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Butenolide Synthesis via Cation-Initiated Ring Expansion/Elimination of β-Lactones

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BUTENOLIDE SYNTHESIS VIA CATION-INITIATED

RING EXPANSION/ELIMINATION OF β-LACTONES

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BUTENOLIDE SYNTHESIS VIA CATION-INITIATED
RING EXPANSION/ELIMINATION OF β-LACTONES

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ABSTRACT

An area of recent research in the Black research group is an exploration of the potential of cation-initiated ß-lactone ring expansions, accompanied by the elimination of a proton or other electrofuge, as a protocol for the synthesis of multisubstituted butenolides.

Γ-Bromo ß-lactones were prepared via bromolactonization of the appropriate ß,Γ-unsaturated acids under basic conditions. The nucleofugal bromine atom on the Γ-carbon was then employed to effect carbocation formation adjacent to the lactone ring oxygen atom; the most efficacious reagent combination was found to be silver nitrate in refluxing acetic acid. Generation of this cation initiated a migration of the ß-lactone ring oxygen atom to the Γ-position, whereupon loss of the α-proton produced butenolides in 30 to 75% yield.

Successful implementation of this conceptually novel strategy will provide a versatile and expedient route for the synthesis of butenolides bearing a wide range of substitution patterns.

Cycloaddition of α-trimethylsilylketene (TMS ketene) to aldehydes bearing carbocation progenitors in the α-position provided α-trimethylsilyl ß-lactones which were then examined as substrates for the ring expansion/elimination sequence. In contrast to aldehydes, ketones were transformed into α,ß-unsaturated acids under the same conditions.

ACKNOWLEDGEMENT

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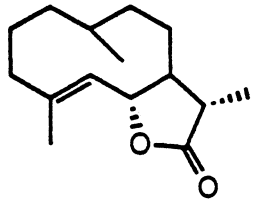
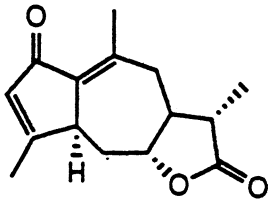
INTRODUCTION

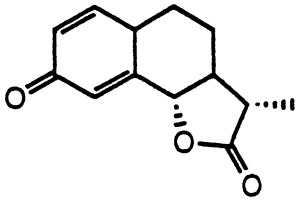
Substituted Γ-butyrolactones and α,ß-butenolides (2(5H)-furanones) have attracted much interest on account of their diverse biological activities and the utility of some of them as synthetic intermediates.[1] Various biologically-active sesquiterpenes contain the Γ-butyrolactone unit;[2] for example, dihydrocostunolide **1**, achillin **2**, and santonin **3**.



Dihydrocostunolide **1**

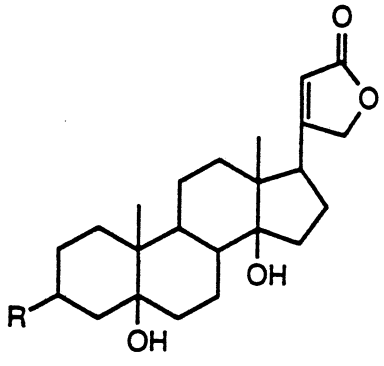


Achillin **2**

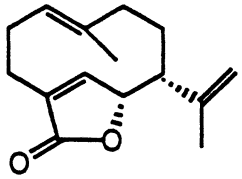


Santonin **3**

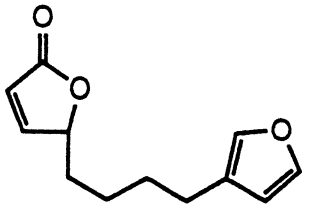
Optically active substituted butenolides are also present in a number of natural products and are found in flavor components and insect sex pheromones.[3] Butenolides are encountered in the side chain of $\Delta^{20(22)}$—cardenolides **4**,[4] which are biologically-active steroid lactones. Bridged germacranolide **5** is a type of



$\Delta^{20(22)}$-Cardenolide **4**



Germacranolide **5**

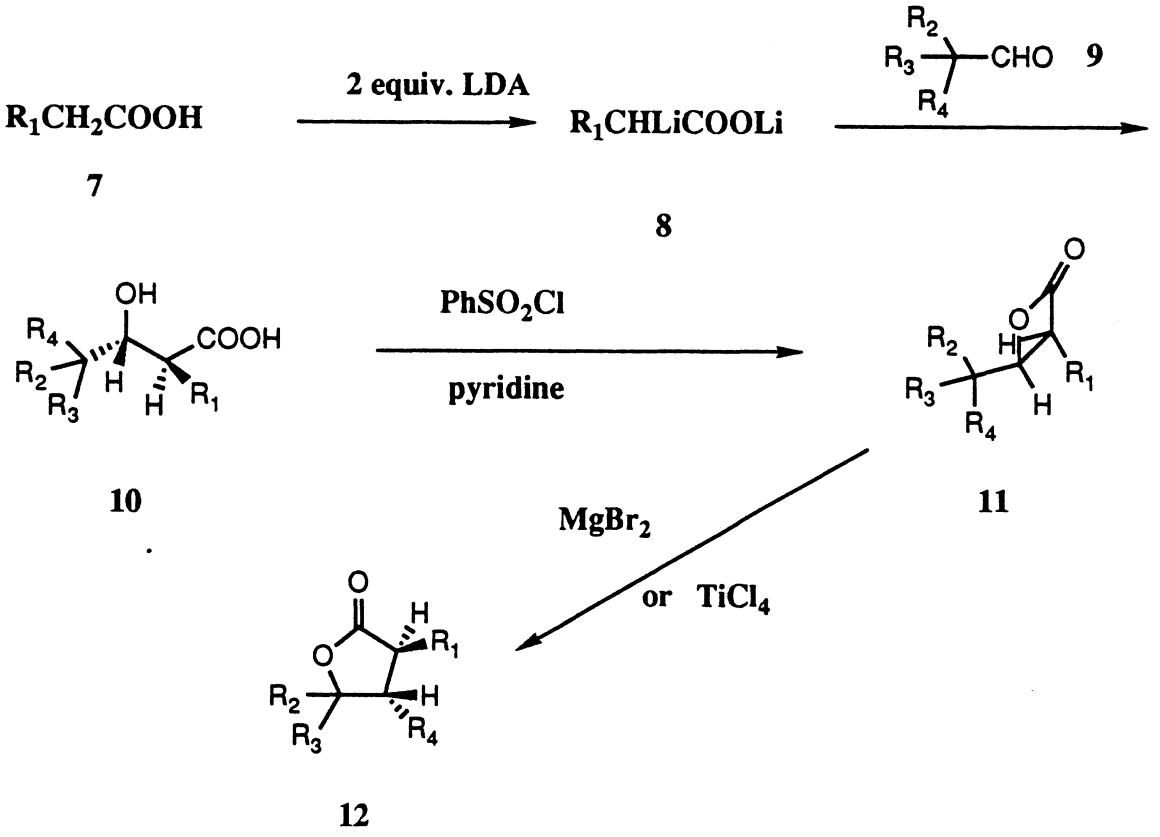


Freelinguite **6**

sesquiterpene lactone containing a 3,5-disubstituted butenolide as an integral moiety.[5] Freelinguite **6**, a furanosesquiterpene, is a biogenetically interesting constituent of the plant *Eremophila Freelingli*.[6]

Our research group has concentrated considerable effort in the investigation of ß-lactone rearrangement reactions, and has developed protocols for the synthesis of a variety of functionalized butyrolactones.[7] The overall sequence is outlined in Scheme I. Treatment of substituted acetic acids **7** with two equivalents of lithium diisopropylamide gave the corresponding dianions **8**; these dianions were then condensed with carbonyl

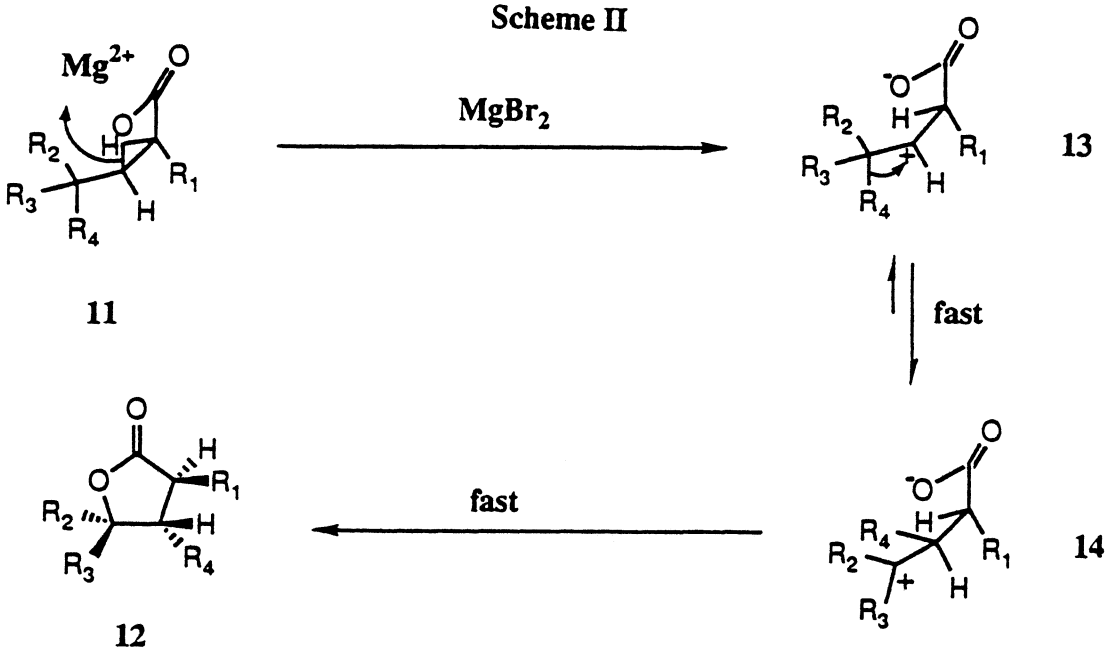
Scheme I



compounds **9** to afford the ß-hydroxy acids **10** which were finally converted to the ß-lactones **11** via treatment with two equivalents of benzenesulfonyl chloride in pyridine at 0 °C. The quasi-dyotropic rearrangement leading to the butyrolactones **12** was initiated by Lewis acid catalysis, employing such agents as magnesium bromide or titanium tetrachloride.

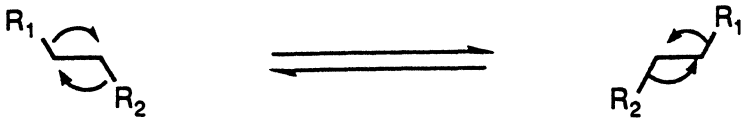
The predominant driving force for the rearrangement step is the considerable ring strain inherent in ß-lactones. This is a multistep mechanism (Scheme II): the ionization of the ß-lactone is rate-determining, followed by a rapid carbocation rearrangement and closure of the Γ-lactone ring via carboxylate attack on the newly-formed carbocation.

Scheme II



A dyotropic rearrangement[8] is strictly defined as a simultaneous positional interchange of two adjacent atoms and is a

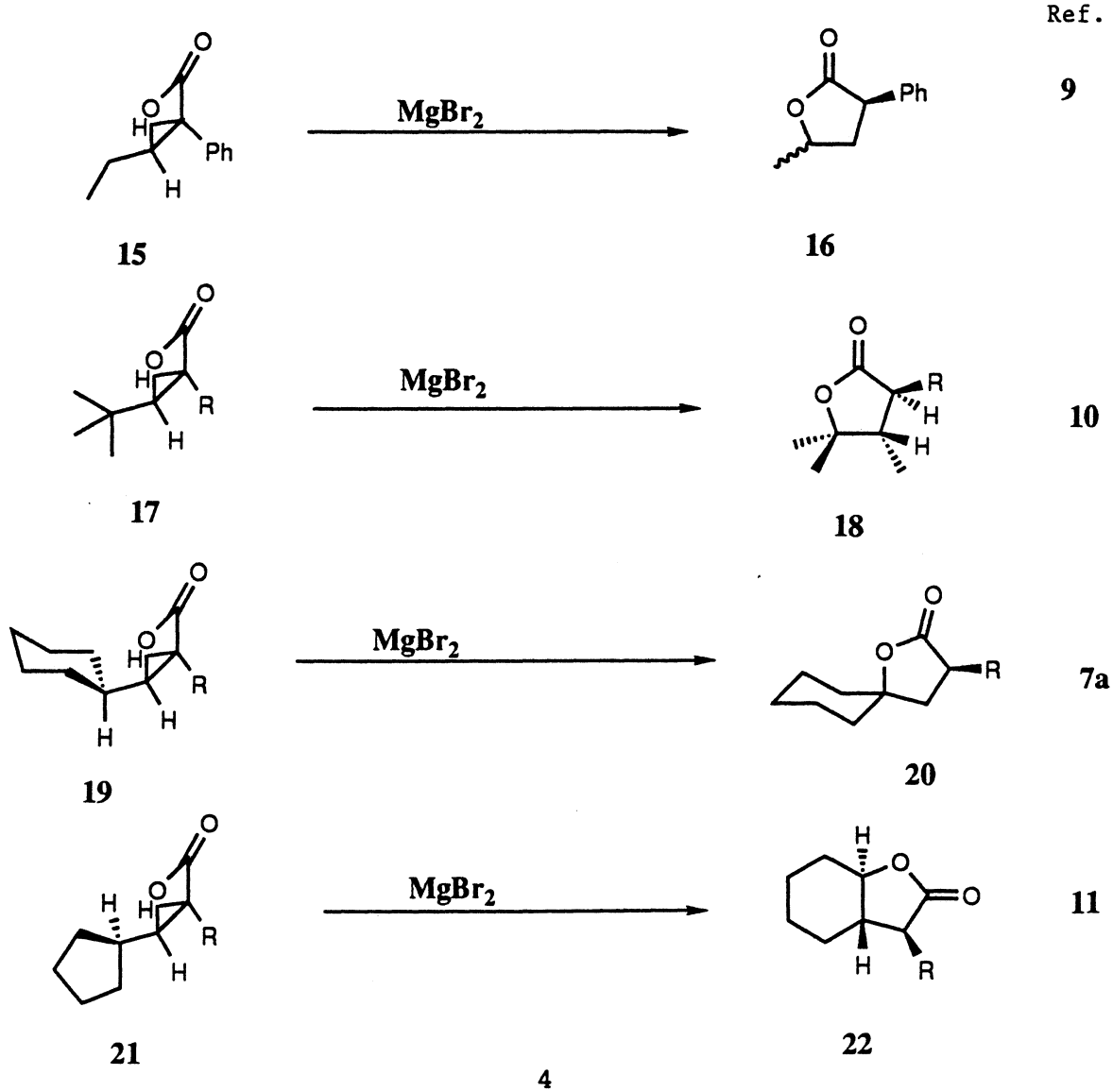
reversible process, requiring an anticoplanar alignment of the migrating bonds as depicted in Eqn. 1:



Eqn. 1

The rearrangement in our system, although superficially resembling a dyotropic process, is more adequately explained by the invocation of cationic intermediates. As shall be seen, the

Scheme III

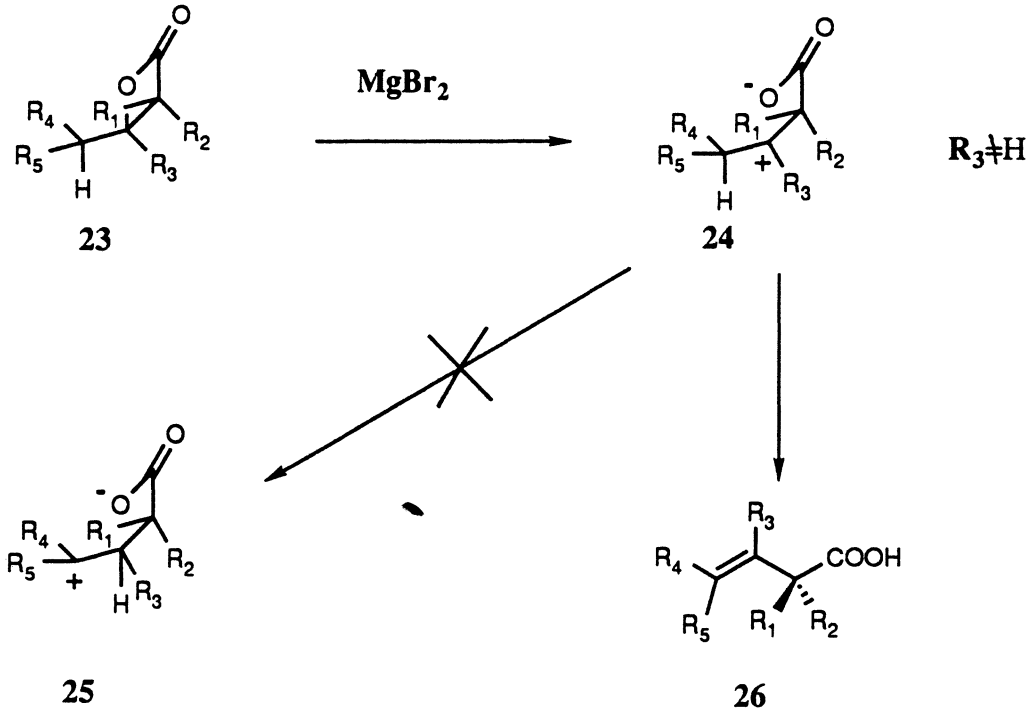


	Ref.
15 → 16	9
17 → 18	10
19 → 20	7a
21 → 22	11

migration of hydride or alkyl groups toward putative carbocations formed via ß-lactone ionization usually tend to form more or equally stable cations. However, the events subsequent to cation formation must be extremely rapid (at least relative to single bond rotation), since very high stereospecificity is observed.

This sequence is very useful since three contiguous asymmetric centers can be stereospecifically fixed in one step (e.g., **21⟶22**). This methodology for the direct stereocontrolled construction of butyrolactones has wide practical application. Various α-substituted monocylic, spiro, and *trans*-fused butyrolactones were synthesized by this procedure (Scheme III). In the case of cyclopentyl ß-lactones, *trans*-fused butyrolactones are formed in place of spiro species due to the exothermic expansion

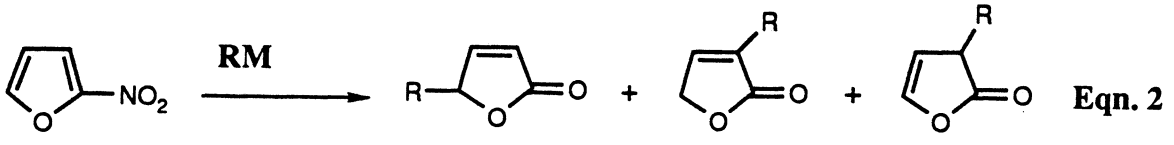
Scheme IV



from a five- to six-membered ring (ca. 6 kcal/mol).[12]

If the ß-lactone ring oxygen atom is affixed to a tertiary carbon, an alternate reaction pathway is followed. The rearrangement from tertiary cation **24** to a secondary, or primary cation **25** is unfavorable in energy, and loss of an adjacent proton (in the Γ-position) to generate an alkene is observed instead of the formation of Γ-lactones. The Γ-hydrogen aligned appropriately with the empty "**p**" orbital of the ß-cation, is lost in preference to the orthogonally-situated α-hydrogen, even though loss of the latter would provide the thermodynamically favored, conjugated alkene. Thus, this sequence provides a new, efficient, and stereocontrolled synthetic method for preparation of ß,Γ-unsaturated acids **26** (Scheme IV).[13]

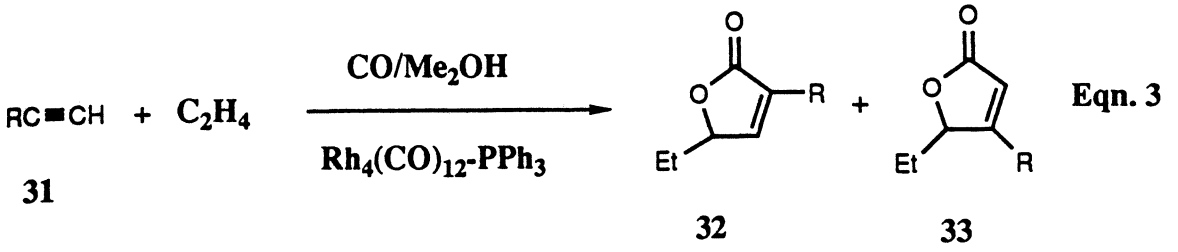
α,ß-Butenolides (2(5H)furanones) are a very common moiety in naturally occurring products possessing sequences of consecutive, highly functionalized carbon atoms. A number of methods have been documented for the preparation of butenolides. Pecunioso reported[14] the conjugate addition of nucleophiles (Grignard reagents) to 2-nitrofuran **27** to give butenolides **28** and **29**, which were contaminated by other alkylfuranones (Eqn. 2).



27 **28** **29** **30** **Eqn. 2**

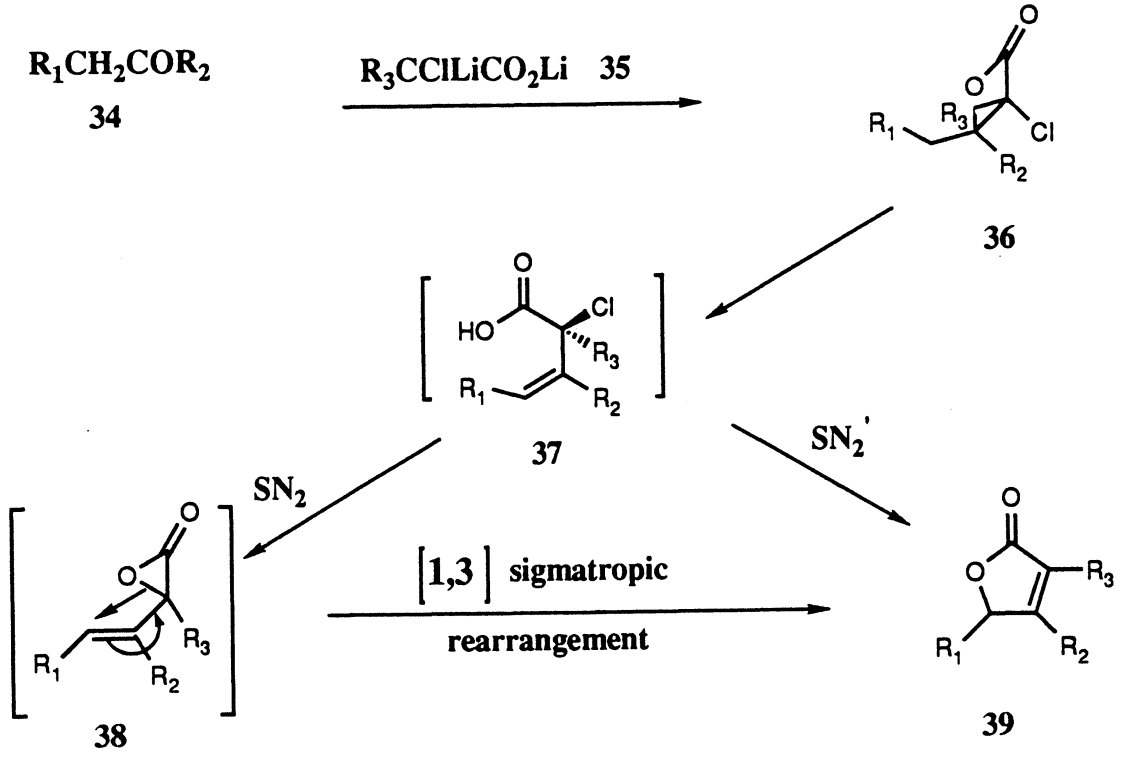
R= n-butyl, n-octyl, i-propyl, etc.

Quite recently, Hong and co-workers[15] published a rhodium-carbonyl-catalyzed method to synthesize butenolides. Cross-hydrocarbonylation of 1-alkyne **31** and ethylene with carbon monoxide in the presence of a $Rh_4(CO)_{12}$-PPh_3 catalyst afforded a mixture of butenolides **32** and **33** (Eqn. 3).



Based on previous research[16] in our group, ß-lactones with a chlorine atom in the α-position (which are available from the dianions **35** of α-chloro acetic acids and carbonyl compounds **34**)

Scheme V



rearrange to butenolides under the influence of Lewis acids (Scheme V). The two most likely mechanisms both involve formation of α-chloro-ß,Γ-unsaturated acid **37**, although it is not known currently which mechanism is operative.

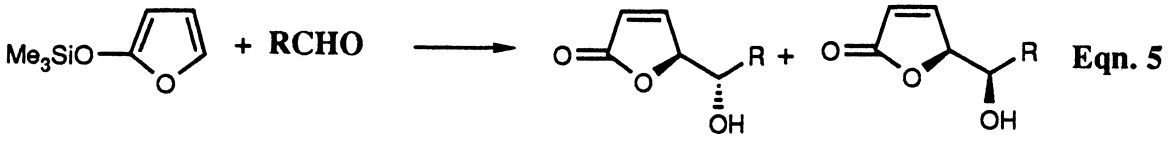
Primary bromides or iodides **40** alkylate[6,17] the commercially available 2-trimethylsilyloxyfuran **41** in the presence of

41 **40** **42** Eqn. 4

X=Br, I; R=Et, n-Pr, n-Bu, n-pentyl, etc.

silver trifluoroacetate to give 5-substituted butenolides **42** (Eqn.4).

Condensation[18] of α-trimethylsilyloxyfuran **41** with aldehydes **43** resulted in the diastereoselective formation of 5-hydroxyalkylbutenolides **44** and **45** (selectivity varied much based on the Lewis acids (Eqn. 5).

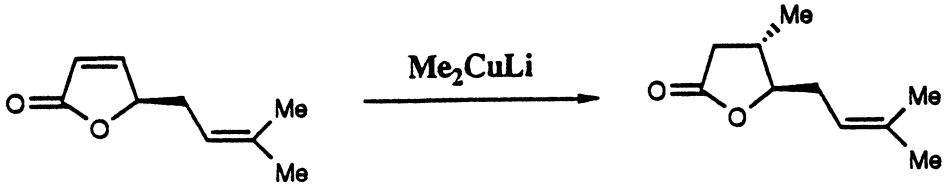


41 **43** **44** **45** Eqn. 5

R= n-pentyl, benzyl, i-Pr, t-Bu

As opposed to silyloxyfurans, the lithium enolate of 2(5H)-furanone condensed[19] with aldehydes to afford a mixture of 5-hydroxyalkyl butenolides with low diastereoselectivity. Buteno-

lides are very useful intermediates due to their potential for further functionalization of the α and ß carbon atoms, and, when employed in enantiopure form, can be used as templates for the enantioselective synthesis of natural products. Additionally, reduction of the double bond to give the corresponding butyrolactone is possible without racemization. The naturally occurring threo and erythro 5-hydroxy-4-decanolides (L factors) were prepared[19] from 5-hydroxyalkyl butenolides by reduction with sodium borohydride ($NaBH_4$). Eldanolide **47**, the sex attractant pheromone of the male African sugar cane borer *Eldana Saccharina*, was synthesized[17a] from butenolide **46** by the conjugate addition of lithium dimethyl-cuprate (Eqn. 6).

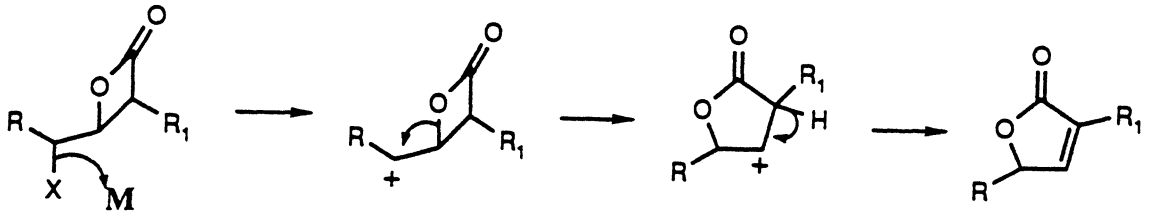


46 **47** **Eqn. 6**

As has been previously mentioned, in the case of a less-substituted carbon affixed to a ß-lactone ring, a ß,Γ-unsaturated acid forms after ring opening and loss of proton (Scheme IV). The purpose of the research described herein was to address the following question: If a nucleofugal group (Br, NR_2, etc.) were introduced at the Γ-position, thus creating a positive center adjacent to the ß-lactone ring oxygen via the influence of appropriate reagents, would this developing cationic charge

initiate a migration of the ß-lactone ring oxygen atom to the Γ-position, followed by loss of an electrofugal species such as a proton or trimethylsilyl group to produce butenolides (Scheme VI)?

Scheme VI



Carbocation formation is known to be initiated by the silver-catalyzed departure of halides,[20] and oxygen atoms may stabilize these carbocations via neighboring-group participation.[21] Thus, the scenario of oxygen migration to an adjacent cationic carbon, especially in light of the strain energy of ß-lactones, seemed very plausible.

An advantage of the proposed protocol was that the ring expansion of ß-lactones would be specifically directed to a less-substituted carbon atom followed by loss of α-proton to produce butenolides in contrast to the formation of ß,Γ-unsaturated carboxylic acids described previously.

Described herein are the full details of our study, including experimental details for the synthesis of various substituted ß-lactones and butenolides, and a discussion of the rearrangement/elimination mechanism of Γ-bromo ß-lactones.

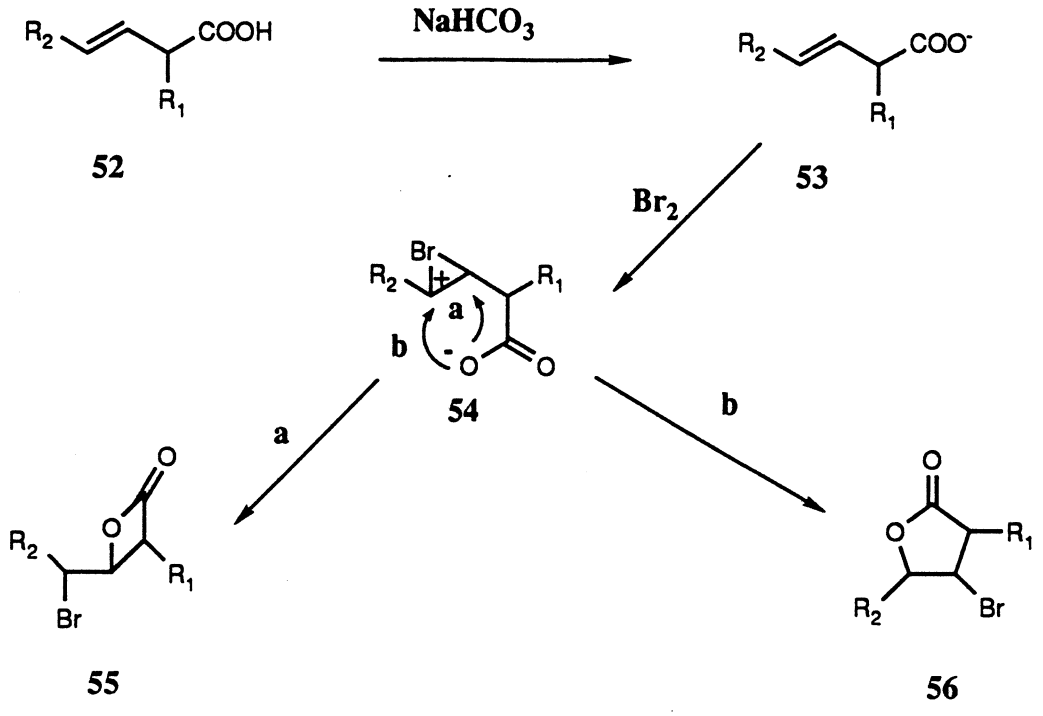
RESULTS AND DISCUSSION

A. Bromolactonization and Ring Expansion/Elimination Reactions of Γ-Bromo ß-Lactones in the Presence of Silver Salts.

Many nucleofugal groups (leaving groups) have been utilized in the formation of carbocations, including halides,[20] sulfonate esters,[22] sulfones,[23] and diazonium ions.[24] All four of these leaving groups can easily be affixed adjacent to a carbonyl group. The first leaving group we examined was the bromine atom. Γ-Bromo ß-lactones were prepared by the cyclofunctionalization of ß,Γ-unsaturated carboxylic acids **52** through treatment with bromine under basic conditions[25] (bromolactonization) as detailed in Scheme VII. ß,Γ-Unsaturated acids were dissolved in saturated sodium bicarbonate to produce clear, colorless solutions of ß,Γ-unsaturated carboxylate salts **53**, which were then treated with bromine to effect the bromolactonization reaction. The three-membered-ring bromonium ion **54** is formed by electrophilic attack of bromine upon the double bond. At this point, nucleophilic intramolecular attack of the carboxylate ion will occur at both positions **"a"** and **"b"**. Attacking at position **"a"** gives Γ-bromo ß-lactones **55** (as a mixture of *cis* and *trans* isomers), and attacking at position **"b"** affords Γ-lactones **56**. The ratio of *cis* and *trans* isomers of the ß-lactones was determined primarily by ^{1}H NMR spectrum.

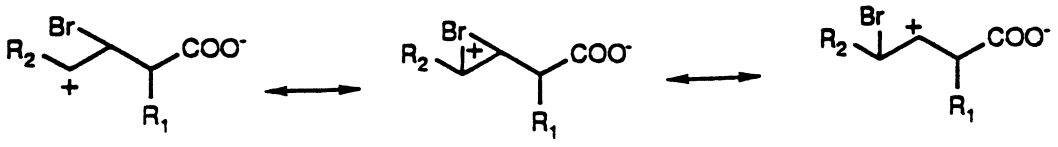
Bromolactonization is known to be a kinetically-controlled process.[26] Formation of ß-lactones is faster than that of Γ-lactones, but the latter are more stable. Long reaction times

Scheme VII



and high temperature favor the formation of the thermodynamically stable Γ-lactone products. Not surprisingly, Γ-bromo ß-lactone **55** was the only product (as ascertained by IR absorptions at 1810-1835 cm^{-1}, ascribed to the ß-lactone carbonyl groups) when R_2 was H, while a mixture of Γ-bromo ß-lactones **55** and ß-bromo Γ-lactones **56** in a ratio of about 50:50 was formed when R_2 was an alkyl group. The ratio of ß- and Γ-isomers was easily established by IR via comparison of the relative magnitudes of

the carbonyl absorption bands (1770 cm^{-1} for butyrolactones). The dependence of product distribution upon substrate structure is rationalized by resonance contributors **57** and **58** of the



Eqn. 7

57 **54** **58**

Table 1: Preparation of Γ-bromo ß-lactones **55** by bromolactonization of ß,Γ-unsaturated acids **52**

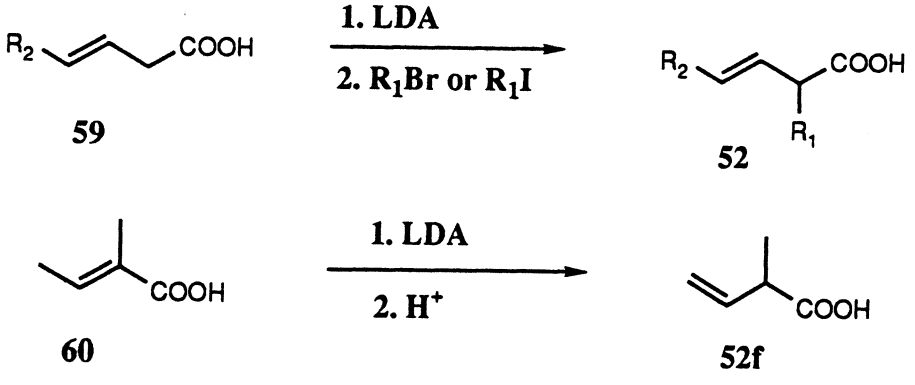
Entry	R_1	R_2	Yield (%)[a]	IR (cm-1)
a	H	H	37.3	1834.2
b	H	Et	60.4	1820, 1770
c	n-Bu	H	65.9	1820
d	Et	H	39.8	1827
e	Et	Et	67.0	1820, 1770
f	Me	H	41.8	1828.9
g[b]	Me	H	25.8	1826.6
h	$PhCH_2$	H	50.3	1818
i	$PhCH_2$	Et	58.4	1828.5, 1770
j	Me_2CH	H	24.0	1820
k	Me_2CH	Et	77.7	1833.9, 1770

Note: a Yield calculated from crude products; in the case of mixtures, the yield represents the sum of ß-lactone and Γ-lactone
b. Iodine in place of bromine.

bromoniun ion **54** (Eqn. 7). In the case of R_2=H, **58** (featuring a secondary carbocation) is more stable than **57** (incorporating a primary carbocation). When R_2 is an alkyl group, both **57** and **58** are secondary cations with similar stability. The ratio of *trans/cis* ß-lactones increased, but the overall chemical yield decreased, by using iodine in place of bromine in the case of R_1=Me and R_2=H. A considerable number of Γ-bromo ß-lactones were synthesized by the bromolactonization of ß,Γ-unsaturated acids, and are compiled in Table 1.

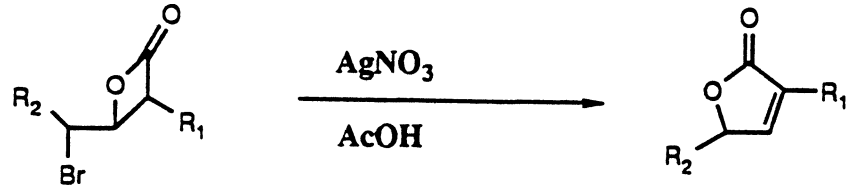
The α-substituted ß,Γ-unsaturated acids used as bromolactonization substrates were prepared by the alkylation of the corresponding ß,Γ-unsaturated acids (commercially available) with alkyl bromides or iodides, or via deconjugation of α,ß-unsaturated acids by treatment with the lithium diisopropylamide followed by kinetic protonation in yields of 40-60%; as shown in Scheme VIII.[27]

Scheme VIII



With a representative supply of Γ-bromo ß-lactones in hand, attention was then directed to the ring expansion/elimination

reactions. After considerable experimentation, the sequence depicted in Eqn. 8 was developed. Γ-Bromo ß-lactones **55** were treated with silver nitrate in refluxing acetic acid, effecting



55 **61** **Eqn. 8**

the anticipated ring expansion followed by the simultaneous elimination of the α-proton, providing the butenolides **61**. The IR absorption bond of the ß-lactone carbonyl groups at 1810-1830

Table 2. Synthesis of substituted butenolides **61** (substituted 2(5H)furanones)

Entry	R_1	R_2	Yield (%)[a]	IR (cm^{-1})
a	H	H	30.7	3060, 1740, 1650
b	n-Bu	H	50.3	1766.4, 1746.6, 1640.6
c	Et	Et	64.4	3028.9, 1750.0, 1651.5
d	H	Et	30.7	3060, 1740, 1650
e	$PhCH_2$	Et	75.1	3064.2, 1754.2, 1652.4
f	Me_2CH	Et	65.5	3085.9, 1752.4, 1640.4
g	Me	H	59.3	3010, 1770, 1740, 1630
h	Me_2CH	H	51.8	1760, 1720, 1620
i	$PhCH_2$	H	52.4	3030.4, 1778.7, 1750.3 1651.7

Note a: Yield calculated from crude products

cm^{-1} completely shifted to about 1750 cm^{-1}, accompanied occasionally by another band around 1770 cm^{-1}. Butenolides are known to often exhibit two carbonyl bands in the IR spectrum due to intramolecular vibrational effects.[28] In any event, this newly developed methodology provides an expedient and efficient route to synthesize 3- or 5-substituted or 3,5-disubstituted butenolides in yields of 50-75%, Results are compiled in Table 2. The bromolactonization and ring expansion/elimination reactions are not air- or water-sensitive and are operationally quite facile. In some cases, purification of butenolides was very difficult since they decomposed partially on attempted column chromatography on silica gel.

To our surprise, we found that relatively high energy was required to effect the ring expansion/elimination process. It was necessary to expose the Γ-bromo ß-lactones to solid silver nitrate in acetic acid, refluxing at 120 °C for 16-20 hours, to force the reaction to completion. The conditions for ring expansion/elimination were investigated by using Γ-bromo α-methyl ß-lactone **55f** as a model substrate. No product was obtained using silver nitrate in CH_3CN with or without concentrated sulfuric acid (room temperature and at reflux temperature), silver nitrate in N,N-dimethylformamide (DMF), silver acetate in acetic acid, or silver trifluoroacetate in acetic acid at room temperature. After these unsuccessful experiments, we heated the last two reagent systems in an attempt to drive the reaction, but observed no obvious improvement compared to silver nitrate in refluxing

acetic acid. It was also found that all of the ß-lactones were consumed after exposure to silver nitrate in N,N-dimethylformamide at 155 °C (the boiling point of N,N-dimethylformamide is 153 °C) for seven hours, and after treatment with silver nitrate

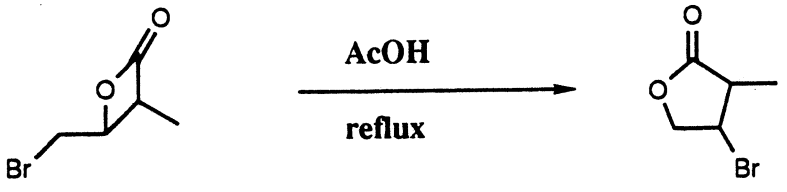
Table 3: Ring expansion/elimination of Γ-bromo α-methyl ß-lactones **55f**

Entry	Reagent[a]	Reaction Temp. & Time	Results
1	$AgNO_3$/AcOH	Rm. Temp., 48h	No reaction
2	$AgNO_3/CH_3CN$	Rm. Temp., 48h	No reaction
3	$AgNO_3/CH_3CN$	Reflux, 20h	No reaction
4	$AgNO_3/CH_3CN/H_2SO_4$	Rm. Temp., 24h	No reaction
5	$AgNO_3/CH_3CN/H_2SO_4$	Reflux, 20h	No reaction
6	AgOAc/AcOH	Rm. Temp., 37h	No reaction
7	AgOAC/AcOH	Reflux, 5h	Incomplete
8	AgOAc/DMF	Reflux, 7h	Complete, 42.4%
9	$AgNO_3$/DMF	Reflux, 6h	Incomplete
10	AgO_2CCF_3/AcOH	Rm. Temp., 42h	Only a little reaction
11	AgO_2CCF_3/AcOH	Reflux, 18h	Complete
12	$AgNO_3$/AcOH	Reflux, 16h	Complete, 59.3%
13	$AgNO_3/AcOH/H_2O$	Reflux, 4h	Complete, 47.5%
14[b]	$AgNO_3$/AcOH	Reflux, 25	Complete, 64.0%

Note: a. The ratio of moles of ß-lactone and $AgNO_3$ is 1:1.5.
b. Substrate is Γ-iodo α-methyl ß-lactone.

in aqueous acetic acid (the quantity of water determined by how much was needed to dissolve the silver nitrate) for four hours. The yields in both cases decreased (42.4% in N,N-dimethylformamide and 47.5% in the mixed solvent). No obvious improvement was observed using the corresponding Γ-iodo ß-lactone in place of the Γ-bromo ß-compound. The results obtained are compiled in Table 3. The most efficacious reagent combination was silver nitrate in refluxing acetic acid.

Γ-Halo ß-lactones are easily isomerized to the corresponding thermodynamically more stable ß-halo Γ-lactones upon heating.[26] So far the mechanism for this rearrangement is not clear, but experimental evidence, including high stereospecificity, suggests a quasi-concerted process. We found that refluxing Γ-bromo α-methyl ß-lactone **55f** in acetic acid (no silver ion present) for 17 hours resulted in partial 1,2 bromine migration accompanied by simultaneous expansion of the ß-lactone to Γ-isomer **56f** (Eqn. 9).



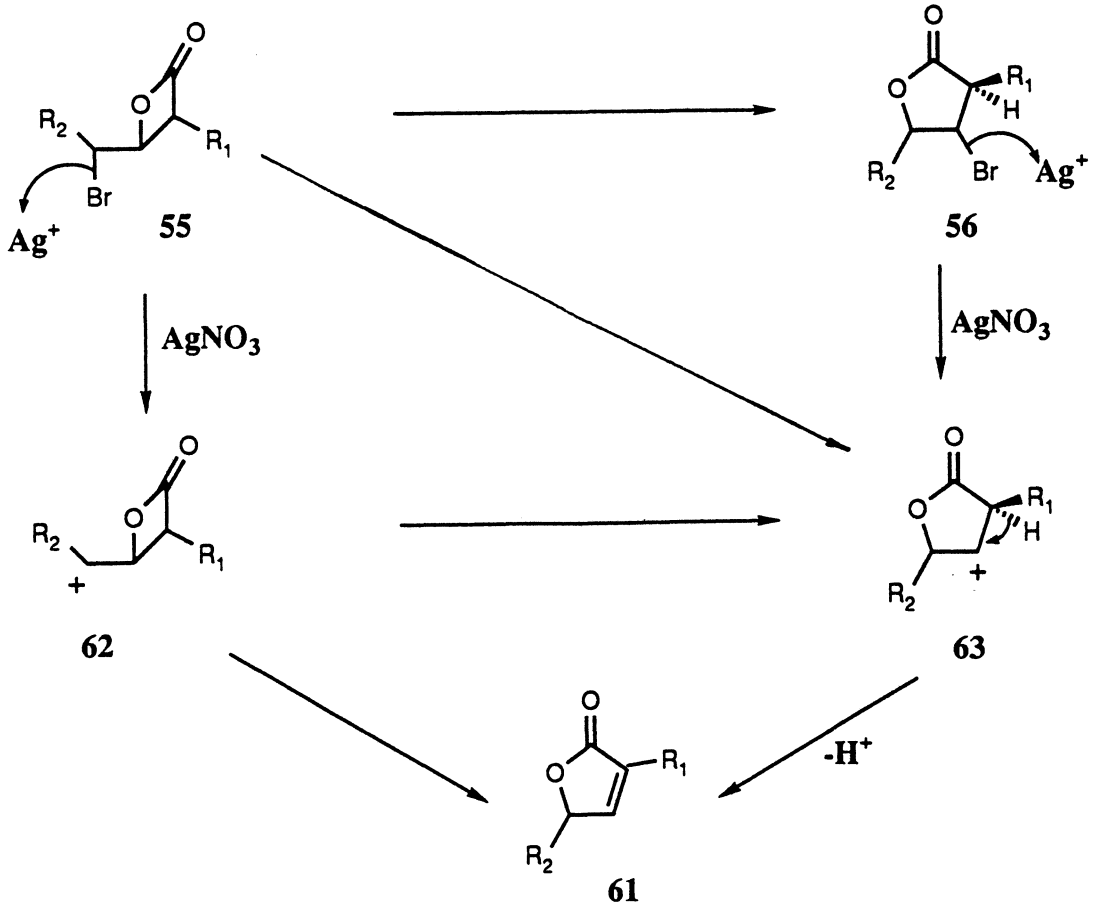
55f **56f** **Eqn. 9**

It is noteworthy in this context that ß-lactones are prone to thermal decarboxylation at high temperature;[29] for example, Γ-(1-bromopropyl) ß-lactone **55d** began to decarboxylate at 150 °C.

On the basis of the results obtained above, we propose the

mechanism depicted below (Scheme IX). It is likely that ß-lactones **55** undergo partial thermal rearrangement to Γ-lactones **56** during heating. The silver cation would then effect departure of bromine (or iodine) from both ß-lactones **55** and Γ-lactones **56**, to create cations **62** and **63**, respectively. These processes most likely occur in a heterogeneous fashion on the surface of the silver nitrate (which is not particularly soluble in acetic acid even at reflux) and are thus relatively slow steps. The positive center adjacent to the ß-lactone ring oxygen then results in ring expansion, forming the new carbocation at the ß-carbon of the intermediate **63**. Elimination of the α-proton finally affords

Scheme IX

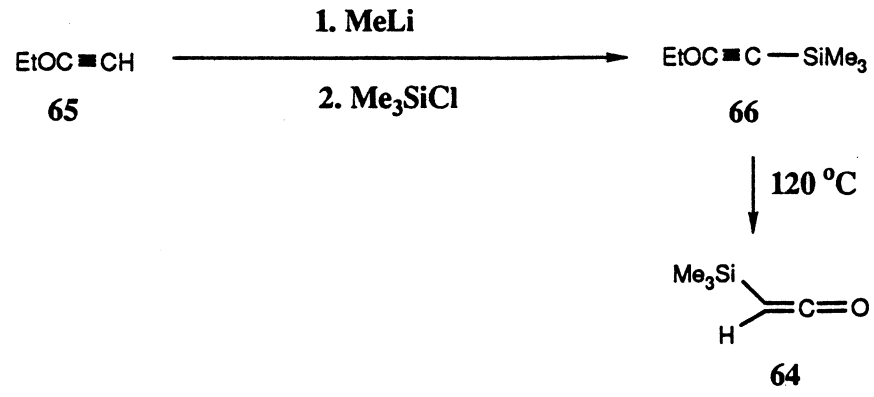


butenolides **61**. The rate of the ring expansion/elimination process has no obvious relation to the nature of the substituents attached to the α- and Γ-position. No acceleration with iodine in place of bromine (which would be expected for a homogeneous reaction in which nucleofuge departure is rate-determining) indicated that the formation of carbocation probably occurs on the surface of silver nitrate (and, of course, is still the slow rate-determining step). Thus, both Γ-bromo ß-lactones and the corresponding ß-bromo Γ-lactones gave the same product without the need for separation. As additional confirmation of the "dual mechanism" theory, we isolated the Γ-bromo ß-lactone **55b** and ß-bromo Γ-lactone **56b** by column chromatography using ethyl acetate-hexane (1:4) as the eluent, and treated them individually with silver nitrate in refluxing acetic acid respectively. Both cases produced the same product (**61d**).

B. Cycloaddition of Trimethylsilylketene to Carbonyl Compounds under $BF_3 \cdot OEt_2$ Catalysis

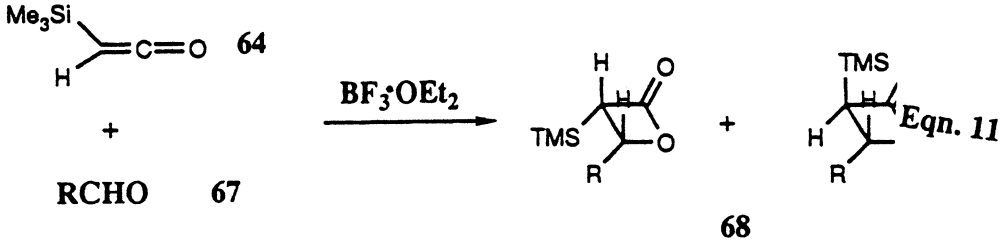
After successful results were obtained with Γ-bromo ß-lactones, we turned to explore the potential of cationic ß-lactone ring expansions accompanied by the elimination of silane electrofuges. Due to the low-energy, vacant d orbitals on the silicon atom, silyl moieties such as the trimethylsilyl group are far more efficacious electrofuges (leaving groups that depart as

positive species, leaving behind their bonding electron pair) than protons; it was anticipated that their presence in the α-position of ß-lactones would hasten the ring expansion/elimination sequence. The α-trimethylsilyl ß-lactones were prepared[29, 30] via the cycloaddition of trimethylsilylketene **64** to aldehydes bearing cation progenitors in the α-position. Unlike other ketenes, trimethylsilylketene is very stable and amenable to storage for long periods. It displays high reactivity, does not dimerize upon heating, does not cycloadd to double bonds, and reacts easily with aldehydes under the catalysis of $BF_3 \cdot OEt_2$ to produce α-trimethylsilyl ß-lactones. There are three methods reported[30c, 31] for the synthesis of trimethylsilylketene **64**; we prepared the material from ethoxyacetylene **65** and chlorotrimethylsilane according to the procedure of Ruden.[30c] As shown in Eqn. 10, trimethylsilylethoxyacetylene **66** was prepared first via deprotonation of commercially available ethyl ethynyl ether, and then underwent pyrolysis at 120 °C to provide the product in 36.6% yield after redistillation.



Eqn. 10

The cycloaddition of trimethylsilylketene **64** to saturated aldehydes **67** in the presence of catalytic $BF_3 \cdot OEt_2$ gave a mixture of *cis* and *trans* α-trimethylsily ß-lactones (3-trimethylsilyl-oxetan-2-ones) **68** in favor of the *trans* isomer, consistent with literature reports(Eqn. 11).[30] The *cis* and *trans* isomers were easily distinguished by the coupling constants for the methinyl hydrogens in ^1H NMR spectrum. The coupling constant for methinyl

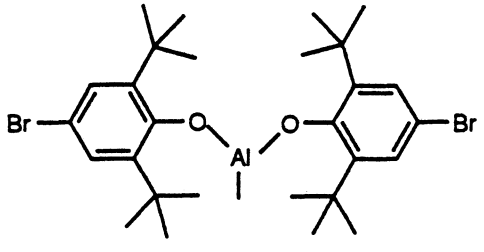


Eqn. 11

68

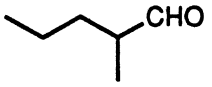
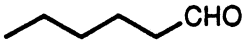
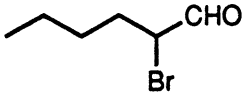
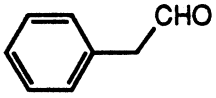
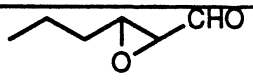
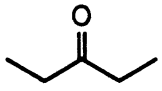
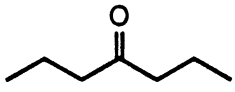
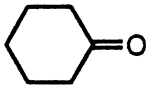
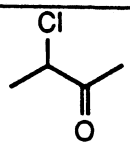
	cis		*trans*
R=i-pentyl	2	:	3
R=n-pentyl	1	:	2

hydrogens in *cis* isomer is 6.0 Hz in contrast to 4.0 Hz for *trans* isomer. Recently, it has been reported that yield and *cis*-selectivity can be dramatically increased by employing a hindered catalyst, methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR).[32]



MABR

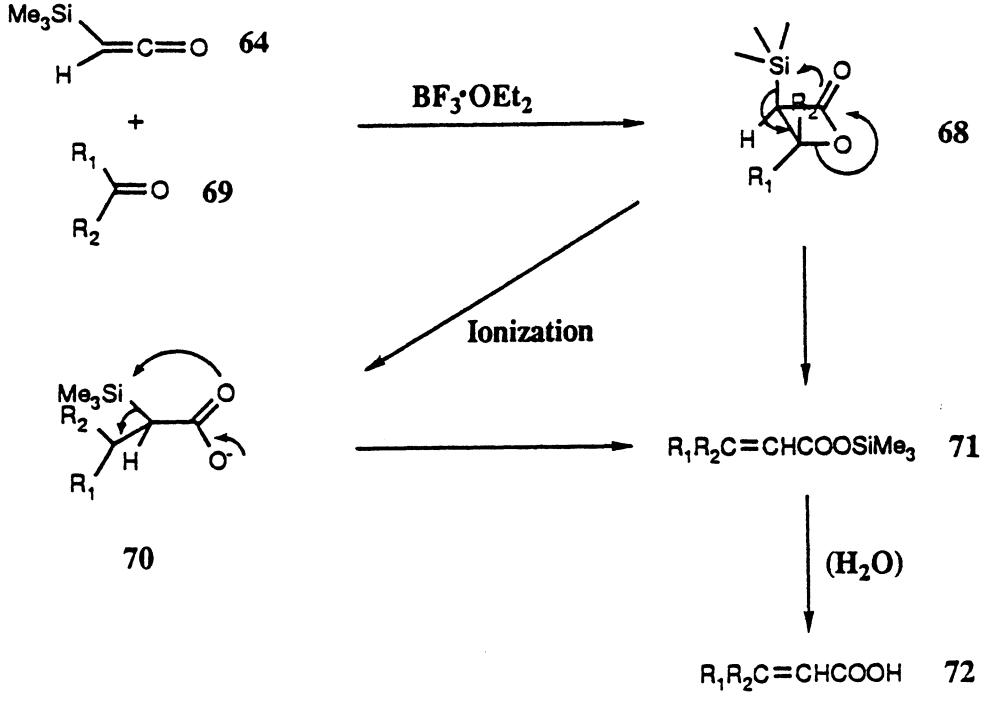
Table 4: Cycloaddition of trimethylsilylketene 64 to aldehydes or ketones.

Entry	Carbonyl compounds[a]	Products	Yield[b] (%)	IR (cm^{-1})
a		68a, 71a, 72a 72a	101.7 40.0	1807, 1696, 1649 3100, 1697, 1648
b		68b, 71b, 72b 68b	98.1 44.9	1800, 1710, 1635 1807.9
c		68c 72c	60 /	1806.2 3210, 1702, 1652
d		68d, 71d, 72d 72d	99.8 60.6	1818, 1712, 1652 3395, 1700, 1652
e		68e, 71e, 72e	89.6	1806.1, 1741.0, 1719.1, 1652.4
f		72f	86.3	3200, 1702.3, 1642.6, 1602.7
g		81, 82	80	3400, 1765, 1732, 1620
h		71h, 72h	51.3	3124, 1709, 1643
i		71i, 72i	80.3	1695, 1650
j		71j, 72j	64.8	3356, 1709, 1636
k		68k, 71k, 72k	36.2	1829.5, 1807.5, 1724.5, 1635.2

Note: a: The ratio of carbonyl compound : 64 was 1:1.05
b: Yield calculated from crude products except entry b for 68b and entry c for 68c (which were calculated from isolated products)

Employing the cycloaddition of trimethylsilylketene **64** to ketones or α,ß-unsaturated aldehydes in order to prepare α-trimethylsilyl ß-lactones is inefficient, since the predominant products are the corresponding unsaturated acids or their trimethylsilyl esters (Table 4). Although the ß-lactones indeed form, subsequent (very facile) ionization of the derived ß-lactones precludes their ready isolation. As outlined in Scheme X, a direct intramolecular rearrangement (**68**⟶**71**) or a silicon migration to oxygen after ionization of ß-lactones (**68**⟶**70**⟶**71**) occurs to produce trimethylsilyl esters **71** once the ß-lactones were formed (Scheme X). Hydrolysis of these esters even under the condition of evaporation of solvent *in vacuo* afforded unsaturated acids **72**. Even though these results are unexpected, they constitute a new, practical route for synthesis of α,ß-

Scheme X

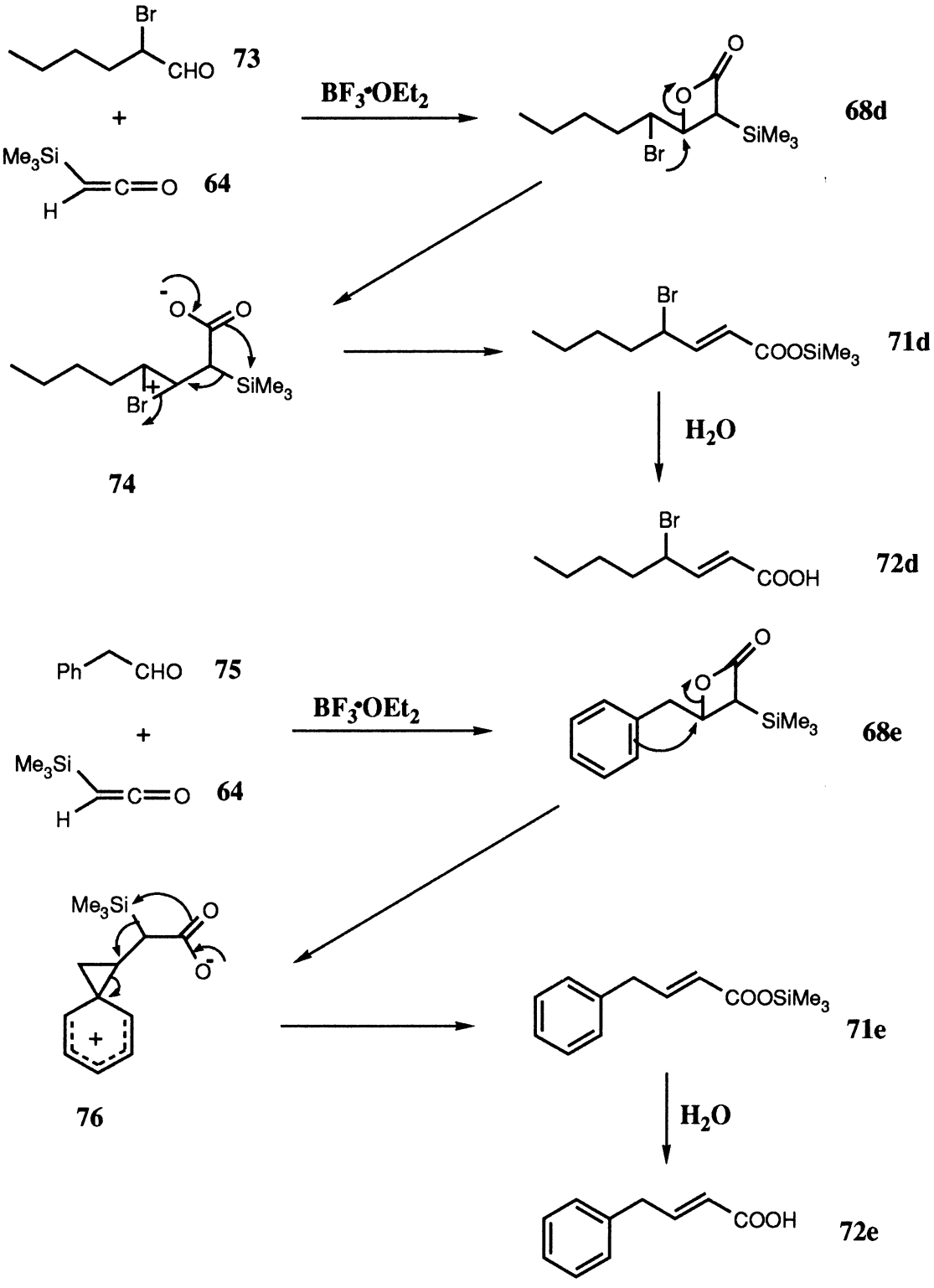


unsaturated acids from carbonyl compounds via a two-carbon homologation reaction. This alternative to conventional Wittig chemistry is worthy of further development and refinement.

The cycloaddition of trimethylsilyketene **64** to 3-chloro-2-butanone gave a mixture of the α,ß-unsaturated acid, its trimethylsilyl ester, and the ß-lactone (that decomposed on attempted column chromatography). The ability to isolate of the ß-lactone for this precursor is probably a consequence of the electron-withdrawing chlorine atom destablizing the intermediate **70b**.

At this point, we attempted to synthesize a Γ-bromo α-trimethylsilyl ß-lactone by the cycloaddition of trimethylsilylketene **64** to 2-bromohexanal **73** (which is available[33] from hexanal, *tert*-butylbromide, and dimethyl sulfoxide in 97.5% yield). The ß-lactone **68d** was detectable via IR spectroscopy in the crude product, but unfortunately only 4-bromo-2-octenoic acid **72d** was recovered after purification by column chromatography on silica gel. It is reasonable to surmise that bromine facilitated the ionization of the α-trimethylsilyl ß-lactone **68d** via anchimeric participation, and that bromonium ion **74** was involved as an intermediate. In an attempt to delineate the operative factors in this entirely unexpected outcome, we used phenylacetaldehyde **75** instead of 2-bromohexanal as a cycloaddition partner, since aromatic rings are well-known electron donors in neighboring group participation reaction, but can not function as nucleo

Scheme XI


Br
CHO
73
+
Me3Si
H
C=O
64
BF3•OEt2
O
O
SiMe3
Br
68d
-O
O
SiMe3
Br
+
74
Br
COOSiMe3
71d
H2O
Br
COOH
72d
Ph
CHO
75
BF3•OEt2
O
O
SiMe3
68e
Me3Si
O
O-
+
76
COOSiMe3
71e
H2O
COOH
72e

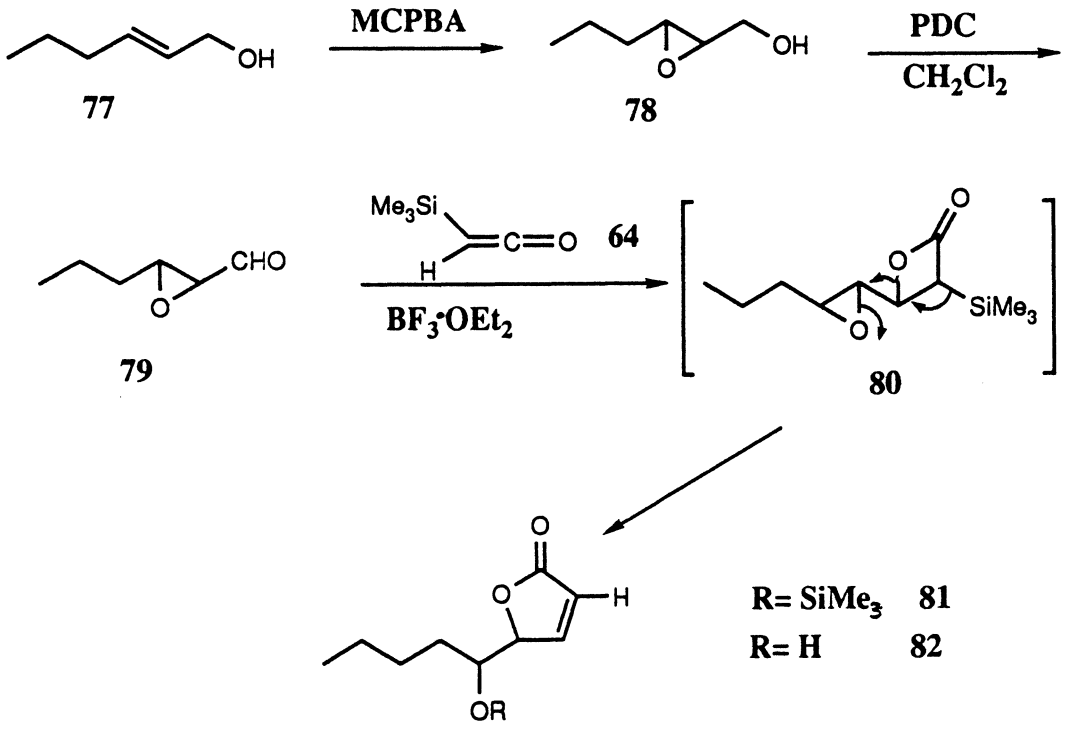
fuges. In this event, an analogous reaction was observed, probably involving intermediate **76** as shown in Scheme XI.

Having succeeded in the separation of the α-trimethylsilyl ß-lactone from hexanal, we focused our attention on the cycloaddition of trimethylsilylketene **64** to 2,3-epoxyhexanal **79**, in the hope of synthesizing a 5-(1-hydroxypentyl) butenolide. We chose an epoxide as a target nucleofuge because epoxides should not interfere in ketene cycloaddition reactions, and are easily opened under the influence of $BF_3 \cdot OEt_2$ in the presence of nucleophiles to afford hydroxy groups. 5-(1-Hydroxyalkyl) butenolides are widely distributed naturally occurring products and are valuable synthetic intermediates. The Sharpless protocol provides highly enantiopure epoxides[34] which, we theorized, could rearrange into 5-(1-hydroxyalkyl) butenolides with complete transfer of chirality. This very significant feature of the sequence arises by virtue of the bond-alignment requirements of the rearrangement and its consequent stereospecificity.

The first goal was to execute the sequence on racemic material. Thus, the plan of attack, as outlined in Scheme XII, involved the epoxidation of *trans*-2-hexen-1-ol **77** by 3-chloroperoxybenzoic acid (MCPBA) to furnish 2,3-epoxyhexan-1-ol **78**, which was then to be oxidized by pyridinium dichromate (PDC) in dichloromethane solvent to afford 2,3-epoxyhexanal **79**.[35] Cycloaddition of trimethylsilylketene **64** to epoxy aldehyde **79** with a catalytic amount of boron trifluoride would then afford the tri

methylsilyl ß-lactone **80**. It was our prediction that the presence of the boron trifluoride used as a cycloaddition catalyst would then initiate the ring expansion/elimination via interaction with the epoxide functionality *in situ* without the need for isolation of the ß-lactone, and then afford the corresponding 5-(1-hydroxypentyl) butenolide. In our experiment, we

Scheme XII



found that it was very difficult to purify the 2,3-epoxyhexanal even though the yield of crude product was quite high. Unfortunately, the cycloaddition reaction with trimethylsilylketene was not clear and afforded the multicomponent mixture (we attempted

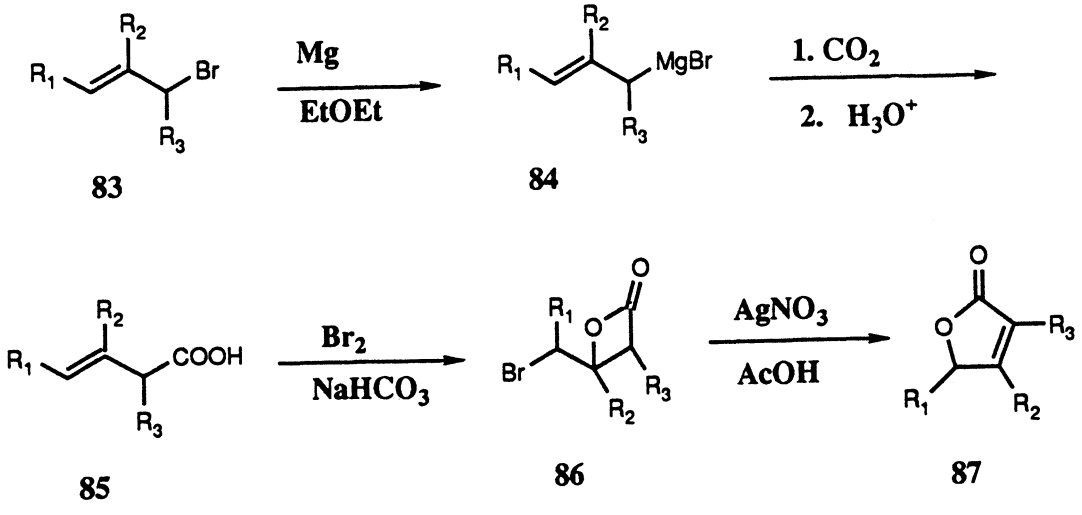
to isolate the pure butenolide, but did not get the satisfactory ^{1}H and ^{13}C NMR spectra). The IR spectrum and the NMR spectra indicated that the butenolide was there.

C. Prospects for Future Research

Even though many promising results were obtained during this study, many areas for productive future research present themselves.

1. A Grignard reaction could be employed to synthesize the multi-substituted ß,Γ-unsaturated acids[36] which then could be transformed to the corresponding ß-lactones **85**. These ß-lactones will generate substituted butenolides **87** in any desired substitution pattern in the presence of silver salts, as diagrammed in Scheme XIII.

Scheme XIII



83 **84** **85** **86** **87**

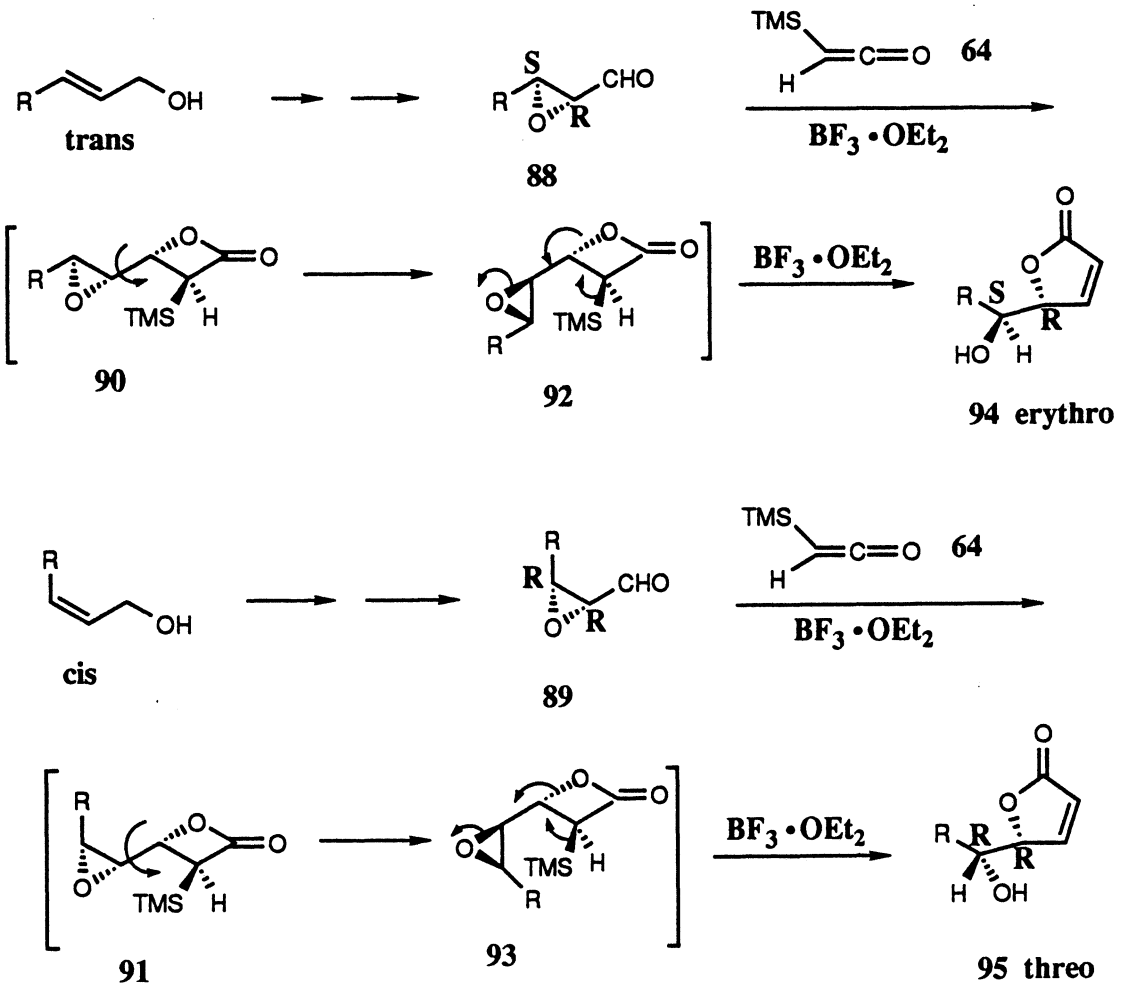
2. Employing different Lewis acids[32] such as diethylaluminum chloride (Et_2AlCl) or methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide (MABR) increases both the chemical yield of ß-lactone in the cycloaddition of trimethylsilylketene to aldehydes. For example, the cycloaddition of trimethylsilylketene to propionaldehyde by Et_2AlCl catalysis produced α-trimethylsilyl ß-lactone in 71% yield, and afforded *cis*-α-trimethylsilyl ß-lactone exclusively in 82% yield with the bulky organoaluminum reagent, MABR.[32] Then, further ring expansion/elimination reaction could be examined on the ß-lactones.

3. Introducing other leaving groups to the α-position of aldehydes, such as methoxyethoxymethyl (MEM),[37] thiophenyl,[38] benzyloxy,[39] dioxolane,[40] dialkylamino,[41] and investigating the cycloaddition of ketene to the above functionalized aldehydes may identify a nucleofuge less liable to initiate ß-lactone ionization than bromine.

4. The chemistry represented in Scheme XII needs to be refined and optimized, at which point analogous chemistry can be examined in the asymmetric series. Employing the Sharpless protocol provides enantiomerically pure epoxyalkanals **88** and **89**, which should cycloadd to trimethylsilylketene under Lewis acid catalysis to generate the corresponding ß-lactones **90** and **91**. It is likely that the boron trifluoride present will then initiate the ring expansion/elimination without the need for isolation of ß-lactones, to produce 5-(1-hydroxyalkyl) butenolides **94** and **95**

in high optical purity via the anti-coplanar orientation required by this rearrangement (Scheme XIV). The geometry of the starting material will determine the diastereomeric configuration of the 5-(1-hydroxyalkyl) butenolides (*cis* ⟶ thero and *trans* ⟶ erythro). This sequence could thus provide a method for the enantioselective synthesis of any of the four possible enantiomers of 5-(1-hydroxyalkyl) butenolides with complete stereocontrolled. This technology is currently not available.

Scheme XIV



CONCLUSION

We prepared Γ-bromo (or Γ-iodo) ß-lactones by cyclofunctionalization of α,ß-unsaturated carboxylic acids with bromine (or iodine) and investigated their ring expansion and elimination chemistry under different conditions. We found that the most efficacious reagent combination was silver nitrate in refluxing acetic acid. Generation of a carbocation via the action of a silver salt on the bromine nucleofuge initiated a migration of the ß-lactone ring oxygen atom to the Γ-position followed by loss of the α-proton to afford the butenolides.

In summary, we have developed a new and expedient method for the synthesis of multisubstituted butenolides in 30 to 75% yield. Extending this basic investigation should prove very useful in the synthesis of butenolide-containing natural products.

Cycloaddition of trimethylsilylketene to aldehydes provided α-trimethylsilyl ß-lactones, which were used for investigations of analogous ring expansion/elimination sequences. Even though the cycloaddition of trimethylsilylketene to ketones and α,ß-unsaturated aldehydes did not afford isolable ß-lactones, the sequence established a new method for the synthesis of unsaturated acids that involves a two-carbon homologation. The potential synthesis of 5-(1-hydroxyalkyl) butenolides, which are widespread in natural products, was investigated by the cycloaddition of ketene to α,ß-epoxy alkanals.

Experimental Section

Materials And Methods. Unless otherwise indicated, all reagents and solvents were purchased from Aldrich Chemical Co. or Spectrum Chemical Mfg. Corp. and used without further purification. Diethyl ether was freshly distilled from sodium and potassium metals and benzophenone under nitrogen, tetrahydrofuran was newly distilled from sodium metal and benzophenone under nitrogen, and dichloromethane was freshly distilled from calcium sulfate under nitrogen. 3-Chloroperoxybenzoic acid (MCPBA) was purified by washing the commercial product (50-60%) in dichloromethane with a phosphate buffer of pH 7.5 and drying the residue under reduced pressure.[42] Boron trifluoride etherate, diisopropylamine, and all aldehydes and ketones were distilled before use. All ^{1}H NMR spectra and ^{13}C NMR spectra were recorded on a GE QE-300 MHz FT-NMR spectrometer using deuteriochloroform ($CDCl_3$) or dimethyl sulfoxide-d_6 (DMSO-d_6) as solvents, employing tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in parts per million (ppm) (for ^{1}H NMR, s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and b, broad). Mass spectra were obtained by CI (70 eV). IR spectra were recorded on a Nicolet 20DX13 FT-IR spectrophotometer or Perkin-Elmer 1310 IR spectrophotometer. Boiling points are uncorrected. Melting points were obtained in capillary tubes with a Thomas Hooover Capillary Melting Point Apparatus and are uncorrected.

Thin-layer chromatography (TLC) was performed on Analtech silica gel GF chromatography plates using ethyl acetate-hexane (1:5 or 1:4) as the eluete. Flash chromatography was carried out on Aldrich silica gel 60 (200-400 mesh) All moisture- and air-sensitive reactions were conducted under a pressure of nitrogen in glassware that was dried at 120 °C for 4 hours before using.

2-Methyl-3-butenoic acid (52f). A solution of diisopropylamine (21.33 g, 30.2 mL, 0.216 mol, 220 mol%) in tetrahydrofuran (THF) (100 mL) in a 500 mL three-necked round bottom flask was cooled to -78 °C. Butyllithium (130 mL (1.58 M in hexane), 0.206 mol, 202 mol%) was added over 10 minutes. The resulting mixture was stirred for 20 minutes to obtain a pale yellow solution of lithium diisopropylamine (LDA). A solution of 2-methyl 2-butenoic acid (10 g, 0.098 mol) in 10 mL of THF was added to the rapidly stirred solution of LDA over a period of 30 min. The bath temperature was kept between -40 and -20 °C during the addition. The reaction mixture was stirred at room temperature for 1 h and then poured into a vigorously-stirred ice-cooled solution of 3M hydrochloric acid (HCl) (240 mL). The organic layer was separated and extracted with ethyl acetate (3 x 40mL). The combined organic extracts were dried over anhydrous magnesium sulfate and filtered. Evaporation of solvent under reduced pressure afforded the crude product as yellow oil, which was purified by distillation to provide the pure product, 58-60 °C/5

mmHg, 6.779 g, 69.2%. IR 3126.6, 2853.8, 2824.0, 1731.3, 1641.3, 1420.7 cm^{-1}; ^{1}H NMR σ 11.5 (b, 1H), 5.9 (m, 1H), 5.2 (m, 1H), 3.2 (m, 1H), 1.3 (d, 3H); ^{13}C NMR σ 181.251, 136.348, 116.409, 43.468, 16.408.

General Procedure for the Preparation of α-Substituted ß,Γ-Unsaturated Acids. A solution of diisopropylamine (31.15 g, 44.1 mL, 31.36 mmol, 205 mol%) in tetrhydrofuran (50 mL) in a 100 mL three-necked round bottom flask was cooled to 0 °C. Butyllithium (30.8 mmol, 12.3 mL, 2.5 M in hexane, 202 mol%) was added with stirring under an atmosphere of nitrogen. After the mixture was stirred for 10 min, a solution of ß,Γ-unsaturated acid (15.3 mmol, 100 mol%) in 10 mL of dried THF was added slowly over a period of 15 min. The resulting mixture was stirred at 0 °C for 45 min to obtain a deep yellow solution. An alkyl bromide or iodide (15.6 mmol, 102 mol%) was added, whereupon the reaction mixture immediately turned colorless. After 30 min at 0 °C and 15 min at room temperature, the pH of the solution was adjusted to 2.5 with 4 N hydrochloric acid. The organic phase was separated. The aqueous layer was saturated with solid sodium chloride and extracted with ethyl acetate (4 x 50 mL). The organic layers were combined and extracted with 5% aqueous sodium bicarbonate solution. Again the pH was adjusted to 2.5 with 4 N hydrochloric acid, and the solution was back-extracted with ethyl acetate (5 x 40 mL) after saturation with solid sodium chloride.

The combined organic layers were dried over anhydrous magnesium sulfate and filtered. Removal of solvents under reduced pressure gave the crude products (sufficiently pure to be used for the next step). Distillation gave a spectroscopically homogeneous material.

2-(n-Butyl)-3-butenoic acid (52c). A yellow oil was obtained from 3-butenoic acid and n-butyl bromide in 55.5% yield. IR 3060, 2940, 2910, 2850, 1690, 1630 cm^{-1}.

2-Ethyl-3-butenoic acid (52d). A pale yellow oil was obtained from 3-butenoic acid and ethyl iodide in 54.8% yield. IR 3060, 2900, 1680, 1625 cm^{-1}.

2-Ethyl-3-hexenoic acid (52e). A yellow oil was obtained from 3-*trans* hexenoic acid and ethyl iodide in 60.5% yield. IR 3050, 2900, 2850, 1685, 1625 cm^{-1}.

2-Phenylmethyl-3-butenoic acid (52h). A brown oil was obtained from 3-butenoic acid and benzyl bromide in 57.6% yield. IR 3010, 2900, 1690, 1635, 1480 cm^{-1}.

2-Phenylmethyl-3-hexenoic acid (52i). A brown oil was obtained from 3-*trans* hexenoic acid and benzyl bromide in 40.5% yield. A spectroscopically pure sample was obtained by distillation (145-150 ^{o}C/1 mmHg). IR 3089.1, 3026.7, 2966.7, 2932.8, 2876.6, 1707.0, 1635.6, 1604.7, 1417.1 cm^{-1}. ^{1}H NMR σ 10.9 (b, 1H), 7.1-7.3 (m, 5H), 5.60 (m, 2H), 3.30 (dd, 1H), 3.15 (dd, 1H), 2.85 (dd, 1H), 2.05 (dq, 2H), 0.97 (t, 3H). ^{13}C NMR σ 180.506, 138.529, 136.204, 129.068, 129.052, 128.227, 126.323, 126.194,

125.177, 50.906, 38.511, 25.416, 13.274.

2-(1-Methylethyl)-3-butenoic acid (52j). A yellow oil was obtained from 3-butenoic acid and 2-propyl iodide in 41.5% yield. IR 3000, 2900, 1685, 1635, 1400 cm^{-1}.

2-(1-methylethyl)-3-hexenoic acid (52k). A yellow oil was obtained from 3-*trans* hexenoic acid and 2-propyl iodide in 55.2% yield. A spectroscopically homogeneous sample was obtained by distillation (130-135 °C/1 mmHg). IR 3150.7, 3022.0, 2961.8, 2919.6, 2875.2, 1702.1, 1635.0, 1415.6, 1285.3 cm^{-1}. ^{1}H NMR σ 10.1 (b, 1H), 5.60 (dt, 1H), 5.40 (ddt, 1H), 2.41 (dd, 1H), 1.9-2.1 (m, 2H), 0.9-1.1 (m, 9H). ^{13}C NMR σ 181.119, 136.579, 124.886, 56.899, 30.621, 25.529, 20.737, 19.558, 13.533.

General Procedure for the Preparation of Γ-Bromo or Γ-Iodo ß-Lactones (4-(1-Haloalkyl)-oxetan-2-ones). A ß,Γ-unsaturated acid (10 mmol) was dissolved in a saturated sodium bicarbonate solution (40 mL) in a 100 mL Erlenmeyer flask to produce a homogeneous aqueous solution. This solution was added dropwise over 10 min at 0 °C with stirring to a solution of bromine (1.62 g, 10.2 mmol) or iodine (2.589, 10.2 mmol) in ether (100 mL) in a 250 mL Erlenmeyer flask. The mixture was stirred for 1 h and then washed with sodium thiosulfate solution (10%) and with water. The organic layer was dried over anhydrous magnesium sulfate and filtered. Removal of the solvent under reduced pressure gave the crude product. When necessary, the ß-lactone could be easily separated from the corresponding Γ-lactone by column

chromatography (hexane-AcOEt, 4:1).

4-Bromomethyloxetan-2-one (55g). Evaporation of ether gave a pale oil in 37.3% yield; the sample was characterized without further purification. IR 3024.7, 2969.2, 1834.2, 1408.0, 1285.6, 1123.1 cm^{-1}. ^1H NMR σ 4.65-4.75 (m, 1H), 3.60-3.70 (m, 2H), 3.50-3.60 (dd, 1H), 3.25-3.35 (dd, 1H). ^{13}C NMR σ 166.794, 68.502, 43.188, 32.412.

4-(1-Bromopropyl)-oxetan-2-one (55d). Yield, 60.4%. A spectroscopically pure sample was obtained by column chromatography (AcOEt:hexane, 1:4). IR 2952, 2918, 2858, 1820, 1100 cm^{-1}. ^1H NMR ($CDCl_3$) σ 4.52 (m, 1H), 3.97 (dt, 1H), 3.61 (dd, 1H), 3.30 (dd, 1H), 2.07 (m, 1H), 1.80 (m, 1H), 1.10 (t, 3H). ^{13}C NMR σ 166.800, 71.139, 56.706, 43.459, 27.631, 11.354. MS. 193 (M^+), 151, 85, 71, 55 (100), 39. $C_6H_9BrO_2$, requires 193.0470, found 192.9866.

4-Bromo-5-ethyl-3,4-dihydro-2(5H)-furanone (56d). IR 2952, 2916, 2860, 1770, 1156 cm^{-1}. ^1H NMR ($CDCl_3$) σ 4.57 (dt, 1H), 4.16 (dt, 1H), 3.15 (dd, 1H) 2.87 (dd, 1H), 1.6-1.9 (m, 2H), 1.04 (t, 3H).

3-(1-Butyl)-4-bromomethyloxetan-2-one (55c). Yield (a mixture of ß and Γ-lactones), 65.9%. IR 2935, 2905, 2840, 1820, 1770, 1450, 1100 cm^{-1}.

3-Ethyl-4-bromomethyloxetan-2-one 55b. Yield, 39.8%. IR 2938, 2900, 2850, 1827, 1455, 1090 cm^{-1}.

3-Ethyl-4-(1-bromopropyl)-oxetan-2-one (55e). Yield (a

mixture of ß and Γ-lactones), 67.0%. IR 2950, 2908, 2855, 1820, 1770, 1450, 1100 cm^{-1}.

3-Methyl-4-bromomethyloxetan-2-one (55f). Yield (*cis* and *trans*,1:2), 41.8%. IR 2978.9, 2940.9, 2880.8, 1828.9, 1457.6, 1363.9, 1050 cm^{-1}. ^{1}H NMR σ 4.80 & 4.38 (two m, 1H, *cis* and *trans*), 3.87 & 3.50 (two m, 2H), 3.60-3.75 (m, 1H, *cis* and *trans*), 1.35-1.55 (two d, 3H). ^{13}C NMR σ 170.029, 75.758, 72.569, 51.758, 48.022, 31.109, 27.290, 12.454, 7.851. R_f (EtOAc:hexane, 1:5): 0.37. MS. 179 (M^+), 135, 85 (100), 71, 55, 39. $C_5H_7BrO_2$, requires 179.0198, found 178.9707.

3-Methyl-4-iodomethyloxetan-2-one (55g). Yield (*cis* and *trans*, 1:9), 25.8%. IR 2976.6, 2938.1, 2878.1, 1826.6, 1456.3, 1122.9, 855.6 cm^{-1}. ^{1}H NMR σ 4.84 & 4.18 (two m (6), 1H, *cis* and *trans* (1:9)), 3.82 & 3.56 (two m(8), 1H, *cis* and *trans* (1:9)), 3.2-3.5 (m, 2H), 1.40 & 1.38 (two d, 2H, *cis* and *trans* (1:9)). ^{13}C NMR σ 170.060, 77.566, 73.690, 53.088, 47.890, 12.738, 3.749, -1.094. R_f (EtOAc:hexane,1:4): 0.47

3-Phenylmethyl-4-bromomethyloxetan-2-one (55h). Yield, 50.3%. IR 3050, 2940, 2900, 2830, 1818, 1603, 1470, 1100 cm^{-1}.

3-Phenylmethyl-4-(1-bromopropyl)-oxetan-2-one (55i). Yield (a mixture of ß and Γ-lactones), 58.4%. A spectroscopically homogeneous sample was obtained by flash chromatography (AcOEt: hexane, 1:5), R_f: 0.26. IR 3151.4, 3071.9, 2955.4, 2930.3, 2861.6, 1828.5, 1456.1 cm^{-1}. ^{1}H NMR σ 7.2-7.6 (m, 5H), 5.10 (dd, 1H), 4.08 (dt, 1H), 3.05 (dd, 1H), 2.82 (dd, 1H), 2.2-2.4 (m, 1H), 1.8-2.0 (m, 1H), 1.12 (t, 3H). ^{13}C NMR σ 174.037, 130.800,

128.391, 127.744, 127.071, 126.845, 125.965, 72.419, 40.852, 27.078, 20.448, 11.805.

3-(2-Propyl)-4-bromomethyloxetan-2-one (55j). Yield, 24.0%. IR, 3000, 2940, 2902, 2850, 1820, 1395, 1100 cm-1.

3-(2-Propyl)-4-(1-bromopropyl)-oxetan-2-one (55k). Yield (a mixture of ß and Γ-lactones), 77.7%; a spectroscopically pure sample was obtained by flash chromatography (AcOEt:hexane, 1:5), R_f:0.68. IR 2989.6, 2937.9, 2880.2, 1833.9, 1464.5, 11178.3 cm^{-1}. ^1H NMR σ 4.2-4.4 (m, 1H), 3.8-4.0 (m, 1H), 3.22 & 2.83 (two dd, *cis: trans*, 2:5). 1.6-2.4 (m, 2H), 1.0-1.2 (m, 9H). ^{13}C NMR σ 173.820, 85.409, 75.641, 63.371, 56.380, 55.457, 44.336, 27.900, 27.399, 20.665, 19.585, 19.247, 18.746, 11.482, 9.494.

General Procedure for Ring Expansion/Elimination of Γ-Bromo or Γ-Iodo ß-Lactones. A Γ-bromo ß-lactone (6 mmol) was dissolved in glacial acetic acid (30 mL) in a 50 mL round-bottomed flask. Silver nitrate (9 to 12 mmol, 150-200 mol%) was added to the solution with stirring. The non-homogeneous mixture was heated to reflux (120 °C) with stirring until TLC (EtOAc:hexane, 1:4) showed no ß-lactone left (16 to 20 h). After removal of acetic acid under reduced pressure, ether (40 mL) was added. The solution was washed with 5% sodium bicarbonate solution and water, dried over anhydrous magnesium sulfate, and the ether was evaporated to afford the crude product as a yellow oil. Purification by distillation and column chromatography gave pure material.

2(5H)Furanone (61a). Yield, 53.1%. IR 2990, 2815, 1770, 1735, 1640, 1365 cm^{-1}. ^{13}C NMR σ 7.20 (m, 1H), 4.8-5.2 (dd, 2H), 1.50 (d, 3H). (Lit.[43] ^{1}H NMR σ 7.27 (m, 1H), 6.16 (m, 1H), 4.99 (m, 2H)).

3-Butyl-2(5H)furanone (62b). Yield, 50.3%. R_f: 0.33 (EtOAc: hexane, 1:4). IR 2980.4, 2934.2, 2871.7, 1766.4, 1746.6, 1640.6, 1374.3, 1278.8 cm^{-1}. ^{1}H NMR σ 7.10 (dd, 1H), 4.75(m, 2H), 2.08 (t, 2H), 1.4-1.8 (m, 4H), 0.98 (t, 3H). ^{13}C NMR σ 177.235, 143.995, 70.954, 43.168, 28.831, 22.285, 13.703. (Lit.[14] IR 1775, 1665 cm^{-1}. ^{1}H NMR σ 7.15-7.09 (m, 1H), 4.78 (dd, 2H), 2.30 (dt, 2H), 1.20-1.70 (m, 4H(, 0.93 (t, 3H). ^{13}C NMR σ 174.68, 144.17, 134.56, 70.00, 29.28, 24.76, 22.01, 13.44).

3,5-Diethyl-2(5H)furanone (61c). Yield, 64.4%. A spectroscopically pure sample was obtained by column chromatography. IR 3028.9, 2973.4, 2938.3, 2882.0, 1750.0, 1651.5 cm^{-1}. ^{1}H NMR ($CDCl_3$) σ 6.98 (m, 1H), 4.82 (m,1H), 2.20-2.35 (qt, 2H), 1.55-1.85 (m, 2H), 1.15 (t, 3H), .96 (t, 3H). ^{13}C NMR ($CDCl_{3)}$ σ 172.456, 146.831, 136.046, 82.185, 26.533, 18.572, 11.712, 9.015. (Lit.[15] IR 1761, 1660 cm^{-1}. ^{1}H NMR σ 7.04 (m, 1H), 4.88 (m, 1H), 2.3 (m, 2H), 1.6-1.9 (m, 2H), 1.12 (t, 3H), 1.02 (t, 3H)).

5-Ethyl-2(5H)furanone (61d). Yield, 30.7%. IR 3060, 2964, 2920, 2860, 1740, 1650, 1160 cm^{-1}; ^{1}H NMR (60MHz, $CDCl_3$) 7.45 (dd, 1H), 6.12 (dd, 1H), 4.90-5.05 (dt, 1H), 1.6-1.9 (m, 2H), 1.0 (t, 3H). ^{13}C NMR σ 173.254, 156.042, 121.669, 84.341, 26.186, 8.959. (Lit.[15] IR 1753, 1640 cm^{-1}. ^{1}H NMR σ 7.48 (dd, 1H), 6.10 (dd, 1H), 5.02 (m, 1H), 1.6-2.0 (m, 2H), 1.01 (t, 3H)).

5-Ethyl-3-phenylmethyl-2(5H)furanone (61e). Yield, 75.1%. A spectroscopically pure sample was obtained by flash chromatography, R_f: 0.33 (EtOAc:hexane, 1:5). IR 3085.5, 3064.2, 2972.8, 2936.1, 2881.3, 1754.2, 1652.4, 1602.8, 1456.3, 1045.7 cm^{-1}. ^1H NMR σ 7.27 (m, 5H), 6.81 (d, 1H), 4.85 (dt, 1H), 3.59 (s, 2H), 1.69 (m, 2H), 0.96 (t, 3H). ^{13}C NMR σ 173.422, 148.881, 137.402, 134.480, 128.845, 128.684, 126.714, 82.347, 31.716, 26.452, 9.017. MS. 202 (M^+), 173, 157, 129 (100), 115, 91. $C_{13}H_{14}O_2$, requires 202.2564, found, 202.0996.

5-Ethyl-3-(1-methylethyl)-2(5H)furanone (61f). Yield, 65.5%. A spectroscopically pure sample was obtained by flash chromatography (AcOEt: hexane, 1:5), R_f: 0.45. IR 3085.9, 2970.3, 2937.8, 2878.5, 1752.4, 1640.4, 1464.4,1058.2 cm^{-1}. ^1H NMR σ 6.96 (d, 1H), 4.82 (dt, 1H), 2.62 (m, 1H), 1.6-1.8 (m, 2H), 1.08 (d, 6H), 0.98 (t, 3H). ^{13}C NMR σ 173.276, 145.666, 140.581, 81.877, 26.547, 25.401, 21.009, 20.848, 8.949. MS. 154 (M^+), 139, 125, 97, 81, 41 (100). $C_9H_{14}O_2$, requires 154.2116, found, 154.0994.

3-Methyl-2(5H)furanone (61g). Yield, 59.3%. IR 3010, 2940, 2896, 2830, 1770, 1740, 1630, 1365, 1220 cm^{-1}. ^1H NMR σ 7.25 (dd, 1H), 4.62 (m, 2H), 1.60 (s, 3H). ^{13}C NMR σ 168.726, 67.126, 15.492. (Lit.[44] IR 1755 cm^{-1}. ^1H NMR σ 7.05-7.20 (m, 1H), 4.67-4.80 (m, 2H), 1.88-1.99 (m, 3H)).

3-(1-Methylethyl)-2(5H)furanone (61h). Yield, 51.8%. IR 2950, 1760, 1720, 1620, 1220 cm^{-1}. ^1H NMR σ 7.12 (m, 1H), 4.50 (m, 2H), 2.0-2.2 (m, 1H), 1.0-1.2 (two d, 6H). ^{13}C NMR σ

168.523, 136.346, 129.160, 71.458, 27.398, 20.100, 13.013. (Lit.[14] ^{1}H NMR σ 7.11 (m, 1H), 4.78 (m, 2H), 2.68 (ds, 1H), 1.16 (d, 6H)).

3-Phenylmethyl-2(5H)furanone (61i). Yield, 52.4%. A spectroscopically pure sample was obtained by flash chromatography, R_f: 0.34 (EtOAc:hexane, 1:4). IR 3063.8, 3030.4, 3002.2, 2961.0, 2932.9, 2870.3, 1778.7, 1750.3, 1651.7, 1603.3, 1374.0, 1148.1. ^{1}H NMR σ 7.05-7.20 (m, 5H), 6.92 (dd, 1H), 4.76 (dd, 2H), 2.18 (s, 1H), 2.00 (s, 1H). ^{13}C NMR σ 170.341, 145.665, 129.074, 128.816, 128.412, 126.931, 126.895, 71.177, 31.881.

Trimethylsilylketene (64). To a 250 mL three-necked round-bottom flask, methyllithium (71 mmol, 51 mL of 1.4 M in ether) was added dropwise via syringe to a cooled (0 °C) solution of 4.776g (68.2 mmol) of ethoxyacetylene in 150 mL of freshly distillated diethyl ether with stirring under an atmosphere of nitrogen. A white precipitate formed during the addition and the solution became difficult to stir. After the mixture was stirred an additional 0.5 h, chlorotrimethylsilane (7.55 g, 70 mmol) was added and the mixture was stirred overnight at room temperature. The mixture was filtered and the precipitate washed well with dry ether. Careful removal of the solvent at reduced pressure afforded trimethylsilylethoxyacetylene (IR 2180, 1241, 842 cm^{-1}) contaminated with lithium chloride. The acetylene was redissolved in dry pentane and filtered. After the pentane was removed, the residue was slowly distilled at bath temperature 120 °C to

produce crude trimethylsilylketene as a colorless mobile oil. A second distillation gave pure trimethylsilylketene: 82-86 °C, 2.832 g, yield 36.6%. IR (neat) 3126, 2100, 1260, 1240, 835 cm^{-1}. ^{1}H NMR σ 1.799 (s, 1H), 0.179 (s, 9H). ^{13}C NMR σ 179.462, 104.950, 0.571. (Lit.[30c] bp.:81-82 °C; IR (λ_{max}) 11.70, 8.00, 7.90; ^{1}H NMR σ_{TMS} 1.5 (s, 1H)).

General Procedure for Preparation of 2-Bromo Aldehydes. A 20 mmol sample of aldehyde was dissolved in 40 mmol of dimethyl sulfoxide and 80 mmol of *tert*-butyl bromide in a 100 mL three-necked round-bottom flask and heated at 60-65 °C for 4 hours under reflux and stirring. The reaction mixture was extracted three times with a H_2O-Et_2O mixture (1:1). The organic phase was washed twice with water, dried over anhydrous magnesium sulfate, and evaporated to small volume. Distillation at the indicated temperature and pressure gave pure 2-bromo aldehyde.

2-Bromohexanal (73). A colorless oil (65-68 °C/ 13 mmHg) was obtained from hexanal, dimethyl sulfoxide, *tert*-butyl bromide in 97.5% yield. IR 2957.7, 2932.3, 2862.7, 2720.3, 1728.9, 1465.3, 1102.3. ^{1}H NMR σ 9.45 (d, 1H), 4.20 (m, 1H), 1.7-2.1 (m, 4H), 1.2-1.6 (m, 2H), 0.97 (t, 3H). ^{13}C NMR σ 192.727, 55.380, 31.275, 28.950, 21.991, 13.709. (Lit.[45] IR 1725: ^{1}H NMR σ 9.25 (d, 1H), 3.99 (dt, 1H), 1.68-1.95 (m, 2H), 1.07-1.46 (m, 4H), 0.88 (t, 3H)).

2,3-Epoxyhexan-1-ol (78). To a stirred solution containing 6.01 g of trans-2-hexen-1-ol (60 mmol) in 200 mL of methylene chloride in a 500 mL round-bottomed flask, cooled in an ice bath, was added dropwise 13 g of pure 3-chloroperoxybenzoic acid[42] (75 mmol) in 250 mL of methylene chloride. This solution was maintained at 0 °C for 2 h and then filtered to remove precipitated 3-chlorobenzoic acid. After removal of solvent *in vacuo*, purification of the resultant oil by distillation gave a colorless oil, 84-88 °C/4 mmHg, 4.49 g (64.6%). IR 3422.3, 2964.1, 2930.8, 2864.4, 1488.9 cm^{-1}. ^{1}H NMR σ 3.817 (dd, 1H), 3.513 (dd, 1H), 3.070 (s, 1H), 2.88 (m, 2H), 1.3-1.6 (m, 4H), 0.887 (t, 3H). ^{13}C NMR 61.74, 58.592, 55.847, 33.389, 19.068, 13.708. (Lit.[35] bp.:31-33/0.30-.40 torr; ^{1}H NMR σ 3.63 (m, 3H), 2.90 (m, 2H), 1.52 (m, 4H), 0.96 (m, 3H))

2,3-Epoxyhexanal (79). Pyridinium dichromate (PDC) (7.752 g, 20.4 mmol) was added to a solution of 2,3-epoxyhexan-1-ol (1.2 g, 19.2 mmol) in dry dichloromethane (180 mL) in a 250 mL round-bottomed flask with stirring under nitrogen. After the mixture was stirred at room temperature for 24 h, 150 mL of diethyl ether was added to the reaction mixture, which was then filtered. Evaporation of solvents under reduced pressure gave the crude product contaminated by PDC. Filtration through silica gel using ether as the eluent gave a colorless solution. The solvent was removed and the residue was purified by distillation to give a colorless oil, 80-90 °C/1 mmHg, 0.958 g (82.3%). A spectroscopi-

cally pure sample was obtained by flash chromatography (EtOAc: hexane, 1:5). IR 2966.4, 2931.2, 2868.0, 2732.2, 1728.9, 1206.6, 920.8 cm^{-1}. ^{1}H NMR σ 9.004 (d, 1H), 3.22 (m(6), 1H), 3.12 (q, 1H), 1.55-1.7 (m, 2H), 1.4-1.55 (m, 2H), 0.95 (t, 3H). ^{13}C σ 198.452,, 59.006, 56.519, 33.077, 19.079, 13.660. R_f(EtOAc: hexane, 1:4): 0.43. (Lit.[35] ^{1}H NMR σ 9.01 (d, 1H), 3.17 (m, 2H), 1.55 (m, 4H), 0.98 (m, 3H); ^{13}C NMR σ 198.1, 59.1, 56.6, 33.3, 19.2, 13.7).

General Procedure for the Cycloaddition of Trimethylsilylketene to Aldehydes and Ketones.

A solution of trimethylsilylketene (0.594 g, 5.2 mmol) in 1 mL of dry ether was added dropwise to a stirred solution of aldehyde or ketone (5 mmol) in 25 mL of dry ether containing 4-5 drops of $BF_3 \cdot OEt_2$ in a 50 mL round-bottomed flask at -15 °C under a nitrogen atmosphere. The mixture was stirred until no aldehyde or ketone was detectable via TLC (3-6 hours). Evaporation of diethyl ether gave crude 3-trimethylsilyl-oxetan-2-ones (α-trimethylsilyl ß-lactones) IR 1810-1830 cm^{-1} (C=O of oxetan-2-one,[29] 1805-1810 cm^{-1}). The oxetan-2-ones were purified by vacuum distillation or column chromatography and further characterized.

4-(1-Methylbutyl)-3-trimethylsilyloxetan-2-one (68b). A 1 mmol (0.114 g) portion of trimethylsilylketene and 1 mmol (0.100 g) of 2-methylpentanal containing 4 drops of $BF_3 \cdot OEt_2$ were reacted to give 96 mg of a spectroscopically homogenous sample after column chromatography (EtOAc:hexane, 1:4), yield 44.9%. IR

2960.6, 2933.6, 2860.8, 1807.9, 1253.9, 861.41 cm^{-1}. ^1H NMR σ 4.20 (*cis* isomer, j = 5.8 Hz), 3.96 (*trans* isomer, j = 3.23 Hz) (two m, 2:3, 2H), 3.30 (*cis* isomer, j =5.8 Hz), 2.93 (*trans* isomer, j = 3.23 Hz) (two dt, 2:3, 2H), 0.9-2.0 (m, 11H), 0.234 (*cis* isomer), 0.172 (*trans* isomer) (two s, 9H). ^{13}C NMR 78.464, 46.222, 46.139, 38.007, 37.859, 36.228, 34.969, 34.697, 34.311, 33.358, 19.779, 19.356, 15.567, 14.852, 14.290, 14.120, 14.093, 13.880, -0.792, -2.955.

4-Pentyl-3-trimethylsilyloxetan-2-one (68c). A pale yellow oil was obtained from trimethylsilylketene and hexanal in 60% yield. IR 2959.4, 2924.2, 2860.0, 1806.2, 1250.0 cm^{-1}. ^1H NMR σ 4.570 & 4.233 (two m, 2H, 2:1), 3.313 & 2.884 (two d, 2H, 2:1), 1.2-2.7 (m, 8H), 0.86 (t, 3H), 0.20 & 0.16 (two s, 9H, 2:1).

Preparation of α,ß-Unsaturated Acids from Carbonyl Compounds and Trimethylsilylketene.

Method A. A mixture of carbonyl compound and trimethylsilylketene in dry ether containing a few drops of $BF_3 \cdot OEt_2$ in a 50 mL round-bottomed flask was maintained at room temperature overnight. Evaporation of solvent and $BF_3 \cdot OEt_2$ under reduced pressure gave a mixture containing the unsaturated acid. Purification by column chromatography or treatment by 10% NaOH and 10% HCl gave the spectroscopically pure α,ß-unsaturated acid.

Method B. A few drops of $BF_3 \cdot OEt_2$ were added to a solution of a 4-substituted 3-trimethylsilyloxten-2-one in dry ether in a

50 mL round-bottomed flask. The reaction mixture was left overnight at room temperature. Removal of ether and $BF_3 \cdot OEt_2$ under reduced pressure gave the crude product.

4-Bromo- 2-octenoic acid (72d). Crude yield, 99.8%. A spectroscopically pure sample was obtained by flash chromatography (EtOAc: hexane, 1:4). IR 3395.4, 3021.1, 2961.8, 2934.0, 2865.1, 1700.1, 1657.2, 1216.2 cm^{-1}. ^1H NMR σ 7.05 (dd, 1H), 6.83 (b, 1H), 6.05 (d, 1H), 4.35 (m, 1H), 1.60 (m, 2H), 1.1-1.5 (m, 4H), 0.90 (t, 3H). ^{13}C NMR 171.476, 152.705, 119.380, 71.076, 36.066, 27.250, 22.474, 13.897. (Lit.[46] ^1H NMR σ 6.6 (-CH=), 5.54 (=CH-COO^-), 4.17 (-CHBr-)).

2-Hexenoic acid (72a). Crude yield, 40% (ß-lactone, 60%). A spectroscopically pure sample was obtained by flash chromatography. IR 3100.4, 2953.2, 2935.5, 2860.9, 1697.4, 1648.4, 1410.8 cm-1. ^1H NMR σ 11.2 (b, 1H), 7.1 & 6.3 (2:1, two dt, 1H), 5.8 (d, 1H), 2.6 & 2.2 (1:2, two m, 2H), 1.50 (m, 2H), 0.91(t, 3H). ^{13}C NMR σ 172.177, 153.162, 152.069, 120.590, 119.058, 34.100, 30.938, 21.994, 20.942, 13.550, 13.444. (Lit[47] ^1H NMR σ 12.0 (s), 6.7-7.3 (m), 5.7 (d), 2.3 (m), 1.5 (m)).

2-Octenoic acid (72c). IR 3205.5, 2959.4, 2931.2, 2860.9, 1700.8, 1651.6 cm^{-1}. ^1H NMR σ 10.8 (s, 1H), 7.10 & 6.40 (two dt, 1H), 5.70 (m, 1H), 2.60 & 2.25 (two m, 2H), 1.1-1.6 (m, 6H), 0.90 (t, 3H). (Lit.[47] ^1H NMR σ 12.2 (s), 6.9-7.4 (m), 5.8 (m), 2.0-2.5 (m), 1.0-1.7 (m), 0.90 (s)).

4-Phenyl-2-butenoic acid (72e). IR 3086.9, 3030.4, 2960.7, 2876.2, 1741.0, 1652.4, 1601.0 cm^{-1}. ^1H NMR σ 9.0 (-COOH), 7.25

($-C_6H_5$), 5.80 (-CH=CH), 3.50 ($Ph-CH_2$). (Lit.[48] methyl 4-phenyl-2-butenoate, IR 1720, 1658, 1605; ^1H NMR σ 5.78 (dt, 1H, 2-H), 3.66 (dd, 2H, 4-H)).

5-(1-Hydroxybutyl)oxetan-2-one (82) and its ester (81). A waxy oil was obtained from 2,3-epoxyhexan-1-al and trimethylsilylketene catalyzed by BF_3 OEt_2 in crude yield of 97%. IR 3481.1, 3020.9, 2982.9, 2934.5, 2875.4, 1775.1, 1734.7 cm^{-1}. (Lit.[49] ^1H NMR σ 7.44 (dd, 1H), 6.02 (dd, 1H), 4.84 (m,1H), 3.73 (m, 1H), 3.54 (b, 1H), 0.95-1.87 (m, 4H), 0.93 (t, 3H)).

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Figure 1: ^{1}H NMR spectrum of 2-methyl 3-butenoic acid 52f

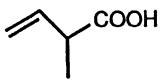


Figure 2: ^{13}C NMR spectrum of 2-methyl 3-butenoic acid 52f

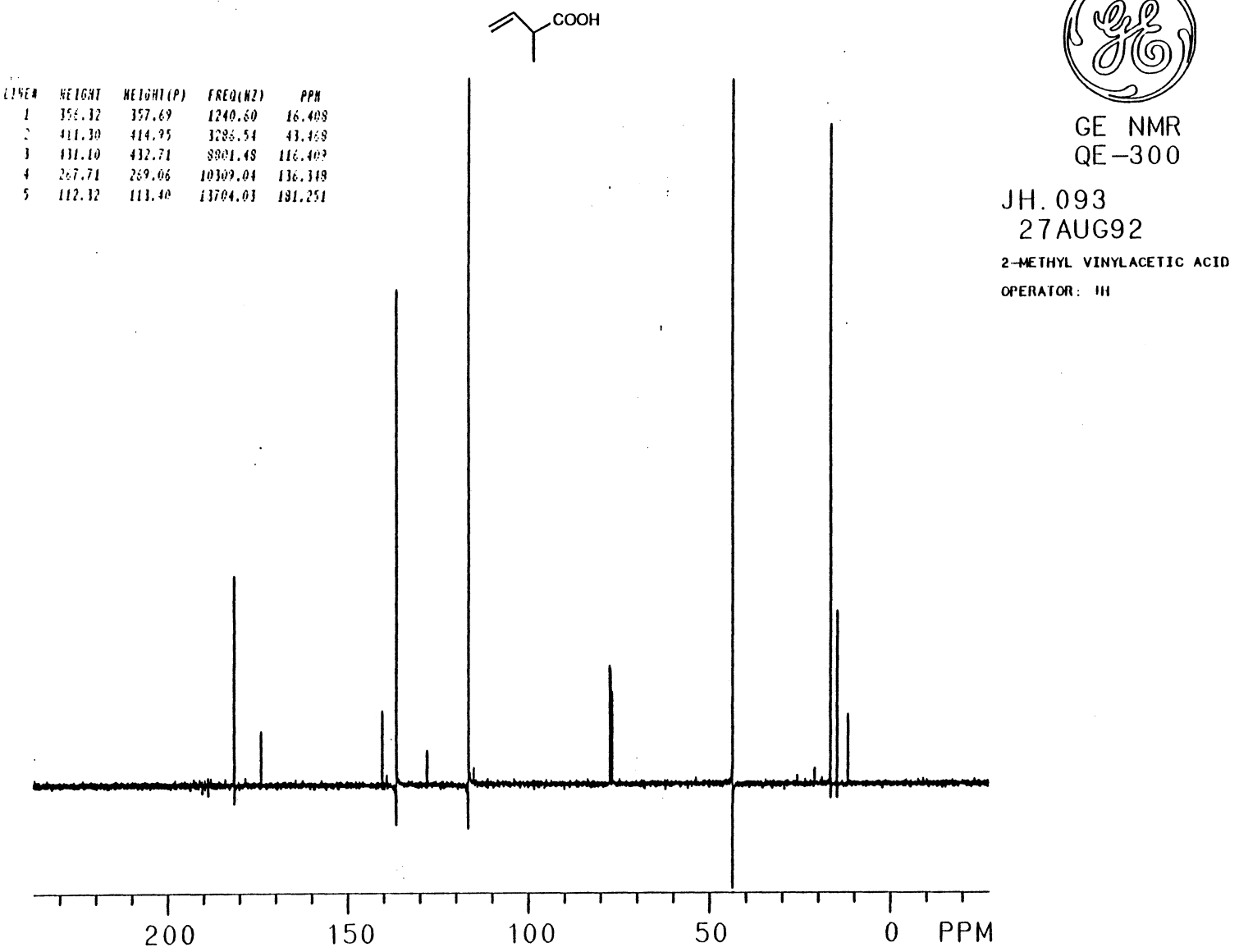


Figure 3: IR spectrum of 2-phenylmethyl 3-hexenoic acid 52h

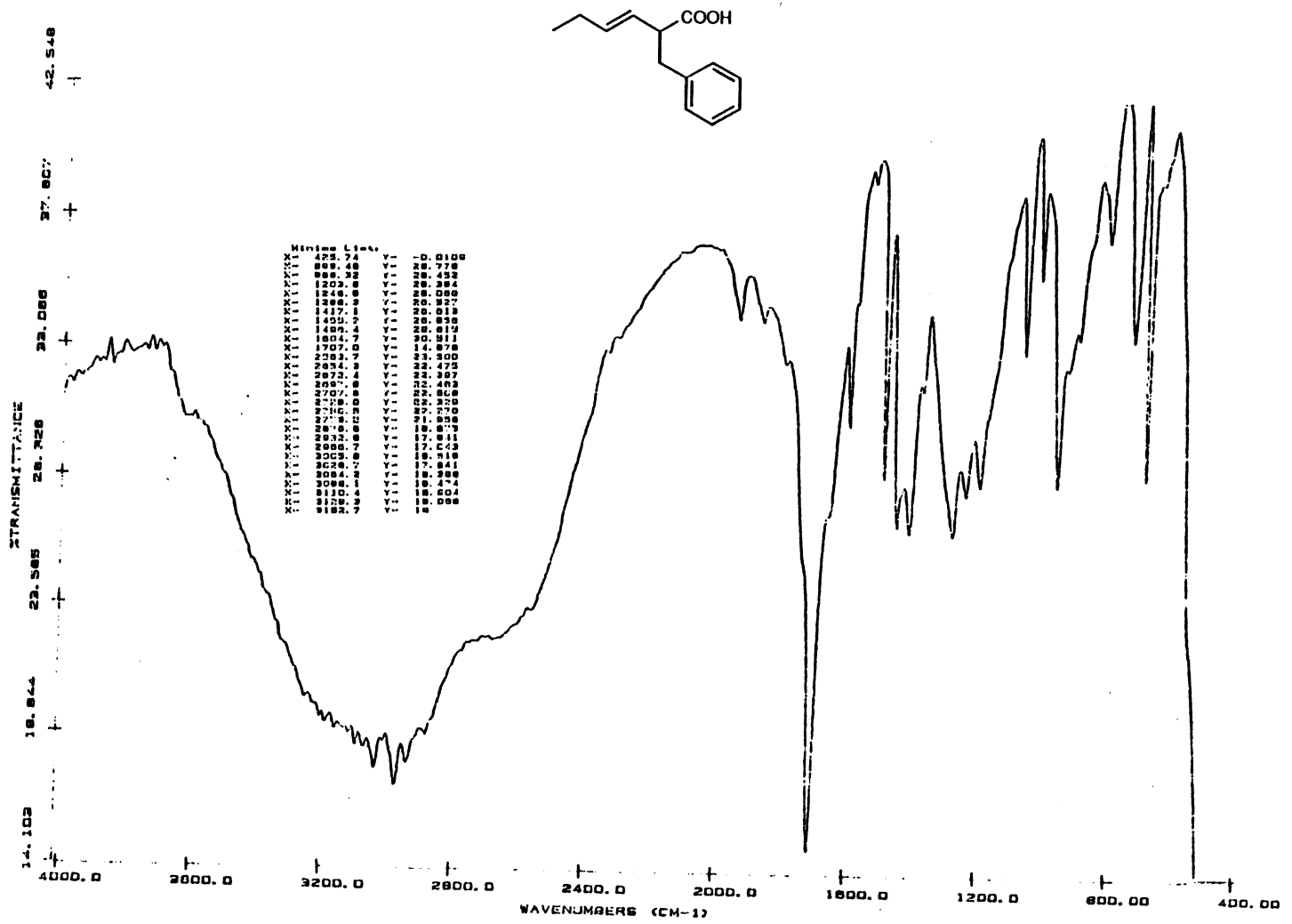


Figure 4: ^{1}H NMR spectrum of 2-phenylmethyl 3-hexenoic acid 52h

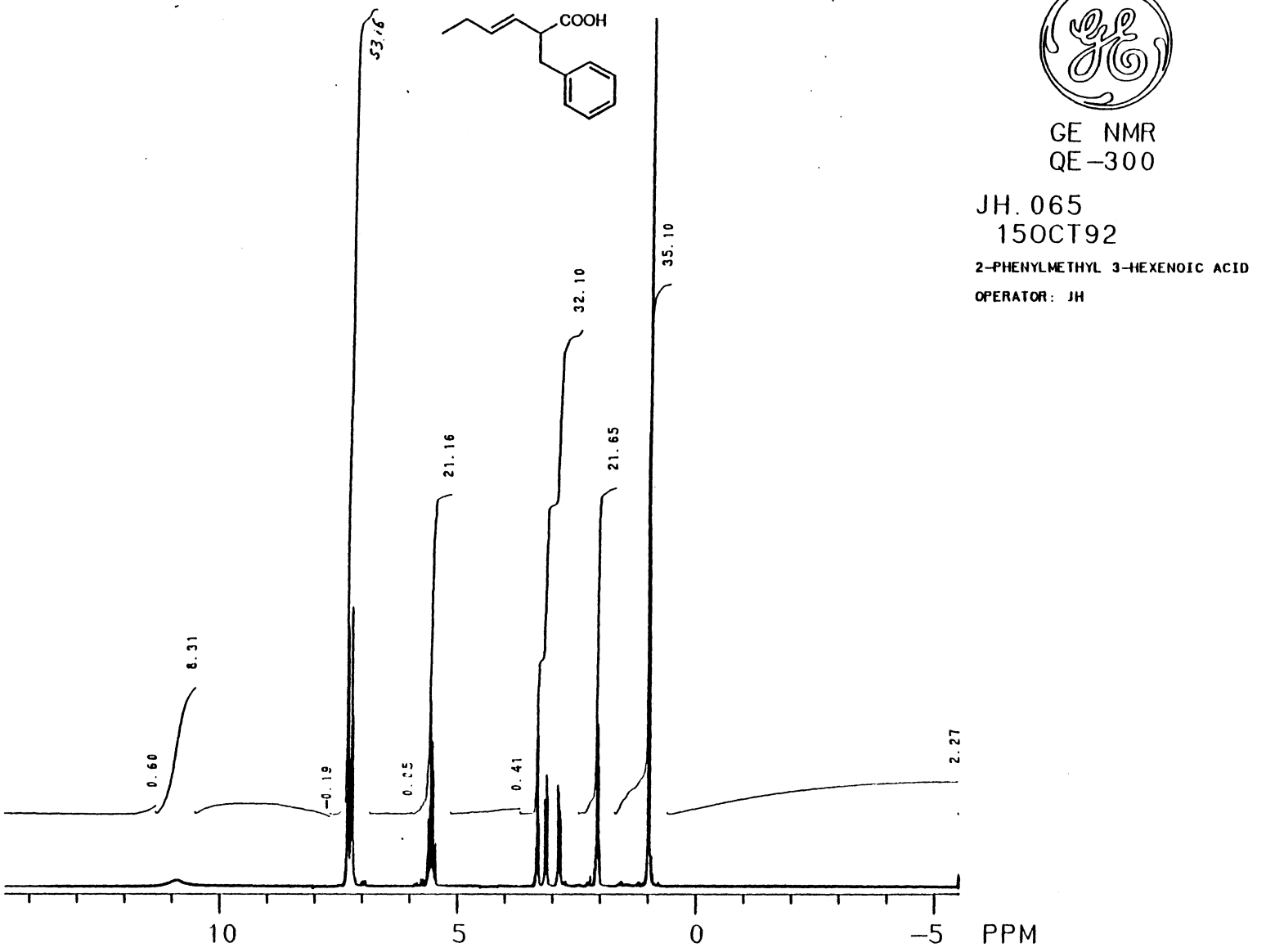
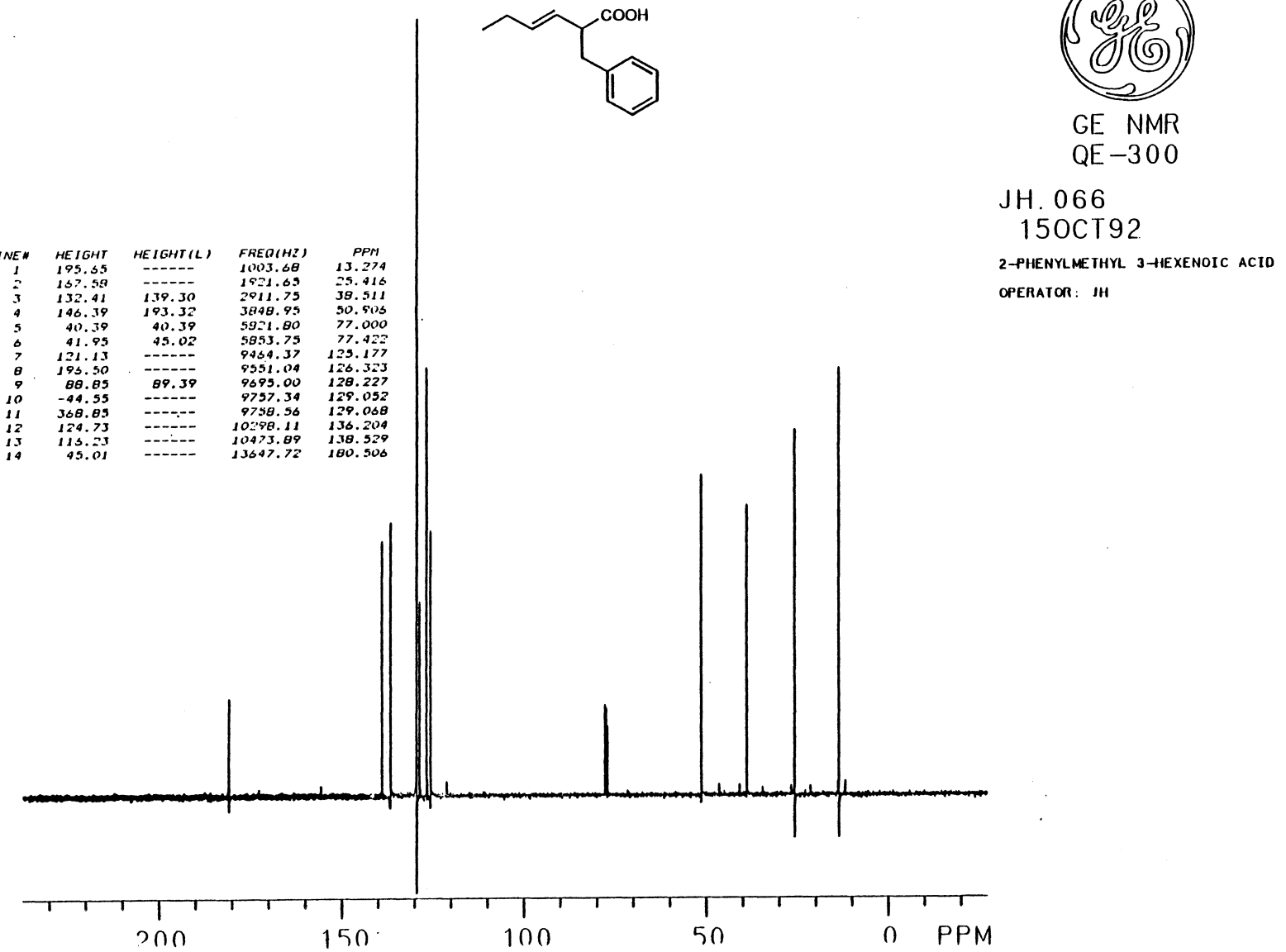


Figure 5: ^{13}C NMR spectrum of 2-phenylmethyl 3-hexenoic acid 52h



LINE#	HEIGHT	HEIGHT(L)	FREQ(HZ)	PPM
1	195.65	------	1003.68	13.274
2	167.58	------	1921.65	25.416
3	132.41	139.30	2911.75	38.511
4	146.39	193.32	3848.95	50.906
5	40.39	40.39	5921.80	77.000
6	41.95	45.02	5853.75	77.422
7	121.13	------	9464.37	125.177
8	196.50	------	9551.04	126.323
9	88.85	89.39	9695.00	128.227
10	-44.55	------	9757.34	129.052
11	368.85	------	9758.56	129.068
12	124.73	------	10298.11	136.204
13	116.23	------	10473.89	138.529
14	45.01	------	13647.72	180.506

Figure 6: IR spectrum of 2-(1-methylethyl)-3-hexenoic acid 52k

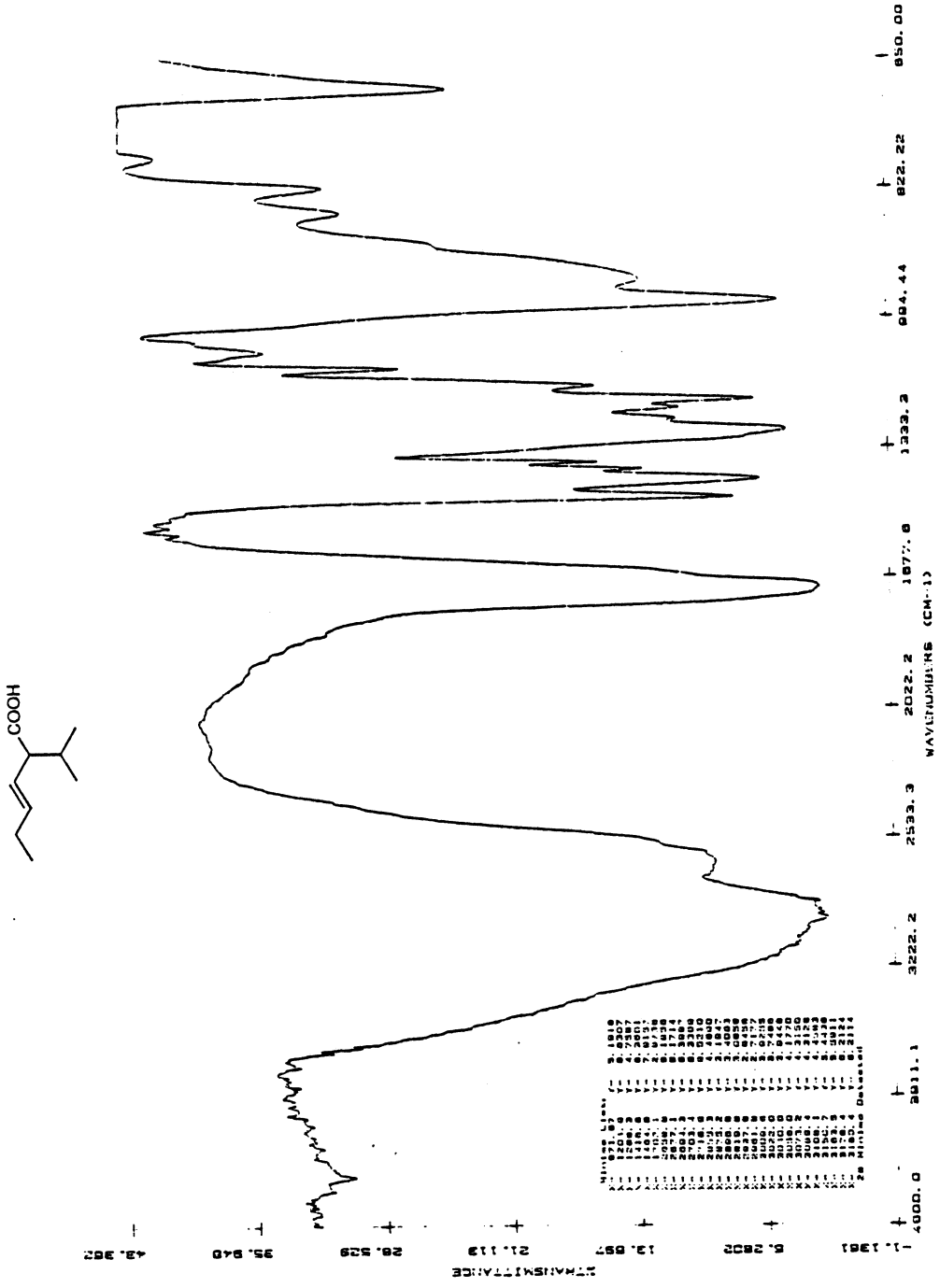


Figure 7: ^{1}H Spectrum of 2-(1-methylethyl)-3-hexenoic acid 52k

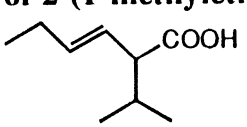
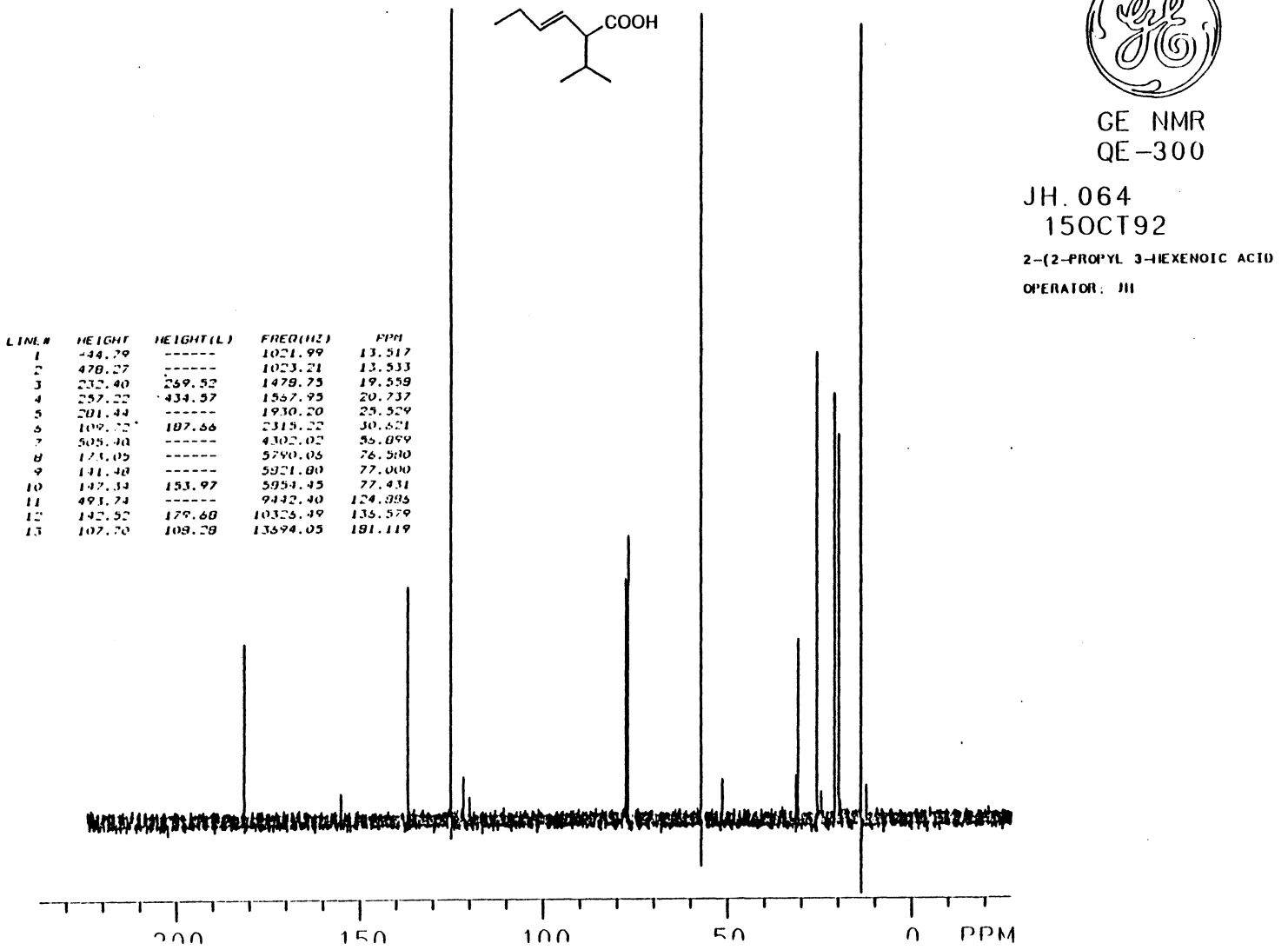


Figure 8: ^{13}C NMR spectrum of 2-(1-methylethyl)-3-hexenoic acid 52k



LINE #	HEIGHT	HEIGHT(L)	FREQ(HZ)	PPM
1	444.79	------	1021.99	13.517
2	478.27	------	1023.21	13.533
3	232.40	269.52	1478.75	19.559
4	257.22	434.57	1567.95	20.737
5	201.44	------	1930.20	25.529
6	109.52	187.66	2319.22	30.681
7	505.40	------	4302.02	56.899
8	173.05	------	5790.06	76.580
9	141.48	------	5921.80	77.000
10	147.34	153.97	5954.45	77.431
11	493.74	------	9442.40	124.886
12	142.52	179.68	10326.49	136.579
13	107.70	108.28	13694.05	181.119

Figure 9: IR spectrum of 4-bromomethyloxetan-2-one 55g

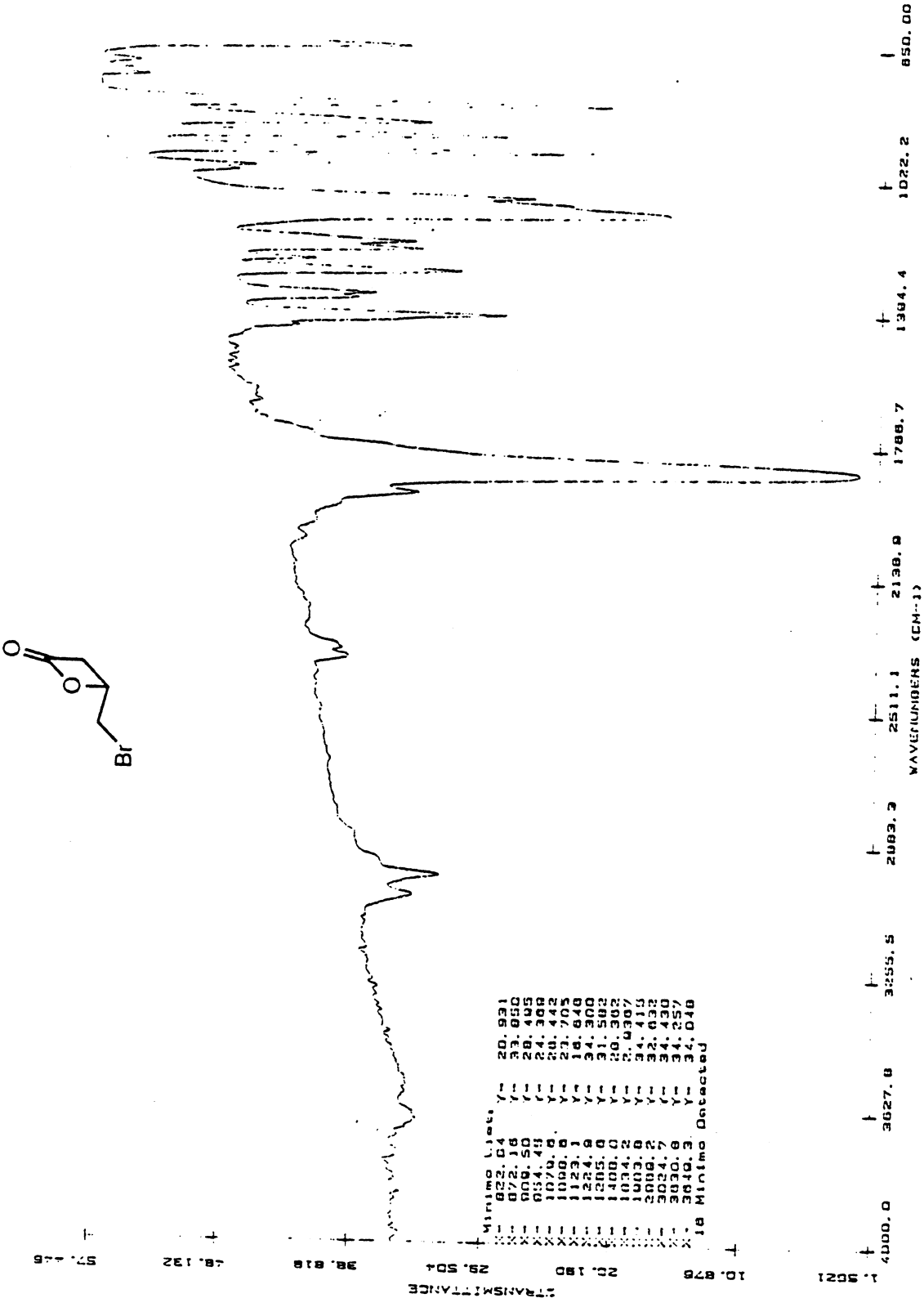


Figure 10: ^{1}H NMR spectrum of 4-bromomethyloxetan-2-one 55g

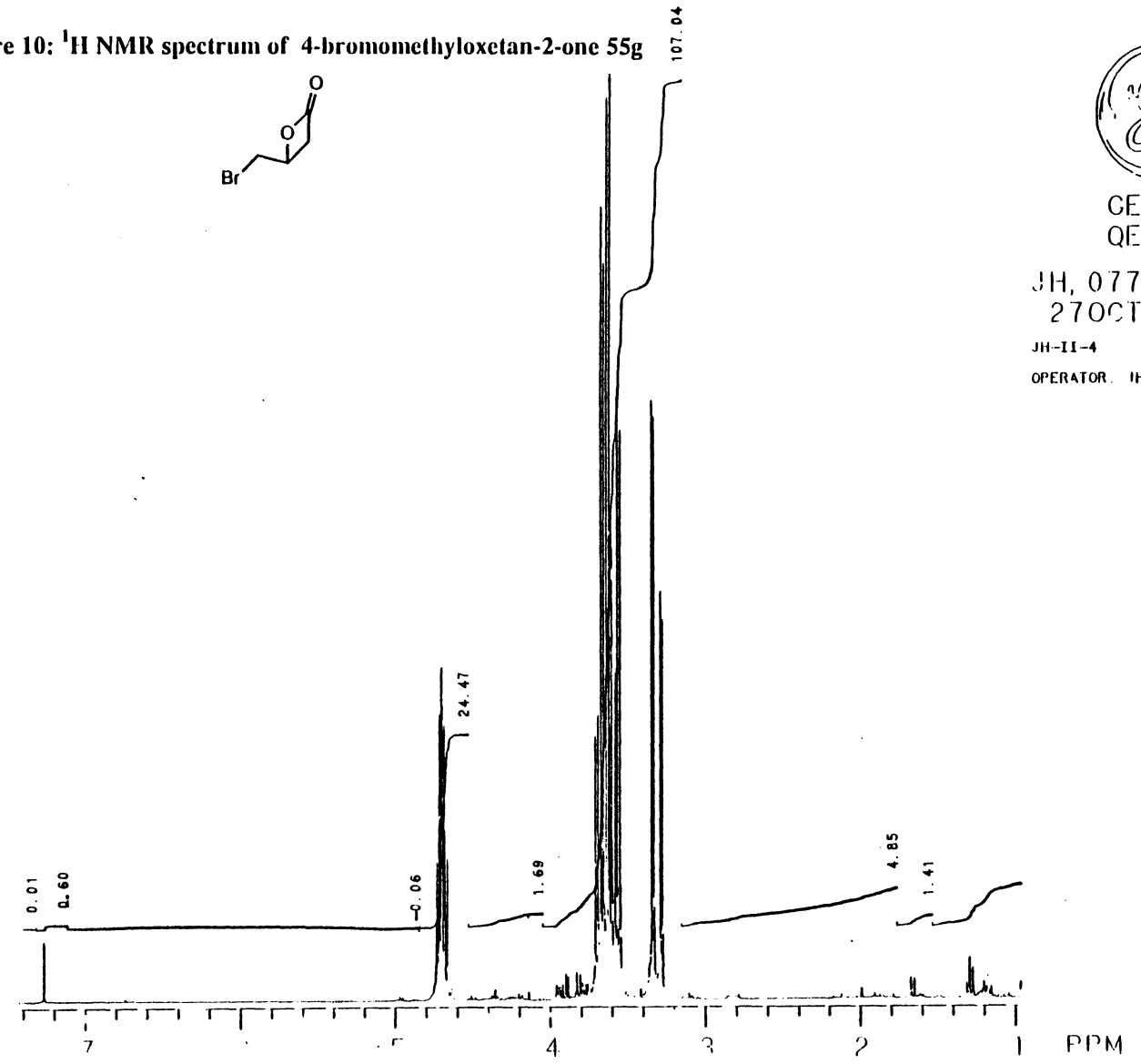
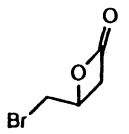


Figure 11: ^{13}C NMR spectrum of 4-bromomethyloxetan-2-one 55g



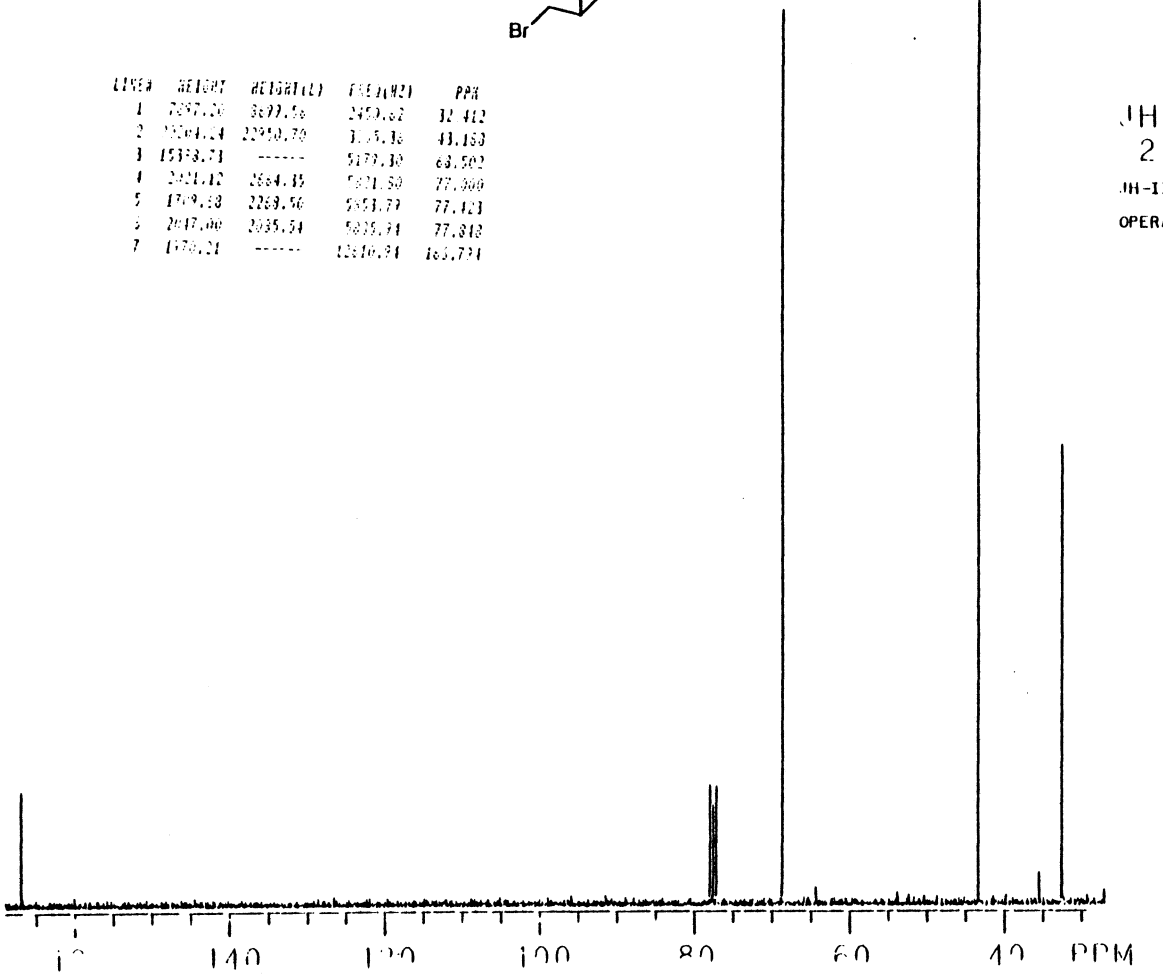
LINE#	HEIGHT	HEIGHT(%)	FREQ(HZ)	PPM
1	2097.20	3677.56	2450.62	32.412
2	3264.34	22950.70	3436.36	43.158
3	15348.71	------	5178.30	68.502
4	2424.12	2564.35	5821.50	77.000
5	1709.58	2268.56	5853.79	77.423
6	2017.00	2035.54	5835.74	77.318
7	1470.21	------	12510.91	163.791

GE NMR
QE-300

JH.084
27OC192

JH-II-4

OPERATOR. JH



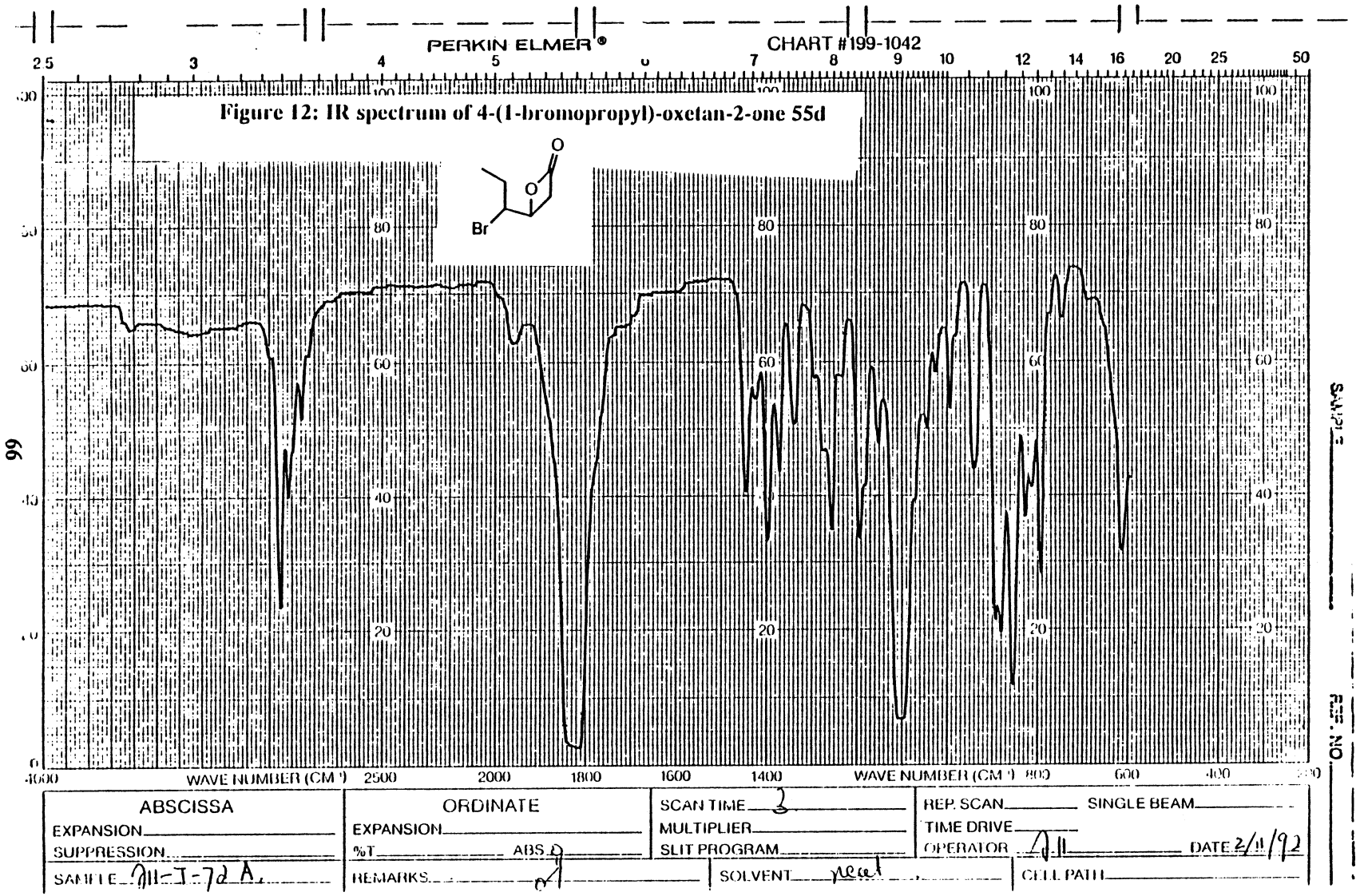

PERKIN ELMER®
CHART #199-1042
Figure 12: IR spectrum of 4-(1-bromopropyl)-oxetan-2-one 55d
O
O
Br
WAVE NUMBER (CM⁻¹)
2500
2000
1800
1600
1400
WAVE NUMBER (CM⁻¹)
800
600
400
ABSCISSA
EXPANSION
SUPPRESSION
SAMPLE 211-I-72 A
ORDINATE
EXPANSION
%T
ABS
REMARKS
SCAN TIME 3
MULTIPLIER
SLIT PROGRAM
SOLVENT neat
REP. SCAN
SINGLE BEAM
TIME DRIVE
OPERATOR
DATE 2/11/92
CELL PATH
99
SAMPLE
REF. NO

Figure 13: ^{1}H NMR spectrum of 4-(1-bromopropyl)-oxetan-2-one 55d

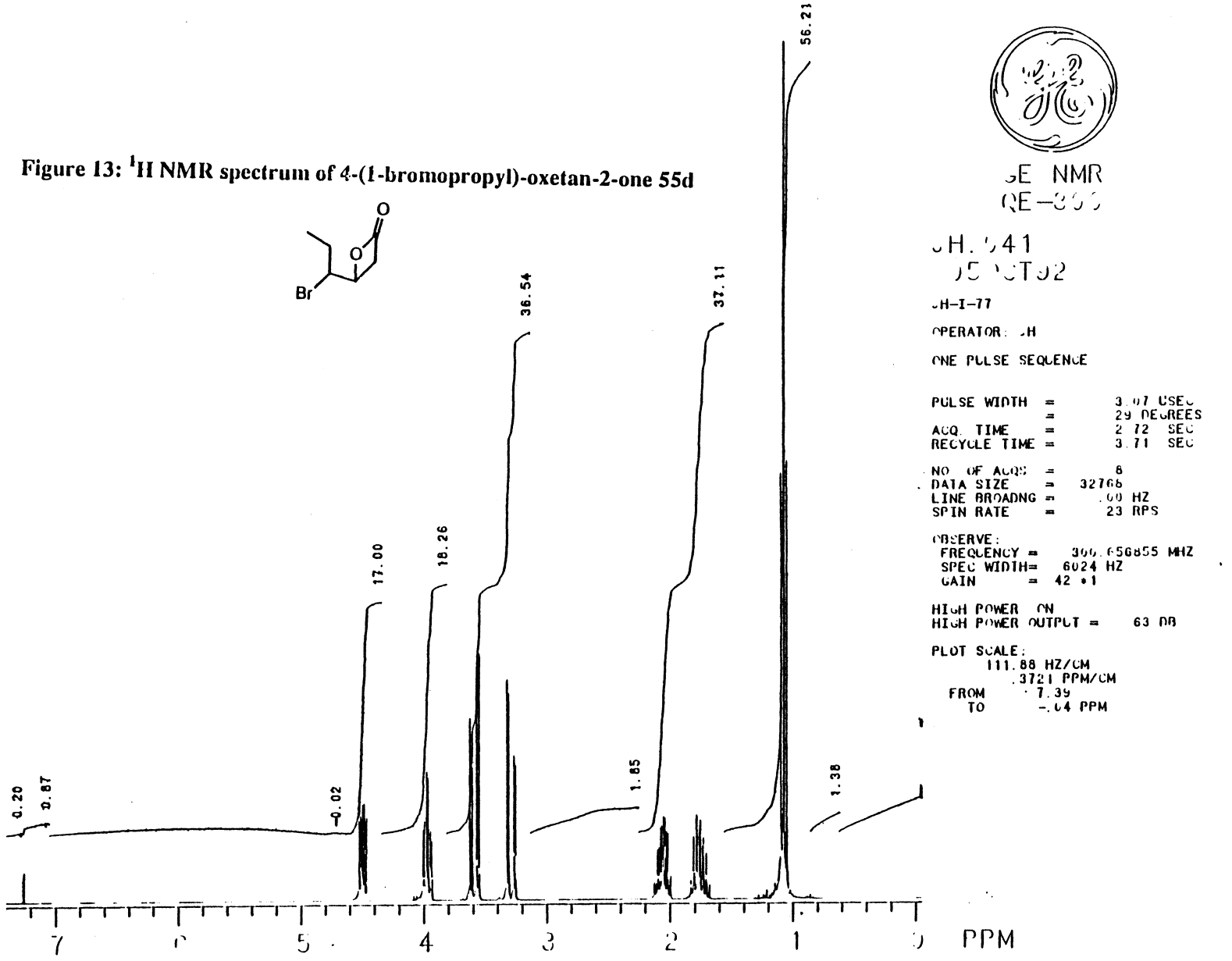
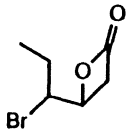
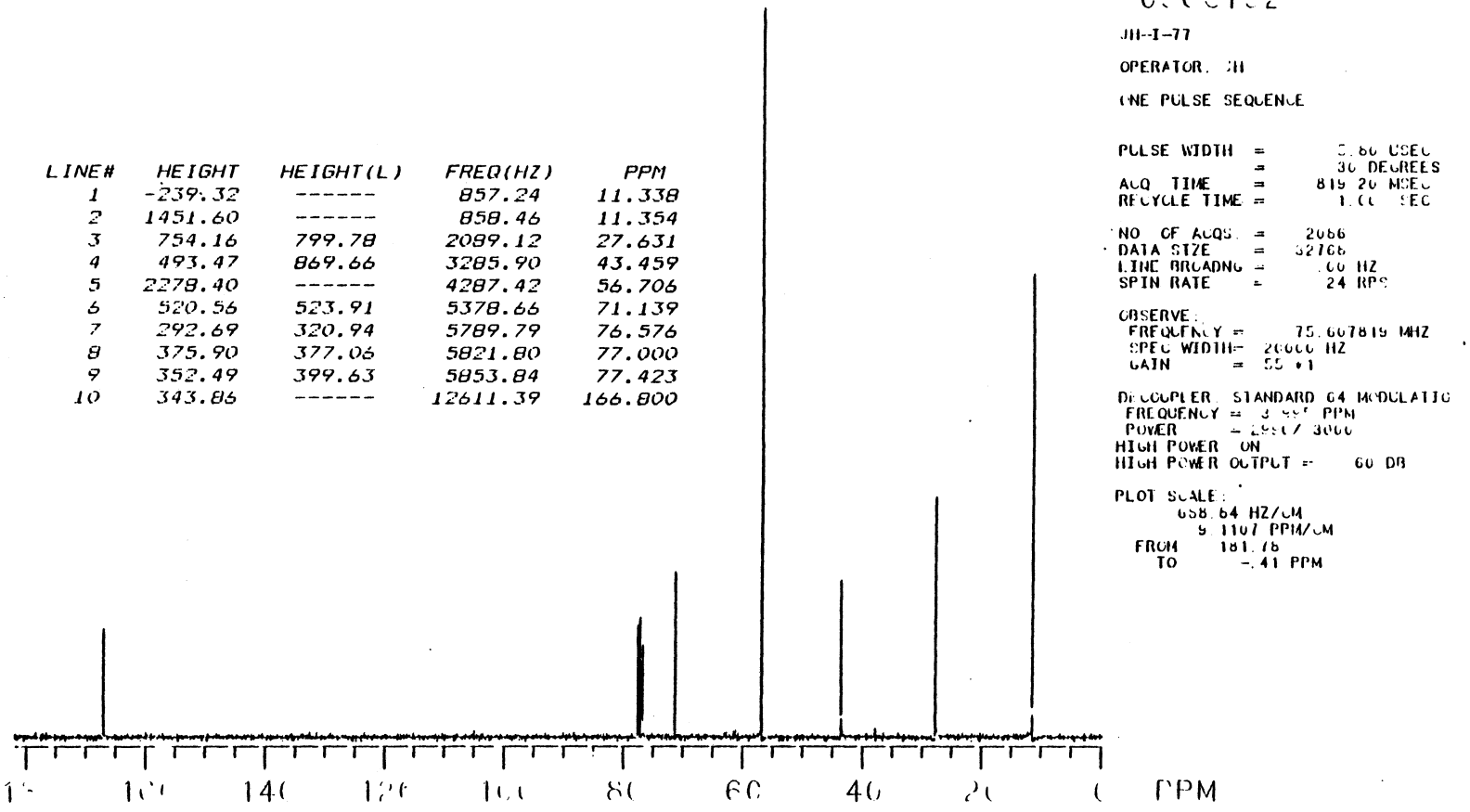


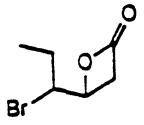
Figure 14: ^{13}C NMR spectrum of 4-(1-bromopropyl)-oxetan-2-one 55d

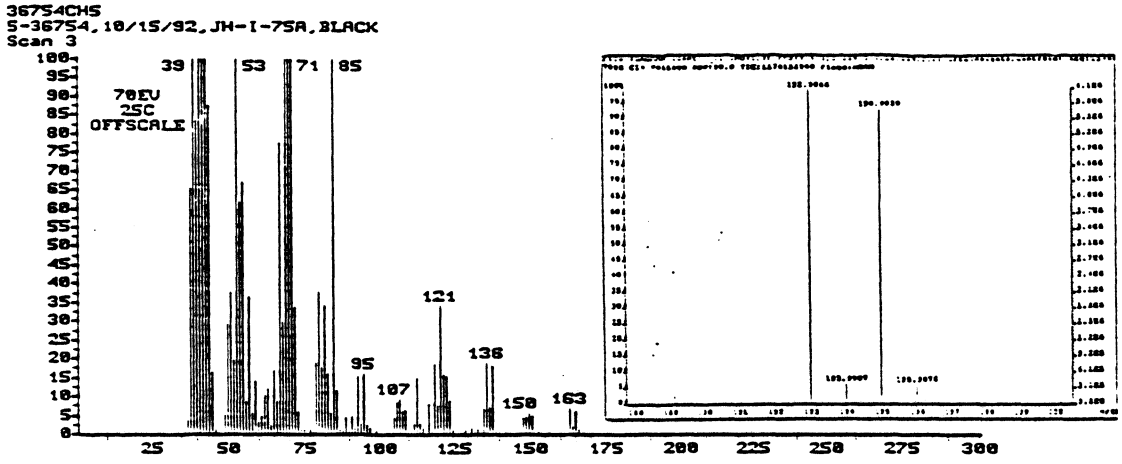




LINE#	HEIGHT	HEIGHT(L)	FREQ(HZ)	PPM
1	-239.32	------	857.24	11.338
2	1451.60	------	858.46	11.354
3	754.16	799.78	2089.12	27.631
4	493.47	869.66	3285.90	43.459
5	2278.40	------	4287.42	56.706
6	520.56	523.91	5378.66	71.139
7	292.69	320.94	5789.79	76.576
8	375.90	377.06	5821.80	77.000
9	352.49	399.63	5853.84	77.423
10	343.86	------	12611.39	166.800

Figure 15: Mass spectrum of 4-(1-bromopropyl)-oxetan-2-one 55d





36754CH5
Scan 3
5-36754,10/15/92,JH-I-75A,BLACK
91 peaks listed

MASS	RI	MASS	RI	MASS	RI	MASS	RI	MASS	RI	MASS	RI
37	3.79	55	67.24	71	100.00	89	4.49	114	3.20	137	7.39
38	65.32	56	9.09	72	34.07	91	4.99	115	1.65	138	18.07
39	100.00	57	36.87	73	6.19	92	1.77	117	8.16	139	1.07
40	83.82	58	5.80	74	1.30	93	15.29	119	18.53	148	4.68
41	100.00	59	14.28	75	1.35	94	3.01	120	7.95	149	4.98
42	100.00	60	3.47	77	1.52	95	16.42	121	34.29	150	5.63
43	100.00	61	5.10	78	1.00	96	2.76	122	15.99	151	4.88
44	87.78	62	10.65	79	19.09	97	1.71	123	15.60	163	7.16
45	16.87	63	12.18	80	37.98	105	4.61	124	8.89	164	2.04
46	1.34	64	2.72	81	17.88	106	8.78	125	1.51	165	6.23
49	5.52	65	17.01	82	34.28	107	9.25	128	1.12	166	1.42
50	29.45	66	9.09	83	16.31	108	6.18	129	1.25		
51	38.03	67	77.56	84	5.87	109	6.64	131	1.66		
52	19.86	68	30.11	85	100.00	111	1.08	133	1.22		
53	100.00	69	100.00	86	11.70	112	2.98	135	7.20		
54	62.05	70	100.00	87	1.37	113	15.13	136	19.08		

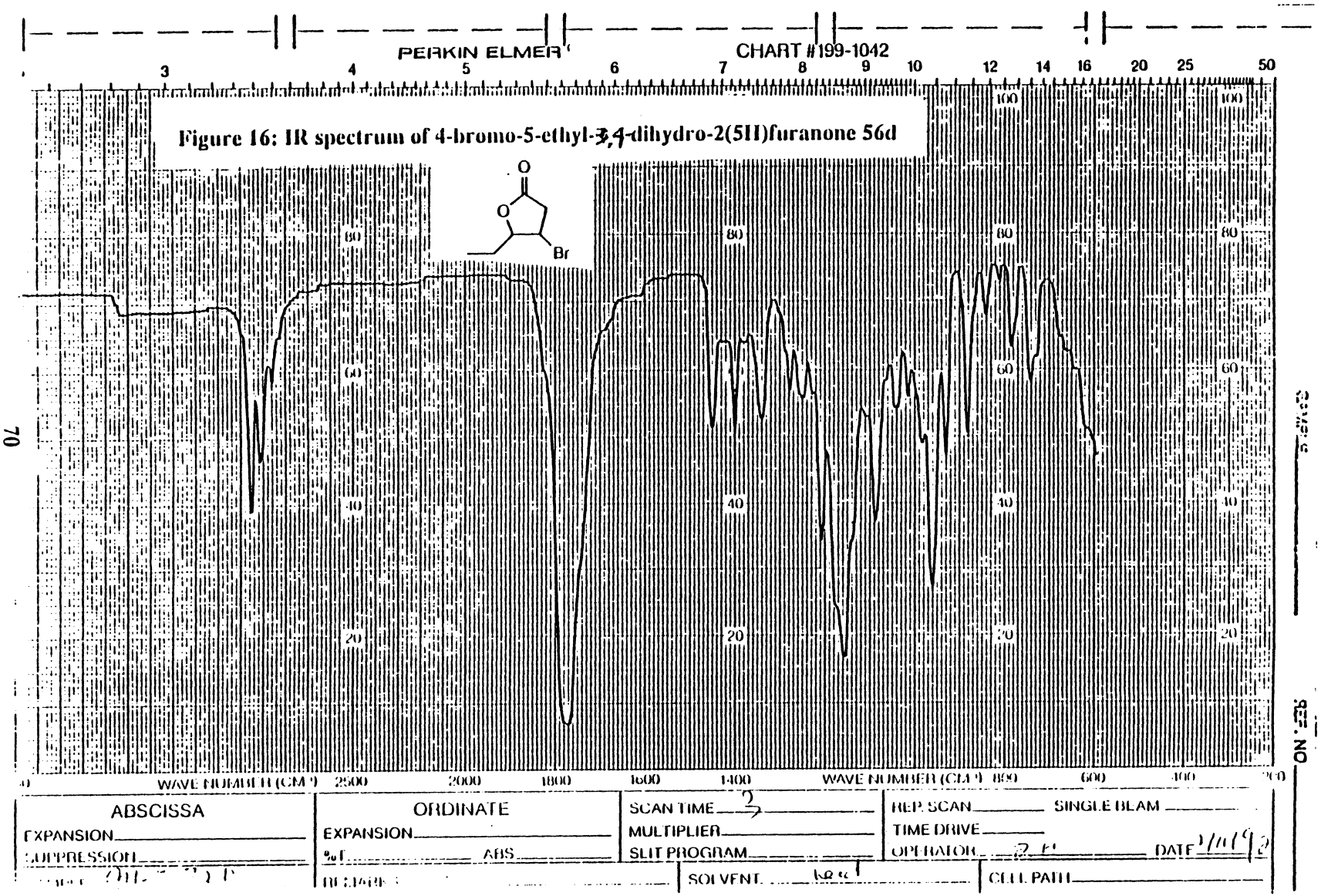


Figure 16: IR spectrum of 4-bromo-5-ethyl-3,4-dihydro-2(5H)furanone 56d

Figure 17: ^{1}H NMR spectrum of 4-bromo-5-ethyl-3,4-dihydro-2(5H)furanone 56d

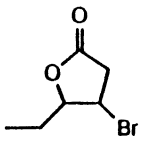


Figure 18: IR spectrum of 3-methyl-4-bromomethyloxetan-2-one 55f

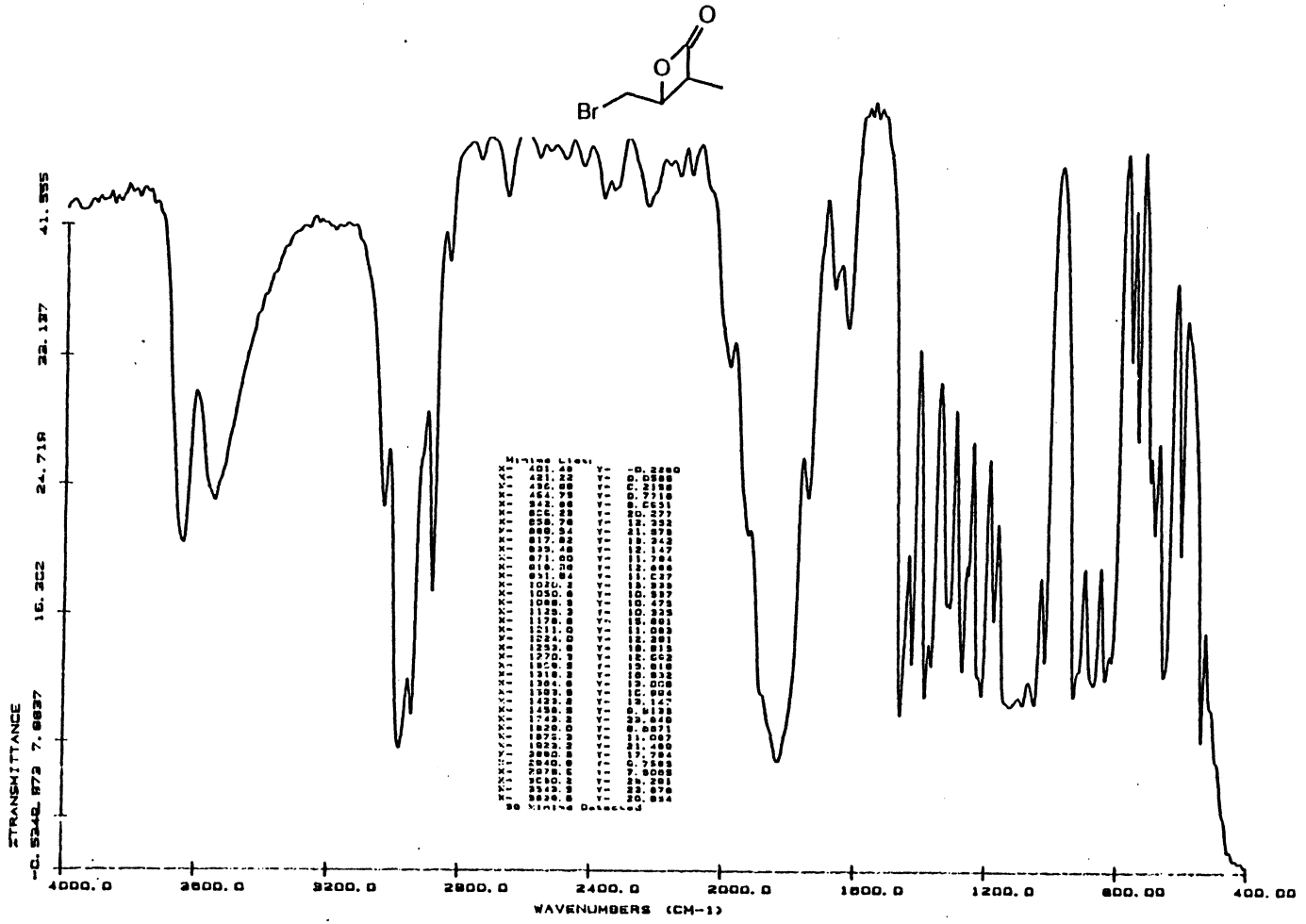
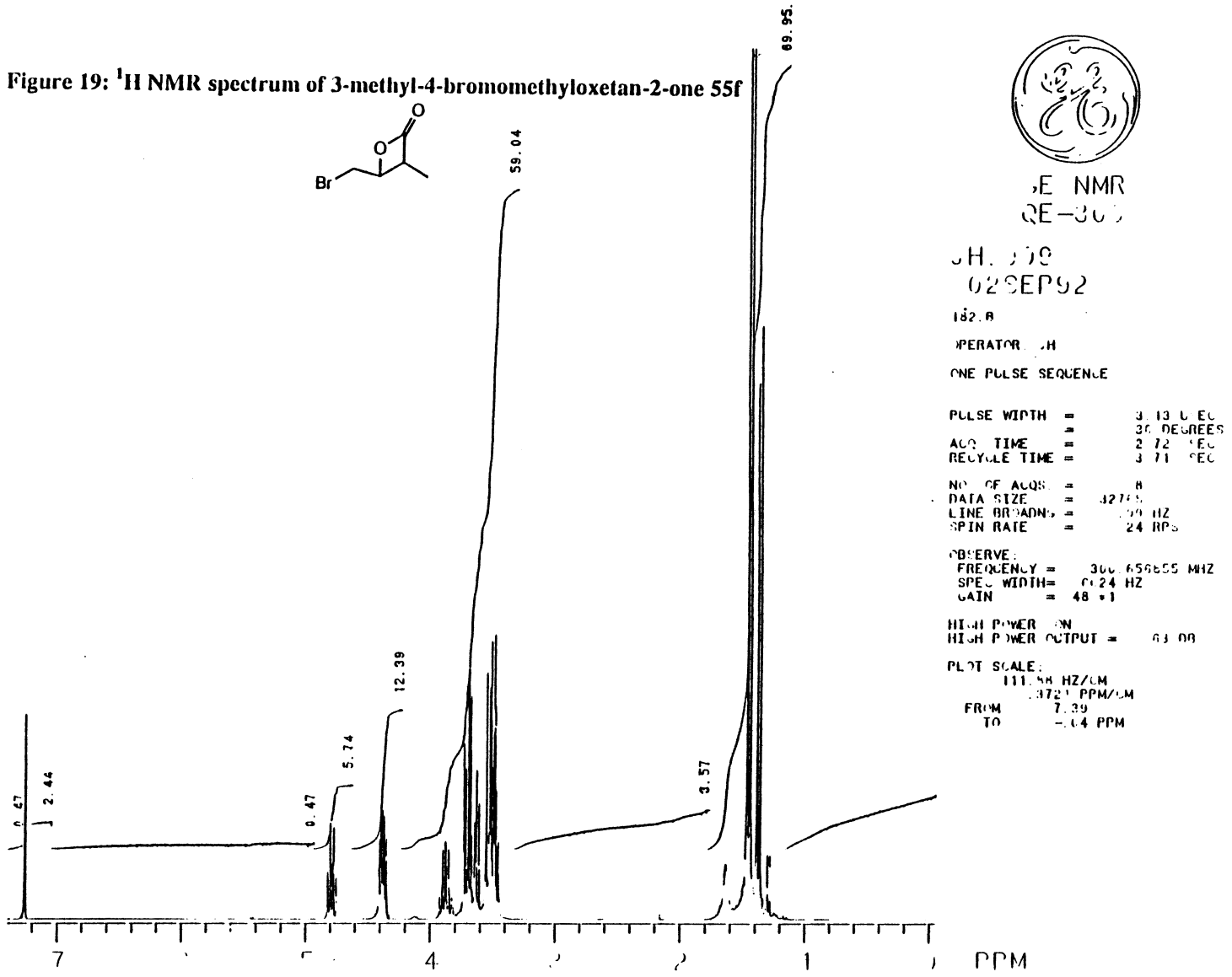


Figure 19: ^{1}H NMR spectrum of 3-methyl-4-bromomethyloxetan-2-one 55f



E NMR
QE-30
H. 09
02SEP92
182.8
PERATOR H
ONE PULSE SEQUENCE

PULSE WIDTH = 3.13 U EC
= 30 DEGREES
ACQ TIME = 2.72 SEC
RECYCLE TIME = 3.71 SEC

NO OF ACQS = 8
DATA SIZE = 32768
LINE BROADNG = .50 HZ
SPIN RATE = 24 RPS

OBSERVE:
FREQUENCY = 300.656655 MHZ
SPEC WIDTH= 6024 HZ
GAIN = 48 +1

HIGH POWER ON
HIGH POWER OUTPUT = 63.00

PLOT SCALE:
111.58 HZ/CM
.3721 PPM/CM
FROM 7.39
TO -.04 PPM

Figure 20: ^{13}C NMR spectrum of 3-methyl-4-bromomethyloxetan-2-one 55f

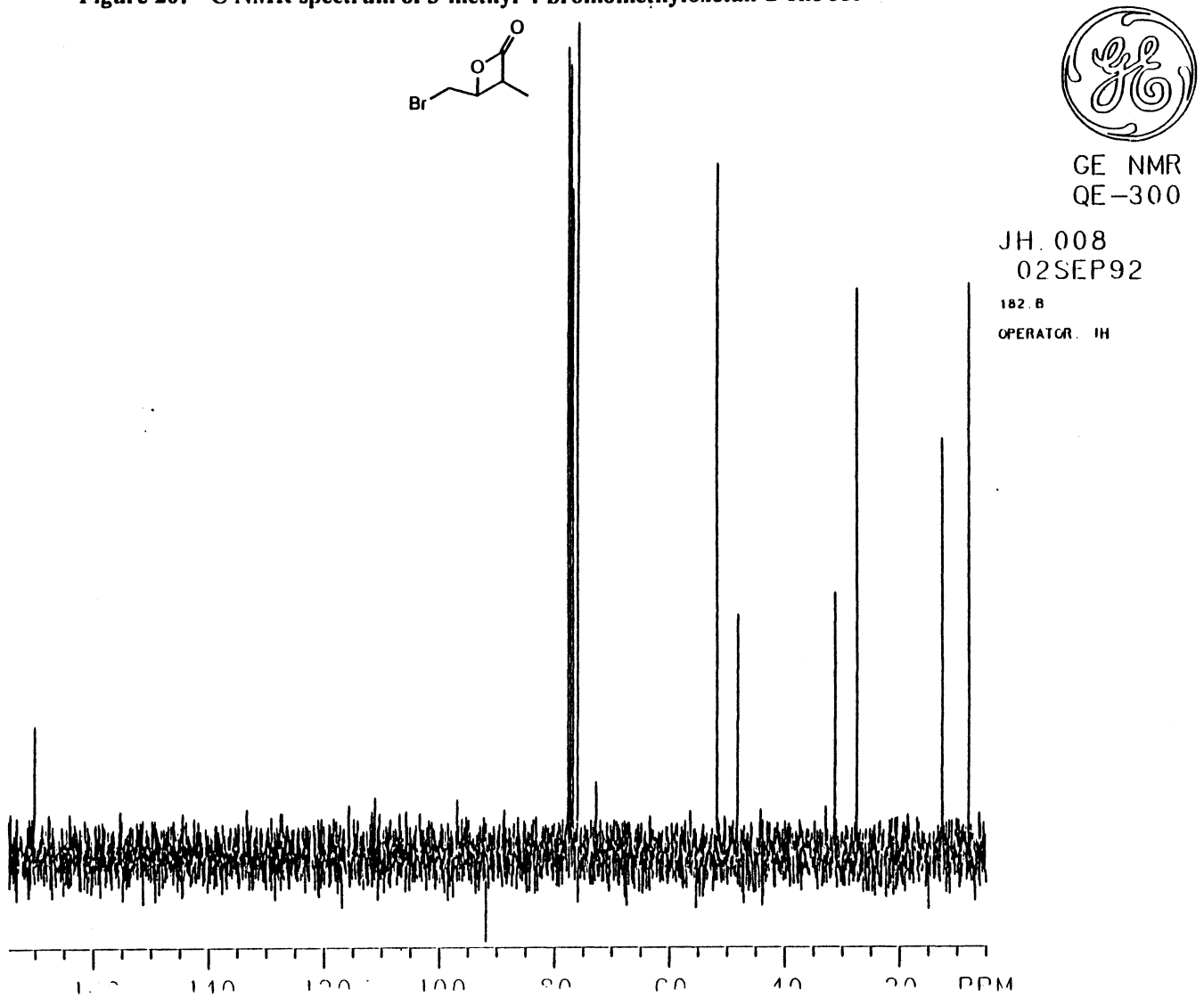
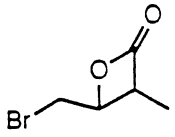
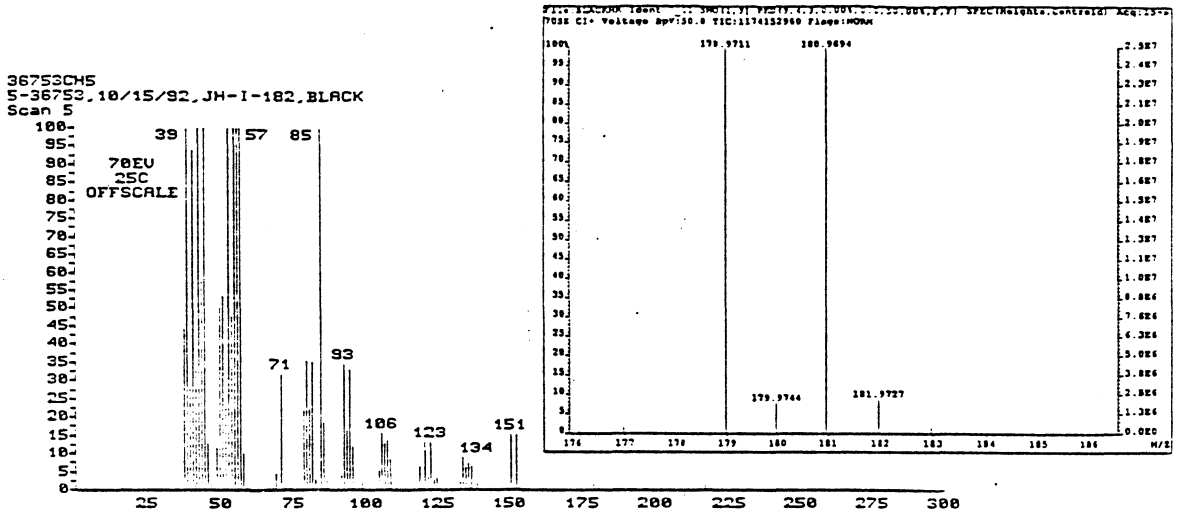


Figure 21: Mass spectrum of 3-methyl-4-bromomethyloxetan-2-one 55f





36753CH5
Scan 5
5-36753,10/15/92,JH-I-182,BLACK
73 peaks listed

MASS	RI	MASS	RI	MASS	RI	MASS	RI	MASS	RI	MASS	RI
38	44.47	51	53.55	71	32.00	93	34.90	119	6.83	139	1.64
39	100.00	52	22.74	72	1.87	94	16.57	120	2.36	150	1.09
40	27.85	53	100.00	79	21.77	95	33.05	121	13.33	151	15.56
41	94.12	54	48.16	80	35.56	96	12.17	122	3.81	152	1.72
42	32.98	55	100.00	81	22.24	98	1.30	123	13.39	153	15.41
43	100.00	56	100.00	82	35.20	99	2.46	124	2.91	179	1.82
44	57.57	57	100.00	83	2.84	104	1.49	125	3.56	181	1.34
45	100.00	58	10.33	84	1.45	105	5.29	126	1.34	217	1.52
46	12.86	59	1.40	85	100.00	106	15.76	133	2.10		
47	1.67	66	1.94	86	18.50	107	13.09	134	8.99		
48	1.28	67	1.23	87	2.48	108	13.73	135	6.13		
49	11.99	69	4.54	91	2.66	109	8.54	136	7.27		
50	50.50	70	1.12	92	4.18	117	1.43	137	6.79		

Figure 22: IR spectrum of 3-methyl-4-iodomethyloxetan-2-one 55g

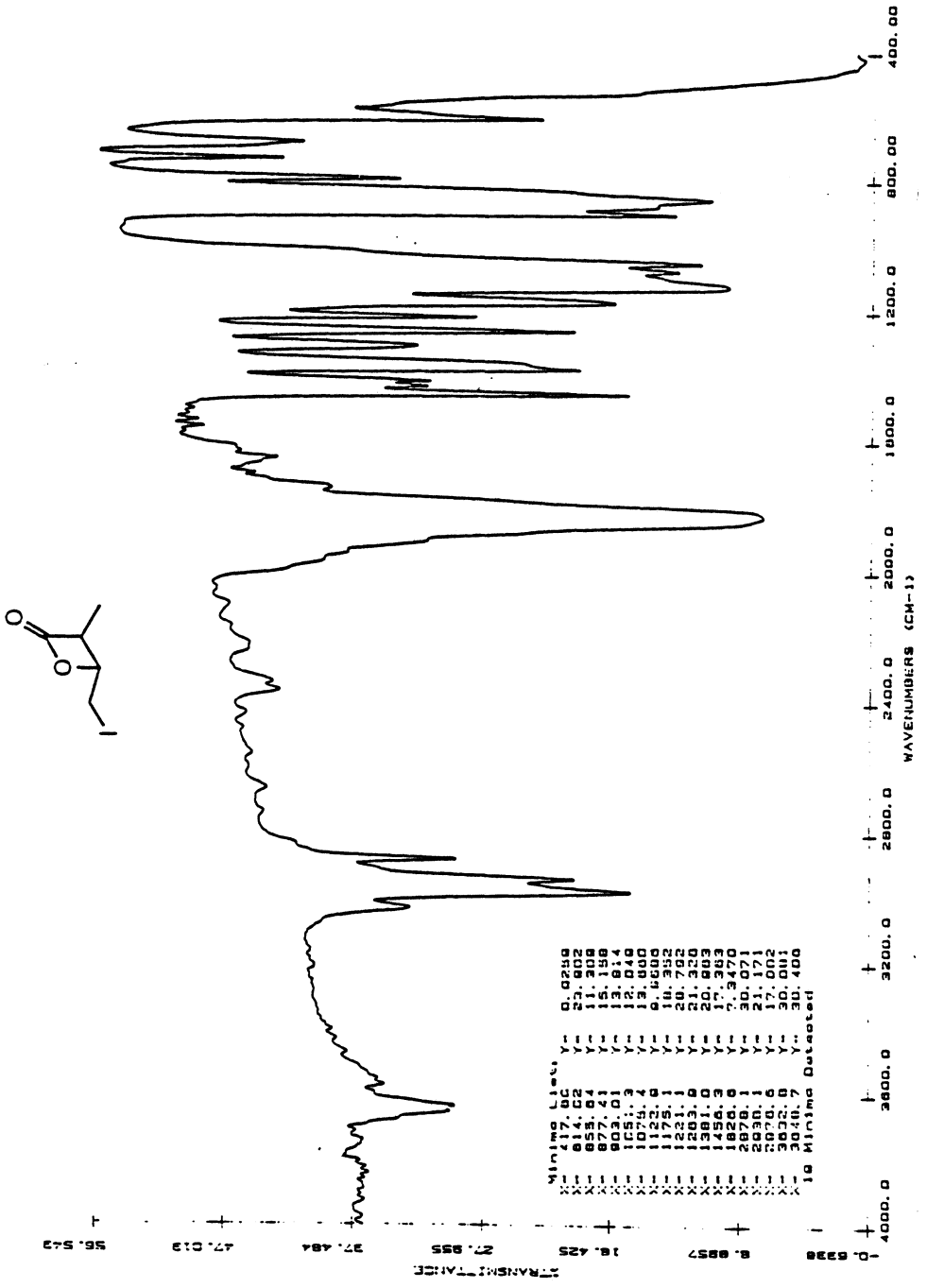
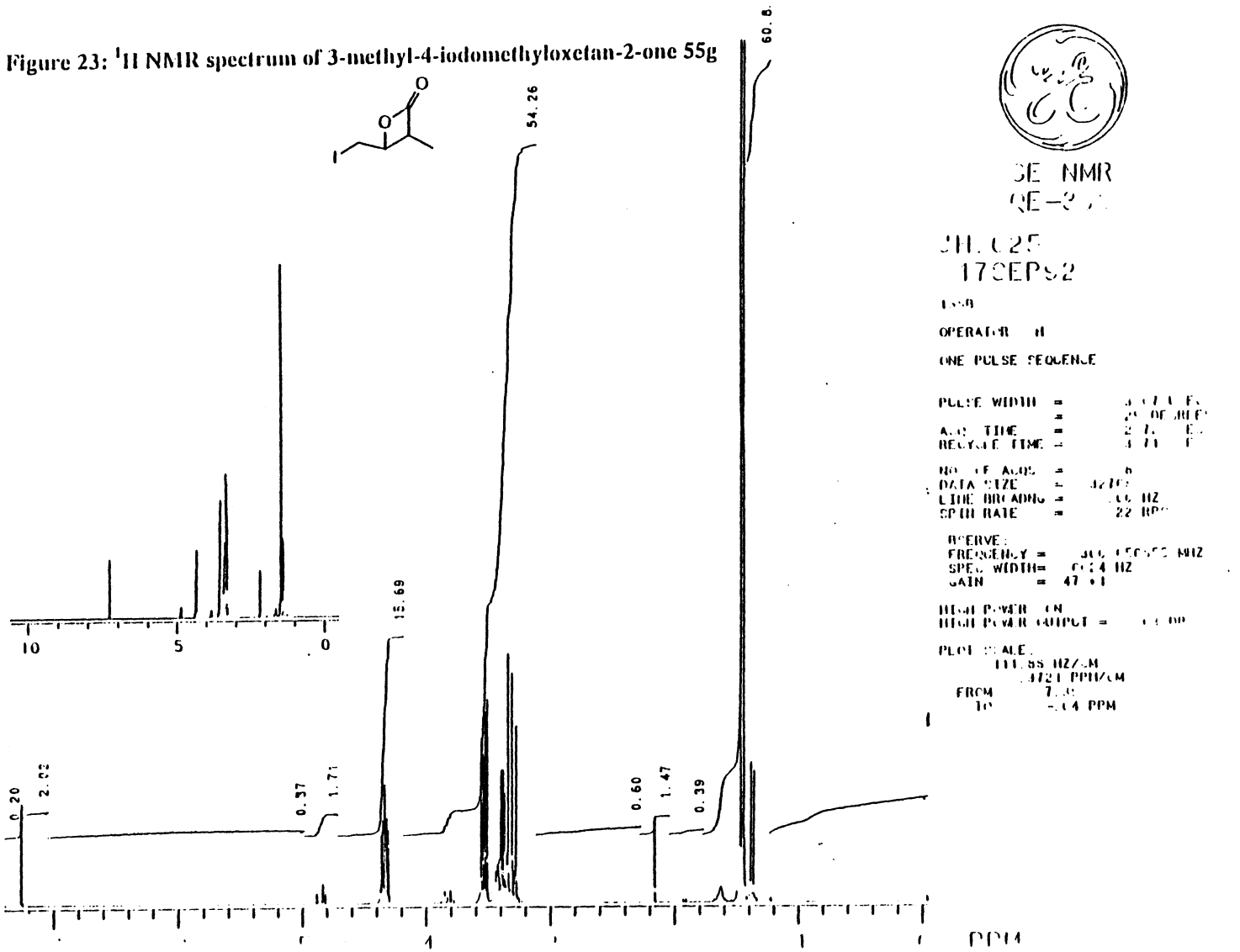
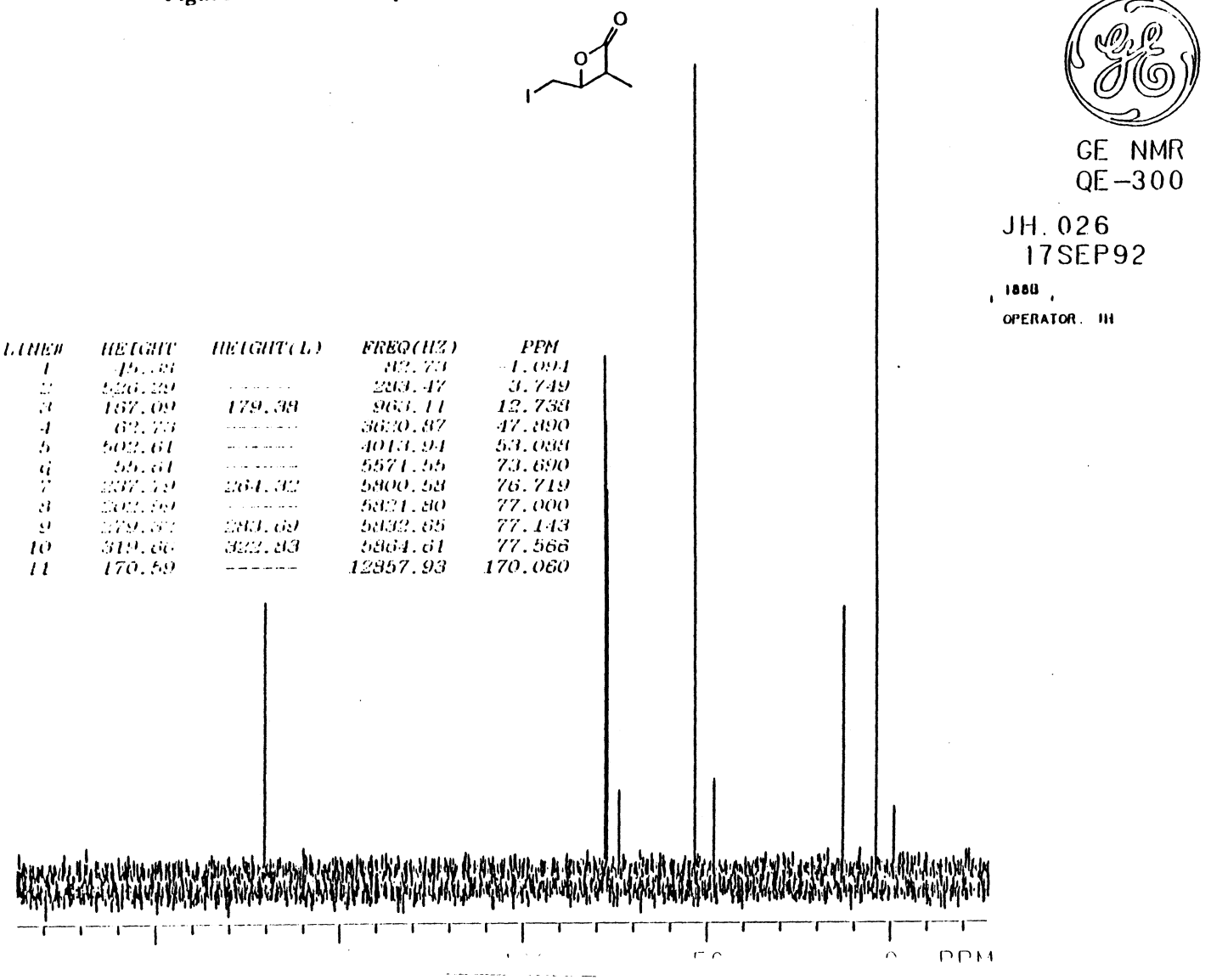


Figure 23: ^{1}H NMR spectrum of 3-methyl-4-iodomethyloxetan-2-one 55g



77

Figure 24: ^{13}C NMR spectrum of 3-methyl-4-iodomethyloxetan-2-one 55g



LINE#	HEIGHT	HEIGHT(L)	FREQ(HZ)	PPM
1	-15.81		82.73	-1.094
2	526.29	------	226.47	3.749
3	167.09	179.38	963.11	12.738
4	69.73	------	3620.87	47.890
5	502.61	------	4013.94	53.038
6	55.61	------	5571.55	73.690
7	237.79	264.32	5800.58	76.719
8	202.59	------	5821.80	77.000
9	279.33	283.69	5832.65	77.143
10	319.66	322.83	5864.61	77.566
11	170.59	------	12857.93	170.060

Figure 25: IR spectrum of 3-(1-methylethyl)-4-(1-bromopropyl)-oxetan-2-one 55j

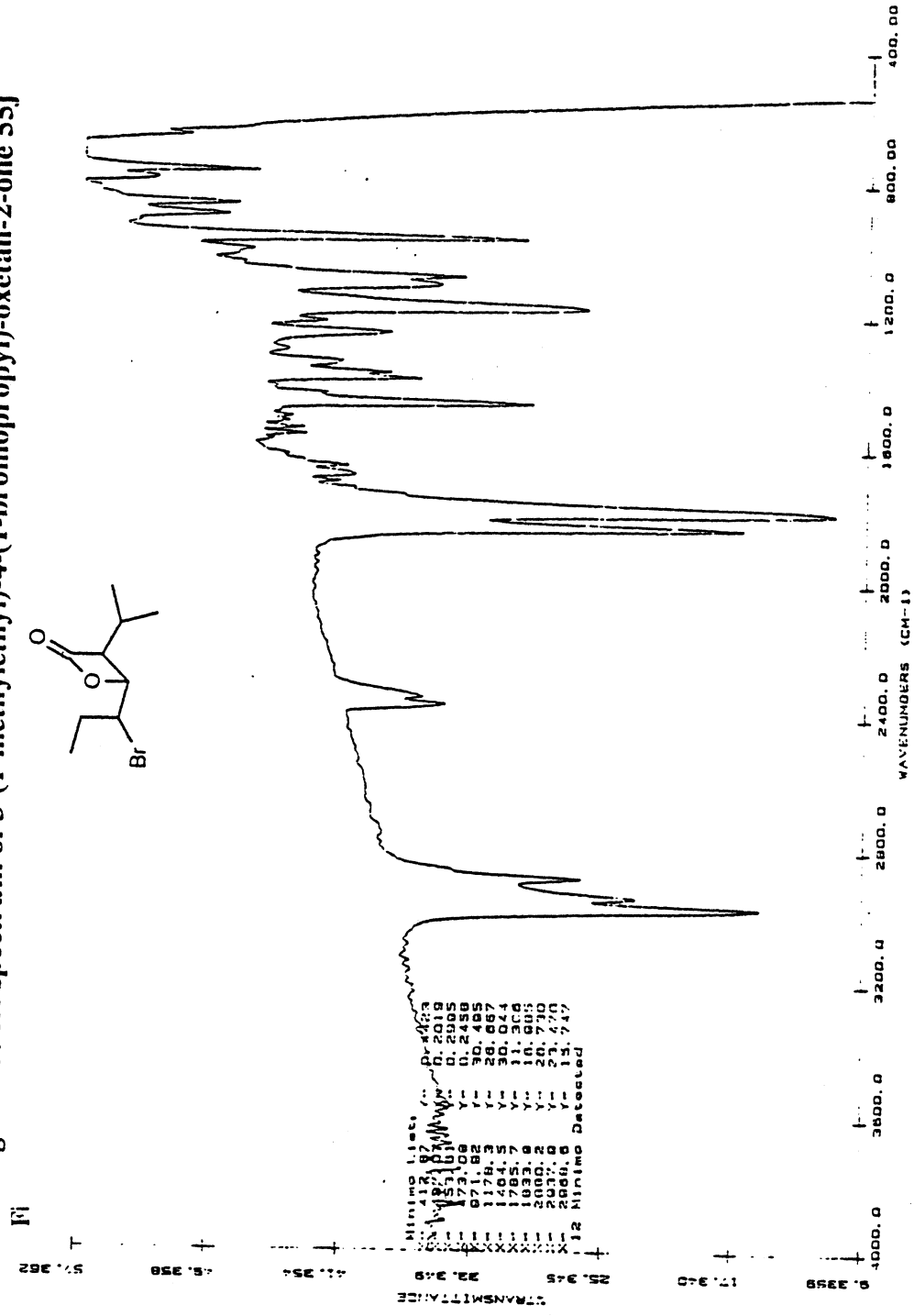
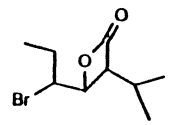


Figure 26: ^{1}H NMR spectrum of 3-(1-methylethyl)-4-(1-bromopropyl)-oxetan-2-one 55j



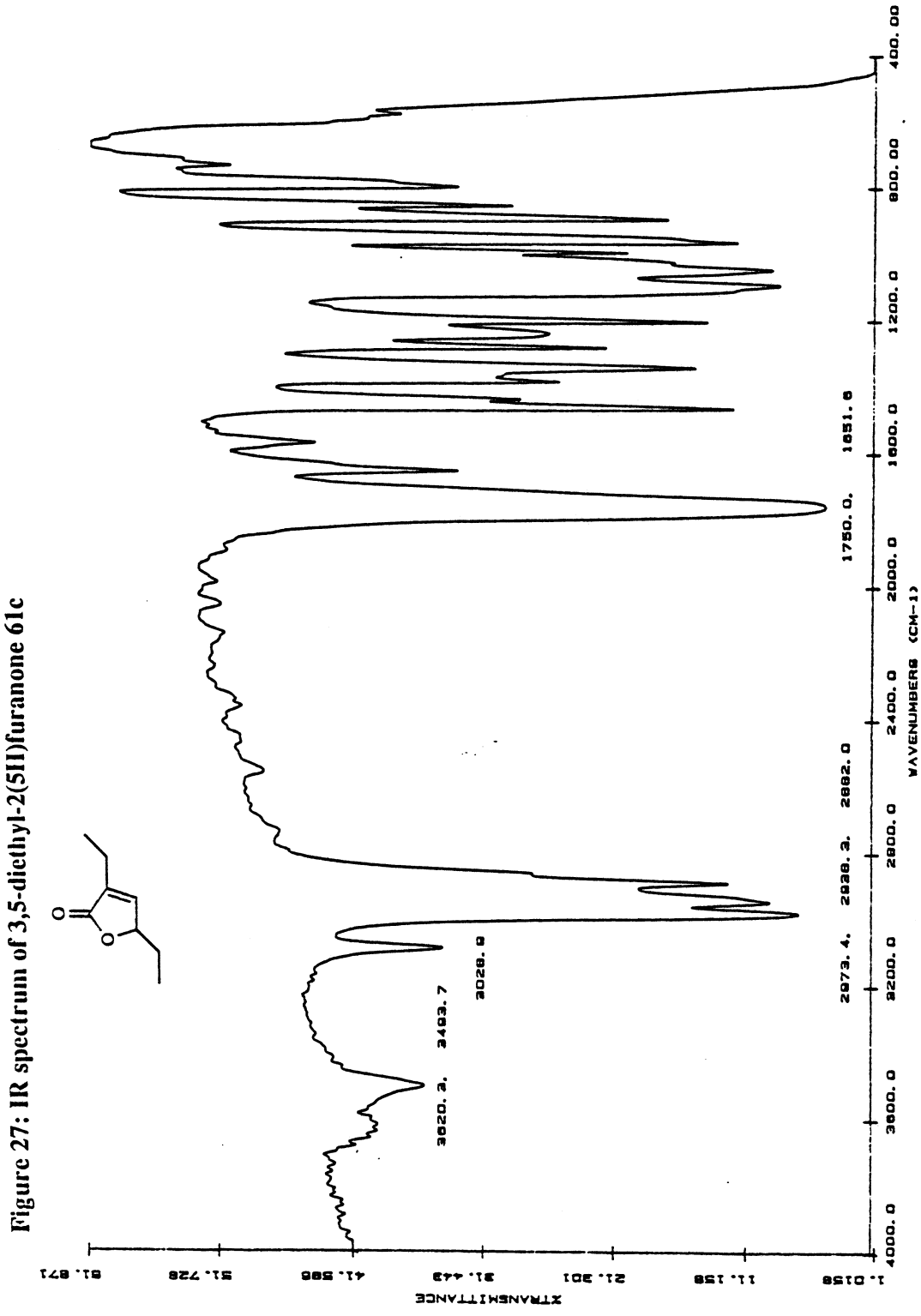


Figure 27: IR spectrum of 3,5-diethyl-2(5H)furanone 61c

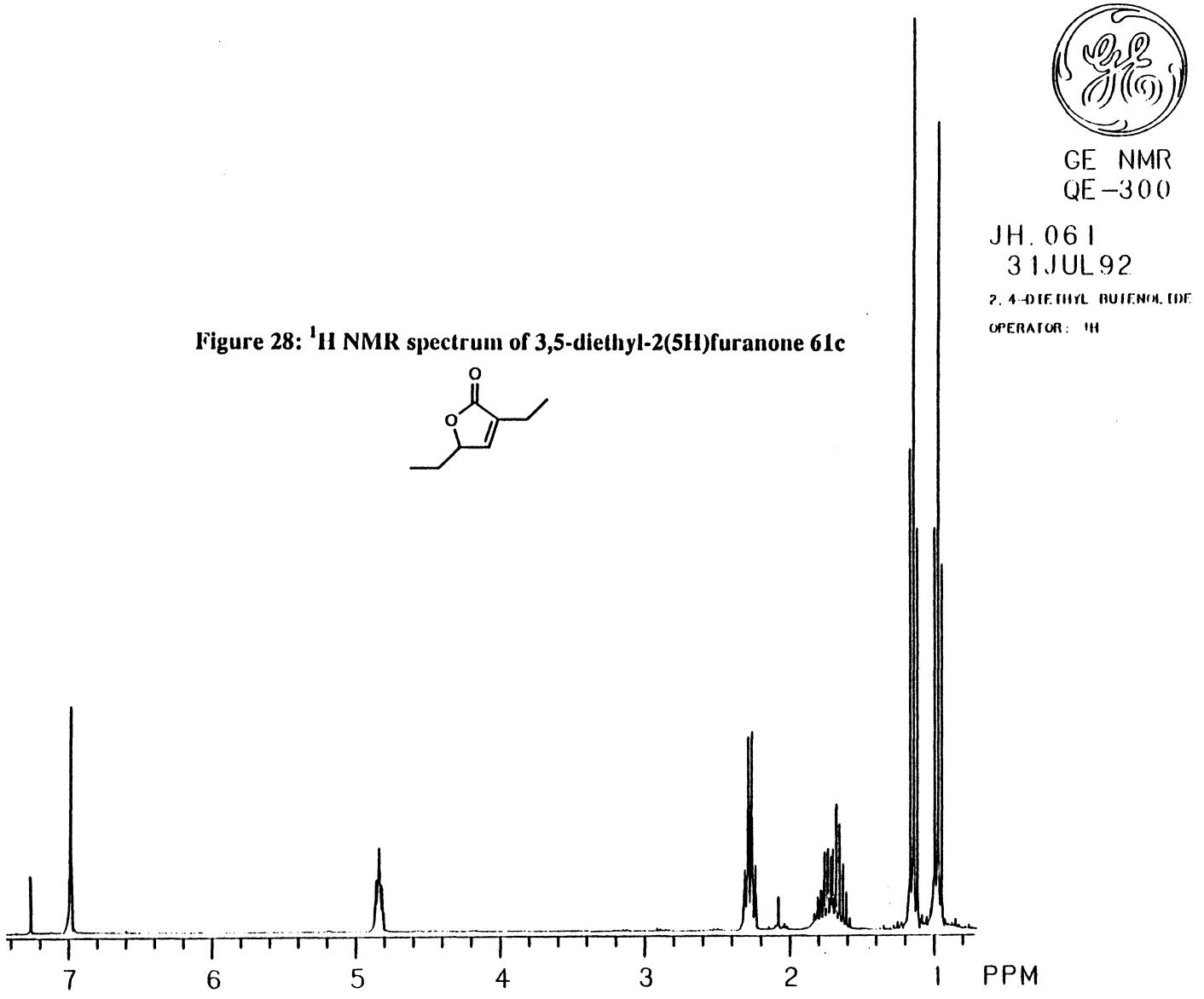
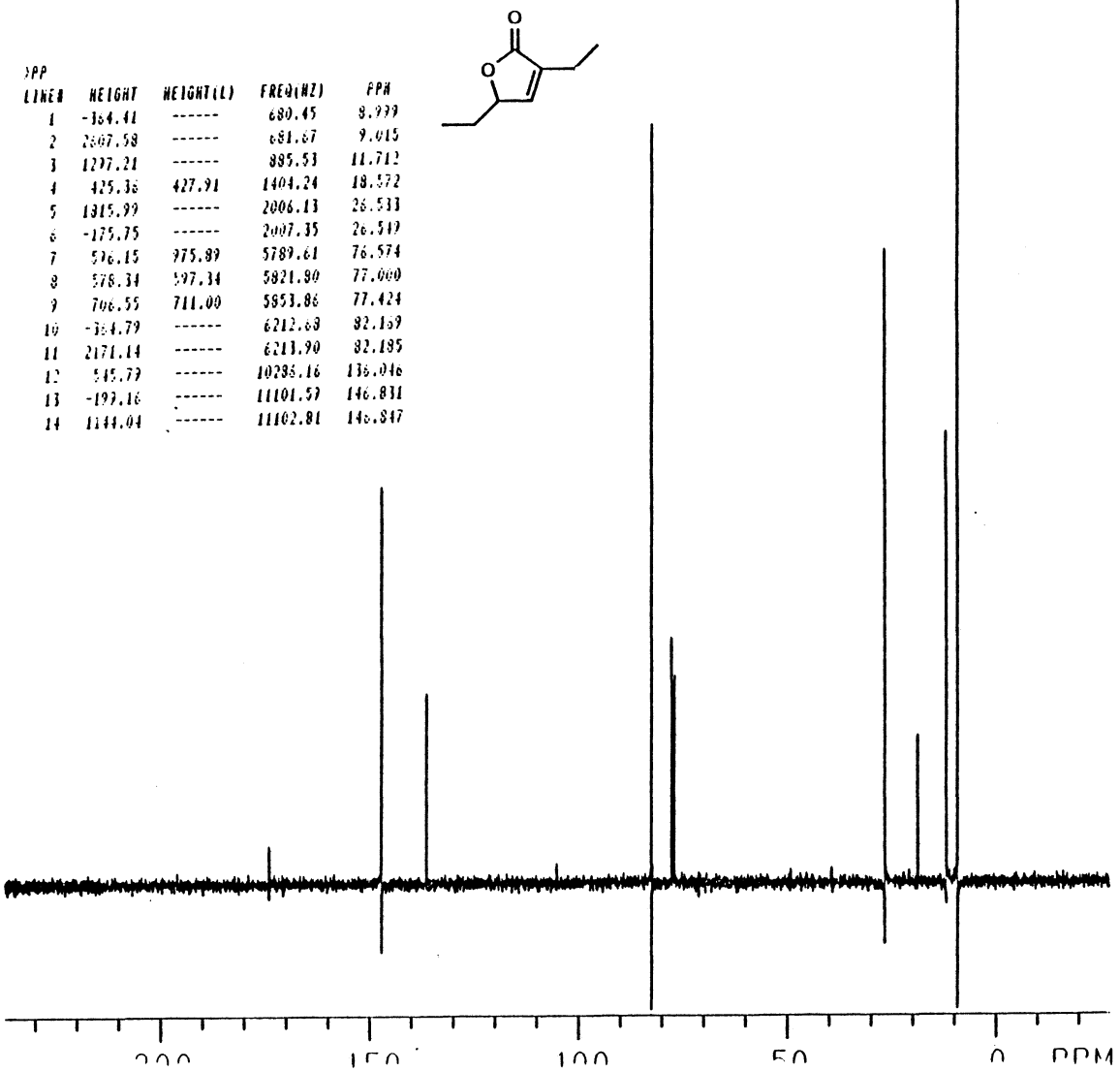


Figure 28: ^{1}H NMR spectrum of 3,5-diethyl-2(5H)furanone 61c

Figure 29: ^{13}C NMR spectrum of 3,5-diethyl-2(5H)furanone 61c



GE NMR
QE-300

JH.062
31JUL92

2,4-DIETHYL BUTENOLIDE

OPERATOR: IH

Figure 30: IR spectrum of 5-ethyl-3-phenylmethyl-2(5H)furanone 61e

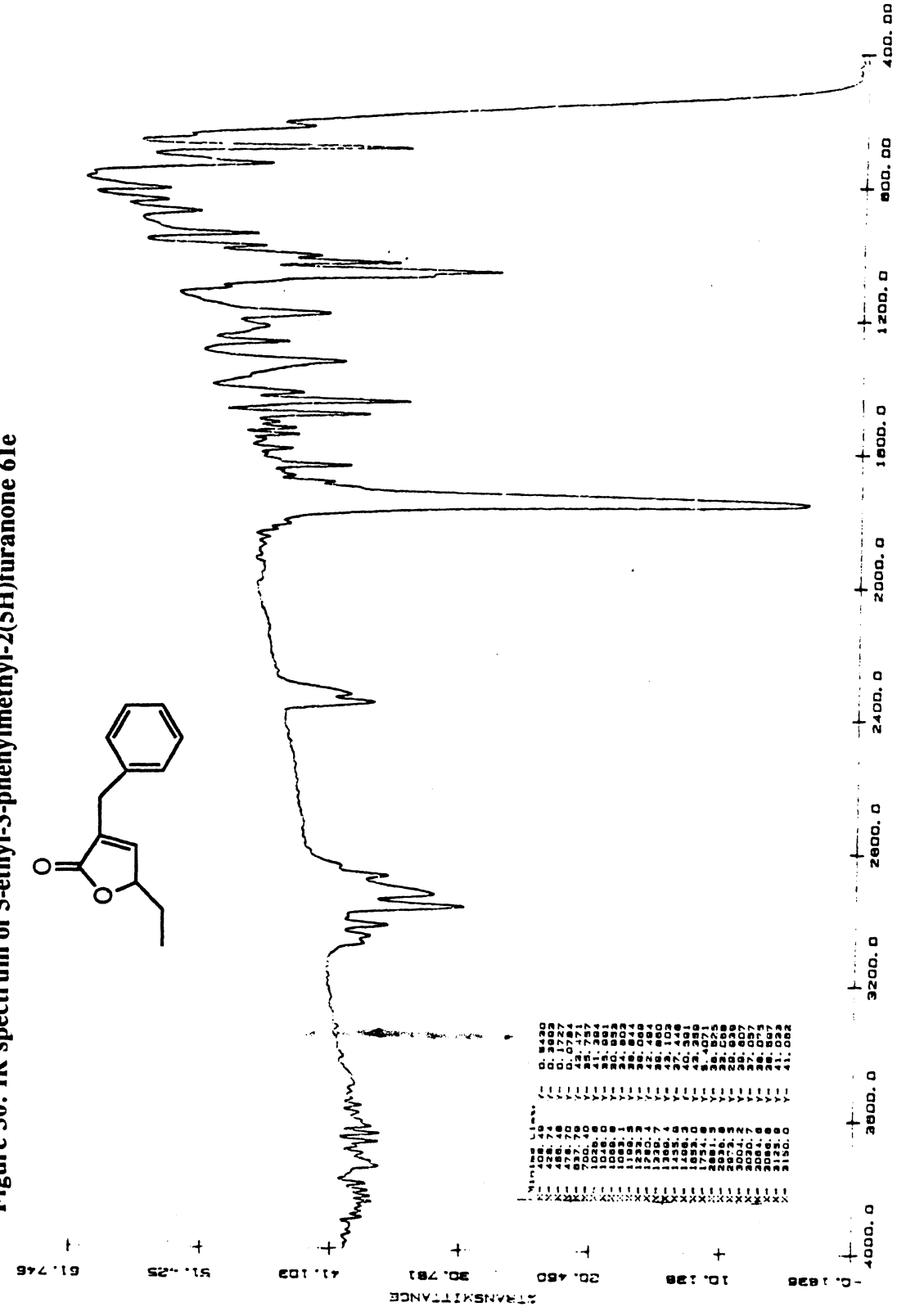


Figure 31: ^{1}H NMR spectrum of 5-ethyl-3-phenylmethyl-2(5H)furanone 61e

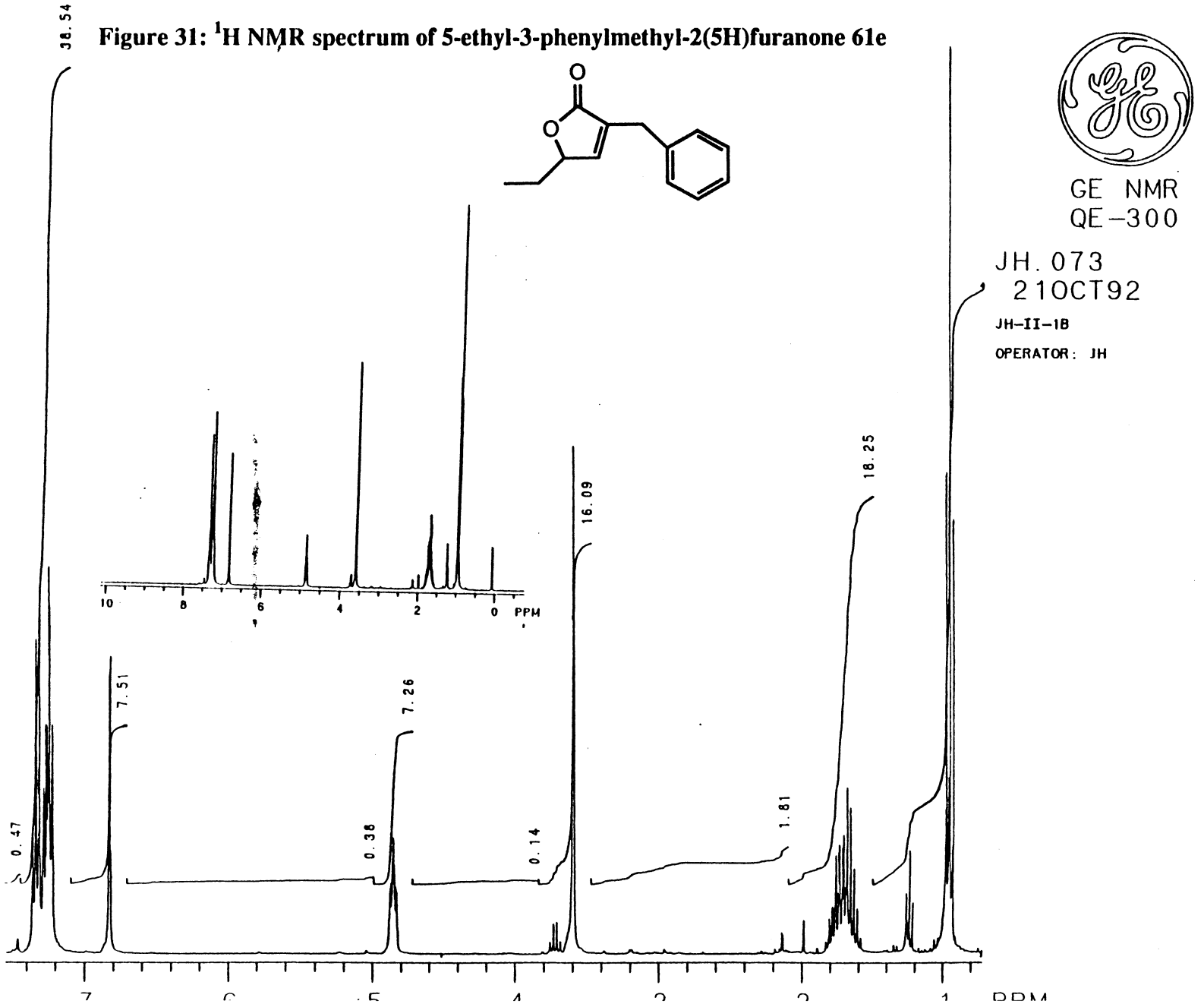
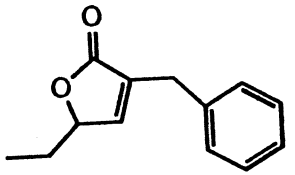


Figure 32: ^{13}C NMR spectrum of 5-ethyl-3-phenylmethyl-2(5H)furanone 61e



LINE#	HEIGHT	HEIGHT(L)	FREQ(HZ)	PPM
1	1319.68	1350.10	681.80	9.017
2	1875.88	1985.61	2000.00	26.452
3	2766.80	------	2397.99	31.716
4	2112.43	2769.92	5789.79	76.576
5	2637.28	2954.09	5821.80	77.000
6	2800.53	2801.38	5953.78	77.423
7	3113.89	------	6226.11	82.347
8	3110.53	------	9580.60	126.714
9	4438.27	------	9729.53	128.684
10	4772.27	------	9741.74	128.845
11	1181.82	------	10157.76	134.480
12	632.03	------	10389.71	137.402
13	3424.35	------	11256.63	148.881
14	476.94	------	13112.10	173.422

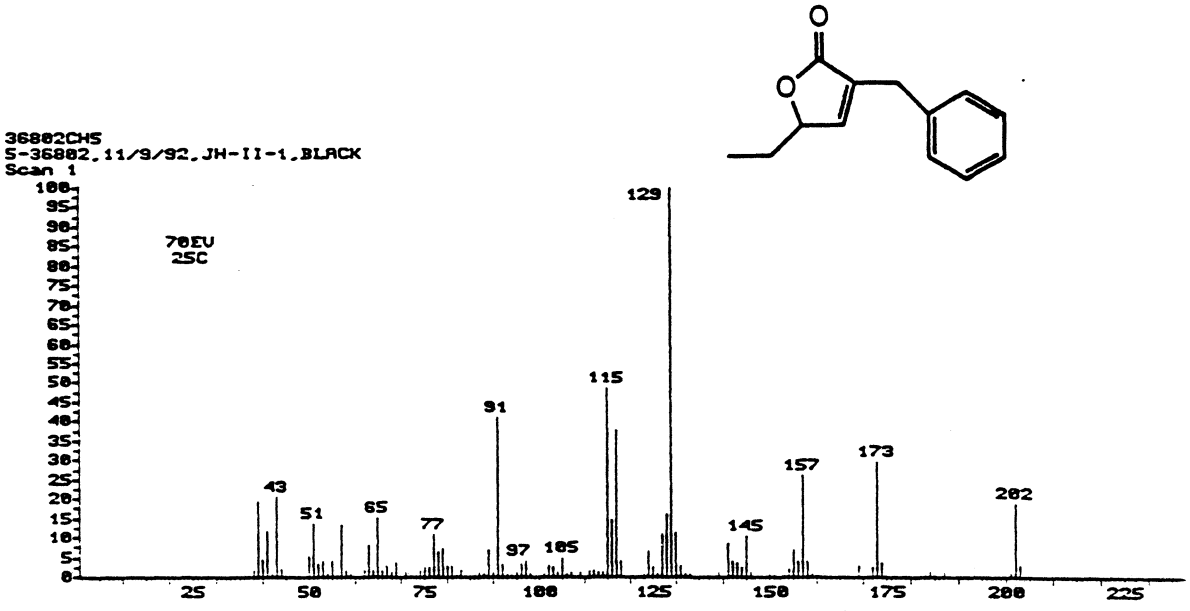
GE NMR
QE-300

JH.074
21OCT92

JH-II-1B

OPERATOR: JH

Figure 33: Mass spectrum of 5-ethyl-3-phenylmethyl-2(5H)furanone 61e



36802CH5
Scan 1
5-36802,11/9/92,JH-II-1,BLACK
83 peaks listed

MASS	RI	MASS	RI	MASS	RI	MASS	RI	MASS	RI	MASS	RI
38	1.61	63	8.12	80	2.94	104	1.56	125	2.62	154	2.2
39	19.57	64	1.96	81	2.87	105	5.12	127	11.19	155	7.1
40	4.75	65	15.48	83	1.71	107	1.25	128	16.44	156	4.0
41	11.97	66	1.94	87	1.43	109	1.55	129	100.00	157	26.2
43	20.66	67	3.10	89	7.08	111	1.67	130	11.27	158	4.1
44	2.05	68	1.46	90	1.48	112	1.64	131	2.93	169	3.0
50	5.51	69	3.93	91	41.35	113	1.49	139	1.21	172	2.6
51	13.94	71	1.30	92	3.60	114	1.43	141	8.81	173	30.1
52	3.49	74	1.64	93	1.12	115	48.70	142	4.31	174	4.0
53	4.23	75	2.51	95	1.31	116	14.69	143	3.83	184	1.3
55	4.05	76	2.70	96	3.23	117	38.06	144	2.65	187	1.4
57	13.47	77	11.14	97	4.04	118	4.22	145	10.69	202	18.9
58	1.81	78	6.61	102	3.11	123	1.06	146	1.48	203	3.2
62	1.94	79	7.28	103	2.69	124	6.74	150	1.13		

Elemental Composition **Date : 11-NOV-1992**

Heteroatom Max: 60 Ion: Both Even and Odd
Limits:

			-0.5	0	0	0
202.099645	10.0		50.0	50	100	6

Mass	mDa	PPM	Calc. Mass	DBE	C	H	O
202.099645	-0.3	-1.3	202.099380	7.0	13	14	2

Figure 34: IR spectrum of 5-ethyl-3-(1-methylethyl)-2(5H)furanone 61f

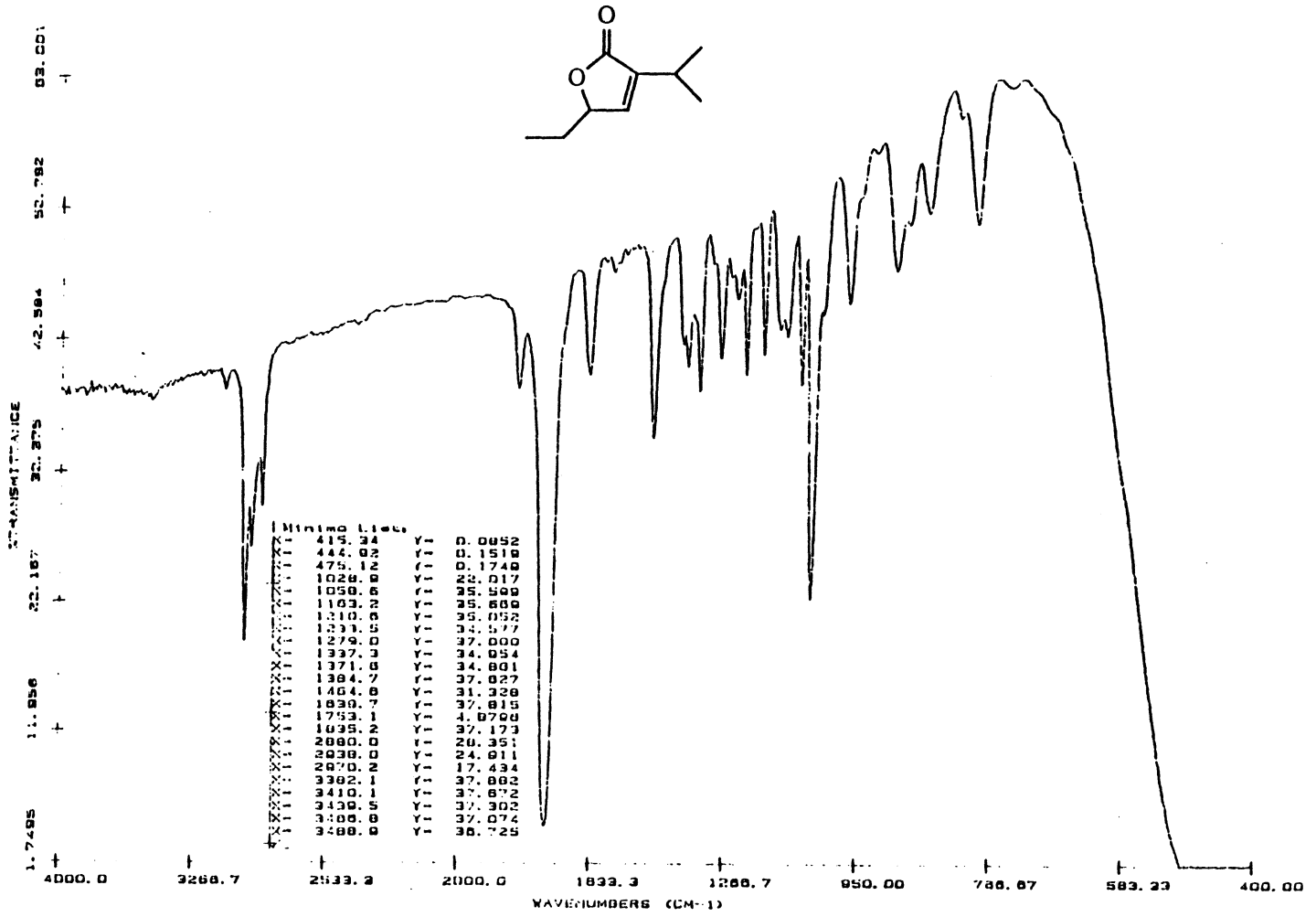


Figure 35: ^{1}H NMR spectrum of 5-ethyl-3-(1-methylethyl)-2(5H)furanone 61f

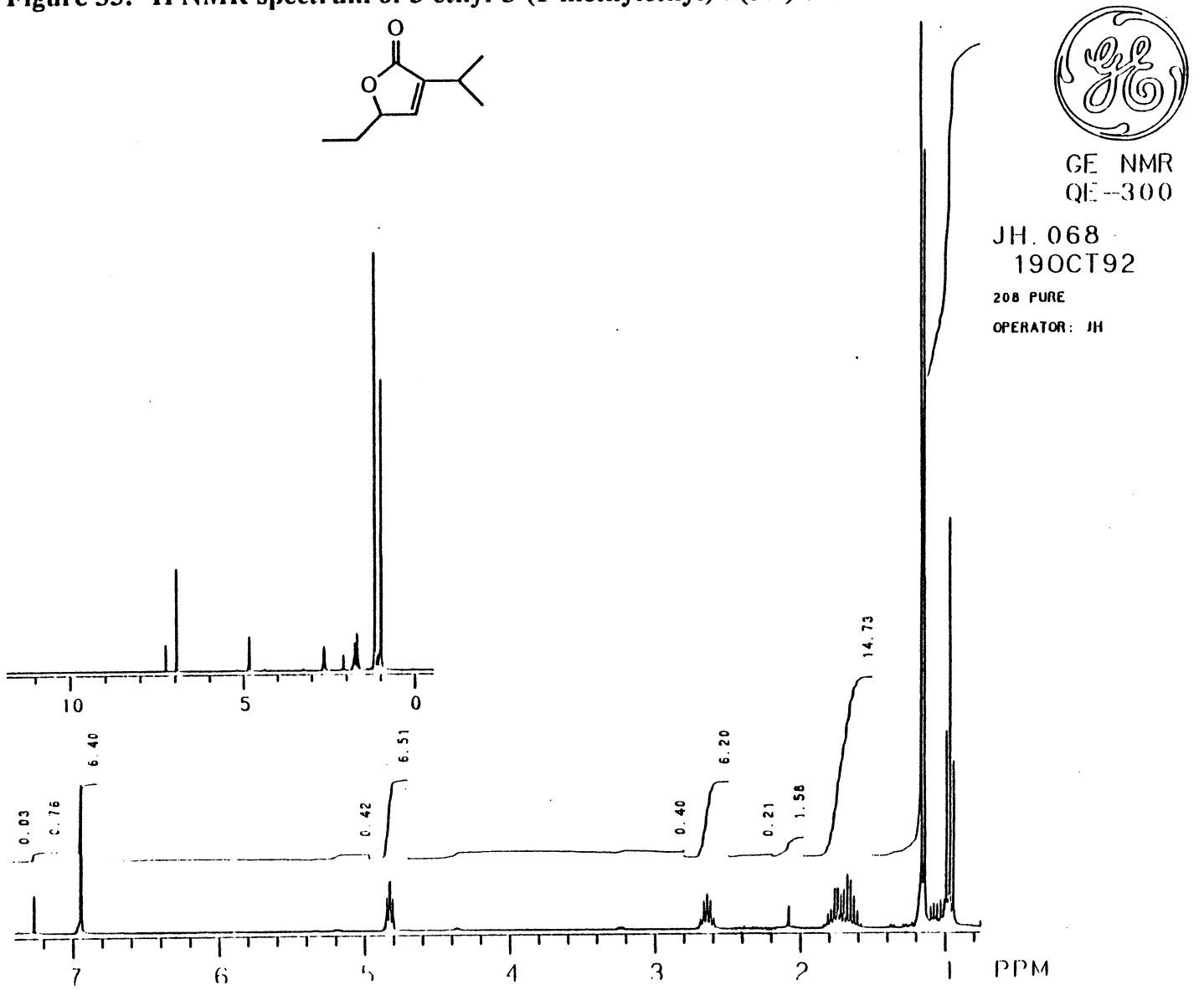


Figure 36: ^{13}C NMR spectrum of 5-ethyl-3-(1methylethyl)-2(5H)furanone 61e

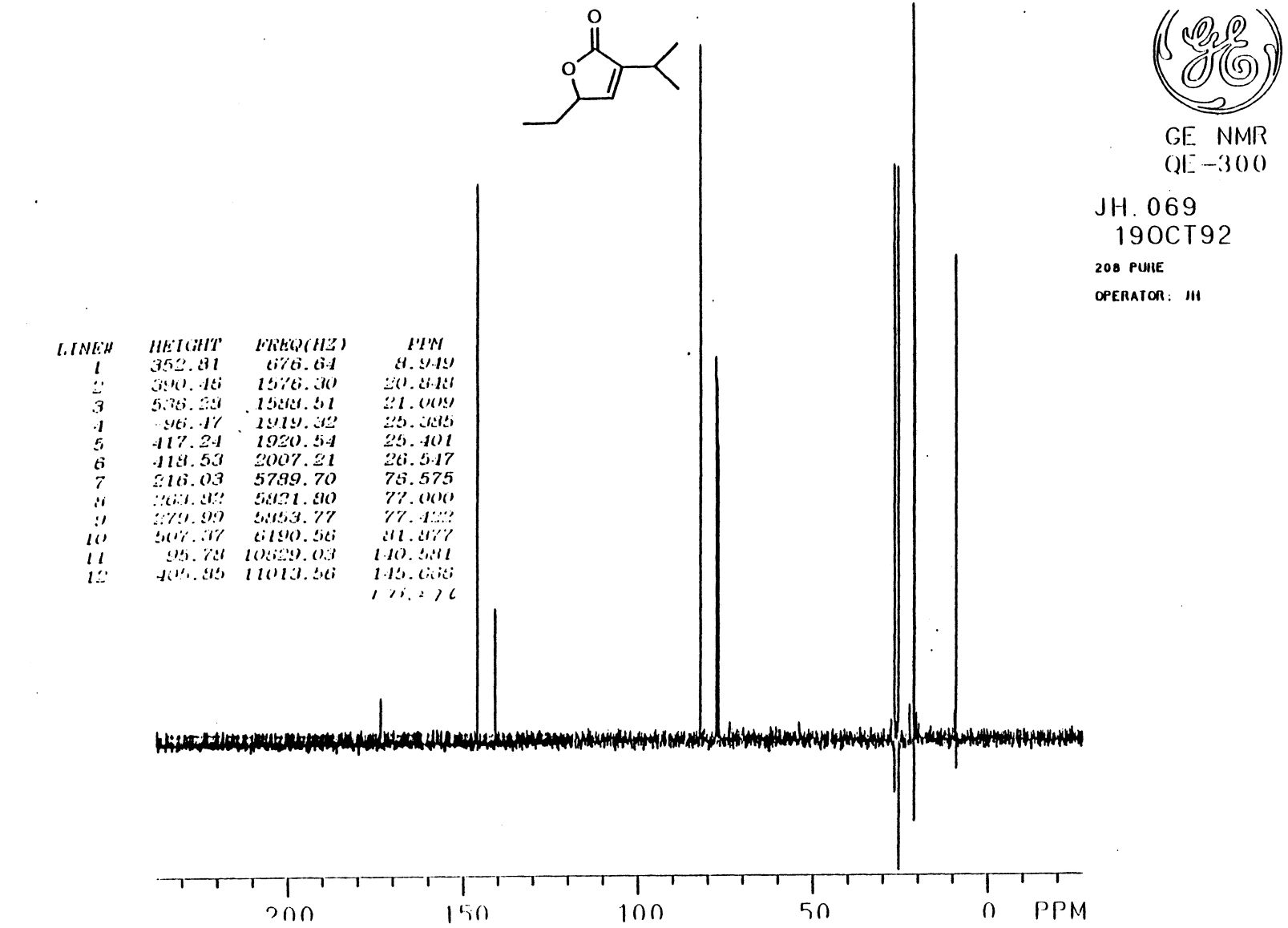
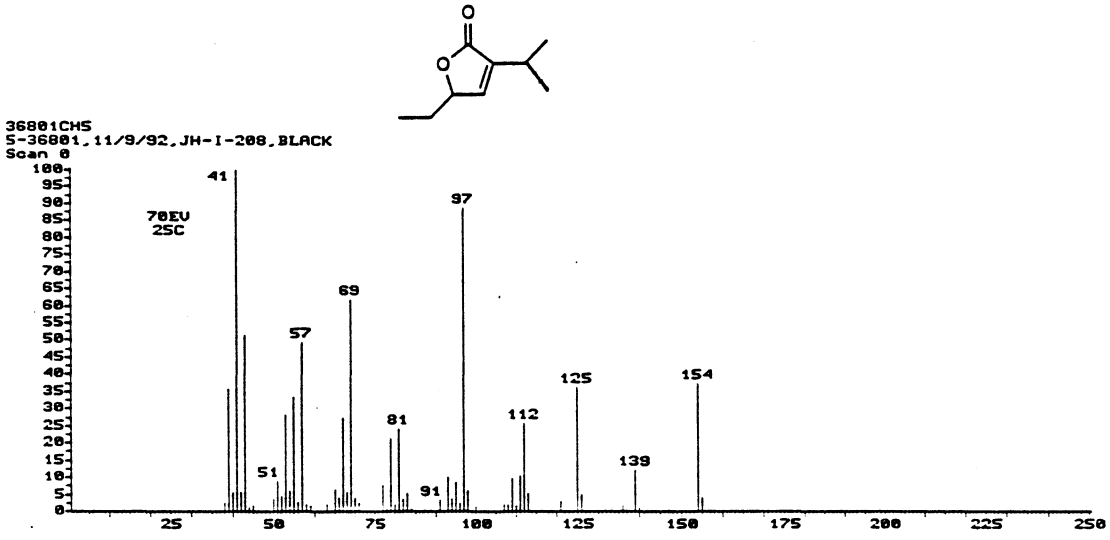


Figure 37: Mass spectrum of 5-ethyl-3-(1-methylethyl)-2(5H)furanone 61e



36801CH5
Scan 0
5-36801,11/9/92,JH-I-208,BLACK
57 peaks listed

MASS	RI	MASS	RI	MASS	RI	MASS	RI	MASS	RI	MASS	RI
38	2.71	52	4.80	66	4.29	81	24.44	98	6.35	125	36.43
39	35.83	53	28.42	67	27.50	82	3.64	100	1.22	126	5.10
40	6.01	54	6.34	68	5.83	83	5.36	107	2.09	136	1.65
41	100.00	55	33.52	69	61.85	84	1.20	108	2.14	139	12.41
42	5.86	56	3.16	70	4.04	91	3.37	109	9.69	140	1.30
43	51.45	57	49.66	71	2.59	93	10.20	110	1.99	154	37.35
44	1.52	58	2.02	77	7.64	94	3.66	111	10.49	155	4.36
45	1.72	59	1.97	78	1.42	95	8.80	112	25.97		
50	3.72	63	2.24	79	21.56	96	2.50	113	5.22		
51	9.17	65	6.63	80	2.34	97	89.12	121	3.04		

Elemental Composition **Date : 11-NOV-1992**

Heteroatom Max: 60 Ion: Both Even and Odd
Limits:

		-0.5	0	0	0	
154.099359	10.0	50.0	50	100	6	

Mass	mDa	PPM	Calc. Mass	DBE	C	H	O
154.099359	0.0	0.1	154.099380	3.0	9	14	2

Figure 38: IR spectrum of trimethylsilylketene 64

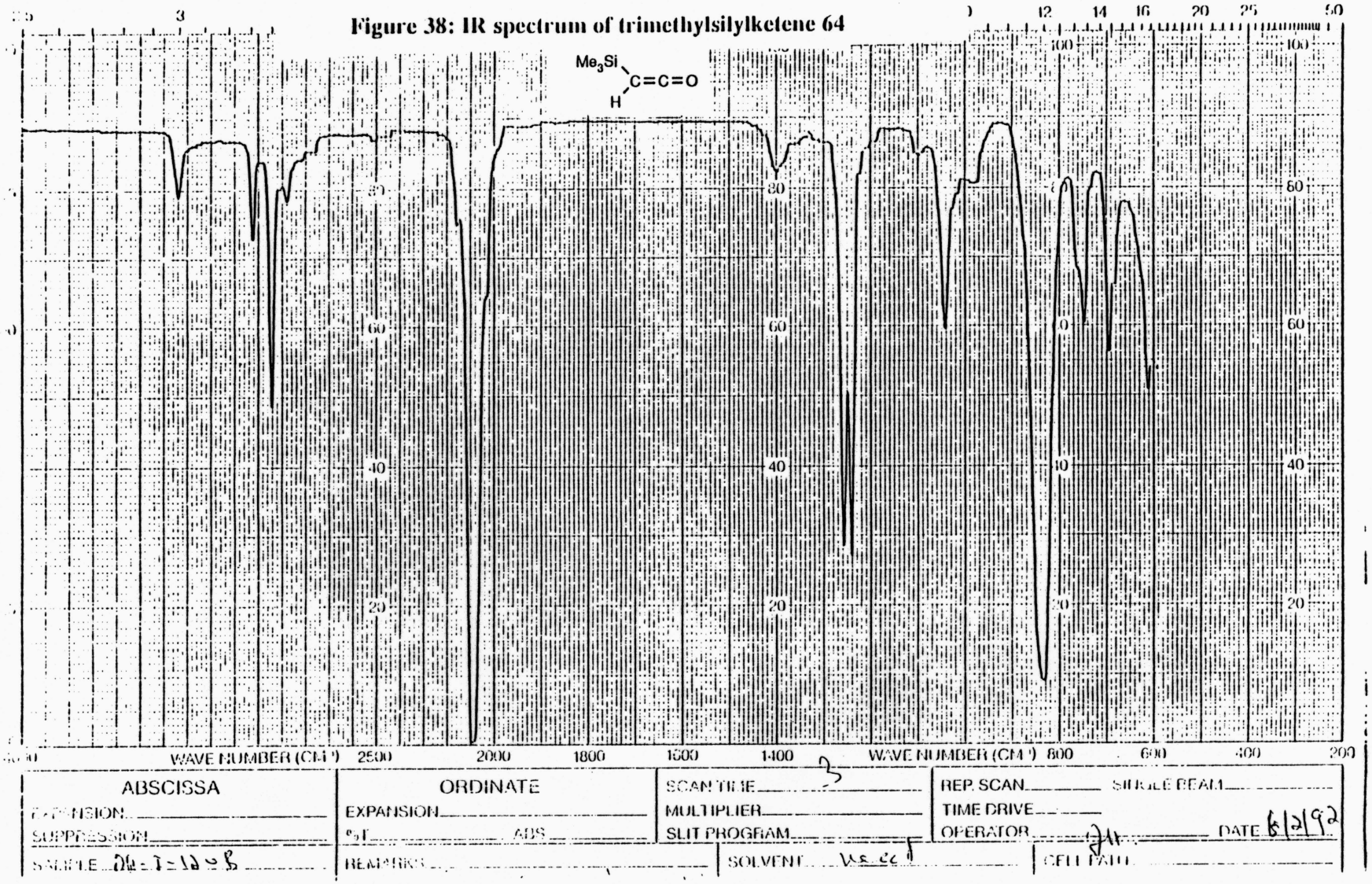


Figure 39: ^{1}H NMR spectrum of trimethylsilylketene 64

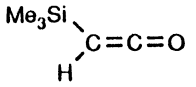


Figure 40: ^{13}C NMR spectrum of trimethylsilylketene 64

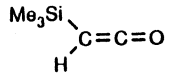


Figure 41: IR spectrum of 2-bromohexanal 73

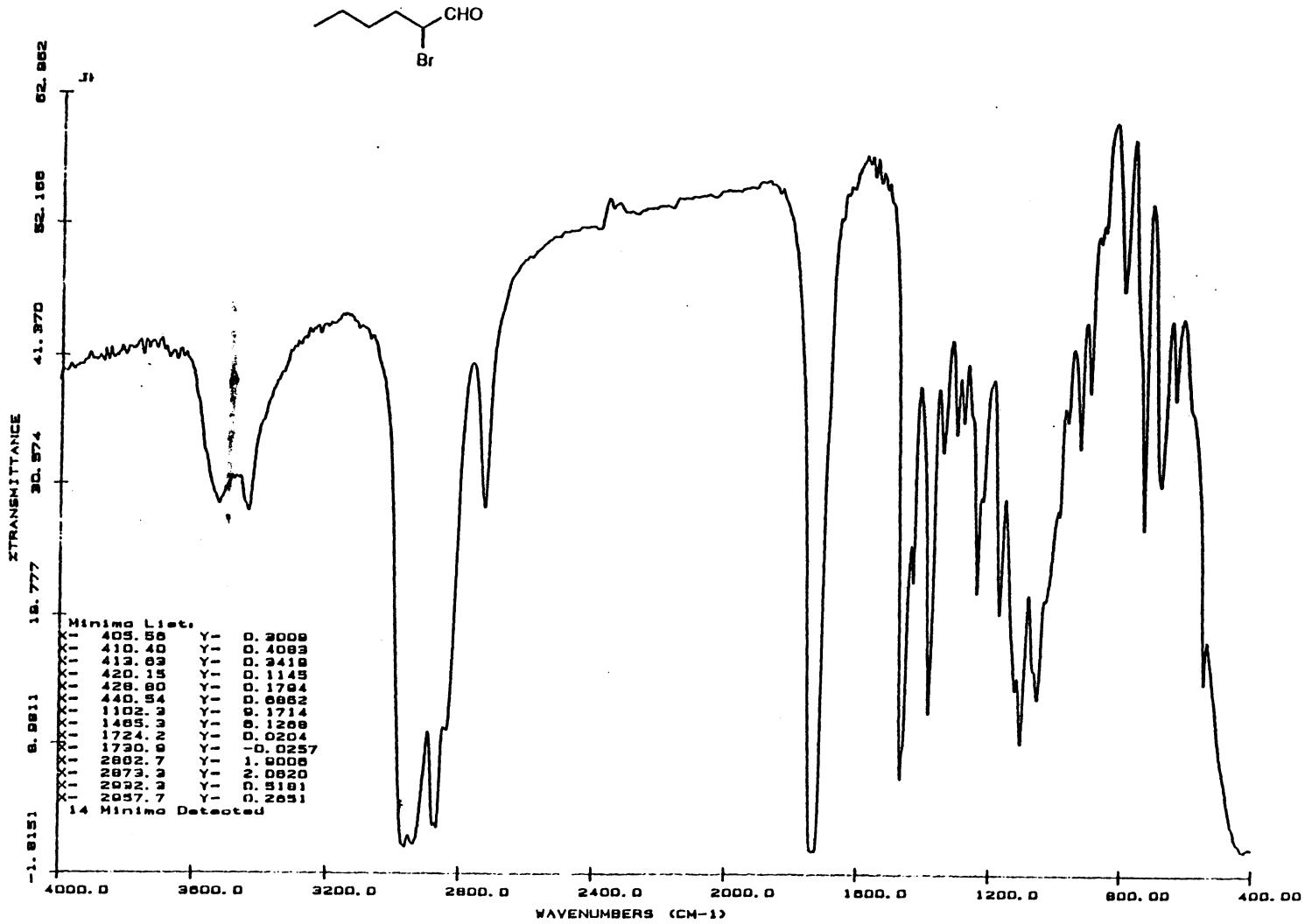


Figure 42: ^{1}H NMR spectrum of 2-bromohexanal 73

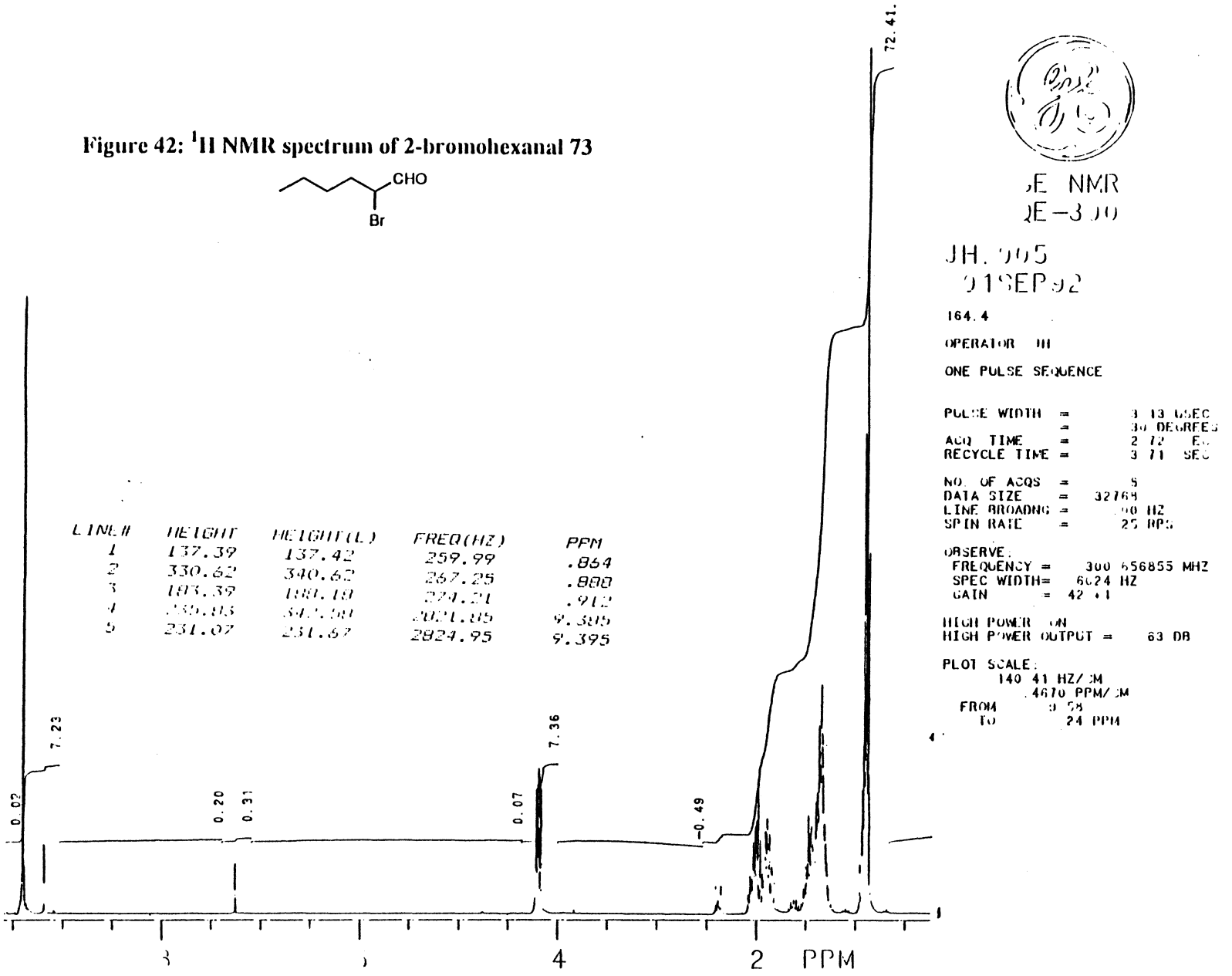
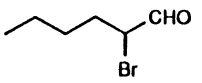


Figure 43: ^{13}C NMR spectrum of 2-bromohexanal 73



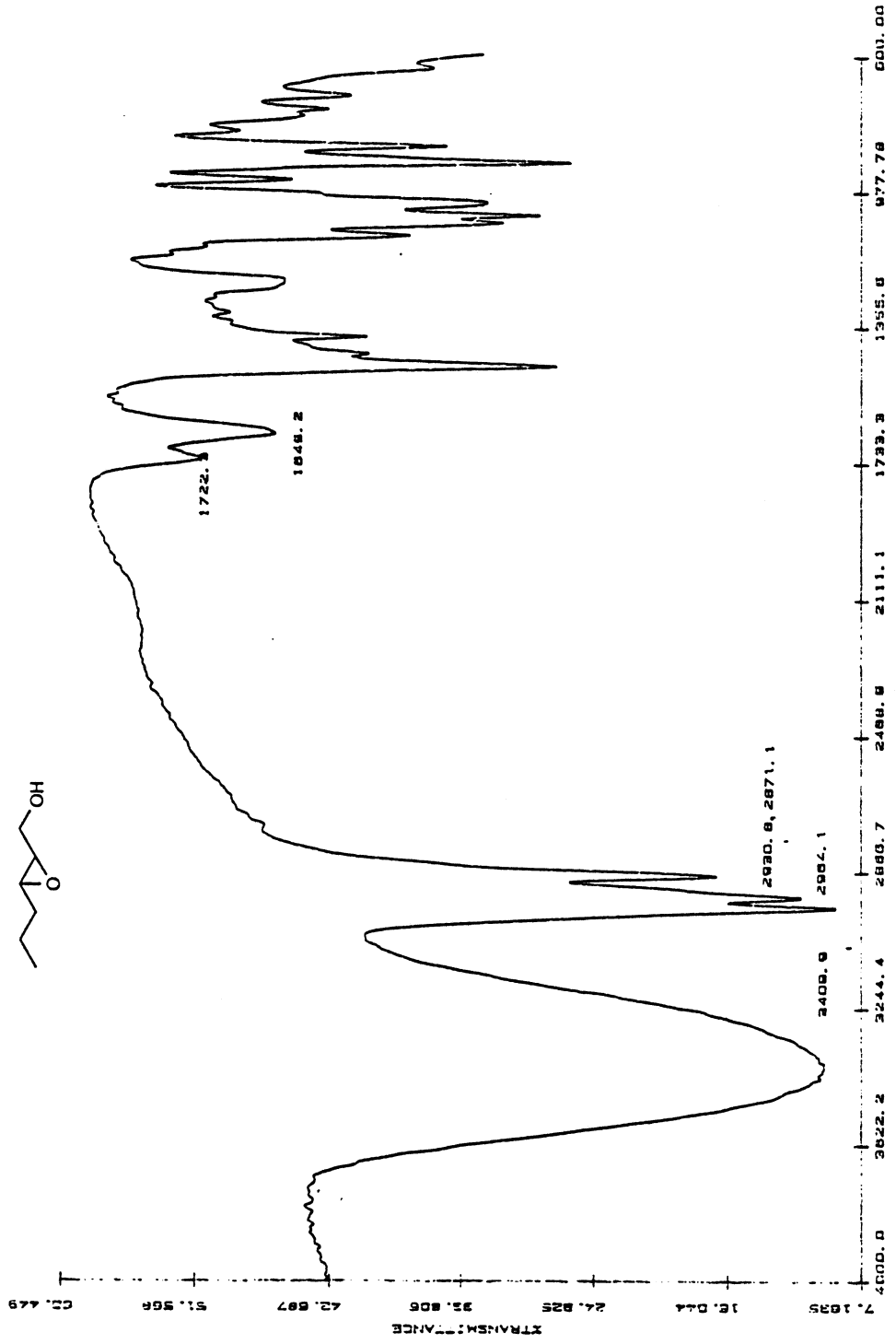


Figure 44: IR spectrum of 2,3-epoxyhexan-1-ol 78

Figure 45: ^{1}H NMR spectrum of 2,3-epoxyhexan-1-ol 78

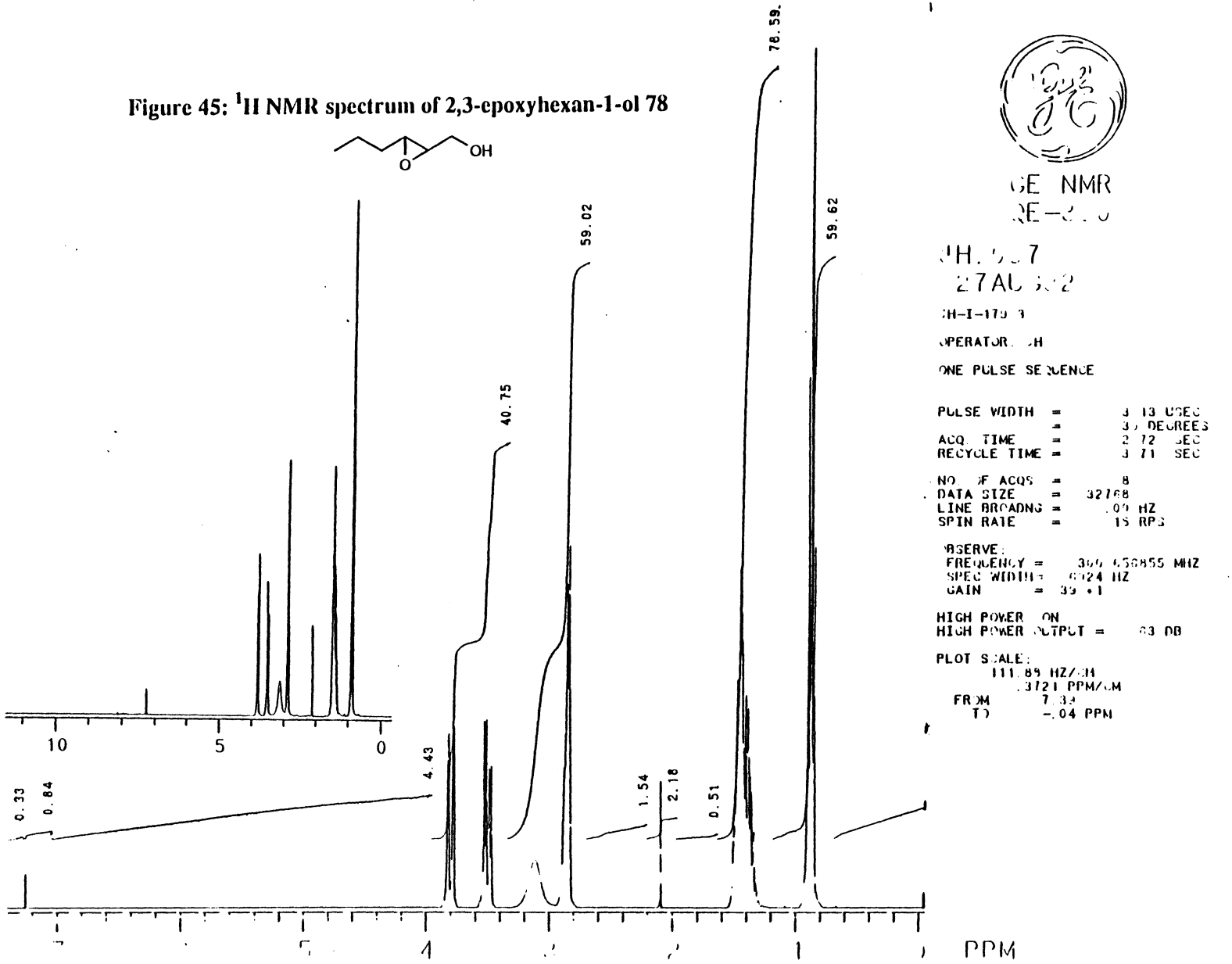
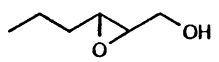


Figure 46: ^{13}C NMR spectrum of 2,3-epoxyhexan-1-ol 78



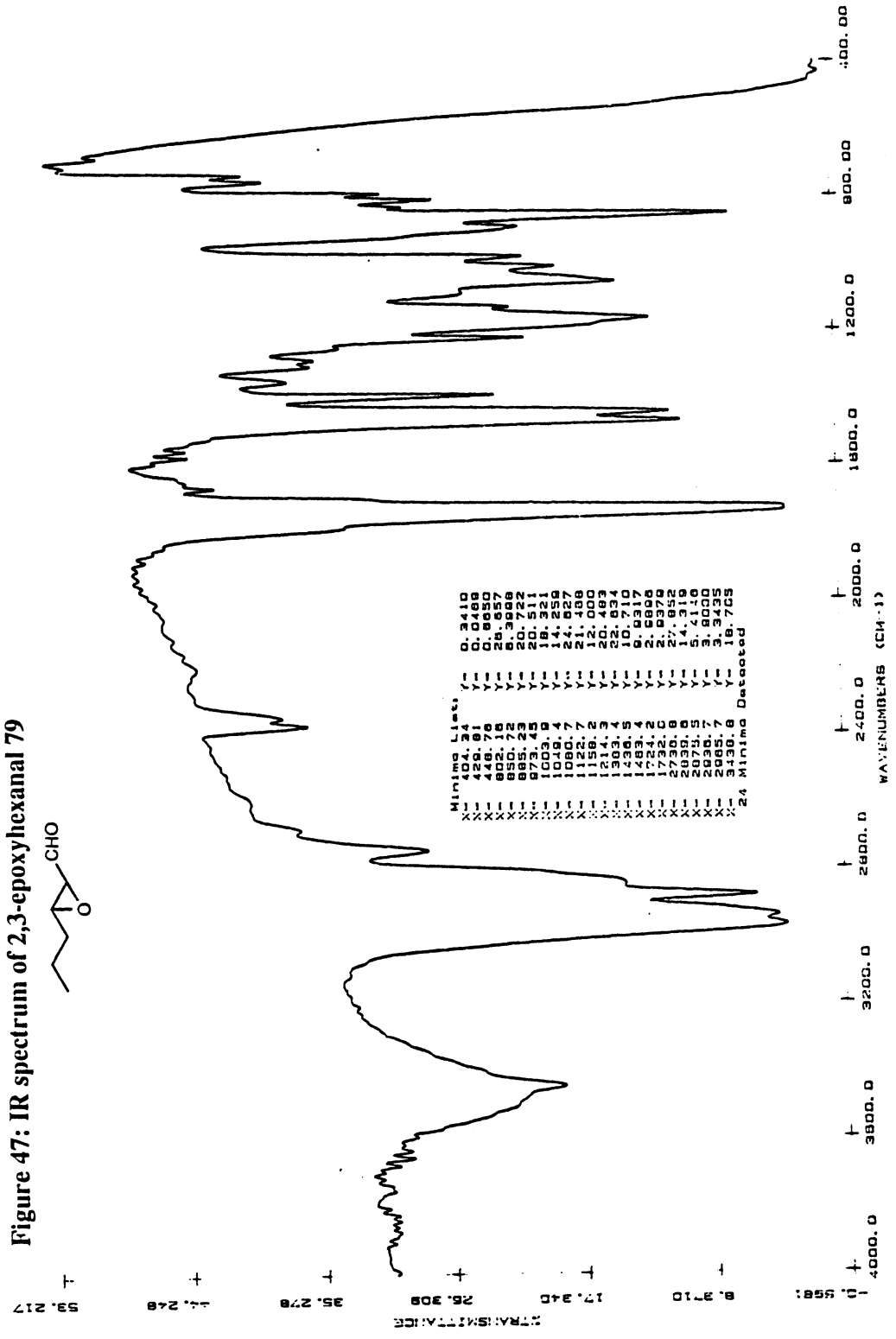


Figure 47: IR spectrum of 2,3-epoxyhexanal 79

Figure 48: ^{1}H NMR spectrum of 2,3-epoxyhexanal 79

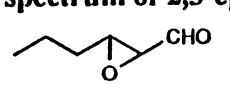
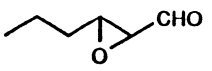
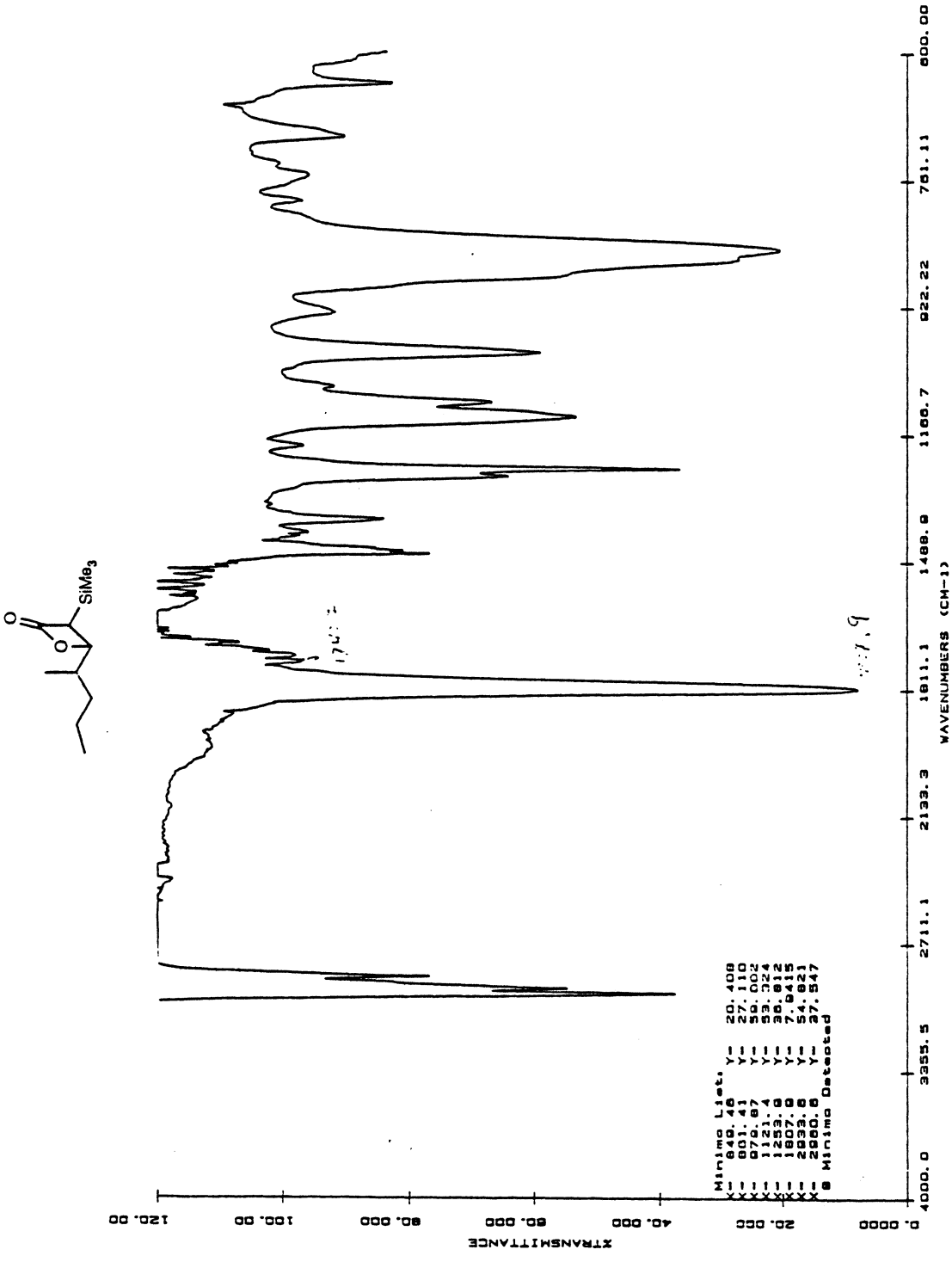


Figure 49: ^{13}C NMR spectrum of 2,3-epoxyhexanal 79



LINE#	HEIGHT	HEIGHT(L)	FREQ(HZ)	PPM
1	104.79	141.09	1032.82	13.660
2	219.79	------	1442.58	19.079
3	-67.61	------	2499.71	33.061
4	512.33	------	2500.93	33.077
5	44.57	53.99	2523.12	33.371
6	45.15	52.88	4265.08	56.410
7	139.25	145.19	4273.27	56.519
8	93.63	------	4461.38	59.006
9	49.30	------	4839.80	64.011
10	102.61	124.04	5789.85	76.577
11	81.61	129.66	5821.80	77.000
12	90.85	93.88	5853.99	77.425
13	192.89	------	15004.59	198.452

Figure 50: IR spectrum of 4-(1-methylethyl)-3-trimethylsilyloxetan-2-one 68b



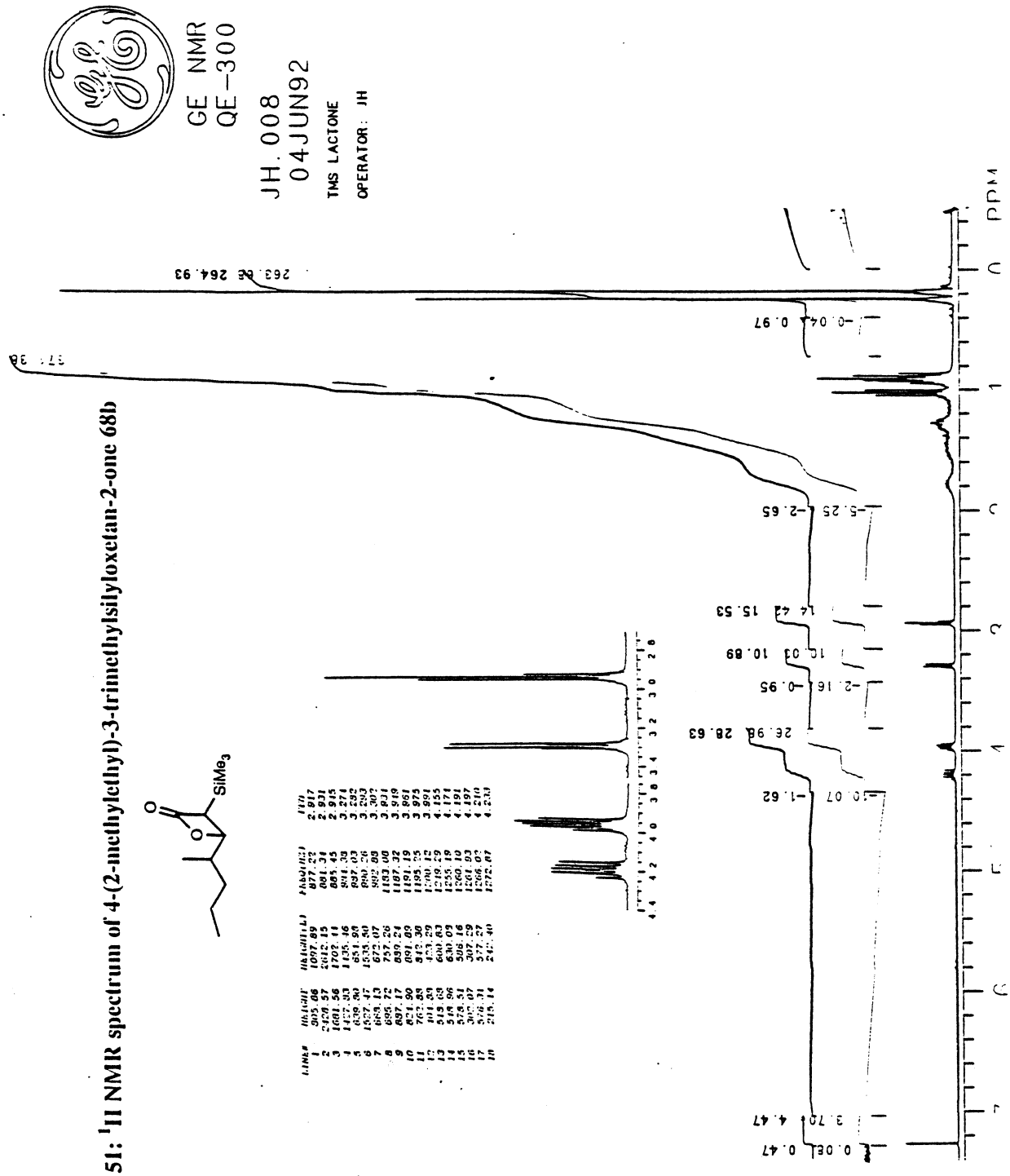


Figure 51: ^{1}H NMR spectrum of 4-(2-methylethyl)-3-trimethylsilyloxetan-2-one 68b

Figure 52: ^{13}C NMR spectrum of 4-(1-methylethyl)-3-trimethylsilyloxetan-2-one 68b

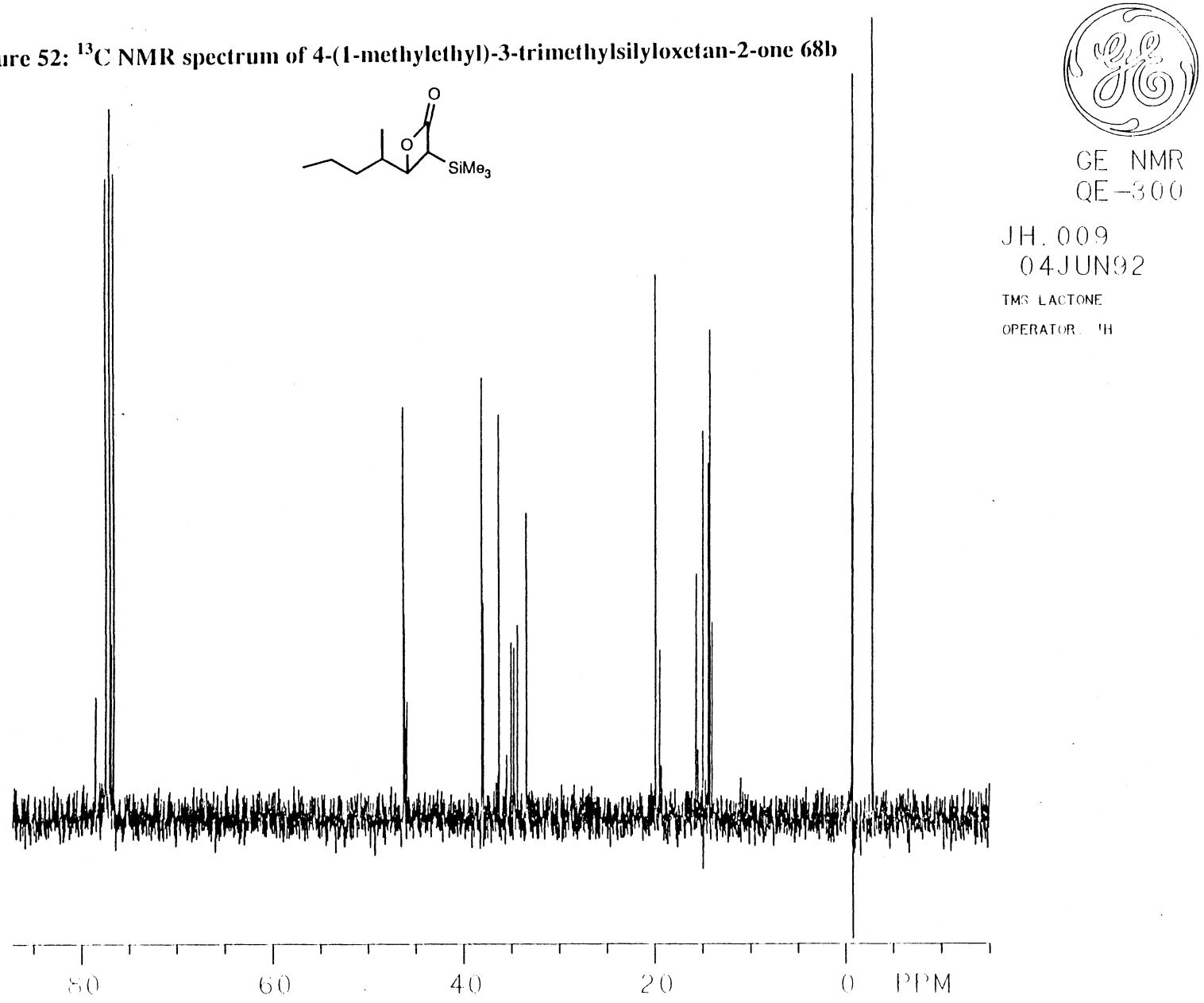


Figure 53: IR spectrum of 4-pentyl-3-trimethylsilyloxetan-2-one 68c

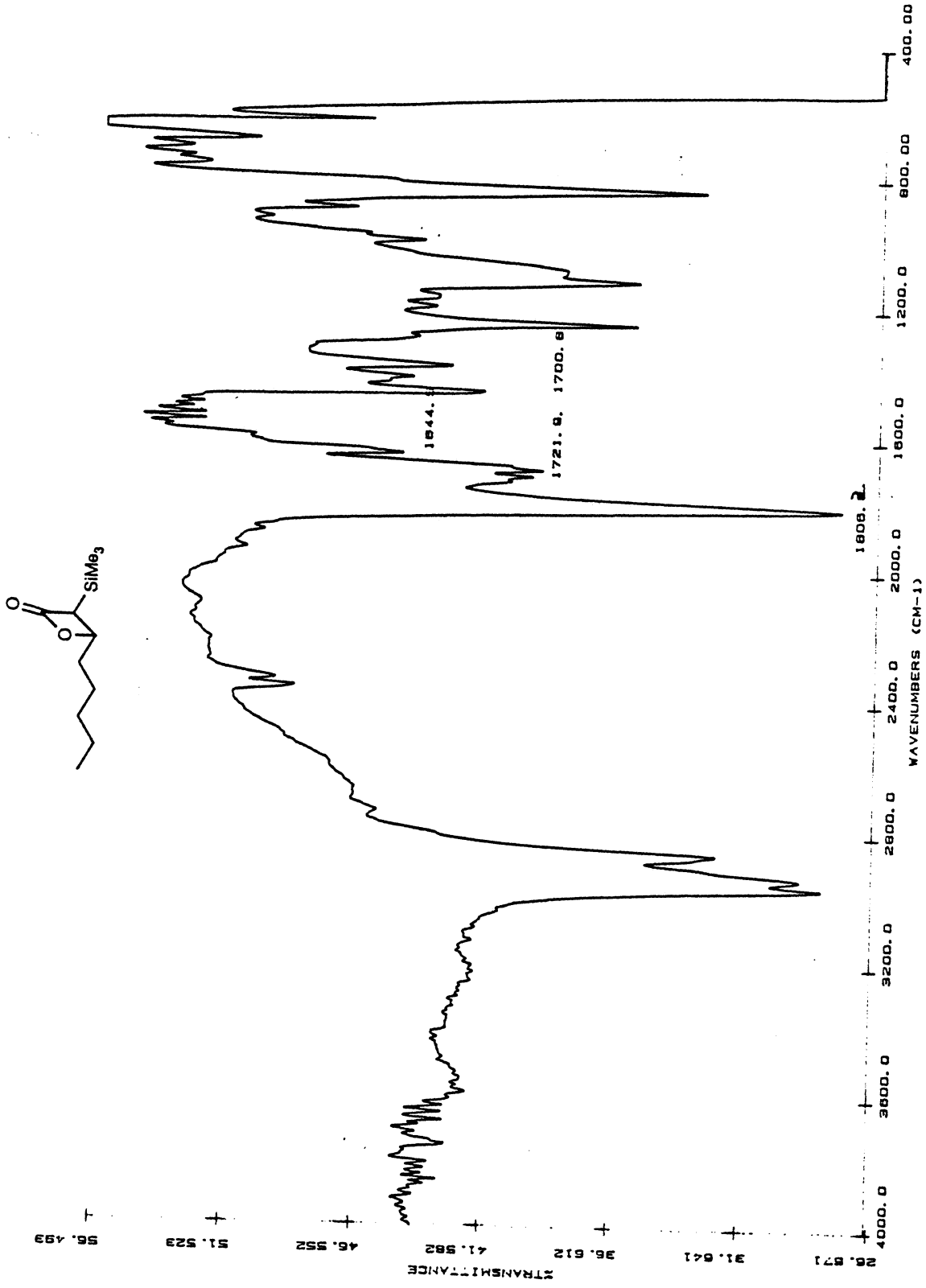
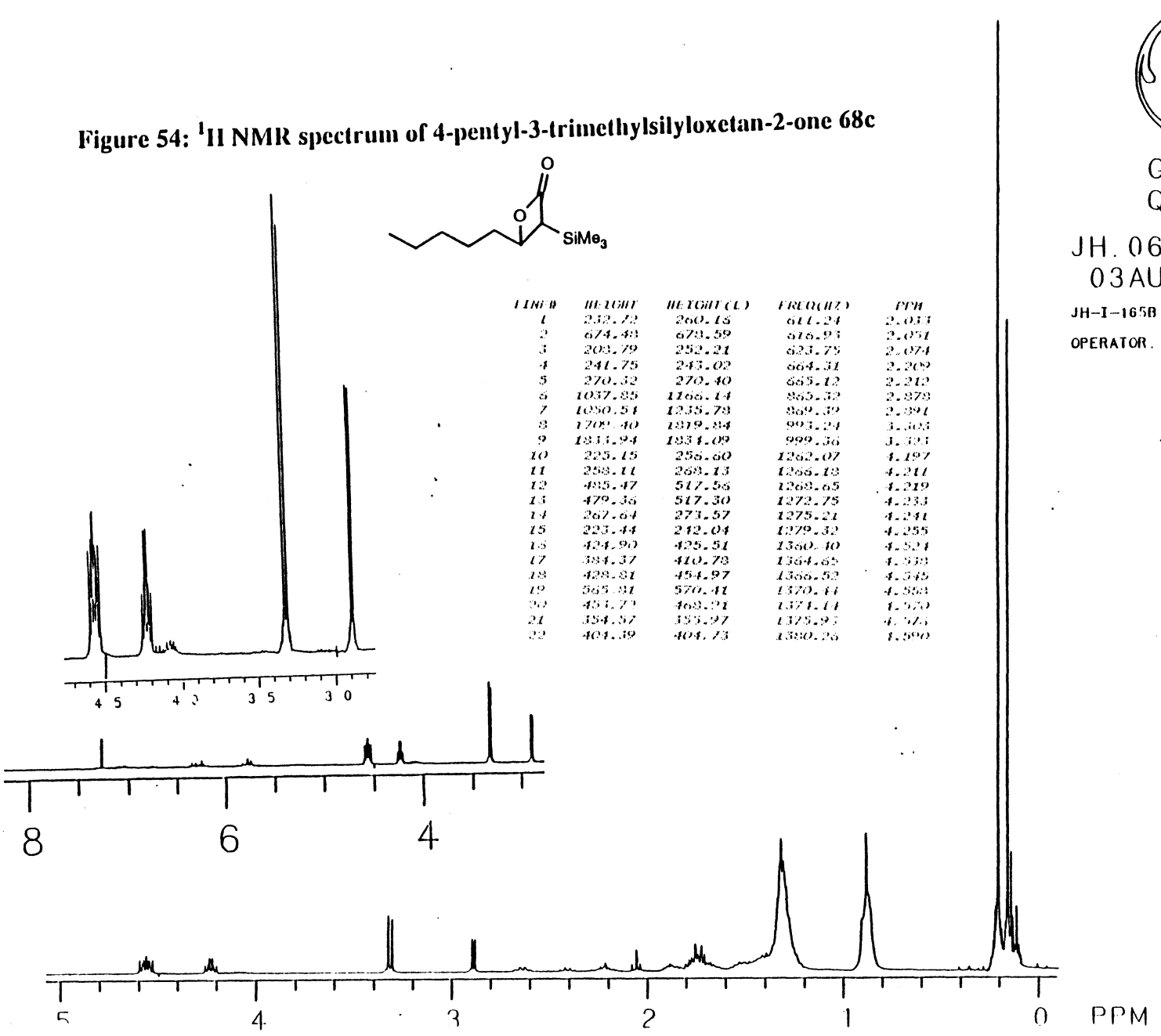
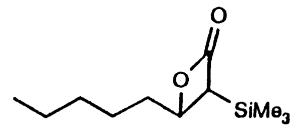


Figure 54: ^{1}H NMR spectrum of 4-pentyl-3-trimethylsilyloxetan-2-one 68c



LINE #	HEIGHT	HEIGHT(L)	FREQ(HZ)	PPM
1	252.72	260.15	611.24	2.033
2	674.48	679.59	616.95	2.051
3	203.79	252.21	623.75	2.074
4	241.75	243.02	664.31	2.209
5	270.32	270.40	665.12	2.212
6	1037.85	1166.14	865.32	2.878
7	1050.54	1235.78	869.39	2.891
8	1708.40	1819.84	903.24	3.003
9	1833.94	1834.09	999.36	3.323
10	225.15	256.60	1262.07	4.197
11	258.11	268.13	1266.18	4.211
12	485.47	517.56	1268.65	4.219
13	479.36	517.30	1272.75	4.233
14	267.64	273.57	1275.21	4.241
15	225.44	242.04	1279.32	4.255
16	424.90	425.51	1360.10	4.524
17	384.37	410.78	1364.65	4.538
18	428.81	454.97	1366.52	4.545
19	565.81	570.41	1370.44	4.558
20	451.71	468.91	1371.11	4.560
21	354.57	355.97	1375.93	4.576
22	404.39	404.73	1380.26	4.590

Figure 55: ^{13}C NMR spectrum of 4-pentyl-3-trimethylsilyloxetan-2-one 68c



LINE #	HEIGHT	HEIGHT (CL)	FREQ(HZ)	PPM
1	959.89	----------	-230.85	-3.053
2	256.51	----------	-107.56	-1.422
3	-258.13	----------	-86.81	-1.148
4	3275.79	----------	-85.59	-1.132
5	1051.95	1549.71	1047.50	13.854
6	[illegible]	701.87	1051.04	13.901
7	285.95	286.14	1689.34	22.343
8	1622.10	----------	1695.41	22.423
9	838.11	----------	1867.53	24.700
10	1122.71	----------	1957.86	25.894
11	681.81	728.78	2368.21	31.322
12	[illegible]	1251.27	2370.28	31.349
13	[illegible]	----------	2529.15	33.450
14	1096.91	----------	2692.72	35.614
15	1771.89	----------	3494.72	46.221
16	1127.71	----------	3646.09	48.223
17	[illegible]	521.48	5495.15	72.682
18	[illegible]	1117.87	5603.12	74.107
19	796.29	836.93	5789.85	76.577
20	690.79	875.19	5821.80	77.000
21	567.31	680.76	5853.81	77.423
22	221.88	----------	8989.11	118.891
23	291.66	302.95	11591.81	153.315
24	248.77	----------	12918.55	170.862

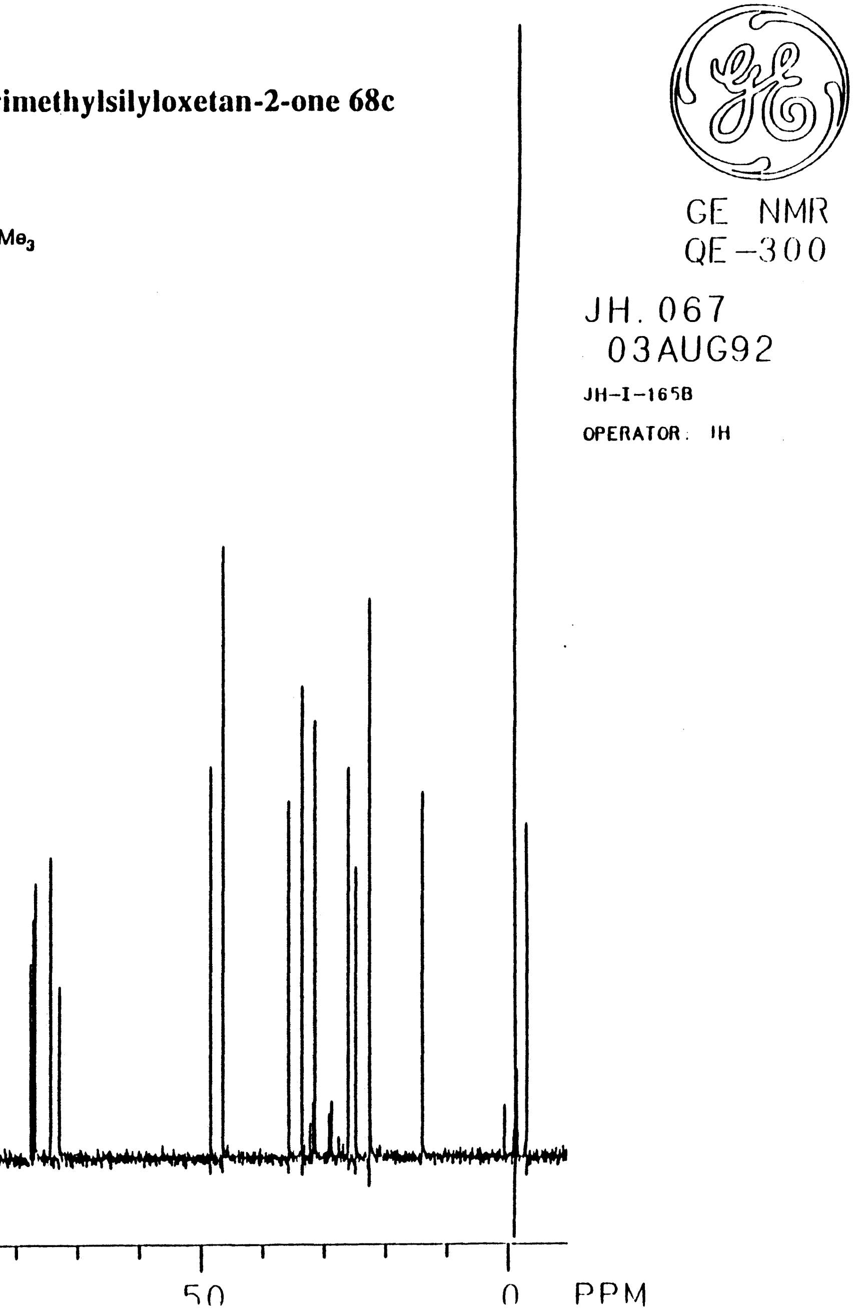


Figure 56: IR spectrum of 4-bromo-2-octenoic acid 72d

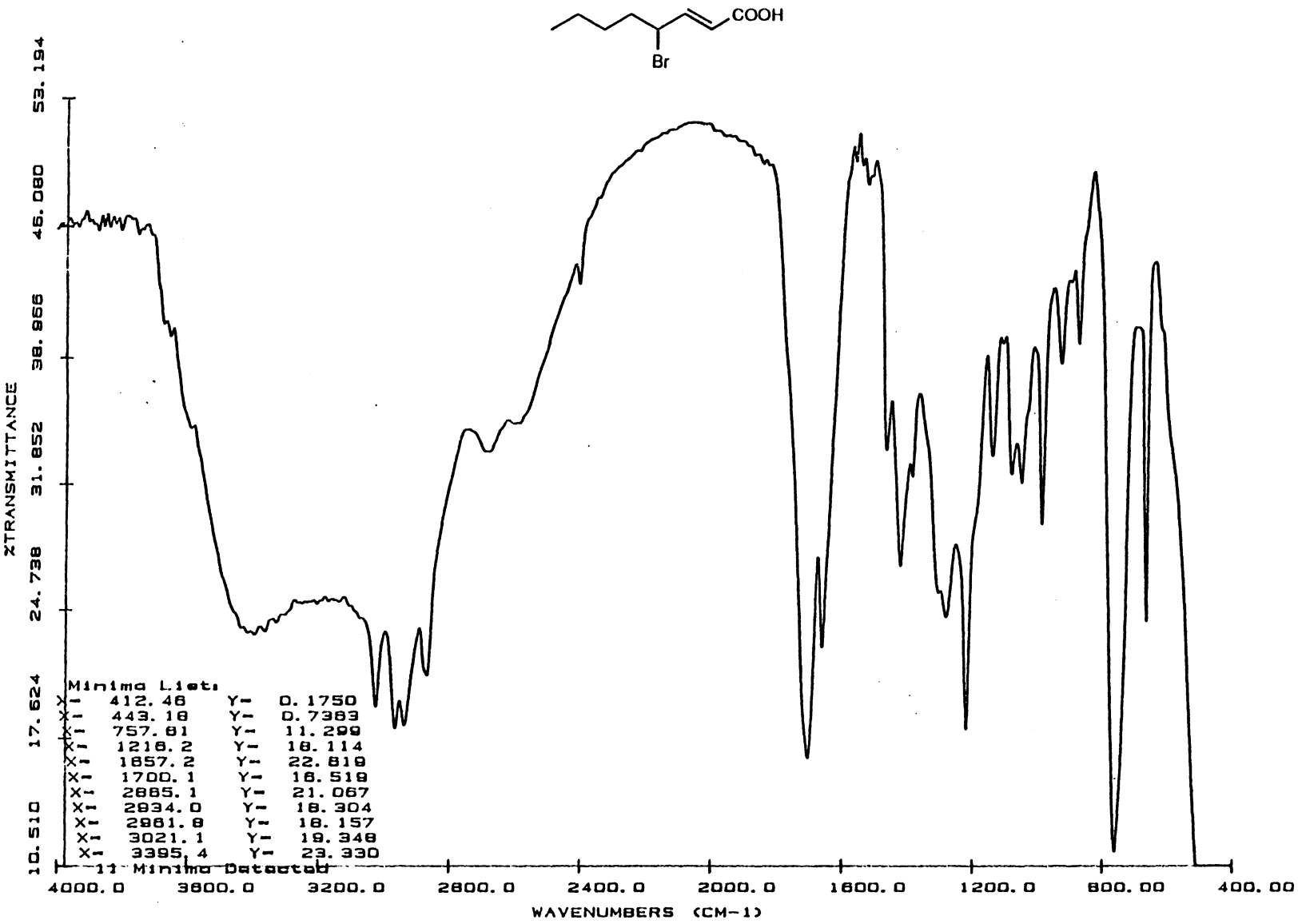


Figure 57: ^{1}H NMR spectrum of 4-bromo-2-octenoic acid 72d

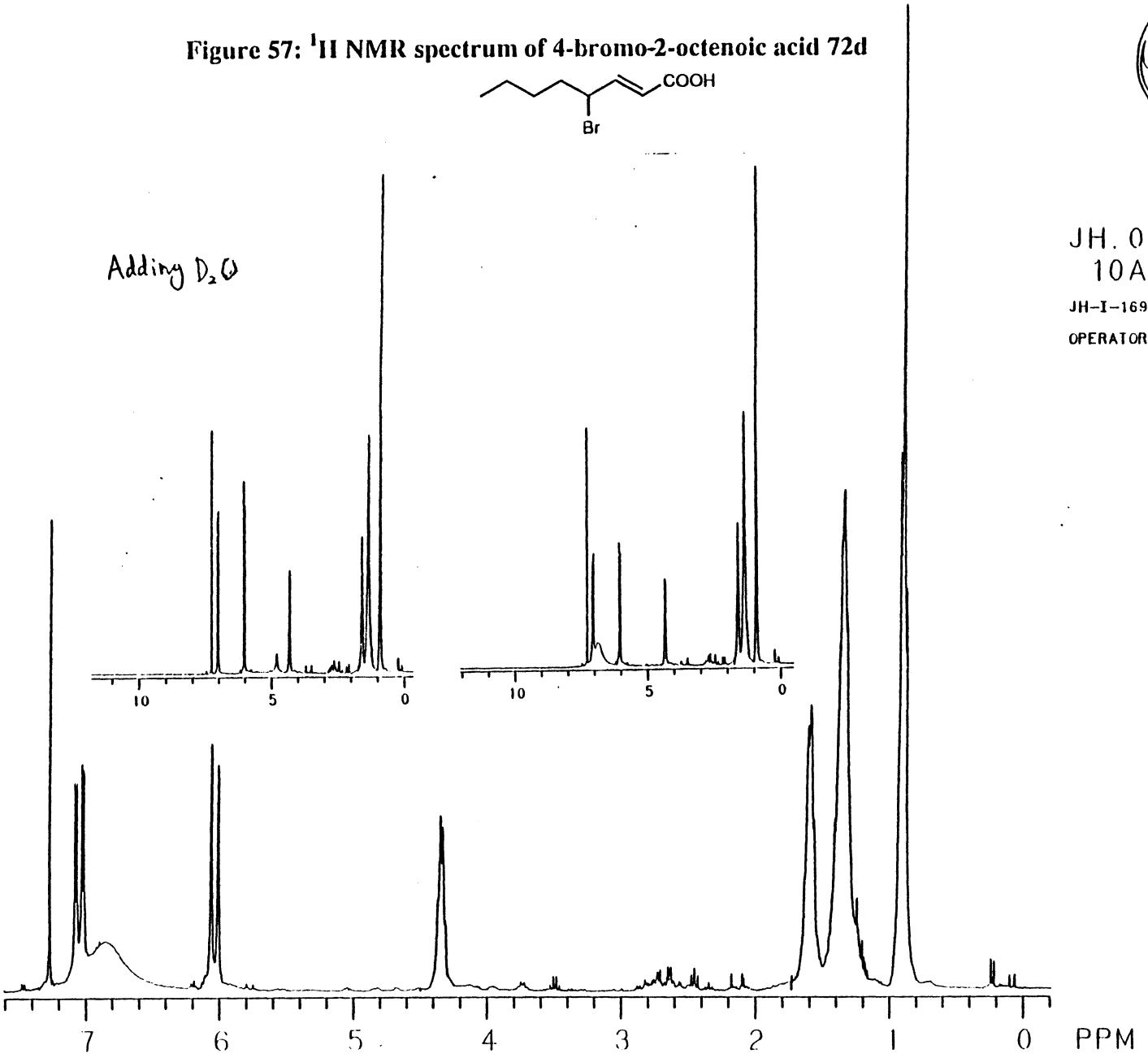
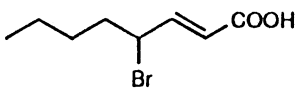


Figure 58: ^{13}C NMR spectrum of 4-bromo-2-octenoic acid 72d



LINE#	HEIGHT	HEIGHT(%)	FREQ(HZ)	PPM
1	1085.99	1203.19	1050.74	13.897
2	722.40	827.33	1699.26	22.474
3	1015.39	------	2060.38	27.250
4	706.63	706.64	2726.89	36.066
5	427.28	808.57	5373.97	71.076
6	509.61	571.44	5789.91	76.578
7	475.81	697.56	5821.80	77.000
8	380.40	------	5853.11	77.414
9	793.74	1479.85	9026.10	119.380
10	550.57	824.32	11545.70	152.705
11	509.65	------	12964.92	171.476

GE NMR
QE-300

JH.076
10AUG92

JH-I-169

OPERATOR. IH