The Development of Novel Electron Transfer Initiated Cyclization (ETIC) Reactions: Discovery of the Diastereoselective ETIC Reaction and Its Application toward the Total Synthesis of Leucascandrolide A.

by

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John Robert Seiders, II, PhD

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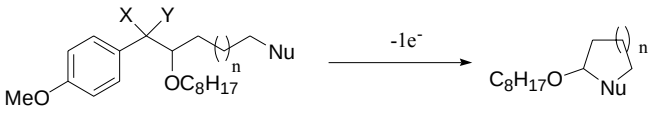
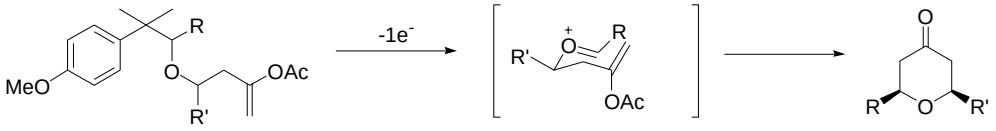
The electron transfer initiated cyclization (ETIC) reaction has been shown to provide the efficient formation of cyclic acetals through the selective activation of carbon-carbon σ-bonds. A simple arithmetical equation has been used to design new substrates with enhanced chemoselectivity and reactivity. The ability to design new cyclization substrates has expanded the scope of the ETIC reaction by providing access to more diverse products. Lowering the oxidation potential of the ETIC substrates led to the development of a ground state chemical-mediated protocol. This also allowed for the incorportation of electron rich olefins as carbon-centered nucleophiles. Substrates which undergo *endo*-cyclizations have shown excellent levels of stereocontrol in the synthesis of *syn*-2,6-dialkyl tetrahydropyranones, which are useful building blocks in natural product synthesis.

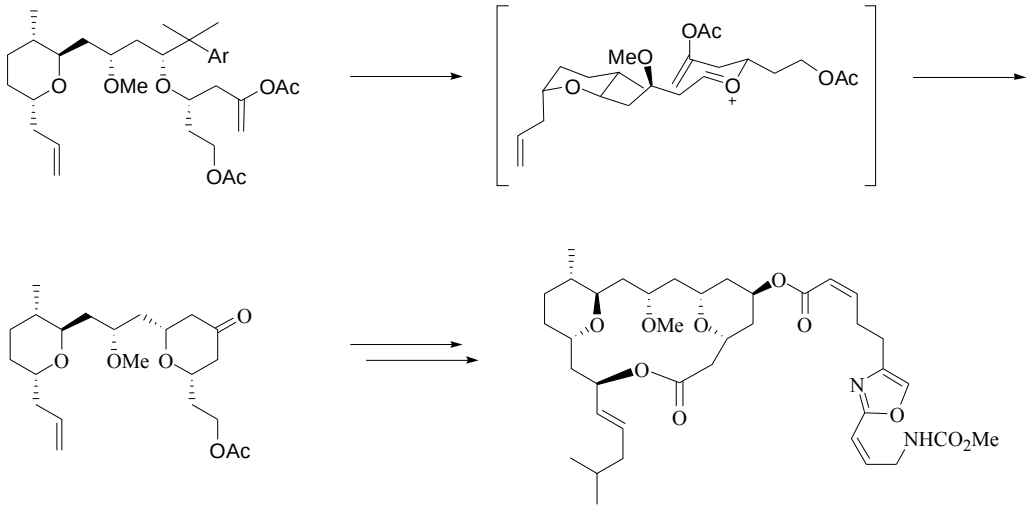


X = Me, vinyl, Ph
Y = Me, H
Nu = OH, propargyl silane, allenyl silane, enol acetate



R = alkyl or vinyl

A highly stereoselective sequence has been developed for the synthesis of leucascandrolide A with the key transformation utilizing the diastereoselective *endo*-ETIC reaction. The homopropargylic ether required for installation of the enol acetate was obtained through the stereoselective opening of a cyclic acetal with allenyltributyltin in the presence of a Lewis acid. A metal mediated addition of acetic acid to the alkyne provided the homobenzylic ether with a suitably tethered enol acetate. The enol acetate was then subjected to the chemical mediated ETIC conditions to afford the desired *syn*-2,6-tetrahydropyranone as a single diastereomer.



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PREFACE

I would like to dedicate this thesis to the family, friends and colleagues who have supported me throughout my graduate career. I definitely did not get through this on my own and I would like to thank all of you for pushing me to succeed.

Mom, Dad, Felicia and Grandma Smith:

A lot has happened over the past five years to get me through my graduate career. But I would not be where I am today without the love and support you have shown me over the past 28 years. Thank you for always being there for me during the good times, and for helping me stay motivated through the tough times. While I'll be the one receiving this degree, we have all earned it together.

Paul:

Thank you for allowing me to join your group and share in the development of new and exciting chemistry. You have shown me the importance of investigating every aspect of a project. Your enthusiasm for exploring the chemical world has been instilled within me, and I hope to someday pass this on to my students.

J. and Lijun:

We have been through quite a bit over the past five years. I want to thank the two of you for keeping me on track and for you helpful suggestions along the way. I know at times it was tough, but we somehow managed to keep moving each other forward. Best of luck in the future, anyone would be lucky to have you on their team.

Floreancig group members:

I would like to thank all of the Floreancig group members past and present. Satish, you were instrumental in helping me to become the chemist I am today. Chris and Danielle, you set an example for the type of graduate student I wanted to be. Alex, Conor, Mike and Shuangyi, I have enjoyed seeing you all grow as chemist over the past two years. The group is in your hands so good luck.

Chapter 1 Tuning the Reactivity and Chemoselectivity of Electron Transfer Initiated Cyclization (ETIC) Reactions: Effects of Aryl and Benzyl Substitution

1.1. Introduction

I. General

The activation of functional groups which are generally inert to a wide range of reaction conditions in a transient and selective manner would provide a powerful approach to designing new synthetic transformations. Due to the rich chemistry available for the formation of carbon-carbon σ-bonds, a method that allows for their selective activation to form potent and transient electrophiles would be of great synthetic utility. Owing to their tendacy to undergo mesolyic cleavage (the fragmentation of a radical ion to provide a radical and an ion) radical cations are attractive candidates for such a process.[1] Generating electrophilic species via radical cation fragmentation is also attractive due to the wide variety of sensitive functional groups that are tolerant of the mild reaction conditions. This high level of functional group compatibility arises from the chemoselectivity of single transfer being dependant on the oxidation potential of the molecule.[2]

Recent studies conducted on the kinetics of fragmentation for a series of radical cations by Freccero and coworkers[1] have provided insight toward predicting their reactive pathways. Studies by Arnold and coworkers have also provided vital information for predicting the reactivity of radical cations based on the substitution of arylalkyl radical cations.[3]

Understanding the elements needed for the predictable and controllable mesolytic bond cleavage of radical cations provides a powerful method of forming highly reactive species for use in organic synthesis. Producing such reactive moieties under single electron transfer allows for novel approaches to the synthesis of natural and non-natural molecules of biological interest. The ability to form potent electrophiles without the use of Lewis-acid mediated activation allows for the incorporation of sensitive functionality, and provides a method to solve problems which were previously insoluble.[2]

II. Radical Cations

Crich and co-workers[3] have recently developed a nonoxidative method for the formation of radical cation intermediates. This method generates the radical cation intermediate through formation of a radical followed by izonization. However, the most common method of generating radical cations in solution is the single electron oxidation of neutral molecules. The radical cation may then undergo mesolytic cleavage to generate a benzyl radical and a cationic intermediate. Nucleophilic attack on the cationic intermediate leads to the newly formed product of substitution, and the benzyl radical is further oxidized to the cation and readily trapped by a nucleophile (**Figure 1**).[2] It has been observed that generation of the radical cation in low concentration leads to clean reactivity.

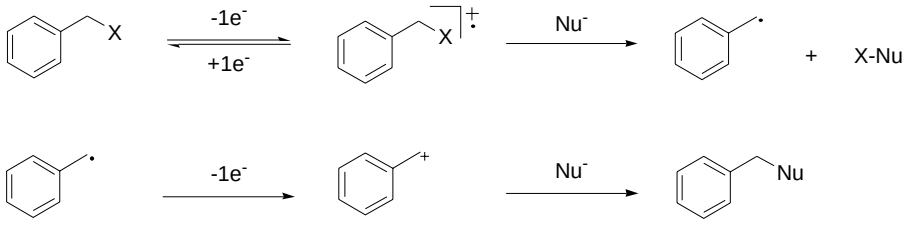


Figure 1: Chemical oxidation of an alkylarene in the presence of a nucleophile

Photoinduced electron transfer (PET) is a powerful method of oxidation that is used for the formation of radical cations. Two mechanisms are possible for the formation of radical cations under PET conditions. The first exploits the ability of electronically excited acceptors to act as strong oxidizing agents, while the second exploits the tendency of electronically excited donor molecules to undergo more facile electron transfer (**Figure 2**). A drawback of PET oxidation is the tendacy for return electron transfer to occur, which leads to formation of the neutral substrate. The rate of return electron transfer may be altered through the proper choice of solvent, the acceptor and the use of cosensitizers.[2]

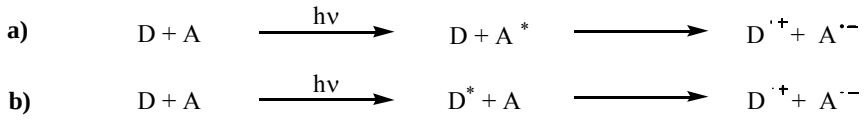
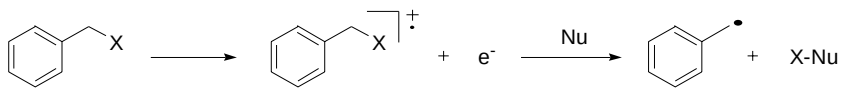


Figure 2: Photoinduced electron transfer of excited state acceptors (a) and donors (b).

Removing an electron from a neutral substrate leads to bond weakening within the resulting radical cation. As a consequence of the bond weakening, mesolytic cleavage can occur to generate a radical fragment and a cationic fragment. Aryl radical cations are known to undergo carbon-hydrogen (deprotonation), carbon-carbon and carbon-silicon bond fragmentation to form a benzyl radical and a cation. The cation generated may then be trapped by a suitable nuecleophile to give the desired substitution product (**Figure 3**).[1]



X = H, CR_3, SiR_3

Figure 3: Nucleophilic assisted mesolytic fragmentation of radical cations.

The tendency of a carbon-carbon bond to undergo mesolytic cleavage, as defined by its bond dissociation energy (BDE_{RC}), may be approximated thermodynamically by knowing the bond dissociation energy of that bond in the neutral substrate (BDE_S), the oxidation potential of the substrate (E_{pa}(S)) and the oxidation potential of the radical which becomes the electrophilic fragment (E_{pa}(E)). The extent of bond weakening can be explained by Equation 1:[4] A schematic representation of the fragmentation of a monoalkyl arene was used to derive Equation 1 (**Figure 4**).

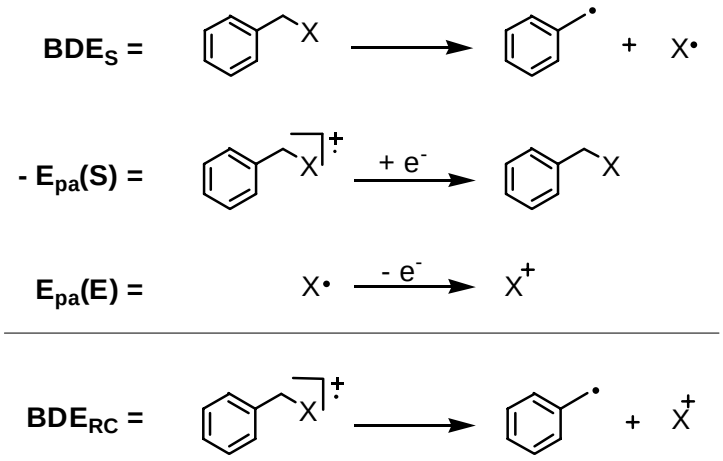


Figure 4: Schematic representation of radical cation mesolytic fragmentation.

$$BDE_{RC} = BDE_S - E_{pa}(S) + E_{pa}(E) \qquad \text{(Eq. 1)}$$

While Equation 1 predicts the proclivity of a particular bond to cleave in a radical cation, the rate with which the bond cleaves is dependent upon the conformation of the molecule. Placing the σ-bond of interest parallel to the arene's π-system leads to the greatest extent of bond weakening (**Figure 5**).[2]

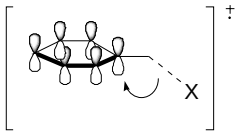


Figure 5: Orbital overlap requirement for mesolytic bond fragmentation.

III. Carbon-Hydrogen Bond Activation

The cyclic voltammetry (CV) studies conducted by Kochi and coworkers[5] on a series of alkylarenes have shown the lifetimes of the radical cations to be less then 100 μs. The short lifetimes and irreversible nature of the CV experiments were attributed to the rapid deprotonation of the benzylic position.

Carbon-hydrogen bond activation was also observed in Freccero and coworkers kinetic studies on the reaction parameters of radical cation fragmentation.[1] In their studies, several substituted anisole derivatives were subjected to single electron oxidation (ceric ammonium nitrate, 355 nm irradiation, acetonitrile) with benzyl nitrates being the major products observed. The proposed mechanism for this apparent substitution reaction is formation of the radical cation through single electron transfer to the nitrate radical. This is followed by the rapid deprotonation of a benzyl hydrogen to form the benzyl radical, which is further oxidized to the benzyl cation by excess cerium (IV) present in the reaction. Finally, the cation is trapped by a nitrate anion (**Figure 6).**

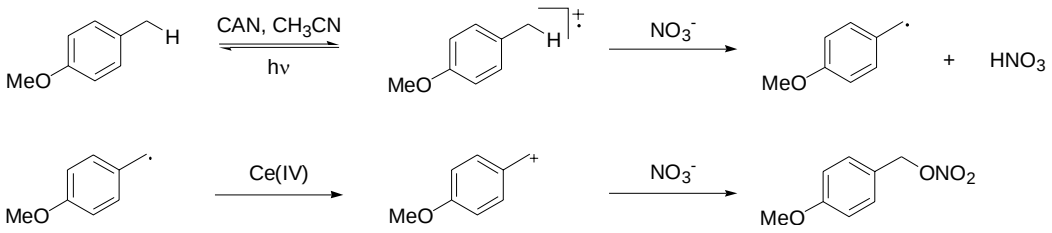


Figure 6: C-H σ-bond activation by single electron oxidation.

IV. Carbon-Carbon σ-Bond Actvation

The ability to selectively activate carbon-carbon σ-bonds to form reactive intermediates in a predictable manner would be of great synthetic utility. Single electron oxidation of alkylarenes to radical cations furnishes such an opportunity. However, studies by Kochi and coworkers have shown *tert*-butyl benzene in contrast to toluene displays reversible behavior when subjected to cyclic voltametry (CV) conditions.[5] These data suggest that sufficient carbon-carbon σ-bond activation to promote bond cleavage is not favorable for simple alkylarenes.

Arnold and coworkers examined the reactivity of a series of alkylarene radical cations under photoinitiated electron transfer (PET) conditions.[4] This work was directed toward developing a way to predict the reactivity of alkylaryl radical cations. Arnold's results showed selective carbon-carbon bond activation was possible with the proper substitution on the alkyl portion of the molecule. For example, in the case of homobenzylic ethers, Arnold observed fragmentation of the radical cation to give exclusively the benzyl radical and the α-alkoxycarbocation. This is demonstrated in the reaction of homobenzylic ether radical cations with methanol to form the dimethyl acetal of acetaldehyde and products consistent with the formation of benzyl radicals (**Figure 7)**. The regiochemistry of fragmentation can be explained

by the observation that fragmentation occurs to give the carbocation of the radical with the lower oxidation potential (see Eq 1). In the present case of homobenzylic ethers, the α-alkoxy radical's oxidation potential is approximately 0.6 V lower than that of the benzyl radical.[6]

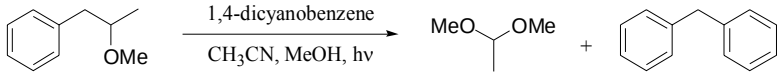


Figure 7: C-C σ-bond activation by photoinitiated electron transfer.

V. Electron Transfer Initiated Cyclization (ETIC) Reactions

Studies in our lab have shown single electron oxidation of homobenzylic ethers, amides and carbamates with pendent nucleophiles leads to the formation of furanosides, pyranosides and acyl aminals.[7] The reaction proceeds through carbon-carbon σ-bond activation via photoinitiated single electron transfer to form the radical cation. The radical cation then undergoes mesolytic carbon-carbon bond cleavage to form a benzyl radical and a potent electrophile (stabilized carbocations in the present case) followed by nucleophilic ring closure (**Figure 8**).

Z = electron donating group
Nu = Nucleophilic group

Figure 8: General ETIC reaction.

Homobenzylic ethers and amides were chosen as the substrates for carbon-carbon bond activation based on three criteria: 1) the benzyl group is inert to a wide range of organic reaction

conditions and can be incorporated early in the substrate synthesis, 2) the essentially neutral reaction conditions allow for the presence of acid-sensitive functionality and 3) the potent electrophile generated under the reaction conditions allows for a wide range of nucleophiles to be employed.

The mechanism of the ETIC reaction (**Figure 9**) was proposed based on the study of a series of substrates.[7a] The first step is the reversible electron transfer from the aromatic cosolvent to photoexcited sensitizer to form the radical cation of the cosolvent. The substrate then undergoes electron transfer to the radical cation of the aromatic cosolvent leading to formation of the radical cation. The radical cation can then undergo an associative (S_N2) nucleophilic cyclization, or a dissociative (S_N1) cyclization. Product ratios from cyclization reactions of diastereomerically pure substrates indicated both pathways were contributing. The extent to which one pathway dominates over the other can be controlled through substrate design. The associative pathway could be suppressed by introducing steric bulk around the electrophilic carbon, building strain in the transition state or by using less reactive bulky nucleophiles. When the rate of cyclization for the dissociative pathway proceeds slowly, the intermediate oxocarbenium ion can recombine with the benzyl radical. This results in formation of the radical cation which may be reduced by *tert*-butylbenzene to regenerate the starting material. This reactive pathway was evidenced by taking a slow reacting single diastereomer to partial conversion and recovering the starting material as a 1:1 mixture of diastereomers.

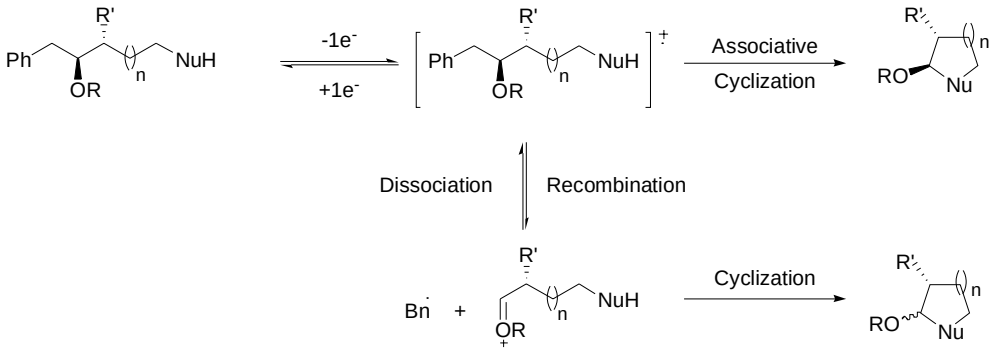


Figure 9: Proposed mechanistic pathway for the ETIC reaction.

An alternative mechanism in which the rate of associative ring closure is slow for one diastereomer and fast for the other could be envisioned. In order for this to occur, the radical cation would have to fragment into a solvated radical-cation pair whose lifetime is such that rotation is faster than recombination. The population of the faster reacting diastereomer is then depleted by rapid cyclization to give the apparent dissociative product, while the slower diastereomer reacts to a lesser extent to give the associative product (**Figure 10**).

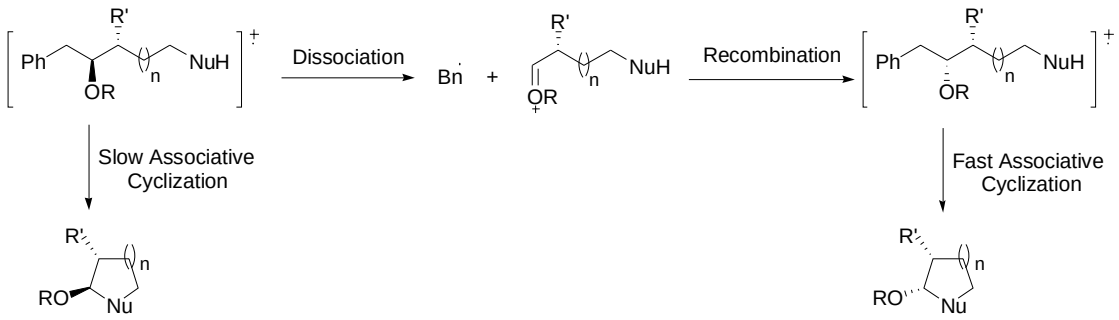
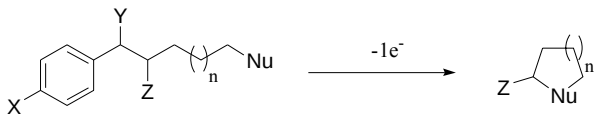


Figure 10: Alternative mechanistic pathway for the ETIC reaction.

VI. Tuning the Chemoselectivity and Reactivity

The ability to design new ETIC substrates with enhanced chemoselectivity and reactivity would provide enhanced synthetic utility for the ETIC reaction. While preferential oxidation of the arene over the nucleophile leads to enhanced chemoselectivity, the reactivity of a substrate is dependent upon the strength of the fragmenting bond. This suggests the relative chemoselectivity and reactivity of a substrate may be controlled through making logical structural alterations to the general ETIC substrate design (**Figure 11**).



X = oxidation potential modulating group
Y = benzylic bond strength modulating group
Z = electron donating group
Nu = nucleophilic group

Figure 11: Design of ETIC substrates with greater chemoselectivity and reactivity.

The chemoselectivity of a substrate is dependent upon the ability to oxidize the arene in preference to the nucleophile. To ensure the arene is preferentially oxidized, its oxidation potential must be lower than that of the nucleophile. The oxidation potential of the arene may be tuned through the introduction of substituents. Incorporation of electron donating groups would result in a lowering of the arene's oxidation potential. For example, the oxidation potential of *p*-methoxytoluene is roughly a 0.5 V (11.5 Kcal/mol)[1,8] lower than toluene (**Figure 12**).

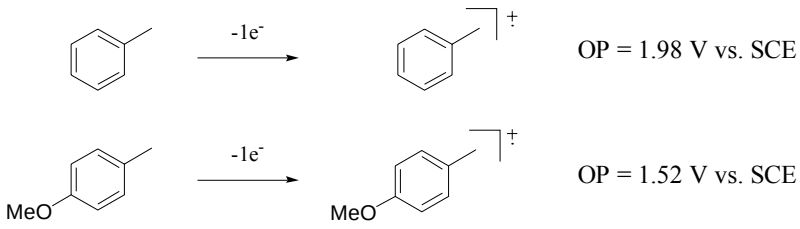
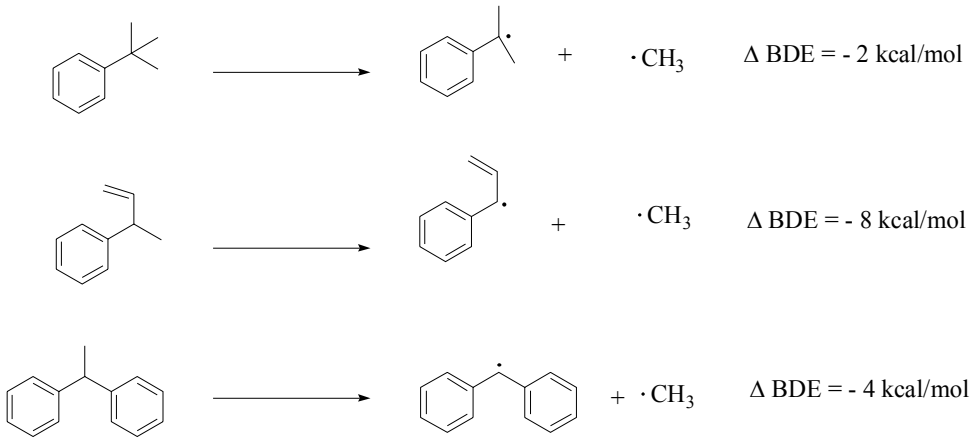


Figure 12: Modulator of oxidation potential.

While lowering the oxidation potential will allow for greater chemoselectivity through selective oxidation of the arene, Equation 1 predicts that lowering the substrate's oxidation potential (E_{pa}(S)) will lead to an increase in the radical cation's bond dissociation energy (BDE_{RC}). This increase in the BDE_{RC} may result in cleavage of the radical cation becoming a disfavored process. If fragmentation of the radical cation is slowed down, the reactivity of the substrate may be negatively impacted.

The reactivity of a substrate is dependent upon the radical cation's ability to undergo fragmentation. The bond dissociation energy of the radical cation (BDE_{RC}) has a strong influence on the extent to which fragmentation occurs. This suggests the reactivity of a substrate may be tuned through manipulation of the BDE_{RC}. The BDE_{RC} must be lowered in order to increase the reactivity of the substrate. Equation 1 shows a direct relationship between the BDE_S and the BDE_{RC}. Therefore, lowering the BDE_S is expected to result in an increase in the reactivity of a substrate. Introducing substituents along the alkyl backbone of the substrate allows for the BDE_S to be decreased.[4] Placing radical stabilizing groups in the benzylic position leads to a decrease in benzylic bond strength (**Figure 13**).[8]



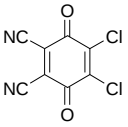
Δ BDE values are relative to the CH_2CH_3 bond of ethyl benzene

Figure 13: Modulators of benzylic bond strength.

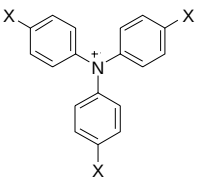
VII. Chemical Oxidants in ETIC Reactions

With the design of substrates possessing lower oxidation potentials, single electron chemical oxidants could be used to initiate ETIC reactions. Chemical oxidation is advantageous for several reasons: 1) the reactions may be run on large scale, 2) the reactions may be conducted using simplified experimental apparati, 3) the reactions can be run with substrates containing photo-labile functionality.

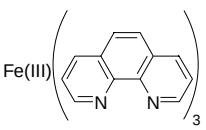
Ceric ammonium nitrate (CAN) is an attractive candidate for chemical oxidation because it is inexpensive (500g of CAN costs $82.50 from Aldrich, approximately 9 cents per mmol), easy to handle and readily available through commercial sources. CAN has been used in the single electron oxidative removal of electron rich arene protecting groups,[10] and the oxidative demethylation of functionalized hydroquinones.[11] The functional group compatibility found in the hydroquinone reactions demonstrates the mildness of CAN oxidations.



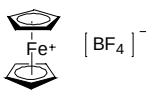
2,3 Dichloro-5,6 dicyano-1,4-benzoquinone (DDQ) is a strong single electron oxidant which is commercially available, may be stored in the freezer for several months and reacts under essentially neutral reaction conditions.[12] However, DDQ is an expensive reagent (100g of DDQ costs $212.40 from Aldrich, approximately $2.07 per mmol) typically used in stoichometric amounts, making it a less desirable oxidant especially for large scale reactions.[13] Another difficulty encountered with DDQ is the removable of HDDQ (reduced by-product) from reaction mixtures. For this reason, several methods have been developed to use DDQ as a catalytic oxidant in the presence of either $FeCl_3$[12] or $Mn(OAc)_3$[13] as the stoichometric oxidants.



Triarylaminium salts are widely used single electron chemical oxidants in organic chemistry. As a group they are attractive candidates due to the ability to tune the reduction potential through arene substitution. $[(C_6H_5Br\text{-}4)_3N]\text{-}[SbCl_6]$ is commercially available, and the other analogs are readily prepared from the corresponding amine.[14] Triarylaminium salts have been used in the oxidative catalysis of Diels-Alder reactions that had not be accomplished through other methods. Oxidation of the dienophile lowers the barrier of cycloaddition to give the radical cation of the Diels-Alder adduct. The product radical cation is then readily reduced by the resulting amine to regenerate the triarylaminium radical cation.[2]



Iron (III) phenanthroline complexes are mild oxidants that have been shown to react solely through an outer-sphere electron transfer process.[15] The reduction potential of these complexes can be easily tuned through substitution of the phenanthroline ligands.[16] This oxidant appears to be a good candidate for small scale reactions, however, the need for 2 equivalents of oxidant to substrate would make isolation and purification of large scale reactions quite difficult.[16]



Ferrocenium salts are extremely mild single electron oxidants that are readily prepared from inexpensive precursors. These oxidants have also been proven to react solely through an outer-sphere electron transfer process, and the reduction potential is easily modulated through substitution on the cyclopentadiene ring.[14] The range of reduction potential available may be too low for use with *p*-methoxy substituted substrates. However, if the oxidation potential of the arene had to be lowered significantly to obtain chemoselective oxidation, these compounds would become useful oxidants.

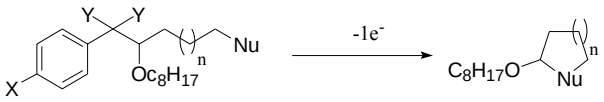
The polyoxometalate $H_5PV_2Mo_{10}O_{40}$ is a mild single electron oxidant and is very stable and easy to handle. While this oxidant is not available from commercial sources, it is easily prepared and only needed in catalytic amounts. This polyoxametalate reacts under extremely mild conditions, and kinetic investigations on the mechanism of electron transfer indicate solely an outer-sphere electron transfer process.[17]

VIII. Goals and Objectives of the Project

The ability to expand the scope and limitations of the ETIC reaction will be explored. This will be accomplished through the generation of substrates that possess greater chemoselectivity and reactivity, development of a chemically initiated method and the formation of carbon-carbon bonds.

The design of substrates for cyclization with lower oxidation potentials requires an understanding of the relationship between the oxidation potential of the substrate and the reactivity of the radical cation. This relationship will be investigated through the synthesis of a

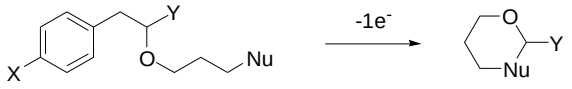
series of substrates containing a *p*-methoxy group on the arene and various radical stabilizing groups in the benzylic position (**Figure 14**).



X = oxidation potential modulating group
Y = benzylic bond strength modulating group

Figure 14: Exploring the scope of the ETIC reaction through substrate design.

With an understanding of the relationship between the oxidation potential and reactivity, the design of an ETIC substrate that undergoes an *endo*-cyclization will be explored (**Figure 15**). This will be explored by placing the modulator of benzylic bond strength in the homobenzylic position. Incorporation of the bond weakening group within the electrophilic fragment would lead to greater atom economy,[18] as well as, the ability to generate more diverse products using the ETIC reaction.

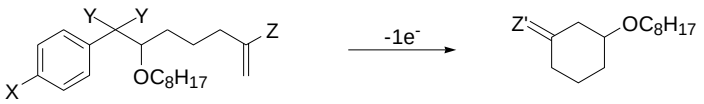


X = modulator of oxidation potential
Y = modulator of benzylic bond strength
Nu = nucleophilic group

Figure 15: Design of an *endo*-ETIC reaction substrate.

While the photo-initiated ETIC reaction has become a well developed method for the formation of heterocyclic compounds, efforts to use chemical oxidants as initiators have failed. Therefore, the benefit of substrates with lower oxidation potentials will be demonstrated in the

development of a chemically initiated variant of the ETIC reaction. Substrates possessing lower oxidation potentials should also display enhanced chemoselectivity allowing for the use of electron rich olefins as nucleophiles (**Figure 16**). The ability to use such nucleophiles would demonstrate the ability to form carbon-carbon bonds using the ETIC reaction.



X = oxidation potential modulating group
Y = benzylic bond strength modulating group
Z = electron donating group (e.g. CH_2SiMe_3, OAc, etc…)
Z' = CH_2, O, etc…

Figure 16: Incorporation of electron rich olefins as nucleophiles in ETIC reactions.

1.2. Results and Discussion

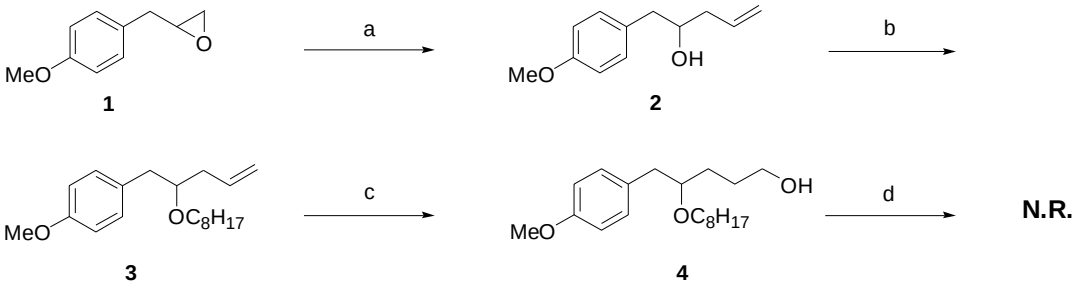
I. Determining the Relationship between Oxidation Potential and Reactivity

The ETIC reaction developed in our lab[7] has demonstrated carbon-carbon σ-bonds of homobenzylic ethers and amides can be selectively activated toward nucleophilic attack under photoinduced single electron transfer. While this method has proven to be successful for the synthesis of heterocyclic molecules, we would like to broaden the scope and applicability of the ETIC reaction through the synthesis of substrates with greater chemoselectivity and comparable reactivity. In order to design such substrates, an understanding of the relationship between the substrate's oxidation potential (OP_S) and the reactivity of the radical cation must be established. Therefore, several substrates containing *p*-methoxy arenes and various benzylic substituents were prepared and subjected to our standard photochemical cyclization conditions.[7b]

The first substrate to be prepared and subjected to the ETIC reaction conditions is shown in **Scheme 1**. Alcohol **2** was obtained in 96% yield by the copper (I) iodide mediated opening of epoxypropyl anisole (**1**) with vinyl magnesium bromide. The alcohol was then converted to octyl ether **3** with sodium hydride and octyl iodide in DMF at 0 °C in 64%. Hydroboration of **3** with BH_3·THF followed by quenching with basic hydrogen peroxide provided substrate **4** in 34% yield.

Substrate **4** was then subjected to photo-initiated ETIC reaction conditions using a catalytic amount of the sensitizer *N*-methylquinolinium hexafluorophophate ($NMQPF_6$). The substrate (**4**) was added to a suspension of $NMQPF_6$ (sensitizer), sodium acetate (insoluble base) and sodium thiosulfate (peroxide reducing agent) in toluene (aromatic cosensitizer) and 1,2-

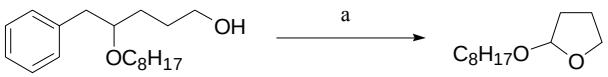
dichloroehtane (solvent). Air (terminal oxidant) was gently bubbled through the mixture as it was irradiated through a Pyrex filter from a medium pressure mercury lamp. After prolonged reaction times, no consumption of substrate **4** was noted and starting material (**4**) was recovered.



Reagents and Conditions: a) CuI, vinyl magnesium bromide, THF, - 78 °C – RT, 2h (96%); b) NaH, octyl iodide, DMF, 0 °C – RT, 12h (64%); c) BH_3·THF, THF, then NaOH and H_2O_2 (34%) ; d) $NMQPF_6$, PhMe, NaOAc, $Na_2S_2O_3$, hν, O_2, DCE.

Scheme 1: Synthesis of the parent *p*-methoxy ETIC substrate.

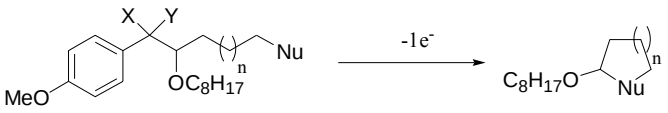
The failure of substrate **4** to cyclize was in contrast to a similar cyclization conducted in our laboratory. An analogous substrate without the *p*-methoxy group cyclizes efficiently when subjected to identical conditions (**Figure 17**).[7b] Therefore lowering the oxidation potential of substrate **4** by incorporating the *p*-methoxy group must account for the lack of reactivity. As stated earlier, Equation 1 predicts that lowering the oxidation potential of a substrate increases the bond dissociation energy of the radical cation (BDE_{RC}). The loss of reactivity observed for substrate **4** indicates the increased BDE_{RC} is negatively impacting fragmentation of the resultant radical cation.



Reagents and Conditions: a) $NMQPF_6$, hν, O_2, NaS_2O_3, NaOAc, DCE, tol. (88%).

Figure 17: Cyclization of the parent ETIC substrate.[7b]

To regain reactivity in substrates containing electron rich arenes, their design must be re-evaluated. If the lack of reactivity is due to the increase in the BDE_{RC}, substrates containing bond weakening groups must be designed. Introducing bond weakening groups in the benzylic position will lead to a lowering of the substrate's bond dissociation energy (BDE_S). Equation 1 shows that lowering the BDE_S leads to a decrease in the BDE_{RC}, which is expected to increase the tendacy of the radical cation to undergo fragmentation. Therefore, a series of substrates were synthesized with radical stabilizing groups in the benzylic position (**Figure 18**).[9]



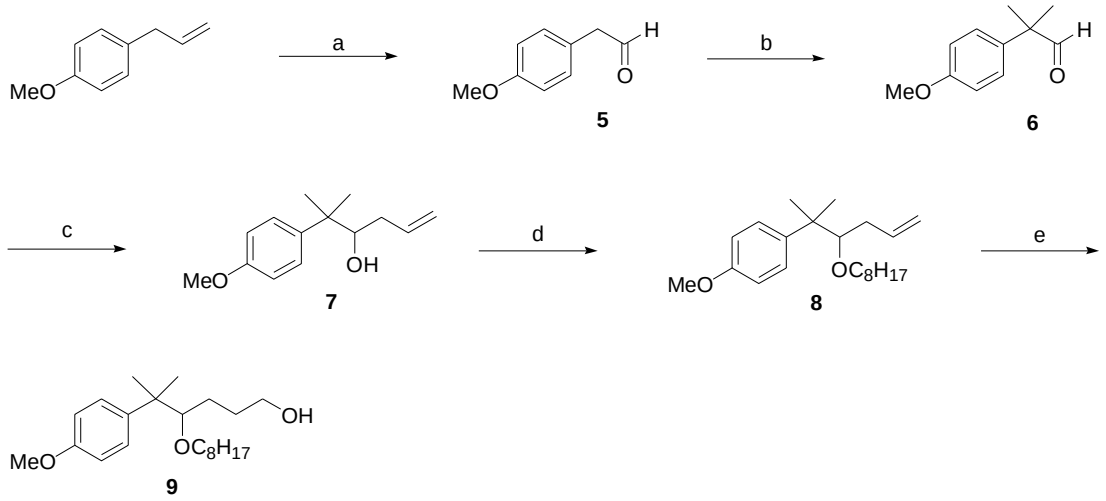
X, Y = Me
X = vinyl, Y = H
X = Ph, Y = H
Nu = nucleophilic group

Figure 18: ETIC reaction of substrates containing modulators of benzylic bond strength.

II. Synthesis of ETIC Substrates with Weakened Benzylic Bonds

The substrate with a geminal methyl group was quickly synthesized in 5 steps (**Scheme 2**) beginning with ozonolysis of *p*-allyl anisole followed by reduction with triphenylphospine to give aldehyde **5** in 65% yield. The resulting aldehyde (**5**) was then bis- alkylated with

potassium *tert*-butoxide and methyl iodide in THF at -78 °C to give dimethyl aldehyde **6** in 21%.[19] Addition of allyl magnesium bromide to aldehyde **6** led to the formation of homobenzylic alcohol **7** in 83% yield. Etherification of the homobenzylic alcohol (**7**) was accomplished with sodium hydride and octyl iodide in DMF at 0 °C to give homobenzylic ether **8** in 60% yield. The terminal olefin was then transformed to a primary alcohol via hydroboration with BH_3·THF at 0 °C in 62% yield to give the desired substrate **9**.



Reagents and Conditions: a) O_3, CH_2Cl_2, -78 °C, then PPh_3, -78 °C – RT (65%); b) KO^{t}Bu, MeI, THF, -78 °C (21%); c) allyl magnesium bromide, THF, -78 °C (83%); d) NaH, octyl iodide, DMF, 0 °C (60%); e) BH_3·THF, THF, then NaOH and H_2O_2 (62%).

Scheme 2: Synthesis of the geminal dimethyl ETIC substrate.

Attempts to prepare a substrate with a vinyl group in the benzylic position proved to be quite difficult, and led to the *in situ* palladium catalyzed preparation of an allyl stannane followed by addition to an aldehyde (**Figure 19**).[20] This reaction begins with the reduction of Pd(II) by $SnCl_2$ to give Pd(0) and $SnCl_4$. The $SnCl_4$ then coordinates to the allyl alcohol followed by oxidative instertion of Pd(0) to form the π-allyl palladium complex. The π-allyl palladium complex is then reduced to the allyl stannane by $SnCl_2$. The allyl stannane then

undergoes addition to the aldehyde with excellent diastereoselectivity due to the well defined transition state.[21]

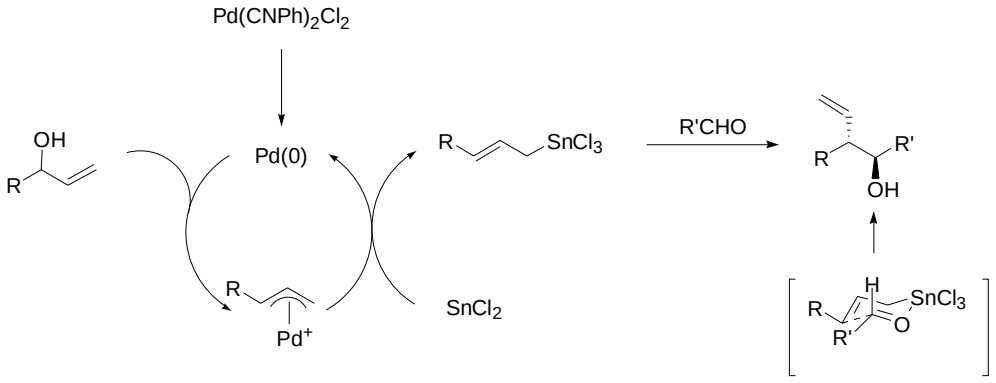
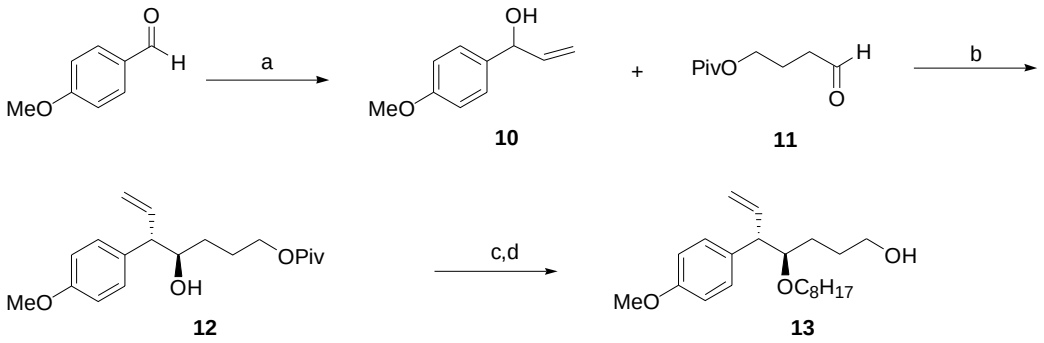


Figure 19: Addition to aldehydes by *in situ* Pd(0) catalyzed allyl stannane formation.

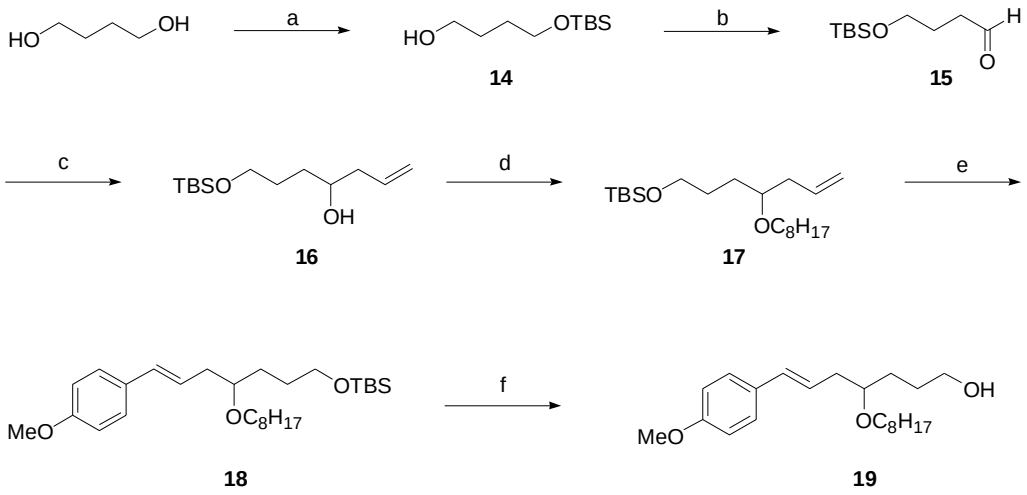
The synthesis of the vinyl-substituted substrate (**Scheme 3**) began with the addition of vinyl magnesium bromide to *p*-anisaldehyde, to give alcohol **10** in 83% yield. Allyl alcohol **10** was converted to the allyl stannane *in situ*, followed by addition to aldehyde **11** providing alcohol **12** as a single diastereomer (36%).[20] The relative stereochemistry of alcohol **12** was assigned through the literature precedent of an analogous reaction.[20] Conversion of alcohol **12** to the octyl ether with sodium hydride and octyl iodide in DMF at 0 °C afforded an inseparable mixture of the desired ether and an unknown by-product. The mixture was then subjected to lithium aluminum hydride to remove the pivalate. Deprotection of the pivalate ester was quite slow and complete conversion was never obtained. However, 8% of the desired substrate (**13**) was isolated, which provided a sufficient amount to test our hypothesis.



Reagents and Conditions: a) vinyl magnesium bromide, THF, -78 °C (83%); b) $Pd(PhCN)Cl_2$, $SnCl_2$, DMI (36%); c) NaH, octyl iodide, DMF, 0 °C; d) LAH, THF, 0 °C – RT (8%).

Scheme 3: Synthesis of a vinyl-substituted ETIC substrate.

The extent to which the BDE_S is lowered is dependent on the stability of the radical formed during homolytic cleavage. Therefore, if two different isomers of a substrate lead to the formation of the same radical, they should possess similar BDE_S and comparable reactivity. To test this hypothesis, a *p*-methoxy cinnamyl substrate (**Scheme 4**) was prepared. The mesolytic cleavage of this substrate would lead to the same radical as that generated in the fragmentation the vinyl-substrate (**13**). Mono-protection of 1,4 butane diol with *tert*-butyldimethylsilyl chloride (TBSCl) provided alcohol **14** in 87% yield.[22] The primary alchohol was then oxidized with trichloroisocyanuric acid (stoichometric oxidant) and TEMPO (catalytic oxidant) in CH_2Cl_2 at 0 °C to give the desired aldehyde (**15**) in 95% yield.[23] Homoallylic alcohol **16** was obtained by the addition of allyl magnesium bromide to the aldehyde **15** in 55%. Etherification of alcohol **16** with sodium hydride and octyl iodide in DMF at 0 °C lead to formation of the ether **17** in 63% yield. Cross metathesis[24] of **17** with *p*-methoxy styrene provided the TBS-protected cinnamyl compound **18** (39%). Deprotection of the TBS-ether with TBAF afforded the desired cyclization substrate **19** with 17% isolated yield. The low isolated yields associated with the isolation of compounds **18** and **19** are most likely due to their instability.

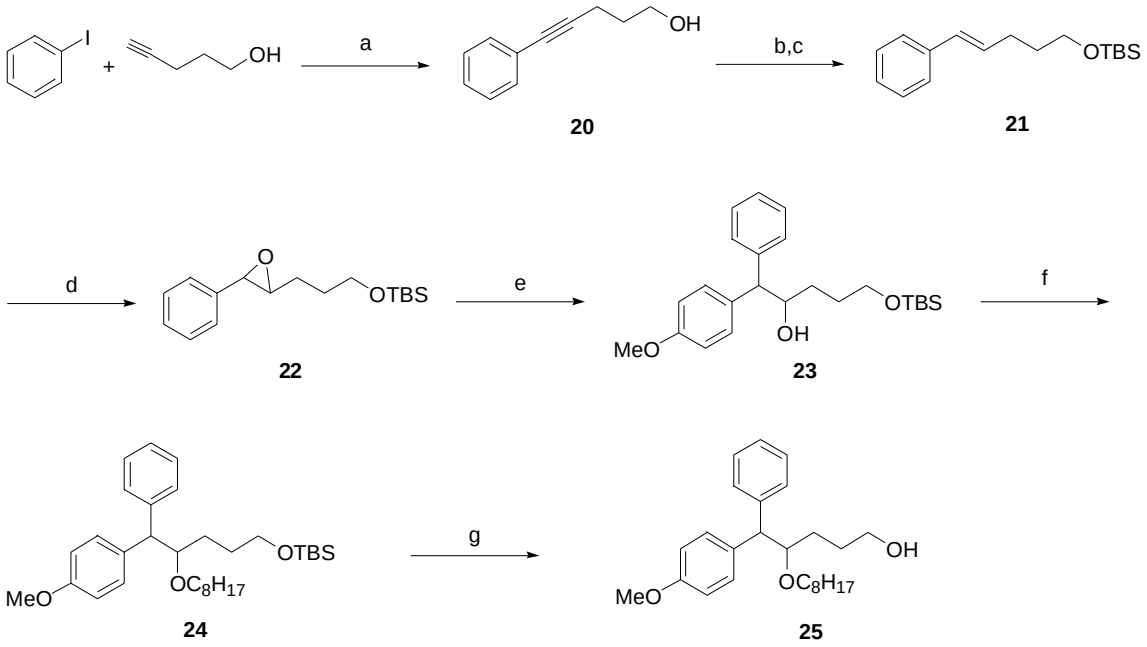


Reagents and Conditions: a) NaH, TBSCl, THF (87%); b) trichloroisocyanuric acid, TEMPO, CH_2Cl_2, 0 °C – RT, 15 min. (95%); c) Allyl magnesium bromide, THF, -78 °C (55%); e) i. NaH, octyl iodide, DMF, 0 °C – RT (63%); ii. benzylidene[1,3-bis(2,4,6-trimethylphenyl)-2-imidazolidinylidene]dichloro(tricyclohexylphosphine)ruthenium, *p*-methoxy styrene, CH_2Cl_2, 40 °C, 12h (39%); f) TBAF, THF, 3h (17%).

Scheme 4: Synthesis of a *p*-methoxy cinnamyl ETIC substrate.

The final substrate synthesized to test the effect of bond weakening groups in ETIC substrates contained a phenyl group in the benzylic position (**Scheme 5**). Sonogashira coupling[25] of iodobenzene and 4-pentyn-1-ol led to the formation of alkynyl arene **20** (99%). Reduction of the alkyne with lithium aluminum hydride (LAH) in refluxing THF furnished the desired arylalkene (99%).[26] Protection of the resulting primary alcohol with TBSCl provided TBS-ether **21** in 95% yield. Epoxide **22** was obtained through the *m*-CPBA epoxidation of olefin **21** in 72% yield. The copper (I) mediated opening of epoxide **22** with *p*-methoxyphenyl magnesium bromide gave homobenzylic alcohol **23** (71%).[27] Secondary alcohol **23** was then alkylated with sodium hydride and octyl iodide in a 40% isolated yield to afford ether **24**. While the isolated yield of ether **24** was low, unreacted alcohol **23** was easily recovered and re-subjected to the

etherification conditions. Deprotection of the TBS-ether (**24**) with acetic acid, water in refluxing THF furnished the desired di-aryl cyclization substrate (**25**) (89%).



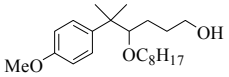
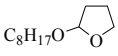
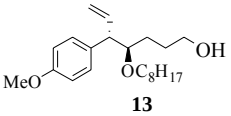
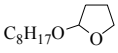
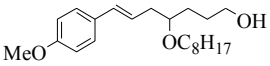
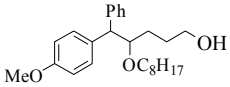
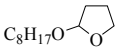
Reagents and Conditions: a) $Pd(PPh_3)_4$, CuI, THF, *i*-Pr_2NH (99%); b) LAH, THF, reflux, 18 h (99%); c) TBSCl, imidazole, DMF, 0 °C (95%); d) *m*-CPBA, CH_2Cl_2, NaOAc, 0 °C – RT (72%); e) CuI, *p*-methoxy phenyl magnesium bromide, THF, -40 °C (71%); f) NaH, octyl iodide, DMF, 0 °C (40%); g) Acetic acid, water, THF (89%).

Scheme 5: Synthesis of a phenyl substituted ETIC substrate.

III. Cyclization of ETIC Substrates with Weakened Benzylic Bonds

The substrates **9**, **13** and **25** were subjected to our standard photochemical cyclization conditions.[7b] A typical cyclization is conducted by adding the substrate to a suspension of $NMQPF_6$ (sensitizer), sodium acetate (insoluble base) and sodium thiosulfate (peroxide reducing agent) in toluene (aromatic cosensitizer) and 1,2-dichloroehtane (solvent). Air (terminal oxidant) was gently bubbled through the mixture as it was irradiated through a Pyrex filter from a medium

pressure mercury lamp. [7b] While substrates **9**, **13**, and **25** provided the acetal **26** in moderate to good yield, substrate **19** led to unidentified decomposition products (**Table 1**). The longer reaction times may explain slightly lower yields obtained for the cyclization of subtrates **9** and **13** due to the volatility of the product (**26**). The successful cyclization of substrates **9**, **13** and **25** indicates the introduction of benzylic bond weakening groups had a favorable impact on the fragmentation of the intermediate radical cations generated.

Entry	Substrate	Product	Yield (%)[a]	Rxn Time (h)[b]
1	 **9**	 **26**	62	3.0
2	 **13**	 **26**	62	4.75
3	 **19**	--	**Decomposition**	
4	 **25**	 **26**	88	1.5

[a] Isolated yields after flash column chromatography;
[b] Reaction times are determined by observing the consumption of starting material by TLC

Table 1: ETIC reactions of substrates with weakened benzylic bonds.

This observation demonstrates the predictive capacity of Equation 1 in the design of ETIC substrates. However Equation 1 does not allow for predictions on the rate of fragmentation for a substrate. Freccero and co-workers investigation of the kinetics of radical cation reactions has shown thermodynamic data alone is insufficient to predict relative rates of

reactivity.[1] Therefore, another factor must be responsible for the difference in the rate of cyclization. Because intramolecular attack of the nucleophile has the same rate for all reactions, the rate of cyclcization must be dependent upon the rate of fragmentation. As mentioned earlier the rate of fragmentation is impacted most by the conformation of the molecule. In cases where the breaking bond is aligned with the π-system of the arene, the rate of fragmentation will be enhanced.[2] This suggests substrates **9**, **13** and **25** do not share a common ground state conformation.

Substrate **9** has several factors which may be influencing the rate at which cyclization occurs. The sterically conjested *neo*-pentyl electrophilic center could lead to a disfavored approach of the nucleophile. There is not going to be a strong conformational preference for placing the alkyl group which leads to favorable fragmentation parallel to the arene's π-system. This is due to the similar steric bulk of the methyl groups with regard to the alkyl chain containing the homo-benzylic ether. Therefore, the rate of fragmentation of the radical cation is not going to be enhanced by stereo-electronic effects.

Fragmentation of substrate **13** was predicted to be the most facile due to the roughly 8 kcal/mol decrease in benzylic bond strength.[9] Although substrate **13** provided the desired cyclization reaction, it was shown to be the slowest of the series. While Freccero and co-workers[1] have demonstrated the impact thermodynamics have on the rate of radical cation fragmentation, this observation re-enforces that thermodynamics alone do not govern the overall rate of reactivity for radical cations. The slow reactivity of substrate **13** can best be rationalized by the absence of a conformational bias to place the desired alkyl group perpendicular to the aromatic plane.

Substrate **25** demonstrated excellent reactivity, and provided the desired acetal (**26**) in good yield. The enhanced reactivity indicates this substrate's ground state conformation is consistent with having the appropriate alkyl group's σ-bond aligned with the π-system of the arene. The reactivity of substrate **25** essentially matched that of the parent ETIC substrate.[7b] While a thorough kinetic study was not performed, the ability to tune the chemoselectivity and reactivity through logical substitutions has been demonstrated.

IV. Development of a Ground State Initiated Chemical Variant of the ETIC Reaction

The photoinitiated ETIC reaction developed in our lab[7] has proven to be an efficient method for the synthesis of heterocyclic compounds. However, photochemical processes require special equipment and are not easily amenable to large scale synthesis. A chemically initiated variant of the ETIC reaction was developed to allow greater synthetic utility. The electron rich substrates developed in our lab have sufficiently low oxidation potentials for use with known chemical oxidants of alkoxyarenes.[11,13]

The first ground state chemical oxidant to be explored as an initiator of ETIC reactions was Ceric ammonium nitrate (CAN). This choice was based on the wide use of CAN in the oxidative deprotection of electron rich arenes.[11] Two equivalents of CAN are needed to ensure oxidation of the electron rich arene and the resulting arylradical. Addition of a base was needed to buffer the nitric acid generated with the use of CAN. Due to the exceptional reactivity observed under the standard photochemical ETIC conditions, substrate **25** was used as to explore the ability of CAN to initiate cyclization. The feasibility of this method was tested by

introducing CAN (oxidant) to mixture of substrate **25** and $NaHCO_3$ (insoluble base) in dichloroethane and acetonitrile (7:3) (**Figure 20**).

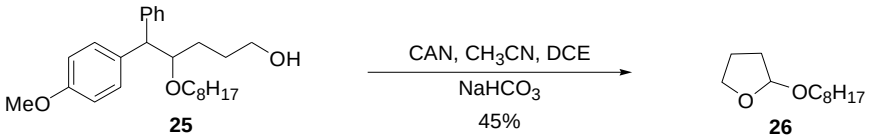


Figure 20: Chemically initiated ETIC reaction with CAN as the oxidant.

Within 5 minutes of adding the CAN, the starting material was consumed and acetal **26** was present. The mixture was then simply filtered, concentrated and purified via flash column chromatography. While this method led to the successful formation of acetal **26** the isolated yield was only 45%. The low isolated yield of acetal **26** was attributed to the formation of acetal **27** (tentatively assigned by crude ^{1}H NMR). This by-product (**27**) is believed to be generated by the Lewis acid activation of acetal **26** by Ce(III) followed the intermolecular attack of alcohol **25** (**Figure 21**).

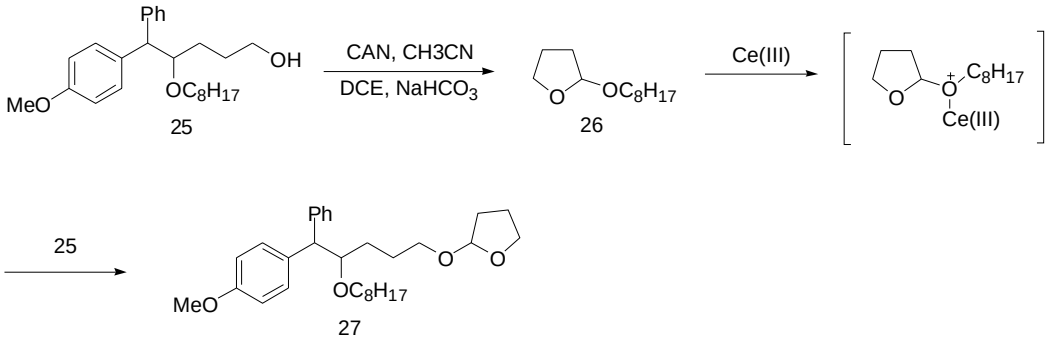
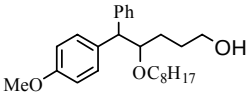
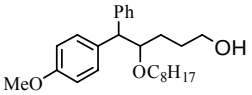
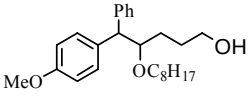
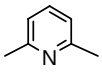
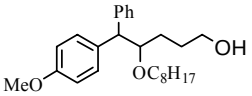
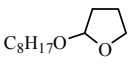
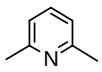
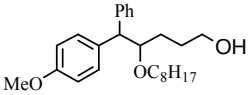
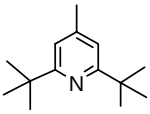


Figure 21: Ce(III) mediated formation of by products.

Another possible explanation for the low isolated yield is the generation of nitric acid during the reaction. The insolubility of $NaHCO_3$ in dichloroethane and acetonitrile hinders its ability to act as a sufficient buffer. Therefore in an attempt to optimize the reaction conditions, several soluble pyridine bases were examined to determine the impact of base concentration on the reaction. Substrate **25** was again subjected to CAN (2 equivalents), a soluble base, and dichloroethane and acetonitrile as solvents (**Table 2**).

Entry	Substrate	Product	Base	T (°C)	t (min)[a]	Yield (%)[b]
1	 **25**	--		RT		N.R.
2	 **25**	--		35		N.R.
3	 **25**	--		RT		N.R.
4	 **25**	 **26**		40	15	42
5	 **25**	--		RT		**Decomposition**

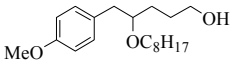
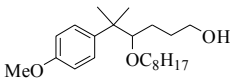
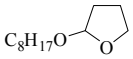
[a] Reaction times were monitored by TLC; [b] Isolated yields after flash column chromatography.

Table 2: Exploring the effect of the base used in chemically initiated ETIC reactions.

The use of pyridine as the base provided no reaction and the starting material was recovered. Gentle warming of the reaction to 35 °C had to no obvious impact on the reaction. The loss of reactivity was attributed to the Lewis acid-base interactions of Ce(IV) and pyridine. When the reaction was run with 2,6-lutidine as base at room temperature, the was no noticeable

consumption of starting material (**25**). However, increasing the reaction temperature to 40 °C in the presence of 2,6-lutidine led to complete consumpion of substrate **25, a**lthough the isolated yield of acetal **26** was still only 42%. The improved reactivity from pyridine to 2,6-lutidine suggests increasing the steric bulk around the nitrogen may have an impact on the reaction. To test this hypothesis 2,6-di-*tert*-butyl-4-methyl pyridine was used as the base. However, no desired reaction occurred and the starting material decomposed. The decomposition of the starting material was attributed to the inability of 2,6-di-*tert*butyl-4-methylpyridine to buffer the HNO_3 generated under the reaction conditions.

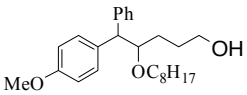
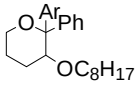
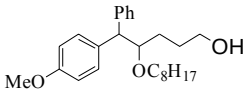
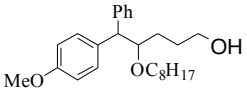
To test the general applicability of CAN as an initiator of ETIC reactions, substrates **4** and **9** were subjected to 2 equivalents of CAN (oxidant) with sodium bicarbonate (insoluble base) in dichloroethane and acetonitrile (**Table 3**). The lack of reactivity noted for substrate **4** was consistent with the photochemical data. The stability of the radical cation is too great to allow for efficient fragmentation to occur. Formation of **26** from **9** demonstrated the ability of CAN to initiate cyclization. The isolation of acetal **26** in 39% yield was consistent with cyclization of substrate **25**. However, the relative rate of reaction was again much slower than that of substrate **25**. Due to the difficulty of obtaining large amounts of the vinyl-substrate **13**, it was not subjected to the chemical cyclization conditions. While the successful cycilization of substrates **9** and **25** demonstrates the ability of CAN to promote ETIC reactions, the low isolated yields suggests this method may not be suitable for acid sensitive functional groups.

Entry	Substrate	Product	Yield (%)[a]	Rxn Time (min)[b]
1	 **4**	--	N.R.	
2	 **9**	 **26**	39	45

[a] isolated yield after flash column chromatography; [b] Reacion times were monitored by TLC

Table 3: Exploring the general applicability of CAN in ETIC reactions.

An exploration of various other chemical oxidants was initiated in an attempt to optimize the isolated yield of the reaction. 2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) is another oxidant which is commonly used for the removal of electron rich aromatic protecting groups.[14] There is also precedent for the use of polyoxometalate ($H_5PV_2Mo_{10}O_{40}$)[17] and iron phthalcyanine in the single electron oxidation of electron rich arenes. The oxidants listed above also share the benefit of being able to effect oxidation under catalytic conditions.[14,17]

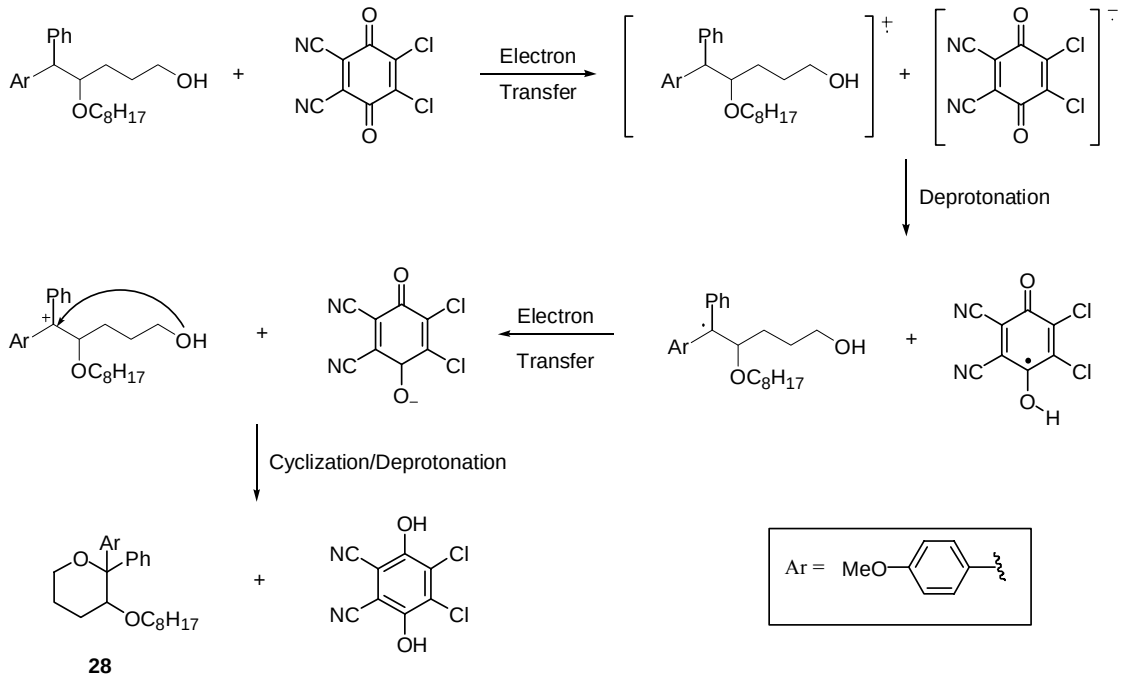
Entry	Substrate	Product[a]	Oxidant	Yield (%)	Rxn Time (h)[b]
1	 **25**	 **28**	DDQ	**55**	3
2	 **25**	--	Polyoxometalate	**N.R.**	
3	 **25**	--	Iron Phthalcyanine	**N.R.**	

[a] Ar = *p*-methoxy phenyl; [b] Reaction times were monitored by TLC; yields refer to isolated purified product.

Table 4: Exploring other chemical oxidants.

The efficacy of the above oxidants to promote ETIC reactions was investigated using compound **25** as the model substrate. Substrate **25** was again chosen due to the enhanced reactivity observed under the photochemical conditions. Treatment of the substrate (**25**) with both the polyoxometalate and iron phthalcyanine provided no reaction, and starting material was recovered. However treatment of substrate **25** with two equivalents of DDQ led to the slow consumption of starting material. After 3 hours, the starting material was consumed and cyclic ether (**28**) resulting from preferential carbon-hydrogen activation was isolated in 55% yield.

While the carbon-hydrogen bond activation which led to the isolation of ether **28** was unexpected, the result can be explained by examining the mechanism of DDQ oxidation (**Scheme 6**). The first step is the electron transfer from the alkylarene to DDQ forming the radical cation of the alkylarene and the radical anion of DDQ. The radical cation is then deprotonated by the radical anion followed by further oxidation of the benzyl radical by the oxygen stabilized radical of DDQ to give the benzyl cation. The benzyl cation is then trapped by the appended nucleophile to give the cyclized product (**28**).



Scheme 6: Mechanism of carbon-hydrogen bond activation by DDQ.

V. Demonstrating the Feasibility of endo-ETIC Reactions

To expand the scope of the products which are available via the ETIC reaction, the design of a substrate to undergo an *endo*-cyclization was explored. The new substrate was designed to maintain both chemoselectivity and reactivity. The choice of a *p*-methoxy arene as the electrophore remained unchanged. However, the modulator of benzylic bond strength was now to be placed in the homo-benzylic position, and the nucleophile was tethered through the ether linkage (**Figure 22**). By placing a vinyl group in the homo-benzylic position, there will be two factors working in concert to lower the BDE_{RC}. The vinyl group is still expected to lower the BDE_S by roughly 8 kcal/mol.[9] Moreover, the vinyl group is also expected to lower the oxidation potential of the resulting electrophilic fragment (OP_E). According to Equation 1 decreasing the

value of these terms will result in a lowering of the BDE_{RC}. In addition to providing a greater range of products available, these substrate design changes will provide improved atom economy.[18] This is the result of the modulator of benzylic bond strength being incorporated into the fragment which becomes the product.

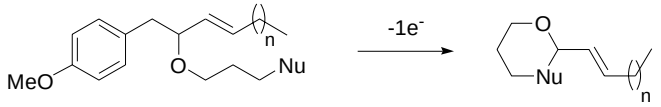
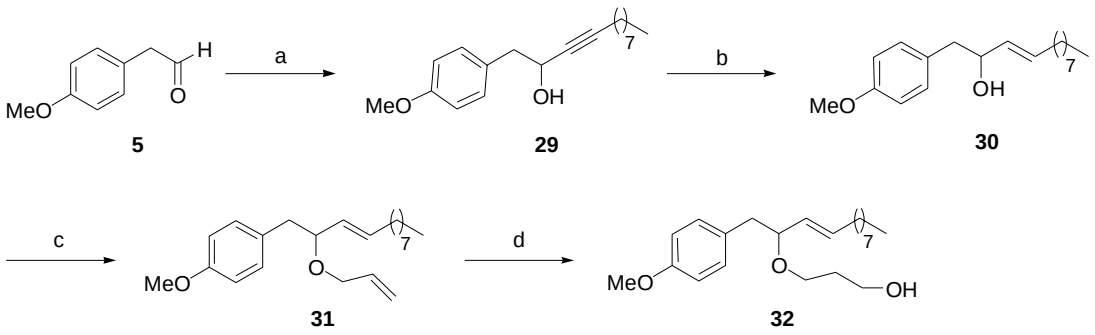


Figure 22: Development of an ETIC substrate to undergo *endo*-cyclizations.

The synthesis of a substrate with the structural attributes mentioned above was developed to test the practicality of *endo*-ETIC reaction (**Scheme 7**). Addition of the lithium anion of 1-decyne to aldehyde **5** provided propargyl alcohol **29** in 69% yield. Reduction of the propargyl alcohol (**29**) with lithium aluminum hydride in refluxing THF afforded the homobenzylic alcohol (**30**) in 87% yield. Treatment of alcohol **30** with sodium hydride and allyl bromide led to the formation of bis-allyl ether **31**. Hydroboration of the terminal olefin in ether **31** would lead to the desired cyclization substrate **32**. However, the presence of both an internal and a terminal olefin made this transformation difficult. Use of the BH_3·THF complex would be expected to readily react with both olefins. Therefore a more selective hydroboration reagent was needed to ensure exclusive reactivity of the terminal olefin. The use of hindered alkyl boranes have been shown to provide such selectivity. Several dialkyl boranes including 9-BBN,[28] di-cyclohexyl borane[29] and di-siamyl borane[30] were reacted with ether **31**. Disiamyl borane proved to be the best reagent for the conversion of terminal olefin of ether **31** to primary alcohol **32** (55%).



Reagents andConditions: a) 1-decyne, *n*-BuLi, -78 °C (69%); b) LAH, THF, reflux, 18h (87%); c) NaH, allyl bromide, DMF, 0 °C (77%); d) di-siamyl borane, THF, -10 °C, then NaOH, H_2O_2 (55%).

Scheme 7: Synthesis of a substrate to undergo an *endo*-ETIC reaction.

To examine the validity of the new substrate design, substrate **32** was subjected to the standard photoinduced ETIC conditions. The photochemical method was explored first due to the greater efficiency noted for the other substrates. A mixture of substrate (**32**), $NMQPF_6$ (sensitizer), NaOAc (insoluble base), $Na_2S_2O_3$ (peroxide reducing agent), air (terminal oxidant) and toluene (aromatic co-sensitizer) in 1,2-dichloroethane was irradiated using a medium pressure mercury lamp for 4 hours (**Figure 23**). While the consumption of substrate **32** was quite slow, the desired cyclic acetal (**33**) was isolated in 77% yield. The successful cyclization of compound **32** re-affirms the ability to use Equation 1 to design new ETIC substrates.

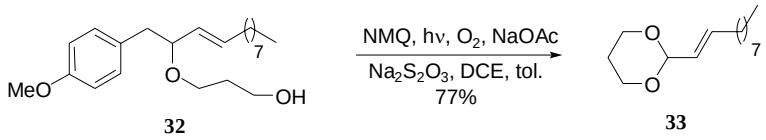


Figure 23: Photoinduced cyclicization of an *endo*-ETIC substrate.

Substrate **32** was then subjected to the Ce(IV) mediated chemical cyclization conditions to examine the reactivity. A solution of CAN in acetonitrile was added dropwise to the

suspension of the substrate (**32**) and $NaHCO_3$ in 1,2-dichloroethane. Consumption of the starting material was evident within five minutes of adding the oxidant. Although analysis of the crude reaction mixture via ^1H NMR spectroscopy did not show the desired cyclic acetal, the only discernible product was enal **34** (**Figure 24**). While subjecting compound **32** to chemical oxidation conditions affected starting material consumption, the in ability to isolate the desired product demonstrated the incapability of the CAN conditions with substrate **32**.

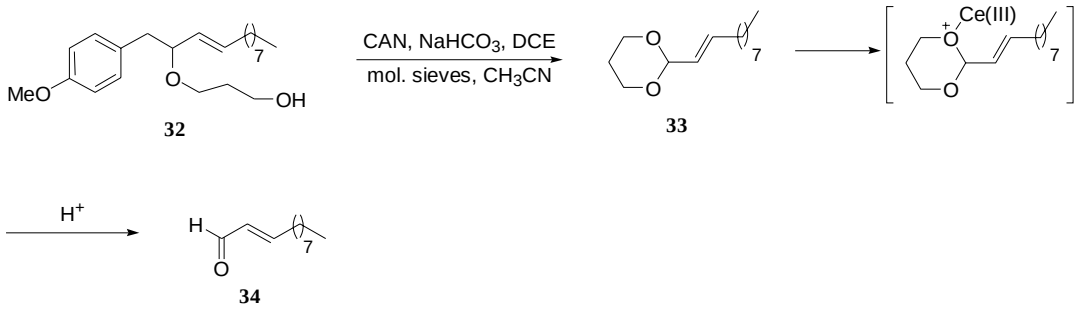


Figure 24: Propsed mechanism of Ce(III) mediated hydrolysis of the cyclic acetal.

Addition of water to the oxocarbenium ion resulting from mesolytic cleavage of the radical cation was initially thought to be causing the formation of enal **34.** To examine this hypothesis, the reaction was performed taking great care to exclude the presence of water. Therefore substrate **32** was re-subjected to the chemical ETIC reaction conditions with the addition of molecular sieves to sequester any water present. However, enal **34** was still the only product obtained from the reaction. This suggests the slight Lewis acidic nature of Ce (III) may be sufficient to promote the hydrolysis of cyclic acetal **33**.

VI. Carbon-Carbon Bond Formation using the ETIC Reation

The design of substrates to undergo oxidative carbon-carbon bond formation would further expand the synthetic utility of the ETIC reaction. Initial attempts to form carbocycles via the ETIC reaction led to decomposition of the substrate. The decomposition was attributed to the preferential oxidation of the nucleophile over the arene. This result indicates the need to design substrates which possess greater chemoselectivity. The chemoselectivity of electron transfer processes is dependent upon the oxidation potential of the electrophore. To ensure selective activation of the benzylic bond, the oxidation potential of the arene must be lower than that of the electron rich olefin. Therefore, substrates with enhanced chemoselectivity and reactivity will be designed with the incorporation of electron rich olefins as carbon centered nucleophiles (**Figure 25**). While oxidation of the electron rich arenes is expected to occur in preference to oxidation of the electron rich olefin, this is merely a first approximation. The ability of the radical cation to undergo intramolecular electron transfer from the olefin to the arene suggests the reactivity may be under Curtin-Hammett contol.

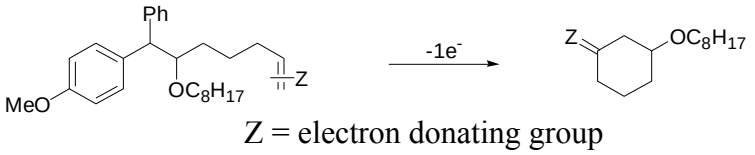
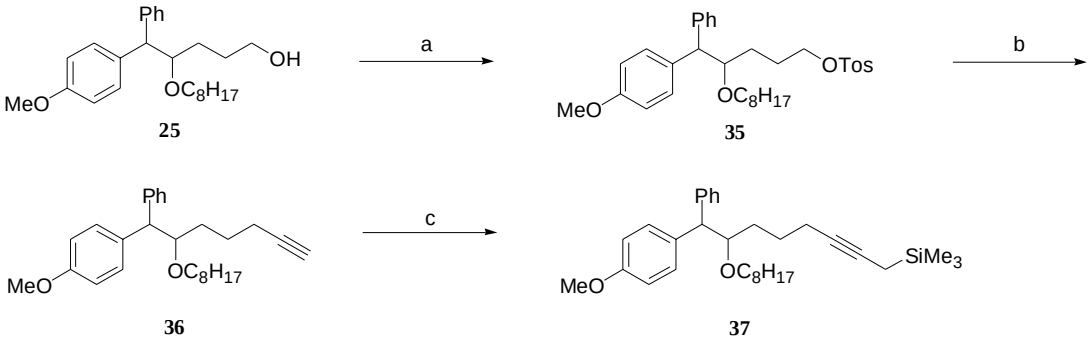


Figure 25: Designing ETIC substrates to undergo carbon-carbon bond formation.

Compound **25** was chosen as the precursor from which to synthesize the first carbon-carbon bond forming ETIC substrate (**Scheme 8**), because of its exceptional reactivity under the standard photochemical reaction conditions. The sequence began with the conversion of alcohol

25 to the corresponding tosylate (**35**). This was followed by displacement of the tosylate to give the desired alkyne (**36**) in 62% yield over two steps. Propargyl silane **37** was then obtained through the alkylation of alkyne **36** with *n*-butyllithium and iodomethyltrimethylsilane (82%).[31]



Reagents and Conditions: a) TsCl, Et_3N, CH_2Cl_2, 0 °C – RT; b) lithium acetylide-ethylene diamine complex, DMSO, 0 °C – RT (62% 2 steps); c) *n*-BuLi, -40 °C – 0 °C, then iodomethyl trimethylsilane, 0 °C - 55 °C (82%).

Scheme 8: Synthesis of a carbon-carbon bond forming ETIC substrate.

Chemical mediated oxidation conditions were chosen to test the ability to form carbon-carbon via an ETIC reaction. Because CAN exhibits milder oxidative conditions with respect to the photochemical process. Subjecting a mixture of propargyl silane **37** and $NaHCO_3$ (insoluble base) in acetonitrile with two equivalents of CAN (oxidant) led to the formation of *exo*cyclic allene **38** (**Figure 26**). The isolation of allene **38** in only 47% yield was believed to partially due to the compound's volatility, and no efforts were made to optimize this reaction. While the isolated yield of the reaction was low, the successful cyclization of substrate **37** demonstrated the ability to form carbon-carbon bonds.

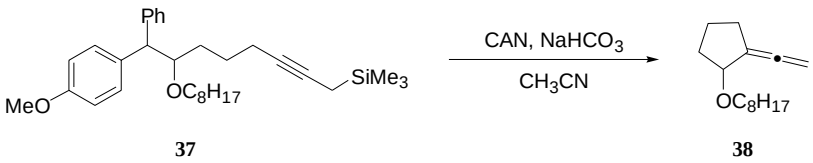
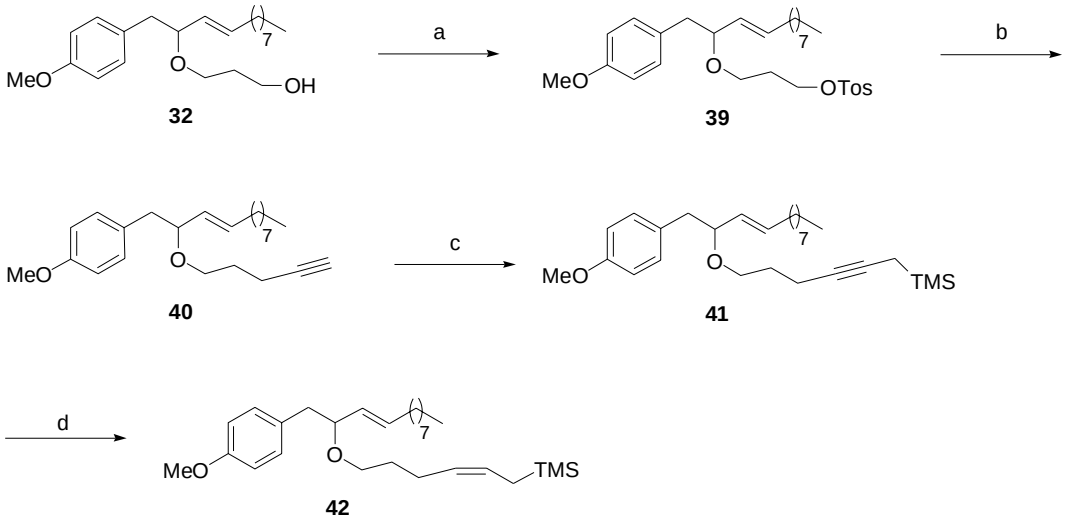


Figure 26: ETIC reaction of a propargyl silane to form a carbon-carbon bond.

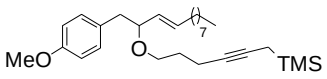
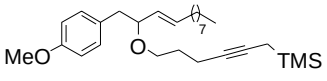
To explore the scope of carbon-carbon bonding forming ETIC reactions, a few substrates were designed to undergo an *endo*-cyclization (**Scheme 9**). Their synthesis began with the conversion of alcohol **32** to the tosylate **39**. The tosylate (**39**) was then displaced with lithium acetylide to provide alkyne **40** in 61% over two steps. Propargyl silane (**41**) was prepared via the alkylation of alkyne **40** with *n*-butyl lithium and iodomethyl trimethylsilane (87%).[31] The propargyl silane was further manipulated to give allylsilane **42** using Lindlar's catalyst under a hydrogen atmosphere (93%).



Reagents and Conditions: a) TsCl, Et_3N, CH_2Cl_2, 0 °C – RT; b) lithium acetylide-ethylene diamine complex, DMSO, 0 °C – RT (61%); c) *n*-BuLi, -40 °C – 0 °C, then iodomethyl trimethylsilane, 0 °C - 55 °C (82%); d) Lindlar's cat., H_2, MeOH (93%).

Scheme 9: Synthesis of a carbon-carbon bond forming substrate via an *endo*-cyclization.

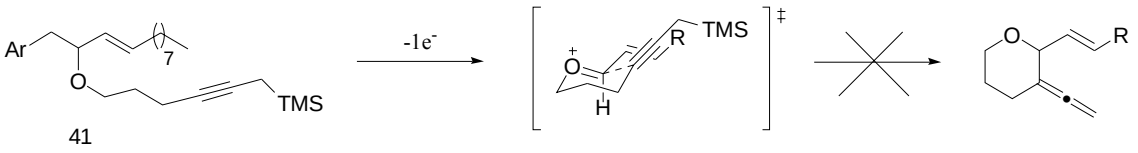
To examine the reactivity of propargyl silane **41**, it was subjected to chemical mediated ETIC conditions. Addition of a solution of CAN in acetonitrile to a mixture of the substrate (**41**), $NaHCO_3$ (insoluble base), 4Å molecular sieves (water scavenger) in 1,2-dichloroethane (solvent) provided no reaction at room temperature. The reaction was then run at 40 °C and 50 °C in an attempt to improve the reactivity, however, the substrate (**41**) failed to provide the desired cyclization product. Substrate **41** was then subjected to the more forcing photochemical reaction conditions. Once again no reaction was observed and the starting material was recovered (**Table 5**).

Entry	Substrate	Product	T (° C)	Yield (%)
1[a]	 **41**	--	RT, 40 & 50	**N.R.**
2[b]	 **41**	--	RT	**N.R.**

a) Reaction conditions: CAN (2 eq.), $NaHCO_3$, mol. sieves, DCE, CH_3CN
b) Reaction conditions: $NMQPF_6$, hν, O_2, NaOAC, $Na_2S_2O_3$, DCE, PhMe

Table 5: Attempts to form carbon-carbon bonds via *endo*-cyclizations.

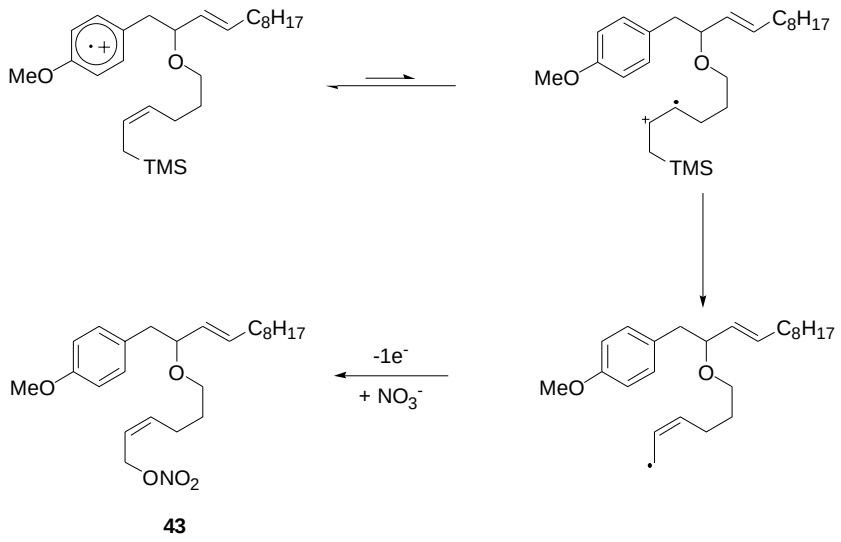
The ability to successfully cyclize ETIC substrates containing hydroxyl nucleophiles via an *endo*-cyclic pathway demonstrates the reactivity of such substrates. Therefore, the failure of substrate **41** to cyclize suggests the reactivity of the nucleophile may be insufficient to affect cyclization. While propargyl silanes have been noted to deomonstrate poor nucleophilicity,[32] another possible explanation for he lack of reactivity could be the significant steric crowding present in the transition state (**Figure 27**).



Ar = *p*-methoxy phenyl
R = C_8H_{17}

Figure 27: Sterically congested transition state of 6 *endo*-cyclization.

Attempts to cyclize allylsilane **42** under our chemical mediated oxidation conditions led to the unexpected formation of allyl nitrate **43**. The rate of allyl nitrate (**43**) formation was essentially instantaneous at room temperature. While allyl nitrate **43** was not easily purified and isolated, analysis of the crude ^{1}H NMR spectrum showed diagnostic peaks of an electron deficient allyl group. Similar allylsilanes have been shown to resist oxidation when subjected to CTAN for extended reaction times.[33] However, an α-tributylstannyl ether served as the electrophore in this case. This suggests the arene may be responsible for the difference in reactivity noted for substrate **42**. The mechanism for this process is postulated to begin with oxidation of the arene in preference to the allylsilane (**Figure 28**).[34] This initial oxidation is then followed by intramolecular electron transfer from the arene to the allylsilane. The rate of this intramolecular electron transfer occurs faster than the desired benzylic bond cleavage, and results in the formation of an allylsilane centered radical cation. The generation of an allyl radical procedes rapidly through the nucleophile (acetonitrile) assisted cleavage of the silane.[35] The resulting allyl radical may be further oxidized to the allyl cation, which is trapped with a nitrate anion to form **43**. Moeller has noted similar antenna effects in the electrochemical oxidations of tertiary amides that contain electron rich arenes.[36]

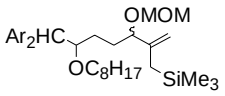
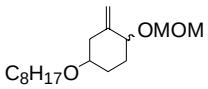
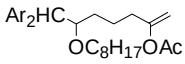
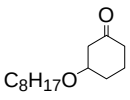
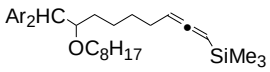
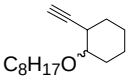


43

Figure 28: Mechanism to explain the antenna effect of allylsilane oxidation.

VII. Exploring the Range of Nucleophiles Tolerated by ETIC Conditions

The successful cyclization of propargy silane **37** demonstrated the ability to form carbon-carbon bonds via ETIC reactions. However, the low isolated yield and poor efficiency of the reaction prompted further examination of this process. Due to the excellent reactivity demonstrated by substrate **25** with hydroxyl nucleophiles, the lack of reactivity must be dependent upon the nature of the nucleophile. To test this hypothesis, Lijun Wang prepared several substrates with various electron rich olefins as nucleophiles.[37] The general structure of these substrates was modeled from compound **25**. This provided a control in the experiment, and allowed for the effect of the nucleophile to be explored (**Table 6**).

Entry[a]	Substrate[b]	Product	Yield (%)[c]
1[d]			71
2			94
3[e]			91

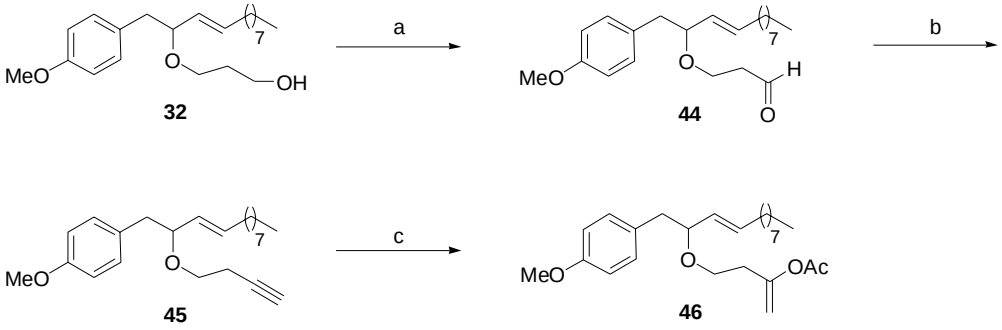
[a] **Reaction conditions:** 2.2 equiv CAN in CH_3CN was added to a suspension of the substrate, $NaHCO_3$, and 4 Å mol. sieves in DCE at room temperature (Entry 1) or 40 °C (Entries 2 and 3); [b] Ar_2CH = *p*-MeOPhC(H)Ph; [c] isolated yields after flash column chromatography; [d] products isolated as a 1.7:1 ratio of diastereomers; [e] reaction provided a 1.2:1 (trans:cis) ratio of diastereomers.

Table 6: Exploring other carbon nucleophiles in ETIC reactions.

The smooth conversion of allylsilane (**Table 6**, entry 1) was quite remarkable given the difficulties in cyclizing previous allylsilanes. However, the difference in reactivity may be explained by the inductively withdrawing protected hydroxyl group present. While entries 2 and 3 required gentle heating to effect reactivity, the process was extremely efficient. The successful cyclization of these substrates once again demonstrates the ability to rationally design substrates through rational structural changes. Incorporation of the above nucleophiles in the design of new ETIC substrates will allow for greater diversity in product formation.

To test the general efficiency of enol acetates to act undergo ETIC reactions, a substrate was designed to undergo an *endo*-cyclic carbon-carbon bond formation. The substrate was designed to reflect the general structure of compound **32** (**Scheme 10**). Therefore, the synthesis began with the oxidation of alcohol **32** to provide aldehyde **44**. The aldehyde (**44**) was then converted to the terminal alkyne (**45**) via Ohira reaction[38] in 18% over two steps. Installation of the enol acetate (**46**) was then affected through the ruthenium catalyzed Markovnikov addition of

acetic acid to alkyne **45**.[39] This method provides a mild and efficient process for the conversion of terminal alkynes to the Markovnikov enol acetate with excellent levels of regiochemical control. The postulated mechanism[40] for this reaction suggests coordination of the ruthenium complex with the alkyne. The complex then undergoes a regioselective addition of the carboxylic acid. The regioselectivity of the reaction is dependent upon the ligands surrounding the ruthenium center (bulky ligands lead to Markovnikov addition). Finally the catalyst is turned over through deprotonation of the vinyl ruthenium species.

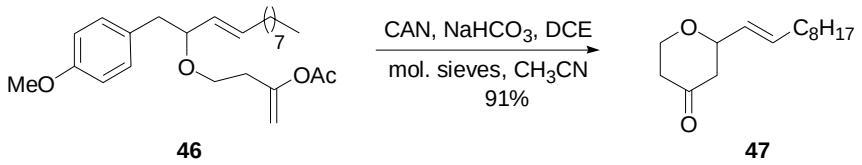


Reagents and Conditions: a) Dess-Martin periodane, $NaHCO_3$, CH_2Cl_2; b) dimethyl (1 – diazo – 2 – oxopropyl) phosphonate, K_2CO_3, MeOH, 0 °C – RT (18% 2 steps); c) Ru[(*p*-cymene)PPh_3Cl], acetic acid, toluene, 80 °C (39%)

Scheme 10: Synthesis and *endo*-cyclization of an enol acetate.

The efficiency with which enol acetates participate in *endo*-cyclic ETIC reactions was determined using the standard chemical mediated oxidation conditions. A mixture of substrate **46**, $NaHCO_3$ (insoluble base) and 4Å molecular sieves (water scavenger) in 1,2-dichloroethane was treated with a solution of CAN in acetonitrile dropwise at 40 °C. After 45 minutes,

tetrahydropyranone **47** was obtained in 91% yield (**Figure 29**). The ability to form the desired tetrahydropyranone in high isolated yield demonstrated the general applicability of enol acetates as nucleophiles in ETIC reactions.



46 **47**

Figure 29: *Endo*-cyclization of an enol acetate to form a 2-alkyltetrahydropyranone.

1.3. Conclusion

The ability to predict the thermodynamic tendacy of a carbon-carbon bond to cleave in a radical cation has been demonstrated using a simple arithematical equation. This requires only knowledge regarding the bond dissociation energy of the desired bond in the ground state, the oxidation potential of the electrophore and the oxidation potential of the radical leading to the cationic fragment. The generality of this relationship is somewhat limited and is most applicable when comparing compounds of a particular series. In the comparison of a series, the relative oxidation potentials and bond dissociation energies are sufficient in predicting trends in radical cation cleavage. This study has demonstrated that lowering the oxidation potential of the substrate leads to stabilization of the radical cation and disfavors the desired fragmentation. However, the propensity of the radical cation to undergo cleavage may be recovered by lowering the bond dissociation energy of the benzylic carbon-carbon bond. This was accomplished through the placement of substituents (radical stabilizing groups) in the benzylic or homobenzylic position.

These structural alterations have allowed for exploration of the ETIC reaction's scope and limitations. The design of substrates with lower oxidation potentials led to the development of a mild chemically initiated variant of the ETIC reaction conditions using ceric ammonium nitrate (CAN). A new method of activating the benzylic position toward nucleophilic attack was also discovered through the use of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ). In addition to the experimental advances, the ability to gain access to more diverse products has been realized. This was accomplished through designing substrates to undergo *endo*-cyclic transformations, as well as, the introduction of electron rich olefins as carbon centered nucleophiles.

1.4. Experimental

General Experimental:

All reactions were performed in oven or flame dried glassware under a nitrogen atmosphere with magnetic stirring unless otherwise noted.

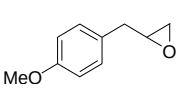
Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometers at 300 MHz and 75 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak or the internal standard tetramethylsilane were used as reference values. For ^{1}H NMR: $CDCl_3$ = 7.27 ppm, TMS = 0.00 ppm. For ^{13}C NMR: $CDCl_3$ = 77.23, TMS = 0.00. For proton data: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; ddt = doublet of doublet of triplets; br = broad; m = multiplet; app t = apparent triplet; app q = apparent quartet; app p = apparent pentet.

High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Gygnus 100 spectrometer.

Analytical thin layer chromatography (TLC) was performed on E. Merck pre-coated (25 nm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash column chromatography was preformed using ICN SiliTech 32-63 60Å silica gel. Reagent grade ethyl acetate and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. Reagent grade methylene chloride (CH_2Cl_2), dicholoroethane ($C_2H_4Cl_2$), acetonitrile (CH_3CN), benzene and toluene were distilled from CaH_2. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketyl prior to use. Anhydrous

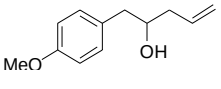
N,N-dimthylformamide (DMF), methanol (MeOH), dimethyl sulfoxide (DMSO) were purchased from Aldrich and used as is.

2-(4-Methoxybenzyl)oxirane (1)



To 4-allylanisole (5.00 g, 33.73 mmol) in CH_2Cl_2 (90 mL) at 0 °C was added NaOAc (27.68 g, 337.30 mmol). The mixture was stirred for 5 minutes and *m*-CPBA (14.50 g, 50.60 mmol) was added, and the reaction was slowly warmed to room temperature. The reaction mixture was stirred for 4.5 hours and additional *m*-CPBA (9.67 g, 33.73 mmol) was added. The reaction was then stirred overnight and quenched by adding aqueous Na_2SO_3. The reaction mixture was extracted with ethyl acetate (2x). The organic layers were then combined and washed with aqueous NaOH (10%), water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography ((15% EtOAc in hexanes) to provide the desired product (1.42 g, 26%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.18 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 3.15-3.10 (m, 1H), 2.80 (dd, *J* = 14.5, 5.5 Hz, 1H), 2.77 (dd, *J* = 14.6, 5.4 Hz, 1H), 2.77-2.74 (m, 1H), 2.53 (dd, *J* = 4.9, 2.6 Hz, 1H).[41]

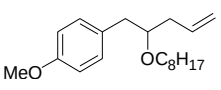
1-(4-Methoxyphenyl)but-3-en-2-ol (2)



To a suspension of CuI (140.1 mg, 0.736 mmol) in THF (10 mL) at -78 °C was added vinyl magnesium bromide (1.0 M, 25.77 mL, 25.77 mmol). The mixture was stirred for 20 minutes and 2-(4-methoxybenzyl)oxirane (1.21 g, 7.36 mmol) was added. The reaction was stirred at -78 °C for 2 hours and then slowly warmed to room temperature. The reaction was then quenched by adding aqueous NH_4Cl. Air was then gently bubbled through the mixture for 2 hours. The mixture was extracted with ethyl acetate (2x). The

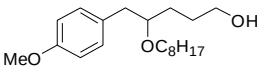
organic layers were then combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The resulting residue was then purified by flash column chromatography (25% EtOAc in hexanes) to provide the desired product (1.36 g, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6, 2H), 5.92-5.80 (m, 1H), 5.20-16 (m, 1H), 5.14-5.13 (m, 1H), 3.86-3.82 (m, 1H), 3.80 (s, 3H), 2.77 (dd, *J* = 13.7, 4.9 Hz, 1H), 2.67 (dd, *J* = 13.7, 7.8 Hz, 1H), 2.38-2.31 (m, 1H), 2.27-2.21 (m, 1H), 1.70 (br, 1H);^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 135.0, 130.7, 118.3, 114.3, 72.0, 55.6, 42.7, 41.4; IR (neat) 3421, 2933, 2835, 1612, 1512, 1246, 807 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{16}O_2$ 192.1150, found 192.1151.

1-Methoxy-4-(2-octyloxybut-3-enyl)benzene (3)



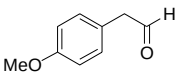
To 1-(4-methoxyphenyl)but-3-en-2-ol (1.30 g, 6.76 mmol) in DMF (20 mL) at 0 °C was added sodium hydride (1.018 g, 25.46 mmol). The mixture was stirred for 15 minutes and octyl iodide (7.64 g, 31.83 mmol) was added. The reaction was slowly warmed to room temperature and stirred overnight, then was quenched with the addition of water at 0 °C. The mixture was extracted with ethyl acetate (2x), and the organic layers were combined and washed with water and brine. The organic layer was then dried Na_2SO_4, filtered and concentrated. The resulting residue was purified by flash column chromatography (5% EtOAc in hexanes) to provide the desired product (1.32 g, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.90-5.84 (m, 1H), 5.10-5.04 (m, 2H), 3.79 (s, 3H), 3.50-3.30 (m, 3H), 2.76 (dd, *J* = 13.8, 6.5 Hz, 1H), 2.69 (dd, *J* = 13.8, 5.9 Hz, 1H), 2.25-2.23 (m, 2H), 1.50 (p, *J* = 6.5 Hz, 2H), 1.24 (bs, 10H), 0.88 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 135.5, 131.6, 130.7, 117.1, 113.9, 80.9, 69.9, 63.3, 55.5, 39.9, 38.5, 32.1, 30.8, 29.7, 29.6, 26.5, 22.9, 14.4; IR (neat) 2927, 2855, 1512, 1247, 1039 cm^{-1}.

4-(4-Methoxyphenyl)-3-octyloxybutan-1-ol (4)



To 1-methoxy-4-(2-octyloxbut-3-enyl)benzene (1.30 g, 4.03 mmol) in THF (5 mL) at 0 °C was added BH_3·THF (1M, 12.09 mL, 12.09 mmol). The reaction was stirred for 10 minutes and quenched by adding water (1 mL) dropwise followed by 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide (1 mL) and saturated Na_2SO_3 (2 mL). The mixture was stirred for an addition 45 minutes. The mixture was extracted with ethyl acetate (2x), and the organic layers were combined and washed with water and brine. The organic layer was dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography (20% EtOAc in hexanes) to provide the desired product (447.9 mg, 34%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.5 Hz, 2H), 6.8 (d, *J* = 8.5 Hz, 2H), 3.78 (s, 3H), 3.61 (t, *J* = 5.8 Hz, 2H), 3.49-3.37 (m, 3H), 2.85 (dd, *J* = 13.7, 5.8 Hz, 1H), 2.64 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.10 (s, 1H), 1.70-1.60 (m, 2H), 1.59-1.43 (m, 4H), 1.25 (bs, 10H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.29, 131.28, 130.63, 113.99, 81.30, 69.95, 55.53, 39.71, 32.14, 30.84, 30.35, 29.73, 29.57, 29.13, 26.48, 22.96, 14.41; IR (neat) 3445, 2928, 2855, 1612, 1512, 1247, 819 cm^{-1}.

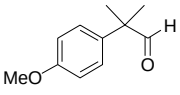
(4-Methoxyphenyl)acetaldehyde (5)



To 2-(4-methoxyphenyl)ethanol (2.00 g, 13.10 mmol) in CH_2Cl_2 (25 mL) at 0 °C was added Dess-Martin Periodane (8.37 g, 19.70 mmol). The mixture was then slowly warmed to room temperature and stirred for 2 hours. The reaction was quenched by the addition of aqueous $NaHCO_3$ (10 mL) followed by aqueous $Na_2S_2O_3$ (15 mL) and water. The mixture was stirred 2 hours and filtered to remove the insoluble material. The filtrate was extracted with CH_2Cl_2 (2x), and the organic layers were combined and washed with water and

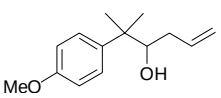
brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The product was obtained without any further purification (1.97 g, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.73 (t, *J* = 2.4 Hz, 1H), 7.12 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.6 Hz, 2H), 3.79 (s, 3H), 3.64 (s, 2H).[42]

2-(4-Methoxyphenyl)-2-methylpropionaldehyde (6)



To (4-methoxyphenyl)ethanol (581.6 mg, 3.87 mmol) in THF (5 mL) at -78 °C was added potassium *tert*-butoxide (956.2 mg, 8.52 mmol) and methyl iodide (1.2093 g, 8.52 mmol). The reaction was stirred at -78 °C for 4 hours and then slowly warmed to room temperature. The reaction mixture was then quenched by the addition of aqueous NH_4Cl. The mixture was extracted with ethyl acetate (2x), and the organic layers were combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography (10% EtOAc in hexanes) to provide the desired product (145.5 mg, 21%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (s, 1H), 7.20 (d, *J* = 8.7 Hz, 2H), 6.92 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 1.46 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.0, 168.9, 158.6, 132.9, 127.7, 114.1, 55.1, 49.6, 22.4; IR (neat) 2971, 2935, 2836, 1723, 1609, 1513, 1465, 1252, 1185, 1034, 909, 829, 796 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{14}O_2$ 178.0994, found 178.0994.

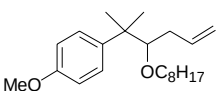
2-(4-Methoxyphenyl)-2-methylhex-5-en-3-ol (7)



To 2-(4-methoxyphenyl)-2-methylpropionaldehyde (145.5 mg, 0.816 mmol) in THF (5 mL) at -78 °C was added allyl magnesium bromide (1.0 M, 4.08 mL, 4.08 mmol). The mixture was then slowly warmed to room temperature over 30 minutes, and stirred at room temperature for an additional 2 hours. The reaction was then quenched by the addition of aqueous NH_4Cl at 0 °C. The mixture was extracted with ethyl acetate (2x), and

the organic layers were combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography (20% EtOAc in hexanes) to provide the desired product (149.6 mg, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.15 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 5.88-5.74 (m, 1H), 5.11-5.08 (m, 1H), 5.05-5.03 (m, 1H), 3.81 (s, 3H), 3.63 (dd, *J* = 10.4, 2.1 Hz, 1H), 2.24-2.17 (m, 2H), 1.35 (s, 3H), 1.33 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 136.7, 127.9, 117.5, 113.9, 78.7, 55.5, 41.9, 36.9, 24.7, 24.3; IR (neat) 3481, 2970, 1610, 1513, 1251, 1185, 1035, 829 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{20}O_2$ 220.1463, found 220.1465.

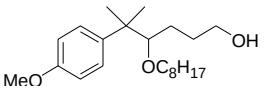
1-(1,1-Dimethyl-2-octyloxypent-4-enyl)-4-methoxybenzene (8)



To 2-(4-methoxyphenyl)-2-methylhex-5-en-3-ol (171.6 mg, 0.778 mmol) in DMF (5 mL) at 0 °C was added NaH (124.6 mg, 3.11 mmol). The mixture was stirred for 15 minutes and octyl iodide (935.2 mg, 3.89 mmol) was added. The mixture was then slowly warmed to room temperature and stirred for 18 hours. The reaction was quenched by the addition of water. The mixture was then extracted with hexanes (2x), and the organic layers were then combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The residue was then purified by flash column chromatography (5% EtOAc in hexanes) to provide the desired product (155.5 mg, 60%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.8 Hz, 2H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.84-5.72 (m, 1H), 4.99-4.98 (m, 1H), 4.93-4.90 (m, 1H), 3.81 (s, 3H), 3.50 (dt, *J* = 8.6, 6.3 Hz, 1H), 3.27-3.20 (m, 2H), 2.01 (app t, 2H), 1.51-1.48 (m, 2H), 1.34 (s, 3H), 1.32 (s, 3H), 1.27-1.25 (m, 10H), 0.91 (t, *J* = 5.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 140.0, 137.3, 127.6, 115.6, 113.2, 88.3, 73.2, 55.2, 42.5, 36.4, 31.9, 30.3, 29.5, 29.3, 26.2, 23.6, 22.6, 14.0; IR (neat) 2924, 2853, 1613,

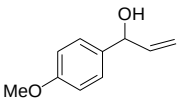
1512, 1464, 1246, 1177, 1040, 920, 806 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{31}O_2$ (M – 41) 291.2324, found 291.2329.

5-(4-Methoxyphenyl)-5-methyl-4-octyloxyhexan-1-ol (9)



To 1-(1,1-dimethyl-2-octyloxypent-4-enyl)-4-methoxybenzene (155.5 mg, 0.467 mmol) in THF (3 mL) at 0 °C was added BH_3-THF (1.0 M, 1.402 mL, 1.402 mmol). The mixture was stirred for 20 minutes and quenched by the drop wise addition of water followed by 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide (1 mL) and saturated Na_2SO_3 (2 mL). The mixture was stirred for an addition 45 minutes. The mixture was then extracted with EtOAc (2x), and the organic layers were then combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The residue was then purified by flash column chromatography (20% EtOAc in hexanes) to provide the desired product (101.0 mg, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 3.80 (s, 3H), 3.55 (t, *J* = 6.4 Hz, 2H), 3.45 (dt, *J* = 8.6, 6.6 Hz, 1H), 3.27-3.16 (m, 2H), 1.72-1.66 (m, 1H), 1.52-1.46 (m, 6H), 1.34 (s, 3H), 1.30 (s, 3H), 1.28-1.22 (m, 10H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 140.2, 127.5, 113.3, 96.9, 73.8, 66.6, 63.2, 55.2, 42.5, 31.8, 30.5, 30.4, 29.7, 29.5, 29.3, 27.9, 26.3, 26.1, 24.6, 23.9, 22.7, 14.1; IR (neat) 3374, 2928, 2855, 1513, 1465, 1249, 1184, 1094, 1038, 828 cm^{-1}.

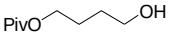
1-(4-Methoxyphenyl)prop-2-en-1-ol (10)



To *p*-anisaldehyde (2.00 g, 14.69 mmol) in THF (20 mL) at – 78 °C was added vinyl magnesium bromide (1.0 M, 29.37 mmol, 29.37 mL). The reaction was then slowly warmed to room temperature over 8 hours and quenched by the addition of NH_4Cl

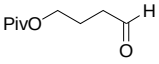
(aq). The mixture was extracted with EtOAc (2x), and the organic layers were then combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (20% EtOAc in hexanes) to provide the desired product (1.99 g, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.7 Hz, 2H), 6.08-6.00 (m, 1H), 5.34 (d, *J* = 16.8 Hz, 1H), 5.21-5.19 (m, 2H), 3.81 (s, 3H), 1.93 (d, *J* = 3.8 Hz, 1H).[20]

2,2-Dimethylpropionic acid-4-hydroxybutyl ester



To 1,4 butane diol (10.00 g, 111.0 mmol) in CH_2Cl_2 (100 mL) at 0 °C was added DMAP (10 mg) and pyridine (17.56 g, 222.0 mmol). The mixture was stirred at 0 °C for 10 minutes and 2,2-dimethyl-propionic acid chloride (5.35 g, 44.38 mmol) was added. The reaction was then slowly warmed to room temperature over 12 hours and quenched by the addition of water. The mixture was then extracted with CH_2Cl_2 (2x), and the organic layers were then combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (20% EtOAc in hexanes) to provide the desired product (6.07 g, 79%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.16 (t, *J* = 6.6 Hz, 2H), 3.68 (t, *J* = 6.2 Hz, 2H), 1.73-1.64 (m, 4H), 1.21 (s, 9H).[40]

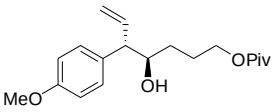
2,2-Dimethylpropionic acid-4-oxobutyl ester (11)



To 2,2-dimethylpropionic acid-4-hydroxy butyl ester (1.50 g, 8.61 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added trichloroisocyanuric acid (2.19 g, 9.47 mmol). The slurry was stirred at 0 °C for 10 minutes and TEMPO (13.4 mg, 0.0861 mmol) was added. The mixture was then slowly warmed to room temperature over 20 minutes. The reaction mixture was then filtered over celite, and the filtrate was washed with $NaHCO_3$ (aq), 1N HCl,

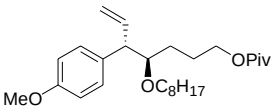
water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The desired product was obtained without the need for further purification (1.3136 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.81 (s, 1H), 4.10 (t, *J* = 6.0 Hz, 2H), 2.52 (t, *J* = 5.9 Hz, 2H), 2.01 (app p, 2H), 1.20 (s, 9H).[43]

2,2-Dimethylpropionic acid-4-hydroxy-5-(4-methoxyphenyl)hept-6-enyl ester (12)



To 2,2-dimethylpropionic acid-4-oxobutyl ester (1.31 g, 7.63 mmol), 1-(4-methoxyphenyl)prop-2-en-1-ol (1.88 g, 11.44 mmol) and $SnCl_2$ (4.33 g, 22.88 mmol) in DMI (30 mL) was added $PdCl_2(CNPh)_2$ (58.5 mg, 0.152 mmol). The reaction was then stirred for 24 hours and was diluted with 240 mL of ether:CH_2Cl_2 (2:1). The mixture was then washed with 10% HCl, $NaHCO_3$ (aq), water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The residue was then purified by flash column chromatography (10% EtOAc in hexanes) to provide the desired product in a greater than 10:1 anti:syn ratio (875.0 mg, 36%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.7 Hz, 2H), 6.87, (d, *J* = 8.7 Hz, 2H), 6.10 (ddd, *J* = 19.6, 10.5, 9.1 Hz, 1H), 5.18 (d, *J* = 19.3 Hz, 1H), 5.14 (d, *J* = 10.5 Hz, 2H), 4.12 (t, *J* = 6.5 Hz, 2H), 3.84-3.74 (m, 2H), 3.79 (s, 3H), 1.89 (br, 1H), 1.88-1.78 (m, 1H), 1.77-1.61 (m, 1H), 1.45-1.28 (m, 2H), 1.12 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 178.75, 158.7, 138.8, 133.6, 129.2, 117.9, 114.6, 73.9, 64.5, 56.7, 55.5, 38.9, 30.8, 27.4, 25.3; HRMS (EI) calcd for $C_{19}H_{26}O_3$ (M – 18) 302.1882, found 302.1887.

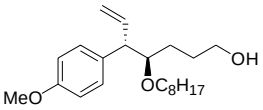
2,2-Dimethylpropionic acid-5-(4-methoxyphenyl)-4-octyloxyhept-6-enyl ester



To 2,2-dimethylpropionic acid-4-hydroxy-5-(4-methoxyphenyl)hept-6-enyl ester (800.0 mg, 2.49 mmol) in DMF (10 mL) at 0 °C was added NaH (399.5 mg, 9.98 mmol). The mixture was stirred at 0 °C for 10 minutes and octyl iodide

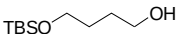
(2.99 g, 12.48 mmol) was added. The reaction was then slowly warmed to room temperature over 12 hours and quenched by the addition of water. The mixture was then extracted with hexanes (2x) and the organic layers were combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The desired product was obtained as an impure mixture which could not be separated.

5-(4-Methoxyphenyl)-4-octyloxyhept-6-en-1-ol (13)



To 2,2-dimethyl-propionic acid 5-(4-methoxyphenyl)-4-octyloxyhept-6-enyl ester (400.0 g, 0.924 mmol) in THF (5 mL) at 0 °C was added LAH (42.1 mg, 1.10 mmol). The reaction was then slowly warmed to room temperature over 4 hours and quenched by the addition of 10% NaOH. The mixture was then extracted with EtOAc (3x) and the organic layers were combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (30% EtOAc in hexanes) to provide the desired product with a ratio of greater than 10:1 anti:syn isomers (11.1 mg, 3%): ^{1}H NMR (300 MHz, CDCl3) δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 6.15 (ddd, *J* = 17.1, 9.9, 2.7 Hz, 1H), 5.10 (d, *J* = 10.0 Hz, 1H), 5.02 (d, *J* = 17.4 Hz, 1H), 3.79 (s, 3H), 3.58 (t, *J* = 5.0 Hz, 2H), 3.51-3.41 (m, 4H), 1.93 (br, 1H), 1.67-1.47 (m, 4H), 1.35-1.28 (m, 12H), 0.89 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 139.1, 134.0, 129.2, 116.0, 113.8, 83.0, 70.63, 63.0, 55.2, 53.0, 31.8, 30.0, 29.4, 29.3, 28.6, 26.2, 22.6, 14.0; IR (neat) 3386, 2928, 2856, 1610, 1511, 1465, 1246, 1178, 1098, 1038, 914, 829 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{34}O_2$ (M – 18) 330.2558, found 330.2565.

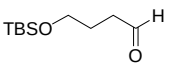
4-(*tert*-Butyldimethylsilanyloxy)butan-1-ol (14)[22]



To 1.4-butane diol (5.00 g, 55.5 mmol) in THF (50 mL) was added NaH (2.22 g,

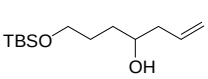
55.5 mmol). The mixture was then stirred for 45 minutes and TBSCl (8.36 g, 55.5 mmol) was added. The reaction was then allowed to stir for 8 hours and was quenched by the addition of water. The mixture was then extracted with EtOAc (2x) and the organic layers were combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The desired product was obtained without the need for further purification (9.83 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.60-3.65 (m, 4H), 1.67-1.63 (m, 4H), 0.90 (s, 9H), 0.04 (s, 6H).

4-(*tert*-Butyldimethylsilanyloxy)butyraldehyde (15)



To 4-*tert*-butyldimethylsilanoxy)butan-1-ol (1.00 g, 4.89 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added trichloroisocyanuric acid (1.25 g, 5.25 mmol). The slurry was then stirred at 0 °C for 10 minutes and TEMPO (0.0076 g, $4.89x10^{-3}$ mmol) was added. The reaction was then slowly warmed to room temperature over 20 minutes. The mixture was then filtered through celite and the filtrate was washed with $NaHCO_3$ (aq), 1N HCl, water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The desired product was obtained without the need for further purification (941.7 mg, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.80 (d, J = 1.6 Hz, 1H), 3.66 (t, J = 6.2 Hz, 2H), 2.50 (td, J = 7.0, 1.6 Hz, 2H), 1.86 (app p, 2H), 0.89 (s, 12H), 0.05 (s, 6H).[44]

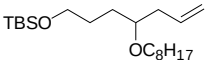
7-(*tert*-Butyldimethylsilanyloxy)hept-1-en-4-ol (16)



To 4-(*tert*-butyldimethylsilanyloxy)butyraldehyde (5.88 g, 29.1 mmol) in THF (50 mL) at – 78 °C was added allyl magnesium bromide (1.0M, 145.5 mmol, 145.5 mL) dropwise. The reaction was then slowly warmed to room temperature over 12 hours and quenched by the addition of NH_4Cl (aq). The mixture was then extracted with EtOAc (2x)

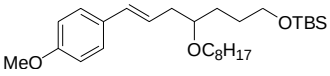
and the organic layers were combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The residue was then purified by flash column chromatography (15% EtOAc in hexanes) to provide the desired product (3.88 g, 55%): ^{1}H NMR (300 MHz, CDCl3) δ 5.86-5.81 (m, 1H), 5.15-5.09 (m, 2H), 3.68-3.62 (m, 3H), 2.25-2.23 (m, 2H), 1.67-1.63 (m, 4H), 1.28 (br, 1H), 0.90 (s, 9H), 0.06 (s, 6H).[45]

tert-Butyldimethyl(4-octyloxyhept-6-enyloxy)silane (17)



To 7-(*tert*-butyldimethylsilanyloxy)hept-1-en-4-ol (3.88 g, 15.88 mmol) in DMF (40 mL) at 0 °C was added NaH (2.54 g, 63.52 mmol). The mixture was then stirred at 0 °C for 20 minutes and octyl idodide (19.07 g, 79.44 mmol) was added. The reaction was then slowly warmed to room temperature over 12 hours and the reaction was quenched by the addition of water. The mixture was then extracted with hexanes (2x) and the organic layers were combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The residue was then purified by flash column chromatography (5% EtOAc in hexanes) to provide the desired product (3.59 g. 63%): ^{1}H NMR (300 MHz, CDCl3) δ 5.89-5.76 (m, 1H), 5.10-5.04 (m, 2H), 3.67-3.59 (m, 2H), 3.49-3.28 (m, 3H), 2.29-2.25 (m, 2H), 1.62-1.57 (m, 4H), 1.29-1.27 (m, 12H), 0.92-0.88 (m, 3H), 0.91 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5, 117.5, 79.1, 69.4, 63.5, 38.8, 33.2, 32.1, 30.5, 30.1, 29.8, 29.6, 29.0, 26.6, 22.9, 18.6, 14.3, -4.9; HRMS (EI) calcd for $C_{21}H_{43}O_2Si$ (M – 1) 355.3032, found 355.3035.

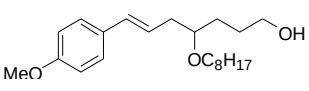
tert-Butyl[7-(4-methoxyphenyl)-4-octyloxyhept-6-enyloxy]dimethylsilane (18)



To *tert*-butyldimethyl(4-octyloxyhept-6-enyloxy)silane (1.00 g, 2.8 mmol) and 4-vinyl anisole (1.88 g, 14.0 mmol) in CH_2Cl_2 (10 mL)

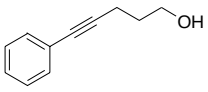
was added Grubbs II (119.1 mg, 0.14 mmol). The reaction mixture was then warmed to 40 °C for 12 hours. The mixture was then cooled to room temperature and filtered through silicia gel (20% EtOAc in hexanes). The filtrate was then concentrated and the residue was purified by flash column chromatography (5% EtOAc in hexanes) to provide the desired product as 3:1 inseperable mixture of isomers (506.6 mg, 39%): ^{1}H NMR (300 MHz, $CDCl_3$, major isomer) δ 7.27 (d, *J* = 8.4 Hz, 2H), 6.85 (d, *J* = 8.4 Hz, 2H), 6.36 (d, *J* = 15.8 Hz, 1H), 6.10 (dt, *J* = 15.8, 7.2 Hz, 1H), 3.80 (s, 3H), 3.63-3.60 (m, 2H), 3.54-3.51 (m, 1H), 3.47-3.40 (m, 2H), 2.44-2.36 (app q, 2H), 1.67-1.60 (m, 4H), 1.34-1.28 (m, 10H), 0.88-0.87 (m, 3H), 0.87 (s, 9H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159, 131.4, 131.3, 130.9, 129.9, 129.3, 127.8, 127.4, 125.2, 114.3, 81.1, 79.6, 69.5, 63,6, 59.9, 55.6, 32.6, 32.1, 30.7, 30.5, 30.3, 29.8, 29.6, 29.2, 29.1, 26.6, 26.3, 22.9, 18.6, 14.3, -4.9.

7-(4-Methoxyphenyl)-4-octyloxyhept-6-en-1-ol (19)



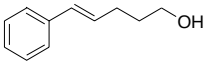
To *tert*-butyl[7-(4-methoxyphenyl)-4-octyloxyhept-6-enyloxy]dimethylsilane (506.6 mg, 1.09 mmol) in THF (5 mL) was added TBAF (372.0 mg, 1.42 mmol). The reaction was stirred at room temperature for 4 hours and quenched by the addition of water. The mixture was extracted with EtOAc (2x) the organic layers were combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography (15% EtOAc in Hexanes) to provide the desired product (63.1 mg, 17%): ^{1}H NMR (300 MHz, CDCl3) δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.82 (d, *J* = 8.7 Hz, 2H), 6.39 (d, *J* = 15.8 Hz, 1H), 6.03 (dt, *J* = 15.5, 7.6 Hz, 1H), 3.80 (s, 3H), 3.65-3.57 (m, 2H), 3.56-3.54 (m, 1H), 3.52-3.46 (m, 2H), 2.51-2.37 (m, 2H), 2.27 (app t, 1H), 1.74-1.71 (m, 4H), 1.59-1.57 (m, 4H), 1.26-1.23 (m, 12H), 0.90-0.88 (m, 3H).

5-Phenylpent-4-yn-1-ol (20)



To a suspension of $Pd(PPh_3)_4$ (549.2 mg, 0.475 mmol) in THF (50 mL) were added 4-pentyn-1-ol (2.00 g, 23.7 mmol), iodobenzene (9.69 g, 47.5 mmol) and diisopropylamine (20 mL). The mixture was stirred at room temperature for 20 minutes and CuI (45.3 mg, 0.237 mmol) was added. The reaction was allowed to stir for 12h. The solvent was then removed under reduced pressure and the resulting residue was dissolved in hexanes. The mixture was then passed through a plug of celite and concentrated. The resulting residue was purified by flash column chromatography (20% EtOAc in hexanes) to provide the desired product (3.74 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.41 (m 2H), δ 7.26 – 7.29 (m, 3H), 3.82 (t, *J* = 6.1 Hz, 2H), 2.54 (t, *J* = 6.9 Hz, 2H), 1.86 (p, *J* = 6.5 Hz, 2H), 1.59 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 131.8, 128.6, 128.5, 127.9, 124.0, 89.6, 85.9, 81.5, 62.1, 31.7, 16.3, 12.7; IR (neat) 3351, 3079, 2947, 2878, 2390, 2200, 1597, 1489, 1441, 1060, 914, 756, 691 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{12}O$ 160.0888, found 160.0890.

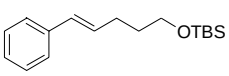
(*E*)-5-Phenylpent-4-en-1-ol



To a suspension of LAH (3.10 g, 81.86 mmol) in THF (40 mL) at 0 °C was added 5-phenylpent-4-yn-1-ol (3.74 g, 23.38 mmol). The mixture was stirred at 0 °C for 20 minutes and slowly warmed to reflux. The reaction was then stirred at reflux for 20 hours. The reaction was then quenched by adding aqueous Na, K tartrate at 0 °C. The reaction mixture was extracted with Ethyl Acetate (2x), and then the organic layers were combined and washed with water and brine. The organic layers were then dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography (20% EtOAc in hexanes) to provide the desired product (3.76 g, 99%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 – 7.36 (m, 5H), 6.45 (d, *J* = 15.8 Hz, 1H), 6.23 (dt *J* = 15.8, 6.7 Hz, 1H), 3.71 (t, *J*

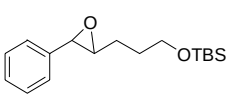
= 6.4 Hz, 2H), 2.30 (q, *J* = 6.8 Hz, 2H), 1.73 (pentet, *J* = 6.9 Hz, 2H), 1.40 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.6, 130.3, 130.0, 128.5, 126.9, 125.9, 62.4, 32.2, 29.3; IR (neat) 3342, 3024, 2935, 2875, 1494, 1447, 1057, 965, 741, 692 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{14}O$ 162.1045, found 162.1050.

tert-Butyldimethyl-(*E*)-(5-phenylpent-4-enyloxy)silane (21)



To (*E*)-5-phenyl-pent-4-en-1-ol (3.76 g, 23.19 mmol) in DMF (40 mL) at 0 °C was added imidazole (3.47g, 51.01 mmol) with stirring. The mixture was stirred for 10 minutes and TBSCl (3.84 g, 25.5 mmol) was added. The reaction was slowly warmed to room temperature overnight. The reaction mixture was quenched with water. The reaction mixture was extracted with diethyl ether (2x), and then the organic layers were combined and washed with aqueous $NaHCO_3$, water and brine. The organic layers were then dried (Na_2SO_4), filtered and concentrated. The desired product was obtained without further purification (6.06 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 – 7.57 (m, 4H), 7.17 – 7.19 (m, 1H), 6.41 (d, *J* = 15.8 Hz, 1H), 6.21 (dt, *J* = 15.8, 6.7 Hz, 1H), 3.65 (t, *J* = 6.3 Hz, 2H), 2.25 (q, *J* = 6.9 Hz, 2H), 1.64 (p, *J* = 6.4 Hz, 2H), 0.90 (s, 9H), 0.057 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.20, 130.85, 130.43, 128.79, 127.14, 126.22, 62.83, 32.79, 29.67, 26.32, 25.40, 18.69, -4.92; HRMS (EI) calcd for $C_{17}H_{28}OSi$ 276.1909, found 276.1907.

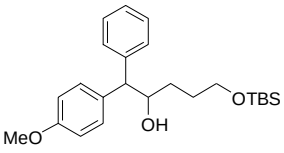
tert-Butyldimethyl-[3-(3-phenyloxiranyl)propoxy]silane (22)



To *tert*-butyldimethyl-(E)-(5-phenylpent-4-enyloxy)silane (6.06 g, 21.9 mmol) dissolved in CH_2Cl_2 (90 mL) at 0 °C was added NaOAc (18.00 g, 219.5 mmol). The mixture was stirred for 10 minutes and *m*-CPBA (5.6 g, 32.92 mmol) was added. The reaction was slowly warmed to room temperature and stirred for 6 hours. The

reaction was then quenched by adding aqueous $Na_2S_2O_3$. The mixture was stirred vigorously for 45 minutes and extracted with diethyl ether (2x). The organic layers were then combined and washed with aqueous $NaHCO_3$, water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography (10% EtOAc in hexanes) to provide the desired product (4.63 g, 72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 – 7.44 (m, 5H), 3.68 (m, 2H), 3.62 (br, 1H), 2.99 (br, 1H), 1.75 (m, 4H), 0.89 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.15, 128.73, 128.30, 125.83, 63.23, 62.88, 59.48, 58.94, 29.39, 29.19, 26.23, - 5.00; IR (neat) 2954, 2929, 2885, 1471, 1462, 1255, 1099, 1005, 966, 835 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{28}O_2Si$ 292.1859, found 292.1848.

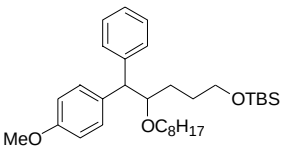
5-(*tert*-Butyldimethylsilanyloxy)-1-(4-methoxyphenyl)-1-phenylpentan-2-ol (23)



To a suspension of CuI (602.3 mg, 3.17 mmol) in THF (50 mL) at -40 °C was added 4-methoxy-phenyl magnesium bromide (1.5 M, 42.28 mL, 63.42 mmol). The mixture was stirred for 15 minutes and epoxide *tert*-butyldimethyl-[3-(3-phenyloxiranyl)propoxy]silane (4.63 g, 15.85 mmol) was added. The reaction was slowly warmed to room temperature and stirred for 6 hours. The reaction mixture was then quenched by adding aqueous NH_4Cl and bubbling air through the mixture overnight. The mixture was extracted with ethyl acetate (2x), and the combined organic layers were washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography (20% EtOAc in hexanes) to provide the desired product (4.50 g, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25 – 7.38 (m, 5H), 7.20 (d, J = 8.7 Hz, 1H), 6.78 (d, J = 8.6 Hz, 2H), 4.32 (t, J = 7.8 Hz, 1H), 3.80 (d, J = 8.3 Hz, 1H), 3.75 (s, 3H), 3.59 (m, 2H), 2.13 (br, 1H), 1.64 (m, 4H), 0.87 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$), δ 142.3, 135.2, 129.7, 129.5, 129.0, 128.9, 126.8, 120.9, 114.3, 114.2, 73.9,

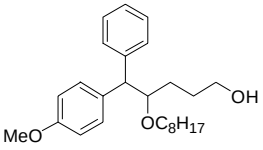
63.5, 58.2, 55.5, 32.2, 29.4, 26.2, 18.6, -5.0; IR (neat) 3445, 3028, 2999, 2953, 2856, 1610, 1511, 1463, 1249, 1178, 1037, 835, 700 cm^{-1}; HRMS (EI) calcd for $C_{24}H_{37}O_3Si$ (M + 1) 401.2512, found 401.2505.

***tert*-Butyl[5-(4-methoxyphenyl)-4-octyloxy-5-phenylpentyloxy]dimethylsilane (24)**



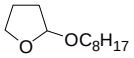
To 5-(*tert*-butyldimethylsilanyloxy)-1-(4-methoxyphenyl)-1-phenylpentan-2-ol (4.50 g, 11.24 mmol) in DMF (50 mL) at 0 °C was added sodium hydride (1.79 g, 44.96 mmol). The mixture was stirred for 15 minutes and octyl iodide (13.50 g, 56.22 mmol) was added. The reaction mixture was slowly warmed to room temperature and stirred for 5 hours. The reaction was quenched by adding water and extracted with hexanes (2x). The organic layers were then combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography (5% EtOAc in hexanes to 20% EtOAc in hexanes) to provide the starting material (1.11 g, 2.78 mmol) and the desired product (2.33 g, 40% isolated): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 8.5 Hz, 2H), 7.28-7.23 (m, 2H), 7.19-7.15 (m, 3H), 6.80 (d, *J* = 8.7 Hz, 2H), 3.4-3.91 (m, 2H), 3.77 (s, 3H), 3.57-3.51 (m, 2H), 3.37 (dt, *J* = 8.7, 6.4 Hz, 1H), 3.04 (dt, *J* = 8.7, 6.7 Hz, 1H), 1.63-1.54 (m, 4H), 1.39-1.06 (m, 12H) 0.88-0.85 (m, 12 H), 0.008 (s, 3H), 0.0001 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 143.3, 135.5, 129.7, 129.2, 128.3, 126.3, 114.1, 82.6, 70.6, 63.5, 55.9, 55.5, 32.1, 30.4, 29.7, 29.5, 29.3, 28.9, 24.2, 22.9, 18.6, 14.4; IR (neat) 2928, 2855, 1511, 1463, 1249, 1098, 1039, 835, 775 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{43}O_3Si$ (M – 57) 455.2981, found 455.2981.

5-(4-Methoxyphenyl)-4-octyloxy-5-phenylpentan-1-ol (25)



To *tert*-butyl[5-(4-methoxyphenyl)-4-octyloxy-5-phenylpentyloxy]dimethylsilane (2.33 g, 4.57 mmol) in THF (5 mL) was added acetic acid (15 mL) and water (5 mL). The mixture was stirred overnight and neutralized with $NaHCO_3$. The mixture was extracted with ethyl acetate (2x). The organic layers were then combined and washed with $NaHCO_3$, water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography (20% EtOAc in hexanes) to provide the desired product (1.61 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34 (d, *J* = 7.2, Hz, 2H), 7.24 (t, *J* = 7.0 Hz, 3H), 7.17 (d, *J* = 8.6 Hz, 2H), 6.80 (d, *J* = 8.6 Hz, 2H), 4.00 (d, *J* = 8.8 Hz 1H), 3.98-3.93 (m, 1H), 3.75 (s, 3H), 3.63-3.47 (m, 2H), 3.38 (dt, *J* = 15.0, 6.3 Hz, 1H), 3.02 (dt, *J* = 15.4, 6.7 Hz, 1H), 2.07 (br, 1H), 1.71-1.61 (m, 3H), 1.56-1.48 (m, 1H), 1.37-1.09 (m, 12H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 142.8, 134.7, 129.8, 129.3, 128.7, 128.4, 128.3, 18.1, 126.1, 113.8, 113.5, 82.2, 70.5, 63.0, 55.2, 55.1, 31.8, 29.9, 29.3, 29.2, 29.1, 28.3, 25.9, 22.6, 14.0; IR (neat) 3431, 2928, 2855, 1610, 1511, 1247, 1178, 1101, 1042, 699 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{20}O_2$ (M – 130) 268.1463, found 268.1462.

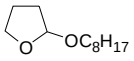
General procedure for photoinduced ETIC reactions



To substrate **9** in dichloroethane (6 mL) in a borosilicate flask at 20 °C were added *N*-methylquinolinium hexafluorophosphate, sodium acetate, anhydrous sodium thiosulfate and toluene (1 mL). The mixture was stirred at room temperature while bubbling air gently and irradiating with a medium pressure mercury lamp for 3 hours. The reaction mixture was filtered through a small plug of silica and the filtrate was concentrated. The resulting residue was purified by flash column chromatography (5% EtOAc in hexanes) to provide the desired product

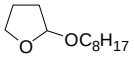
(35.2 mg, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.11 (dd, *J* = 3.9, 1.5 Hz, 1H), 3.93-3.82 (m, 2H), 3.65 (dt, *J* = 9.5, 6.8 Hz, 1H), 3.37 (dt, *J* = 9.5, 6.7 Hz, 1H), 2.04-1.79 (m, 4H), 1.58-1.51 (m, 2H), 1.31-1.28 (m, 10H), 0.88 (t, *J* = 6.4 Hz, 3H). The ^{1}H NMR data and R_f of compound **26** was consistent with an authentic sample prepared by V. S. Kumar.[7a]

2-Octyloxytetrahydrofuran (26)



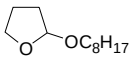
To alcohol **13** (37.3 mg, 0.107 mmol) in dichloroethane (6 mL) in a borosilicate flask at 20 °C were added *N*-methylquinolinium hexafluorophosphate (1.5 mg, 0.0051 mmol), sodium acetate (74.0 mg, 0.88 mmol), anhydrous sodium thiosulfate (74.0 mg, 0.46 mmol) and toluene (1 mL). The mixture was stirred at room temperature while bubbling air gently and irradiating with a medium pressure mercury lamp for 4 hours to provide acetal **26** (13.3 mg, 62%). The ^{1}H NMR data and R_f of compound **26** was consistent with an authentic sample prepared by V. S. Kumar.[7a]

2-Octyloxytetrahyrdofuran (26)



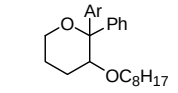
To alcohol **25** (100.0 mg, 0.251 mmol) in dichloroethane (6 mL) in a borosilicate flask at 20 °C were added *N*-methylquinolinium hexafluorophosphate (7.2 mg, 0.0251 mmol), sodium acetate (200.0 mg, 2.44 mmol), anhydrous sodium thiosulfate (200.0 mg, 1.26 mmol) and toluene (1 mL). The mixture was stirred at room temperature while bubbling air gently and irradiating with a medium pressure mercury lamp for 1.5 hours to give acetal **26** (44.6 mg, 88%). The ^{1}H NMR data and R_f of compound **26** was consistent with an authentic sample prepared by V. S. Kumar.[7a]

Ceric ammonium nitrate (CAN) cyclization to give 2-octyloxytetrahydrofuran (26)



To alcohol **25** (100.0 g, 0.251 mmol) in dichloroethane (7.0 mL) was added $NaHCO_3$ (200.0 mg, 2.38 mmol). The mixture was stirred at room temperature for 10 minutes. Ceric ammonium nitrate (0.275 g, 0.501 mmol) was then added dropwise in acetonitrile (3.0 mL). The reaction was stirred for 5 minutes and filtered through a plug of silica. The filtrate was then concentrated and the residue was purified by flash column chromatography (5% EtOAc in hexanes) to provide the desired product (21.0 mg, 45%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.11 (dd, *J* = 3.9, 1.5 Hz, 1H), 3.93-3.82 (m, 2H), 3.65 (dt, *J* = 9.5, 6.8 Hz, 1H), 3.37 (dt, *J* = 9.5, 6.7 Hz, 1H), 2.04-1.79 (m, 4H), 1.58-1.51 (m, 2H), 1.31-1.28 (m, 10H), 0.88 (t, *J* = 6.4 Hz, 3H).[7a] (See **Table 2**)

2-(4-Methoxyphenyl)-3-octyloxy-2-phenyltetrahydropyran (28)

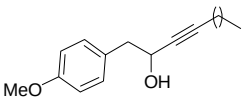


Ar = *p*-methoxyphenyl

To **25** (50.0 mg, 0.125 mmol) in DCE (2 mL) was added $NaHCO_3$ (100.0 mg, 1.20 mmol) and DDQ (56.9 mg, 0.250 mmol). The reaction was then stirred at room temperature for 3 hours and filtered through a silica plug. The filtrate was then concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (5% EtOAc in Hexanes) to provide ether **28** (27.0 mg, 55%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.56 (m, 2H), 7.36-7.17 (m, 5H), 6.84-6.78 (m, 2H), 3.82-3.78 (m, 1H), 3.79 (s, 3H), 3.62-3.60 (m, 2H), 3.36-3.33 (m, 1H), 2.85-2.83 (m, 1H), 1.98-1.95 (m, 4H), 1.55-1.53 (m, 2H), 1.29-1.23 (m, 12H), 0.89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 158.3, 158.1, 145.8, 143.9, 137.5, 135.3, 129.5, 128.4, 127.8, 127.2, 126.7, 126.4, 113.2, 82.4, 82.2, 81.5, 70.7, 62.2, 55.2, 31.9, 29.9, 29.4, 29.3, 26.2, 26.1, 25.8, 25.5, 23.8, 22.7, 14.2; IR

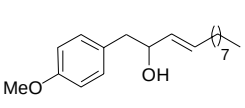
(neat) 2928, 2855, 1509, 1249, 1080, 1036 cm^{-1}; HRMS (EI) calcd for $C_{26}H_{36}O_3$ (M^+) 396.2664, found 396.2676.

1-(4-Methoxyphenyl)dodec-3-yn-2-ol (29)



To 1-decyne (2.71 g, 19.65 mmol) in THF (20 mL) at -78 °C was added n-Butyl lithium (1.6 M, 22.27 mmol, 13.91 mL). The mixture was stirred for 20 minutes and (4-methoxy-phenyl)-acetaldehyde (1.96 g, 13.10 mmol) was added drop wise. The reaction was then slowly warmed to room temperature overnight. The reaction was then quenched by the addition of NH_4Cl (aq) and extracted with EtOAc (2x). The organic layers were then combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography (15% EtOAc in hexanes) to provide the desired product (2.59 g, 69%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.53 (tt, *J* = 6.3, 1.8 Hz, 1H), 3.80 (s, 3H), 2.95 (dd, *J* = 13.6, 6.1 Hz, 1H), 2.90 (dd, *J* = 13.5, 6.1 Hz, 1H), 2.20 (td, *J* = 6.9, 1.9 Hz, 2H), 1.90 (s, 1H), 1.49 (app pentet, 2H), 1.36-1.28 (m, 12H), 0.90 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.5, 130.7, 128.7, 86.5, 80.6, 63.5, 55.2, 43.5, 31.8, 29.3, 29.0, 28.8, 28.6, 22.6, 18.6, 14.0; IR (neat) 3418, 2927, 2855, 1613, 1512, 1464, 1246, 1177, 1036, 819, 760 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{28}O_2$ 288.2089, found 288.2088.

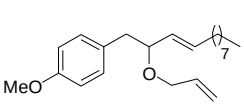
1-(4-Methoxyphenyl)dodec-3-en-2-ol (30)



To a suspension of LAH (786.2 mg, 20.72 mmol) in THF (20 mL) at 0 °C was slowly added 1-(4-methoxyphenyl)dodec-3-yn-2-ol (1.99 g, 6.90 mmol). The mixture was then warmed to reflux and stirred for 18 hrs. The reaction was then cooled to 0 °C and quenched by the addition of NaOH (10% aq). The mixture was then

extracted with EtOAc (2x) and the organic layers were combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by column chromatography (15% EtOAc in hexanes) to provide the desired product (1.74 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.64 (dt, *J* = 15.4, 6.5 Hz, 1H), 5.51 (dd, *J* = 15.4, 6.5 Hz, 1H), 4.25 (app q, *J* = 6.2 Hz, 1H), 3.80 (s, 3H), 2.80 (dd, *J* = 13.6, 5.3 Hz, 1H), 2.72 (dd, *J* = 13.6, 7.6 Hz, 1H), 2.02 (app q, *J* = 6.6 Hz, 2H), 1.56 (s, 1H), 1.38-1.27 (m, 12H), 0.89 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 132.6, 132.2, 130.8, 130.3, 114.2, 73.9, 55.5, 43.5, 32.5, 32.2, 29.7, 29.5, 29.4, 22.9, 14.3; IR (neat) 3396, 2924, 2853, 1612, 1512, 1464, 1300, 1246, 1177, 1038, 969, 820 cm^{-1}.

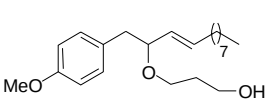
1-(2-Allyloxydodec-3-enyl)-4-methoxybenzene (31)



To 1-(4-methoxyphenyl)dodec-3-en-2-ol (330.0 mg, 1.14 mmol) in DMF (5 mL) at 0 °C was added NaH (136.4 mg, 3.41 mmol). The mixture was stirred for 20 minutes and ally bromide (412.3 mg, 3.41 mmol) was added. The mixture was then slowly warmed to room temperature and stirred for 12 hours. The reaction was quenched by the addition of water. The mixture was extracted with hexanes (2x) and the organic layers were combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography (5% EtOAc in hexanes) to provide the desired product (291.3 mg, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.57 Hz, 2H), 6.81 (d, 8.59 hz, 2H), 5.85 (ddd, *J* = 17.2, 10.4, 5.2 Hz, 1H), 5.47 (dt, *J* = 15.4, 6.7 Hz, 1H), 5.24 (dd *J* = 15.3, 8.0, Hz, 1H), 5.19 (dd, *J* = 17.2, 1.7 Hz, 1H), 5.10 (dd, *J* = 10.38, 1.4 Hz, 1H), 4.01 (dd, *J* = 12.9, 7.7 Hz, 1H), 3.85 – 3.77 (m, 2H), 3.77 (s, 3H), 2.87 (dd *J* = 13.7, 6.7 Hz, 1H), 2.70 (dd, *J* = 13.7, 6.4 Hz, 1H), 2.00 (q, *J* = 6.7 Hz, 2H),

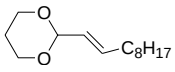
1.30-1.24 (m, 12H), 0.88 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 135.3, 134.4, 130.7, 130.6, 130.0, 116.2, 113.4, 81.3, 68.9, 55.2, 41.6, 32.2, 31.8, 29.7, 29.4, 29.3, 29.2, 29.0, 22.6, 14.0; IR (neat) 2927, 2854, 1613, 1513, 1464, 1300, 1247, 1177, 1109, 1074, 1039, 970, 821, 734 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{29}O_1$ (M – 57) 273.2218, found 273.2206.

3-[1-(4-Methoxybenzyl)undec-2-enyloxy]propan-1-ol (32)



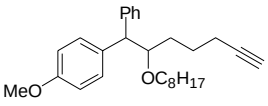
To a stirred solution of 2-methyl butene (247.2 mg, 3.52 mmol) in THF (10 mL) at -10 °C was added BH_3-THF (1.0 M, 1.76 mmol, 1.76 mL) drop wise. The mixture was stirred for 45 minutes and 1-(2-allyloxydodec-3-enyl)-4-methoxybenzene (291.3 mg, 0.882 mmol) was added. The reaction was stirred for 3 hours and quenched by the addition of water, NaOH (10% aq) and H_2O_2 (30%). The mixture was then vigorously stirred overnight and extracted with EtOAc (2x). The organic layers were then combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated. The resulting residue was purified by flash column chromatography (10% EtOAc in hexanes) to provide the desired product (169.0 mg, 55%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, J = 8.6 Hz, 2H), 6.81 (d, J = 8.6 Hz, 2H), 5.53 (dt, J = 15.4, 6.7 Hz, 1H), 5.26 (dd, J = 15.4, 8.0 Hz, 1H), 3.79-3.75 (m, 1H), 3.78 (s, 3H), 3.70-3.63 (m, 3H), 3.35 (dt, J = 11.4, 5.7 Hz, 1H), 2.79 (dd, J = 13.8, 7.2 Hz, 1H), 2.69 (dd, J = 13.8, 5.8 Hz, 1H), 2.01 (app q, J = 6.7 Hz, 2H), 1.75 (app p, J = 5.5 Hz, 2H), 1.35-1.25 (m, 12H), 0.88 (t, J = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 134.4, 130.5, 130.4, 129.9, 113.6, 82.5, 67.7, 62.3, 55.2, 41.7, 32.1, 32.0, 31.8, 29.4, 29.2, 29.1, 29.0, 22.6, 14.0; IR (neat) 3388, 2955, 2925, 2854, 1512, 1464, 1442, 1300, 1247, 1087, 1040, 970 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{36}O_3$ (M – 76) 272.2140, found 272.2145.

2-Dec-1-enyl-[1,3]dioxane (33)



To 3-[1-(4-methoxybenzyl)undec-2-enyloxy]propan-1-ol (101.0 mg, 0.287 mmol) in dichloroethane (6 mL) in a borosilicate flask at 20 °C were added *N*-methylquinolinium hexafluorophosphate (7.2 mg, 0.0251 mmol), sodium acetate (200.0 mg, 2.44 mmol), anhydrous sodium thiosulfate (200.0 mg, 1.26 mmol) and toluene (1 mL). The mixture was stirred at room temperature while bubbling air gently and irradiating with a medium pressure mercury lamp for 4 hours. The reaction mixture was filtered through a small plug of silica and the filtrate was concentrated. The resulting residue was purified by flash column chromatography (5% EtOAc in hexanes) to provide the desired product (50.0 mg, 77.02%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (dt, *J* = 15.7, 6.6 Hz, 1H), 5.50 (ddt, *J* = 15.7, 5.1, 1.3 Hz, 1H), 4.93 (d, *J* = 5.1 Hz, 1H), 4.14 (dd, *J* = 10.6, 4.9 Hz, 2H), 3.83 (td, *J* = 12.3, 2.4 Hz, 2H), 2.20-2.02 (m, 4H), 1.41-1.26 (m, 12 H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.7, 126.8, 101.2, 66.9, 32.0, 31.9, 29.4, 29.2, 28.6, 25.7, 22.6, 14.0; IR (neat) 2955, 2924, 2852, 1377, 1237, 1142, 1087, 996, 967 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{25}O_2$ (M – 1) 225.1854, found 225.1853.

1-Methoxy-4-(2-octyloxy-1-phenylhept-6-ynyl)benzene (36)

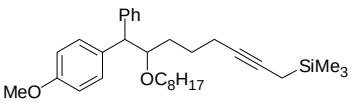


To 5-(4-methoxyphenyl)-4-octyloxy-5-phenylpentan1-ol (1.00 g, 2.5 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added triethyl amine (1.0155 g, 10.0 mmol). The mixture was stirred for 5 minutes and tosyl chloride (716.8 mg, 3.76 mmol) was added. The mixture was slowly warmed to room temperature over 5 hours and quenched by the addition of water. The mixture was then extracted with CH_2Cl_2 (2x) and the organic layers were combined and washed with water and brine. The organic layer was then dried (Na_2SO_4),

filtered and concentrated under reduced pressure. The tosylate **35** was then used without further purification.

To tosylate **35** (1.38 g, 2.5 mmol) in DMSO (10 mL) at 0 °C was added lithium acetylide (690.5 g, 7.5 mmol). The reaction was then warmed to room temperature and stirred for 12 hours. The reaction was then quenched by the addition of NH_4Cl (aq) and extracted with ethyl acetate (2x). The organic layers were then combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was then purified by flash column chromatography (5% EtOAc in hexanes) to provide the desired product (627.0 mg, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (d, *J* = 7.3 Hz, 2H), 7.27 (t, *J* = 7.3 Hz, 3H), 7.19 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 3.97-3.90 (m, 2H), 3.77 (s, 3H), 3.37 (dt, *J* = 8.6, 6.3 Hz, 1H), 3.03 (dt, *J* = 8.6, 6.5 Hz, 1H), 2.13 (td, *J* = 6.6, 2.5 Hz, 2H), 1.91 (t, *J* = 2.5 Hz, 1H), 1.75-1.59 (m, 4H), 1.35-1.13 (m, 12H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 142.7, 134.9, 129.3, 128.8, 128.4, 128.0, 126.0, 113.7, 84.4, 81.9, 70.4, 68.3, 55.5, 55.1, 31.9, 31.8, 30.0, 29.3, 29.2, 26.0, 24.3, 22.6, 18.5, 14.0.

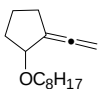
[8-(4-Methoxyphenyl)-7-octyloxy-8-phenyloct-2-ynyl]trimethylsilane (37)



To 1-methoxy-4-(2-octyloxy-1-phenylhept-6-ynyl)benzene (200.0 mg, 0.492 mmol) in THF (5 mL) at -30 °C was added *n*-butyl lithium (1.6M, 0.500 mL, 0.738 mmol). The mixture was then stirred at -30 °C for 15 minutes and warmed to 0 °C for 15 minutes. The iodomethy trimethylsilane (158.0 mg, 0.738 mmol) was then added drop wise. The reaction flask was then covered in aluminum foil and heated to 55 °C for 12 hours. The reaction was then cooled to room temperature and quenched by the addition of water. The mixture was extracted with ethyl acetate (2x) and the combined organic layers were washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered

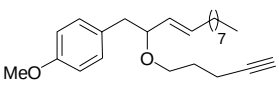
and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (3% EtOAc in hexanes) to provide the desired product (173.1 mg, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 (d, *J* = 7.2 Hz, 2H), 7.26 (t, *J* = 7.1 Hz, 3H), 7.17 (d, *J* = 8.3 Hz, 2H), 6.81 (d, *J* = 8.7 Hz, 2H), 3.96-3.84 (m, 2H), 3.77 (s, 3H), 3.35 (dt, *J* = 8.7, 6.4 Hz, 1H), 3.03 (dt, *J* = 8.7, 6.6 Hz, 1H), 2.06-1.94 (m, 2H), 1.63-1.48 (m, 4H), 1.39 (t, *J* = 2.5 Hz, 2H), 1.33-1.12 (m, 12H), 0.88 (t, *J* = 7.1 Hz, 3H), 0.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.3, 143.2, 135.5, 129.7, 129.3, 128.3, 127.9, 126.3, 114.1, 82.5, 78.9, 74.5, 55., 55.5, 32.4, 32.1, 30.4, 29.7, 26.4, 25.7, 22.9, 19.4, 14.4, 7.22, -1.8; HRMS (EI) calcd for $C_{32}H_{48}O_2Si$ 492.3424, found 492.3418.

1-Octyloxy-2-vinylidene-cyclopentane (38)



To [8-(4-methoxyphenyl)-7-octyloxy-8-phenyloct-2-ynyl]trimethylsilane (50.0 mg, 0.101 mmol) in acetonitrile (5 mL) at room temperature was added $NaHCO_3$ (100.0 mg, 1.20 mmol). The mixture was then stirred for 10 minutes and CAN (138.4 mg, 0.252 mmol) was added. The reaction was then allowed to stir for 1.5 hours and the mixture was filtered through a silica plug. The filtrate was concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (5% EtOAc in hexanes) to provide the desired product (10.6 mg, 47.3%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (td, *J* = 6.1, 1.9 Hz, 2H), 4.29 (br, 1H), 3.56 (dt, *J* = 9.3, 6.8 Hz, 1H), 3.36 (dt, *J* = 9.3, 6.6 Hz, 1H), 2.53-2.51 (m, 1H), 2.39-2.31 (m, 1H), 1.85-1.78 (m, 4H), 1.53-1.51 (m, 4H), 1.28-1.25 (m, 12H), 0.88 (t, *J* = 6.5 Hz, 3H).

1-Methoxy-4-(2-pent-4-ynyloxydodec-3-enyl)benzene (40)

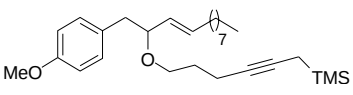


To 3-[1-(4-methoxybenzyl)undec-2-enyloxy]propan-1-ol (1.63 g, 4.70

mmol) in CH_2Cl_2 (15 mL) at 0 °C was added triethyl amine (1.904 g, 18.8 mmol). The mixture was stirred for 5 minutes and tosyl chloride (1.34 g, 7.05 mmol) was added. The mixture was slowly warmed to room temperature over 5 hours and quenched by the addition of water. The mixture was then extracted with CH_2Cl_2 (2x) and the organic layers were combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The tosylate **39** was then used without further purification.

To tosylate **39** (2.67 g, 4.70 mmol) in DMSO (20 mL) at 0 °C was added lithium acetylide (865.4 mg, 9.40 mmol). The reaction was then warmed to room temperature and stirred for 4 hours. The reaction was then quenched by the addition of NH_4Cl (aq) and extracted with ethyl acetate (2x). The organic layers were then combined and washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was then purified by flash column chromatography (5% EtOAc in hexanes) to provide the desired product (1.01 g, 61%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.51 (dt, *J* = 15.4, 6.7 Hz, 1H), 5.29 (dd, *J* = 15.4, 7.7 Hz, 1H), 3.79 (s, 3H), 3.79-3.71 (m, 1H), 3.55 (dt, *J* = 9.6, 6.1 Hz, 1H), 3.28 (dt, *J* = 9.6, 6.1 Hz, 1H), 2.83 (dd, *J* = 13.7, 7.0 Hz, 1H), 2.67 (dd, *J* = 13.7, 5.9 Hz, 1H), 2.18 (td, *J* = 7.1, 2.6 Hz, 2H), 2.00 (app q, 2H), 1.91 (t, *J* = 2.6 Hz, 1H), 1.71 (app p, 2H), 1.31-1.26 (m, 12H), 0.89 (t, *J* = 6.3 Hz, 3H).

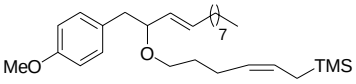
{6-[1-(4-Methoxybenzyl)undec-2-enyloxy]hex-2-ynyl}trimethylsilane (41)



To 1-methoxy-4-(2-pent-4-ynyloxydodec-3-eny)benzene (1.00 g, 2.80 mmol) in THF (10 mL) at -30 °C was added *n*-butyl lithium (1.6M, 2.63 mL, 4.20 mmol). The mixture was then stirred at -30 °C for 15 minutes and warmed to 0 °C for 15 minutes. The iodomethy trimethylsilane (1.01 g, 4.76 mmol) was then added drop wise. The reaction flask was then covered in aluminum foil and heated to 55 °C for 12 hours.

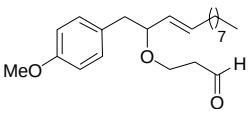
The reaction was then cooled to room temperature and quenched by the addition of water. The mixture was extracted with ethyl acetate (2x) and the combined organic layers were washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The resulting residue was purified by flash column chromatography (3% EtOAc in hexanes) to provide the desired product (1.0872 g, 88%): ^{1}H NMR (300 MHz, CDCl3) δ 7.12 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.48 (dt, *J* = 15.4, 6.6 Hz, 1H), 5.29 (dd, *J* = 15.4, 7.8 Hz, 1H), 3.79 (s, 3H), 3.79-3.69 (m, 1H), 3.54 (dt, *J* = 9.4, 6.3 Hz, 1H), 3.27 (dt, *J* = 9.4, 6.3 Hz, 1H), 2.84 (dd, *J* = 13.7, 6.8 Hz, 1H), 2.66 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.19-2.12 (m, 2H), 2.08-2.00 (app q, 2H), 1.67 (app p, 2H), 1.41 (t, *J* = 2.6 Hz, 2H), 1.27-1.25 (m, 10H), 0.89 (t, *J* = 6.5 Hz, 3H), 0.08 (s, 9H).

{6-[1-(4-Methoxybenzyl)undec-2-enyloxy]hex-2-enyl}trimethylsilane (42)



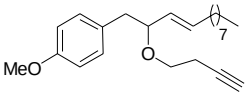
To {6-[1-(4-methoxybenzyl)undec-2-enyloxy]hex-2-ynyl}trimethylsilane (54.0 mg, 0.121 mmol) in MeOH (5 mL) was added Linlard's catalyst (5.0 mg) with stirring. The reaction mixture was then purged with hydrogen (3x) and allowed to stir for 18 hours. The mixture was then filtered over celite and the filtrate was concentrated under reduced pressure. The resulting residue was then purified by flash column chromatography (3% EtOAc in hexanes) to provide the desired product (50.0 mg, 93%): ^{1}H NMR (300 MHz, CDCl3) δ 7.15 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.52-5.22 (m, 4H), 3.79 (s, 3H), 3.69-3.64 (m, 1H), 3.46-3.30 (m, 2H), 3.29-3.20 (m, 1H), 2.82 (dd, *J* = 12.5, 6.7 Hz, 1H), 2.70 (dd, *J* = 12.5, 7.6 Hz 1H), 2.05-2.00 (m, 4H), 1.96-1.87 (m, 2H), 1.46-1.44 (m, 2H), 1.29-1.26 (m, 12H), 0.89 (t, *J* = 6.4 Hz, 3H), 0.02 (s, 9H).

3-[1-(4-Methoxybenzyl)undec-2-enyloxy]propionaldehyde (44)



To 3-[1-(4-methoxybenzyl)undec-2-enyloxy]propan-1-ol (500.0 mg, 1.43 mmol) in CH_2Cl_2 (5 mL) at 0 °C was added $NaHCO_3$ (1.201 g, 14.3 mmol). The mixture was stirred at 0 °C for 5 minutes and DMPI (915.0 mg, 2.15 mmol) was added. The reaction was then slowly warmed to room temperature and stirred for 2 hours. The reaction was then quenched by the addition of water and $Na_2S_2O_3$ (aq). The mixture was then filtered through celite and the organic layer was washed with water and brine. The organic layer was then dried (Na_2SO_4), filtered and concentrated under reduced pressure. The aldehyde was used without further purification.

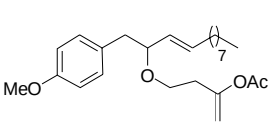
1-(2-But-3-ynyloxydodec-3-enyl)-4-methoxybenzene (45)



To dimethyl (1-diazo-2-oxopropyl) phosphonate[32] (533.0 mg, 2.77 mmol) in methanol (3 mL) at 0°C was added K_2CO_3 (193.3 mg, 1.39 mmol). The mixture was stirred at 0 °C for 30 minutes and 3-[1-(4-methoxbenzyl)undec-2-enyloxy]propionaldehyde (481.1 mg, 1.39 mmol) was added in methanol. The reaction was then slowly warmed to room temperature over 12 hours, and the solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography (5% EtOAc in hexanes) to provide the desired product (134.2 mg, 28%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.51 (dt, *J* = 15.4, 6.6 Hz, 1H), 5.30 (dd, *J* = 15.4, 7.9 Hz), 3.80-3.77 (m, 1H), 3.79 (s, 3H), 3.59 (dt, *J* = 9.3, 7.2 Hz, 1H), 3.36 (dt, *J* = 9.4, 7.1 Hz), 2.86 (dd, *J* = 13.7, 6.8 Hz, 1H), 2.67 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.38 (td, *J* = 7.2, 2.6 Hz, 2H), 2.02 (app q, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.35-1.25 (m, 12H), 0.89 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 134.3, 130.7, 130.5, 129.9, 113.5, 82.3, 81.6, 69.0, 66.4, 55.2, 41.6,

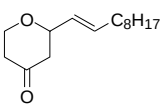
32.1, 31.9, 29.4, 29.3, 29.1, 29.0, 22.6, 19.9, 14.0; IR (neat) 3311, 2925, 2854, 1740, 1512, 1246, 1092, 1040 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{34}O_2$ 342.2559, found 342.2549.

Acetic acid-3-[1-(4-methoxybenzyl)undec-2-enyloxy]-1-methylenepropyl ester (46)



To 1-(-but-3-ynyloxydodec-3-enyl)-4-methoxybenzene (134.2 mg, 0.39 mmol) in toluene (5 mL) was added Ru(*p*-cymene)PPh_3Cl (2.2 mg, 0.0039 mmol) and acetic acid (23.4 mg, 0.39 mmol). The mixture was then warmed to 80 °C and stirred for 12 hours. The reaction was then cooled to room temperature and the solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography (10% EtOAc in hexanes) to provide the desired product (61.7 mg, 39%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.48 (dt, *J* = 15.4, 6.7 Hz, 1H), 5.30 (ddt, *J* = 15.4, 8.0, 1.1 Hz, 1H), 4.71 (d, *J* = 1.3 Hz, 1H), 4.68 (d, *J* = 1.5 Hz, 1H), 3.79-3.74 (m, 1H), 3.78 (s, 3H), 3.62 (dt, *J* = 9.5, 6.6 Hz, 1H), 3.35 (dt, *J* = 9.5, 6.6 Hz, 1H), 2.84 (dd, *J* = 13.7, 6.8 Hz, 1H), 2.62 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.43 (app t, *J* = 6.2 Hz, 2H), 2.11 (s, 3H), 2.08 (app q, 2H), 1.37-1.27 (m, 12H), 0.89 (t, *J* = 6.5 Hz); ^{13}C NMR (75 MHz, CDCl3) δ 168.9, 157.9, 153.7, 134.8, 130.7, 130.6, 130.0, 113.3, 102.4, 65.0, 55.1, 41.6, 34.0, 32.1, 29.5, 29.3, 29.1, 28.9, 22.6, 20.9, 14.0; IR (neat) 2925, 2854, 1758, 1667, 1612, 1441, 1465, 1370, 1300, 1246, 1179, 1090, 1039, 1020, 970, 880, 827, 733 cm^{-1}; HRMS (ESI) calcd for $C_{25}H_{38}O_4Na$ ($M + Na^+$) 425.2668, found 425.2668.

2-dec-1-enyltetrahydropyran-4-one (47)



To acetic acid-3-[1-(4-methoxybenzyl)undec-2-enyloxy]-1-methylenepropyl ester (61.7 mg, 0.153 mmol) in dichloroethane (3.5 mL) was added 4 Å molecular sieves (120.0 mg), and $NaHCO_3$ (120.0 mg, 1.42 mmol). The mixture was then warmed to 40 °C

and stirred for 15 minutes. Ceric Ammonium Nitrate (168.0 mg, 0.306 mmol) was then added dropwise in CH_3CN (1.5 mL) and the reaction was stirred at 40 °C for 1 hour. The reaction mixture was then filtered through silica and the filtrate was concentrated. The resulting residue was purified by flash column chromatography (5% EtOAc in hexanes) to provide the desired product (33.1 mg, 90.83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (dt, *J* = 15.5, 6.6 Hz, 1H), 5.55 (ddt, *J* = 15.5, 6.3, 1.3 Hz, 1H), 4.31 (ddd, *J* = 11.5, 7.2, 1.8 Hz), 4.10 (m, 1H), 3.72 (td, *J* = 11.6, 3.0 Hz, 1H) 2.61 (m, 1H), 2.45 (s, 1H), 2.43 (m, 1H), 2.37 (m, 1H), 2.05 (app q, 2H), 1.38-1.26 (m, 12H), 0.88 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 206.5, 134.1, 128.8, 78.3, 66.1, 48.3, 42.2, 32.2, 31.8, 31.6, 29.7, 29.4, 29.2, 29.1, 28.9, 22.6, 14.0; IR (neat) 2925, 2853, 1721, 1466, 1369, 1247, 1156, 1082, 969 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{26}O_2$ 238.1933, found 238.1940.

1.5. References

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Chapter 2 Development of the Diastereoselective Electron Transfer Initiated Cyclization (ETIC) Reaction: Synthesis of 2,6-*syn*-Disubstituted Tetrahydropyranones.

2.1. Introduction

The ETIC reaction has proven to be an excellent method for generating reactive intermediates such as oxocarbenium and acyliminium ions. When an appropriate nucleophile is appended, these electrophiles undergo efficient cyclization to provide a variety of products. A major limitation of the ETIC reaction has been the inability to obtain high levels of stereochemical control. The lack of diastereoselectivty exhibited in ETIC reactions has been attributed to the lack of a conformational preference in the transition state.

However, in exploring the functional group compatibility of homobenzylic amides as cyclization substrates, it was noted that incorporation of methyl group in the bishomobenzylic position led to preferential formation of the *anti* cyclic acyl aminal.[1] While the stereoselectivity observed for the cyclization of secondary homobenzylic amides was poor (2:1), excellent levels of diastereoselectivity were observed in the cyclization of tertiary homobenzylic amides (>19:1). Cyclization of the tertiary amide led to excellent levels of diastereoselectivity whether the substrate was a single diastereomer or a mixture of diastereomers. This indicates the formation of a discrete acyliminum ion intermediate, followed by diastereoselective attack of the appended nucleophile (**Figure 30**). The extent of stereochemical control is attributed to the development of steric interactions in the transition state to form the *syn* product.

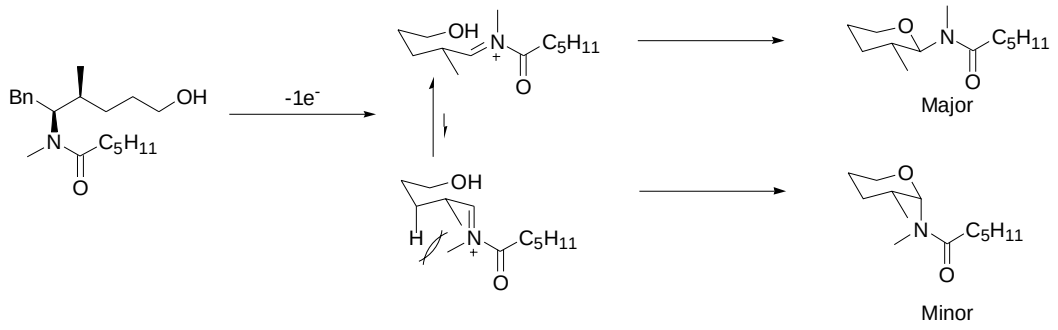


Figure 30: Diastereoselective cyclic acyl aminal formation.

Synthetically useful levels of diastereoselectivity have also been noted in the formation of amido trioxadecalin ring systems.[2] Single electron oxidation of the substrate led to the formation of the acyliminium ion intermediate, which upon attack of the tethered nucleophile provided a 10:1 mixture in favor of the undesired amido trioxadecalin product (**Figure 31**). The unexpected stereochemical outcome suggests a late transition state where the conformation is controlled by the stability of the *cis* trioxadecalin ring system.

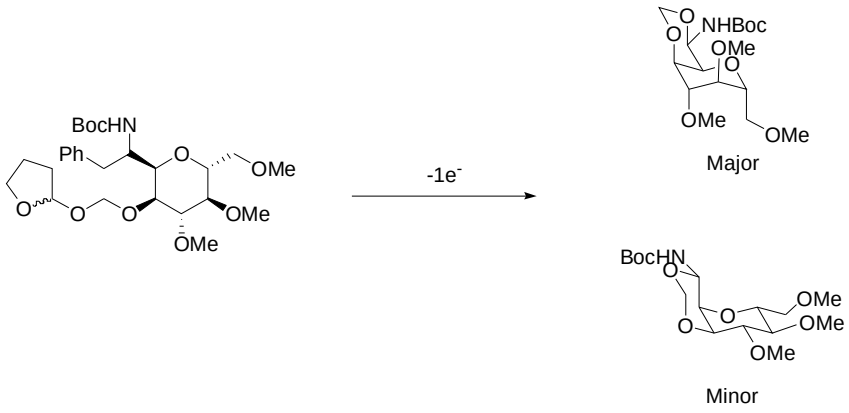


Figure 31: Oxidative cyclization to provide the amido trioxadecalin ring system.

While the ETIC reaction provided excellent levels of diastereocontrol in the synthesis of some cyclic acyl aminals[1] and amido trioxadecalins,[2] *exo*-cylclizations utilizing carbon centered nucleophiles have shown poor levels of stereocontrol.[3] However, excellent levels of diastereoselectivity are expected for suitably substituted ETIC substrates which under 6-*endo*-cyclizations. This is based on the strong preference of 6-*endo*-cyclizations to proceed through chair transition states is well precedented.[4] This conformational bias coupled with the (*E*)-configuration of the resulting intermediate oxocarbenium ion[5] is expected to provide excellent levels of diastereocontrol. The efficiency of the enol acetate as a nucleophile in 6-*endo*-cyclizations along with the prevalence of 2,4,6-trisubstituted tetrahydropyrans in biologically active[6] molecules prompted an investigation into the synthesis of substrates to provide *syn*-2,6-disubstituted tetrahydropyranones (**Figure 32**).

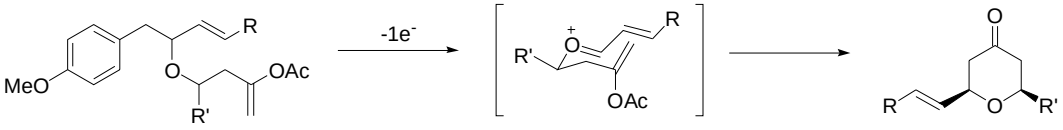


Figure 32: Diastereoselective cyclization in an *endo*-ETIC reaction.

To synthesize substrates with this general design, a solution to the nontrivial construction of an ether linkage between two secondary carbons was required (**Figure 33**). The Lewis acid-mediated opening of cyclic acetals in the presence of a metalloallene provided the requisite bond connectivity. Manipulation of the resulting primary alcohol provides access to the homopropargylic ether which may be directly converted to the desired enol acetate.[7] The ability to obtain a stable easily handled nucleophile under mild, inexpensive and non-toxic conditions further illustrates the utility of enol actates in ETIC reactions.

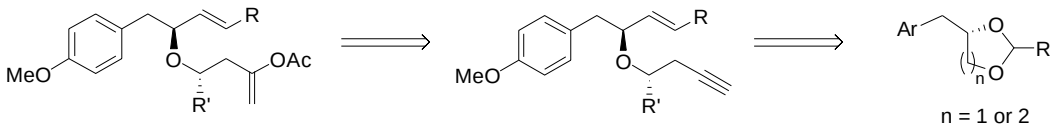


Figure 33: Retrosynthesis of the diastereoselective ETIC substrate.

This sequence allows for the possibility of a highly diastereoselective synthesis of the ETIC substrates provided the acetal opening occurs in a stereoselective manner. Several groups[8] have demonstrated the ability to obtain high levels of diastereocontrol in the ring opening reactions with careful control of the reaction conditions. The high levels of stereocontrol may be explained through the mechanism of the reaction (**Figure 34**). Initial complex formation between the Lewis acid and the least congested oxygen of the acetal leads to the formation of an (*E*)-oxocarbenium ion[5] intermediate. The *Si* face of the intermediate is blocked due to ion pairing, and the nucleophile attacks from the *Re* face.

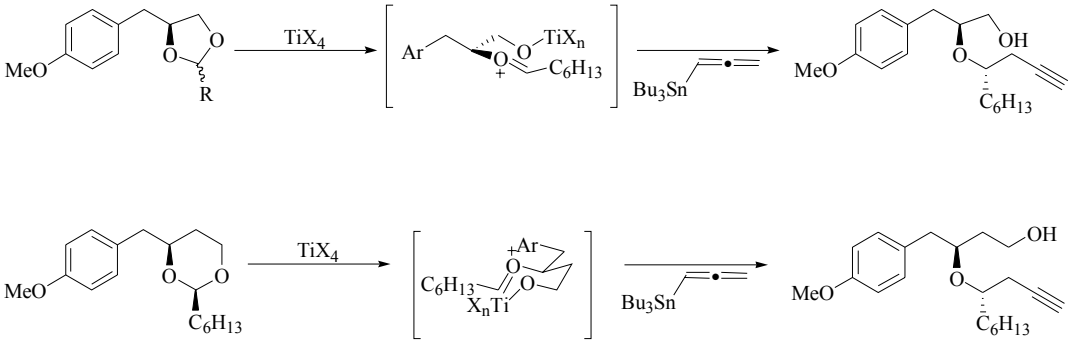


Figure 34: Mechanism for diastereoselective cyclic acetal opening.

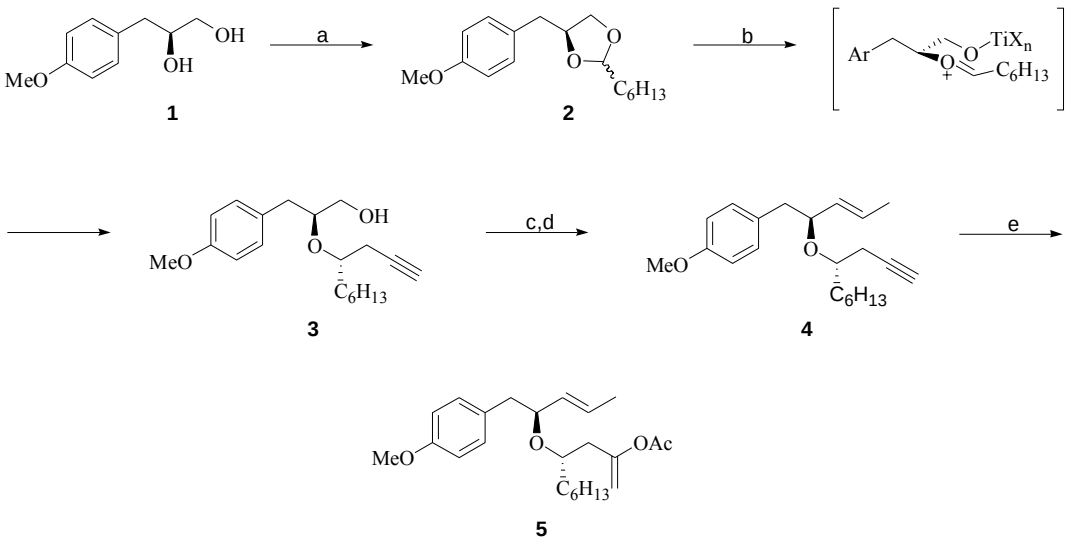
Of note for this sequence, is the formation of the homopropargylic stereocenter relative to that of the benzylic stereocenter in the cyclic acetal opening reaction. These roles are then

reversed during the ETIC reaction, and the stereogenicity of the benzylic bond is dictated by the homopropargylic stereocenter. This method could therefore be considered as a cationic variant of Seebach's[9] self-reproduction of chirality. Given the strong precedent for the diastereoselective opening of cyclic acetals, this sequence allows for the enantioselective synthesis of *syn*-2,6-disubstituted tetraydropyranones from enantiopure acetals.

2.2. Results and Discussion

I. Synthesis of Vinyl ETIC Substrates to Undergo Stereoselective Cyclization

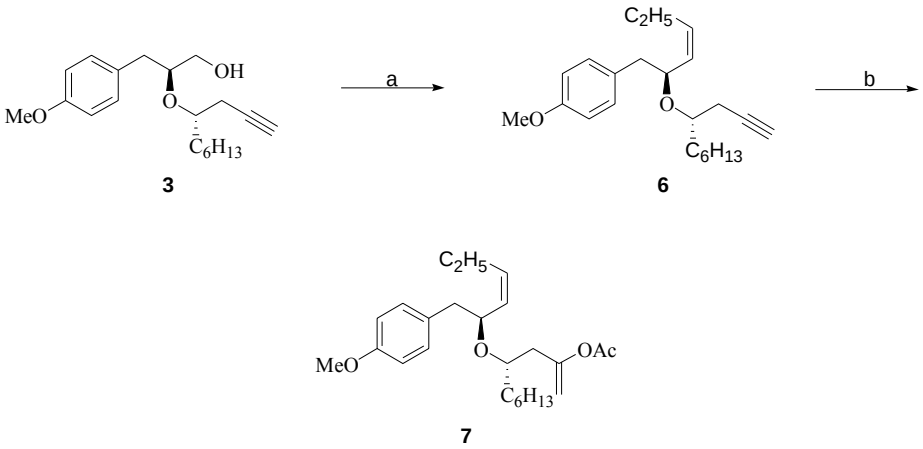
A substrate containing an *E*-disubstituted olefin as the bond weakening group was synthesized to test validity of this design (**Scheme 1**). Known[10] diol **1** was prepared as a single enantiomer via an asymmetric dihydroxylation[11] of 4-allylanisole. Condensation of **1** with heptanal led to the formation of acetal **2** as a 1.7:1 mixture of inseparable diastereomers (84%). Acetal **2** was then treated with $TiCl_4$[12] in the presence of allenyltributyltin to provide homopropargylic ether **3** as a single diastereomer in 84% yield. The excellent level of stereocontrol noted for this reaction is consistent with the formation of a rapidly equilibrating oxocarbenium ion to give the (*E*)-configuration.[5] Reaction of the nucleophile then occurred from the face opposite the metal oxide/oxocarbenium ion pair. To the best of our knowledge, this is the first example of a diastereoselective cyclic acetal opening via an allenylstannane reagent. Oxidation of the primary alcohol (**3**) with Dess-Martin periodinane followed by a Julia-Kocienski olefination[13] furnished compound **4**. While the yield of compound **4** was quite low, a single geometric isomer was isolated. Exposure of compound **4** to a mixture of $[Ru(p\text{-cymene})Cl_2]_2$ and tri-2-furylphosphine led to the Markovnikov addition of acetic acid to give enol acetate **5**.[7]



Reagents and conditions: a) *n*-Heptanal, *p*-TsOH, benzene, reflux, 12h (84%); b) Allenyltributyltin, $TiCl_4$, CH_2Cl_2, - 78 °C (84%); c) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2; d) Ethyl 1-phenyl-1*H*-tetrazolyl-Sulfone, KHMDS, DME, - 60 °C (19%, 2 steps); e) HOAc, Na_2CO_3, $P(Fur)_3$, $[Ru(p\text{-cymene})Cl_2]_2$, PhMe 80 °C (42%).

Scheme 11: Synthesis a *trans*-olefin substrate.

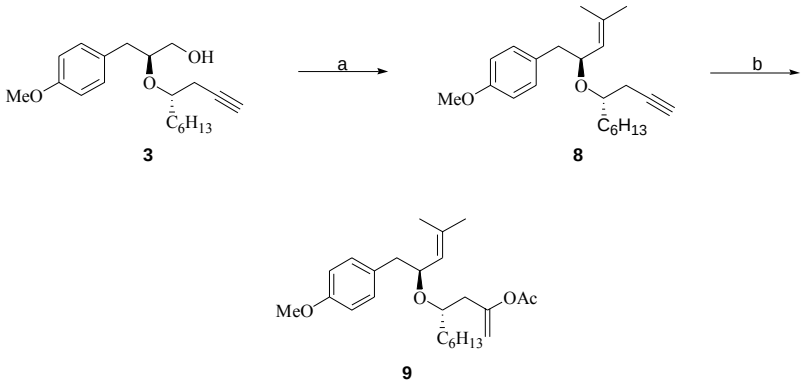
To determine whether the introduction of a *Z*-olefin would have an effect on the outcome of the cyclization, substrate **7** was prepared (**Scheme 12**). The synthesis began with oxidation of primary alcohol **3** followed by a Wittig reaction[14] with *n*-propyltriphenylphosphonium bromide and LHMDS to provide *cis* alkene **6**. Compound **6** was isolated as a single geometric isomer. The resulting homopropargylic alkyne was converted to the enol acetate (**7**) via a $[Ru(p\text{-cymene})Cl_2]_2$/tri-2-furylphosphine mediated addition of acetic addition.[7]



Reagents and Conditions: a)) i. Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2; ii. propyltriphenylphosphonium bromide, LHMDS, THF, 0 °C (47% 2 steps); b) HOAc, Na_2CO_3, $P(fur)_3$ $[Ru(p\text{-cymene})Cl_2]_2$, 80 °C (64%).

Scheme 12: Synthesis of a *cis*-olefin substrate.

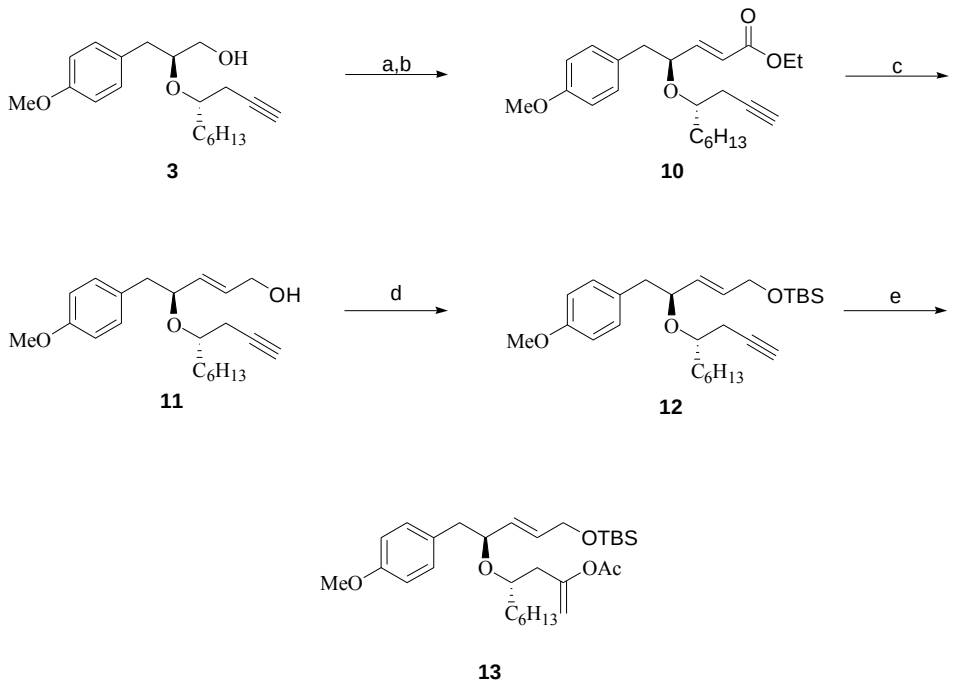
A substrate possessing a trisubstituted olefin was synthesized to explore the limitations of olefin substitution in the *endo*-cyclization of enol acetates (**Scheme 13**). Once again this sequence began with the oxidation of alcohol **3** followed by a Wittig reaction with isopropyltriphenylphosphonium iodide and *n*-butyl lithium[15] provided alkyne **8**. Installation of the enol acetate was accomplished through the addition acetic acid across the alkyne in the presence of $[Ru(p\text{-cymene})Cl_2]_2$ and tri-2-furylphosphine to provide substrate **9**.[7]



Reagents and Conditions: a)) i. Dess-Martin periodinae, $NaHCO_3$, CH_2Cl_2; ii. *i*-propyltriphenylphosphonium iodide, *n*-BuLi, THF, 0 °C (10% 2 steps); b) HOAc, Na_2CO_3, $P(fur)_3$ $[Ru(p\text{-cymene})Cl_2]_2$, 80 °C (39%).

Scheme 13: Synthesis of a substrate containing a trisubstituted olefin.

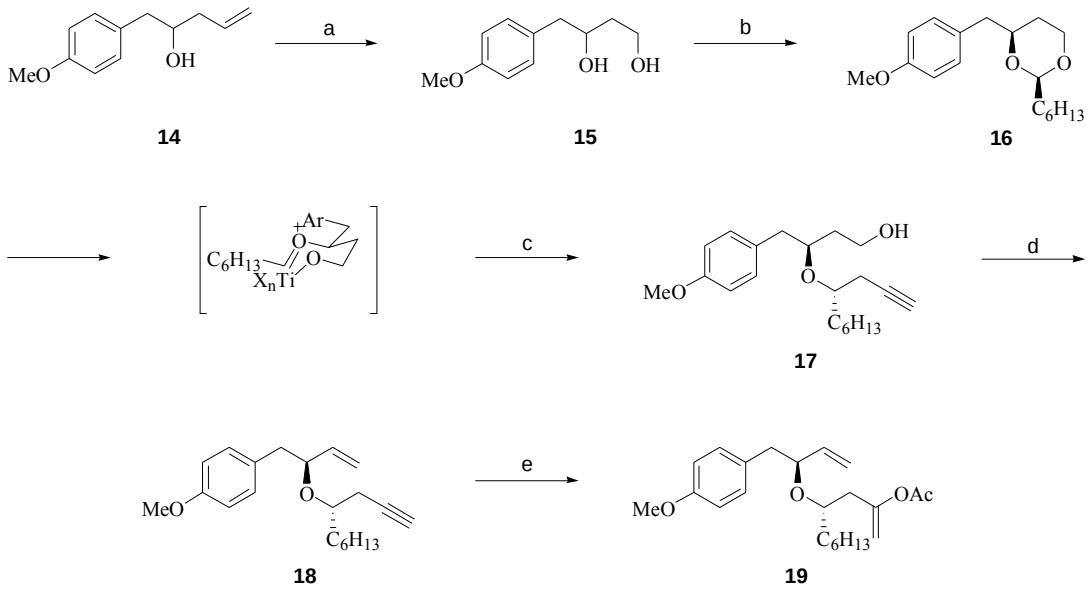
In an effort to explore the range of functional groups tolerated under the cyclization conditions, a substrate (**13**) was prepared with an allyl siloxy ether (**Scheme 14**). The synthesis began with a Horner-Wittig[16] reaction on the aldehyde obtained from oxidation of alcohol **3** to provide α,β-unsaturated ester **10** as a single geometrical isomer. The ester was then reduced to allylic alcohol **11** with DIBAL, followed by silyl protection to yield compound **12**. Substrate **13** was obtained through conversion of the alkyne in **12** to the corresponding enol acetate via the Markovnikov addition of acetic acid in the presence of $[Ru(p\text{-cymene})Cl_2]_2$/tri-2-furylphosphine.[7]



Reagents and Conditions: a) Dess-Martin periodinane, $NaHCO_3$, CH_2Cl_2; b) Triethylphosphonoacetate, NaH, THF, 0 °C (72% 2 steps); c) DIBAL-H, CH_2Cl_2, - 78 °C (49%); d) TBSCl, imidazole, DMAP, CH_2Cl_2 (82%); e) HOAc, Na_2CO_3, $P(fur)_3$, $[Ru(p\text{-cymene})Cl_2]_2$, 80 °C (45%).

Scheme 14: Synthesis of a substrate containing an allylic siloxy ether.

Finally, to determine whether a terminal olefin was sufficient to promote the cyclization reaction, substrate was synthesized (**Scheme 15**). The synthesis began with ozonolysis of known[3] homoallyic alcohol **14** and reduction with sodium borohydride to give diol **15**. The diol (**15**) was then condensed with *n*-heptanal in refluxing benzene to give acetal **16**. Homopropargylic ether **17** was obtained as a single diastereomer via the Lewis acid mediated[8] opening of acetal **16** in the presence of allenyltributyltin. The stereoselectivity of this reaction was consistent with previous results. The primary alcohol was then transformed to the terminal olefin (**18**) following Greico's[17] protocol. Substrate **19** was prepared through the Markovnikov addition of acetic acid to the alkyne in the presence of $[Ru(p\text{-cymene})Cl_2]_2$/trifurylphospine.[7]

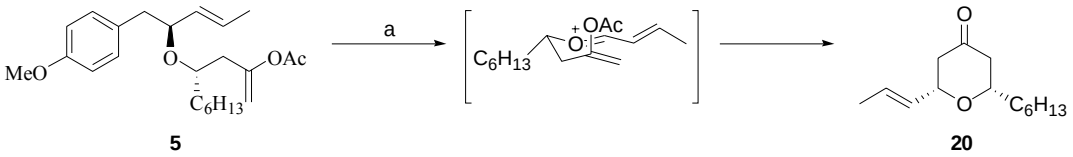


Reagents and Conditions: a) i. O_3(g), CH_2Cl_2, - 78 °C, ii. MeOH, $NaBH_4$, 0 °C – rt (71%); b) heptanal, *p*-TsOH, benzene, reflux (58%); c) allenyltributyltin, $TiCl_4/Ti(iPrO)_4$ (6:5), CH_2Cl_2, - 78 °C (80%); d) i. PhSeCN, PBu_3, THF, 0 °C; ii. H_2O_2, THF, 0 °C – rt (96% 2 steps); f) HOAc, Na_2CO_3, P(fur)$_3$, $[Ru(p\text{-cymene})Cl_2]_2$, 80 °C (62%).

Scheme 15: Synthesis of substrate with a terminal olefin.

II. Cyclization of First Generation Substrates to Exhibit Diastereocontrol

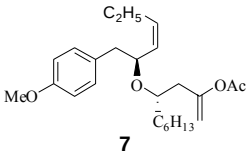
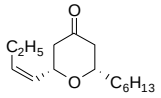
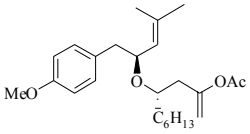
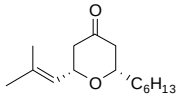
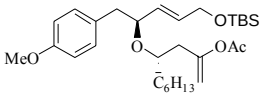
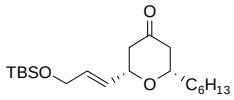
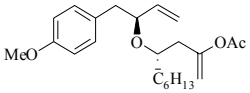
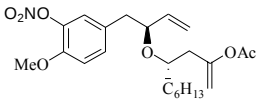
To examine the validity of our first generation substrate design to provide excellent levels of diastereocontrol, substrate **5** was subjected to our standard chemical oxidation conditions.[3] Exposure of **5** to CAN at room temperature resulted in oxidative cleavage and cyclization to form tetrahydropyranone **20** in 80% isolated yield within 20 minutes as a single stereoisomer (**Figure 35**). The selective formation of the *syn*-2,6-stereoisomer was consistent with the formation of a discrete oxoxcarbenium ion intermediate followed by cyclization to give the product with retention of configuration.



Reagents and Conditions: a) $NaHCO_3$ (s), 4Å mol. sieves, DCE; CAN (4 eq) in CH_3CN (80%).

Figure 35: Stereoselective *endo*-cyclization to form a *syn*-2,6-disubstituted tetrahydropyranone.

The efficient cyclization of substrate **5** demonstrated the ability to construct *syn*-2.6-disubstituted tetrahydropyranones. To explore the generality of the first generation substrate design the remaining substrates were subjected to the chemical mediated oxidative cyclization conditions (**Table 7**). The isolation of compound **21** as a single geometric isomer from the cyclization of substrate **7** established that olefin geometry is retained throughout the reaction (entry 1). The *syn*-relationship between the C2 and C6 hydrogens was verified through an enhancement observed in the nOe spectrum. Trisubstituted olefins (entry 2) have also been shown to be effective substrates in the process. Despite the potential for a competitive vinylogous pinacol rearrangement upon oxocarbenium ion formation, allylic silyl ethers (entry 3) are tolerated under the oxidative cyclization conditions. Surprisingly, simple terminal olefins (entry 4) do not sufficiently weaken the benzylic carbon-carbon bond to promote oxocarbenium ion formation and cyclization. Instead, an alternative pathway in which the arene is attack by nitrate occurs to form compound **24** as the only discernible product. Because olefin substitution has a small impact on allylic bond strength, but significantly lowers the oxidation potential of allylic radicals,[18] the importance of E_{pa}(E) in Equation 1 is highlighted.

Entry	Substrate[a]	Product	Yield (%) [b]
1	 **7**	 **21**	70
2	 **9**	 **22**	80
3	 **13**	 **23**	79
4	 **19**	 **24**	19

Reagents and Conditions: A solution of CAN (2-4 eq) in CH_3CN was added to the substrate (1 eq), $NaHCO_3$ (4-9 eq) and powdered 4Å mol. sieves (2 wt eq) in DCE at room temp. [a] All substrates were single isomers. [b] Yields refer to pure isolated material.

Table 7: Exploring the effect of olefin substitution on *endo*-ETIC reactions.

III. Synthesis of Substrates to Generate Non-Stabilized Oxocarbenium Ions

While the first generation of substrates provided excellent levels of stereocontrol, their generality is limited by the need for a stabilized oxocarbenium ion. In order to facilitate cyclization in the absence of the homobenzylic olefin, substrates would have to be designed with weakened carbon-carbon bonds. Previous studies[3] have shown the introduction of methyl groups in the benzylic position leads to sufficient benzylic carbon-carbon bond weakening. Therefore, a

series of substrates were designed with this premise to explore the scope of the diastereoselective carbon-carbon bond forming reactions (**Figure 36**).

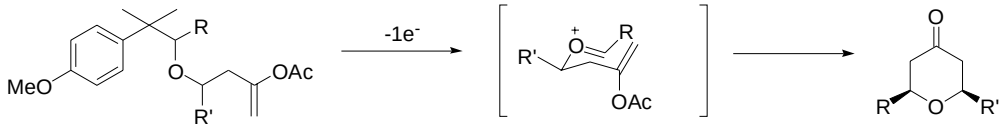
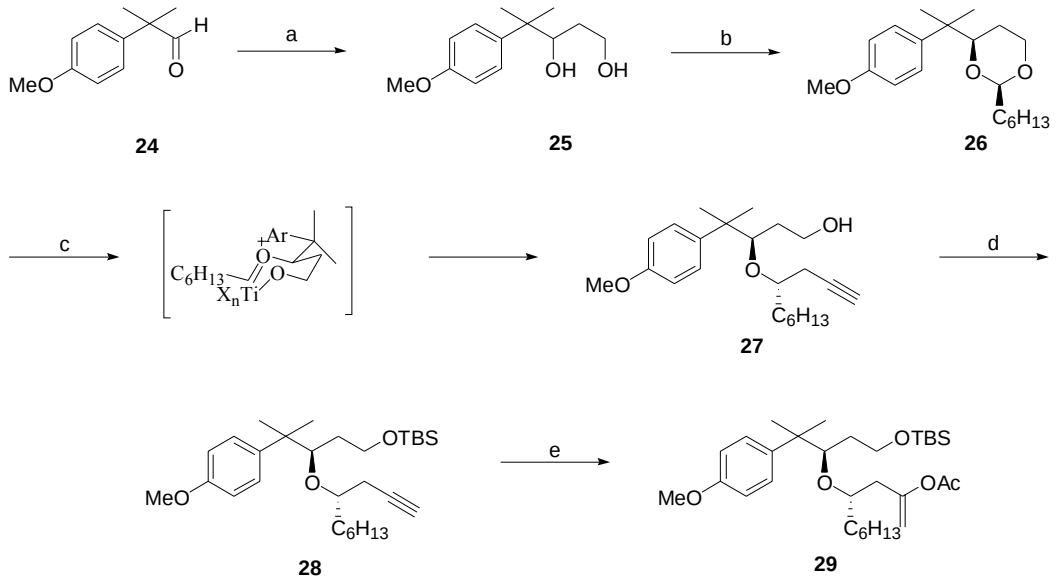


Figure 36: Incorporation of benzylic substituents in the design of *endo*-ETIC substrates.

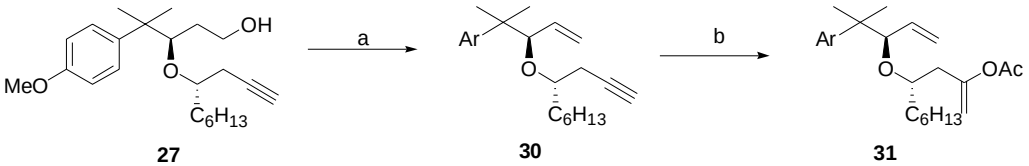
The synthesis of the first substrate (**Scheme 16**) to test the validity of this design began with aldehyde **24** which is readily prepared in gram quantities through a two step sequence.[19] Allylation of aldehyde **24** followed by ozonolysis and reduction with sodium borohydride provided diol **25**. While the allylation was conducted to provide a racemic mixture, enantiopure material can be readily obtained through the use of various nucleophilic chiral allylation reagents.[20] The diol (**25**) was then converted to acetal **26** through acid-mediated condensation in refluxing benzene. Acetal **26** was then subjected to the Lewis acidic cyclic acetal opening conditions in the presence of allenyltributyltin to afford homopropargylic ether **27**. This reaction also proceeded with excellent levels of diasterocontrol, which is consistent with previous opening of this type. The resulting primary alcohol was protected as the silyl ether (**28**), and converted to the enol acetate (**29**).



Reagents and Conditions: a) i. Allyl magnesium bromide, THF, - 78 °C (99.5%); ii. O_3(g), CH_2Cl_2, - 78 °C, iii. MeOH, $NaBH_4$, 0 °C – rt (68%); b) *n*-heptanal, *p*-TsOH, benzene, reflux (80%); c) allenyltributyltin, $TiCl_4$/Ti(*i*PrO)$_4$ (6:5), CH_2Cl_2, - 78 °C (86%); d) TBSCl, imidazole, DMF (85%); e) HOAc, Na_2CO_3, P(fur)$_3$, [Ru(*p*-cymene)Cl_2]$_2$, 80 °C (48%).

Scheme 16: Synthesis of an *endo*-ETIC substrate containing benzylic bond weakening groups.

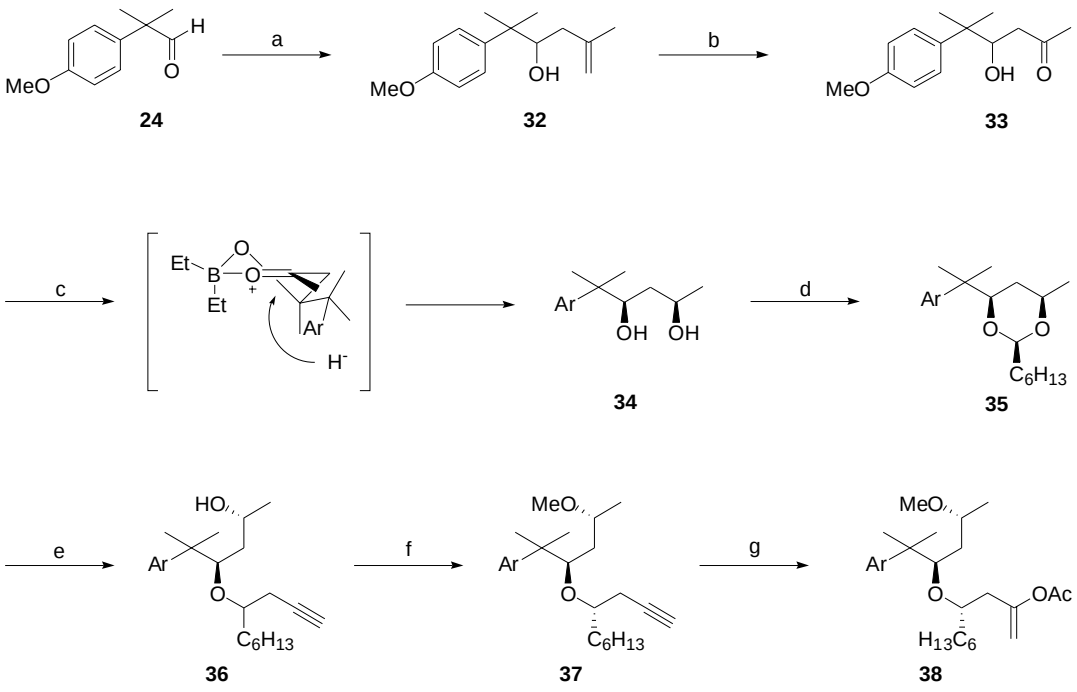
A substrate with a terminal olefin was prepared to examine the extent to which the incorporation of the methyl groups weakened the benzylic carbon-carbon bond (**Scheme 17**). The synthesis began with conversion of primary alcohol **27** to the terminal olefin (**30**) according to Greico's protocol. The resulting compound was then subjected to the ruthenium mediated addition of acetic acid to provide the desired enol acetate **31**.



Reagents and Conditions: a) i. PhSeCN, PBu_3, 0 °C, THF; ii. *m*CPBA, pyr. DHP, CH_2Cl_2 - 78 °C – 0 °C (75%); b) HOAc, Na_2CO_3, P(fur)$_3$, [Ru(*p*-cymene)Cl_2]$_2$, 80 °C (45%).

Scheme 17: Incorporation of a terminal olefin and benzylic weakening groups.

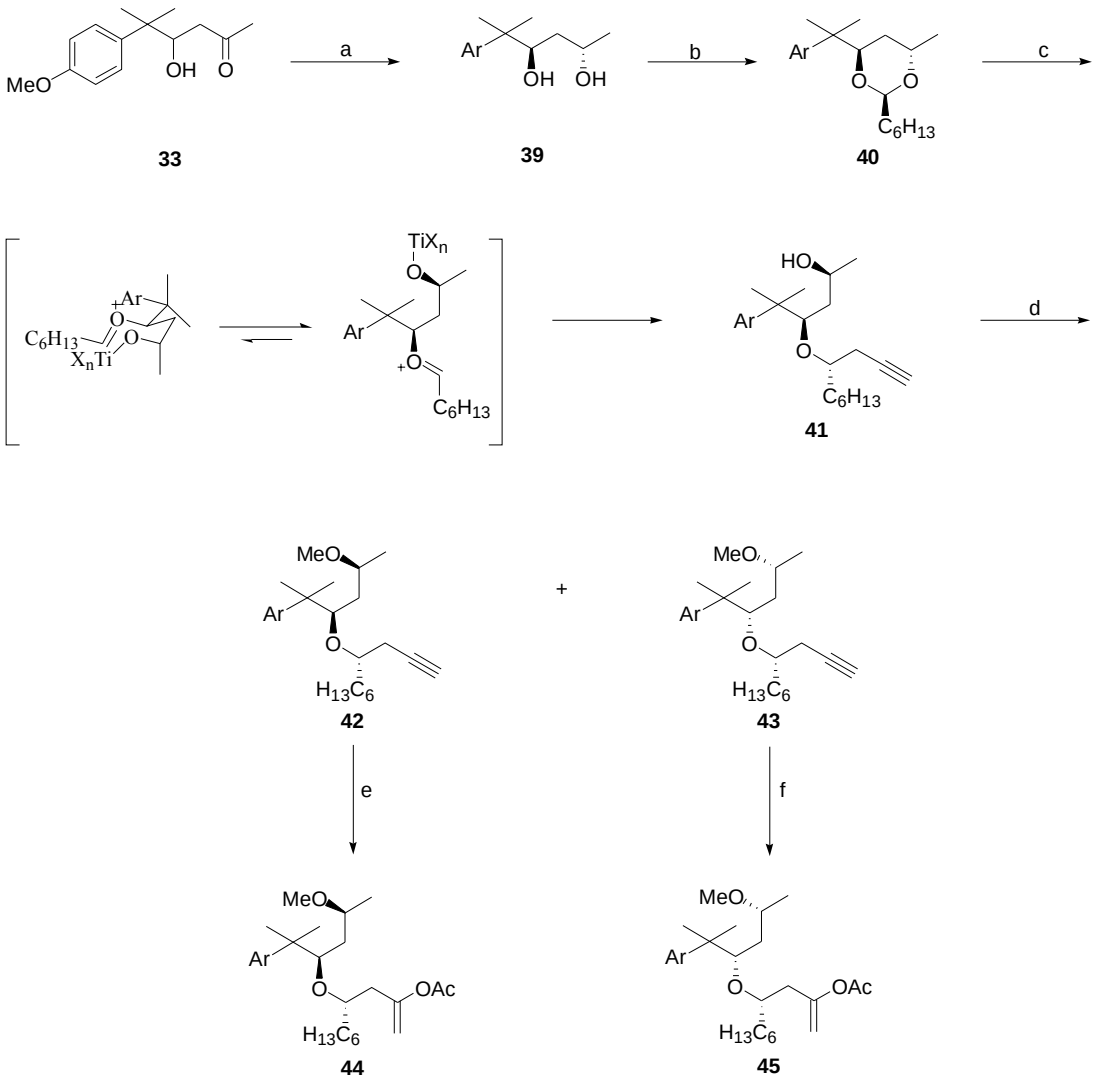
To test the capacity of the reaction to be used in complex molecule synthesis, a substrate was prepared that contained a stereocenter in the side chain (**Scheme 18**). The synthesis began with methallylation of aldehyde **24** to provide homoallyic alcohol **32**. Ozonolysis of the resulting olefin led to β-keto alchol **33**, which was selectively reduced with sodium borohydride in the presence of diethylboron methoxide[21] to give a 15:1 mixture of separable diastereomers in favor of *syn*-1,3-diol **34**. Diol **34** was then condensed with heptanal in refluxing benzene to give acetal **35**. The acetal was then opened with allenyltributyltin in the presence of a mixed titanium Lewis acid to provide **36** as a 3:1 inseparable mixture of diastereomers. Methylation of the resulting alcohol led to a separable mixture of methyl ethers. The major diastereomer, whose structure was defined via literature precedent,[8] (**37**) was then converted to the enol acetate (**38**).



Reagents and Conditions: a) Methallyl lithium, THF, - 78 °C – rt (76%); b) i. O_3(g), CH_2Cl_2, -78°C; ii. PPh_3, - 78 °C – rt (81%); c) Et_2BOMe, $NaBH_4$, THF, - 78 °C (15:1 dr; 76%); d) *n*-heptanal, *p*-TsOH, benzene, reflux (84%); e) allenyltributyltin, $TiCl_4$/Ti(*i*PrO)$_4$ (9:3), CH_2Cl_2, - 78 °C (3:1 dr; 54%); f) NaH, MeI, DMF, 0 °C – rt (38%), g) HOAc, Na_2CO_3, P(fur)$_3$, [Ru(*p*-cymene)Cl_2]$_2$, 80 °C (63%).

Scheme 18: Synthesis of a substrate with a stereocenter in the side chain.

To determine whether incorporation of a stereocenter in the side chain impacted the stereoselectivity of the reaction, the other possible diastereomers were synthesized (**Scheme 19**). The synthesis began with the tetra-*N*-methylammonium triacetoxyborohydride[22] reduction of β-keto alcohol **33** to give *anti*-1,3-diol **39** as the only isolable product. Attempts to condense diol **39** with *n*-heptanal in refluxing benzene under acid catalysis failed to produce the desired acetal. Therefore, diol (**39**) was converted to the bis-trimethylsilyl ether, which upon treatment with TMSOTf in the presence of *n*-heptanal provided acetal **40**.[23] The acetal (**40**) was then subjected to the Lewis acid mediated opening conditions in the presence of allenyltributyltin to afford a 1:1 inseparable mixture of diastereomers (**41**). The lack of stereoselectivity in this reaction is consistent with the oxocarbenium ion existing in the non-ion paired conformation. Opening of the *anti* [1,3] dioxane to give the non-ion paired conformation is believed to result from the strain associated with the equatorial neopentyl group. This strain may be relieved through bond rotations to give an acyclic oxocarbenium ion. The tendacy of this oxocarbenium ion to exist in an extended conformation is consistent with the difficulties associated with acetal formation. Due to the non-ion paired nature of the intermediate oxocarbenium ion, both the *re* and *si* faces are equally accessible to nucleophilic attack. Alkylation of alcohol **41** with methyl iodide afforded a separable mixture of methyl ethers **42** and **43**. The alkynes were then transformed to the corresponding enol acetates **44** and **45**.

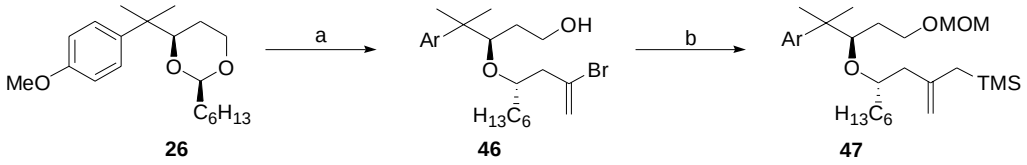


Reagents and Conditions: a) $Me_4NBH(OAc)_3$, CH_3CN:AcOH (2:1), -78 °C – - 20 °C (94%); b) i. TMSCl, imidazole, CH_2Cl_2; ii. TMSOTf, *n*-heptanal, CH_2Cl_2, - 78 °C (70% 2 steps); c) allenyltributyltin, $TiCl_4$/Ti(*i*PrO)$_4$ (6:5), CH_2Cl_2, - 78 °C (98%); NaH, MeI, DMF, 0 °C – rt (69%) e) HOAc, Na_2CO_3, P(fur)$_3$, [Ru(*p*-cymene)Cl_2]$_2$, 80 °C (43%); f) HOAc, Na_2CO_3, P(fur)$_3$, [Ru(*p*-cymene)Cl_2]$_2$, 80 °C (34%).

Scheme 19: Synthesis of the remaining diastereomers containing secondary methyl ethers.

The ability to open the acetal (**26**) with a variety of nucleophiles prompted the synthesis of a substrate containing an allylsilane as the nucleophile (**Scheme 20**). This synthesis began with the Lewis acid-mediated opening of **26** in the presence of 2-bromoallyltrimethylsilane to furnish homoallylic ether **46** with moderate stereocontrol (~2:1). This result is consistent with

the use of a less potent nucleophile in the acetal opening reaction, weaker nucleophiles do not react with the less electophilic ion paired intermediate.[8e] The primary alcohol was then protected as the MOM-ether, and the vinyl bromide was coupled with trimethylsilyl methylmagnesium chloride in the presence of palladium (0) to give substrate **47**.



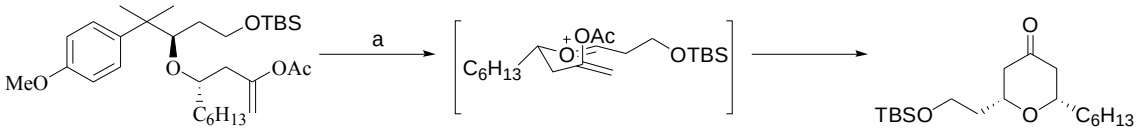
26 **46** **47**

Reagents and Conditions: a) 2-bromoallyltrimethylsilane, $TiCl_4$, CH_2Cl_2, - 78 °C (63%); b) i. MOMCl, *N*-*N*-diisopropyl-*N*-ethyl amine, CH_2Cl_2, reflux (95%); ii. trimethylsilylmethyl magnesium chloride, $Pd(PPh_3)_4$, THF, reflux (64%).

Scheme 20: Synthesis of a substrate with an allylsilane nucleophile.

IV. Cyclization of Non-Stabilized Oxocarbenium Ions

Substrate **29** was subjected to our standard chemical oxidation[3] conditions to test the necessity of a stabilized oxocarbenium ion to obtain efficient and stereoselective cyclization. Within minutes of adding the oxidant (CAN) to the reaction mixture the starting material was consumed, and the desired *syn*-2,6-disubstituted tetrahydropyranone (**48**) was obtained in 88% yield as a single stereoisomer (**Figure 37**). Validation of the *syn*-relationship between the C2 and C6 protons was determined through the strong correlation observed in the NOESY spectrum. The reactivity exhibited by **29** demonstrates that conjugated oxocarbenium ion intermediates are not required for efficient *endo*-cyclization to occur, and that substrates containing bond weaking groups in the benzylic position are well-suited for this reaction.

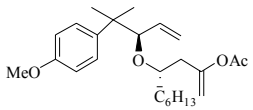
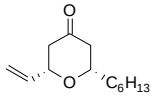
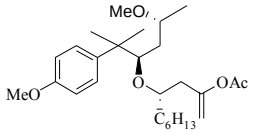
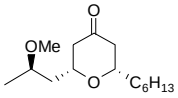
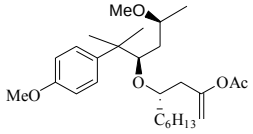
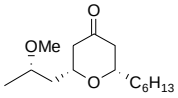
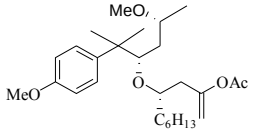
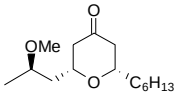
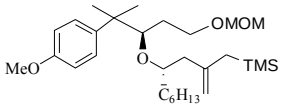
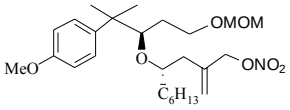


29 **48**

Reagents and Conditions: a) $NaHCO_3$ (s), 4Å mol. sieves, DCE; CAN (4 eq) in CH_3CN (88%).

Figure 37: Cyclization of a non-stabilized oxocarbenium ion.

To test the overall efficiency of this second generation design, substrates **31**, **38**, **44**, **45** and **47** were subjected to our chemical-mediated oxidation conditions (**Table 8**).[3] The smooth formation of compound **49** in 70% yield (entry 1), reinforces the benefit of placing bond activating groups in the benzylic position. By introducing bond weakening groups in the benzylic position, a simple terminal olefin may be tolerated under the reaction conditions. The excellent efficiency exhibited by substrates **38**, **44** and **45** (entries 2, 3 and 4) to provide single stereoisomers confirms that secondary ethers do not inhibit the reaction and have no impact on the stereoselectivity. In fact, these substrates showed the greatest efficiency of all the compounds tested, with yields in excess of 95% for each cyclization. Isolation of compound **50** from the cyclization of both substrates **38** and **45** demonstrates the homobenzylic stereocenter is inconsequential to the stereochemical outcome of the reaction. Of particular note, the functionality of compound **50** maps well onto the C2 – C10 portion of the marine macrolide leucascandrolide A.[6a,24]

Entry	Substrate[a]	Product	Yield (%) [b]
1	 **31**	 **49**	70
2	 **38**	 **50**	100
3	 **44**	 **51**	97
4	 **45**	 **50**	96
5	 **47**	 **52**	75

Reagents and Conditions: A solution of CAN (2-4 eq) in CH_3CN was added to the substrate (1 eq), $NaHCO_3$ (4-9 eq) and powdered 4Å mol. sieves (2 wt eq) in DCE at room temp. [a] All substrates were single isomers. [b] Yields refer to pure isolated material.

Table 8: Exploring the scope of *endo*-substates containing bond activating groups.

An attempt to form a *syn*-2,6-methylene tetrahydropyran from the cyclization of substrate **47** resulted in oxidation of the allylsilane to form nitrate **52** (**Table 8**, entry 5). Based on their expected oxidation potentials, the arene is predicted to be oxidized in preference to the allylsilane.[25] This result is consistent with oxidation of a similarly appendend allylsilane, and suggests an antenna effect[26] is resulting is intramolecular electron transfer to give the allylsilane

centered radical cation. The radical cation rapidly losses a trimethylsilyl cation and the resulting allyl radical is futher oxidized to the allyl cation, which reacts with a nitrate ion to give compound **52**. The unexpected reactivity exhibited by this substrate supports the hypothesis that oxidation of a previous allylsilane nucleophile (**Table 6**, entry 1) was inhibited by the protective induction through the allylic ether.

2.3. Conclusion

A mild and efficient method has been developed for the stereoselective formation of carbon-carbon bonds through 6-*endo*-ETIC reactions. The excellent diastereocontrol exhibited in these reactions is attributed to the strong tendency of 6-*endo*-cyclizations to proceed through well defined chairlike transition states. These reactions proceed within minutes at room temperature to provide good to excellent yields of *syn*-2,6-disubstituted tetrahydropyranones, which are useful intermediates in the synthesis of biologically active natural products.

The challenge of synthesizing substrates containing an ether linkage between two secondary carbons was accomplished through the Lewis acid-mediated opening of a cyclic acetal in the presence of allenyltributyltin. This method provided excellent levels of stereochemical control, and allowed for the efficient synthesis of substrates as single diastereomers. To the best of our knowledge, this is the first example of a diastereoselective opening of a cyclic acetal using an allenylstannane. The homopropargylic ethers obtained from the acetal opening can be readily converted to enol acetates via a ruthenium-catalyzed Markovnikov addition of acetic acid to quickly obtain the desired cyclization substrates.

2.4. Experimental

General Experimental:

All reactions were performed in oven or flame dried glassware under a nitrogen atmosphere with magnetic stirring unless otherwise noted.

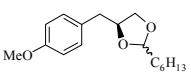
Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometers at 300 MHz and 75 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak or the internal standard tetramethylsilane were used as reference values. For ^{1}H NMR: $CDCl_3$ = 7.27 ppm, TMS = 0.00 ppm. For ^{13}C NMR: $CDCl_3$ = 77.23, TMS = 0.00. For proton data: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; ddt = doublet of doublet of triplets; br = broad; m = multiplet; app t = apparent triplet; app q = apparent quartet; app p = apparent pentet.

High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Gygnus 100 spectrometer.

Analytical thin layer chromatography (TLC) was performed on E. Merck pre-coated (25 nm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash column chromatography was preformed using ICN SiliTech 32-63 60Å silica gel. Reagent grade ethyl acetate and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. Reagent grade methylene chloride (CH_2Cl_2), dicholoroethane ($C_2H_4Cl_2$), acetonitrile (CH_3CN), benzene and toluene were distilled from CaH_2. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were dried by passing through aluminum drying column. Dimethoxyethane (DME) was distilled from Na/benzophenone. Anhydrous N,N-

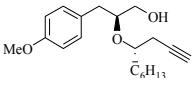
dimthylformamide (DMF), methanol (MeOH), dimethyl sulfoxide (DMSO) were purchased from Aldrich and used as is.

2-Hexyl-4-(4-methoxybenzyl)-[1,3]dioxolane (2)



To 3-(4-methoxyphenyl)propane-1,2-diol[10] (3.32 g, 18.25 mmol) in benzene (30 mL) was added freshly distilled heptaldehyde (2.08 g, 18.25 mmol, 2.54 mL) and PTSA (10 mg). The reaction mixture was then warmed to reflux and stirred for 15 h, while removing water via a Dean-Stark trap. After cooling to room temperature, the reaction was neutralized by the addition of Et_3N (2 mL) and the solvent was removed under reduced pressure. The resulting residue was then purified via flash column chromatography (5% EtOAc in Hexanes) to provide the desired product (4.27 g, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.14 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 5.02 (t, *J* = 4.8 Hz, 0.35H), 4.91 (t, *J* = 4.7 Hz, 0.65H), 4.28 (p, *J* – 6.7 Hz, 0.48H), 3.84 (dd, *J* = 7.7, 7.0 Hz, 0.74H), 3.78 (s, 3H), 3.62 (dd, *J* = 7.7, 6.2 Hz, 0.73H), 3.55 (appt t, *J* = 4.3 Hz, 0.45H), 2.96 (dd, *J* = 13.8, 6.3 Hz, 1H), 2.73 (dd, *J* = 13.8, 7.0 Hz, 1H), 1.73-1.66 (m, 2H), 1.46-1.42 (m, 2H), 1.33-1.29 (m, 8H), 0.93-0.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 129.9, 129.2, 113.6, 104.7, 103.9, 76.3, 69.6, 68.8, 54.8, 38.8, 38.2, 33.9, 31.4, 28.9, 23.6, 22.2, 13.8; IR (neat) 2929, 2858, 1612, 1513, 1441, 1248, 1037 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{26}O_3$ (M^+) 278.1882, found 278.1883.

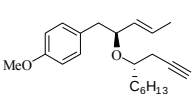
3-(4-Methoxyphenyl)-2-(1-prop-2-ynylheptyloxy)-propan-1-ol (3)



To 2-hexyl-4-(4-methoxybenzyl)-[1,3]dioxolane (3.00 g, 10.7 mmol) and allenyltributyl tin (4.25 g, 12.9 mmol, 3.84 mL) in CH_2Cl_2 (50 mL) at -78 °C was added $TiCl_4$ (2.44 g, 12.9 mmol, 1.41 mL) rapidly. The reaction was then stirred at -78 °C for 15 min and methanol (2 mL) was added slowly. The mixture was then poured into water and

extracted with EtoAc (2x). The combined organic layers were then washed with water and 10% aqueous KF, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (15-20% EtOAc in Hexanes) to provide the desired product (2.86 g, 84%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 3.79 (s, 3H), 3.67-3.60 (m, 2H), 3.55-3.37 (m, 2H), 2.89 (dd, *J* = 13.7, 5.9 Hz, 1H), 2.73 (dd, *J* = 13.7, 7.1 Hz, 1H), 2.23 (dd, *J* = 5.7, 2.6 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 1H), 1.85-1.81 (m, 1H), 1.70-1.56 (m, 2H), 1.30-1.28 (m, 10H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.2, 130.5, 130.3, 113.9, 81.4, 80.0, 70.0, 63.7, 55.3, 37.3, 34.3, 31.8, 29.4, 25.5, 24.5, 22.7, 14.2; IR (neat) 3453, 3308, 2929, 2857, 1612, 1512, 1465, 1247, 1038 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{30}O_3$ (M^+) 318.2195, found 318.2198.

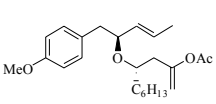
1-Methoxy-4-[2-(1-prop-2-ynylheptyloxy)-pent-3-enyl]-benzene (4)



To 3-(4-methoxyphenyl)-2-(1-prop-2-ynylheptyloxy)-propan-1-ol (1.00 g, 3.14 mmol) in CH_2Cl_2 (10 mL) at 0°C was added $NaHCO_3$ (2.63 g, 31.4 mmol). The mixture was then stirred for 10 min and DMPI (1.73 g, 4.08 mmol) was added. The reaction mixture then slowly warmed to room temperature and stirred for 1.5 h, filtered to remove insoluble materials and concentrated under reduced pressure. The resulting residue was then taken up in DME (5 mL) and 5-ethylsulfonyl-1-phenyl-1*H*-tetrazole (971.0 mg, 4.08 mmol) was added. The mixture was then cooled to -60 °C and KHMDS (919.0 mg, 4.61 mmol) in DME (10 mL) was added over 45 min via syringe pump. The reaction was then stirred at -60 °C for 12 h and the quenched by the addition of water while warming to room temperature. The mixture was then extracted with EtOAc (2x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (3% EtOAc in Hexanes) to provide

the desired product (191.8 mg, 19%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 5.50 (dq, *J* = 15.3, 6.4 Hz, 1H), 5.32 (dd, *J* = 15.3, 8.3 Hz, 1H), 3.86 (q, *J* = 7.5 Hz, 1H), 3.79 (s, 3H), 3.45-3.39 (m, 1H), 2.83 (dd, *J* = 13.7, 7.0 Hz, 1H), 2.66 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.25-2.12 (m, 2H), 1.93 (t, *J* = 2.5 Hz, 1H), 1.67 (d, *J* = 6.2 Hz, 3H), 1.56-1.41 (m, 4H), 1.29-1.27 (m, 8H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 131.9, 130.8, 130.6, 113.2, 81.8, 80.4, 74.0, 69.5, 55.1, 41.8, 34.5, 31.8, 29.1, 25.3, 23.5, 22.6, 17.6, 14.1; IR (neat) 3310, 2931, 2857, 1512, 1247, 1039 cm^{-1}; HRMS (EI) calcd for $C_{22}H_{32}O_2$ (M^+), found 328.2393.

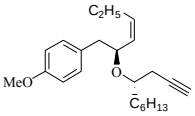
Acetic acid-3-[1-(4-methoxybenzyl)-but-2-enyloxy]-1-methylenenonyl ester (5)



To 1-methoxy-4-[2-(1-prop-2-ynylheptyloxy)-pent-3-enyl]-benzene (100.0 mg, 0.30 mmol) in toluene (3 mL) was added Na_2CO_3 (4.00 mg, 0.04 mmol) and acetic acid (36.0 mg, 0.60 mmol, 35.0 μL). The mixture was then stirred at room temperature for 10 min and [Ru(*p*-cymene)Cl_2]$_2$ (6.0 mg, 0.012 mmol) and 2-trifurylphosphine (4.0 mg, 0.024 mmol). The reaction mixture was then warmed to 80 °C and stirred for an additional 15 h. The mixture was then cooled to room temperature and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (5% EtOAc in Hexanes) to provide the desired product (48.9 mg, 42%): $[\alpha]_D^{20}$ = -8.3 (*c* = 1.4 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.0 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 5.44 (dq *J* = 15.3, 6.1 Hz, 1H), 5.28 (ddd, *J* 15.3, 8.1, 1.3 Hz, 1H), 4.72 (s, 1H), 4.65 (s, 1H), 3.85-3.78 (m, 1H), 3.78 (s, 3H), 3.44 (p, *J* = 6.3 Hz, 1H), 2.83 (dd, *J* = 13.5, 6.3 Hz, 1H), 2.63 (dd, *J* = 13.5, 6.7 Hz, 1H), 2.33 (dd, *J* = 14.7, 5.5 Hz, 1H), 2.20 (dd, *J* = 14.7, 6.6 Hz, 1H), 2.11 (s, 3H), 1.65 (dd, *J* = 6.1, 1.0 Hz, 2H), 1.48-1.39 (m, 2H), 1.28-1.25 (m, 8H), 0.89 (t, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 157.8, 153.7, 132.4, 103.6, 130.3, 128.3, 113.3, 103.4, 80.2,

72.8, 55.1, 41.7, 38.7, 34.9, 31.8, 29.1, 25.4, 22.6, 21.0, 17.5, 14.0; IR (neat) 2930, 2857, 1758, 1512, 1369, 1039 cm^{-1}; HRMS (EI) calcd for ($C_{24}H_{36}O_4$) 388.2613 found 388.26022.

1-Methoxy-4-[2-(1-prop-2-ynylheptyloxy)hex-3-enyl]benzene (6)

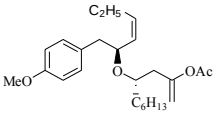


To 3-(4-methoxyphenyl)-2-(1-prop-2-ynylheptyloxy)-propan-1-ol (1.50 g, 4.7 mmol) in CH_2Cl_2 (15 mL) at 0°C was added $NaHCO_3$ (3.94 g, 47.0 mmol). The mixture was then stirred for 10 min and DMPI (2.60 g, 6.10 mmol) was added. The reaction mixture then slowly warmed to room temperature and stirred for 1.5 h, filtered to remove insoluble materials and concentrated under reduced pressure and the crude aldehyde was used without further purification.

To *n*-propyltriphenylphosphonium bromide (913.1 mg, 2.37 mmol), dried via azeotroping with benzene (3x), in THF (10 mL) at – 78 °C was addede LHMDS (2.37 mL, 2.37 mmol) dropwise. The slurry was then warmed to room temperature and the mixture turned bright red. The mixture was then cooled to – 78 °C and the crude aldehyde (500.0 mg, 1.58 mmol) was added. The reaction mixture was then slowly warmed to room temperature and stirred for an additional 15 h, and was quenched by the addition of water. The mixture was then extracted with EtOAc (2x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (5% EtOAc in Hexanes) to provide the desired product (254.2 mg, 47%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.5 Hz, 2H), 6.78 (d, *J* = 8.5 Hz, 2H), 5.45 (dt, *J* = 10.9, 7.3 Hz, 1H), 5.19 (dd, *J* = 10.9, 9.5 Hz, 1H), 4.30 (q, *J* = 7.9 Hz, 1H), 3.78 (s, 3H), 3.41 (p, *J* = 6.1 Hz, 1H), 2.87 (dd, *J* = 13.3, 5.8 Hz, 1H), 2.57 (dd, *J* = 13.3, 7.6 Hz, 1H), 2.34 (dd, *J* = 14.7, 8.9 Hz, 1H), 2.27 (dd, *J* = 14.7, 6.4 Hz, 1H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.86 (dq, *J* = 14.7, 7.1 Hz, 1H), 1.73 (dq, *J* = 14.7, 7.4 Hz, 1H), 1.43-.134 (m, 2H), 1.33-

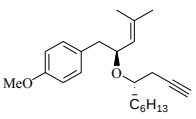
1.25 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H), 0.74 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 134.7, 130.5, 130.1, 129.9, 113.6, 81.3, 75.4, 67.1, 55.7, 41.8, 38.7, 35.3, 31.8, 29.2, 25.5, 22.5, 21.3, 20.8, 14.1.

Acetic acid-3-[1-(4-methoxybenzyl)-pent-2-enyloxy]-1-methylenenonyl ester (7)



To 1-methoxy-4-[2-(1-prop-2-ynylheptyloxy)hex-3-enyl]benzene (243.0 mg, 0.71 mmol) in toluene (3 mL) was added Na_2CO_3 (12.0 mg, 0.11 mmol) and acetic acid (85.0 mg, 1.40 mmol, 85.0 μL). The mixture was then stirred at room temperature for 10 min and [Ru(*p*-cymene)Cl_2]$_2$ (17.3 mg, 0.028 mmol) and tri-2-furyl phosphine (13.1 mg, 0.056 mmol) were added. The reaction mixture was then warmed to 80 °C and stirred for an additional 15 h. The mixture was then cooled to room temperature and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (5% EtOAc in Hexanes) to provide the desired product (182.5 mg, 64%): $[\alpha]_D^{20}$ = -7.4 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.0, (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 5.46 (dt, J = 10.9, 7.3 Hz, 1H), 5.19 (dd, J = 10.9, 9.5 Hz, 1H), 4.76 (s, 1H), 4.71 (s, 1H), 4.30 (q, J = 7.9 Hz, 1H), 3.78 (s, 3H), 3.41 (p, J = 6.1 Hz, 1H), 2.87 (dd, J = 13.3, 5.8 Hz, 1H), 2.57 (dd, J = 13.3, 7.6 Hz, 1H), 2.34 (dd, J = 14.7, 8.9 Hz, 1H), 2.27 (dd, J = 14.7, 6.4 Hz, 1H), 2.11 (s, 3H), 1.86 (dq, J = 14.7, 7.1 Hz, 1H), 1.73 (dq, J = 14.7, 7.4 Hz, 1H), 1.43-1.34 (m, 2H), 1.33-.125 (m, 8H), 0.88 (t, J = 6.9 Hz, 3H), 0.74 (t, J = 7.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 169.1, 158.0, 153.8, 134.5, 130.7, 130.5, 130.2, 113.5, 103.8, 74.6, 73.7, 55.3, 41.7, 38.9, 35.1, 31.9, 29.3, 25.5, 22.7, 21.2, 20.9, 14.2; IR (neat) 2931, 2857, 1758, 1665, 1612, 1464, 1246, 1196, 1038 cm^{-1}; HRMS (EI): calcd for $C_{25}H_{38}O_4$ (M^+) 402.2770, found 402.2754.

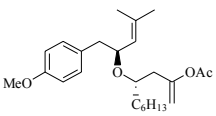
1-Methoxy-4-[4-methyl-2-(1-prop-2-ynyl-heptyloxy)pent-3-enyl]benzene (8)



To 3-(4-methoxyphenyl)-2-(1-prop-2-ynylheptyloxy)-propan-1-ol (689.0 mg, 2.16 mmol) in CH_2Cl_2 (5 mL) at 0°C was added $NaHCO_3$ (1.81 g, 21.6 mmol). The mixture was then stirred for 10 min and DMPI (1.19 g, 2.8 mmol) was added. The reaction mixture then slowly warmed to room temperature and stirred for 1.5 h, filtered to remove insoluble materials and concentrated under reduced pressure and the crude aldehyde was used without further purification.

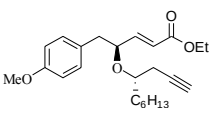
To *i*-propyltriphenylphosphonium iodide (553.0 mg, 1.27 mmol), dried via azeotroping with benzene (3x), in THF (5 mL) at 0 °C was added *n*-butyl lithium (0.79 mL, 1.27 mmol) dropwise. The mixture was then stirred at 0 °C for an additional 20 minutes and the crude aldehyde (270.0 mg, 0.85 mmol) was added in THF (0.5 mL). The reaction mixture was then slowly warmed to room temperature and stirred for an additional 14 h. The reaction was then quenched by the addition of saturated NH_4Cl (aq) and extracted with EtOAc (3x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtere and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (4% EtOAc in Hexanes) to give the desired product (28.4 mg, 10%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.4 Hz, 2H), 6.80 (d, *J* = 8.4 Hz, 2H), 5.06 (d, *J* = 8.3 Hz, 1H), 4.23 (q, *J* = 6.7 Hz, 1H), 3.79 (s, 3H), 3.42-3.41 (m, 1H), 2.86 (dd, *J* = 13.3, 6.3 Hz, 1H), 2.59 (dd, *J* = 13.6, 6.9 Hz, 1H), 2.28-2.18 (m, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.69 (s, 3H), 1.49-1.47 (m, 2H), 1.41 (s, 3H), 1.30-1.18 (m, 8H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 157.7, 135.1, 130.6, 126.1, 113.2, 81.9, 75.7, 74.1, 69.4, 55.1, 41.7, 34.7, 31.8, 29.1, 25.7, 25.3, 23.8, 22.6, 18.1, 14.1.

Acetic acid-3-[1-(4-methoxybenzyl)-3-methylbut-2-enyloxy]-1-methylenenonyl ester (9)



To 1-methoxy-4-[4-methyl-2-(1-prop-2-ynyl-heptyloxy)pent-3-enyl]benzene (63.0 mg, 0.18 mmol) in toluene (2 mL) was added Na_2CO_3 (2.5 mg, 0.48 mmol) and acetic acid (18.0 mg, 0.36 mmol, 17.0 μL). The mixture was then stirred at room temperature for 10 min and [Ru(*p*-cymene)Cl_2]$_2$ (3.8 mg, 0.007 mmol) and tri-2-furylphosphine (2.7 mg, 0.014 mmol) were added. The reaction mixture was then warmed to 80 °C and stirred for an additional 16 h. The mixture was then cooled to room temperature and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (4% EtOAc in Hexanes) to provide the desired product (28.1 mg, 39%): $[\alpha]_D^{20}$ = -7.7 (*c* = 0.7 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.07 (d, *J* = 8.6 Hz, 2H), 6.78 (d, *J* = 8.6 Hz, 2H), 5.02 (d, *J* = 9.3 Hz, 1H), 4.75 (s, 1H), 4.69 (s, 1H), 4.23-4.16 (m, 1H), 3.78 (s, 3H), 3.40 (p, *J* = 5.9 Hz, 1H), 2.84 (dd, *J* = 13.3, 5.9 Hz, 1H), 2.55 (dd, *J* = 13.3, 7.4 Hz, 1H), 2.37 (dd, *J* = 14.6, 5.6 Hz, 1H), 2.24 (dd, *J* = 14.6, 6.5 Hz, 1H), 2.11 (s, 3H), 1.67 (s, 3H), 1.48-1.47 (m, 2H), 1.37 (s, 3H), 1.30-1.18 (m, 8H), 0.89 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 168.7, 157.9, 153.8, 134.7, 130.9, 130.8, 126.6, 113.7, 103.4, 75.6, 73.2, 55.2, 41.7, 38.8, 29.2, 25.6, 25.3, 22.6, 21.0, 17.9, 14.0; IR (neat) 2929, 2856, 1758, 1512,1052 cm^{-1}; MS: m/z(%): 281 (12) [$C_{17}H_{29}O_3^+$].

5-(4-Methoxyphenyl)-4-(1-prop-2-ynyl-heptyloxy)pent-2-enoic acid ethyl ester (10)

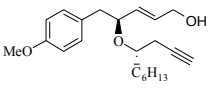


To 3-(4-methoxyphenyl)-2-(1-prop-2-ynylheptyloxy)-propan-1-ol (689.0 mg, 2.16 mmol) in CH_2Cl_2 (5 mL) at 0°C was added $NaHCO_3$ (1.81 g, 21.6 mmol). The mixture was then stirred for 10 min and DMPI (1.19 g, 2.8 mmol) was added. The reaction mixture then slowly warmed to room temperature and stirred for 1.5 h, filtered to remove

insoluble materials and concentrated under reduced pressure and the crude aldehyde was used without further purification.

To a suspension of NaH (47.0 mg, 1.18 mmol) in THF (2.5 mL) at 0 °C was added triethylphosphonoacetate (265.0 mg, 1.18 mmol) dropwise. The mixture was then stirred at 0 °C for 45 minutes and the crude aldehyde (250.0 mg, 0.79 mmol) was added dropwise in THF (0.5 mL). The reaction mixture was then slowly warmed to room temperature and stirred for an additional 16 hours. The reaction was then quenched by the addition of water and extracted with EtOAc (2x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (10% EtOAc in Hexanes) to provide the desired product (220.5 mg, 72%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, *J* = 8.6 Hz, 2H), 6.86-6.77 (m, 3H), 5.88 (dd, *J* = 15.7, 1.0 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 3.79 (s, 3H), 3.38 (p, *J* = 6.2 Hz, 1H), 2.88 (dd, *J* = 13.7, 7.0 Hz, 1H), 2.73 (dd, *J* = 13.7, 6.1 Hz, 1H), 2.17-2.15 (m, 2H), 1.95 (t, *J* = 2.6 Hz, 1H), 1.56-1.50 (m 2H), 1.36-1.26 (m, 10H), 0.88 (t, *J* = 5.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 158.2, 148.3, 130.7, 129.6, 122.2, 113.8, 81.2, 79.1, 75.9, 69.8, 60.3, 55.1, 41.1, 34.4, 31.7, 29.6, 25.0, 23.6, 22.5, 14.1, 14.0; IR (neat) 3293, 2931, 2857, 1720, 1513, 1248, 1037 cm^{-1}.

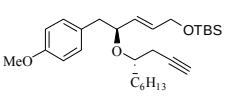
5-(4-Methoxyphenyl-4-(1-prop-2-ynyl-heptyloxy)pent-2-en-1-ol (11)



To 5-(4-methoxyphenyl)-4-(1-prop-2-ynyl-heptyloxy)pent-2-enoic acid ethyl ester (192.0 mg, 0.49 mmol) in CH_2Cl_2 (2 mL) at – 78 °C was added DIBAL (1.09 mL, 1.09 mmol) dropwise. The reaction was ten stirred at – 78 °C for 30 minutes and quenched by the addition of saturated Na,K-tartrate (aq). The mixture was then stirred vigorously for 1h at room temperature and the organic layer was separated. The aqueous layer

was then extracted with CH_2Cl_2 (2x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (25% EtOAc in Hexanes) to furnish the desired product (84.2 mg, 49%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.69 (dt, *J* = 15.6, 4.9 Hz, 1H), 5.57 (dd, *J* = 15.6, 7.3 Hz, 1H), 4.11 (d, *J* = 4.9 Hz, 2H), 3.98 (q, *J* = 6.8 Hz, 1H), 3.79 (s, 3H), 3.45-3.40 (m, 1H), 2.86 (dd, *J* = 13.6, 6.9 Hz, 1H), 2.68 (dd, *J* = 13.6, 6.2 Hz, 1H), 2.18-2.13 (m, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.62-1.51 (m, 2H), 1.28-1.26 (m, 8H), 0.89 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 132.3, 131.7, 130.6, 130.4, 113.5, 81.6, 79.6, 74.9, 69.6, 62.9, 55.2, 41.7, 4.5, 31.8, 29.2, 25.3, 23.6, 22.6, 14.1.

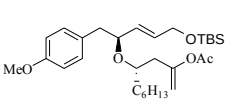
tert-Butyl-[5-(4-methoxyphenyl)-4-(1-prop-2-ynylheptyloxy)pent-2-enyloxy]dimethylsilane (12)



To 5-(4-methoxyphenyl-4-(1-prop-2-ynyl-heptyloxy)pent-2-en-1-ol (84.0 mg, 0.24 mmol) in DMF at 0 °C was added imidazole (35.0 mg, 0.52 mmol). The mixture was then stirred at 0 °C for 5 minutes and TBSCl (40.0 mg, 0.26 mmol) and DMAP (small crystal) were added. The reaction mixture was then slowly warmed to room temperature over 12 hours and quenched by the addition of water. The mixture was then extracted with EtOAc (2x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (5% EtOAc in Hexanes) to give the desired product (89.7 mg, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.5 Hz, 2H), 6.80 (d, *J* = 8.5 Hz, 2H), 5.58-5.56 (m, 2H), 4.13 (d, *J* = 2.2 Hz, 2H), 3.96 (q, *J* = 6.4 Hz, 1H), 3.79 (s, 3H), 3.45-3.41 (m, 1H), 2.85 (dd, *J* = 13.6, 7.0 Hz, 1H), 2.68 (dd, *J* = 13.6, 5.9 Hz, 1H), 2.17-2.12 (m, 2H),

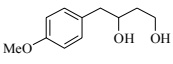
1.93 (t, J = 1.3 Hz, 1H), 1.60-1.50 (m, 2H), 1.28-1.25 (m, 8H), 0.90 (s, 9H), 0.90-0.86 (m, 3H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 132.2, 130.7, 130.3, 113.4, 81.8, 79.9, 74.7, 69.7, 63.0, 55.2, 41.9, 34.6, 31.9, 29.4, 26.0, 25.5, 23.6, 22.7, 18.4, 14.2, -5.1; IR (neat) 3312, 2929, 2856, 1612, 1512, 1248, 836 cm^{-1}.

Acetic acid-3-[4-(*tert*-butyldimethylsilanyloxy)-1-(4-methoxybenzyl)but-2-enyloxy]-1-methylenenonyl ester (13)



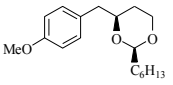
To *tert*-butyl-[5-(4-methoxyphenyl)-4-(1-prop-2-ynylheptyloxy)pent-2-enyloxy]dimethylsilane (89.7 mg, 0.195 mmol) in toluene (2 mL) was added Na_2CO_3 (3.3 mg, 0.031 mmol) and acetic acid (23.0 mg, 0.39 mmol, 20.0 μL). The mixture was then stirred at room temperature for 10 min and [Ru(*p*-cymene)Cl_2]$_2$ (4.0 mg, 0.007 mmol) and tri-2-furylphosphine (3.0 mg, 0.014 mmol) were added. The reaction mixture was then warmed to 80 °C and stirred for an additional 15 h. The reaction was then cooled to room temperature and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (5% EtOAc in Hexanes) to provide the desired product (45.4 mg, 45%): $[\alpha]_D^{20}$ = -7.5 (c = 0.5 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.09 (d, J = 8.6, Hz, 2H), 6.79 (d, J = 8.6 Hz, 2H), 5.58-5.47 (m, 2H), 4.72 (s, 1H), 4.64 (s, 1H), 4.12 (d, J = 2.8 Hz, 2H), 3.95 (app q, J = 6.6 Hz, 1H), 3.78 (s, 3H), 3.42 (p, J = 5.7 Hz, 1H), 2.83 (dd, J = 13.5, 6.5 Hz, 1H), 2.65 (dd, J = 13.5, 6.5 Hz, 1H), 2.32 (dd, J = 14.7, 5.5 Hz, 1H), 2.21 (dd, J = 14.7, 6.4 Hz, 1H), 2.11 (s, 3H), 1.47-1.37 (m, 2H), 1.30-1.25 (m, 8H), 0.90 (s, 9H), 0.91-0.89 (m, 3H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 168.8, 157.9, 153.7, 132.2, 130.6, 130.5, 113.4, 103.4, 98.2, 79.6, 73.5, 62.9, 55.1, 46.8, 41.8, 38.4, 34.9, 31.8, 29.3, 25.8, 25.4, 22.6, 21.0, 20.6, 18.3, 14.0, -5.2; IR (neat) 2954, 2929, 2856, 1758, 1512, 1463, 1248, 1196, 1108 cm^{-1}; HRMS (EI): calcd for $C_{26}H_{41}O_5Si$ (M^+ - C_4H_9) 461.2723, found 461.2718.

4-(4-Methoxyphenyl)butane-1,3-diol (15)



To 1-(4-methoxyphenyl)pent-4-en-2-ol (5.00 g, 26.0 mmol) in CH_2Cl_2 (50 mL) at – 78 °C was bubbled O_3(g) gently for 25 min. The reaction was then purged with N_2(g) and MeOH (50 mL) and $NaBH_4$ (4.9 g, 130.0 mmol) were added. The reaction mixture was then slowly warmed to room temperature and stirred for an additional 14 h. The reaction was then quenched by the careful addition of water and the mixture was extracted with EtOAc (3x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (45% EtOAc in Hexanes) to provide the desired product (3.64 g, 71 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.11 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 4.05-4.02 (m, 1H), 3.91-3.76 (m, 2H), 3.79 (s, 3H), 2.75-2.70 (m, 2H), 2.40 (br s, 2H), 1.78-1.71 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 131.1, 130.2, 113.6, 70.9, 56.2, 55.7, 43.2, 40.1.

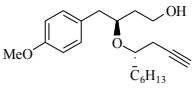
2-Hexyl-4-(4-methoxybenzyl)-[1,3]dioxane (16)



To 4-(4-methoxyphenyl)butane-1,3-diol (669.1 mg, 3.41 mmol) in benzene (10 mL) at room temperature was added heptaldehyde (370.0 mg, 3.24 mmol) and *p*TsOH (64.7 mg, 0.34 mmol). The reaction mixture was then warmed to reflux and stirred at that temperature for an additional 2.5 hours. The reaction was then cooled to room temperature and quenched by the addition of Et_3N (2.0 mL). The solvent was then removed under reduced pressure and the resulting residue was purified via flash column chromatography (4% EtOAc in Hexanes) to give the desired product (582.6 mg, 58%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.2 Hz, 2H), 6.83 (d, *J* = 8.2 Hz, 2H), 4.49 (t, *J* = 5.3 Hz, 1H), 4.08 (dd, *J* = 11.5, 4.9 Hz, 1H), 3.80 (s, 3H), 3.75-3.70 (m, 1H), 3.64 (dd, *J* = 12.2, 1.7 Hz, 1H), 2.92 (dd, *J* = 13.7, 6.4 Hz, 1H), 2.62 (dd, *J* = 13.7, 6.8 Hz, 1H), 1.69-1.58 (m, 2H), 1.39-1.35 (m, 4H), 1.28-1.24 (m, 6H), 0.88 (t,

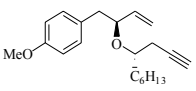
J = 5.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.5, 131.5, 130.1, 113.7, 101.2, 73.9, 65.6, 55.7, 41.2, 39.1, 36.5, 32.1, 30.7, 24.1, 20.2, 14.1.

4-(4-Methoxyphenyl)-3-(1-prop-2-ynyl heptyloxy)butan-1-ol (17)



To 2-hexyl-4-(4-methoxybenzyl)-[1,3]dioxane (500.0 mg, 1.70 mmol) and allenyltributyltin (1.11 g, 3.4 mmol) in CH_2Cl_2 (20 mL) at – 78 °C was added $TiCl_4$/Ti(*i*-PrO)$_4$ (6:5) in CH_2Cl_2 (30 mL) over 2 hour via a syringe pump. The reaction mixture was then stirred at – 78 °C for an additional 1 hour and 2 equivalents (1.11 g, 3.4 mmol) of allenyltributyltin were added. The reaction was then stirred at – 78 °C for 14 hours and quenched by the addition of MeOH (2.0 mL) and poured into water. The mixture was then extracted with EtOAc (3x). The combined organic layers were then washed with water and 10% aqueous KF, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (10% EtOAc in Hexanes) to give the desired product (467.9 mg, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.10 (d, J = 8.5 Hz, 2H), 6.82 (d, J = 8.5 Hz, 2H), 3.79 (s, 3H), 3.79-3.75 (m, 3H), 3.53 (p, J = 5.8 Hz, 1H), 2.95 (dd, J = 13.6, 5.5 Hz, 1H), 2.65 (dd, J = 13.6, 7.6 Hz, 1H), 2.47 (t, J = 4.7 Hz, 1H), 2.30-2.26 (m, 2H), 1.99 (t, J = 2.6 Hz, 1H), 1.74-1.62 (m, 2H), 1.37-1.26 (m, 8H), 0.89 (t, J = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 140.1, 127.6, 113.4, 82.3, 70.1, 61.1, 55.3, 42.3, 34.4, 33.3, 31.9, 29.5, 27.9, 26.2, 25.3, 23.5, 22.7, 14.2.

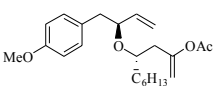
1-Methoxy-4-[2-(1-prop-2-ynyl-heptyloxy)but-3-enyl]benzene (18)



To 4-(4-methoxyphenyl)-3-(1-prop-2-ynyl heptyloxy)butan-1-ol (288.0 mg, 0.86 mmol) and phenylselenocyanate (236.7 mg, 1.3 mmol) in THF (10 mL) at – 10 °C was added PBu_3 (263.0 mg, 1.3 mmol) dropwise. The reaction mixture was then stirred

at – 10 °C for 18 hours, and the solvent was removed under reduced pressure. The resulting residue was passed through a short silica plug. The filtrate was then concentrated under reduced pressure and taken up in CH_2Cl_2 (5 mL). The solution was then cooled to – 78 °C and *m*CPBA (148.9 mg, 0.86 mmol) was added. The reaction mixture was then stirred at – 78 °C for 30 min and DHP (306.0 mg, 4.3 mmol) and pyridine (340.0 mg, 4.3 mmol) were added. The reaction mixture was then warmed to 40 °C and stirred for an additional 14 hours. The solvent was then removed under reduced pressure and the resulting residue was purified via flash column chromatography (4% EtOAc in Hexanes) to provide the desired product (262.1 mg, 96%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.13 (d, *J* = 8.6 Hz, 2H), 6.81 (d, *J* = 8.6 Hz, 2H), 5.68 (ddd, *J* = 17.5, 10.2, 7.9 Hz, 1H), 5.12 (d, *J* = 10.2 Hz, 1H), 5.07 (d, *J* = 17.5 Hz, 1H), 3.93 (q, *J* = 6.8 Hz, 1H), 3.79 (s, 3H), 3.48-3.40 (m, 1H), 2.86 (dd, *J* = 13.6, 6.9 Hz, 1H), 2.70(dd, *J* = 13.6, 6.2 Hz, 1H), 2.23-2.14 (m, 2H), 1.94 (t, *J* = 2.6 Hz, 1H), 1.60-1.38 (m, 2H), 1.28-1.27 (m. 10H), 0.89 (t, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 138.9, 130.6, 130.4, 116.9, 113.4, 81.6, 80.9, 74.7, 69.6, 55.2, 41.6, 34.5, 31.8, 29.2, 25.3, 23.5, 22.6, 14.1.

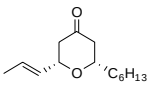
Acetic acid-3-[1-(4-methoxybenzyl)allyloxy]-1-methylenenonyl ester (19)



To 1-methoxy-4-[2-(1-prop-2-ynyl-heptyloxy)but-3-enyl]benzene (0.95 g, 3.01 mmol) in toluene (15 mL) was added Na_2CO_3 (51.0 mg, .48 mmol) and acetic acid (.36 g, 6.02 mmol, (35.0 μL). The mixture was then stirred at room temperature for 10 min and [Ru(*p*-cymene)Cl_2]$_2$ (74.8 mg, 0.12 mmol) and tri-2-furylphosphine (55.9 mg, 0.24 mmol) were added. The reaction mixture was then warmed to 80 °C and stirred for an additional 16 h. The mixture was then cooled to room temperature and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (3% EtOAc in Hexanes) to provide the desired product (699.0 mg, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ=

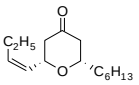
7.10 (d, *J* = 8.5 Hz, 2H), 6.81 (d, *J* = 8.5 Hz, 2H), 5.73-5.60 (m, 1H), 5.11 (d, *J* = 10.2 Hz, 1H), 5.03 (d, *J* = 17.2 Hz, 1H), 4.73 (s, 1H), 4.66 (s, 1H), 3.90 (q, *J* = 6.7 Hz, 1H), 3.79 (s, 3H), 3.45 (p, *J* = 5.6 Hz, 1H), 2.84 (dd, *J* = 13.5, 6.4 Hz, 1H), 2.66 (dd, *J* = 13.5, 6.7 Hz, 1H), 2.35 (dd, *J* = 14.7, 5.6 Hz, 1H), 2.22 (dd, *J* = 14.7, 6.5 Hz, 1H), 2.11 (s, 3H), 1.45-1.43 (m, 2H), 1.30-1.25 (m, 8H), 0.88 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 168.9, 157.9, 153.6, 139.2, 130.6, 130.2, 1117.0, 113.3, 103.5, 80.7, 73.4, 55.1, 41.5, 38.3, 34.8, 31.7, 30.9, 29.2, 25.3, 22.6, 21.0, 14.0; IR (neat) 2930, 2857, 1757, 1665, 1465, 1247, 1038 cm^{-1}; HRMS (EI): calcd for $C_{23}H_{34}O_4$ (M^+) 374.2457, found 374.2461.

2-Hexyl-6-propenyltetrahydropyran-4-one (20)



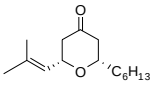
To acetic acid-3-[1-(4-methoxybenzyl)-but-2-enyloxy]-1-methylenenonyl ester (48.0 mg, 0.12 mmol) in DCE (2.2 mL) was added $NaHC0_3$ (100.0 mg, 1.19 mmol) and 4Å molecular sieves (100.0 mg). The mixture was then stirred at room temperature for 10 min and CAN (275.0 mg, 0.50 mmol) in CH_3CN (1.2 mL) was added dropwise. The reaction was then stirred for an additional 30 min and filtered through a silica plug. The filtrate was then concentrated under reduced pressure and purified via flash column chromatography (5% EtOAc in Hexanes) to provide the desired product (21.5 mg, 80%): $[\alpha]_D^{20}$ = -2.3 (*c* = 0.9 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (dqd, *J* = 15.3, 6.3, 0.8 Hz, 1H), 5.56 (ddq, *J* = 15.3, 6.2, 1.5 Hz, 1H), 4.09-4.01 (m, 1H), 3.64-3.56 (m, 1H), 2.38-2.20 (m, 4H), 1.74 (d, *J* = 6.3 Hz, 3H), 1.29-1.26 (m, 10H), 0.88 (t, *J* = 6.6, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.4, 130.4, 128.4, 47.8, 47.7, 36.4, 31.7, 29.1, 25.1, 22.6, 17.7, 14.0; IR (neat) 2928, 2857, 1721 cm^{-1}; HRMS (EI) calcd for ($C_{14}H_{24}O_2$) 224.1776 found 224.1759.

2-But-1-enyl-6-hexyltetrahydropyran-4-one (21)



To acetic acid-3-[1-(4-methoxybenzyl)-pent-2-enyloxy]-1-methylenenonyl ester (100.0 mg, 0.25 mmol) in DCE (2.4 mL) was added $NaHCO_3$ (200.0 mg, 2.38 mmol) and 4Å molecular sieves (200 mg). The mixture was then stirred at room temperature for 10 min and CAN (544.0 mg, 0.99 mmol) in CH_3CN (1.5 mL) was added dropwise. The reaction mixture was then stirred at room temperature for an additional 30 min and filtered through a silica plug. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified via flash column chromatography (3% EtOAc in Hexanes) to provide the desired product (41.1 mg, 70%): $[\alpha]_D^{20}$ = -2.5 (*c* = 0.9 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 5.58 (dtd, *J* = 10.9, 7.4, 0.9 Hz, 1H), 5.40 (ddt, *J* = 10.9, 7.6, 1.4 Hz, 1H), 4.38 (dddd, *J* = 12.4, 7.6, 5.3, 0.8 Hz, 1H), 3.62 (dtd, *J* = 11.2, 4.7, 2.6 Hz, 1H), 2.40-2.24 (m, 2H), 2.16-2.00 (m, 2H), 1.75-1.62 (m, 2H), 1.58-1.40 (m, 2H), 1.38-1.25 (m, 8H), 0.99 (t, *J* = 7.5 Hz, 3H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 207.3, 135.3, 128.2, 73.1, 48.0, 47.7, 36.4, 31.7, 29.1, 28.8, 25.1, 22.9, 22.5, 21.3, 14.1; IR (neat) 2959, 2939, 2858, 1722 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{26}O_2$ (M^+) 238.1933, found 238.1936.

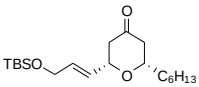
2-Hexyl-6-(2-methylpropenyl)tetrahydropyran-4-one (22)



To acetic acid-3-[1-(4-methoxybenzyl)-3-methylbut-2-enyloxy]-1-methylenenonyl ester (28.0 mg, 0.06 mmol) in DCE (2.0 mL) was added $NaHCO_3$ (60.0 mg, 0.71 mmol) and 4Å molecular sieves (60 mg). The mixture was then stirred at room temperature for 10 min and CAN (152.0 mg, 0.27 mmol) in CH_3CN (1.0 mL) was added dropwise. The reaction mixture was then stirred at room temperature for an additional 30 min and filtered through a silica plug. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified via flash column chromatography (3% EtOAc in Hexanes) to provide the desired

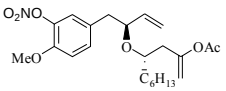
product (11.4 mg, 80%): $[\alpha]_D^{20}$ = -2.3 (*c* = 0.6 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 5.25 (d, *J* = 7.8 Hz, 1H), 4.29 (dd, *J* = 14.0, 7.9 Hz, 1H), 3.66-3.57 (m, 1H), 2.40-2.20 (m, 4H), 1.76 (s, 3H), 1.69 (s, 3H), 1.53-1.37 (m, 2H), 1.33-1.26 (m, 8H) 0.88 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 207.4, 137.3, 124.5, 74.1, 48.0, 47.8, 36.5, 31.7, 29.6, 29.1, 25.6, 25.2, 22.5, 18.4, 14.0; IR (neat) 2928, 2857, 1720, 1052 cm^{-1}; HRMS (EI): calcd for $C_{15}H_{26}O_2$ (M^+) 238.1932 found 238.1935.

2-[3-(*tert*-Butyldimethylsilanyloxy)propenyl]-6-hexyltetrahydropyran-4-one (23)



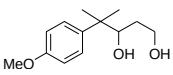
To acetic acid-3-[4-(*tert*-butyldimethylsilanyloxy)-1-(4-methoxybenzyl)but-2-enyloxy]-1-methylenenonyl ester (45.0 mg, 0.08 mmol) in DCE (2.2 mL) was added $NaHCO_3$ (90.0 mg, 1.07 mmol) and 4Å molecular sieves (90.0 mg). The mixture was then stirred at room temperature for 10 min and CAN (190.0 mg, 0.34 mmol) in CH_3CN (1.0 mL) was added dropwise. The reaction mixture was then stirred at room temperature for an additional 10 min and filtered through a silica plug. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified via flash column chromatography (5% EtOAc in Hexanes) to provide the desired product (24.2 mg, 79%): $[\alpha]_D^{20}$ = -2.2 (*c* = 1.0 in $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ= 5.84 (dt, *J* = 15.5, 3.8 Hz, 1H), 5.76 (dd, *J* = 15.5, 4.9 Hz, 1H), 4.20 (dd, *J* = 3.8, 1.1 Hz, 2H), 4.14-4.08 (m, 1H), 3.66-3.57 (m, 1H), 2.46-2.41 (m, 2H), 2.40-2.37 (m, 1H), 2.30-2.21 (m, 1H), 1.75-1.70 (m, 1H), 1.59-1.50 (m, 1H), 1.30-1.26 (m, 8H), 0.92 (s, 9H), 0.93-0.90 (m, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 207,3, 131.4, 128.7, 63.0, 47.8, 36.4, 31.8, 29.2, 26.0, 25.3, 22.6, 18.5, 14.1, -5.1; IR (neat) 2929, 2856, 1722, 1254, 1057 cm^{-1}; HRMS (EI): calcd for $C_{20}H_{38}O_3Si$ (M^+) 354.2590, found 354.2553.

Acetic acid-3-[1-(4-methoxy-3-nitrooxybenzyl)allyloxy]-1-methylenenonyl ester (24)



To acetic acid-3-[1-(4-methoxybenzyl)allyloxy]-1-methylenenonyl ester (50.0 mg, 14 mmol) in DCE (2.2 mL) was added $NaHCO_3$ (100.0 mg, 1.19 mmol) and 4Å molecular sieves (100.0 mg). The mixture was then stirred at room temperature for 15 min and CAN in CH_3CN (1.0 mL) was added dropwise. The reaction was then stirred for an additional 20 min and passed through a silica plug. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified via flash column chromatography (20% EtOAc in Hexanes) to provide the nitrated product (12.0 mg, 19%): ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.71 (s, 1H), 7.37 (d, *J* = 8.5 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 5.63 (ddd, *J* = 17.3, 10.2, 8.3 Hz, 1H), 5.15 (d, *J* = 10.2 Hz, 1H), 5.07 (d, *J* = 17.3 Hz, 1H), 3.94 (s, 3H), 3.94-3.89 (m, 1H), 3.44 (p, *J* = 6.0 Hz, 1H), 2.83 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.73 (dd, *J* = 13.7, 5.6 Hz, 1H), 2.31 (dd, *J* = 14.6, 5.7 Hz, 1H), 2.21 (dd, *J* = 14.6, 6.3 Hz, 1H), 2.11 (s, 3H), 1.44-1.42 (m, 2H), 1.26-1.24 (m, 8H), 0.88 (t, *J* = 5.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 168.9, 153.4, 151.4, 138.7, 135.6, 130.7, 126.8, 117.7, 112.9, 103.6, 79.9, 73.4, 56.5, 41.0, 38.4, 34.8, 31.7, 29.2, 25.2, 22.6, 21.0, 14.0; MS: m/z(%): 389 (6) [M^+ - NO_2], 360 (6) [M^+ - CH_3NO_2].

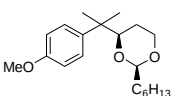
4-(4-Methoxyphenyl)-4-methylpentane-1,3-diol (25)



To 2-(4-methoxyphenyl)-2-methylhex-5-en-3-ol (3.09 g, 14.0 mmol) in CH_2Cl_2 (30 mL) at – 78 °C was gently bubble O_3 (g) for 20 min. The solution was then purged with nitrogen, and MeOH (30 mL) was added followed by $NaBH_4$ (2.65 g, 70.3 mmol). The reaction mixture was then warmed to 0 °C, and the reaction mixture was slowly warmed to room temperature. After stirring at room temperature for 12 h, the reaction was quenched by the careful addition of water. The CH_2Cl_2 and MeOH were then removed under reduced pressure, and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were then

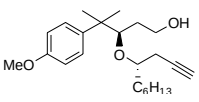
washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (80% EtOAc in Hexanes) to provide the desired product (2.13 g, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.8 Hz, 2H), 6.88 (d, *J* = 8.8 Hz, 2H), 3.83-3.78 (m, 3H), 3.80 (s, 3H), 2.35 (s, 1H), 1.61-1.56 (m, 2H), 1.33 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.0, 138.7, 127.6, 113.8, 80.3, 62.6, 55.3, 41.9, 32.8, 24.4, 23.4; IR (neat) 3396, 2963, 2836, 1737, 1513, 1464, 1250, 1035 cm^{-1}; HRMS (EI) calcd for $C_{13}H_{20}O_3$ (M^+) 224.1412, found 224.1416.

2-Hexyl-4-[1-(4-methoxyphenyl)-1-methylethyl]-[1,3]dioxane (26)



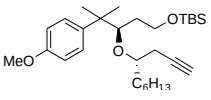
To 4-(4-methoxyphenyl)-4-methylpentane-1,3-diol (1.59 g, 6.8 mmol) in benzene (15 mL) was added PTSA (10 mg) and freshly distilled heptaldehyde (778.4 mg, 6.8 mmol, 0.95 mL). The reaction mixture was then warmed to reflux and stirred for 15 h, while removing water via a Dean-Stark trap. After cooling to room temperature, the reaction mixture was neutralized by the addition of Et_3N (2 mL), and the solvent was removed under reduced pressure. The resulting residue was then purified via flash column chromatography (5% EtOAc in Hexanes) to afford the desired product (1.75 g, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.9 Hz, 2H), 6.84 (d, *J* = 8.9 Hz, 2H), 4.48 (t *J* = 5.1 Hz, 1H), 4.02 (ddd, *J* = 11.2, 4.8, 1.3 Hz, 1H), 3.79 (s, 3H), 3.63 (dd, *J* = 12.1, 2.5 Hz, 1H), 3.53 (dd, *J* = 12.1, 2.1 Hz, 1H), 2.41-2.20 (m, 1H), 1.64-1.57 (m, 4H), 1.34 (s, 3H), 1.32 (s, 3H), 1.03 (dq, *J* = 11.6, 2.2 Hz, 2H), 0,89 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 138.8, 127.7, 113.2, 102.3, 84.1, 66.7, 55.1, 40.6, 35.0, 31.8, 29.1, 28.7, 25.9, 23.9, 22.8, 22.5, 14.0; IR (neat) 2956, 2856, 1513, 1465, 1250, 1185, 1036 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{32}O_3$ (M^+) 320.2351, found 320.2346.

4-(4-Methoxyphenyl)-4-methyl-3-(1-prop-2-ynylheptyloxy)pentan-1-ol (27)



To 2-hexyl-4-[1-(4-methoxyphenyl)-1-methylethyl]-[1,3]-dioxane (200.0 mg, 0.62 mmol) in CH_2Cl_2 (6 mL) at – 78 °C was added $TiCl_4$/Ti(*i*-PrO)$_4$ (6:5) in CH_2Cl_2 (9 mL) over 2h (via syringe pump). The reaction mixture was then quenched by the dropwise addition of MeOH (1 mL), and poured directly into water. The mixture was then extracted with EtOAc (2x). The combined organic layers were then washed with water, 10% aqueous KF and brine, dried over Na_2SO_4 filtered, and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (15% EtOAc in Hexanes) to provide the desired product as a 19:1 mixture of separable diastereomers (191.5 mg, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 3.67 (dd, *J* = 6.9, 4.6 Hz, 1H), 3.52-3.49 (m, 2H), 3.31 (p, *J* = 5.8 Hz, 1H), 2.27 (dd, *J* = 5.2, 2.6 Hz, 2H), 1.99 (t, *J* = 2.6 Hz, 1H), 1.76-1.75 (m, 2H), 1.68-1.57 (m, 4H), 1.36 (s, 3H), 1.30 (s, 3H), 1.30-1.27 (m, 6H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 140.1, 127.6, 113.4, 82.3, 81.6, 70.1, 61.1, 55.3, 42.3, 34.4, 33.3, 31.9, 29.5, 27.9, 26.2, 25.3, 23.9, 23.5, 22.7, 14.2; IR (neat) 3309, 2955, 2857, 1513, 1465, 1250, 1037 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{36}O_3$ (M^+) 360.2664, found 360.2674.

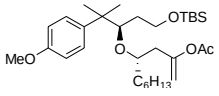
***tert*-Butyl-[4-(4-methoxyphenyl)-4-methyl-3-(1-prop-2-ynylheptyloxy)pentyloxy] dimethylsilane (28)**



To 4-(4-methoxyphenyl)-4-methyl-3-(1-prop-2-ynylheptyloxy)pentan-1-ol (325.4 mg, 0.90 mmol) in DMF (3 mL) was added imidazole (134.7 mg, 1.98 mmol) and DMAP (30 mg) at 0 °C. The mixture was then stirred for 5 min and TBSCl (149.0 mg, 0.99 mmol) and the cold bath was removed. The reaction mixture was then stirred at room temperature for 1.5 h, and quenched by the addition of water. The mixture was then extracted

with EtOAc (2x). The combined organic layers were then washed with water and brine dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (5% EtOAc in Hexanes) to provide the desired product (363.7 mg, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 3.60 (dd, *J* = 6.4, 3.8 Hz, 1H), 3.50 (p, *J* = 6.3 Hz, 1H), 3.42-3.38 (m, 1H), 3.33-3.28 (m, 1H), 2.32 (dq, *J* = 16.7, 2.7 Hz, 1H), 2.20 (dd, *J* = 16.7, 2.7 Hz, 1H), 1.97 (t, *J* = 2.7 Hz, 1H), 1.45-1.38 (m, 4H), 1.34 (s, 3H), 1.31 (s, 3H), 1.34-1.30 (m, 8H), 0.92 (t, *J* = 5.0 Hz, 3H), 0.88 (s, 9H), -0.01 (s, 3H), -0.03 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 140.0, 127.6, 113.2, 81.9, 80.3, 75.7, 69.6, 60.6, 55.1, 42.0, 35.3, 33.9, 31.8, 29.4, 26.8, 25.9, 25.1, 23.2, 22.6, 18.2, 14.0, -5.4, -5.5; IR (neat) 3312, 2954, 2857, 1611, 1513, 1464, 1251, 1086, 1039, 833; HRMS (EI) calcd for $C_{33}H_{46}O_2Si$ (M^+) 474.3497, found 474.3508.

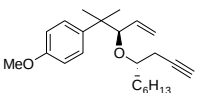
Acetic acid-3-[1-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-2-(4-methoxyphenyl)-2-methylpropoxy]-1-methylenenonyl ester (29)



To *tert*-butyl[4-(4-methoxyphenyl)-4-methy-3-(1-prop-2-ynylheptyloxy)pentyloxy] dimethylsilane (363.0 mg, 0.76 mmol) in toluene (5 mL) was added Na_2CO_3 (13.0 mg, 0.12 mmol) and acetic acid (46.0 mg, 0.76 mmol, 46.0 μL). The mixture was then stirred at room temperature for 10 min and [Ru(*p*-cymene)Cl_2]$_2$ (18.7 mg, 0.03 mmol) and tri-2-furylphosphine (14.2 mg, 0.06 mmol) were added. The reaction mixture was then warmed to 80 °C and stirred for an additional 20 h. The mixture was then cooled to room temperature and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (5% EtOAc in Hexanes) to provide the desired product (194.0 mg, 48%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 2H), 6.83 (d, *J* = 8.6 Hz, 2H), 4.79 (s, 1h), 4.75 (s, 1H), 3.79 (s, 3H), 3.54 (dd, *J* = 7.1, 3.3 Hz, 1H), 3.42-3.28 (m,

3H), 2.42 (dd, *J* = 14.7, 5.1 Hz, 1H), 2.29 (dd, *J* = 14.7, 6.9 Hz, 1H), 2.11 (s, 3H), 1.59-1.48 (m, 4H), 1.33 (s, 3H), 1.27 (s, 3H), 1.33-1.27 (m, 8H), 0.91-0.85 (m, 3H), 0.85 (s, 9H), -0.03 (s, 3H), -0.06 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 157.8, 154.1, 140.5, 127.9, 110.7, 103.8, 80.2, 76.1, 61.1, 55.4, 42.6, 38.2, 35.8, 34.0, 32.1, 29.7, 26.9, 25.2, 23.8, 22.9, 21.4, 14.3, -5.0: IR (neat) 2955, 2929, 1755, 1513, 1251, 1194 cm^{-1}; HRMS (EI) calcd for $C_{27}H_{45}O_5Si$ (M^+) 477.3036, found 477.3027.

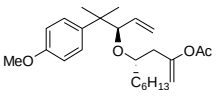
1-[1,1-Dimethyl-2-(1-methylbut-3-ynyloxy)but-3-enyl]-4-methoxybenzene (30)



To 4-(4-methoxyphenyl)-4-methyl-3-(1-prop-2-ynylheptyloxy)pentan-1-ol (293.0 mg, 0.81 mmol) in THF (5 mL) at 0 °C was added phenylselenocyanate (221.0 g, 1.2 mmol). The mixture was then stirred at 0 °C for 5 minutes and PBu_3 (244.8 mg, 1.2 mmol) was added dropwise. The reaction mixture was then slowly warmed to room temperature and stirred for an additional 12 hours. The mixture was then filtered through a short silica plug and the filtrate was concentrated under reduced pressure. The resulting residue was taken up in CH_2Cl_2 (5 mL) and cooled to – 78 °C. *m*CPBA (178.8 mg, 0.81 mmol) was then added and the reaction mixture was stirred at – 78 °C for 1 hour. Pyridine (822.0 mg, 10.4 mmol) and DHP (737.0 mg, 10.4 mmol) were then added and the reaction was warmed to room temperature and stirred for an additional 18 hours. The solvent was then removed under reduced pressure and the resulting residue was purified via flash column chromatography (5% EtOAc in Hexanes) to give the desired product (208.2 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.12 (d, *J* = 8.5 Hz, 2H), 6.83 (d, *J* = 8.5 Hz, 2H), 5.79 (ddd, *J* = 17.4, 10.3, 7.3 Hz, 1H), 5.13 (d, *J* = 17.4 Hz, 1H), 5.08 (d, *J* = 10.3 Hz, 1H), 4.07 (q, *J* = 6.9 Hz, 1H), 3.80-3.72 (m, 1H), 3.79 (s, 3H), 2.92 (dd, *J* = 13.7, 6.7 Hz, 1H), 2.68 (dd, *J* = 13.7, 6.9 Hz, 1H), 2.27-2.15 (m, 1H), 2.11-2.09 (m, 1H), 1.89 (t, *J* = 2.5 Hz, 1H), 1.54-1.52 (m, 2H), 1.30-1.27 (m, 12H), 0.89 (t, *J* = 5.8 Hz, 3H); ^{13}C NMR (75

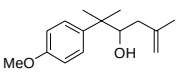
MHz, $CDCl_3$) 158.4, 135.3, 130.8, 130.6, 117.1, 114.1, 78.8, 61.0, 55.5, 40.2, 39.2, 36.0, 33.9, 32.0, 29.8, 25.4, 22.9, 14.3.

Acetic acid-3-{1-[1-(4-methoxyphenyl)-1-methylethyl]allyloxy}-1-methylenenonyl ester (31)



To 1-[1,1-dimethyl-2-(1-methylbut-3-ynyloxy)but-3-enyl]-4-methoxybenzene (208.2 mg, 0.607 mmol) in toluene (5 mL) was added Na_2CO_3 (10.2 mg, 0.097 mmol) and acetic acid (72.0 mg, 1.21 mmol, 71.0 μL). The mixture was then stirred at room temperature for 10 min and [Ru(*p*-cymene)Cl_2]$_2$ (14.8 mg, 0.024 mmol) and tri-2-furylphosphine (11.2 mg, 0.048 mmol) were added. The reaction mixture was then warmed to 60 °C and stirred for an additional 18 h. The mixture was then cooled to room temperature and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (4% EtOAc in Hexanes) to provide the desired product (110.4 mg, 45%): ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.29 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 5.42 (ddd, *J* = 17.2, 10.3, 8.4 Hz, 1H), 5.11 (dd, *J* = 10.3, 2.0 Hz, 1H), 4.99 (dd, *J* = 17.2, 2.0 Hz, 1H), 4.73 (s, 1H), 4.67 (s, 1H), 3.80 (s, 3H), 3.64 (d, *J* = 8.4 Hz, 1H), 3.40-3.32 (m, 1H), 2.40 (dd, *J* = 14.7, 4.8 Hz, 1H), 2.19-2.07 (m, 1H), 2,12 (s, 3H), 1.56-1.16 (m, 10 H), 1.28 (s, 3H), 1.16 (s, 3H), 0.87 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 168.9, 157.4, 153.8, 134.1, 136.9, 128.0, 118.3, 112.7, 103.4, 86.6, 72.7, 55.0, 40.9, 37.8, 34.5, 31.7, 29.2, 25.1, 25.0, 22.5, 21.0, 14.0; IR (neat) 2930, 2857, 1758, 1665, 1514, 1464, 1250, 1188, 1038 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{38}O_4$ (M^+) 402.2770, found 402.2767.

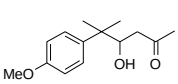
2-(4-Methoxyphenyl)-2,5-dimethylhex-5-en-3-ol (32)



To 2-(4-methoxyphenyl)-2-methylpropionaldehyde (3.00 g, 16.8 mmol) in THF (30 mL) at – 78 °C was added methyallyl lithium (42.0 ml, 42.0 mmol) dropwise. The reaction

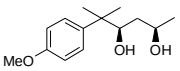
mixture was then slowly warmed to room temperature and stirred for an additional 1.5 hours. The reaction was then quenched by the addition of saturated NH_4Cl (aq), and extracted with EtOAc (2x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (7% EtOAc in Hexanes) to provide the desired product (2.99 g, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.9 Hz, 2H), 6.88 (d, *J* = 8.9 Hz, 2H), 4.84 (s, 1H), 4.75 (s, 1H), 3.81 (s, 3H), 3.75 (d, *J* = 10.5 Hz, 1H), 2.04 (d, *J* = 6.5 Hz, 1H), 1.88 (dd, *J* = 13.7, 11.0 Hz, 1H), 1.70 (s, 3H), 1.65 (s, 1H), 1.37 (s, 3H), 1.34 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 143.6, 139.0, 127.5, 113.4, 112.9, 55.1, 41.4, 40.5, 25.0, 23.4, 22.1; IR (neat) 3557, 2967, 1611, 1513, 1251, 1184, 1036, 830 cm^{-1}.

4-Hydroxy-5-(4-methoxyphenyl)-5-methylhexan-2-one (33)



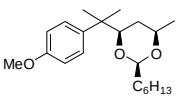
To 2-(4-methoxyphenyl)-2,5-dimethylhex-5-en-3-ol (3.00 g, 12.8 mmol) in CH_2Cl_2 (30 mL) at – 78 °C was gently bubbled O_3(g) over 25 minutes. The reaction was then purged with N_2(g) followed by the addition of PPh_3 (3.35 g, 12.8 mmol). The reaction mixture was then warmed to room temperature and stirred for 3 hours. The solvent was then removed under reduced pressure and the resulting residue was purified via flash column chromatography (35% EtOAc in Hexanes) to provide the desired product (2.46 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.8 Hz, 2H), 6.86 (d, *J* = 8.8 Hz, 2H), 4.12 (p, *J* = 4.1 Hz, 1H), 3.78 (s, 3H), 2.89 (s, 1H), 2.36-2.33 (m, 2H), 2.07 (s, 3H), 1.33 (s, 3H), 1.30 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 209.7, 157.8, 138.5, 127.5, 113.5, 74.7, 55.0, 45.3, 41.0, 30.6, 25.5, 22.7, 14.0.

5-(4-Methoxyphenyl)-5-methylhexane-2,4-diol (34)



To 4-hydroxy-5-(4-methoxyphenyl)-5-methylhexan-2-one (508.2 mg, 2.1 mmol) in THF at – 78 °C was added Et_2BOMe (230.9 mg, 2.3 mmol) and the mixture was stirred for 10 minutes. $NaBH_4$ (476.4 mg, 12.6 mmol) was then added and the reaction mixture was stirred for an additional 5 hours at – 78 °C. The reaction was then quenched by the addition of saturated NH_4Cl (aq) and warmed to room temperature. The mixture was then extracted with EtOAc (3x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue taken up in THF (5 mL) and pH 7.0 buffer (10 mL) was added followed by 30% H_2O_2 (7 mL). The mixture was then vigorously stirred at room temperature for 3 hours. The mixture was then extracted with EtOAc (3x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatograpy (25% EtOAc in Hexanes) to give the desired product (378.7 mg, 76%, 15:1 dr): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, J = 8.6 Hz, 2H), 6.88 (d, J = 8.6 Hz, 2H), 4.01-3.99 (m, 1H), 3.85 (d, J = 10.4 Hz, 1H), 3.81 (s, 3H), , 1.57-1.55 (m, 2H), 1.32 (s, 3H), 1.29 (s, 3H), 1.17 (d, J = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.1, 137.9, 127.3, 113.2, 75.4, 65.8, 55.5, 42.0, 39.1, 24.3, 23.7, 23.1; IR (neat) 3443, 2929, 1610, 1513, 1250, 1058, 829 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}O_3$ 238.1568, found 238.1571.

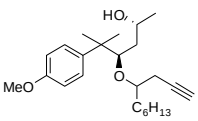
2-Hexyl-4-[1-(4-methoxyphenyl)-1-methylethyl]-6-methyl-[1,3]dioxane (35)



To 5-(4-methoxyphenyl)-5-methylhexane-2,4-diol (301.7 mg, 1.26 mmol) in CH_2Cl_2 (5 mL) was added *p*TsOH (few crystals). The mixture was then stirred for 5 minutes and 1,1-dimethoxyheptane (304.0 mg, 1.89 mmol) was added. The reaction was then stirred for 12 hours at room temperature. The solvent was then removed under reduced

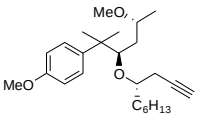
pressure and the resulting reside was purified via flash column chromatography (7% EtOAc in Hexanes) to provide the desired product (357.1 mg, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.8 Hz, 2H), 6.84 (d, *J* = 8.8 Hz, 2H), 4.49 (t, *J* = 5.2 Hz, 1H), 3.80 (s, 3H), 3.61-3.50 (m, 2H), 1.67-1.61 (m, 2H), 1.34 (s, 3H), 1.32 (s, 3H), 1.39-1.30 (m, 10H), 1.15 (d, *J* = 6.2 Hz, 3H), 0.89 (t, *J* = 6.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 139.2, 128.0, 113.5, 102.1, 84.1, 72.8, 55.4, 40.8, 35.2, 33.5, 32.1, 29.4, 26.3, 24.4, 23.0, 22.8, 21.9, 14.3.

5-(4-Methoxyphenyl)-5-methyl-4-(1-prop-2-ynylheptyloxy)hexan-2-ol (36)



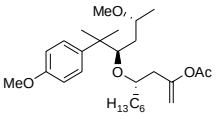
To 2-hexyl-4-[1-(4-methoxyphenyl)-1-methylethyl]-6-methyl-[1,3]dioxane (100.0 mg, 0.29 mmol) and allenyltributyltin (588.0 mg, 1.78 mmol) in CH_2Cl_2 (2 mL) at – 78 °C was added $TiCl_3$(*i*-PrO) (3.57 mmol) in CH_2Cl_2 (5.0 mL) via syringe pump over 2 hours. The reaction was then stirred for an additional 10 minutes and quenched by the addition of MeOH (2.0 mL). The mixture was then poured into water and extracted with EtOAc (3x). The combined organic layers were then washed with water nd 10% aqueous KF, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (8% EtOAc in Hexanes) to give the desired produce (58.1 mg, 54%; 3:1 dr): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 3.89-3.8 (m, 1H), 3.80 (s, 3H), 3.29 (p, *J* = 5.7 Hz, 1H), 3.12-3.01 (m, 1H), 2.44-2.16 (m, 2H), 2.00 (t, *J* = 2.5 Hz, 1H), 1.67-1.57 (m, 2H), 1.50-1.45 (m, 2H), 1.36 (s, 3H), 1.26 (s, 3H), 1.27-1.25 (m, 8H), 1.07-1.04 (m, 3H), 0.89 (t, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 157.7, 140.2, 140.0, 127.3, 113.4, 84.2, 83.5, 81.1, 80.8, 75.5, 70.4, 66.9, 55.1, 42.5, 42.2, 40.3, 39.8, 34.3, 31.7, 29.4, 29.3, 25.4, 25.0, 24.5, 23.6, 23.4, 22.9, 22.5, 14.0.

1-Methoxy-4-[4-methoxy-1,1-dimethyl-2-(1-methylbut-3-ynyloxy)pentyl]benzene (37)



To 5-(4-methoxyphenyl)-5-methyl-4-(1-prop-2-ynylheptyloxy)hexan-2-ol (104.4 mg, 0.28 mmol) in DMF (2.0 mL) at 0 °C was added NaH (34.0 mg, 0.86 mmol). The mixture was then stirred for 10 minutes and MeI (164.0 mg, 1.15 mmol) was added dropwise. The reaction mixture was then slowly warmed to room temperature and stirred for an additional 2.5 hours. The reaction was then quenched by the careful addition of water, and extracted with EtOAc (2x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (5% EtOAc in Hexanes) to give the desired product (40.0 mg, 50%; 3:1 dr): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.55-3.45 (m, 2H), 3.17 (s, 3H), 2.66 (app q, *J* = 6.0 Hz, 1H), 2.34 (ddd, *J* = 16.6, 6.8, 2.6 Hz, 1H), 2.23 (ddd, *J* = 16.7, 9.5, 2.6 Hz, 1H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.61-1.56 (m, 2H), 1.47-1.38 (m, 2H), 1.34 (s, 3H), 1.28 (s, 3H), 1.30-1.26 (m, 8H), 0.90-0.88 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.5, 139.6, 127.8, 113.1, 82.1, 80.7, 75.2, 74.4, 69.5, 56.1, 55.1, 42.0, 40.0, 34.2, 31.8, 30.9, 29.4, 27.0, 25.1, 22.9, 22.6, 22.4, 19.0, 14.1.

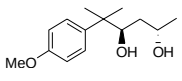
Acetic acid-3-{3-methoxy-1-[1-(4-methoxyphenyl)-1-methyl]butoxy}-1-methylenenonyl ester (38)



To 1-methoxy-4-[4-methoxy-1,1-dimethyl-2-(1-methylbut-3-ynyloxy)pentyl]benzene (45.5 mg, 0.12 mmol) in toluene (3 mL) was added Na_2CO_3 (2.1 mg, 0.02 mmol) and acetic acid (14.0 mg, 0.24 mmol, 14.0 μL). The mixture was then stirred at room temperature for 10 min and $[Ru(p\text{-cymene})Cl_2]_2$ (3.1 mg, 0.005 mmol) and tri-2-furylphosphine (2.4 mg, 0.01 mmol) were added. The reaction mixture was then warmed to 80 °C and stirred for an additional 15 h. The mixture was then cooled to room temperature and

concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (4% EtOAc in Hexanes) to provide the desired product (33.1 mg, 63.4%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26 (d, *J* = 8.5 Hz, 2H), 6.82 (d, *J* = 8.5 Hz, 2H), 4.76 (s, 1H), 4.75 (s, 1H), 3.78 (s, 3H), 3.52 (p, *J* = 5.7 Hz, 1H), 3.45 (t, *J* = 4.9 Hz, 1H), 3.17 (s, 3H), 2.70-2.63 (m, 1H), 2.44 (dd, *J* = 14.7, 6.8 Hz, 1H), 2.32 (dd, *J* = 14.7, 5.7 Hz, 1H), 1.55-1.46 (m, 4H), 1.32 (s, 3H), 1.26 (s, 3H), 1.28-1.25 (m, 8H), 0.92-0.87 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.9, 157.6, 154.1, 139.9, 127.8, 113.1, 103.1, 80.9, 75.4, 73.7, 56.0, 55.1, 42.4, 40.0, 38.7, 33.1, 31.8, 29.6, 26.7, 25.1, 22.9, 21.1, 19.0, 14.0: IR (neat) 2929, 2858, 1758, 1513, 1465, 1250, 1038 cm^{-1}; (HRMS) (EI) calcd for $C_{17}H_{31}O_4$ (M^+ - $C_{10}H_{13}O$) 299.2222, found 299.2214.

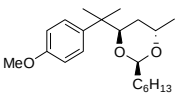
5-(4-Methoxyphenyl)-5-methylhexane-2,4-diol (39)



To 4-hydroxy-5-(4-methoxyphenyl)-5-methylhexan-2-one (500.0 mg, 2.1 mmol) in CH_3CN (10 mL) at – 78 °C was added a solution of $Me_4NBH(OAc)_3$ (2.78 g, 10.5 mmol) in CH_3CN (10 mL)/AcOH (10 mL) dropwise. The reaction was then warmed to – 20 ° C and stirred at that temperature for an additional 12 hours. The reaction was then diluted with EtOAc and water followed by the addition of $NaHCO_3$(s). The mixture was then warmed to room temperature and stirred for 30 minutes. The organic layer was then separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (35% EtOAc in Hexanes) to give the desired product (471.6 mg, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 4.06-4.04 (m, 1H), 3.95 (dd, *J* = 9.3, 3.3 Hz, 1H), 3.80 (s, 3H), 2.05 (s, 2H), 1.48-1.43 (m, 2H), 1.32 (s, 3H), 1.30 (s, 3H), 1.20 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 138.9, 127.6, 113.7, 75.9, 65.7, 55.3, 41.7, 39.0, 24.5, 23.5, 23.4; IR

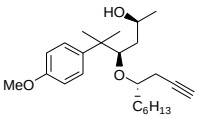
(neat) 3404, 2966, 1610, 1513, 1251, 1185, 831 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{22}O_3$ 238.1568, found 238.1574.

2-Hexyl-4-[1-(4-methoxyphenyl)-1-methylethyl]-6-methyl-[1,3]dioxane (40)



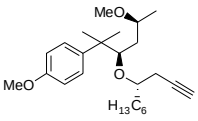
To 5-(4-methoxyphenyl)-5-methylhexane-2,4-diol (1.10 g, 4.6 mmol) in DMF at 0 °C was added imidazole (1.39 g, 20.4 mmol) and TMSCl (1.11 g, 10.2 mmol). The reaction mixture was then slowly warmed to room temperature and stirred for an additional 12 hours. The reaction was then quenched by the addition of water, and the mixture was extracted with hexanes (3x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then taken up in CH_2Cl_2 (10 mL) and cooled to – 78 °C. Heptaldehyde (818.0 mg, 3.8 mmol) was then added followed by the dropwise addition of TMSOTf (84.0 mg, 0.38 mmol). The reaction mixture was then stirred at – 78 °C for 45 minutes and pyridine (36.0 mg, 0.45 mmol) was added. The mixture was then warmed to room temperature and poured into water. The organic layer was then separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were then wahed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (6% EtOAc in Hexanes) to give the desired product (1.08 g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 4.80 (t, *J* = 5.1 Hz, 1H), 4.21 (p, *J* = 6.6 Hz, 1H), 3.80 (s, 3H), 3.73 (dd, *J* = 11.9, 1.5 Hz, 1H0, 1.69 (td, *J* = 12.3, 6.0 Hz, 1H), 1.57-1.52 (m, 2H), 1.33, (s, 3H), 1.31 (s, 3H), 1.33-1.25 (m, 11H), 0.89 (t, *J* = 5.6 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 138.8, 127.8, 113.2, 94.8, 78.7, 68.0, 55.2, 40.6, 35.3, 31.9, 29.6, 29.2, 26.1, 24.1, 22.9, 22.7, 17.3, 14.2; IR (neat) 2930, 2857, 1741, 1612, 1514,1464, 1250, 829 cm^{-1}; HRMS (EI) calcd for $C_{21}H_{34}O_3$ 334.2507, found 334.2497.

1-Methoxy-4-[4-methoxy-1,1-dimethyl-2-(1-methylbut-3-ynyloxy)pentyl]benzene (41)

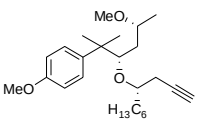


To 2-hexyl-4-[1-(4-methoxyphenyl)-1-methylethyl]-6-methyl-[1,3]dioxane (400.0 mg, 1.1 mmol) and allenlytributyltin (1.56 g, 4.76 mmol) in CH_2Cl_2 (10 mL) was added $TiCl_4$/Ti(*i*-PrO)$_4$ (6:5) in CH_2Cl_2 (20 mL) via syringe pump over 2 hours at – 78 °C. The reaction mixture was then stirred for an additional 20 minutes and quenched by the addition of MeOH (4.0 mL). The mixture was then poured into water and extracted with EtOAc (3x). The combined organic layers were then washed with water and 10% aqueous KF, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (10% EtOAc in Hexanes) to give the desired product (420.3 mg, 98%; 1:1 dr): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.27 (m, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 4.05-4.00 (m, 1H), 3.80 (s, 3H), 3.83-3.73 (m, 1H), 3.47 (app p, *J* = 5.6 Hz, 1H), 3.25 (app p, *J* = 5.2 Hz, 1H), 2.56-2.25 (m, 2H), 1.99 (t, *J* = 2.5 Hz, 1H), 1.64-1.55 (m, 2H), 1.35 (s, 3H), 1.32 (s, 3H), 1.45-1.26 (m, 10H), 1.11-1.06 (m, 3H), 0.89 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.7, 140.5, 140.2, 127.7, 127.5, 113.4, 81.8, 81.4, 70.3, 70.0, 65.2, 64.3, 55.2, 42.5, 42.3, 41.5, 41.0, 34.1, 33.6, 31.9, 29.5, 26.7, 26.0, 25.6, 25.1, 24.8, 24.5, 24.0, 23.5, 22.9, 22.7, 14.2.

1-Methoxy-4-[4-methoxy-1,1-dimethyl-2-(1-methylbut-3-ynyloxy)pentyl]benzene (42 & 43)



42

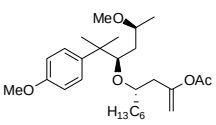


43

To 1-methoxy-4-[4-methoxy-1,1-dimethyl-2-(1-methylbut-3-ynyloxy)pentyl]benzene (420.3 mg, 1.16 mmol) in DMF at 0 °C was added NaH (186.0 mg, 4.66 mmol), and the mixture was stirred for an additional 15 minutes. MeI (496.0 mg, 3.49 mmol) was then added dropwise and the reaction mixture was slowly warmed to room temperature. The reaction mixture was then stirred for an additional 12 hours and quenched by the careful addition of water. The

mixture was then extracted with EtOAc (3x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (4% EtOAc in Hexanes) to give a separable mixture of diastereomers (297.9 mg, 69%; 1:1 dr): Faster diastereomer (**42**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, *J* = 8.8 Hz, 2H), 6.83 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 3.69 (dd, *J* = 8.8, 2.1 Hz 1H), 3.38-3.29 (m, 2H), 3.21 (s, 3H), 2.25 (ddd, *J* = 16.8, 7.4, 2.6 Hz, 1H), 2.15 (ddd, *J* = 16.8, 8.9, 2.6 Hz, 1H), 1.97 (t, *J* = 2.6 Hz, 1H), 1.63-1.57 (m, 2H), 1.52-1.42 (m, 1H), 1.33 (s, 3H), 1.30 (s, 3H), 1.33-1.25 (m, 9H), 1.03 (d, *J* = 6.0 Hz, 3H), 0.90 (t, *J* = 6. Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 157.5, 140.3, 127.7, 113.1, 81.9, 80.2, 72.9, 69.7, 55.1, 54.9, 41.9, 39.9, 33.6, 31.8, 29.5, 26.0, 25.1, 24.6, 23.4, 22.5, 19.0, 14.0; IR (neat) 3310, 2929, 1611, 1513, 1465, 1250, 829 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{40}O_3$ 388.2977, found 388.2985. Slower diastereomer (**43**) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 3.80 (s, 3H), 3.46 (t, *J* = 5.0 Hz, 1H), 3.39 (t, *J* = 5.6 Hz, 1H), 3.18 (s, 3H), 2.81 (app q, *J* = 6.3 Hz, 1H), 2.37-2.35 (m, 2H), 1.97 (t, *J* = 2.5 Hz, 1H), 1.63-1.56 (m, 2, H) 1.34 (s, 3H), 1.29 (s, 3H), 1.44-1.27 (m, 10H), 0.93-0.88 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 139.8, 127.6, 113.1, 81.8, 81.7, 74.9, 69.7, 55.9, 55.1, 42.5, 40.210, 33.5, 31.8, 29.5, 26.5, 25.1, 23.6, 22.8, 22.6, 19.0, 14.1; IR (neat) 3310, 2929, 1611, 1513, 1250, 1185, 1088, 829 cm^{-1}.

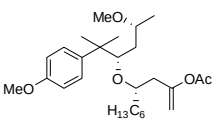
Acetic acid-3-{3-methoxy-1-[1-(4-methoxyphenyl)-1-methylethyl]butoxy}-1-methylenenonyl ester (44)



To 1-methoxy-4-[4-methoxy-1,1-dimethyl-2-(1-methylbut-3-ynyloxy)pentyl]benzene (33.0 mg, 0.08 mmol) in toluene (2 mL) was added Na_2CO_3 (1.2 mg, 0.0012 mmol) and acetic acid (9.6 mg, 0.16 mmol, 16 μL). The mixture was then stirred at room temperature for 10 min and [Ru(*p*-cymene)Cl_2]$_2$ (2.0 mg, 0.003 mmol) and

tri-2-furylphosphine (1.6 mg, 0.006 mmol) were added. The reaction mixture was then warmed to 60 °C and stirred for an additional 15 h. The mixture was then cooled to room temperature and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (5% EtOAc in Hexanes) to provide the desired product (14.9 mg, 43%): ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.28 (d, *J* = 8.8 Hz, 2H), 6.83, (d, *J* = 8.8 Hz, 2H), 4.78 (s, 1H), 4.74 (s, 1H), 3.79 (s, 3H), 3.71 (dd, *J* = 9.0, 1.9 Hz, 1H), 3.34-3.26 (m, 2H), 3.21 (s, 3H), 2.62 (dd, *J* = 14.4, 4.9 Hz, 2.16 (dd, *J* = 14.4, 7.7 Hz, 1H), 2.11 (s, 3H), 1.51-1.47 (m, 1H), 1.45-1.42 (m, 3H), 1.31 (s, 3H), 1.27 (s, 3H), 1.28-1.19 (m, 8H), 1.03 (d, *J* = 5.9 Hz, 0.90 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 168.8, 157.5, 154.0, 140.5, 127.6, 113.7, 103.1, 79.5, 75.9, 72.8, 55.1, 54.9, 42.1, 39.8, 38.2, 34.0, 31.8, 29.6, 25.6, 25.1, 22.6, 21.1, 18.9, 14.0; IR (neat) 2929, 2857, 1758, 1513, 1465, 1250, 1194, 1038 cm^{-1}; HRMS (EI): calcd for $C_{17}H_{31}O_4$ (M^+ - $C_{10}H_{13}O$) 299.2222, found 299.2224.

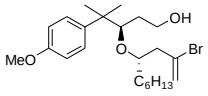
Acetic acid-3-{3-methoxy-1-[1-(4-methoxyphenyl)-1-methylethyl]butoxy}-1-methylenenonyl ester (45)



To 1-methoxy-4-[4-methoxy-1,1-dimethyl-2-(1-methylbut-3-ynyloxy)pentyl]benzene (146.4 mg, 0.39 mmol) in toluene (3 mL) was added Na_2CO_3 (6.0 mg, 0.062 mmol) and acetic acid (46.9 mg, 0..78 mmol, 44.0 μL). The mixture was then stirred at room temperature for 10 min and [Ru(*p*-cymene)Cl_2]$_2$ (9.0 mg, 0.015 mmol) and tri-2-furylphosphine (7.0 mg, 0.030 mmol) were added. The reaction mixture was then warmed to 60 °C and stirred for an additional 15 h. The mixture was then cooled to room temperature and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (6% EtOAc in Hexanes) to provide the desired product (60.0 mg, 34%): ^{1}H NMR (300 MHz, $CDCl_3$) δ= 7.30 (d, *J* = 8.9 Hz, 2H), 6.83 (d, *J* = 8.9 Hz, 2H), 4.78 (s, 1H),

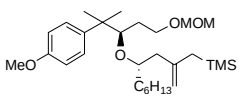
4.73 (s, 1H), 3.79 (s, 3H), 3.64 (dd, *J* = 8.7, 2.4 Hz, 1H), 3.36-3.27 (m, 2H), 3.20 (s, 3H), 2.39 (dd, *J* = 14.7, 4.9 Hz, 1H), 2.24 (dd, *J* = 14.7, 7.1 Hz, 1H), 2.09 (s, 3H), 1.55-1.42 (m, 4H), 1.31-1.21 (m, 8H), 1.31 (s, 3H), 1.27 (s, 3H), 1.02 (d, *J* = 6.0 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 168.9, 157.5, 153.8, 140.3, 127.7, 113.1, 103.5, 79.8, 72.9, 55.1, 54.9, 42.1, 39.9, 37.8, 33.2, 31.8, 29.5, 25.0, 24.7, 22.6, 21.0, 18.9, 14.0; IR (neat) 2930, 2858, 1758, 1513, 1465, 1250, 1038 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{31}O_4$ (M^+ - $C_{10}H_{13}O$) 299.2222, found 299.2224.

3-[1-(2-Bromoallyl)heptyloxy]-4-(4-methoxyphenyl)-4-methylpentan-1-ol (46)



To **26** (200.0 mg, 0.62 mmol) and 2-bromoallyltrimethyl silane (239.0 mg, 1.24 mmol) in CH_2Cl_2 (5.0 mL) at – 78 °C was added $TiCl_4$ (130.0 mg, 0.68 mmol). The reaction mixture was then stirred at – 78 °C for an additional 15 minutes and quenched by the addition of $NaHCO_3$ (aq). The mixture was then warmed to room temperature and extracted with CH_2Cl_2 (3x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (8% EtOAc in Hexanes) to give the desired product as a 2:1 inseparable mixture of diastereomers (171.3 mg, 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 5.60 (s, 1H), 5.44 (s, 1H), 3.79 (s, 3H), 3.73-3.71 (m, 1H), 3.65-3.60 (m, 1H), 3.52-3.48 (m, 2H), 2.76-2.70 (m, 1H), 2.46-2.42 (m, 1H), 1.71-1.57 (m, 4H), 1.31 (s, 3H), 1.29 (s, 3H), 1.33-1.27 (m, 8H), 0.92-0.89 (m, 3H).

{4-[1-(2-Methoxymethoxyethyl)-2-(4-methoxyphenyl)-2-methylpropoxy]-2-methylenedecyl}trimethylsilane (47)

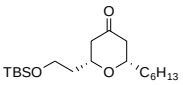


To **46** (161.5 mg, 0.37 mmol) in CH_2Cl_2 (1.0 mL) at room temperature was

added DIPEA (1.0 mL) and MOMCl (44.0 mg, 0.55 mmol). The reaction mixture was then warmed to 40 °C and stirred at that temperature for an additional 5 hours. The reaction mixture was then cooled to room temperature and quenched by the addition of water. The mixture was then extracted with CH_2Cl_2 (2x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (5% EtOAc in Hexanes) to give the desired product (171.6 mg, 95%) which was used immediately in the following reaction.

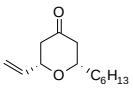
To 1-{2-[1-(2-Bromoallyl)heptyloxy]-4-methoxymethoxy-1,1-dimethylbutyl}-4-methoxy benzene (170.0 mg, 0.35 mmol) in THF (2.0 mL) at room temperature was added $Pd(PPh_3)_4$ (20.0 mg, 0.017 mmol) and trimethylsilylmethyl magnesium chloride (1.75 mL, 1.75 mmol). The reaction mixture was then warmed to 80 °C and stirred at that temperature for an additional 4 hours. The reaction mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The resulting residue was then purified via flash column chromatography (5% EtOAc in Hexanes) to give the desired product (109.8 mg, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 4.60-4.54 (m, 2H), 4.51-4.48 (m, 2H), 3.79 (s, 3H), 3.60-3.55 (m, 2H), 3.36-3.30 (m, 2H), 3.28 (s, 3H), 2.27 (td, *J* = 13.1, 4.8 Hz, 1H), 1.90 (td, *J* = 13.1, 7.6 Hz, 1H), 1.6-1.63 (m, 2H), 1.55-1.52 (m, 4H), 1.34 (s, 3H), 1.30 (s, 3H), 1.30-1.27 (m, 6H), 0.92-0.88 (m, 3H), 0.05 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.6, 145.0, 127.7, 113.3, 109.7, 96.3, 80.1, 55.3, 55.2, 42.5, 32.33, 32.0, 29.8, 27.2, 25.3, 22.8, 14.2, -1.1; IR (neat) 2930, 1513, 1465, 1296, 1249, 1109, 1077 cm^{-1}; HRMS (EI) calcd for $C_{31}H_{51}O_4Si$ (M^+) 515.3557, found 515.3535.

2-[2-(*tert*-Butyldimethylsilanyloxy)ethyl]-6-hexyltetrahydropyran-4-one (48)



To acetic acid-3-[1-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-2-(4-methoxyphenyl)-2-methylpropoxy]-1-methylenenonyl ester (30.0 mg, 0.056 mmol) in DCE (1.2 mL) was added $NaHCO_3$ (60.0 mg, 0.7 mmol) and 4 Å molecular sieves (60.0 mg). The mixture was then stirred at room temperature for 10 min and CAN (122.0 mg, 0.22 mmol) in CH_3CN (0.5 mL) was added dropwise. The reaction was then stirred for an additional 20 min and filtered through a silica plug. The filtrate was then concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (7% EtOAc in Hexanes) to provide the desired product (16.8 mg, 88%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.86-3.75 (m, 3H), 3.60-3.56 (m, 1H), 2.40 (d, J = 14.2 Hz, 2H), 2.31-2.22 (m, 2H), 1.86-1.82 (m, 1H), 1.77-1.74 (m, 2H), 1.52-1.50 (m, 2H), 1.33-1.28 (m, 8H), 0.92 (s, 9H), 0.92-0.89 (m, 3H), 0.08 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 207.6, 73.6, 58.9, 48.0, 39.4, 36.5, 31.7, 29.1, 25.9, 25.3, 22.5, 14.0, -5.3; IR (neat) 2930, 2856, 1723, 1470, 1252, 1093 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{37}O_3Si$ (M^+ - H): 341.2512, found 341.2520.

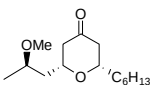
2-Hexyl-6-vinyltetrahydropyran-4-one (49)



To acetic acid-3-{1-[1-(4-methoxyphenyl)-1-methylethyl]allyloxy}-1-methylenenonyl ester (33.0 mg, 0.08 mmol) in DCE (2.2 mL) was added $NaHCO_3$ (66.0 mg, 0.78 mmol) and 4Å molecular sieves (66.0 mg). The mixture was then stirred at room temperature for 15 min and CAN (190.0 mg, 0.34 mmol) in CH_3CN (1.0 mL) was added dropwise. The reaction was then stirred for an additional 20 min and filtered through a silica plug. The filtrate was then concentrated and the resulting residue was purified via flash column chromatography (4% EtOAc in Hexanes) to provide the desired product (12.1 mg, 70%): ^{1}H

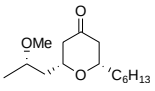
NMR (300 MHz, $CDCl_3$) δ= 5.92 (ddd, *J* = 17.2, 10.5, 5.4 Hz, 1H), 5.32, (dt, *J* = 17.2, 1.3 Hz, 1H), 5.21 (dt, *J* = 10.5, 1.2 Hz, 1H), 4.10 (dddd, *J* = 11.2, 6.5, 3.0, 1.2 Hz, 1H), 3.63 (dtd, *J* = 14.5, 4.7, 2.7 Hz, 1H), 2.47-2.39 (m, 2H), 2.38-2.21 (m, 2H), 1.73-1.67 (m, 1H), 1.60-1.52 (m 1H), 1.36-1.24 (m, 8H), 0.88 (t, *J* = 6. Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 206.9, 137.3, 115.9, 47.8, 47.4, 36.4, 31.7, 29.1, 25.1, 22.5, 14.0; IR (neat) 2929, 2857, 1722, 1251, 1061 cm^{-1}; HRMS (EI): calcd for $C_{13}H_{22}O_2$ (M^+) 210.1619, found 210.1609.

2-Hexyl-6-(2-methoxypropyl)tetrahydropyran-4-one (50)



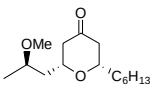
To acetic acid-3-{3-methoxy-1-[1-(4-methoxyphenyl)-1-methyl]butoxy}-1-methylenenonyl ester (33.1 mg, 0.076 mmol) in DCE (1.2 mL) was added $NaHCO_3$ (66.0 mg, 0.78 mmol) and 4Å molecular sieves (66.0 mg). The mixture was then stirred at room temperature for 15 min and CAN (167.0 mg, 0.30 mmol) in CH_3CN (0.5 mL) was added dropwise. The reaction mixture was then stirred for an additional 15 min and filtered through a silica plug. The filtrate was then concentrated under reduced pressure and the resulting residue was purified via flash column chromatography (6% EtOAc in Hexanes) to provide the desired product (19.4 mg, 100%): ^1H NMR (300 MHz, $CDCl_3$) δ 3.83-3.76 (m, 1H), 3.63-3.53 (m, 1H), 3.33 (s, 3H), 2.35 (ddt, *J* = 12.6, 7.7, 1.9 Hz, 2H), 2.25-2.16 (m, 2H), 1.73-1.63 (m, 2H), 1.54-1.44 (m, 2H), 1.32-1.28 (m, 8H), 1.17 (d, *J* = 6.1 Hz, 3H), 0.89 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$ δ 207.5, 73.7, 73.1, 56.3, 48.2, 48.1, 44.2, 36.4, 31.7, 29.0, 25.4, 22.6, 19.4, 14.0: IR (neat) 2929, 2857, 1721, 1091 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{28}O_3$ (M^+) 256.2038, found 256.2035.

2-Hexyl-6-(2-methoxypropyl)tetrahydropyran-4-one (51)



To acetic acid-3-{3-methoxy-1-[1-(4-methoxyphenyl)-1-methylethyl]butoxy}-1-methylenenonyl ester (40.5 mg, 0.09 mmol) in DCE (2.2 mL) was added $NaHCO_3$ (80.0 mg, 0.95 mmol) and 4Å molecular sieves (80.0 mg). The mixture was then stirred at room temperature for 15 min and CAN (195.0 mg, 0.36 mmol) in CH_3CN (1.0 mL) was added dropwise. The reaction mixture was then stirred for an additional 10 min and filtered through a silica plug. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified via flash column chromatography (6% EtOAc in Hexanes) to provide the desired product (22.3 mg, 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ= 3.73-3.66 (m, 1H), 3.56-3.46 (m, 2H), 3.31 (s, 3H), 2.37 (ddt, *J* = 14.5, 9.2, 2.3 Hz, 2H), 2.26-2.17 (m, 2H), 2.02 (p, *J* = 6.8 Hz, 1H), 1.68-1.50 (m, 5H), 1.34-1.25 (m, 6H), 1.18 (d, *J* = 3.1 Hz, 3H), 0.89 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 207.4, 74.0, 73.3, 55.9, 48.0, 47.9, 42.7, 36.4, 31.7 29.0, 25.3, 22.5, 18.9, 14.0; IR (neat) 2929, 2857, 1721, 1375, 1091 cm^{-1}; HRMS (EI): calcd for $C_{15}H_{28}O_3$ (M^+) 256.2038 found 256.2035.

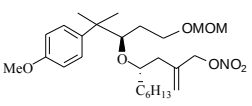
2-Hexyl-6-(2-methoxypropyl)tetrahydropyran-4-one (50)



To acetic acid 3-{3-methoxy-1-[1-(4-methoxyphenyl)-1-methylethyl]butoxy}-1-methylenenonyl ester (60.4 mg, 0.13 mmol) in DCE (2.2 mL) was added $NaHCO_3$ (120.0 mg, 1.4 mmol) and 4Å molecular sieves (120.0 mg). The mixture was then stirred at room temperature for 15 min and CAN (295.0 mg) in CH_3CN (1.0 mL) was added dropwise. The reaction mixture was then stirred for an additional 15 min and filtered through a silica plug. The filtrate was then concentrated under reduced pressure, and the resulting residue was purified via flash column chromatography (6% EtOAc in Hexanes) to provide the desired product (32.1 mg, 96%): ^{1}H NMR (500 MHz, $CDCl_3$) δ= 3.81-3.77 (m, 1H), 3.62-3.55 (m, 2H), 3.33 (s, 3H),

2.35 (app. t, J = 7.6 Hz, 2H), 2.24-2.18 (m, 2H), 1.71-1.68 (m, 1H), 1.63-1.57 (m, 1H), 1.51-1.47 (m, 2H), 1.30-1.26 (m, 8H), 1.16 (d, J = 6.1 Hz, 3H), 0.89 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ= 207.9, 73.4, 72.9, 56.5, 48.1, 44.0, 36.3, 31.7, 29.0, 25.5, 22.6, 19.3, 14.1; IR (neat) 2929, 2857, 1721, 1091 cm^{-1}; HRMS (EI): calcd for $C_{15}H_{28}O_3$ (M^+) 256.2038, found 256.3031.

1-Methoxy-4-{4-methoxymethoxy-1,1-dimethyl-2-[1-(2-nitrooxymethylallyl) heptyloxy]butyl}benzene (52)



To {4-[1-(2-methoxymethoxyethyl)-2-(4-methoxyphenyl)-2-methylpropoxy]-2-methylenedecyl}trimethylsilane (40.4 mg, 0.08 mmol) in DCE (2.5 mL) was added 4Å molecular sieves (80.0 mg) and $NaHCO_3$ (80.0 mg, 0.9 mmol). The reaction mixture was then stirred for 10 min and CAN (89.0 mg, 0.16 mmol) in CH_3CN (1.2 mL) dropwise. After 5 min, the reaction mixture was concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (7% EtOAc in Hexanes) to provide the nitrated product (28.7 mg, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, J = 8.7 Hz, 2H), 6.83 (d, J = 8.7 Hz, 2H), 5.17 (s, 1H), 5.06 (s, 1H), 4.87 (s, 2H), 4.51 (s, 2H), 3.79 (s, 3H), 3.54 (dd, 6.4, 3.9 Hz, 1H), 3.34-3.22 (m, 3H), 3.29 (s, 3H), 2.30 (dd, J = 14.0, 6.4 Hz, 1H), 2.20 (dd, J = 14.0, 5.5 Hz, 1H), 1.75-1.65 (m, 2H), 1.44-1.36 (m, 4H), 1.32 (s, 3H), 1.28 (s, 3H), 1.25-1.23 (m, 6H), 0.90 (t, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.8, 139.9, 139.0, 127.7, 117.4, 113.3, 96.3, 80.4, 75.7, 65.7, 55.3, 42.1, 38.2, 33.2, 32.3, 31.9, 29.7, 26.1, 25.3, 24.0, 22.7, 14.2; IR (neat) 2931, 1633, 1513, 1252, 1037 cm^{-1}; HRMS (EI) calcd for $C_{28}H_{42}NO_7$ (M^+) 504.2961, found 504.2921.

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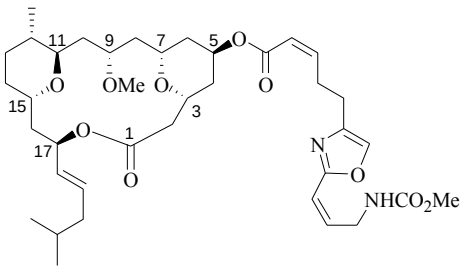
Chapter 3 Efforts toward the Total Synthesis of Leucascandrolide A

3.1. Introduction

I. Background

(+)-Leucascandrolide A (**1**), a marine macrolide, was isolated in 1996 off the coast of New Caledonia from the calcareous sponge *Leucascandra caveolata* Borojevic and Klautau by Pietra and co-workers (**Figure 38**).[1] While leucocandrolide A was isolated in significant quantities from sponges collected in 1989 (0.03%), sponge samples collected in 1994 did not provide any leucascandrolide A.[2] The exact origin of leucascandrolide A is still unknown, however, the samples of sponge collected in 1989 showed extensive dead portions and are believed to have been heavily colonized. This, along with the failure to isolate **1** from the 1994 harvest, suggests leucascandrolide A was produced by microorganisms. Due to the inability to reliably isolate **1** from natural sources, total synthesis provides the only predictable method of obtaining access to this interesting molecule.

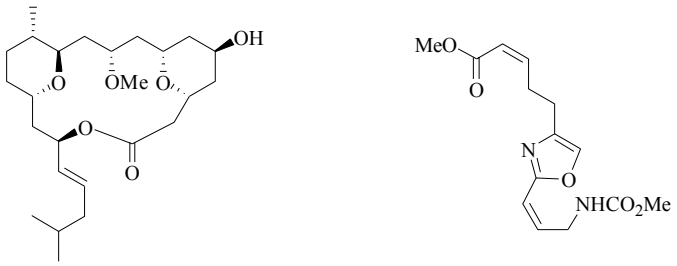


1

Figure 38: (+)-Leucascandrolide A.

The structure of leucascandrolide A (**1**) was assigned using HR-EI-MS, ^{13}C NMR, DEPT and advanced two dimensional NMR experiments.[1] The core of leucascandrolide A consists of a 18-membered macrolactone containing two bridging tetrahedrapyran rings, one of which contains a 2,6-*syn*-substitution pattern. Leucascandrolide A's structure is characterized by extensive 1,3 dioxygenation throughout the macrolide core, and contains an unusual ester side chain with an α,β-unsaturated oxazole at C5. The absolute configuration of leucascandrolide A was determined through hydrolysis of the C5 ester followed by inversion of the C5 stereocenter and formation of the Mosher esters. Analysis of the ^{1}H data provided an unambiguous assignment of leucascandrolide A's absolute configuration.

Leucascandrolide A was the first potently biologically active metabolite isolated from a calcareous sponge.[2] The raw sponge extracts proved to be highly antimicrobial, toxic and cyctoxic with the activity being attributed to leucascandrolide A.[1] Purified samples of leucascandrolide A exhibited potent cyctoxic acitivity *in vitro* on human KB throat epithelial cancer cells (IC_{50} = 71.0 nM), and slightly less potent activity against P388 murine leukemia cells (IC_{50} = 350.0 nM).[1] Leucascandrolide A has also shown potent antifungal activity against *Candida albicans*, a pathogenic yeast that attacks AIDS patients. Pietra and co-workers[1] were able to isolate macrolide (**2**) away from the oxzaole containing side chain (**3**) and analyzed their respective biological activities (**Figure 39**). These experiments demonstrated that macrolide (**2**) is essential for cyctoxicity while the oxazole containing side chain (**3**) is necessary for antifungal activity.

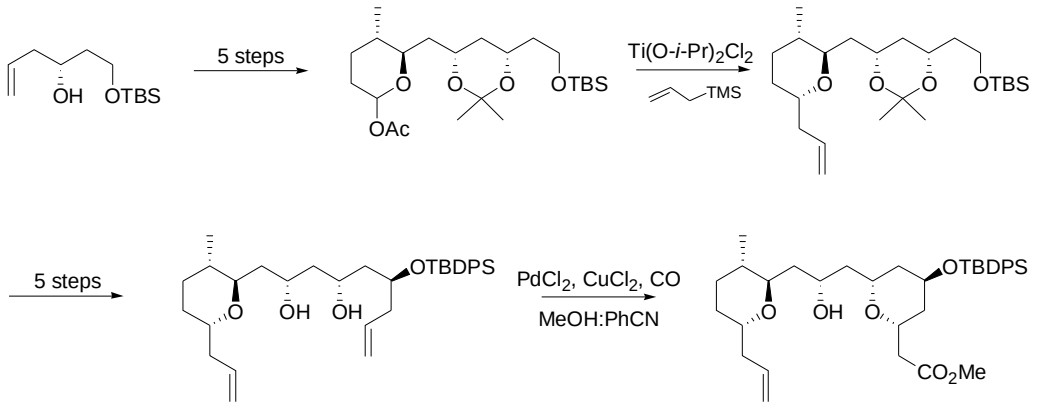


2 **3**

Figure 39: Macrolide (**2**) and oxazole containing side chain (**3**) of leucascandrolide A.

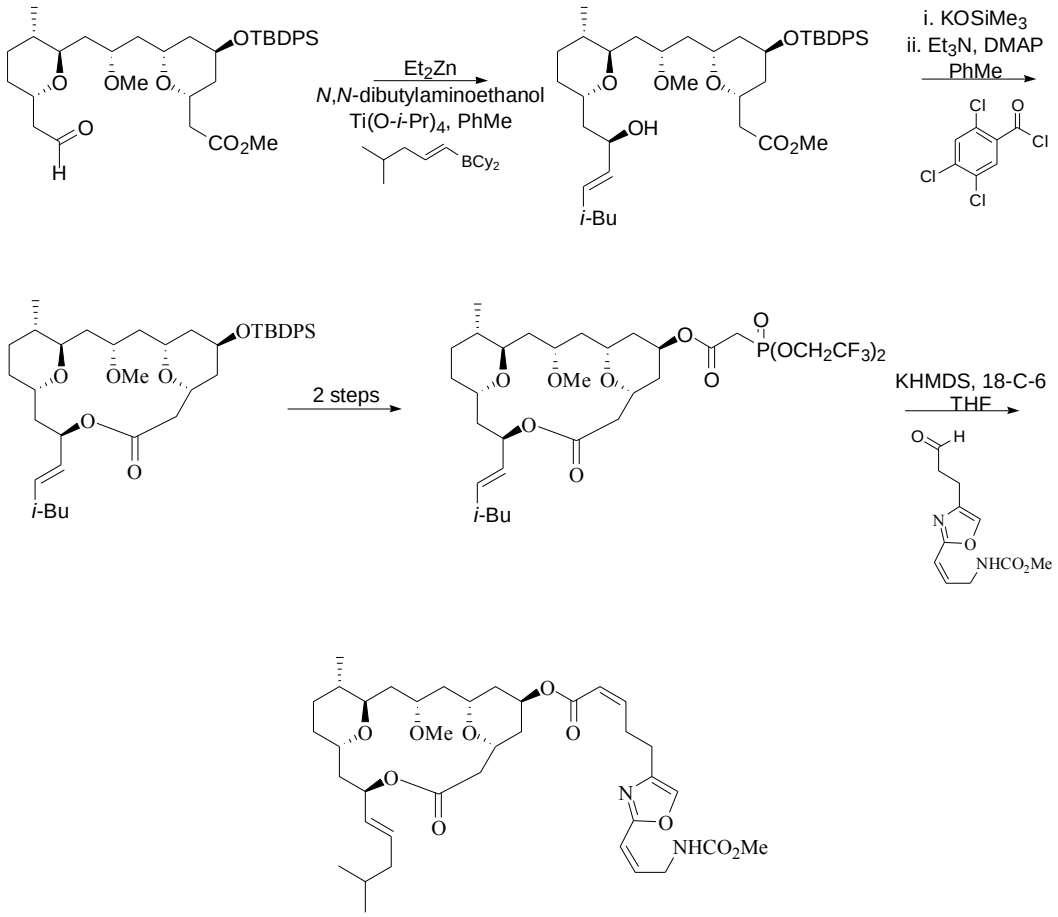
II. Previous Syntheses

The first total synthesis of leucascandrolide A was reported 2000 by Leighton and co-workers.[4] Leighton's synthesis proceeds in 20 steps (longest linear sequence) and is highlighted by the efficient use of carbonylation chemistry to introduce the requisite oxygenation present. The C11-C15 *trans*-2,6-tetrahydropyran was obtained through an anomeric alkylation, while an intramolecular alkoxycarbonylation was used to introduce the C3-C7 *syn*-2,6-tetrahydropyran according to Semmelhack's protocol.[5] Both reactions provided the respective tetrahydropyrans with excellent levels of diastereocontrol (> 10:1) (**Scheme 21**).



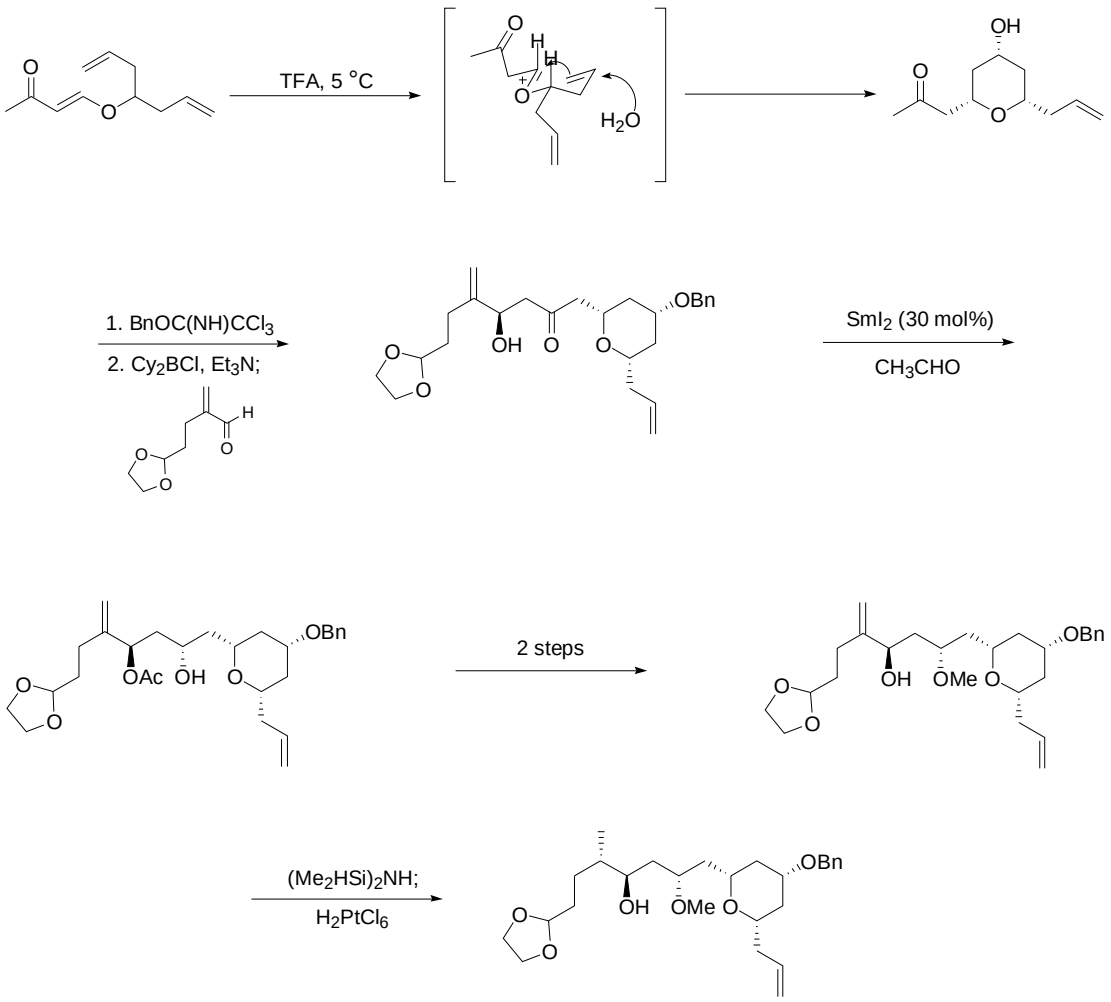
Scheme 21: Leighton's synthesis of Leucascandrolide A's bis-THP backbone.

Elaboration of the C15 side chain was achieved through the diastereoselective addition of a vinylzinc species to the C17 aldehyde. Although this method provided the desired bond construction, the selectivity of the addition was a modest 3:1. The macrolide synthesis was then completed by exposure of the seco-acid and immediate macrolactonization using the Yaonemitsu-modified Yamaguchi protocol.[6] The C5 ester side chain was appended via esterification followed by a Still-Gennari coupling to provide a 7:1 mixture of olefin isomers in favor of the required (*Z*)-isomer (**Scheme 22**).



Scheme 22: Completion of Leucascandrolide A.

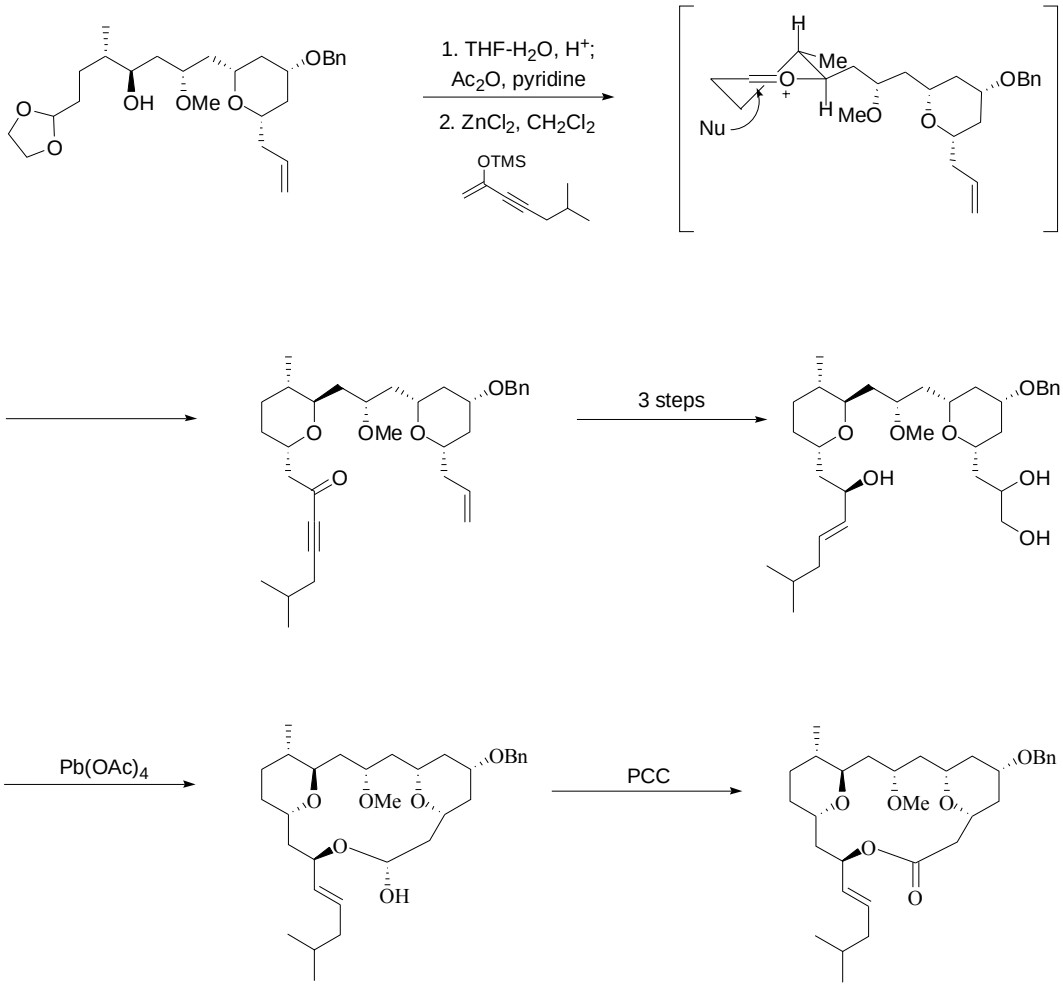
In 2001, Kozmin[7] reported an elegant and efficient stereocontrolled synthesis of the C1-C15 fragment of leucascandrolide A. The synthesis began with a highly selective construction of the all *syn*-2,4,6-tetrahydropyran using a Prins desymmetrization strategy (**Scheme 23**). The all equatorial arrangemet was confirmed through DQF COSY and NOESY NMR experiments. With the desired relative stereochemistry of the tetrahydropyran, Kozmin implemented a boron-enolate mediated aldol with excellent levels of 1,5-*anti* diastereocontrol (>95:5) following Paterson's protocol.[8] A samarium mediated[9] *anti*-selective reduction of the resulting β-hydroxy ketone provided the requiste 1,3-*anti* dioxygenation. A hydrosilyation/desilyation protocol was effective in providing the remaining stereocenter as an 87:13 mixture of diastereomers.



Scheme 23: Kozmin's approach to the C1-C15 fragment of leucascandrolide A.

Kozmin's total synthesis of leucascandrolide A began with formation of the *trans*-2,6-tetrahydropyran and subsequent incorporation of the C15 side chain (**Scheme 24**). This proceeded through removal of the C15 acetal followed by trapping of the intermediate lactol with acetic anhydride. Lewis acid mediated C-glycosidation of the acyl lactol provided the *trans*-2,6-tetrahydropyran as a single diastereomer with incorporation of the C15 side chain's carbon skeleton. Moderate levels of diastereocontrol were obtained in setting the C17, however the undesired isomer is also a viable synthetic intermediate. In addition to the elegant use of

substrate control to establish leucascandrolide A's relative stereochemistry, Kozmin observed an unprecedented macrolactolization while completing the synthesis. While this provided an expedient method for closing the macrolactone, it also demonstrates the unusual thermodynamic stability of this macrocycle.



Scheme 24: Kozmin's unexpected route to macrolactonization.

The ability to efficiently set the C17 stereocenter with high levels of selectivity was established by Paterson and co-workers in their 2003 total synthesis of leucascandrolide A. Paterson envisioned a 1,3-*syn*-selective reduction (**Figure 40**) of the enone resulting from C-

glycosidation, with subsequent Mitsunobu macrolactonization. Therefore, several reducing agents were screened in the presence of chelating Lewis acids with lithium tri*ert*butoxyaluminum hydride/zinc bromide providing only moderate control (5:1). Interestingly, use of lithium tri*ert*-butoxyaluminum hydride alone resulted in formation of the C17 stereocenter with excellent levels of diastereocontrol (>32:1). This suggests the reduction may be proceeding through a non-chelated intermediate and that Evans polar model[12] may explain the high levels of stereocontrol.

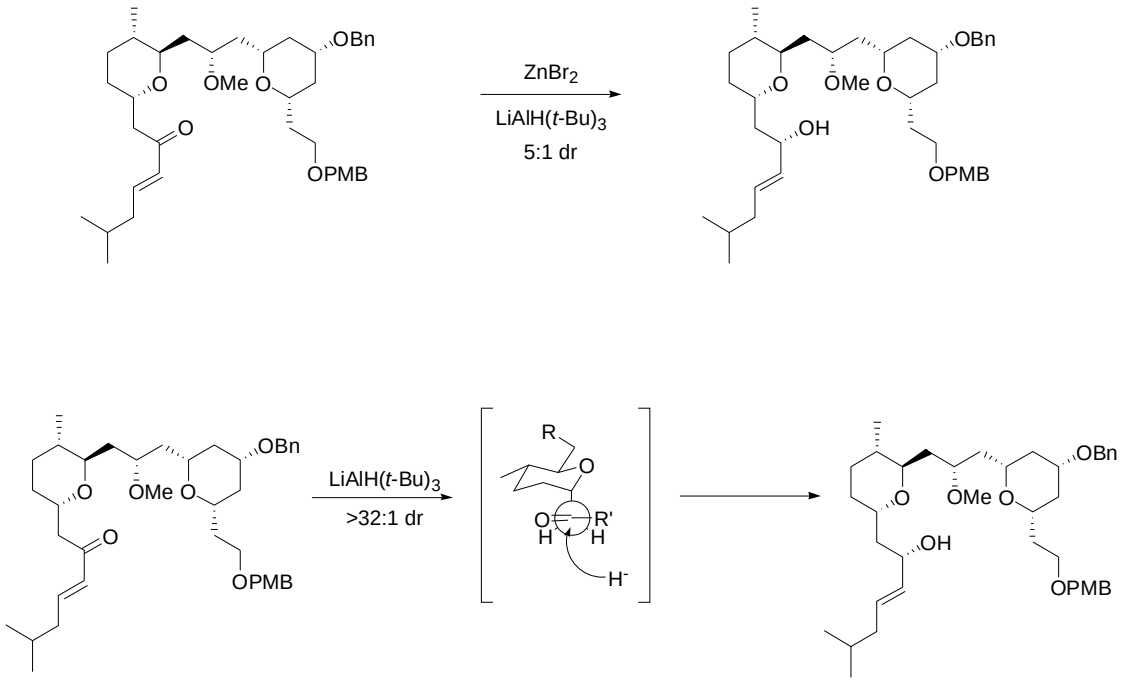
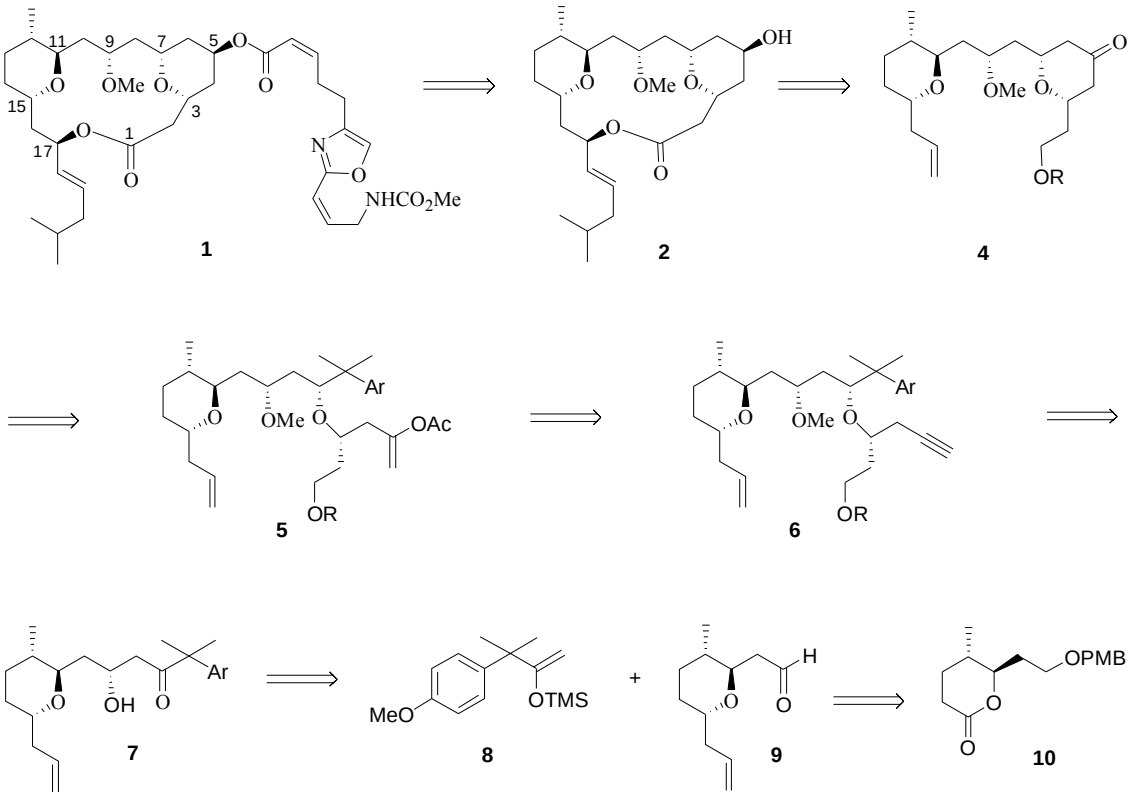


Figure 40: Paterson's stereocontrolled reduction of the C17 stereocenter.

III. Retrosynthesis

The retrosynthesis of leucascandrolide A outlined in **Figure 41** allows for introduction of the C3-C7 *syn*-2,6-tetrahydropyran ring to be introduced via a diastereoselective *endo*-ETIC reaction. The initial disconnection at the C5 ester side chain leads to the leucascandrolide A macrolide **2**, which contains all of the stereogenic centers found in the natural product. Elaboration of the C15 side chain of **4** followed by macrolactonization would provide the desire macrolide **2**. The *syn*-2,6-tetrahydropyranone was to arise from the diastereoselective cyclization of enol acetate **5** using the ETIC reaction developed in our lab.[13] Enol acetate **5** can be derived from the metal mediated addition of acetic acid to homopropargylic ether **6**, which arises from a diastereoselective opening of a cyclic acetal. The cyclic acetal was expected to come from the *syn*-1,3-diol obtaining by the directed reduction of β-hydroxy ketone **7**. The β-hydroxy ketone (**7**) would be formed through a Mukaiyama aldol between silyl enol ether **8** and aldehyde **9**. Aldehyde **9**, was envisioned to arise from a straight forward four step sequence from lactone **10.** Lactone **10** was to be derived from a tandem hydroesterification/lactonization[14] of a homoallylic alcohol.



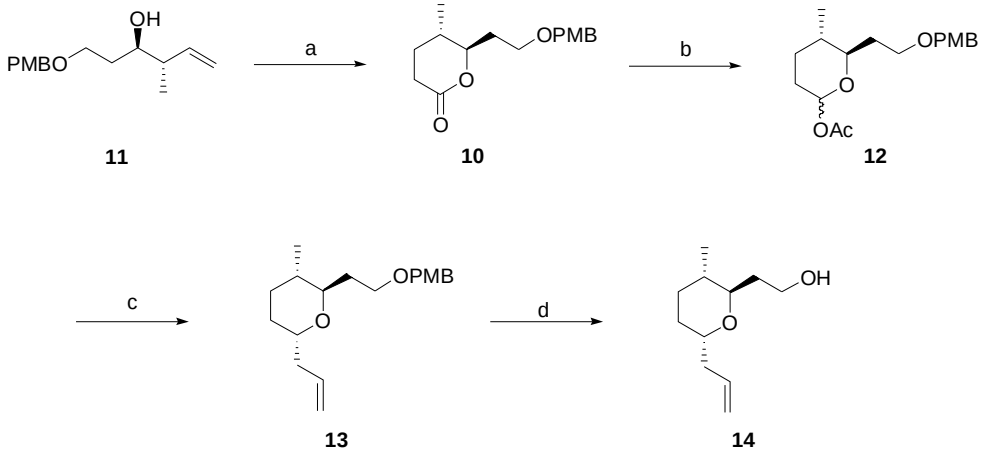
Ar = *p*-methoxyphenyl.

Figure 41: Retrosynthetic approach to leucascandrolide A.

3.2. Results and Discussion

The synthesis of leucascandrolide A began with the preparation of *trans*-2,6-tetrahydropyran **14** (**Scheme 25**). This proceeded through a highly diastereoselective four step sequence beginning with the known racemic alcohol **11**.[15] Alcohol **11** was subjected to the ruthenium catalyzed hydroesterification/lactonization protocol developed in our labs[14] to give lactone **10** in 51% yield. Lactone **10** was then converted to the acyl lactol **12** according to Rychnovsky's[16] one pot reduction/acylation condtions. Treatment of the acyl lactol **12** with

$BF_3{\cdot}OEt_2$ in the presence of allyltrimethylsilane provided tetrahydropyran **13** as a single diastereomer.[17] The conformation of **13** was determined through coupling constant analysis of the ^1H NMR spectrum. The *p*-methoxybenzyl ether was then oxidatively removed using DDQ to give alcohol **14** in nearly quantitative yield.



Reagents and Conditions: a) i. $Ru_3(CO)_{12}$ (5 mol%), 2-pyridylmethyl formate, NMO (15 mol%), 110 °C; ii. HOAc/THF/H_2O (1:2:1), 85 °C (51%); b) i. DIBAL, CH_2Cl_2, - 78 °C; ii. pyridine, DMAP, Ac_2O, - 78 °C – - 35 °C (92%); c) $BF_3{\cdot}OEt_2$, allyltrimethylsilane, CH_2Cl_2, - 78 °C (78%), d) DDQ, CH_2Cl_2:pH 7 buffer (10:1) (quant).

Scheme 25: Synthesis of the *trans*-2,6-tetrahydropyran.

The highly stereoselective nature of the C-glycosidation reaction results axial attack of the ground state conformation in which both the akyl groups occupy pseudo equatorial positions. Axial delivery of the nucleophile from the ring flip conformation is highly disfavored due to the developing *syn*-pentane interaction, and the pseudo axial orientation of the alkyl groups (**Figure 42)**.

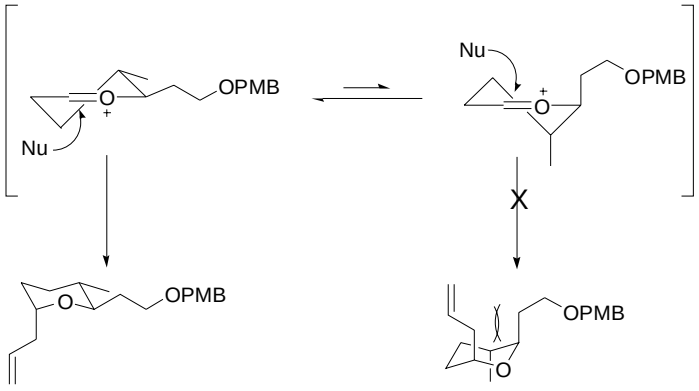
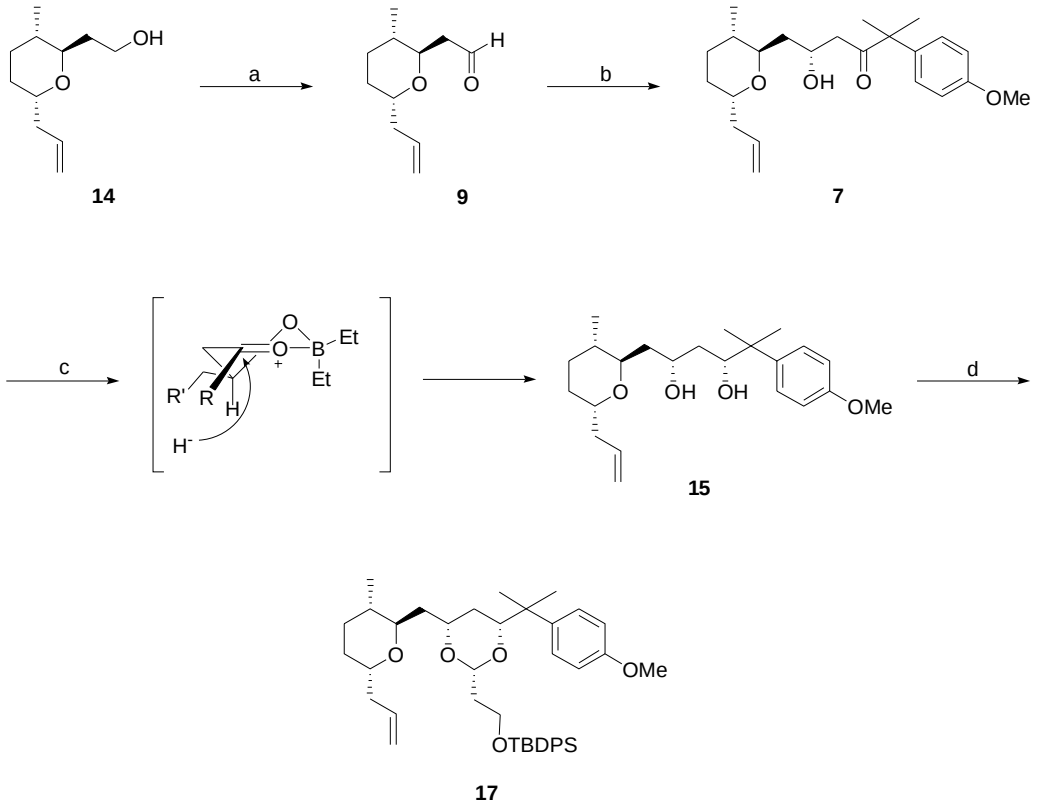


Figure 42: Mechanism for the stereocontrol in the C-glycosidation reaction.

Oxidation of alcohol **14** with Dess-Martin periodinane provided aldehyde **9** which was used immediately in the following reaction (**Scheme 26**). Treatment of aldehyde **9** $BF_3 \cdot OEt_2$ in the presence of silyl enol ether **8**[18] provided β-hydroxy ketone **7** as a single diastereomer in 76% yield. The β-hydroxy ketone (**7**) was then selectively reduced to the *syn*-1,3-diol (**15**) with $LiBH_4$ and Et_2BOMe[19] as a chelating group as a 5:1 mixture of separable diastereomers. Condensation of the major diastereomer with known[20] aldehyde (**16**) under refluxing benzene with catalytic *p*-TsOH failed to provide the desired acetal. However following Noyori's protocol,[21] diol **15** was converted to the bis-trimethylsilyl ether and reacted with aldehyde **16** in the presence of catalytic TMSOTf afforded acetal **17** in 76% over 2 steps.



Reagents and Conditions: a) Dess-Martin periodinane, pyridine, CH_2Cl_2 (89%); b) **9**, $BF_3{\cdot}OEt_2$, propionitrile, - 78 °C (76%); c) i. Et_2BOMe, THF, -78°C, 1h; ii. $LiBH_4$, THF, - 78 °C (84%, 3.2:1 dr); d) i. TMSOTf, 2,6-lutidine, - 78 °C; ii. **18**, TMSOTf, - 78 °C – - 55 °C (76% over 2 steps).

Scheme 26: Formation of cyclic acetal **17**.

Excellent levels of 1,3-*anti* diastereocontrol may be obtained in additions to β-alkoxy aldehydes through the use of a chelating Lewis acid in the presence of a nucleophile.[22] However, the Mukaiyama aldol used to construct β-hydroxy ketone **7** was performed with $BF_3{\cdot}OEt_2$, which is non-chelating Lewis acid. Evans' polar model provides a transition state which explains the

highly selective nature of this transformation.[12] This model predicts the reactive conformer will exist in a dipole minimized arrangement, and places the largest alkyl group perpendicular to the aldehyde's π-system. The alkyl group then blocks one face of the aldehyde from nucleophilic attack, and the nucleophile attacks from the opposite face (**Figure 43**).

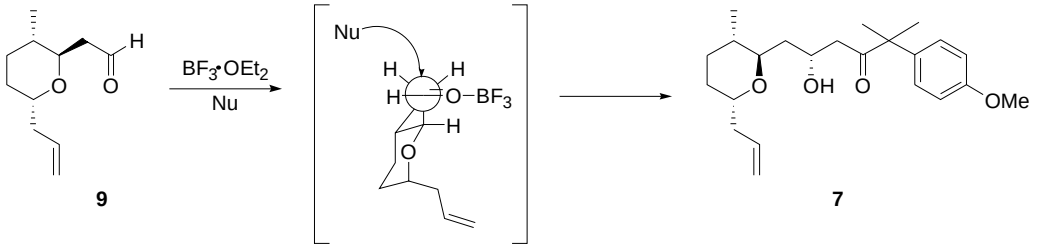
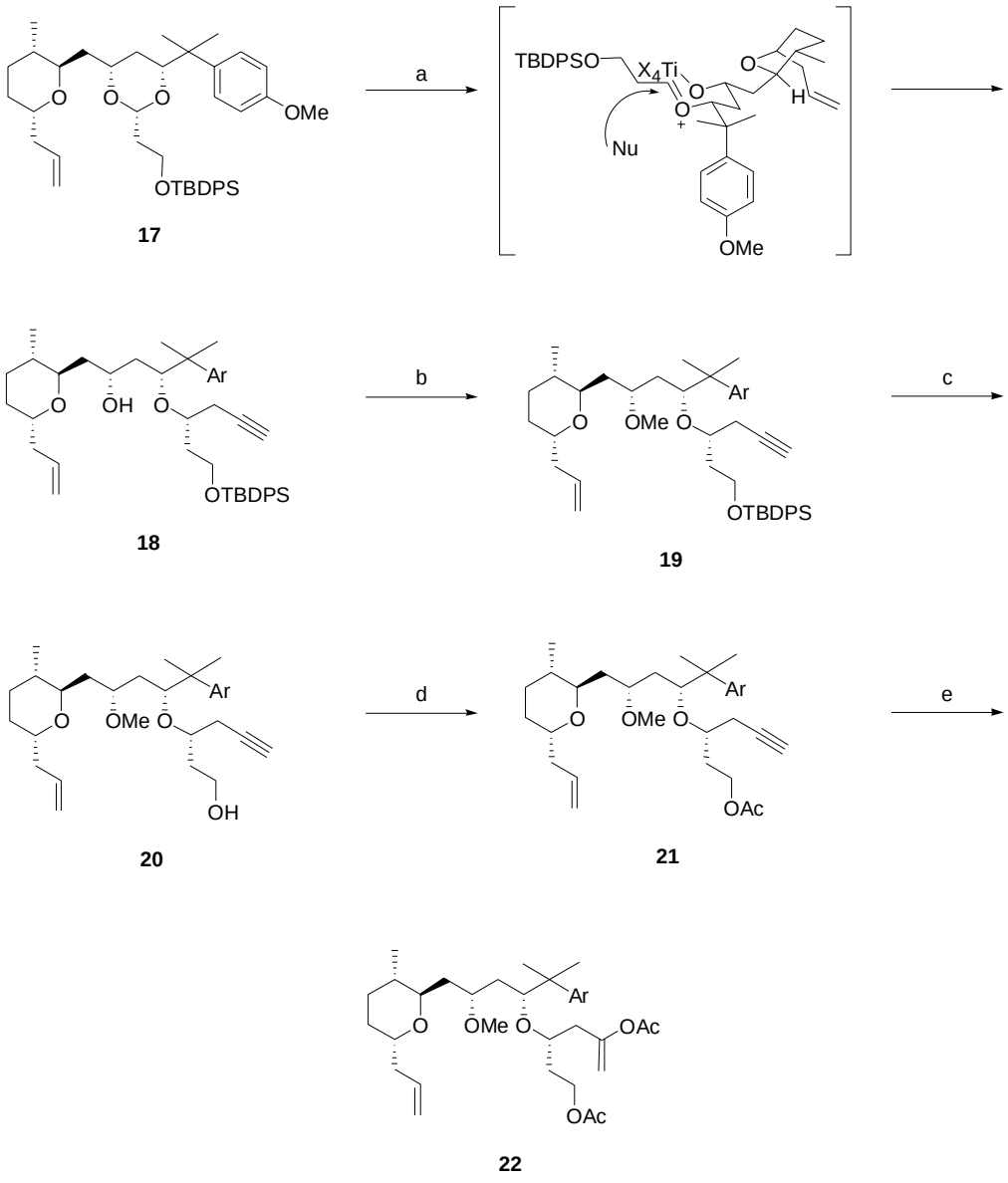


Figure 43: Transition state for the Mukaiyama aldol to form β-hydroxy ketone **9**.

Efficient formation of cyclic acetal **17** provided a suitable intermediate to undergo a diastereoselective Lewis acid-mediated acetal opening (**Scheme 27**). This method has been demonstrated to give synthetically useful levels of diastereocontrol with the careful choice of reaction conditions, and allows for the construction of an ether between two secondary carbons.[13] Therefore, acetal **17** was opened with allenyltributyltin in the presence of a mixed Lewis acid ($TiCl_4$/Ti(*i*-PrO)$_4$ (9:3) to give the homopropargylic ether **18** as a single diastereomer. The resulting hindered alcohol was then alkylated with MeOTf and 2,6-di*tert*butylpyridine to give compound **19**.[23] Attempts to convert the alkyne of **19** to the enol acetate under metal mediated conditions led to no reaction and recovery of starting material. Exposure of **19** to prolonged reaction conditions gave non-descript decomposition. The lack of desired reactivity prompted an investigation on the impact of the protecting group used for the primary alcohol. Removal of the *tert*butyldiphenylsilyl group with TBAF provided alcohol **20**, which was converted to the

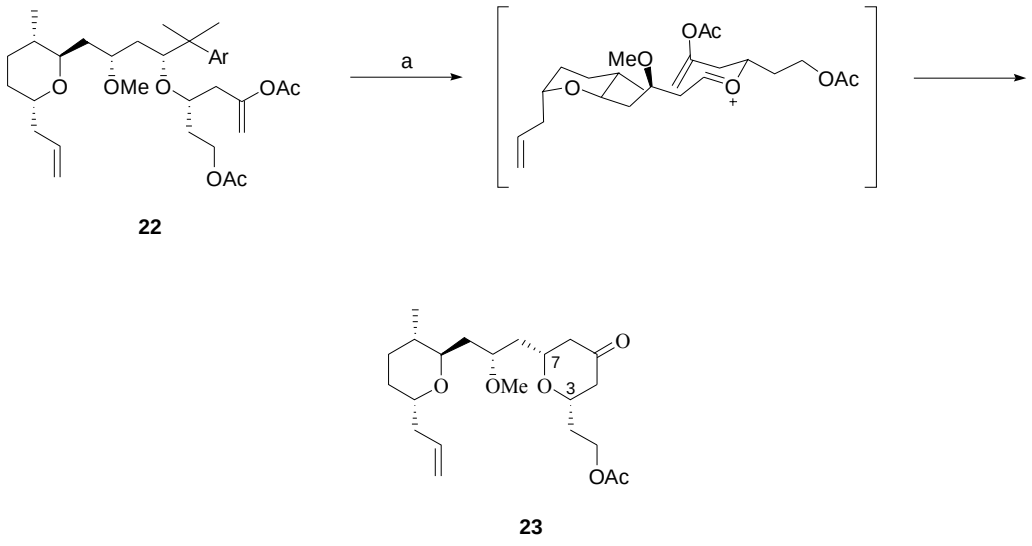
corresponding acetate **21**. Subjecting compound **21** to [Ru(*p*-cymene)Cl_2]$_2$, fur$_3$P, Na_2CO_3 and acetic acid in toluene at 80 °C furnished the desired enol acetate **22** in a moderate 44% yield.[24]



Reagents and Conditions: a) allenyltributyltin, $TiCl_4$/Ti(*i*PrO)$_4$ (9:3), CH_2Cl_2, - 42 °C (89%); b) MeOTf, 2,6-di*tert*butylpyridine, CH_2Cl_2, 0 °C – rt (83%); c) TBAF, THF(wet), 0 °C – rt (94%); d) Ac_2O, pyridine, DMAP, CH_2Cl_2, 0 °C – rt (94%); e) HOAc, Na_2CO_3, P(fur)$_3$, [Ru(*p*-cymene)Cl_2]$_2$, 80 °C (44%). Ar = *p*-methoxyphenyl.

Scheme 27: Synthesis of enol acetate **24**.

The key transformation in the synthesis involved the stereoselective formation of the C3-C7 *syn*-2,6-tetrahydropyran ring utilizing the ETIC method developed in our lab. The successful synthesis of enol acetate **22** allowed for the general applicability of this cyclization to the synthesis of complex molecules to be examined (**Scheme 28**). Therefore, **22** was subjected to our standard chemical mediated ETIC conditions,[25] and within 45 minutes complete consumption of starting material was observerd. Purification of the crude reaction product led to the isolation of the desired bis-tetrahydropyran backbone (**23**) of leucascandrolide A in 67% as a single diastereomer. The highly stereoselective ring closure was consistent with previous studies performed on analogous substructures.[13] The 2,6-*syn* relationship between the C3 and C7 hydrogens was established through a strong correlation in NOESY spectrum of **23**.



Reagents and Conditions: a) $NaHCO_3$ (s), 4Å mol. sieves, DCE; CAN (4 eq) in CH_3CN (67%).
Ar = *p*-methoxyphenyl

Scheme 28: Formation of the *syn*-2,6-tetrahydropyranone ring via an *endo*-ETIC reaction.

3.3. Outlook

While an efficient synthesis for the C1-C18 fragment of leucascandrolide A has been developed, several aspects of the sequence have yet to be optimized. For example the current synthetic sequence would provide a racemic mixture of leucascandrolide A. However, the high levels of stereocontrol obtained throughout the sequence, suggest an enantiopure synthesis would arise from an asymmetric crotylation. Although the tandem hydroesterification/lactonizaiton reaction provides quick access to the desired lactone, efforts are underway to improve the yield of this reaction. Attempts to minimize the number of synthetic steps are being explored through the use of an alternative protecting group for the C1 alcohol. Identification of a single protecting group that withstand both acetal opening and not inhibit enol acetate formation would eliminate two steps from the sequence. Continued synthetic effort will also be directed toward an elegant method for assembling the C15 side chain as well as the macrolactone.

3.4. Conclusion

The synthesis of leucascandrolide A is currently being pursued through a highly stereoselective sequence. Utilizing the tandem hydroesterification/lactonization method developed in our lab,[14] provides expedient access to the 2,6-*trans*-tetrahydropyran (C11-C15 ring). A 1,3-*anti*-selective Mukaiyamma aldol led to a β-hydroxy ketone which was reduced to the 1,3-s*yn*-diol and subjected to acetal formation. The acetal was then opened with allenytributyltin in the presence of a Lewis acid to give the homopropargylic ether as a single diastereomer. Alkylation of the hindered secondary alcohol followed by protecting group manipulation of the C1 alcohol gave the suitably functionalized alkyne for enol acetate formation. Introduction of the enol acetate via a ruthenium mediated addition of acetic acid provided the key intermediate for conducting the ETIC reaction. The ETIC reaction furnished the desired *syn*-2,6-tertrahydropyranone as a single diastereomer, as well as, completing a racemic synthesis of the C1-C18 fragment of leucascandrolide A.

3.5. Experimental

General Experimental:

All reactions were performed in oven or flame dried glassware under a nitrogen atmosphere with magnetic stirring unless otherwise noted.

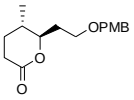
Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometers at 300 MHz and 75 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak or the internal standard tetramethylsilane were used as reference values. For ^{1}H NMR: $CDCl_3$ = 7.27 ppm, TMS = 0.00 ppm. For ^{13}C NMR: $CDCl_3$ = 77.23, TMS = 0.00. For proton data: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; dd = doublet of doublets; dt = doublet of triplets; ddt = doublet of doublet of triplets; br = broad; m = multiplet; app t = apparent triplet; app q = apparent quartet; app p = apparent pentet.

High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Gygnus 100 spectrometer.

Analytical thin layer chromatography (TLC) was performed on E. Merck pre-coated (25 nm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash column chromatography was preformed using ICN SiliTech 32-63 60Å silica gel. Reagent grade ethyl acetate and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. Reagent grade methylene chloride (CH_2Cl_2), dicholoroethane ($C_2H_4Cl_2$), acetonitrile (CH_3CN), benzene and toluene were distilled from CaH_2. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were dried by passing through aluminum drying column. Dimethoxyethane (DME) was distilled from Na/benzophenone. Anhydrous N,N-

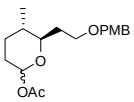
dimthylformamide (DMF), methanol (MeOH), dimethyl sulfoxide (DMSO) were purchased from Aldrich and used as is.

6-[2-(4-Methoxybenzyloxy)-ethyl]-5-methyltetrahydropyran-2-one (10)



To a slurry of NMO (1.75 g, 14.9 mmol) and $Ru_3(CO)_{12}$ (3.19 g, 4.99 mmol) in 2-pyridyl methyl formate (29.8 g, 219.5 mmol) was added 1-(4-methoxybenzyloxy)-4-methylhex-5-en-3-ol[15] (25.0 g, 99.8 mmol). The flask was then sealed with a wired rubber septum and heated to 110 °C for 40 hours. The reaction mixture was then cooled to room temperature and carefully vented. THF (100 mL), AcOH (200 mL) and water (100 mL) were then added and the mixture was heated to 85 °C for an additional 12 hours. The mixture was then poured into water and thoroughly washed with saturated $NaHCO_3$ (aq), water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purifiend via flash column chromatography (25% EtOAc in Hexanes) to give the desired product (14.1 g, 51%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.6 Hz, 2H), 6.85 (d, *J* = 8.6 Hz, 2H), 4.42 (s, 1H), 4.41 (s, 1H), 4.07 (td, *J* = 9.4, 2.4 Hz, 1H), 3.77 (s, 3H), 3.67-3.60 (m, 2H), 2.63-2.52 (m, 1H), 2.49-2.37 (m, 1H), 2.09-1.99 (m, 1H), 1.92-1.61 (m, 3H), 1.58-1.45 (m, 1H), 0.98 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.8, 159.5, 130.7, 129.5, 114.1, 83.1, 73.1, 65.9, 55.5, 34.2, 32.9, 29.7, 28.0, 17.6; IR (neat) 2958, 1731, 1612, 1513, 1093, 1034, 820 cm^{-1}; HRMS (EI) calcd for $C_{16}H_{22}O_4$ 278.1518, found 278.1511.

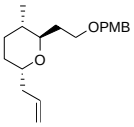
Acetic acid-6-[2-(4-methoxybenzyloxy)ethyl]-5-methyltetrahydropyran-2-yl ester (12)



To 6-[2-(4-methoxybenzyloxy)-ethyl]-5-methyltetrahydropyran-2-one (5.00g, 17.9 mmol) in CH_2Cl_2 (45 mL) at – 78 °C was added DIBAL (19.7 mL, 19.7 mmol) dropwise. The reaction mixture was then stirred at – 78 °C for 2 hours and pyridine (4.26 g, 53.8

mmol). The reaction mixture was then stirred for 5 minutes and DMAP (2.41 g, 19.7 mmol) was added in CH_2Cl_2 (5 mL) followed by acetic anhydride (7.33 g, 71.8 mmol). The reaction mixture was then allowed to warm to – 35 °C and stirred for an additional 12 hours. The reaction was then quenched by the addition of Na,K-tartrate (aq) and warmed to room temperature. After stirring at room temperature for 30 minutes, the mixture was passed through a pad of Celite. The organic layer was then separated and dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then filtered through a short plug of silica and used immediately.

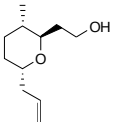
6-Allyl-2-[2-(4-methoxybenzyloxy)ethyl]-3-methyltetrahydropyran (13)



To acetic acid-6-[2-(4-methoxybenzyloxy)ethyl]-5-methyltetrahydropyran-2-yl ester (5.30 g, 16.4 mmol) and allyltrimethyl silane (3.75 g, 32.8 mmol) in CH_2Cl_2 (50 mL) at – 78 °C was added $BF_3{\cdot}OEt_2$ (2.56 g, 18.0 mmol). The reaction mixture was then stirred for an additional 1 hour at – 78 °C and quenched by the addition of $NaHCO_3$ (aq). The mixture was then warmed to room temperature and the organic layer was separated. The aqueous layer was then extracted with CH_2Cl_2 (2x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (6% EtOAc in Hexanes) to provide the desired product (3.90 g, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27 (d, *J* = 8.6 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.79 (ddt, *J* = 17.0, 10.1, 3.1 Hz, 1H), 5.06 (d, *J* = 17.0 Hz, 1H), 5.03 (d, *J* = 10.1 Hz, 1H), 4.43 (s, 2H), 3.81 (s, 3H), 3.54 (td, *J* = 7.5, 2.2 Hz, 2H), 3.43 (ddd, *J* = 9.8, 7.1, 3.2 Hz, 1H), 2.46 (ddd, *J* = 14.4, 6.7, 6.4 Hz, 1H), 2.17 (ddd, *J* = 13.8, 6.8, 6.6 Hz, 1H), 1.90-1.83 (m, 1H), 1.79-1.74 (m, 1H), 1.70-1.59 (m, 2H), 1.53-1.49 (m, 2H), 1.43-1.30 (m, 2H), 0.93 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.0, 135.5, 130.7, 129.1, 116.2, 113.6, 73.1,

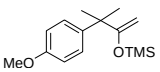
72.6, 71.1, 67.0, 55.1, 36.5, 34.0, 32.9, 27.3, 26.6, 18.1; IR (neat) 2929, 1640, 1613, 1247, 820; HRMS (EI) calcd for $C_{19}H_{28}O_3$ 304.2038, found 304.2047.

2-(6-Allyl-3-methyltetrahydropyran-2-yl)ethanol (14)



To 6-allyl-2-[2-(4-methoxybenzyloxy)ethyl]-3-methyltetrahydropyran (3.90 g, 12.8 mmol) in CH_2Cl_2 (40 mL) and pH 7.0 buffer (4 mL) was added DDQ (2.90 g, 12.8 mmol). The reaction mixture was then stirred at room temperature for 2.5 hours and the solvent was removed under reduced pressure. The resulting residue was then purified via flash column chromoatography (20% EtOAc in Hexanes) to give the desired product (2.36 g, 100%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (ddt, *J* = 17.5, 10.0, 2.6 Hz, 1H), 5.12 (d, *J* = 17.5 Hz, 1H), 5.08 (d, *J* = 10.0 Hz, 1H), 4.00-3.92 (m, 1H), 3.80-3.67 (m, 2H), 3.46 (td, *J* = 9.0, 2.8 Hz, 1H), 2.60 (ddd, *J* = 14.4, 8.8, 5.5 Hz, 1H), 2.17 (ddd, *J* = 13.6, 7.2, 6.4 Hz, 1H), 1.84-1.25 (m, 8H), 0.87 (d, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 116.8, 71.6, 61.7, 35.6, 34.9, 34.6, 27.7, 26.8, 18.0; IR (neat) 3418, 2930, 1641, 1459, 1439, 1052, 912 cm^{-1}; HRMS (EI) calcd for $C_{11}H_{21}O_2$ 185.1541, found 185.1536.

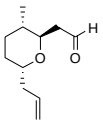
2-(4-methoxyphenyl-2-methyl-1-methylenepropoxy]trimethylsilane (8)



To 3-(4-methoxyphenyl)-3-methylbutan-2-one (1.92 g, 10.0 mmol) in THF at – 78 °C was added a centrifuged solution of Et_3N/TMSCl (2.85 mL, 10.0 mmol) followed by the addition of LHMDS (13.0 mL, 13.0 mmol). The reaction mixture was then stirred at – 78 °C for an additional 1 hour and poured into saturated $NaHCO_3$ (aq). The organic layer was then separated and the aqeous layer was extracted with Et_2O (2x). The combined organic layers were then washed with brine and dried over $MgSO_4$, filtered and concentrated under reduced pressure.

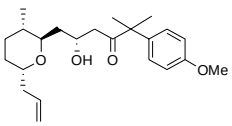
The resulting residue was then placed in a Kugelrohr and heated at 100 °C at ~1.0 mmHg for 1hour and used immediately.

(6-allyl-3-methyltetrahydropyran-2-yl)acetaldehyde (9):



To 2-(6-allyl-3-methyltetrahydropyran-2-yl)ethanol (500.0 mg, 2.7 mmol) in CH_2Cl_2 (5 mL) was added pyridine (854.0 mg, 10.8 mmol) followed by the addition of Dess-Martin periodinane (2.30 g, 5.4 mmol) at 0 °C. The reaction mixture was then warmed to room temperature and stirred for an additional 1 hour, and quenched by the addition of $Na_2S_2O_3$ (aq) : $NaHCO_3$ (aq) (1:5 v:v). The mixture was then stirred vigorously for 15 minutes, and the organic layer was separated. The aqueous layer was then extracted with CH_2Cl_2 (2x). The combined organic layers were then washed with NH_4Cl (aq) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then used without further purification.

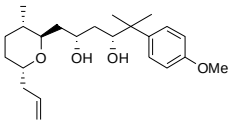
6-(6-Allyl-3-methyl-tetrahydropyran-2-yl)-5-hydroxy-2-(4-methoxyphenyl)-2-methylhexan-3-one (7)



To (6-allyl-3-methyltetrahydropyran-2-yl)acetaldehyde (850.0 mg, 4.66 mmol) and 2-(4-methoxyphenyl-2-methyl-1-methylenepropoxy]trimethylsilane (1.84 g, 6.99 mmol) in propionitrile (10 mL) at – 78 °C was added freshly distilled $BF_3{\cdot}OEt_2$ (661.9 mg, 4.66 mmol) dropwise. The reaction mixture was then stirred at – 78 °C for an additional 45 minutes and quenched by the addition of saturated aqueous NH_4Cl (10 mL). After warming to room temperature, the organic layer was separated and the aqueous layer was extracted with EtOAc (2x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced

pressure. The resulting residue was then purified via flash column (15% EtOAc in Hexanes) to provide the desired product (1.32 g, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (d, *J* = 8.7 Hz, 2H), 6.85 (d, *J* = 8.7 Hz, 5.75 (ddd, *J* = 17.1, 10.2, 6.9 Hz, 1H), 5.08 (d, *J* = 17.1 Hz, 1H), 5.01 (d, *J* = 10.2 Hz, 1H), 4.22-4.16 (m, 1H), 3.90-3.81 (m, 1H), 3,79 (s, 3H), 3.38 (td, *J* = 8.6, 2.7 Hz, 1H), 2.49-2.39 (m, 3H), 2.13 (ddd, *J* = 13.5, 6.7, 6.5 Hz, 1H), 1.73-1.17 (m, 8H), 1.47 (s, 3H), 1.43 (s, 3H), 0.83 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 213.5, 158.4, 135.6, 127.2, 116.4, 114.1, 72.7, 71.6, 65.0, 55.1, 51.5, 44.2, 38.7, 35.6, 34.4, 27.5, 26.9, 25.3, 24.8, 17.9; IR (neat) 3489, 2932, 1702, 1609, 1512, 1462, 1034, 736 cm^{-1}; HRMS (EI) calcd for $C_{23}H_{34}O_4$ 374.2457, found 374.2445.

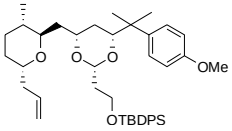
1-(6-Allyl-3-methyltetrahydropyran-2-yl)-5-(4-methoxyphenyl)-5-methylhexane-2,4-diol (15)



To 6-(6-allyl-3-methyl-tetrahydropyran-2-yl)-5-hydroxy-2-(4-methoxyphenyl)-2-methylhexan-3-one (2.00 g, 5.34 mmol) in THF (20 mL) at – 78 °C was added Et_2BOMe (587.0 mg, 5.87 mmol) dropwise. The mixture was then stirred for 1 hour and $LiBH_4$ (348.9 mg, 16.0 mmol) was added. The reaction mixture was then stirred at – 78 °C for an additional 16 hours and quenched by the addition of 10% NaOH (aq) (15 mL) and 30% H_2O_2 (15 mL). The mixture was then warmed to room temperature and vigorously stirred for 2 hours. The organic layer was then separated and the aqueous layer was extracted with EtOAc (3x). The combined organic layers were then washed with water, Na_2SO_3 (aq) and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (25% EtOAc in Hexanes) to afford a 5:1 separable mixture of diastereomers (1.53 g, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.6 Hz, 2H), 6.84 (d, *J* = 8.6 Hz, 2H), 5.82 (ddd, *J* = 17.3, 11.1, 6.1 Hz, 1H), 5.12 (d, *J* = 17.3

Hz, 1H), 5.07 (d, *J* = 11.1 Hz, 1H), 4.04-3.94 (m, 2H), 3.88 (dd, *J* = 6.3, 4.9 Hz, 1H), 3.79 (s, 3H), 3.41 (td, *J* = 9.0, 2.9 Hz, 1H), 3.29-3.18 (br s, 2H), 2.58 (ddd, *J* = 14.6, 8.8, 5.8 Hz, 1H), 2.14 (ddd, *J* = 13.2, 6.0, 5.9 Hz, 1H), 1.81-1.74 (m, 1H), 1.63-1.58 (m, 2H), 1.54-1.48 (m, 2H), 1.42-1.30 (m, 4H), 1.32 (s, 3H), 1.30 (s, 3H), 0.82 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 157.6, 139.4, 135.9, 127.5, 116.7, 113.4, 80.2, 72.4, 71.8, 70.0, 55.1, 41.6, 39.9, 37.4, 35.3, 34.9, 27.8, 27.0, 25.1, 23.1, 17.9; IR (neat) 3443, 2931, 1640, 1513, 1461, 1036, 830 cm^{-1}; HRMS (ESI) calcd for $C_{23}H_{36}O_4Na$ 399.2511, found 399.2530.

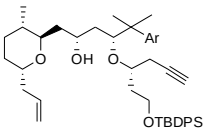
(2-{4-(6-Allyl-3-methyltetrahydropyran-2-ylmethyl)-6-[1-(4-methoxyphenyl)-1-methylethyl]-[1,3]dioxin-2-yl}-ethoxy)-*tert*butyldiphenyl silane (17)



To 1-(6-allyl-3-methyltetrahydropyran-2-yl)-5-(4-methoxyphenyl)-5-methylhexane-2,4-diol (550.0 mg, 1.46 mmol) in CH_2Cl_2 (5 mL) at – 78 °C was added 2,6-lutidine (923.0 mg, 5.84 mmol). The mixture was then stirred for 5 minutes and TMSOTf (714.0 mg, 3.21 mmol) was added dropwise. The reaction mixture was then stirred for an additional 20 minutes at – 78 °C and poured into water. The organic layer was then separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were then washed with 10% HCl, water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then taken up in CH_2Cl_2 (5 mL) and cooled to – 78 °C. 3-(*tert*butyldiphenylsilanoxy) propionaldehyde[17] (344.9 mg, 1.10 mmol) was then added followed by TMSOTf (24.4 mg, 0.11 mmol). The reaction mixture was then slowly warmed to – 45 °C and stirred for an additional 12 hours. The reaction was then quenched by the addition of pyridine (12.6 mg, 0.16 mmol) and poured into water. The organic layer was then separated and the aqeous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were then

washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (4% EtOAc in Hexanes) to give the desired product (738.0 mg, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) 7.69-7.67 (m, 4H), 7.45-7.37 (m, 6H), 7.23 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 5.73 (ddd, *J* = 17.0, 10.1, 6.9 Hz, 1H), 5.03 (d, *J* = 17.0 Hz, 1H), 5.00 (d, *J* = 10.1 Hz, 1H), 4.71 (dd, *J* = 6.4, 4.0 Hz, 1H), 3.84-3.77 (m, 4H), 3.77 (s, 3H), 3.55-3.51 (m, 1H), 3.43 (app t, *J* = 8.1 Hz, 1H), 2.49 (ddd, *J* = 15.3, 8.0, 7.3 Hz, 1H), 2.14-1.84 (m, 5H), 1.77-1.57 (m, 5H), 1.50-1.46 (m, 2H), 1.35-1.27 (m, 3H), 1.29 (s, 3H), 1.27 (s, 3H), 1.07 (s, 9H), 0.85 (d, *J* = 6.0 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 157.6, 138.8, 135.6, 134.0, 129.6, 127.8, 116.5, 113.2, 99.2, 83.9, 72.9, 71.7, 71.3, 60.0, 55.2, 40.6, 39.7, 38.2, 35.9, 34.8, 32.3, 28.0, 27.2, 26.9, 26.2, 22.9, 19.3, 18.2; IR (neat) 2930, 1612, 1513, 1250, 702 cm^{-1}; HRMS (ESI) calcd for $C_{42}H_{58}O_5NaSi$ 693.3951, found 693, 3951.

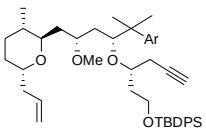
1-(6-Allyl-3-methyl-tetrahydropyran-2-yl)-4-{1-[2-(*tert*butyldiphenylsilanoxy)ethyl]but-3-ynyloxy}-5-(4-methoxyphenyl)-5-methylhexan-2-ol (18)



To (2-{4-(6-allyl-3-methyltetrahydropyran-2-ylmethyl)-6-[1-(4-methoxyphenyl)-1-methylethyl]-[1,3]dioxin-2-yl}-ethoxy)-*tert*butyldiphenyl silane (200.0 mg, 0.29 mmol) and allenyltributyltin (294.0 mg, 0.89 mmol) in CH_2Cl_2 (3 mL) at – 40 °C was added $TiCl_3$(*i*-PrO) (3.4 mmol) in CH_2Cl_2 (5 mL). The reaction mixture was then stirred for an addition 25 minutes at – 40 °C, and poured into saturated $NaHCO_3$ (aq). The organic layer was then separated and the aqeous layer was extracted with EtOAc (3x). The combined organic layers were then washed with water and 10 KF (aq), dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (7% EtOAc in Hexanes) to give the desired product (187.4 mg,

89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.64 (m, 4H), 7.46-7.40 (m, 6H), 7.29 (d, *J* = 8.8 Hz, 2H), 6.79 (d, *J* = 8.8 Hz, 2H), 5.77 (ddd, *J* = 16.9, 10.1, 3.1 Hz, 1H), 5.05 (dd, *J* = 16.9, 1.8 Hz, 1H), 4.99 (dd, *J* = 10.1, 1.8 Hz, 1H), 3.83-3.75 (m, 3H), 3.68 (t, *J* = 5.3 Hz, 2H), 3.35-3.32 (m, 2H), 3.25 (s, 1H), 2.63-2.41 (m, 1H), 2.39-2.27 (m, 1H), 2.16-2.10 (m, 1H), 1.96 (t, *J* = 2.5 Hz, 1H), 1.94 (dd, *J* = 12.2, 6.12 Hz, 1H), 1.70-1.62 (m, 1H), 1.55-1.53 (m, 2H), 1.48-1.41 (m, 4H), 1.34 (s, 3H), 1.26 (s, 3H), 1.37-1.26 (m, 4H), 1.05 (s, 9H), 0.73 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 140.1, 136.0, 135.8, 134.3, 134.2, 129.8, 128.2, 128.0, 127.9, 116.7, 113.5, 81.9, 73.2, 72.4, 71.8, 70.3, 67.0, 61.0, 55.4, 42.5, 39.9, 36.7, 35.8, 34.3, 28.0, 27.3, 27.0, 23.5, 23.2, 19.5, 18.3; IR (neat) 3497, 3308, 2930, 1610, 1513, 1427, 1251, 1098, 829, 703 cm^{-1}; HRMS (ESI) calcd for $C_{45}H_{62}O_5NaSi$ 733.4264, found 733.4268.

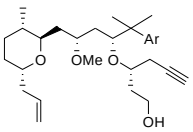
(3-{4-(6-Allyl-3-methyltetrahydropyran-2-yl)-3-methoxy-1-[1-(4-methoxyphenyl)-1-methylethylbutoxy}hex-5-ynyloxy)*tert*butyldiphenyl silane (19)



To 1-(6-allyl-3-methyl-tetrahydropyran-2-yl)-4-{1-[2-(*tert*butyldiphenylsilanoxy)ethyl]but-3-ynyloxy}-5-(4-methoxyphenyl)-5-methylhexan-2-ol (100.0 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added 2,6-di*tert*butylpyridine (107.0 mg, 0.56 mmol). The mixture was then stirred for 10 minutes at 0 °C and MeOTf (69.0 mg, 0.42 mmol) was added dropwise. The reaction was then slowly warmed to room temperature over 12 hours and quenched by the addition of saturated $NaHCO_3$ (aq). The organic layer was then separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (4% EtOAc in Hexanes) to give the desired product (84.7 mg, 83%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.69 (m, 4H), 7.44-7.37 (m, 6H), 7.28 (d, *J* = 8.8 Hz, 2H),

6.79 (d, *J* = 8.8 Hz, 2H), 5.72 (ddd, *J* = 17.0, 10.1, 6.72 Hz, 1H), 5.04 (d, *J* = 17.0 Hz, 1H), 4.98 (d, *J* = 10.1 Hz, 1H), 3.80-3.76 (m, 3H), 3.77 (s, 3H), 3.73-3.66 (m, 1H), 3.41 (t, *J* = 4.1 Hz, 1H), 3.29-3.21 (m, 1H), 3.16 (s, 3H), 2.99-2.91 (m, 1H), 2.39-2.32 (m, 2H), 2.21-2.14 (m, 1H), 1.96 (t, *J* = 2.5 Hz, 1H), 1.95-1.91 (m, 2H), 1.69-1.54 (m, 4H), 1.50-1.41 (m, 2H), 1.39-1.25 (m, 4H), 1.31 (s, 3H), 1.26 (s, 3H), 1.05 (s, 9H), 0.81 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 157.9, 142.7, 139.9, 135.9, 135.8, 134.3, 129.7, 128.2, 127.8, 116.6, 113.4, 82.1, 80.6, 73.1, 72.0, 71.2, 70.1, 61.2, 57.5, 55.4, 51.7, 42.6, 38.7, 38.1, 37.5, 37.2, 35.7, 34.3, 29.9, 27.3, 27.2, 27.0, 26.8, 23.4, 23.3, 19.5, 18.5; IR (neat) 3309, 2930, 1610, 1513, 1462, 1298, 1251, 1184, 1036, 828 cm^{-1}; HRMS (ESI) calcd for $C_{46}H_{64}O_5NaSi$ 747.4421, found 747.4431.

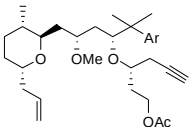
3-{4-(6-Allyl-3-methyltetrahydropyran-2-yl)-3-methoxy-1-[1-(4-methoxyphenyl)-1-methylethyl]butoxy}hex-5-ynyl-1-ol (20):



To (3-{4-(6-allyl-3-methyltetrahydropyran-2-yl)-3-methoxy-1-[1-(4-methoxyphenyl)-1-methylethylbutoxy}hex-5-ynyloxy)*tert*butyldiphenyl silane (160.0 mg, 0.22 mmol) in wet THF (3 mL) at 0 °C was added TBAF (115.3 mg, 0.44 mmol). The reaction mixture was then slowly warmed to room temperature over 12 hours and quenched by the addition of water. The mixture was then extracted with EtOAc (3x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (25% EtOAc in Hexanes) to give the desired product (100.1 mg, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.85 (d, *J* = 8.5 Hz, 2H), 5.79 (ddd, *J* = 16.8, 10.1, 6.6 Hz, 1H), 5.15 (d, *J* = 16.8 Hz, 1H), 5.05 (d, *J* = 10.1 Hz, 1H), 3.93 (app sep, *J* = 4.4 Hz, 1H), 3.83-3.66 (m, 3H), 3.80 (s, 3H), 3.50 (t, *J* = 4.4 Hz, 1H), 3.34 (s, 3H), 3.34-3.30 (m, 1H), 3.10 (app p, 6.5 Hz, 1H), 2.47-2.34 (m, 2H), 2.27-2.12 (m, 2H), 1.99 (t, *J* = 2.5 Hz, 1H),

1.89-1.80 (m, 3H), 1.63-1.50 (m, 4H), 1.35 (s, 3H), 1.31 (s, 3H), 1.35-1.29 (m, 4H), 0.86 (d, J = 6.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 157.6, 138.9, 135.5, 127.7, 116.4, 113.1, 81.7, 81.1, 74.8, 72.6, 71.1, 70.1, 60.3, 57.2, 55.0, 41.9, 38.2, 36.5, 36.4, 34.1, 29.5, 27.0, 26.4, 23.1, 18.1; IR (neat) 3450, 3308, 2929, 1610, 1513, 1462, 1251, 1083, 830 cm^{-1}; HRMS (ESI) calc for $C_{30}H_{46}O_5Na$ 509.3243, found 509.3259.

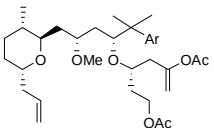
Acetic acid-3-{4-(6-allyl-3-methyltetrhydropyran-2-yl)-3-methoxy-1-[1-(4-methoxyphenyl)-1-methylethyl]butoxy}hex-5-ynyl ester (21)



To 3-{4-(6-allyl-3-methyltetrahydropyran-2-yl)-3-methoxy-1-[1-(4-methoxyphenyl)-1-methylethyl]butoxy}hex-5-ynyl-1-ol (50.0 mg, 0.10 mmol) in CH_2Cl_2 (2 mL) at 0 °C was added pyridine (23.7 mg, 0.30 mmol) and DMAP (1 crystal). The mixture was then stirred at 0 °C for 10 minutes and acetic anhydride (21.9 mg, 0.20 mmol) was added. The reaction mixture was then warmed to room temperature over 3 hours and quenched by the addition of water. The organic layer was then separated and the aqueous layer was extracted with CH_2Cl_2 (2x). The combined organic layers were then washed with water and brine, dried over Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was then purified via flash column chromatography (15% EtOAc in Hexanes) to provide the desired product (51.2 mg, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, J = 8.7 Hz, 2H), 6.84 (d, J = 8.7 Hz, 2H), 5.78 (ddd, J = 16.9, 10.3, 6.6 Hz, 1H), 5.07 (d, J = 16.9 Hz, 1H), 5.02 (d, J = 10.3 Hz, 1H), 4.27-4.11 (m, 2H), 3.77-3.64 (m, 3H), 3.77 (s, 3H), 3.42 (t, J = 4.4 Hz, 1H), 3.26 (s, 3H), 2.96 (app p, J = 6.8 Hz, 1H), 2.38-2.31 (m, 2H), 2.25-2.20 (m, 2H), 2.03 (s, 3H), 1.98 (t, J = 2.5 Hz, 1H), 1.96-1.93 (m, 1H), 1.61-1.57 (m, 2H), 1.51-1.44 (m, 2H), 1.36-1.26 (m, 6H), 1.32 (s, 3H), 1.30 (s, 3H), 0.84 (d, J = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.2, 158.0, 139.8, 135.9, 128.2, 123.1, 116.6, 113.5, 81.5, 80.9, 73.1, 71.5, 71.3, 70.5, 66.8, 61.7,

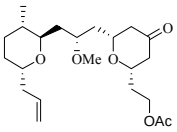
57.6, 55.4, 42.4, 38.8, 38.2, 37.2, 34.9, 34.4, 33.6, 27.3, 26.8, 23.3, 21.2, 18.5; IR (neat) 3306, 2931, 1739, 1641, 1513, 1440, 1251, 1036, 914, 830 cm^{-1}; HRMS (ESI) calcd for $C_{32}H_{48}O_6Na$ 551.3349, found 551.3337.

Acetic acid-5-acetoxy-3-{4-(6-allyl-3-methyltetrahydropyran-2-yl)-3-methoxy-1-[1-(4-methoxyphenyl)-1-methylethyl]butoxy}-1-methylenepentyl ester (22)



To acetic acid-3-{4-(6-allyl-3-methyltetrhydropyran-2-yl)-3-methoxy-1-[1-(4-methoxyphenyl)-1-methylethyl]butoxy}hex-5-ynyl ester (10.0 mg, 0.018 mmol) was added a solution of $[Ru(p\text{-cymene})Cl_2]_2$ (0.4 mg, 0.75 μmol), fur_3P (0.3 mg, 1.5 μmol) and AcOH (2.2 mg, 0.037 mmol) in toluene (1 mL) followed by Na_2CO_3 (0.3 mg, 3.0 μmol). The reaction mixture was then warmed to 80 °C and stirred for an additional 14 hours. The mixture was then cooled to room temperature and the solvent was removed under reduced pressure. The resulting residue was then purified via flash column chromagtography (8% EtOAc in Hexanes) to give the desired product (4.9 mg, 44%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8.7 Hz, 2H), 6.83 (d, *J* = 8.7 Hz, 2H), 5.77 (ddd, *J* = 17.0, 10.1, 7.0 Hz, 1H), 5.06 (d, *J* = 17.0 Hz, 1H), 5.03 (d, *J* = 10.1 Hz, 1H), 4.80 (s, 1H), 4.78 (s, 1H), 4.24-4.20 (m, 1H), 4.19-4.11 (m, 1H), 3.78 (s, 3H), 3.75-3.70 (m, 1H), 3.69-3.64 (m, 1H), 3.39 (t, *J* = 4.4 Hz, 1H), 3.29-3.24 (m, 1H), 3.27 (s, 3H), 2.97-2.92 (m, 1H), 2.59 (dd, *J* = 14.7, 3.92 Hz, 1H), 2.39 (dd, *J* = 13.8, 6.7 Hz, 1H), 2.28-2.20 (m, 1H), 2.12 (s, 3H), 2.11-2.04 (m, 1H), 2.03 (s, 3H), 1.98-1.93 (m, 1H), 1.80-1.73 (m, 1H), 1.64-1.60 (m, 2H), 1.51-1.44 (m, 2H), 1.30 (s, 3H), 1.27 (s, 3H), 1.34-1.27 (m, 5H), 0.82 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR ($CDCl_3$) δ 171.1, 169.2, 158.0, 153.6, 140.0, 135.9, 128.2, 116.6, 113.5, 80.7, 72.9, 71.4, 71.3, 61.9, 57.5, 55.4, 42.5, 39.0, 38.3, 38.1, 37.0, 34.6, 33.4, 29.9, 27.7, 26.8, 26.7, 23.3, 21.3, 20.9, 18.4; IR (neat) 2931, 1740, 1513, 1462, 1368, 1250, 1036, 914, 733 cm^{-1}; HRMS (ESI) calcd for $C_{34}H_{52}O_8Na$ 611.3560, found 611.3552.

Acetic acid-2-{6-[3-(6-allyl-3-methyltetrahydropyran-2-yl)-2-methoxypropyl]-4-oxotetrahydropyran-2-yl}ethyl ester (23)



To acetic acid 5-acetoxy-3-{4-(6-allyl-3-methyltetrahydropyran-2-yl)-3-methoxy-1-[1-(4-methoxyphenyl)-1-methylethyl]butoxy}-1-methylenepentyl ester (10.0 mg, 0.016 mmol) in DCE (0.75 mL) was added $NaHCO_3$ (20.0 mg) and 4 Å molecular sieves (20.0 mg). The mixture was then stirred for 20 minutes and a solution of CAN (37.2 mg, 0.067 mmol) in CH_3CN (0.40 mL) was added dropwise. The reaction mixture was then stirred for an additional 45 minutes and filtered through a small silica plug. The filtrate was then concentrated under reduced pressure and the resulting residue was purified via flash column chromatography (40% EtOAc in Hexanes) to provide the desired product (4.5 mg, 67%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (ddd, *J* = 17.0, 10.2, 6.8 Hz, 1H), 5.08 (d, *J* = 17.0 Hz, 1H), 5.04 (d, *J* = 10.2 Hz, 1H), 4.29-4.25 (m, 1H), 4.20-4.15 (m, 1H), 3.84-3.81 (m, 1H), 3.75-3.69 (m, 1H), 3.58-3.56 (m, 1H), 3.49-3.46 (m, 2H), 2.50-2.44 (m, 2H), 2.42-2.37 (m, 2H), 2.04 (s, 3H), 1.97-1.90 (m, 3H), 1.88-1.83 (m, 2H), 1.73-1.16 (m, 3H), 1.58-1.50 (m, 3H), 0.94 (d, *J* = 6.2 Hz, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 206.9, 171.2, 135.9, 116.6, 74.7, 74.1, 73.9, 72.9, 71.6, 61.0, 57.0, 48.4, 47.9, 40.7, 38.9, 36.9, 35.4, 34.7, 27.7, 27.0, 21.1, 18.5; IR (neat) 2926, 1740, 1238, 1090 cm^{-1}; HRMS (ESI) calcd for $C_{19}H_3O_6$ (M^+ - C_3H_5) 355.2121, found 355.2115.

3.6. References

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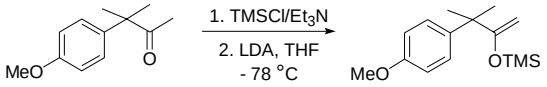
18. Silyl enol ether **10** was prepared from 3-(-methoxyphenyl)-3-methylbutan-2-one:



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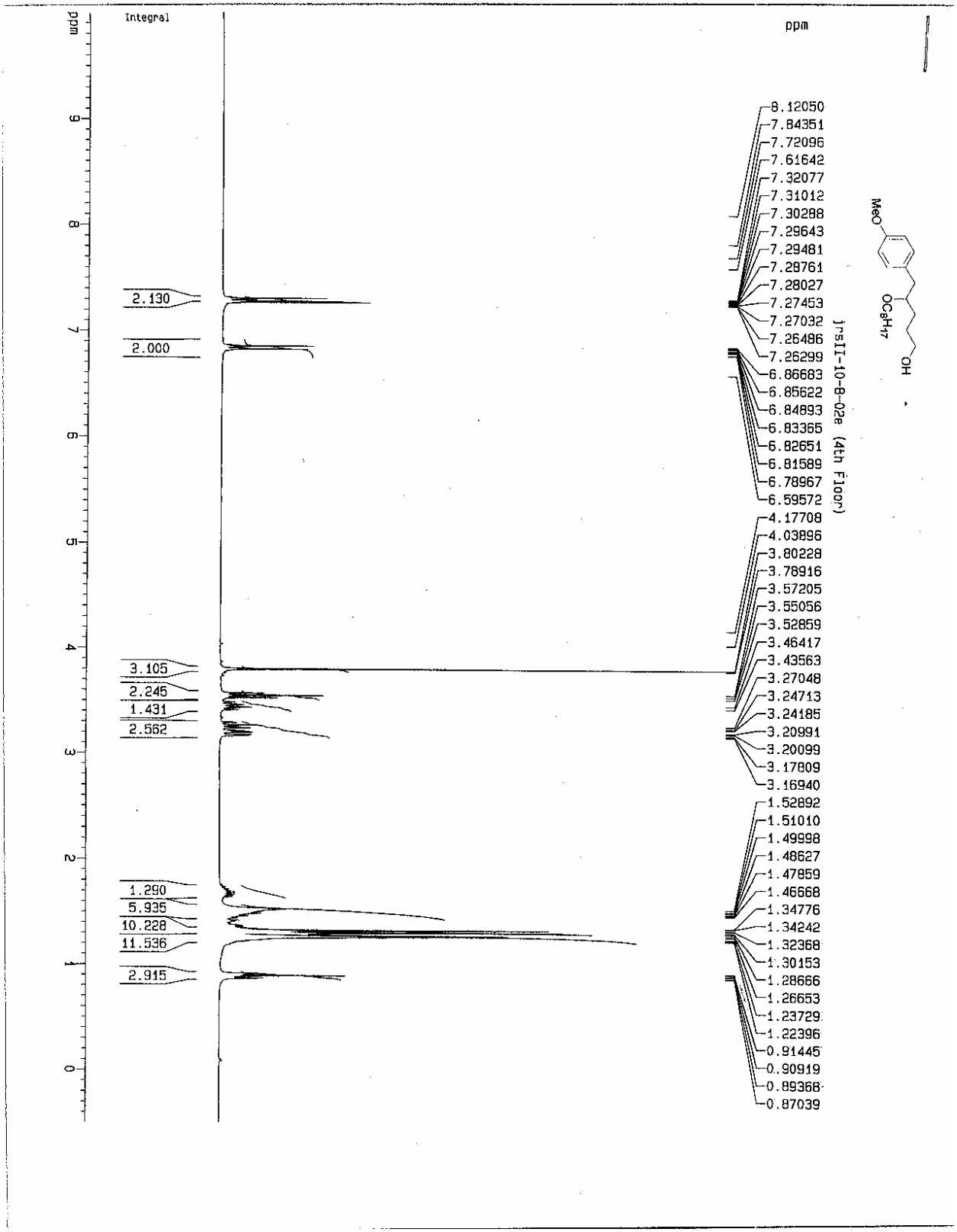
APPENDIX A

Tuning the Reactivity and Chemoselectivity of Electron Transfer Initiated Cyclization (ETIC) Reactions: Effects of Aryl and Benzyl Substitution (Supporting Information) (^{1}H and ^{13}C NMR Spectra)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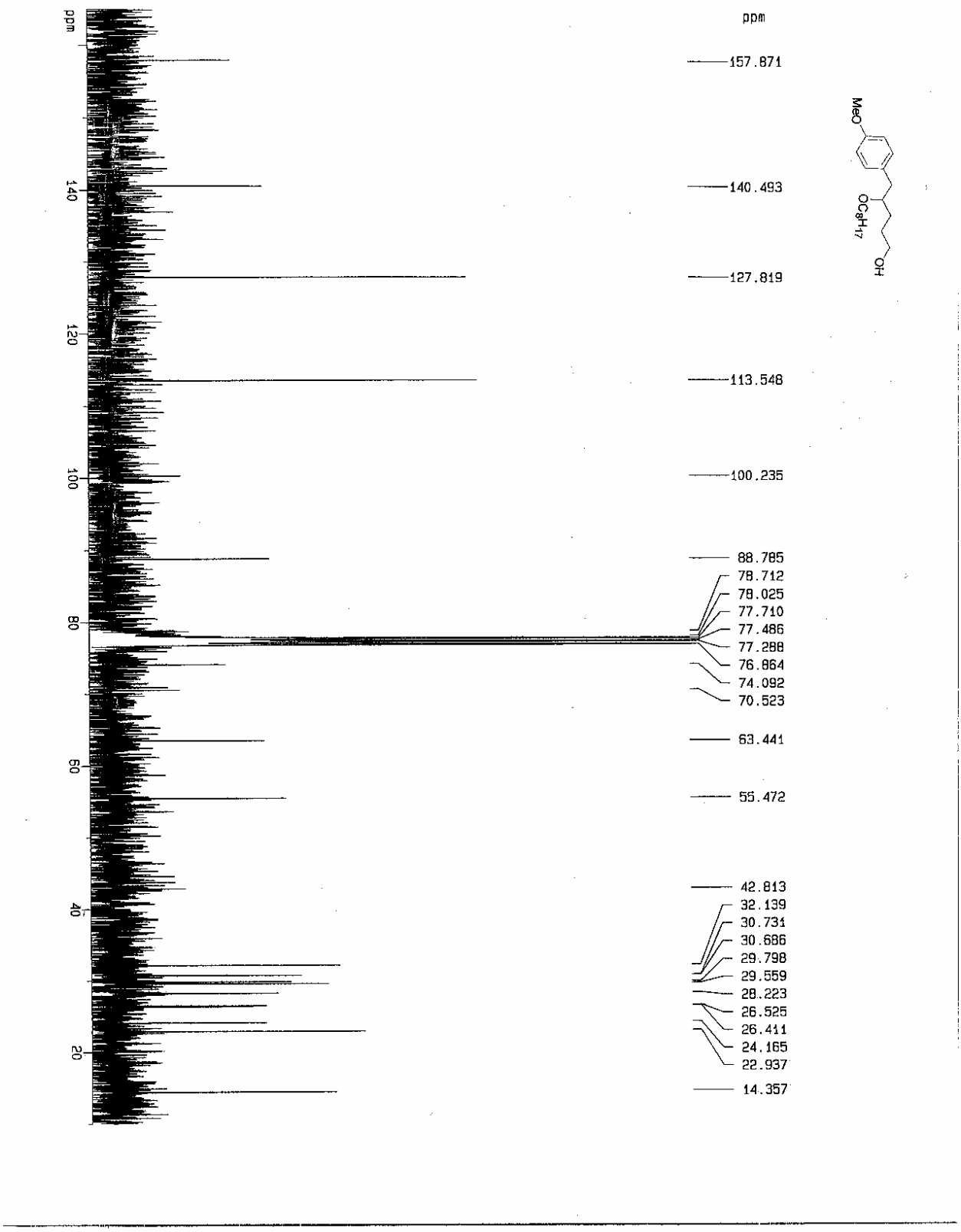
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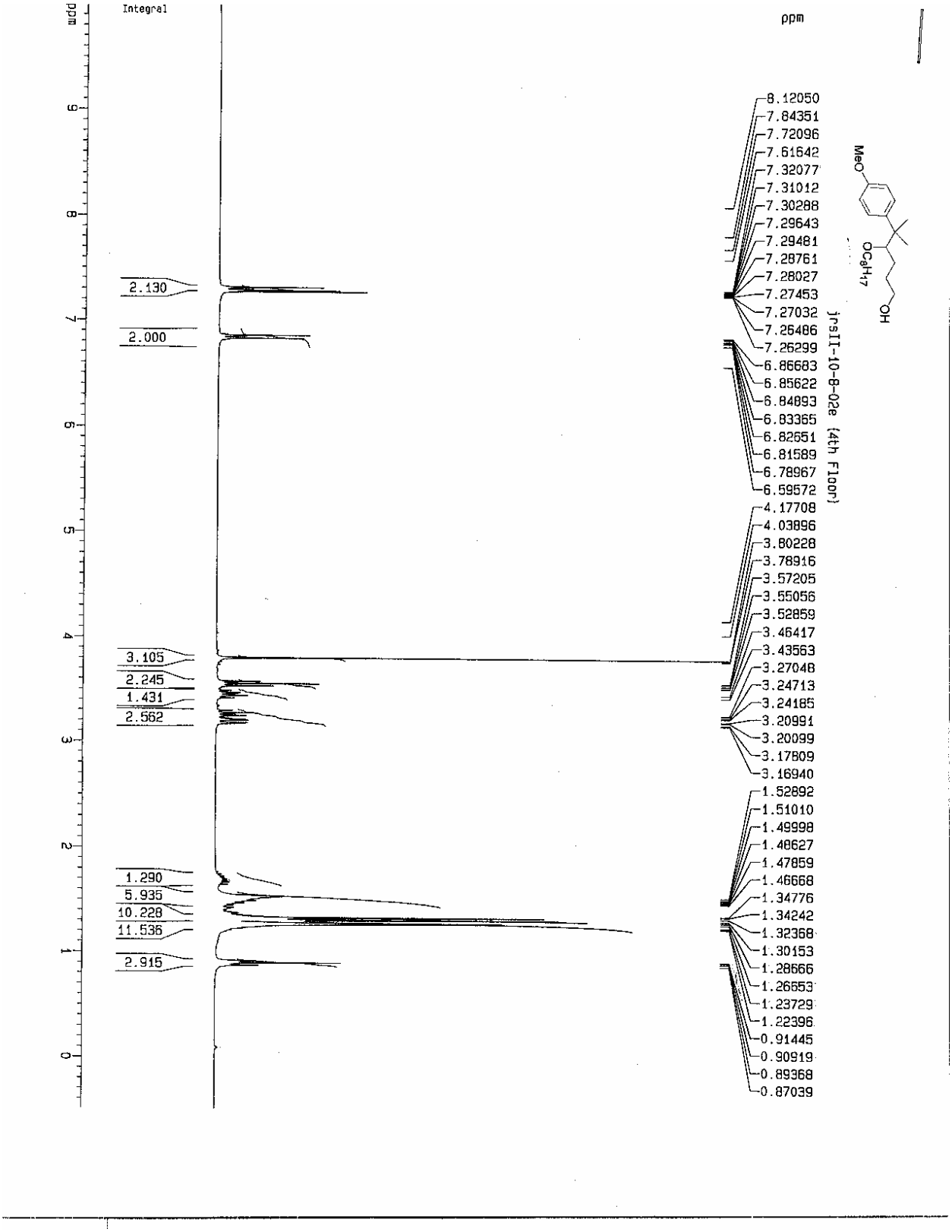
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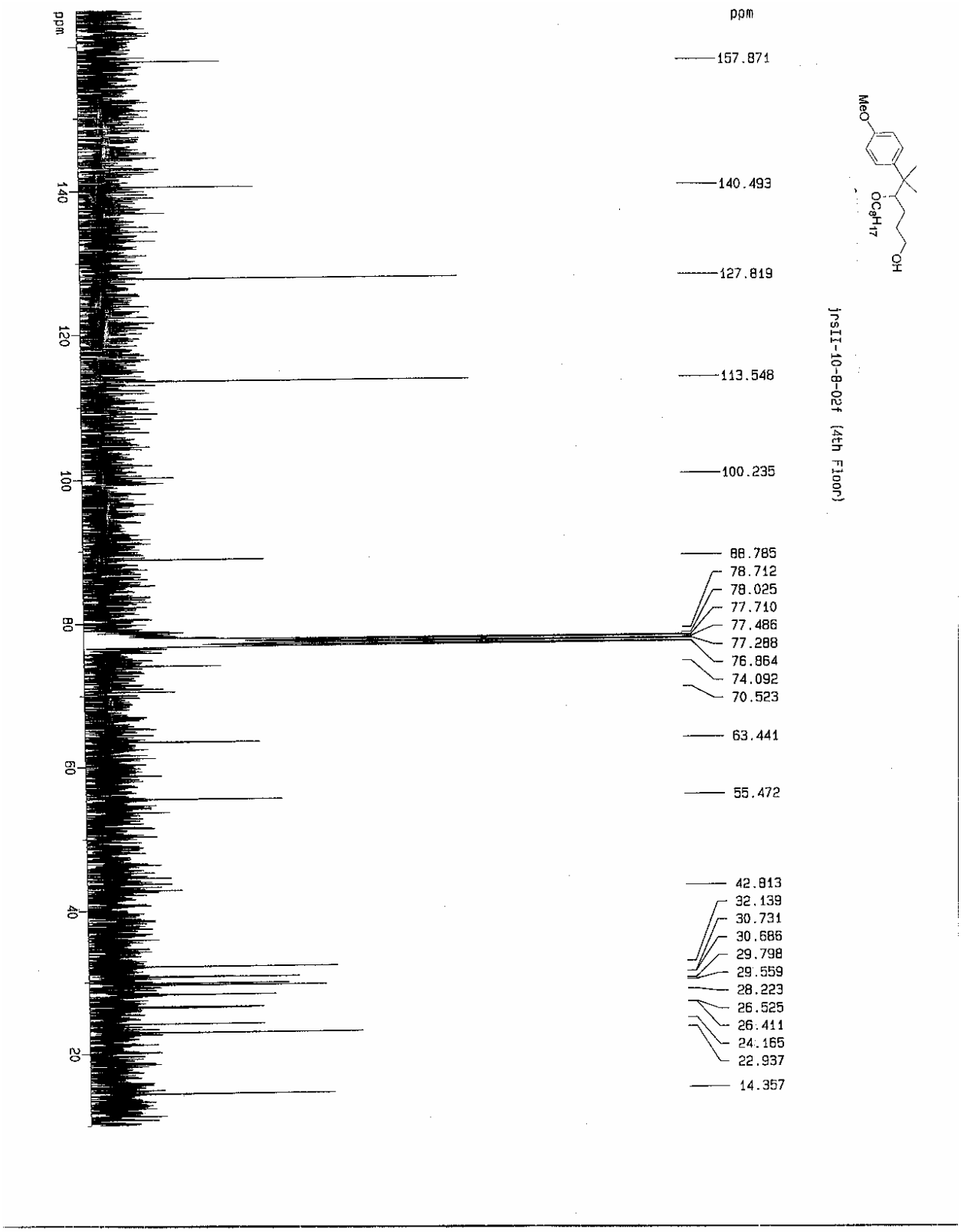
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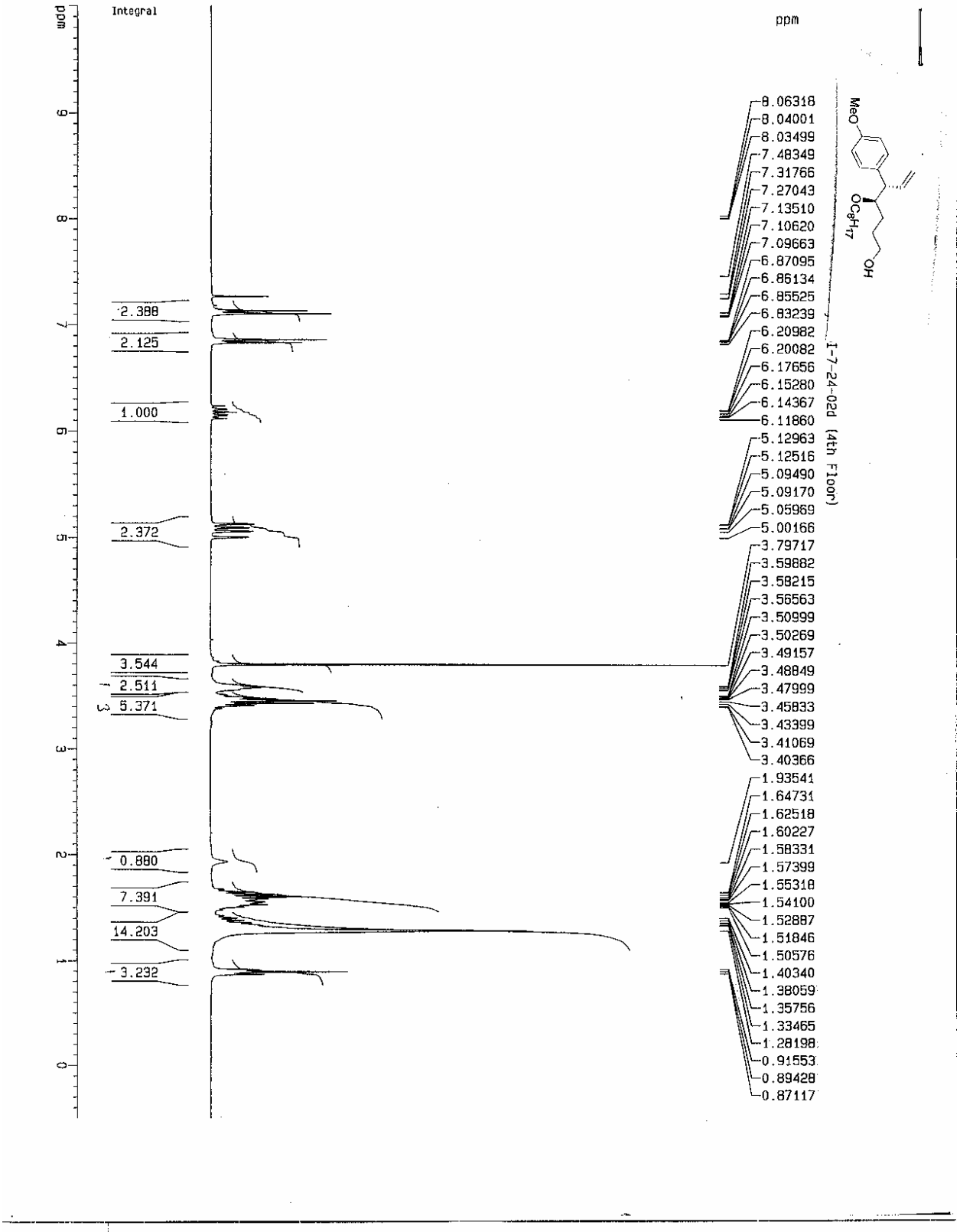
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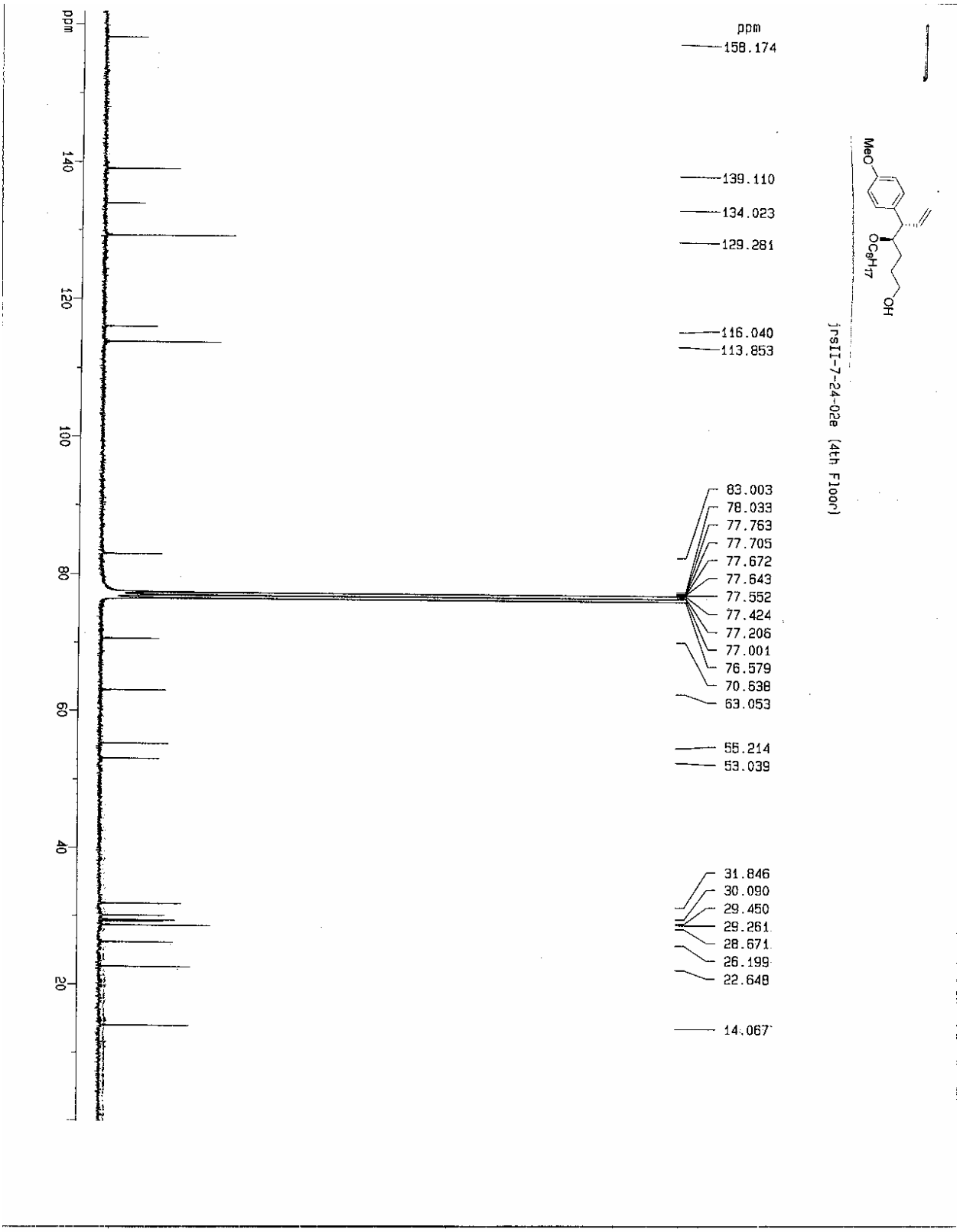
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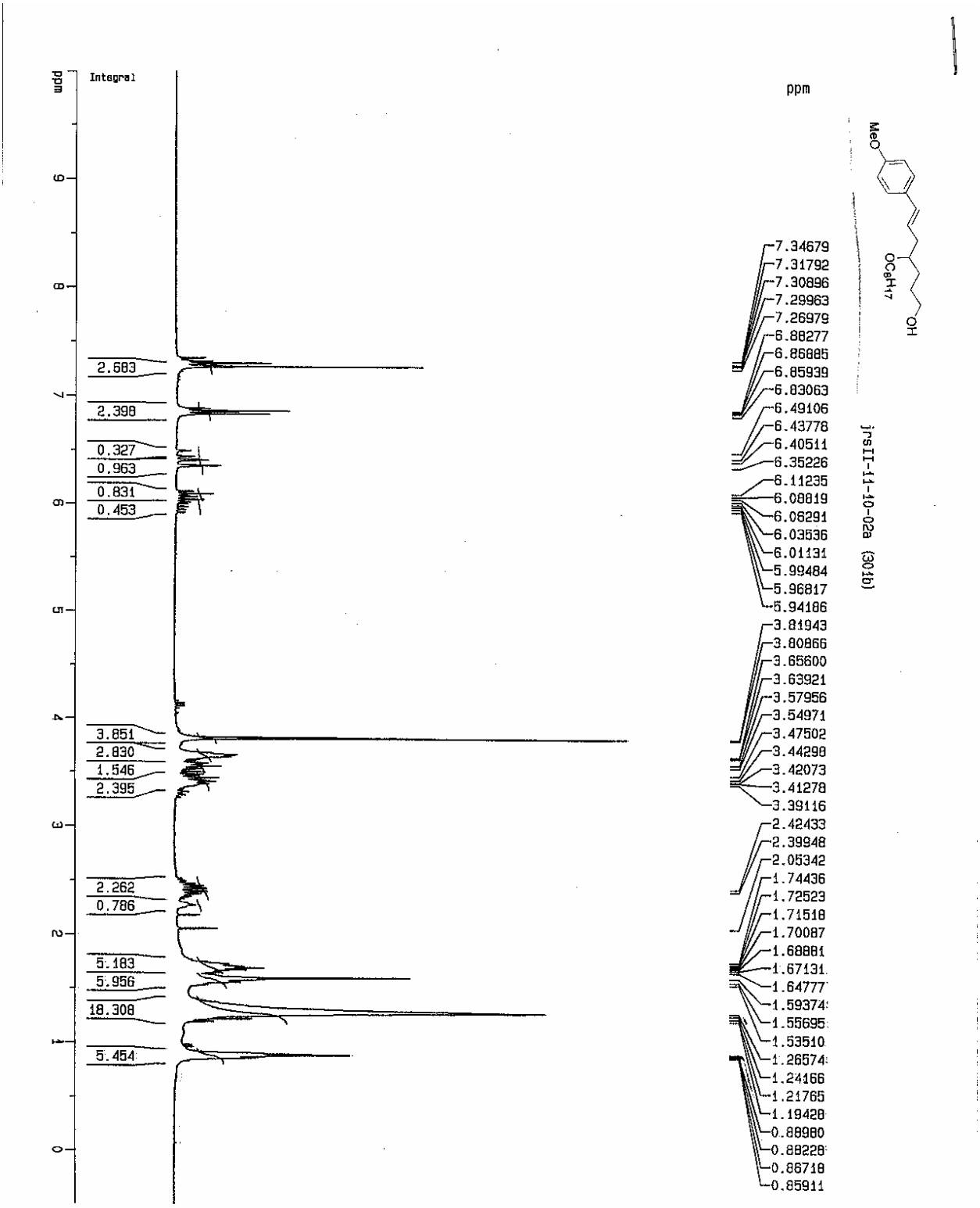
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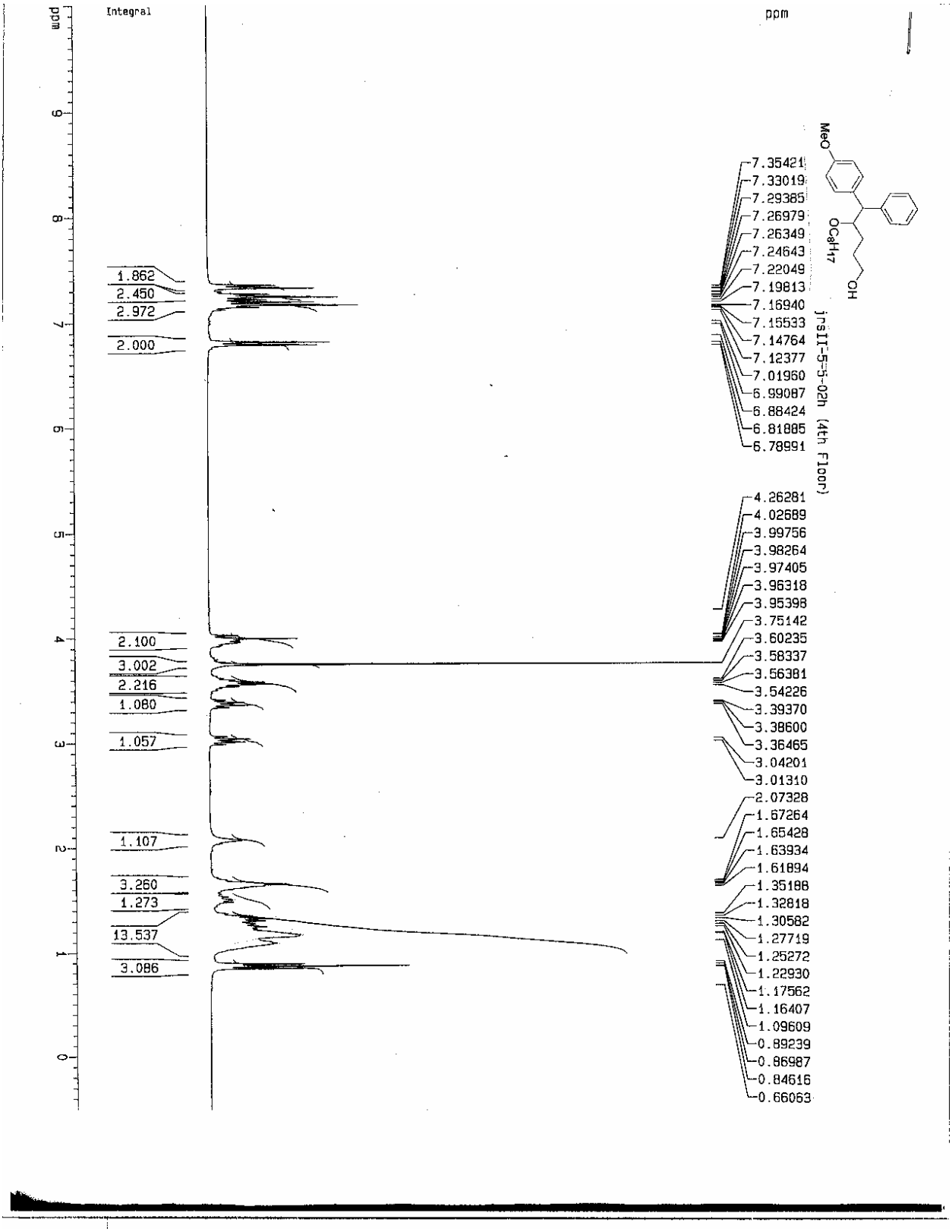
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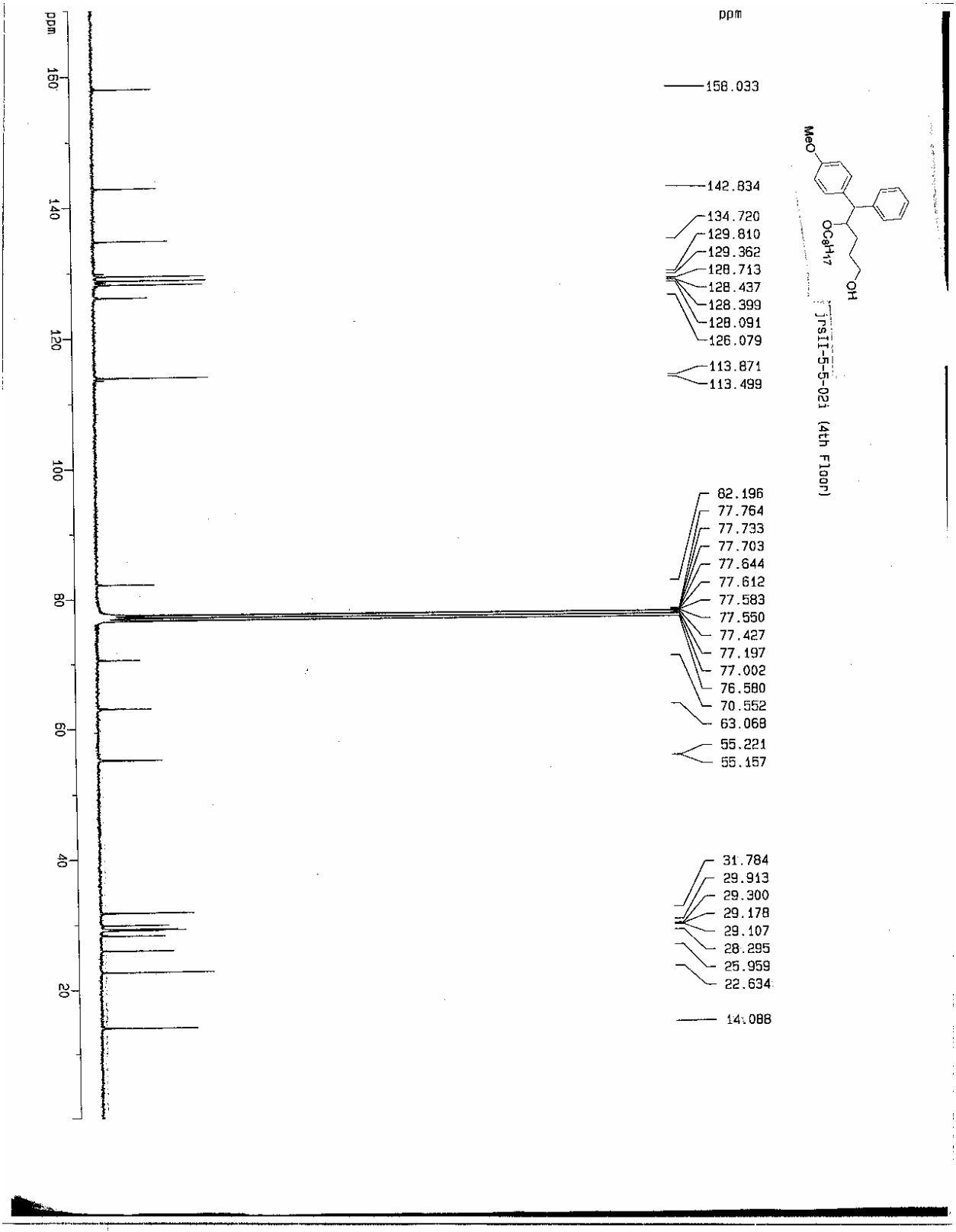
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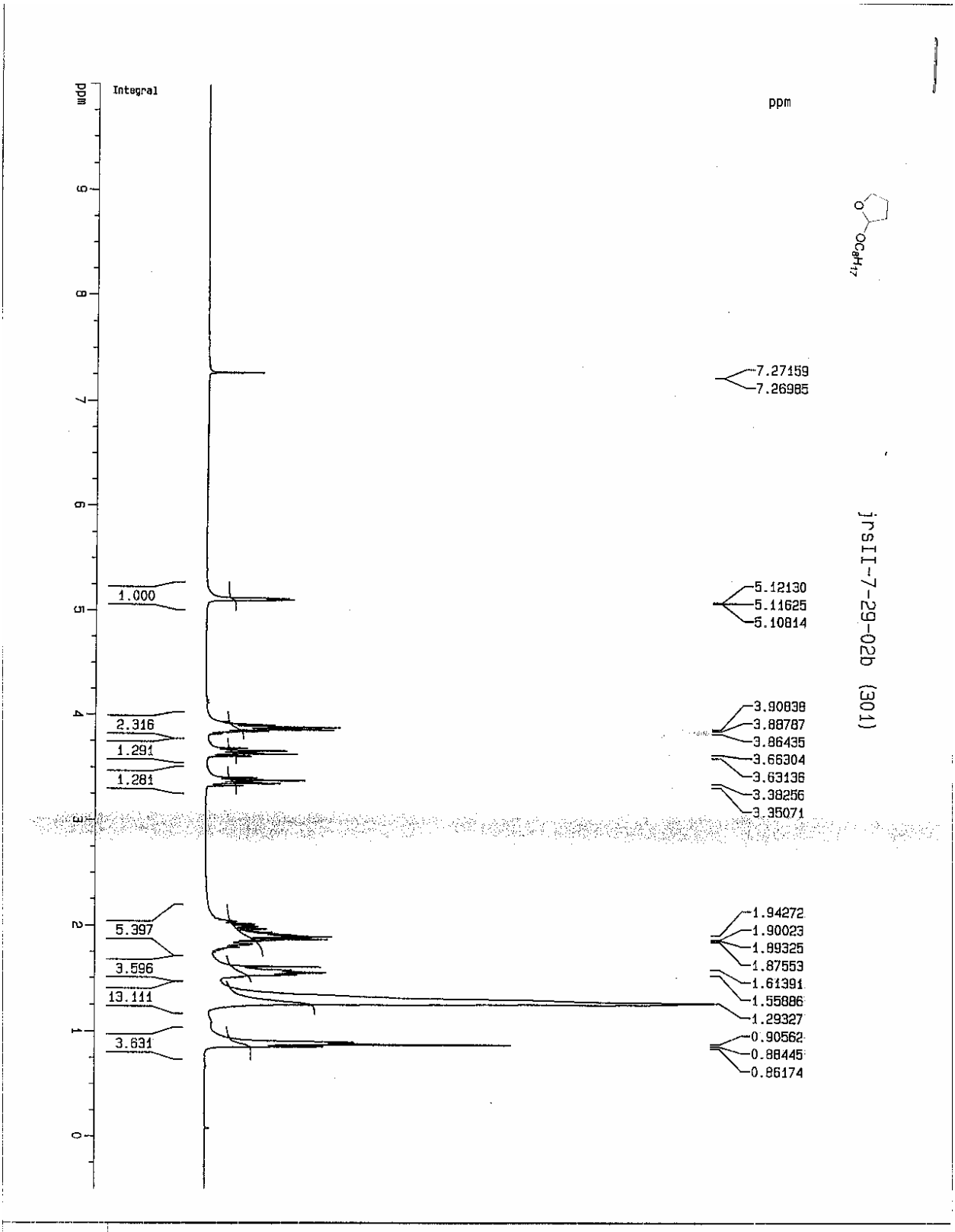
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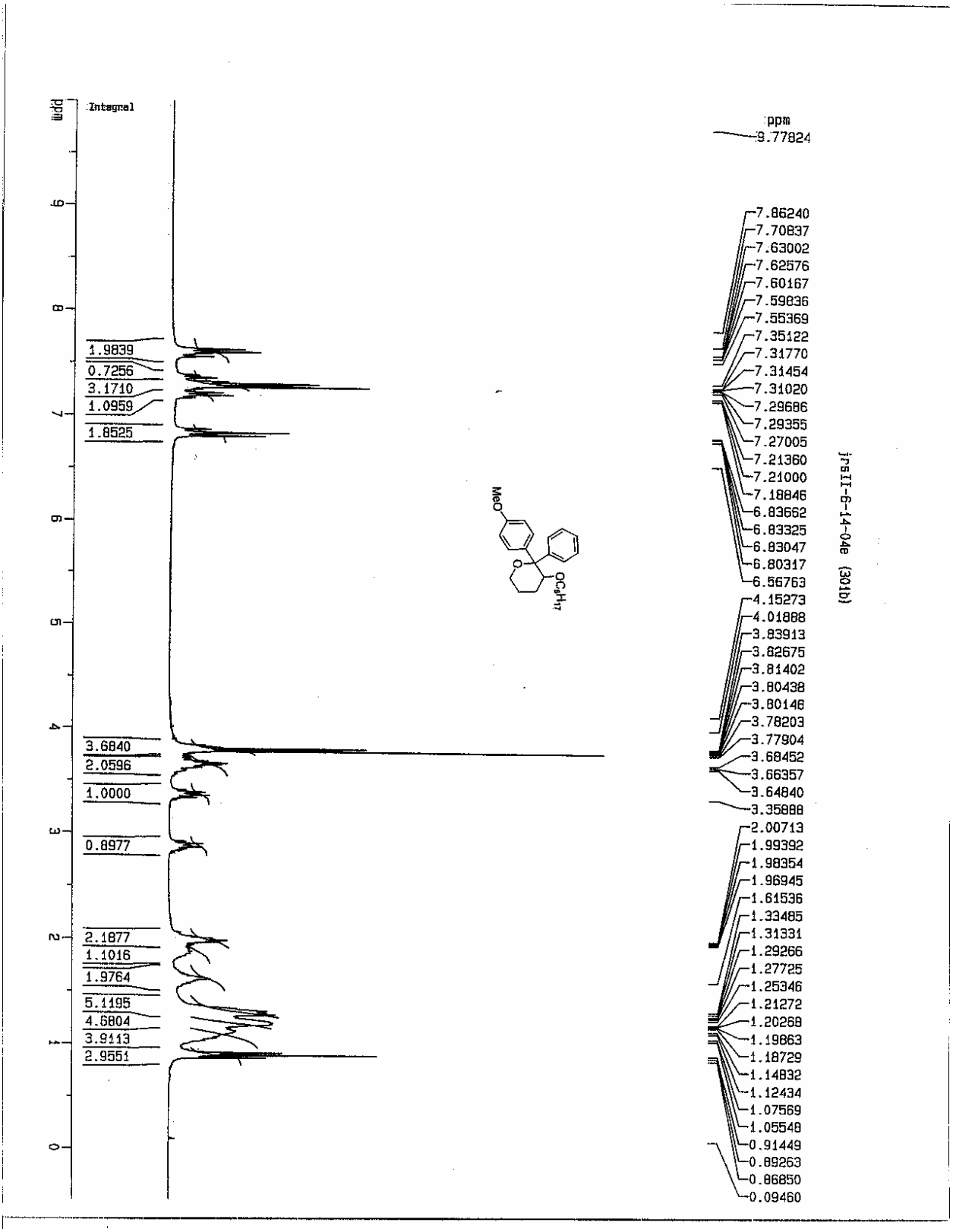
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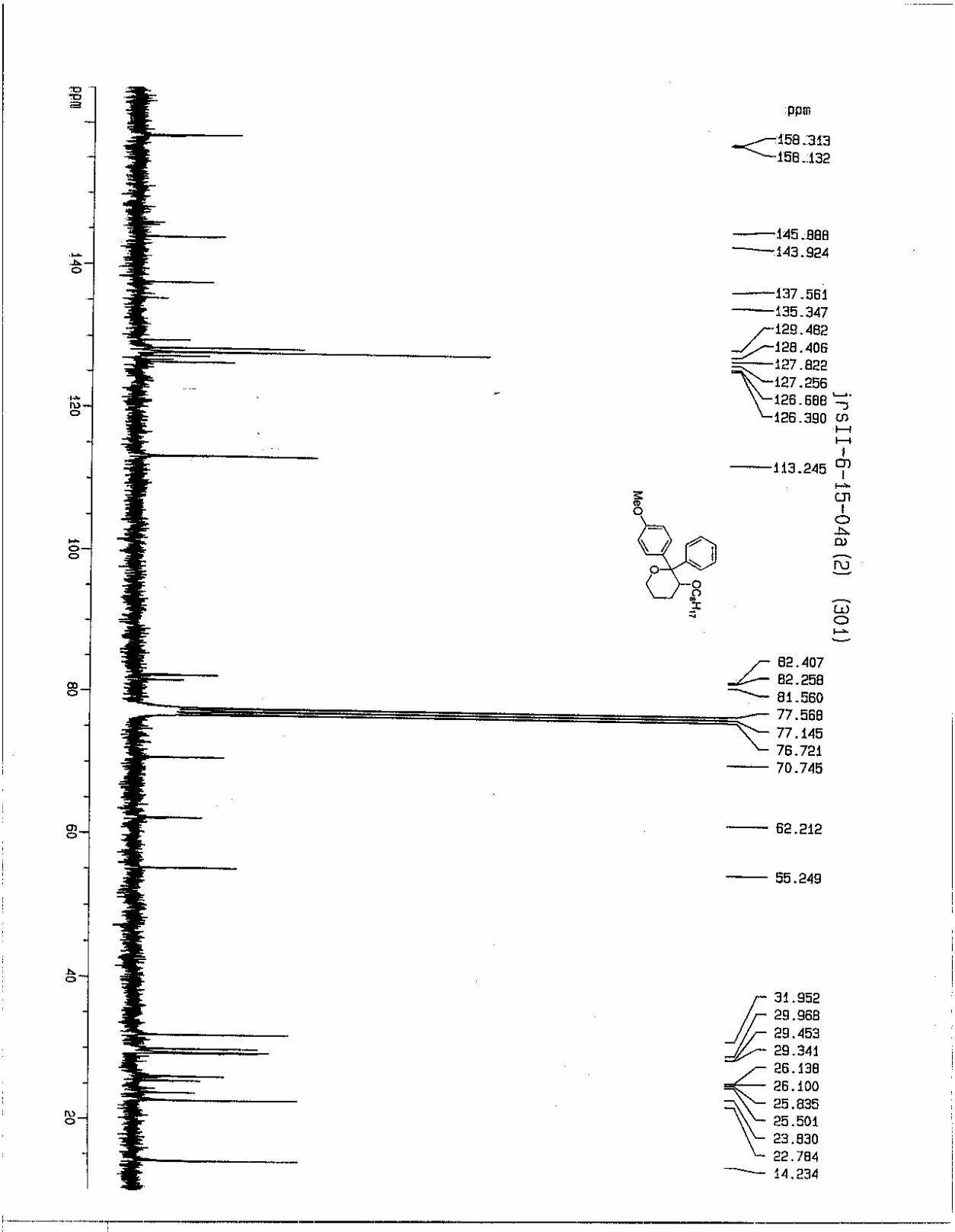
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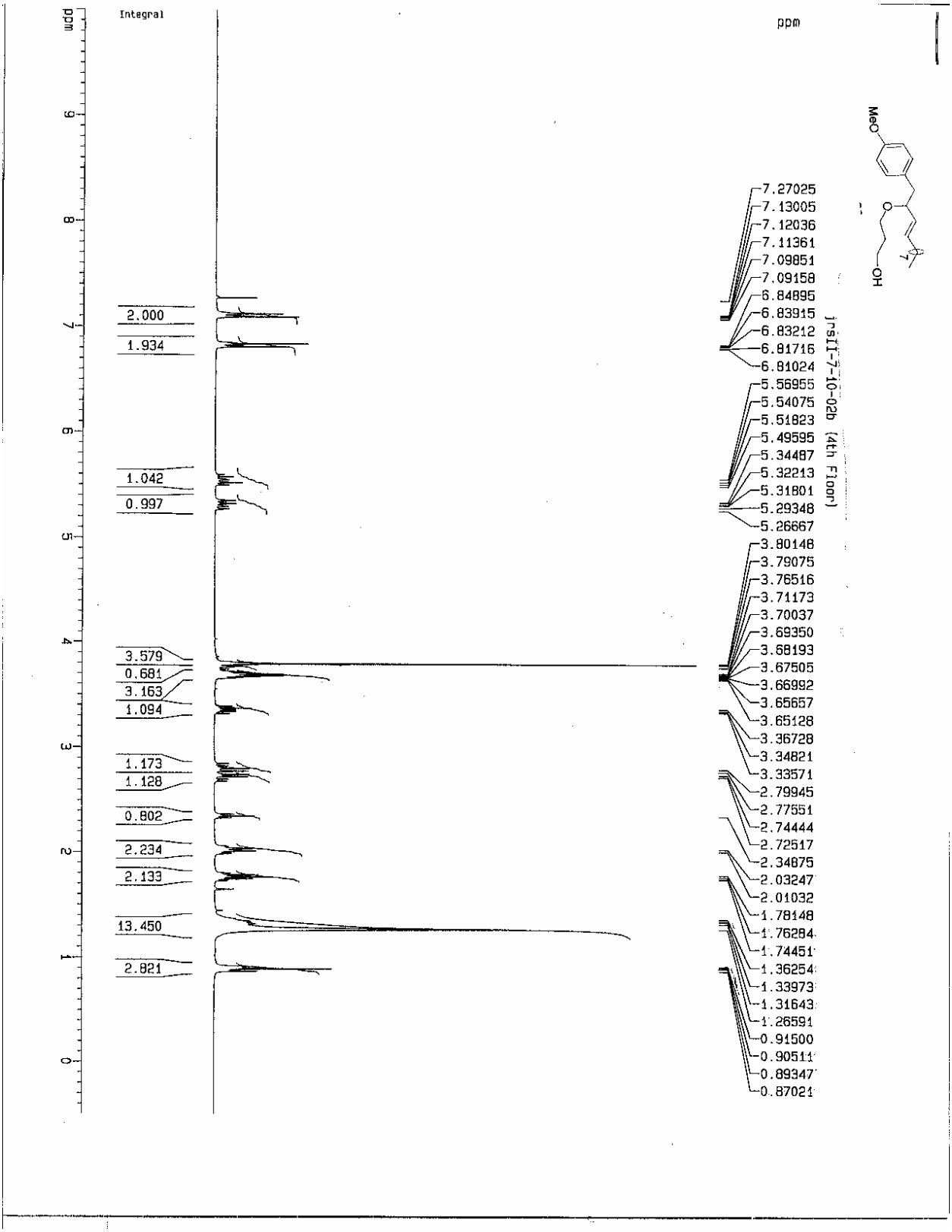
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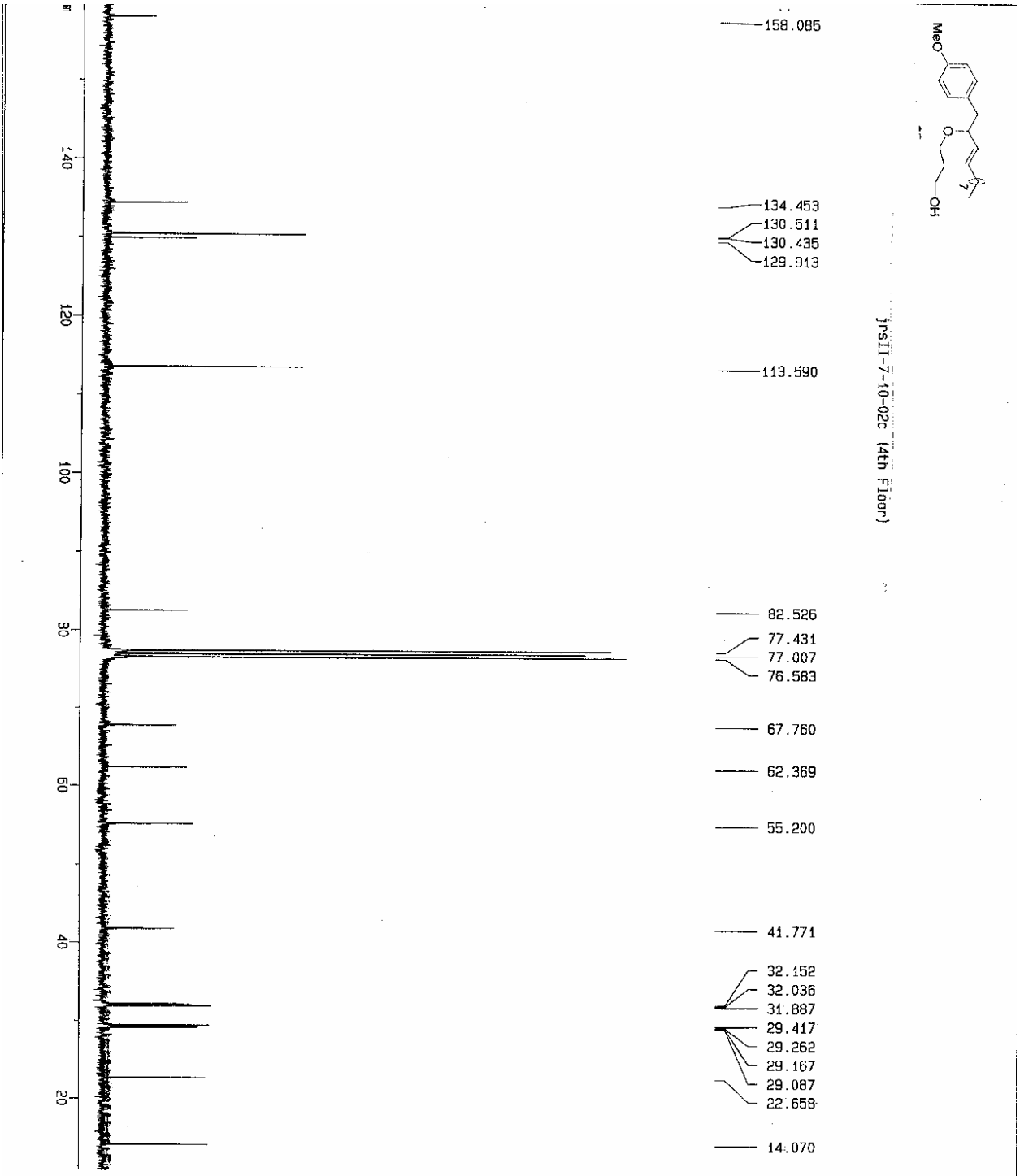
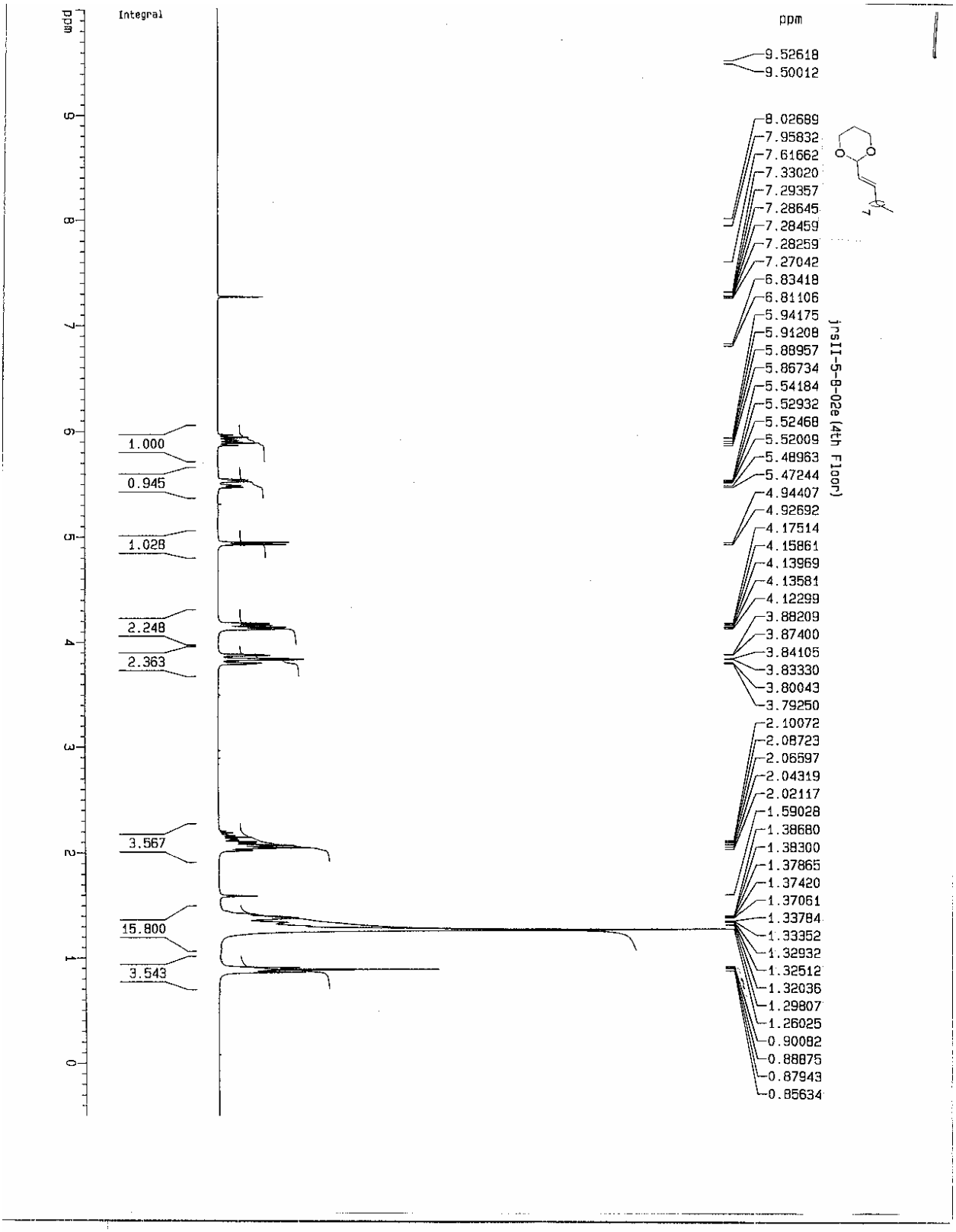
2.821
7.27025
7.13005
7.12036
7.11361
7.09851
7.09158
6.84895
6.83915
6.83212
6.81716
6.81024
5.56955
5.54075
5.51823
5.49595
5.34487
5.32213
5.31801
5.29348
5.26667
3.80148
3.79075
3.76516
3.71173
3.70037
3.69350
3.68193
3.67505
3.66992
3.65657
3.65128
3.36728
3.34821
3.33571
2.79945
2.77551
2.74444
2.72517
2.34875
2.03247
2.01032
1.78148
1.76284
1.74451
1.36254
1.33973
1.31643
1.26591
0.91500
0.90511
0.89347
0.87021
jrsii-7-10-02b (4th Floor)
MeO
OH


158.085
134.453
130.511
130.435
129.913
113.590
82.526
77.431
77.007
76.583
67.760
62.369
55.200
41.771
32.152
32.036
31.887
29.417
29.262
29.167
29.087
22.658
14.070
MeO
OH
jrsii-7-10-02c (4th Floor)
140
120
100
80
60
40
20


Integral
ppm
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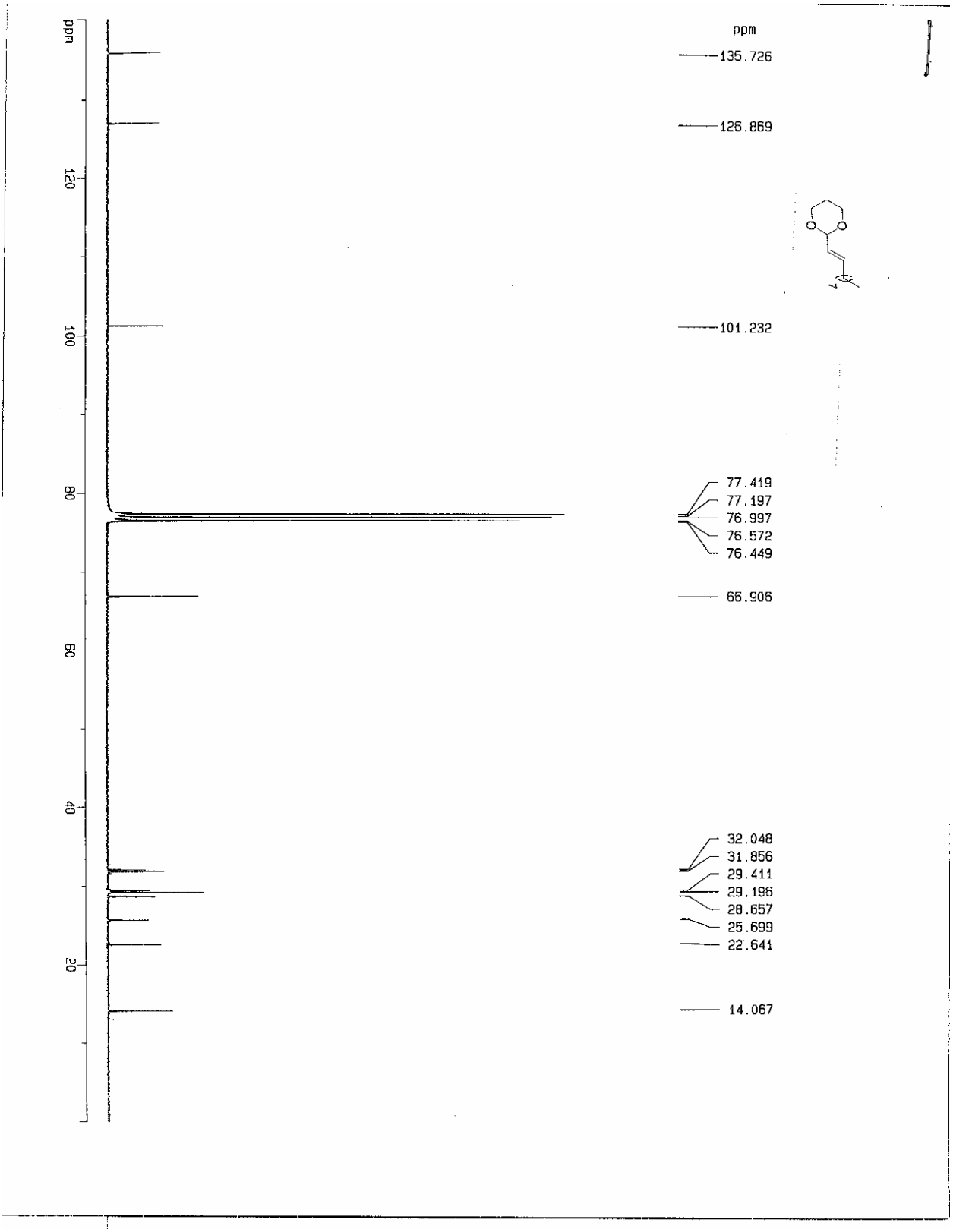
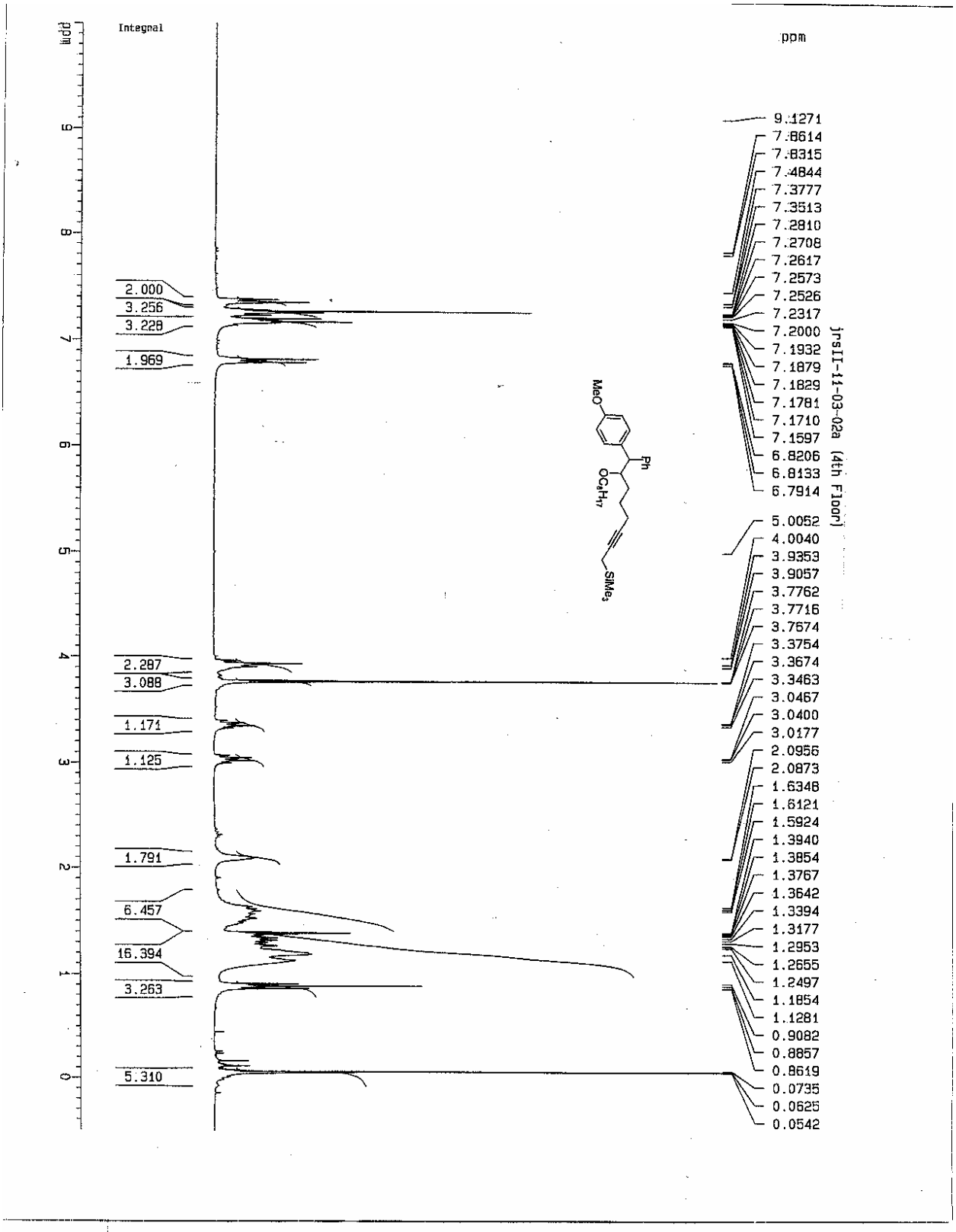
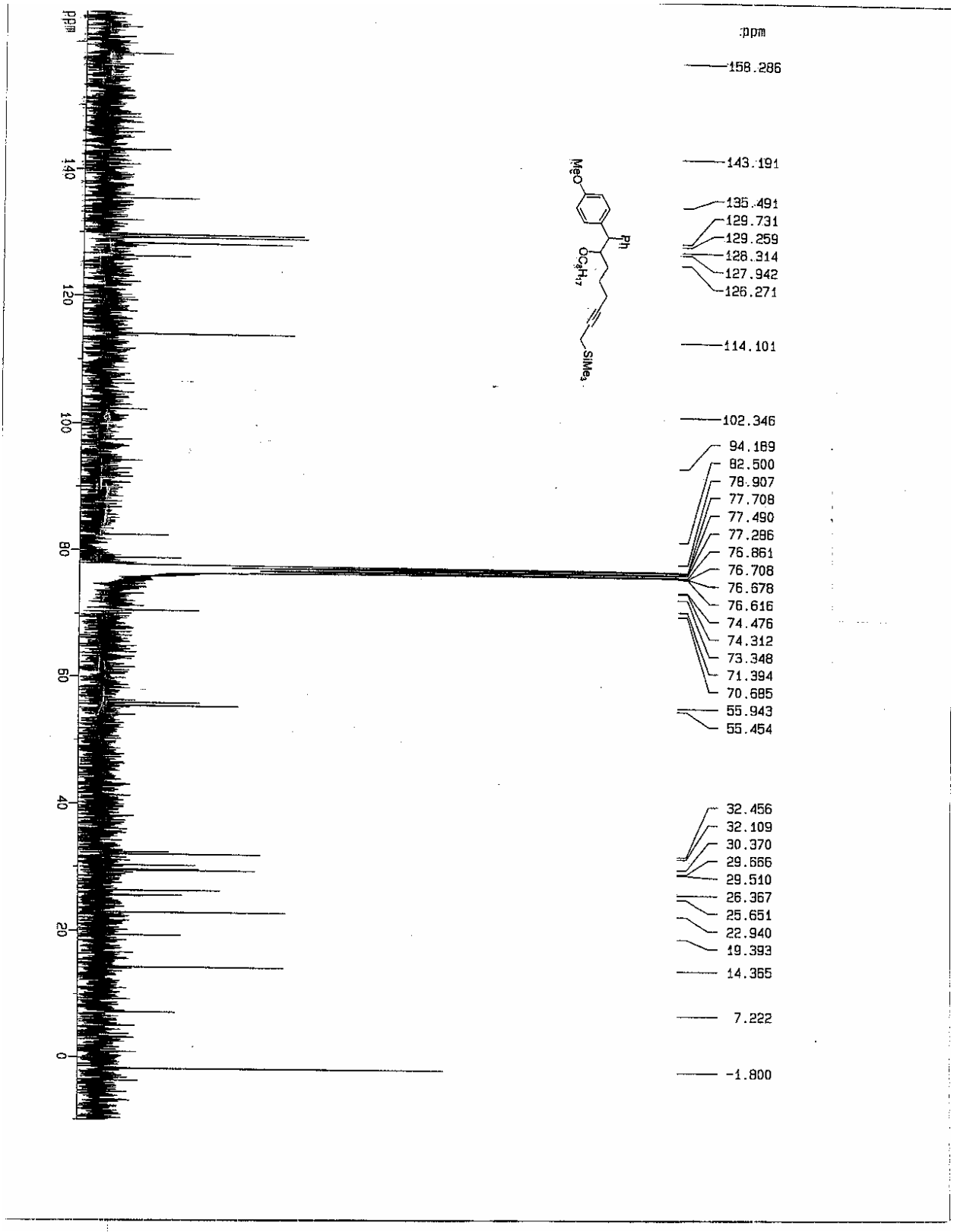
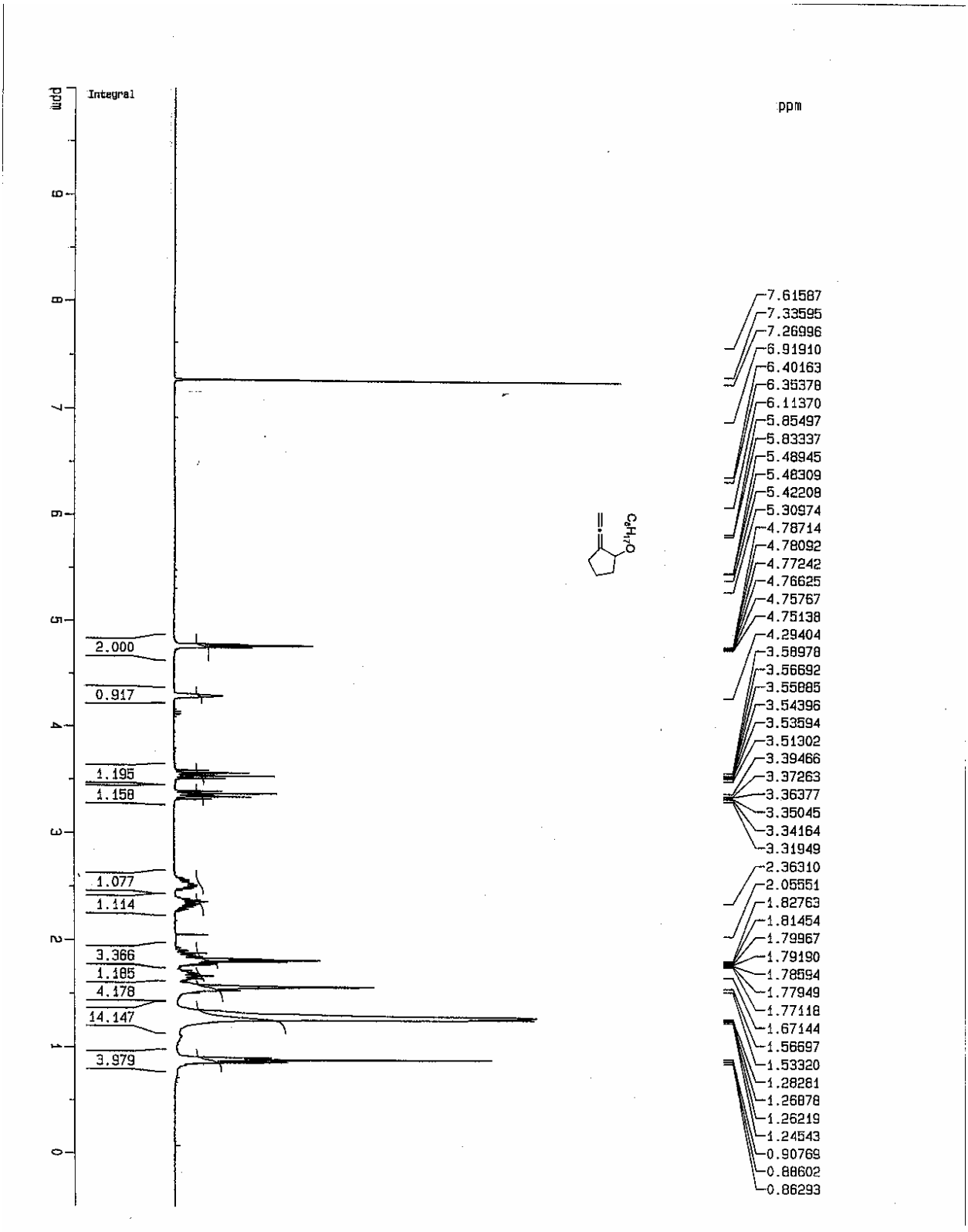
9.50012
8.02689
7.95832
7.61662
7.33020
7.29357
7.28645
7.28459
7.28259
7.27042
6.83418
6.81106
5.94175
5.91208
5.88957
5.86734
5.54184
5.52932
5.52468
5.52009
5.48963
5.47244
4.94407
4.92692
4.17514
4.15861
4.13969
4.13581
4.12299
3.88209
3.87400
3.84105
3.83330
3.80043
3.79250
2.10072
2.08723
2.06597
2.04319
2.02117
1.59028
1.38680
1.38300
1.37865
1.37420
1.37061
1.33784
1.33352
1.32932
1.32512
1.32036
1.29807
1.26025
0.90082
0.88875
0.87943
0.85634
1.000
0.945
1.028
2.248
2.363
3.567
15.800
3.543
jrsII-5-8-02e (4th Floor)


ppm
135.726
126.869
101.232
77.419
77.197
76.997
76.572
76.449
66.906
32.048
31.856
29.411
29.196
28.657
25.699
22.641
14.067
ppm
120
100
80
60
40
20


Integral
ppm
2.000
3.256
3.228
1.969
2.287
3.088
1.171
1.125
1.791
6.457
16.394
3.263
5.310
9.1271
7.8614
7.8315
7.4844
7.3777
7.3513
7.2810
7.2708
7.2617
7.2573
7.2526
7.2317
7.2000
7.1932
7.1879
7.1829
7.1781
7.1710
7.1597
6.8206
6.8133
6.7914
5.0052
4.0040
3.9353
3.9057
3.7762
3.7716
3.7674
3.3754
3.3674
3.3463
3.0467
3.0400
3.0177
2.0956
2.0873
1.6348
1.6121
1.5924
1.3940
1.3854
1.3767
1.3642
1.3394
1.3177
1.2953
1.2655
1.2497
1.1854
1.1281
0.9082
0.8857
0.8619
0.0735
0.0625
0.0542
jrsII-11-03-02a (4th Floor)
MeO
Ph
OC6H17
SiMe3


ppm
140
120
100
80
60
40
20
0
MeO
Ph
OC8H17
SiMe3
ppm
158.286
143.191
135.491
129.731
129.259
128.314
127.942
126.271
114.101
102.346
94.189
82.500
78.907
77.708
77.490
77.296
76.861
76.708
76.678
76.616
74.476
74.312
73.348
71.394
70.685
55.943
55.454
32.456
32.109
30.370
29.666
29.510
26.367
25.651
22.940
19.393
14.365
7.222
-1.800


Integral
ppm
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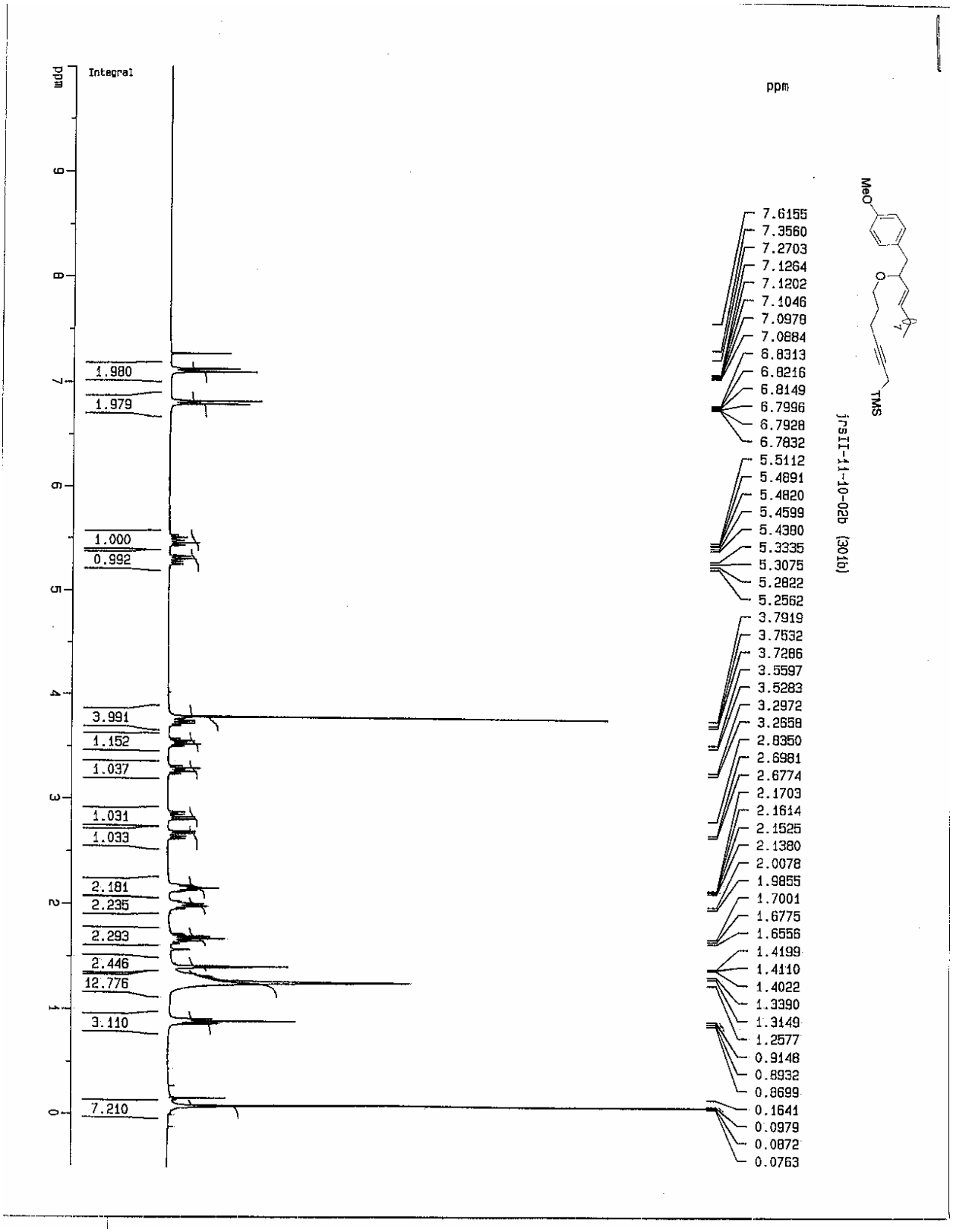
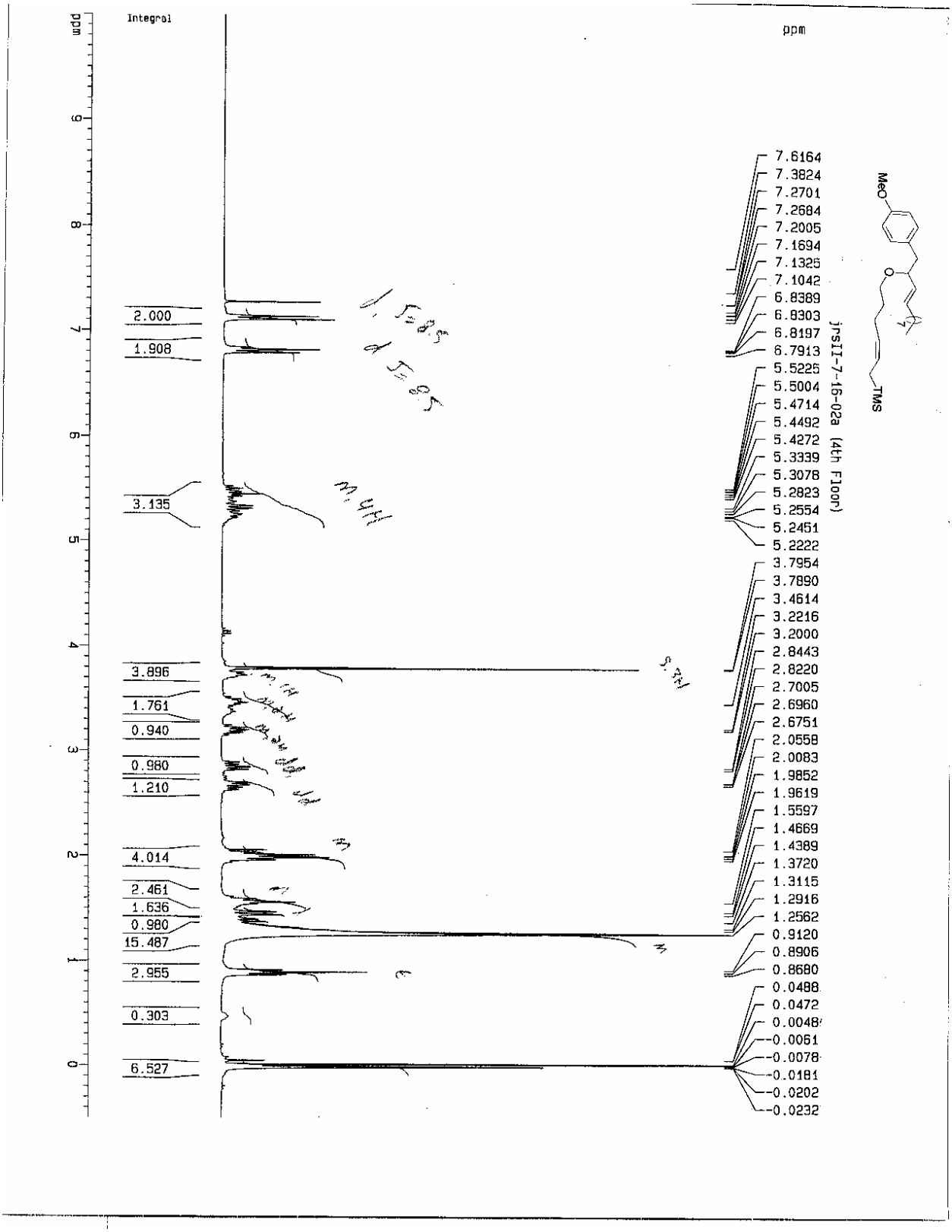
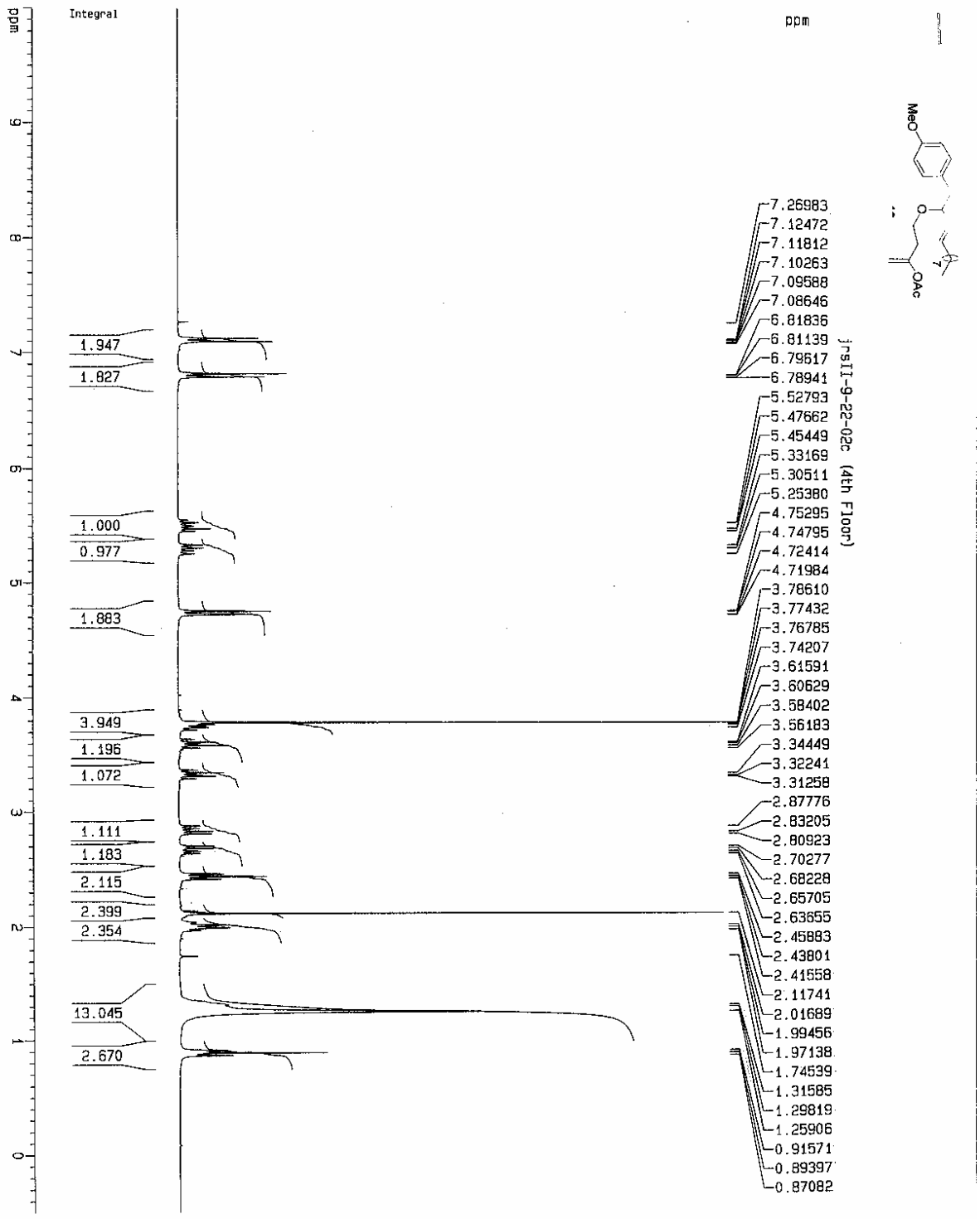
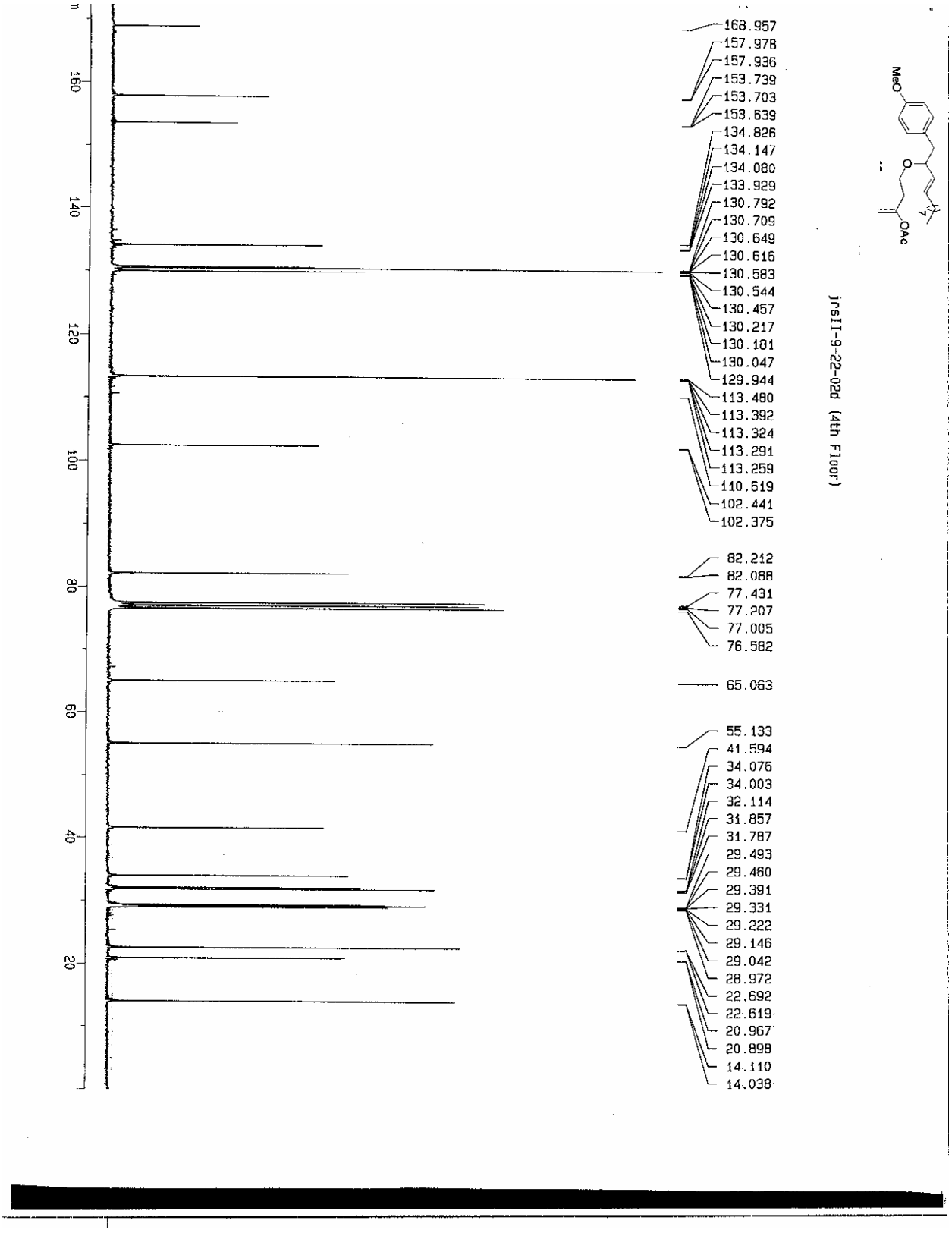
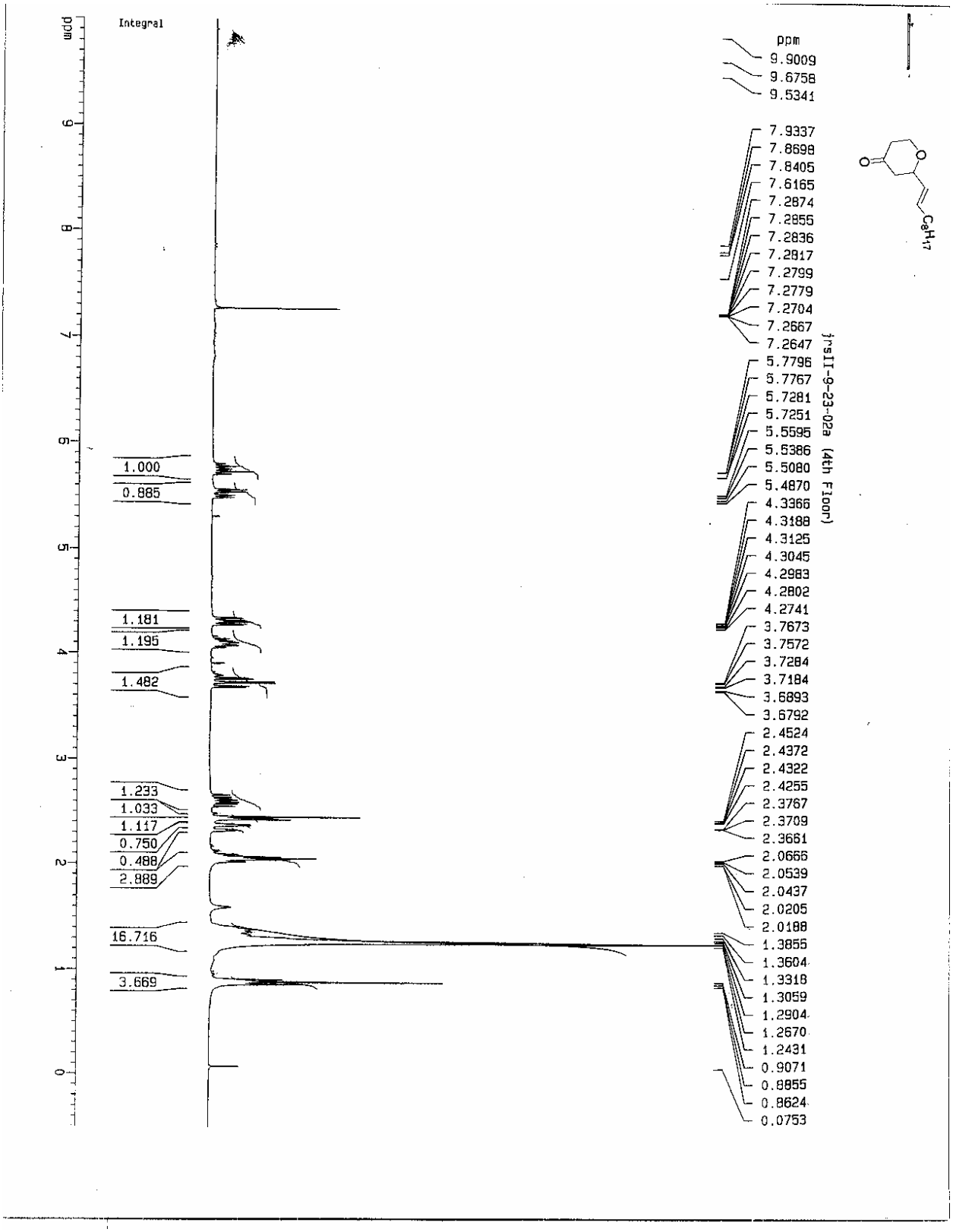
0.917
1.195
1.158
1.077
1.114
3.366
1.185
4.178
14.147
3.979
7.61587
7.33595
7.26996
6.91910
6.40163
6.35378
6.11370
5.85497
5.83337
5.48945
5.48309
5.42208
5.30974
4.78714
4.78092
4.77242
4.76625
4.75767
4.75138
4.29404
3.58978
3.56692
3.55085
3.54396
3.53594
3.51302
3.39466
3.37263
3.36377
3.35045
3.34164
3.31949
2.36310
2.05551
1.82763
1.81454
1.79967
1.79190
1.78594
1.77949
1.77118
1.67144
1.56697
1.53320
1.28281
1.26878
1.26219
1.24543
0.90769
0.88602
0.86293

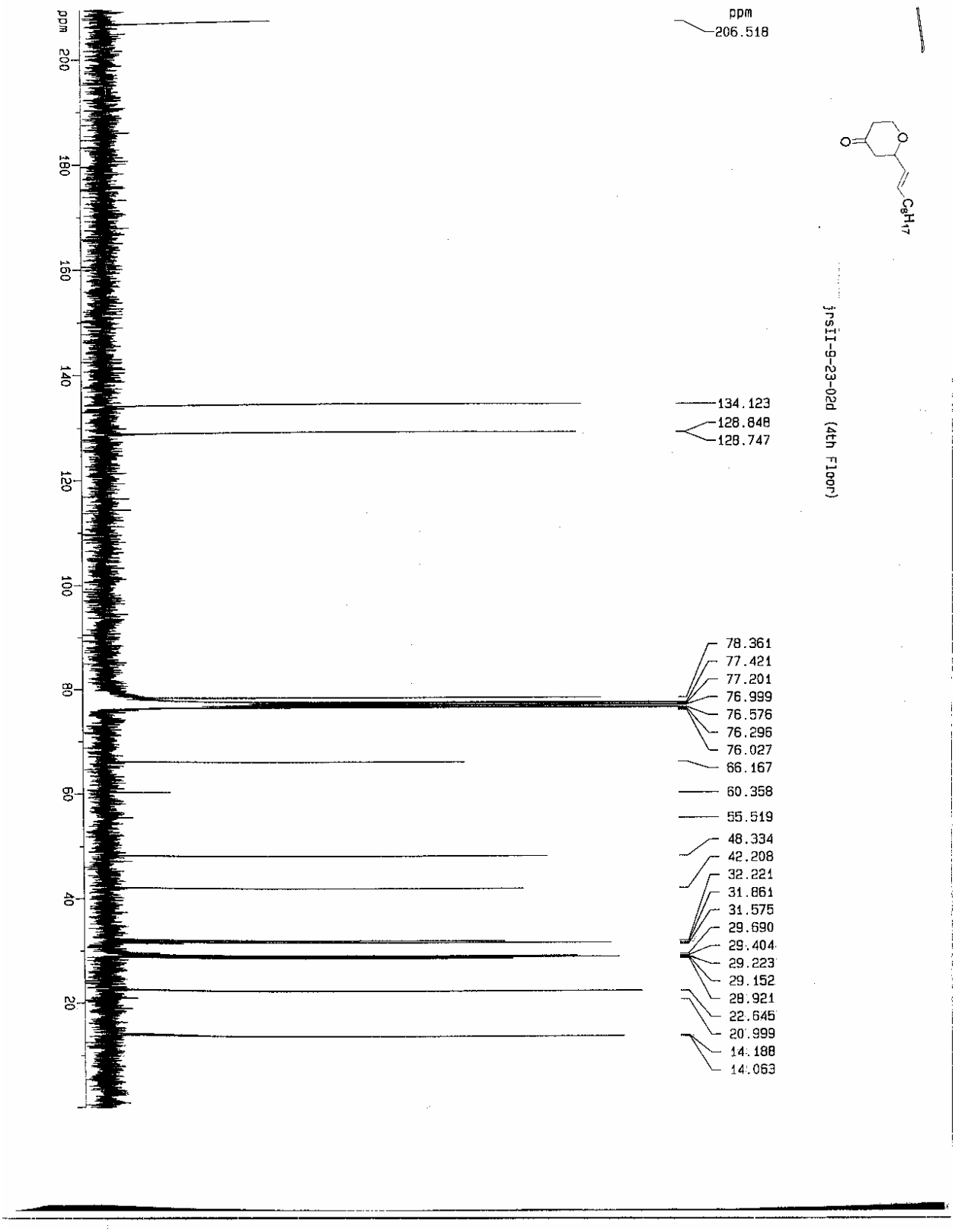

Integral
ppm
MeO
TMS
jrsII-11-10-02b (301b)
1.980
1.979
1.000
0.992
3.991
1.152
1.037
1.031
1.033
2.181
2.235
2.293
2.446
12.776
3.110
7.210
7.6155
7.3560
7.2703
7.1264
7.1202
7.1046
7.0978
7.0884
6.8313
6.8216
6.8149
6.7996
6.7928
6.7832
5.5112
5.4891
5.4820
5.4599
5.4380
5.3335
5.3075
5.2822
5.2562
3.7919
3.7532
3.7286
3.5597
3.5283
3.2972
3.2658
2.8350
2.6981
2.6774
2.1703
2.1614
2.1525
2.1380
2.0078
1.9855
1.7001
1.6775
1.6556
1.4199
1.4110
1.4022
1.3390
1.3149
1.2577
0.9148
0.8932
0.8699
0.1641
0.0979
0.0872
0.0763


Integral
ppm
jrsII-7-16-02a (4th Floor)
MeO
TMS
2.000
1.908
3.135
3.896
1.761
0.940
0.980
1.210
4.014
2.461
1.636
0.980
15.487
2.955
0.303
6.527
7.6164
7.3824
7.2701
7.2684
7.2005
7.1694
7.1325
7.1042
6.8389
6.8303
6.8197
6.7913
5.5225
5.5004
5.4714
5.4492
5.4272
5.3339
5.3078
5.2823
5.2554
5.2451
5.2222
3.7954
3.7890
3.4614
3.2216
3.2000
2.8443
2.8220
2.7005
2.6960
2.6751
2.0558
2.0083
1.9852
1.9619
1.5597
1.4669
1.4389
1.3720
1.3115
1.2916
1.2562
0.9120
0.8906
0.8680
0.0488
0.0472
0.0048
-0.0061
-0.0078
-0.0181
-0.0202
-0.0232


Integral
ppm
jrsii-9-22-02c (4th Floor)
MeO
OAc
1.947
1.827
1.000
0.977
1.883
3.949
1.196
1.072
1.111
1.183
2.115
2.399
2.354
13.045
2.670
7.26983
7.12472
7.11812
7.10263
7.09588
7.08646
6.81836
6.81139
6.79617
6.78941
5.52793
5.47662
5.45449
5.33169
5.30511
5.25380
4.75295
4.74795
4.72414
4.71984
3.78610
3.77432
3.76785
3.74207
3.61591
3.60629
3.58402
3.56183
3.34449
3.32241
3.31258
2.87776
2.83205
2.80923
2.70277
2.68228
2.65705
2.63655
2.45883
2.43801
2.41558
2.11741
2.01689
1.99456
1.97138
1.74539
1.31585
1.29819
1.25906
0.91571
0.89397
0.87082

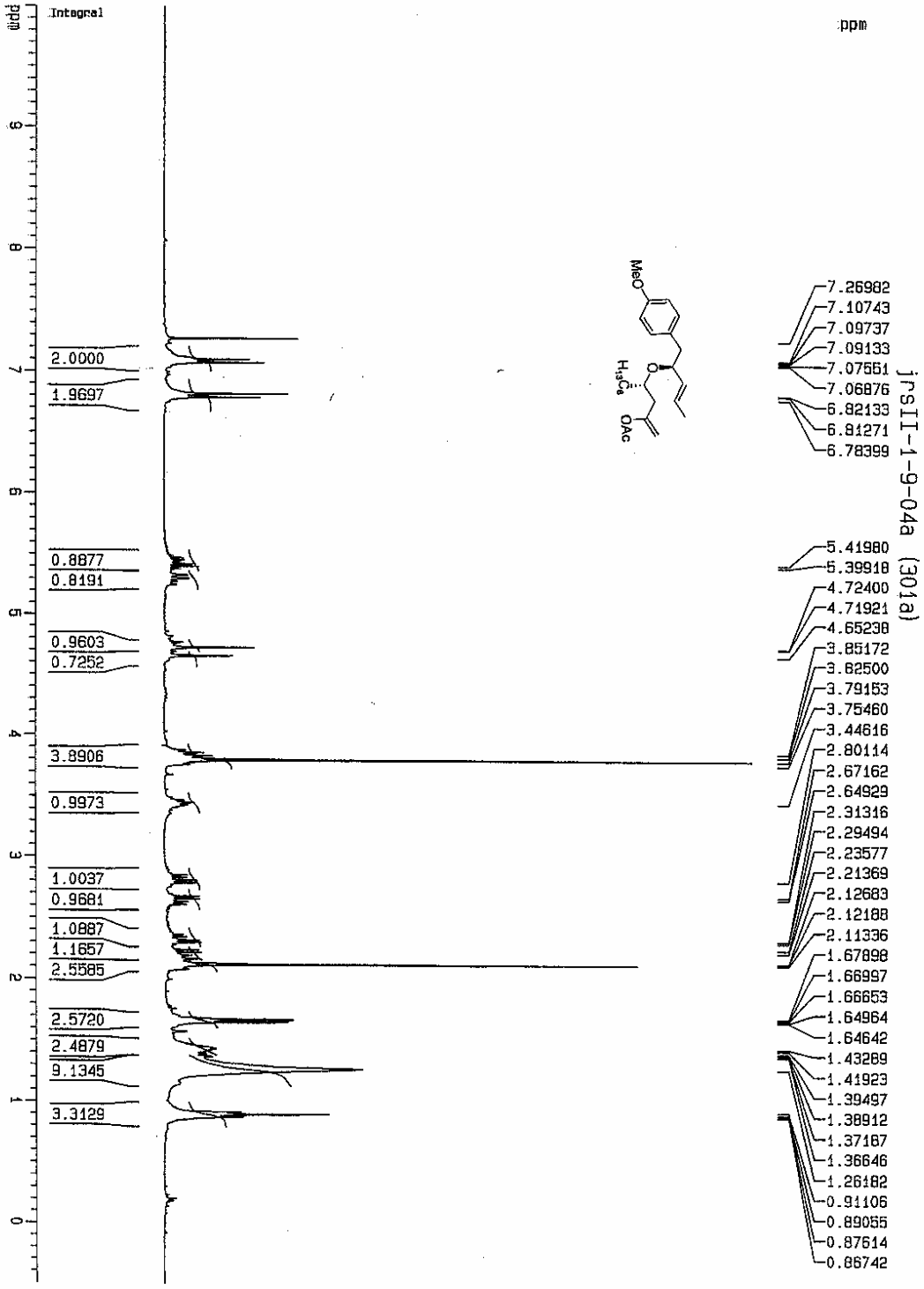

168.957
157.978
157.936
153.739
153.703
153.639
134.826
134.147
134.080
133.929
130.792
130.709
130.649
130.616
130.583
130.544
130.457
130.217
130.181
130.047
129.944
113.480
113.392
113.324
113.291
113.259
110.619
102.441
102.375
82.212
82.088
77.431
77.207
77.005
76.582
65.063
55.133
41.594
34.076
34.003
32.114
31.857
31.787
29.493
29.460
29.391
29.331
29.222
29.146
29.042
28.972
22.692
22.619
20.967
20.898
14.110
14.038
MeO
OAc
jrsII-9-22-02d (4th Floor)

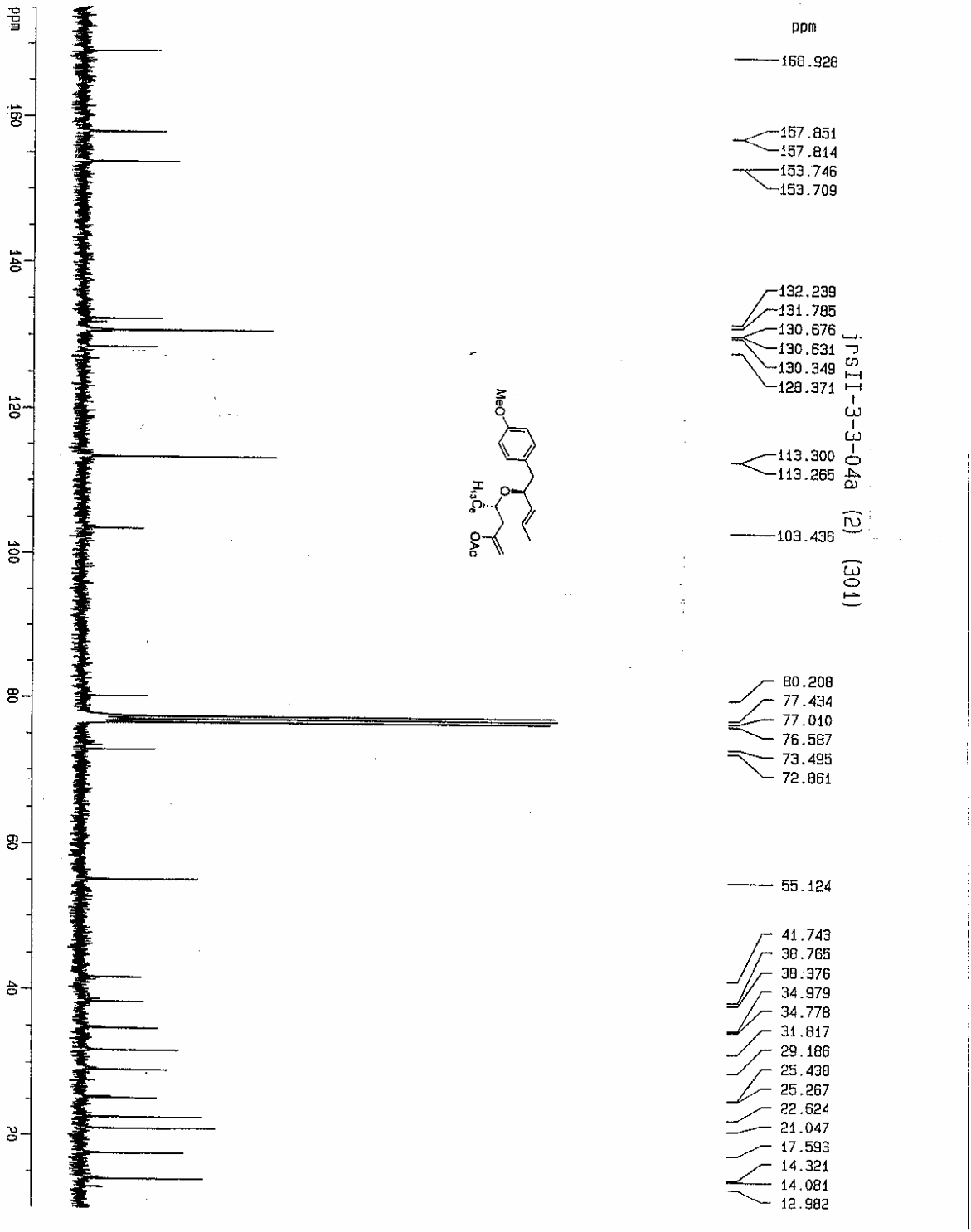

Integral
ppm
1.000
0.885
1.181
1.195
1.482
1.233
1.033
1.117
0.750
0.488
2.889
16.716
3.669
ppm
9.9009
9.6758
9.5341
7.9337
7.8698
7.8405
7.6165
7.2874
7.2855
7.2836
7.2817
7.2799
7.2779
7.2704
7.2667
7.2647
5.7796
5.7767
5.7281
5.7251
5.5595
5.5386
5.5080
5.4870
4.3366
4.3188
4.3125
4.3045
4.2983
4.2802
4.2741
3.7673
3.7572
3.7284
3.7184
3.6893
3.6792
2.4524
2.4372
2.4322
2.4255
2.3767
2.3709
2.3661
2.0666
2.0539
2.0437
2.0205
2.0188
1.3855
1.3604
1.3318
1.3059
1.2904
1.2670
1.2431
0.9071
0.8855
0.8624
0.0753
jrsII-9-23-02a (4th Floor)
C8H17

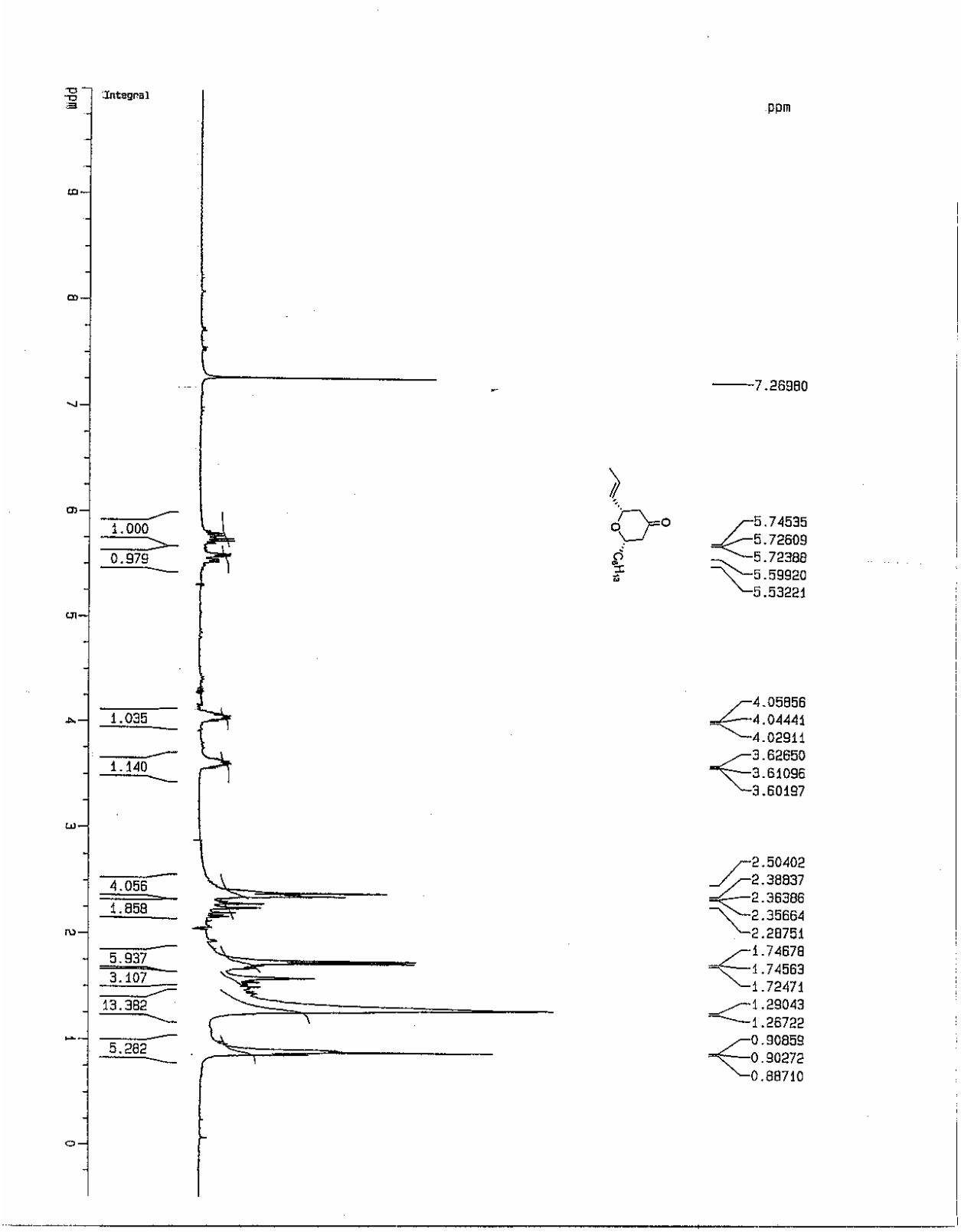

ppm
206.518
134.123
128.848
128.747
78.361
77.421
77.201
76.999
76.576
76.296
76.027
66.167
60.358
55.519
48.334
42.208
32.221
31.861
31.575
29.690
29.404
29.223
29.152
28.921
22.645
20.999
14.188
14.063
jrsi-9-23-02d (4th Floor)
C8H17
ppm
200
180
160
140
120
100
80
60
40
20

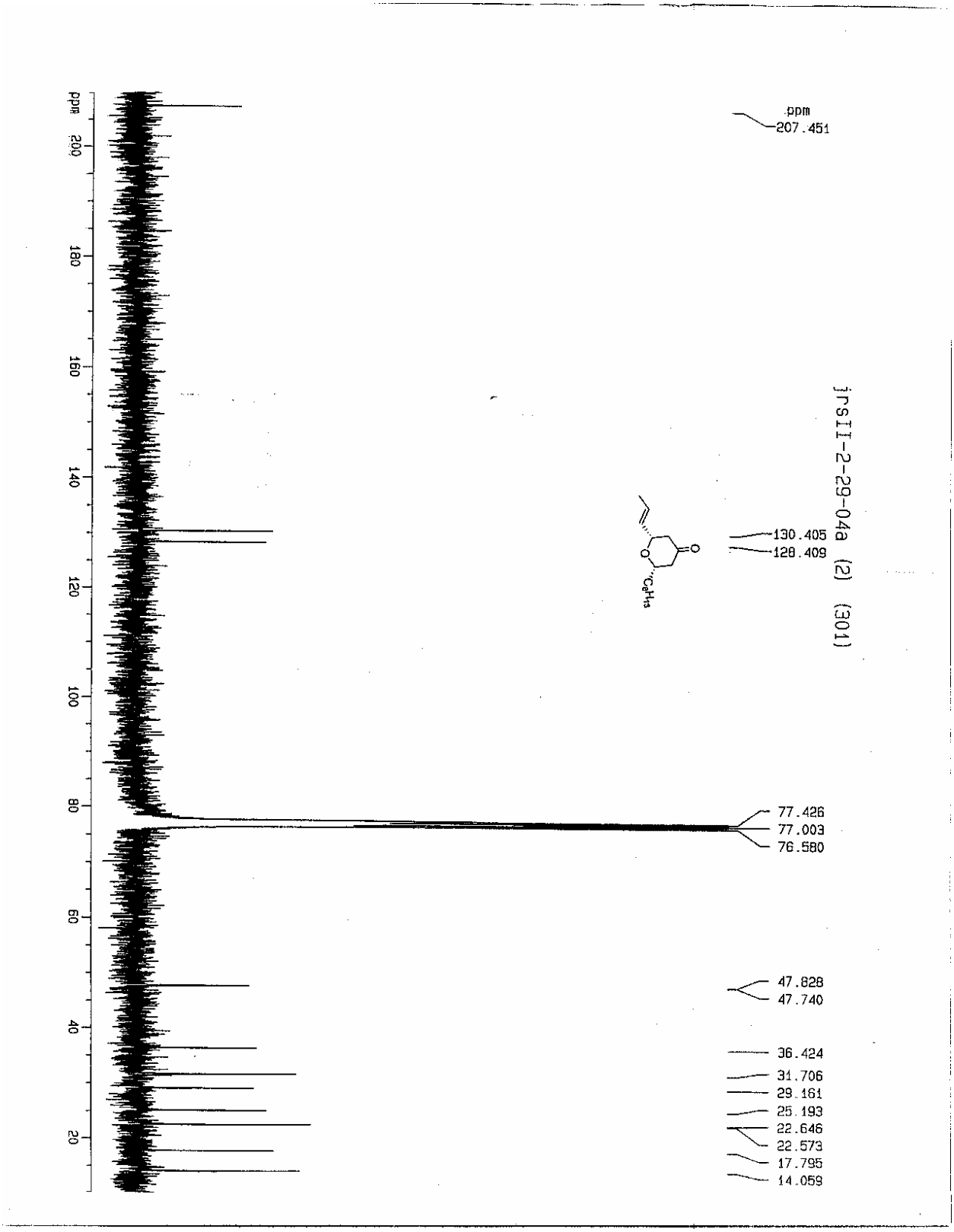
APPENDIX B

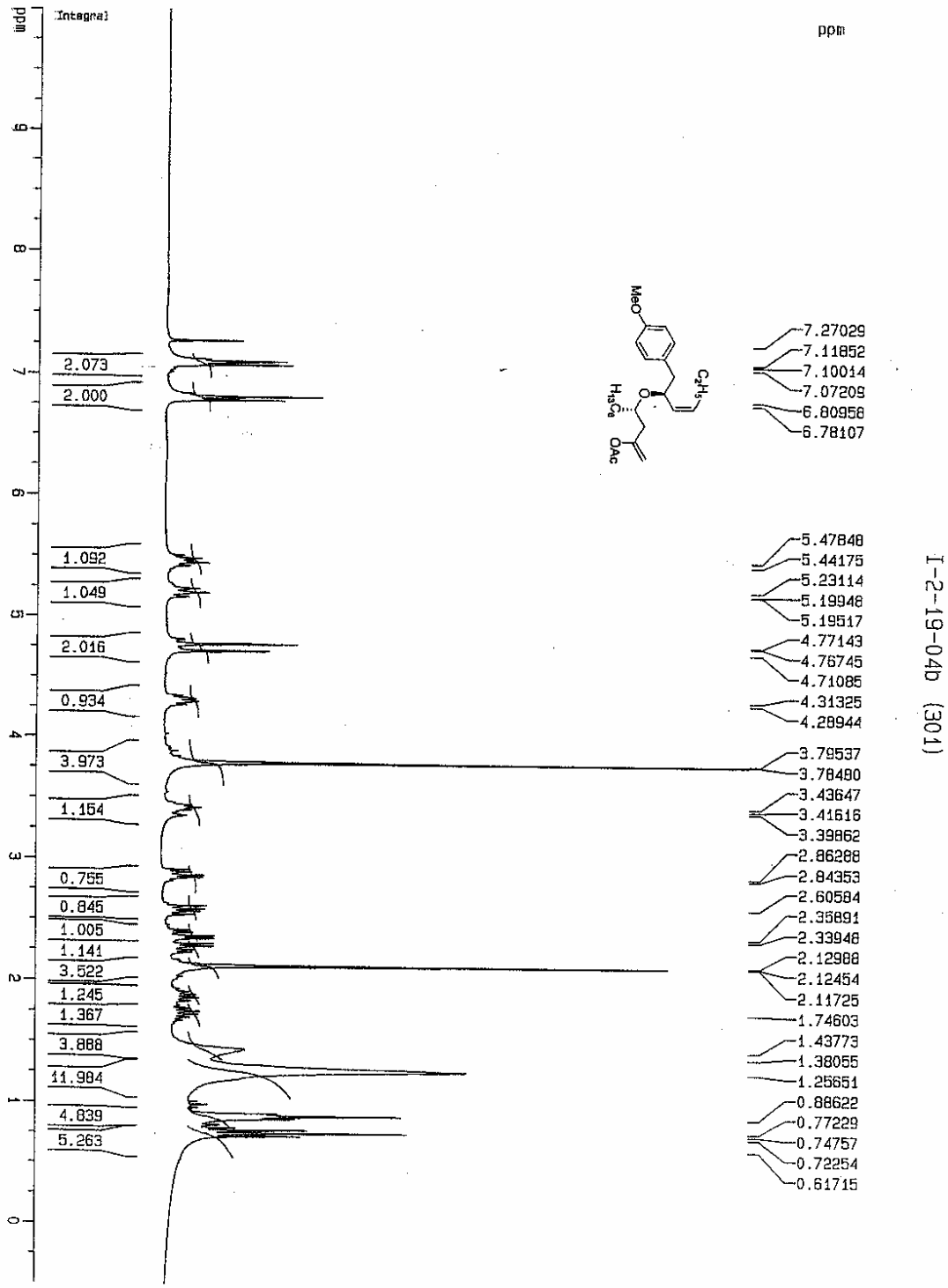
Development of the Diastereoselective Electron Transfer Initiated Cyclization (ETIC) Reaction: Synthesis of 2,6-*syn*-Tetrahydropyranones (Supporting Information) (^{1}H and ^{13}C NMR Spectra and Selected 2-D Spectra)


Integral
ppm
2.0000
1.9697
0.8877
0.8191
0.9603
0.7252
3.8906
0.9973
1.0037
0.9681
1.0887
1.1657
2.5585
2.5720
2.4879
9.1345
3.3129
MeO
OAc
7.26982
7.10743
7.09737
7.09133
7.07551
7.06876
6.82133
6.81271
6.78399
5.41980
5.39918
4.72400
4.71921
4.65238
3.85172
3.82500
3.79153
3.75460
3.44616
2.80114
2.67162
2.64929
2.31316
2.29494
2.23577
2.21369
2.12683
2.12188
2.11336
1.67898
1.66997
1.66653
1.64964
1.64642
1.43289
1.41923
1.39497
1.38912
1.37187
1.36646
1.26182
0.91106
0.89055
0.87614
0.86742
jrsII-1-9-04a (301a)

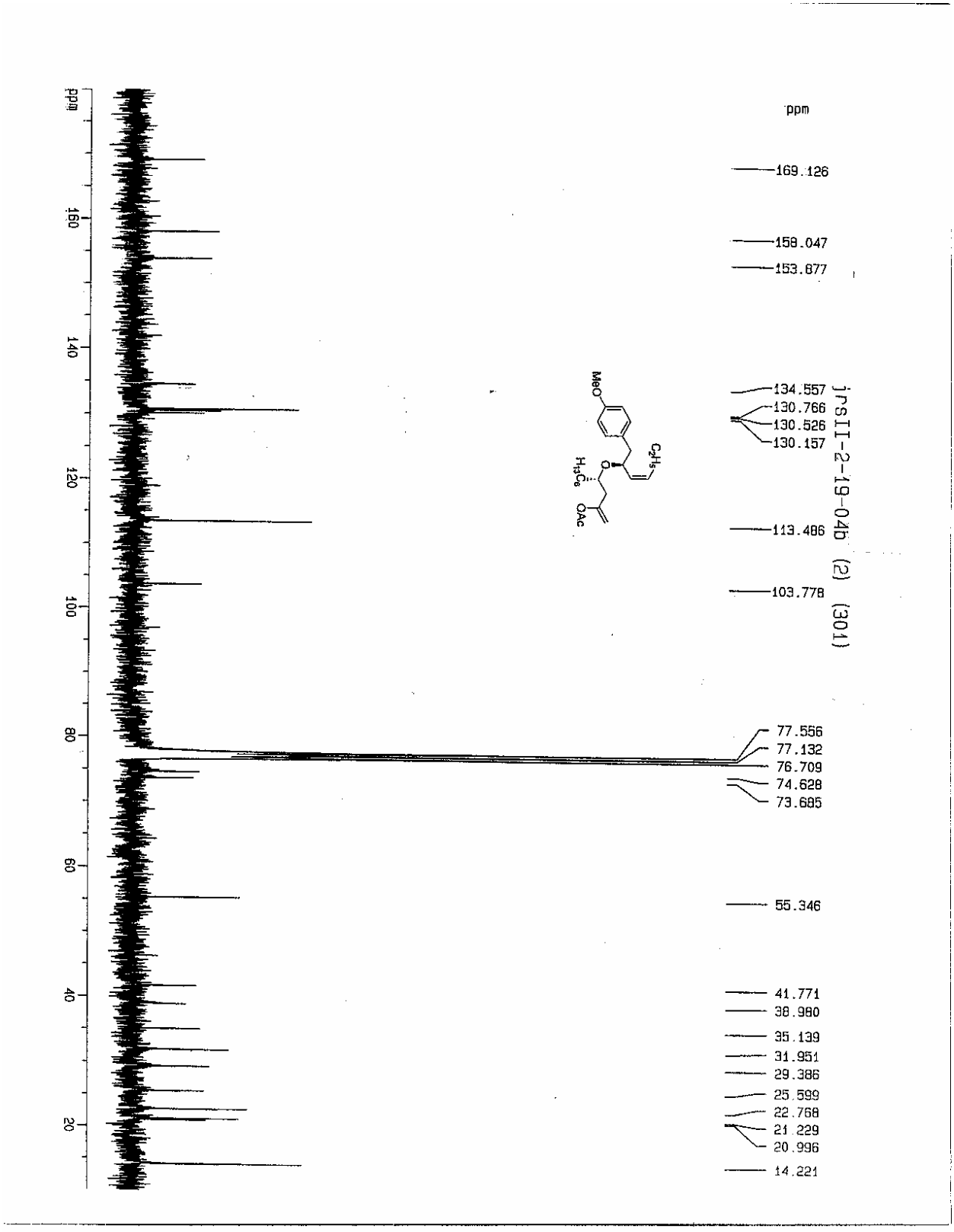

ppm
160
140
120
100
80
60
40
20
MeO
H3C
OAc
ppm
168.928
157.851
157.814
153.746
153.709
132.239
131.785
130.676
130.631
130.349
128.371
113.300
113.265
103.436
80.208
77.434
77.010
76.587
73.495
72.861
55.124
41.743
38.765
38.376
34.979
34.778
31.817
29.186
25.438
25.267
22.624
21.047
17.593
14.321
14.081
12.982
jrsII-3-3-04a (2) (301)

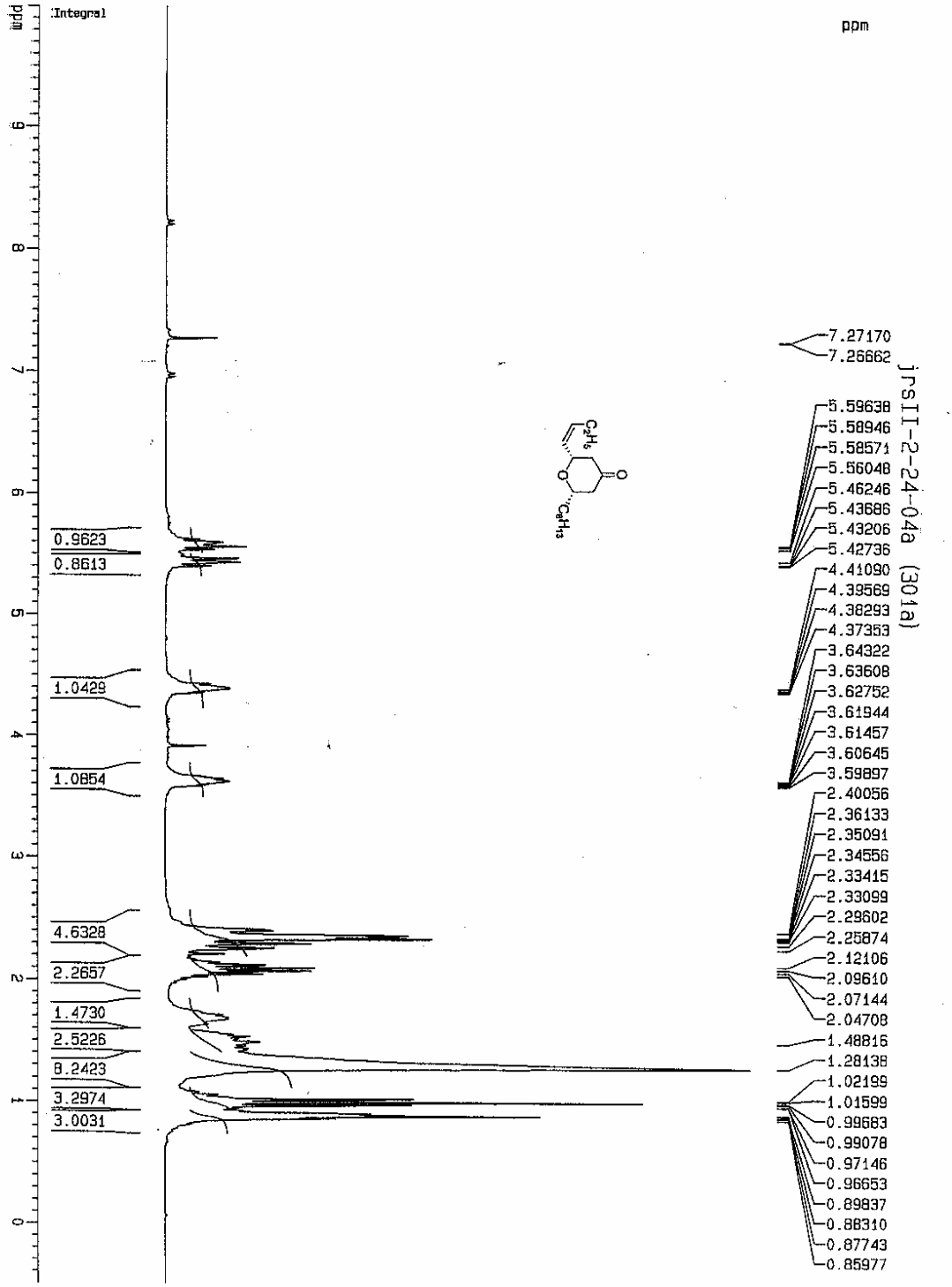

Integral
ppm
7.26980
5.74535
5.72609
5.72388
5.59920
5.53221
4.05856
4.04441
4.02911
3.62650
3.61096
3.60197
2.50402
2.38837
2.36386
2.35664
2.28751
1.74678
1.74563
1.72471
1.29043
1.26722
0.90859
0.90272
0.88710
1.000
0.979
1.035
1.140
4.056
1.858
5.937
3.107
13.382
5.282

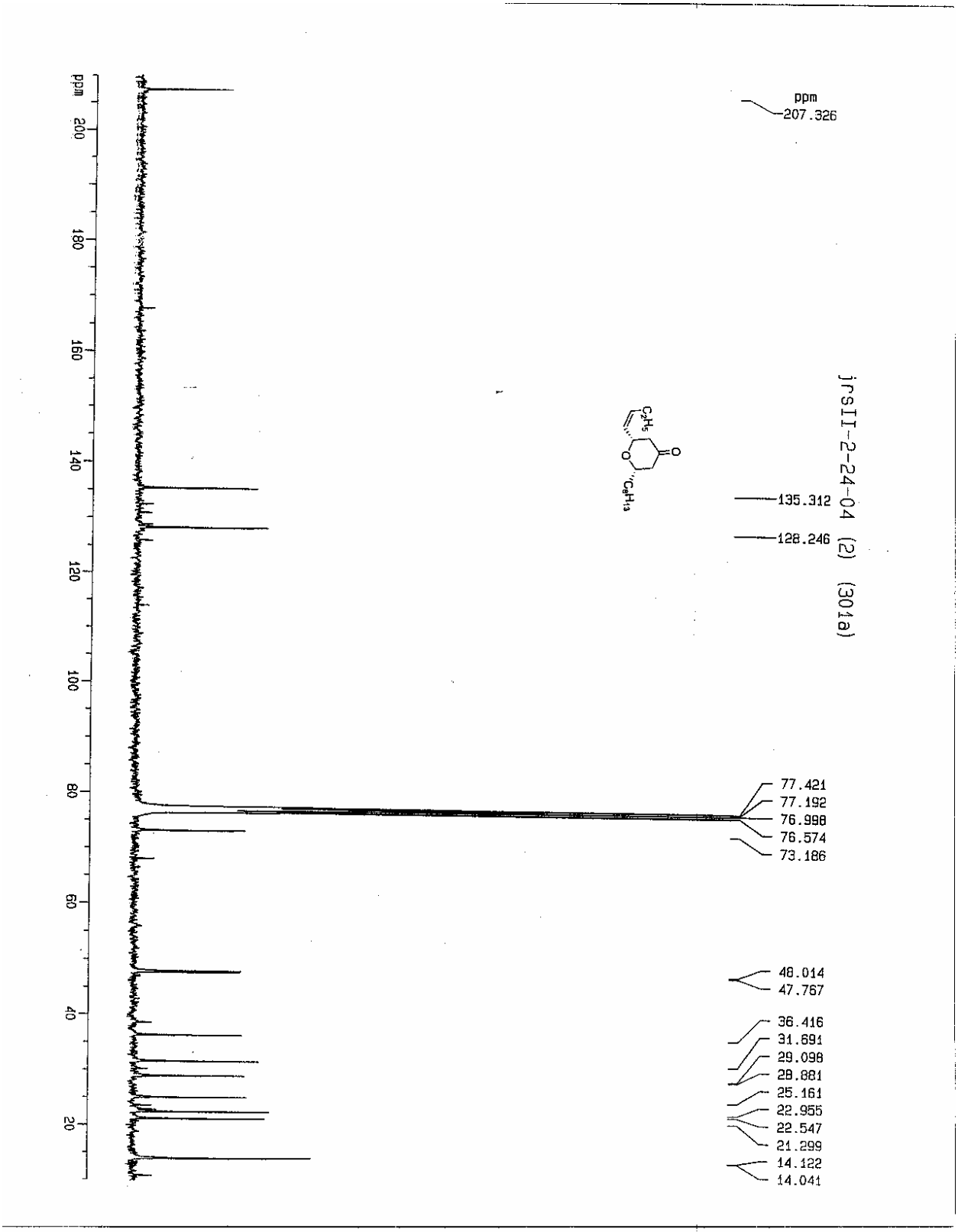

ppm
207.451
130.405
128.409
77.426
77.003
76.580
47.828
47.740
36.424
31.706
29.161
25.193
22.646
22.573
17.795
14.059
jrsII-2-29-04a (2) (301)
ppm
200
180
160
140
120
100
80
60
40
20


Integral
ppm
2.073
2.000
1.092
1.049
2.016
0.934
3.973
1.154
0.755
0.845
1.005
1.141
3.522
1.245
1.367
3.888
11.984
4.839
5.263
MeO
OAc
ppm
7.27029
7.11852
7.10014
7.07209
6.80958
6.78107
5.47848
5.44175
5.23114
5.19948
5.19517
4.77143
4.76745
4.71085
4.31325
4.28944
3.79537
3.78480
3.43647
3.41616
3.39862
2.86288
2.84353
2.60584
2.35891
2.33948
2.12988
2.12454
2.11725
1.74603
1.43773
1.38055
1.25651
0.88622
0.77229
0.74757
0.72254
0.61715

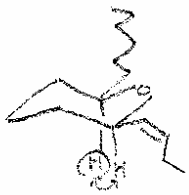
I-2-19-04b (301)

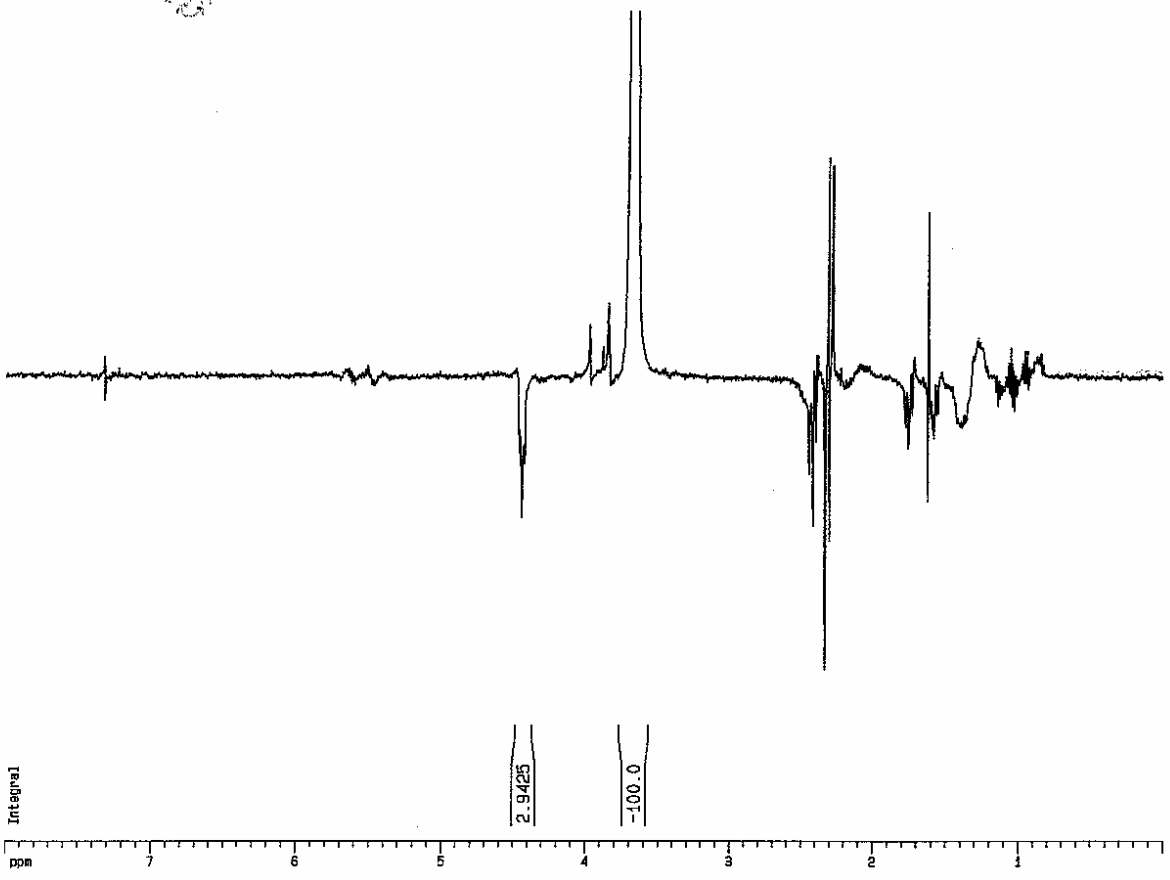

ppm
169.126
158.047
153.877
134.557
130.766
130.526
130.157
113.486
103.778
77.556
77.132
76.709
74.628
73.685
55.346
41.771
38.980
35.139
31.951
29.386
25.599
22.768
21.229
20.996
14.221
jrsII-2-19-04b (2) (301)
MeO
OAc
160
140
120
100
80
60
40
20


Integral
ppm
jrsII-2-24-04a (301a)
7.27170
7.26662
5.59638
5.58946
5.58571
5.56048
5.46246
5.43686
5.43206
5.42736
4.41090
4.39569
4.38293
4.37353
3.64322
3.63608
3.62752
3.61944
3.61457
3.60645
3.59897
2.40056
2.36133
2.35091
2.34556
2.33415
2.33099
2.29602
2.25874
2.12106
2.09610
2.07144
2.04708
1.48816
1.28138
1.02199
1.01599
0.99683
0.99078
0.97146
0.96653
0.89837
0.88310
0.87743
0.85977
0.9623
0.8613
1.0429
1.0854
4.6328
2.2657
1.4730
2.5226
8.2423
3.2974
3.0031


jrsII-2-24-04 (2) (301a)
ppm
207.326
135.312
128.246
77.421
77.192
76.998
76.574
73.186
48.014
47.767
36.416
31.691
29.098
28.881
25.161
22.955
22.547
21.299
14.122
14.041
ppm
200
180
160
140
120
100
80
60
40
20

John Seiders 05-01-03 12 2 500 MHz CDCl3 irr. 1835.98 Hz
2,6 pyranone





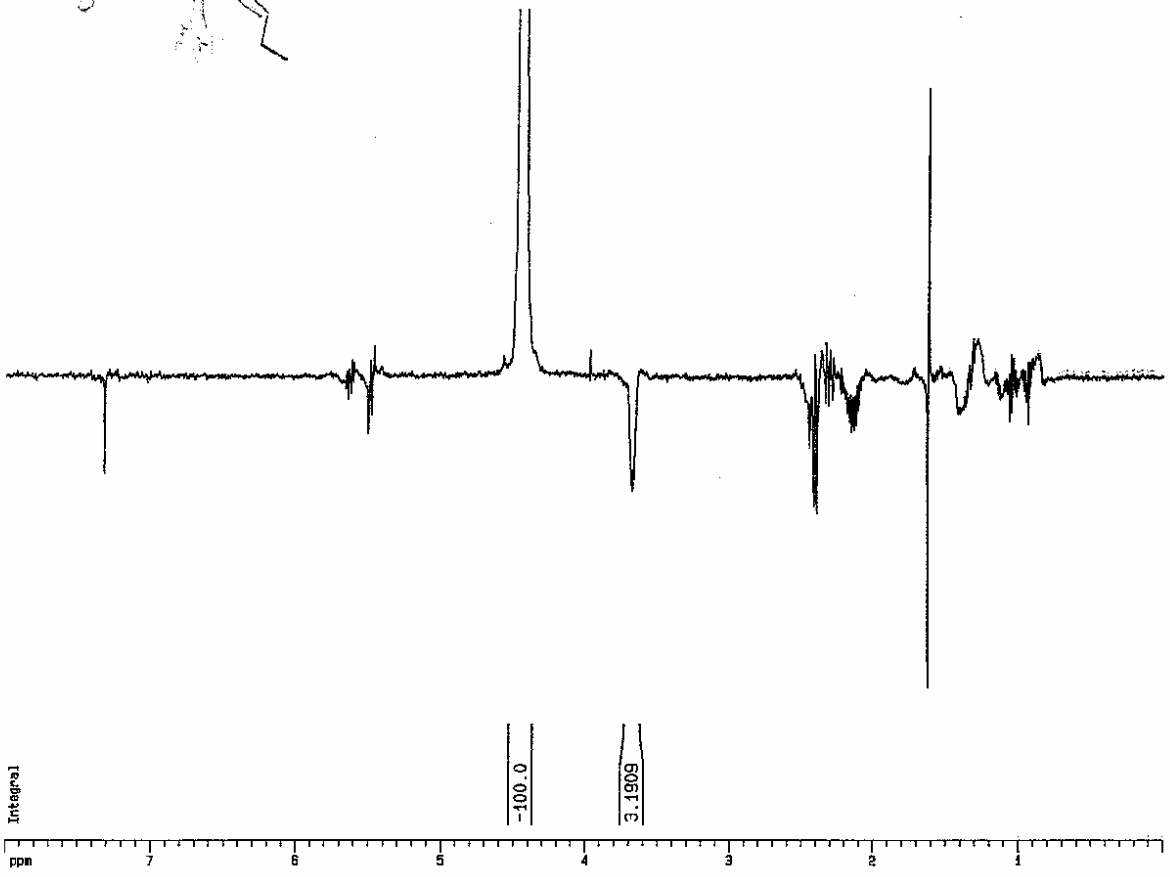
Current Data Parameters
NAME jrsII050103
EXPNO 12
PROCNO 2

F2 - Acquisition Parameters
Date_ 500000
Time 13.25
INSTRUM spect
PROBHD 5 mm TXI 13C
PULPROG noesygpl
TD 16384
SOLVENT CDCl3
NS 136
DS 0
SWH 7507.507 Hz
FIDRES 0.458222 Hz
AQ 1.0912244 sec
RG 20.2
DW 66.600 usec
DE 6.00 usec
TE 290.0 K
d11 0.0300000 sec
d12 0.0000200 sec
PL14 65.00 dB
D1 4.00000000 sec
FQ2LIST noedif.2
L4 1
D20 0.60000002 sec
SFO2 500.1300000 MHz
NUC2 1H
PL2 120.00 dB
P1 10.00 usec
DE 6.00 usec
SFO1 500.1330008 MHz
NUC1 1H
PL1 0.00 dB

F2 - Processing parameters
SI 8192
SF 500.1300000 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 0.10

1D NMR plot parameters
CX 20.00 cm
F1P 8.000 ppm
F1 4001.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 200.05200 Hz/cm

John Sieders 05-01-03 11 2 500 MHz CDCl3 irr. 2219.06 Hz
2,6 pyranone

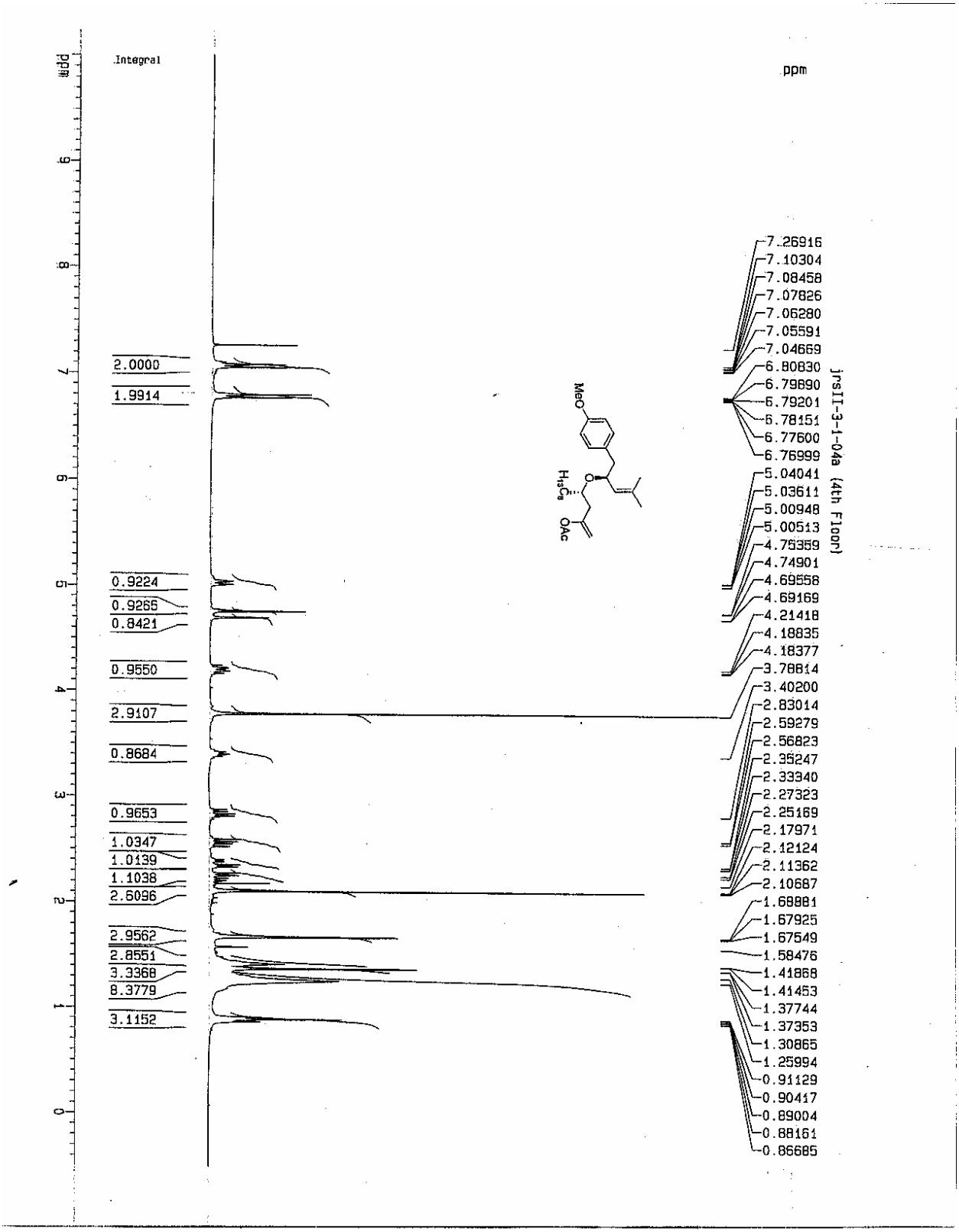


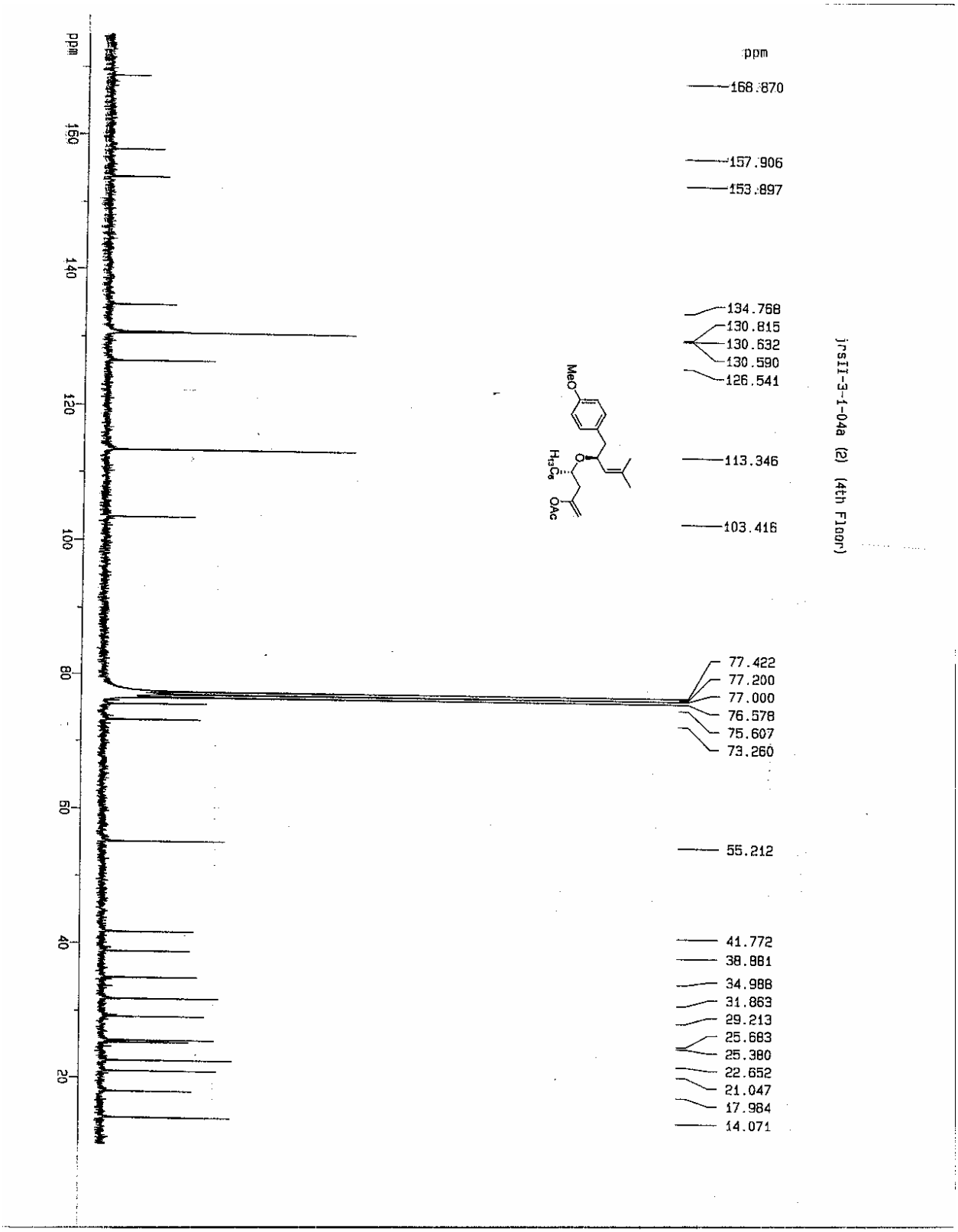
Current Data Parameters
NAME jrsII050103
EXPNO 11
PROCNO 2

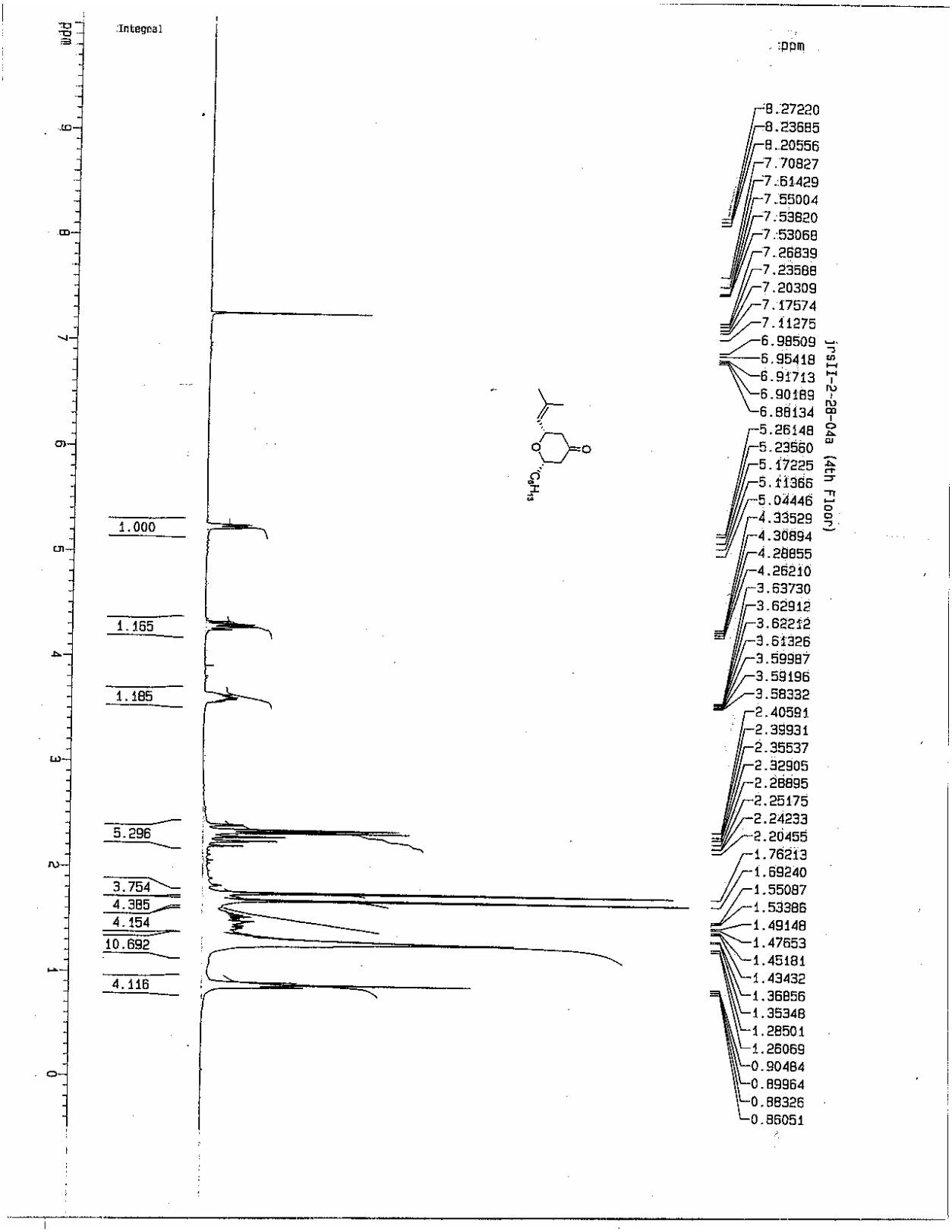
F2 - Acquisition Parameters
Date_ 500000
Time 13.24
INSTRUM spect
PROBHD 5 mm TXI 13C
PULPROG noemu1
TD 16384
SOLVENT CDCl3
NS 136
DS 0
SWH 7507.507 Hz
FIDRES 0.458222 Hz
AQ 1.0912244 sec
RG 20.2
DW 66.600 usec
DE 6.00 usec
TE 290.0 K
d11 0.0300000 sec
d12 0.0000200 sec
PL14 65.00 dB
D1 4.00000000 sec
FG2LIST noedif.1
L4 1
D20 0.60000002 sec
SF02 500.1300000 MHz
NUC2 1H
PL2 120.00 dB
P1 10.00 usec
DE 6.00 usec
SF01 500.1330008 MHz
NUC1 1H
PL1 0.00 dB

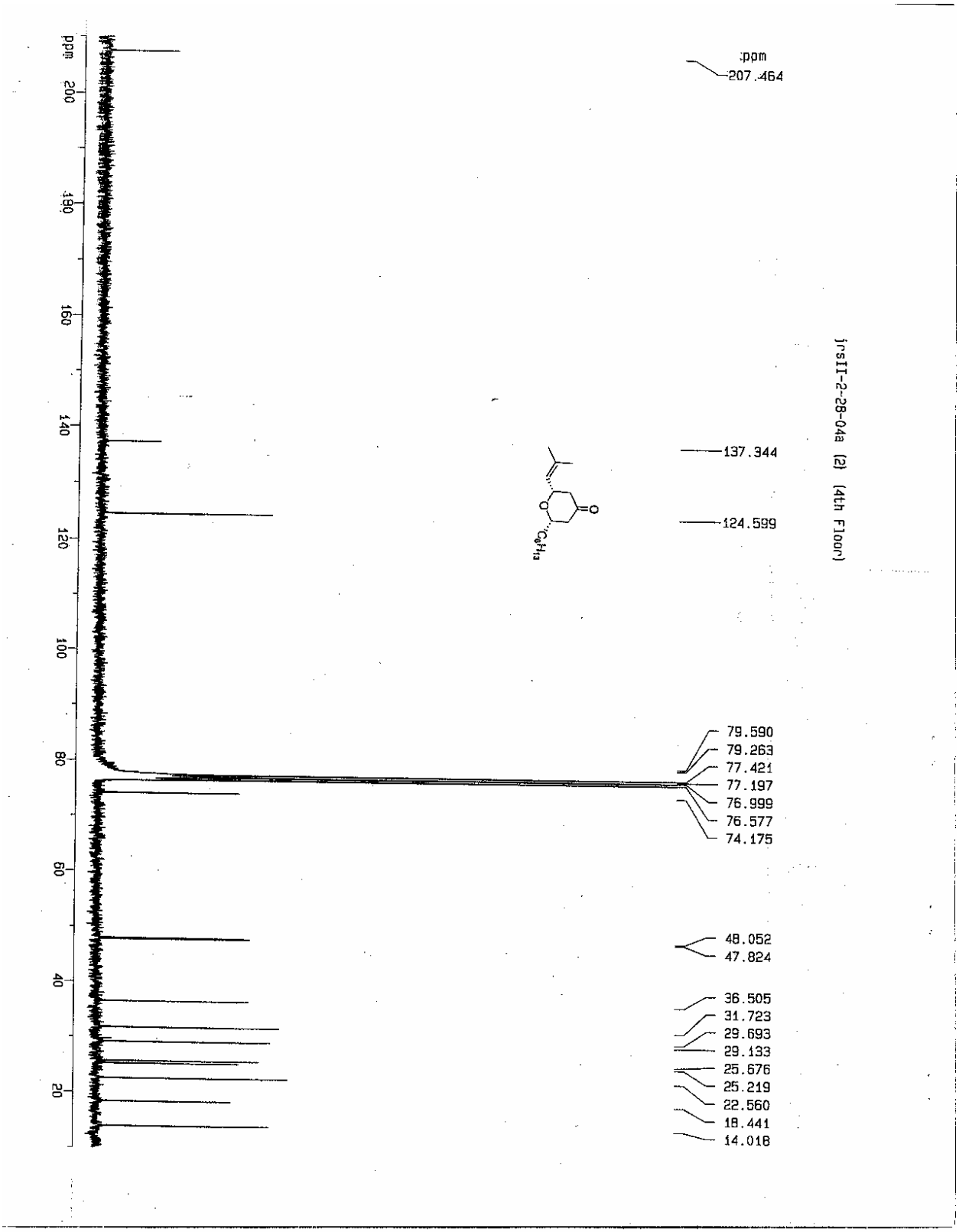
F2 - Processing parameters
SI 8192
SF 500.1300000 MHz
WDW EM
SSB 0
LB 1.00 Hz
GB 0
PC 0.10

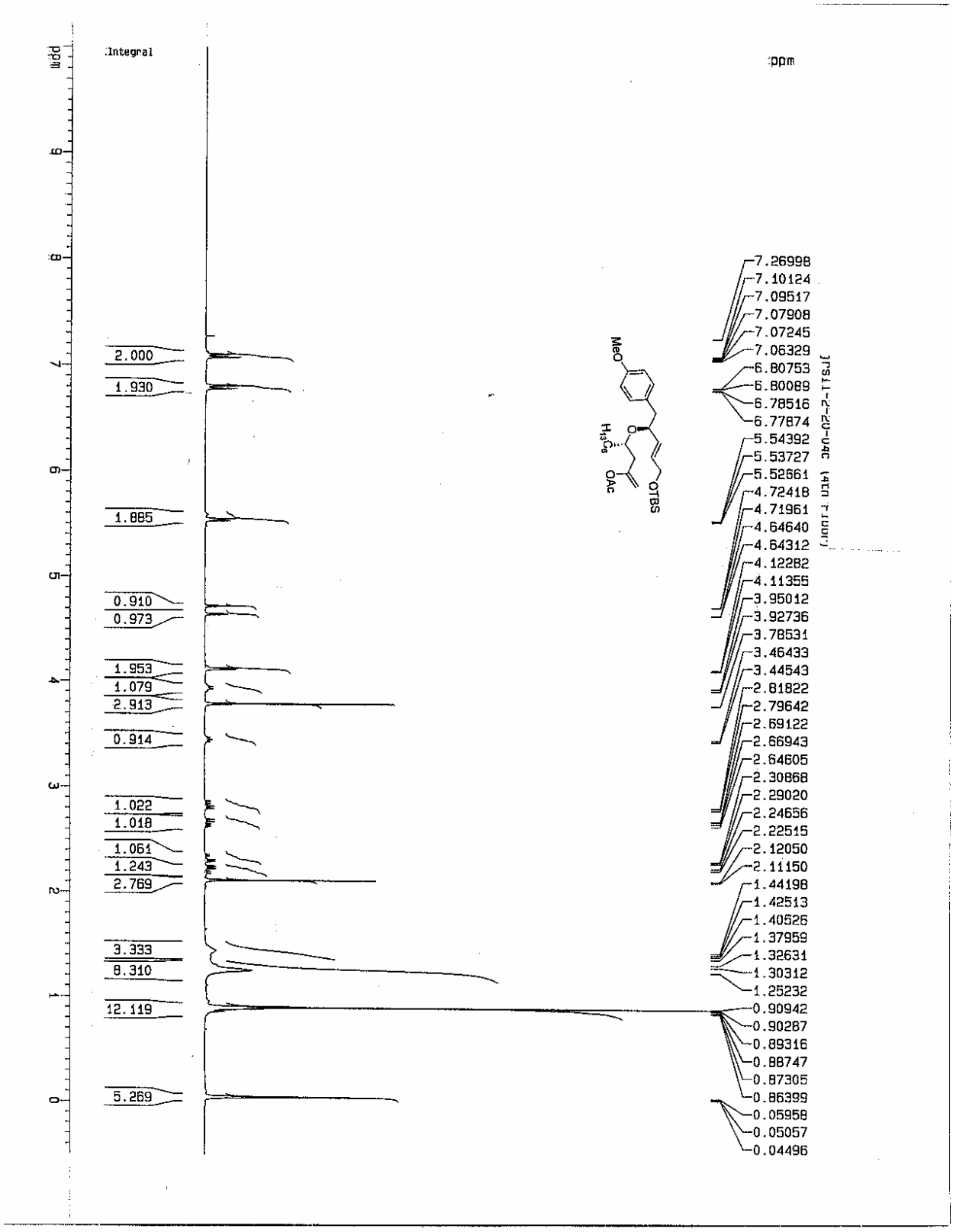
1D NMR plot parameters
CX 20.00 cm
F1P 8.000 ppm
F1 4001.04 Hz
F2P 0.000 ppm
F2 0.00 Hz
PPMCM 0.40000 ppm/cm
HZCM 200.05200 Hz/cm

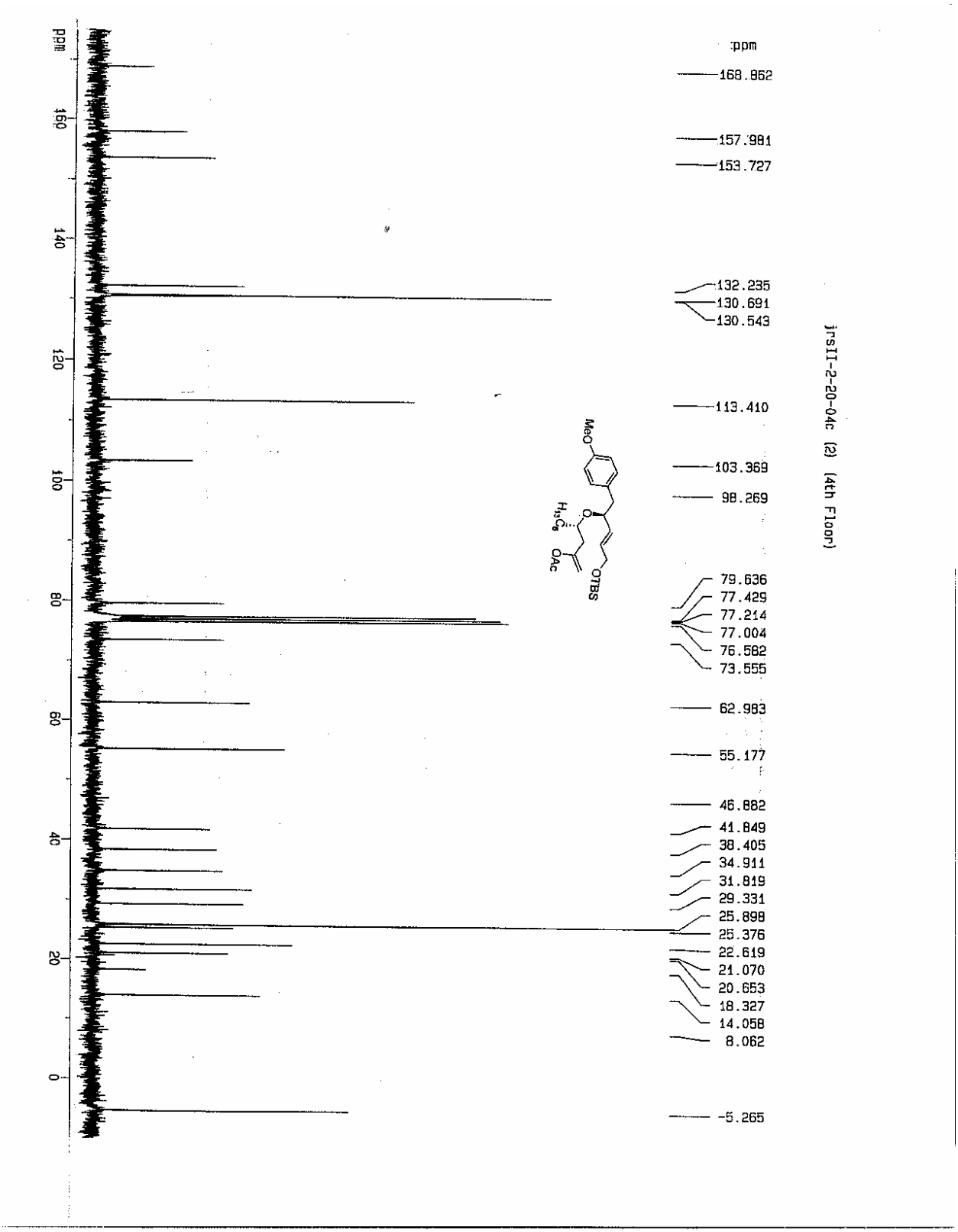

Integral
ppm
2.0000
1.9914
0.9224
0.9265
0.8421
0.9550
2.9107
0.8684
0.9653
1.0347
1.0139
1.1038
2.6096
2.9562
2.8551
3.3368
8.3779
3.1152
MeO
OAc
7.26916
7.10304
7.08458
7.07826
7.06280
7.05591
7.04669
6.80830
6.79890
6.79201
6.78151
6.77600
6.76999
5.04041
5.03611
5.00948
5.00513
4.75359
4.74901
4.69558
4.69169
4.21418
4.18835
4.18377
3.78814
3.40200
2.83014
2.59279
2.56823
2.35247
2.33340
2.27323
2.25169
2.17971
2.12124
2.11362
2.10687
1.68881
1.67925
1.67549
1.58476
1.41868
1.41453
1.37744
1.37353
1.30865
1.25994
0.91129
0.90417
0.89004
0.88161
0.86685
jrsII-3-1-04a (4th Floor)

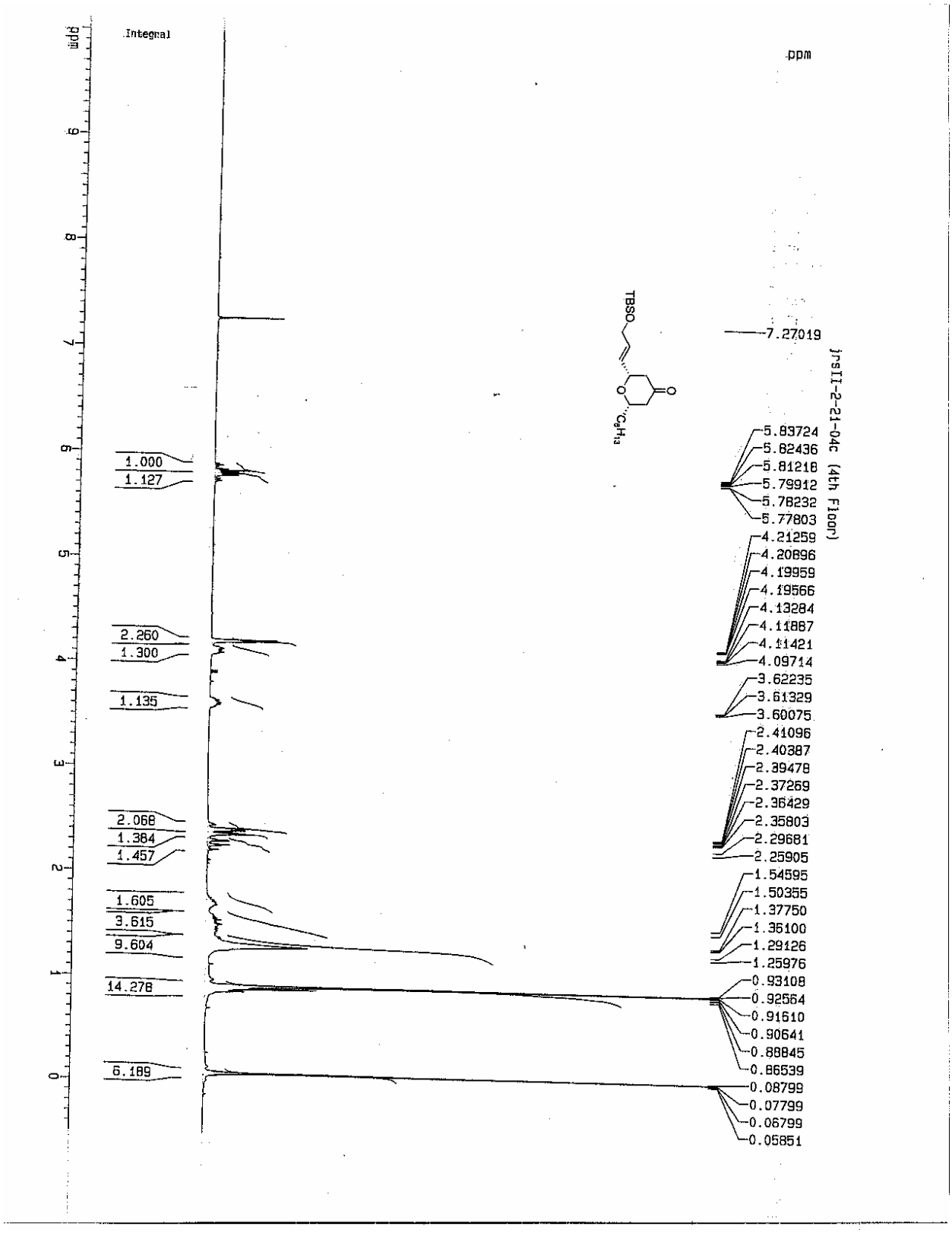

ppm
168.870
157.906
153.897
134.768
130.815
130.632
130.590
126.541
113.346
103.416
77.422
77.200
77.000
76.578
75.607
73.260
55.212
41.772
38.881
34.988
31.863
29.213
25.683
25.380
22.652
21.047
17.984
14.071
MeO
OAc
jrsii-3-1-04a (2) (4th Floor)

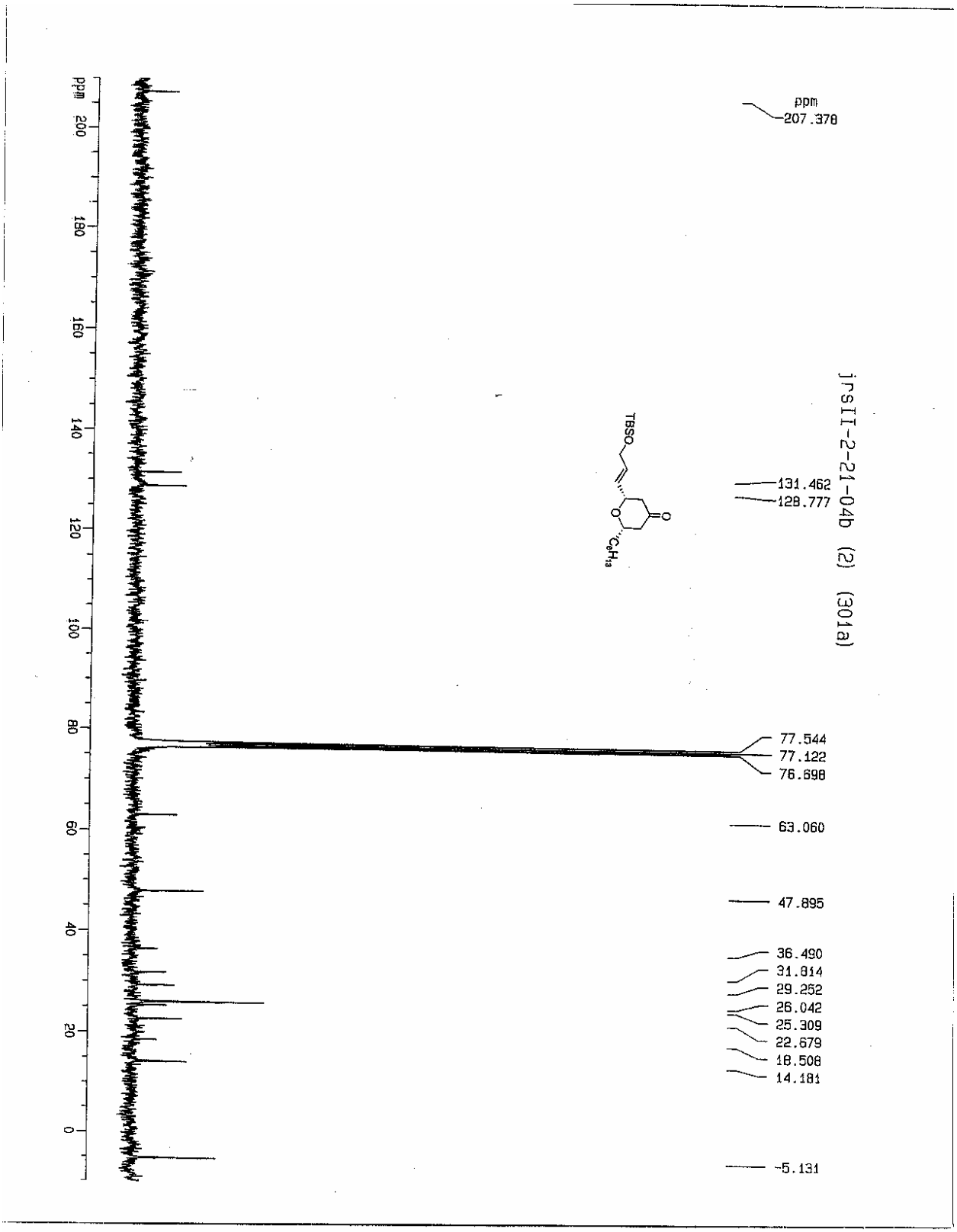

Integral
ppm
8.27220
8.23685
8.20556
7.70827
7.61429
7.55004
7.53820
7.53068
7.26839
7.23588
7.20309
7.17574
7.11275
6.98509
6.95418
6.91713
6.90189
6.88134
5.26148
5.23560
5.17225
5.11366
5.04446
4.33529
4.30894
4.28855
4.26210
3.63730
3.62912
3.62212
3.61326
3.59987
3.59196
3.58332
2.40591
2.39931
2.35537
2.32905
2.28895
2.25175
2.24233
2.20455
1.76213
1.69240
1.55087
1.53386
1.49148
1.47653
1.45181
1.43432
1.36856
1.35348
1.28501
1.26069
0.90484
0.89964
0.88326
0.86051
jrsI-2-28-04a (4th Floor)
1.000
1.165
1.185
5.296
3.754
4.385
4.154
10.692
4.116

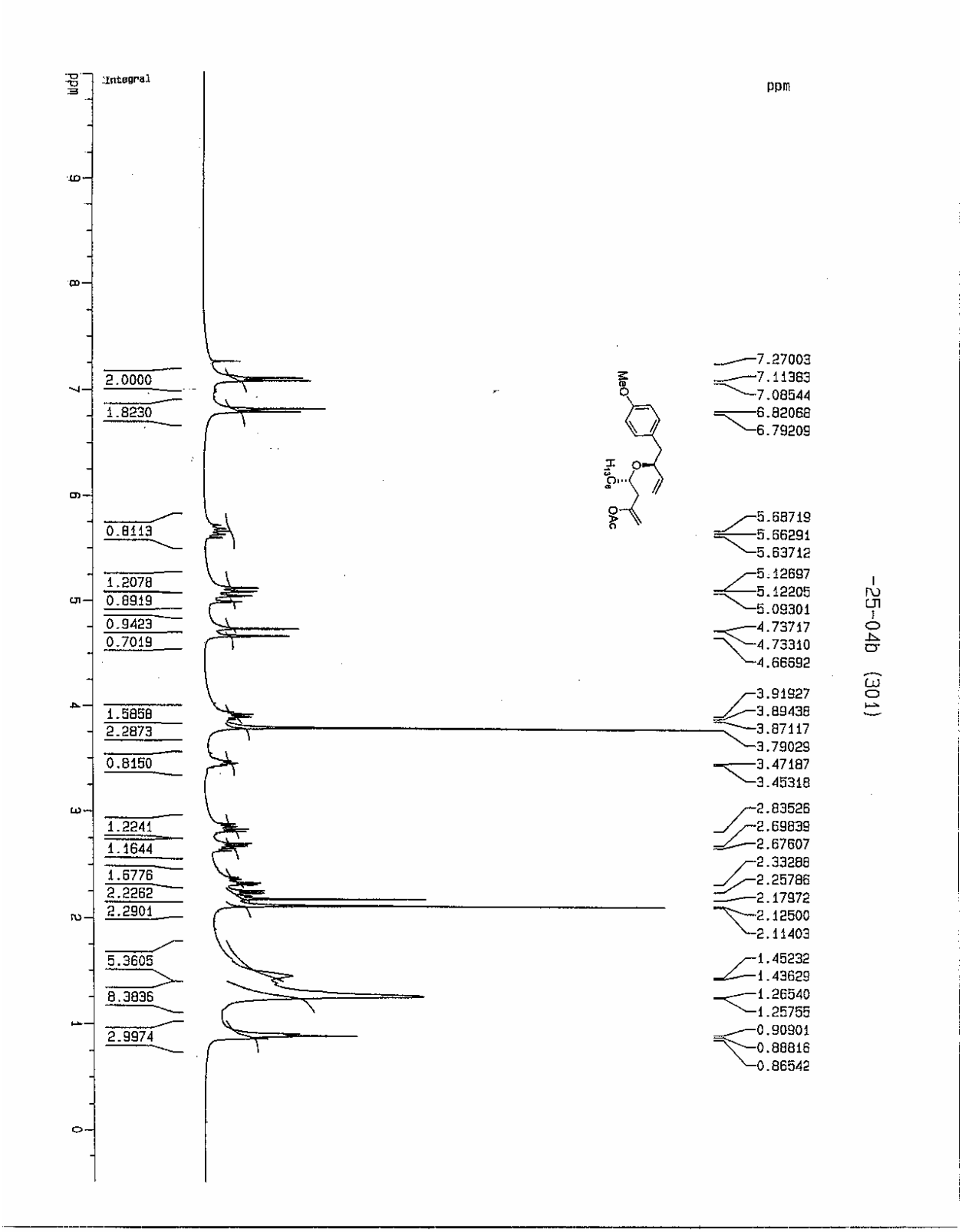

ppm
207.464
137.344
124.599
79.590
79.263
77.421
77.197
76.999
76.577
74.175
48.052
47.824
36.505
31.723
29.693
29.133
25.676
25.219
22.560
18.441
14.018
jrsII-2-28-04a (2) (4th Floor)

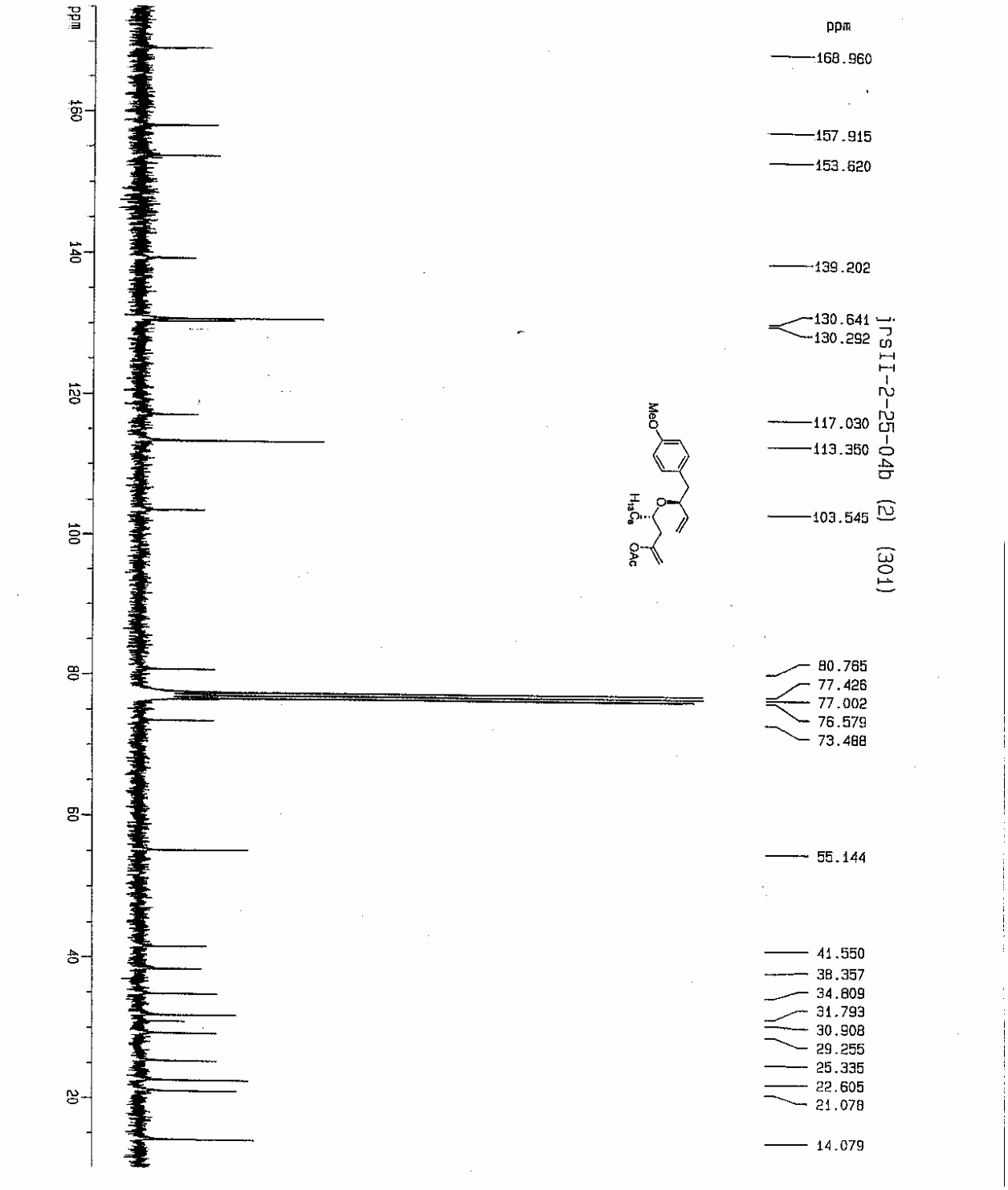

Integral
ppm
2.000
1.930
1.885
0.910
0.973
1.953
1.079
2.913
0.914
1.022
1.018
1.061
1.243
2.769
3.333
8.310
12.119
5.269
MeO
OAc
OTBS
7.26998
7.10124
7.09517
7.07908
7.07245
7.06329
6.80753
6.80089
6.78516
6.77874
5.54392
5.53727
5.52661
4.72418
4.71961
4.64640
4.64312
4.12282
4.11355
3.95012
3.92736
3.78531
3.46433
3.44543
2.81822
2.79642
2.69122
2.66943
2.64605
2.30868
2.29020
2.24656
2.22515
2.12050
2.11150
1.44198
1.42513
1.40525
1.37959
1.32631
1.30312
1.25232
0.90942
0.90287
0.89316
0.88747
0.87305
0.86399
0.05958
0.05057
0.04496

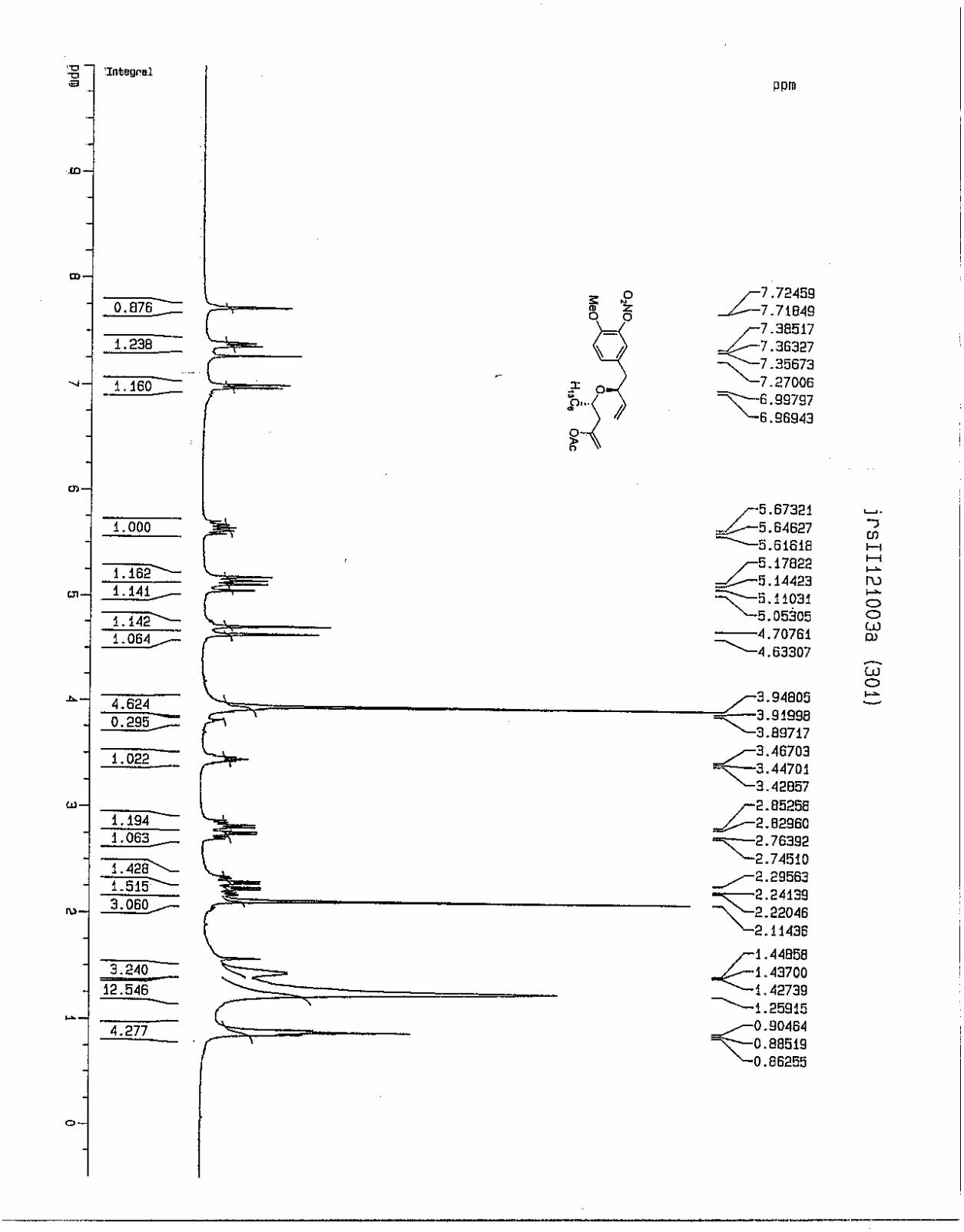

ppm
168.862
157.981
153.727
132.235
130.691
130.543
113.410
103.369
98.269
79.636
77.429
77.214
77.004
76.582
73.555
62.983
55.177
46.882
41.849
38.405
34.911
31.819
29.331
25.898
25.376
22.619
21.070
20.653
18.327
14.058
8.062
-5.265
MeO
OAc
OTBS
jrsII-2-20-04c (2) (4th Floor)

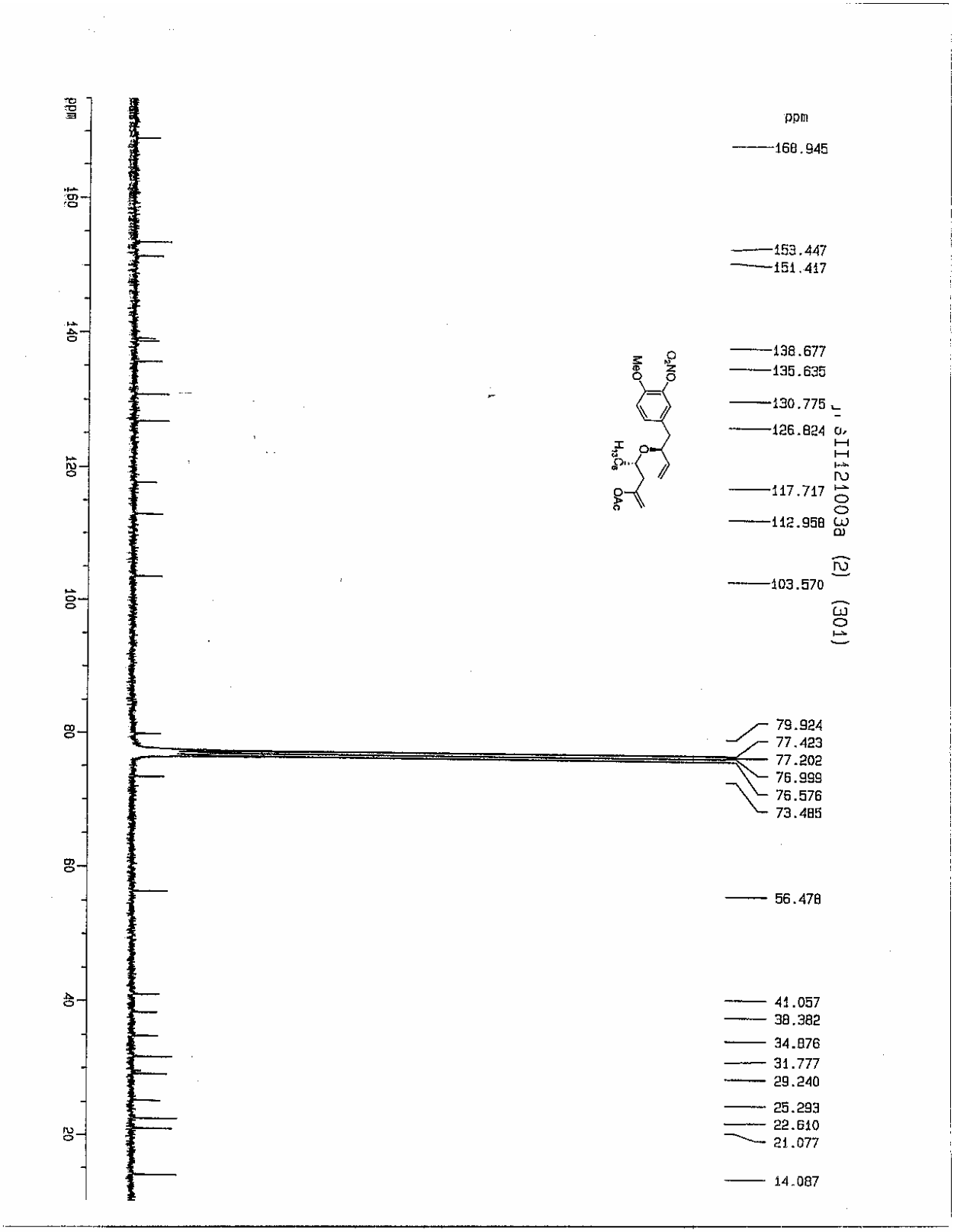

Integral
ppm
jrsII-2-21-04c (4th Floor)
TBSO
C_6H_{13}
1.000
1.127
2.260
1.300
1.135
2.068
1.384
1.457
1.605
3.615
9.604
14.278
6.189
7.27019
5.83724
5.82436
5.81218
5.79912
5.78232
5.77803
4.21259
4.20896
4.19959
4.19566
4.13284
4.11887
4.11421
4.09714
3.62235
3.61329
3.60075
2.41096
2.40387
2.39478
2.37269
2.36429
2.35803
2.29681
2.25905
1.54595
1.50355
1.37750
1.36100
1.29126
1.25976
0.93108
0.92564
0.91610
0.90641
0.88845
0.86539
0.08799
0.07799
0.06799
0.05851

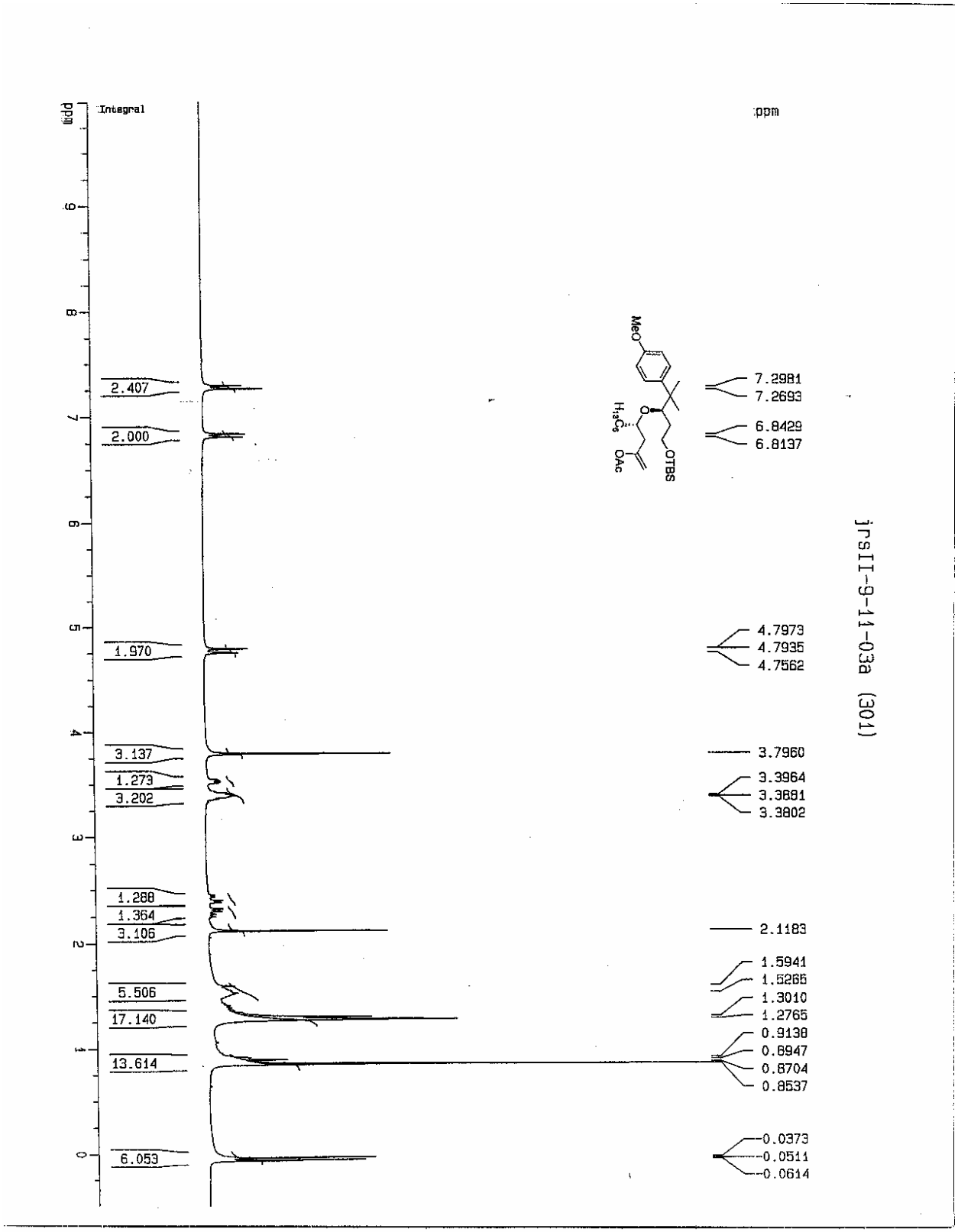

jrsII-2-21-04b (2) (301a)
ppm
207.378
131.462
128.777
77.544
77.122
76.698
63.060
47.895
36.490
31.814
29.252
26.042
25.309
22.679
18.508
14.181
-5.131
TBSO
C_6H_{13}
ppm
200
180
160
140
120
100
80
60
40
20
0

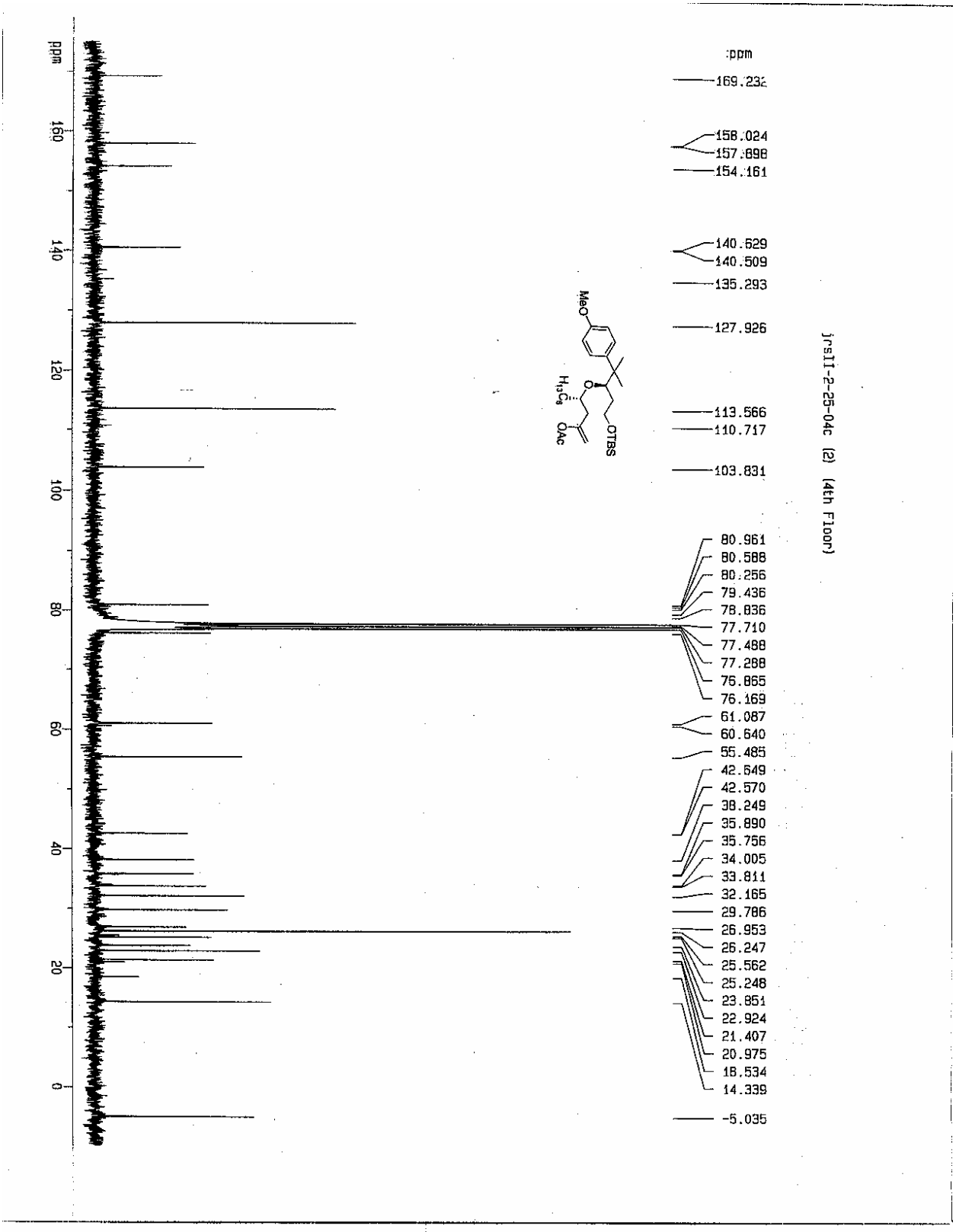

Integral
ppm
2.0000
1.8230
0.8113
1.2078
0.8919
0.9423
0.7019
1.5858
2.2873
0.8150
1.2241
1.1644
1.6776
2.2262
2.2901
5.3605
8.3836
2.9974
7.27003
7.11383
7.08544
6.82068
6.79209
5.68719
5.66291
5.63712
5.12697
5.12205
5.09301
4.73717
4.73310
4.66692
3.91927
3.89438
3.87117
3.79029
3.47187
3.45318
2.83526
2.69839
2.67607
2.33288
2.25786
2.17972
2.12500
2.11403
1.45232
1.43629
1.26540
1.25755
0.90901
0.88816
0.86542
MeO
OAc
-25-04b (301)

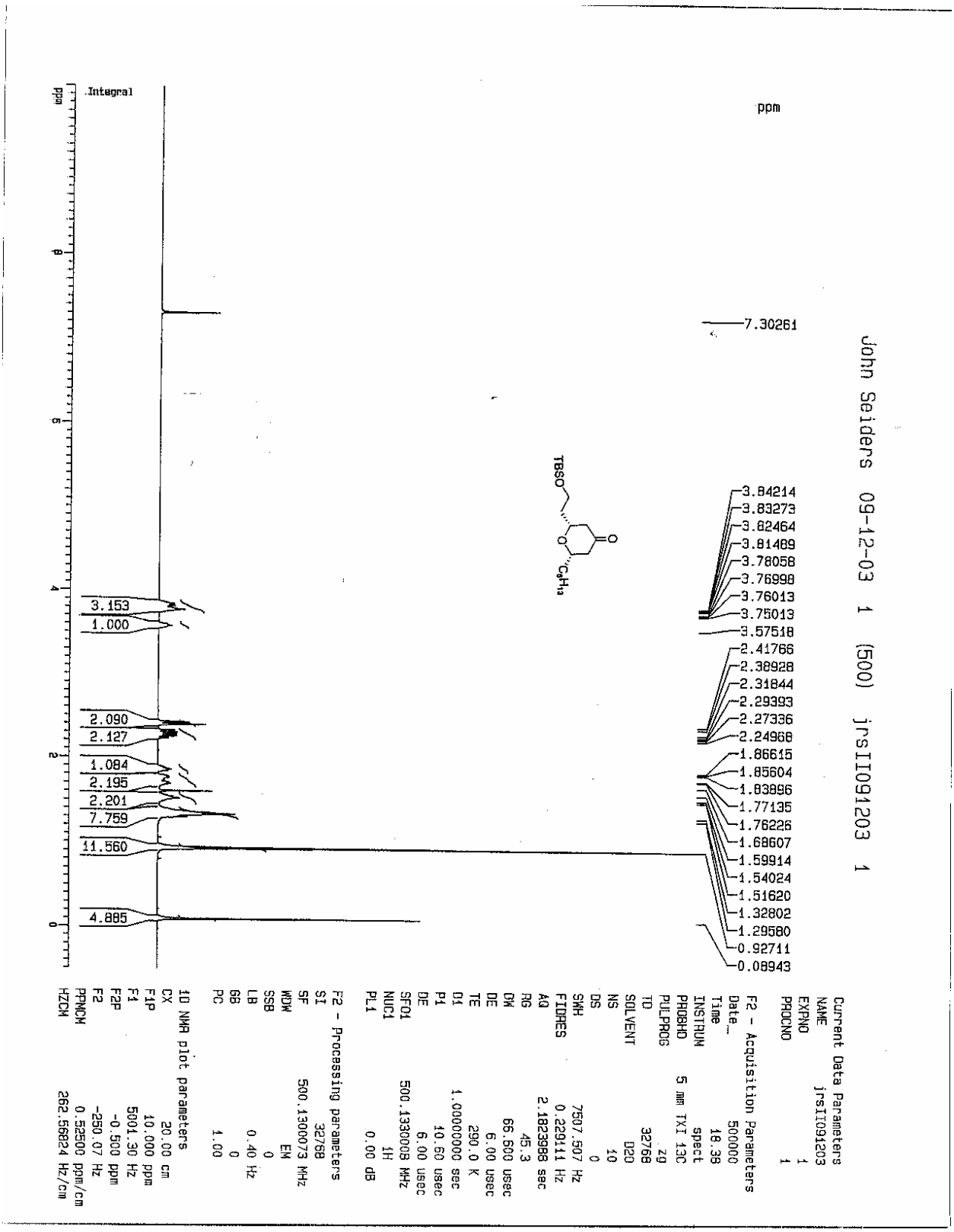

ppm
168.960
157.915
153.620
139.202
130.641
130.292
117.030
113.350
103.545
80.765
77.426
77.002
76.579
73.488
55.144
41.550
38.357
34.809
31.793
30.908
29.255
25.335
22.605
21.078
14.079
jrsII-2-25-04b (2) (301)
MeO
OAc
160
140
120
100
80
60
40
20

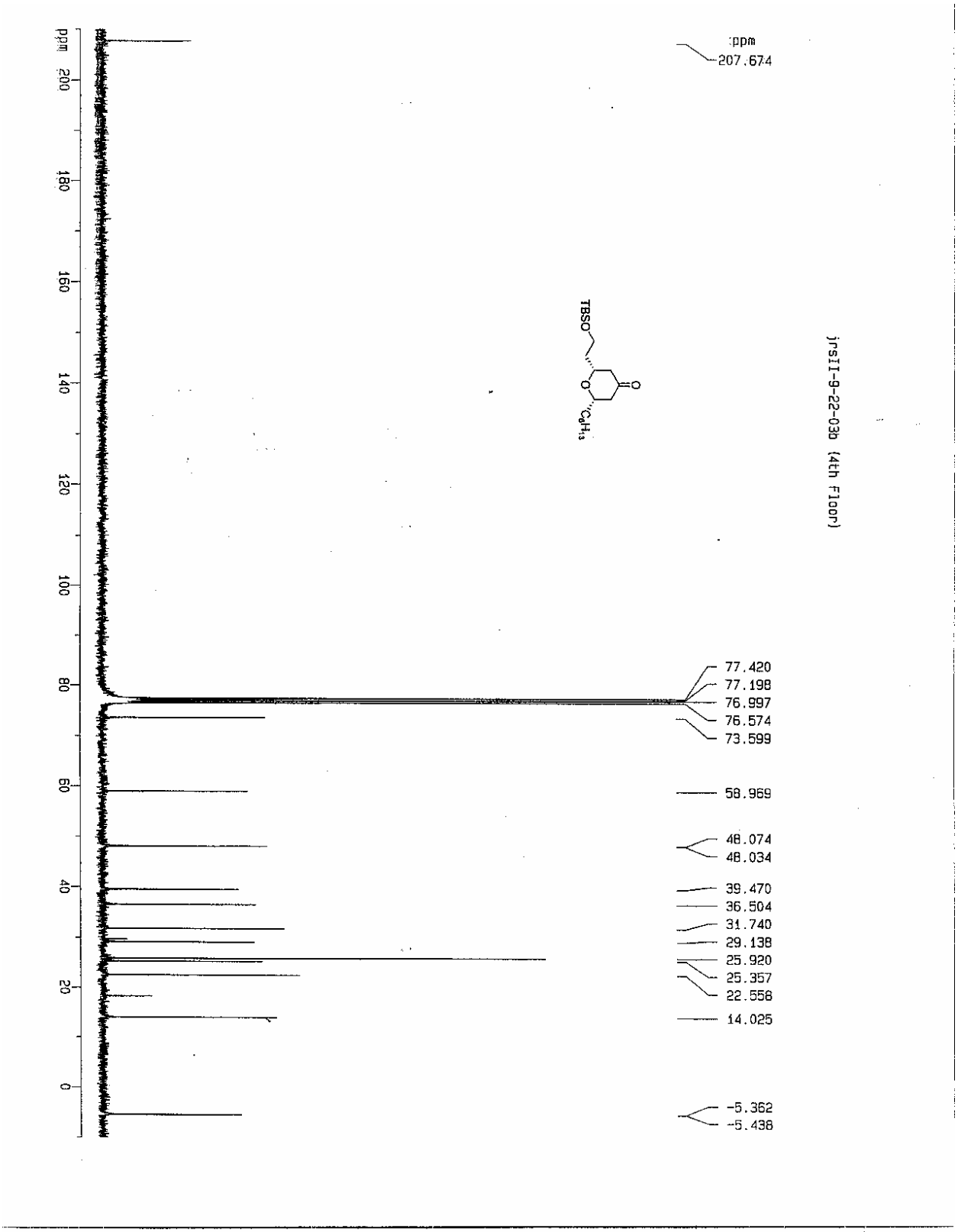

Integral
ppm
0.876
1.238
1.160
1.000
1.162
1.141
1.142
1.064
4.624
0.295
1.022
1.194
1.063
1.428
1.515
3.060
3.240
12.546
4.277
MeO
O2NO
H3Cq
OAc
7.72459
7.71849
7.38517
7.36327
7.35673
7.27006
6.99797
6.96943
5.67321
5.64627
5.61618
5.17822
5.14423
5.11031
5.05305
4.70761
4.63307
3.94805
3.91998
3.89717
3.46703
3.44701
3.42857
2.85258
2.82960
2.76392
2.74510
2.29563
2.24139
2.22046
2.11436
1.44858
1.43700
1.42739
1.25915
0.90464
0.88519
0.86255
jrsII121003a (301)

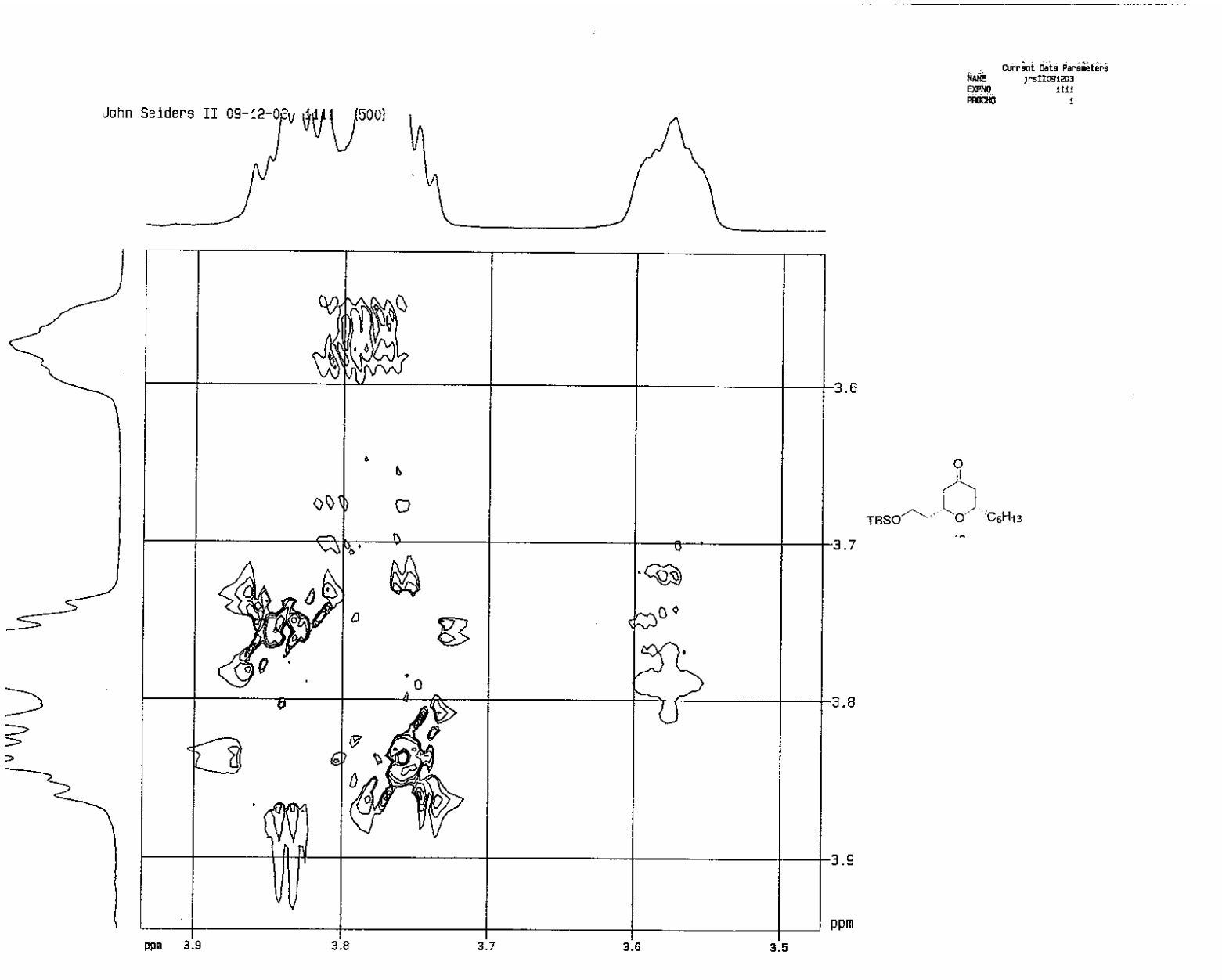

ppm
168.945
153.447
151.417
138.677
135.635
130.775
126.824
117.717
112.958
103.570
79.924
77.423
77.202
76.999
76.576
73.485
56.478
41.057
38.382
34.876
31.777
29.240
25.293
22.610
21.077
14.087
MeO
O2NO
H3Cs
OAc
JI_SII121003a (2) (301)
ppm
160
140
120
100
80
60
40
20

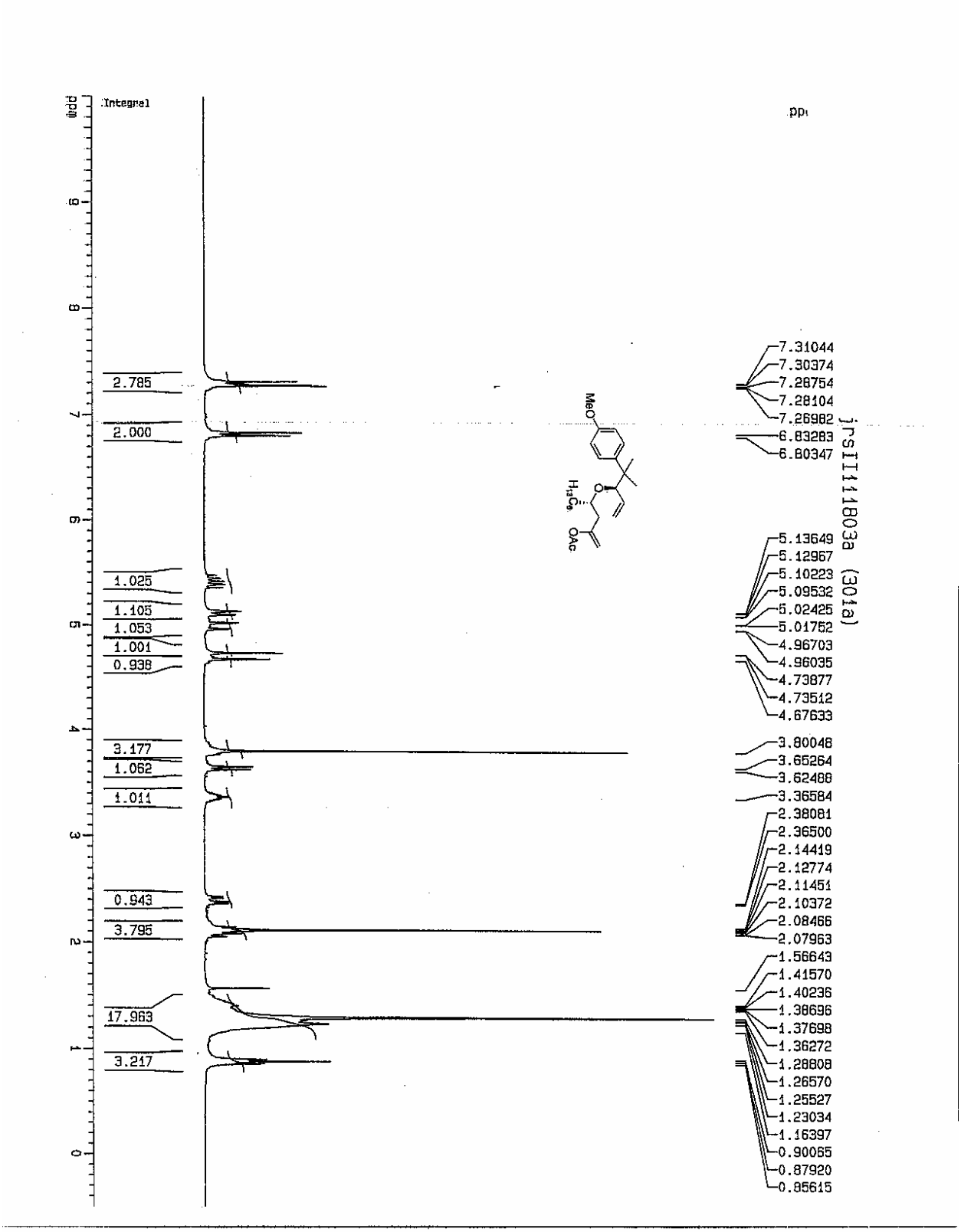

Integral
ppm
2.407
2.000
1.970
3.137
1.273
3.202
1.288
1.364
3.106
5.506
17.140
13.614
6.053
MeO
OAc
OTBS
7.2981
7.2693
6.8429
6.8137
4.7973
4.7935
4.7562
3.7960
3.3964
3.3881
3.3802
2.1183
1.5941
1.5265
1.3010
1.2765
0.9138
0.8947
0.8704
0.8537
-0.0373
-0.0511
-0.0614
jrsII-9-11-03a (301)

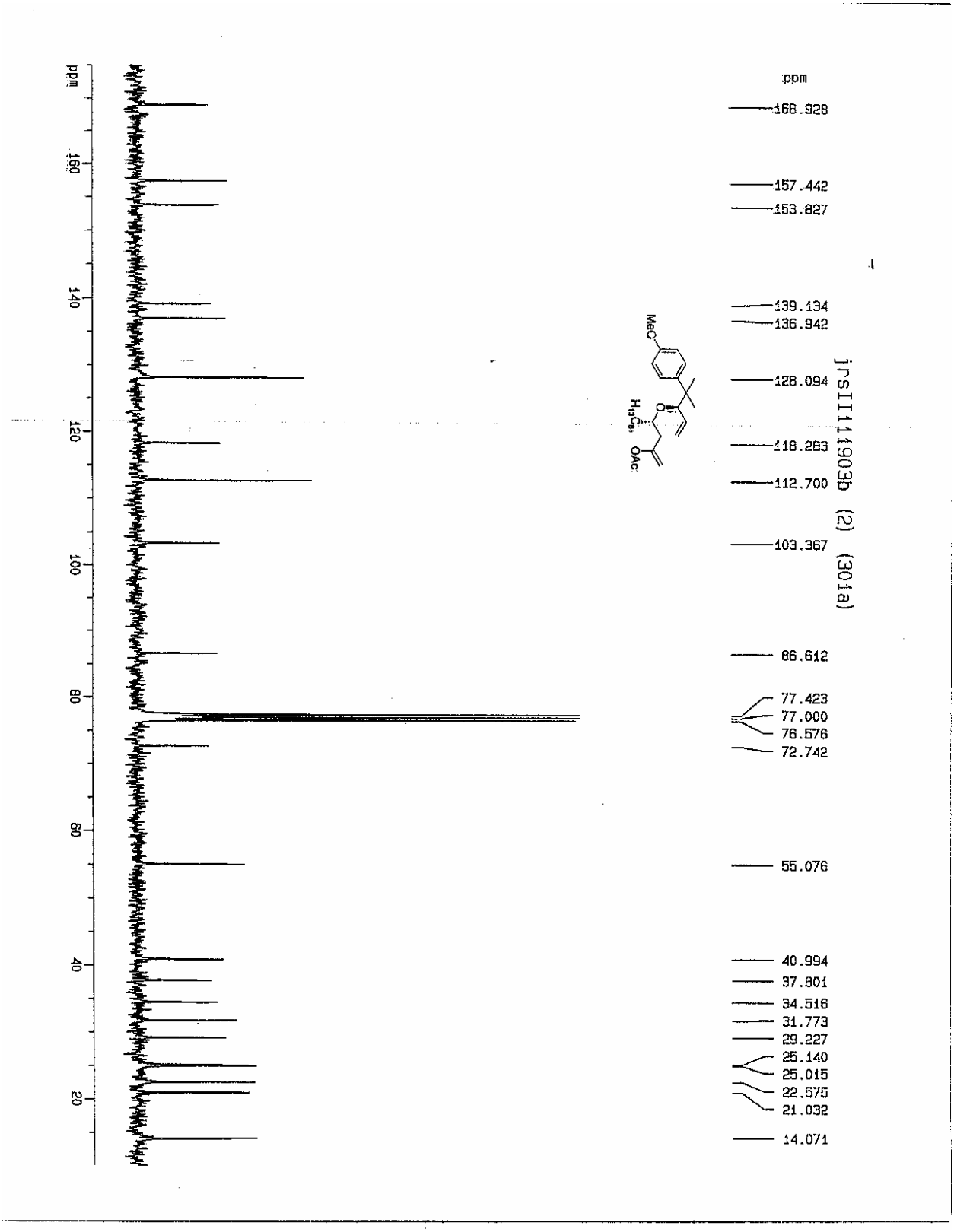

ppm
160
140
120
100
80
60
40
20
0
:ppm
169.232
158.024
157.898
154.161
140.629
140.509
135.293
127.926
113.566
110.717
103.831
80.961
80.588
80.256
79.436
78.836
77.710
77.488
77.288
76.865
76.169
61.087
60.640
55.485
42.649
42.570
38.249
35.890
35.756
34.005
33.811
32.165
29.786
26.953
26.247
25.562
25.248
23.851
22.924
21.407
20.975
18.534
14.339
-5.035
MeO
OAc
OTBS
jrsII-2-25-04c (2) (4th Floor)

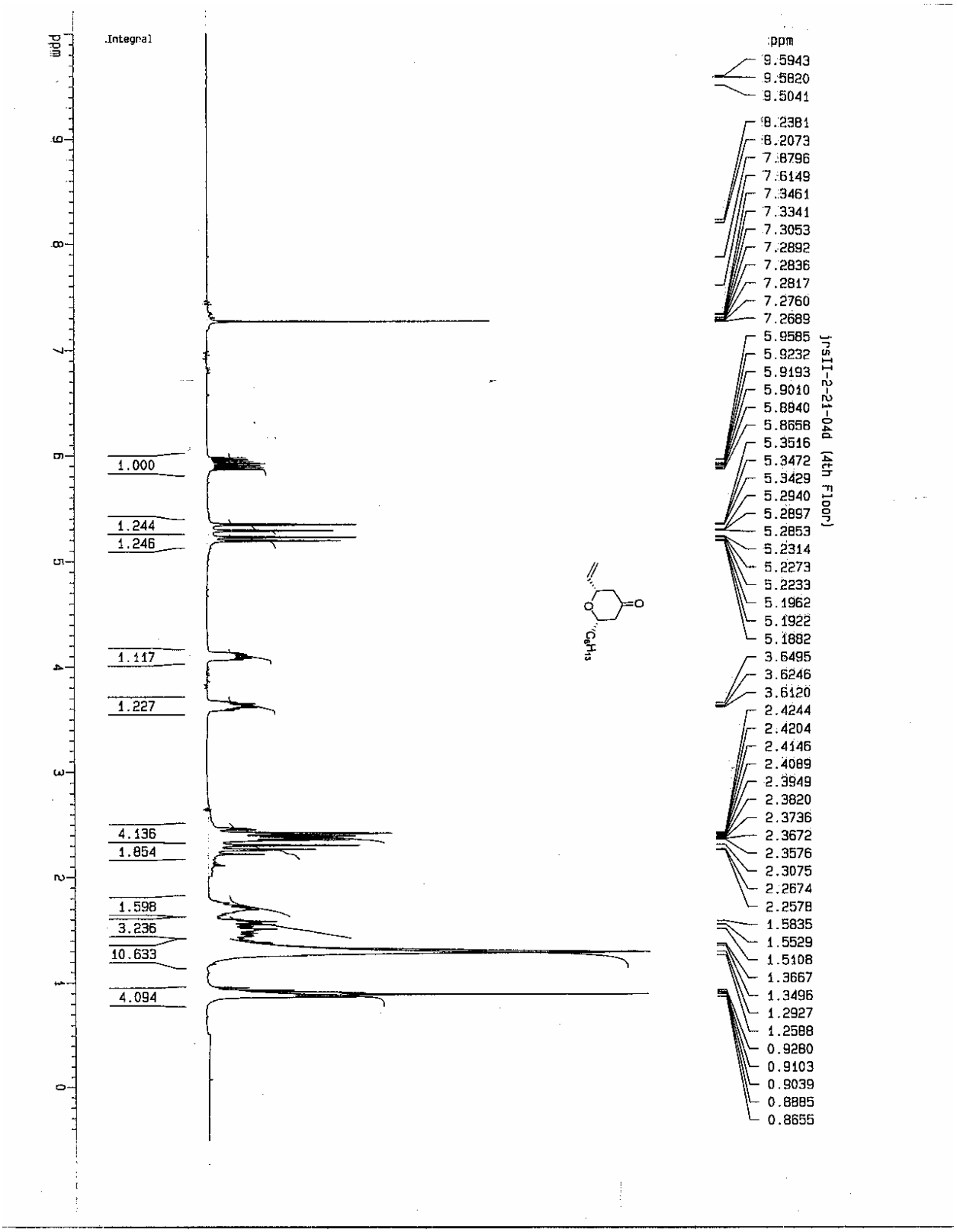

John Seiders 09-12-03 1 (500) jrsII091203 1
ppm
Integral
7.30261
3.84214
3.83273
3.82464
3.81489
3.78058
3.76998
3.76013
3.75013
3.57518
2.41766
2.38928
2.31844
2.29393
2.27336
2.24968
1.86615
1.85604
1.83996
1.77135
1.76226
1.68607
1.59914
1.54024
1.51620
1.32802
1.29580
0.92711
0.08943
3.153
1.000
2.090
2.127
1.084
2.195
2.201
7.759
11.560
4.885
TBSO
Current Data Parameters
NAME jrsII091203
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 500000
Time 18.38
INSTRUM spect
PROBHD 5 mm TXI 13C
PULPROG zg
TD 32768
SOLVENT D20
NS 10
DS 0
SWH 7507.507 Hz
FIDRES 0.229111 Hz
AQ 2.1823988 sec
RG 45.3
DW 66.600 usec
DE 6.00 usec
TE 290.0 K
D1 1.00000000 sec
P1 10.60 usec
DE 6.00 usec
SFO1 500.1330008 MHz
NUC1 1H
PL1 0.00 dB
F2 - Processing parameters
SI 32768
SF 500.1300073 MHz
WDW EM
SSB 0
LB 0.40 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 10.000 ppm
F1 5001.30 Hz
F2P -0.500 ppm
F2 -250.07 Hz
PPMCM 0.52500 ppm/cm
HZCM 262.56824 Hz/cm

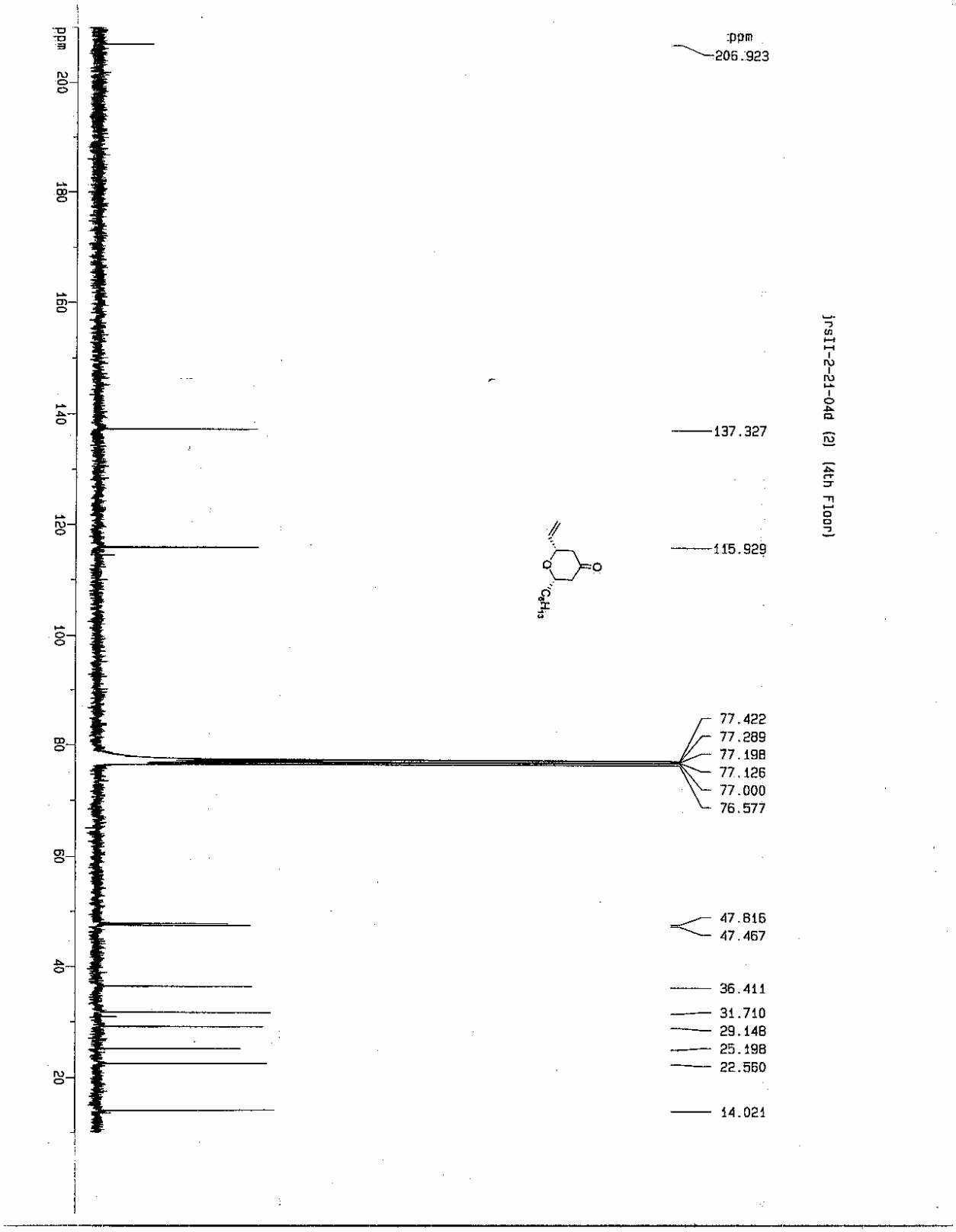

ppm
207.674
77.420
77.198
76.997
76.574
73.599
58.969
48.074
48.034
39.470
36.504
31.740
29.138
25.920
25.357
22.558
14.025
-5.362
-5.438
TBSO
jrsII-9-22-03b (4th Floor)

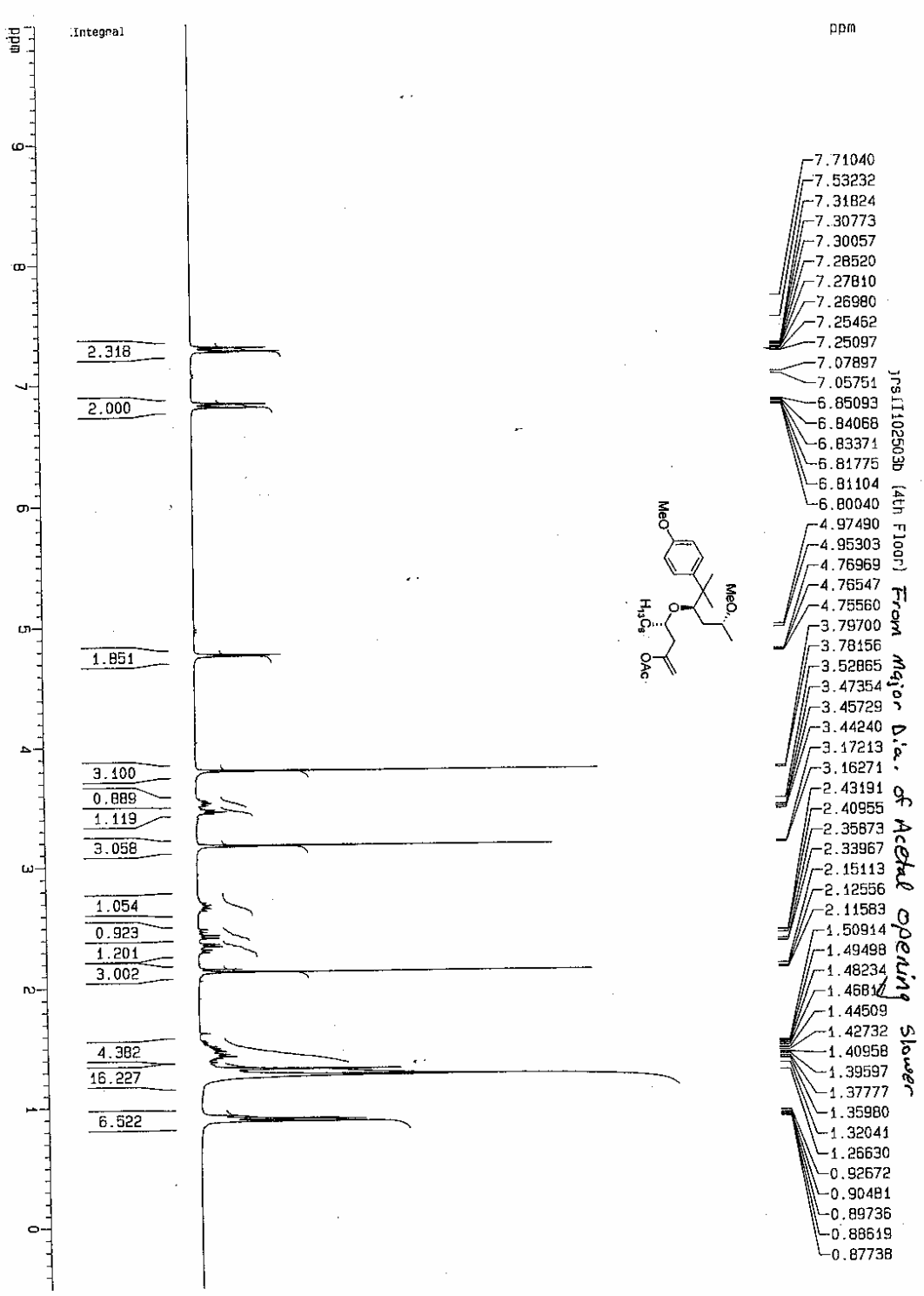

Current Data Parameters
NAME jrsII091203
EXPNO 1111
PROCNO 1
John Seiders II 09-12-03 (1111 (500)
3.6
3.7
3.8
3.9
ppm
ppm 3.9 3.8 3.7 3.6 3.5
TBSO
O
O
C6H13

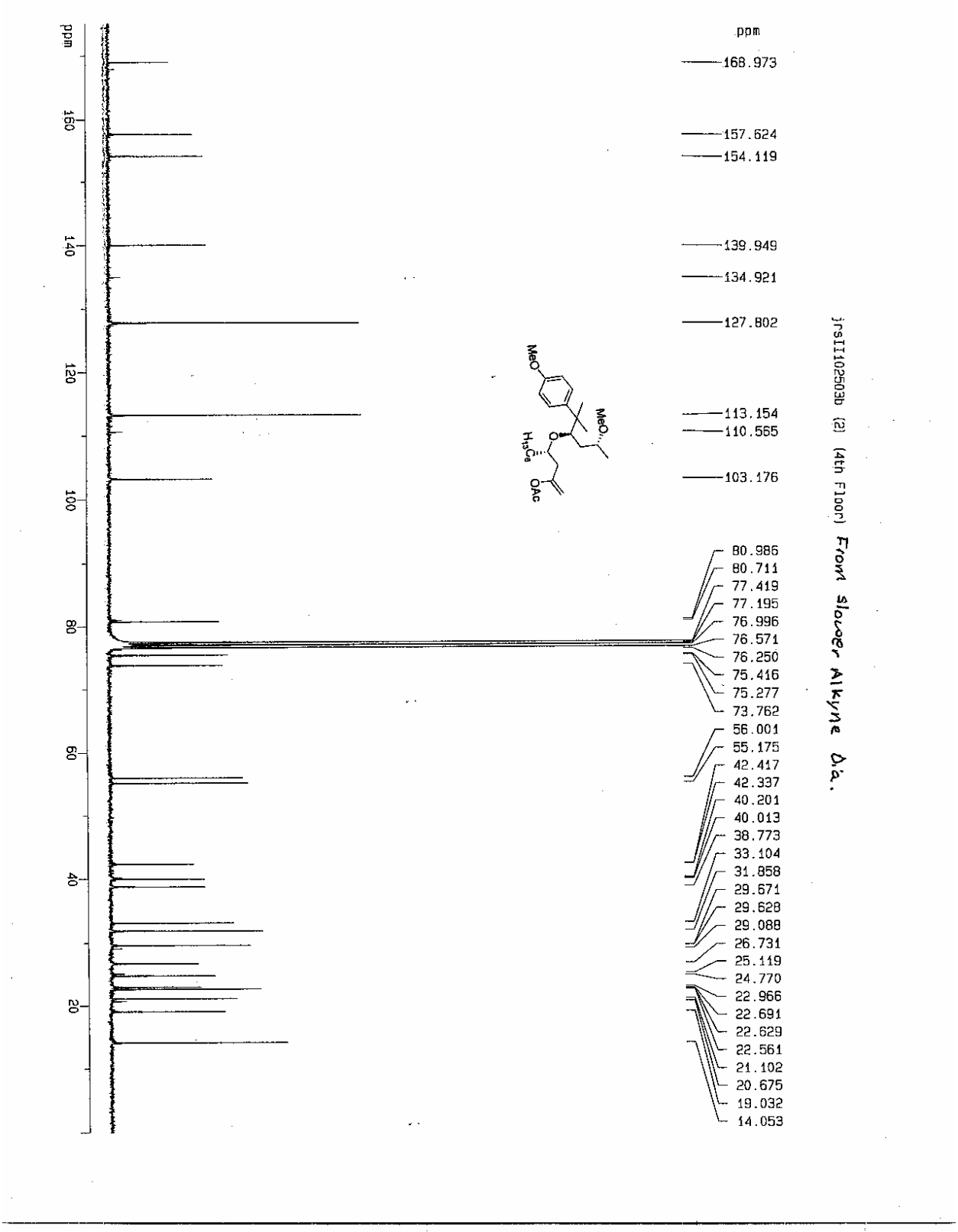

Integral
ppm
2.785
2.000
1.025
1.105
1.053
1.001
0.938
3.177
1.062
1.011
0.943
3.795
17.963
3.217
MeO
OAc
7.31044
7.30374
7.28754
7.28104
7.26982
6.83283
6.80347
5.13649
5.12967
5.10223
5.09532
5.02425
5.01752
4.96703
4.96035
4.73877
4.73512
4.67633
3.80048
3.65264
3.62488
3.36584
2.38081
2.36500
2.14419
2.12774
2.11451
2.10372
2.08466
2.07963
1.56643
1.41570
1.40236
1.38696
1.37698
1.36272
1.28808
1.26570
1.25527
1.23034
1.16397
0.90065
0.87920
0.85615
jrsII111803a (301a)

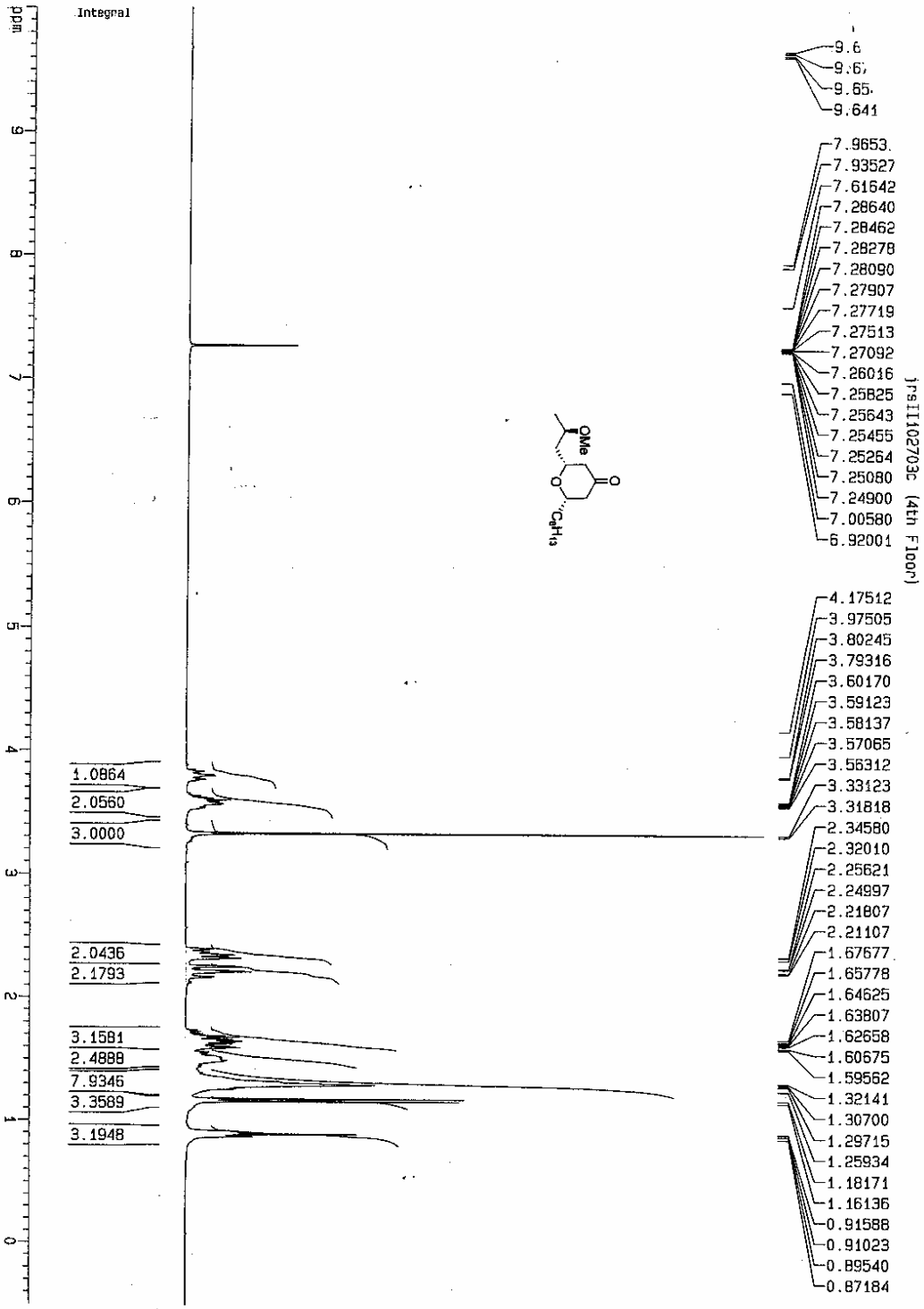

ppm
160
140
120
100
80
60
40
20
MeO
OAc
ppm
168.928
157.442
153.827
139.134
136.942
128.094
118.283
112.700
103.367
86.612
77.423
77.000
76.576
72.742
55.076
40.994
37.801
34.516
31.773
29.227
25.140
25.015
22.575
21.032
14.071
jrsII111903b (2) (301a)

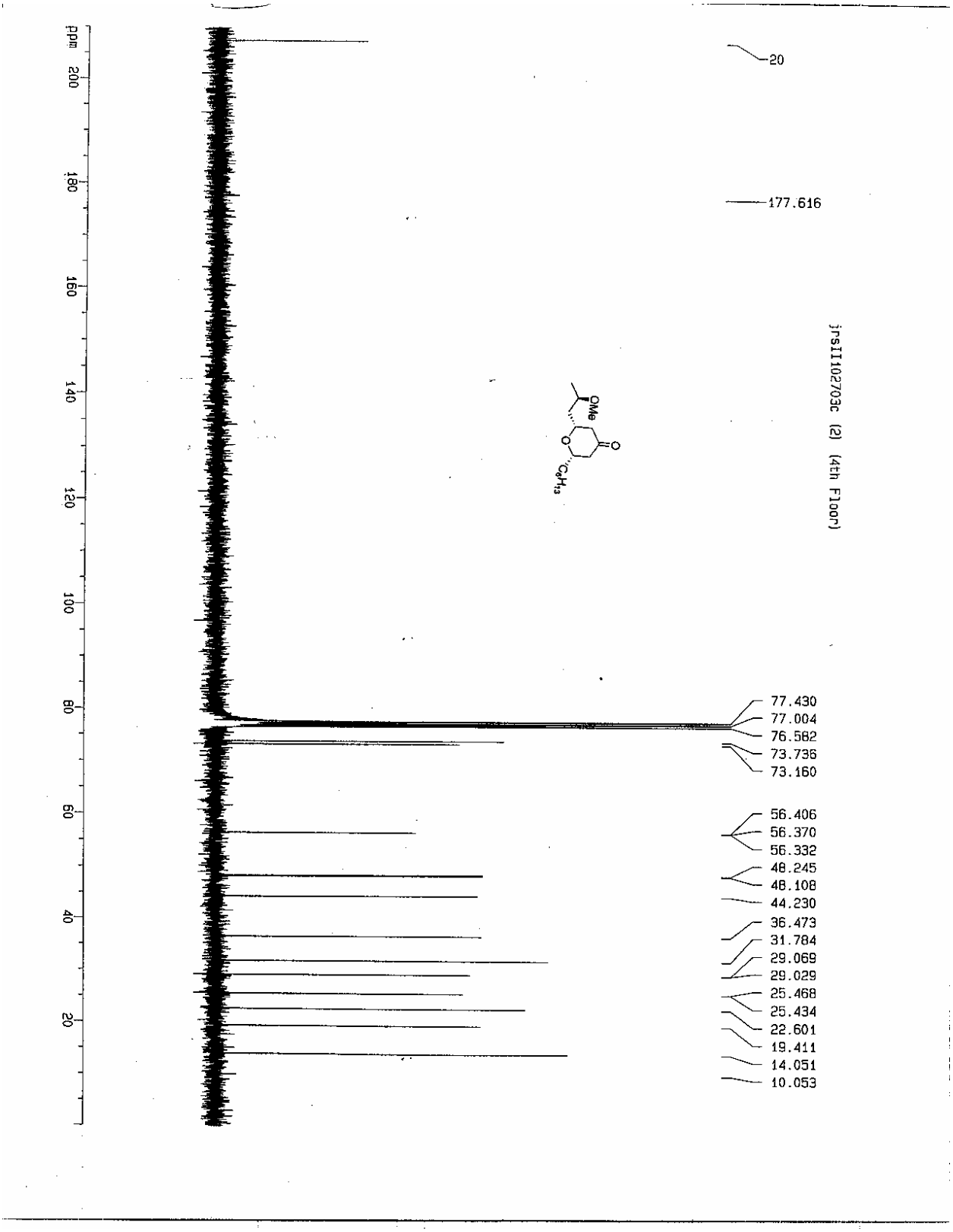

Integral
ppm
1.000
1.244
1.246
1.117
1.227
4.136
1.854
1.598
3.236
10.633
4.094
ppm
9.5943
9.5820
9.5041
8.2381
8.2073
7.8796
7.6149
7.3461
7.3341
7.3053
7.2892
7.2836
7.2817
7.2760
7.2689
5.9585
5.9232
5.9193
5.9010
5.8840
5.8658
5.3516
5.3472
5.3429
5.2940
5.2897
5.2853
5.2314
5.2273
5.2233
5.1962
5.1922
5.1882
3.6495
3.6246
3.6120
2.4244
2.4204
2.4146
2.4089
2.3949
2.3820
2.3736
2.3672
2.3576
2.3075
2.2674
2.2578
1.5835
1.5529
1.5108
1.3667
1.3496
1.2927
1.2588
0.9280
0.9103
0.9039
0.8885
0.8655
jrsII-2-21-04d (4th Floor)

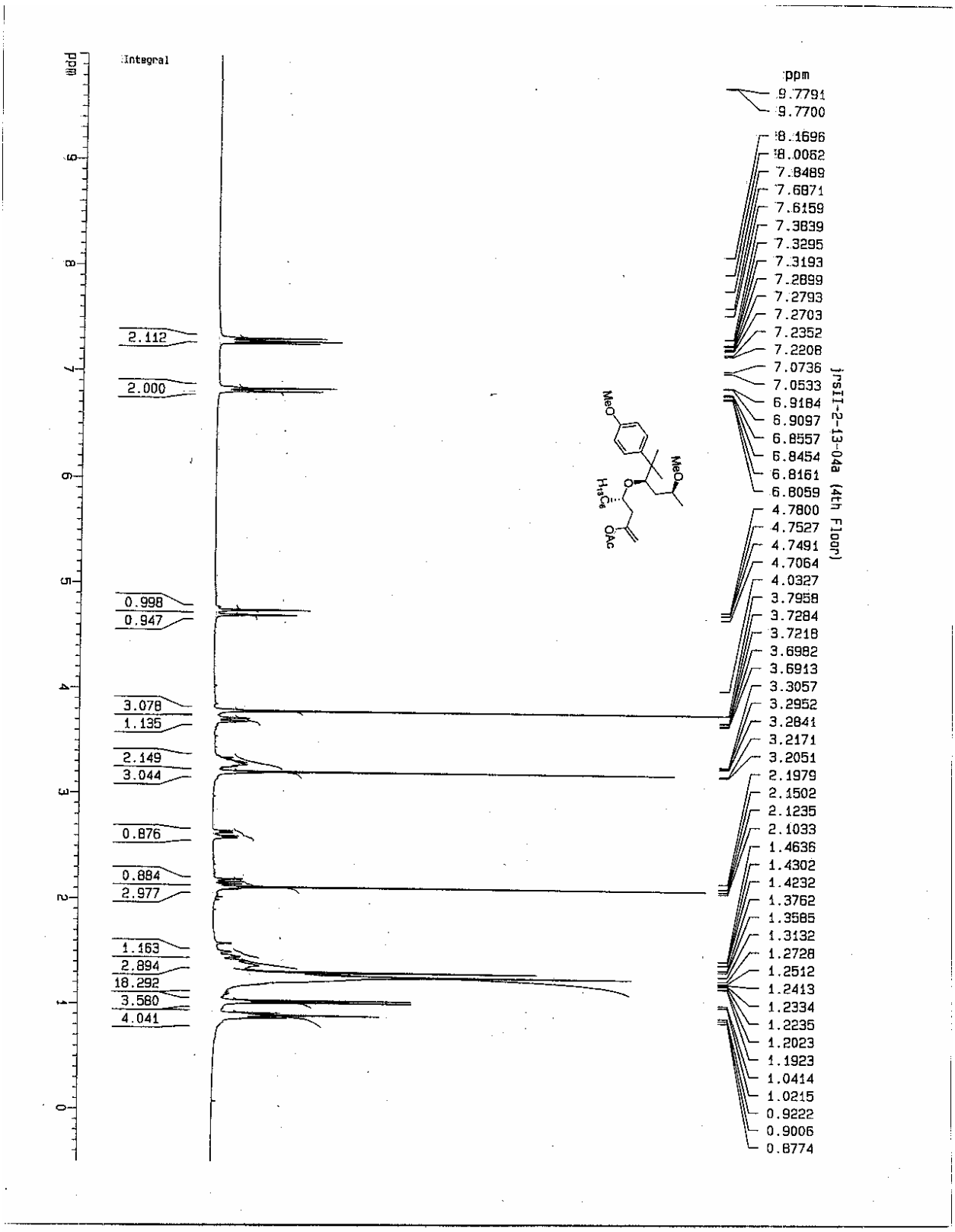

ppm
206.923
137.327
115.929
77.422
77.289
77.198
77.126
77.000
76.577
47.816
47.467
36.411
31.710
29.148
25.198
22.560
14.021
jrsII-2-21-04d (2) (4th Floor)

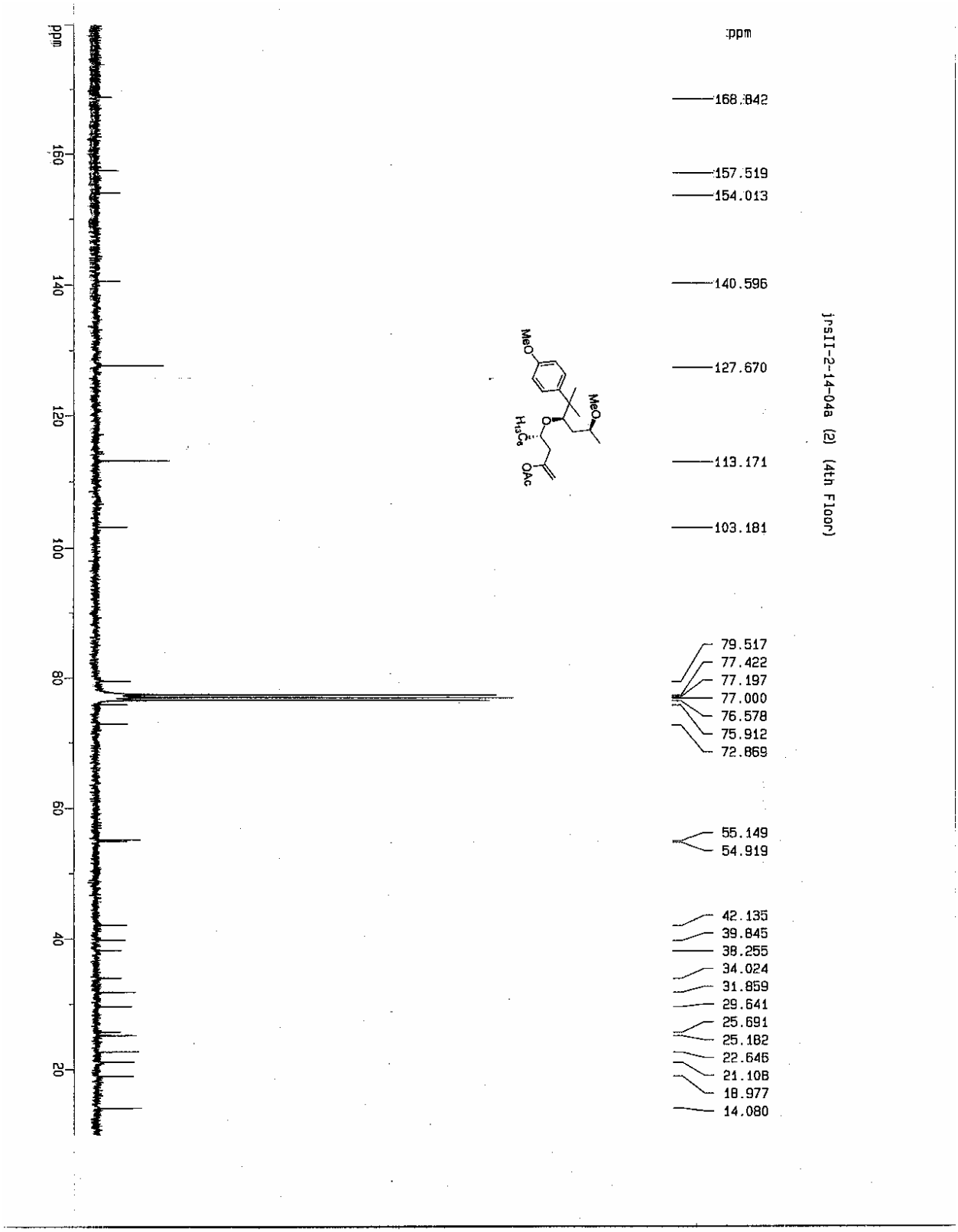

Integral
ppm
2.318
2.000
1.851
3.100
0.889
1.119
3.058
1.054
0.923
1.201
3.002
4.382
16.227
6.522
MeO
MeO
OAc
7.71040
7.53232
7.31824
7.30773
7.30057
7.28520
7.27810
7.26980
7.25462
7.25097
7.07897
7.05751
6.85093
6.84068
6.83371
6.81775
6.81104
6.80040
4.97490
4.95303
4.76969
4.76547
4.75560
3.79700
3.78156
3.52865
3.47354
3.45729
3.44240
3.17213
3.16271
2.43191
2.40955
2.35873
2.33967
2.15113
2.12556
2.11583
1.50914
1.49498
1.48234
1.46811
1.44509
1.42732
1.40958
1.39597
1.37777
1.35980
1.32041
1.26630
0.92672
0.90481
0.89736
0.88619
0.87738
jrs[I102503b (4th Floor) From Major D.a. of Acetal opening Slower

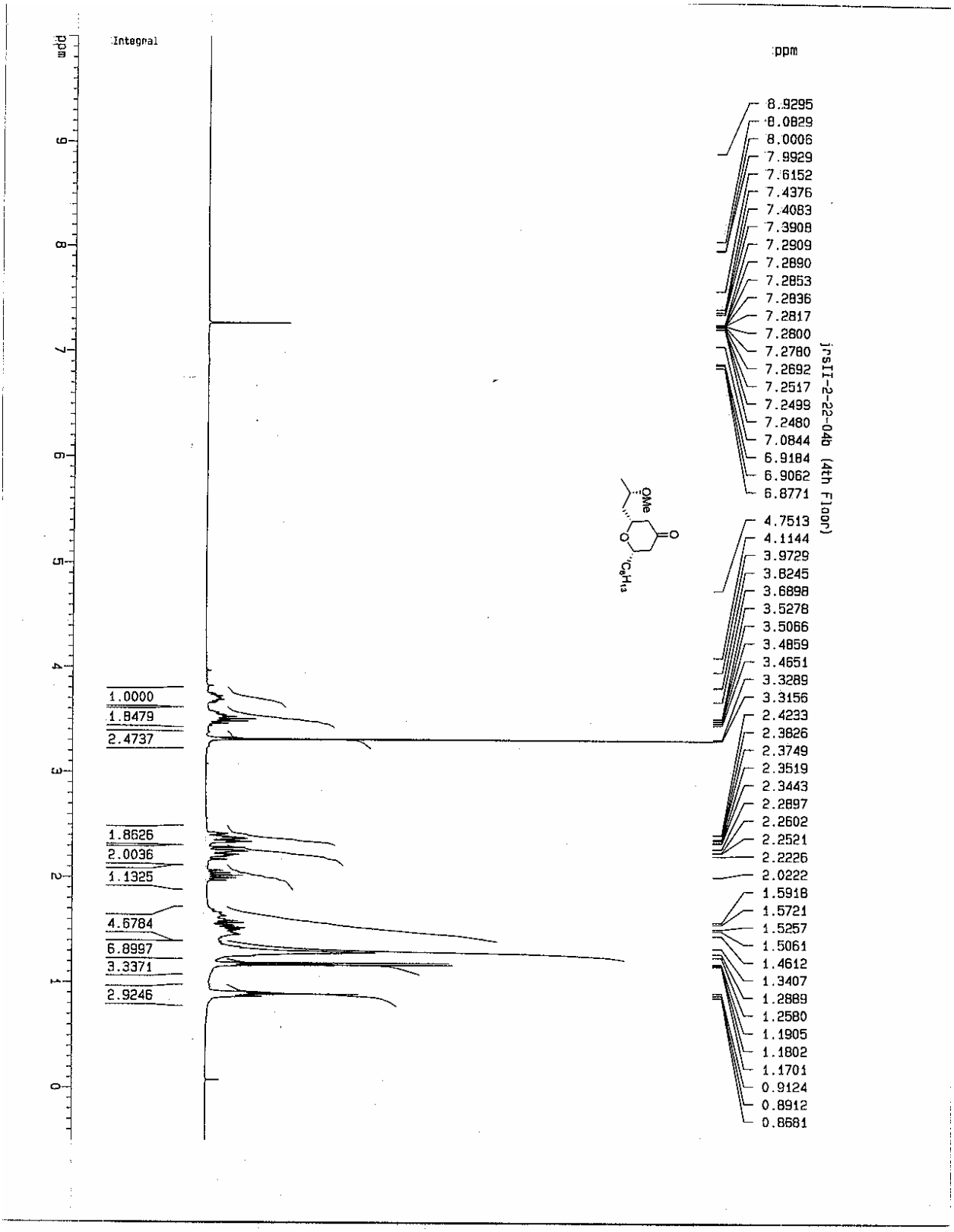

ppm
168.973
157.624
154.119
139.949
134.921
127.802
113.154
110.565
103.176
80.986
80.711
77.419
77.195
76.996
76.571
76.250
75.416
75.277
73.762
56.001
55.175
42.417
42.337
40.201
40.013
38.773
33.104
31.858
29.671
29.628
29.088
26.731
25.119
24.770
22.966
22.691
22.629
22.561
21.102
20.675
19.032
14.053
MeO
MeO
OAc
jrsII102503b (2) (4th Floor) Front slower Alkyne Dia.

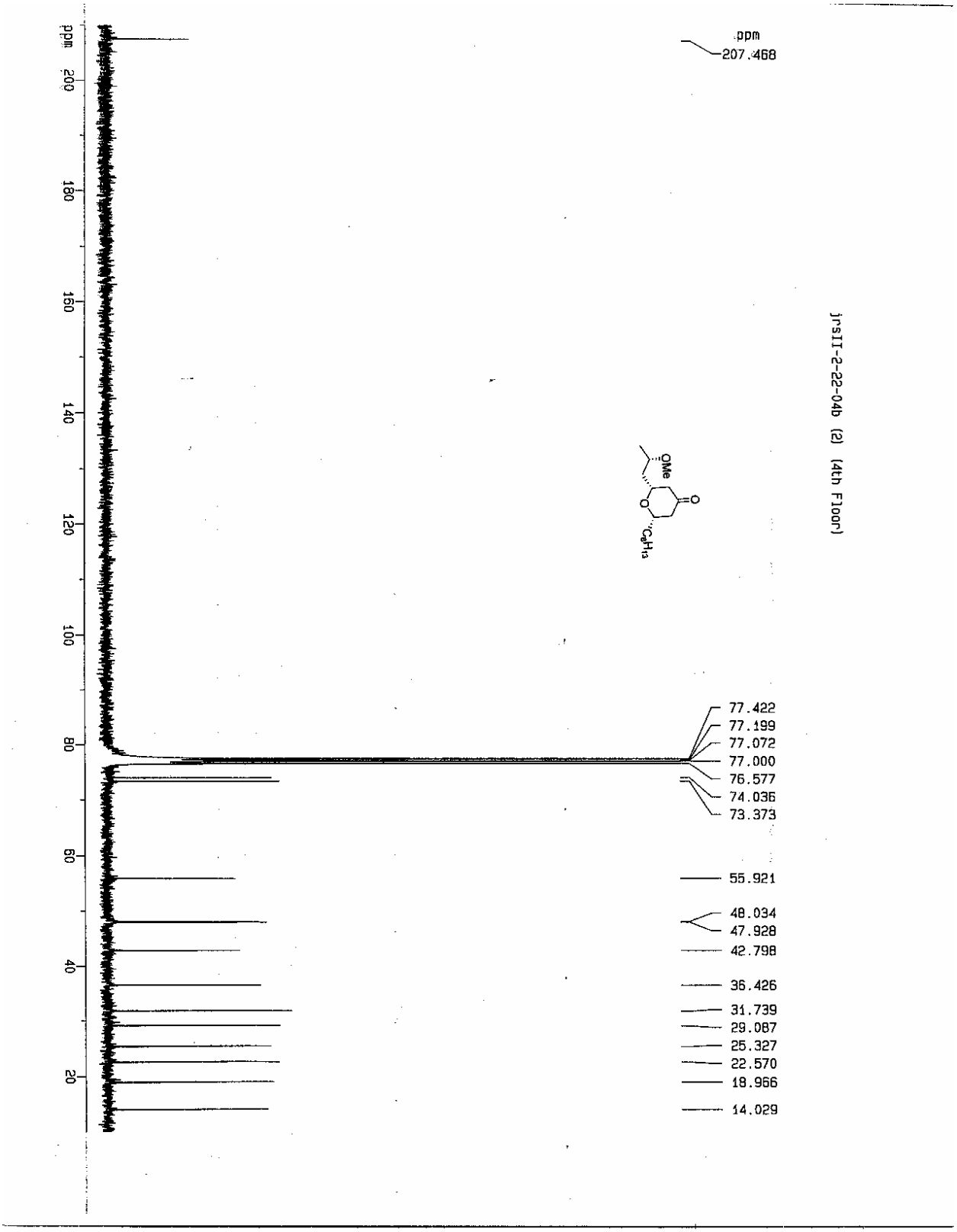

Integral
ppm
9.6
9.67
9.65
9.641
7.9653
7.93527
7.61542
7.28640
7.28462
7.28278
7.28090
7.27907
7.27719
7.27513
7.27092
7.26016
7.25825
7.25643
7.25455
7.25264
7.25080
7.24900
7.00580
6.92001
4.17512
3.97505
3.80245
3.79316
3.60170
3.59123
3.58137
3.57065
3.56312
3.33123
3.31818
2.34580
2.32010
2.25621
2.24997
2.21807
2.21107
1.67677
1.65778
1.64625
1.63807
1.62658
1.60675
1.59562
1.32141
1.30700
1.29715
1.25934
1.18171
1.16136
0.91588
0.91023
0.89540
0.87184
1.0864
2.0560
3.0000
2.0436
2.1793
3.1581
2.4888
7.9345
3.3589
3.1948
OMe
O
O
C8H13
jrsII102703c (4th Floor)

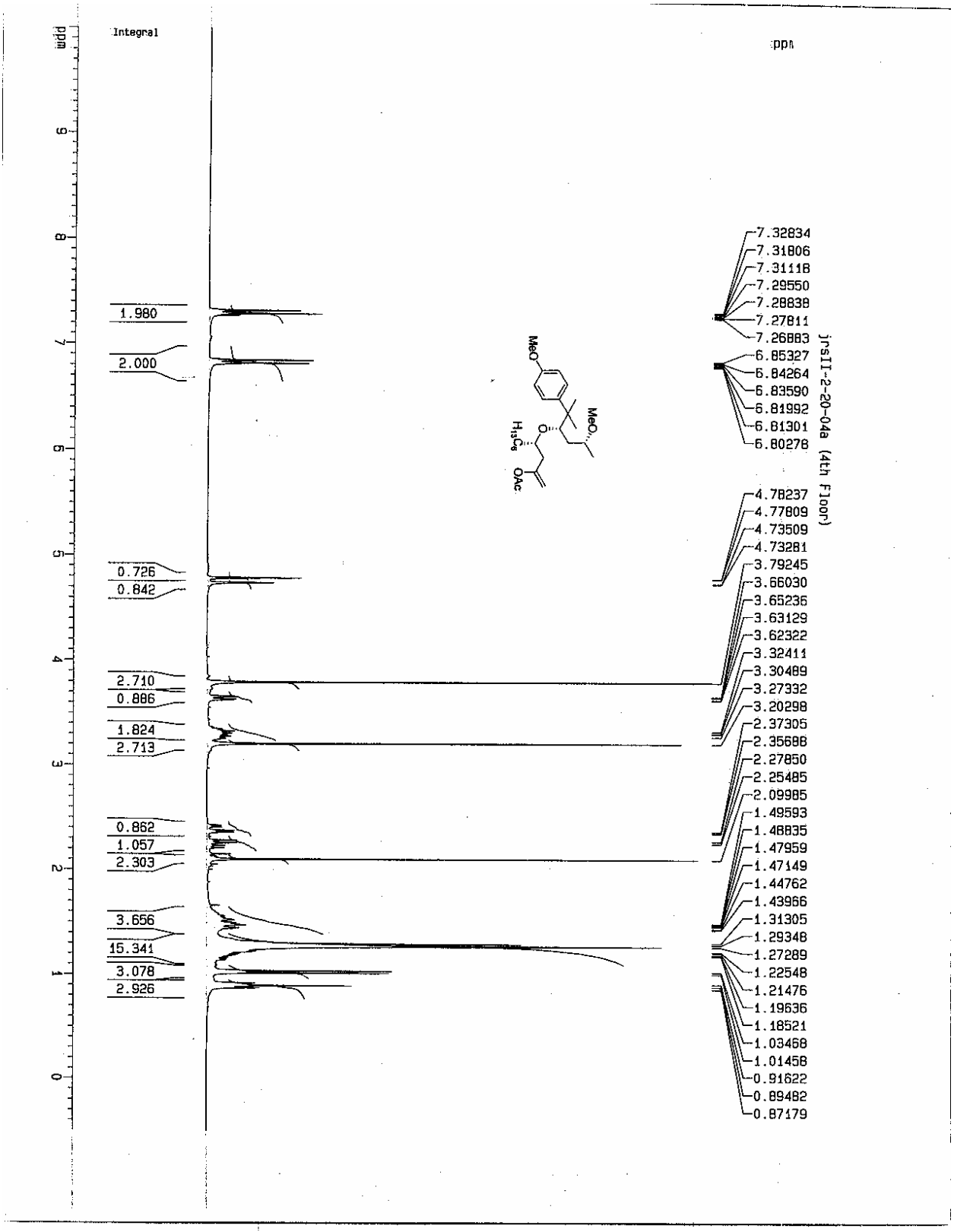

ppm
200
180
160
140
120
100
80
60
40
20
20
177.616
77.430
77.004
76.582
73.736
73.160
56.406
56.370
56.332
48.245
48.108
44.230
36.473
31.784
29.069
29.029
25.468
25.434
22.601
19.411
14.051
10.053
OMe
O
O
C9H19
jrsII102703c (2) (4th Floor)

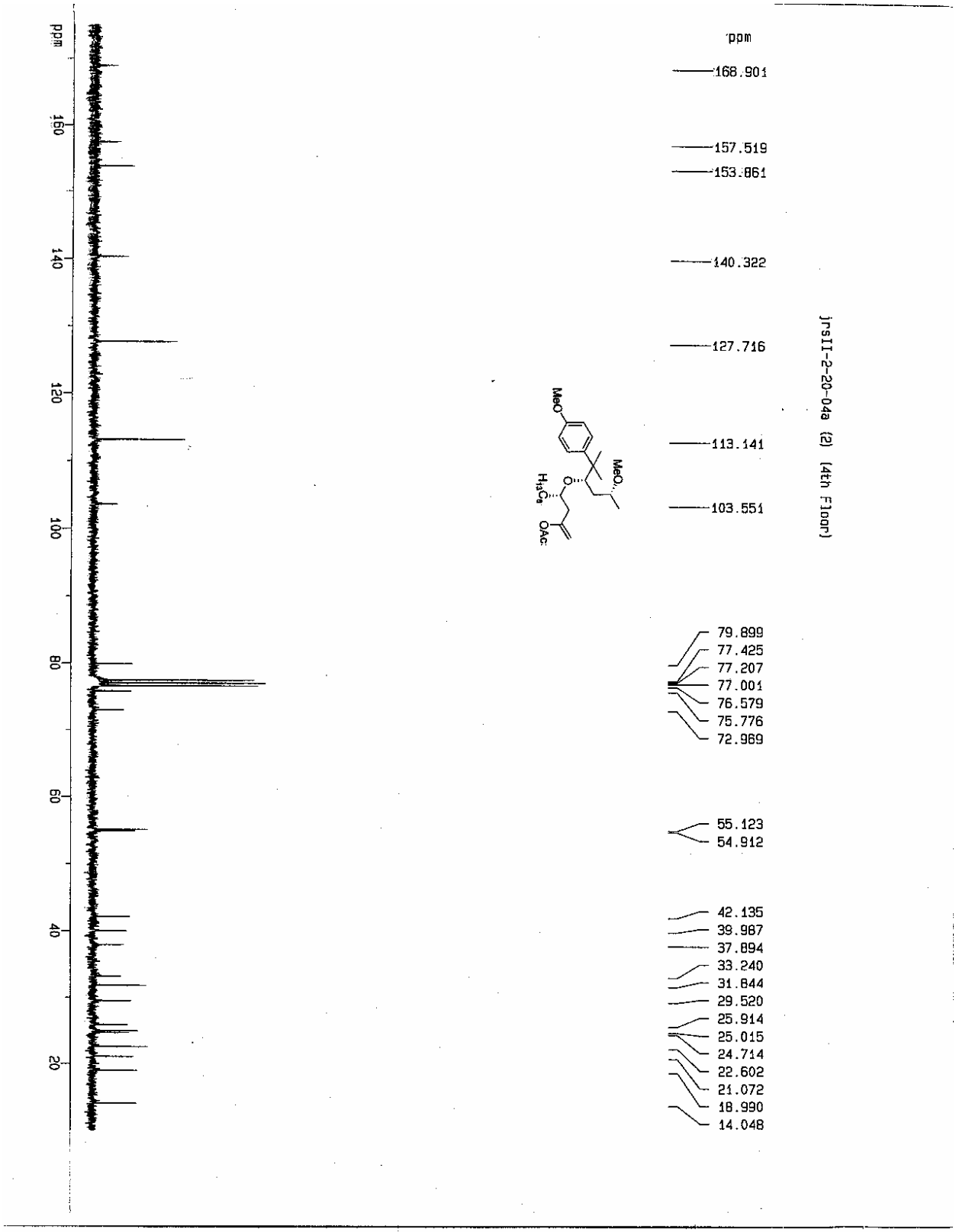

Integral
ppm
2.112
2.000
0.998
0.947
3.078
1.135
2.149
3.044
0.876
0.884
2.977
1.163
2.894
18.292
3.580
4.041
MeO
MeO
H3C
OAc
jrsII-2-13-04a (4th Floor)
ppm
9.7791
9.7700
8.1696
8.0062
7.8489
7.6871
7.6159
7.3839
7.3295
7.3193
7.2899
7.2793
7.2703
7.2352
7.2208
7.0736
7.0533
6.9184
6.9097
6.8557
6.8454
6.8161
6.8059
4.7800
4.7527
4.7491
4.7064
4.0327
3.7958
3.7284
3.7218
3.6982
3.6913
3.3057
3.2952
3.2841
3.2171
3.2051
2.1979
2.1502
2.1235
2.1033
1.4636
1.4302
1.4232
1.3762
1.3585
1.3132
1.2728
1.2512
1.2413
1.2334
1.2235
1.2023
1.1923
1.0414
1.0215
0.9222
0.9006
0.8774

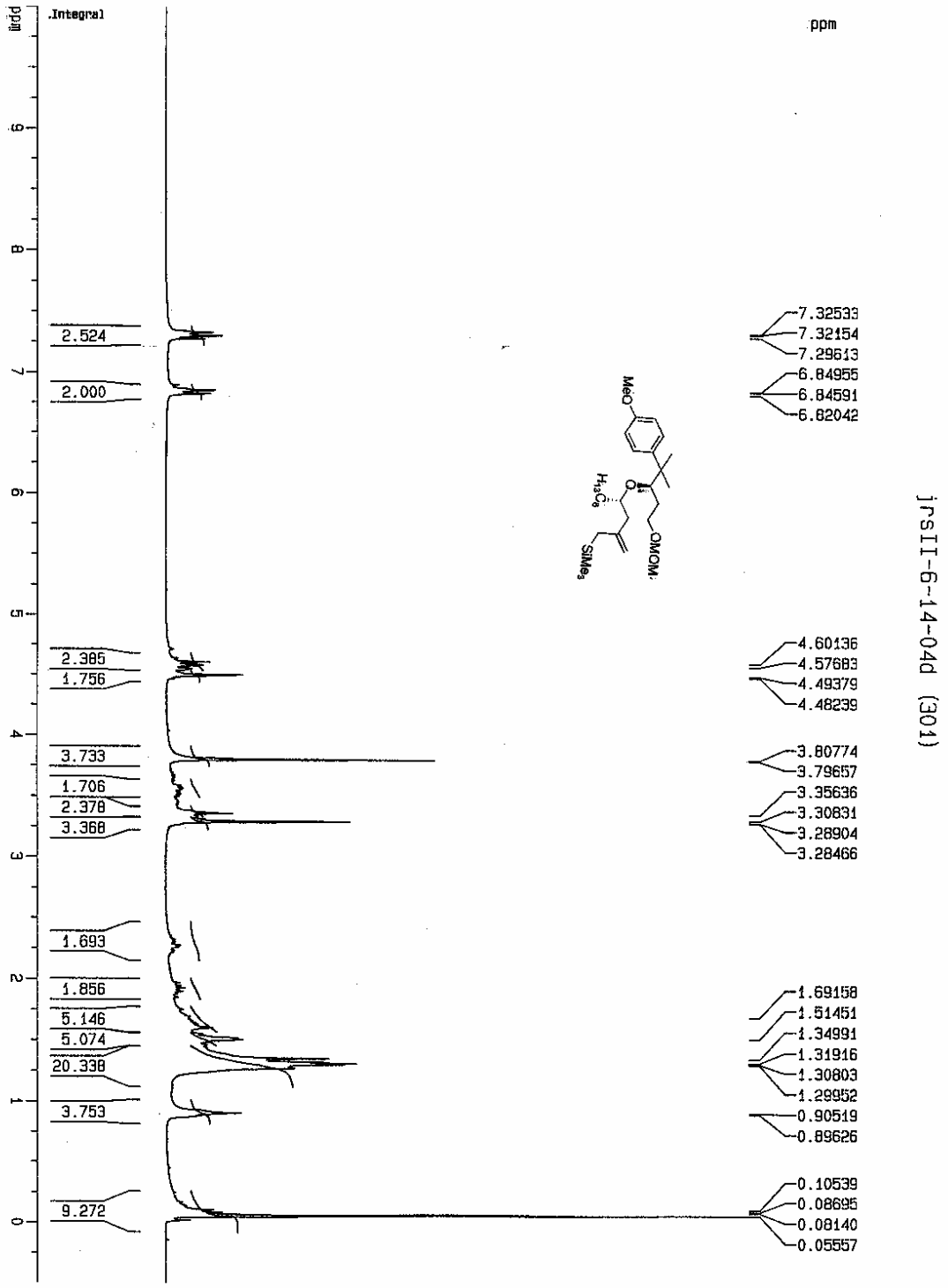

ppm
168.842
157.519
154.013
140.596
127.670
113.171
103.181
79.517
77.422
77.197
77.000
76.578
75.912
72.869
55.149
54.919
42.135
39.845
38.255
34.024
31.859
29.641
25.691
25.182
22.646
21.108
18.977
14.080
MeO
MeO
OAc
jrsII-2-14-04a (2) (4th Floor)

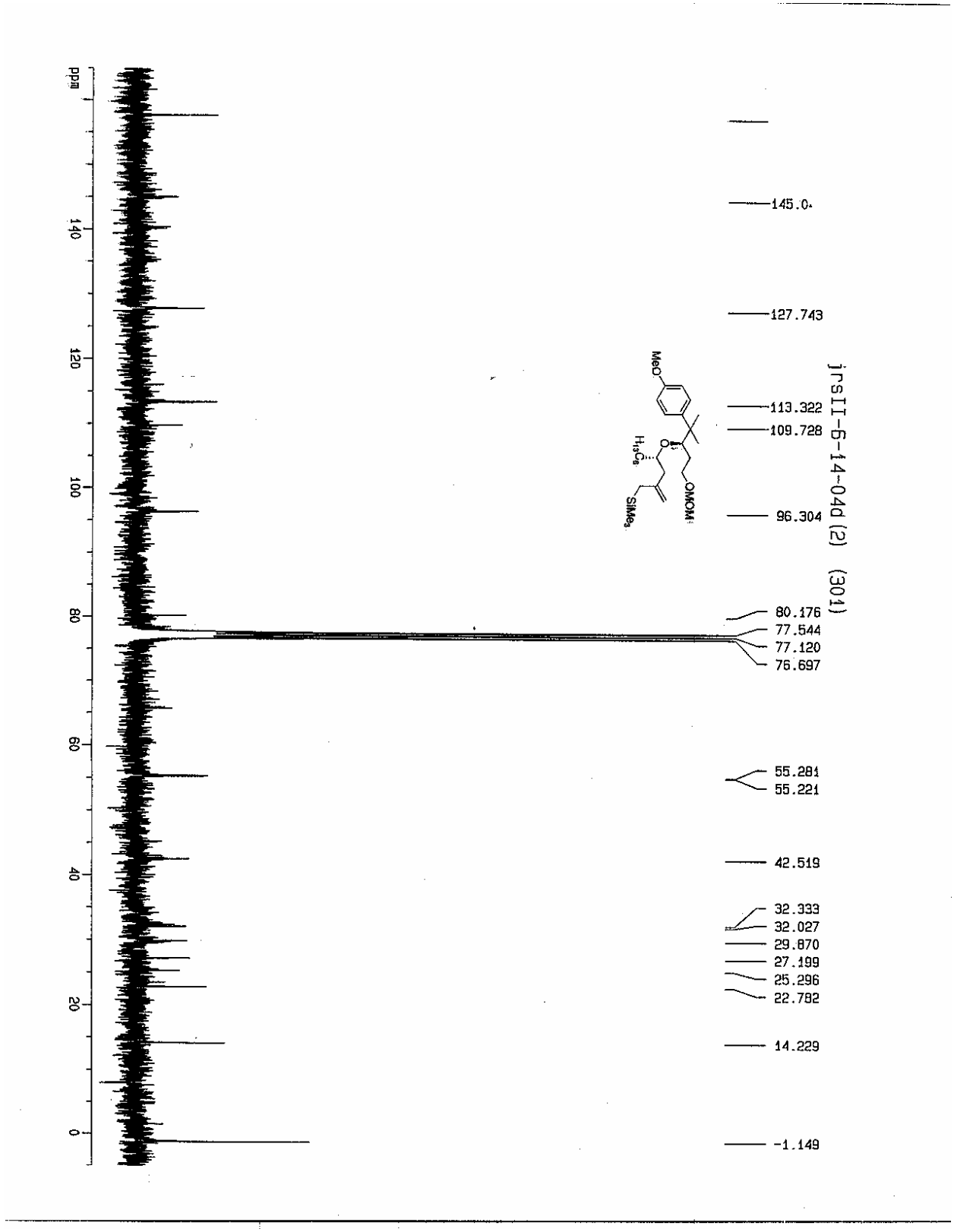

Integral
ppm
1.0000
1.8479
2.4737
1.8626
2.0036
1.1325
4.6784
6.8997
3.3371
2.9246
OMe
O
O
C6H13
ppm
8.9295
8.0829
8.0006
7.9929
7.6152
7.4376
7.4083
7.3908
7.2909
7.2890
7.2853
7.2836
7.2817
7.2800
7.2780
7.2692
7.2517
7.2499
7.2480
7.0844
6.9184
6.9062
6.8771
4.7513
4.1144
3.9729
3.8245
3.6898
3.5278
3.5066
3.4859
3.4651
3.3289
3.3156
2.4233
2.3826
2.3749
2.3519
2.3443
2.2897
2.2602
2.2521
2.2226
2.0222
1.5918
1.5721
1.5257
1.5061
1.4612
1.3407
1.2889
1.2580
1.1905
1.1802
1.1701
0.9124
0.8912
0.8681
jrsII-2-22-04b (4th Floor)

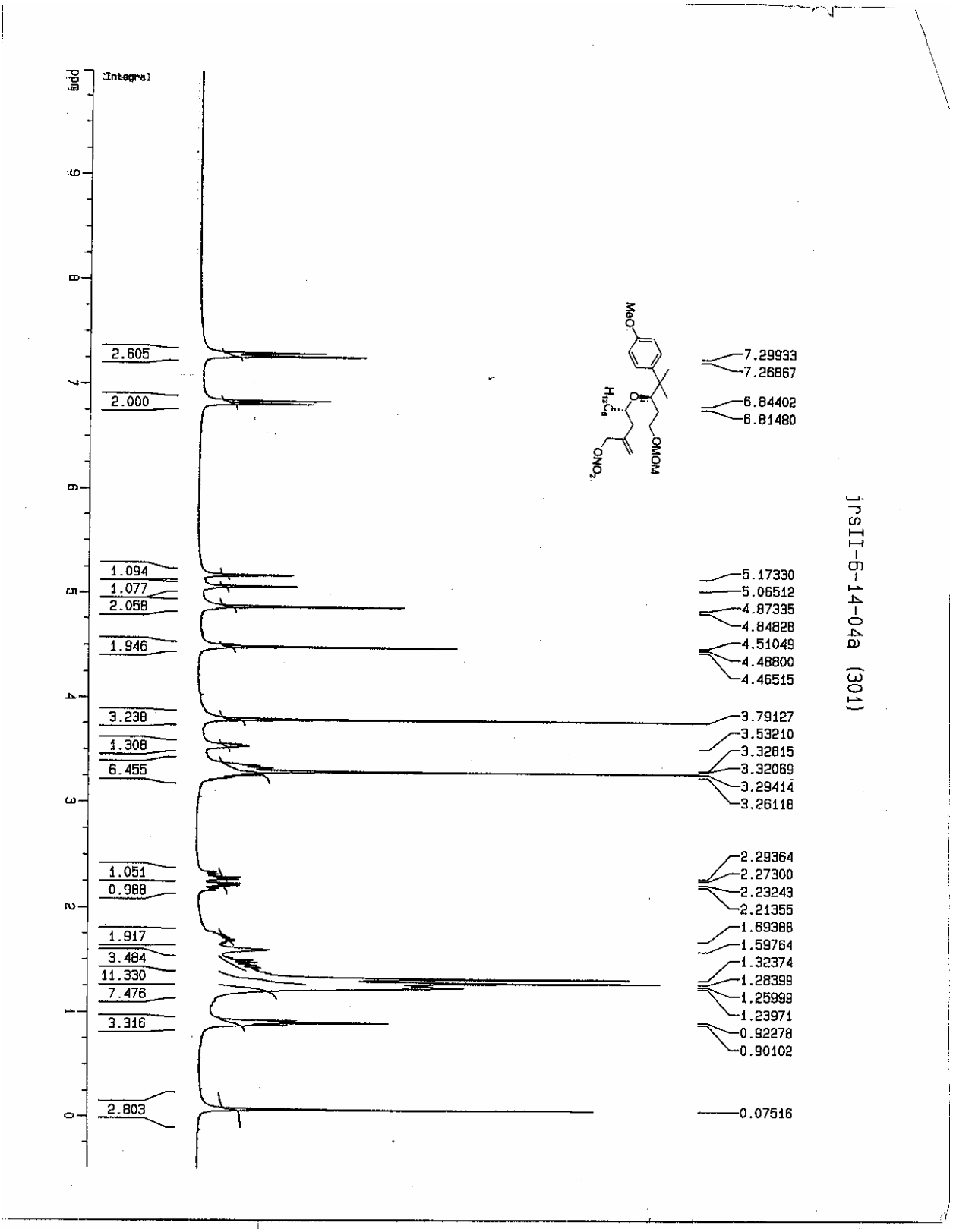

ppm
207.468
77.422
77.199
77.072
77.000
76.577
74.036
73.373
55.921
48.034
47.928
42.798
36.426
31.739
29.087
25.327
22.570
18.966
14.029
OMe
jrsII-2-22-04b (2) (4th Floor)

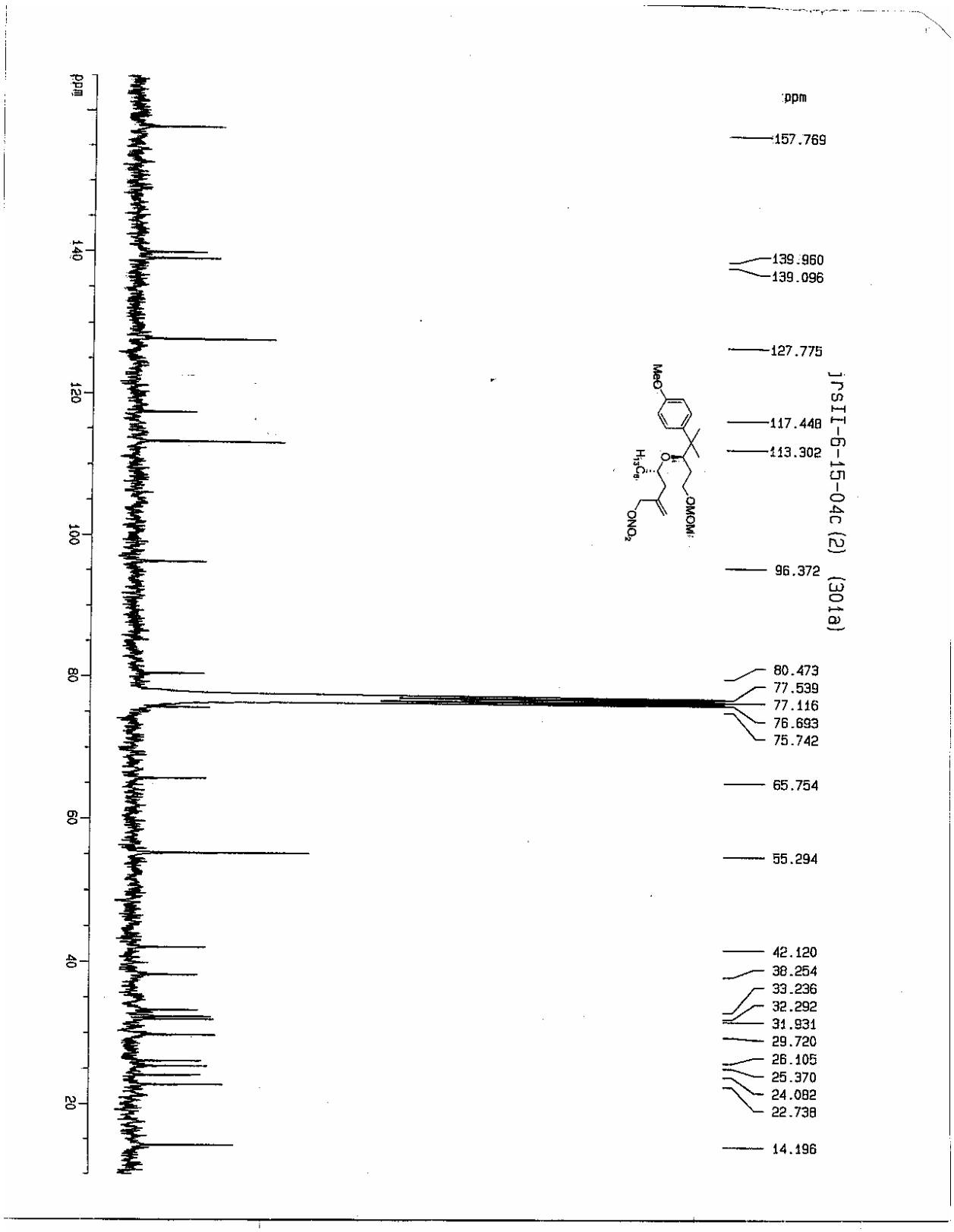

Integral
ppm
1.980
2.000
0.726
0.842
2.710
0.886
1.824
2.713
0.862
1.057
2.303
3.656
15.341
3.078
2.926
MeO
MeO
OAc
ppm
7.32834
7.31806
7.31118
7.29550
7.28838
7.27811
7.26883
6.85327
6.84264
6.83590
6.81992
6.81301
6.80278
4.78237
4.77809
4.73509
4.73281
3.79245
3.66030
3.65236
3.63129
3.62322
3.32411
3.30489
3.27332
3.20298
2.37305
2.35688
2.27850
2.25485
2.09985
1.49593
1.48835
1.47959
1.47149
1.44762
1.43966
1.31305
1.29348
1.27289
1.22548
1.21476
1.19636
1.18521
1.03468
1.01458
0.91622
0.89482
0.87179
jrsII-2-20-04a (4th Floor)


ppm
160
140
120
100
80
60
40
20
ppm
168.901
157.519
153.861
140.322
127.716
113.141
103.551
79.899
77.425
77.207
77.001
76.579
75.776
72.969
55.123
54.912
42.135
39.987
37.894
33.240
31.844
29.520
25.914
25.015
24.714
22.602
21.072
18.990
14.048
MeO
MeO
OAc
jrsII-2-20-04a (2) (4th Floor)


Integral
ppm
2.524
2.000
2.385
1.756
3.733
1.706
2.378
3.368
1.693
1.856
5.146
5.074
20.338
3.753
9.272
7.32533
7.32154
7.29613
6.84955
6.84591
6.82042
4.60136
4.57683
4.49379
4.48239
3.80774
3.79657
3.35636
3.30831
3.28904
3.28466
1.69158
1.51451
1.34991
1.31916
1.30803
1.29952
0.90519
0.89626
0.10539
0.08695
0.08140
0.05557
MeO
OMOM
SiMe3
jrsII-6-14-04d (301)

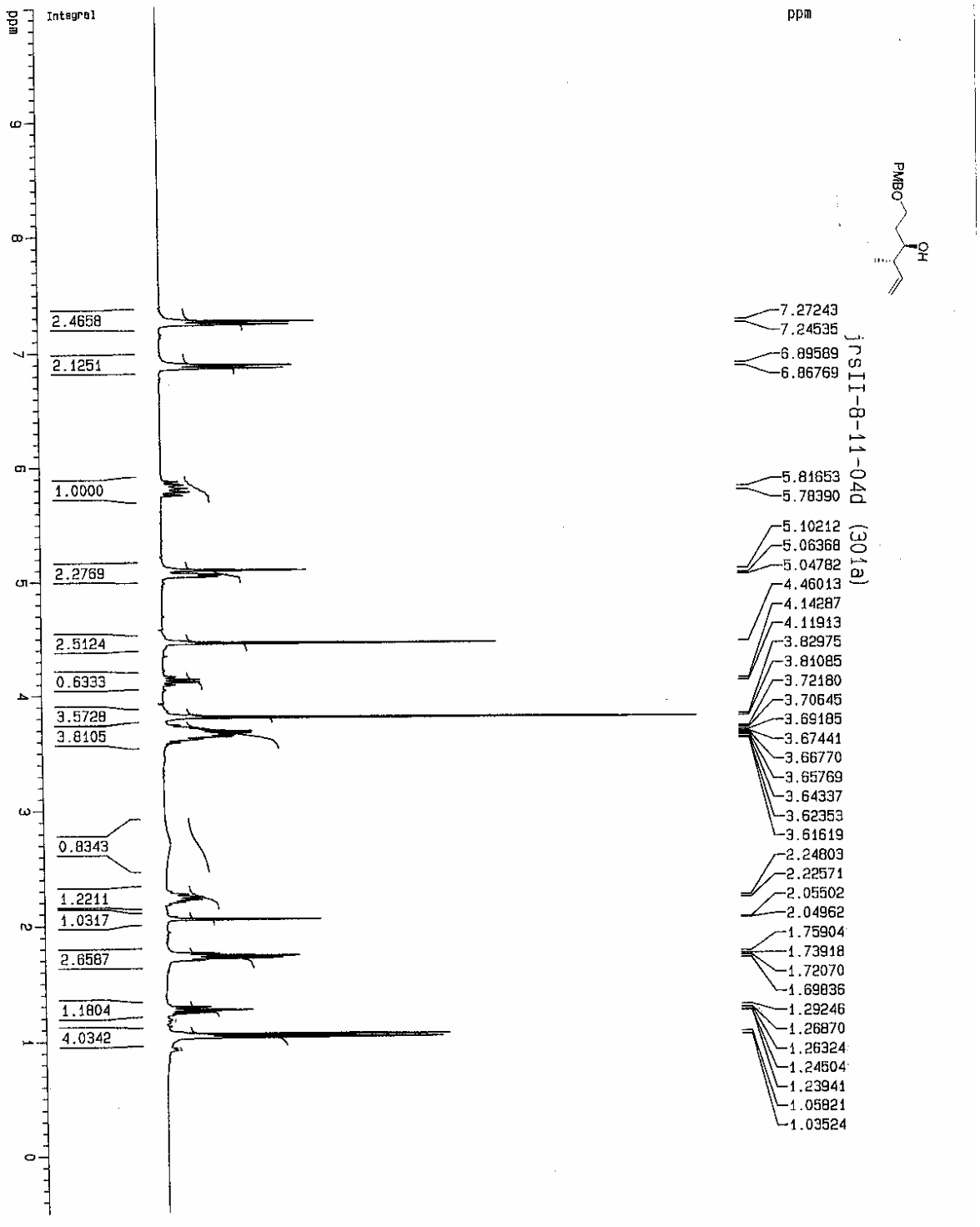

jrsII-6-14-04d (2) (301)
145.0
127.743
113.322
109.728
96.304
80.176
77.544
77.120
76.697
55.281
55.221
42.519
32.333
32.027
29.870
27.199
25.296
22.782
14.229
-1.149
MeO
OMOM
SiMe3
H13C6
ppm
140
120
100
80
60
40
20
0

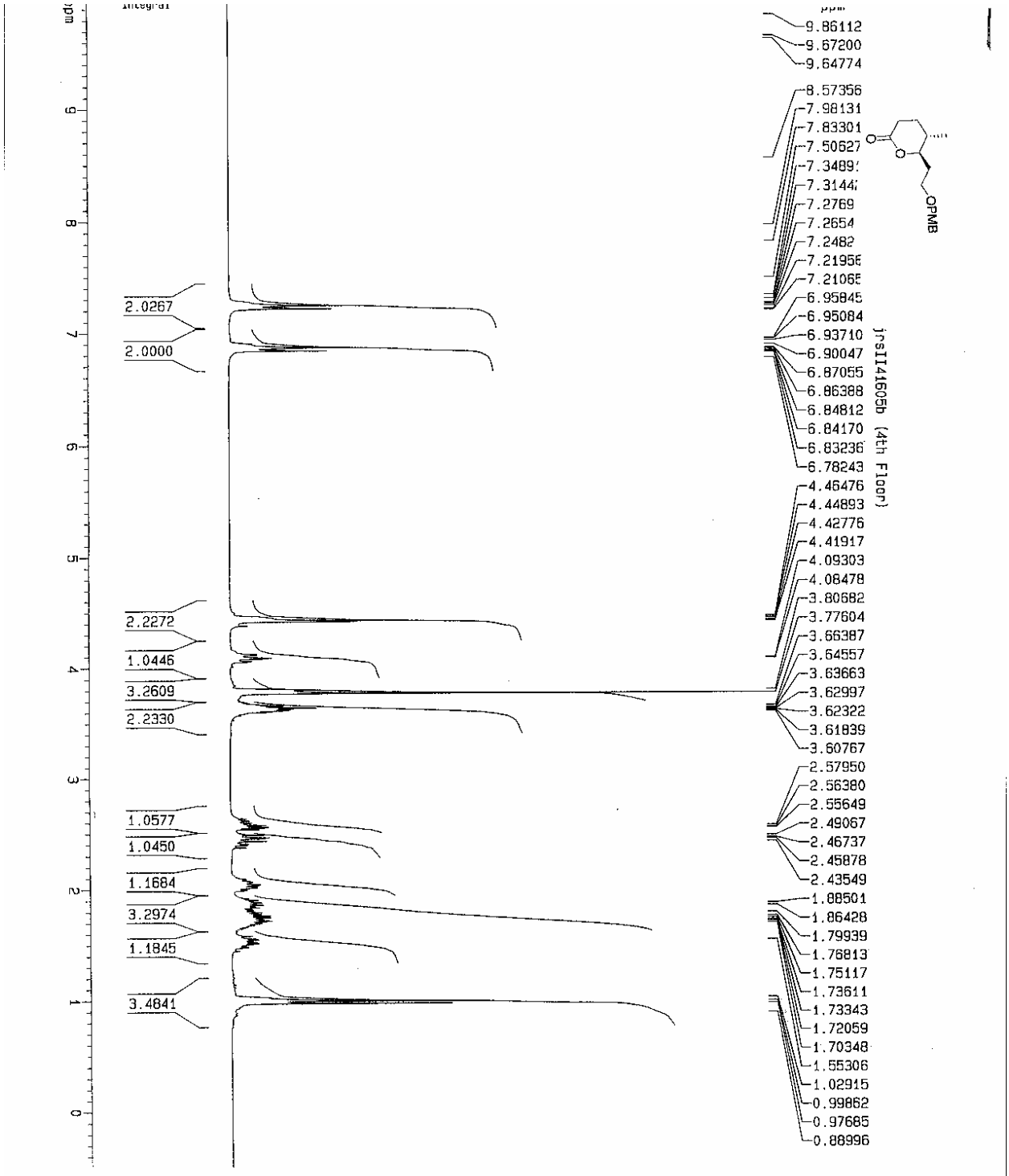

Integral
ppm
2.605
2.000
1.094
1.077
2.058
1.946
3.238
1.308
6.455
1.051
0.988
1.917
3.484
11.330
7.476
3.316
2.803
MeO
OMOM
ONO2
7.29933
7.26867
6.84402
6.81480
5.17330
5.06512
4.87335
4.84828
4.51049
4.48800
4.46515
3.79127
3.53210
3.32815
3.32069
3.29414
3.26118
2.29364
2.27300
2.23243
2.21355
1.69386
1.59764
1.32374
1.28399
1.25999
1.23971
0.92278
0.90102
0.07516
jrsII-6-14-04a (301)

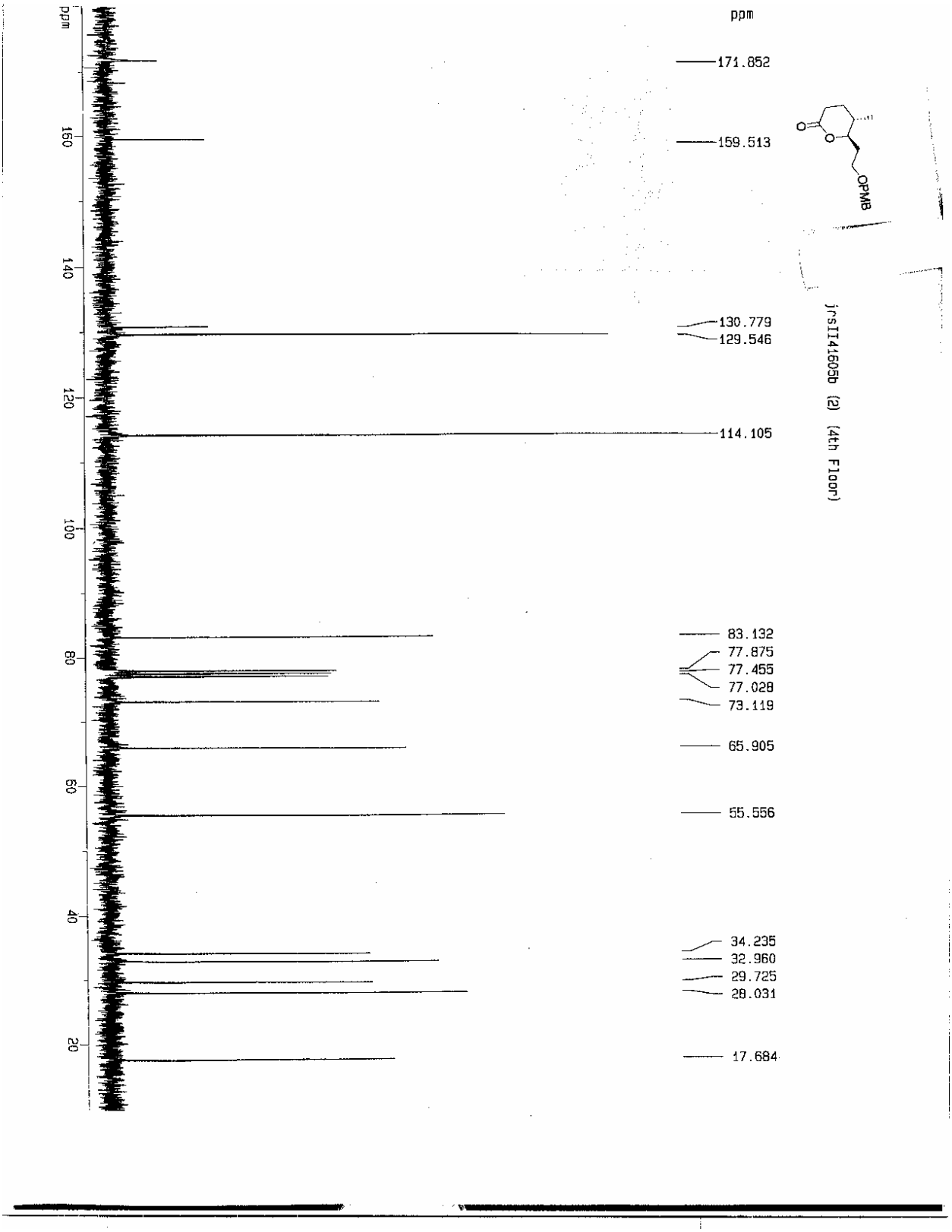

ppm
140
120
100
80
60
40
20
ppm
157.769
139.960
139.096
127.775
117.448
113.302
96.372
80.473
77.539
77.116
76.693
75.742
65.754
55.294
42.120
38.254
33.236
32.292
31.931
29.720
26.105
25.370
24.082
22.738
14.196
MeO
OMOM
ONO2
jrsII-6-15-04c (2) (301a)

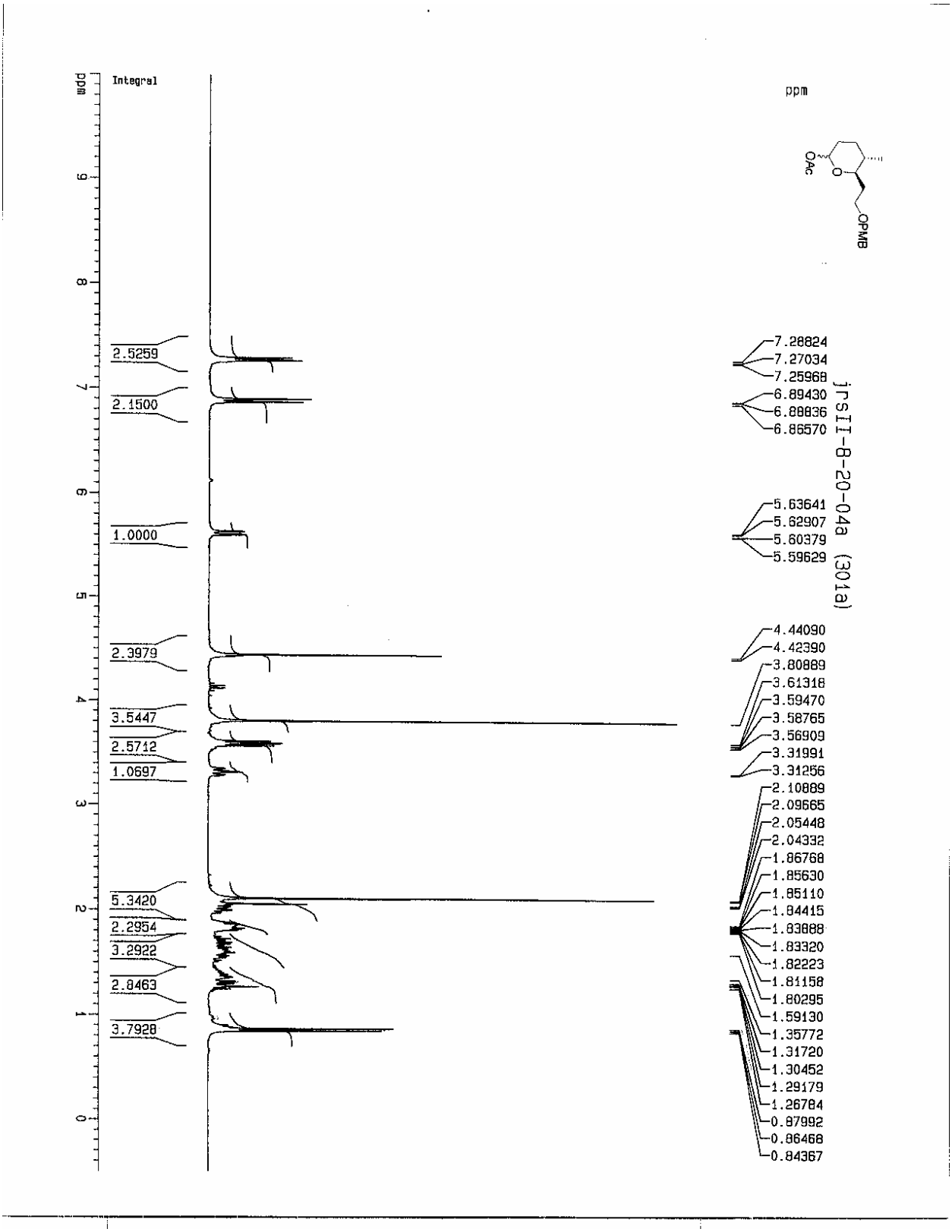
APPENDIX C

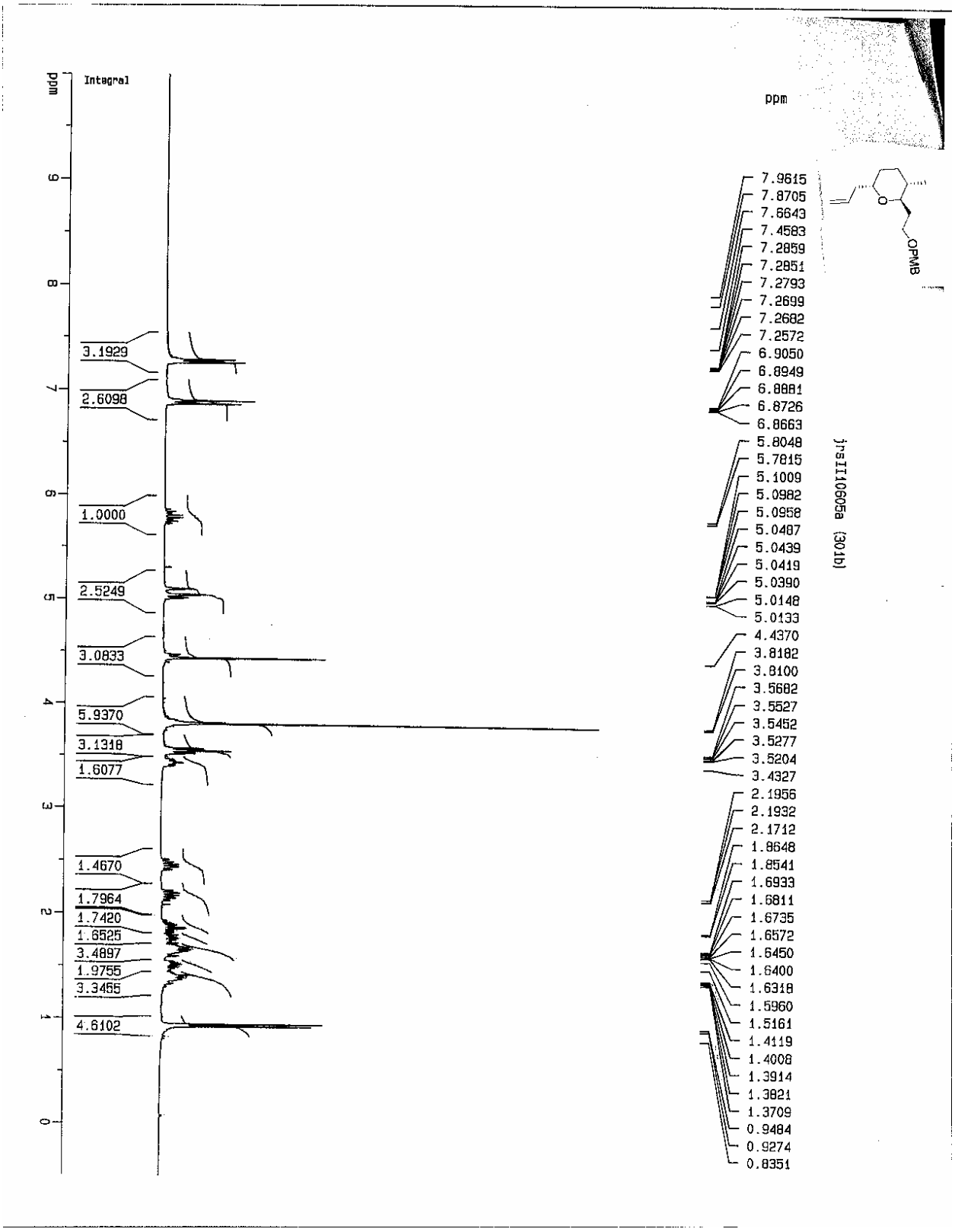
Efforts toward the Total Synthesis of Leucascandrolide A (Supporting Information) (^{1}H and ^{13}C NMR Spectra and Selected 2-D Spectra)

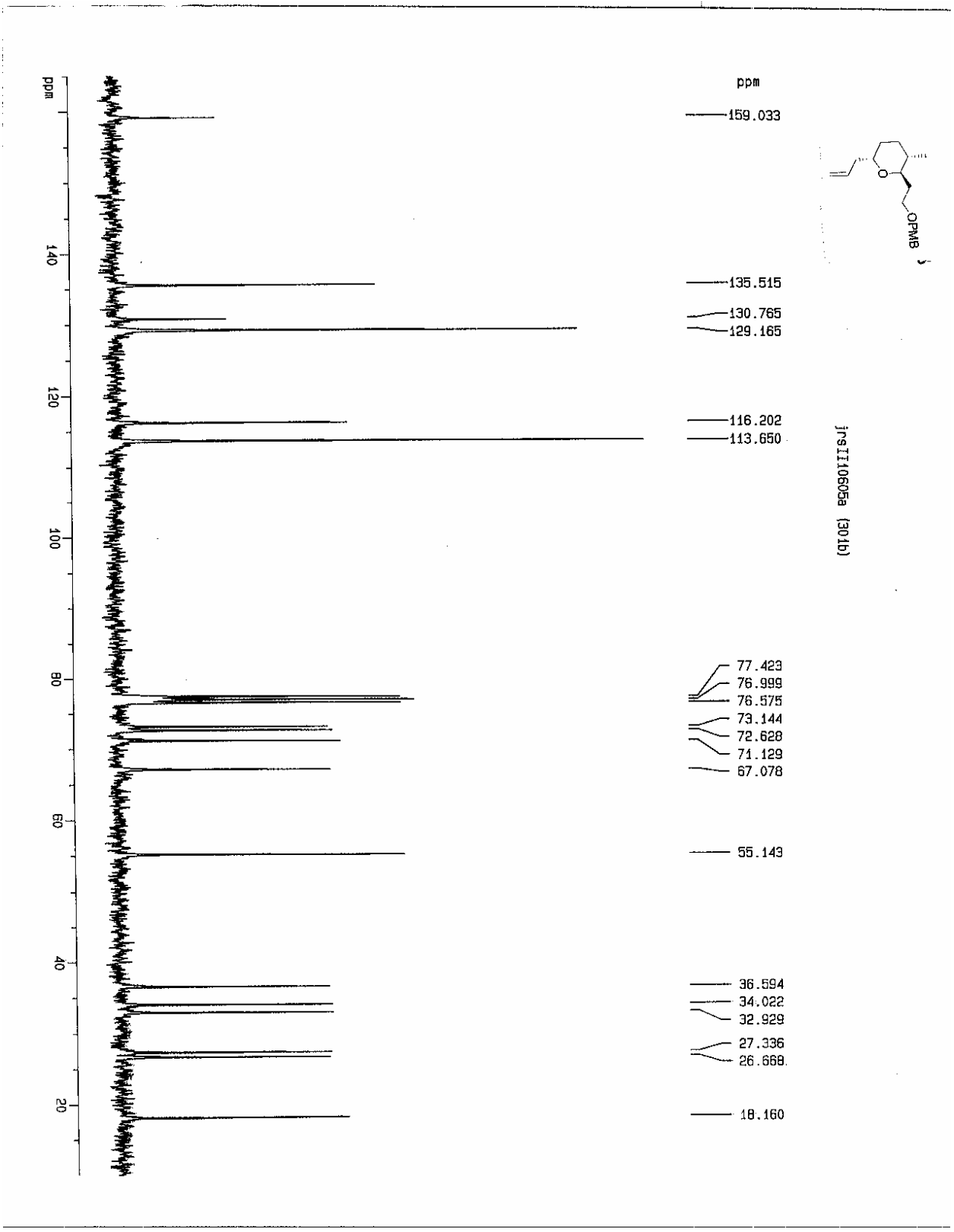

Integral
ppm
jrsII-8-11-04d (301a)
PMBO
OH
2.4658
2.1251
1.0000
2.2769
2.5124
0.6333
3.5728
3.8105
0.8343
1.2211
1.0317
2.6587
1.1804
4.0342
7.27243
7.24535
6.89589
6.86769
5.81653
5.78390
5.10212
5.06368
5.04782
4.46013
4.14287
4.11913
3.82975
3.81085
3.72180
3.70645
3.69185
3.67441
3.66770
3.65769
3.64337
3.62353
3.61619
2.24803
2.22571
2.05502
2.04962
1.75904
1.73918
1.72070
1.69836
1.29246
1.26870
1.26324
1.24504
1.23941
1.05821
1.03524

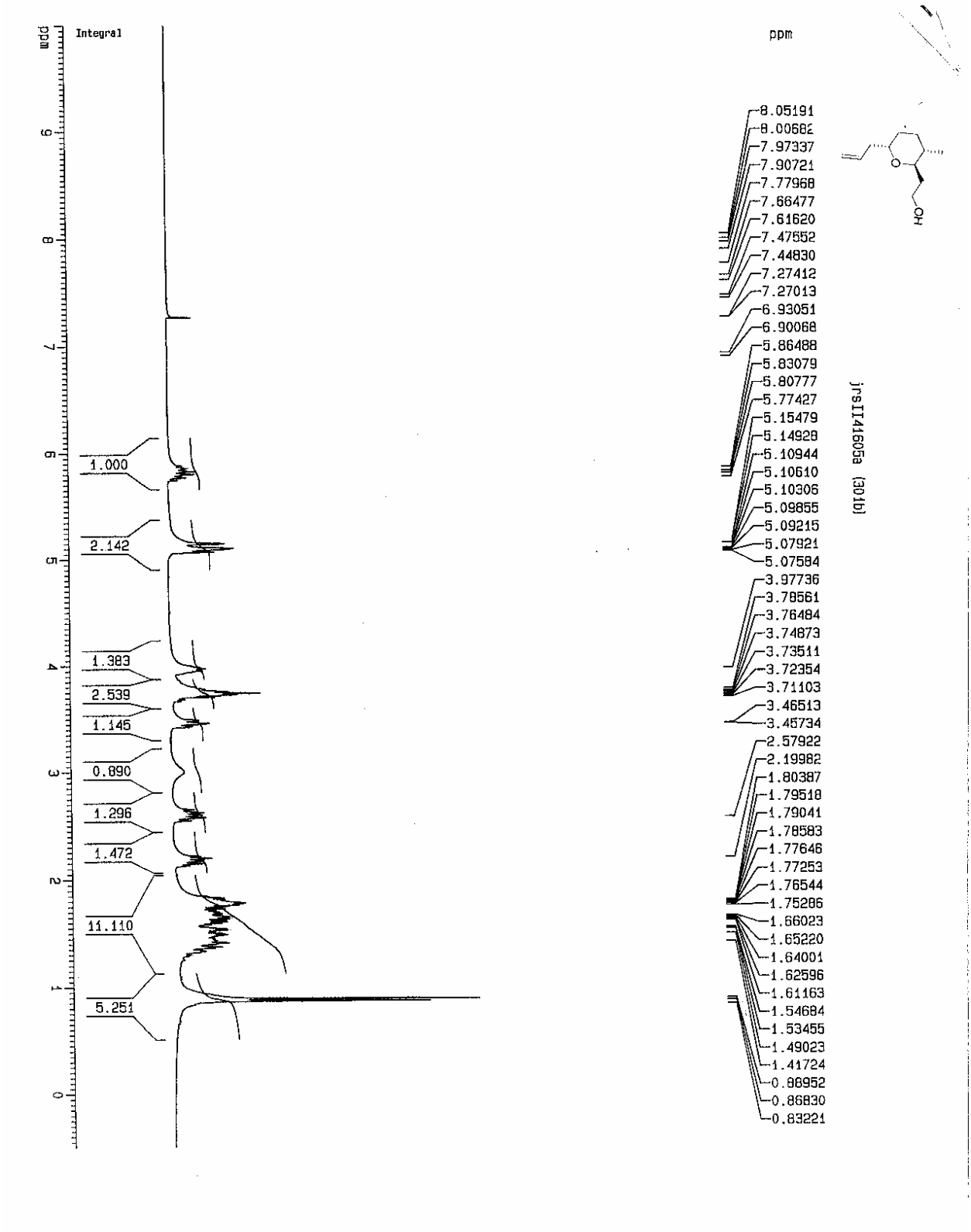

Integral
2.0267
2.0000
2.2272
1.0446
3.2609
2.2330
1.0577
1.0450
1.1684
3.2974
1.1845
3.4841
9.86112
9.67200
9.64774
8.57356
7.98131
7.83301
7.50627
7.34891
7.31441
7.2769
7.2654
7.2482
7.21956
7.21065
6.95845
6.95084
6.93710
6.90047
6.87055
6.86388
6.84812
6.84170
6.83236
6.78243
4.46476
4.44893
4.42776
4.41917
4.09303
4.08478
3.80682
3.77604
3.66387
3.64557
3.63663
3.62997
3.62322
3.61839
3.60767
2.57950
2.56380
2.55649
2.49067
2.46737
2.45878
2.43549
1.88501
1.86428
1.79939
1.76813
1.75117
1.73611
1.73343
1.72059
1.70348
1.55306
1.02915
0.99862
0.97685
0.88996
OPMB
jrsII41605b (4th Floor)


ppm
171.852
159.513
130.779
129.546
114.105
83.132
77.875
77.455
77.028
73.119
65.905
55.556
34.235
32.960
29.725
28.031
17.684
OPMB
jrsII416O5b (2) (4th Floor)


Integral
ppm
OAc
O
OPMB
2.5259
2.1500
1.0000
2.3979
3.5447
2.5712
1.0697
5.3420
2.2954
3.2922
2.8463
3.7928
7.28824
7.27034
7.25968
6.89430
6.88836
6.86570
5.63641
5.62907
5.60379
5.59629
4.44090
4.42390
3.80889
3.61318
3.59470
3.58765
3.56909
3.31991
3.31256
2.10889
2.09665
2.05448
2.04332
1.86768
1.85630
1.85110
1.84415
1.83888
1.83320
1.82223
1.81158
1.80295
1.59130
1.35772
1.31720
1.30452
1.29179
1.26784
0.87992
0.86468
0.84367
jrsII-8-20-04a (301a)


ppm
Integral
3.1929
2.6098
1.0000
2.5249
3.0833
5.9370
3.1318
1.6077
1.4670
1.7964
1.7420
1.6525
3.4897
1.9755
3.3465
4.6102
ppm
7.9615
7.8705
7.8643
7.4583
7.2859
7.2851
7.2793
7.2699
7.2682
7.2572
6.9050
6.8949
6.8881
6.8726
6.8663
5.8048
5.7815
5.1009
5.0982
5.0958
5.0487
5.0439
5.0419
5.0390
5.0148
5.0133
4.4370
3.8182
3.8100
3.5682
3.5527
3.5452
3.5277
3.5204
3.4327
2.1956
2.1932
2.1712
1.8648
1.8541
1.6933
1.6811
1.6735
1.6572
1.6450
1.6400
1.6318
1.5960
1.5161
1.4119
1.4008
1.3914
1.3821
1.3709
0.9484
0.9274
0.8351
OPMB
jrsII10605a (301b)


ppm
159.033
135.515
130.765
129.165
116.202
113.650
77.423
76.999
76.575
73.144
72.628
71.129
67.078
55.143
36.594
34.022
32.929
27.336
26.668
18.160
OPMB
jrs1110605a (301b)
ppm
140
120
100
80
60
40
20


Integral
ppm
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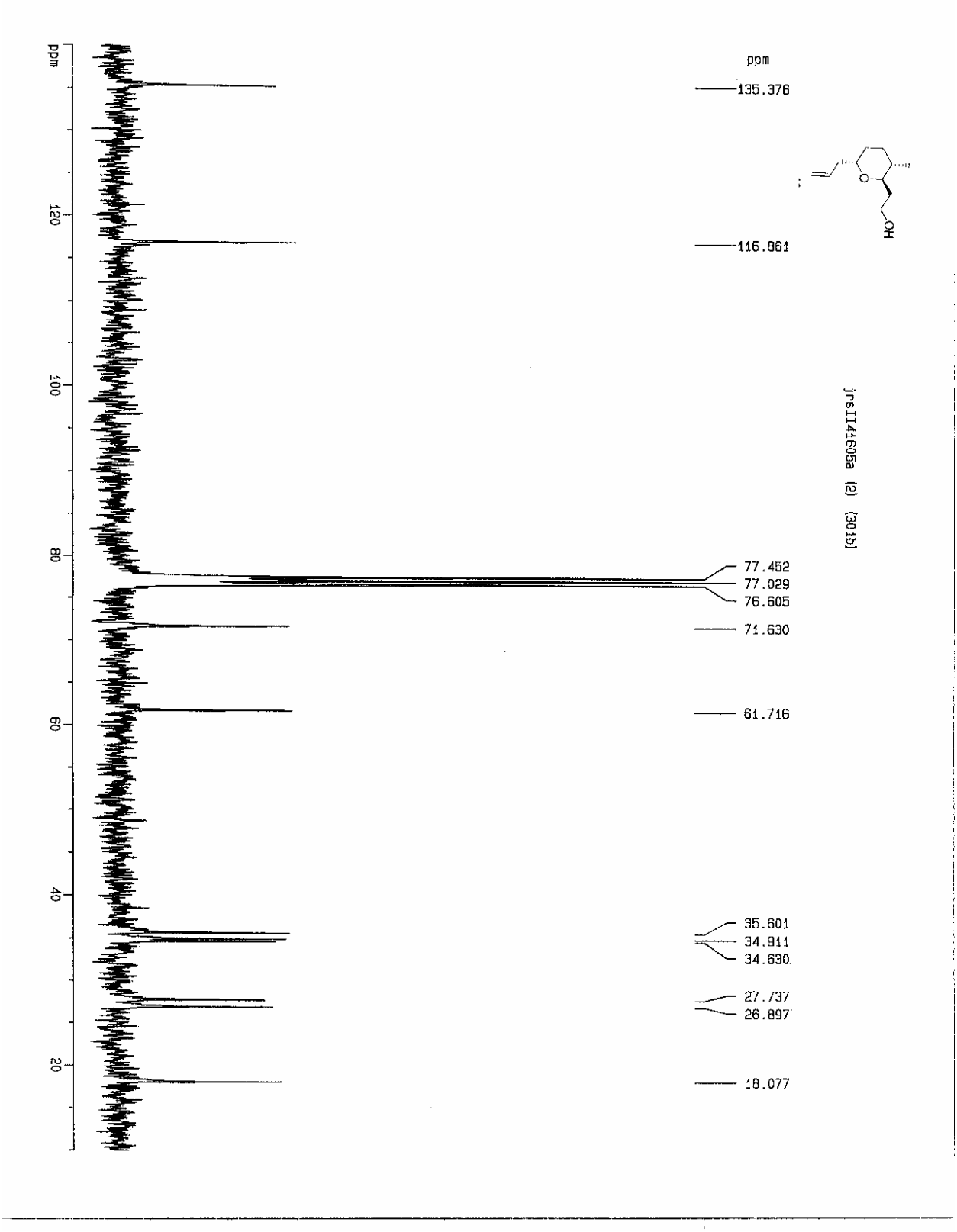
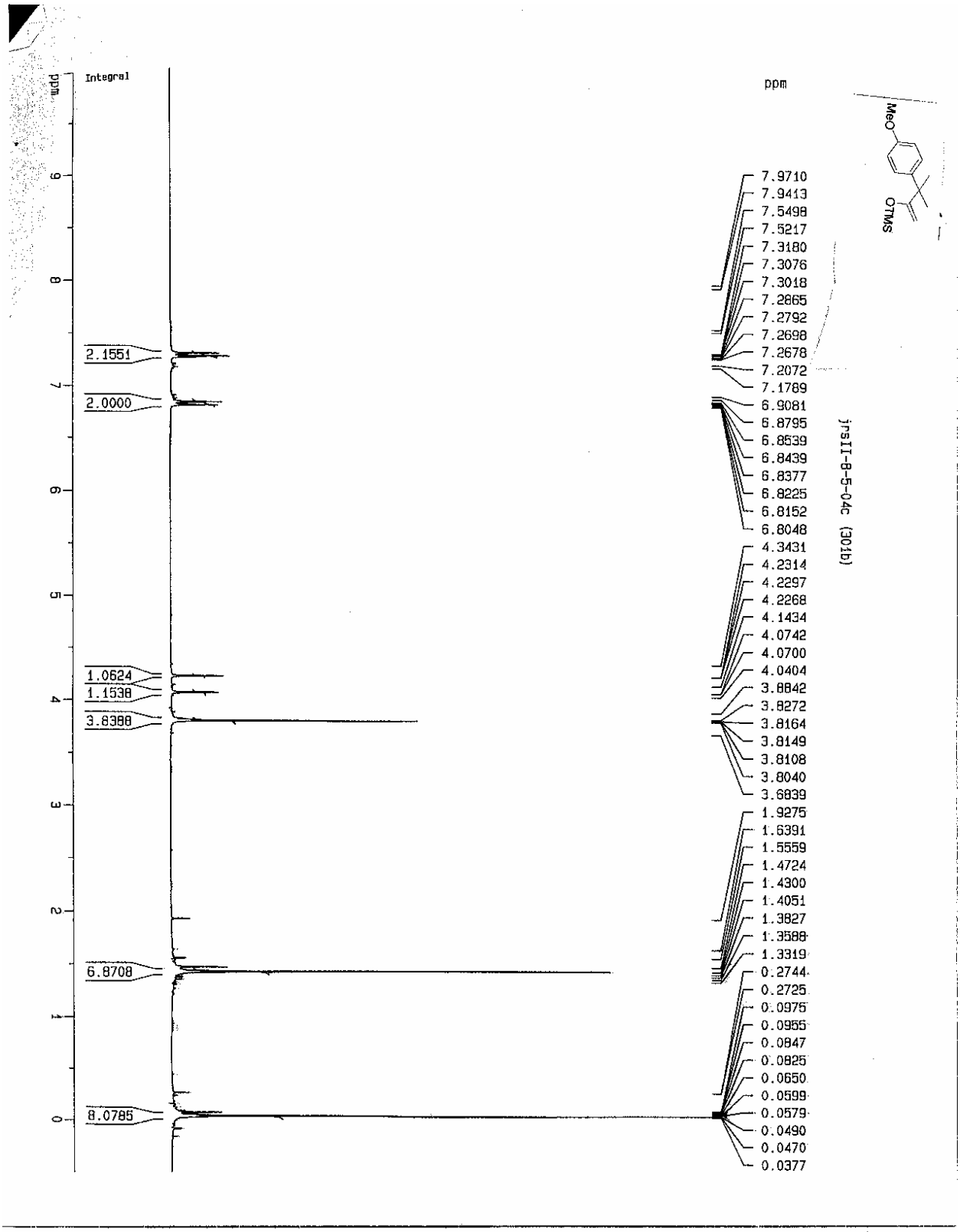
1.383
2.539
1.145
0.890
1.296
1.472
11.110
5.251
8.05191
8.00682
7.97337
7.90721
7.77968
7.66477
7.61620
7.47552
7.44830
7.27412
7.27013
6.93051
6.90068
5.86488
5.83079
5.80777
5.77427
5.15479
5.14928
5.10944
5.10610
5.10306
5.09855
5.09215
5.07921
5.07584
3.97736
3.78561
3.76484
3.74873
3.73511
3.72354
3.71103
3.46513
3.45734
2.57922
2.19982
1.80387
1.79518
1.79041
1.78583
1.77646
1.77253
1.76544
1.75286
1.66023
1.65220
1.64001
1.62596
1.61163
1.54684
1.53455
1.49023
1.41724
0.88952
0.86830
0.83221
OH
jrsII41605a (301b)


ppm
135.376
116.861
77.452
77.029
76.605
71.630
61.716
35.601
34.911
34.630
27.737
26.897
18.077
jrsII41605a (2) (301b)
ppm
120
100
80
60
40
20
OH


Integral
ppm
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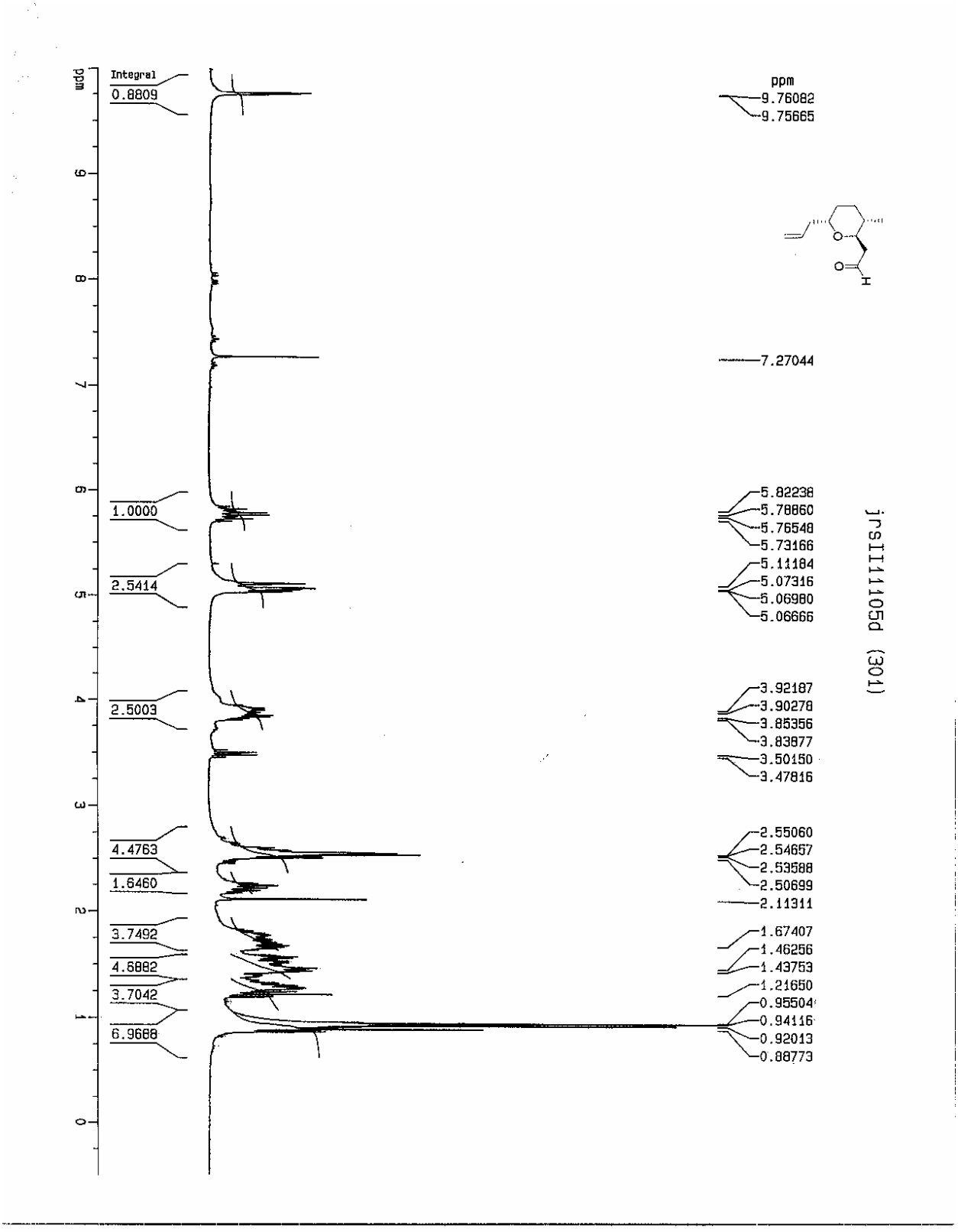
2.0000
1.0624
1.1538
3.8388
6.8708
8.0785
ppm
7.9710
7.9413
7.5498
7.5217
7.3180
7.3076
7.3018
7.2865
7.2792
7.2698
7.2678
7.2072
7.1789
6.9081
6.8795
6.8539
6.8439
6.8377
6.8225
6.8152
6.8048
4.3431
4.2314
4.2297
4.2268
4.1434
4.0742
4.0700
4.0404
3.8842
3.8272
3.8164
3.8149
3.8108
3.8040
3.6839
1.9275
1.6391
1.5559
1.4724
1.4300
1.4051
1.3827
1.3588
1.3319
0.2744
0.2725
0.0975
0.0955
0.0847
0.0825
0.0650
0.0599
0.0579
0.0490
0.0470
0.0377
MeO
OTMS
jrsI-8-5-04c (301b)


Integral
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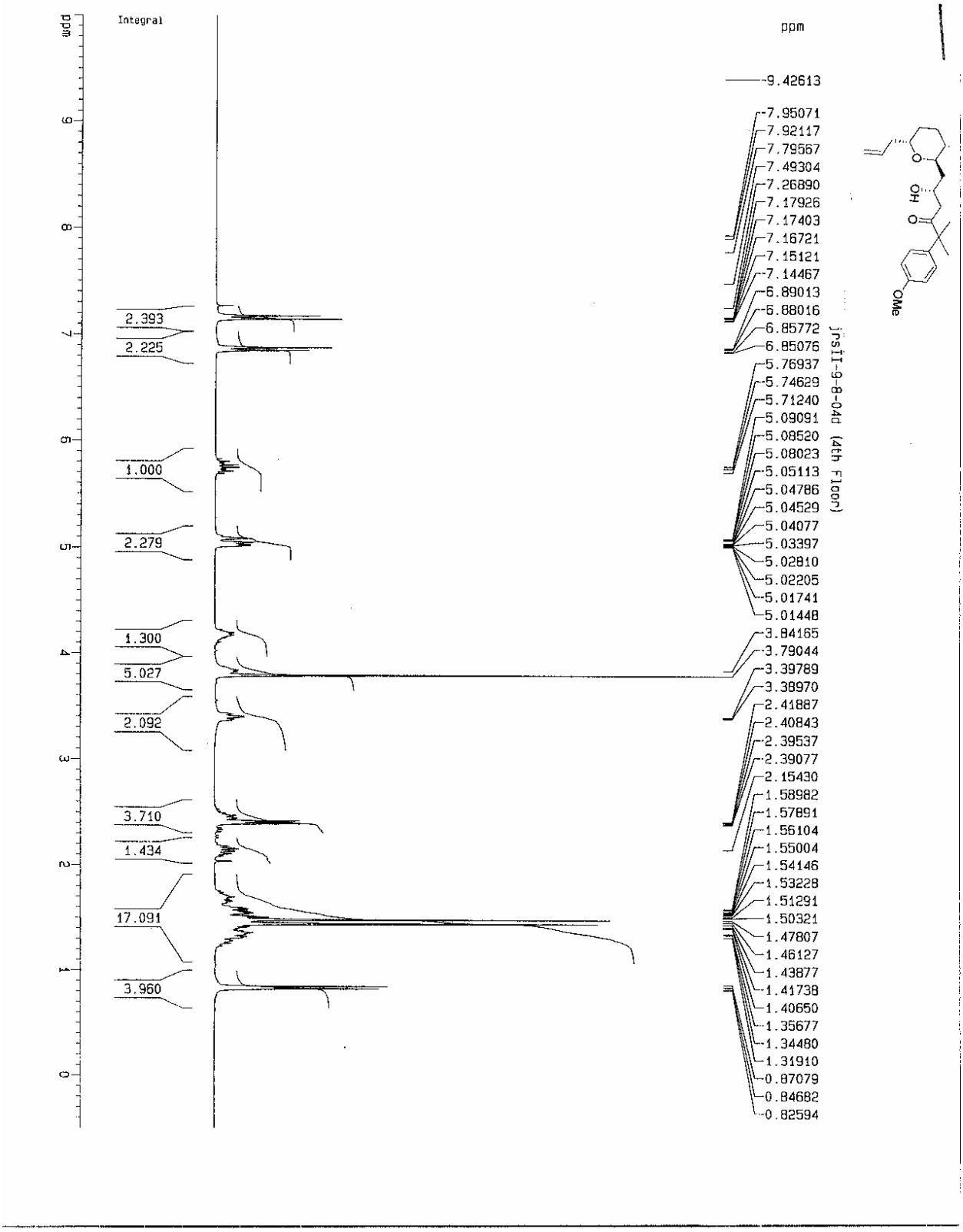
2.5414
2.5003
4.4763
1.6460
3.7492
4.6882
3.7042
6.9668
ppm
9.76082
9.75665
7.27044
5.82238
5.78860
5.76548
5.73166
5.11184
5.07316
5.06980
5.06665
3.92187
3.90278
3.85356
3.83877
3.50150
3.47816
2.55060
2.54657
2.53588
2.50699
2.11311
1.67407
1.46256
1.43753
1.21650
0.95504
0.94116
0.92013
0.88773
jrsII111105d (301)


ppm
Integral
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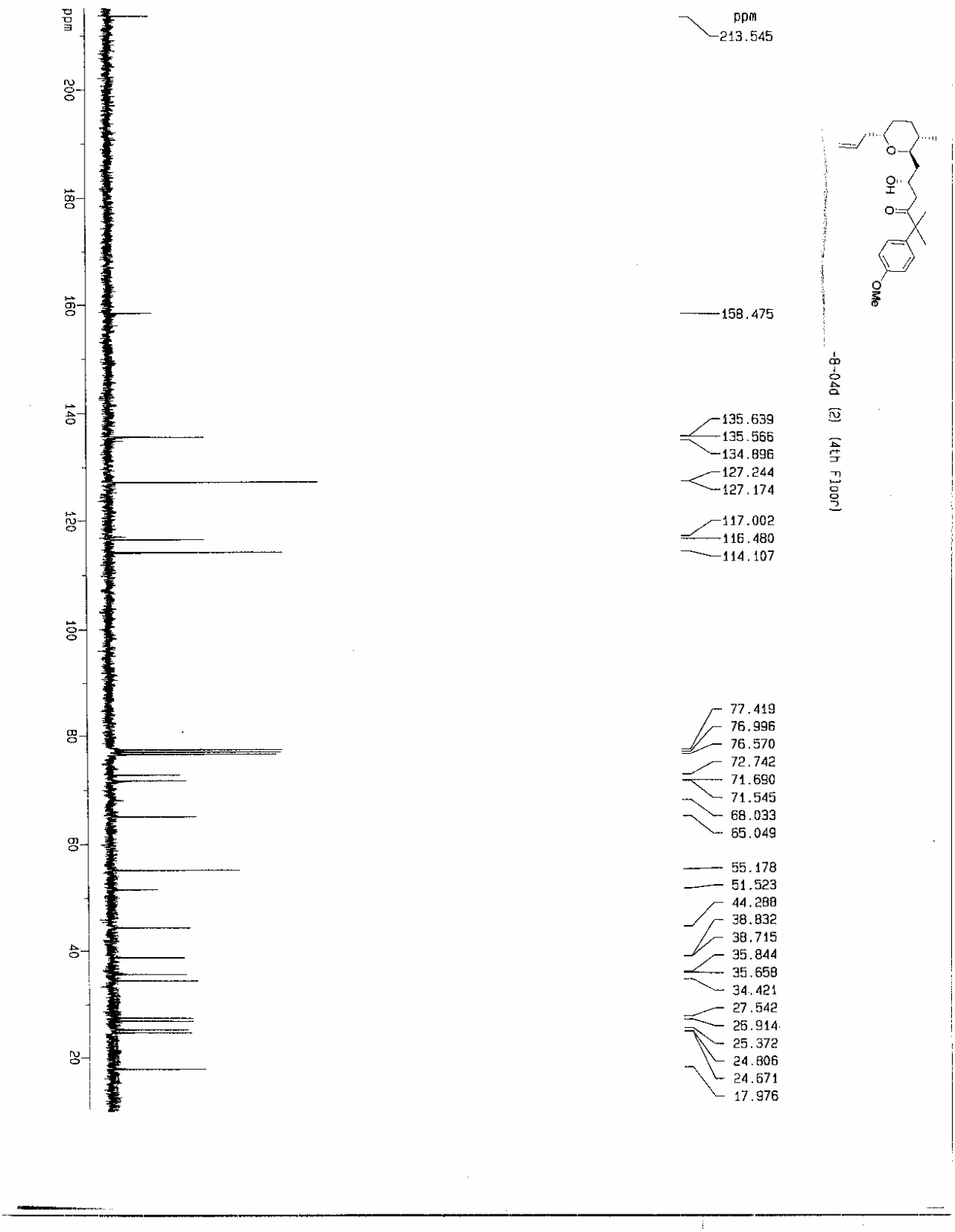
2.225
1.000
2.279
1.300
5.027
2.092
3.710
1.434
17.091
3.960
ppm
9.42613
7.95071
7.92117
7.79567
7.49304
7.26890
7.17926
7.17403
7.16721
7.15121
7.14467
6.89013
6.88016
6.85772
6.85076
5.76937
5.74629
5.71240
5.09091
5.08520
5.08023
5.05113
5.04786
5.04529
5.04077
5.03397
5.02810
5.02205
5.01741
5.01448
3.84165
3.79044
3.39789
3.38970
2.41887
2.40843
2.39537
2.39077
2.15430
1.58982
1.57891
1.56104
1.55004
1.54146
1.53228
1.51291
1.50321
1.47807
1.46127
1.43877
1.41738
1.40650
1.35677
1.34480
1.31910
0.87079
0.84682
0.82594
jrsII-9-8-04d (4th Floor)
OH
O
OMe


ppm
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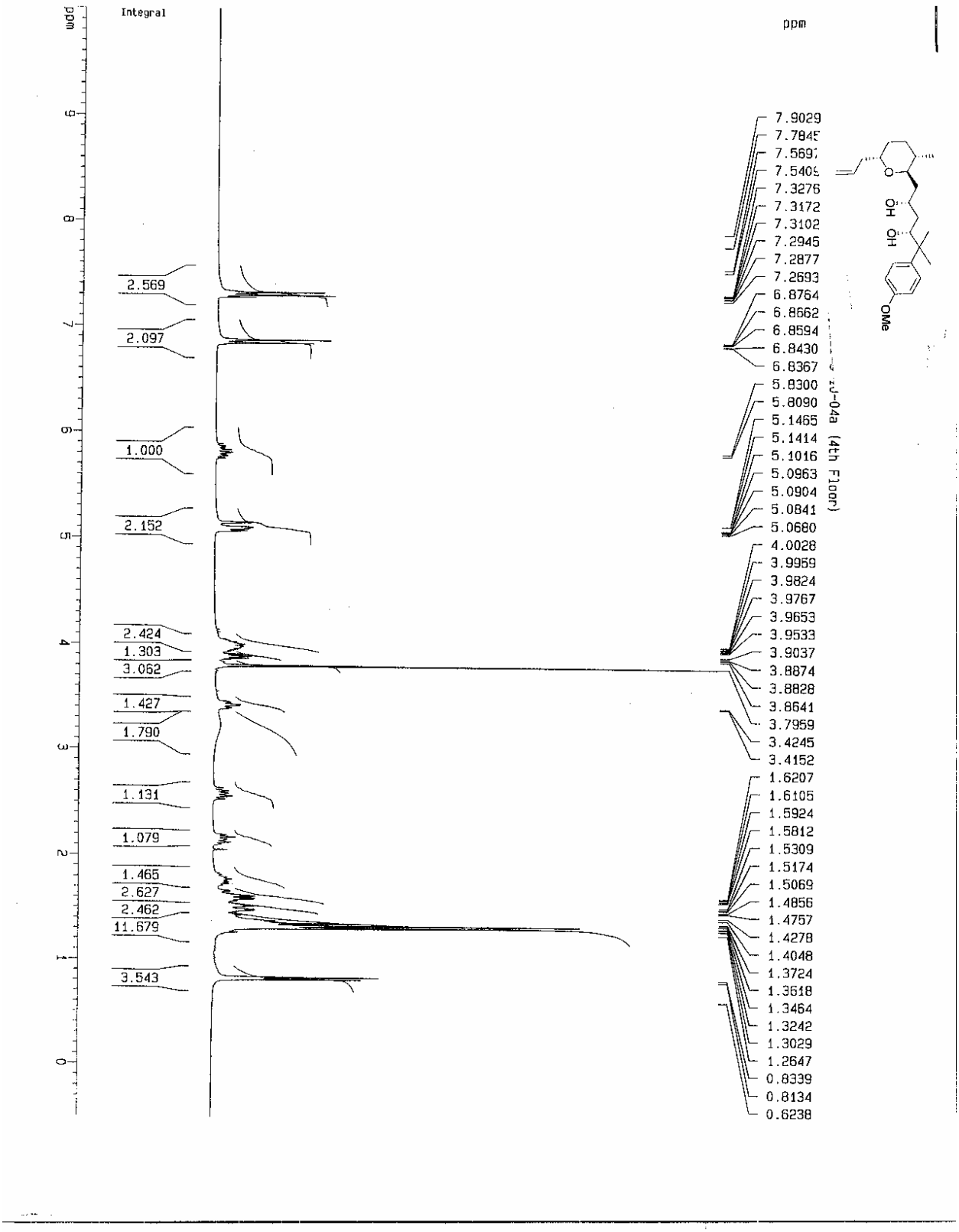
135.639
135.566
134.896
127.244
127.174
117.002
116.480
114.107
77.419
76.996
76.570
72.742
71.690
71.545
68.033
65.049
55.178
51.523
44.288
38.832
38.715
35.844
35.658
34.421
27.542
26.914
25.372
24.806
24.671
17.976
OH
O
OMe
-8-04d (2) (4th Floor)
ppm
200
180
160
140
120
100
80
60
40
20


Integral
ppm
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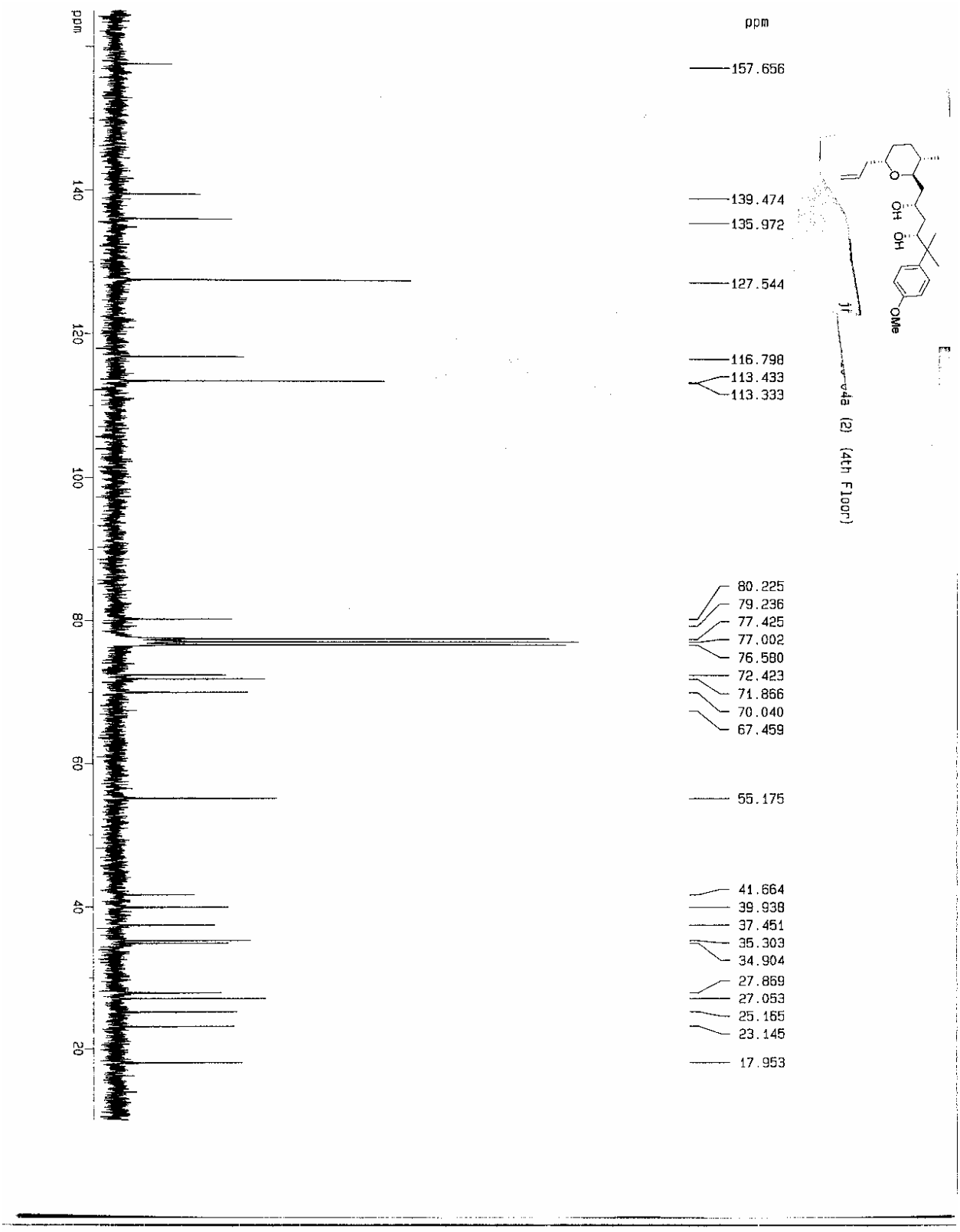
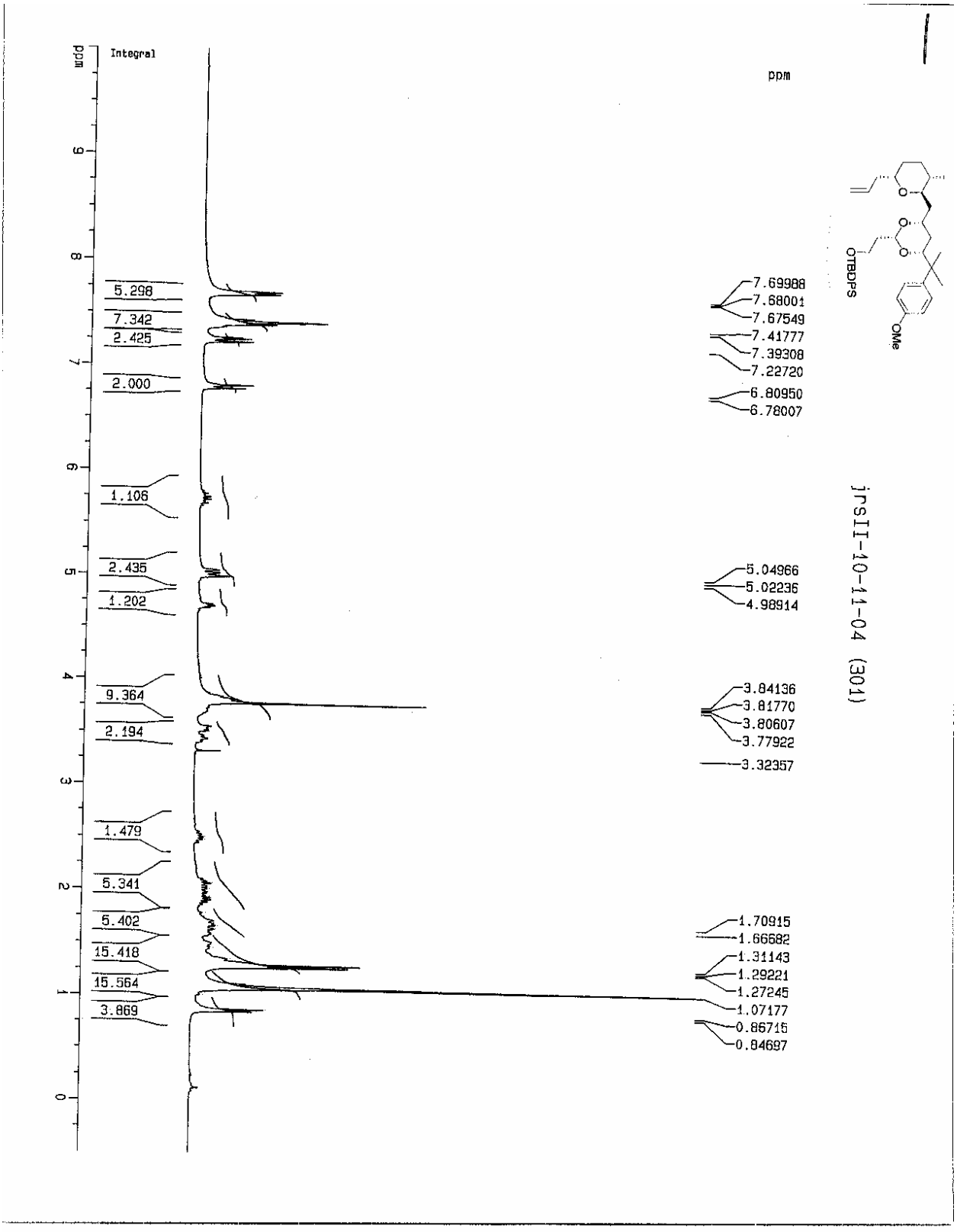
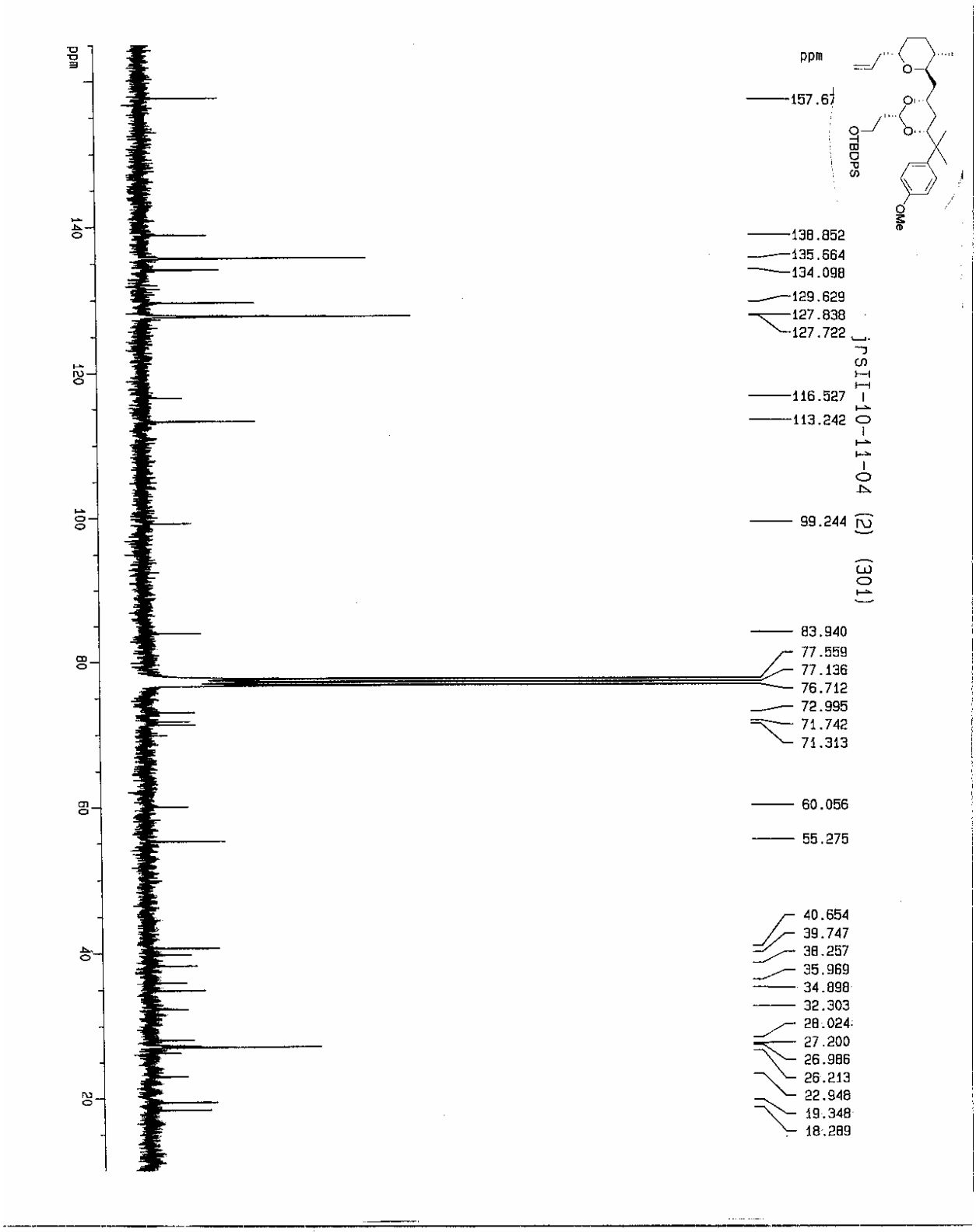
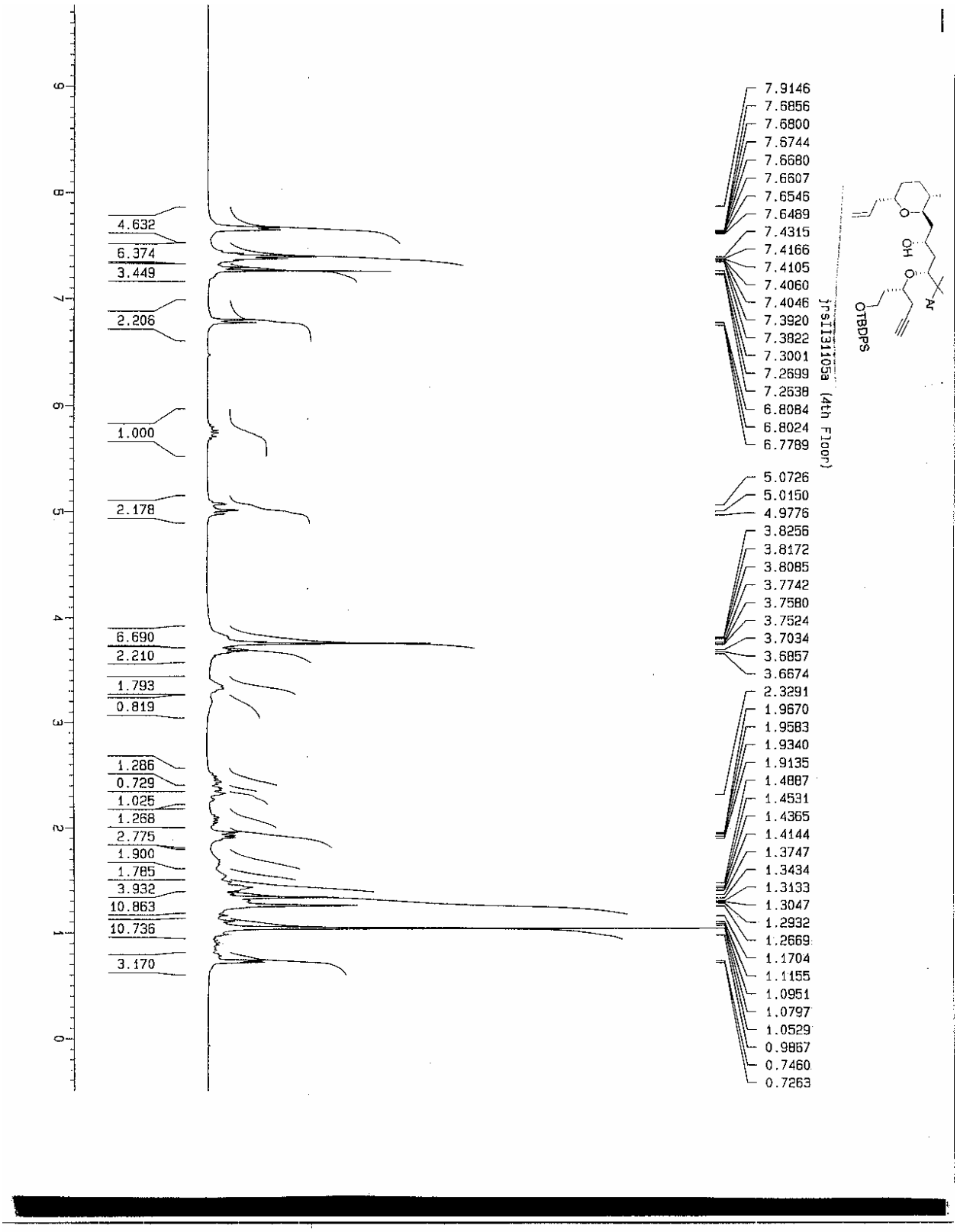
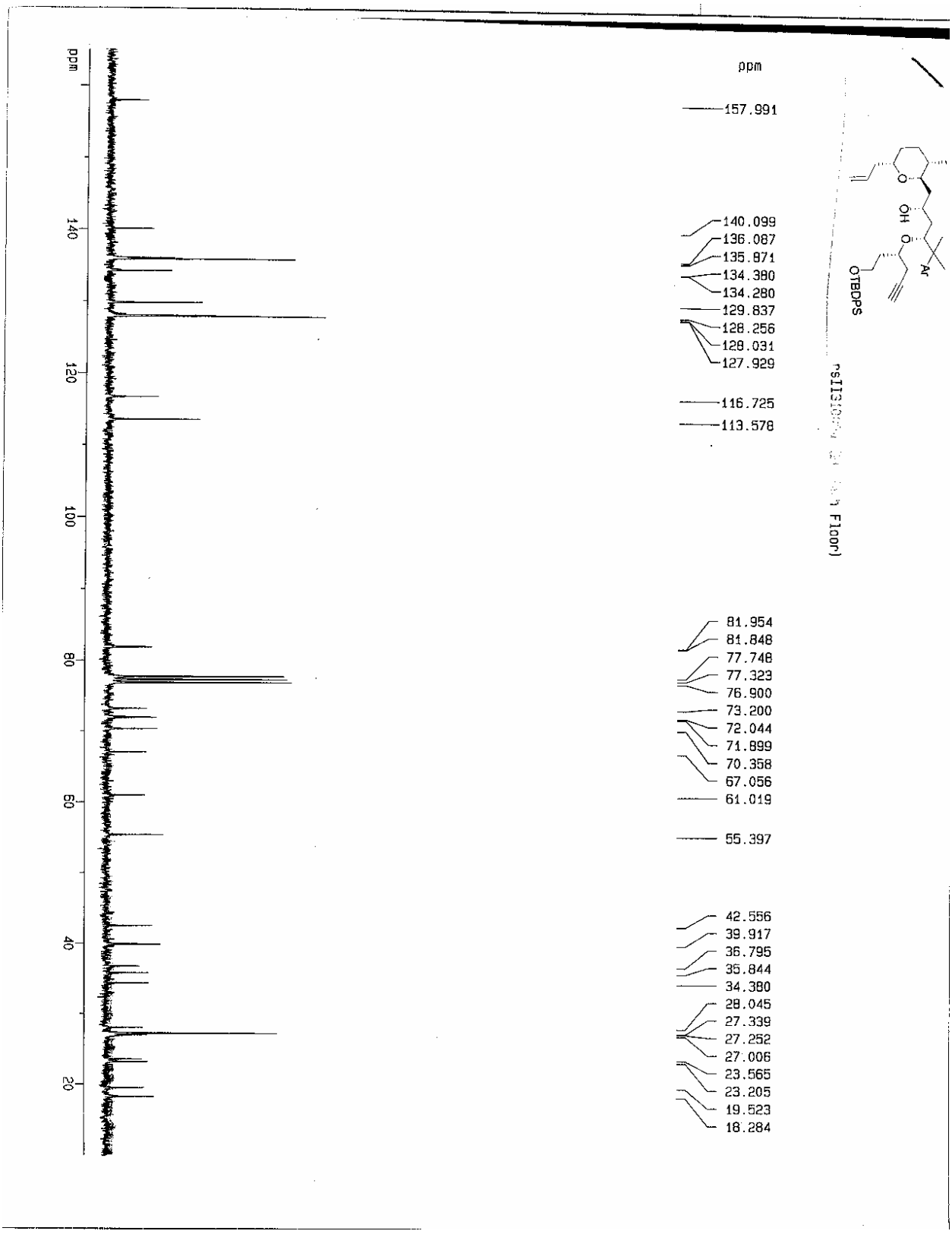
1.000
2.152
2.424
1.303
3.062
1.427
1.790
1.131
1.079
1.465
2.627
2.462
11.679
3.543
7.9029
7.7845
7.5697
7.5405
7.3276
7.3172
7.3102
7.2945
7.2877
7.2693
6.8764
6.8662
6.8594
6.8430
6.8367
5.8300
5.8090
5.1465
5.1414
5.1016
5.0963
5.0904
5.0841
5.0680
4.0028
3.9959
3.9824
3.9767
3.9653
3.9533
3.9037
3.8874
3.8828
3.8641
3.7959
3.4245
3.4152
1.6207
1.6105
1.5924
1.5812
1.5309
1.5174
1.5069
1.4856
1.4757
1.4278
1.4048
1.3724
1.3618
1.3464
1.3242
1.3029
1.2647
0.8339
0.8134
0.6238
OH
OH
OMe

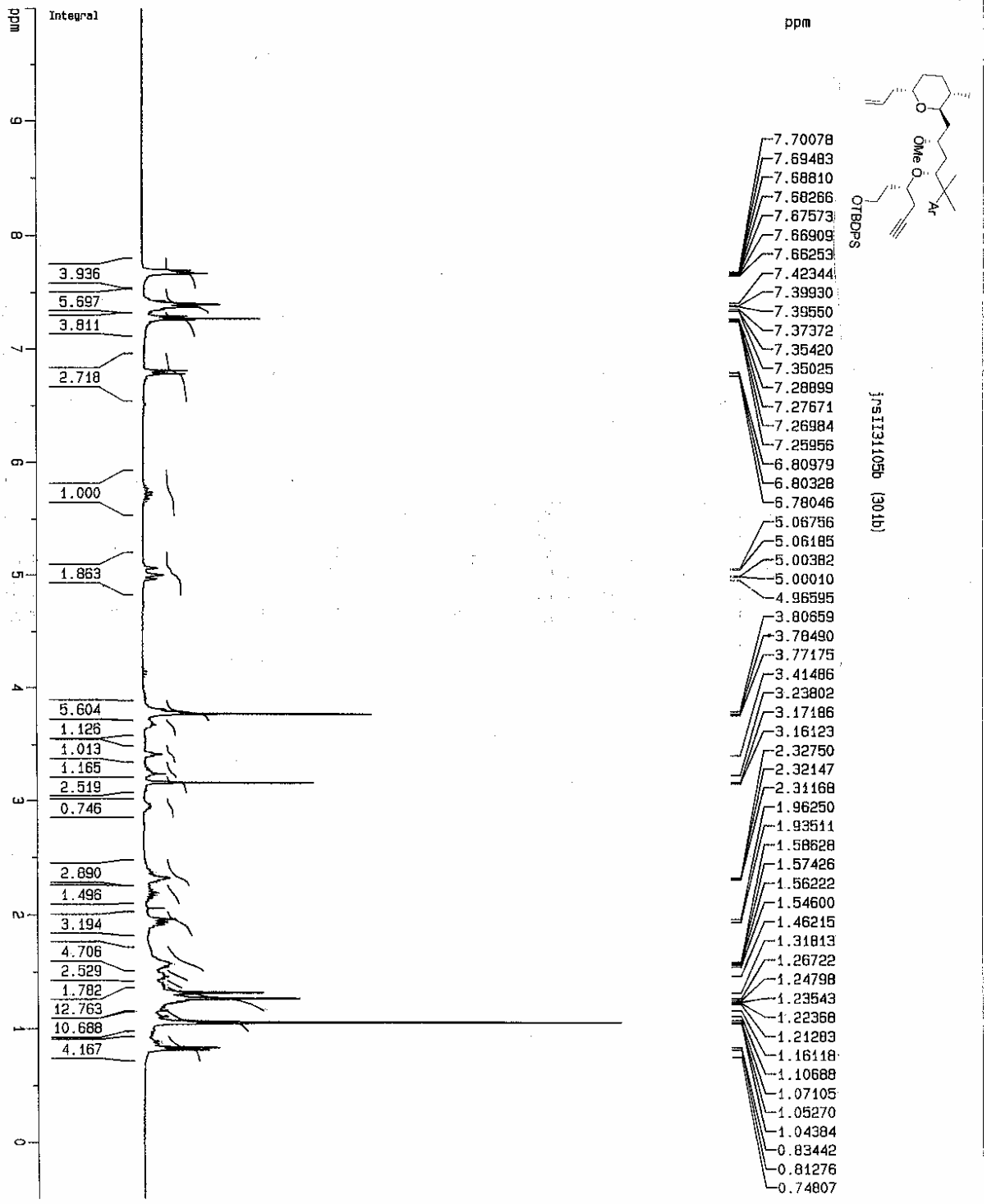

ppm
157.656
139.474
135.972
127.544
116.798
113.433
113.333
80.225
79.236
77.425
77.002
76.580
72.423
71.866
70.040
67.459
55.175
41.664
39.938
37.451
35.303
34.904
27.869
27.053
25.165
23.145
17.953
OH
OH
OMe
jf
c4a (2) (4th Floor)

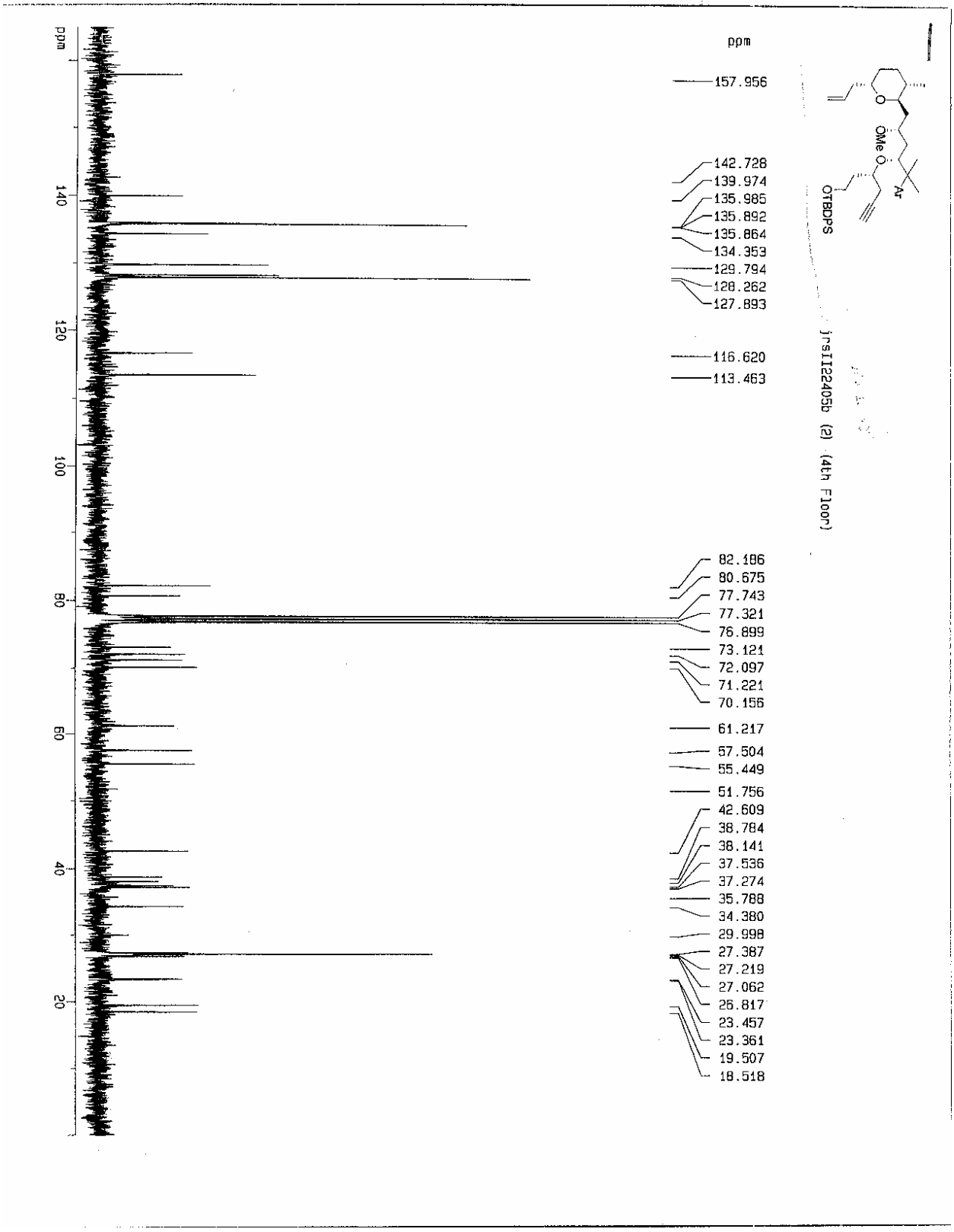

Integral
ppm
5.298
7.342
2.425
2.000
1.106
2.435
1.202
9.364
2.194
1.479
5.341
5.402
15.418
15.564
3.869
7.69988
7.68001
7.67549
7.41777
7.39308
7.22720
6.80950
6.78007
5.04966
5.02236
4.98914
3.84136
3.81770
3.80607
3.77922
3.32357
1.70915
1.66682
1.31143
1.29221
1.27245
1.07177
0.86715
0.84697
OTBDPS
OMe
jrsII-10-11-04 (301)


ppm
157.67
138.852
135.664
134.098
129.629
127.838
127.722
116.527
113.242
99.244
83.940
77.559
77.136
76.712
72.995
71.742
71.313
60.056
55.275
40.654
39.747
38.257
35.969
34.898
32.303
28.024
27.200
26.986
26.213
22.948
19.348
18.289
OTBDPS
OMe
jrsII-10-11-04 (2) (301)
ppm
140
120
100
80
60
40
20


4.632
6.374
3.449
2.206
1.000
2.178
6.690
2.210
1.793
0.819
1.286
0.729
1.025
1.268
2.775
1.900
1.785
3.932
10.863
10.736
3.170
7.9146
7.6856
7.6800
7.6744
7.6680
7.6607
7.6546
7.6489
7.4315
7.4166
7.4105
7.4060
7.4046
7.3920
7.3822
7.3001
7.2699
7.2638
6.8084
6.8024
6.7789
5.0726
5.0150
4.9776
3.8256
3.8172
3.8085
3.7742
3.7580
3.7524
3.7034
3.6857
3.6674
2.3291
1.9670
1.9583
1.9340
1.9135
1.4887
1.4531
1.4365
1.4144
1.3747
1.3434
1.3133
1.3047
1.2932
1.2669
1.1704
1.1155
1.0951
1.0797
1.0529
0.9867
0.7460
0.7263
jrs1131105a (4th Floor)
OH
OTBDPS
Ar


ppm
157.991
140.099
136.087
135.871
134.380
134.280
129.837
128.256
128.031
127.929
116.725
113.578
81.954
81.848
77.748
77.323
76.900
73.200
72.044
71.899
70.358
67.056
61.019
55.397
42.556
39.917
36.795
35.844
34.380
28.045
27.339
27.252
27.006
23.565
23.205
19.523
18.284
OH
OTBDPS
Ar
Floor)


ppm
Integral
3.936
5.697
3.811
2.718
1.000
1.863
5.604
1.126
1.013
1.165
2.519
0.746
2.890
1.496
3.194
4.706
2.529
1.782
12.763
10.688
4.167
ppm
7.70078
7.69483
7.68810
7.68266
7.67573
7.66909
7.66253
7.42344
7.39930
7.39550
7.37372
7.35420
7.35025
7.28899
7.27671
7.26984
7.25956
6.80979
6.80328
6.78046
5.06756
5.06185
5.00382
5.00010
4.96595
3.80659
3.78490
3.77175
3.41486
3.23802
3.17186
3.16123
2.32750
2.32147
2.31168
1.96250
1.93511
1.58628
1.57426
1.56222
1.54600
1.46215
1.31813
1.26722
1.24798
1.23543
1.22358
1.21283
1.16118
1.10688
1.07105
1.05270
1.04384
0.83442
0.81276
0.74807
OTBDPS
OMe
Ar
O
jrsII31105b (301b)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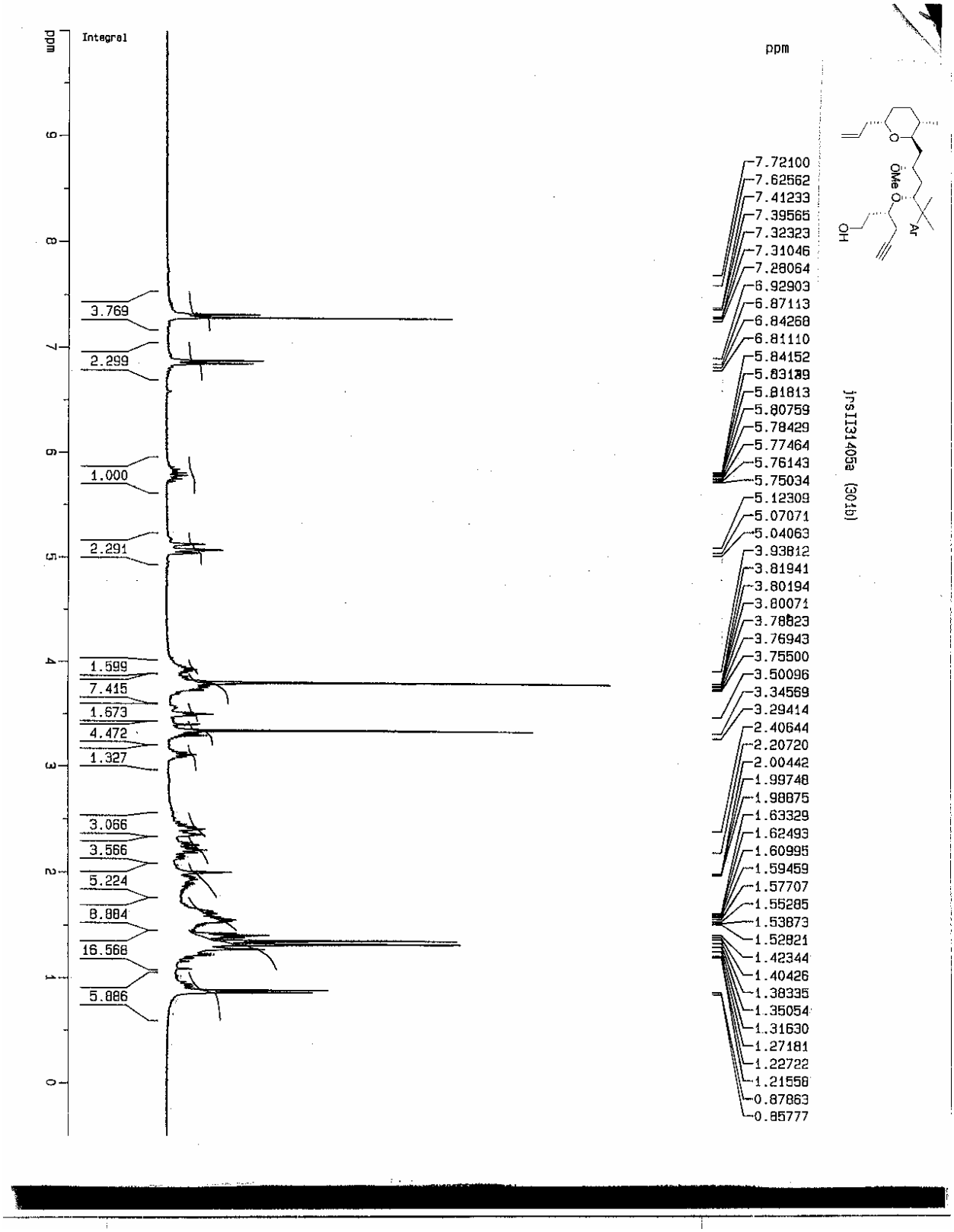
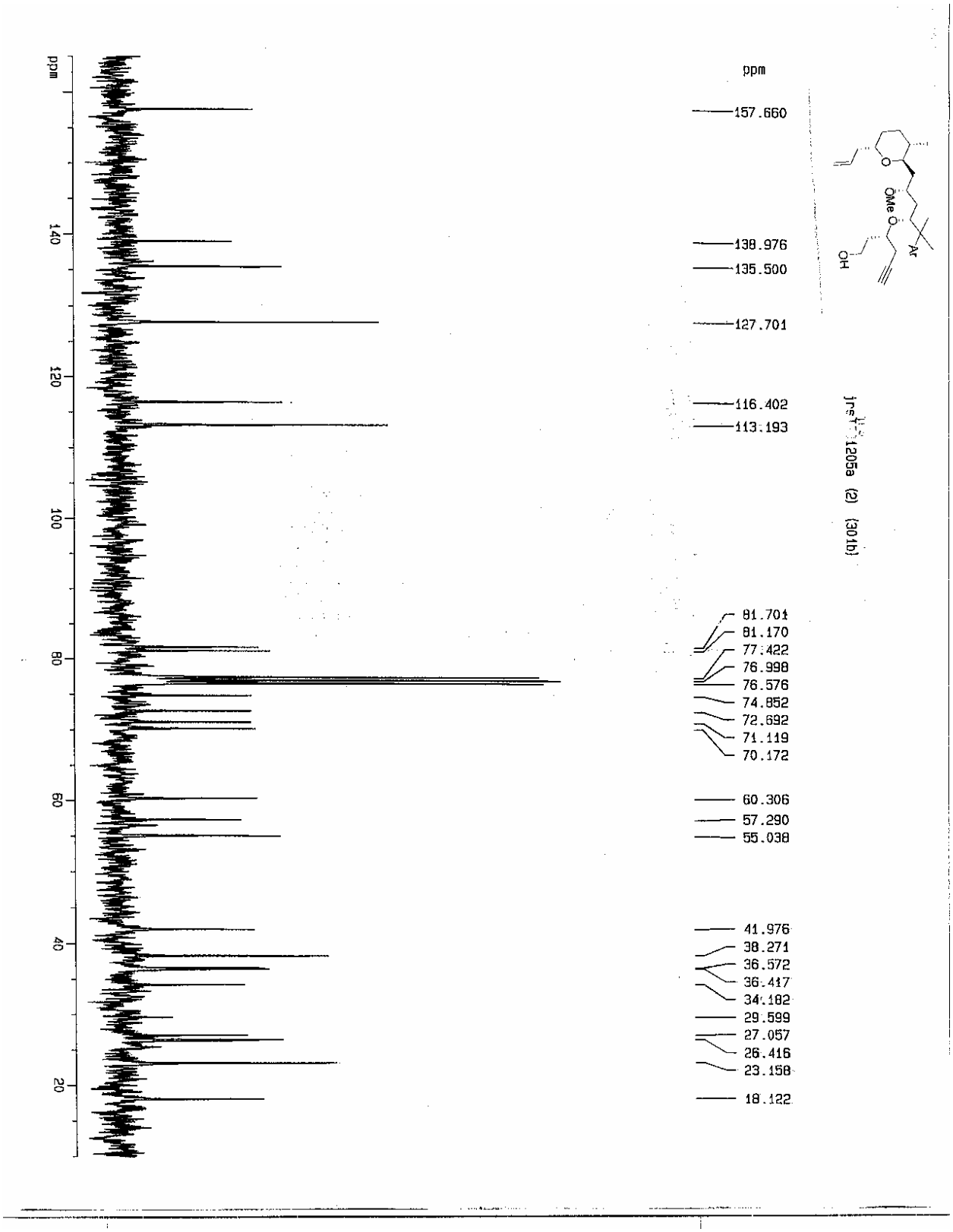
157.956
142.728
139.974
135.985
135.892
135.864
134.353
129.794
128.262
127.893
116.620
113.463
82.186
80.675
77.743
77.321
76.899
73.121
72.097
71.221
70.156
61.217
57.504
55.449
51.756
42.609
38.784
38.141
37.536
37.274
35.788
34.380
29.998
27.387
27.219
27.062
26.817
23.457
23.361
19.507
18.518
OMe
Ar
OTBDPS
jrsII22405b (2) (4th Floor)


Integral
ppm
3.769
2.299
1.000
2.291
1.599
7.415
1.673
4.472
1.327
3.066
3.566
5.224
8.884
16.568
5.886
ppm
7.72100
7.62562
7.41233
7.39565
7.32323
7.31046
7.28064
6.92903
6.87113
6.84268
6.81110
5.84152
5.83139
5.81813
5.80759
5.78429
5.77464
5.76143
5.75034
5.12309
5.07071
5.04063
3.93812
3.81941
3.80194
3.80071
3.78823
3.76943
3.75500
3.50096
3.34569
3.29414
2.40644
2.20720
2.00442
1.99748
1.98875
1.63329
1.62493
1.60995
1.59459
1.57707
1.55285
1.53873
1.52821
1.42344
1.40426
1.38335
1.35054
1.31630
1.27181
1.22722
1.21556
0.87863
0.85777
OMe
OH
Ar
jrsII31405a (30.1)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157.660
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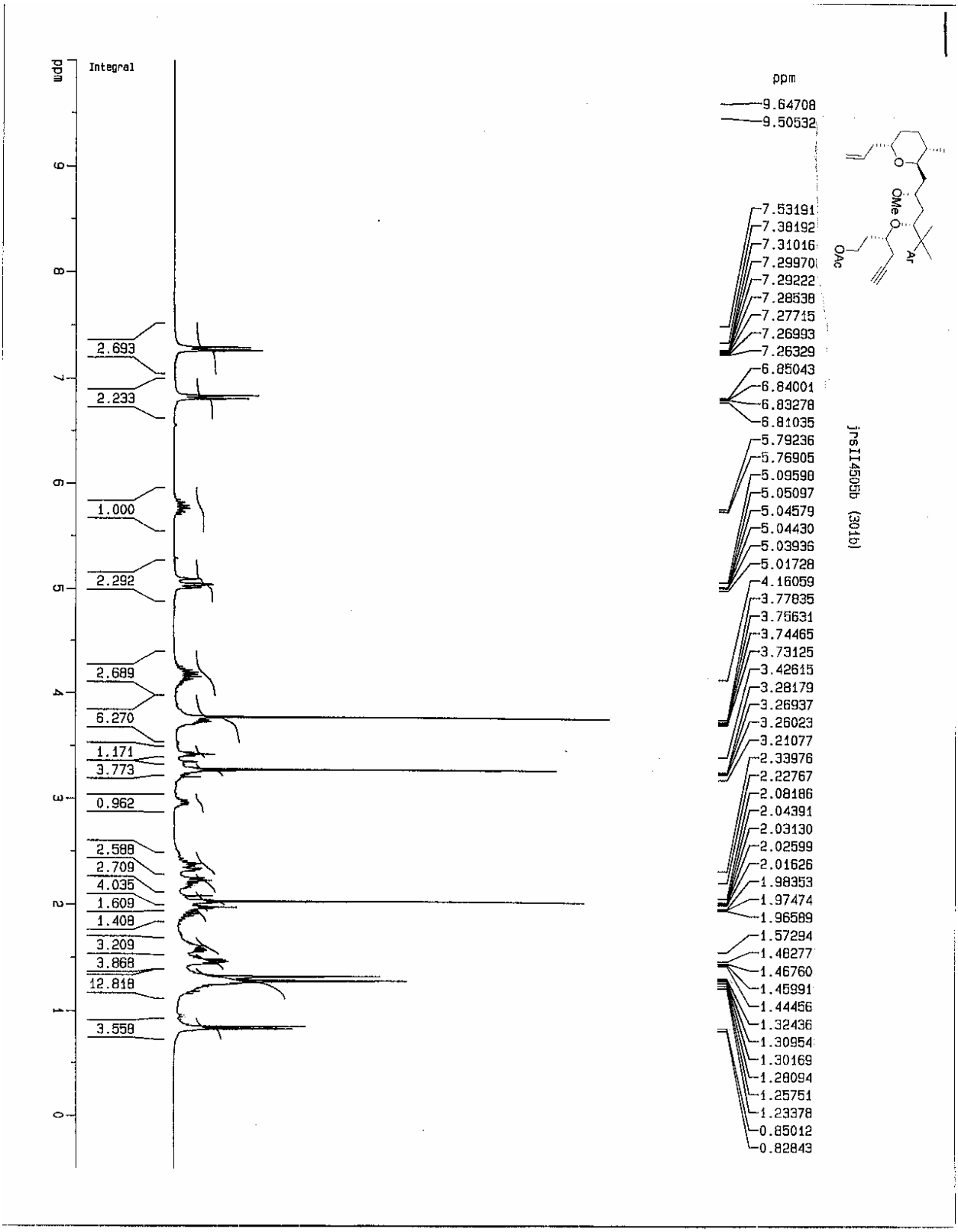
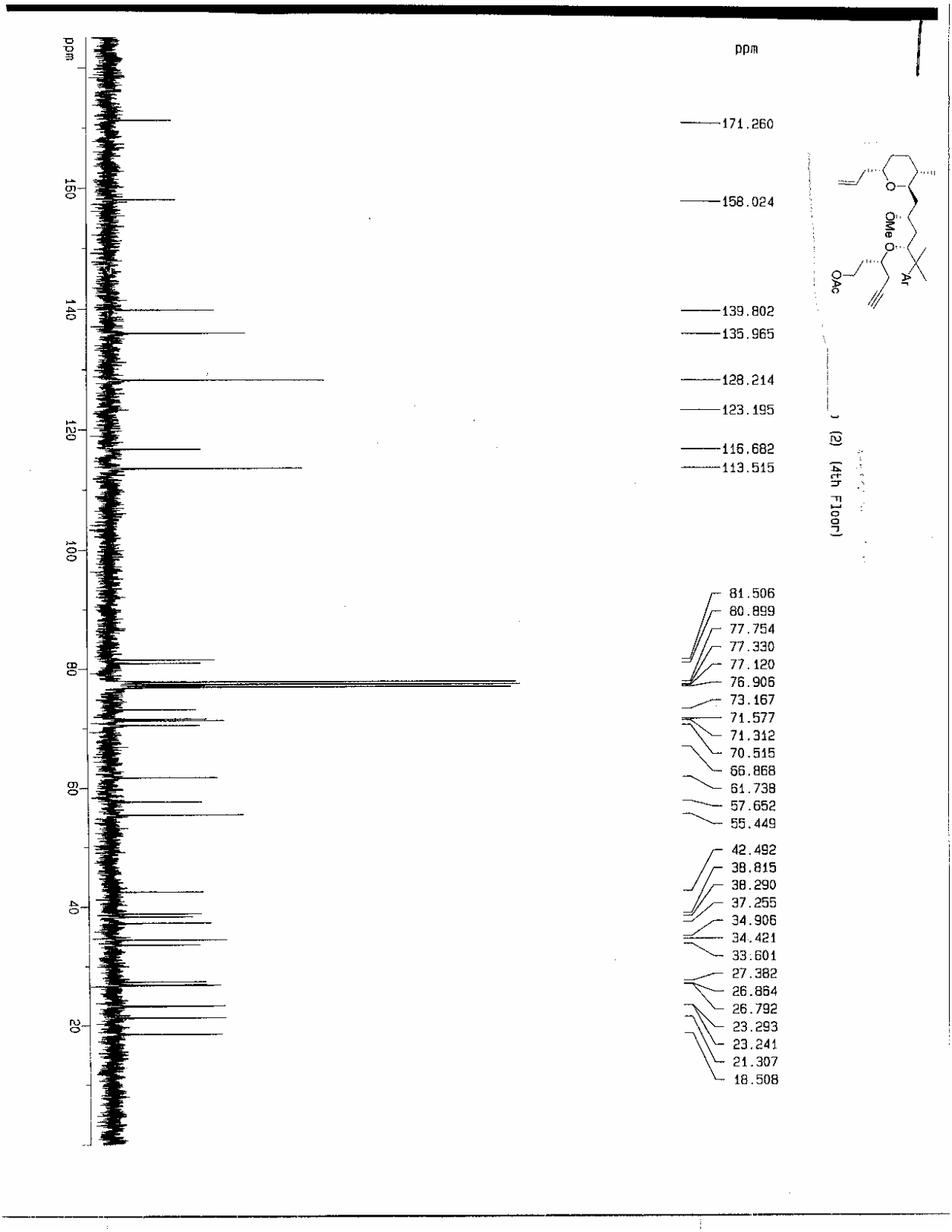
135.500
127.701
116.402
113.193
81.701
81.170
77.422
76.998
76.576
74.852
72.692
71.119
70.172
60.306
57.290
55.038
41.976
38.271
36.572
36.417
34.182
29.599
27.057
26.416
23.158
18.122
OMe
OH
Ar
jrs1205a (2) (301b)


ppm
Integral
2.693
2.233
1.000
2.292
2.689
6.270
1.171
3.773
0.962
2.588
2.709
4.035
1.609
1.408
3.209
3.868
12.818
3.558
ppm
9.64708
9.50532
7.53191
7.38192
7.31016
7.29970
7.29222
7.28538
7.27715
7.26993
7.26329
6.85043
6.84001
6.83278
6.81035
5.79236
5.76905
5.09598
5.05097
5.04579
5.04430
5.03936
5.01728
4.16059
3.77835
3.75631
3.74465
3.73125
3.42615
3.28179
3.26937
3.26023
3.21077
2.33976
2.22767
2.08186
2.04391
2.03130
2.02599
2.01626
1.98353
1.97474
1.96589
1.57294
1.48277
1.46760
1.45991
1.44456
1.32436
1.30954
1.30169
1.28094
1.25751
1.23378
0.85012
0.82843
OMe
OAc
Ar
jrsII4505b (301b)


ppm
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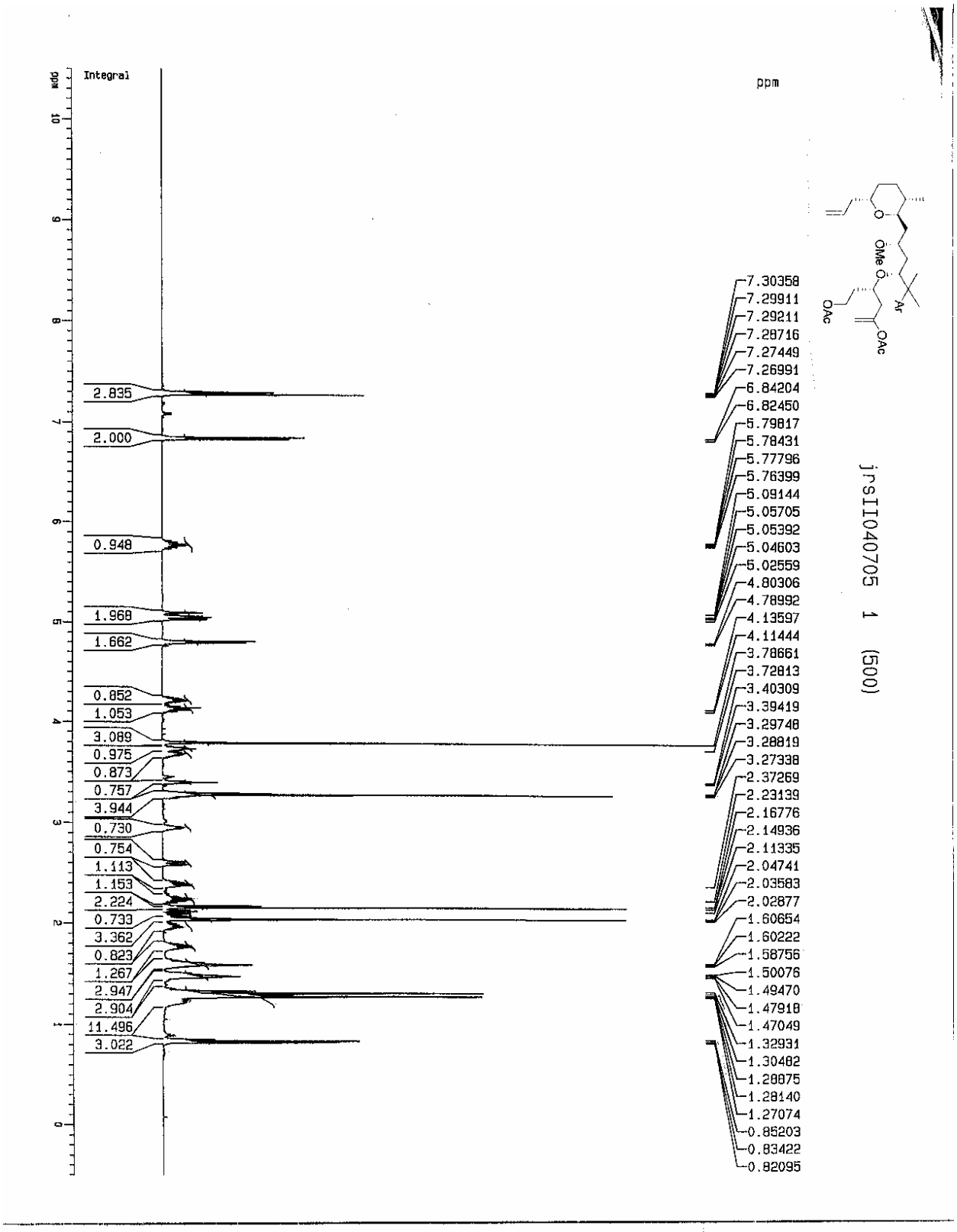
135.965
128.214
123.195
116.682
113.515
81.506
80.899
77.754
77.330
77.120
76.906
73.167
71.577
71.312
70.515
66.868
61.738
57.652
55.449
42.492
38.815
38.290
37.255
34.906
34.421
33.601
27.382
26.864
26.792
23.293
23.241
21.307
18.508
OMe
OAc
Ar
(2) (4th Floor)


Integral
ppm
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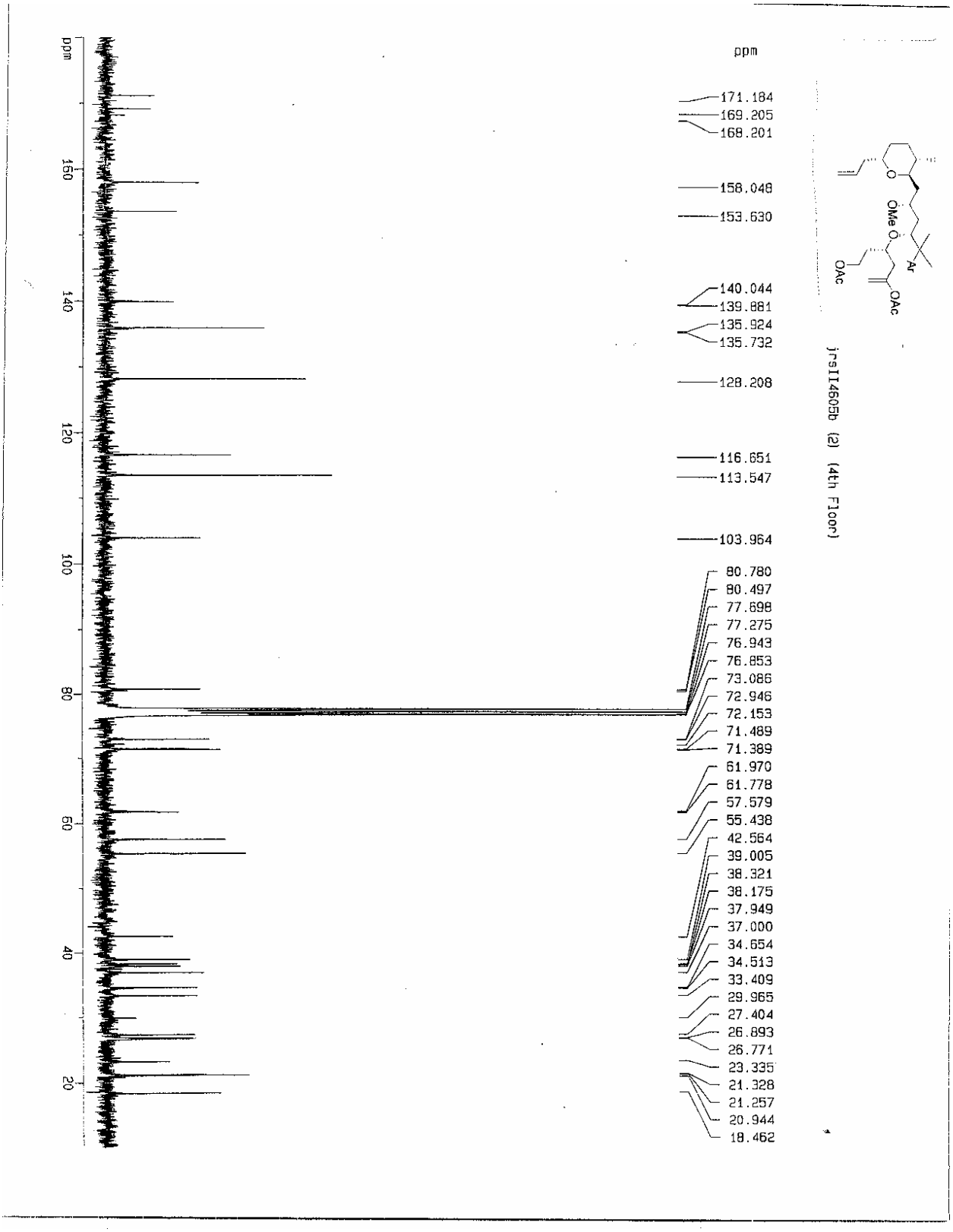
2.000
0.948
1.968
1.662
0.852
1.053
3.089
0.975
0.873
0.757
3.944
0.730
0.754
1.113
1.153
2.224
0.733
3.362
0.823
1.267
2.947
2.904
11.496
3.022
7.30358
7.29911
7.29211
7.28716
7.27449
7.26991
6.84204
6.82450
5.79817
5.78431
5.77796
5.76399
5.09144
5.05705
5.05392
5.04603
5.02559
4.80306
4.78992
4.13597
4.11444
3.78661
3.72813
3.40309
3.39419
3.29748
3.28819
3.27338
2.37269
2.23139
2.16776
2.14936
2.11335
2.04741
2.03583
2.02877
1.60654
1.60222
1.58756
1.50076
1.49470
1.47918
1.47049
1.32931
1.30482
1.28075
1.28140
1.27074
0.85203
0.83422
0.82095
OMe
OAc
Ar
OAc
jrsII040705 1 (500)


ppm
160
140
120
100
80
60
40
20
ppm
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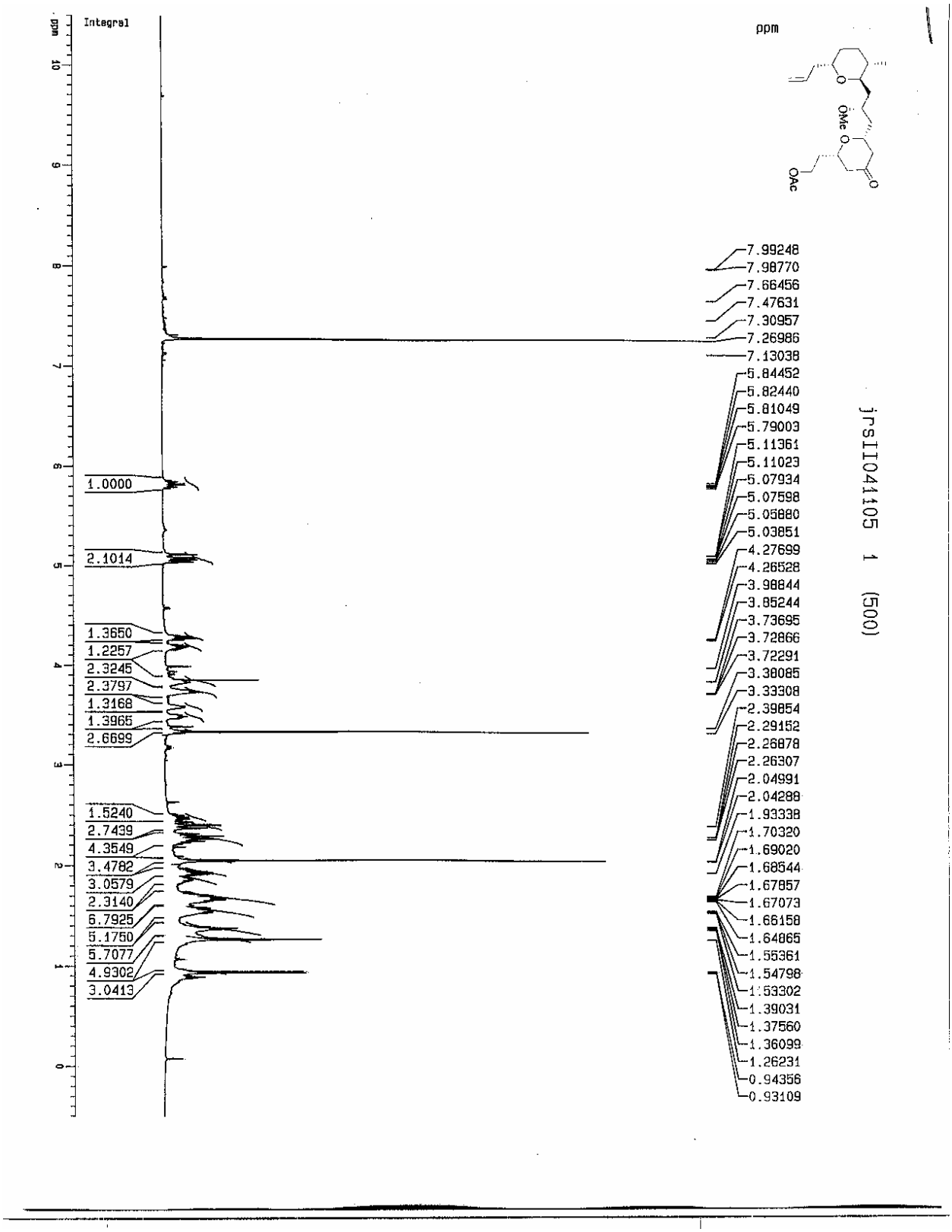
169.205
168.201
158.048
153.630
140.044
139.881
135.924
135.732
128.208
116.651
113.547
103.964
80.780
80.497
77.698
77.275
76.943
76.853
73.086
72.946
72.153
71.489
71.389
61.970
61.778
57.579
55.438
42.564
39.005
38.321
38.175
37.949
37.000
34.654
34.513
33.409
29.965
27.404
26.893
26.771
23.335
21.328
21.257
20.944
18.462
OMe
OAc
Ar
OAc
jrsII4605b (2) (4th Floor)


Integral
ppm
jrsII041105 1 (500)
OMe
OAc
7.99248
7.98770
7.66456
7.47631
7.30957
7.26986
7.13038
5.84452
5.82440
5.81049
5.79003
5.11361
5.11023
5.07934
5.07598
5.05880
5.03851
4.27699
4.26528
3.98844
3.85244
3.73695
3.72866
3.72291
3.38085
3.33308
2.39854
2.29152
2.26878
2.26307
2.04991
2.04288
1.93338
1.70320
1.69020
1.68544
1.67857
1.67073
1.66158
1.64865
1.55361
1.54798
1.53302
1.39031
1.37560
1.36099
1.26231
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0.93109
1.0000
2.1014
1.3650
1.2257
2.3245
2.3797
1.3168
1.3965
2.6699
1.5240
2.7439
4.3549
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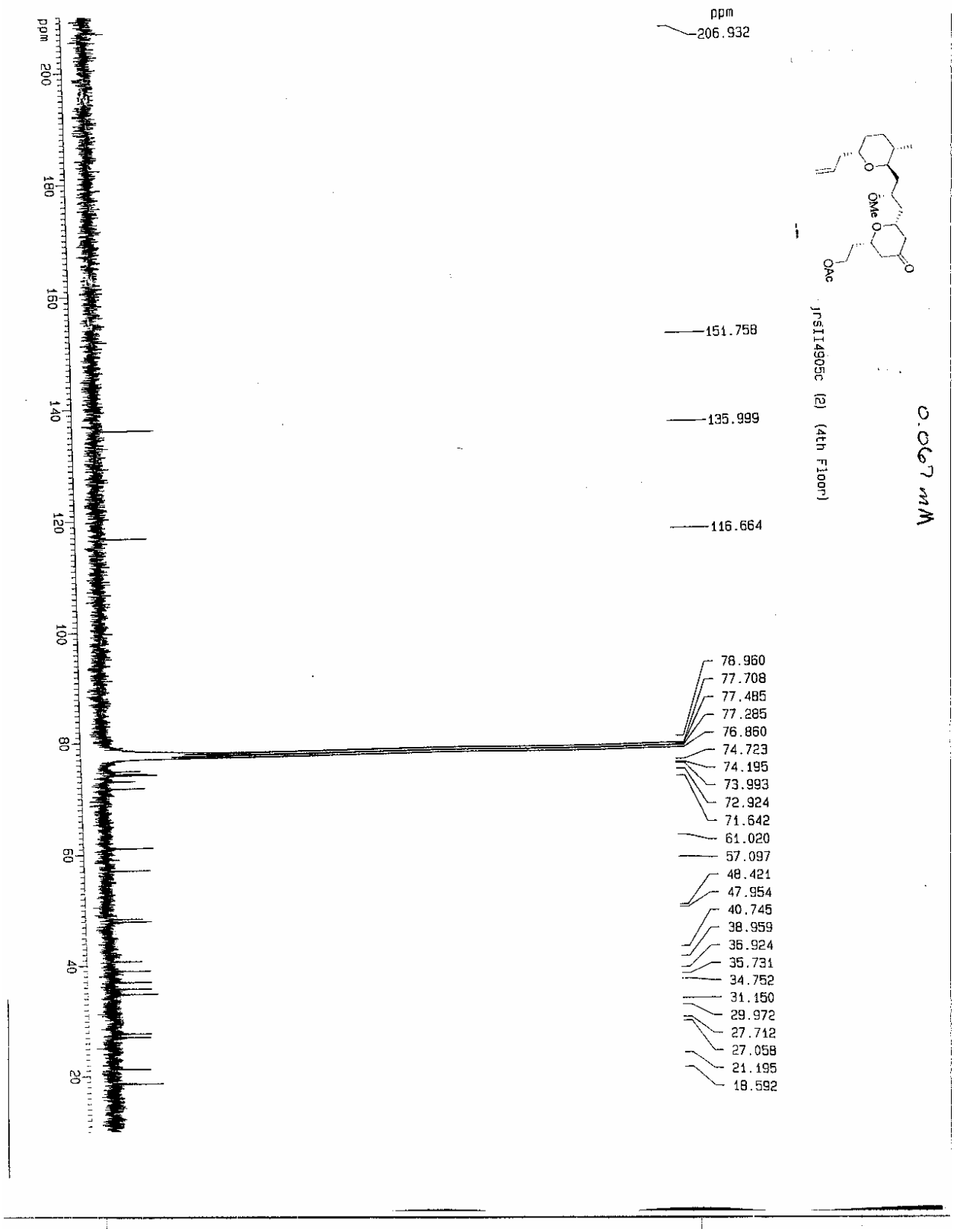
3.0579
2.3140
6.7925
5.1750
5.7077
4.9302
3.0413


ppm
206.932
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116.664
78.960
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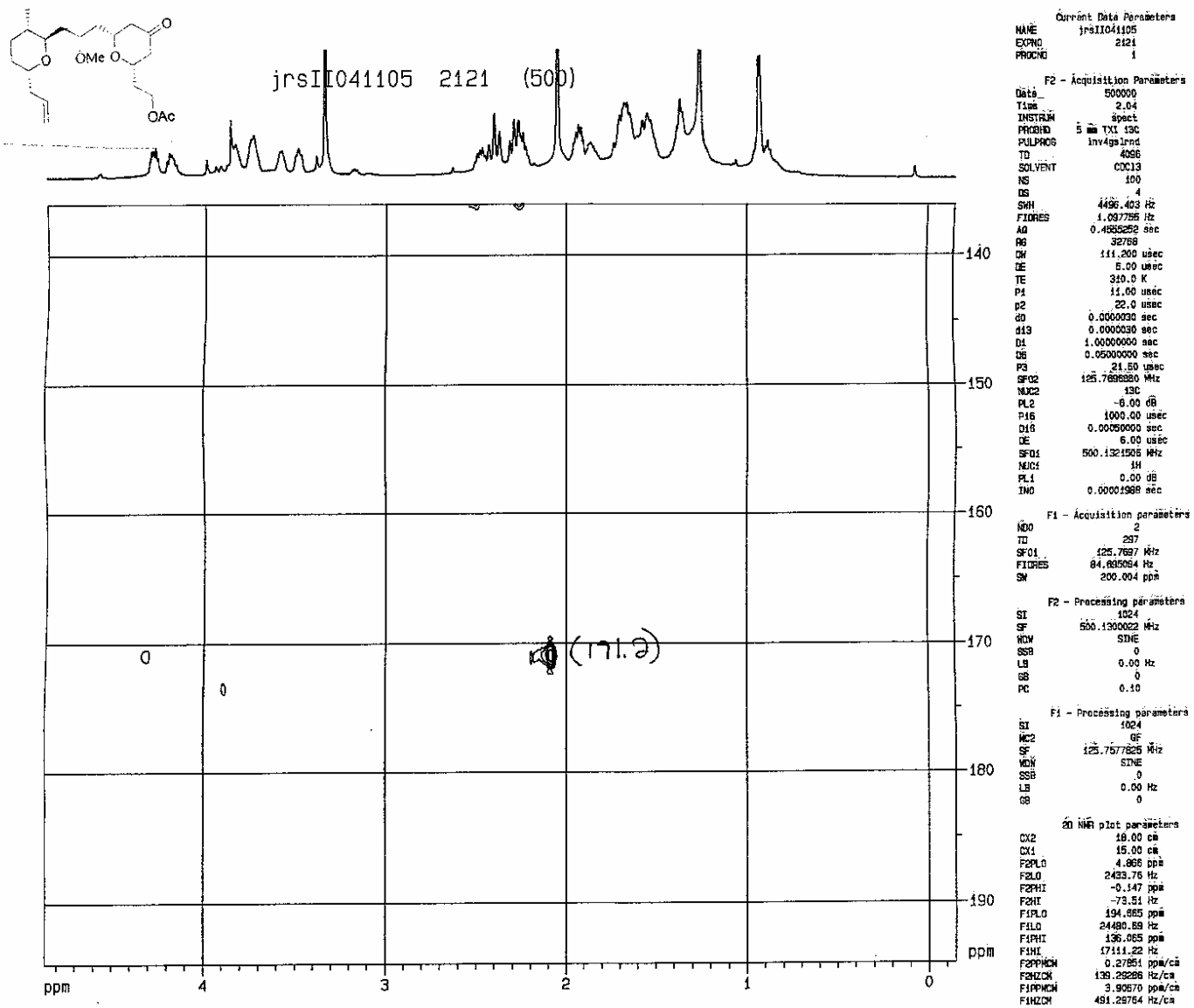
76.860
74.723
74.195
73.993
72.924
71.642
61.020
57.097
48.421
47.954
40.745
38.959
36.924
35.731
34.752
31.150
29.972
27.712
27.058
21.195
18.592
jrsI4905c (2) (4th Floor)
0.067 mM



Current Data Parameters

NAME	jrsII041105
EXPNO	2121
PROCNO	1

F2 - Acquisition Parameters

Date_	500000
Time	2.04
INSTRUM	spect
PROBHD	5 mm TXI 13C
PULPROG	inv4gslrnd
TD	4096
SOLVENT	CDCl3
NS	100
DS	4
SWH	4496.403 Hz
FIDRES	1.097755 Hz
AQ	0.4555252 sec
RG	32768
DW	111.200 usec
DE	6.00 usec
TE	310.0 K
P1	11.60 usec
p2	22.0 usec
d0	0.0000030 sec
d13	0.0000030 sec
D1	1.00000000 sec
D6	0.05000000 sec
P3	21.50 usec
SFO2	125.7698880 MHz
NUC2	13C
PL2	-6.00 dB
P16	1000.00 usec
D16	0.00050000 sec
DE	6.00 usec
SFO1	500.1321505 MHz
NUC1	1H
PL1	0.00 dB
IN0	0.00001988 sec

F1 - Acquisition parameters

NDO	2
TD	297
SFO1	125.7697 MHz
FIDRES	84.685064 Hz
SW	200.004 ppm

F2 - Processing parameters

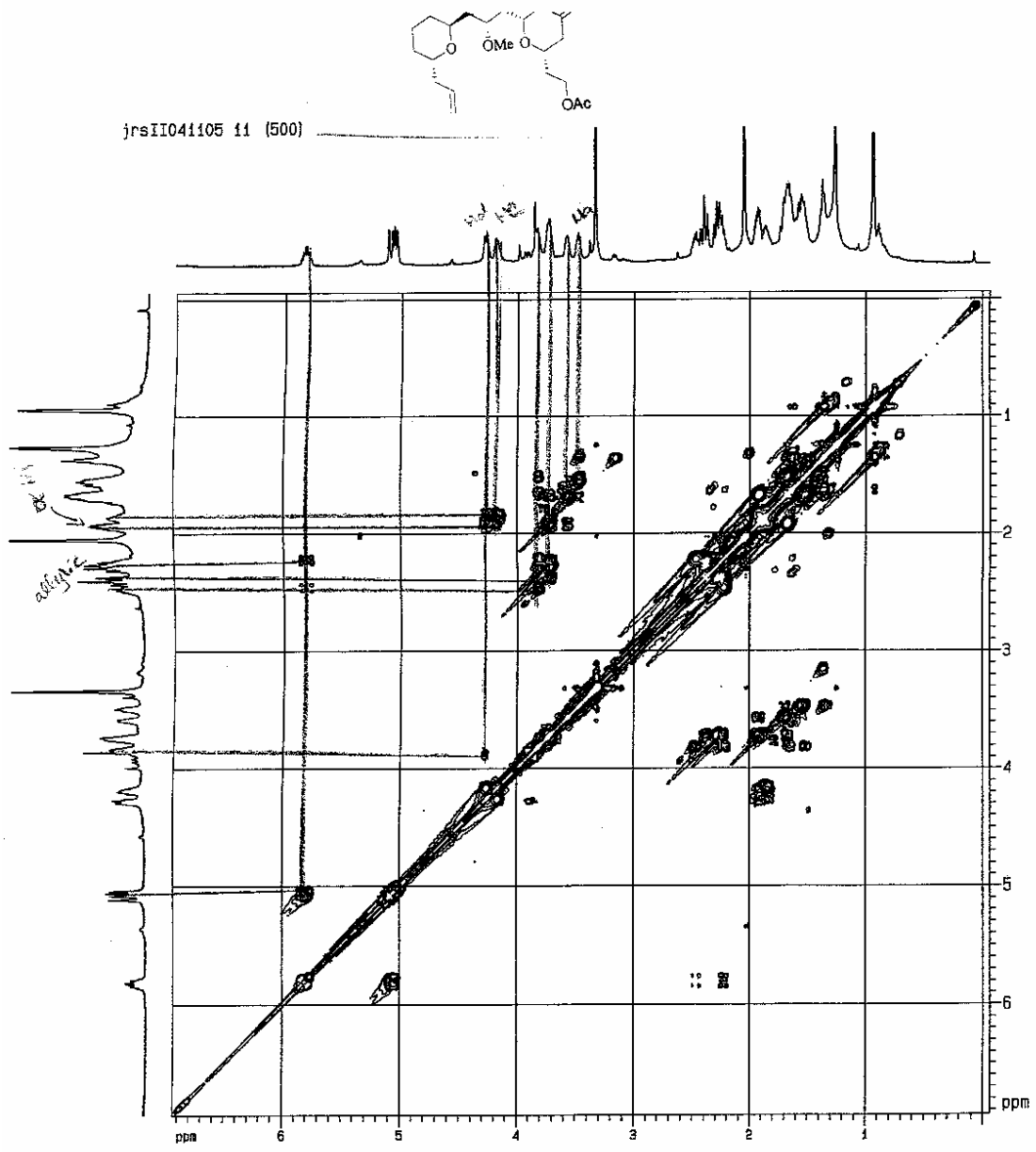
SI	1024
SF	500.1300022 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	0.10

F1 - Processing parameters

SI	1024
MC2	QF
SF	125.7577825 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	18.00 cm
CX1	15.00 cm
F2PLO	4.866 ppm
F2LO	2433.76 Hz
F2PHI	-0.147 ppm
F2HI	-73.51 Hz
F1PLO	194.665 ppm
F1LO	24480.69 Hz
F1PHI	136.065 ppm
F1HI	17111.22 Hz
F2PPMCM	0.27851 ppm/cm
F2HZCM	139.29286 Hz/cm
F1PPMCM	3.90570 ppm/cm
F1HZCM	491.29764 Hz/cm



Current Data Parameters

NAME	jrsII041105
EXPNO	11
PROCNO	1

F2 - Acquisition Parameters

Date_	500000
Time	16.20
INSTRUM	spect
PROBHD	5 mm TXI 13C
PULPROG	cosy
TD	1024
SOLVENT	CDCl3
NS	32
DS	8
SWH	2501.401 Hz
FIDRES	3.419337 Hz
AQ	0.1462772 sec
RG	287.4
DW	142.800 usec
DE	6.00 usec
TE	298.0 K
d0	0.00000030 sec
D1	1.00000000 sec
P1	10.60 usec
PO	10.60 usec
DE	6.00 usec
SFO1	500.1317505 MHz
NUC1	1H
PL1	0.00 dB
IN0	0.00028560 sec

F1 - Acquisition parameters

NDO	1
TD	256
SFO1	500.1319 MHz
FIDRES	13.677434 Hz
SW	7.001 ppm

F2 - Processing parameters

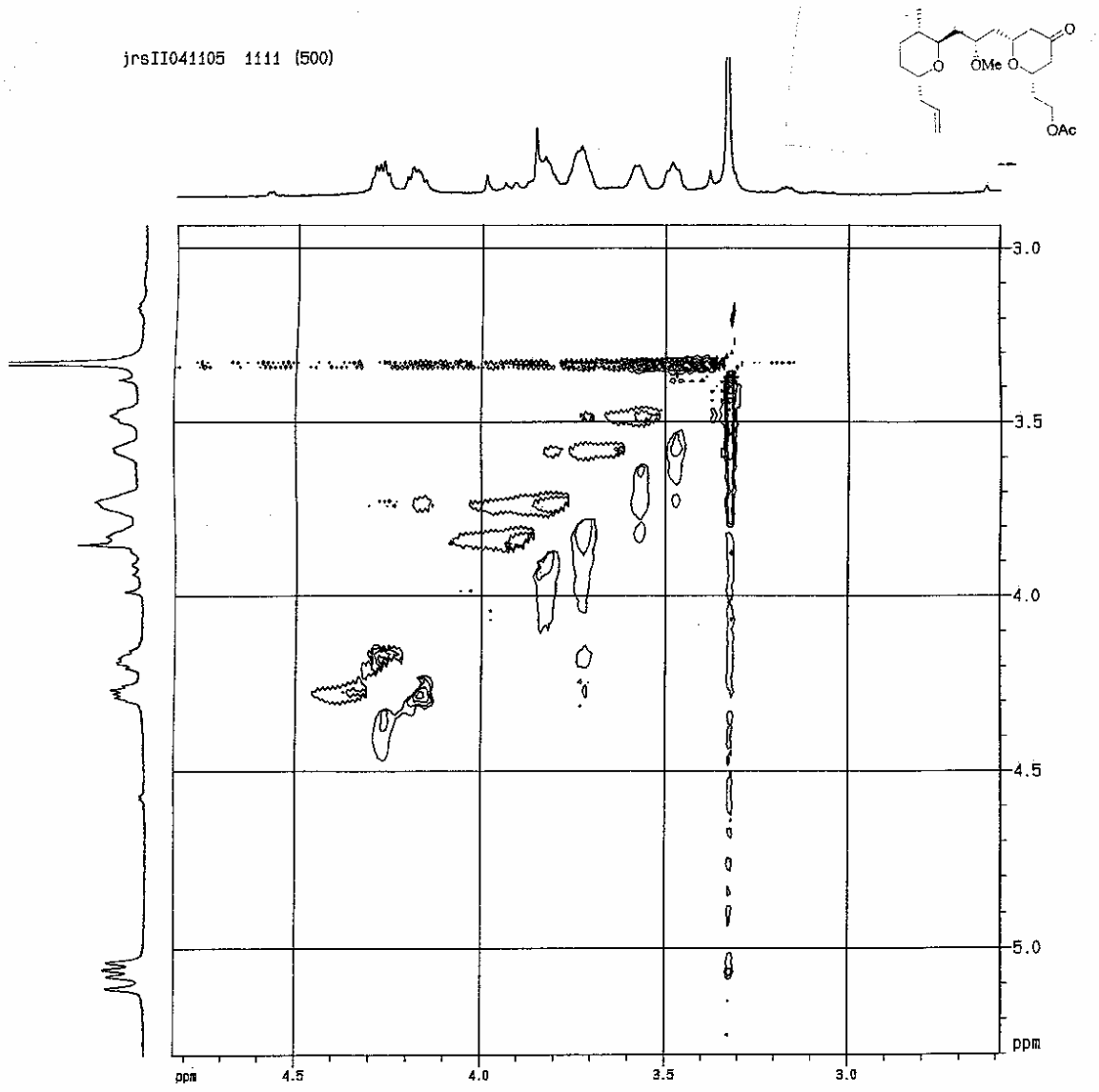
SI	512
SF	500.1300309 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	512
MC2	QF
SF	500.1301316 MHz
WDW	SINE
SSB	0
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	6.535 ppm
F2LO	3470.30 Hz
F2PHI	-0.052 ppm
F2HI	-24.10 Hz
F1PLO	6.537 ppm
F1LO	3469.52 Hz
F1PHI	-0.064 ppm
F1HI	-31.80 Hz
F2PPMCM	0.46673 ppm/cm
F2HZCM	233.42668 Hz/cm
F1PPMCM	0.46673 ppm/cm
F1HZCM	233.42819 Hz/cm



Current Data Parameters

NAME	jrsII041105
EXPNO	1111
PROCNO	1

F2 - Acquisition Parameters

Date_	500000
Time	19.03
INSTRUM	spect
PROBHD	5 mm TXI 13C
PULPROG	noesytp
TD	1024
SOLVENT	CDCl3
NS	32
DS	16
SWH	3501.401 Hz
FIDRES	3.419337 Hz
AQ	0.1462772 sec
RG	287.4
DW	142.800 usec
DE	6.00 usec
TE	290.0 K
d0	0.0000030 sec
D1	1.00000000 sec
P1	10.60 usec
DB	0.34999999 sec
DE	6.00 usec
SFO1	500.1317505 MHz
NUC1	1H
PL1	0.00 dB
IN0	0.00014280 sec

F1 - Acquisition parameters

ND0	2
TD	512
SFO1	500.1318 MHz
FIDRES	6.838719 Hz
SW	7.001 ppm

F2 - Processing parameters

SI	1024
SF	500.1300286 MHz
WDW	SINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	512
MC2	TPPI
SF	500.1300230 MHz
WDW	SINE
SSB	2
LB	0.00 Hz
GB	0

2D NMR plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	4.831 ppm
F2LO	2415.99 Hz
F2PHI	2.588 ppm
F2HI	1294.44 Hz
F1PLO	5.300 ppm
F1LO	2650.69 Hz
F1PHI	2.934 ppm
F1HI	1467.80 Hz
F2PPMCM	0.14950 ppm/cm
F2HZCM	74.76949 Hz/cm
F1PPMCM	0.15771 ppm/cm
F1HZCM	78.87323 Hz/cm