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A Novel Synthesis of Cyclic and Acyclic 3-Alkenoic Acids via Ionization/Elimination of β-Lactones

Stephen Lucas Maluleka
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A NOVEL SYNTHESIS OF CYCLIC AND ACYCLIC 3-ALKENOIC ACIDS VIA IONIZATION/ELIMINATION OF β-LACTONES

(TITLE)

BY

STEPHEN LUCAS MALULEKA

Bachelor of Arts
Grinnell College
Grinnell, IA
May, 1987

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Master of Science (Chemistry)

IN THE GRADUATE SCHOOL, EASTERN ILLINOIS UNIVERSITY
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1989
YEAR

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A NOVEL SYNTHESIS OF CYCLIC AND ACYCLIC 3-ALKENOIC ACIDS VIA IONIZATION/ELIMINATION OF β-LACTONES

Thesis Approved

Dr. T. H. Black, Thesis Advisor

Dr. D. H. Buchanan, Department Head

Dr. B. E. Miller

Dr. M. E. McGuire

ABSTRACT

A NOVEL SYNTHESIS OF CYCLIC AND ACYCLIC 3-ALKENOIC ACIDS

VIA

IONIZATION/ELIMINATION OF ß-LACTONES.

BY

STEPHEN LUCAS MALULEKA

Under the supervision of Dr.T. Howard Black.

Exposure of spiro ß-lactones and 3-substituted 4,4-dialkyl oxetan-2-ones to magnesium bromide in diethyl ether solvent resulted in the smooth generation of ß,γ-unsaturated acid derivatives in high yield and isomeric purity. It is believed that this reaction occurs via the formation of a stable tertiary carbocation at the ß-carbon resulting from cleavage of the carbon-oxygen sigma bond due to the complexation of magnesium cation with the ring oxygen atom. Rapid loss of an adjacent proton then furnishes the unsaturated acids. The ß-lactone precursors were prepared by the dehydration of ß-hydroxy acid derivatives (obtained from the condensation of ketones with acetic acid dianions) employing benzenesulfonyl chloride in pyridine solvent. Since this synthetic method offers ready access to a wide range of ß,γ -unsaturated acids which were previously difficult to obtain, a detailed synthetic methodology and suggestions pertaining to the reaction mechanism are of prime interest and are discussed in detail.

ACKNOWLEDGEMENT

Special thanks to Dr. T. Howard Black, whose professional help and suggestions in this work were so valuable.

It has also been my good fortune and privilege to be associated with a large number of dedicated research collaborators, who have contributed in a significant way to the progress in this research. To them as well as previous members of my group, I offer my heartiest thanks and best wishes.

The work described in this thesis was made possible through donations from Petroleum Research Fund, administered by the American Chemical Society, along with Eastern Illinois University.

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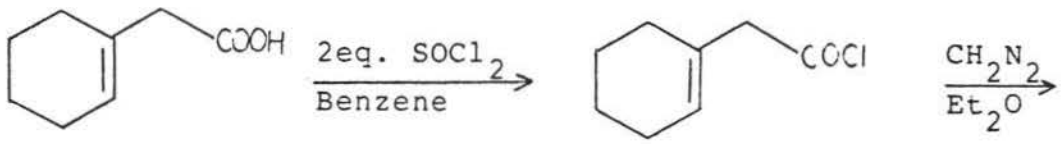
INTRODUCTION

Both cyclic and acyclic 3-alkenoic acids have found widespread application in the synthesis of theoretically interesting unnatural compounds as well as the synthesis of natural products. Many of these compounds are very important in organic chemistry and are useful as synthetic precursors and target molecules; for example, cyclohexenyl acetic acid derivatives have been utilized in a wide variety of reactions, serving as cyclization precursors via cycloadditions,[1] vinylogous Wolff rearrangements[2] and halo- or selenolactonizations.[3]

Vinylogous Wolff Rearrangement



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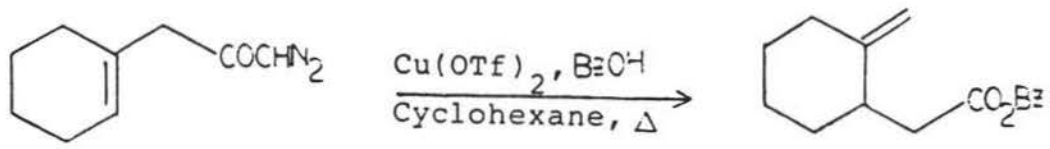
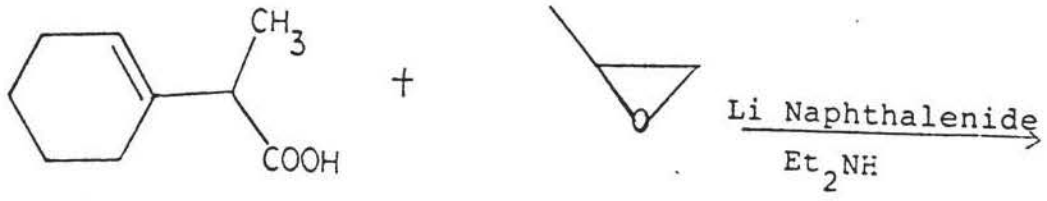


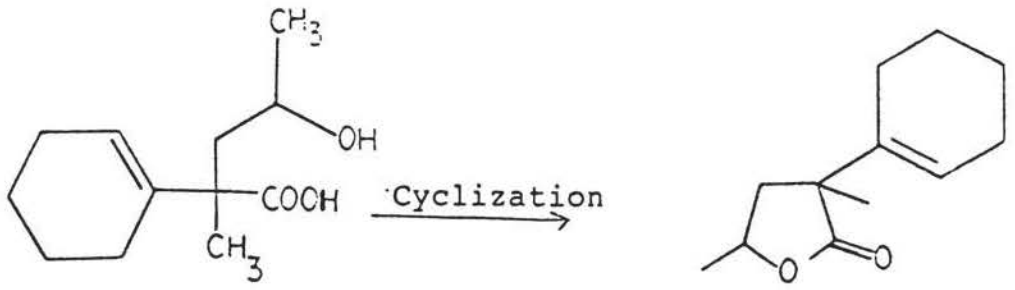
3 4

They have also been found to be readily convertible to other important classes of compounds such as 2,4-

dialkyl-2-cycloalkenyl-γ-butyrolactones[4] which are sweet-smelling and are used as perfumery materials, and naturally occurring lactones[5] which are the components of the essential oil of Menta piperita L. (Mitcham peppermint). For instance, 2-(cyclohexen-1-yl)-2,4-dimethyl-γ-butyrolactone 8 has been prepared from the cyclization of 2-(cyclohexen-1-yl)-4-hydroxy-2-methylpentanoic acid 7 derived from the reaction of 2-(cyclohexen-1-yl)propanoic acid 5 and propylene oxide 6 using lithium naphthalenide in the presence of diethylamine (Et_2NH).



5 6

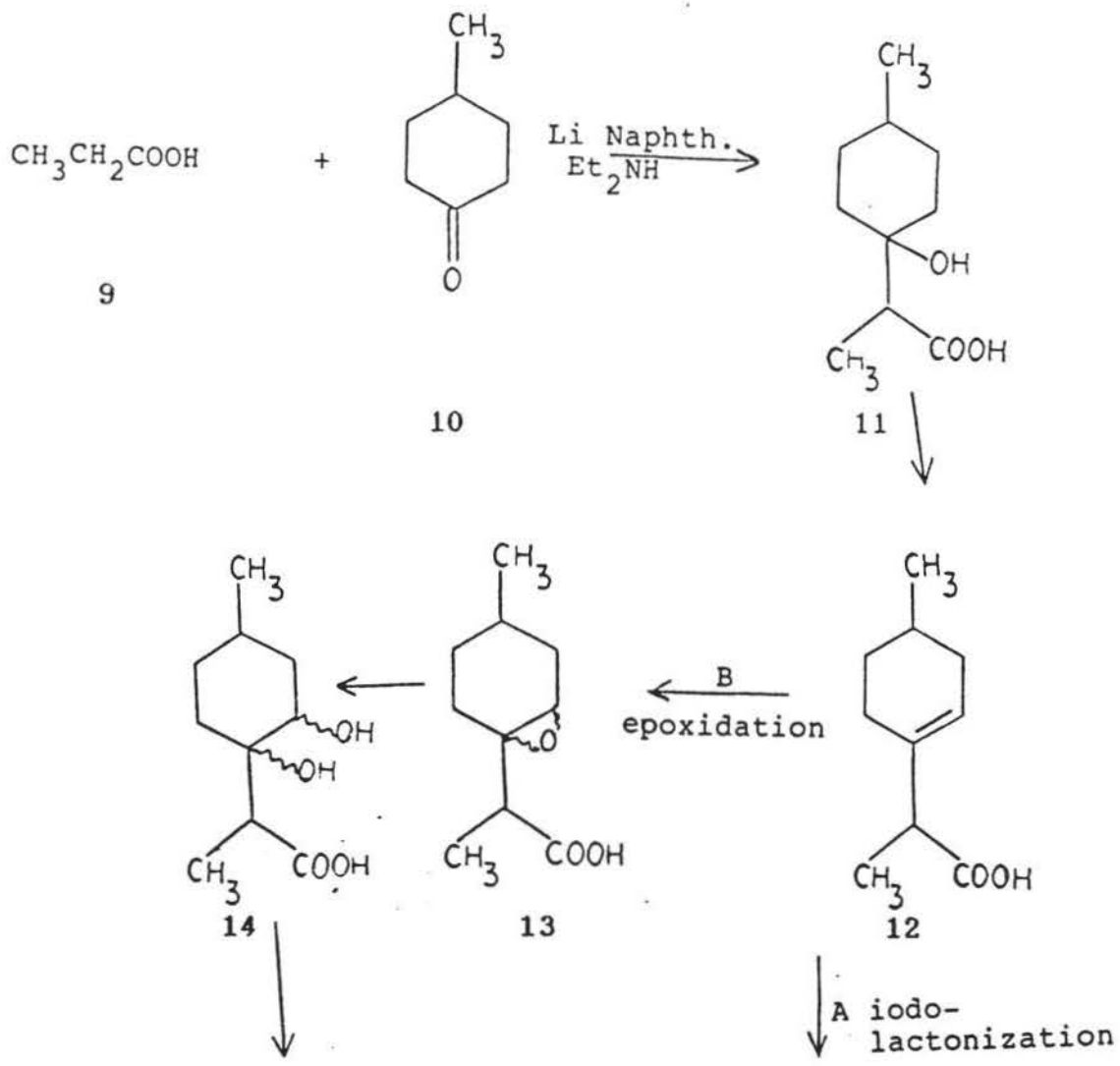


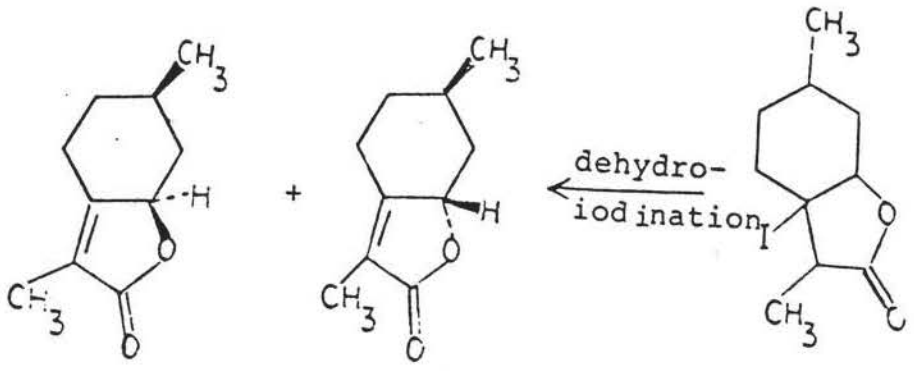
7 8

The naturally occurring lactones mintlactone 16 and isomintlactone 17,[5] which are commercial flavoring materials, have been obtained from 2-(2-hydroxy-4-

methylcyclohexylidine) propanoic acid 12 via either pathway A or B. Compound 11 was prepared from the reaction of propanoic acid 9 with 4-methylcyclohexanone 10 employing lithium napthalenide in the presence of diethylamine (Et_2NH) base.

The Preparation of Mintlactone (16) and Isomintlactone (17)

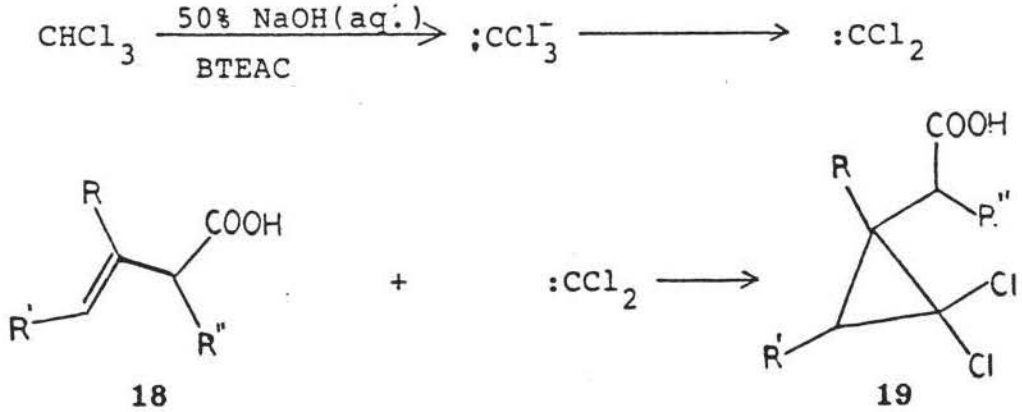




17 16 15

Commercially, the α-substituted cyclohexenyl acetic acids are of value as precursors to insecticides[6] and as antirust/antiwear compounds.[7] As potent insecticides against female houseflies of the Takatsuki strain in Japan, carboxylic acids containing dichloropropane ring systems can be synthesized from α-

The General Preparation of Carboxylic Acid Containing Dichloropropane Ring System.



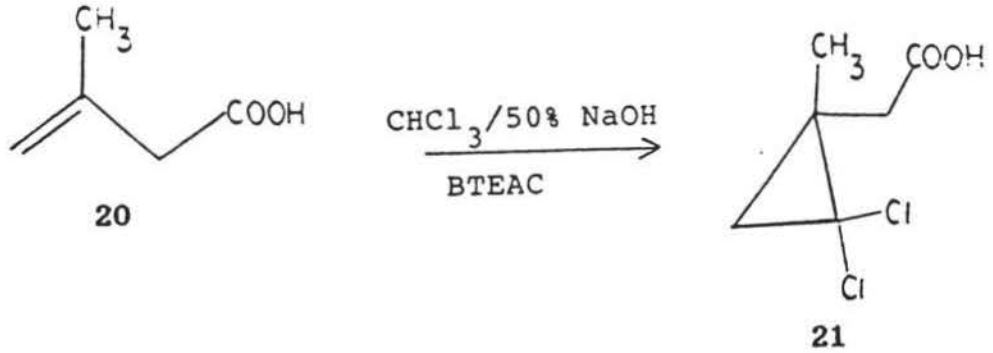
18 19

substituted cycloalkenyl acetic acids and dichlorocarbene (prepared from 50% sodium hydroxide solution, chloroform and benzyltriethylammonium chloride (BTEAC)).

With various fatty acids such as hexanedecanoic, tetradecanoic, etc., α-substituted (1-cyclohexenyl) acetic acids react to produce triethanolamine salts in lithium napththaledine/Et_2NH solution. These water-soluble salts have been found to possess excellent antirust actions against cast steel panels and iron chips.

Trisubstituted acyclic alkenoic acids have been found to have special importance in their own right. They are of significance as synthetic precursors, to the

Reaction of 3-Methyl-3-butenoic acid (20) with Dichlorocarbene to form 21.



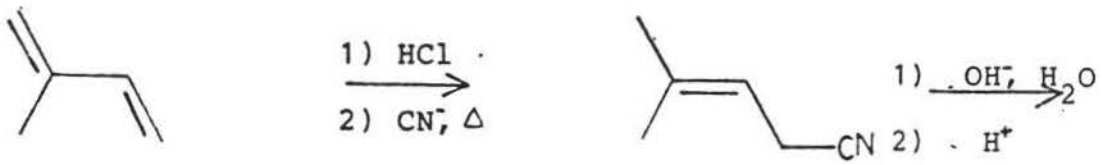
20 **21**

preparation of various dichloropropane ring carboxylic acids.[4] Carboxylic acids such as 2-(2,2-dichloro-1-

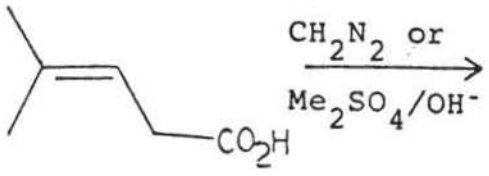
methylcyclopropyl) ethanoic acid 21 have been successfully made from 3-methyl-3-butenoic acid 20 and dichlorocarbene, (prepared as before via phase-transfer catalysis).

C.F. Garber et al.[8] have also found 3-alkenoic acids to be particularly useful as synthetic intermediates in the preparation of naturally occurring terpenoids such as chrysanthemic acid 30 via electrophilic addition pathways. Various ester derivatives of this acid are active insecticidal components of pyrethrum flowers.

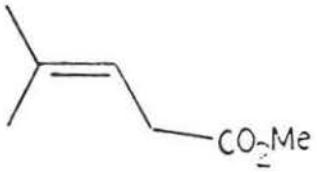
Synthesis of Chrysanthemic Acid via the Trisubstituted acid (24) Intermediate.



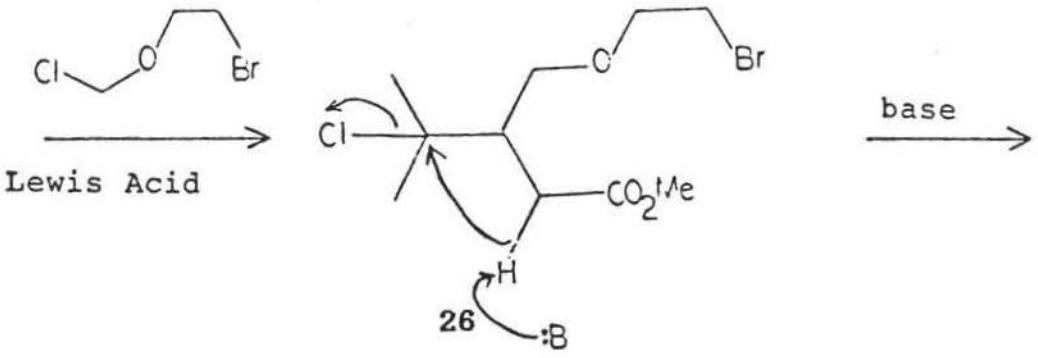
22 **23**

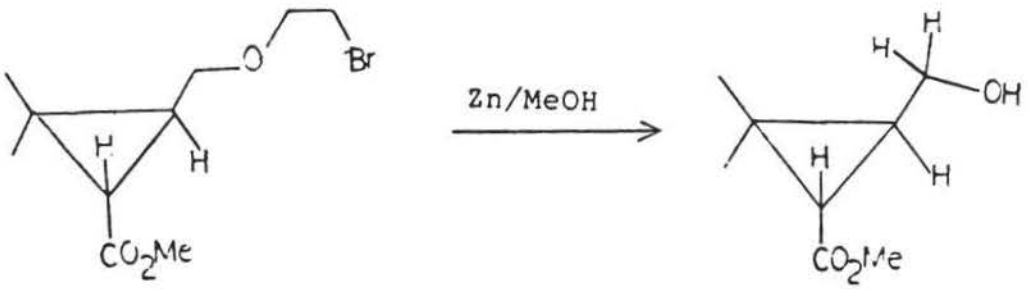

CH_2N_2 or
Me_2SO_4/OH^-
CO_2H

24


CO_2Me

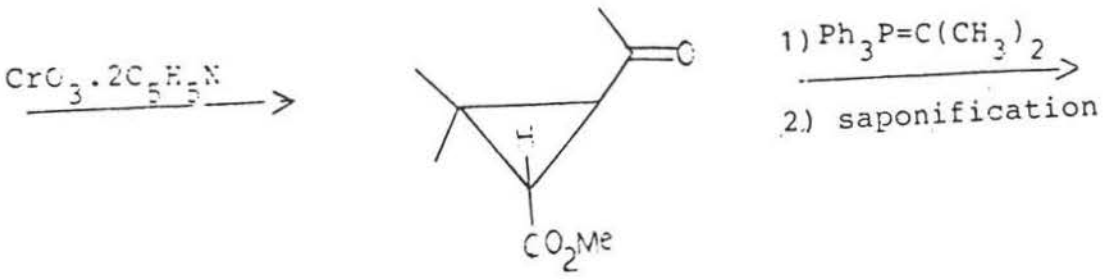
25


Cl
O
Br
Lewis Acid
Cl
O
Br
CO_2Me
H
26
:B
base

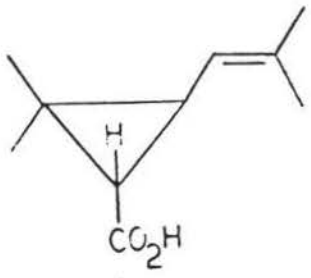

O
Br
H
H
CO_2Me
Zn/MeOH
H
H
OH
H
H
CO_2Me

27

28



29

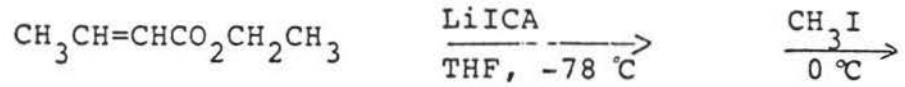


30
Chrysanthemic acid

Although several approaches aimed at the construction of cyclic and acyclic 3-alkenoic acids have been reported, to date,[9,10,11] there are no simple and straightforward synthetic routes leading to them on record. The known syntheses of these 3-alkenoic acid

derivatives are generally multi-step and/or low-yield procedures. The following may be cited as difficulties in acquiring these acids:

Low regioselectivity The positional stereochemistry of the newly formed double bonds in these molecules can be very difficult to control. Thus, most of the procedures cited in literature suffer from low regioselectivity in which the desired ß,γ-unsaturated acids were contaminated with undesired (usually conjugated) isomers. For example, a mixture of both the α,ß- and ß,γ-unsaturated isomers has been reported[10a] in the preparation of non-conjugated esters from α,ß unsaturated esters.



ethyl crotonate

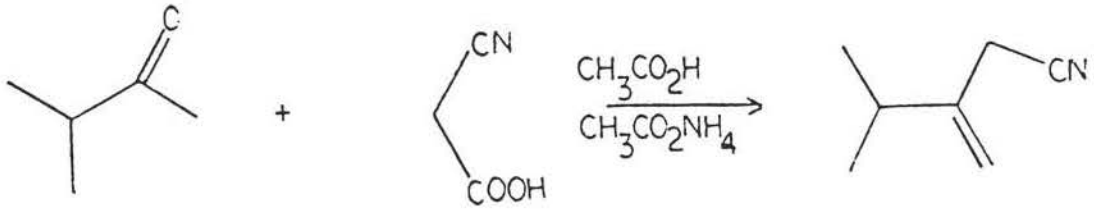
31

32 33

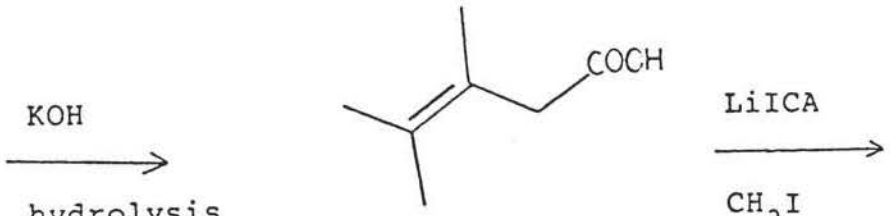
Lack of the carboxylic acid functionality: The targeted ß,γ-unsaturated adducts lacked the carboxylic acid functionality and were obtained

as esters, ketones or other functional group derivatives.[10](see the subsequent reaction route).This necessitated one or more additional steps to be performed before the final product was reached.[10c] Of course, multi-step sequences lead to diminished yields of the desired products.

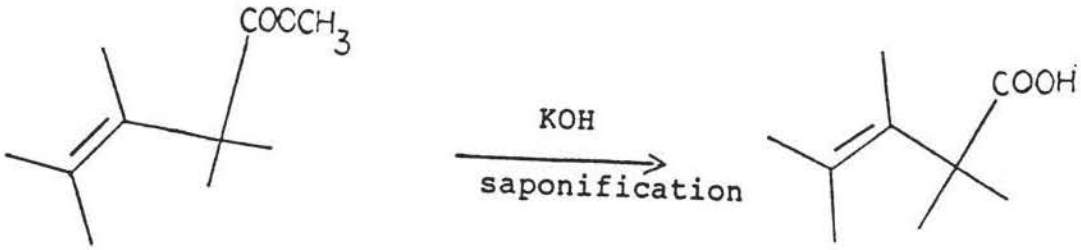
Limitation to simple α-alkyl substituents: The targeted molecules had no alkyl groups already affixed to the α-carbon. Most substituents were attached via the alkylation of enolates derived from carboxylic acids; a procedure limited to only simple alkyl groups e.g methyl ($-CH_3$) and not applicable to bulky and resonance stabilized groups such as -Ph, -OPh, napthyl etc. for the attachment of the latter substituents via the enolate mode has proved to be very difficult. In earlier procedures,[13] the alkylation enolates derived from carboxylic acids were unsuccessful due to the interference of the proton from the carboxylic functionality, and hence it was first necessary to protect the carboxylic acid 38 by esterification, then alkylate 39 and finally saponify to afford the desired ß,γ-unsaturated acid 40.[10c]



35 36 37



38



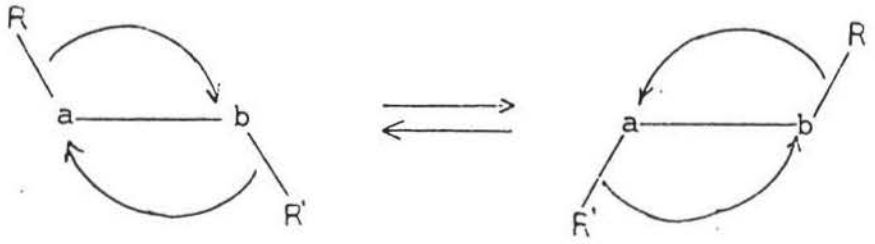
39 40

MP: 53 - 55 °C

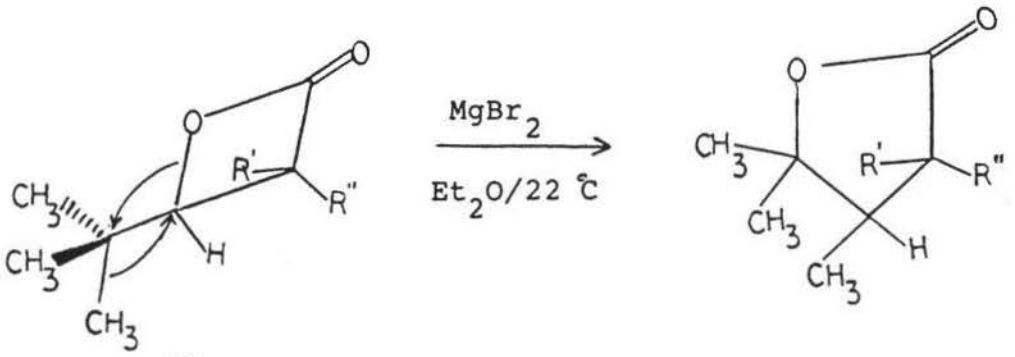
Thus, the three problems mentioned above clearly indicate that a new, efficient, and stereocontrolled synthetic method for the 3-alkenoic acids had yet to be developed.

Recent advances in organic chemistry have demonstrated that dyotropic-type rearrangements[13] can be

applied to the stereocontrolled synthesis of numerous organic molecules. In its simple definition, a dyotropic rearrangement involves a reversible and simultaneous exchange of sigma bonds by two adjacent atoms as depicted below:



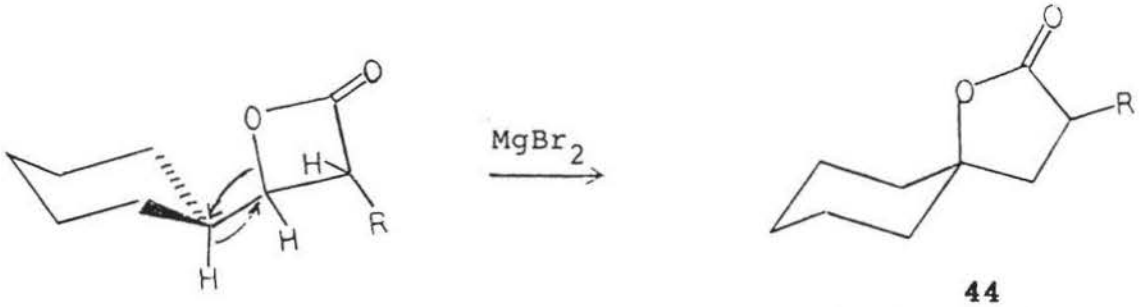
This process requires a catalyst and was originally confined to silicon, germanium, and other atoms having low-lying d orbitals as migrating groups. Later, a dyotropic-type rearrangement was found to be extendable to processes that involve expansions from four-membered to five-membered ring butyrolactones.[14]



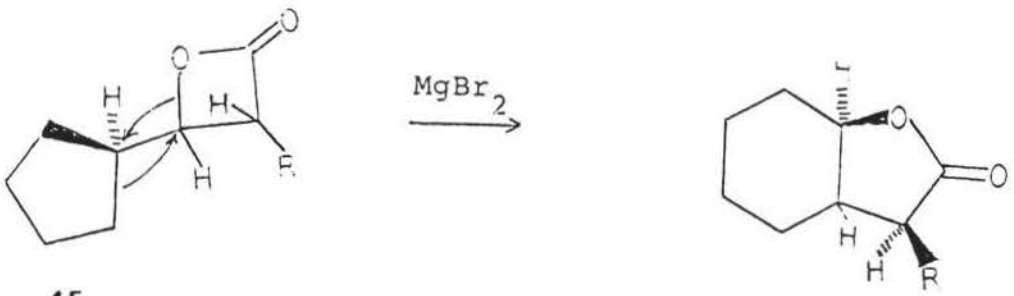
41 42

Very recently, stereospecific syntheses of spiro[15] or

fused[16] α - substituted butyrolactones were successfully achieved by this process.

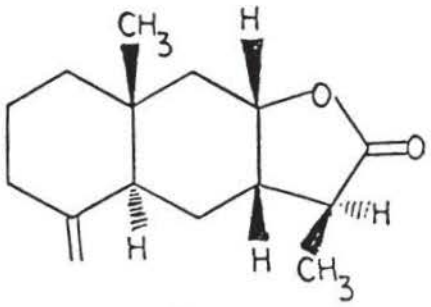


43 44 spiro butyrolactone



45 46 trans-fused butyrolactone

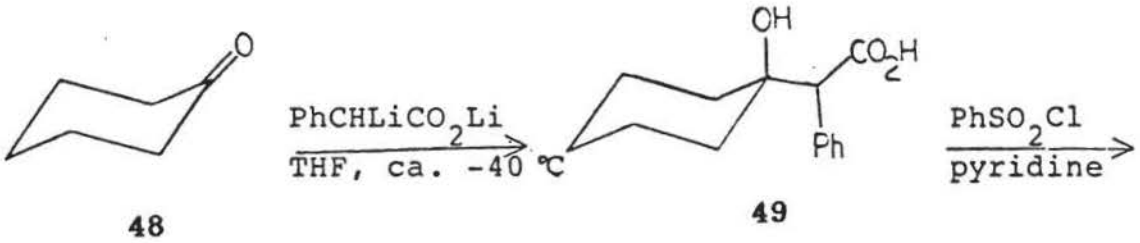
In an effort to extend the scope and utility of dyotropic-type rearrangement as a tool for the construction of cis-fused butyrolactones which occur in a variety of eudesmane sesquiterpene natural products,[17a,b] e.g dl-dihydrocallitrisin 47, a new, general, and facile three step method for the preparation of 3-alkenoic acid compounds was accidentally discovered.[18] The reaction sequence is outlined in Scheme I.



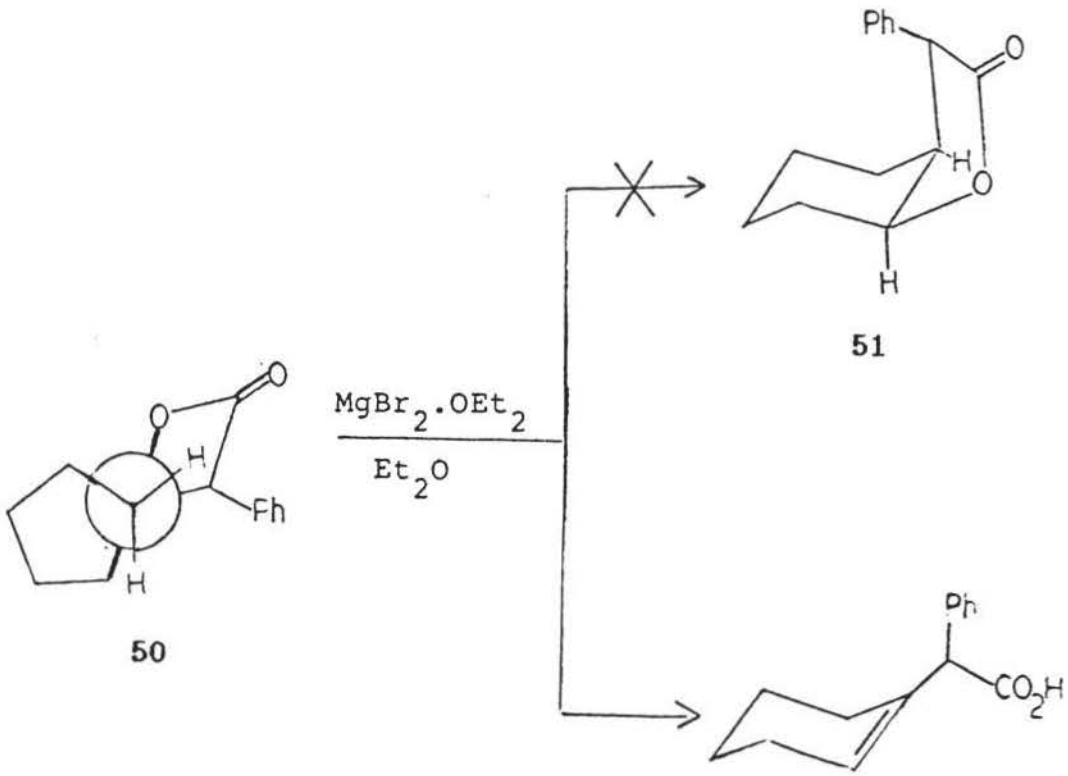
47

dl-dihydrocallitrisin

SCHEME I:

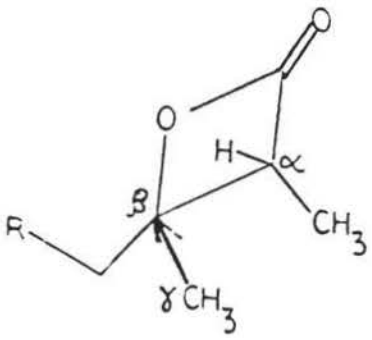


48 49



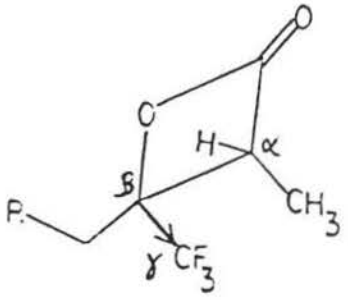
As shall be seen, the rearrangement from step 2 to step 3 in the above synthetic sequence is postulated to transpire via an ionization/elimination mechanism. The most intriguing feature about this sequence is that in order for the transformation of the ß-lactone 50 to the 3-alkenoic acid 52 to take place, it is imperative for the lactone progenitor to have a tertiary carbocation center. The extent of ionization from the ß-lactone precursor has been found to be greatly affected by the nature of the substituent directly affixed to the

beta(ß) carbon.



53

vs



54

$-CH_3$ is electron-donating; the ß-carbon is electron-rich and C-O bond cleavage is easier.

$-CF_3$ is electron-withdrawing; the ß-carbon is electron-poor and C-O bond cleavage is relatively difficult.

The more electronegative the substituents, the less stable the ß-center, and hence the probability that ionization would be effected is diminished. For example, ionization was not possible in cases where the tertiary ß carbon bore an electron withdrawing group such as trifluoromethyl($-CF_3$) at the γ position. This will be addressed in greater detail in the next section.

This thesis specifically reports results of this model study, which features experimental details for the highly stereoselective synthesis of a number of (1-cyclohexenyl) acetic acids and 2,3-dialkyl-3-alkenoic acids; including the discussion of the ionization/elimination mechanism.

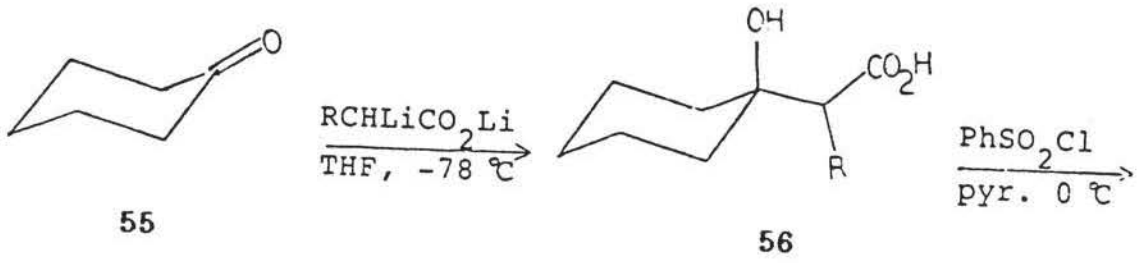
RESULTS AND DISCUSSION

The recognition that α-substituted ß-lactones undergo an ionization/elimination reaction to give carbon-carbon double bonds forms the basis for the stereoselective syntheses of cyclic and acyclic 3-alkenoic acids with the α alkyl group already in place. As part of this project, the regiospecific synthesis of a series of α-substituted (1-cyclohexenyl) acetic acids was executed as illustrated in the reaction Scheme II.

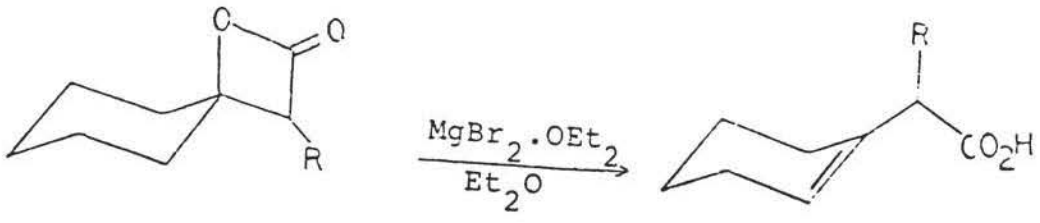
The formation of the ß,γ-unsaturated acetic acid derivative from step 3 to step 4 was unexpected, since from earlier investigations[15] and molecular model conformational studies, it was proposed that the dyotropic-type rearrangement of the spiro-ß-lactone 50 would likely result in the cis-fused γ-lactone 51 as the only product, as outlined earlier (Scheme I).

The reaction pathway was expected to take place without any complications, as expansions from four-membered ring to five-membered ring lactones are accompanied by approximately 22Kcal/mol energy release.[14] Moreover, it was envisaged that this rearrangement would be extremely facile, since the γ

SCHEME II:



55 56



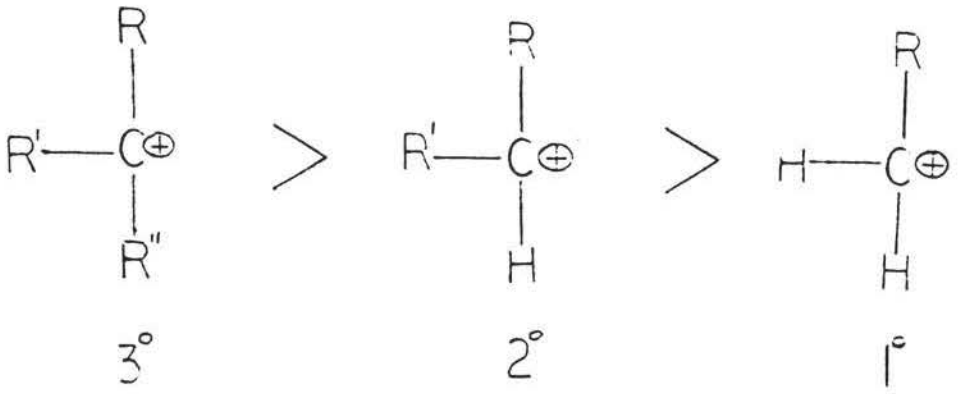
57 58

where R= $-CH_3$, -Ph,-OPh, SPh, p-OCH_3Ph, naphthyl etc.

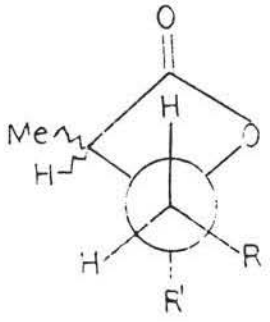
carbon-hydrogen and the ß carbon-oxygen bonds are perfectly aligned in an anticoplanar fashion. Interestingly, the α -substituted spiro-ß-lactones (Scheme I) were transformed into (1-cyclohexenyl) acetic acid derivatives 52 instead of the anticipated cis-fused γ -lactones 51. The causative factors behind the former alternative pathway can be mainly attributed to two determinants: (i) a requirement that the carbocation intermediate from the spiro-ß-lactone be tertiary at the

ß-position and (ii) stereoelectronic factors in the carbocation intermediate which determine whether the subsequent elimination process would result in the formation of a ß,γ- or α,ß-unsaturated acids.

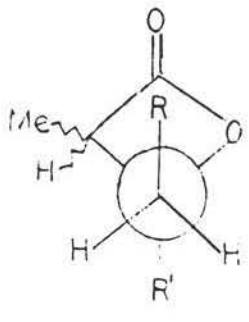
Both factors have an effect on the ionization/elimination process leading to cyclic and acyclic 3-alkenoic acids. It makes sense for requirement (i) to have a major bearing on the course of this rearrangement because, in typical ionization/elimination reactions, the order of stability of carbocation intermediate is tertiary > secondary > primary.



For stereoelectronic reasons (ii), elimination should take place most readily when the γ hydrogen atom and the carbonyl group (C=O) are in position 1 rather than in position 2 in the ß-lactone precursor to the tertiary carbocation intermediate in the acyclic analogs.

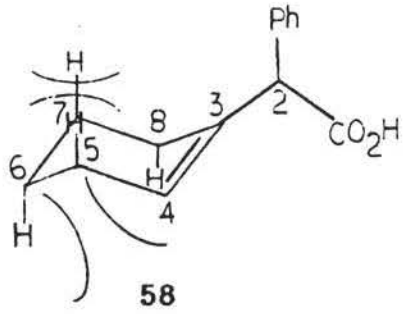


1



2

Obviously, a mixture of two geometric isomers, i.e the Z and E isomers, should independently be formed as elimination can take place in two ways. The stereoelectronic situation also has an influence on the direction (geometry) of the resulting product in the cyclic system as the hydrogens are symmetrically located on the more rigid cyclohexyl ring. This is demonstrated by the regiospecific transformation of the spiro-ß-lactone in Scheme II in which the resulting (1-cyclohexenyl) acetic acid assumes a flattened cyclohexene conformation with only two diaxial interactions at C_6, C_8 and C_5 and C_7.



58

As shall be later observed, stereoelectronic factors do have a major impact on whether the ß,γ or α,ß positional isomers would be formed in both the cyclic and acyclic cases.

Thus, this overall transformation has provided a general solution to the stereospecificity in α-substituted (1-cyclohexenyl) acetic acid syntheses and also has the virtue of being applicable to the stereoselective preparation of trisubstituted 3-alkenoic acids.

Synthesis of 2-(1-Cyclohexenyl)-2-alkylacetic acids: The synthetic sequence outlined in Scheme II reveals that ß-hydroxy acid preparations are accomplished by the treatment of a substituted acetic acid derivative with 2 equivalents of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) to form an acetic acid dianion, which, upon the addition of cyclohexanone 55 and subsequent protonation, affords the desired ß-hydroxy acid 56. Note that the resulting ß-hydroxy acid has one chiral center, hence it is a racemic mixture (i.e., it contains both the R and S enantiomers). Impurities were routinely removed via recrystallization from suitable solvents such as cyclohexane, heptane or toluene.

The dehydration of the pure ß-hydroxy acids in

pyridine at 0 ^{o}C in the presence of benzenesulfonyl chloride[19] gave the spiro-ß-lactones 57. The distinctive feature about these compounds is that they exhibited carbonyl stretchings at 1817-1821 cm^{-1}, with wavenumbers ca. 137 cm^{-1} higher than the corresponding ß-hydroxy acids, indicating that they are more sterically strained and thermally unstable than the latter. Due to this, additional purification of the ß-lactone was conducted without any delay either via filtration through a silica gel column employing dichloromethane as an eluent, or via recrystallization from appropriate solvents.

Subsequent conversion of the spiro-ß-lactone into the corresponding 2-(1-cyclohexenyl)2-alkyl acetic acid 58 was effected by subjecting the former to treatment with magnesium bromide in diethyl ether at room temperature to afford the latter in good to nearly quantitative yields. A single recrystallization or filtration through a silica gel column (CH_2Cl_2) rendered the α-substituted (1-cyclohexenyl) acetic acids sufficiently pure for subsequent data acquisition. The yields (unoptimized) are gathered in Table I.

The stereochemistry and purity of the 2-(1-cyclohexenyl)-2-alkylacetic acids were established primarily by ^{1}H and/or ^{13}C NMR. As evidenced by the NMR spectra attached in the appendix, the alkenoic acids were exceptionally clean and uncontaminated with the

Table I:

Yield Data for 2-(1-Cyclohexenyl)-2-Alkylacetic acid Synthesis

Suffix	R	Yield of 56	Yield of 57	Yield of 58
a	methyl	63	96	99
b	phenyl	95	80	74
c	phenoxy	77	77	99
d	thiophenoxy	84	74	80
e	p-methoxyphenyl	92	84	92
f	1-naphthyl	60	40	93

conjugated isomers. In all cases, only the ß,γ unsaturated isomer was detected and the allylic proton (=C<u>H</u>) appeared as a broad singlet between 5.10 and 5.80ppm. The upfield vinylic proton (=C<u>H</u>) was distinguished from the downfield carboxylic proton

(COO<u>H</u>) in that unlike the latter, it did not exchange with deuterium when D_2O drops were added to the deuteriochloroform NMR solution.

Although initial reports[20] indicated that a shorter reaction time (<u>ca.</u> 6h) was sufficient to achieve complete conversion, the reaction was found to be extremely sensitive to the size of the α alkyl group (R). In general, a longer reaction time was required when moving from a small alkyl group such as a methyl (-CH_3) to the largest group like napthyl (-$C_{10}H_7$). Substituting titanium(IV) chloride ($TiCl_4$) for $MgBr_2$-etherate as a catalyst may accelerate this process.[21]

At this juncture, it appeared that the ionization/elimination pathway was operative, instead of the expected dyotropic-type rearrangement. Furthermore, it occurred to us that angular strain inherent in the cyclohexane ring as well as restricted rotation about the cyclohexyl ring and the butyrolactone junction in the spiro-ß-lactone might play a major role in prohibiting the formation of a cis-fused butyrolactone. To examine this point, an auxiliary investigation similar to Scheme II was performed except that an acyclic analog, 3-pentanone, was employed in the place of cyclohexanone to generate the desired ß-hydroxy acid. Originally, the preparation of a ß-hydroxy acid from these two moieties proved to be unsuccessful. In

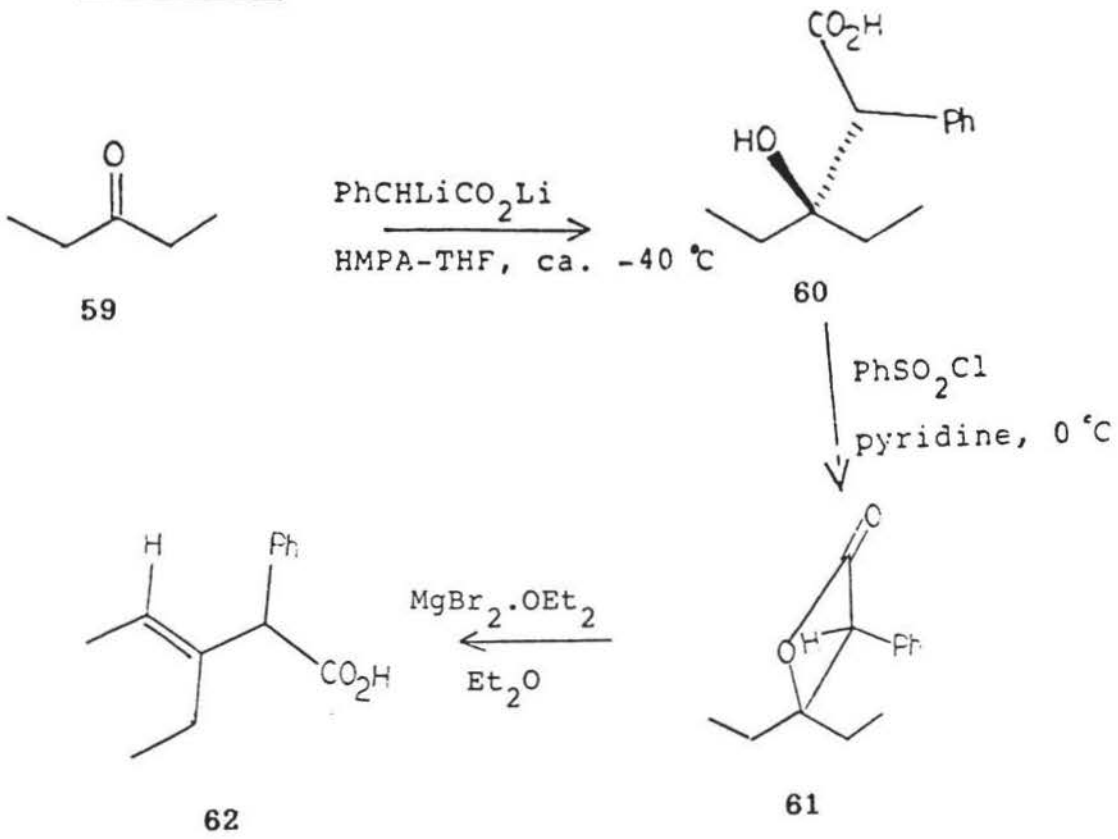
retrospect, this was not surprising since the angle strain from the cyclohexanone renders it more electrophilic towards the phenyl acetic acid dianion than ordinary simple acyclic ketones.[22] The angular strain in cyclohexanone is due to the sp^2 hybridized carbonyl group which forces it to adopt a planar cyclohexene conformation (120° bond angle) rather than a regular cyclohexane chair conformation with 109.5° bond angles.

Utilization of 2 equivalents of hexamethylphosphoric triamide (HMPA) as a powerful cation (e.g. Li^+) solvator,[10b] allowed the successful reaction of the less strongly solvated phenyl acetic acid dianion to generate 3-ethyl-3-hydroxy-2-phenylpentanoic acid **60**, in 88% yield, from which 4,4-diethyl-2-phenyloxetan-2-one **61** was prepared. Exposure of **61** to magnesium bromide, as usual, resulted in the formation of 3-ethyl-2-phenyl-3-pentenoic acid **62** in 98% yield. Scheme III depicts this reaction sequence.

At this stage, it remained to be seen whether the above synthetic sequence could be generalized. In previous investigations,[23] related ß-lactones (e.g **63** with a secondary ß-carbon center) have been found to rearrange to the γ-lactones **64** as shown in Scheme IV.

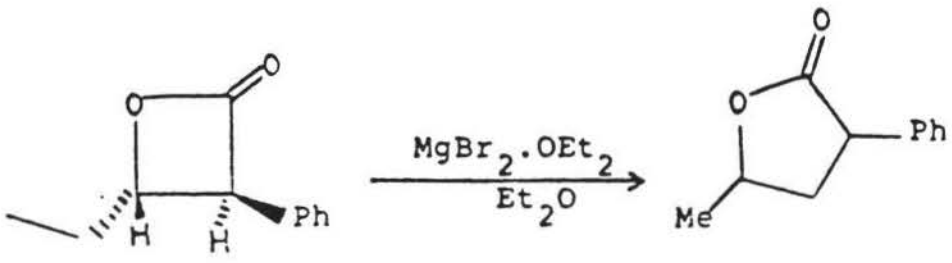
It can therefore be deduced that for the

SCHEME III:



59 60 61 62

SCHEME IV:



63 64

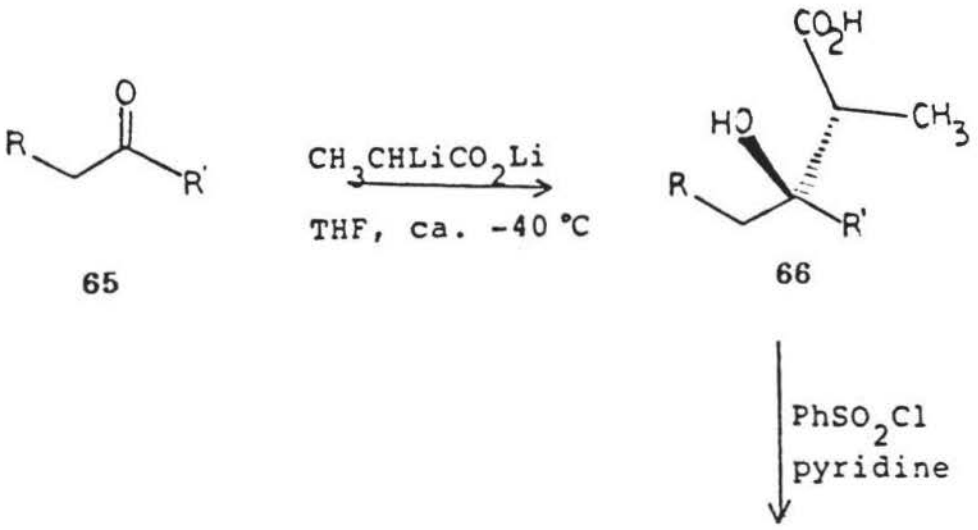
ionization/elimination reaction to occur, the formation of a tertiary carbocation as a result of ß-lactone ionization is a necessary condition. Since the ß,γ-

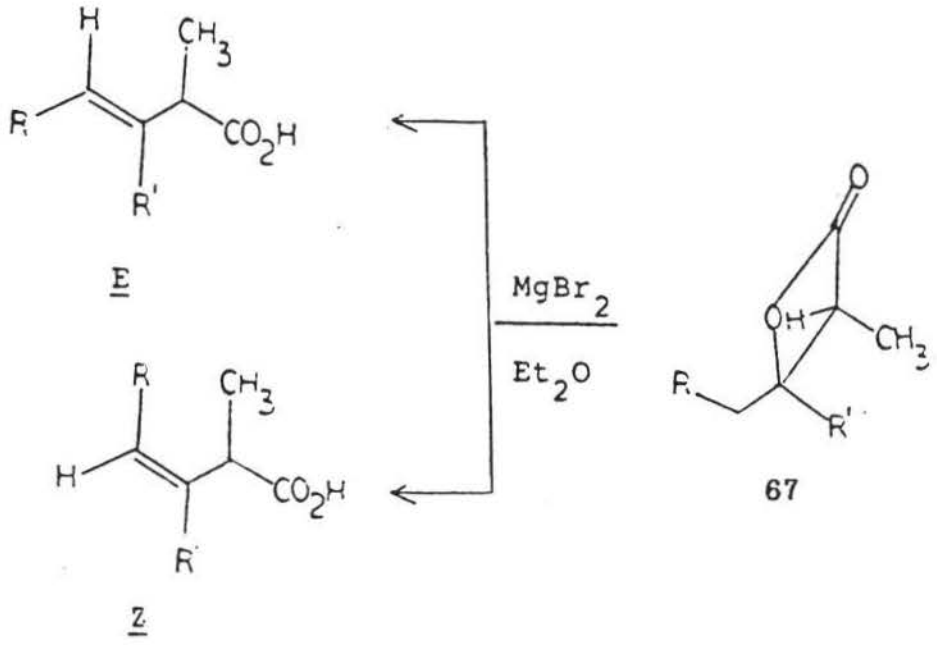
unsaturated acids were the sole products, stereoelectronic factors obviously play a major role in the ultimate elimination process.

Synthesis of 2,3-Dialkyl-3-alkenoic acids:

To define the potential scope and limitations of this new reaction, various acyclic ketones such as 2-butanone, 2-pentanone, 2-hexanone, etc. were used as precursors to prepare a series ß-hydroxy acids. The unsymmetrical ketones were chosen in order to establish the direction of alkene bond formation in the non-symmetrical ß-lactones. A detailed synthetic methodology which begins with acyclic ketone moieties, where R and R′ are alkyl groups of variable chain lengths, is outlined in Scheme V.

SCHEME V:





68

Unlike Scheme II, where different acetic acid derivatives were used in each case, propionic acid was employed in all cases, since the α-methyl would simplify spectral interpretation. Propionic acid dianion was generated in the usual manner[24] and was treated with an acyclic ketone to afford the corresponding ß-hydroxy acid 66. Most notable is the fact that the ß-hydroxy acids produced had two chiral centers at the α and ß positions. This then suggests that four stereoisomers are possible, since the number of isomers formed $=2^n$, where n= the number of chiral centers within the molecule. However, earlier work by Multzer and co-

workers[25] demonstrated that the formation of the threo diastereoisomer was favored over the erythro pair in these types of reactions. Nonetheless, it should be pointed out that the purification as well as the separation of these diastereomeric pairs prior to dehydration was impossible since the ß-hydroxy acids produced were oils which eliminated water upon attempted distillation.

The dehydration of the crude ß-hydroxy acids at 0 ^{o}C in the presence of benzenesulfonyl chloride in pyridine gave two products, the cis and trans ß-lactones **67**, which were inseparable on TLC. Since these were rather unstable, they were used in the next step without any delay after filtration through a silica gel column employing dichloromethane as an eluent. The rearrangement was effected by treating **67** with magnesium bromide in diethyl ether at room temperature to afford the ß,γ-unsaturated acid **68** as a product. The overall yield data for this series is arranged in Table II.

With the exception of 3-alkenoic acids **68i** and **68j**, in which the two possible isomers were obtained essentially in equal proportions, isomers in which elimination was toward the more highly substituted carbon atom were exclusively formed in each system. This is in accordance with Saytzeff's rule[26] which states that in (E1) elimination reactions, the double bond is

Table II:

Yield Data for 2,3-Dialkyl-3-Alkenoic Acid Synthesis from Ketones 65

Suffix	R	R′	Yield of 66	Yield of 67	Yield of 68
a	Me	Me	85	100	94
b	Et	Me	62	51	64
c	Me	Et	93	99	60
d	Pr	Me	93	85	74
e	Bu	Me	84	94	100
f	Et	Pr	98	63	100
g	C_5H_{11}	Me	100	80	56
h	Pr	Bu	50	67	100
i	Pr	Et	100	79	77
j	Bu	Et	96	70	90

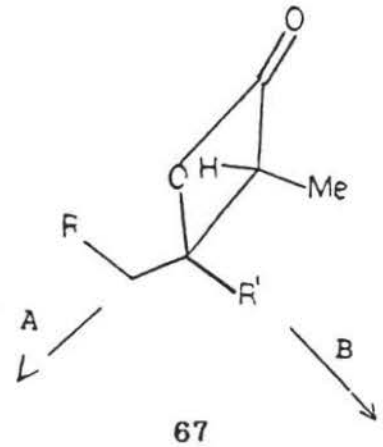
always oriented toward the more highly substituted carbon.

These highly substituted alkene isomers were obtained as a mixture of Z and E 3-alkenoic acids, in which a modest stereoselectivity (E/Z ratio ca. 2:1) was observed. The geometric purity and the number of isomers

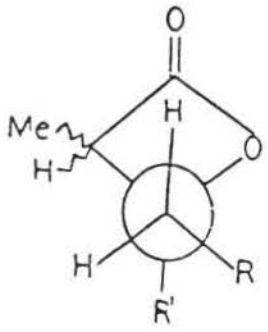
produced were established by proton NMR (60MHz) or ^{13}C NMR (125MHz). As in previous work,[27] the ^{1}H NMR exhibited a distinct difference in the vinyl proton chemical shifts and spin coupling constants for E versus Z isomer. In all cases, the well-resolved C-H quartet for the E isomer was shifted further upfield than its Z counterpart, with the former having a larger spin coupling constant (J_{C-H} = 7.2 Hz) than the latter (J_{C-H} = 7.0 Hz). The integration of the vinyl proton absorption signals revealed that the E conformation was preferred over the Z form in a 2:1 ratio. This observation was further confirmed by comparison of the relative peak heights corresponding to the allylic (=CH) carbon atom in the carbon-13 NMR.[28a,b]

That the E isomer is preferred is probably due to steric differences displayed by the two rotomers **69a** and **69b** just prior to the ionization/elimination process as illustrated by the two representative rotomers in the figures on the following page.[29]

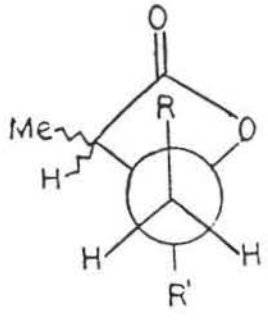
Considering the two modes of reactions (pathway A versus B), two different configurations can be envisaged as seen in the Newman projection formulae **69a** and **69b** above. The individual ß-lactone molecules may exist in state **69a** in which the smaller γ hydrogen atom is eclipsed with the ring carbonyl (C=O) group or state **69b** in which the larger alkyl group (R) is eclipsed with the



67

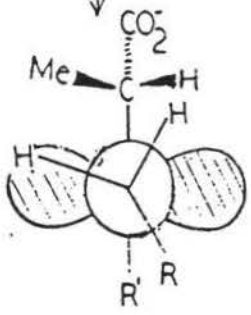


69a

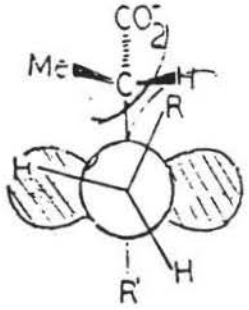


69b

ionization



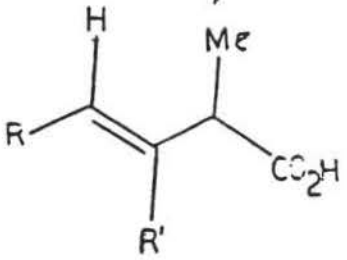
70a



70b

ionization

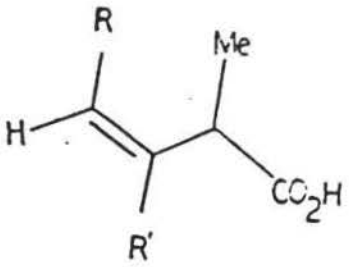
elimination



E (trans) isomer

68a

elimination



Z (cis) isomer

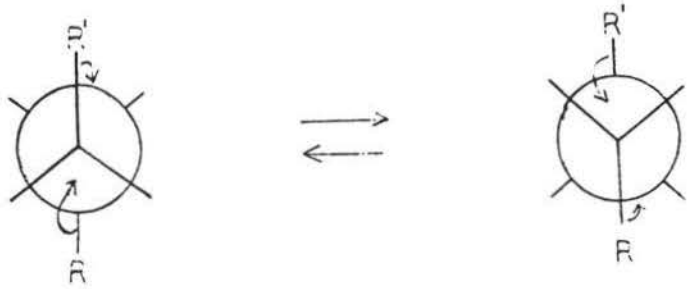
68b

carbonyl functional group. Obviously, due to less steric interaction between the carbonyl group and the smaller hydrogen atom, the total energy of the individual ß-lactone molecules in configuration **69a** would be relatively lower than that in the more congested configuration **69b**. Assuming that the system is free to fluctuate between the two configurations, **69a** is more likely to occur than **69b** because it is energetically favored, and thus would be more populated. At equilibrium, this population would remain virtually constant even though the identities of the molecules in state **69a** or **b** may change due to collision. With the ionization/elimination process taking place at the same rates in pathway A and B, the highly populated rotomer **69a** would eventually form the E geometric isomer **68a** while rotomer **69b** would rearrange to give the Z isomer **68b**.

Suggested Mechanism:

Previously, it has been established that in the presence of magnesium bromide etherate, ß-lactones rearrange to spiro-γ-lactones[15] as a result of proton-oxygen migration or to trans-γ-lactones[16] in the case of carbon-oxygen migration. Up to this point, these processes were believed to occur via a concerted reaction mechanism which would occur under conditions wherein the two migrating groups are positioned in an

anticoplanar fashion.[13]

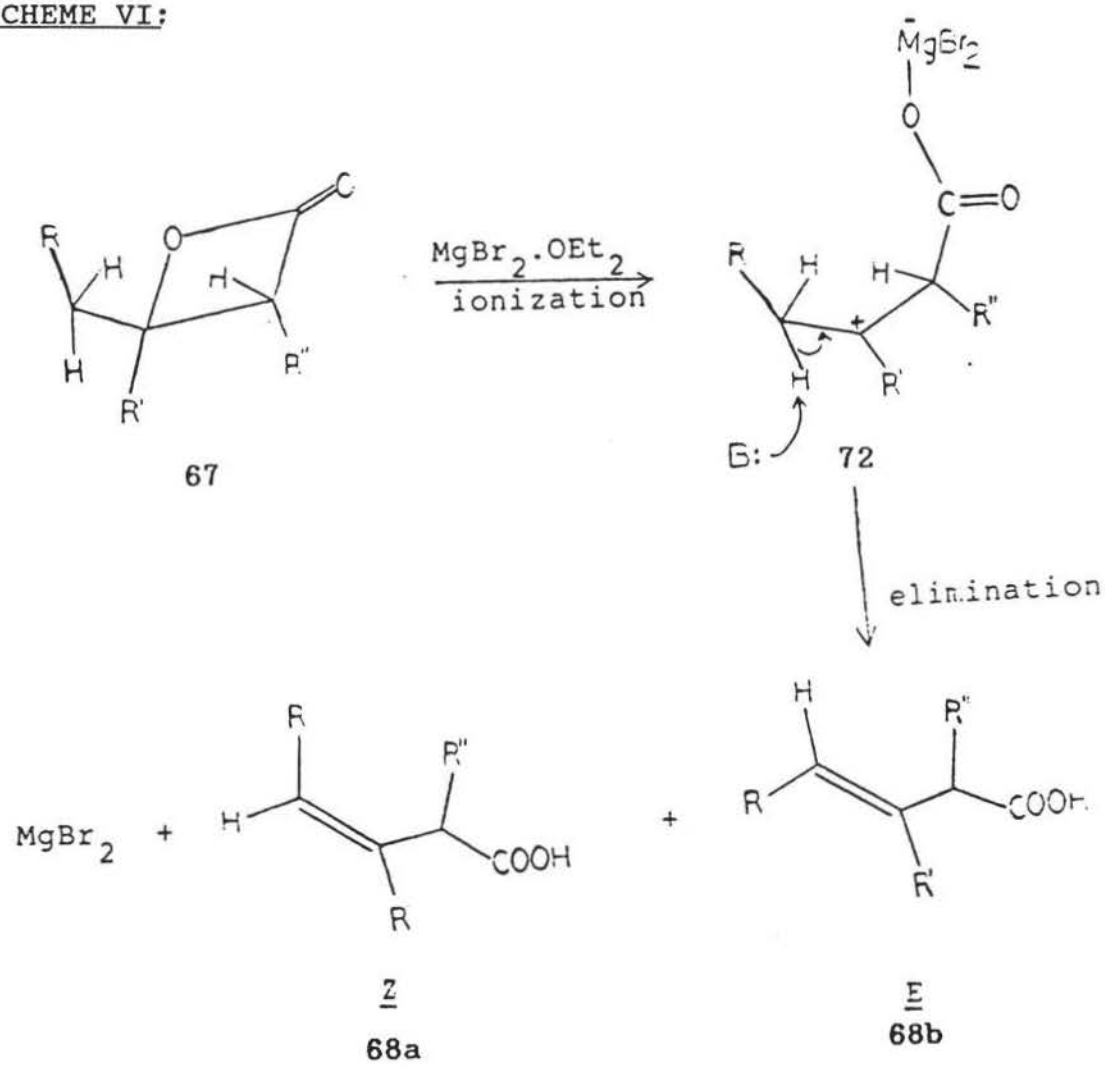


71a 71b

In an attempt to synthesize the cis-γ-lactone 51, by the rearrangement of the spiro cyclohexyl β-lactone 50 in Scheme I, a new reaction route for the stereoselective preparation of cyclic and as well as acyclic 3-alkenoic acids via the ionization/elimination of β-lactones was accidentally encountered.[18] The mechanism suggested for this process is shown in Scheme VI.

The formation of the β,γ-unsaturated acid suggests a reaction mechanism probably involving an intermediate with carbocation character, as outlined above. Initially, the magnesium bromide complexes with the oxygen in the β-lactone ring. The electron density is then withdrawn from the β carbon toward the oxygen atom,

SCHEME VI:



67 72 Z 68a E 68b

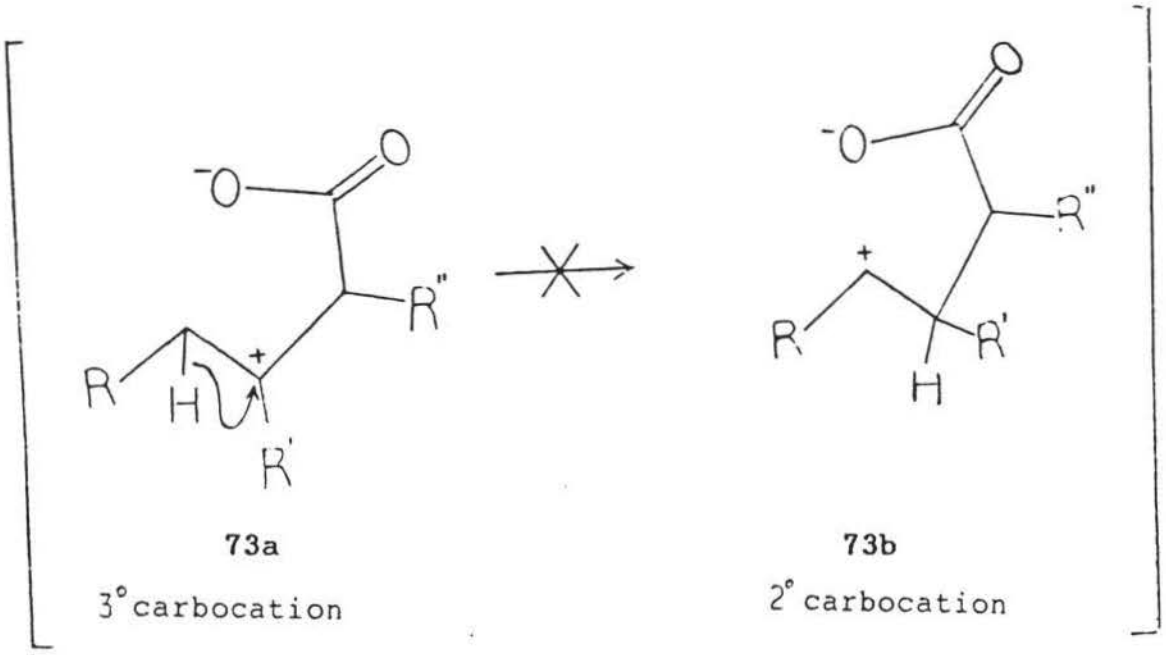
where R, R'=cyclohexenyl ring or separate acyclic groups and R''= alkyl group.

which then results in the carbon-oxygen sigma bond cleavage. Due to this ionization, a carbocation is formed at the ß carbon of the intermediate 72. This is followed by an elimination step in which a proton at the

position is abstracted by a carboxylate anion formed during the ß-lactone ionization to generate a ß,γ-unsaturated acid 68.

The formation of a stable carbocation intermediate in the above reaction sequence appears to be an essential prerequisite for the proposed ionization/elimination reaction. In earlier investigations,[23] γ-lactones were formed from ß-lactones that bore secondary ß-centers (e.g 63 with R'= H). However, in contrast to these findings, ß-lactones 67, which can form relatively stable tertiary carbocation intermediates 72, (R'= an alkyl group e.g $-CH_3$, $-CH_2CH_3$ etc.) formed ß,γ-unsaturated acids exclusively. These observations suggest that the stability of a potential positive charge at the ß-position of the lactone determines the type of product that will be formed. The observation that no butyrolactone products are formed is thus not surprising, since hydride migration is highly unlikely, as the carbocation intermediate so generated would have a relatively less stable secondary center.

As far as the elimination process is concerned, stereoelectronic factors are the controlling influence in both cyclic and acyclic carbocation precursors in determining whether ß,γ- or α,ß-unsaturated positional isomers would prevail. The sigma electrons of the γ C-H bond are parallel with the empty p orbital at the ß



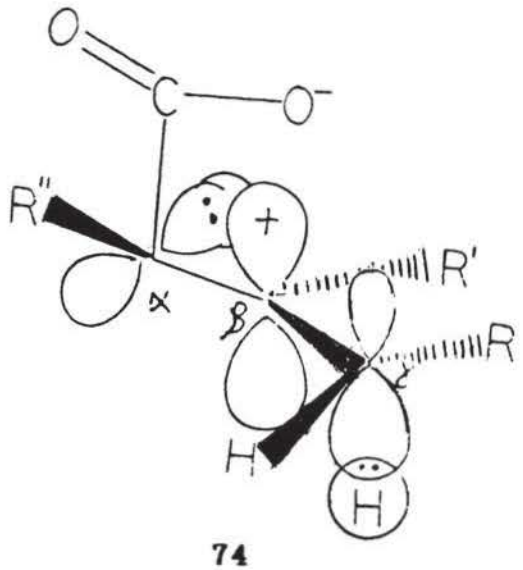
73a

3° carbocation

73b

2° carbocation

carbocation, while those of the α C-H bond adopt a perpendicular position as graphically depicted below:

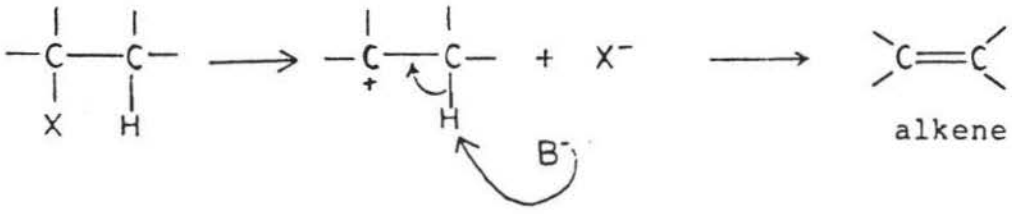


74

It is therefore obvious that the γ C-H sigma electrons are more favorably located for overlap with the empty p orbital at the ß carbon to form a pi bond

than are the sigma electrons at the α carbon. A rotation of approximately 90° about the $C_\alpha - C_\beta$ bond would be required for the latter sigma electrons to be properly aligned with the vacant p orbital. Since only the ß, γ positional isomer is formed, the γ hydrogen is evidently preferentially and very rapidly removed before this rotation can take place. This difference in p orbital alignment is apparently enough to shift the elimination reaction in favor of the ß,γ positional isomer.

As can be observed, this ionization/elimination mechanism is in some respect analogous to the unimolecular elimination (E1) mechanism shown below:



where X = e.g halogen, -OH, -OCOR, OSO_2Ar, $\overset{+}{N}R_3$, $\overset{+}{S}R_2$ and B- = an external base.

In the above E1 mechanism, the carbocation is first formed by the rate-determining departure of X-, which must be a good leaving group. The subsequent proton abstraction by an external base (B-) in solution results in the formation of an alkene bond.

However, unlike some elimination processes, the

proton abstraction step in the ionization/elimination mechanism is not promoted by a solvent or by an added base, as evidenced by the fact that alkene bond formation proceeded with the same efficiency in non-basic solvents such as dichloromethane. In order to rule out the E2 mechanism as a possible pathway, bases such as triethylamine and very powerful sterically hindered bases such as tert-butoxide (^{t}BuOK) and 1,5 diazobicyclo[3.4.0]non-5-ene (DBN) were tested in the absence of magnesium bromide and found to be ineffective in initiating this process. It thus seems that this elimination most likely involves proton abstraction by a carboxylate anion which is formed during the ß-lactone ionization.

As an additional support for the E1 reaction a dilution experiment, described in the next section, was performed. The reaction data are collected in Table III.

The mechanism in Scheme VI shows the reaction to be unimolecular because it involves the ionization of one chemical species (ß-lactone) on the reactant side, which upon elimination rearranges to form a new product (ß,γ-unsaturated acid). This ionization/elimination should lead to a first-order equation, a phenomenon which is common to all unimolecular reactions. Since the order of

Table III

run #	g of ß-lact.	mmol of ß-lact.	ml of ether	conc. of ß-lactone in M	t (min)
1	0.1	0.490	5	0.098	20
2	"	"	10	0.049	43
3	"	"	15	0.033	60
4	"	"	20	0.024	92
5	"	"	25	0.020	103

the equation can be empirically determined, the rate equation for this process was investigated by measuring the rate at which this ß-lactone **67** was converted to the ß,γ-unsaturated acid **68** at various concentrations of the ß-lactone.

Evidence from the reaction data in a Table III indicates that the reaction rate is dependent upon the concentration of the ß-lactone. The higher the concentration of the ß-lactone, the faster the reaction rate. A plot of ln C versus time gave a straight line (especially for the first three points) implying that in this region, the rate is directly proportional to the first power of the concentration as shown by the

equation:

$$-d[\text{ß-lactone}]/dt = k\,[\text{ß-lactone}]$$

Thus, these data seem to verify as well as reinforce the general idea that this ionization/elimination process might be E1 in nature since a first order kinetics is followed. As can be observed from Table III, for the last two points, i.e, at a low ß-lactone concentration, the reaction rate becomes independent of the ß-lactone concentration. This is due to the fact that the reaction mixture is so dilute that the reaction progress is difficult to monitor by thin-layer chromatography. However, further experimentation is necessary to test the precision of the dilution data collected in Table III. It would also be interesting to establish whether this elimination process is intramolecular in which immediately after the ionization process, the anionic carboxylate group from the same molecule abstracts its own proton or intermolecular, in which the carboxylate anion from another molecule participates as a proton abstracting base.

As it was deemed desirable to further substantiate the involvement of a carbocation in this process, the effect of carbocation destabilizing groups on the ß-

position of the ß-lactone 53 was investigated. The rearrangement was carried out on 4-butyl-4-trifluoromethyl-3-methyl oxetan-2-one 54 in solvents such as diethyl ether, dichloromethane and chloroform employing magnesium bromide etherate. Attempted rearrangements in all these solvents (even when refluxing) were unsuccessful.

This is not unexpected, as the $-CF_3$ group deactivates the ß carbon due to the strongly electron-withdrawing inductive effect of the fluorine atom which makes the cleavage of the C-O bond very difficult. The electron-withdrawing groups on the ß carbon have been found to make ionization less likely and to shift similar reactions away from the E1 mechanism.[30] This effect has been studied in several ways. The best way is by the comparison of Hammet σ constant which measures the carboanion character on the ß carbon in the transition state. The greater the positive σ value, the more the carboanion character in the transition state and the farther the reaction moves away from the E1 mechanism. Experimental results report the σ values for $CF_3 > CH_3$ which are .532 > -.129, respectively.[31] This shows that CF_3 has the greatest positive value and hence, has the capability to destabilize the transition state leading to the carbocation by removing the electron-density away from the ß carbon, and thus

ensuring that C-O bond breaking does not occur.

These experimental results thus suggest that the initial ionization depends upon the nature of the substituent directly attached to ß carbon in a particular lactone. Electron-donating groups e.g, $-CH_3$ lead exclusively to C-O bond cleavage and subsequent carbocation formation while strong electron-withdrawing substituents like $-CF_3$ discourage this process. The fact that a stable carbocation could not form in the $-CF_3$ case supports the contention that this rearrangement is E1, or at least relies on the accrual of significant positive charge on the ß carbon, and proceeds via the ionization/elimination route rather than the concerted mechanism.

CONCLUSION

Using a newly developed approach, the stereoselective syntheses of a series of (1-cyclohexenyl) acetic acids and 2,3-dialkyl-3-alkenoic acids have been successfully achieved. In terms of chemical yield, isomeric purity, and the simplicity of execution, this new synthetic approach is far superior to other methods previously reported.

Accumulated facts support a first-order ionization/elimination mechanism consistent with a unimolecular elimination (E1) reaction. This mechanism

involves the slow rate-determining ionization of the ß-lactone followed the rapid loss of adjacent proton to generate the ß,γ-unsaturated acid. The proton-abstracting base is the carboxylate anion formed during the ß lactone ionization. Most notable is the fact that for the ß-lactone to be transformed to the desired 3-alkenoic acid via this mechanism, it is requisite that the former possess an incipient stable tertiary ß-carbocation center. The initial ionization process is governed by the nature of the substituents directly attached to the ß carbon; the more electronegative the substituent, the less likely that ionization will take place.

EXPERIMENTAL SECTION

General: Glassware was routinely oven-dried at 120 ^{o}C for a minimum of 4hrs, and all the reactions were performed under nitrogen atmosphere. Anhydrous solvents were obtained by distillation prior to use: tetrahydrofuran (from benzophenone and sodium or potassium), diisopropylamide and pyridine (from barium oxide). All weights were taken on a Sartorius weighing balance. Thin-layer chromatography (TLC) with ethyl acetate (EtOAc) or dichloromethane (CH_2Cl_2) as an eluent was employed for qualitative analysis of reaction intermediates and final products. Melting points were obtained on a Thomas-Hoover capillary melting point apparatus. Infrared spectra were recorded on a Nicolet Model 20DXB Fourier Transform spectrometer unit with absorption maxima reported in wavenumbers (cm^{-1}). Proton nuclear magnetic spectra were recorded on a Varian T-60 or a General Electric GN-500 NMR spectrometer. All ^{1}H-NMR chemical shifts were measured in deuteriochloroform ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6) solutions with respect to 1% tetramethylsilane (TMS) as an internal reference standard. When necessary, proton coupled or APT ^{13}C-NMR spectra were also obtained at 125MHz applied field. Both the ^{1}H-NMR and ^{13}C-NMR chemical shifts are reported in parts per million (ppm) downfield from TMS. Peak multiplicities are abbreviated

as follows: singlet, s; doublet, d; triplet, t; quartet, q; multiplet, m; envelope, e. The final products were also characterized by High Resolution Mass Spectrometry employing 70eV electron impact.

General Procedure for the Preparation of ß-Hydroxy Acids:[32] Tetrahydrofuran (60mL) and diisopropylamine (11.22mL, 80mmol) were combined in a 250mL three-necked round bottom flask, equipped with a low temperature thermometer, nitrogen inlet, rubber septum and a magnetic stirring bar. The solution was stirred and cooled to below -30 ^{o}C with a chloroform-liquid nitrogen bath. To this solution was added 2.5M n-butyllithium solution in hexane (80mmol, 32ml) over a 30 minute period. The resulting yellow solution was stirred at approximately -40 ^{o}C for 1 hour at which point the acetic acid derivative (40mmol) was added. Cyclohexanone **48** or an acyclic ketone **65** (40 mmol) was slowly added, causing the temperature to rise rapidly to ca. 35 ^{o}C. Upon the addition of the last drop of the ketone, the yellow milky mixture became clear and yellow. The reaction was allowed to proceed overnight under a nitrogen atmosphere, at which point the yellow solution was poured onto ca. 50g of ice. The water layer was separated and was extracted twice with 20mL of diethyl ether. The organic layers were discarded and the aqueous layer was acidified with 6N hydrochloric acid after

which it was extracted thrice with 20mL portions of ether. The combined ether extracts were washed with brine and then dried over anhydrous magnesium sulfate. The drying agent was removed via filtration and the solvent was removed in vacuo to afford the following ß-hydroxy acids.

Cyclohexyl ß-Hydroxy acids

3-Cyclohexyl-3-hydroxy-2-methylpropionic acid (56a), a light-yellow oil, was obtained in 63% yield; purification of the oil not possible because it eliminated water upon distillation and thus the crude material was used directly in the next step: IR (film) 2975, 2934, 2860, 1708, 1458, 1216 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.2 (s, 1H, COOH), 3.90-3.25 (q, 1H, CHCH$_3$), 2.76-0.74 (m, 13H, CH$_2$ + CH$_3$); TLC (EtOAc) R_f 0.52.

3-Cyclohexyl-3-hydroxy-2-phenylpropionic acid (56b), a white crystalline solid, was obtained in 96% yield; recrystallization from toluene furnished the analytical sample: mp 129-130 °C; IR (KBr) 2948, 2929, 2847, 1681, 1385, 1222 cm^{-1}; ^{1}H-NMR (DMSO) δ 7.59-7.10 (m, 5H, ArH), 3.56 (s, 1H, PhH), 1.79-1.18 (e, 8H, CH$_2$); TLC (EtOAc) R_f 0.40.

3-Cyclohexyl-3-hydroxy-2-phenoxypropionic acid

(56c), a white crystalline solid, was obtained in 77% yield; recrystallization from toluene afforded the analytical sample: mp 154-155 ^{o}C; IR (KBr) 2930, 2861, 1704, 1492, 1209, 987 cm-^{1}; ^{1}H-NMR (DMSO) δ 7.64-7.18 (m, 5H, Ar$\underline{H}$), 3.63 (s, 1H, OPh$\underline{H}$), 1.76-1.18 (e, 8H, C$\underline{H}_2$); TLC (EtOAc) R_f 0.12.

3-Cyclohexyl-3-hydroxy-2-thiophenylpropionic acid (56d), a white crystalline solid, was obtained in 95% yield; recrystallization from toluene furnished the analytical sample: mp 103-105 ^{o}C; IR (KBr) 3384, 2973, 2940, 1697, 1201 cm-^{1}; ^{1}H-NMR (DMSO) δ 7.59-7.17 (m, 5H, Ar$\underline{H}$), 3.70 (s, 1H, SPh$\underline{H}$), 1.87-1.28 (e, 8H, C$\underline{H}_2$); TLC (EtOAc) R_f 0.21.

3-Cyclohexyl-3-hydroxy-2-p-methoxyphenylpropionic acid (56e), a white, crystalline solid was obtained in 92% yield; recrystallization from toluene furnished the analytical sample: mp 142-144 ^{o}C; IR (KBr) 2898, 2855, 2837, 1680, 1513, 1256 cm-^{1}; ^{1}H-NMR (DMSO) δ 7.51-6.73 (m, 4H, Ar$\underline{H}$), 3.89 (s, 3H, OC$\underline{H}_3$), 3.53 (s, 1H, C$\underline{H}$C$_6$H$_4$), 1.81-1.10 (e, 8H, C$\underline{H}_2$); TLC (EtOAc) R_f 0.22.

3-Cyclohexyl-3-hydroxy-2-naphthylpropionic acid (56f), a cream-white, crystalline solid, was obtained in 60% yield; recrystallization from cyclohexane afforded

the analytical sample: mp 142-144 °C; IR (KBr) 2929, 2925, 2917, 1693, 1410, 1216 cm^{-1}; ^{1}H-NMR δ 8.12-7.32 (m, 7H, NaphthH), 2.23 (s, 1H, CHNaphth), 1.98-1.08 (e, 8H, CH_2), TLC (EtOAc) R_f 0.44.

3-Ethyl-3-Hydroxy-2-phenylpentanoic acid (60), a white, crystalline solid, was obtained in 88% yield; an analytical sample was secured via recrystallization from heptane: mp 130-131 °C; IR (KBr) 2968, 2944, 2930, 2880, 1681, 1220 cm^{-1}; ^{1}H-NMR (DMSO) δ 7.55-7.05 (m, 5H, ArH), 3.66-3.45 (d, 1H, PhH), 2.65-2.32 (d, 6H, J=9.6Hz, CH_3), 1.75-0.30 (m, 4H, CH_2); TLC (EtOAc) R_f 0.30.

Acyclic β-Hydroxy Acids

3-Hydroxy-2,3-dimethylpentanoic acid (66a), a dark yellow oil, was obtained in 85% yield and was used without further purification in the next reaction: IR (film) 2981, 2947, 2886, 1711, 1462, 1204 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.12 (s, 1H, COOH), 3.98-3.33 (q, 1H, $CHCH_3$), 2.85-0.68 (m, 11H, CH_2 + CH_3); TLC (EtOAc) R_f 0.49.

3-Hydroxy-2,3-dimethylhexanoic acid (66b), a yellow oil, was obtained in 62% yield and used as obtained in the next step: IR (film) 2963, 2939, 2876, 1707, 1460, 1202 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.64 (s, 1H, COOH), 3.95-3.30 (q, 1H, $CHCH_3$), 2.80-0.67 (m, 13H, CH_2 + CH_3); TLC

(EtOAc) R_f 0.50.

3-Hydroxy-2,3-dimethylheptanoic acid (66d), a light-yellow oil, was obtained in 93% yield and used directly in the next step: IR (film) 2958, 2940, 2875, 1712, 1463, 1202 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.20 (s, 1H, COO$\underline{H}$), 3.95-3.45 (q, 1H, C$\underline{H}CH_3$), 2.44-0.60 (m, 15H, C$\underline{H}_2$ + C$\underline{H}_3$); TLC (EtOAc) R_f 0.57.

3-Hydroxy-2,3-dimethyloctanoic acid (66e), a yellow oil, was obtained in 84% yield and used as obtained in the subsequent reaction: IR (film) 2956, 2937, 2873, 1710, 1462, 1200 cm^{-1}; ^{1}H-NMR (DMSO) δ 3.63-3.27 (q, 1H, C$\underline{H}CH_3$), 2.33-0.52 (m, 17H, C$\underline{H}_2$ + C$\underline{H}_3$); TLC (EtOAc) R_f 0.59.

3-Hydroxy-2,3-dimethylnonanoic acid (66g), a sea-green oil, was obtained in quantitative yield: IR (film) 2956, 2835, 2861, 1709, 1461, 1209 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.47 (s, 1H, COO$\underline{H}$), 3.92-3.30 (q, 1H, C$\underline{H}CH_3$), 2.80-0.56 (m, 19H, C$\underline{H}CH_3$); TLC (EtOAc) R_f 0.55.

3-Ethyl-3-hydroxy-2-methylpentanoic acid (66c), a colorless oil, was obtained in 93% yield: IR (film) 2973, 2940, 2877, 1710, 1461, 1203 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.15 (s, 1H, C$\underline{H}CH_3$), 3.90-3.50 (t, 1H, C$\underline{H}CH_3$), 2.81-

0.59 (m, 13H, $C\underline{H}_2$ + $C\underline{H}_3$); TLC (EtOAc) R_f 0.65.

3-Hydroxy-2-methyl-3-propylhexanoic acid (66f), a yellow oil, was obtained in 98% yield: IR (film) 2961, 2937, 2876, 1707, 1460, 1198 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 7.70 (s, 1H, COO$\underline{H}$), 4.00-3.30 (q, 1H, $C\underline{H}CH_3$), 2.89-0.61 (m, 17H, $C\underline{H}_2$ + $C\underline{H}_3$); TLC (EtOAc) R_f 0.64.

3-Butyl-3-hydroxy-2-methylheptanoic acid (66h), a yellow oil, was obtained in 56% yield: IR (film) 2956, 2941, 2873, 1683, 1220, 981 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.32 (s, 1H, COO$\underline{H}$), 3.98-3.32 (q, 1H, $C\underline{H}CH_3$), 2.92-0.70 (m, 21H, $C\underline{H}_2$ + $C\underline{H}_3$); TLC (EtOAc) R_f 0.61.

3-Ethyl-2-methylheptanoic acid (66i), a colorless oil, was obtained in 100% yield: IR (film) 2959, 2944, 2875, 1709, 1461, 1199 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.49 (s, 1H, COO$\underline{H}$), 3.97-3.29 (q, 1H, $C\underline{H}CH_3$), 2.86-0.50 (m, 17H, $C\underline{H}_2$ + $C\underline{H}_3$); TLC (EtOAc) R_f 0.59.

3-Ethyl-2-methyloctanoic acid (66j), a clear, colorless oil, was obtained in 96% yield: IR (film) 2957, 2945, 2874, 1709, 1461, 1197 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.79 (s, 1H, COO$\underline{H}$), 4.00-3.48 (q, 1H, $C\underline{H}CH_3$), 2.89-0.60 (m, 19H, $C\underline{H}_2$ + $C\underline{H}_3$); TLC (EtOAc) R_f 0.66.

3-Hydroxy-2-methyl-3-trifluoromethylheptanoic acid, an orange oil, was obtained in 56% yield: IR (film) 2964, 2938, 2877, 1712, 1465, 1220 cm^{-1}; ^{1}H-NMR δ ($CDCl_3$) 8.03 (s, 1H, COO<u>H</u>), 3.95-3.28 (m, 1H, C<u>H</u>CH_3), 3.10-0.67 (m, 12H, C<u>H</u>$_2$ + C<u>H</u>$_3$); TLC (EtOAc) R_f 0.34.

General Procedure for the Preparation of ß-Lactones:[32] A portion of the ß-hydroxy acid (<u>ca</u> 500mg) and pyridine (25ml) were placed in an oven dried three-necked round bottom flask equipped with a thermometer, rubber septum, magnetic stirrer, and a nitrogen inlet. The solution was cooled to approximately 0 ^{o}C and benzenesulfonyl chloride (2 equiv.) was added dropwise via a syringe. The light yellow reaction mixture was left to stir for at least 15 minutes at the same temperature, after which it was stored in the refrigerator overnight.

The resulting orange/red solution was poured onto <u>ca.</u> 50g of ice, and the resulting mixture was extracted with three 20ml portions of ether. The combined ether extracts were washed sequentially with 5% hydrochloric acid, saturated sodium bicarbonate, distilled water, and finally brine. The ether phase was then dried over anhydrous magnesium sulfate, filtered, and then, rotary evaporated to yield the desired product. Purification of the crude material via recrystallization or

filtration through silica gel using specified solvents and final drying in vacuo gave the following ß-lactones.

Cyclohexyl ß-Lactones

9-Methyl-7-oxaspiro[5.3]nonan-8-one (57a), a yellow oil, was obtained in 97% yield; an analytical sample was secured via filtration through silica gel, employing dichloromethane as an eluent: IR (film) 2930, 2873, 2856, 1817, 1449, 1188 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.45-2.98 (q, 1H, J=7.8Hz, C<u>H</u>CH_3), 2.19-1.36 (e, 8H, C<u>H</u>$_2$), 1.36-1.12 (d, 3H,J=8.0Hz, C<u>H</u>CH_3); TLC (EtOAc) R_f 0.63.

9-Phenyl-7-oxaspiro[5.3]nonan-8-one (57b), a yellow oil, was obtained in 66% yield; an analytical sample was secured via filtration through silica gel, employing dichloromethane as an eluent. The evaporation of dichloromethane and further drying in vacuo afforded a yellow crystalline solid: mp 57-60 °C; IR (KBr) 2946, 2921, 2866, 1799, 1455, 1196 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.55-7.04 (m, 5H, Ar<u>H</u>), 4.47 (s, 1H, Ph<u>H</u>), 2.23-1.05 (e, 8H, C<u>H</u>$_2$); TLC (EtOAc) R_f 0.62.

9-Phenoxy-7-oxaspiro[5.3]nonan-8-one (57c), a white crystalline solid, was obtained in 77% yield;

purification via recrystallization from cyclohexane furnished the analytical sample: mp 89-90 °C; IR (KBr) 2937, 2860, 1797, 1493, 1201, 802 cm-^{1}; ^{1}H-NMR ($CDCl_3$) δ 7.34-7.12 (m, 5H, Ar$\underline{H}$), 4.47 (s, 1H, OPh$\underline{H}$), 2.00-1.00 (e, 10H, C$\underline{H}_2$); TLC (EtOAc) R_f 0.76.

9-Thiophenyl-7-oxaspiro[5.3]nonan-8-one (57d), an orange oil, was obtained in 74% yield; an analytical sample secured via filtration through silica gel, employing dichloromethane as an eluent: IR (film) 2937, 2931, 1822, 1448, 1259, 804 cm-^{1}; ^{1}H-NMR ($CDCl_3$) δ 7.50-6.80 (m, 5H, Ar$\underline{H}$), 5.81 (s, 1H, SPh$\underline{H}$), 2.55-0.57 (e, 10H, C$\underline{H}_2$); TLC (EtOAc) R_f 0.77.

9-p-Methoxyphenyl-7-oxaspiro[5.3]nonan-8-one (57e), a white crystalline solid, was obtained in 84% yield; an analytical sample was secured via recrystallization from pentane: mp 56-58 °C; IR (film) 2938, 2960, 1813, 1449, 1253, 806 cm-^{1}; ^{1}H-NMR ($CDCl_3$) δ 7.43-6.69 (m, 4H, $C_6\underline{H}_4$), 4.35 (s, 1H, C$\underline{H}C_6H_4OCH_3$), 3.8 (s, 3H, OCH_3), 2.55-1.10 (e, 10H, C$\underline{H}_2$), TLC (EtOAc) R_f 0.76.

9-Naphthyl-7-oxaspiro[5.3]nonan-8-one (57f), an orange oil, was obtained in 40% yield; an analytical sample was obtained via filtration through silica gel, using dichloromethane as an eluent: IR (film) 2933,

1810, 1545, 1262, 801 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.13-6.25 (m, 7H, $C_{10}\underline{H}_7$), 5.13 (s, 1H, $C\underline{H}C_{10}H_7$) 4.25-1.25 (e, 10H, $C\underline{H}_2$); TLC (EtOAc) 0.78.

4,4-Diethyl-2-phenyloxetan-2-one (61), an orange crystalline solid, was obtained in 95% yield; was used without further purification in the next reaction: mp 59-60 ^{o}C; IR (KBr) 2972, 2944, 1806, 1453, 1206, 703 cm^{-1}; ^{1}H-NMR ($CDCl_3$) 7.56- 6.92 (m, 5H, Ar$\underline{H}$), 4.65 (s, 1H, Ph$\underline{H}$), 2.35-0.54 (m, 10H, $C\underline{H}_2C\underline{H}_3$); TLC (EtOAc) R_f 0.69.

Acyclic ß-lactones

4-Ethyl-3,4-dimethyloxetan-2-one(67a), a brown oil, was obtained in quantitative yield; an analytical sample was secured via filtration through silica gel, employing dichloromethane as an eluent: : IR (film) 2974, 2933, 1817, 1449, 1294 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.58-3.00 (q, 1H, J=7.8Hz, $C\underline{H}CH_3$), 2.09-0.30 (m, 11H, $C\underline{H}_2$ + $C\underline{H}_3$); TLC (EtOAc) R_f 0.69.

3,4-Dimethyl-4-propyloxetan-2-one (67b), a brown oil, was obtained in 51% yield; an analytical sample was secured via column chromatography, employing dichloromethane as an eluent: IR (film) 2965, 2940, 2877, 1820, 1468, 1216 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.58-3.00 (q, 1H, J=7.8Hz, $C\underline{H}CH_3$), 2.09-0.30 (m, 13H, $C\underline{H}_2$ + $C\underline{H}_3$);

TLC (EtOAc) R_f 0.72.

4-Butyl-3,4-dimethyloxetan-2-one (67d), a brown oil, was obtained in 85% yield; an analytical sample was secured via filtration through silica gel, employing dichloromethane as an eluent: IR (film) 2961, 2938, 2875, 1819, 1468, 1209 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.58-3.02 (q, 1H, J=7.8Hz, C$\underline{H}$$CH_3$), 2.25-0.50 (m, 15H, C$\underline{H}_2$ + C$\underline{H}_3$); TLC (EtOAc) R_f 0.66.

3,4-Dimethyl-4-pentyloxetan-2-one (67e), an orange oil, was obtained in 63% yield; a pure analytical sample was obtained via filtration through silica gel, using dichloromethane as an eluent: IR (film) 2958, 2936, 2863, 1819, 1466, 1111 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.54-3.11 (q, 1H, J=7.8Hz, C$\underline{H}$$CH_3$), 2.14-0.44 (m, 17H, C$\underline{H}_2$ + C$\underline{H}_3$); TLC (EtOAc) R_f 0.71.

4-Hexyl-3,4-dimethyloxetan-2-one (67g), an orange oil, was obtained in 94% yield; a pure analytical sample secured via filtration through silica gel (CH_2Cl_2): IR (film) 2958, 2934, 2861, 1819, 1487, 1200cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.55-3.06 (q, 1H, J=7.8Hz, C$\underline{H}$$CH_3$), 2.16-0.45 (m, 19H, C$\underline{H}_2$ + C$\underline{H}_3$); TLC (EtOAc) R_f 0.75.

4,4-Diethyl-3-methyloxetan-2-one (67c), an orange

oil, was obtained in 99% yield; purification by filtration through silica gel column, employing dichloromethane as an eluent: IR (film) 2971, 2940, 2893, 1819, 1457, 1083 cm-^{1}; ^{1}H-NMR ($CDCl_3$) δ 3.55-3.07 (q, 1H, J=7.8 Hz, C$\underline{H}$C$\underline{H}_3$), 2.12-0.72 (m, 13H, C$\underline{H}_2$ + C$\underline{H}_3$); TLC (CH_2Cl_2) R_f 0.95.

3-Methyl-4,4-dipropyloxetan-2-one (67f), an orange oil, was obtained in 63% yield; purification via filtration through silica gel column (CH_2Cl_2) afforded an analytical sample: IR (film) 2962, 2939, 2877, 1820, 1466, 1212 cm-^{1}; ^{1}H-NMR ($CDCl_3$) δ 3.56-3.05 (q, 1H, J=7.8Hz, C$\underline{H}$C$\underline{H}_3$), 2.46-0.68 (m, 17H, C$\underline{H}_2$ + C$\underline{H}_3$); TLC (EtOAc) R_f 0.75.

4,4-Dibutyl-3-methyloxetan-2-one (67h), an orange oil, was obtained in 67% yield; filtration through silica gel column employing dichloromethane as an eluent rendered the material sufficiently pure for analytical purpose: IR (film) 2959, 2937, 2874, 1821, 1467, 1209 cm-^{1}; ^{1}H-NMR ($CDCl_3$) δ 3.56-3.48 (q, 1H, J=7.8Hz, C$\underline{H}$C$\underline{H}_3$), 2.48-0.63 (m, 21Hz, C$\underline{H}_2$ + C$\underline{H}_3$); TLC (EtOAc) R_f 0.75.

4-Butyl-4-ethyl-3-methyloxetan-2-one (67i), a yellow oil, was obtained in 79% yield; an analytical

sample secured via filtration through silica gel, employing dichloromethane as an eluent: IR (film) 2961, 2941, 2875, 1820, 1462, 1212 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.69-3.10 (q, 1H, J=7.8Hz, C<u>H</u>CH_3), 2.56-0.20 (m, 17H, C<u>H</u>$_2$ + C<u>H</u>$_3$); TLC (EtOAc) R_f 0.73.

4-Ethyl-3-methyl-4-pentyloxetan-2-one (67j), a brown oil, was obtained in 70% yield; purification was accomplished by filtration through a silica gel column (CH_2Cl_2) IR (film) 2958, 2936, 2873, 1820, 1462, 1211 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.60-3.07 (q, 1H, J=7.8Hz, C<u>H</u>CH_3), 2.18-0.55 (m, 19H, C<u>H</u>$_2$ + C<u>H</u>$_3$); TLC (EtOAc) R_f 0.69.

4-Butyl-4-trifluoromethyl-3-methyloxetan-2-one, an orange oil was obtained in 80% yield; purification was accomplished by filtration through a silica gel, employing ethyl acetate as an eluent: IR (film) 2965, 2939, 2879, 1852, 1470, 1204 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 4.07-3.47 (q, 1H, J=7.2Hz, C<u>H</u>CH_3), 2.22-0.35 (m, 12H, C<u>H</u>$_2$ + C<u>H</u>$_3$); TLC (EtOAc) R_f 0.73.

General Procedure for the Preparation of ß,γ Unsaturated Acids:[32] A 200mg portion of a ß-lactone (<u>ca.</u> 200mg was dissolved in diethyl ether (25ml) in an oven-dried three-necked round bottom flask. To this was

added 2 equivalents of magnesium bromide etherate in one portion. The reaction was allowed to proceed with stirring overnight under nitrogen atmosphere.

The reaction was quenched by the slow addition of distilled water (10ml). The water and the ether layers were separated and the ether phase was dried over anhydrous magnesium sulfate, filtered, and rotary evaporated to furnish the desired ß,γ-unsaturated acid. Purification via recrystallization (using suitable solvents) or base extraction techniques rendered the material sufficiently pure for analytical data acquisition.

2-(1-Cyclohexenyl)-2-acetic acids

2-(1-Cylohexenyl)-2-methylacetic acid (58a), a light-yellow oil, was obtained in 99% yield; purification of the oil was not possible, and thus the crude material was used directly in the next step: IR(film) 2970, 2933, 2862, 1708, 1458, 1159 cm^{-1}. ^1H-NMR ($CDCl_3$) δ 11.92 (s, 1H, COO<u>H</u>), 5.78-5.41 (br. s, 1H, =C<u>H</u>), 3.30-2.87 (q, J=7.2, 1H, C<u>H</u>CH_3), 2.29-1.33 (e, 8H, C<u>H</u>$_2$), 2.29-0.95 (m, 11H, C<u>H</u>$_2$); TLC(EtOAc) R<u>f</u> 0.58; HRMS calcd for $C_9H_4O_2$ 154.0994, found 154.0994.

2-(1-Cyclohexenyl)-2-phenylacetic acid (58b), a white, crystalline solid was obtained in 74% yield;

recrystallization from hexane furnished the analytical sample: mp 80-82 ^{o}C; IR (KBr) 3088, 3083, 2988, 1697, 1220, 700 cm-^{1}; ^{1}H-NMR ($CDCl_3$) δ 7.60-7.00 (m, 5H, Ar$\underline{H}$), 5.65 (s, 1H, =C$\underline{H}$), 4.27 (s, 1H, PhC$\underline{H}$), 2.30-1.51 (e, 8H, C$\underline{H}_2$); TLC (EtOAc) R_f 0.53; HRMS calcd for $C_{14}H_{16}O_2$ 216.1151, found 216.1150.

2-(1-Cyclohexenyl)-2-phenoxyacetic acid (58c), a white, highly crystalline solid,was obtained in 99% yield; recrystallization from hexane afforded the analytical sample: mp 95-98 ^{o}C; IR(KBr) 3030, 3003, 2934, 1711, 1490, 1296 cm-^{1}; ^{1}H-NMR (DMSO) δ 7.65-7.14 (m, 5H, Ar$\underline{H}$), 5.68-5.14 (s, 1H, =C$\underline{H}$), 4.18 (s, 1H, OPhC$\underline{H}$), 2.23-1.29 (e, 8H, C$\underline{H}_2$); TLC(EtOAc) R_f 0.63; HRMS calcd for $C_{14}H_{16}O_3$ 232.1100, found 250.0762.

2-(1-Cyclohexenyl)-2-thiophenylacetic acid (58d), a dark brown oil, was obtained in 80% yield; an analytical sample was secured via purification by silica gel column chromatography, employing CH_2Cl_2 as an eluent: IR(film) 3074, 3060, 2927,1708, 1439, 1293 cm-^{1} ; ^{1}H-NMR ($CDCl_3$) δ 12.38 (s, 1H, COO$\underline{H}$), 7.59-7.00 (m, 5H, Ar$\underline{H}$), 5.80-5.40 (br. s, 1H, =C$\underline{H}$), 4.20 (s, 1H, SPhC$\underline{H}$), 2.41-0.39 (e, 8H, C$\underline{H}_2$); TLC(EtOAc) R_f 0.35; HRMS calcd for $C_{14}H_{16}O_2S$ 248.0872, found 248.0869.

2-(1-Cyclohexenyl)-2-p-methoxyphenylacetic acid (58e), a clear, colorless oil, was obtained in 92% yield: IR (film) 2932, 2836, 1705, 1512,1214, 1179 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.30-6.68 (m, 4H, $C_6\underline{H}_4$), 5.78-5.48 (br. s, 1H, =C$\underline{H}$), 4.27- 4.09 (br. s, 1H, $C_6H_4OCH_3C\underline{H}$), 3.88 (s, 3H, -OC$\underline{H}_3$), 2.19-0.65 (e, 8H, C$\underline{H}_2$); TLC(EtOAc) R_f 0.62; HRMS calcd for $C_{15}H_{18}O_3$, 246.1256, found 246.1256.

2-(1-Cyclohexenyl)-2-naphthylacetic acid (58f), a brown oil, was obtained in 93% yield: IR (film) 3048, 2929, 2856, 1707, 1215, 1167 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 8.04-6.95 (m, 7H, Ar$\underline{H}$), 5.75-5.41 (br. s, 1H, =C$\underline{H}$), 5.06-4.79 (s, 1H, $C_{10}H_7C\underline{H}$), 2.18-0.48 (e, 8H, C$\underline{H}_2$); TLC(EtOAc) R_f 0.30; HRMS calcd for $C_{18}H_{18}O_2$ 266.1307, found 266.1307.

3-Ethyl-2-phenyl-3-pentenoic acid (62), a brown oil, was obtained in 98% yield: IR(film) 2968, 2935, 1708, 1454, 1214, 699 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 7.68-6.98 (m, 5H, Ar$\underline{H}$), 5.79-5.23 (m, 1H, =C$\underline{H}$), 4.90 (s, 1H, PhC$\underline{H}$), 2.19-0.74(m, 8H, C$\underline{H}_2$ + C$\underline{H}_3$); TLC(EtOAc) R_f 0.40; HRMS calcd for $C_{13}H_{16}O_2$ 204.1151, found 204.1157.

<u>2,3-Dialkyl-3-Alkenoic acids</u>

2,3-Dimethyl-3-pentenoic acid (68a), a yellow oil,

12.83 (s, 1H, COO$\underline{H}$), 5.66-4.90 (m, 1H, =C$\underline{H}$), 3.88-3.44 (q, 1H, J=7.2Hz, C$\underline{H}$CH$_3$, ($\underline{E}$)), 3.44-2.93 (q, 1H, J=7.0Hz, C$\underline{H}$CH$_3$, ($\underline{Z}$)), 2.39-0,49 (m, 15H, C$\underline{H}_2$ + C$\underline{H}_3$); TLC (EtOAc) R_f 0.60; HRMS calcd for $C_{10}H_{18}O_2$ 170.1307, found 170.1307.

2,3-Dimethyl-3-nonenoic acid (68g), an orange oil, was secured in 56% yield: IR (film) 2959, 2931, 2859,1708, 1460, 1234 cm-^{1}; ^{1}H-NMR ($CDCl_3$) δ 13.20 (s, 1H, COO$\underline{H}$), 5.52-4.75 (m, 1H, =C$\underline{H}$), 3.88-3.41 (q, 1H, J=7.2Hz, C$\underline{H}$CH$_3$ ($\underline{E}$)), 3.41-2.82 (q, 1H, J=7.0Hz, C$\underline{H}$CH$_3$ ($\underline{Z}$)), 2.68-0.40 (m, 17H, C$\underline{H}_2$ + C$\underline{H}_3$); TLC (EtOAc) R_f 0.69; HRMS calcd for $C_{11}H_{20}O_2$ 184.1446, found 184.1463.

3-Ethyl-2-methyl-3-pentenoic acid (68c), an orange oil, was obtained in 60% yield: IR (film) 3047, 3006, 2962, 1706, 1216, 756 cm-^{1}; ^{1}H-NMR ($CDCl_3$) δ 12.71 (s, 1H, COO$\underline{H}$), 5.68-5.10 (m, 1H, =C$\underline{H}$), 3.88-3.30 (q, 1H, J=7.2Hz, C$\underline{H}$CH$_3$, ($\underline{E}$)), 3.30-2.80 (q, 1H, J=7.0Hz, C$\underline{H}$CH$_3$, ($\underline{Z}$)), 2.38-0.66 (m, 11H, C$\underline{H}_2$ + C$\underline{H}_3$); TLC (EtOAc) R_f 0.53; HRMS calcd for $C_{18}H_{14}H_2$ 142.0994, found 141.0009.

2-Methyl-3-propyl-3-hexenoic acid (68f), a light-yellow oil, was obtained in quantitative yield: IR (film) 2962, 2936, 2875, 1708, 1459,1230 cm-^{1}; ^{1}H-NMR ($CDCl_3$) δ 12.80 (s, 1H, COO$\underline{H}$), 5.50-4.98 (m, 1H, =C$\underline{H}$),

was obtained in 94% yield: IR (film) 2980, 2940, 2888, 1708, 1413, 1235 cm-$^{-1}$; ^{1}H-NMR ($CDCl_3$) δ 13.00 (s, 1H, COO$\underline{H}$), 5.70-5.10 (m, 1H, =C$\underline{H}$), 3.89-3.41 (q, 1H, J=7.2Hz, C$\underline{H}CH_3$, ($\underline{E}$)), 3.41-2.81 (q, 1H, J=7.0Hz, C$\underline{H}CH_3$, ($\underline{Z}$)), 2.40-0.44 (m, 9H, C$\underline{H}_2$ + C$\underline{H}_3$); TLC (EtOAc) R_f 0.60 ; HRMS calcd for $C_7H_{12}O_2$ 128.0838, found 128.0837.

2,3-Dimethyl-3-hexenoic acid (68b), a yellow oil, was obtained in 64% yield: IR (film) 2965, 2937, 2876, 1708, 1480, 1233 cm-$^{-1}$; ^{1}H-NMR ($CDCl_3$) δ 12.85 (s, 1H, COO$\underline{H}$), 5.52-4.80 (m 1H, =C$\underline{H}$), 3.87-3.35 (q, 1H, J=7.2Hz, C$\underline{H}CH_3$, ($\underline{E}$)), 3.35-2.85 (q, 1H, J=7.0Hz, C$\underline{H}CH_3$, ($\underline{Z}$)), 2.20-0.49 (m, 11H, C$\underline{H}_2$ + C$\underline{H}_3$); TLC (EtOAc) R_f 0.71; HRMS calcd for $C_8H_{14}O_2$ 142.0994, found 142.0994.

2,3-Dimethyl-3-heptenoic acid (68d), a light-yellow oil, was obtained in 74% yield: IR (film) 2962, 2935, 2874, 1708, 1459, 1228 cm-$^{-1}$; ^{1}H-NMR ($CDCl_3$) δ 12.91 (s, 1H, COO$\underline{H}$), 5.57-5.04 (t, 1H, =C$\underline{H}$), 3.89-3.40 (q, 1H, J=7.2Hz, C$\underline{H}CH_3$, ($\underline{E}$)), 3.32-2.89 (q, 1H, J=7.0Hz, C$\underline{H}CH_3$, ($\underline{Z}$)), 2.44-0.50 (m, 13H, C$\underline{H}_2$ + C$\underline{H}_3$; TLC (EtOAc) R_f 0.64; HRMS calcd for $C_9H_{16}O_2$ 156.1151, found 156.1147.

2,3-Dimethyl-3-octenoic acid (68e), a light-yellow oil, was secured in quantitative yield: IR (film) 2960, 2929, 2860, 1708, 1460, 1233 cm-$^{-1}$; ^{1}H-NMR ($CDCl_3$) δ

3.77-2.49 (q, 1H, J=7.2Hz, C<u>H</u>CH_3, (<u>E</u>)), 3.49-2.80 (q, 1H, J=7.0Hz, C<u>H</u>CH_3, (<u>Z</u>)), 2.72-0.50 (m, 15H, C<u>H</u>$_2$ + C<u>H</u>$_3$); TLC (EtOAc) R_f 0.61; HRMS calcd for $C_{10}H_{18}O_2$ 170.1307, found 170.1304.

3-Butyl-2-methyl-heptenoic acid (68h), a light-yellow oil, was obtained in quantitative yield: IR (film) 2960, 2932, 2874, 1707, 1459, 1231 cm-^{1}; ^{1}H-NMR ($CDCl_3$) δ 12.43 (s, 1H, COO<u>H</u>), 5.48-4.84 (m, 1H, =C<u>H</u>), 3.74-3.26 (q, 1H, J=7.2Hz, C<u>H</u>CH_3, (<u>E</u>)), 3.26-2.70 (q, 1H, J=7.0Hz, C<u>H</u>CH_3, (<u>Z</u>)), 2.60-0.40 (m, 19H, C<u>H</u>$_2$ + C<u>H</u>$_3$);TLC (EtOAc) R_f 0.70; HRMS calcd for $C_{12}H_{22}O_2$ 198.1621, found 198.1620.

3-Ethyl-2-methyl-heptenoic acid (68i), a yellow oil, was obtained in 77% yield: IR (film) 2962, 2935, 2875, 1707, 1413, 1234 cm-^{1}; ^{1}H-NMR ($CDCl_3$) δ 12.70 (s, 1H, COO<u>H</u>), 5.64-5.03 (m, 1H, =C<u>H</u>), 3.60-3.30 (qd, 1H, J=7.2Hz, C<u>H</u>CH_3 (<u>E</u>)), 3.30-2.80 (q, 1H, J=7.0Hz, C<u>H</u>CH_3 (<u>Z</u>)), 2.40-0.44 (m, 15H, C<u>H</u>$_2$ + C<u>H</u>$_3$); TLC (EtOAc) R_f 0.67; HRMS calcd for $C_{10}H_{18}$ 170.1307, found 170.1305.

3-Ethyl-2-methyl-3-octenoic acid (68j), a yellow oil, was secured in 90% yield: IR (film) 2960, 2933, 2861, 1707, 1461, 1234 cm-^{1}; ^{1}H-NMR ($CDCl_3$) δ 12.35 (s, 1H, COO<u>H</u>), 5.78-4.98 (m, 1H, =C<u>H</u>), 3.75-3.26 (qd, 1H,

J=7.2Hz, C<u>H</u>CH_3, (<u>E</u>)), 3.26-2.75 (q, 1H, J=7.0Hz, C<u>H</u>CH_3, (<u>Z</u>)), 2.32-0.35 (m,17H, C<u>H_2</u> + C<u>H_3</u>); TLC (EtOAc) R_f 0.68; HRMS calcd for $C_{11}H_{20}O_2$ 184.1446, found 184.1463.

The Preparation of 1,1,1-Trifluoromethyl-2-hexanone:[33] Into a 500ml three-necked oven-dried bottom flask fitted with a nitrogen inlet, a reflux condenser, and a thermometer was placed crushed magnesium metal (14.4g, 592mmol). To the metal was then slowly added <u>n</u>-bromobutane (63.6ml, 592mmol), diluted with anhydrous diethyl ether (150ml), from a 250ml separatory funnel. The Grignard reaction started after the addition of 20ml of the 1-bromobutane solution as evidenced by the refluxing of the reaction mixture, with the temperature rising and remaining constant at <u>ca.</u> 35 ^{o}C. The addition was continued over a period of 40 minutes, during which time the reaction became dark-grey in color. Trifluoroacetic acid (15.4 ml, 200mmol) was slowly added via a syringe over a 1 hour period, while the reaction mixture was maintained at <u>ca.</u> 10^{o}C with an ice-bath. The reaction mixture was stirred for 3 hours under a nitrogen atmosphere after which time it was quenched by the careful addition of distilled water (50ml) followed by 150ml 6N hydrochloric acid from a separatory funnel. The aqueous and the organic layers were separated. The aqueous layer was then extracted three times with

diethyl ether (100ml), and the combined ether extracts were finally dried over anhydrous magnesium sulfate, filtered, and fractionally distilled to afford a colorless liquid (bp 90-92°C) in 30% yield. The identity of the ketone obtained was confirmed by IR and NMR spectra.

IR (film): 2966, 2940, 1766, 1211, 1154, 1032 cm^{-1}; ^{1}H-NMR ($CDCl_3$): δ 3.90-3.20 (quint., 2H, $C\underline{H}_2CO$), 2.88-2.40 (t, 2H, $C\underline{H}_2$), 2.04-0.66 (m, 5H, $C\underline{H}_3C\underline{H}_2$).

Dilution Experiment:

Five oven-dried 50ml three-necked round bottom flasks equipped with nitrogen inlets, stirring bars and rubber septa were separately set up. To each was introduced 100mg (.490 mmol) of 9-Phenyl-7-oxaspiro[5.3]nonan-5-one spiro-ß-lactone. Then, anhydrous ether was added in 5ml increments so that the concentrations of the samples were varied from 0.098M to 0.020M from flask 1 to flask 5. With constant stirring, magnesium bromide (.252g, 0.997 mmol) was added at once in each reaction flask. The reaction mixtures were allowed to stir for 5 minutes under nitrogen atmosphere at ambient temperature. The progress of each reaction was then constantly monitored and followed by thin layer chromatography (TLC) whereby samples were collected and immediately spotted on TLC slides along with the pure starting material after every 5 minutes. The reactions

were judged to be complete by observing the disappearance of the starting material as well as the appearance of a new product. For results refer to Table III in the results and discussion section.

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Figure I: IR spectrum of 3-cyclohexyl-3-hydroxy-2-phenylpropionic acid.

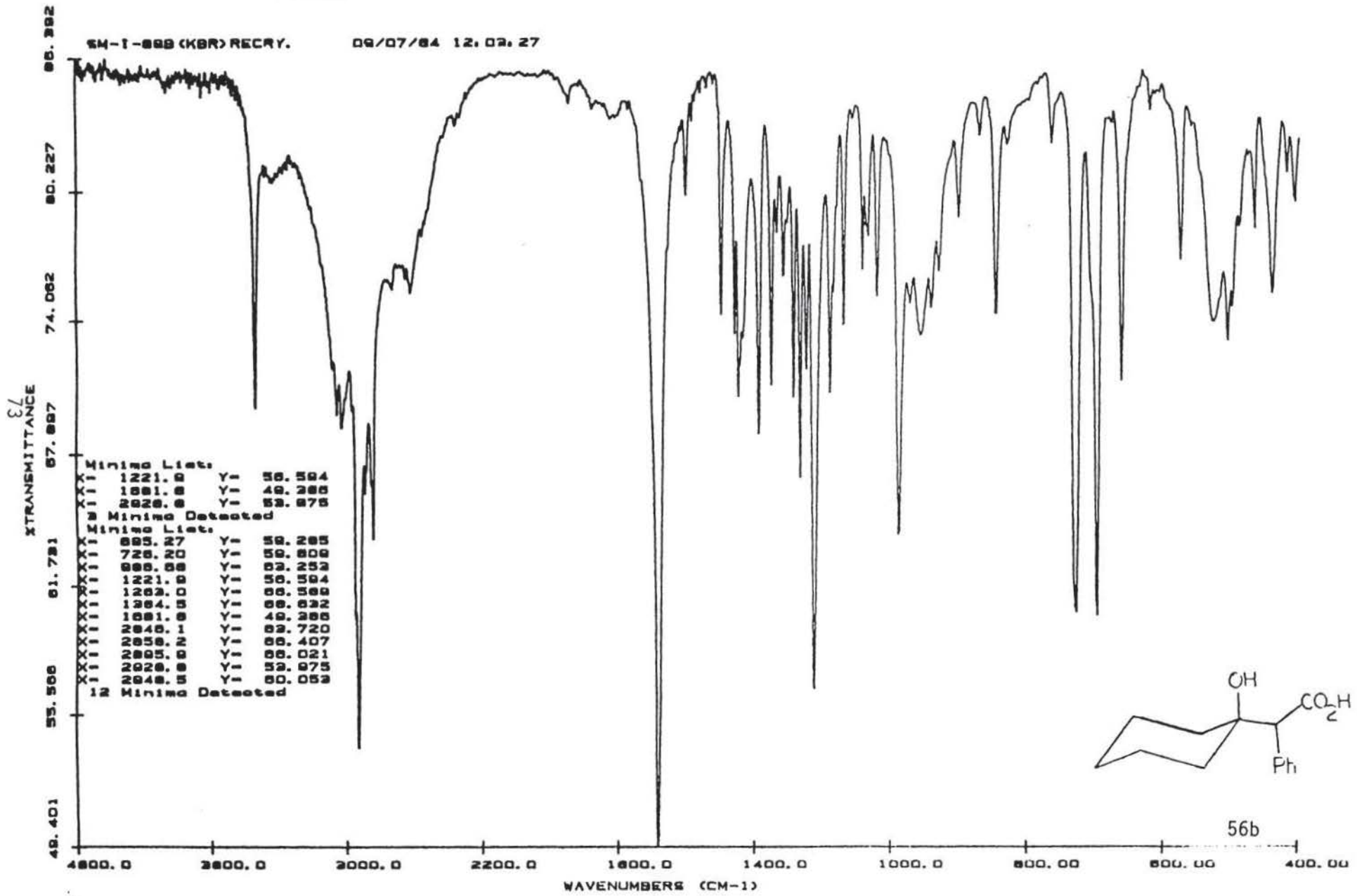
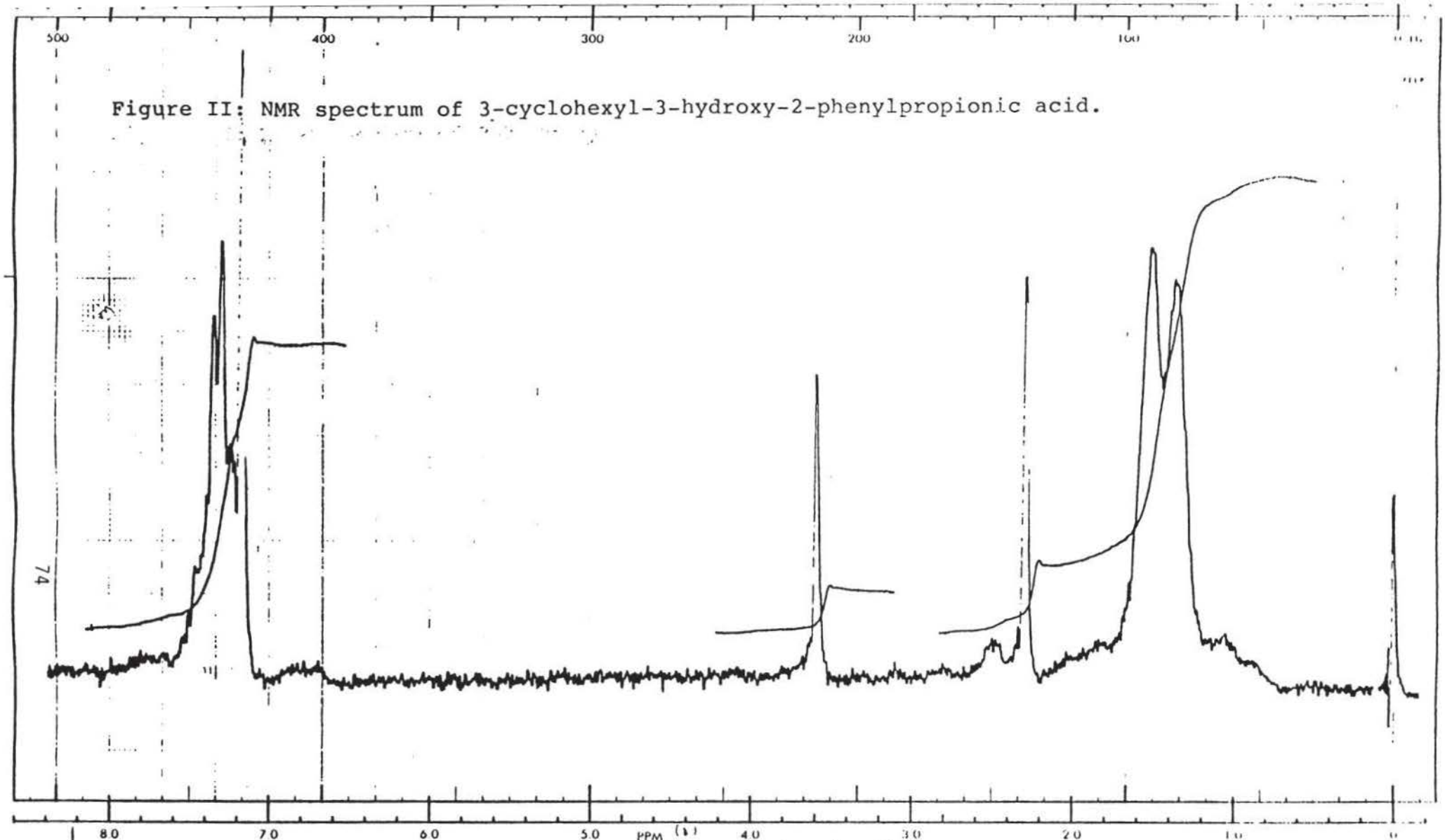


Figure II: NMR spectrum of 3-cyclohexyl-3-hydroxy-2-phenylpropionic acid.



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INTEGRAL AMPLITUDE: 4
SPINNING RATE (RPS): 40

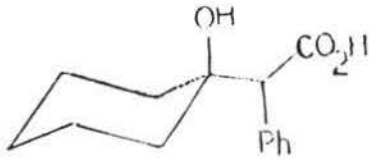
MANUAL
SWEEP TIME (SEC): [50] [250]
SWEEP WIDTH (Hz): [25] [50] [100] [250] [500]
FILTER: [1] [2] [3] [4] [5] [6] [7] [8]
RF POWER LEVEL: 24

AUTO [ ]
(250)
(500)
(2)
(.05)

SAMPLE: SM-3-81B

SOLVENT: DMSO

REMARKS:



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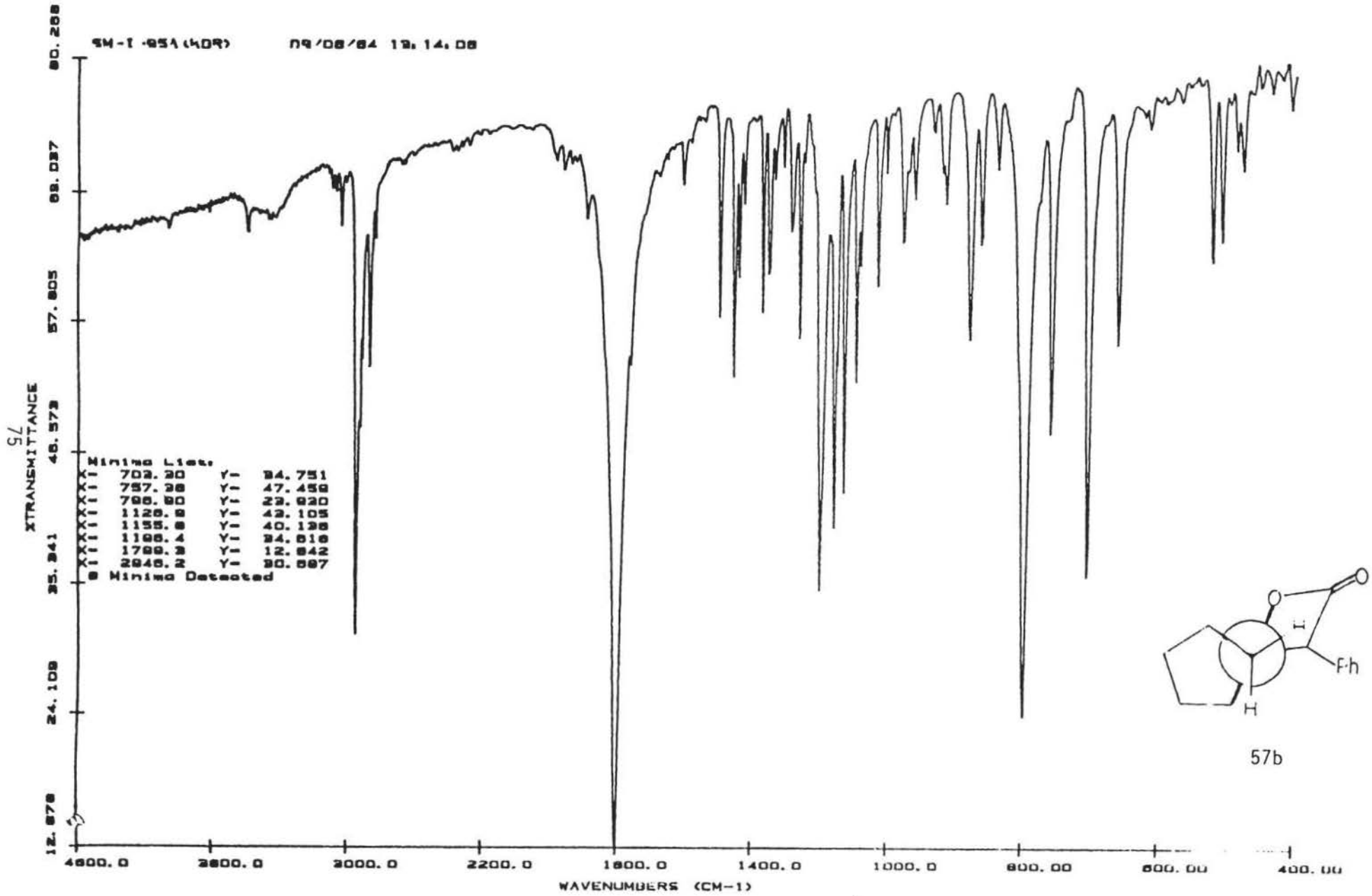
OPERATOR: Abdulkadir

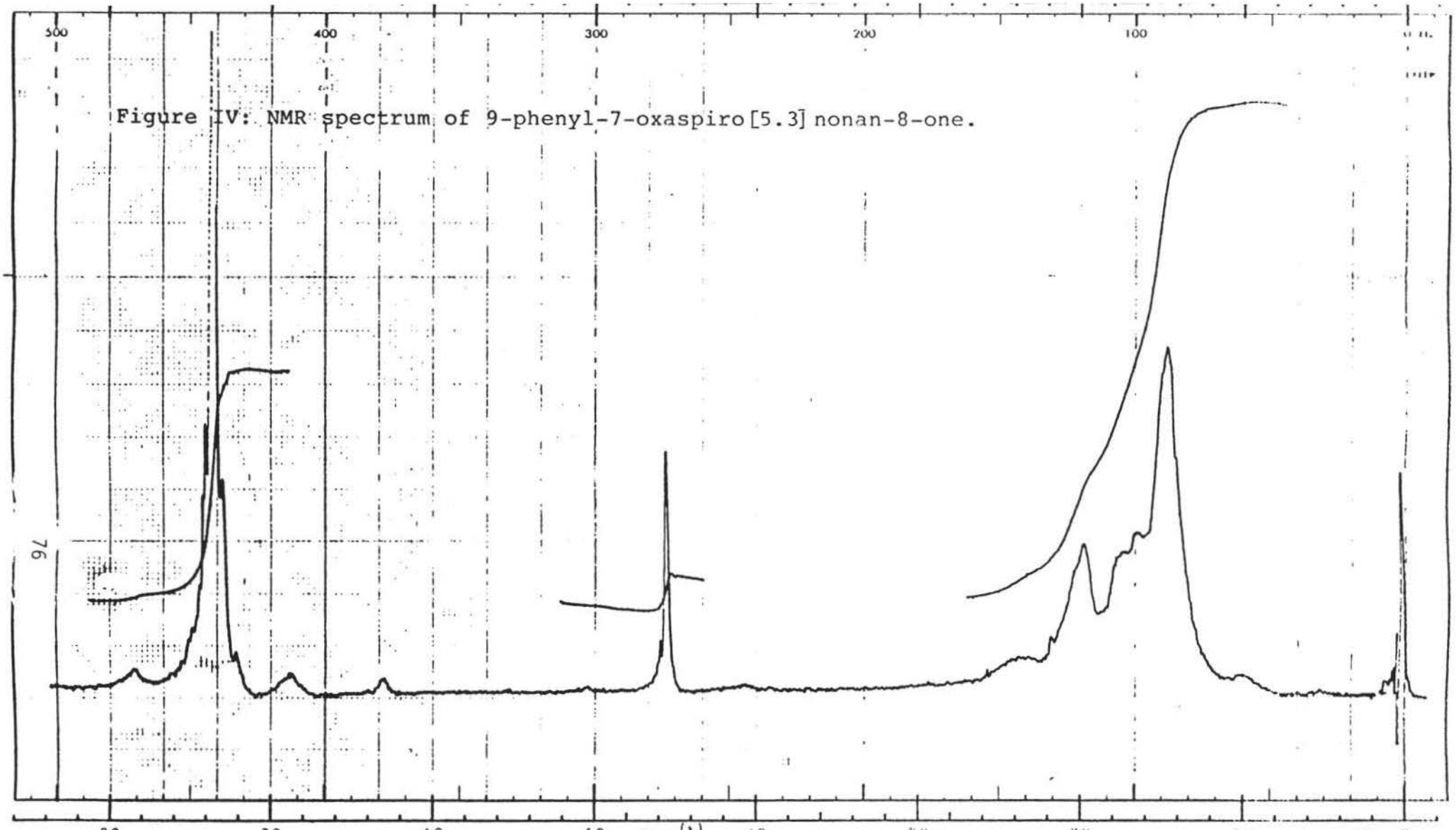
60 MHz NMR SPECTRUM NO. 56b

Figure III: IR spectrum of 9-phenyl-7-oxaspiro[5.3]nonan-8-one.



57b

Figure IV: NMR spectrum of 9-phenyl-7-oxaspiro[5.3]nonan-8-one.



SWEEP OFFSET (Hz): 0.00
SPECTRUM AMPLITUDE: 20
INTEGRAL AMPLITUDE: 5
SPINNING RATE (RPS): 40

MANUAL
SWEEP TIME (SEC): [50] [250]
SWEEP WIDTH (Hz): [25] [50] [100] [250] [500]
FILTER. [1] [2] [3] [4] [5] [6] [7] [8]
RF POWER LEVEL: .04

AUTO [ ]
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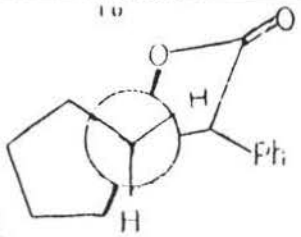
(500)
(2)
(05)

SAMPLE: SM-I-95A

SOLVENT: $CDCl_3$

REMARKS:



60 MHz NMR SPECTRUM NO

DATE: 08/17/1989

OPERATOR: Mazumder

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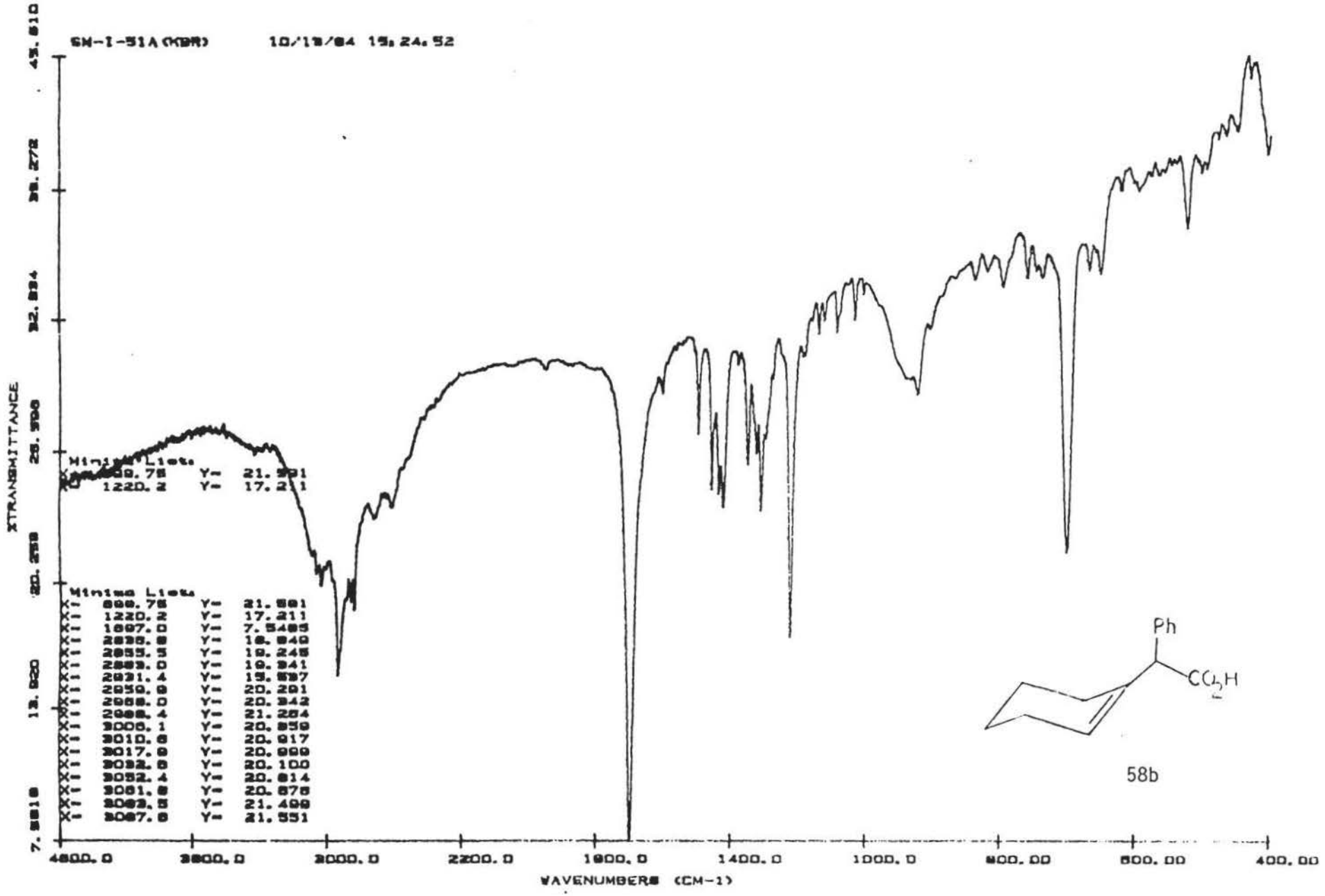
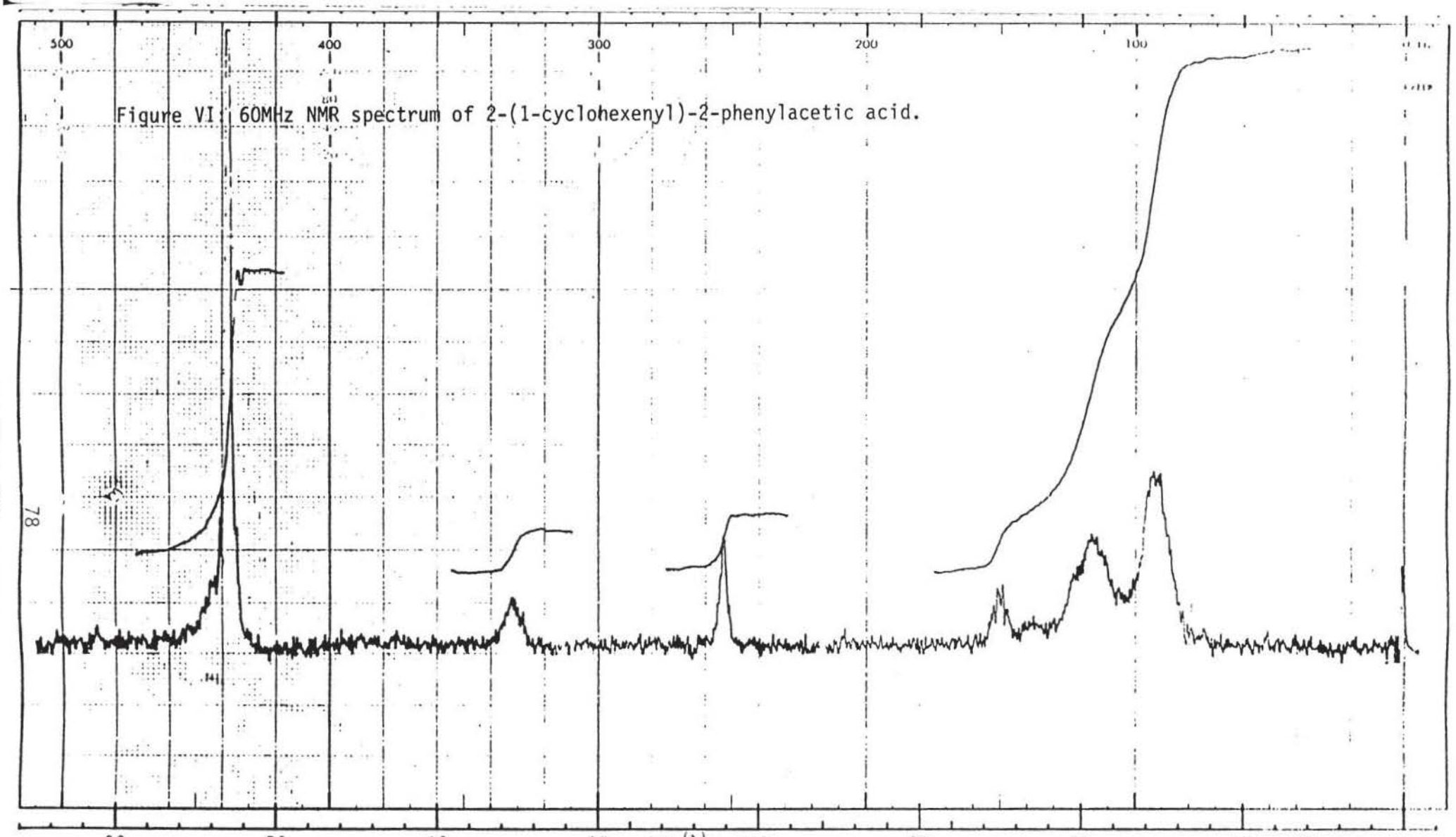
Figure V: IR spectrum of 2-(1-cyclohexenyl)-2-phenylacetic acid.



58b

Figure VI: 60MHz NMR spectrum of 2-(1-cyclohexenyl)-2-phenylacetic acid.



SWEEP OFFSET (Hz): 0.00
SPECTRUM AMPLITUDE: 30
INTEGRAL AMPLITUDE: 8
SPINNING RATE (RPS): 48

MANUAL
SWEEP TIME (SEC): 50 (250)
SWEEP WIDTH (Hz): 25 50 100 250 (500)
FILTER: 1 (2) 3 4 5 6 7 8
RF POWER LEVEL: .04

AUTO
(250)
(500)
(2)
(.05)

SAMPLE: 57 DA

REMARKS:

SOLVENT: DMSO

DATE: 09/12/1988

OPERATOR: Stephen Hanessian

60 MHz NMR SPECTRUM NO 58b

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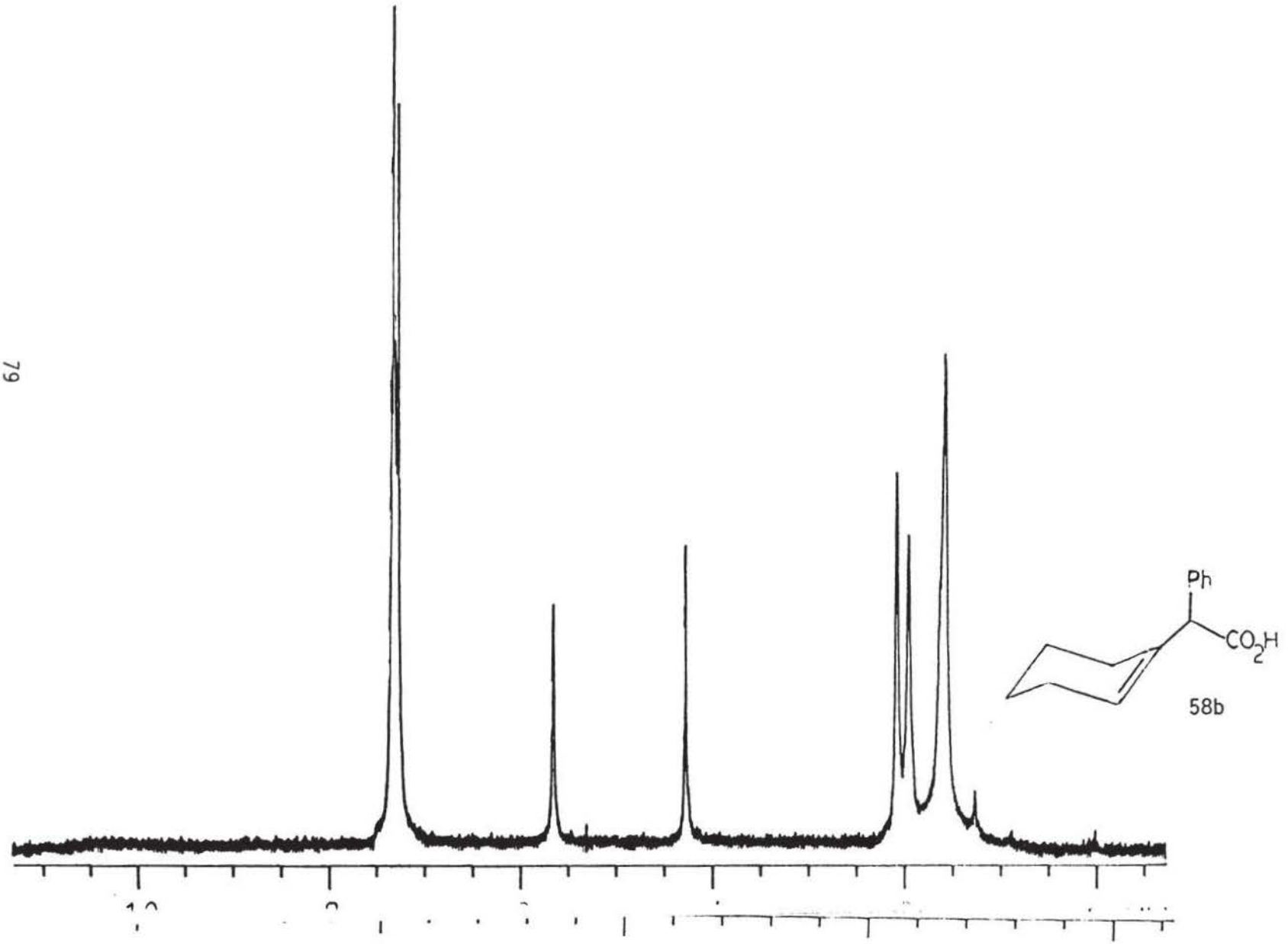
Figure VII: 500MHz NMR spectrum of 2-(1-cyclohexenyl)-2-phenylacetic acid.



58b

Figure VIII: C-NMR spectrum of 2-(1-cyclohexenyl)-2-phenylacetic acid.

Figure VIII: C-NMR spectrum of 2-(1-cyclohexenyl)-2-phenylacetic acid.

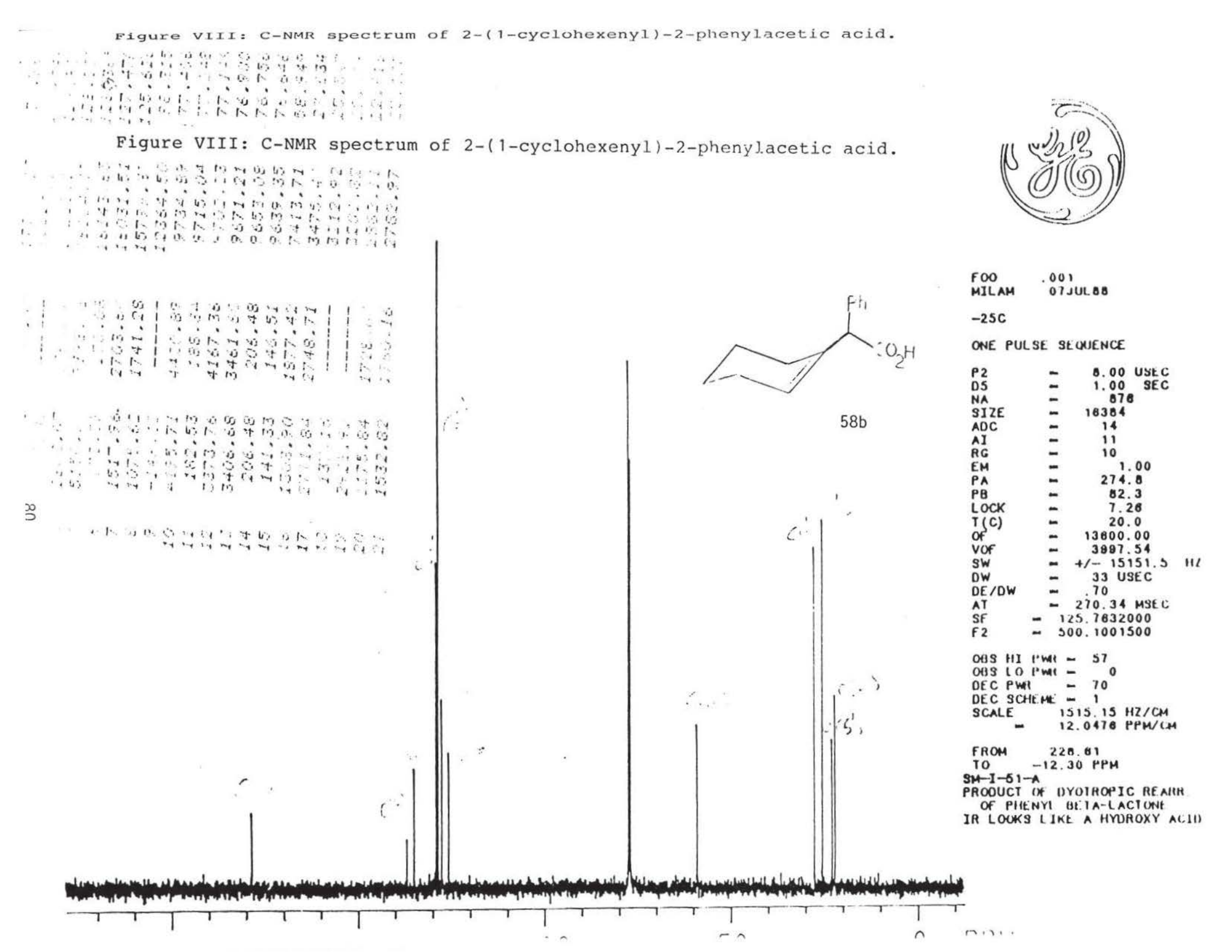


Figure 1x: Mass spectrum of 2-(1-cyclohexenyl)-2-phenylacetic acid.

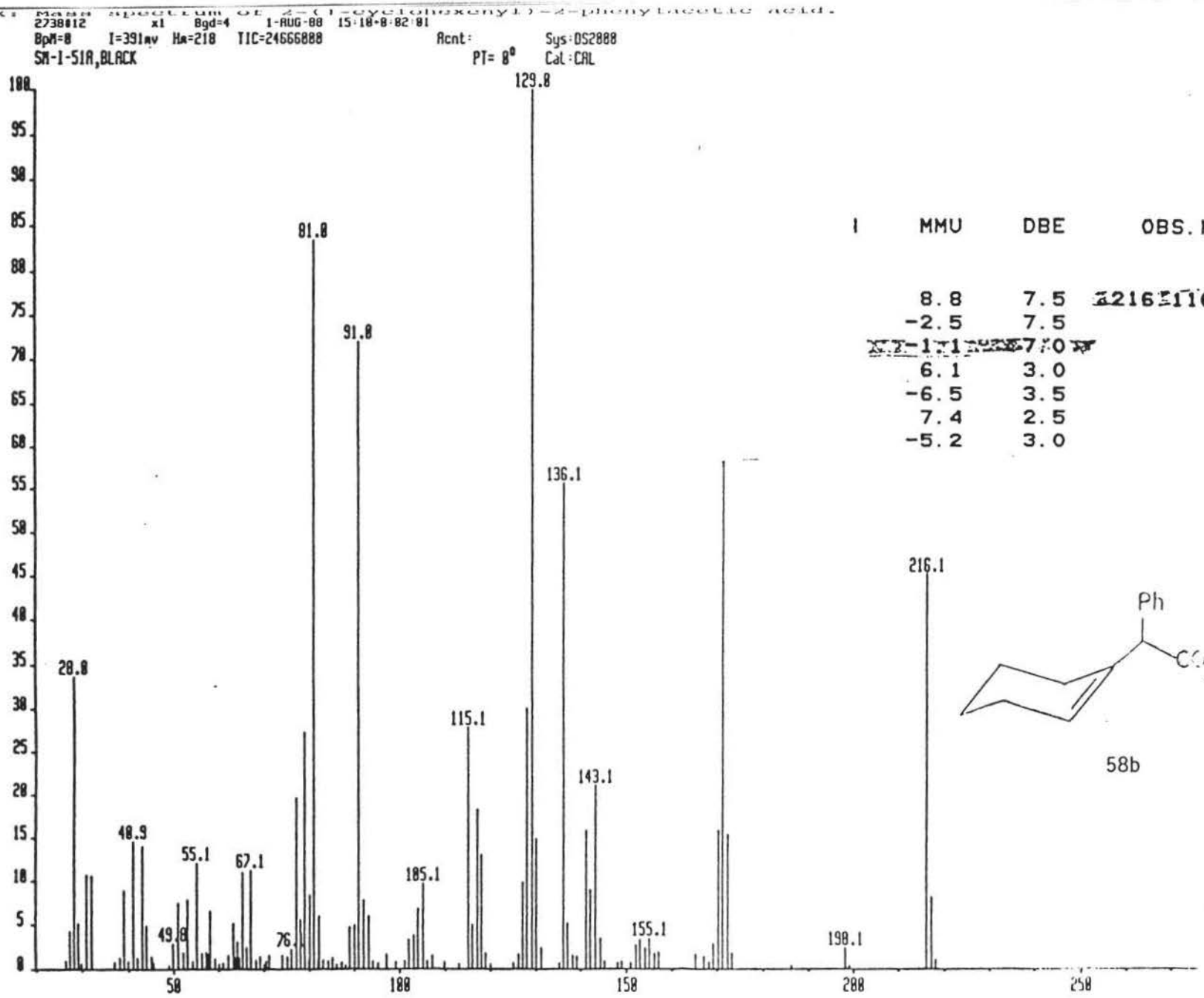


Figure X: IR spectrum of 3-ethyl-3-hydroxy-2-phenylpentanoic acid.

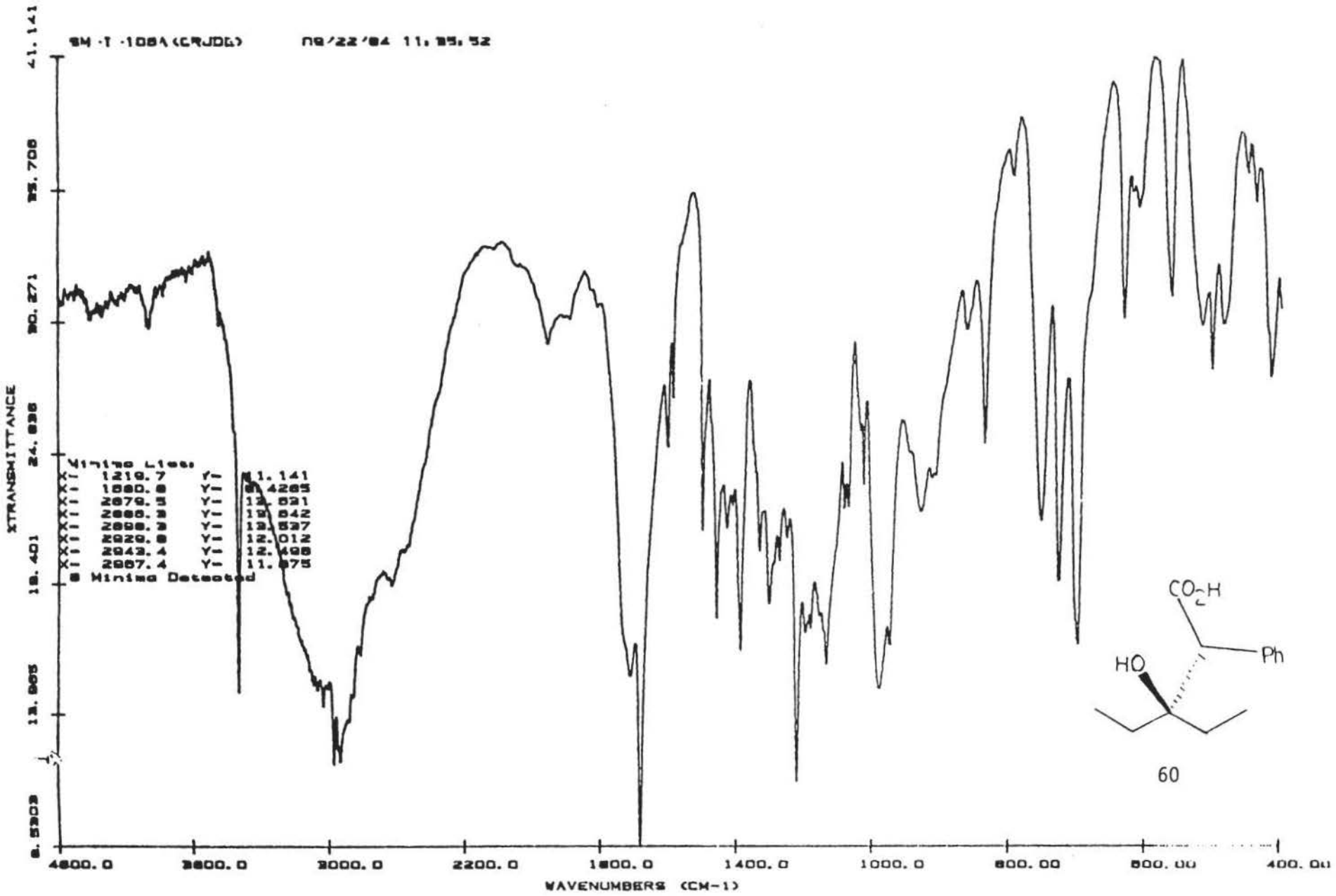
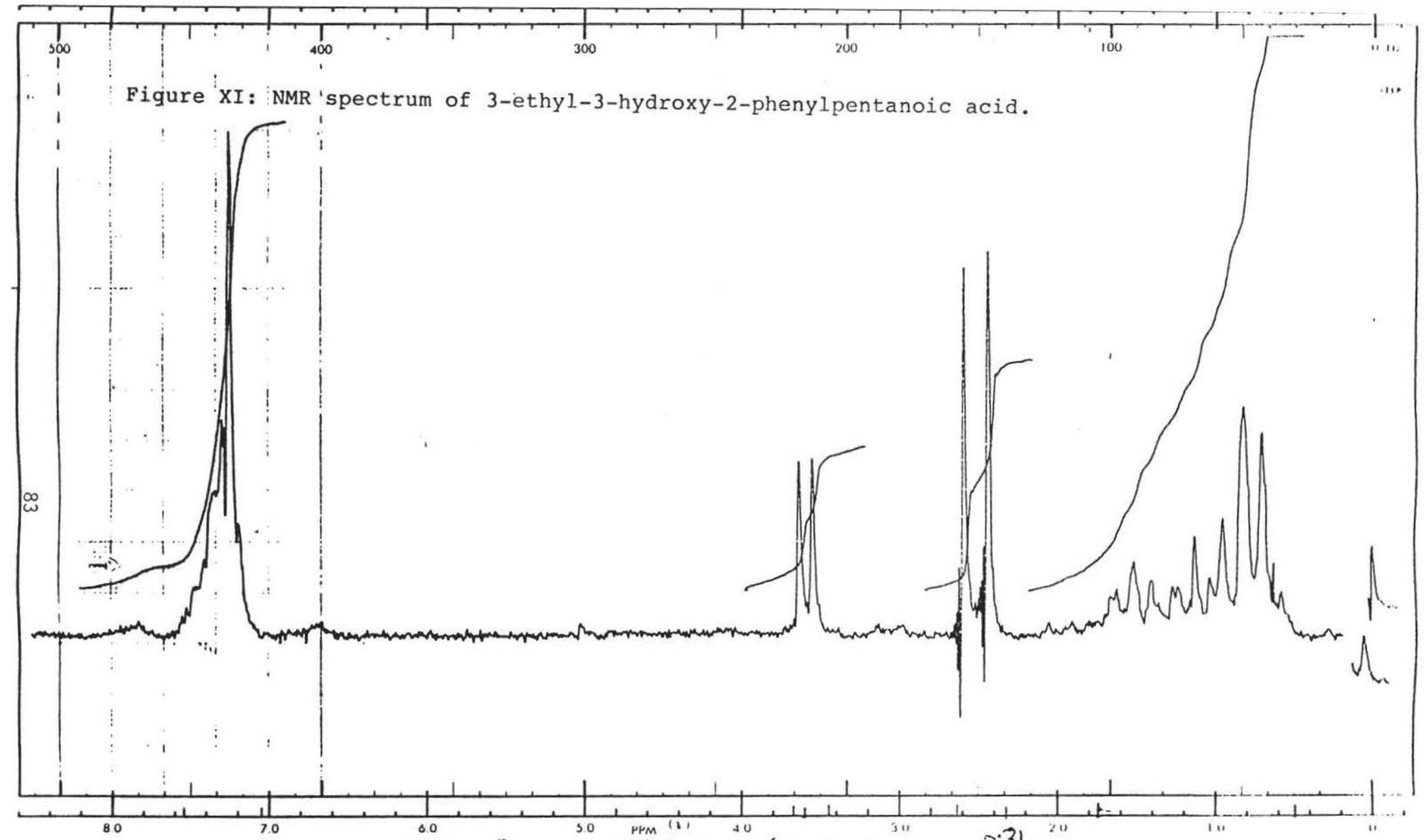


Figure XI: NMR spectrum of 3-ethyl-3-hydroxy-2-phenylpentanoic acid.



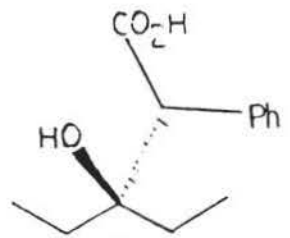
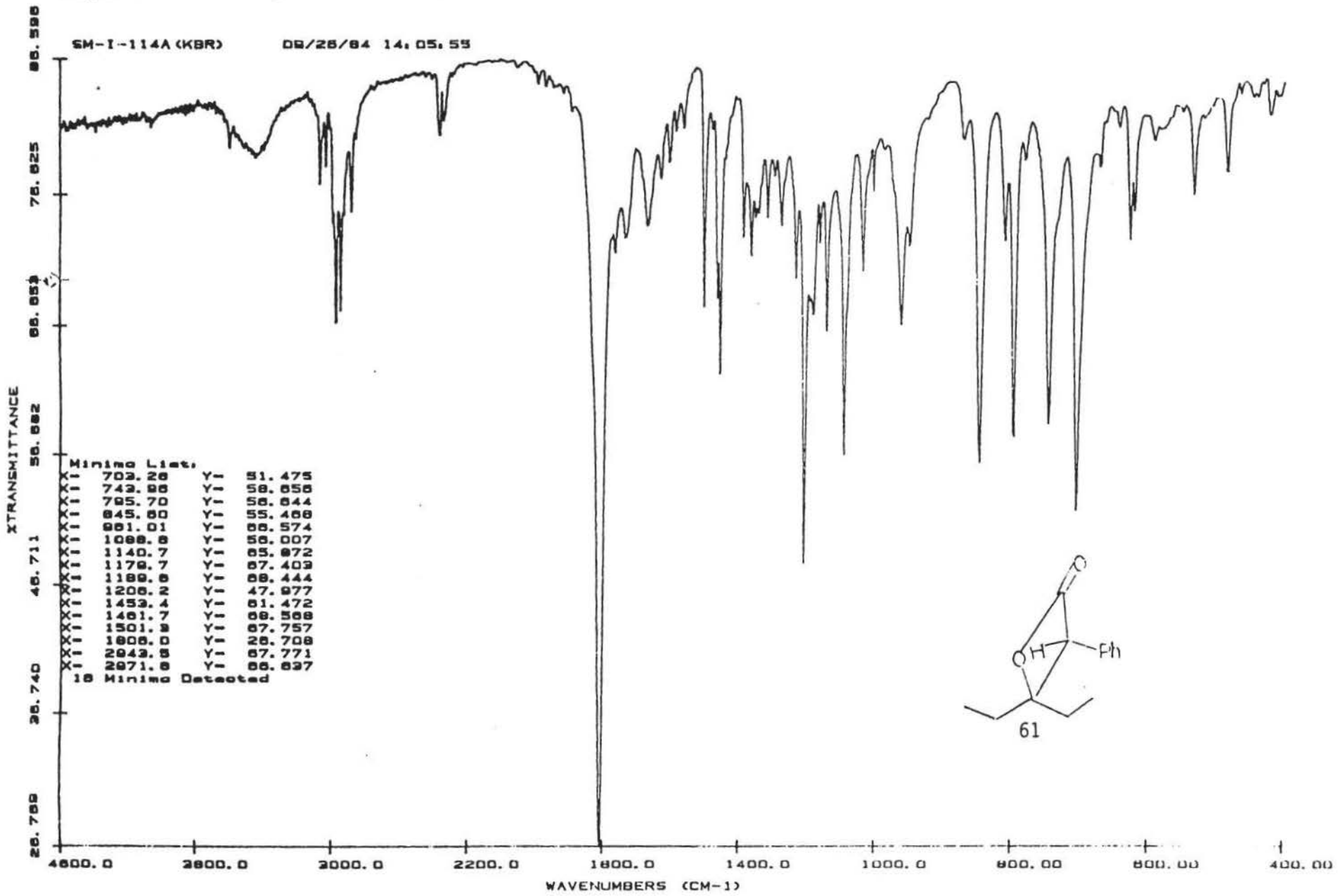
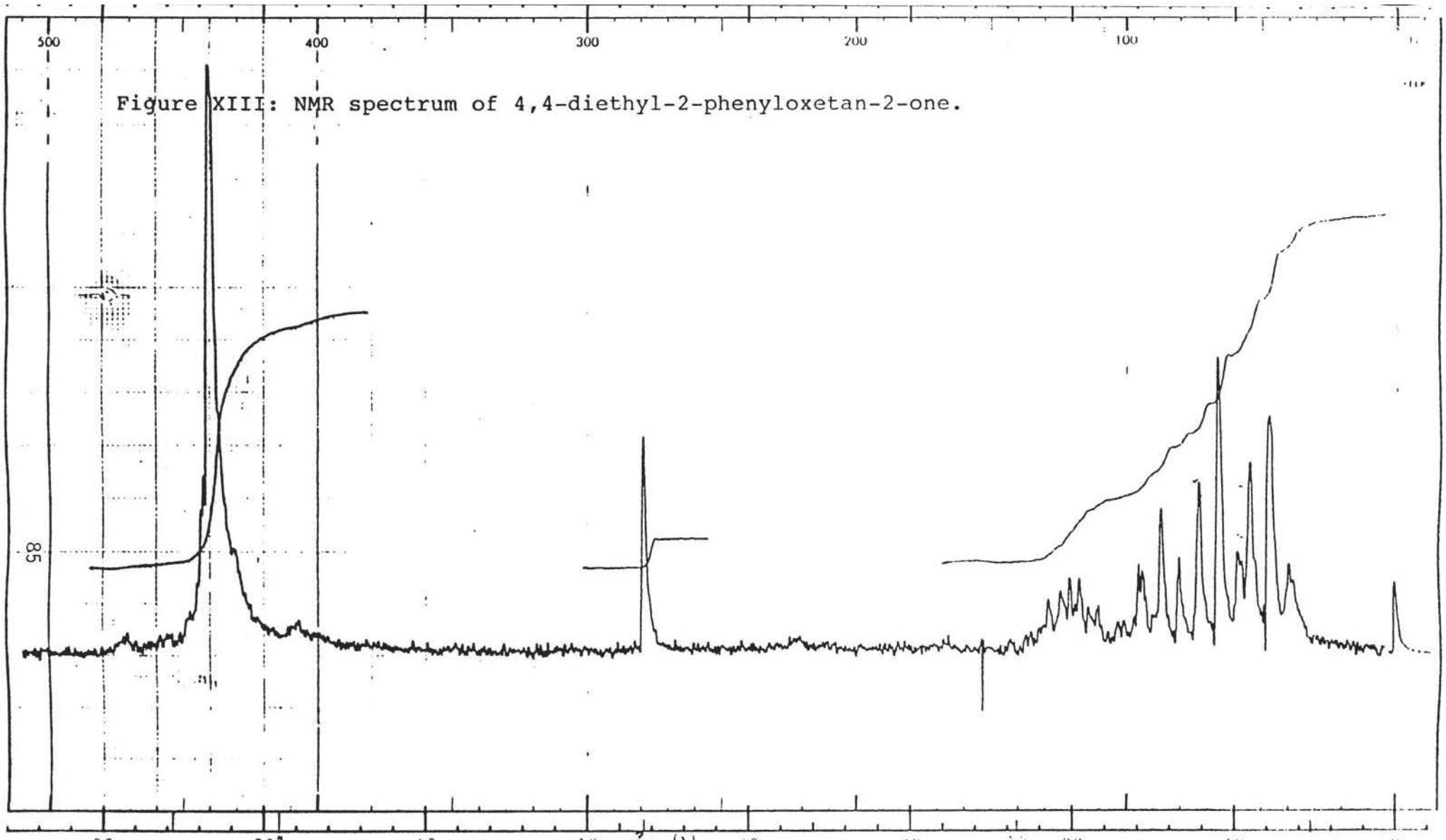


Figure XII: IR spectrum of 4,4-diethyl-2-phenyloxetan-2-one.



61

Figure XIII: NMR spectrum of 4,4-diethyl-2-phenyloxetan-2-one.



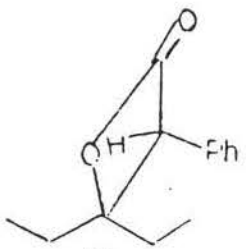
SWEEP OFFSET (Hz): 0.00
SPECTRUM AMPLITUDE: 50
INTEGRAL AMPLITUDE: 5
SPINNING RATE (RPS): 36

MANUAL | AUTO
SWEEP TIME (SEC): 50 (250)
SWEEP WIDTH (Hz): 25 50 100 250 (500)
FILTER: 1 2 3 4 5 6 7 8 (2)
RF POWER LEVEL: .04 (.05)

SAMPLE: SM-I-114A
SOLVENT: $CDCl_3$
REMARKS

DATE: 09/26/86
OPERATOR: Mallekar

60 MHz NMR SPECTRUM NO



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NO. VN 1009 (S-60T)

Figure XIV: IR spectrum of 3-ethyl-2-phenyl-3-pentenoic acid.

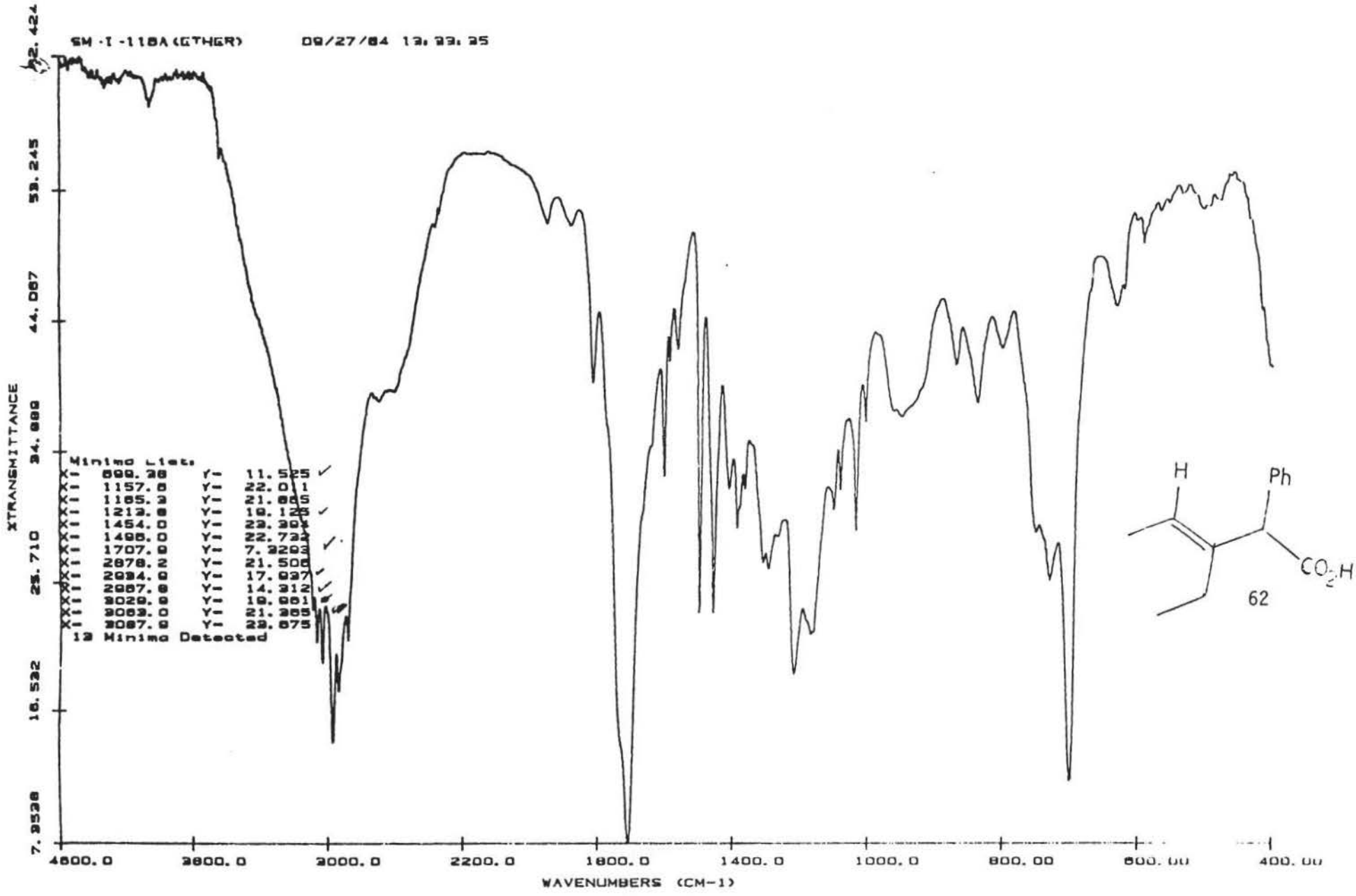
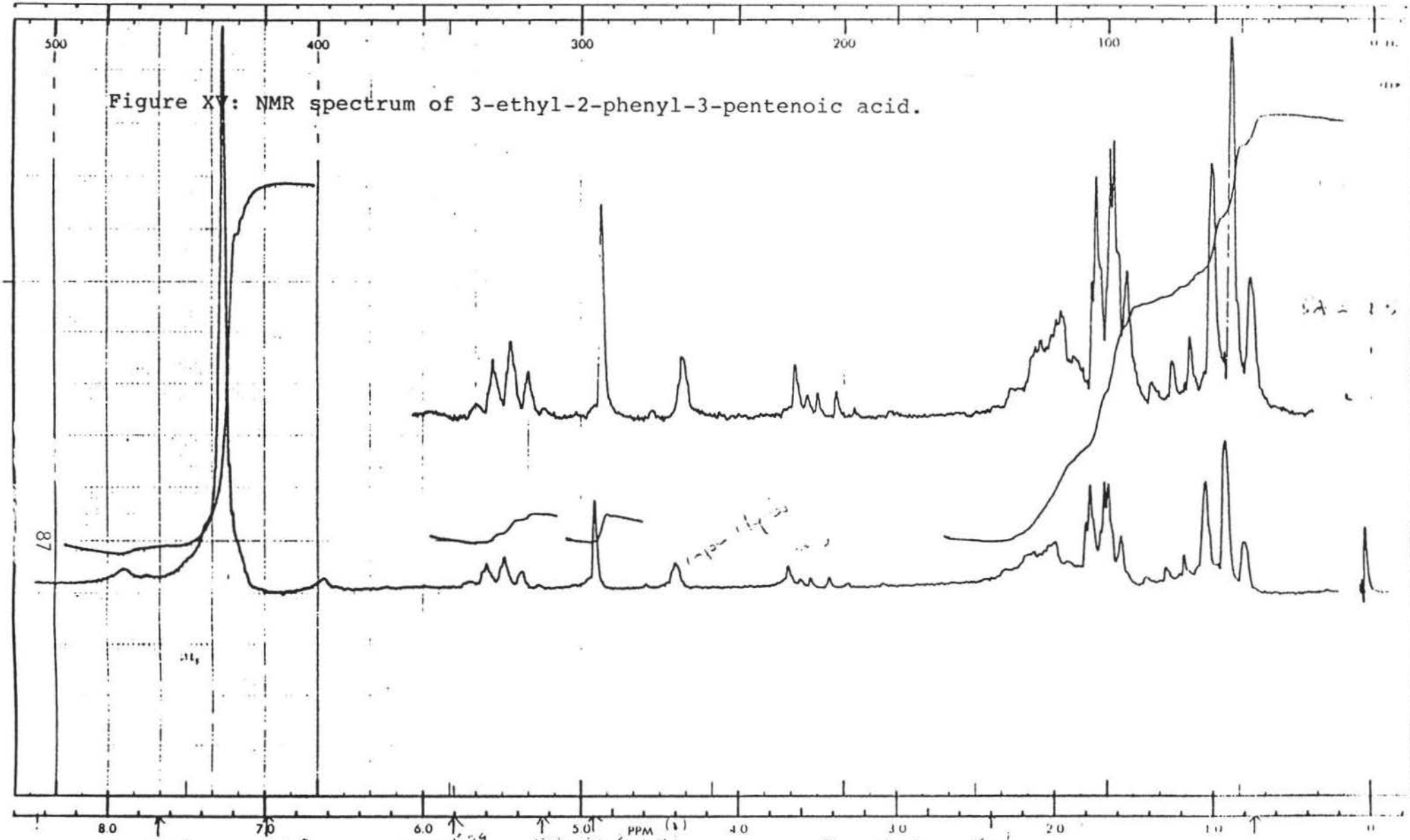


Figure XV: NMR spectrum of 3-ethyl-2-phenyl-3-pentenoic acid.



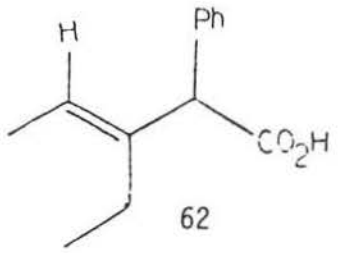


Figure XVII: IR spectrum of 3-hydroxy-2,3-dimethyloctanoic acid.

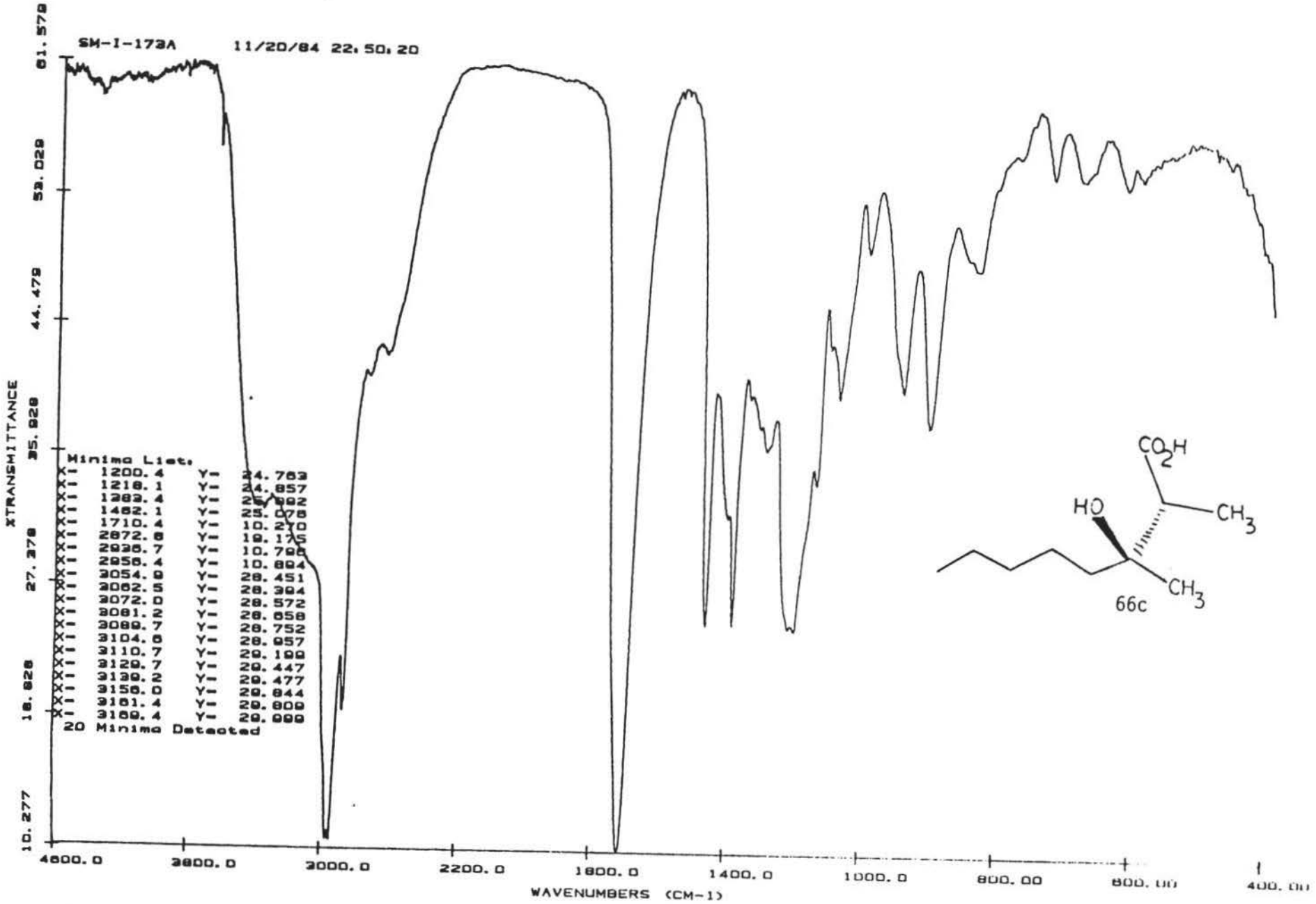
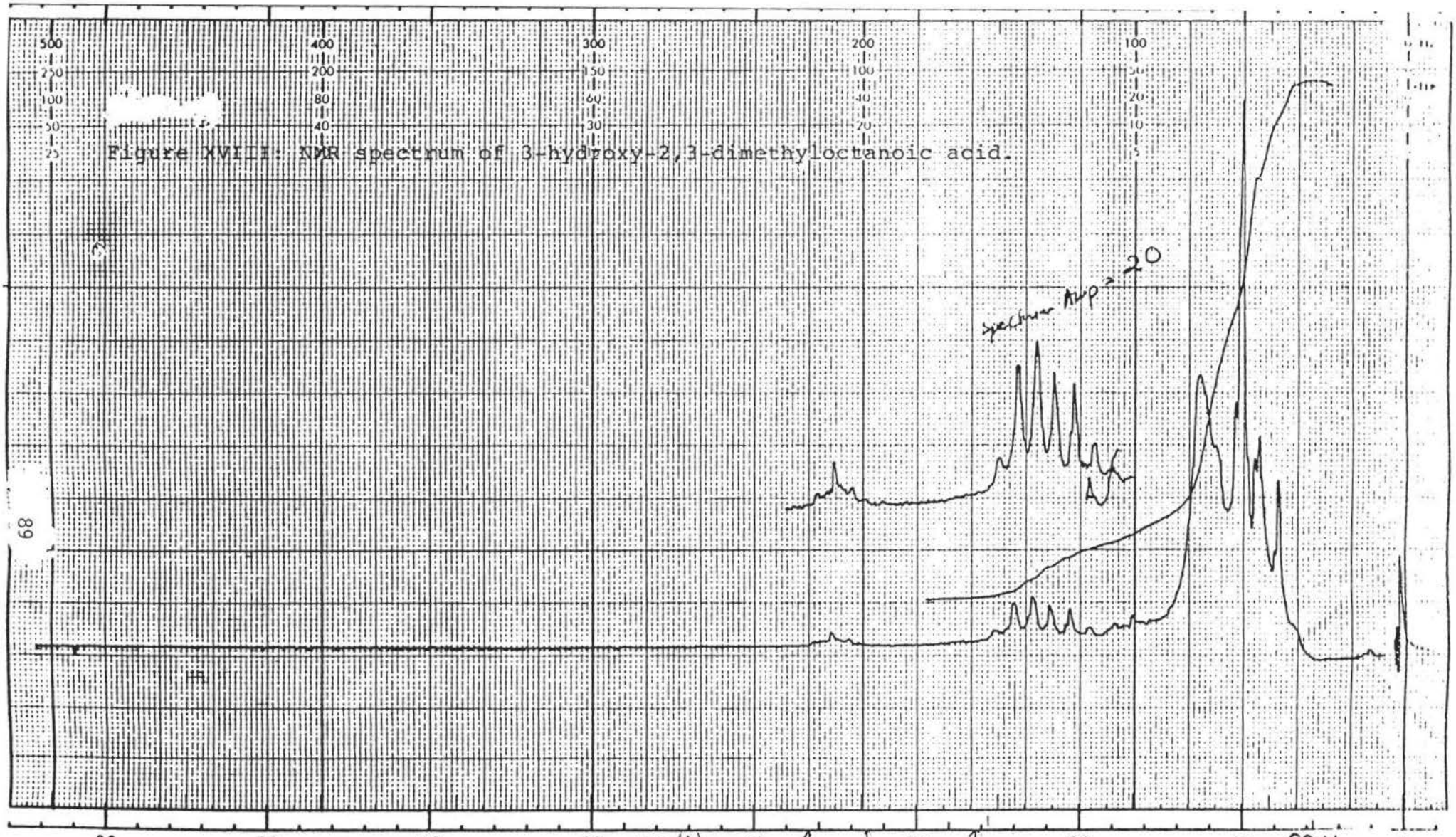


Figure XVIII: NMR spectrum of 3-hydroxy-2,3-dimethyloctanoic acid.



SWEEP OFFSET (Hz): 136
SPECTRUM AMPLITUDE: 6.3
INTEGRAL AMPLITUDE:
SPINNING RATE (RPS): 46

MANUAL
SWEEP TIME (SEC): 50 (100)
SWEEP WIDTH (Hz): 25 50 100 250 (500)
FILTER: 1 (2) 3 4 5 6 7 8
RF POWER LEVEL: .04

AUTO ☐
(250)
(500)
(2)
(.05)

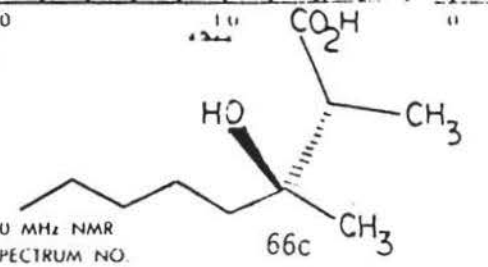
SAMPLE: SM-I-173A

REMARKS.

SOLVENT: DMSO

DATE: 11/20/78

OPERATOR: Mahadeo



60 MHz NMR SPECTRUM NO. 66c

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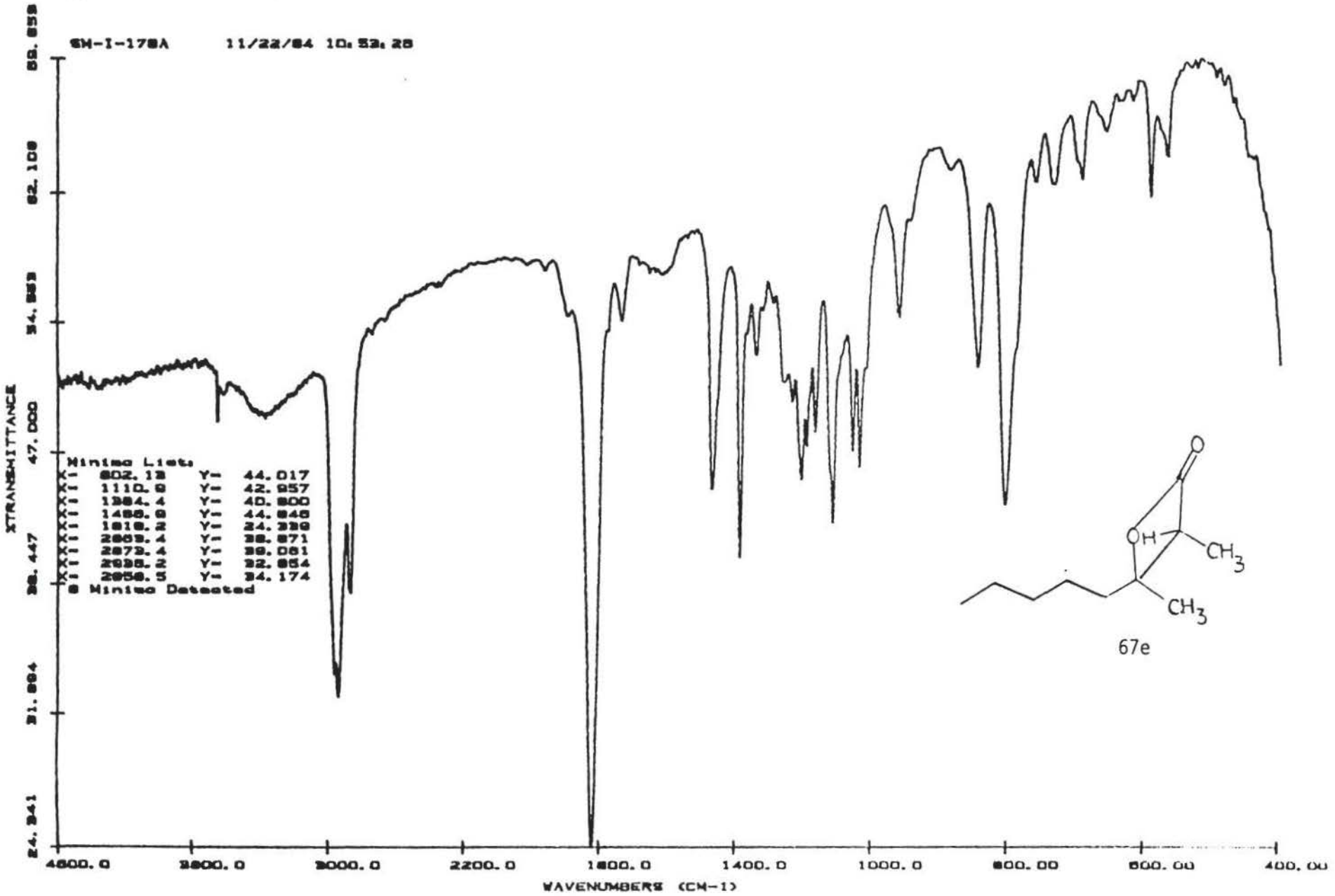
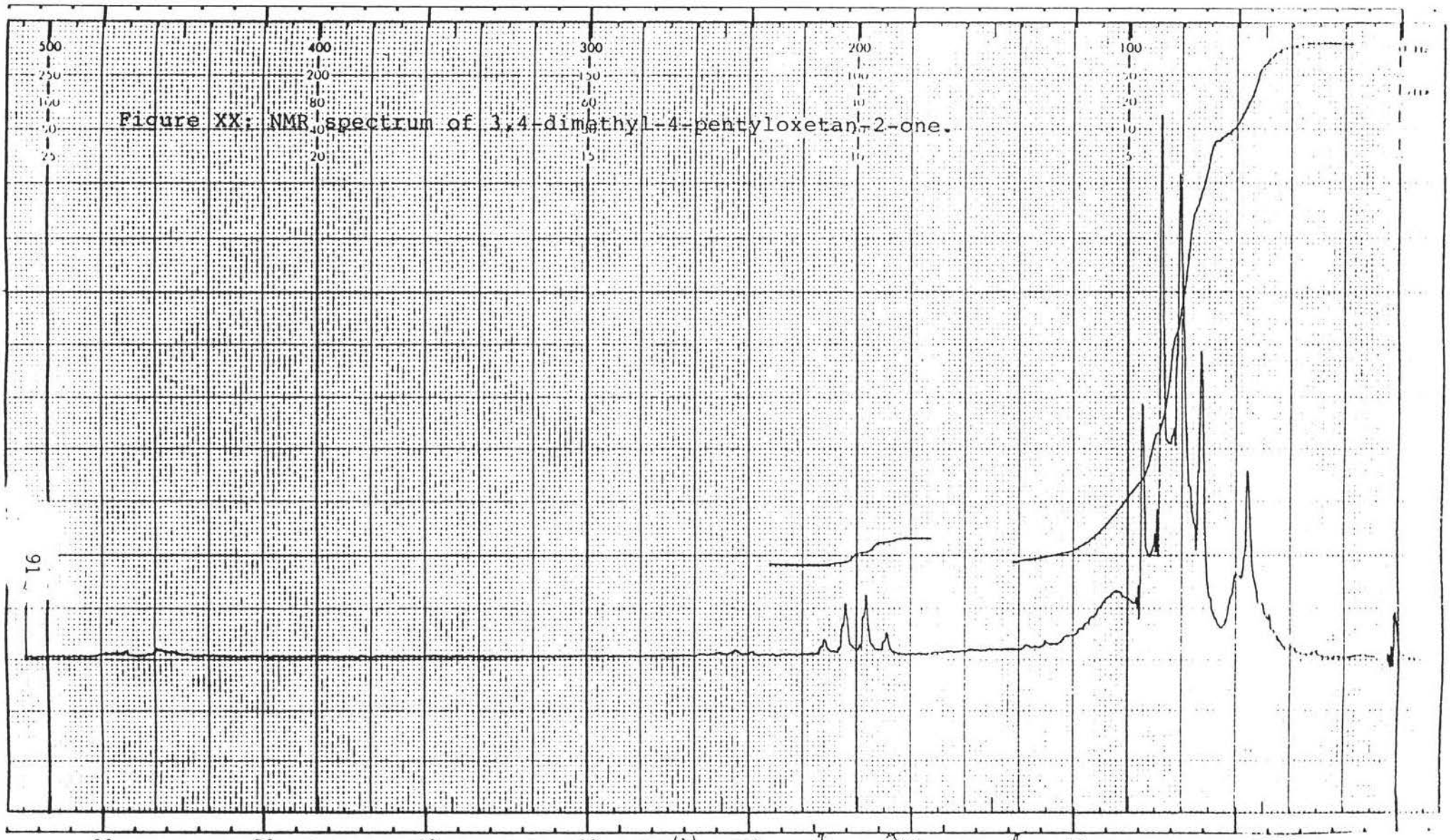
Figure XIX: IR spectrum of 3,4-dimethyl-4-pentyloxetan-2-one.



67e

Figure XX: NMR spectrum of 3,4-dimethyl-4-pentyloxetan-2-one.



SWEEP OFFSET (Hz): 0.00
SPECTRUM AMPLITUDE: 10
INTEGRAL AMPLITUDE: 5
SPINNING RATE (RPS): 4.2

MANUAL
SWEEP TIME (SEC): [50] [250]
SWEEP WIDTH (Hz): [25] [50] [100] [250] [500]
FILTER: [1] [2] [3] [4] [5] [6] [7] [8]
RF POWER LEVEL: .09

AUTO [_]
(250)
(500)
(2)
(.05)

SAMPLE: SM-I-178A

REMARKS

SOLVENT: $CDCl_3$

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DATE: 11/22/88

OPERATOR: Michelle Lee

60 MHz NMR
SPECTRUM NO.

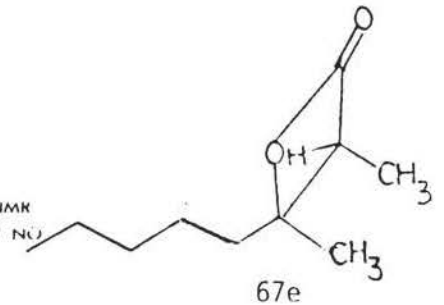
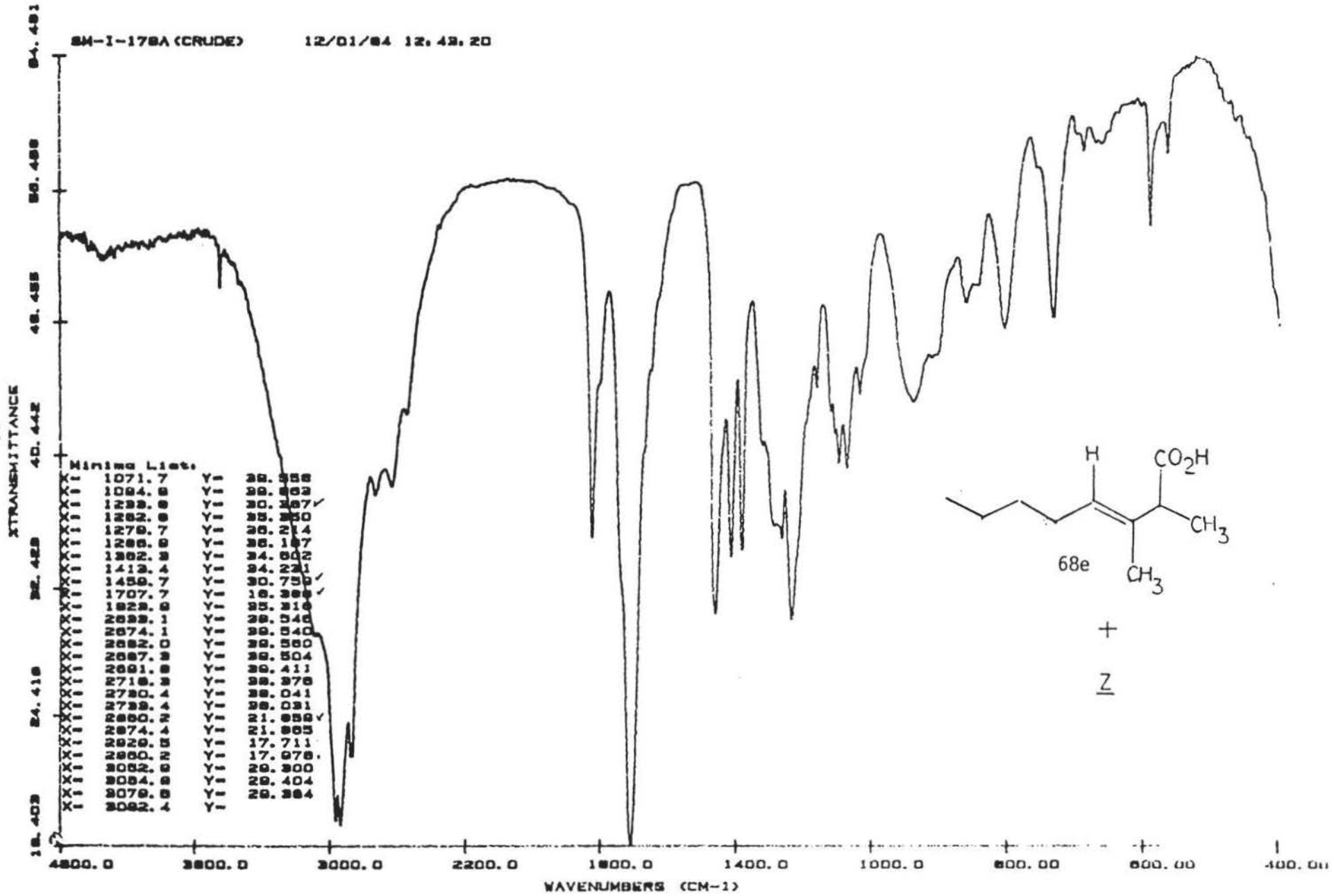


Figure XXI: IR spectrum of 2,3-dimethyl-3-octenoic acid.



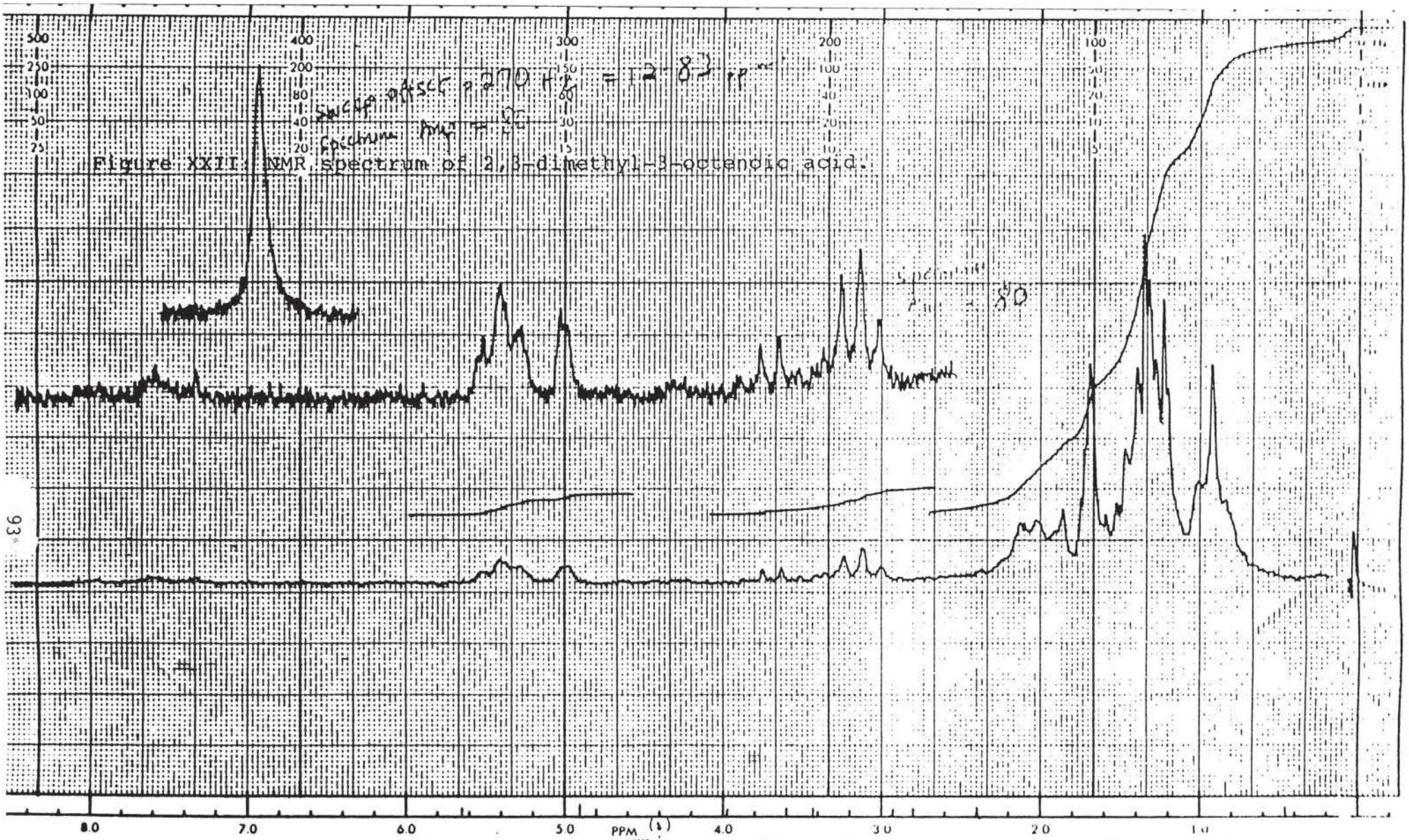


Figure XXII: NMR spectrum of 2,3-dimethyl-3-octanoic acid.

SWEEP OFFSET (Hz): 0 00
SPECTRUM AMPLITUDE: 20
INTEGRAL AMPLITUDE: 4
SPINNING RATE (RPS): 40

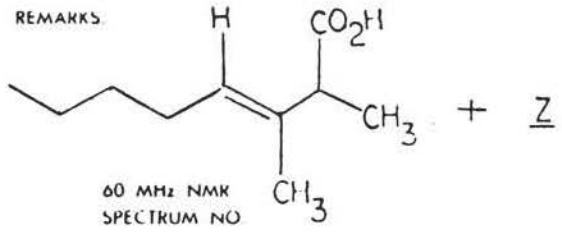
MANUAL
SWEEP TIME (SEC): 50 250
SWEEP WIDTH (Hz): 25 50 100 250 500
FILTER: 1 2 3 4 5 6 7 8
RF POWER LEVEL: 54

AUTO
(250)
(500)
(2)
(05)

SAMPLE: SM-I-174A

SOLVENT: $CDCl_3$

REMARKS



+ Z

60 MHz NMR SPECTRUM NO

DATE: 11/27/73

OPERATOR:

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No. VN 1009 (S-60T)

200 150 100 50 0 PPM

Figure XXIII: C-NMR spectrum of 2,3-dimethyl-3-octenoic acid.

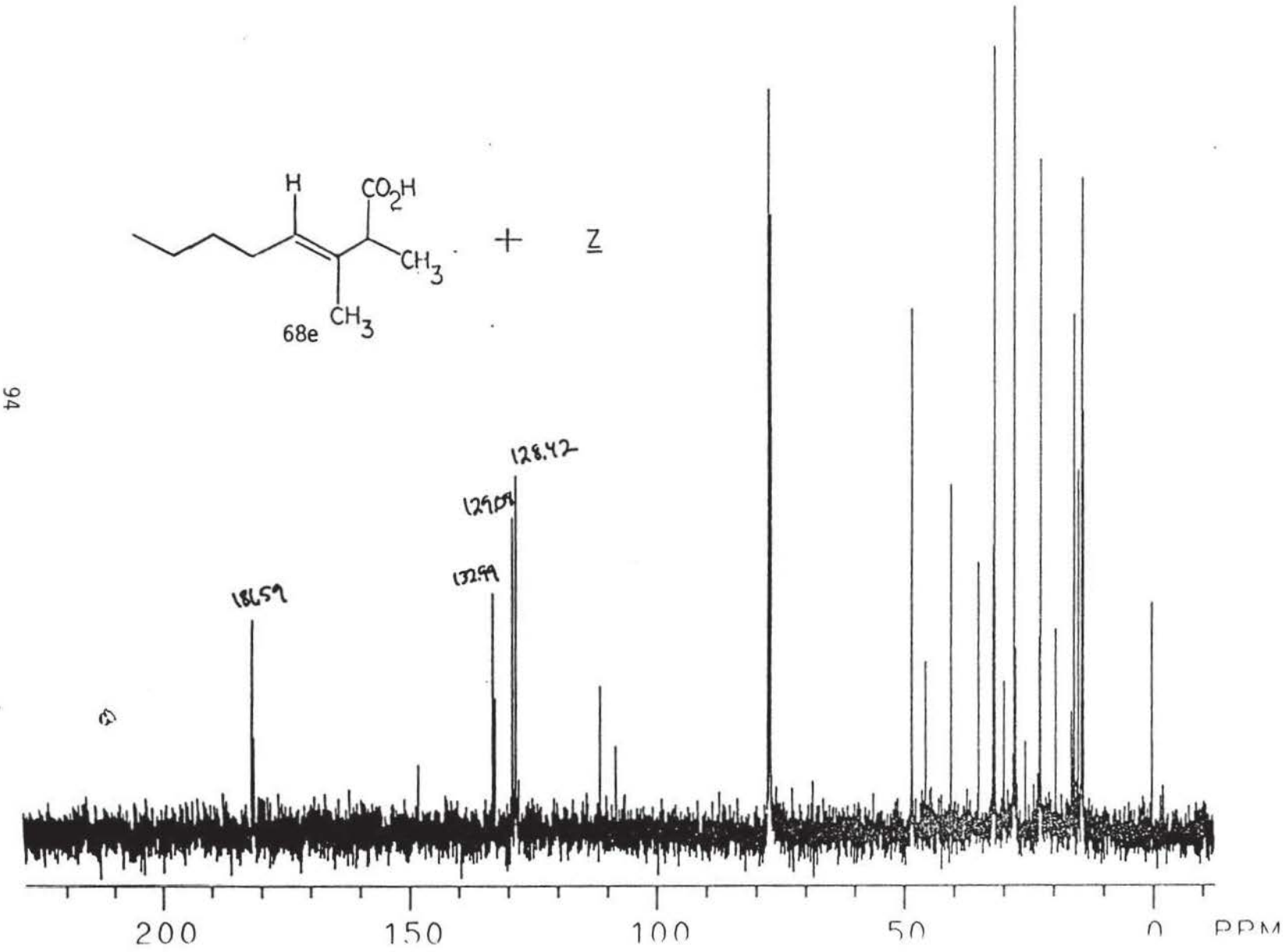
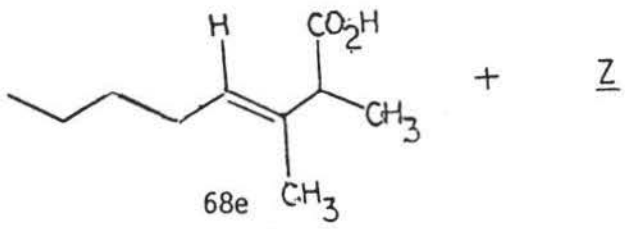


Figure XXIV: Mass spectrum of 2,3-dimethyl-3-octenoic acid.



68e + Z

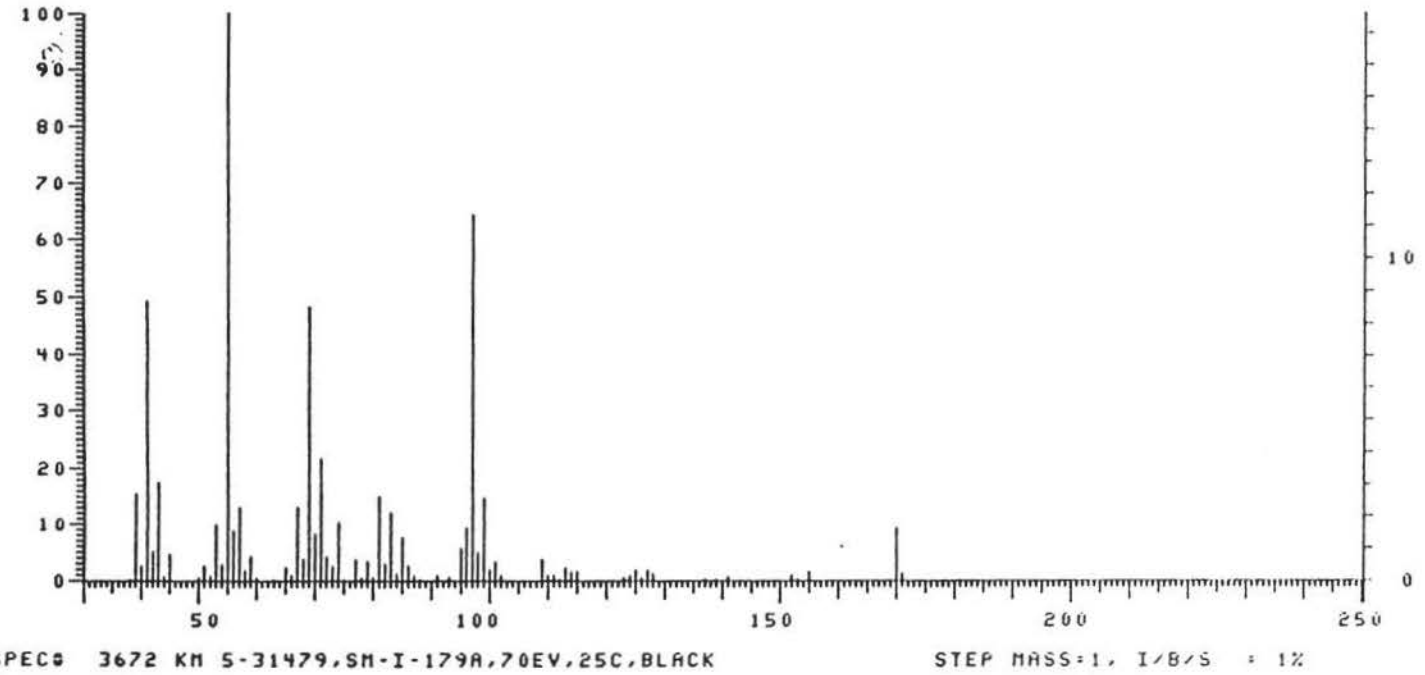


Figure XXV: IR spectrum of 1,1,1-trifluoromethyl-2-hexanone.

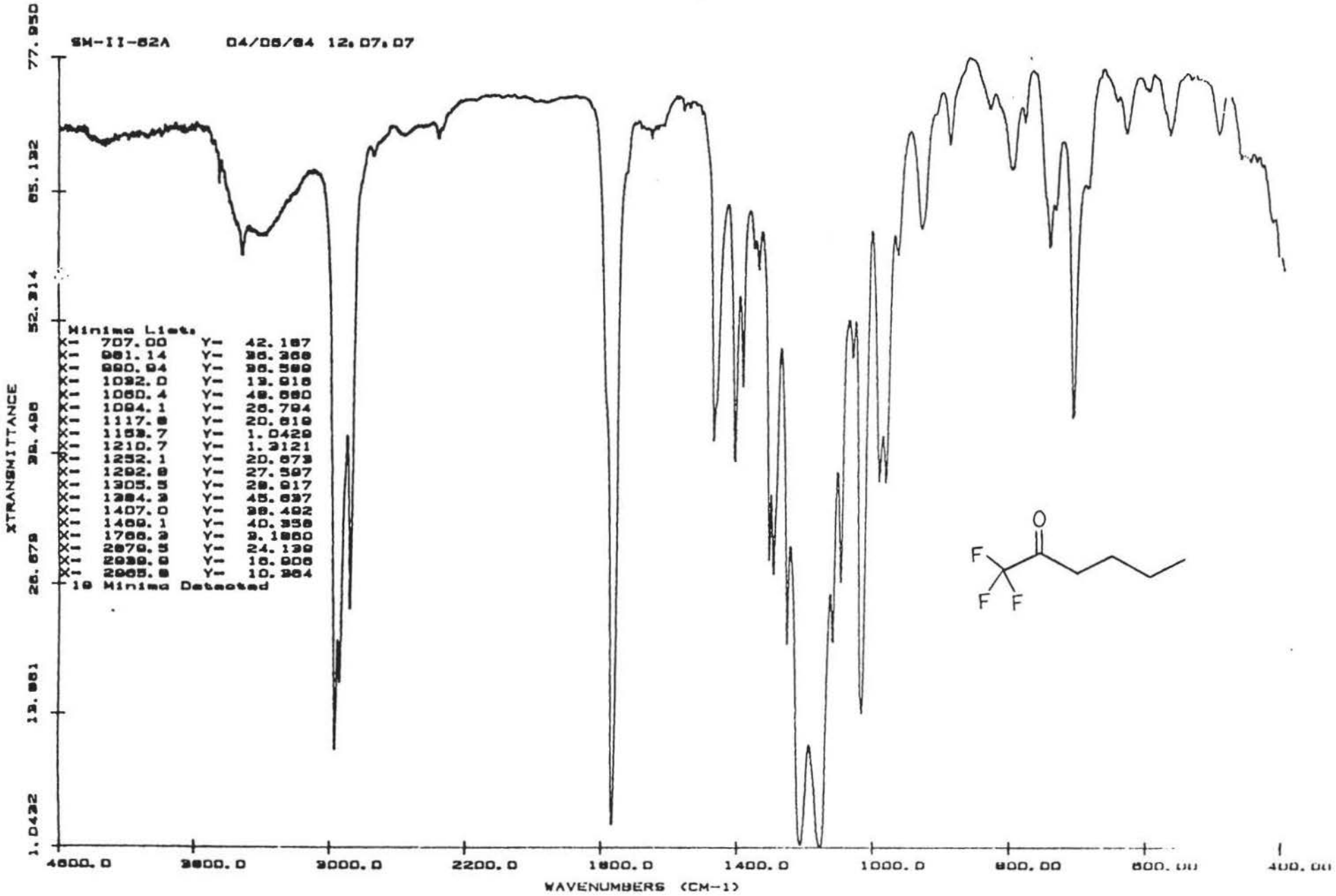
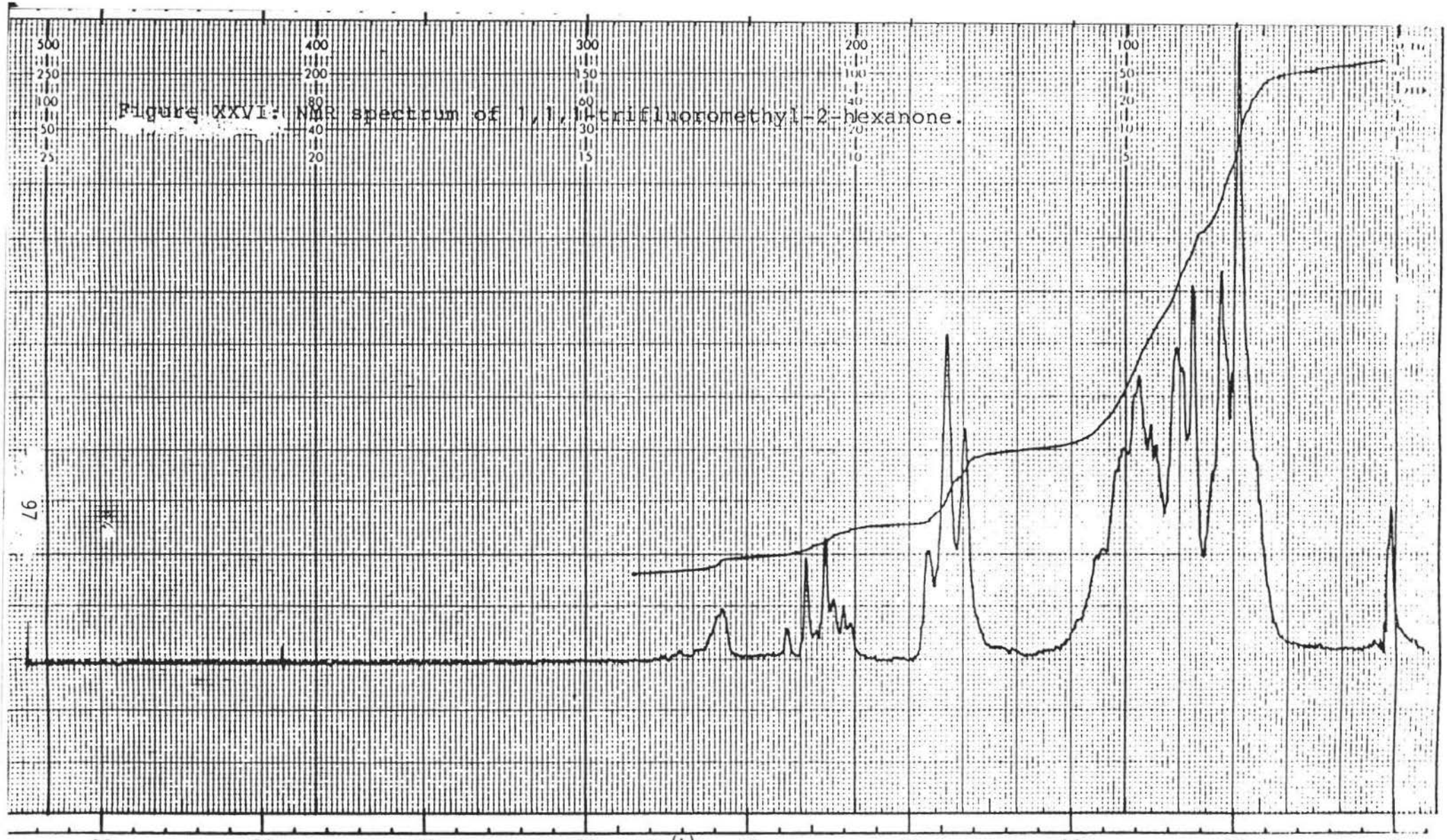


Figure XXVI: NMR spectrum of 1,1,1-trifluoromethyl-2-hexanone.



WEEP OFFSET (Hz): 0.00

PECTRUM AMPLITUDE: 25

NTEGRAL AMPLITUDE: 1.5

PINNING RATE (RPS): 40

MANUAL

SWEEP TIME (SEC): 50 250

SWEEP WIDTH (Hz): 25 50 100 250 500

FILTER: 1 2 3 4 5 6 7 8

RF POWER LEVEL: .04

AUTO ☐

(250)

(500)

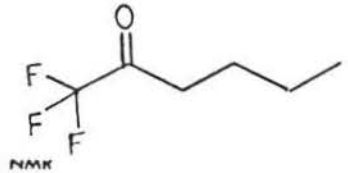
(2)

(.05)

SAMPLE: SM-II-63A

SOLVENT: $CDCl_3$

REMARKS:



60 MHz NMR SPECTRUM NO.

DATE: 04/11/1987

OPERATOR: Stephen Hawthorne

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NO. VN 1009 (S-60T)

Figure XXVII: IR spectrum of 3-hydroxy-2-methyl-3-trifluoromethylheptanoic acid.

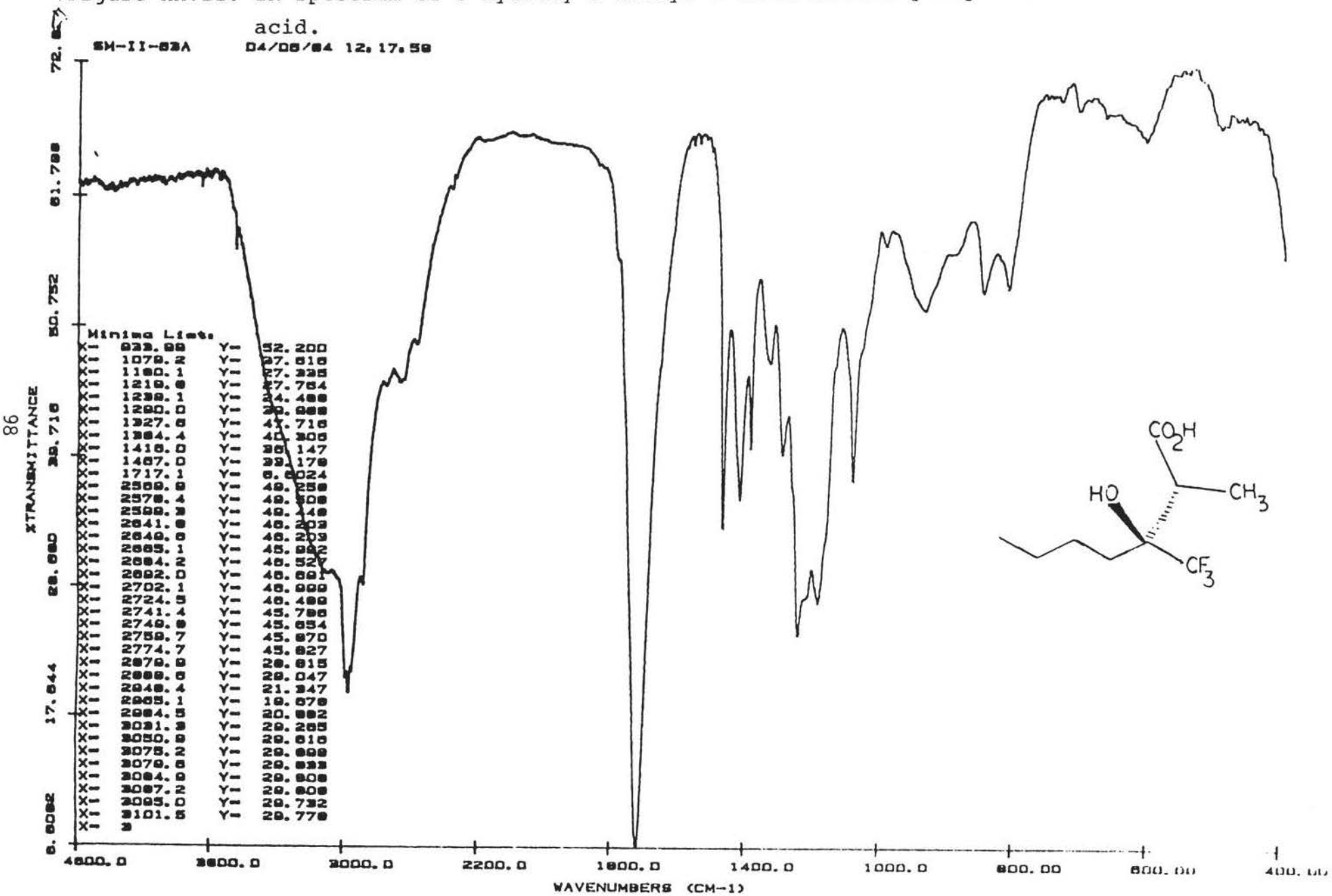
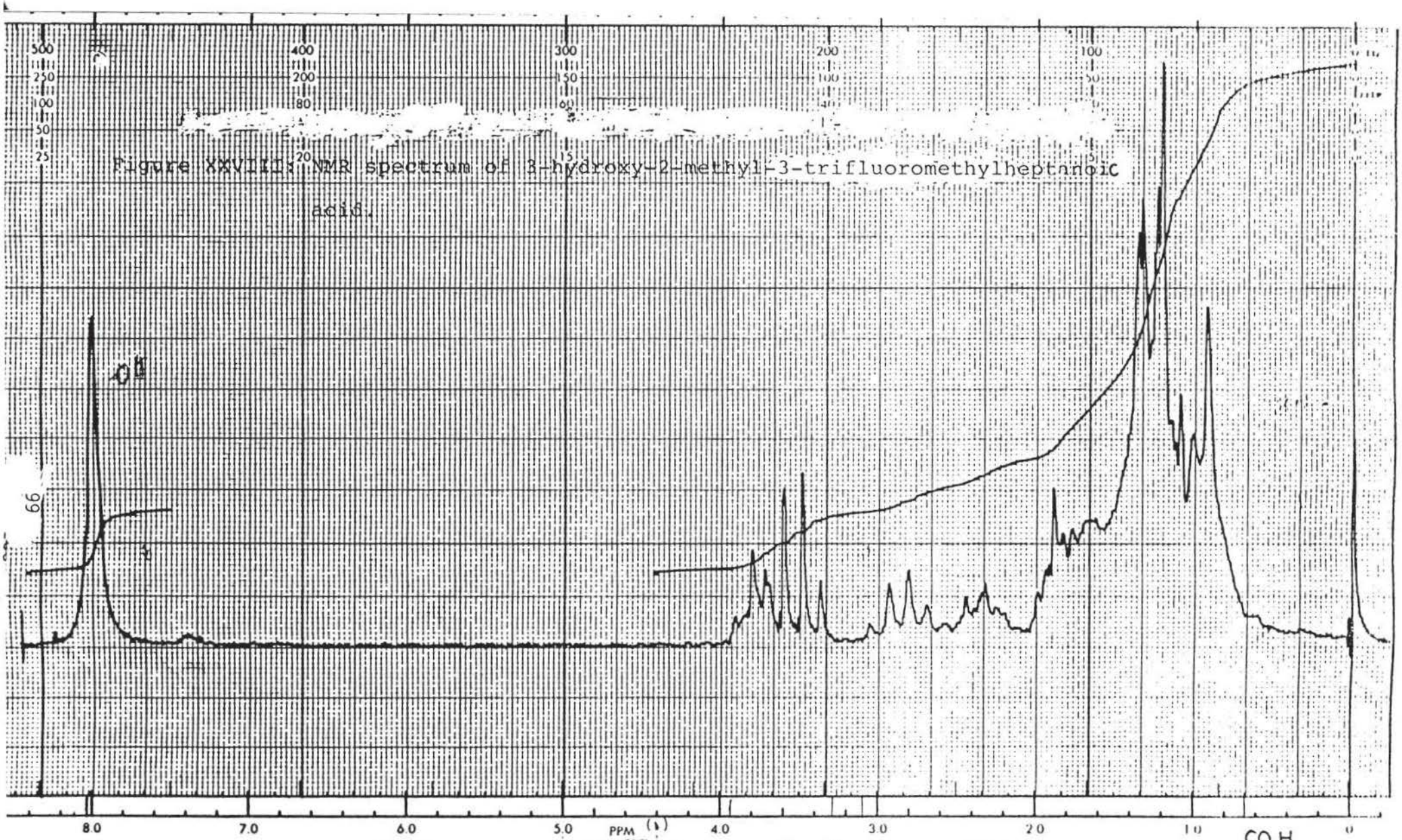


Figure XXVIII: NMR spectrum of 3-hydroxy-2-methyl-3-trifluoromethylheptanoic acid.



SWEEP OFFSET (Hz): 0.00
SPECTRUM AMPLITUDE: 25
INTEGRAL AMPLITUDE: 2
SPINNING RATE (RPS): 40

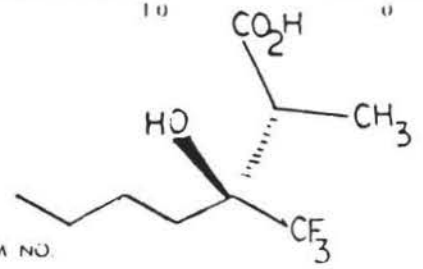
MANUAL
SWEEP TIME (SEC): 50 250
SWEEP WIDTH (Hz): 25 50 100 250 500
FILTER: 1 2 3 4 5 6 7 8
RF POWER LEVEL: 0.1

AUTO
(250)
(500)
(2)
(.05)

SAMPLE:

SOLVENT: CDCl3

REMARKS:



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No. VN 1009 (S-60T)

DATE: 04/14/87

OPERATOR:

60 M
SPECTRUM NO.

Figure XXIX: IR spectrum of 4-butyl-4-trifluoromethyl-3-methyloxetan-2-one.

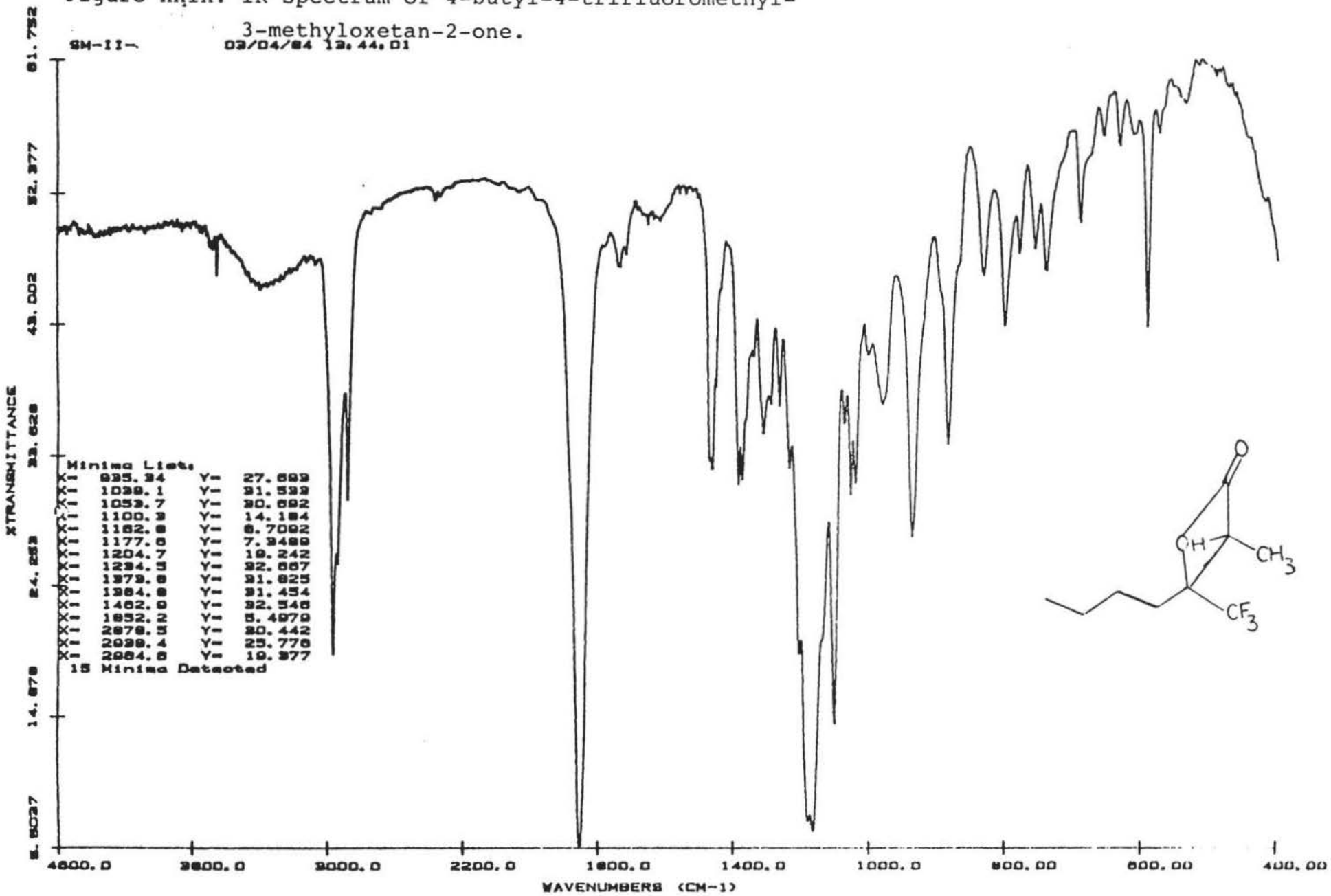
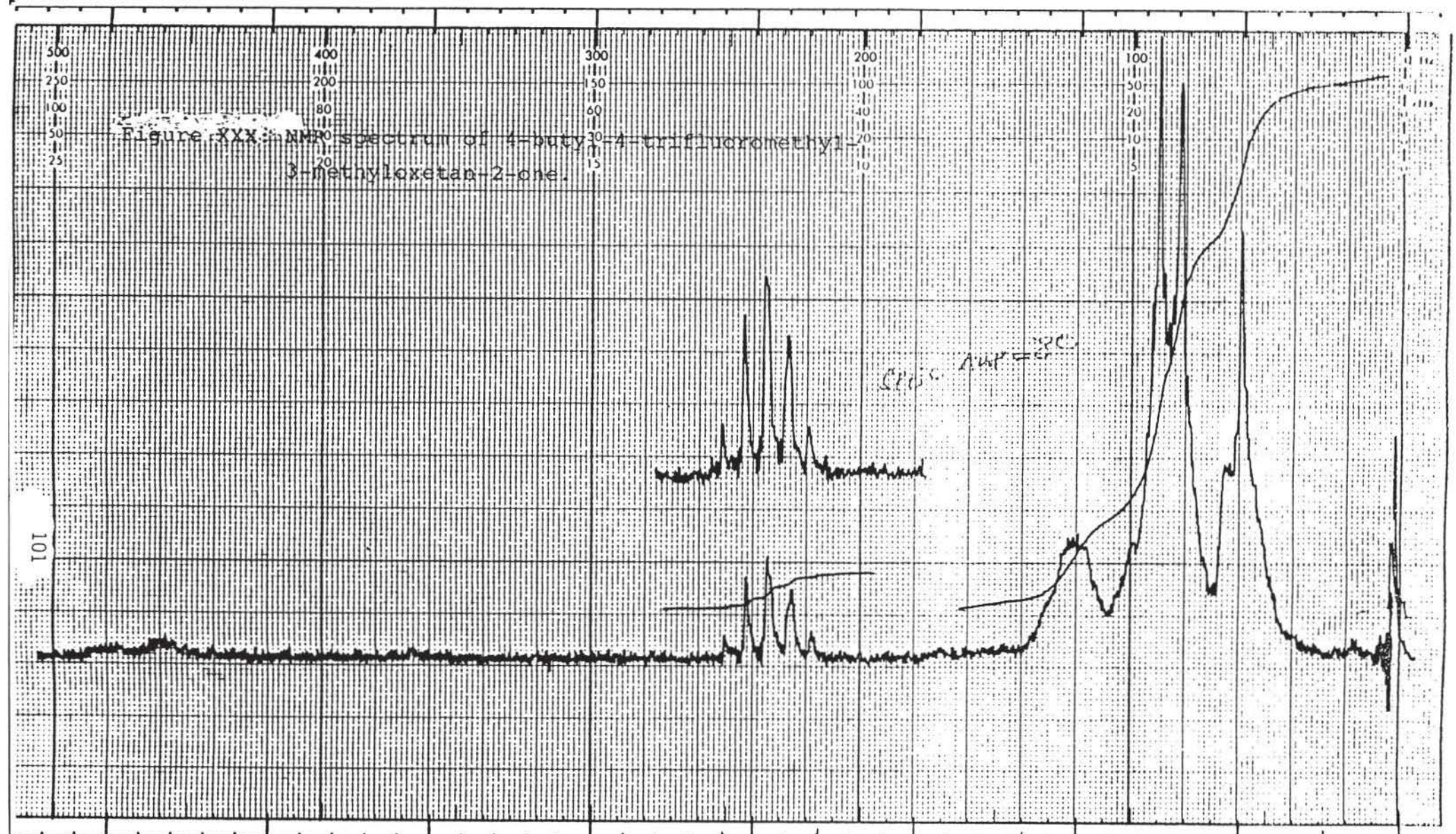


Figure XXX: NMR spectrum of 4-butyl-4-trifluoromethyl-3-methyloxetan-2-one.



SWEEP OFFSET (Hz): 0.00
SPECTRUM AMPLITUDE: 40
INTEGRAL AMPLITUDE: 2.5
SPINNING RATE (RPS): 40

MANUAL
SWEEP TIME (SEC): 50 250
SWEEP WIDTH (Hz): 25 50 100 250 500
FILTER: 1 2 3 4 5 6 7 8
RF POWER LEVEL: .04

AUTO ☐
(250)
(500)
(2)
(.05)

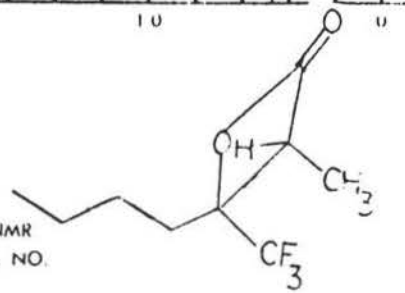
SAMPLE: SM-II-67()

REMARKS.

SOLVENT: $CDCl_3$

DATE: 04/13/1984

OPERATOR:



60 MHz NMR SPECTRUM NO.

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No. VN 1009 (S-60T)

VITA

Name: STEPHEN LUCAS MALULEKA

Permanent Address: 36 Matsemela Street
Saulsville
0125
Pretoria
Transvaal
South Africa

Date of Birth: November 8, 1959

Collegiate Institutions:

Attended	Year	Degree
Grinnell College, Iowa	1983-1987	B.A.
Eastern Illinois University	1987-1989	M.S.

Major: Chemistry

Positions Held:	Year	Employer
Graduate Assistant	1987-1989	Chemistry Department Eastern Illinois University, U.S.A.