The Development of an Electron Transfer Initiated Cyclization Approach Toward the Total Synthesis of Mycalamide B. The Synthesis of the N_7-C_{25} Fragment of Psymberin

by

Jason Christopher Rech

B.S., Allegheny College, 2000

Submitted to the Graduate Faculty of

Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Philosophy

University of Pittsburgh

2005

UNIVERSITY OF PITTSBURGH

FACULTY OF ARTS AND SCIENCES

This dissertation was presented

by

Jason Christopher Rech

It was defended on

November 2, 2005

and approved by

Prof. Peter Wipf

Prof. Kazinori Koide

Prof. Jeff Hildebrand

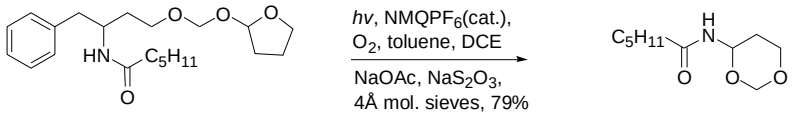
Prof. Paul E. Floreancig
Dissertation Director

The Development of an Electron Transfer Initiated Cyclization Approach Toward the Total Synthesis of Mycalamide B. The Synthesis of the N_7-C_{25} Fragment of Psymberin

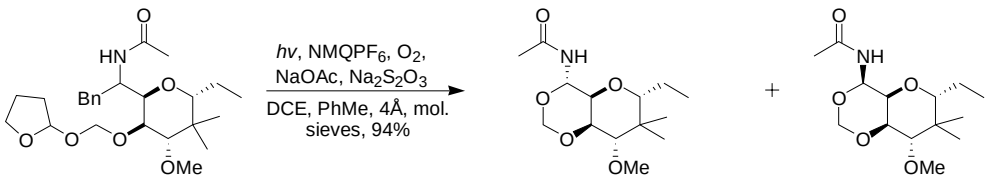
Jason Christopher Rech, PhD

University of Pittsburgh, 2005

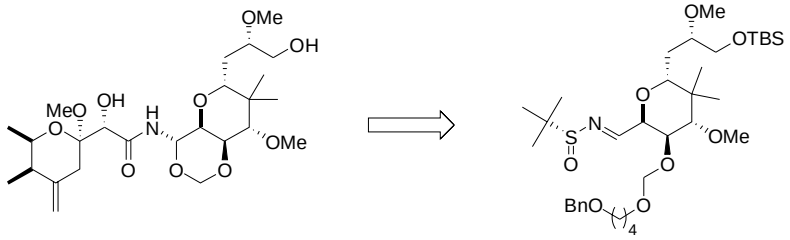
The electron transfer initiated cyclization (ETIC) has been shown to be an efficient method for the generation of cyclic amido acetals. The tetrahydrofuranyloxy methyl ether was shown to be a stable nucleophilic hemiacetal surrogate allowing for the incorporation of a formaldehyde equivalent in the ETIC reaction.



The ETIC reaction was employed in the stereoselective synthesis of amido trioxadecalin systems relevant to the synthesis of the mycalamides, onnamides and theopederins. The stereoselectivity resulting from these cyclizations was controlled by the substituents of the tetrahydropyran ring and the conformational bias of the developing trioxadecalin system. The epimerization of the *N*-acylaminal center of the amido trioxadecalin system was possible under mildly acidic conditions.

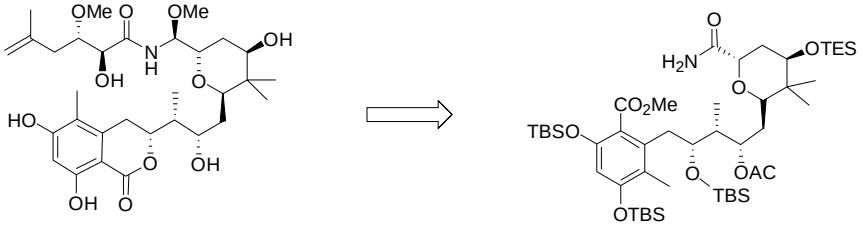


An efficient and stereoselective synthetic route has been developed that intends to employ the ETIC reaction to selectively generate the *N*-acylaminal of mycalamide B. A linear approach to the generation of the right half of mycalamide B has been applied allowing for expedient access to the dimethyl tetrahydropyran core. The synthetic sequence employs an asymmetric Leighton allylation, selective boron mediated aldol, 1,3-*syn*-reduction, and selective epoxidation and *syn*-vinylation to establish the stereochemistry of the right hand fragment of mycalamide B.



Mycalamide B

The stereoselective synthesis of the N_7-C_{24} fragment of psymberin was developed. The synthesis is highlighted by the de novo generation of the C_{25}-C_{17} pentasubstituted arene that allows for the expedient generation of multigram quantities of this intermediate. The stereochemistry of this fragment was established by an asymmetric Brown crotylation and Leighton allylation, selective Mukaiyama aldol addition, 1,3-*syn*-reduction, and a selective Lewis acid catalyzed TMSCN displacement of an acyl lactol.



Psymberin

TABLE OF CONTENTS

PREFACE xi
1. The Development of the Electron Transfer Initiated Cyclization for Application in the Synthesis of Amido Trioxadecalin Systems 1
1.1 Introduction 1
I. General 1
II. The Radical Cation 2
III. Carbon-Carbon σ-Bond Activation 4
IV. The Electron Transfer Initiated Cyclization (ETIC) 7
V. Project Goals and Objectives 11
1.2 Results and Discussion 12
I. Synthesis and Evaluation of the Hemiacetal Nucleophile 13
II. Synthesis of Formaldehyde Hemiacetal Surrogates 15
III. Formaldehyde Hemiacetal Surrogates in the ETIC Reaction 17
1.3 Conclusions 20
1.4 Experimentals 21
1.5 References 31
2. Efforts Toward the Total Synthesis of Mycalamide B 35
2.1 Introduction 35
I. Isolation and Structural Determination of Mycalamide A and B 36
II. Biological Activity 38
III. Structure Activity Relationships of Mycalamides A and B 40
IV. Previous Syntheses 40
V. Project Goals and Retosynthesis 49
2.2 Results and Discussion 51
I. Synthesis of ETIC Substrates: Model Systems for Mycalamide B 51
II. Generation of the Amido Trioxadecalin System by the ETIC Reaction 56
III. Synthetic Efforts Toward Mycalamide B 62
2.3 Conclusions 68
2.4 Experimentals 69
2.5 References 99
3. Synthesis of the N_7-C_{25} Fragment of Psymberin 111
3.1 Introduction 111
I. Isolation and Structural Determination 112
II. Biological Activity 116
III. The First Total Synthesis of Psymberin 117
IV. Retrosynthesis 120
3.2 Results and Discussion 122
3.3 Conclusions 130
3.4 Experimentals 131
3.5 References 146
APPENDIX A 149

The Development of the Electron Transfer Initiated Cyclization for Application in the Synthesis of Amido Trioxadecalin Systems 149
(Supporting Information) 149
(^{1}H and ^{13}C NMR spectra) 149
APPENDIX B 172
Efforts Toward the Total Synthesis of Mycalamide B 172
(Supporting Information) 172
(^{1}H and ^{13}C NMR Spectra) 172
APPENDIX C 248
Synthesis of the N_7-C_{25} Fragment of Psymberin 248
(Supporting Information) 248
(^{1}H and ^{13}C NMR Spectra) 248

LIST OF TABLES

Table 1: Activity of Psymberin against Various Cancer Cell Lines 117

LIST OF FIGURES

Figure 1: The Core Structure of the Mycalamide, Onnamides, and Theopederins 1
Figure 2: Reaction Pathways of Radical Cations 3
Figure 3: Photoinduced Electron Transfer Oxidation 3
Figure 4: Orbital Alignment Required for Mesolytic Cleavage 4
Figure 5: Carbon-Carbon Bond Cleavage in Arene Radical Cations 5
Figure 6: Mechanism for Photosensitized Carbon-Carbon Bond Cleavage 6
Figure 7: Bond Dissociation Energy of an Alkylaryl Radical Cation 7
Figure 8: A General ETIC Reaction 8
Figure 9: Aerobic Oxidation Mechanism of the ETIC Reaction 8
Figure 10: Mechanism of the ETIC Reaction 9
Figure 11: Cyclic Acylaminal Formation with the ETIC reaction 10
Figure 12: Retrosynthetic Evaluation of Cyclic Amido Acetals 12
Figure 13: ETIC Substrates Containing Potential Formaldehyde Donor Nucleophiles 13
Figure 14: Suarez Oxidative Cyclization to Generate the TFM Ether 17
Figure 15: ETIC Reaction of the SEM Ether Substrate 17
Figure 16: Fates of the Oxonium Ion Generated in the ETIC Reaction 18
Figure 17: ETIC Cyclization of TFM Ether 19
Figure 18: Pederin and Mycalamide A and B 35
Figure 19: Structure of Mycalamide A and B 36
Figure 20: Long-Range HETCOR Analysis of the Pederic Acid Fragment of Mycalamide A 37
Figure 21: Pertinent nOe Enhancements of the Amido Trioxadecalin Fragment 38
Figure 22: Relevant Functionality for Biological Activity 40
Figure 23: Synthetic Approaches toward the *N*-Acylaminal 42
Figure 24: Rawal's Coupling to Synthesize Mycalamide A 46
Figure 25: Retrosynthetic Analysis of Mycalamide B 50
Figure 26: Amido Trioxadecalin ETIC Model Systems 51
Figure 27: ETIC Reaction of the D-Glucal Based Model System 56
Figure 28: Conformation of the Amido Trioxadecalin Products of the ETIC Reaction 57
Figure 29: Mechanism of Amido Trioxadecalin Formation 58
Figure 30: Conformations of the Amido Trioxadecalin System 59
Figure 31: Relative Energies of a Mycalamide-Like Amido Trioxadecalin System 60
Figure 32: Cyclization of the Ethyl Pyran ETIC Model 61
Figure 33: Epimerization of the Amido Trioxadecalin System 62
Figure 34: Methylation of the Dihydropyran Precursor to Mycalamide B 65
Figure 35: Mechanism of the Ferrier Degradation 66
Figure 36: Psymberin/Irciniastatin A and Related Compounds 111
Figure 37: Irciniastatin A Reported by Pettit 113
Figure 38: Psymberin Reported by Crews 113
Figure 39: Structure of Psymberin Proposed by Williams 115
Figure 40: Structure of Psymberin Proposed by Floreancig 116
Figure 41: De Brabander's Retrosynthetic Analysis 117
Figure 42: Retrosynthetic Scheme for Psymberin 121

Figure 43: Mukaiyama Aldol to Generate the C_{15} Stereocenter of Psymberin..... 125
Figure 44: Nitrile Hydration and Completion of the N_7-C_{25} Fragment of Psymberin..... 128
Figure 45: Chemical Shift and Coupling Constant Analysis of the Synthetic Fragment 129

LIST OF SCHEMES

Scheme 1: Synthesis of Homobenzylic Amide 14
Scheme 2: Evaluation of *In Situ* Hemiactal Formation in the ETIC Reaction 14
Scheme 3: Synthesis of SEM Ether ETIC Substrate 15
Scheme 4: Synthesis of ETIC Cyclization Substrates 16
Scheme 5: Kishi's Generation of the Azido Trioxadecalin System 43
Scheme 6: Kishi's Completion of Mycalamides A and B 44
Scheme 7: Rawal's Synthesis of the Amino Trioxadecalin System of Mycalamide A 45
Scheme 8: Roush's Approach to Mycalamide A 47
Scheme 9: Roush's Completion of Mycalamide A 48
Scheme 10: Epoxidation and Trivinylalane Addition of Tri-*O*-Methyl D-Glucal 52
Scheme 11: Synthesis of D-Glucal ETIC Model System 53
Scheme 12: Generation of the Dihydropyran Precursor to the ETIC Ethyl Pyran Model 54
Scheme 13: Completion of the Ethyl Pyran ETIC Substrate 55
Scheme 14: Asymmetric Allylation and Boron-Mediated Aldol Reactions 63
Scheme 15: *Syn*-Reduction of the β-Hydroxyketone 64
Scheme 16: Generation of the Dihydropyran Precursor to Mycalamide B 65
Scheme 17: Generation of a Stable Intermediate in the Synthesis of Mycalamide B 67
Scheme 18: De Brabander's Psymberin Synthesis: Fragment 3 118
Scheme 19: De Brabander's Psymberin Synthesis: Fragment 2 119
Scheme 20: De Brabander's Psymberin Synthesis: Completion 120
Scheme 21: Synthesis of the Psymberin Arene 122
Scheme 22: Generation of C_{14}-C_{25} Fragment of Pysmberin 123
Scheme 23: Synthesis of the C_7-C_{13} Fragment of Psymberin 124
Scheme 24: *Syn*-Reduction of Psymberin Aldol Adduct 126
Scheme 25: Tetrahydropyran Formation 127

PREFACE

I would like to take this opportunity to thank the people that supported me throughout my graduate career.

Paul:

Thank you for patience, guidance and support. I've enjoyed my time in your group and feel that I've grown significantly as a researcher and person.

Mom, Dad, and Amanda:

I'm certain that I wouldn't have made it this far if it weren't for your unwavering love and support. You've always been there to help me through the tough times and celebrate the good times. I am eternally grateful for the sacrifices that you've made for me.

Butch and Lijun:

We joined the group together and I couldn't ask for better people to work with. You guys are great chemists and even better people. I wish you the best of luck and I have no doubt that you will continue to be successful.

Mike:

It's been great sharing projects with you. Thank you for all your help and keep up the good work.

1. The Development of the Electron Transfer Initiated Cyclization for Application in the Synthesis of Amido Trioxadecalin Systems

1.1 Introduction

I. General

Nature continually provides synthetic challenges in the form of complex, biologically active natural products. The challenges presented by these compounds demand the continual development of new synthetic methods and the creative application of established chemistry. The isolation of the family of natural products represented by mycalamides A,[1] B[2] and D,[3] onnamides A-F[4-7] and theopederins A-F[8,9], K and L[10] has generated unique challenges for the synthetic chemist. These compounds have a common core structure, shown in Figure 1, and all have displayed potent biological activity. The scarce availability of these compounds from natural sources has inhibited the thorough examination of their therapeutic potential.

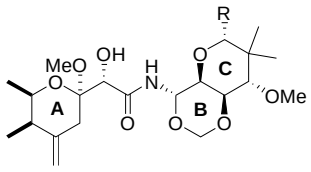


Figure 1: The Core Structure of the Mycalamide, Onnamides, and Theopederins

The complex structure and biological activity of the mycalamides, onnamides, and theopederins has generated a considerable amount of synthetic study that has resulted in

significant advances in organic chemistry. The amido trioxadecalin system, in particular the **B** ring including the *N*-acylaminal functional group, has been particularly difficult to synthesize. Two methods have been developed to generate this sensitive functional groups, but are either limited by efficiency or selectivity. The synthetic efforts devoted to these and related compounds will be discussed in detail in Chapter 2.

A novel approach to the generation of the **B** ring of the mycalamides, onnamides and theopederins is through the use of photosensitized electron transfer (PET). Recently, Floreancig and coworkers[21] reported the development of an electron transfer initiated cyclization (ETIC) reaction that allows for the generation of acetal and *N*-acylaminal functional groups under essentially neutral conditions. The following describes the basic principles of radical cations in the context of the ETIC reaction and discusses our development (Chapter 1) and application of the ETIC reaction for the synthesis of amido trioxadecalin systems (Chapter 2).

II. The Radical Cation

Radical cations are singly electron deficient intermediates that can undergo a variety of transformations.[11] These intermediates are commonly generated from neutral molecules by single electron oxidations utilizing chemical, anodic or photoinduced electron transfer (PET) conditions. Non-oxidative methods have been reported, such as the combination of a radical with a cation and the protonation of a radical species, but are employed with less frequency.[12] Common reaction pathways available to radical cations include bond cleavage (**1**), radical based processes (**2**) and reactions initiated by nucleophiles (**3**, Figure 2).[11]

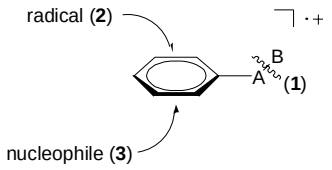


Figure 2: Reaction Pathways of Radical Cations

PET oxidation is a powerful method for the generation of radical cations. This type of oxidation can occur through two possible reaction pathways. The first pathway utilizes the ability of electronically excited acceptors molecules (A^*) to serve as strong single electron oxidants (**1**, Figure 3) to generate a radical cation/radical anion pair. The second pathway relies on the ability of electronically excited donor molecules (D^*) to function as strong single electron donors (**2**, Figure 3) to generate the radical cation/radical anion pair. A common and facile reaction pathway of radical cation/radical anion pairs is return electron transfer regenerating the neutral ground state species. The impact of this nonproductive, but nondestructive, pathway can be minimized with the proper choice of solvent, acceptor and cosensitizer.[12]

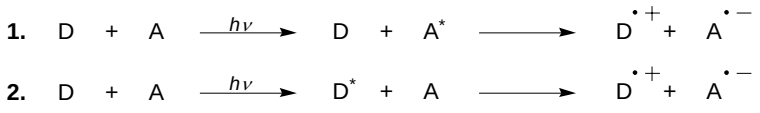


Figure 3: Photoinduced Electron Transfer Oxidation

The electron deficient nature of radical cations decreases the electron density and weakens the bonds around the periphery of molecule. The benzylic bonds of arene radical cations are weakened to the greatest extent when the benzylic C-C σ-bond is orthogonal to the arene (Figure 4).[12] The weakened benzylic bonds can result in fragmentation generating a radical and a cationic species.[11] This type of bond cleavage is known as mesolytic cleavage.[13]

Mesolytic cleavage has been shown to be a relevant reaction pathway when radical cations are generated in solution.[12] Benzylic carbon-hydrogen, carbon-carbon, and carbon-silicon bonds of aryl radical cations have been shown to undergo mesolytic cleavage generating the aryl radical and the corresponding cation.[14]

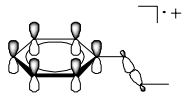


Figure 4: Orbital Alignment Required for Mesolytic Cleavage

III. Carbon-Carbon σ-Bond Activation

Cyclic voltammetry studies by Kochi and coworkers[15] of alkyl arenes established that arene radical cations have lifetimes less than ~100 μs. The cyclic voltammogram of *tert*-butyl benzene in acetonitrile has been shown to be reversible, consistent with an oxidative process to generate a radical cation and a reductive process to regenerate a neutral species. Additionally, the *tert*-butyl benzene radical cation displayed a longer lifetime than the radical cations of other alkyl benzenes, such as toluene and ethyl benzene, that did not display reversible cyclic voltammograms. The shorter lifetimes and nonreversible cyclic voltammograms of the alkyl benzene radical cations were attributed to the presence of benzylic C-H bonds in these compounds. Mesolytic cleavage of the benzylic C-H bonds in aryl radical cations has been shown to limit the lifetimes of these species. This study indicated that for simple aliphatic arene radical cations carbon-hydrogen bond activation is favored over carbon-carbon bond acitivation.[15]

Arnold and coworkers have demonstrated that with the appropriate alkyl substitution carbon-carbon bond cleavage can efficiently compete with carbon-hydrogen bond cleavage in arene radical cations. They demonstrated that when methyl 2,2-diphenylethyl ether (**1**) was irradiated in acetonitrile and methanol (3:1) at 10 °C in the presence of 1,4-dicyanobenzene fragmentation occurred to generate diphenylmethane (**2**) and dimethoxymethane (**3**) as the only products (Figure 5).[16]

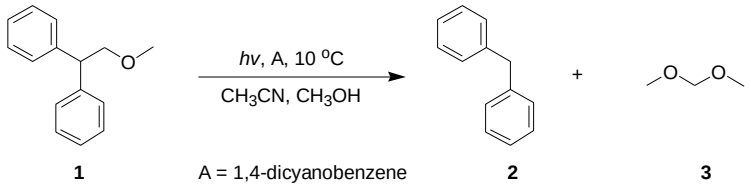


Figure 5: Carbon-Carbon Bond Cleavage in Arene Radical Cations

The mechanism proposed by Arnold and coworkers[17] for the carbon-carbon bond cleavage of arene radical cations is shown in Figure 6. Photoexcitation of the of the acceptor (A) to generate a strong single electron oxidant is the initial step of the reaction mechanism (**1**, Figure 6).[17] The excitation wavelength of the photosensitizer, 1,4-dicyanobenzene, extends beyond the absorption cutoff of the Pyrex filter (280 nm), while aryl alkanes are not electronically excited when a Pyrex filter is employed during irradiation.[17]

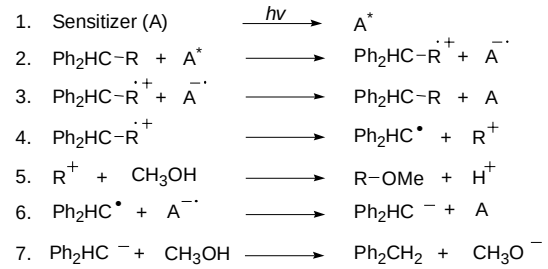
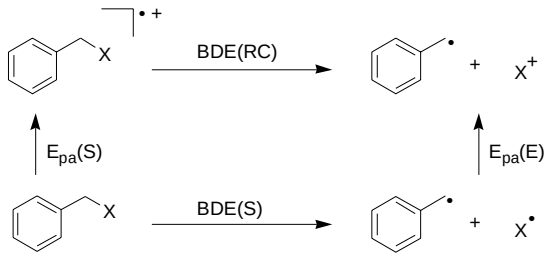


Figure 6: Mechanism for Photosensitized Carbon-Carbon Bond Cleavage

The second step of the mechanism is single electron transfer from the arene to the electronically excited acceptor (**2**, Figure 6). Single electron transfer between the singly excited 1,4-dicyanobenzene and arylalkanes has been shown to occur at a diffusion-controlled rate. The resulting radical cation/radical anion pair can undergo return electron transfer to regenerate the neutral species (**3**, Figure 6) or mesolytic cleavage can occur to generate the aryl radical and an α-alkoxy cation (**4**, Figure 6).[17]

The thermodynamic propensity for a radical cation carbon-carbon bond to undergo mesolytic cleavage can be evaluated by examining the bond dissociation energy of the radical cation (BDE(RC)) (Figure 7). The BDE(RC) can be approximated from the bond dissociation energy of the substrate (BDE(S)), the oxidation potential of the substrate (E_{pa}(S)) and the oxidation potential of the radical precursor to the electrophilic fragment (E_{pa}(E)), as shown in Figure 7.[17] Mesolytic cleavage of the radical cation occurs to generate the carbocation of the radical fragment with the lower oxidation potential, as described by the relationship in Figure 7.[16] In the case of the homobenzylic ether (**1**, Figure 5) the oxidation potential of the α-alkoxy radical is approximately 0.6 V lower than that of the biphenyl radical.[18]



BDE(RC) = BDE(S) - E_{pa}(S) + E_{pa}(E)

Figure 7: Bond Dissociation Energy of an Alkylaryl Radical Cation

The cation fragment generated from mesolytic cleavage can then undergo nucleophilic attack from the solvent to generate an ether (**5**, Figure 6). Single electron transfer between the biphenyl methyl radical (generated from mesolytic cleavage of the radical cation) and the radical anion of the acceptor regenerates the ground state acceptor (**6**, Figure 6) and protonation of the resulting biphenyl methyl anion provides biphenyl methane (**7**, Figure 6).[17]

IV. The Electron Transfer Initiated Cyclization (ETIC)

Recently Floreancig and coworkers[19] reported the synthesis of furanosides and pyranosides from the single electron oxidation of homobenzylic ethers (Figure 8). The radical cation of the homobenzylic ether is generated by photoinduced electron transfer resulting in the weakening of the benzylic carbon-carbon σ-bond. Subsequent mesolytic cleavage generates a benzyl radical and an α-alkoxy carbocation. Nucleophilic attack by the pendent nucleophile (alcohol or ether) onto the cationic intermediate completes the reaction.

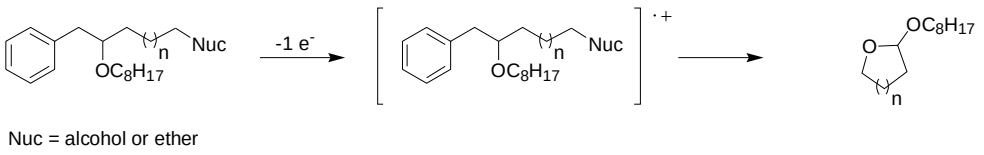


Figure 8: A General ETIC Reaction

The ETIC reactions are conducted in dichloroethane (DCE, solvent) by irradiating a substrate with a medium pressure mercury lamp through a Pyrex filter in the presence of either stoichiometric or catalytic *N*-methylquinolinium hexafluorophosphate (NMQ, photosensitizer), *tert*-butyl benzene or toluene (cosensitizer), sodium thiosulfate ($Na_2S_2O_4$, reducing agent) and sodium acetate (NaOAc) (insoluble base). The cationic photosensitizer (NMQ) was employed in these reactions to minimize return electron transfer.[19] The ETIC reaction can be conducted under anaerobic or aerobic conditions. Aerobic conditions are generally preferred since catalytic amounts of NMQ can be employed. In the aerobic ETIC reaction oxygen serves as the stoichiometric oxidant by regenerating NMQ, **4**, from the *N*-methylquinoline radical, **5**, generated during the single electron oxidation of the cosensitizer (Figure 9).[21]

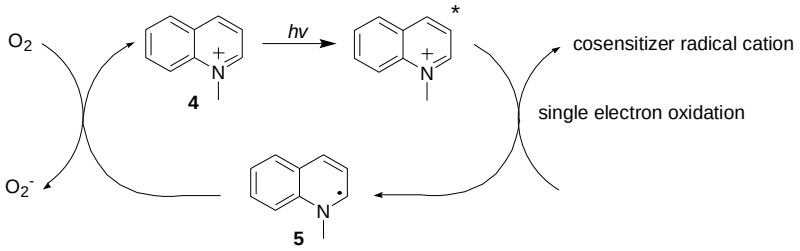


Figure 9: Aerobic Oxidation Mechanism of the ETIC Reaction

The mechanism of the ETIC reaction begins when NMQ is irradiated (318 nm) and promoted to its singly excited state. A single electron transfer occurs between toluene

(cosensitizer) and the photoexcited NMQ generating the radical cation of toluene and the *N*-methylquinoline radical. The lack of coulombic attraction between the radical cation and the *N*-methylquinoline radical allows for rapid diffusion limiting return electron transfer. A reversible electron transfer from the homobenzylic ether to the radical cation of toluene generates the substrate radical cation (Figure 10). At this point cyclization can occur through an associative S_N2-like pathway that leads to stereochemical inversion at the electrophilic center or a dissociative S_N1-like pathway can occur resulting in a planar cationic intermediate and a racemic mixture.[19]

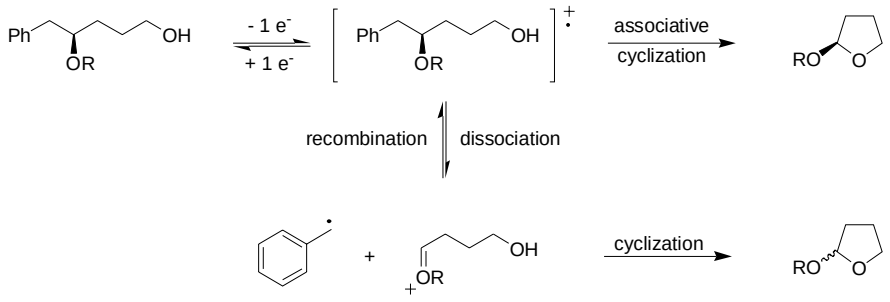


Figure 10: Mechanism of the ETIC Reaction

The extent to which the ETIC reaction proceeds through an associative or dissociative pathway is highly substrate dependent. Substrates possessing good nucleophiles with unhindered transition states were shown to proceed through an associative mechanism, while substrates containing weaker or bulky nucleophiles or that generated steric repulsion in the transition state proceeded through the dissociative pathway.[19] However, as the catalog of ETIC reactions increases the dissociative pathway appears to be the more common mechanistic pathway.

When cyclization is slow the oxidatively generated radical cation can undergo fragmentation to generate the cation and radical fragments (Figure 10). In the absence of

nucleophilic attack the radical and cation fragments can recombine to regenerate the radical cation species. This dissociation/recombination mechanism can result in a loss of stereochemical identity at the homobenzylic position. Evidence for this process was obtained by taking a diastereomerically pure substrate to partial conversion and isolating a diastereomeric mixture in the recovered starting material.[19]

The ETIC reaction has also shown to be efficient for the generation of cyclic *N*-acylaminals (Figure 11). Unlike their homobenzylic ether counterparts, the homobenzylic amides have been shown to only react through a dissociative pathway generating an *N*-acyliminium ion as the reactive intermediate.[21] These highly reactive intermediates undergo facile nucleophilic addition of mild, pendent nucleophiles to generate cyclic *N*-acylaminals. As shown by the carbamate (Figure 11), these reactions tolerate inductively withdrawing substituents in the β-position which have been shown to increase the bond dissociation energy of the radical cation by increasing the oxidation potential of the amidoalkyl radial. In these systems oxidation likely occurs at the amide or carbamate since the oxidation potential of tertiary amides and carbamates is approximatiely 0.5 V lower than monoalkyl arenes.[21]

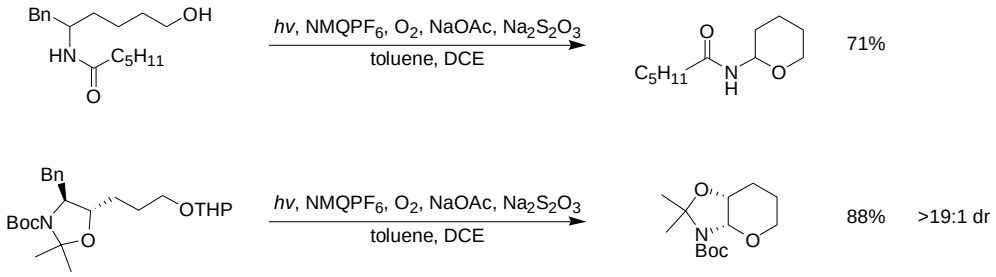


Figure 11: Cyclic Acylaminal Formation with the ETIC reaction

The ETIC reaction is a useful method for generating acetals and *N*-acyl aminals and provides a powerful new method for synthetic organic chemists. The advantages of this process are centered on the use of a benzyl group as the precursor to reactive functionality. The benzyl group is relatively inert to most reaction conditions, which allows for its early incorporation into a synthetic sequence. Additionally, the single electron oxidation of the benzyl moieties and subsequent fragmentation to generate the oxocarbenium and *N*-acyliminium ions occurs under essentially neutral conditions allowing for the incorporation of sensitive functionality into the ETIC substrates. Also the highly reactive electrophiles generated in these reactions allows for the use of a wide range of mild, pendent nucleophiles.

V. Project Goals and Objectives

The ability to expand the scope of the ETIC reaction to include the generation of cyclic amido acetals and ultimately the amido trioxadecalin ring system of the mycalamides, onnamides, and theopederins was examined. The following section describes the generation of a cyclic amido acetal model compound relevant for the synthesis of compounds containing amido trioxadecalin ring systems. This study also resulted in the development of a stable nucleophile that can serve as the functional equivalent of a formaldehyde hemiacetal.

1.2 Results and Discussion

The ETIC reaction provides a powerful method for the generation of acyliminium ions from homobenzylic amides and carbamates under mild reaction conditions. The nucleophilic addition of pendent nucleophiles, such as alcohols or ethers, to oxidatively generated acyliminium ions has resulted in the generation of cyclic *N*-acylaminals under essentially neutral conditions.[21] While this method was successful for the generation of a variety of *N*-acylaminals, there was no precedent for the generation of cyclic amido acetals, such as **1**, a ring system prevalent in the mycalamide, theopederins and onnamides (Figure 12).

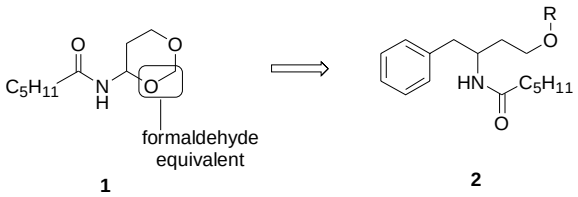


Figure 12: Retrosynthetic Evaluation of Cyclic Amido Acetals

This study was designed to extend the scope of the ETIC reaction to include the synthesis of cyclic amido acetal **1** by employing a nucleophile that would serve as a formaldehyde hemiacetal surrogate, shown in Figure 12. To this end homobenzylic amides **3-5** (Figure 13) were evaluated based on their ability to donate a formaldehyde equivalent in the ETIC reaction. The synthesis and reactivity of these substrates are described in the following section. A majority of this chapter has been published as a communication and a full paper.[24,25]

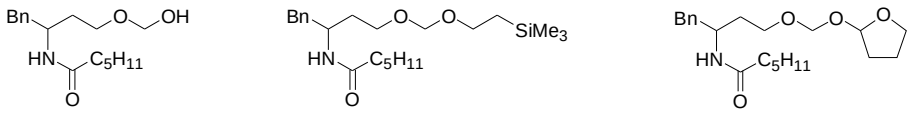


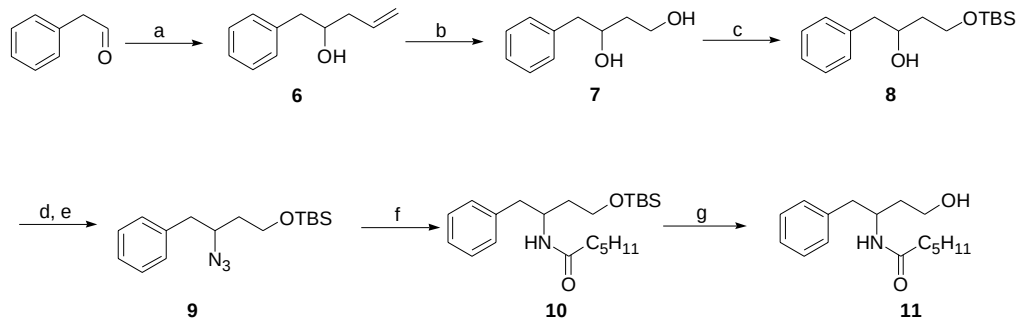
Figure 13: ETIC Substrates Containing Potential Formaldehyde Donor Nucleophiles

I. Synthesis and Evaluation of the Hemiacetal Nucleophile

The successful application of alcohol nucleophiles in the ETIC reaction prompted us to examine the use of a hemiacetal nucleophile in these reactions. The use of a hemiacetal nucleophile would expand the scope of the ETIC to include the generation of cyclic amido acetals. As a result of the highly unstable nature of the hemiacetal that precludes its efficient isolation, this functional group will be generated *in situ*. The *in situ* generation of ETIC substrate **3** (Figure 13) from alcohol **11** (Scheme 1) has been examined under ETIC reaction conditions modified to promote hemiacetal formation.

Alcohol **11** was synthesized in a 7 step sequence starting from phenylacetaldehyde. The addition of allylmagnesium bromide to phenylacetaldehyde generated alcohol **6** in an 88% yield (Scheme 1). Ozonolysis of **6** followed by reduction with $NaBH_4$ resulted in diol **7** in a 78% yield. Selective protection of the primary alcohol of diol **7** proceeded smoothly in the presence of *tert*-butyldimethylsilyl chloride (TBSCl) and imidazole at reduced temperatures to provide silyl ether **8** in a 93% yield. Mesylation of the secondary alcohol of **8** followed by nucleophilic mesylate displacement with sodium azide generated azide **9** in a 68% yield over 2 steps. Reduction of azide **9** proceeded smoothly to the corresponding amine under Staudinger conditions. The crude reaction mixture was treated with triethylamine and hexanoyl chloride to

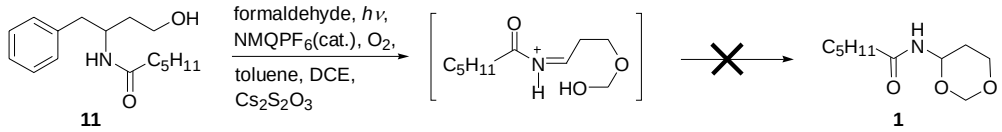
generate amide **10** in an 88% yield. TBAF deprotection of **10** resulted in the desired alcohol **11** in 93% yield.



Reagents: (a) allylmagnesium bromide, THF, -78 °C to rt, 88%; (b) O_3, CH_2Cl_2 , -78 °C, then $NaBH_4$, MeOH, rt, 78%; (c) TBSCl, imidazole, CH_2Cl_2, -42 °C, 93%; (d) MsCl, NEt_3, CH_2Cl_2, 0 °C; (e) NaN_3, Bu_4NI, DMF, 40 °C, 69% over 2 steps; (f) PPh_3, THF, rt, then H_2O, then Et_3N and hexanoyl chloride, 88%; (g) TBAF, THF, 93%.

Scheme 1: Synthesis of Homobenzylic Amide

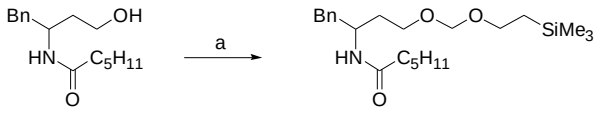
Alcohol **11** was subjected to modified ETIC conditions that included formaldehyde and cesium carbonate (to facilitate hemiacetal formation), NMQ (sensitizer), sodium thiosulfate (peroxide reducing agent), toluene (aromatic cosensitizer) and 1,2-dichloroethane (DCE, solvent). Air (O_2 serves as terminal oxidant) was bubbled through the reaction mixture while it was irradiated with a medium pressure mercury lamp through a Pyrex filter (Scheme 2). The irradiation of the reaction mixture lasted for 6 hours and resulted in complete degradation of starting material with no isolable products. The lack of cyclization was attributed to the prohibitively short lifetime of the hemiacetal under the modified ETIC conditions.



Scheme 2: Evaluation of *In Situ* Hemiactal Formation in the ETIC Reaction

II. Synthesis of Formaldehyde Hemiacetal Surrogates

In addition to the *in situ* hemiacetal generation, we were interested in examining more stable functional groups that could serve as formaldehyde hemiacetal surrogates. The trimethylsilylethoxymethyl (SEM) ether protecting group was an attractive option because it could be generated in one step from commercially available starting material and the electron rich silyl functional group was expected to promote the desired fragmentation. SEM ether **4** was generated in a single step in 92% yield by treating alcohol **11** with commercially available trimethylsilylethyloxymethyl chloride (SEM-Cl) in the presence of diisopropylethylamine (DIPEA) at 45 °C (Scheme 3).



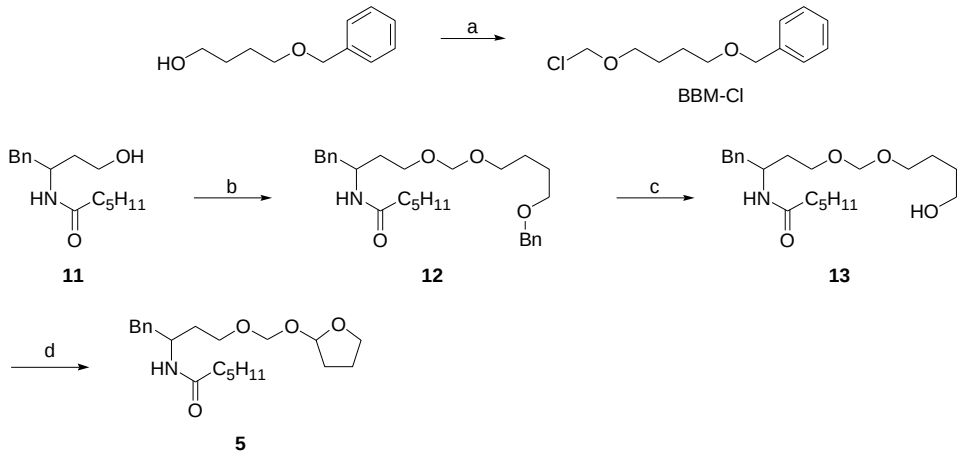
11 **4**

Reagents: (a) SEM-Cl, DIPEA, CH_2Cl_2, 45 °C, 92%.

Scheme 3: Synthesis of SEM Ether ETIC Substrate

Our previous success employing THP ethers as nucleophiles in the EITC reaction led us to examine the tetrahydrofuranyloxymethyl (TFM) ether (**5**, Scheme 4) as a formaldehyde hemiacetal surrogate. TFM ether **5** was generated from alcohol **11** by a three step sequence that required the development of the benzyloxybutoxymethyl (BBM) ether protecting group. BBM ether **12** was generated in a 93% yield by treating alcohol **11** with benzyloxybutoxymethyl chloride (BBM-Cl) in the presence of DIPEA at 45 °C. BBM-Cl was generated in quantitative yield by bubbling anhydrous HCl through a solution of commercially available

benzyloxybutanol and formaldehyde in CH_2Cl_2 at 0 °C. Cleavage of the benzyl ether followed by oxidative etherification employing conditions developed by Suarez and coworkers[22] generated the TFM ether **5** in an 85% yield over 2 steps.



Reagents: (a) paraformaldehyde, HCl(g), CH_2Cl_2, 0 °C 100%; (b) BBM-Cl, DIPEA, CH_2Cl_2, 42 °C, 93%; (c) Pd/C, H_2, EtOH; (d) $PhI(OAc)_2$, I_2, *hv*, cyclohexane, 85% over 2 steps.

Scheme 4: Synthesis of ETIC Cyclization Substrates

The generation of the TFM ether under the Suarez oxidative etherification conditions was rationalized by invoking a radical based mechanism, as shown in Figure 14. Suarez and coworkers have proposed the *in situ* generation of acyl hypoiodite (2AcOI) from the reaction of (diacetoxyiodo)benzene ($PhI(OAc)_2$) and molecular iodine. The oxygen-iodine bond, generated from the reaction of the acyl hypoiodite with the primary alcohol of **13**, undergoes homolytic cleavage when irradiated with a medium pressure mercury lamp through a Pyrex filter. The resulting alkoxy radical abstracts the α-alkoxy proton generating the lower energy α-alkoxy radical. Single electron oxidation of the α-alkoxy radical generates an oxocarbenium ion and subsequent addition of the pendent alcohol completes the formation of the TFM ether.

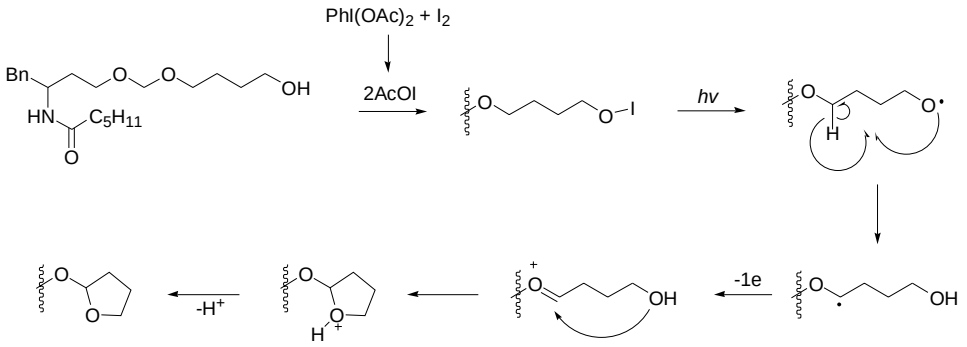
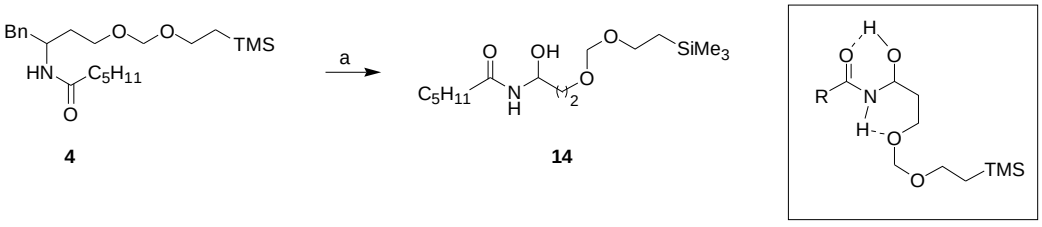


Figure 14: Suarez Oxidative Cyclization to Generate the TFM Ether.

III. Formaldehyde Hemiacetal Surrogates in the ETIC Reaction

Subjecting SEM ether **4** to standard ETIC conditions (NMQ (cat.), *hv*, O_2, NaOAc, $Na_2S_2O_3$, 1,2-dichloroethane and toluene) resulted in the isolation of *N*-acyl hemiaminal **14** in a 67% yield (Figure 15). *N*-Acyl hemiaminal **14** was isolated by standard chromatography and was found to be surprisingly stable. The stability of the *N*-acyl hemiaminal was attributed to intermolecular hydrogen bonding interactions between the *N*-acyl hemiaminal hydroxyl functional group and the amide carbonyl and the amide proton with the proximal acetal oxygen (Figure 15). The stability of similar *N*-acyl hemiaminals has been attributed to this type of hydrogen bonding interactions.[23]



Reagents: (a) *hv*, $NMQPF_6$ (cat.), O_2, NaOAc, $Na_2S_2O_4$, DCE, toluene, 67%.

Figure 15: ETIC Reaction of the SEM Ether Substrate

The generation of *N*-acyl hemiaminal **14** was explained by examining the fate of the intermediate oxonium ion generated from the ETIC reaction (Figure 16). Single electron oxidation followed by mesolytic cleavage resulted in the generation of an *N*-acyliminium ion/benzyl radical pair. Nucleophilic addition by the distal oxygen of the acetal generates an oxonium species that can react through two separate reaction pathways. If R^+ loss is faster than the ring opening process the cyclic amido acetal is generated. If the loss of R^+ is slow, then the regeneration of the acyliminium ion is the dominant pathway allowing for the addition of H_2O into the *N*-acyl iminium ion generating the *N*-acyl hemiaminal. This mechanism is supported by the facile addition of H_2O to the oxidatively generated *N*-acyliminium ion of **4** (Figure 15), which is inconsistent with the extremely slow addition of H_2O observed with other cation ion/radical pairs generated during previous ETIC reactions. This would suggest that the addition of H_2O must occur into a more reactive free *N*-acyliminium ion generated from the ring opening of the oxonium ion (no longer a cation/radial pair). According to the mechanism described in Figure 16, increasing the rate of the R^+ group loss following oxonium ion formation would allow for the generation of the desired cyclic amido acetal.

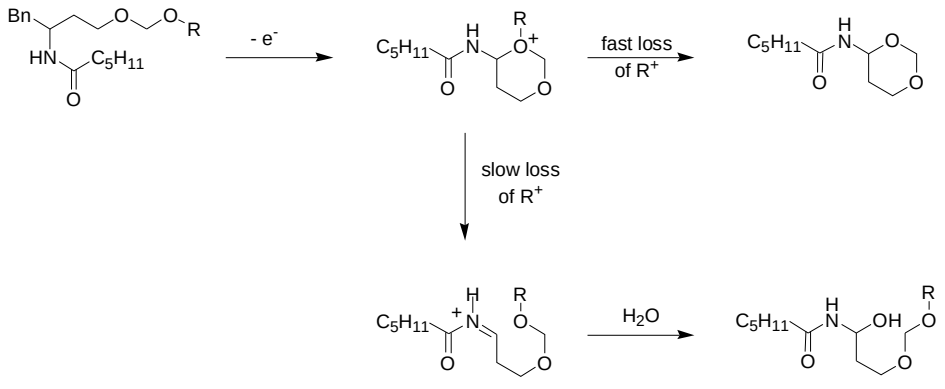
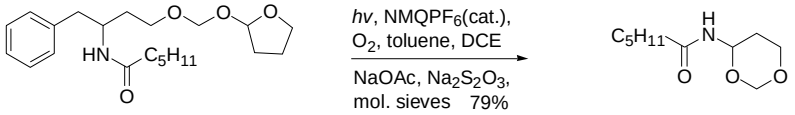


Figure 16: Fates of the Oxonium Ion Generated in the ETIC Reaction

The success of tetrahydropyranyl ethers as nucleophiles in previously reported ETIC reactions prompted our investigation of the TFM ether **5**. The increased ability of the tetrahydrofuranyl moiety to stabilize a cation was expected to increase the rate of fragmentation of the oxonium ion generated during the ETIC reaction favoring the formation of the cyclic amido acetal. Additionally, 4 Å molecular sieves were added to the ETIC reaction conditions to minimize the concentration of alternative nucleophiles. When **5** was subjected to the standard ETIC conditions in the presence of 4 Å molecular sieves the cyclic amido acetal **1** was generated in a 79% yield (Figure 17). The efficient generation of the cyclic amido acetal supported our proposed mechanism (Figure 16) and indicated that the TFM ether can be used as a stable nucleophilic hemiacetal surrogate. The role of the 4 Å molecular sieves is consistent with that of a desiccant, although the possibility for surface catalysis cannot be ruled out.



5 **1**

Figure 17: ETIC Cyclization of TFM Ether

1.3 Conclusions

The scope of the ETIC reaction has been extended to include the generation of cyclic amido acetals. This study demonstrated that the *in situ* generated hemiacetal functionality does not serve as an efficient nucleophile in the ETIC reaction. Also the SEM ether was shown to function as competent nucleophile in the ETIC reaction; however the slow decomposition the resulting oxonium ion intermediate limited its utility for the generation of the cyclic amido acetal. The generation of the desired cyclic amido acetal was made possible by the development of the tetrahydrofuranyloxymethyl (TFM) ether group. The stability of the tetrahydrofuranyl cation allowed for the fast decomposition of the oxonium ion intermediate resulting in the generation of the desired cyclic amido acetal. The development of the TFM ether also provides a formaldehyde hemiacetal surrogate that could be useful in a variety of other applications.

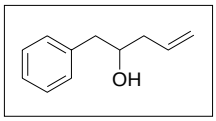
1.4 Experimentals

General Experimental:

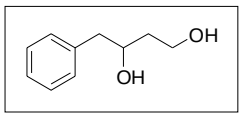
Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometers at 300 MHz and 75 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak or the internal standard tetramethylsilane were used as reference values. For ^{1}H NMR: $CDCl_3$ = 7.27 ppm, TMS = 0.00. 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 doublets of triplets; br = broad; m = multiplet; app t = apparent triple; 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 (245 nm). Flash column chromatography was preformed using ICN SiliTech 32-63 60 Å 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), dichloroethane ($C_2H_4Cl_2$), acetonitrile (CH_3CN), benzene and toluene were distilled from CaH_2. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketal prior to use. Anhydrous *N,N*-dimethylformamide (DMF), methanol (MeOH), dimethylformamide (DMF), methanol (MeOH), dimethyl sulfoxide (DMSO) were purchased from Aldrich and used as is. All reactions were conducted under nitrogen atmosphere, unless otherwise specified.

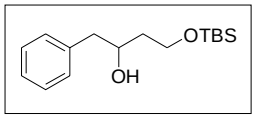


Phenylpent-4-en-2-ol, 6:[20] To phenylacetaldehyde (4.87 g, 40.58 mmol) in THF (100 mL) at -78 °C was added allylmagnesium bromide (1M in THF, 60.0 mL, 60.00 mmol). The reaction mixture was stirred for 1 h at -78 °C then allowed to warm to room temperature and stirred for 2 hours. Saturated aqueous NH_4Cl (10 mL) was added and the resulting mixture was stirred for 10 minutes then extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (10% EtOAc in hexanes) to provide the desired product (5.81 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.21 (m, 5H), δ 5.94-5.82 (m, 1H), δ 5.20-5.12 (m, 2 H), δ 3.93-3.84 (m, 1H), δ 3.80 (dd, J = 13.6, 5.0 Hz, 1H), δ 2.70 (dd, J = 13.5, 7.9 Hz, 1H), δ 2.39-30 (m, 1H), δ 2.45-2.17 (m, 1 H), δ 1.67 (bs, 1H).

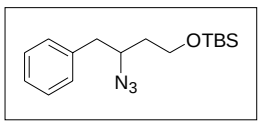


4-Phenylbutane-1,3-diol, 7: Ozone was bubbled through a solution of **6** (7.00 g, 43.1 mmol) in CH_2Cl_2 (50 mL) at -78 °C until the reaction mixture sustained a dark blue color. Methanol (50 mL) was added to the solution at -78 °C followed by the slow addition of $NaBH_4$ (6.53 g, 172 mmol). The reaction was stirred at -78 °C for 1 hour then slowly warmed to room temperature and stirred for 4 hours. The reaction was concentrated under reduced pressure and extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with water (2 x 10 mL) and brine (2 x 10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (40% EtOAc in hexanes) to provide the desired product (5.21 g, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.22 (m, 5H), 4.12-4.08 (m, 1H), 3.89-3.82 (m, 2H), 2.83-2.77

(m, 2H), 2.28 (bs, 2H), 1.80-1.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.9, 129.4, 128.6, 126.6, 73.1, 61.7, 44.3, 37.7; IR (neat) 3349, 3026, 2938, 1052 cm^{-1}; HRMS (EI) calcd. for $C_{10}H_{14}O_2$ (M^+) 166.0993, found 166.0996.

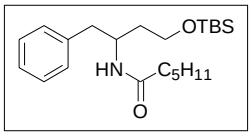


4-(*tert*-Butyldimethylsilanyloxy)-1-phenylbutan-2-ol, 8: To a solution of **7** (1.72 g, 10.2 mmol) in CH_2Cl_2 (50 mL) at room temperature was added imidazole (1.51 g, 22.4 mmol). The solution was stirred for 10 minutes then cooled to -42 °C. TBSCl (1.64 g, 11.2 mmol) was added to the reaction mixture which was stirred for two hours at -42 °C. Saturated aqueous NH_4Cl (10 mL) was added and the reaction mixture was warmed to room temperature. The reaction mixture was extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (30% EtOAc in hexanes) to provided the desired product (2.63 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.18 (m, 5H), 4.11-4.03 (m, 1H), 3.92-3.85 (m, 1H), 3.82-3.74 (m, 1H), 3.32 (bs, 1H), 2.85 (dd, *J* = 13.5, 7.0 Hz, 1H), 2.73 (dd, *J* = 13.5, 6.2 Hz, 1H), 1.72-1.60 (m, 2H), 0.90 (s, 9H), 0.07 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 129.5, 128.4, 126.3, 72.8, 62.5, 44.0, 36.9, 25.8, 18.1, -5.5; IR (neat) 3450, 2953, 2857 cm^{-1}; HRMS (EI) calcd. for $C_{16}H_{28}O_2Si$ (M^+) 280.1858, found 280.1815.



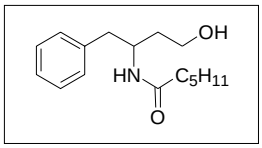
3-Azido-4-phenylbutoxy-*tert*-butyldimethylsilane, 9: To a solution of **8** (9.36 g, 33.2 mmol) in DMF (100 mL) was added triethylamine (13.4 g, 0.132 mol) and the solution was cooled to 0 °C. Methanesulfonyl chloride (5.70 g, 49.8 mmol) was added drop wise and the reaction mixture was stirred for 3.5 hours at 0 °C. Brine (10 mL)

was added and the reaction was allowed to warm to rt. The reaction mixture was extracted with hexanes (2 x 10 mL). The organic layers were combined, washed with H_2O (20 mL), dried with $MgSO_4$, filtered and concentrated under reduced pressure. The resulting oil was dissolved in DMF (60 mL) and NaN_3 (10.3g, 0.158 mol) and tetrabutylammonium iodide (0.031 g, 0.080 mmol) were added. The solution was stirred at 55 °C for 14 hours. The reaction was allowed to cool to rt, H_2O (10 mL) was added and the reaction mixture was extracted with hexanes (2 x 10 mL). The organic layers were combined, dried with $MgSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (5% EtOAc in hexanes) to provide the desired product (6.93 g, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.21 (m, 5H), 3.77-3.71 (m, 1H), 3.74-3.71 (m, 2H), 2.85 (dd, *J* = 13.8, 6.0 Hz, 1H), 2.84 (dd, *J* = 13.8, 7.8 Hz, 1H), 1.78-1.76 (m, 1H), 1.67-1.62 (m, 1H), 0.89 (s, 9H), 0.05 (s, 3H), 0.04 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 129.3, 128.5, 126.7, 60.8, 59.5, 41.1, 37.0, 25.9, 18.1, -5.4; IR (neat) 2955, 2930, 2857, 2100, 1812, 1742 cm^{-1}; HRMS (EI) calcd. for $C_{16}H_{27}N_3OSi$ (M-C_4H_9) 248.1201, found 248.1207.

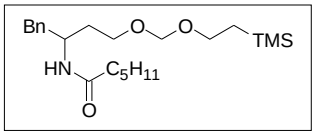


Hexanoic acid 1-benzyl-3-*tert*-butyldimethylsilanyloxypropyl amide, 10: To a solution of **9** (1.20 g, 3.93 mmol) in THF (20 mL) was added triphenylphosphine (1.24 g, 4.72 mmol), and the reaction mixture was stirred for 6 hours at rt. To the reaction mixture was added H_2O (4 mL). The reaction mixture was stirred for 8 hours at room temperature. To the reaction mixture was added triethylamine (1.19 g, 11.8 mmol) followed by hexanoyl chloride (1.05 g, 7.86 mmol). The reaction mixture was stirred for 6 hours at room temperature. The reaction mixture was extracted with EtOAc (2 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried with Na_2SO_4, filtered, and concentrated

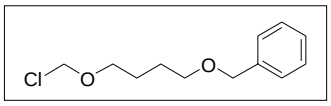
under reduced pressure. The resulting oil was purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (1.31 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.19 (m, 5H), 6.17 (d, *J* = 7.5 Hz, 1H), 4.34-4.23 (m, 1H), 3.83 (ddd, *J* = 10.5, 8.7, 4.5 Hz, 1H), 3.72-3.64 (m, 1H), 3.00 (dd, *J* = 13.5, 5.5 Hz, 1H), 2.74 (dd, *J* = 13.5, 8.2 Hz, 1H), 2.11 (t, *J* = 7.2 Hz, 2H), 1.81-1.70 (m, 1H), 1.67-1.51 (m, 3H), 1.35-1.24 (m, 4H), 0.92 (s, 9 H), 0.89 (t, *J* = 7.1 Hz, 3H), 0.08 (s, 3H), 0.07 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.6, 138.4, 129.4, 128.3, 126.3, 60.6, 49.3, 40.0, 37.1, 34.8, 33.9, 31.2, 25.9, 24.4, 22.4, 13.9, -5.4; IR (neat) 3287, 2930, 2858, 1711, 1643, 1097 cm^{-1}; HRMS (EI) calcd. for $C_{21}H_{36}NO_2Si$ (M-CH_3) 362.2515, found 362.2521.



Hexanoic acid 1-benzyl-3-hydroxypropylamide, 11: To a solution of **10** (549 mg, 1.45 mmol) in THF (13 mL) at 0 °C was added tetrabutylammonium fluoride (TBAF) (1.14 g, 4.35 mmol). The reaction mixture was warmed to room temperature and stirred for 2 hours. H_2O (10 mL) was added the reaction mixture was extracted with EtOAc (2 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (343 mg, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.13 (m, 5H), 5.52 (d, *J* = 8.4 Hz, 1H), 4.43-4.34 (m, 1H), 3.71 (bs, 1H), 3.61-3.64 (m, 2H), 2.87 (dd, *J* = 14.0, 6.0 Hz, 1H), 2.73 (dd, *J* = 14.0, 7.8 Hz, 1H), 2.13-2.06 (m, 2H), 1.92-1.84 (m, 1H), 1.48 (p, *J* = 7.2, 2H), 1.36-1.27 (m, 1H), 1.24-1.07 (m, 4H), 0.82 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5, 137.5, 129.1, 128.6, 126.7, 58.4, 46.8, 41.2, 37.8, 36.6, 31.2, 25.4, 22.3, 13.9; IR (neat) 3280, 2929, 1647, 1621, 1544, 1054 cm^{-1}; HRMS (EI) calcd. for $C_{16}H_{25}NO_2$ (M^+) 263.1885, found 263.1886.

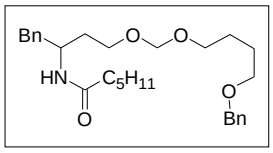


Hexanoic acid 1-benzyl-3-(2-trimethylsilanylethoxymethoxy)-propyl amide, 4: To a solution of **11** (0.10 g, 0.38 mmol) in CH_2Cl_2 (2 mL) at room temperature was added *N,N*-diisopropylethylamine (DIPEA) (2 mL) followed by 2-(trimethylsilyl)ethoxymethyl chloride (0.13 g, 0.76 mmol). The reaction mixture was heated to 45 °C for 8 hours. The reaction mixture was cooled to room temperature and H_2O (5 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with 10% aqueous acid (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (0.14 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.16 (m, 5H), 5.79 (d, *J* = 8.2 Hz, 1H), 4.63 (s, 2H), 4.35-4.23 (m, 1H), 3.71-3.55 (m, 4H), 2.89 (dd, *J* = 13.6, 6.0 Hz, 1H), 2.79 (dd, *J* = 13.6, 8.1 Hz, 1H), 2.10 (t, *J* = 8.1 Hz, 2H), 1.88-1.77 (m, 1H), 1.65-1.50 (m, 3H), 1.33-1.17 (m, 4H), 0.92 (t, *J* = 8.5 Hz, 2H), 0.87 (t, *J* = 6.8 Hz, 3H), 0.01 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 137.9, 129.3, 128.3, 126.3, 94.9, 65.2, 48.4, 40.3, 36.9, 32.9, 25.3, 22.3, 21.0, 18.0, 13.8, -1.5; IR (neat) 3282, 2954, 1639, 1549, 1060 cm^{-1}; HRMS (EI) calcd. for $C_{22}H_{39}NO_3Si$ (M^+) 393.2699, found 393.2706.

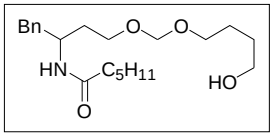


4-Chloromethoxybutoxymethylbenzene: To a solution of 4-benzyloxybutanol (1.22 g, 6.78 mmol) in CH_2Cl_2 (50 mL) was added paraformaldehyde (0.200 g, 6.78 mmol) and the suspension was cooled to 0 °C. HCl gas was bubbled through the reaction mixture until the paraformaldehyde was consumed (approximately 1 hour). The reaction mixture was place under HCl atmosphere and stirred for an additional 4

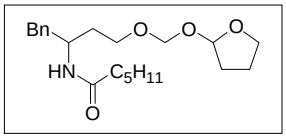
hours at 0 °C. Nitrogen was bubbled through the solution to remove the HCl, the solution was dried with Na_2SO_4, filtered, concentrated under reduced pressure providing the desired product in quantitative yield. The product was used without purification: crude ^{1}H NMR (300 MHz, C_6D_6) δ 7.28-7.15 (m, 5H), 5.07 (s, 2H), 4.35 (s, 2H), 3.43-3.38 (m, 2H), 3.32-3.25 (m, 2H), 1.63-1.55 (m, 4H).



Hexanoic acid 1-benzyl-3-(4-benzyloxybutoxymethoxy)-propyl amide, 12: To a solution of **5** (0.20 g, 0.77 mmol) in CH_2Cl_2 (2 mL) at room temperature was added DIPEA (2 mL) followed by 4-chloromethoxybutoxymethylbenzene (0.30 g, 1.2 mmol). The reaction mixture was heated to 45 °C for 8 hours. The reaction mixture was cooled to room temperature and H_2O (5 mL) was added. The reaction mixture was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with 10% aqueous acid (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (0.32 g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.17 (m, 10H), 5.65 (d, *J* = 8.2 Hz, 1H), 4.64 (s, 2H), 4.50 (s, 2H), 4.29 (br, 1H), 3.69-3.47 (m, 6H), 2.90 (dd, *J* = 13.6, 5.9 Hz, 1H), 2.77 (dd, *J* = 13.6, 7.3 Hz, 1H), 2.15-2.10 (m, 2H), 1.89-1.79 (m, 1H), 1.72-1.52 (m, 7H), 1.32-1.18 (m, 4H), 0.89 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.8, 138.9, 138.3, 129.8, 128.7, 128.6, 127.9, 127.8, 126.7, 95.8, 73.2, 70.4, 68.1, 65.4, 48.8, 40.8, 37.3, 33.4, 31.7, 26.8, 26.8, 25.7, 22.7, 17.2; IR (neat) 3290, 2928, 1641, 1547, 1113 cm^{-1}; HRMS (EI) calcd. for $C_{21}H_{34}NO_4$ (M-C_7H_7) 364.2488, found 364.2495.

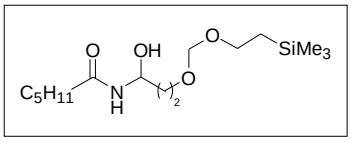


Hexanoic acid 1-benzyl-3-(4-hydroxy-butoxymethoxy)-propyl-amide, 13: To a solution of **12** (0.22 g, 0.49 mmol) in ethanol at room temperature was added Pd/C (44 mg, 20 wt%). The reaction mixture was placed under hydrogen atmosphere and stirred at room temperature for 8 hours. The reaction mixture was filtered through a pad of celite, concentrated under reduced pressure and purified by flash chromatography (20% hexanes in EtOAc) to provide the desired product (0.17 g, 98% yield): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.17 (m, 5H), 5.67 (d, *J* = 8.0 Hz, 1H), 4.66 (s, 2H), 4.38-4.26 (m, 1H), 3.69-3.51 (m, 6H), 2.91 (dd, *J* = 13.7, 6.2 Hz, 1H), 2.79 (dd, *J* = 13.7, 7.1 Hz, 1H), 2.26 (bs, 1H), 2.11 (t, *J* = 6.7 Hz, 2H), 1.91-1.82 (m, 1H), 1.71-1.49 (m, 7H), 1.34-1.17 (m, 4H), 0.86 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.7, 137.9, 129.5, 138.4, 126.4, 95.5, 68.0, 65.2, 62.5, 48.3, 40.7, 36.9, 33.4, 31.4, 29.8, 26.4, 25.4, 33.4, 13.9; IR (neat) 3289, 2930, 1643, 1549, 1046 cm^{-1}; HRMS (EI) calcd. for $C_{21}H_{36}NO_4$ (M+H) 366.2644, found 366.2632.

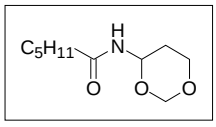


Hexanoic acid 1-benzyl-3-(tetrahydro-furan-2-yloxymethoxy)-propyl-amide, 5: To a solution of **13** (0.17 g, 0.48 mmol) in cyclohexane was added iodobenzene diacetate (0.34 g, 1.1 mmol) and iodine (96 mg, 0.76 mmol). The reaction mixture was irradiated for 2 hours. The reaction mixture was extracted with EtOAc, washed with saturated aqueous $Na_2S_2O_3$ (10 mL) and brine (10 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product as a mixture of diastereomers (0.10 g, 59%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.17 (m, 5H), 5.80 (d, *J* = 7.9 Hz, 1H), 5.36-5.32 (m, 1H), 4.90-4.85 (m, 1H), 4.64-4.58 (m, 1H), 4.32-4.24 (m, 1H), 3.96-3.81 (m, 1H), 3.79-3.71 (m, 1H), 3.70-3.62 (m, 1H), 3.56-3.48 (m, 1H), 2.96-2.86 (m, 1H), 2.81-2.74 (m, 1H), 2.13-2.00 (m,

2H), 1.99-1.75 (m, 5H), 1.67-1.52 (m, 3H), 1.34-1.15 (m, 4H), 0.88 (t, J = 6.7 Hz, 3H); ^{13}C NMR (300 MHz, $CDCl_3$) δ 172.6, 138.1, 129.4, 129.1, 126.3, 101.5, 92.7, 67.3, 65.7, 48.8, 48.4, 40.4, 36.9, 32.7, 31.4, 25.4, 23.5, 23.2, 13.9; IR (neat) 3289, 2929, 1614, 1544 cm^{-1}; HRMS (EI) calcd. for $C_{19}H_{28}NO_4$ (M-C_2H_5) 334.2018, found 334.2036.



Hexanoic acid 1-hydroxy-3-(2-trimethylsilanyl-ethoxymethoxy)-propyl-amide, 14: To a solution of **5** (0.11 g, 0.28 mmol) in dichloroethane (6 mL) at room temperature was added *N*-methylquinolinium hexafluorophosphate (NMQ) (4.0 mg, 0.01 mmol), NaOAc (0.22 g, 200 wt.%), $Na_2S_2O_3$ (0.22 g, 200 wt.%) and toluene (1 mL). Air was gently bubbled through the suspension and the solution was irradiated for 4 hours. The reaction mixture was filtered through a small plug of silica, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (80% EtOAc in hexanes) to provide **15** (60 mg, 65%): ^{1}H NMR (300 MHz, CD_2Cl_2) δ 6.85 (br, 1H), 5.44-5.38 (m, 1H), 4.65 (s, 2H), 3.94 (d, J = 3.2 Hz, 1H), 3.82-3.75 (m, 1H), 3.67-3.54 (m, 3H), 2.14 (t, J = 7.3 Hz, 2H), 1.92-1.84 (m, 2H), 1.63-1.53 (m, 2H), 1.36-1.24 (m, 4H), 0.96-0.87 (m, 5H), 0.02 (s, 9H); ^{13}C NMR (75 MHz, CD_2Cl_2) δ 175.1, 95.3, 73.8, 65.6, 63.9, 37.1, 34.7, 31.7, 25.4, 22.7, 18.4, 14.0, -1.4; IR (neat) 3299, 2955, 1654, 1538, 1249, 1060 cm^{-1}; LRMS (EI): *m/z* 320, 302, 262, 246, 232, 202, 188, 172.



Hexanoic acid 1,3-dioxan-4-ylamide, 1: To a solution of **5** (90 mg, 0.25 mmol) in dichloroethane (6 mL) at room temperature was added NMQ (3.5 mg, 0.01 mmol), NaOAc (0.18 g, 200 wt.%), $Na_2S_2O_3$ (0.18 g, 200 wt.%), 4 Å molecular sieves (0.18 g, 200 wt.%) and toluene (1 mL). Air was gently bubbled through the suspension while it

was irradiated for 4 hours. The reaction mixture was filtered through a small plug of silica, and concentrated under reduced pressure. The resulting oil was purified by column flash chromatography (50% EtOAc in hexanes) to provide the desired product (39 mg, 79%): ^{1}H NMR (300 MHz, CD_2Cl_2) δ 5.92 (br, 1H), 5.43 (td, *J* = 10.0, 2.8 Hz, 1H), 5.05 (d, *J* = 6.5 Hz, 1H), 4.83 (d, *J* = 6.5 Hz, 1H), 4.15 (app dd, *J* = 11.6, 4.9 Hz, 1H), 3.79 (td, *J* = 11.7, 2.8 Hz, 1H), 2.22 (t, *J* = 7.3 Hz, 2H), 1.91-1.78 (m, 1H), 1.75-1.60 (m, 3H), 1.35-1.26 (m, 4H), 0.90 (t, *J* = 6,9 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 172.7, 92.8, 77.2, 65.9, 36.7, 32.1, 31.3, 25.0, 22.4, 13.9; IR (neat) 3325, 2927, 1661, 1540, 1015 cm^{-1}; HRMS (EI) calcd. for $C_{10}H_{19}NO_3$ (M^+) 201.1365, found 201.1361.

1.5 References

1. Perry, N. B.; Blunt, J. W.; Munro, M. G. H.; Pannell, L. K. "Mycalamide A, an Antiviral Compound from a New Zealand Sponge of the Genus *Mycale*" *J. Am. Chem. Soc.* **1988**, *110*, 4850-4851.
2. Perry, N. B.; Blunt, J. W.; Munro, M. G. H.; Pannell, L.K.; Thompson, A. M. "Antiviral and Antitumor Agents from a New Zealand Sponge, *Mycale* sp. 2. Structures and Solution Conformations of Mycalamide A and B" *J. Org. Chem.* **1990**, *55*, 223-227.
3. Simpson, S.; Garson, M. J.; Blunt J. W.; Munro, M. H. G.; Hooper, J. N. A. "Mycalamide C and D, Cytotoxic Compounds from the Marine Sponge *Stylinos* n. Species" *J. Nat. Prod.* **2000**, *63*, 704-706.
4. Sakemi, S.; Ichiba, T.; Kohmoto, S.; Saucy G.; Higa, T. "Isolation and Structural Elucidation of Onnamide A, a New Bioactive Metabolite of a Marine Sponge, *Theonella* sp" *J. Am. Chem. Soc.* **1988**, *110*, 4851-4853.
5. Matsunaga, S.; Fusetani, N.; Nakao, Y. "Eight New Cytotoxic Metabolites Related to Onnamide A from Two Marine Sponges of the Genus *Theonella*" *Tetrahedron* **1992,** *48*, 8369-8376.
6. Kobayashi, J.; Itagaki, H.; Shigemori, T.; Sasaki, J. "Three New Onnamide Congeners from the Okinawan Marine Sponge *Theonella sp.*" *J. Nat. Prod.* **1993**, *56*, 976-981.
7. Vuong, D.; Capon, R. J.; Lacey, E.; Jennifer, G. H.; Heiland, K.; Friedel, T. "Onnamide F: A New Nematocide from a Southern Australian Marine Sponge, *Trachycladus laevispirulifer*" *J. Nat. Prod.* **2001**, *64*, 640-642.

8. Fusetani, N.; Sugawara, T.; Matsunaga, S. "Bioactive Marine Metabolites. 41. Theopederins A-E, Potent Antitumor Metabolites from a Marine Sponge *Theonella* sp." *J. Org. Chem.* **1992**, *57*, 3828-3832.
9. Tsukamoto, S.; Matsunaga, S.; Fusentani, N.; Toh-e, A. "Theopederins F-J: Five New Antifungal and Cytotoxic Metabolites from the Marine Sponge, *Theonella swinhoei*" *Tetrahedron* **1999**, *55*, 13697-13702.
10. Paul, G. K.; Dunasekera, S. P.; Longley, R. E.; Pomponi, S. A. "Theopederins K and L Highly Potent Cytotoxic Metabolites from a Marine Sponge *Discodermia* Species" *J. Nat. Prod.* **2002**, *65*, 59-61.
11. Schmittel, M; Ghorai, M. K. "Reactivity Patterns or Radical Ions – A Unifying Picture of Radical-Anion and Radical-Cation Transfromations" *Electron Transfer in Chemistry, Vol. 2 Organic Molecules* Wiley-CHV, Weinheim, **2001**.
12. Schmittel, M.; Burghart, A. "Understanding Reactivity Patterns of Radical Cations" *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2550-2589.
13. Maslak, P.; Vallombroso, T. M.; Chapman W. H. Jr.; Narvaez, J. N. "Free-Energy Relationships for Mesolytic Cleavage of C-C Bonds" *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 73-75.
14. Freccero, M.; Pratt, A.; Albini, A.; Long, C. "A Kinetic Evaluation of Carbon-Hydrogen, Carbon-Carbon, and Carbon-Silicon Bond Activation in Benzylic Radical Cations" *J. Am. Chem. Soc.* **1998**, *120*, 284-297.
15. Howell, J. O.; Concalves, J. M.; Amatore, C.; Klasinc, L.; Wightman, R. M.; Kochi, J. K. "Electron Transfer from Aromatic Hydrocarbons and Their π-Complexes with

Metals. Comparison of the Standard Oxidation Potentials and Vertical Ionization Potentials" *J. Am. Chem. Soc.* **1984**, *106*, 3968-3976.

16. Arnold, D. R.; Lamont, L. J. "Photosensitized (Electron Transfer) Carbon-Carbon Bond Cleavage of Radical Cations: The 2-Phenylethyl Ether and Acetal Systems" *Can. J. Chem.* **1989**, *67*, 2119-2127.
17. Popielarz, R.; Arnold, D. R. "Radical Ions in Photochemistry. Part 24. Carbon-Carbon Bond Cleavage of Radical Cations in Solution: Theory and Application" *J. Am. Chem. Soc.* **1990**, *112*, 3068-3082.
18. Wayner, D. D. M.; McPhee, D. J.; Griller, D. "Oxidation and Reduction Potentials of Transient Free Radicals" *J. Am. Chem. Soc.* **1988**, *110*, 132-137.
19. Kumar, S. V.; Floreancig, P. E. "Electron Transfer Initiated Cyclizations: Cyclic Acetal Synthesis through Carbon-Carbon σ-Bond Activiation" *J. Am. Chem. Soc.* **2001**, *123*, 3842-3843.
20. Kumar, S. V.; Aubele, D. L.; Floreancig, P. E. "Aerobic Organocatalytic Photoinitiated Arene Oxidation: Application to Electron Transfer Initiated Cyclization Reactions" *Org. Lett.* **2001**, *3*, 4123-4125.
21. Aubele, D. L.; Floreancig, P. E. "Oxidative Synthesis of Cyclic Acyl Aminals through Carbon-Carbon σ-Bond Activation" *Org. Lett.* **2002**, *4*, 3443-3446.
22. De Armas, P.; Concepcion, J. I.; Francisco, C. G.; Hernandez, R.; Salazar, J. A.; Suarez, E. "Intramolecular Hydrogen Abstraction. Hypervalent Organoiodine Compounds, Convenient Reagents for Alkoxy Radical Generation" *J. Chem. Soc. Perkin. Trans. I* **1989**, 405-411.

23. Troast, D. M.; Porco, J. A. "Studies Toward the Synthesis of (-)-Zampanolide: Preparation of *N*-Acyl Hemiaminal Model Systems" *Org. Lett.* **2002**, *4*, 991-994.

24. Rech, J. C.; Floreancig, P. E. "An Oxidative Entry into the Amido Trioxadecalin Ring System" *Org. Lett.* **2003**, *5*, 1495-1498.

25. Aubele, D. L.; Rech, J. C.; Floreancig, P. E. "Catalytic Aerobic Generation of Acyliminium Ions through Electron-Transfer-Mediated Carbon-Carbon Bond Activitation" *Adv. Synth. Catal.* **2004**, *346*, 359-366.

2. Efforts Toward the Total Synthesis of Mycalamide B

2.1 Introduction

The mycalamides A-D,[1-4] onnamides A-F,[5-8] theopederins A-L[9-11] and psymberin/iriciniastatin A[12,13] are members of a class of natural products structurally related to pederin[14] (Figure 18). Most of these compounds have been shown to exhibit potent biological activity; however their limited availability from natural sources has hindered the thorough examination of their therapeutic potential. The interesting structure, biological activity and scarce availability of these compounds has generated a considerable amount of interest among the synthetic community. Matsumoto,[15-18] Meinwald,[19-22] Kishi,[23,24] Kocienski,[25-38] Roush,[39-42] Nakata,[43-46] Ihara,[47,48] Hoffman,[49] Trost,[50] Rawal,[51] and De Brabander[52] have reported synthetic studies directed toward the generation of these compounds.

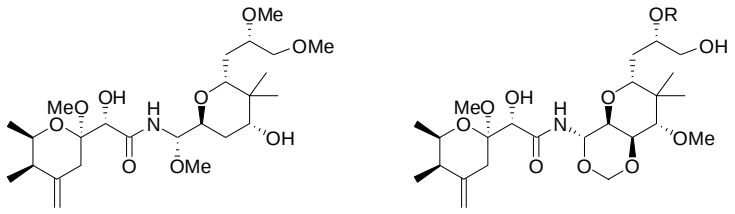


Figure 18: Pederin and Mycalamide A and B

The structure of pederin[14] was reported in 1965 from the dermestid beetle, *Psiderus fusipes*. Pederin's structure was considered to be unique until 1988 when Blunt and coworkers[1] reported mycalamide A (isolated from a New Zealand sponge of the genus *Mycale*) and Furusaki

and coworkers[5] reported onnamide A (isolated from Okinawan sponge of the genus *Theonella*). The remaining members of the pederin family were isolated in virtually all parts of the world from a variety of marine sponges belonging to the class *Demospongiae*. The highly diverse nature of the source organisms for the pederin family of natural products has led to the speculation that these compounds may have a common bacterial origin.[53]

I. Isolation and Structural Determination of Mycalamide A and B

Mycalamide A[1] was isolated in 1988 and mycalamide B[2] in 1990 by Blunt and coworkers from a marine sponge of the genus *Mycale* native to the Otago Harbour of New Zealand (Figure 19). Reverse phase, gel permeation and silica gel chromatography techniques were utilized in the isolation of these compounds. The purification of extract resulting from 200 g of *mycale* sponge generated approximately 3.7 mg of mycalamide A, which was reported to be nearly twice as abundant as mycalamide B.[1,2]

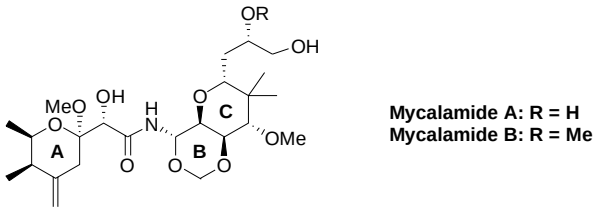


Figure 19: Structure of Mycalamide A and B

The structure of mycalamide A was determined using mass spectrometry and NMR and IR spectroscopy.[1] HRMS-EI provided a weak molecular ion peak (503.2722 daltons) corresponding to the molecular formula $C_{24}H_{41}NO_{10}$. The presence of 4 exchangeable protons

was identified through CIMS using ND_3 as the reagent gas. ^{1}H NMR indicated the presence of a secondary amide with a one proton doublet (δ 7.49 (d, J = 9.8 Hz, 1 H)) that slowly disappeared upon treatment with D_2O. The presence of the amide was confirmed by the ^{13}C NMR (δ 171.5) and IR (1700 cm^{-1}) spectrum. The ^{13}C NMR spectrum also indicated the presence of a 1,1′-disubstituted olefin (δ 110.4, 145.4).[1]

The pederic acid fragment of mycalamide A was further examined by HETCOR, COSY, long-range HETCOR and nOe experiments. The connectivity was established by long-range HETCOR (Figure 20). A comparison of the ^{1}H NMR spectra of the left hand fragments of mycalamide A and pederin suggested these fragments were nearly identical providing a benchmark for the assignment of the stereochemistry.[1] nOe analysis indicated the dominant conformation of the pederic acid fragment is a chair-like conformation that places the C6-OCH_3 in the axial position, consistent with the anomeric effect.[2]

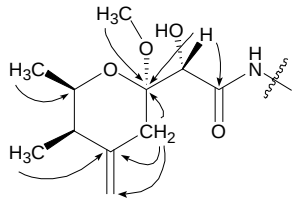


Figure 20: Long-Range HETCOR Analysis of the Pederic Acid Fragment of Mycalamide A

The conformation and connectivity of the amido trioxadecalin fragment of mycalamide A was determined by a series of nOe experiments.[1] The nOe data were consistent with a *cis*-fused trioxadecalin system with both rings residing in a chair conformation.[2] The defining nOe enhancements are shown in Figure 21. Mycalamide B was isolated as a less polar component in

the purification of mycalamide A. Similar analyses were employed to determine the structure of mycalamide B.[2]

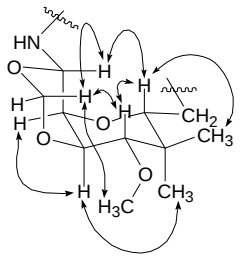


Figure 21: Pertinent nOe Enhancements of the Amido Trioxadecalin Fragment

II. Biological Activity

Mycalamides A and B possess potent biological activity with the potential for use in three separate therapeutic areas. These compounds have been shown to be inhibitors of tumor cell proliferation[54] and potent immunosuppressive agents.[55] They have also displayed moderate antiviral activity.[56]

Burres and Clement[54] demonstrated that mycalamides A and B inhibit the proliferation of murine leukemia P388 cell replication at IC_{50} values of 5.2 nM and 1.3 nM, respectively. Nanomolar range inhibition was also observed with the human promyelocytic (HL-60) leukemia, and human lung (A549) and colon (HT-29) carcinoma cells. Additionally, mycalamides A and B performed well against the P388 *in vivo* leukemia model showing a 40% (10 μg/kg) and 50% (2.5 μg/kg) increase in lifespan, respectively. Increases in lifespan were observed with other *in vivo* models, such as, M5076 ovarian carcinoma and B16 melanoma. Mycalamide A was also

shown to inhibit the growth of solid tumor models (Lewis Lung, M5076, and Burkitt's Lymphoma).[54]

Mycalamide A was also shown to efficiently block the activation of $CD4^{+}$T cells with an IC_{50} of 1 pM. When concentrations approached 10 pM T cell proliferation is abrogated. The immunosuppressive activity of mycalamide A is 40 fold and 1000 fold more potent than the clinical immunosuppressive agents FK506 and cyclosporine, respectively.[55] The antiviral activity of mycalamides A and B was observed by Perry and coworkers when these compounds were exposed to Hav-NRK cell cultures. Mycalamide A induced a positive morphological change at 20 μM, while the same response was generated by mycalamide B at 2 μM.[56]

The biological activity of mycalamides A and B appears to result from their ability to inhibit protein biosynthesis. The incorporation of radiolabeled leucine in P388 cells following treatment with mycalamide A and B showed a significant decrease in protein synthesis with complete inhibition at 2 μM for mycalamide A and 0.2 μM for mycalamide B.[54] In Hav-NRK cells protein synthesis was inhibited by 50% at concentrations of 12 μM and 3 μM for mycalamides A and B, respectively.[56] Moreover, it was determined that mycalamides A and B preferentially inhibited the biosynthesis of p21 protein,[56] which participates in temporarily arresting cell replication in response to the detection of DNA damage.[57] In a recent study competitive binding experiments suggest that pederin and related compounds inhibit protein biosynthesis by selectively binding to the 60S large ribosomal subunit.[58]

III. Structure Activity Relationships of Mycalamides A and B

An examination of the effects of structure on the biological activity of mycalamides A and B has indicated that the C_{10} *N*-acylaminal, C_7 hydroxy and C_6 methoxy functional groups are required for potent biological activity (Figure 22).[59-62] Derivatives of the C_{10} *N*-acylaminal, including *N*-methylation and C_{10} stereochemical inversion, resulted in a >1000 fold and 100 fold loss in activity, respectively. Significant reductions (50–1000 fold) in biological activity were also observed when derivatives of the C_6 methoxy and/or C_7 hydroxy groups were generated. Other functional groups such as the exocyclic olefin, the C_{12} alkoxy and the C_{17} and C_{18} positions of the side chain where shown to tolerate synthetic manipulation, exhibiting only moderate changes in biological activity.[59-62]

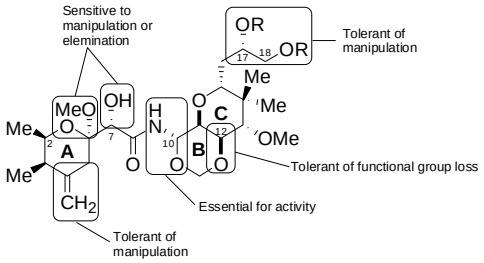


Figure 22: Relevant Functionality for Biological Activity

IV. *Previous Syntheses*

The limited availability from natural sources, structural complexity and interesting biological activity of mycalamides A and B has resulted in a considerable amount of synthetic interest in these compounds. Total syntheses have been reported by Kish,[23] Roush,[42] Kocienski,[36] Nakata[44] and Rawal[51] and formal or partial syntheses have been Ihara,[47] Hoffman,[49]

Mienwald[19] and Trost.[50] Despite the numerous synthetic efforts devoted toward these compounds only two general methods have been developed for the generation of the C_{10} *N*-acylaminal (Figure 23).

The first approach, developed by Hong and Kishi,[23] utilizes an *N*-acylation of the nucleophilic amino trioxadecalin system by a pederic acid derivative to complete the formation of the *N*-acylaminal functional group (Figure 23). While the nucleophilicity of the amino trioxadecalin system allows for facile coupling to the pederic acid fragment, the instability of the hemiaminal functional group resulted in rapid epimerization generating a diastereomeric mixture at the C_{10} *N*-acylaminal center.[23] Recently, the utility of this approach was significantly increased by Rawal and coworkers[51] when they reported *N*-acylation conditions that allowed for the selective generation of the C_{10} *N*-acylaminal of mycalamide A from the coupling of the amino trioxadecalin and pederic acid fragments.

Roush and coworkers[40] reported an alternative approach that employs a Curtius reaction to generate the C_{10} *N*-acylaminal (Figure 23). While this method allows for the stereoselective synthesis of the *N*-acylaminal functional group, the low reactivity of the resulting carbamate precluded its coupling to pederic acid derivatives. The following is a detailed account of the synthetic approaches utilized by Kishi, Roush and Rawal in their syntheses of mycalamides A and B.

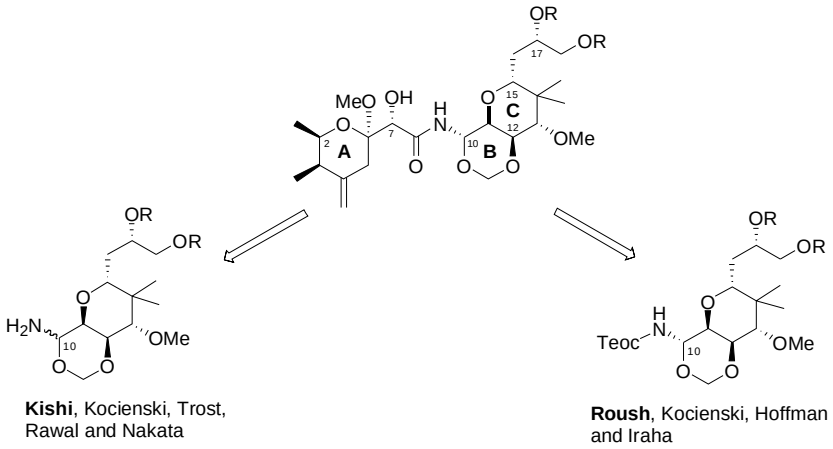
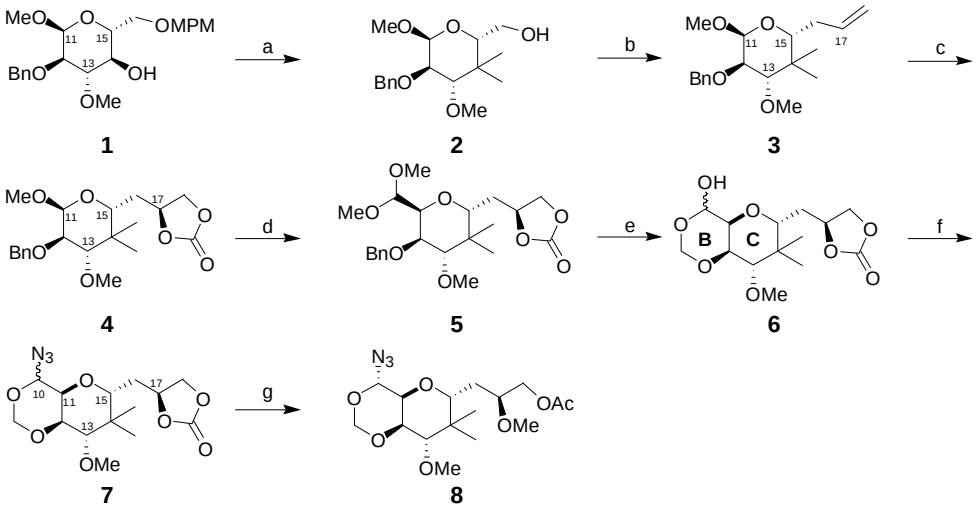


Figure 23: Synthetic Approaches toward the *N*-Acylaminal

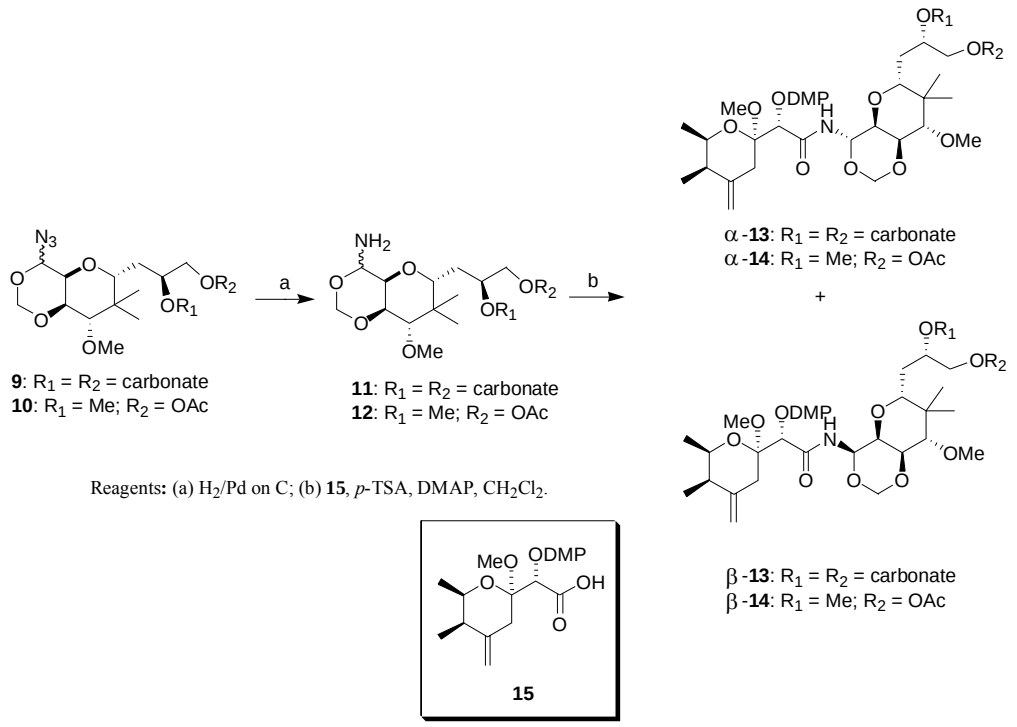
The first total synthesis of mycalamides A and B was published by Hong and Kishi[23] in 1990, two years after the isolation of mycalamide A was reported. Mycalamides A and B were generated in 29 and 35 linear steps, respectively, from glycoside **1** (Scheme 5), which was derived in 6 steps from commercially available α-D-glucopyranoside. The requisite stereochemistry at the C_{12}, C_{13} and C_{15} centers was inherent to glycoside **1**. The remaining C_{11} and C_{17} stereocenters were established by an anomeric propargylation and an asymmetric dihydroxylation, respectively. A three step sequence generated the B ring as a hemiacetal that was subsequently converted to the azido trioxadecalin system (**7**, Scheme 5) as an inseparable mixture of diastereomers. The azido trioxadecalin system **7** served as the precursor to mycalamide A. Subsequent protecting group manipulation of the C_{15} side chain generated the precursor to mycalamide B (**8**, Scheme 5) as a separable mixture of diastereomers.



Reagents: (a) 7 steps, 62 %; (b) 5 steps, 79 %; (c) OsO_4/*N,N*-bis trimethyl benzyl-S,S-diphenyl-1,2-diaminoethane then carbonate formation, 6:1 mixture, 75 %; (d) propargyltrimethylsilane, TMSOTf then ozonolysis and acetalization, 60%; (e) H_2/$Pd(OH)_2$ on carbon then paraformaldehyde and HCl, 2:1 mixture, 86%: (f) MsCl, NEt_3, DMAP then Bu_4NN_3; (g) 6 steps, 2:1 seperable mixture, 76%.

Scheme 5: Kishi's Generation of the Azido Trioxadecalin System

Azide reduction generated the amino trioxadecalin systems (**11** and **12**, Scheme 6) that were shown to be configurationally unstable to acidic, basic and neutral conditions.[23] The amino trioxadecalin systems (**11** and **12**) readily coupled with pederic acid derivative **15** yielding separable mixtures of α-**13** (38% yield) and β-**13** (40% yield) or α-**14** (59% yield) and β-**14** (26% yield), with the α-diastereomer possessing the natural configuration. Both β-**13** and β-**14** were shown to undergo an epimerization at the C_{10} *N*-acylaminal center to generate the corresponding natural α-configuration under basic conditions (*t*-BuOK/THF/reflux). The alkaline treatment of β-**13** resulted in almost complete epimerization to the natural diastereomer and β-**14** epimerized to a 1:1 mixture of natural (α-**14**) and unnatural (β-**14**) diastereomers. Deprotection of α-**13** and α-**14** generated mycalamide A and B, respectively.

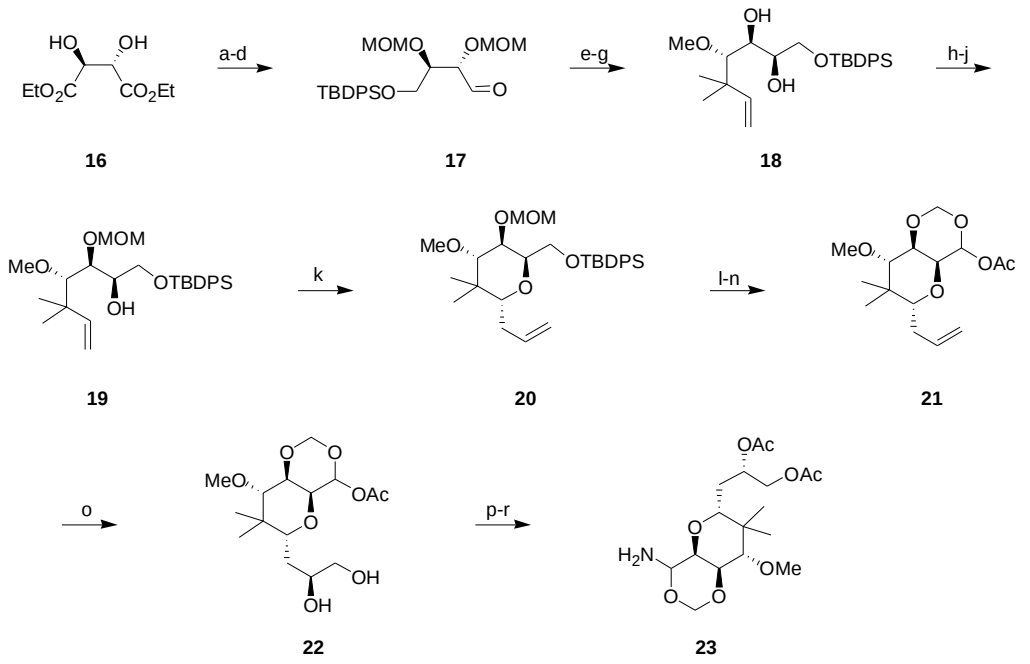


Scheme 6: Kishi's Completion of Mycalamides A and B

Kishi has since published a total synthesis of onnamide A, wherein the synthesis of the mycalamide core was considerably improved. However, epimerization of the amino trioxadecalin system continued to be a problem.[24]

Rawal's synthesis of the amino trioxadecalin fragment of mycalamide A began with the desymmetrization of D-tartrate generating aldehyde **17** in good yield (Scheme 7).[51] The tartrate stereocenters were utilized to effectively control the remaining stereochemistry of the amino trioxadecalin ring through a prenylation and a lewis acid promoted lactol allylation. The dioxane ring was generated by the treatment with formaldehyde under acidic conditions and subsequent lactol acylation generated **21** in good yield. An asymmetric dihydroxylation of the olefin of **21** established the side chain stereochemistry with moderate selectivity (**22**, Scheme 7) and the Lewis acid mediated TMSCN displacement of the acyllactol **22** generated the azide precursor to

the amine functional group. Reduction of the azide resulted in the generation of the amino trioxadecalin coupling partner, **23**.

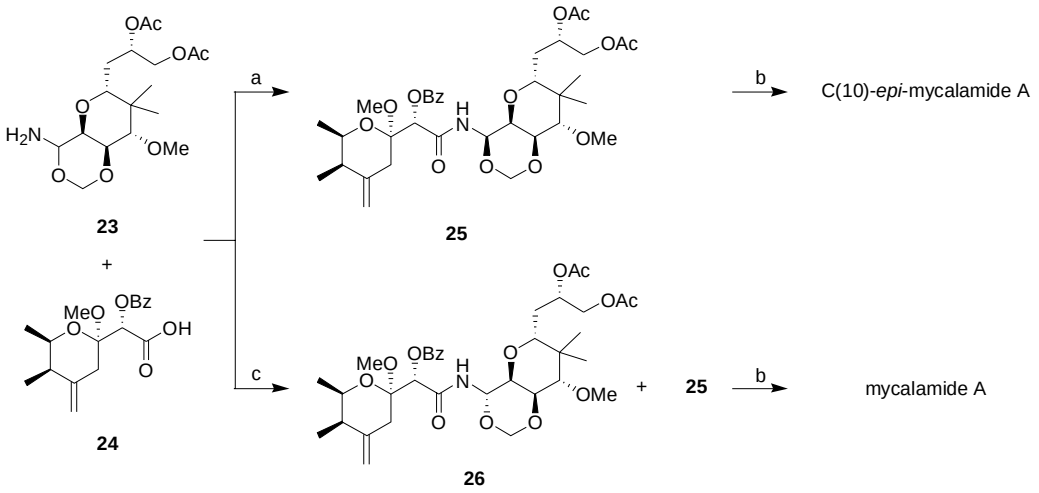


Reagents: (a) $(MeO)_2CH_2$, P_2O_5, CH_2Cl_2, 100%; (b) LAH, Et_2O, 86%; (c) *n*-BuLi; TBDPSCl, THF, 100%; (d) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 90%; (e) $Me_2CCHCH_2SnBu_2$, $ZnBr_2$, CH_2Cl_2, 90%, 50:1 dr; (f) NaH, MeI, THF, 98%; (g)$ZnBr_2$, *n*-BuSH, CH_2Cl_2, 98%; (h) BzCl, DIPEA, CH_2Cl_2, 80%; (i) $CH_2(OMe)_2$, P_2O_5, CH_2Cl_2, 91%; (j) K_2CO_3, MeOH, 83%; (k) O_3, Me_2S, CH_2Cl_2; Ac_2O, DMAP, pyr; BF_3•OEt_2, CH_2CHCH_2TMS, CH_2Cl_2, 66%; (l) TBAF, THF, 91%; (m) $(COCl)_2$, DMSO, NEt_3, CH_2Cl_2; (n) $(CHO)_n$, concd HCl, THF; Ac_2O, DIPEA, pyr, 63%; (o) OsO_4, $(DHQ)_2PYR$, K_2CO_3, $K_3Fe(CN)_6$, *t*-BuOH/H_2O, 83%, 5:1 dr; (p) Ac_2O, DIPEA, DMAP, CH_2Cl_2, 92%; (q) $TMSN_3$, TMSOTf, CH_3CN, 100%; (r) H_2, Pd/C, EOAc, 90%.

Scheme 7: Rawal's Synthesis of the Amino Trioxadecalin System of Mycalamide A

A highlight of the Rawal synthesis of mycalamide A was the enhanced selectivity reported in the coupling of the amino trioxadecalin fragment **23** with pederic acid derivative **24** (Figure 24).[51] Rawal reported the generation of the precursor to C_{10}-*epi*-mycalamide A, **25**, as a single diastereomer in 61% yield when PyAOP was employed in the presence of DIPEA to generate the activated ester of **24** prior to coupling with **23**. Under conditions that employed DCC and DMAP the coupling proceeded in a 56% yield with 5:1 diastereoselectivity in favor of

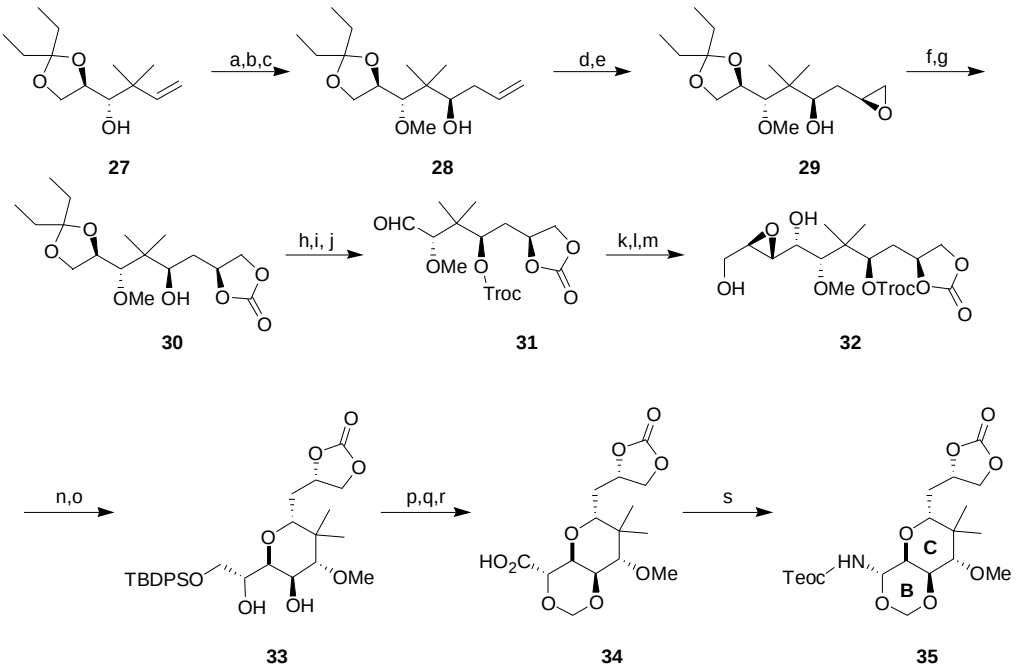
the natural diastereomer, **26**. Methyl ester hydrolysis of the coupling product completed the synthesis of mycalamide A. The selectivity observed by Rawal and coworkers is a marked improvement over the conditions reported by Kishi and significantly increases the utility of this method.



Reagents: (a) PyAOP, DIPEA, CH_2Cl_2, 61%; (b) 1N LiOH, THF, 75%; (c) DCC, DMAP, CH_2Cl_2, 56%, 5:1 dr.

Figure 24: Rawal's Coupling to Synthesize Mycalamide A

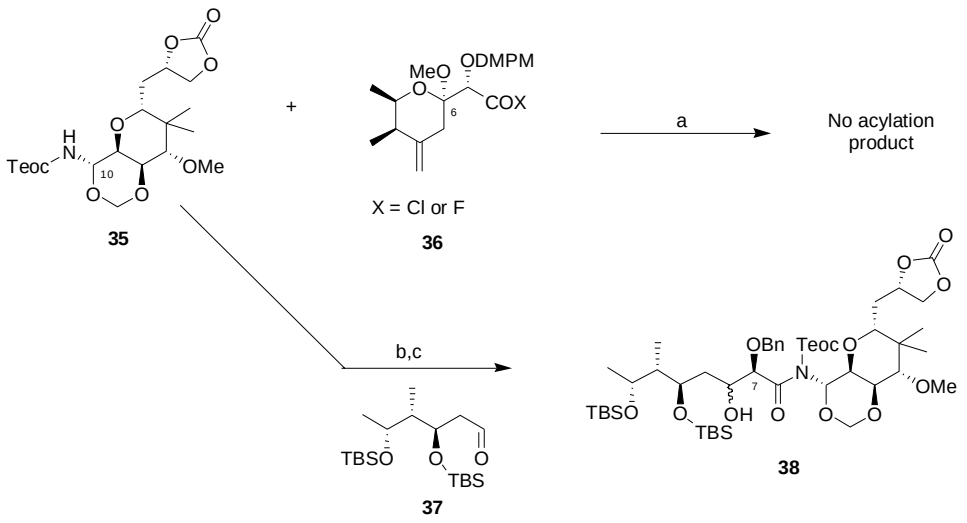
In 2000, Roush and coworkers[41,42] reported the total synthesis of mycalamide A and 7-*epi*-mycalamide A wherein they describe the stereoselective formation of the C_{10} *N*-acylaminal by a Curtius reaction (Scheme 8).[41] The synthesis began with alcohol **27** generated from the asymmetric prenylboration of D-glyceraldehyde 3-pentylidene ketal and relies heavily on reagent control to establish the remaining stereochemistry of the **B** and **C** rings. The C_{10} *N*-acylaminal was generated from the configurationally stable trioxadecalin carboxylic acid **34** by a Curtius reaction that proceeded with retention of configuration to provide the amido trioxadecalin precursor to mycalamide A (**35**, Scheme 8).



Reagents: (a) MeI, NaH; (b) O_3, Ph_3P, 82% over two steps; (c) Ipc_2BAll, 89%, >98:2; (d) BuLi then BOC-ON; (e) IBr then NaOH, 77% and 25:1; (f) NaOAc, DMF, H_2O; (g) triphosgene and pyridine, 64% over 2 steps; (h) Troc-Cl, pyridine; (i) HOAc-H_2O; (j) KIO_4, 65% over 3 steps; (k) *E*-γ -(trimethylsilyl)allylboronate, 93% with >98:2; (l) DMDO, then MeOH-HOAc; (m) SAE, 77%; (n) Zn, HOAc; (o) TBDPS-Cl, imidazole, 73% over 2 steps; (p) P_2O_5, methylal; (q) TBAF; (r) Jones, 76% over 3 steps; (s) $(PhO)_2(O)N_3$, NEt_3, $TMS(CH_2)_2OH$, 64%.

Scheme 8: Roush's Approach to Mycalamide A

To complete the synthesis Roush and coworkers[42] attempted to couple the carbamate **35** with a pederic acid derivatives **36** but were unsuccessful (Scheme 9). The lack of reactivity was attributed to the steric congestion surrounding the C_6-ketal and C_{10}-*N*-acylaminal functional groups. To complete the synthesis carbamate **35** was acylated with benzyloxyacetyl chloride. The resulting *N*-acylaminal was subjected to a titanium mediated aldol addition into aldehyde **37** that generated **38** as a mixture of diastereomers favoring the unnatural stereochemistry at the C_7-stereocenter. Further elaborations of aldol adduct **38** allowed for the completion of the total synthesis of mycalamide A.



Reagents: (a) *n*-BuLi or $LiN(TMS)_2$-HMPA or $KN(TMS)_2$, THF, -78 ^oC then **36** (b) LiHMDS, THF, -78 ^oC; (c) $BnOCH_2COCl$, DMAP, CH_2Cl_2, 76%; (c) $TiCl_4$, *i*-Pr_2NEt, CH_2Cl_2, -78 ^oC then **37**, 84%, 5:4:1:1 d.r.

Scheme 9: Roush's Completion of Mycalamide A

Mycalamides A and B, in particular the *N*-acylaminal functional group, have proven to be a formidable synthetic challenge. The coupling approach developed by Kishi, including the advances reported by Rawal, is an effective method for the synthesis of the requisite functional groups with an adequate level of selectivity. The method developed by Roush is highly selective for the generation of the desired *N*-acylaminal functional group, but is limited by the reactivity of subsequent intermediates. These methods focus largely on the generation C-N amide bond of the *N*-acylaminal to complete the synthesis of the amido trioxadecalin system. An alternative approach to this functional group would increase the available synthetic options providing an enhanced opportunity to increase the selectivity and efficiency of the synthetic approaches to mycalamides A and B.

V. Project Goals and Retrosynthesis

The generation of the amido trioxadecalin system through the nucleophilic addition of a pendent formaldehyde hemiacetal equivalent into an *N*-acyliminium ion provides a novel approach to the synthesis of mycalamides A and B (Figure 25). This approach allows for the generation of the *N*-acylaminal late in the synthetic sequence, allowing for the inherent chirality of the C ring to control the resulting stereochemistry of the C_{10} *N*-acylaminal (**TS-40**). The sensitivity of the substrate and product of this transformation require that the generation of the acyliminium ion occur under mild conditions.

As described in Chapter 1, cyclic amido acetals were efficiently generated by the ETIC reaction under essentially neutral conditions making it an ideal choice for this application. Homobenzylic amide **41** will serve as the ETIC precursor to the acyliminium ion. The cleavage of the C-N amide bond of **41** (Figure 26) was chosen as the next disconnection generating amine **42** and a pederic acid derivative (not shown). Based on the coupling described by Kishi[23] and Rawal,[51] the nucleophilic amine **42** will readily couple to the pederic acid fragment. Amine **42** is expected to arise from pyran **43** though a sequence that includes acetal and imine formation followed by nucleophile addition into the imine to install the benzyl functionality. Pyran **43** could be generated from a selective epoxidation and *syn*-vinylation of dihydropyran **44**. Dihydropyran **44** was expected to arise from the *syn*-reduction, cyclization and dehydration of **45**. An asymmetric allyation and selective boron-mediated methyl ketone aldol addition are expected to generate **45** from ketoaldehyde **46** that can be easily generated in multi-gram quantities.

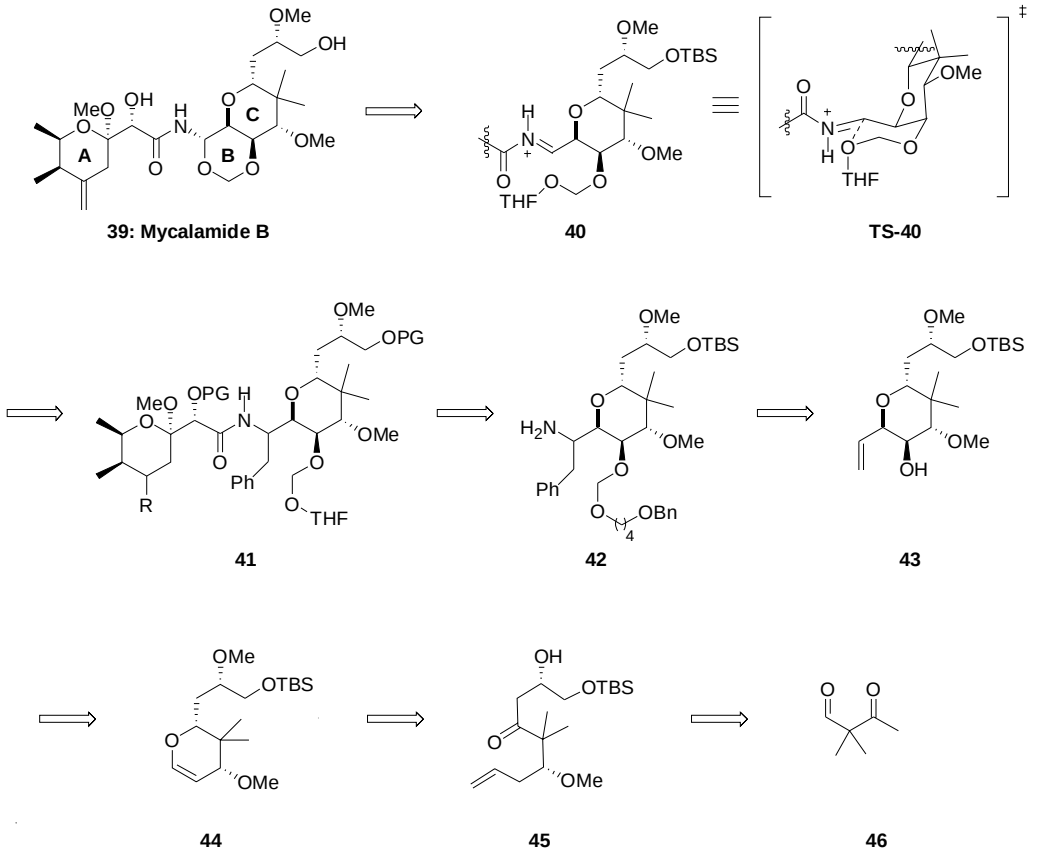


Figure 25: Retrosynthetic Analysis of Mycalamide B

Prior to initiating the synthesis of mycalamide B, studies were conducted that extended the scope of the ETIC reaction to include the synthesis of the amido trioxadecalin system. In addition to exploring the scope and limitations of the ETIC reaction, the synthesis of these model systems also allowed for the evaluation of synthetic methods for use in the later stages of the synthesis of mycalamide B. The following is an account of the ETIC model studies directed toward the generation of the amido trioxadecalin system followed by a description of our progress toward the total synthesis of mycalamide B.

2.2 Results and Discussion

Model systems **47** and **48** are structurally similar to the ETIC substrates required to generate mycalamides A and B (Figure 26). These compounds have provided the opportunity to evaluate the efficiency and selectivity of the ETIC reaction for the generation of the amido trioxadecalin system. Additionally, they have provided valuable information that will allow the ETIC reaction to be employed in the total synthesis of mycalamide B. Portions of this chapter have been published as a communication and a full paper.[87, 88]

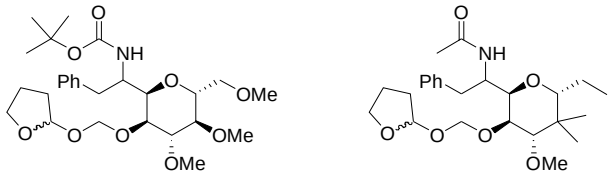
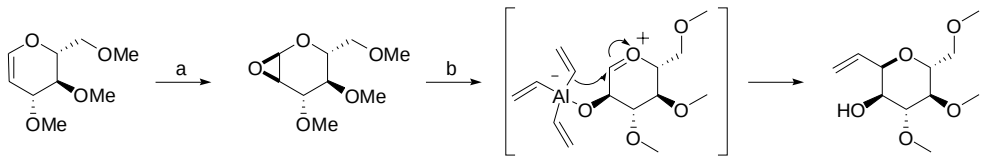


Figure 26: Amido Trioxadecalin ETIC Model Systems

I. *Synthesis of ETIC Substrates: Model Systems for Mycalamide B*

The model ETIC substrate **47** was generated in 12 linear steps from tri-*O*-methyl-D-glucal (Scheme 10).[63] The diastereoselective glycal epoxidation[64] of **49** with dimethyl dioxirane[65-67] generated the highly sensitive epoxide **50** that was carried on without purification. Opening of the epoxide by treatment with trivinylalane (**51**) and subsequent vinyl addition into the oxocarbenium ion generated **52** as a single diastereomer. The epoxidation/*syn*-vinylation protocol was developed by Rainier and coworkers[68] for the synthesis of C-glycosides.

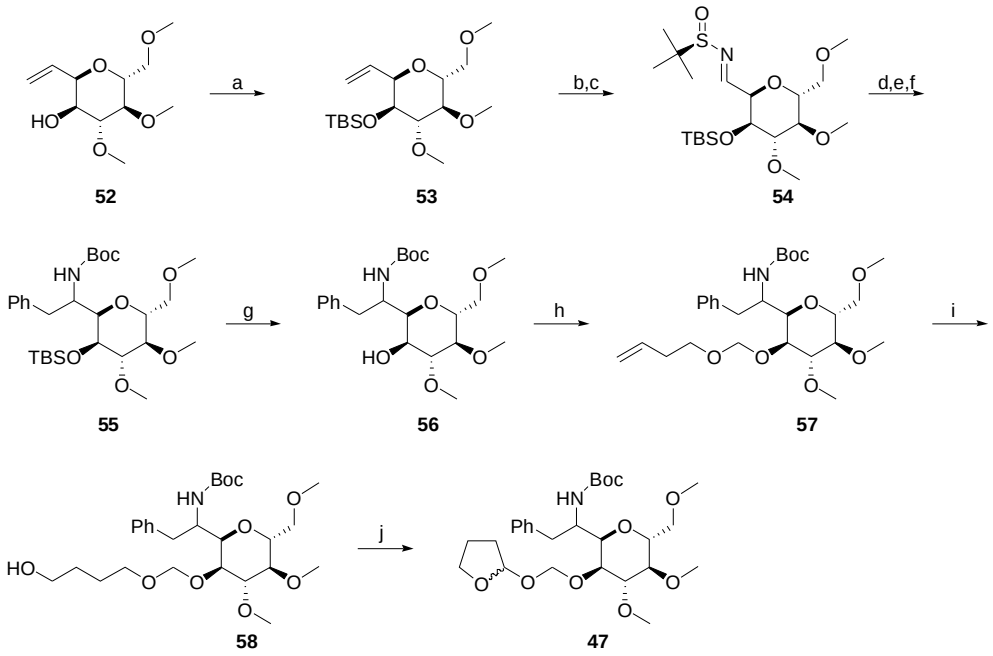


49 **50** **51** **52**

Reagents: (a) DMDO, CH_2Cl_2, 0 ^oC; (b) trivinylalane, CH_2Cl_2, 62% over 2 steps.

Scheme 10: Epoxidation and Trivinylalane Addition of Tri-*O*-Methyl D-Glucal

The hydroxyl group of **52** was protected under standard conditions (TBSOTf, 2,6-lutidine) providing silyl ether **53** in a 77% yield (Scheme 11). Oxidative cleavage of the olefin in **53** by treatment with ozone followed by triphenylphosphine generated a highly unstable aldehyde that was carried on without purification. Condensation of the aldehyde with Ellman's (*R*)-*tert*-butanesulfinamide[69] in the presence of Ti(O*i*Pr)$_4$ provided **54** in a 71% yield from **53**. The addition of benzyl magnesium chloride into **54** followed by acid cleavage of the resulting sulfinamide and subsequent carbamate formation provided the homobenzylic carbamate **55** in a 68% yield over three steps. The Grignard addition proceeded selectively to generate a single diastereomer,[70] however the identity of this stereocenter is inconsequential to the outcome of the ETIC reaction and thus was not rigorously defined. The silyl ether of **55** was removed by treatment with TBAF generating **56** in a 76% yield. The acetal of **57** was generated by treatment with 3-butenyloxymethylchloride[71] in the presence of DIPEA to provide **57** in a 97% yield. Hydroboration of **57** generated **58** in a 93% yield and oxidative etherification under Suarez's conditions[72] (described in Chapter 1) provide the ETIC cyclization substrate **47** in a 64% yield.

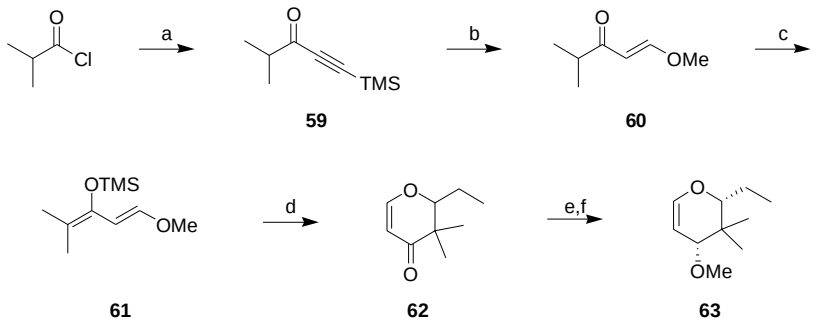


Reagents: (a) TBSOTf, 2,6-lutidine, CH_2Cl_2, 77%; (b) O_3, CH_2Cl_2, -78 ^oC then PPh_3; (c) (R)-*tert*-butanesulfinamide, $Ti(OiPr)_4$, THF, 71%, over 2 steps; (d) BnMgCl, CH_2Cl_2, -78 ^oC; (e) 4M HCl in MeOH; (f) $(Boc)_2O$, NEt_3, CH_2Cl_2, reflux 68%, over 3 steps; (g) TBAF, THF, 76%; (h) 3-butenyloxymethylchloride, DIPEA, CH_2Cl_2, 40 ^oC, 97%; (i) BH_3•THF, THF, 0 ^oC then NaOOH, 93%; (j) $PhI(OAc)_2$, I_2, *hν,* cyclohexane, 64%;

Scheme 11: Synthesis of D-Glucal ETIC Model System

The synthesis of the ethyl pyran ETIC model system **48** (Figure 26) commenced with a Friedel Crafts-like acylation of *bis*-trimethylsilylacetylene by isobutyryl chloride in the presence of aluminum chloride generating **59** (Scheme 12) in a 92% yield.[73] Treatment of **59** with 1,4-diazabicyclo[2.2.2]octane (DABCO) in methanol resulted in desilylation followed by the Michael addition of methanol generating **60** in 75% yield.[74] The formation of silyl enol ether **61** was accomplished in 75% yield by treating **60** with TMSOTf and Et_3N in diethyl ether. Treatment of **61** with BF_3•OEt_2 in the presence of propionaldehyde promoted a hetero-Diels Alder reaction[75] that generated **62** in an 81% yield. The Luche[76] reduction of **62** followed by methylation of the resulting alcohol generated **63** in a 67% yield over 2 steps. Optimal yields

were observed when the alcohol resulting from the Luche reduction was carried into the methylation without purification.

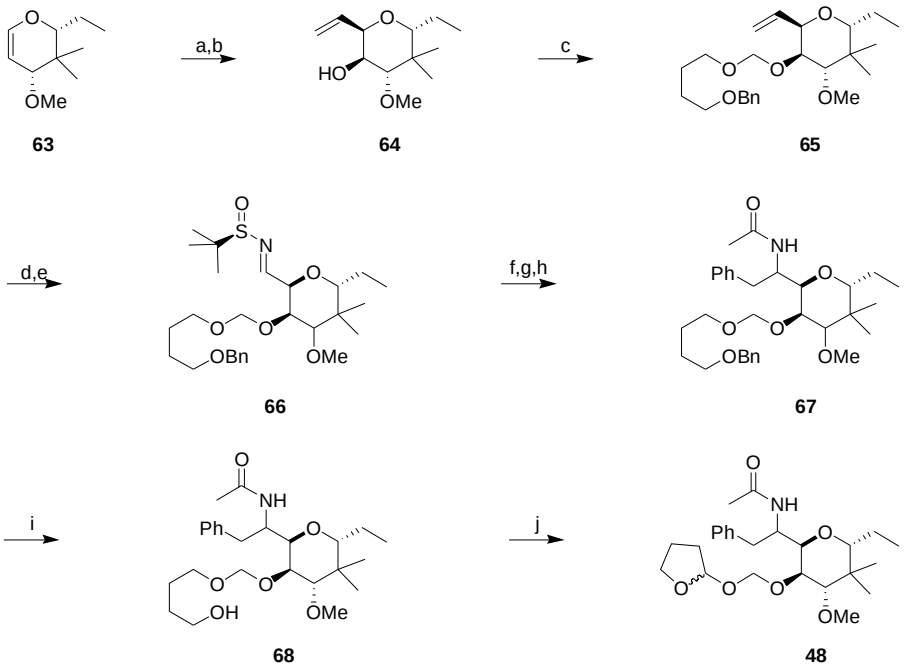


Reagents: (a) *bis*-trimethylsilylacetylene, $AlCl_3$, CH_2Cl_2, 0 °C, 92%; (b) DABCO, MeOH, 75%; (c) TMSOTf, NEt_3, Et_2O, 75%; (d) propionaldehyde, BF_3•OEt_2, EtCN, -5 °C, 81%; (e) $CeCl_3$, $NaBH_4$, MeOH, 0 °C; (f) NaH, MeI, DMF, 67%

Scheme 12: Generation of the Dihydropyran Precursor to the ETIC Ethyl Pyran Model

Further synthetic elaboration of dihydropyran **63** proceeded in a similar fashion to the generation of the D-glucal based ETIC substrate, described previously. The diastereoselective epoxidation[64] of **63** with dimethyldioxirane[65-67] followed by treatment with trivinylalane, as per the Rainier[68] protocol, generated **64** in an 80% yield as a single diastereomer (Scheme 13). The benzyloxybutoxymethyl ether was installed by treating **64** with BBMCl (Chapter 1, pg 16) in the presence of DIPEA generating **65** in a 76% yield. Olefin cleavage of **65** under oxidatitive conditions (O_3, -78 °C, then PPh_3) followed by condensation with Ellman's (*R*)-*tert*-butanesulfinamide[69] generated **66** in a 67% yield as an inseparable mixture of diastereomers. The installation of the benzyl group was accomplished by treating **66** with benzylmagnesium chloride. The resulting sulfinamide was taken crude into acidic cleavage and subsequent acylation of the resulting amine generated amide **67** in a 73% yield over three steps. The benzylmagnesium chloride addition into **68** proceeded selectively generating approximately a 1:1 separable mixture of diastereomers.[70] The diastereomers were separated and advanced through

the synthetic sequence separately exhibiting identical reactivity. The stereochemistry of the diastereomers was not determined because their identity did not have a significant impact on this study. However, the potential for the resolution of diastereomers at this stage in the synthetic sequence could be potentially useful for the synthesis of the mycalamides and related compounds. Treatment of **67** with palladium on carbon under an atmosphere of H_2 resulted in the removal of the benzyl ether generating **68** in an 80% yield. Oxidative etherification under conditions developed by Suarez[72] resulted in the generation of ETIC substrate **48** in an 89% yield.

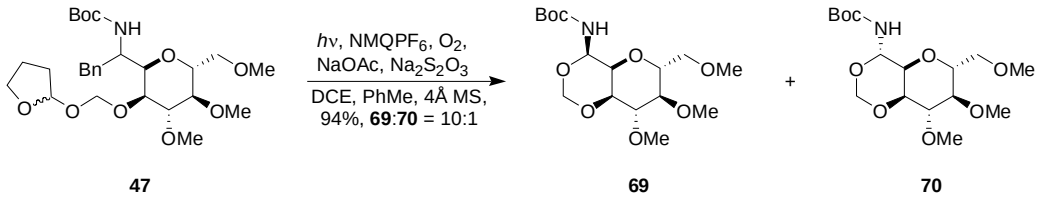


Reagents: (a) DMDO, CH_2Cl_2, 0 °C; (b) trivinylalane, CH_2Cl_2, -72 °C, 80% over 2 steps; (c) BBMCl, DIPEA, CH_2Cl_2, 35 °C, 76%; (d) O_3, CH_2Cl_2, -78 °C the PPh_3, rt; (e) (R)-*tert*-butanesulfinamide, Ti(O*i*Pr)$_4$, THF, 67% over 2 steps; (f) BnMgCl, CH_2Cl_2, -78 to 0 °C; (g) 4 M HCl, MeOH, 0 °C; (h) acetyl chloride, Et_3N, CH_2Cl_2, 0 °C, 72% yield over 3 steps: at this point diastereomers could be seperated; (i) H_2, Pd/C, EtOH, 80%; (j) $h\nu$, iodobenzene diacetate, I_2, cyclohexane, 89%.

Scheme 13: Completion of the Ethyl Pyran ETIC Substrate

II. Generation of the Amido Trioxadecalin System by the ETIC Reaction

Subjecting **47** to the ETIC conditions developed for the generation of cyclic amido acetals (cat. NMQ, *hv*, air, toluene, NaOAc, $Na_2S_2O_3$, 4 Å molecular sieves, DCE) resulted in the formation of the amido trioxadecalin system in a 94% yield as a 10:1 mixture of separable diastereomers at the *N*-acylaminal center (Figure 27). The diastereomeric mixture was separated by column chromatography and the stereochemistry and conformations of amido trioxadecalin systems **69** and **70** were determined through the analysis of ^{1}H NMR and nOeSY spectrum.



47 **69** **70**

Figure 27: ETIC Reaction of the D-Glucal Based Model System

The analysis of the ^{1}H-^{1}H coupling constants and nOe enhancements observed in the NMR spectrum of the amido trioxadecalin systems **69** and **70** revealed an interesting conformational preference inherent in this system (Figure 28). The small ^{1}H-^{1}H vicinal coupling constants (~1-2 Hz) observed for the protons around the tetrahydropyran ring (shown in blue) of the major diastereomer (**69**, Scheme 28) are indicative of an equatorial-equatorial relationship and suggested that the amido trioxadecalin system resides in the conformation that places the majority of the substituents attached to the pyran ring in an axial orientation. The predominantly axial or "inverted" conformation of **68** was confirmed by observing the nOe enhancements (shown by the red double headed arrows) that were present for the axial protons of the *N*-

acylaminal ring and an enhancement between the axial proton of the tetrahydropyran ring and the α-methoxy proton of the ring substituent during a nOeSY analysis.

The larger ^{1}H-^{1}H vicinal coupling constants (~10 Hz) observed for the protons of the pyran ring (shown in blue) of the minor diastereomer (**70**, Scheme 28) are indicative of an axial-axial relationship suggesting a conformation where the majority of the tetrahydropyranyl substituents are oriented in an equatorial position, or "normal" conformation. The conformation of **70** was confirmed by observing nOe enhancements between the axial protons across the tetrahydropyran and *N*-acylaminal rings, shown in Figure 28. The stereochemistry of amido trioxadecalin **70** is that which is required for the generation of mycalamide B.

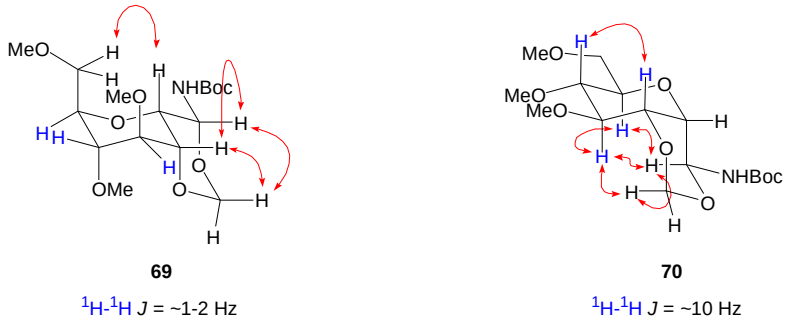


Figure 28: Conformation of the Amido Trioxadecalin Products of the ETIC Reaction

The product distribution and the unexpected stereochemistry and conformation of the "inverted" amido trioxadecalin ring system (**69**, Figure 28) resulting from the ETIC reaction can be rationalized by invoking a mechanism that accounts for the energetic preferences of the developing ring systems, shown in Figure 29. We proposed the acyliminium ion generated during ETIC reaction exists in a conformational equilibrium between a conformer that places a

majority of the tetrahydropyran substituents in an axial orientation (**71**) and a conformer that places these substituents in the equatorial orientation (**72**). The proposed conformational lability of the *N*-acyliminium ion is supported by the ^{1}H-^{1}H vicinal coupling constants of the protons attached to the tetrahydropyran ring of **47** that exhibit a ~4 Hz coupling constant, indicative of a 1:1 mixture of conformers (Figure 29). While significant structural differences exist between the homobenzylic amide **47** and the *N*-acyliminium ion (**71** and **72**), the conformational lability of **47** indicates that the methoxy and methylmethoxy substituents of the tetrahydropyran are not sufficient conformational locks to restrict the *N*-acyliminium ion to a single ring conformation. The conformationally labile *N*-acyliminium ion provides access to two cyclization pathways that lead to the generation of the observed amido trioxadecalin systems, **69** and **70**.

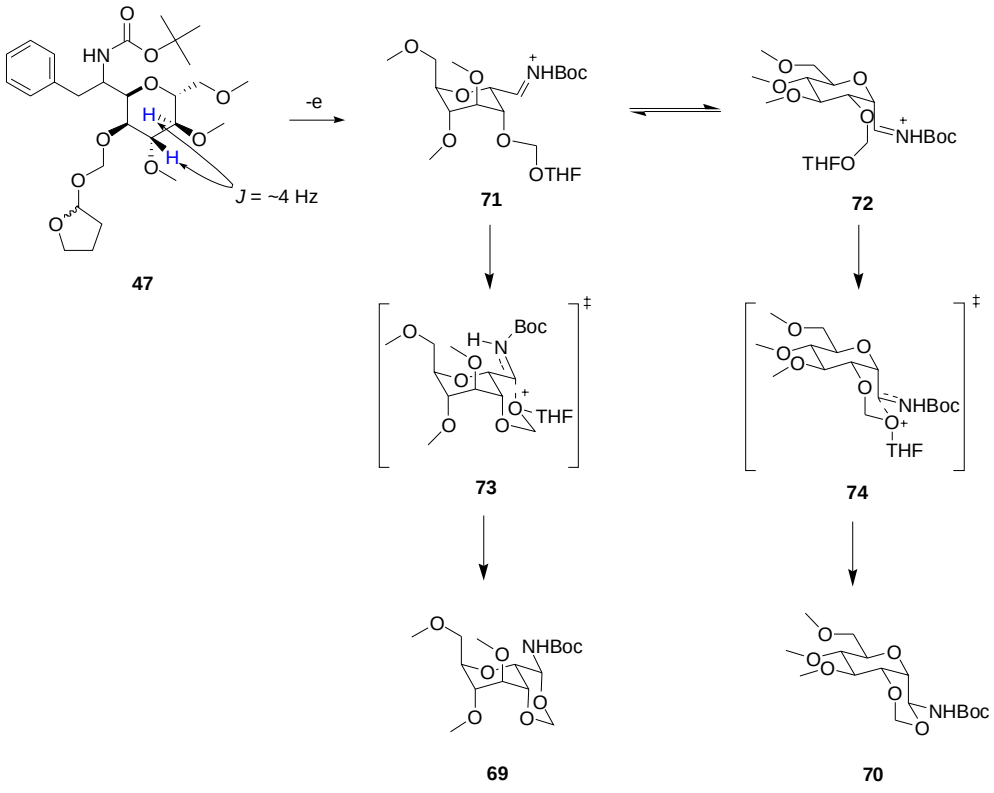


Figure 29: Mechanism of Amido Trioxadecalin Formation

Our previous studies concerning the ETIC generation of cyclic amido acetals suggest that the oxonium ions (**73** and **74**) are higher in energy than the acyliminium ions (**71** and **72**) suggesting these cyclizations proceeded through late transitions states (Figure 29). By this reasoning the relative energies of the transition states **73** and **74** should reflect the relative energies of the products, **69** and **70**. Therefore, the preferential formation of **69** indicated that transition state **73** is lower in energy than transition state **74**. The energetic difference between transition states **73** and **74** can be attributed to the conformational preference of the developing trioxadecalin ring system and the steric and electronic interactions of the substituents on the tetrahydropyran ring system. Fuchs and coworkers[77] calculated that the core trioxadecalin system favors conformation **75** (observed in transition state **73**) (Figure 30) by 4.3 kcal/mol over conformation **76** (observed in transition state **74**). This energy difference was attributed to the presence of two COCC gauche interactions (shown in red) present when the trioxadecalin ring system resides in conformation **76**.

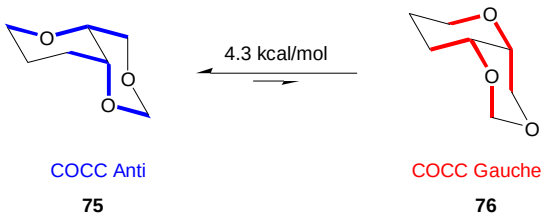
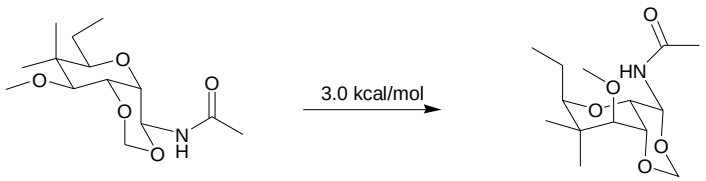


Figure 30: Conformations of the Amido Trioxadecalin System

To gain further insight into the relative energies of transition states **73** and **74** the relative energies of the cyclization products **69** and **70** were evaluated. Calculations (MM3) of the relative energies of the cyclization products (**69** and **70**, Figure 29) have indicated that amido

trioxadecalin ring system **69** is 4.4 kcal/mol lower in energy than **70** (Figure 29).[89,90] These calculations are consistent with the outcome of the cyclization and the postulate that these reactions proceed through a late transition state. Even though the evaluation of the relative energies of the products resulting from the cyclization overestimates the observed selectivity, it provides a useful method to predict the outcome of these reactions.

Interestingly, a similar calculation performed on the ethyl pyran ETIC model system, that includes the geminal dimethyl functionality in the 4 position of the pyran, predicted a reversal in selectivity. This calculation indicated that the "normal" ETIC cyclization product (**77**, Figure 31) is favored by 3.0 kcal/mol over the "inverted" cyclization product (**78**). The predicted reversal in selectivity can be attributed to the incorporation of geminal dimethyl functionality into the tetrahydropyran of amidotrioxadecalin systems **77** and **78**. The energetic benefit obtained from the minimization of the gauche interactions of the tetrahydropyran substituents (as seen with the previous model system) is eliminated by the incorporation of the geminal dimethyl functionality at the 4 position of the tetrahydropyran.



77 **78**

Figure 31: Relative Energies of a Mycalamide-Like Amido Trioxadecalin System

To further enhance our understanding of these systems, **48** was subjected to the modified ETIC conditions (cat. NMQ, *hν*, air, toluene, NaOAc, $Na_2S_2O_3$, 4 Å molecular sieves, in DCE) resulting in the generation of the amido trioxadecalin systems **77** and **78** in a 94% yield as a 1.6:1

mixture of separable diastereomers, respectively (Figure 32). The amido trioxadecalin ring system **77** generated from the ETIC reaction resides in the expected conformation possessing the stereochemistry required for the synthesis of mycalamide B. The stereochemistry and conformation of the amido trioxadecalin systems **77** and **78** were confirmed by the appropriate NMR analysis, as was described for the previous system.

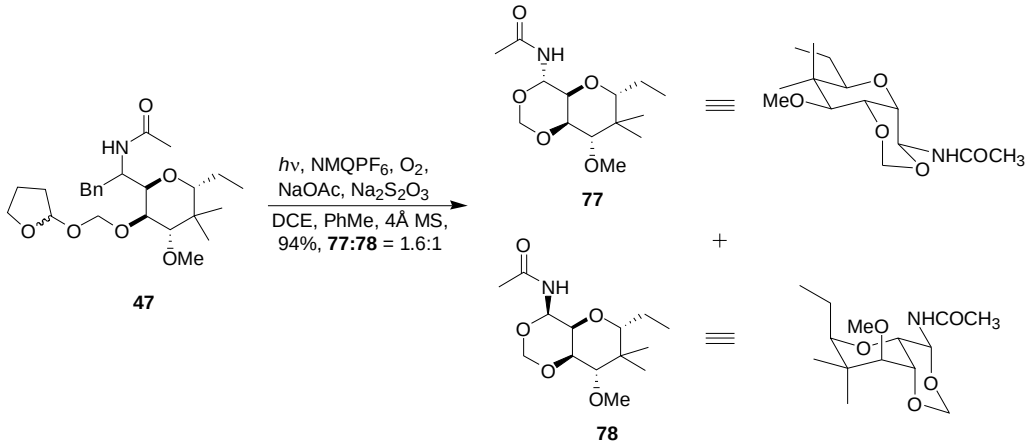


Figure 32: Cyclization of the Ethyl Pyran ETIC Model

During our evaluation of amido trioxadecalin systems **77** and **78** we observed the epimerization of the acylaminal under mildly acidic conditions. Subjecting **78** to catalytic amounts of *para*-toluenesulfonic acid in trifluorethanol at room temperate for 4 hours resulted in the epimerization of the *N*-acylaminal center generating a 1.6:1 mixture of diastereomer in favor of **77** (Figure 33). No degradation of the amido trioxadecalin system was observed even during extended exposure (24 hours) to these reaction conditions. Amido trioxadecalin system **77** was also observed to undergo an identical epimerization under these conditions. The epimerization conditions described here are considerably milder than those utilized by Kishi (KO*t*Bu, THF, reflux) during the total synthesis of mycalamides A and B.

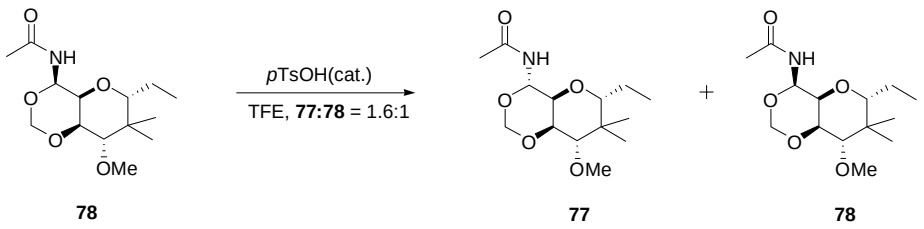
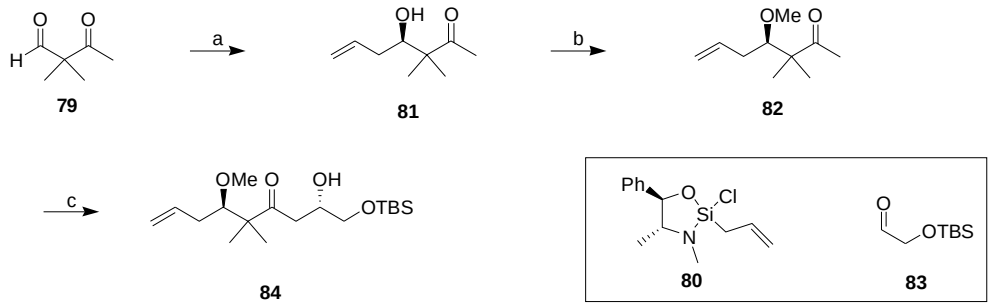


Figure 33: Epimerization of the Amido Trioxadecalin System

III. Synthetic Efforts Toward Mycalamide B

Once the scope of the ETIC reactions had been expanded to include the synthesis of amido trioxadecalin systems, we initiated a research effort aimed at developing an efficient and flexible total synthesis of mycalamide B. Subjecting **79**[78] to the (*R,R*)-pseudoephedrine derived allylating agent (**80**, Scheme 14), described by Leighton and coworkers,[79] resulted in the generation of alcohol **81** in a 94% yield with a 91% ee, as determined by GC (Chiraldex™ G-TA column). No products resulting from the ketone allylation of **79** were observed during this process. The methylation of **81** under nonanionic conditions (MeOTf, 2,6-di-*tert*-butylpyridine) generated **82** in an 88% yield. Nonanionic methylation conditions were employed to avoid a facile retro-aldol reaction that occurs upon generation of the alkoxy anion. Treatment of methyl ketone **82** with diethylboron triflate in the presence of DIPEA generated the diethylboron enolate that underwent a smooth addition into aldehyde **83** generating the aldol adduct **84** in an 83% yield as a 3:1 mixture of inseparable diastereomers. The 1,5-*anti*-diastereomer was generated as the major product from the aldol addition (**85**, Scheme 14) and was the result of asymmetric induction originating from the β-alkoxy substituent of **82**. The 1,5-asymmetric control resulting from β-alkoxy boron enolates was first observed by Masamune[81] and has been subsequently

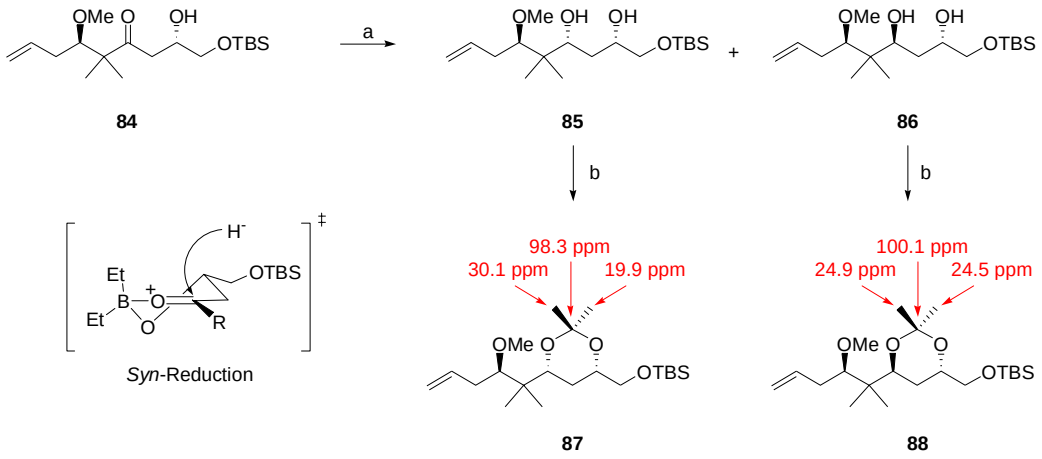
explored by Patterson[82] and Evans.[83] The 3:1 inseparable mixture of diastereomers persisted through the synthetic sequence until separation was possible following the methylation of dihydropyran **92** (Figure 34, pg 65).



Reagents: (a) **80**, toluene, -15 ^{o}C, 94%, 91% ee; (b) MeOTf, 2,6-di-*tert*-butylpyridine, CH_2Cl_2, 88%; (c) Et_2BOTf, DIPEA, Et_2O, -78 ^{o}C then **83**, 83%, 3:1 dr.

Scheme 14: Asymmetric Allylation and Boron-Mediated Aldol Reactions

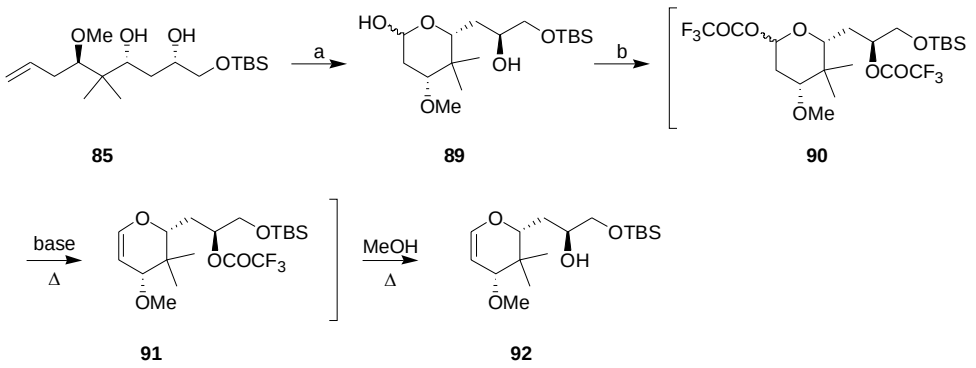
The β-hydroxyketone **84** was selectively reduced by lithium borohydride with diethylboron methoxide as a chelating agent,[84] generating diols **85** and **86** in a 98% yield as a 10:1 separable mixture of diastereomers favoring the 1,3-*syn* diol **85** (Scheme 15). The identities of the diols were confirmed by the ^{13}C NMR acetonide analysis developed by Rychnovsky and coworkers.[85] Diols **85** and **86** were separated and individually treated with catalytic *para*-toluenesulfonic acid in dimethoxypropane generating acetonides **87** and **88** in excellent yield. The carbon shifts observed for the *syn* and *anti* acetonides (**87** and **88** respectively) were consistent with the values reported by Rychchnovsky[85] for *syn* and *anti* acetonides (Scheme 15).



Reagents: (a) Et_2BOMe, THF, -78 ^{o}C then $LiBH_4$, 98%, 10:1 dr; (b) *p*TsOH (cat.), dimethoxypropane, >90%.

Scheme 15: *Syn*-Reduction of the β-Hydroxyketone

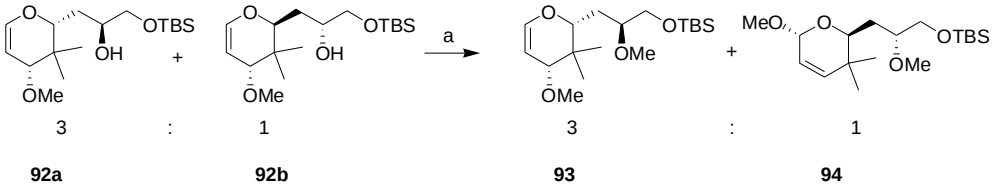
Oxidative olefin cleavage of **85** resulted in the generation of lactol **89** in a 98% yield containing minor impurities (Scheme 16). The highly sensitive lactol could not withstand a lengthy chromatographic purification and was flushed through a plug of silica to remove the triphenylphosphine and triphenylphosphine oxide. Dehydration of **89** to generate dihydropyran **92** occurred through a one pot protocol beginning with the bisacylation of the lactol and side chain alcohol functional groups by treatment with trifluoroacetic anhydride in the presence of DIPEA (**90**, Scheme 16). Heating the reaction mixture resulted in the elimination of the more reactive acyl lactol functional group generating the monoacylated dihydropyran **91**. To our surprise the remaining trifluoroacetate ester was resistant to hydrolysis and could be isolated by silica gel chromatography (**91**, Scheme 16). The addition of methanol directly to the reaction mixture and subsequent heating (gentle reflux for 8 hours) resulted in the complete removal of the trifluoroacetate ester generating dihydropyran **92** in a 99% yield.



Reagents: (a) O_3, CH_2Cl_2, -78 ^oC then PPh_3, 99%; (b) i. $(COCF_3)_2O$, DIPEA, CH_2Cl_2, -78 ^oC -> reflux, ii. then MeOH, 60^oC, 99%.

Scheme 16: Generation of the Dihydropyran Precursor to Mycalamide B

The propagation of the 3:1 mixture of diastereomers generated during the boron-mediated aldol addition (Scheme 14, pg 63) resulted in the formation of dihydropyran **92** as a 3:1 mixture of inseparable diastereomers **92a** and **92b** (Figure 34). Treatment of the mixture of **92a** and **92b** with nonanionic methylation conditions (MeOTf and 2,6-di-*tert*-butylpyridine) resulted in the generation of dihydropyrans **93** and **94** in a 96% yield as a 3:1 mixture of separable constitutional isomers. Dihydropyran **93** was generated from **92a** by methylation of the secondary alcohol, while the formation of **94** from **92b** can be explained by a reaction sequence that includes the methylation of the secondary alcohol followed by a Ferrier[86] rearrangement brought upon by the conformational lability of **92b**.



Reagents: (a) MeOTf, di-*tert*-butylpyridine, CH_2Cl_2, 96%, 3:1 = **93**:**94**

Figure 34: Methylation of the Dihydropyran Precursor to Mycalamide B

The 4,6-*anti*-relationship of the substituents attached to dihydropyran **92b** generates a conformational equilibrium between the ring conformations **A** and **B** (Figure 35). This is supported by the ^{1}H NMR of **92** (diastereomeric mixture) where the minor diastereomer (**92b**) of the mixture is shown to exist in approximately a 1.5:1 mixture of conformational isomers. Conformation **B** places the methoxy functionality in the axial orientation providing the required orbital alignment of the π-orbitals of the olefin and the antibonding σ-orbital of the methoxy group to allow for Lewis acid catalyzed oxocarbenium ion formation (**95**, Figure 35). Subsequent addition of methanol or its functional equivalent into the oxocarbenium ion resulted in the formation of **94** as a single diastereomer. The ^{1}H NMR of the major diastereomer (**92a**, Figure 34) of this mixture exhibited no such conformational equilibrium. Dihydropyran **93** (Scheme 17) was advanced through the synthetic sequence as a single diastereomer.

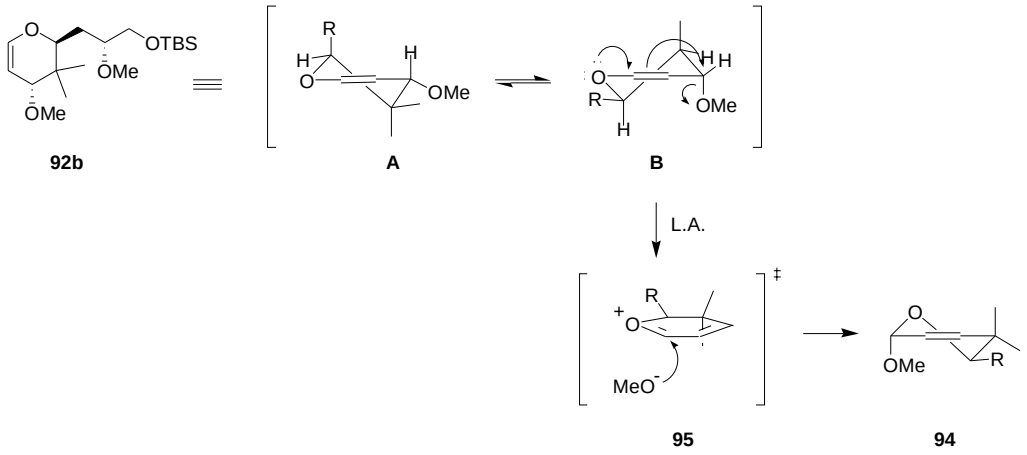
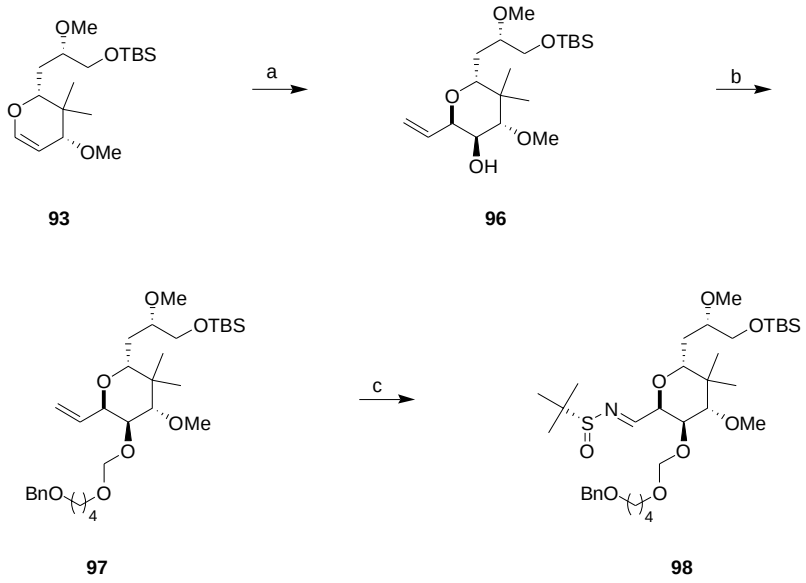


Figure 35: Mechanism of the Ferrier Degradation

The required 1,2-*syn* relationship of the pyran was, once again, established by employing the Rainier[68] protocol (Scheme 17). The selective DMDO[65-67] epoxidation of **93** followed by treatment with trivinylalane resulted in the generation **96** in an 85% yield as a single

diastereomer. Subjecting **96** to BBMCl (Chapter 1, pg 16) in the presence of DIPEA generated **97** in an 80% yield. Oxidative cleavage of **97** followed by condensation of the resulting aldehyde with Ellman's (*R*)-*tert*-butanesulfinamide[69] generated **98** in a 62% yield. At this point the completion of the synthesis of mycalamide B has been delayed until the appropriate pederic acid derivative can be generated (an ongoing project in our laboratory). **98** provided a stable intermediate to stockpile material until the synthesis can resume.



Reagents: (a) i. DMDO, CH_2Cl_2, 0 ^oC, ii. trivinylalane, CH_2Cl_2, -72 ^oC to rt, 85%; (b) Benzyloxybutoxymethyl chloride, DIPEA, CH_2Cl_2, reflux 80%; (c) i. O_3, CH_2Cl_2, -78 ^oC, then PPh_3, ii. (*R*)-*tert*-butanesulfinamide, $Ti(OiPr)_4$, THF, 62%.

Scheme 17: Generation of a Stable Intermediate in the Synthesis of Mycalamide B

2.3 Conclusions

We have demonstrated that the amido trioxadecalin ring system, prevalent in mycalamide B and related compounds, can be efficiently and stereoselectively generated by the ETIC reaction. We have also established that these reactions likely proceed through a late transition state whereby the relative energies of the potential products can be used to predict the outcome of the cyclization. It was also observation that the amidotrioxadecalin system epimerizes under mildly acidic conditions.

The synthesis of mycalamide B is currently being pursued through an efficient and selective synthetic sequence. An asymmetric Leighton allylation was employed to generate the initial stereocenter of this sequence from which all others were generated. The generation of the 1,5-*anti*-stereochemical relationship was established with moderate selectivity through a boron-mediated aldol addition that led to a β-hydroxyketone. The 1,3-*syn*-diol relationship was generated by the chelate controlled reduction of the β-hydroxyketone. Oxidative olefin cleavage, dehydration and methylation resulted in the generation of the 4,6-*syn*-dihydropyan. The remaining stereochemistry was established by an epoxidation and trivinylalane ring opening/addition. Once the appropriate pederic acid derivative can be generated the synthesis of mycalamide B will be completed.

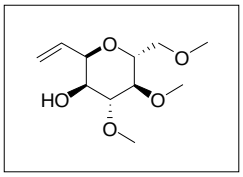
2.4 Experimentals

General Procedures:

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. For ^{13}C NMR: $CDCl_3$ = 77.0, 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 doublets of triplets; br = broad; m = multiplet; app t = apparent triple; 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.

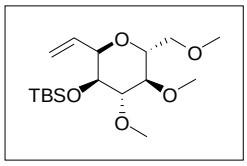
Analytical thin layer chromatography (TLC) was performed on E. Merck pre-coated (25 nm) silica gel 60F-254 plates. Visualization was done under UV (245 nm). Flash column chromatography was preformed using ICN SiliTech 32-63 60Å silica gel. Reagent grade ethyl acetate and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography. Reagent grade methylene chloride (CH_2Cl_2), dichloroethane ($C_2H_4Cl_2$), acetonitrile (CH_3CN), benzene and toluene were distilled from CaH_2. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were distilled from sodium benzophenone ketal prior to use. Anhydrous *N,N*-dimethylformamide (DMF), methanol (MeOH), dimethylformamide (DMF), methanol (MeOH), dimethyl sulfoxide (DMSO) were purchased from Aldrich and used as is. All reactions were conducted under nitrogen atmosphere, unless otherwise specified.



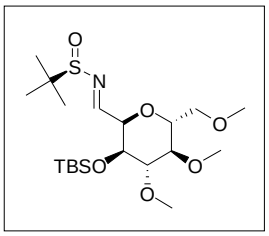
4,5-Dimethoxy-6-methoxymethyl-2-vinyltetrahydropyran-3-ol (52): *Preparation of 0.10 M trivinylalane*: To a suspension of $AlCl_3$ (4.44 g, 33.3 mmol) in CH_2Cl_2 (233 mL) at room temperature was added vinylmagnesium bromide (1 M in THF, 100 mL, 100 mmol) drop wise, over a period of 1 hour. The solution was cooled when necessary to prevent reflux and stirred at room temperature for 4 hours.

Synthesis of 4,5-dimethoxy-6-methoxymethyl-2-vinyltetrahydropyran-3-ol (52): To a solution of **49** (3.00 g, 16.0 mmol) in CH_2Cl_2 (10 mL) cooled to 0 °C was added dimethyldioxirane (0.2 M, 76.8 mL, 17.2 mmol) and the solution was stirred for 30 minutes. The reaction mixture was concentrated under reduced pressure, dissolved in CH_2Cl_2 (60 mL), and added drop wise over a period of 1 hour to a solution of trivinylalane (0.010 M, 333 mL) cooled to -72 °C. The reaction mixture was allowed to slowly warm to room temperature and stir for 8 hours. The reaction was carefully quenched with H_2O, 10% aqueous HCl was added until the aluminum salts were dissolved, and the solution was extracted with ether. The organic layers were combined, washed with 10% HCl (2 x 10 mL) and brine, dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (60% EtOAc) to provide the desired product (2.52 g, 62 %): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.05 (ddd, *J* = 16.2, 10.8, 5.4 Hz, 1H), 5.42 (ddd, *J* = 17.5, 1.7, 1.7 Hz, 1H), 5.37 (ddd, *J* = 10.7, 1.7, 1.7 Hz, 1H), 4.46 (ddd, *J* = 5.1, 1.6, 1.6 Hz, 1H), 3.83 (app dt, *J* = 7.8, 4.1 Hz, 1H), 3.71 (dd, *J* = 7.6, 5.0 Hz, 1H), 3.60 (dd, *J* = 10.0, 4.7 Hz, 1H), 3.59 (dd, *J* = 10.4, 3.7 Hz, 1H), 3.59 (s, 3H), 3.50 (s, 3H), 3.44 (s, 3H), 3.34 (app t, *J* = 7.2 Hz, 1H), 3.28 (app t, *J* = 7.2 Hz, 1H), 2.28 (bs, 1H); ^{13}C (125 MHz, $CDCl_3$) 132.7, 119.2, 82.0, 78.8, 73.9, 72.8, 71.0, 70.5, 59.9, 59.4, 59.2; IR (neat) 3450,

2930, 1081 cm^{-1}; $[\alpha]^{25}_D$ +98.87° (*c* 3.20, $CHCl_3$); HRMS (EI) calcd. for $C_{11}H_{20}O_5$ (M^+) 232.1311, found 232.1303.

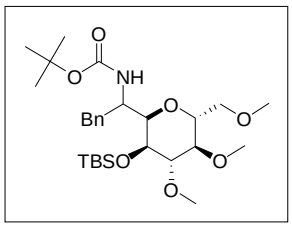


***tert*-Butyl-(4,5-dimethoxy-6-methoxymethyl-2-vinyltetrahydropyran-3-yloxy)dimethylsilane (53):** To a solution of **52** (0.40 g, 1.6 mmol) in CH_2Cl_2 (1.6 mL) was added 2,6-lutidine (0.35 g, 3.2 mmol). The solution was cooled to 0 °C and TBSOTf (0.64 g, 3.4 mmol) was added dropwise. The reaction mixture was allowed to warm to room temperate and was stirred for 30 minutes. The reaction was quenched with saturated aqueous NH_4Cl (5 mL) and extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (5% EtOAc in hexanes) to provide the desired product (0.43 g, 77%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.08 (ddd, *J* = 17.6, 11.0, 3.4 Hz, 1H), 5.45-5.36 (m, 2H), 4.39-4.36 (m, 1H), 3.77-3.72 (m, 1H), 3.63-3.53 (m, 3H), 3.58 (s, 3H), 3.53 (s, 3H), 3.40 (s, 3H), 3.17 (app t, *J* = 9.0 Hz, 1H), 3.10 (app t, *J* = 9.0 Hz, 1H), 0.89 (s, 9H), 0.11 (s, 3H), 0.05 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 131.9, 119.1, 85.2, 80.3, 76.3, 72.7, 71.6, 71.5, 61.2, 60.4, 59.2, 25.7, 17.9, -4.7, -4.9; IR (neat) 2931, 2894, 1114, 1093 cm^{-1}; $[\alpha_D]^{25}_D$ +81.5° (*c* 3.2, $CHCl_3$); HRMS (ES) calcd. for $C_{17}H_{34}KO_5Si$ (M + K) 385.1813, found 385.1800.



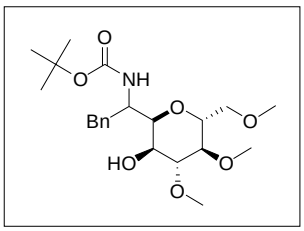
2-Methylpropane-2-sulfinic acid 3-(*tert*-butyldimethylsilanyloxy)-4,5-dimethoxy-6-methoxymethyltetrahydropyran-2-ylmethyleneamide (54): A solution of **53** (0.387 g, 1.12 mmol) in CH_2Cl_2 was cooled to -78 °C and ozone was gently bubbled through the solution until it sustained a

deep purple color. Triphenylphosphine (0.587 g, 2.24 mmol) was added at -78 °C and the reaction mixture was warmed to room temperature and stirred for 2 hours. The reaction mixture was concentrated under reduced pressure, dissolved in THF (4 mL) and at room temperature $Ti(O\textit{i}Pr)_4$ (1.59 g, 5.60 mmol) was added followed by the addition of (R_s)-*tert*-butanesulfinamide (0.245 g, 2.00 mmol). The reaction mixture was stirred for 4 hours at room temperature. The reaction mixture was poured into an equal volume of brine, filtered through a pad of Celite and extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (20% EtOAc in hexanes) to provide the desired product (0.396 g, 71 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.34 (d, *J* = 2.3 Hz, 1H), 4.60 (dd, *J* = 6.7, 2.3 Hz, 1H), 3.95 (m, 2H), 3.62-3.55 (m, 2H), 3.57 (s, 3H), 3.53 (s, 3H), 3.41 (s, 3H), 3.42 (app t, *J* = 9.2 Hz, 1H), 3.09 (app t, *J* = 9.4 Hz, 1H), 1.12 (s, 9H), 0.91 (s, 9H), 0.14 (s, 3H), 0.12 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 166.3, 85.6, 80.0, 76.6, 73.8, 72.8, 71.1, 61.2, 60.4, 59.1, 57.1, 25.8, 22.4, 18.0, -4.7, -4.9; IR (neat) 2929, 1712, 1095 cm^{-1}; $[\alpha]^{25}_D$ +28.27° (*c* 0.53, $CHCl_3$); HRMS (EI) calcd. for $C_{19}H_{38}NO_6SSi$ (M - CH_3) 436.2189 found 436.2170.



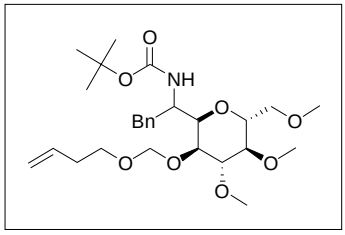
1-3-(*tert*-Butyldimethylsilanyloxy)-4,5-dimethoxy-6-methoxymethyltetrahydropyran-2-yl-2-phenylethylcarbamic acid *tert*-butyl ester (55): To a solution of **54** (0.380 g, 0.811 mmol) in CH_2Cl_2 cooled to -78 °C was treated with benzylmagnesium chloride (1 M in diethylether, 1.63 mL, 1.63 mmol) and the reaction mixture was stirred at -78 °C for 1 hour. The reaction was quenched with saturated aqueous NH_4Cl (5 mL), warmed to room temperature and extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The resulting oil was dissolved

in methanol (5 mL) and aqueous HCl (4 M, 2.00 mL, 8.16 mmol) was added. The reaction mixture was stirred for 1 hour at room temperature. The reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was dissolved in CH_2Cl_2 (3 mL), triethylamine (2 mL) and di-*tert*-butyl dicarbonate (0.712 g, 3.26 mmol) were added and the solution was heated to 43°C for 8 hours. The reaction was cooled to room temperature, extracted with CH_2Cl_2 (3 x 5 mL), washed with 5 % aqueous HCl (5 mL) and brine (5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (0.270 g, 68 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.17 (m, 5 H), 4.66 (br, 1 H), 4.17 (br, 1 H), 3.83 (dd, *J* = 7.6, 5.1 Hz, 1 H), 3.74 (app t, *J* = 5.5 Hz, 1 H), 3.75-3.63 (m, 1H), 3.54 (s, 3 H), 3.54-3.48 (m, 2 H), 3.48 (s, 3 H), 3.40 (s, 3H), 3.30 (d, *J* = 5.5 Hz, 1 H), 3.25 (d, *J* = 5.5, 1 H), 3.23-3.17 (m, 1 H), 2.52 (br, 1 H), 1.32 (s, 9 H), 0.93 (s, 9 H), 0.14 (s, 3 H), 0.09 (s, 3 H); ^{13}C (75 MHz, $CDCl_3$) δ 155.1, 138.4, 129.6, 128.2, 126.1, 84.0, 79.7, 77.6, 76.5, 73.2, 72.4, 71.5, 60.2, 59.4, 59.1, 51.8, 34.1, 28.3, 26.0, 18.0, -4.4, -4.6; IR (neat) 2930, 1710, 1109, 1030 cm^{-1}; $[\alpha]^{25}_D$ +36.49° (*c* 0.57, $CHCl_3$); HRMS (EI) calcd. for $C_{24}H_{40}N0_6Si$ (M - C_4H_9O) 466.2625, found 466.2261.



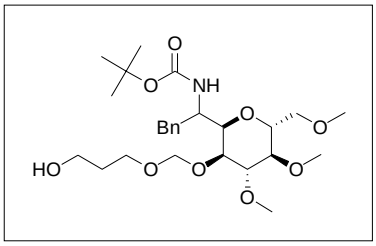
1-(3-Hydroxy-4,5-dimethoxy-6-methoxymethyltetrahydropyran-2-yl)-2-phenylethylcarbamic acid *tert*-butyl ester (56): To a solution of **55** (230 mg, 0.431 mmol) in THF (5 mL) was added TBAF (340 mg, 1.29 mmol). The reaction mixture was stirred for 1 hour at room temperature, quenched with H_2O (10 mL) and extracted with EtOAc (3 x 10 mL). The organic

layers were combined, washed with brine (10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (80% EtOAc in hexanes) to provide the desired product (140 mg, 76 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.18 (m, 5H), 4.82 (br, 1H), 4.12 (br, 1H), 4.03-3.94 (m, 1H), 3.84 (br, 1H), 3.72 (m, 1H), 3.66 (dd, *J* = 10.3, 6.9 Hz, 1H), 3.51-3.47 (m, 2H), 3.47 (s, 3H), 3.41 (s, 3H), 3.40 (s, 3H), 3.28 (app t, *J* = 3.4 Hz, 1H), 2.98 (d, *J* = 6.6, 2H), 1.61 (bs, 1H), 1.40 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 155.8, 138.3, 129.3, 128.1, 126.1, 79.0, 78.5, 76.6, 74.0, 70.2, 69.2, 68.5, 58.8, 58.2, 58.0, 53.8, 37.3, 28.2; IR (neat) 3360, 2930, 1712, 1114 cm^{-1}; $[\alpha]^{25}_D$ +7.41° (*c* 0.27, $CHCl_3$); HRMS (EI) calcd. for $C_{18}H_{26}NO_6$ (M-C_4H_9O) 352.1760 found 352.1768.



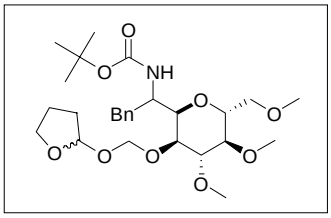
1-(3-But-3-enyloxymethoxy-4,5-dimethoxy-6-methoxymethyltetrahydropyran-2-yl)-2-phenylethylcarbamic acid *tert*-butyl ester (57): To a solution of **56** (428 mg, 1.01 mmol) in CH_2Cl_2 (5 mL) and DIPEA (3 mL) was added 4-chloromethoxybut-1-ene (608 mg, 5.05 mmol) and the reaction mixture was heated to 40 °C and stirred for 8 hours. The solution was cooled to room temperature, saturated aqueous NH_4Cl (5 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2 x 5 mL). The organic layers were combined, washed with 5% aqueous HCl (5 ml), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (497 mg, 97%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.18 (m, 5H), 5.87-5.74 (m, 1H), 5.12-5.02 (m, 2H), 4.93 (d, *J* = 7.3 Hz, 1H), 4.79 (d, *J* = 6.8 Hz, 1H), 4.69 (d, *J* = 6.9 Hz, 1H), 4.07 (br, 1H), 3.89-3.79 (m, 2H), 3.73 (br, 1H), 3.70-3.55 (m, 3H), 3.52-3.45 (m, 2H), 3.46 (s, 3H), 3.45 (s, 3H), 3.39 (s, 3H), 3.15 (app t, 1

H), 3.04 (dd, J = 13.6, 6.4 Hz, 1H), 2.86 (br, 1H), 2.32 (m, 2H), 1.34 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 155.3, 138.3, 135.1, 129.6, 128.3, 126.2, 116.6, 95.9, 78.1, 75.9, 73.5, 71.4, 70.7, 67.7, 65.6, 60.0, 59.1, 58.8, 58.7, 52.0, 34.1, 32.8, 28.3; IR (neat) 2930, 1720, 1172 cm^{-1}; $[\alpha]^{25}_D$ +18.7° (*c* 3.2, $CHCl_3$); HRMS (EI) calcd. for $C_{27}H_{44}NO_8$ (M+H) 510.3067, found 510.3079.

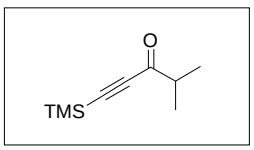


1,3-(4-Hydroxybutoxymethoxy)-4,5-dimethoxy-6-methoxymethyltetrahydropyran-2-yl-2-phenylethylcarbamic acid *tert*-butyl ester (58) To a solution of **57** (481 mg, 0.944 mmol) in THF (30 mL) cooled to -10° C was added BH_3·THF (4.72 mL, 1 M, 4.72 mmol) and the reaction mixture was stirred for 4 hours at -10 °C. The excess borane was quenched with H_2O followed by the addition of NaOH/HOOH solution (20% NaOH/30% HOOH, 1:1 by volume) (5 mL) and the reaction mixture was stirred for 2 hours at room temperature. Saturated aqueous NaS_2O_3 (10 mL) was added and the reaction mixture was stirred for 1 hour at room temperature. The reaction mixture was extracted with EtOAc (3 x 10 ml). The organic layers were combined, washed with brine (10 mL), dried with $NaSO_4$, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (461 mg, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.17 (m, 5H), 4.95 (br, 1H), 4.80 (d, J = 6.9 Hz, 1H), 4.69 (d, J = 6.9 Hz, 1H), 4.05 (br, 1H), 3.84 (br, 1H), 3.81 (dd, J = 5.6, 3.6 Hz, 1H), 3.73 (br, 1H), 3.66-3.37 (m, 7H), 3.46 (s, 3H), 3.45 (s, 3H), 3.39 (s, 3H), 3.19 (br, 1H), 3.04 (dd, J = 13.6, 6.5 Hz, 1H), 2.85 (br, 1H), 1.96 (br, 1H), 1.69-1.63 (m, 4H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 138.3, 129.6, 128.2, 126.2, 95.7, 78.0, 77.4, 75.8, 73.5, 73.5, 71.3, 70.5, 68.4, 62.5, 59.1, 58.9, 58.7, 52.0, 37.3,

29.6, 28.3, 26.2; IR (neat) 3452, 2932, 1707, 1107 cm^{-1}; $[\alpha]^{25}_D$ +14.2° (*c* 2.4, $CHCl_3$); HRMS (EI) calcd. for $C_{20}H_{38}NO_9$ ($M-C_7H_7$) 436.2547, found 436.2553.

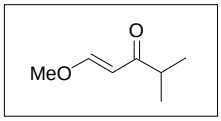


1-(4,5-Dimethoxy-6-methoxymethyl)-3-(tetrahydrofuran-2-yloxymethoxy)-tetrahydropyran-2-yl-2-phenylethylcarbamic acid *tert*-butyl ester (47) To a solution of **58** (47 mg, 0.09 mmol) in cyclohexane (10 mL) was added iodobenzene diacetate (63 mg, 0.20 mmol) and iodine (18 mg, 0.14 mmol) at room temperature. The reaction mixture was irradiated for 2 hours. The reaction mixture was extracted with EtOAc (10 mL), washed with saturated aqueous $NaSO_4$ (5 mL) and brine (5 ml), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (30 mg, 64%) as an inseperable mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.15 (m, 5H), 5.41 (m, 0.6H), 5.37 (m, 0.4H), 4.98 (d, *J* = 6.8 Hz, 0.4H), 4.97 (d, *J* = 6.8 Hz, 0.6H), 4.91 (br, 1H), 4.77 (d, *J* = 6.8 Hz, 0.4H), 4.65 (d, *J* = 6.8, 0.6H), 4.10-4.02 (m, 1H), 3.87-3.70 (m, 5H), 3.55-3.40 (m, 4H), 3.44 (s, 3H), 3.43 (s, 3H), 3.37 (s, 3H), 3.20 (br, 1H), 3.06 (d, *J* = 10.7, 5.0 Hz, 1H), 2.83 (br, 1H), 2.02-1.70 (m, 4H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.30, 155.23, 138.4, 138.3, 129.6, 128.2, 126.0, 100.9, 92.5, 91.3, 81.4 81.1, 79.0, 78.6, 75.1, 73.3, 73.3, 71.3, 71.2, 70.5, 67.1, 59.0, 58.9, 58.7, 51.7, 38.5, 38.2, 32.2, 32.1, 28.2, 23.2, 23.1; IR (neat) 2930, 1709, 1668, 1105 cm^{-1}; $[\alpha]^{25}_D$ + 28.0° (*c* 0.99, $CHCl_3$).

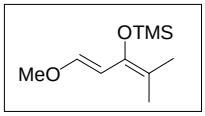


4-Methyl-1-trimethylsilanylpentyn-3-one (59): To a stirred solution of bis(trimethylsilyl)acetylene (3.50 g, 20.5 mmol) and isobutyryl chloride (2.00 g, 18.8 mmol) in CH_2Cl_2 (45 mL) at 0 °C was slowly added $AlCl_3$ (3.00g, 22.5 mmol).

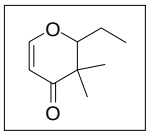
The reaction mixture was stirred for 2 hours at 0 °C, warmed to rt and stirred for an additional 2 hours. The resulting black solution was poured into a mixture of ice (50 g) and 10% aqueous HCl (50 mL) and biphasic mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (5% EtOAc in hexanes) to provide the desired product (2.92 g, 92%). The crude product can used without purification: ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.72 (sept, J = 7.0 Hz, 1H), 1.26 (d, J = 7.0, 6H), 0.32 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.9, 100.9, 98.6, 42.7, 17.7, -0.9; IR (neat) 2969, 1678, 1252, 1067, 847 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_9H_{16}OSi$ (M^+) 168.0970 found 168.09665.



1-Methoxy-4-methylpent-1-en-3-one (60): To a stirred solution of **59** (2.21 g, 13.1 mmol) in methanol at rt was *slowly* added 1,4-diazabicyclo[2.2.2]octane (DABCO) (2.91 g, 25.9 mmol). The solution was stirred at rt for 20 minutes, concentrated under reduced pressure, taken up in EtOAc (20 mL), washed with brine (2 x 10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (10% EtOAc in hexanes) to provide the desired product (1.22 g, 75%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.62 (d, J = 12.5, 1H), 5.63 (d, J = 12.5, 1H), 3.72 (s, 3H), 2.69 (sept, J = 6.8, 1H), 1.11 (d, J = 6.8, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 202.5, 162.5, 103.3, 57.5, 39.5, 18.6; IR (neat) 2969, 1686, 1620, 1595, 1244, 1205, 1054 cm^{-1}; HRMS (EI) *m/z* calculated for $C_7H_{12}O_2$ (M^+) 128.0837 found 128.0836.

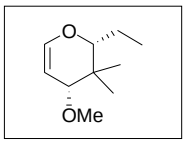


1-(2-Methoxy-vinyl)-2-methylpropenyloxytrimethylsilane(61): A stirred solution of **60** (4.05 g, 31.6 mmol) in diethyl ether (60 mL) and triethylamine (6.40 g, 63.2 mmol) cooled to -10 °C was added dropwise trimethylsilylmethyl triflate (TMSOTf) (7.84 g, 33.18 mmol). The reaction mixture was slowly warmed to 5 °C over 5 hrs. The reaction mixture was diluted with pentane (60 mL) and transferred to a separatory funnel. The lower layer was removed and the upper, organic layer was washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (2 x 10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The product was distilled (38.0 – 41.0 °C, 0.2 torr) from the crude oil to provide the desired product (4.71 g, 75%): ^{1}H NMR (300 MHz, C_6D_6) δ 6.94 (d, J = 12.2 Hz, 1H), 5.79 (d, J = 12.2 Hz, 1H), 3.16 (s, 3H), 1.73 (s, 3H), 1.62 (s, 3H), 0.18 (s, 9H).

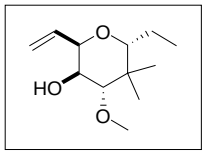


2-Ethyl-3,3-dimethyl-2,3-dihydro-pyran-4-one (62): To a stirred solution of **61** (4.57 g, 22.8 mmol) and propionaldehyde (1.59 g, 27.3 mmol) in CH_2Cl_2 (50 mL) cooled to -5 °C was added BF_3•OEt_2 (0.32 g, 2.28 mmol) and the reaction was stirred for 3 hours at -5 °C. Triflouroacetic acid (2 mL) was added to the reaction mixture at -5 °C and the reaction mixture was warmed to rt and stirred for 4 hours. H_2O (5 mL) was added and the reaction was quenched via slow addition of solid $NaHCO_3$. The reaction mixture was stirred for 1 hour at rt and extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (20% Et_2O in pentane) to provide the desired product (2.85 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (d, J = 5.8 Hz, 1H), 5.33 (d, J = 5.8 Hz, 1H), 3.90 (dd, J = 10.5, 2.6 Hz, 1H), 1.79-1.60 (m, 2H), 1.11 (s, 3H), 1.10 (t, J = 7.4 Hz, 3H), 1.02 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 198.7, 161.6, 105.1, 88.3, 44.4, 21.3, 19.8, 17.9,

10.7; IR (neat) 2971, 1673, 1602, 1276 cm^{-1}; HRMS (EI) *m/z* calculated for $C_9H_{15}O_2$ (M + H) 155.1067, found 155.1072.

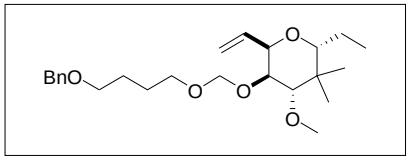


2-Ethyl-4-methoxy-3,3-dimethyl-3,4-dihydro-2H-pyran (63): To a stirred solution of **62** (3.48 g, 22.6 mmol) in 0.50 M $CeCl_3$ in methanol (56.0 ml) cooled to -10 °C was *slowly* added $NaBH_4$ (2.56 g, 48.6 mmol). The reaction mixture was slowly warmed to rt and stirred for 1 hour. Brine (50 ml) was added and the reaction mixture was repeatedly extracted with diethyl ether (5 x 30 ml). The resulting organic layers were combined, washed with brine (2 x 20 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was taken up in DMF (20 ml) and cooled to 0 °C. NaH (2.71 g, 67.7 mmol) was added and the reaction mixture was stirred for 30 min. at 0 °C then warmed to rt and stirred for an additional 30 min. The reaction mixture was cooled to 0 °C, methyl iodide (4.81 g, 67.7 mmol) was added and the reaction was slowly warmed to rt and stirred for 8 hours. The excess NaH was quenched by slow addition of H_2O and the reaction mixture was extracted with pentane (3 x 20 mL). The resulting organic layers were combined, washed with brine (10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (10% Et_2O in pentane) providing the desired product (2.61 g, 67%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.35 (dd, *J* = 6.2, 1.0 Hz, 1H), 4.79 (dd, *J* = 6.2, 1.8 Hz, 1H), 3.45-3.36 (m, 2H), 3.36 (s, 3H), 1.62-1.54 (m, 2H), 1.0 (t, *J* = 7.4, 3H), 0.96 (s, 3H), 0.86 (s, 3H); ^{13}C (75 MHz, $CDCl_3$) δ 114.3, 100.1, 84.6, 80.8, 57.3, 35.6, 23.6, 21.0, 13.8, 11.1; IR (neat) 2964, 1647, 1239, 1103 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{10}H_{17}O_2$ (M - H) 169.1220, found 169.1229.

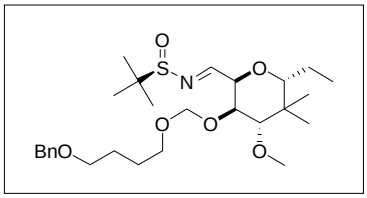


6-Ethyl-4-methoxy-5,5-dimethyl-2-vinyltetrahydropyran-3-ol (64): Preparation of 0.10 M trivinylalane: To a suspension of $AlCl_3$ (4.44 g, 33.3 mmol) in CH_2Cl_2 (233 mL) at rt was added vinylmagnesium bromide (1 M in THF, 100 mL, 100 mmol) drop wise, over a period of 1 hour. The solution was cooled when necessary to prevent reflux and stirred at rt for 4 hours.

Synthesis of **64**: To a stirred solution of **63** (2.20 g, 12.9 mmol) in CH_2Cl_2 (15 mL) cooled to 0 °C was added dimethyldioxirane (71.0 mL, 0.2 M) dropwise and the reaction mixture was stirred at 0 °C for 30 minutes. The reaction mixture was concentrated under reduced pressure and taken up in CH_2Cl_2 (80 mL). The resulting solution was added dropwise over a period of 1 hour to a 0.10 M solution trivinylalane (333 mL) cooled to -72 °C. The resulting reaction mixture was allowed to slowly warm to rt and stir for 6 hours. H_2O (10 mL) was slowly added to quench the excess trivinylalane. 10% aqueous HCl (100 mL) was added to the reaction mixture and the solution was stirred for 30 min. The organic phase was collected and the resulting aqueous phase was extracted with CH_2Cl_2 (20 mL). The organic layers were combined, washed with 10% aqueous HCl (2 x 30 mL) and brine (2 x 30 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting yellow oil was purified by flash chromatography (20% EtOAc in hexanes) to provide the desired product (2.21 g, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.14 (ddd, *J* = 16.2, 11.3, 5.3 Hz, 1H), 5.84-5.38 (m, 2H), 4.56-4.54 (m, 1H), 3.92-3.87 (m, 1H), 3.75 (s, 3H), 3.27 (dd, *J* = 9.8, 0.7 Hz, 1H), 2.78 (d, *J* = 10.0 Hz, 1H), 2.34 (bs, 1H), 1.49-1.43 (m, 1H), 1.33-1.25 (m, 1H), 0.97 (t, *J* = 7.3 Hz, 3H), 0.92 (s, 3H), 0.87 (s, 3H): ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.7, 119.0, 87.7, 78.6, 75.6, 69.9, 62.6, 41.6, 23.5, 21.8, 13.9, 11.5; IR (neat) 3444, 2964, 2877, 1469, 1106, 1038, 926 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{12}H_{22}O_3$ (M^+) 214.1564, found 214.1568.

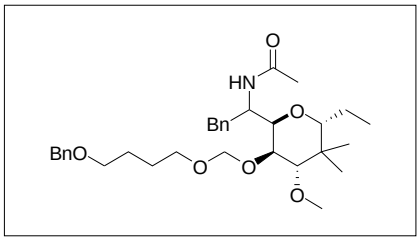


5-(4-Benzyloxybutoxymethoxy)-2-ethyl-4-methoxy-3,3-dimethyl-6-vinyltetrahydropyran (65): To a stirred solution of **64** (2.01 g, 9.39 mmol) in CH_2Cl_2 (7 mL) at rt was added DIPEA (3 mL) followed by BBMCl (Chapter 1, pg 27) (2.90 g, 11.2 mmol) and the reaction mixture was heated to 35 °C for 8 hours. The reaction mixture was cooled to rt, saturated aqueous ammonium chloride (5 mL) was added, the reaction mixture was stirred for 30 minutes and extracted with CH_2Cl_2 (2 x 20 mL). The organic layers were combined, washed with 10% aqueous HCl (2 x 20 mL) and brine (2 x 20 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting orange oil was purified by flash chromatography (10% EtOAc in hexanes) to provide the desired product (2.91 g, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.26 (m, 5H), 6.12 (ddd, *J* = 15.5, 10.9, 4.5 Hz, 1H), 5.48-5.36 (m, 2H), 4.76 (d, *J* = 6.7 Hz, 1H), 4.73 (d, *J* = 6.7 Hz, 1H), 4.57-4.54 (m, 1H), 4.50 (s, 2H), 3.83 (dd, *J* = 10.1, 6.7 Hz, 1H), 3.65-3.60 (m, 1H), 3.52 (s, 3H), 3.51-3.45 (m, 3H), 3.24 (dd, *J* = 8.9, 0.5 Hz, 1H), 2.81 (d, *J* = 10.1 Hz, 1H), 1.72-1.62 (m, 4H), 1.52-1.38 (m, 1H), 1.36-1.23 (m, 1H), 0.98 (t, *J* = 7.3 Hz, 3H), 0.90 (s, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 133.4, 128.3, 127.5, 127.4, 118.5, 95.8, 85.9, 78.3, 76.7, 74.9, 72.8, 70.0, 67.8, 61.9, 41.7, 26.5, 26.4, 23.1, 21.9, 13.8, 11.5; IR (neat) 2934, 2875, 1107, 1038 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{24}H_{38}NaO_5$ (M + Na) 429.2617, found 429.2591.



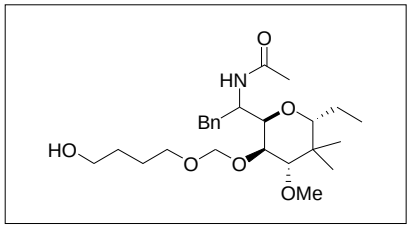
2-Methylpropane-2-sulfinic acid 3-(4-benzyloxybutoxymethoxy)-6-ethyl-4-methoxy-5,5-dimethyltetrahydropyran-2-ylmethyleneamide (66): A stirred solution of **(65)** (0.80 g, 2.0 mmol)

in CH_2Cl_2 (20 mL) cooled to -78 °C was subjected to ozone via gently bubbling for 20 minutes (until the reaction mixture sustained a pale blue color). Triphenylphosphine (1.0 g, 3.9 mmol) was added to the reaction mixture at -78 °C which was then warmed to rt and stirred for 2 hours. The reaction mixture was concentrated, the resulting residue was taken up in THF (8 mL) and Ti(O*i*Pr)$_4$ (2.8 g, 9.9 mmol) was added followed by (R)-*tert*-butanesulfinamide (0.36 g, 3.0 mmol). The reaction mixture was stirred at rt for 6 hours and poured in to an equal volume of brine. EtOAc (30 mL) was added and the resulting emulsion was stirred for 30 minutes. The emulsion was filtered through a pad of celite, the celite was washed with EtOAc (2 x 20 mL) and the organic phase was collected. The organic phase was washed with brine (2 x 20 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to provide the desired product as an inseparable mixture of diastereomers (0.67 g, 67%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (dd, *J* = 9.9, 3.6 Hz, 1H), 7.39-7.26 (m, 5H), 4.85-4.73 (m, 3H), 4.50 (s, 2H), 4.05-3.97 (m, 1H), 3.68-3.62 (m, 1H), 3.55-3.39 (m, 4H), 3.50 (s, 3H), 2.81 (dd, *J* = 15.5, 10.2 Hz, 1H), 1.75-1.63 (m, 4H), 1.52-1.40 (m, 1H), 1.35-1.25 (m, 1H), 1.27 (s, 5H), 1.22 (s, 4H), 1.01-0.93 (m, 3H), 0.90 (s, 3H), 0.87 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1, 166.8, 138.6, 128.3, 127.6, 127.5, 96.1, 96.0, 86.5, 80.8, 80.7, 76.1, 76.0, 72.8, 70.0, 68.3, 68.2, 62.1, 62.0, 57.1, 57.0, 41.7, 26.5, 26.4, 26.4, 23.1, 22.9, 22.6, 22.4, 22.2, 22.1, 13.6, 11.5, 11.4; IR (neat) 2961, 2874, 1363, 1103 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{27}H_{45}NO_6NaS$ 534.2865, found 534.2823.

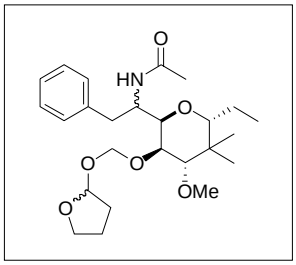


***N*-1-3-(4-Benzyloxybutoxymethoxy)-6-ethyl-4-methoxy-5,5-dimethyltetrahydropyran-2-yl-2-phenylethylacetamide (67):** To a stirred solution of **(66)** (0.85 g, 1.7 mmol) in CH_2Cl_2 (15 mL) at -78 °C was added benzylmagnesium chloride (1 M, 5.0 mL, 5.0

mmol). The reaction mixture was stirred at -78 °C for 5 minutes, warmed to 0 °C and stirred for 1.5 hours. Saturated aqueous NH_4Cl (5 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The resulting oil was taken up in methanol (5 mL), cooled to 0 °C, treated with HCl (4 M in dioxane) and stirred at 0 °C for 2 hours. Aqueous 10% sodium hydroxide (5 mL) was added and the reaction was warmed to rt and stirred for 0.5 hours. The reaction mixture was extracted with EtOAc (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL) dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was taken up in CH_2Cl_2 (4 mL), triethylamine (2 mL) was added and reaction mixture was cooled to -10 °C. Acetyl chloride (0.26 g, 3.3 mmol) was slowly added. The reaction mixture was stirred at 0 °C for 0.5 hours, H_2O (3 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with 10 % aqueous HCl (5 mL) and brine (2 x 5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (0.80 g, 72 %) as a separable mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.20 (m, 10H), 5.74 (d, *J* = 8.0 Hz, 1H), 4.78 (d, *J* = 6.6 Hz, 1H), 4.74 (d, *J* = 6.6 Hz, 1H), 4.53-4.46 (m, 1H), 4.50 (s, 2H), 3.89 (dd, *J* = 6.8, 4.7 Hz, 1H), 3.75 (dd, *J* = 6.8, 4.7 Hz, 1H), 3.65-3.57 (m, 2H), 3.53-3.46 (m, 2H), 3.43 (s, 3H), 3.24-3.11 (m, 2H), 3.01 (d, *J* = 7.0 Hz, 1H), 2.86 (dd, *J* = 13.7, 6.2 Hz, 1H), 1.89 (s, 3H), 1.71-1.68 (m, 4H), 1.58-1.42 (m, 2H), 1.02 (s, 3H), 0.91 (t, *J* = 7.3 Hz, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.0, 138.5, 138.1, 129.8, 128.3, 128.2, 127.6, 127.5, 126.2, 96.2, 85.1, 81.3, 75.5, 72.8, 70.0, 69.4, 68.4, 60.7, 49.6, 39.3, 38.9, 26.5, 26.4, 25.1, 23.6, 21.2, 17.7, 11.6; IR (neat) 3285, 2935, 2876, 1646, 1103 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{32}H_{48}NO_6$ (M + H) 542.3482, found 542.3469.



***N*-1-6-Ethyl-3-(4-hydroxybutoxymethoxy)-4-methoxy-5,5-dimethyltetrahydropyran-2-yl-2-phenylethylacetamide (68):** To a stirred solution of a single diastereomer **(67)** (0.27 g, 0.50 mmol) (both diastereomers react identically) in ethanol (5 mL) at rt was added 20% palladium on carbon (26 mg, 0.05 mmol) and the reaction mixture was placed under H_2 atmosphere and stirred for 8 hours. The reaction mixture was filtered through a plug of celite. The celite was washed with EtOAc (20 mL) and the organic phase was collected from the resulting biphasic mixture. The aqueous phase was extracted with EtOAc (20 mL). The organic phases were combined, washed with brine (2 x 20 ml), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (99 % EtOAc in hexanes) to provide the desired product (0.20, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.15 (m, 5H), 5.85 (d, *J* = 7.7 Hz, 1H), 4.78 (d, *J* = 6.7 Hz, 1H), 4.73 (d, *J* = 6.7 Hz, 1H), 3.92-3.88 (m, 1H), 3.89 (dd, *J* = 6.2, 4.4 Hz, 1H), 3.71 (dd, *J* = 6.2, 4.4 Hz, 1H), 3.67-3.60 (m, 4H), 3.40 (s, 3H), 3.17-3.13 (m, 2H), 2.98 (d, *J* = 6.5 Hz, 1H), 2.89 (dd, *J* = 13.7, 6.0 Hz, 1H), 1.91 (s, 3H), 1.72-1.67 (m, 4H), 1.57-1.49 (m, 1H), 1.43-1.37 (m, 1H), 1.04 (s, 3H), 0.92 (t, *J* = 7.3 Hz, 3H), 0.86 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2, 138.2, 129.8, 128.2, 126.3, 95.8, 84.8, 81.7, 75.2, 68.8, 68.6, 62.4, 60.5, 50.0, 39.0, 29.6, 26.3, 25.5, 23.6, 21.1, 18.3, 11.7; IR (neat) 3420, 3280, 2936, 1652, 1107, 1033 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{25}H_{41}NO_6$ (M^+) 451.2934, found 451.2956.

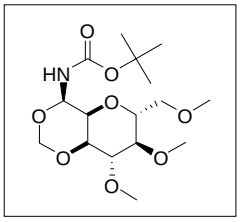


N-1-6-Ethyl-4-methoxy-5,5-dimethyl-3-tetrahydrofuran-2-yloxymethoxytetrahydropyran-2-yl]-2-phenylethylacetamide (48): To a stirred solution of **(68)** (0.10 g, 0.23 mmol) in cyclohexane was added

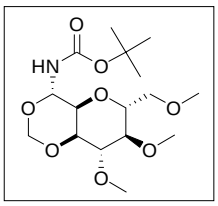
iodobenzene diacetate (0.16 g, 0.51 mmol) and iodine (47 mg, 0.37 mmol) and the reaction mixture was stirred for 20 minutes at rt. The reaction mixture was irradiated for 2 hours and the reaction mixture was extracted with EtOAc (20 mL). The organic phase was washed with saturated aqueous $Na_2S_2O_3$ (2 x 10 mL) and brine (2 x 10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (70 % EtOAc in hexanes) to provide the desired product (0.92 g, 89 %) as an inseparable mixture of diastereomers: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.17 (m, 5H), 5.84 (d, *J* = 8.0 Hz, 0.65H), 5.75 (d, *J* = 8.0 Hz, 0.35H), 5.43-5.40 (m, 1H), 5.03 (d, *J* = 6.6 Hz, 0.35H), 4.96 (d, *J* = 6.6 Hz, 0.65H), 4.80 (d, *J* = 6.6 Hz, 0.35H), 4.57 (d, *J* = 6.6 Hz, 0.65H), 4.52-4.40 (m, 1H), 3.94-3.86 (m, 3H), 3.83-3.71 (m, 1H), 3.46 (s, 1.05H), 3.43 (s, 1.95H), 3.24-3.09 (m, 2H), 3.04-2.89 (m, 2H), 2.06-1.90 (m, 4H), 1.60-1.36 (m, 2H), 1.04 (s, 1.95H), 1.00 (s, 1.05H), 0.95-0.86 (m, 3H), 0.93 (s, 1.05H), 0.86 (s, 1.95H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.1, 138.3, 138.2, 129.9, 129.8, 128.1, 126.2, 101.2, 100.9, 92.8, 92.2, 85.2, 84.9, 81.5, 81.1, 76.2, 75.4, 67.2, 60.7, 60.6, 49.8, 49.5, 39.5, 39.1, 38.8, 38.4, 32.3, 32.2, 25.3, 24.9, 23.5, 23.5, 23.3, 23.2, 21.2, 21.1, 11.6; IR (neat) 3283, 2967, 1642, 1561, 1101 cm^{-1}; HRMS (ES) calcd. for $C_{25}H_{39}NO_6$ (M^+) 449.2777, found 449.2797.

7,8-Dimethoxy-6-methoxymethylhexahydropyrano-(3,2)-(1,3)dioxin-4-ylcarbamic acid *tert*-butyl ester (69 and **70)** To a solution of **47** (29 mg, 0.05 mmol) in DCE (6 mL) was added NMQ (0.8 mg, .003 mmol), NaOAc (58 mg, 200 wt.%), $Na_2S_2O_3$ (58 mg, 200 wt.%), molecular sieves (58 mg, 200 wt.%) and toluene (1 mL). The suspension was stirred at room temperature for 30 minutes. Air was gently bubbled through the suspension while it was irradiated for 2 hours. The reaction mixture was filtered through a small plug of silica and concentrated under

reduced pressure. The resulting oil was purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (18 mg, 94%) a 10:1 mixture of diastereomers:



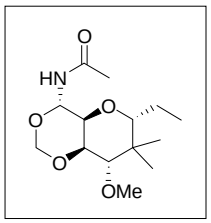
major diastereomer (69): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.97 (d, *J* = 9.7 Hz, 1H), 5.12 (d, *J* = 6.7 Hz, 1H), 5.08 (dd, *J* = 9.7, 1.4 Hz, 1H), 4.84 (d, *J* = 6.7 Hz, 1H), 4.17 (dt, *J* = 7.8, 4.0 Hz, 1H), 3.92 (dd, *J* = 1.8, 1.8, 1H), 3.72 (dd, *J* = 1.8, 1.8 Hz, 1H), 3.62-3.60 (m, 2H), 3.50 (dd, *J* = 3.8, 2.5 Hz, 1H), 3.47 (s, 3H), 3.47 (s, 3H), 3.42 (s, 3H), 3.31-3.29 (m, 1H) 1.47 (s, 9H); ^{13}C (125 MHz, $CDCl_3$) δ 154.9, 91.6, 80.7, 80.5, 79.6, 76.8, 74.5, 73.5, 71.5, 65.5, 59.3, 58.4, 57.7, 28.3; IR (neat) 2922, 1724, 1500 cm^{-1}; $[\alpha]^{25}_{D}$ +17.87° (*c* 0.62 $CHCl_3$); HRMS (ES) calcd. for $C_{16}H_{29}NO_8Na$ (M + Na) 386.1791, found 386.1828.



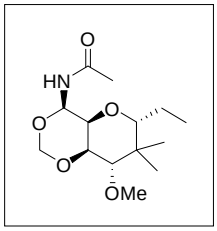
minor diastereomer (70): ^{1}HNMR (300 MHz, $CDCl_3$) δ 5.44 (dd, *J* = 9.3, 8.6 Hz, 1H), 5.17 (d, *J* = 9.3 Hz, 1H), 5.10 (d, *J* = 7.0 Hz, 1H), 4.88 (d, *J* = 7.0 Hz, 1H), 4.14 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.87 (app t, *J* = 9.0 Hz, 1H), 3.76 (dd, *J* = 9.6, 6.3 Hz, 1H), 3.70-3.64 (m, 1H), 3.64 (s, 3H), 3.75-3.50 (m, 2H), 3.54 (s, 3H), 3.38 (s, 3H), 3.27-3.20 (m, 1H), 1.47 (s, 9H); ^{13}C (75 MHz, $CDCl_3$) δ 155. 86.9, 81.1, 79.8, 79.0, 78.7, 77.9, 73.5, 71.2, 70.9, 60.8, 60.7, 59.3, 30.0, 28.5; $[\alpha]^{25}_{D}$ +47.53° (*c* 0.65 $CHCl_3$).

***N*-6-Ethyl-8-methoxy-7,7-dimethylhexahydropyrano-3,2-d-1,3-dioxin-4-yl acetamide (77** and **78):** To a stirred solution of **(48)** (82 mg, 0.18 mmol) in DCE (6 mL) at rt was added was added $NMQPF_6$ (5.7 mg, .02 mmol), NaOAc (0.16 g, 200 wt.%), $Na_2S_2O_3$ (0.16 g, 200 wt.%), 4 Å molecular sieves (0.16 g, 200 wt.%) and toluene (1 mL). The suspension was stirred at rt for 30 minutes. Air was gently bubbled through the suspension while it was irradiated for 2 hours. The

reaction mixture was filtered through a small plug of silica and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (18 mg, 94%) a 1.6:1 mixture of diastereomers:



major diastereomer; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.98 (d, *J* = 9.8 Hz, 1H), 5.80 (app t, *J* = 9.8 Hz, 1H), 5.17 (d, *J* = 7.0 Hz, 1H), 4.86 (d, *J* = 7.0 Hz, 1H), 4.26 (dd, *J* = 10.5, 6.8 Hz, 1H), 3.81 (dd, *J* = 10.0, 6.8 Hz, 1H), 3.6 (s, 3H), 3.46 (d, *J* = 10.5 Hz, 1H), 3.11 (dd, *J* = 10.1, 1.7 Hz, 1H), 2.05 (s, 3H), 1.51-1.39 (m, 1H), 1.29-1.21 (m, 1H), 0.98 (s, 3H), 0.86 (t, *J* = 7.3 Hz, 3H), 0.85 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.3, 86.8, 80.6, 79.6, 75.1, 73.8, 70.9, 61.8, 41.9, 23.2, 23.0, 21.6, 13.2, 11.0; IR (neat) 3299, 2965, 1673, 1546, 1109 cm^{-1}; HRMS (ES) calcd for $C_{14}H_{26}NO_5$ (M+H) 288.1811, found 288.1806.

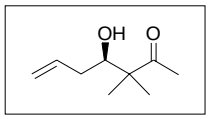


minor diastereomer; ^{1}HNMR (300 MHz, $CDCl_3$) δ 6.79 (d, *J*= 9.1 Hz, 1H), 4.43 (dd, *J* = 9.5, 2.1 Hz, 1H), 5.10 (d, *J* = 6.6 Hz, 1H), 4.86 (d, *J* = 6.6 Hz, 1H), 3.71 (app t, *J* = 1.8 Hz, 1H), 3.55 (app bs, 1H), 3.45 (dd, *J* = 12.1, 3.3 Hz, 1H), 3.39 (s, 3H), 2.91 (app d, *J* = 2.0 Hz, 1H), 2.04 (s, 3H), 1.24 (s, 3H), 0.94 (s, 3H), 0.88 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, CDCl3) δ 169.8, 91.6, 84.0, 83.6, 76.6, 73.0, 60.9, 59.3, 36.7, 27.8, 23.3, 22.5, 20.0, 10.8; IR (neat) 3299, 2965, 1673, 1546, 1109 cm^{-1}; HRMS (EI) calcd for $C_{14}H_{26}NO_5$ (M+H) 288.1811, found 288.1805.

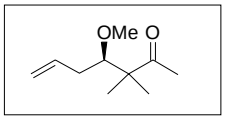
Epimerization Study

To a solution of amido trioxadecalin (**77** and **78**) (5.0 mg, 0.02 mmol) (major or minor diastereomer) in trifluoroethanol (3 mL) at rt was added a catalytic amount (small crystal) of p-toluenesulfonic acid monohydrate. The reaction mixture was stirred at rt for 4 hours and H_2O (5 mL) was added and the reaction mixture was extracted with EtOAc (2 x 5 mL). The organic

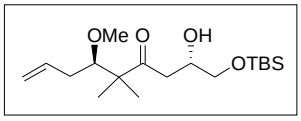
layers were combined, washed with brine (2 x 5 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The crude NMR showed a 1.6:1 mixture of diastereomers identical to that observed in the reaction.



4-Hydroxy-3,3-dimethylhept-6-en-2-one, 81: To a solution of **80**[79] (24.0 g, 89.6 mmol) in toluene (450 mL) at -15 °C was added **79**[78] (8.20 g, 72.0 mmol) dropwise and the reaction mixture was stirred at -15 °C for 24 hours. 10% aqueous HCl (200 mL) was added at -15 °C and the reaction mixture was warmed to rt and stirred for 10 minutes. The organic layer was collected and the aqueous layer was extracted with toluene (3 X 10 mL). The organic layers were combined, washed with 10% aqueous HCl (20 mL) and brine (20 mL), dried with Na_2SO_4, filtered and applied directly to a silica gel flash column packed in pentane. The toluene was eluted from the column with pentane and the product was eluted with 20% ether in pentane to provide the desired product (10.1 g, 90%, 94% ee) The enantioselectivity was determined by GC with a chiral stationary phase. The chira CG column emplyed was a Chiraldex™ G-TA column (Advanced Separation Technologies, Inc.) using a flow rate 0.5 mL/min, method: 100 °C for 20 minutes, T_r (min.) (R) 21.361, (S) 23.013): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.94-5.80 (m, 1H), 5.18-5.11 (m, 2H), 3.77 (ddd, *J* = 10.3, 4.2, 2.4 Hz, 1H), 2.36 (d, *J* = 10.3 Hz, H), 2.32-2.23 (m, 1H), 2.19 (s, 3H), 2.09-1.96 (m, 1H), 1.17 (s, 3H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.5, 135.8, 117.9, 75.3, 51.6, 36.4, 26.3, 21.7, 19.4: IR (neat) 3462, 3076, 2977, 1701, 1641, 1469, 1356, 1129, 1070, 915 cm^{-1}; HRMS(EI) *m/z* calcd for $C_9H_{17}O_2$ (M + H) 157.122855, found 157.122995; $[\alpha]^{20}_D$ +12.0° (*c* 1.10, $CHCl_3$).

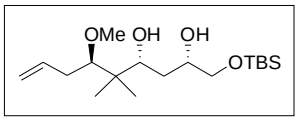


4-Methoxy-3,3-dimethyl-hept-6-en-2-one 82: To a solution of **81** (6.50 g, 41.6 mmol) in CH_2Cl_2 (20 mL) at 0 °C was added 2,6-di-*tert*-butyl pyridine (11.9 g, 62.4 mmol) followed by the drop wise addition of methyl trifluoromethanesulfonate (8.88 g, 54.1 mmol). The reaction mixture was stirred for 8 hours at rt, H_2O (5 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with $NaHCO_3$ (2 x 10 ml) (*caution:* vigorous gas evolution), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (CH_2Cl_2) to provide the desired product (7.01 g, 99%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.96-5.82 (m, 1H), 5.15-5.08 (m, 1H), 5.06-5.03 (m, 1H), 3.43 (dd, J = 6.5, 5.5 Hz, 1H), 3.39 (s, 3H), 2.21-2.15 (m, 2H), 2.17 (s, 3H), 1.16 (s, 3H), 1.09 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 212.9, 136.0, 116.4, 86.0, 59.9, 52.4, 36.7, 26.5, 20.9, 20.2; IR (neat) 2977, 2827, 1704, 1469, 1100 cm^{-1}; $[\alpha]^{25}_D$ +11.60° (*c* 1.00, $CHCl_3$).



1-*tert*-Butyldimethylsilanyloxy-2-hydroxy-6-methoxy-5,5-dimethylnon-8-en-4-one 84: To a solution of **82** (4.00 g, 23.5 mmol) in ether (23.5 mL) at -78 °C was added *N,N*-diisopropylethylamine (3.96 g, 30.6 mmol) followed by the dropwise addition of freshly prepared diethylboron trifluoromethanesulfonate (5.38 g, 24.7 mmol). The reaction mixture was stirred at -78 °C for 1 hour and *tert*-butyldimethylsilyloxyacetaldehyde **83** (4.92, 28.2 mmol) was added dropwise as 1 M solution in ether. The reaction mixture was stirred at -78 °C for 14 hours and methanol (5 mL) was added. The reaction mixture was warmed to 0 °C and pH 7 buffer (30 mL) was added followed by 30% aqueous hydrogen peroxide (10 mL). The reaction mixture was stirred at rt for 2 hours and extracted with EtOAc (3 x 30 mL). The organic layers were combined, washed with brine (2 x

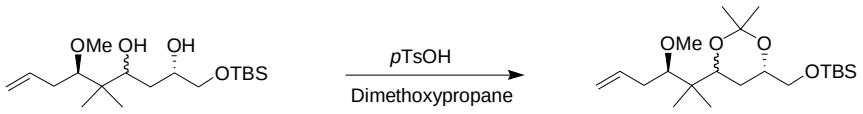
10 mL) and saturated aqueous Na_2SO_3 (2 x 10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (10% EtOAc in hexanes) to provide the desired product as a 3:1 inseparable mixture of diastereomers by ^{1}H NMR (6.40 g, 80%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.94-5.75 (m, 1H), 5.15-5.12 (m, 1H), 5.21-5.00 (m, 1H), 4.13-4.05 (m, 1H), 3.58 (m, 2H), 3.43 (app. t, *J* = 6.1 Hz, 1H), 3.37 (s, 0.75H), 3.36 (s, 2.25H), 3.04 (br d, *J* = 3.5 Hz, 1H), 2.77-2.61 (m, 2H), 2.25-2.15 (m, 2H), 1.16 (s, 3H), 1.08 (s, 3H), 0.90 (s, 9H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 215.7, 136.4, 117.0, 86.5, 68.7, 66.6, 60.3, 52.9, 42.1, 36.0, 26.1, 21.5, 20.5, 18.6, -5.1; IR (neat) 3492, 2929, 2857, 1699, 1471 cm^{-1}; HRMS (ES) *m/z* calcd. for (M + Na) 367.2281, found 367.2264; $[\alpha]^{25}_D$ -7.50° (*c* 1.04, $CHCl_3$).



***tert*-Butyldimethylsilanyloxy-6-methoxy-5,5-dimethyl-non-8-ene-2,4-diol 85:** To a solution of **84** (6.40 g, 18.6 mmol) in THF (120 mL) at -78 °C was added diethylboron methoxide (1.86 g, 18.6 mmol) and the reaction mixture was stirred at -78 °C for 1 hour. Lithium borohydride (1.20 g, 55.3 mmol) was added and the reaction mixture was stirred at -78 °C for 48 hours. The reaction mixture was poured into ice cooled pH 7 buffer (50 mL) and 30% aqueous hydrogen peroxide was added. The reaction mixture was stirred at rt for 12 hours and was extracted with EtOAc (4 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL) and saturated aqueous Na_2SO_3 (2 x 10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (8% EtOAc in hexanes) to provide the desired product as a 10:1 separable mixture of diastereomers (6.30 g, 98%): *syn diastereomer, **85**:* ^{1}NMR ($CDCl_3$, 500 MHz) δ 5.96-5.88 (m, 1H), 5.14-5.11 (m, 1H), 5.06-5.02 (m, 1H), 3.90-3.80 (m, 1H), 3.81

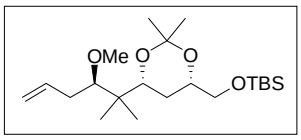
(d, J = 6.5 Hz, 1H), 3.74 (br d, J = 6.3 Hz, 1H), 3.62 (dd, J = 5.9, 3.4 Hz, 1H), 3.54 (d, J = 3.4 Hz, 1H), 3.50 (dd, J = 5.8, 3.7 Hz, 1H), 3.45 (s, 2.25H), 3.42 (s, 0.75H), 3.22-3.20 (m, 1H), 2.45-3.32 (m, 1H), 2.31-2.18 (m, 1H), 1.74-1.70 (m, 1H), 1.44-1.36 (m, 1H), 0.95 (s, 2.25H), 0.93 (s, 0.75H), 0.90 (s, 9H), 0.84 (s, 2.25H), 0.79 (s, 0.75H), 0.08 (s, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.1, 136.6, 116.6, 116.2, 89.7, 88.3, 78.3, 77.5, 73.1, 73.0, 67.1, 67.0, 60.2, 59.8, 42.3, 41.4, 35.3, 35.1, 34.1, 33.7, 25.9, 21.5, 20.5, 18.3, 17.0, -5.3; IR (neat) 3440, 2956, 2928, 1471, 1255, 1095 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{14}H_{29}O_4Si$ (M – C_4H_9) 289.1835, found 289.1842; $[\alpha]^{25}_D$ -2.83° (*c* 0.92, $CHCl_3$).

anti diastereomer, ***86****:* ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.99-5.85 (m, 1H), 5.10 (ddd, J = 17.1, 3.1, 1.5 Hz, 1H), 5.04 (m, 1H), 3.97-3.91 (m, 1H), 3.86 (dd, J = 10.6, 2.2 Hz, 1H), 3.66 (dd, J = 9.9, 4.2 Hz, 1H), 3.50 (dd, J = 9.9, 7.4 Hz, 1H), 3.43 (s, 3H), 3.21 (dd, J = 7.1, 3.8 Hz, 1H), 2.50-2.42 (m, 1H), 3.32-2.18 (m, 1H), 1.60 (ddd, J = 13.9, 10.3, 8.0 Hz, 1H), 1.44 (ddd, J = 14.0, 10.3, 3.5 Hz, 1H), 0.92 (s, 3H), 0.90 (s, 9H), 0.78 (s, 3H), 0.08 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.4, 116.5, 89.9, 74.8, 69.8, 67.5, 60.0, 42.3, 35.7, 34.1, 26.1, 21.4, 18.5, 16.5, -5.0, -5.1.

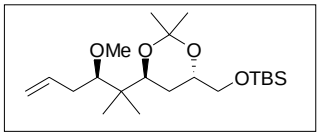


Representative procedure for acetonide formation: To a solution of **85** (50 mg, 0.14 mmol) in 2,2-dimethoxypropane (2 mL) was added catalytic amounts *para*-toluenesulfonic acid and the reaction mixture was stirred at rt for 8 hours. Triethylamine (0.1 mL) was added, H_2O (5 mL) and the reaction mixture was extracted with EtOAc (3 x 5 mL). The organic layers were combined, washed with brine (2 x 5 mL), dried with Na_2SO_4, filtered, concentrated and purified by flash chromatography (10% EtOAc in hexanes) to provide the desired product with yields

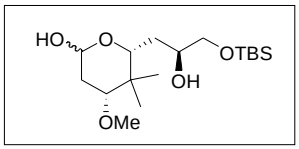
consistently greater than 90%. The resulting acetonides are described below are described below.



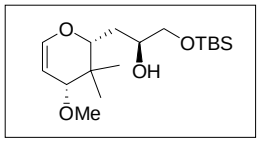
***tert*-Butyl-6,2-methoxy-1,1-dimethylpent-4-enyl-2,2-dimethyl-1,3-dioxan-4-ylmethoxydimethylsilane 87:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.99-5.90 (m, 1H), 5.12-5.07 (dd, *J* = 16.9, 10.7 Hz, 1H), 5.02 (d, *J* = 10.0 Hz, 1H), 3.96 (bd, *J* = 11.9 Hz, 0.75H), 3.92-3.76 (m, 1H), 3.73 (bd, *J* = 11.6 Hz, 0.25H), 3.70-3.65 (m, 1H), 3.51-3.47 (m, 1H), 3.40 (s, 2.25H), 3.39 (s, 0.75H), 3.28 (dd, *J* = 8.3, 2.7 Hz, 0.75H), 3.13-3.10 (m, 0.25H), 2.4-2.28 (m, 1H), 2.23-2.11 (m, 1H), 1.50-1.45 (m, 1H), 1.46 (s, 2.25H), 1.41 (s, 0.75H), 1.37 (s, 3H), 1.27-1.19 (m, 1H), 0.94 (s, 0.75H), 0.90 (s, 11.25H), 0.79 (s, 2.25H), 0.77 (s, 0.75H), 0.07 (s, 3H), 0.07 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.6, 115.8, 98.3, 85.8, 83.9, 72.7, 71.0, 70.3, 70.2, 67.2, 67.1, 60.4, 60.2, 41.7, 35.5, 35.3, 30.1, 28.2, 27.7, 25.9, 19.9, 18.9, 18.8, 18.3, 18.2, 17.3, -5.2, -5.3.



***tert*-Butyl-6,2-methoxy-1,1-dimethyl-pent-4-enyl-2,2-dimethyl-1,3-dioxan-4-ylmethoxydimethylsilane 88:** ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.98-5.90 (m, 1H), 5.09 (d, *J* = 17.0 Hz, 1H), 5.01 (d, *J* = 10.0 Hz, 1H), 3.83-3.78 (m, 1H), 3.71 (dd, *J* = 9.8, 6.3 Hz, 1H), 3.63 (dd, *J* = 10.7, 6.3 Hz, 1H), 3.56 (dd, *J* = 10.7, 4.7 Hz, 1H), 3.39 (s, 3H), 3.09 (dd, *J* = 8.6, 2.3 Hz, 1H), 2.36 (dd, *J* = 14.1, 5.7 Hz, 1H), 2.19-2.13 (m, 1H), 1.80-1.74 (m, 1H), 1.45-1.39 (m, 1H), 1.32 (s, 3H), 1.32 (s, 3H), 0.94 (s, 3H), 0.90 (s, 9H), 0.77 (s, 3H), 0.07 (s, 3H), 0.06 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 137.5, 115.9, 100.1, 85.8, 70.1, 68.3, 66.3, 60.4, 41.5, 35.4, 29.4, 25.9, 24.9, 24.5, 18.7, 18.5, 18.3, -5.1, -5.3.

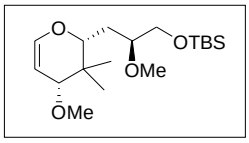


6,3-*tert*-Butyldimethylsilanyloxy-2-hydroxypropyl-4-methoxy-5,5-dimethyltetrahydropyran-2-ol 89: Ozone was gently bubbled through a solution of **85** (7.00 g, 20.2 mmol) in CH_2Cl_2 (100 mL) at -78 °C until the reaction mixture sustained a deep blue color. Triphenylphosphine (6.86 g, 26.3 mmol) was added and the reaction mixture was warmed to rt and stirred for 3 hours. The resulting solution was concentrated and purified by flash chromatography (40% EtOAc in hexanes) via a short column to separate excess triphenylphosphine and triphenylphosphine oxide from the product (6.40g, 91%). The product was used in the next step with minor of impurities. *A lengthy chromatographic separation resulted in decreased yields.*

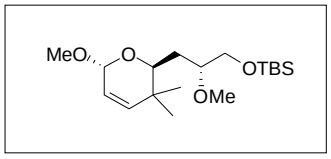


1-*tert*-Butyl-dimethyl-silanyloxy-3,4-methoxy-3,3-dimethyl-3,4-dihydro-2H-pyran-2-ylpropan-2-ol 92: To a solution of **89** (3.72 g, 10.7 mmol) in CH_2Cl_2 (67 mL) at -78 °C was added diisopropylethylamine (8.28 g, 64.0 mmol) followed by trifluoroacetic anhydride (4.71 g, 22.4 mmol). The resulting reaction mixture was stirred at -78 °C for 10 minutes, warmed to 0 °C and stirred at 0 °C for 1 hour. The reaction mixture was then heated to gentle reflux for 12 hours. The reaction mixture was cooled to rt, methanol (20 mL) was added and the reaction mixture was heated to gentle reflux for 8 hours. The reaction mixture was cooled to rt, diluted with brine (50 mL) and extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, washed with brine (30 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (5 % EtOAc in hexanes) to provide the desired product (3.50 g, 99%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.40 (d, J = 6.0 Hz, 0.25H), 6.32 (dd, J = 6.2, 1.4 Hz, 0.75H), 4.99 (dd, J = 6.0, 5.2 Hz, 0.25H), 4.82 (dd, J = 6.2, 1.9 Hz, 0.75H), 3.91-3.81 (m, 1.25H), 3.73 (dd, J = 10.7,

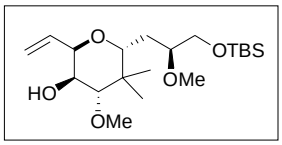
2.4 Hz, 0.75H), 3.61-3.50 (m, 2.25H), 3.45 (app t, 0.75H), 3.37 (s, 2.25H), 3.33 (s, 0.75H), 2.97 (d, *J* = 5.2 Hz, 0.15H), 2.95 (d, *J* = 2.6, 0.10H), 2.89 (d, *J* = 2.8, 0.75H), 1.90-1.83 (m, 1H), 1.80-1.65 (m, 1H), 0.96 (s, 3H), 0.89 (s, 9H), 0.86 (s, 2.25H), 0.82 (s, 0.75H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 144.9, 143.5, 100.8, 99.4, 82.2, 80.4, 78.1, 77.9, 71.3, 71.3, 66.3, 57.2, 56.3, 36.3, 35.5, 31.9, 31.5, 29.7, 25.8, 23.4, 21.5, 18.9, 18.2, 13.7, -5.4; IR (neat) 3571, 2956, 1649, 1100 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{17}H_{34}O_4NaSi$ (M + Na) 353.2124, found 353.2149; $[\alpha]^{25}_D$ -66.9° (*c* 1.00, $CHCl_3$).



***tert*-Butyl-2-methoxy-3,4-methoxy-3,3-dimethyl-3,4-dihydro-2H-pyran-2-ylpropoxydimethylsilane 93:** To a solution of **92** (1.80g, 5.45 mmol) in CH_2Cl_2 (10.9 mL) at 0 °C was added 2,6-di-*tert*-butylpyridine (2.09 g, 10.9 mmol) followed by methyltrifluoromethanesulfonate (1.34 g, 8.18 mmol). The reaction mixture was warmed to rt and stirred for 14 hours. H_2O (10 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with saturated aqueous $NaHCO_3$ (2 x 10 mL) and brine (10 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (3 % EtOAc in hexanes) to provide the desired product (1.20 g, 85%) and the degradation product (0.35 g, 81%). ^{1}H NMR ($CDCl_3$, 300 HMz) δ 6.32 (dd, *J* = Hz, 1H), 4.80 (dd, *J* = 6.2, 1.8 Hz, 1H), 3.74-3.63 (m, 3H), 3.45-3.43 (m, 1H), 3.42-3.36 (m, 1H), 3.39 (s, 3H), 3.37 (s, 3H), 1.85-1.79 (m, 2H), 0.95 (s, 3H), 0.90 (s, 9H), 0.88 (s, 3H), 0.07 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 144.4, 100.6, 81.0, 80.1, 79.8, 77.3, 64.2, 57.6, 35.7, 29.8, 26.2, 23.9, 18.6, 14.0, -5.0; IR (neat) 2929, 2650, 1463, 1250, 1102 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{17}H_{33}O_3Si$ (M – OMe) 313.2199, found 313.2195; $[\alpha]^{25}_D$ -u27.46° (*c* 0.63, $CHCl_3$).



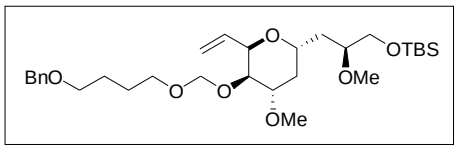
***tert*-Butyl-2-methoxy-3,6-methoxy-3,3-dimethyl-3,6-dihydro-2H-pyran-2-ylpropoxydimethylsilane 94:** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.72 (dd, *J* = 10.0, 1.0 Hz, 1H), 5.57 (dd, *J*= 10.0, 2.8 Hz, 1H), 4.79 (d, *J* = 2.8 Hz, 1H), 3.77 (dd, *J* = 11.1, 3.2 Hz, 1H),3.69 (dd, *J* = 11.1, 4.7 Hz, 1H), 3.61 (dd, *J* = 10.7, 1.4 Hz, 1H), 3.5-3.8 (m, 1H), 3.42 (s, 3H), 3.41 (s, 3H), 1.80 (ddd, *J* = 14.0, 9.1, 1.7 Hz, 1H), 1.62 (ddd, *J* = 14.0, 10.9, 4.1 Hz, 1H), 0.91 (s, 3H), 0.88 (s, 12H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 141.4, 122.3, 95.7, 79.9, 72.3, 63.5, 57.2, 55.5, 34.3, 30.5, 25.9, 24.9, 20.1, 18.3, -5.4; IR (neat) 2956, 2857, 1470, 1253, 1107 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{18}H_{36}O_4NaSi$ (M + Na) 367.2281, found 367.2298; $[\alpha]^{25}_D$ -6.41° (*c* 1.06, $CHCl_3$).



6-(3-*tert*-Butyl-dimethyl-silanyloxy-2-methoxypropyl)-4-methoxy-5,5-dimethyl-2-vinyltetrahydropyran-3-ol 96: *Preparation of 0.10 M trivinylalane*:[2] To a suspension of $AlCl_3$ (4.44 g, 33.3 mmol) in CH_2Cl_2 (233 mL) at rt was added vinylmagnesium bromide (1 M in THF, 100 mL) over a period of 1 hour. The reaction mixture was cooled with an ice bath when necessary throughout the addition to prevent reflux. Following the addition the reaction mixture was stirred at rt for 4 hours at which point trivinylalane formation is complete.

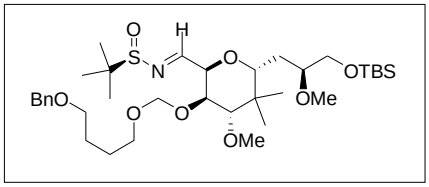
*Synthesis of **96***: To a solution of **93** (1.21 g, 3.48 mmol) in CH_2Cl_2 (10 mL) at 0 °C was added dimethyldioxirane[3] (0.2 M, 26 mL, 5.22) and the reaction mixture was stirred at 0 °C for 45 minutes. The reaction mixture was concentrated, the resulting oil was dissolved in CH_2Cl_2 (30 mL) and added drop wise to a solution of trivinylalane (0.10 M, 104 mL, 10.4 mmol) at -72 °C. The resulting reaction mixture was stirred at -72 °C for 1 hour, warmed to rt and stirred for 8

hours. The reaction mixture was carefully quenched with the addition of H_2O (20 mL). Saturated aqueous sodium potassium tartrate (100 mL) was added and the reaction mixture was stirred at rt for 8 hours. The reaction mixture was extracted with CH_2Cl_2 (3 x 20 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried with Na_2SO_4, filtered, concentrated under reduced pressure and purified by flash chromatography (20% EtOAc in hexanes) to provide the desired product (1.15 g, 85%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.17 (ddd, *J* = 17.2, 10.7, 6.2 Hz, 1H), 5.44 (ddd, *J* = 14.3, 1.7, 1.7 Hz, 1H), 5.42 (ddd, *J* = 7.5, 1.7, 1.7 Hz, 1H), 4.51-4.45 (m, 1H), 3.87 (ddd, *J* = 10.2, 6.6, 4.0 Hz, 1H), 3.68-3.59 (m, 1H), 3.63 (dd, *J* = 6.4, 3.7 Hz, 1H), 3.58 (s, 3H), 3.43 (dd, *J* = 10.1, 1.5 Hz, 1H), 3.36 (s, 3H), 3.36-3.31 (m, 1H), 2.81 (d, *J* = 10.0 Hz, 1H), 2.37 (d, *J* = 4.1 Hz, 1H), 1.72 (ddd, *J* = 14.1, 8.4, 1.8 Hz, 1H), 1.52 (ddd, *J* = 14.1, 10.2, 4.0 Hz, 1H), 0.91 (s, 3H), 0.88 (s, 9H), 0.87 (s, 3H), 0.05 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 132.4, 120.2, 87.6, 79.8, 76.1, 74.1, 69.7, 64.0, 62.5, 57.2, 41.5, 30.3, 25.9, 23.5, 18.3, 13.8, -5.4; IR (neat) 3448, 2930, 1471, 1109 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{20}H_{40}O_5Si$ (M + Na) 411.2543, found 411.2574; $[\alpha]^{25}_D$ +84.33° (*c* 1.02, $CHCl_3$).



3,5-(4-Benzyloxybutoxymethoxy)-4-methoxy-6-vinyltetrahydropyran-2-yl-2-methoxypropoxy-*tert*-butyldimethylsilane (97): To a solution of **96** (2.42 g, 6.23 mmol) in CH_2Cl_2 (4 mL) at rt was added diisopropylethylamine (4 mL). Benzyloxybutoxymethyl chloride (1.71 g, 7.47 mmol) was added and the reaction mixture was warmed to 40 °C and stirred for 8 hours. The reaction mixture was cooled to rt, H_2O (5 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with 10% HCl (10 mL) and brine (2 x 10 mL), dried with Na_2SO_4, filtered and concentrated. The resulting oil was purified

by flash chromatography (10 % EtOAc in hexanes) to provide the desired product (3.2 g, 89 %): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.61-7.27 (m, 5H), 6.19 (ddd, *J* = 17.0, 10.8, 5.8 Hz, 1H), 5.47-5.38 (m, 2H), 4.79 (d, *J* = 6.7 Hz, 1H), 4.71 (d, *J* = 6.7 Hz, 1H), 4.62-4.45 (m, 1H) 4.51 (s, 3H), 3.81 (dd, *J* = 10.0, 6.5 Hz, 1H), 3.66-3.57 (m, 3H), 3.52 (s, 3H), 3.52-3.43 (m, 2H), 3.41-3.31 (m, 2H), 3.38 (s, 3H), 2.86 (d, *J* = 10.1 Hz, 1H), 1.75-1.66 (m, 5H), 1.57-1.52 (m, 1H), 0.90 (s, 12H), 0.85 (s, 3H), 0.06 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 138.9, 133.9, 128.6, 127.9, 127.8, 119.9, 96.1, 86.1, 77.5, 76.7, 75.6, 74.1, 73.2, 70.4, 68.2, 64.5, 62.3, 57.5, 42.0, 30.7, 26.8, 26.7, 26.2, 23.4, 18.6, 14.0, -5.0; IR (neat) 2930, 1471, 1361, 1112 cm^{-1}; HRMS (ES) *m/z* calcd. for $C_{32}H_{56}O_7NaSi$ (M + Na) 603.3693, found 603.3718; $[\alpha]^{25}_D$ +31.40° (*c* 1.07, $CHCl_3$).



2-Methylpropane-2-sulfinic acid 3-benzyloxybutoxymethoxy-6,3-*tert*-butyldimethylsilanyloxy-2-methoxypropyl-4-methoxy-5,5-dimethyltetrahydropyran-2-ylmethyleneamide 98: Ozone was bubbled through a solution of **97** (0.20 g, 0.34 mmol) in CH_2Cl_2 (10 mL) at -78 °C until the solution sustained a deep blue color. Triphenylphosphine (0.18 g, 0.69 mmol) was added and the reaction mixture was warmed to rt and stirred for 3 hours. The reaction mixture was concentrated under vacuum and the resulting oil was dissolved in THF (4.5 mL) and Ti(O*i*Pr)$_4$ (0.49 g, 1.72 mmol) was added at rt followed by (R)-*tert*-butanesulfinamide[5] (0.06 g, 0.52 mmol). The reaction mixture was stirred for 8 hours, poured into an equal volume of brine and the resulting mixture was filtered through a plug of celite. The celite was washed thoroughly with EtOAc and the eluent was combined. The eluent was washed with brine (10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (20% EtOAc in

hexanes) to provide the desired product (0.13 g, 62%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.38 (d, *J* = 2.6 Hz, 1H), 7.37-7.26 (m, 5H), 4.84 (d, *J* = 6.8 Hz, 1H), 4.78-4.74 (m, 1H), 4.77 (d, *J* = 6.8 Hz, 1H), 4.50 (s, 2H), 4.01 (dd, *J* = 10.2, 7.1 Hz, 1H), 3.69-3.63 (m, 3H), 3.53-3.42 (m, 5H), 3.51 (s, 3H), 3.35 (s, 3H), 2.78 (d, *J* = 10.3 Hz, 1H), 1.84-1.76 (m, 1H), 1.67-1.66 (m, 4H), 1.55-1.52 (m, 1H), 1.22 (s, 9H), 0.89 (s, 15H), 0.06 (s, 3H), 0.05 (s, 3H); ^{13}C NMR ($CDCl_3$, 300 MHz) δ 166.6, 138.4, 128.1, 127.4, 127.3, 96.0, 86.2, 79.2, 76.4, 76.1, 75.9, 72.6, 69.8, 68.0, 63.0, 61.9, 56.9, 56.7, 41.5, 29.9, 26.3, 26.3, 25.8, 22.8, 18.1, 13.4, -5.5; IR (neat) 2929, 1619, 1471, 1362, 1091 cm^{-1}; HRMS (ES) *m/z* calcd for $C_{35}H_{63}NO_8NaSiS$ 708.3941, found 708.3926; $[\alpha]^{25}_{D}$ +0.36° (*c* 1.10, CH_3Cl).

2.5 References

1. Perry, N. B.; Blunt, J. W.; Munro, M. G. H.; Pannell, L. K. "Mycalamide A, an Antiviral Compound from a New Zealand Sponge of the Genus *Mycale*" *J. Am. Chem. Soc.* **1988**, *110*, 4850-4851.
2. Perry, N. B.; Blunt, J. W.; Munro, M. G. H.; Pannell, L. K.; Thompson, A. M. "Antiviral and Antitumor Agents from a New Zealand Sponge, *Mycale* sp. 2. Structures and Solution Conformations of Mycalamides A and B" *J. Org. Chem.* **1990**, *55*, 223-227.
3. Simpson, S.; Garson, M. J.; Blunt J. W.; Munro, M. H. G.; Hooper, J. N. A. "Mycalamides C and D, Cytotoxic Compounds from the Marine Sponge *Stylinos* n. Species" *J. Nat. Prod.* **2000**, *63*, 704-706.
4. West, L. M.; Northcote, P. T.; Hood, K. A.; Miller, J. H.; Page. M. J. "Mycalamide D, a New Cytotoxic Amide from the New Zealand Marine Sponge *Mycale* Species" *J. Nat. Prod.* **2000**, 707-709.
5. Sakemi, S.; Ichiba, T.; Kohmoto, S.; Saucy G.; Higa, T. "Isolation and Structural Elucidation of Onnamide A, a New Bioactive Metabolite of a Marine Sponge, *Theonella* sp" *J. Am. Chem. Soc.* **1988**, *110*, 4851-4852.
6. Matsunaga, S.; Fusetani, N.; Nakao, Y. "Eight New Cytotoxic Metabolites Related to Onnamide A from Two Marine Sponges of the Genus *Theonella*" *Tetrahedron* **1992,** *48*, 8369-8376.
7. Kobayashi, J.; Itagaki, H.; Shigemori, T.; Sasaki, J. "3 New Onnamide Congeners from the Okinawan Marine Sponge *Theonella sp.*" *J. Nat. Prod.* **1993**, *56*, 976.

8. Vuong, D.; Capon, R. J.; Lacey, E.; Gill, J. H.; Heiland, K.; Friedel, T. "Onnamide F: A New Nematocide from a Southern Australian Marine Sponge, *Trachycladus laevispirulifer*" *J. Nat. Prod.* **2001**, *64*, 640-642.
9. Fusetani, N.; Sugawara, T.; Matsunaga, S. "Theopederins A-E, Potent Antitumor Metabolites from a Marine Sponge *Theonella* sp." *J. Org. Chem.* **1992**, *57*, 3828-3832.
10. Tsukamoto, S.; Matsunaga, S.; Fusetani, N.; Toh-e, A. "Theopederins F-J: Five New Antifungal and Cytotoxic Metabolites from the Marine Sponge, *Theonella swinhoei*" *Tetrahedron*, **1999**, *55*, 13697-13702.
11. Paul, G. K.; Dunasekera, S. P.; Longley, R. E.; Pomponi, S. A. "Theopederins K and L Highly Potent Cytotoxic Metabolites from a Marine Sponge *Discodermia* Species" *J. Nat. Prod.* **2002**, *65*, 59-61.
12. Petit, G. R.; Xu, J-P.; Chapuis, J-C.; Petit, R. K.; Tackett, L. P.; Doubek, D. L. Hooper, J. N. A.; Schmidt, J. M. "Antineoplastic Agents. 520. Isolation and Structure of Irciniastatins A and B from the Indo-Pacific Marine Sponge *Ircinia ramose*" *J. Med. Chem.* **2004**, *47*, 1149-1152.
13. Cichewicz, R. H.; Valeriote, F. A.; Crews, P. "Psymberin, a Potent Sponge-Derived Cytotoxin from *Psammocinia* Distantly Related to the Pederin Family" *Org. Lett.* **2004**, *6*, 1951-1954.
14. Cardani, C.; Ghiringhelli, D.; Mondelli, R.; Quilico. A. "The Structure of Pederin" *Tetrahedron Lett.* **1965**, *6*, 2537–2545.
15. Mitsutoshi, Y.; Matsuda, F.; Hadegewa, K.; Matsumoto, T. "Total Synthesis of (+)-Pedamide" *Tetrahedron Lett.* **1982**, *23*, 4039-4042.

16. Matsuda, F.; Yanagiya, M.; Matsumoto, T. "Total Synthesis of (+)-Pederine. A Simple Synthetic Method for *N*-(1-Methoxylalkyl) Amides" *Tetrahedron Lett.* **1982**, *23*, 4043-4046.

17. Matsuda, F.; Tomiyoshi, N.; Yanagiya, M.; Matsumoto, T. "A New Stereocontrolled Synthesis of (+)-Pederine. Unusual Conformation Around C-10-C-11 Bond in Pederine Derivatives" *Tetrahedron Lett.* **1983**, *24*, 1277-1280.

18. Matsuda, F.; Nobuya, T.; Mitsutoshi, N.; Matsumoto, T. "Stereocontrolled Total Synthesis of (+)-Pederine" *Tetrahedron Lett.* **1988**, *44*, 7063-7080.

19. Mienwald, J. "An Approach to the Synthesis of Pederin" *Pure Appl. Chem.* **1977**, *49*, 1275-1290.

20. Meinwald, J.; Adams, M.; Duggan, A. J. "An Adventurous Synthesis of Pederinolactone" *Heterocycles* **1977**, *7*, 989-995.

21. Adams, M. A.; Duggan, A. J.; Smolanoff, J.; Meinwald, J. "Total Synthesis of (±)-Pederamide" *J. Am. Chem. Soc.* **1979**, *101*, 5364-5370.

22. Wratten, S. J.; Meinwald, J. "An Investigation of the Mechanism of the Pederenal Transformation" *Tetrahedron Lett.* **1980**, *21*, 3164-3166.

23. Hong, C. Y.; Kishi, Y. "Total Synthesis of Mycalamides A and B" *J. Org. Chem.* **1990**, *55*, 4242-4245.

24. Hong, C. Y.; Kishi, Y. "Total Synthesis of Onnamide A" *J. Am. Chem. Soc.* **1991**, *113*, 9693-9694.

25. Isaac, K.; Kocienski, P.; Cambell, S. "Synthetic Approaches to Pederin. A Synthesis of Ethyl Pederate" *J. Chem. Soc., Chem. Commun.* **1983**, 249-250.

26. Kocienski, P.; Wilson, T. M. "Synthetic Approaches to Pederin. A Synthesis of (±)-Benzoylpedamide" *J. Chem. Soc., Chem. Commun.* **1984**, 1011-1012.

27. Wilson, T.; Kocienski, P.; Faller, A.; Campbell, S. "The Total Synthesis of (±)-Pederin" *J. Chem. Soc., Chem. Commun.* **1987**, 106-108.

28. Jorowicki, K.; Kocienski, P.; Marczak, S.; Willson, T. "A Synthesis of (+)-Pederin. The Metallated Dihydropyran Approach" *Tetrahedron Lett.* **1990**, *31*, 3433-3436.

29. Wilson, T. M.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Faller, A.; Cambell, S. F.; Bordner, J. "Studies Related to the Synthesis of (±)-Pederin. Part 1. Synthesis of Ethyl Pederate and Benzoylselenopederic Acid" *Tetrahedron*, **1990**, *46*, 1757-1766.

30. Wilson, T. M.; Kocienski, P.; Jarowski, K.; Isaac, K.; Hitchcock, P. M.; Faller, A.; Cambell, S. F. "Studies Related to the Synthesis of Pederin. Part 2. Synthesis of Pederol Dibenzoate and Benzoylpedamide." *Tetrahedron* **1990**, *46*, 1767-1782.

31. Kocienski, P.; Jarowicki, K.; Marczak, S. "Pederin: The Metallated Dihydropyran Approach. Stereoselective Reduction of *N*-Acylimidates *via* Rhodium-Catalyzed Hydroboration" *Synthesis*, **1991**, 1191-1200.

32. Jarowicki, K.; Kocienski, P.; Marczak, S.; Willson, T. "A Synthesis of (+)-Pederin, the Metalated Dihydropyran Approach." *Tetrahedron Letters* **1990**, *31*, 3433-3436

33. Willson, T. M.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Hitchcock, P. M.; Faller, A.; Campbell, S. F. "Studies Related to the Synthesis of Pederin. Part 2. Synthesis of Pederol Dibenzoate and Benzoylpedamide." *Tetrahedron* **1990**, *46*, 1767-1782.

34. Willson, T. M.; Kocienski, P.; Jarowicki, K.; Isaac, K.; Faller, A.; Campbell, S. F.; Bordner, J. "Studies Related to the Synthesis of (+)-Pederin. Part 1. Synthesis of Ethyl Pederate and Benzoylselenopederic Acid." *Tetrahedron* **1990**, *46*, 1757-1766.

35. Kocienski, P.; Raubo, P.; Davis, J. K.; Boyle, F. T.; Davies, D. E.; Richter, A. "A Synthesis of 18-*O*-Methyl Mycalamide B" *J. Chem. Soc., Perkin Trans. 1* **1996**, 1797-1808.

36. Kocienski, P.; Narquizian, R.; Raubo, P.; Smith, C.; Boyle, F. T. "A Synthesis of Mycalamide B" *Synlett.* **1998**, 869-872.

37. Kocienski, P.; Narquizian, R.; Raubo, P.; Smith, C.; Boyle, F. T. "A Synthesis of Theopederin D and a Formal Synthesis of Pederin" *Synlett.* **1998**, 1432-1434.

38. Kocienski, P.; Narquizian, R.; Raubo, P.; Smith, C.; Farrugia L. J.; Muir, K.; Boyle F. T. "Synthetic Studies on the Pederin Family of Antitumor Agents. Syntheses of Mycalamide B, Theopederin D, and Pederin" *J. Chem. Soc., Perkin Trans. 1* **2000**, 2357-2384.

39. Roush, W. R.; Marron, T. G. "Toward the Synthesis of Mycalamides A, B and Onnamide A: A Highly Stereoselective Synthesis of the Trioxadecalin Ring System" *Tetrahedron Lett.* **1993**, *34*, 5421-5424.

40. Marron, T. G.; Roush, W. R. "Diastereoselective Synthesis of *N*-Benzoyl Mycalamide, the Fully Elaborated Trioxadecalin Nucleus of Mycalamide A. Control of the Key N-Acyl Aminal Stereocenter via Carbamate Acylation" *Tetrahedron Lett.* **1995**, *36*, 1581-1584.

41. Roush, W. R.; Pfeifer, L. A. "Stereoselective *N*-Acylation Reactions of α-Alkoxy Carbamates" *J. Org. Chem.* **1998**, *63*, 2062-2063.

42. Roush, W. R.; Pfeifer, L. A. "Total Synthesis of Mycalamide A and 7-*epi*-Mycalamide A" *Org. Lett.* **2000**, *2*, 859-862.

43. Nakata, T.; Nagao, S.; Mori, N.; Oishi, T. "Total Synthesis of (+)-Pederin. 1. Stereocontrolled Synthesis of (+)-Benzoylpedamide" *Tetrahedron Lett.* **1985**, *26*, 6461-6464.

44. Nakata, T.; Fukui, H.; Nakagawa, T.; Matsukura, H. "Total Synthesis of Mycalamide A. Further Synthetic Study of the Right Half" *Heterocycles*, **1996**, *42*, 159-164.

45. Trotter, N. S.; Takahashi, S.; Nakata, T. "Simple and Efficient Synthesis of (+)-Methyl 7-Benzoylpederate, a Key Intermediate Toward the Mycalamides" *Org. Lett.* **1999**, *1*, 957-959.

46. Takahiro, T.; Nishi, Y.; Takahashi S.; Kobayashi, J.; Nakata, T. "Total synthesis of Pederin, a Potent Insect Toxin: the Efficient Synthesis of the Right Half, (+)-Benzoylpedamide" *Tetrahedron* **2002**, *58*, 6359-6365.

47. Toyota, M.; Hirota, M.; Hirano, H.; Ihara, M. "A Stereoselective Synthesis of the C-10 to C-18 (Right Half) Fragment of Mycalamides Employing Lewis Acid Promoted Intermolecular Aldol Reaction" *Org. Lett.* **2000**, *2*, 2031-2034.

48. Toyota, M.; Hirota, M.; Nishikawa, Y.; Fukumoto, K.; Ihara, M. "Palladium-Catalyzed Intramolecular Allylic Alkylation Reaction in Marine Natural Product Synthesis: Enantioselective Synthesis of (+)-Methyl Pederate, a Key Intermediate in Synthesis of Mycalamides." *J. Org. Chem.* **1998**, *63*, 5895-5902.

49. Hoffman, R. W.; Schlapbach, A. "Synthesis of the Trioxadecalin-Part of Mycalamide B" *Tetrahedron Lett.* **1993**, *34*, 7903-7906.

50. Trost, B. M.: Yang, H.; Probst, G. D. "A Formal Synthesis of (–)-Mycalamide A" *J. Am. Chem. Soc.* **2004**, *126*, 48-49.

51. Sohn, J-H.; Waizumi, N.; Zhong, M.; Rawal, V. H. "Total Synthesis of Mycalamide A" *J. Am. Chem. Soc.* **2005**, *127*, 7290-7291.

52. Jiang, X; Garcia-Fortanet, J.; De Brabander J. K. "Synthesis and Complete Stereochemical Assignment of Psymberin/Irciniastatin A" *J. Am. Chem. Soc.* **2005**, *127*, 11254-11255.

53. Piel, J.; Burtzke, D.; Fusetani, N.; Hui, D.; Platzer, M.; Wen, G.; Matsunaga, S. "Exploring the Chemistry of Uncultivated Bacterial Symbionts: Antitumor Polyketides of the Pederin Family" *J. Nat. Prod.* **2005**, *68*, 472-479.

54. Burres, N. S. and Clement, J. J. "Antitumor Activity and Mechanism of Action of the Novel Marine Natural Products Mycalamides A and B and Onnamide" *Cancer Res*. **1989**, *49*, 2935-2940.

55. Galvin, F.; Freeman, G. J.; Razi-Wolf, Z.; Benacerraf, B.; Naler, L.; Reiser, H.; "Effects of Cyclosporine, F506, and Mycalamide A on the Activation of Murine $CD4^+$ T Cells by the Murine B7 Antigen" *Eur. J. Immunol.* **1993**, *23*, 283.

56. Ogawara, H.; Higashi, K.; Uchino, K.; Perry, N. B. "Change of *ras*-Transformed NRK-Cells Back to Normal Morphology by Mycalamides A and B, Antitumor Agents from a Marine Sponge" *Chem. Pharm. Bull*. **1991**, *39*, 2152-2154.

57. Han, Z.; Wei, W.; Dunaway, S.; Darnowski, J. W.; Calabresi, P.; Sedivy, J.; Hendrickson, E. A.; Balan, K. V.; Pantazis, P.; Wyche, J. "Role of p21 in Apoptosis and Senescence of Human Colon Cancer Cells Treated with Camptothecin" *J. Biol. Chem.* **2002**, *277*, 17154-17160.

58. Nishimura, S.; Matsunaga, S.; Yoshida, M.; Hirota, H.; Yokoyama, S.; Fusetani, N. "13-Deoxytedanolide, a Marine Sponge-Derived Antitimor Macrolide, Binds to the 60S Ribosomal Subunit" *Bioorganic and Medicinal Chem.* **2005**, *13*, 449-454.

59. Thompson, A. M.; Blunt, J. W.; Munro M. H. G.; Perry, N. B.; Pannell, L. K.; "Chemistry of the Mycalamides, Antiviral and Antitumor Compounds from a Marine Sponge. Part 3. Acyl, Alkyl and Silyl Derivatives" *J. Chem. Soc., Perkin Trans. 1* **1992**, 1335-1342.

60. Thompson, A. M.; Blunt, J. W.; Murray, H. G.; Munro, H. G.; Clark, B. M. "Chemistry of the Mycalamides. Part 4. Reactions of Mycalamide A and Alkyl Derivatives with Basic Nucleophiles" *J. Chem. Soc., Perkin Trans. 1* **1994**, 1025-1031.

61. Thompson, A. M.; Blunt, J. W.; Munro M. H. G.; Perry, N. B. "Chemistry of the Mycalamides, Antiviral and Antitumor Compounds from a Marine Sponge. Part 5. Acid-Catalyzed Hydrolysis and Acetal Exchange, Double Bond Additions and Oxidation Reactions" *J. Chem. Soc., Perkin Trans. 1* **1995**, 1233-1241.

62. Abell, A. D.; Blunt, J. W.; Founds, G. J.; Munro, M. H. G. "Chemistry of the Mycalamides, Antiviral and Antitumor Compounds from a Marine Sponge. Part 6. The Synthesis and Testing of Analogues of the C(7)-C(10) Fragment" *J. Chem. Soc., Perkin Trans. 1* **1997**, 1647-1654.

63. Dinkerton, L. V.; Adair, N. K.; Euske, J. M.; Brady, K. T.; Robinson, P. D. "Regioselective Synthesis of Substituted 1-Thiohex-2-enopyransoides" *J. Org. Chem.* **1988**, *53*, 845-850.

64. Halcomb, R. L.; Danishefsky, S. J. "On the Direct Epoxidation of Glycals: Application of a Reiterative Strategy for the Synthesis of β-Linked Oligosaccharides" *J. Am. Chem. Soc.* **1989**, *111*, 6661-6666.

65. Adam, W.; Bialas, J.; Hadjiarapoglou, L. "A Convenient Preparation of Acetone Solutions of Dimethyldioxirane" *Chem. Be*r. **1991**, *12*4, 2377.

66. Gilbert, M.; Ferrer, G.; Sanchez-Baeza, F.; Messeguer, A. "Easy Availability Of More Concentrated and Versatile Dimethyldioxirane Solutions" *Tetrahedron Lett.* **1996**, *37*, 3585-3586.

67. Gilbert, M.; Ferrer, G.; Sanchez-Baeza, F.; Messeguer, A. "Availability and Reactivity of Concentrated Dimethyldioxirane Solutions in Solvents other than Acetone" *Tetrahedron* **1997**, *53*, 8643-8650.

68. Rainier, J. D.; Cox, J. M. "Aluminium- and Boron-Mediated C-Glycoside Synthesis from 1,2-Anhydroglycosides" *Org. Lett.* **2000**, *2*, 2707-2709.

69. Ellman, J. A.; Owens, T. D.; Tang, T. P. "*N-tert*-Butanesulfinyl Imines: Versatile Intermediates for the Asymmetric Synthesis of Amines" *Acc. Chem. Res.* **2002**, *35*, 984-995.

70. Evans, J. W.; Ellman, J. A. "Stereoselective Synthesis of 1,2-Disubstituted *β*-Amino Alcohols by Nucleophilic Addition to *N-tert*-Butanesulfinyl α-Alkoxyaldimines" *J. Org. Chem.* **2003**, *68*, 9948-9957.

71. Bedford, C. D.; Harris, R. N.; Howd R. A.; Goff, D. A.; Koolpe G. A.; Petesch, M.; Koplovitz, I.; Sultan, W. E.; Musallam, H. A. "Quaternary Salt of 2-[(Hydroxyimino)methyl]imidazole. 3. Synthesis and Evaluation of (Alkenyloxy)-, (Alkynyloxy)-, and (Aralkyloxy)methyl Quaternarized 2-[(Hydroxyimino)methyl]-1-

Alkylimidalolium Halides as Reactivators and Therapy for Soman Intoxication" *J. Med. Chem.* **1989**, *32*, 504-516.

72. De Armas, P.; Concepcion, J. I.; Francisco, C. G.; Hernandez, R.; Salazar, J. A.; Suarez, E. "Intramolecular Hydrogen Abstraction. Hypervalent Organoiodine Compounds, Convenient Reagents for Alkoxy Radical Generation" *J. Chem. Soc. Perkin. Trans. I* **1998**, 405-411.
73. Philips, R. S.; Heiss, C. H. "Asymmetric Reduction of Ethynyl Ketones and Ethynylketoesters by Secondary Alcohol Dehydrogenase from *Thermoanaerobacter ethanolicus*" *J. Chem. Soc., Perkin Trans. 1* **2000**, 2821-2825.
74. Bromidge, S. M.; Entwistle, D. A.; Goldstein, J.; Orlek, B. S. "A Convenient Synthesis of Masked β-Ketoaldehydes by the Controlled Addition of Nucleophiles to (Trimethylsilyl)ethynyl Ketones" *Synth. Commun.* **1993**, *23*, 487-494.
75. Danishefsky, S. D.; Larson, E.; Askin D.; Kato, N. "On The Scope, Mechanism, and Stereochemistry of the Lewis Acid Catalyzed Cyclocondensation of Activated Dienes with Aldehydes: An Application to the Erythronolide Problem" *J. Am. Chem. Soc.* **1985**, *107*, 1246-1255.
76. Luche, J. L. "Lanthanoids in Organic Synthesis. 1. Selective 1,2-Reductions of Conjugated Ketones" *J. Am. Chem. Soc.* **1978**, *100*, 2226-2227.
77. Golender, L.; Senderowitz, H.; Fuches, B. "Relative Stabilities and Conformational Ring Inversion Potentials in Heterocyclic Decalin Systems and Stereoelectronic Implications" *J. Mol. Struct. (Theochem)* **1996**, *370*, 221-236.
78. Inukai, T.; Yoshizawa, R. "Preparation of *β*-Ketoaldehydes by Acylation of Aldehyde Enamines" *J. Org. Chem.* **1967**, *32*, 404-407.

79. Kinnaird, J. W. A.; Ng, P. Y., Kubota, K.; Wang, X; Leighton, J. A. "Strained Silacycles in Organic Synthesis: A New Reagent for the Enantioselective Allylation of Aldehydes" *J. Am. Chem. Soc.* **2002**, *124*, 7920-7921.

80. Lou, S.; Westbrook, J. A.; Schaus, S. E. "Decarboxylative Aldol Reactions of Allyl β-Keto Esters via Heterobimetallic Catalysis" *J. Am. Chem. Soc.* **2004**, *126*, 11440-11441.

81. Blanchette, M. A.; Malamas, M. S.; Nantz, M. H.; Roberts, J. C.; Somfai, P.; Whritenour, D. C.; Masamune, S. "Synthesis of Bryostatins. 1. Construction of the C(1)-C(16) Fragment" *J. Org. Chem.* **1989**, *54*, 2817-2825.

82. Paterson, I.; Gibson, K. R.; Oballa, R. M. "Remote, 1,5-*Anti* Stereoinduction in the Boron-Mediated Aldol Reactions of β-Oxygenated Methyl Ketones" *Tetrahedron Lett.* **1996**, *37*, 8585-8588.

83. Evans, D. A.; Cote, B.; Coleman, P. J.; Connell, B. "1,5-Asymmetric Induction in Boron-Mediated β-Alkoxy Methyl Ketone Aldol Addition Reactions" *J. Am. Chem. Soc.* **2003**, *125*, 10893-1089.

84. Chen, K.; Hardmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. "1,3-*Syn* Diastereoselective Reduction of β-Hydroxyketones Utilizing Alkoxydialkylboranes" *Tetrahedron Lett.* **1987**, *28*, 155-158.

85. Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. "Configurational Assignment of Polyene Mactolide Antibiotics Using the [C^{13}]Acetonide Analysis" *Acc. Chem. Res.* **1998**, *31*, 9-17.

86. Ferrier, R. J. "Unsaturatured Carbohydrates. Part 21. A Carbocyclic Ring Closure of a Hex-5-enopyranoside Derivative" *J. Chem. Soc. Perkin Trans. 1* **1979**, 1455.

87. Rech, J. C.; Floreancig, P. E. “An Oxidative Entry into the Amido Trioxadecalin Ring System” *Org. Lett.* **2003**, *5*, 1495-1498.

88. Aubele, D. L.; Rech, J. C.; Floreancig, P. E. “Catalytic Aerobic Generation of Acyliminium Ions through Electron-Transfer-Mediated Carbon-Carbon Bond Activation” *Adv. Synth. Catal.* **2004**, *346*, 359-366.

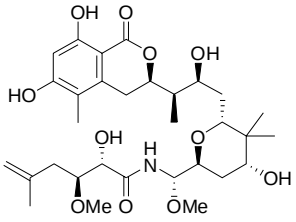
89. Ma, B.; Lii, J.; Allinger, N. L. “Molecular Polarizabilities and Induced Dipole Moments in Molecular Mechanics” *J. Comput. Chem.* **2000**, *21*, 825.

90. Still, W. C.; Tempczyk, A.; Hendrickson, T. J. “Semianalytical Treatment of Solvation of Molecular Mechanics and Dynamics” *J. Am. Chem. Soc.* **1990**, *112*, 6127-6129.

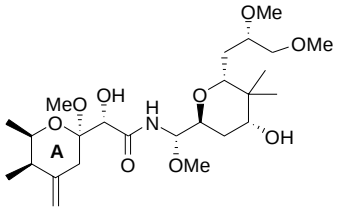
3. Synthesis of the N_7-C_{25} Fragment of Psymberin

3.1 Introduction

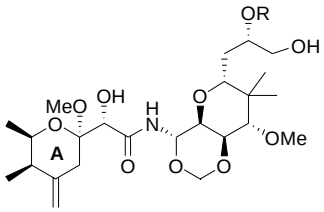
The natural product psymberin[1]/irciniastatin A[2] was isolated independently from two marine sponges of the same family (Ircinidae family). The geminal dimethyl tetrahydropyran and the *N*-acylaminal functionalities suggest that psymberin/irciniastatin A is related to the pederin family of natural products, though psymberin/irciniastatin A would be the first member of this family that does not contain the highly conserved pederic acid tetrahydropyran ring system (**A**, Figure 36).



Psymberin/Irciniastatin A



Pederin



Mycalamide A: R = H
Mycalamide B: R = Me

Figure 36: Psymberin/Irciniastatin A and Related Compounds

I. Isolation and Structural Determination

In 2004 Pettit and coworkers[2] reported the isolation of irciniastatin A from the marine sponge *Ircinia ramose* native to the Indo-Pacific region. Irciniastatin A was isolated from the methanol-CH_2Cl_2 extract of *Ircinia ramose* sponge by gel permeation and reverse phase HPLC. The extraction and purification of 1 kilogram (wet) of sponge resulted in the isolation of 34.7 mg of irciniastatin A.

The structure of irciniastatin A was assigned through the use of mass spectrometry and NMR spectroscopy (Figure 37). The high-resolution FAB mass spectrum showed a pseudomolecular ion peak at *m/z* 610.3228 [M + H] indicating a molecular formula of $C_{31}H_{48}NO_{11}$.[2] The use of 2D-COSY, TOCSY and HMBC experiments provided the necessary information to establish the connectivity of the natural product. Interpretation of the HMBC spectrum was particularly useful allowing for the identification of the amide linkage from a correlation of the amide proton (N-H) to the C_6 carbonyl carbon (Figure 37). Additionally, correlations from the C_{29} proton to the carbons of the aromatic ring (C_{18}-C_{21} and C_{23}) were integral for determining the connectivity of the dihydroisocourmarin. The nOe enhancements, shown in Figure 37, led to the assignment of the relative stereochemistry of the *N*-acylaminal and the geminal dimethyl tetrahydropyran subunits reported by Pettit.[2] While Pettit and coworkers were able to establish the carbon skeleton of the irciniastatin A, their reported structure was largely devoid of stereochemical information.

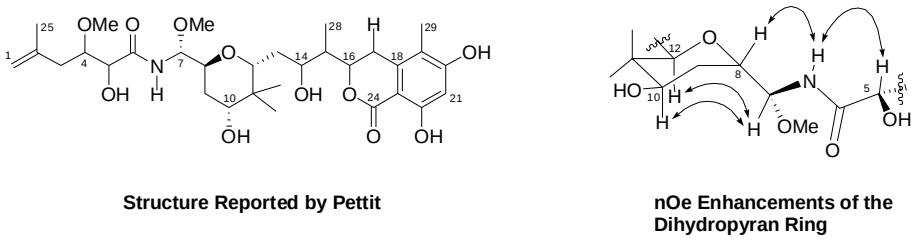


Figure 37: Irciniastatin A Reported by Pettit

Crews and coworkers[1] reported the isolation of psymberin in 2004 (shortly following the report from Pettit and coworkers[2]) from the marine sponge *Psammocinia* collected from the waters of Papau, New Guinea (Figure 38, the numbering schemes of Pettie and Crews differ slightly, the Crews scheme will be used for the remainder). The structural determination of psymberin was accomplished by Crews and coworkers by employing techniques and analyses similar to those used by Pettit and coworkers in their structural determination of irciniastatin A.[2] Crews assigned the relative and absolute stereochemistry for most of the chiral centers in psymberin by analyzing ^{1}H NMR coupling constants, nOeSy and COSY correlation data and by comparing the chemical shifts and coupling constants of the ^{1}H NMR of psymberin to the spectral data reported for pederin.[1] The C_{16} stereocenter was assigned based on the circular dichroism spectrum that displayed a positive Cotton effect at 280 nm generated by the chiral dihydroisocourmarin. Crews and coworkers were unable to assign the configuration of the freely rotating C4 center.[1]

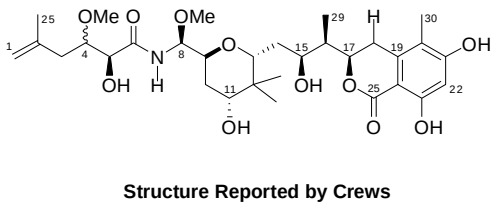


Figure 38: Psymberin Reported by Crews

The structures of irciniastatin A and psymberin proposed by Petit and Crews, respectively, share an identical carbon skeleton and relative stereochemistry of the dihydropyran ring but differ in their assignment of the relative stereochemistry of the *N*-acylaminal center.[1,2] The similarities in the structures reported by Petit and Crews led to the speculation that irciniastatin A and psymberin were identical compounds.[1] A direct comparison of the NMR spectrum of irciniastatin A and psymberin was not possible because the NMR spectrum were recorded in $CDCl_3$ and CD_3OD, respectively.[1,2]

The incomplete stereochemical assignment of the C_1-C_6 side chain has resulted in two studies that have defined the relative and absolute stereochemistry of the C_4 position. Kiren and Williams[4] employed the use of a ^1H and ^{13}C NMR chemical shift homology analysis to postulate that the stereocenters of the C_4 and C_5 positions of psymberin have an *anti*-relationship. This analysis was performed by comparing the ^1H and ^{13}C NMR spectrum of the *syn* and *anti* model compounds (Figure 39), generated in 11 steps from D-glyceraldehyde acetonide, to the spectral data reported by Crews.[1] The coupling constants and chemical shifts for the *anti*-model compound were consistent with the reported values for the natural product.[4] While significant deviation from the reported values was observed in the chemical shifts of the ^1H and ^{13}C NMR spectrum of the *syn*-model compound, with the largest differences occurring for data corresponding to the C3-C5 positions.

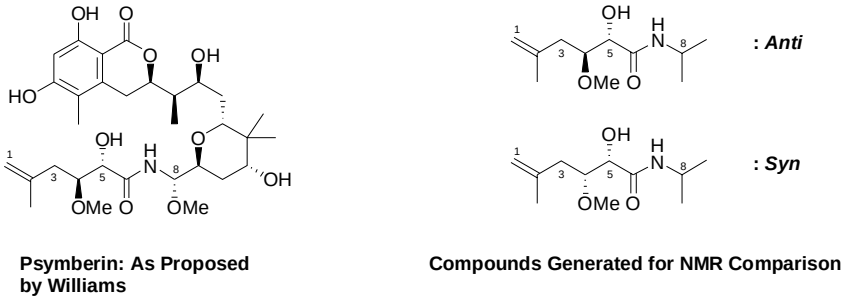


Figure 39: Structure of Psymberin Proposed by Williams

The absolute and relative stereochemistry of the C4 and C5 positions of psymberin were confirmed by Floreancig and coworkers[5] through the examination of the acidic methanolysis products of psymberin. To conduct this study the four possible stereoisomers of the methyl ester derivatives of the psymberic acid fragment (C_1-C_6 side chain of psymberin) were generated from D- and L-serine in 8 steps (the 4*S*,5*S* derivative is shown in Figure 40). Each methyl ester was individually subjected to acidic methanolysis conditions (H_2SO_4, MeOH, 40 °C, 24 h) resulting in the cationic cyclization to generate the corresponding furan. The furans were analyzed by gas chromatography employing a chiral stationary phase and compared to the products resulting from the acidic methanolysis of psymberin. The furan resulting from the methanolysis of psymberin was consistent in mass and retention time with the *anti*-4*S*,5*S* furan generated from the corresponding methyl ester (Figure 40). The 4*S*,5*S* configuration of psymberin determined through the acidic methanolysis study is consistent with the configuration predicted by the chemical shift homology study of Kiren and Williams.[4]

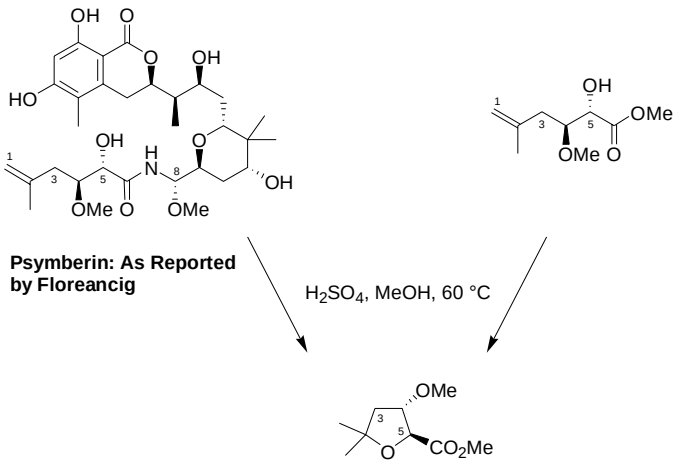


Figure 40: Structure of Psymberin Proposed by Floreancig

II. Biological Activity

The biological activity of psymberin makes it an unusual member of the pederin family of natural products. Unlike the other members of the pederin family that exhibit equipotent cytotoxicity over a broad spectrum of cancer cell models, psymberin has displayed selective cytotoxicity for a number of cancer cell lines (Table 1). Psymberin has shown a $>10^4$ fold activity difference for select melanoma, breast and colon cancer cell lines.[2] The differential cytotoxicity observed for psymberin, as compared to the pederin family of natural products, has led to speculation that the dihydroisocourmarin and/or the vinylic methyl terminus may be responsible for the selective activity.[2]

cell line	LC_{50} (M)	cell line	LC_{50} (M)
melanoma		breast cancer	
LOX IMVI	$>2.5 \times 10^{-5}$	MCF7	$>2.5 \times 10^{-5}$
MALME-3M	**$>2.5 \times 10^{-9}$**	HS 578T	$>2.5 \times 10^{-5}$
SK-MEL-2	$>2.5 \times 10^{-5}$	**MDA-MB-435**	**$>2.5 \times 10^{-9}$**
SK-MEL-5	**$>2.5 \times 10^{-9}$**	NCI/ADR-RES	1.9×10^{-5}
SK-MEL-28	1.41×10^{-5}	T-47D	1.4×10^{-5}
UACC-257	$>2.5 \times 10^{-5}$		
UACC-62	**$>2.5 \times 10^{-9}$**	colon cancer	
		HCC-2998	3.8×10^{-7}
		HCT-116	**$>2.5 \times 10^{-9}$**
		HT29	$>2.5 \times 10^{-5}$
		SW-620	$>2.5 \times 10^{-5}$

Table 1: Activity of Psymberin against Various Cancer Cell Lines

III. The First Total Synthesis of Psymberin

Recently, De Brabander and coworkers[3] reported the first total synthesis of psymberin/irciniastatin A wherein they demonstrated the compounds isolated by Pettit[1] and Crews[2] were identical. For the remainder of this chapter this natural product will be referred to as psymberin. The approach taken by De Brabander was highly convergent and divided psymberin into three fragments (Figure 41). The synthesis of fragment **1** will not be discussed as it is not directly related to the research described herein.

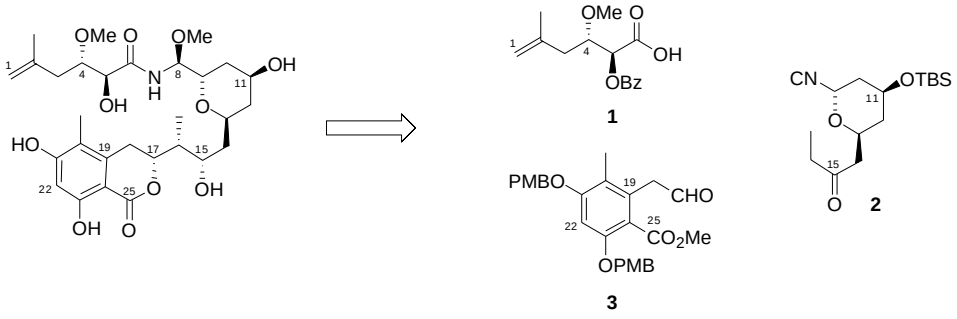
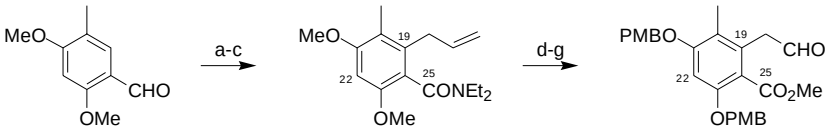


Figure 41: De Brabander's Retrosynthetic Analysis

De Brabander and coworkers[3] generated fragment **3** (Figure 41) from a 7 step sequence with a 43% overall yield starting from the previously reported aldehyde **4**, generated in one step from 2,4-dimethoxytoluene (Scheme 18). The allyl group of **5** was installed in good yield from the oxidation and amidation of aldehyde **4** followed by *ortho*-metallation and subsequent allylation. A four step sequence that included methyl ether deprotection, methyl ester formation, phenol protection and oxidative olefin cleavage completed the synthesis of fragment **3** from amide **5**.

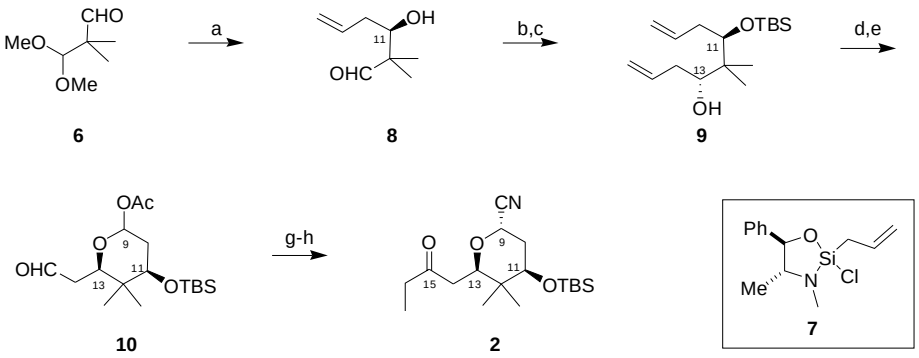


4 **5** **3**

Reagents: (a) NaH_2PO_4, $NaClO_2$, 2-methyl-2-butene, *t*-BuOH/H_2O; (b) $SOCl_2$, benzene; Et_2NH; (c) *sec*-BuLi, CuBr•SMe_2, allylBr, THF, -78 °C, 69% over 3 steps; (d) BBr_3, CH_2Cl_2, -78 °C to 25 °C; (e) Me_3OBF_4, CH_2Cl_2; Na_2CO_3, MeOH; (f) PMBCl, Bu_4NI, K_2CO_3, DMF, -15 °C; (g) cat. OsO_4, NMO, THF/H_2O; $NaIO_4$, aq MeOH, 77% over 4 steps.

Scheme 18: De Brabander's Psymberin Synthesis: Fragment 3

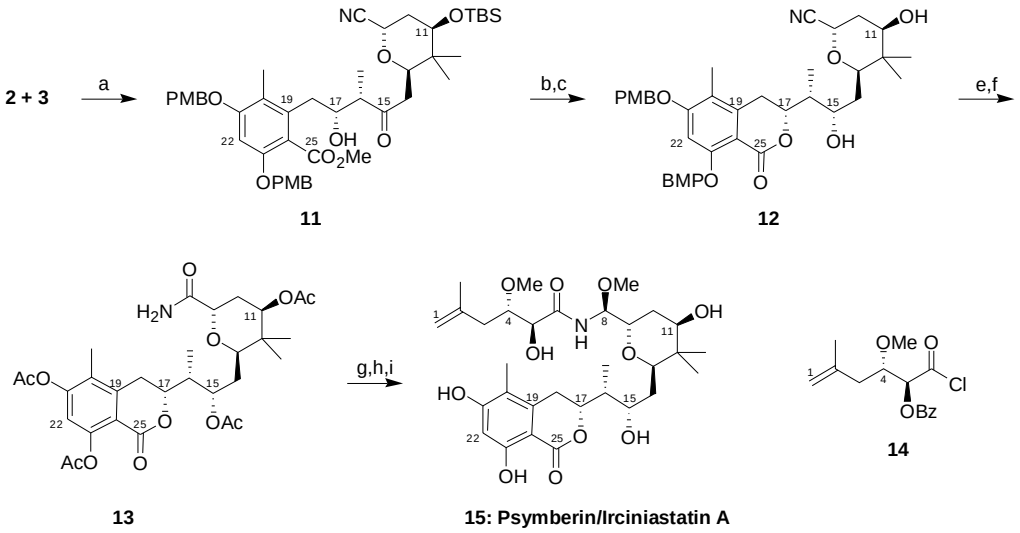
The C_{11} and C_{13} stereocenters of fragment **2** (Figure 41) were established with good enatantio- and diastereoselectivity, respectively, through a sequence of asymmetric Leighton allylations beginning with monoprotected aldehyde **6** (Scheme 19).[3] Monosilylation of the resulting diol generated **9** in good yield. Oxidative olefin cleavage of **9** and subsequent acylation of the resulting lactol generated acyl lactol **10**. The configuration of the C9 center was established by the diastereoselective Lewis acid catalyzed acetate displacement of the acyl lactol by TMSCN, as part of a 3 step sequence to complete the synthesis of fragment **2**.



Reagents: (a) **7**, toluene, -15 °C, 69%, 94% ee; (b) **7**, toluene, -15 °C; dr 17:1 (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 77% over 2 steps; (d) O_3, CH_2Cl_2, then PPh_2; (e) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C, 81% over 2 steps; (f) *N,N'*-(1R,2R-cyclohexane-1,2-diyl)bis(trifluoromethanesulfonamide), Ti(O*i*Pr)$_4$, Et_2Zn, PhMe, -15 °C; (g) TMSCN, ZnI_2, MeCN, 0 °C; aq 1 N HCl; (h) Dess-Martin periodinane, CH_2Cl_2, 70% over 3 steps.

Scheme 19: De Brabander's Psymberin Synthesis: Fragment 2

Fragments **2** and **3** were joined by a boron-mediated aldol addition resulting in aldol adduct **11**, where the resulting C_{16} and C_{17} stereocenters were effectively controlled by the β-alkoxy substituent of the boron enolate (Scheme 20).[3] The C_{15} stereocenter was generated by a 1,3-*syn* reduction of aldol adduct **11** followed by silyl ether cleavage generating **12** in excellent yield. The hydration of the nitrile was accomplished by employing the Ghaffar and Parkin catalyst. Subsequent protecting group manipulation of the resulting amide provided **13** in good yield. Coupling of the imidate generated from **13** with the acid chloride derivative of fragment **1** (**14**, also generated by Da Brabander and coworkers) and subsequent borohydride reduction generated the *N*-acylaminal at the C_8 center with modest selectivity in favor of the natural configuration. Removal of the acetate protecting groups generated **15**, which was determined to be identical to psymberin and irciniastatin A by a comparison of spectral and optical rotation data.[3] Note, this synthesis does not resolve the issue of the C_8 *N*-acylaminal stereochemistry.



Reagents: (a) $PhBCl_2$, DIPEA, CH_2Cl_2, -78 °C, 88%, 12:1 dr; (b) catecholborane, THF, 0 °C; aq 2 N NaOH; (c) TBAF, THF, 95% over 2 steps; (d) cat. $[PtH(PMe_2OH)(PMe_2O)_2H]$, $EtOH/H_2O$, 80 °C; (e) 10% Pd/C, H_2, EtOH; (f) Ac_2O, pyridine, 89% over 3 steps; (g) Me_3OBF_4, polyvinylpyridine, CH_2Cl_2, filter; (h) **14**, DIPEA, PhMe, 40 °C; then add $NaBH_4$, EtOH, 0 °C, 79:21 dr; (i) LiOH, MeOH; 56% over 4 steps

Scheme 20: De Brabander's Psymberin Synthesis: Completion

IV. Retrosynthesis

We have initiated synthetic studies directed toward the generation of psymberin as part of our interest in the pederin family of natural products. The following is an account of our synthesis of the N_7-C_{25} fragment of psymberin. The majority of this chapter has been published as a communication.[19]

The retrosynthesis of psymberin outlined in Figure 42 focuses on the generation of the N_7-C_{25} fragment of this natural product, which was the focus of our research effort. The cleavage of the C-N bond of the *N*-acylaminal generated amide **16** and a psymberic acid derivative (not shown). This disconnection was employed by De Brabander and coworkers and was developed for use in the synthesis of pederin and related natural products. A 2 step sequence that included the selective cyanide displacement and subsequent nitrile hydrolysis was

expected to generate amide **16** from acyl lactol **17**. The acyl lactol **17** was expected to arise from the oxidative olefin cleavage of **18** followed by acylation of the resulting lactol. Disconnection of the C_{15}-C_{14} bond generates ketone **19** and aldehyde **20**. The joining of these fragments is expected to occur through a selective aldol addition establishing the C_{15} stereocenter that will be subsequently used to control the C_{12} stereocenter during a 1,3-*syn*-reduction. The stereocenter in ketone **19** can be generated from an asymmetric allyation (as described in Chapter 2) and the stereochemistry of aldehyde **20** can be generated from the asymmetric crotylation of an aldehyde derived from arene **21**. Arene **21** can be generated from allene **22** and diene **23**.

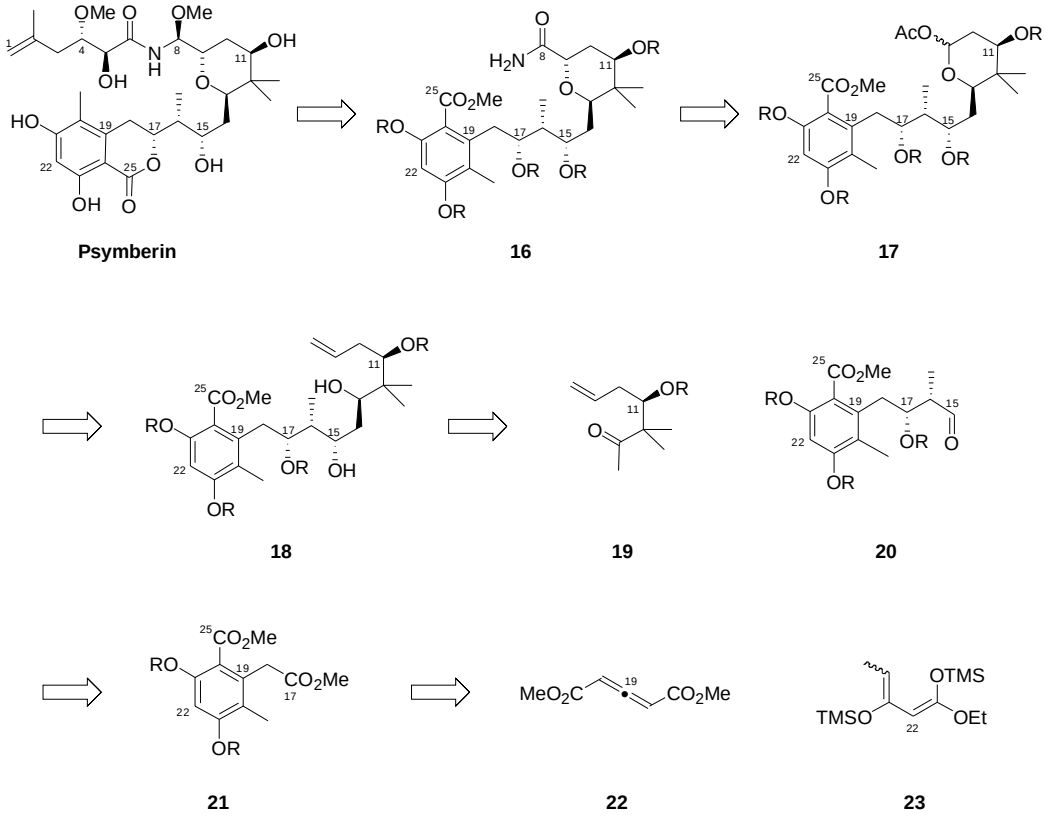
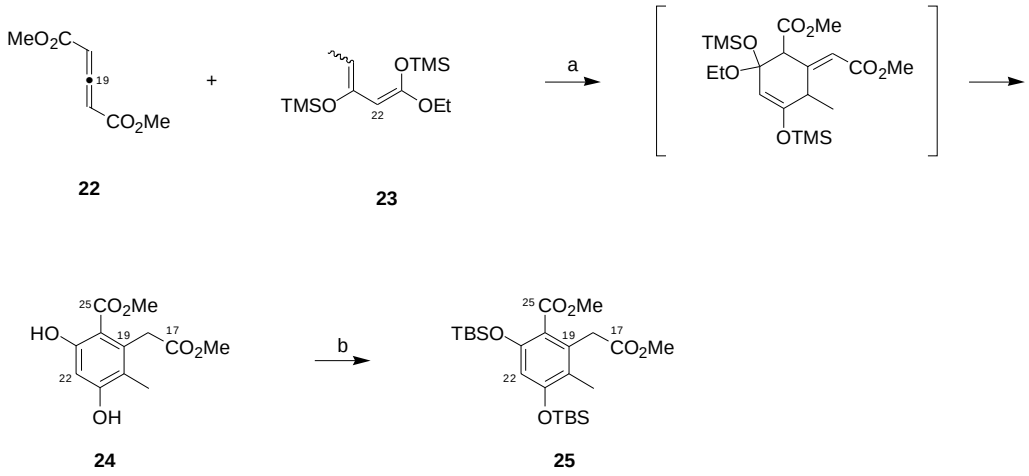


Figure 42: Retrosynthetic Scheme for Psymberin

3.2 Results and Discussion

The synthesis of the N_7-C_{25} fragment of psymberin commenced with the generation of arene **24** (Scheme 21). The cycloaddition[6] of allene **22**,[7] available in one step from commercially available 1,3-acetonedicarboxylate, with silylketene acetal **23**[8] followed by fluoride mediated aromatization generated arene **24** in a 70% yield. The cycloaddition proceeded at ambient temperature in the absence of solvent and can be used to generate multigram quantities of arene **24**. Protection of the phenolic functional groups under standard conditions (TBSOTf, 2,6-lutidine) provided *bis*-silyl ether **25** in nearly quantitative yield.



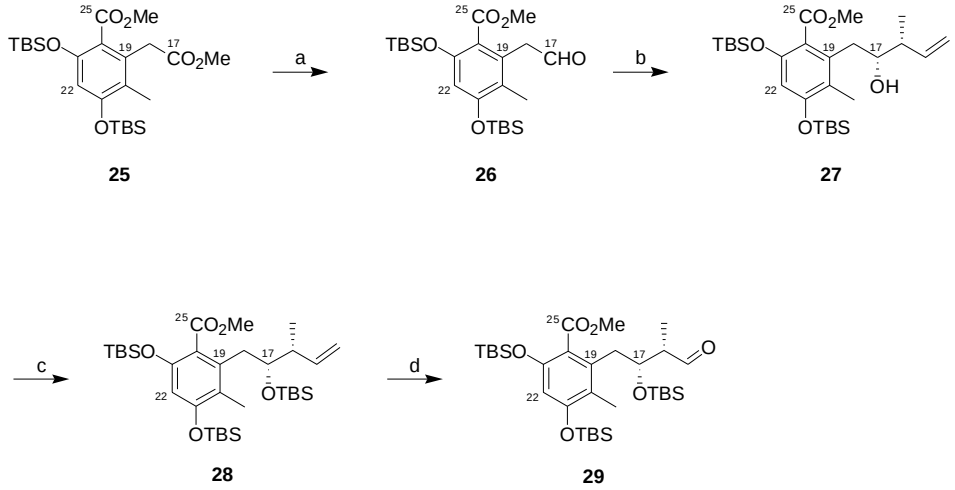
22 **23** **24** **25**

Reagents: (a) **22** + **23** neat, rt, 6 hours; then Et_3N•HF, EtOH, 70%; (b) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C to rt, 99%.

Scheme 21: Synthesis of the Psymberin Arene

The aliphatic methyl ester of arene **25** was selectively reduced with a single equivalent of di-*iso*-butylaluminum hydride (DIBAL), generating aldehyde **26** in sufficient purity to eliminate the need for purification (Scheme 22). The C_{16} and C_{17} stereocenters were established through a

Brown crotylation reaction[9] that generated **27** as a single diastereomer in a 65% yield over 2 steps with a 90% ee determined by HPLC analysis (Chiralcel OD-H column). Silyl ether protection of the resulting alcohol proceeded in nearly quantitative yield generating **28** upon treatment of **27** with TBSOTf in the presence of 2,6-lutidine. Oxidative olefin cleavage of **28** under standard ozonolysis conditions proceeded smoothly to generate aldehyde **29** in a 93% yield. Aldehyde **29** constitutes the aldehyde partner for a subsequent Mukaiyama aldol reaction.

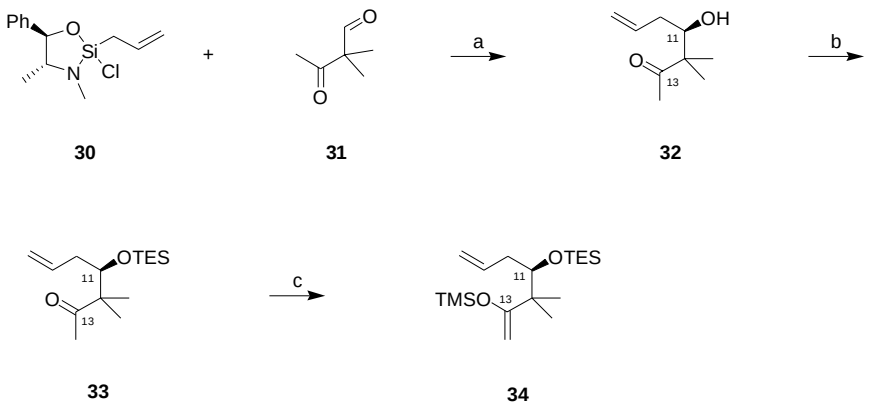


Reagents: (a) DIBAL, CH_2Cl_2, -78 °C; (b) (Z)-(-)-$Ipc_2BCH_2CH{=}CHCH_3$, THF, -78 °C, 65% yield over 2 steps, 90% ee; (c) TBSOTf, 2,6-lutidine, CH_2Cl_2, 0 °C, 99%; (d) O_3, CH_2Cl_2, -78 °C, then PPh_3, 93%.

Scheme 22: Generation of C_{14}-C_{25} Fragment of Pysmberin

The silyl enol ether Mukaiyama aldol partner (**34**, Scheme 23) was generated in 3 steps from ketoaldehyde **31**.[10] The stereoselective Leighton[11] allylation of ketoaldehyde **31**[10] generated β-hydroxyketone **32** in 90% yield and 94% ee determined by GC analysis (Chiraldex G-TA column) (Scheme 23). Treatment of β-hydroxyketone **32** with triethylsilyl chloride (TESCl) in the presence of imidizole resulted in the formation of silyl ether **33** in quantitative

yield. Treatment of **33** with TMSOTf in the presence of Et_3N generated silyl enol ether **34** with sufficient purity that it was used without purification in the subsequent Mukaiyama aldol.



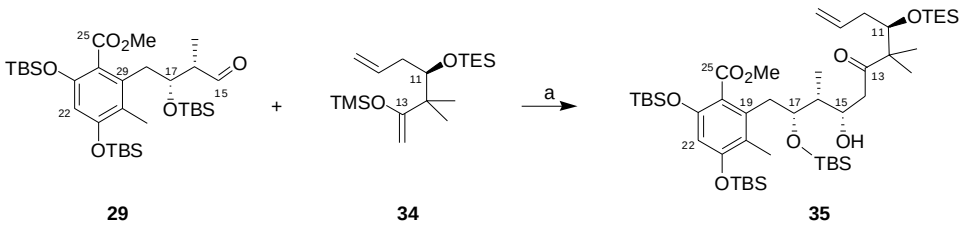
Reagent: (a) toluene, -15 °C, 90%, 94% ee; (b) TESCl, imidazole, DMF, 100%; (c) TMSOTf, Et_3N, Et_2O, 100%.

Scheme 23: Synthesis of the C_7-C_{13} Fragment of Psymberin

The Mukaiyama aldol addition[12] of silyl enol ether **34** into aldehyde **29** proceeded in 95% yield generating the C_{15} stereocenter as a 6:1 mixture of inseparable diastereomers (Figure 43). The generation of the *syn*,*syn*-stereotriad, observed in aldol adduct **35**, is the result of the Felkin-Ahn[13] addition of the silyl enol ether **34** into aldehyde **29**. The *syn,syn*-stereochemical relationship resulting from the Mukaiyama aldol addition was tentatively assigned by analyzing the chemical shifts and coupling constants in the ^1H NMR spectrum of aldol adduct **35**. The ^1H NMR patterns generated by aldol adduct **35** were consistent with the patterns reported by Roush[16] for *syn*,*syn*-aldol adducts. This assignment was further verified in subsequent intermediates.

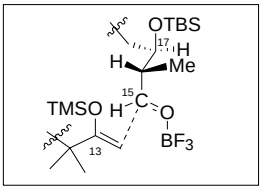
The 1,2-asymmertic induction generated from the α-position (C_{16}) of aldehyde **29** conflicts with the 1,3-asymmertic induction generated from the β-position (C_{17}).[15] The generation of the *syn,syn*-stereotriad is expected to occur from the Felkin-Ahn approach of the

nucleophile, whereby the α-substituent controls the stereochemistry generated from the addition.[13] The generation of the *anti,syn*-stereotriad would be expected arise if the approach of the nucleophile was controlled by the β-siloxy substituent (1,3-asymmertic induction).[14] Evans and coworkers have demonstrated that in similar systems α-control overrides β-control when sterically encumbered nucleophiles are employed. In these cases the steric interactions that generally dictate 1,2-asymmertic induction have a more pronounced influence than the electrostatic effects that are invoked to explain the asymmetric induction generated by the β-alkoxy stereocenter.[15] Based on this reasoning the transition state for the Mukaiyama aldol is shown in Figure 43.



29 **34** **35**

Reagents: (a) **29** + **34**, BF_3•OEt_2, CH_2Cl_2, -78 °C, 95%, dr = 6:1.

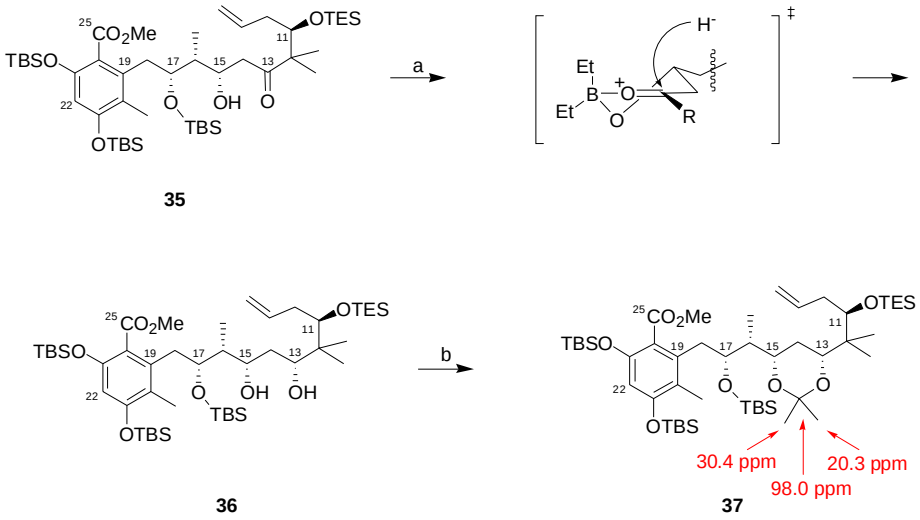


Transition State for the Mukaiyama Aldol

Figure 43: Mukaiyama Aldol to Generate the C_{15} Stereocenter of Psymberin

The reduction of aldol adduct **35** under chelation-control conditions with Et_2BOMe as the chelating agent generated the *syn*-diol **36** with excellent selectivity (Scheme 24).[17] The inseparable mixture of aldol diastereomers was now separable as the diol intermediate. The

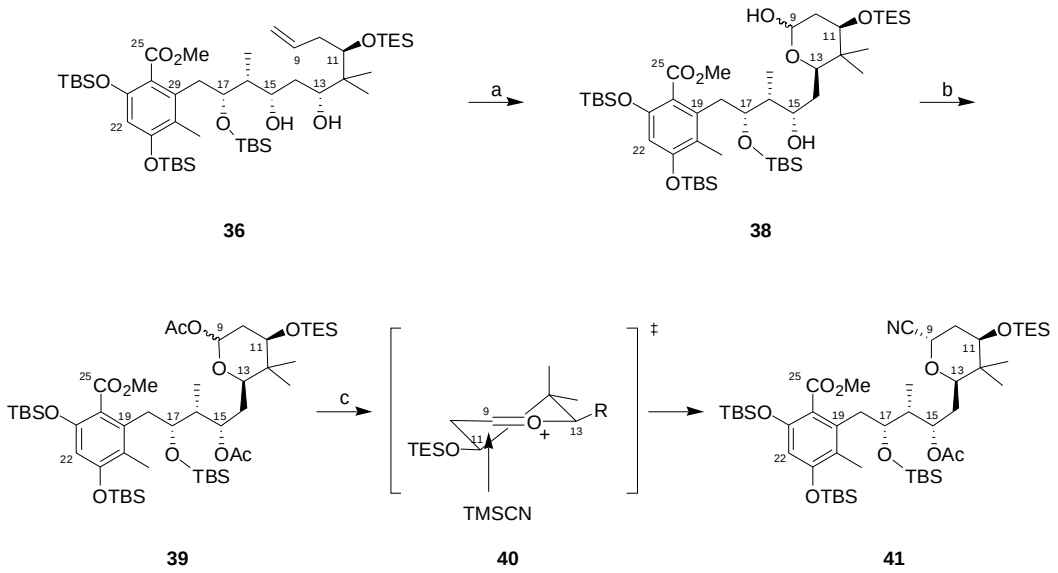
acetonide of **36** was generated and the *syn*-diol relationship was confirmed through ^{13}C NMR acetonide analysis. The observed ^{13}C NMR chemical shifts of acetonide **37** were consistent with values reported by Rychnovsky[18] and coworkers for related *syn*-acetonides.



Reagents: (a) Et_2BOMe, $NaBH_4$, MeOH, THF, -78 °C, 74%; (b) *p*-TsOH, dimethoxypropane, 98%.

Scheme 24: *Syn*-Reduction of Psymberin Aldol Adduct

The generation of the requisite geminal dimethyl tetrahydropyran commenced with the oxidative olefin cleavage of diol **36** generating lactol **38** in a 76% yield (Scheme 25). The unstable lactol was directly subjected to acetic anhydride in the presence of DMAP resulting in acylation at both the C_9 and C_{15} centers in a 76% yield. Treating acyl lactol **39** with $BF_3{\cdot}OEt_2$ resulted in the formation of an oxocarbenium ion that was selectively trapped with TMSCN to generate nitrile **41** in a 98% yield as a single diastereomer. The selectivity observed in the nitrile formation arises from the axial addition of TMSCN into oxocarbenium ion **40**.



Reagent: (a) O_3, CH_2Cl_2, then PPh_3, 76%; (b) Ac_2O, pyr, DMAP, CH_2Cl_2, 76%; (c) TMSCN, BF_3•OEt_2, CH_2Cl_2, -78 °C, 97%.

Scheme 25: Tetrahydropyran Formation

Hydration of nitrile **41** under the commonly employed basic peroxide conditions resulted in partial nitrile hydration accompanied by varying degrees of silyl ether cleavage. To avoid silyl group loss in the nitrile hydration the platinum catalyst **42**, reported by Ghaffar and Parkin,[19] was employed (Figure 44). Heating nitrile **41** to 80 °C in ethanol and water in the presence of **42** resulted in the generation of amide **43** in 96% yield with no detectable silyl group loss. Catalyst **42** facilitates nitrile hydration by coordinating to the *N*-terminus of the nitrile allowing for the intermolecular addition of dimethylphosphine oxide ligand generating an imidate intermediate. Subsequent water addition into the imidate followed and collapse of the tetrahedral intermediate generates the amide and regenerates catalyst **42**. The generation of amide **43** completes our synthesis of the N_7-C_{25} fragment of psymberin.

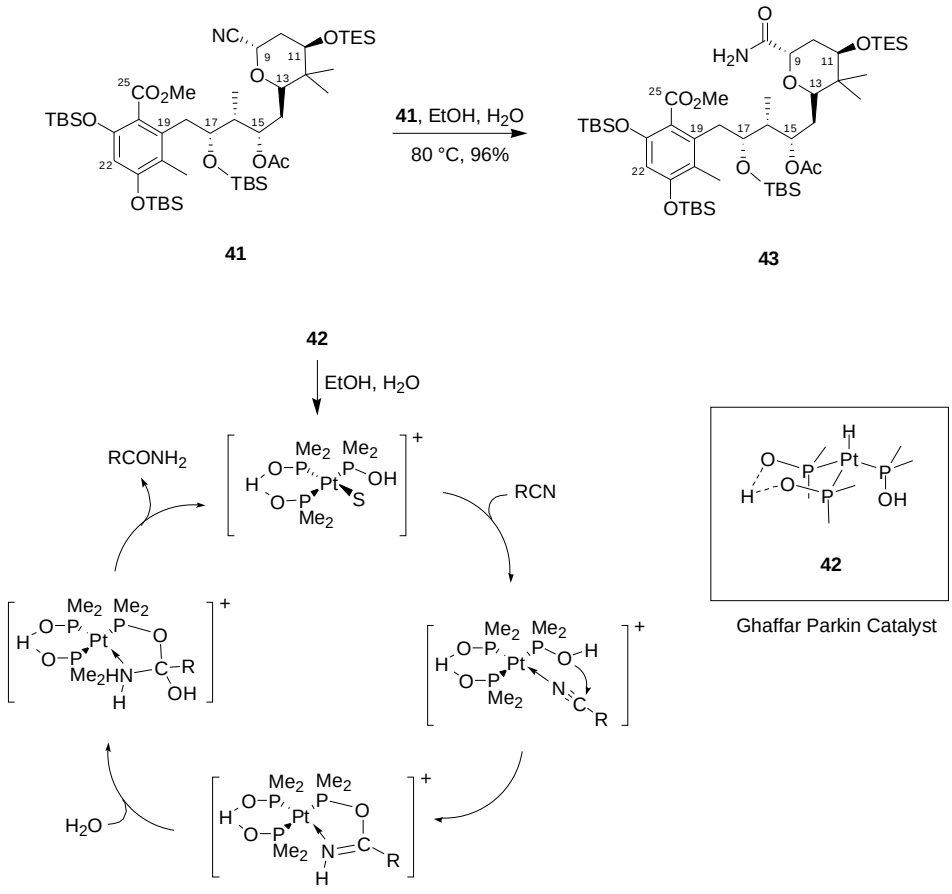


Figure 44: Nitrile Hydration and Completion of the N_7-C_{25} Fragment of Psymberin

During the optimization of the workup conditions for the TMSCN displacement of the acyl lactol **39** (Scheme 25) varying amounts of partially deprotected nitrile were isolated (**44**, Figure 45). To explore our deprotection strategy and the generation of the dihydroisocourmarin, nitrile **44** was subjected to tetrabutylammonium fluoride (TBAF) in THF resulting in cleavage of the silyl ethers and closure of the dihydroisocoumarin ring. The removal of the acetate group was accomplished by treatment with basic methanol generating dihydroisocourmarin **44**. The ^{1}H NMR of dihydroisocourmarin **44** was recorded in CD_3OD and matched remarkably well with the C_{10}-C_{25} fragment of psymberin. The chemical shifts and coupling constants observed from the ^{1}H NMR of dihydroisocoumarin **45** are shown in red and the reported values for the

corresponding protons in psymberin are shown in blue (Figure 45). The strong correlation in the ^{1}H NMR of **45** and psymberin provided convincing evidence that the structure reported by Crews and coworkers is accurate.

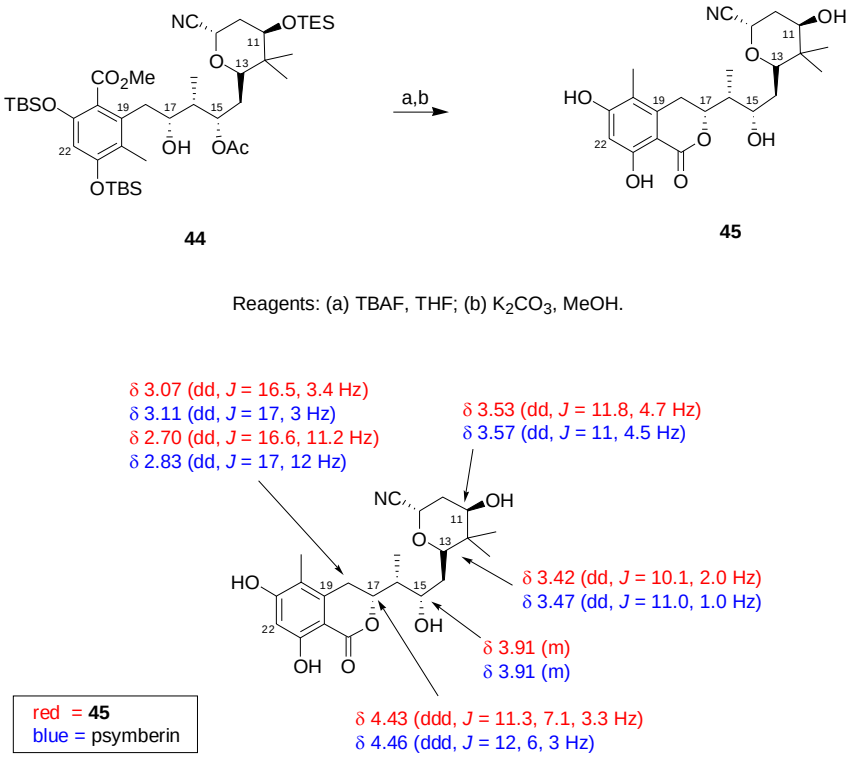


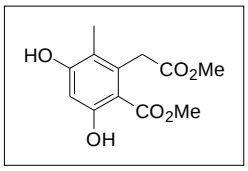
Figure 45: Chemical Shift and Coupling Constant Analysis of the Synthetic Fragment

3.3 Conclusions

We have developed an efficient and stereoselective synthesis of the N_7-C_{25} fragment of psymberin. The synthesis is highlighted by the de novo generation of the C_{25}-C_{17} pentasubstituted arene that allows for the expedient generation of multigram quantities of this intermediate. The C_{16} and C_{17} stereocenters were generated with good yield and selectivity by a Brown crotylation and the C_{11} stereocenter was generated with excellent yield and selectivity from an asymmetric Leighton allylation. The C_9, C_{13}, and C_{15} stereocenters were established by a selective Lewis acid mediated lactol displacement, *syn*-reduction and Mukaiyama aldol reaction, respectively, where the stereochemistry resulting from these transformations was controlled by the substrate. The flexibility of this synthesis allows for easy access to derivatives that can be use to explore the origins of the selective cytotoxicity of psymberin.

3.4 Experimentals

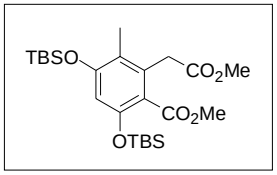
General Procedures: Optical rotations were measured on a Perkin-Elmer 241 digital polarimeter with a sodium lamp at ambient temperature as follows: $[\alpha]_\lambda$ (*c*, g/100mL). Infrared spectra were recorded on a Nicoler Avatar 360 FT-IR spectrometer. NMR spectra were recorded on a Bruker Avance-300, 500, or 600 spectrometer with chemical shifts reported relative to residual $CHCl_3$ (7.27 ppm) for ^1H and $CDCl_3$ (77.0 ppm) for ^{13}C spectra. Unless otherwise stated, all reactions were performed in dry glassware under a nitrogen atmosphere using standard inert atmosphere techniques for the manipulation of solvents and reagents. Anhydrous methylene chloride (CH_2Cl_2) was obtained by distillation over calcium hydride and THF and diethyl ether were obtained by passage through an alumina packed column on a solvent purification system. Flash chromatography was performed on EM silica gel 60 (230-240 mish).



4,6-Dihydroxy-2-methoxycarbonylmethyl-3-methyl benzoic acid methyl ester, 24:[6] To neat dimethyl allenedicarboxylate[7] **22** (12.0 g, 76.9 mmol) at 0 °C was added 1-methoxy-1,3-bis(trimethylsilyloxy)-1,3-pentadiene[4] **23** (92.3 mmol, 26.6 g) and the reaction mixture was warmed to rt and stirred for 6 hours. The reaction mixture was cooled to 0 °C and treated with $NEt_3 \cdot HF$ (1 M in ethanol, 120 mL)(see below for preparation of this reagent). The resulting solution was stirred at rt for 15 minutes, diluted with H_2O (200 mL) and extracted with EtOAc (6 x 50 mL). The organic layers were combined, washed with brine (50 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The desired product appeared as a white precipitate and was isolated by filtration. Product remaining in the crude oil was purified by flash column chromatography

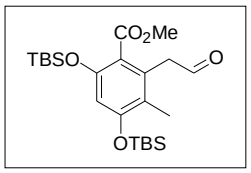
(20% EtOAc in hexane). The solids were combined providing the desired product as a white powder (13.1 g, 70%): ^{1}H NMR (d_6-DMSO, 300 MHz) δ 10.06 (s, 1H), 9.98 (s, 1H), 6.37 (s, 1H), 3.72 (s, 3H), 3.69 (s, 2H), 3.59 (s, 3H), 1.95 (s, 3H); ^{13}C NMR (d_6-DMSO, 75 MHz) δ 170.9, 169.3, 158.8, 156.8, 134.2, 116.1, 109.7, 101.4, 51.6, 51.5, 36.1, 11.1; IR (dry film) 3303, 1701, 1647, 1596, 1328, 1225 cm^{-1}; HRMS(EI) *m/z* calcd for $C_{12}H_{14}O_6$ (M^+) 254.0790, found 254.0799; m.p. 188-189 °C.

Preparation of 1.0 M Et_3N•HF in ethanol: To a solution of commercially available Et_3N•3HF (12.3 g, 76.3 mmol) in absolute ethanol (42.8 mL) at rt was added freshly distilled Et_3N (152.6 mmol, 15.4 g) and the resulting solution was stored in a Nalgene® polyethylene bottle at rt.

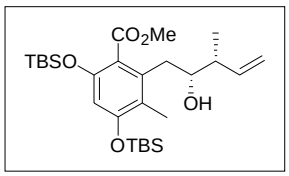


4,6-Bis-*tert*-butyldimethylsilanyloxy-2-methoxycarbonylmethyl-3-methyl benzoic acid methyl ester (25): To a solution of **24** (3.20 g, 13.3 mmol) in CH_2Cl_2 (50 mL) at 0 °C was added 2,6-lutidine (5.71 g, 53.3 mmol) followed by the dropwise addition *tert*-butyldimethylsilyl trifluoromethanesulfonate (TBSOTf) (7.75 g, 29.3 mmol). The reaction mixture was warmed to rt and stirred for 6 hours. H_2O (50 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2 x 25 mL). The organic layers were combined, washed with 10% aq. HCl (20 mL) and brine (50 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (10% EtOAc in hexanes) to provide the desired product (6.40 g, 99%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.28 (s, 1H), 3.83 (s, 3H), 3.67 (s, 3H), 3.66 (s, 2H), 2.09 (s, 3H), 1.01 (s, 9H), 0.96 (s, 9H), 0.22 (s, 6H), 0.20 (s, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 171.0, 168.8, 155.3, 151.2, 132.7, 121.7, 120.2, 109.0, 51.9, 51.8, 36.2, 25.7, 25.5, 18.3, 18.0, 12.2, -4.2, -4.4;

(IR neat) 2953, 2859, 1737, 1594, 1472, 1435, 1419, 1261, 1163, 863, 840, 781 cm^{-1}; HRMS(ES) *m/z* calcd for $C_{24}H_{42}O_6NaSi_2$ (M + Na) 505.2418, found 505.2395.

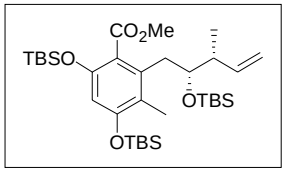


4,6-Bis-*tert*-butyldimethylsilanyloxy-3-methyl-2,2-oxoethyl benzoic acid methyl ester (26): To a solution of **25** (6.10 g, 12.6 mmol) in CH_2Cl_2 (80 mL) at -78 °C was added DIBAL (in hexanes)(12.7 mL, 12.7 mmol) and the reaction mixture was stirred at -78 °C for 2 hours. EtOAc (5 mL) was added and the reaction mixture was poured into saturated aqueous sodium potassium tartrate (100 mL) at 0 °C. The resulting reaction mixture was warmed to rt, stirred for 4 hours, and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was used without purification.



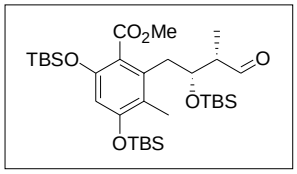
4,6-Bis-*tert*-butyldimethylsilanyloxy-2-2-hydroxy-3-methylpent-4-enyl-3-methyl benzoic acid methyl ester, 27: To a suspension of predried KO*t*Bu (1.70 g, 15.1 mmol) in THF (5 mL) at -78 °C was added *cis*-2-butene (1.70 g, 30.2 mmol). At -78 °C 1.6 M *n*-butyl lithium in hexane (9.45 mL, 15.1 mmol) was added slowly over a period of 15 minutes. The resulting yellow reaction mixture was warmed to -45 °C for 10 minutes then cooled to -78 °C and (-)-methoxydiisopinocamphenyl borane (5.58 g, 17.6 mmol) in ether (17 mL) was added dropwise. The reaction mixture was stirred for 30 minutes at -78 °C. Freshly distilled BF_3•OEt_2 (2.86 g, 20.2 mmol) was added to the reaction mixture at -78 °C followed by the dropwise addition of **26** (12.7 mmol, crude) in THF (5 mL). The reaction mixture was stirred at -78 °C for 2.5 hours and saturated aqueous

NH_4Cl (5 mL) was added. The reaction mixture was poured into 20 mL of pH 7 buffer at 0 °C, 30% hydrogen peroxide (5 mL) was added and the reaction mixture was warmed to rt and stirred for 10 hours. The reaction mixture was extracted with EtOAc (3 x 15 mL). The organic layers were combined, washed with saturated aqueous $NaSO_3$ (10 mL) and brine (2 x 10 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography (2% EtOAc in hexane) to provide the desired product as a single diastereomer by NMR (5.03 g, 65%, 90% ee). Enantioselectivity was determined by HPLC using a Diacel Chiralcel^{TM} OD-H column with 1% isopropanol in hexane as the mobile phase and a flow rate of 1ml/min at 700 psi. The retentions times were T_r (min.) 3.43 (S,S) and 3.68 (R,R)): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.24 (s, 1H), 5.89 (ddd, *J* = 17.7, 10.4, 7.7 Hz, 1H), 5.12 (d, *J* = 17.3 Hz, 1H), 5.08 (d, *J* = 11.1 Hz, 1H), 3.86 (s, 3H), 3.63-3.58 (m, 1H), 3.24 (d, *J* = 6.1 Hz, 1H), 2.94 (dd, *J* = 14.3, 2.6 Hz, 1H), 2.46 (dd, *J* = 14.3, 10.8 Hz, 1H), 2.36-2.30 (m, 1H), 2.09 (s, 3H), 1.13 (d, *J* = 6.8, 3H), 1.01 (s, 9H), 0.96 (s, 9H), 0.23 (s, 3H), 0.22 (s, 3H), 0.21 (s, 3H), 0.18 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 170.8, 155.5, 151.0, 140.9, 137.6, 120.8, 120.2, 114.8, 108.0, 74.2, 52.2, 45.1, 35.8, 25.6, 25.5, 18.2, 17.9, 15.4, 12.2, -4.3, -4.3, -4.4, -4.5; (IR neat) 3465, 2956, 2930, 2888, 2859, 1729, 1701, 1590, 1471, 1258 cm^{-1}; HRMS(ES) *m/z* calcd for $C_{27}H_{48}O_5Si_2$ (M^+) 508.3038, found 508.3040; $[\alpha]^{20}_D$ +36.3° (*c* 1.50, $CHCl_3$).



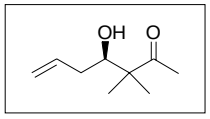
4,6-Bis-*tert*-butyldimethylsilanyloxy-2-2-*tert*-butyldimethylsilanyloxy- 3-methylpent-4-enyl-3-methyl benzoic acid methyl ester 28: To a solution of **27** (4.57 g, 8.98 mmol) in CH_2Cl_2 (60 mL) at 0 °C was added 2,6-lutidine (1.92 g, 18.0 mmol) followed by the dropwise addition of TBSOTf (2.61 g, 9.88 mmol) and the reaction mixture was stirred at 0 °C for 15 minutes. H_2O

(20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with 10% HCl (10 mL) and brine (2 x 10 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (5% EtOAc in hexane) to provide the desired product (5.51 g, 99%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 6.19 (s, 1H), 6.05 (ddd, *J* = 16.9, 10.6, 5.9 Hz, 1H), 5.09 (dd, *J* = 10.6, 1.2 Hz, 1H), 5.04 (dd, *J* = 17.5, 1.2 Hz, 1H), 3.87 (ddd, *J* = 10.2, 3.5, 3.5 Hz, 1H), 3.82 (s, 3H), 2.73 (dd, *J* = 14.0, 10.4 Hz, 1H), 2.59 (dd, *J* = 14.0, 3.3 Hz, 1H), 2.34-2.41 (m, 1H), 2.12 (s, 3H), 1.03 (d, *J* = 6.8 Hz, 3H), 1.01 (s, 9H), 0.97 (s, 9H), 0.79 (s, 9H), 0.21 (s, 6H), 0.20 (s, 3H), 0.19 (s, 3H), -0.02 (s, 3H), -0.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 169.5, 154.8, 150.6, 140.1, 137.8, 122.4, 120.7, 114.3, 107.6, 76.7, 51.6, 43.5, 32.9, 26.0, 25.7, 25.6, 18.3, 18.1, 18.0, 14.6, 12.8, -4.1, -4.2, -4.4, -5.2; IR (neat) 2956, 2930, 2858, 1729, 1590, 1417, 1256, 1162 cm^{-1}; HRMS (ES) *m/z* calcd for $C_{33}H_{62}O_5NaSi_3$ (M + Na) 645.3803, found 645.3828; $[\alpha]^{20}_D$ +52.0° (*c* 1.00, $CHCl_3$).



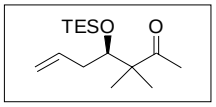
4,6-Bis-*tert*-butyldimethylsilanyloxy-2-2-*tert*-butyldimethylsilanyloxy-3-methyl-4-oxobutyl-3-methyl benzoic acid methyl ester, 29: Ozone was gently bubbled through a solution of **28** (0.9 g, 1.5 mmol) in CH_2Cl_2 (15 mL) at -78 °C until the reaction mixture sustained a deep blue color. Triphenylphosphine (1.2 g, 4.5 mmol) was added, the cold bath was removed and the reaction mixture was stirred at rt for 2 hours. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (2% EtOAc → 10% EtOAc in hexanes) to provide the desired product (0.83 g, 93%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.86 (s, 1 H), 6.23 (s, 1 H), 4.37 (ddd, *J* = 9.1, 5.0, 3.7 Hz, 1H), 3.84 (s, 3H), 2.84 (dd, *J* = 14.0, 9.1 Hz, 1H), 2.74

(dd, J = 5.0 Hz, 1H), 2.40-2.51 (qd, J = 7.0, 3.4 1H), 2.14 (s, 3H), 1.09 (d, J = 7.0 Hz, 3H), 1.02 (s, 9H), 0.97 (s, 9H), 0.81 (s, 9H), 0.22 (s, 6H), 0.20 (s, 3H), 0.19 (s, 3H), -0.05 (s, 3H), -0.34 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 204.8, 169.3, 155.1, 150.8, 136.2, 122.0, 120.4, 108.0, 72.9, 52.1, 51.8, 34.8, 25.8, 25.6, 25.5, 18.2, 18.0, 17.8, 12.7, 8.5, -4.3, -4.5, -5.1, -5.3; IR (neat) 2954, 2858, 1727, 1591, 1163, 863 cm^{-1}; HRMS(ES) *m/z* calcd for $C_{32}H_{60}O_6NaSi_3$ (M + Na) 647.3595, found 647.3566; $[\alpha]^{20}_D$ +51.0° (*c* 1.24, $CHCl_3$).

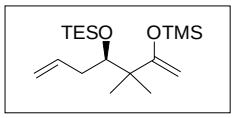


4-Hydroxy-3,3-dimethylhept-6-en-2-one, 32: To a solution of **30**[10] (24.0 g, 89.6 mmol) in toluene (450 mL) at -15 °C was added **31**[11] (8.20 g, 72.0 mmol) dropwise and the reaction mixture was stirred at -15 °C for 24 hours. 10% aqueous HCl (200 mL) was added at -15 °C and the reaction mixture was warmed to rt and stirred for 10 minutes. The organic layer was collected and the aqueous layer was extracted with toluene (3 X 10 mL). The organic layers were combined, washed with 10% aqueous HCl (20 mL) and brine (20 mL), dried with Na_2SO_4, filtered and applied directly to a silica gel flash column packed in pentane. The toluene was eluted from the column with pentane and the product was eluted with 20% ether in pentane to provide the desired product (10.1 g, 90%, 94% ee) The enantioselectivity was determined by GC with a chiral stationary phase. The chira CG column emplyed was a Chiraldex^{TM} G-TA column (Advanced Separation Technologies, Inc.) using a flow rate 0.5 mL/min, method: 100 °C for 20 minutes, T_r (min.) (R) 21.361, (S) 23.013): ^{1}H NMR ($CDCl_3$, 300 MHz): δ 5.94-5.80 (m, 1H), 5.18-5.11 (m, 2H), 3.77 (ddd, J = 10.3, 4.2, 2.4 Hz, 1H), 2.36 (d, J = 10.3 Hz, 1H), 2.32-2.23 (m, 1H), 2.19 (s, 3H), 2.09-1.96 (m, 1H), 1.17 (s, 3H), 1.14 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 214.5, 135.8, 117.9, 75.3, 51.6, 36.4, 26.3, 21.7, 19.4: IR

(neat) 3462, 3076, 2977, 1701, 1641, 1469, 1356, 1129, 1070, 915 cm^{-1}; HRMS(EI) *m/z* calcd for $C_9H_{17}O_2$ (M + H) 157.122855, found 157.122995; $[\alpha]^{20}_D$ +12.0° (*c* 1.10, $CHCl_3$).

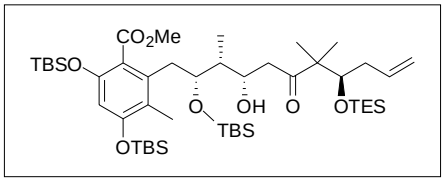


4-Triethylsilanyloxy-3,3-dimethylhept-6-en-2-one (33): To a solution of **32** (2.00, 12.8 mmol) in DMF (2 mL) at rt was added imidazole (2.60, 38.4 mmol). The reaction mixture was stirred for 30 minutes at rt and cooled to 0 °C. Chlorotriethylsilane (2.74, 19.2 mmol) was added at 0 °C and the reaction mixture was warmed to rt and stirred for 8 hours. H_2O (10 mL) was added and the reaction mixture was extracted with hexanes (5 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (5% EtOAc in hexanes) to provide the desired product (3.47, 100%): ^{1}H NMR ($CDCl_3$, 500 MHz) δ 5.86-5.78 (dddd, *J* = 17.2, 10.1, 7.1, 7.1 Hz, 1H), 5.10-5.05 (m, 2H), 3.98 (dd, *J* = 7.2, 4.3 Hz, 1H), 2.24-2.20 (m, 1H), 2.18 (s, 3H), 2.17-2.13 (m, 1H), 1.15 (s, 3H), 1.13 (s, 3H), 0.99 (t, *J* = 8.0 Hz, 9H), 0.64 (q, *J* = 8.0, 6H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 213.3, 136.0, 116.8, 77.0, 53.0, 38.7, 27.0, 21.7, 20.4, 6.9, 5.3; IR (neat) 2956, 2877, 1704, 1467, 1094, 739 cm^{-1}; HRMS(EI) *m/z* calcd for $C_{13}H_{25}O_2Si$ (M - C_2H_5) 241.1624, found 241.1622; $[\alpha]^{20}_D$ +9.14° (*c* 1.17, $CHCl_3$).



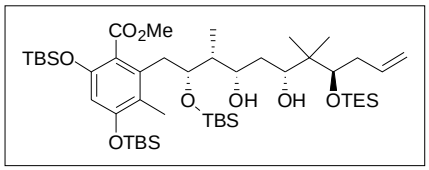
4-Triethylsilanyloxy-3,3-dimethyl-2-trimethylsilanyloxyhepta-1,6-diene (34): To a solution of **33** (0.20 g, 0.8 mmol) in diethyl ether (4 mL) at 0 °C was added triethylamine (0.24 g, 2.4 mmol) followed by the drop-wise addition of trimethylsilyl triflate (TMSOTf) (0.26 g, 1.2 mmol). The reaction mixture was warmed to rt and stirred for 4 hours. The reaction mixture was diluted with pentane (10 mL) and washed with saturated

aqueous $NaHCO_3$ (2 x 10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure to provide the desired product (0.27 g, 100%). The product was used without further purification: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.91-5.77 (m, 1H), 5.04-4.97 (m, 2H), 4.11 (d, *J* = 1.4 Hz, 1H), 3.96 (d, *J* = 1.4 Hz, 1H), 3.85 (dd, *J* = 8.4, 2.7 Hz, 1H), 2.29-2.22 (m, 1H), 2.07-1.97 (m, 1H), 1.05 (s, 3H), 0.96 (s, 3H), 0.95 (t, *J* = 7.9 Hz, 9H), 0.60 (q, *J* = 7.9 Hz, 6H), 0.21 (s, 9H); ^{13}C NMR ($CHCl_3$, 125 MHz) δ 164.8, 137.7, 115.6, 87.5, 76.5, 45.3, 38.0, 24.4, 19.1, 7.0, 5.5, -0.1.



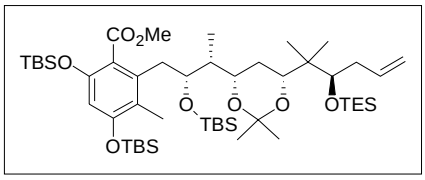
4,6-Bis-*tert*-butyldimethylsilanyloxy-2,2-*tert*-butyldimethylsilanyloxy-4-hydroxy-3-methyl-6-oxo-8-triethylsilanyloxyundec-10-enyl-3-methyl benzoic acid methyl ester (35): To a solution of **29** (0.650 g, 1.04 mmol) in CH_2Cl_2 (10 mL) was added **34** (0.544 g, 1.56 mmol). The reaction mixture was cooled to -78 °C and freshly distilled BF_3•OEt_2 (0.174 g, 1.25 mmol) was added dropwise. The reaction mixture was stirred at -78 °C for 10 hours. Saturated aqueous NH_4Cl (5 mL) was added and the reaction was warmed to rt and extracted with CH_2Cl_2 (2 x 10 mL). The organic layers were combined, washed with brine (2 x 10 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (3% EtOAc in hexane) to provide the desired product (0.88, 95%, ~6:1 dr by NMR): ^{1}H NMR ($CDCl_3$, 600 MHz) δ 6.20 (s, 1H), 5.79-5.74 (m, 1H), 5.08-5.02 (m, 2H), 4.33-4.27 (m, 1H), 4.02 (dd, *J* = 7.2, 4.5 Hz, 0.85H), 3.99 (dd, *J* = 7.2, 4.5 Hz, 0.15H), 3.94 (ddd, *J* = 10.2, 3.3, 3.3 Hz, 1H), 3.82 (s, 3H), 3.27 (d, *J* = 2.6 Hz, 0.85H), 3.24 (d, *J* = 2.6 Hz, 0.15H), 2.93 (dd, *J* = 14.2, 10.4 Hz, 1H), 2.85 (dd, *J* = 17.7, 1.2 Hz, 0.15 H), 2.79 (dd, *J* = 18.3, 1.8 Hz, 0.86H), 2.73 (dd, *J* = 14.2, 3.4 Hz, 1H), 2.66 (dd, *J* = 18.3, 10.1 Hz,

0.85H), 2.57 (dd, *J* = 18.3, 10.1 Hz, 0.15H), 2.19-2.00 (m, 2H), 2.15 (s, 3H), 1.60-1.55 (m, 1H), 1.13 (s, 3H), 1.11 (s, 3H), 1.02 (s, 9H), 1.01 (d, *J* = 7.0 Hz, 3H), 0.96 (s, 9H), 0.97 (t, *J* = 7.9 Hz, 9H) 0.80 (s, 9H), 0.61 (q, *J* = 7.9 Hz, 6H), 0.22 (s, 6H), 0.20 (s, 3H), 0.19 (s, 3H), -0.13 (s, 3H), -0.44 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 217.4, 169.5, 154.8, 150.6, 137.7, 135.9, 122.3, 120.5, 117.0, 107.6, 77.0, 74.0, 67.1, 53.3, 51.8, 44.7, 44.4, 38.9, 33.0, 26.0, 25.7, 25.5, 22.3, 19.6, 18.2, 18.0, 17.9, 12.9, 11.2, 7.0, 5.4, -4.1, -4.2, -4.2, -4.4, -5.1,-5.3; IR (neat) 3540, 2955, 2858, 1729, 1590, 1434, 1191 cm^{-1}; HRMS(ES) *m/z* calcd for $C_{47}H_{90}O_8NaSi_4$ (M + Na) 917.5611, found 917.5706; $[\alpha]^{20}_D$ +12.87° (*c* 1.27, $CHCl_3$).



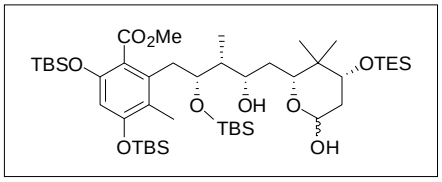
4,6-Bis-*tert*-butyldimethylsilanyloxy-2,2-*tert*-butyldimethylsilanyloxy-4,6-dihydroxy-3,7,7-trimethyl-8-triethylsilanyloxyundec-10-enyl-3-methyl benzoic acid methyl ester (36): To a solution of **35** (0.83 g, 0.93 mmol) in THF (10 mL) and methanol (1 mL) at -78 °C was added diethylmethoxyborane (0.10 g, 1.01 mmol) and the reaction mixture was stirred at -78 °C for 1 hour. Sodium borohydride (0.11, 2.78 mmol) was added and the reaction mixture was stirred for 8 hours at -78 °C. The temperature was slowly increased to -35 °C over a period of 5 hours. The reaction mixture was poured into ice cooled pH 7 buffer (50 mL) and diluted with EtOAc (25 mL). At 0 °C hydrogen peroxide (30%, 10 mL) was added and the reaction mixture was warmed to rt and stirred for 12 hours. The reaction mixture was extracted with EtOAc (3 x 20 mL) and the organic layers were combined, washed with saturated aqueous $NaSO_3$ (2 x 10 mL) and brine (20 mL), dried with Na_2SO_4, filtered, and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (4% EtOAc in hexane) to provide the desired product (0.62 g, 74%). At this point the it was possible to

separate the undesired aldol adduct: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.19 (s, 1H), 5.94-8.80 (m, 1H), 5.14-5.06 (m, 2H), 4.80 (bs, 1H), 4.09 (bs, 1H), 4.08-4.03 (m, 2H), 3.91 (ddd, *J* = 10.0, 3.4 Hz, 1H), 3.82 (s, 3H), 3.61 (dd, *J* = 7.2, 3.7 Hz, 1H), 2.93 (dd, *J* = 14.0, 10.2 Hz, 1H), 2.73 (dd, *J* = 14.0, 6.3 Hz, 1H), 2.55-2.40 (m, 1H), 2.38-2.28 (m, 1H), 2.15 (s, 3H), 1.66-1.48 (m, 3H), 1.01 (s, 9H), 0.96 (s, 9H), 1.02-0.94 (m, 18H), 0.80 (s, 9H), 0.67 (q, *J* = 8.0 Hz, 6H), 0.22 (s, 3H), 0.21 (s, 3H), 0.20 (s, 3H), 0.19 (s, 3H), -0.11 (s, 3H), -0.46 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.5, 154.8, 150.6, 138.1, 136.3, 122.4, 120.7, 117.0, 107.5, 83.7, 77.8, 76.7, 72.5, 51.8, 45.7, 40.9, 37.5, 36.8, 33.3, 29.7, 26.0, 25.7, 25.6, 23.1, 20.6, 18.3, 18.1, 17.9, 12.9, 11.2, 6.9, 5.5, 5.3, -4.1, -4.2, -4.4, -5.1, -5.2; IR (thin film) 3390, 2955, 2858, 1728, 1590, 1191 cm^{-1}; HRMS(ES) *m/z* calcd for $C_{47}H_{92}O_8NaSi_4$ (M + Na) 919.5767, found 919.5847; $[\alpha]^{25}_D$ +27.17° (*c* 0.72, $CHCl_3$).

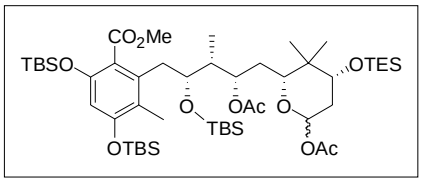


4,6-Bis-(*tert*-butyldimethylsilanyloxy)-2-[2-(*tert*-butyldimethylsilanyloxy)-4,6-dihydroxy-3,7,7-trimethyl-8-triethylsilanyloxyundec-10-enyl]-3-methyl benzoic acid methyl ester (37): To a solution of **17** (50 mg, 0.06 mmol) in 2,2-dimethoxypropane (2 mL) at rt was added catalytic amounts of *para*-toluenesulfonic acid and the reaction mixture was stirred for 2 hours. Triethylamine (0.1 mL) was added followed by H_2O (2 mL). The reaction mixture was extracted with EtOAc (2 x 5 mL). The organic layers were combined, washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (2% EtOAc in hexane) to provide the desired product (49 mg, 98%): ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.18 (s, 1H), 5.92-5.83 (m, 1H), 5.06-4.98 (m, 2H), 4.15-4.09 (m, 1H), 3.94-3.87 (m, 1H), 3.85-3.77 (m, 1H), 3.81 (s, 3H), 3.47 (dd, *J* = 9.6, 3.8 Hz, 1H),

2.93-2.89 (m, 1H), 2.68-2.63 (m, 1H), 2.33-2.29 (m, 1H), 2.15-2.11 (m, 1H), 2.13 (s, 3H), 1.57-1.45 (m, 1H), 1.33-1.25 (m, 2H), 1.27-0.82 (m, 24H), 1.01 (s, 9H), 0.96 (s, 9H), 0.80 (s, 9H), 0.61 (q, J = 7.9 Hz, 6H), 0.22 (s, 3H), 0.21 (s, 3H), 0.19 (s, 3H), 0.18 (s, 3H), -0.12 (s, 3H), -0.49 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.6, 154.8, 150.6, 138.1, 137.6, 122.3, 120.6, 115.8, 107.5, 98.0, 75.9, 75.8, 72.4, 67.6, 51.7, 44.6, 42.3, 38.1, 33.0, 30.4, 29.8, 25.9, 25.7, 25.6, 20.3, 18.6, 18.3, 18.2, 18.1, 17.9, 12.9, 10.7, 7.1, 5.8, -4.1, -4.2, -4.4, -5.1,-5.3.

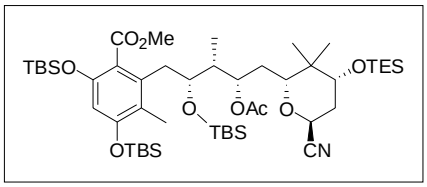


4,6-Bis-*tert*-butyldimethylsilanyloxy-2,2-*tert*-butyldimethylsilanyloxy-4-hydroxy-5,6-hydroxy-3,3-dimethyl-4-triethylsilanyloxytetrahydropyran-2-yl-3-methylpentyl-3-methyl benzoic acid methyl ester (38): Ozone was gently bubbled through a solution of **36** (0.59 g, 0.66 mmol) in CH_2Cl_2 (50 mL) at -78 °C until the reaction mixture sustained a deep blue color. Triphenylphosphine (0.69, 2.6 mmol) was added and the reaction mixture was warmed to rt and stirred for 3 hours. The reaction mixture was concentrated under reduced pressure and purified by flash chromatography (10% EtOAc in hexanes) to provide the desired product containing minimal amounts of inseparable impurities (0.45 g, 76%). The resulting material was used without further purification. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.21 (s, 0.4H), 6.20 (s, 0.6H), 5.30 (bs, 0.6H), 4.67-4.62 (m, 0.4H), 3.98-3.92 (m, 4H), 3.87-3.81 (m, 1H), 3.84 (s, 1.2H), 3.83 (s, 1.8H), 3.81-3.78 (m, 0.6H), 2.60 (bs, 0.4H), 3.50-3.48 (m, 0.6H), 3.37-3.35 (m, 0.4H), 3.14 (bs, 0.4H), 3.11 (bs, 0.6H), 2.96-2.87 (m, 1H), 2.75 (dd, J = 14.0, 4.4 Hz, 1H), 2.16 (s, 1.2H), 2.15 (s, 1.8H), 1.80-1.49 (m, 5H), 1.02 (s, 9H), 1.02-0.92 (m, 11H), 0.96 (s, 9H), 0.85-0.82 (m, 6H), 0.83 (s, 9H), 0.61-0.58 (m, 6H), 0.22 (s, 3H), 0.20 (s, 3H), 0.19 (s, 3H), -0.06 (bs, 3H), -0.33 (s, 1.2H), 0.38 (s, 1.8H).



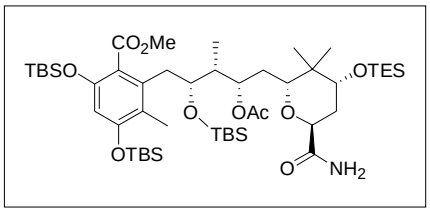
2,4-Acetoxy-5,6-acetoxy-3,3-dimethyl-4-triethylsilanyloxytetrahydropyran-2-yl-2-*tert*-butyldimethylsilanyloxy-3-methylpentyl-4,6-bis-*tert*-butyldimethylsilanyloxy-3-methyl benzoic acid methyl ester (39): To a solution of **38** (0.43 g, 0.47 mmol) in pyridine (2 mL) and CH_2Cl_2 (1 mL) at 0 °C was added acetic anhydride (0.49 g, 4.70 mmol) followed by a catalytic amount of DMAP. The reaction mixture was warmed to rt and stirred for 10 hours. H_2O (5 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The resulting oil was quickly purified by flash chromatography (10 % EtOAc in hexane) to provide the desired product (0.35 g, 76%) containing minor impurities. *Note*: extended exposure to silica gel resulted decomposition of **39**; ^{1}H ($CDCl_3$, 300 HMz) δ 6.19 (bs, 1H), 5.54 (dd, *J* = 10.1, 2.4 Hz, 0.5H), 5.34-5.28 (m, 1.5H), 3.92-3.87 (m, 1H), 3.82 (s, 1.5H), 3.81 (s, 1.5H), 3.75-3.70 (m, 1H), 3.45-3.43 (m, 0.5H), 3.32 (bd, 0.5H), 2.78-2.57 (m, 2H), 2.12 (s, 3H), 2.12 (s, 3H), 2.00 (s, 1.5H), 1.98 (s, 1.5H), 1.89-1.62 (m, 5H), 1.01 (s, 9H), 1.01-0.96 (m, 3H), 0.96 (s, 9H), 0.96-0.92 (m, 9H), 0.86-0.79 (m, 6H), 0.81 (s, 9H), 0.59 (q, *J* = 7.7 Hz, 6H), 0.21 (s, 6H), 0.19 (s, 3H), 0.19 (s, 3H), -0.11 (s, 2H), -0.12 (s, 1H), -0.45 (s, 2H), -0.50 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.7, 170.6, 169.8, 169.3, 168.6, 154.7, 150.6, 150.5, 137.2, 122.2, 120.5, 107.5, 92.7, 91.5, 80.0, 77.5, 75.6, 74.0. 72.4, 72.2, 70.8, 51.7, 43.6, 43.3, 39.6, 39.0, 36.2, 34.5, 33.9, 33.4, 32.9, 25.9, 25.6, 25.5, 22.7, 22.5, 21.3, 21.2, 21.2, 21.0, 18.2, 18.0, 17.8, 12.8, 12.8, 12.2, 11.6, 11.5, 11.3, 12.8, 12.2, 11.6, 11.5, 11.3, 6.8, 5.0, -4.2, -4.3, -4.5, -5.2, -5.3; IR (thin film) 2956, 2883, 1732, 1590 1251 cm^{-1}; HRMS

(ES) *m/z* calcd for $C_{50}H_{94}O_{11}NaSi_4$ (M + Na) 1005.5771, found 1005.5771; $[\alpha]^{25}_D$ +60.48° (1.28, $CHCl_3$).

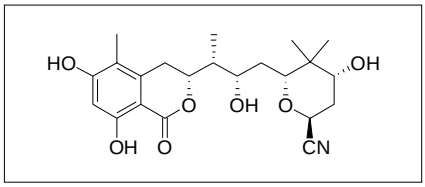


2,4-Acetoxy-2-*tert*-butyldimethylsilanyloxy-5,6-cyano-3,3-dimethyl-4-triethylsilanyloxytetrahydropyran-2-yl-3-methylpentyl-4,6-bis-*tert*-butyldimethylsilanyloxy-3-methyl benzoic acid methyl ester 41: To a solution of **39** (0.10 g, 0.10 mmol) in CH_2Cl_2 (5 mL) at -78 °C was added TMSCN (27 mg, 0.30 mmol) followed by a dropwise addition of BF_3•OEt_2 (17 mg, 0.12 mmol). The reaction mixture was stirred at -78 °C for 10 minutes then warmed to -42 °C and stirred for 1.5 hours. The reaction mixture was poured into a stirred mixture of pH 7 buffer (10 mL) and CH_2Cl_2 (10 mL) at 0 °C. The resulting mixture was warmed to rt and extracted with CH_2Cl_2 (3 x 10 mL). The organic layers were combined, washed with brine (10 mL), dried with Na_2SO_4, filtered and concentrated under reduced pressure. The resulting oil was purified by flash chromatography (10 % EtOAc in hexanes) to provide the desired product (92 mg, 97%); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.19 (s, 1H), 5.28 (app. q, 1H), 4.79 (app. d, 1H), 3.96 (ddd, *J* = 9.3, 3.8, 3.8 Hz, 1H), 3.82 (s, 3H), 3.70 (dd, *J* = 11.5, 4.5 Hz, 1H), 3.54 (app d, 1H), 2.81 (dd, *J* = 13.9, 9.8 Hz, 1H), 2.68 (dd, *J* = 13.9, 4.2 Hz, 1H), 2.12 (s, 3H), 2.08 (s, 3H), 2.00-1.88 (m, 3H), 1.78-1.65 (m, 2H), 1.01 (s, 9H), 1.01-1.00 (m, 3H), 0.97-0.91 (m, 12H), 0.96 (s, 9H), 0.83-0.80 (m, 3H), 0.82 (s, 9H), 0.60 (q, *J* = 7.9 Hz, 6H), 0.22 (s, 6H), 0.19 (s, 6H), -0.06 (s, 3H), -0.50 (s, 3H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 170.3, 169.6, 154.8, 150.6, 137.3, 122.4, 120.7, 117.4, 107.5, 79.1, 76.1, 74.4, 72.2, 72.1, 63.3, 51.8, 41.7, 39.9, 33.6. 32.4, 26.0, 25.7, 25.6, 22.5, 21.4, 18.2, 18.0, 17.9, 12.9, 12.1, 11.4, 6.8, 5.0, -4.2, -4.2, -4.2, -4.4,

-5.0, -5.1; IR(thin film) 2956, 2858, 1735, 1690, 1162 cm^{-1}; HRMS(ES) *m/z* calcd for $C_{49}H_{91}NO_9NaSi_4$ (M + Na) 972.5669, found 972.5681; $[\alpha]^{25}_D$ +39.90° (*c* 0.99, $CHCl_3$).



2,4-Acetoxy-2-*tert*-butyldimethylsilanyloxy-5,6-carbamoyl-3,3-dimethyl-4-triethylsilanyloxytetrahydropyran-2-yl-3-methylpentyl-4,6-bis-*tert*-butyldimethylsilanyloxy-3-methyl benzoic acid methyl ester 43: To a solution of **41** (93 mg, 0.10 mmol) in ethanol (4 mL) and H_2O (0.6 mL) was added $(Me_2PO)_2HPt(Me_2POH)$[18] (2.1 mg, 5.0 μmol) and the reaction mixture was placed into an oil bath preheated to 80 °C. The reaction mixture was stirred at 80 °C for 8 hours, cooled to rt, filtered through a short silica gel column with a Na_2SO_4 plug on top of the silica gel and washed with adequate amounts of EtOAc (50 mL). The eluent was collected, concentrated and purified by flash chromatography (20% EtOAc in hexanes) to provide the desired product (92 mg, 96%); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.49 (bs, 1H), 6.20 (s, 1H), 5.41 (bs, 1H), 5.21-5.18 (m, 1H), 5.26 (dd, *J* = 5.8, 2.4 Hz, 1H), 3.94-3.85 (m, 1H), 3.83 (s, 3H), 3.39 (dd, *J* = 10.6, 4.2 Hz, 1H), 3.27 (dd, *J* = 10.2, 2.7 Hz, 1H), 2.69 (m, 2H), 2.31-2.26 (m, 1H), 2.10 (s, 3H), 2.02 (s, 3H), 1.85-1.60 (m, 4H), 1.00 (s, 9H), 1.00-0.89 (m, 24H), 0.83 (s, 12H), 0.81-0.83 (m, 6H), 0.22 (s, 3H), 0.21 (s, 3H), 0.19 (s, 3H), 0.18 (s, 3H), -0.08 (s, 3H), -0.32 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 174.1, 171.7, 169.4, 155.0, 150.8, 136.9, 121.9, 120.6, 107.7, 80.4, 74.6, 73.2, 73.0, 72.5, 51.9, 43.7, 38.8, 33.7, 33.4, 29.8, 25.9, 25.7, 25.6, 23.4, 21.7, 18.2, 18.0, 18.0, 14.4, 12.9, 11.0, 6.9, 5.0, -4.2, -4.2, -4.3, -4.7, -5.1; IR (neat) 2955, 2858, 1727, 1692, 1591, 1471 cm^{-1}; HRMS (ES) *m/z* calcd for $C_{49}H_{93}NO_{10}NaSi_4$ (M + Na) 990.5774, found 990.5798; $[\alpha]^{25}_D$ +23.26° (*c* 0.89, $CHCl_3$).



6,3-(6,8-Dihydroxy-5-methyl-1-oxoisochroman-3-yl)-2-hydroxybutyl-4-hydroxy-5,5-dimethyltetrahydropyran-2-carbonitrile 45: To a solution of **44** (10 mg 14 μmol))(obtained from unoptimized TMSCN addition into **39**) in THF (2 mL) was added TBAF (74 mg, 0.28 mmol) and the reaction mixture was stirred for 5 hours. H_2O (2 mL) was added and teh reaction mixture was extracted with EtOAc (3 x 5 mL). The organic layers were combined, washed with brine, dried with Na_2SO_4, filtered and concentrated under reduced pressure. The resulting residue was taken up in MeOH (2 mL) and K_2CO_3 (10 mg) and the reaction mixture was stirred at rt for 3 hours. H_2O was added to stop the reaction at partial conversion and the reaction mixture was extracted with EtOAc (3 x 5 mL). The organic layers were combined, dried with Na_2SO_4, concentrated under reduced pressure and purified by preparatory TLC (100% EtOAc) to provide the desired product (~1 mg, 17%). ^{1}H NMR (CD_3OD, 300 MHz) δ 6.19 (s, 1H), 4.95 (dd, *J* = 6.0, 1.0 Hz, 1H), 4.44 (ddd, *J* = 11.3, 7.1, 3.3 Hz, 1H), 3.98-3.93 (ddd, *J* = 7.7, 5.2, 2.5 Hz, 1H), 3.53 (dd, *J* = 11.8, 4.7 Hz, 1H), 3.42 (dd, *J* = 10.1, 2.0 Hz, 1H), 3.07 (dd, *J* = 16.6, 3.4 Hz, 1H), 2.79 (dd, *J* = 16.6, 11.2 Hz, 1H), 2.00 (s, 3H), 1.96-1.88 (m, 2H), 1.80-1.74 (m, 2H), 1.69-1.61 (m, 1H), 1.06 (d, *J* = 6.9 Hz, 3H), 0.92 (s, 3H), 0.81 (s, 3H); IR (dry film) 3438, 2926, 1650, 1467, 1376, 1252, 1173, 1101 cm^{-1}; HRMS (EI) *m/z* calcd. for $C_{22}H_{29}NO_7Na$ (M + Na) 442.1842, found 442.1818.

3.5 References

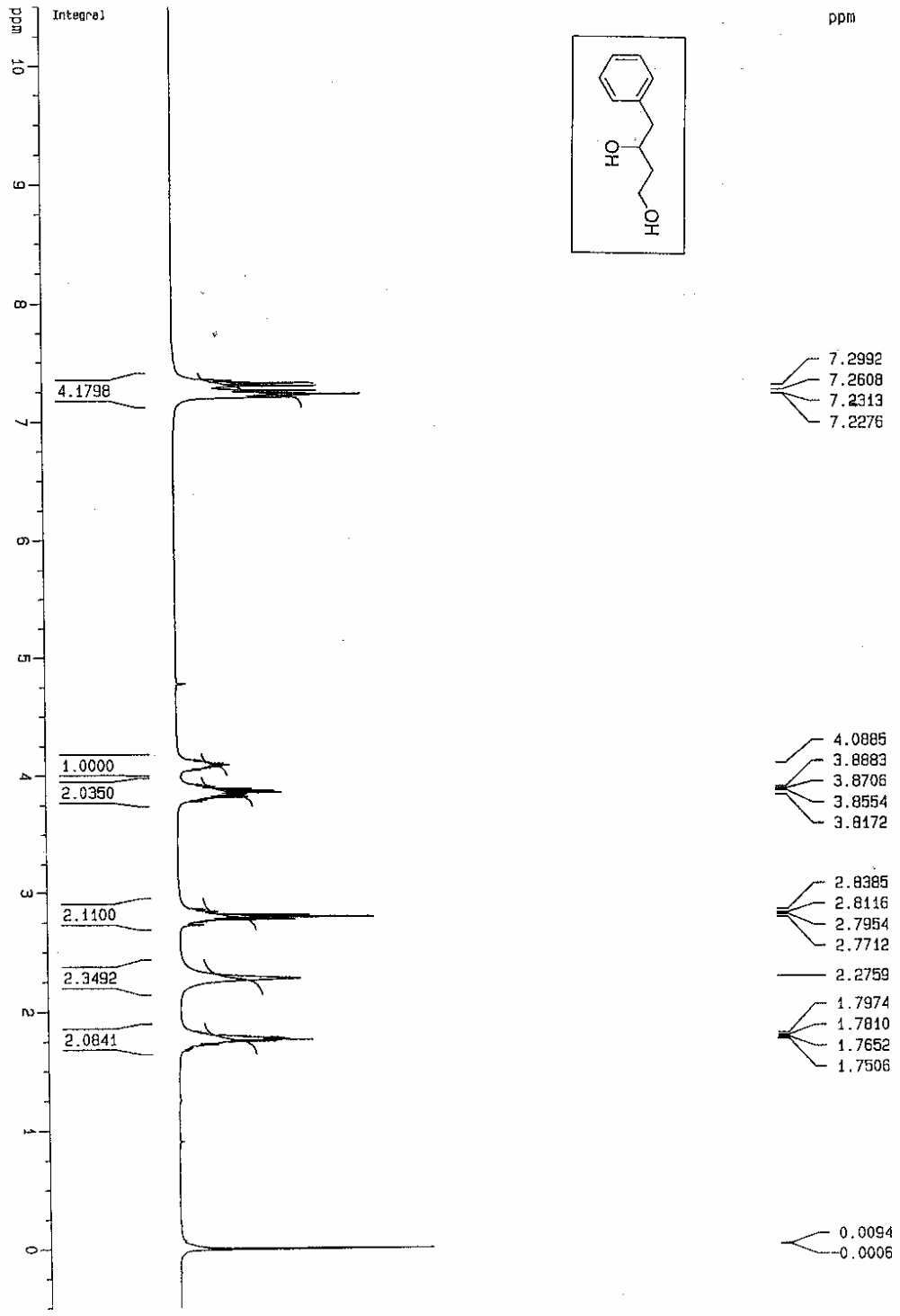
1. Cichewicz, R. H.; Valeriote, R. A.; Crews, P. "Psymberin, A Potent Sponge-Derived Cytotoxin from *Psammocinia* Distantly Related to the Pederin Family" *Org. Lett.* **2004**, *6*, 1951-1951.
2. Petit, G. R.; Xu, J-P.; Chapuis, J-C.; Pettit, R. K.; Tackett, L. P.; Doubek, D. L.; Hooper, J. N. A.; Schmidt, J. M. "Antineoplastic Agents. 520. Isolation and Structure of Irciniastatins A and B from the Indo-Pacific Marine Sponge *Ircinia ramose*" *J. Med. Chem.* **2004**, *47*, 1149-1152.
3. Jiang, X.; Garcia-Fortanet, J.; De Brabander, J. K. "Synthesis and Complete Stereochemical Assignment of Psymberin/Irciniastatin A" *J. Am. Chem. Soc.* **2005**, *127*, 11254-11255.
4. Kiren, S.; Williams, L. J. "Configuration of the Psymberin Amide Side Chain" *Org. Lett*. **2005**, *7*, 2905-2908.
5. Green, M. E.; Rech, J. C.; Floreancig, P. E. "Stereochemical Assignment of the C_1-C_6 Fragment of Psymberin by Synthesis and Natural Product Degradation" *Org. Lett.* **2005**, *7*, 4117-4120.
6. Langer, P.; Kracke, B. "Regioselective Synthesis of Functionalized Homophthalates by Cyclization of 1,3-Bis-(trimethylsiloxy)-1,3-Butadienes with α-Allenylesters" *Tetrahedron Lett.* **2000**, *41*, 4545-4547.
7. Node, M.; Fujiwara, T.; Ichihashi, S.; Nishide, K. "A New Synthetic Method for Allene-1,3-dicarboxylates Using DMC and a Novel Tandem Cyclization to a Pyrolizidine Alkaloid Skeleton" *Tetrahedron Lett.* **1998**, *39*, 6331-6334.

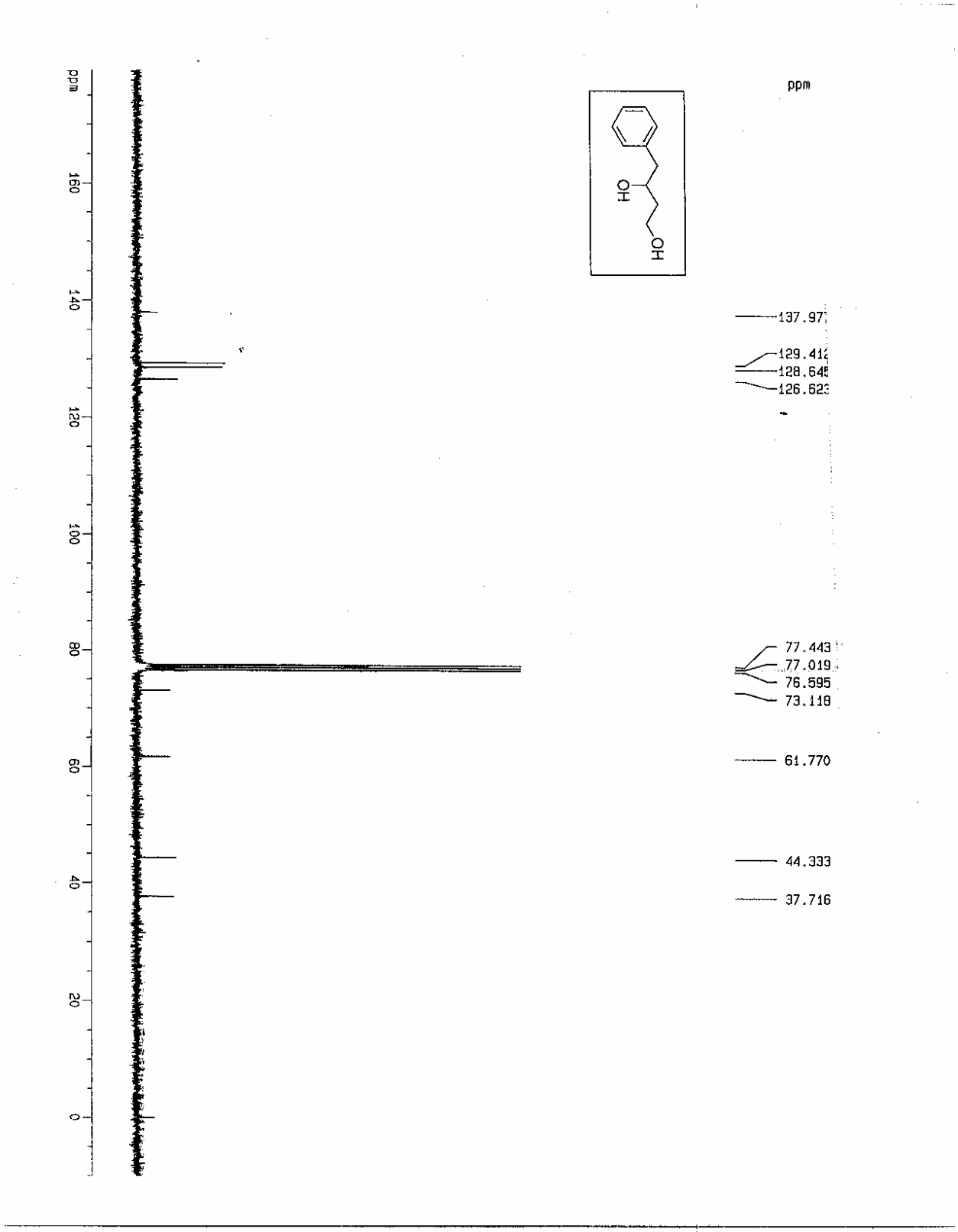
8. Langer, P.; Schneider, T.; Stoll, M. "Domino Reaction of 1,3-Bis(trimethylsilyloxy)-1,3-dienes with Oxalyl Chloride: General and Stereoselective Synthesis of γ-Alkylidenebutenolides" *Chem. Eur. J.* **2000**, *6*, 3204-3214.
9. Brown, H. C.; Bhat, K. S. "Enantiomeric (*Z*)- and (*E*)-Crotyldiisopinocampheylboranes. Synthesis in High Optical Purity of All Four Possible Stereoisomers of *β*-Methylhomoallyl Alcohols" *J. Am. Chem. Soc.* **1986**, *108*, 293-294.
10. Inukai, T.; Yoshizawa, R. "Preparation of *β*-Ketoaldehydes by Acylation of Aldehyde Enamines" *J. Org. Chem.* **1967,** *32*, 404-407.
11. Kinnaird, J. W. A.; Ng, P. Y.; Kubota, K.; Wang, X.; Leighton, J. A. "Strained Silacycles in Organic Synthesis: A New Reagent for the Enantioselective Allylation of Aldehydes" *J. Am. Chem. Soc.* **2002**, *124*, 7920-7921.
12. Mukaiyama T.; Banno, K.; Narasaka, K. "New Cross-Aldol Reactions. Reactions of Silyl Enol Ethers with Carbonyl Compounds Activated by Titanium Tetrachloride" *J. Am. Chem. Soc.* **1974**, *96*, 7501-7509.
13. Lodge, E. P.; Heathcock, C. H. "Steric Effects, as well as σ^*-Orbital Energies, Are Important in Diastereoface Differentiation in Additions to Chiral Aldehydes" *J. Am. Chem. Soc.* **1987**, *109*, 3353-3361.
14. Evans, D. A.; Duffy J. L.; Dart, M. J. "1,3-Asymmertric Inductions in the Aldol Addition Reactions of Methyl Ketone Enolates and Enolsilanes to β-Substituted Aldehydes. A Model for Chirality Transfer" *Tetrahedron Lett.* **1994**, *46*, 8537-8540.
15. Evans, D. A.; Dart, M. J.; Duffy, J. L.; Yang, M. G. "A Stereochemical Model for Merged 1,2- and 1,3-Asymmertic Induction in Diastereoselective Mukaiyama Aldol Addition Reactions and Related Processes" *J. Am. Chem. Soc.* **1996**, *118*, 4322-4343.

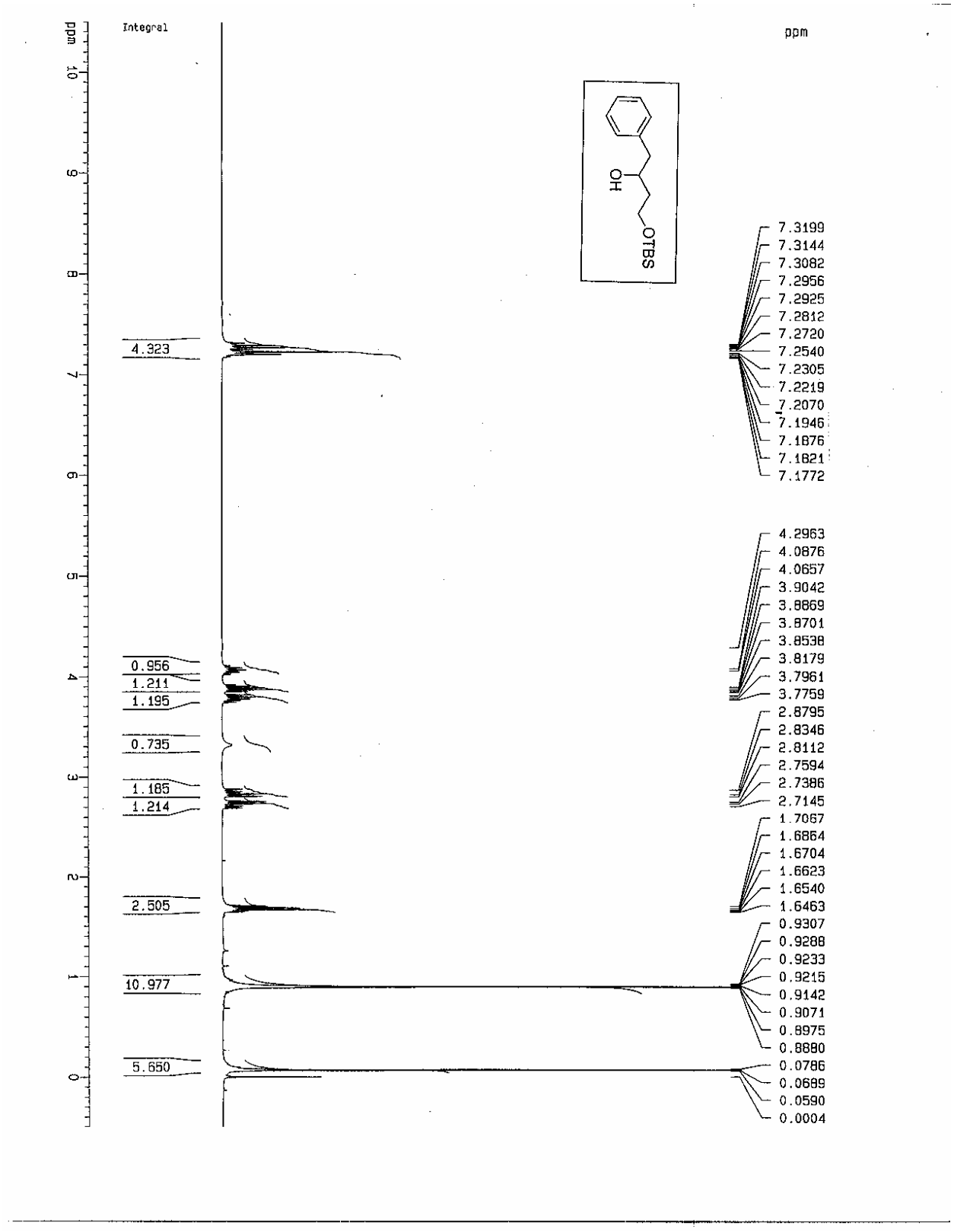
16. Roush, W. R.; Bannister, T. D.; Wendt, M. D.; VanNieuwenhze, M. S.; Gustin, D. J.; Dilley, G. J.; Lane, G. C.; Scheidt, K. A.; Smith, W. J. III "An NMR Method for Assigning Relative Stereochemistry to β-Hydroxy Ketones Deriving from Aldol Reactions of Methyl Ketones" *J. Org. Chem.* **2002**, *67*, 4284-4289.
17. Chen, K.; Hardmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. "1,3-*Syn* Diastereoselective Reduction of β-Hydroxyketones Utilizing Alkoxydialkylboranes" *Tetrahedron Lett.* **1987**, *28*, 155-158.
18. Rychnovsky, S. D.; Rogers, B. N.; Richardson, T. I. "Configurational Assignment of Polyene Mactolide Antibiotics Using the [C^{13}]Acetonide Analysis" *Acc. Chem. Res.* **1998**, *31*, 9-17.
19. Ghaffar, T.; Parkins, A. "The Catalytic Hydration of Nitriles to Amides Using a Platinum Phosphinito Catalyst" *J. Mol. Cat. A.* **2000**, *160,* 249-261.
20. Rech, J. C.; Floreancig, P. E. "Concise and Stereoselective Synthesis of the N_7-C_{24} Fragment of Psymberin" *Org. Lett.* **2005**, ASAP.

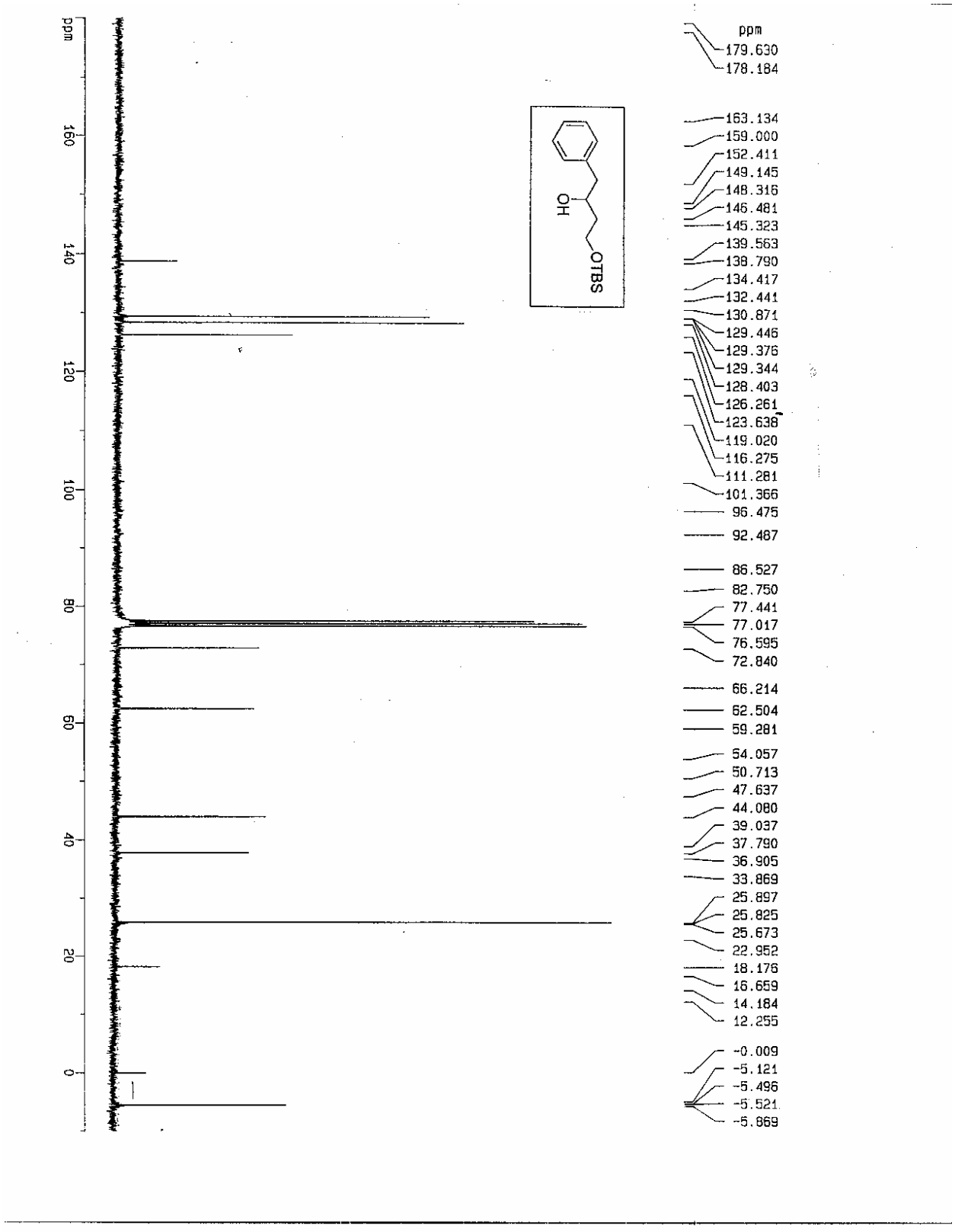
APPENDIX A

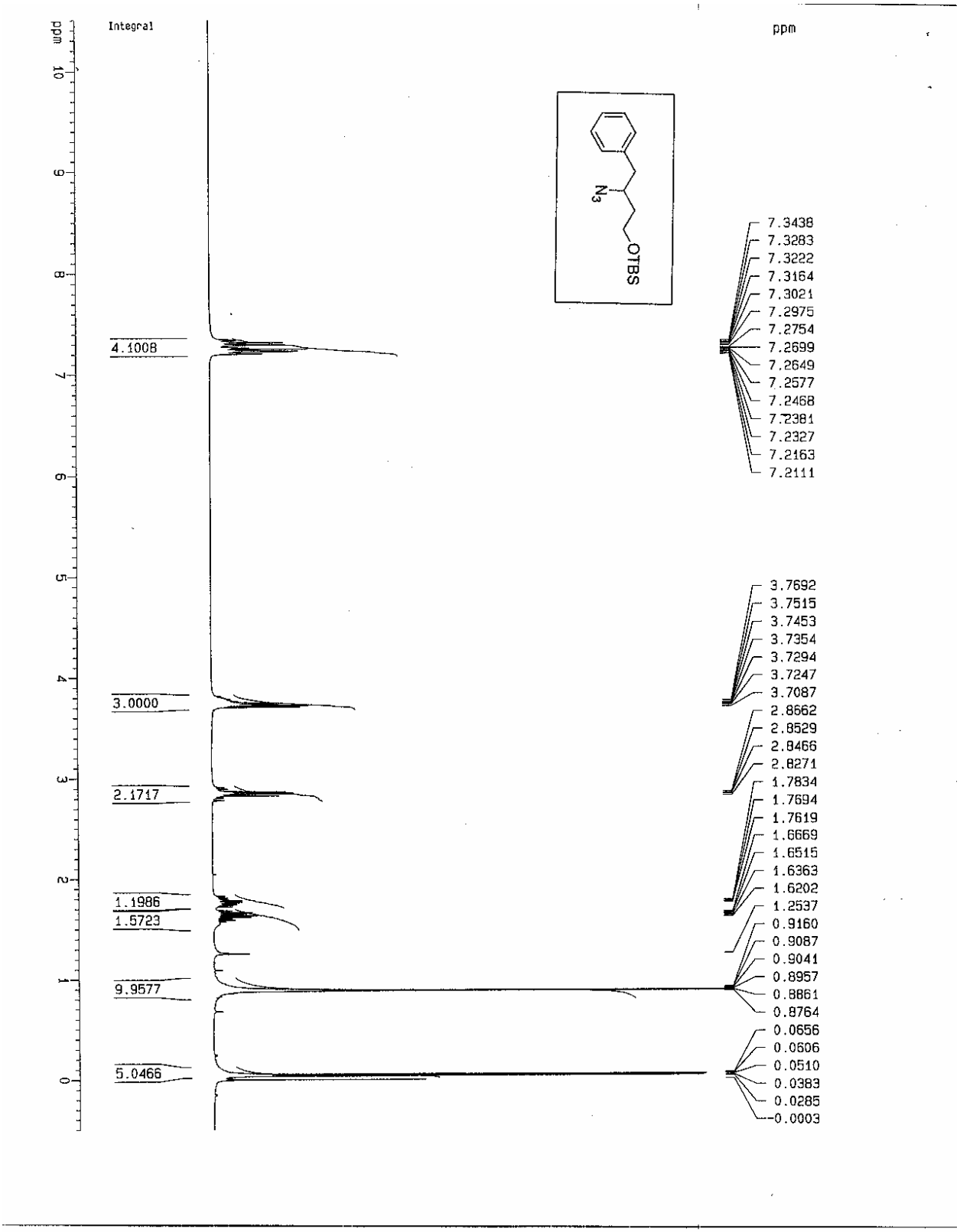
The Development of the Electron Transfer Initiated Cyclization for Application in the Synthesis of Amido Trioxadecalin Systems
(Supporting Information)
(^{1}H and ^{13}C NMR spectra)

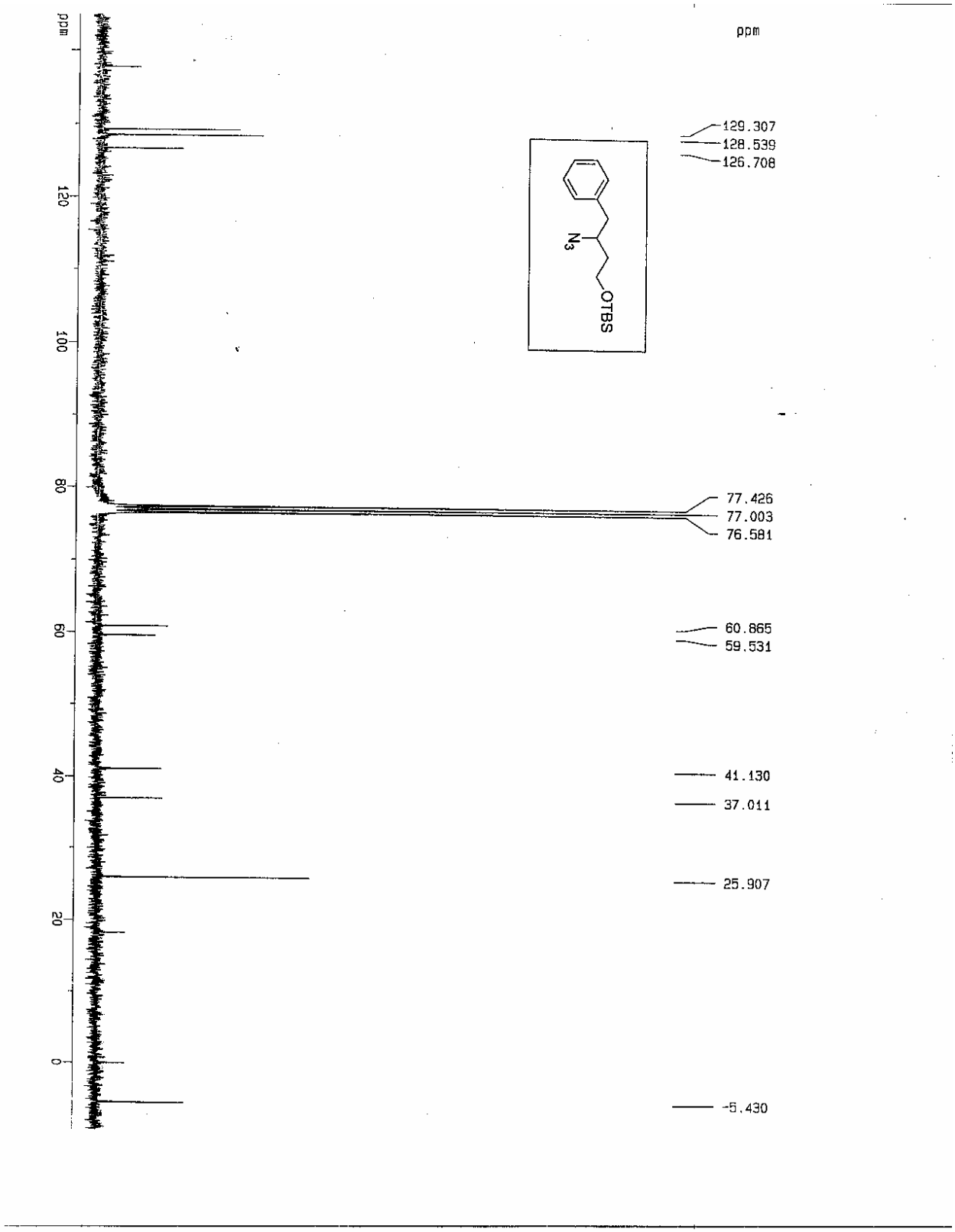

Integral
ppm
HO
OH
4.1798
1.0000
2.0350
2.1100
2.3492
2.0841
7.2992
7.2608
7.2313
7.2276
4.0885
3.8883
3.8706
3.8554
3.8172
2.8385
2.8116
2.7954
2.7712
2.2759
1.7974
1.7810
1.7652
1.7506
0.0094
0.0006

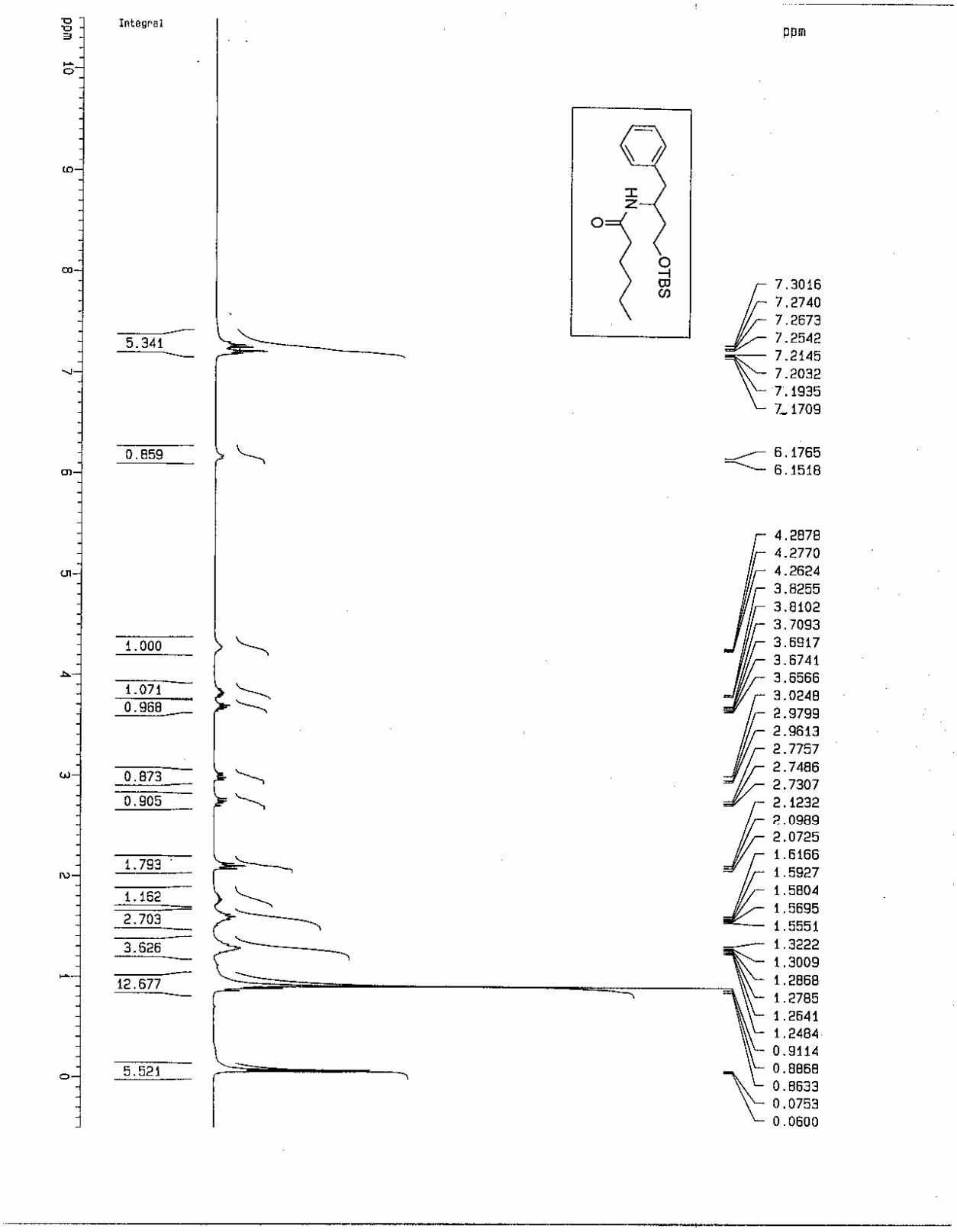

ppm
160
140
120
100
80
60
40
20
0
OH
OH
ppm
137.97
129.41
128.64
126.62
77.443
77.019
76.595
73.118
61.770
44.333
37.716

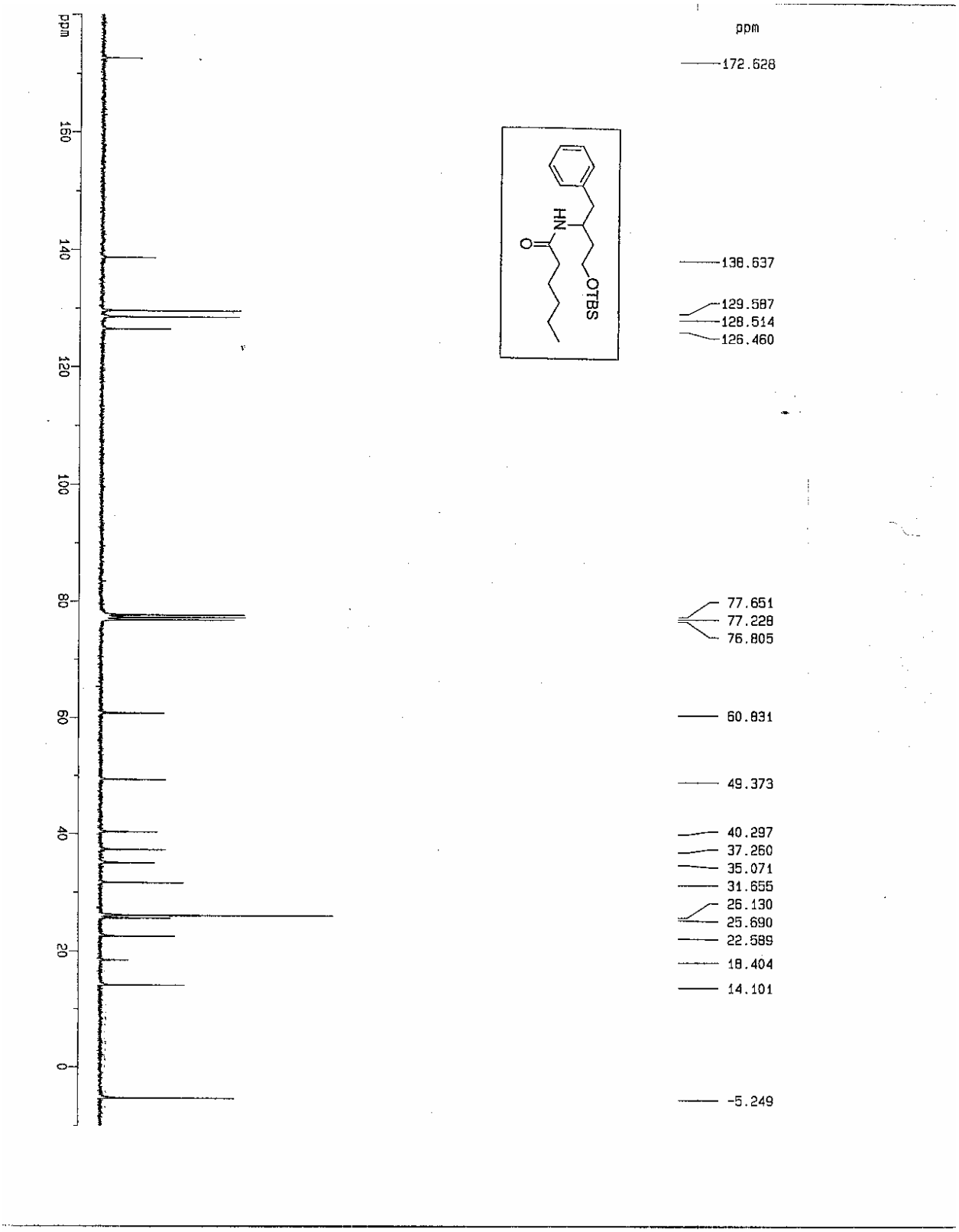

Integral
ppm
OH
OTBS
4.323
0.956
1.211
1.195
0.735
1.185
1.214
2.505
10.977
5.650
7.3199
7.3144
7.3082
7.2956
7.2925
7.2812
7.2720
7.2540
7.2305
7.2219
7.2070
7.1946
7.1876
7.1821
7.1772
4.2963
4.0876
4.0657
3.9042
3.8869
3.8701
3.8538
3.8179
3.7961
3.7759
2.8795
2.8346
2.8112
2.7594
2.7386
2.7145
1.7067
1.6864
1.6704
1.6623
1.6540
1.6463
0.9307
0.9288
0.9233
0.9215
0.9142
0.9071
0.8975
0.8880
0.0786
0.0689
0.0590
0.0004

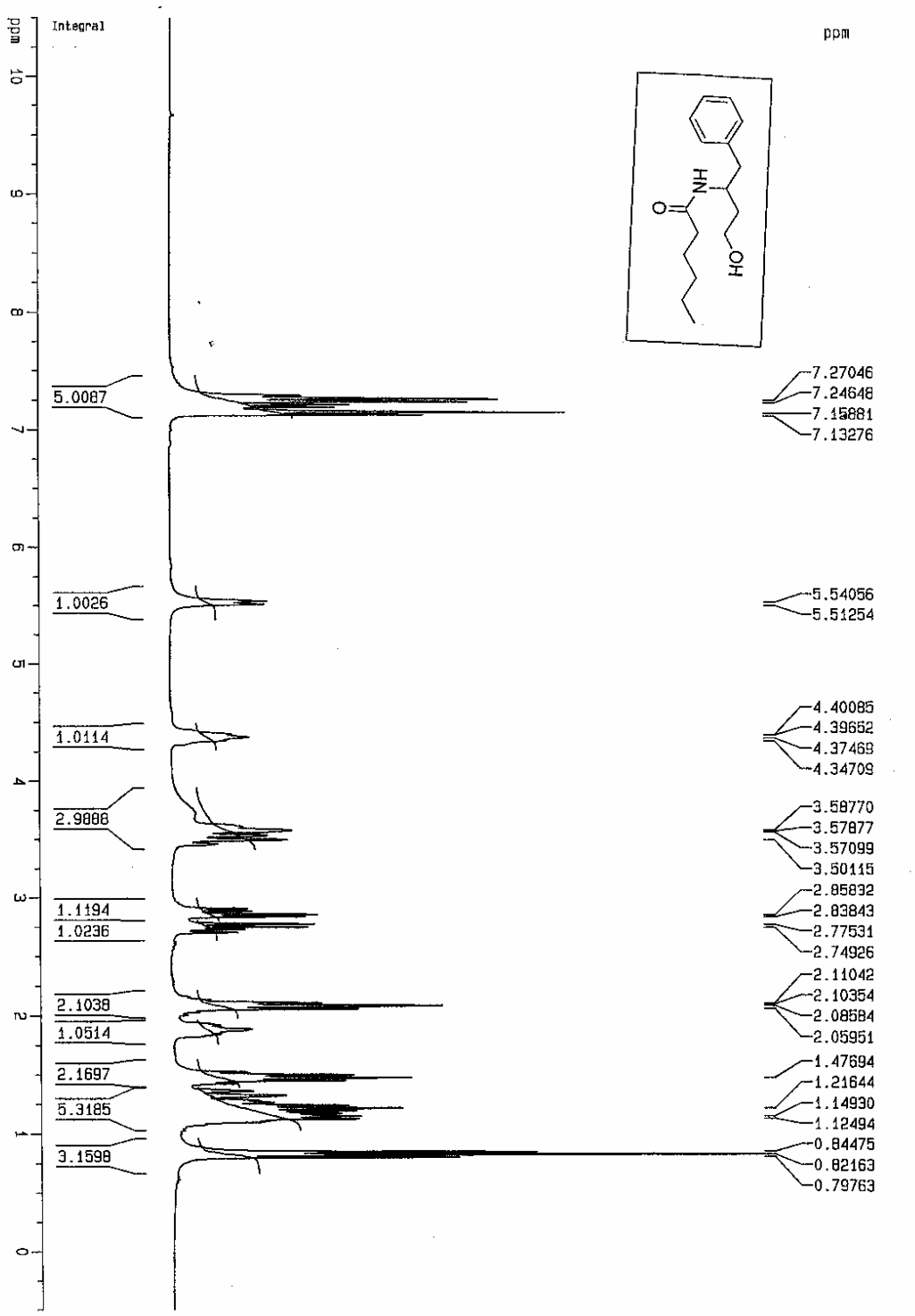

ppm
160
140
120
100
80
60
40
20
0
OH
OTBS
ppm
179.630
178.184
163.134
159.000
152.411
149.145
148.316
146.481
145.323
139.563
138.790
134.417
132.441
130.871
129.446
129.376
129.344
128.403
126.261
123.638
119.020
116.275
111.281
101.366
96.475
92.487
86.527
82.750
77.441
77.017
76.595
72.840
66.214
62.504
59.281
54.057
50.713
47.637
44.080
39.037
37.790
36.905
33.869
25.897
25.825
25.673
22.952
18.176
16.659
14.184
12.255
-0.009
-5.121
-5.496
-5.521
-5.869

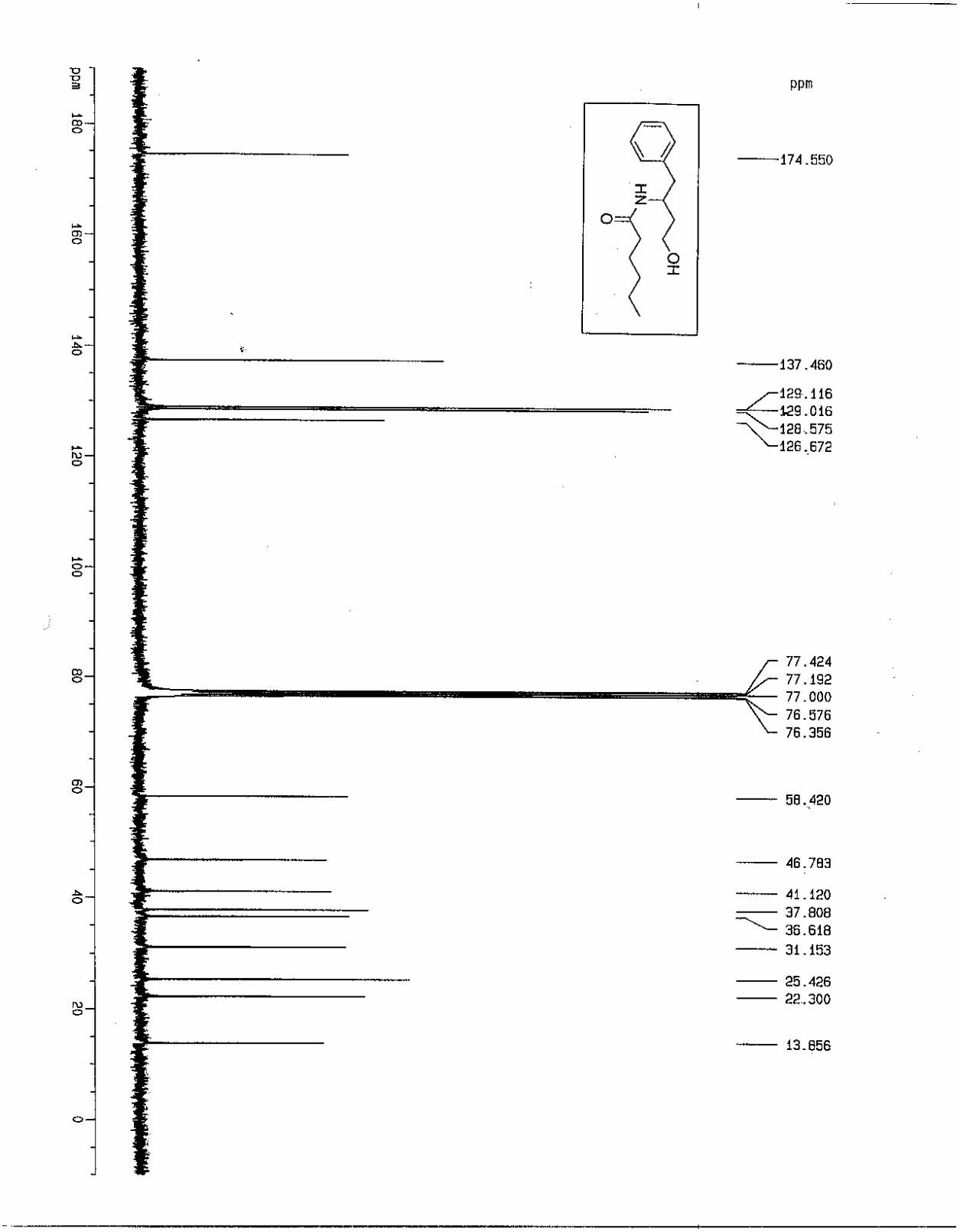

Integral
ppm
4.1008
3.0000
2.1717
1.1986
1.5723
9.9577
5.0466
N3
OTBS
7.3438
7.3283
7.3222
7.3164
7.3021
7.2975
7.2754
7.2699
7.2649
7.2577
7.2468
7.2381
7.2327
7.2163
7.2111
3.7692
3.7515
3.7453
3.7354
3.7294
3.7247
3.7087
2.8662
2.8529
2.8466
2.8271
1.7834
1.7694
1.7619
1.6669
1.6515
1.6363
1.6202
1.2537
0.9160
0.9087
0.9041
0.8957
0.8861
0.8764
0.0656
0.0606
0.0510
0.0383
0.0285
-0.0003

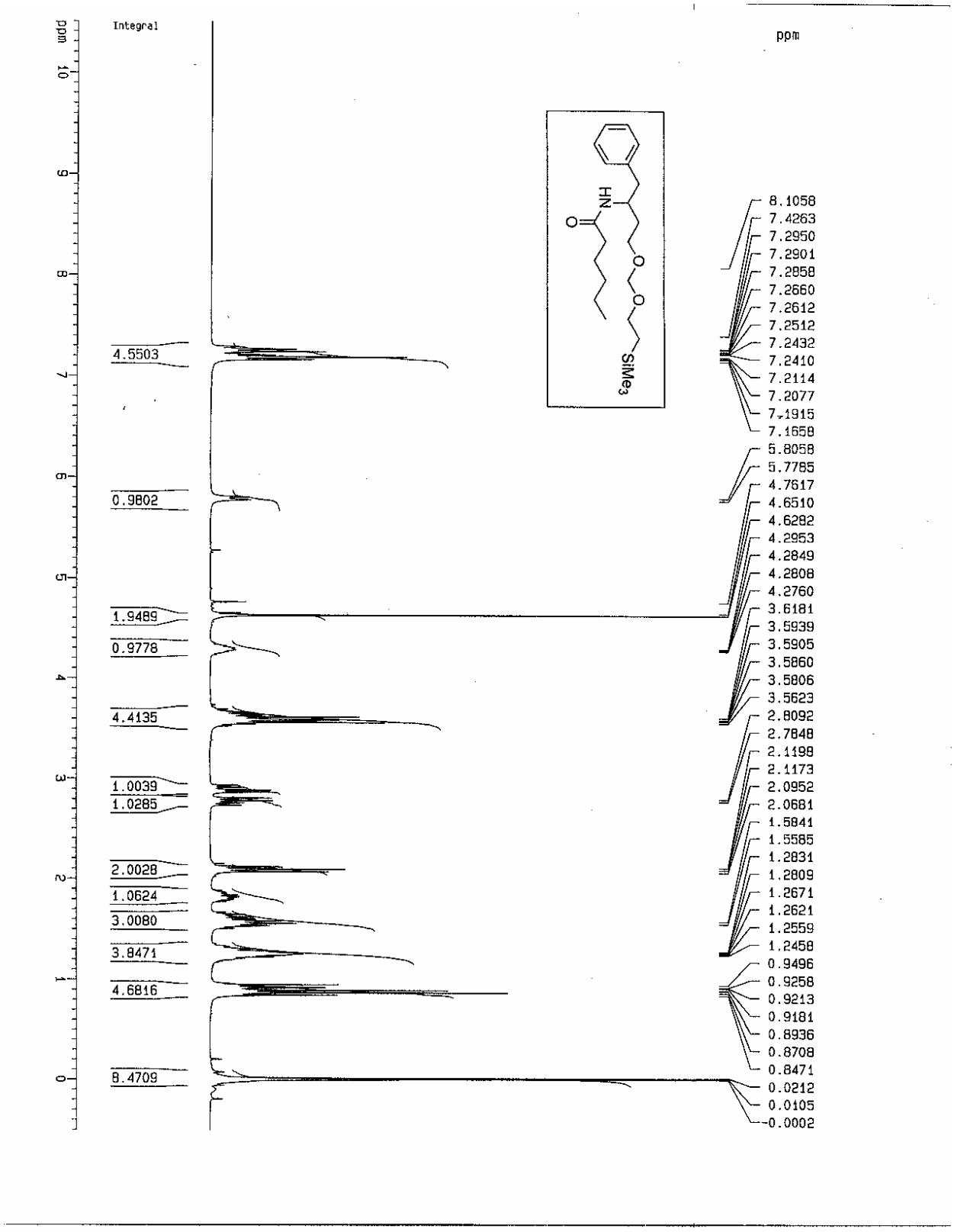

ppm
129.307
128.539
126.708
77.426
77.003
76.581
60.865
59.531
41.130
37.011
25.907
-5.430
OTBS
N3

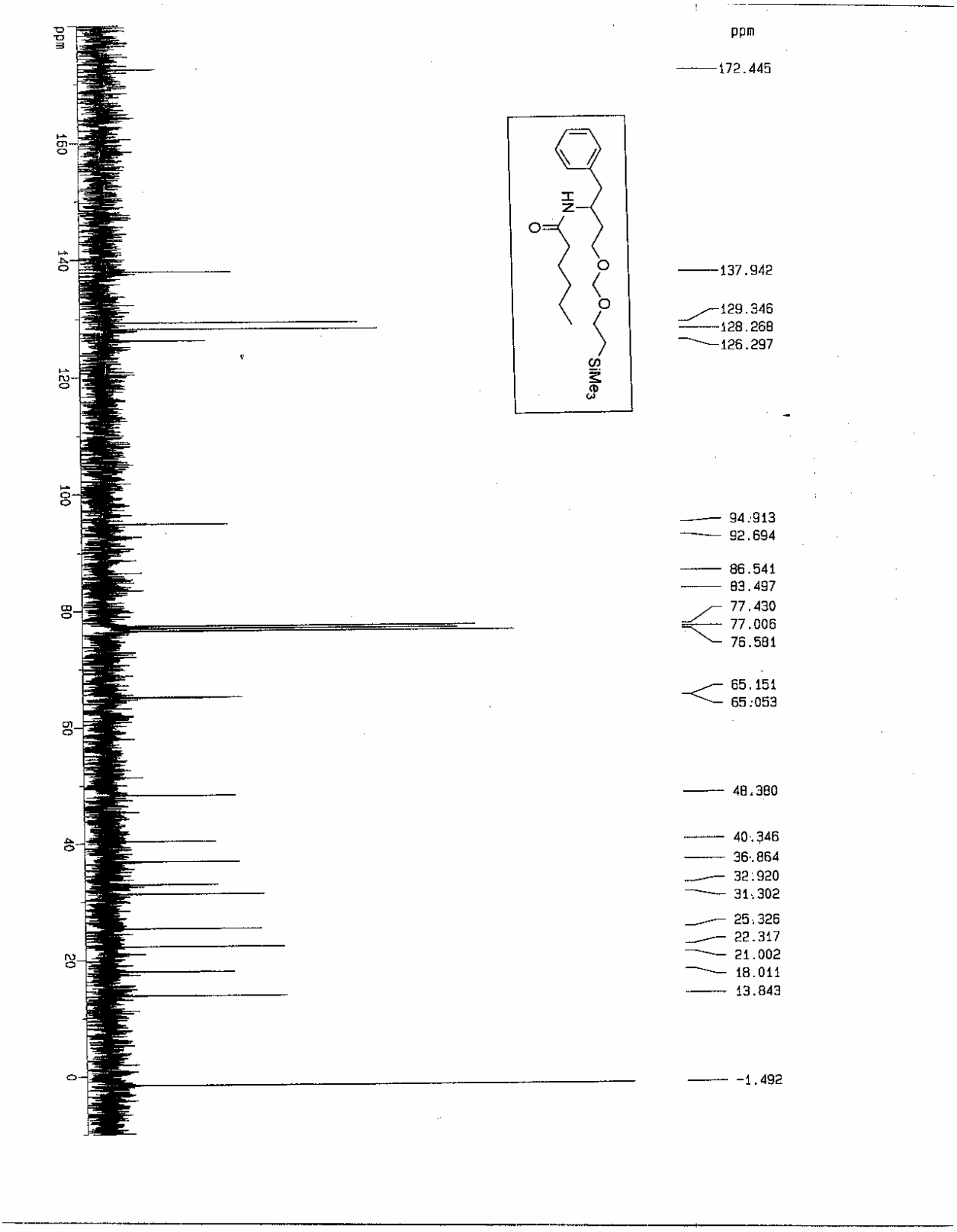

Integral
ppm
5.341
0.859
1.000
1.071
0.968
0.873
0.905
1.793
1.162
2.703
3.626
12.677
5.521
HN
O
OTBS
7.3016
7.2740
7.2673
7.2542
7.2145
7.2032
7.1935
7.1709
6.1765
6.1518
4.2878
4.2770
4.2624
3.8255
3.8102
3.7093
3.6917
3.6741
3.6566
3.0248
2.9799
2.9613
2.7757
2.7486
2.7307
2.1232
2.0989
2.0725
1.6166
1.5927
1.5804
1.5695
1.5551
1.3222
1.3009
1.2868
1.2785
1.2641
1.2484
0.9114
0.8868
0.8633
0.0753
0.0600

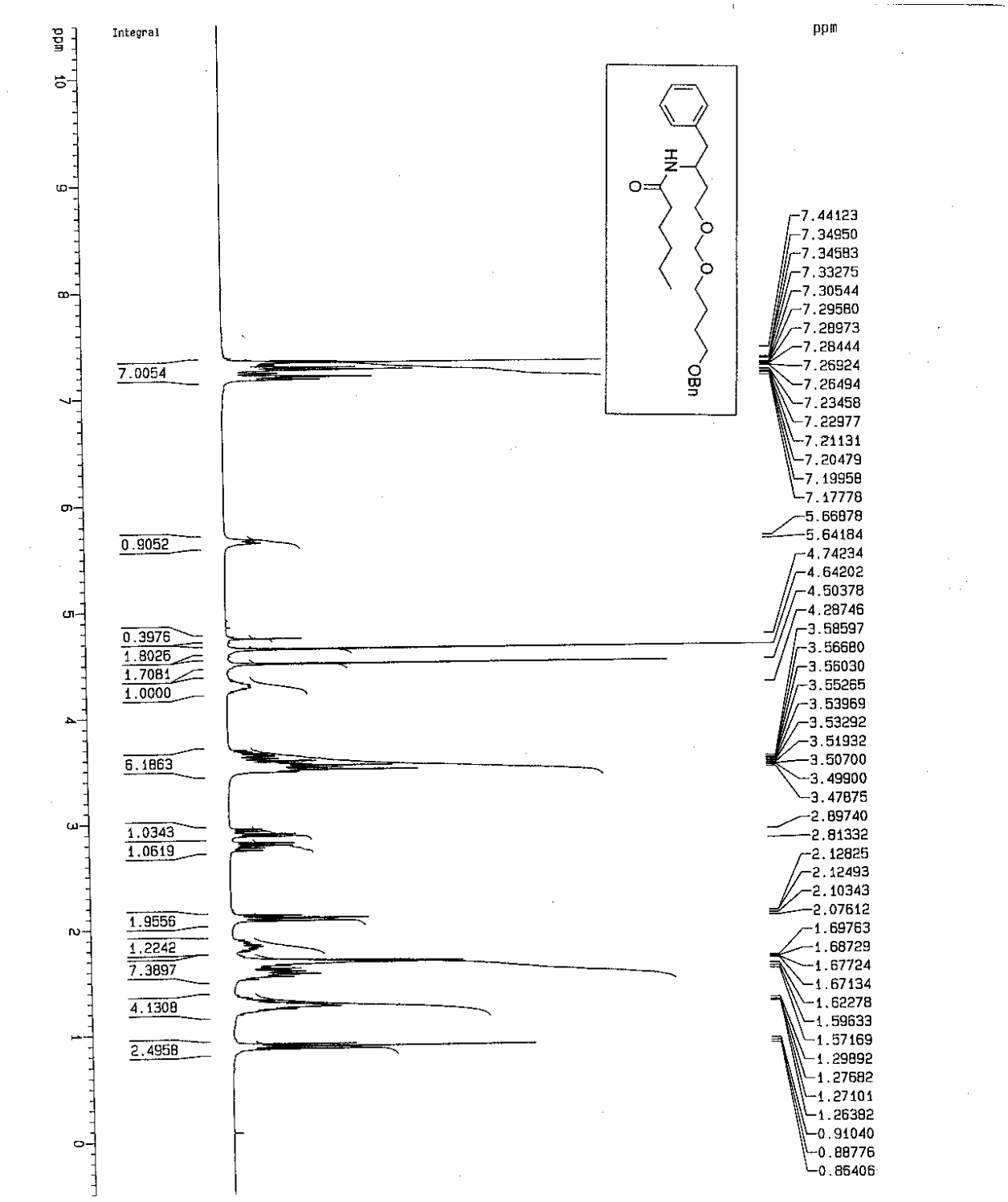

ppm
160
140
120
100
80
60
40
20
0
NH
O
OTBS
ppm
172.628
138.637
129.587
128.514
126.460
77.651
77.228
76.805
60.831
49.373
40.297
37.260
35.071
31.655
26.130
25.690
22.589
18.404
14.101
-5.249

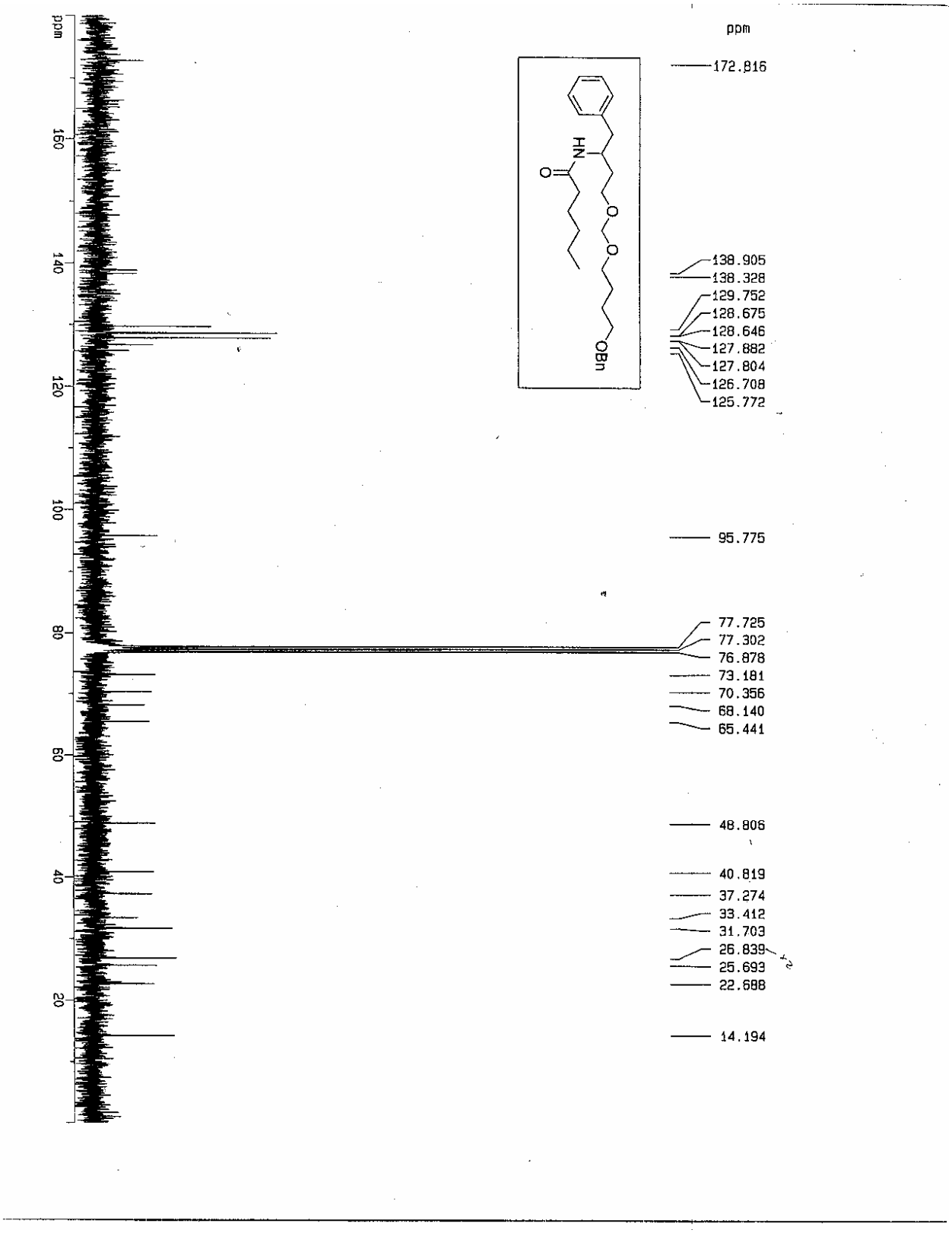

Integral
ppm
ppm
NH
O
OH
5.0087
1.0026
1.0114
2.9888
1.1194
1.0236
2.1038
1.0514
2.1697
5.3185
3.1598
7.27046
7.24648
7.15881
7.13276
5.54056
5.51254
4.40085
4.39652
4.37469
4.34709
3.58770
3.57877
3.57099
3.50115
2.85832
2.83843
2.77531
2.74926
2.11042
2.10354
2.08584
2.05951
1.47694
1.21644
1.14930
1.12494
0.84475
0.82163
0.79763

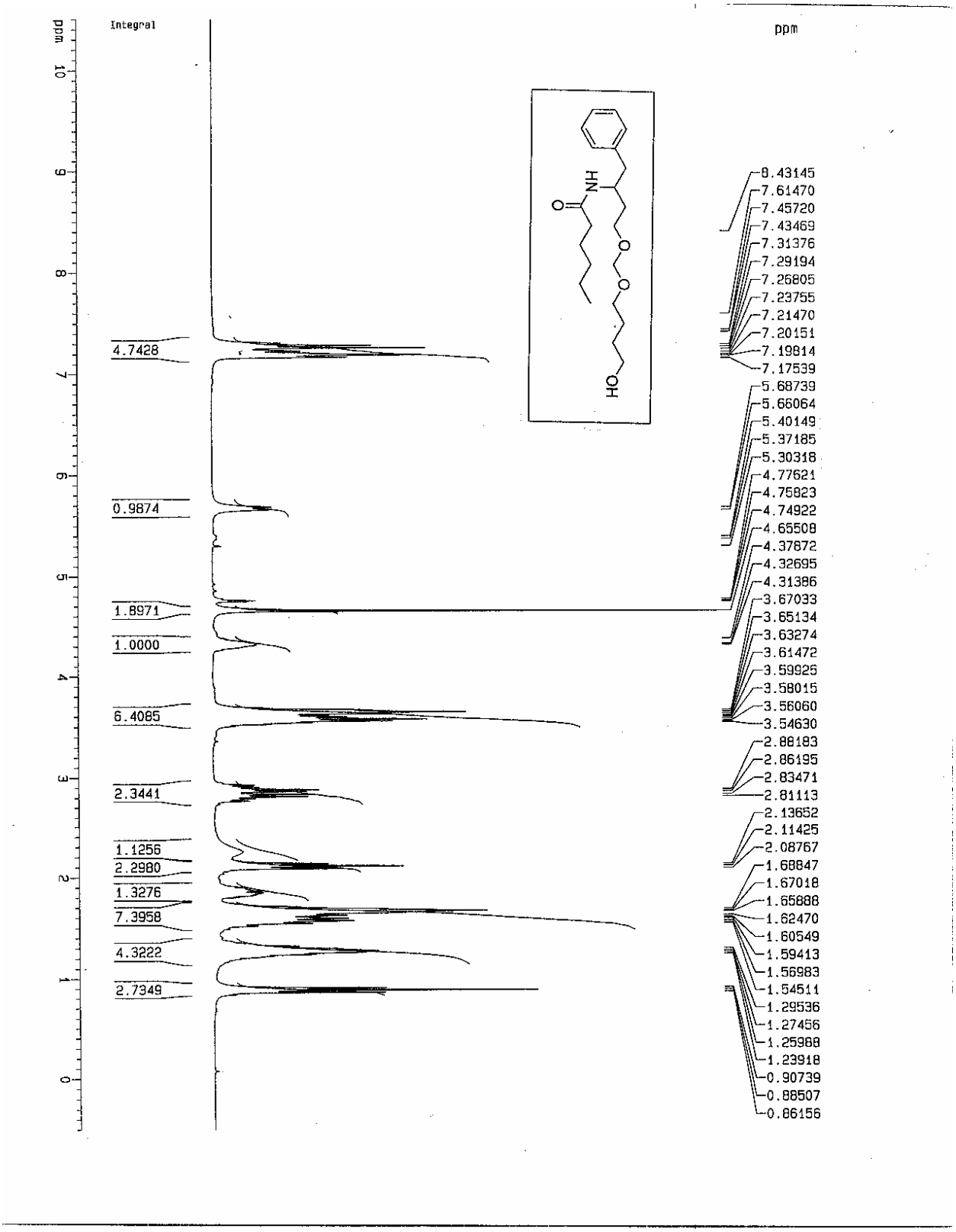

ppm
180
160
140
120
100
80
60
40
20
0
HN
O
OH
ppm
174.550
137.460
129.116
129.016
128.575
126.672
77.424
77.192
77.000
76.576
76.356
58.420
46.783
41.120
37.808
36.618
31.153
25.426
22.300
13.856

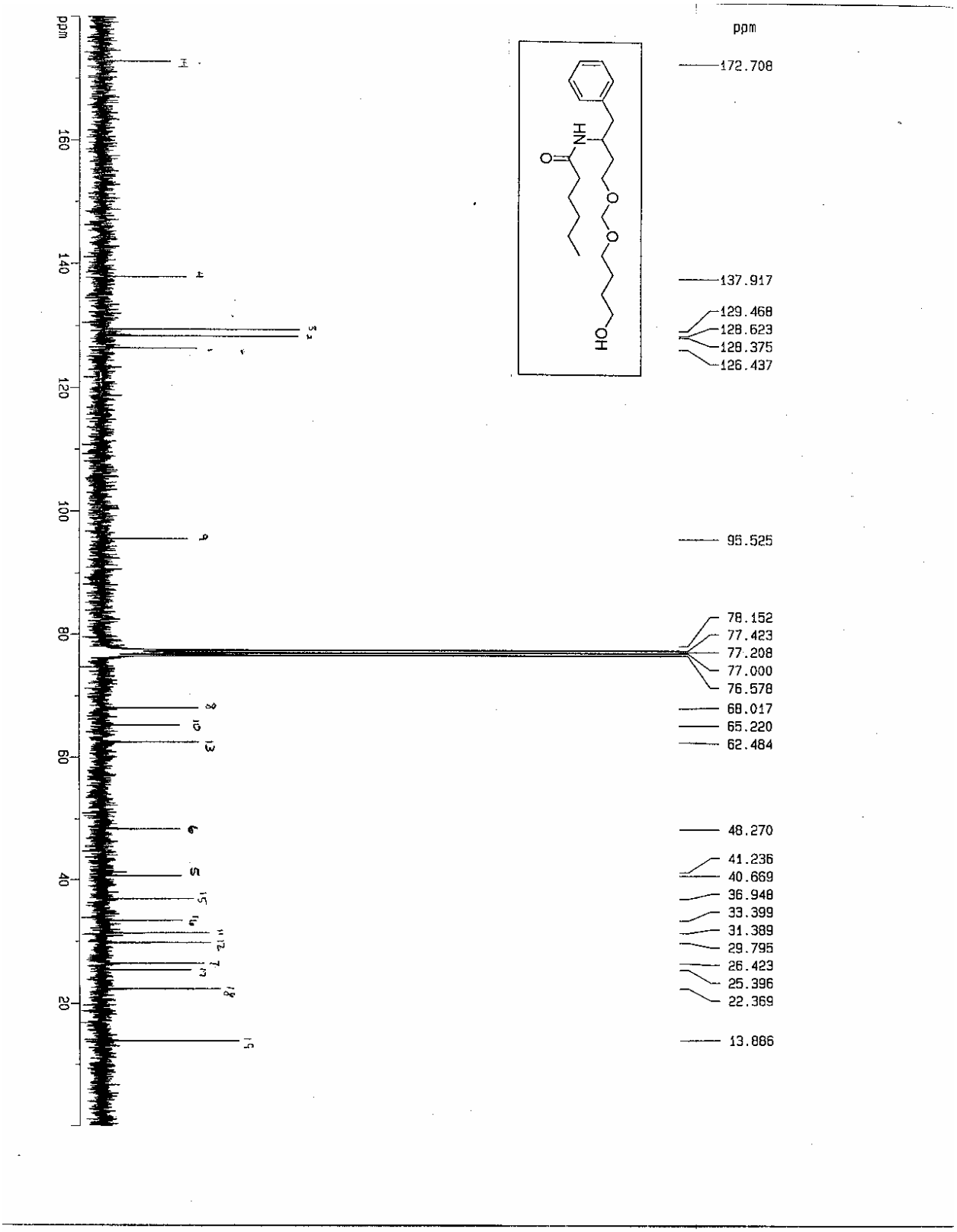

Integral
ppm
4.5503
0.9802
1.9489
0.9778
4.4135
1.0039
1.0285
2.0028
1.0624
3.0080
3.8471
4.6816
8.4709
HN
O
O
O
SiMe3
8.1058
7.4263
7.2950
7.2901
7.2858
7.2660
7.2612
7.2512
7.2432
7.2410
7.2114
7.2077
7.1915
7.1658
5.8058
5.7785
4.7617
4.6510
4.6282
4.2953
4.2849
4.2808
4.2760
3.6181
3.5939
3.5905
3.5860
3.5806
3.5623
2.8092
2.7848
2.1198
2.1173
2.0952
2.0681
1.5841
1.5585
1.2831
1.2809
1.2671
1.2621
1.2559
1.2458
0.9496
0.9258
0.9213
0.9181
0.8936
0.8708
0.8471
0.0212
0.0105
-0.0002

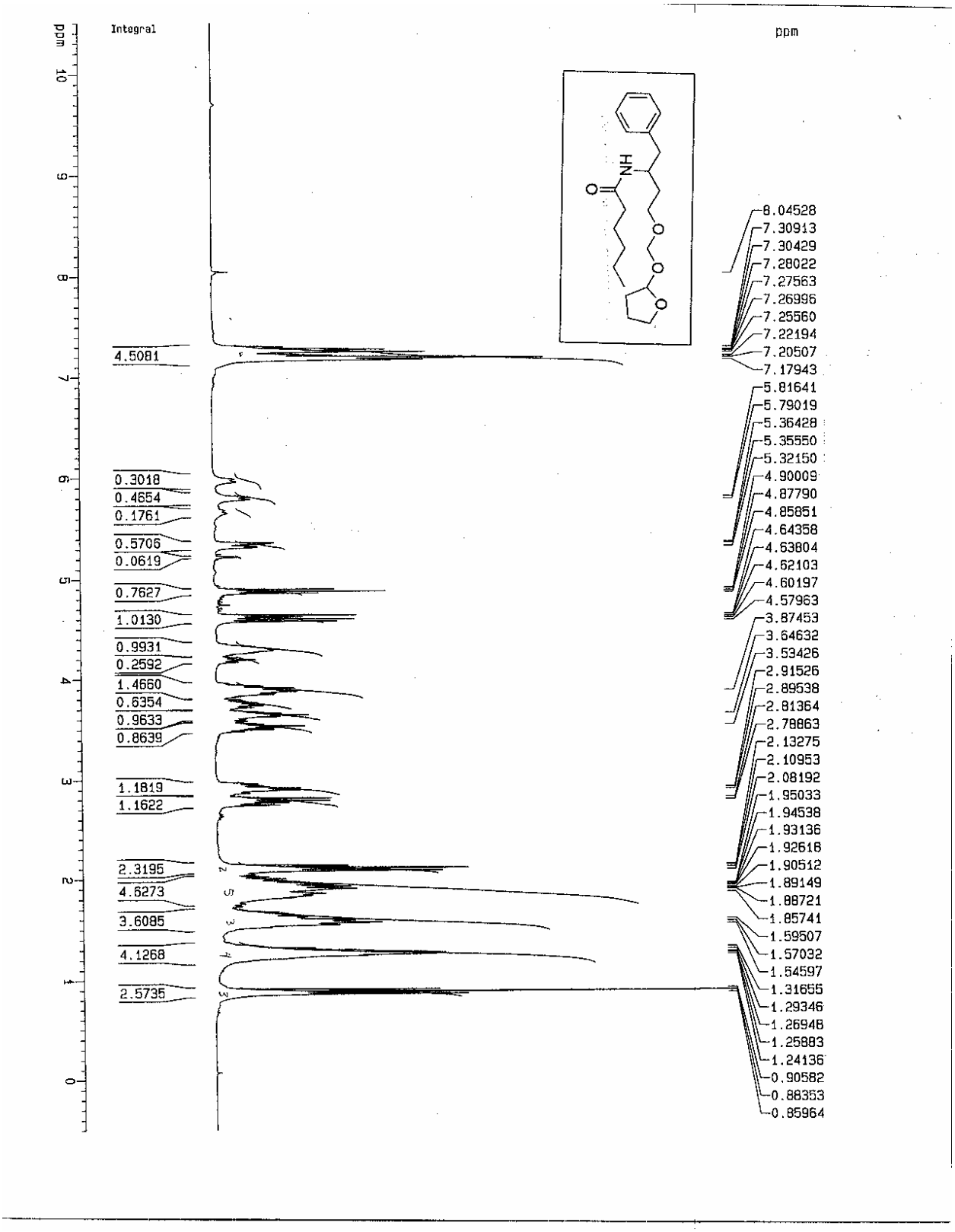

ppm
160
140
120
100
80
60
40
20
0
ppm
172.445
137.942
129.346
128.268
126.297
94.913
92.694
86.541
83.497
77.430
77.006
76.581
65.151
65.053
48.380
40.346
36.864
32.920
31.302
25.326
22.317
21.002
18.011
13.843
-1.492
HN
O
O
O
SiMe3

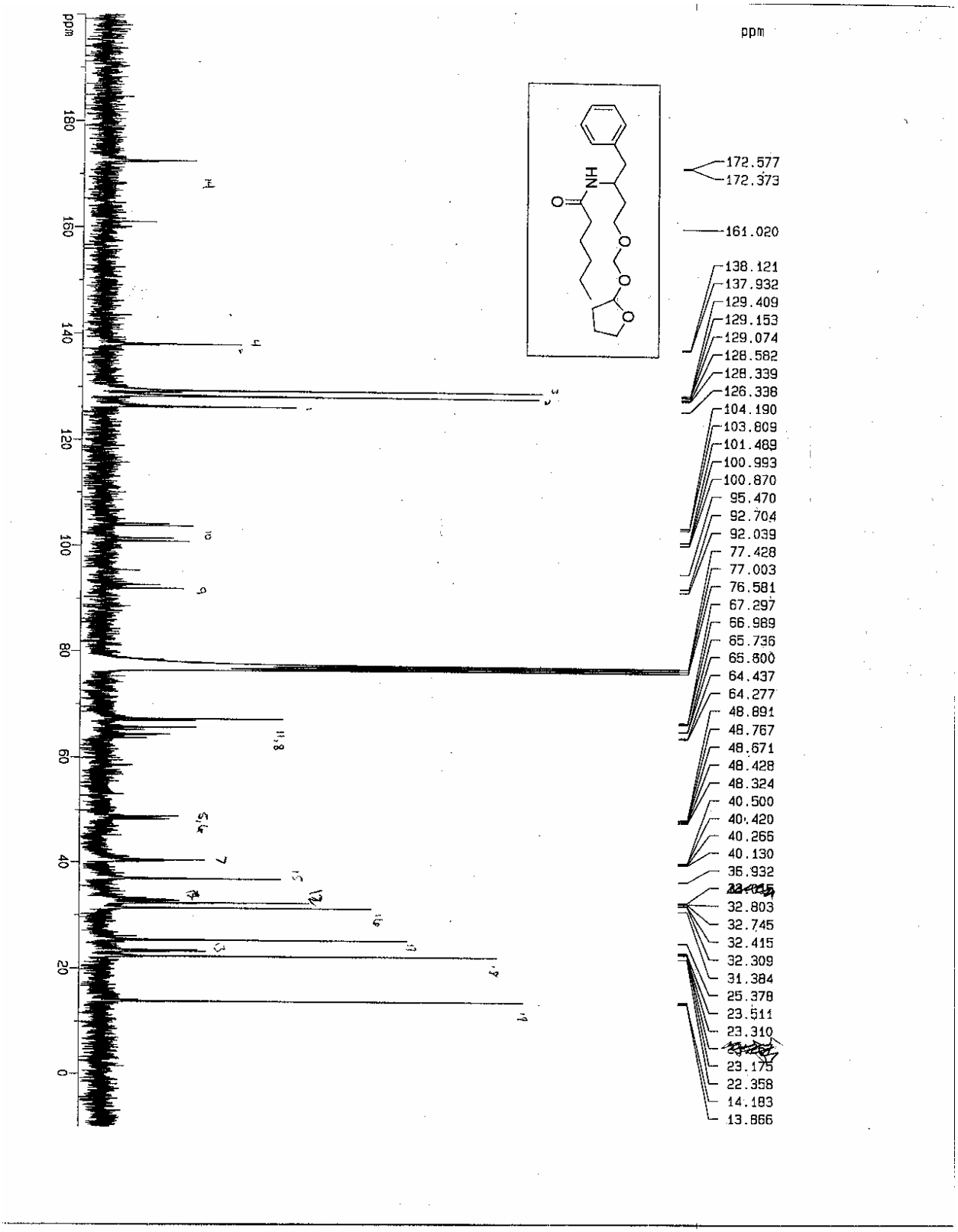

Integral
ppm
HN
O
O
O
OBn
7.0054
0.9052
0.3976
1.8026
1.7081
1.0000
6.1863
1.0343
1.0619
1.9556
1.2242
7.3897
4.1308
2.4958
7.44123
7.34950
7.34583
7.33275
7.30544
7.29580
7.28973
7.28444
7.26924
7.26494
7.23458
7.22977
7.21131
7.20479
7.19958
7.17778
5.66878
5.64184
4.74234
4.64202
4.50378
4.28746
3.58597
3.56680
3.56030
3.55265
3.53969
3.53292
3.51932
3.50700
3.49900
3.47875
2.89740
2.81332
2.12825
2.12493
2.10343
2.07612
1.69763
1.68729
1.67724
1.67134
1.62278
1.59633
1.57169
1.29892
1.27682
1.27101
1.26382
0.91040
0.88776
0.86406

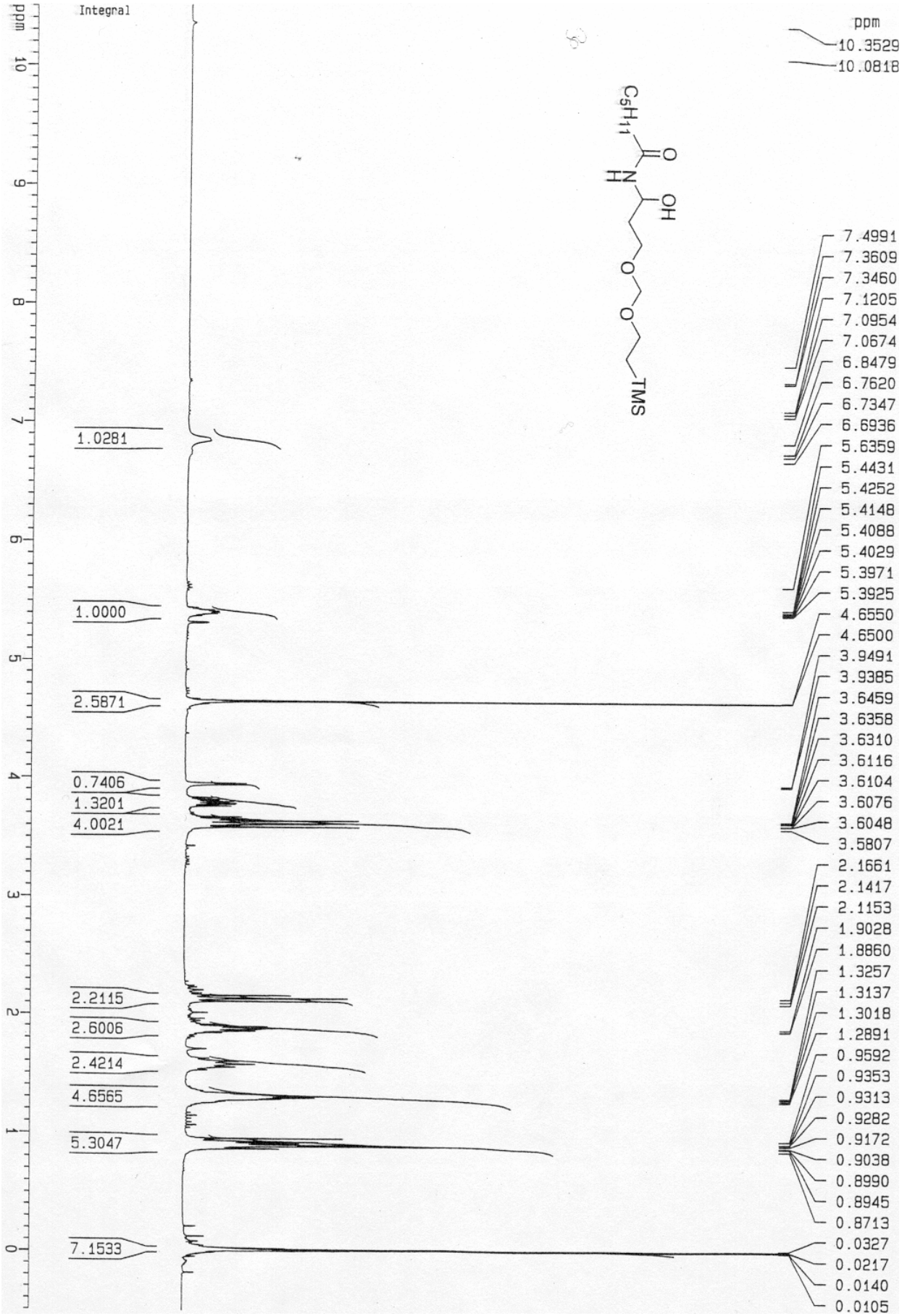

ppm
172.816
138.905
138.328
129.752
128.675
128.646
127.882
127.804
126.708
125.772
95.775
77.725
77.302
76.878
73.181
70.356
68.140
65.441
48.806
40.819
37.274
33.412
31.703
26.839
25.693
22.688
14.194
HN
O
O
O
OBn

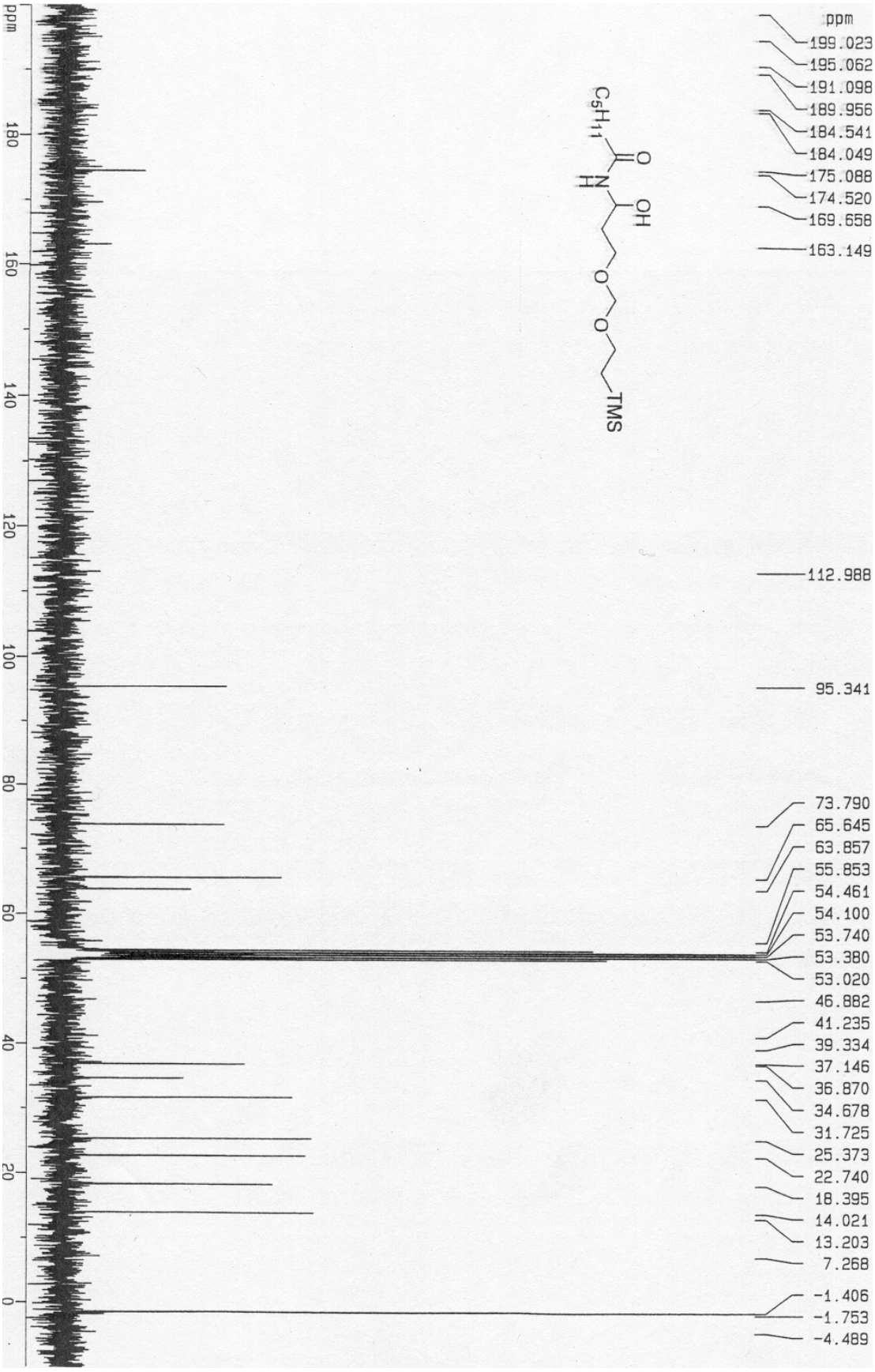

Integral
ppm
4.7428
0.9874
1.8971
1.0000
6.4085
2.3441
1.1256
2.2980
1.3276
7.3958
4.3222
2.7349
NH
O
O
O
HO
8.43145
7.61470
7.45720
7.43469
7.31376
7.29194
7.26805
7.23755
7.21470
7.20151
7.19814
7.17539
5.68739
5.66064
5.40149
5.37185
5.30318
4.77621
4.75823
4.74922
4.65508
4.37672
4.32695
4.31386
3.67033
3.65134
3.63274
3.61472
3.59925
3.58015
3.56060
3.54630
2.88183
2.86195
2.83471
2.81113
2.13652
2.11425
2.08767
1.68847
1.67018
1.65888
1.62470
1.60549
1.59413
1.56983
1.54511
1.29536
1.27456
1.25988
1.23918
0.90739
0.88507
0.86156

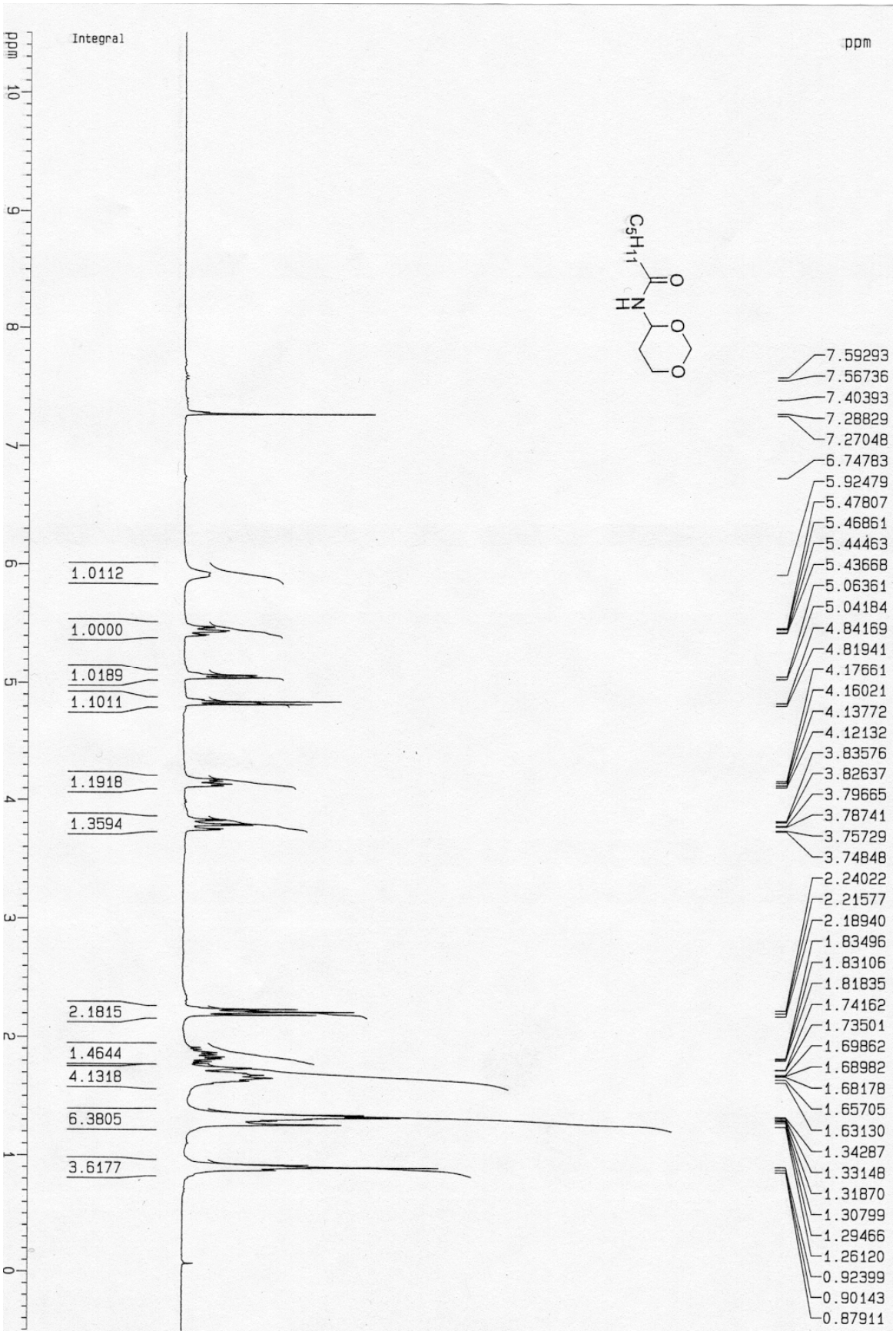

ppm
172.708
137.917
129.468
128.623
128.375
126.437
95.525
78.152
77.423
77.208
77.000
76.578
68.017
65.220
62.484
48.270
41.236
40.669
36.948
33.399
31.389
29.795
26.423
25.396
22.369
13.886
NH
O
OH

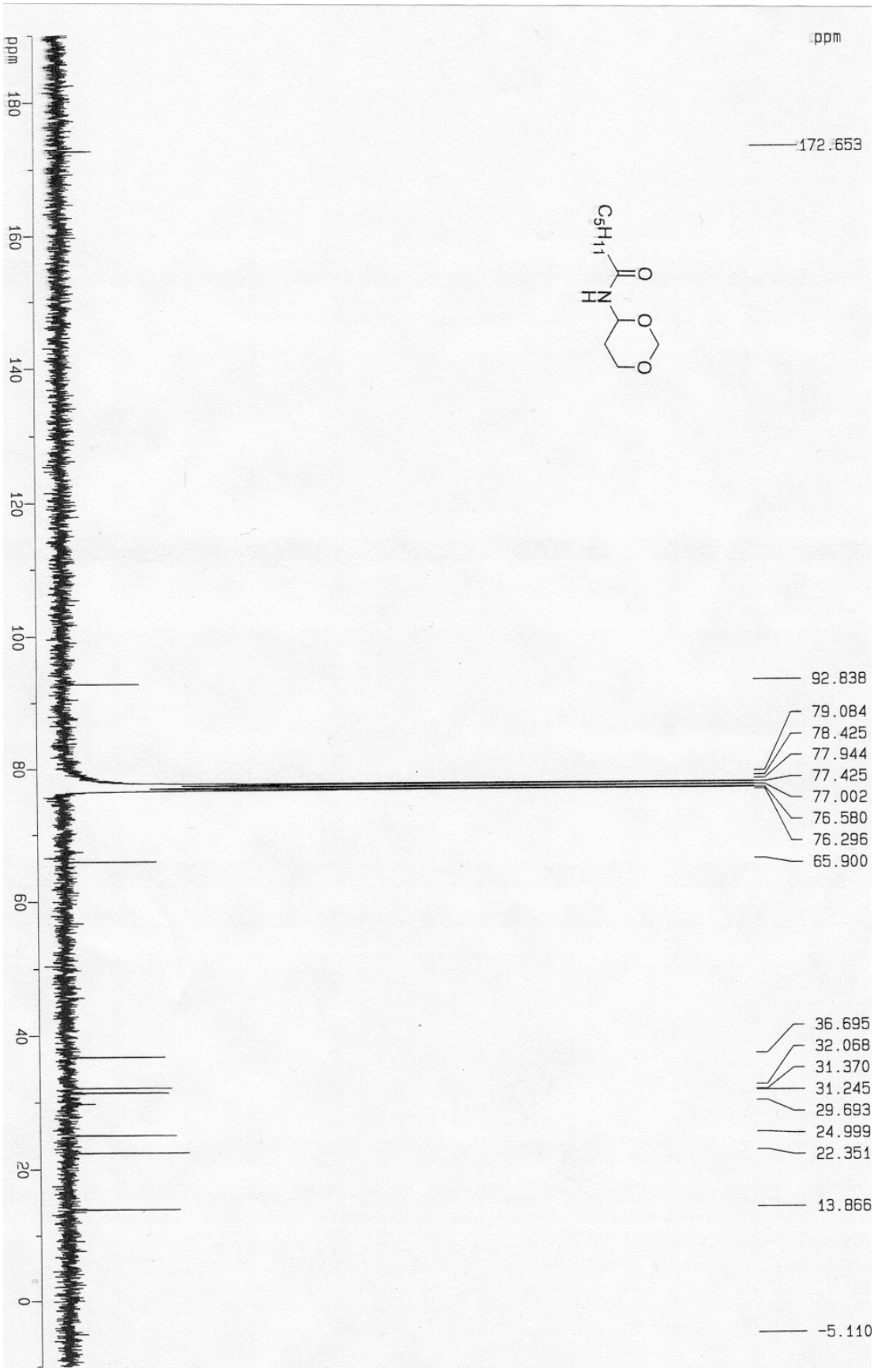

Integral
ppm
4.5081
0.3018
0.4654
0.1761
0.5706
0.0619
0.7627
1.0130
0.9931
0.2592
1.4660
0.6354
0.9633
0.8639
1.1819
1.1622
2.3195
4.6273
3.6085
4.1268
2.5735
8.04528
7.30913
7.30429
7.28022
7.27563
7.26996
7.25560
7.22194
7.20507
7.17943
5.81641
5.79019
5.36428
5.35550
5.32150
4.90009
4.87790
4.85851
4.64358
4.63804
4.62103
4.60197
4.57963
3.87453
3.64632
3.53426
2.91526
2.89538
2.81364
2.78863
2.13275
2.10953
2.08192
1.95033
1.94538
1.93136
1.92618
1.90512
1.89149
1.88721
1.85741
1.59507
1.57032
1.54597
1.31655
1.29346
1.26948
1.25883
1.24136
0.90582
0.88353
0.85964


ppm
ppm
NH
O
O
O
O
O
172.577
172.373
161.020
138.121
137.932
129.409
129.153
129.074
128.582
128.339
126.338
104.190
103.809
101.489
100.993
100.870
95.470
92.704
92.039
77.428
77.003
76.581
67.297
66.989
65.736
65.600
64.437
64.277
48.891
48.767
48.671
48.428
48.324
40.500
40.420
40.266
40.130
36.932
32.803
32.745
32.415
32.309
31.384
25.378
23.511
23.310
23.175
22.358
14.183
13.866


Integral
ppm
10.3529
10.0818
7.4991
7.3609
7.3460
7.1205
7.0954
7.0674
6.8479
6.7620
6.7347
6.6936
5.6359
5.4431
5.4252
5.4148
5.4088
5.4029
5.3971
5.3925
4.6550
4.6500
3.9491
3.9385
3.6459
3.6358
3.6310
3.6116
3.6104
3.6076
3.6048
3.5807
2.1661
2.1417
2.1153
1.9028
1.8860
1.3257
1.3137
1.3018
1.2891
0.9592
0.9353
0.9313
0.9282
0.9172
0.9038
0.8990
0.8945
0.8713
0.0327
0.0217
0.0140
0.0105
1.0281
1.0000
2.5871
0.7406
1.3201
4.0021
2.2115
2.6006
2.4214
4.6565
5.3047
7.1533
TMS
OH
O
N
H
O
O
C5H11

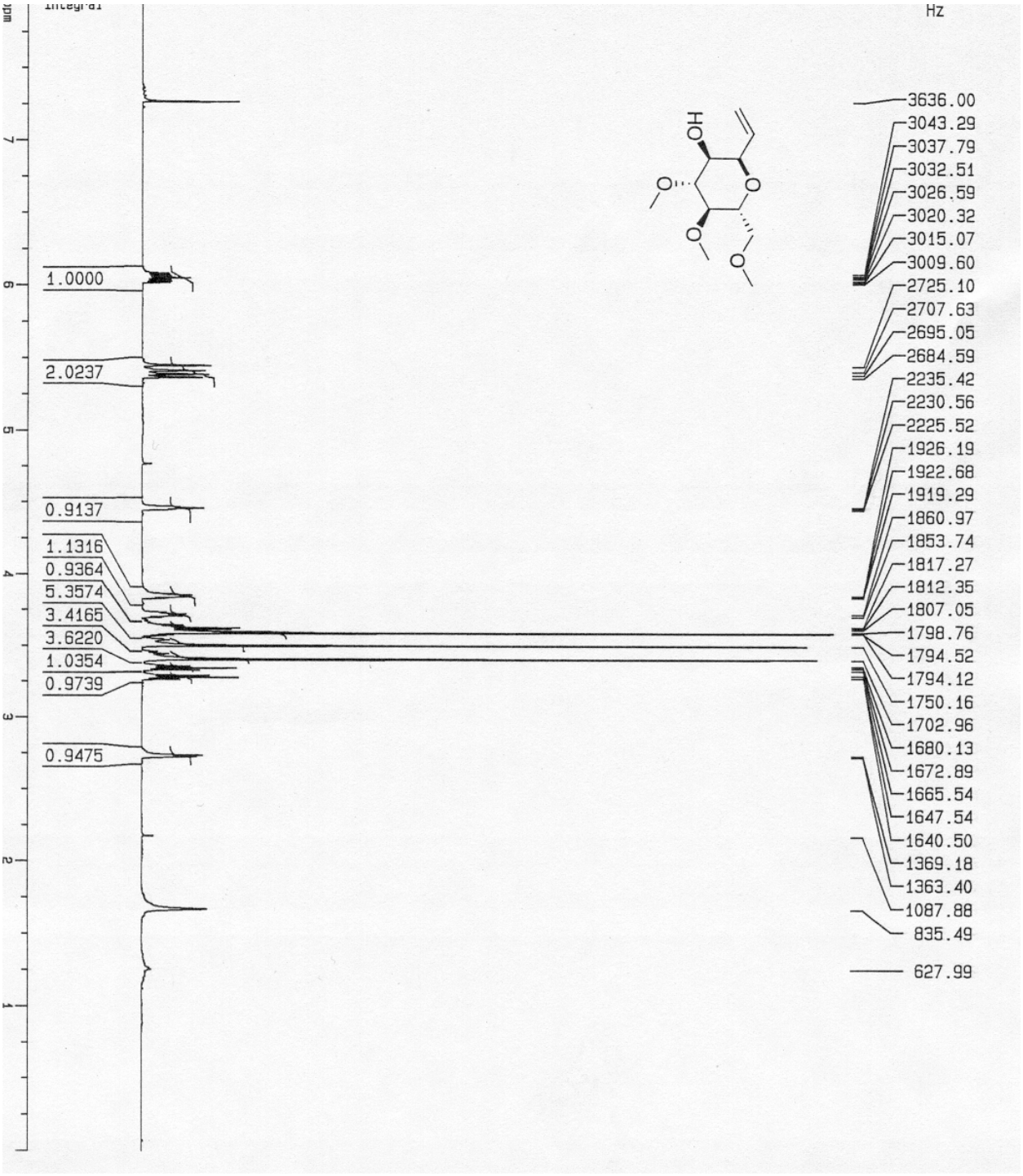

ppm
199.023
195.062
191.098
189.956
184.541
184.049
175.088
174.520
169.658
163.149
112.988
95.341
73.790
65.645
63.857
55.853
54.461
54.100
53.740
53.380
53.020
46.882
41.235
39.334
37.146
36.870
34.678
31.725
25.373
22.740
18.395
14.021
13.203
7.268
-1.406
-1.753
-4.489
C5H11
O
N
H
OH
O
O
TMS

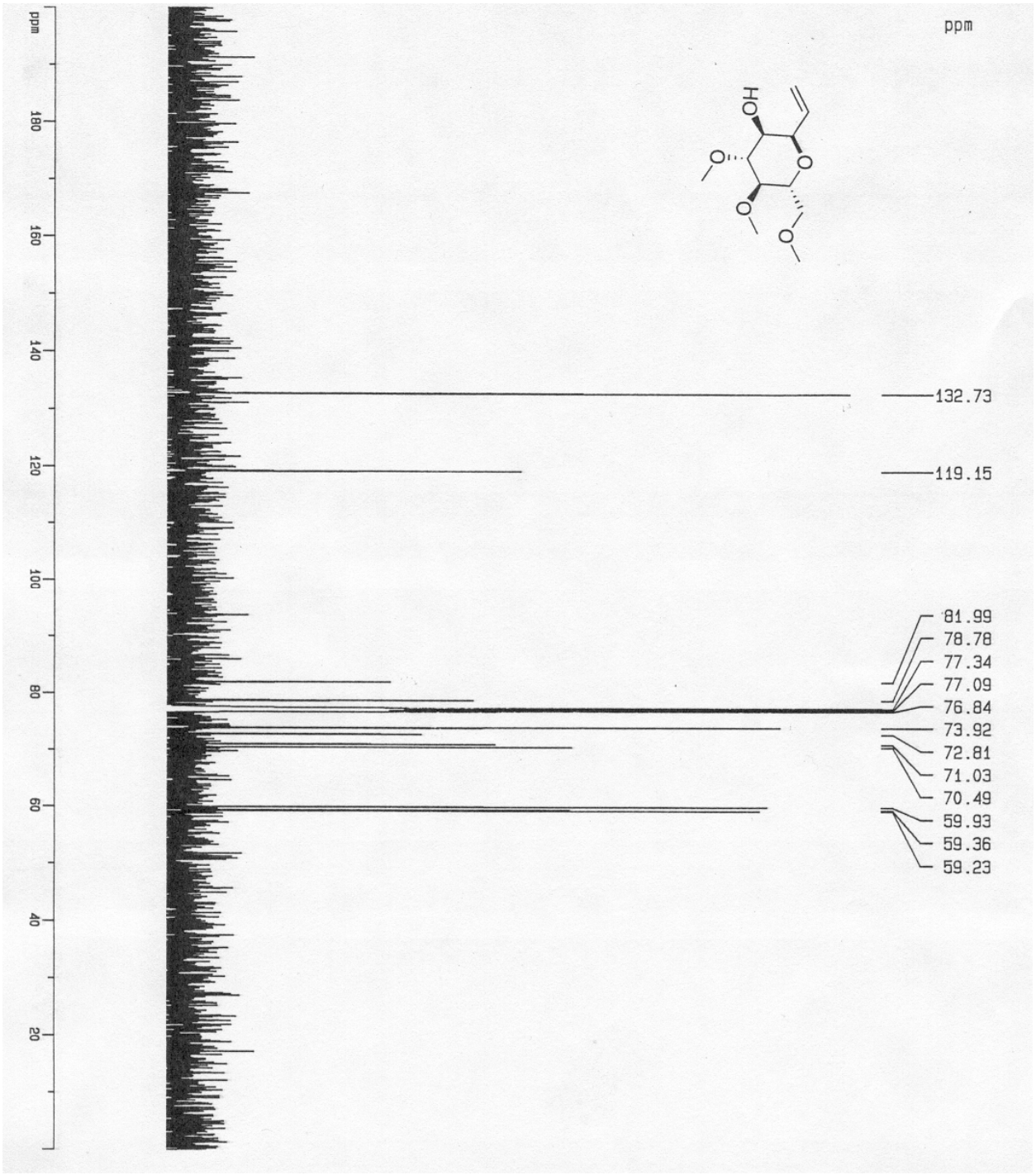

Integral
ppm
1.0112
1.0000
1.0189
1.1011
1.1918
1.3594
2.1815
1.4644
4.1318
6.3805
3.6177
7.59293
7.56736
7.40393
7.28829
7.27048
6.74783
5.92479
5.47807
5.46861
5.44463
5.43668
5.06361
5.04184
4.84169
4.81941
4.17661
4.16021
4.13772
4.12132
3.83576
3.82637
3.79665
3.78741
3.75729
3.74848
2.24022
2.21577
2.18940
1.83496
1.83106
1.81835
1.74162
1.73501
1.69862
1.68982
1.68178
1.65705
1.63130
1.34287
1.33148
1.31870
1.30799
1.29466
1.26120
0.92399
0.90143
0.87911

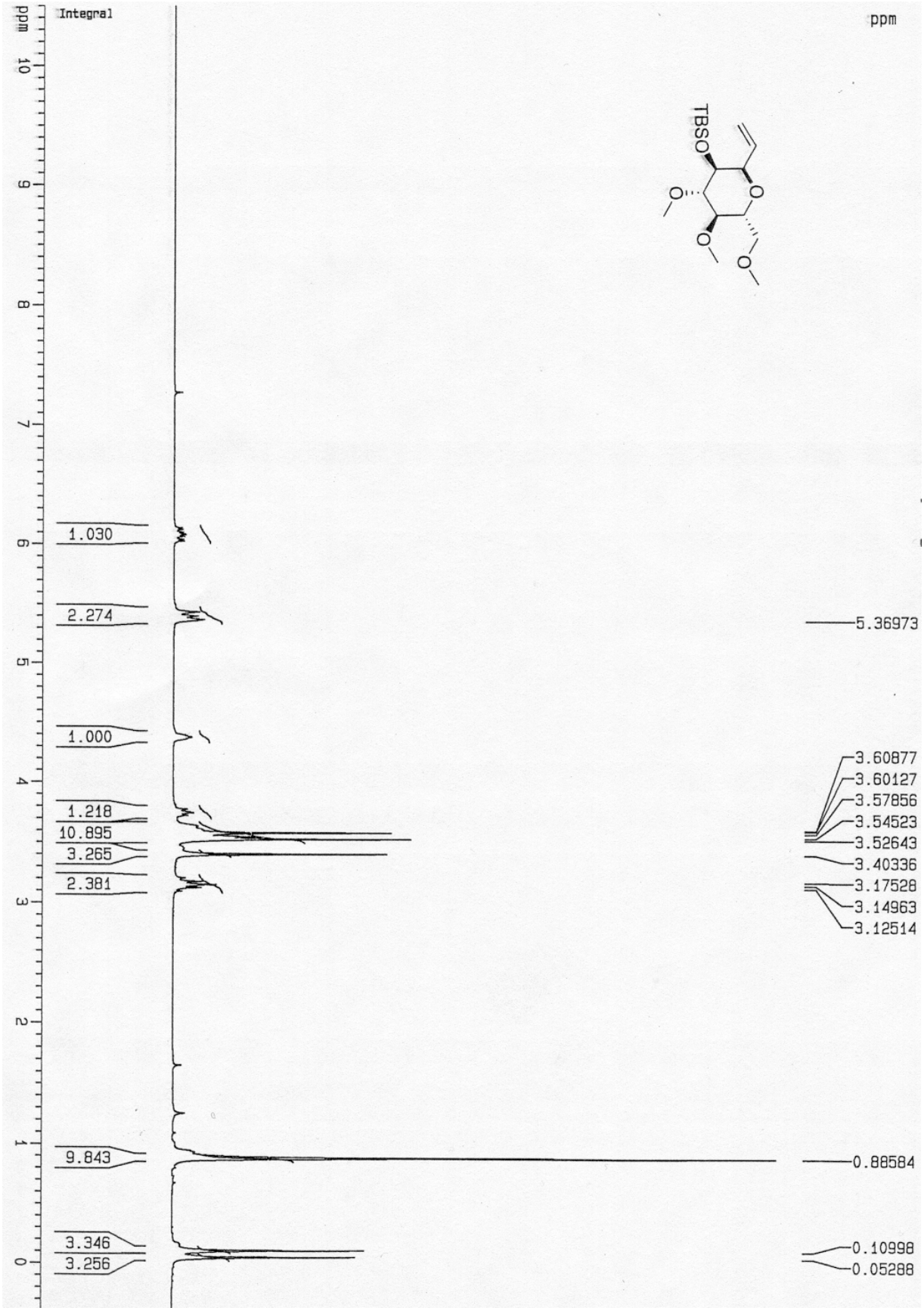

ppm
172.653
92.838
79.084
78.425
77.944
77.425
77.002
76.580
76.296
65.900
36.695
32.068
31.370
31.245
29.693
24.999
22.351
13.866
-5.110
ppm
180
160
140
120
100
80
60
40
20
0

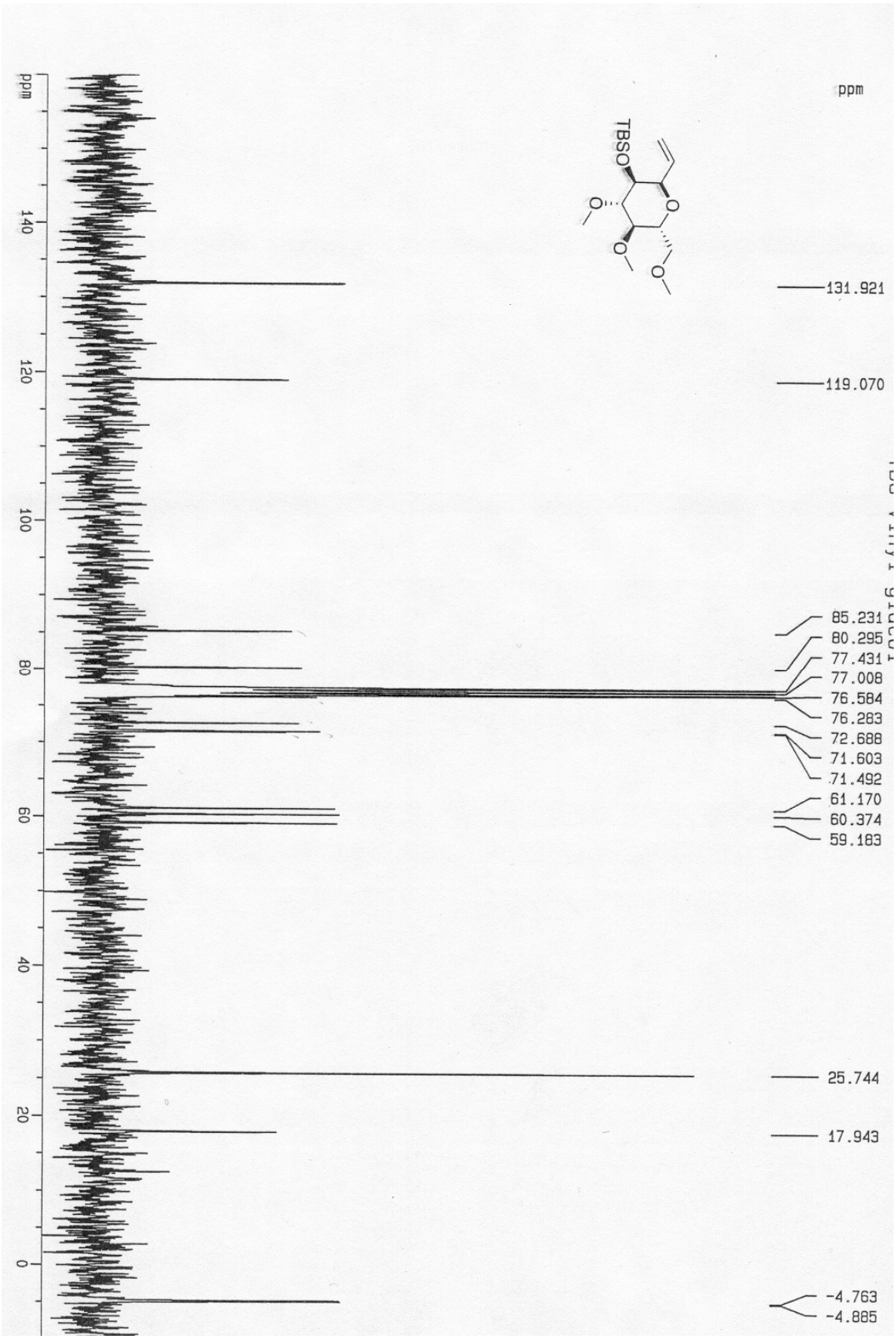
APPENDIX B

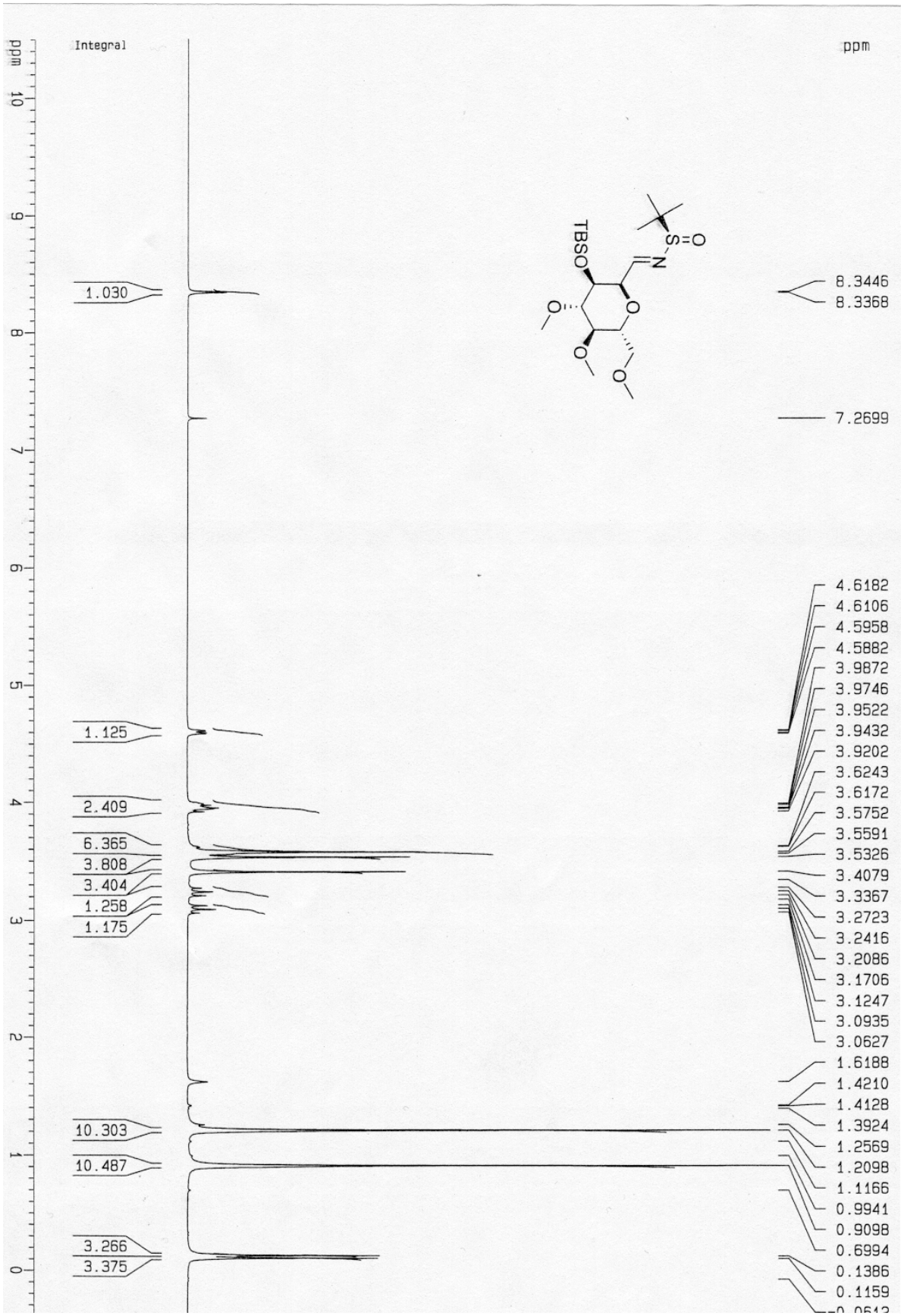
Efforts Toward the Total Synthesis of Mycalamide B
(Supporting Information)
(^{1}H and ^{13}C NMR Spectra)

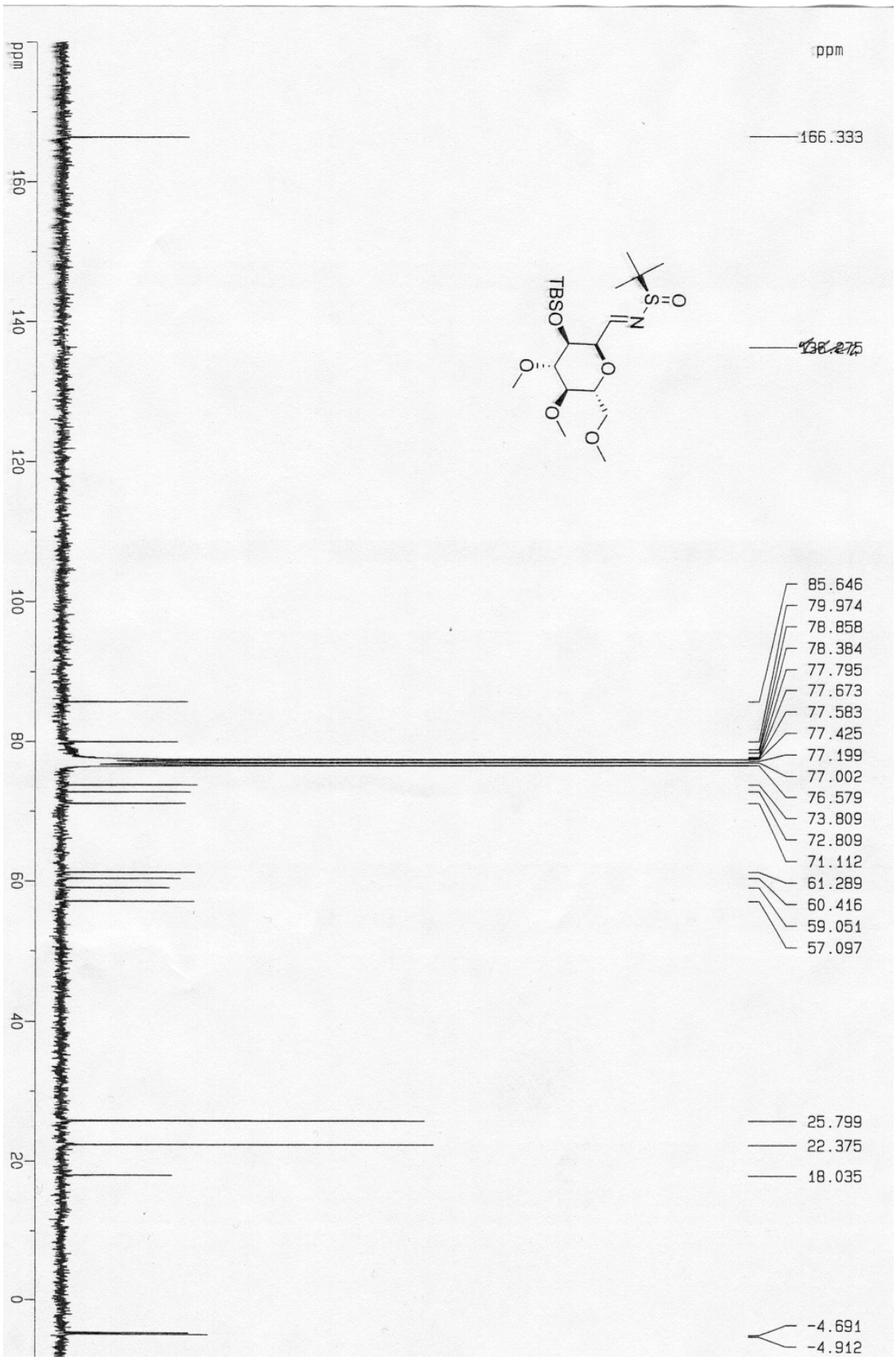

Integral
ppm
Hz
1.0000
2.0237
0.9137
1.1316
0.9364
5.3574
3.4165
3.6220
1.0354
0.9739
0.9475
OH
O
O
O
O
3636.00
3043.29
3037.79
3032.51
3026.59
3020.32
3015.07
3009.60
2725.10
2707.63
2695.05
2684.59
2235.42
2230.56
2225.52
1926.19
1922.68
1919.29
1860.97
1853.74
1817.27
1812.35
1807.05
1798.76
1794.52
1794.12
1750.16
1702.96
1680.13
1672.89
1665.54
1647.54
1640.50
1369.18
1363.40
1087.88
835.49
627.99

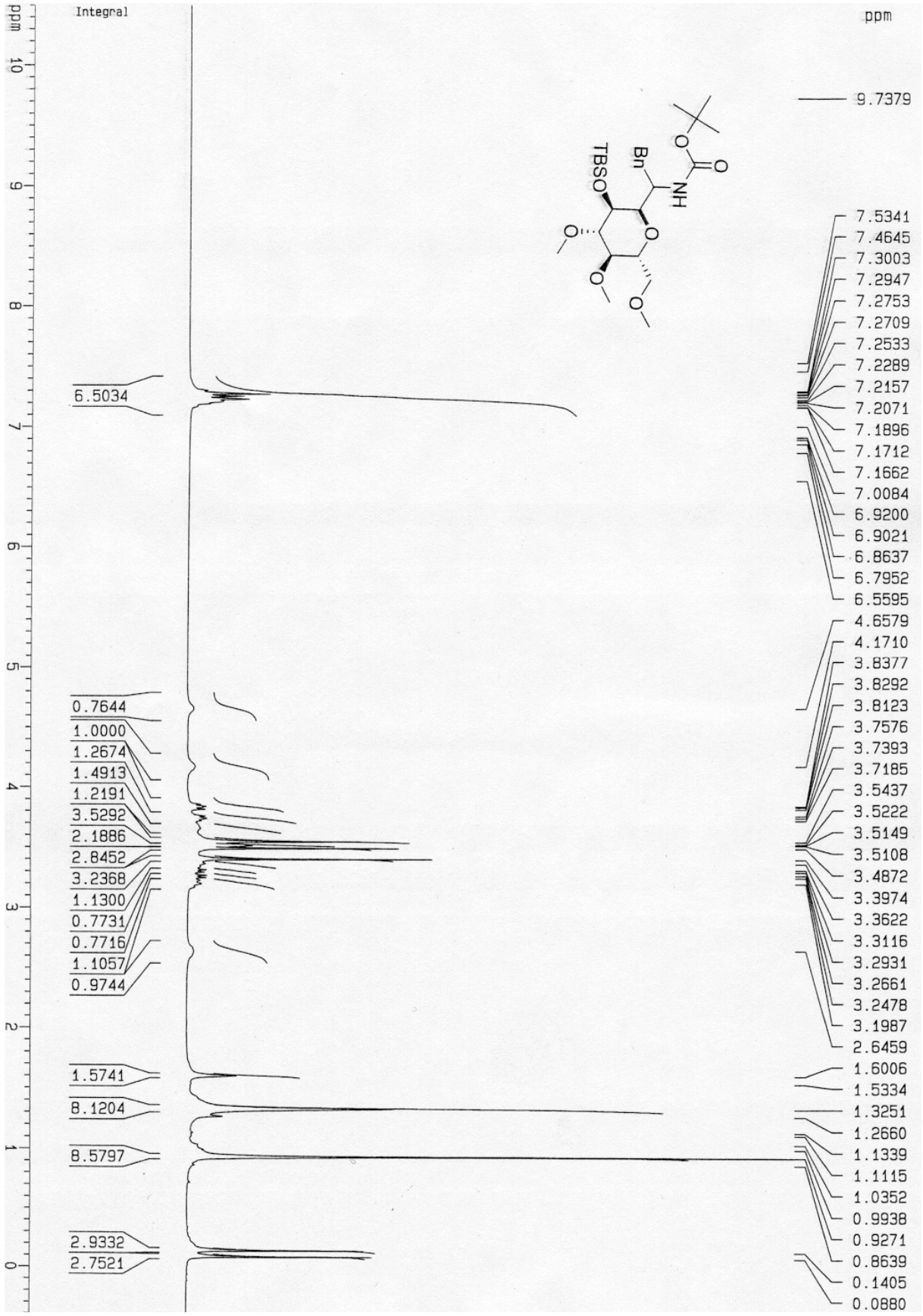

ppm
ppm
180
160
140
120
100
80
60
40
20
OH
O
O
O
O
132.73
119.15
81.99
78.78
77.34
77.09
76.84
73.92
72.81
71.03
70.49
59.93
59.36
59.23

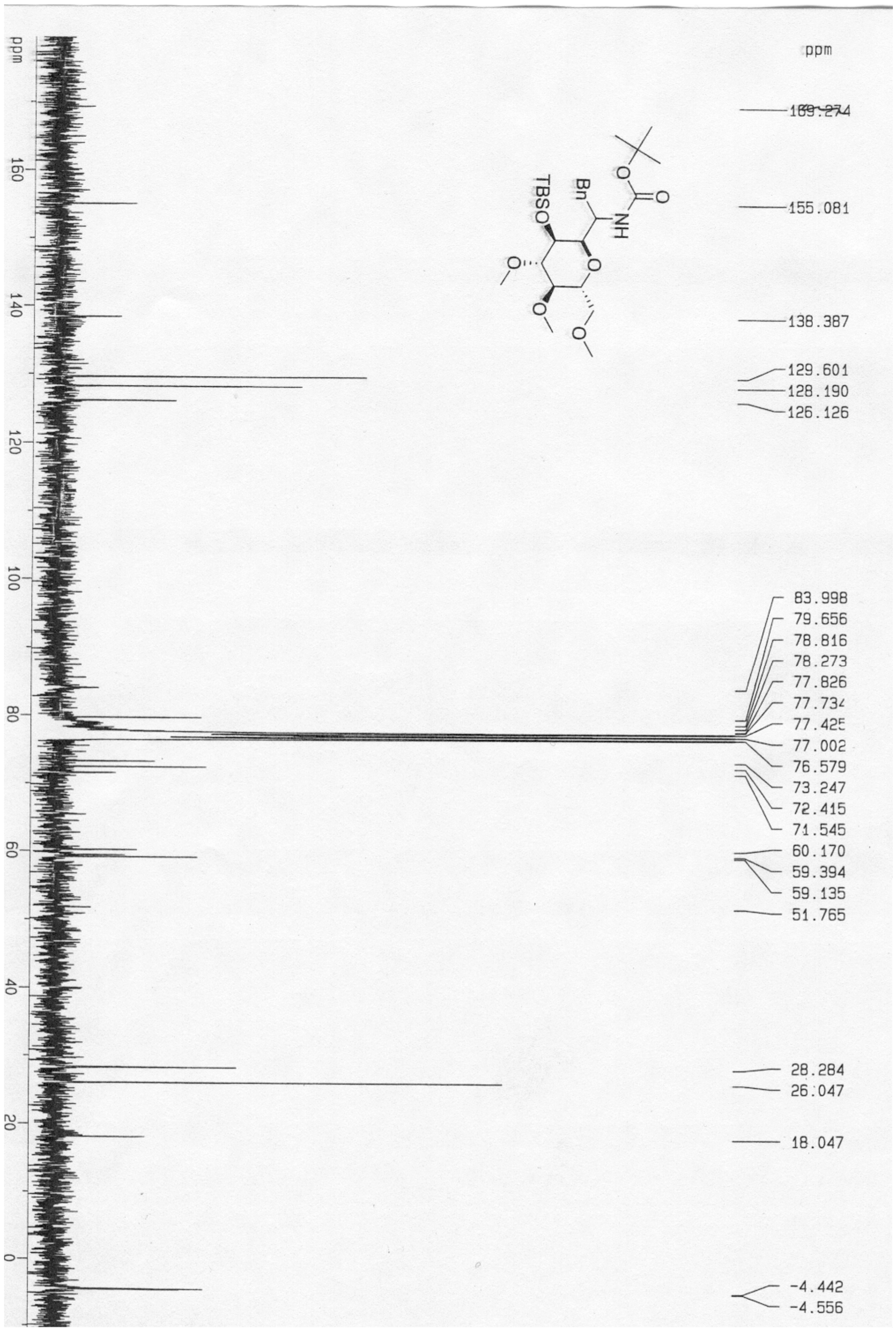

Integral
ppm
TBSO
1.030
2.274
1.000
1.218
10.895
3.265
2.381
9.843
3.346
3.256
5.36973
3.60877
3.60127
3.57856
3.54523
3.52643
3.40336
3.17528
3.14963
3.12514
0.88584
0.10998
0.05288

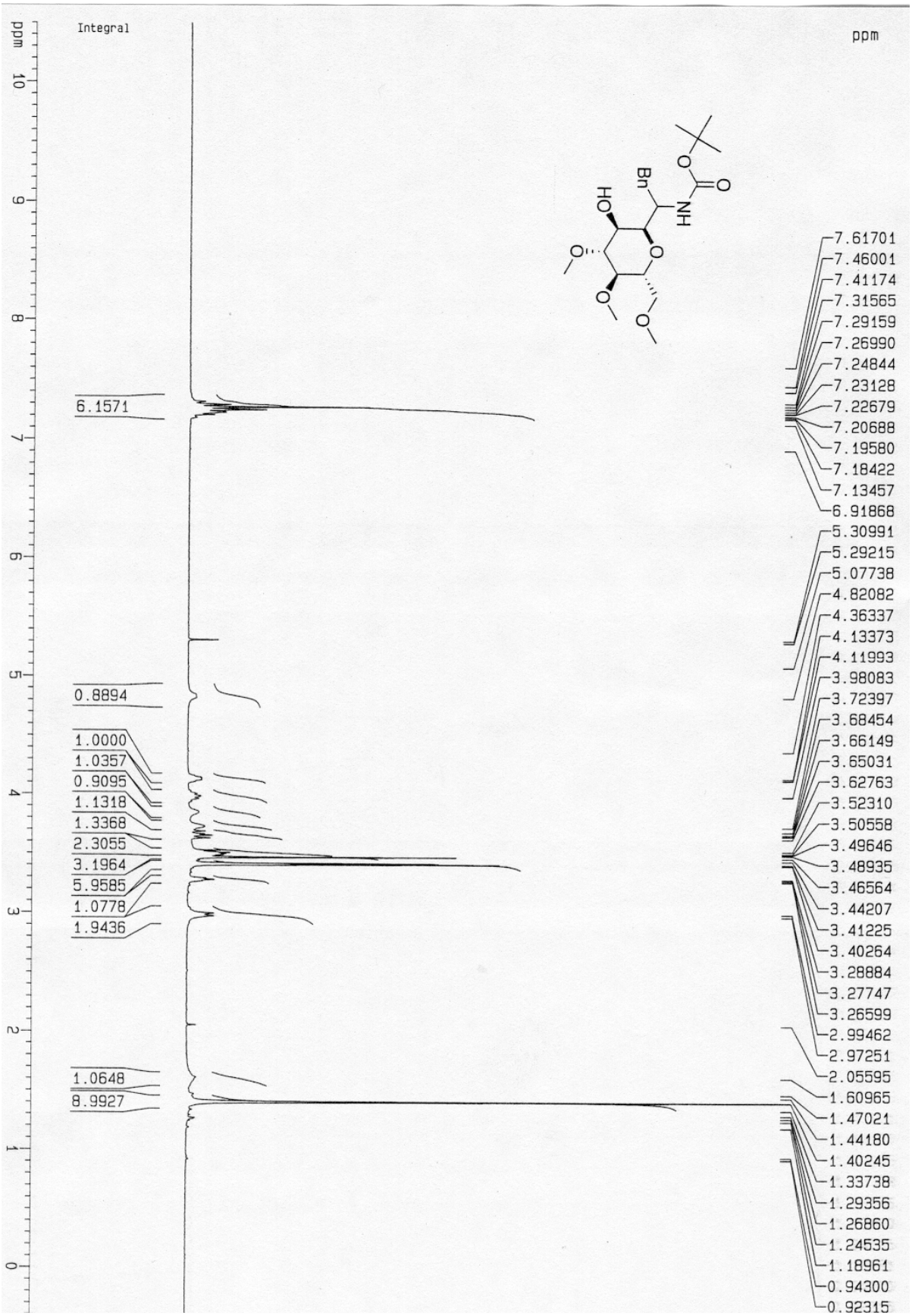

ppm
TBSO
O
O
O
O
131.921
119.070
85.231
80.295
77.431
77.008
76.584
76.283
72.688
71.603
71.492
61.170
60.374
59.183
25.744
17.943
-4.763
-4.885
ppm
140
120
100
80
60
40
20
0

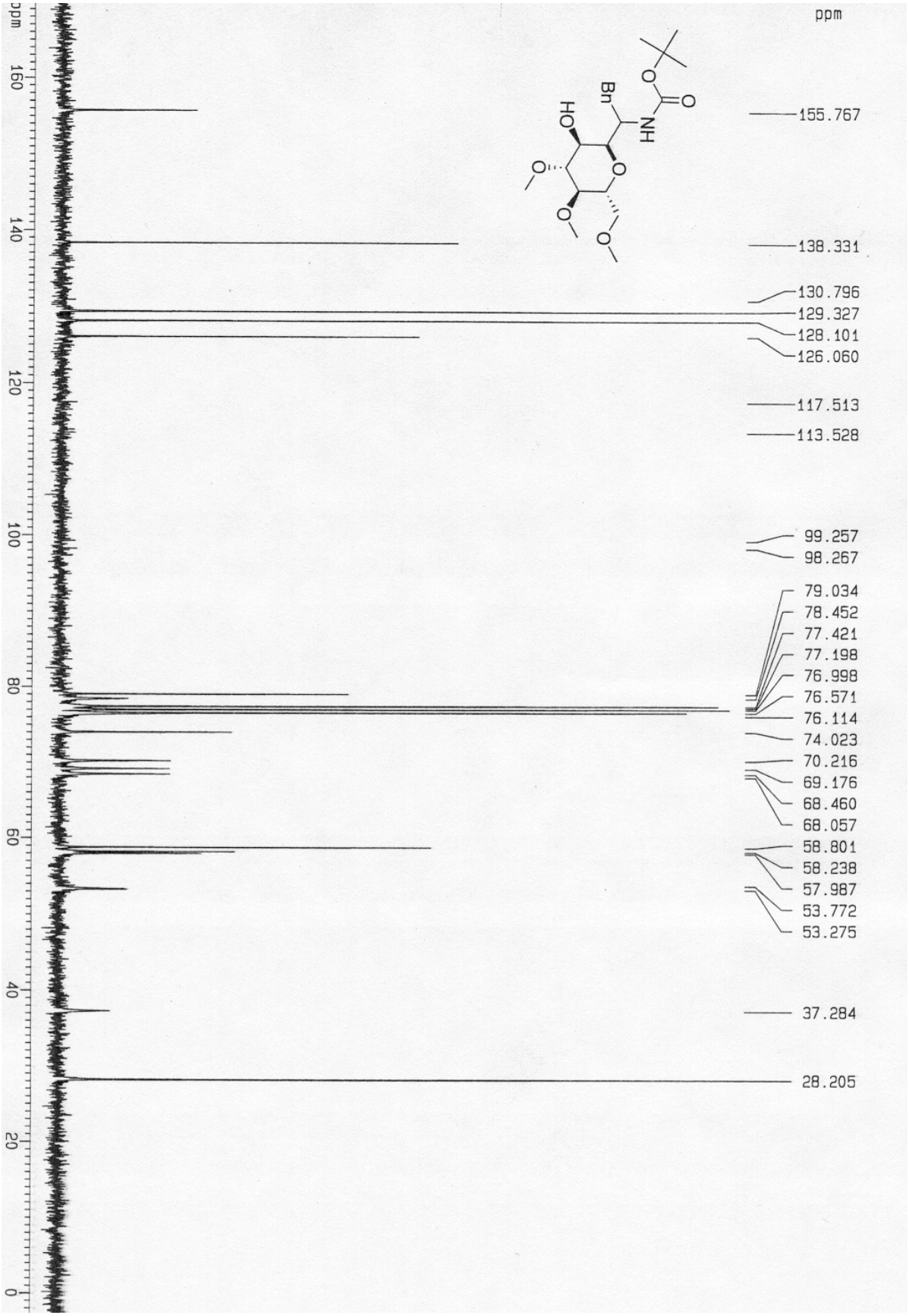

Integral
ppm
TBSO
S=O
N
O
O
O
O
1.030
1.125
2.409
6.365
3.808
3.404
1.258
1.175
10.303
10.487
3.266
3.375
8.3446
8.3368
7.2699
4.6182
4.6106
4.5958
4.5882
3.9872
3.9746
3.9522
3.9432
3.9202
3.6243
3.6172
3.5752
3.5591
3.5326
3.4079
3.3367
3.2723
3.2416
3.2086
3.1706
3.1247
3.0935
3.0627
1.6188
1.4210
1.4128
1.3924
1.2569
1.2098
1.1166
0.9941
0.9098
0.6994
0.1386
0.1159

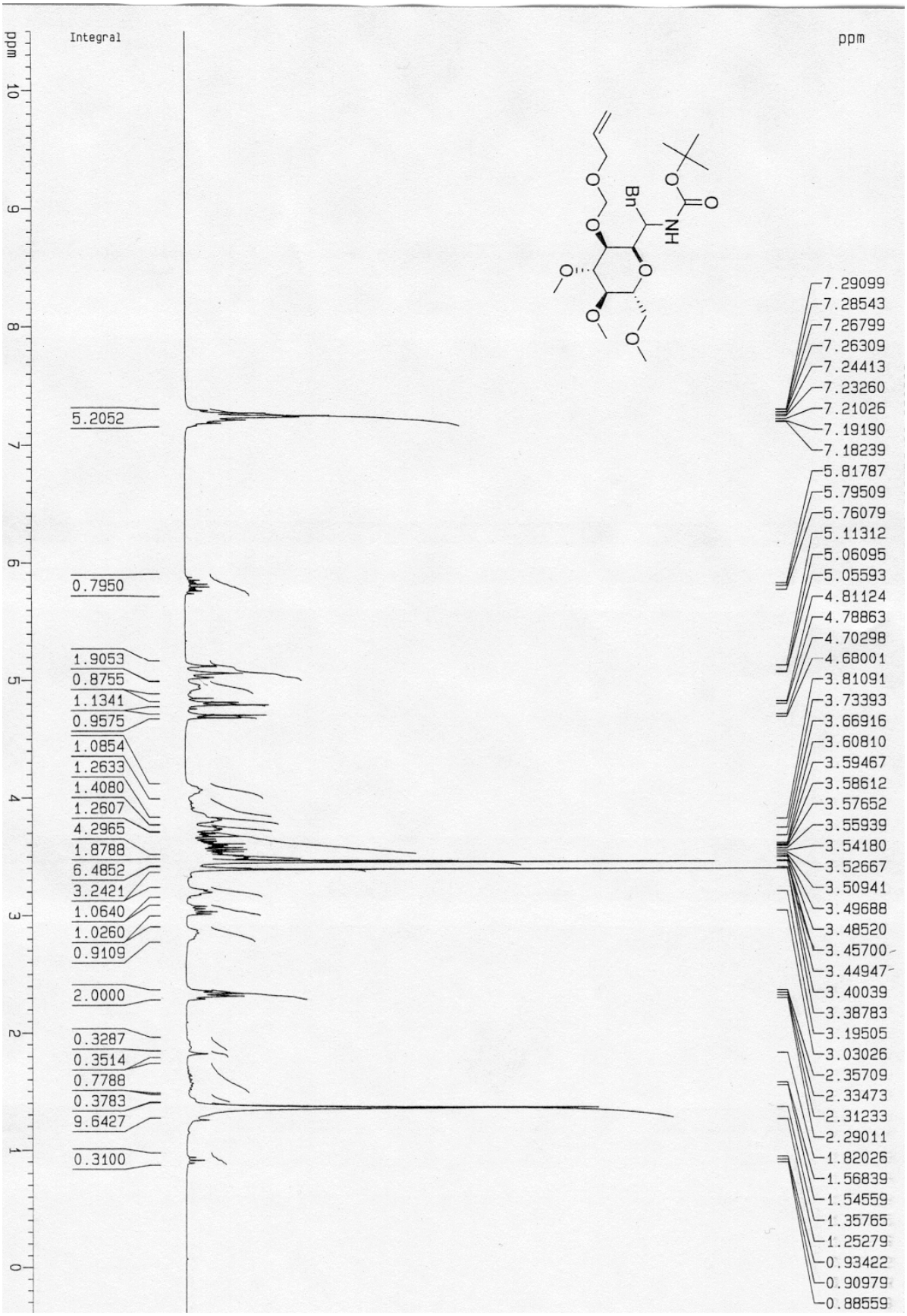

ppm
166.333
85.646
79.974
78.858
78.384
77.795
77.673
77.583
77.425
77.199
77.002
76.579
73.809
72.809
71.112
61.289
60.416
59.051
57.097
25.799
22.375
18.035
-4.691
-4.912
TBSO
O
N
S
O

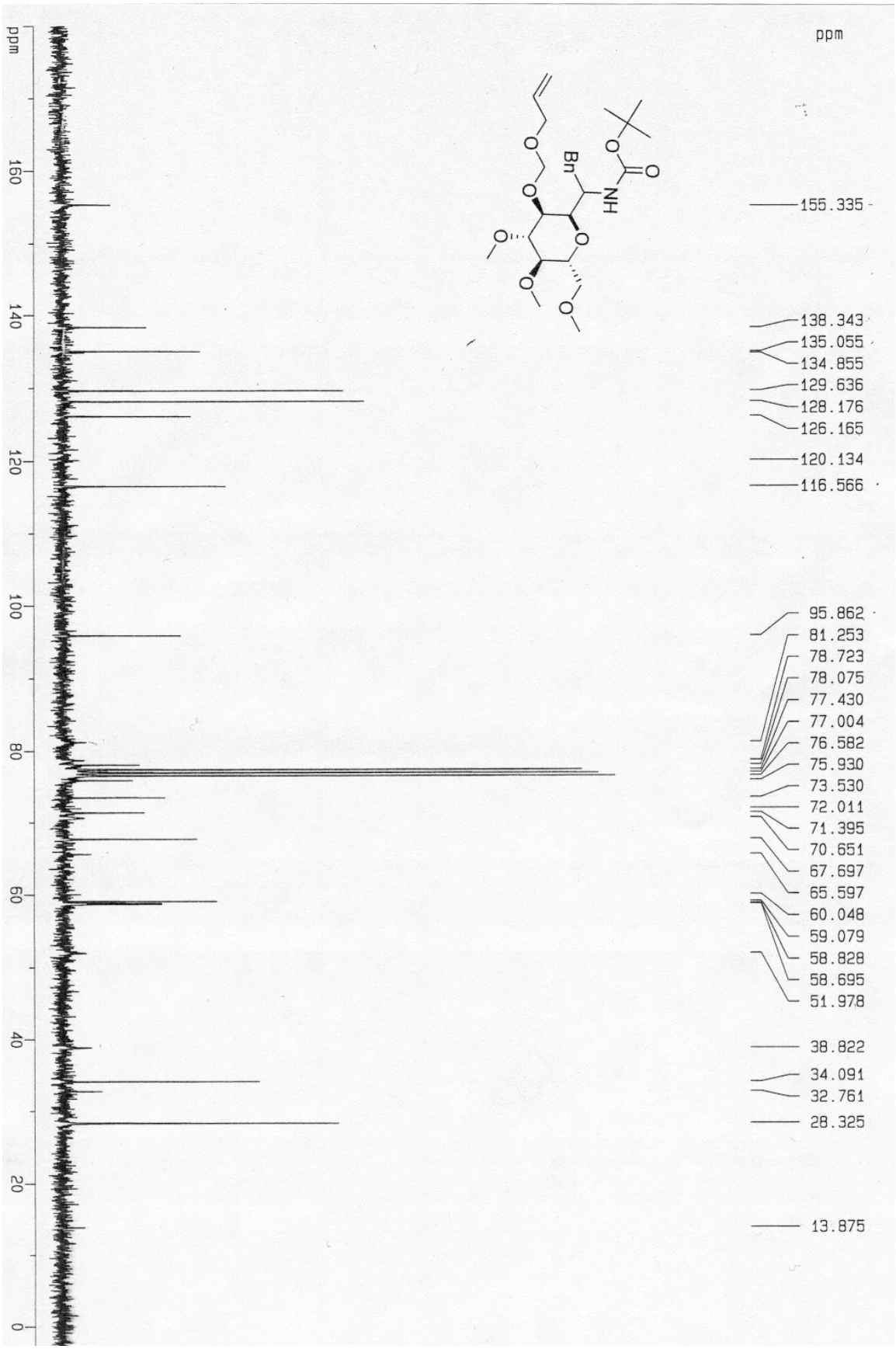

Integral
ppm
TBSO
Bn
NH
O
6.5034
0.7644
1.0000
1.2674
1.4913
1.2191
3.5292
2.1886
2.8452
3.2368
1.1300
0.7731
0.7716
1.1057
0.9744
1.5741
8.1204
8.5797
2.9332
2.7521
9.7379
7.5341
7.4645
7.3003
7.2947
7.2753
7.2709
7.2533
7.2289
7.2157
7.2071
7.1896
7.1712
7.1662
7.0084
6.9200
6.9021
6.8637
6.7952
6.5595
4.6579
4.1710
3.8377
3.8292
3.8123
3.7576
3.7393
3.7185
3.5437
3.5222
3.5149
3.5108
3.4872
3.3974
3.3622
3.3116
3.2931
3.2661
3.2478
3.1987
2.6459
1.6006
1.5334
1.3251
1.2660
1.1339
1.1115
1.0352
0.9938
0.9271
0.8639
0.1405
0.0880

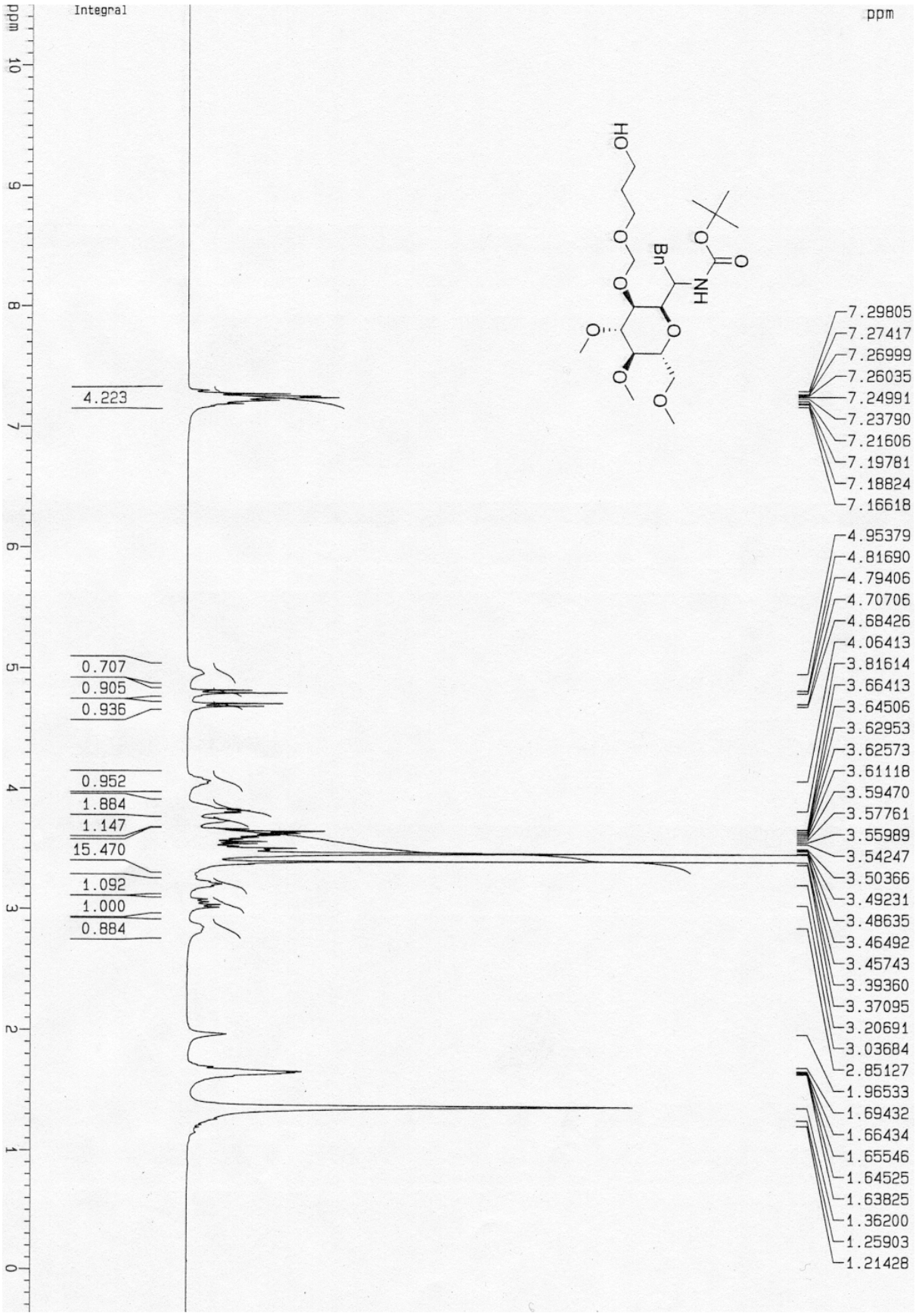

ppm
169.274
155.081
138.387
129.601
128.190
126.126
83.998
79.656
78.816
78.273
77.826
77.734
77.425
77.002
76.579
73.247
72.415
71.545
60.170
59.394
59.135
51.765
28.284
26.047
18.047
-4.442
-4.556
TBSO
Bn
NH
O
ppm
160
140
120
100
80
60
40
20
0

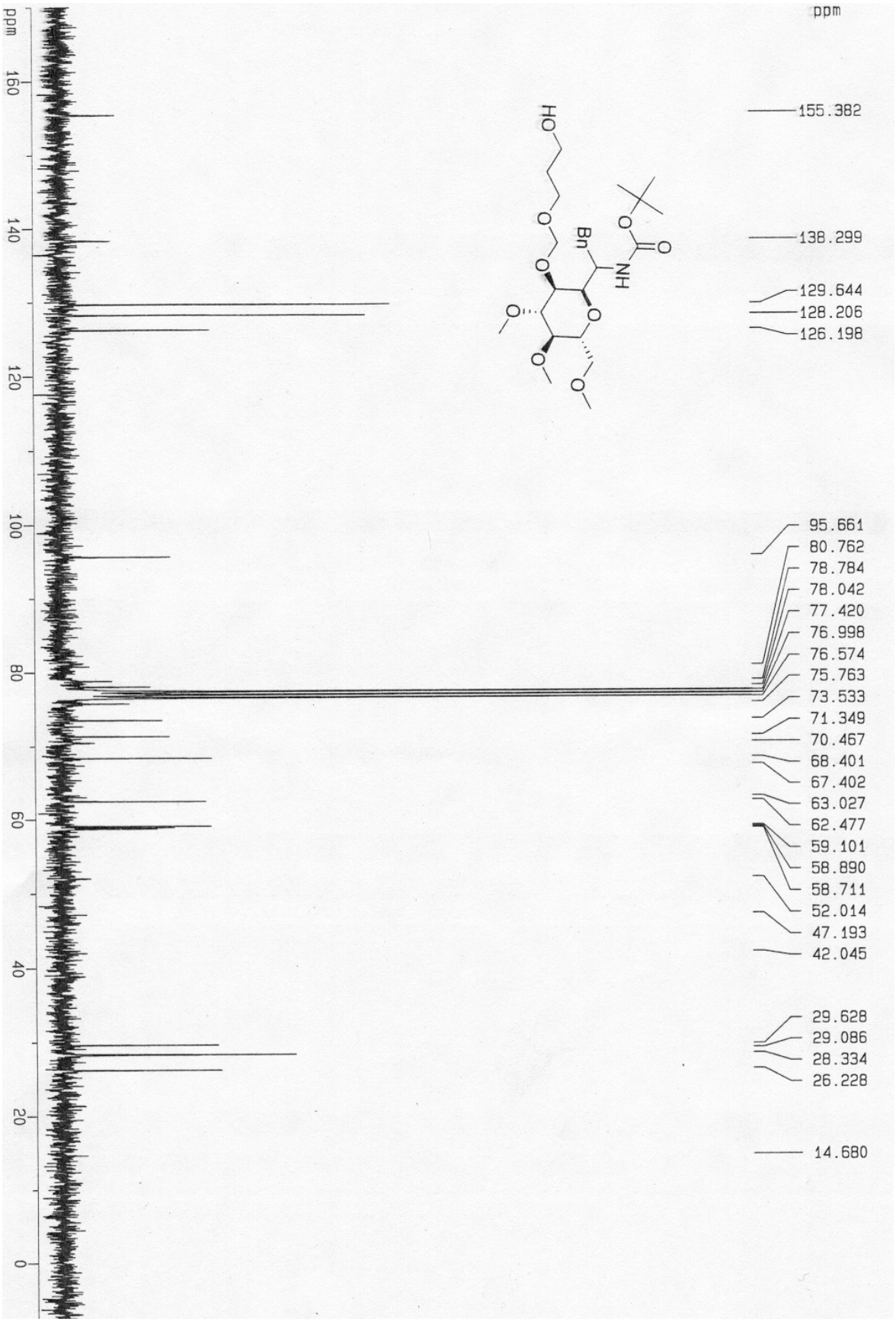

Integral
ppm
6.1571
0.8894
1.0000
1.0357
0.9095
1.1318
1.3368
2.3055
3.1964
5.9585
1.0778
1.9436
1.0648
8.9927
ppm
7.61701
7.46001
7.41174
7.31565
7.29159
7.26990
7.24844
7.23128
7.22679
7.20688
7.19580
7.18422
7.13457
6.91868
5.30991
5.29215
5.07738
4.82082
4.36337
4.13373
4.11993
3.98083
3.72397
3.68454
3.66149
3.65031
3.62763
3.52310
3.50558
3.49646
3.48935
3.46564
3.44207
3.41225
3.40264
3.28884
3.27747
3.26599
2.99462
2.97251
2.05595
1.60965
1.47021
1.44180
1.40245
1.33738
1.29356
1.26860
1.24535
1.18961
0.94300
0.92315
Bn
OH
NH
O

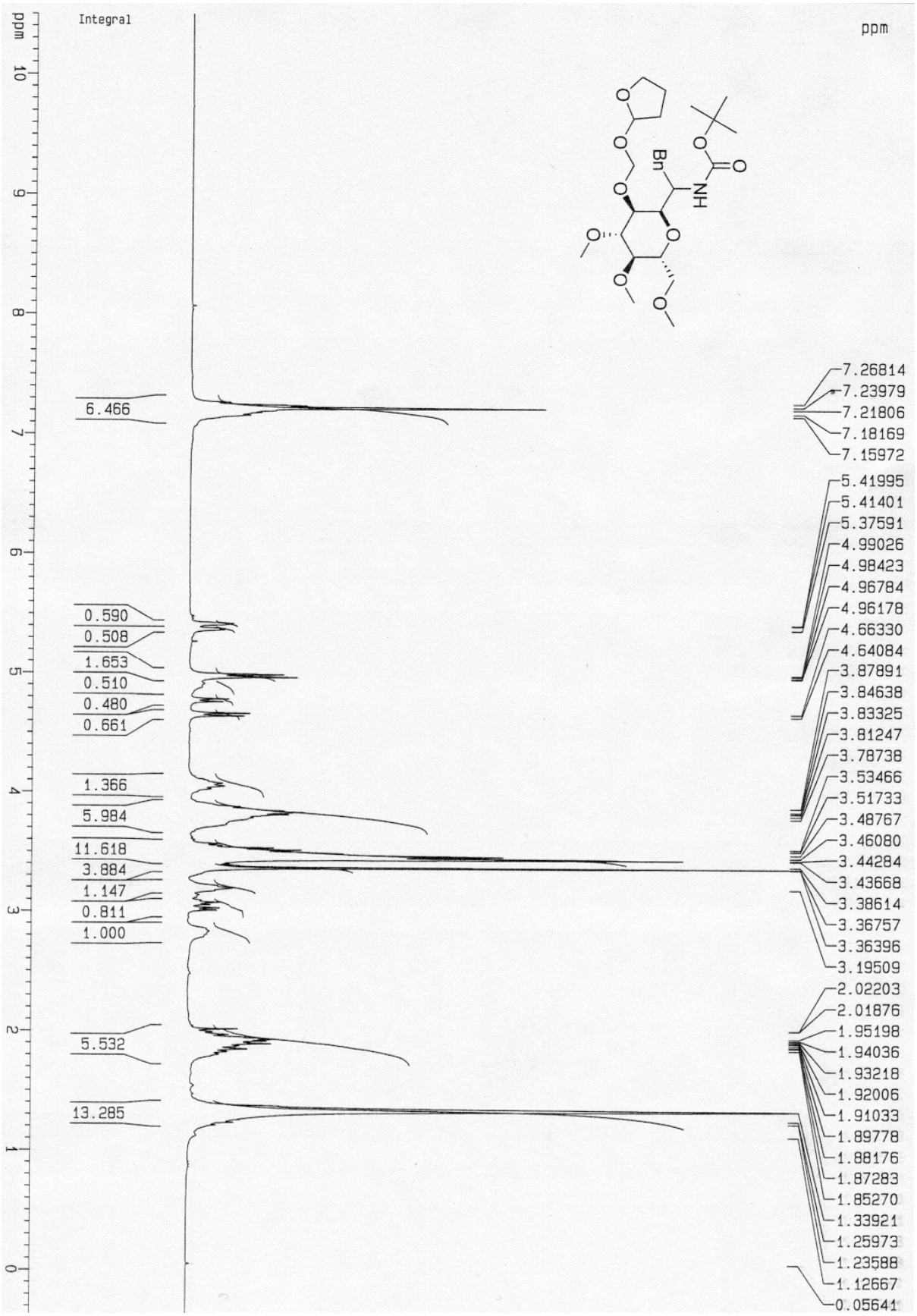

ppm
155.767
138.331
130.796
129.327
128.101
126.060
117.513
113.528
99.257
98.267
79.034
78.452
77.421
77.198
76.998
76.571
76.114
74.023
70.216
69.176
68.460
68.057
58.801
58.238
57.987
53.772
53.275
37.284
28.205
Bn
HO
NH
O

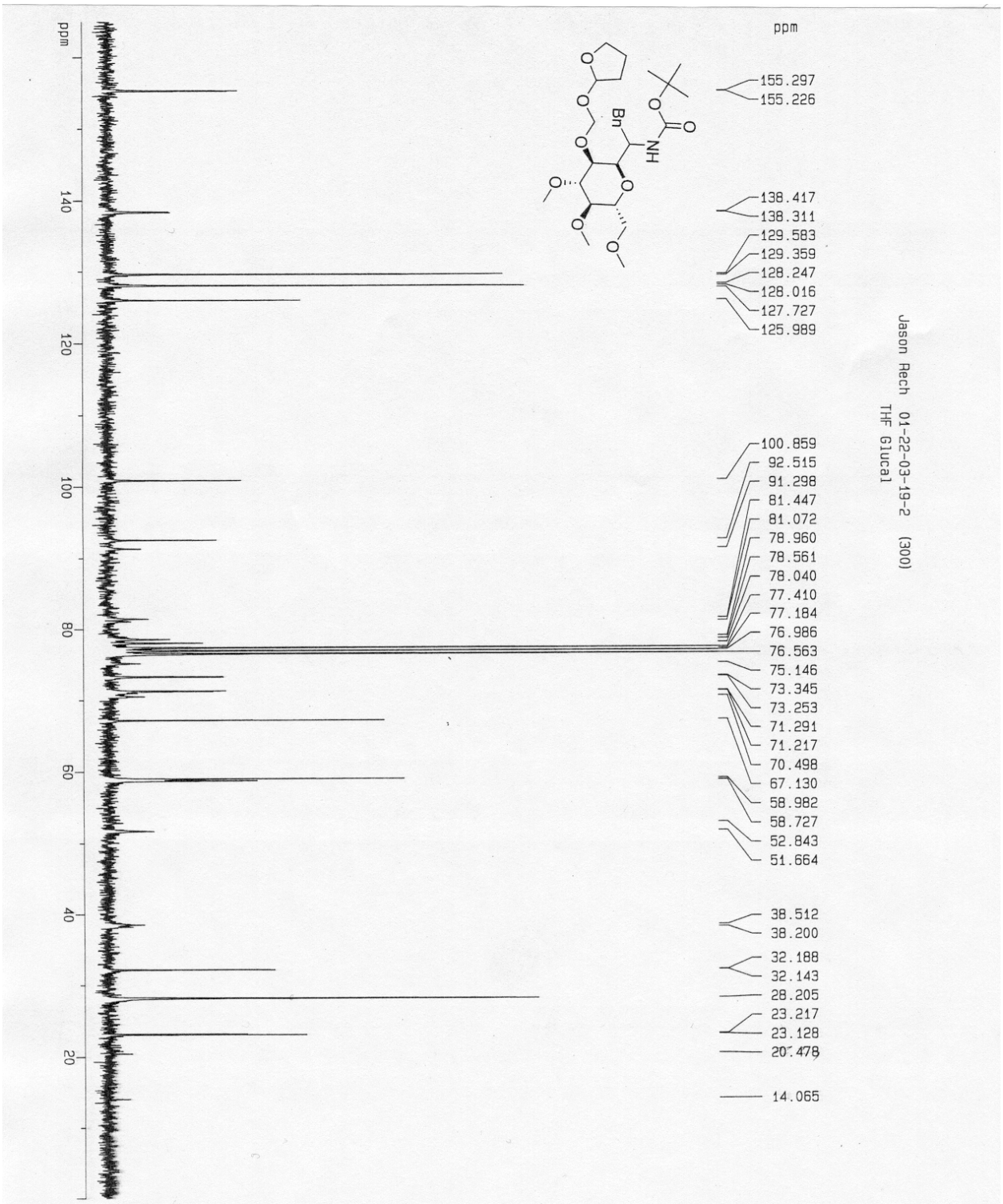

Integral
ppm
5.2052
0.7950
1.9053
0.8755
1.1341
0.9575
1.0854
1.2633
1.4080
1.2607
4.2965
1.8788
6.4852
3.2421
1.0640
1.0260
0.9109
2.0000
0.3287
0.3514
0.7788
0.3783
9.6427
0.3100
Bn
NH
O
7.29099
7.28543
7.26799
7.26309
7.24413
7.23260
7.21026
7.19190
7.18239
5.81787
5.79509
5.76079
5.11312
5.06095
5.05593
4.81124
4.78863
4.70298
4.68001
3.81091
3.73393
3.66916
3.60810
3.59467
3.58612
3.57652
3.55939
3.54180
3.52667
3.50941
3.49688
3.48520
3.45700
3.44947
3.40039
3.38783
3.19505
3.03026
2.35709
2.33473
2.31233
2.29011
1.82026
1.56839
1.54559
1.35765
1.25279
0.93422
0.90979
0.88559

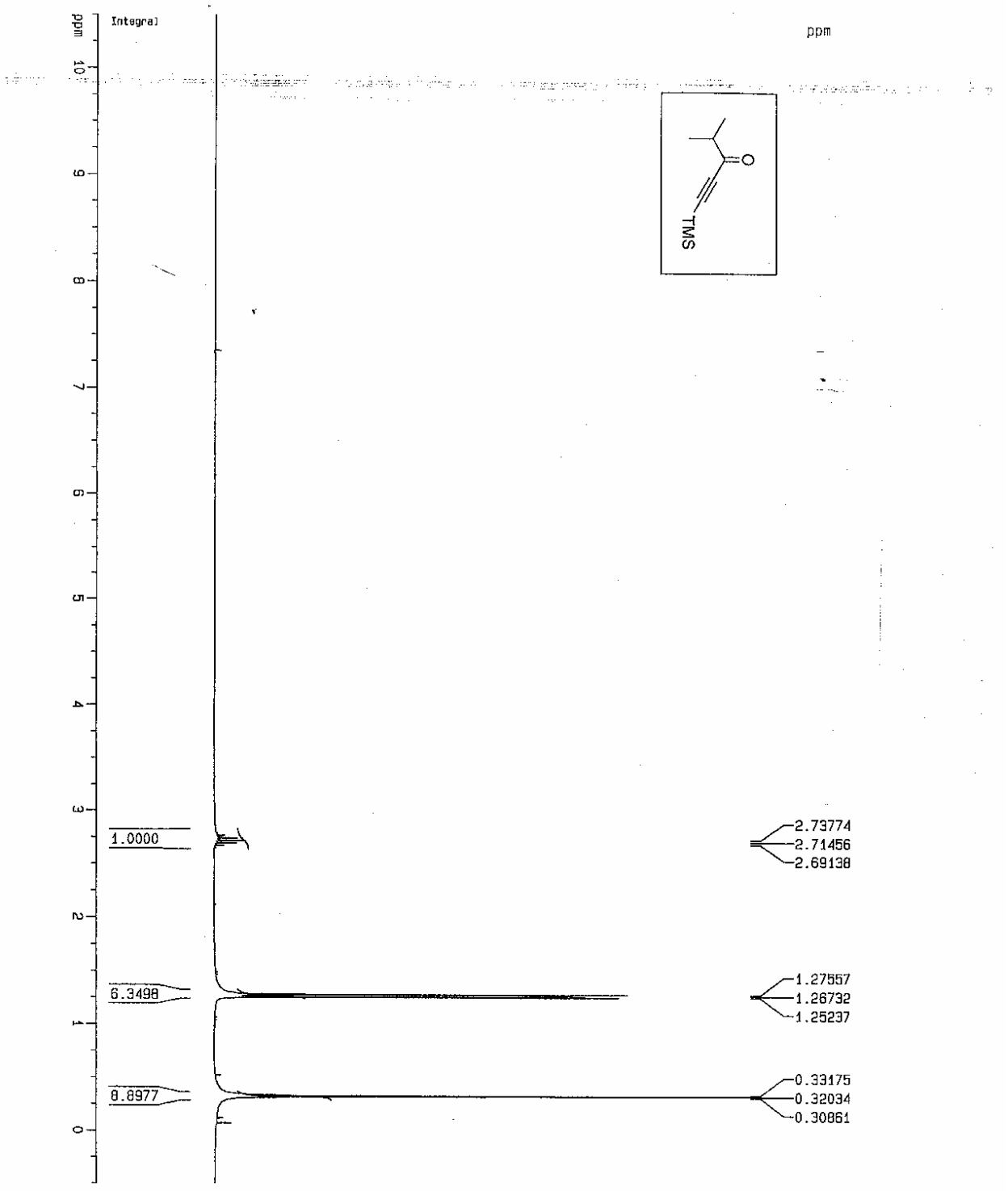

ppm
155.335
138.343
135.055
134.855
129.636
128.176
126.165
120.134
116.566
95.862
81.253
78.723
78.075
77.430
77.004
76.582
75.930
73.530
72.011
71.395
70.651
67.697
65.597
60.048
59.079
58.828
58.695
51.978
38.822
34.091
32.761
28.325
13.875
Bn
NH
O
ppm
160
140
120
100
80
60
40
20
0

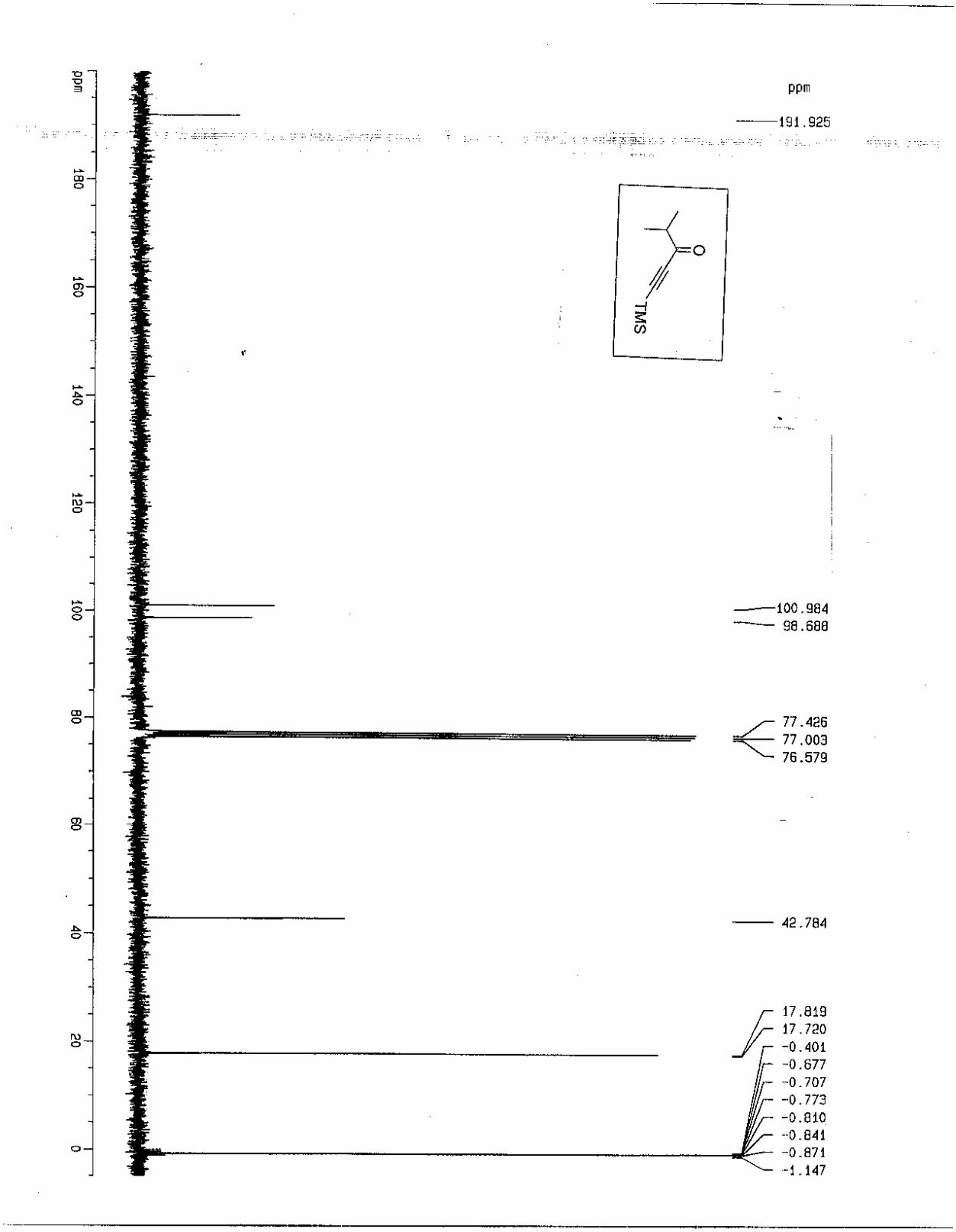

Integral
ppm
4.223
0.707
0.905
0.936
0.952
1.884
1.147
15.470
1.092
1.000
0.884
7.29805
7.27417
7.26999
7.26035
7.24991
7.23790
7.21606
7.19781
7.18824
7.16618
4.95379
4.81690
4.79406
4.70706
4.68426
4.06413
3.81614
3.66413
3.64506
3.62953
3.62573
3.61118
3.59470
3.57761
3.55989
3.54247
3.50366
3.49231
3.48635
3.46492
3.45743
3.39360
3.37095
3.20691
3.03684
2.85127
1.96533
1.69432
1.66434
1.65546
1.64525
1.63825
1.36200
1.25903
1.21428

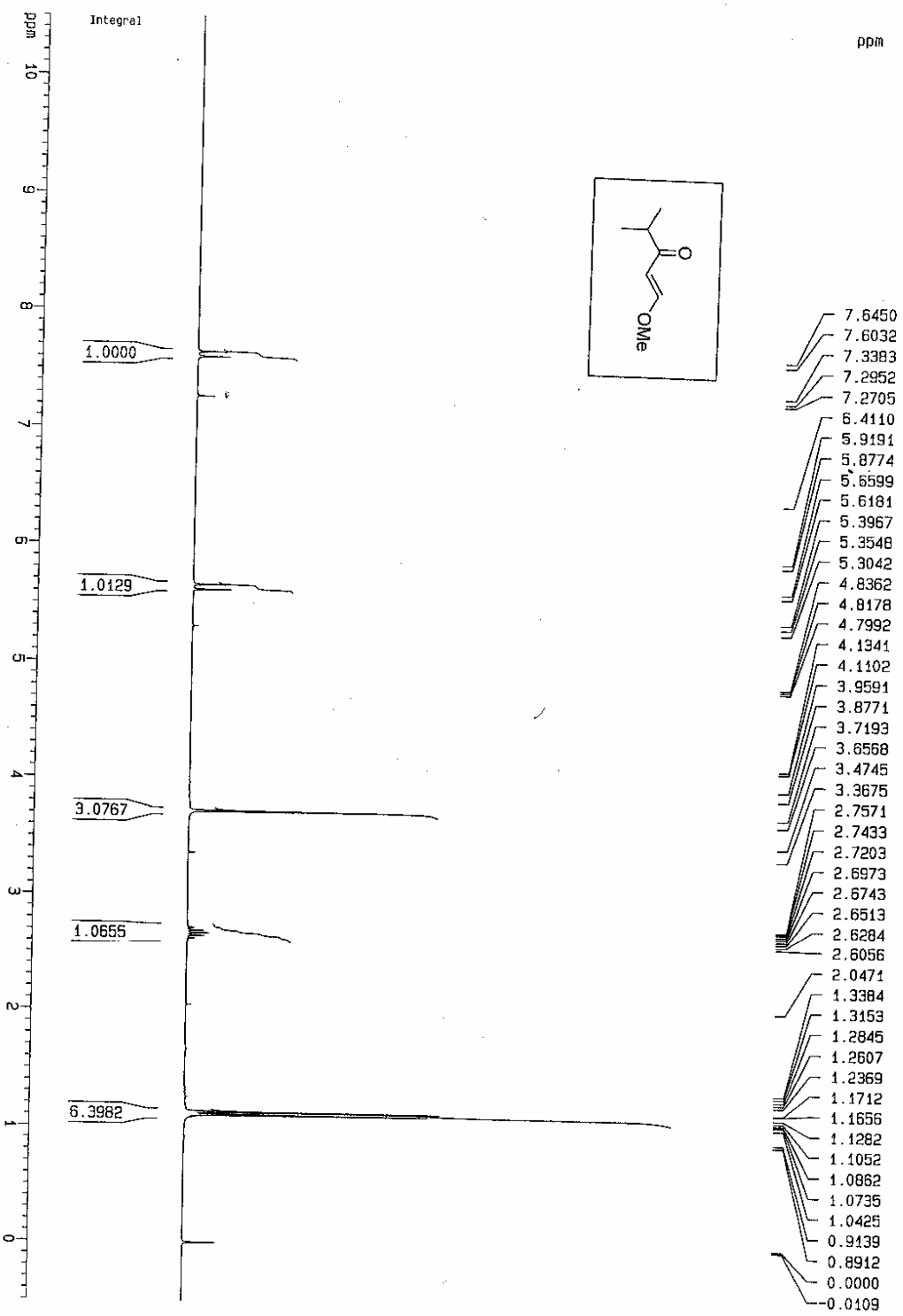

ppm
160
140
120
100
80
60
40
20
0
HO
Bn
NH
O
155.382
138.299
129.644
128.206
126.198
95.661
80.762
78.784
78.042
77.420
76.998
76.574
75.763
73.533
71.349
70.467
68.401
67.402
63.027
62.477
59.101
58.890
58.711
52.014
47.193
42.045
29.628
29.086
28.334
26.228
14.680

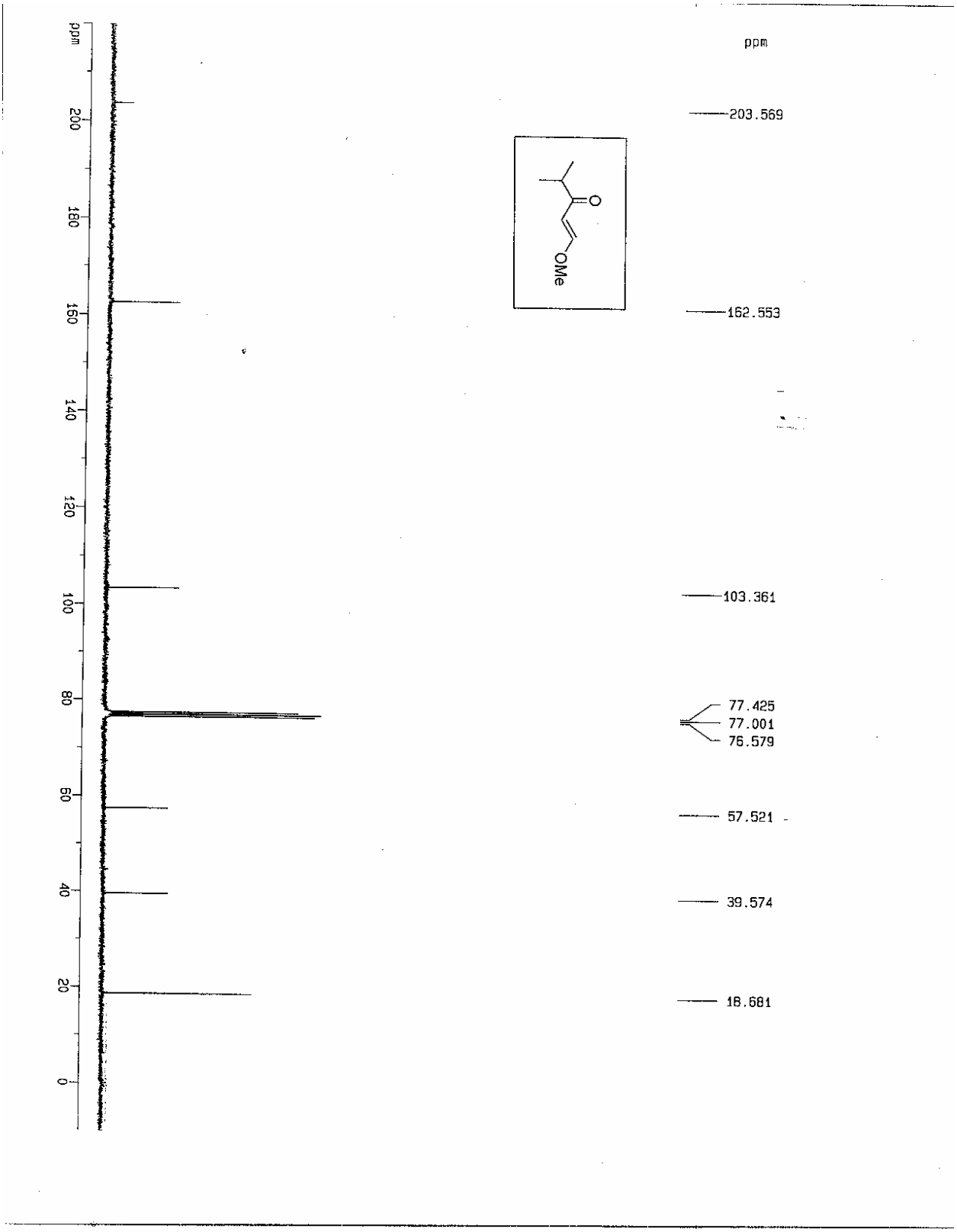

Integral
ppm
ppm
Bn
NH
6.466
0.590
0.508
1.653
0.510
0.480
0.661
1.366
5.984
11.618
3.884
1.147
0.811
1.000
5.532
13.285
7.26814
7.23979
7.21806
7.18169
7.15972
5.41995
5.41401
5.37591
4.99026
4.98423
4.96784
4.96178
4.66330
4.64084
3.87891
3.84638
3.83325
3.81247
3.78738
3.53466
3.51733
3.48767
3.46080
3.44284
3.43668
3.38614
3.36757
3.36396
3.19509
2.02203
2.01876
1.95198
1.94036
1.93218
1.92006
1.91033
1.89778
1.88176
1.87283
1.85270
1.33921
1.25973
1.23588
1.12667
0.05641

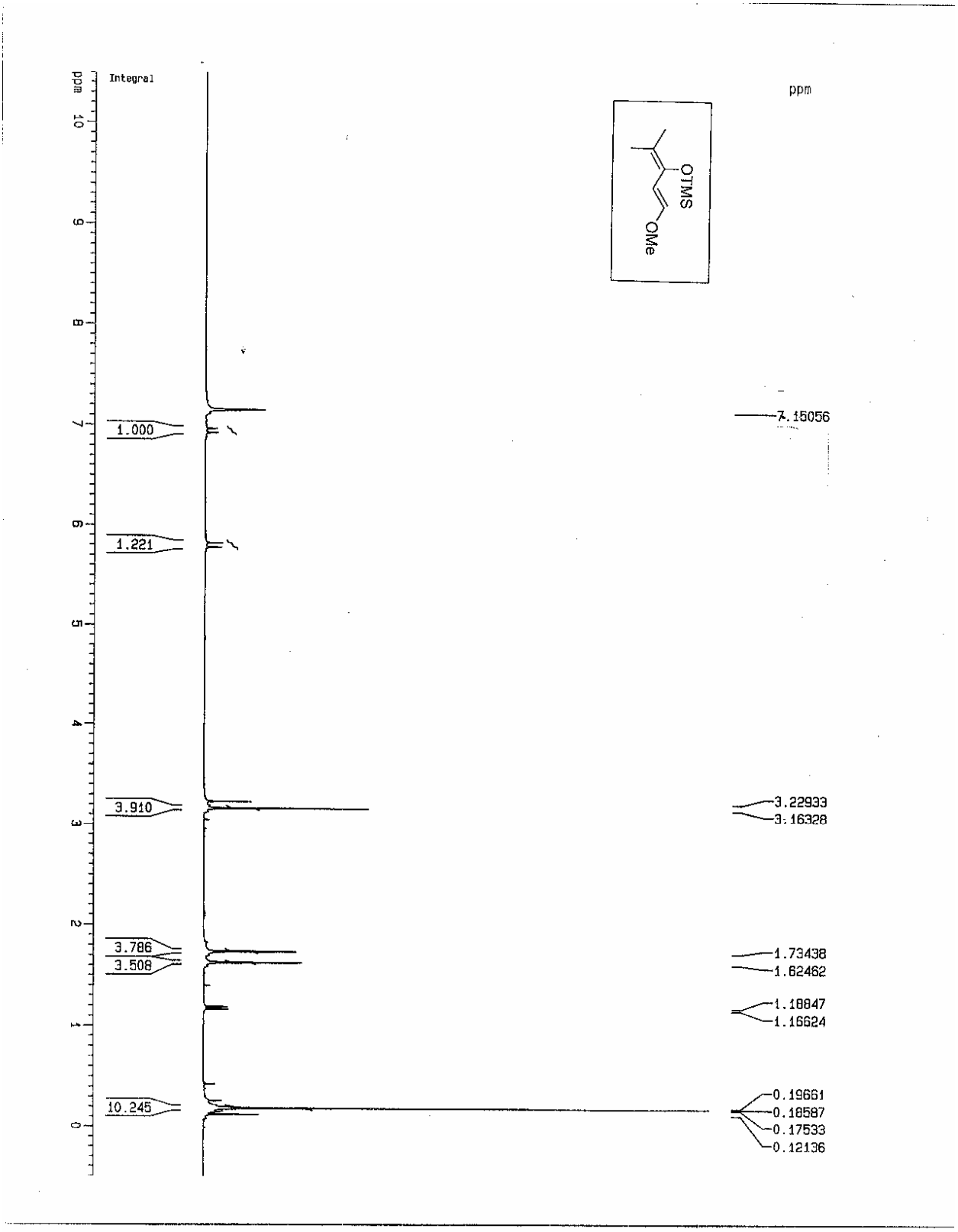

ppm
155.297
155.226
138.417
138.311
129.583
129.359
128.247
128.016
127.727
125.989
100.859
92.515
91.298
81.447
81.072
78.960
78.561
78.040
77.410
77.184
76.986
76.563
75.146
73.345
73.253
71.291
71.217
70.498
67.130
58.982
58.727
52.843
51.664
38.512
38.200
32.188
32.143
28.205
23.217
23.128
20.478
14.065
Bn
NH
Jason Rech 01-22-03-19-2 (300)
THF Glucal

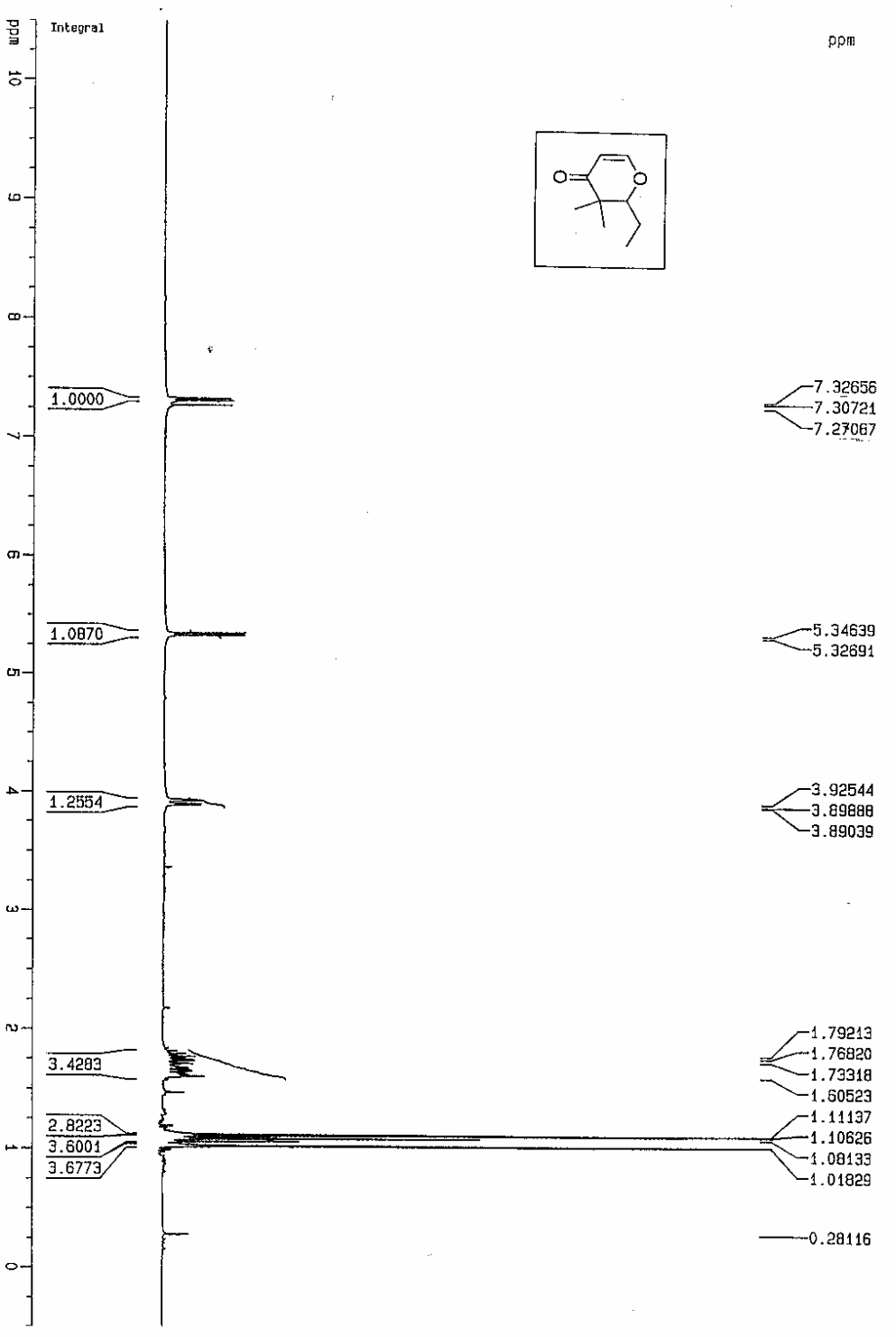

Integral
ppm
TMS
1.0000
6.3498
8.8977
2.73774
2.71456
2.69138
1.27557
1.26732
1.25237
0.33175
0.32034
0.30861

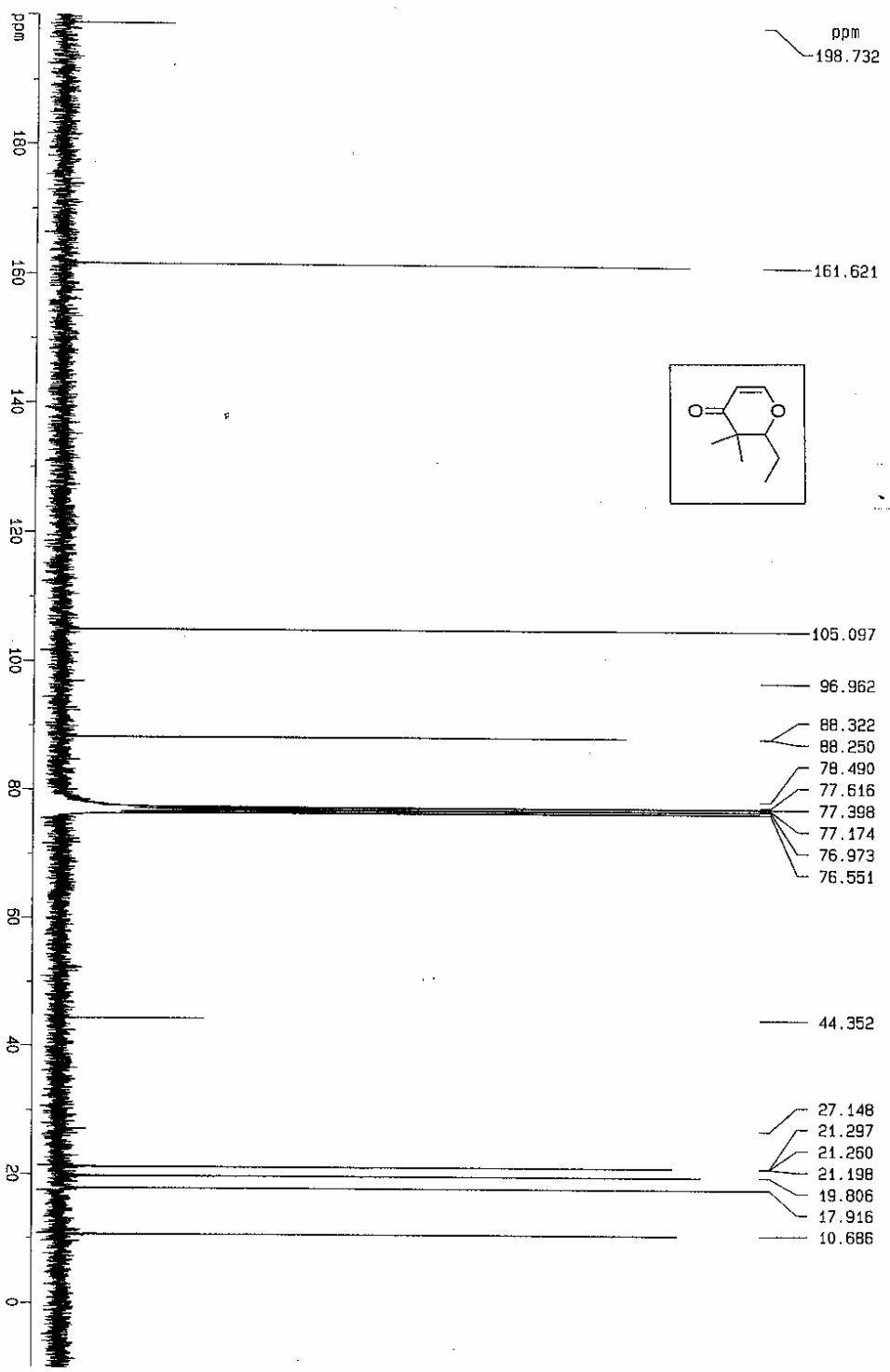

ppm
191.925
100.984
98.688
77.426
77.003
76.579
42.784
17.819
17.720
-0.401
-0.677
-0.707
-0.773
-0.810
-0.841
-0.871
-1.147
TMS
O
ppm
180
160
140
120
100
80
60
40
20
0

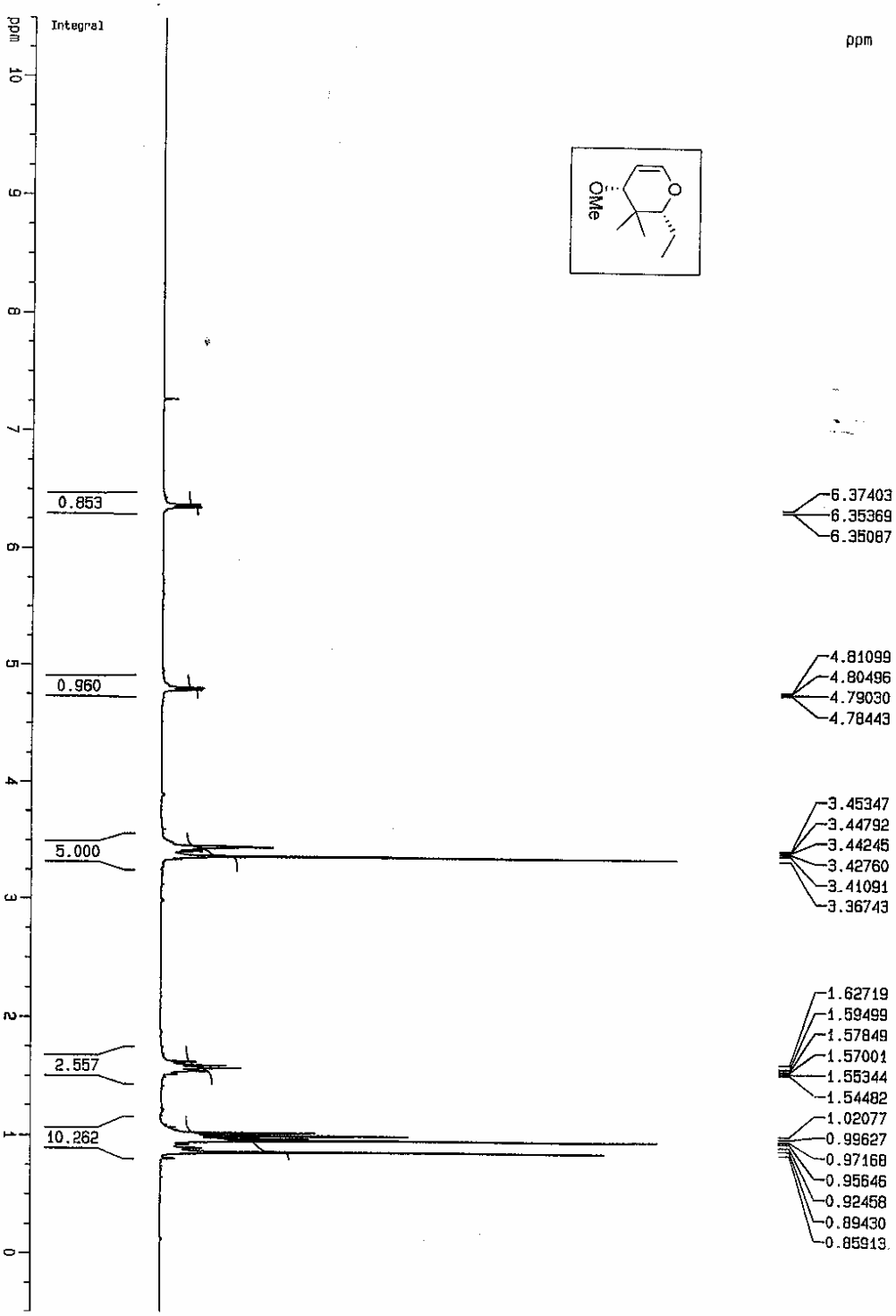

Integral
ppm
1.0000
1.0129
3.0767
1.0655
6.3982
OMe
ppm
7.6450
7.6032
7.3383
7.2952
7.2705
6.4110
5.9191
5.8774
5.6599
5.6181
5.3967
5.3548
5.3042
4.8362
4.8178
4.7992
4.1341
4.1102
3.9591
3.8771
3.7193
3.6568
3.4745
3.3675
2.7571
2.7433
2.7203
2.6973
2.6743
2.6513
2.6284
2.6056
2.0471
1.3384
1.3153
1.2845
1.2607
1.2369
1.1712
1.1656
1.1282
1.1052
1.0862
1.0735
1.0425
0.9139
0.8912
0.0000
-0.0109

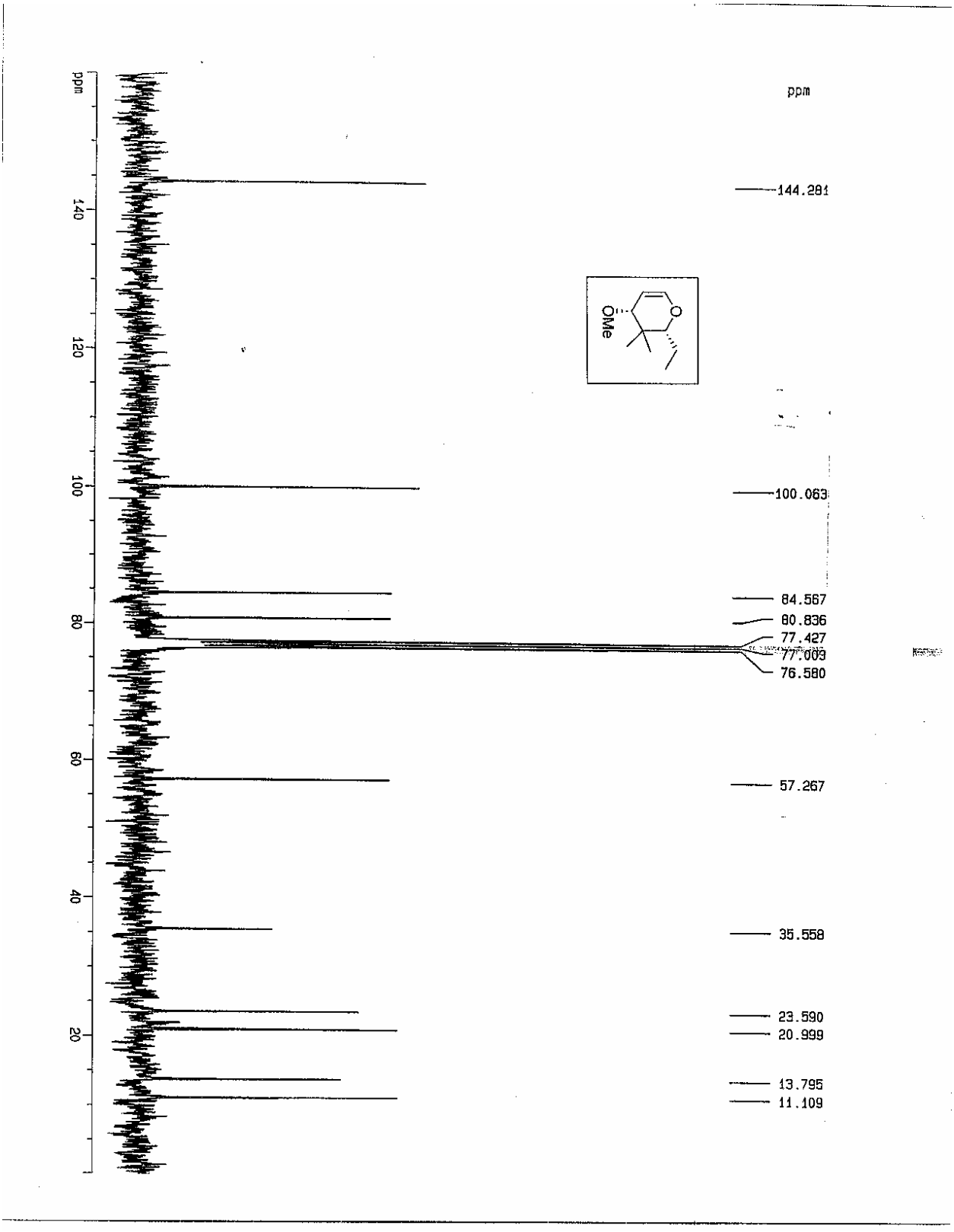

ppm
203.569
162.553
103.361
77.425
77.001
76.579
57.521
39.574
18.681
OMe
O
ppm
200
180
160
140
120
100
80
60
40
20
0

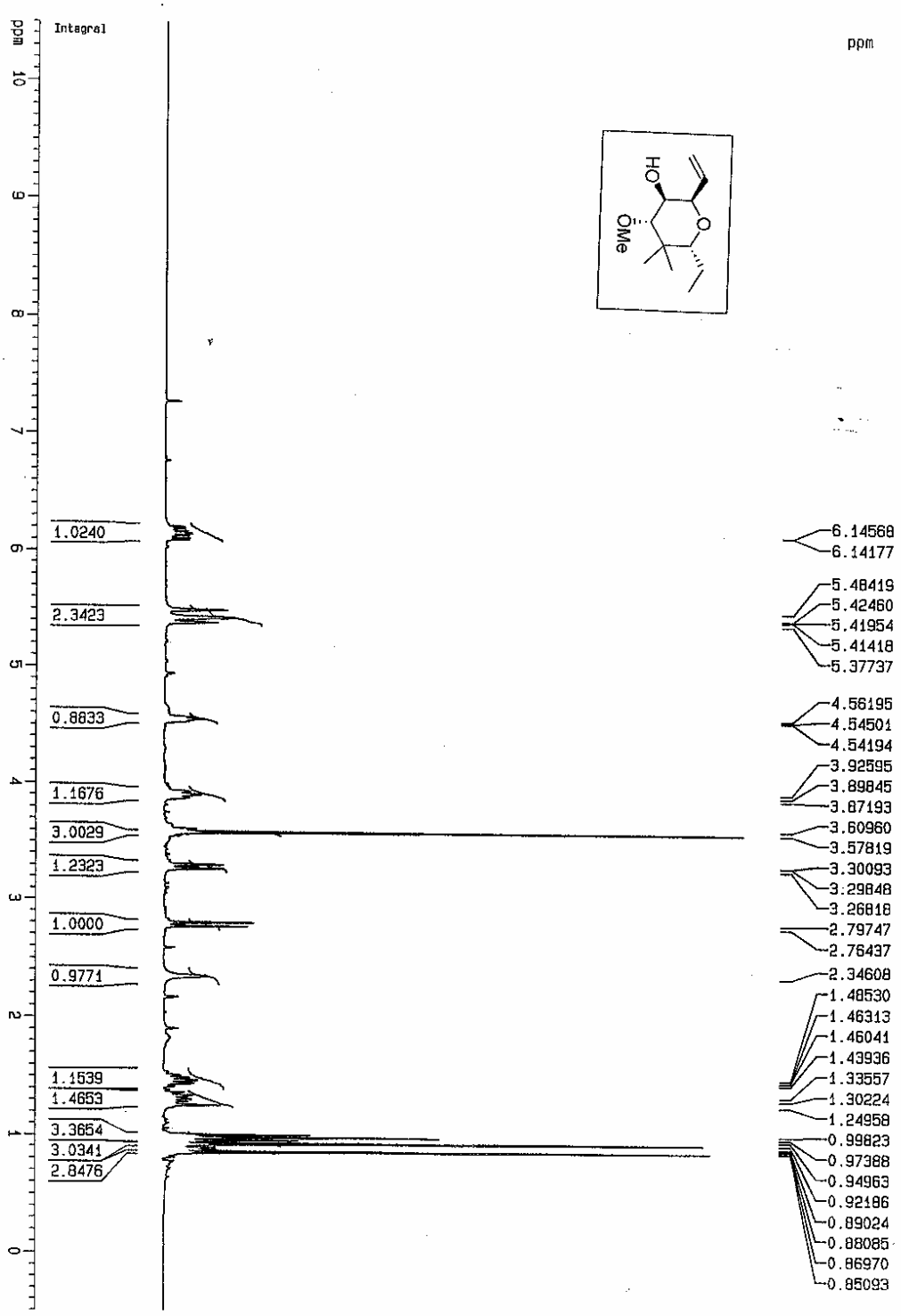

Integral
ppm
OTMS
OMe
1.000
1.221
3.910
3.786
3.508
10.245
7.15056
3.22933
3.16328
1.73438
1.62462
1.18847
1.16624
0.19661
0.18587
0.17533
0.12136

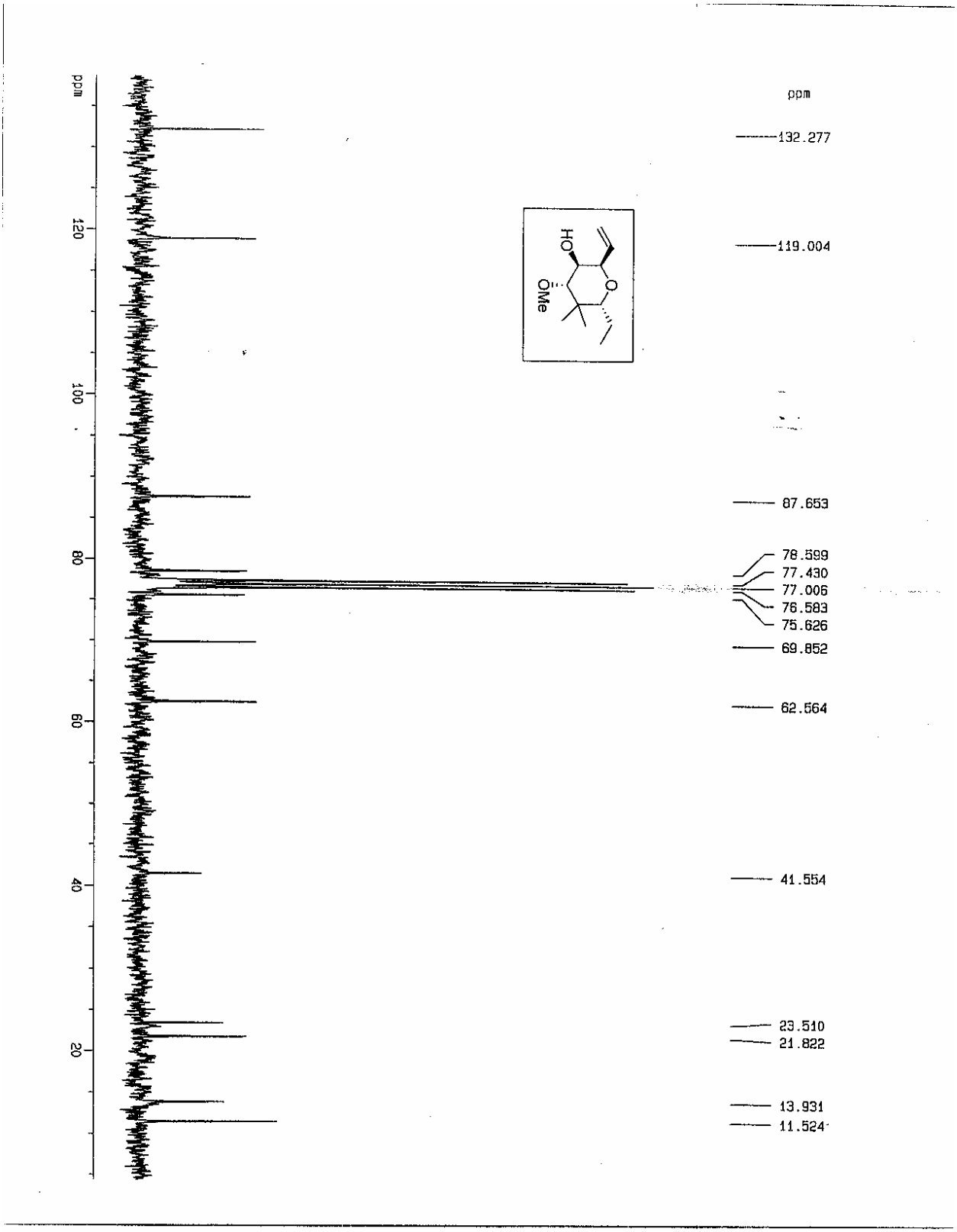

Integral
ppm
1.0000
1.0870
1.2554
3.4283
2.8223
3.6001
3.6773
7.32656
7.30721
7.27067
5.34639
5.32691
3.92544
3.89888
3.89039
1.79213
1.76820
1.73318
1.60523
1.11137
1.10626
1.08133
1.01829
0.28116

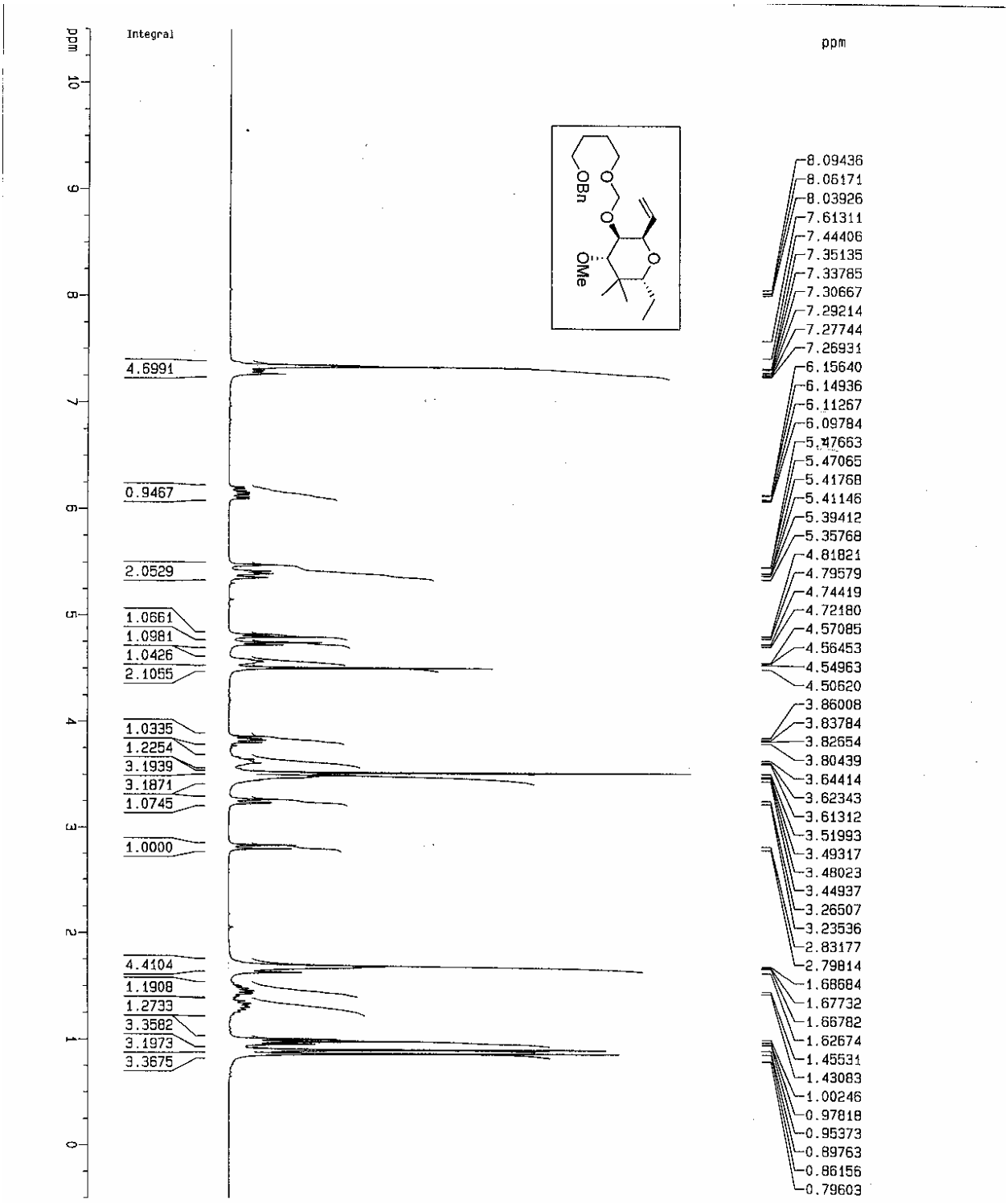

ppm
198.732
161.621
105.097
96.962
88.322
88.250
78.490
77.616
77.398
77.174
76.973
76.551
44.352
27.148
21.297
21.260
21.198
19.806
17.916
10.686
ppm
180
160
140
120
100
80
60
40
20
0

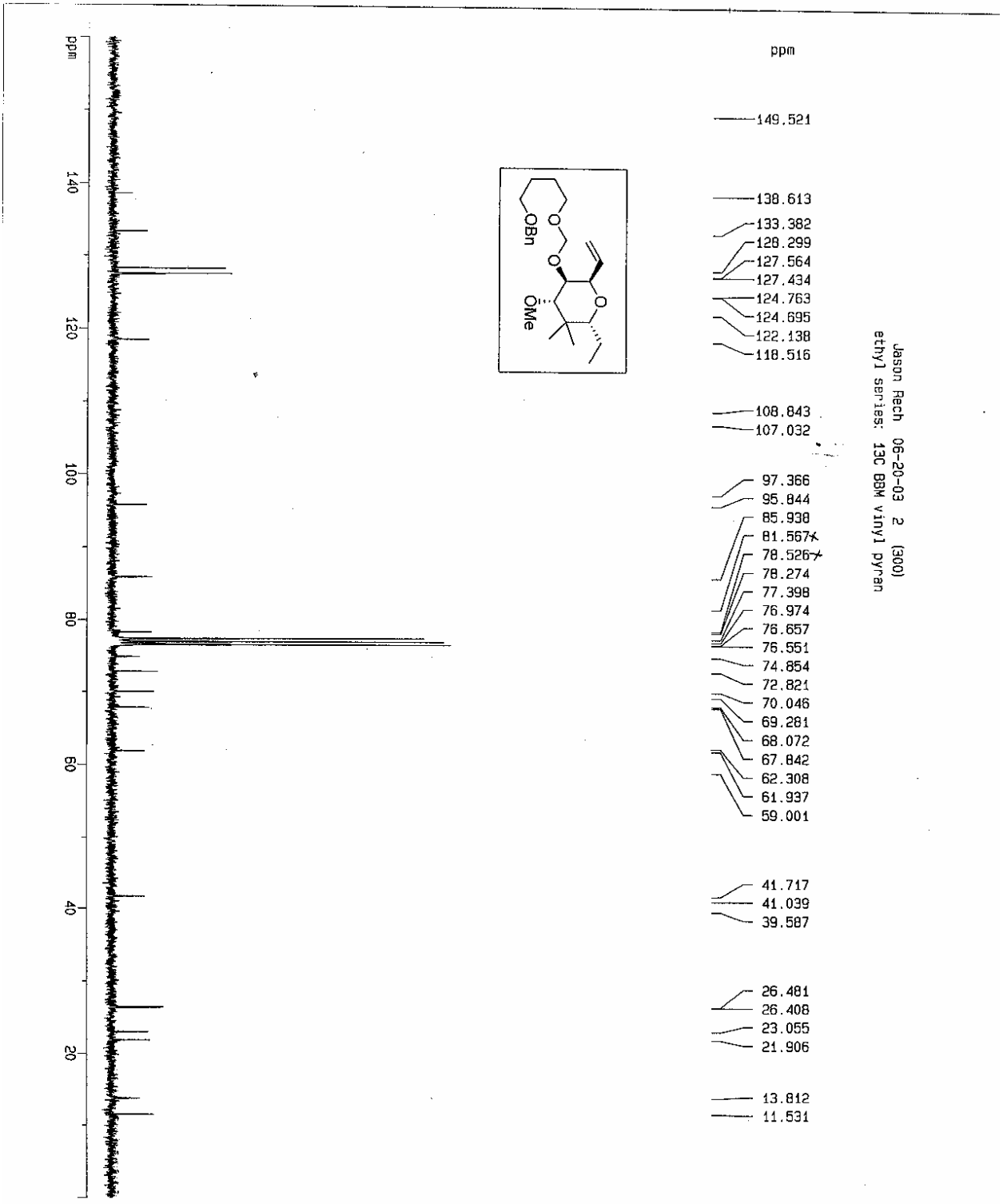

Integral
ppm
OMe
0.853
0.960
5.000
2.557
10.262
6.37403
6.35369
6.35087
4.81099
4.80496
4.79030
4.78443
3.45347
3.44792
3.44245
3.42760
3.41091
3.36743
1.62719
1.59499
1.57849
1.57001
1.55344
1.54482
1.02077
0.99627
0.97168
0.95646
0.92458
0.89430
0.85913

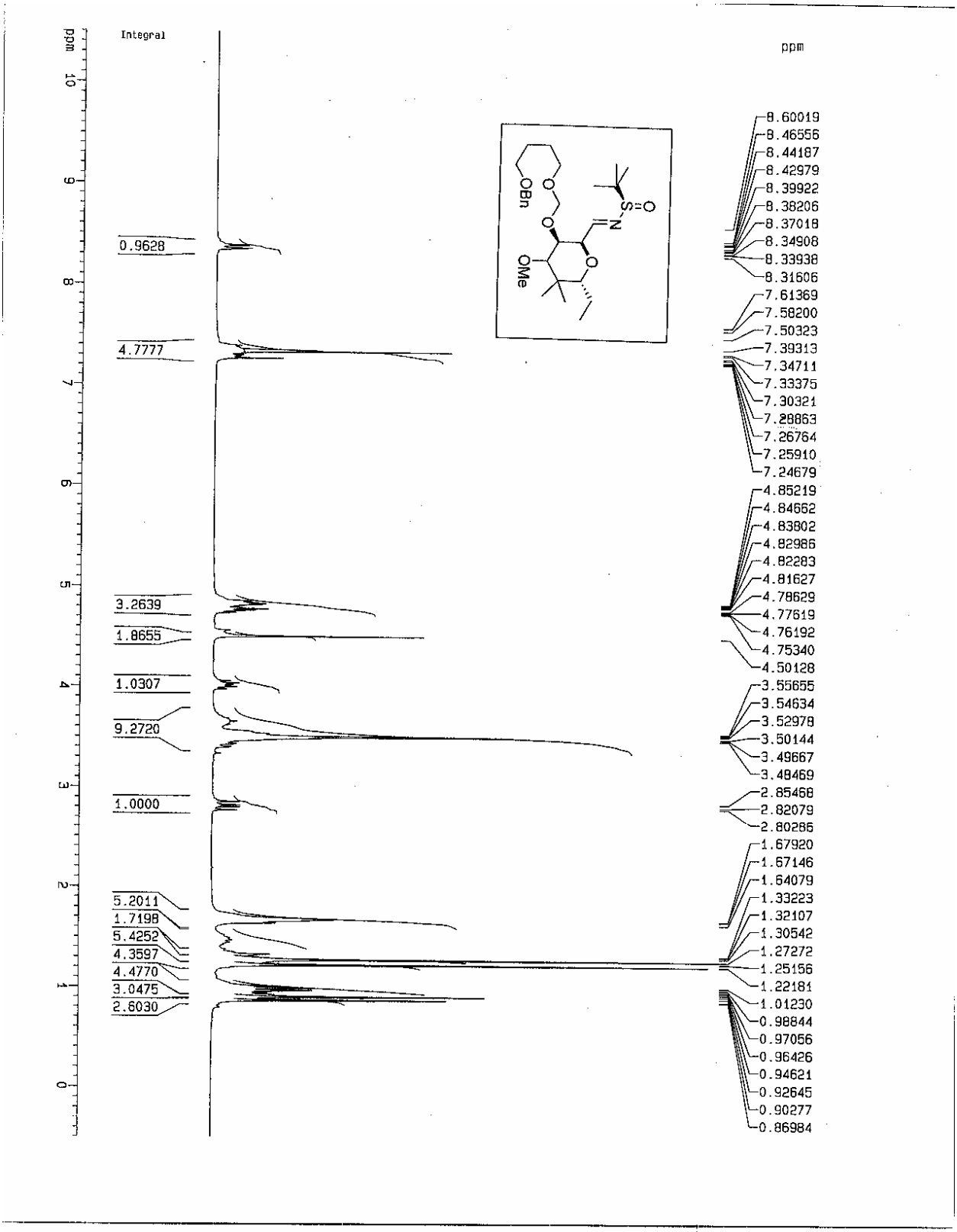

ppm
140
120
100
80
60
40
20
OMe
ppm
144.281
100.063
84.567
80.836
77.427
77.003
76.580
57.267
35.558
23.590
20.999
13.795
11.109

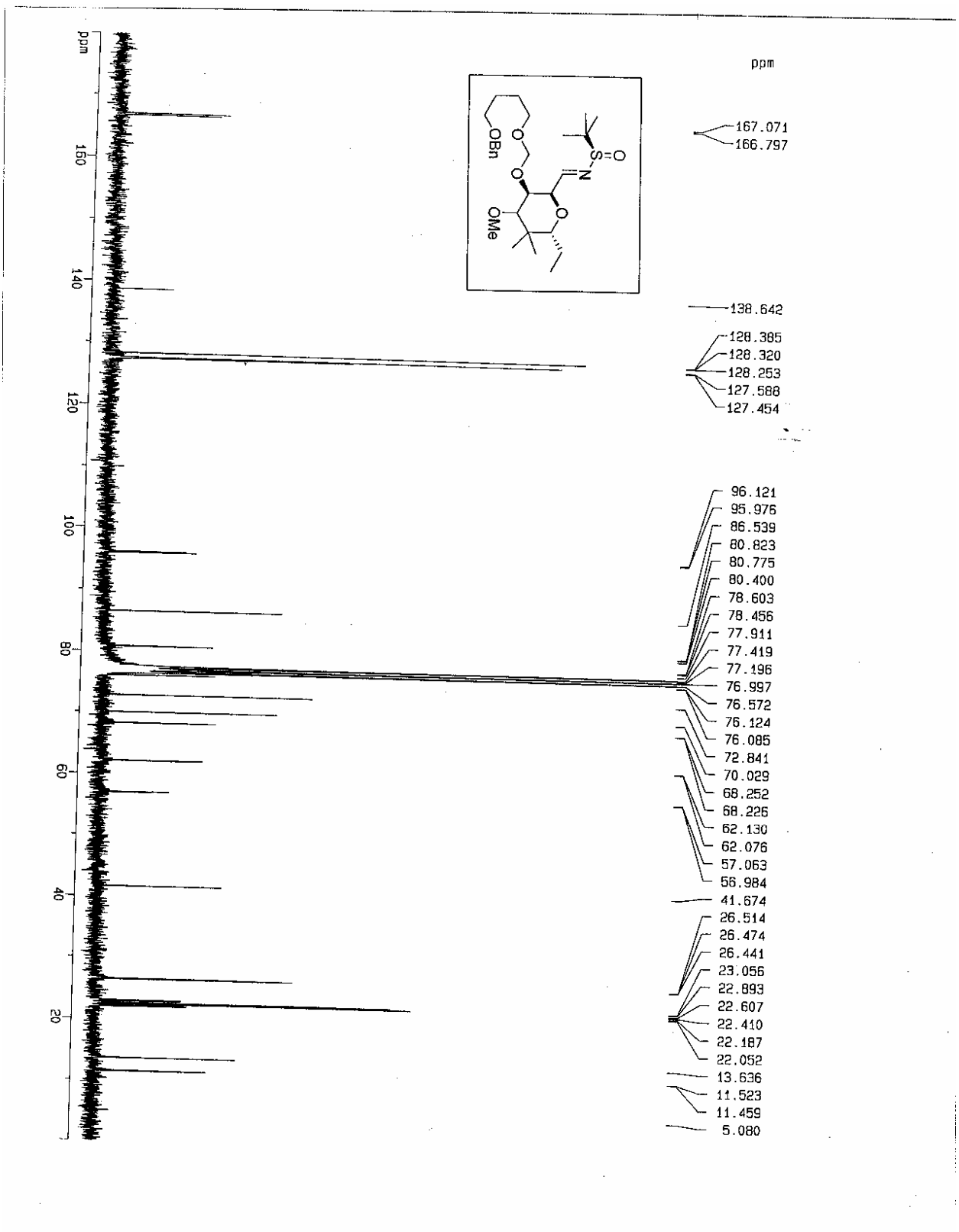

Integral
ppm
1.0240
2.3423
0.8833
1.1676
3.0029
1.2323
1.0000
0.9771
1.1539
1.4653
3.3654
3.0341
2.8476
HO
OMe
O
ppm
6.14568
6.14177
5.48419
5.42460
5.41954
5.41418
5.37737
4.56195
4.54501
4.54194
3.92595
3.89845
3.87193
3.60960
3.57819
3.30093
3.29848
3.26818
2.79747
2.76437
2.34608
1.48530
1.46313
1.46041
1.43936
1.33557
1.30224
1.24958
0.99823
0.97388
0.94963
0.92186
0.89024
0.88085
0.86970
0.85093

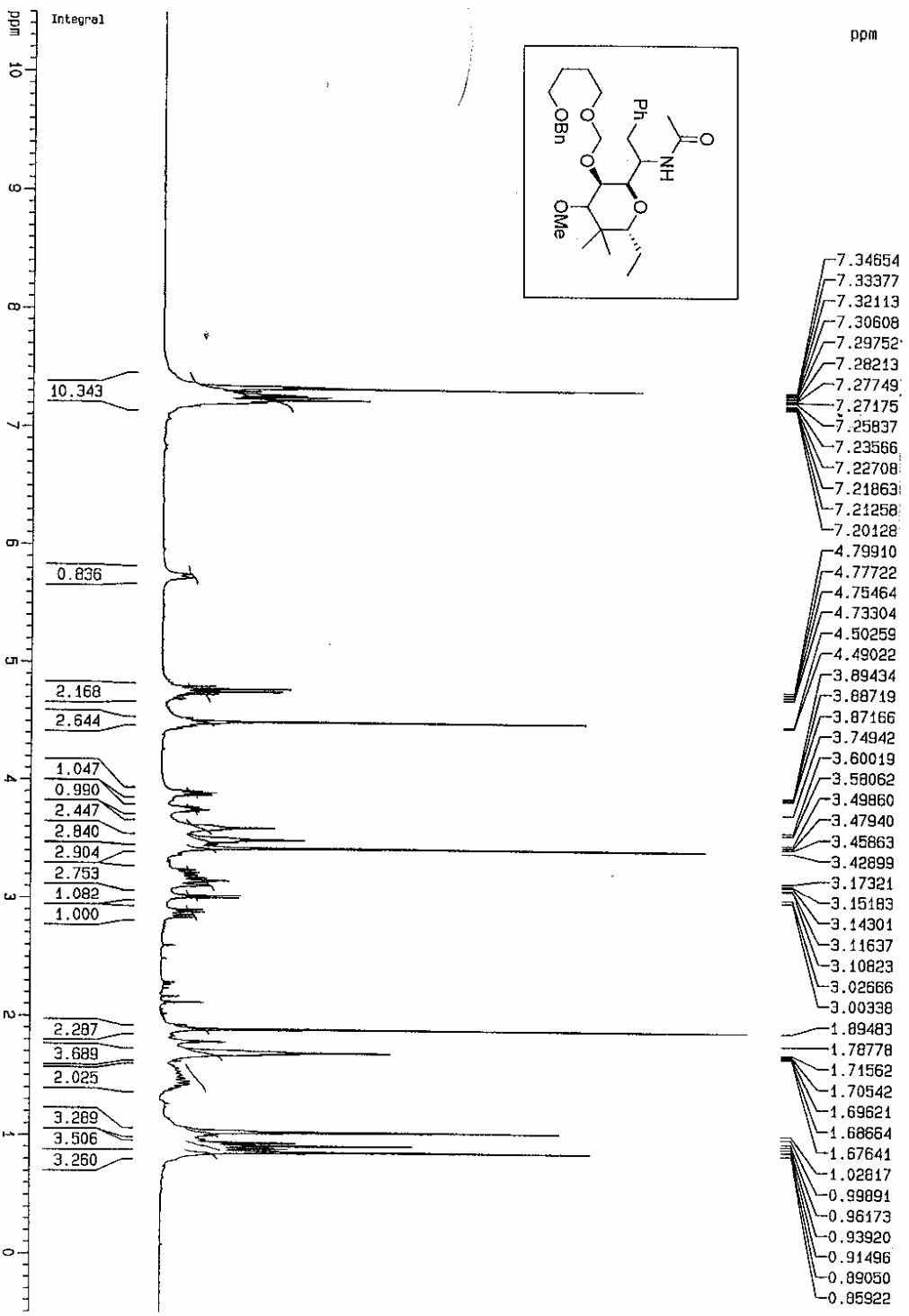

ppm
120
100
80
60
40
20
HO
OMe
O
ppm
132.277
119.004
87.653
78.599
77.430
77.006
76.583
75.626
69.852
62.564
41.554
23.510
21.822
13.931
11.524

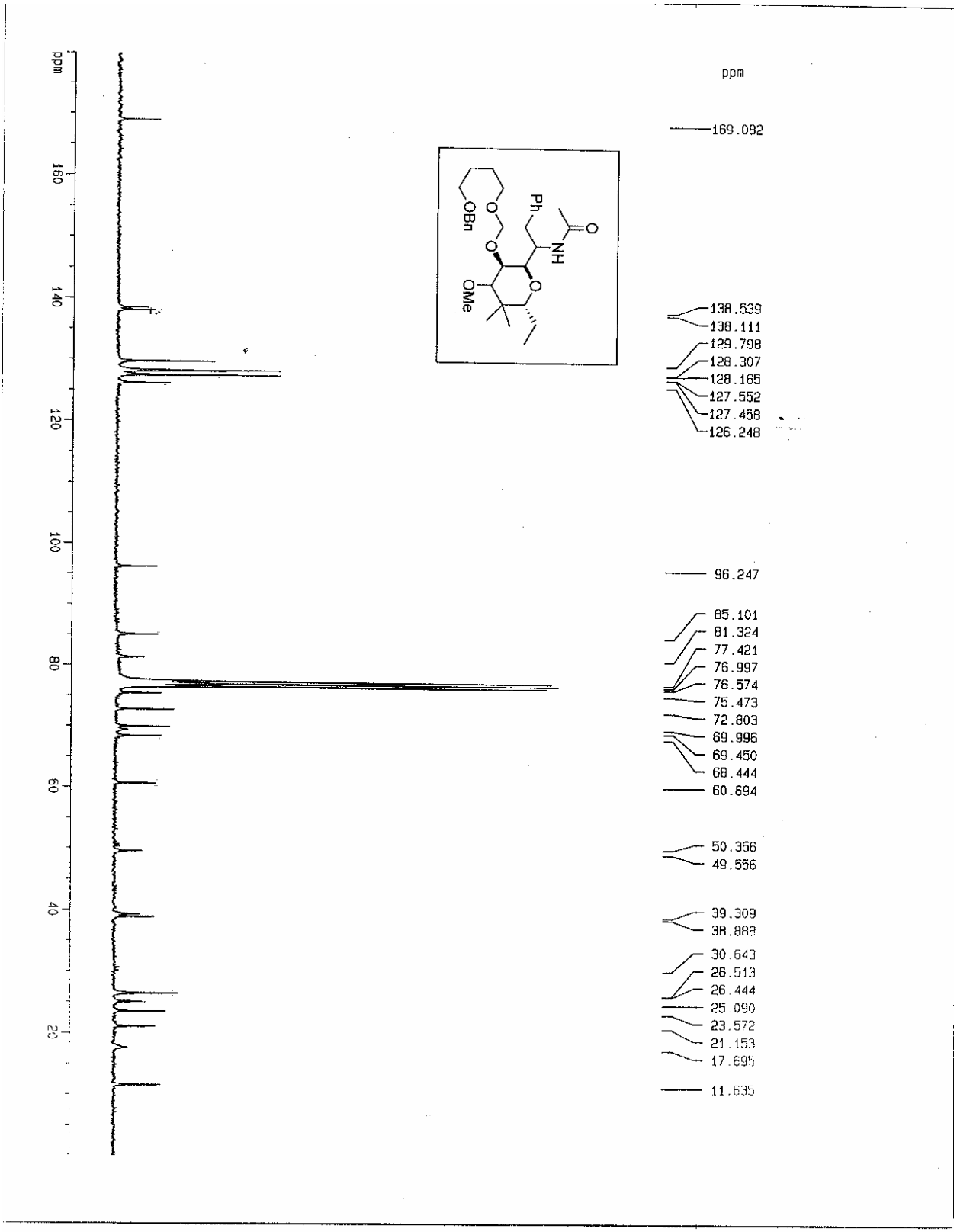

Integral
ppm
OBn
OMe
4.6991
0.9467
2.0529
1.0661
1.0981
1.0426
2.1055
1.0335
1.2254
3.1939
3.1871
1.0745
1.0000
4.4104
1.1908
1.2733
3.3582
3.1973
3.3675
8.09436
8.06171
8.03926
7.61311
7.44406
7.35135
7.33785
7.30667
7.29214
7.27744
7.26931
6.15640
6.14936
6.11267
6.09784
5.47663
5.47065
5.41768
5.41146
5.39412
5.35768
4.81821
4.79579
4.74419
4.72180
4.57085
4.56453
4.54963
4.50620
3.86008
3.83784
3.82654
3.80439
3.64414
3.62343
3.61312
3.51993
3.49317
3.48023
3.44937
3.26507
3.23536
2.83177
2.79814
1.68684
1.67732
1.66782
1.62674
1.45531
1.43083
1.00246
0.97818
0.95373
0.89763
0.86156
0.79603

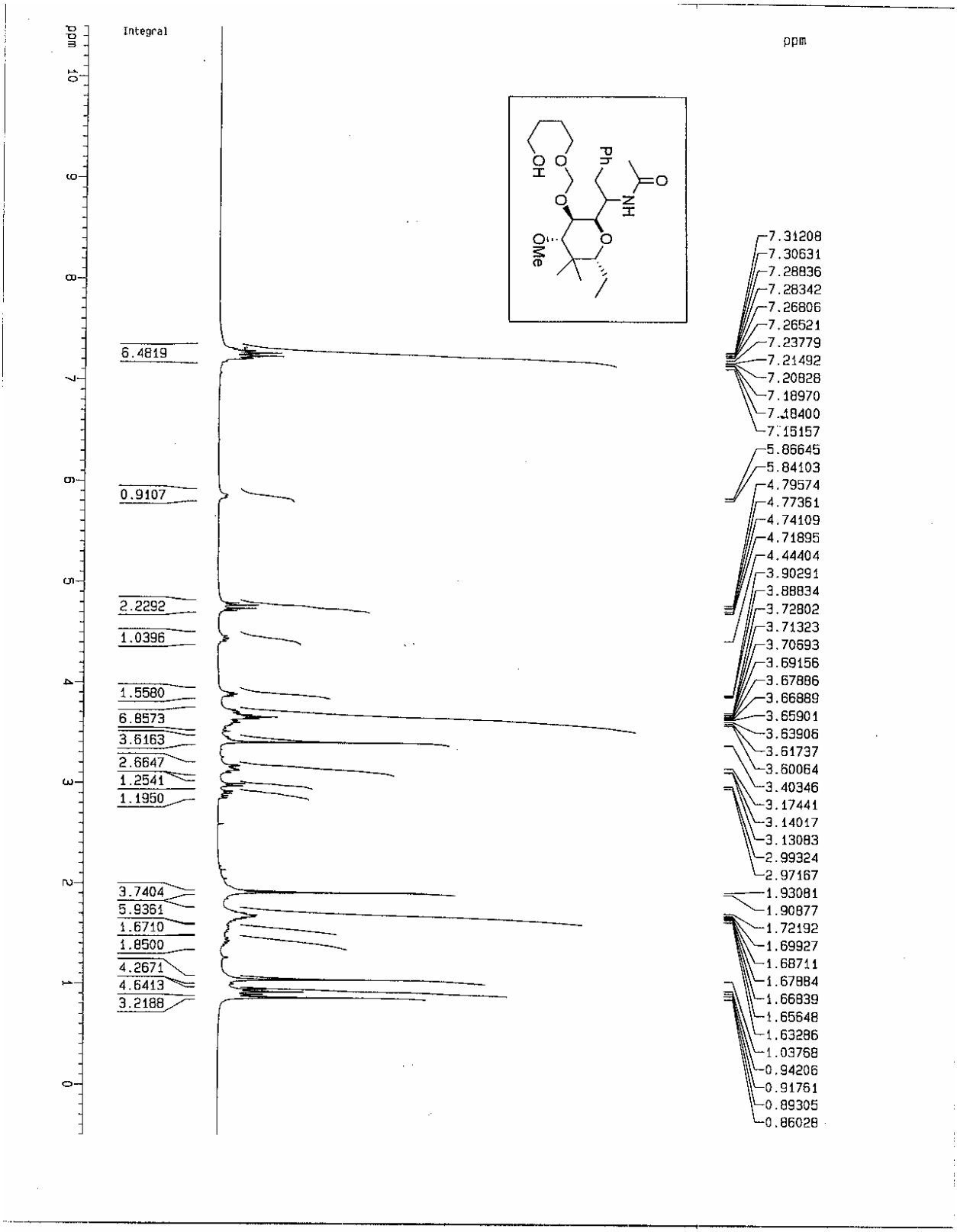

ppm
140
120
100
80
60
40
20
OBn
OMe
ppm
149.521
138.613
133.382
128.299
127.564
127.434
124.763
124.695
122.138
118.516
108.843
107.032
97.366
95.844
85.938
81.567
78.526
78.274
77.398
76.974
76.657
76.551
74.854
72.821
70.046
69.281
68.072
67.842
62.308
61.937
59.001
41.717
41.039
39.587
26.481
26.408
23.055
21.906
13.812
11.531
Jason Rech 06-20-03 2 (300)
ethyl series: 13C BBM vinyl pyran

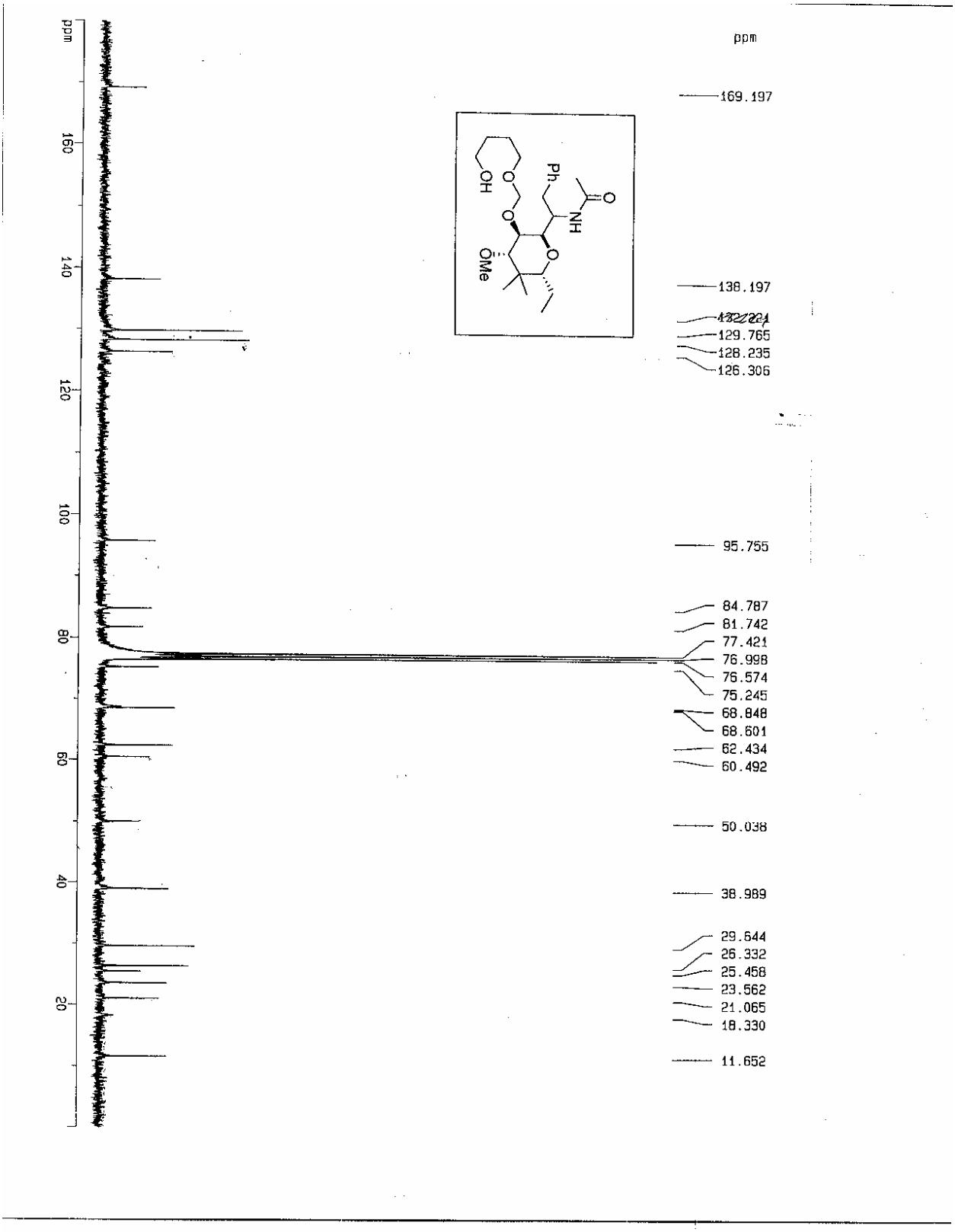

Integral
ppm
0.9628
4.7777
3.2639
1.8655
1.0307
9.2720
1.0000
5.2011
1.7198
5.4252
4.3597
4.4770
3.0475
2.6030
OBn
OMe
S=O
N
8.60019
8.46556
8.44187
8.42979
8.39922
8.38206
8.37018
8.34908
8.33938
8.31606
7.61369
7.58200
7.50323
7.39313
7.34711
7.33375
7.30321
7.28863
7.26764
7.25910
7.24679
4.85219
4.84662
4.83802
4.82986
4.82283
4.81627
4.78629
4.77619
4.76192
4.75340
4.50128
3.55655
3.54634
3.52978
3.50144
3.49667
3.48469
2.85468
2.82079
2.80286
1.67920
1.67146
1.64079
1.33223
1.32107
1.30542
1.27272
1.25156
1.22181
1.01230
0.98844
0.97056
0.96426
0.94621
0.92645
0.90277
0.86984

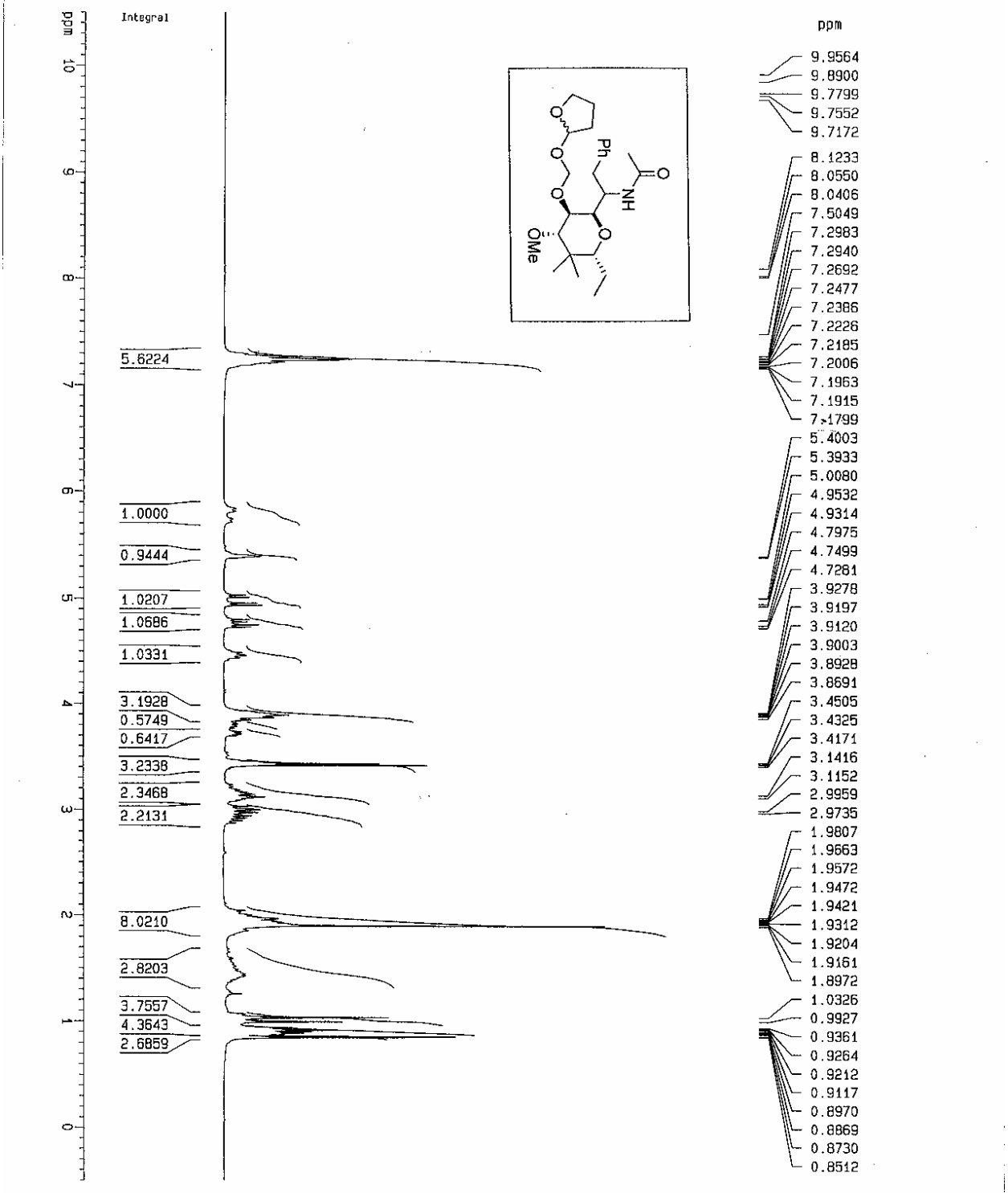

ppm
150
140
120
100
80
60
40
20
OBn
OMe
S=O
N
ppm
167.071
166.797
138.642
128.385
128.320
128.253
127.588
127.454
96.121
95.976
86.539
80.823
80.775
80.400
78.603
78.456
77.911
77.419
77.196
76.997
76.572
76.124
76.085
72.841
70.029
68.252
68.226
62.130
62.076
57.063
56.984
41.674
26.514
26.474
26.441
23.056
22.893
22.607
22.410
22.187
22.052
13.636
11.523
11.459
5.080

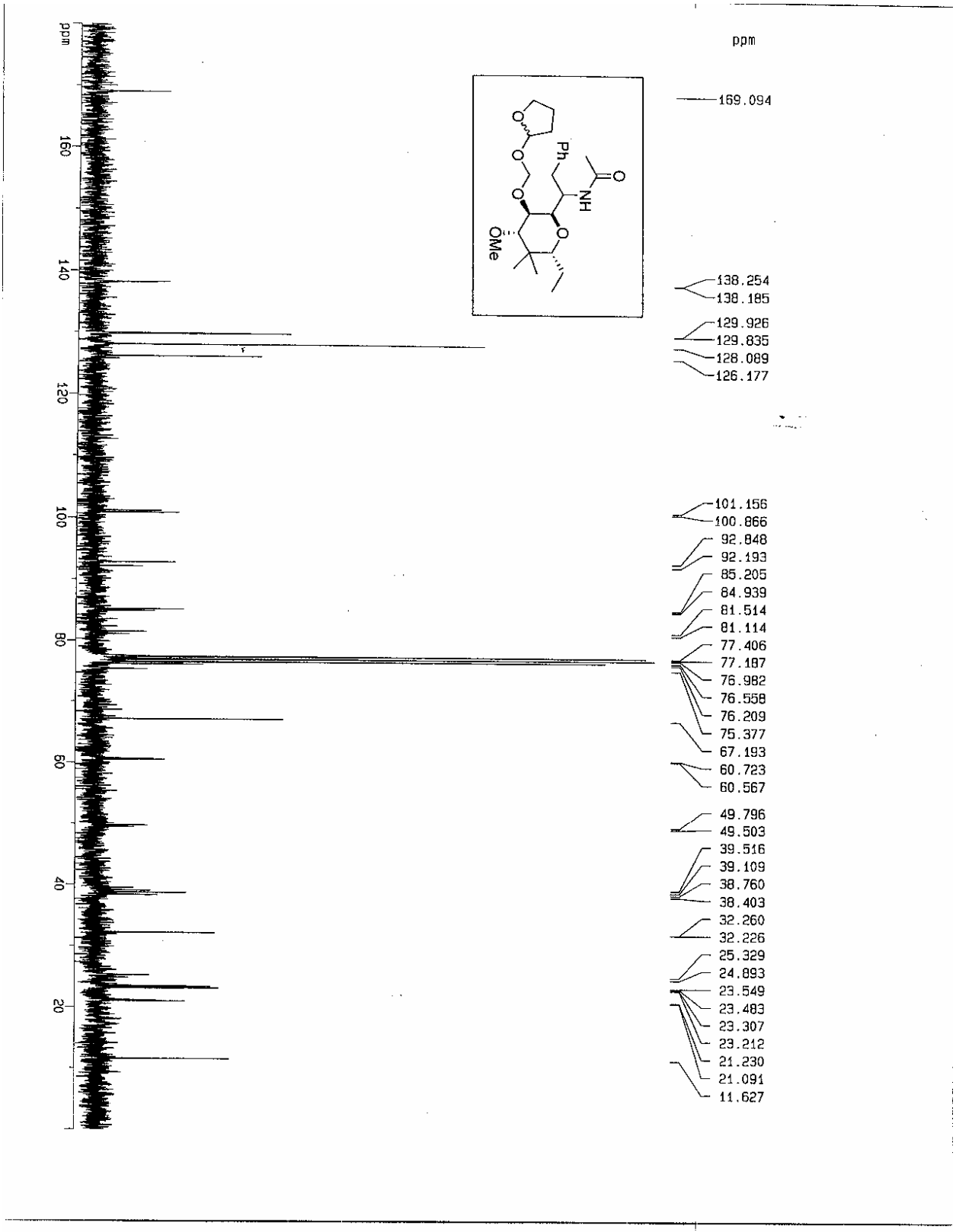

ppm
Integral
10.343
0.836
2.168
2.644
1.047
0.990
2.447
2.840
2.904
2.753
1.082
1.000
2.287
3.689
2.025
3.289
3.506
3.260
OBn
Ph
NH
OMe
ppm
7.34654
7.33377
7.32113
7.30608
7.29752
7.28213
7.27749
7.27175
7.25837
7.23566
7.22708
7.21863
7.21258
7.20128
4.79910
4.77722
4.75464
4.73304
4.50259
4.49022
3.89434
3.88719
3.87166
3.74942
3.60019
3.58062
3.49860
3.47940
3.45863
3.42899
3.17321
3.15183
3.14301
3.11637
3.10823
3.02666
3.00338
1.89483
1.78778
1.71562
1.70542
1.69621
1.68664
1.67641
1.02817
0.99891
0.96173
0.93920
0.91496
0.89050
0.85922

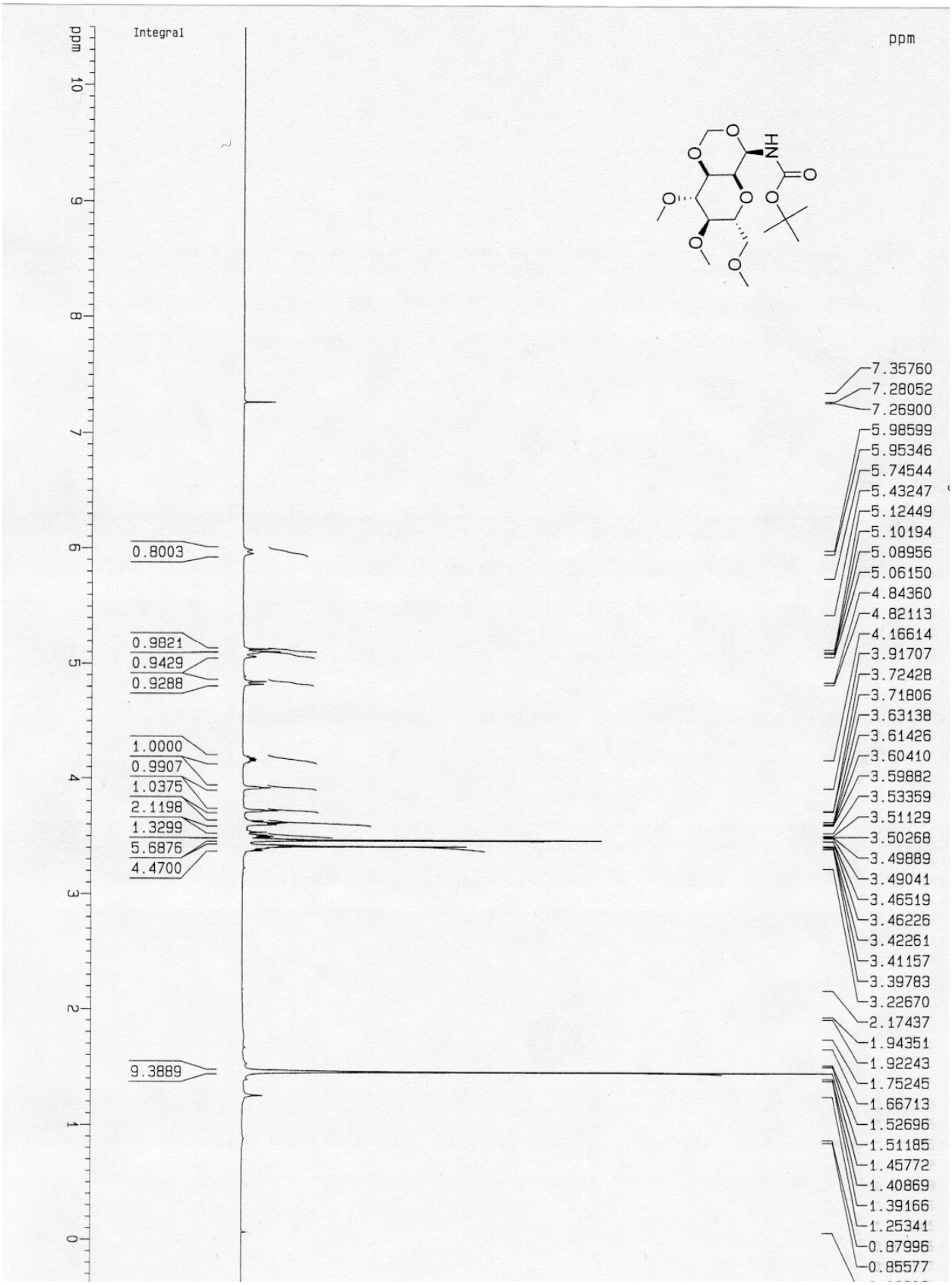

ppm
160
140
120
100
80
60
40
20
OBn
Ph
NH
OMe
ppm
169.082
138.539
138.111
129.798
128.307
128.165
127.552
127.458
126.248
96.247
85.101
81.324
77.421
76.997
76.574
75.473
72.803
69.996
69.450
68.444
60.694
50.356
49.556
39.309
38.888
30.643
26.513
26.444
25.090
23.572
21.153
17.695
11.635

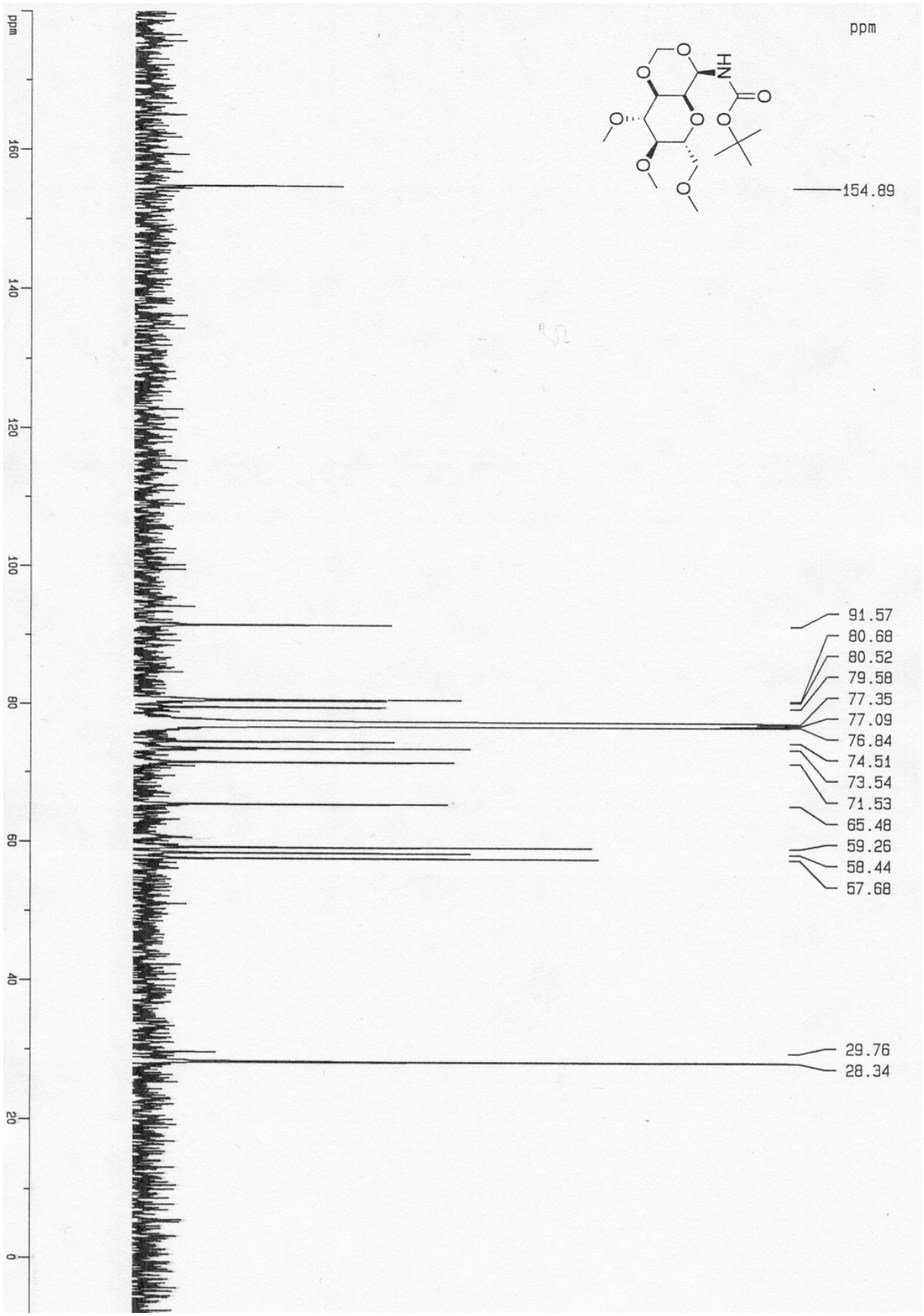

Integral
ppm
6.4819
0.9107
2.2292
1.0396
1.5580
6.8573
3.6163
2.6647
1.2541
1.1950
3.7404
5.9361
1.6710
1.8500
4.2671
4.6413
3.2188
OH
O
O
O
Ph
NH
O
OMe
7.31208
7.30631
7.28836
7.28342
7.26806
7.26521
7.23779
7.21492
7.20828
7.18970
7.18400
7.15157
5.86645
5.84103
4.79574
4.77361
4.74109
4.71895
4.44404
3.90291
3.88834
3.72802
3.71323
3.70693
3.69156
3.67886
3.66889
3.65901
3.63906
3.61737
3.60064
3.40346
3.17441
3.14017
3.13083
2.99324
2.97167
1.93081
1.90877
1.72192
1.69927
1.68711
1.67884
1.66839
1.65648
1.63286
1.03768
0.94206
0.91761
0.89305
0.86028

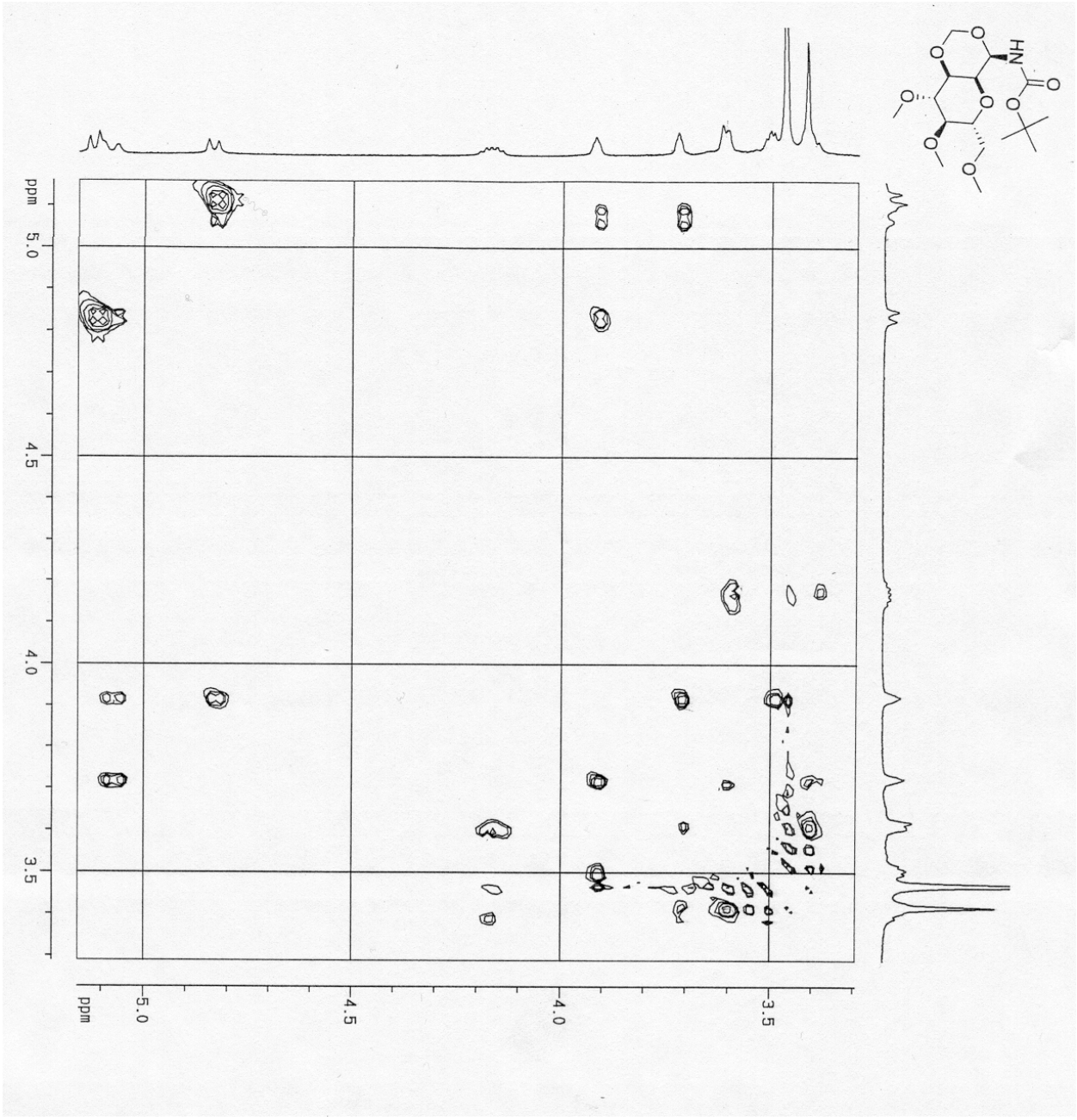

ppm
160
140
120
100
80
60
40
20
OH
O
O
OMe
Ph
NH
O
O
ppm
169.197
138.197
129.765
128.235
126.306
95.755
84.787
81.742
77.421
76.998
76.574
75.245
68.848
68.601
62.434
60.492
50.038
38.989
29.644
26.332
25.458
23.562
21.065
18.330
11.652

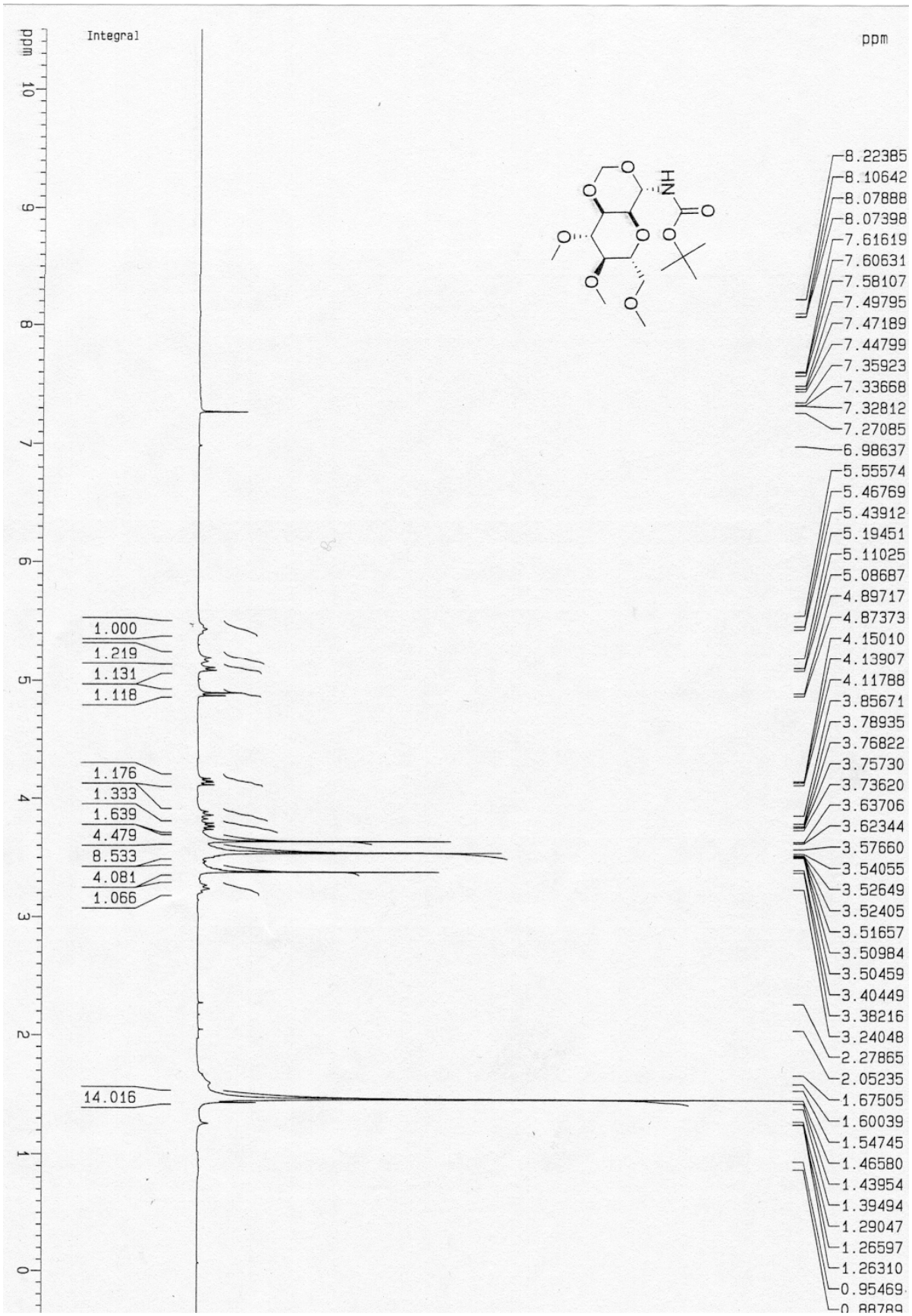

Integral
ppm
5.6224
1.0000
0.9444
1.0207
1.0686
1.0331
3.1928
0.5749
0.6417
3.2338
2.3468
2.2131
8.0210
2.8203
3.7557
4.3643
2.6859
Ph
NH
O
OMe
9.9564
9.8900
9.7799
9.7552
9.7172
8.1233
8.0550
8.0406
7.5049
7.2983
7.2940
7.2692
7.2477
7.2386
7.2226
7.2185
7.2006
7.1963
7.1915
7.1799
5.4003
5.3933
5.0080
4.9532
4.9314
4.7975
4.7499
4.7261
3.9278
3.9197
3.9120
3.9003
3.8928
3.8691
3.4505
3.4325
3.4171
3.1416
3.1152
2.9959
2.9735
1.9807
1.9663
1.9572
1.9472
1.9421
1.9312
1.9204
1.9161
1.8972
1.0326
0.9927
0.9361
0.9264
0.9212
0.9117
0.8970
0.8869
0.8730
0.8512

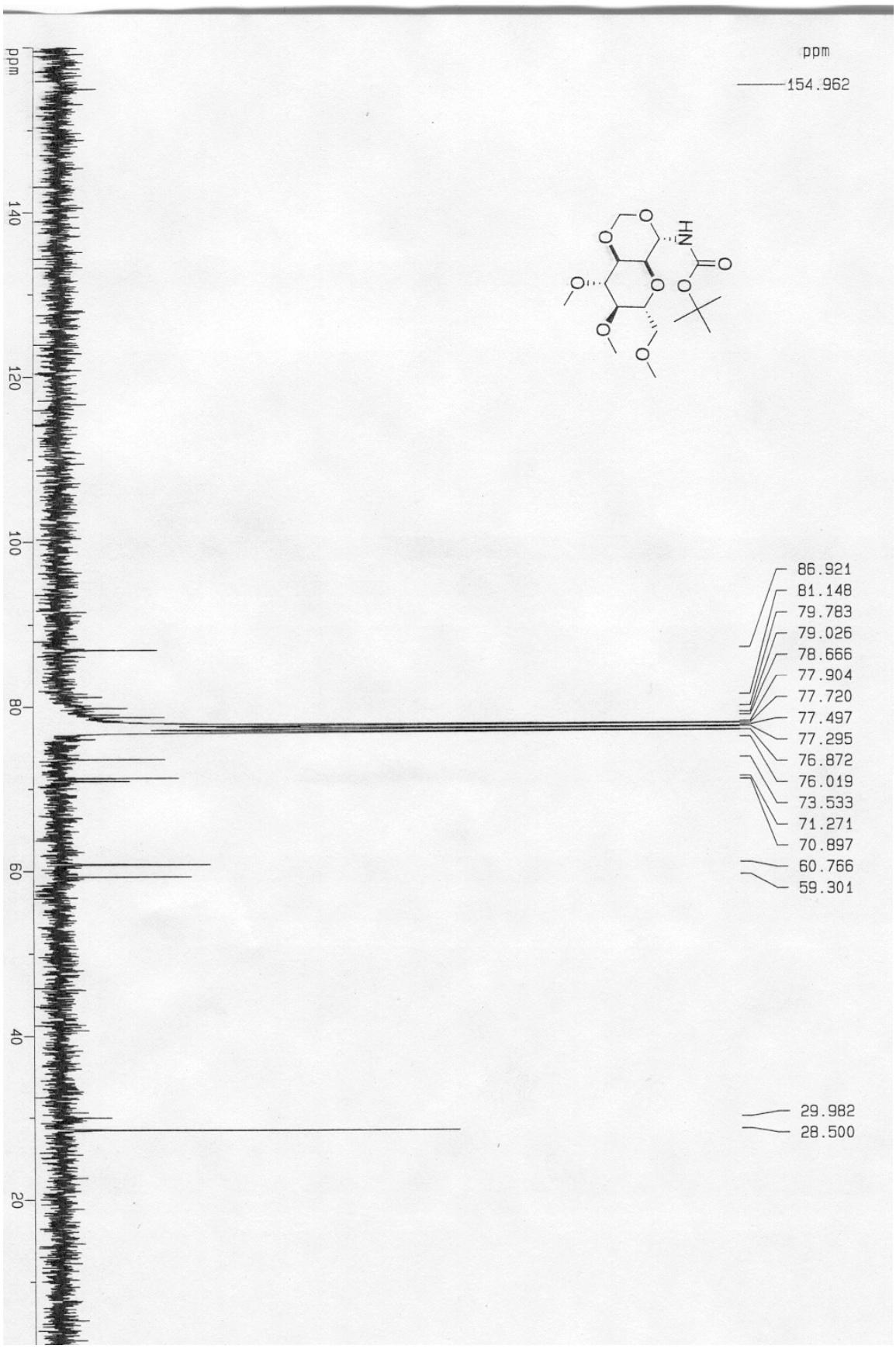

ppm
160
140
120
100
80
60
40
20
Ph
NH
O
OMe
ppm
169.094
138.254
138.185
129.926
129.835
128.089
126.177
101.156
100.866
92.848
92.193
85.205
84.939
81.514
81.114
77.406
77.187
76.982
76.558
76.209
75.377
67.193
60.723
60.567
49.796
49.503
39.516
39.109
38.760
38.403
32.260
32.226
25.329
24.893
23.549
23.483
23.307
23.212
21.230
21.091
11.627

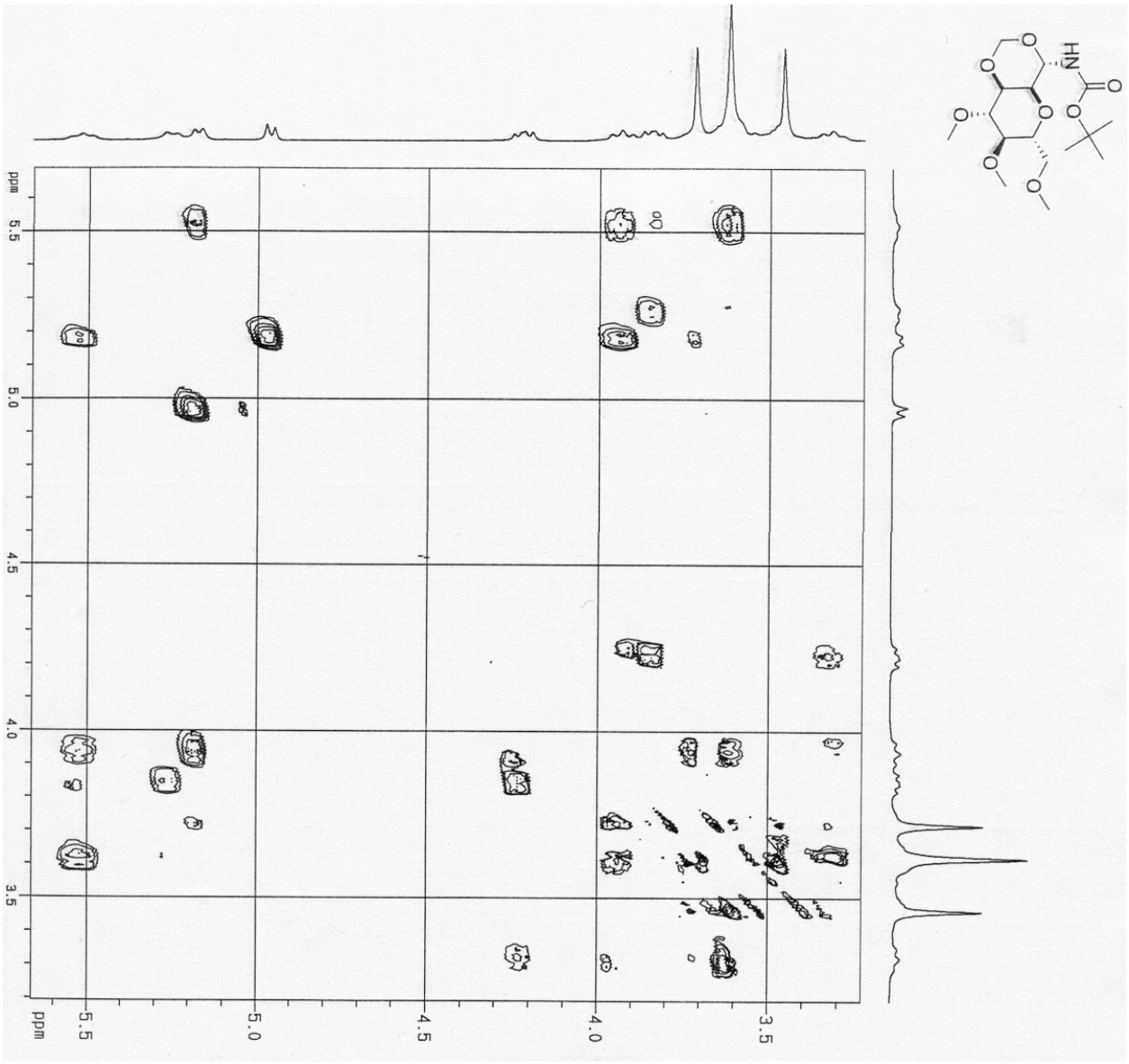

Integral
ppm
0.8003
0.9821
0.9429
0.9288
1.0000
0.9907
1.0375
2.1198
1.3299
5.6876
4.4700
9.3889
7.35760
7.28052
7.26900
5.98599
5.95346
5.74544
5.43247
5.12449
5.10194
5.08956
5.06150
4.84360
4.82113
4.16614
3.91707
3.72428
3.71806
3.63138
3.61426
3.60410
3.59882
3.53359
3.51129
3.50268
3.49889
3.49041
3.46519
3.46226
3.42261
3.41157
3.39783
3.22670
2.17437
1.94351
1.92243
1.75245
1.66713
1.52696
1.51185
1.45772
1.40869
1.39166
1.25341
0.87996
0.85577

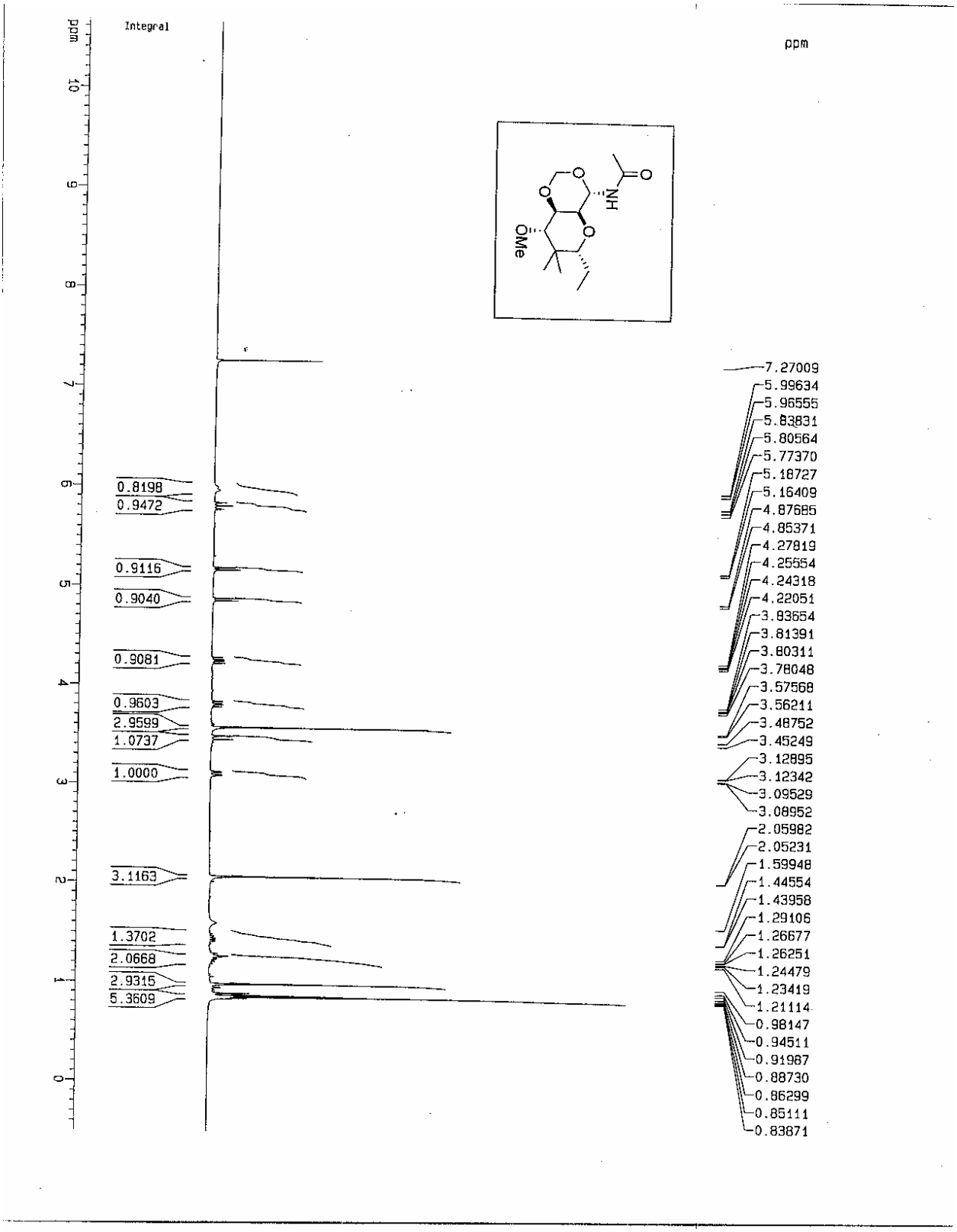

ppm
160
140
120
100
80
60
40
20
0
ppm
154.89
91.57
80.68
80.52
79.58
77.35
77.09
76.84
74.51
73.54
71.53
65.48
59.26
58.44
57.68
29.76
28.34

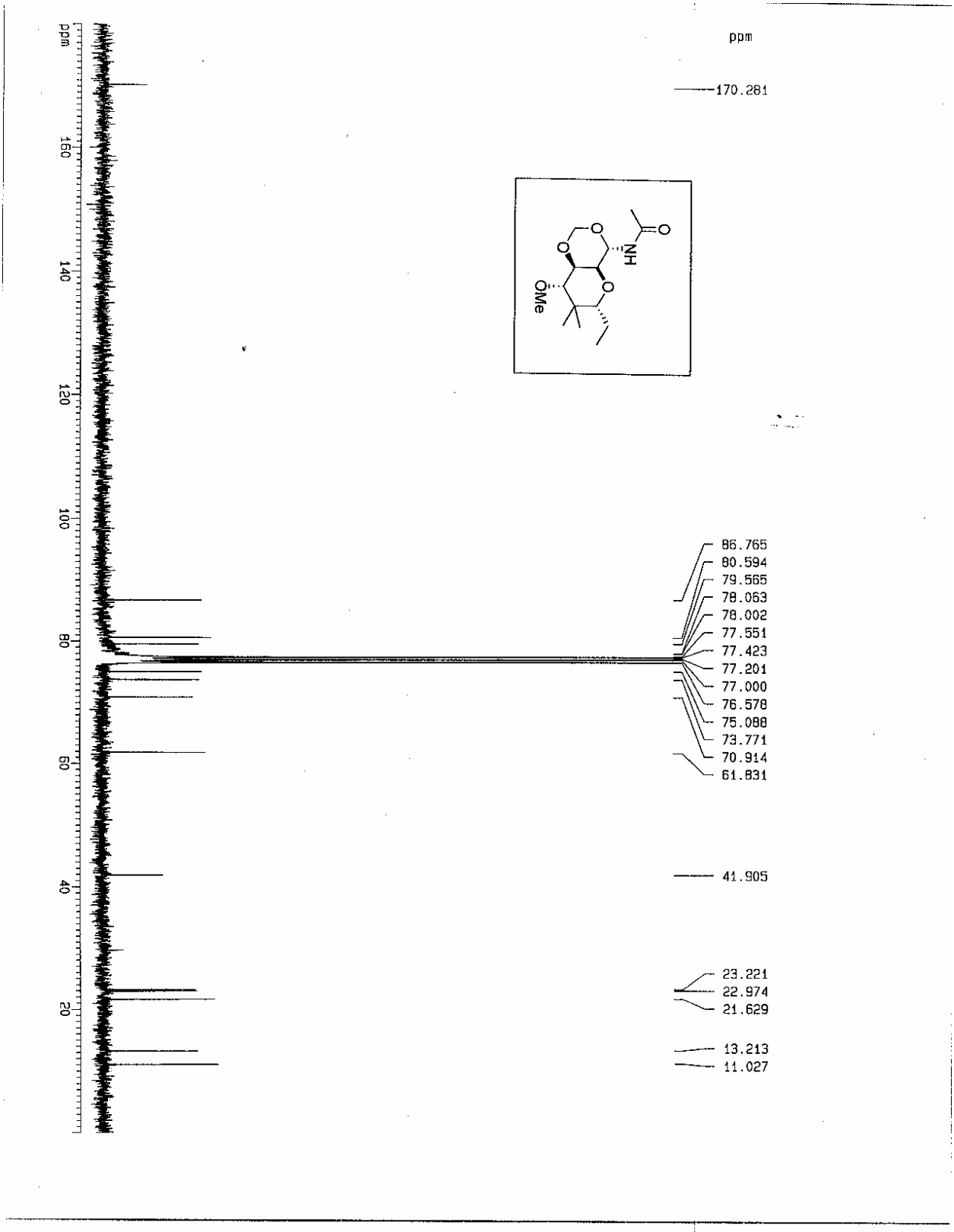

ppm
5.0
4.5
4.0
3.5
NH
O

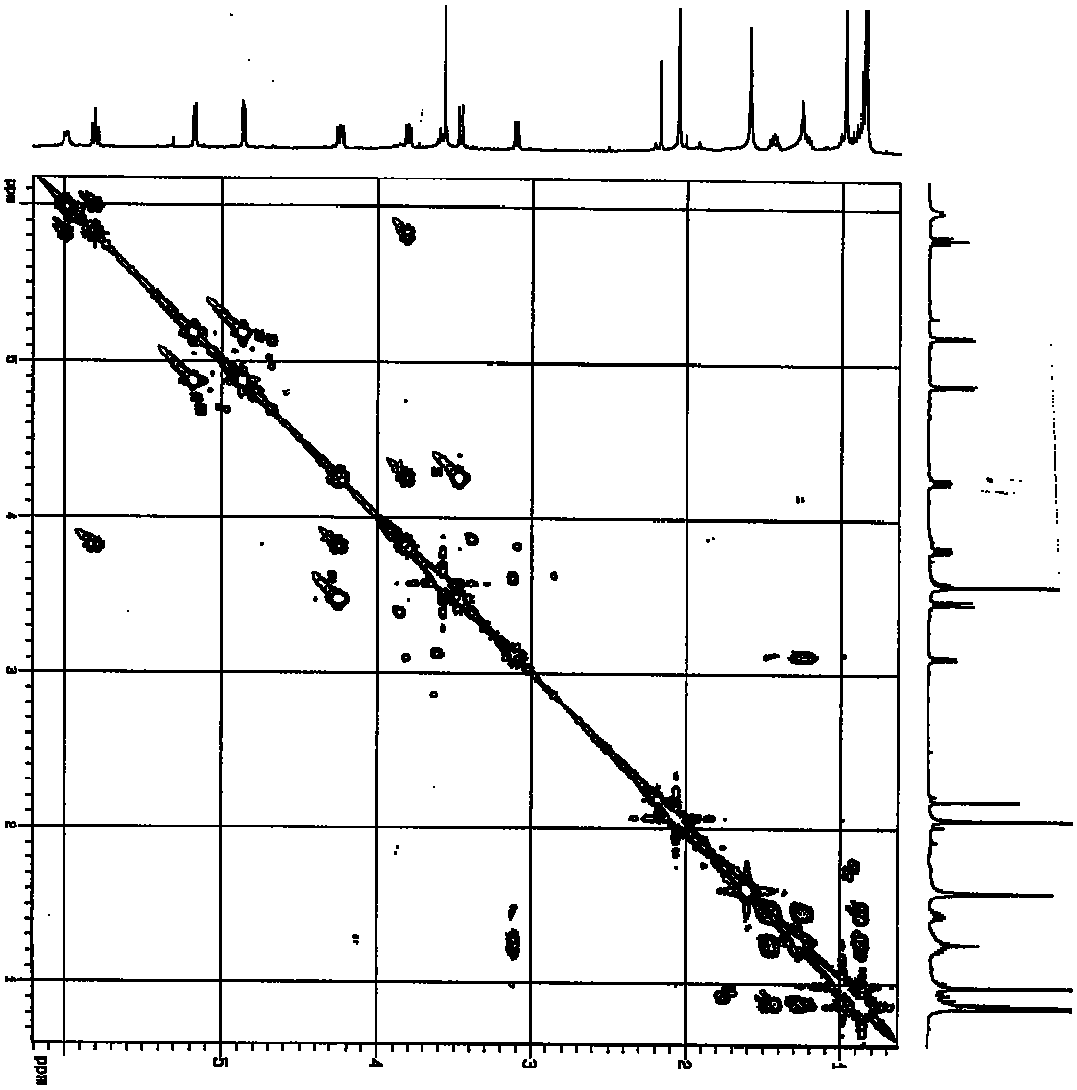

Integral
ppm
1.000
1.219
1.131
1.118
1.176
1.333
1.639
4.479
8.533
4.081
1.066
14.016
8.22385
8.10642
8.07888
8.07398
7.61619
7.60631
7.58107
7.49795
7.47189
7.44799
7.35923
7.33668
7.32812
7.27085
6.98637
5.55574
5.46769
5.43912
5.19451
5.11025
5.08687
4.89717
4.87373
4.15010
4.13907
4.11788
3.85671
3.78935
3.76822
3.75730
3.73620
3.63706
3.62344
3.57660
3.54055
3.52649
3.52405
3.51657
3.50984
3.50459
3.40449
3.38216
3.24048
2.27865
2.05235
1.67505
1.60039
1.54745
1.46580
1.43954
1.39494
1.29047
1.26597
1.26310
0.95469

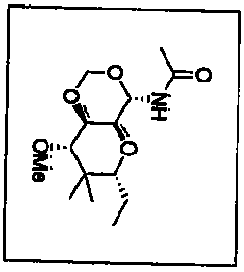

ppm
154.962
86.921
81.148
79.783
79.026
78.666
77.904
77.720
77.497
77.295
76.872
76.019
73.533
71.271
70.897
60.766
59.301
29.982
28.500
ppm
140
120
100
80
60
40
20

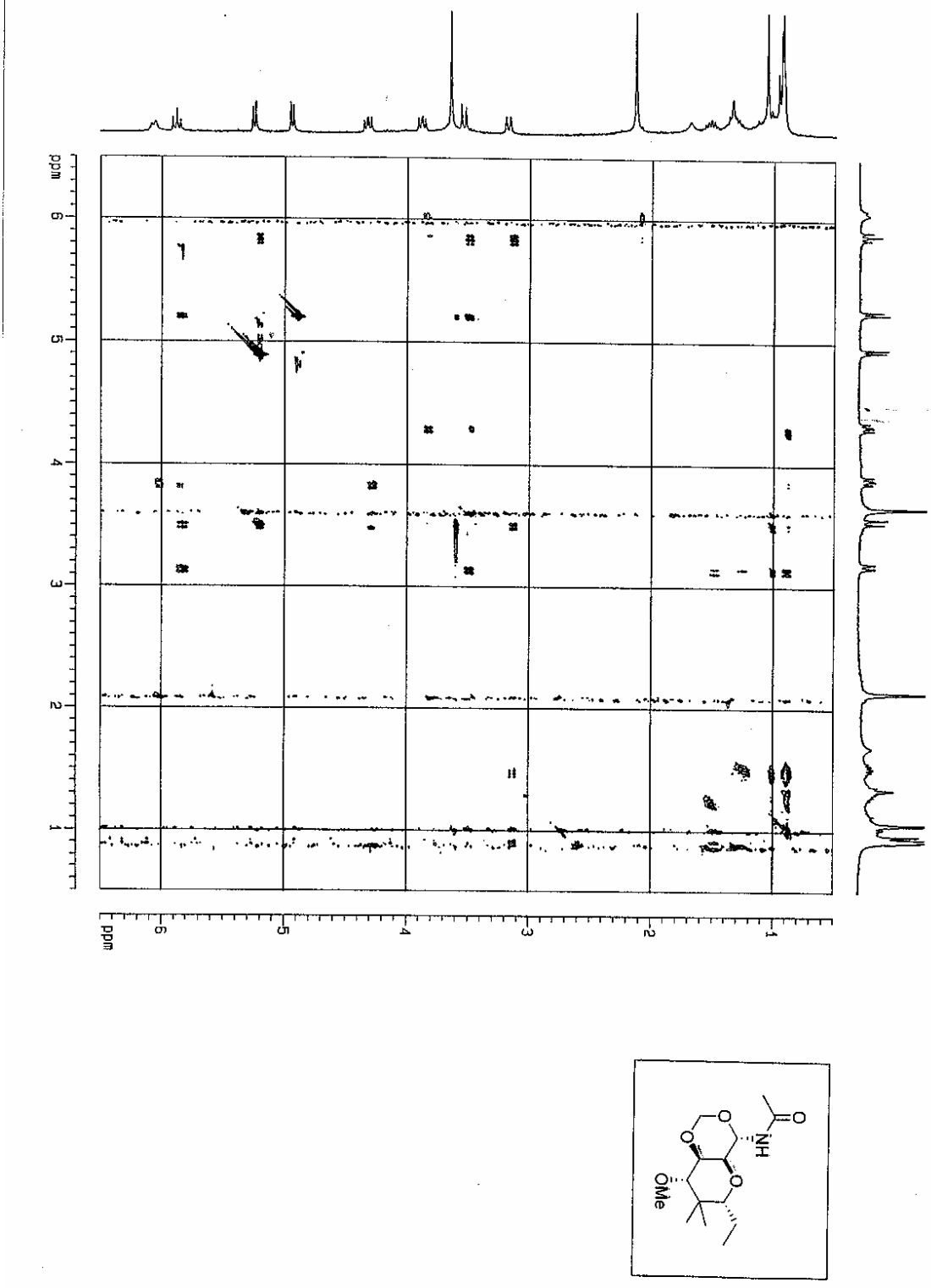

ppm
5.5
5.0
4.5
4.0
3.5
ppm
5.5
5.0
4.5
4.0
3.5
HN
O
O
O
O
O
O
O

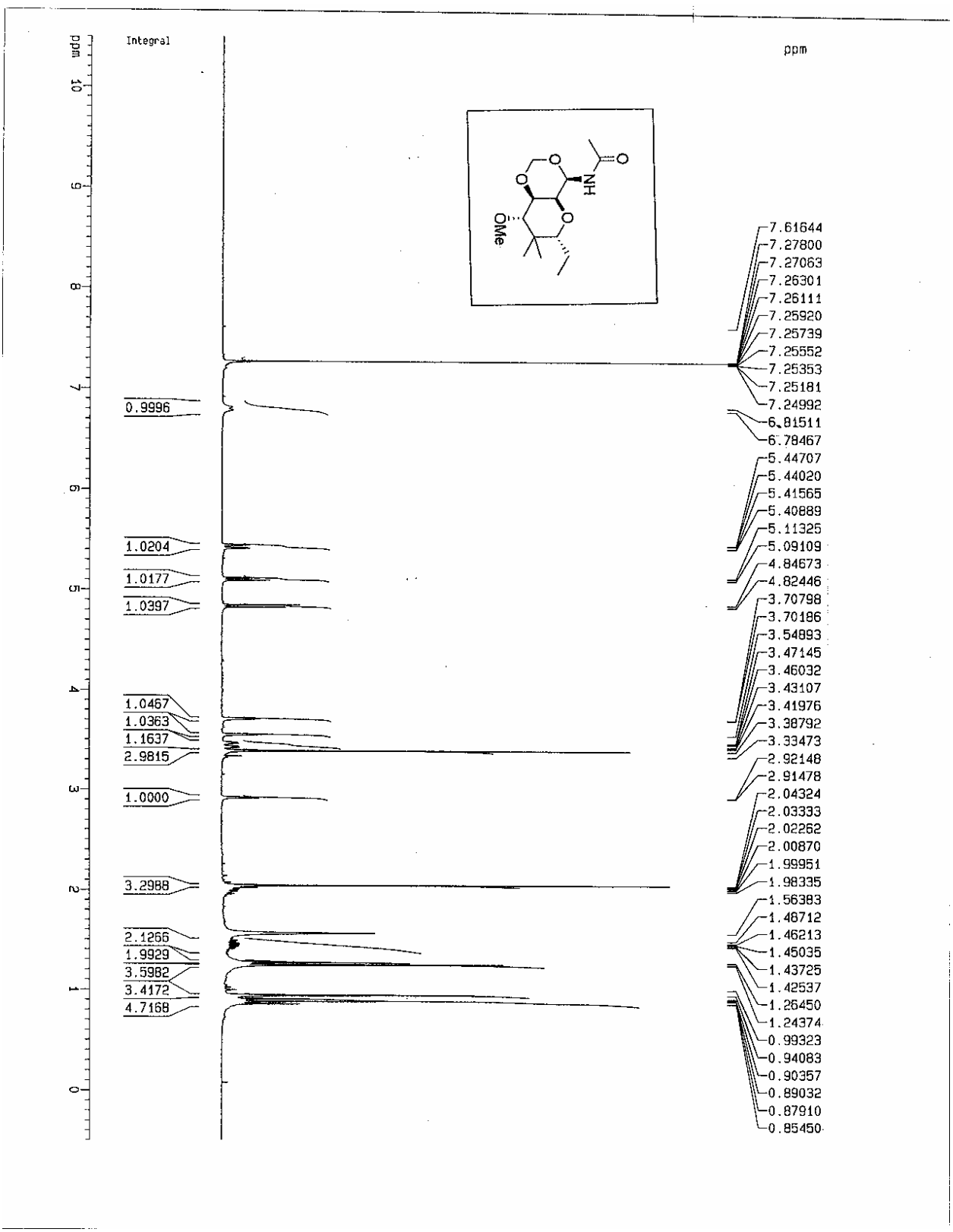

Integral
ppm
0.8198
0.9472
0.9116
0.9040
0.9081
0.9603
2.9599
1.0737
1.0000
3.1163
1.3702
2.0668
2.9315
5.3609
NH
OMe
ppm
7.27009
5.99634
5.96555
5.83831
5.80564
5.77370
5.18727
5.16409
4.87685
4.85371
4.27819
4.25554
4.24318
4.22051
3.83654
3.81391
3.80311
3.78048
3.57568
3.56211
3.48752
3.45249
3.12895
3.12342
3.09529
3.08952
2.05982
2.05231
1.59948
1.44554
1.43958
1.29106
1.26677
1.26251
1.24479
1.23419
1.21114
0.98147
0.94511
0.91987
0.88730
0.86299
0.85111
0.83871

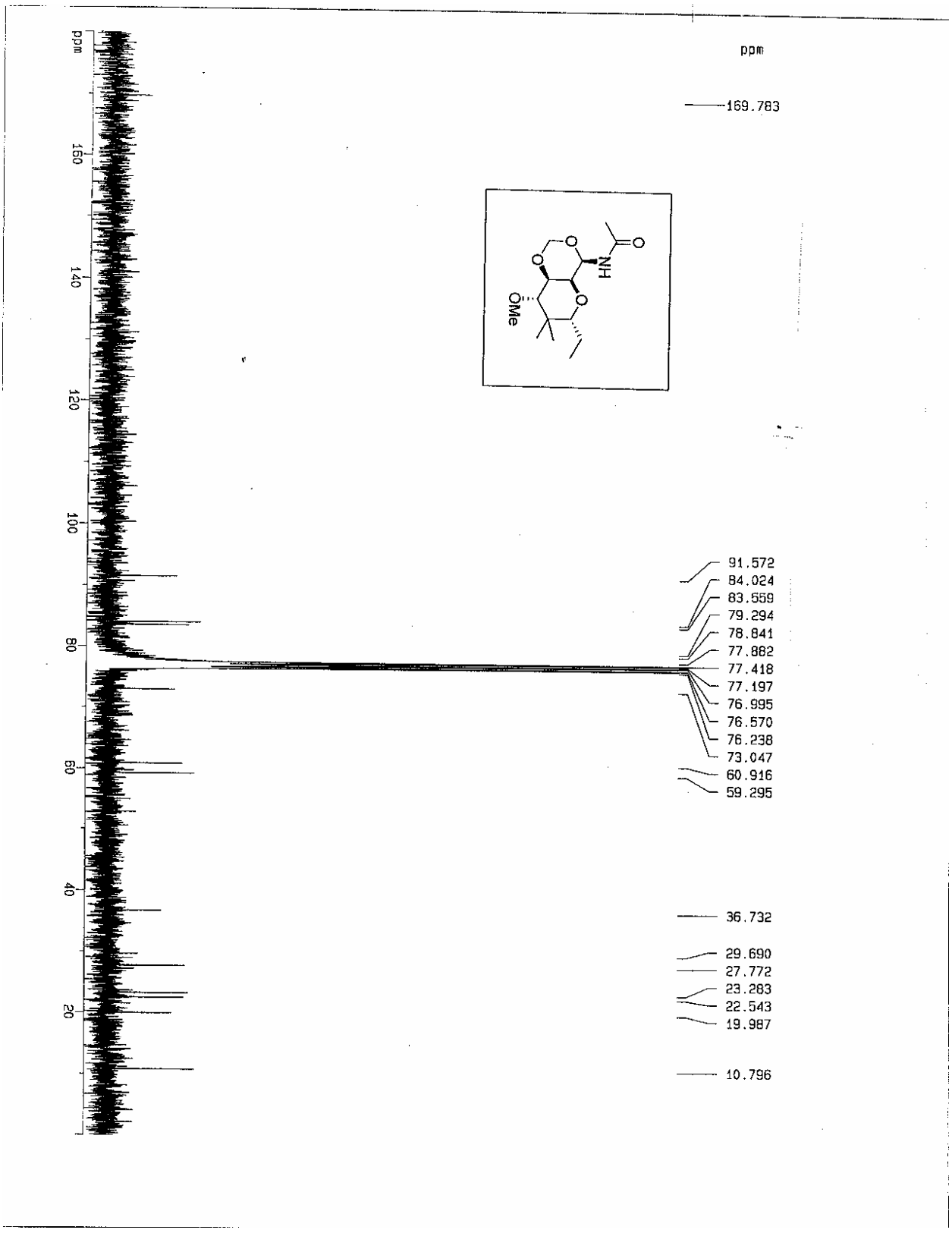

ppm
170.281
86.765
80.594
79.565
78.063
78.002
77.551
77.423
77.201
77.000
76.578
75.088
73.771
70.914
61.831
41.905
23.221
22.974
21.629
13.213
11.027
OMe
NH
O

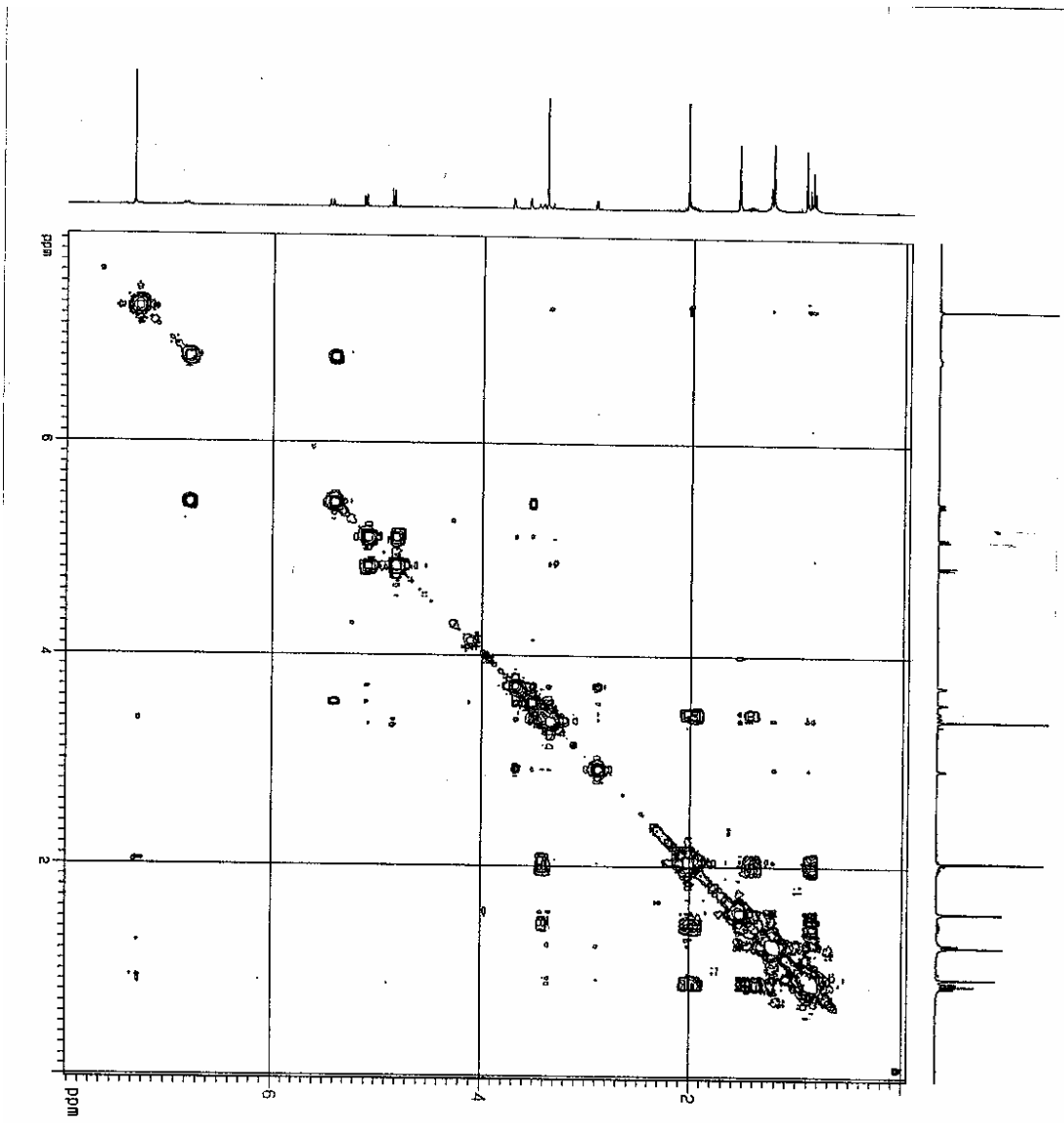

ppm
1
2
3
4
5

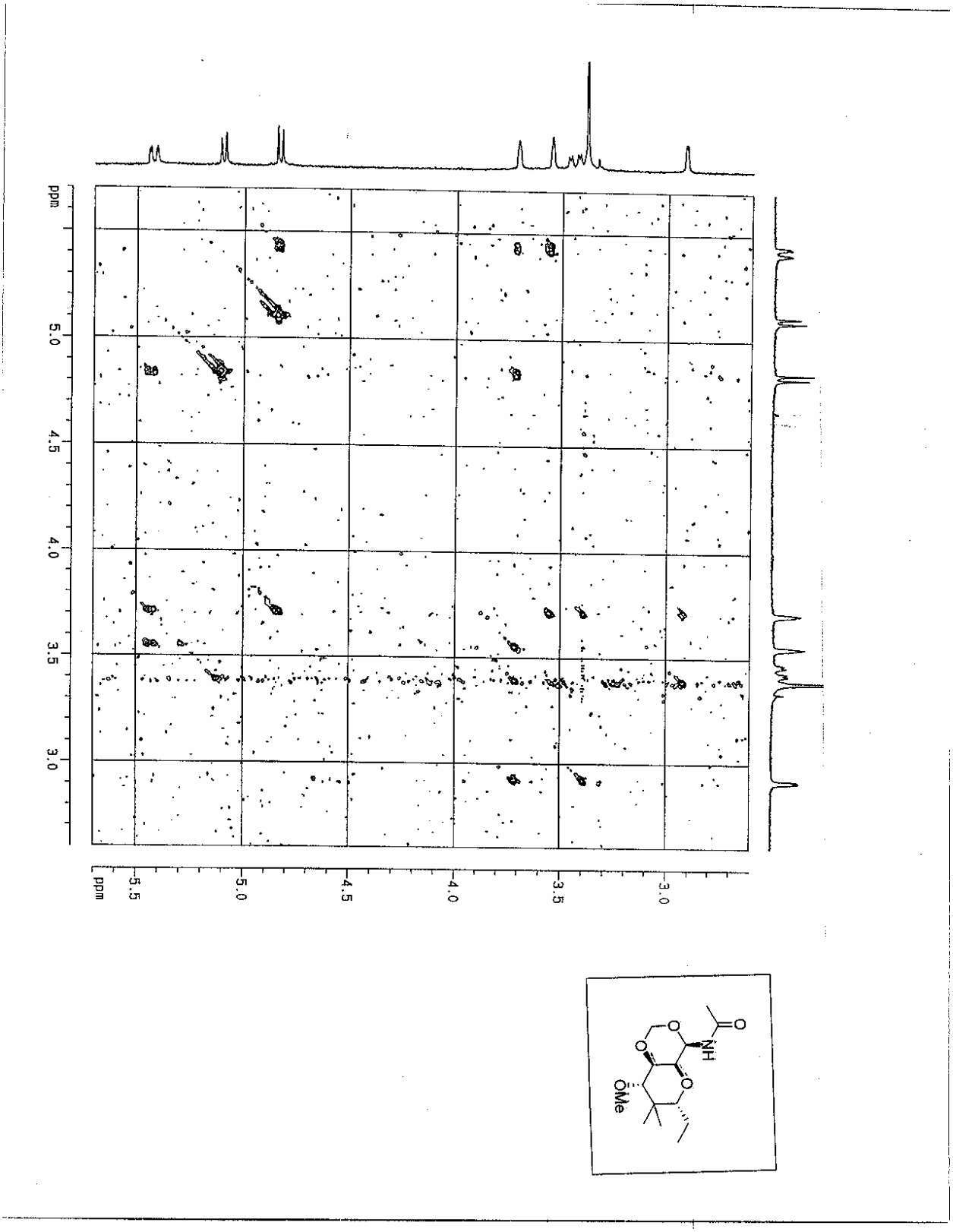

O
NH
O
O
O
OMe

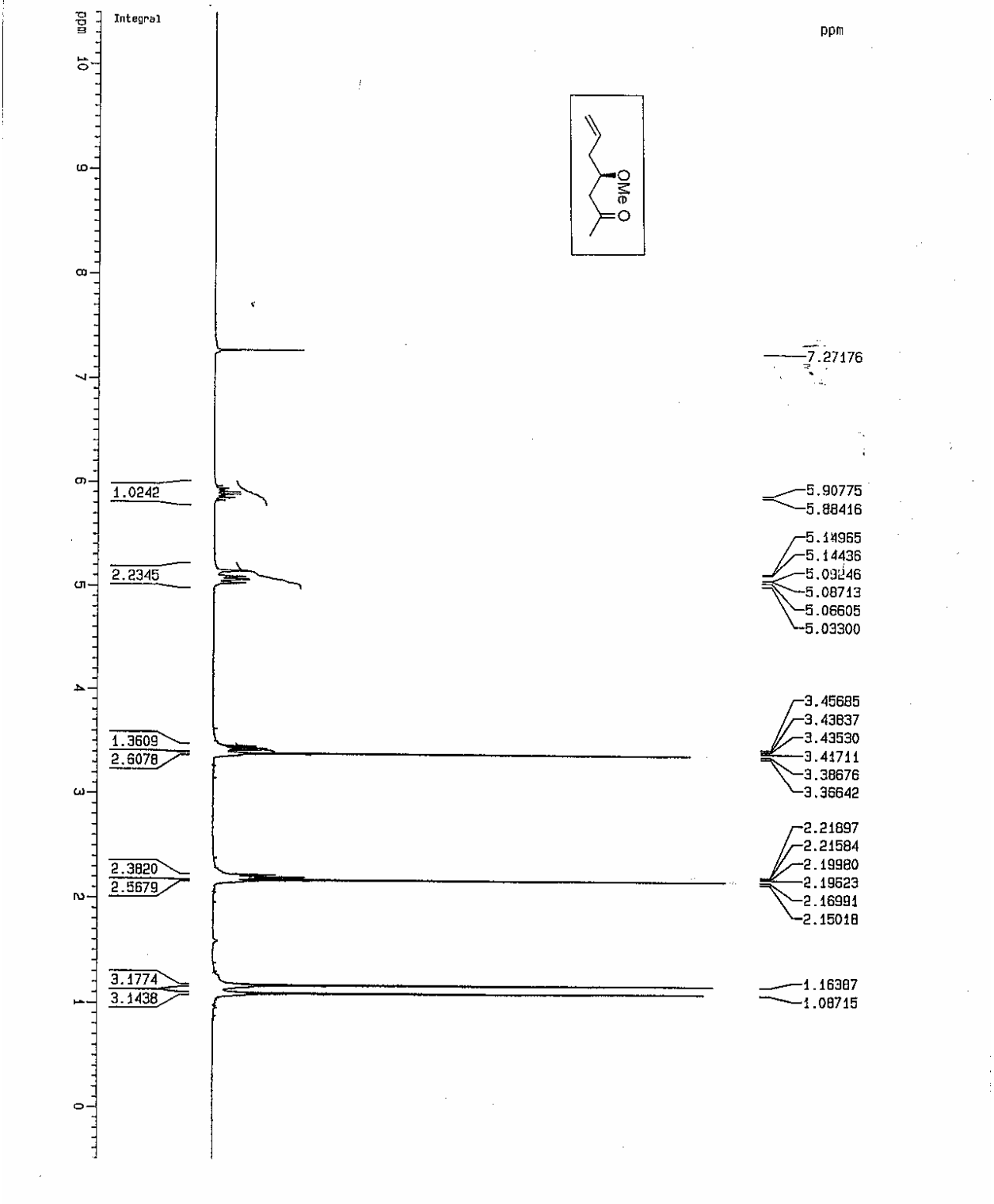

ppm
6
5
4
3
2
1
ppm
6
5
4
3
2
1
O
NH
O
O
OMe

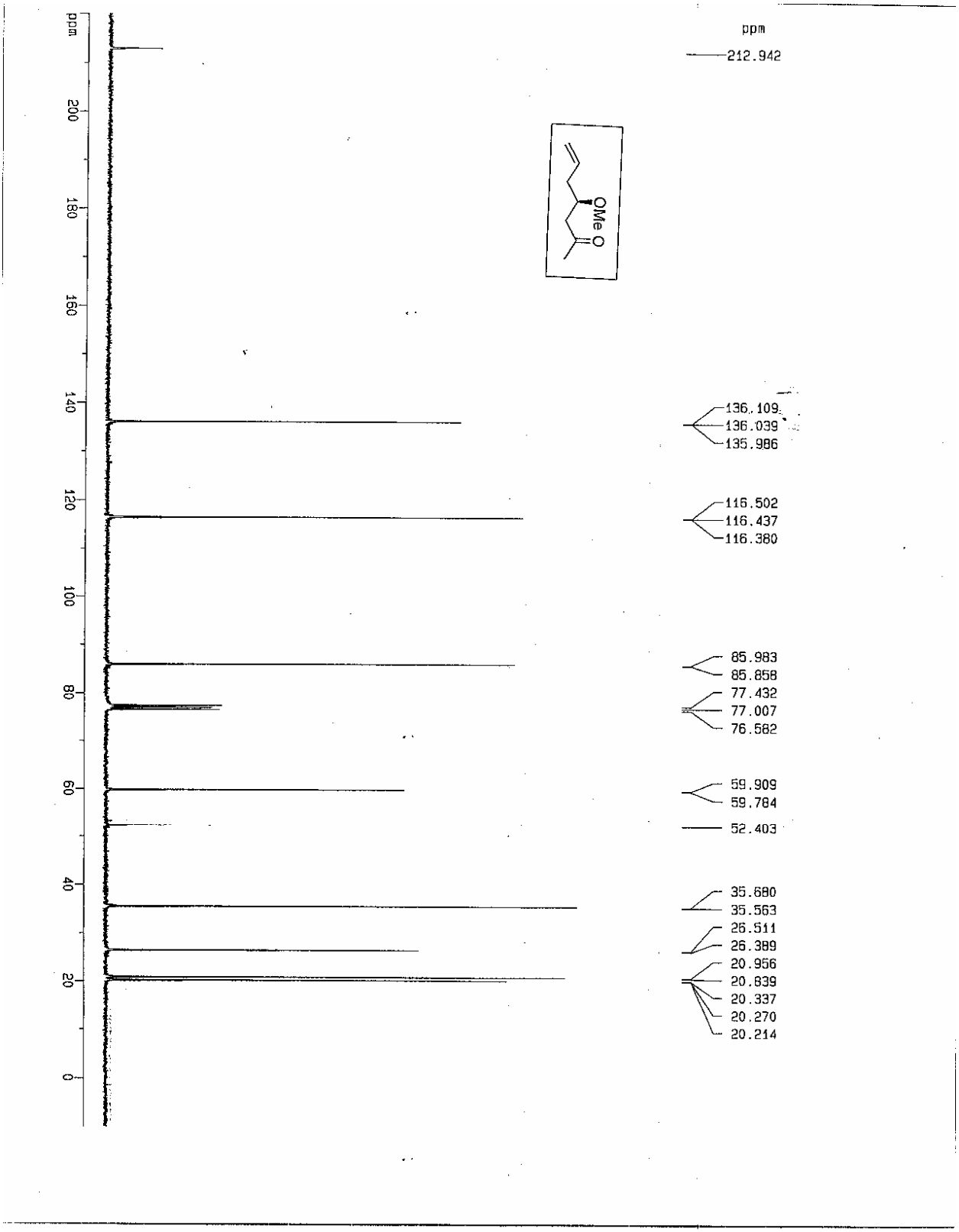

Integral
ppm
NH
OMe
0.9996
1.0204
1.0177
1.0397
1.0467
1.0363
1.1637
2.9815
1.0000
3.2988
2.1266
1.9929
3.5982
3.4172
4.7168
7.61644
7.27800
7.27063
7.26301
7.26111
7.25920
7.25739
7.25552
7.25353
7.25181
7.24992
6.81511
6.78467
5.44707
5.44020
5.41565
5.40889
5.11325
5.09109
4.84673
4.82446
3.70798
3.70186
3.54893
3.47145
3.46032
3.43107
3.41976
3.38792
3.33473
2.92148
2.91478
2.04324
2.03333
2.02262
2.00870
1.99951
1.98335
1.56383
1.46712
1.46213
1.45035
1.43725
1.42537
1.26450
1.24374
0.99323
0.94083
0.90357
0.89032
0.87910
0.85450

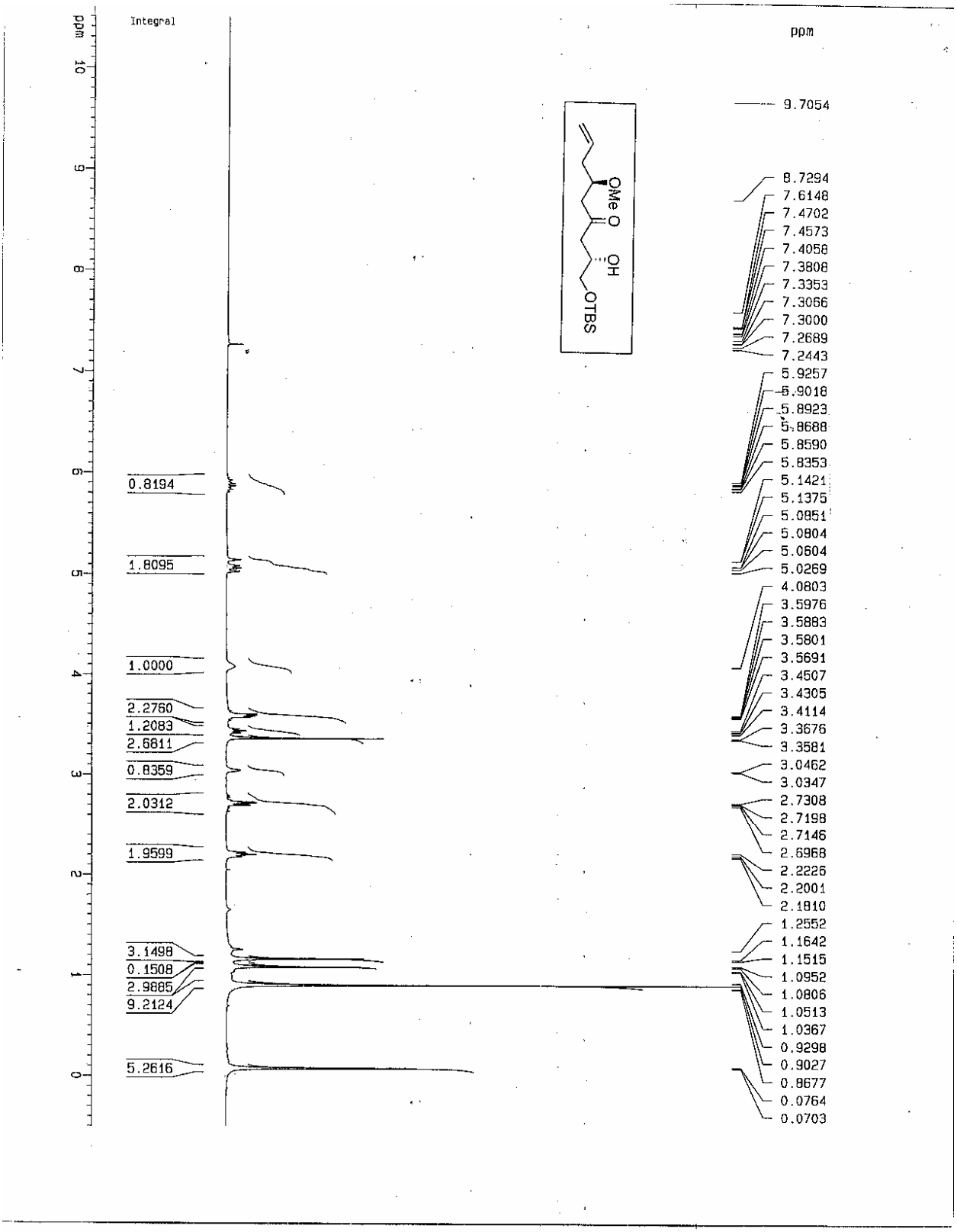

ppm
169.783
91.572
84.024
83.559
79.294
78.841
77.882
77.418
77.197
76.995
76.570
76.238
73.047
60.916
59.295
36.732
29.690
27.772
23.283
22.543
19.987
10.796
NH
OMe

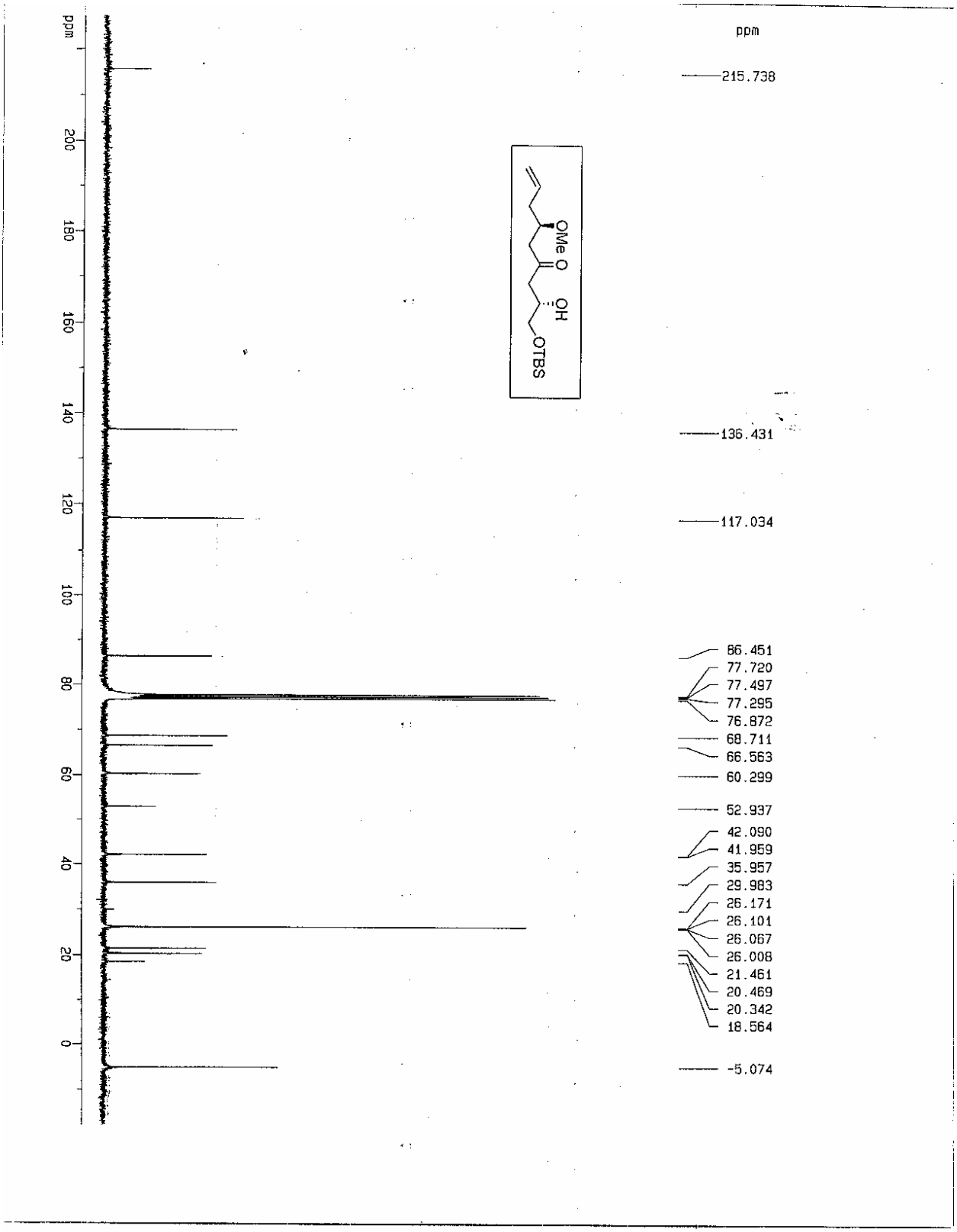

ppm
6
4
2
NH
OMe

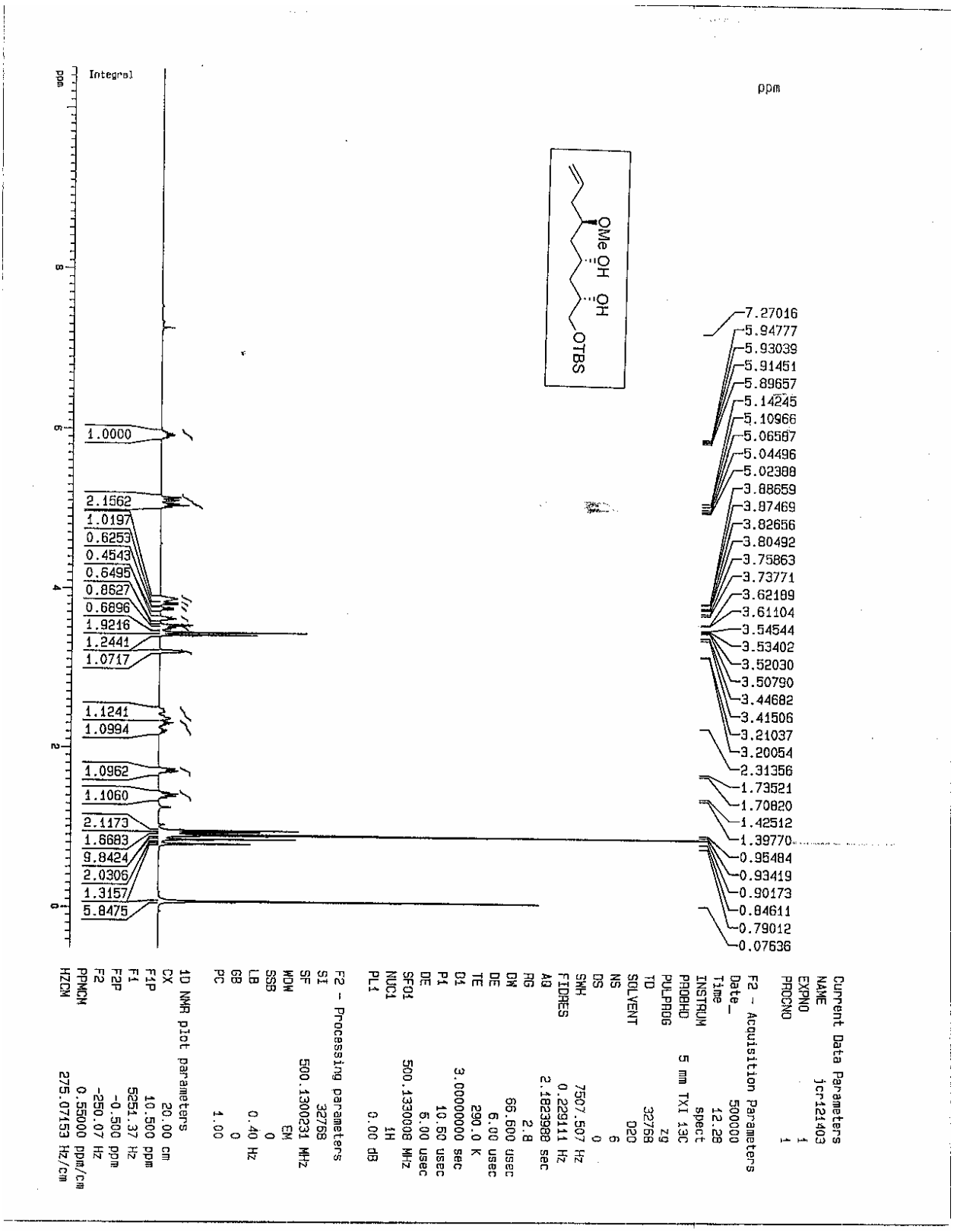

ppm
5.0
4.5
4.0
3.5
3.0
ppm
5.5
5.0
4.5
4.0
3.5
3.0
O
NH
O
O
O
OMe

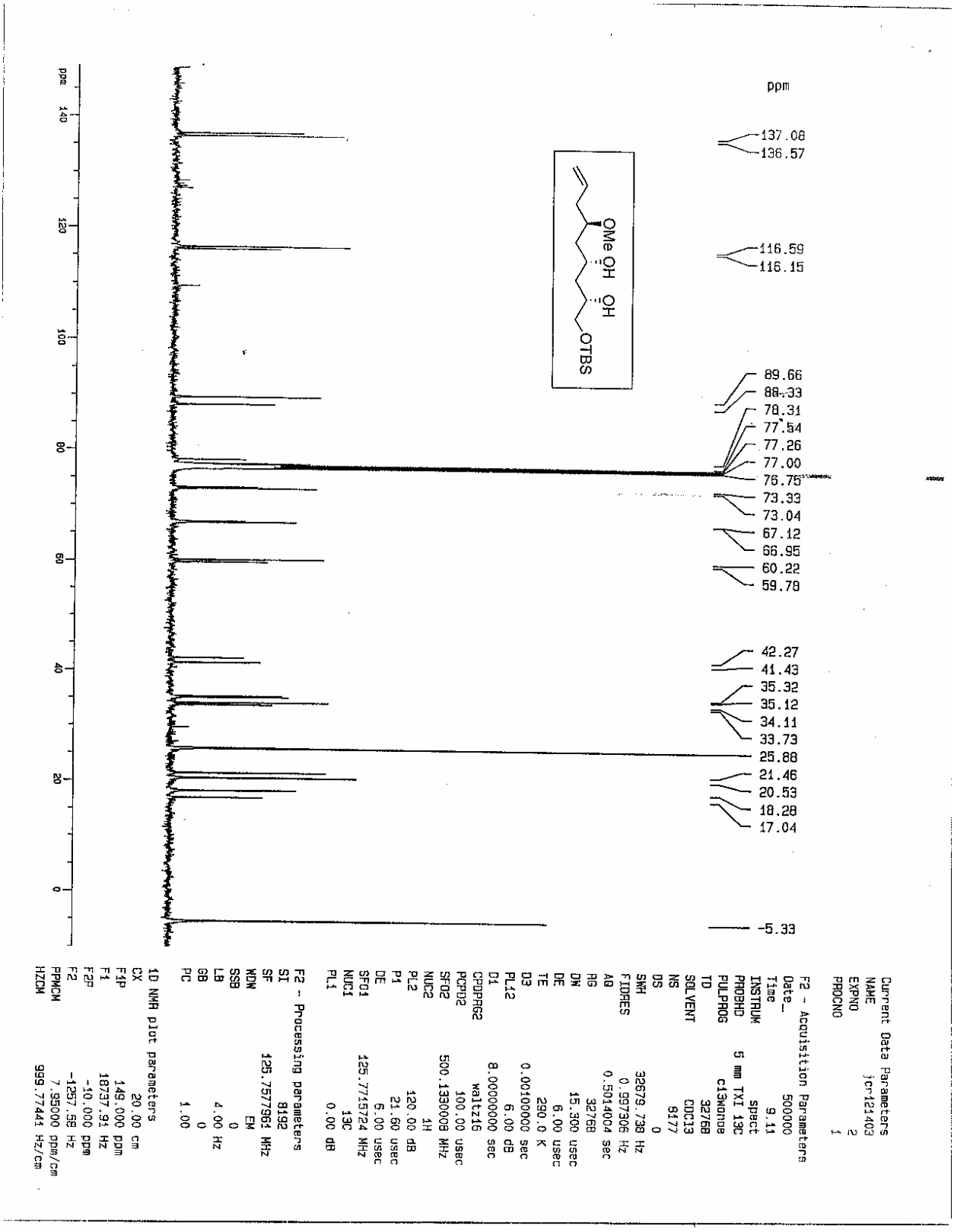

Integral
ppm
OMe
O
7.27176
5.90775
5.88416
5.14965
5.14436
5.09246
5.08713
5.06605
5.03300
3.45685
3.43837
3.43530
3.41711
3.38676
3.36642
2.21697
2.21584
2.19980
2.19623
2.16991
2.15018
1.16387
1.08715
1.0242
2.2345
1.3609
2.6078
2.3820
2.5679
3.1774
3.1438

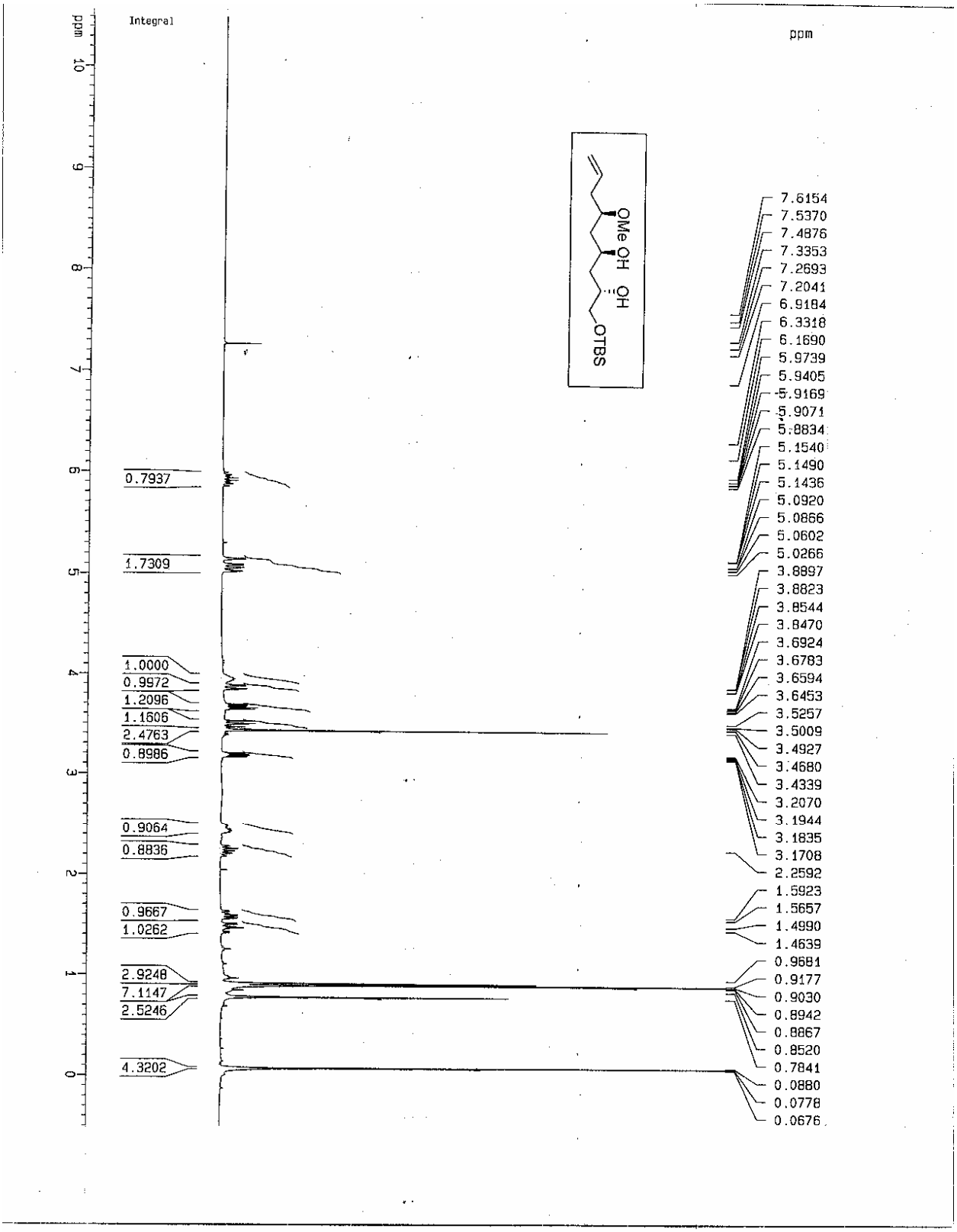

ppm
212.942
OMe O
136.109
136.039
135.986
116.502
116.437
116.380
85.983
85.858
77.432
77.007
76.582
59.909
59.784
52.403
35.680
35.563
26.511
26.389
20.956
20.839
20.337
20.270
20.214
ppm
200
180
160
140
120
100
80
60
40
20
0

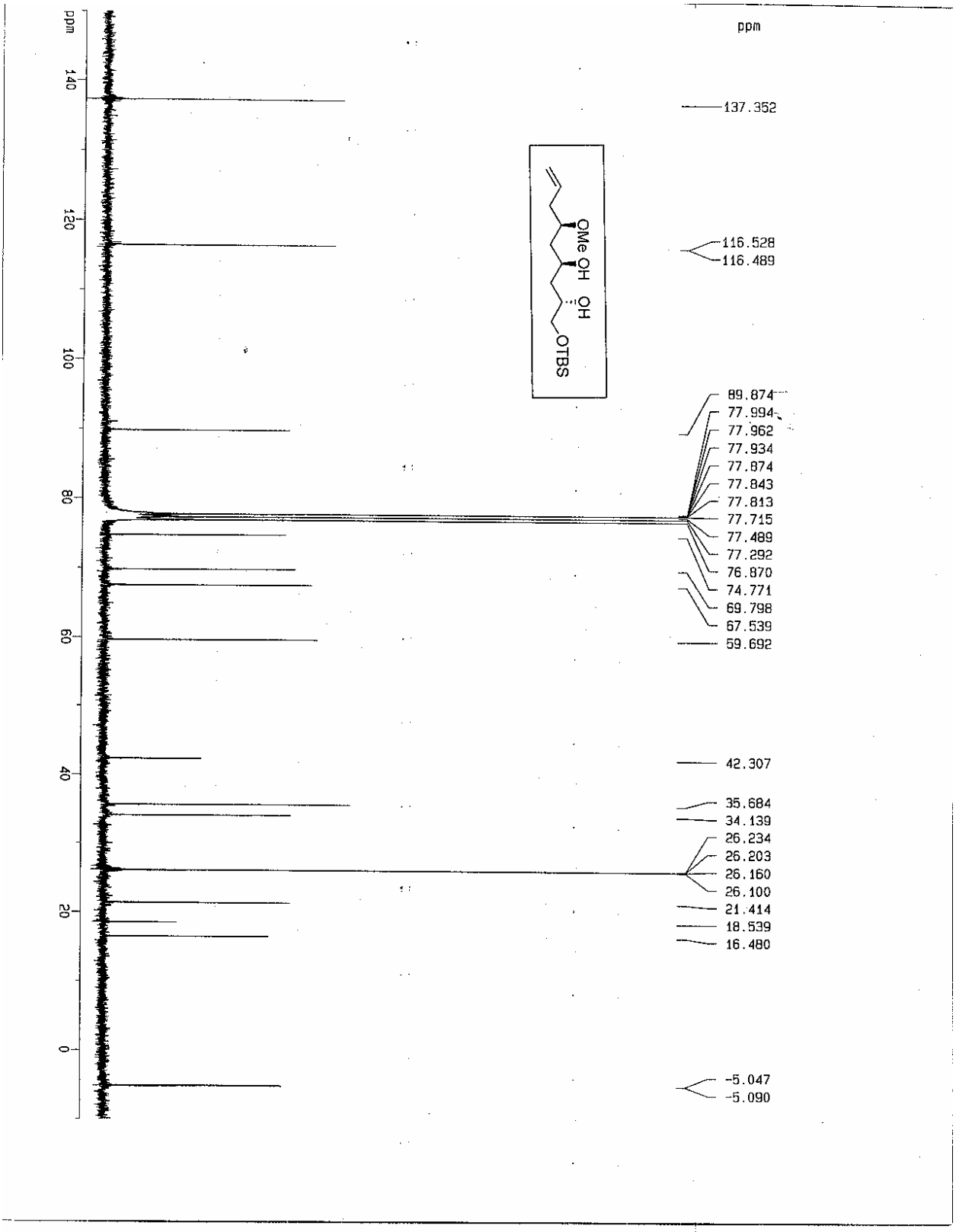

Integral
ppm
OMe O
OH
OTBS
0.8194
1.8095
1.0000
2.2760
1.2083
2.6811
0.8359
2.0312
1.9599
3.1498
0.1508
2.9885
9.2124
5.2616
9.7054
8.7294
7.6148
7.4702
7.4573
7.4058
7.3808
7.3353
7.3066
7.3000
7.2689
7.2443
5.9257
5.9018
5.8923
5.8688
5.8590
5.8353
5.1421
5.1375
5.0851
5.0804
5.0604
5.0269
4.0803
3.5976
3.5883
3.5801
3.5691
3.4507
3.4305
3.4114
3.3676
3.3581
3.0462
3.0347
2.7308
2.7198
2.7146
2.6968
2.2226
2.2001
2.1810
1.2552
1.1642
1.1515
1.0952
1.0806
1.0513
1.0367
0.9298
0.9027
0.8677
0.0764
0.0703

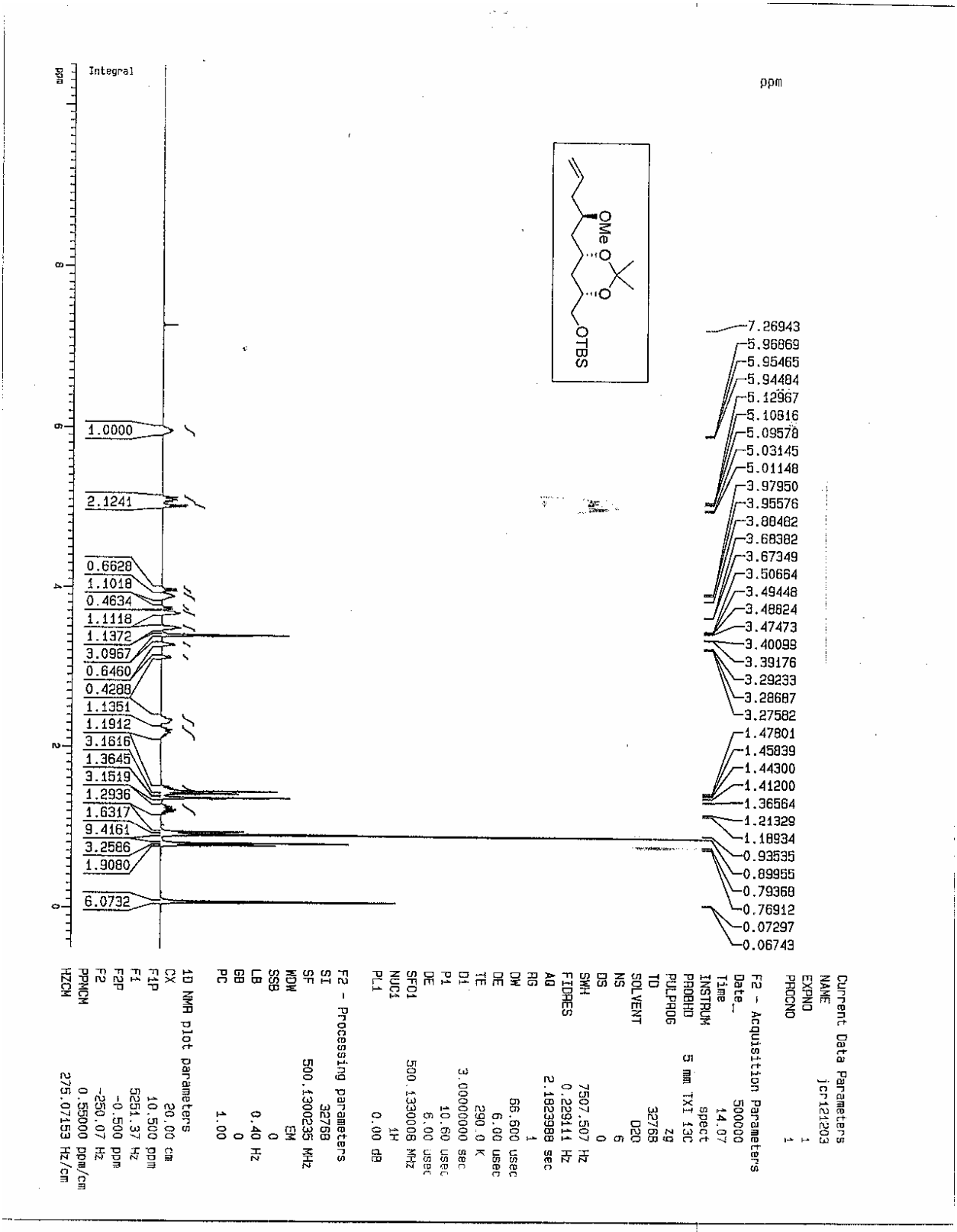

ppm
215.738
136.431
117.034
86.451
77.720
77.497
77.295
76.872
68.711
66.563
60.299
52.937
42.090
41.959
35.957
29.983
26.171
26.101
26.067
26.008
21.461
20.469
20.342
18.564
-5.074
OMe O
OH
OTBS

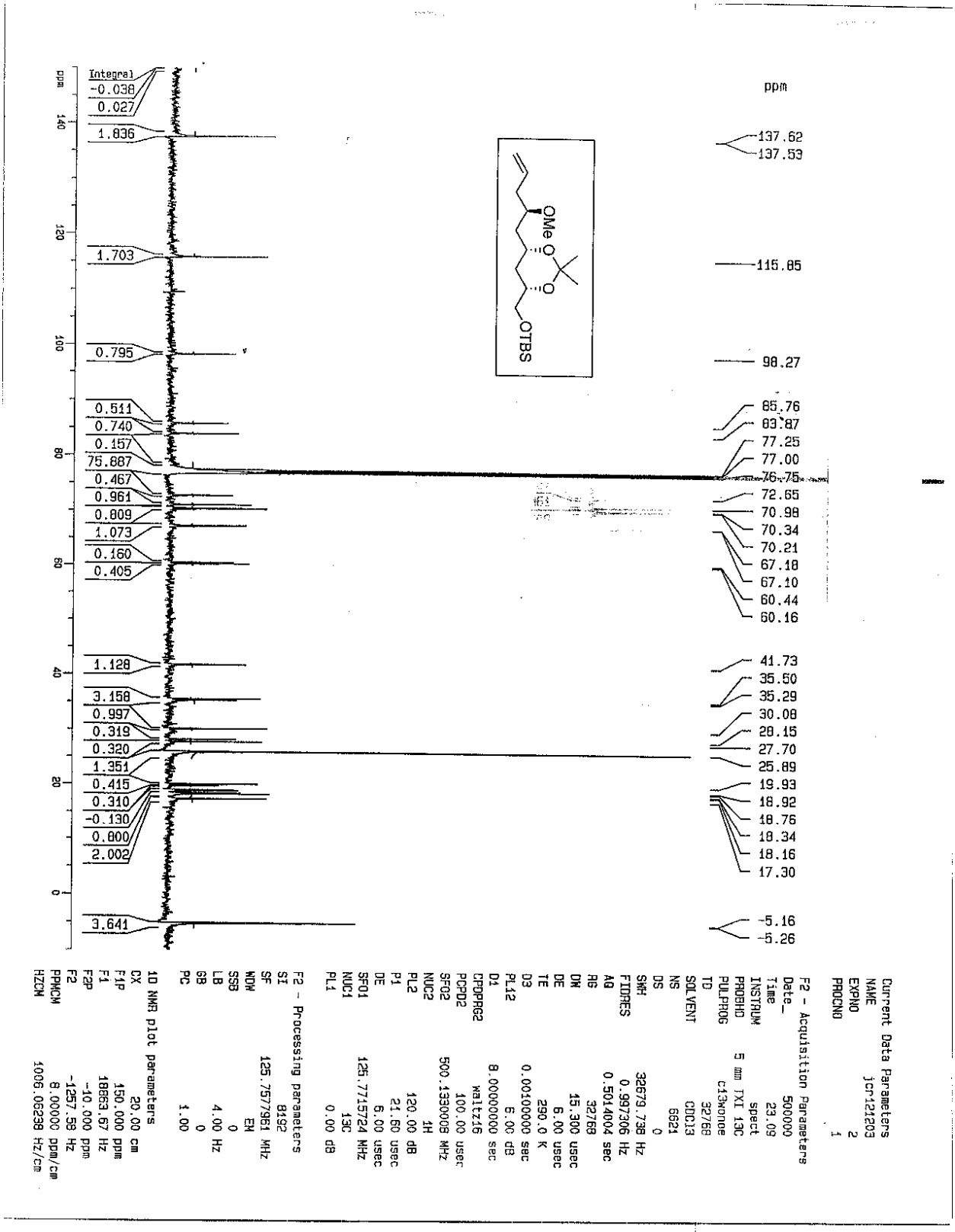

Integral
ppm
OMe OH OH
OTBS
1.0000
2.1562
1.0197
0.6253
0.4543
0.6495
0.8527
0.6896
1.9216
1.2441
1.0717
1.1241
1.0994
1.0962
1.1060
2.1173
1.6683
9.8424
2.0306
1.3157
5.8475
7.27016
5.94777
5.93039
5.91451
5.89657
5.14245
5.10966
5.06567
5.04496
5.02398
3.88659
3.87469
3.82656
3.80492
3.75863
3.73771
3.62189
3.61104
3.54544
3.53402
3.52030
3.50790
3.44682
3.41506
3.21037
3.20054
2.31356
1.73521
1.70820
1.42512
1.39770
0.95484
0.93419
0.90173
0.84611
0.79012
0.07636
Current Data Parameters
NAME jcr121403
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 500000
Time 12.28
INSTRUM spect
PROBHD 5 mm TXI 13C
PULPROG zg
TD 32768
SOLVENT D20
NS 6
DS 0
SWH 7507.507 Hz
FIDRES 0.229111 Hz
AQ 2.1823988 sec
RG 2.8
DW 66.600 usec
DE 6.00 usec
TE 290.0 K
D1 3.00000000 sec
P1 10.50 usec
DE 5.00 usec
SFO1 500.1330008 MHz
NUC1 1H
PL1 0.00 dB
F2 - Processing parameters
SI 32768
SF 500.1300231 MHz
WDW EM
SSB 0
LB 0.40 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 10.500 ppm
F1 5254.37 Hz
F2P -0.500 ppm
F2 -250.07 Hz
PPMCM 0.55000 ppm/cm
HZCM 275.07153 Hz/cm

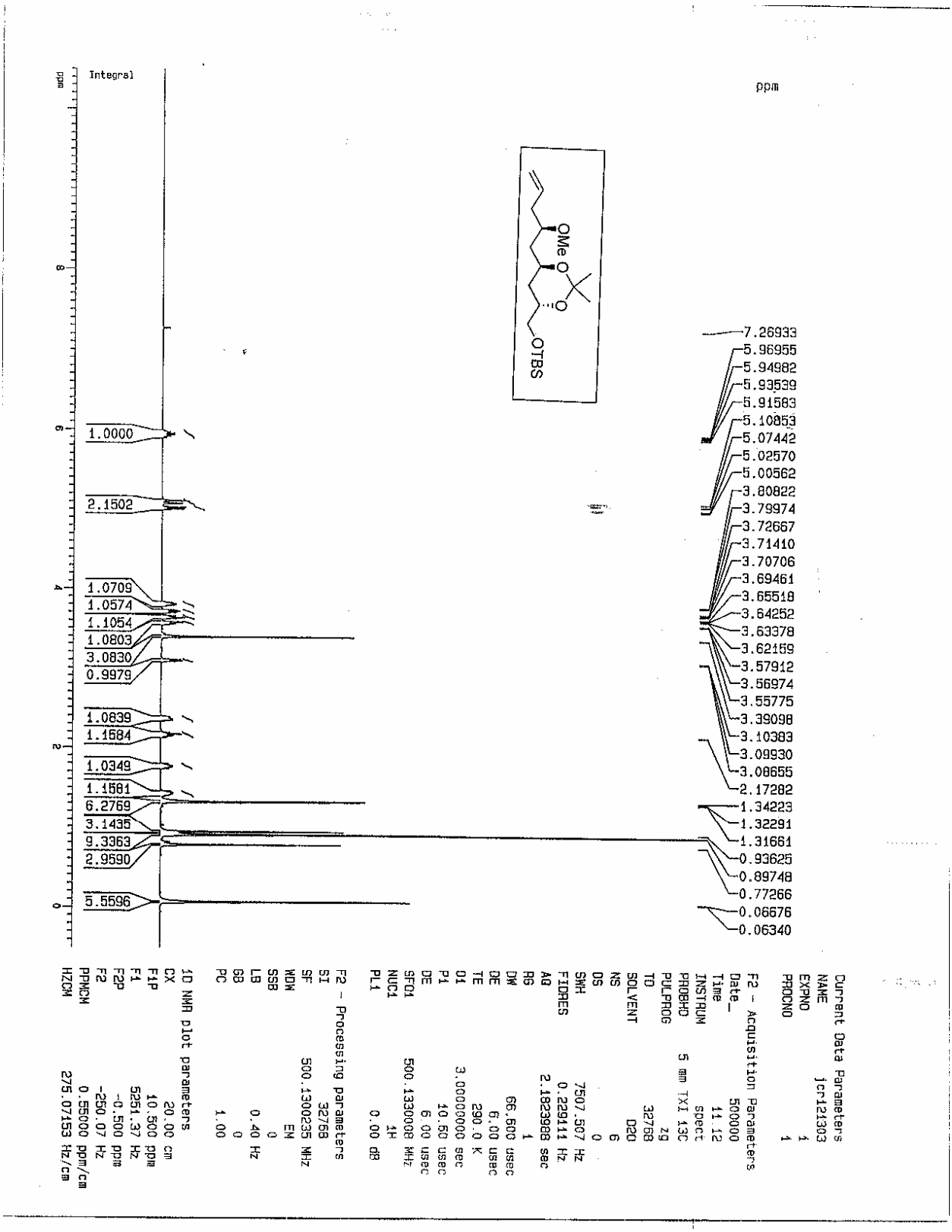

ppm
137.08
136.57
116.59
116.15
89.66
88.33
78.31
77.54
77.26
77.00
76.75
73.33
73.04
67.12
66.95
60.22
59.78
42.27
41.43
35.32
35.12
34.11
33.73
25.88
21.46
20.53
18.28
17.04
-5.33
OMe
OH
OH
OTBS
ppm
140
120
100
80
60
40
20
0
Current Data Parameters
NAME jcr121403
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 500000
Time 9.11
INSTRUM spect
PROBHD 5 mm TXI 13C
PULPROG c13mgtaue
TD 32768
SOLVENT CDCl3
NS 8477
DS 0
SWH 32679.738 Hz
FIDRES 0.997306 Hz
AQ 0.5014004 sec
RG 32768
DW 15.300 usec
DE 6.00 usec
TE 290.0 K
D3 0.00100000 sec
PL12 6.00 dB
D1 8.00000000 sec
CPDPRG2 waltz16
PCPD2 100.00 usec
SFO2 500.1330008 MHz
NUC2 1H
PL2 120.00 dB
P1 21.60 usec
DE 6.00 usec
SFO1 125.7715724 MHz
NUC1 13C
PL1 0.00 dB
F2 - Processing parameters
SI 8192
SF 125.7577964 MHz
WDW EM
SSB 0
LB 4.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 149.000 ppm
F1 18737.91 Hz
F2P -10.000 ppm
F2 -1257.58 Hz
PPMCM 7.95000 ppm/cm
HZCM 999.77441 Hz/cm

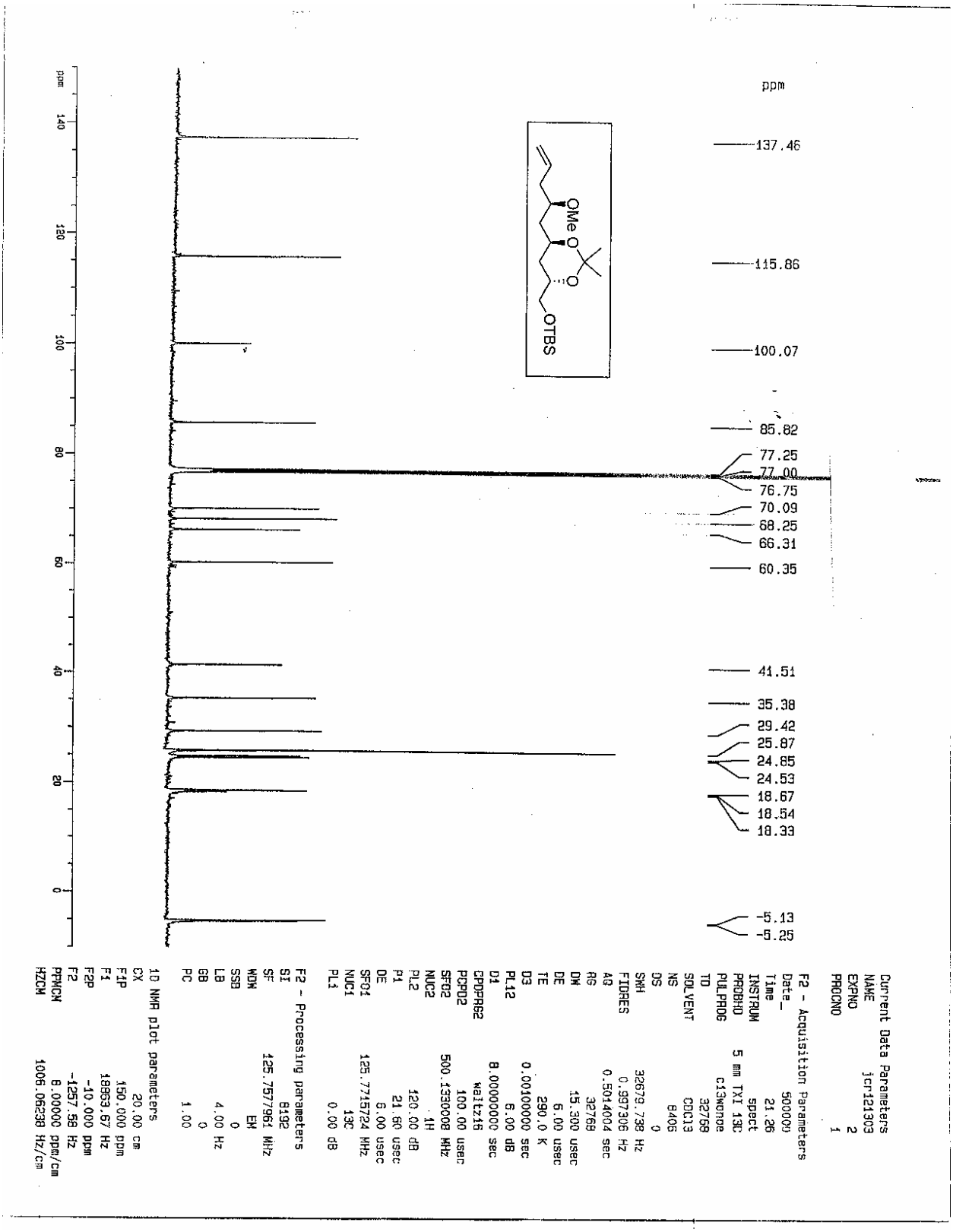

Integral
ppm
OMe OH OH
OTBS
0.7937
1.7309
1.0000
0.9972
1.2096
1.1606
2.4763
0.8986
0.9064
0.8836
0.9667
1.0262
2.9248
7.1147
2.5246
4.3202
7.6154
7.5370
7.4876
7.3353
7.2693
7.2041
6.9184
6.3318
6.1690
5.9739
5.9405
5.9169
5.9071
5.8834
5.1540
5.1490
5.1436
5.0920
5.0866
5.0602
5.0266
3.8897
3.8823
3.8544
3.8470
3.6924
3.6783
3.6594
3.6453
3.5257
3.5009
3.4927
3.4680
3.4339
3.2070
3.1944
3.1835
3.1708
2.2592
1.5923
1.5657
1.4990
1.4639
0.9681
0.9177
0.9030
0.8942
0.8867
0.8520
0.7841
0.0880
0.0778
0.0676

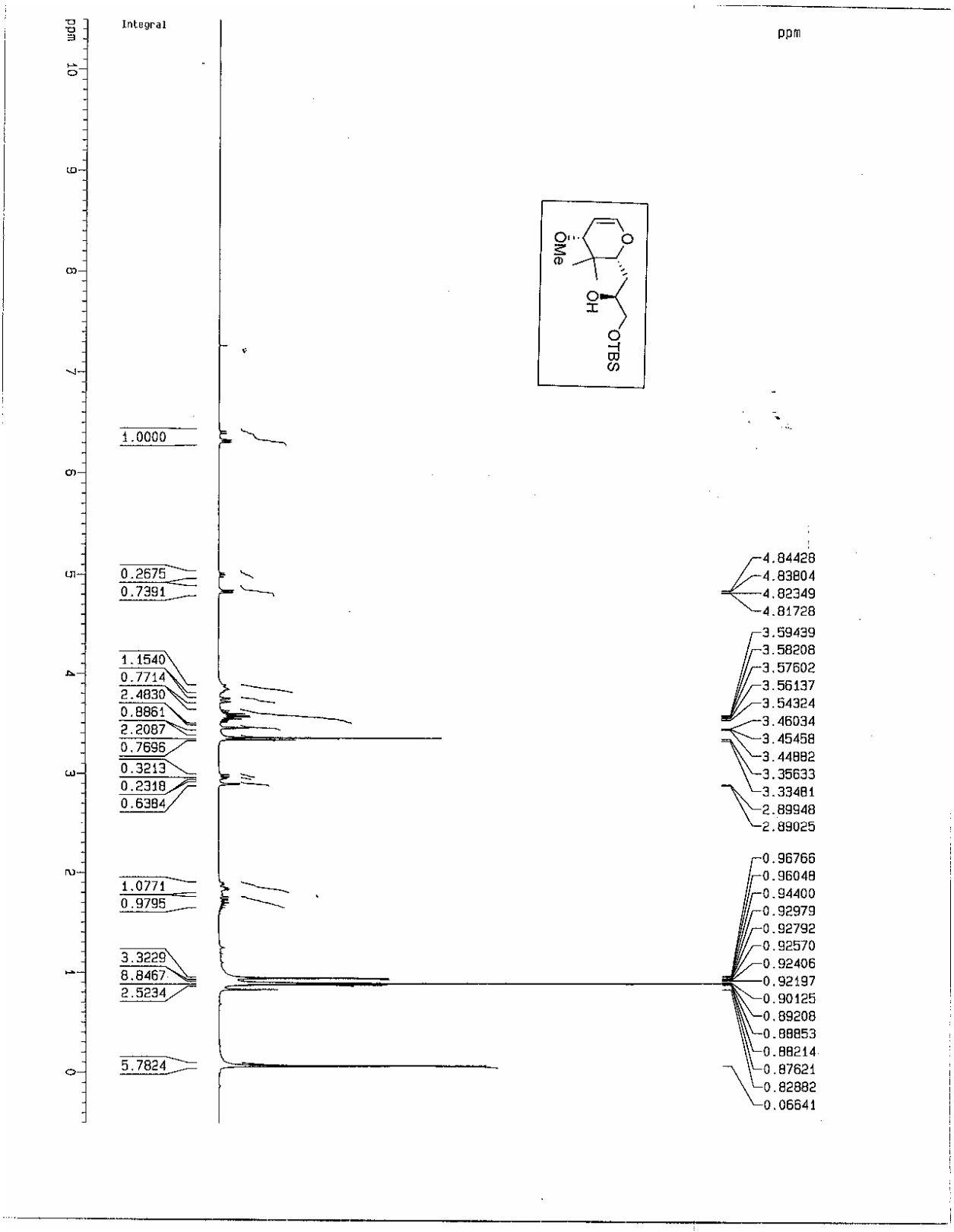

ppm
140
120
100
80
60
40
20
0
ppm
137.352
116.528
116.489
OMe
OH
OH
OTBS
89.874
77.994
77.962
77.934
77.874
77.843
77.813
77.715
77.489
77.292
76.870
74.771
69.798
67.539
59.692
42.307
35.684
34.139
26.234
26.203
26.160
26.100
21.414
18.539
16.480
-5.047
-5.090

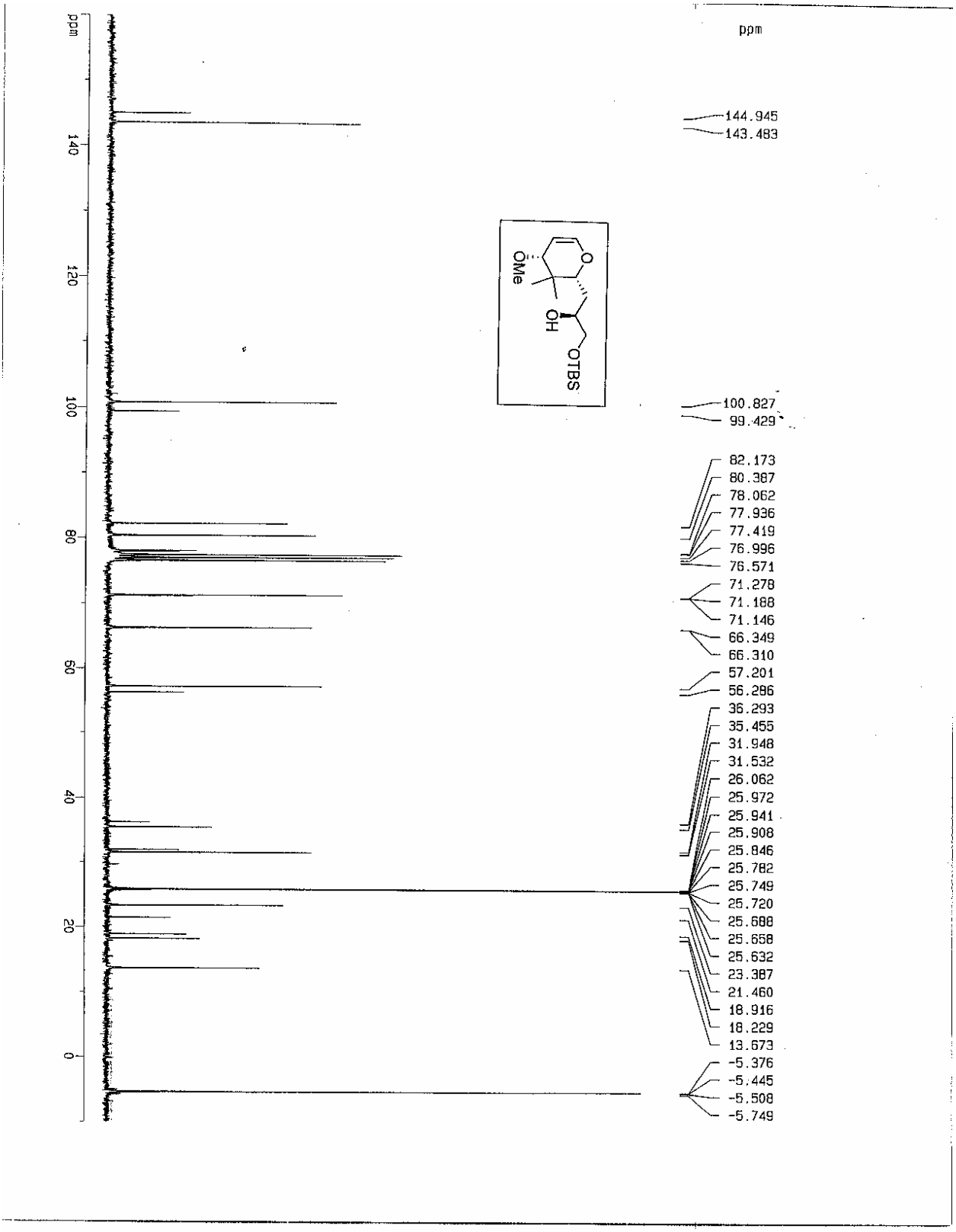

Integral
ppm
OMe
OTBS
1.0000
2.1241
0.6628
1.1018
0.4634
1.1118
1.1372
3.0967
0.6460
0.4288
1.1351
1.1912
3.1616
1.3645
3.1519
1.2936
1.6317
9.4161
3.2586
1.9080
6.0732
7.26943
5.96869
5.95465
5.94484
5.12967
5.10816
5.09578
5.03145
5.01148
3.97950
3.95576
3.88462
3.68382
3.67349
3.50664
3.49448
3.48824
3.47473
3.40099
3.39176
3.29233
3.28687
3.27582
1.47801
1.45839
1.44300
1.41200
1.36564
1.21329
1.18934
0.93535
0.89955
0.79368
0.76912
0.07297
0.06743
Current Data Parameters
NAME jcr12203
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 500000
Time 14.07
INSTRUM spect
PROBHD 5 mm TXI 13C
PULPROG zg
TD 32768
SOLVENT D2O
NS 6
DS 0
SWH 7507.507 Hz
FIDRES 0.229111 Hz
AQ 2.1823988 sec
RG 1
DW 66.600 usec
DE 6.00 usec
TE 290.0 K
D1 3.00000000 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 500.1300235 MHz
WDW EM
SSB 0
LB 0.40 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 10.500 ppm
F1 5251.37 Hz
F2P -0.500 ppm
F2 -250.07 Hz
PPMCM 0.55000 ppm/cm
HZCM 275.07153 Hz/cm

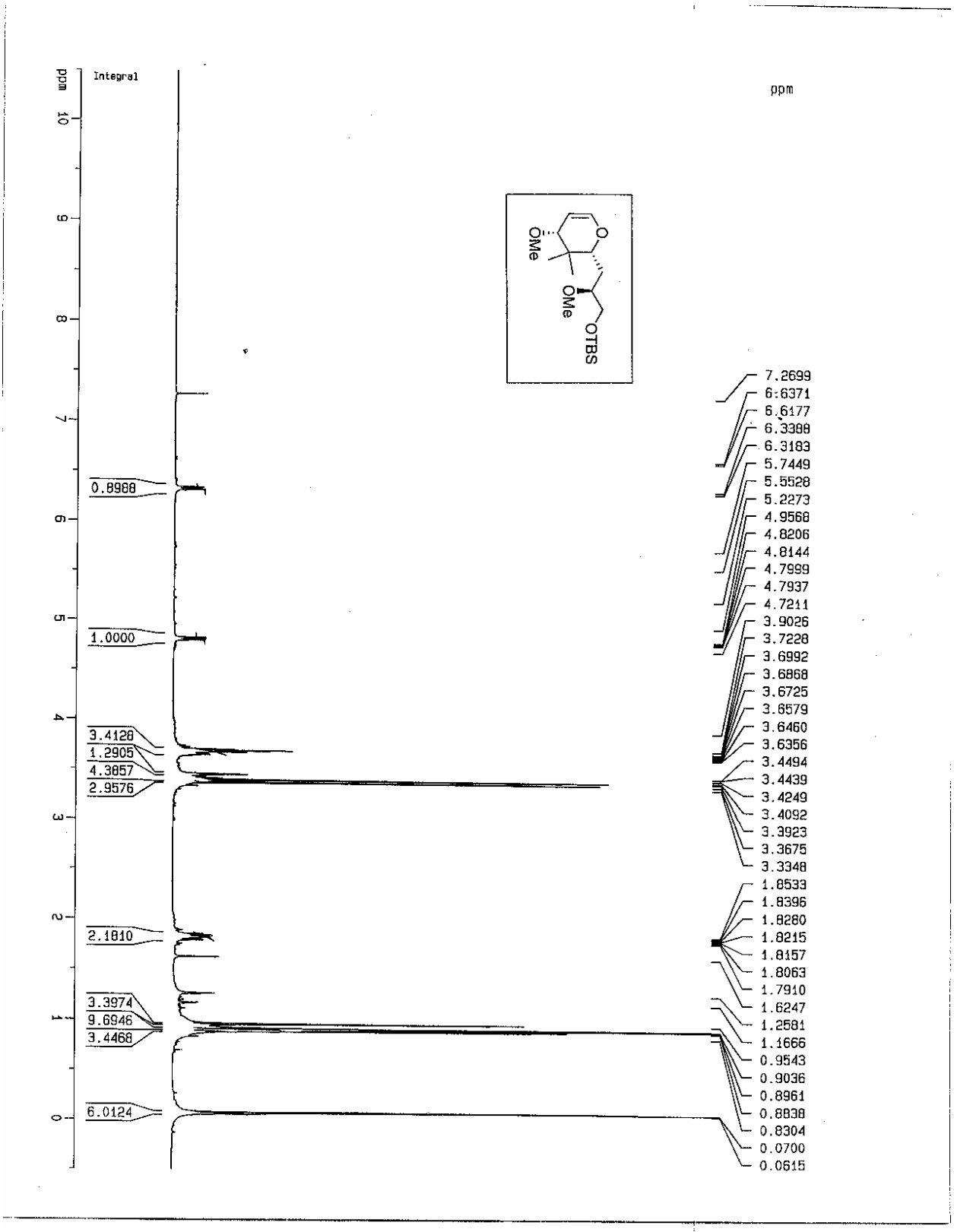

Integral
-0.038
0.027
1.836
1.703
0.795
0.511
0.740
0.157
75.887
0.467
0.961
0.809
1.073
0.160
0.405
1.128
3.158
0.997
0.319
0.320
1.351
0.415
0.310
-0.130
0.800
2.002
3.641
ppm
OMe
OTBS
137.62
137.53
115.85
98.27
85.76
83.87
77.25
77.00
76.75
72.65
70.98
70.34
70.21
67.18
67.10
60.44
60.16
41.73
35.50
35.29
30.08
28.15
27.70
25.89
19.93
18.92
18.76
18.34
18.16
17.30
-5.16
-5.26
Current Data Parameters
NAME jcr121203
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 500000
Time 23.09
INSTRUM spect
PROBHD 5 mm TXI 13C
PULPROG c13wnoe
TD 32768
SOLVENT CDCl3
NS 6621
DS 0
SWH 32679.738 Hz
FIDRES 0.997306 Hz
AQ 0.5014004 sec
RG 32768
DW 15.300 usec
DE 6.00 usec
TE 290.0 K
D3 0.00100000 sec
PL12 6.00 dB
D1 8.00000000 sec
CPDPRG2 waltz16
PCPD2 100.00 usec
SFO2 500.1330008 MHz
NUC2 1H
PL2 120.00 dB
P1 21.60 usec
DE 6.00 usec
SFO1 125.7715724 MHz
NUC1 13C
PL1 0.00 dB
F2 - Processing parameters
SI 8192
SF 125.7577961 MHz
WDW EM
SSB 0
LB 4.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 150.000 ppm
F1 18863.67 Hz
F2P -10.000 ppm
F2 -1257.58 Hz
PPMCM 8.00000 ppm/cm
HZCM 1006.05238 Hz/cm

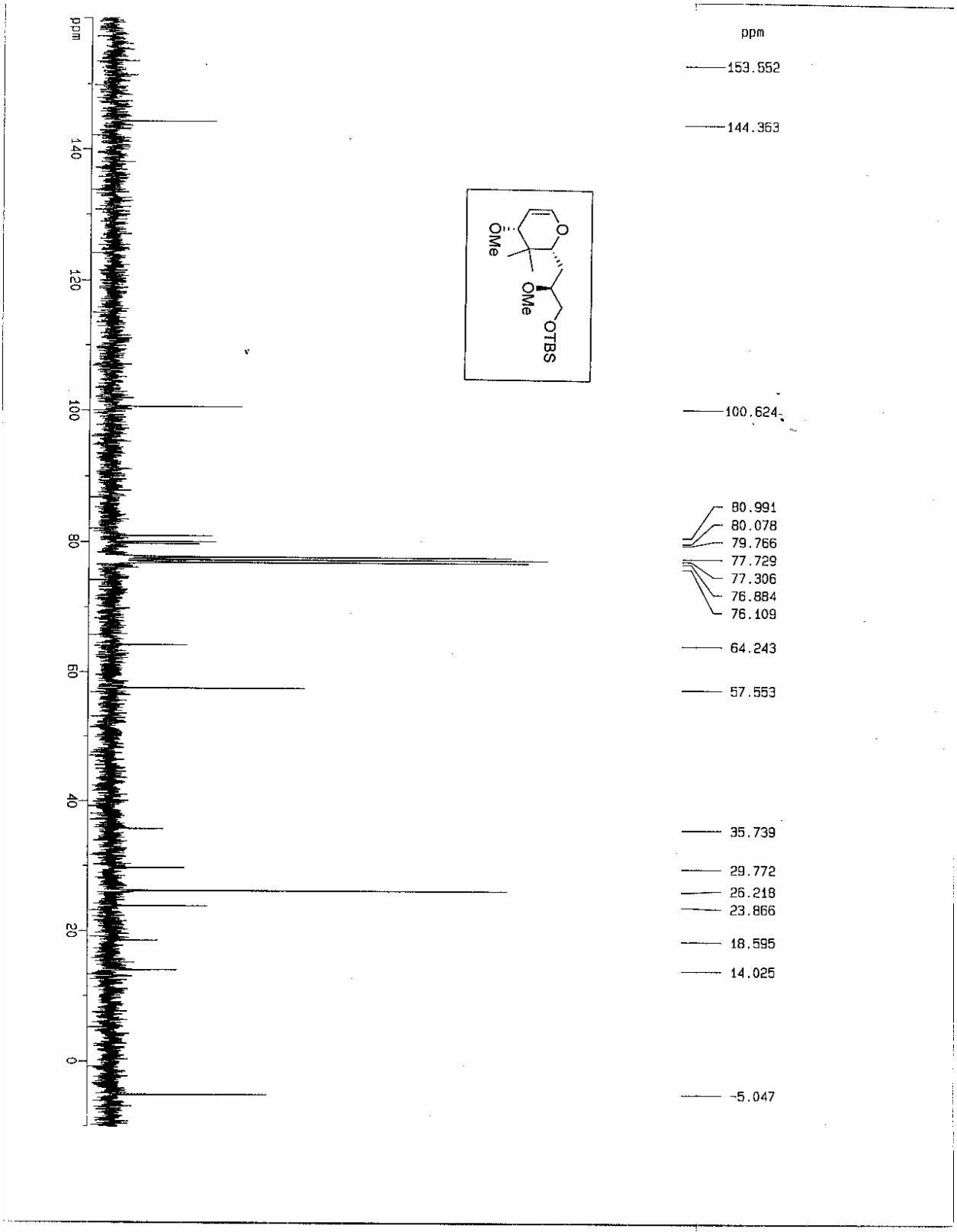

Integral
ppm
1.0000
2.1502
1.0709
1.0574
1.1054
1.0803
3.0830
0.9979
1.0839
1.1684
1.0349
1.1581
6.2769
3.1435
9.3363
2.9590
5.5596
OMe
O
O
OTBS
7.26933
5.96955
5.94982
5.93539
5.91583
5.10853
5.07442
5.02570
5.00562
3.80822
3.79974
3.72667
3.71410
3.70706
3.69461
3.65518
3.64252
3.63378
3.62159
3.57912
3.56974
3.55775
3.39098
3.10383
3.09930
3.08655
2.17282
1.34223
1.32291
1.31681
0.93625
0.89748
0.77266
0.06676
0.06340
Current Data Parameters
NAME jcr121303
EXPNO 4
PROCNO 1
F2 - Acquisition Parameters
Date_ 500000
Time 11.12
INSTRUM spect
PROBHD 5 mm TXI 13C
PULPROG zg
TD 32768
SOLVENT D2O
NS 6
DS 0
SWH 7507.507 Hz
FIDRES 0.229111 Hz
AQ 2.1823988 sec
RG 1
DW 66.600 usec
DE 6.00 usec
TE 290.0 K
D1 3.00000000 sec
P1 10.50 usec
DE 6.00 usec
SFO1 500.1330008 MHz
NUC1 1H
PL1 0.00 dB
F2 - Processing parameters
SI 32768
SF 500.1300235 MHz
WDW EM
SSB 0
LB 0.40 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 10.500 ppm
F1 5251.37 Hz
F2P -0.500 ppm
F2 -250.07 Hz
PPMCM 0.55000 ppm/cm
HZCM 275.07153 Hz/cm

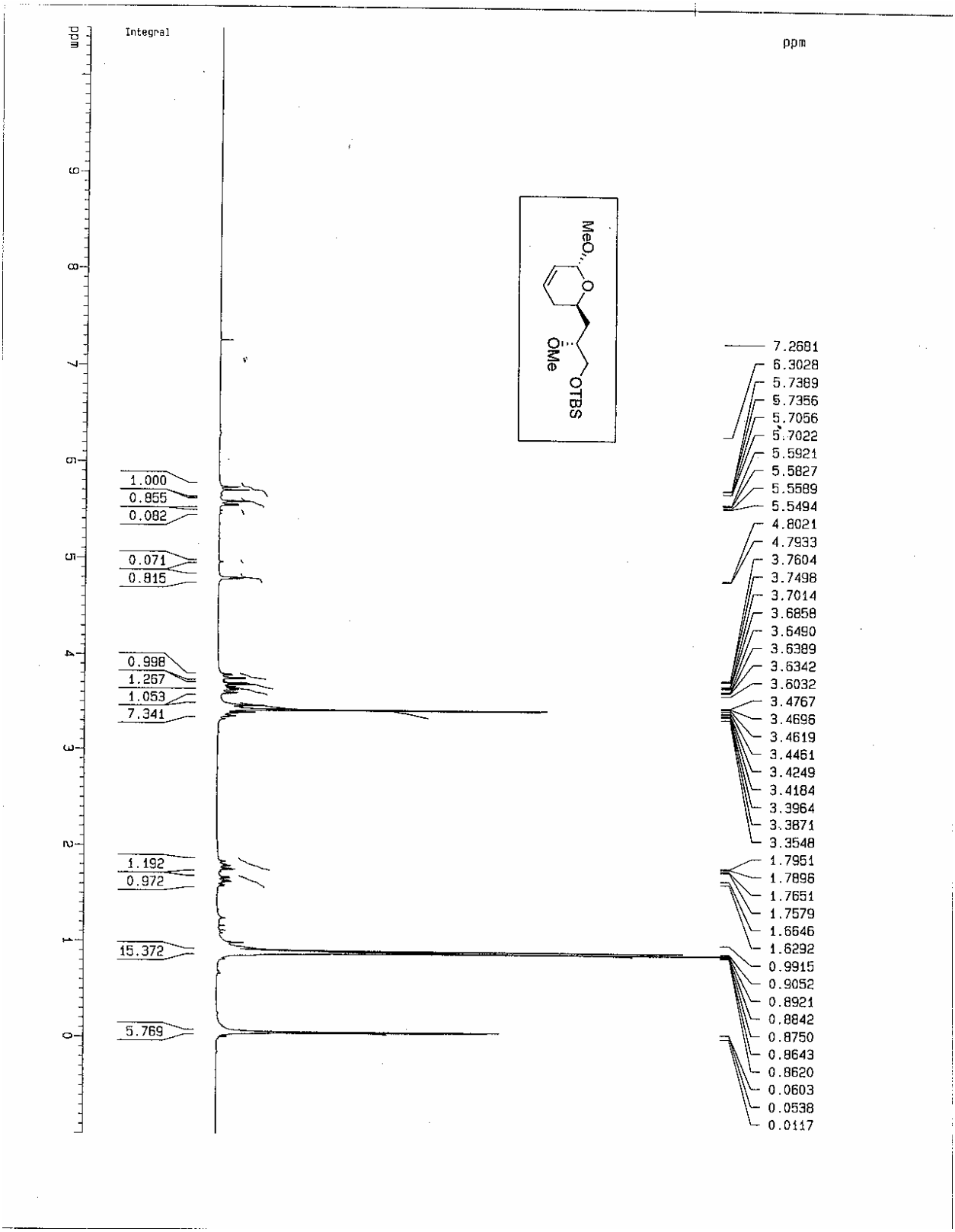

OMe
OTBS
ppm
137.46
115.86
100.07
85.82
77.25
77.00
76.75
70.09
68.25
66.31
60.35
41.51
35.38
29.42
25.87
24.85
24.53
18.67
18.54
18.33
-5.13
-5.25
Current Data Parameters
NAME jcr121303
EXPNO 2
PROCNO 1
F2 - Acquisition Parameters
Date_ 50000y
Time 21.26
INSTRUM spect
PROBHD 5 mm TXI 13C
PULPROG c13mgpsp
TD 32768
SOLVENT CDCl3
NS 8406
DS 0
SWH 32679.738 Hz
FIDRES 0.997306 Hz
AQ 0.5014004 sec
RG 32769
DW 15.300 usec
DE 6.00 usec
TE 290.0 K
D3 0.00100000 sec
PL12 6.00 dB
D1 8.00000000 sec
CPDPRG2 waltz16
PCPD2 100.00 usec
SFO2 500.1330008 MHz
NUC2 1H
PL2 120.00 dB
P1 21.60 usec
DE 6.00 usec
SFO1 125.7715724 MHz
NUC1 13C
PL1 0.00 dB
F2 - Processing parameters
SI 8192
SF 125.7577961 MHz
WDW EM
SSB 0
LB 4.00 Hz
GB 0
PC 1.00
1D NMR plot parameters
CX 20.00 cm
F1P 150.000 ppm
F1 18863.67 Hz
F2P -10.000 ppm
F2 -1257.58 Hz
PPMCM 8.00000 ppm/cm
HZCM 1006.06238 Hz/cm
ppm
140
120
100
80
60
40
20
0

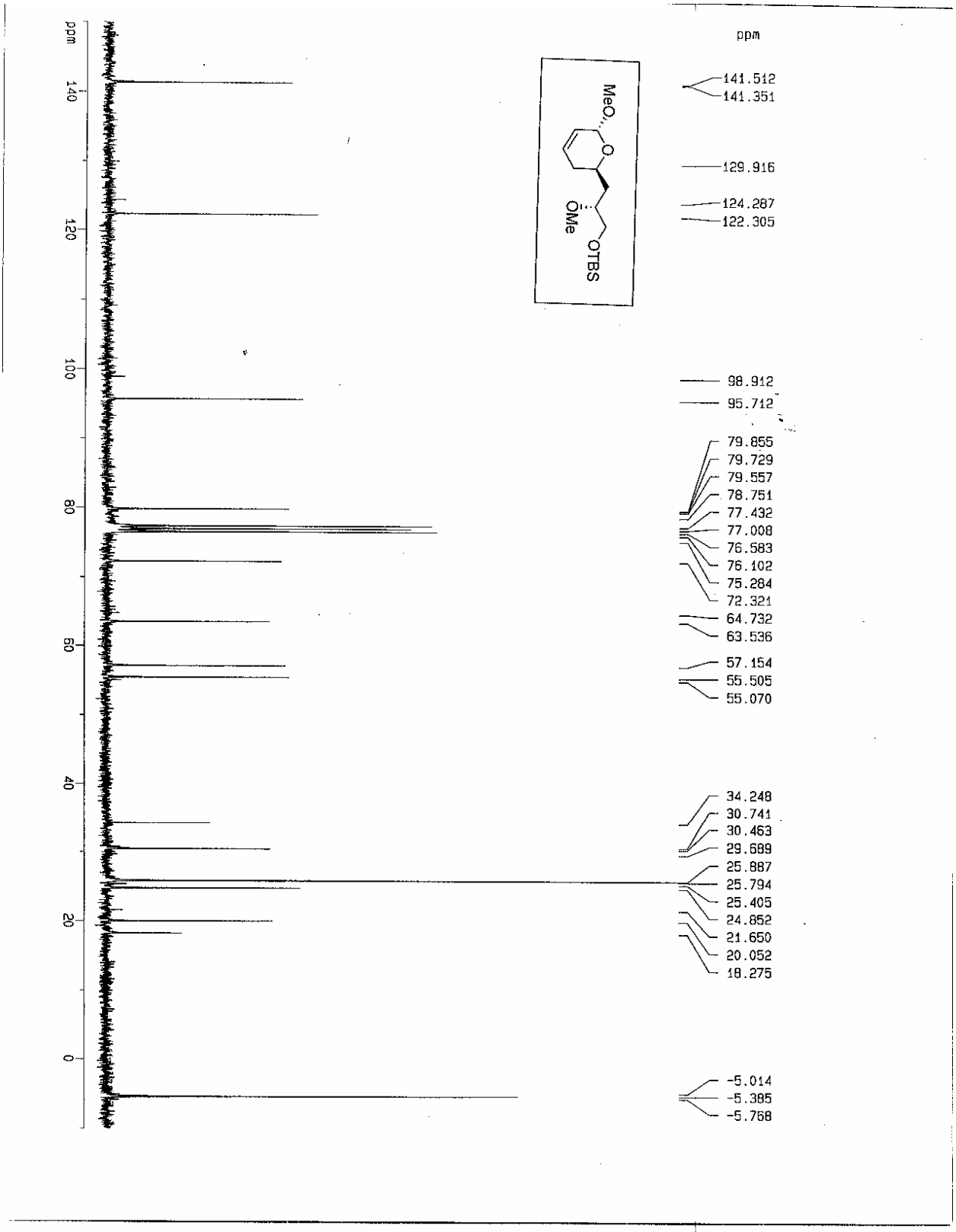

Integral
ppm
1.0000
0.2675
0.7391
1.1540
0.7714
2.4830
0.8861
2.2087
0.7696
0.3213
0.2318
0.6384
1.0771
0.9795
3.3229
8.8467
2.5234
5.7824
OMe
OH
OTBS
4.84428
4.83804
4.82349
4.81728
3.59439
3.58208
3.57602
3.56137
3.54324
3.46034
3.45458
3.44882
3.35633
3.33481
2.89948
2.89025
0.96766
0.96048
0.94400
0.92979
0.92792
0.92570
0.92406
0.92197
0.90125
0.89208
0.88853
0.88214
0.87621
0.82882
0.06641

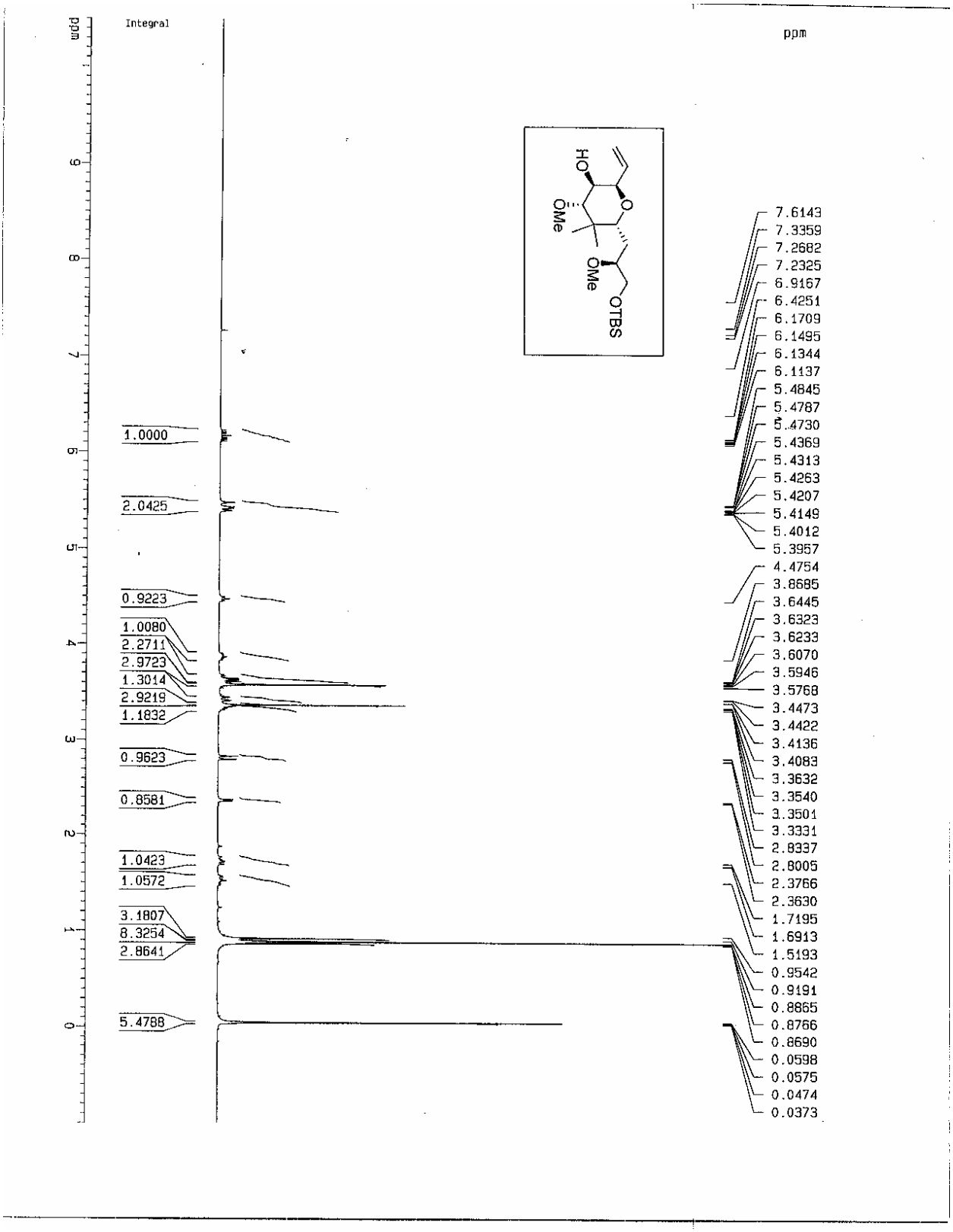

ppm
144.945
143.483
100.827
99.429
82.173
80.387
78.062
77.936
77.419
76.996
76.571
71.278
71.188
71.146
66.349
66.310
57.201
56.286
36.293
35.455
31.948
31.532
26.062
25.972
25.941
25.908
25.846
25.782
25.749
25.720
25.688
25.658
25.632
23.387
21.460
18.916
18.229
13.673
-5.376
-5.445
-5.508
-5.749
OMe
OH
OTBS

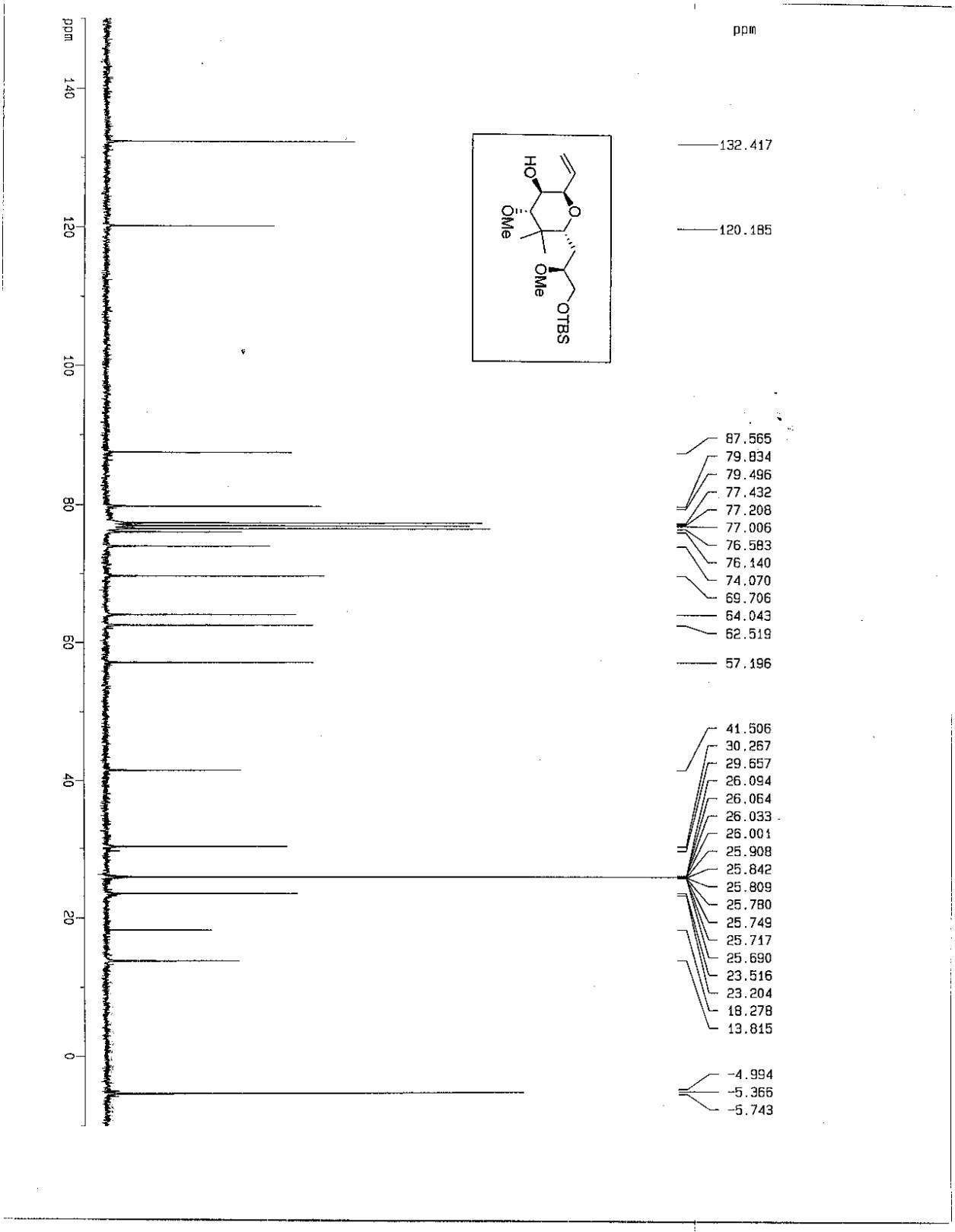

Integral
ppm
10
9
8
7
6
5
4
3
2
1
0
0.8988
1.0000
3.4128
1.2905
4.3857
2.9576
2.1810
3.3974
9.6946
3.4468
6.0124
OMe
OMe
OTBS
ppm
7.2699
6.6371
6.6177
6.3388
6.3183
5.7449
5.5528
5.2273
4.9568
4.8206
4.8144
4.7999
4.7937
4.7211
3.9026
3.7228
3.6992
3.6868
3.6725
3.6579
3.6460
3.6356
3.4494
3.4439
3.4249
3.4092
3.3923
3.3675
3.3348
1.8533
1.8396
1.8280
1.8215
1.8157
1.8063
1.7910
1.6247
1.2581
1.1666
0.9543
0.9036
0.8961
0.8838
0.8304
0.0700
0.0615

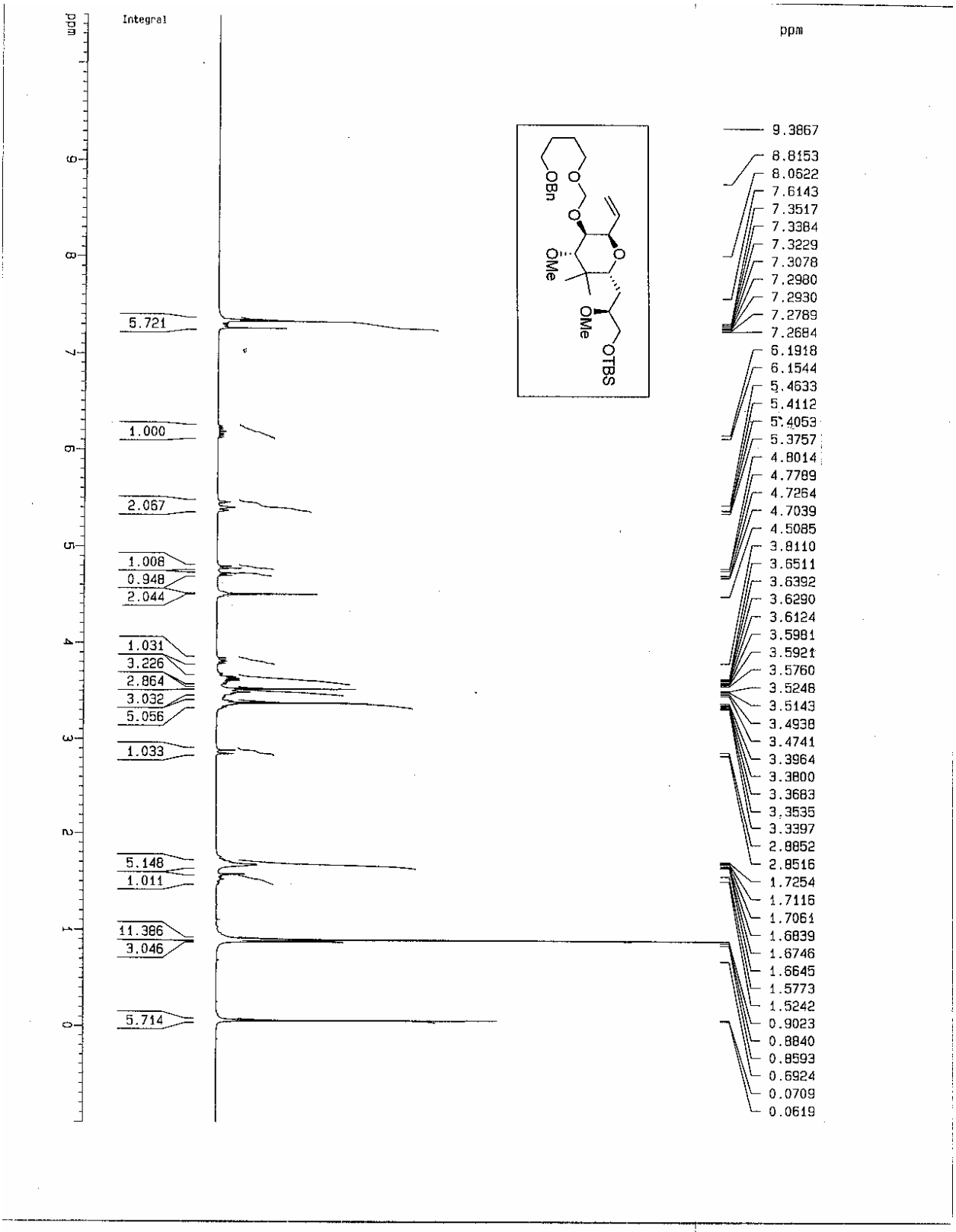

ppm
153.552
144.363
100.624
80.991
80.078
79.766
77.729
77.306
76.884
76.109
64.243
57.553
35.739
29.772
26.218
23.866
18.595
14.025
-5.047
OMe
OMe
OTBS
O
ppm
140
120
100
80
60
40
20
0

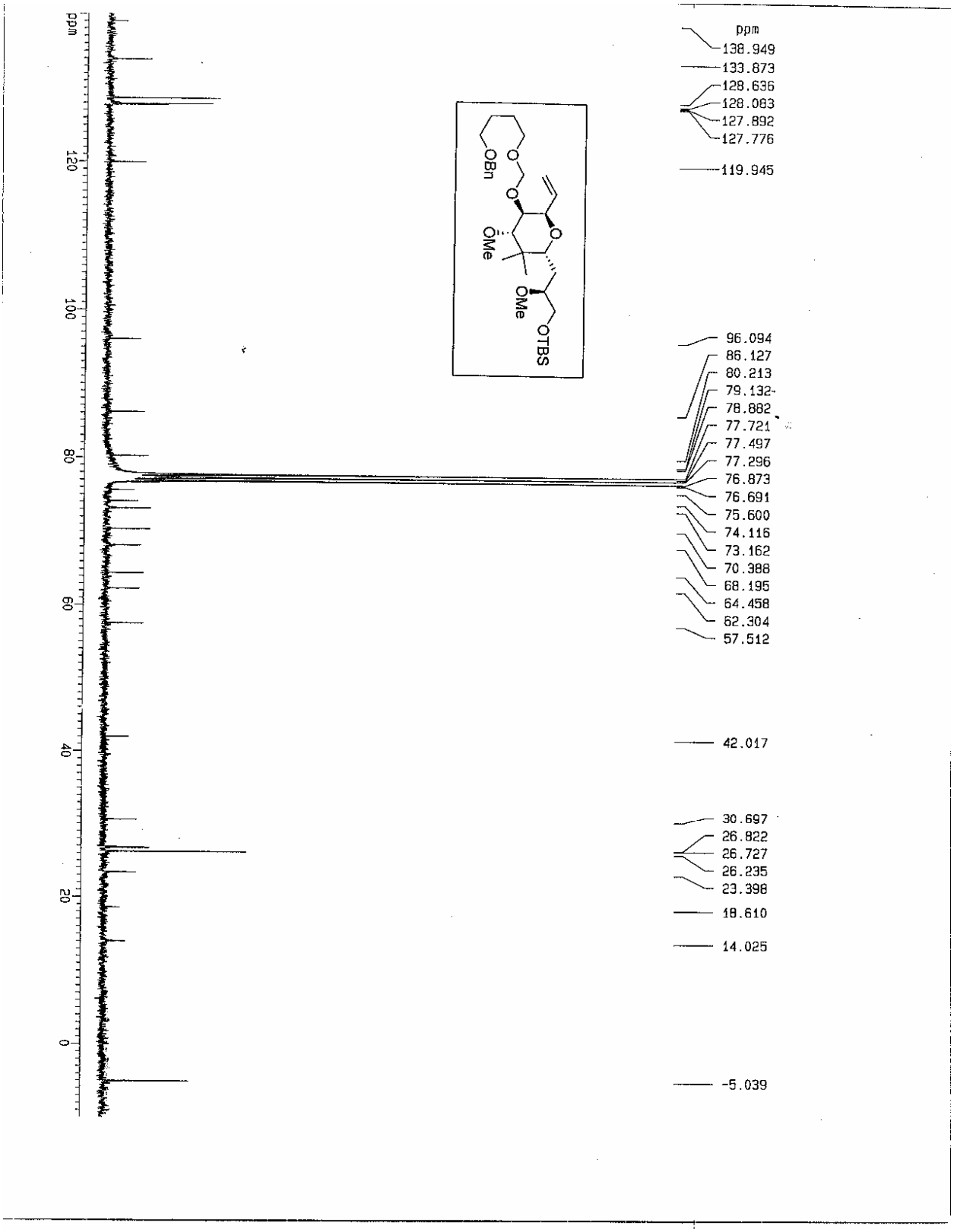

Integral
ppm
MeO
O
OMe
OTBS
1.000
0.855
0.082
0.071
0.815
0.998
1.267
1.053
7.341
1.192
0.972
15.372
5.769
7.2681
6.3028
5.7389
5.7356
5.7056
5.7022
5.5921
5.5827
5.5589
5.5494
4.8021
4.7933
3.7604
3.7498
3.7014
3.6858
3.6490
3.6389
3.6342
3.6032
3.4767
3.4696
3.4619
3.4461
3.4249
3.4184
3.3964
3.3871
3.3548
1.7951
1.7896
1.7651
1.7579
1.6646
1.6292
0.9915
0.9052
0.8921
0.8842
0.8750
0.8643
0.8620
0.0603
0.0538
0.0117

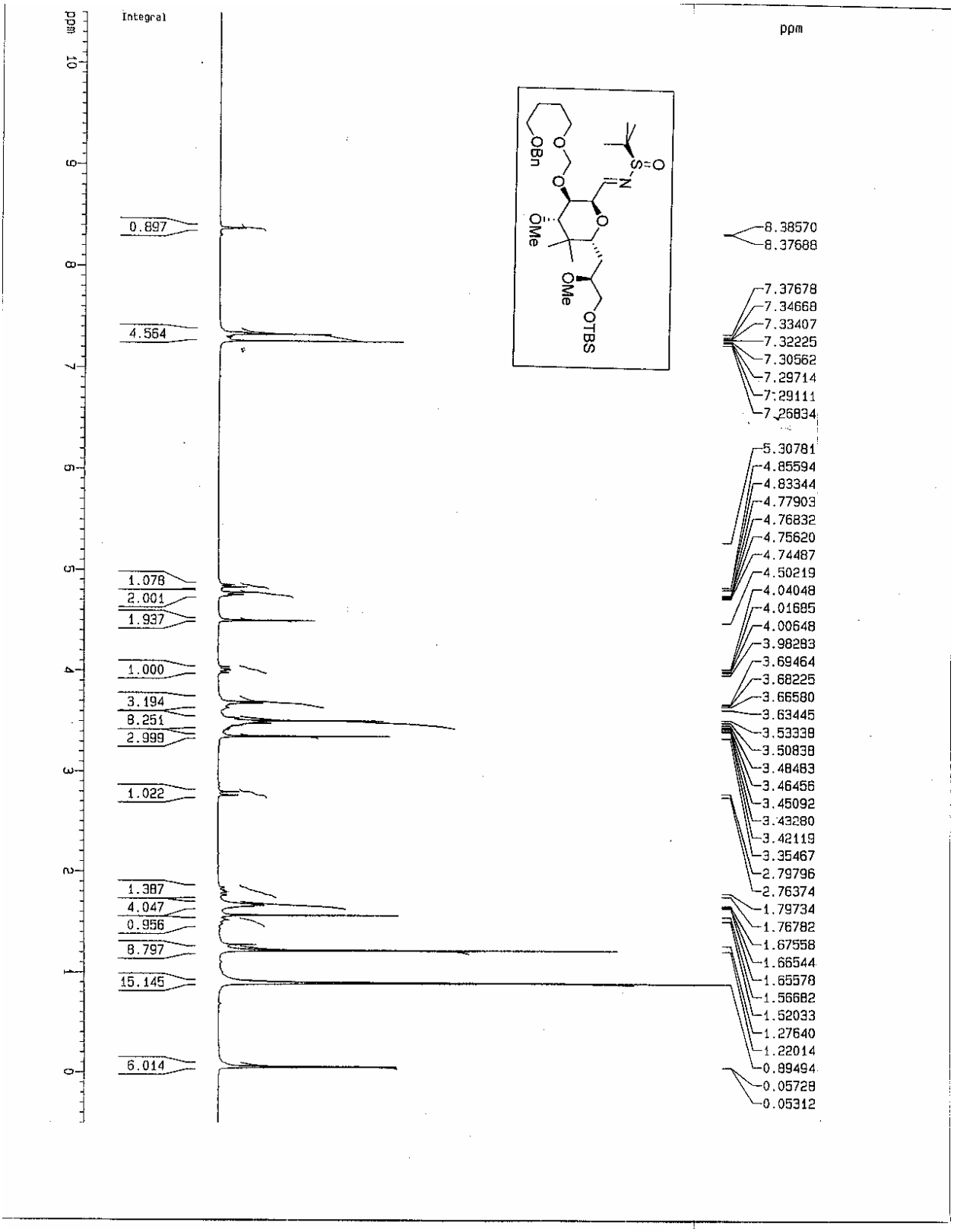

ppm
140
120
100
80
60
40
20
0
MeO
O
OMe
OTBS
ppm
141.512
141.351
129.916
124.287
122.305
98.912
95.712
79.855
79.729
79.557
78.751
77.432
77.008
76.583
76.102
75.284
72.321
64.732
63.536
57.154
55.505
55.070
34.248
30.741
30.463
29.689
25.887
25.794
25.405
24.852
21.650
20.052
18.275
-5.014
-5.385
-5.768

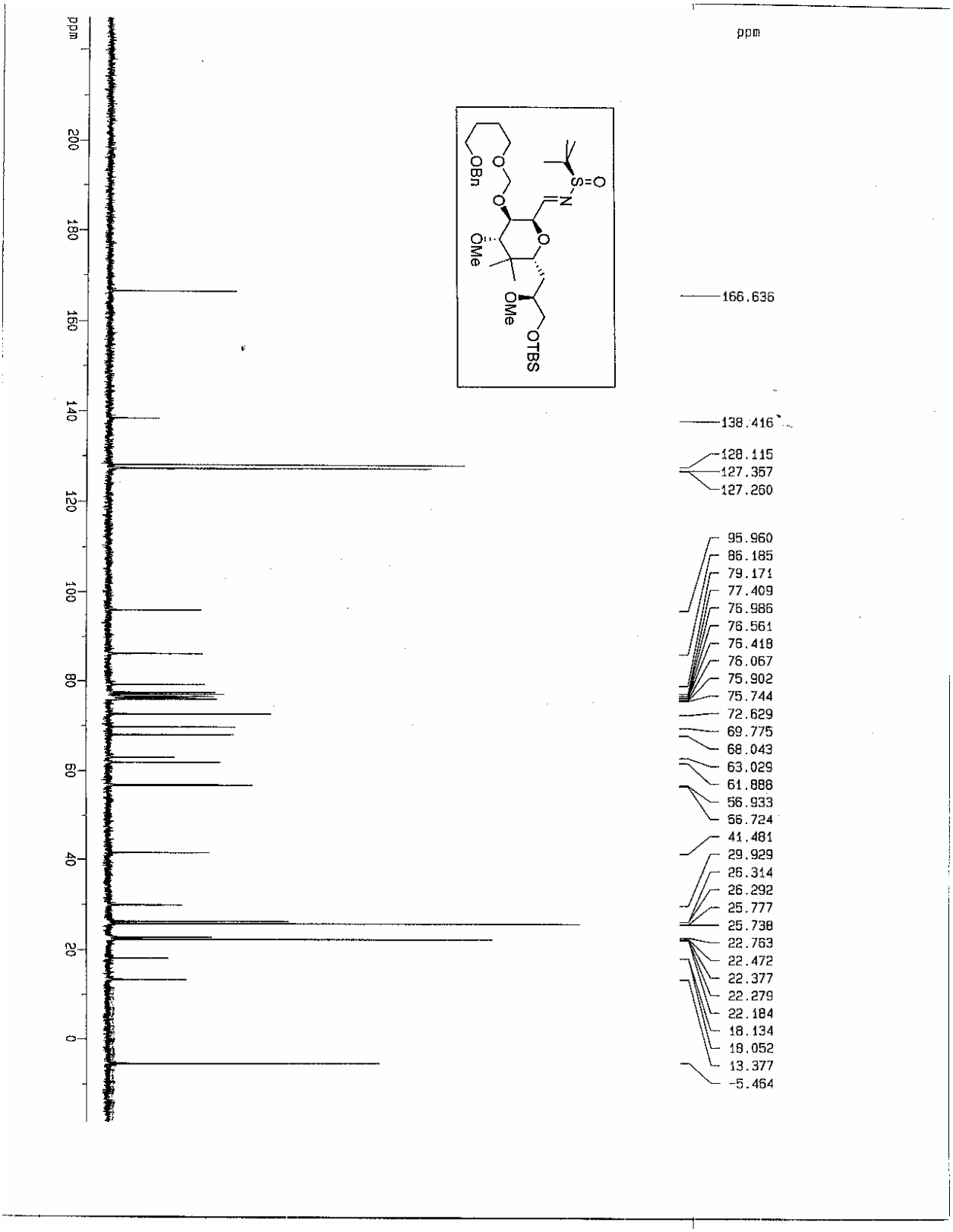

Integral
ppm
HO
OMe
OMe
OTBS
1.0000
2.0425
0.9223
1.0080
2.2711
2.9723
1.3014
2.9219
1.1832
0.9623
0.8581
1.0423
1.0572
3.1807
8.3254
2.8641
5.4788
7.6143
7.3359
7.2682
7.2325
6.9167
6.4251
6.1709
6.1495
6.1344
6.1137
5.4845
5.4787
5.4730
5.4369
5.4313
5.4263
5.4207
5.4149
5.4012
5.3957
4.4754
3.8685
3.6445
3.6323
3.6233
3.6070
3.5946
3.5768
3.4473
3.4422
3.4136
3.4083
3.3632
3.3540
3.3501
3.3331
2.8337
2.8005
2.3766
2.3630
1.7195
1.6913
1.5193
0.9542
0.9191
0.8865
0.8766
0.8690
0.0598
0.0575
0.0474
0.0373


ppm
140
120
100
80
60
40
20
0
HO
O
OMe
OMe
OTBS
ppm
132.417
120.185
87.565
79.834
79.496
77.432
77.208
77.006
76.583
76.140
74.070
69.706
64.043
62.519
57.196
41.506
30.267
29.657
26.094
26.064
26.033
26.001
25.908
25.842
25.809
25.780
25.749
25.717
25.690
23.516
23.204
18.278
13.815
-4.994
-5.366
-5.743


Integral
ppm
5.721
1.000
2.067
1.008
0.948
2.044
1.031
3.226
2.864
3.032
5.056
1.033
5.148
1.011
11.386
3.046
5.714
OBn
OMe
OMe
OTBS
9.3867
8.8153
8.0622
7.6143
7.3517
7.3384
7.3229
7.3078
7.2980
7.2930
7.2789
7.2684
6.1918
6.1544
5.4633
5.4112
5.4053
5.3757
4.8014
4.7789
4.7264
4.7039
4.5085
3.8110
3.6511
3.6392
3.6290
3.6124
3.5981
3.5921
3.5760
3.5248
3.5143
3.4938
3.4741
3.3964
3.3800
3.3683
3.3535
3.3397
2.8852
2.8516
1.7254
1.7116
1.7061
1.6839
1.6746
1.6645
1.5773
1.5242
0.9023
0.8840
0.8593
0.6924
0.0709
0.0619

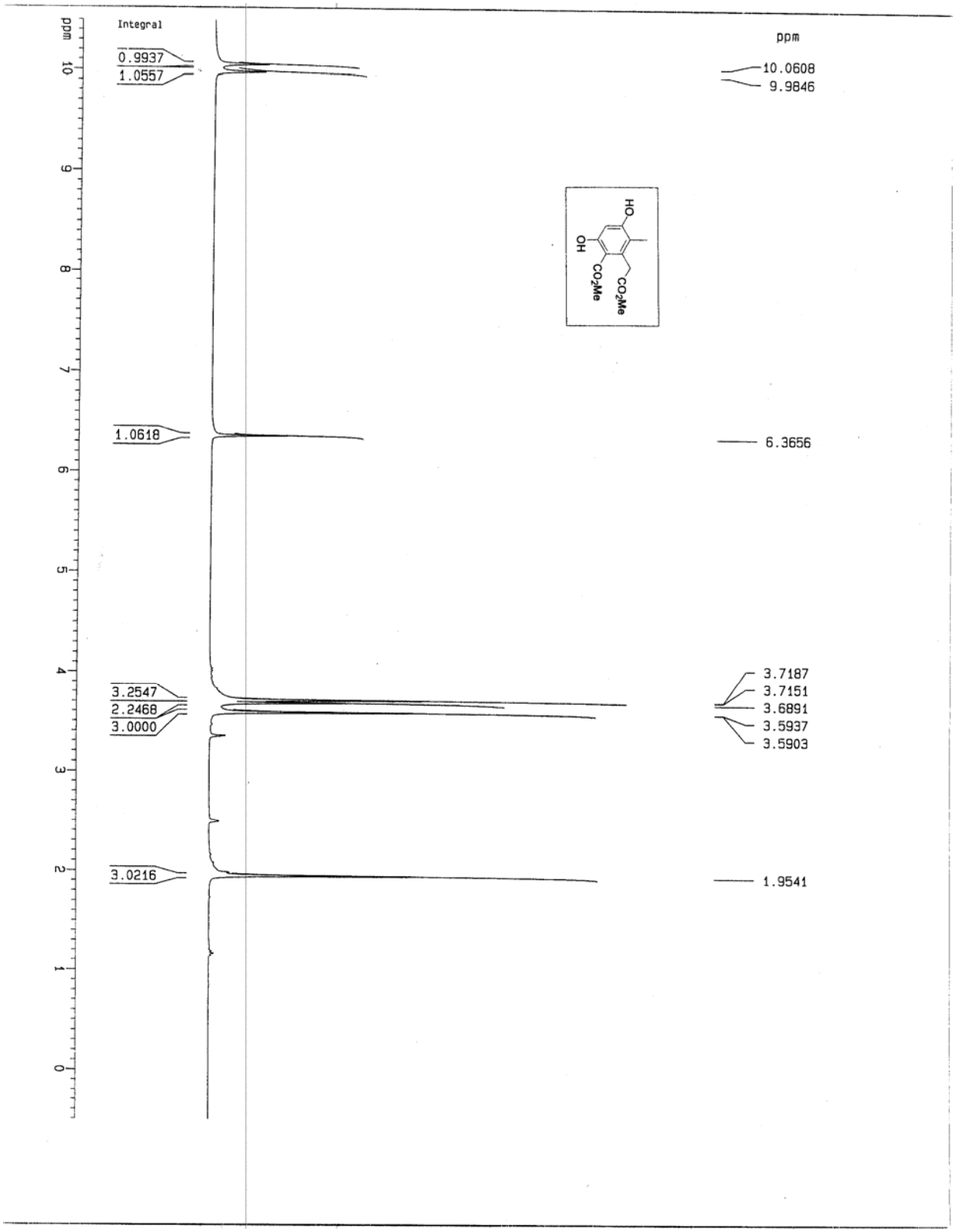

ppm
138.949
133.873
128.636
128.083
127.892
127.776
119.945
96.094
86.127
80.213
79.132
78.882
77.721
77.497
77.296
76.873
76.691
75.600
74.116
73.162
70.388
68.195
64.458
62.304
57.512
42.017
30.697
26.822
26.727
26.235
23.398
18.610
14.025
-5.039
OBn
OMe
OMe
OTBS

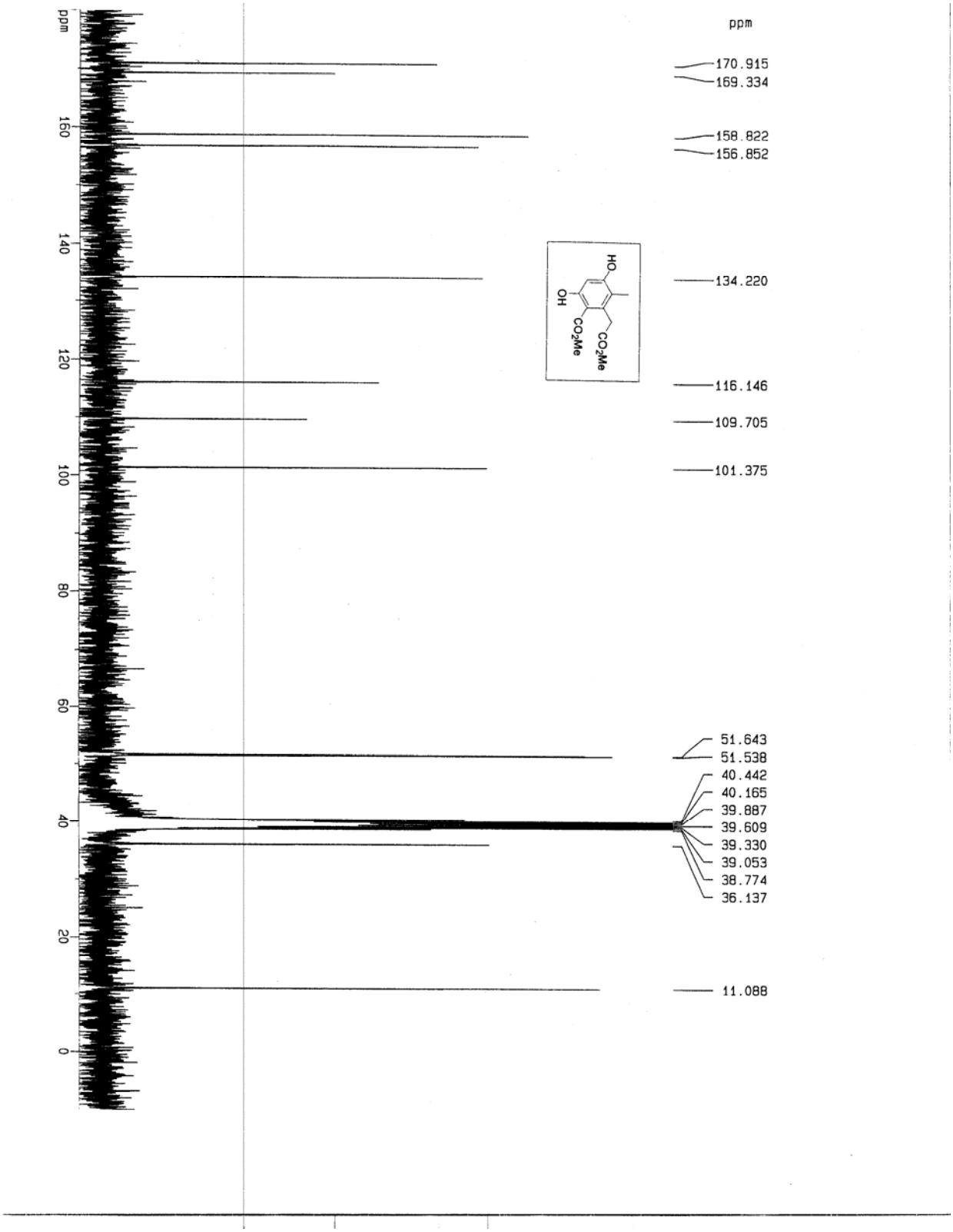

Integral
ppm
0.897
4.564
1.078
2.001
1.937
1.000
3.194
8.251
2.999
1.022
1.387
4.047
0.956
8.797
15.145
6.014
OBn
OMe
OMe
OTBS
8.38570
8.37688
7.37678
7.34668
7.33407
7.32225
7.30562
7.29714
7.29111
7.26834
5.30781
4.85594
4.83344
4.77903
4.76832
4.75620
4.74487
4.50219
4.04048
4.01685
4.00648
3.98283
3.69464
3.68225
3.66580
3.63445
3.53338
3.50838
3.48483
3.46456
3.45092
3.43280
3.42119
3.35467
2.79796
2.76374
1.79734
1.76782
1.67558
1.66544
1.65578
1.56682
1.52033
1.27640
1.22014
0.89494
0.05728
0.05312

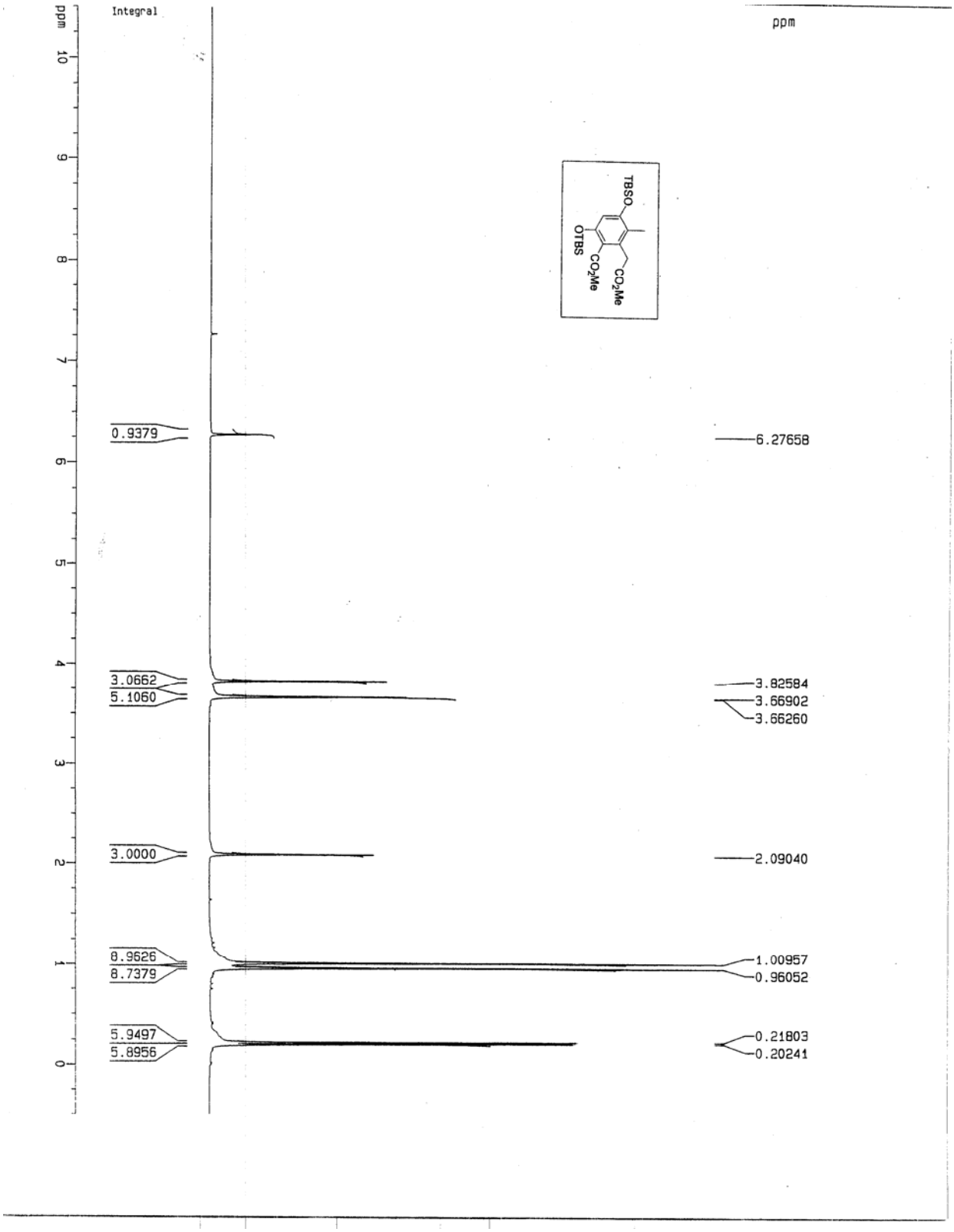

ppm
200
180
160
140
120
100
80
60
40
20
0
OBn
OMe
OMe
OTBS
S
O
N
ppm
166.636
138.416
128.115
127.357
127.260
95.960
86.185
79.171
77.409
76.986
76.561
76.418
76.067
75.902
75.744
72.629
69.775
68.043
63.029
61.888
56.933
56.724
41.481
29.929
26.314
26.292
25.777
25.738
22.763
22.472
22.377
22.279
22.184
18.134
18.052
13.377
-5.464

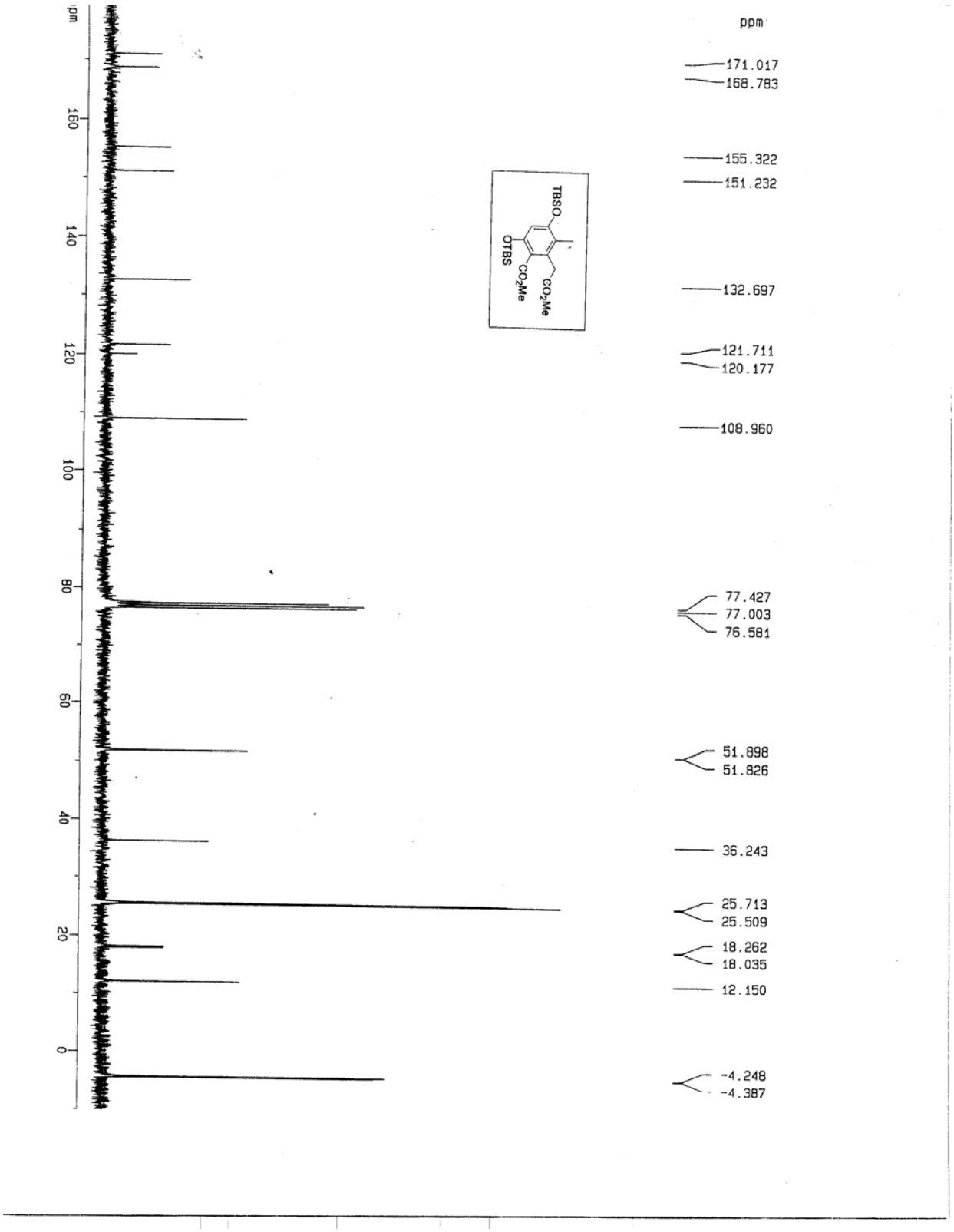
APPENDIX C

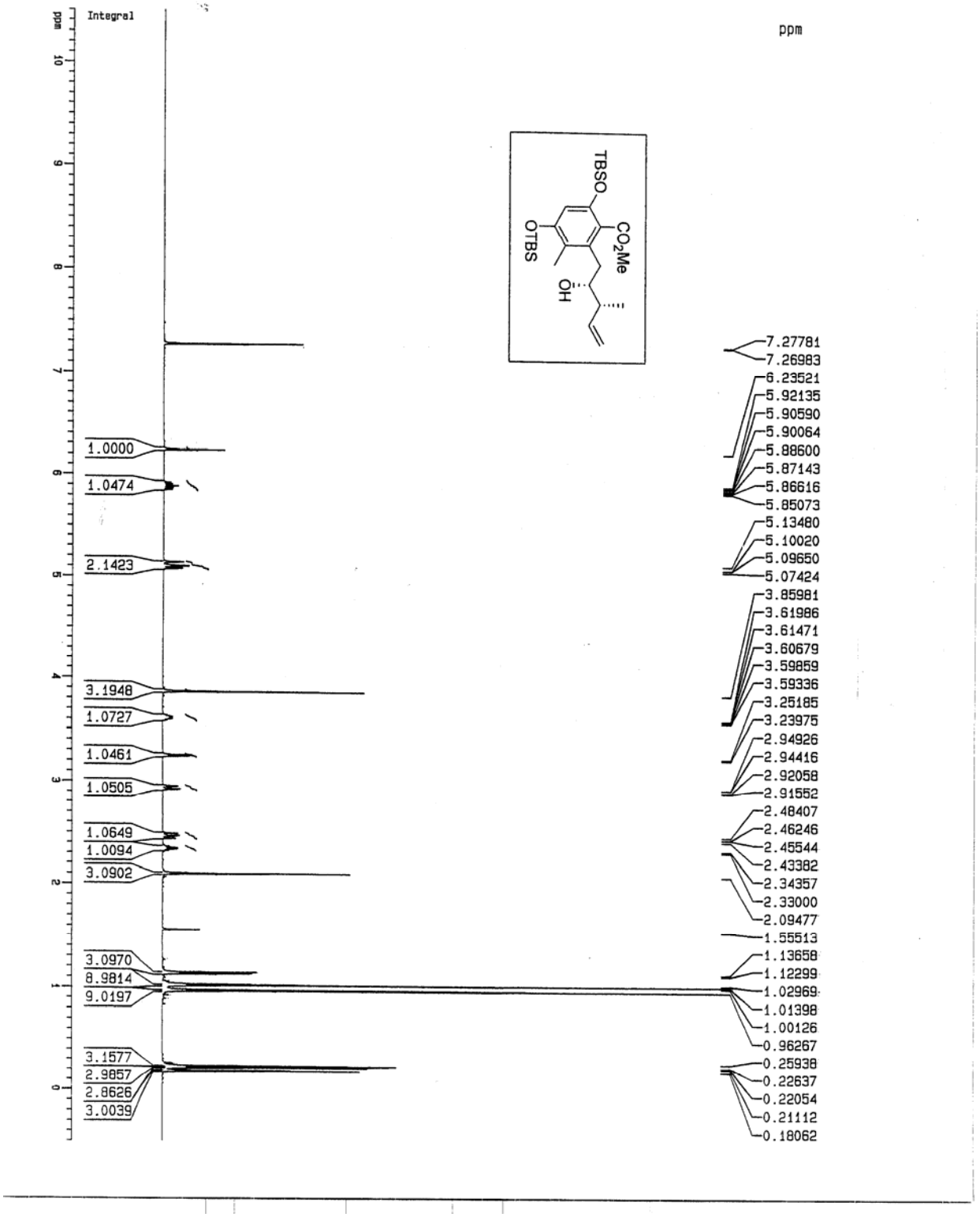
Synthesis of the N_7-C_{25} Fragment of Psymberin (Supporting Information) (^{1}H and ^{13}C NMR Spectra)

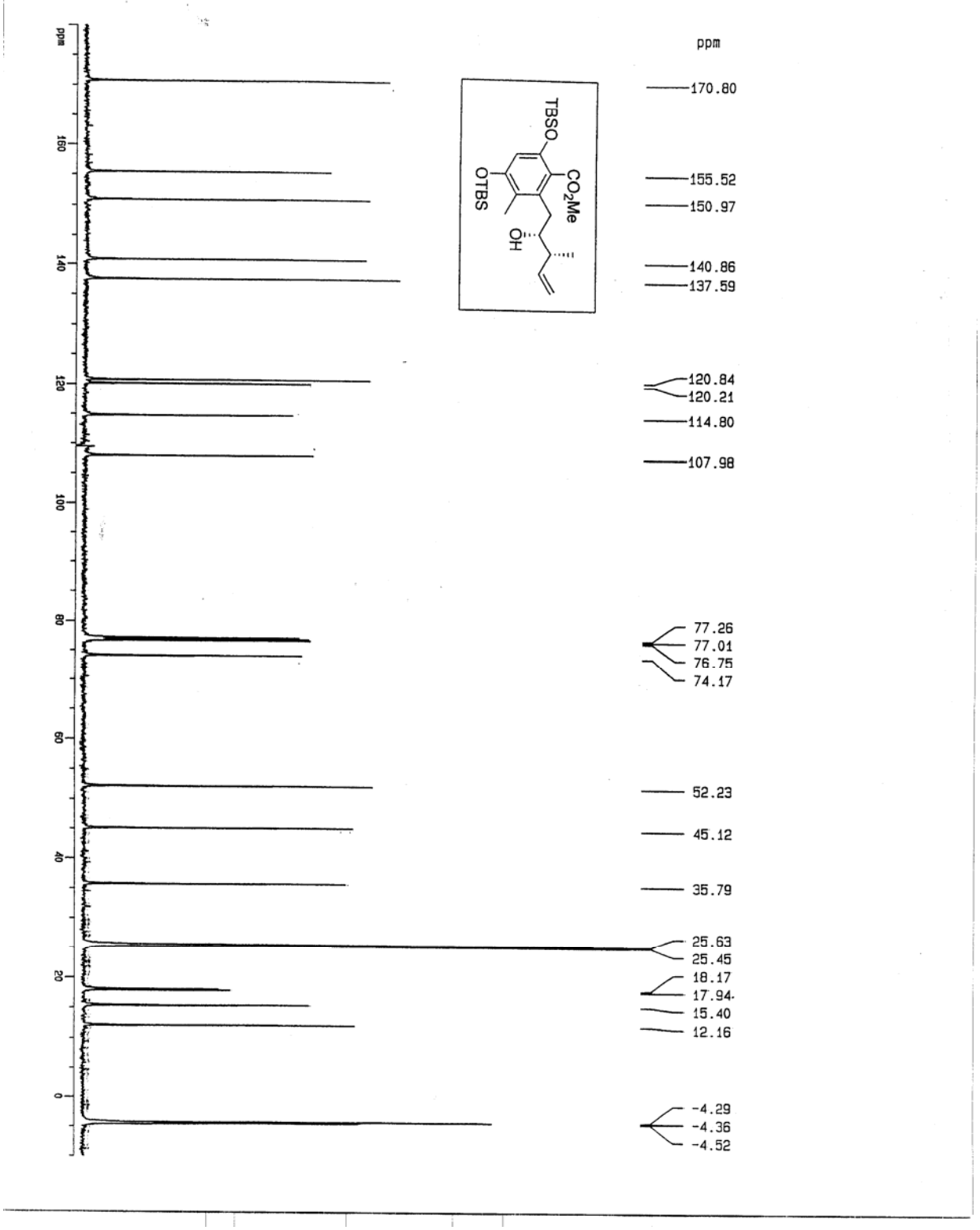

Integral
0.9937
1.0557
1.0618
3.2547
2.2468
3.0000
3.0216
ppm
10.0608
9.9846
6.3656
3.7187
3.7151
3.6891
3.5937
3.5903
1.9541
HO
OH
CO2Me
CO2Me

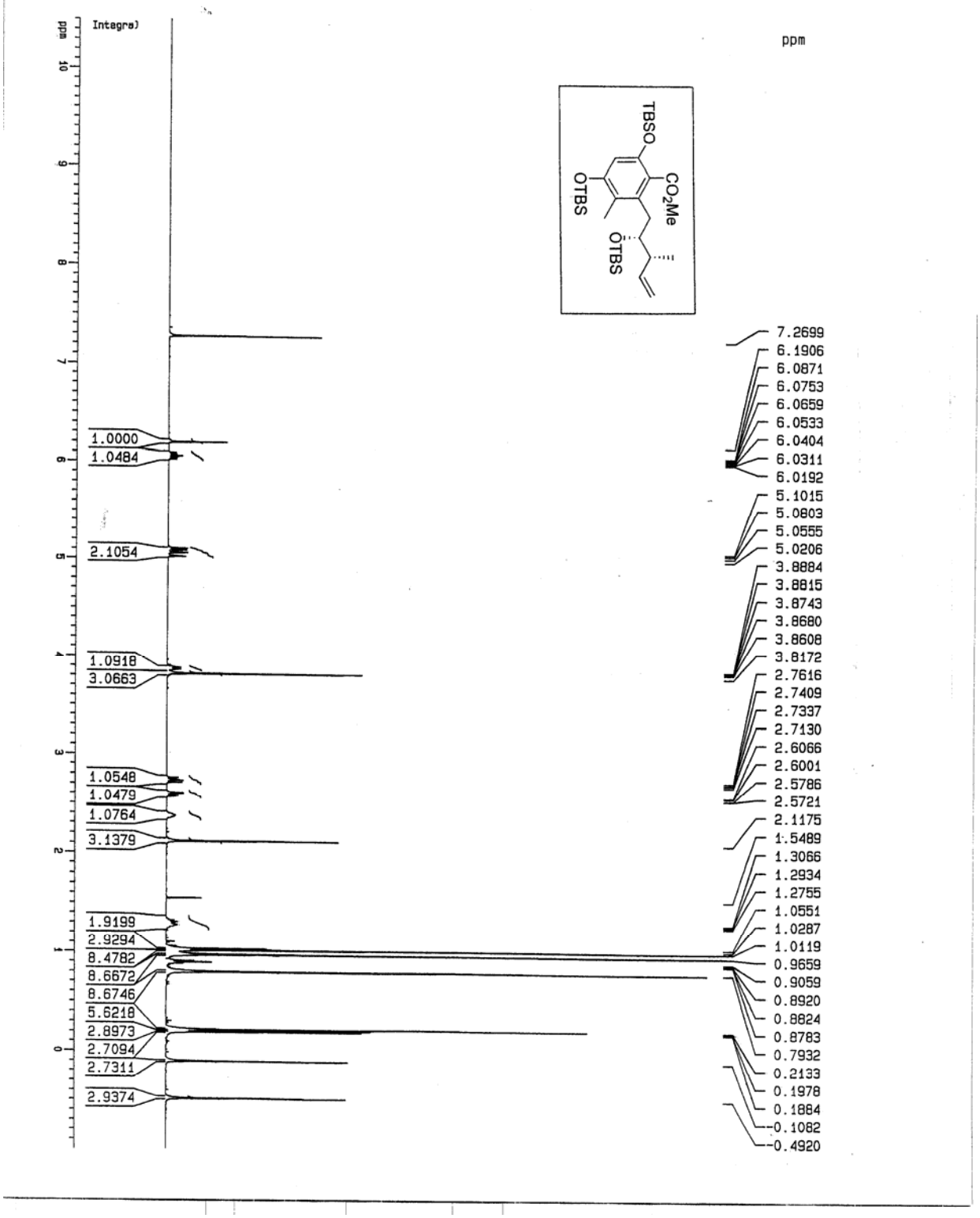

ppm
170.915
169.334
158.822
156.852
134.220
116.146
109.705
101.375
51.643
51.538
40.442
40.165
39.887
39.609
39.330
39.053
38.774
36.137
11.088
HO
OH
CO2Me
CO2Me

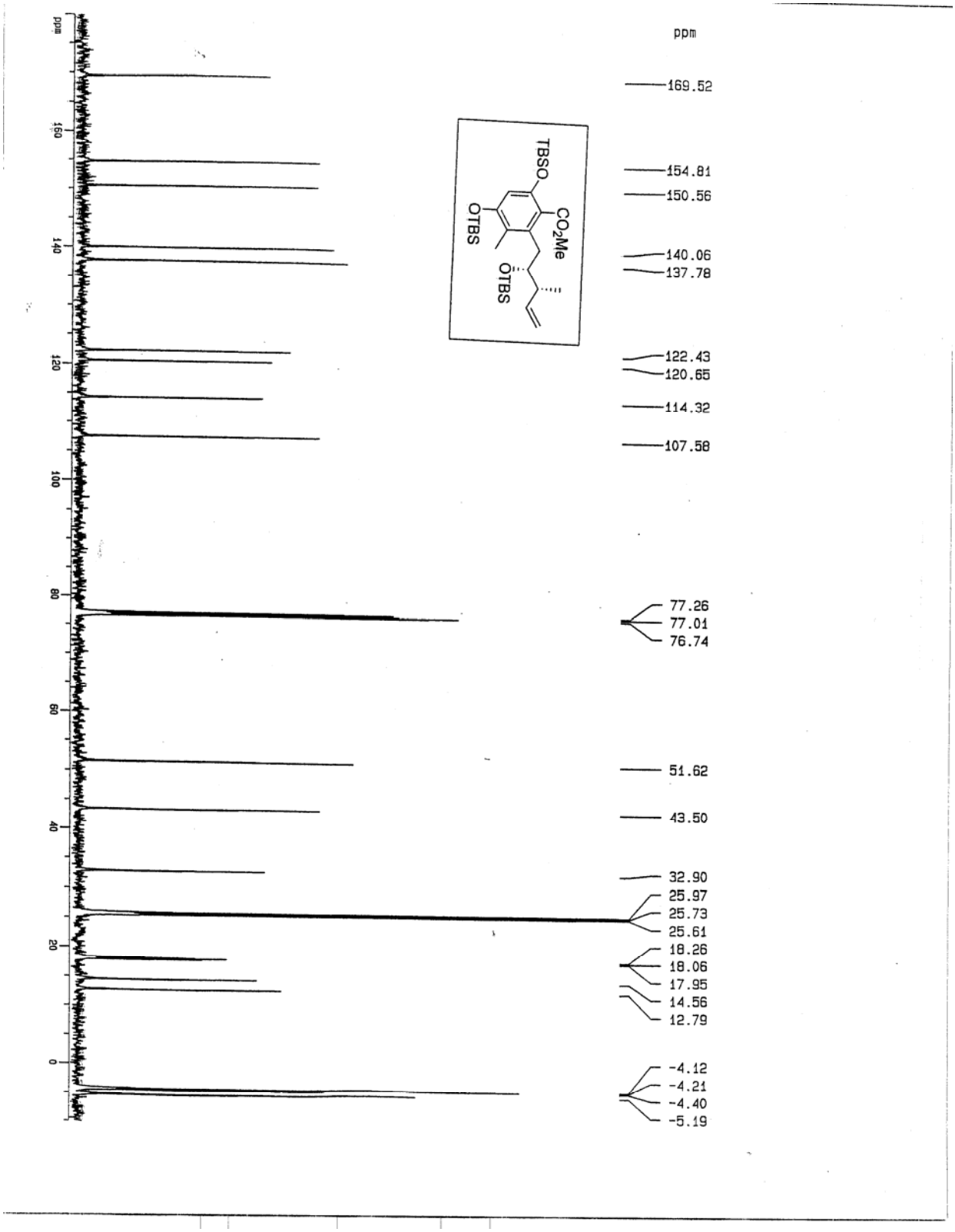

Integral
ppm
TBSO
OTBS
CO2Me
CO2Me
0.9379
3.0662
5.1060
3.0000
0.9626
0.7379
5.9497
5.8956
6.27658
3.82584
3.66902
3.66260
2.09040
1.00957
0.96052
0.21803
0.20241

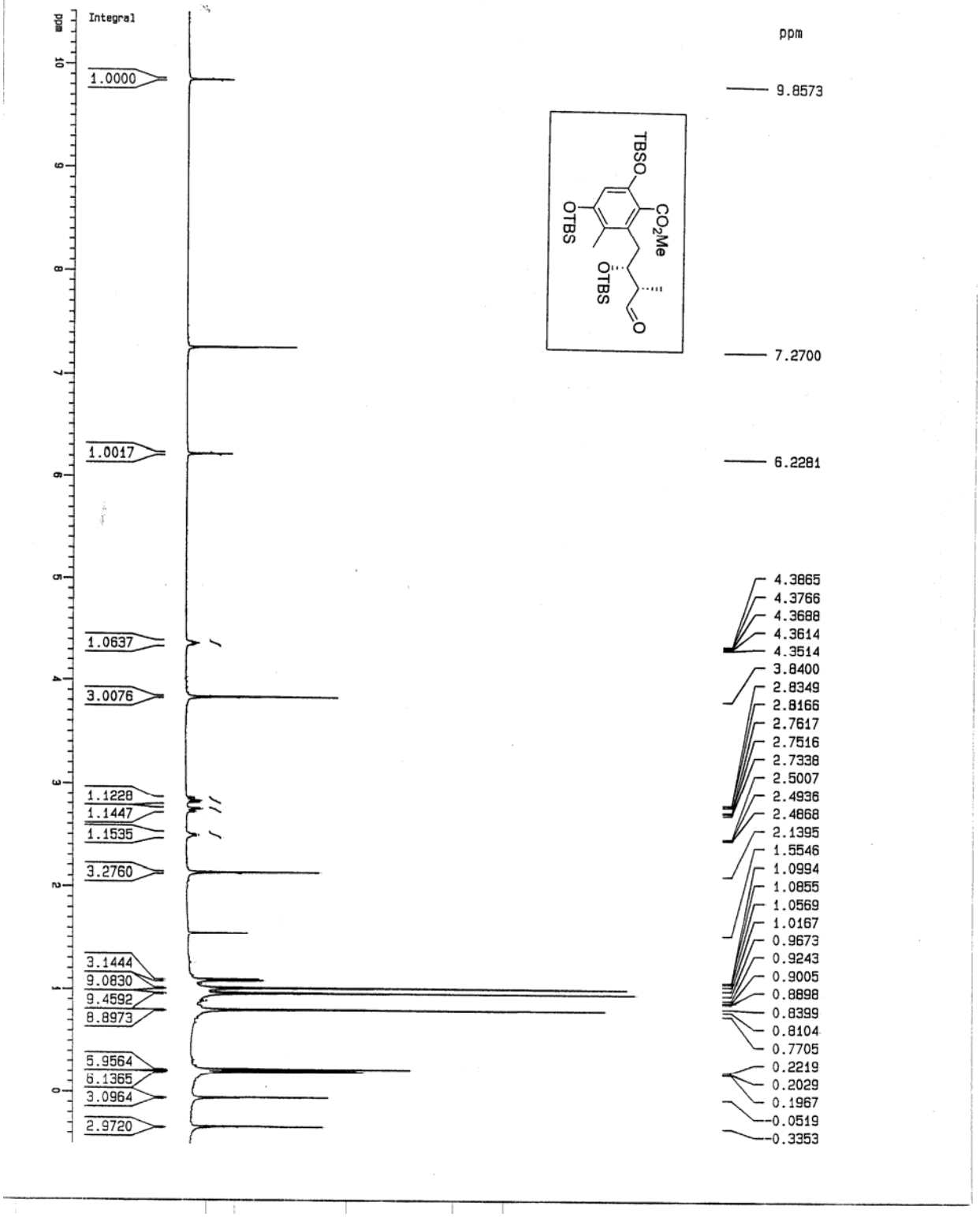

ppm
171.017
168.783
155.322
151.232
132.697
121.711
120.177
108.960
77.427
77.003
76.581
51.898
51.826
36.243
25.713
25.509
18.262
18.035
12.150
-4.248
-4.387
TBSO
OTBS
CO2Me
CO2Me

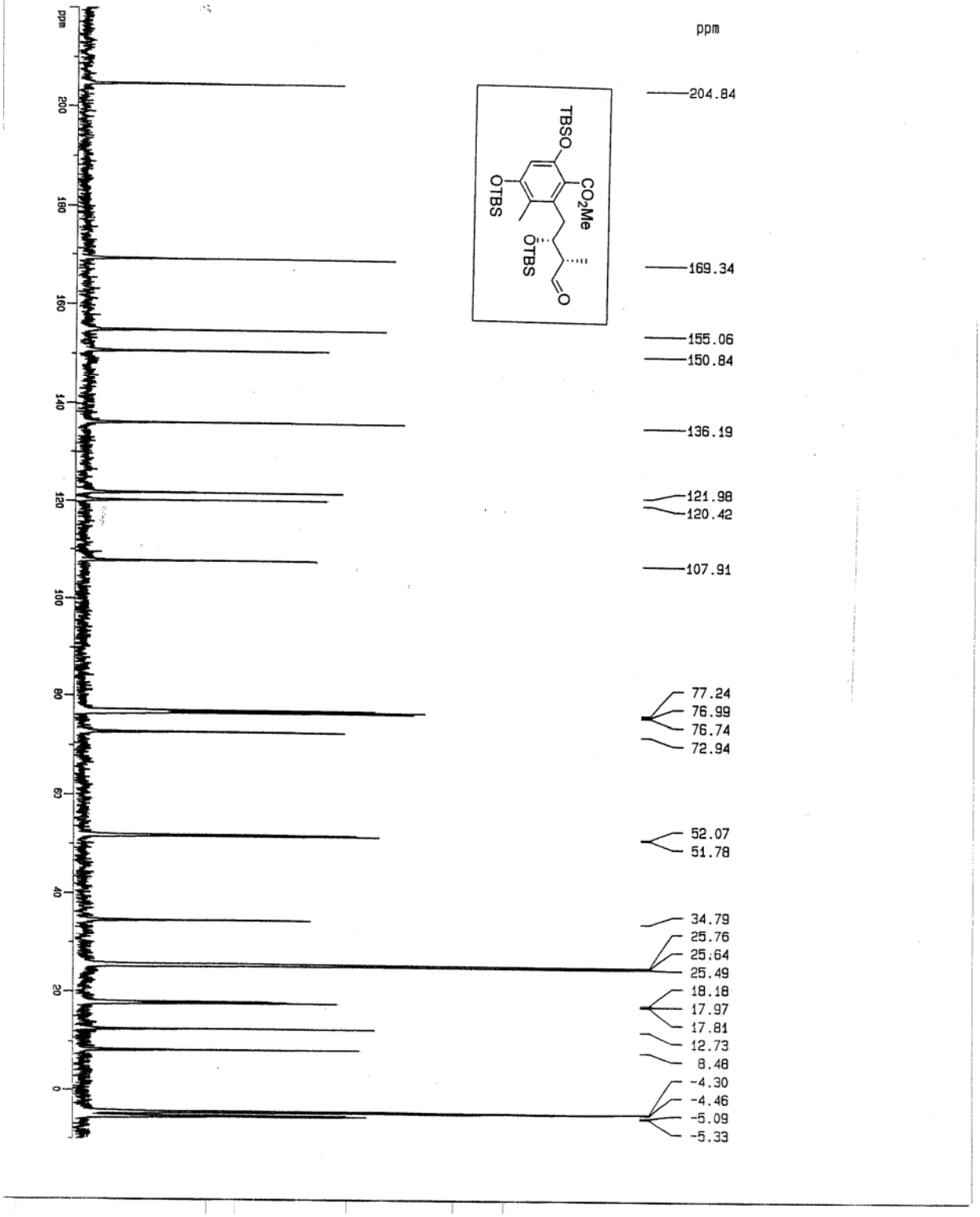

Integral
ppm
TBSO
CO2Me
OTBS
OH
1.0000
1.0474
2.1423
3.1948
1.0727
1.0461
1.0505
1.0649
1.0094
3.0902
3.0970
8.9814
9.0197
3.1577
2.9857
2.8626
3.0039
7.27781
7.26983
6.23521
5.92135
5.90590
5.90064
5.88600
5.87143
5.86616
5.85073
5.13480
5.10020
5.09650
5.07424
3.85981
3.61986
3.61471
3.60679
3.59859
3.59336
3.25185
3.23975
2.94926
2.94416
2.92058
2.91552
2.48407
2.46246
2.45544
2.43382
2.34357
2.33000
2.09477
1.55513
1.13658
1.12299
1.02969
1.01398
1.00126
0.96267
0.25938
0.22637
0.22054
0.21112
0.18062

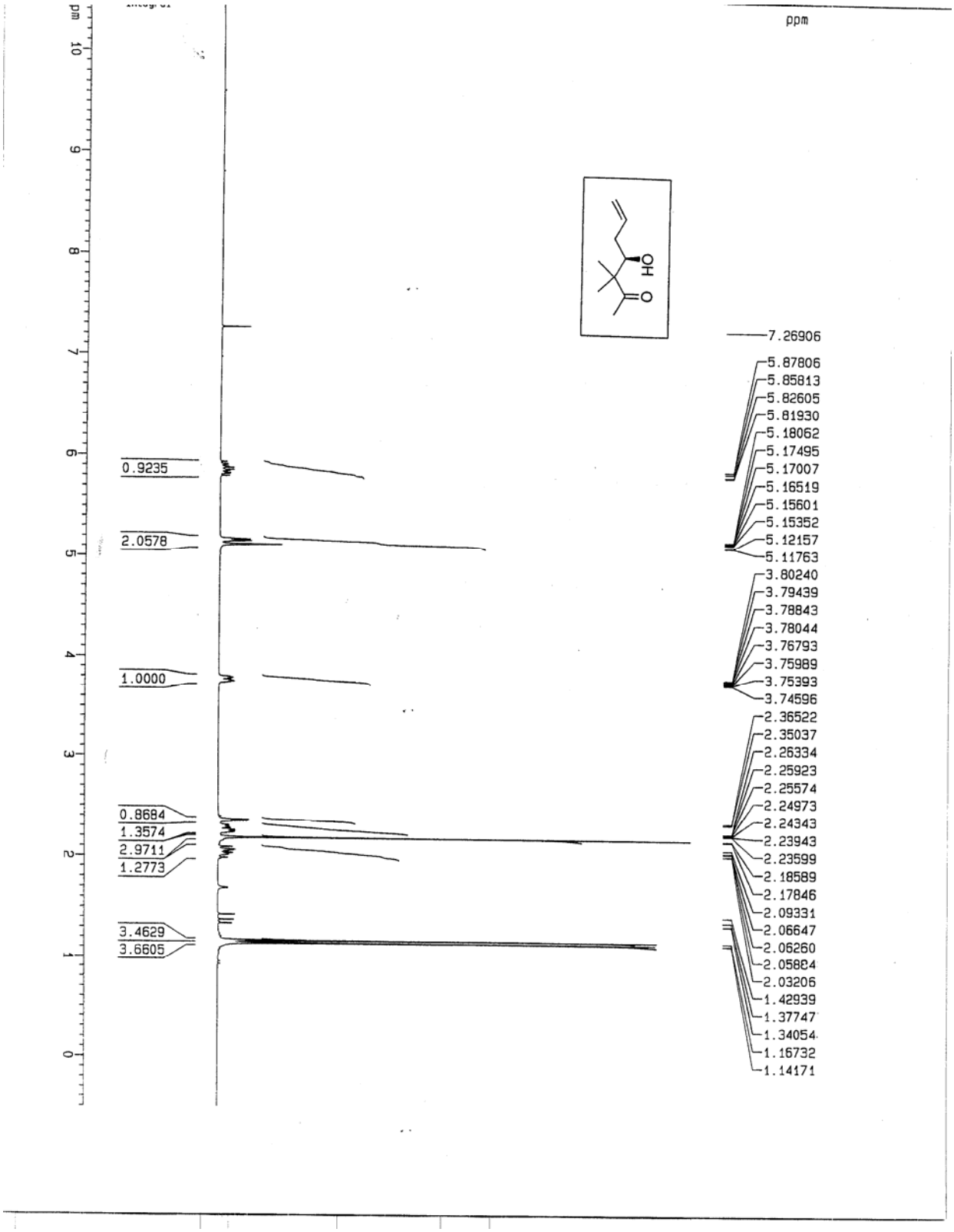

ppm
TBSO
OTBS
CO2Me
OH
170.80
155.52
150.97
140.86
137.59
120.84
120.21
114.80
107.98
77.26
77.01
76.75
74.17
52.23
45.12
35.79
25.63
25.45
18.17
17.94
15.40
12.16
-4.29
-4.36
-4.52

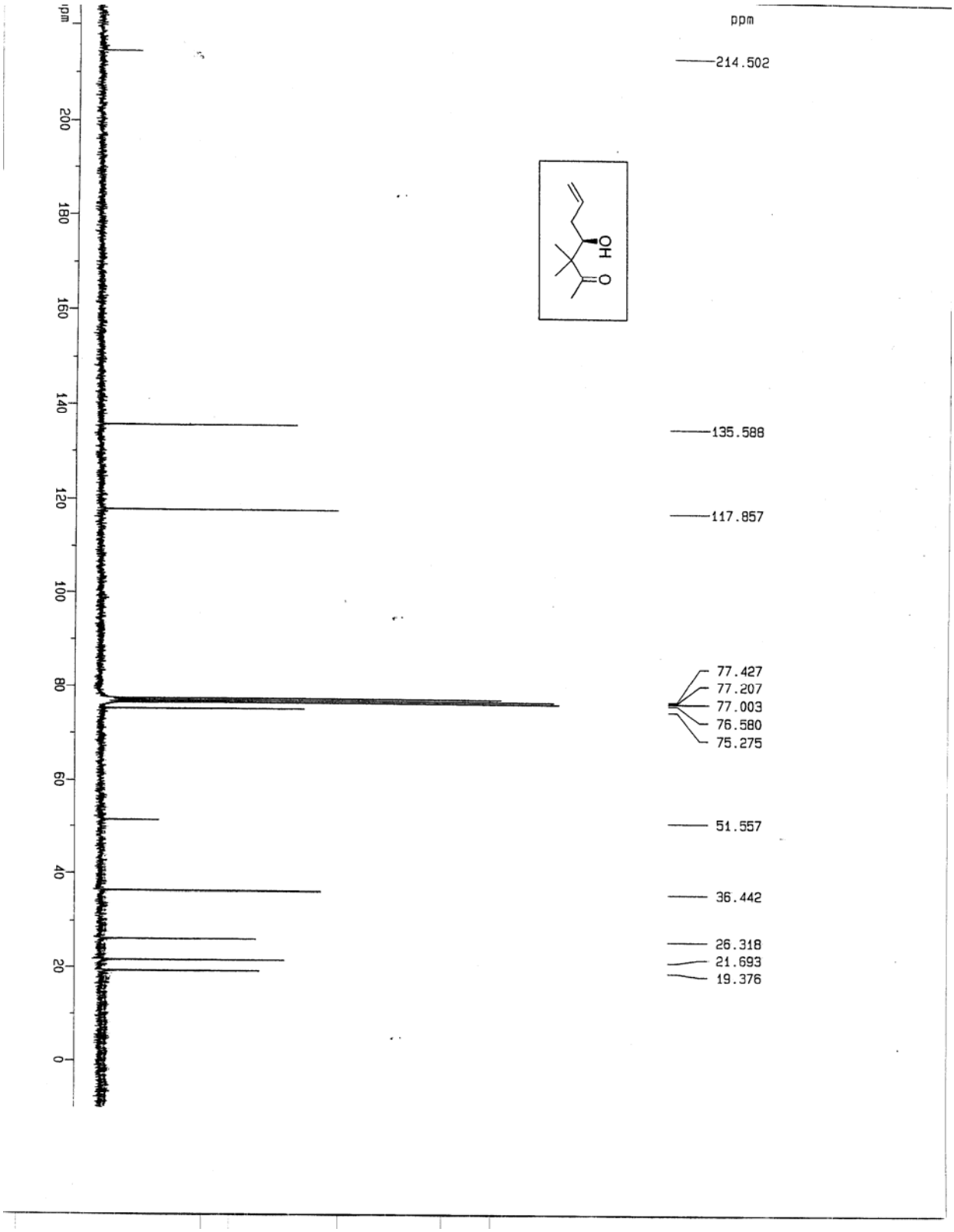

Integral
ppm
TBSO
CO2Me
OTBS
OTBS
1.0000
1.0484
2.1054
1.0918
3.0663
1.0548
1.0479
1.0764
3.1379
1.9199
2.9294
8.4782
8.6672
8.6746
5.6218
2.8973
2.7094
2.7311
2.9374
7.2699
6.1906
6.0871
6.0753
6.0659
6.0533
6.0404
6.0311
6.0192
5.1015
5.0803
5.0555
5.0206
3.8884
3.8815
3.8743
3.8680
3.8608
3.8172
2.7616
2.7409
2.7337
2.7130
2.6066
2.6001
2.5786
2.5721
2.1175
1.5489
1.3066
1.2934
1.2755
1.0551
1.0287
1.0119
0.9659
0.9059
0.8920
0.8824
0.8783
0.7932
0.2133
0.1978
0.1884
-0.1082
-0.4920

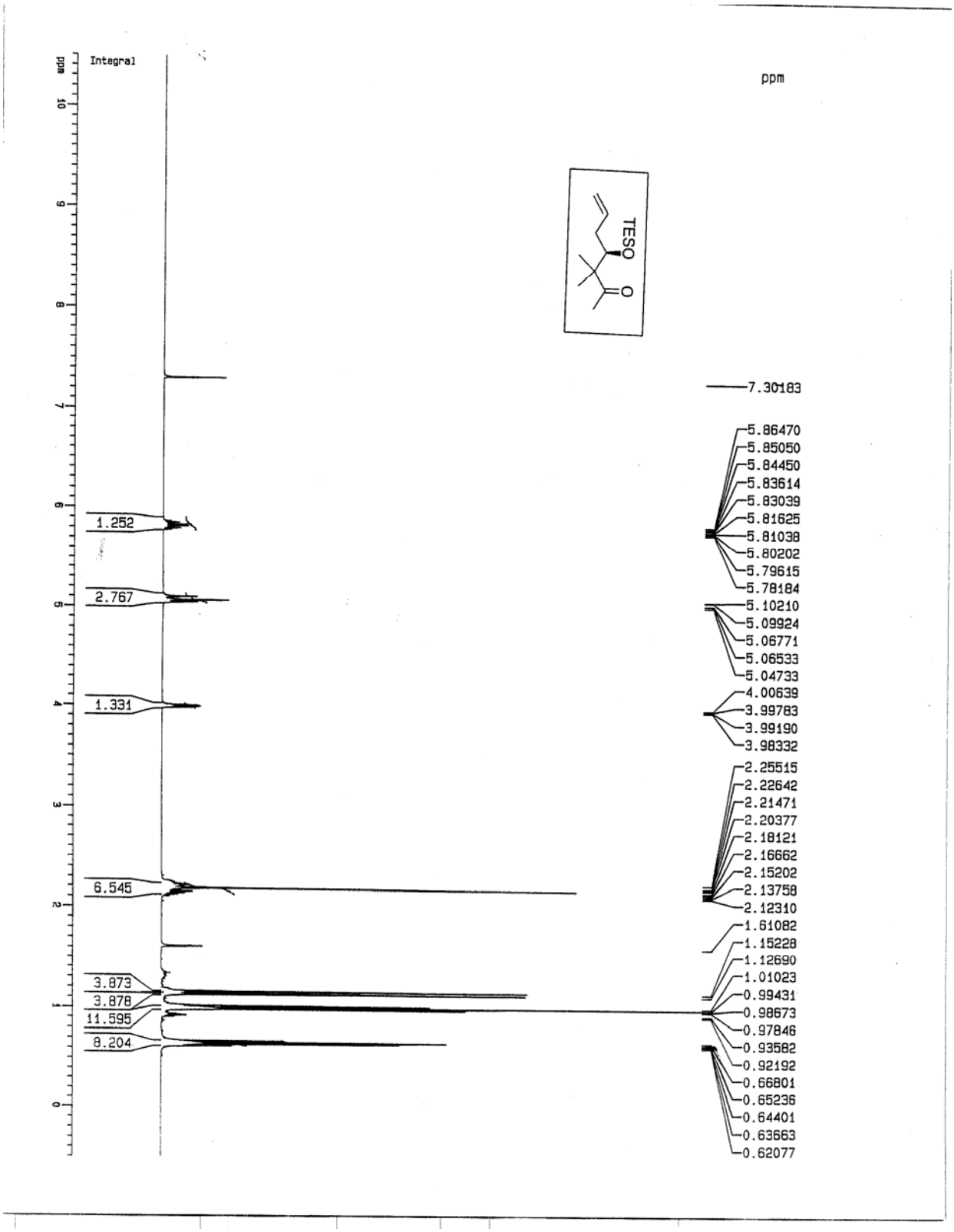

ppm
169.52
154.81
150.56
140.06
137.78
122.43
120.65
114.32
107.58
77.26
77.01
76.74
51.62
43.50
32.90
25.97
25.73
25.61
18.26
18.06
17.95
14.56
12.79
-4.12
-4.21
-4.40
-5.19
TBSO
CO2Me
OTBS
OTBS

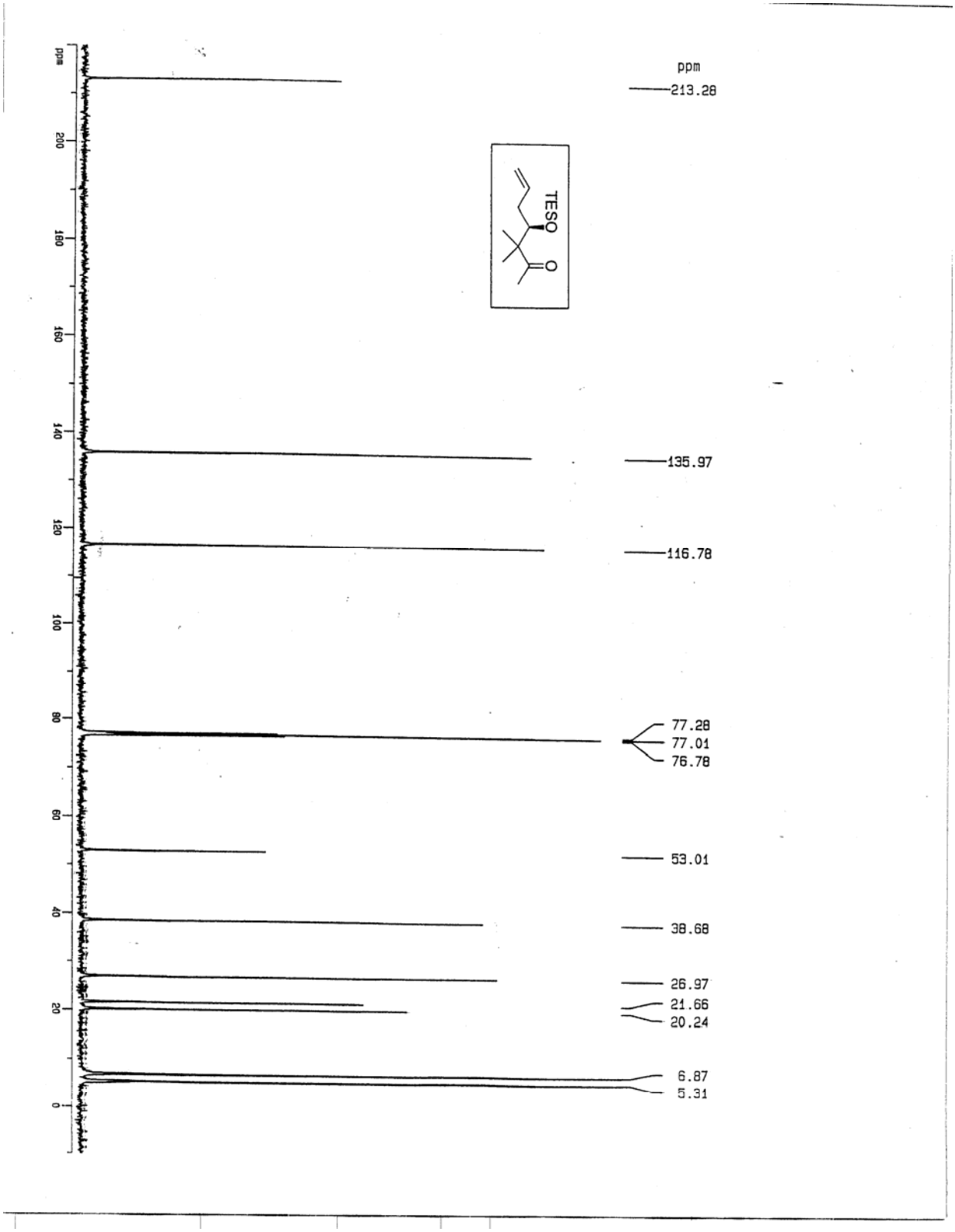

Integral
ppm
1.0000
1.0017
1.0637
3.0076
1.1228
1.1447
1.1535
3.2760
3.1444
9.0830
9.4592
8.8973
5.9564
6.1365
3.0964
2.9720
9.8573
7.2700
6.2281
4.3865
4.3766
4.3688
4.3614
4.3514
3.8400
2.8349
2.8166
2.7617
2.7516
2.7338
2.5007
2.4936
2.4868
2.1395
1.5546
1.0994
1.0855
1.0569
1.0167
0.9673
0.9243
0.9005
0.8898
0.8399
0.8104
0.7705
0.2219
0.2029
0.1967
-0.0519
-0.3353
TBSO
CO2Me
OTBS
OTBS
O

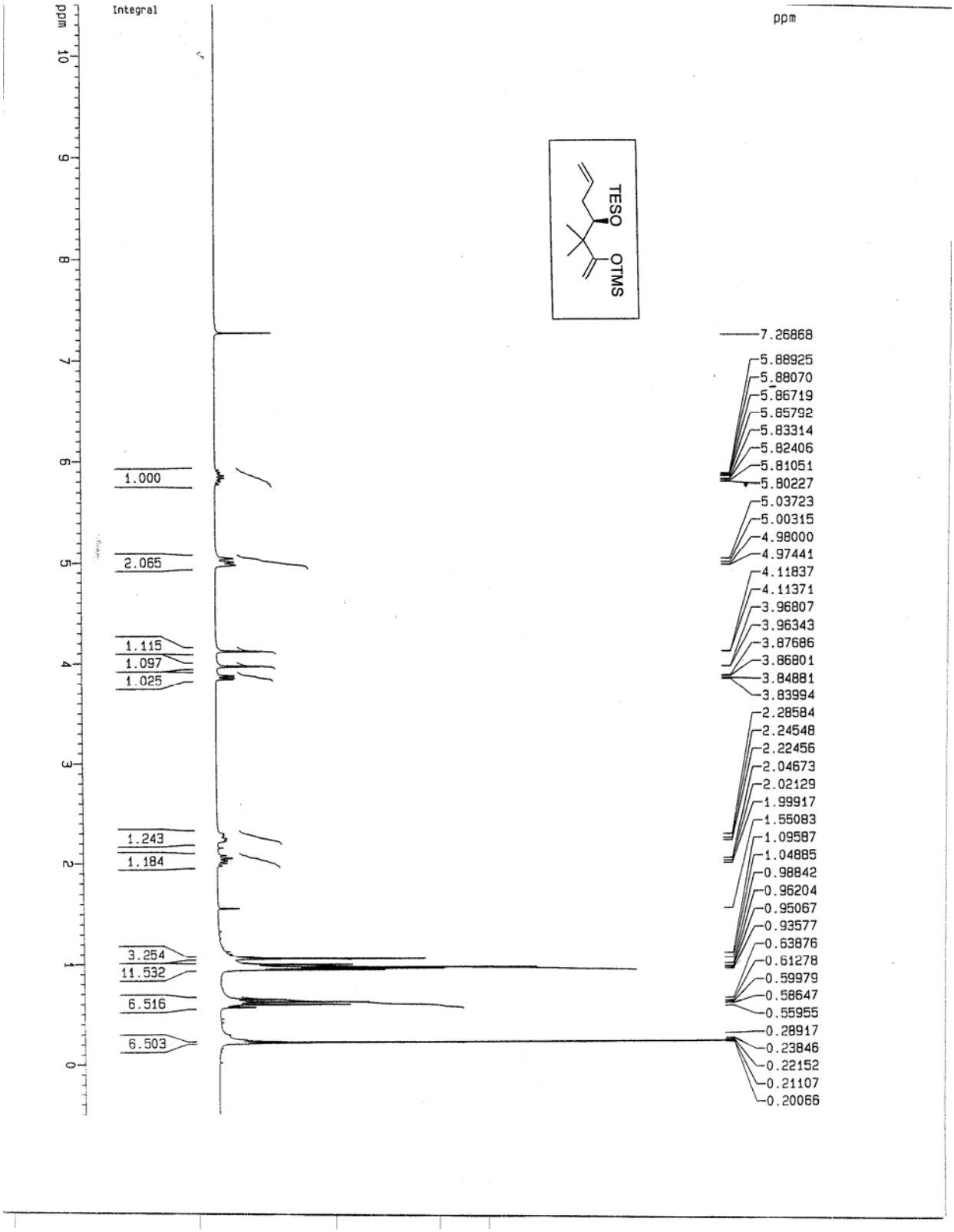

ppm
TBSO
CO2Me
OTBS
OTBS
O
204.84
169.34
155.06
150.84
136.19
121.98
120.42
107.91
77.24
76.99
76.74
72.94
52.07
51.78
34.79
25.76
25.64
25.49
18.18
17.97
17.81
12.73
8.48
-4.30
-4.46
-5.09
-5.33

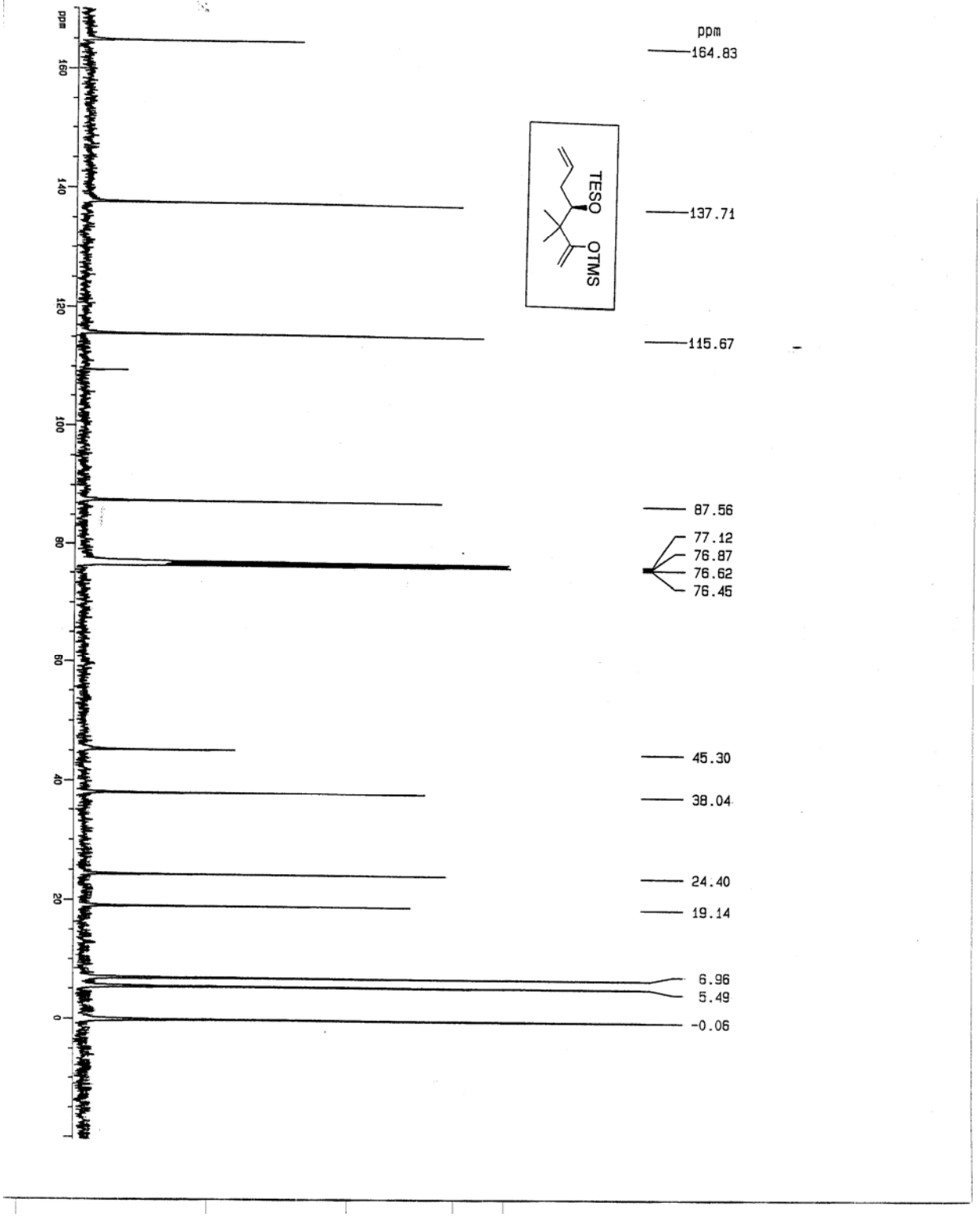

ppm
0.9235
2.0578
1.0000
0.8684
1.3574
2.9711
1.2773
3.4629
3.6605
OH
O
7.26906
5.87806
5.85813
5.82605
5.81930
5.18062
5.17495
5.17007
5.16519
5.15601
5.15352
5.12157
5.11763
3.80240
3.79439
3.78843
3.78044
3.76793
3.75989
3.75393
3.74596
2.36522
2.35037
2.26334
2.25923
2.25574
2.24973
2.24343
2.23943
2.23599
2.18589
2.17846
2.09331
2.06647
2.06260
2.05884
2.03206
1.42939
1.37747
1.34054
1.16732
1.14171

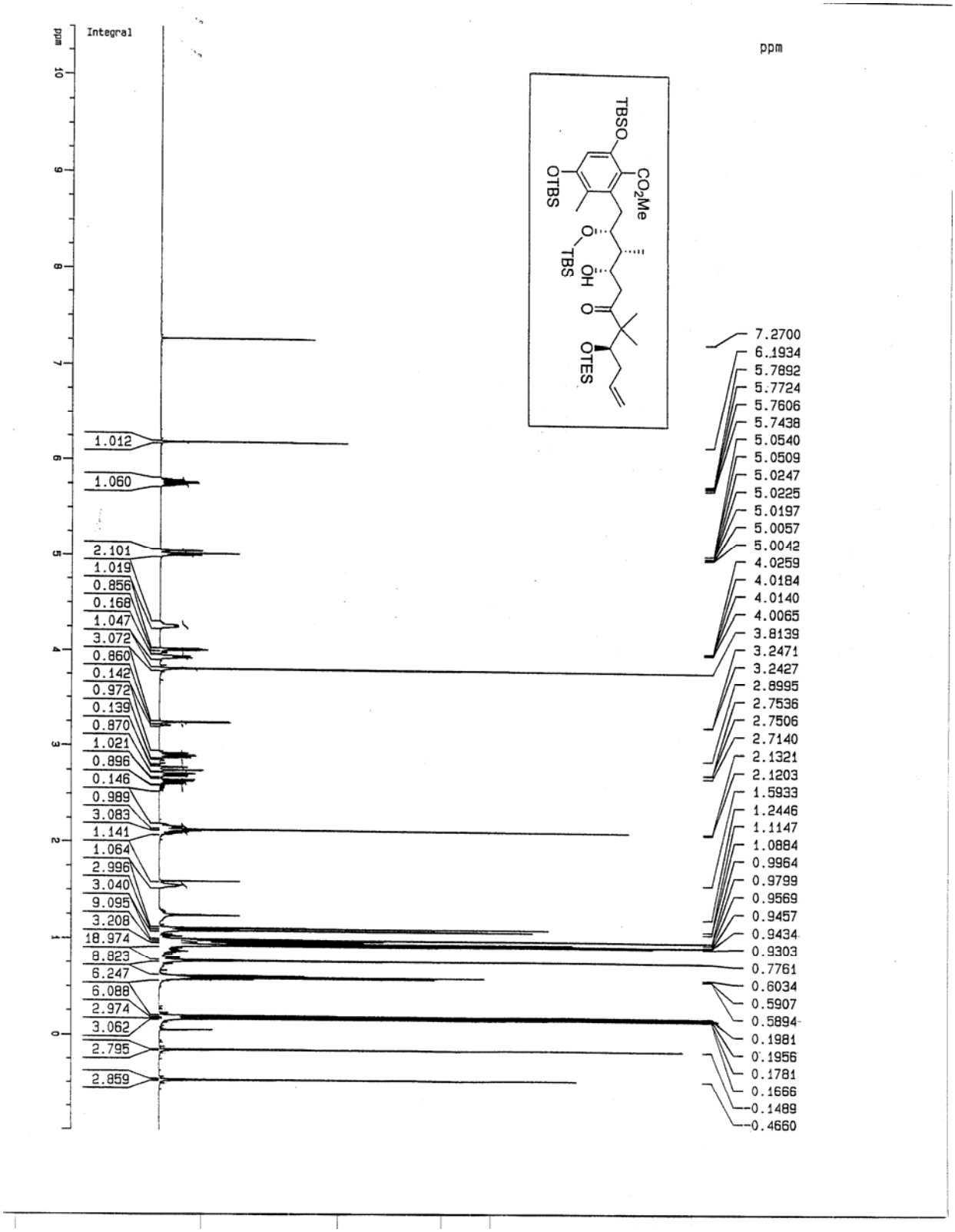

ppm
214.502
135.588
117.857
77.427
77.207
77.003
76.580
75.275
51.557
36.442
26.318
21.693
19.376
OH
O

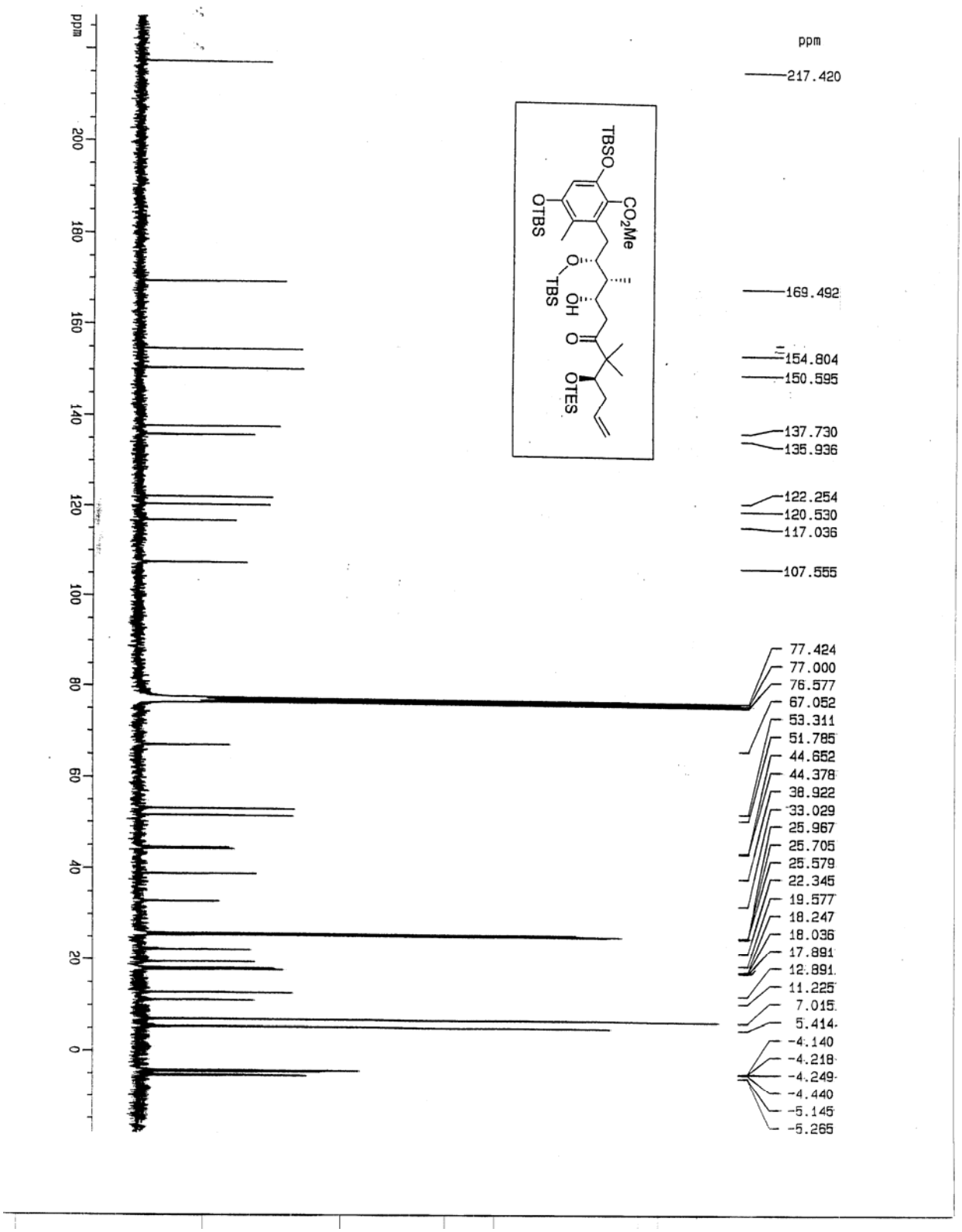

Integral
ppm
TESO
O
7.30183
5.86470
5.85050
5.84450
5.83614
5.83039
5.81625
5.81038
5.80202
5.79615
5.78184
5.10210
5.09924
5.06771
5.06533
5.04733
4.00639
3.99783
3.99190
3.98332
2.25515
2.22642
2.21471
2.20377
2.18121
2.16662
2.15202
2.13758
2.12310
1.61082
1.15228
1.12690
1.01023
0.99431
0.98673
0.97846
0.93582
0.92192
0.66801
0.65236
0.64401
0.63663
0.62077
1.252
2.767
1.331
6.545
3.873
3.878
11.595
8.204

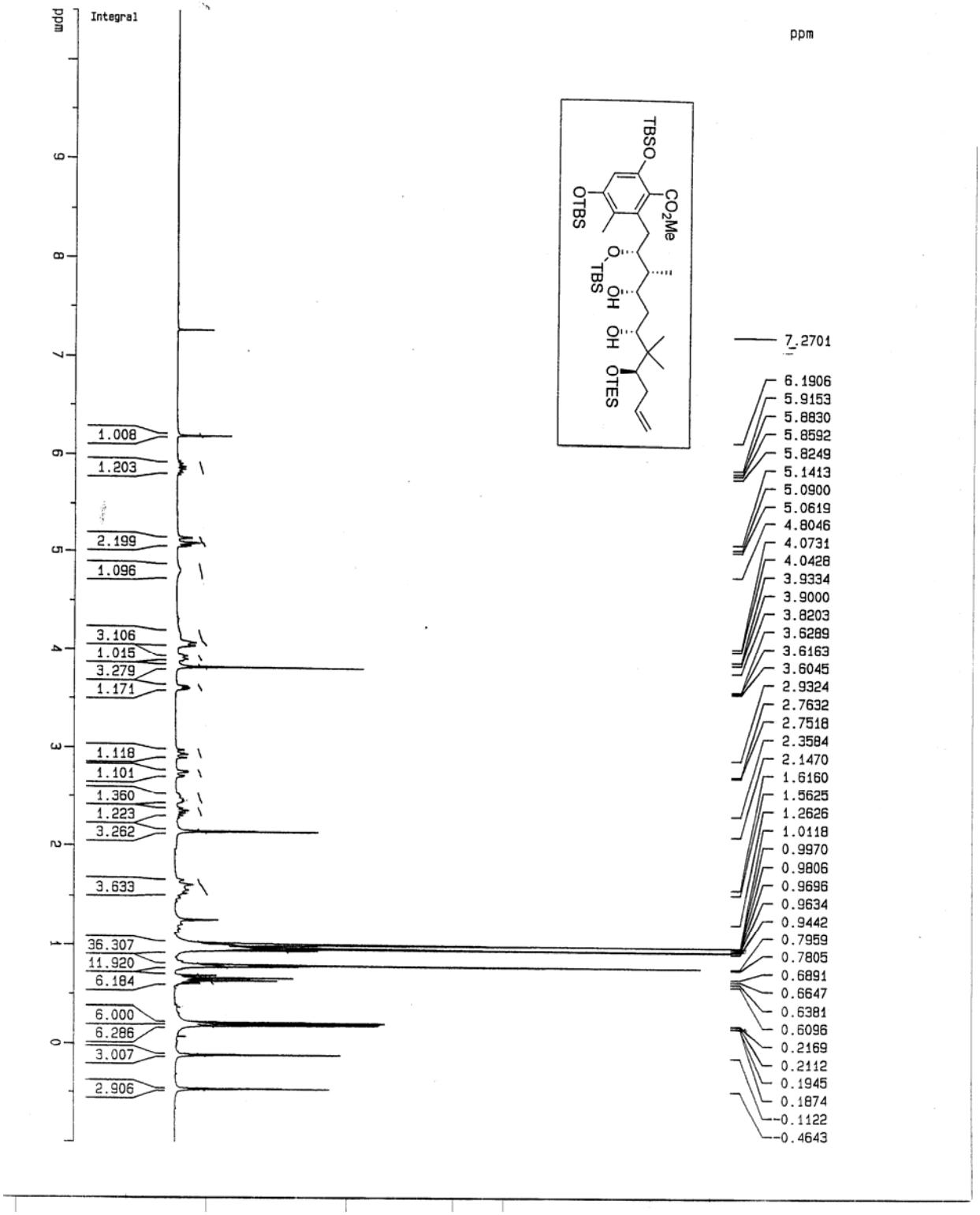

ppm
213.28
TESO
O
135.97
116.78
77.28
77.01
76.78
53.01
38.68
26.97
21.66
20.24
6.87
5.31
ppm
200
180
160
140
120
100
80
60
40
20
0

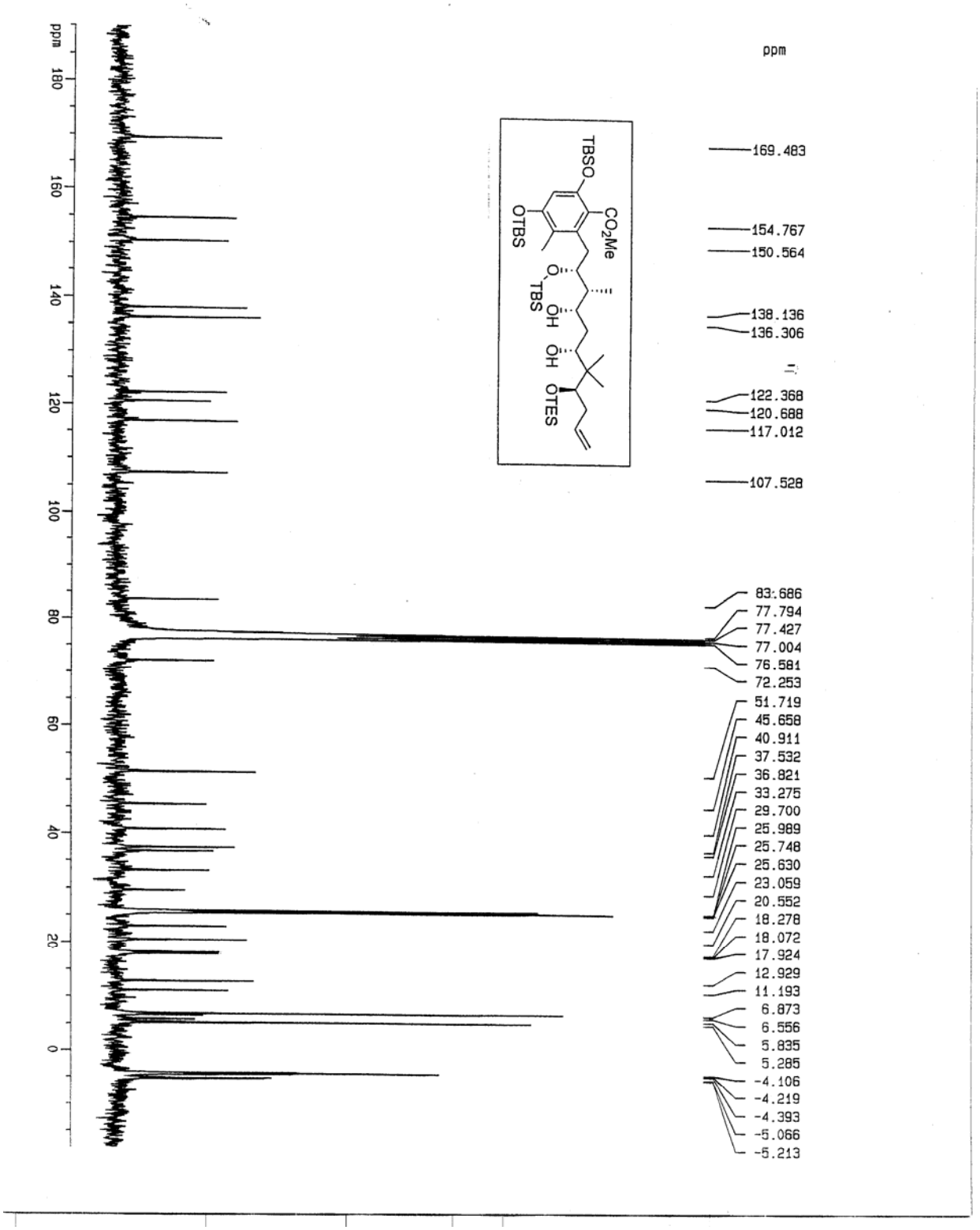

Integral
ppm
TESO
OTMS
7.26868
5.88925
5.88070
5.86719
5.85792
5.83314
5.82406
5.81051
5.80227
5.03723
5.00315
4.98000
4.97441
4.11837
4.11371
3.96807
3.96343
3.87686
3.86801
3.84881
3.83994
2.28584
2.24548
2.22456
2.04673
2.02129
1.99917
1.55083
1.09587
1.04885
0.98842
0.96204
0.95067
0.93577
0.63876
0.61278
0.59979
0.58647
0.55955
0.28917
0.23846
0.22152
0.21107
0.20066
1.000
2.065
1.115
1.097
1.025
1.243
1.184
3.254
11.532
6.516
6.503

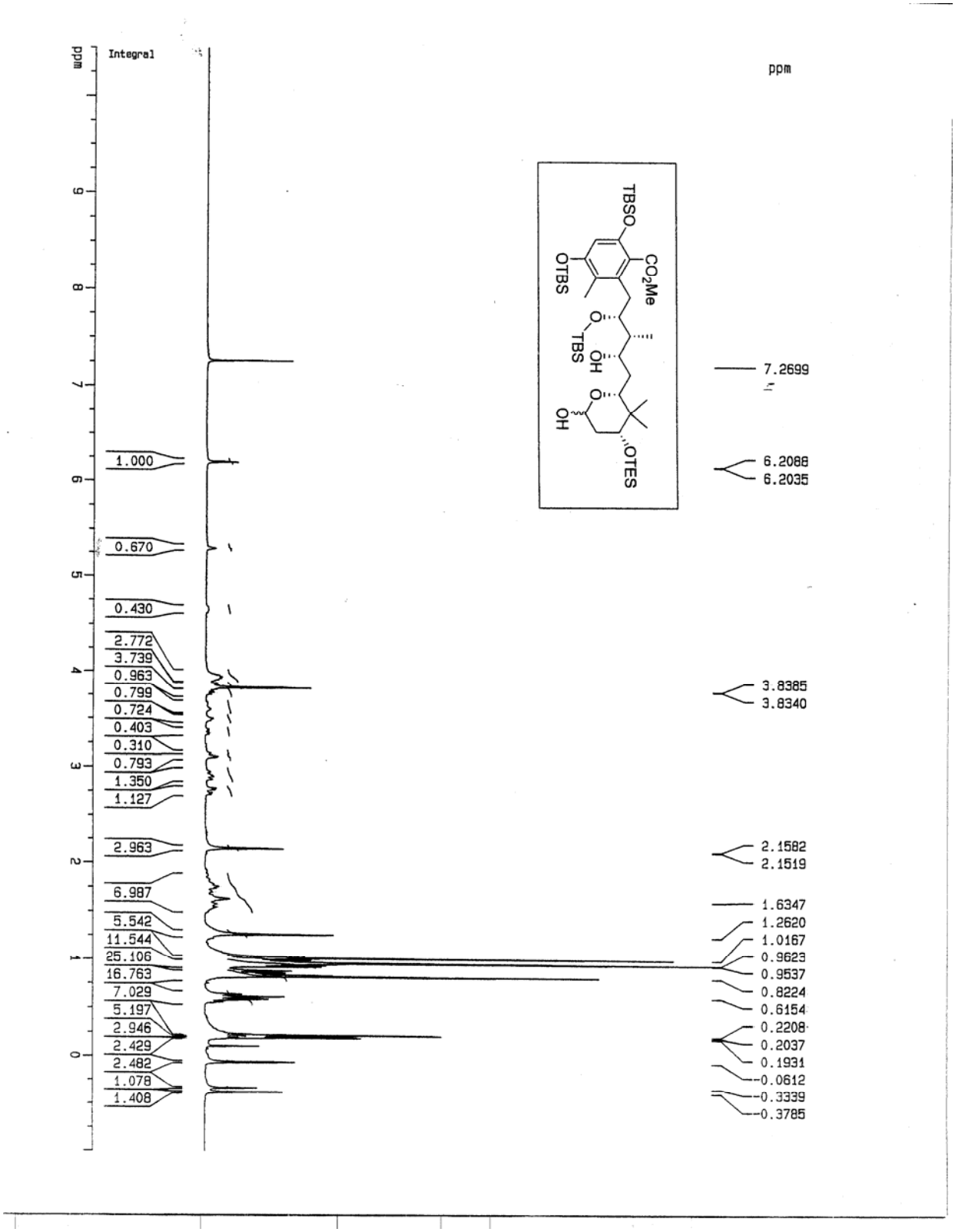

ppm
164.83
137.71
115.67
87.56
77.12
76.87
76.62
76.45
45.30
38.04
24.40
19.14
6.96
5.49
-0.06
TESO
OTMS

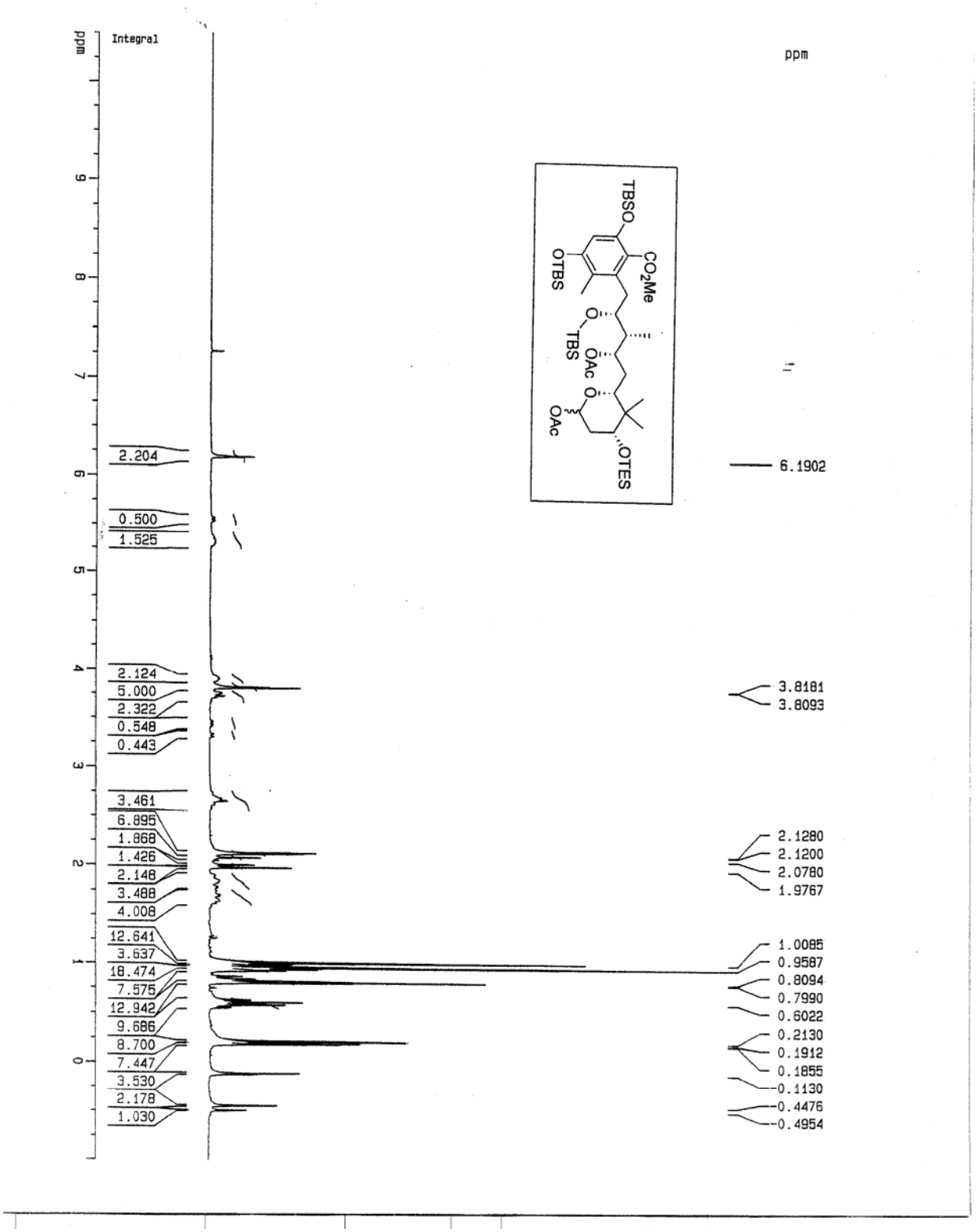

Integral
ppm
TBSO
CO2Me
OTBS
OTBS
OH
O
OTES
1.012
1.060
2.101
1.019
0.856
0.168
1.047
3.072
0.860
0.142
0.972
0.139
0.870
1.021
0.896
0.146
0.989
3.083
1.141
1.064
2.996
3.040
9.095
3.208
18.974
8.823
6.247
6.088
2.974
3.062
2.795
2.859
7.2700
6.1934
5.7892
5.7724
5.7606
5.7438
5.0540
5.0509
5.0247
5.0225
5.0197
5.0057
5.0042
4.0259
4.0184
4.0140
4.0065
3.8139
3.2471
3.2427
2.8995
2.7536
2.7506
2.7140
2.1321
2.1203
1.5933
1.2446
1.1147
1.0884
0.9964
0.9799
0.9569
0.9457
0.9434
0.9303
0.7761
0.6034
0.5907
0.5894
0.1981
0.1956
0.1781
0.1666
0.1489
0.4660

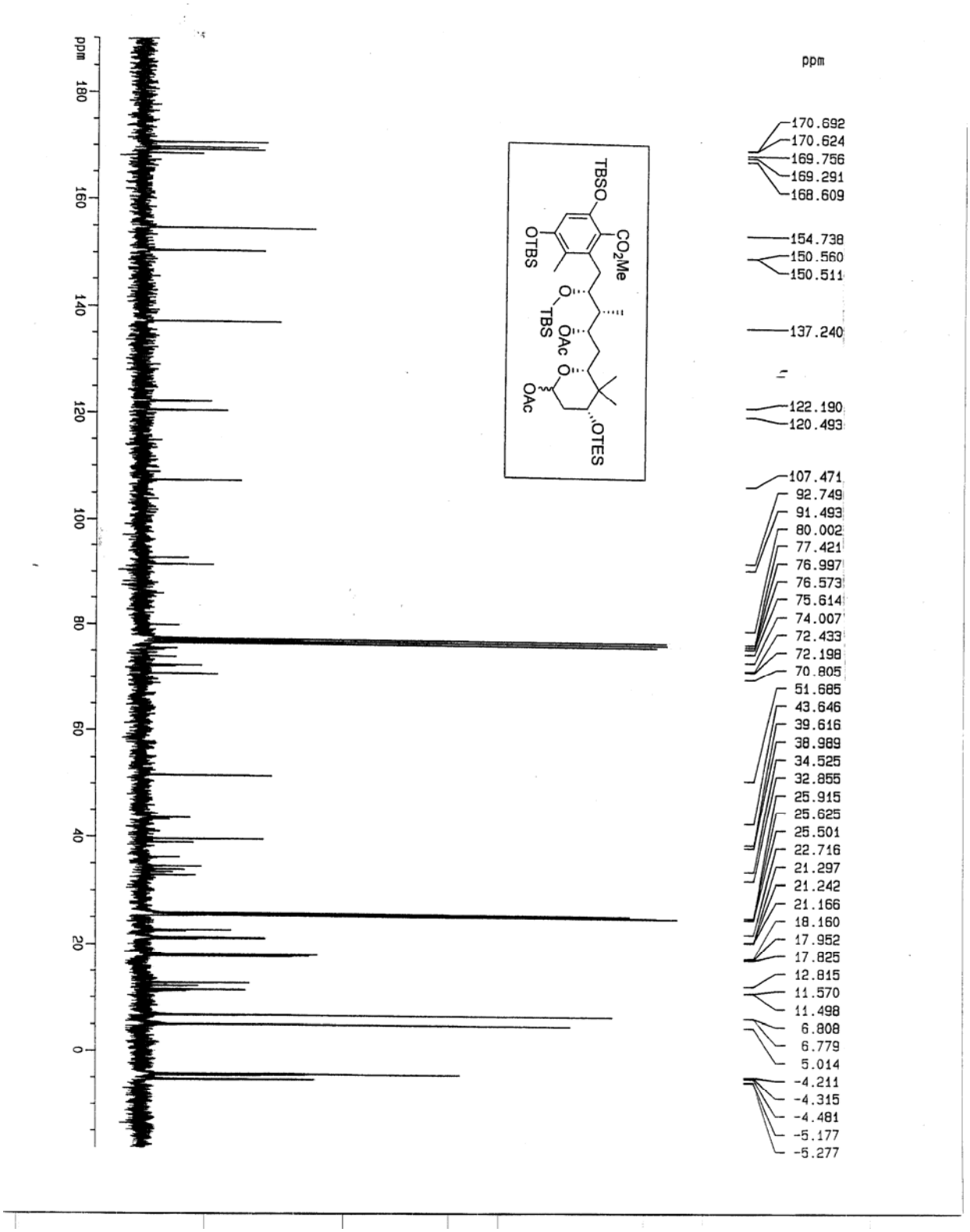

ppm
217.420
169.492
154.804
150.595
137.730
135.936
122.254
120.530
117.036
107.555
77.424
77.000
76.577
67.052
53.311
51.785
44.652
44.378
38.922
33.029
25.967
25.705
25.579
22.345
19.577
18.247
18.036
17.891
12.891
11.225
7.015
5.414
-4.140
-4.218
-4.249
-4.440
-5.145
-5.265
TBSO
CO2Me
OTBS
TBS
OH
O
OTES

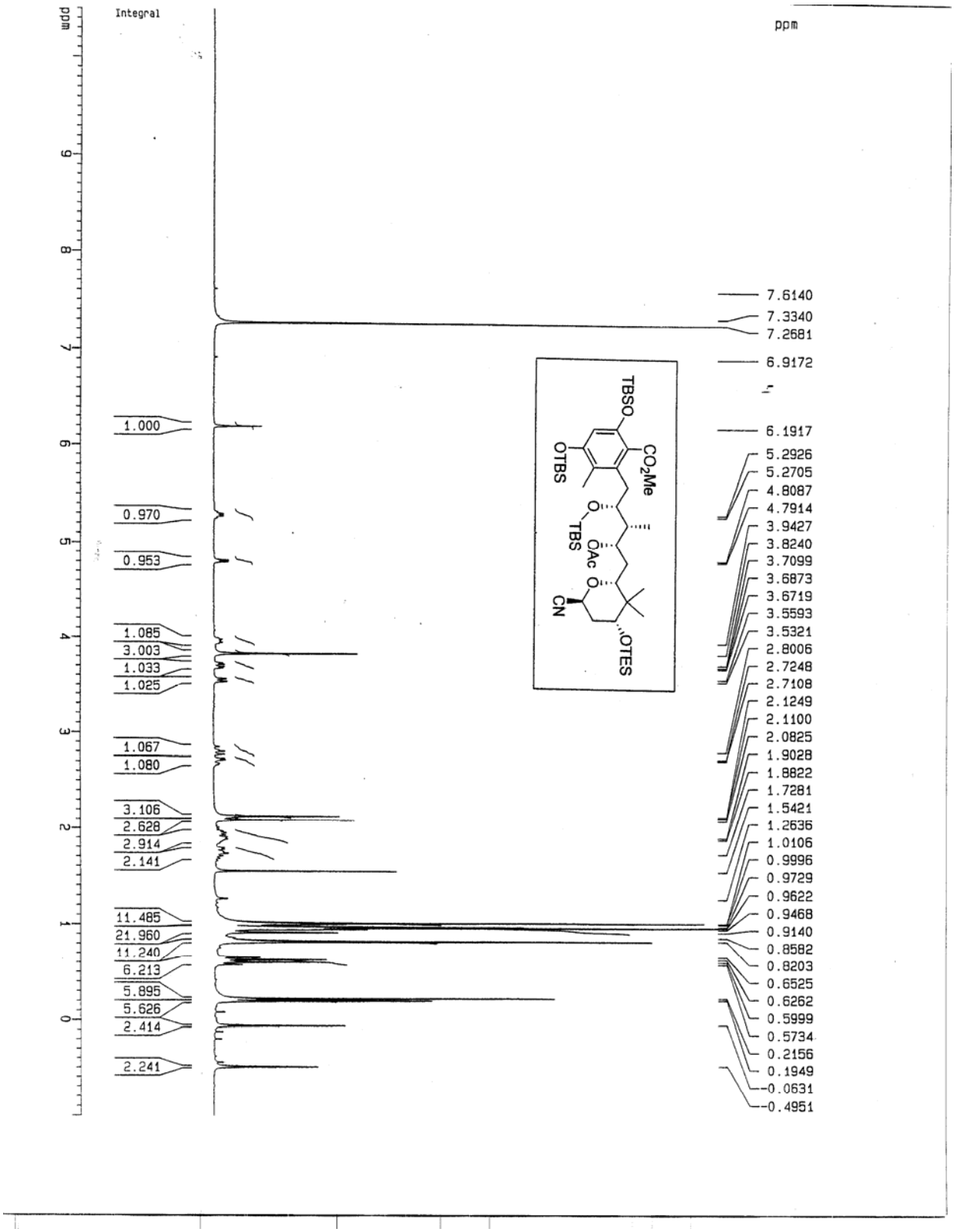

ppm
Integral
ppm
TBSO
CO2Me
OTBS
OTBS
OH
OH
OTES
1.008
1.203
2.199
1.096
3.106
1.015
3.279
1.171
1.118
1.101
1.360
1.223
3.262
3.633
36.307
11.920
6.184
6.000
6.286
3.007
2.906
7.2701
6.1906
5.9153
5.8830
5.8592
5.8249
5.1413
5.0900
5.0619
4.8046
4.0731
4.0428
3.9334
3.9000
3.8203
3.6289
3.6163
3.6045
2.9324
2.7632
2.7518
2.3584
2.1470
1.6160
1.5625
1.2626
1.0118
0.9970
0.9806
0.9696
0.9634
0.9442
0.7959
0.7805
0.6891
0.6647
0.6381
0.6096
0.2169
0.2112
0.1945
0.1874
-0.1122
-0.4643

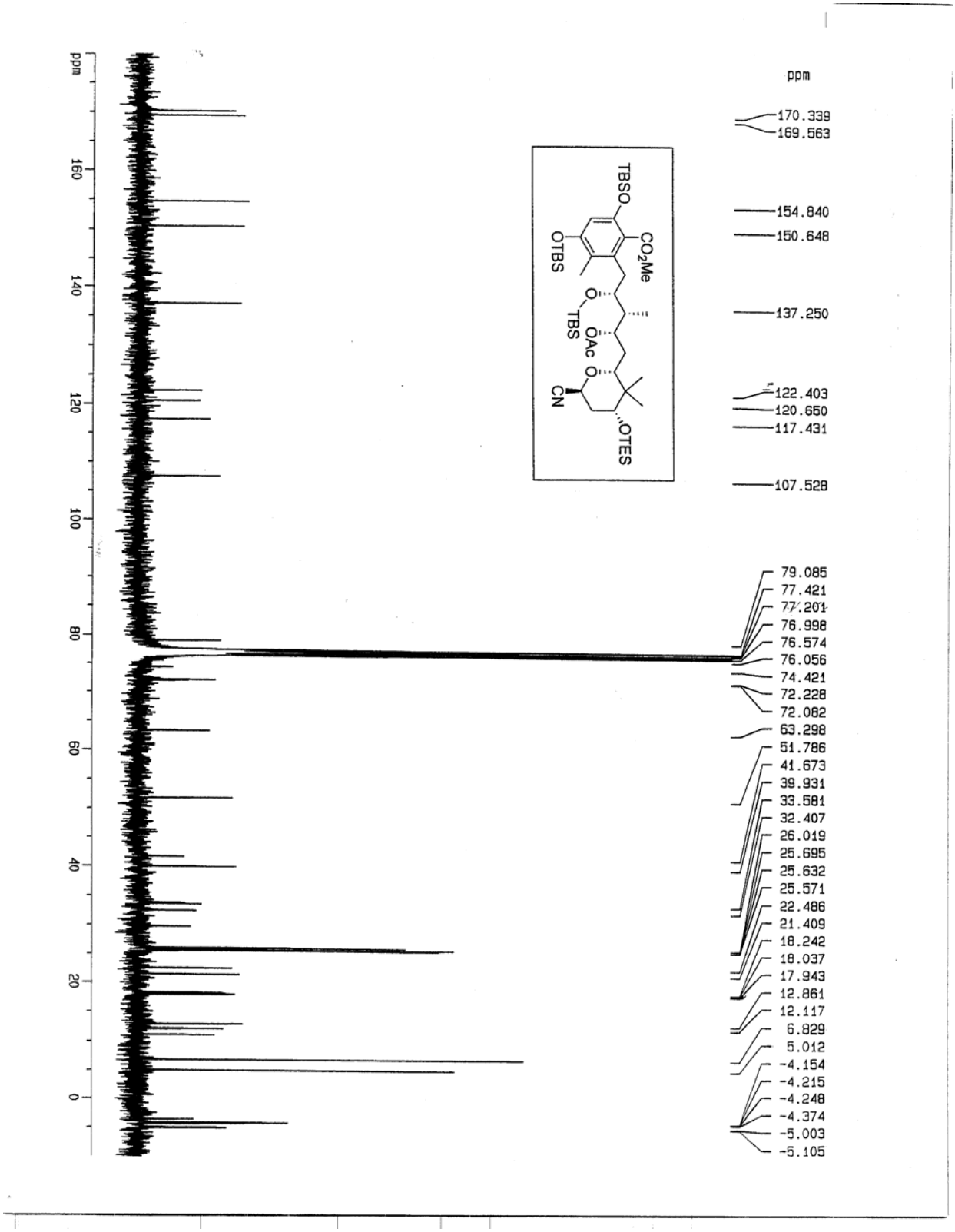

ppm
180
160
140
120
100
80
60
40
20
0
TBSO
CO2Me
OTBS
OTBS
OH
OH
OTES
ppm
169.483
154.767
150.564
138.136
136.306
122.368
120.688
117.012
107.528
83.686
77.794
77.427
77.004
76.581
72.253
51.719
45.658
40.911
37.532
36.821
33.275
29.700
25.989
25.748
25.630
23.059
20.552
18.278
18.072
17.924
12.929
11.193
6.873
6.556
5.835
5.285
-4.106
-4.219
-4.393
-5.066
-5.213

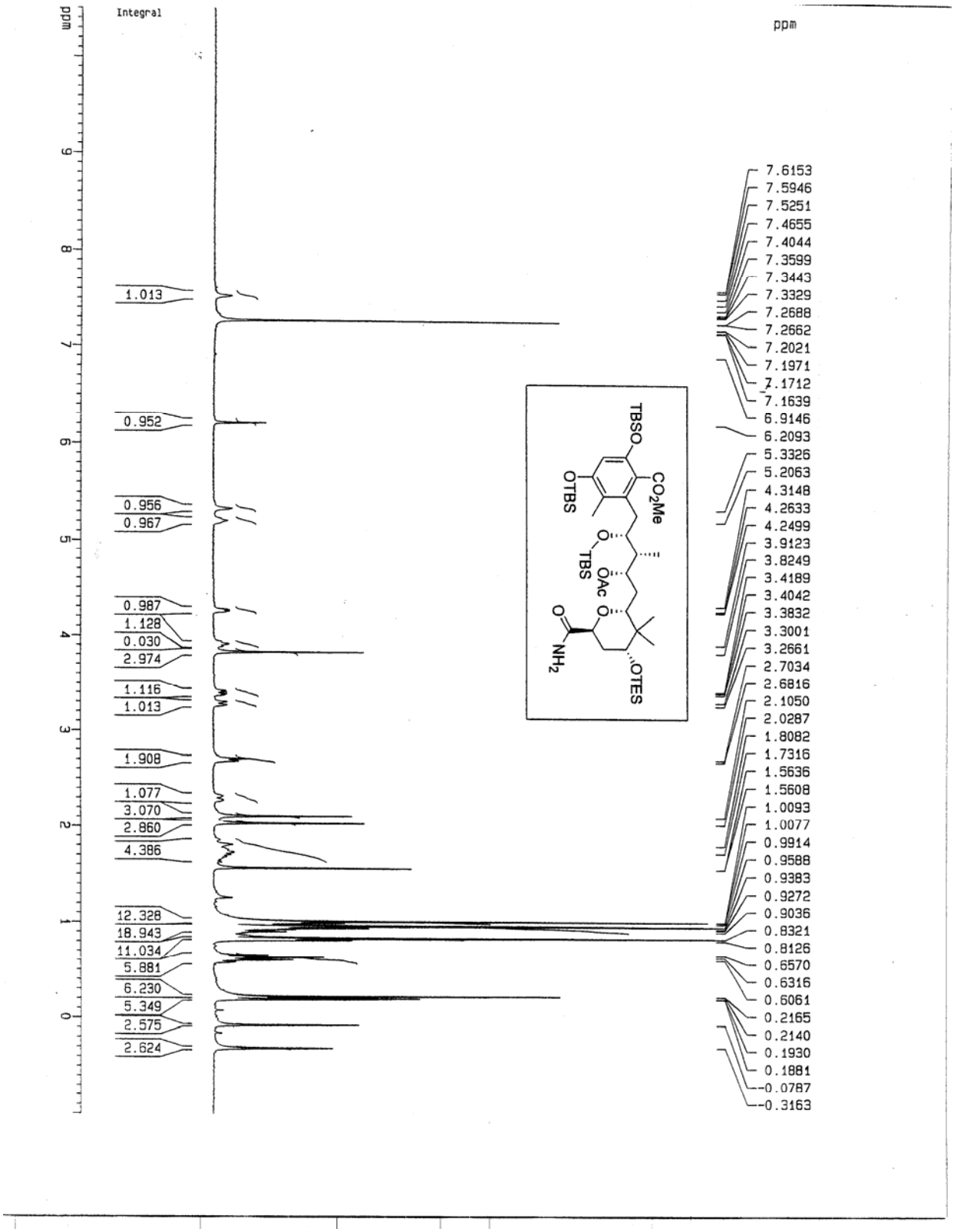

Integral
ppm
TBSO
CO2Me
OTBS
TBS
OH
OH
OTES
1.000
0.670
0.430
2.772
3.739
0.963
0.799
0.724
0.403
0.310
0.793
1.350
1.127
2.963
6.987
5.542
11.544
25.106
16.763
7.029
5.197
2.946
2.429
2.482
1.078
1.408
7.2699
6.2088
6.2035
3.8385
3.8340
2.1582
2.1519
1.6347
1.2620
1.0167
0.9623
0.9537
0.8224
0.6154
0.2208
0.2037
0.1931
-0.0612
-0.3339
-0.3785

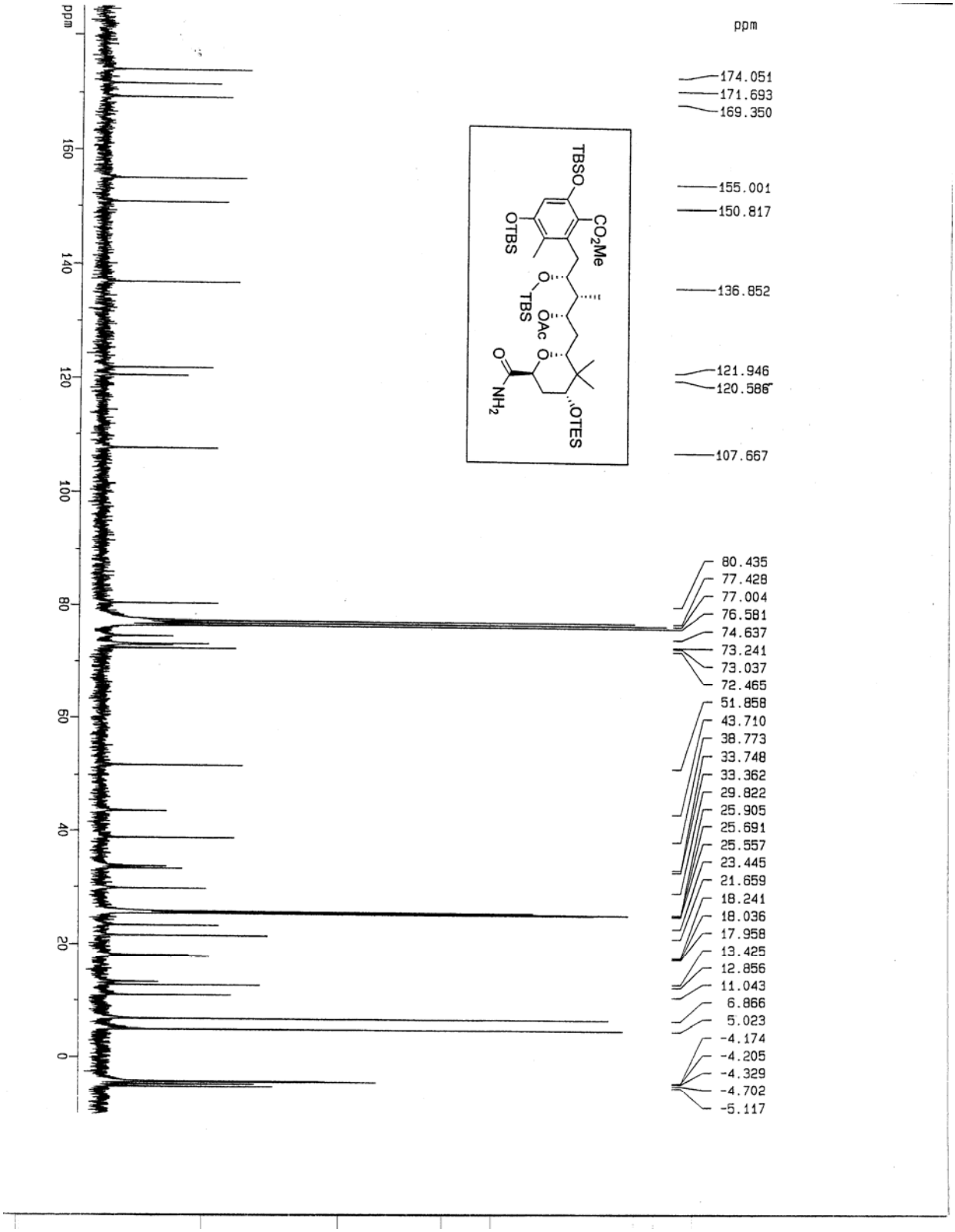

Integral
ppm
TBSO
CO2Me
OTBS
TBS
OAc
OAc
OTES
2.204
0.500
1.525
2.124
5.000
2.322
0.548
0.443
3.461
6.895
1.868
1.426
2.148
3.488
4.008
12.641
3.637
18.474
7.575
12.942
9.686
8.700
7.447
3.530
2.178
1.030
6.1902
3.8181
3.8093
2.1280
2.1200
2.0780
1.9767
1.0085
0.9587
0.8094
0.7990
0.6022
0.2130
0.1912
0.1855
-0.1130
-0.4476
-0.4954

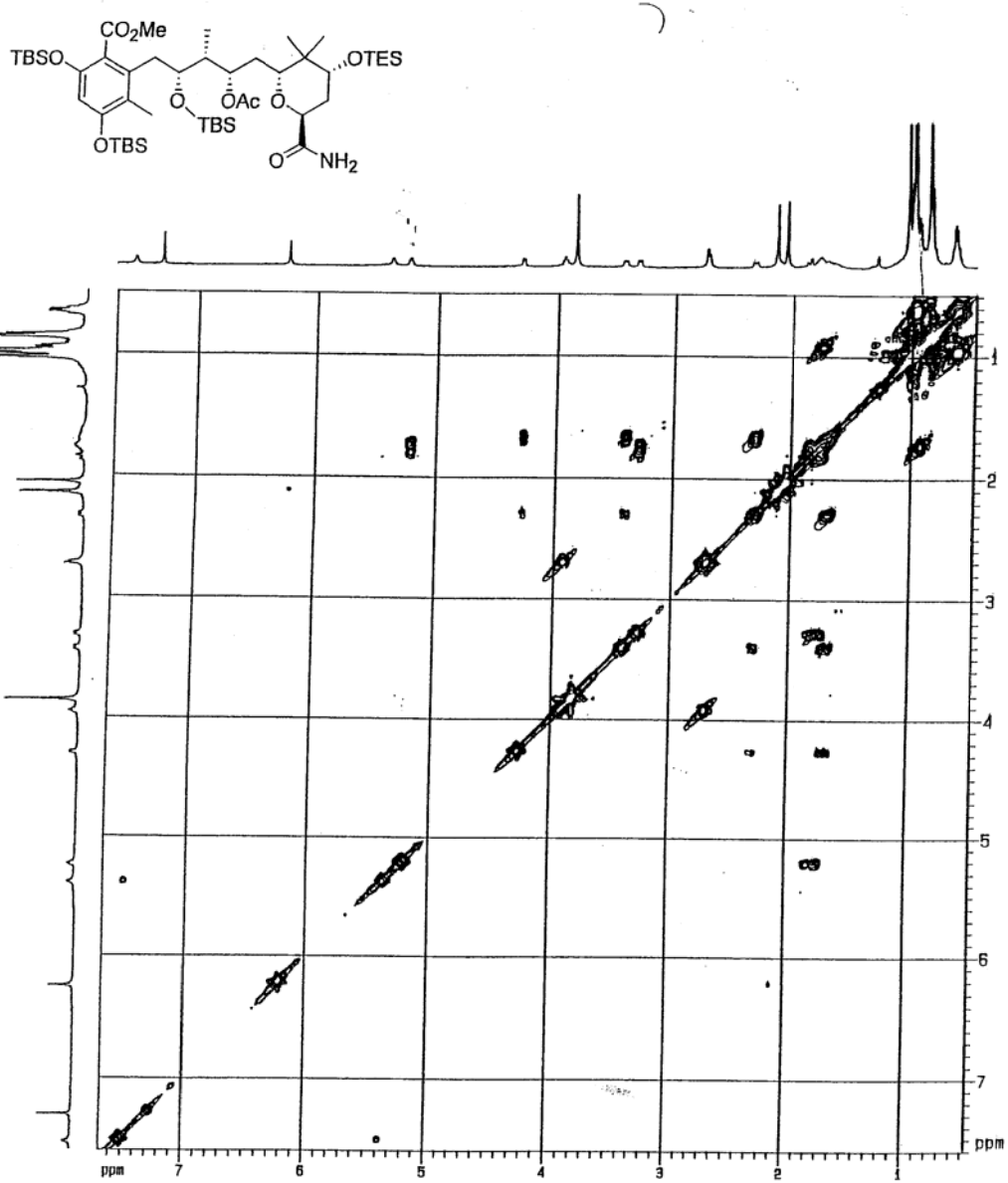

ppm
180
160
140
120
100
80
60
40
20
0
TBSO
CO2Me
OTBS
TBS
OAc
OAc
OTES
ppm
170.692
170.624
169.756
169.291
168.609
154.738
150.560
150.511
137.240
122.190
120.493
107.471
92.749
91.493
80.002
77.421
76.997
76.573
75.614
74.007
72.433
72.198
70.805
51.685
43.646
39.616
38.989
34.525
32.855
25.915
25.625
25.501
22.716
21.297
21.242
21.166
18.160
17.952
17.825
12.815
11.570
11.498
6.808
6.779
5.014
-4.211
-4.315
-4.481
-5.177
-5.277


ppm
Integral
ppm
TBSO
CO2Me
OTBS
OTBS
OAc
CN
OTES
1.000
0.970
0.953
1.085
3.003
1.033
1.025
1.067
1.080
3.106
2.628
2.914
2.141
11.485
21.960
11.240
6.213
5.895
5.626
2.414
2.241
7.6140
7.3340
7.2681
6.9172
6.1917
5.2926
5.2705
4.8087
4.7914
3.9427
3.8240
3.7099
3.6873
3.6719
3.5593
3.5321
2.8006
2.7248
2.7108
2.1249
2.1100
2.0825
1.9028
1.8822
1.7281
1.5421
1.2636
1.0106
0.9996
0.9729
0.9622
0.9468
0.9140
0.8582
0.8203
0.6525
0.6262
0.5999
0.5734
0.2156
0.1949
-0.0631
-0.4951


ppm
160
140
120
100
80
60
40
20
0
TBSO
CO2Me
OTBS
O
TBS
OAc
O
CN
OTES
ppm
170.339
169.563
154.840
150.648
137.250
122.403
120.650
117.431
107.528
79.085
77.421
77.201
76.998
76.574
76.056
74.421
72.228
72.082
63.298
51.786
41.673
39.931
33.581
32.407
26.019
25.695
25.632
25.571
22.486
21.409
18.242
18.037
17.943
12.861
12.117
6.829
5.012
-4.154
-4.215
-4.248
-4.374
-5.003
-5.105


ppm
Integral
1.013
0.952
0.956
0.967
0.987
1.128
0.030
2.974
1.116
1.013
1.908
1.077
3.070
2.860
4.386
12.328
18.943
11.034
5.881
6.230
5.349
2.575
2.624
TBSO
CO2Me
OTBS
TBS
OAc
NH2
OTES
ppm
7.6153
7.5946
7.5251
7.4655
7.4044
7.3599
7.3443
7.3329
7.2688
7.2662
7.2021
7.1971
7.1712
7.1639
6.9146
6.2093
5.3326
5.2063
4.3148
4.2633
4.2499
3.9123
3.8249
3.4189
3.4042
3.3832
3.3001
3.2661
2.7034
2.6816
2.1050
2.0287
1.8082
1.7316
1.5636
1.5608
1.0093
1.0077
0.9914
0.9588
0.9383
0.9272
0.9036
0.8321
0.8126
0.6570
0.6316
0.6061
0.2165
0.2140
0.1930
0.1881
-0.0787
-0.3163


ppm
174.051
171.693
169.350
155.001
150.817
136.852
121.946
120.586
107.667
80.435
77.428
77.004
76.581
74.637
73.241
73.037
72.465
51.858
43.710
38.773
33.748
33.362
29.822
25.905
25.691
25.557
23.445
21.659
18.241
18.036
17.958
13.425
12.856
11.043
6.866
5.023
-4.174
-4.205
-4.329
-4.702
-5.117
TBSO
CO2Me
OTBS
TBS
OAc
NH2
OTES



Current Data Parameters
NAME jcr061405
EXPNO 11
PROCNO 1

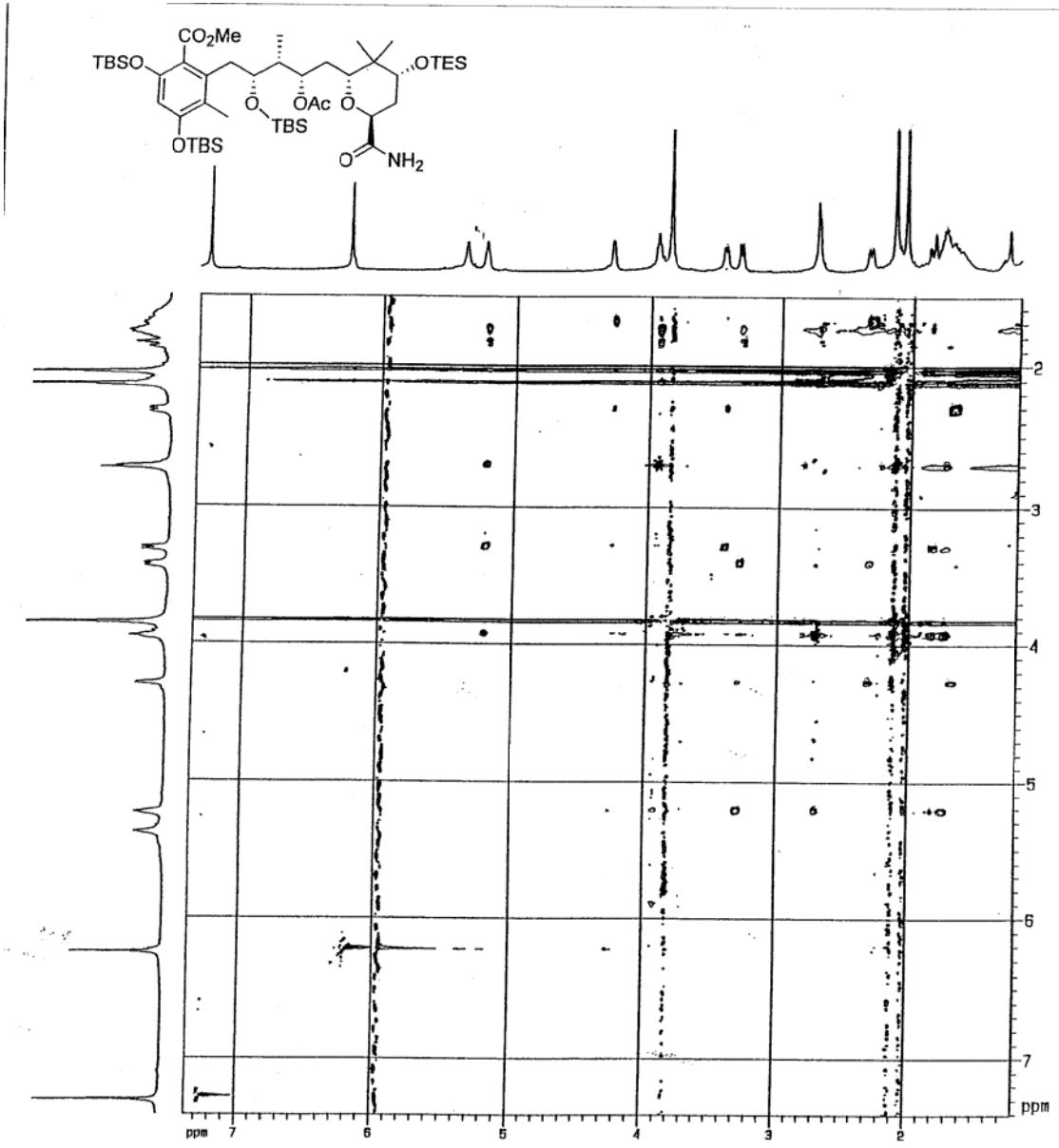
F2 - Acquisition Parameters
Date_ 500000
Time 10.03
INSTRUM spect
PROBHD 5 mm TXI j3C
PULPROG cosy
TD 1024
SOLVENT CDCl3
NS 32
DS 16
SWH 4006.410 Hz
FIDRES 3.912510 Hz
AQ 0.1278452 sec
RG 181
DW 124.800 usec
DE 6.00 usec
TE 299.0 K
D0 0.0000030 sec
D1 1.00000000 sec
P1 10.50 usec
PO 10.80 usec
CE 6.00 usec
SFO1 500.1320005 MHz
NUC1 1H
PL1 0.00 dB
IN0 0.00024960 sec

F1 - Acquisition parameters
NDO 1
TD 512
SFO1 500.1319 MHz
FIDRES 7.825030 Hz
SW 8.011 ppm

F2 - Processing parameters
SI 512
SF 500.1300201 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0
PC 1.00

F1 - Processing parameters
SI 512
MC2 QF
SF 500.1298717 MHz
WDW SINE
SSB 0
LB 0.00 Hz
GB 0

2D NMR plot parameters
CX2 15.00 cm
CX1 15.00 cm
F2PLO 7.684 ppm
F2LO 3842.77 Hz
F2PHI 0.471 ppm
F2HI 235.44 Hz
F1PLO 7.602 ppm
F1LO 3802.02 Hz
F1PHI 0.483 ppm
F1HI 241.53 Hz
F2PPMCM 0.48085 ppm/cm
F2HZCM 240.48694 Hz/cm
F1PPMCM 0.47460 ppm/cm
F1HZCM 237.35924 Hz/cm



Current Data Parameters

NAME	jcr061405
EXPNO	1111
PROCNO	1

F2 - Acquisition Parameters

Date_	500000
Time	15.30
INSTRUM	spect
PROBHD	5 mm TXI 13C
PULPROG	noesytp
TD	1024
SOLVENT	CDCl3
NS	32
DS	16
SWH	4006.410 Hz
FIDRES	3.912510 Hz
AQ	0.1278452 sec
RG	287.4
DW	124.800 usec
DE	6.00 usec
TE	290.0 K
d0	0.0000030 sec
D1	1.00000000 sec
P1	10.50 usec
DB	0.34999998 sec
DE	6.00 usec
SFO1	500.1320005 MHz
NUC1	1H
PL1	0.00 dB
IN0	0.00012400 sec

F1 - Acquisition parameters

ND0	2
TD	1024
SFO1	500.132 MHz
FIDRES	3.912515 Hz
SW	8.011 ppm

F2 - Processing parameters

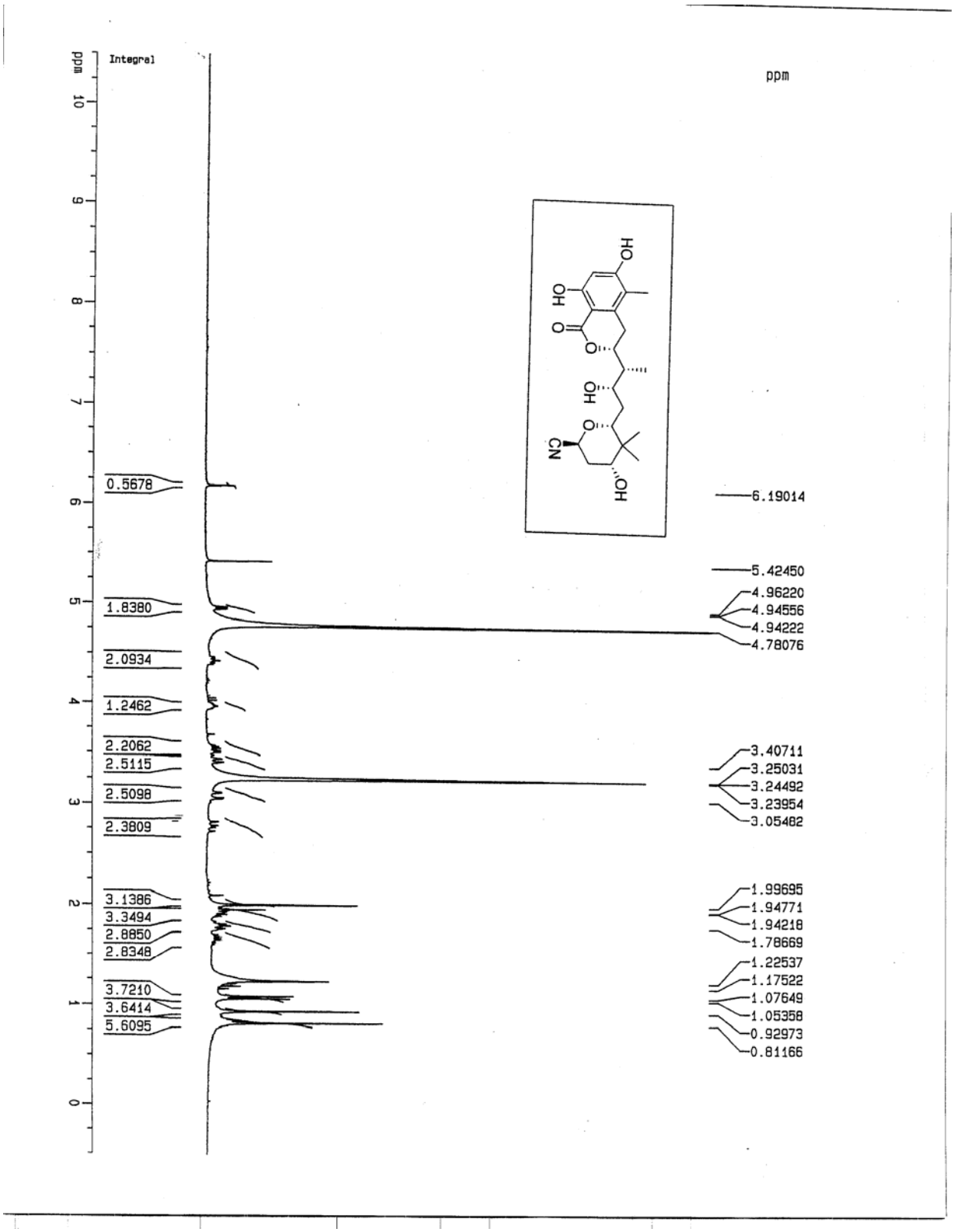
SI	1024
SF	500.1300213 MHz
WDW	SINE
SSB	2
LB	0.00 Hz
GB	0
PC	1.00

F1 - Processing parameters

SI	1024
MC2	TPPI
SF	500.1300211 MHz
WDW	SINE
SSB	2
LB	0.00 Hz
GB	0

2D NOESY plot parameters

CX2	15.00 cm
CX1	15.00 cm
F2PLO	7.376 ppm
F2LO	3688.94 Hz
F2PHI	1.204 ppm
F2HI	601.97 Hz
F1PLO	7.408 ppm
F1LO	3704.85 Hz
F1PHI	1.509 ppm
F1HI	754.81 Hz
F2PPMCM	0.41149 ppm/cm
F2HZCM	205.79803 Hz/cm
F1PPMCM	0.39324 ppm/cm
F1HZCM	196.66910 Hz/cm


Integral
ppm
0.5678
1.8380
2.0934
1.2462
2.2062
2.5115
2.5098
2.3809
3.1386
3.3494
2.8850
2.8348
3.7210
3.6414
5.6095
ppm
6.19014
5.42450
4.96220
4.94556
4.94222
4.78076
3.40711
3.25031
3.24492
3.23954
3.05482
1.99695
1.94771
1.94218
1.78669
1.22537
1.17522
1.07649
1.05358
0.92973
0.81166