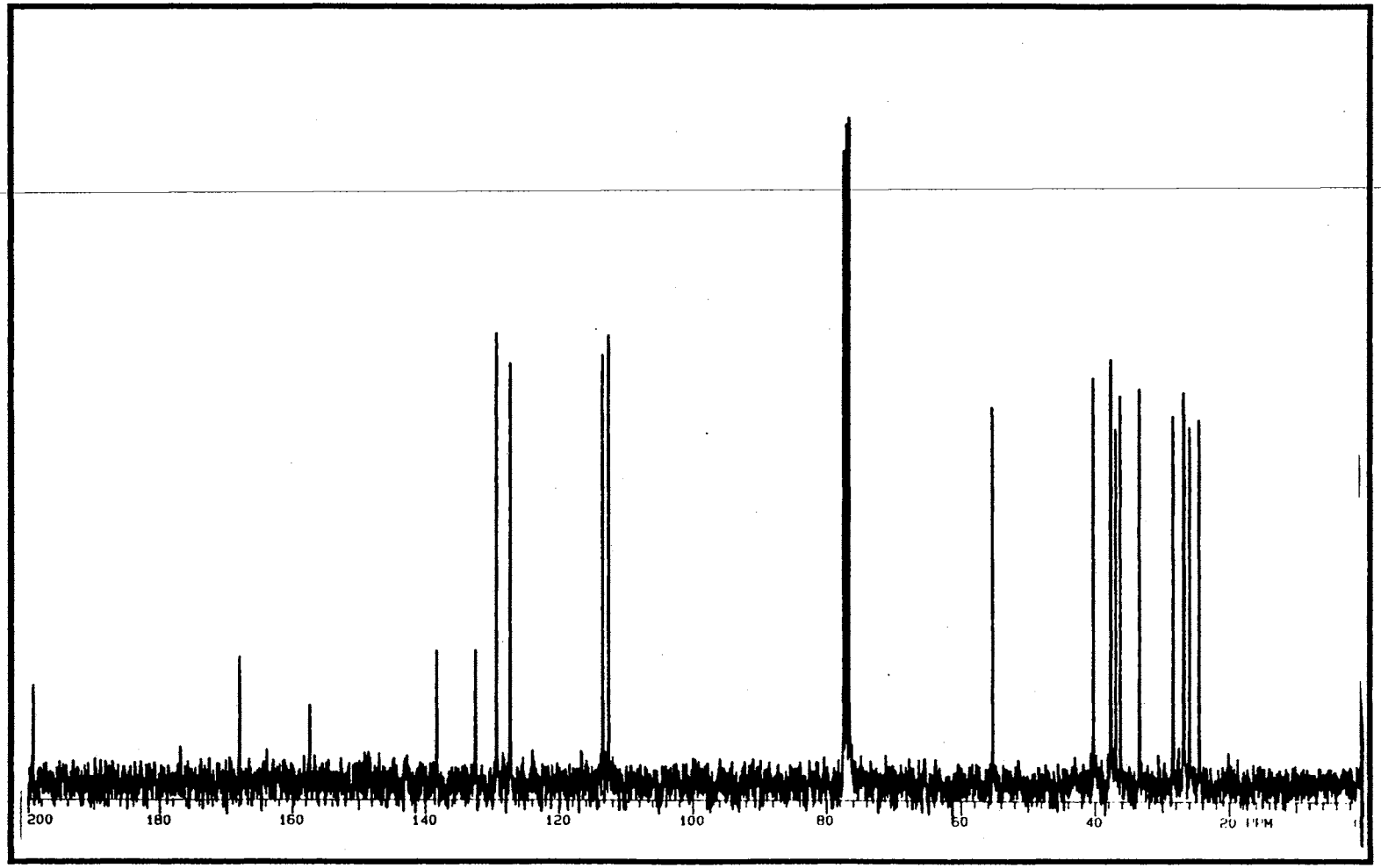
Spectrum 9a. ^{1}H NMR of 1,5,6,6aα,6bβ,11,12,12aβ,12bα,12c-decahydro-9-methoxydibenzo[*a*,*g*]biphenlen-3(2*H*)-one (**62**) mixture.



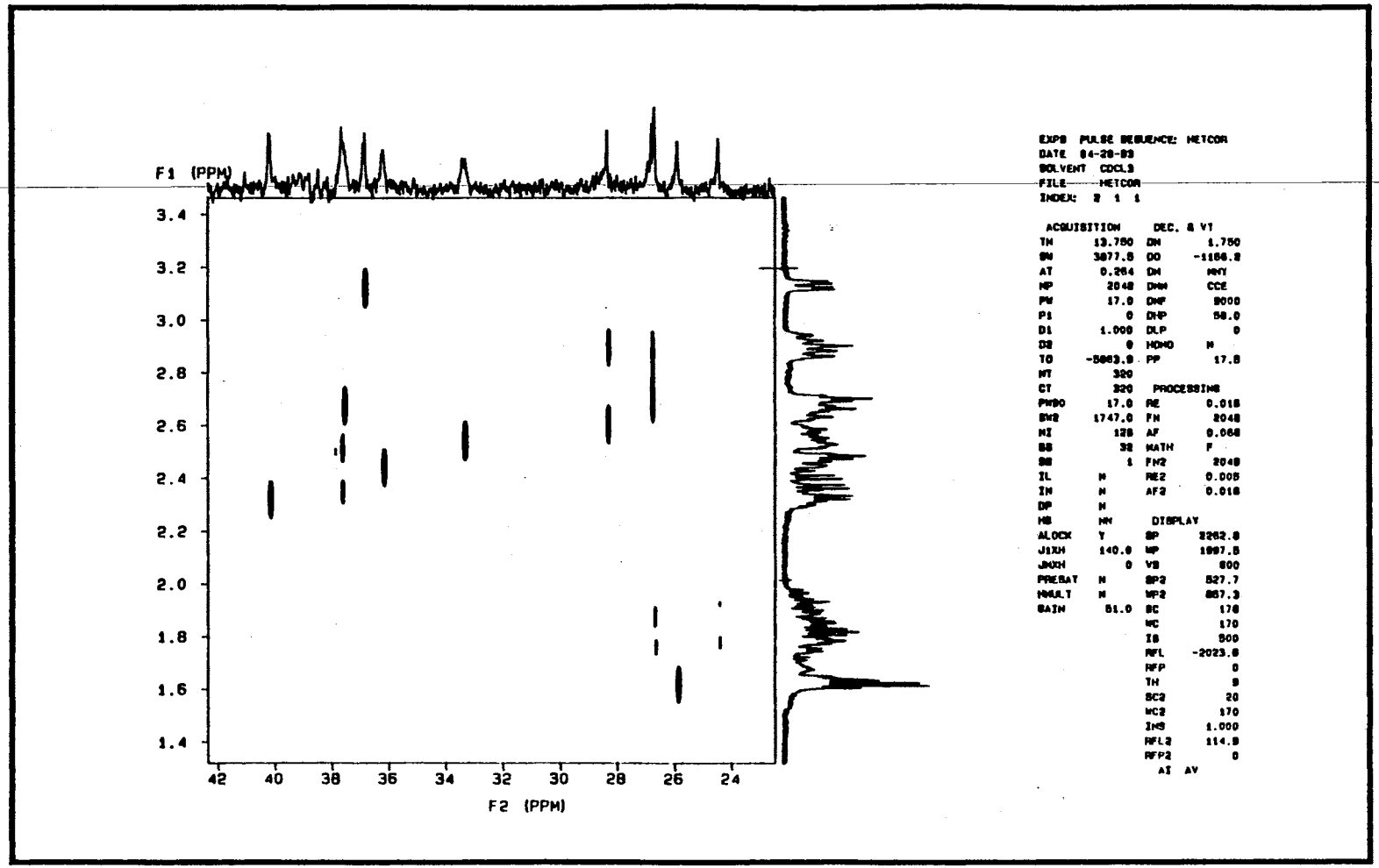
Spectrum 9b. ^{13}C NMR of 1,5,6,6aα,6bβ,11,12,12aβ,12bα,12c-decahydro-9-methoxydibenzo[*a,g*]biphenlen-3(2*H*)-one (**62**) mixture.



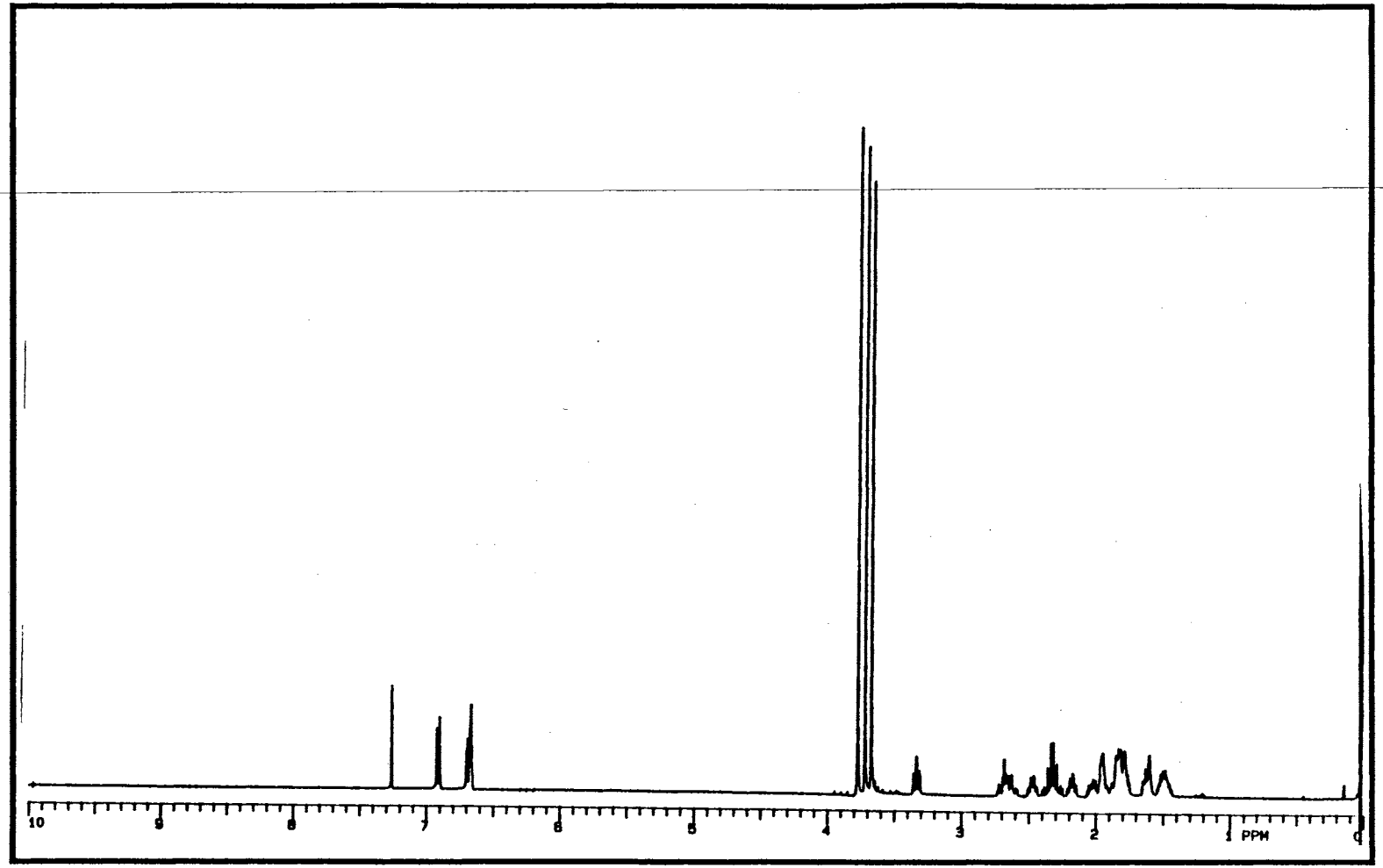
Spectrum 10a. ^{1}H NMR of 1,5,6,6aα,6bβ,11,12,12aβ,12bα,12cβ-decahydro-9-methoxydibenzo[*a,g*]biphenlen-3(2*H*)-one (**62**).



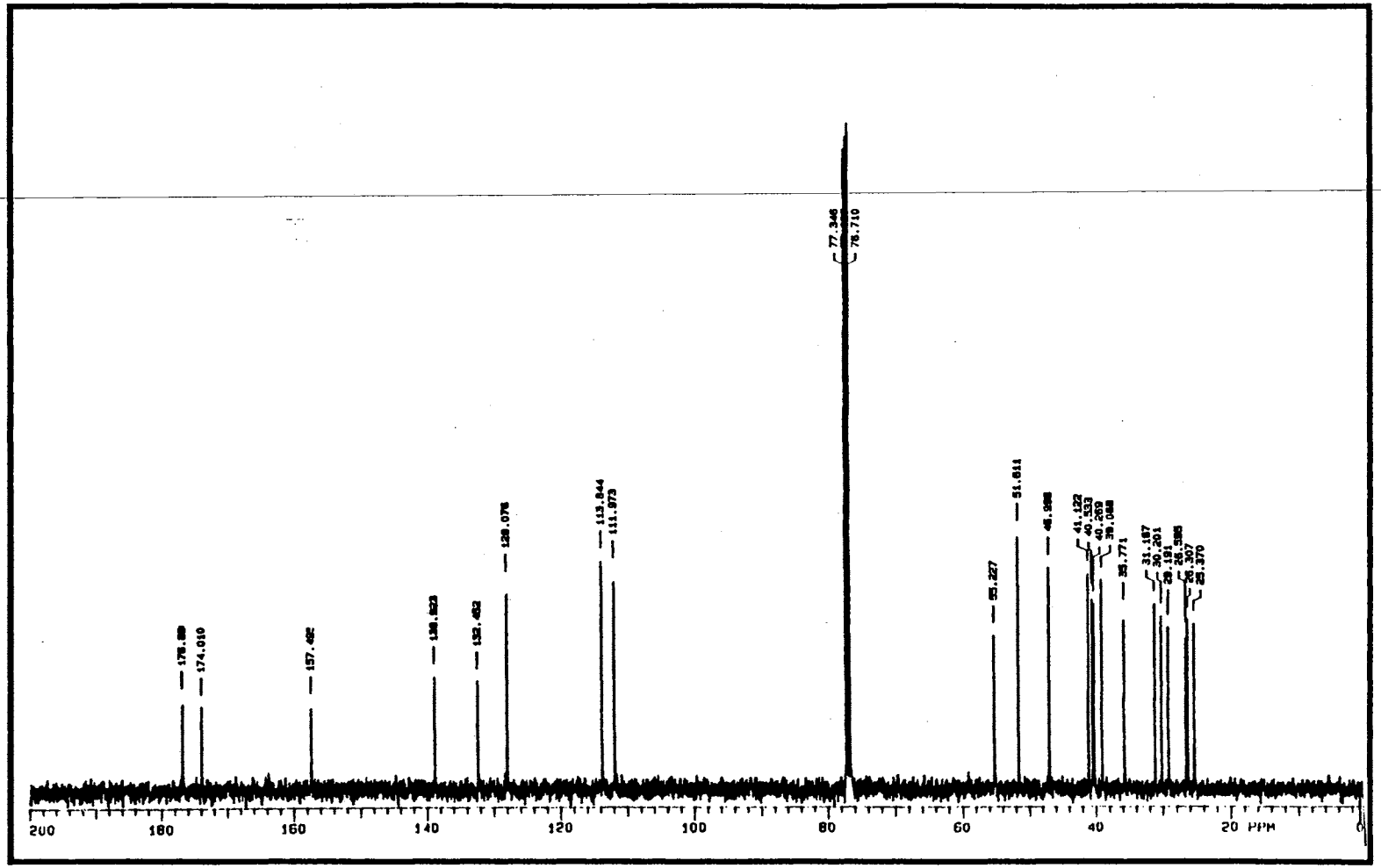
Spectrum 10b. ^{13}C NMR of 1,5,6,6aα,6bβ,11,12,12aβ,12bα,12cβ–decahydro-9-methoxydibenzo[*a,g*]biphenlen-3(2*H*)-one (**62**).



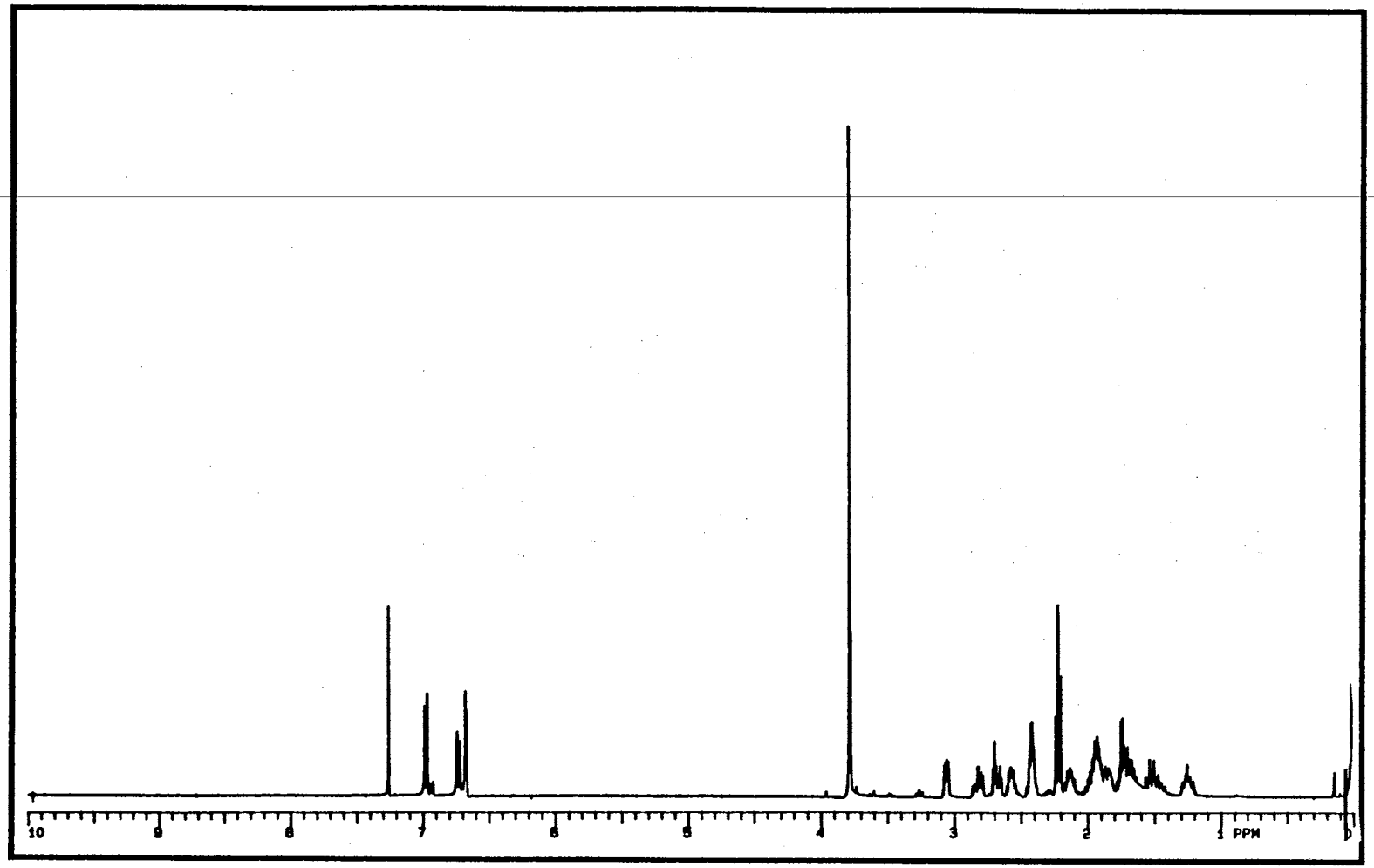
Spectrum 10c. HETCOR of 1,5,6,6aα,6bβ,11,12,12aβ,12bα,12cβ–decahydro-9-methoxydibenzo[*a,g*]biphenlen-3(2*H*)-one (**62**).



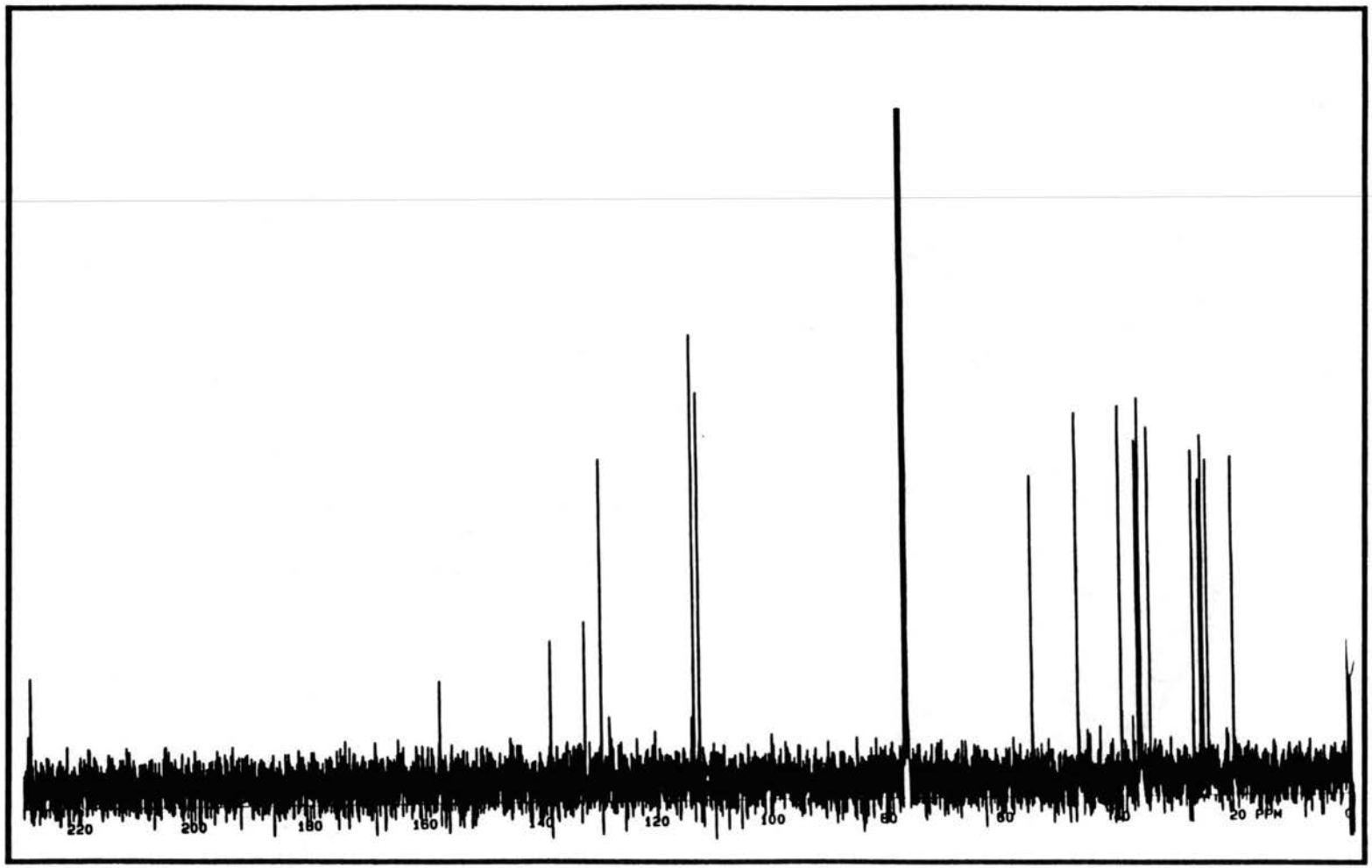
Spectrum 11a. ^{1}H NMR of methyl 5,6,6aα,6bβ,7,8,9,10,10aβ,10bα-decahydro-3-methoxy-8-(methoxycarbonyl)-benzo[*a*]biphenylene-7-propionate (**64**)



Spectrum 11b. ^{13}C NMR of methyl 5,6,6aα,6bβ,7,8,9,10,10aβ,10bα-decahydro-3-methoxy-8-(methoxycarbonyl)-benzo[*a*]biphenylene-7-propionate (**64**)



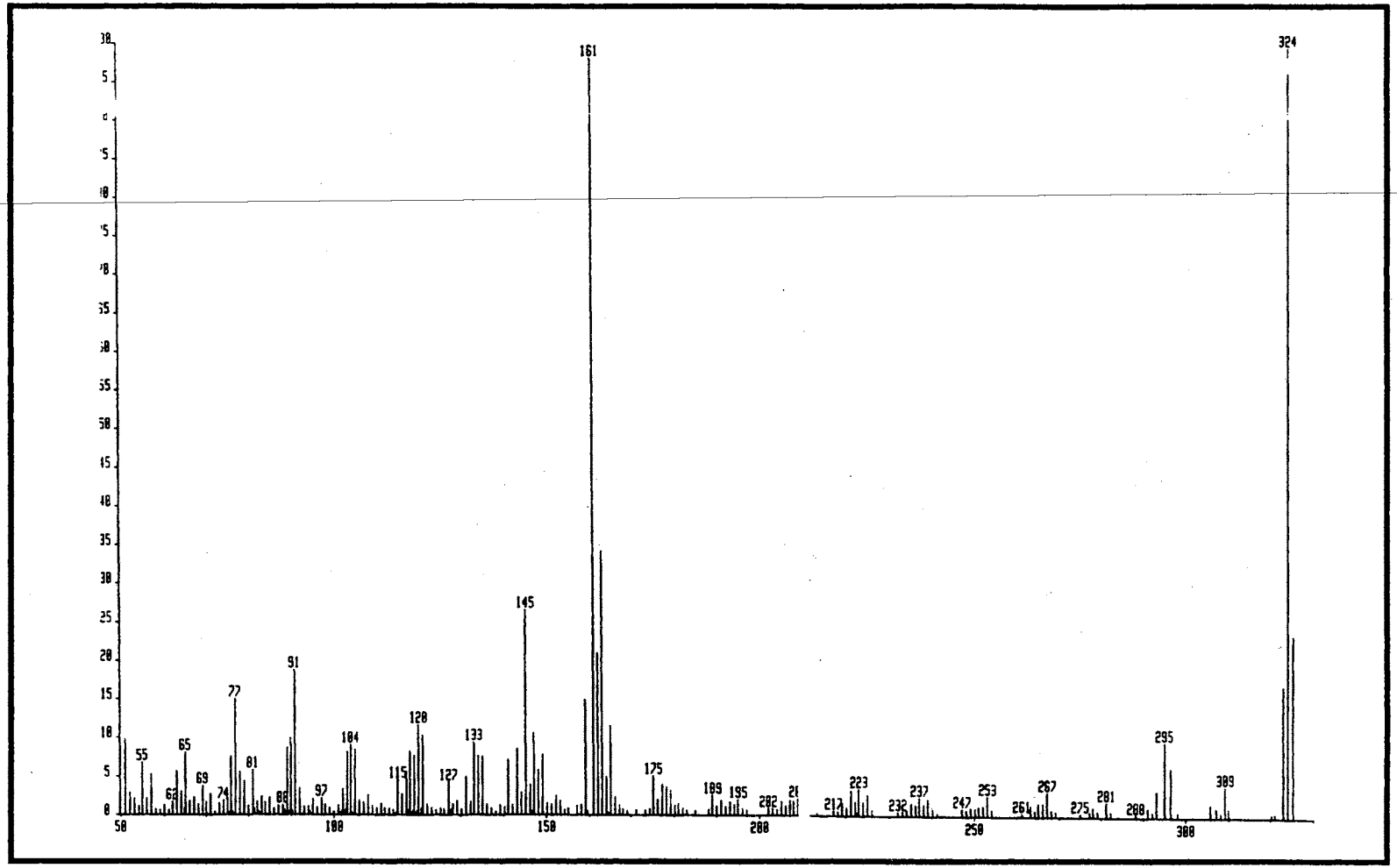
Spectrum 12a. ^{1}H NMR of 1,2,3aα,4,5,5aα,5bβ,10,11,11aβ,11bα,11cβ-dodecahydro-8-methoxy-3*H*-benzo[*a*]cyclopenta[*g*]biphenylen-3-one (**56b**).



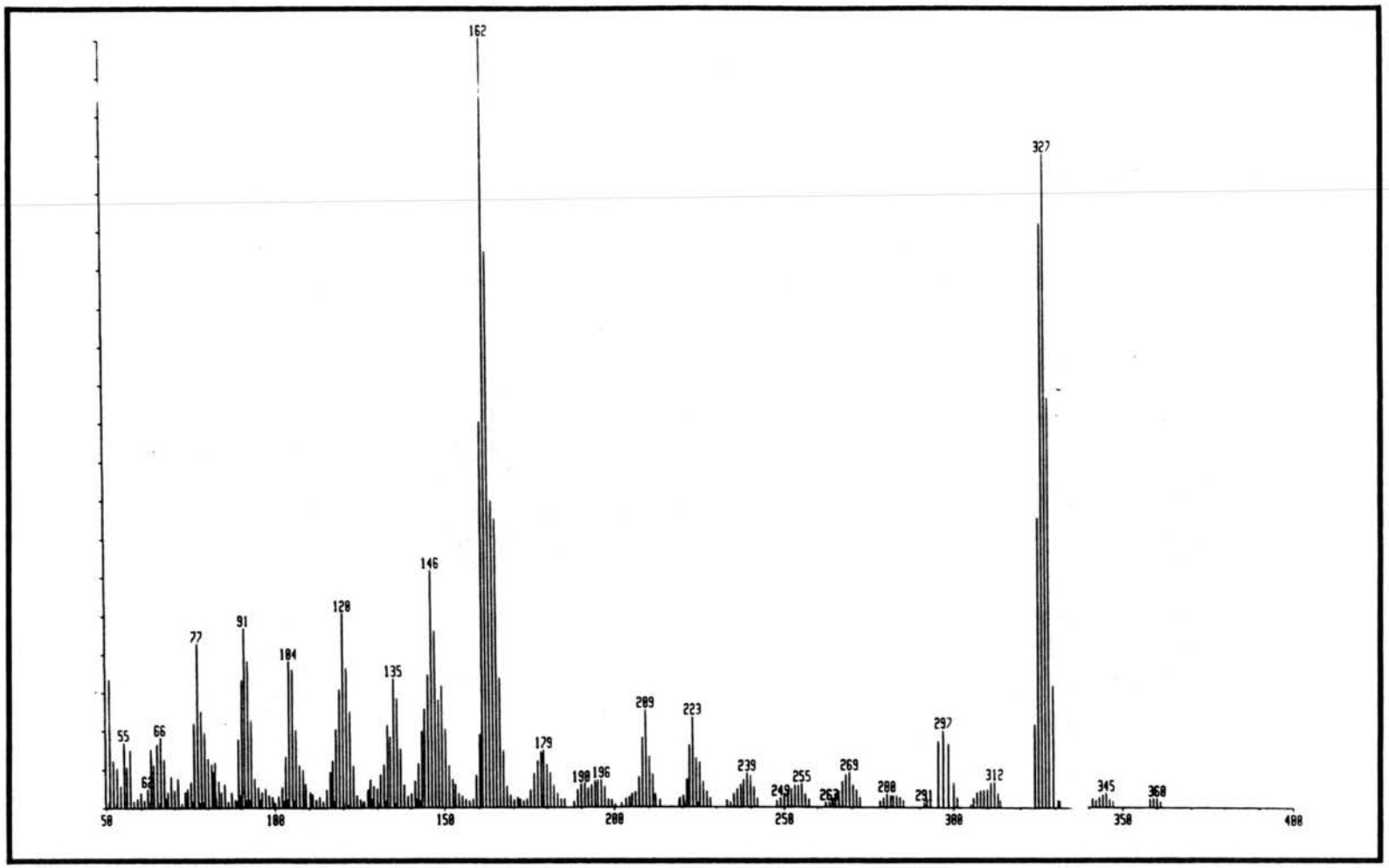
Spectrum 12b. ^{13}C NMR of 1,2,3aα,4,5,5aα,5bβ,10,11,11aβ,11bα,11cβ-dodecahydro-8-methoxy-3*H*-benzo[*a*]cyclopenta[*g*]biphenylen-3-one (**56b**).

APPENDIX C

SELECTED MS SPECTRA



Spectrum 1a. Mass spectrum of 5,14-dimethoxy[3,3]metacyclophane (**51**).



Spectrum 1b. Mass spectrum of base exchanged 5,14-dimethoxy[3,3]metacyclophane (**51**).

APPENDIX D

X-RAY ANALYSIS AND EXPERIMENTAL

X-Ray Analysis Experimental

Unit Cell Dimensions for 5,14-Dimethoxy[3.3]metacyclophane-1,10-dione (**51**).

Formula	$C_{20}H_{18}O_4$
MWT	322.35
a	8.106(4)Å
b	11.724(6)
c	8.499(5)
α	90.0°
β	103.14(4)
γ	90.0
V	786.6(7)Å^3
F(000)	340
μMoK_α	0.881 cm^{-1}
λMoK_α	0.71069Å
D_{calc}	1.361 g cm^{-3}
Z	2
Space group	$P2_1/a$
Obs. Refl.	676
Octants meas.	±h, k, l
R/R_w	4.8/6.2%
G.O.F.	0.37

Positional Parameters for 5,14-Dimethoxy[3.3]metacyclophane-1,10-dione (**51**)

Atom	X(SIG(X))	Y(SIG(Y))	Z(SIG(Z))
O1	0.4821(4)	0.6600 (3)	0.5676(3)
O2	0.0773(3)	0.3394(2)	0.9487(3)
C1	0.0318(4)	0.4773(3)	0.7453(4)
C2	0.1481(5)	0.4106(3)	0.8567(4)
C3	0.3202(5)	0.4183(4)	0.8647(5)
C4	0.3794(5)	0.4900(4)	0.7616(4)
C5	0.2686(5)	0.5578(3)	0.6508(4)
C6	0.0963(5)	0.5518(3)	0.6499(4)
C7	0.3367(5)	0.6259(3)	0.5354(4)
C8	0.2232(5)	0.6496(4)	0.3682(4)
C9	-0.1551(5)	0.4599(3)	0.7258(4)
C10	0.1890(6)	0.2721(4)	1.0689(5)
H3	0.3974	0.3626	0.9338
H4	0.5120	0.4915	0.7585
H6	0.0238	0.6094	0.5769
H81	0.1218	0.7004	0.3859
H82	0.2863	0.7009	0.2992
H91	-0.2009	0.4656	0.8345
H92	-0.2138	0.5320	0.6730
H101	0.2799	0.3197	1.1368
H102	0.1044	0.2378	1.1417
H103	0.2314	0.1970	1.0190

Anisotropic Thermal Parameters for 5,14-Dimethoxy[3.3]metacyclophane-1,10-dione (**51**).

Anisotropic Thermal Parameters in the Format:

$exp[-2\pi^2(U11h2a^{*2} + U22k2b^{*2} + U3312c^{*2} + 2U12hka^*b^* + 2U13hla^*c^* + 2U23klb^*c^*)] \times 10^3$

O1	40(1)	88(2)	49(1)	-25(1)	-12(1)	9(1)
O2	39(1)	62(2)	35(1)	-4(1)	-11(1)	15(1)
C1	28(2)	41(2)	22(1)	0(1)	-4(1)	-4(1)
C2	37(2)	39(2)	25(2)	-1(1)	-5(1)	1(1)
C3	31(2)	48(2)	36(2)	3(2)	-15(1)	3(2)
C4	27(2)	49(2)	32(2)	0(1)	-8(1)	-2(2)
C5	31(2)	40(2)	25(2)	-4(1)	-4(1)	-6(1)
C6	36(2)	37(2)	22(1)	0(1)	-8(1)	-5(1)
C7	30(2)	49(2)	34(2)	-8(2)	-3(1)	-4(2)
C8	33(2)	49(2)	35(2)	-2(2)	-1(1)	5(2)
C9	27(2)	51(2)	31(2)	3(1)	0(1)	0(2)
C10	58(3)	51(2)	34(2)	-2(2)	-16(2)	10(2)

Bond Distances (Å) for 5,14-Dimethoxy[3.3]metacyclophane-1,10-dione (**51**).

C1 - C2	1.412(5)
C1 - C6	1.373(6)
C1 - C9	1.500(5)
C2 - C3	1.384(6)
C2 - O2	1.357(5)
C3 - C4	1.376(6)
C4 - C5	1.393(5)
C5 - C6	1.397(6)
C5 - C7	1.466(6)
O2 - C10	1.438(5)
C7 - O1	1.215(5)
C7 - C8	1.532(5)
C8 - C9'	1.546(6)

Bond Angles (°) for 5,14-Dimethoxy[3.3]metacyclophane-1,10-dione (**51**).

C2-C1-C6	117.6(3)
C2-C1-C9	120.1(3)
C6-C1-C9	122.2(3)
C1-C2-C3	120.6(4)
C1-C2-O2	115.0(3)
O2-C2-C3	124.4(3)
C2-C3-C4	120.1(3)
C3-C4-C6	120.9(4)
C4-C5-C6	117.7(4)
C4-C5-C7	118.7(3)
C6-C5-C7	123.5(3)
C5-C6-C1	122.9(3)
C2-O2-C10	117.8(3)
C5-C7-O1	121.4(3)
C5-C7-C8	118.7(3)
O1-C7-C8	119.8(4)
C7-C8-C9'	113.4(3)
C1-C9-C8'	113.8(3)

APPENDIX E

MOPAC OPTIMIZED DATA

MOPAC Optimized Data for *Anti*-Conformation of 5,14-Dimethoxy[3.3]meta-cyclophane-1,10-dione (**51**).

Z- Matrix

Atom			Bond			Bond	
		NA	Length (Å)	NB	Angle Degrees	NC	Angle Degrees
1	C						
2	C	1	1.401				
3	C	1	1.497	2	119.9		
4	C	3	1.525	1	116.1	2	-172.9
5	O	3	1.216	1	122.3	4	-180.0
6	C	4	1.539	3	110.9	1	82.8
7	C	6	1.496	4	110.2	3	-122.0
8	C	7	1.404	6	121.4	4	-82.8
9	C	8	1.403	7	120.7	6	171.8
10	C	7	1.392	8	118.4	6	-173.8
11	C	10	1.397	7	121.3	8	7.3
12	C	11	1.398	10	119.0	7	-7.7
13	O	8	1.392	7	119.6	9	175.0
14	C	13	1.411	8	113.7	7	109.6
15	C	2	1.387	1	120.0	3	177.5
16	C	1	1.394	2	117.9	3	-176.7
17	C	16	1.396	1	123.4	2	3.8
18	C	17	1.405	16	117.3	1	-6.1
19	O	18	1.385	15	113.9	17	174.2
20	C	17	1.499	18	124.8	16	-176.2
21	C	19	1.407	18	117.2	15	130.3

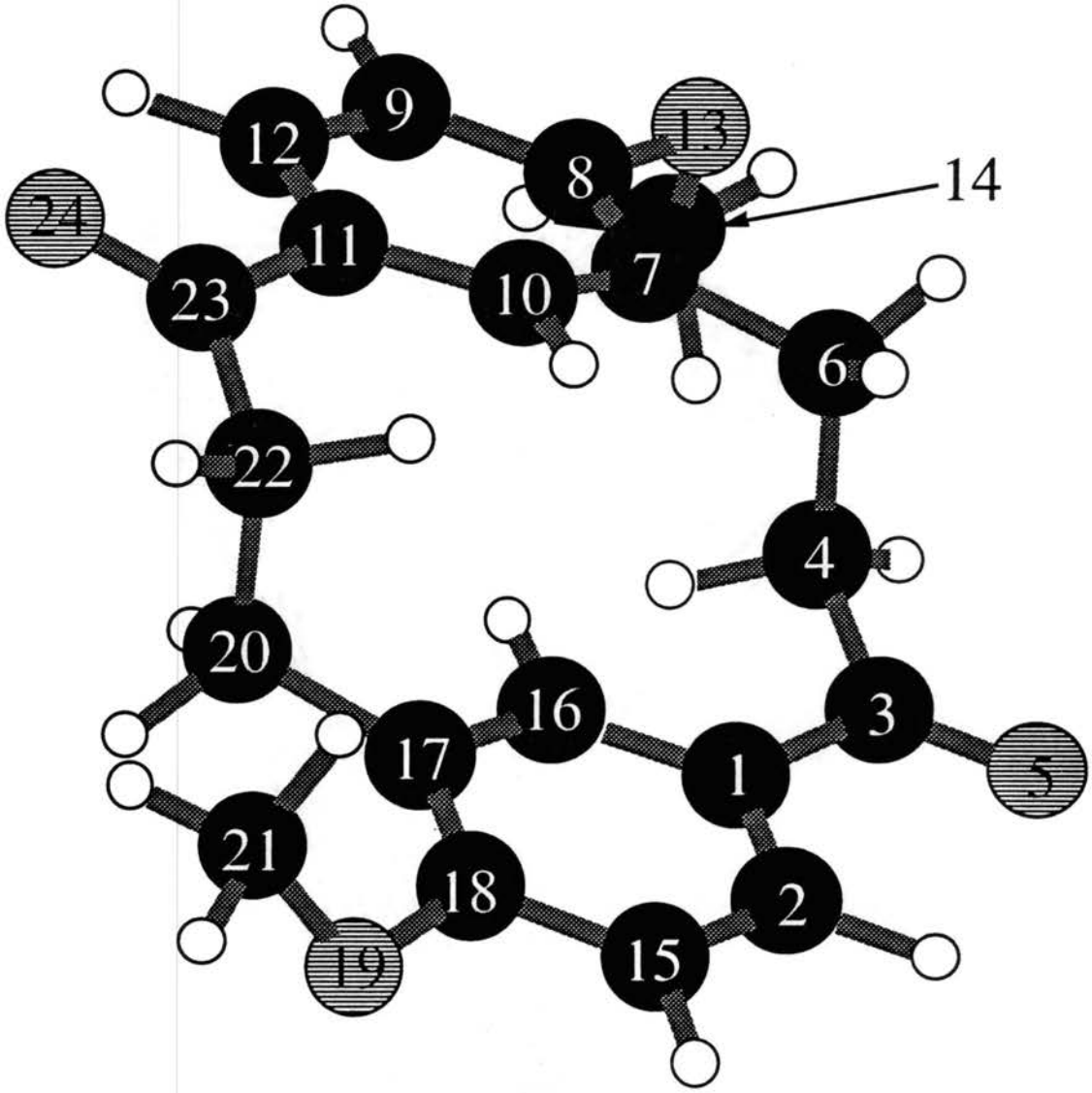
22	C	20	1.537	17	110.4	18	92.9
23	C	11	1.491	12	120.8	10	-176.8
24	O	23	1.217	11	122.1	22	-179.6
25	H	4	1.107	3	110.5	6	122.1
26	H	4	1.112	3	108.8	6	-122.1
27	H	6	1.109	4	111.2	7	121.8
28	H	6	1.108	4	110.3	7	-122.1
29	H	9	1.096	8	120.3	12	-178.8
30	H	12	1.097	9	119.8	11	179.9
31	H	10	1.104	7	119.9	11	176.7
32	H	14	1.096	13	112.5	8	58.5
33	H	14	1.093	13	102.7	32	118.5
34	H	14	1.097	13	111.6	32	-123.5
35	H	2	1.097	1	119.7	15	179.4
36	H	15	1.097	2	119.5	18	-179.7
37	H	16	1.105	1	117.6	17	-179.7
38	H	20	1.108	17	109.6	22	122.5
39	H	20	1.113	17	110.5	22	-121.5
40	H	21	1.095	19	113.1	18	-45.8
41	H	21	1.100	19	111.0	40	123.6
42	H	21	1.093	19	102.4	19	-118.9
43	H	22	1.109	20	109.7	23	123.3
44	H	22	1.114	20	110.3	23	-120.7

Cartesian Coordinates

Atom	X	Y	Z	Charge
1 C	0.0000	0.0000	0.0000	-0.1878
2 C	1.4008	0.0000	0.0000	-0.0247
3 C	-0.7473	1.2971	0.0000	0.3325
4 C	-2.2601	1.1993	0.1701	-0.1596
5 O	-0.1882	2.3698	-0.1280	-0.3094
6 C	-2.6372	1.0739	1.6569	-0.0368
7 C	-3.4174	-0.1819	1.8883	-0.1082
8 C	-4.8001	-0.2395	1.6492	0.0878
9 C	-5.4863	-1.4616	1.7061	-0.1425
10 C	-2.7542	-1.3593	2.2230	-0.0623
11 C	-3.4020	-2.5957	2.1756	-0.1764
12 C	-4.7798	-2.6314	1.9436	-0.0311
13 O	-5.5147	0.9390	1.4556	-0.2059
14 C	-5.9601	1.1213	0.1293	0.0539
15 C	2.0945	-1.2003	0.0522	-0.1433
16 C	-0.6529	-1.2296	0.0715	-0.0654
17 C	0.0135	-2.4467	0.2197	-0.1328
18 C	1.4178	-2.4237	0.1676	0.1078
19 O	2.2453	-3.5326	0.0931	-0.1997
20 C	-0.8119	-3.6658	0.5035	-0.0405
21 C	2.1058	-4.5084	1.0972	0.0426
22 C	-1.1190	-3.7663	2.0059	-0.1641
23 C	-2.6162	-3.8573	2.2992	0.3280
24 O	-3.1336	-4.9138	2.6098	-0.3073
25 H	-2.7581	2.0839	-0.2726	0.0792

26 H	-2.6297	0.3231	-0.4065	0.0747
27 H	-1.7347	1.0756	2.3020	0.0626
28 H	-3.2228	1.9568	1.9812	0.0770
29 H	-6.5703	-1.4950	1.5454	0.1220
30 H	-5.3070	-3.5939	1.9515	0.1215
31 H	-1.6808	-1.3316	2.4798	0.1236
32 H	-6.6026	0.3023	-0.2130	0.0265
33 H	-6.5330	2.0496	0.1932	0.0515
34 H	-5.1202	1.2428	-0.5655	0.0244
35 H	1.9446	0.9616	-0.0518	0.1239
36 H	3.1909	-1.1933	0.0076	0.1235
37 H	-1.7556	-1.2291	0.0008	0.1236
38 H	-1.7464	-3.6287	-0.0909	0.0665
39 H	-0.2795	-4.5829	0.1667	0.0731
40 H	2.0501	-4.0826	2.1050	0.0298
41 H	1.2229	-5.1387	0.9148	0.0345
42 H	3.0197	-5.0968	0.9807	0.0525
43 H	-0.5896	-4.6401	2.4373	0.0772
44 H	-0.7191	-2.8761	2.5422	0.0778

Dipole	X	Y	Z	Total
Point Charge	-0.316	-0.635	-0.574	0.913
Hybrid	-0.223	-0.233	-0.022	0.324
Sum	-0.540	-0.868	-0.596	1.184


9
12
13
8
14
24
11
7
23
10
6
22
4
20
16
3
17
1
5
21
18
2
19
15

MOPAC Optimized Data for *syn*-Conformation of 5,14-Dimethoxy[3.3]metacyclophane-1,10-dione (**51**).

Z- Matrix

Atom			Bond		Bond		
	Twist	NA	Length (Å)	NB	Angle Degrees	NC	Angle Degrees
1	C						
2	C	1	1.392				
3	C	1	1.487	2	118.8		
4	C	3	1.683	1	116.6	2	-61.5
5	O	3	1.207	4	118.9	1	178.7
6	C	1	1.396	2	119.9	3	-179.3
7	C	2	1.393	1	120.5	6	-1.1
8	C	6	1.400	1	120.5	2	4.0
9	C	8	1.406	6	119.1	1	-4.1
10	O	9	1.395	7	117.1	8	-175.1
11	C	10	1.413	9	114.0	7	-98.4
12	C	4	1.630	3	102.9	1	-62.3
13	C	12	1.501	4	128.8	3	70.6
14	C	13	1.397	12	120.4	4	-110.6
15	C	14	1.391	13	120.2	12	172.0
16	C	15	1.393	14	122.1	13	4.4
17	C	13	1.412	14	117.4	12	-177.1
18	C	17	1.406	13	121.9	14	2.4
19	C	15	1.465	14	120.9	16	-178.6
20	O	17	1.407	13	123.4	18	174.4
21	C	8	1.471	9	120.7	6	-179.1

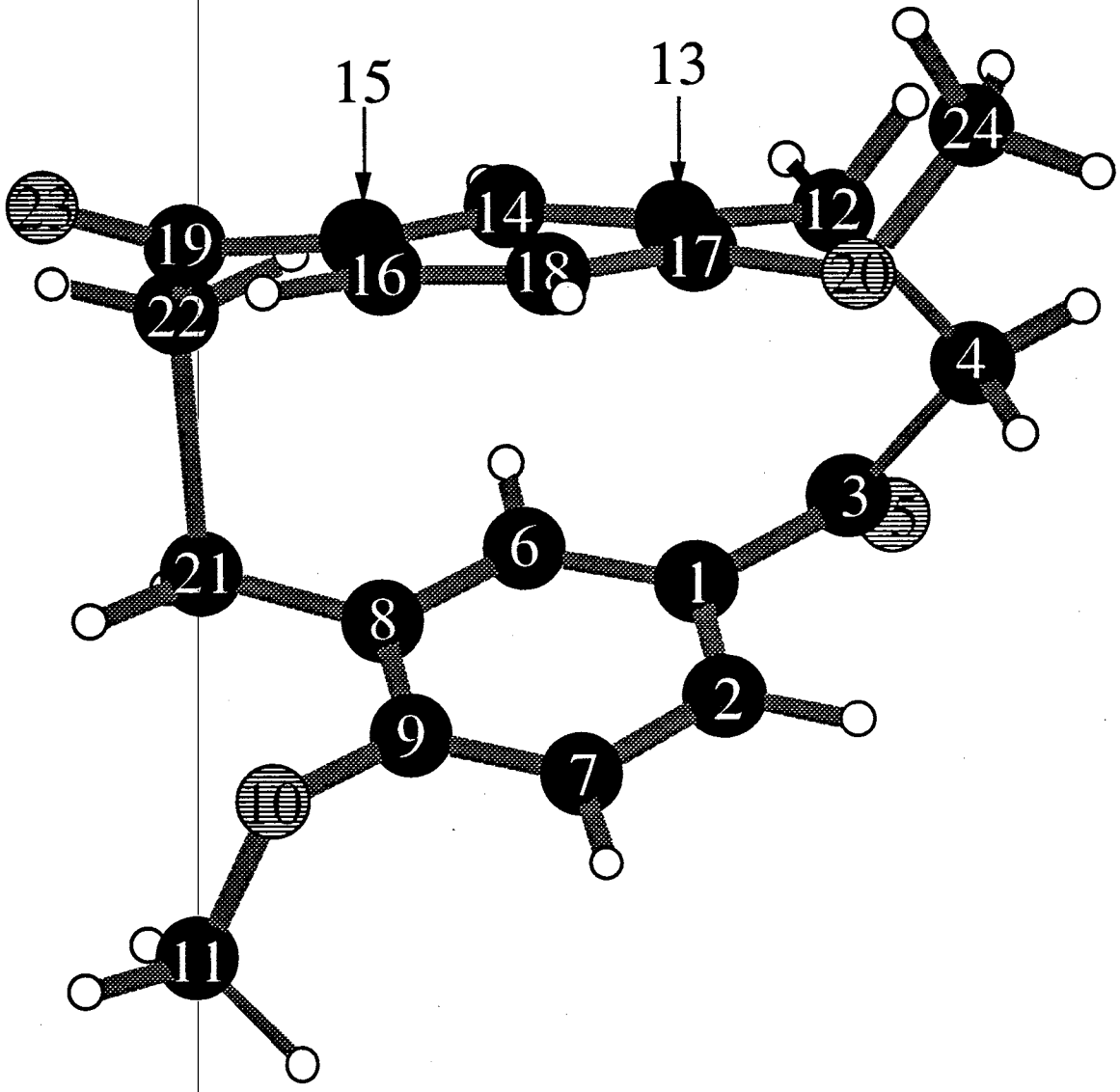
22	C	21	2.025	8	107.1	9	120.6
23	O	19	1.205	15	133.4	22	179.4
24	C	20	1.408	17	118.0	13	68.6
25	H	4	1.094	3	110.3	12	119.3
26	H	4	1.092	3	113.2	12	-117.3
27	H	2	1.101	1	120.0	7	-179.3
28	H	7	1.099	2	119.8	9	-178.6
29	H	6	1.097	1	120.2	8	178.6
30	H	11	1.117	10	107.9	9	65.9
31	H	11	1.092	10	105.9	30	117.8
32	H	11	1.099	10	113.3	30	-121.8
33	H	12	1.108	4	107.5	13	123.4
34	H	12	1.107	4	104.7	13	-125.9
35	H	14	1.098	13	119.2	15	-177.1
36	H	16	1.096	15	120.7	18	179.9
37	H	18	1.099	16	119.9	17	-178.7
38	H	22	1.085	19	112.3	21	114.7
39	H	22	1.086	19	109.6	21	-117.7
40	H	21	1.091	8	116.6	22	110.4
41	H	21	1.091	8	117.5	22	-113.8
42	H	24	1.118	20	109.1	17	66.8
43	H	24	1.094	20	107.3	42	118.5
44	H	24	1.101	20	111.8	42	-121.1

Cartesian Coordinates

Atom	X	Y	Z	Charge
1 C	0.0000	0.0000	0.0000	-0.1492
2 C	1.3919	0.0000	0.0000	-0.0544
3 C	-0.7172	1.3027	0.0000	0.3108
4 C	-0.4502	2.3092	1.3223	-0.0943
5 O	-1.4814	1.6616	-0.8623	-0.2953
6 C	-0.6953	-1.2106	0.0155	-0.0428
7 C	2.0982	-1.1997	0.0376	-0.1205
8 C	-0.0056	-2.4250	0.1163	-0.1001
9 C	1.4007	-2.4150	0.1146	0.0803
10 O	2.1572	-3.5726	0.2939	-0.2096
11 C	2.4059	-4.2871	-0.8992	0.0543
12 C	-1.0182	1.4286	2.5712	-0.0661
13 C	-0.4419	0.1868	3.1857	-0.1046
14 C	-1.0884	-1.0428	3.0345	-0.0489
15 C	-0.4726	-2.2147	3.4598	-0.1543
16 C	0.7509	-2.2077	4.1259	-0.0362
17 C	0.7889	0.1928	3.8769	0.0909
18 C	1.3784	-0.9898	4.3559	-0.1273
19 C	-1.0796	-3.5217	3.1944	0.3307
20 O	1.5782	1.3460	4.0444	-0.2207
21 C	-0.7470	-3.6896	0.2431	-0.0144
22 C	-1.8971	-3.5428	1.9036	-0.2186
23 O	-1.0592	-4.5766	3.7762	-0.3048
24 C	1.0871	2.3677	4.8801	0.0513
25 H	0.6181	2.5207	1.4297	0.0679

26 H	-1.0072	3.2463	1.2691	0.0736
27 H	1.9421	0.9540	-0.0176	0.1101
28 H	3.1971	-1.1874	0.0292	0.1212
29 H	-1.7915	-1.2174	-0.0276	0.1151
30 H	3.0566	-3.6538	-1.5492	0.0218
31 H	2.9406	-5.1910	-0.6009	0.0520
32 H	1.4898	-4.5595	-1.4420	0.0264
33 H	-1.1162	2.1085	3.4401	0.0538
34 H	-2.0609	1.1844	2.2915	0.0493
35 H	-2.0647	-1.0769	2.5331	0.1208
36 H	1.2092	-3.1446	4.4637	0.1236
37 H	2.3385	-0.9610	4.8899	0.1234
38 H	-2.5203	-4.4278	1.8243	0.0769
39 H	-2.4437	-2.6095	1.8026	0.0660
40 H	-1.5240	-3.8771	-0.4993	0.0621
41 H	-0.1706	-4.5935	0.4474	0.0759
42 H	1.0577	1.9964	5.9338	0.0225
43 H	1.7836	3.2078	4.8093	0.0528
44 H	0.0789	2.6928	4.5802	0.0288

Dipole	X	Y	Z	Total
Point Charge	1.267	1.572	-0.265	2.036
Hybrid	-0.319	0.267	0.077	0.423
Sum	0.948	1.839	-0.187	2.077


15
13
24
23
19
14
12
16
18
17
20
22
4
3
6
21
1
8
2
9
7
10
11

MOPAC Optimized Data for mono-enolate of 5,14-Dimethoxy[3.3]metacyclophane-1,10-dione (**51**).

Z- Matrix

Atom		Bond			Bond	
		NA	Length (Å)	NB	Angle Degrees	NC	Angle Degrees
1	C						
2	C	1	1.394				
3	C	2	1.390	1	119.3		
4	C	3	1.397	2	122.4	1	-7.8
5	C	4	1.401	3	117.2	2	8.6
6	C	5	1.404	4	120.7	3	-3.7
7	C	4	1.511	3	117.6	2	-166.9
8	C	7	1.493	4	104.9	3	43.4
9	C	8	1.350	7	127.1	4	-102.0
10	C	9	1.485	8	117.1	7	143.2
11	C	10	1.401	9	113.0	8	-86.0
12	C	11	1.388	10	121.8	9	156.4
13	C	12	1.411	11	117.2	10	12.2
14	C	13	1.401	12	120.4	11	-3.8
15	C	14	1.393	13	120.6	12	-4.7
16	C	2	1.500	3	117.2	4	170.4
17	C	16	1.525	2	115.0	1	96.2
18	C	17	1.537	16	115.3	2	126.6
19	O	5	1.393	6	119.5	1	-177.6
20	C	19	1.410	5	113.6	4	106.5

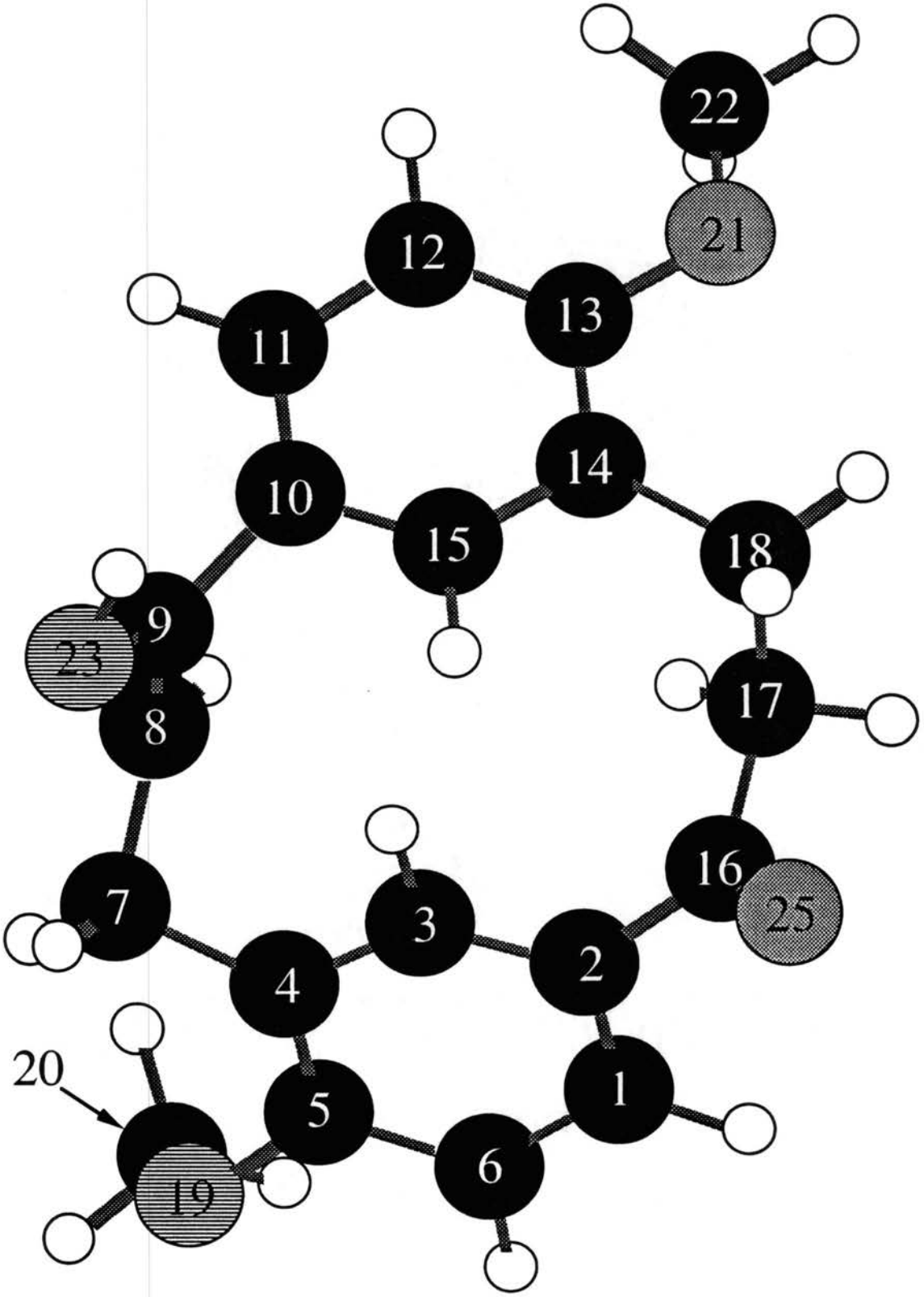
21	O	13	1.381	12	116.2	11	174.5
22	C	21	1.409	13	116.7	12	163.8
23	O	9	1.367	8	121.1	7	-22.9
24	H	23	0.949	9	107.1	8	171.4
25	O	16	1.214	2	122.3	1	-83.3
26	H	1	1.095	2	120.4	3	-177.8
27	H	3	1.100	2	119.0	1	173.4
28	H	6	1.096	5	119.7	4	179.2
29	H	20	1.096	19	112.2	5	58.6
30	H	20	1.093	19	102.9	5	177.1
31	H	20	1.096	19	111.6	5	-64.8
32	H	7	1.107	4	111.3	5	-11.7
33	H	7	1.106	4	110.4	5	106.2
34	H	8	1.098	7	114.5	4	64.0
35	H	14	1.101	13	119.3	12	177.8
36	H	15	1.095	14	120.3	13	-173.4
37	H	11	1.102	10	119.4	9	-17.5
38	H	22	1.092	21	102.8	13	164.5
39	H	22	1.095	21	110.6	13	-77.6
40	H	22	1.100	21	113.1	13	45.2
41	H	17	1.108	16	109.4	2	1.9
42	H	17	1.108	16	106.9	2	-111.9
43	H	18	1.106	17	109.4	16	137.4
44	H	18	1.108	17	110.9	16	21.5

Cartesian Coordinates

Atom	X	Y	Z	Charge
1 C	0.0000	0.0000	0.0000	-0.0574
2 C	1.3938	0.0000	0.0000	-0.1560
3 C	2.0740	1.2115	0.0000	-0.0899
4 C	1.4208	2.4362	-0.1598	-0.0779
5 C	0.0196	2.4222	-0.1381	0.0679
6 C	-0.6829	1.2106	-0.0399	-0.1293
7 C	2.2722	3.6513	-0.4461	0.0226
8 C	3.2679	3.1926	-1.4593	-0.2296
9 C	4.5605	2.8674	-1.2424	0.0860
10 C	5.1158	1.7384	-2.0303	-0.1246
11 C	4.8787	0.4898	-1.4397	-0.0789
12 C	4.8650	-0.6813	2.1853	-0.1098
13 C	5.3550	-0.6109	-3.5065	0.1072
14 C	5.7561	0.6168	-4.0506	-0.1916
15 C	5.5870	1.7999	-3.3342	-0.0304
16 C	2.2217	-1.2497	-0.0428	0.3295
17 C	2.7015	-1.6576	-1.4318	-0.1537
18 C	4.2158	-1.8837	-1.5639	-0.0284
19 O	-0.6815	3.6255	-0.1268	-0.2061
20 C	-1.3012	3.9293	-1.3569	0.0554
21 O	5.4422	-1.8076	-4.1894	-0.1871
22 C	5.5841	-1.7286	-5.5886	0.0458
23 O	5.2375	3.3487	-0.1564	-0.2210
24 H	6.0707	2.8961	-0.1239	0.2000
25 O	2.4797	-1.8907	0.9549	-0.2995

26 H	-0.5536	-0.9439	0.0366	0.1082
27 H	3.1681	1.2083	0.1099	0.1254
28 H	-1.7789	1.2193	-0.0107	0.1158
29 H	-2.0084	3.1518	-1.6682	0.0233
30 H	-1.8329	4.8586	-1.1384	0.0475
31 H	-0.5630	4.0928	-2.1503	0.0237
32 H	1.6614	4.4857	-0.8410	0.0647
33 H	2.7412	4.0212	0.4851	0.0741
34 H	2.8321	2.8904	-2.4210	0.1095
35 H	6.1700	0.6442	-5.0700	0.1219
36 H	5.8011	2.7653	-3.8040	0.1117
37 H	4.5976	0.4392	-0.3756	0.1212
38 H	5.9119	-2.7357	-5.8567	0.0533
39 H	4.6227	-1.5012	-6.0616	0.0285
40 H	6.3280	-0.9821	-5.9047	0.0348
41 H	2.3628	-0.9064	-2.1727	0.0768
42 H	2.1695	-2.5937	-1.6946	0.0733
43 H	4.3998	-2.7922	-2.1679	0.0702
44 H	4.6724	-2.0891	-0.5750	0.0730

Dipole	X	Y	Z	Total
Point Charge	0.237	0.117	-4.261	4.269
Hybrid	0.283	-0.273	-0.951	1.029
Sum	0.519	-0.157	-5.212	5.240


22
21
12
13
11
14
10
15
18
9
23
17
8
16
25
7
3
2
4
1
20
5
6
19

VITA

Mike Douglas Cagle

Candidate for the Degree of

Doctor of Philosophy

Thesis: I. STEREOSELECTIVE EXCHANGE OF KETONE α-PROTONS IN TRIFLUOROACETIC ACID-*d*

II. SYNTHESIS OF ESTROGENIC STEROID HOMOLOGS

Major Field: Chemistry

Biographical:

Personal Data: Born in El Paso, Texas, May 21, 1964, the son of Mr. and Mrs. Melvin D. Cagle.

Education: Graduated from Anson High School, Anson, Texas, in May, 1982; received the Bachelor of Science Degree in Chemistry, Math, and Physics from Hardin-Simmons University, Abilene, Texas, in May 1987, received Master of Science degree at Oklahoma State University in May, 1990, completed requirements for the Doctor of Philosophy degree at Oklahoma State University in July, 1993.

Professional Experience: Graduate Teaching Assistant, Oklahoma State University, 1987-1991. Research Assistant, Oklahoma State University, 1991-1993. Member of Kappa Mu Epsilon, Mathematical Honor Society, Phi Lamda Upsilon, Honorary Chemical Society, and the American Chemical Society.