2000

Investigations into the Synthesis and Transformations of an Epoxy β-Lactone

John Farrell
Eastern Illinois University

THESIS/FIELD EXPERIENCE PAPER
REPRODUCTION CERTIFICATE

TO: Graduate Degree Candidates (who have written formal theses)

SUBJECT: Permission to Reproduce Theses

The University Library is receiving a number of request from other institutions asking permission to reproduce dissertations for inclusion in their library holdings. Although no copyright laws are involved, we feel that professional courtesy demands that permission be obtained from the author before we allow these to be copied.

PLEASE SIGN ONE OF THE FOLLOWING STATEMENTS:

Booth Library of Eastern Illinois University has my permission to lend my thesis to a reputable college or university for the purpose of copying it for inclusion in that institution's library or research holdings.

_____ 01-16-01

Author's Signature Date

I respectfully request Booth Library of Eastern Illinois University **NOT** allow my thesis to be reproduced because:

_____

_____

_____

_____ _____

Author's Signature Date

INVESTIGATIONS INTO THE SYNTHESIS AND TRANSFORMATIONS OF AN EPOXY β-LACTONE

BY,

John Farrell

B.S. in Chemistry

Eastern Illinois University

Charleston, Illinois

December, 2000

Submitted in partial fulfillment of the requirements for the degree of Master of Science in

Chemistry at the Graduate School of Eastern Illinois University

CHARLESTON, ILLINOIS
2000

Submitted in partial fulfillment of the requirements for the degree of Master of Science in

Chemistry at the Graduate School of Eastern Illinois University

CHARLESTON, ILLINOIS
2000

INVESTIGATIONS INTO THE SYNTHESIS AND TRANSFORMATIONS OF AN EPOXY β-LACTONE

BY,

John Farrell

THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF

MASTER OF SCIENCE IN CHEMISTRY

IN THE GRADUATE SCHOOL, EASTERN ILLINOIS UNIVERSITY
CHARLESTON, ILLINOIS

2000

I HEREBY RECOMMEND THIS THESIS BE ACCEPTED AS FULFILLING THIS PART OF THE GRADUATE DEGREE CITED ABOVE

1/8/01
DATE

ADVISER

1/08/01
DATE

DEPARTMENT HEAD

Certificate of Comprehensive Knowledge

For the Awarding of a Graduate Degree

Department of Chemistry
Eastern Illinois University

We certify that _____ SS# _____, has successfully demonstrated comprehension of her/his field of study and recommend that the degree

Master of Science in Chemistry

be awarded.

Signatures of Examining Committee

_____

_____

_____

_____

Date 12/5/00 Advisor _____

Rev.: 7/99

Table of Contents

Abstract

In connection with the continuing interests in the stereoselective rearrangements of β-lactones, an investigation of the synthesis and transformations of the epoxy β-lactone 4-(1,2-epoxypentyl)-3-trimethylsilyloxetan-2-one was undertaken. Two synthetic strategies to the desired epoxy β-lactone were studied. The first route was a two-step reaction sequence involving the aldol reaction of trimethylsilylacetic acid with (2*R*,3*S*)-epoxyhexanal, followed by lactonization of the resulting β-hydroxy acid with benzenesulfonyl chloride. Complications in preparing the requisite β-hydroxy acids under typical aldol reaction conditions rendered this route unworkable. The complexity and intractability of the aldol reaction mixtures was attributed to the multiple possibilities of intermolecular reactivity between trimethylsilylacetic acid dianion and (2*S*,3*S*)-epoxyhexanal, in addition to intramolecular transformations of the highly functionalized aldol adduct. The second synthetic route investigated was based on the [2+2] cycloaddition reaction between trimethylsilylketene and (2*R*,3*S*)-epoxyhexanal. No direct evidence supporting the formation of epoxy-β-lactone was found; however, the formation of the 5-(1-O-trimethylsilylpropyl)-2-(5*H*)-furanone suggests that the desired epoxy β-lactone was formed but was unstable under the [2+2] reaction conditions. Literature precedence supports this contention, and a thorough literature investigation was conducted with the purpose of elucidating possible transformations of the epoxy β-lactone.

Acknowledgements

Incalculable thanks to Dr. Black for sharing his expertise of organic chemistry and his instruction during the last two years of research. Also, gracious thanks to professors of Eastern Illinois University for bestowing in me the knowledge of their disciplines. And, to my lovely wife Kumiko, I thank you for your support and companionship throughout my college career.

Also, I thank the Eastern Illinois Chemistry Department for their support through the graduate assistantship, as well as the National Institute of Health (GM52677-01) for making my research project financially possible.

List of Tables:

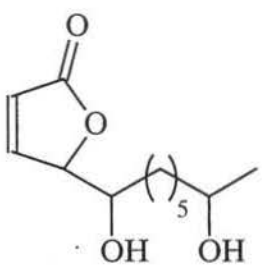
List of Figures:

List of Spectra:

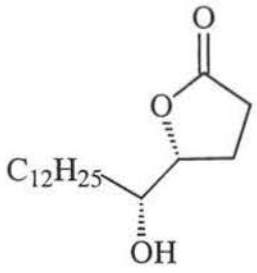
Introduction

Chiral α,β–butenolides (2-(5*H*)-furanones) and butyrolactones (2-(3*H*)-furanones) are medicinally important moieties as well as ubiquitous structural features among natural molecules.[1] Representative examples of naturally occurring butyrolactones are presented in Chart 1; they include *iso*-cladospolide (**1**), a hexaketide compound isolated from a marine fungal species,[2] and (-)-muricatacin (**2**), a natural product of *Anon Murata* having cytotoxic effects on human tumor cell lines.[3] Osmunda lactone (**3**), a 5-(1-hydroxyalkyl) butenolide, is isolated from the plant *Osmunda japonica*,[4] and the spirobutenolide andirolactone (**4**) is isolated from the medicinal plant *Cedrus libanotica*.[5]

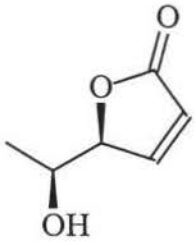
Chart 1



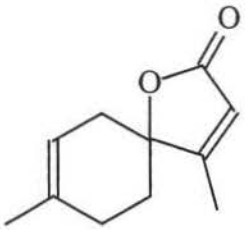
1



2



3



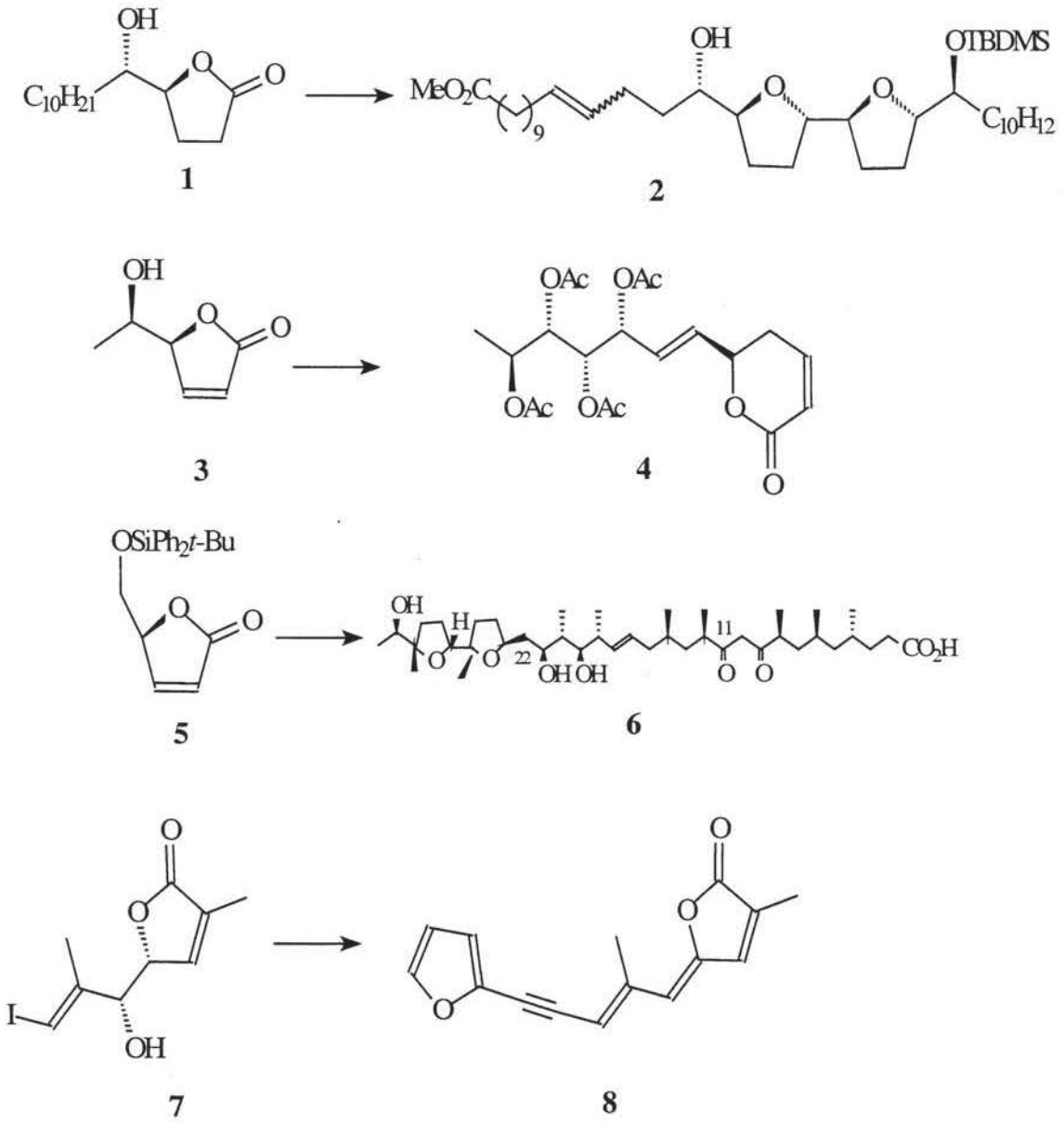
4

Natural molecules **1-4** can be obtained from their respective natural sources. However, isolation of these molecules from complicated natural mixtures can be an arduous task, necessitating destructive natural product extraction techniques that may damage an oftentimes-rare natural source. In an effort to negate the shortcomings of natural molecule extraction, organic chemists have devised totally synthetic routes to

achiral **4** and optically pure **1-3** despite the synthetic challenges presented by the contiguous stereogenic centers in **1-3**.

Chiral α,β–butenolides and butyrolactones are also utilized as synthetically versatile templates that have figured in numerous syntheses of medicinally important agents and rare natural molecules. (-)-*nor*-Muricatacin (**A1**) features in the synthesis of (-)-desoxyasimicin (**A2**), a template used to construct natural acetogenins of Annonaceae displaying cytotoxicity.[6] The high concentration of functional groups within the butenolide template make these molecules particularly useful synthons.[7] Osmunda lactone (**A3**) is the chiral building block employed in the synthesis of (+)-anamarine (**A4**).[4] Butenolide **A5** was utilized in the stereocontrolled syntheses of hydroxyl and alkyl substituted acyclic chains like the C_{11}-C_{22} segment of ionomycin (**A6**),[8] and optically enriched forms of **A7** have been employed in the stereoselective syntheses of the γ-alkylidene butenolide Z-freelingyne (**A8**), a constituent of wood oil from *Eremophila freelingii*.[9]

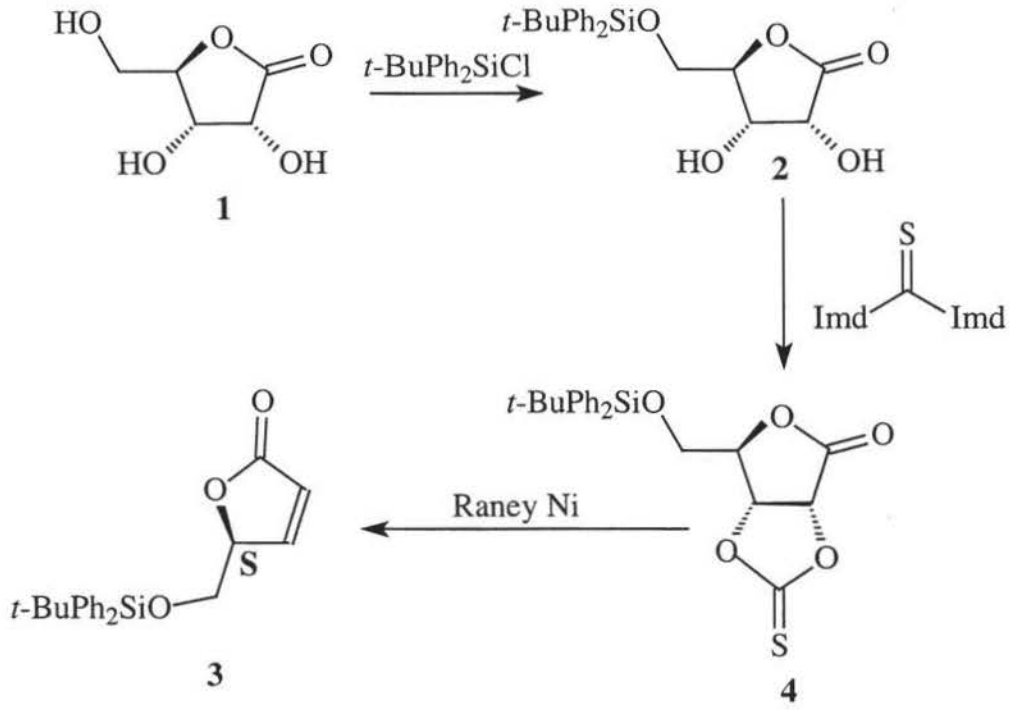
Scheme A



Specific procedures for the preparation of both 4R and 4S configurations of 5-(1-hydroxyalkyl) butenolides have been reported. Hanessian and Murray have procured the S-enantiomer of 5-(1-hydroxyalkyl) butenolide **B3** in optically pure form starting from

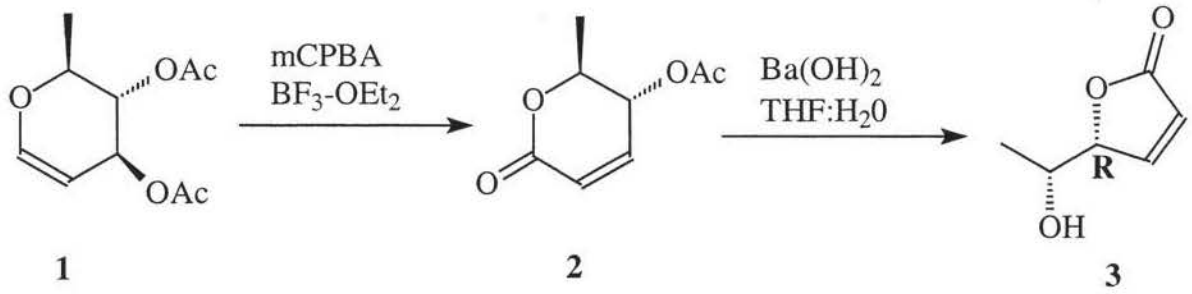
ribonolactone **B1.**[8] The reaction sequence involves the protection of the primary hydroxyl group of **B1** with chloro-*tert*-butyldiphenylsilane, followed by reaction of diol **B2** with thiocarbonyldiimidazole and reduction of the resulting thionocarbonate **B4** to give (*S*)-5-hydroxymethyl-(5*H*)-furan-2-one (**B3**).

Scheme B



A protocol for the synthesis of 5-(1-hydroxyalkyl) butenolides having a 4R configuration, which are not readily available from the chiral pool, has been developed by Sanchez-Sancho and coworkers (Scheme C).[4] The synthetic sequence begins with the reaction of 3,4-di-O-acetyl-L-rahmnal (**C1**) with mCPBA, followed by treatment with the Lewis acid boron trifluoride diethyl etherate to give hexenolide **C2**. Hydrolysis of **C2** in the presence of barium hydroxide afforded osmunda lactone (**C3**) in good chemical yield and in high diastereoselectivity.

Scheme C



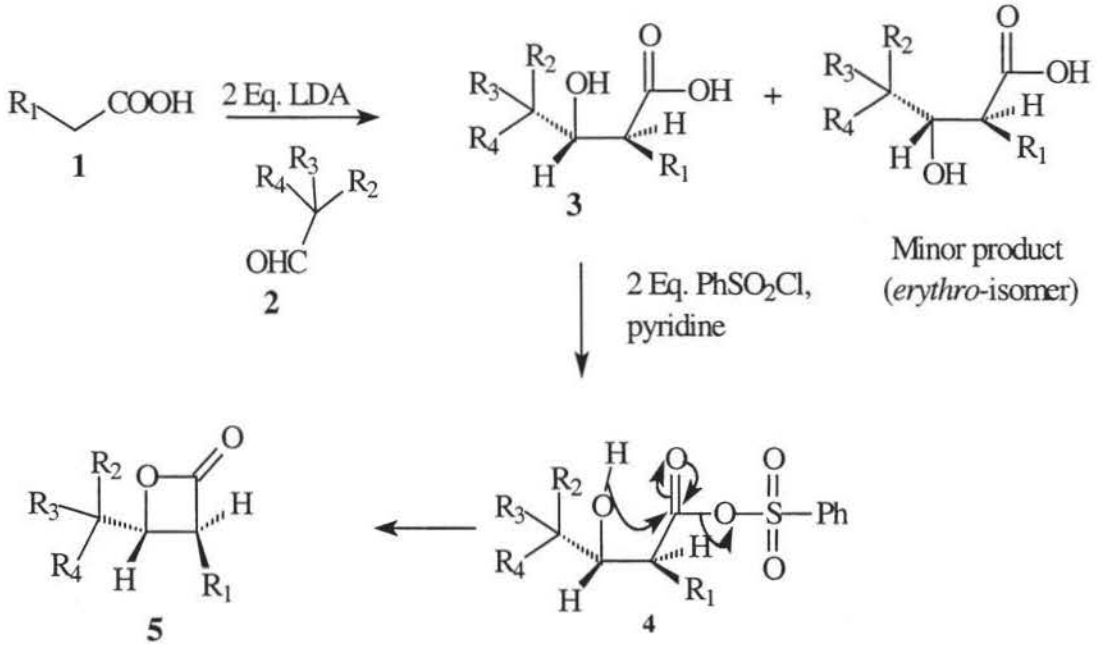
1 **2** **3**

As shown in the above examples, 4R and 4S isomers of 5-(1-hydroxylakyl) α,β–butenolides are derived from completely different synthetic methods. Furthermore, the stereoselective synthesis becomes increasingly challenging when the desired 5-(hydroxyalkyl) α,β-butenolide bears an adjacent chiral center at C_5 (as in **C3**). A versatile procedure for the diastereoselective synthesis of all four diastereomeric isomers of 5-(hydroxyalkyl) α,β-butenolide would be a valuable capability for synthetic organic chemists.

The Black research laboratory has over the years developed protocols for the synthesis of butyrolactones,[10] α,β-butenolides,[11] α,β-unsaturated carboxylic acids,[12] and β,γ–unsaturated carboxylic acids[13] utilizing β-lactone precursors. Two synthetic routes to a structurally diverse class of β-lactones have been successfully employed. Scheme D illustrates a two-step reaction sequence to β-lactones such as **D5** that begins with an aldol reaction between carboxylic acid **D1** and aldehyde **D2** to yield β-hydroxy acid **D3**. In this reaction, the carboxylic acid is activated towards electrophilic attack of the aldehyde by treatment with two equivalents of lithium diisopropylamine (LDA) in THF at -40 °C; this affords the acid dianion. Lactonization of the thermodynamically favored *threo*

diastereomer **D3** is effected with benzenesulfonyl chloride in pyridine to give the desired β-lactone **D5**. Stereocontrol in this reaction is observed because extended reaction times

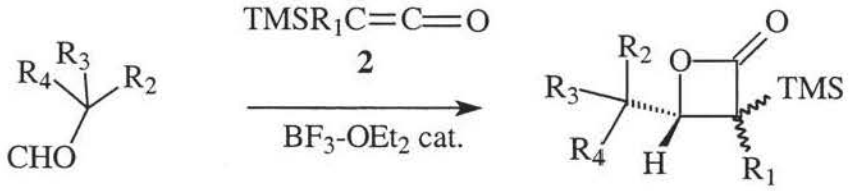
Scheme D



employed for the aldol reaction favors the formation of *trans* diastereomer, which can be exclusively isolated in high isomeric purity via recrystallization of the crude product. Consequently, the relative configuration about C_2 and C_3 is controlled.

The second route to β-lactones involves the single-step boron trifluoride-catalyzed [2+2] cycloaddition reaction between trimethylsilylketene (TMS-ketene) derivatives **E2** and aldehydes **E1** to give the α-trimethylsilyl β-lactone products **E3**. Our lab has expended considerable effort in the investigation of α-trimethylsilyl β-lactone transformations initiated by Lewis acid catalysts.

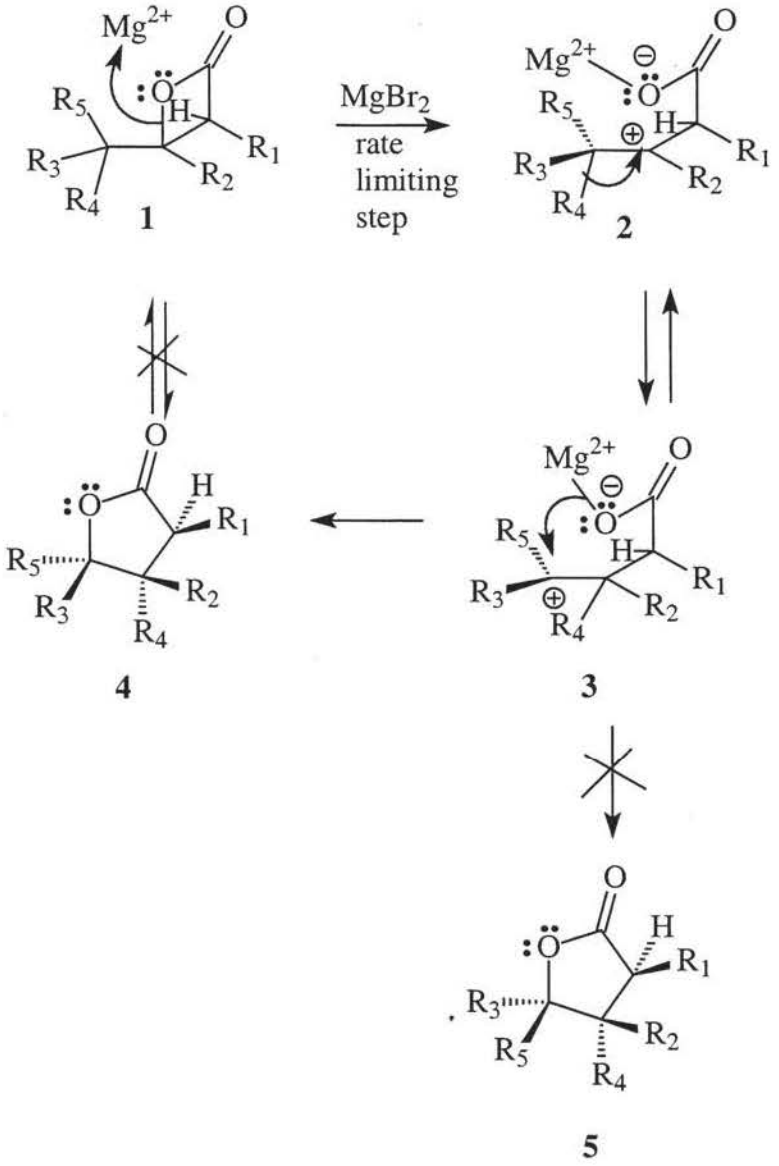
Scheme E



1 **3**

Consider the reaction of β-lactone **F1** with the Lewis acid magnesium bromide ($MgBr_2$). Ionization of **F1**, which has been shown to be the rate-determining step of the rearrangement, is initiated by certain Lewis acids (especially magnesium bromide and titanium (IV) chloride), and results in the formation of β-carbocation **F2**. Carbocations tend to rearrange to thermodynamically more or equally stable carbocations and, in the case of **F2** where R_2=hydrogen, bond migration of R_4 (R_4= hydrogen, alkyl) occurs, placing the carbocation at a more substituted γ-carbon (as in **F3**). Carboxylate attack on the γ-carbocation results in ring closure to give butyrolactone **F4.**

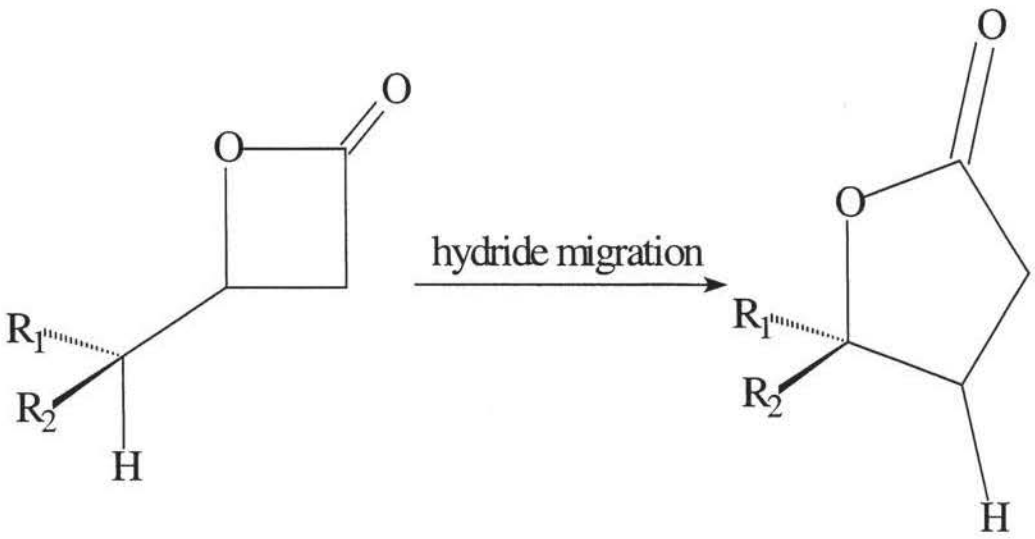
Scheme F



The rearrangement appears at first glance to be dyotropic in nature. However, the two criteria of dyotropic rearrangement are 1) the migrating bonds must be aligned in an anticoplanar fashion, and 2) the process is reversible.[14] β-Lactone ring expansions have been shown to require an anticoplanar alignment of migrating atoms (Figure 1); however,

ring contraction from a five to four membered ring (**F4→F1**) would be a endothermic and thermodynamically unfavorable rearrangement and has thus far not been observed in these investigations.

Figure 1



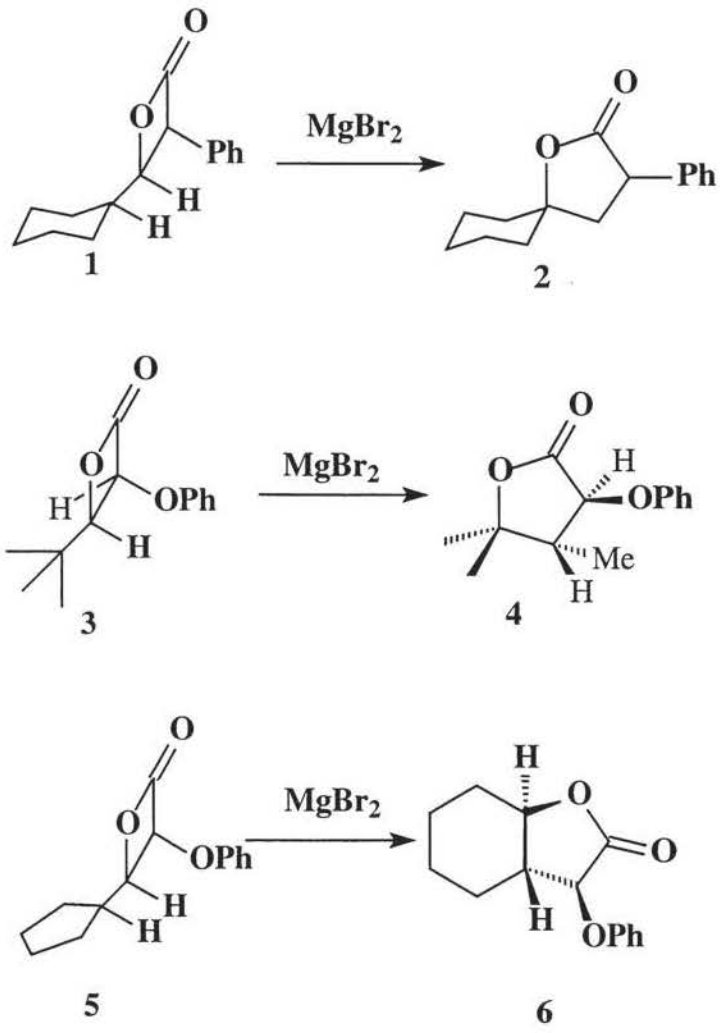
Migrating hydrogen and oxygen bonds have an anticoplanar geometry, a requisite for bond migration during lactone β–rearrangement

The stereospecific nature of the rearrangement suggests that the lifetime of carbocations **F2** and **F3** must be short-lived relative to the rate of free rotation around the involved carbon-carbon bond. If the rate of rotation of the β-carbon/γ-carbon bond were faster than carbocation equilibration, the formation of **F5** would be observed. However, the fact that no **F5** is formed supports the contention that carbocations **F2** and **F3** are short-lived.

Three examples of β-lactone rearrangements to butyrolactones are depicted in Scheme G. β-Lactone **G1** theoretically has three substituents at its γ-

position that could potentially migrate. However, the ring expansion of the pendant cyclohexyl group from six- to seven-member ring is endothermic and thermodynamically unfavorable. Furthermore, the migratory aptitude of hydrogen over carbon migration for these reactions [10a] predisposes the molecule toward hydride migration, given that the migrating bonds are able to adopt the requisite anticoplanar alignment. Thus, ionization of **G1** results in the rearrangement to spiro butyrolactone **G2.** β-Lactone **G3** possesses a quaternary γ-carbon. Again, the migrating atoms of the β-lactone are arranged in an anticoplanar fashion, and ionization results in carbon migration, leaving the cation at the more stable tertiary carbon. Ring closure by nucleophilic attack on the γ-carbon by the carboxylate anion gives the 3,4,5,5-tetrasubstituted butyrolactone **G4**. In β-lactone **G5,** the γ-carbon is incorporated into a cyclopentyl ring, and ionization of the lactone results in the simultaneous expansion of both the lactone and cyclopentyl ring systems. In this case, the exothermicity of a ring expansion from a five to six memberred ring (6 kcal/mol)[15] favors carbon bond migration over hydrogen, affording *trans*-fused butyrolactones **G6**.[10a] This methodology is particularly powerful (**G5→G6**) because it establishes the relative stereochemistry of three chiral centers in a single step.

Scheme G



Since potential cation migrations are based on the thermodynamic stability of the involved cations, some β-lactones favor elimination over bond migration upon ionization. For example, migration of the carbocation from the β-carbon to the γ-carbon (**H2**→**H4**) would require the thermodynamically unfavorable cation shift from tertiary to secondary carbon upon ionization. Consequently, rearrangement to a butyrolactone is not observed; rather, elimination occurs, giving rise to β,γ-unsaturated acids **H3**.[13] Elimination of the γ-

proton is kinetically favored, since the orbital of the γ-proton is aligned properly for overlap with the empty *p* orbital of the tertiary cation (Figure 2). Thus, no α,β-unsaturated acids were observed in this study, although transformations of **H1** to conjugated double bond systems are thermodynamically favored.

Scheme H

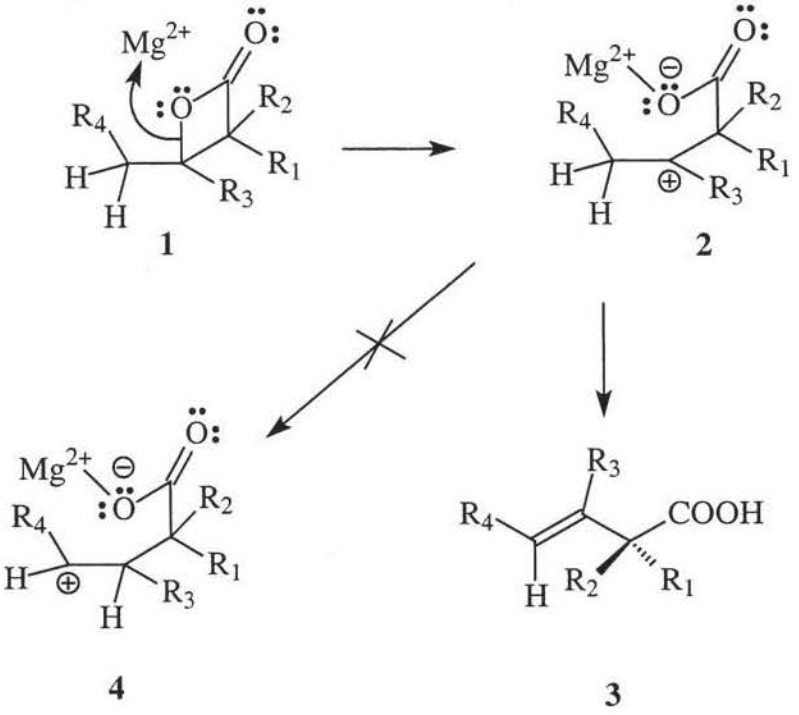
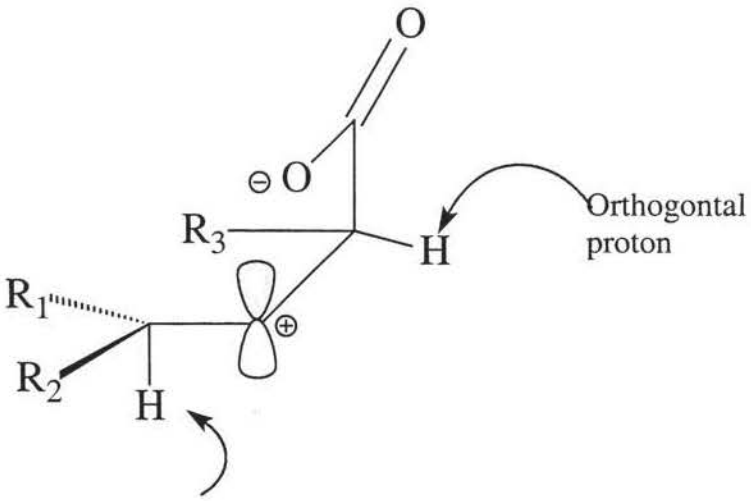


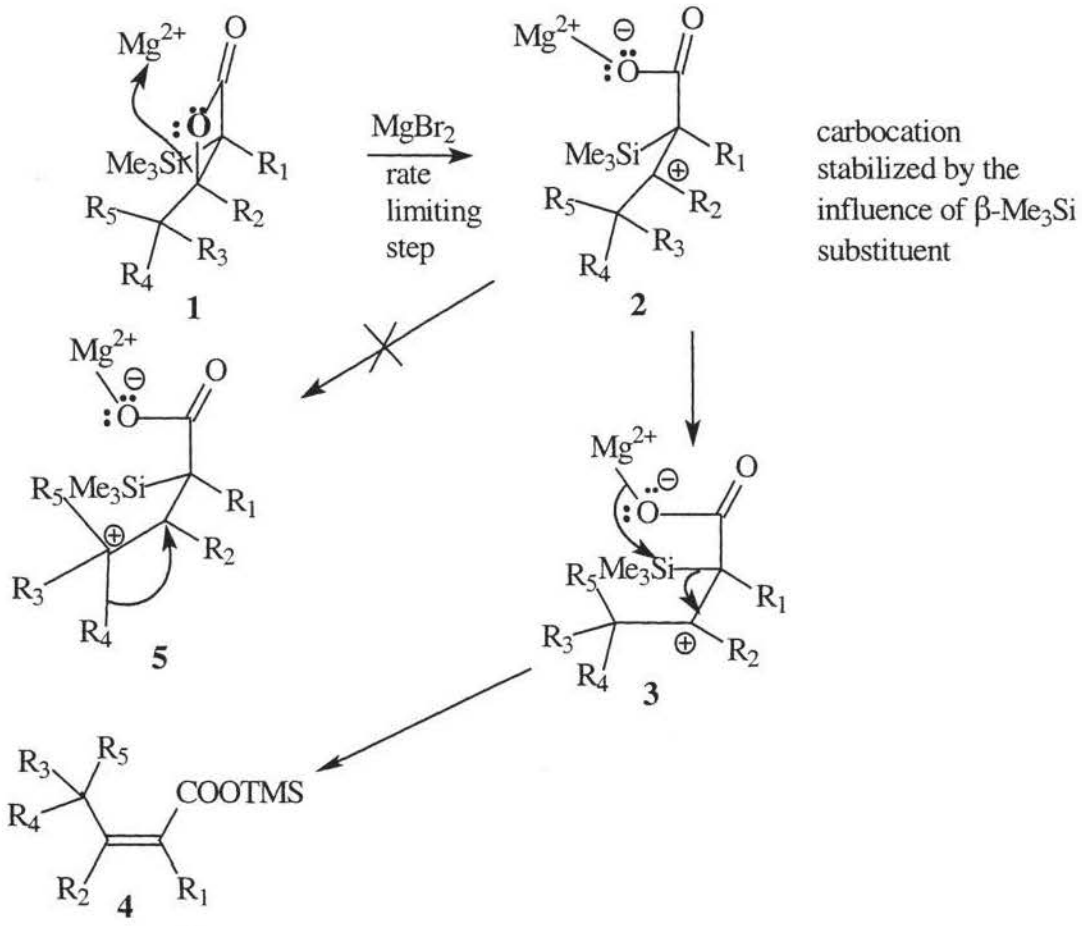
Figure 2



Aligned correctly for overlap
with *p* orbital and favored for elimination
over orthognally aligned proton

β-Lactone **I1**, bearing a trimethylsilyl substituent at the α–carbon, undergoes a different transformation upon ionization. These lactones are ionized by treatment with the same Lewis acids as in previous examples; however, the thermodynamic driving force of carbocation migration (**I2**→**I5**) is diminished due to the tendency of a neighboring silicon atom to stabilize β-cations through a σ-π conjugation.[16] Consequently, **I5** does not form and **I2** undergoes elimination of the cationic trimethylsilyl group ($SiMe_3^+$) to give α,β-unsaturated trimethylsilyl ester (**I3**→**I4**), which can be converted to the corresponding α,β-unsaturated acid upon treatment with hydrochloric acid.

Scheme I

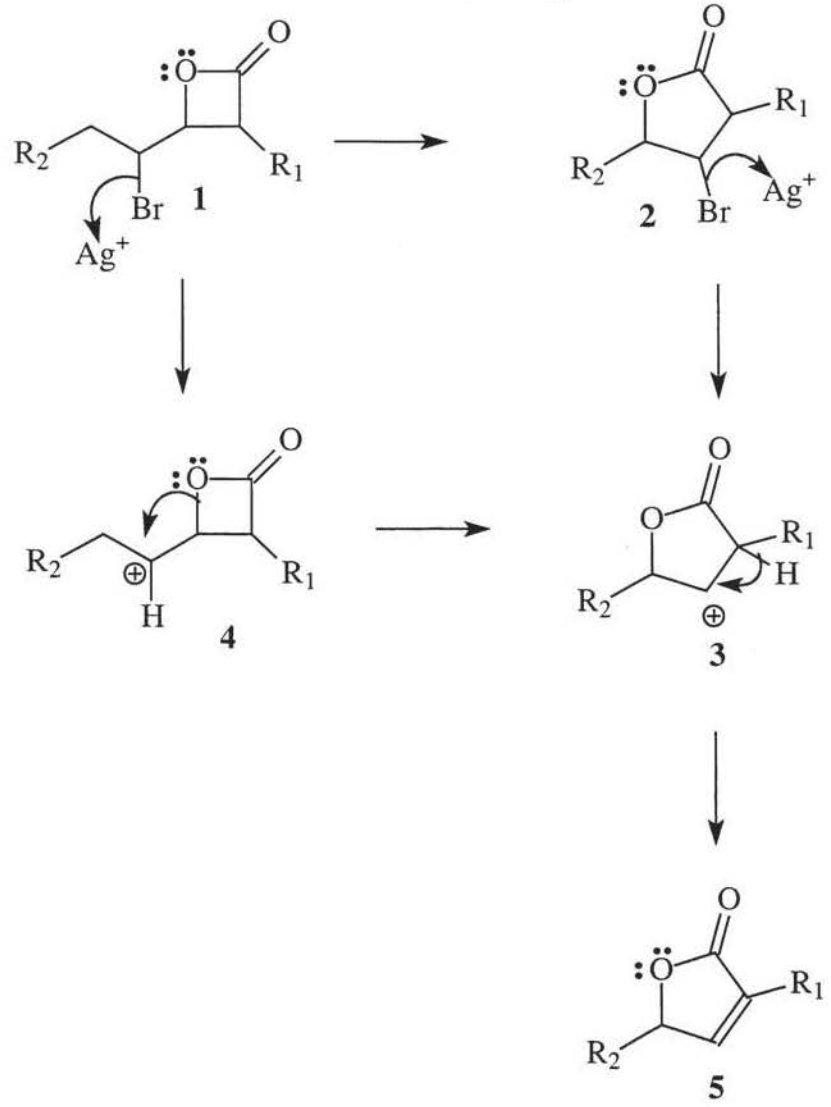


Perhaps the most intriguing transformation observed by our lab is the cation-initiated rearrangements of β-lactone. Whereas the previous examples of rearrangements to butyrolactones involved ionization of the β-lactone followed by cation migration to a more or equally stable cation at the γ-position, cation-initiated rearrangements are based on the formation of a carbocation adjacent to the β-lactone. The Lewis acid employed in cation-initiated rearrangements functions to facilitate the formation of the γ-carbocation.

Using the cation-initiated rearrangement methodology, 2,4-disubstituted butenolides (**J5**) have been procured from γ-bromo β-lactones(such as **J1**)

γ-Bromo-β-lactones **J1** have been prepared by our lab via bromolactonization.[11] When refluxed in acetic acid in the presence of silver nitrate, **J1** underwent rearrangement and elimination to give α,β-butenolide **J5**. The mechanism of this rearrangement has yet to be settled, however; one possible mechanism involves the bromolactone **J1** undergoing a rearrangement to the β-bromo-γ-lactone **J2**, which then undergoes elimination to give 2,4-substituted butenolide **J5**. An alternative possibility involves an S_N1 type reaction mechanism in which the nucleofugal bromine leaves a carbocation adjacent to the β-lactone (as in **J4**). Ring expansion from **J4**→**J3** would then place the carbocation at the β-position, which could then be annihilated via elimination. This finding that β-lactones bearing halo-substituents at their γ-carbons could be treated with silver (I) ion to affect rearrangement to α,β-butenolides prompted us to consider cation-initiated rearrangements of a structurally different class of lactone.

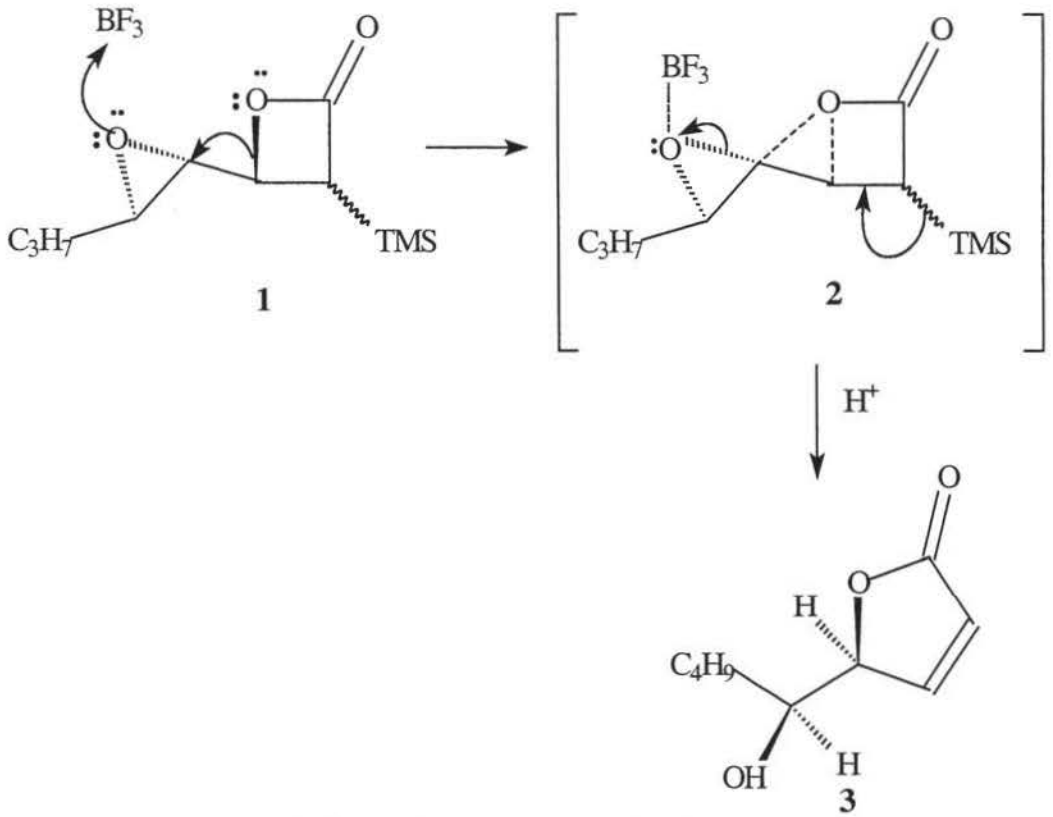
Scheme J



We were particularly interested in investigating the cation-initiated rearrangements of β-lactones bearing C_4 nucleofugal groups with a proclivity for S_N2-type displacements. The Baeyer strain inherent in the oxirane ring makes the incorporated oxygen atom an outstanding nucleofuge; for this reason, an epoxide oxygen atom was chosen (see β-lactone **K1**). Consequently, epoxides can be opened by a variety of nucleophiles. Furthermore, the oxirane's propensity for S_N2 type displacement (illustrated in transition state **K2**) makes oxirane ring opening reactions stereospecific,

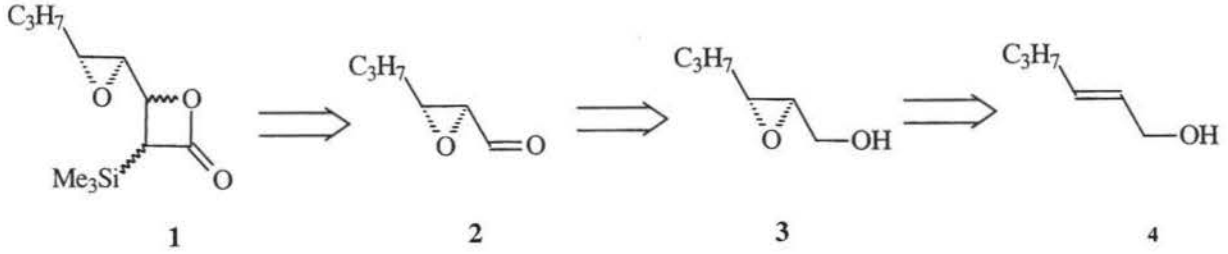
with inversion of configuration occurring at the attacked chiral center and retention of configuration of the adjacent oxirane carbon.

Scheme K



The immediate synthetic challenge presented by this project was the preparation of α-trimethylsilyl β-lactones like **L1** having an adjacent chiral epoxide moiety. We wished to prepare **L1** from chiral (2*R*,3*S*)-epoxyhexanal (**L2**). Chiron **L2** can be prepared

Scheme L

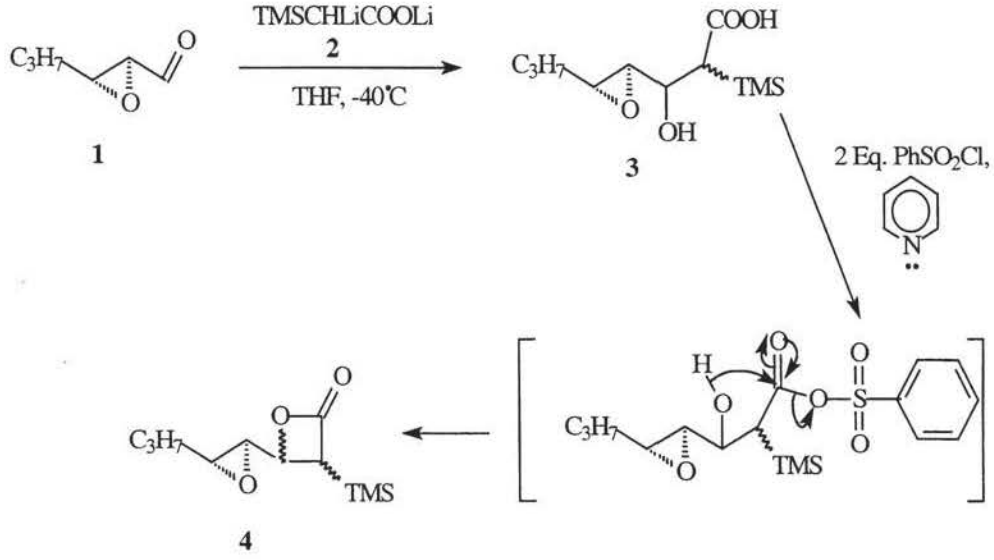


from the selective oxidation of enantiopure (2*S*,3*S*)-epoxyhexan-1-ol (**L3**), which in turn is available via the well-established asymmetric epoxidation reaction of allylic alcohol **L4**.

To our knowledge, there is no precedence for the synthesis the high-energy epoxy lactone **L1**. However, we attempted to secure a source of **L1** via two synthetic routes.

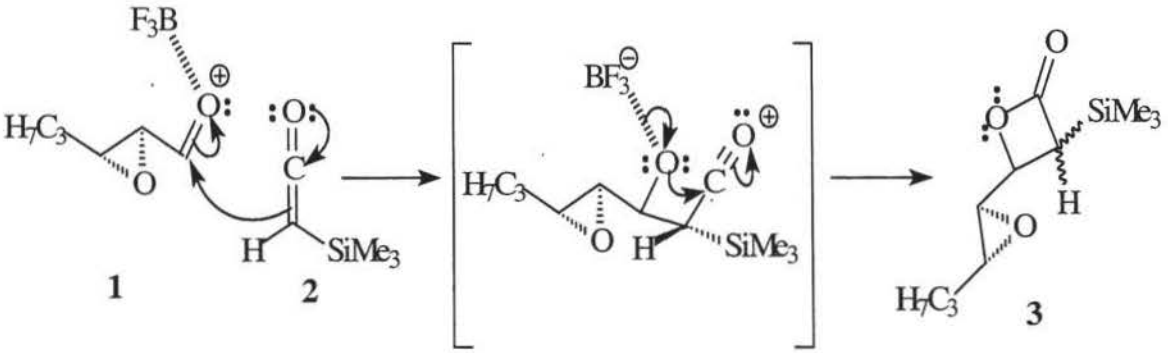
The first route involves a two-step reaction sequence beginning with the condensation of **M1** with the lithium dianion of trimethylsilylacetic acid (**M2**) to afford aldol adduct **M3**. Previous researchers in our lab have successfully employed condensation reactions to prepare a structurally diverse group of β–hydroxy acids; however, the preparation of γ,δ-epoxy β-hydroxy α-trimethylsilyl carboxylic acids (as in **M3**) would be a novel accomplishment. If procurable, we then wanted to determine if benzensulfonylchloride would effect lactonization of the aldol adduct **M3** to give the desired epoxy β-lactone **M4**.

Scheme M



The second synthetic route to epoxy β-lactone **N3** is based on a well-established procedure for the preparation of α-trimethylsilyl-β-lactones and involves the Lewis acid-catalyzed [2+2] cycloaddition of ketenes to carbonyl compounds. This procedure is widely used for the preparation of α-trimethylsilyl-β-lactones.[18] Indeed, isoelectronic analogs (for example, α-alkoxy and β-alkoxy alkanals) of 2,3-epoxyalkanals have been used in this reaction as carbonyl substrates with great success.[19] It seemed to us that we could extend this method to reactions between trimethylsilylketene (**N2**) and (2*R*,3*S*)-epoxyhexanal (**N1**). Furthermore, we wanted to see if the boron trifluoride Lewis acid essential to this reaction would serve the dual purpose of 1) catalyzing the [2+2] cylcoaddition to form the β-lactone and 2) initiating the epoxide opening/lactone ring expansion cascade. If this were the case, chiral 5-(1-hydroxyalkyl) butenolides could be prepared in a single step from the chiral epoxy aldehyde **N1**.

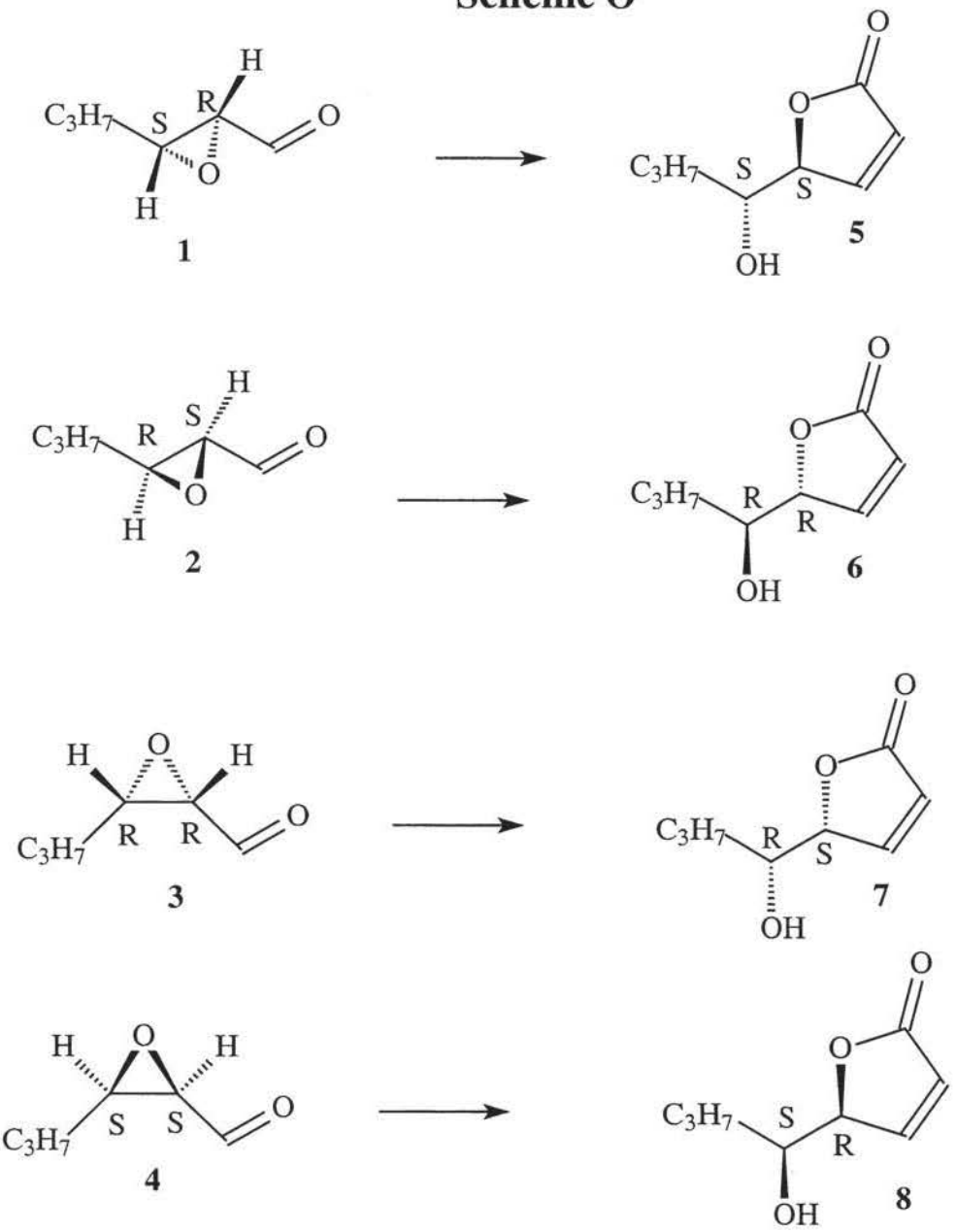
Scheme N



The potential versatility in the two synthetic routes of Scheme M and Scheme N arises from the fact that a structurally diverse class of 2,3-epoxy alkanals (**O1-O4**) can

be prepared enantioselectively by well-known procedures, allowing for the diastereoselective synthesis of any of the four possible diastereomers (**O5-O8**).

Scheme O



Herein, the remainder of this thesis describes the details of this project, including results and discussion, experimental, and data sections.

Results and Discussion

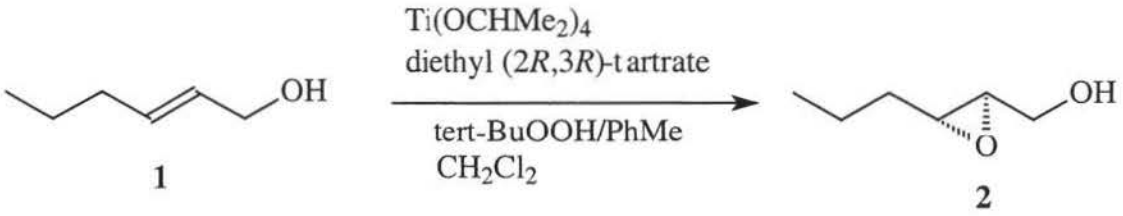
One of the first objectives of this project was to establish an efficient method for the preparation of an enantiopure (2,3)-epoxy alkanal. This chiron would be used as a source of aldehyde in the two synthetic routes depicted in Scheme M and Scheme N. However, before procuring the epoxy alkanal, a method for the large-scale preparation of enantiopure synthesis of 2,3-epoxy alkan-1-ols was needed.

The asymmetric catalytic allylic epoxidation procedure devised by Sharpless[20] for the epoxidation of allylic alcohols seemed a good starting point. The Sharpless epoxidation reaction is a well-established procedure for the enantioselective synthesis of 2,3-epoxy alkanols proven to give good chemical yields in > 90% enantiomeric excess.[21] In addition, this procedure is highly versatile, and has been used to enantioselectively epoxidize allyl alcohols irrespective of their substitution patterns, giving rise to structurally varied 2,3-epoxy alakan-1-ols. Both E and Z allyl alcohols were considered for epoxidation. However, the epoxidation of E allyl alcohols is reported to be more efficient than that of the corresponding Z isomer.[22] Furthermore, E allyl alcohol isomers are much more affordable than the corresponding Z isomers.

The water solubility of the epoxidized product and the ease of isolation through distillation were also considered. The six-carbon epoxy alcohol made from *trans*-2-hexen-1-ol represents the lower limit of water solubility and could be purified via distillation under reduced pressure at relatively low temperatures. [20] Thus, 96% *trans*-2-hexen-1-ol seemed an ideal allyl alcohol for epoxidation. Diethyl (2*R*, 3*R*)-tartrate was selected as asymmetric catalytic ligand, as it is readily available from the chiral pool and considerably less expensive than diethyl (2*S*,3*S*)-tartrate. Using *trans*-2-hexen-1-ol (**P1**)

and (2*R*,3*R*)-tartrate as chiral ligand, the synthesis of (2*S*,3*S*)-epoxyhexan-1-ol (**P2**) was undertaken .

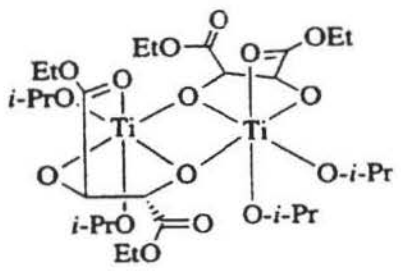
Scheme P



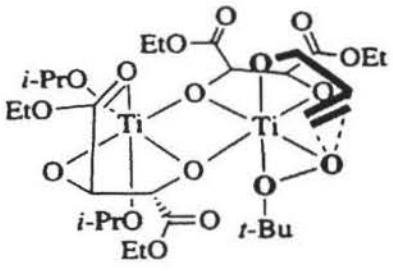
1 **2**

The catalytically active species of this reaction have reportedly been difficult to identify. The mechanism of catalysis is thought to involve two titanium (IV) dimeric species **5** and **6** (Chart 2) complexed with isopropoxide.[23] Each of the titanium centers of **5** is an equivalent catalytic site and the epoxidation of the alkenyl group is thought to occur at a single titanium center in an arrangement resembling structure **6**. The isopropoxide ligands of **5** serve as a source of base for the deprotonation of the allylic alcohol and the hydroperoxide.

Chart 2



5

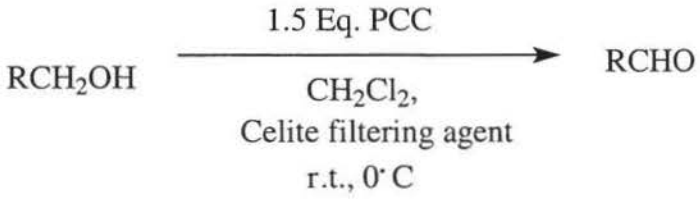


6

The reaction illustrated in Scheme P was undertaken and 20.8 grams of **P2** was obtained in 70.7% yield. IR, and ^{1}H, and ^{13}C NMR data confirmed the identity of the product. It should be noted that a second minor spot ($R_f = 0.32$ in methylene chloride), just leading the epoxy alcohol was visible via thin layer chromatography on silica gel when phosphomolybdic acid was used for development. The unidentified component was collected (~1 gram) as distillate at a slightly lower temperature than that of the desired product and evidently co-distills to a lesser extent throughout the collection of **P2** (as indicated by TLC). Perhaps higher grades of purity of **P1** would be obtained by using a better source (>96% *trans*-2-hexen-1-ol) of starting material allyl alcohol.

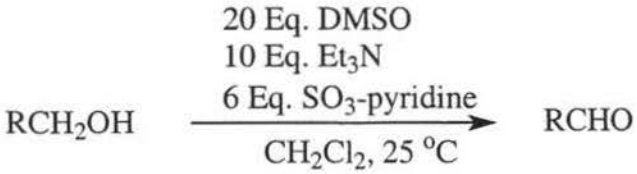
After having secured ~ 20 grams of the epoxy alcohol, a method for the gentle oxidation of the epoxy alcohol to the corresponding (2*R*,3*S*)-epoxyhexanal was needed. Initially, the Corey method depicted in Scheme Q was employed using pyridinium chlorochromate as the oxidizing agent.[24] A pilot reaction using octan-1-ol gave a crude aldehyde in 80% yield (confirmed using IR; absorption band for carbonyl stretch @ 1728 cm^{-1}). However, application of this method to (2*S*,3*S*)-epoxyhexan-1-ol gave crude product that was predominately starting material. (indicated by the OH stretching band at 3600 cm^{-1} band in IR and the lack of a C=O stretching band, in addition to TLC monitoring of the reaction mixture). The lack of success for this reaction, in addition to the disposal issues presented by hexavalent and trivalent chromate ion, prompted us to consider alternative methods of oxidation.

Scheme Q



The Doering method, [25] depicted in Scheme R, was investigated as a possible method for the gentle oxidation of epoxy alcohols. Escudier *et al.* [26] and Urabe *et al.*[27] reported the successful oxidation of epoxy alcohols using a modified version of the Doering method. The economic feasibility of the sulfur trioxide-pyridine reagent (SO_3•pyr), in addition to the short reaction times and near ambient reaction temperatures made this an attractive method. Furthermore, the sulfur trioxide-pyridine complex reportedly produced negligible (methylthio)methyl ether derivative, a common by-product of reactions using other DMSO activating agents (dicyclohexylcarbodiimide;[28] phosphorous pentoxide[29]).

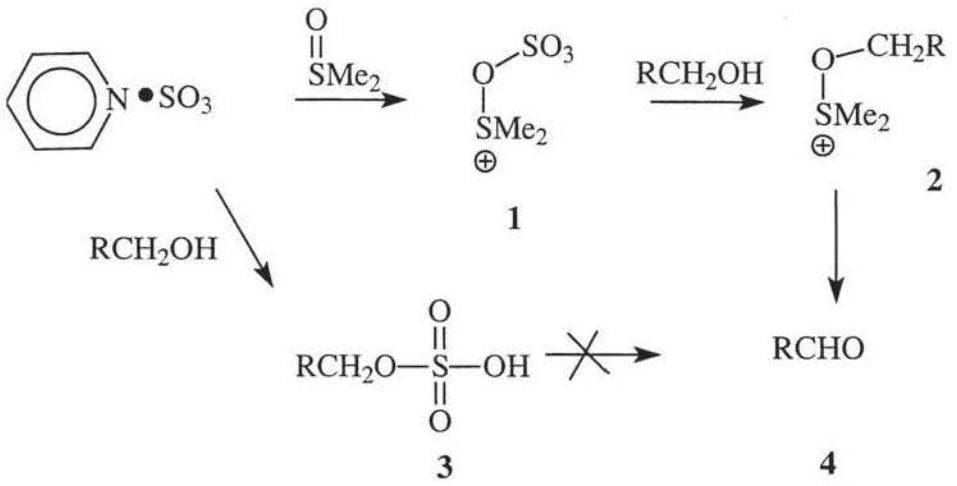
Scheme R



Numerous attempts at the oxidation of (2*S*,3*S*)-epoxyhexan-1-ol gave reaction mixtures in which the starting alcohol was only partially consumed according to TLC monitoring. Extended reaction times, in addition to excess activating reagent, were independently tested in an attempt to drive the reaction to completion but were unsuccessful as indicated by TLC monitoring of the reaction mixture. The temperature at which the oxidant was introduced was also varied from 0-25 °C. Introducing the sulfur trioxide at room temperature appeared to have an adverse affect on reactions carried out on scales greater than five grams. These larger scale reactions were highly exothermic upon addition of the oxidant. Temperature variation had no noticeable affect on smaller reaction scales according to crude product yields, which were consistently ~50% .

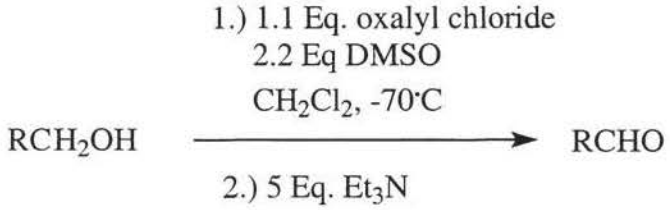
Doering's original procedure was different from the modified procedures reported by Escudier *et al.* and Urabe *et al.* in that the reaction required the delivery of the oxidant in DMSO solution to ensure the formation of O-dimethylsulfoxonium sulfate **S1**, the activated ylide species, and to circumvent the formation of hydrogen sulfate of the alcohol **S3**.[25] Thus, oxidant was delivered as a DMSO solution but was not found to affect crude product yield or reaction progression, as evidenced by TLC monitoring of the reaction mixture.

Scheme S



Perhaps the low yields of the (2*R*,3*S*)-epoxyhexanal oxidation product using this method can be attributed to the slight water solubility of the relatively small aldehyde molecule. During workup, copious amounts of aqueous washes were necessary to cleanse the product-containing organic layer of pyridine. The complete removal of the pyridine from the crude product was necessary to prevent decomposition of the product during distillation. Attempts to extract the aqueous layer with ether and/or methylene chloride only reintroduced the pyridine into the crude product, as indicated by TLC and the blue color of aqueous $CuSO_4$ washes. It should be noted that the epoxy alcohols reportedly oxidized by Doering,[25] Escudier[26] and Urabe[27] were much larger (cholestanone and 4-benzyloxy-2,3-epoxy butan-1-ols) and presumably the water solubility of these oxidation products would not have been an issue. An alternative route to the desired (2*R*,3*S*)-epoxyhexanal was needed.

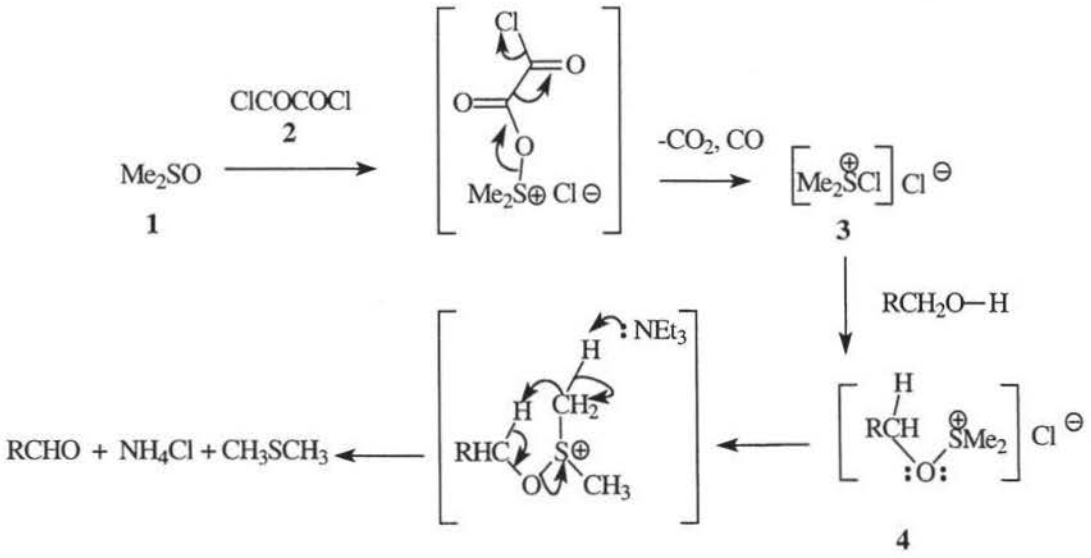
Scheme T



Our attention was then turned to the Swern method of oxidation devised for the oxidation of long chain alcohols (reaction conditions shown in Scheme T) .[30] This particular procedure utilizes an oxalyl chloride-activated DMSO complex **U3** as the oxidant is advantaged by of negligible formation of (methylthio)methyl ether derivative of the alcohol. Additionally, the Swern oxidation is reputedly a clean reaction (all the organic by-products: carbon monoxide, carbon dioxide, and dimethyl sulfide, are all gaseous) and we wished to be able to carry on aldehyde crude product without further purification.

The mechanism of the Swern oxidation has been investigated by Marks and Tidwell.[31] The oxalyl chloride (**U2**) is thought to react with dimethylsulfoxide (**U1**) to form chlorodimethylsulfonium chloride (**U3**) . Activated DMSO ylide complex (**U3**) further reacts with the alcohol at -60 °C to form ylide **U4**. Treatment with triethylamine base completes the oxidation reaction to give the aldehyde.

Scheme U



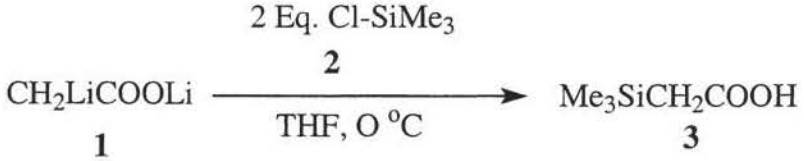
Of the three oxidation methods attempted, this reaction was most successful, giving the desired (2*R*,3*S*)-epoxyhexanal in 63 % yield (Confirmed by IR, ^{13}C NMR). Due to the presence of unidentified components in the crude product, the (2*R*,3*S*)-epoxyhexanal required purification, which could be performed by Kugelrohr distillation. However, this method of purification was inefficient, as the boiling point of the product under reduced pressure (1 mm Hg) was determined to be 29 °C, and it is suspected that some product is lost to the distillation trap during these reduced pressure distillation. The aldehyde product was not amenable to ambient pressure distillations due to thermal decomposition. Alternately, column separations using 20% ether:hexane eluent consistently gave higher yields of purer product (indicated by GC).

TLC analysis of the Swern reaction mixture indicated that no starting alcohol remained after the reaction mixture had warmed to room temperature. As with the

Doering method, excessive aqueous washes were needed to cleanse the crude product of triethylammonium hydrogen chloride salt, perhaps explaining the modest yields for the reaction. Based on the investigations of the epoxy alcohols performed in this project future epoxy alkanals should be larger to attenuate the water -solubility of the products.

With the (2*R*,3*S*)-epoxyhexanal in hand, our efforts could be focused on the synthesis of trimethylsilylacetic acid. This compound was available from Aldrich but its price was prohibitively expensive. Trimethylsilylacetic acid was not only a requisite material for the first step of the sequence in Scheme M, but the preparation of trimethylsilylketene (the critical reagent for Scheme N synthetic route) from trimethylsilylacetic acid had been reported by Olah *et al*..[32]

Scheme V

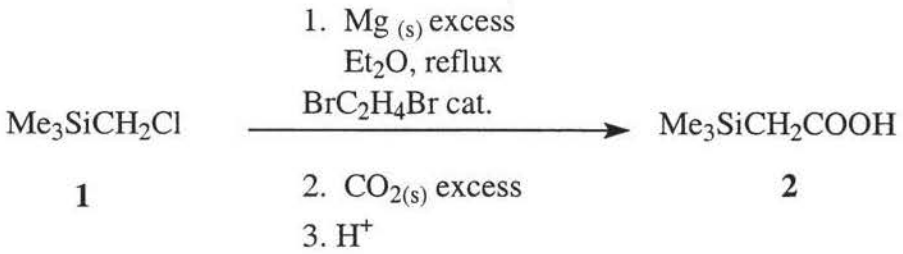


The first attempt at preparing trimethylsilylacetic acid (**V3**) involved the reaction of the lithium dianion of acetic acid (**V1**) with two equivalents of chlorotrimethylsilane (**V2**).[33] The availability and affordability of the reagents used in this reaction made this method particularly attractive. When carried out, this procedure gave low crude product yields (~25%) of a yellow oil, in contradiction with the colorless trimethylsilylacetic acid crystal product (mp 40 °C) reported by Otohiko.[33] In an effort to increase the purity and mass of crude products, a modified extractive workup specific for carboxylic acids was used.[34] This method of workup involved quenching the reaction mixture with aqueous

alkali (Saturated sodium bicarbonate), separation of the biphasic solution and acidification with 6N hydrochloric acid, followed by extracting the acidic aqueous layer with ether, drying the organic layer, and finally *in vacuo* evaporation to give crude product. This method of workup improved neither crude product yield nor purity.

A second attempt at preparing trimethylsilylacetic acetic involved a reaction between the Grignard reagent derived from chloromethyltrimethylsilane (**W1**) and solid carbon dioxide. The starting material **W1** for this reaction was rather expensive and the use of this method would have to be justified with modestly successful yields.

Scheme W



The Grignard reaction depicted in Scheme W was carried out using 1,2-dibromoethane as a catalyst. Heat was applied to initiate this reaction using a hot air gun and the vigor of this reaction necessitated the use of a double condenser to prevent the reaction solvent from escaping the apparatus. Additionally, an ice water bath was made accessible to cool the Grignard reaction mixture in the event that solvent began to escape. Crude product yield was 76% (47.0 grams). Furthermore, the crude product was pure enough (confirmed by ^{1}H and ^{13}C NMR and mp) to use without further purification.

It was discovered that trimethylsilylacetic acid did not store well, especially at room temperature and was later found to be prone to isomerization to the trimethylsilyl

acetate.[33] This product was best stored in the freezer and was distilled using a Kugelrohr apparatus as needed.

Attempts were also made to prepare 2-trimethylsilylphenylacetic acid. We wished to use this α-trimethylsilyl acid derivative as a nucleophile in aldol reactions with enantiopure (2,3)-epoxy alkanals (Scheme M, Step 1). Additionally, a literature procedure exists for the synthesis of phenyl(trimethylsilyl)ketene from 2-trimethylsilylphenylacetic acid. Both 2-trimethylsilylphenylacetic acid and phenyl(trimethylsilyl)ketene would be valuable reagents and their preparation could potentially allow for the synthesis of 3-phenyl-3-trimethylsilyl-furan-2-ones via β-hydroxy acid lactonization (Scheme M, Step 2) or [2+2] cylcoaddition reactions (Scheme N), a class of compounds not yet synthesized by our lab.

Initial efforts to synthesize 2-trimethylsilylphenylacetic acid involved the reaction of the lithium dianion of phenylacetic acid with two equivalents of chlorotrimethylsilane in THF. TLC monitoring of this reaction mixture after forty-eight hours showed the phenylacetic acid starting material to be essentially unreacted. In a second reaction, ten equivalents of chlorotrimethylsilane were used and, when TLC indicated unreacted phenylacetic acid after forty-eight hours of stirring at room temperature, the reaction mixture was heated to 33 °C for one hour. Quenching of this reaction mixture with 1.5N HCl followed by extractive workup with ethyl ether and evaporation of solvent gave light yellow crystals. TLC and mp after recrystallization showed the product to be unreacted phenylacetic acid.

Brady and coworkers report the preparation of 2-trimethylsilylphenylacetic acid from benzyltrimethylsilane.[36] The procedure involves the deprotonation of

benzyltrimethylsilane using 1.1 equivalents of freshly titrated *n*-butyllithium in ethyl ether solvent. The deprotonation reaction is reported to occur over a 24-hour period at room temperature, whereupon carbonation of the reaction mixture followed extractive workup gave the target 2-trimethylsilylphenylacetic acid in good yield.

However; in our hands and under these reaction conditions, only starting material was recovered as indicated by TLC. Reaction conditions in which 2.2 equivalents of *n*-butyllithium base was used and the solvent changed from ethyl ether to the more polar tetrahydrofuran were still unsuccessful. Inconsistent with Brady's reported observations; the reaction mixture never acquired an orange-dark brown color, but rather a subtle color change from clear to light yellow was observed. A significant color change to dark green was observed when the reaction mixture in tetrahydrofuran was heated to >38 °C. However, inseparable polar mixtures resulted when dark green reaction mixtures were carbonated.

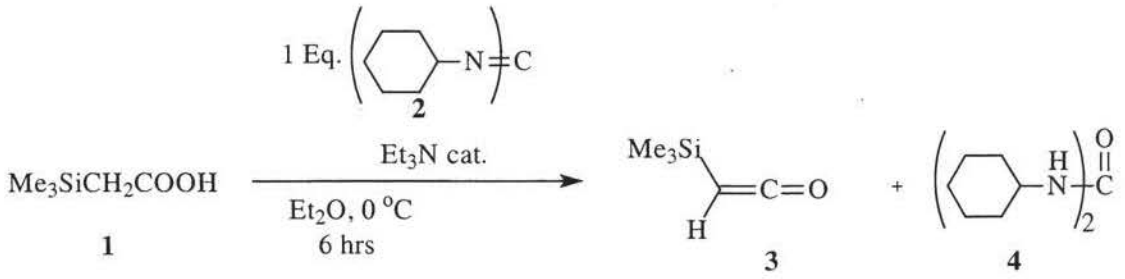
An experiment was performed to determine if *n*-butylithium was an adequate base to extract the benzylic proton from benzyltrimethylsilane. The reaction was performed following the reported conditions, however; the reaction mixture was quenched with deuterium oxide rather than carbon dioxide. The resulting reaction mixture was then dried with magnesium sulfate and the drying agent filtered out. The solvent was evaporated and integration of the ^{1}H NMR signal corresponding to benzylic protons indicated the deprotonation and subsequent deuteration was incomplete (integration of benzylic ^{1}H =1.88, 6 % effective at deprotonation).

These results are consistent with Peterson's finding that benzyltrimethylsilane is relatively unreactive towards *n*-butyllithium, and instead employs *n*-BuLi•TMEDA

(N,N,N'N'-tetramethylethylenediamine) complex to deprotonate the substrate.[37] *n*-BuLi•TMEDA complex is reported to rapidly metallate at the benzylic position of aromatic hydrocarbons[38] and should be considered in future endeavors for 2-trimethylsilylphenylacitic acid. Alternately, *n*-butyllithium in HMPA (hexamethylphosphoramide) was reported to be 85% effective in deprotonation of benzyltrimethylsilane.[41c]

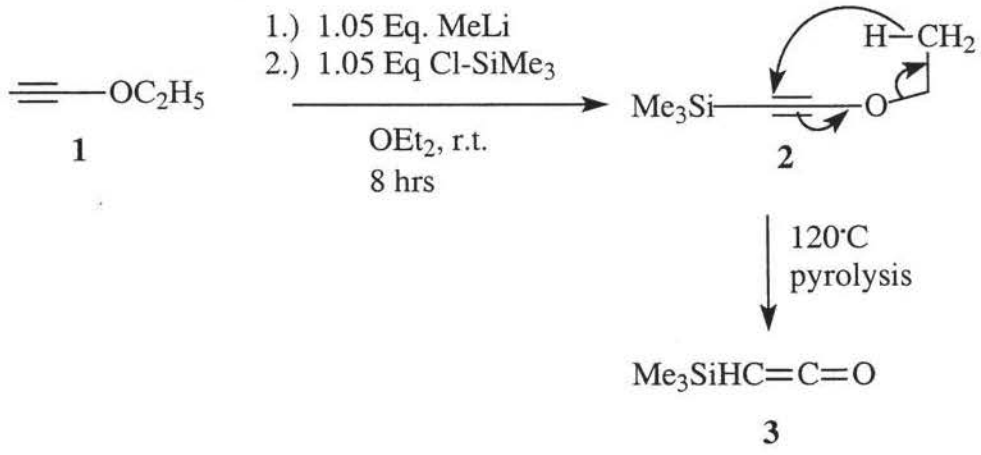
Trimethylsilyketene (**X3**) was a critical compound that was required for the cycloaddition reaction in Scheme N. Our first attempt at its preparation was according to a procedure reported by Olah,[32] who reported the dehydration of trimethylsilylacetic acid (**X1**) (as well as other 2-trimethylsilylacetic acid derivatives) with dicyclohexylcarbodiimide (**X2**) (DCC). Due to the moisture sensitive nature of the DCC reagent, it was always Kugelrohr distilled prior to its use and anhydrous ether was freshly opened. Progression of this reaction was evidenced by the formation of a white precipitate. After reacting for six hours, the precipitous mixture was concentrated via rotary evaporator, and distillation attempts were made to separate the product **X3** from the reaction mixture. Simple distillation of the reaction mixture often resulted in decomposition of the white mixture with no collection of trimethylsilylketene. When the distillation was performed under aspirator pressure, mixtures of trimethylsilylketene (evidenced by the ketene carbonyl stretching band at 2180 cm^{-1}) with unidentified products were isolated, which readily turned from a clear liquid to a slightly brown liquid upon sitting at room temperature for brief periods. Attempts to isolate **X3** from these simple distillation collections resulted in further decomposition and no collection of desired ketene product.

Scheme X



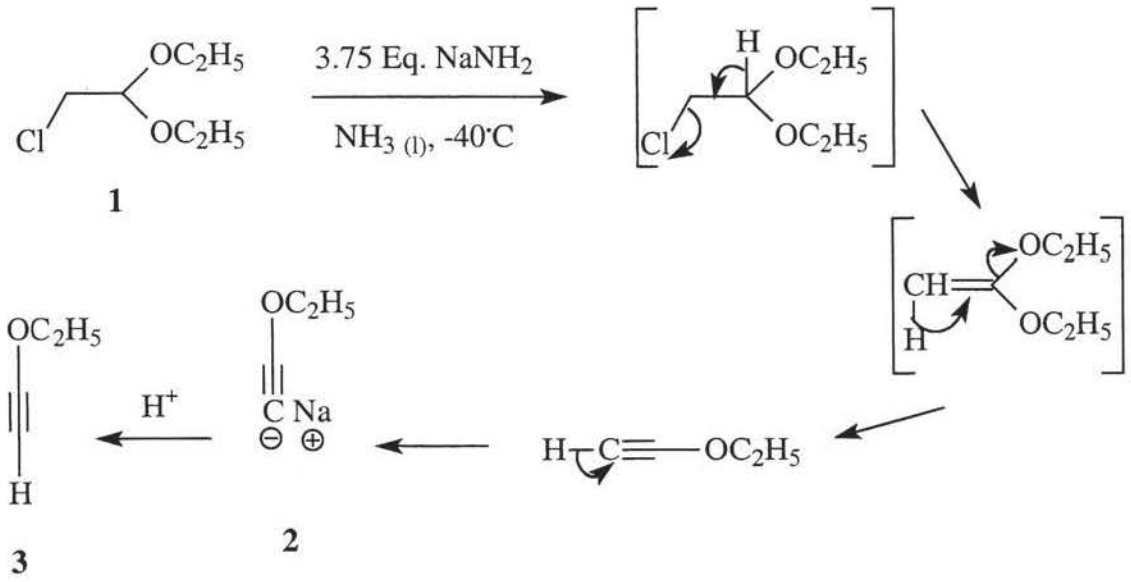
Trimethylsilylketene (**Y3**) was successfully prepared from the pyrolysis reaction of trimethylsilylethoxyacetylene (**Y2**) prepared by a procedure reported by Ruden.[39] This procedure involved the deprotonation of ethoxyacetylene (**Y1**) by methyllithium, followed by the reaction of the derived anion with chlorotrimethylsilane to form an alkynyl silane, which upon heating to 120 °C, underwent pyrolysis to give the desired trimethylsilylketene in 55 % yield.

Scheme Y



Ethoxyacetylene (**Z3**) was available from Aldrich Chemicals but was extremely expensive. Furthermore, the reagent was only available as a solution in hexanes, requiring fractional distillation prior to use. Bearing these shortcomings in mind, we opted to prepare ethoxyacetylene (**Z3**) via a double elimination reaction of chloroacetaldehyde diethyl acetal (**Z1**) using sodium amide as base. Preceding research collaborators in our research group prepared sodium amide *in situ* by the addition of metallic sodium to a liquid ammonia solution of ferric nitrate ($FeNO_3$). However, *in situ* preparation of sodium amide necessitated four hours of stirring at temperatures below -40 °C.

Scheme Z



Our attention was then turned to the Swern method of oxidation devised for the oxidation of long chain alcohols (reaction conditions shown in Scheme T) .[30] This particular procedure utilizes an oxalyl chloride-activated DMSO complex **U3** as the oxidant is advantaged by of negligible formation of (methylthio)methyl ether derivative of the alcohol. Additionally, the Swern oxidation is reputedly a clean reaction (all the organic by-products: carbon monoxide, carbon dioxide, and dimethyl sulfide, are all gaseous) and we wished to be able to carry on aldehyde crude product without further purification.

Extreme caution was taken when hydrolyzing the sodium acetylide (**Z2**) reaction mixture. Failure to adequately cool the reaction flask to -70 °C resulted in violent pyrolysis of the reaction mixture. Attempts to isolate product from pyrolyzed reaction mixtures gave no yield of ethoxyacetylene product. Additionally, reaction mixtures that were allowed to sit for extended periods were on occasion observed to violently decompose, regardless of the source of sodium amide used.

Having developed methods for the preparation of (2*R*,3*S*)-epoxyhexanal and trimethylsilyacetic acid, we were prepared to investigate the aldol condensation reaction depicted in the first step of the proposed reaction sequence in Scheme N. An obvious challenge presented by this condensation reaction was the presence of multiple electrophilic sites within the epoxy aldehyde. We suspected that perhaps the oxirane carbons would compete with the carbonyl carbon for the trimethylsilyl acetic acid lithium dianion nucleophile. Indeed, literature precedence reveals that anionic reactions of trimethylsilyacetic acid with aldehydes[40] and epoxides[41] occur under similar conditions.

Therefore, it was imperative that we find reaction conditions that would favor exclusive attack at the carbonyl carbon and not the adjacent oxirane carbons.

A thorough literature search revealed a procedure for the successful reaction between the lithium anion of esters and 4-benzyloxy-2,3-epoxy butanal derivatives.[26] The procedure called for the formation of the lithium anion at 0 °C in ethyl ether over thirty minutes, followed by dropwise addition of the aldehyde at -78 °C and subsequent quenching of the reaction mixture with weak acid after fifteen minutes of reaction time. When (2*R*,3*S*)-epoxyhexanal was added to a stirred solution of trimethylsilyacetic acid dianion at -78° C and the reactants stirred for fifteen minutes at this reduced temperature, only starting material was present (indicated by TLC). Several variations of the reported procedure, including extended reaction times, an alternative dianionic nucleophile, the use of tetrahydrofuran as solvent, and increased reaction temperature were investigated and are summarized in Table 1.

Table 1. Summary of aldol reactions performed.

Dianion *	solvent	reaction temperature (°C)	Duration (approximate)	Results**
1	ethyl ether	-70	15 minutes	no reaction
1	ethyl ether	-70	1 hour	no reaction
1	ethyl ether	warmed from -70 to 0	1 hour	intractable product mixture
2	ethyl ether	-70	1 hour	no reaction
2	THF	-70	1 hour	no reaction
2	THF	0 °C, allowed to warm to r.t.	> 5 hours	intractable product mixture
2	ethyl ether	0 °C, allowed to warm to r.t.	> 5 hours	intractable product mixture

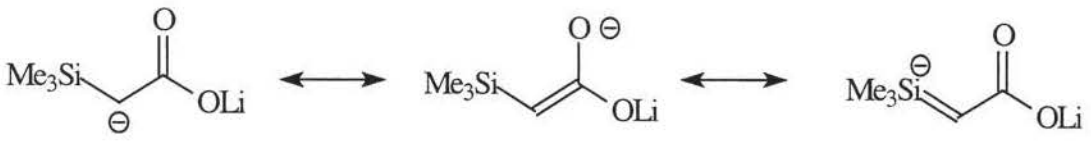
* 1= trimethylsilylacetic acid dianion, 2=phenylacetic acid dianion
** Reactions were montiored using silica gel TLC and either developed under UV light or chemically using phosphomolybdic acid.

As can be seen in the Table 1, no reaction is observed at the lower temperatures, regardless of the solvent, duration of reaction, or species of dianion. Typically, as the reaction mixture warmed, acquired a brown color and the partial consumption of aldehyde was observed (as indicated by TLC). Multiple polar products appeared to form as the reaction mixture warmed. The predominant component of the reaction mixtures appeared to be located at the origin in everything but the most polar mobile phases. Introduction of aldehyde at room temperature in THF resulted in a large exotherm and instantaneous darkening of the reaction mixture. The experimental data of Table 1 show

that the lithium dianion of both trimethylsilylacetic acid and phenylacetic acid were inert to the aldehyde substrate at lower temperatures (-70 °C); and, upon warming, intractable mixtures of polar compounds were formed.

The lack of reactivity of dianionic trimethylsilylacetic acid nucleophile with (2*R*, 3*S*)-epoxyhexanal in this seemingly straightforward reaction was initially eluding. Trimethylsilyacetic acid is readily metalated by lithium diisopropylamide,[42] and it was our expectation that the α-trimethylsilyl substituent would increase the nucleophilicity of the dianion by the inductive release of electrons to the α-carbon by the silicon atom. However, several studies have presented evidence that suggests that a silicon atom stabilizes rather destabilizes α-carbanions.[43] Evidently, lone pair electrons of α-carbanions can be delocalized into the *d*-orbitals of the silicon atom.[43a] This stabilization affect can be conceptualized by the resonance structure **AA3** in which the negative charge is located on the silicon atom. Resonance structure **AA3** would be further stabilized due to its newly formed conjugated double bond system. Backbonding between dπ orbitals of silicon atom and pπ C-C bond of resonance structure **AA2** may also reduce electron density at the anionic site.[43c]

Scheme AA

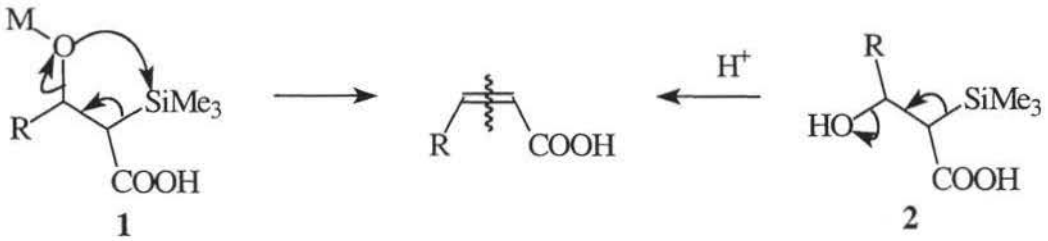


1 **2** **3**

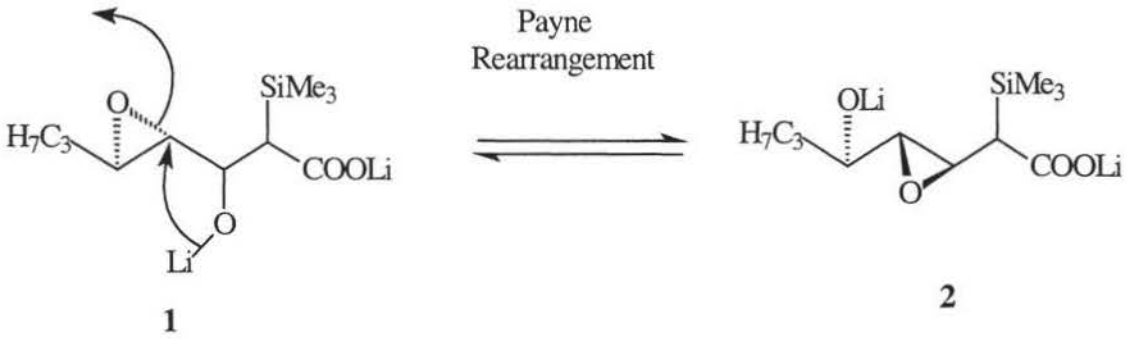
The α-anion stabilizing effect of the silicon atom and decreasing nucleophilic affect observed in vinyl silanes perhaps explains the lack of reactivity of the trimethylsilyl acetic acid dianion with the epoxy aldehyde at lower temperatures (-70 °C). Furthermore, the phenylacetic acid dianion is undoubtedly stabilized by the phenyl substituent, probably explaining the lack of reactivity of this nucleophile at reduced temperatures as well.

Literature research on the reactivity of β-silylcarbinols suggests that perhaps isolation of the aldol adduct **M3** would be difficult due to the tendency of β-silylcarbinols (like **BB1** and **BB3**) to spontaneously eliminate in both acidic and basic conditions to afford unsaturated carbonyl compounds.[40,41] Indeed, a structurally diverse group of unsaturated acids have been prepared using this methodology.[42] Lending additional instability to **M3** is the observation that metalated hydroxyl groups adjacent to oxirane moieties undergo Payne rearrangement[44] to produce an equilibrated mixture of epoxy alcohols (such as **CC1** and **CC2**).

Scheme BB



Scheme CC



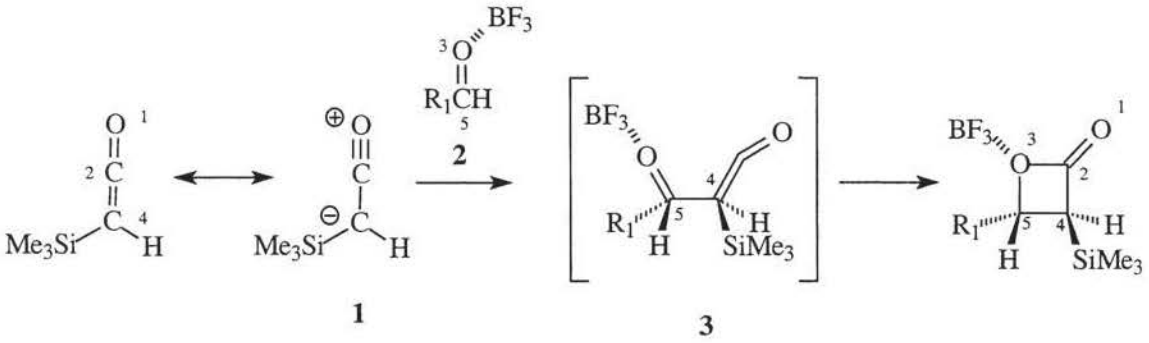
Due to the experimental difficulties presented by the condensation reaction shown in Scheme M, in addition to the potential complications inherent in isolating β-hydroxy-α-silylcarbonyl compound **M3**, investigations into this synthetic route were discontinued. Efforts to prepare the desired epoxy β-lactone were redirected to the [2+2] cycloaddition route depicted in Scheme N .

The [2+2] cycloaddition reaction between ketenes and carbonyl compounds has been known for almost a century now.[45a] However, the cycloaddition between silylketenes and carbonyl compounds was not performed until 1975,[18a] and the synthetic utility of this method was illustrated by Brady and Saidi only in1979.[36] Since then, silylketenes have been used to prepare a variety of β-lactones. Unfortunately, mechanistic studies of [2+2] cycloaddition reaction between silylketenes and carbonyl compounds are rare.[18a] Consequently, the mechanism of the reaction is unsettled.[46]

The mechanism of ketene [2+2] cycloaddition appears to be dependent on the type of ketene , the nature of its substituents, the species of Lewis acid, and the species of the ketenophile present. Perhaps most germane to this project are the recent *ab initio* and semi-empirical studies of [2+2] reactions between formaldehyde and ketene in the presence of boron trifluoride catalyst. Indeed, these studies find experimental support by the diastereoselectivity of [2+2] cycloaddition adducts observed by Zemribo and Romo.[19]

These studies corroborate a mechanism in which the nucleophilic ketene attacks an electrophilic aldehyde, activated by coordination with a Lewis acid (**DD2**). The process is thought to be a concerted, but asynchronous, closed-shell mechanism, featuring the preliminary formation of the C_4-C_5 bond. The ketene and aldehyde approach each other in a synperiplanar fashion and the formed transition state **DD3**, having a strong zwitterionic character.[47]

Scheme DD



Epoxides are known to possess enhanced reactivity in the presence of Lewis acids.[56] Therefore, we wanted to confirm that the chiron (2*R*,3*S*)-epoxyhexanal would be stable in the presence of the boron trifluoride catalyst under the anticipated reaction conditions. A control experiment was performed in which (2*R*,3*S*)-epoxyhexanal was stirred in the presence of catalytic amount of Lewis acid at 0 °C in ethyl ether for approximately two hours, at which time the reaction mixture was warmed to room temperature. No reaction was observed as indicated by TLC analysis. However, when the aldehyde-catalyst solution was concentrated *in vacuo*, the solution became a black gelatinous solid. These results showed that (2*R*,3*S*)-epoxyhexanal would be stable under the reaction conditions, but the catalyst would have to be quenched (with methanol) prior to *in vacuo* concentration of reaction mixtures containing (2*R*,3*S*)-epoxyhexanal and BF_3.

Typical [2+2] cycloaddition procedures involve the slow addition of trimethylsilylketene in ether to a stirring solution of (2*S*, 3*S*)-epoxyhexanal and a catalytic amount of boron trifluoride at 0 °C.[36] However, when this protocol was followed, (2*R*,3*S*)-epoxyhexanal was consumed immediately as indicated by TLC. The resulting reaction mixture contained multiple components, with the predominant

component being immobile in many solvent systems tested and was not amenable to chromatographic separation. IR analysis of the crude reaction mixture showed no evidence of the formation of the desired β-lactone (carbonyl band >1800 cm^{-1})[36] or butenolide (carbonyl band 1750-1760 cm^{-1}).[48]

Mead and coworkers reported in their investigations that the success of the [2+2] cycloaddition was dependent on the order in which the reagents were combined.[49] Thus, under similar conditions to those described in the previous paragraph, experiments were performed in which 1) (2*R*,3*S*)-epoxyhexanal was introduced to a solution of trimethylsilylketene-catalyst or 2) the catalyst was added to a solution of aldehyde-trimethylsilylketene. The order in which reagents were combined gave similar complicated mixtures in which no single component was isolable.

We reasoned that there were two possible possibilities for the absence of β-lactone within the reaction mixture and crude product. First, we thought that perhaps the weakly basic oxirane oxygen atom might be interfering with the functioning of the Lewis acid catalyst in the cycloaddition reaction. However, Zembribo and Romo[19] reported excellent yields of β-lactone when trimethylsilylketene was reacted with aldehydes bearing ether oxygen atoms at α or β-positions. These results suggested that an adjacent epoxide oxygen, as is present in (2R,3S)-epoxyhexanal, would not likely interfere with the functioning of the Lewis acid in the [2+2] cycloaddition reaction and that the formation of epoxy β-lactone should be possible.

The second possibility considered was that the cycloaddition reaction was occurring, however; the instability of the derived β-lactone did not allow for its isolation. Certainly, the fact that IR spectra of reaction mixture aliquots showed no evidence of the

formation of β-lactone suggested that, if formed, the β-lactone was only a transient species in the reaction mixture, and at 0 °C and in the presence of catalytic amounts of boron trifluoride, the β-lactone instantly underwent transformation to other undesirable products.

Therefore, we set out to determine if the β-lactone was actually forming. We sought to do this by using IR to determine if the signature β-lactone carbonyl peak could be detected in reaction mixture aliquots or 2) by identifying other components of the reaction mixture that might have formed through a β-lactone intermediate (such as the desired butenolide or α,β-unsaturated γ,δ-epoxy silylesters).

In an effort to minimize or altogether eliminate the undesirable reactions giving intractable mixtures, the [2+2] reaction between trimethylsilylketene and (2*R*,3*S*)-epoxyhexanal was performed at reduced temperatures (-40 °C). Again, the aldehyde was nearly consumed after only a few minutes of reaction. As expected, IR spectra of reaction mixture aliquots showed no absorption band >1800 cm^{-1} corresponding to of β-lactone carbonyl stretching. The reaction performed at reduced temperature still gave product mixtures that were difficult to separate using silica gel chromatography; however, some components of the reaction mixture could be isolated.

One such component having a Rf value of 0.43 (7.5% ethyl acetate: hexane) was isolated. The structure of this component followed from its IR spectrum which showed stretching bands for 3060 cm^{-1}(vinylic hydrogens), 2959 cm^{-1}(C-H), 1755 cm^{-1} (C=O), 1667 cm^{-1}(C=C), 1138 and 1101 cm^{-1} (C-O-C), 959 cm^{-1} (vinylic hydrogens, out of plane stretch), and 844 cm^{-1} (Si-$(CH_3)_3$). This component was presumed to be the desired 5-(1-

O-trimethylsilylpropyl)-2-(5*H*)-furanone. This product was isolated in no better than 5% yield. Such small samples did not allow for NMR analysis.

. Inspection of Table 2 shows that the butenolide product was isolated for only those reactions performed below -40 °C. Yields could not be improved by further reducing reaction temperatures or by increasing the concentration of the boron trifluoride catalyst. It should be noted that under no reaction conditions was there direct evidence for the formation of β-lactone. However, it can be inferred that the 1-(5-O-trimethylsilylpropyl) butenolide was derived from an epoxy β-lactone intermediate.

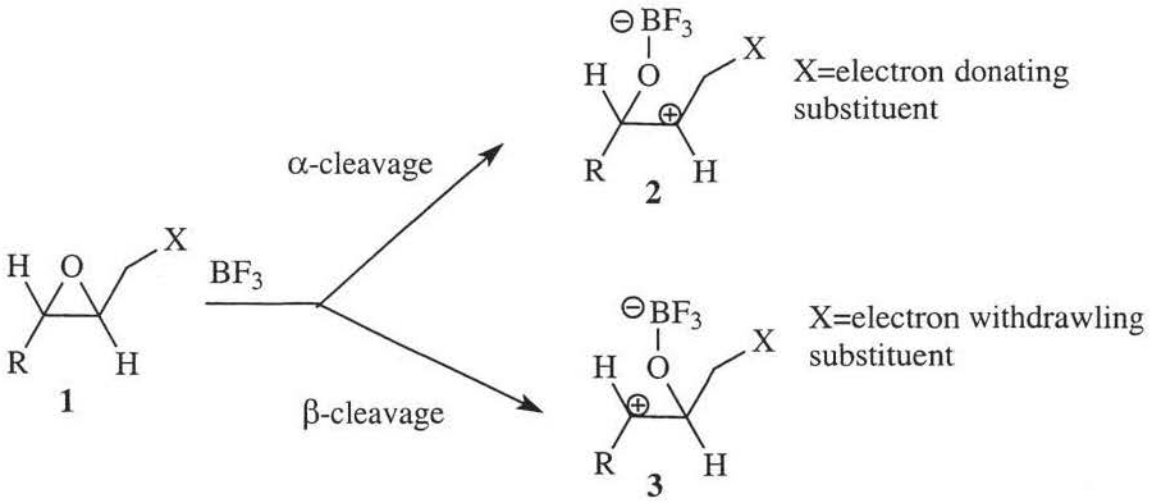
Table 2. Results of [2+2] cyloaddition under various reaction conditions

reaction temperature (Celsius)	borontrifluoride diethyl etherate	duration (Minutes)	butenolide present
0-warm to r.t.	cat.	overnight	N
0-warm to r.t.	excess	overnight	N
0	cat.	70	N
0	excess	60	N
0	cat.	30	N
0	cat.	20	N
0	cat.	10	N
-20	excess	15	N
-30	cat.	20	N
-40	excess	80	Y
-50	cat.	50	Y
-50	excess	120	Y
-70	excess	90	Y

Based on the results of previous investigations of α-trimethylsilyl-β-lactone transformations in our lab, we anticipated the formation of γ,δ-epoxy α,β-unsaturated silylesters (derived from the transformations depicted in Scheme H). However, no evidence of the allylic epoxide was found. Perhaps separations via silica gel chromatography would not have separated the unsaturated silylesters, as allylic epoxides are, at least in some cases, not amenable to silica gel separations.[10]

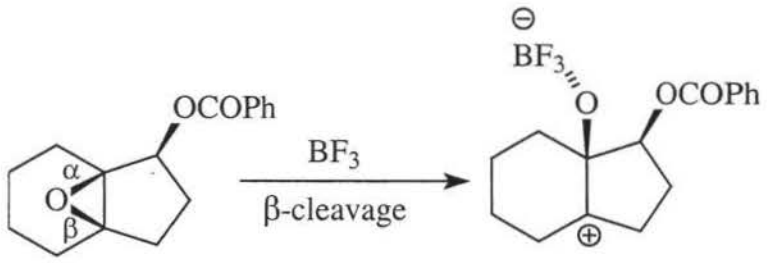
Unfortunately, the reactivity of epoxy-β-lactones is unprecedented and only a limited amount of information exists regarding the reactivity and transformations of structural analog α,β-epoxy acylates.[50b] In principle, tetrasubstituted epoxides, *in the absence of outside influences*, should have equal probability for cleavage of either C-O bond and ring opening transformations should be nonregioselective[51a] This principle should also be applicable to bi-substituted epoxides. However, when vicinal effects (steric and electronic) are present as in the epoxy β-lactone, epoxide ring opening transformations may become regioselective. The functionalization of carbon atoms adjacent to the epoxide ring and within the epoxide ring[52a] are known to influence the regioselectivity of the oxirane ring opening, and the regioselective cleavage of the oxirane ring is governed to some extent by the electron-inducing nature of the vicinal substituent X in epoxide **EE1** . For example, epoxides bearing adjacent electron donating substituents (X = hydroxyl, hydroxy derivatives) readily rearrange in the presence of boron trifluoride to give α-cleavage products **EE2**.[53,54] Additionally, epoxides bearing electron-withdrawing substituents [50,51,55] (X = acyloxy, ketone) have an inductive effect on the oxirane moiety that destabilizes cationic charge α to the electron withdrawing substituent, and consequently products arising from β-cleavage (as in **EE3**) are observed.

Scheme EE

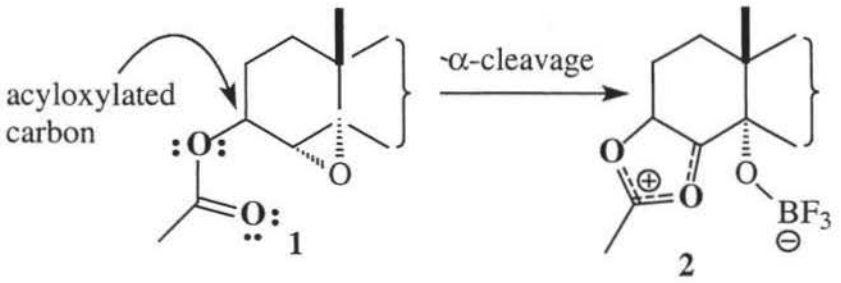


Kita *et al.* published work on the rearrangement reaction of tetra- and tri-substituted epoxy acylates.[51] In these studies, the boron trifluoride initiated rearrangement products of epoxy acylates arose from carbocationic intermediates of β-cleavage (Scheme FF). Similarly, Coxon and coworkers[50] investigated the boron trifluoride catalyzed rearrangement of six α,β-epoxy acylate compounds, five of which gave major products evolving from β-cleavage. Indeed, those epoxy acylates undergoing α-cleavage rearrangements were rationalized by invoking a dioxenium ion intermediate **GG2**,[50b] a transition state which would not be permitted in the epoxy β-lactone having its "acyl" moiety incorporated in the cyclic lactone ring. Indeed, the epoxy acylates investigated by Coxon and Kita readily underwent β-cleavage, as reaction times for these rearrangements were as short as two minutes.[50b] Thus, the rearrangement of the epoxy-β-lactone to the desired butenolide would have to be extremely fast to compete with reaction pathways presented from C-O β-cleavage.

Scheme FF



Scheme GG

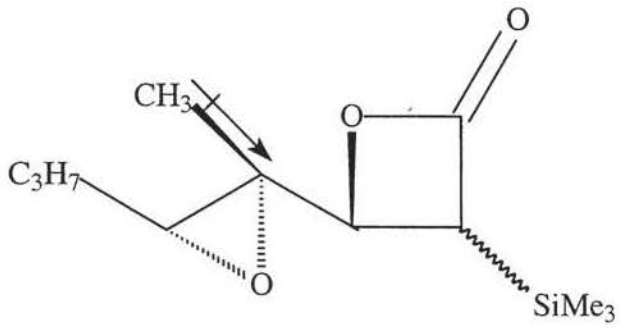


A dioxenium reaction intermediate would would be impossible due to the mobility constraints imposed by the lactone ring.

In addition to the steric and electronic factors that influence the oxirane chemistry, Henbest and Wrigley found epoxide transformations in the presence of boron trifluoride to be solvent dependent.[52d] This observation was corroborated by Goldsmith's observation that completely different product ratios were obtained when the solvent was changed from ether to benzene. Evidently, the solvent affects the oxophilic nature of the boron trifluoride nucleus.[52c] Thus, future attempts to prepare epoxy β-lactones in the presence of boron trifluoride should carefully consider the solvent system to be used. Solvent systems other than ethyl ether which have been used successfully in [2+2] cycloaddition reactions include toluene, benzene, and dichloromethane.

Future investigations into the rearrangement of epoxy β-lactones should try to minimize the inductive effect imposed by the lactone ring oxygen. One possibility for attaining this goal would be to structurally modify the oxirane moiety in a way that counterbalances the inductive effect of the adjacent lactone oxygen. Perhaps one possibility would be to use the trisubstituted β-lactone shown in Figure 3. In this way, the inductive effect would be lessened by the electron rich alkyl group, perhaps attenuating the tendency for β-cleavage. Furthermore, any cationic character induced by coordination of the Lewis acid with the oxirane oxygen would be thermodynamically favored at the more substituted oxirane carbon, leaving the stereogenic center adjacent to the β-lactone susceptible to S_N2 displacement.

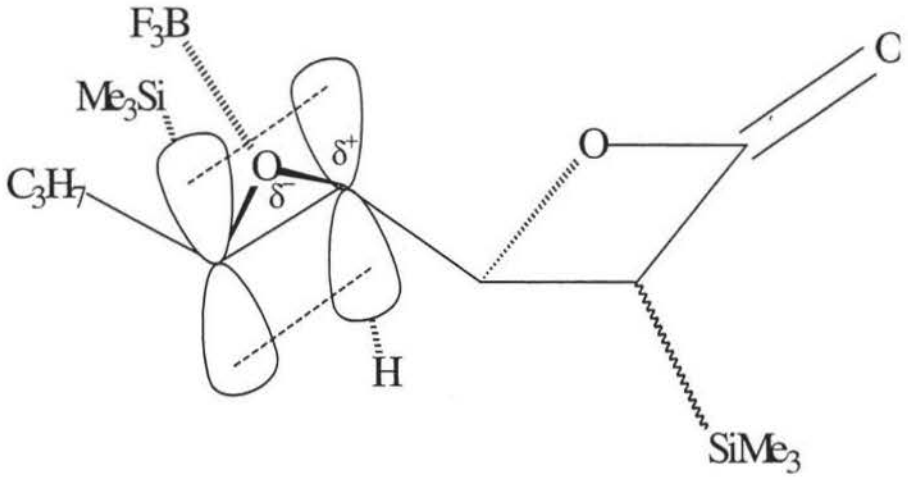
Figure 3



This trisubstituted epoxide
would perhaps negate the inductive
effects of the lactone ring oxygen

Another structural modification that might stabilize the oxirane moiety is the presence of a trimethylsilyl substituent at the stereogenic center homo of the β-lactone (Figure 4). The requisite (2*R*,3*S*)-epoxy-3-trimethylsilylhexanal chiron has been prepared from known procedures in good yields and excellent ee.[27] The β effect of the silicon atom would potentially stabilize cationic character on the carbon adjacent to the β-lactone ring oxygen and minimize the inductive effect presented by the β-lactone. Additionally, the trimethylsilyl group could be removed by treament with potassium fluoride diyhdrate.

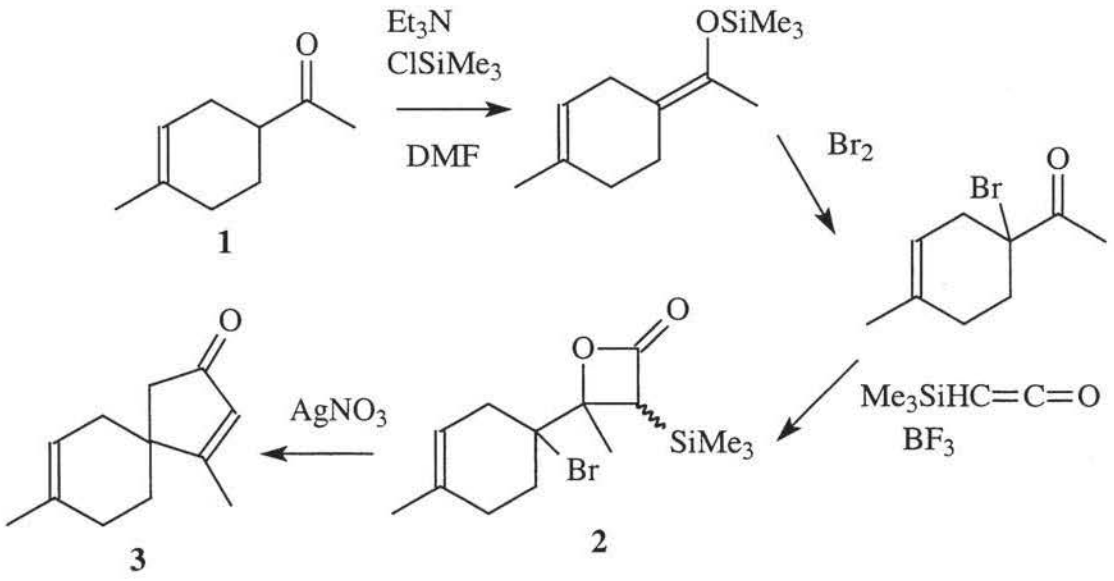
Figure 4



Suspecting that the oxirane ring oxygen was responsible for the lack of success in the 5-(1-hydroxyalkyl) butenolide synthesis, we decided to expand on the project started by Huang (Scheme J) based on the transformations of γ-bromo β-lactones in the presence of silver (I) catalyst. However, unlike the β-lactones investigated by Huang, the β-lactones of this project would bear a α-trimethylsilyl substituent and a tertiary γ-bromo carbon. We thought that the 3° halide would be a better leaving group than the 2° halides investigated by Huang due to the longer Br-C bond in the 3° halide and the more stable cation formed by the departure of the bromine nucleofuge.

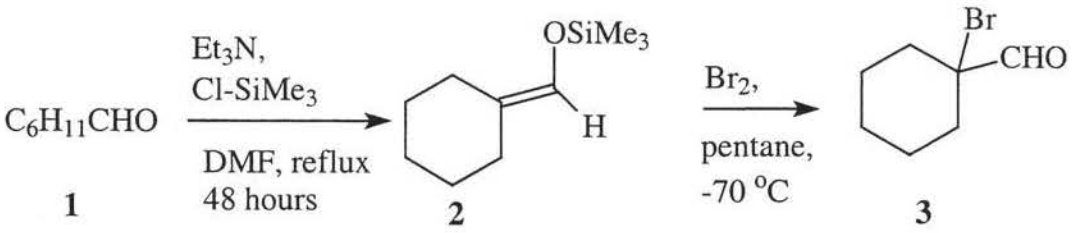
We wished to prepare the desired β-lactone via the two-step sequence (Scheme D) or alternately the [2+2] cycloaddition reactions between α-bromoaldehydes and trimethylsilylketene (Scheme E). We chose 1-bromocyclohexanecarboxaldehyde as a source of aldehyde for the pilot reaction. This reagent we wished to prepare from the readily available cyclohexanecarboxaldehyde. In the case that this reaction were successful, we intended to apply this methodology to the preparation of medicinally important andirolactone (**HH3**) arising from the transformation of β-lactone **HH2**, which in turn could be prepared from readily available and inexpensive 4-acetyl-1-methylcyclohexene (**HH1**).

Scheme HH



The first attempts at the preparation of 1-bromocyclohexanecarboxaldehyde **II3** were based on a two step reaction sequence involving first the formation of the trimethylsilyl enol ether of the aldehyde **II2**, followed by the bromination of the enol double bond with elemental bromine.

Scheme II

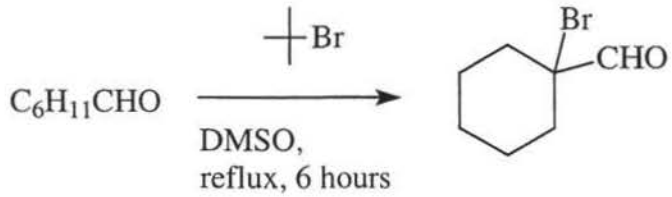


The trimethylsilyl enol ether **II2** was easily prepared by refluxing aldehyde **II1** for 48 hours in the presence of proton scavenger triethylamine base and chlorotrimethylsilane. ^{13}C-NMR and IR (νC=C absorption band at 1679 cm^{-1}) are consistent with the structure of the trimethylsilyl enol ether of cyclohexanecarboxaldehyde. However, discrepancies in the ^{1}H NMR spectrum exist between expected and observed splitting. Observed in the ^{1}H NMR spectrum of **II2** is the presence of two quartets, rather than the expected triplets, located at 1.91-1.94 and 2.14-2.18 ppm respectively. Each of these signals integrates precisely to two hydrogen atoms and presumably corresponds to the allylic protons of the silyl enol ether. Furthermore, the signal for the vinylic proton at 5.98 ppm is a triplet, rather than the expected singlet. Regardless of these incongruencies in expected and observed spectrum, ^{1}H NMR integration supports the structural identity of **II2**. Furthermore, **II2**, when carried on to the bromination step, gave the desired 1-bromocyclohexanecarboxaldehyde (**II3**) in modest yield (67.0%), as evidenced by IR, ^{1}H and ^{13}C NMR.

A more convenient preparation of the 1-bromocyclohexanecarboxaldehyde was sought. An uncited procedure for the single step preparation of α-bromoaldehydes was found in Huang's thesis (Scheme JJ). The reaction required only six hours and did not

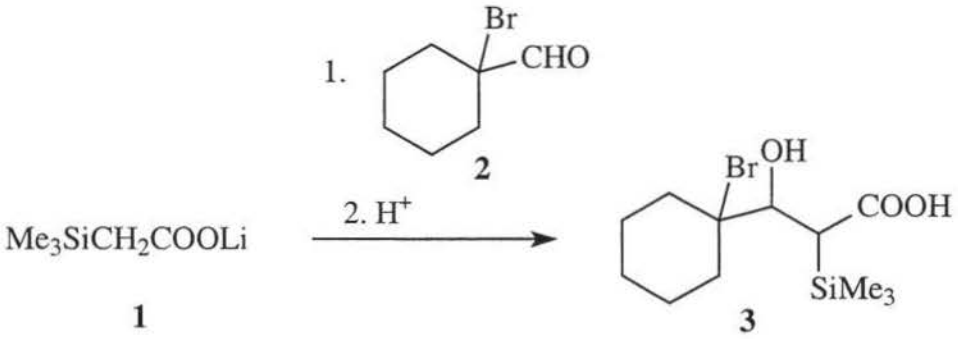
necessitate the extremely low reaction temperatures needed for the bromination of silyl enol ethers. When this procedure was followed, the 1-bromocyclohexanecarboxaldehyde was prepared in a single step in 82.6% yield. Additionally, this protocol proved to be a versatile method for α-bromination and could be applied to the bromination of 2-phenylpropionaldehyde to give 2-bromo-2-phenylpropianaldehyde in 61.2% yield.

Scheme JJ



With 2-bromocyclohexanecarboxaldehyde in hand, we began to investigate the synthetic procedures that would afford β-lactone **LL1**. Following the procedure of Black *et al.*, we investigated the condensation reaction between 1-bromocyclohexanecarboxaldehyde (**KK2**) and trimethylsilylacetic acid dianion **KK1**.[10a] This reaction upon workup gave low crude product yields (less than 50%). Recrystallization of the crude product gave a colorless crystalline product with an mp of 133-136 °C in 14.4% yield. The structure of this product followed from its IR, ^1H and ^{13}C NMR spectrum and is the unsaturated acid 3-(1-bromocyclohexyl)-2-propenoic acid, rather than the desired β-hydroxy acid **KK3**. The presence of (Si-Me_3) absorbance band (844 cm^{-1}) in the IR spectrum and the singlet in the ^1H NMR spectrum located at 0.11 ppm can be explained by the presence of trimethylsilylhydroxide contaminant that would

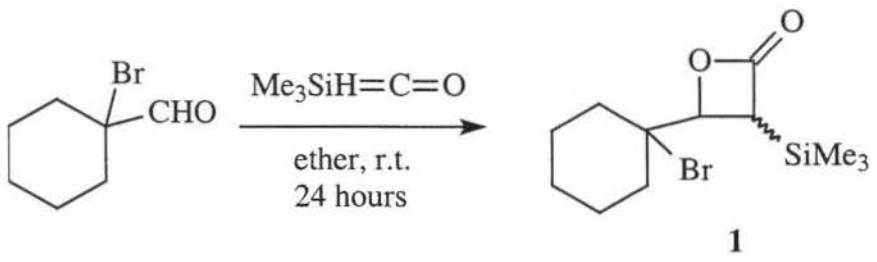
Scheme KK



have been produced during the acidic workup of the reaction mixture.

Unable to prepare β-hydroxy acid **KK3** requisite for the synthetic sequence of Scheme M, we proceeded to investigate the [2+2] cycloaddition reaction between trimethylsilylketene and 1-bromocyclohexanecarboxaldehyde, depicted in Scheme LL. This reaction proceeded slowly and resulted in incomplete reaction of the starting material aldehyde, as evidenced by TLC analysis of the reaction mixture. IR analysis of the crude products after 12 and 24 hours showed the C=O stretching absorption band corresponding to the β-lactone and the 2-bromocyclohexanecarboxaldehyde to be of equal intensity, confirming that the starting aldehyde was not completely consumed. The use of excess ketene (2 equivalents) did nothing to further reaction progress. Nonetheless, the β-lactone **LL1** was isolated in 46% yield as a pale crystalline solid mp

Scheme LL



81-84°C using silica gel chromatography (5% ether:hexane eluant). The structure of the lactone was confirmed by its IR. Furthermore, ^{1}H NMR indicated the presence of the C_3 and C_4 protons as doublets at 4.25-4.26 (1H) and 3.30-3.36 (1H) ppm, in excellent agreement with literature data.[57] ^{13}C NMR spectrum also provided supporting evidence for the structure of the β-lactone with the characteristic carbonyl carbon signal at 170 ppm. Unfortunately, the NMR analysis of this product was delayed and quality spectra of the purified β-lactone are not available. Consequently spectra presented for this compound do not represent the pure β-lactone.

Investigations into the cation initiated ring expansion of γ-bromo-β-lactone**LL1** were only partially complete, and attempts to initiate the transformation of **LL1** using the silver (I) catalytic system were limited; thus, the status of this project is considered to be open.

Conclusions

Two synthetic routes for the preparation of epoxy β-lactone **K1** have been investigated. The first step of the reaction sequence in Scheme M presented insurmountable obstacles. The aldol reaction was studied under a variety of reaction temperatures/times and solvent systems, but no combination of the above variables produced β-hydroxy acid **M3**. The lack of success of this reaction was attributed to the existence of multiple intermolecular reaction pathways availed by the three contiguous nucleophilic sites within chiron **M1**, as well as the numerous conceivable intramolecular transformations in highly functionalized aldol adduct **M3**.

The [2+2] cycloaddition of trimethylsilylketene to **N1** was studied under various reaction temperatures, reaction durations, and catalyst concentrations. No direct evidence for the formation of β-lactone **N3** was found; however, the presence of 5-(1-O-trimethylsilylpropyl)-2-(5*H*)-furanone in <5% yield, which was identified by IR, suggests that perhaps β-lactone **N3** is formed during cycloaddition reactions performed below -40 °C but readily undergoes further indeterminate transformations in the presence of the boron trifluoride etherate catalyst. Literature research on the boron trifluoride catalyzed rearrangement of epoxy acylates reveals that perhaps the inductive effect of the vicinal lactone ring oxygen may present reaction pathways previously not considered. Therefore, strategies involving structural modification of the epoxy β-lactone **K1** (as in Figures 3 and 4) and alternative solvent systems have been suggested.

Efforts were also made to expand on the project of γ-bromo-β-lactone transformations discovered by Huang. It was determined that the preparation of γ-bromo-β-hydroxy- α-silyl acid **KK3** was not possible via known methods of β-hydroxy acid

preparation previously used in our lab, and consequently the synthetic strategy of Scheme KK is not a viable protocol to β-lactone **LL1**. The product of condensation reactions between dianionic trimethylsilylacetic acid and 2-bromocyclohexanecarboxaldehyde gave 3-(1-bromocyclohexyl)-2-propenoic acid, rather than the desired silyl carbinol acid **KK3**. Fortunately, the [2+2] cycloaddition reaction between trimethylsilylketene and 2-bromocyclohexancarboxaldehyde gave the desired γ-bromo-β-lactone **LL1** 46% yield.

In summary, two of the most commonly used routes to β-lactones were exhaustively investigated in an effort to prepare epoxy-β-lactone **K1**. Unfortunately, manipulation of the reaction conditions in these two routes did not lead to the development of a protocol for **K1**. However, current literature research has exposed other factors not previously considered by our lab.

General Methods

All reagents and solvents were purchased from Aldrich Chemical Company unless otherwise stated. Anhydrous diethyl ether was obtained from Fisher Scientific and was used without further purification. Tetrahydrofuran (THF) was also purchased from Fisher Scientific and was freshly distilled from sodium/potassium benzophenone ketyl indicator under nitrogen. Methylene chloride was freshly distilled from calcium hydride; dimethyl sulfoxide, and triethylamine were distilled periodically from calcium hydride and stored under nitrogen in serum bottles (DMSO stored over 3A molecular sieves). Diisopropylamine was distilled from barium hydroxide and stored under nitrogen in serum bottles. ^{13}C NMR spectra were recorded on a GE QE-300 MHz FT-NMR spectrometer using deuteriochloroform ($CDCl_3$) as lock solvent. ^{1}H NMR spectra were acquired using the EFT-360 60 MHz NMR spectrometer or GE QE-300 MHz FT-NMR . In analytical samples bearing a trimethylsilyl functional group, a TMS (tetramethylsilane) standard was not used; rather spectra were aligned with respect to the chloroform solvent peak at 7.26 ppm. 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). IR spectra were acquired using Nicolet Avatar 360 FT-IR spectrophotometer. GC analysis was performed using a GOW-MAC isothermal GC (¼"x4' 20% Carbowax 20M on Chromosorb AW-DMCS 80/100 mesh, column temperature 100 °C, flow rate ~60 mL per minute) Boiling points are uncorrected. Melting points were obtained in capillary tubes with Laboratory Device, USA Mel-Temp II apparatus and are uncorrected. Thin layer

chromatography (TLC) was performed on Analtech silica gel GF chromatography plates. Silica gel media for preparative chromatography was 200-400mesh, particle size 60 Angstrom. All moisture and air sensitive reactions were conducted under nitrogen gas flow in glassware that was dried at 120 $^{\circ}$C prior to use.

Experimental

(2S,3S)-epoxyhexan-1-ol (1).

A 2-L three-necked, round-bottomed flask equipped with a mechanical stirrer with Teflon blades, thermometer, and nitrogen inlet was charged with 1 L of anhydrous methylene chloride and 40 mL (38.1 g, 0.134 mol) of titanium (IV) isopropoxide. The flask contents were cooled under nitrogen in a methanol-liquid nitrogen bath to –70 °C. The flask were then charged with 27.5 mL (33.1 g, 0.161mol) of diethyl (2*R*,3*R*)-tartrate and 30.65 g (0.313 mol) of *E*-2-hexen-1-ol. To the flask was then added, in one shot portions, 185 mL (0.500 mol) of 2.71 M anhydrous *tert*-butyl hydroperoxide in toluene that had been precooled to –20 °C. A 10 °C exotherm was observed, and the reaction mixture was allowed to warm to room temperature over approximately two hours.

When the light green reaction solution had reached room temperature, it was poured into a 4 L beaker equipped with a magnetic stirring bar and containing a 0 °C solution of 125 grams of ferrous sulfate and 50 grams of tartaric acid in a total volume of 500 mL of deionized water. The resulting reaction was mildly exothermic. The solution was stirred for 30 minutes, during which time the solution became a dark, rust brown mixture. The contents of the beaker were transferred to a 1L separatory funnel and the aqueous phase was separated and extracted with two 250 mL portions of ether. The combined organic layers were dried over magnesium sulfate and the drying agent was removed by vacuum filtration. The solvent was removed with light heating on a rotary evaporator and the resulting oil was stored overnight in the freezer.

A 2 L, three necked, round-bottomed flask equipped with a thermometer and a mechanical stirrer with Teflon blades was charged with a solution of the reaction product in the 750 mL of ether. The contents of the flask were cooled with an ice-brine bath to 0 °C before adding a precooled 500 mL solution of brine containing 20 grams (0.50 mol) of sodium hydroxide. The biphasic mixture was stirred vigorously for one hour with continued cooling, at which time it was transferred to a 1 L separatory funnel. The aqueous phase was separated and extracted with two 150 mL portions of ether and the combined organic extracts were dried over magnesium sulfate and filtered. The solvent was removed with mild heating on a rotary evaporator and the crude product was distilled through a 15 cm Vigreaux column and 20.05 grams (70.6% yield) of (2*S*,3*S*)-epoxyhexan-1-ol was collected between 73-76°C (Lit.[58] bp 31-33°C/0.3-0.4 torr) under aspirator vacuum.

TLC (CH_2Cl_2) Rf = 0.23. IR (neat): 3418, 2961, 2933, 2874, 1465, 1045, 900 cm^{-1}. ^1H NMR δ_{CDCl3}: 0.96 (m, 3H), 1.53 (m, 4H), 2.95 (m, 2H), 3.70 (m, 3H) ppm (Lit.[58] ^1H NMR δ_{CDCl3}: 0.96 (m, 3H), 1.52 (m, 4H), 2.90 (m, 2H), 3.63 (m, 3H) ppm). ^{13}C NMR δ_{CDCl3}: 13.72, 19.02, 33.40, 55.82, 58.59, 61.74 ppm.

(2R,3*S*)-epoxyhexanal (2).

A 50 mL three neck rounded bottom flask equipped with magnetic stir bar and low temperature thermometer was charged with 20 mL of anhydrous methylene chloride and 2.4 mL (4.7 mmol) of a 2.0 M methylene chloride solution of oxalyl chloride. The contents of the flask were cooled to –60 °C and 0.67 mL dimethyl sulfoxide (0.74 grams, 9.4 mmol) in 3 mL of methylene chloride was delivered dropwise over five minutes. The

reaction solution was stirred until effervescence ceased (about ten minutes). (2*S*,3*S*)-Epoxyhexan-1-ol (500 mg, 4.31 mmol) in 2 mL of methylene chloride was then added slowly while maintaining the reaction temperature below –50 °C. The mixture was stirred for an additional fifteen minutes before slowly adding 3.0 mL (2.1 grams, 21.5 mmol) of triethylamine. This light yellow mixture was stirred an additional five minutes before allowing it to warm slowly to room temperature over one hour. The mixture was quenched with water and the resulting biphasic solution was separated. The aqueous layer was back-extracted once with 30 mL of methylene chloride and the organic layers were combined and washed sequentially with 1.5N HCl, water, saturated sodium bicarbonate, and finally water. The remaining organic layer was dried over magnesium sulfate and evaporated to give a golden oil. Kugelrohr distillation gave pure (2*R*,3*S*)-epoxyhexanal (308 mg) in 62.7 % yield.

TLC (CH_2Cl_2) Rf = 0.72. Bp 29°C at 1 mm Hg. IR (neat): 2963, 2934, 2875, 1728, 851 cm^{-1} (Lit.[58] IR (neat): 2900, 1725, 1205, 920, 870 cm^{-1}). ^{13}C NMR δ_{CDCl3}: 13.76, 19.07, 33.07, 56.53, 59.01, 198.47 ppm (Lit.[58] ^{13}C NMR δ_{CDCl3}: 13.7, 19.2, 33.3, 56.6, 59.1, 198.1 ppm).

Trimethylsilylacetic acid (3).

A 1 L three neck rounded bottom flask equipped with a stir bar, rubber septum, and double condenser was charged with 400 mL of anhydrous ether. Magnesium turnings (15.72 grams, 0.648 mol) were added to the stirring solvent followed by a catalytic amount of 1,2-dibromoethane (~0.2 mL). The mixture was heated to reflux and 59 mL (50.5 g, 0.460 mol) of chlorotrimethylsilane was delivered slowly with vigorous stirring. The Grignard reaction was evidenced by the formation of a dark gray mixture, at

which time the heat was removed. An ice bath was applied intermittently to control the rate of reaction. The mixture was stirred for four hours, before it was carefully poured into a 2-L filter flask equipped with bubbler and stopper and containing ~ 200 grams of crushed dry ice. A second ~200 gram portion of carbon dioxide pellet was delivered 30 minutes later. The remaining solid was allowed to off gas overnight.

To the filter flask was added 1 L of ether, followed by 400 mL 1.5 N HCl. With vigorous stirring, the biphasic mixture became a biphasic solution. The two layers were separated and the aqueous layer was extracted sequentially with 300 mL of ether and 300 mL of methylene chloride. The organic layers were combined, dried with magnesium sulfate and evaporated to give a 46.97 grams (76.5% yield) of a clear oil, which crystallized only upon refrigeration.

Mp 38-40 °C (Lit.[30] mp 40°C). IR (neat): 2964, 2651, 1677, 1439, 1300, 1250, 1138, 1116, 857 cm^{-1}. ^{1}H NMR δ_{CDCl3}: 0.15 (9H, s), 1.92 (1H, s) ppm (Lit.[30] ^{1}H NMR δ_{CDCl3}: 0.23, 9H, s), 1.98 (2H, s) ppm). ^{13}C NMR δ_{CDCl3}: -1.56, 27.17, 180.0 ppm.

Ethoxyacetylene (4).

A 2 L, three-necked, round-bottomed flask equipped with a mechanical stirrer and a Teflon blade, a cold-finger condenser, and a gas exhaust outlet was cooled to –50 °C with a liquid nitrogen-ethanol bath. The flask was charged with 1 L of anhydrous ammonia, and 85.92 grams (2.09 mol) of 95% sodium amide powder was added in small portions over a ten minute period with vigorous stirring. The resulting suspension was stirred at –40 °C for ten minutes. During this time, the condenser was replaced with a rubber septum.

To the stirring –40 °C suspension was then added 83.7 mL (85.2 grams, 0.558 mol) chloroacetaldehyde diethyl acetal dropwise over one hour . The reaction mixture was stirred for an additional thirty minutes at –40 °C, when the bath was removed and the ammonia allowed to evaporate overnight under a nitrogen atmosphere.

The reaction flask was then cooled to –80 °C and the resulting yellow sodium acetylide solid was hydrolyzed with 450 mL of –5 °C brine over a thirty minute period. The aqueous mixture was stirred until all of the solid was dissolved, and then was transferred to a 1 L round-bottomed flask. The biphasic mixture was then heated and 28.06 g of ethoxyacetylene was distilled off under nitrogen between 46-48 °C. The distillate was then dried with anhydrous magnesium sulfate. The drying agent was filtered off to afford 25.00 grams (64% yield) as a colorless, volatile liquid having a bp 48 °C (760 mm) (Lit.[39] bp 48-50°C).

IR (neat): 3317, 2155, 1129, 1098 cm^{-1}(Lit.[39] IR (neat): 3300, 2145 cm^{-1}). ^{1}H NMR $\delta_{CDCl3:}$ 1.39 (3H, t), 1.53 (1H, s), 3.96 (2H, q) ppm (Lit.[39] ^{1}H NMR $\delta_{CDCl3:}$ 1.37 (3H, t), 1.53 (1H, s), 4.23 (4H, q) ppm). ^{13}C NMR $\delta_{CDCl3:}$ 14.08, 26.34, 74.49, 90.69 ppm.

Trimethylsilylketene (5).

A 500 mL three necked rounded bottom flask equipped with nitrogen inlet, magnetic stir bar and rubber septum was charged with 300 mL of anhydrous ether and 8.85 grams (0.126 mol) of ethoxyacetylene; the solution was cooled to 0 °C with brine-ice bath. 1.4 M Methyllithium (93 mL of a 1.4M solution, 0.130 mol) was delivered dropwise over forty minutes. A white mixture formed and was stirred an additional twenty minutes. 16.79 mL of chlorotrimethylsilane (14.37 grams, 0.132 mmol) was then

delivered slowly over twenty minutes and the reaction mixture was stirred at room temperature for twenty hours. The white reaction mixture was then filtered through an oven dried medium frit filter, the yellow filtrate was collected, and the ether slowly distilled off with gentle heating. The residual oil was then heated to 120 °C and trimethylsilylketene was collected under aspirator vacuum in 56% yield as a clear oil from 78-82 °C (Lit.[50] bp 82 °C 760 mm Hg).

IR (neat): 2959, 2927, 2873, 2115, 1270, 1262, 1052, 844 cm^{-1}. ^1H NMR δ_{CDCl3}: 0.178 (9H, s), 1.79 (1H, s) ppm.

5-(1-O-trimethylsilylpropyl)-2-(5*H*)-furanone (6).

A 25 mL three necked, rounded-bottom flask equipped with a magnetic stir bar, nitrogen inlet, and rubber septum was charged with ~10 mL of anhydrous ether. (2R,3S)-Epoxyhexanal (85 mg, 0.74 mmol) and trimethylsilylketene (110 mg, 0.965 mmol) were delivered to the stirring solvent at room temperature. The solution was cooled to -70 °C using an ethyl acetate-liquid nitrogen bath, and boron trifluoride diethyl etherate (eight drops) was added. The reaction mixture was stirred at this reduced temperature for two hours before quenching with ten drops of methanol and allowing the mixture to warm to room temperature. The resulting solution was evaporated *in vacuo*; whereupon separation using silica gel chromatography (7.5% ethyl acetate: hexane eluant) gave the desired 5-(1-O-trimethylsilylpropyl) α,β-butenolide as a clear oil in no greater than 5 % yields.

TLC (7.5% ethyl acetate:hexane) Rf = 0.43. IR (neat): 3060 cm^{-1}(vinylic hydrogens), 2959 cm^{-1} (C-H), 1755 cm^{-1} (C=O), 1667 cm^{-1} (C=C), 1138 and 1101 cm^{-1} (C-O-C), 959

cm^{-1} (vinylic hydrogens, out of plane stretch), and 844 cm^{-1} ($Si-(CH_3)_3$. NMR data not available for this compound.

Trimethylsilyl enol ether of cyclohexanecarboxaldehyde (cyclohexylidenemethoxytrimethylsilane) (7).

In a 100 mL rounded bottom flask equipped with a condenser, stir bar and heating mantle was charged with 15 mL of dimethylformamide, 16.82 mL (12.14 grams, 120 mmol) of triethylamine, 7.61 mL (7.04 grams, 61.5 mmol) of cyclohexanecarboxaldehyde. A white mixture formed immediately upon addition of the chlorotrimethylsilane, which became a light orange upon heating. The mixture was allowed to reflux for 48 hours under nitrogen gas flow, at which time the mixture was a dark orange brown. The reaction mixture was diluted with 40 mL hexane and cooled in the refrigerator, along with 40 mL of 1.5N hydrochloric acid and 160 mL of saturated sodium bicarbonate.

The reaction mixture was washed rapidly with three 40mL portions of precooled sodium bicarbonate solution and the combined aqueous washes were back extracted with 40mL hexane and 60 mL of pentane. The combined organic layers were then washed rapidly in succession with 40 mL of 1.5 N hydrochloric acid and sodium bicarbonate. The resulting orange organic layer was then dried over magnesium sulfate. The drying agent was removed by vacuum filtration and the filtrate was evaporated *in vacuo* to give crude product which was purified using a Kugelrohr distillation apparatus to give 8.82 grams (78% yield) of a clear colorless oil.

IR (neat): 2980, 2926, 2853, 1678, 1252, 1213, 1154, 909, 874, 843 cm^{-1}(Lit.[59] IR (neat): 1677 cm^{-1}). ^1H NMR δ_{CDCl3}: 1.477 (m, 6H), 1.90-1.94 (q, 2H), 2.14-2.18 (q, 2H), 5.98 (t, 1H) ppm (Lit[59] ^1H NMR δ_{CDCl3}: 5.96 (s, 1H), 2.14 (br, s, 2H), 1.91 (br s, 2H), 1.55 (m, 2H), 0.37 (s, 9H) ppm). ^{13}C NMR δ_{CDCl3}: -.63, 25.29, 26.97, 28.41, 30.52, 122.39, 130.03 ppm (Lit.[59] ^{13}C NMR δ_{CDCl3}: 130.1, 122.6, 30.6, 28.5, 27.1, 25.4, 0.4 ppm).

1-bromocyclohexanecarboxaldehyde (8).

A 100 mL three necked rounded bottomed flask equipped with a magnetic stir bar, rubber septum, low temperature thermometer, and nitrogen inlet was charged with 50 mL of pentane and 1.0 gram (5.4 mmol) of **7** and cooled to –60 °C with methanol-liquid nitrogen bath. Bromine (0.30 ml, 5.4 mmol), dissolved in 5 mL of pentane, was added over fifteen minutes while maintaining the temperature of the reaction flask contents below -60 °C. The orange reaction mixture was allowed to warm to room temperature, at which time it became an orange solution. The solvent and bromotrimethylsilane by-product were removed *in vacuo* to yield an orange oil. The oil was distilled using a 15 cm Vigreaux column and **8** was collected as a clear oil between 37 and 39 °C/ 1 mm Hg in 67.0% yield.

TLC (10% ethyl acetate:hexane) Rf = 0.42. IR (neat): 2937, 2857, 1724, 1448, 1113, 1032 cm^{-1}(Lit.[60] IR (film):1730 cm^{-1}). ^1H NMR δ_{CDCl3}: 1.55-1.72 (6H, m), 1.87-2.03 (4H, m), 9.35 (1H, s) ppm (Lit.[60] ^1H NMR δ_{CCl4}: 9.32 (s, 1H), 1.4-2.2 (m, 10H) ppm). ^{13}C NMR δ_{CDCl3}: 23.08, 24.85, 34.35, 71.57, 192.69 ppm.

General Procedure for the α-Bromination of Aldehydes Using *tert*-Butylbromide.

A 250 mL rounded bottom flask equipped with a heating mantle, magnetic stir bar, and condenser was charged with 53.7 mmol of aldehyde, 7.60 mL (8.36 grams, 107 mmol) of dimethyl sulfoxide, and 24.65 mL (29.3 grams,214 mmol) of *t*-butyl bromide. The solution was heated at reflux for six hours under nitrogen.

The heating mantle was removed and the reaction solution was allowed to cool to room temperature before being diluted 1:1 with ether. The resulting solution was washed three times with equivalent volumes of water, and once with brine. The organic layer was dried over magnesium sulfate and evaporated. Distillation of the residue at the indicated conditions gave the α-bromo aldehyde in pure form.

1-Bromocyclohexanecarboxaldehyde (8).

Distilled using a 15 cm Vigreaux column and collected as a clear oil between 37 and 39 °C/ 1 mm Hg in 82.6% yield.

2-Bromo-2-phenylpropanal (9). Purified via Kugelrohr distillation to give a bright yellow, clear oil in 61.2% yield. IR (neat): 2979, 1724, 1493, 1446, 1051, 760, 696 cm^{-1}. ^1H NMR δ_{CDCl3}: 2.15 (3H, s), 7.41-7.45 (5H, m), 9.56 (1H, s) ppm(Lit.[61] ^1H $NMR_{\delta ald}$ 9.53 ppm; Lit.[62] NMR δ_{CDCl3}: 2.2 (s, 3), (7.4 (m, 5H), 9.55 (s, 1H) ppm). ^{13}C NMR δ_{CDCl3}: 21.39, 25.12, 36.80, 71.96, 117.73, 145.19, 157.15, 172.06 ppm.

3-(1-Bromocyclohexyl)-2-propenoic acid (10).

A 50 mL three necked rounded bottom flask was equipped with a mechanical stirrer, low temperature thermometer, and nitrogen inlet was charged with 25 mL of tetrahydrofuran

and 2.11 mL (1.52 grams, 15.1 mmol) of diisopropylamine. The flask was cooled to -40 °C and 9.4 mL (15.0 mmol) of *n*-butyllithium in hexanes (1.4M) was added dropwise to the stirring solution. After the mixture stirred for fifteen minutes at -40 °C, trimethylsilylacetic acid (1.00g, 7.53 mmol) was added dropwise as a THF solution. The reaction mixture was allowed to warm to 0 °C over thirty minutes, was recooled to -70 °C, and 1.44 grams (7.53 mmol) of **8** in THF solution was added slowly. The reaction mixture was warmed to room temperature and stirred overnight.

The white reaction mixture was poured into precooled water. The layers were separated and the aqueous layer extracted twice with 30 mL portions of ether. The organic layers were discarded and the aqueous layer was acidified with 6 N hydrochloric acid, resulting in the formation of a white precipitate. The resulting mixture was extracted twice with 30 mL portions of diethyl ether and the organic layers were combined and washed sequentially with water and brine and dried over magnesium sulfate. The drying agent was removed via filtration, and the organic layer was evaporated *in vacuo* to give 1.04 grams of a yellow oil which upon recrystallization from 5% ethanol:hexane yielded colorless crystals of 3-(1-bromocyclohexyl)-2-propenoic acid in 14.4% yield.

3-(1-bromocyclohexyl)-2-propenoic acid is a crystalline solid. mp 133-136 °C. TLC (ethyl acetate) Rf = 0.11. IR (neat): 2930, 2855, 1697, 1252, 844 cm^{-1}. ^{1}H NMR δ_{CDCl3}: 1.63 (m, 10H), 6.04-6.09 (d, 1H), 7.09-7.14 (d, 1H) ppm. ^{13}C NMR δ_{CDCl3}: -1.664, 21.39, 25.12, 36.78, 71.97, 117.74, 145.21, 157.16, 172.07 ppm. (HRMS is being acquired)

4-(1-bromocyclohexyl)-2-trimethylsilyloxetan-2-one (11).

A 25 mL three necked, rounded-bottom flask equipped with a magnetic stir bar, nitrogen inlet, and rubber septum was charged with about 10 mL anhydrous ether. Aldehyde **8** (221 mg, 1.16 mmol) and trimethylsilylketene (245 mg, 2.1 mmol) were delivered to the stirring solvent at room temperature. The solution was cooled to 0 °C a brine-ice water bath, and seven drops of boron trifluoride diethyl etherate were added. The reaction solution was allowed to warm slowly to room temperature overnight.

The yellow reaction solution was quenched with methanol (about 10 drops) and the solution was evaporated *in vacuo*. The β-lactone was then isolated from the crude product mixture using silica gel chromatography (5% ether:hexane eluent), which yielded 164 mg (46% yield) of a pale crystalline solid.

4-(1-bromocyclohexyl)-2-trimethylsilyloxetan-2-one was isolated as a pale colored solid, mp 81-84 °C. IR (neat): 2950, 1813, 1280, 1110, 847 cm^{-1}. ^{1}H NMR δ_{CDCl3}: 3.30-3.33 (d, 1H), 4.25-4.26 (d, 1H), 0.25 (s, 9H) ppm. ^{13}C NMR δ_{CDCl3}: 170 ppm (C=O).

References

1. a) Rao, Y.S. *Chem. Rev.* **1976**, 76, 625-690. b) Hanessian, S.; Murray, P.J. *J. Org. Chem.* **1987**, *52*, 1170-1172.

2. Smith, C. J.; Abbanat, D.; Bernan, V.S.; Maiese, W.M.; Greenstein, M.; Jompa, J.; Tahir, A.; Ireland, C.M. *J. Nat. Prod.* **2000**, *63*, 142-145.

3. a) Couladouros, E.A.; Mihou, A.P. *Tetrahedron Lett.* **1999**, *40,* 4861-4862. b) Gravier-Pelletier, C.; Saniere, M.; Charvet, I.; Merrer, Y.L.; Depezay, J-C. *Tetrahedron Lett.* **1994** *35*, 115-118.

4. Sanchez-Sancho, F.; Valverde, S.; Herradon, B. *Tetrahedron: Asymmetry* **1996**, *7*, 3209-3246.

5. a) Ortuno, R.M. *Synth. Commun.* **1994**, *24*, 651-658. b) Srikrishna, A.; Veera, R. S. *Tetrahedron Lett.* **1988**, *29*, 6487-6488.

6. Figadere, B.; Peyrat, J.F.; Cave, A. *J. Org. Chem.* **1997**, *62*, 3428-3429.

7. Cardellach, J.; Estopa, C.; Font, J.; Moreno-Manas, M.; Ortuno, R.M.; Sanchez-Ferrando, F.; Valle, S.; Vilamajo, L. *Tetrahedron* **1982**, *38*, 2377-2394.

8. Hanessian, S.; Murray, P.J. *Tetrahedron* **1987,** *43*, 5055-5072.

9. Ohe, F.; Bruckner, R. *Tetrahedron Lett.* **1998**, *39*, 1909-1910.

10. a) Black, T.H.; Dubay, W.J.; Tully, P.S. *J. Org. Chem.* **1988**, *53*, 5922. b) Black, T.H.; Maluleka, S.L. *Tetrahedron Lett.* **1989**, *30*, 531. c) Black, T.H.; McDermott, T.S.; Eisengbeis, S.A. *Tetrahedron Lett.* **1990**, *31*, 6617.

11. a) Black, T.H.; McDermott, T.S.; Brown, G.A. *Tetrahedron Lett.* **1991**, *32*, 6501-6502. b) Black, T.H.; Huang, J. *Tetrahedron Lett.* **1993**, *34*, 1411.

12. Black, T.H.; Zhang, Y.; Huang, J. Smith, D.C.; Yates, B.E. *Syn. Comm.* **1995**, *25*, 15-20.

13. a)Black, T.H.; Maluleka, S.L. *Tetrahedron Lett.* **1989**, *30* 531. b) Black, T.H.; Eisenbeis, S.A. *Tetrahedron Lett.* **1989**, *19* 2243. c) Black, TlH.; Maluleka, S.L. *Synth. Commun.* **1989**, *19*, 2885. d) Black, T.H.; Eisenbeis, S.A.; McDermott, T.S.; Maluleka, S.L. *Tetrahedron* **1990**, *46*, 2307.

14. Mulzer, J.; Bruntrup, G.; *Angew, Chem. Internat. Ed. Engl.* **1979**, *18*, 793.

15. Krapcho, A.P.; Jahngen, E.G.E. *J. Org. Chem.* **1974**, *39*, 1650.

16. a) Lambert, J. B.; Zhao, Y.; Emblidge, R.W.; Salvador, L.A.; L., Xiaoyang; S., Jeung-Ho; Chelius, E.C. *Acc. Chem. Res.* **1999**, *32*, 183-190. b) Lambert, J.B.; L., Xiaoyang *J. Organomet. Chem.* **1996**, *521*, 203-210. Nguyen, K.A.; Gordon, M.S.; Wang, G.T.; Lambert, J.B. *Organometallics* **1991**, *10*, 2798-803. c) Lambert, J.B.; Chelius, E.C. *J. Am. Chem. Soc.* 1990, 112, 8120-6. d) Lambert, J.B. *Tetrahedron* **1990**, *46*, 2677-89.

17. 59. Cornel, V. in *Encyclopedia of Reagents for Organic Synthesis*, ed. Paquette, L.A., **1995**, *Vol. 1*, 664-673.

18. a) Pommier, A.; Pons, J-M. *Synthesis* **1993**, 441-459. b) Brady, W.T.; Cheng, T.C. *J. Organomet. Chem.* **1977**, 137, 287-292.

19. Zembribo, R.; Romo, D.; *Tetrahedron. Lett.* **1995**, *36*, 4159-4162.

20. Hill, J.G.; Sharpless, K.B.; Exon, C.M.; Regenye, R. *Org. Synth.* Coll. Vol. 7, **1990**, 461-467.

21. Finn, M.G.; Sharpless, K.B. in *'Asymmetric Synthesis'*, **1985,** ed. Morrison, J.D., Academic Press, New York, *Vol. 5*, 247.

22. Vidal Ferran, A.; Moyano, A.; Pericas, M.A.; Riera, A. *J. Org. Chem.* **1997**, *62*, 4970-4982.

23. a) Woodard, S.S.; Ginn, M.G.; Sharpless, K.B. *J. Am. Chem. Soc.* **1991**, *113*, 106. b) Finn, M.G. Sharpless, D.B. *J. Am. Chem. Soc.* **1991**, 113.

24. Corey, E.J.; Suggs, J.W. *Tetrahedron Lett.* **1975**, 2647-2650.

25. Parikh, J.R.; Von Doering, E.W. *J. Am. Chem. Soc.* **1967**, *89*, 5505-5507.

26. Escudier, J-M.; Baltas, M.; Gorrichon, L *Tetrahedron.* **1993**, *49*, 5253-5266.

27. Urabe, H.; Matsuka, T.; Sato, F. *Tetrahedron Lett.* **1992**, *33*, 4179-4182.

28. Pfitzner, K.E.; Moffatt, J.G. *J. Am. Chem. Soc.* **1963**, *85*, 3027.

29. Taber, D.; Amedio, J.; Jung, K.; *J. Org. Chem.***1987**, *52*, 5621-5622.

30. Mancuso, A.J.; Huang, S.L-.; Swern, D. *J. Org. Chem.* **1978,** *43*, 2480.

31. Marx, M.; Tidwell, T.T. *J. Org. Chem.* **1984**, *49*, 790-793.

32. Olah, G.A.; An-hsiang, W.; Farooq, O. *Synthesis*, **1989,** 568.

33. Ottohiko, T.; Kanemasa, S., Suzuki, T.; Matsuda, K.*Bull. Chem. Soc. Japan* **1986**, *59*, 2851-2860.

34. Perrin, D.D.; Armarego, W.; *Purification of Laboratory Chemicals*, Permagon Press: New York, **1989,** 363.

35. . Ager, D.J. in *Encyclopedia of Reagents for Organic Synthesis*, ed. Paquette, L.A., **1995**, *Vol. 7*, 5229.

36. Brady, W.T.; Saidi, K. *J. Org. Chem.* **1979**, *40*, 733-737.

37. Peterson, D.J. *J. Org. Chem.* **1968**, *33*, 780-784.

38. Eberhardt, G.G.; Butte, W.A. *J. Org. Chem.* **1964**, 2928-2932.

39. Ruden, R.A. *J. Org. Chem.* **1974**, 3607.

40. Ager, D.J. *Organic Reactions* **1990**, 38, 1.

41. a) Hartzell, S.T.; Sullivan, D.F.; Rathke, M.W. *Tetrahedron Let.* **1974**, 1403-1406. b) Staley, S.W.; Orvedal, A.W.; *J. Am. Chem. Soc.* **1974**, 1620-1621. c) Chan, T.H.; Chang, E.; Vinokur, E. *Tetrahedron Lett.* **1970**, 1137-1140. d) Hudrlik, P.F.; Peterson, D.; *Tetrahedron Lett.* **1974**, 1133-1136. e) Carey, F.A.; Court, A.S.; *J. Org. Chem.* **1972**,*37*,939-943.

42. Grieco, P.A.; Wang, C-L.J.; Burke, S.D. *J. Chem. Soc., Chem. Comm.* **1975**, 537-538.

43. a) Cook, M.A.; Eaborn, C.; Jukes, A.E.; Walton, D.R.M. *J. Organomet. Chem.* **1970**, *24*, 529. b) Brook, A.G.; Duff, J.M.; Anderson, D.G. *Can. J. Chem.* **1970**, *48*, 561. c) Buell, G.R. Corriu, R.; Guerin, C.; Spialter, L.; *J. Am. Chem. Soc.* **1970**, *92*, 7424.

44. a) Payne, G.B. *J. Org. Chem.* **1962**, *27*, 3819. b) Behrens, C.H.; Ko, S.Y.; Sharpless, K.B.; Walker, F.J.; *J. Org. Chem.* **1985**,*50*, 5687-5696. c) Koizumi, N.; Ishiguro, M.; Yasuda, M.; Kiekawa, J. *J. Chem. Soc., Perkin Trans. 1* **1983**, 1401. d)Rokach, J.; Lau, C.-K.; Zamboni, R.; Guindon, Y. *Tetrahedron Lett.* **1981**, *22*, 2763.

45. a) Lecea, B.; Arrieta, A.; Roa, G.; Ugalde, J.M.; Cossio, F.P.; *J. Am. Chem. Soc.* **1994**, *116*, 9613-9619. b)Lecea, B.; Arrieta, A.; Lopez, X.; Ugalde, J.M.; Cossio, F.P. *J. Am. Chem. Soc.* **1995**, *117*, 12314-12321.

46. Shinichi, Y.; Kuwata, K.; Minato, T. *Theo. Chem. Acc.***1999**, *102*, 139-146.

47. Pons, J-M; Oblin, M.; Pommier, A.; Rajzmann, M.; Liotard, D. *J. Am. Chem. Soc.* **1997**, *119*, 3333-3338.

48. a) Black, T.H.; Brown, G.A.; Smith, D.C.; Martinie, S.M. *Synth. Commun.* **1995**, *25*, 479-483. b) Cardellach, J.; Estopa, C.; Font, J.; Moreno-Manas, M.; Ortuno, R.M.; Sanchez-Ferrando, F.; Valle, S.; Vilamajo, L. *Tetrahedron*, **1982**, *38*, 2377-2394.

49. Mead, K.T.; Samuel, B. *Tetrahedron Lett.*, **1988**, *29*, 6573-6576.

50. a) Coxon, J.M.; Gartshorn,M.P.; Kirk, D.N. *Tetrahedron* **1964**, *20*, 2531. b) Coxon, J.M.; Gartshorn, M.P.; Kirk, D.N. *Tetrahedron* **1964**, *20*, 2547.

51. a) Kita, Y.; Yoshida, Y.; Kitagaki, S.; Mihara, S.; Fang, D-F.; Furukawa, A.; Higuchi, K.; Fujioka, H. *Tetrahedron* **1999**, *55*, 4979-4998. b) Kita, Y.; Yoshida, Y.; Kitagaki, S.; Mihara, S.; Fang, D-F.; Furukawa, A.; Higuchi, K.; Fujioka, H.*Tetrahedron Lett.* **1997**, *38*, 1061-1064. c) Fujioka, H.; Kitagaki, S.; Imai, R.; Kondo, M.; Okamoto, S.; Yoshida, Y. Akai, S.; Kita, Y. *Tetrahedron Lett.* **1995**, *36*, 3219-3222.

52. a) Dauben, W.G.; Boswell, G.A.; Templeton, W.; McFarland, J.W.; Berezin, G.H. *J. Am. Chem. Soc.* **1963**, *85*, 1672. b) Hanbest, H.B.; Wrigley, T.I. *J. Chem Soc.* **1957**, 4765. c) Hanbest, H.B.; Wrigley, T.I. *J. Chem Soc.* **1957**, 4596. d) Goldsmith, *J.Am. Chem. Soc.* **1962**, *84*, 3913.

53. a) Maruoka, K.; Hasegawa, M.; Yamamoto, H. *J. Chem. Soc.* **1986**, *108*, 3827-3829. b) Suzuki, D.; Miyazawa, M.; Tsuchihashi, G-I. *Tetrahedron Lett.* **1987**,,*28*, 3515-3518. c) Maruoka, K.; Sato, J.; Yamamoto, H. *Tetrahedron*, **1992**, *48*, 3749.

54. a) Shimazaki, K.; Hara, H.; Suzuki, K.; Tsuchihashi, G-I. *Tetrahedron Lett.* **1987**, *28*, 5891-5894. b) Suzuki, K.; Shimazaki, M.; G-I., Tsuchihashi. *Tetrahedron Lett.* **1986**, *27*, 6233-6236. c) Marson, C.M.; Walker, A.J.; Pickering, J.; Hobson, A.D.; Wrigglesworth, R.; Edge, S.J. *J. Org. Chem.*, **1993**, *58*, 5944.

55. House, H.O.; Wasson. R.L. *J. Am. Chem. Soc.* **1957**, *79*, 1488-1492.

56. a) Alexakis, A.; Jachiet, D.; Mormant, J.F. *Tetrahedron* **1986**, *42*, 5607-5619. b) Alexakis, A.; Jachiet, D. *Tetrahedron* **1989**, *45*, 6197-6202.

57. Gordon, A.J.; Ford, R.A. *The Chemist's Companion, A Handbook of Practical Data, Techniques, and References.* Wiley-Interscience, New York, 1972, 259.

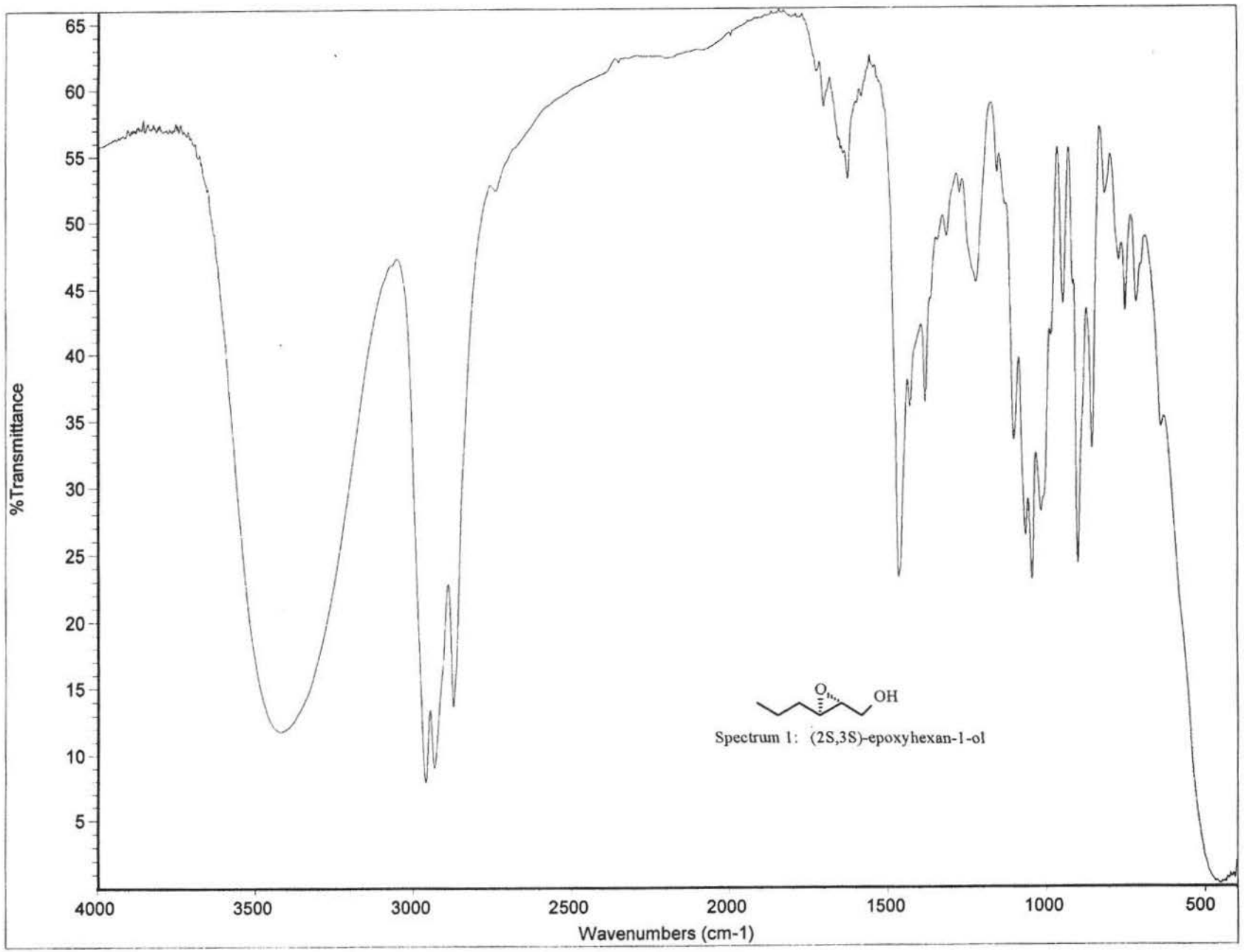
58. Nair, V.; Jahnke, T.S. *Tetrahedron* **1987**, *43*, 4257-4264.

59. Hydrio, J.; Weghe, P-V.; Collin, J. *Synthesis* **1997**, 68-70.

60. Bloch, R. *Synthesis* **1978**, 140-142.

61.Paulmier, C.; Outurquin, F.; Plaquevent, J-C. *Tetrahedron Letters* **1988**, *29*, 5893-5896.

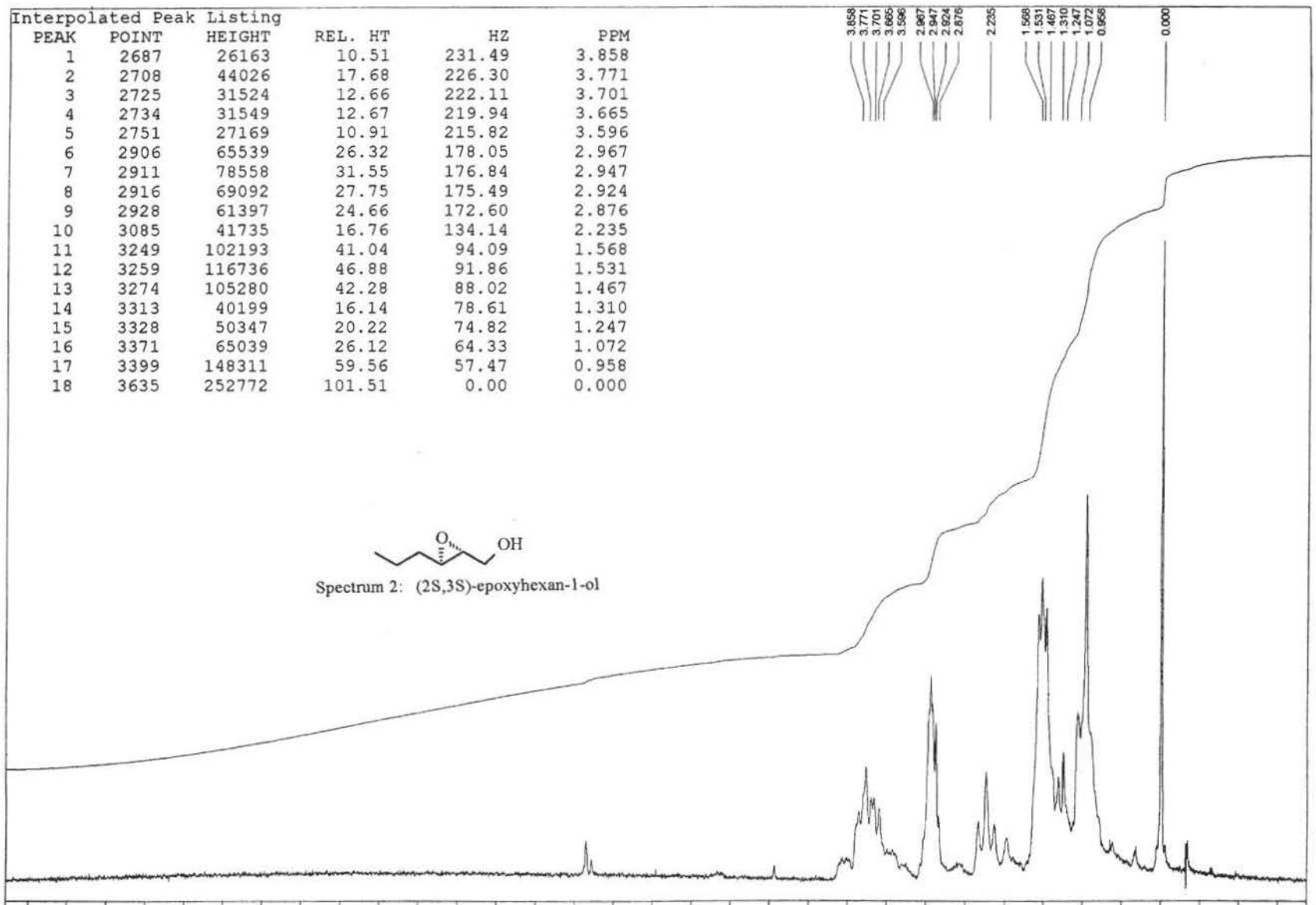
62. Reuss, R.H.; Hassner, A. *J. Org. Chem.* **1974**, *39*, 1785-1788.



Spectrum 1: (2S,3S)-epoxyhexan-1-ol

Interpolated Peak Listing

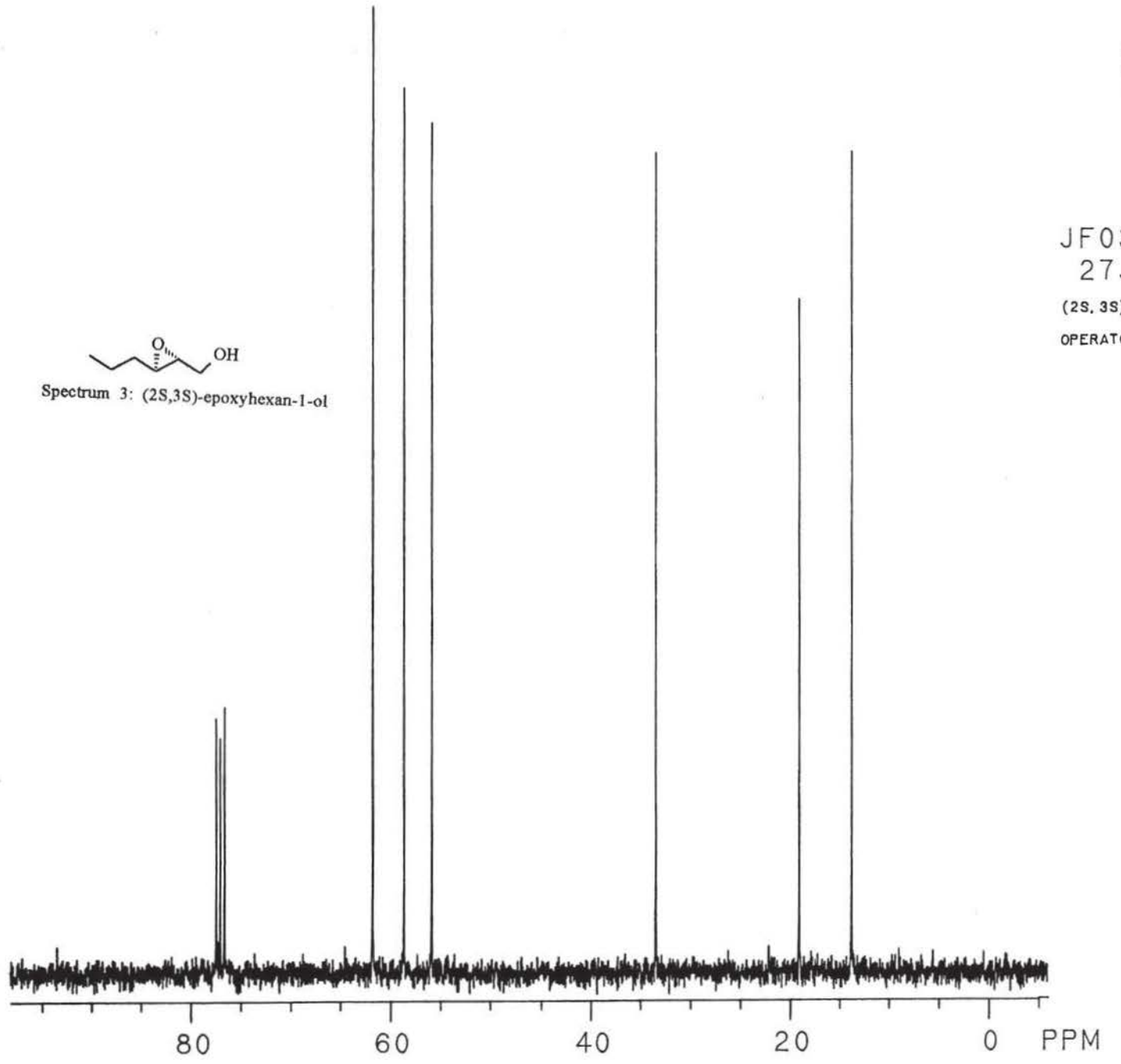
PEAK	POINT	HEIGHT	REL. HT	HZ	PPM
1	2687	26163	10.51	231.49	3.858
2	2708	44026	17.68	226.30	3.771
3	2725	31524	12.66	222.11	3.701
4	2734	31549	12.67	219.94	3.665
5	2751	27169	10.91	215.82	3.596
6	2906	65539	26.32	178.05	2.967
7	2911	78558	31.55	176.84	2.947
8	2916	69092	27.75	175.49	2.924
9	2928	61397	24.66	172.60	2.876
10	3085	41735	16.76	134.14	2.235
11	3249	102193	41.04	94.09	1.568
12	3259	116736	46.88	91.86	1.531
13	3274	105280	42.28	88.02	1.467
14	3313	40199	16.14	78.61	1.310
15	3328	50347	20.22	74.82	1.247
16	3371	65039	26.12	64.33	1.072
17	3399	148311	59.56	57.47	0.958
18	3635	252772	101.51	0.00	0.000



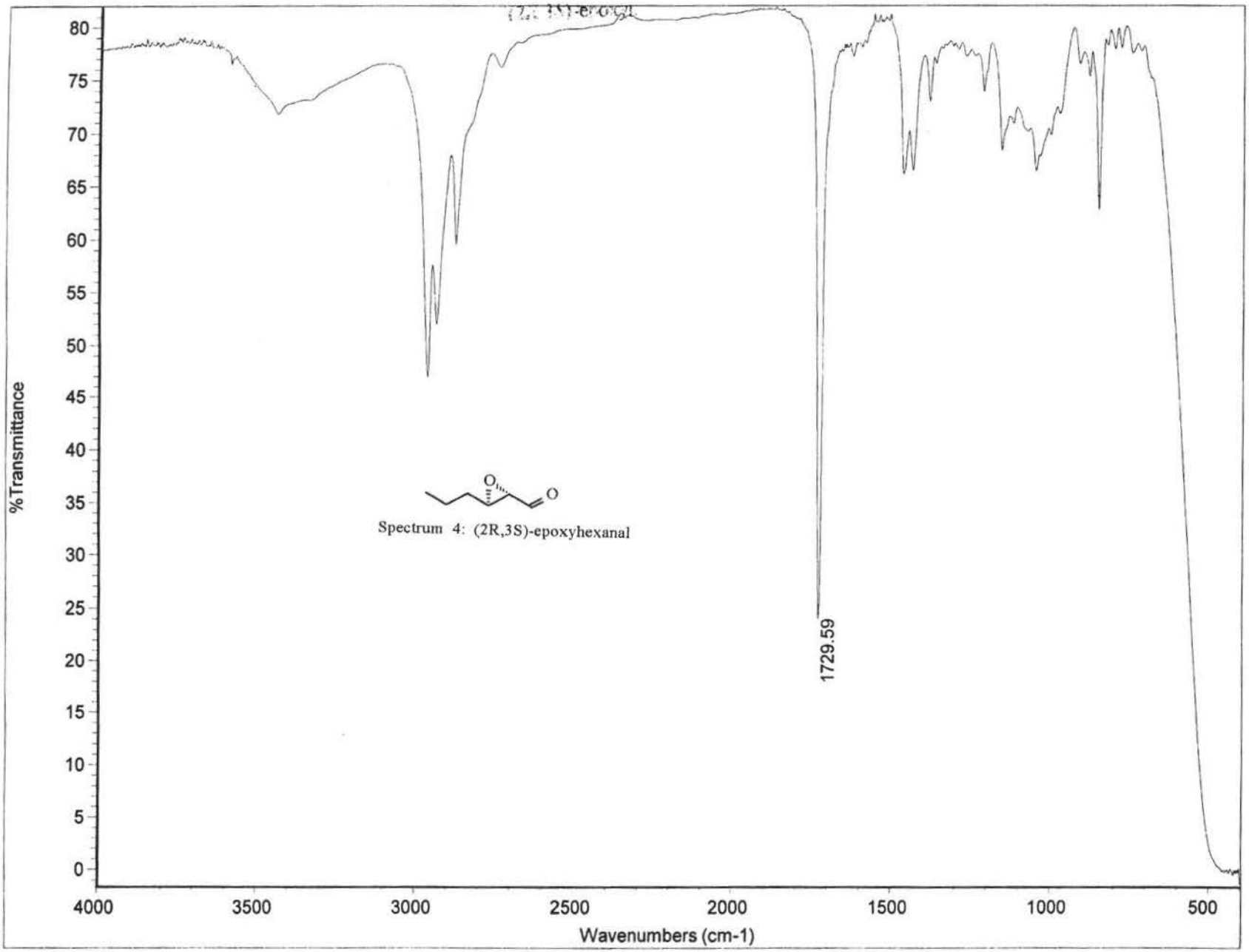
Spectrum 2: (2S,3S)-epoxyhexan-1-ol

LYBRICS Imported file USER: -- DATE:

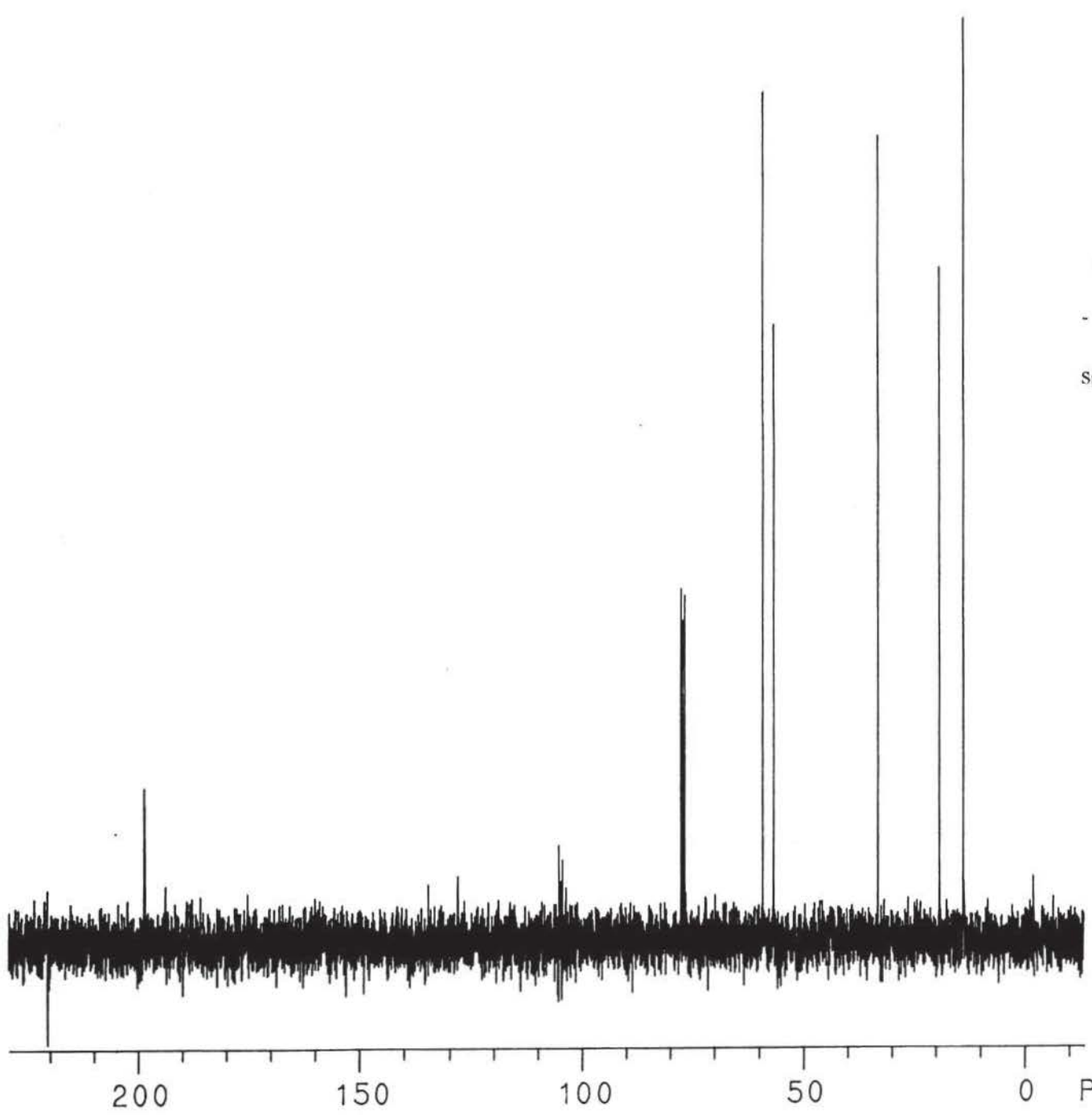
F1: 60.010		SW1: 1000		OF1: 387.5		PTS1d: 4096
EX:		PW: 4.8 usec	PD: 1.0 sec	NA: 8	LB: 0.0	WinNuts - $pnmr.fid



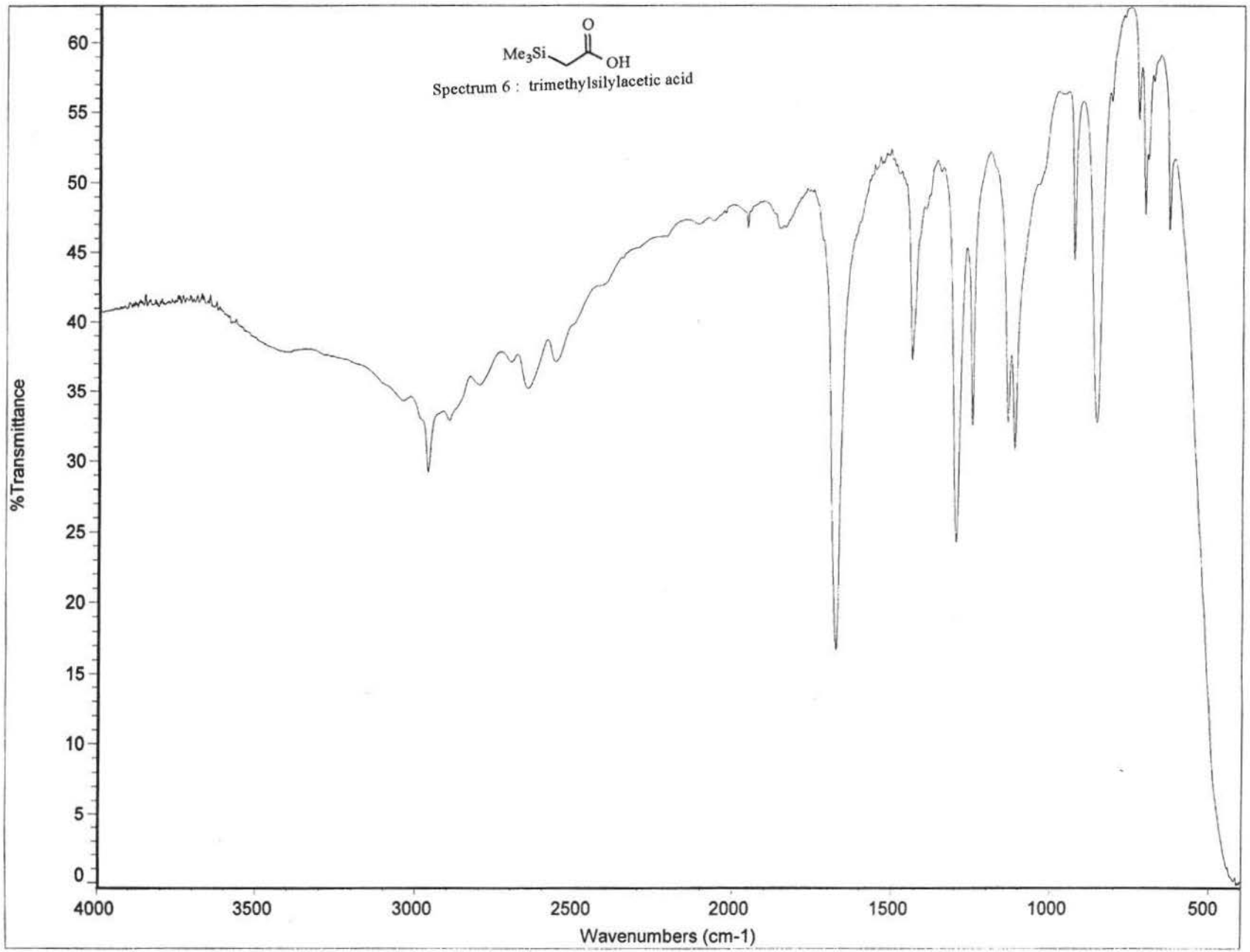
Spectrum 3: (2S,3S)-epoxyhexan-1-ol

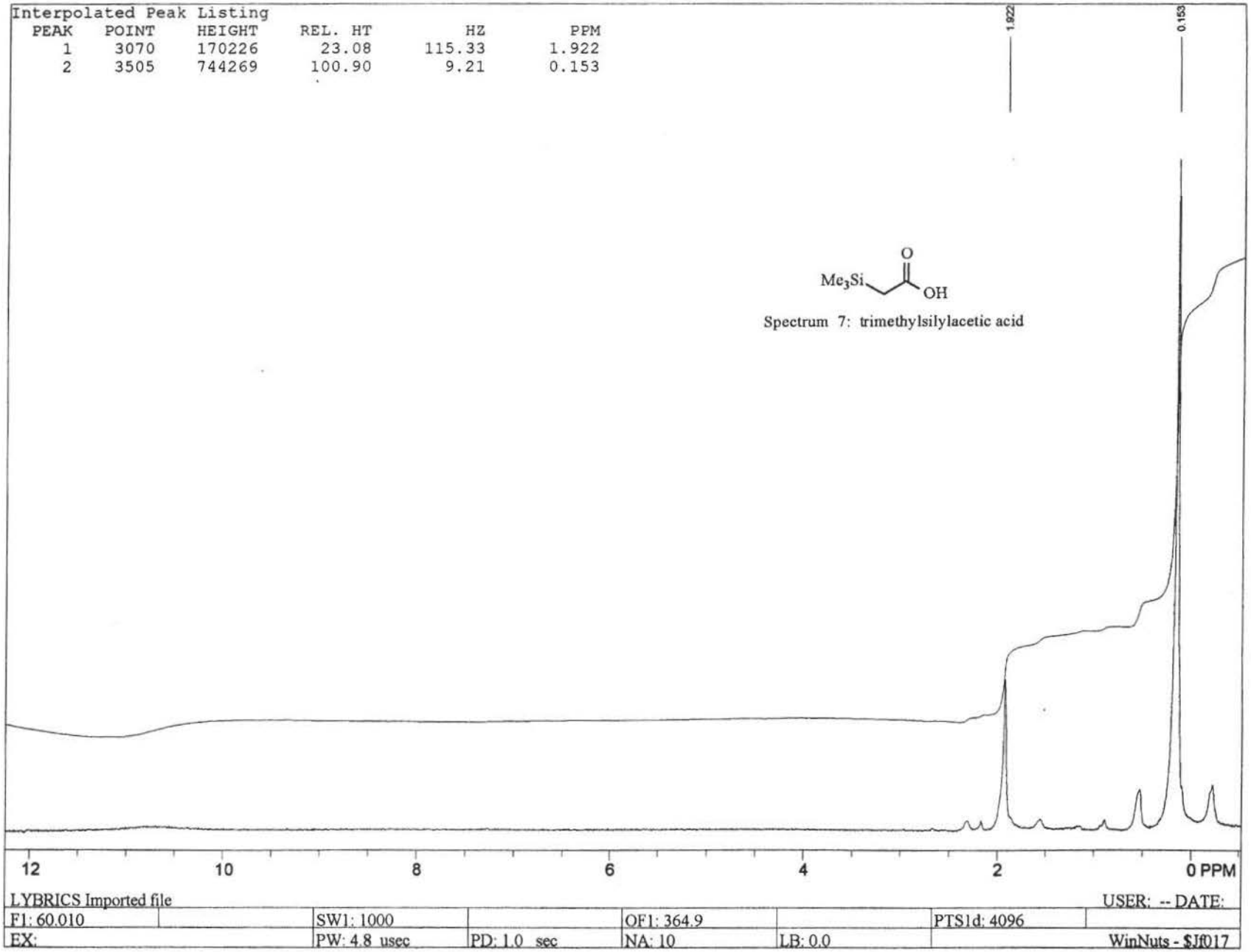


Spectrum 4: (2R,3S)-epoxyhexanal

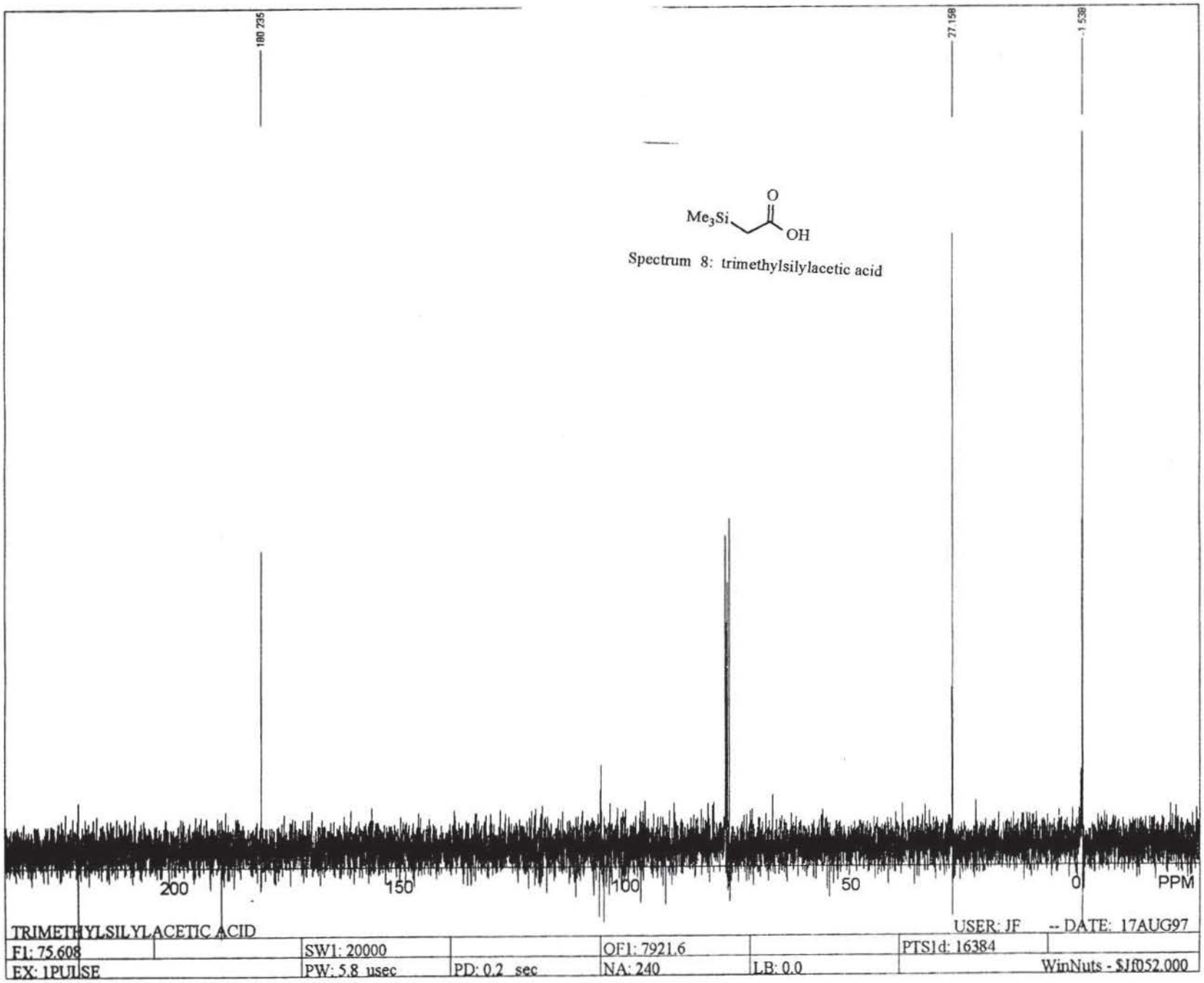


Spectrum 5: (2R,3S)-epoxyhexanal

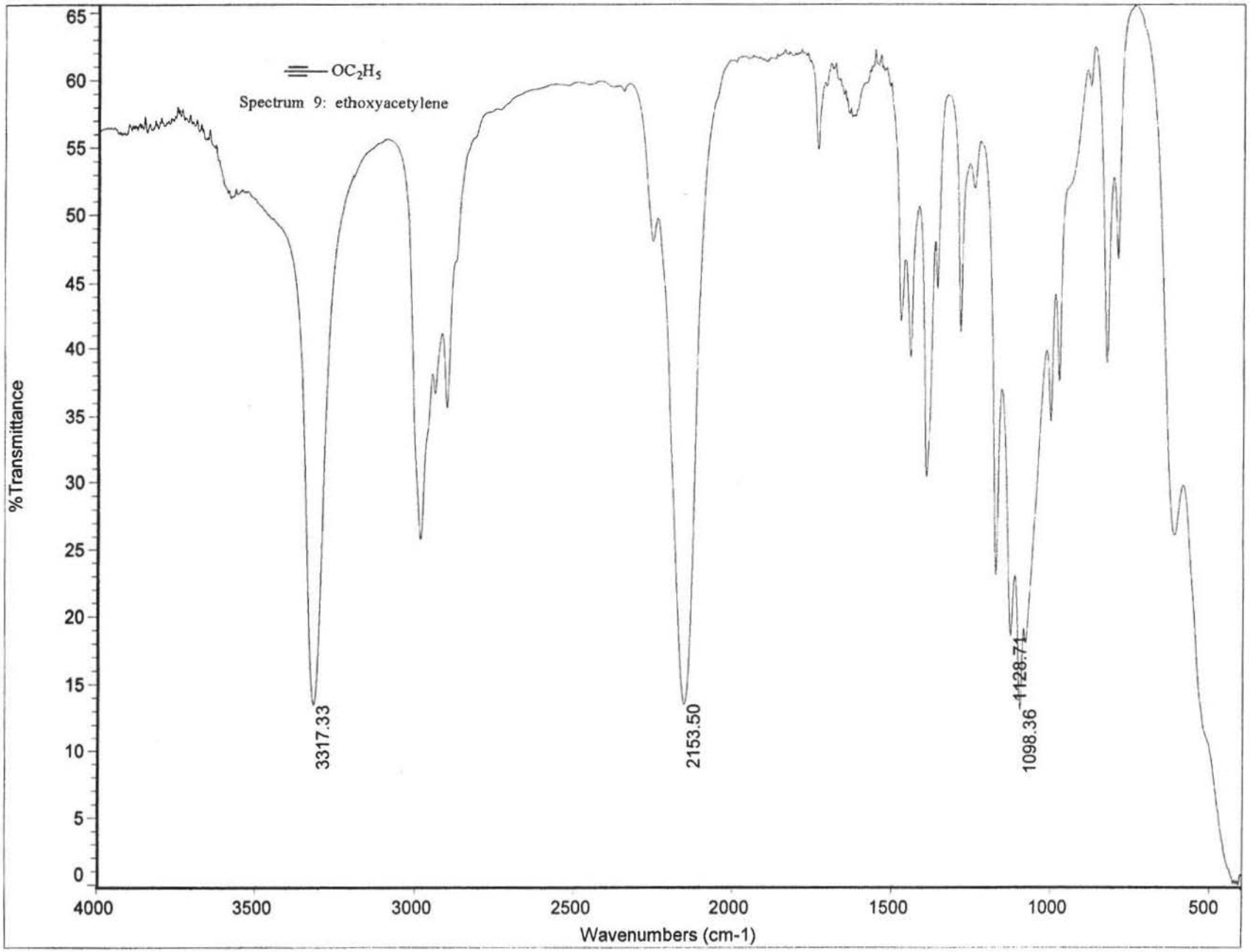

Me3Si
O
OH
Spectrum 6 : trimethylsilylacetic acid
%Transmittance
60
55
50
45
40
35
30
25
20
15
10
5
0
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)



Spectrum 7: trimethylsilylacetic acid

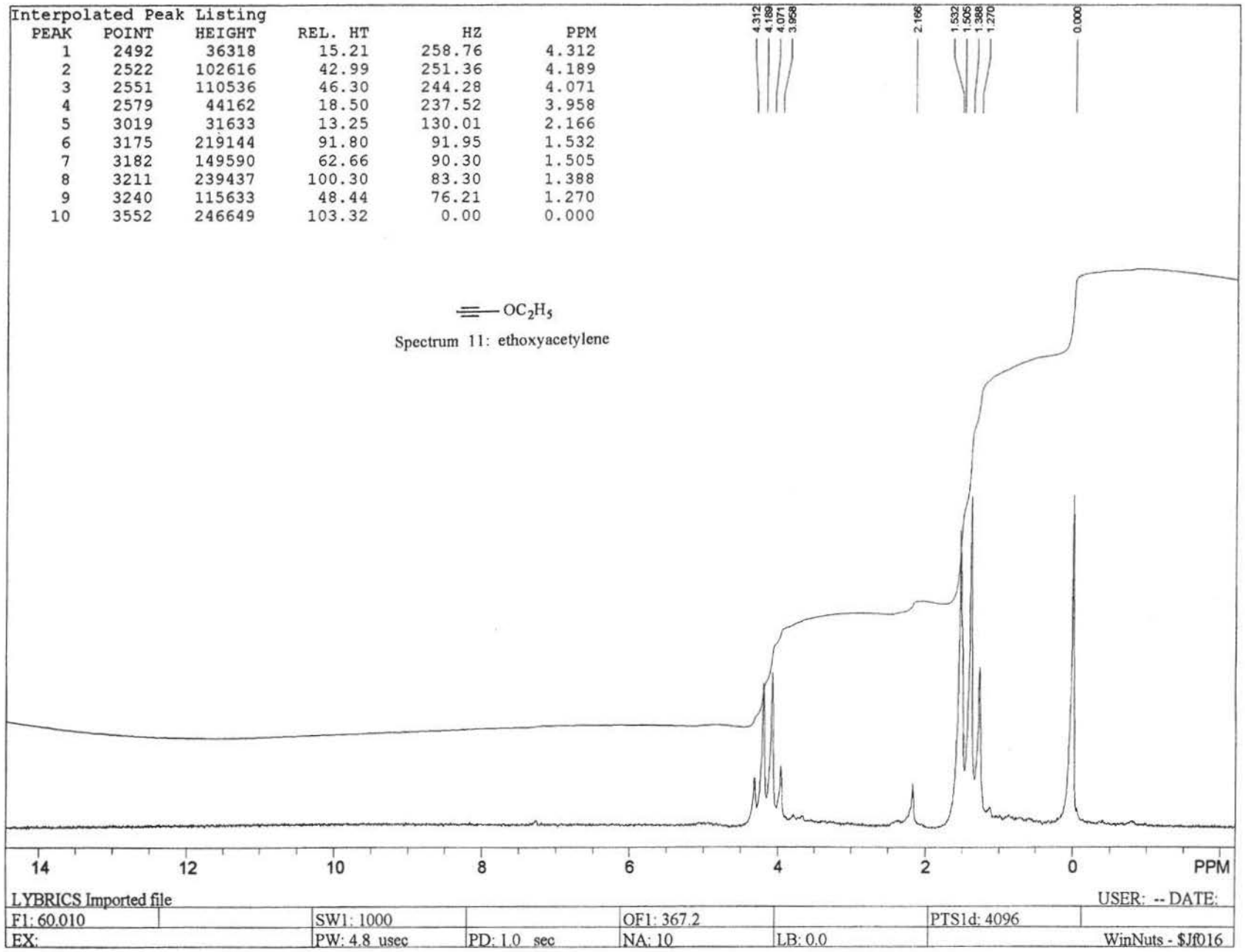


Spectrum 8: trimethylsilylacetic acid

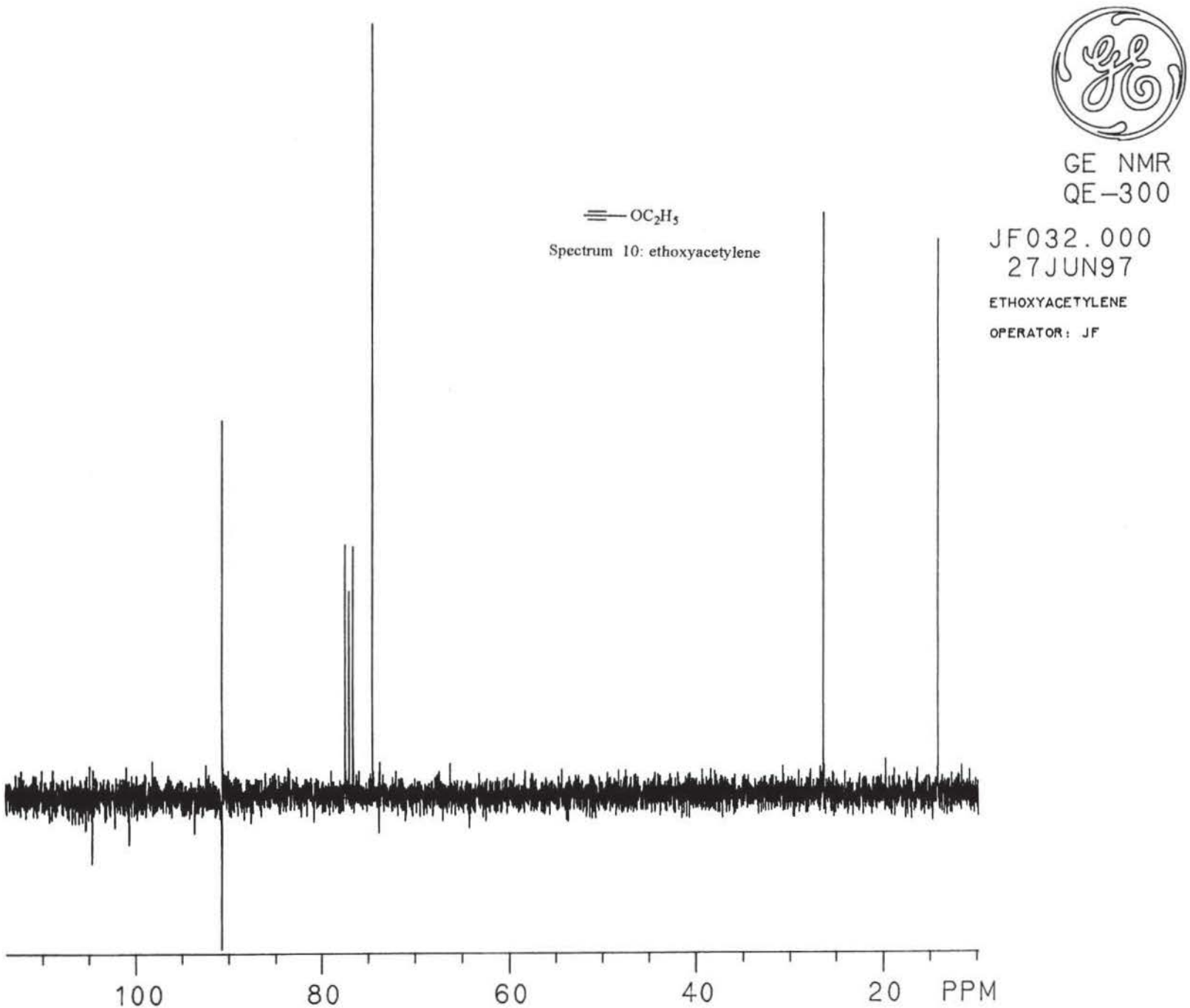

OC_2H_5
Spectrum 9: ethoxyacetylene
%Transmittance
65
60
55
50
45
40
35
30
25
20
15
10
5
0
3317.33
2153.50
1128.71
1098.36
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

Interpolated Peak Listing

PEAK	POINT	HEIGHT	REL. HT	HZ	PPM
1	2492	36318	15.21	258.76	4.312
2	2522	102616	42.99	251.36	4.189
3	2551	110536	46.30	244.28	4.071
4	2579	44162	18.50	237.52	3.958
5	3019	31633	13.25	130.01	2.166
6	3175	219144	91.80	91.95	1.532
7	3182	149590	62.66	90.30	1.505
8	3211	239437	100.30	83.30	1.388
9	3240	115633	48.44	76.21	1.270
10	3552	246649	103.32	0.00	0.000

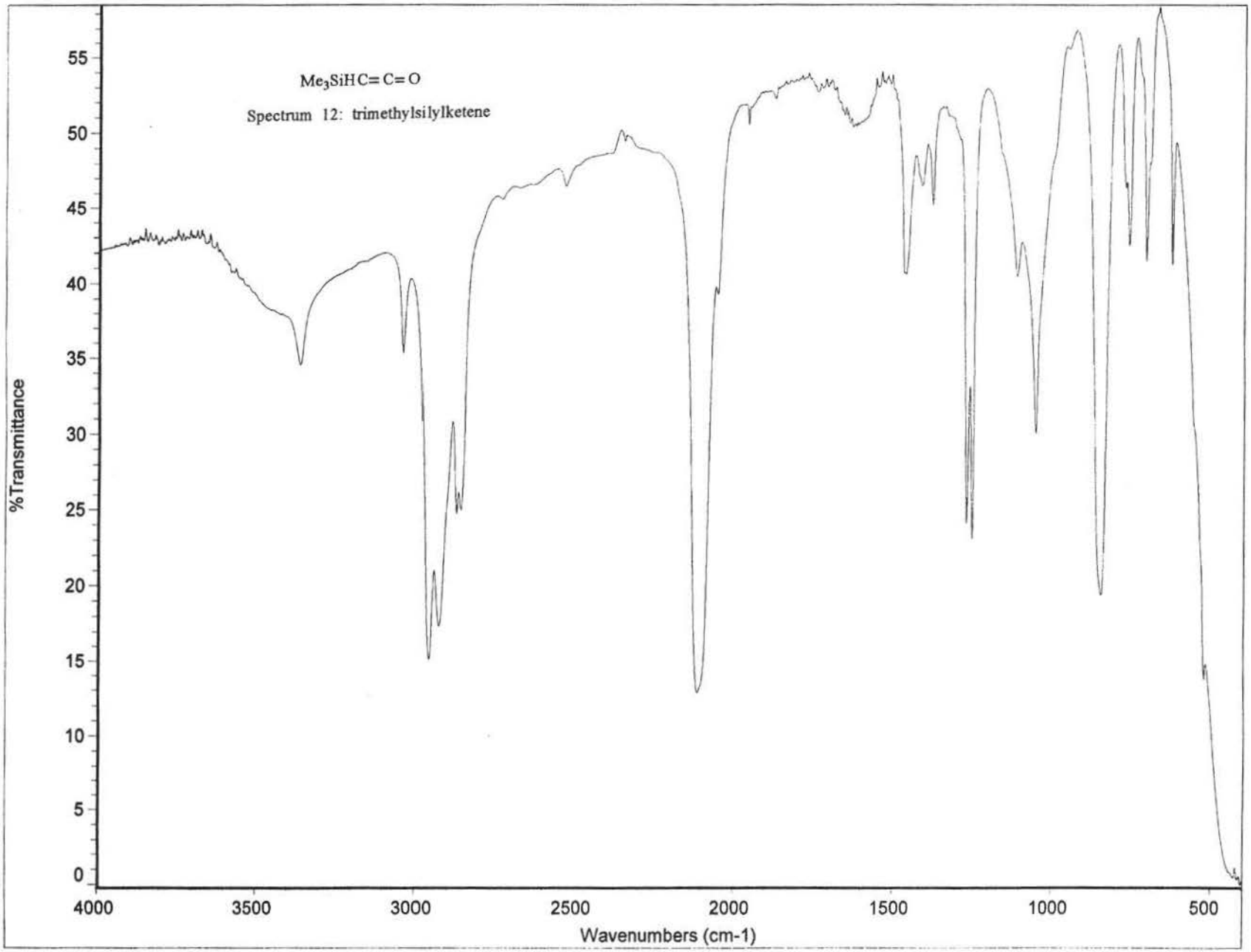


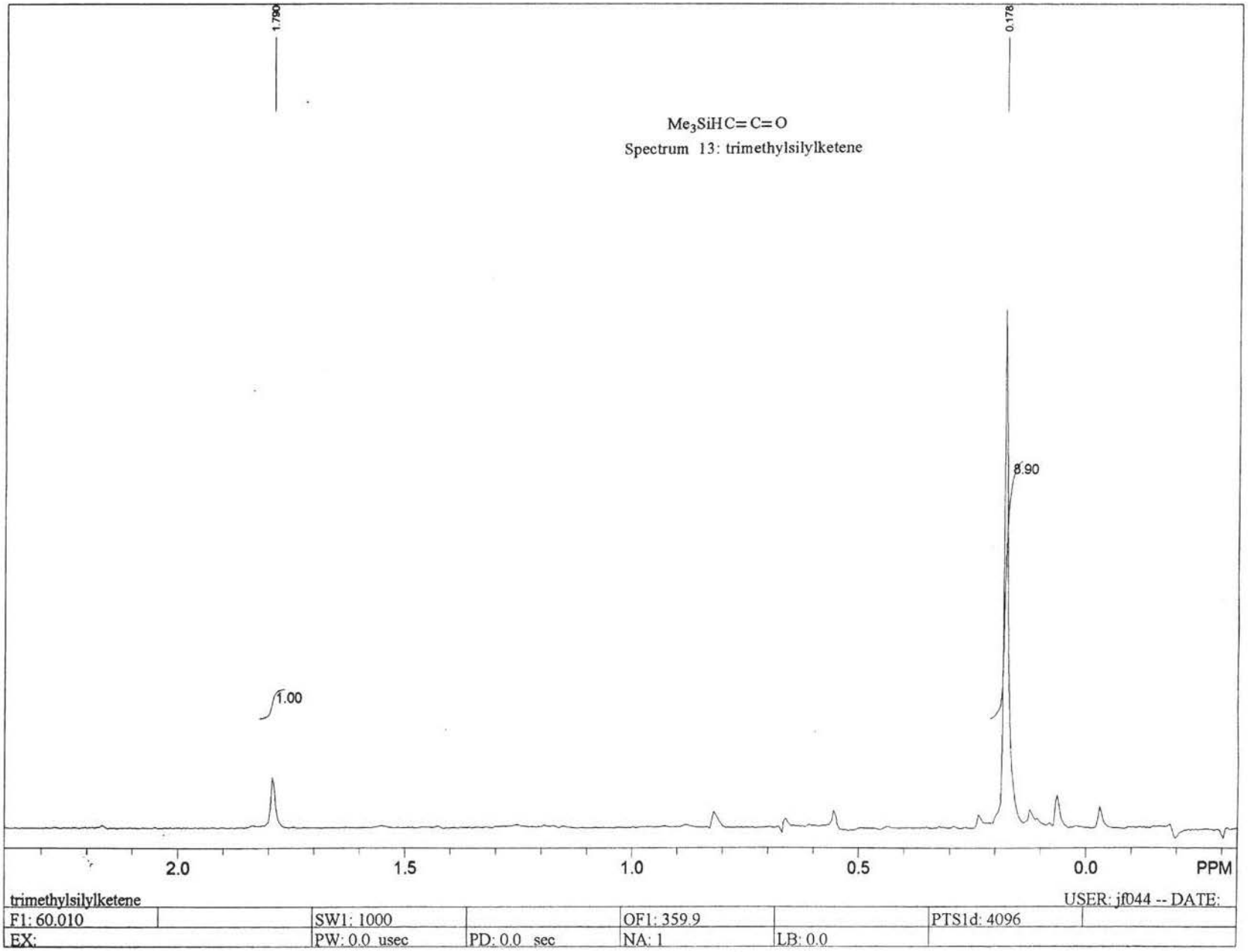
Spectrum 11: ethoxyacetylene

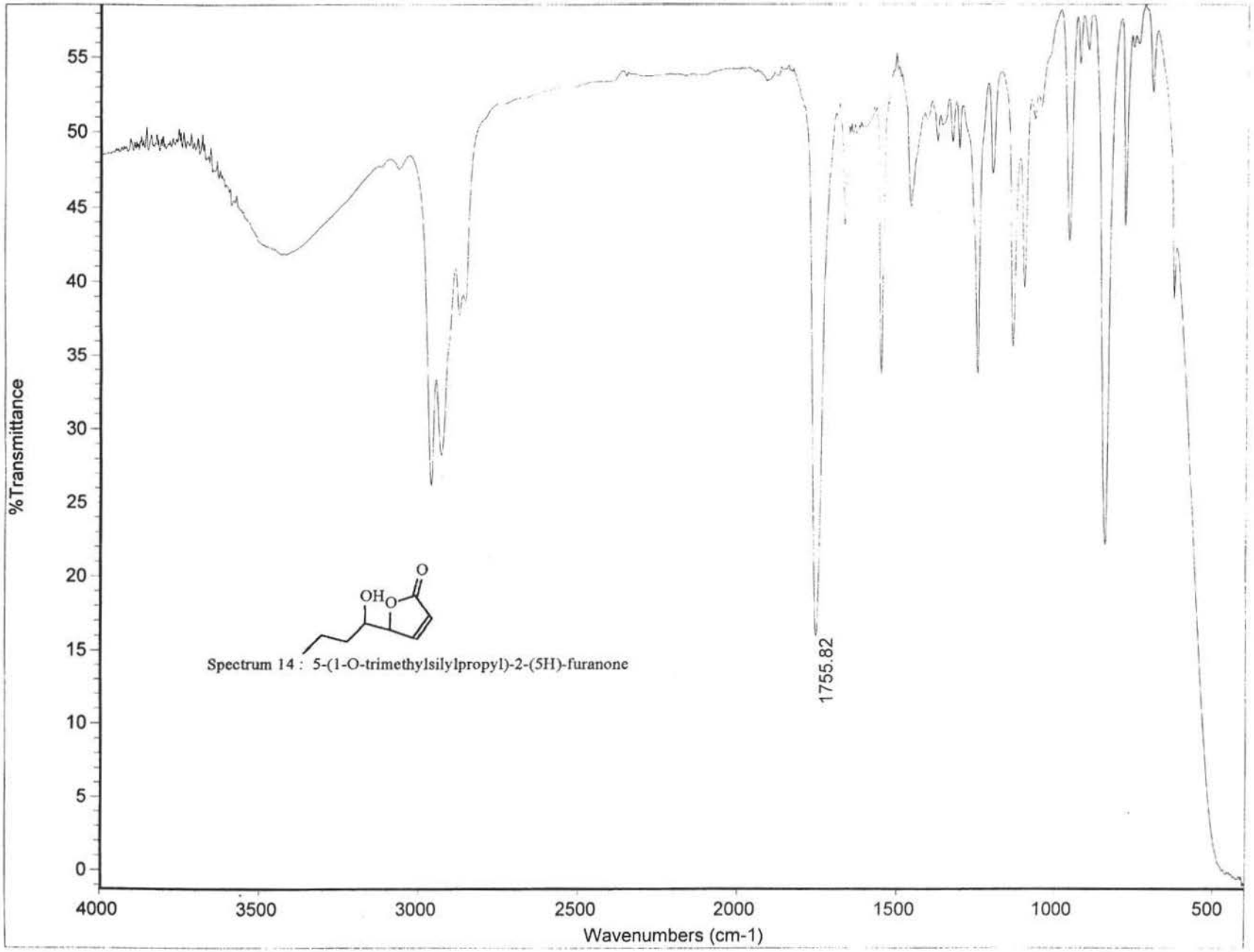


$\equiv\!\!-OC_2H_5$

Spectrum 10: ethoxyacetylene


$Me_3SiHC=C=O$
Spectrum 12: trimethylsilylketene
%Transmittance
55
50
45
40
35
30
25
20
15
10
5
0
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

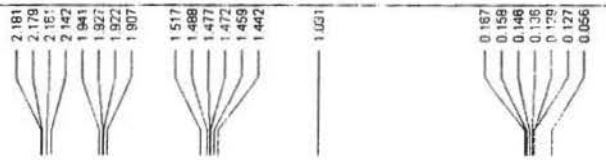

1.790
0.178
Me3SiHC=C=O
Spectrum 13: trimethylsilylketene
8.90
1.00
2.0
1.5
1.0
0.5
0.0
PPM
trimethylsilylketene
USER: jf044 -- DATE:
F1: 60.010
SW1: 1000
OF1: 359.9
PTS1d: 4096
EX:
PW: 0.0 usec
PD: 0.0 sec
NA: 1
LB: 0.0

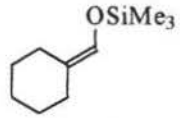


Spectrum 14 : 5-(1-O-trimethylsilylpropyl)-2-(5H)-furanone

Integrated Peak Listing

PEAK	POINT	HEIGHT	REL. HT	HZ	PPM
1	6993	380480	3.71	1799.17	5.984
2	6996	530551	5.18	1798.16	5.981
3	6999	316115	3.08	1797.12	5.977
4	10102	235100	2.29	655.82	2.181
5	10105	248713	2.43	655.01	2.179
6	10119	318155	3.10	649.65	2.161
7	10134	219126	2.14	644.04	2.142
8	10298	238732	2.33	583.72	1.941
9	10311	327117	3.19	579.22	1.927
10	10314	316537	3.09	577.84	1.922
11	10326	215497	2.10	573.48	1.907
12	10646	207782	2.03	456.01	1.517
13	10669	591998	5.78	447.32	1.488
14	10678	427207	4.17	444.18	1.477
15	10682	448963	4.38	442.60	1.472
16	10693	381405	3.72	438.78	1.459
17	10706	224923	2.20	433.69	1.442
18	11043	385282	3.76	310.07	1.031
19	11750	372238	3.63	50.10	0.167
20	11757	1022K	9.98	47.45	0.158
21	11766	11523K	112.45	43.99	0.146
22	11775	585225	5.71	40.83	0.136
23	11780	235291	2.30	38.87	0.129
24	11782	222801	2.17	38.05	0.127
25	11840	1118K	10.92	16.74	0.056

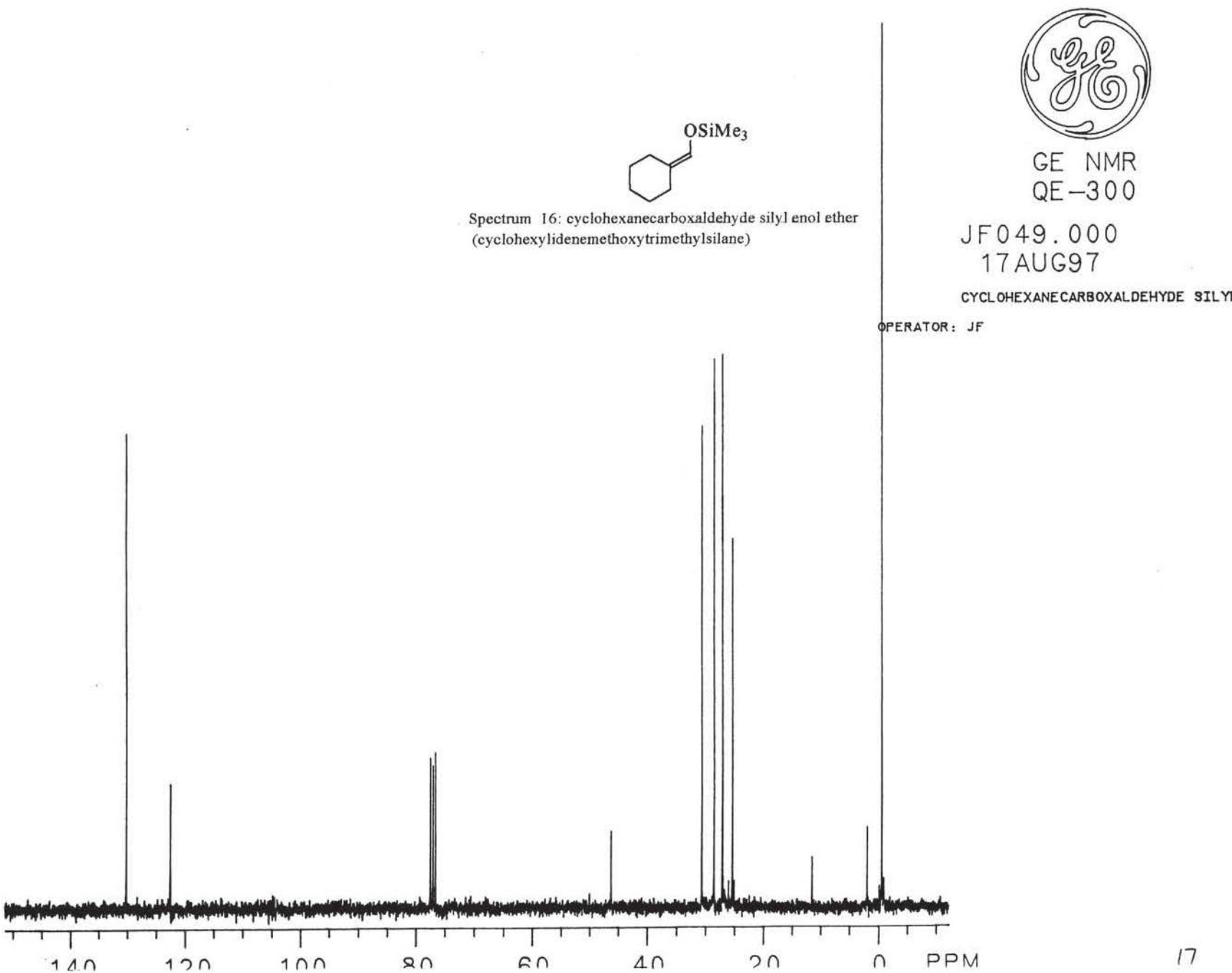




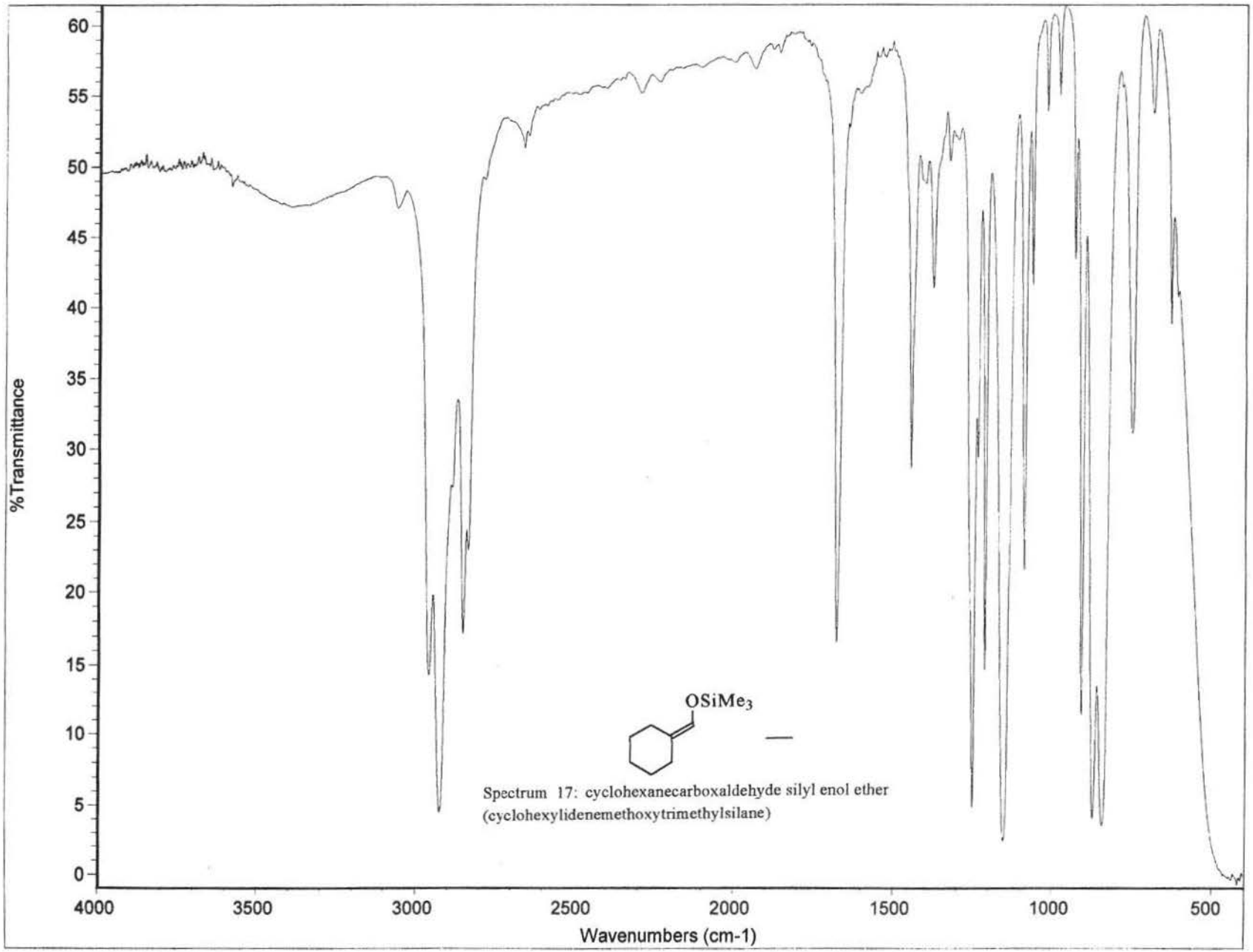
Spectrum 15: cyclohexanecarboxaldehyde silyl enol ether (cyclohexylidenemethoxytrimethylsilane)

CYCLOHEXANECARBOXALDEHYDE SILYL ENOL ETHER USER: JF -- DATE: 17AUG97

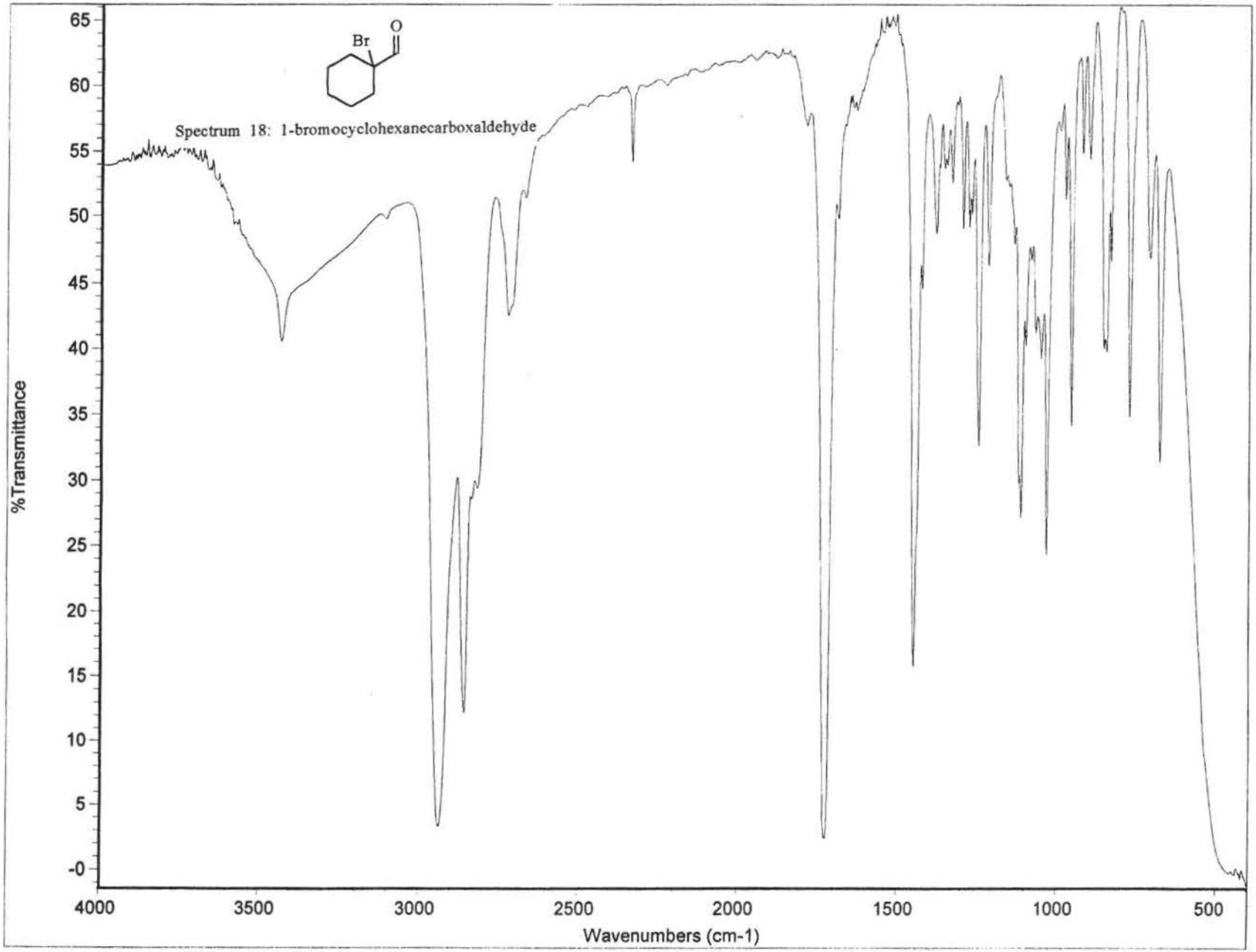
F1: 300.656		SW1: 6024		OF1: 1358.3		PTS1d: 16384	
EX: 1PULSE		PW: 3.1 usec	PD: 1.0 sec	NA: 8	LB: 0.0		WinNuts - $Jf048.000



Spectrum 16: cyclohexanecarboxaldehyde silyl enol ether
(cyclohexylidenemethoxytrimethylsilane)

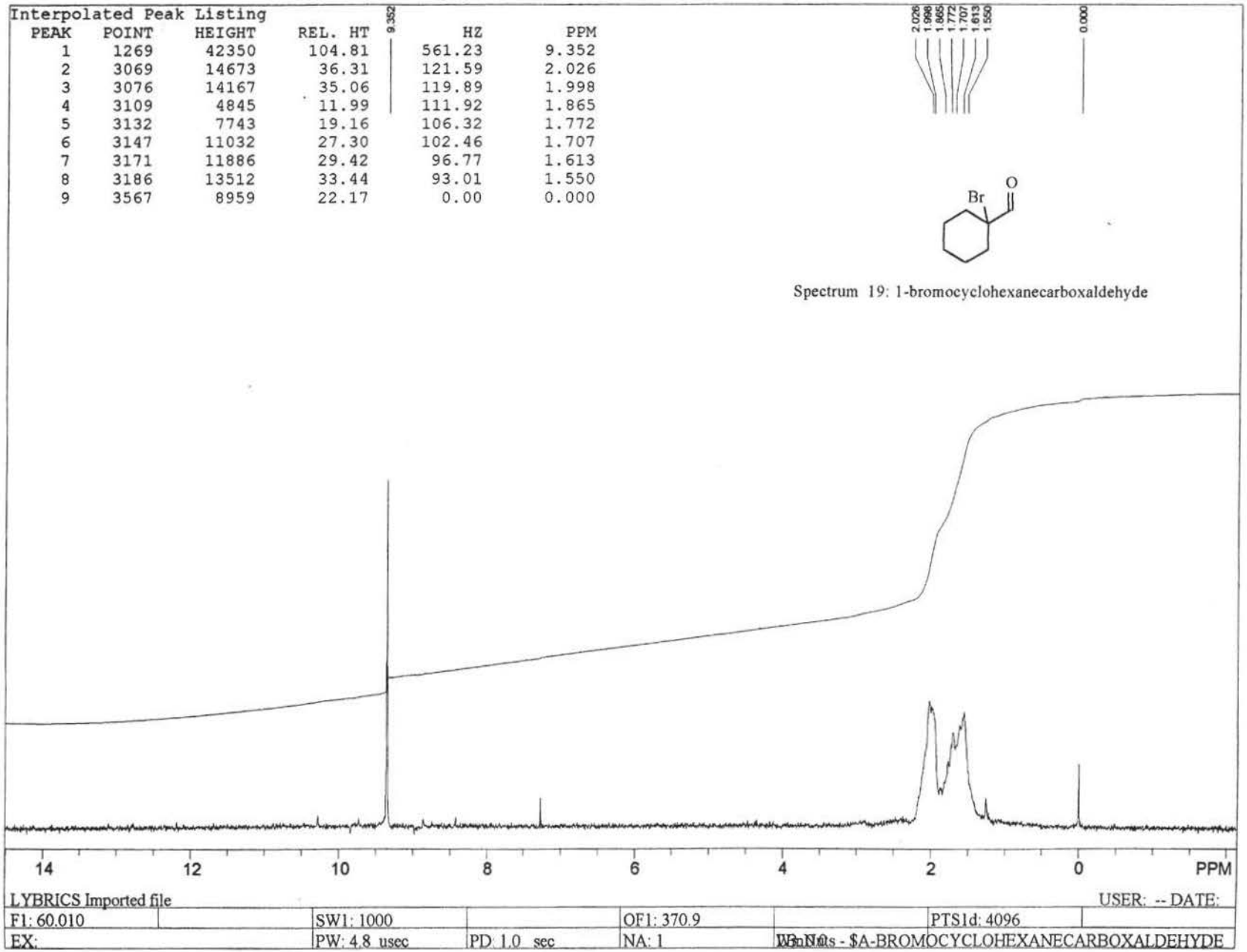


Spectrum 17: cyclohexanecarboxaldehyde silyl enol ether
(cyclohexylidenemethoxytrimethylsilane)

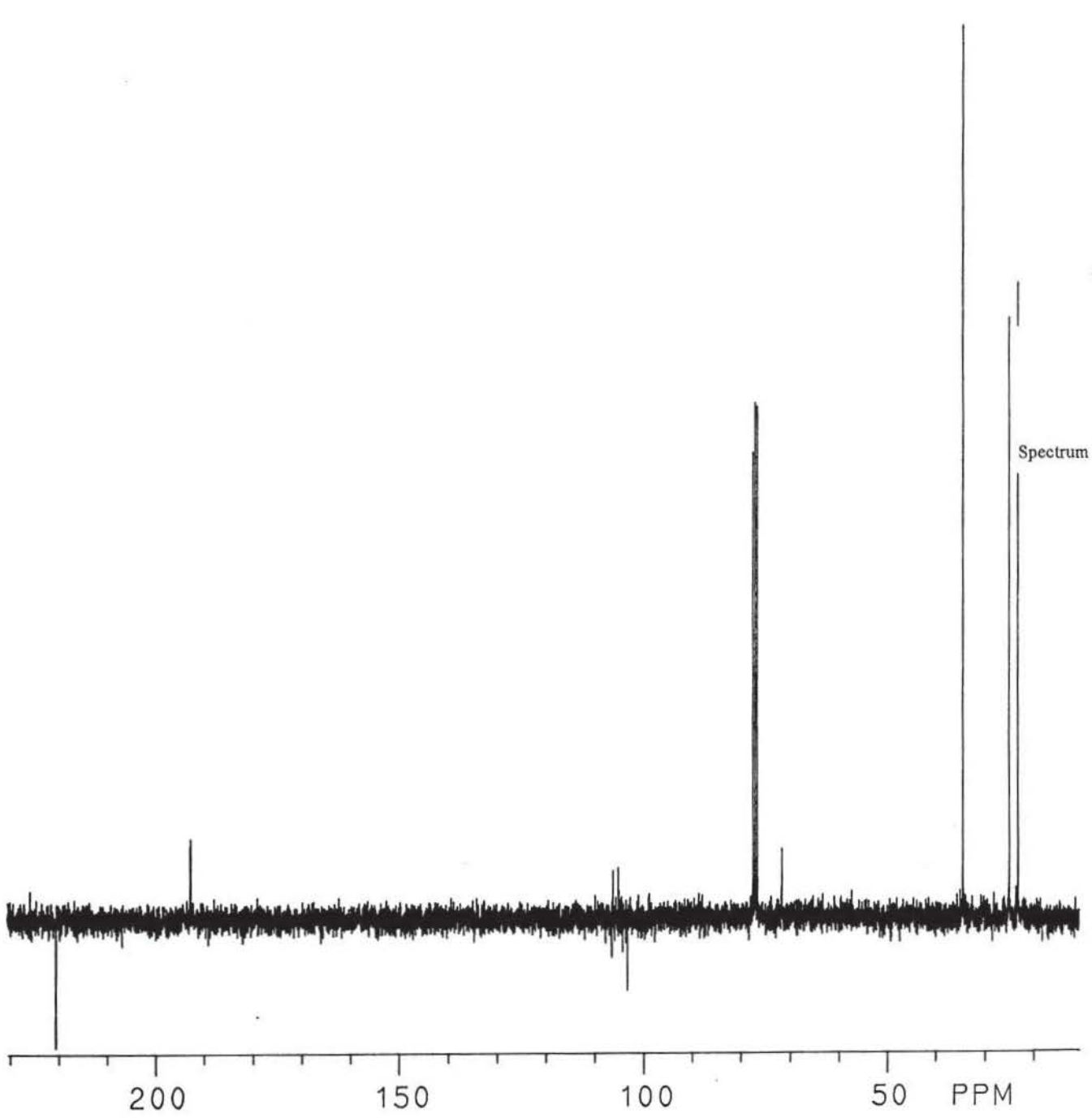

Br
O
Spectrum 18: 1-bromocyclohexanecarboxaldehyde
%Transmittance
65
60
55
50
45
40
35
30
25
20
15
10
5
-0
4000
3500
3000
2500
2000
1500
1000
500
Wavenumbers (cm-1)

Interpolated Peak Listing

PEAK	POINT	HEIGHT	REL. HT	HZ	PPM
1	1269	42350	104.81	561.23	9.352
2	3069	14673	36.31	121.59	2.026
3	3076	14167	35.06	119.89	1.998
4	3109	4845	11.99	111.92	1.865
5	3132	7743	19.16	106.32	1.772
6	3147	11032	27.30	102.46	1.707
7	3171	11886	29.42	96.77	1.613
8	3186	13512	33.44	93.01	1.550
9	3567	8959	22.17	0.00	0.000

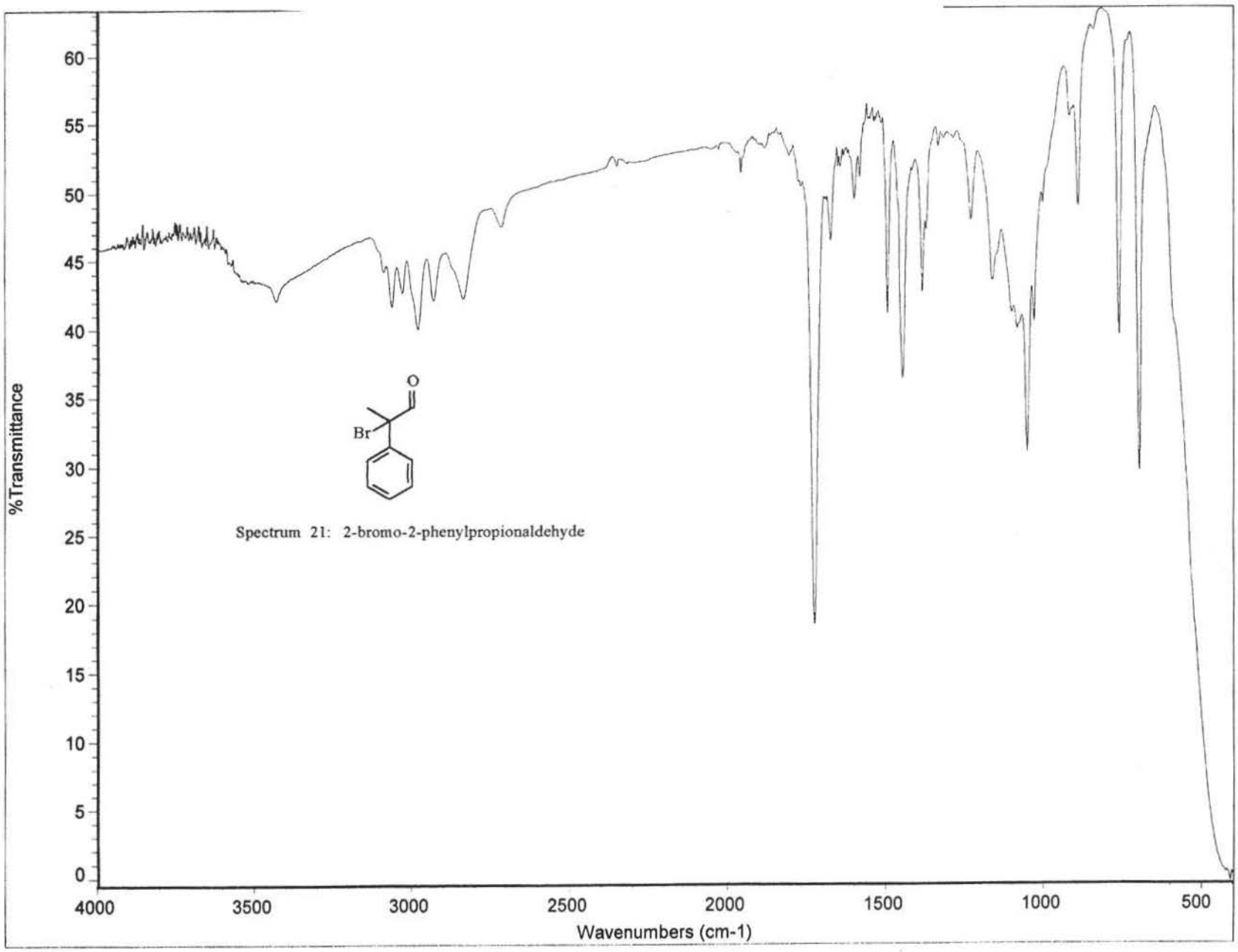


Spectrum 19: 1-bromocyclohexanecarboxaldehyde

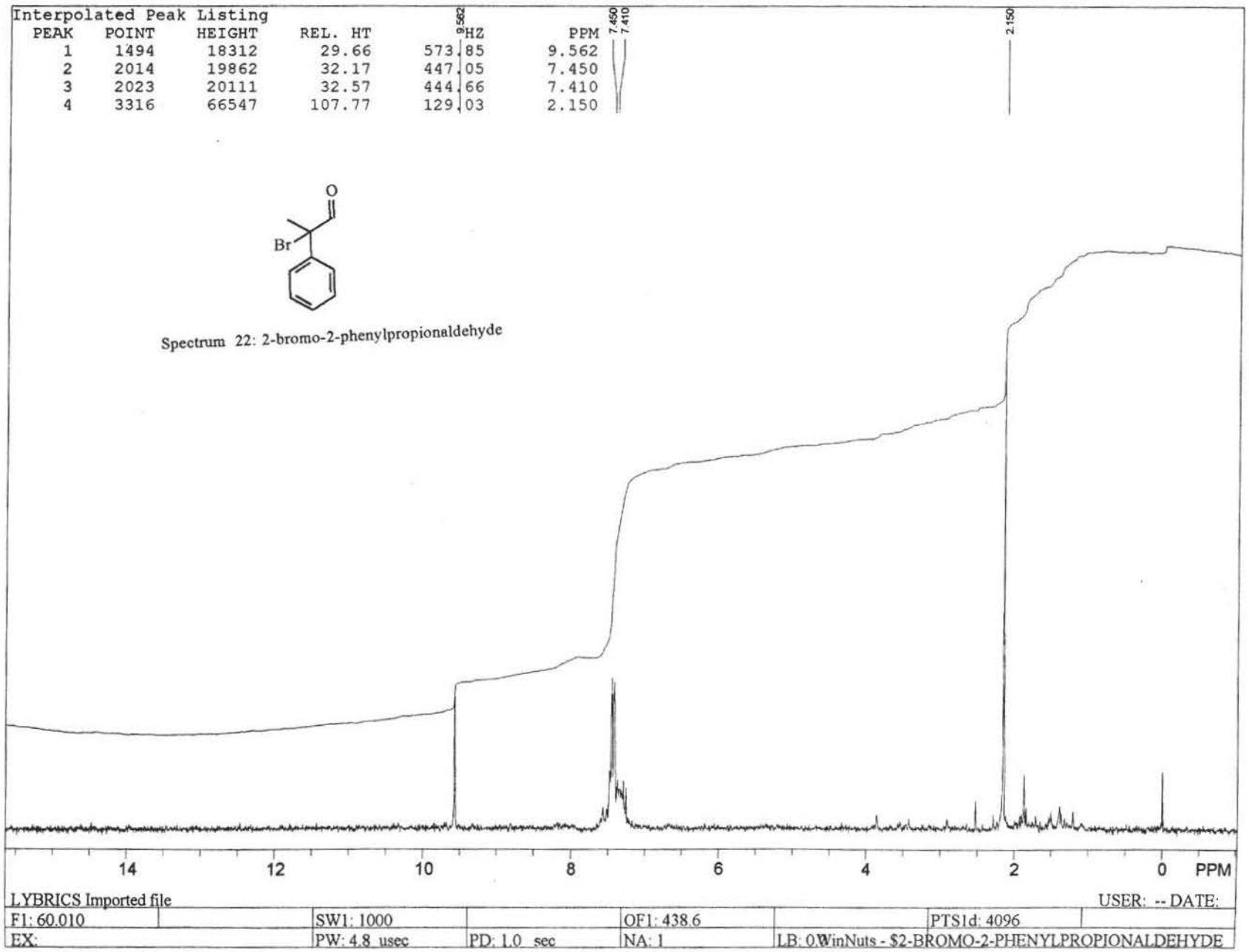


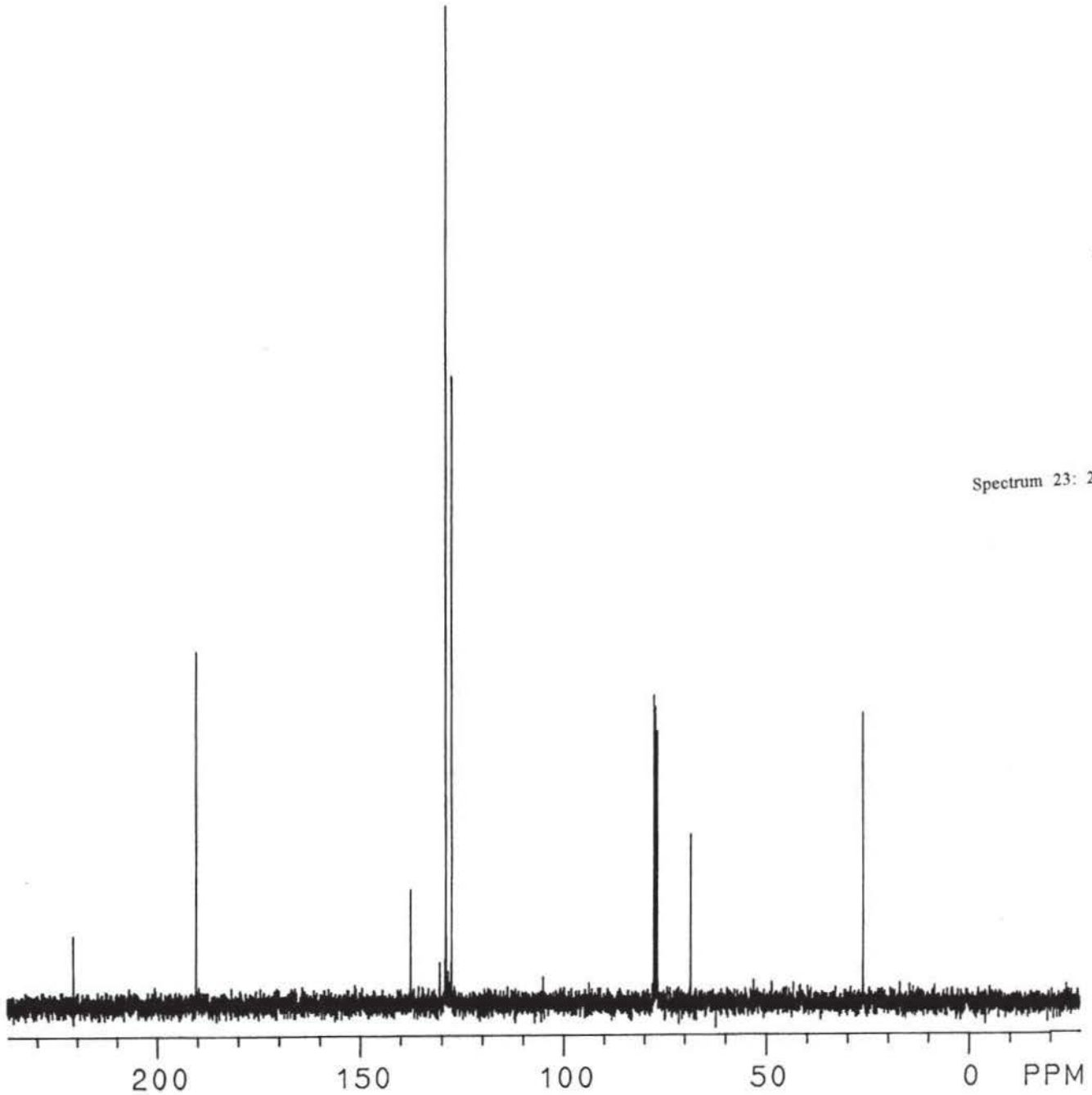
Spectrum 20: 1-bromocyclohexanecarboxaldehyd

Spectrum 21: IR spectrum of 3-bromo-3-phenylpropionaldehyde 9

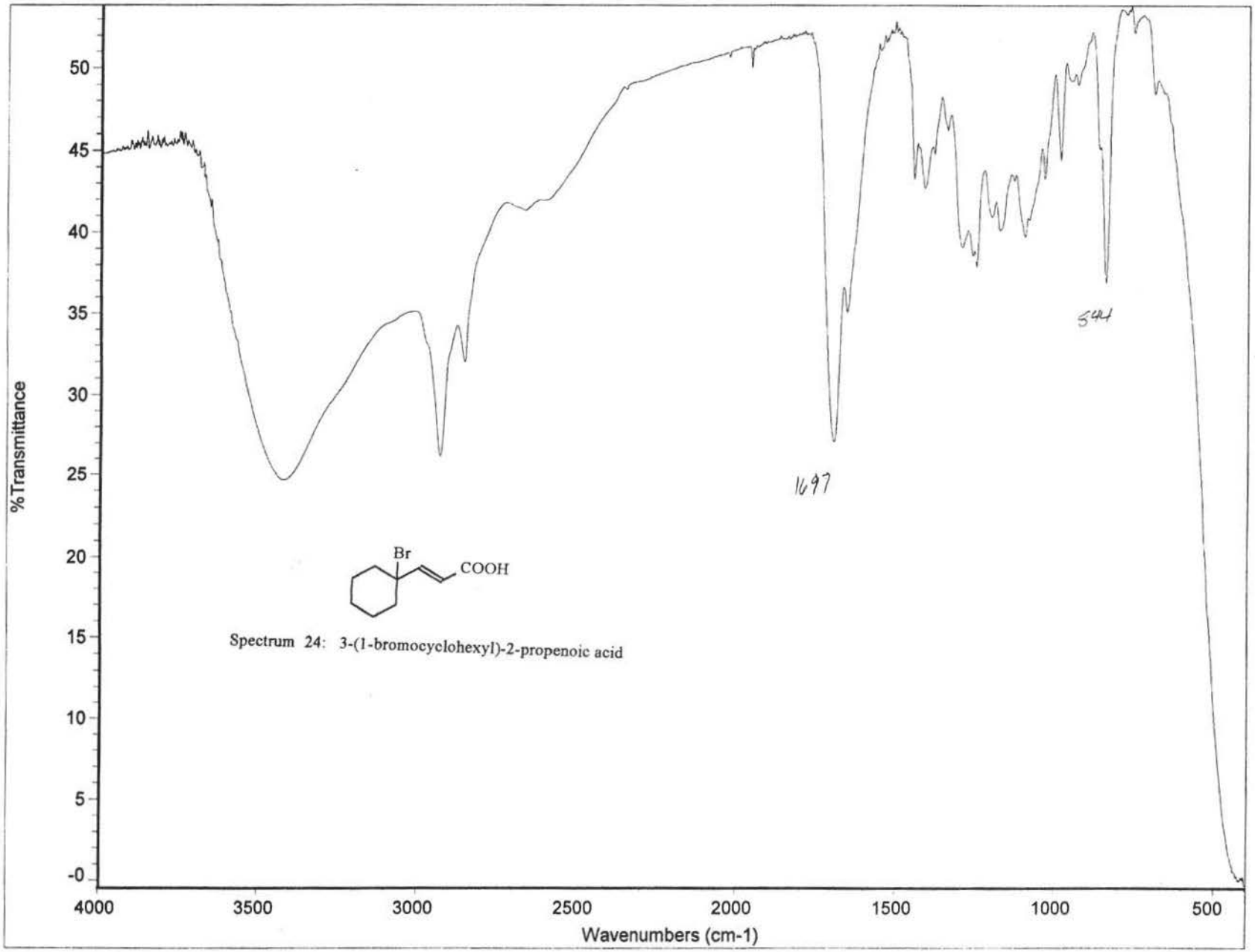


Spectrum 21: 2-bromo-2-phenylpropionaldehyde


Interpolated Peak Listing
PEAK POINT HEIGHT REL. HT HZ PPM
1 1494 18312 29.66 573.85 9.562
2 2014 19862 32.17 447.05 7.450
3 2023 20111 32.57 444.66 7.410
4 3316 66547 107.77 129.03 2.150
9.562
7.450
7.410
2.150
O
Br
Spectrum 22: 2-bromo-2-phenylpropionaldehyde
14
12
10
8
6
4
2
0
PPM
LYBRICS Imported file
USER: -- DATE:
F1: 60.010
SW1: 1000
OF1: 438.6
PTS1d: 4096
EX:
PW: 4.8 usec
PD: 1.0 sec
NA: 1
LB: 0.WinNuts - $2-BROMO-2-PHENYLPROPIONALDEHYDE



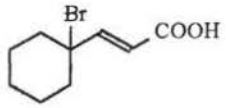
Spectrum 23: 2-bromo-2-phenylpropionaldehyde



Spectrum 24: 3-(1-bromocyclohexyl)-2-propenoic acid

Interpolated Peak Listing

PEAK	POINT	HEIGHT	REL. HT	HZ	PPM
1	6052	2131K	30.86	2145.71	7.137
2	6094	1898K	27.50	2130.30	7.086
3	6909	1933K	28.01	1830.44	6.088
4	6951	2406K	34.85	1815.21	6.037
5	10541	773875	11.21	494.94	1.646
6	10555	908203	13.15	490.11	1.630
7	10583	3422K	49.56	479.50	1.595
8	10591	4060K	58.81	476.69	1.586
9	11796	7813K	113.16	33.53	0.112
10	11894	1869K	27.07	-2.34	-0.008



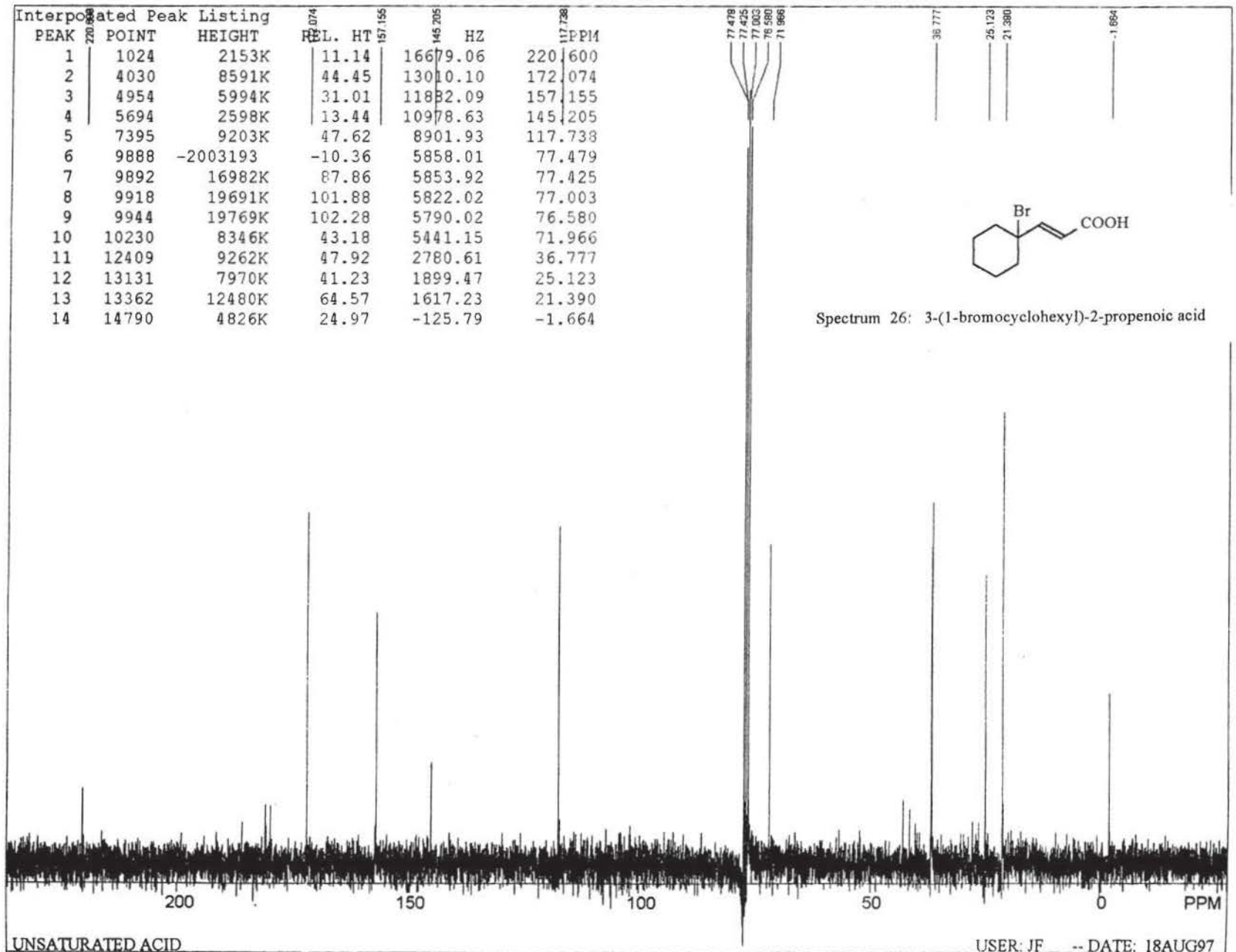
Spectrum 25: 3-(1-bromocyclohexyl)-2-propenoic acid

UNSATURATED ACID USER: JF -- DATE: 18AUG97

F1: 300.656	SW1: 6024		OF1: 1358.8		PTS1d: 16384
EX: 1PULSE	PW: 3.1 usec	PD: 1.0 sec	NA: 32	LB: 0.0	WinNuts - $Jf063.000

Interpolated Peak Listing

PEAK	POINT	HEIGHT	REL. HT	HZ	PPM
1	1024	2153K	11.14	16679.06	220.600
2	4030	8591K	44.45	13010.10	172.074
3	4954	5994K	31.01	11832.09	157.155
4	5694	2598K	13.44	10978.63	145.205
5	7395	9203K	47.62	8901.93	117.738
6	9888	-2003193	-10.36	5858.01	77.479
7	9892	16982K	87.86	5853.92	77.425
8	9918	19691K	101.88	5822.02	77.003
9	9944	19769K	102.28	5790.02	76.580
10	10230	8346K	43.18	5441.15	71.966
11	12409	9262K	47.92	2780.61	36.777
12	13131	7970K	41.23	1899.47	25.123
13	13362	12480K	64.57	1617.23	21.390
14	14790	4826K	24.97	-125.79	-1.664



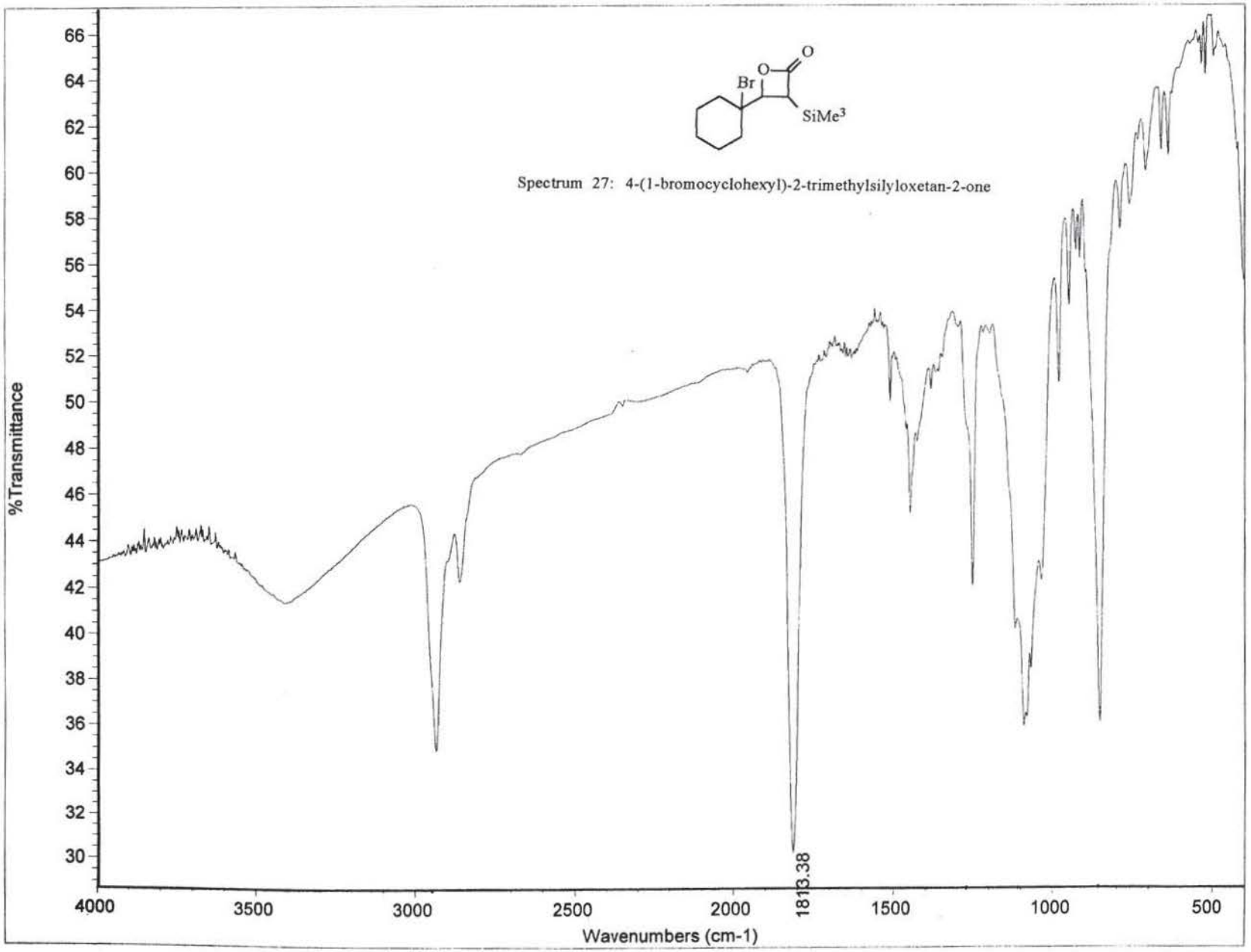
Spectrum 26: 3-(1-bromocyclohexyl)-2-propenoic acid

UNSATURATED ACID

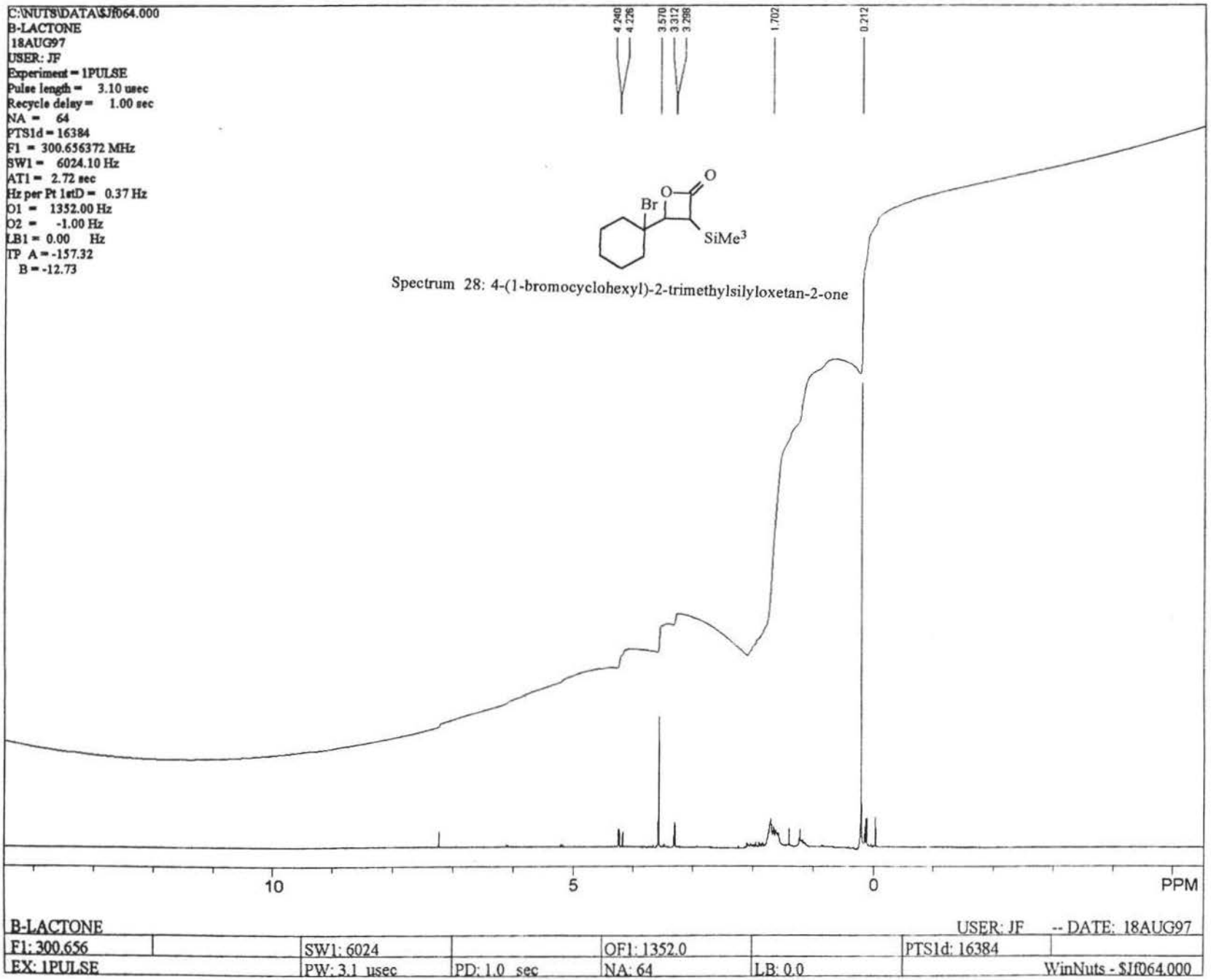
USER: JF -- DATE: 18AUG97

F1: 75.608		SW1: 20000		OF1: 7928.7		PTS1d: 16384
EX: 1PULSE		PW: 5.8 usec	PD: 0.2 sec	NA: 2288	LB: 0.0	WinNuts - SJf062.000

JF-II-167A



Spectrum 27: 4-(1-bromocyclohexyl)-2-trimethylsilyloxetan-2-one



Spectrum 28: 4-(1-bromocyclohexyl)-2-trimethylsilyloxetan-2-one