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Carbonyl Homologation via α-Trimethylsilyl β-Lactone Rearrangement: A Nonbasic Wittig Alternative

Yong Zhang

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CARBONYL HOMOLOGATION VIA α-TRIMETHYLSILYL
β-LACTONE REARRANGEMENT: A NONBASIC WITTIG ALTERNATIVE

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8/10/94
Date — Dr. Norbert C. Furumo

Table of Contents

CARBONYL HOMOLOGATION VIA α-TRIMETHYLSILYL β-LACTONE REARRANGEMENT: A NONBASIC WITTIG ALTERNATIVE

(TITLE)

BY

Yong Zhang

THESIS

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Abstract

Our research group has been interested in β-lactones as useful synthetic intermediates. Transformations of β-lactones, generally ring expansion/opening processes initiated by Lewis acids via ionization/cation-rearrangement or elimination mechanisms, provide efficient protocols for the syntheses of biologically important butyrolactones, β,γ-unsaturated carboxylic acids, or butenolides.[1]

α-Trimethylsilyl β-lactones, synthesized via the BF_3-catalyzed [2+2] cycloaddition of trimethylsilylketene to carbonyl compounds, spontaneously undergo ionization and trimethylsilyl group migration to form α,β-unsaturated trimethylsilyl esters. The trimethylsilyl moiety facilitates the ionization process because of its β-cation stabilizing ability.[2] The two-carbon homologated α,β-unsaturated acids are formed in yields from moderate to high (41-99%) upon aqueous workup. This one-pot procedure, which occurs under mildly acidic conditions, provides an effective, nonbasic alternative to the Wittig reaction.

The only current drawback to this method is that α,β-unsaturated acids are formed as an approximately 1:1 mixture of E/Z isomers, which reflects the *cis-trans* ratio of the β-lactone intermediates. The low stereoselectivity, probably a consequence of the stereorandom nature of the trimethylsilylketene cycloaddition reaction, could possibly be

improved by employing more sterically demanding alkyl silyl ketenes or Lewis acids.[3]

1. a) Black, T.H.; Huang, J. *Tetrahedron Lett.* **1993,** *9,* 1411. b) Black, T.H.; McDermott, T.S.; Brown, G.A. *Tetrahedron Lett.* **1991,** *32,* 6501. c) Black, T.H.; Eisenbeis, S.A.; McDermott, T.S.; Maluleka, S.M. *Tetrahedron* **1990,** *46,* 2307. d) Black, T.H.; McDermott, T.S.; Eisenbeis, S.A. *Tetrahedron Lett.* **1990,** *31,* 6617. e) Black, T.H.; Dubay, W.J.; Tully, P.S. *J. Org. Chem.* **1988,** *53,* 5922. f) Black, T.H.; Fields, J.D. *Synth. Commun.* **1988,** *18,* 125. g) Black, T.H.; Hall, J.A.; Sheu, R.G. *J. Org. Chem.* **1988,** *53,* 2371.

2. Lambert, J.B. *Tetrahedron* **1990,** *46,* 2677.

3. Maruoka, K.; Concepcion, A.B.; Yamamoto, H. *Synlett.* **1992,** 31.

For my wife, Yuming,

and my parents, Guiying and Zhihong Zhang

With love

Acknowledgement

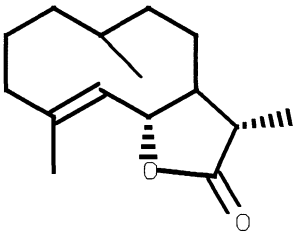
I would like to express my appreciation to my advisor, Dr. T. Howard Black, for his guidance, encouragement and financial support during this research. I also like to thank members in our research group for their assistance and contribution, especially Mr. Jianhua Huang for his early research efforts. I am grateful to the faculty of the Chemistry Department for their wide-ranging help. This work was supported by the National Science Foundation (CHE-9203760) and the Petroleum Research Fund.

List of Tables

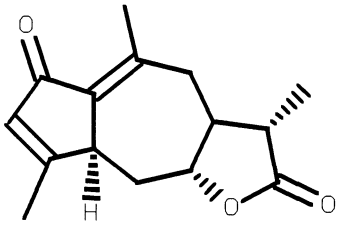
List of Spectra

Introduction

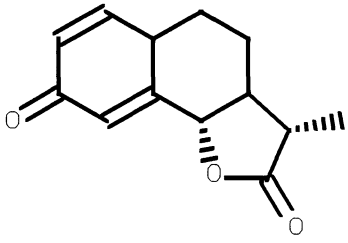
Over the years, the Black research group has successfully developed protocols for syntheses of γ-butyrolactones and α,β-butenolides (2(5*H*)-furanones) via transformations of β-lactones. γ-Butyrolactones and α,β-butenolides are both found widely in biologically-active sesquiterpenes, flavor components, insect sex pheromones, and other natural products;[4,5,6] for example, dihydrocostunolide **1**, achillin **2**, santonin **3**, β-angelica lactone **4**, osmunda lactone **5** and marmelolactone **6**. Chiral butenolides are also important synthetic intermediates, with particaular utility as templates ("chirons") for the construction of optically active complex



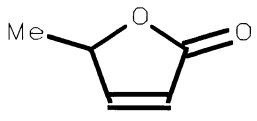
Dihydrocostunolide **1**



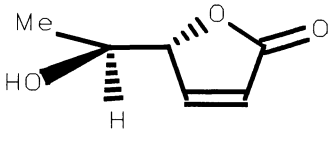
Achillin **2**



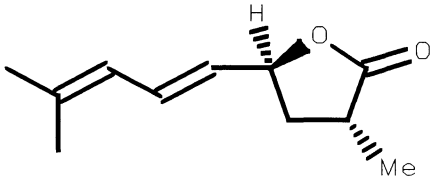
Santonin **3**



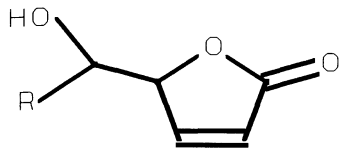
β-angelica lactone **4** (*R or S*)



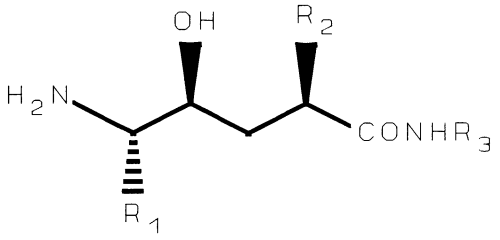
Osmunda lactone **5** (4*R*, 5*S*)



Marmelolactone **6** (2*R*, 4*S*)



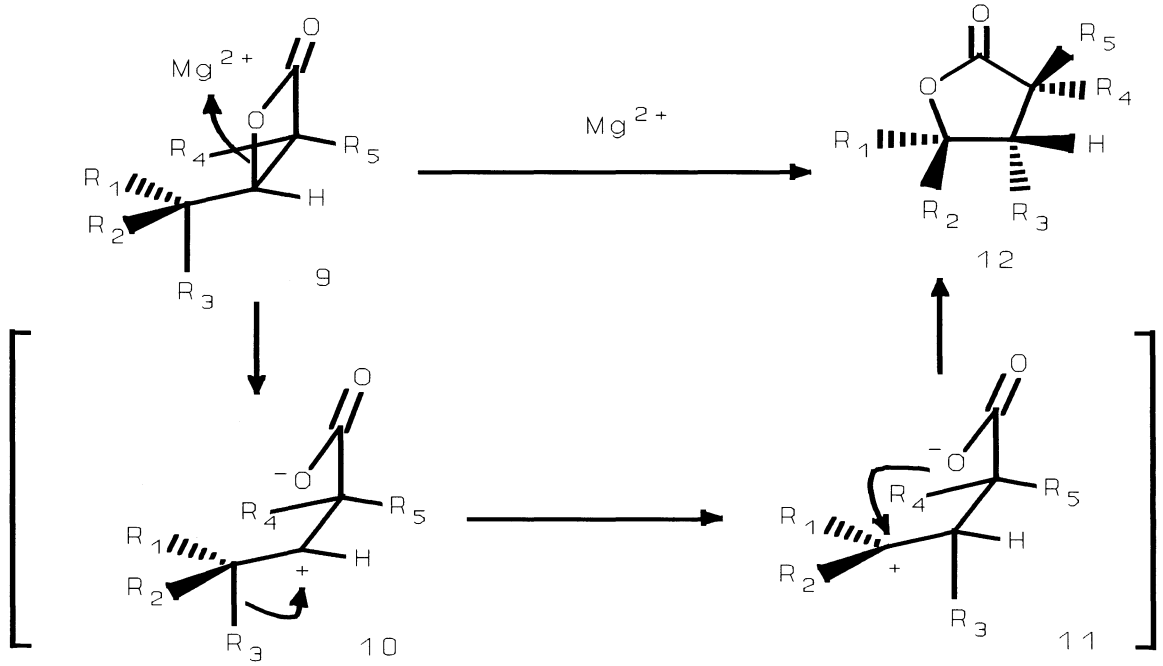
Chiron (*any diastereomer*) **7**



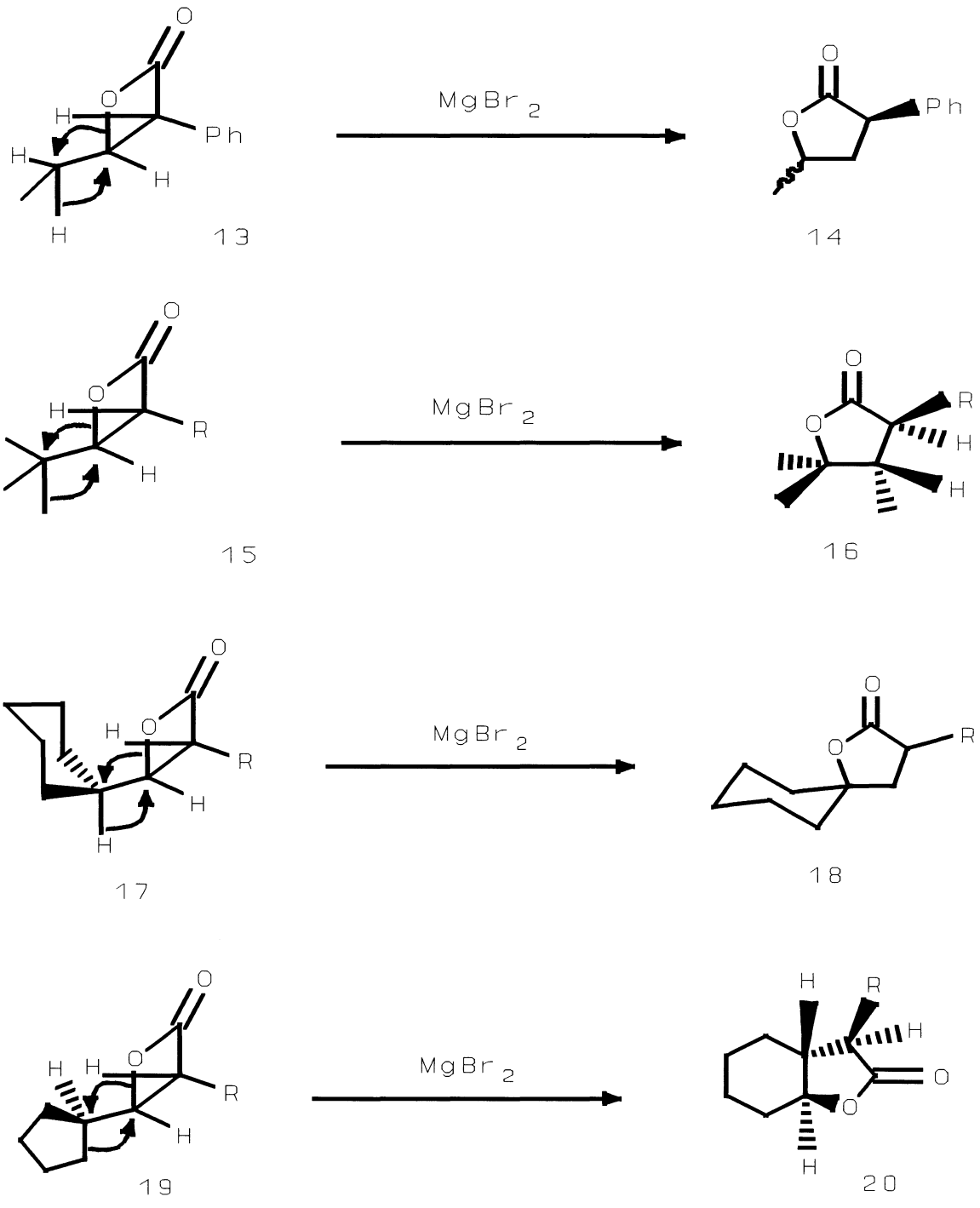
Hydroxyethylene dipeptide isosteres **8**

molecules. Homochiral derivatives of **7** have been employed for the syntheses of hydroxyethylene dipeptide isosteres **8**, which are potential drugs for the treatment of hypertensive and HIV-related disease.

Scheme I



Scheme II



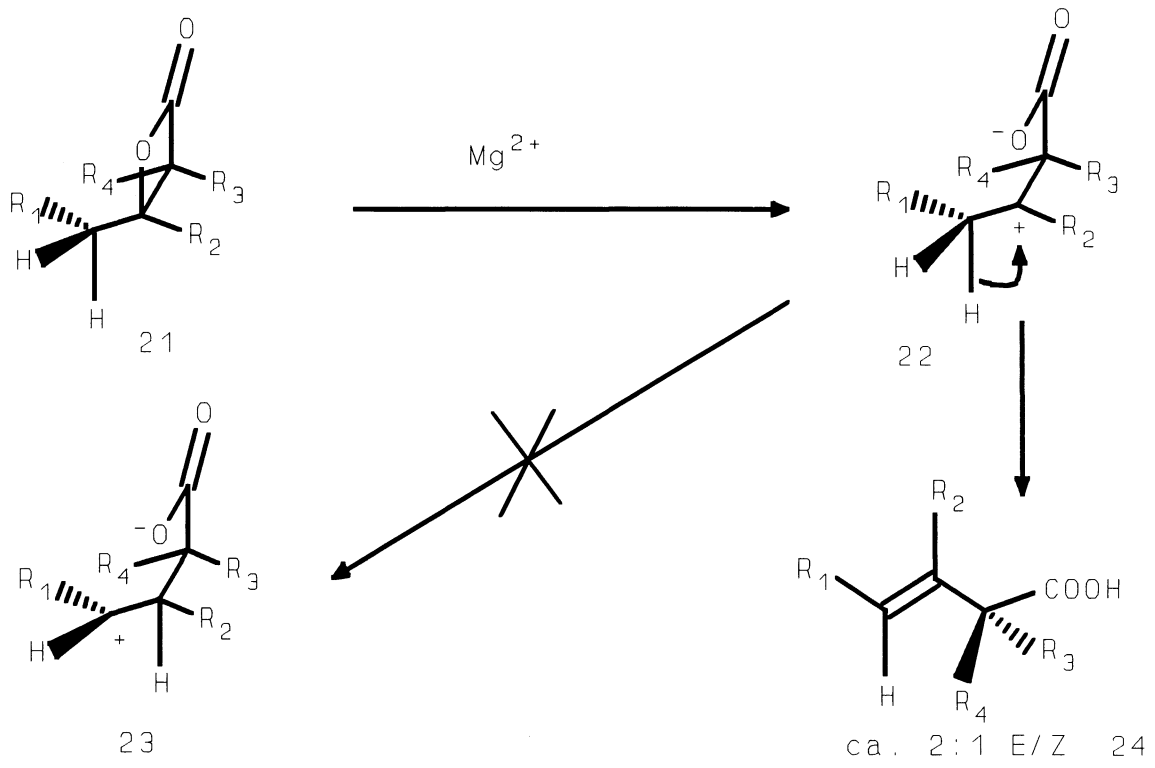
Most β-lactones' transformations developed in our lab possess similar mechanisms and features: cation ionization is

initiated by Lewis acids, cation-rearrangement pathways are based on thermodynamic considerations, relief of β-lactone ring strain is the driving force, and the migrating bonds usually align with each other in an anticoplanar manner.

The general mechanism for butyrolactone synthesis is summarized in **Scheme I** and some representative examples are listed in **Scheme II**.[1d,e,f,g] This procedure, featuring very high stereospecificity, has wide application for the synthesis of monocyclic, spiro, and trans-fused butyrolactones. It can elegantly fix several contiguous chiral centers in one step (*e.g.*, **19** → **20**).

Since potential cation migrations are based on the relative thermodynamic stability of the involved cations, some β-lactones undergo elimination processes following initial β-lactone ring ionization, instead of ring expansion, to form β,γ-unsaturated acids when unfavorable cation shift situations are encountered. For instance, as shown in **Scheme III**, a 3° to 2° cation shift would be necessary in order for a ring expansion, producing a butryolactone, to occur. Since this is an unfavorable process, the adjacent hydrogen is lost rather than undergoing migration; the overall sequence thus resembles an E1 elimination. No α,β-unsaturated acids were observed in the study, despite their greater thermodynamic stability. This most likely occurs for kinetic reasons[1c] since the γ-proton, which is aligned properly for overlap with the 3° cation empty **p** orbital (**Fig I**), is eliminated much more

Scheme III

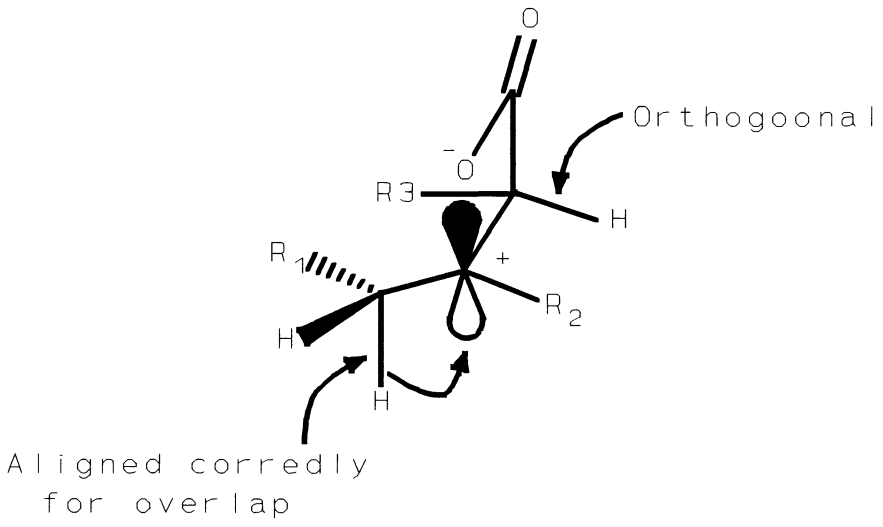


R_2=alkyl,cycloalkyl; R_3=H,alkyl

rapidly than the α-proton, which is orthogonally situated.

There are two primary methods developed in our lab for the synthesis of butenolides, as outlined in **Schemes IV** and **V**. The α-chloro β-lactones **25** are more resistant to ionization than non-halogenated analogs due to the electron withdrawal by the halogen. Nevertheless, these were converted to multisubstituted butenolides **26** in high yield under the conditions of using magnesium bromide, dichloromethane as a solvent, and relatively longer reaction time.[1b]

Fig I

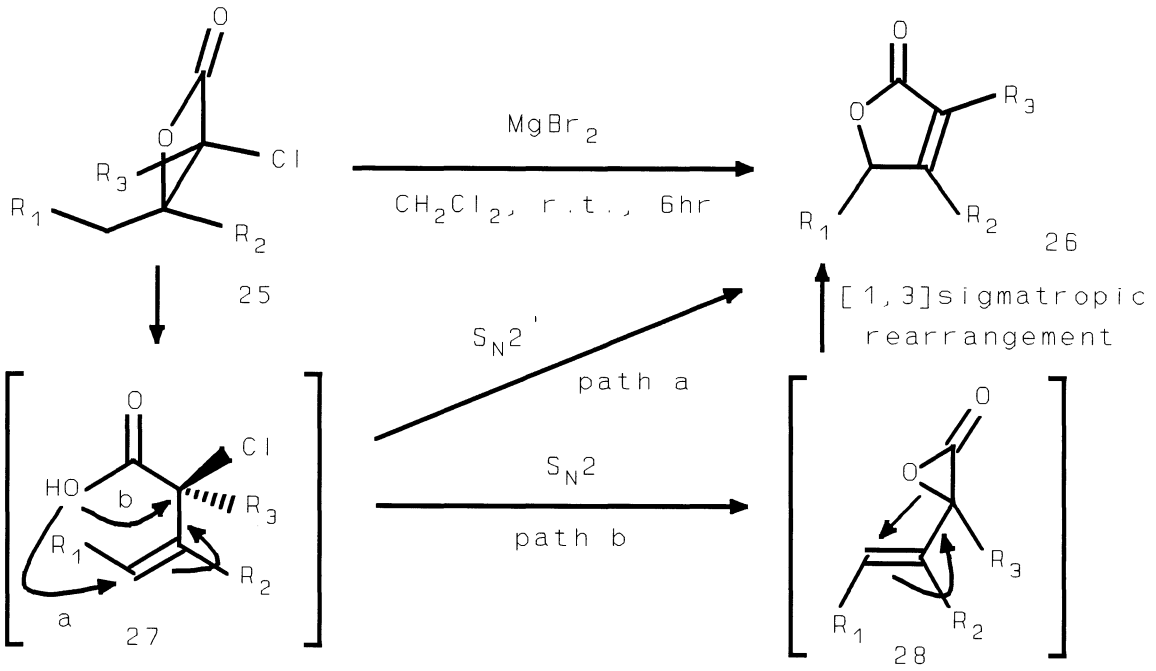


22

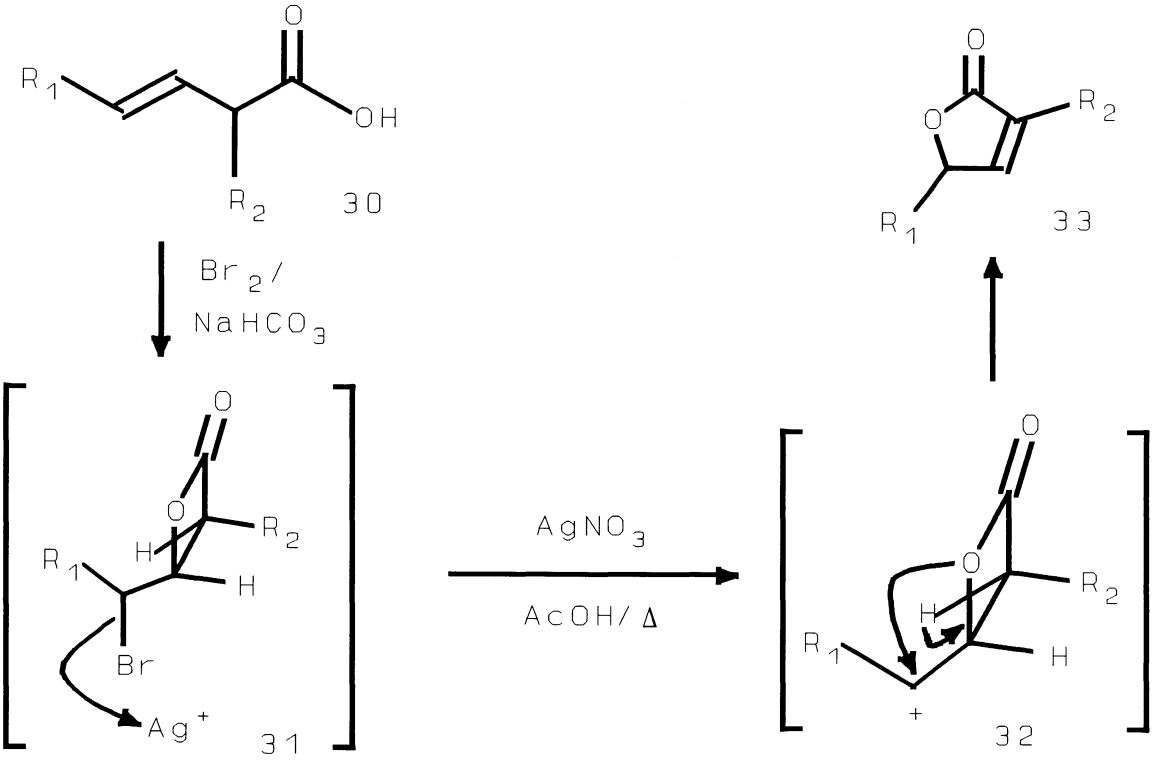
Mechanistically, the α-chloro-β,γ-unsaturated acids **27** are probably formed first according to the same mechanism discussed in **Scheme III**; these acids then rearrange to butenolides **26** via one of the two likely pathways (**Scheme IV**). Path A represents a S_N2' mechanism, which features carboxylate group attack on the β,γ-double bond, with expulsion of the allylic chloride. Path B is an intramolecular S_N2 reaction followed by a [1,3] sigmatropic rearrangement. The carboxylate group attacks on the chloride first to form a highly strained transient α-lactone, which then rearranges via a process similar to the well-known vinyl cyclopropanone-cyclopentenone rearrangement.

Bromoalkyl β-lactones **31** were treated with silver ion to form butenolides **33**.[1a] Conceptually distinct from other

Scheme IV



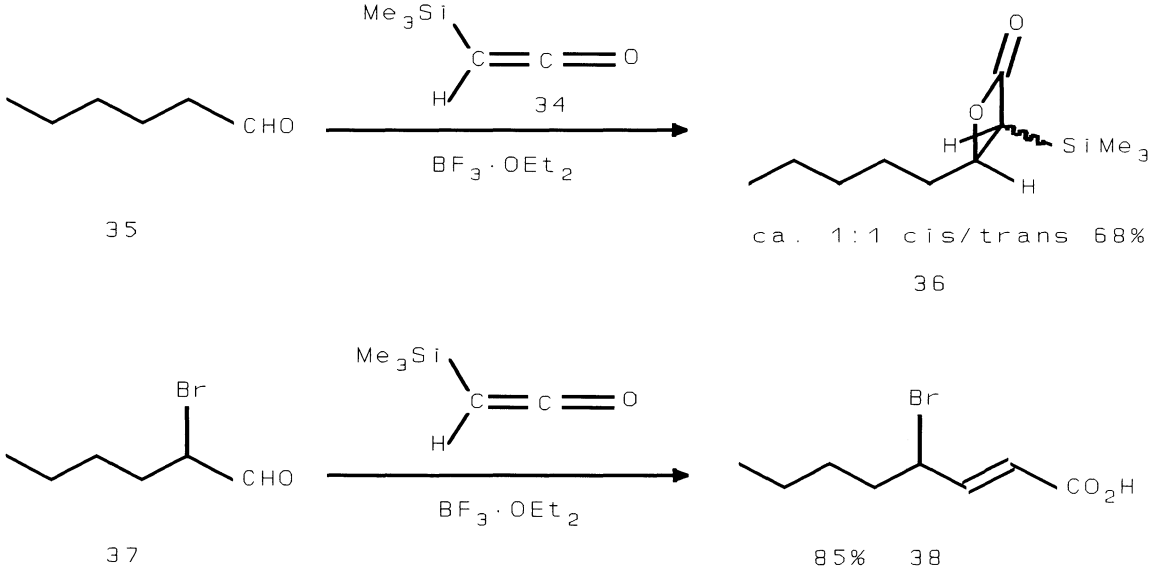
Scheme V



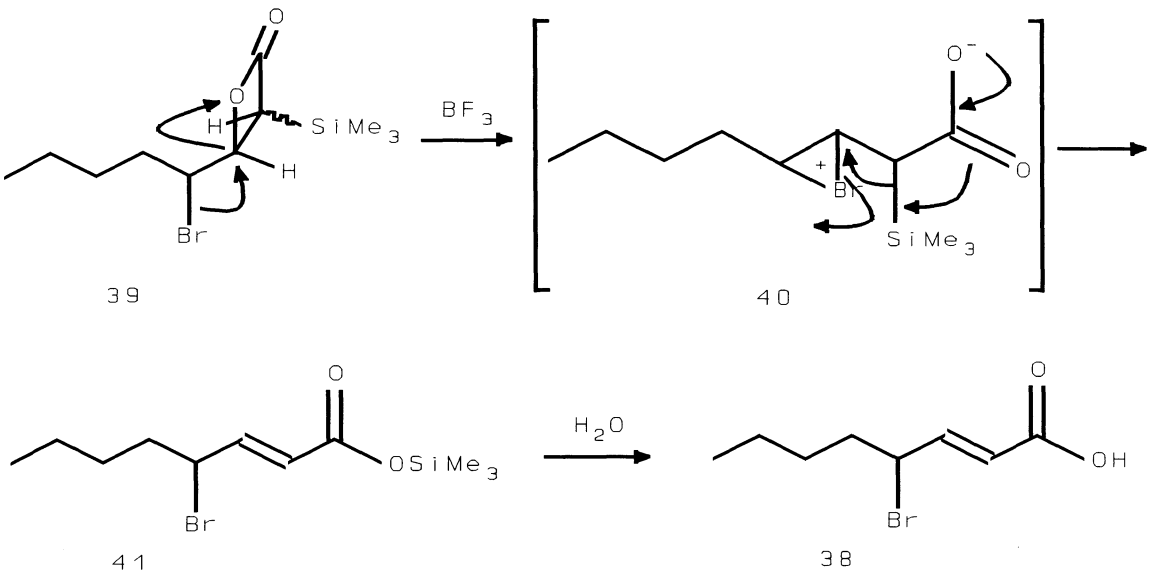
approaches discussed above, ring expansion in this case is initiated by the formation of a cation **32** adjacent to the β-lactone ring oxygen atom via departure of bromine atom (nucleofuge) with silver ion. Elimination of an α-proton forms desired butenolides **33** (**Scheme V**).

Hoping to expand on this discovery that Lewis acids can initiate cation formation/ring expansion by the abstraction of a γ-nucleofuge, we were interested in the investigation of potentially useful transformations of α-trimethylsilyl β-lactones. These moieties are readily available via the [2+2] cycloaddition of trimethylsilylketene to carbonyl compounds catalyzed by boron trifluoride etherate ($BF_3 \bullet OEt_2$);[7] the silicon atom was expected to facilitate the β-lactone

Scheme VI

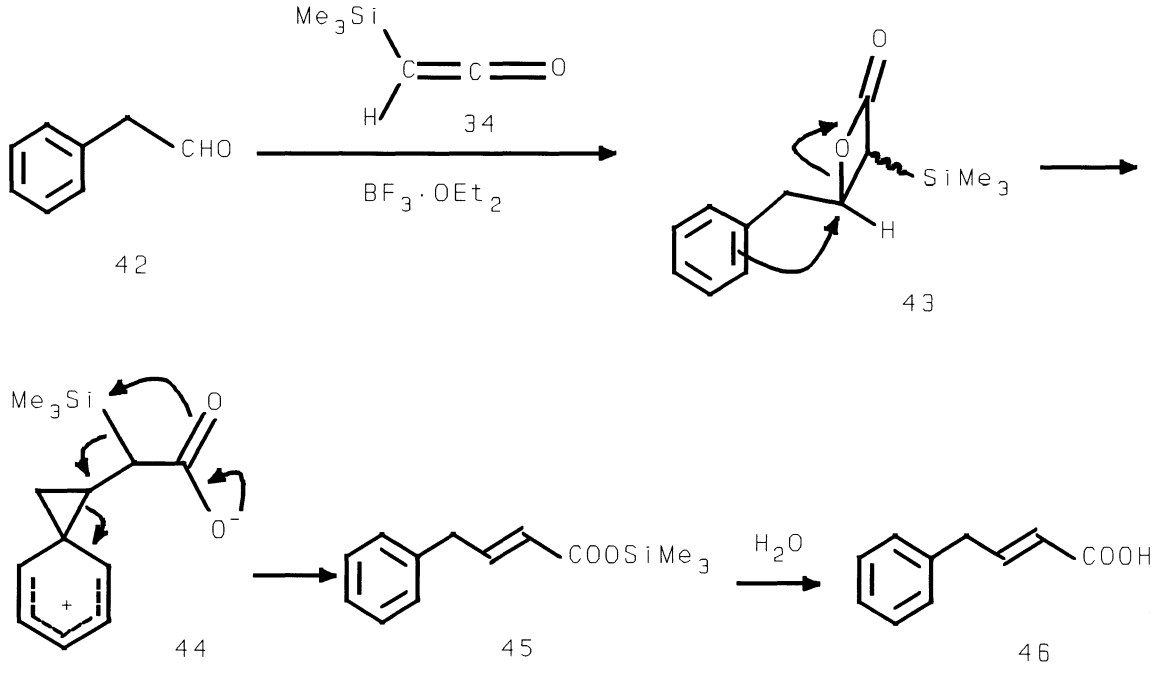


Scheme VII



ionization process because of its β-cation stabilization properties.[2] While the reaction of trimethylsilylketene with hexanal **35** provided the expected β-lactone **36** in 68% yield, similar treatment with 2-bromohexanal **37** yielded 4-bromo-2-octenoic acid **38** in 85% in our initial research (**Scheme VI**). We reasoned that the likely mechanism behind this unexpected behavior was that bromine might anchimerically assist the ionization process to such a degree that isolation of the β-lactone was not possible (**Scheme VII**). Additional support for this proposed mechanism was provided by the reaction of trimethylsilylketene with phenylacetaldehyde **42**, which should assist the ionization in a similar manner (**Scheme VIII**). Phenyl groups, although not typically nucleofugal, are well-known for their anchimeric participation in cation-mediated

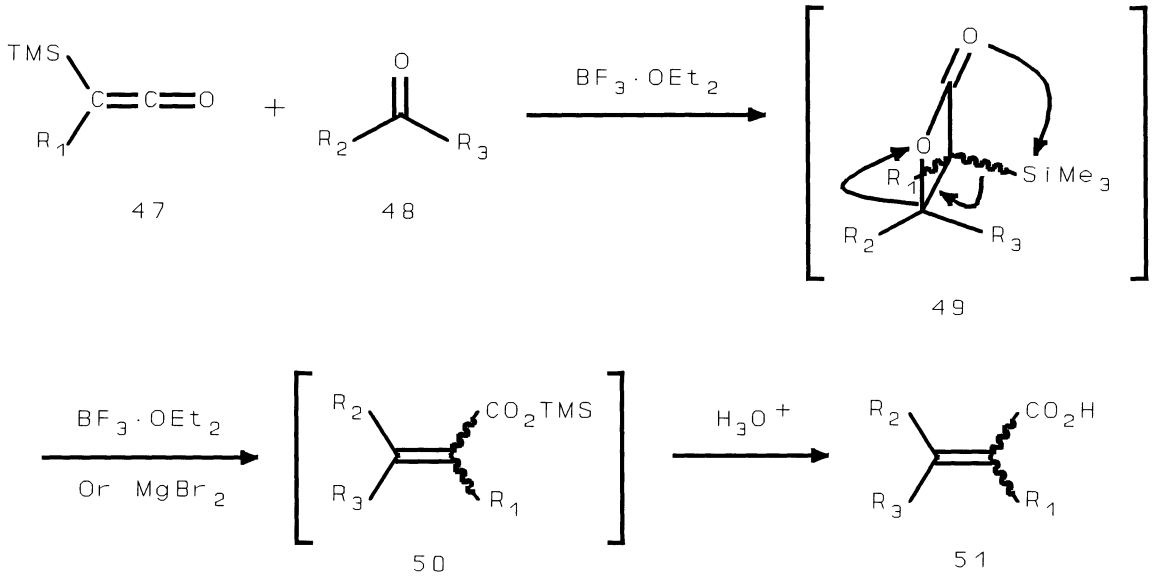
Scheme VIII



reactions. It was also reported by another research group that silyl ketene reactions with α,β-unsaturated carbonyl compounds yielded homologous α,β-unsaturated trimethylsilyl esters.[7]

Foreseeing that this conversion might be a useful nonbasic alternative to the Wittig reaction, several β-lactones prepared from saturated aldehydes were treated with magnesium bromide, which is an effective catalyst for initiating β-lactone ionization. The corresponding α,β-unsaturated acids were obtained in high yields. We improved the reaction, streamlining it to a one-pot procedure, by prolonging the treatment with the cycloaddition catalyst boron trifluoride etherate ($BF_3 \bullet OEt_2$); thus, the two-carbon

Scheme IX



homologous α,β-unsaturated acids were produced without the separation of intermediate α-trimethylsilyl β-lactones and without the need for a separate additional catalyst (**Scheme IX**).

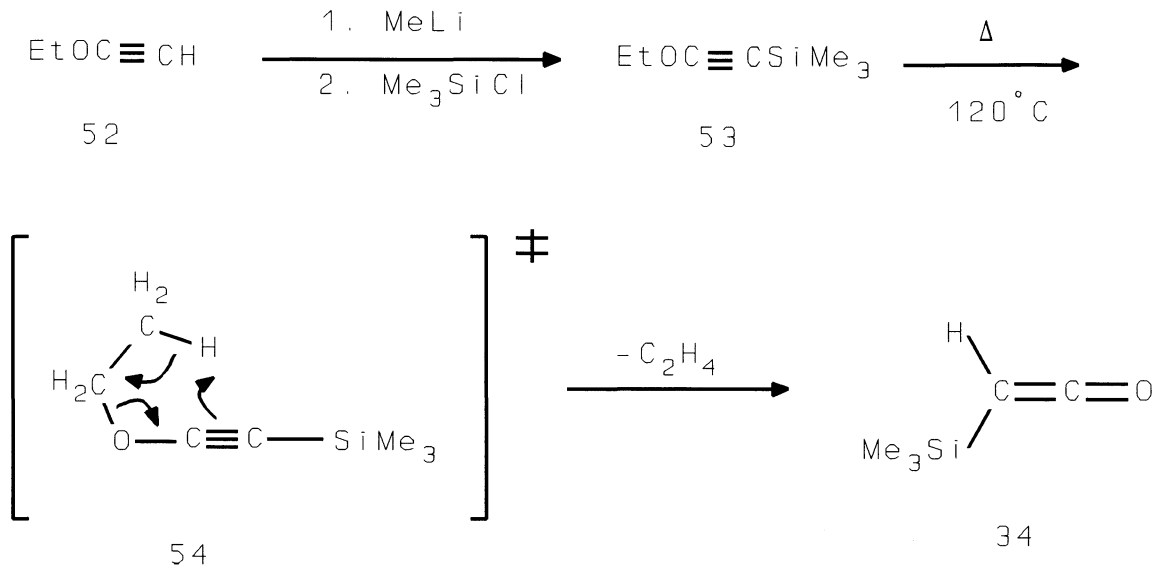
The study is described in full detail in the remainder of this thesis, which includes mechanistic discussions, summary of results, and experimental section.

Results and Discussion

Trimethylsilylketene **34**, first made in 1965,[8] is very reactive under certain conditions but unique among ketenes in its unusual stability. Its synthetic utility is just begining to be appreciated by the synthetic community. It reacts with hindered amines and tertiary alcohols as an acylation reagent, it undergoes olefination with stabilized phosphorus ylides,[9] and it reacts with aldehydes via [2+2] cycloaddition reactions to form α-trimethylsilyl β-lactones under the influence of boron trifluoride etherate ($BF_3 \bullet EtO_2$).[7] Unlike other ketenes which are prone to spontaneously dimerize, trimethylsilylketene has great resistance towards dimerization; it can be stored in a refrigerator for weeks without noticeable decay. Kinetic studies of the low reactivity of trimethylsilylketene in water reveal its remarkable ground state stability.[10] There are some suggestions that the trimethylsilyl group might act as a $\sigma \rightarrow \pi$ donor[11] or a $\pi \rightarrow \sigma$ back donor-acceptor.[12] However, those arguments are not consistent with molecular orbital level calculation results.[13] So far there is no complete, satisfactory explanation for this phenomenon.

There are three common ways for preparing trimethylsilylketene.[9,14] We prepared trimethylsilylketene **34** by employing the pyrolysis of (trimethylsilyl)ethoxyacetylene **53** according to the procedure of Ruden (**Scheme X**).[9]

Scheme X

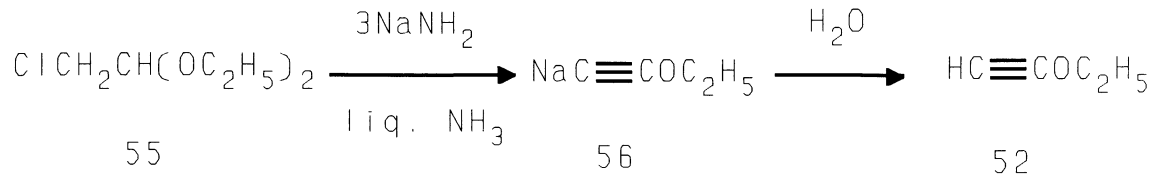


52 53 54 34

Ethoxyacetylene **52** was deprotonated by methyllithium; the derived anion then reacted with chlorotrimethylsilane to form alkynyl silane **53**, which was carefully heated to 120°C to produce the volatile, colorless liquid trimethylsilylketene **34** in 65% yield.

Ethoxyacetylene **52** (ethyl ethnyl ether) is commercially available but extremely expensive and not particularly pure; thus it was synthesized from chloroacetaldehyde diethyl acetal **55** by following the procedure of Jones *et al.* (**Scheme XI**).[15] Treated with sodium amide in liquid ammonia at low temperature, chloroacetaldehyde diethyl acetal **55** underwent a double elimination reaction and was quenched by water with extreme care to yield the volatile, colorless liquid ethoxyacetylene **52** in 60-65% yield.

Scheme XI

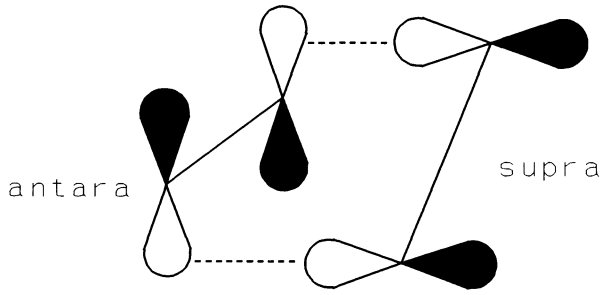


With trimethylsilylketene in hand, we were able to examine the [2+2] cycloaddition reaction catalyzed by Lewis acids with different carbonyl compounds, including saturated and unsaturated aldehydes and ketones.

A [2+2] cycloaddition reaction, more completely designated as a $[2\pi_s+2\pi_a]$ process, involves two π systems. According to Woodward-Hoffmann rules for cycloaddition,[16] it can only happen with one of the components in antarafacial manner, as shown in **Fig II**, in order to achieve proper orbital overlap and to close the four-membered ring. Most [2+2] cycloadditions involve ketenes since their *sp*-hybridized linear geometry provides the least steric repulsion in the antarafacial transition state.[17]

It is known that ethoxy ketenes react with alkenes via a concerted, nonsynchronous process,[18] while alkyl ketenes react with imines (Staudinger reaction) via a step-wise mechanism.[19] A zwitterion, the principal intermediate of the Staudinger reaction, conrotates to close the ring. In our study, we made no efforts to distinguish the operative mechanism of

Fig II



57

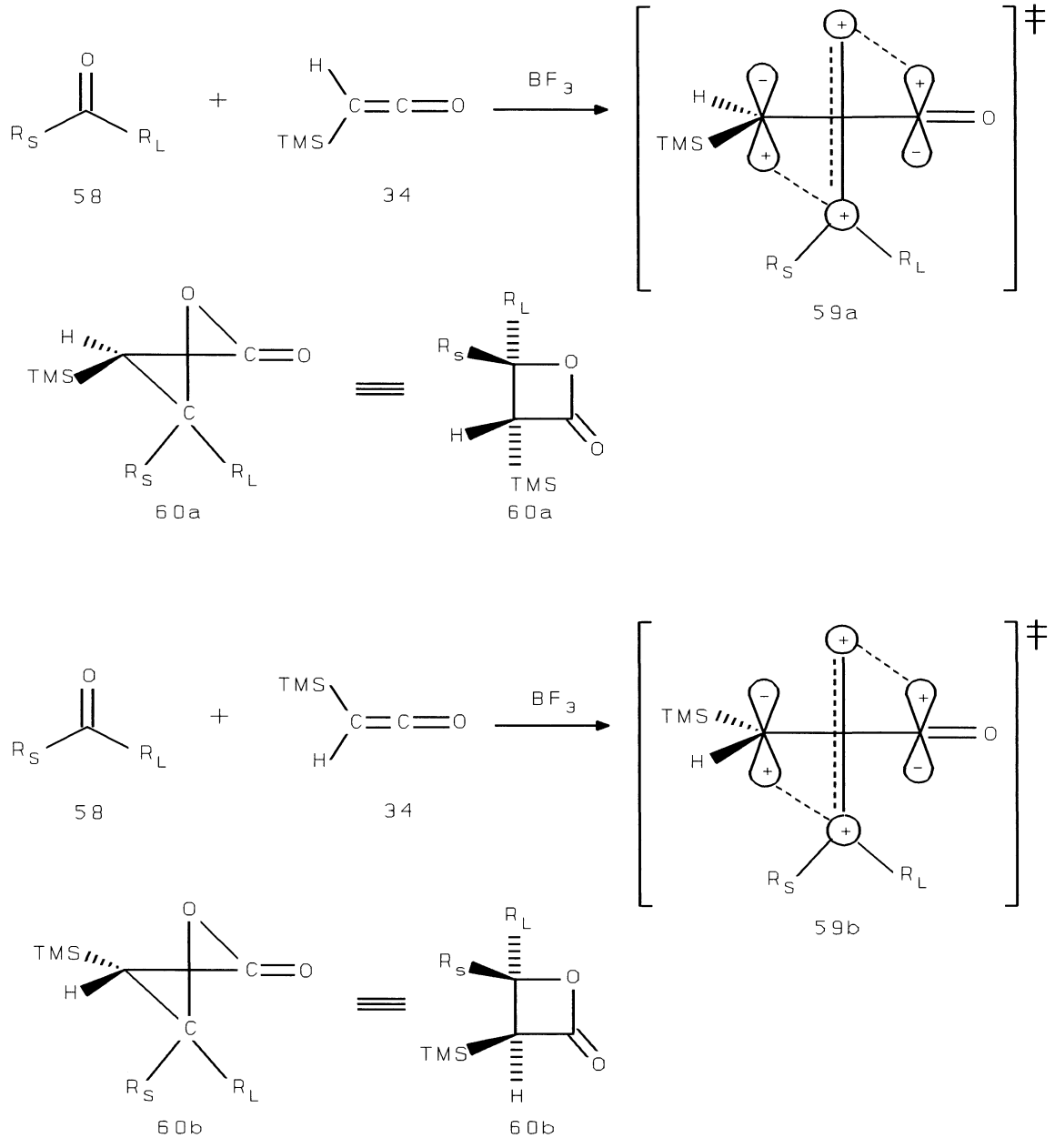
supra/antara Möbius system

trimethylsilylketene reactions with carbonyl compounds. Both possible mechanisms are shown (**Schemes XII, XIII and XIV**) and discussed below.

Scheme XII shows the possible concerted mechanism. According to frontier orbital theory, the HOMO of the carbonyl compound should react with LUMO of trimethylsilylketene's ethylenic portion (antara component). For steric reasons, the trimethylsilyl group and R_L group would like to take positions far away from each other in the transition state **59**.

Since trimethylsilylketene has a planar structure and the three atoms C=C*=O are arranged linearly (C* *sp*-hybridized), both transition states **59a** and **59b** have the maximum distance between the trimethylsilyl group and R_L group. Transition state **59a** leads to *cis* β-lactone **60a**, while **59b** yields *trans* product **60b**. In other words, there is no sterically mandated

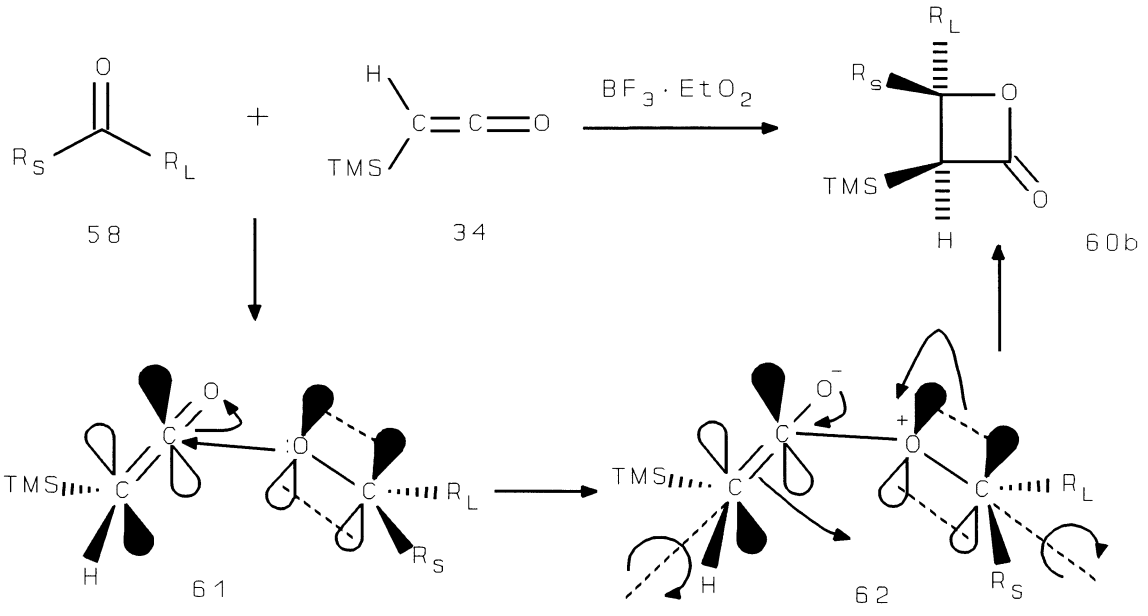
Scheme XII



preference for the *si* or *re* face of the carbonyl compounds in this cycloaddition reaction. It could thus be expected that β-lactones would yield approximately 1:1 *cis-trans* ratio, if the nature of this reaction is not overruled by other factors.

Scheme XIII and **Scheme XIV** delineate the possible stepwise mechanism. The zwitterion-like intermediate **62** or **63** conrotates to close the ring. Though **62** has a planar structure, the distance between the trimethylsilyl group and R_L or R_S group is much greater than that in **59**. So, for **62**, it would not be as important as in **59** that the trimethylsilyl group and R_L group occupy distant positions, though it would still of course be favored to some degree. Based on the reason discussed above, intermediate **62**, which leads to *trans* β-lactones **60b**, will be favored in a large degree only when R_L group is a much more sterically demanding group than R_S.

Scheme XIII



However, in terms of silicon's γ-positive charge stabilization,[2] it has been confirmed that its interactions with the γ-positive charge are equally facile from both the W and the sickle conformations of the open chain (**Scheme XIV**).[2,20] This supports the stereorandom results observed. The details of this mechanism are still under debate and the factors controlling the stereochemistry are quite complicated.[19]

In either mechanism, the stereoselectivity of β-lactones (*cis-trans* ratio) is influenced by many factors such as structures of the ketene and the other reactant, catalyst, solvent, reaction rate, temperature and the order of addition

Scheme XIV

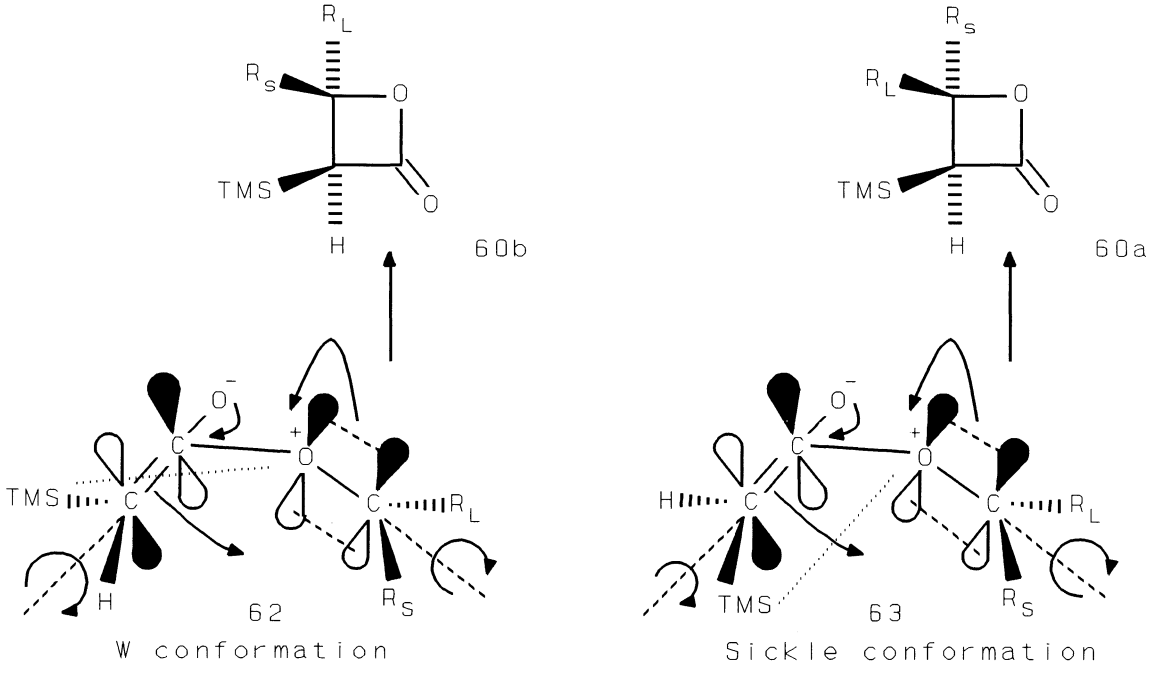
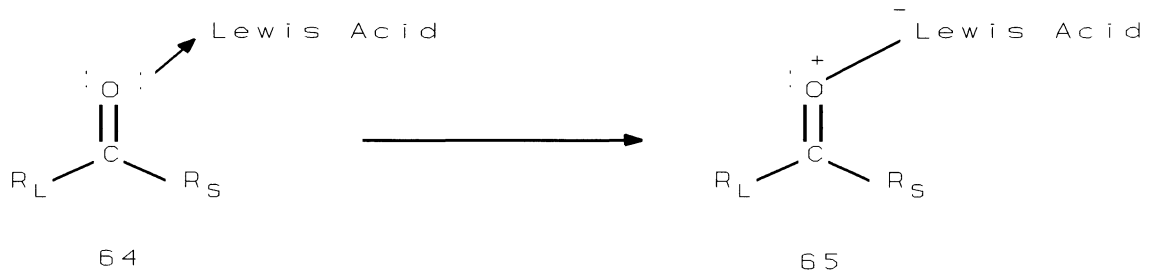
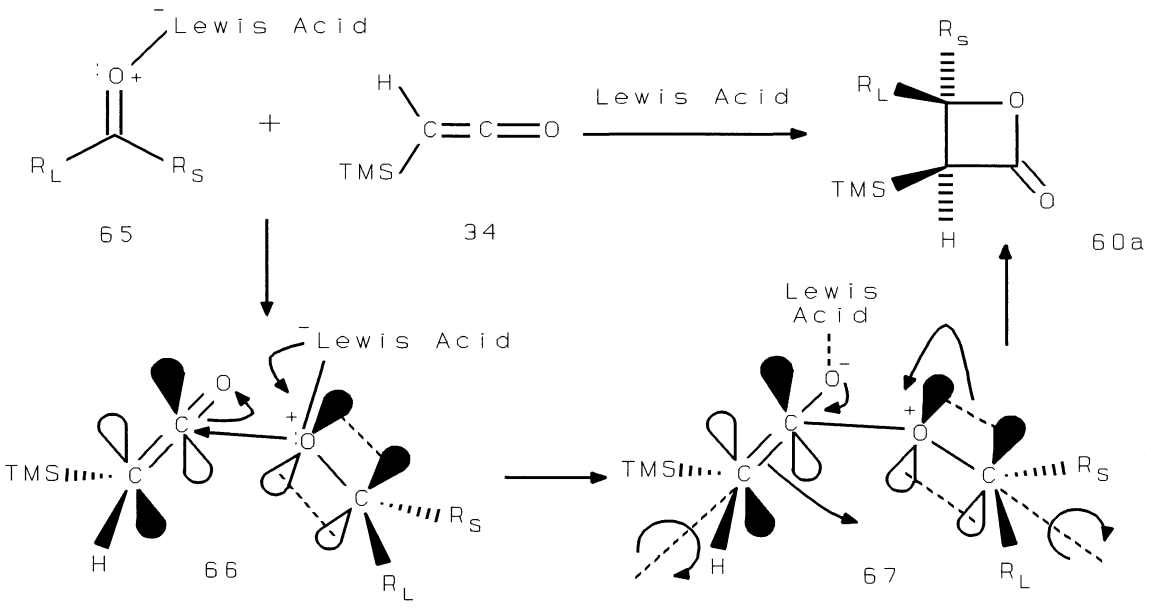


Fig III



Scheme XV



of reagents.[14,21]

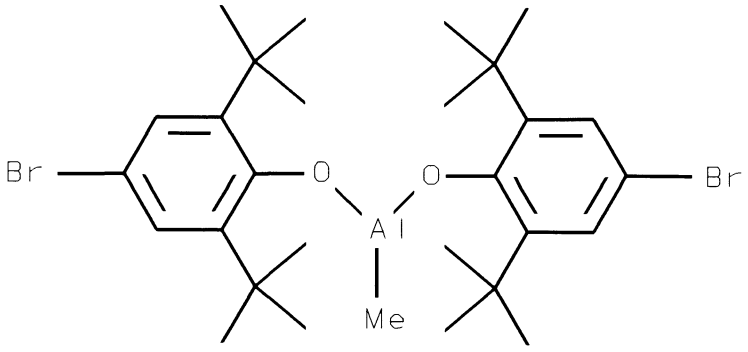
The Lewis acid catalysts play an essential role in this synthetic method. Lewis acids fulfill three major functions: activation of the carbonyl compounds towards [2+2] cycloaddition reaction,[9] initiation of the β-lactones' ionization, and stabilization of the ionized β-lactones via

interaction with the negative oxygen.

Trimethylsilylketene does not react with dienes or olefins, nor with carbonyl compounds without Lewis acids. Lewis acids probably activate the carbonyl compounds towards cycloaddition reaction via complexation with carbonyl oxygen (**Fig III**).[9] There are two facets of the complexation effect: energy level change, which usually increases the reactivity, and orbital distortion which improves the stereoselectivity.[22] The complexation changes the carbonyl HOMO orbital energy and shrinks the energy gap between the HOMO of carbonyl group and the LUMO of trimethylsilylketene's ethylenic portion. The complexation will also favor *cis* β-lactones since Lewis acids should be *trans* to R_L group (**Fig III**) and thus intermediate **67** is favored (**Scheme XV**). It is obvious that the stereoselectivity is greatly influenced by the differentiation between R_L and R_S groups and the sterically demanding degree of the Lewis acid.

Boron trifluoride, though a mild Lewis acid and capable of catalyzing the reaction efficiently, is not sterically demanding. Recently, a Japanese research group succeeded in synthesizing *cis* β-lactones from aldehydes with high stereoselectivity by using methylaluminum *bis*(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR **68**),[3] which is a Lewis acid that is highly sterically demanding and gentle in nature.

The β-lactones formed by using MABR as the catalyst have been improved greatly in both stereoselectivity and yield

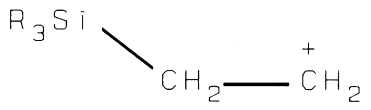


MABR 68

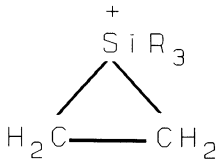
compared to that by using boron trifluoride. Some reactions yielded *cis* β-lactones exclusively. Diethylaluminum chloride (Et_2AlCl) also showed better catalytic effect than boron trifluoride in the case of propanal, and the *cis/trans* ratio of the β-lactones was 92:8.[3]

The α-trimethylsilyl β-lactones prepared during our study were not separated, but allowed to undergo ionization initiated by the Lewis acid. The α-trimethylsilyl β-lactones are more prone towards ionization than other β-lactones discussed in the Introduction,[1b-g] because the derived cations benefit from β-silicon stabilization.[2]

There are two possible ways that silicon stabilizes β-cations: vertical participation **69** (pure hyperconjugation effect) and non-vertical participation **70** (three-membered ring siliconium ion). Both models can explain the β-cation effect equally well.

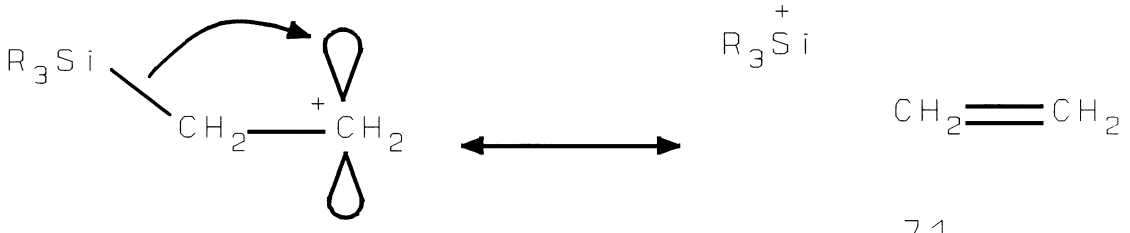


69



70

Scheme XVI



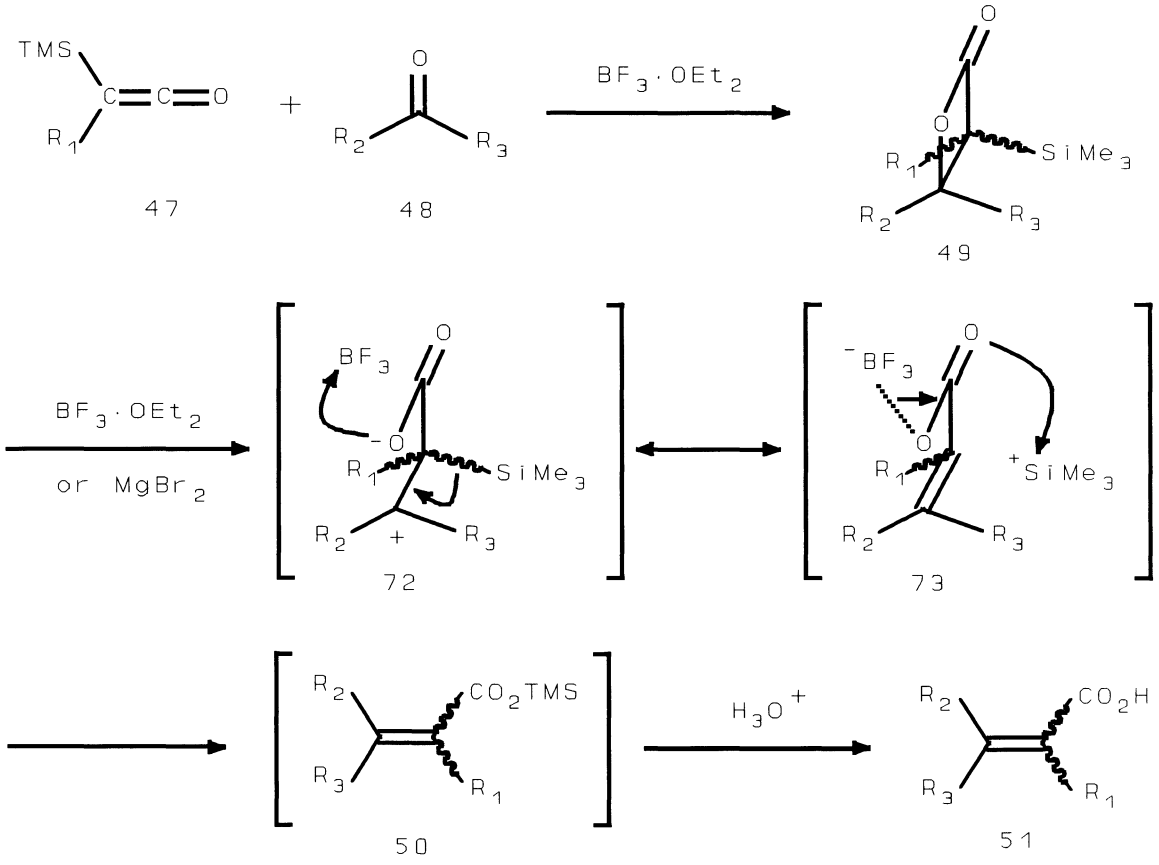
69

71

Due to its highly polarizable and electron-donating character, a Si-C bond stabilizes the β-cation through $Si^+/C=C$ hyperconjugation (**Scheme XVI**). Resonance form **71** contributes greatly to the stabilization because of its stable C=C double bond and positive charge on silicon. Silicon is a better positive charge acceptor than hydrogen or carbon. Intermediate **70** changes geometry for maximum hyperconjugation: a shorter C-C bond (1.443Å → 1.360Å) and a smaller Si-C-C angle (119.6° → 94.3°). The Si-C bond hyperconjugation provides much more stable β-cations to the degree of about 29 kcal/mol lower in energy for a primary cation system and 22 kcal/mol for a secondary system.[2]

Ionized forms **72** and **73** of β-lactone **49** are stabilized by

Scheme XVII



both the silicon β-cation effect and by complexation of the Lewis acid with the negative oxygen. Cation migration/ring expansion is not likely due to the cation rearrangement thermodynamics discussed earlier, in addition to the excellent electrofugal character of the trimethylsilyl substituent, and has not been observed. In fact, the silicon γ-cation effect is much weaker than the silicon β-cation effect, and a tertiary cation is only about 9-10 kcal/mol (in solvent SO_2ClF) lower in energy than a secondary cation.[23] So even if there were a possibility for forming a tertiary cation, *i.e.*,

the existence of a 3° cation adjacent to the β-lactone ring, it still would not be a favorable process.

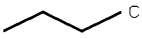
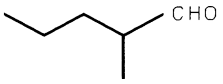
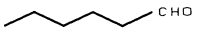
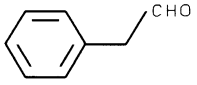
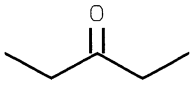
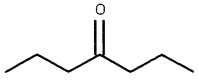
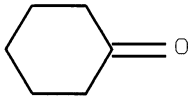
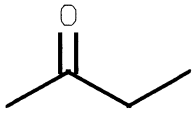
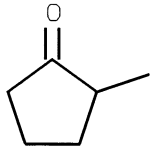
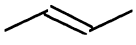
β-Lactones derived from trimethylsilylketene and α,β-unsaturated carbonyl compounds proceed to ionize spontaneously, because the incipient cation is extremely stable, being both allylic and β to the trimethylsilyl moiety.[7] Isolation of these β-lactones is not possible.

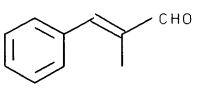
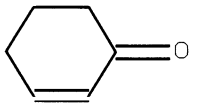
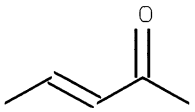
Major resonance form **73** carries a positive charge on the trimethylsilyl group, which migrates to oxygen. Conjugated α,β-unsaturated trimethylsilyl esters **50** are formed and thereafter upon aqueous workup the corresponding acids **51** are produced in high yield. The *Z/E* ratio of silyl ester **50** and acid **51** probably corresponds to *cis/trans* ratio of the β-lactone.

We treated trimethylsilylketene with a variety of carbonyl compounds, including saturated and unsaturated aldehydes and ketones. The reaction mixture was stirred overnight without separating the intermediates. Evaporation of solvent and hydrolysis by 5% hydrochloric acid or filtration through silica gel yielded the desired α,β-unsaturated acids. The results are summarized in **Table I**.

Saturated aldehydes produce acids in generally higher yield than saturated ketones. The results are influenced by both electronic and steric effects. Aldehydes are more polarized and less sterically hindered than ketones. Both effects are important to [2+2] cycloaddition reactions, as

Table I: Cycloadditon of Trimethylsilylketene with Carbonyl Compounds

Entry	Carbonyl Compounds	Yield (%)	Major IR (cm^{-1})
a		99	1720,1670
b		98	1680
c		60	1702,1652
d		90	1719,1650
e		51	1709,1643
f		80	1700
g		65	1709,1636
h		50	1690,1650
i		41	1710,1625
j		70	1702,1642,1603

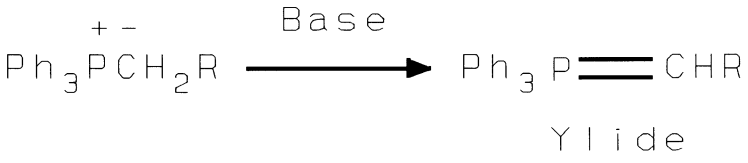
k		88	1670,1610
l		70	1690,1630,1590
m		98	1700,1570

Note: a: Trimethylsilylketene:Carbonyl Compound stoichiometry=1.1:1

b: Yield calculated from crude products

discussed earlier. Unsaturated aldehydes and ketones provide similar yields, probably as a consequence of the extremely stable allylic cations overriding the difference between them. Cyclic ketones, with significantly less rotational flexiblility, were homologated in slightly lower yields than acyclic ketones.

Scheme XVIII



Base: NaH; $NaNH_2$; n-BuLi; NaOH

This two-carbon homologation reaction provides an efficient and expedient nonbasic alternative to the Wittig reaction, which usually generates phosphorus ylides *in situ* via strong base deprotonation of phosphonium salts (**Scheme XVIII**).[24]

Conclusion

We have developed a new method for the syntheses of α,β-unsaturated acids from trimethylsilylketene and carbonyl compounds under the catalysis of boron trifluoride etherate ($BF_3 \bullet Et_2O$). A variety of carbonyl compounds were examined and this one-pot procedure has been proved to be efficient and expedient. The two-carbon homologated α,β-unsaturated acids were produced in yields from 41-99%.

The low stereoselectivity, the only drawback at the current time, may possibly be improved by changing the following factors: a) Replacing boron trifluoride etherate by sterically demanding Lewis acids, *e.g.*, MABR or diethylaluminum chloride.[3] Bulky Lewis acids have a major impact on the stereoselectivity (**Fig III** and **Scheme XV**). Of cause, this would increase the *cis*-selectivity; a different strategy will have to be developed to effect *trans*-selective cycloaddition reactions. b) Employing other alkyl silyl ketenes instead of trimethylsilylketene; for example, *t*-butyldimethylsilylketene (TBDMS). There is almost no research reported using alkyl silyl ketenes other than trimethylsilylketene, which is the only silyl ketene whose potential synthetic applications have been explored to any extent. The influence of more stericically demanding silyl ketenes is worthy of investigation. c) Polar solvent systems may be worth trying, *i.e.*, dichloromethane. Polar solvents

should increase the reaction rate by virtue of increasing the silicon β-cation effect and also by polarizing the carbonyl group towards cycloaddition. The effect of polar solvents on stereoselectivity may be modest and best examined in combination with different catalysts and ketenes.

In summary, this one-pot conversion of carbonyl compounds to two-carbon homologated α,β-unsaturated acids under mild, nonbasic conditions, provides an extremely efficient and facile nonbasic Wittig alternative. Refinement of the method in terms of stereoselectivity will expand its synthetic utility in situations wherein high stereoselectivity is crucial.

Experimental Section

Material and General Methods: All the reagents were purchased from Aldrich Chemical Company, Inc. unless otherwise indicated. Diethyl ether was distilled from sodium and potassium metal, in combination with benzophenone under nitrogen, before use. Dichloromethane was freshly distilled from calcium hydride under nitrogen. Aldehydes and ketones were distilled under nitrogen before use. Boron trifluoride etherate was redistilled under nitrogen whenever necessary. IR spectra were obtained on a Nicolet 20DXB FT-IR spectrophotometer or Perkin-Elmer 1319 IR spectrophotometer using sodium chloride plates. ^{1}H NMR spectra were acquired on GE QE-300 FT-NMR spectrometer or Varian T-60 NMR spectrometer. ^{13}C NMR spectra were recorded on GE QE-300 FT-NMR spectrometer. $CDCl_3$ was used as the solvent. Chemical shifts are reported in parts per million (ppm) (^{1}H NMR: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad). Mass spectra were obtained on Hewlett Packard 5890 Series II Gas Chromatograph and Hewlett Packard 5971 Series Mass Selective Detector. Boiling points are uncorrected. Thin-layer chromatography (TLC) was performed on Analtech silica gel GF chromatography plates using a dichloromethane-hexane solution (1:1) as the eluant. Flash chromatography was carried out on Aldrich silica gel 60 (200-400 mesh). All the reactions were performed under nitrogen and glassware was dried in an oven at

120 °C for at least four hours before use.

Ethoxyacetylene (52, ethyl ethnyl ether): CAUTION: This reaction must be carried out in a hood! An approximately 0.5g quantity of hydrated ferric nitrate ($Fe(NO_3)_3 \bullet 9H_2O$) was added to a three-necked flask equipped with cold-finger condenser (cooled with liquid nitrogen and ethyl acetate), gas inlet, and magnetic stirring bar. Liquid ammonia (1000ml) was introduced into the flask cooled by ice, whereupon freshly cut sodium (38g, 1.65 mole) was added slowly over one hour. After stirring another 20 minutes, chloroacetaldehyde diethyl acetal (**55**, 76.5g, 0.50 mole) was added dropwise via syringe. After 30 minutes, the ammonia solution was allowed to evaporate. The reaction mixture was left overnight under nitrogen. The flask was cooled to -70°C with a liquid nitrogen and ethyl acetate bath. About 325ml of saturated sodium chloride was cooled to -20°C and added portionwise with strong stirring. The reaction mixture temperature was raised slowly to room temperature. The mixture was then slowly heated to 80°C and the crude product was distilled out at a head temperature of around 50°C. A second fractional distillation produced 22.8g of a colorless and volatile liquid (b.p. 50-51°C/760mm Hg), 65% yield (high 29.8g, 85% yield). (Lit:[15] 20-21.2g, 57-60%, b.p. 49-51°C/749mm Hg, n_D^{25} 1.3790). ^1H NMR δ_{CDCl3}: 1.348 (3H, t), 1.498 (1H, s), 4.09 (2H, q). IR (neat): 3320, 2960, 2140 cm^{-1}. (Lit.[25] b.p. 50-2°C/760mm Hg, IR: 3300, 2140 cm^{-1}).

Trimethylsilylketene (34): Ethoxyacetylene (**52**, 4.0g, 57.1 mmol) was dissolved in with 200ml of diethyl ether at 0°C in a 500ml three-necked flask equipped with magnetic stirring bar and nitrogen inlet. Methyllithium (1.4M, 41.0ml, 57.4 mmol) was added dropwise over 20 minutes. A white precipitate was formed during the addition. After half hour stirring, chlorotrimethylsilane (**55**, 6.2g, 57.1 mmol) was added slowly. The reaction mixture was raised to room temperature and stirred overnight. After filtration of the reaction mixture, the diethyl ether was removed via distillation at 35-40°C. The residue was carefully heated to 120°C, affording crude trimethylsilylketene **34** with a boiling point around 80°C. A second fractional distillation yielded 4.24g, 65% yield of pure trimethylsilylketene **34** (b.p. 80-81°C/760mm Hg). IR (neat): 3340, 3020, 2940, 2100, 1260, 1240, 1040, 840 cm^{-1}; ^{1}H NMR δ_{CDCl3}: 0.10 (9H, s), 1.72 (1H, s); ^{13}C NMR δ: 179.264, 0.373. (Lit.[9] b.p.: 81-82°C; IR (λ_{max}): 4.70, 7.90, 8.00, 11.70 μm; δ_{TMS}^{CCl4}: 1.5 (CH, s)).

General Procedure for Preparation of α,β-Unsaturated Acids from Carbonyl Compounds and Trimethylsilylketene.

Carbonyl compounds (5 mmol), along with a few drops of boron trifluoride etherate, were dissolved in diethyl ether (15-20ml) at -20°C in a three-necked flask (25ml or 50ml) equipped with a nitrogen inlet and a magnetic stirring bar. Trimethylsilylketene (**34**, 0.63g, 5.5 mmol) was added dropwise

via syringe to the mixture. Upon consumption of the carbonyl compounds (monitored by TLC, dichloromethane-hexane 1:1), the reaction mixture was raised to room temperature slowly and stirred overnight. The solvent was removed via rotary evaporation, and the residue was treated in one of two ways: A) The residue was treated with 5% hydrochloric acid (5ml) in a 25ml flask for twenty minutes. The solution was then extracted three times with diethyl ether (5ml). The organic phase was combined and dried over anhydrous magnesium sulfate, and the solvent was removed under reduced pressure to afford the α,β-unsaturated acids. B) The residue could be simply filtered through a silica gel (dichloromethane-hexane 1:1) to yield α,β-unsaturated acids.

2-Hexenoic acid (51a): Yield: 99%. IR (neat): 2940, 2920, 2860, 1720, 1670, 1450, 1240, 1170 cm^{-1}; ^1H NMR δ_{CDCl3}: 7.2 (weak, 1H), 5.1 (*trans* isomer, d, 1H), 4.10 (*cis* isomer, d, 1H), 2.2 (q, 4H), 1.6 (m, 4H), 0.9 (m, 6H). (Lit. *trans*-2-Hexenoic acid IR[26]: 1709, 1653 cm^{-1}; ^1H NMR[27] δ_{CDCl3}: 12.0 (s, 1H), 7.0 (m, 1H), 5.7 (d, 1H), 2.2 (q, 2H), 1.5 (m, 2H), 0.9 (t, 3H)).

4-Methyl-2-heptenoic acid (51b): Yield: 98%. IR (neat): 3500-2500 (broad), 1680 (broad), 1420, 1180, 1250, 1130, 1100, 840 cm^{-1}; ^1H NMR δ_{CDCl3}: 10.4 (s, 1H), 7.2 (weak, 1H), 5.8 (weak, 1H), 3.0-1.0 (b, 9H); mass spectrum, parent peak *m/e* 142,

found *m/e* 142.

2-Octenoic acid (51c): Yield: 60%. IR (neat): 3500-2500, 1701.6, 1651.6, 1433 cm^{-1}; ^1H NMR δ_{CDCl3}: 11.7 (s, 1H), 7.5 (m, 1H), 5.9 (m, 1H), 2.6-2 (m, 2H), 1.5 (m, 6H), 0.9 (m, 3H). (Lit. *trans*-2-Octenoic acid: IR:[28] 3300-2500, 1694.9 1652.9, 1428.6, 1282 cm^{-1}; ^1H NMR[29] δ_{CDCl3}: 12.16 (s, 1H), 7.1 (m, 1H), 5.8 (d, 1H), 2.3 (m, 2H), 1.4 (m, 6H), 0.9 (m, 3H)).

4-Phenyl-2-butenoic acid (51d): Yield: 90%. IR (neat): 3086.9, 3030.4, 2960.7, 2876.2, 1719.1, 1652.4, 1601.0 cm^{-1}; ^1H NMR δ_{CDCl3}: 7.25 ($-C_6H_5$), 5.80 (-CH=CH), 3.50 ($Ph-CH_2$). (Lit.[30] *trans*-4-phenyl-2-butenoic acid: IR: 3500-2500, 1700, 1650, 975 cm^{-1}; ^1H NMR δ_{CDCl3}: 11.24 (s, 1H), 7.00-7.60 (m, 6H), 5.76 (1H), 3.55 (d, 2H)).

3-Ethyl-2-pentenoic acid (51e): Yield: 51%. IR (neat): 3500-2500, 1709, 1642.6, 1461, 1412.1, 1290.9 cm^{-1}; ^1H NMR δ_{CDCl3}: 6.2 (s, weak, 1H), 2.1-1.7 (m, 4H), 1.2-0.9 (m, 6H); mass spectra, parent peak *m/e* 128, found 128.

3-Propyl-2-hexenoic acid (51f): Yield: 80%. IR (neat): 2950, 1700 (broad), 1595, 1450 cm^{-1}; ^1H NMR δ_{CDCl3}: 12.9 (s, 1H), 5.9 (s, 1H), 2.5-2.0 (m, 4H), 1.5 (m, 4H), 0.9 (m, 6H); mass spectrum, parent peak *m/e* 154, found *m/e* 154.

Cyclohexylideneacetic acid (51g): Yield: 65%. IR (neat): 3500-2500, 1709, 1635.9 cm^{-1}; ^1H NMR δ_{CDCl3}: 5.7 (s, weak, 1H), 2.5-1.3 (m); mass spectrum, parent paek *m/e* 140, found *m/e* 140.

3-Methyl-2-pentenoic acid (51h): Yield: 50%. IR (neat): 1690, 1650 cm^{-1}; ^1H NMR δ_{CDCl3}: 6.05 (d, 1H), 2.3 (m, 2H), 1.8 (m, 3H), 1.0 (m, 3H); mass spectrum, parent *m/s* 114, found *m/s* 114.

2-Methyl-cyclopentylideneacetic acid (51i): Yield: 41%. IR (neat): 3500-2500, 1700 (broad), 1410, 1250, 840 cm^{-1}; ^1H NMR δ_{CDCl3}: 6.2 (s, weak, 1H), 2.4-2.2 (m, b, 3H), 1.2-0.9 (m, b, 5H); mass spectrum, parent peak *m/e* 140, found *m/e* 140.

2,4-Hexadienoic acid (51j, sorbic acid): Yield: 70%. IR (neat): 3500-2500, 1702.3, 1642.6, 1602.7, 841.7 cm^{-1}; ^1H NMR δ_{CDCl3}: 11.75 (s, 1H), 7.40 (m, 1H), 6.5-5.4 (m, 3H), 1.9 (m, 3H). (Lit.[31] IR: 3500-2500, 1694.9, 1639.3, 1600 cm^{-1}; Lit.[7] Trimethylsilyl 2,4-Hexadienoate: IR: 1690, 1640 cm^{-1}; ^1H NMR δ_{CCl4}: 7.5-5.7 (m, 4H), 1.0 (d, 3H), 0.35 (*Z,E* isomer), 0.3 (*E,E* isomer) (two s, 9H)).

4-Methyl-5-phenyl-2,4-pentadienoic acid (51k, γ-methyl-β-styrylacrylic acid): Yield: 88%. IR (neat): 3500-2500, 1660, 1595 cm^{-1}; ^1H NMR δ_{CDCl3}: 7.5 (b, 5H), 7.0-5.8 (m, C=CH), 2.05

(m, CH_3), 1.7 (s, b, COOH); mass spectrum, parent peak *m/e* 188, found *m/e* 188. (Lit.[7] Trimethylsily 4-Methyl-5-phenyl-2,4-pentdienoate: IR: 1625, 1680 cm^{-1}; ^1H NMR δ_{CCl4}: 7.3 (d, 1H), 7.2 (s, 5H), 6.7 (s 1H), 5.8 (d, 1H), 0.3 (s, 9H)).

2-Cyclohexenylideneacetic acid (51l): Yield: 70%. IR (neat): 3500-2500, 1690, 1630, 1590 cm^{-1}; ^1H NMR δ_{CDCl3}: 7.0 (m, 1H), 6.5 (d, 1H), 6.1 (m, 1H), 2.4 (m, 2H), 2.0 (m, 2H), 1.7 (s, b, COOH), 0.9 (m, 3H); mass spectrum, parent peak *m/e*: 138, found *m/e*: 138.

3-Methyl-2,4-hexadienoic acid (51m): Yield: 98%. IR (neat): 3500-2500, 1700 (broad), 1570, 1240, 840 cm^{-1}; ^1H NMR δ_{CDCl3}: 9.7 (s, 1H), 7.4-6.1 (m, 2H), 2.8-1.7 (m, 6H). (Lit.[32] IR (CH_2Cl_2): 1703.6 cm^{-1}; ^1H NMR δ_{CDCl3}: 7.58 (m, 1H), 6.60-5.46 (m, 3H, vinyl H and OH), 1.97 (m, 6H)).

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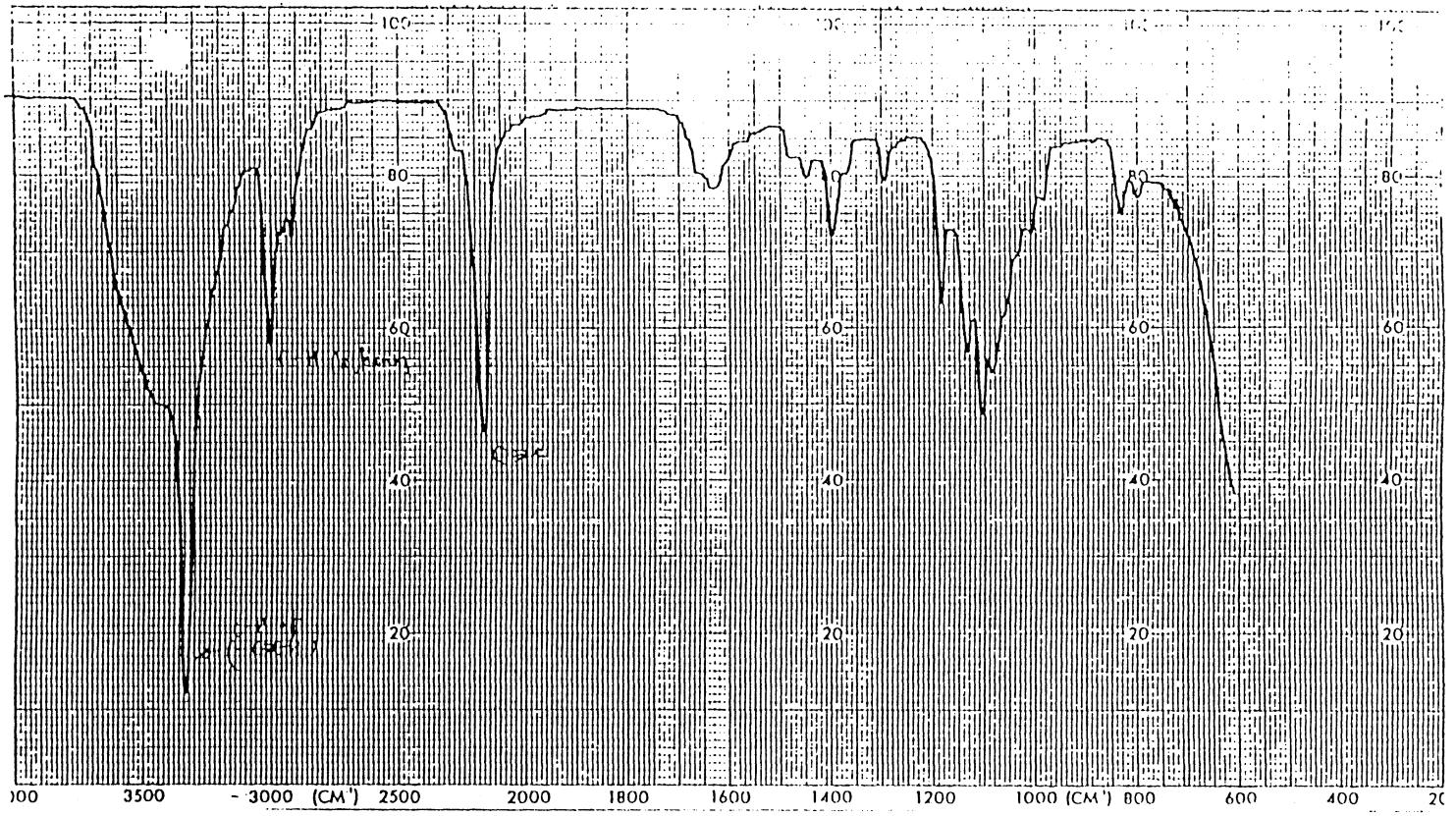
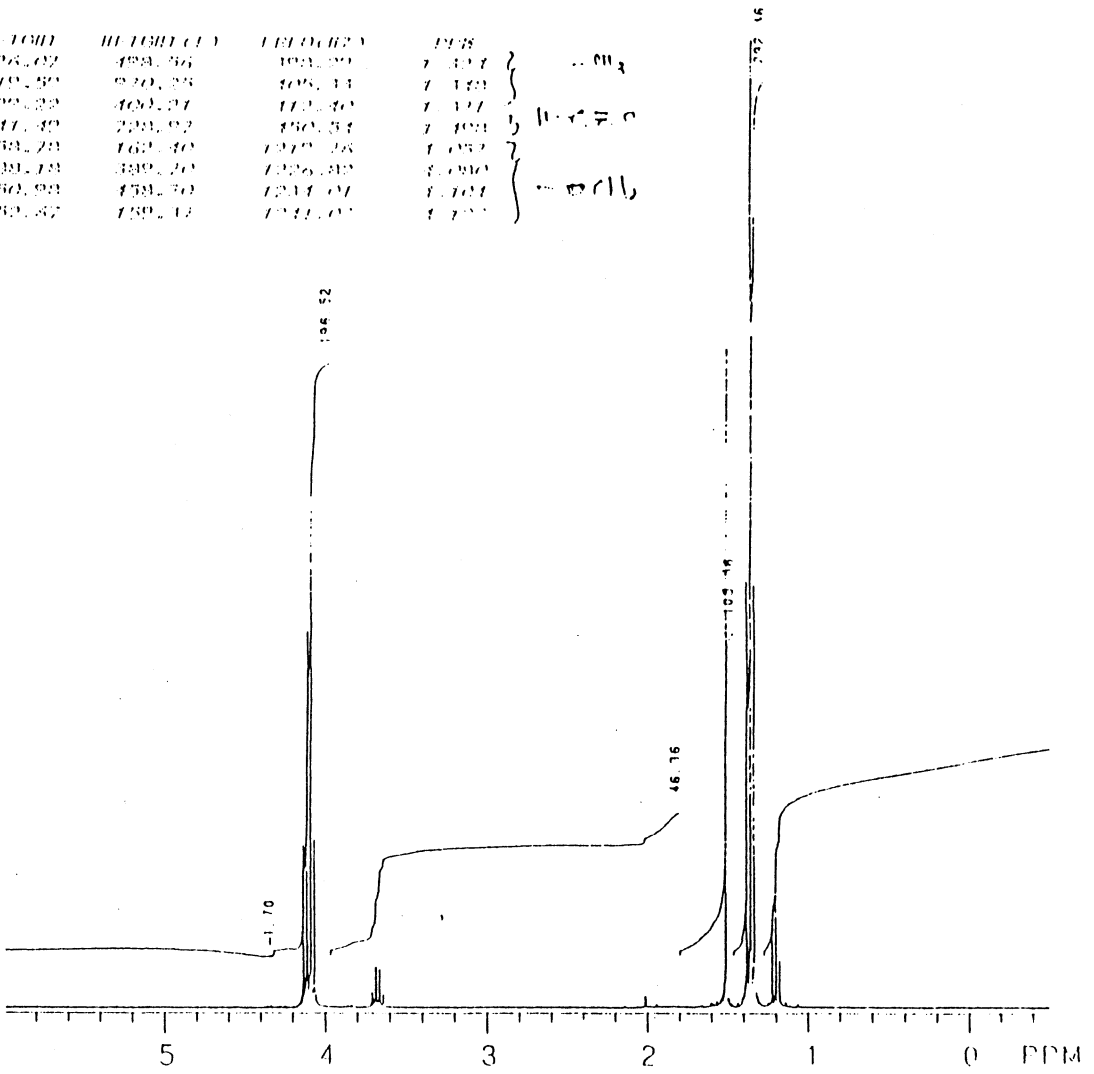
Ethoxyacetylene 52

(EtO) C≡CH



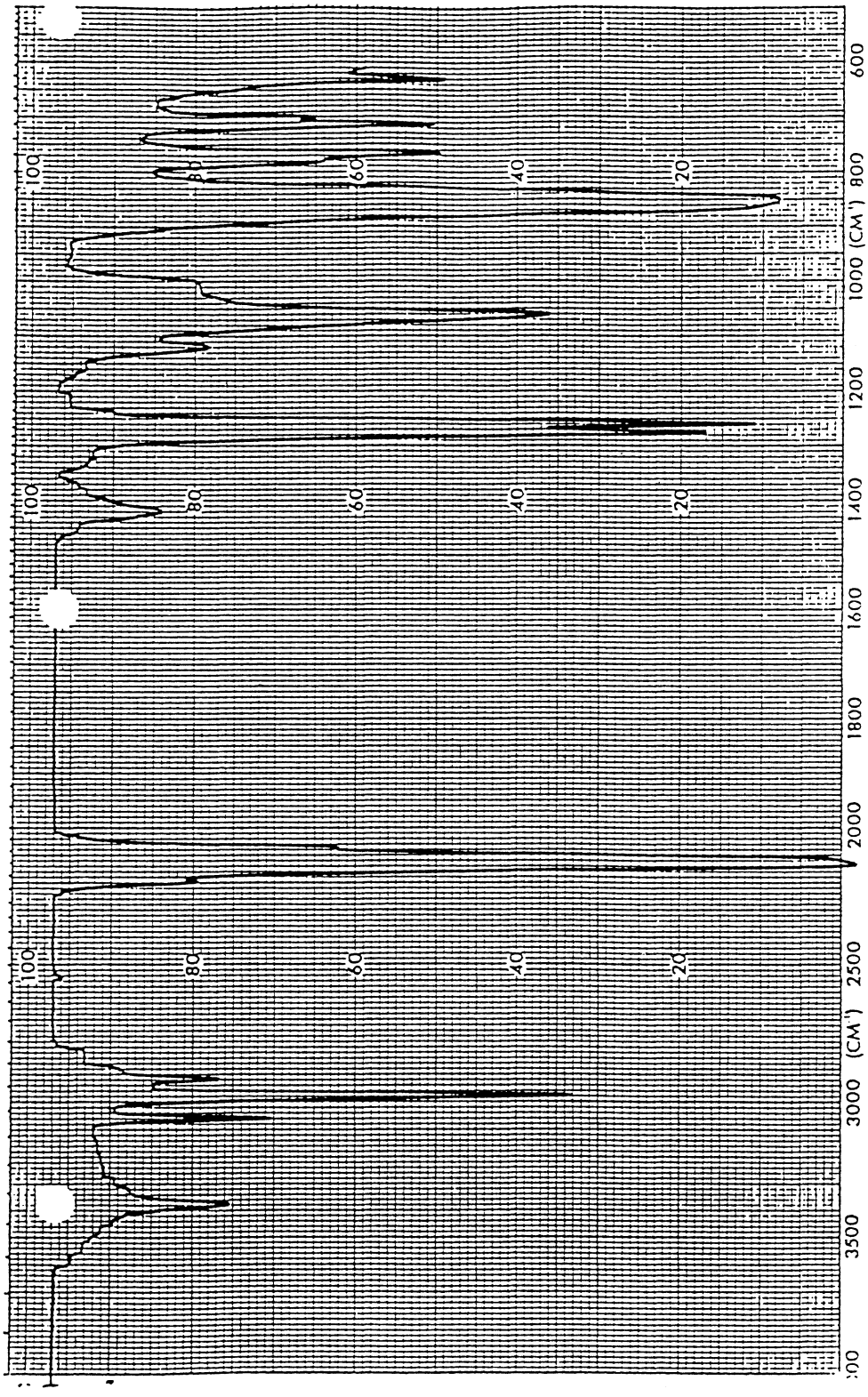
Ethoxyacetylene 52

(EtO)C≡CH



Trimethylsilylketene (34)

TMS(H)C=C=O



Trimethylsilylketene (34)

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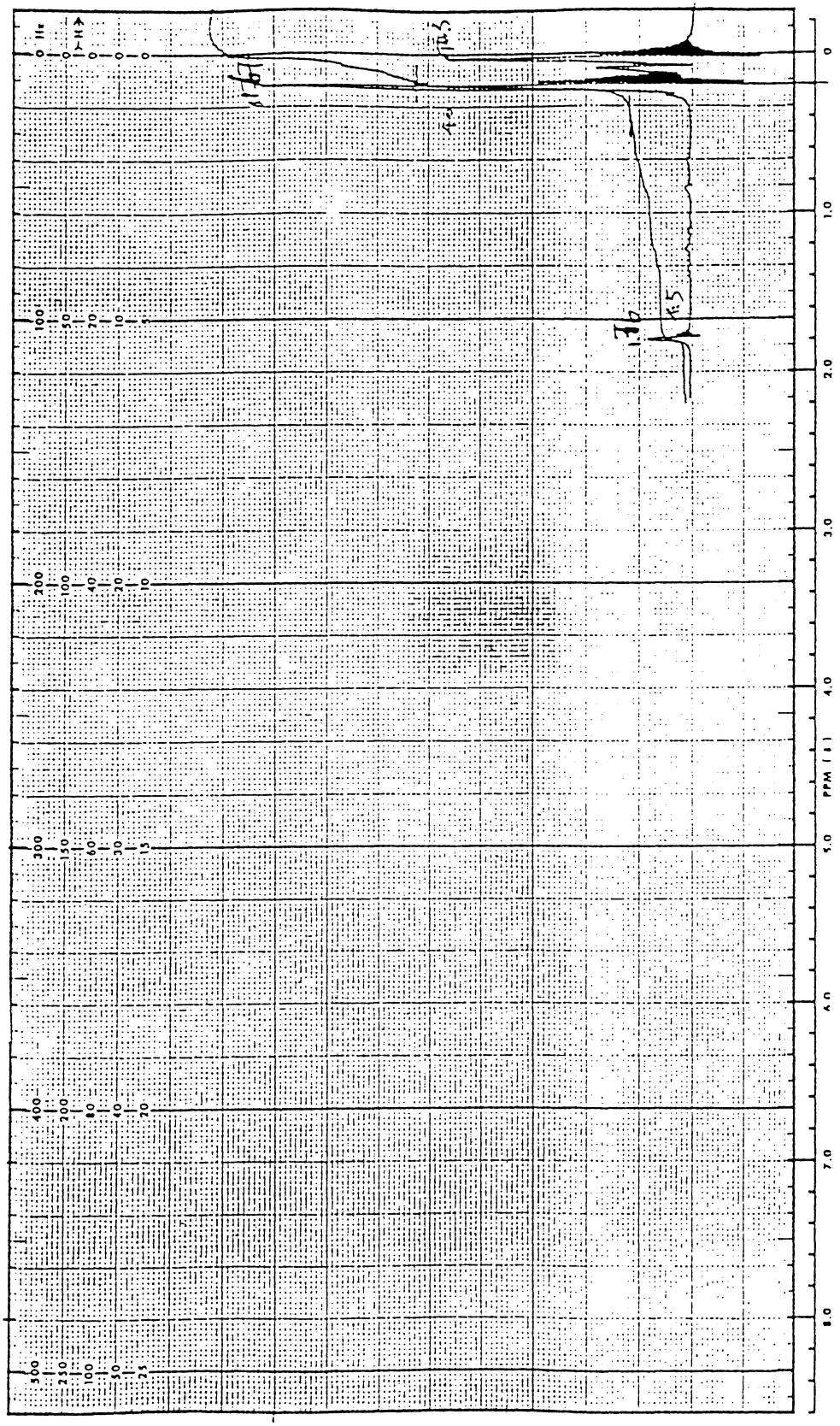
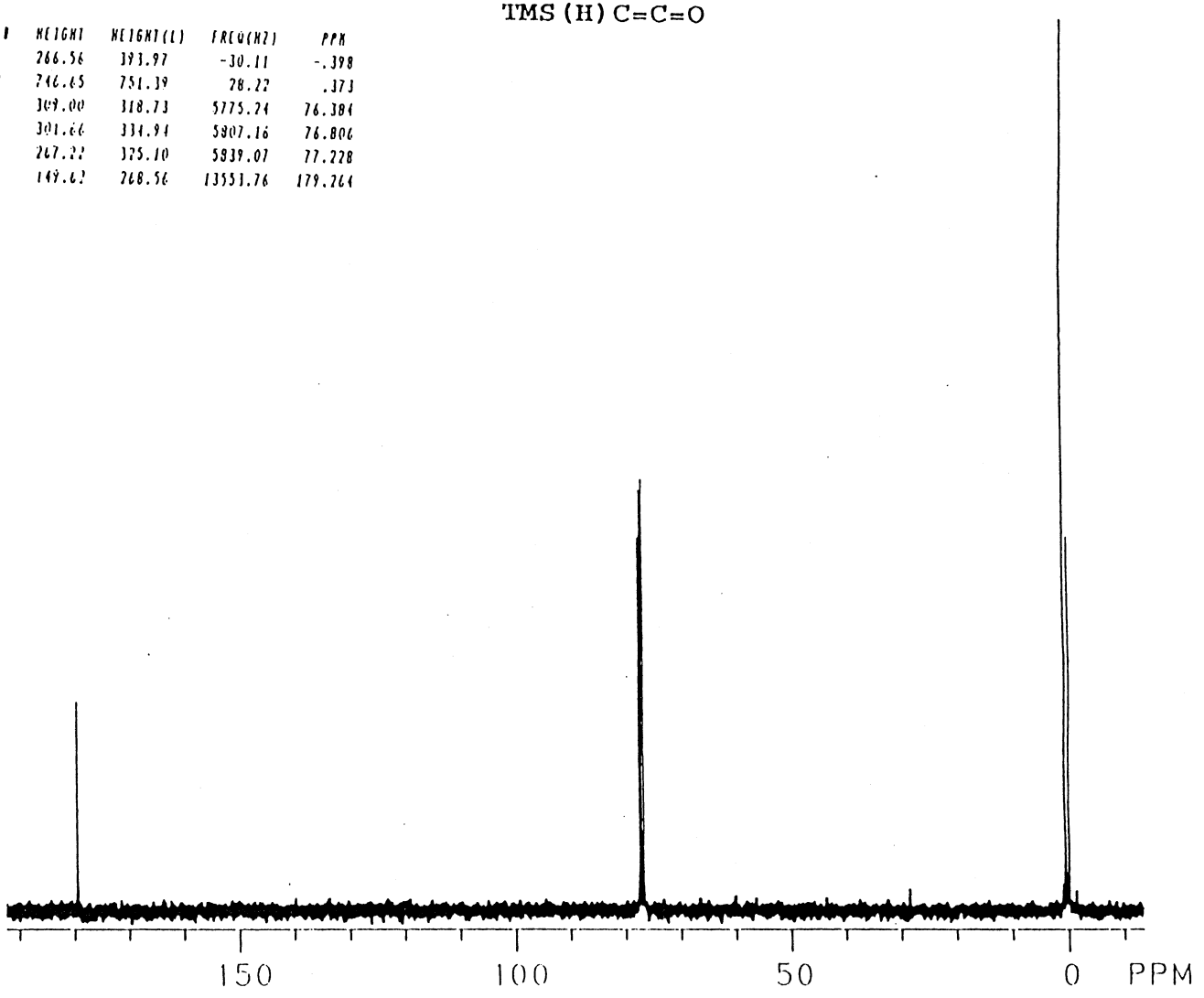


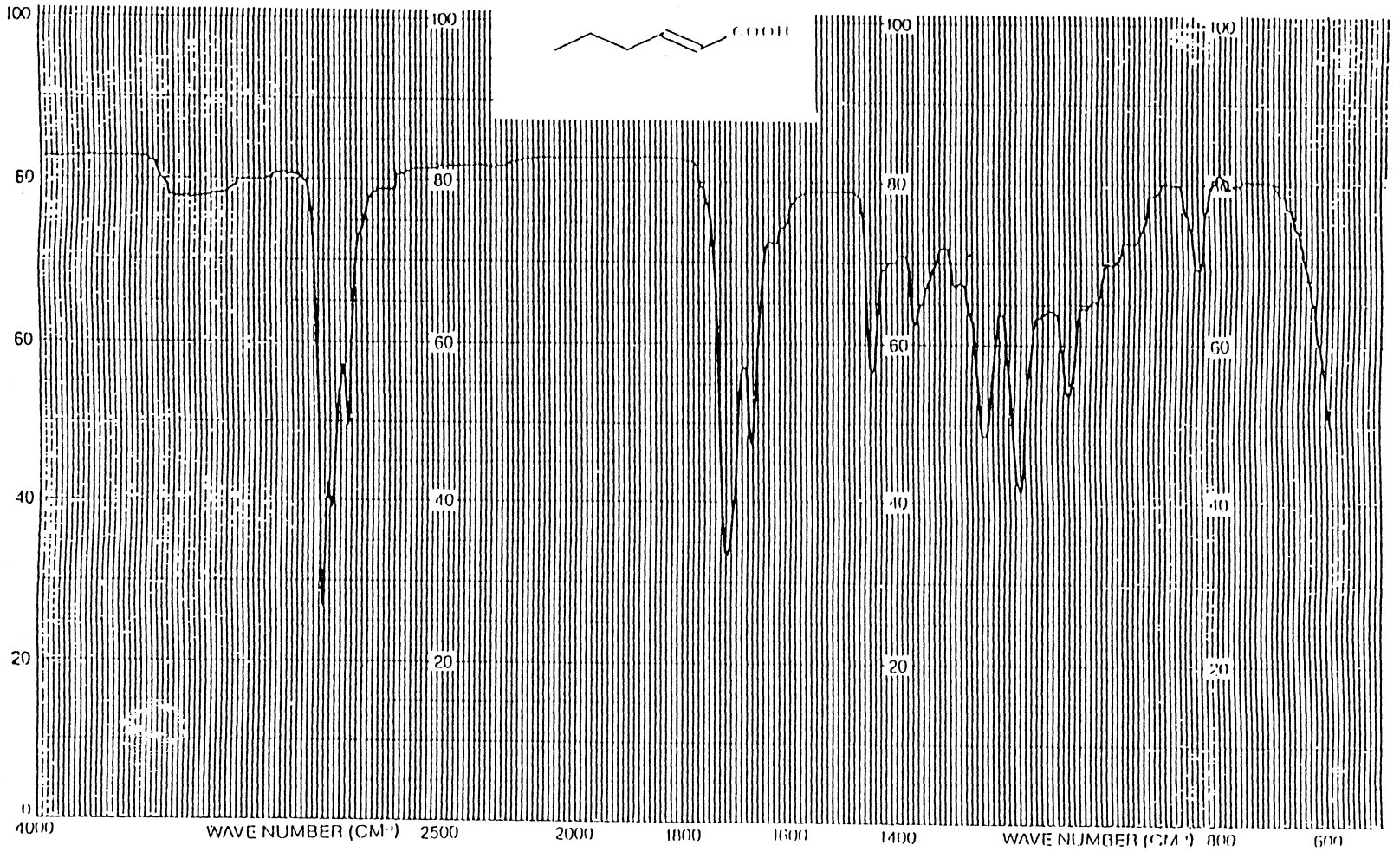
Trimethylsilylketene (34)

TMS (H) C=C=O

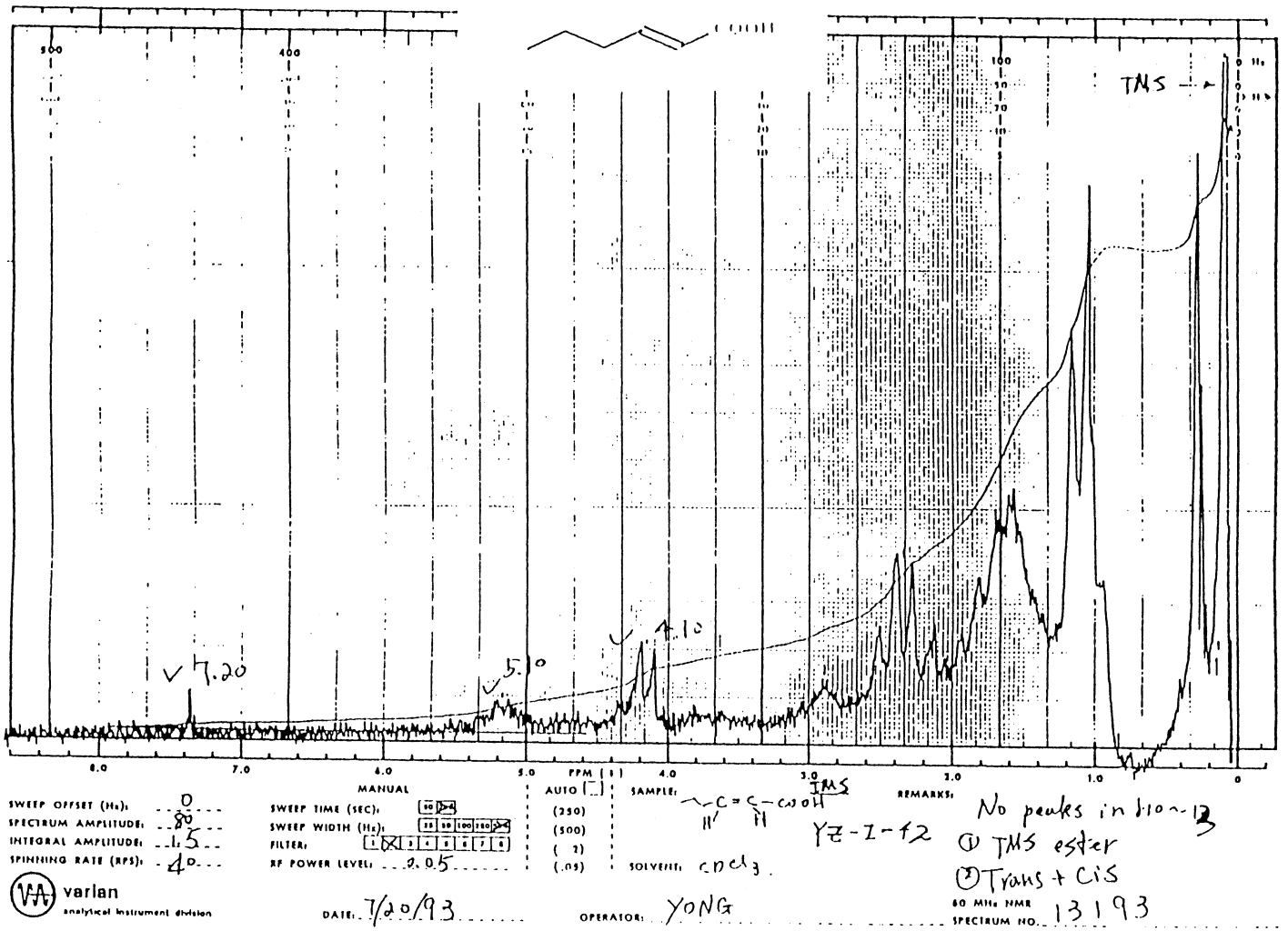
LINE#	HEIGHT	HEIGHT(I)	FREQ(HZ)	PPM
1	266.56	393.97	-30.11	-.398
2	246.65	751.39	28.22	.373
3	309.00	318.73	5775.24	76.384
4	301.66	334.94	5807.16	76.806
5	267.22	375.10	5839.07	77.228
6	149.62	768.56	13551.76	179.264



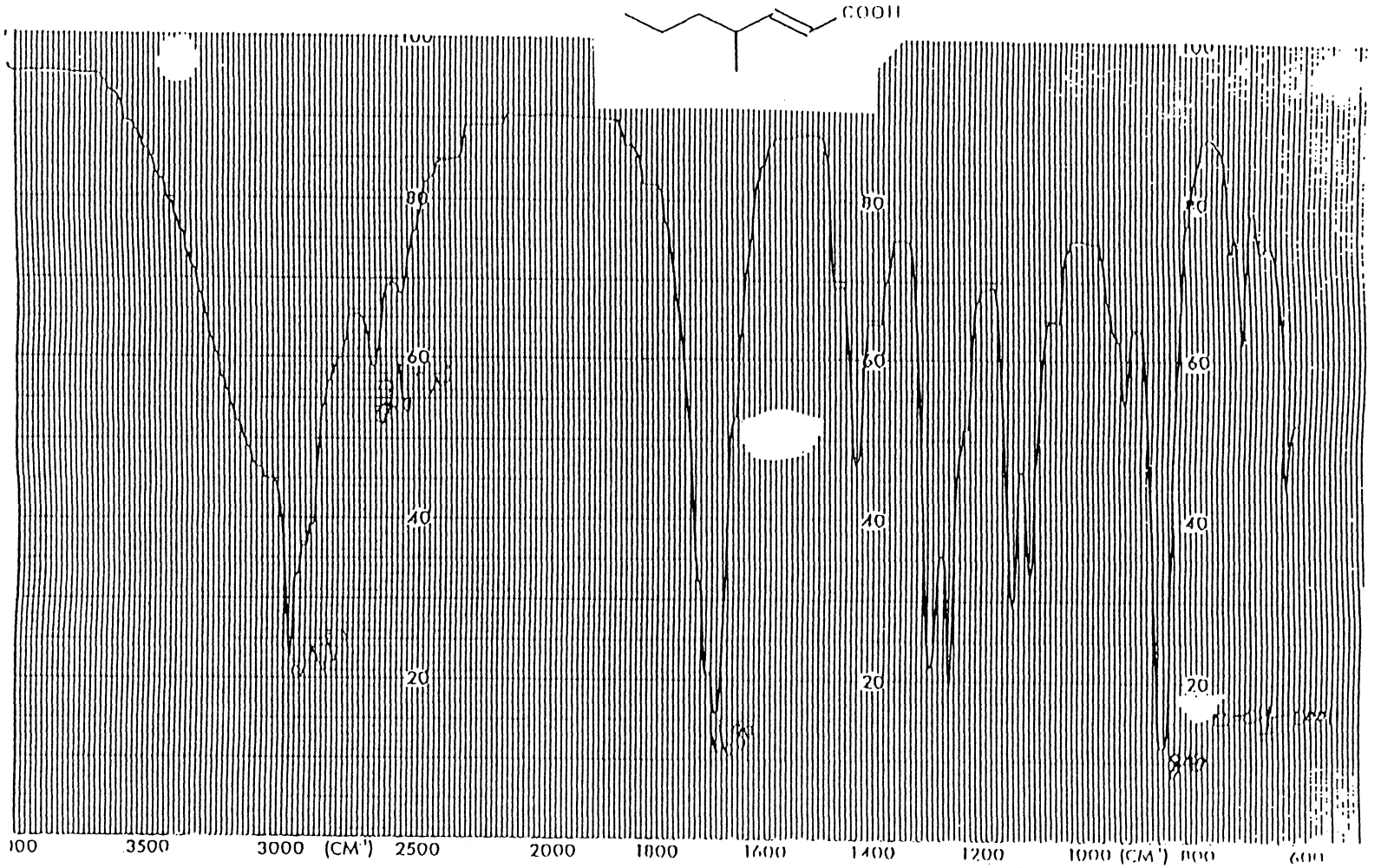
2-Hexenoic acid (51a)



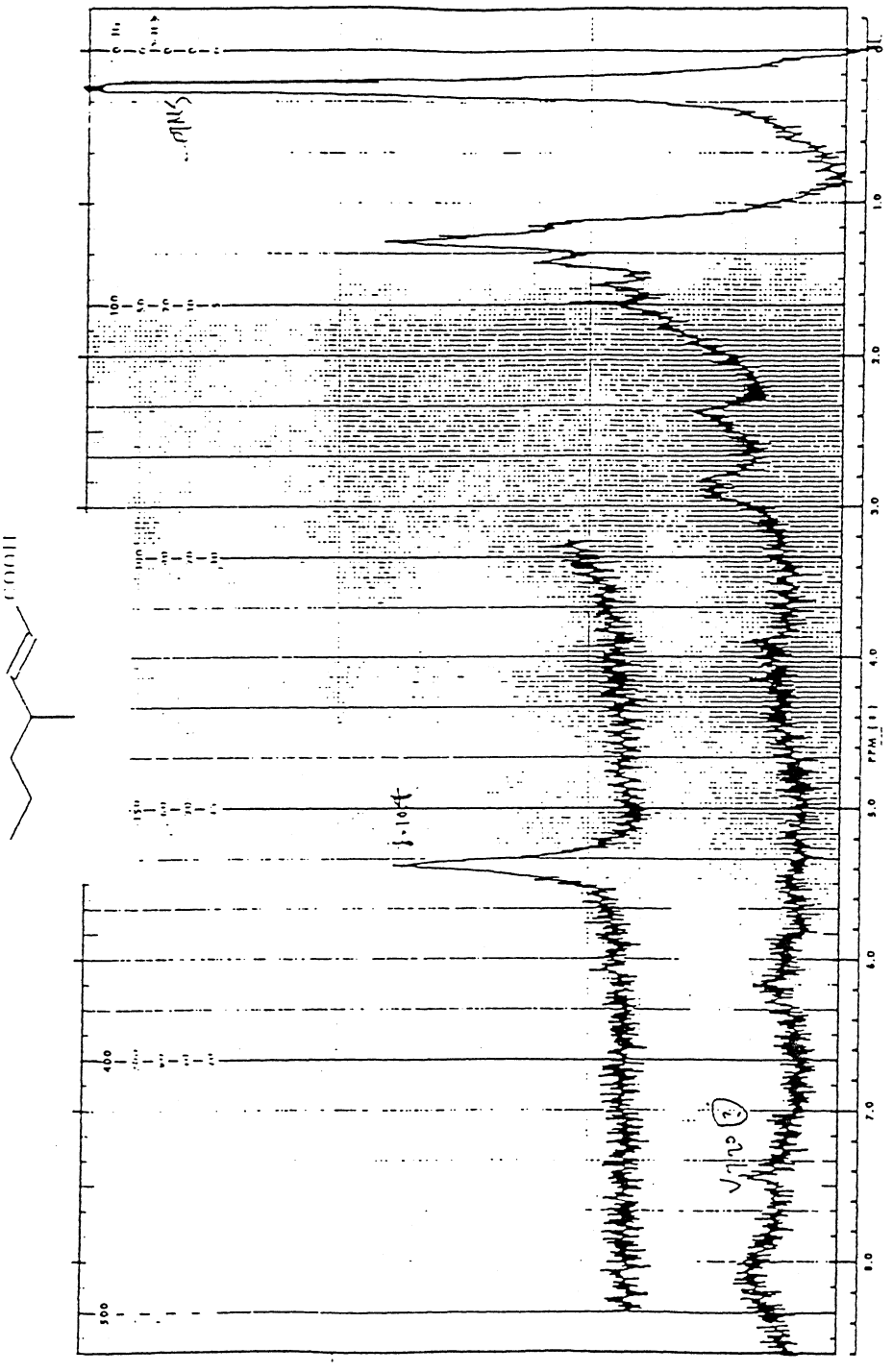
2-Hexenoic acid (51a)



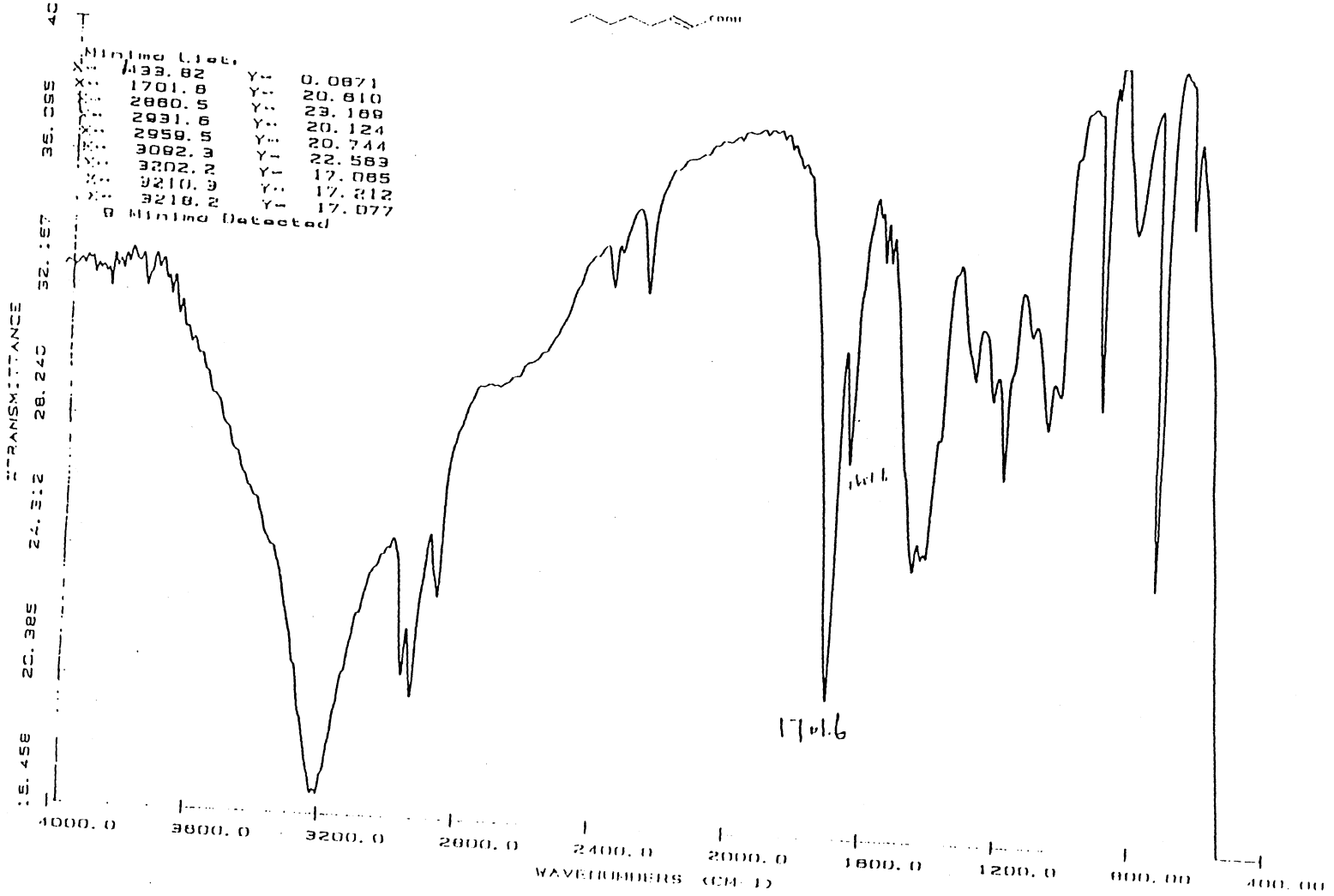
4-Methyl-2-haptenoic acid (51b)

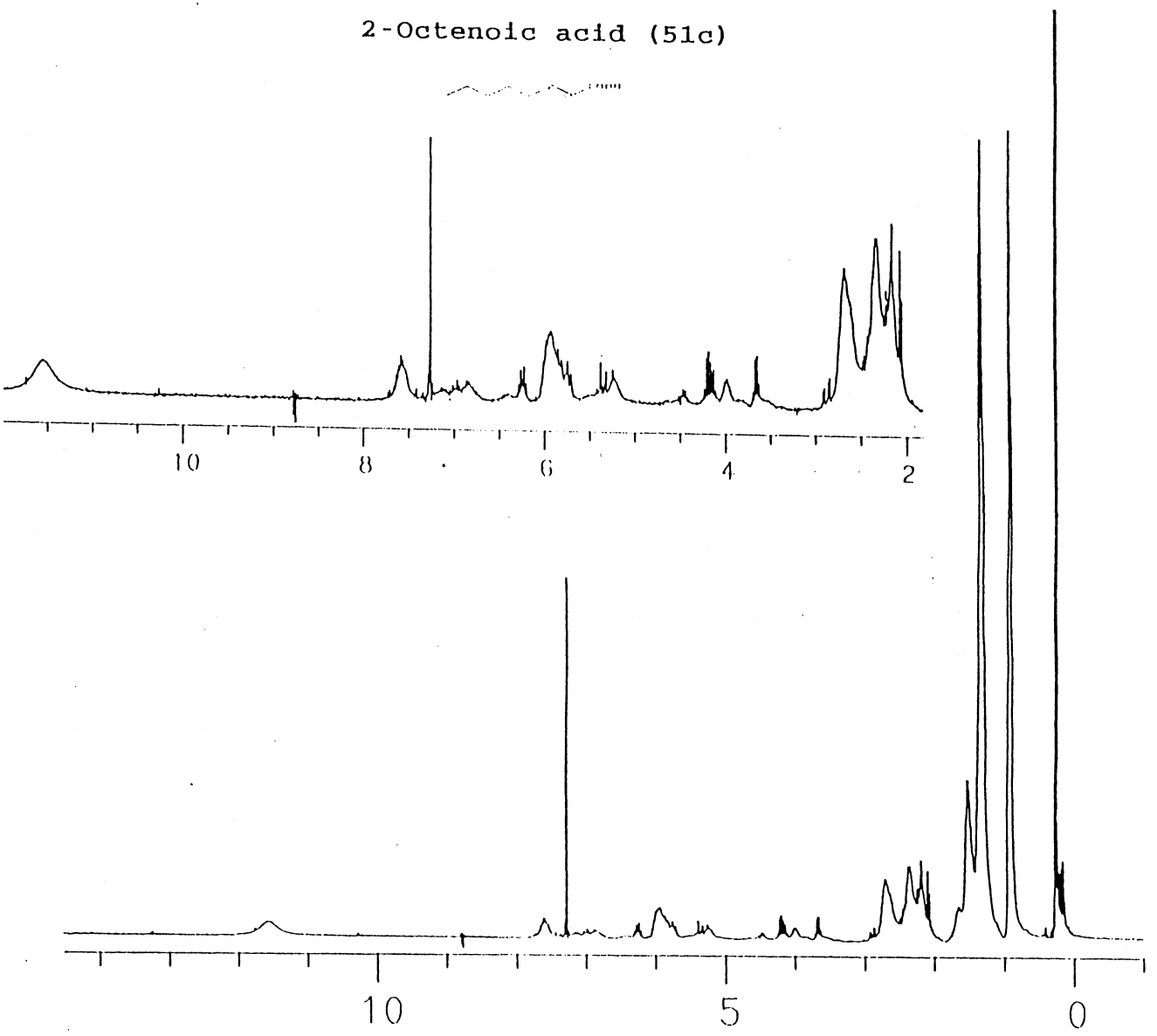


4-Methyl-2-haptenoic acid (51b)

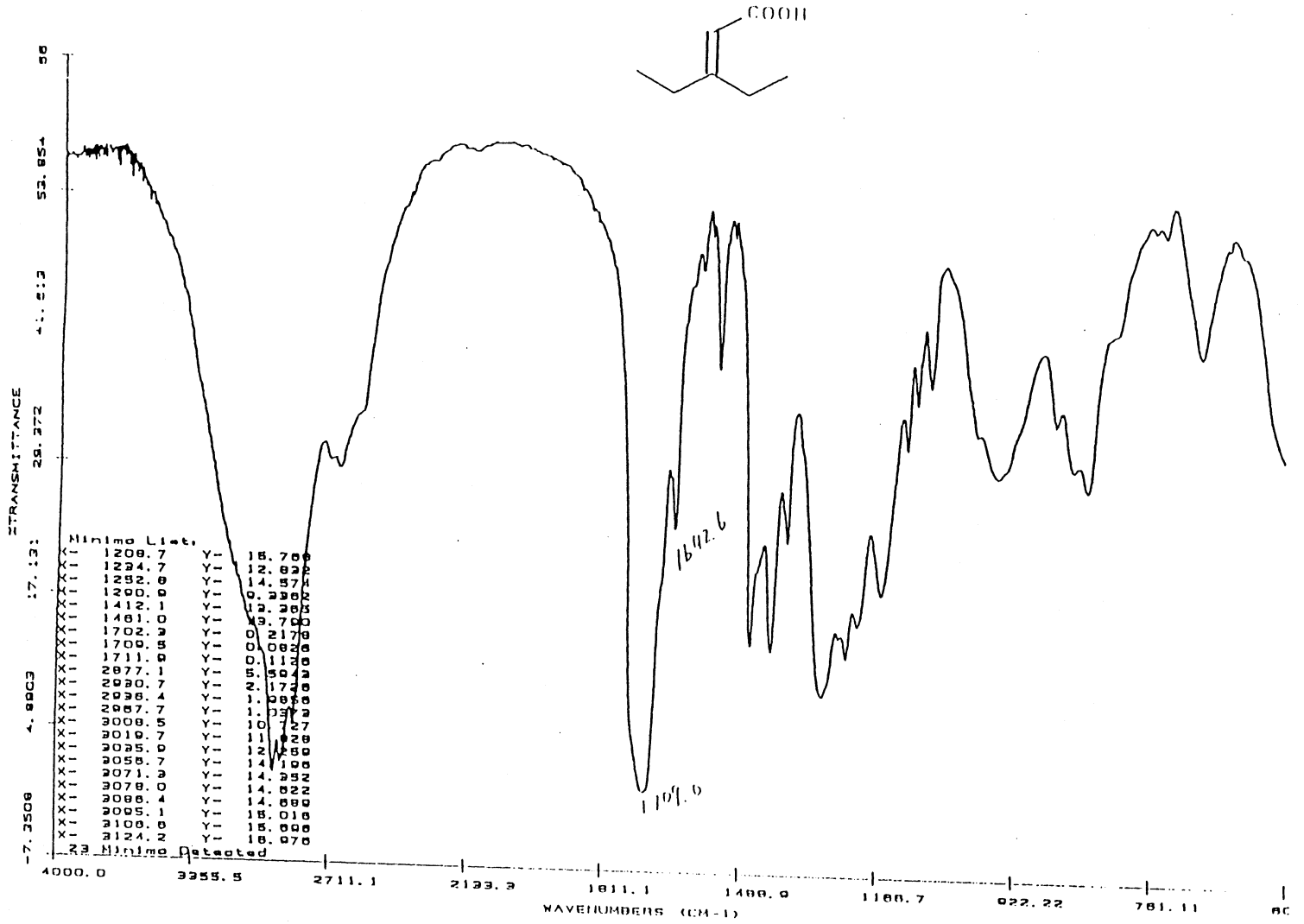


2-Octenoic acid (51c)

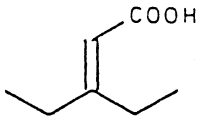


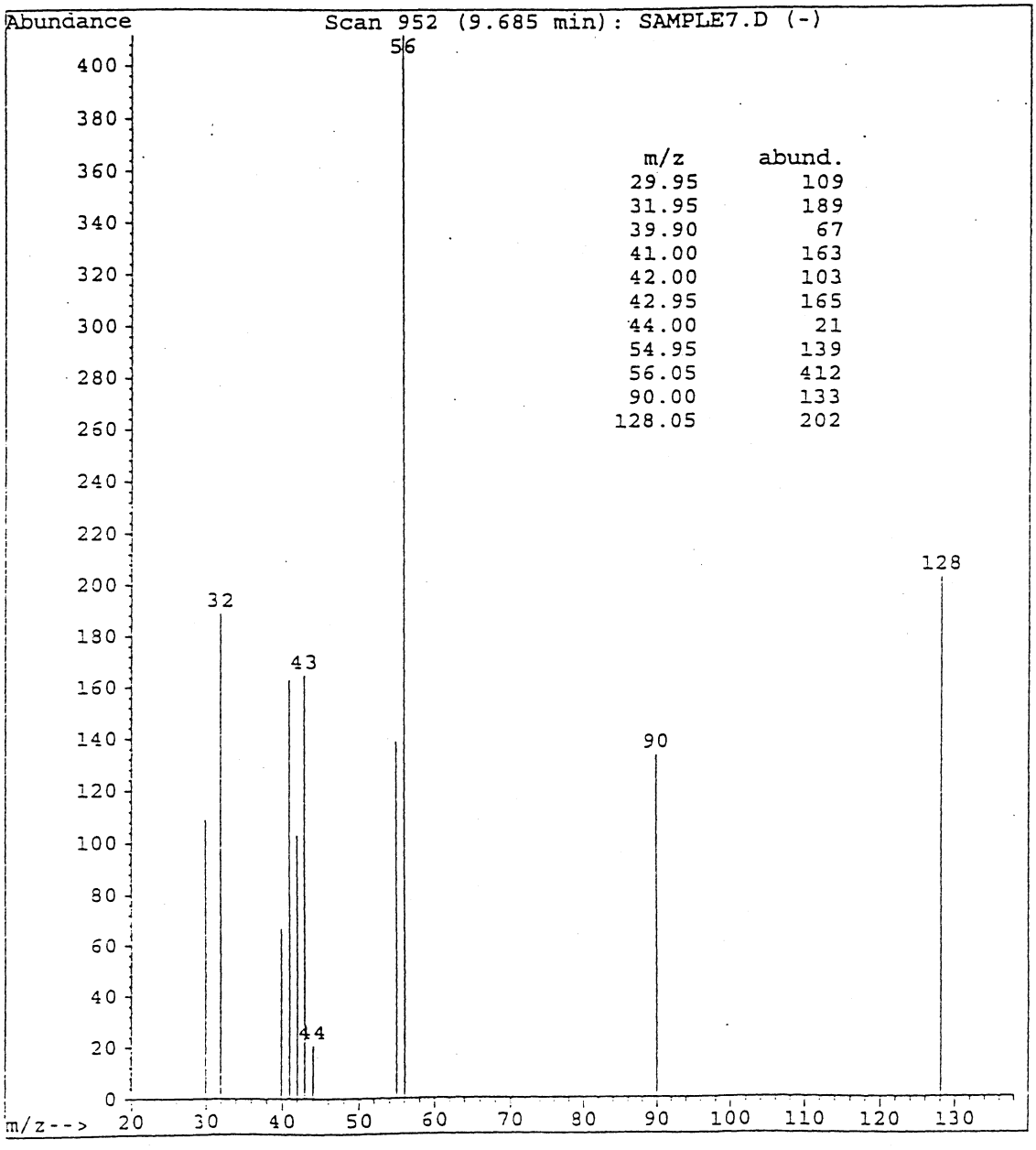

2-Octenoic acid (51c)
10
8
6
4
2
10
5
0

3-Ethyl-2-pentenoic acid (51e)

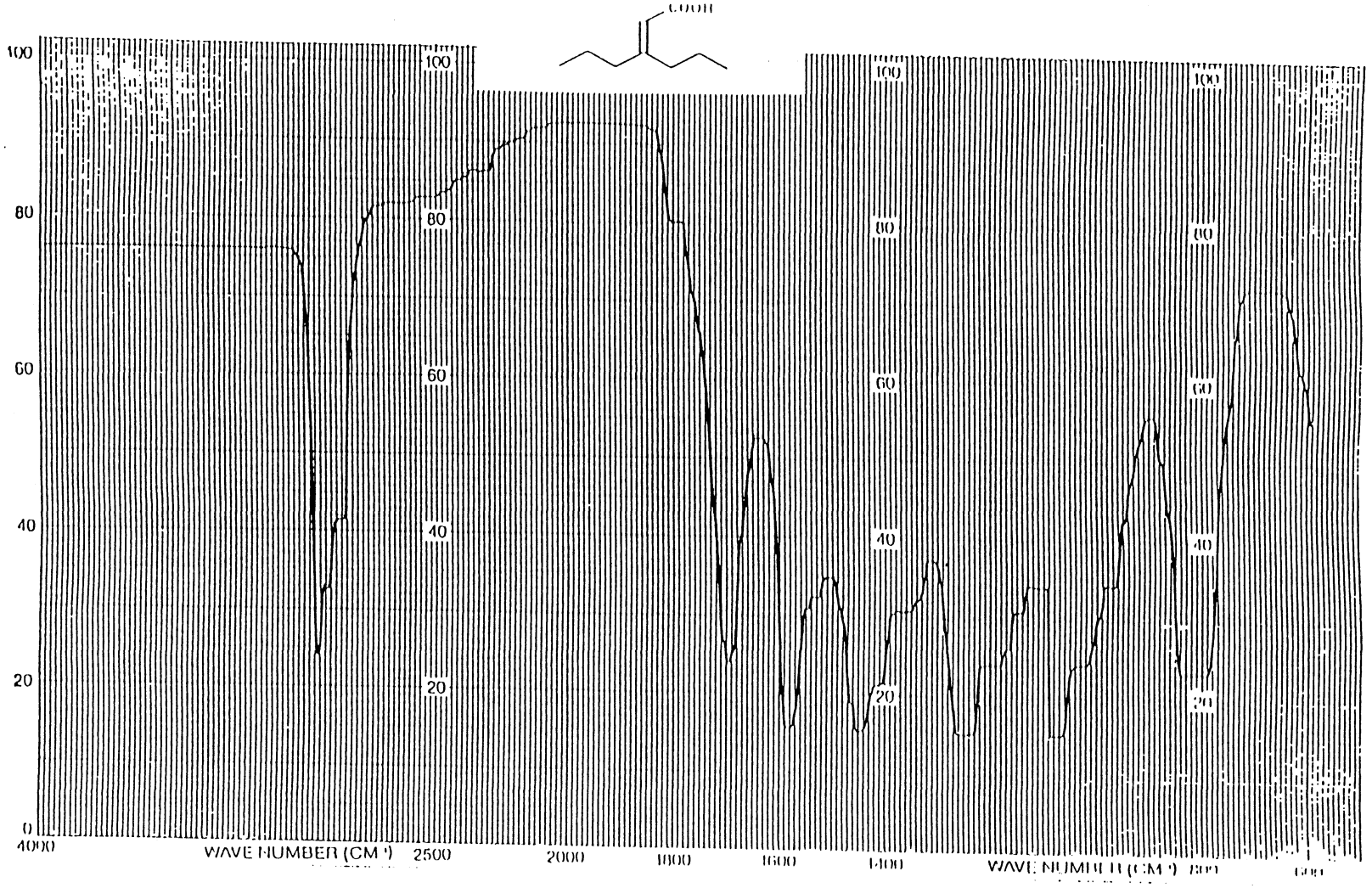


3-Ethyl-2-pentenoic acid (51e)

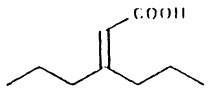




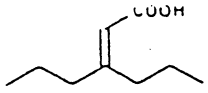
3-Propyl-2-hexenoic acid (51f)

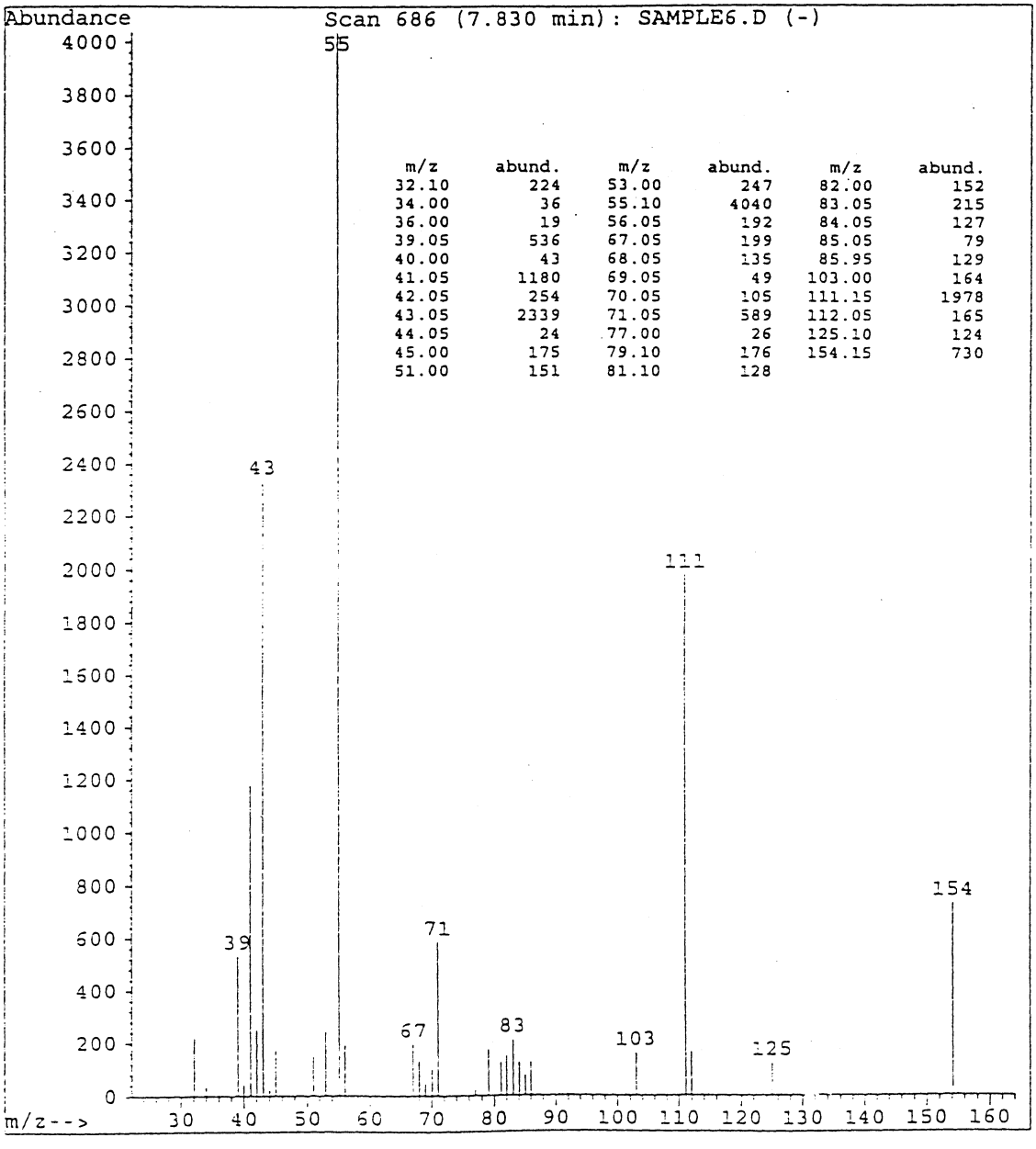


3-Propyl-2-hexenoic acid (51f)



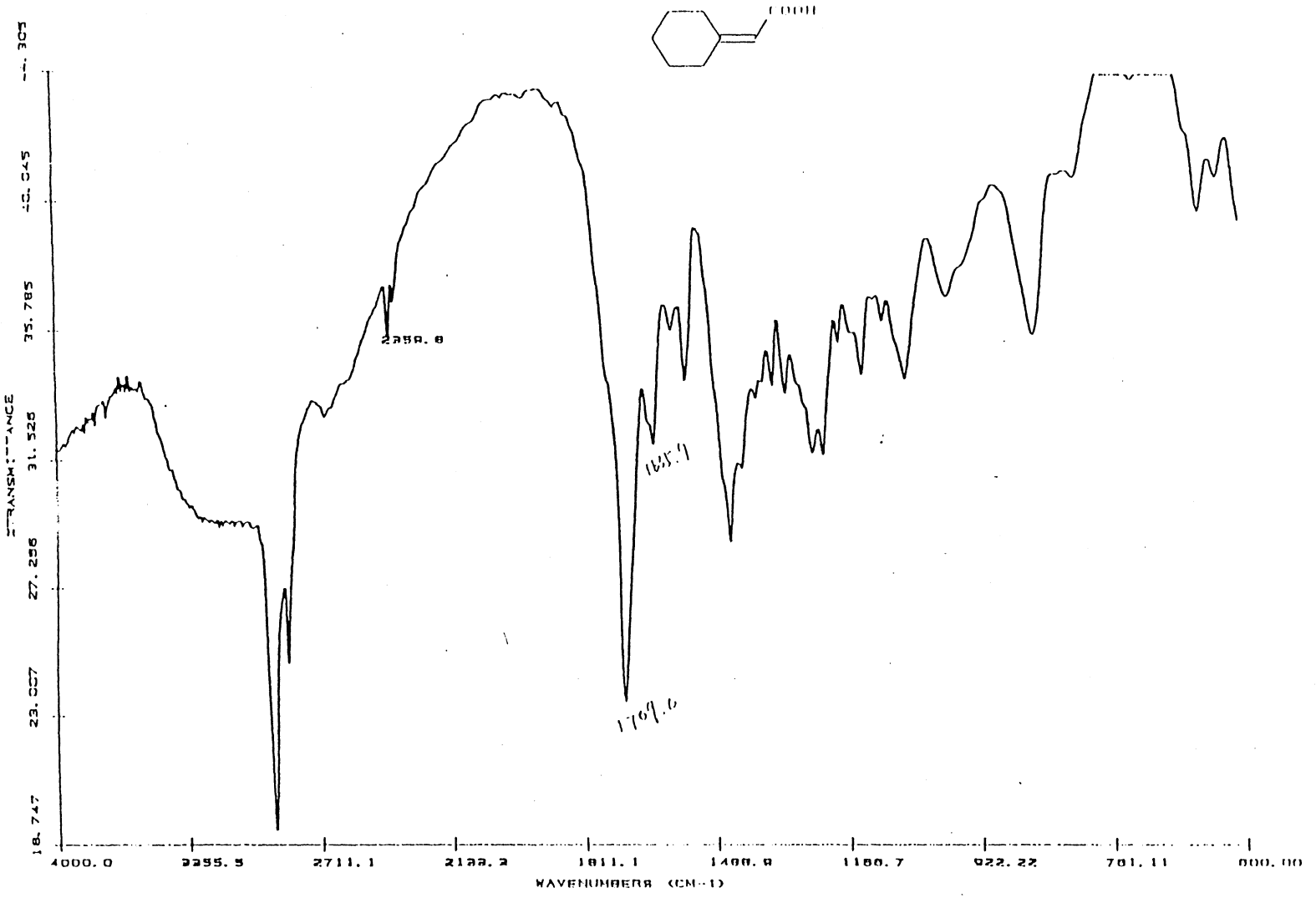
3-Propyl-2-hexenoic acid (51f)



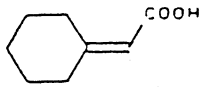


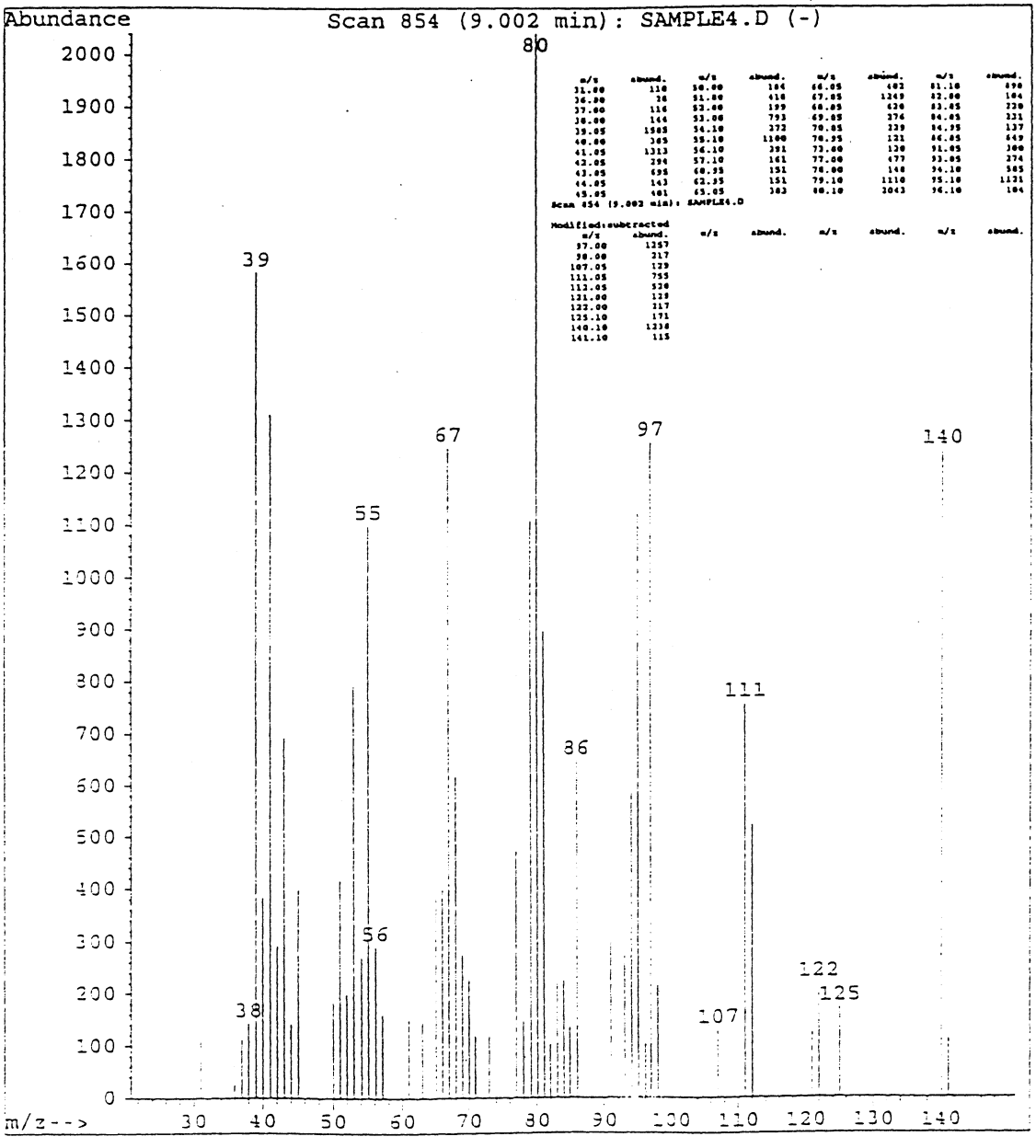
m/z	abund.	m/z	abund.	m/z	abund.
32.10	224	53.00	247	82.00	152
34.00	36	55.10	4040	83.05	215
36.00	19	56.05	192	84.05	127
39.05	536	67.05	199	85.05	79
40.00	43	68.05	135	85.95	129
41.05	1180	69.05	49	103.00	164
42.05	254	70.05	105	111.15	1978
43.05	2339	71.05	589	112.05	165
44.05	24	77.00	26	125.10	124
45.00	175	79.10	176	154.15	730
51.00	151	81.10	128		

Cyclohexylideneacetic acid (51g)

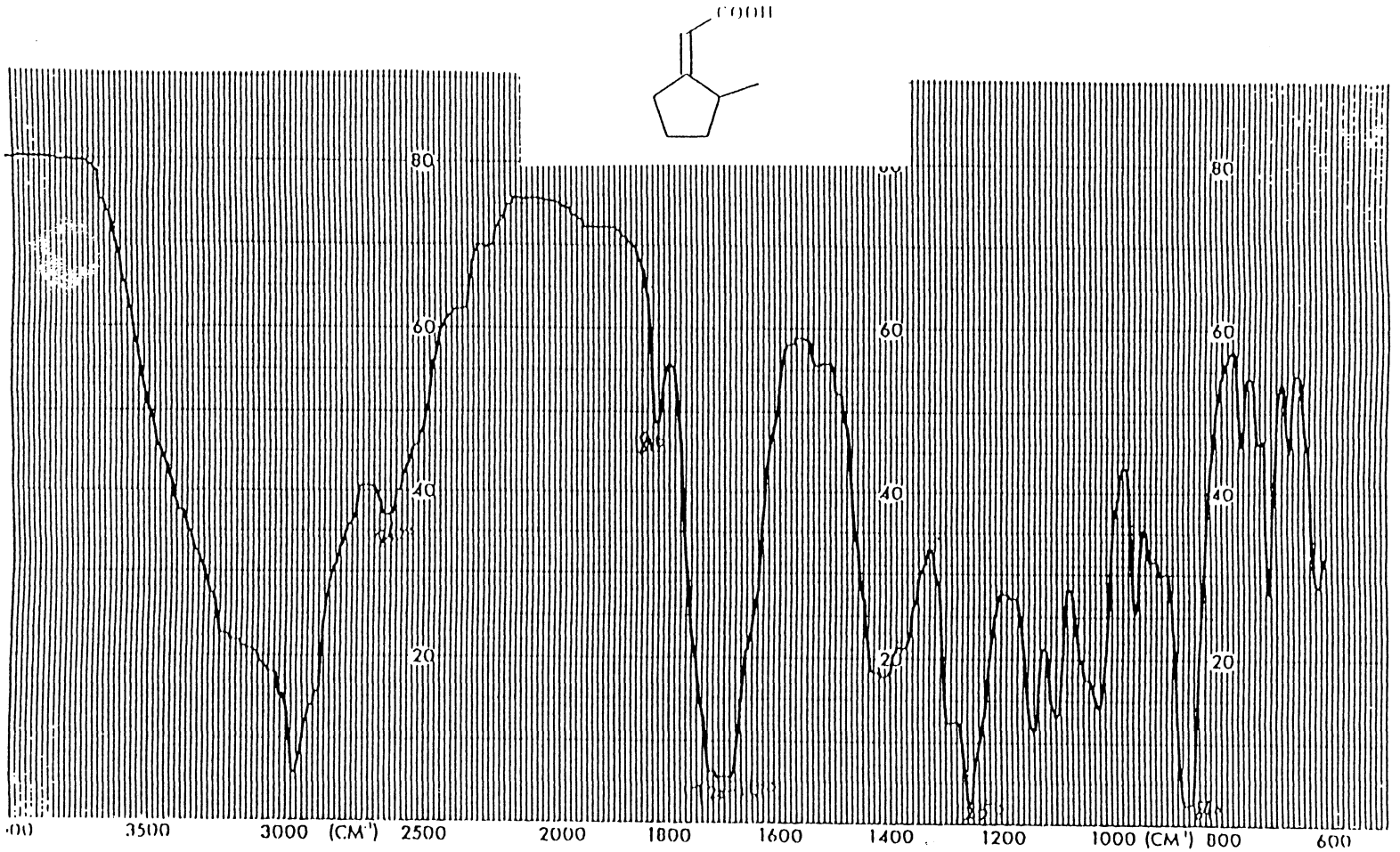


Cyclohexylideneacetic acid (51g)

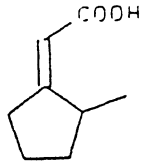


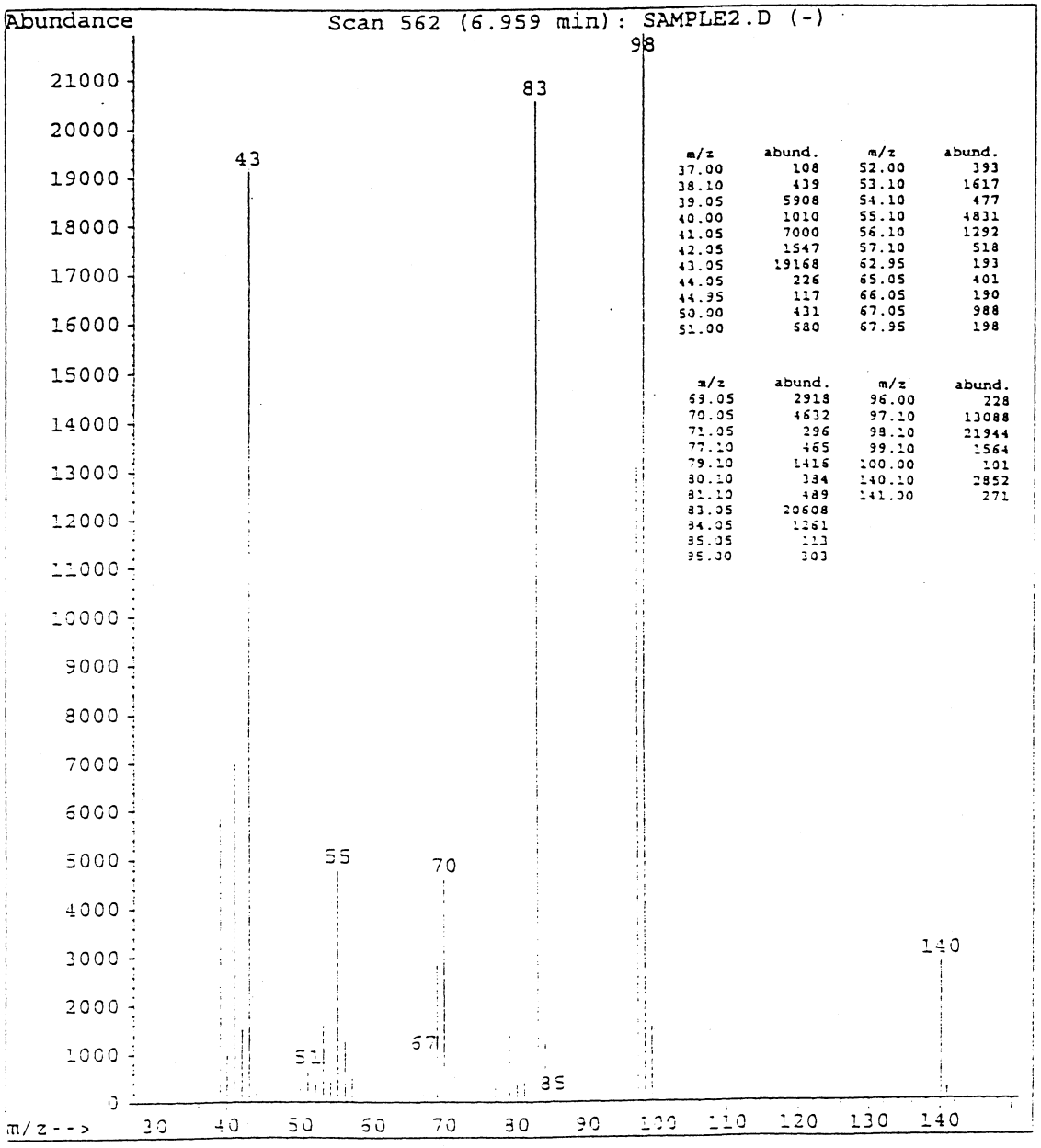


2-Methylcyclopentylideneacetic acid (51i)



2-Methylcyclopentylideneacetic acid (51i)

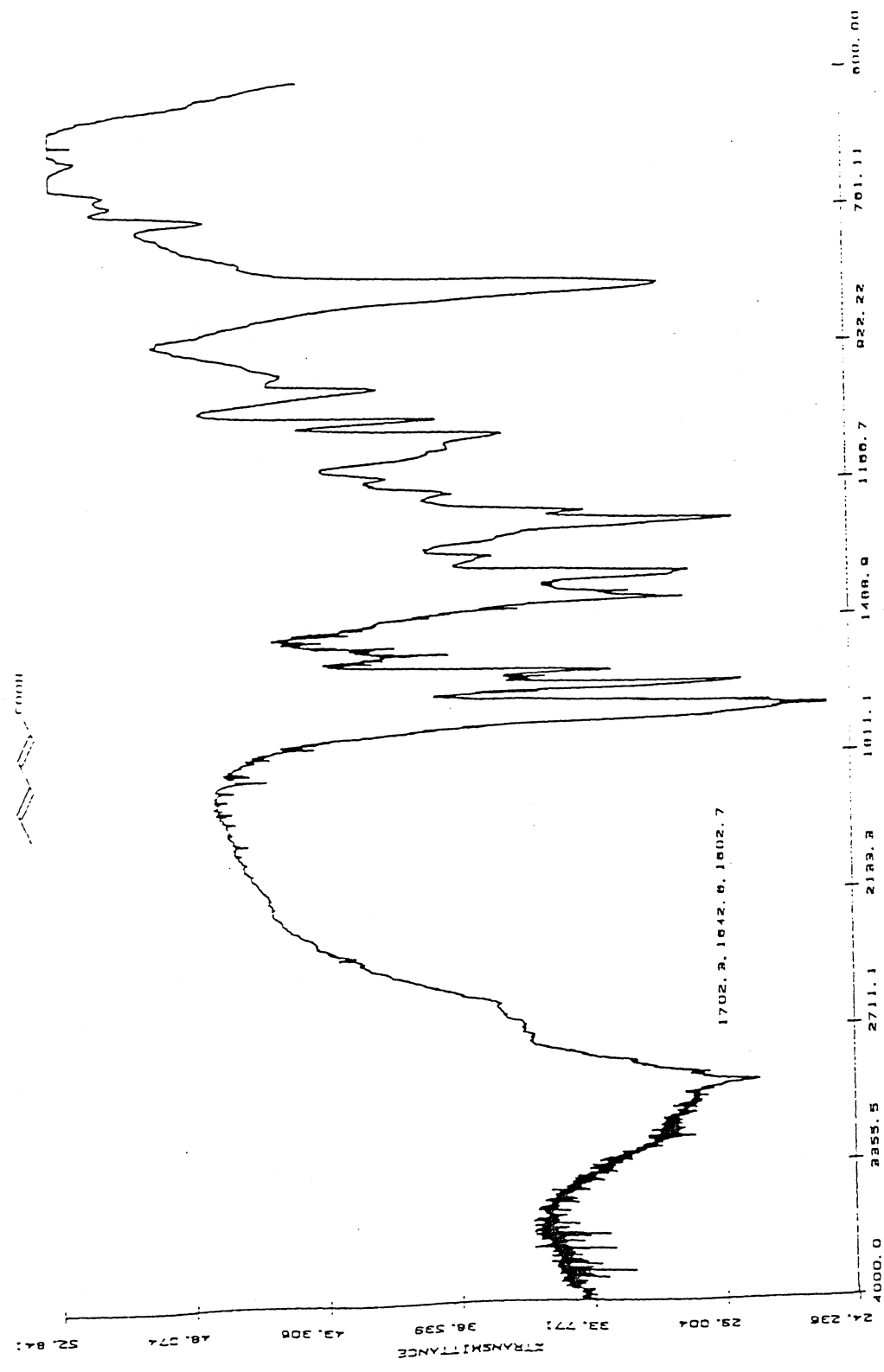




m/z	abund.	m/z	abund.
37.00	108	52.00	393
38.10	439	53.10	1617
39.05	5908	54.10	477
40.00	1010	55.10	4831
41.05	7000	56.10	1292
42.05	1547	57.10	518
43.05	19168	62.95	193
44.05	226	65.05	401
44.95	117	66.05	190
50.00	431	67.05	988
51.00	580	67.95	198

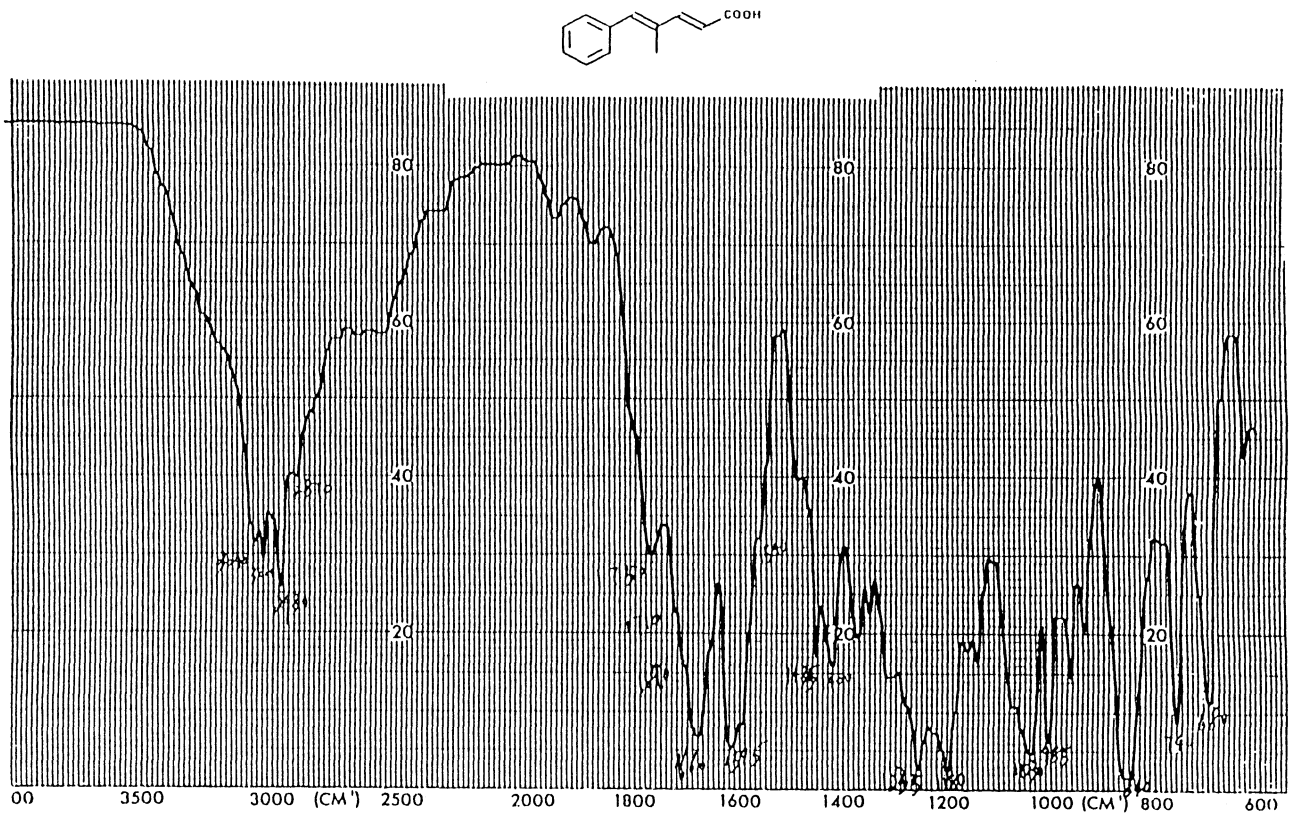
m/z	abund.	m/z	abund.
69.05	2918	96.00	228
70.05	4632	97.10	13088
71.05	296	98.10	21944
77.10	465	99.10	1564
79.10	1416	100.00	101
80.10	384	140.10	2852
81.10	489	141.00	271
83.05	20608		
84.05	1261		
85.05	113		
95.00	303		

2,4-Hexadienoic acid (51j, sorbic acid)

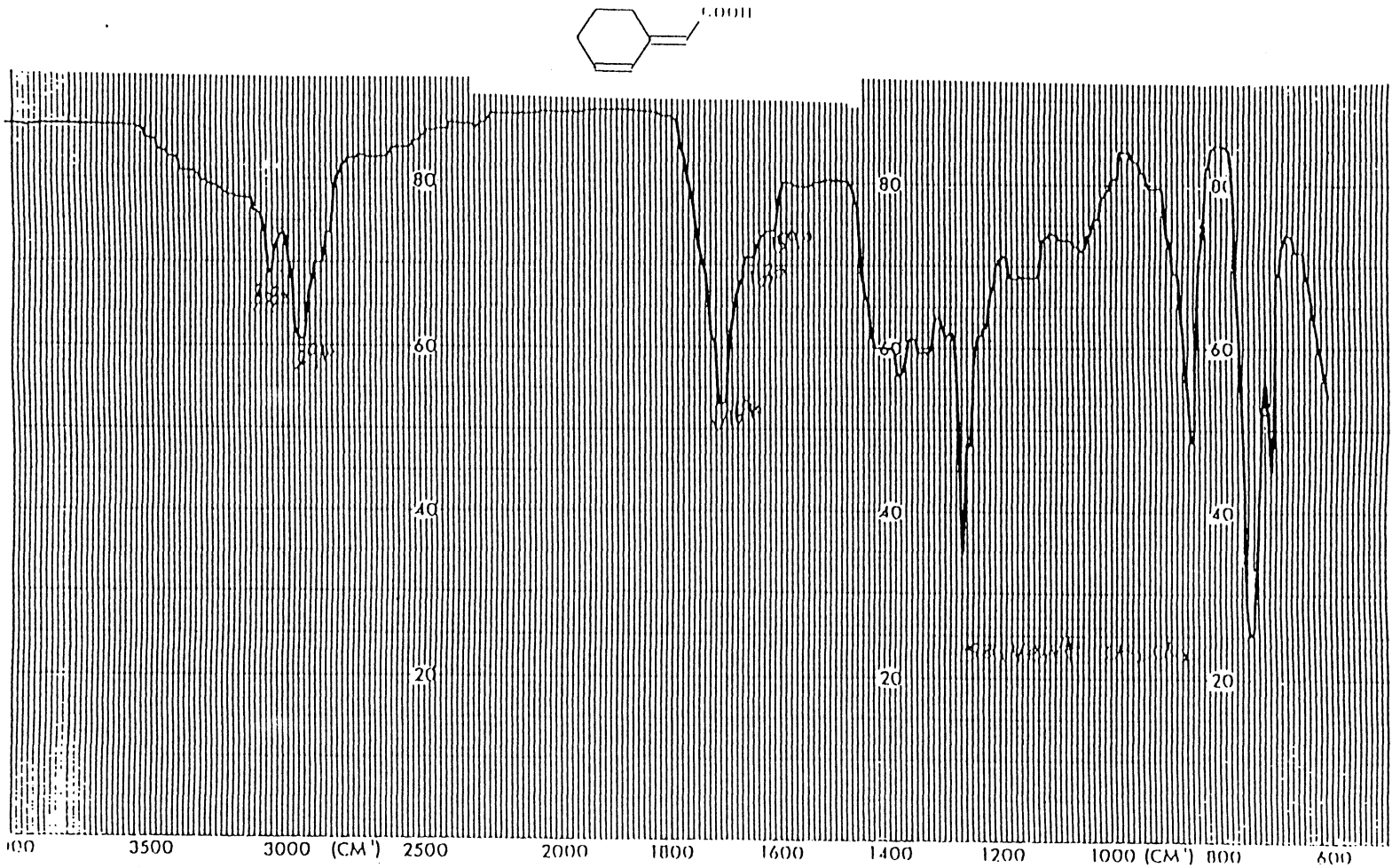


2,4-Hexadienoic acid (51j, sorbic acid)

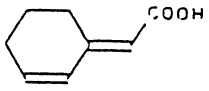
4-Methyl-5-phenyl-2,4-pentadienoic acid 51k

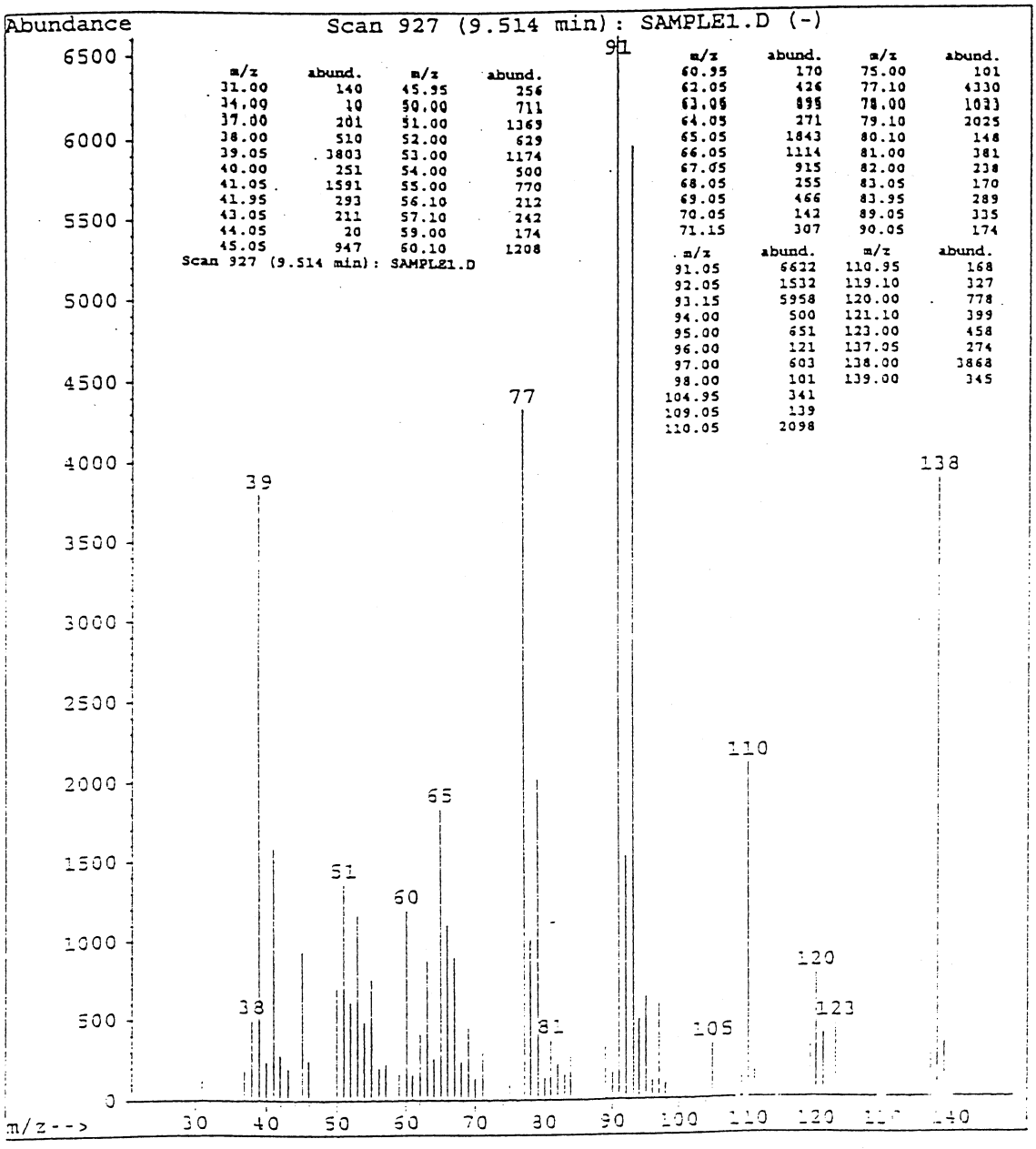


2-Cyclohexenylideneacetic acid (511)



2-Cyclohexenylideneacetic acid (511)



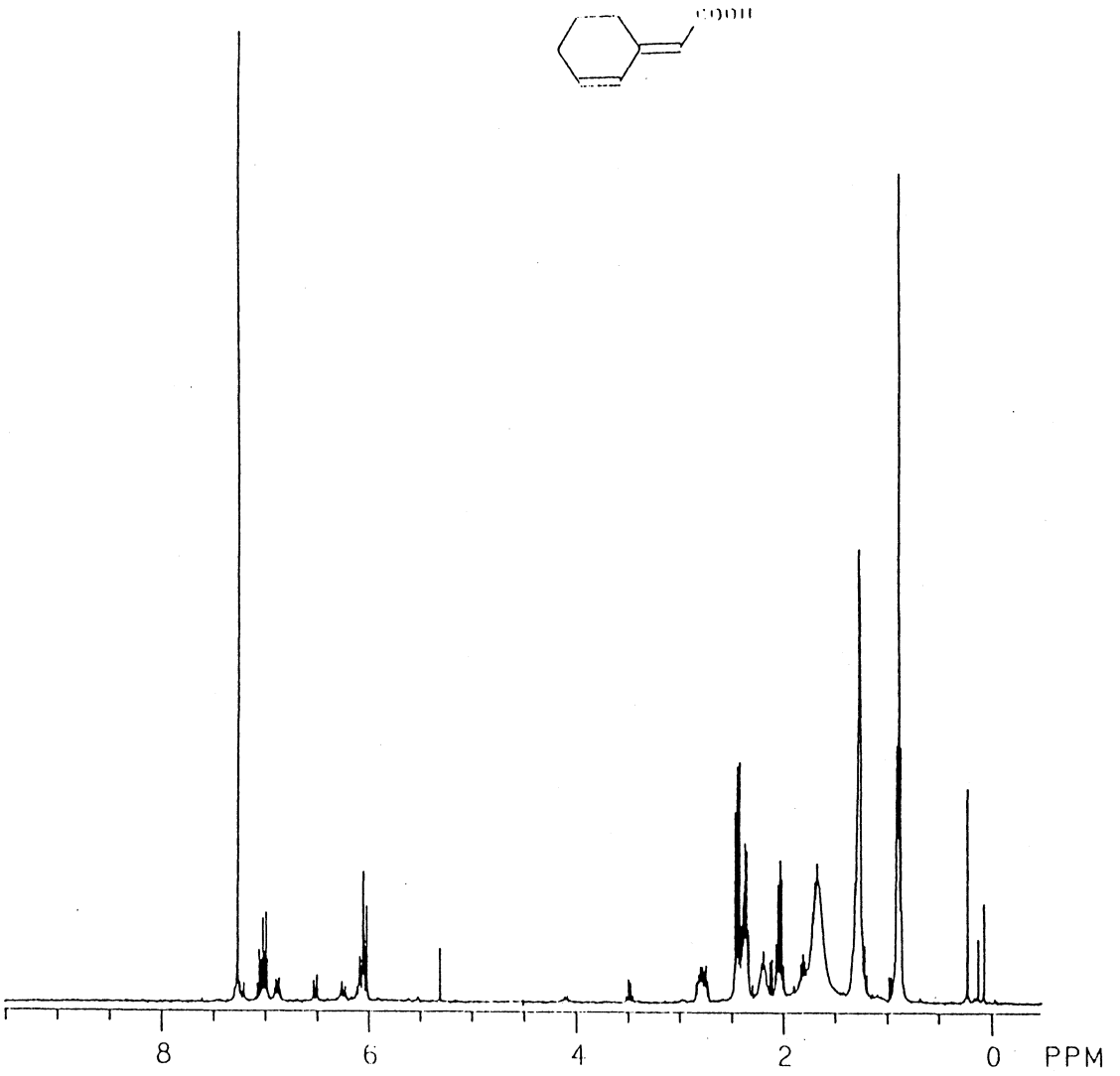


m/z	abund.	m/z	abund.
31.00	140	45.95	256
34.00	10	50.00	711
37.00	201	51.00	1369
38.00	510	52.00	629
39.05	3803	53.00	1174
40.00	251	54.00	500
41.05	1591	55.00	770
41.95	293	56.10	212
43.05	211	57.10	242
44.05	20	59.00	174
45.05	947	60.10	1208

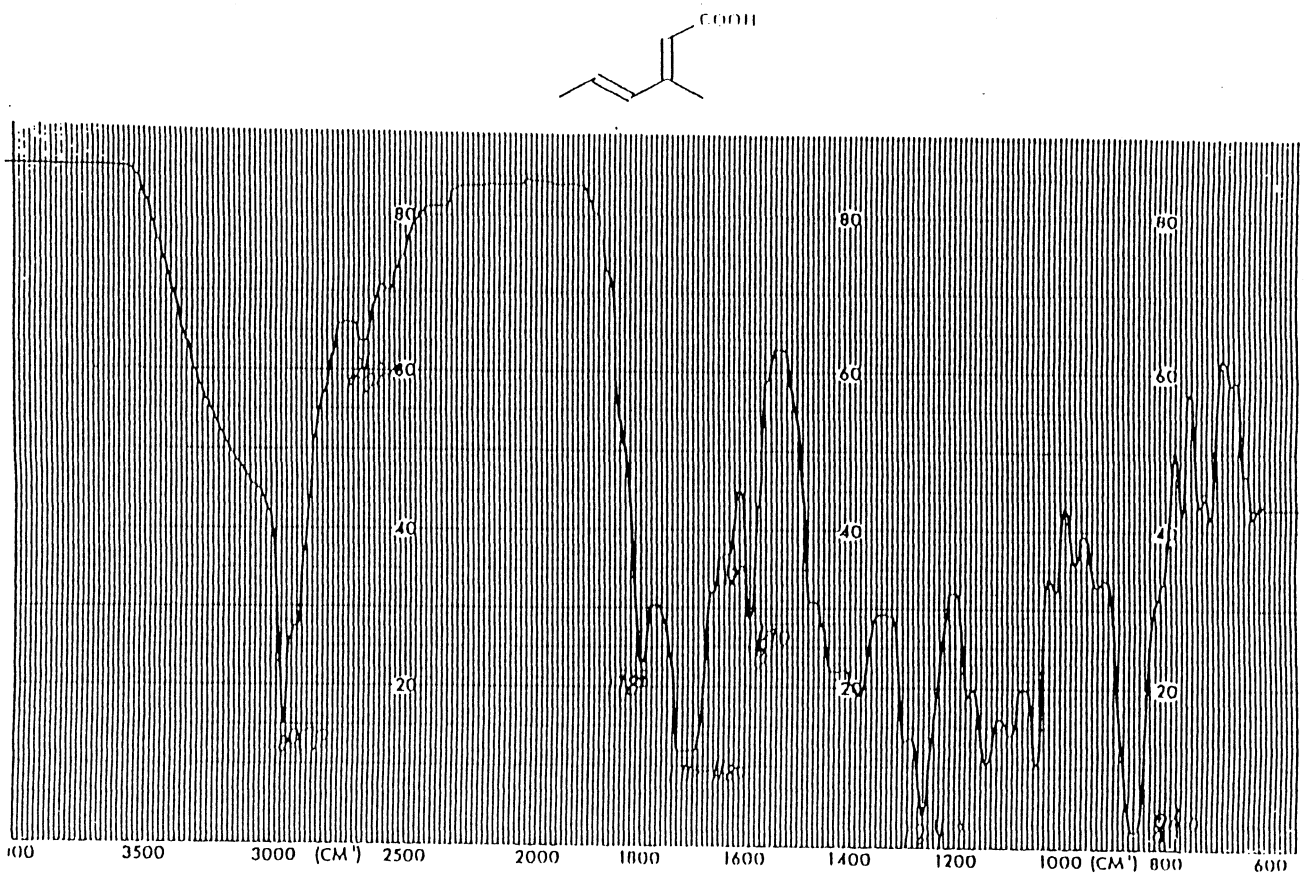
Scan 927 (9.514 min): SAMPLE1.D

m/z	abund.	m/z	abund.
60.95	170	75.00	101
62.05	426	77.10	4330
63.05	895	78.00	1033
64.05	271	79.10	2025
65.05	1843	80.10	148
66.05	1114	81.00	381
67.05	915	82.00	238
68.05	255	83.05	170
69.05	466	83.95	289
70.05	142	89.05	335
71.15	307	90.05	174
m/z	abund.	m/z	abund.
91.05	6622	110.95	168
92.05	1532	119.10	327
93.15	5958	120.00	778
94.00	500	121.10	399
95.00	651	123.00	458
96.00	121	137.05	274
97.00	603	138.00	3868
98.00	101	139.00	345
104.95	341		
109.05	139		
110.05	2098		

2-Cyclohexenylideneacetic acid (511)



3-Methylhexa-2,4-dienoic acid (51m)



3-Methylhexa-2,4-dienoic acid (51m)