MECHANISTIC AND STEREOCHEMICAL STUDIES OF PHOTOINDUCED ELECTRON TRANSFER CYCLIZATION REACTIONS: THE ROLE OF NITROGEN. THE AQUEOUS PRINS REACTION AND EFFORTS TOWARDS THE TOTAL SYNTHESIS OF (+)-DACTYLOLIDE

by

Danielle L. Aubele

B.S., Allegheny College, 1999

M.S., University of Pittsburgh, 2002

Submitted to the Graduate Faculty of

Arts and Sciences in partial fulfillment

of the requirements for the degree of

Doctor of Chemistry

University of Pittsburgh

2004

UNIVERSITY OF PITTSBURGH

FACULTY OF ARTS AND SCIENCES

This dissertation was presented

by

Danielle L. Aubele

It was defended on

Wednesday, August 18th, 2004

and approved by

Dennis P. Curran

Kay Brummond

Billy Day

Paul E. Floreancig
Dissertation Director

Copyright by Danielle L. Aubele, 2004

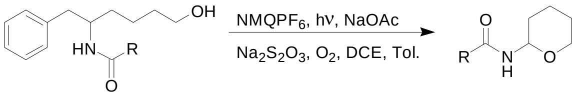
Paul E. Floreancig

MECHANISTIC AND STEREOCHEMICAL STUDIES OF PHOTOINDUCED ELECTRON TRANSFER CYCLIZATION REACTIONS: THE ROLE OF NITROGEN. THE AQUEOUS PRINS REACTION AND EFFORTS TOWARDS THE TOTAL SYNTHESIS OF (+)-DACTYLOLIDE

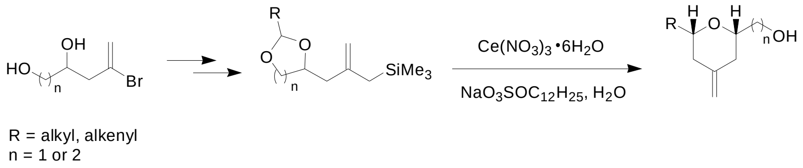
Danielle L. Aubele, PhD

University of Pittsburgh, 2004

A novel method for catalytic electron transfer initiated cyclization reaction for the formation of cyclic acyl aminals through a unique method of carbon-carbon σ-bond activation has been developed. This new cyclization strategy employs a potent electrophile, generated by a photoinitiated single electron oxidation of a homobenzylic amide or *t*-butyl carbamate, which reacts with an appended nucleophile allowing for the formation of cyclic acyl aminals.



The Lewis acid-surfactant-combined catalyst (LASC) was employed in a novel method for effecting intramolecular Prins cyclization reactions in water. Acetals of 1,2 and 1,3 di- and tri- substituted alcohols with a tethered allyl silane have been converted to 2,6-syn-tetrahydropyrans. The LASCs are generated in situ by the addition of cerium nitrate to a solution of sodium dodecylsulfate and acetal in water. A heterogeneous reaction environment is created in which the acetal is trapped within the hydrophobic core of the immediately generated micelle. Intarmolecular Prins cyclization is catalyzed upon interaction of the acetal with Lewis acidic cerium cations located at the surface of the micelle. LASC mediated intramolecular Prins cyclization reactions are efficient, high yielding, and an environmentally benign method of generating 2,6-*cis*-tetrahydropyrans.



A highly convergent route towards the total synthesis of the marine macrolide (+)-dactylolide is currently being pursued. The route involves the condensation of two highly functionalized segments of the molecule, an α,β-unsaturated aldehyde and a 1,3-*syn*-diol, to form a cyclic α,β-unsaturated acetal. Both enantiopure segments arise from vinylogous aldol reactions, providing the three necessary stereocenters. The key synthetic transformation involves intramolecular Prins cyclization of a cyclic α,β-unsaturated acetal with a pendent allylsilane to provide the 2,6-*cis*-disubstituted-4-methylenetetrahydropyran core of the molecule efficiently and stereoselectively. Other key transformations include a completely *trans* selective selenoxide-selenate [2,3] sigmatropic rearrangement and the selective oxidation of a primary allylic alcohol in the presence of a secondary alcohol with Dess-Martin periodinane.

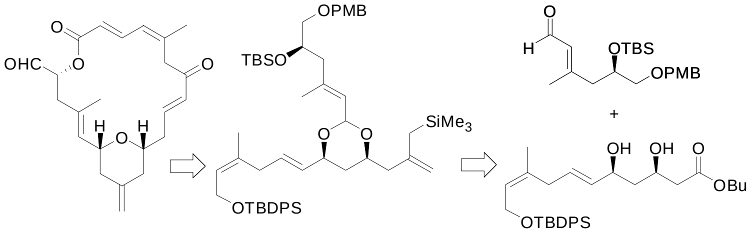


TABLE OF CONTENTS

PREFACE xi

1. Mechanistic and stereochemical studies of photoinduced electron transfer initiated cyclization reactions: the role of nitrogen 1
   - 1.1. Introduction to electron transfer 1
   - 1.2. Results 20
   - 1.3. Discussion of electron transfer initiated cyclization reactions 44
   - 1.4. Conclusion 52
   - 1.5. Experimental 54
   - 1.6. References 100
2. The aqueous Prins reaction 104
   - 2.1. Introduction 104
   - 2.2. Results and Discussion 117
   - 2.3. Conclusion 130
   - 2.4. Experimental 132
   - 2.5. References 151
3. Efforts towards the total synthesis of (+)-Dactylolide 154
   - 3.1. Introduction 154
   - 3.2. Results and Discussion 166
   - 3.3. Conclusion 183
   - 3.4. Experimental 184
   - 3.5. References 203

APPENDIX A 207
   Mechanistic and stereochemical studies of photoinduced electron transfer initiated cyclization reactions: the role of nitrogen (Supporting Information) 207

APPENDIX B 260
   The aqueous Prins reaction (Supporting Information) 260

APPEDIX C 291
   Efforts towards the total synthesis of (+)-Dactylolide (Supporting information) 291

LIST OF TABLES

Table 1.1: Variations of ETIC reaction conditions 28
Table 1.2**:** Altering aromatic cosolvents 32
Table 1.3: Substrates tested under catalytic aerobic ETIC conditions 35
Table 1.4: Additional homobenzylic stabilizing groups 38
Table 1.5: Nitrogen as a nucleophile 41
Table 1.6: ETIC conditions with varying base and solvent 76
Table 1.7: ETIC conditions with varyiation in aromatic cosolvent 76
Table 1.8: Catalytic aerobic ETIC conditions 77
Table 2.1: Intramolecular Prins cyclization with Lewis/Brønstead acids 120
Table 2.2: Optimal surfactant chain length 124
Table 2.3: Cost/benefit analysis of cerium III salts 125
Table 2.4: Summary of intramolecular Prins cyclization substrates 131
Table 3.1: Screening of viable Prins cyclization conditions 177

LIST OF FIGURES

Figure 1.1: Electronic transition resulting from photoexcitation 3
Figure 1.2: Photochemical pathways 3
Figure 1.3: IP and EA of both the ground and excited state species 4
Figure 1.4: Ground state redox reactions 5
Figure 1.5: Photoinitiated electron transfer 6
Figure 1.6: Primary reaction pathways for radical cations 7
Figure 1.7: PET induced mesolytic cleavage of C-C bond 9
Figure 1.8: Mechanism for mesolytic C-C bond cleavage 10
Figure 1.9: PET reactions of 2-phenyl ether systems, Sens. = 1,4-dicyanobenzene 10
Figure 1.10: Schematic of the BDE of the radical cation 12
Figure 1.11: Radical cation bond dissociations studied by Camaioni 13
Figure 1.12: Kinetically preferred conformation for C-C bond cleavage 13
Figure 1.13: Kinetic preference for C-C bond cleavage 14
Figure 1.14: Stereospecific nucleophilic attack onto a radical cation 15
Figure 1.15: Electron transfer initiated cyclization 15
Figure 1.16: Cation sensitized photoinitiated single electron transfer 17
Figure 1.17: Proposed mechanistic pathways 18
Figure 1.18: ETIC involving homobenzylic amides or carbamates 19
Figure 1.19: Synthetic targets 19
Figure 1.20**:** Relative stereochemical relationship of amide **15** 24
Figure 1.21**:** ETIC reaction of amide **24** 27
Figure 1.22**:** ETIC reaction of amide **26** 29
Figure 1.23: ETIC reaction of amide **28** 29
Figure 1.24: A catalytic aerobic ETIC reaction 32
Figure 1.25: ETIC reaction under new aerobic conditions 32
Figure 1.26: Catalytic aerobic ETIC reaction with $Na_2S_2O_3$ 34
Figure 1.27: Attempted trapping of carbamate radical cation 40
Figure 1.28: ETIC reaction of trifluoromethyl-substituted arenes 43
Figure 1.29: Stereocontrol in tertiary amide cyclizations 45
Figure 1.30: Proposed dissociative mechanism 47
Figure 1.31: Comparison of ETIC reactions 48
Figure 1.32: Two possible mesolytic cleavages 48
Figure 1.33: Mechanism for formation of amide **27** 49
Figure 1.34: Possible radical cations 50
Figure 1.35: Ideal geometries for β-alkoxy carbamate radical cation C-C bond fragmentation .. 50
Figure 2.1: Generally accepted Prins mechanism 105
Figure 2.2: Generally accepted Prins mechanism involving allyl and vinylsilanes 106
Figure 2.3: Allylic transposition of allylsilanes 106
Figure 2.4: Pinacol-terminated Prins cyclization 107
Figure 2.5: Prins cyclization to form THPs 108
Figure 2.6: ISMS and ISMC reactions 108
Figure 2.7: Two-step THP formation 109

Figure 2.8: MAP cyclization reaction 109
Figure 2.9: Heteroatom substituted [3,3]-sigmatropic rearrangements 110
Figure 2.10: Origin of 2,6-*trans*-dihydropyran selectivity 111
Figure 2.11: 2,6-*cis*-substituted dihydropyrans with side chain exchange 111
Figure 2.12: Mechanism of 2,6-*cis*-disubstituted dihydropyran formation 113
Figure 2.13: Proposed mechanistic pathway for epimerization 114
Figure 2.14: Test of proposed oxonia-Cope boat transition state 114
Figure 2.15: Substrate design 116
Figure 2.16: Initially observed intramolecular Prins cyclization 117
Figure 2.17: Schematic of aqueous Prins reaction 122
Figure 2.18: Intramolecular Prins contained within a micelle 123
Figure 3.1: (+)-Dactylolide (**1**) and (-)-Zampanolide (**2**) 155
Figure 3.2: Sphinxolides and reidispongiolides 156
Figure 3.3: Smith's retrosynthetic analysis of (+)-dactylolide 158
Figure 3.4: Petasis-Ferrier rearrangement 159
Figure 3.5: Completion of advanced intermediate (-)-**B** 160
Figure 3.6: Completion of (+)-dactylolide 161
Figure 3.7: Strategic bond disconnections in the Hoye synthesis 162
Figure 3.8: Hoye's Prins cyclization to form the core of (-)-dactylolide 163
Figure 3.9: Completion of (-)-dactylolide 164
Figure 3.10: Retrosynthetic analysis 166
Figure 3.11: Vinylogous aldol transition state 167
Figure 3.12: Carreira vinylogous aldol catalytic cycle 170
Figure 3.13: One-pot transformation 175

LIST OF SCHEMES

Scheme 1.1: Synthesis of initial cyclization substrates 22
Scheme 1.2: Stereoselective synthesis of cyclization substrates 23
Scheme 1.3: Synthesis of a diastereomeric mixture of amides 26
Scheme 1.4: Stereoselective synthesis of methyl ether substrates 26
Scheme 1.5: Diastereoselective carbamate synthesis 30
Scheme 1.6: Synthesis of trifluoroacetamide **37** 36
Scheme 1.7: Oxazolidinone synthesis 37
Scheme 1.8: Oxazoline synthesis 37
Scheme 1.9: Substrates containing appended nitrogen nucleophiles 39
Scheme 1.10: Sulfonamide synthesis 41
Scheme 1.11: Synthesis of 3-(trifluoromethyl)phenylalanine 42
Scheme 1.12: Synthesis of trifluoromethyl-substituted arenes 43
Scheme 2.1: Synthesis of initial Prins substrate 118
Scheme 2.2: Intramolecular Prins cyclization with an allylsilane 118
Scheme 2.3: α,β-Unsaturated acetal synthesis 119
Scheme 2.4: Cyclization with specifically designed substrate 119
Scheme 2.5: Initial aqueous Prins reaction 121
Scheme 2.6: Synthesis of tetrahydropyran **46** 125
Scheme 2.7: Prins cyclization of secondary ether **54** 126
Scheme 2.8: Prins cyclization with an acid-sensitive functional group 127
Scheme 2.9: Prins cyclization of a 1,3-dioxolane **64** 128
Scheme 2.10: Synthesis of enantioenriched cyclic-unsaturated acetal (-)-**72** 129
Scheme 3.1: Synthesis of enal (+)-**38** 167
Scheme 3.2: Synthesis of aldehyde **35** 169
Scheme 3.3: Carreira vinylogous aldol 170
Scheme 3.4: Denmark vinylogous aldol 171
Scheme 3.5: Synthesis of diol (-)-**37** 172
Scheme 3.6: Formation of cyclic α,β-unsaturated acetal (+)-**39** 173
Scheme 3.7: Intramolecular Prins Cyclization 174
Scheme 3.8: Altered quenching method 176
Scheme 3.9: Wharton epoxy ketone fragmentation 179
Scheme 3.10: Hydrazone formation with BTBSH 180
Scheme 3.11: Selenoxide-selenate rearrangement 181
Scheme 3.12: Double allylic oxidation 181
Scheme 3.13: Selective oxidation 182

PREFACE

Mom, Dad, Michael and Ryan:

THANKS! Those six letters can never fully express my love and appreciation for you guys. Thankyou for standing by me, for laughing and crying with me, for sharing in the joy and the sweat, for picking me up in the toughest of times and riding high with me during the great times. Thankyou for every sacrifice you made for me, for your unconditional love and for every opportunity you have provided me. This is for you.

Paul:

Thank you for taking a chance on me. Thanks for your patience, for your tenacity, and for bringing out the best in me, for your genuine concern and drive to finish. It was a long, tough haul, but we made it. That's one molecule down and one thousand more to go. Your Noble Prize awaits !!!

Floreancig group members:

Jay, Butch, Lijun, and Chris…There is light at the end of the tunnel. Thanks for your support, for you helpful suggestions and for sharing in this experience with me. You are all unbelievably talented and will no doubt go extremely far. Keep up the good work.

1. Mechanistic and stereochemical studies of photoinduced electron transfer initiated cyclization reactions: the role of nitrogen

1.1. Introduction to electron transfer

I. General

Photochemistry has become a widely accepted, fundamental branch of organic chemistry, playing an integral role in many syntheses.[1] Photochemical transformations often provide routes to synthetic targets that cannot be attained by conventional transformations. Photoinduced electron transfer (PET) is the branch of photochemistry that exploits the ability of certain photoexcitied molecules to act as strong oxidizing or reducing species, and induce a permanent chemical change in a ground state molecule through an electron transfer mechanism. After being oxidized or reduced by a photosensitizer, an organic substrate is transformed into a reactive intermediate that is capable of undergoing a variety of reactions. PET reactions provide a novel route to approaching difficult synthetic targets that could not be realized by conventional means.[2]

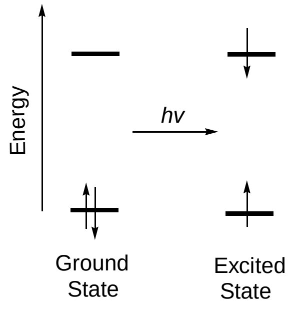
Photoinduced electron transfer processes have widespread application in semiconductor photocatalysis,[2] imaging systems, such as silver halide photography,[3] spectral sensitization[4] and xerography.[5] Nature frequently invokes electron transfer in a variety of enzymatic processes such as oxidative phosphorylation,[6] the DNA-photolyase reaction[7] and photosynthesis. Despite the numerous applications and biological examples, the use of electron transfer reactions in preparative organic synthesis is limited to include a few examples such as the Birch reduction,[8] acyloin condensation,[9] Ullmann coupling,[10] formation of Grignard reagents,[11] protecting group removal, and $S_{RN}1$ reactions.[12]

The perceived complexities of electron transfer processes are often responsible for their minimal utilization in reaction design. The reluctance to invoke these processes could be attributed to the lack of applicable data for predicting reaction outcomes as well as the inability to control various side reactions associated with the odd electron species generated. Over the past years an increased understanding of the kinetics, thermodynamics and primary reaction pathways of radical ions has renewed interest in their application toward reaction design. The ability to exploit the full potential of photoinduced electron transfer in reaction design requires an understanding of the principles of photochemistry and underlying theory of electron transfer.

II. Photochemical Principles

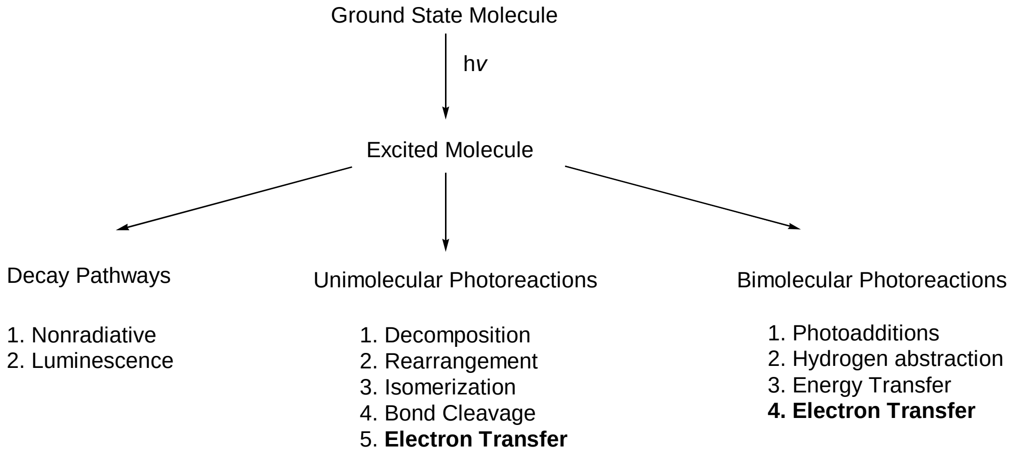
The absorption of light provides the impetus for all photochemical reactions. Core electrons and electrons in lower energy orbitals are normally not perturbed by the absorption of light. However, electrons in high lying molecular orbitals are susceptible to photoexcitation in the ultraviolet and visible regions of the electromagnetic spectrum (100-700 nm). The absorption of light generates an excited state species that is generally more reactive than its ground state analog. Most commonly one electron from the highest occupied orbital (HOMO) is promoted into the lowest unoccupied molecular orbital (LUMO) (Figure 1.1).[13]

Figure 1.1: Electronic transition resulting from photoexcitation


Energy
hv
Ground State
Excited State

Molecules cannot remain in the excited state for an extended length of time and therefore must lose their extra energy in some manner. Excited species can react in a variety of different ways, as shown in Figure 1.2.

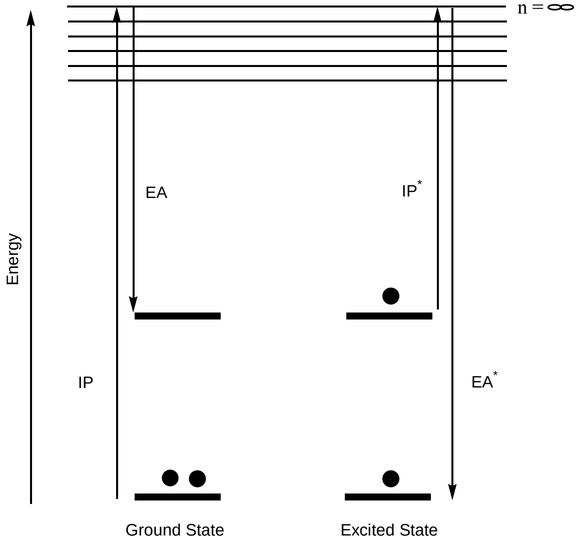
Figure 1.2: Photochemical pathways


Ground State Molecule
hv
Excited Molecule
Decay Pathways
1. Nonradiative
2. Luminescence
Unimolecular Photoreactions
1. Decomposition
2. Rearrangement
3. Isomerization
4. Bond Cleavage
5. Electron Transfer
Bimolecular Photoreactions
1. Photoadditions
2. Hydrogen abstraction
3. Energy Transfer
4. Electron Transfer

Photoexcited molecules are able to induce transitory or permanent changes in neighboring molecules through an electron transfer pathway. Electronic transitions create vacancies in low-lying bonding or non-bonding orbitals, called *holes*, which serve as much better electron acceptors than unoccupied orbitals of higher energy. Energy is released upon the transfer of one electron from an orbital of infinite separation from the nucleus of the donor into a low-lying, vacant orbital nearer to the nucleus of the acceptor. The absorbed light can be converted to chemical energy by the transfer of an electron either to or from the excited state species in an energetically favorable, exothermic process.

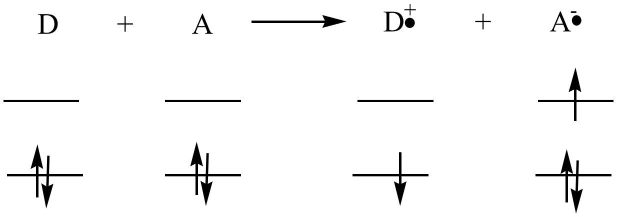
The energy change associated with the excitation of a bound electron from its orbital into an orbital at infinite distance, or the difference in orbital energies between the low-lying bonding and higher nonbonding orbitals, is referred to as ionization potential (IP) (Figure 1.3). The reverse process, the amount of energy required to bring an electron from an infinite distance into a low-lying vacant orbital, is referred to as electron affinity (EA). IP's and EA's are quantities used to describe gas phase molecules, which are not directly applicable in describing molecules in solution.

Figure 1.3: IP and EA of both the ground and excited state species



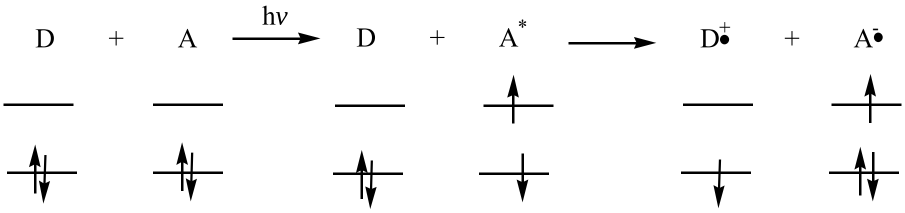
The solvation of ions is an important factor in solution phase chemistry, resulting in the need for the solution phase analogs of IP and EA, oxidation and reduction potentials.[14] Oxidation potential is the potential at which an electron is removed from a molecule, and reduction potential is the potential at which an electron is added to a molecule. Variations in oxidation and reduction potentials parallel those in ionization potentials and electron affinities. Plots of redox potentials versus ionization potentials and electron affinities for structurally related compounds often show linear correlations.[15] A ground state example of the redox process is shown in Figure 1.4, where electron transfer occurs between a donor and acceptor molecule. In the ground state the free energy change for the electron transfer process is the difference in redox potentials of the donor and acceptor. Because of the large HOMO-LUMO gap in the ground state of organic molecules, electron transfer would be a largely endothermic process.

Figure 1.4: Ground state redox reactions



In addition to a donor (D), and an acceptor (A), PET reactions require an electronic excitation source (light). In PET the electronically excited species serves as the oxidizing or reducing species, as shown in Figure 1.5. Here, the free energy change associated with electron transfer, which includes the redox potentials of the donor and acceptor, is made more negative by an additional term corresponding to the excitation energy. Electronic excitation exploits the large HOMO-LUMO gap, making electron transfer an energetically more favorable process.

Figure 1.5: Photoinitiated electron transfer



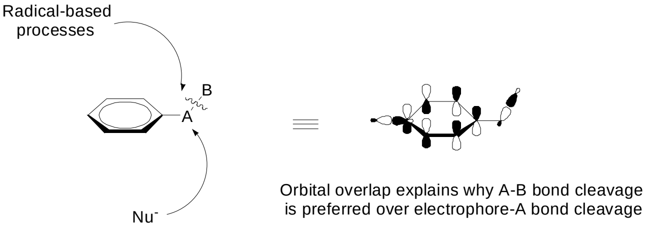
The Rehm-Weller equation[16] provides a useful expression for calculating the free energy change associated with PET reactions. For most PET reactions the number of electrons transferred, represented by n, is usually one and the charge associated with the transfer of one mole of electrons, the unit of Faraday, is represented by F. For most electron transfer processes this quantity, nF, is approximately equal to one and can be disregarded in the calculations. The oxidation potential of the donor (OP_D), the reduction potential of the acceptor (OP_R), and the equilibrium excitation energy (ΔG_{00}), based on the wavelength of excitation, factor into the thermodynamic condition for spontaneous electron transfer. The work term, w_p, describes the coulombic attraction between ions generated by electron transfer. This term is not applicable to cases where electron transfer occurs between a charged and neutral species, due to the lack of electrostatic attraction between the species, and can therefore be disregarded.

$$\Delta G_{ET} = nF[OP_D - OP_R - \Delta G_{00} - w_p] \qquad \text{Rehm-Weller Equation}$$

III. The Radical Cation

The most commonly observed primary reaction pathways for radical cations are: 1. A-B bond cleavage at the periphery of the electrophore (A-B = C-H, C-C, C-X, A-H, X-Y), 2. reactions initiated by attack of nucleophiles, and 3. radical based processes such as ET, dimerization, reactions with radicals, and hydrogen transfer (Figure 1.6).[17] Over the past decade a broad body of knowledge concerning the primary reactions of radical cations has accumulated. For radical cations generated in solution a highly selective, predictable mode of fragmentation usually operates to give a neutral radical and a cation.[18] This unimolecular bond dissociation is referred to as mesolytic cleavage.[19] Fragmentation in solution is quite efficient, but the synthetic utility has been limited mostly to C-H, O-M, S-R, Si-Si, C-Si, C-Ge, C-N and C-Sn bonds.[20]

Figure 1.6: Primary reaction pathways for radical cations


Radical-based processes
B
A
Nu⁻
Orbital overlap explains why A-B bond cleavage is preferred over electrophore-A bond cleavage

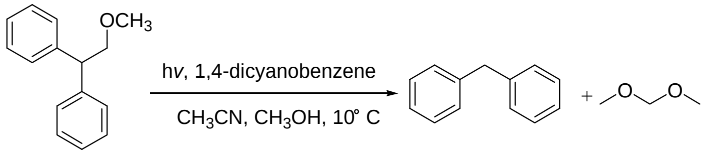
PET reactions exploit the ability of electronically excited molecules to function as strong oxidants and have proven to be an excellent method for generating radical cations in solution. In radical cations strong bonds, such as C-C, can be selectively cleaved to generate radicals and cations from unconventional precursors under mild reaction conditions. The majority of examples of C-C fragmentation stem from PET reactions of strained carbocyclic compounds,[21-22] where strain release provides the driving force for bond scission. Examples of unstrained mesolytic C-C bond cleavage occur mostly in aromatic substrates with aliphatic side chains. The addition of alkyl, aryl, hydroxyl, siloxy and alkoxy substituents was found to lower the barrier to mesolytic C-C bond cleavage of the radical cation due to increased stabilization of the resulting cationic fragment through electron donation.[20] However, deprotonation is a competing process that reduces synthetic utility.

IV. C-C Bond Fragmentation

During measurements of standard oxidation potentials of a series of alkylbenzenes, Kochi and coworker's[23] were able to demonstrate that the lifetimes of the radical cations in acetonitrile were less than 100 μs. One important trend noticed during this study was that cyclic voltamograms (CV) of *tert*-butyl substituted benzenes were found to be reversible. The reversibility of the CV's was associated with the absence of benzyl protons in the *tert*-butyl group, allowing for the extended lifetime of the radical cation. The shortened lifetime of alkylbenzenes having labile benzyl protons indicated that C-H bond activation was favored over C-C bond activation.

Arnold and coworker's[24] work with the irradiation of an acetonitrile-methanol (3:1) solution of 2,2-diphenylethyl methylether and 1,4-dicyanobenzene to yield exclusively diphenyl methane and the dimethyl acetal of formaldehyde provided the first example of a PET reaction involving a homobenzylic ether (Figure 1.7). This study revealed that with the appropriate substitution in the alkyl chain of alkylarenes, C-C bond activation effectively competed with C-H bond activation. It also provided a simple system for the study of the theory and application of C-C bond cleavages of radical cations in solution.

Figure 1.7: PET induced mesolytic cleavage of C-C bond



Arnold[25] proposed a stepwise mechanism for the radical cation cleavage reaction (Figure 1.8). The first step in the mechanism is excitation of the sensitizer, 1,4-dicyanobenzene. Substitution of the singlet excited state energy and reduction potential into the Rehm-Weller equation[16] showed that photoexcited 1,4-dicyanobenzene was capable of oxidizing any substituent with an oxidation potential of less than 2.4 V at the diffusion controlled rate of 1.8×10^{10} $M^{-1}s^{-1}$. Given that the oxidation potentials of the 2-phenylethyl ether systems chosen were below the limit (2.01-2.29 V) and the electron transfer process was energetically favorable by –3 kcal/mol it follows that formation of the radical cation would occur. The third step accounts for the competing process of return electron transfer from the sensitizer to the substrate. Return electron transfer is an exothermic process that usually occurs on the microsecond timescale. It is most often observed when the tight ion pair that results from the electrostatic attraction of the radical anion for the radical cation is unable to separate. Arnold found that this process was slowed in cases were the free energy change for return electron transfer was very exergonic. This large energy gap slowed the process of back electron transfer so that the rate fell into the Marcus[26] inverted region. Thus, the rate of return electron transfer became slower than the rate of solvent separation of the radical ion pairs.

Figure 1.8: Mechanism for mesolytic C-C bond cleavage

1. Sensitizer (A) $\xrightarrow{h\nu}$ A^*

2. $Ph_2CH\text{-}R + A^* \longrightarrow Ph_2CH\text{-}R^{+\bullet} + A^{-\bullet}$

3. $Ph_2CH\text{-}R^{+\bullet} + A^{-\bullet} \longrightarrow Ph_2CH\text{-}R + A$

4. $Ph_2CH\text{-}R^{+\bullet} \longrightarrow Ph_2CH^{\bullet} + R^+$

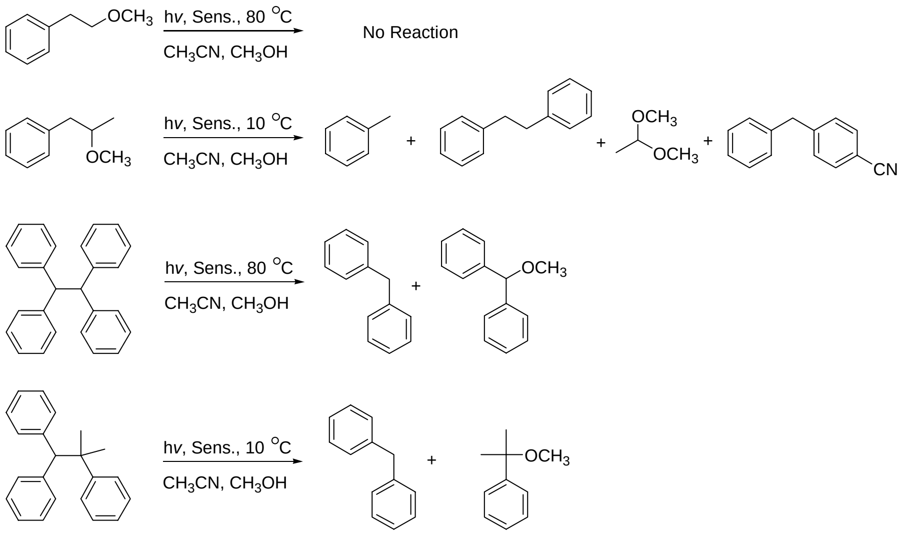
5. $R^+ + CH_3OH \longrightarrow R\text{-}OCH_3 + H^+$

6. $Ph_2CH^{\bullet} + A^{-\bullet} \longrightarrow Ph_2CH^- + A$

7. $Ph_2CH^- + CH_3OH \longrightarrow Ph_2CH_2 + CH_3O^-$

The fourth step in the mechanism represents C-C bond cleavage of the radical cation. Through subsequent work on a variety of aromatic substrates it was found that C-C bond cleavage depends upon the bond dissociation energy (BDE) of the C-C bond in the radical cation (Figure 1.9). An activation barrier of 10-15 kcal/mol was estimated for the C-C bond cleavage of the radical cation.[25]

Figure 1.9: PET reactions of 2-phenyl ether systems, Snes. = 1,4-dicyanobenzene


OCH3
hv, Sens., 80 °C
CH3CN, CH3OH
No Reaction
OCH3
hv, Sens., 10 °C
CH3CN, CH3OH
+
+
OCH3
OCH3
+
CN
hv, Sens., 80 °C
CH3CN, CH3OH
+
OCH3
hv, Sens., 10 °C
CH3CN, CH3OH
+
OCH3

In order to decrease the BDE of the radical cation enough to force C-C bond cleavage to be the major reaction pathway, either the BDE of the C-C bond must be decreased, or the oxidation potential of the fragment that becomes the cation must be decreased through appropriate substitution. Gas phase BDEs are most often derived from experimental data by the use of thermodynamic cycles as shown in Equations 1-4.[27]

$$\mathrm{BDE} = \Delta H_f°(R^+) + \Delta H_f°(R^\bullet) - \Delta H_f°(R - R^{\bullet+}) \qquad (1)$$

$$\mathrm{BDE} = (\Delta H_f°(R^\bullet) + \mathrm{IP}(R^\bullet)) - \Delta H_f°(R^\bullet) - (\Delta H_f°(R\text{-}R) + \mathrm{IP}(R\text{-}R)) \qquad (2)$$

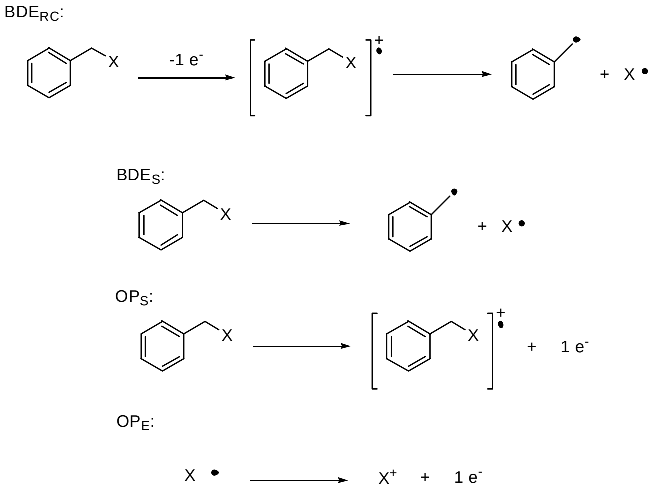
$$D° = 2\Delta H_f°(R^\bullet) - \Delta H_f°(R\text{-}R) \qquad (3)$$

$$\mathrm{BDE} = D° + \mathrm{IP}(R^\bullet) - \mathrm{IP}(R\text{-}R) \qquad (4)$$

Substituting oxidation potentials for ionization potentials allows for the determination of solution phase BDEs. Through modulated photolysis/phase sensitive voltametry[14] the oxidation and reduction potentials of transient free radicals can be determined, and applied to Equation 5 to provide a more accurate description of the behavior of free radicals in solution and BDE's of radical cations. In Equation 5, $\mathrm{BDE_S}$ represents the bond dissociation energy of the ground state molecule, $\mathrm{OP_S}$ represents the oxidation potential of the substrate, and $\mathrm{OP_E}$ represents the oxidation potential of the electrophilic fragment. Figure 1.10 uses a simple schematic, where a monoalkylarene serves as the substrate, to illustrate the BDE of the radical cation.

$$\mathrm{BDE_{RC}} = \mathrm{BDE_S} - \mathrm{OP_S} + \mathrm{OP_E} \qquad (5)$$

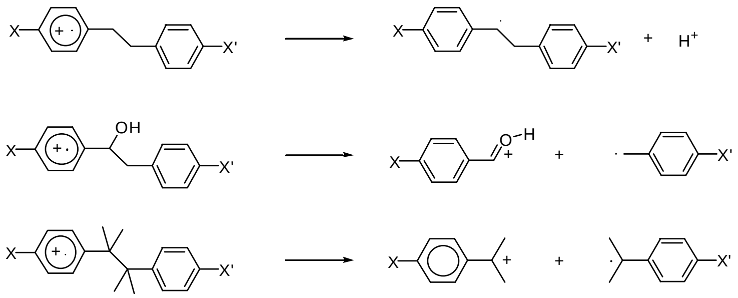
Figure 1.10: Schematic of the BDE of the radical cation



Arnold found that a significant decrease in the BDE of the radical cation could be achieved by substitution of an α-oxymethyl for one benzyl group. Upon bond dissociation of a homobenzylic ether, a π-stabilized radical and more stabilized α-oxycarbocation was formed. Arnold postulated that the regioselectivity of the reaction was dependent upon the redox properties of the two radicals formed upon homolytic bond cleavage. Bond cleavage occurred in such a way as to give the carbocation of the radical fragment that had the lower oxidation potential. In cases involving radical cations of ethers, the fragment containing the α-oxygen had a lower oxidation potential than the benzylic radical.[19] Thus, the ether serves to stabilize the formed carbocation as well as weaken the benzylic C-C bond.

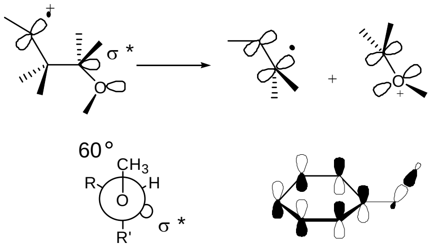
Arnold's findings were supported by the work of Camaioni[26] with α-Me and -OH substituted bibenzylic systems. Camaioni was able to show through the use of semiempirical calculations of bond dissociation energies (BDE) of bibenzyl radical cations with Me or OH substituents on the ethylene bridge, that mesolytic C-C bond cleavage was the primary reaction pathway. The substantially reduced C-C BDE in the substrates tested was attributed to the ability of the electron donating groups to stabilize the cleavage products. Kinetic studies of side chain fragmentation reactions of arylalkanol radical cations and the effects of α- and β-OR groups by Baciocchi[28] further supported Arnold's findings. Baciocchi showed that in homobenzylic ethers the dominant reactive pathway upon photoinitiated oxidation was mesolytic cleavage of the benzyl C-C bond, as shown in Figure 1.11.

Figure 1.11: Radical cation bond dissociations studied by Camaioni



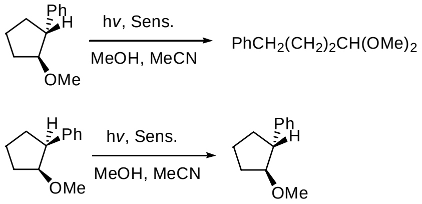
A kinetic preference for cleavage of the C-C bond parallel to the π system of the arene, allowing for orbital overlap and stabilization, was also demonstrated.[25] In order for the alkoxy group to provide maximum stabilization of the incipient carbocation, one of the lone pairs of electrons on the oxygen atom must overlap with the C-C anti-bonding (σ^*) orbital to stabilize the transition state for C-C bond cleavage, as shown in Figure 1.12.

Figure 1.12: Kinetically preferred conformation for C-C bond cleavage



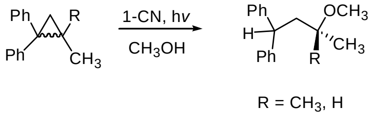
Maximum stabilization, calculated using semiempirical methods, was found to occur when the dihedral angle between the non-bonding pair of electrons of the oxygen and the adjacent C-C anti-bonding (σ^*) orbital was 0°. When the dihedral angle was 90°, stabilization was found to be at a minimum. This leads to the hypothesis that if a preferred conformation of the ether does not have the alkoxy group oriented in such a way that a lone pair of electrons on the oxygen can overlap with the adjacent C-C anti-bonding (σ^*) orbital, cleavage may be inhibited. Maximum overlap between the π system and the C-C bond being broken is also required. This was confirmed through Arnold's[28] study of methyl 2-phenylcyclopentyl ether radical cations (Figure 1.13). PET of *trans*-methyl 2-phenylcyclopentyl ether led to mesolytic cleavage of the benzyl, whereas the *cis* compound underwent isomerization under identical conditions.

Figure 1.13: Kinetic preference for C-C bond cleavage



The fifth step in Arnold's proposed mechanism for mesolytic C-C bond cleavage involves nucleophilic attack on the carbocation by methanol to form the methyl ether. An example of a stereospecific nucleophilic attack in a PET reaction comes from the work of Dinnocenzo.[21] PET reactions of 1,1-diphenyl-2-methylcyclopropane and 1,1-diphenyl-2,2-dimethylcyclopropane were shown to undergo ring opening by a three-electron S_N2 substitution at C-2 (Figure 1.14). The inversion of configuration was rationalized to be the result of backside nucleophilic attack onto the ring-closed radical cation. The bimolecular rate constants were measured and found to be between 10^6 and 10^8 $M^{-1}s^{-1}$, which point to rather rapid, nucleophile induced C-C bond cleavage.[29] These cyclizations are rare examples of highly selective tertiary and neopentyl nucleophilic substitutions that are controlled by electronic factors rather than steric factors.

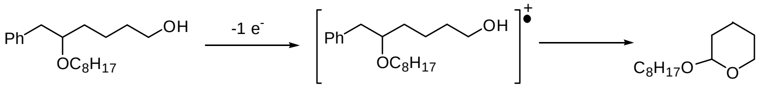
Figure 1.14: Stereospecific nucleophilic attack onto a radical cation



V. Electron Transfer Initiated Cyclizations (ETIC)

The extensive studies of PET reactions of alkyl arenes, C-C bond cleavage and mechanistic studies of radical cations, and more specifically homobenzylic ethers, have prompted the development of a new electron transfer initiated cyclization method[30] through carbon-carbon σ-bond activation of homobenzylic ethers (Figure 1.15).

Figure 1.15: Electron transfer initiated cyclization

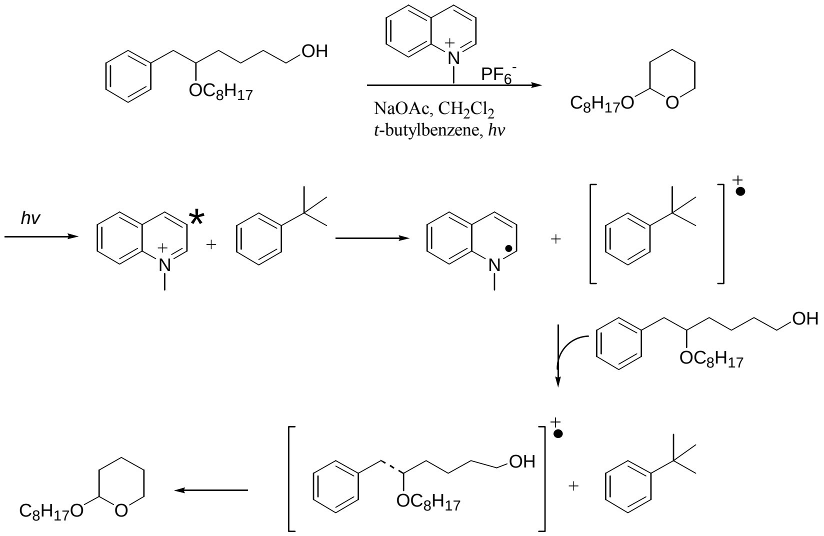


This new method utilizes attack of an appended nucleophile on a homobenzylic ether following single electron oxidation to generate cyclic acetals. As demonstrated by Arnold and Camaioni the benzylic bond of homobenzylic ethers is significantly weakened upon single electron oxidation and allows for nucleophilic displacement of a benzyl radical. This method of C-C σ-bond activation was chosen for five main reasons: (1) substrate synthesis is facilitated by the generally inert benzyl group, (2) the mild reaction conditions allow for the inclusion of acid and base sensitive functionalitity in the cyclization substrate, (3) the oxidation potential of the substrate, and chemoselectivity of the oxidation can be altered in a rational manner through the introduction of substituents on the arene, (4) the reactivity of the system can be tuned by the introduction of substituents at the benzylic position, and (5) the highly electrophilic nature of the radical cations should allow a wide variety of nucleophiles to be employed in the reaction.[30]

Initial attempts at cyclization of a homobenzylic ether using a variation of Arnold's conditions[28] resulted in little or no product formation. The inefficiency of cyclization was postulated to result from rapid regeneration of starting materials through return electron transfer in the tight ion pair formed by the radical anion of dicyanobenzene and the radical cation of the homobenzylic ether.

A study of nucleophile-assisted cleavage of benzyltrialkylsilane cation radicals by Dinnocenzo[31] showed that the rate of return electron transfer could be slowed through the use of a cationic sensitizer and a neutral cosensitizer. Employing *N*-methylquinolinium hexafluorophosphate (NMQPF$_6$) as the cationic sensitizer in a photoinitiatied electron transfer cyclization, coupled with the use of the aromatic cosolvent *tert*-butylbenzene, dramatically increases the efficiency of the electron transfer initiated cyclization reaction. In these cyclizations, the photoexcited sensitizer NMQPF$_6$ serves as a single electron oxidant that oxidizes the aromatic cosolvent *tert*-butylbenzene to its radical cation. Facile electron transfer between the radical cation of *tert*-butylbenzene and the homobenzylic ether ensues to form the radical cation of the homobenzylic ether. Upon radical cation formation of the homobenzylic ether, the benzylic bond is so significantly weakened that it allows for attack by the appended nucleophile and displacement of a benzyl radical to form the desired cyclic acetal (Figure 1.16).

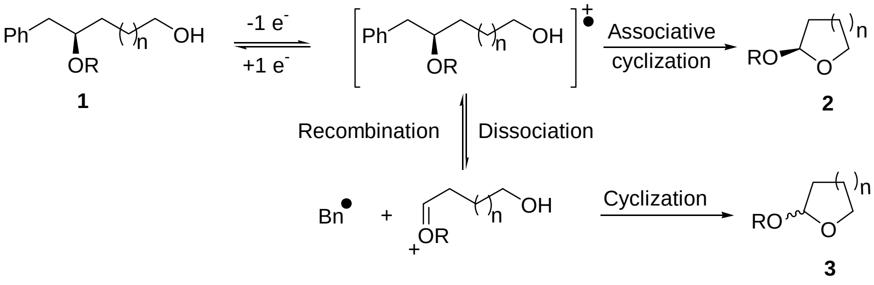
Figure 1.16: Cation sensitized photoinitiated single electron transfer



Because electron transfer depends on the proximity of the molecules involved, the aromatic cosolvent *tert*-butylbenzene is employed to facilitate the diffusion controlled electron transfer process. Electron transfer between a homobenzylic ether and the radical cation of *tert*-butylbenzene (generated by electron transfer to the photoexcited cationic sensitizer $NMQPF_6$) is postulated to be an isoenergetic process, because electron transfer is occurring between two monoalkylarenes having essentially the same oxidation potential. Therefore, the effective concentration of radical cations in solution was effectively increased through the use of the aromatic cosolvent.

Under these new cation sensitized electron transfer conditions cyclic acetals ranging in ring size from 5 to 8 carbons could be generated efficiently and in high yield.[30] The proposed mechanism inferred from the product distribution is shown in Figure 1.17. The two possible reactive pathways involve either an associative (S_N2) type pathway leading to stereochemical inversion at the electrophilic center yielding cyclic acetal **2**, or through a dissociative, stereorandom S_N1-type pathway, yielding cyclic acetal **3**. The majority of products isolated appear to have resulted from a dissociative pathway. However, partitioning between the two pathways could be controlled through substrate structure, thus leading to a unique strategy for controlling anomeric stereochemistry.[29]

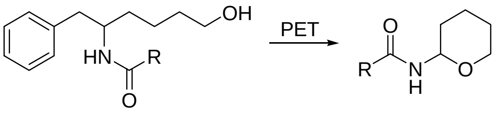
Figure 1.17: Proposed mechanistic pathways



VI. Project Goal

The new ETIC method developed in this group allows for the efficient generation of a variety of cyclic acetals that can be further manipulated and serve as advanced synthetic intermediates. It is known that alkyl, aryl, hydroxyl, siloxy and alkoxy substituents[20] serve as stabilizing groups and can facilitate C-C bond cleavage upon single electron oxidation of a monoalkylarene, but little is known about the incorporation of nitrogen as a stabilizing group in the homobenzylic position in reactions involving radical cations. The same highlighted reasons for the choice of homobenzylic ethers for cyclization substrates apply toward the use of homobenzylic amides and carbamates in ETIC reactions. Cyclizations involving these moieties could produce mixed acylaminals (Figure 1.18).

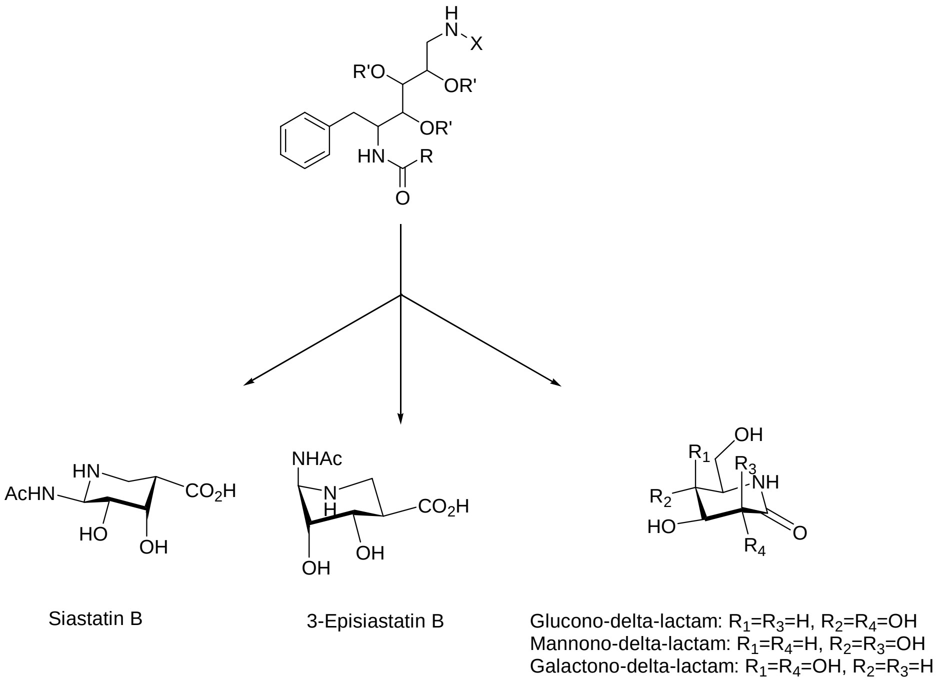
Figure 1.18: ETIC involving homobenzylic amides or carbamates


OH
PET
HN
R
O
O
R
N
H
O

R = C_5H_{11} or OC_4H_9

Developing a mild cyclization method is of interest because it would allow for the facile generation of iminosugars and glyconic-δ-lactams, both of which represent classes of compounds that have exhibited biological and enzyme inhibitory activity (Figure 1.19).[32-33] The mild ETIC reaction conditions would allow for the incorporation of acid sensitive functional groups in the substrate that would not be tolerated under conventional cyclization conditions. Therefore, studies into the synthetic and stereochemical aspects of photoinitiated single electron transfer initiated cyclization reactions of homobenzylic amides and carbamates, as well as homobenzylic ethers containing nitrogen nucleophiles, have been undertaken and are detailed herein.

Figure 1.19: Synthetic targets


H
N
X
R'O
OR'
OR'
HN
R
O
HN
AcHN
CO2H
HO
OH
NHAc
N
H
CO2H
OH
OH
OH
R1
R3
NH
R2
HO
O
R4
Siastatin B
3-Episiastatin B
Glucono-delta-lactam: R1=R3=H, R2=R4=OH
Mannono-delta-lactam: R1=R4=H, R2=R3=OH
Galactono-delta-lactam: R1=R4=OH, R2=R3=H

1.2. Results

The pioneering work[30] on homobenzylic ethers following single electron oxidation showed that ETIC reactions were a viable synthetic method for carbon-carbon bond activation. The goal of the present work was to extend this method and to test the applicability of nitrogen in ETIC substrates. Incorporation of nitrogen in an ETIC reaction requires that it be protected as an amide, carbamate, or sulfonamide, rather than a free amine, which could be easily oxidized under the reaction conditions. If incorporated into an ETIC substrate as an amide or carbamate, nitrogen could function as a stabilizing group in the homobenzylic position. Also, the role of nitrogen containing groups as nucleophiles could be examined. We therefore set out synthesize and test nitrogen containing substrates for ETIC reactions, while simultaneously optimizing cyclization conditions and examining the stereochemical aspects of the reaction.

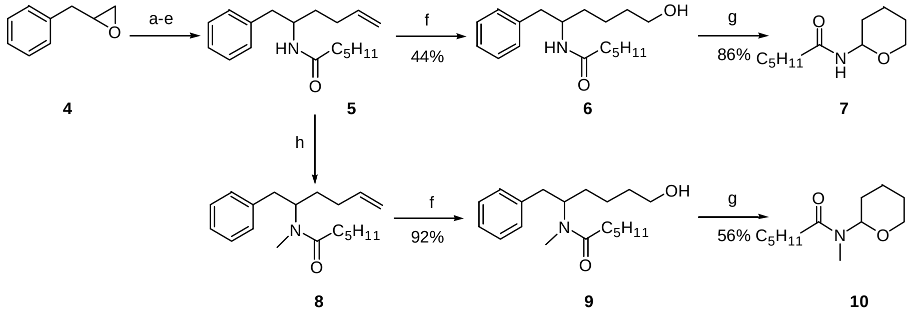
The first two substrates synthesized and tested under ETIC conditions are shown in Scheme 1.1. Starting from epoxypropylbenzene (**4**), amide **5** was obtained in 5 steps. Opening of the epoxide with allylmagnesium bromide at 0 ºC led to the corresponding alcohol in 95% yield. The alcohol was converted to the mesylate and then displaced with sodium azide in DMF at room temperature using tetrabutylammonium iodide as a phase transfer agent. The azide was reduced to the amine via the Staudinger[34] reaction. The amine was then acylated with hexanoyl chloride in the presence of triethylamine to give a 41% yield of amide **5**. Subsequent hydroboration of amide **5** with 9-BBN and quenching with basic hydrogen peroxide yielded the cyclization substrate, amide **6**, in 44% yield.

Amide **6** was subjected to ETIC cyclization conditions using a slight excess (1.2 equivalents) of the sensitizer $NMQPF_6$, the aromatic cosolvent *tert*-butylbenzene, the insoluble base NaOAc, dichloroethane as the solvent, and Pyrex-filtered irradiation from a medium pressure mercury lamp. The desired cyclic acylaminal (**7**) was obtained in 86% isolated yield after five hours of irradiation. This result indicated that amides, which could be easily synthesized from the corresponding alcohol, served as excellent stabilizing groups in the homobenzylic position.

Tertiary amide **8** was formed in 82% by reaction of amide **5** with methyl iodide and sodium hydride at 0 ºC in DMF. Hydroboration with 9-BBN followed by quenching with basic hydrogen peroxide provided the desired cyclization substrate, tertiary amide **9**, in 92% yield. Amide **9** was subjected to the standard ETIC reaction conditions, 1.2 equivalents of $NMQPF_6$, *tert*-butylbenzene, NaOAc, and dichloroethane and the desired cyclic acylaminal **10** was obtained in an isolated yield of 56%.

Reaction times of four and six hours were required for ETIC reactions of both amide **6** and amide **9**. Purification of cyclic acylaminals **7** and **10** was difficult and required flash chromatography on SiO_2 followed by preparatory thin layer chromatography. A change in color of the reaction mixture from colorless to dark red was observed for both cyclization reactions. Nonetheless, the cyclized products of both the secondary and tertiary amide were obtained and provided evidence that ETIC reactions involving homobenzylic amides are indeed a synthetically viable method for the generation of cyclic acyl aminals through nucleophilic attack on acyl imminium ions generated under mild reaction conditions.

Scheme 1.1: Synthesis of initial cyclization substrates



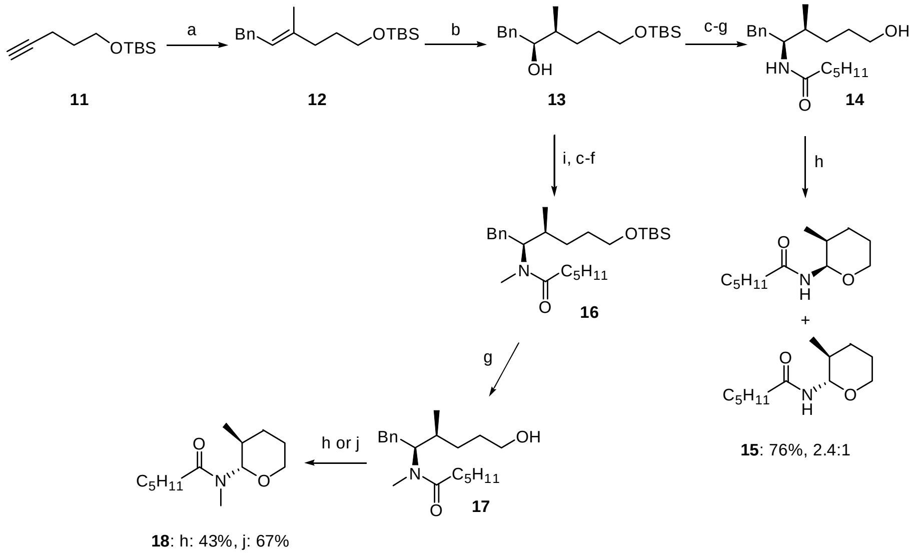
Reagents: a) allyl-MgBr, THF, 95% b) Ms-Cl, Et_3N, CH_2Cl_2, c) NaN_3, DMF, d) Ph_3P, H_2O, e) $C_5H_{11}COCl$, Et_3N, THF, 41% f) 0.5 M 9-BBN-THF, H_2O_2, NaOH, THF, g) NMQ, *t*BB, NaOAC, DCE, h) MeI, NaH, DMF, 82%

With two examples of successful ETIC reactions, the next step was to use stereochemistry as a mechanistic probe. This was done through the incorporation of a methyl group in the bishomobenzylic position as shown in Scheme 1.2. The hydroxyl group of 4-pentyn-1-ol was protected with *tert*-butyldimethylsilyl chloride and imidazole in DMF to provide **11** as the starting material for the synthesis of cyclization substrates **14** and **17**. Olefin **12** was formed by carboalumuniation with trimethylaluminum and Cp_2ZrCl_2 followed by palladium catalyzed coupling with benzyl chloride.[35] This reaction proved problematic in that initial attempts were low yielding and long reactions times were required. As much as a four-fold excess of trimethylaluminum was required, and made purification laborious. The moderate 76% yield was partially attributed to the inability to separate the desired olefin from the aluminum salts generated upon quenching. Performing the carboalumination reaction at -23 °C with one equivalent of water and one equivalent of trimethyl aluminum, based on Wipf's procedure,[36] successfully decreased reaction time from two days to two hours, and facilitated product purification.

Olefin **12** was hydroborated with $BH_3 \cdot THF$ and quenched with basic hydrogen peroxide to provide an 81% yield of alcohol **13**. The alcohol was converted to the mesylate with mesyl chloride and triethylamine in CH_2Cl_2, and then displaced with sodium azide at 55 °C in DMF.

The azide was reduced to the amine via the Staudinger[34] reaction and then acylated with hexanoyl chloride in the presence of triethylamine to give the desired amide in 61% yield. The TBS ether was deprotected with TBAF to provide amide **14** in 96% yield. Amide **14** was subjected to standard ETIC reaction conditions to form a 2.4:1 mixture of diastereomers of cyclic acylaminal **15** in 76% yield. The mixture of diastereomers was purified by flash chromatography and the diastereomers were ultimately separated by preparative thin layer chromatography.

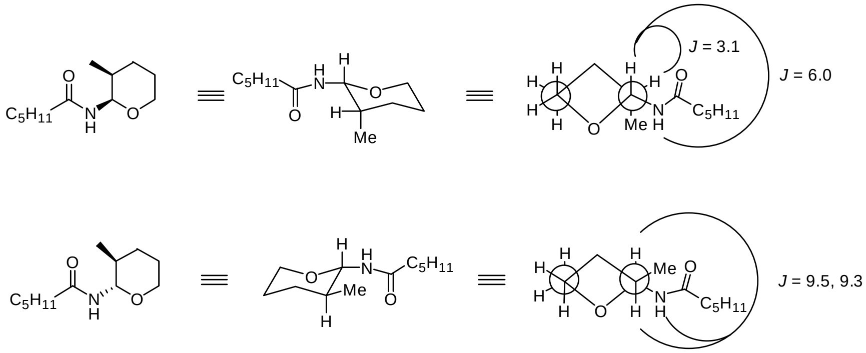
Scheme 1.2: Stereoselective synthesis of cyclization substrates



Reagents: a) (1) 2.0M Me_3Al-hexanes, Cp_2ZrCl_2, H_2O,CH_2Cl_2, (2) $Pd(PPh_3)_4$, BnCl, THF, 76% b) 1.0 M BH_3-THF, NaOH, H_2O_2, 81% c) Ms-Cl, Et_3N, CH_2Cl_2, d) NaN_3, DMF, e) $(Ph)_3P$, H_2O, THF, f) $C_5H_{11}COCl$, Et_3N, THF, 61% g) TBAF, THF, 96% h) h*v* NMQ, *t*BB, NaOAC, DCE, i) MeI, NaH, DMF, 36% j) hv, NMQ, $NaHCO_3$, CH_3CN, *t*BB

The stereochemical relationships between the amide and methyl ring substituent for acylaminal **15** were determined by comparison of coupling constants of the anomeric hydrogens (Figure 1.20). With a *syn* relationship between the amide and methyl substituent, the anomeric hydrogen appeared in the ^1H NMR spectrum as a doublets of doublets, showing a small coupling to the methyne hydrogen (3.1 Hz) and a large coupling to the amide hydrogen ($J = 6.0$ Hz). Upon addition of D_2O to the ^1H NMR sample and exchange of the amide proton for a deuterium the signal corresponding to the anomeric hydrogen changed to a doublet with a small coupling to the methine hydrogen (J = 2.4 Hz) and the signal corresponding to the amide hydrogen was no longer apparent. In **15b** the *anti* relationship between the amide and methyl substituent resulted in the appearance of the anomeric hydrogen as a doublet of doublets, showing a large coupling to both the methine hydrogen and the amide hydrogen (J = 9.5 Hz). Upon deuterium exchange the signal corresponding to the anomeric hydrogen changed to a doublet with a large coupling to the methine hydrogen (9.3 Hz) and the signal corresponding to the amide hydrogen was no longer apparent.

Figure 1.20: Relative stereochemical relationship of amide **15**



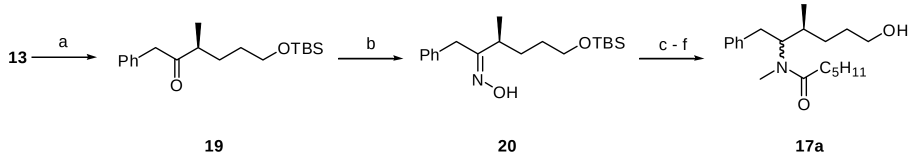
Amide **17** was synthesized to test the ability of teriary amides to control the diastereoselectivity of ETIC reactions. Amide **16** was obtained in 36% yield by reaction of the TBS protected form of amide **14** with sodium hydride and methyl iodide in DMF as shown in Scheme 2. Deprotection of the TBS ether with TBAF provided amide **17** in 78% yield. When tertiary amide **17** was subjected to standard ETIC reaction conditions a single diastereomer of cyclic acylaminal **18** was isolated in 43% yield. A 67% yield was obtained when the cyclization was performed using the more polar solvent, acetonitrile, and $NaHCO_3$ as the base.

^{1}H NMR analysis of acylaminal **18** showed two doublets at 5.36 ppm (J = 9.8 Hz) and 4.45 ppm (J = 9.4 Hz), each corresponding to the anomeric hydrogen. The anomeric hydrogen exhibited a large coupling to the methyne hydrogen, indicating that the relative stereochemistry was that of an *anti* relationship between the amide and methyl substituent of the ring. The existence of two separate signals corresponding to the same anomeric hydrogen was caused by restricted rotation around the amide bond. A variable temperature ^{1}H NMR study done in DMSO at 10 degree intervals from 298K to 378K showed the collapse of these two signals into a single signal above 358K.

Several attempts to synthesize the *anti* diastereomer of amide **17** to test the stereoselectivity of the cyclization reaction were unsuccessful. Mitsonobu reactions on alcohol **13** led only to elimination back to an inseparable mixture of alkene **12** and the conjugated styrene adduct. Attempted hydroboration-amination[37] of alkene **12** was also unsuccessful. Because of the hindered nature of the tri-substituted olefin, only the alkyl borane was isolated out of the reaction mixture.

The mixture of diastereomers of amide **17a**, shown also in Table 3, was synthesized in six steps starting from alcohol **13** (Scheme 1.3). Alcohol **13** was oxidized to ketone **19** in 74% yield via the Swern[38] oxidation. Reaction of the ketone with hydroxylamine hydrochloride in ethanol buffered with NaOAc provided oxime **20** in 88% yield. The oxime was reduced to the amine in the presence of nickel chloride and lithium aluminum hydride[39] at room temperature in ether. The resulting amine was acylated with hexanoyl chloride in the presence of triethylamine to yield 63% of the corresponding amide. The amide was alkylated with methyl iodide and sodium hydride in DMF. The TBS protecting group was removed with TBAF to give amide **17a** in 91% yield. Subjecting amide **17a** to catalytic aerobic ETIC reaction conditions provided the desired product in 56% yield, having an *anti* relationship between the amide and the methyl group. Catalytic aerobic ETIC reaction conditions will be discussed in detail later in the manuscript (Figure 1.24).

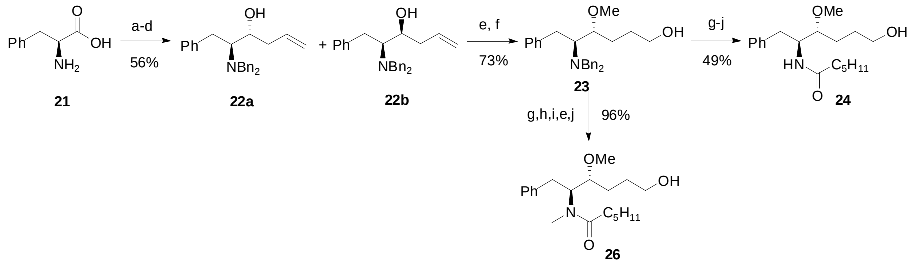
Scheme 1.3: Synthesis of a diastereomeric mixture of amides



Reagents: a) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, 74% b) NH_2OH-HCl, NaOAc, CH_3CH_2OH, c) LAH, $NiCl_2$, Et_2O, 88% d) $C_5H_{11}COCl$, Et_3N, THF, 63% e) CH_3I, NaH, DMF, f) TBAF, THF, 91%

Having gleaned the desired stereochemical information from the cyclization reactions of **14** and **17** and **17a**, the next logical step was to increase the level of complexity of the functional groups on the tether of the substrate. The lack of information pertaining to the effects of placing electron withdrawing groups adjacent to the reactive center, coupled with the end goals in the development of this cyclization method for application in the total synthesis of glycosidase inhibitors and aminosugars, which are poly-oxygenated species, led to the synthesis of substrates with an oxygen containing functional group adjacent to the reactive center. Having a methoxy group in the bishomobenzylic position provides a handle for the examination of the stereochemical outcome of cyclization as well the desired increased functionality in the form of an easily synthetically installed, relatively non-reactive functional group (Scheme 1.4).

Scheme 1.4: Stereoselective synthesis of methyl ether sunbstrates

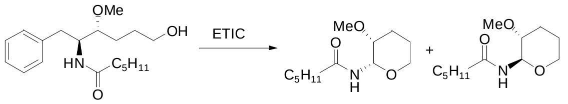


Reagents: a) BnBr, NaOH, K_2CO_3, H_2O, b) LAH, Et_2O, c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, d) allylMgBr, THF, e) MeI, NaH, DMF, f) 1.0M BH_3^-THF, NaOH, THF, g) Piv$^-$Cl, Et_3N, CH_2Cl_2, h) Pd/C, $CHO_2^-NH_4^+$, CH_3OH, i) $C_5H_{11}COCl$, Et_3N, THF, j) Na, CH_3OH

Amide **24** was obtained in eight steps starting from L-phenylalanine. The 3:1 mixture of the diastereomeric β-amino alcohols **22a** and **22b** was prepared according to the Reetz[39] procedure. This involved benzylation of phenylalanine by refluxing with benzyl bromide, potassium carbonate and sodium hydroxide. The benzyl ester was reduced to the alcohol with lithium aluminum hydride. Swern oxidation led to the aldehyde, and addition to the carbonyl with allyl magnesium bromide provided **22a** and **22b**. The alcohols were separated by flash chromatography, but could never be completely purified. Overall yield for the four steps was 56%.

Each of the diastereomers was carried separately through the synthetic sequence shown in Scheme 4. Formation of the methyl ether with sodium hydride and methyl iodide in DMF followed by hydroboration with BH_3·THF and quenching with basic hydrogen peroxide afforded a 73% yield of alcohol **23**. Debenzylation proved to be the most problematic step in the sequence, never yielding more than 50%. Initial attempts using ammonium formate and Pd/C in refluxing methanol followed by acylation with hexanoyl chloride were very low yielding and resulted in a mixture of products including the monobenzylamine, the formamide, and the *O*-acylated amide. Debenzylation using 1,4-cyclohexadiene and Pd/C was also low yielding and required lengthy reaction times. Protection of the alcohol with pivaloyl chloride prior to debenzylation with ammonium formate and Pd/C in refluxing methanol proved to be the optimum conditions for debenzylation. The pivalate was easily removed with sodium methoxide in methanol to yield the desired cyclization substrate **24** in 49% yield.

Figure 1.21: ETIC reaction of amide 24



24 **25a** **25b**

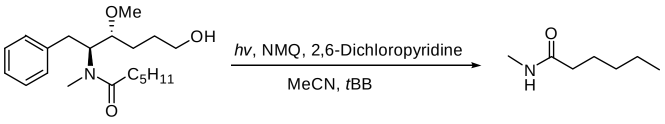
Amide **24** was subjected to a variety of ETIC reaction conditions as shown in Table 1.1. Solvent and base were varied, while the use of *tert*-butylbenzene as the aromatic cosolvent and an excess of the sensitizer $NMQPF_6$ remained constant. The mixture of cyclic acylaminals **25a** and **25b**, shown in Figure 1.21, was purified by flash chromatography and then the diastereomers were separated by thin layer preparative chromatography. Using insoluble bases such as NaOAc and $NaHCO_3$ in the reaction mixture resulted in a lower than expected yield and isolation of a mixture of diastereomers **25a** and **25b**. Switching to the soluble base 2,6-dichloropyridine in DCE resulted in a four-fold increase in yield, and the isolation of a single diastereomer. Purification of both the starting material and the cyclization product were difficult, as was visualization of the reaction by TLC. Therefore, the discrepancy in diastereomeric ratios isolated from the reactions could again be attributed to these difficulties rather than any stereoelectronic factors.

Table 1.1: Variations of ETIC reaction conditions

Solvent	**Base**	**Percent Yield**
$C_2H_4Cl_2$	NaOAc	6
$C_2H_4Cl_2$	2,6-dichloropyridine	21
CH_3CN	2,6-dichloropyridine	38
CH_3CN	$NaHCO_3$	5

As was seen with the ETIC reactions of amide **17**, alkylation to form the tertiary amide results in isolation of a single diastereomer. Tertiary amide **26** was synthesized to demonstrate both stereoselectivity and tolerance of increased functionality in ETIC reactions. Methylating the amide of the pivalate ester with sodium hydride and methyl iodide prior to pivalate deprotection with sodium in methanol gave the desired starting material for cyclization, amide **26,** in 96% yield. Subjecting amide **26** to the conditions shown to give the highest cyclization yields for amide **24** (excess $NMQPF_6$, 2,6-dichloropyridine and acetonitrile) failed to yield the desired cyclized product (Figure 1.22). Rather, amide **27** proved to be the only isolable product in 10% yield, resulting from nucleophilic attack of water on the acylimminium ion.

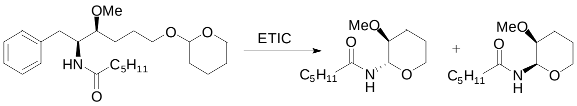
Figure 1.22: ETIC reaction of amide **26**



26 **27**

Because the reaction substrates were difficult to purify and visualize, having the alcohol protected during the debenzylation process facilitated substrate synthesis, and early work done in the Floreancig group with homobenzylic ethers showed that THP ethers could serve as nucleophiles in ETIC reactions, amide **28** (Figure 1.23) was synthesized and subjected to ETIC reaction conditions. The synthesis entailed protection of the diastereomer of alcohol **18** as the THP ether rather than the pivalate prior to debenzylation. This facilitated not only substrate purification, but also allowed for cleaner ETIC reactions and ease of reaction monitoring by TLC. An 18% isolated yield, as a 1:1 mixture of diastereomers was obtained when the reaction was only taken to 70% conversion.

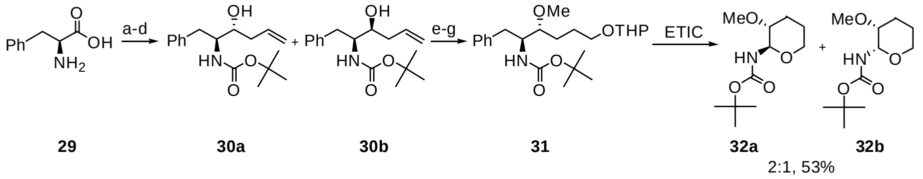
Figure 1.23: ETIC reaction of amide **28**



28 **25a** **25b**

From the results of the ETIC reactions with α-amido ethers **24, 26**, and **28,** the need for a change in the form of the homobenzylic nitrogen stabilizing group was apparent. One slight modification to the system that also alleviated the problematic debenzylation step in the synthesis of the substrates, was switching from the homobenzylic amide to the *t*-butyl carbamate.

Scheme 1.5: Diastereoselective carbamate synthesis



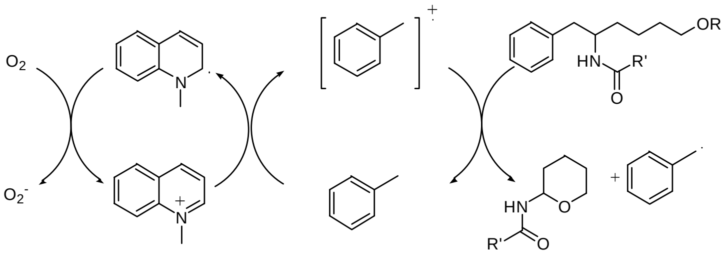
Reagents: a) LAH, THF, b) $(Boc)_2O$, CH_2Cl_2, c) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, d) allylMgBr, THF, 54% e) CH_3I, NaH, DMF, f) 1.0M BH_3-THF, NaOH, H_2O_2, 65% g) DHP, PTSOH, CH_2Cl_2**, 91%**

Starting from L-phenylalanine, a 6:1 diastereomeric mixture of alcohols **30a** and **30b** was prepared in 54% yield by reduction with lithium aluminum hydride, protection with "Boc" anhydride, Swern oxidation and addition of allyl magnesium bromide into the aldehyde (Scheme 1.5). Diastereomers **30a** and **30b** could be separated by flash chromatography, and **30a** was carried through the synthesis. The hydroxyl of **30a** was protected as the methyl ether with sodium hydride and methyl iodide in DMF. Subsequent hydroboration with BH_3·THF and quenching with basic hydrogen peroxide provided the desired alcohol in 65% yield. The alcohol was protected as THP ether with dihydropyran and *p*-toluenesulfonic acid to give carbamate **31** in 91% yield. Under ETIC reaction conditions (1.2 equivalents of $NMQPF_6$, NaOAc, toluene, and dicholorethane) a 2:1 ratio of the desired cyclized products **32a** and **32b** was obtained in 35% isolated yield (53% at 70% conversion). The aromatic cosolvent toluene was conveiniently substituted for *tert*-butylbenzene due to similar oxidation potentail, increased volatility and increased cost effectiveness. This reaction was a vast improvement from the ETIC reaction with the homobenzylic amides in terms of increased yields, and facile visualization and purification of products.

An admirable improvement in yield was also observed upon switching from an amide to a carbamate stabilizing group in the homobenzylic position. However, the reaction still could not be performed at the desired efficiency. Difficult purification, due to the number of the aromatic side products formed from the excess $NMQPF_6$, which co-eluted with the desired products, and long reaction times played a significant role in decreasing both reaction efficiency and yield. Throughout the course of the reactions a color change from colorless to deep, dark red was observed, presumably resulting from the oxidative decomposition of quinoline derived products. Reactions often did not proceed to complete conversion due to the formation of covalent adducts between the *N*-methylquinolyl radical (NMQ*) produced from the initial electron transfer and the benzyl radical produced in the displacement reaction. Once formed, these adducts can be oxidized in preference to the cyclization substrate, feed into the electron transfer cascade and produce a variety of aromatic waste products while consuming the photosensitizer. Deposition of the solid base onto the walls of the reaction flask was also observed, requiring the flask to be rotated periodically throughout the course of the reaction so as not to allow the deposition to impede the amount of light entering into the reaction. Nevertheless, the majority of problems with the reaction associated with the use of excess amounts of NMQPF$_6$ and the production of large quantities of aromatic waste products could presumably be eliminated through the use of a catalytic amount NMQPF$_6$.

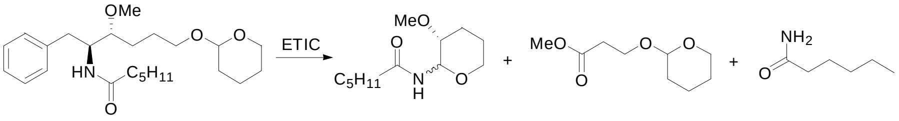
Dinnocenzo[31] reported that in transient absorption spectroscopic studies of NMQ-sensitized arene oxidations reactions the reduced form of NMQ reacts with dissolved oxygen at or close to the diffusion-controlled limit, whereas radical cations did not. Thus, NMQ$^\bullet$ could be oxidized to NMQ$^+$ through a single electron transfer reaction involving O_2 as the terminal oxidant, regenerating the photosensitizer without affecting the electron transfer cascade or impeding the desired cyclization reaction. This information was used to develop a catalytic photosensitized electron transfer cyclization reaction under aerobic conditions (Figure 1.24).

Figure 1.24: A catalytic aerobic ETIC reaction



This new strategy was tested by subjecting amide **28a** to the ETIC reaction conditions while simultaneously bubbling air through the reaction mixture and using only 0.5 equivalents of $NMQPF_6$ (Figure 1.25).

Figure 1.25: ETIC reaction under new aerobic conditions



28a **32c, d** **33** **34**

The first aerobic cyclization was done using benzene as the aromatic cosolvent (Table 1.2). The additional products isolated from the reaction mixture resulted from decomposition of the starting material. Changing the aromatic cosolvent to toluene, as well as switching to the soluble base 2,6-dichloropyridine, failed to increase reaction yield.

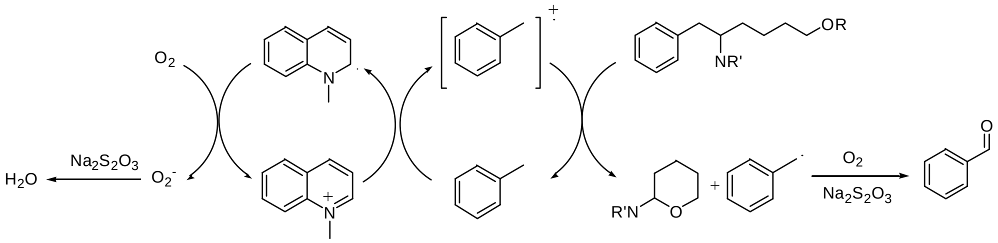
Table 1.2: Altering aromatic cosolvents

Solvent	Base	Cosensitizer	Percent Yield (Stoichiometric NMQ)	Percent Yield (Catalytic NMQ)
$C_2H_4Cl_2$	NaOAc	Benzene	25	30
$C_2H_4Cl_2$	2,6-Dichloropyridine	Toluene	33	33

Even though the yield of the reaction was not dramatically increased, the catalytic aerobic conditions alleviated the majority of the difficulties previously associated with the cyclization reaction. Reaction times were decreased from 5 hours to 2 hours, and purification was facilitated due to the lack of aromatic side products. Deposition on the walls of the reaction flask and the characteristic deep red color were no longer observed. More importantly, decomposition products **33** and **34** could be isolated, providing an explanation for the low yields and lack of mass balance observed in previous cyclization attempts.

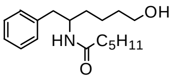
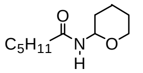
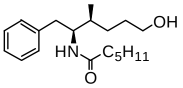
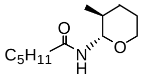
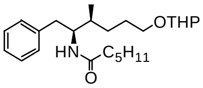
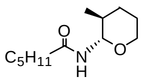
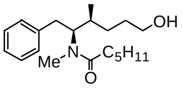
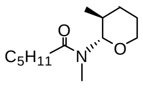
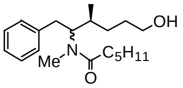
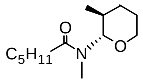
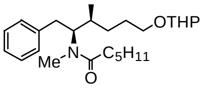
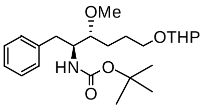
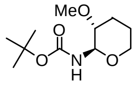
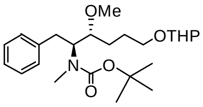
Under the aerobic cyclization reaction conditions undesired reactive oxygen species are generated from molecular oxygen and benzyl peroxy radical. These unwanted reactive oxygen species decrease reaction yields, despite complete consumption of starting materials, especially on large scale. This was observed in reactions of homobenzylic ethers, where oxidative decomposition reactions resulting from the accumulation of reactive oxygen species was believed to be the cause of the drastic reduction in yield from 86% to 15%, when reactions were performed on a larger than a 1.0 g scale.[40] One way of suppressing unwanted oxidative decomposition reactions associated with the accumulation of superoxide and benzyl peroxy radicals without inhibiting the cyclization was through the use of the mild reducing agent $Na_2S_2O_3$. Soluble reducing agents such as DMSO were found to completely inhibit the cyclization reaction, whereas solid $Na_2S_2O_3$ did not impede the electron transfer process, but rather reduced the superoxide and any unwanted reactive oxygen species. Having a reducing agent with low solubility in organic solvents was advantageous, in that electron transfer was not quenched, but rather the limited solubility allowed for enhanced reaction efficiency through the reduction of the unwanted reactive oxygen species. As shown in Figure 1.26, the products of the peroxide and superoxide reductions by $Na_2S_2O_3$ are water and benzaldehyde, neither of which was found to impede the cyclization reaction.

Figure 1.26: Catalytic aerobic ETIC reaction with $Na_2S_2O_3$



Under catalytic aerobic cyclization conditions (0.025 equivalents of $NMQPF_6$, toluene, NaOAc, dichloroethane and the gentle bubbling of air through the reaction mixture) both the reaction efficiency and ease of product isolation of amide **28a** increased. Therefore, it was desirable to test the scope and generality of these conditions. The substrates tested under these new conditions are shown in Tables 1.3 and 1.4. All of the substrates previously cyclized under standard stoichiometric ETIC reaction conditions were subjected to the new catalytic conditions.

Table 1.3: Substrates tested under catalytic aerobic ETIC conditions

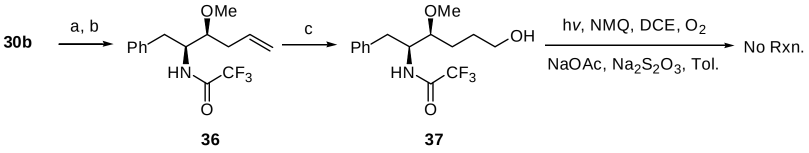
	Substrate	Product	Yield (%)		D.R
			Stoich.	Cat.	
7			86	75	
14			75	72	2:1
14a				70	2.3:1
17			67	58	
17a				56	
17b		Decomposition			
31			53	63	2:1
35		Decomposition			

For amides **7, 14** and **17**, the yield under catalytic conditions was within the same range as those observed under stoichiometric conditions. The difference, though, was in the ease of purification of the catalytic cyclization, and the 50 percent decrease in reaction time under catalytic conditions. Switching from the hydroxyl to the THP ether in **14a** facilitated purification of the starting material, but resulted in a slight decrease in yield of the cyclized product. Cyclization with the THP ether of a tertiary amide, **17b**, was unsuccessful. This was attributed to the combination of the decrease in nucleophilicity of the THP ether relative to the hydroxyl, and the decreased oxidation potential of the tertiary amide. Subjecting carbamate **31** to the catalytic cyclization conditions resulted in a 10% increase in yield and decreased the reaction time from 4 to 2 hours. Cyclization with the tertiary carbamate, **35**, resulted in complete decomposition.

A variety of substrates were synthesized to test what other nitrogen containing functional groups could be used as stabilizing groups in the homobenzylic position. The use of trifluoracetamides and oxazolidinones was thought to be a way of increasing the oxidation potential at the homobenzylic position without drastically altering the cyclization substrates.

Trifluoroacetamide **37** was synthesized as shown in Scheme 1.6. The Boc group of carbamate **30b** was removed in trifluoroacetic acid. The free amine was protected as the trifluoroacetamide by reaction with trifluoroacetic anhydride in the presence of pyridine to give **36** in 45% yield. Subsequent hydroboration with BH_3·THF and quenching with basic hydrogen peroxide provided trifluoroacetamide **37** in 65% yield. No desired cyclized product was obtained when trifluoroacetamide **37** was subjected to catalytic aerobic ETIC reaction conditions for 3.5 h, and 80% of the starting material was recovered.

Scheme 1.6: Synthesis of trifluoroacetamide **37**

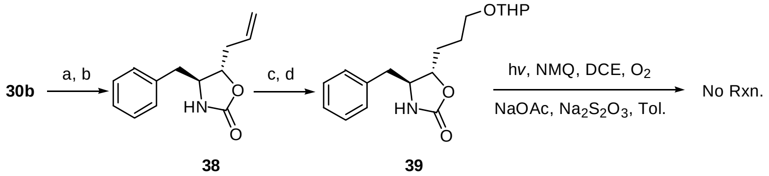


Reagents: a) TFA, b) $(CF_3CO)_2O$, pyr., CH_2Cl_2, 45%c) 1.0M BH_3-THF, NaOH, H_2O_2, THF, 65%

Oxazolidinone **39** was synthesized in four steps from carbamate **30b**, as shown in Scheme 1.7. The Boc group of carbamate **30b** was removed with trifluoroactetic acid, and oxazolidinone **38** was formed by reaction of the free amine with carbonyl diimidazole. The alkene was then hydroborated with BH_3·THF and quenched with basic hydrogen peroxide to provide the corresponding alcohol. The alcohol was protected as the THP ether with dihydropyran and *p*-toluenesulfonic acid to provide oxazolidinone **39** in 25% yield.

Oxazolidinone **39** was subjected to the catalytic aerobic cyclization conditions. However, after 12 hours no product formation was observed and 33% of the starting material was recovered.

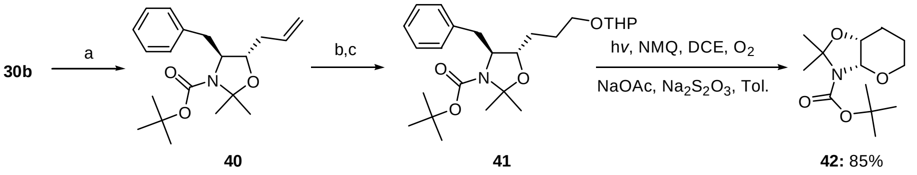
Scheme 1.7: Oxazolidinone synthesis



Reagents: a) TFA, b) CDI, DMAP, THF, c) 1.0M BH_3-THF, NaOH, H_2O_2, THF, d) DHP, pTSOH, CH_2Cl_2, 25%

Because excellent stereocontrol had been exhibited in the reactions of tertiary amides **17** and **17a** cyclization reactions involving an oxazoline were attempted. The synthesis of oxazoline **41** is shown in Scheme 1.8.[42]

Scheme 1.8: Oxazoline synthesis



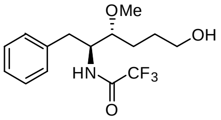
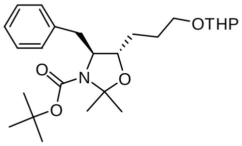
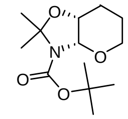
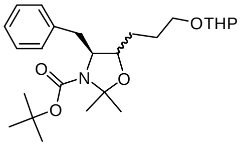
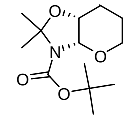
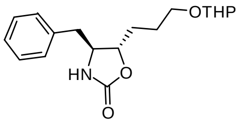
Reagents: a) 2,2-dimethoxypropane, PPTS, Tol., 32% b) 1.0M BH_3-THF, NaOH, H_2O_2, 71% c) DHP, PPTS, CH_2Cl_2, 90%

Carbamate **30b** was reacted with 2,2-dimethoxypropane in refluxing toluene to give oxazoline **40** in 32% yield. Subsequent hydroboration with BH_3·THF and quenching with basic hydrogen peroxide provided the corresponding alcohol in 71% yield. The alcohol was protected as the THP ether with dihydropyran and *p*-toluenesulfonic acid to provide oxazoline **41** in 90% yield. Cyclization of oxazoline **41** under catalytic conditions resulted in the isolation of a single diastereomer, the *cis*-6,5-ring fusion with retention of configuration at the nitrogen center, in 85% isolated yield.

The cyclization was then repeated with a mixture of diastereomers, **41a**, to test the stereoselectivity and proposed dissociative mechanism. The diastereomeric mixture was prepared in the same manner as shown in Scheme 8, with the exception that a mixture of **30a** and **30b** was employed as the starting material. The cyclization provided a single diastereomer in 88% isolated yield.

Table 1.4 provides a summary of the cyclization substrates tested under catalytic aerobic ETIC reaction conditions to examine the scope and generality of nitrogen containing stabilizing groups that could be used in the homobenzylic position.

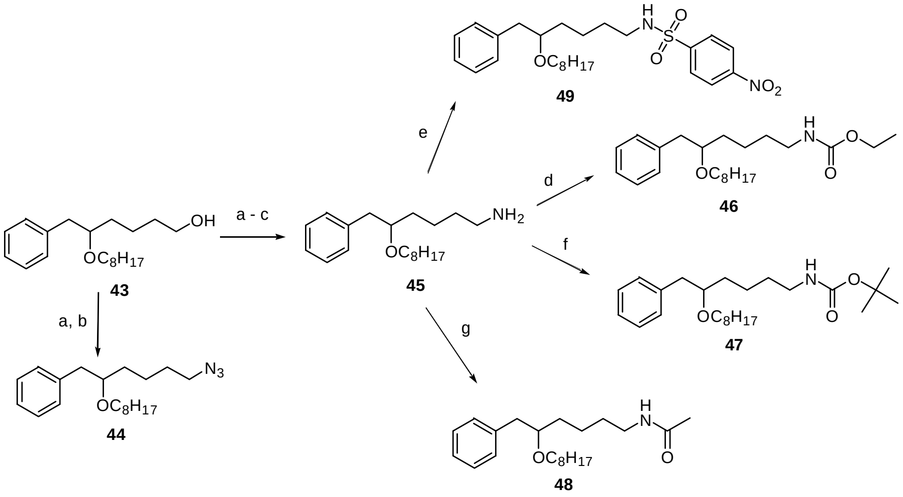
Table 1.4: Additional homobenzylic stabilizing groups

	Substrate	Product	Yield (%)	D.R
37		No Reaction		
41			82	99:1
41a			88	99:1
39		No Reaction		

After successfully demonstrating the utility of several amides and *t*-butylcarbamates as stabilizing groups in the homobenzylic position we wanted to explore the range of nitrogen nucleophiles that could be employed in ETIC reactions. In order to do this, a reversion back to the use of homobenzylic ethers as the cyclization substrate was the initial step. A wide variety of successful ETIC reactions of homobenzylic ethers using appended oxygen nucleophiles had been demonstrated,[30] and preliminary results of ETIC reactions of homobenzylic ethers with an appended acetamide were promising.[43] Therefore, it was of interest to expand upon these results.

Alcohol **43** served as the starting material for the synthesis of all of the substrates shown in Scheme 1.9. The alcohol was converted to the mesylate with mesyl chloride and triethylamine. The mesylate was then displaced with sodium azide in DMF to provide azide **44** in 87% yield. Azide **44** was the first substrate containing a potential nitrogen nucleophile subjected to catalytic aerobic ETIC reaction conditions. No reaction was observed after three hours, and the starting material was re-isolated.

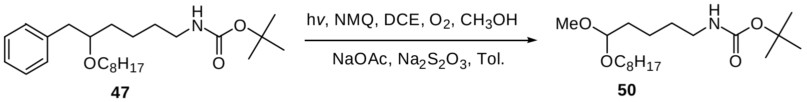
Scheme 1.9: Substrates containing appended nitrogen nucleophiles



Reagents: a) Ms-Cl, Et_3N, CH_2Cl_2, b) NaN_3, DMF, c) TPP, H_2O, THF, d) C_2H_5OCOCl, K_2CO_3, Acetone, e) $C_6H_4NO_4SCl$, Et_3N, CH_2Cl_2, f) $(Boc)_2O$, Et_3N, Dioxane:H_2O (1:1), g) $(C_2H_3O)_2O$, Et_3N, DMAP, CH_2Cl_2

Ethyl carbamate **46** and *tert*-butyl carbamate **47**, were both formed from amine **45**, which was obtained by reduction of azide **44** via the Staudinger reaction. Ethyl carbamate **46** was formed in 56% yield by reaction of amine **45** with potassium carbonate and ethyl chloroformate. Carbamate **47** was formed in 81% yield by reaction of amine **45** with Boc anhydride and triethylamine in a 1:1 mixture of dioxane and water. Neither carbamate **46** nor carbamate **47** provided the desired cyclization products when subjected to catalytic aerobic ETIC reaction conditions. In both cases, one major product was isolated from the reaction mixture, but the identities of those products have yet to be determined. For both carbamates it was believed that oxidation of the carbamate followed by fragmentation was the operative reaction pathway. Subjecting the *tert*-butyl carbamate to the catalytic ETIC conditions with one equivalent of methanol tested this hypothesis (Figure 1.27). If preferential oxidation of the carbamate were occurring, the hemiaminal resulting from nucleophilic attack of the methanol would have been isolated. This however, did not occur and hemiacetal **50** was isolated from the reaction mixture.

Figure 1.27: Attempted trapping of carbamate radical cation

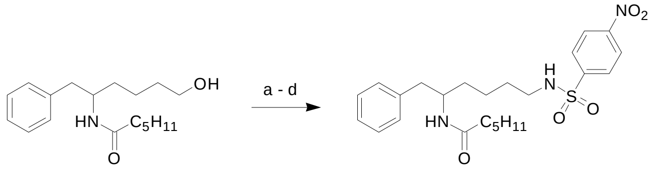


Acetamide **48** was prepared in 69% yield by acylation of amine **45** with acetic anhydride in the presence of a catalytic amount of DMAP. No desired cyclization products were observed when this substrate was subjected to catalytic aerobic ETIC conditions, only 20% of the starting material was recovered, and no identifiable decomposition products were isolated.

Sulfonamide **49** was formed in 34% yield by reaction of amine **45** with 4-nitrobenzylsulfonyl chloride and triethylamine. Sulfonamide **49** proved to be an excellent substrate for cyclization. No decomposition of the starting material was observed, and the cyclized product was obtained in 68% yield. Use of the nitrophenyl sulfonamide as a nucleophile proved advantageous because of the ease of removal following cyclization to allow for further synthetic manipulation.[41]

Sulfonamide **50** was prepared as shown in Scheme 1.10. The alcohol of amide **6** was converted to the mesylate with mesyl chloride and triethylamine. The mesylate was displaced with sodium azide in DMF at 55 ºC. The azide was reduced to the corresponding amine via the Staudinger reaction, and the amine was sulfonylated with 4-nitrobenzenesulfonyl chloride and triethylamine in CH_2Cl_2 to afford sulfonamide **50** in 34% yield over four steps. Catalytic aerobic ETIC reaction of sulfonamide **50** afforded (*N*, *N*) acyl aminal **51** was in 64% yield.

Scheme 1.10: Sulfonamide synthesis

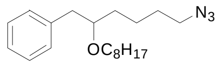
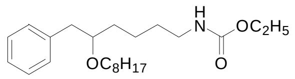
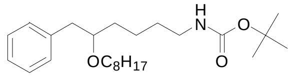
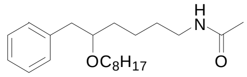
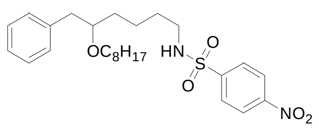
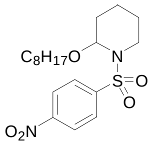
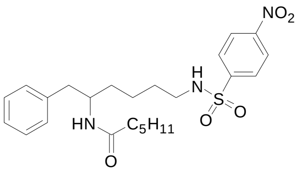
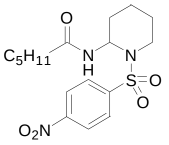


6 → 50

Reagents: a) MsCl, Et_3N, CH_2Cl_2, b) NaN_3, DMF, 55 C, c) Ph_3P, THF, H_2O, d) *p*-$NO_2C_6H_4SO_2Cl$, Et_3N, CH_2Cl_2 (four steps) 34%

Table 1.5 summarizes the variety of homobenzylic ethers with appended nitrogen nucleophiles tested under catalytic aerobic ETIC conditions.

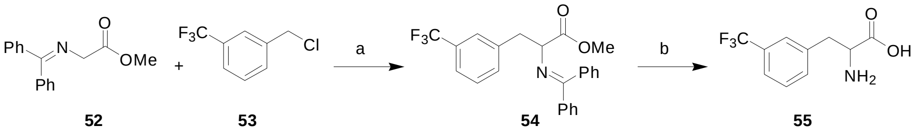
Table 1.5: Nitrogen as a nucleophile

	Substrate	Product	Yield (%)
44		No Reaction	
46		Decomposition	
47		Decomposition	
48		Decomposition	20% Recvd. SM
49			68
50			64

In addition to probing the mechanism of the ETIC reaction, the chemoselectivity of the single electron oxidation was examined through the incorporation of a trifluoromethyl group on the arene. Incorporation of this group was predicted to increase the oxidation potential of the arene by 0.3V,[42] effectively prohibiting its oxidation under the reaction conditions.

3-(Trifluoromethyl)phenylalanine (**55**)[43] served as the starting material for the synthesis of both trifluoromethyl-substituted arenes, **57** and **58**, as shown in Scheme 1.11. Ketimine **52**[44] was easily obtained by condensation of benzophenone immine and glycine methyl ester hydrochloride in CH_2Cl_2. Alkylation of ketimine **52** with the commercially available 3-(trifluoromethyl)benzyl chloride **(53)** in the presence of sodium hydride in DMF provided ketimine **54** in excellent yield. Hydrolysis of **54** with 6N HCl, followed by saponification of the hydrochloride salt with 15% NaOH in MeOH provided the desired starting material **55** in 92% yield.

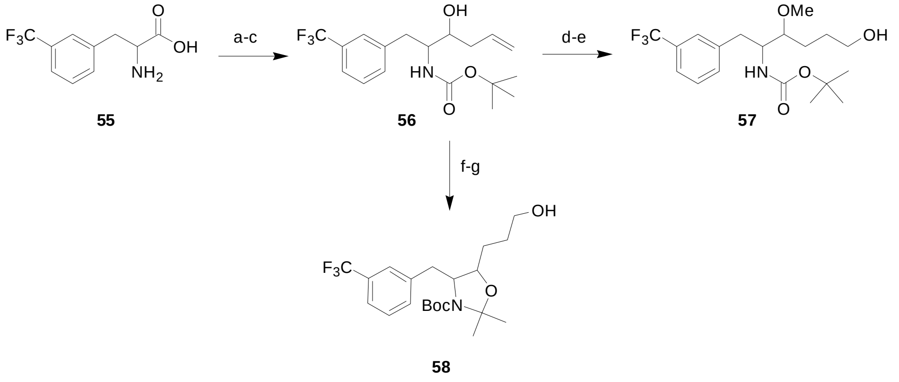
Scheme 1.11: Synthesis of 3-(trifluoromethyl)phenylalanine



Reagents: a) NaH, DMF, 95% b) 1. 6N HCl, 15% NaOH, MeOH, 92%

3-(Trifluoromethyl)phenylalanine (**55**) was reduced to the amino alcohol with LAH in THF, then reacted with di-*tert*-butyldicarbonate in one pot to provide the Boc-protected amino alcohol (Scheme 1.12). The alcohol was oxidized to the aldehyde with Dess-Martin periodinane, which was subsequently reacted with allylmagnesium bromide to provide alcohol **56**. The trifluoromethyl arene **57** was obtained in a 2% overall yield from alcohol **56** through methyl ether formation with methyl iodide and sodium hydride in DMF followed by hydroboration with BH_3•THF. Trifluoromethyl-substituted arene **58** was obtained in a 6% yield from alcohol **56** by oxazoline formation with dimethoxypropane and PPTS in refluxing toluene followed by hydroboration with BH_3•THF.

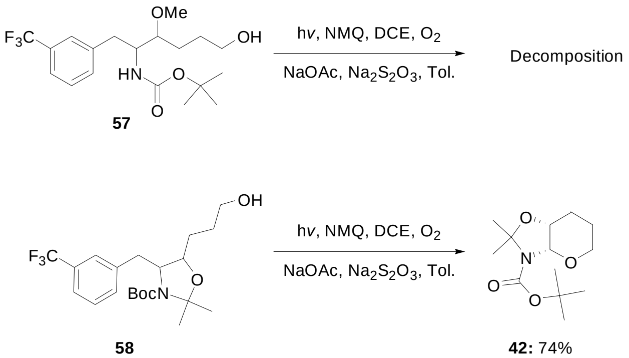
Scheme 1.12: Synthesis of trifluoromethyl-substituted arenes


F3C
O
OH
NH2
55
a-c
OH
HN
O
56
d-e
OMe
OH
57
f-g
BocN
58

Reagents: a) 1.LAH, Et_2O, THF, 2. Boc_2O, CH_2Cl_2, 91% b), DMPI, CH_2Cl_2, c) allylmagnesium bromide, THF, d) MeI, NaH, DMF, e) 1. BH_3 THF, 2. NaOH, H_2O_2 (2% over 5 steps), f) dimethoxy propane, PPTS, PhMe, g) 1. BH_3 THF, 2. NaOH, H_2O_2, (6% over 5 steps)

Both trifluoromethyl-susbstituted arenes **57** and **58** were subjected to catalytic aerobic ETIC reaction conditions. As shown in Figure 1.28, ETIC reaction of **57** lead only to decomposition of the starting material, while ETIC reaction of **58** provided the desired *cis*-6,5-ring fused product **42** as a single diastereomer in 74% yield.

Figure 1.28: ETIC reaction of trifluoromethyl-substituted arenes


F3C
OMe
OH
HN
O
57
hν, NMQ, DCE, O2
NaOAc, Na2S2O3, Tol.
Decomposition
BocN
58
42: 74%

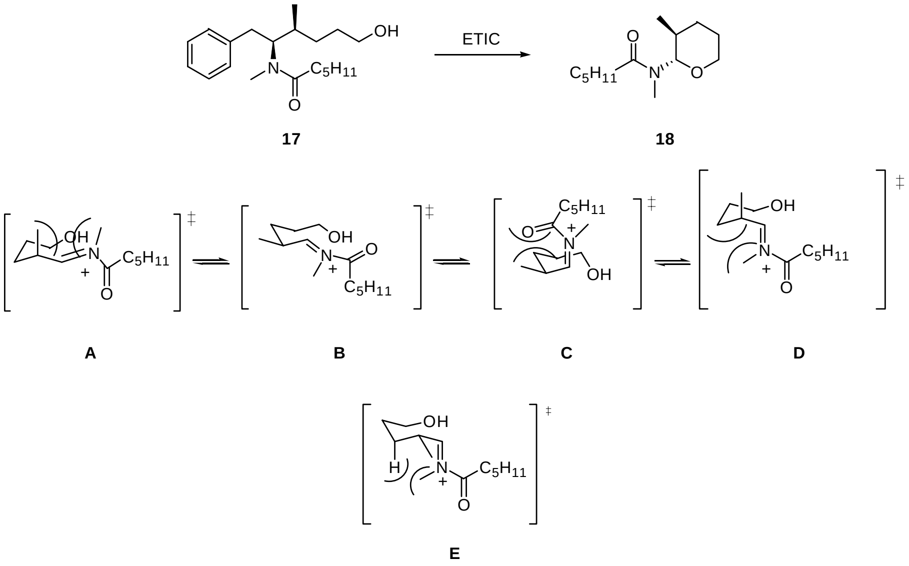
1.3. Discussion of electron transfer initiated cyclization reactions

I. Reaction Stereochemistry

The incorporation of a methyl group, or methoxy group adjacent to the reactive center provided a means of exploring the stereochemical outcome of ETIC reactions of homobenzylic amides and carbamates through the analysis of coupling constants. Subjecting secondary amides to ETIC reaction conditions resulted in the isolation of a mixture of diastereomers. However, ETIC reactions of tertiary amides and tertiary carbamates were stereoselective processes.

When tertiary amide **17** was subjected to standard ETIC conditions the single diastereomer **18** was isolated. The relative stereochemistry of cyclic acylaminal **18** can be explained by examination of the transition state. If the transformation proceeds through an early transition state, allylic strain would be the dominant controlling factor, and the *anti* relationship between the methyl and amide would result from a desire to minimize steric interactions. Figure 1.29 illustrates the four possible chair-like early transition states that can be assumed: (**A**) illustrates the 1,3 allylic strain between the amide methyl and the backbone methyl, (**B**) depicts the preferred transition state and (**C**) and (**D**) show steric clashes between the carbonyl and methylene of the ring and the methyl of the iminium ion and methylene group, respectively. If a late transition state (**E**) is the operative mode, developing unfavorable diaxal interactions of the amide methyl with the hydrogens of the ring force the equatorial preference.

Figure 1.29: Stereocontrol in tertiary amide cyclizations



Subjecting the mixture of diastereomers, amide **17** to standard ETIC reaction conditions also resulted in the isolation of cyclic acylaminal **18**. This result provided additional evidence for a dissociative mechanism, which will be discussed in a later portion of the document.

II. Optimization

Initial ETIC reactions of homobenzylic amides and carbamates were successful and the desired cyclic acylaminals were obtained in high yields. However, these yields varied due to difficulty in purifying the desired product. Earlier work done with the cyclization reactions of homobenzylic ethers[31] demonstrated that using less than a stoichiometric amount of sensitizer resulted in recovery of starting materials, and excess was required for complete conversion. The use of 1.2 equivalents of $NMQPF_6$ created aromatic by-products from radical-radical coupling reactions. Mesolytic cleavage of the benzylic bond of the radical cation generates a benzyl radical as a reactive intermediate, which can participate in unwanted side reactions. Purification by flash chromatography followed by preparatory thin layer chromatography was necessary. In addition to the purification difficulties, long reaction times, on the order of 4 to 6 hours, were required. During the course of the reaction, deposition of the solid NaOAc on the walls of the reaction flask, as well as a color change from colorless to a deep, dark red were observed. Both the color change and the deposition were thought to impede the course of the reaction.

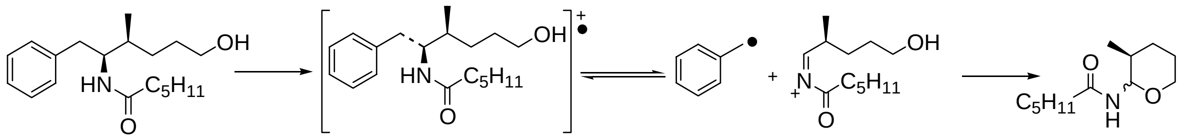
In an attempt to optimize the reaction conditions, a catalytic photosensitized electron transfer cyclization reaction under aerobic conditions was developed. The gentle bubbling of air through the reaction mixture during irradiation regenerated the photosensitizer $NMQPF_6$. This allowed for the use of 0.25 mole percent of $NMQPF_6$, which alleviated the purification difficulties associated with the use of excess photosensitizer. This also allowed for the isolation of decomposition products, and reduced reaction times from 5 to 2 hours. Any unwanted reactive oxygen species generated during the catalytic cycle could be reduced by the addition of solid sodium thoisulfate into the reaction mixture.

III. Mechanistic Insights

The isolation of a mixture of diastereomers resulting from ETIC reactions of secondary amides and carbamtes indicated that the reaction proceedes by a largely dissociative, rather than associative pathway involving discrete acyiminium ion formationas a result of mesolytic cleavage of the benzylic C-C bond. Had the product isolated from these reactions been a single diastereomer with inversion of configuration at the reactive center, an associative mechanism would have been assumed.

Figure 1.30 illustrates the proposed mechanism. Upon single electron oxidation of the homobenzylic amide **14** the radical cation is formed. The benzylic bond of the radical cation then fragments to give a stabilized benzyl radical and an acyliminium ion. The cation is then attacked by the appended hydroxyl group, and upon proton transfer the desired product is formed. Because the intermediate is a sp^2 hybrodized carbon, attack from either face is possible, resulting in a mixture of diastereomers. Subjecting a 2:1 mixture of diastereomers of **15** to ETIC reaction conditions for 4 hours resulted in recovery of the same 2:1 mixture. To discount the possibility that the 2:1 mixture was an equilibrium mixture, the *syn* diasteromer (**15b)** was subjected to the aerobic catalytic ETIC reaction conditions. Over prolonged reaction times approximately 10% epimerization was observed. However, this rate of epimerization is not sufficient to account for the observed product ratios.

Figure 1.30: Proposed dissociative mechanism



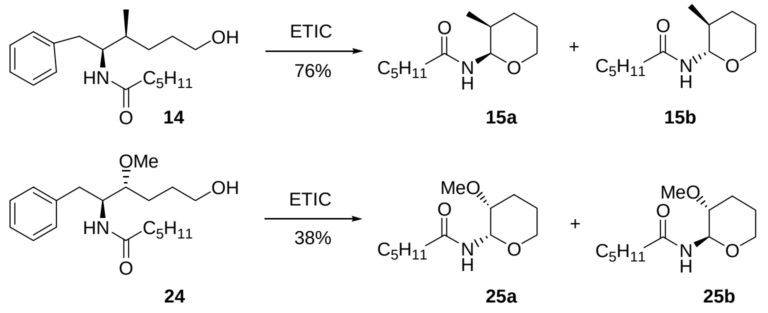
14

15

Further evidence for a dissociative mechanism was provided by subjecting mixtures of diastereomers of tertiary amides as well as acyloxazolines to ETIC reaction conditions. In both cases the single diastereomer that was isolated, was the same as that which was isolated from ETIC reactions of single diastereomers of tertiary amides or oxazolines.

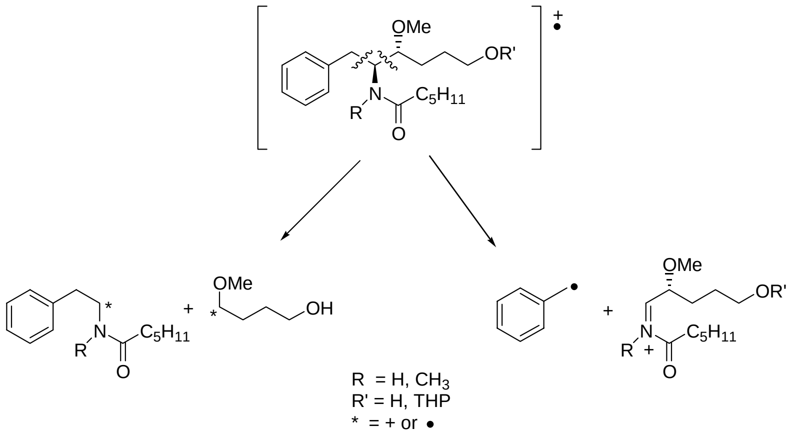
Changing from a methyl adjacent to the reactive center to a methoxy group had a definite impact on the ETIC reaction. As is evident by examination of ETIC reactions of amides **24** and **26**, oxygen containing functional groups placed adjacent to the reactive center result in decreased yields. Comparison of the ETIC reaction of amide **14** to that of amide **24** shows a 50% decrease in yield upon incorporation of the methoxy group, as shown in Figure 1.31.

Figure 1.31: Comparison of ETIC reactions



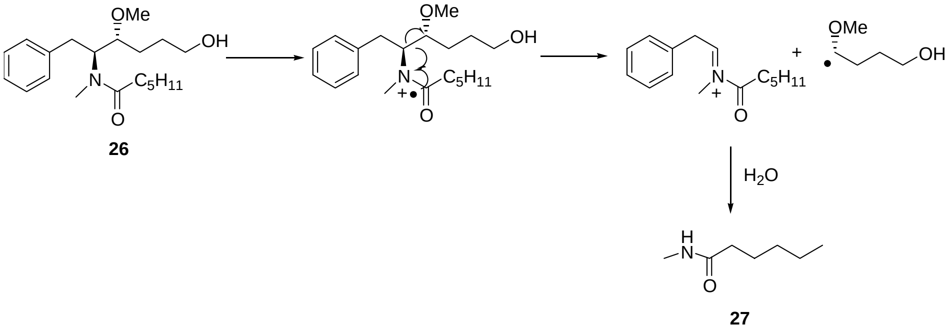
In addition to the benzylic bond, the C-C bond between the amide and methyl ether of the radical cations of amides **24**, and **26** could be cleaved. Having a stabilizing group such as the methyl ether adjacent to the reactive center lowers both the bond dissociation energy of the substrate, as well as the oxidation potential of the electrophilic fragment. Upon formation of the radical cation two mesolytic bond cleavages are possible, the benzylic C-C bond or the C-C bond between the amide and methyl ether. Both bond cleavages result in a cation stabilized by the amide to form the acyl imminium ion (Figure 1.32).

Figure 1.32: Two possible mesolytic cleavages



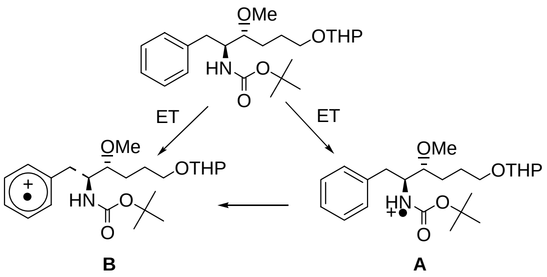
These two possible bond dissociations played an even larger role in the cyclization reaction of tertiary amide **26**, where no cyclization was observed and the only product isolated was amide **27** resulting from cleavage of the bis-homobenzylic bond. According to electrochemical oxidation potentials, the tertiary amide is more readily oxidized than the secondary amide by as much as 0.80 V.[41] Figure 1.33 shows a suggested a mechanism for the formation of amide **27**. After mesolytic cleavage of the bis-homobenzylic bond, the imminium ion is attacked by adventitious water present in the system. Proton transfer from the water to the nitrogen of the hemiaminal followed by formation of the carbonyl displaces amide **27**.

Figure 1.33: Mechanism for formation of amide **27**



Even though the electrochemical oxidation potentials[42] of carbamates are known to be lower than those of amides, higher yields and cleaner reactions were observed with homobenzylic *tert*-butyl carbamates having an oxygen containing functional group adjacent to the reactive center than with the corresponding homobenzylic amides. The mechanism is not fully understood, given that there are two easily oxidizable substituents within the substrate. Theoretically, the nitrogen of the carbamate can be oxidized in preference to the arene to form radical cation **A** (Figure 1.34). Alternatively, the steric bulk of the *tert*-butylcarbamate might limit oxidation of the nitrogen, allowing for preferential oxidation of the arene, radical cation **B**. In either case, mesolytic cleavage of the benzylic C-C bond to form the acyliminium ion is possible.

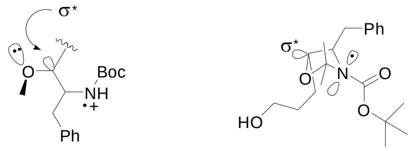
Figure 1.34: Possible radical cations



Homobenzylic Boc protected oxazolines proved to be outstanding ETIC substrates. Superb stereocontrol was exhibited and excellent yields were observed despite the lower oxidation potential of the tertiary carbamate. The increased yields, relative to the acyclic cyclization substrate **31**, can be explained through molecular orbital analysis of the radical cation. Proper orbital alignment of the SOMO of the carbamate radical cation and the benzylic C-C bond is required for mesolytic benzylic bond cleavage. If proper orbital overlap of the lone pair of the ether oxygen with the σ^* of the homobenzylic C-C bond can be achieved, the alternative reactive pathway involving mesolytic cleavage of the homobenzylic C-C bond becomes an operative reactive pathway.

Figure 1.35 shows that the dihedral angle between the lone pair of the ether oxygen in the oxazoline cyclization substrate **41** and the σ^* orbital of the homobenzylic bond cannot attain proper alignment for bond cleavage. Alternatively, in the acyclic substrate **31** the proper orbital overlap can be achieved allowing for the undesired bond cleavage and decreasing reaction yield.

Figure 1.35: Ideal geometries for β-alkoxy carbamate radical cation C-C bond fragmentation



Additional support for the reaction proceeding through amide or carbamate oxidation was provided by ETIC reactions of trifluoromethyl-substituted arenes **57** and **58**. Incorporation of the trifluoromethyl group is expected to increase the oxidation potential of the arene by 0.3V[45] thereby inhibiting the reaction if oxidation of the arene is the relevant reaction pathway. Cyclization of **58** provided the desired bicyclo [4.3.0] fused product **42** in good yield, whereas subjecting trifluoromethyl-substituted arene **57** to ETIC reaction conditions resulted in complete decomposition of the starting material.

The scope and generality of the ETIC reaction of substrates having an oxygen containing functional group adjacent to the reactive center was further tested by varying the stabilizing group in the homobenzylic position. ETIC reactions with homobenzylic trifluoroacetamides and oxizolidinones were unsuccessful. Neither group was able to stabilize the cation formed from mesolytic cleavage of the benzylic bond. Due to the electron withdrawing nature of both the trifluoromethyl group and the oxizolidinone, the nitrogen was unable to form the acyliminium ion necessary for cyclization.

1.4. Conclusion

A new photoinitiated single electron transfer cyclization reaction has been developed. Amides and carbamates can be used a stabilizing groups in the homobenzylic position of alkyl arenes with appended nucleophiles. Upon single electron oxidation of the alkyl arene a radical cation is formed in which the benzyl C-C bond can selectively undergo mesolytic cleavage leading to a benzyl radical and a cationic fragment. The cationic fragment is then subject to nuceophilic attack by the appended nucleophile to form the desired heterocycle.

Through the course of development of this cyclization method it was discovered that both amides and *t*-butyl carbamates act as stabilizing groups in the homobenzylic position. Placing oxygen containing functional groups in the bis-homobenzylic position decreases reaction yields and allows for the operation of alternative reactive pathways. However, the use of homobenzylic *t*-butyl carbamates in substrates bearing oxygen containing functional groups in the bis-homobenzylic position leads to more efficient cyclization reactions.

A catalytic variant of the single electron transfer cyclization reaction has been developed. Regeneration of the photoactivated sensitizer *N*-methylquinolinium hexafluorophosphate can be achieved under aerobic conditions. The addition of the mild, partially soluble reducing agent sodium thiosulfate into the reaction mixture suppresses decomposition attributed to the formation of unwanted reactive oxygen species. Switching from the stoichiometric to the catalytic variant of the cyclization reaction facilitates purification and reaction efficiency.

Mechanistically, the electron transfer initiated cyclization reactions appear to be following a dissociative route. The use secondary amides and carbamtes in the homobenzylic position leads to diastereomeric mixtures of products. Tertiary, homobenzylic amides and oxazolines provide superb, complementary stereocontrol.

Nitrogen can be used as a nucleophile in electron transfer initiated cyclization reactions. Homobenzylic ethers as well as homobenzylic carbamates containing appended sulfonamide nucleophiles have been subjected to the catalytic ETIC reaction conditions, and the resulting (*N*, *N*) and (*N*, *O*) acylaminals have been isolated in good yields.

1.5. Experimental

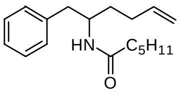
General Procedures. All reactions were performed in oven or flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.

Instrumentation. Proton (^{1}H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 spectrometers at 300 MHz and 75 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak or the internal standard tetramethylsilane were used as reference values. For ^{1}H NMR: $CDCl_3$ = 7.27 ppm, TMS = 0.00 ppm. For ^{13}C NMR: $CDCl_3$ = 77.23, TMS = 0.00. For the proton data: s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; b = broad. High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2.

Materials. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done 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 ketyl prior to use. Anhydrous N,N-dimethylformamide (DMF), methanol, dimethyl sulfoxide (DMSO) and *tert*-butylbenzene were purchased from Aldrich and used as is.

Compounds originating from phenylalanine were found to have racemized during the synthesis.

Hexanoic acid (1-benzylpent-4-enyl)amide (5)

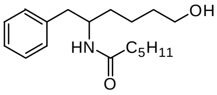


5

To 1-Phenylhex-5-en-2-ol (2.51 g, 14.22 mmol) in CH_2Cl_2 (35 mL) at 0 ºC were added methanesulfonyl chloride (2.44 g, 21.3 mmol) and triethylamine (5.76 g, 56.8 mmol). The reaction mixture was stirred for 3 h at room temperature then was quenched with water. The reaction mixture was extracted with CH_2Cl_2, then the organic layer was washed with water and saturated NaCl, dried (Na_2SO_4) and concentrated. The resulting residue was dissolved in DMF (35 ml) at 23 ºC under N_2. Sodium azide (9.24 g, 14.2 mmol) and tetrabutyl ammonium iodide (50 mg) were added. The reaction mixture was stirred for 18 h, then was quenched with water, and extracted into hexanes. The organic layer was washed with saturated NaCl, dried (Na_2SO_4), and concentrated. The resulting residue was then dissolved in THF (15 mL) at 23 ºC under N_2 and triphenylphosphine (1.73 g, 6.59 mmol) was added. The reaction mixture was allowed to stir for 18 h then was quenched with water (2 mL). The reaction mixture was then allowed to stir for an additional 18 h. The temperature was decreased to 0 ºC and hexanoyl chloride (1.63 g, 8.25 mmol) and triethylamine (1.11 g, 10.9 mmol) were added. After 1 h the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with saturated NaCl (2x 10 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product (0.612 g, 40.7%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.16 (m, 5H), 5.78 (m, 1H), 5.19 (b s, 1H), 4.98 (d, *J* = 14.0, 2H), 4.95 (d, *J* = 8.5, 2H) 4.23 (m, 1H), 2.76 (t *J* = 5.15 , 2H), 2.14-

2.07 (m, 6H), 1.62-1.21 (m, 6H), 0.88 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1 137.94, 129.5, 128.6, 114.8, 49.7, 40.9,36.7, 33.3, 31.3, 30.3, 22.4, 14.1; IR (neat) 3290, 3066, 3027, 2933, 2855, 1643, 1544, 1453, 894, 748 cm^{-1}; HRMS (EI) calcd for $C_{18}H_{27}NO$ 273.2093, found 273.2100.

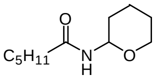
Hexanoic acid (1-benzyl-5-hydroxypentyl)amide (6)



6

To hexanoic acid (1-benzylpent-4-enyl)amide (0.212 g, 0.777 mmol) in THF (10 mL) at 23 ºC was added 9-BBN (0.5 M in THF, 3.11 ml, 1.55 mmol). The reaction was stirred for 3.5 h, then quenched at 0 ºC with water (2 mL) followed by 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide solution (1 mL) and saturated Na_2SO_3 (2 mL). The reaction mixture was stirred for an addition hour, then was extracted with ethyl acetate, washed with saturated NaCl (2x 10 mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified by column chromatography (50% EtOAc in hexanes) to afford the desired product (0.099 g, 43.7%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.16 (m, 5H), 5.23 (bd, *J* = 3.2 Hz 1H), 4.23 (m, 1H) 3.62 (t, *J* = 5.7 Hz, 2H) 2.79 (d, *J* = 7.6 Hz, 2H), 2.11 (m. 2H), 1.58-1.21 (m, 12H), 0.87 (t, *J* = 6.7 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 138.1, 129.5, 128.4, 126.5, 62.4, 49.9, 41.1, 37.0, 33.9, 32.4, 31.4, 25.6, 22.5, 22.3, 14.0; IR (neat) 3281, 2933, 2860, 1638, 1552, 1445, 1053, 748, 701 cm^{-1}; HRMS (EI) cald for $C_{18}H_{29}NO_2$ 291.2198, found 292.2270.

Hexanoic acid (tetrahydropyran-2-yl)amide (7)

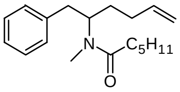


7

This procedure is representative of a standard ETIC reaction. To hexanoic acid (1-benzyl-5-hydroxypentyl)amide (0.050 g, 0.172 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 ºC were added *N*- methylquinolinium hexafluorophosphate (0.059 g, 0.206 mmol), and sodium acetate (0.100 g, 1.21 mmol). The mixture was stirred at room temperature while irradiating for 5 h at 320nm with a medium pressure mercury lamp. The distance between the reaction flask and lamp was 4 cm. The lamp was cooled by a cold water circulation through a pyrex jacket surrounding the lamp. The pyrex cold jacket also served as a filter to remove all wavelengths below 290 nm emitted by the lamp. Upon completion, the reaction mixture was filtered, concentrated, and purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (0.029 g, 86%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6. 05 (d, J = 7.9 Hz, 1H), 5.09 (dt, J = 8.3, 2.3 Hz, 1H), 3.96 (m, 1H), 3.58 (m, 1H), 2.16 (m, 1H) 1.64 – 1.26 (m, 10H), 0.87 (t, J = 6.7 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 77.8, 36.9, 31.7, 31.5, 25.3, 25.2, 23.0, 22.5, 22.3, 14.0; IR (neat) 3286, 2950, 2855, 1660, 1544, 1453, 1208, 1083, 1032, 903 cm^{-1}; HRMS (EI) cald for $C_{11}H_{21}NO_2$ 199.1572, found 199.158809.

This procedure is representative of an ETIC reaction done under catalytic aerobic conditions. To hexanoic acid (1-benzyl-5-hydroxypentyl)amide (0.089 g, 0.306 mmol) in dichloroethane (10 mL) and toluene (2 mL) in a borosilicate flask at 20 ºC were added *N*- methylquinolinium hexafluorophosphate (0.002 g, 0.007 mmol), sodium acetate (0.178 g, 2.17 mmol), and sodium thiosulfate (0.178 g, 1.13 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 3 h at a distance of 4 cm from a medium pressure mercury lamp. The lamp was cooled by a cold water circulation through a pyrex jacket surrounding the lamp. The pyrex cold jacket also served as a filter to remove all wavelengths below 290 nm emitted by the lamp. The reaction mixture was filtered, concentrated, and purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (0.045 g, 75%)

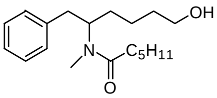
Hexanoic acid (1-benzylpent-4-enyl)methylamide (8)



8

To a suspension of sodium hydride (60% dispersion in mineral oil, 0.234 g, 5.85 mmol) in DMF (20 mL) at 0 °C was added hexanoic acid (1-benzylpent-4-enyl)amide (0.400 g, 1.46 mmol). The reaction mixture was stirred for 30 minutes then methyl iodide (2.07 g, 14.6 mmol) was added. The reaction mixture stirred for 12 h then was quenched with water (2 mL), extracted with EtOAc (3 x 15 mL), washed with water and saturated NaCl, dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (0.345 g, 82%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.08 (m, 5H), 5.89 (m, 1H), 4.99 (m, 1H), 3.91 (m, 1H), 2.85 (s, 3H), 2.74 (m, 5H), 2.17 (dt, *J* = 4.9, 2.4, 1H), 2.01 (m, 2H), 1.73-1.06 (m, 10H), 0.86 (m, 3H).

Hexanoic acid (1-benzyl-5-hydroxypentyl)methylamide (9)

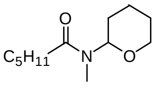


9

To hexanoic acid (1-benzylpent-4-enyl)methylamide (0.345 g, 1.20 mmol) in THF (20 mL) at 23 °C was added 9-BBN (0.5 M in THF, 4.80 ml, 2.40 mmol). The reaction was stirred for 3 h, then quenched at 0 ºC with water (2 mL) followed by 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide solution (1 mL) and saturated Na_2SO_3 (2 mL). The reaction mixture was stirred for an addition hour, then was extracted with ethyl acetate, washed with saturated NaCl, dried (Na_2SO_4) and concentrated. The resulting residue was purified by column chromatography (50% EtOAc in hexanes) to afford the desired

product (0.339 g, 92%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.29-7.08 (m, 5H), 5.02 (bs, 1H), 3.92 (m, 1H), 3.62 (m, 2H), 2.85 (m, 5H), 2.17 (m, 2H), 2.03 (m, 1H), 1.63-1.18 (m, 12H), 0.86 (m, 3H).

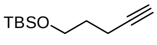
Hexanoic acid methyl(tetrahydropyran-2-yl)amide (10)



10

To Hexanoic acid (1-benzyl-5-hydroxypentyl)methylamide (0.100g, 0.327 mmol) in dichloroethane (7 mL) and *tert*-butylbenzene (1 mL) in a borosilicate flask at 20 ºC were added *N*- methylquinolinium hexafluorophosphate (0.114 g, 0.393 mmol) and sodium acetate (0.227 g, 2.67 mmol). The mixture was stirred for 6 h at 20 ºC while irradiating. The reaction mixture was filtered, concentrated, and purified by flash chromatography (50% Acetone in hexanes) to provide the desired product (0.039 g, 55%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.64 (dd, *J* = 5.6, 3.27 1H), 4.82 (dd *J* = 8.5, 1.8 1H), 4.02 (bt, *J* = 12.9 2H), 3.58 (m, 1H), 2.91 (s, 3H), 2.88 (s, 3H), 2.41 – 2.25 (m, 4H), 1.99 – 1.24 (m, 12H), 0.88 (t, *J* = 5.5, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 173.3, 85.42, 81.16, 68.35, 34.14, 33.49, 31.67, 29.69, 29.17, 28.58, 27.34, 25.34, 25.18, 25.08, 24.52, 23.54, 23.43, 23.12, 22.56, 14.03; IR (neat) 2933, 2855, 1660, 1462, 1410, 1372, 1316, 1079, 1036, 911 cm^{-1}; HRMS (EI) cald for $C_{12}H_{23}NO_2$ 213.1728, found 213.1732.

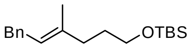
tert-Butyldimethylpent-4-ynyloxy-silane (11)



11

To 4-pentyn-1-ol (1.99 g, 23.7 mmol) in DMF (20 mL) at 0 ºC were added imidazole (2.42 g, 35.6 mmol) and *tert*-butyldimethylsilyl chloride (3.94 g, 26.1 mmol). The reaction was stirred at 20 ºC for 18 h, and then quenched with saturated NH_4Cl, extracted with hexanes, washed with saturated NaCl, dried (Na_2SO_4) and concentrated. The resulting residue was purified by column chromatography (10% EtOAc in hexanes) to afford the desired product (4.49 g, 95%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.73 (t, *J* = 6.0 2H), 2.30 (dt, *J* = 2.7, 4.5 2H) 1.96 (t, *J* = 2.7 1H), 1.78 (m, 2H), 0.93 (s, 9H), 0.08 (s, 6H).

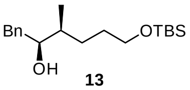
***tert*-Butyldimethyl-(4-methyl-6-phenylhex-4-enyloxy)silane (12)**



12

To a room temperature suspension of bis(cyclopentadienyl)zirconium dichloride (5.00 g, 17.24 mmol) in CH_2Cl_2 (100 mL) was added trimethylaluminum (2.0 M in hexanes, 22.68 mL, 45.36 mmol). The reaction mixture was stirred for 30 min. before *tert*-Butyl-dimethyl-pent-4-ynyloxy-silane (3.42 g, 17.24 mmol) was added. The reaction mixture was stirred for 18 h then a solution of benzyl chloride (2.23 g, 17.24 mmol) and palladium *tetrakis*-triphenylphosphine (0.597 g, 0.517 mmol) in THF (20 mL) was added. The reaction mixture was stirred for 12 h then quenched at -78 ºC with ethanol (3 mL) and stirred for 2 h with saturated sodium potassium tartrate (15 mL). The mixture was extracted with ether and the organic layer was washed with water and saturated NaCl, dried (Na_2SO_4) and concentrated. The resulting residue was purified by column chromatography (5% EtOAc in hexanes) to afford *tert*-Butyl-dimethyl-(4-methyl-6-phenyl-hex-4-enyloxy)-silane (5.98 g, 76%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.18 (m, 5H), 5.38 (t, *J* = 1.2, 1H), 3.63 (t, *J* = 6.6, 2H), 3.40 (d, *J* = 7.3, 2H), 2.11 (t, *J* = 7.2, 2H), 1.75 (s, 3H), 1.69 (m, 2H), 0.92 (s, 9H), 0.06 (s, 6H).

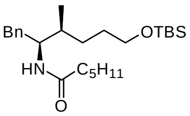
6-(*tert*-Butyldimethylsilanyloxy)-(3*S*)-methyl-1-phenylhexan-(2*R*)-ol (13)



13

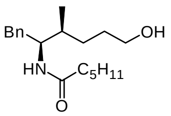
To *tert*-Butyldimethyl-(4-methyl-6-phenylhex-4-enyloxy)silane (0.200 g, 0.656 mmol) in THF (10 mL) at 0 ºC was added diborane (1.0 M in THF, 1.97 mL, 1.97 mmol). The reaction was allowed to stir for 3 h, then quenched at 0 ºC with water (2 ml) followed by 20% aqueous NaOH (1 ml), 30% aqueous hydrogen peroxide solution (1 ml) and saturated Na_2SO_3 (2 ml). The reaction mixture was stirred for an addition hour, then was extracted with ethyl acetate, washed with saturated NaCl (2x 10 mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified by column chromatography (20% EtOAc in hexanes) to afford 6-(*tert*-butyldimethylsilanyloxy)-(3*S*)-methyl-1-phenyl-hexan-2R-ol (0.171 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.22 (m, 5H), 3.63 (m, 3H), 2.89 (dd, *J* = 10.5, 3.1, 1H), 2.58 (dd, *J* = 9.7, 3.8, 1H), 1.67-1.50 (m, 3H), 1.26 (m, 2H), 1.02 (d, *J* = 6.7, 3H), 0.91 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 129.4, 128.6, 126.4, 76.7, 63.6, 40.1, 38.2, 30.5, 28.3, 26.1, 18.4, 15.5, -5.13; HRMS EI calcd for $C_{15}H_{25}O_2Si$ (M-40) 265.1623, found 265.1628.

Hexanoic acid [1-benzyl-5-(*tert*-butyldimethylsilanyloxy)-(2*S*)-methylpentyl]amide



To 6-(*tert*-butyldimethylsilanyloxy)-(3*S*)-methyl-1-phenylhexan-(2*R*)-ol (0.620 g, 1.92 mmol) in CH_2Cl_2 (10 mL) at 0 ºC were added methanesulfonyl chloride (0.330 g, 2.88 mmol) and triethyl amine (0.778 g, 7.69 mmol). The reaction mixture was stirred for 3 h at room temperature, and was then quenched with water. The reaction mixture was extracted with CH_2Cl_2, and then the organic layer was washed with water and saturated NaCl, dried (Na_2SO_4) and concentrated. The resulting residue was dissolved in DMF (10 mL), sodium azide (9.24 g, 14.2 mmol) was added and the reaction mixture was stirred at 55 ºC for 12 h. The reaction mixture was quenched with water and extracted with hexanes. The organic layer was washed with saturated NaCl, dried (Na_2SO_4), and concentrated. The resulting residue was then dissolved in THF (10 mL) at 23 ºC under N_2 and triphenylphosphine (0.299 g, 1.14 mmol) was added. The reaction mixture was allowed to stir for 18 h then was quenched with water (1 mL). The reaction mixture was then allowed to stir for an additional 18 h. The temperature was decreased to 0 ºC and hexanoyl chloride (0.192 g, 1.42 mmol) and triethylamine (0.192 g, 1.90 mmol) were added. After 1 hour the reaction mixture was quenched with water and extracted with ethyl acetate. The organic layer was washed with saturated NaCl (2x 10 mL), dried (Na_2SO_4) and concentrated. The crude product was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product (0.399 g, 61%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.17 (m, 5H), 5.19 (d, *J* = 9.4, 1H), 4.26 (m, 1H), 3.56 (m, 2H), 2.75 (m, 2H), 2.35 (t, *J* = 7.5, 2H), 2.07 (m, 2H), 1.53-1.18 (m, 9H), 0.88 (m, 12H), 0.05 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 138.5, 129.1, 128.4, 126.4, 63.3, 53.3, 38.5, 37.1, 35.1, 31.4, 30.5, 29.8, 26.0, 25.5, 22.4, 14.6, 14.0, -5.17; IR (neat) 3437, 2958, 2934, 2859, 2253, 1663, 1508, 1465, 1386, 1259, 1097, 906 cm^{-1}; HRMS (EI), (M-57) calcd for $C_{21}H_{36}NO_2Si$ 362.2515, found 362.2520.

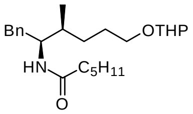
Hexanoic acid (1-benzyl-5-hydroxy-(2S)-methylpentyl)amide (14)



14

To hexanoic acid [1-benzyl-5-(*tert*-butyldimethylsilanyloxy)-(2*S*)-methylpentyl]amide (0.244 g, 0.581 mmol) at 23 ºC in THF (10 mL) was added tetrabutlylammonium fluoride hydrate (0.228 g, 0.872 mmol). The reaction mixture was stirred for 12 h, and then quenched with saturated NH_4Cl (2 mL), extracted with ethyl acetate, dried (Na_2SO_4) and concentrated. The resulting residue was purified by column chromatography (50% EtOAc in hexanes) to afford the desired product (0.170 g, 96%): ^1H NMR (300 MHz, $CDCl_3$) δ 7.27-7.14 (m, 5H), 5.55 (d, *J* = 9.4, 1H), 4.31 (m, 1H), 3.72 (m, 3H), 3.54 (m, 2H), 2.72 (m, 2H), 2.06 (m, 2H), 1.83 (m, 3H), 1.57-1.44 (m, 6H), 1.23-1.15 (m, 4H), 0.92 (d, *J* = 6.8, 3H), 0.83 (t, *J* = 7.3, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.1, 138.4, 129.1, 129.0, 128.4, 126.4, 62.8, 52.7, 38.7, 37.0, 35.5, 31.3, 30.4, 29.9, 25.5, 22.4, 14.5, 13.9; IR (neat) 3286, 3070, 2933, 2873, 1638, 1544, 1453, 1062, 735, 696 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{24}NO_2$ (M-91) 214.1807, found 214.1812.

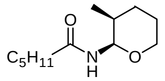
Hexanoic acid [1-benzyl-2-methyl-5-(tetrahydropyran-2-yloxy)pentyl]amide (14a)



14a

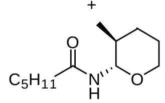
To hexanoic acid (1-benzyl-5-hydroxy-(2*S*)-methylpentyl)amide (0.178 g, 0.583 mmol) at 0 ºC in CH_2Cl_2 (10 mL) was added dihydropyran (0.0732 g, 0.871 mmol) and *p*-toluenesulfonic acid (0.133 g, 0.699 mmol). The reaction mixture was stirred for 12 h, then diluted with ether (15 mL), washed with $NaHCO_3$ (2 x 15 mL) and saturated NaCl (2 x 15 mL), dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to provide the desired product (0.137 g, 60%): ^1H NMR (30 MHz, $CDCl_3$) δ 7.24-7.16 (m, 5H), 5.62 (d, *J* = 9.2, 1H), 4.52 (bs, 1H), 4.25 (bs, 1H), 3.82 (m, 1H), 3.68 (m, 1H), 3.47 (m, 1H), 3.32 (m, 1H), 2.75 (m, 2H), 2.06 (m, 2H), 1.51 (m, 12H), 1.19 (m, 4H), 0.93 (d, *J* = 6.8, 3H), 0.84 (t, *J* = 6.9, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4, 128.8, 128.0, 125.9, 98.62, 98.56, 67.34, 62.07, 60.13, 54.00, 52.99, 38.22, 36.62, 35.06, 31.08, 30.51, 29.95, 27.11, 25.30, 25.24, 22.16, 20.78, 19.44, 15.83, 14.27, 13.95, 13.70; IR (neat) 3291, 3065, 3025, 2922, 2867, 1635, 1544, 1453, 1136, 1029; HRMS (EI) calcd for $C_{24}H_{39}NO_3$ 389.2929, found 389.2937.

Hexanoic acid ((3*S*)-methyl-tetrahydropyran-2-yl)amide (15a,b)



15a

+

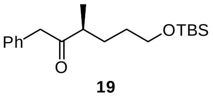


15b

Hexanoic acid (1-benzyl-5-hydroxy-(2*S*)-methylpentyl)amide (0.016g, 0.053 mmol) was subjected to both standard ETIC reaction conditions. The reaction mixture was filtered, concentrated, and purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product as a separable mixture of diastereomers (0.008 g, 75%): **Hexanoic acid ((3S)-methyltetrahydropyran-2S-yl)amide (15a)** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.96 (bd, *J* = 7.65, 1H), 5.31 (dd, *J* = 3.1, 6.0, 1H), 3.85 (m, 1H), 3.67 (m, 1H), 2.21 (t, *J* = 7.4, 2H), 1.98-1.31 (m, 13H), 0.97 (d, *J* = 6.9, 3H), 0.90 (t, *J* = 1.7, 3H); ^{1}H NMR (330MHz, $CDCl_3$, D_2O) δ 5.31 (d, *J* = 2.4, 1H), 3.85 (m, 1H), 3.67 (m, 1H), 2.21 (t, *J* = 7.4, 2H), 1.98-1.31 (m, 13H), 0.97 (d, *J* = 6.9, 3H), 0.90 (t, *J* = 1.7, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 79.1, 65.7, 37.1, 36.39, 31.92, 31.61, 29.0, 25.4, 22.5, 21.8, 14.1, 13.1; IR (neat) 3440, 2954, 2851, 1655, 1466, 1075, 997, 731 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{23}NO_2$ 213.1728, found 213.1731. **Hexanoic acid ((3*S*)-methyltetrahydropyran-2*R*-yl)amide (15b)** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.75 (bs, 1H), 4.79 (t, *J* = 9.5, 1H), 3.00 (m, 1H), 3.57 (m, 1H), 2.20 (t, *J* = 7.15, 2H), 1.90 (m, 1H), 1.63-1.26 (m, 12H), 0.89 (m, 6H)); ^{1}H NMR (330MHz, $CDCl_3$, D_2O) δ 4.79 (d, *J* = 9.3, 1H), 3.00 (m, 1H), 3.57 (m, 1H), 2.20 (t, *J* = 7.15, 2H), 1.90 (m, 1H), 1.63-1.26 (m, 12H), 0.89 (m, 6H)); ^{13}C NMR (75MHz, $CDCl_3$) δ 173.3, 82.9, 67.8, 37.1, 36.4, 32.1, 31.6, 26.0, 25.4, 22.5, 17.4, 14.1.

Hexanoic acid (1-benzyl-5-hydroxypentyl)amide (0.064 g, 0.212 mmol) was subjected to catalytic aerobic cyclization conditions. The reaction mixture was filtered, concentrated, and purified by flash chromatography (70% EtOAc in hexanes) to provide the desired product (0.032 g, 72%)

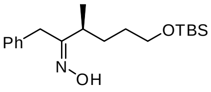
6-(*tert*-Butyldimethylsilanyloxy)-3*S*-methyl-1-phenylhexan-2-one (19)



19

To a solution of DMSO (0.242 g, 3.10 mmol) and oxallyl chloride (0.243 g, 1.86 mmol) in CH_2Cl_2 at –78 °C was added 6-(*tert*-butyldimethylsilanyloxy)-(3*R*)-methyl-1-phenylhexan-(2*R*)-ol (0.200g, 0.620 mmol). The reaction mixture was stirred at –78 °C for 30 min. before triethylamine (0.313 g, 3.10 mmol) was added. The reaction mixture was warmed to room temperature, quenched with water, washed with saturated NaCl (2 x 15 mL), dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (10% EtOAc in hexanes) to yield the desired product (0.147 g, 74%): ^1H NMR (300 Mhz, $CDCl_3$) δ 7.29-7.20 (m, 5H), 3.72 (s, 2H), 3.53 (t, *J* = 5.9, 2H), 2.67 (m, 1H), 1.69 (m, 1H), 1.40 (m, 3H), 1.07 (d, *J* = 6.9, 3H), 0.08 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 211.9, 134.4, 129.7, 128.8, 127.1, 63.0, 48.5, 45.4, 30.4, 29.3, 26.1, 18.5, 16.6, 0.21, -5.08; IR (neat) 2930, 1716, 1459, 1246, 1101, 832, 770, 696 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{32}O_2Si$ 320.2171, found 320.2156.

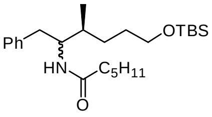
6-(*tert*-Butyldimethylsilanyloxy)-3*S*-methyl-1-phenylhexan-2-one oxime (20)



20

To 6-(*tert*-butyldimethylsilanyloxy)-(3*S*)-methyl-1-phenylhexan-2-one (0.147 g, 0.458 mmol) in EtOH (5 mL) at 23 °C were added ammonium hydroxide hydrochloride (0.063 g, 0.917 mmol) and sodium acetate (0.150 g, 1.83 mmol). A white precipitate was immediately observed. The reaction mixture was stirred for 1 h, then quenched with water, extracted with CH_2Cl_2, dried ($NaSO_4$) and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to yield the desired product (0.134 g, 88%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.21 (m, 5H), 3.72 (s, 2H), 3.51 (m, 2H), 3.27 (m, 1H), 2.37 (m, 1H), 1.43-1.39 (m, 3H), 1.02 (dd, *J* = 6.9, 7.5, 3H), 0.88 (s, 9H), 0.01 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 129.4, 129.1, 128.6, 128.5, 126.7, 126.4, 106.5, 63.1, 38.3, 37.4, 32.3, 32.0, 31.0, 30.6, 30.5, 30.0, 26.1, 18.5, 17.5, 0.21, -5.08; IR (neat) 3260, 3075, 2924, 1462, 1247, 1096, 946, 838, 778, 696 cm^{-1}; HRMS (EI) calcd for $C_{19}H_{33}NO_2Si$ 335.2280, found 335.2283.

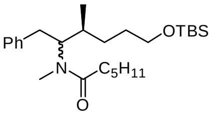
Hexanoic acid [1-benzyl-5-(tert-butyldimethylsilanyloxy)-(2*S*)-methylpentyl]amide



To a suspension of nickel chloride (0.311 g, 2.39 mmol) in ether (10 mL) at 23 °C was added lithium aluminum hydride (0.091 g, 2.39 mmol). A black precipitate formed immediately and the reaction mixture was stirred for 5 minutes before 6-(*tert*-butyldimethylsilanyloxy)-3*R*-methyl-1-phenylhexan-2-one oxime (0.134 g, 0.399 mmol) was added. The reaction mixture was stirred for 10 minutes, then quenched with water (3 mL), filtered over celite, washed with CH_2Cl_2 (2 x 15 mL) and methanol (2 x 15 mL). The filtrate was made basic by the addition of 15 % NaOH, then extracted in CH_2Cl_2 and washed with saturated NaCl (2 x 15 ml), dried ($NaSO_4$) and concentrated. The resulting residue was dissolved in THF

(10 mL) and at 0 °C under N_2 hexanoyl chloride (0.085 g, 0.599 mmol) and triethylamine (0.278 g, 1.99 mmol) were added. The reaction mixture was stirred for 1 h, then quenched with water, washed with NaCl, dried ($NaSO_4$) and concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to yield the desired product (0.105 g, 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.19 (m, 5H), 5.13 (d, *J* = 9.2, 1H), 4.24 (m, 1H), 3.58 (m, 2H), 2.91-2.72 (m, 2H), 2.35 (t, *J* = 7.5, 2H), 2.06 (m, 2H), 1.69-1.20 (m, 10H), 0.90 (m, 12H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 138.6, 129.3, 129.2, 128.6, 126.5, 63.5, 63.4, 54.4, 53.4, 37.4, 37.2, 35.8, 35.2, 31.5, 31.4, 30.8, 30.6, 29.9, 28.4, 26.1, 25.6, 24.6, 22.6, 22.5, 16.4, 14.7, 14.1, 0.21, -5.02; IR (neat) 3290, 2954, 2855, 1724, 1643, 1544, 1458, 1380, 1251, 1088, 843, 774, 701; HRMS calcd for $C_{25}H_{46}NO_2Si$ 420.3297, found 420.3302.

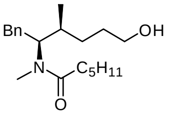
Hexanoic acid [1-benzyl-5-(*tert*-butyldimethylsilanyloxy)-(2)-methylpentyl]-methylamide



To a suspension of sodium hydride (60% dispersion in mineral oil, 0.234 g, 5.85 mmol) in DMF (20 mL) at 0 °C was added hexanoic acid [1-benzyl-5-(*tert*-butyldimethylsilanyloxy)-(2*S*)-methylpentyl]amide (0.338 g, 1.23 mmol). The reaction mixture was stirred for 30 minutes then methyl iodide (1.75 g, 12.4 mmol) was added. The reaction mixture stirred for 12 h then was quenched with water (2 mL), extracted in EtOAc, washed with water and saturated NaCl, dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (0.193 g, 36%): ^{1}H NMR (30 MHz, $CDCl_3$) δ 7.27-7.06 (m, 5H), 3.68 (m, 2H), 3.55 (m, 1H), 3.03 (m, 1H), 2.84 (s, 3H), 2.66 (m, 2H), 2.08 (m, 1H), 1.78-0.69 (m, 25H), 0.06 (s, 6H); HRMS (EI) (M- 57) calcd for $C_{22}H_{38}NO_2Si$ 376.2671, found 376.2670.

This procedure was repeated using a mixture of both hexanoic acid [1S-benzyl-5-(*tert*-butyldimethylsilanyloxy)-2S-methylpentyl]amide and hexanoic acid [1R-benzyl-5-(*tert*-butyldimethylsilanyloxy)-2S-methylpentyl]amide to yield the desired mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.23 (m, 5H), 3.62 (m, 2H), 3.01 (m, 1H), 2.97 (m, 1H), 2.83 (s, 3H), 2.61 (m, 4H), 2.25 (m, 1H), 2.01 (m, 2H), 1.70-0.67 (m, 22H), 0.03 (m, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.7, 139.1, 129.2, 129.1, 128.9, 128.7, 128.3, 126.7, 126.2, 65.2, 64.6, 63.5, 63.4, 36.5, 36.1, 35.8, 35.6, 35.4, 32.6, 31.7, 30.7, 30.3, 30.1, 29.9, 27.7, 26.1, 24.8, 24.6, 22.6, 22.5, 17.5, 16.7, 14.1, 0.21, -5.03.

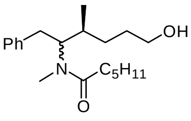
Hexanoic acid (1-benzyl-5-hydroxy-(2*S*)-methylpentyl)methylamide (17)



17

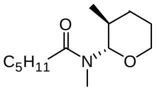
To hexanoic acid [1-benzyl-5-(*tert*-butyldimethylsilanyloxy)-(2*S*)-methylpentyl]methylamide (0.193 g, 0.671 mmol) at 23 ºC in THF (10 mL) was added tetrabutlylammonium fluoride hydrate (0.263 g, 1.00 mmol). The reaction mixture was stirred for 12 h, then quenched with saturated NH_4Cl (2 mL), extracted in ethyl acetate, dried (Na_2SO_4) and concentrated. The resulting residue was purified by column chromatography (50% EtOAc in hexanes) to afford the desired product (0.110 g, 78%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.06 (m, 5H), 3.74 (t, *J* = 6.2, 1H), 3.67 (t, *J* = 4.9, 1H), 3.55 (dt, *J* = 2.3, 8.2, 1H), 3.12 (dd, *J* = 4.8, 9.9, 1H), 3.03 (dd, *J* = 2.9, 11.1, 1H), 2.84 (s, 3H), 2.67 (s, 3H), 2.06 (m, 1H), 1.83-0.78 (m, 13H).

(17a)


17a

This procedure was repeated using a mixture of both hexanoic acid [1*S*-benzyl-5-(*tert*-butyldimethylsilanyloxy)-2*S*-methylpentyl]-methylamide and hexanoic acid [1R-benzyl-5-(*tert*-butyldimethylsilanyloxy)-2*S*-methylpentyl]methylamide to yield the desired mixture of diastereomers. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.27-7.05 (m, 5H), 3.72-3.49 (m, 3H), 3.12-2.99 (m, 2H), 2.83 (s, 3H), 2.64 (m, 5H), 2.10-2.00 (m, 3H), 1.77-0.79 (m, 16H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.2, 138.8, 129.0, 128.7, 128.6, 128.2, 126.6, 126.1, 65.2, 64.5, 62.8, 62.7, 60.5, 59.0, 36.3, 35.5, 33.8, 32.4, 31.5, 30.0, 29.8, 29.7, 29.2, 28.9, 25.8, 24.7, 24.5, 24.1, 22.4, 19.8, 16.3, 14.0, 13.7.

Hexanoic acid methyl-((3*S*)-methyltetrahydropyran-2*R*-yl)amide (18)

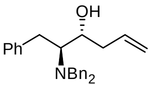

18

Hexanoic acid (1-benzyl-5-hydroxy-(2S)-methylpentyl)methylamide (0.036 g, 0.113 mmol) was subjected to standard ETIC reaction conditions. The reaction mixture was filtered, concentrated, and purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (0.011 g, 43%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.36 (d, *J* = 9.8, 1H), 4.45 (d, *J* = 9.4, 1H), 4.02 (m, 2H), 3.54 (m, 2H), 2.91 (d, *J* = 11.8, 3H), 2.31 (m, 3H), 1.99- 1.25 (m, 6H), 0.90 (m, 3H), 0.80 (m, 3H); ^{1}H NMR (300 MHz, DMSO, 378K) δ 4.85 (bs, 1H), 4.02 (m, 2H), 3.54 (m, 2H), 2.91 (d, *J* = 11.8, 3H), 2.31 (m, 3H), 1.99- 1.25 (m, 6H), 0.90 (m, 3H), 0.80 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.3, 90.9, 86.0, 68.5, 34.3, 33.7, 33.3, 32.5, 32.2, 31.9, 26.4, 26.1, 25.4, 22.7, 17.0, 16.7, 14.1; IR (neat) 2952, 2853, 1654, 1456, 1073, 1005; HRMS (EI) calcd for $C_{13}H_{25}NO_2$ 227.1885, found 227.1891.

To hexanoic acid (1-benzyl-5-hydroxy-(2S)-methylpentyl)methylamide (0.036 g, 0.113 mmol) in acetonitrile (5 mL) and *tert*-butylbenzene (1 mL) in a borosilicate flask at 23 ºC were added *N*-methylquinolinium hexafluorophosphate (0.039 g, 0.136 mmol) and sodium bicarbonate (0.078 g, 0.929 mmol). The mixture was stirred for 3 h at 23 ºC while irradiating. The reaction mixture was filtered, concentrated, and purified by flash chromatography (50% EtOAc in hexanes) to provide the desired product (0.011 g, 43%).

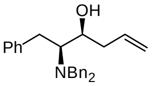
Hexanoic acid (1-benzyl-5-hydroxy-(2S)-methylpentyl)methylamide (0.064 g, 0.212 mmol) was subjected to catalytic aerobic ETIC reaction conditions. The reaction mixture was filtered, concentrated, and purified by flash chromatography (90% EtOAc in hexanes) to provide the desired product as seperable mixture of diastereomers (0.032 g, 72%).

2-Dibenzylamino-1-phenylhex-5-en-3-ol (22)



22a

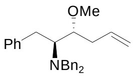
+



22b

To a solution of potassium carbonate (18.28 g, 132.2 mmol) and sodium hydroxide (5.281 g, 132.2 mmol) in water (100 mL) at 23 °C was added L-phenylalanine (10.00 g, 66.13 mmol). Benzyl bromide (33.92 g, 198.3 mmol) was added drop wise to the reaction mixture over a period of one hour while refluxing. The reaction mixture was refluxed for 1 h, cooled and the organic layer was separated, washed with saturated NaCl and dried ($MgSO_4$) and concentrated. The resulting residue was dissolved in ether (10 mL) and added drop wise to a suspension of $LiAlH_4$ (95% dispersion in mineral oil, 0.6822 g, 17.08 mmol) at 0°C under N_2 in ether (60 mL). The reaction mixture was stirred at 23 °C for 2 h, then quenched with water (1 mL), 15% NaOH (3mL), water (3 mL) and filtered. The filtrate was washed with saturated NaCl, dried ($MgSO_4$), concentrated, and placed under vacuum at 40 °C for 16 h. The resulting residue was added to solution of DMSO (2.444 g, 31.31 mmol) and oxalyl chloride (2.0M solution in CH_2Cl_2, 7.826 ml, 15.65 mmol) at –78 °C in CH_2Cl_2. The reaction mixture was allowed to stir for 30 minutes before. The reaction mixture was stirred for 2 h at –78 °C, then quenched with triethyl amine (7.199 g, 71.15 mmol), warmed to 23 °C, quenched with water (2 mL), extracted in CH_2Cl_2, washed with water, saturated NaCl, dried ($MgSO_4$), and concentrated. The resulting residue was dissolved in ether (50 mL) and added to a solution of allyl magnesium bromide (1.0M in ether, 42.69 mL, 42.69 mmol) at –78 °C under N_2. The reaction mixture was stirred for 1.5 h, then quenched with saturated NH_4Cl, extracted with EtOAc, washed with water (2 x 15 mL), saturated NaCl, dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes). The mixture of diastereomers was separated during the purification process. **2-Dibenzylamino-1-phenylhex-5-en-(3*S*)-ol (22a)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.20 (m, 15H), 5.69 (m, 1H), 5.08 (m, 2H), 3.87 (m, 1H), 3.76 (m, 4H), 3.01 (m, 3H), 2.48 (m, 1H), 2.14 (m, 1H), 1.86 (bs, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) 141.1, 139.9, 135.4, 129.6, 128.6, 128.5, 127.1, 126.0, 118.2, 70.9, 63.2, 55.0, 40.0, 32.3. **2-Dibenzylamino-1-phenylhex-5-en-(3*R*)-ol (22b)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.22 (m, 5H), 5.77 (m, 1H) 4.96 (m, 2H), 4.36 (m, 1H), 3.97 (d, *J* = 13.2, 2H), 3.68 (dt, *J* = 5.3, 3.07 1H), 3.43 (d, J = 13.3, 2H), 3.15-2.73 (m, 3H), 2.23 (m, 1H), 1.94 (m, 1H).

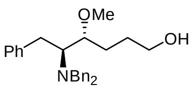
Dibenzyl-(1-benzyl-2-methoxypent-4-enyl)amine



To a suspension of NaH (60% dispersion in mineral oil, 0.251 g, 6.29 mmol) in DMF

(30 mL) at 0 ºC was added 2-Dibenzylamino-1-phenylhex-5-en-(3S)-ol (0.668 g, 1.79 mmol). The reaction mixture was stirred for 30 minutes then methyl iodide (1.27 g, 8.99 mmol) was added. The reaction mixture was quenched after 1.5 h with ice chips, extracted with hexanes, washed with saturated NaCl, dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to provide the desired product, dibenzyl-(1-benzyl-2S-methoxypent-4-enyl)amine (0.652 g, 94%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44-7.16 (m, 15H), 5.38 (m, 1H), 4.82 (m, 2H), 4.23 (d, *J* = 13.5, 2H), 3.58 (d, *J* = 13.6, 2H), 3.32 (s, 3H), 3.12-2.90 (m, 3H), 2.47 (m, 2H);); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 140.8, 136.1, 129.4, 129.4, 128.5, 128.4, 128.3, 126.9, 125.9, 116.2, 82.6, 61.4, 58.4, 55.7, 35.5, 30.1; IR (neat) 3058, 3027, 2920, 2817, 1952, 1879, 1806, 1643, 1595, 1496, 1449, 1372, 1096, 903, 744, 701; HRMS (EI) cacld for 384.2327, found 384.2333. **Dibenzyl-(1-benzyl-2R-methoxypent-4-enyl)-amine:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.09 (m, 15H), 5.58 (m, 1H), 4.91 (m, 2H), 3.82 (d, *J* = 14.0, 2H), 3.54 (bd, *J* = 13.9, 3H), 3.37 (s, 3H), 2.97 (m, 3H), 2.41 (m, 1H), 2.20 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 134.9, 129.8, 128.9, 128.1, 126.7, 125.8, 117.5, 80.7, 61.0, 57.0, 54.4, 36.4, 32.0.

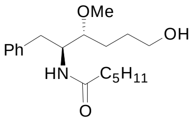
5S-Dibenzylamino-4-methoxy-6-phenylhexan-1-ol (23)



23

To Dibenzyl-(1-benzyl-2S-methoxypent-4-enyl)amine (0.652 g, 1.69 mmol) in THF (20 mL) at 0 ºC was added BH_3 (1.0 M in THF, 5.07 mL, 5.07 mmol). The reaction was allowed to stir for 1 h, then quenched at 0 ºC with water (2 mL) followed by 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide solution (1 mL) and saturated Na_2SO_3 (2 mL). The reaction mixture was stirred for an addition hour, then was extracted with ethyl acetate, washed with saturated NaCl, dried ($MgSO_4$) and concentrated. The resulting residue was purified by column chromatography (30% EtOAc in hexanes) to afford the desired product, 5S-Dibenzylamino-4S-methoxy-6-phenyl-hexan-1-ol (0.500 g, 73%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.18 (m, 15H), 4.18 (d, *J* = 13.38, 2H), 3.55 (d, *J* = 13.34, 2H), 3.40 (m, 3H), 3.28 (s, 3H), 3.12 (m, 2H), 2.99 (m, 2H), 1.82 (m, 1H), 1.64 (m, 1H), 1.14 (m, 1H), 0.99 (m, 1H), 0.72 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.1, 129.5, 129.4, 128.5, 128.4, 126.9, 125.9, 82.3, 63.2, 60.5, 57.8, 55.7, 30.2, 29.0, 25.6; IR (neat) 3359, 3058, 3023, 2933, 2821, 1961, 1879, 1806, 1604, 1501, 1458, 1367, 1096, 744, 705; HRMS (EI) cacld for 402.2433, found 402.2422. **5S-Dibenzylamino-4*R*-methoxy-6-phenylhexan-1-ol:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.20 (m, 15H), 3.81 (d, *J* = 13.9, 2H), 3.66 (d, *J* = 14.0, 2H), 3.53 (m, 3H), 3.36 (s, 3H), 3.05-2.90 (m, 3H), 1.70 (m, 1H), 1.56 (m, 3H), 1.32 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 140.2, 129.6, 128.8, 128.1, 126.7, 125.7, 81.4, 62.9, 61.1, 56.9, 54.5, 32.2, 28.5, 27.4.

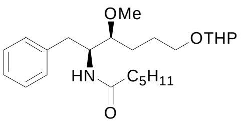
Hexanoic acid (1-benzyl-5-hydroxy-2-methoxypentyl)amide (24)



24

To 5S-dibenzylamino-4*S*-methoxy-6-phenyl-hexan-1-ol (0.553 g, 1.37 mmol) in CH_2Cl_2 at 0 ºC was added treithylamine (0.624 g, 6.17 mmol), pivaloyl chloride (0.331 g, 2.74 mmol), and DMAP (cat.). The reaction mixture was allowed to stir for 12 h, then was quenched with water, washed with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated. The resulting residue was dissolved in EtOH (20 mL) at 23 ºC under N_2 and palladium (10% on carbon, 0.400g) and 1,4 cyclohexadiene (0.328 g, 4.10 mmol) were added. The reaction mixture stirred at 40 ºC for 12 h, filtered over celite, washed with EtOH, and concentrated. The resulting residue was dissolved in THF (10 mL) and triethylamine (0.083 g, 0.820 mmol) and hexanoyl chloride (0.055 g, 0.615 mmol) were added at 0 ºC under N_2. The reaction mixture was stirred for 1.5 h, then quenched with water, washed with saturated NaCl (2 x 15 mL), dried ($MgSO_4$) and concentrated. The resulting residue was dissolved in MeOH (5 mL) and Na (small piece) was added at 0 ºC under N_2. The reaction mixture was stirred at 40 ºC for 12 h, the quenched with water, concentrated, redissolved in EtOAc (25 mL), washed with NaCl, dried ($MgSO_4$), and concentrated. The resulting residue was purified by flash chromatography (50% acetone in hexanes) to yield the desired product (0.088 g, 49%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.21 (m, 5H), 5.73 (d, *J* = 9.26, 1H), 4.35 (m, 1H), 3.57 (m, 2H), 3.42 (s, 3H), 3.08 (t, *J* = 5.9, 1 H), 2.87 (dd, *J* = 4.9, 2.2, 2H), 2.14 (m, 2H), 1.91 (bs, 1H), 1.58-1.18 (m, 10H), 0.87 (t, *J* = 7.1, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 172.6, 138.3, 129.2, 128.5, 126.4, 80.2, 62.5, 57.8, 51.8, 38.4, 36.8, 31.3, 28.7, 26.2, 25.4, 22.4, 13.9; IR (neat) 3433, 3156, 2930, 2867, 1659, 1504, 1465, 1378, 1093, 906, 649. **Hexanoic acid (1-benzyl-5-hydroxy-2*R*-methoxypentyl)amide:** ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.19 (m, 5H), 5.57 (d, *J* = 8.9, 1H), 4.44 (m, 1H), 3.66 (m, 2H), 3.42 (s, 3H), 3.32 (m, 1H), 2.94 (dd, *J* = 5.0, 9.2, 1H), 2.80 (dd, *J* = 4.8, 9.4, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.0, 138.2, 129.2, 128.7, 126.6, 82.3, 62.7, 58.0, 51.5, 37.0, 35.4, 31.4, 28.7, 26.4, 25.5, 22.5, 14.1.

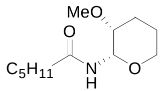
Hexanoic acid [1-benzyl-2-methoxy-5-(tetrahydropyran-2-yloxy)pentyl]amide (28)



28

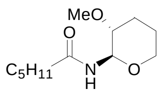
To hexanoic acid (1-benzyl-5-hydroxy-2*S*-methoxypentyl)amide (0.087 g, 0.273 mmol) in CH_2Cl_2 at 0 °C was added dihydropyran (0.115 g, 1.36 mmol) and pyridinium p-toluene sulfonic acid (cat.). The reaction mixture was stirred for 12 h, then diluted with ether (15 mL), washed with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to afford the desired product, hexanoic acid [1-benzyl-2*S*-methoxy-5-(tetrahydropyran-2-yloxy)-pentyl]-amide (0.062 g, 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.18 (m, 5H), 5.78 (d, *J* = 9.2, 1H), 4.51 (m, 1H), 4.31 (m, 1H), 3.28 (m, 1H), 3.67 (m, 1H), 3.44 (m, 1H), 3.42 (s, 3H), 3.30 (m, 1H), 3.12 (m, 1H), 2.87 (m, 2h), 2.14 (t, *J* = 2.1, 2 H), 1.66-1.48 (m, 16H), 0.89 (t, *J* = 6.8, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.9, 138.6, 129.4, 128.6, 126.5, 98.9, 79.9, 67.4, 62.4, 58.2, 52.2, 38.6, 37.0, 31.5, 30.8, 27.2, 25.8, 25.7, 22.5, 19.8, 14.1; HRMS (EI) calcd for $C_{19}H_{31}NO_3$ 321.2303, found 321.3214.

Hexanoic acid (3-methoxytetrahydropyran-2-yl)amide (25)



25a

+



25b

Hexanoic acid (1-benzyl-5-hydroxy-2S-methoxypentyl)amide (0.045 g, 0.139 mmol) was subjected to standard ETIC reaction conditions. The reaction mixture was filtered, concentrated, and purified by flash chromatography (50% acetone in hexanes) to provide the desired product as a separable mixture of diastereomers (0.001 g, 4%): **Hexanoic acid (3*S*-methoxytetrahydropyran-2*R*-yl)amide (25a)** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.88 (bd, *J* = 7.4, 1H), 4.96 (dd, *J* = 8.5, 8.55, 1H), 3.88 (m, 1H), 3.55 (dt, *J* = 2.7, 8.8, 1H), 3.36 (s, 3H), 3.02 (m, 1H), 2.23 (t, *J* = 7.4, 2H), 1.69-1.26 (m, 10H), 0.88 (m, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.3, 82.9, 67.8, 37.1, 36.4, 32.1, 31.6, 29.9, 26.0, 25.4, 22.6, 17.4, 14.1; IR (neat) 3431, 2952, 2930, 2848, 1683, 1504, 1463, 1382, 1211, 1092, 1070, 1044, 907; HRMS (EI), (M-32) calcd for $C_{11}H_{19}NO_2$ 197.1415, found 197.1420. **Hexanoic acid (3*S*-methoxytetrahydropyran-2*S*-yl)amide (25b)**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.54 (d, *J* = 7.9, 1H), 5.19 (dd, *J* = 1.5, 7.8, 1H), 3.94 (m, 1H), 3.62 (dt, *J* = 2.2, 9.4, 2H), 3.40 (s, 3H), 3.28 (m, 1H), 2.21 (t, *J* = 7.8, 2H), 1.64-1.25 (m, 10H), 0.91 (t, *J* = 6.5, 3H); ^{13}C NMR ($CDCl_3$) δ 173.2, 75.2, 66.8, 56.7, 36.9, 31.6, 29.9, 25.3, 25.0, 22.6, 19.9, 14.1.

The cyclization reaction was repeated using the various conditions shown in Table 1.6.

Table 1.6: ETIC conditions with varying base and solvent

Solvent	Base	Time	Yield	D.R
DCE	2, 6-dichloropyridine	5 h	21	100:0
MeCN	2,6-dichloropyridine	5 h	38	3:1
MeCN	$NaHCO_3$	5 h	5	100:0

The cyclization reaction was repeated with hexanoic acid [1-benzyl-2-methoxy-5-(tetrahydropyran-2-yloxy)pentyl]amide (**28**) using the various reaction conditions shown in Table 1.7.

Table 1.7: ETIC conditions with variation in aromatic cosolvent

SOLVENT	BASE	COSENSITIZER	TIME	YIELD	D.R
DCE	NaOAc	tert-Butylbenzene	2.5	18	1:1
DCE	NaOAc	Benzene	1.5	25	2:1

Hexanoic acid [1-benzyl-2-methoxy-5-(tetrahydropyran-2-yloxy)pentyl]amide **(28)** (0.040 g, 0.0.098 mmol) was subjected to catalytic aerobic ETIC reaction conditions. The reaction mixture was filtered, concentrated and purified by flash chromatography (70% EtOAc in hexanes) to afford the desired product as a mixture of diastereomers, hexanoic acid (3-methoxytetrahydropyran-2-yl)amide (0.007 g, 30%), as well as **4-(tetrahydropyran-2-yloxy)butyric acid methyl ester (33)** (0.0037 g, 0.0183 mmol) ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (t, *J* = 2.7, 1H), 3.83-

3.72 (m, 2H), 3.67 (s, 3H), 3.51-3.39 (m, 2H), 2.42 (dt, *J* = 1.5, 7.5), 1.94 (m, 2H), 1.81-1.49 (m, 6H); ^{13}C NMR ($CDCl_3$) δ 174.1, 129.6, 129.1, 128.5, 127.8, 98.8, 66.4, 62.2, 51.6, 44.5, 37.5, 31.3, 31.1, 30.7, 25.5, 25.2, 23.9, 22.5, 19.5, 14.0; IR 2990, 1794, 1651, 1469, 1382, 1097, 913; HRMS (EI) (M - 84) calcd for 117.0551, found 117.0553.

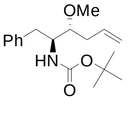
The cyclization reaction was repeated using the various conditions shown in Table 1.8.

Table 1.8: Catalytic aerobic ETIC conditions

Solvent	**Base**	**Cosensitizer**	**Time**	**Yield**	**D.R**
*DCE	NaOAc	Benzene	3	6	100:0
DCE	2,6-dichloropyridine	Toluene	2	33	2.5:1

* Molecular sieves were added to the reaction mixture

(1-Benzyl-2-methoxypent-4-enyl)carbamic acid *tert*-butyl ester (30a)

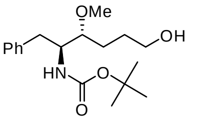


30a

To a suspension of lithium aluminum hydride (1.31 g, 36.3 mmol) refluxing in THF under N_2 L-phenylalanine (3.00 g, 18.1 mmol) was added in small portions. The reaction mixture was stirred for 12 h, then cooled to 0 ºC and quenched with water (1 mL), NaOH, 15%, 1.5 mL), water (5 mL), and di-*tert*-butyl-dicarbonate (in 20 mL of CH_2Cl_2, 3.95 g, 18.2 mmol) was added. The reaction was stirred at 60 ºC for 12 h, cooled and filtered through a pad of Na_2SO_4. The resulting residue was added to a solution of oxalyl chloride (2.0 M in CH_2Cl_2, 6.97 mL, 13.9 mmol) and DMSO (1.23 g, 15.9 mmol) in CH_2Cl_2 at -78 ºC under N_2. The reaction mixture was stirred for 1 h, then quenched with triethylamine (4.02 g, 39.8 mmol), warmed to room temperature, quenched with water, extracted with CH_2Cl_2, washed with saturated NaCl, dried ($MgSO_4$) and concentrated. The resulting residue was dissolved in THF

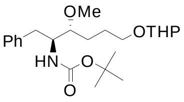
(30 mL) and vinyl magnesium bromide (1.0 M in THF, 23.8 mL, 23.8 mmol) was added at 0 ºC under N_2. The reaction was stirred for 12 h, then quenched with saturated NH_4Cl, acidified to pH 4.0, extracted with EtOAc, dried (Na_2SO_4) and concentrated. The resulting residue was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.065 g, 1.61 mmol) in DMF (10 mL) at 0 ºC under N_2. The reaction mixture was stirred for 30 minutes, and then methyl iodide (1.14 g, 8.06 mmol) was added. The reaction mixture was stirred for 3 h, then quenched with water, washed with saturated NaCl, dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash chromatography (10% EtOAc in hexanes) to afford the desired product as a separable mixture of diastereomers (0.237 g, 54%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.20 (m, 5H), 5.66 (m, 1H), 5.30 (m, 2H), 4.89 (d *J* = 9.6, 1H), 3.93 (m, 1H), 3.36 (s, 3H), 3.07 (m, 1H), 2.82 (m, 2H), 2.33 (m, 1H), 2.14 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.4, 138.4, 133.9, 129.1, 128.2, 126.0, 117.5, 79.5, 78.7, 57.6, 53.3, 38.7, 34.7, 28.2; IR (neat) 3440, 3341, 3062, 2980, 2924, 1698, 1496, 1440, 1363, 1238, 1169, 1096.

(1-Benzyl-5-hydroxy-2-methoxypentyl)carbamic acid *tert*-butyl ester



To (1-benzyl-2-methoxypent-4-enyl)carbamic acid *tert*-butyl ester (0.437 g, 1.43 mmol) in THF (10 mL) at 0 ºC was added BH_3 (1.0 M in THF, 4.30 mL, 4.30 mmol). The reaction was allowed to stir for 1 h, then quenched at 0 ºC with water (2 mL) followed by 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide solution (1 mL) and saturated Na_2SO_3 (2 mL). The reaction mixture was stirred for an addition hour, then was extracted with ethyl acetate, washed with saturated NaCl (2x 10 mL), dried ($MgSO_4$) and concentrated. The resulting residue was purified by column chromatography (30% EtOAc in hexanes) to afford the desired product (0.302 g, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.15 (m, 5H), 4.83 (d, *J* = 9.5, 1H), 3.93 (m, 1H), 3.57 (m, 2H), 3.55 (s, 3H), 3.02 (m, 1H), 2.80 (m, 2H), 1.79 (bs, 1H), 1.62-1.44 (m, 4H), 1.36 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.7, 129.4, 128.6, 126.4, 80.4, 79.4, 62.7, 57.9, 53.6, 38.8, 28.9, 28.5, 26.2; IR (neat) 3445, 3346, 2978, 2930, 2871, 1695, 1497, 1366, 1172, 1069; HRMS (EI) calcd for $C_{18}H_{30}NO_4$ 324.2174, found 324.2177.

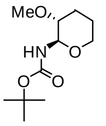
[1-Benzyl-2-methoxy-5-(tetrahydropyran-2-yloxy)pentyl]carbamic acid *tert*-butyl ester (31)

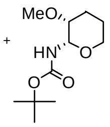


31

To **(**1-benzyl-5-hydroxy-2-methoxypentyl)carbamic acid *tert*-butyl ester (0.200 g, 0.618 mmol) in CH_2Cl_2 at 0 °C was added dihydropyran (0.078 g, 0.927 mmol) and pyridinium p-toluene sulfonic acid (0.199 g, 0.742 mmol). The reaction mixture was stirred for 12 h, then diluted with ether (15 mL), washed with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product, [1-benzyl-2-methoxy-5-(tetrahydropyran-2-yloxy)-pentyl]carbamic acid tert-butyl ester, (0.228 g, 91%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 155.8, 139.2, 138.8, 129.4, 129.2, 129.1, 128.5, 128.4, 128.3, 126.3, 126.1, 99.0, 83.2, 82.4, 80.1, 79.3, 67.6, 67.4, 62.4, 58.5, 58.1, 53.8, 38.8, 35.4, 35.1, 30.8, 28.5, 27.0, 25.8, 25.7, 19.7.

(3-Methoxytetrahydropyran-2-yl)carbamic acid *tert*-butyl ester (32a,b)


32a

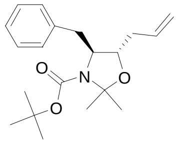

32b

[1-Benzyl-2-methoxy-5-(tetrahydropyran-2-yloxy)pentyl]carbamic acid tert-butyl ester (0.055 g, 0.135 mmol) was subjected to standard ETIC reaction conditions. The reaction mixture was filtered, concentrated, and purified by flash chromatography (30% acetone in hexanes) to provide the desired product as a separable mixture of diastereomers (0.011 g, 53%): **(3*S*-Methoxytetrahydropyran-2S-yl)carbamic acid *tert*-butyl ester (32a):** ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (bs, 1H), 4.90 (bd, *J* = 9.4, 1H), 3.93 (m, 1H), 3.53 (dt, *J* = 2.3, 9.48, 1H), 3.38 (s, 3H), 3.31 (m, 1H), 2.11 (m, 1H), 1.80-1.25 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 79.8, 75.5, 66.2, 56.7, 28.4, 25.5, 20.3; IR (neat) 3443, 3338, 2930, 1719, 1490, 1367, 1163, 1064, 984, 878 cm^{-1}.

(3*S*-Methoxytetrahydropyran-2*R*-yl)carbamic acid *tert*-butyl ester (32b): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.11 (bs, 1H), 4.66 (t, *J* = 8.4, 1H), 3.88 (m, 1H), 3.50 (dt, *J* = 2.2, 9.2, 1H), 3.38 (s, 3H), 2.98 (m, 1H), 2.22 (m, 1H), 1.68-1.44 (m, 12H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3, 83.0, 80.4, 66.5, 56.7, 29.9, 28.5, 24.8.

[1-Benzyl-2-methoxy-5-(tetrahydropyran-2-yloxy)pentyl]carbamic acid *tert*-butyl ester **(31)** (0.055 g, 0.135 mmol) was subjected to catalytic aerobic ETIC reaction conditions. The reaction mixture was filtered, concentrated and purified by flash chromatography (30% EtOAc in hexanes) to provide the desired product as a separable mixture of diastereomers.

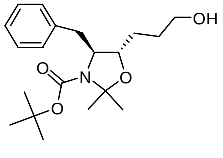
5R-Allyl-4S-benzyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (40)



40

To (1-benzyl-2R-hydroxypent-4-enyl)carbamic acid tert-butyl ester (1.25 g, 4.29 mmol) in toluene (15 mL) at 23 ºC was added 2,2-dimethoxypropane (5.36 g, 51.5 mmol) and pyridinium p-toluene sulfonic acid (cat.). The reaction mixture was stirred at 80 ºC for 3 h, then concentrated and purified by flash chromatography (5% EtOAc in hexanes) to afford the desired product (0.454 g, 32%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.19 (m, 5H), 5.55 (M, 1H), 4.93 (m, 2H), 3.95 (m, 2H), 3.85 (m,1H), 3.24 (dd, J = 2.6, 10.5, 1H), 2.85 (m, 1H), 2.11 (m, 2H), 1.62-1.25 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 137.9, 133.9, 130.0, 129.6, 128.5, 126.6, 117.7, 94.8, 93.9, 80.2, 79.0, 62.8, 40.0, 39.6, 38.9, 37.7, 28.7, 27.8, 27.2; IR (neat), 3066, 2976, 2929, 1703, 1376, 1260, 1174, 1083, 916, 705 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{24}NO_3$ 290.1756, found 290.1754.

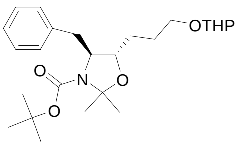
4S-Benzyl-5R-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester



To 5R-allyl-4S-benzyl-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (0.432 g, 1.30 mmol) in THF (10 mL) at 0 ºC was added BH_3 (1.0 M in THF, 3.91 mL, 3.91 mmol). The reaction was allowed to stir for 1 h, then quenched at 0 ºC with water (2 mL) followed by 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide solution (1 mL) and saturated Na_2SO_3 (2 mL). The reaction mixture was stirred for an additional hour, then was extracted with ethyl acetate, washed with saturated NaCl (2x 10 mL), dried ($MgSO_4$) and concentrated. The resulting residue was purified by column chromatography (20% EtOAc in hexanes) to afford the desired product (0.325 g, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.22

(m, 5H), 3.94 (m, 1H), 3.82 (m, 1H), 3.53 (m, 2H), 3.27 (dd, *J* = 2.5, 10.5, 1H), 2.83 (m, 1H), 1.78-1.29 (m, 19H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 137.7, 129.8, 129.4, 128.5, 126.6, 80.0, 79.3, 78.3, 63.7, 63.3, 62.5, 39.8, 37.4, 31.7, 31.0, 28.9, 28.5, 27.5, 26.9; IR (neat) 3457, 3065, 1683, 1493, 1477, 1457, 1398, 1176, 1085, 906, 728 cm^{-1}; HRMS (EI) calcd for $C_{20}H_{32}NO_4$ 350.2331, found 350.2336.

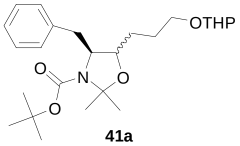
4-Benzyl-2,2-dimethyl-5-[3-(tetrahydropyran-2-yloxy)propyl]oxazolidine-3-carboxylic acid ***tert*-butyl ester (41)**



41

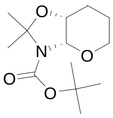
To (4S-Benzyl-5R-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (0.296 g, 0.845 mmol) in CH_2Cl_2 (15 mL) at 0 °C was added dihydropyran (0.106 g, 1.26 mmol) and pyridinium *p*-toluenesulfonic acid (cat.). The reaction mixture was stirred for 3 h, then concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford the desired product (0.2329 g, 90%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.23 (m, 5H), 4.52 (m, 1H), 3.82 (m, 1H), 3.63 (m, 1H), 3.50 (m, 1H), 3.25 (m, 1H), 2.86 (m, 1H), 1.72-1.30 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.5, 138.1, 129.8, 129.4, 128.6, 128.4, 126.6, 98.7, 79.9, 66.9, 63.7, 62.3, 39.9, 30.7, 28.6, 27.3, 25.7, 25.5, 19.6; IR (neat) 3025, 2938, 2863, 1691, 1453, 1390, 1255, 1176, 1116, 1077, 1029, 910, 732 cm^{-1}; HRMS (EI) calcd for $C_{25}H_{40}NO_5$ 434.2906, found 434.2896.

(41a)


41a

This procedure was repeated with a mixture of (4S-Benzyl-5R-(3-hydroxypropyl)2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester and (4S-Benzyl-5S-(3-hydroxypropyl)-2,2-dimethyloxazolidine-3-carboxylic acid *tert*-butyl ester (0.216 g, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.25-7.18 (m, 5H), 4.50 (m, 1H), 4.25 (m, 1H), 4.15 (m, 1H), 4.04 (m, 1H), 3.91 (m, 1H), 3.78 (m, 1H), 3.60 (m, 1H), 3.46 (m, 1H), 3.24 (m, 1H), 1.73-1.34 (m, 25H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.1, 151.8, 139.3, 138.0, 129.5, 129.4, 129.2, 128.5, 128.4, 128.3, 126.2, 126.0, 125.47, 98.8, 98.7, 92.8, 92.2, 80.0, 79.6, 77.5, 77.4, 67.1, 67.0, 62.3, 62.2, 62.1, 60.9, 60.7, 36.6, 36.0, 30.8, 30.79, 28.7, 28.5, 28.4, 28.1, 27.8, 27.6, 27.3, 26.8, 26.7, 26.4, 26.3, 25.8, 25.6, 25.0, 23.8, 21.6, 19.6, 19.5.

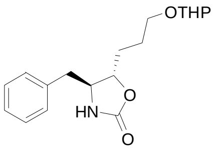
2,2-Dimethyl-tetrahydropyrano[2,3-d]oxazole-3-carboxylic acid *tert*-butyl ester (42)


42

4S-Benzyl-2,2-dimethyl-5R-[3-(tetrahydropyran-2-yloxy)propyl]oxazolidine-3-carboxylic acid *tert*-butyl ester (0.100 g, 0.230 mmol) was subjected to catalytic aerobic ETIC reaction conditions. The reaction mixture was filtered, concentrated and purified by flash chromatography (10% EtOAc in hexanes) to provide the desired product as a single diastereomer (0.503 g, 85%). ^{1}H NMR (300 MHz, $CDCl_3$, 323K) δ 5.15 (bs, 1H), 3.97 (m, 1H), 3.88 (m, 2H), 3.43 (dt, *J* = 2.8, 8.5, 2H), 2.13-2.08 (m, 2H), 1.95-1.38 (m, 17H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.9, 128.4, 100.2, 93.9, 83.2, 77.4, 71.2, 63.7, 31.5, 28.4, 24.8, 22.5, 19.7, 13.9; IR (neat) 2974, 2934, 2871, 1706, 1457, 1394, 1263, 1180, 1081, 1017 cm^{-1}; HRMS (EI) calcd for $C_{12}H_{20}NO_4$ 242.1392, found 242.1402.

This procedure was repeated with the mixture of 4S-Benzyl-2,2-dimethyl-5R-[3-(tetrahydropyran-2-yloxy)propyl]oxazolidine-3-carboxylic acid *tert*-butyl ester and 4S-Benzyl-2,2-dimethyl-5S-[3-(tetrahydropyran-2-yloxy)propyl]oxazolidine-3-carboxylic acid *tert*-butyl ester and the addition of 200 weight percent of $Na_2S_2O_3$ to yield a mixture of enantiomers of 2,2-dimethyl-tetrahydro-pyrano[2,3-d]oxazole-3-carboxylic acid *tert*-butyl ester (0.042 g, 88%).

4S-Benzyl-5S-[3-(tetrahydro-pyran-2-yloxy)propyl]oxazolidin-2-one (39)

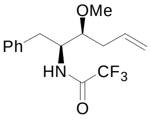


39

To trifluoroacetic acid (10 mL) at 0 °C was added (1-benzyl-2S-hydroxypent-4-enyl)-carbamic acid tert-butyl ester (0.410 g, 1.40 mmol). The reaction mixture was stirred for 15 minutes, and then concentrated. The resulting residue was redissolved in CH_2Cl_2, washed with saturated $NaHCO_3$, dried (Na_2SO_4) and concentrated. The resulting residue was dissolved in THF (10 mL) and carbonyl diimidazole (0.342 g, 2.11 mmol) and DMAP (cat.) were added. The reaction mixture was stirred for 12 h, quenched with water, extracted with EtOAc, washed with saturated NaCL (2 x 15 ml), dried (Na_2SO_4) and concentrated. The resulting residue was dissolved in THF (10 mL) and BH_3 (1.0 M in THF, 3.91 mL, 3.91 mmol) was added at 0 °C under N_2. The reaction was allowed to stir for 1 h, then quenched at 0 ºC with water (2 mL) followed by 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide solution (1 mL) and saturated Na_2SO_3 (2 mL). The reaction mixture was stirred for an addition hour, then was extracted with ethyl acetate, washed with saturated NaCl, dried ($MgSO_4$) and concentrated. The resulting residue was dissolved in CH_2Cl_2 (10 mL) and dihydropyran (0.0.091 g, 1.08mmol) and pyridinium p-toluene sulfonic acid (0.165 g, 0.869 mmol) were added at 0 °C under N_2. The reaction mixture was stirred for 3 h, then concentrated, redissolved in CH_2Cl_2, washed with saturated $NaHCO_3$, dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (40% EtOAc in hexanes) to yield the desired product (0.058 g, 25%): ^{1}H NMR (300 MHz, $CDCl_3$) δ7.35-7.17 (m, 5H), 5.12 (bs, 1H), 4.72 (m, 1H), 4.59 (m, 1H), 4.00 (m, 1H), 3.87 (m, 2H), 3.48 (m, 2H), 2.93 (dd, *J* = 3.4, 9.4, 1H), 2.69 (dd, *J* = 11.3, 13.0, 1H), 1.95-1.27 (m, 11H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.7, 136.7, 129.1, 127.2, 99.2, 79.8, 66.8, 62.6, 56.9, 36.3, 26.3, 25.5, 19.8; IR (neat) 3281, 2972, 2864, 1754, 1445, 1384, 1126, 1070, 1023, 984, 731, 696 cm^{-1}.

To 4S-Benzyl-5S-[3-(tetrahydropyran-2-yloxy)propyl]oxazolidin-2-one (0.058 g, 0.182 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 ºC were added *N*-methylquinolinium hexafluorophosphate (0.003 g, 0.012 mmol) and sodium acetate (0.116 g, 1.41 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 12 hours. The reaction mixture was filtered, concentrated. No desired cyclization product was obtained, and the starting material (0.019g, 33%) was re-isolated by flash chromatography (40% EtOAc in hexanes).

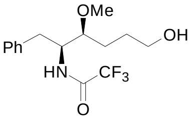
N-(1S-Benzyl-2R-methoxypent-4-enyl)-2,2,2-trifluoroacetamide (36)



36

To trifluoroacetic acid (10 mL) at 0 °C was added (1-benzyl-2R-methoxypent-4-enyl)-carbamic acid tert-butyl ester (0.158 g, 519 mmol). The reaction mixture was stirred for 15 minutes, and then concentrated. The resulting residue was redissolved in CH_2Cl_2, washed with saturated $NaHCO_3$, dried (Na_2SO_4) and concentrated. The resulting residue was dissolved in CH_2Cl_2 (10 mL) and trifluoroacetic anhydride (0.250 g, 1.19 mmol) and pyridine (0.129 g, 1.63 mmol) were added at 0 °C under N_2. The reaction mixture was stirred for 3 h and then concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to yield the desired product (0.071 g, 45%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.28-7.15 (m, 5H), 6.38 (d, *J* = 6.45, 1H), 5.82 (m, 1H), 5.19 (m, 1H), 4.35 (m, 1H), 3.43 (s, 4H), 3.04 (dd, *J* = 4.5, 9.8, 1H), 2.73 (dd, *J* = 3.9, 10.0, 1H), 2.53 (m, 1H), 2.30 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.8, 137.2, 133.5, 129.2, 128.7, 127.0, 118.4, 81.3, 58.0, 53.3, 34.8, 34.5; IR (neat) 3303, 3062, 3027, 2933, 1686, 1445, 1195, 1096, 916, 756, 701 cm^{-1}; HRMS (EI) calcd for $C_{15}H_{18}NO_2F_3$ 301.1289, found 301.1277.

N-(1S-Benzyl-5-hydroxy-2R-methoxypentyl)-2,2,2-trifluoroacetamide (37)

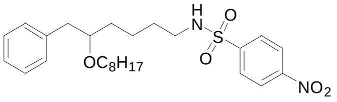


37

To N-(1-Benzyl-2R-methoxy-pent-4-enyl)-2,2,2-trifluoroacetamide (0.071 g, .237 mmol) in THF (10 mL) was added BH_3 (1.0 M in THF, 3.91 mL, 3.91 mmol) at 0 °C under N_2. The reaction was allowed to stir for 2 h, then quenched at 0 ºC with water (2 mL) followed by 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide solution (1 mL) and saturated Na_2SO_3 (2 mL). The reaction mixture was stirred for an addition hour, then was extracted with ethyl acetate, washed with saturated NaCl, dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to yield the desired product (0.049 g, 65%) ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29-7.15 (m, 5H), 6.63 (d, *J* = 8.4, 1H), 4.37 (m, 1H), 3.64 (m, 2H), 3.41 (s, 3H), 3.33 (m, 1H), 2.97 (dd, *J* = 4.9, 9.2, 1H), 2.79 (dd, *J* = 4.8, 9.5, 1H), 2.04 (bs, 1H), 1.69 (m, 4H), ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.9, 137.2, 129.2, 128.7, 126.9, 121.6, 117.8, 81.9, 65.1, 60.7, 53.0, 35.3, 29.8, 28.2, 26.1, 21.1, 18.9, 14.2; IR (neat) 3307, 3092, 2937, 1707, 1561, 1453, 1372, 1182, 1083, 873, 744, 705 cm^{-1}; HRMS (EI) (M-18) calcd for $C_{15}H_{18}NO_2F_3$ 301.1289, found 301.1283.

To N-(1-benzyl-5-hydroxy-2R-methoxypentyl)-2,2,2-trifluoroacetamide (0.045 g, 0.140 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 ºC were added *N*-methylquinolinium hexafluorophosphate (0.001 g, 0.003 mmol), sodium acetate (0.090 g, 1.09 mmol), and sodium thiosulfate (0.090 g, 0.569 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 3.5 h. The reaction mixture was filtered, concentrated. No desired cyclization product was obtained, and the starting material (0.035 g, 80%) was re-isolated by flash chromatography (50% EtOAc in hexanes).

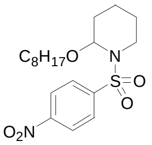
4-Nitro-N-(5-octyloxy-6-phenylhexyl)benzenesulfonamide (49)



49

To 5-Octyloxy-6-phenylhexan-1-ol (0.200 g, 0.652 mmol)) in CH_2Cl_2 (35 ml) at 0 ºC were added methanesulfonyl chloride (0.111g, 0.978 mmol) and triethyl amine (0.264 g, 2.61 mmol). The reaction mixture was stirred for 3 hrs. at room temperature then was quenched with water. The reaction mixture was extracted in CH_2Cl_2, and then the organic layer was washed with water and saturated NaCl, dried (Na_2SO_4) and concentrated. The resulting residue was dissolved in DMF (10 mL) at 23 ºC under N_2 and sodium azide (0.051 g, 0.783 mmol) was added. The reaction mixture was stirred at 55 °C for 12 h then was quenched with water, extracted into hexanes, washed with saturated NaCl, dried (Na_2SO_4), and concentrated. The resulting residue was then dissolved in THF (15 mL) at 23 ºC under N_2 and triphenylphosphine (0.132 g, 0.503 mmol) was added. The reaction mixture was allowed to stir for 18 h then was quenched with water (0.5 mL). The reaction mixture was then allowed to stir for an additional 8 h and concentrated. The resulting residue was dissolved in CH_2Cl_2 (10 mL) and at 0 °C triethylamine (0.132 g, 1.30 mmol) and 4-nitrobenzylsulfonyl chloride (0.108 g, 0.491 mmol) were added. The reaction mixture was stirred at 23 °C for 12 h, then quenched with water (2 mL), washed with saturated NaCl, dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to yield the desired product (0.055 g, 34%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.68, 2H), 8.04 (d, *J* = 8.61, 2H), 7.29-7.13 (m, 5H), 4.98 (t, *J* = 5.88, 1H), 3.36 (m, 4H), 2.98 (m, 2H), 2.84 (dd, *J* = 5.9, 7.7, 1H), 2.63 (dd, *J* = 6.5, 7.0, 1H), 1.48-1.13 (m, 18H), 0.87 (t, *J* = 6.87, 3H); ^{13}C NMR δ 150.1, 146.1, 138.9, 129.5, 128.4, 126.2, 124.5, 80.7, 69.8, 43.3, 42.3, 40.7, 33.3, 31.9, 30.2, 29.7, 29.5, 29.4, 26.3, 22.8, 22.6, 14.2; IR (neat) 3208, 3092, 3023, 2924, 2855, 1600, 1522, 1458, 1333, 1088, 855, 739, 705 cm^{-1}; HRMS (CI), (M+1 = 491).

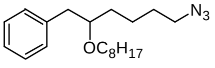
1-(4-Nitrobenzenesulfonyl)-2-octyloxypiperidine (49a)



49a

4-Nitro-N-(5-octyloxy-6-phenylhexyl)benzenesulfonamide (0.055 g, 0.113 mmol) was subjected to catalytic aerobic ETIC reaction conditions. The reaction mixture was filtered, concentrated. The resulting residue was purified by flash chromatography (10% EtOAc in hexanes) to yield the desired product (0.031 g, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.35 (d, *J* = 8.8, 2H), 8.04 (d, *J* = 8.9, 2H), 5.22 (m, 1H), 3.61 (dd, *J* = 2.9, 10.0, 1H), 3.36 (m, 2H), 3.07 (t, *J* = 2.7, 10.1, 1H), 1.89 (m, 1H), 1.62-1.23 (m, 18H), 0.88, (t, *J* = 7.0, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) 130.1, 124.2, 84.6, 67.9, 63.2, 41.5, 33.1, 29.9, 29.6, 29.5, 26.4, 24.8, 22.7, 21.2, 18.1, 14.3, 14.1; IR (neat) 3561, 3101, 2924, 2855, 1604, 1535, 1466, 1350, 1165, 1105, 937, 847, 744; HRMS (EI) calcd for $C_{19}H_{30}N_2O_5S$ 398.1875, found 398.1868.

(5-Azido-2-octyloxy-pentyl)benzene (44)

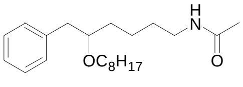


44

To 4-Octyloxy-5-phenylpentan-1-ol (0.200 g, 0.652 mmol) in CH_2Cl_2 (10 mL) at 0 ºC were added methanesulfonyl chloride (0.112 g, 0.978 mmol) and triethylamine (0.264 g, 2.61 mmol). The reaction mixture was stirred for 3 h at room temperature then was quenched with water. The reaction mixture was extracted with CH_2Cl_2, and then the organic layer was washed with water and saturated NaCl, dried (Na_2SO_4) and concentrated. The resulting residue was dissolved in DMF (10 ml) at 23 ºC under N_2 and sodium azide (0.051 g, 0.784 mmol) was added. The reaction mixture was stirred for 18 h at 0 °C, then was quenched with water, and extracted into hexanes. The organic layer was washed with saturated NaCl, dried (Na_2SO_4), and concentrated. The resulting residue was purified by column chromatography (10% EtOAc in hexanes) to yield the desired product (0.189 g, 87%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.18 (m, 5H), 3.42 (m, 3H), 3.26 (t, *J* = 6.6, 2H), 2.88 (dd, *J* = 6.1, 7.49, 1H), 2.70 (dd, *J* = 6.4, 7.1, 1H), 1.62-1.27 (m. 16H), 0.90 (t, *J* = 6.9, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 129.7, 128.4, 126.2, 80.8, 69.9, 51.6, 41.0, 33.8, 32.0, 30.4, 29.6, 29.5, 29.1, 26.4, 23.0, 22.9, 14.3.

To (5-Azido-2-octyloxy-pentyl)benzene (0.050 g, 0.151 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 ºC were added *N*- methylquinolinium hexafluorophosphate (0.001 g, 0.003 mmol), sodium acetate (0.100 g, 1.22 mmol), and sodium thiosulfate (0.100 g, 0.595 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 3 h. The reaction mixture was filtered, concentrated. No desired cyclization product was obtained, and the starting material was re-isolated by flash chromatography (10% EtOAc in hexanes).

N-(4-Octyloxy-5-phenylpentyl)acetamide (48)

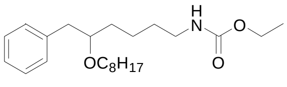


48

To (5-azido-2-octyloxypentyl)benzene (0.818 g, 2.47 mmol) in THF (15 mL) at 23 ºC was triphenylphosphine (1.73 g, 6.59 mmol). The reaction mixture was allowed to stir for 18 h then was quenched with water (2 mL). The reaction mixture was then allowed to stir for an additional 18 h, and concentrated. The resulting residue was dissolved in CH_2Cl_2 (10 mL) and triethylamine (0.134 g, 1.31 mmol) and acetic anhydride (0.037 g, 0.360 mmol) were added at 0 °C under N_2. The reaction mixture was stirred for 1.5 h, and then quenched with water, extracted into CH_2Cl_2, washed with saturated NaCl, dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to yield the desired product (0.75 g, 69%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.26-7.16 m, 5H), 5.84 (bs, 1H), 3.38 (m, 3H), 3.20 (m, 2H), 2.82 (dd, *J* = 6.1, 7.49, 1H), 2.68 (dd, *J* = 6.4, 7.14, 1H), 1.93 (s, 3H), 1.46-1.25 (m, 18H), 0.88 (t, *J* = 6.78, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2, 139.1, 129.5, 128.2, 126.1, 80.8, 69.7, 40.8, 39.7, 33.7, 31.9, 30.2, 29.6, 29.5, 29.3, 26.3, 23.3, 23.0, 22.7, 14.2; IR (neat) 3286, 3083, 2929, 2855, 1651, 1552, 1449, 1363, 1290, 1101; HRMS (EI) calcd for $C_{22}H_{38}NO_2$ 348.2902, found 348.2900.

To N-(4-octyloxy-5-phenylpentyl)acetamide (0.075 g, 0.216 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 ºC were added *N*-methylquinolinium hexafluorophosphate (0.001 g, 0.003 mmol), sodium acetate (0.150 g, 1.83 mmol), and sodium thiosulfate (0.150 g, 0.893 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 19 h. The reaction mixture was filtered, concentrated. No desired cyclization product was obtained, and the starting material (0.015 g, 20%) was re-isolated by flash chromatography (50% EtOAc in hexanes).

(4-Octyloxy-5-phenylpentyl)carbamic acid ethyl ester (46)

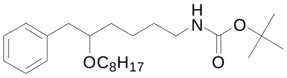


46

To (5-azido-2-octyloxypentyl)benzene (0.539 g, 1.63 mmol) in THF (15 mL) at 23 ºC was added triphenylphosphine (0.513 g, 1.95 mmol). The reaction mixture was allowed to stir for 18 h then was quenched with water (2 mL). The reaction mixture was then allowed to stir for an additional 18 h, and concentrated. The resulting residue was dissolved in acetone (10 mL) and potassium carbonate (0.676 g, 4.89 mmol) and ethyl chloroformate (0.353 g, 0.3.26 mmol) were added under N_2. The reaction mixture was refluxed for 1.5 h, filtered to remove the solid potassium carbonate, and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to yield the desired product (0.172 g, 56%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-7.25 (m, 5H), 4.76 (bs, 1H), 4.19 (q, *J* = 7.04, 2H), 3.46 (m, 3H), 3.22 (m, 2H), 2.93 (dd, *J* = 6.1, 7.45, 1H), 2.76 (dd, *J* = 6.3, 7.3, 1H), 1.54-1.28 (m, 18H), 0.96 (t, *J* = 6.9, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3, 129.7, 129.6, 128.4, 128.3, 126.1, 80.8, 69.8, 60.8, 40.9, 33.8, 32.0, 30.3, 29.6, 29.4, 26.4, 22.8, 14.8, 14.3; IR (neat) 3337, 3027, 2916, 2855, 1698, 1531, 1449, 1376, 1341, 1247, 1096, 774, 744; HRMS (EI) calcd for $C_{23}H_{40}NO_3$ 378.3008, found 378.3009.

To (4-octyloxy-5-phenylpentyl)carbamic acid ethyl ester (0.080 g, 0.212 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 ºC were added *N*-methylquinolinium hexafluorophosphate (0.002 g, 0.005 mmol), sodium acetate (0.160 g, 1.95 mmol), and sodium thiosulfate (0.160 g, 0.952 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 5 h. The reaction mixture was filtered, concentrated. No desired cyclization product was obtained, but one major product was obtained from the reaction mixture: ^{1}H NMR (300 MHz, $CDCl_3$, 343 K), 6.74 (dt, *J* = 1.9, 6.7, 1H), 5.34 (bs, 1H), 4.90 (m, 1H), 4.08 (m, 3H), 3.81 (m, 1H), 3.52 (m, 2H), 3.40 (t, *J* = 6.4, 2H), 3.31 (t, *J* = 6.41, 2H), 3.06 (bs, 4H), 2.89 (dt, *J* = 2.9, 9.9, 1H), 2.50 (bs, 1H), 1.99 (m, 2H), 1.80-1.17 (m, ?H), 0.87 (t, *J* = 6.93, 3H); IR (neat) 3488, 2924, 2855, 1707, 1651, 1415, 1372, 1337, 1264, 1234, 1174, 1118, 1092, 1049, 989 cm^{-1} HRMS (EI) calcd for $C_{16}H_{32}NO_3$ 286.2382, found 286.2371; HRMS (FAB) calcd for $C_{16}H_{31}NO_3$ 285.2303, found 285.2301.

(4-Octyloxy-5-phenylpentyl)carbamic acid *tert*-butyl ester (47)



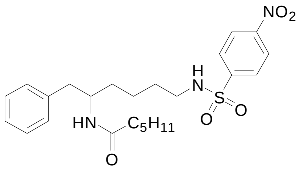
47

To (5-azido-2-octyloxypentyl)benzene (0.139 g, 419 mmol) in THF (10 mL) at 23 ºC was added triphenylphosphine (0.132 g, 0.503 mmol). The reaction mixture was allowed to stir for 18 h then was quenched with water (2 mL). The reaction mixture was then allowed to stir for an additional 18 h, and concentrated. The resulting residue was dissolved in a solution of dioxane (5 mL) and water (5mL) and triethylamine (0.0636 g, 0.629 mmol) and di-*tert*-butyldicarbonate (0.101 g, 0.462 mmol) were added at 0 °C. The reaction mixture was stirred for 2 h, and then concentrated. The resulting residue was redissolved in EtOAc and washed with water and saturated NaCl, dried (Na_2SO_4) and concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to yield the desired product (0.137 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.18 (m, 5H), 4.51 (bs, 1H), 3.37(m, 3H), 3.10 (m, 2H), 2.85 (dd, *J* = 6.1, 7.5, 1H), 2.69 (dd, *J* = 6.3, 7.3, 1H), 1.53-1.26, (m, 27H), 0.88 (t, *J* = 6.9, 3H); ^{13}C NMR (75MHz, $CDCl_3$) δ 156.1, 139.3, 129.6, 128.3, 126.1, 80.9, 69.8, 40.9, 33.9, 32.0, 30.3, 29.6, 29.4, 28.6, 27.6, 26.4, 22.9, 14.3; IR (neat) 3357, 2930, 2856, 1719, 1515, 1456, 1367, 1252, 1172, 1092, 872, 743, 702 cm^{-1}.

To (4-octyloxy-5-phenylpentyl)carbamic acid *tert*-butyl ester (0.050 g, 0.123 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 ºC were added *N*-methylquinolinium hexafluorophosphate (0.001 g, 0.003 mmol), sodium acetate (0.100 g, 1.22 mmol), and sodium thiosulfate (0.100 g, 0.595 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 2 h. The reaction mixture was filtered, and then concentrated. No desired cyclization product was obtained, and small quantities of several unidentifiable side products were isolated.

To (4-octyloxy-5-phenylpentyl)carbamic acid *tert*-butyl ester (0.050 g, 0.123 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 ºC were added *N*-methylquinolinium hexafluorophosphate (0.001 g, 0.003 mmol), methanol (0.003 g, 0.123 mmol), sodium acetate (0.100 g, 1.22 mmol), and sodium thiosulfate (0.100 g, 0.595 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 3 h. The reaction mixture was filtered, and then concentrated. No desired cyclization product was obtained, starting material (0.010 g, 20%), and small quantities of several unidentifiable side products were isolated, along with (4-Methoxy-4-octyloxy-butyl)-carbamic acid tert-butyl ester ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.57 (bs, 1H), 4.39 (t, *J* = 5.6, 1H), 3.51-3.38 (m, 6H), 3.28 (s, 3H), 1.41-1.15 (m, 25H), 0.85 (m, 3H).

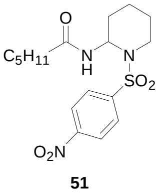
Hexanoic acid [1-benzyl-5-(4-nitrobenzenesulfonylamino)pentyl]amide (50)



50

Dry EtOAc (2 mL) was added to a reaction flask containing Pd/C (0.25 g) fitted with an H_2 balloon. The system was evacuated, then purged with H_2 five times to ensure a H_2 atmosphere, and the reaction mixture was then stirred for 1h. (5-Azido-2-octyloxy-pentyl)benzene (0.11 g, 0.34 mmol, in 2 mL EtOAc) was added and the pump/purge with H_2 technique was repeated five times. The reaction mixture was stirred for 1.5h, then filtered over Celite. The Celite was washed with EtOAc (100 mL) and the filtrate was concentrated. The resulting residue was dissolved in CH_2Cl_2 (10 mL) and the temperature was decreased to 0 ºC before triethylamine (0.13 g, 1.37 mmol) and 4-nitrobenzenesulfonyl chloride (0.11 g, 0.51 mmol) were added. The reaction mixture was stirred for 18h, then quenched with H_2O. The two layers were separated, and the organic layer was washed with saturated NaCl (2 x 10 mL), dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography to afford the desired product (0.09 g, 61%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.46 (d, *J* = 7.2 Hz, 2H), 8.17 (d, *J* = 7.3 Hz, 2H), 7.37 (m, 5H), 6.11 (t, *J* = 5.7 Hz, 1H), 5.60 (d, *J* = 8.9 Hz, 1H), 4.30 (m, 1H), 3.07 (dd, *J* = 5.8, 12.0 Hz, 2H), 2.87 (t, *J* = 6.2 Hz, 2H), 2.22 (add, *J* = 3.1, 7.2, 11.1 Hz, 2H), 1.67-1.26 (m, 12H), 0.97 (t, *J* = 7.3 Hz, 3H); 173.61, 149.97, 146.32, 137.90, 129.36, 128.58, 128.39, 126.67, 124.42, 49.50, 43.02, 41.33, 37, 01, 33.89, 31.43, 28.84, 25.59, 22.62, 22.49, 22.31, 17.00, 14.07; IR (neat) 3378, 3287, 2930, 2859, 1643, 1524, 1350, 1156, 1093, 847, 740 cm^{-1}; HRMS (EI) calcd for (M+H) $C_{24}H_{34}N_3O_5S$ 476.221918, found 476.218065.

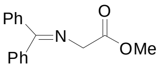
Hexanoic acid [1-(4-nitro-benzenesulfonyl)-piperidin-2-yl]-amide (51)



51

To 4-nitro-N-(5-octyloxy-6-phenyl-hexyl)benzenesulfonamide (**10**) (0.040 g, 0.084 mmol) in dichloroethane (5 mL) and toluene (1 mL) in a borosilicate flask at 20 ºC were added *N*- methylquinolinium hexafluorophosphate (0.002 g, 0.007 mmol), sodium acetate (0.100 g, 1.21 mmol), and sodium thiosulfate (0.100 g, 0.632 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 5 h, then filtered, and concentrated. The resulting residue was purified by flash chromatography to yield the desired product **11** (0.021 g, 64%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.9, 2H), 8.04 (d, *J* = 8.9, 2H), 6.10 (m, 1H), 5.90 (m, 1H), 3.80 (m, 1H), 2.91 (dt, *J* = 8.3, *J* = 3.2), 1.79 (m, 4H), 1.22 (m, 10H), 0.84 (t, *J* = 6.8); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.0, 150.0, 146.0, 128.8, 124.5, 58.4, 42.0, 36.6, 31.4, 31.1, 25.2, 22.4, 18.8, 14.0; IR (neat) 3313, 2939, 2861, 1650, 1527, 1354, 1147, 1097, 924, 740 cm^{-1}; HRMS (EI) calcd for $C_{17}H_{26}N_3O_5S$ 384.1593, found 384.1583.

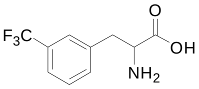
Methyl N-(diphenylmethylene)glycinate (52)



52

To a stirring solution of benzophenone immine (1.21 g, 6.66 mmol) in CH_2Cl_2 (20 mL) was added glycine methyl ester hydrochloride (0.83 g, 6.66 mmol). The reaction mixture was stirred at room temperature for 18h, then filtered to remove NH_4^+Cl and concentrated. The resulting residue was purified by flash chromatography (30% EtOAc in hexanes) to afford the desired product (1.43 g, 85%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68-7.18 (m, 10H), 4.23 (s, 2H), 3.75 (s, 3H).

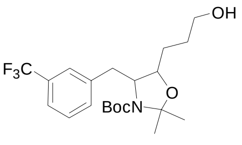
3-(Trifluoromethyl)phenylalanine (53)



53

To a suspension of sodium hydride (60% dispersion in mineral oil, 0.15 g, 3.95 mmol) in DMF (10 mL) at 0 ºC was added methyl *N*-(diphenylmethylene)glycinate (52) (1.00 g, 3.95 mmol, in 5 mL DMF). The reaction mixture was stirred for 15 min. before 3-(trifluoromethyl)benzyl chloride (0.61 g, 3.95 mmol) was added. The reaction mixture was stirred for 2h at room temperature, then was quenched with ice chips. The reaction mixture was extracted into ether, washed with saturated NaCl, dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes). The resulting residue was dissolved in 6N HCl (5 mL) and heated to reflux for 6.5h. The reaction mixture was then cooled to 0 ºC and stirred for 1h. The reaction mixture was filtered and the hydrochloride salt was washed with cold acetone. The hydrochloride salt was dissolved in MeOH (10 mL) and the temperature was decreased to 0 ºC. The pH was increased to 9 by dropwise addition of 15% NaOH and the reaction mixture was stirred for 15 min. The reaction mixture was concentrated and the resulting residue was redissolved in EtOAc (5 mL) and washed with saturated NaCl (5 mL). The organic layer was dried ($MgSO_4$) and concentrated to afford the desired product (0.84 g, 92%): ^{1}H NMR (300 MHz, D_2O) δ 7.51 (m, 2H), 7.41 (m, 2H), 3.94 (ddd, *J* = 1.9, 5.6, 7.6 Hz, 1H), 3.22 (dd, *J* = 5.4, 14.6 Hz, 1H), 3.08 (dd, *J* = 7.8, 14.6 Hz, 1H).

5-(3-Hydroxypropyl)-2,2-dimethyl-4-(3-trifluoromethylbenzyl)oxazolidine-3-carboxylic acid tert-butyl ester (54)

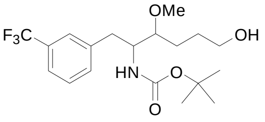


54

To a suspension of lithium aluminum hydride (0.27 g, 7.24 mmol) refluxing in THF (25 mL) was added 3-(trifluoromethyl)phenylalanine (0.84 g, 3.62 mmol) was added in small portions. The reaction mixture was stirred for 18 h, then cooled to 0 ºC and quenched with 15% NaOH (1.5 mL) and water (5 mL). Di-*tert*-butyl-dicarbonate (0.95 g, 4.34 mmol, in 5 mL CH_2Cl_2) was added. The reaction was stirred at 60 ºC for 6 h, cooled and filtered through a pad of Na_2SO_4 and concentrated. The resulting residue was added dropwise to a solution of oxalyl chloride (0.73 g, 5.76 mmol) and DMSO (0.51 g, 6.59 mmol) in CH_2Cl_2 (30 mL) at -78 ºC. The reaction mixture was stirred for 1 h, then quenched with triethylamine (1.66 g, 16.4 mmol), warmed to room temperature and quenched with water (5 mL). The two layers were separated and the organic layer was washed with saturated NaCl (15 mL), dried ($MgSO_4$) and concentrated. The resulting residue was dissolved in THF (10 mL) and the temperature was decreased to 0 ºC. Allyl magnesium bromide (1.0 M in THF, 9.85 mL, 9.85 mmol) was added and the reaction mixture was stirred at room temperature for 2 h, then quenched with saturated NH_4Cl and extracted into EtOAc. The organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes). To a solution of the resulting residue in toluene (10 mL) was added PPTS (0.02 g) and dimethoxypropane (4.06 g, 39.54 mmol). The reaction mixture was heated to reflux for 3 h, then cooled to room temperature, concentrated and purified by flash chromatography (5% EtOAc in hexanes). To a stirring solution of the resulting residue was dissolved in THF (5 mL) and the temperature was decreased to 0 ºC. BH_3 (1.0 M in THF, 5.07 mL, 5.07 mmol). The reaction was allowed to stir for 1 h, then quenched at 0 ºC with a solution of basic hydrogen peroxide [(2 mL) 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide (1 mL)] and saturated Na_2SO_3 (2 mL). and saturated Na_2SO_3 (2 mL). The reaction mixture was stirred for an addition hour, then was extracted with ethyl acetate, washed with saturated NaCl, dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to afford the desired product (0.03 g, 2%): ^{1}H NMR (300 MHz, CH_3Cl) δ 7.49 (m, 4H), 4.26 (dd, *J* = 6.3, 11.4 Hz, 1H), 4.10 (m, 1H), 3.83 (bs, 1H), 3.56 (m, 2H), 3.14 (m, 1H), 2.88 (m, 1H), 1.53 (m, 13H), 1.40 (s, 3H), 1.29 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.27, 140.39, 133.54, 133.20, 132.97, 130.74, 129.09, 128.85, 126.80, 126.23, 123.60, 123.8193.35, 92.72, 80.61, 80.38, 80.0163.64, 63.02, 62.52, 60.85, 60.67, 36.85, 36.52, 35.86, 31.01, 29.99, 29.07, 28.65, 28.47, 28.18, 27.85, 27.62, 27.00, 26.33, 25.09, 23.89; IR (neat) 3447, 2978, 2933, 2866, 1678, 1399, 1326, 1170, 1125, 1069; HRMS (EI) calcd for $C_{21}H_{31}NO_4F_3$ (M+H) 418. 220519, found 418.219120.

To 5-(3-hydroxypropyl)-2,2-dimethyl-4-(3-trifluoromethylbenzyl)oxazolidine-3-carboxylic acid tert-butyl ester (54) (0.030 g, 0.0718 mmol) in dichloroethane (2.5 mL) and toluene (0.5 mL) in a borosilicate flask at 20 ºC were added *N*- methylquinolinium hexafluorophosphate (0.002 g, 0.007 mmol), sodium acetate (0.060 g, 0.714 mmol), and sodium thiosulfate (0.060 g, 0.379 mmol). The mixture was stirred at room temperature while bubbling air gently and irradiating for 2.5 h, then filtered, and concentrated. The reaction mixture was purified by flash chromatography (45% EtOAc in hexanes) to provide the desired product **42** as a single diastereomer (0.010 g, 56%).

[5-Hydroxy-1-(3-trifluoromethyl-benzyl)pentyl]carbamic acid tert-butyl ester (55)



55

To a suspension of lithium aluminum hydride (0.21 g, 5.44 mmol) refluxing in THF (25 mL) was added 3-(trifluoromethyl)phenylalanine (0.63 g, 2.27 mmol) was added in small portions. The reaction mixture was stirred for 18 h, then cooled to 0 ºC and quenched with 15% NaOH (1.5 mL) and water (5 mL). Di-*tert*-butyl-dicarbonate (0.59 g, 2.72 mmol, in 5 mL CH_2Cl_2) was added. The reaction was stirred at 60 ºC for 6 h, cooled and filtered through a pad of Na_2SO_4 and concentrated. To a solution of the resulting residue in CH_2Cl_2 (5 mL) at 0 ºC was added Dess-Martin periodinane (0.15 g, 0.35 mmol). The reaction mixture was stirred at room temperature for 1h, then quenched slowly with saturated $NaHCO_3$ (1.5 mL). The two layers were separated and the organic layer was washed with saturated NaCl (5 mL), dried ($MgSO_4$) and concentrated. To a solution of the resulting residue in THF (5 mL) at 0 ºC was added allylmagnesium bromide (1.0 M in THF, 0.35 mL, 0.35 mmol). The reaction mixture was stirred at 0 ºC for 30 min, then quenched with saturated NH_4Cl (1.5 mL) and warmed to room temperature. The reaction mixture was extracted into EtOAc (10 mL), washed with saturated NaCl (5 mL), dried ($MgSO_4$) and concentrated. The resulting residue (in 1 mL DMF) was added to a suspension of sodium hydride (60% dispersion in mineral oil, 0.02 g, 0.38 mmol) in DMF (5 mL) at 0 ºC. The reaction mixture was stirred for 30 min. before methyl iodide (0.05 g, 0.33 mmol) was added. The reaction mixture was stirred for 3 h, then quenched with ice chips and extracted into Et_2O. The organic layer was washed with saturated NaCl (5 mL), dried ($MgSO_4$) and concentrated. To a solution of the resulting residue in THF (5 mL) at 0 ºC was added BH_3 (1.0 M in THF, 0.49 mL, 0.49 mmol). The reaction was allowed to stir for 1 h, then quenched at 0 ºC with a solution of basic hydrogen peroxide [(2 mL) 20% aqueous NaOH (1 mL), 30% aqueous hydrogen peroxide (1 mL)] and saturated Na_2SO_3 (2 mL). The reaction mixture was stirred for an additional hour, then was extracted with ethyl acetate, washed with saturated NaCl, dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (60% EtOAc in hexanes) to afford the desired product (0.04 g, 2%): ^1H NMR (300 MHz, CH_3Cl) δ 7.42 (M, 4H), 3.66 (m, 2H), 3.51 (m, 1H), 3.45 (s, 3H), 3.25 (m, 1H), 2.73 (m, 2H), 2.54 (bs, 1H), 1.76-1.67 (m, 4 H), 1.34 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.95, 140.28, 132.49, 128.81, 125.75, 123.17, 122.46, 83.00, 82.68, 82.02, 79.75, 63.06, 62.71, 58.39, 58.18, 58.07, 35.11, 34.90, 34.09, 29.79, 28.75, 28.25, 28.15, 27.49, 27.15, 26.61, 26.39, 24.12 IR (neat) 3369, 2978, 2933, 1806, 1739, 1711, 1505, 1326, 1159, 1120; HRMS (EI) calcd for $C_{16}H_{21}NO_3F_3$ (M–C_3H_7O) 332.147354, found 332.147026.

1.6. References

---

[1] Mattay, J.; Griesbeck, A.; eds. *Photochemical Key Steps in Organic Synthesis*, VCH Verlagsgesellschaft mbH, Weinheim, **1994**.

[2] Kisch, H.; Lindner, W. “Synthesis via semiconductor photocatalysis” *Chemie in Unserer Zeit*, **2001**, *35*, 250-257.

[3] Gould, I. R.; Lenhard, J. R.; Muenter, A. A.; Godleski, S. A.; Farid, S. “New approach to silver halide photography using radical cation chemistry” *Pure Appl. Chem.* **2001**, *73*, 455-458.

[4] Gratzel, M. “Molecular photovoltaics that mimic photosynthesis” *Pure Appl. Chem.* **2001**, *73*, 459-467.

[5] Pan, J. Y.; Scherf, U.; Schreiber, A. “Photoconduction study on a ladder-type poly(para-phenylene)” *Synthetic Meth.* **2000**, *115*, 79-82

[6] Korzeniewski, B.; Zoladz, J. A. “A model of oxidative phosphorylation in mammalian skeletal muscle” *Biophys. Chem.* **2001**, *92*, 17-34.

[7] Aubert, C.; Vos, M. H.; Mathias, P.; Eker, A. P.; Brettel, K. “Intraprotein radical transfer during photoactivation of DNA photolyase” *Nature* **2000**, *407*, 926-926

[8] Schultz, A. G. “The asymmetric Birch reduction and reduction-alkylation strategies for synthesis of natural products” *Chem. Commun.* **1999,** *14*, 1263-1271.

[9] Sheehan, J. C.; Coderre, R. C. “The formation of 5membered and 6-membered rings by the acyloin condensation. 3. Cyclization of diethyl 2-carboxy-2-methylcyclohexane-1-acetate” *J. Am. Chem. Soc.* **1953**, *75*, 3997-3999.

[10] Hamdouchi, C.; de Blas, J.; Ezquerra, J. “A novel application of the Ullmann coupling reaction for the alkylsulfenylation of 2-amino-imidazo[1,2-a]pyridine” *Tetrahedron* **1999**, *55*, 541-548.

[11] Pandeyg, G.; Das, P.; Reddy, P. Y. “Photoinduced electron transfer (PET) promoted oxidative activation of 1-(N-benzyl-N-methylglycyl)-(S)-prolinol: Development of novel strategies towards enantioselective syntheses of alpha-amino acids, their N’-methyl derivatives and alpha-hydroxy acids employing (S)-prolinol as a recyclable chiral auxiliary” *Eur. J. Org. Chem.* **2000**, *4*, 657-664.

[12] Bunnet, J. F. “Aromatic-substitution by $S_{RN}1$ mechanism” *Accounts Chem. Res.* **1978**, 413-420.

[13] Kavarnos, G. J. *Fundamentals of Photoinduced Electron Transfer*, VHC Publishers, New York, 1993; Chapter 1.

---

[14] 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.

[15] Eberson, L. “Electron Transfer Reactions in Organic-Chemistry” *Adv. Phys. Org. Chem.* **1982**, *18*, 79-185.

[16] Rehm, D.; Weller, A. “Kinetics of Fluorescence Quenching by Electron Transfer and H-atom Transfer” *Is. J. Chem.* **1970**, *8*, 259-271.

[17] Schmittel, M.; Ghorai, M. K. “Reactivity Patterns of Radical Ions – A Unifying Picture of Radical-anion and Radical-cation Transformations” *Electron Transfer in Chemistry, Vol. 2 Organic Molecules* Wiley-VCH, Weinheim, **2001**.

[18] Mella, M.; Fagoni, M.; Freccero, M.; Fasani, E.; Albini, A. “New synthetic methods *via* radical cation fragmentation” *Chem. Soc. Rev.* **1998**, *27*, 81-89.

[19] Maslak, P.; Vallombroso, T.; Chapman, W. H.; Narvaez, J. N. “Free-Energy Relationship for Mesolytic Cleavage of C-C Bonds” *Angew. Chem. Int. Ed. Engl.* **1994**, *33*, 73-75.

[20] Schmittel, M.; Burghart, A. “Understanding Reactivity Patterns of Radical Cations” *Angew. Chem. Int. Ed. Engl.* **1997**, *36*, 2550-2589.

[21] Abe, M.; Nojima, A.; Oku, A. **“**Photoinduced Electron Transfer Reactions of Cyclopropanone Acetal with Conjugated Enones in the Presence of a Redox-Type Photosensitizer” *Tetrahedron Lett.* **1996**, *37*, 1833-1836.

[22] Adam, W.; Heidenfelder, T. “Regio- and diastereoselective rearrangement of cyclopentane-1,3-diyl radical cations generated by electron transfer” *Chem. Soc. Rev.* **1999**, *28*, 359-365.

[23] Howell, J. O.; Goncalves, J. M.; Amatore, C.; Klasnic, 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.

[24] Popielarz, R.; Arnold, D. R. “Radical Ions in Photochemistry. Carbon-Carbon Bond Cleavage of Radical Cations in Solution: Theory and Application” *J. Am. Chem. Soc.* **1990**, *112*, 3068-3082.

[25] Marcus, R. A. “Electron Transfer Reactions in Chemistry: Theory and Experiment (Nobel Lecture)” *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1111-1122.

[26] Camaioni, D. M. “Calculation of Structures and Bond Dissociation Energies of Radical Cations: The Importance of Through-Bond Delocalization in Bibenzylic Systems” *J. Am. Chem. Soc.* **1990**, *112*, 9475-9483.

---

[27] Baciocchi, E.; Bietti, M.; Lanzalunga, O.; Steenken, S. "Side Chain Fragmentation of Arylalkanol Radical Cations. Carbon-Carbon and Carno-Hydrogen Bond Cleavage and the role of α- and β-OH Groups" *J. Am. Chem. Soc.* **1998**, *120*, 11516-11517.

[28] Arnold D. R.; Lamont, L. J.; Perrott, A. L. "1,n-Radical ions. Photosensitized (electron transfer) carbon-carbon bond cleavage. Formation of 1,6-radical cations" *Can. J. Chem.* **1990**, *69*, 225-233.

[29] Dinnocenzo, J. P.; Lieberman, D. R.; Simpson, T. R. "Inverse Effects of Alkyl Substitution on Three-Electron S_N2 Reactions" *J. Am. Chem. Soc.* **1993**, *115*, 366-367.

[30] Kumar, S. V.; Floreancig, P. E. "Electron Transfer Initiated Cyclizations: Cyclic Acetal Synthesis through Carbon-Carbon σ-Bond Activation" *J. Am. Chem. Soc.* **2001**, *123*, 3842-3843.

[31] Dockery, K. P.; Dinnocenzo, J. P.; Farid, S.; Goodman, J. L.; Gould, I. R.; Todd, W. P. "Nucleophile-Assisted Cleavage of Benzyltriaklysilane Cation Radicals" *J. Am. Chem. Soc.* **1997**, *119*, 1876-1883.

[32] Knapp, S.; Zhao, D. "Synthesis of the Salidase Inhibitor Siastatin B" *Org. Lett.* **2000**, *2*, 4037-4040.

[33] Nishimura, Y.; Satoh, T.; Adachi, H.; Kondo, S.; Takeuchi, T.; Azetaka, M.; Fukuyasu, H.; Iizuka, Y. "The First L-Iduronic Acid-Type 1-*N*-Iminosugars Having Inhibitory Activity of Experimental Metastasis" *J. Am. Chem. Soc.* **1996**, *118*, 3051-3052.

[34] Scriven, E. F.; Turnbull, K. "Azides: Their Preparation and Synthetic Uses" *Chem. Rev.* **1988**, *2*, 298-368.

[35] Negishi, E.; Liou, SY; Xu, CD "A general method for the synthesis of E and/or Z oligoisoprenoids based on Pd-catallyzed homoallyl-alkenyl and homopropargyl-alkenyl cross-coupling and Zr-catalyzed carboalumination" *Polyhedron*, **2000**, *19*, 591-592.

[36] Wipf, P.; Lim, S. "Rapid Carboalumination of Alkynes in the Presence of Water" *Angew. Chem. Int. Ed. Engl.* **1993**, *32*, 1068-1071.

[37] Brown, H. C.; Heydkamp, W. R.; Breuer, E.; Murphy, W. S. "The Reaction of Organoboranes with Chloramine and with Hydroxylamine-*O*-sulfonic Acid. A Convenient Synthesis of Amines from Olefins *via* Hydroboration" *J. Am. Chem. Soc.* **1964**, *86*, 3565-3566.

[38] Tamiya, J.; Sorensen, E. J. "A Concise Synthesis of (-)-Hispidospermidin Guided by a Postulated Biogenesis" *J. Am. Chem. Soc.* **2000**, *122*, 9556-9557.

[39] Reetz, M. T.; Drewes, M. W.; Schmitz, A. "Stereoselective Synthesis of β-Amino Alcohols from Optically Active α-Amino Acids" *Angew. Chem. Int. Ed. Engl.* **1987**, *11*, 1141-1143.

---

[40] Kumar, S. V.; Aubele, D. L.; Floreancig, P. E. "Aerobic Organocatalytic Photointiated Arene Oxidations: Application to Electron Transfer Initiated Cyclization Reactions" *Org. Lett.* **2001**, *25*, 4123-4125.

[41] a) Veeresa, G. "Stereoselective synthesis of (-)-*N*-boc-AHPPA" *Syn. Comm.* **2000**, *30*, 1479-1487. b) Nihei, K.; Kato, M. J.; Yamane, T.; Palma, M. S.; Konno, K "2-nitro- and 2,4-dinitrobenzenesulfonamides as protecting groups for primary amines**"** *Synlett*, **2001**, *7*, 1167-1169.

[42] Rosenstock, H. M.; Draxl, K.; Steiner, B. W., Herron, J. T. *J. Chem. Phys. Ref. Data* **1997**, *6*, Suppl. 1.

[43] Pirrung, M.; Krishnamurthy, N.; "Prepartion of (*R*)-phenylalanine analougues by enantioselective destruction using L-amino acid oxidase" *J. Org. Chem.* **1993**, *58*, 957-958.

[44] O'Donnell, M. J.; Polt, R.; "A mild and efficient route to Schiff base derivates of amino acids" *J. Org. Chem.* **1982**, *47*, 2663-2665.

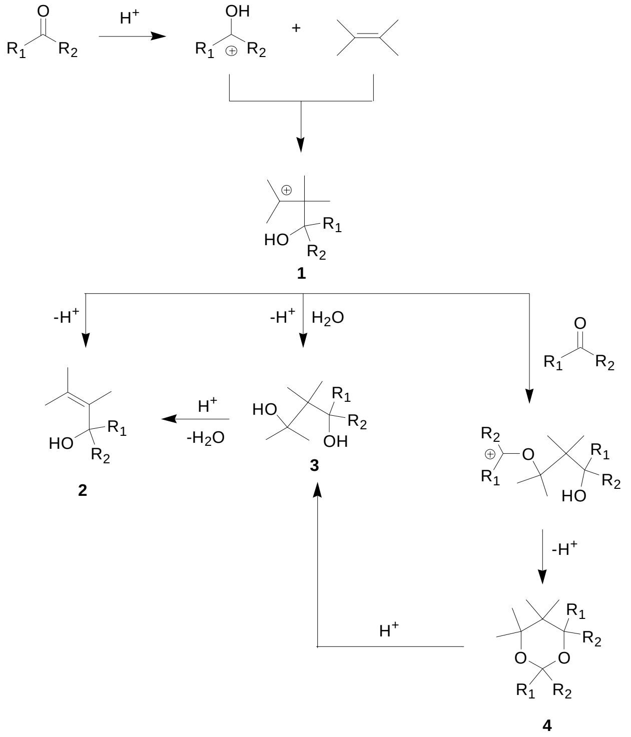
2. The aqueous Prins reaction

2.1. Introduction

I. Introduction

The Prins reaction,[45] first discovered in 1899, is the condensation of an alkene and formaldehyde in the presence of an acid at an elevated temperature to afford either an allylic alcohol, a 1,3-diol, or a 1,3-dioxane (Figure 2.1). The product composition is dependent on the specific alkene as well as the reaction conditions. The reaction appears to proceed partly by an electrophlic addition of a protonated aldehyde to an alkene, and partly through an ene reaction when the reaction is initiated thermally in the absence of a catalyst. Despite numerous investigations into the mechanism[46] and extensive postulation, it is generally accepted that the complex product mixtures that arise are a result of general acid catalysis, but are not consistent with a mechanism of simple carbenium ion formation.

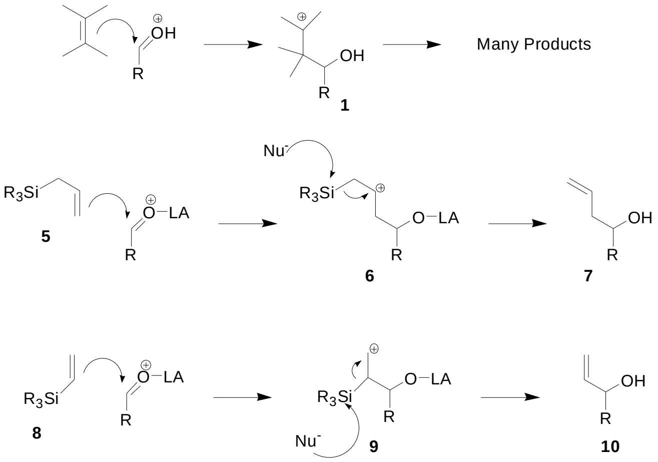
Figure 2.1: Generally accepted Prins mechanism



The initial electrophilic addition of the protonated aldehyde to the olefin is generally considered to proceed in a stepwise manner leading to the formation of carbenium ion **1**. This carbenium ion can then react further with any of the species present in the reaction mixture to form the allylic alcohol **2**, 1,3-diol **3**, or the 1,3-dioxane **4**. Each of these products may in turn react further increasing the complexity of the product composition.

One method of controlling the product distribution of the Prins reaction is through controlling the formation of the cationic intermediates. Incorporating a silyl group into the nucleophilic component of the reaction either in the allylic (**5**) or vinyl (**8**) position encourages the formation of cationic intermediates **6** and **9**, (Figure 2.2). These cations, unlike cation **1**, are thermodynamically stabilized by hyperconjugation of the adjacent carbon-silicon bond, and kinetically unstable with respect to loss of the silicon group. Therefore, homoallylic alcohols (**7**) are formed specifically.

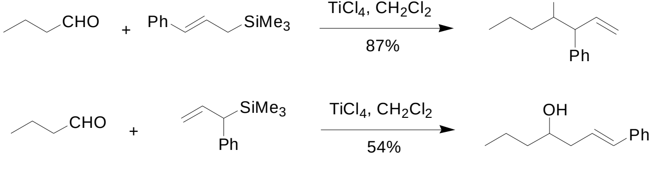
Figure 2.2: Generally accepted Prins mechanism involving allyl and vinylsilanes


OH
R
OH
R
1
Many Products
Nu⁻
R3Si
O−LA
R
5
R3Si
O−LA
R
6
OH
R
7
R3Si
O−LA
R
8
R3Si
O−LA
R
Nu⁻
9
OH
R
10

Unlike Prins reactions of alkenes, reactions incorporating allylsilanes are often catalyzed with Lewis acids rather than protic acids. Protic acids can induce protodesilylation in competition with carbon-carbon bond formation, whereas Lewis acids are less likely to attack the carbon-carbon double bond. The existence of cationic intermediate **6** has not yet been proved for this type of reaction. However, circumstantial evidence is provided through the observed formation of oxepins without loss of the silyl group.[47]

Allylsilanes are thermally stable with respect to allylic shift of the silyl group. Consequently, regioisomeric allylsilanes react in a reliable manner with the electrophile always bonding to the terminus of the allyl unit remote from the silyl group, to afford regiospecific products, as shown in Figure 2.3. Under Lewis acidic conditions, carbon-carbon bond formation occurs exclusively at the γ-carbon of the allylsilane, with clean allylic transposition leading to the formation of homoallylic alcohols.[48]

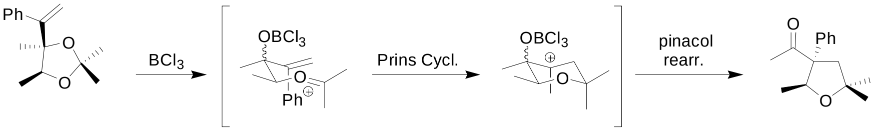
Figure 2.3: Allylic transposition of allylsilanes


CHO
+
Ph
SiMe3
TiCl4, CH2Cl2
87%
OH
Ph
CHO
+
SiMe3
Ph
TiCl4, CH2Cl2
54%
OH
Ph

Acetals and ketals serve as exceptional electrophiles for Prins reactions. When these intermediate oxocarbenium ions are tethered to alkenes, intramolecular additions occur to generate cyclic oxocarbenium ions from which a variety of products can arise depending on the method of termination. This variant of the Prins reaction, cyclic acetal ionization under strongly acidic conditions and intramolecular electrophilic addition of a pendent alkene, provides a powerful method for access into cyclic ethers through carbon-carbon bond construction.

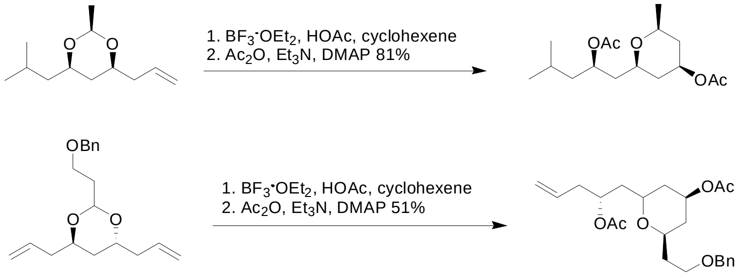
Early examples of intermolecular Prins reactions of mixed acetals to form tetrahydrofurans[49] are known. Overman has greatly expanded the scope of the reaction and has successfully used intramolecular pinacol-terminated Prins cyclization reactions as the key strategic element in the total synthesis of a variety of natural products.[50] Through the ionization of cyclic acetals, intramolecular Prins cyclization, and termination via pinacol rearrangement, as shown in Figure 2.4, Overman has accessed highly functionalized acyltetrahydrofuran derivatives.

Figure 2.4: Pinacol-terminated Prins cyclization



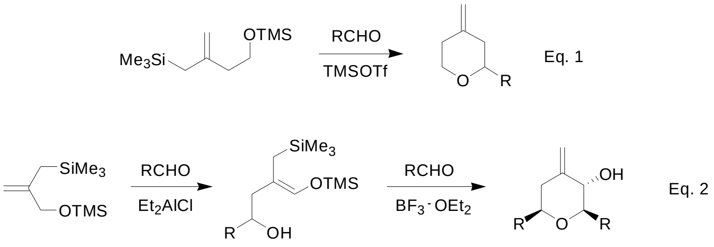
Tetrahydropyrans (THP) are critical substructural motifs in a variety of biologically significant natural products, and a number of methods for the formation of these oxacycles have been developed based on the basic Prins reaction. Rychnovsky used intramolecular Prins cyclizations of saturated acetals followed by subsequent trapping with oxygen nucleophiles as an entry into oxygenated tetrahydropyrans[51] (Figure 2.5).

Figure 2.5: Prins cyclization to form THPs


1. BF3·OEt2, HOAc, cyclohexene
2. Ac2O, Et3N, DMAP 81%
OAc
OAc
OBn
1. BF3·OEt2, HOAc, cyclohexene
2. Ac2O, Et3N, DMAP 51%
OAc
OAc
OBn

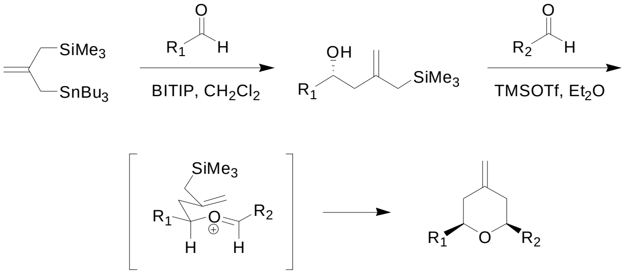
Many have realized the utility and enhanced reactivity of allylsilanes as intramolecular traps for oxocarbenium ions generated in various ways and have exploited this reactivity. Marko has done extensive studies in this area, and developed an efficient tetrahydropyran synthesis that combines the Noyori[52] method for generation of oxocarbenium ions with intramolecular silyl modified Sakurai (ISMS) reaction (Eq. 1, Figure 2.6). Marko has also coined the term “IMSC” (intramolecular Sakurai cyclization) in reference to the cyclization of hydroxy allylsilanes in sequences leading to pyrans via an “ene” type reaction[53] (Eq. 2, Figure 2.6).

Figure 2.6: ISMS and ISMC reactions


Me3Si
OTMS
RCHO
TMSOTf
R
Eq. 1
SiMe3
OTMS
RCHO
Et2AlCl
SiMe3
OTMS
R
OH
RCHO
BF3·OEt2
OH
R
R
Eq. 2

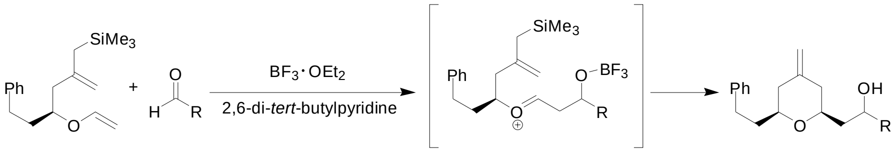
Recently, Keck reported a facile enantioselective synthesis of 2,6-*cis*-disubstituted-4-methylenetetrahydropyran systems through a two-step process[54] (Figure 2.7). The first step is asymmetric allylation of an aldehyde in the presence of a BINOL titanium isopropoxide catalyst to generate the enantiopure hydroxyl allylsilane. The second step, TMSOTf–promoted annulation of the silane with a second aldehyde, affords the 2,6-*cis*-tetrahydropyran containing an *exo*-methylene in the 4 position.

Figure 2.7: Two-step THP formation



In a similar approach, Rychnovsky has also reported a Mukaiyama aldol-Prins (MAP) cyclization reaction effectively utilizing allylsilanes in the synthesis of tetrahydropyrans[55] (Figure 2.8). The cascade reaction involves the Mukaiyama aldol condensation of an aldehyde and an alkyl enol ether to generate an intermediate oxocarbenium ion. The oxocarbenium ion is then trapped with an allylsilane in an intramolecular Prins cyclization. This method was applied in a formal total synthesis of leucascandrolide A, and has since expanded to include condensation with ketones followed by intramolecular Prins cyclization.[56]

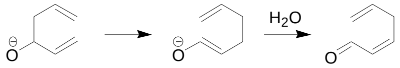
Figure 2.8: MAP cyclization reaction



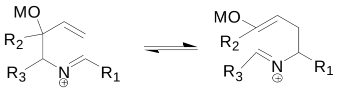
II. The role of the oxonia-Cope rearrangement in the Prins reaction

It is known that the substitution of a carbon for a charged heteroatom in [3,3]-sigmatropic rearrangements leads to significant rate increases. Typical examples of these types of reactions are the anionic oxy-Cope rearrangement and the 2-azonia-Cope rearrangement, shown in Figure 2.9. The oxygen analog of the 2-azonia-Cope rearrangement is the oxonia-Cope rearrangement, which has been invoked as a competitive pathway in Prins cyclizations and related transformations.[57] This competitive cationic [3,3]-sigmatropic rearrangement leads to undesired stereochemical outcomes and side chain scrambling in Prins reactions.

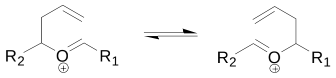
Figure 2.9: Heteroatom substituted [3,3]-sigmatropic rearrangements



Anionic oxy-Cope Rearrangement



azonia-Cope rearrangement

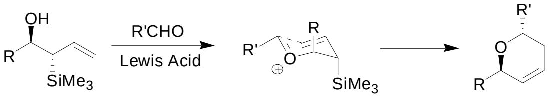


oxonia-Cope rearrangement

In his studies of Lewis acid-induced π-cyclization reactions of a variety of α-methoxy oxocarbenium ions, Speckamp found that the oxonia-Cope rearrangement played an important role in the formation of 5- and 6-membered cyclic ethers. The influence of the [3,3]-sigmatropic rearrangement on the regio- and stereochemical outcome of the cyclization reaction was examined through the influence of side chain substituents, the type of π-nucleophile (allyl- or vinylsilane) and the cyclization of enantio-pure substrates. The controlling factors in whether or not rearrangement would occur were found to be the nature of the π-nucleophile, with vinylsilanes more apt to rearrange to form the allylsilane, and the substitution pattern of the oxocarbenium ion intermediate, with rearrangement occurring to form the more stable sigmatropisomer. Retention of stereochemical integrity was observed in the cyclization of enantiopure substrates. However, oxonia-Cope cyclization was observed in Prins cyclization reactions of vinylsilanes.

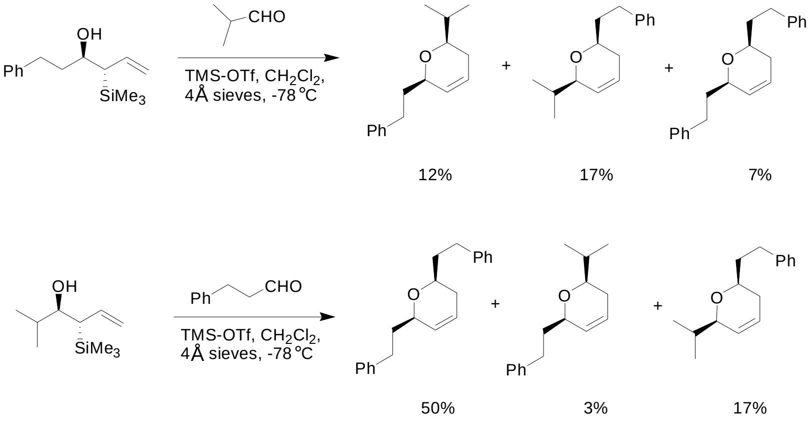
In the course of studies on the synthesis of 2,6-disubstituted dihydropyrans, Roush found the oxonia-Cope rearrangement to be a competitive reaction pathway in intramolecular Prins cyclization reactions of allylsilanes.[58] The goal of the study was the development of a novel method for the synthesis of 2,6-*trans*-disubstituted dihydropyrans through the reaction of a β-hydroxyallylsilane with an aldehyde in the presence of a Lewis acid to generate an intermediate oxocarbenium ion that would subsequently undergo intramolecular Prins cyclization (Figure 2.10). The strong stereoelectronic preference of silyl substituents to adopt an axial orientation in reactions that develop cationic character in the β-position was expected to be the origin of the *trans* selectivity.

Figure 2.10: Origin of 2,6-*trans*-dihydropyran selectivity


OH
R
SiMe3
R'CHO
Lewis Acid
R'
R
O
⊕
SiMe3
R'
O
R

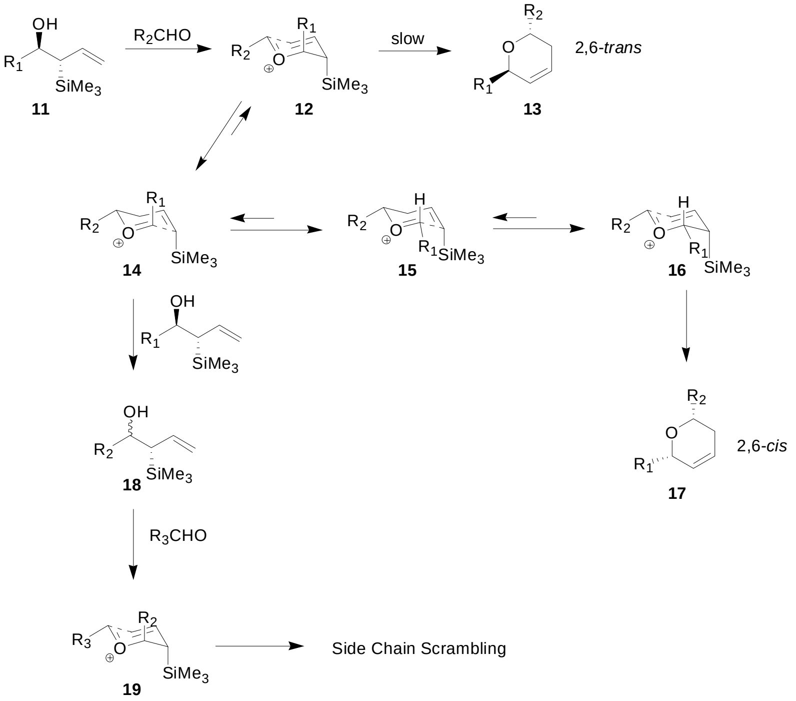
In initial studies to optimize reaction conditions, the isolated products, surprisingly, consisted of 2,6-*cis*-disubstituted dihydropyrans rather than the targeted *trans* diastereomer. Attempts to extend the method to include a variety of β-hydoxyallylsilane-aldehyde combinations and achieve the desired *trans* selectivity led only to complex reaction mixtures with side chain exchange (Figure 2.11).

Figure 2.11: 2,6-*cis*-substituted dihydropyrans with side chain exchange


OH
Ph
SiMe3
CHO
TMS-OTf, CH2Cl2,
4Å sieves, -78 °C
O
Ph
+
O
Ph
+
O
Ph
Ph
12%
17%
7%
OH
SiMe3
Ph
CHO
TMS-OTf, CH2Cl2,
4Å sieves, -78 °C
Ph
O
Ph
+
O
Ph
+
Ph
O
50%
3%
17%

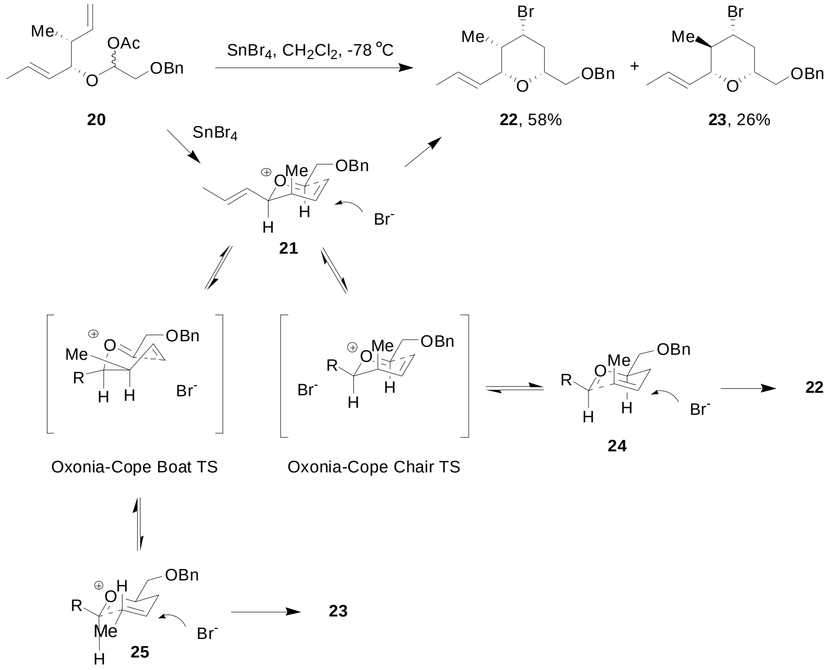
The unexpected exchange of allylsilane side chains and the preferential 2,6-*cis*-disubstituted dihydropyran formation was explained through the facile oxonia-Cope rearrangement prior to intramolecular Prins cyclization, as shown in Figure 2.12. The reaction was initially predicted to proceed through oxocarbenium ion intermediate **12,** which could cyclize via a chair transition state to give the desired product, **13**. However, oxonia-Cope rearrangement occurs at a faster rate than intramolecular Prins cyclization to give oxocarbenium ion intermediate **14**, placing the alkyl substituent in the thermodynamically unfavorable axial position. Intermediate **14** can then isomerize through a reversible nucleophilic addition to give **15**, which is structurally equivalent to intermediates proposed by Speckamp[13] in observed oxonia-Cope rearrangements of vinylsilanes in attempted intramolecular Prins cyclizations. Intermediate **15** can cyclize directly to form the 2,6-*cis*-disubstituted dihydropyran, **17**. The intermediacy of **14** and **15** also account for the observed side chain scrambling, where the addition of TMSOH creates the opportunity for release of one aldehyde equivalent and recombination with another.

Figure 2.12: Mechanism of 2,6-*cis*-disubstituted dihydropyran formation


OH
R1
SiMe3
11
R2CHO
R1
R2
O
SiMe3
12
slow
R2
O
R1
13
2,6-trans
R1
R2
O
SiMe3
14
H
R2
O
R1SiMe3
15
H
R2
O
R1
SiMe3
16
OH
R1
SiMe3
OH
R2
SiMe3
18
R3CHO
R2
R3
O
SiMe3
19
Side Chain Scrambling
R2
O
R1
17
2,6-cis

Rychnovsky demonstrated recently that oxonia-Cope rearrangements are faster than intramolecular Prins cyclization reactions when simple alkenes[59] are employed as nucleophiles. The oxonia-Cope rearrangement was first observed when an unexpected epimerization product was isolated from an intramolecular Prins cyclization (Figure 2.13). The α-acetoxy ether **20** was cyclized in the presence of $SnBr_4$ to produce the desired product **22** and its C3 epimer **23**. The intermediate oxocarbenium ion **24** could cyclize directly to afford the desired product, or undergo oxonia-Cope rearrangement via a chair transition state and then cyclize to give the desired product. However, oxonia-Cope rearrangement of oxocarbenium ion **21** through a boat transition state, ring flip and subsequent cyclization through a chair transition state explains the formation of the undesired C3 epimer, **23**.

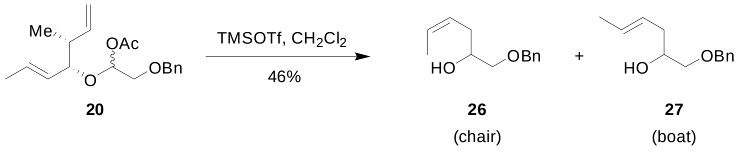
Figure 2.13: Proposed mechanistic pathway for epimerization



Me
OAc
OBn
O
20
SnBr4, CH2Cl2, -78 °C
Br
Me
O
OBn
22, 58%
+
Br
Me
O
OBn
23, 26%
SnBr4
Me
O
OBn
H
H
Br-
21
Me
O
OBn
R
H H
Br-
Oxonia-Cope Boat TS
R
Me
O
OBn
Br-
H
H
Oxonia-Cope Chair TS
R
Me
O
OBn
H
H
Br-
24
22
H
O
OBn
R
Me
H
25
Br-
23

Due to the unexpected boat transition state invoked in the oxonia-Cope rearrangement, Rychnovsky sought further evidence of the intermediacy of **25** in the formation of the undesired epimer by treatment of the starting material with TMSOTf. The reaction produced the *E* and *Z* alkenes **26** and **27** (Figure 2.14), both of which presumably arise from the hydrolysis of oxocarbenium ion intermediates **24** and **25**. Thus, it was concluded that the oxonia-Cope rearrangement plays an important role in the Prins cyclization of simple alkenes, providing unexpected outcomes.

Figure 2.14: Test of proposed oxonia-Cope boat transition state



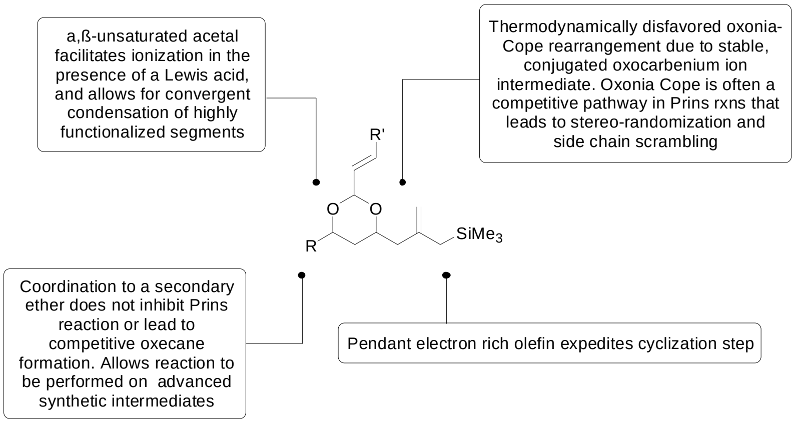
Me
OAc
OBn
O
20
TMSOTf, CH2Cl2
46%
HO
OBn
26
(chair)
+
HO
OBn
27
(boat)

III. Substrate Design

Tetrahydropyrans serve as the core of numerous marine natural products and are key structural features in a variety of polyether antibiotics and pheromones.[60] They also are the structural core of the majority of carbohydrates, which are the most abundant biological molecules on earth.[61] Numerous methods exist for the synthesis of highly functionalized tetrahydropyrans, such as hetero Diels-Alder reactions, oxiranyl anions, carbonyl ylides, Claisen rearrangements, ring opening of epoxides, iodolactonization, and ring closing metathesis. During the course of the present work towards the total synthesis of (+)-dactylolide the development of a new method for the construction 2,6-*cis*-disubstituted-4-methylenetetrahydropyrans became of interest.

As shown through the work of Overman and Rychnovsky, the ionization of cyclic acetals followed by intramolecular Prins cyclization provides a powerful entry into 2,4,6-trisubstituted tetrahydropyrans through carbon-carbon bond construction. The incorporation of allylsilanes in intramolecular Prins reactions has led to the formation of 2,6-*cis*-disubstituted-4-methylenetetrahydropyrans.[10] Based on the combination of these two results, the design of substrates that will efficiently and stereoselectively undergo intramolecular Prins cyclization at ambient temperature with mild Lewis acids that will tolerate other acid sensitive functional groups contained within the molecule should be possible.

Figure 2.15: Substrate design


a,ß-unsaturated acetal facilitates ionization in the presence of a Lewis acid, and allows for convergent condensation of highly functionalized segments
Thermodynamically disfavored oxonia-Cope rearrangement due to stable, conjugated oxocarbenium ion intermediate. Oxonia Cope is often a competitive pathway in Prins rxns that leads to stereo-randomization and side chain scrambling
R'
O
O
SiMe3
R
Coordination to a secondary ether does not inhibit Prins reaction or lead to competitive oxecane formation. Allows reaction to be performed on advanced synthetic intermediates
Pendant electron rich olefin expedites cyclization step

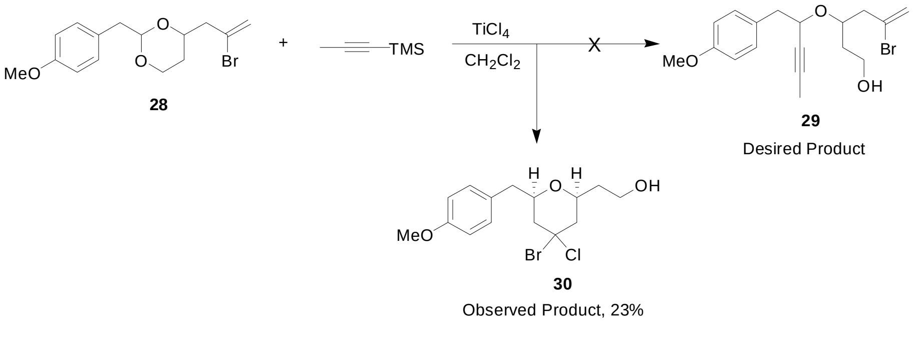
The general cyclization substrate consists of a cyclic α,β-unsaturated acetal with a pendent allylsilane (Figure 2.15). Given that Prins cyclization is initiated through ionization, it was postulated that this step could be facilitated through the use of cyclic α,β-unsaturated acetals. The use of cyclic acetals allows for the convergent condensation of highly functionalized aldehydes and 1,3-diols, alleviating the need for lengthy synthetic sequences and numerous protecting group manipulations. Employment of an α,β-unsaturated acetal provides a relatively stable conjugated oxocarbenium ion upon ionization. This is expected to thermodynamically disfavor the oxonia-Cope rearrangement which is often a competitive reaction pathway in Prins cyclizations and has been known to lead to stereorandomization and sidechain scrambling. Substrates are also designed with a pendent electron rich olefin in the form of an allylsilane, which is expected to expedite the cyclization step. Finally, as the objective is to develop a method applicable to advanced synthetic intermediates, cyclization reactions involving secondary ethers were examined to determine if the reaction is in any way inhibited, or oxacene formation becomes a competitive reaction pathway.

2.2. Results and Discussion

An intramolecular Prins cyclization reaction was first observed in the Floreancig labs in the course of efforts towards the total synthesis of (+)-dactylolide. Construction of the core of the molecule, a 2,6-*cis*-disubstituted-4-methylenetetrahydropyran, was envisioned to occur through an electron transfer initiated cyclization (ETIC) reaction.[62] However, during the synthesis of a model substrate for the ETIC reaction, the intramolecular Prins cyclization provided an undesired, although serendipitous result.

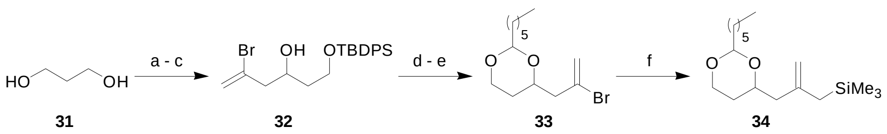
The reaction attempted was the addition of trimethylsilyl propyne into acetal **28** in the presence of titanium tetrachloride, as shown in Figure 2.16. The desired product, propargyl ether **29,** was not detected; rather, the only isolable product was a single diastereomer at the 2 and 6 positions of tetrahydropyran **30**. Tetrahydropyran **30** was postulated to arise from the intramolecular Prins cyclization with the pendent vinyl bromide upon ionization of the acetal and termination by trapping with chloride. Because of the interest in the generation of 2,6-*cis*-disubstituted-4-methylenetetrahydropyrans, utilizing pendent allylsilanes in the development of a novel method for intramolecular Prins cyclization reactions of cyclic acetals to provide these moieties became the primary focus.

Figure 2.16: Initially observed intramolecular Prins cyclization



Synthesis of the test substrate, cyclic acetal **34** containing a pendent allylsilane, began with 1,3-propane diol (Scheme 2.1). Monoprotection of the diol as the *tert*-butyldiphenylsilyl ether followed by Dess-Martin periodinane oxidation afforded the aldehyde, which was then reacted with 2,3-dibromopropene in the presence of metallic tin[63] and HBr to give homoallylic alcohol **32**. The silyl ether was removed with TBAF, and the diol was condensed with commercially available heptaldehyde to provide acetal **33**. Palladium-mediated coupling of the vinyl bromide with trimethylsilylmethylmagnesium chloride afforded the cyclization substrate, **34**, in good yield. These conditions will be used as the standard allylsilane formation conditions.

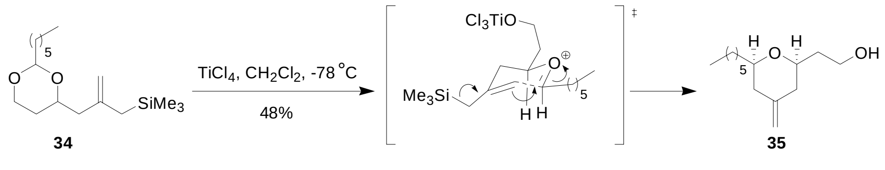
Scheme 2.1: Synthesis of initial Prins substrate



Reagents: a) TBDPSCl, NaH, DMF, b) DMPI, $NaHCO_3$, CH_2Cl_2, c) 2,3-dibromopropene, HBr, Sn, Et_2O:H_2O (1:1) (42% over 3 steps), d) TBAF, THF, 32%, e) heptaldehyde, PTSA, PhH, reflux, 64%, f) Me_3SiCH_2MgCl, $Pd(PPh_3)_4$, THF, 88%

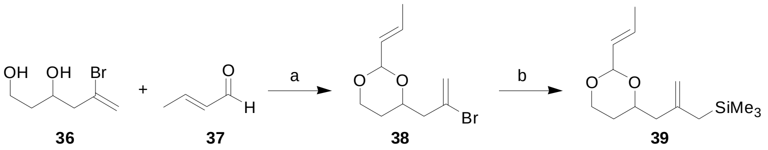
Intramolecular Prins cyclization of cyclic acetal **34** was performed using the same conditions under which the Prins reaction was initially observed. The acetal was treated with two equivalents of titanium tetrachloride in methylene chloride at -78 ºC, and 2,6-*cis*-substituted-4-methylenetetrahydropyran **35**, was isolated as a single diastereomer (Scheme 2.2). The *cis* stereochemical relationship between the C2 and C6 methines was confirmed through the strong correlation observed in the NOESY spectrum. The origin of the *cis* selectivity is assumed to be the preference of the two alkyl groups to adopt a pseudoequitorial orientation in the transition state.

Scheme 2.2: Intramolecular Prins cyclization with an allylsilane



With adequate proof that the cyclization reaction could be performed with complete stereoselectivity, and in accord with the desire to carry out this transformation on advanced synthetic intermediates, intramolecular Prins cyclizations of a variety of α,β-unsaturated acetals were examined. Cyclic α,β-unsaturated acetal **39** served as the primary cyclization substrate, and also as the substrate on which cyclization reaction conditions would be optimized. Cyclic α,β-unsaturated acetal **39** was synthesized in the same manner as cyclic acetal **34**, excepting the substitution of crotonaldehyde for heptaldehyde in the acid mediated acetal formation (Scheme 2.3)

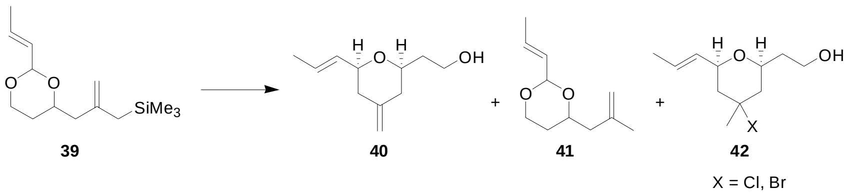
Scheme 2.3: α,β-Unsaturated acetal synthesis



Reagents: a) PTSA, PhH, reflux, 84%, b) Me_3SiCH_2MgCl, $Pd(PPh_3)_4$, THF, 92%

Intramolecular Prins cyclization of cyclic α,β-unsaturated acetal **39** to form 2,6-*cis*-substituted-4-methylenetetrahydropyran **40** was carried out using a variety of organic solvents and both Lewis and Brønstead acids (Scheme 2.4), the results of which are shown in Table 2.1.

Scheme 2.4: Cyclization with specifically designed substrate



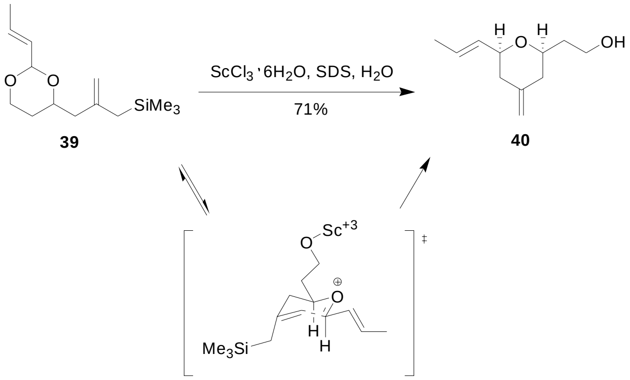
The initial conditions, using titanium tetrachloride as the Lewis acid, proved too harsh and led only to decomposition of the starting material. Switching to $BF_3•OEt_2$ afforded the desired cyclized tetrahydropyran in a moderate yield, as did reaction with trimethylaluminum. Use of the mild Lewis acids cerium chloride and cerium bromide also provided the desired tetrahydropyran in moderate yield. However, the lack of solubility of the cerium coupled with the associated nucleophilic counterions played a major role in the reaction, leading to the incorporation of both chlorine and bromine into the cyclized products **(42)** and promoting formation of the protodesylilated product **41** in varying yields. In situ generation of a soluble cerium (III) source through the combination of ceric ammonium nitrate and hydroquinone proved ineffective at initiating the cyclization reaction. Use of *p*-toluenesulfonic acid yielded a 1:1 mixture of the desired cyclized product in combination with protodesilylated product **41**. Both acetic acid and Montmorillonite K-10 clay also proved ineffective at initiating intramolecular Prins cyclization. Through the reaction conditions examined, it became clear that the enhanced reactivity afforded as a result of the α,β-unsaturated acetal required that cyclization be initiated with a mild Lewis acid bearing non-nucleophilic counterions to avoid decomposition, unproductive protodesilylation and incorporation of the counterion into the desired product.

Table 2.1: Intramolecular Prins cyclization with Lewis/Brønstead acids

Entry	Lewis/Brønstead acid	Solvent	Temperature	Product (%)
1	$TiCl_4$	CH_2Cl_2	-78 ºC	decomposition
2	BF_3•OEt_2	CH_2Cl_2	-78 ºC	**40** (52%)
3	$AlMe_3$	CH_2Cl_2	r.t.	**40** (55%)
4	$CeCl_3$	CH_3CN	r.t.	**40** (57%), **41** (22%)
5	$CeCl_3$	THF	r.t.	No rxn
6	$CeCl_3$	THF:H_2O	r.t.	No rxn
7	$CeCl_3$ on silica	CH_2Cl_2	r.t.	No rxn
8	$CeBr_3$	CH_3CN	r.t.	**40** (47%), **41** (12%)
9	CAN/Hydroquinone	CH_3CN	r.t.	No rxn
10	PTSA	CH_2Cl_2	r.t.	**40** (55%), **41** (3%)
11	PPTS	CH_2Cl_2	r.t.	decomposition
12	Montmorillonite K-10	CH_3CN	r.t.	No rxn
13	AcOH	CH_2Cl_2	r.t.	No rxn

Kobayashi's Lewis acid surfactant combined catalyst (LASC)[64] provided a solution to this problem. LASCs are composed of water-stable Lewis acidic cations, such as scandium (III) ions, and anionic surfactants, such as dodecyl sulfate that form stable colloidal dispersions rapidly in the presence of water. These catalysts act both as a Lewis acid, as well as a surfactant to simultaneously activate substrate molecules and form a hydrophobic reaction environment, effectively utilizing the concept of organic microsolvation to allow for rapid organic reactions in water. Kobayashi successfully employed these catalysts in carbon-carbon bond forming reactions such as aldol, allylation, and Mannich-type reactions, but had not demonstrated that they could be employed in reactions where the reactive electrophilic intermediates could be irreversibly consumed by water. Therefore, it was pleasing to observe that the addition of 10 mol % $ScCl_3$ to a suspension of allylsilane **39** and 30 mol% of sodium dodecylsulfate (SDS) in water rapidly generated a colloidal dispersion that afforded a 71% yield of the desired 2,6-*cis*-substituted-4-methylenetetrahydropyran **40** as a single diastereomer in the first aqueous Prins cyclization reaction (Scheme 2.5). The *cis* stereochemical relationship of the C2 and C6 protons was verified through the strong correlation observed in the NOESY spectrum.

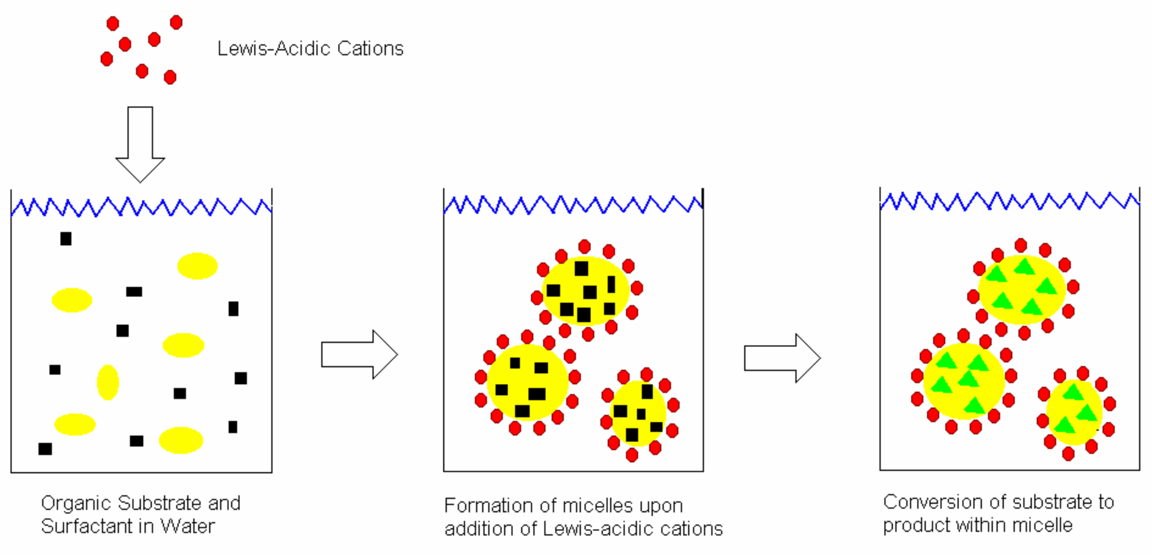
Scheme 2.5: Initial aqueous Prins reaction



The aqueous Prins reaction conditions are mild and procedurally simple. The reaction is performed in water at ambient temperature without need for organic cosolvents. The reaction mixture appears as a colloidal dispersion in which the cyclization reaction proceeds efficiently and stereoselectively inside micelles. Micelles are generated *in situ* by the addition of Lewis acid into a rapidly stirring suspension of the cyclization substrate and the surfactant (Figure 2.17).

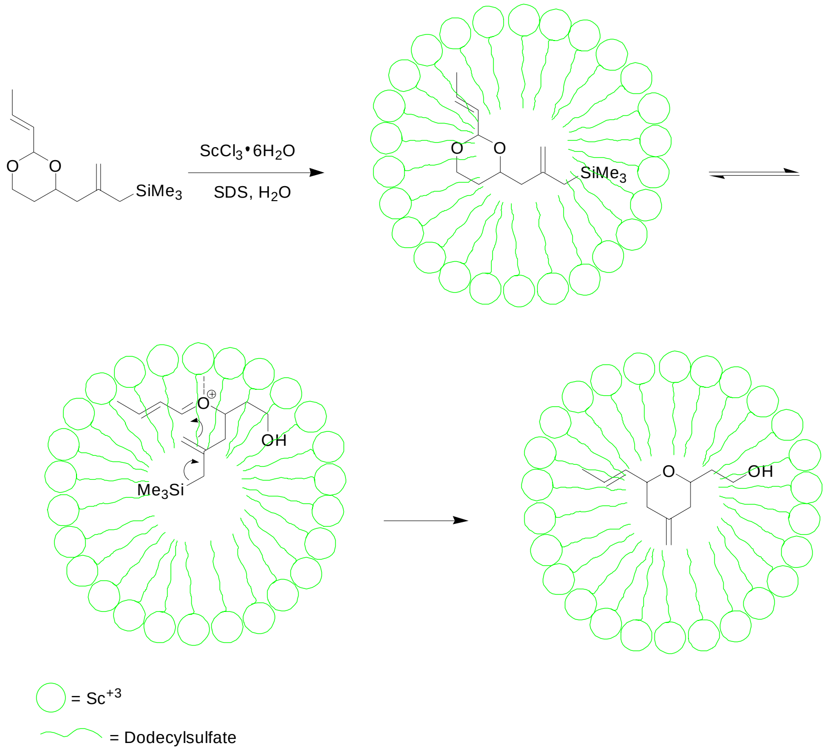
Only a catalytic amount of both the Lewis acid and surfactant are needed to effect reaction. In the absence of the cyclization substrate, with simply the combination of the Lewis acid and surfactant in water, the reaction mixture appears homogeneous and no micelle formation is observed. Stirring a mixture of the water soluble Lewis acid and the cyclization substrate in water for extended periods of time failed to yield any of the desired cyclization product and resulted in recovery of the starting material with minimal acetal hydrolysis.

Figure 2.17: Schematic of aqueous Prins reaction


Lewis-Acidic Cations
Organic Substrate and Surfactant in Water
Formation of micelles upon addition of Lewis-acidic cations
Conversion of substrate to product within micelle

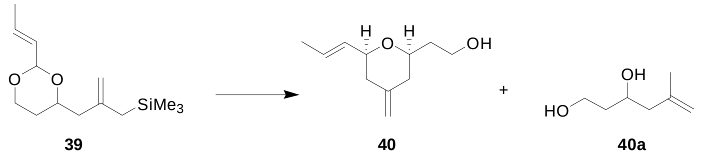
Based on the inability to hydrate the exocyclic olefin by resubjecting the resulting tetrahydropyran to the reaction conditions, and the inability to effect reaction in the absence of the surfactant, it is postulated that all starting materials, intermediates and products are contained within the hydrophobic interior of the micelle for the duration of the reaction. Nucleation by the cyclization substrate and micelle formation occurs upon addition of the Lewis acid to the suspension. Once viable micelles are formed, the substrate can be envisioned to diffuse through the hydrophobic interior to the periphery of the micelle where it can encounter and coordinate to the Lewis acidic cations. Ionization of the acetal ensues to form the intermediate oxocarbenium ion which is rapidly trapped with the pendent allylsilane resulting in the formation of a 2,6-*cis*-disubstituted-4-methylenetetrahydropyran, as shown in Figure 2.18.

Figure 2.18: Intramolecular Prins contained within a micelle



The effect of surfactant chain length on micelle and stability was examined. As summarized in Table 2.2, the dodecanesulfonate provided the best yields, while surfactants with shorter or longer alkyl chains resulted in lower yields. In addition to surfactant alkyl chain length, concentration proved to be a significant factor in micelle formation. Acheivement of a critical micelle concentration was necessary for formation and maintenance of viable micelles for extended reaction times. The critical micelle concentration could typically be achieved by performing the reaction at a 0.5 M concentration with respect to the cyclization substrate, 10 mol% of the Lewis acid $ScCl_3$•$6H_2O$ and 40 mol% of sodium dodecylsulfate.

Table 2.2: Optimal surfactant chain length



Entry	Lewis Acid	Surfactant	Concentration (with respect to substrate)	Product (%)
1	$ScCl_3$•$6H_2O$	$NaO_4SC_{10}H_{21}$	0.5 M	**40** (64%), **40a** (20%)
2	$ScCl_3$•$6H_2O$	$NaO_4SC_{12}H_{25}$	0.5 M	**40** (74%), **40a** (23%)
3	$ScCl_3$•$6H_2O$	$NaO_4SC_{18}H_{30}$	0.5 M	**40** (50%), **40a** (9%)

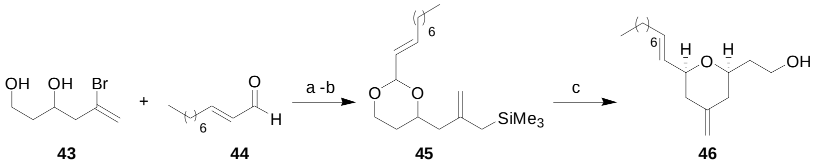
In an effort to make the cyclization a more cost effective reaction, the use of various cerium (III) salts was examined. Cerium was the Lewis acid of choice based on cost as well as predicted compatibility with reactions in aqueous media.[65] Cerium has a hydrolysis constant (pK_h) of 8.3 and an exchange rate constant for substitution of inner-sphere water ligands (WERC) of 2.7×10^8 $M^{-1}s^{-1}$, making it an ideal Lewis acid for use in aqueous conditions. The appropriate range for sufficient Lewis acidity of a metal cation in water is a pK_h between 4.3 and 10.8. A value of less than 4.3 indicates that the metal cation is easily hydrolyzed. Conversely, any metal cation with a pK_h value greater than 10.8 is deemed too stable. A WERC value greater than 3.2×10^6 $M^{-1}s^{-1}$ is also required for sufficient Lewis acidity. The cost/benefit analysis of the various cerium (III) salts based on a 0.4 mmol scale reaction with respect to the cyclization substrate is shown in Table 2.3. Although slightly less reactive than $Ce(OTf)_3$-based micelles, $Ce(NO_3)_3$•$6H_2O$ provides an attractive alternative to $ScCl_3$•$6H_2O$ that effectively catalyzes the intramolecular Prins cyclization at a fraction of the cost.

Table 2.3: Cost/benefit analysis of cerium III salts

Entry	Lewis Acid	Scale (with respect to Lewis acid)	Surfactant	Product (%)	Cost/rxn
1	$ScCl_3$•$6H_2O$	0.04 mmol	$NaO_4SC_{12}H_{25}$	**40** (74%)	$0.20
2	$CeCl_3$•$6H_2O$	0.04 mmol	$NaO_4SC_{12}H_{25}$	**40** (67%)	$0.01
3	$Ce(OTf)_3$•H_2O	0.04 mmol	$NaO_4SC_{12}H_{25}$	**40** (77%)	$0.33
4	$Ce(NO_3)_3$•$6H_2O$	0.04 mmol	$NaO_4SC_{12}H_{25}$	**40** (76%)	$0.003

The extent to which the hydrophobic nature of the molecule influences the aqueous Prins reaction was examined through the cyclization reaction of **45**. Cyclic α,β-unsaturated acetal **45** was synthesized in the same manner as acetal **34**, excepting the substitution of 2-decenal for heptaldehyde in the acid mediated acetal formation (Scheme 2.6). Intramolecular Prins cyclization was performed using $ScCl_3$-micelle conditions, to afford the desired tetrahydropyran **46** in a 73% yield, indicating that increasing the hydrophobicity of the substrate has a negligible effect on reaction yield.

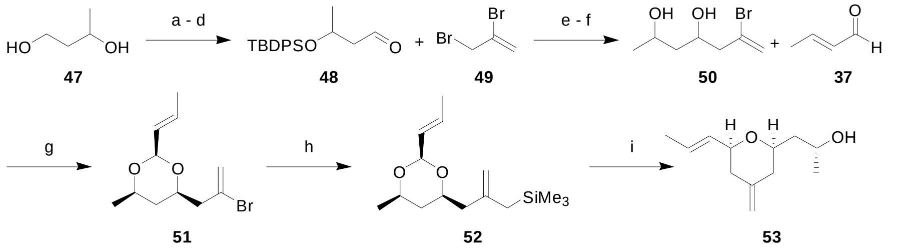
Scheme 2.6: Synthesis of tetrahydropyran **46**



Reagents: a) PTSA, PhH, reflux, 78%, b) Me_3SiCH_2MgCl, $Pd(PPh_3)_4$, THF, 71% c) $ScCl_3$•$6H_2O$, SDS, H_2O, 73%

As the objective is to develop a method applicable to advanced synthetic intermediates, cyclization reaction involving secondary ether **52** was examined to determine if reaction was in any way inhibited, or oxacene formation became a competitive reaction pathway (Scheme 2.7). The synthesis of **52** began with protection of the primary alcohol as the pivalate ester, followed by protection of the secondary alcohol as the silyl ether. The pivalate ester was removed with sodium methoxide in methanol and the resulting alcohol was oxidized with Dess-Martin periodinane to provide aldehyde **48**. Aldehyde **48** was then reacted with 2,3-dibromopropene in the presence of metallic tin and HBr to afford the resulting homoallylic alcohol, which followed by silyl ether deprotection afforded diol **50**. The diol was condensed with crotonaldehyde to provide cyclic acetal **51**, which was converted to the allylsilane **52** by the standard palladium-mediated coupling with trimethylsilylmethylmagnesium chloride. Intramolecular Prins cyclization of **52** using $Ce(NO_3)_3$-based micelles provided tetrahydropyran **53** in 80% yield indicating that the secondary ether does not inhibit cyclization or lead to competitive oxecene formation.

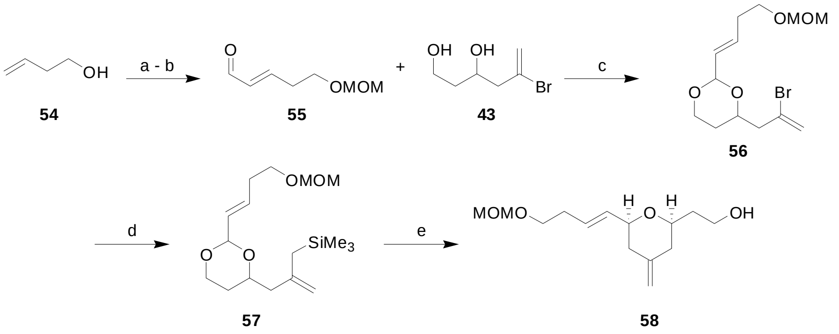
Scheme 2.7: Prins cyclization of secondary ether **54**



Reagents: a) Piv-Cl, Et_3N, CH_2Cl_2, b) TBDPSCl, imidazole, DMF, c) Na, MeOH, d) DMPI, CH_2Cl_2, (48% over 4 steps), e) Sn, HBr, Et_2O:H_2O, f) TBAF, THF (91% over 2 steps), g) PTSA, PhH, refulx, 70%, h) Me_3SiCH_2MgCl, $Pd(PPh_3)_4$, THF, 68%, i) $Ce(NO_3)_3 \cdot 6H_2O$, SDS, H_2O, 80%.

The mild nature of the reaction conditions, specifically their compatibility with other acid-sensitive functional groups contained within the cyclization substrate, was examined through the cyclization of cyclic α,β-unsaturated acetal **57** (Scheme 2.8). Synthesis of the acetal commenced with protection of 3-butenol as the methoxymethyl ether, followed by cross metathesis with acrolein using Grubbs 2nd generation catalyst to provide aldehyde **55**. The aldehyde was condensed with diol **43** to form acetal **56** using *p*-toluenesulfonic acid and magnesium sulfate[66] in methylene chloride. The vinyl bromide was converted to the allyl silane using the standard palladium mediated coupling conditions to provide acetal **57**. Intramolecular Prins cyclization of cyclic α,β-unsaturated acetal **57** with $Ce(NO_3)_3$-based micelles provided tetrahydropyran **58** in reasonable yield, indicating the compatibility of these reaction conditions with acid-sensitive functional groups.

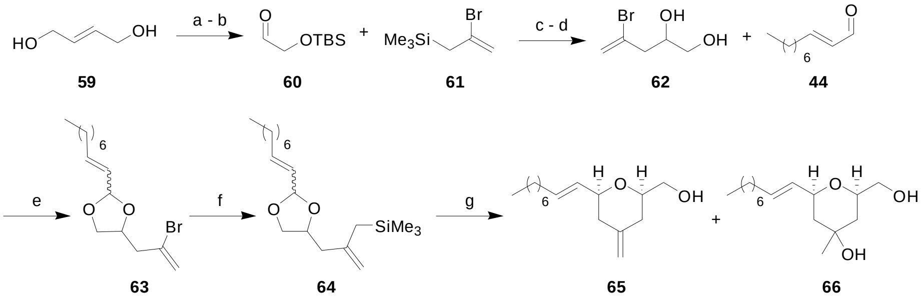
Scheme 2.8: Prins cyclization with an acid-sensitive functional group



Reagents: a) MOM-Cl, DIPEA, CH_2Cl_2, 60%, b) Grubbs II, CH_2Cl_2, acrolien, 28%, c) PTSA, $MgSO_4$, CH_2Cl_2, 76%, d) Me_3SiCH_2MgCl, $Pd(PPh_3)_4$, THF, 80%, e) $Ce(NO_3)_3 \cdot 6H_2O$, SDS, H_2O, 43%.

Cyclization reaction of 1,3-dioxolanes was examined, as shown in Scheme 2.9. The synthesis of cyclic acetal **64** began with the protection of 1,4-butene diol with *tert*-butyldimethylsilyl chloride and sodium hydride in DMF to afford the bis-silyl ether. Ozonalysis followed by reduction with triphenylphosphine provided aldehyde **60**. Allylation of aldehyde **60** with 2-bromoallyltrimethylsilane[67] **61** followed by silyl deprotection afforded diol **62**. Acid mediated condensation of diol **62** with decenal provided cyclic acetal **63**. The vinyl bromide was converted to the allylsilane through palladium mediated coupling with trimethylsilylmethylzinc bromide[68] (prepared in situ from trimethylsilylmethylmagnesium bromide and zinc bromide). While reaction of cyclic acetal **64** with both the $ScCl_3$- and $Ce(NO_3)_3$-based micelles afforded the desired tetrahydropyran **65**, the $ScCl_3$-based micelles provided higher yields. The major byproduct isolated only from $Ce(NO_3)_3$-based micelle reactions was the tertiary alcohol **66** rather than the exocyclic olefin.

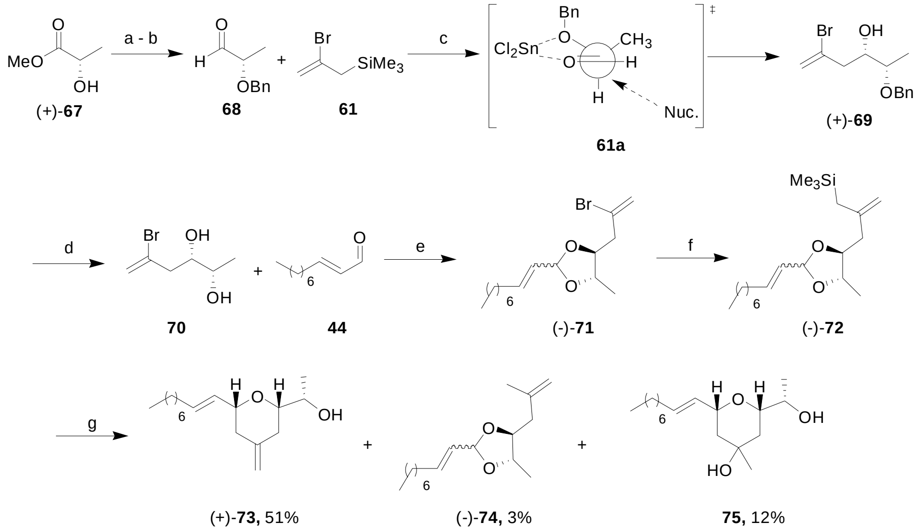
Scheme 2.9: Prins cyclization of a 1,3-dioxolane **64**



Reagents: a) TBSCl, NaH, DMF, b) i. O$_3$, CH$_2$Cl$_2$, ii. PPh$_3$, (51% over two steps), c) TiCl$_4$, CH$_2$Cl$_2$, -78 °C, 75%, d) TBAF, THF, 83%, e) PTSA, PhH, reflux, 78%, f) ZnBr$_2$, Me$_3$SiCH$_2$MgCl, Pd(PPh$_3$)$_4$, THF, 78%, g) ScCl$_3$•6H$_2$O, SDS, H$_2$O, 77%.

Cyclization of enantiomerically enriched cyclic α,β-unsaturated acetal (-)-**72** was examined in order to determine if oxonia-Cope rearrangement was indeed a competitive reaction pathway in the intramolecular Prins cyclization. The starting material for the synthesis, as shown in Scheme 2.10, was (+)-(*S*)-methyl lactate, which was protected as the benzyl ether using benzyl bromide in the presence of silver (I) oxide.[69] The ester was reduced with DIBAL-H to provide aldehyde **68**. Allylation with 2-bromoallyltrimethylsilane in the presence of tin tetrachloride provided allyl alcohol **69** in 45:1 diastereoselectivity and 79% ee. The benzyl protecting group was removed with titanium tetrachloride to give diol **70**, which was subjected to acid mediated condensation with decenal to provide vinyl bromide **71**. The vinyl bromide was converted to the allylsilane through palladium-mediated coupling with trimethylsilylmethylzinc bromide to provide cyclic α,β-unsaturated acetal (-)-**72**. In accord with the cyclization of cyclic α,β-unsaturated acetal **64**, ScCl$_3$-based micelles provided higher yields of the desired tetrahyropyran (+)-**73**. Tetrahydropyran (+)-**73** was isolated as a single diastereomer, and the *cis* stereochemical relationship of the C2/C6 methine protons was confirmed through the strong correlation observed in the NOESY spectrum. HPLC analysis of the benzyl ester of tetrahydropyran (+)-**73** showed no loss of ee, indicating that the oxonia-Cope rearrangement is not a competitive reaction pathway in intramolecular Prins cyclization reactions of cyclic α,β-unsaturated acetals.

Scheme 2.10: Synthesis of enantioenriched cyclic -unsaturated acetal **(-)-72**



Reagents: a) Ag_2O, Bn-Br, Et_2O, 63%, b) DIBAL, CH_2Cl_2, -98 C, c) $SnCl_4$, -78°C, (61% over two steps, 45:1 d.e, 79% ee), d) $TiCl_4$, CH_2Cl_2, 0° C, 82%, e) PTSA, $MgSO_4$, CH_2Cl_2, -20° C, 85%, f) $ZnBr_2$, Me_3SiCH_2MgCl, $Pd(PPh_3)_4$, THF, 89%,g) $ScCl_3 \cdot 6H_2O$, SDS.

In addition to 2,6-*cis*-disubstituted-4-methylenetetrahydropyran (+)-**73**, the protodesilylated product (-)-**74** and tertiary alcohol **75** were isolated as byproducts of the reaction. Resubjecting tetrathydropyran (+)-**73** to the cyclization reaction conditions for an extended time failed to yield tertiary alcohol **75** and resulted in the complete recovery of starting material. Therefore, tertiary alcohol **75** is proposed to result from intramolecular Prins cyclization of alkene (-)-**74** followed by trapping of the intermediate cation with either water or dodecyl sulfate. The enhanced reactivity afforded through the use of 1,3-dioxolanes allows for significantly faster cyclization reactions than those of 1,3-dioxanes, as well as for the use of less nucleophilic, unactivated olefins as nucleophiles.

Methyl glycolate severed as the starting material for the synthesis of the racemate of tetrahydropyran **73**, which was used for HPLC analysis of enantiomeric excess. Methyl glycolate was protected with benzyl bromide in the presence of silver (I) oxide. The benzyl ether was then alkylated[70] with methyl iodide and reduced with DIBAL-H to provide the racemate of aldehyde

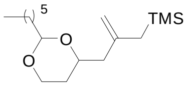
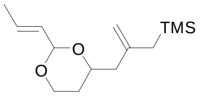
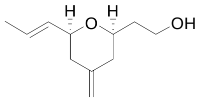
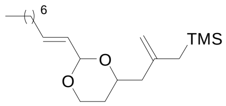
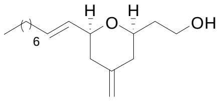
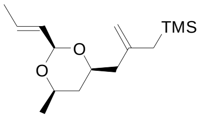
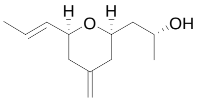
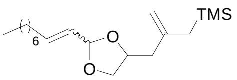
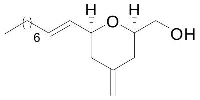
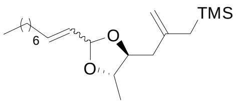
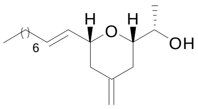
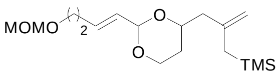
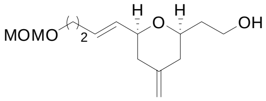
68. The aldehyde was carried through the synthesis in the same manner to ultimately yield *rac*-**73**.

2.3. Conclusion

An innovative variant of the Prins cyclization has been developed in which cyclization reactions occur efficiently and stereoselectively under mild conditions when cyclic α,β-unsaturated acetals are ionized in the presence of allysilanes to provide 2,6-*cis*-disubstituted-4-methylenetetrahydropyrans. These cost-effective reactions are procedurally simplistic, and utilize the environmentally benign solvent, water, without need for organic cosolvents. The reactions are catalyzed by Lewis acid surfactant combined catalysts (LASCs) generated in situ through the combination of either Lewis acid $ScCl_3{\cdot}6H_2O$ or $Ce(NO_3)_3{\cdot}6H_2O$ and the surfactant sodium dodecylsulfate (SDS) in the presence of the cyclization substrate in water at ambient temperature. These reaction conditions effectively utilize the concept of organic microsolvation to provide a sufficiently anhydrous environment to protect oxocarbenium ion intermediates from hydrolysis. Both α,β-unstaurated 1,3-dioxanes and 1,3-dioxolanes having pendent electron rich olefins in the form of allylsilanes react under these conditions to provide a variety of 2,6-*cis*-disubstituted-4-methyletetrahydropyrans. The reaction conditions are sufficiently mild so as to tolerate the incorporation of acid-sensitive functional groups within the cyclization substrate.

Table 2.4 provides a summary of the cyclic α,β-unsaturated acetals subjected to intramolecular Prins cyclization reactions using the aqueous Prins reaction conditions. Reactions are performed using either 10 mol % $ScCl_3{\cdot}6H_2O$ or $Ce(NO_3)_3{\cdot}6H_2O$, 30-60 mol % SDS, at 0.5 M with respect to the acetal and isolated yields of purified products are reported.

Table 2.4: Summary of intramolecular Prins cyclization substrates

Entry	Substrate	Product	% Yield
1.		No Reaction	
2.			74
3.			73
4.			80
5.			77
6.			51
7.			43

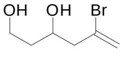
2.4. Experimental

General Procedures. All reactions were performed in oven or flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.

Materials. Tetrahydrofuran and diethyl ether were dried by passage through an activated alumina column under positive N_2 pressure. Methylene chloride was distilled under N_2 from CaH. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography.

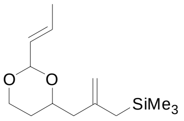
Instrumentation. High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. 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 was used as a reference value, for ^{1}H NMR: $CDCl_3$ = 7.27 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; b = broad). HPLC analysis was performed with a HP series 1100 instrument using either a Chiralcel OD-H or OJ or CHIRAPAK AD column.

5-Bromo-hex-5-ene-1,3-diol (36)


36

To 1,3-propanediol (1.00 g, 13.14 mmol) in THF (20 mL) was added sodium hydride (60% dispersion in mineral oil, 0.54 g, 13.14 mmol). The reaction mix was stirred for 30 min. then *tert*-butylchlorodiphenylsilane (3.62 g, 13.14 mmol) was added. The reaction mixture was stirred for 1.5 h then quenched with ice chips, extracted into ether, dried ($MgSO_4$), and concentrated. The resulting residue was dissolved in CH_2Cl_2 (20 mL) under N_2 and the temperature was decreased to 0 ºC before Dess-Martin periodinane (6.70 g, 15.77 mmol) was added. The reaction mixture was stirred at 23 ºC for 30 min. then quenched with saturated aqueous $NaHCO_3$ (5 mL) and saturated aqueous $Na_2S_2O_3$ (5 mL). The reaction mixture was stirred for an additional 20 min. before the two layers were separated. The organic layer was dried ($MgSO_4$), and concentrated. To a stirring suspension of tin powder (1.95 g, 16.42 mmol) in an ether-water mixture (25 mL:12.5 mL) were added a few drops of HBr, 2,3-dibromopropene (3.15 g, 15.76 mmol) and the resulting residue (in 10 mL of ether). The reaction mixture was stirred for 18 h before it was filtered through a pad of Celite. The filtrate was washed with brine. The organic layer was dried ($MgSO_4$), concentrated, and filtered through a plug of silica gel. The resulting residue was dissolved in THF (10 mL) under N_2 and tetrabutylammonium fluoride (1.72 g, 5.56 mmol) was added. The reaction mixture was stirred for 1 h, then concentrated and purified by flash chromatography (5% hexanes in EtOAc) to afford the desired product (0.84 g, 32%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (s, 1H), 5.51 (s, 1H), 4.16 (m, 1H), 3.85 (m, 3H), 2.62 (dd, J = 14.4, 7.8 Hz, 1H), 2.55 (dd. J = 14.3, 4.9 Hz, 1H), 1.75 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.5, 119.6, 69.2, 61.1, 49.6, 37.8; IR (neat) 3349, 2939, 1736, 1634, 1424, 1372, 1255, 1050, 886 cm^{-1}; HRMS (EI): *m/z* calcd for C_4H_5BrO (M – C_2H_7O) 147.952376, found 147.9523.

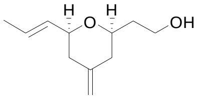
Trimethyl[2-(2-propenyl[1,3]dioxan-4-ylmethyl)allyl]silane (39)



39

This procedure is representative of a standard acetal formation followed by palladium mediated coupling to afford the desired cyclization substrate. To **36** (0.20 g, 1.02 mmol) in benzene (5 mL) was added crotanaldehyde (0.08 g, 0.82 mmol) and *p*-toluenesulfonic acid (cat.). The reaction mixture was refluxed for 2 h, then cooled to room temperature and triethylamine (0.2 mL) was added. The reaction mixture was stirred for 20 min. then extracted into ether, washed with 10% aqueous NaOH and brine, dried ($MgSO_4$), and concentrated. The resulting residue was flashed through a silica gel column (10% EtOAc in hexanes) then dissolved in THF (5 mL). Palladium tetrakistriphenylphosphine (0.03 g, 0.03 mmol) was added followed by trimethylsilylmethylmagnesium chloride (1.0 M in ether, 3.29 mmol, 3.29 mL). The reaction mixture was heated to reflux for 3 h, then cooled to room temperature and quenched with saturated aqueous NH_4Cl. The reaction mixture was extracted into ethyl acetate, washed with H_2O, dried ($MgSO_4$), and concentrated. The resulting residue was purified by flash chromatography (10% triethylamine, 5% EtOAc in hexanes) to afford the desired product (0.15 g, 92%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (dq, *J* = 15.5, 6.5 Hz, 1H), 5.57 (m, 1H), 4.95 (d, *J* = 5.1 Hz, 1H), 4.66 (s, 1H), 4.61 (s, 1H), 4.15 (m, 1H), 3.80 (m, 2H), 2.38 (dd, *J* = 13.9, 5.7 Hz, 1H), 2.10 (dd, *J* = 13.9, 7.5 Hz, 1H), 1.75 (d, *J* = 1.5 Hz, 1H), 1.72 (d, *J* = 1.5 Hz, 1H), 1.64 (m, 2H), 1.55 (d, *J* = 2.9 Hz, 3H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 129.8, 129.0, 110.0, 101.0, 75.9, 66.9, 45.1, 31.5, 27.6, 19.6, -1.4; IR (neat) 3069, 2952, 1723, 1658, 1440, 1374, 1374, 1309, 1287, 1258, 1192, 1054, 974, 836 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{14}H_{26}O_2Si$ (M^+) 254.170209, found 254.170992.

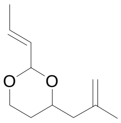
2-(4-Methylene-6-propenyl-tetrahydropyran-2-yl)-ethanol (40)



40

To a suspension of cerium chloride (0.19 g, 0.79 mmol) in acetonitrile (5 mL) was added **39** (0.10 g, 0.39 mmol). The reaction mixture was sonicated for 3 h, then quenched by the addition of saturated aqueous $NaHCO_3$. The reaction mixture was extracted with ether (2 x). The combined organic layers were dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (2% Et_2O in pentanes) to afford the desired product **2** (0.04 g, 57%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (dq, *J* = 15.4, 1.0 Hz, 1H), 5.49 (ddq, *J* = 16.9, 6.2, 1.5 Hz, 1H), 4.75 (d, *J* = 1.7 Hz, 1H), 4.74 (d, *J* = 1.7 Hz, 1H), 3.79 (m, 3H), 3.58 (m, 1H), 2.76 (bs, 1H), 2.22 (dd, *J* = 15.0, 11.2 Hz, 2H), 2.05 (dd, *J* = 12.5, 12.3 Hz, 2H), 1.85 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 131.9, 127.2, 109.0, 79.2, 78.7, 61.4, 41.1, 40.8, 38.4, 17.8; IR (neat) 3410, 3069, 2916, 2850, 1701, 1650, 1440, 1389, 1309, 1258, 1185, 1054 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{11}H_{18}O_2$ (M^+) 182.130680, found 182.130982.

4-(2-Methylallyl)-2-propenyl-[1,3]dioxane (41)

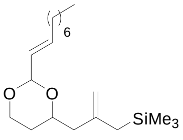


41

41 results from desilylation of the starting material (0.02 g, 22%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.91 (m, 1H), 5.54 (ddq, *J* = 15.5, 4.9, 1.3 Hz, 1H), 4.92 (d, *J* = 4.9 Hz, 1H), 4.79 (s, 1H), 4.73 (s, 1H), 4.13 (dd, 11.4, 4.8 Hz, 1H), 3.79 (m, 2H), 2.38 (dd, *J* = 13.9, 6.3 Hz, 1H), 2.16 (dd, 13.9, 6.7 Hz, 1H), 1.74 (s, 3H), 1.71 (d, *J* = 6.5 Hz, 3H), 1.61 (ddd, 23.8, 11.8, 4.9 Hz, 1H), 1.42 (d, *J* = 13.3 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.6, 130.4, 128.5, 113.0, 100.8, 75.4, 66.7, 44.7, 31.1, 23.0, 17.8; IR (neat) 3076, 2960, 2916, 2850, 2727, 1687, 1636, 1440, 1367, 1316, 1243, 1134, 1076, 1010, 960, 887 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{11}H_{17}O_2$ (M^+) 181.122855, found 181.122805.

This procedure is representative of a standard aqueous Prins reaction. To trimethyl[2-(2-propenyl[1,3]dioxan-4-ylmethyl)allyl]silane (0.10 g, 0.39 mmol) in H_2O (1 mL) was added sodium dodecylsulfate (0.03 g, 0.12 mmol) followed by cerium nitrate hexahydrate (0.01 g, 0.04 mmol). Micelles formed immediately upon the addition of the cerium nitrate and the reaction mixture was stirred at 1100 rmp for 18 h. The reaction mixture was extracted into ether, washed with 10% aqueous HCl, dried ($MgSO_4$), and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product **2** (0.06 g, 76%).

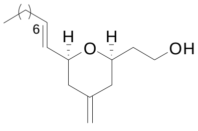
Trimethyl-[2-(2-non-1-enyl-[1,3]dioxan-4-ylmethyl)-allyl]-silane (45)



45

This cyclization substrate was obtained using standard acid mediated acetal formation conditions with **36** (0.50 g, 2.56 mmol) and trans-2-decenal (0.39 g, 2.56 mmol). A portion of the resulting residue (250 mg, 0.75 mmol) was subjected to standard palladium-mediated coupling conditions using palladium tetrakistriphenylphosphine (0.09 g, 0.08 mmol) and trimethylsilylmethylmagnesium chloride (1.0 M in ether, 3.77 mmol, 3.77 mL) to afford the desired cyclization substrate (0.18 g, 71%): ^1H NMR (300 MHz, $CDCl_3$) δ 5.92 (dt, *J* = 14.9, 6.6 Hz, 1H), 5.53 (ddt, *J* = 15.1, 5.0, 1.4 Hz, 1H), 4.95 (d, *J* = 5.0 Hz, 1H), 4.65 (s, 1H), 4.61 (s, 1H), 4.15 (ddd, 11.4, 4.8, 1.2 Hz, 1H), 3.82 (m, 2H), 2.38 (dd, *J* = 13.9, 5.5 Hz, 1H), 2.08 (m, 3H), 1.72 – 1.26 (m, 14H), 0.87 (t, *J* = 6.5 Hz, 3H), 0.03 (s, 9H)); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 135.4, 127.4, 110.0, 101.1, 76.3, 66.8, 45.1, 32.2, 32.0, 31.4, 29.4, 29.3, 28.9, 27.5, 22.8, 14.4, -0.58; IR (neat) 2952, 2923, 2850, 1672, 1636, 1461, 1352, 1243, 1134, 1018, 967, 858 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{20}H_{38}O_2Si$ (M^+) 338.264109, found 338.263779.

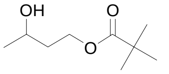
2-(4-Methylene-6-non-1-enyl-tetrahydropyran-2-yl)ethanol (46)



46

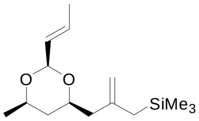
Trimethyl-[2-(2-non-1-enyl-[1,3]dioxan-4-ylmethyl)-allyl]-silane (**45**) (0.10 g, 0.29 mmol) was subjected to standard aqueous Prins cyclization conditions using scandium chloride hexahydrate (0.004 g, 0.03 mmol) and sodium dodecylsulfate (0.03 g, 0.09 mmol) to afford the desired product (0.06 g, 73%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.66 (dtd, *J* = 15.4, 6.6, 0.9 Hz, 1H), 5.47 (ddt, *J* = 15.4, 6.2, 1.3 Hz, 1H), 4.73 (s, 2H), 3.79 (t, *J* = 5.0 Hz, 2H), 3.74 (m, 1H), 3.57 (m, 1H), 2.76 (s, 1H), 2.26 – 1.97 (m, 6H), 1.80 (m, 2H), 1.26 (m, 10H), 0.87 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 132.7, 130.5, 108.9, 79.3, 78.7, 61.3, 41.2, 40.8, 38.4, 32.4, 32.0, 29.8, 22.8, 14.1; IR (neat) 3396, 2923, 2850, 1650, 1461, 1425, 1352, 1309, 1054, 960, 894 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{17}H_{30}O_2$ (M^+) 266.224580, found 266.225400.

2,2-Dimethylpropionic acid 3-hydroxy-butyl ester



To 1,3-butanediol (1.50 g, 16.64 mmol) in CH_2Cl_2 (15 mL) at 0 ºC was added triethylamine (7.58 g, 74.89 mmol) followed by pivaloyl chloride (2.20 g, 18.31 mmol). The reaction mixture was stirred for 4 h at room temperature then quenched with H_2O. The two layers were separated and the organic layer was dried ($MgSO_4$), concentrated and purified by flash chromatography (40% EtOAc in hexanes) to afford the desired product (79%, 2.28 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.36 (m, 1H), 4.11 (m, 1H), 3.86 (m, 1H), 2.05 (br s, 1H), 1.74 (m, 2H), 1.26 (d, *J* = 4.8 Hz, 3H), 1.18 (s, 9H).[1]

Trimethyl-[2-(6-methyl-2-propenyl-[1,3]dioxan-4-ylmethyl)-allyl]-silane (52)

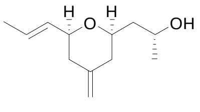


52

To 2,2-dimethyl-propionic acid 3-hydroxybutyl ester (2.28 g, 13.08 mmol) in DMF (15 mL) was added triethylamine (1.58 g, 15.70 mmol) followed by *tert*-butylchlorodiphenylsilane (3.95 g, 14.39 mmol). The reaction mixture was stirred for 48 h, and then quenched with H_2O. The two layers were separated and the organic layer was dried ($MgSO_4$), and concentrated. Sodium (0.299 g, 13.08 mmol) was dissolved in MeOH (20 mL) under N_2 at 0 ºC. The resulting residue (in 5 mL of MeOH) was added drop wise. The reaction mixture was heated to 40 ºC for 12 h, then cooled to room temperature, quenched with H_2O and extracted with EtOAc. The organic layer was dried ($MgSO_4$), concentrated and purified by flash chromatography (20% EtOAc in hexanes) to afford the desired primary alcohol (2.05 g, 48%). The resulting alcohol was dissolved in CH_2Cl_2 (30 mL) under N_2 and the temperature was decreased to 0 ºC before Dess-Martin periodinane (3.19 g, 7.50 mmol) was added. The reaction mixture was stirred for 1 h at room temperature. The temperature was then decreased to 0 ºC and the reaction mixture was quenched with saturated aqueous $NaHCO_3$ and saturated aqueous $Na_2S_2O_3$. The reaction mixture was warmed to room temperature and stirred for 30 min. before the two layers were separated. The organic layer was dried ($MgSO_4$) and concentrated. To a stirring suspension of tin powder (0.93 g, 7.82 mmol) in an ether-water mixture (15 mL:7 mL) were added a few drops of HBr, 2,3-dibromopropene (1.87 g, 7.50 mmol) and the resulting residue (in 5 mL of ether). The reaction mixture was stirred for 18 h before it was filtered through a pad of Celite. The filtrate was washed with brine, dried ($MgSO_4$), and concentrated. The resulting residue was dissolved in THF (15 mL) and TBAF (1.26 g, 4.84 mmol). The reaction mixture was stirred for 3h, then filtered through a plug of silica (EtOAc) to afford the desired diol (0.76 g, 91%).

The cyclic α,β-unsaturated acetal was obtained using standard acid mediated acetal formation conditions with 6-bromo-hept-6-ene-2,4-diol (0.50 g, 2.39 mmol), crotonaldehyde (0.15 g, 2.15 mmol) and *p*-toluenesulfonic acid. The resulting residue was purified by flash chromatography. The all *cis*-substituted product was isolated and subjected to standard palladium mediated coupling conditions using palladium tetrakistriphenylphosphine (0.06 g, 0.05 mmol) and trimethylsilylmethylmagnesium chloride (1.0 M in ether, 5.35 mmol, 5.35 mL) in THF (10 mL) to afford the desired cyclization substrate (0.19 g, 68%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (dq, *J* = 15.5, 6.5 Hz, 1H), 5.59 (m, 1H), 4.97 (d, *J* = 5.3 Hz, 1H), 4.65 (s, 1H), 4.61 (s, 1H), 3.80 (m, 1H), 2.36 (dd, *J* = 13.8, 5.7 Hz, 1H), 2.09 (dd, *J* = 13.8, 7.5 Hz, 1H), 1.74 (dd, *J* = 6.5, 1.4 Hz, 3H), 1.58 (m, 2H), 1.25 (m, 5H), 0.02 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.3, 130.3, 128.9, 109.8, 100.7, 74.1, 72.8, 44.9, 38.7, 27.5, 21.9, 14.2, -1.09; IR (neat) 2943, 2906, 2857, 1714, 1419, 1376, 1235, 1124, 1100, 1032, 842 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{15}H_{28}O_2Si$ (M^+) 268.185859, found 268.185834.

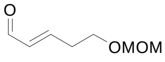
1-(4-Methylene-6-propenyltetrahydropyran-2-yl)propan-2-ol (53)



53

2-Bromo-6-(*tert*-butyl-diphenyl-silanyloxy)-hept-1-en-4-ol (**52**) (0.10 g, 0.37 mmol) was subjected to standard aqueous Prins cyclization conditions using cerium nitrate hexahydrate (0.01 g, 0.04 mmol) and sodium dodecylsulfate (0.05 g, 0.19 mmol), to afford the desired product (0.06 g, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.70 (dq, *J* = 15.4, 6.2 Hz , 1H), 5.51 (ddq, *J* = 15.4, 6.2, 1.3 Hz, 1H), 4.74 (s, 2H), 4.03 (m, 1H), 3.78 (m, 1H), 3.58 (m, 1H), 2.15 (m, 4H), 1.63 (m, 5H), 1.18 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.8, 131.4, 127.7, 109.3, 79.7, 79.1, 68.3, 44.5, 41.0, 40.8, 23.6, 18.0; IR (neat) 3418, 3069, 2923, 2850, 1643, 1440, 1374, 1309, 1061, 960, 887 cm^{-1}; HRMS (EI) *m/z* calcd for $C_{12}H_{20}O_2$ (M^+) 196.146330, , 0.06 g found 196.146690.

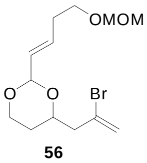
5-Methoxymethoxypent-2-enal (55)



55

To 3-butenol (1.00 g, 13.86 mmol) in CH_2Cl_2 (10 mL) at 0 ºC was added *N, N'*-diisopropylethylamine (2.68 g, 20.80 mmol), and chloromethyl methyl ether (1.67 g, 20.80 mmol). The reaction mixture was stirred for 1.5 h at room temperature, then poured into a separatory funnel containing Et_2O: 1N HCl and extracted. The organic layer was dried ($MgSO_4$) and concentrated. To a solution of the resulting residue in CH_2Cl_2 (10 mL) was added acrolein (0.49 g, 8.61 mmol) and triclyclohexylphosphine[1,3-bis(2,4,6-trimethylphenyl)-4,5-dihydroimidazol-2-ylidene] [benzylidine]ruthenium (IV) dichloride (Grubbs second generation catalyst) (0.18 g, 0.22 mmol). The reaction mixture was heated to reflux for 18 h, cooled to room temperature and concentrated. The resulting residue was purified by flash chromatography (30% Et_2O in pentanes) to afford the desired product (0.17 g, 28%): ^1H NMR (300 MHz, $CDCl_3$) δ 9.55 (d, *J* = 7.8 Hz, 1H), 6.88 (dt, *J* = 15.7, 6.7 Hz, 1H), 6.22 (dd, *J* = 15.7, 7.8 Hz, 1H), 4.65 (s, 2H), 3.73 (t, *J* = 6.2, 2H), 3.37 (s, 3H), 2.64 (m, 2H).

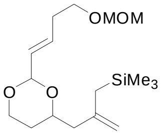
4-(2-Bromoallyl)-2-(4-methoxymethoxy-but-1-enyl)-[1,3]dioxane (56)



56

To **36** (0.23 g, 1.21 mmol) in CH_2Cl_2 (5 mL) at -20 ºC was added 5-methoxymethoxypent-2-enal (0.17 g, 1.21 mmol), *p*-toluenesulfonic acid (0.02 g, 0.12 mmol), and anhydrous $MgSO_4$ (0.17 g, 1.39 mmol). The reaction mixture was stirred for 18 h, quenched with saturated aqueous $NaHCO_3$ (2 mL) and allowed to warm to room temperature. The two layers were separated, and the organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (20% Et_2O in pentanes) to afford the desired product (0.29 g, 76%): ^1H NMR (300 MHz, $CDCl_3$) δ 5.92 (dt, *J* = 15.7, 6.7 Hz, 1H), 5.66 (s, 1H), 5.60 (ddt, *J* = 15.7, 4.6, 1.4 Hz, 1H), 5.48 (d, *J* = 1.5 Hz, 1H), 4.96 (d, *J* = 4.6 Hz, 1H), 4.60 (s, 2H), 4.11 (dd, *J* = 11.4, 4.9 Hz, 1, H), 3.99 (m, 1H), 3.80 (dt, *J* = 11.9, 2.6 Hz, 1H), 3.57 (t, *J* = 6.7 Hz, 2H), 3.33 (s, 3H), 2.75 (dd, *J* = 14.4, 6.7 Hz, 1H), 2.49 (dd, *J* = 14.4, 6.3 Hz, 1H), 2.36 (m, 2H), 1.64 (m, 1H), 1.48 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.6, 128.9, 119.6, 100.5, 96.4, 74.2, 66.7, 66.5, 55.3, 47.7, 32.6, 30.5; IR (neat) 2945, 2916, 2850, 1694, 1629, 1432, 1352, 1243, 1149, 1134, 1032, 974; HRMS (EI) *m/z* calcd for $C_{13}H_{20}O_4Br$ (M^+) 319.054495, found 319.054353.

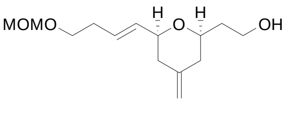
{2-[2-(4-Methoxymethoxybut-1-enyl)-[1,3]dioxan-4-ylmethyl]allyl}-trimethylsilane (57)



57

To **56** (0.29 g, 0.92 mmol) in THF (5 mL) was added trimethylsilylmethylmagnesium chloride (1.0 M in Et_2O, 4.59 mmol, 4.59 mL) and palladium tetrakistriphenylphosphine (0.05 g, 0.05 mmol). The reaction mixture was heated to reflux for 3h, cooled to 0 ºC, and quenched with saturated aqueous NH_4Cl. The reaction mixture was warmed to room temperature and extracted into Et_2O. The organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (10% triethylamine, 20% Et_2O in pentanes) to afford the desired product (0.24 g, 80%): ^1H NMR (300 MHz, $CDCl_3$) δ 5.93 (dt, *J* = 15.7, 6.7 Hz, 1H), 5.63 (ddt, 15.7, 3.4, 1.3 Hz, 1H), 4.97 (d, *J* = 4.7 Hz, 1H), 4.65 (s, 1H), 4.63 (s, 3H), 4.15 (dd, *J* = 11.4, 4.9 Hz, 1H), 3.80 (m, 2H), 3.60 (t, *J* = 6.8 Hz, 2H), 3.35 (s, 3H), 2.37 (m, 2H), 2.10 (dd, *J* = 13.9, 7.3 Hz, 2H) 1.53 (m, 2H), 1.24 (s, 2H), 0.35 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.2, 131.4, 129.2, 110.0, 100.6, 96.5, 75.7, 66.8, 55.3, 44.8, 32.6, 31.2, 27.3, -1.19; IR (neat) 3076, 2952, 2850, 1687, 1621, 1367, 1243, 1149, 1112, 1047, 967, 850; HRMS (EI): *m/z* calcd for $C_{17}H_{31}O_4Si$ (M^+) 327.199163 found, 327.199646.

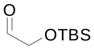
2-[6-(4-Methoxymethoxybut-1-enyl)-4-methylenetetrahydropyran-2-yl]ethanol (58)



58

{2-[2-(4-Methoxymethoxybut-1-enyl)-[1,3]dioxan-4-ylmethyl]allyl}-trimethylsilane (**57**) (0.10 g, 0.304 mmol) was subjected to standard aqueous Prins cyclization conditions using scandium chloride hexahydrate (0.004 g, 0.03 mmol) and sodium dodecylsulfate (0.04 g, 0.12 mmol) to afford the desired product (0.04 g, 53%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.65 (m, 2H), 4.75 (d, *J* = 1.6 Hz, 1H), 4.74 (d, *J* = 1.6 Hz, 1H), 4.61 (s, 2H), 3.73 (t, *J* = 5.1 Hz, 3H), 3.57 (t, *J* = 6.8 Hz, 3H), 3.35 (s, 4H), 2.33 (m,2H), 2.17 (m, 4H), 1.80 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7, 132.4, 128.5, 109.2, 96.4, 78.9, 78.8, 67.1, 61.4, 55.2, 40.7, 40.5, 38.0, 32.8; IR (neat) 3440, 3069, 2930, 2880, 1658, 1425, 1352, 1316, 1149, 1105, 1047, 960, 901; HRMS (EI): *m/z* calcd for $C_{14}H_{24}O_4$ (M^+) 256.167460, found 256.167673.

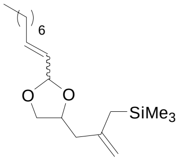
(tert-Butyldimethylsilanyloxy)-acetaldehyde (60)



60

Ozone was bubbled through a solution of 1,4-bis(*tert*-butyldimethylsilanyloxy)but-2-ene (3.00 g, 9.47 mmol) in CH_2Cl_2 (30 mL) at -78 ºC. The flow of ozone was stopped after 45 min. and triphenylphosphine (2.48 g, 9.47 mmol) was added to the reaction mixture. The mixture was allowed to stir for 12 h while slowly warming to room temperature. The reaction mixture was concentrated to a third of its volume, placed directly on a silica gel column and purified by flash chromatography (CH_2Cl_2) to afford the desired aldehyde (3.03 g, 51%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.71 (s, 1H), 4.23 (s, 2H), 0.94 (s, 9H), 0.11 (s, 6H).

Trimethyl[2-(2-non-1-enyl[1,3]dioxolan-4-ylmethyl)allyl]silane (64)

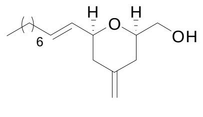


64

To a solution of (2-bromo-allyl)-trimethylsilane (1.85 g, 9.58 mmol) in CH_2Cl_2 (15 mL) at -78 ºC was added **60** (1.11 g, 6.39 mmol) followed by titanium tetrachloride (1.51 g, 7.98 mmol). Then reaction mixture was stirred for 35 min., then cannulated into a stirring saturated aqueous $NaHCO_3$ (25 mL) at 0 ºC. The mixture was stirred while warming to room temperature. The two layers were separated. The water layer was washed with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford the desired product (1.10 g, 59%). To 4-bromo-1-(*tert*-butyldimethylsilanyloxy)pent-4-en-2-ol (1.10 g, 3.73 mmol) on THF (10 mL) under N_2 was added tetrabutylammonium fluoride (1.07 g, 4.11 mmol). The reaction mixture was stirred for 12 h then concentrated. The crude mixture was purified by flash chromatography (EtOAc). The resulting residue was subjected to standard acid mediated acetal formation conditions using trans-2-decenal (0.51 g, , 0.51 g 3.28 mmol). A solution of zinc bromide (0.71 g, 3.15 mmol) in THF (3 mL) was added dropwise to a solution of trimethylsilylmethylmagnesium chloride (1.0 M in ether, 3.15 mmol, 3.15 mL) and was stirred for 18 h. A solution of the resulting residue from the acetal formation in THF (2 mL) was added, followed by palladium tetrakistriphenylphosphine (0.04 g, 0.03 mmol). The reaction mixture was stirred for 18 h, and was then quenched with saturated aqueous NH_4Cl. The two layers were separated and the aqueous layer was washed with ether. The organic layers were combined, dried

(MgSO$_4$), concentrated and purified by flash chromatography (10% triethylamine, 5% ether in pentanes) to afford the desired product: ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.91 (m, 1H), 5.48 (m, 1H), 5.32 (d, *J* = 6.6 Hz, 1H), 5.20 (d, *J* = 6.8 Hz, 1H), 4.64 (m, 1H), 4.60 (s, 1H), 4.26 (m, 1H), 4.14 (dd, *J* = 8.1, 6.0 Hz, 1H), 3.96 (dd, *J* = 7.7, 6.5 Hz, 1H), 3.61 (dd, *J* = 7.7, 6.4 Hz, 1H), 3.52 (dd, *J* = 8.1, 6.9 Hz, 1H), 2.40 (m, 2H), 2.21 (m, 2H), 1.25 (m, 12H), 0.02 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 143.8, 143.6, 138.0, 137.2, 126.9, 109.7, 104.7, 103.9, 75.6, 74.8, 70.5, 69.8, 42.6, 42.1, 32.2, 32.0, 29.0, 28.9, 27.6, 22.8, 14.2, -1.12; IR (neat) 3061, 2945, 2923, 1730, 1665, 1643, 1461, 1403, 1243, 1127, 1061, 967, 850; HRMS (EI): *m/z* calcd for $C_{19}H_{36}O_2Si$ (M^+) 324.248459, found 324.247900.

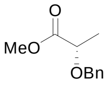
(4-Methylene-6-non-1-enyl-tetrahydropyran-2-yl)methanol (65)



65

(4-Methylene-6-non-1-enyl-tetrahydropyran-2-yl)methanol (**64**) (0.05 g, 0.15 mmol) was subjected to standard aqueous Prins cyclization conditions using scandium chloride hexahydrate (0.002 g, 0.02 mmol) and sodium dodecylsulfate (0.04 g, 0.15 mmol) to afford the desired product (0.03 g, 77%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 5.70 (dt, *J* = 15.5, 6.5 Hz, 1H), 5.49 (dd, *J* = 15.5, 6.4 Hz, 1H), 4.77 (s, 2H), 3.79 (m, 1H), 3.61 (m, 2H), 3.47 (m, 1H), 2.05 (m, 7H), 1.57 (m, 3H), 1.26 (m, 10H), 0.88 (t, *J* = 5.5 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 143.8, 133.2, 130.3, 109.4, 79.2, 78.6, 66.1, 41.2, 36.3, 32.5, 32.0, 29.8, 29.3, 22.8, 14.3; IR (neat) 3418, 3069, 2930, 2850, 1650, 1461, 1345, 1098, 1054, 967, 894; HRMS (EI): *m/z* calcd for $C_{16}H_{28}O_2$ (M^+) 252.208930, found 252.209094.

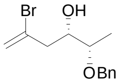
2-Benzyloxy-propionic acid methyl ester (+)-67



(+)-**67**

To a suspension of silver oxide (4.45 g, 19.21 mmol) in ether (15 mL) was added methyl-(*S*)-(-)-lactate (1.00 g, 9.60 mmol) and benzyl bromide (2.45 g, 14.40 mmol). The reaction mixture was stirred for 48 h, then filtered through a pad of Celite and concentrated. The resulting residue was purified by flash chromatography (10% Et_2O in pentanes) to afford the desired product (1.09 g, 63%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.72 (d, *J* = 11.6 Hz, 1H), 4.48 (d, *J* = 11.6 Hz, 1H), 4.09 (q, *J* = 6.9 Hz, 1H), 3.76 (s, 3H), 1.44 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.8, 137.6, 128.5, 128.1, 74.1, 72.1, 52.0, 18.8; $[\alpha]_D^{23}$ -92.3º ($CDCl_3$, *c* 0.37); lit: $[\alpha]_D^{23}$ 78.5º ($CDCl_3$, *c* 0.37) for the (R)-(-) enantiomer.

2-Benzyloxy-5-bromo-hex-5-en-3-ol (+)-69



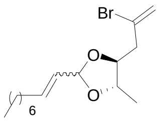
(+)-**69**

To (+)-**67** in CH_2Cl_2 (10 mL) at -98 ºC was added diisobutyl aluminum hydride (1.0 M in hexanes, 3.33 mmol, 3.33 mL). The reaction mixture was stirred for 1 h, then quenched with ethyl acetate (2 mL) and stirred for 10 min. before a solution of saturated sodium, potassium tartrate (10mL) was added. The reaction mixture was warmed to room temperature and stirred for 2 h before the two layers were separated. The water layer was washed with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$) and concentrated. The resulting residue was added to a solution of (2-bromo-allyl)-trimethyl-silane (0.64 g, 3.33 mmol) under N_2 at -78 ºC in CH_2Cl_2 (10 mL). Tin (IV) chloride (1.0 M in CH_2Cl_2, 5.55 mmol, 5.55 mL) was added and the reaction mixture was stirred for 45 min. before being quenched with H_2O (10 mL). The reaction mixture was warmed to room temperature and the two layers were separated. The aqueous layer was washed with CH_2Cl_2 and the combined organic layers were dried ($MgSO_4$)

and concentrated. The resulting residue was purified by flash chromatography (10% Et_2O in pentanes) to afford the desired product (0.46 g, 62%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (m, 5H), 5.66 (d, *J* = 1.3 Hz, 1H), 5.15 (d, *J* = 1.5 Hz, 1H), 4.70 (d, *J* = 11.5 Hz, 1H), 4.47 (d, *J* = 11.5 Hz, 1H), 3.85 (m, 1H), 3.52 (dq, *J* = 4.8, 6.2 Hz, 1H), 2.60 (d, *J* = 6.1 Hz, 2H), 1.28 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 130.8, 128.7, 128.0, 119.4, 76.5, 72.6, 71.1, 45.5, 15.8; IR (neat) 3447, 3083, 3061, 3025, 2952, 2923, 2872, 1621, 1505, 1447, 1374, 1207, 1069, 901, 734, 698 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{13}H_{17}O_2$ (M^+) 284.041191, found 284.041088; $[\alpha]_D^{23}$ 14.7° ($CHCl_3$, *c* 5.0).

The ee was determined to be 80% by chiral HPLC analysis using a chiracel OD-H column. Conditions: Hex:*i*-PrOH 90:10, 0.80 mL/min.

4-(2-Bromo-allyl)-5-methyl-2-non-1-enyl-[1,3]dioxolane (-)-71

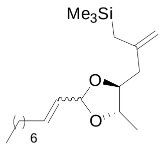


(-)-**71**

To (+)-**69** (0.31 g, 1.08 mmol) in CH_2Cl_2 (10 mL) at 0 ºC was added titanium (IV) chloride (0.25 g, 1.36 mmol). The reaction mixture was stirred for 2h, and then quenched with saturated aqueous $NaHCO_3$ (5 mL) and allowed to warm to room temperature. The reaction mixture was extracted into ethyl acetate, and the aqueous layer was washed (5 x) with ethyl acetate. The combined organic layers were dried ($MgSO_4$) and concentrated and flashed through a silica gel plug using ethyl acetate. To a solution of the resulting residue in CH_2Cl_2 (5 mL) at -20 ºC under N_2 was added *trans*-2-decenal (0.12 g, 0.78 mmol), *p*-tolunesulfonic acid (0.01 g, 0.08 mmol), and anhydrous $MgSO_4$ (0.11 g, 0.89 mmol). The reaction mixture was stirred for 18 h, then was quenched with saturated aqueous $NaHCO_3$ (2 mL) and warmed to room temperature. The two layers were separated and the organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography

(5% Et_2O in pentanes) to afford the desired product (0.22 g, 85%): ^1H NMR (300 MHz, $CDCl_3$) δ 5.93 (dt, *J* = 15.3, 6.6 Hz, 1H), 5.75 (m, 1H), 5.53 (d, *J* = 1.7 Hz, 1H), 5.47 (m, 1H), 5.36 (d, *J* = 6.8 Hz, 1H), 5.30 (d, *J* = 6.9, Hz, 1H), 3.87 (m, 2H), 2.79 (m, 1H), 2.58 (dtd, *J* = 13.4, 4.3, 0.85 Hz, 1H), 2.05 (m, 2H), 1.37 (d, *J* = 5.9 Hz, 3H), 1.26 (m, 10H), 0.87 (t, *J* = 6.5 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.0, 137.7, 129.3, 129.2, 127.1, 127.0, 119.4, 103.7, 103.5, 81.0, 79.9, 78.0, 76.6, 45.2, 44.7, 32.2, 32.0, 29.3, 28.8, 22.8, 18.3, 18.2, 15.4, 14.2; IR (neat) 3105, 2952, 2923, 2850, 1672, 1629, 1454, 1410, 1374, 1316, 1214, 1127, 1083, 1061, 974, 894; HRMS (EI): *m/z* calcd for $C_{16}H_{26}O_2Br$ (M^+) 329.11616, found 329.110518; $[\alpha]_D^{23}$ -10.9° (CH_2Cl_2 , *c* 5.7).

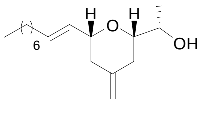
Trimethyl[2-(5-methyl-2-non-1-enyl-[1,3]dioxolan-4-ylmethyl)allyl]silane (-)-72



(-)-**72**

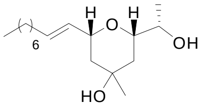
A solution of zinc bromide (0.57 g, 2.54 mmol) in THF (3 mL) was added dropwise to a solution of trimethylsilylmethylmagnesium chloride (1.0 M in ether, 2.54 mmol, 2.54 mL) and was stirred for 18 h. A solution of (-)-**71** (0.17 g, 0.508 mmol) in THF (2 mL) was added, followed by palladium tetrakistriphenylphosiphine (0.03 g, 0.03 mmol). The reaction mixture was stirred for 18 h, and was then quenched with saturated aqueous NH_4Cl. The two layers were separated and the aqueous layer was washed with ether. The organic layers were combined, dried ($MgSO_4$), concentrated and purified by flash chromatography (5% Et_2O in pentanes, the silica was neutralized with 10% triethylamine in pentanes) to afford the desired cyclization substrate (0.15 g, 89%): ^1H NMR (300 MHz, $CDCl_3$) δ 5.19 (dt, *J* = 15.3, 6.6 Hz, 1H), 5.50 (m, 1H), 5.34 (d, *J* = 6.7 Hz, 1H), 5.30 (d, *J* = 6.8 Hz, 1H), 4.72 (s, 1H), 4.63 (s, 1H), 3.74 (m, 2H), 2.33 (m, 1H), 2.05 (m, 3H), 1.57 (s, 3H), 1.26 (m, 12H), 0.88 (t, *J* = 6.8 Hz, 3H), 0.04 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.5, 143.4, 138.2, 138.0, 127.0, 110.3, 103.4, 103.2, 82.1, 80.7, 78.5, 66.0, 41.5, 32.2, 31.9, 29.3, 28.8, 27.1, 22.8, 18.2, 14.3, -1.1; IR (neat) 3069, 2952, 2916, 2850, 1680, 1629, 1454, 1410, 1381, 1250, 1163, 1120, 1076, 1047, 960, 843; HRMS (EI): *m/z* calcd for $C_{20}H_{38}O_2Si$ (M^+) 338.264109, found 338.263645; $[\alpha]_D^{23}$ -12.8° (CH_2Cl_2 , *c* 5.0).

1-(4-Methylene-6-non-1-enyltetrahydropyran-2-yl)ethanol (+)-73



(+)-**73**

Trimethyl[2-(5-methyl-2-non-1-enyl-[1,3]dioxolan-4-ylmethyl)allyl] (-)-**72** (0.05 g, 0.15 mmol) was subjected to standard aqueous Prins cyclization conditions using scandium chloride hexahydrate (0.002 g, 0.01 mmol) and sodium dodecylsulfate (0.04 g, 0.15 mmol) to afford the desired product (0.02 g, 51%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.69 (dtd, *J* = 15.5, 5.8, 0.76 Hz, 1H), 5.47 (ddt, *J* = 15.5, 6.2, 1.2 Hz, 1H), 4.78 (s, 2H), 3.74 (m, 1H), 3.66 (m, 1H), 3.11 (m, 1H), 2.81 (s, 1H), 2.22 (m, 2H), 2.02 (m, 4H), 1.27 (m, 10H), 1.18 (d, *J* = 6.3 Hz, 3H), 0.88 (t, *J* = 6.4 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 132.7, 130.5, 109.5, 82.9, 79.1, 70.7, 41.2, 36.7, 32.5, 32.0, 29.3, 22.8, 18.4, 14.2; IR (neat) 3440, 3076, 2916, 2850, 1650, 1469, 1367, 1250, 1061, 967, 887; HRMS (EI): *m/z* calcd for $C_{17}H_{30}O_2$ (M^+) 266.224580, found 266.224580; $[\alpha]_D^{23}$ +0.218° (CH_2Cl_2 , *c* 16.0).

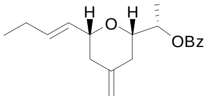


75

2-(1-Hydroxyethyl)-4-methyl-6-non-1-enyl-tetrahydropyran-4-ol (75)

(0.006, 12%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.68 (dt, *J* = 15.4, 6.8 Hz, 1H), 5.47 (dd, *J* = 15.6, 6.1 Hz, 1H), 4.17 (m, 1H), 3.85 (m, 1H), 3.64 (m, 2H), 3.16 (m, 1H), 2.04 (m, 2H), 1.62 (m, 4H), 1.36 (s, 3H), 1.27 (m, 10H), 1.17 (d, *J* = 6.3 Hz, 3H), 0.89 (t, *J* = 6.8, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 133.0, 130.3, 79.9, 75.7, 73.6, 70.7, 69.5, 46.4, 44.6, 41.9, 40.18, 32.5, 32.0, 29.9, 29.3, 26.3, 22.8, 18.3, 14.3; IR (neat) 3374, 2952, 2923, 2858, 1469, 1367, 1294, 1090, 1054, 967; HRMS (EI): *m/z* calcd for $C_{17}H_{32}O_3$ (M^+) 284.235145, found 284.235687.

Benzoic acid 1-(4-methylene-6-non-1-enyltetrahydropyran-2-yl)ethyl ester



To (+)-**73** (0.02 g, 0.08 mmol) in CH_2Cl_2 (1 mL) was added benzoyl chloride (0.01 g, 0.11 mmol), anhydrous pyridine (1 mL), and a catalytic amount of DMAP. The reaction was stirred for 18 h, then concentrated and purified by flash chromatography (5% Et_2O in pentanes) to afford the desired product (0.02 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.05 (d, *J* = 7.0 Hz, 2H), 7.56 (dd, *J* = 7.3, 7.3 Hz, 1H), 7.45 (dd, *J* = 7.2, 6.5 Hz, 2H), 5.66 (dt, *J* = 15.5, 6.4 Hz, 1H), 5.52 (dd, *J* = 15.5, 5.8 Hz, 1H), 5.27 (m, 2H), 4.78 (s, 2H), 3.76 (m, 1H), 3.52 (m, 1H), 2.15 (m, 6H), 1.40 (d, *J* = 6.5 Hz, 3H), 1.27 (m, 10H), 0.86 (t, *J* = 6.9 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.2, 144.1, 133.0, 132.4, 130.8, 130.4, 129.8, 128.4, 109.5, 79.2, 72.3, 41.2, 35.7, 32.5, 32.0, 29.3, 22.8, 15.7, 14.3; IR (neat) 3061.8, 2923.6, 2850.9, 1716.3, 1650.9, 1592.7, 1447.2, 1352.7, 1309.1, 1280.0, 1170.9, 1112.7, 960.0, 887.2; HRMS (EI): *m/z* calcd $C_{24}H_{34}O_3$ (M^+) 370.250795 found, 370.252609; $[\alpha]_D^{23}$ 0.986º (CH_2Cl_2 , *c* 5.0).

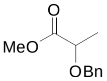
The ee was determined to be 86% by chiral HPLC analysis using a chirapak AD column. Conditions: Hex:*i*-PrOH 90:10, 0.40 mL/min.

Benzyloxy-acetic acid methyl ester

To a suspension of silver (I) oxide (5.15 g, 22.20 mmol) in Et_2O (10 mL) was added methyl glycolate (1.0 g, 11.10 mmol) and benzyl bromide (2.85 g, 16.65 mmol). The reaction mixture was heated to reflux and stirred for 18 h, cooled to room temperature, filtered through a pad of

Celite and concentrated. The resulting residue was purified by flash chromatography (10% Et_2O in pentanes) to afford the desired product (82%, 1.64 g): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33 (m, 5H), 4.64 (s, 2H), 4.15 (s, 2H), 3.77 (s, 3H).

2-Benzyloxy-propionic acid methyl ester



To a stirring solution of lithium bis(trimethylsilyl)amide (1.0 M in THF, 5.55 mmol, 5.55 mL) and hexamethylphosphoramide (0.05 g, 0.28 mmol) at -78 ºC was added benzyloxy-acetic acid methyl ester (0.50 g, 2.77 mmol). The reaction mixture was stirred for 30 min, and then iodomethane (1.96 g, 13.87 mmol) was added. The reaction mixture was stirred for 3 h, then quenched with saturated aqueous NH_4Cl and allowed to warm to room temperature. The reaction mixture was extracted into Et_2O and the aqueous layer was washed with Et_2O. The combined organic layers were dried ($MgSO_4$), and concentrated. The resulting residue was purified by flash chromatography (10% Et_2O in pentanes) to afford the desired product (0.25 g, 46%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (m, 5H), 4.72 (d, J = 11.6 Hz, 1H), 4.48 (d, J = 11.6 Hz, 1H), 4.09 (q, J = 6.9 Hz, 1H), 3.76 (s, 3H), 1.44 (d, J = 6.8 Hz, 3H).

The racemic form of benzoic acid 1-(4-methylene-6-non-1-enyltetrahydropyran-2-yl)ethyl ester was synthesized in the same manner as the enantiopure form starting from 2-Benzyloxy-propionic acid methyl ester. The racemic form was used as a standard for HPLC analysis and ee determination.

2.5. References

---

[45] Adams, D. R.; Bhatnagar, S. P. “The Prins Reaction” *Synthesis*, **1977**, 661-672.

[46] a) Sissman, E. E.; Schnettler, P. S.; Portoghese, J. “Mechanism of the Prins reaction. Stereoaspects of the formation of 1,3-dioxanes" *J. Org. Chem.* **1965**, *30*, 797. b) Wilkins, C. L.; Marianelli, R. S. “Mechanism of the Prins reaction of styrenes: The Prins reaction of *trans*-β-deuterostyrene” *Tetrahedron* **1970**, *26*, 4131. c) Dolby, J. L.; Meneghini, F. A.; Koizumi, T. “The mechanism of the Prins reaction. VI. The solvolysis of optically active trans-2-hydroxymethylcyclohexyl bosylate and related arenesulfonates” *J. Org. Chem.* **1968**, *33*, 3060.

[47] Fleming, I. in *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I.; Heathcock, C.; Ed.: Pergamon Press: New York, 1991; Vol. 2, pp 563-593.

[48] Hosomi, A.; Sakurai, H. “Synthesis of γ,δ-unsaturated alcohols from allylsilanes and carbonyl compounds in the presence of titanium tetrachloride” *Tet. Lett.*, **1976**, 1295-1298.

[49] Rychnovsky, S., D.; Hu, Y.; Skalitzky, J. “Prins cyclization of 4-allyl-1,3-dioxanes prepared from 1,3-diol synthons. A rapid entry into functionalized tetrahydropyrans” *Tet. Lett.* **1996**, *37*, 8679-8682.

[50] Overman, L. E.; Pennington, L. D. “Strategic use of pinacol-terminated Prins cyclizations in target-oriented total synthesis” *J. Org. Chem.* **2003**, *68*, 7143-7157.

[51] Rychnovsky, S. D.; Yang, G.; Hu, Y.; Khire, U. “Prins desymmetrization of a C_2-symmetric diol: Application to the synthesis of 17-dexyroflamycoin” *J. Org. Chem.* **1997**, *62*, 3022-3023.

[52] Murata, S.; Suzuki, M.; Noyori, R. “Trimethylsilyl triflate catalyzed aldol-type reation of enol silyl ethers and acetals or related compounds” *Tetrahedron*, **1988**, *44*, 4259-4275.

[53] Mekhalfia, A.; Marko, I.; Adams, H. “The intramolecular silyl modified Sakurai (ISMS) reaction. A novel and highly convergent synthesis of oxecenes” *Tet. Lett.*, **1991**, *32*, 4783-4786.

[54] Keck, G. E.; Covel, J. A.; Schiff, T.; Yu, T. “Pyran annulation: Asymetric synthesis of 2,6-*cis*-disubstituted-4-methylenetetrahydropyrans” *Org. Lett.*, **2002**, *4*(7), 1189-1192.

[55] Kopecky, D. J.; Rychnovsky, S. D. “Mukaiyama aldol-Prins cyclization cascade reaction: A formal total synthesis of Leucascandrolide A” *J. Am. Chem. Soc.*, **2001**, *123*, 8420-8421.

[56] Patterson, B.; Rychnovsky, S. D. “Mukaiyama aldol-Prins cyclization with ketones” *Synlett*, **2004**, *3*, 543-545.

---

[57] Lolkema, L. D.; Semeyn, C.; Ashek, L.; Heinstra, H.; Speckamp, W. N. "Studies on the role of the 2-oxonia-Cope rearrangement in π-cyclizations of α-methoxycarbonyl oxocarbenium ions" *Tetrahedron*, **1994**, *50*(24), 7129-7140.

[58] Roush, W. R.; Dilley, G. J. "Studies on the synthesis of 2,6-disubstituted dihydropyrans: intervention of oxonia-Cope rearrangements in the Lewis acid mediated cyclodehydrative reactions of aldehydes and β-hydroxyallylsilanes" *Synlett*, **2001**, 955-959.

[59] Rychnovsky, S. D.; Marumoto, S.; Jaber, J. "Role of 2-oxonia Cope rearrangements in Prins cyclization reactions" *Org. Lett.,* **2001**, *3*(23), 3815-3818.

[60] Cloninger, M. J.; Overman, L. "Stereocontrolled synthesis of trisubstituted tetrahydropyrans" *J. Am. Chem. Soc.,* **1999**, *121*, 1092-1093.

[61] Viswanathan, G. S.; Yang, J.; Li, C. "A novel stereoselective cyclization to functionalized dihydropyrans" *Org. Lett.*, **1999**, *1*(7), 993-995.

[62] a) Kumar, S. V.; Floreancig, P. E. "Electron Transfer Initiated Cyclizations: Cyclic Acetal Synthesis through Carbon-Carbon σ-Bond Activation" *J. Am. Chem. Soc.* **2001**, *123*, 3842-3843. b) Kumar, S. V.; Aubele, D. L.; Floreancig, P. E. "Aerobic Organocatalytic Photointiated Arene Oxidations: Application to Electron Transfer Initiated Cyclization Reactions" *Org. Lett.* **2001**, *25*, 4123-4125.

[63] Mandai, T.; Nokami, J.; Yano, T.; Yoshinaga, Y.; Otera, J. "Facile one-pot synthesis of homoallyl alcohols and 1,3-keto acetates via allyltin intermediates" *J. Org. Chem.*, **1984**, *49*, 172-174.

[64] Manabe, K.; Mori, Y.; Wakabayashi, T.; Nagayama, S.; Kobayashi, S. "Organic synthesis inside particles in water: Lewis-acid-surfactant-combined catalysts for reactions in water using colloidal dispersions as reaction media" *J. Am. Chem. Soc.* **2000,** *122,* 7202-7207.

[65] Kobayashi, S; Nagayama, S.; Busujima, T. "Lewis acid catalyst stable in water. Correlation between catalytic activity in water and hydrolysis constants and exchange rate constants of inner-sphere water ligands" *J. Am. Chem. Soc.*, **1998**, *120*, 8287-8288.

[66] Corminboeuf, O.; Overman, L. E.; Pennington, L. D. "Enatioselective synthesis of Briarellins E and F: the first total synthesis of Briarellin diterpenes" *J. Am. Chem. Soc.*, **2003**, *125*, 6650-6652.

[67] Nishiyama, H.; Yokoyama, H.; Narimatzu, S.; Itoh, K. "Preparation and synthetic application of 2-bromoallyltrimethylsilane as a 1-hydroxymethylvinyl anion equivalent", *Tet. Lett.*, **1982**, *23*(12), 1267-1270.

[68] Mi, Y.; Schreiber, J.; Corey, E. J. "Total synthesis of (+)-α-Onocerin in four steps via four-component coupling and tetracyclization steps" *J. Am. Chem. Soc.*, **2002**, *124*, 11290-11291.

---

[69] Bauer, S. M.; Armstrong, R. W. "The total synthesis Motuporin (Nodularin-V)" *J. Am. Chem. Soc.*, **1999**, *121*, 6355-6366.

[70] Yu, H.; Ballard, E.; Boyle, P. D.; Wnag, B. "An inexpensive carbohydrate derivative used as a chiral auxiliary in the synthesis of α-hydroxy carboxylic acids" *Tetrahedron*, **2002**, *58*, 7663-7679.

3. Efforts towards the total synthesis of (+)-dactylolide

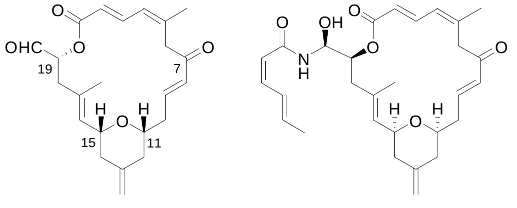
3.1. Introduction

I. Background

Over 70% of the earth's surface is covered by water.[71] The oceans endow us with a complex biological environment that consists of an extensive assemblage of life forms. These life forms thrive in extreme habitats and continuously endure tremendous variations in pressure, salinity, and temperature, as well as attack from a wide array of predators. Consequently, they have developed unique metabolic and physiological capabilities that ensure survival. It is this potential for the production of unique bioactive metabolites, unlike any isolated from terrestrial organisms, that drives the isolation and analysis of these marine systems. Sponges and marine bacteria serve as fertile sources for these structurally diverse, bioactive molecules. Although isolated from phyogenetically diverse marine sources, macrolides are emerging as an increasingly interesting and important category of molecule based on the wide spectrum of biological and pharmacological properties they exhibit.

Macrolactones are a class of macrolides that provide a great number of cytotoxic agents. (+)-Dactylolide (**1**) is one such cytotoxic macrolactone recently isolated from the Vanuata sponge *Dactylospongia* sp. by Riccio and coworkers[72] (Figure 3.1). The crude extract from this sponge was selected based on preliminary pharmacological screening. The biologically active metabolites were obtained following methanol extraction of the lyophilized organism. The methanolic extract was then subjected to a modified Kupchan partition procedure to afford four extracts. Mycothiazole,[73] latrunculin A[74], isolaulimalide[75] and laulimalide were isolated as pure compounds after medium pressure liquid chromatography of the most active CCl_4 extract. (+)-Dactylolide was isolated as a pure metabolite following elution with 80% hexanes under medium pressure liquid chromotagraphy and further purification by C-18 reverse phase HPLC ($MeOH/H_2O$ 70:30).

Figure 3.1: (+)-Dactylolide (**1**) and (-)-Zampanolide (**2**)



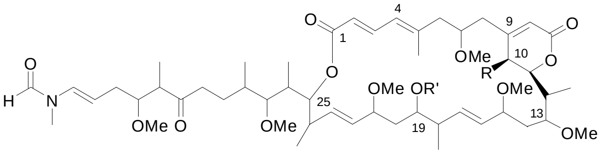
1

2

Extensive spectroscopic analysis revealed the structure of **1**[2]. (+)-Dactylolide posses a hydrocarbon skeleton bearing three remote stereogenic centers. The major architectural elements are the highly unsaturated 20-membered macrolactone containing two di- and two trisubstituted olefins,the α-acyloxyaldehyde, and the remote C19 stereocenter. The core of the molecule is composed of a 2,6-*cis*-disubstituted-4-methylenetetrahydropyran, giving rise to the two remaining C11 and C15 stereocenters. While the relative stereochemistry of the core was determined during the initial structural analysis, the absolute stereochemistry and the assignment of the C19 stereocenter was not made until completion of the first total synthesis by Smith[76] in 2001.

(+)-Dactylolide's cytotoxicity was expressed through a 63% inhibition against L1210 (lymphatic leukemia of mice) and 40% inhibition against SK-OV-3 (carcinoma of the overies) tumor cell lines at 3.2 μg/mL. Other interesting examples of macrolides that bear close structural relationship to (+)-dactylolide are the sphinxolides and reidispongiolides (Figure 3.2). This new class of cyctotoxic macrolides are characterized by a very similar 26-membered macrolactone ring which has proven effective against human bronchopulmonary, nasopharyngeal, breast and colon tumor cell lines, as well as murine leukemia.[77] In particular, the cytotoxicity of the sphinxolides is associated with cell cycle arrest in G2-M and induction of apoptosis. Sphinxolides were found to cause rapid loss of microfilaments in cultured cells without affecting microtubule organization, and potently inhibited actin polymerization in vitro. More importantly, both the sphinxolides and reidispongiolides were shown to circumvent multidrug resistance mediated by overexpression of either P-glycoprotein or MPR.[78] Therefore, these macrolides, as well as (+)-dactylolide may be efficacious in treatment of drug resistant tumors.

Figure 3.2: Sphinxolides and reidispongiolides

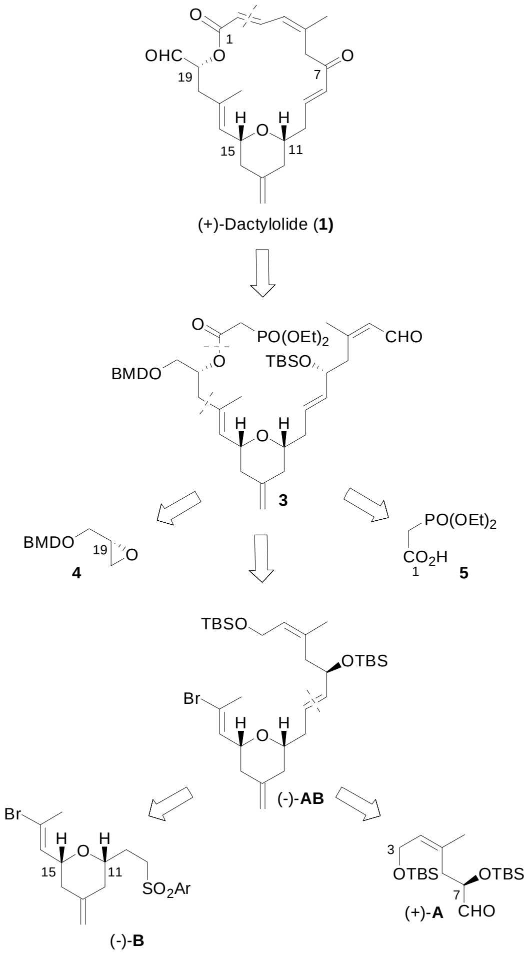


R=H, R'=Me Reidispongiolide A
R=H, R'=H Reidispongiolide B
R=OH, R'=Me Sphinxolide B
R=OH, R'=H Sphinxolide D

II. Previous Syntheses

Smith's interest in the total synthesis of (+)-dactylolide stemmed from its structural similarity to (-)-zampanolide (**2**), another cytoxic marine macrolide (Figure 3.1). Although isolated in 1996 from the Okinawan sponge *Fasciospongia rimosa*, (-)-zampanolide's skeletal structure is also a sparsely functionalized 20-membered macrolactone incorporating a 2,6-*cis*-disubstituted-4-methylenetetrahydropyran, differing only in the stereochemical configuration about the tetrahydropyran ring and bearing an unusual *N*-acyl hemiaminal side chain. The absolute stereochemistry of (-)-zampanolide was unknown until Smith reported the first total synthesis and tentative stereochemical assignment of the non-naturally-occuring antipode, (+)-zampanolide.[79] Assuming that (+)-dactylolide and (-)-zampanolide would be biosynthetically related and possess the same relative stereochemical assignment at the C19 center, Smith employed the advanced intermediate (-)-**AB** (Figure 3.3) from his total synthesis of (+)-zampanolide in the first total synthesis and determination of the absolute stereochemical configuration of (+)-dactylolide[3].

Figure 3.3: Smith's retrosynthetic analysis of (+)-dactylolide

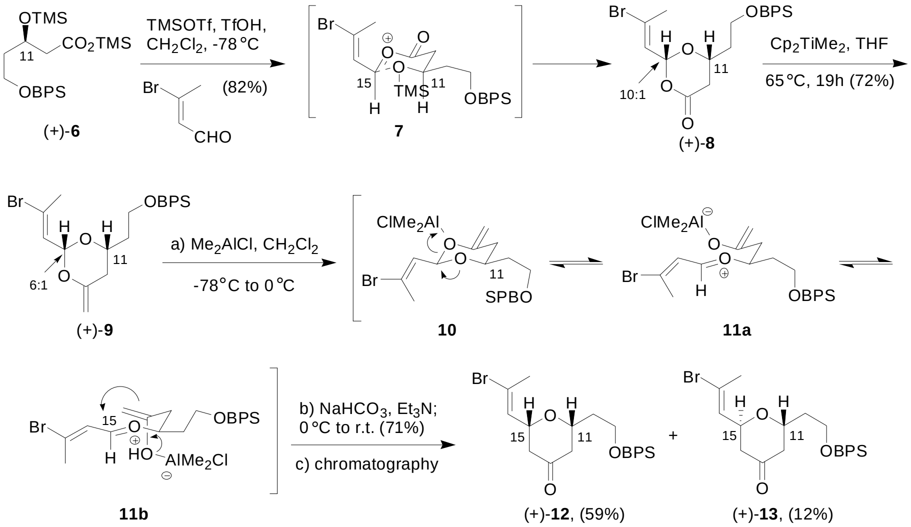


Smith arrived at (+)-dactylolide in a total of thirty-five steps, with the longest linear sequence involving thirteen steps and the key Petasis-Ferrier[80] rearrangement to form the 2,6-*cis*-disubstituted-4-methylenetetrahydropyran core. Three strategic disconnections led to the formation of the macrocycle. Scission of the C2-C3 olefin afforded the Horner-Emmons macrocyclization[81] substrate **3**. Disconnection of the acyl phosphonate linkage provided the commercially available diethylphosphonoacetic acid, **5**. Disconnection of the C17-C18 bond simplifies to the higher order cuprate[82] coupling of vinyl bromide (-)-**AB** and epoxide **4**.

Cleavage of the C9-C8 olefin gave rise to the Kocienski-Julia olefination[83] partners (-)-**B** and (+)-**A**.

The Petasis-Ferrier rearrangement[5] was effectively utilized by Smith for the formation of the 2,6-*cis*-disubstituted-4-methylenetertahydropyran core in the synthesis of sulfone (-)-**B** (Figure 3.4). Trimethylsilyl ether (+)-**6** was synthesized in five steps from a known aldehyde, using a Brown asymmetric allylation[84] to set what will ultimately become the C11 stereocenter. Following condensation of 2(*E*)-3-bromobut-2-enal and (+)-**6,** a 10:1, inseparable mixture of dioxanones (+)-**8** was isolated. Reaction of the mixture of dioxanones (+)-**8** with the Petasis-Tebbe reagent (Cp_2TiMe_2)[85] furnished (+)-**9** as a 6:1, inseparable mixture of enol ethers. Treatment of the mixture of enol ethers with one equivalent of dimethylaluminum chloride at -78 ºC effected the Petasis-Ferrier rearrangement to provide a separable mixture of *cis*-pyranones, affording the desired pyranone (+)-**12** in 59% yield.

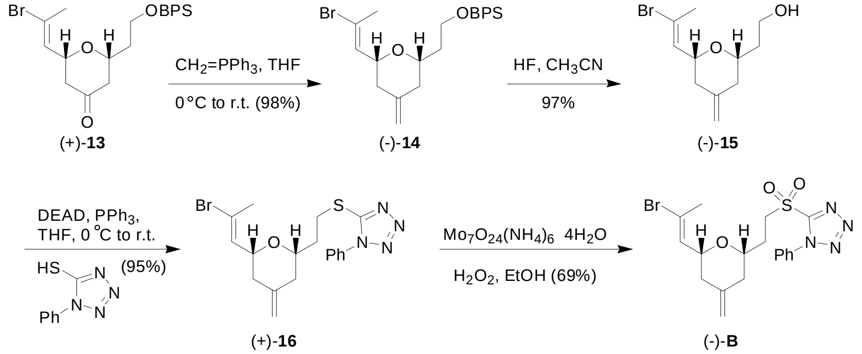
Figure 3.4: Petasis-Ferrier rearrangement


OTMS
11
CO2TMS
OBPS
(+)-6
TMSOTf, TfOH,
CH2Cl2, -78 °C
Br
CHO
(82%)
Br
O
O
O
15
11
TMS
H
H
OBPS
7
Br
OBPS
H
H
O
11
10:1
O
O
(+)-8
Cp2TiMe2, THF
65 °C, 19h (72%)
Br
OBPS
H
H
O
11
6:1
O
(+)-9
a) Me2AlCl, CH2Cl2
-78°C to 0 °C
ClMe2Al
O
O
Br
11
SPBO
10
ClMe2Al
O
O
Br
H
OBPS
11a
Br
15
O
H
HO
AlMe2Cl
OBPS
11b
b) NaHCO3, Et3N;
0 °C to r.t. (71%)
c) chromatography
Br
H
H
O
15
11
OBPS
O
(+)-12, (59%)
+
Br
H
H
O
15
11
OBPS
O
(+)-13, (12%)

Standard Wittig reaction with pyranone (+)-**12** provided the exocylic methylene to complete the tetrahydropyran core of the molecule (Figure 3.5). Removal of the BPS protecting group followed by introduction of the thiotetrazole using the Mitsunobu protocol[86] provided (+)-

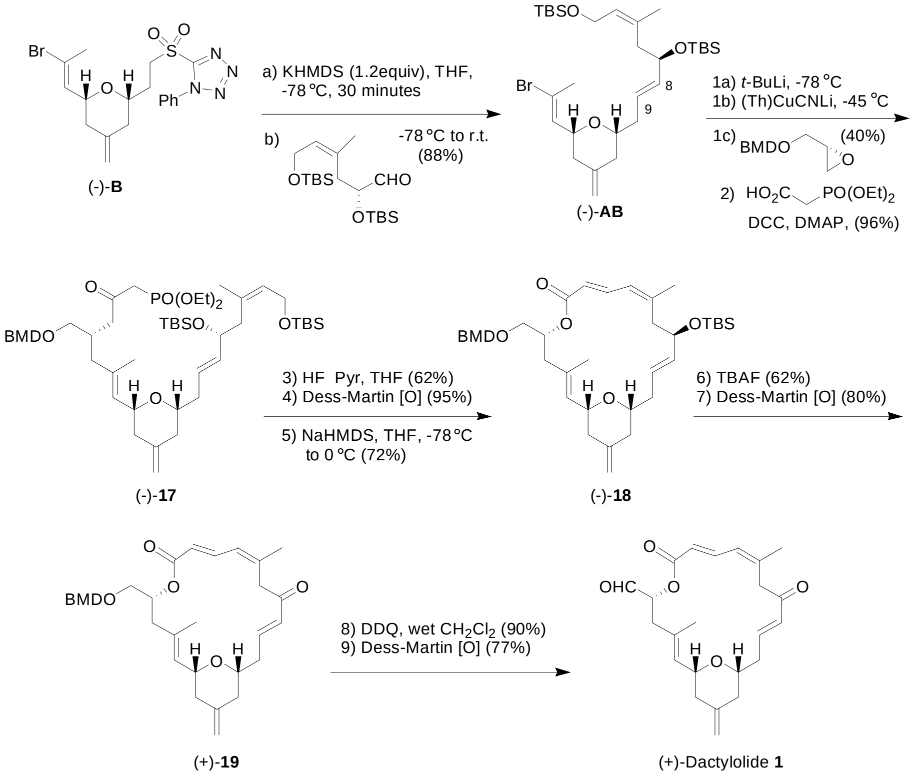
16. The sulfide was then oxidized to the sulfone to afford advanced intermediate (-)-**B**. Thus, the 2,6-*cis*-disubstituted-4-methylenetetrahydropyran core of (+)-dactylolide was realized in the longest linear sequence of the total synthesis. Starting from a known aldehyde, a total of thirteen steps were utilized to furnish (-)-**B** in a 12% overall yield, with key cyclization reaction involving the Petasis-Ferrier rearrangement.

Figure 3.5: Completion of advanced intermediate (-)-**B**



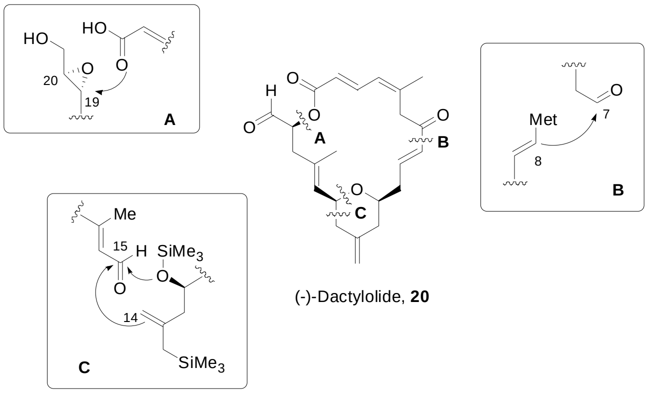
Following the construction of the 2,6-disubstituted-4-methylenetetrahydropyran core, completion of the molecule proceeded quickly and uneventfully (Figure 3.6). The most difficult step involved reaction of the higher order cuprate of (-)-**AB** with epoxide **4**, only providing the desired secondary alcohol in moderate yield. Acylation with the commercially available diethylphosphonoacetic acid **5** afforded (-)-**17** in excellent yield. Subsequent selective desilylation of the primary silyl ether, oxidation to the aldehyde with Dess-Martin periodinane (DMPI) and Horner-Emmons macrocyclization provided (-)-**18** in good yield. Following two successive deprotection oxidation steps Smith arrived at the natural product (+)-dactylolide, assigning both the absolute and relative stereochemistries.

Figure 3.6: Completion of (+)-dactylolide


(-)-B
a) KHMDS (1.2equiv), THF, -78 °C, 30 minutes
b) -78 °C to r.t. (88%)
OTBS
CHO
OTBS
(-)-AB
8
9
1a) t-BuLi, -78 °C
1b) (Th)CuCNLi, -45 °C
1c) BMDO (40%)
2) HO2C PO(OEt)2 DCC, DMAP, (96%)
(-)-17
3) HF Pyr, THF (62%)
4) Dess-Martin [O] (95%)
5) NaHMDS, THF, -78 °C to 0 °C (72%)
(-)-18
6) TBAF (62%)
7) Dess-Martin [O] (80%)
(+)-19
8) DDQ, wet CH2Cl2 (90%)
9) Dess-Martin [O] (77%)
(+)-Dactylolide 1

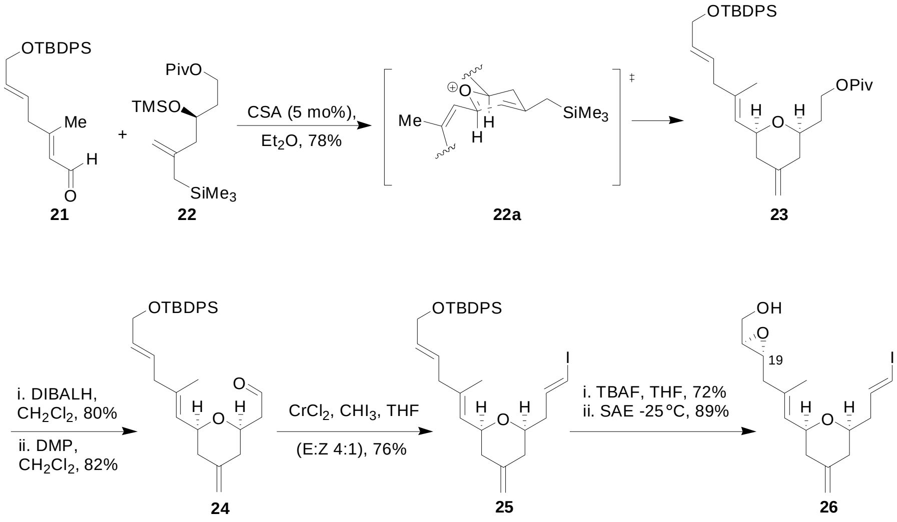
Hoye recently reported the total synthesis of the antipode, (-)-dactylolide **20**, coupled with a synthetic effort towards zampanolide, in which the key transformations involved a unique macrocyclization and Prins cyclization for the formation of the 2,6-*cis*-disubstituted-4-methylenetetrahydropyran core.[87] The strategic disconnections are shown in Figure 3.6. Bond scission **A** gives rise to the titanium (IV)-mediated epoxide opening by a carboxylic acid (Box **A**, Figure 3.7). Formation of bond **B** was envisioned through a C8-vinyl anion addition to a C7-aldehyde (Box **B**, Figure 3.7). Construction of the 2,6-*cis*-disubstituted-4-methylenetetrahydropyran core was envisioned to occur via a Prins cyclization reaction between a C15-enal and an allylsilane (Box **C**, Figure 3.7).

Figure 3.7: Strategic bond disconnections in the Hoye synthesis



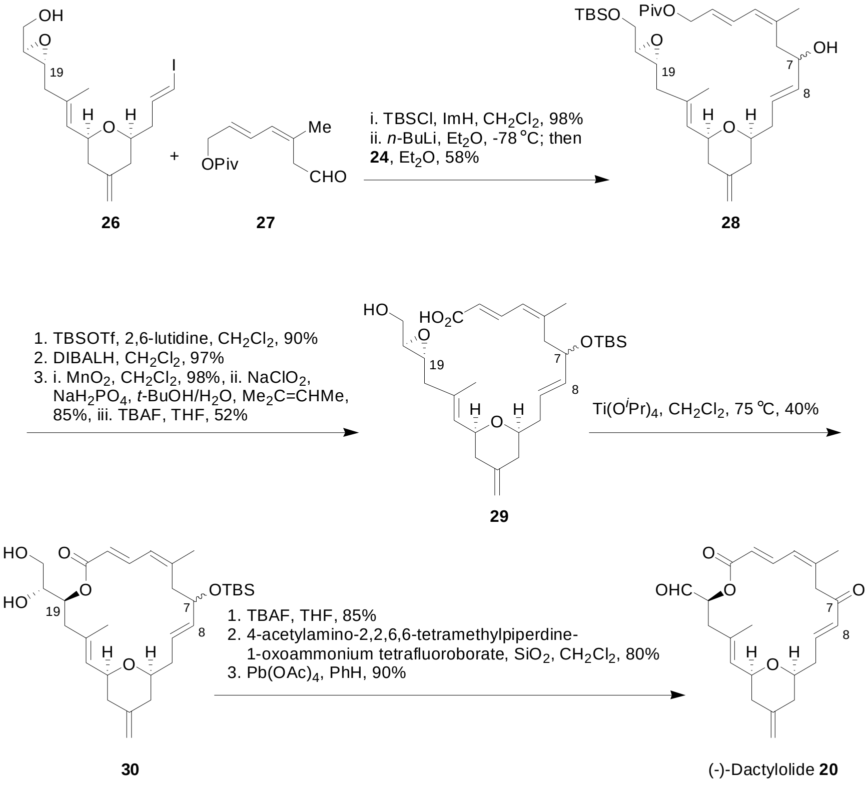
Synthesis of the 2,6-*cis*-disubstituted-4-methylenetetrahydropyran core is shown in Figure 3.8. Condensation of aldehyde **21** and silyl ether **22** in the presence of camphorsulfonic acid (CSA) provided intermediate oxocarbenium ion **22a**, which underwent intramolecular Prins cyclization to form 2,6-*cis*-disubstituted-4-methylenetetrahydropyran **23**. Tetrahydropyran **23** was isolated as a single diastereomer in good yield. Initial attempts at cyclization using Lewis acids (BF_3•OEt_2 or TMSOTf) provided better yields, but unacceptable 2:1 cis/trans stereoselectivity. Removal of the pivalate protecting group followed by DMPI oxidation furnished aldehyde **24**. Aldehyde **24** was transformed via a Takai reaction into iodoalkene **25** with 4:1 *E:Z* selectivity. The silyl ether was removed with TBAF to reveal the allyl alcohol. Deprotection of the silyl ether with the fluoride source TBAF proved beneficial in that the minor, inseperable *Z* isomer underwent facile E2-elimination to give the more polar, seperable alkyne. Sharpless asymmetric epoxidation[88] provided advanced intermediate **26**, setting the C19 stereocenter with 25:1 diastereoselectivity.

Figure 3.8: Hoye's Prins cyclization to form the core of (-)-dactylolide


OTBDPS
Me
H
O
21
+
PivO
TMSO
SiMe3
22
CSA (5 mo%),
Et2O, 78%
Me
H
H
SiMe3
‡
22a
OTBDPS
OPiv
H
O
H
23
i. DIBALH,
CH2Cl2, 80%
ii. DMP,
CH2Cl2, 82%
OTBDPS
O
24
CrCl2, CHI3, THF
(E:Z 4:1), 76%
OTBDPS
I
25
i. TBAF, THF, 72%
ii. SAE -25°C, 89%
OH
O
19
I
26

The final manipulations for macrolactonization and completion of the synthesis are shown in Figure 3.9. The C7-C8 bond of tetrahydropyran **28** was formed via addition of the vinyl lithium derived from vinyl iodide **26** into aldehyde **27**. Protecting group manipulations followed by oxidation to the carboxylic acid provided the key macrocyclization substrate **29**. Exposure of **29** to titanium isopropoxide and heat afforded a modest yield of the macrolactone via Lewis acid assisted opening of the epoxide by the carboxylic acid inverting the C19 stereocenter. The efficiency of the cyclization was limited by unproductive macrolactone formation through closure at C20 rather than C19, and C1 isopropyl ether formation. Given the accumulation of undesired side products with extended reaction times, macrolactonization was never carried to more than 50% conversion. Silyl ether removal, chemoselective oxidation of the allylic alcohol and final cleavage of the diol with lead tetraacetate provided (-)-dactylolide, **20**. The natural product was realized in thirteen total steps through the coupling of three highly advanced intermediates.

Figure 3.9: Completion of (-)-dactylolide

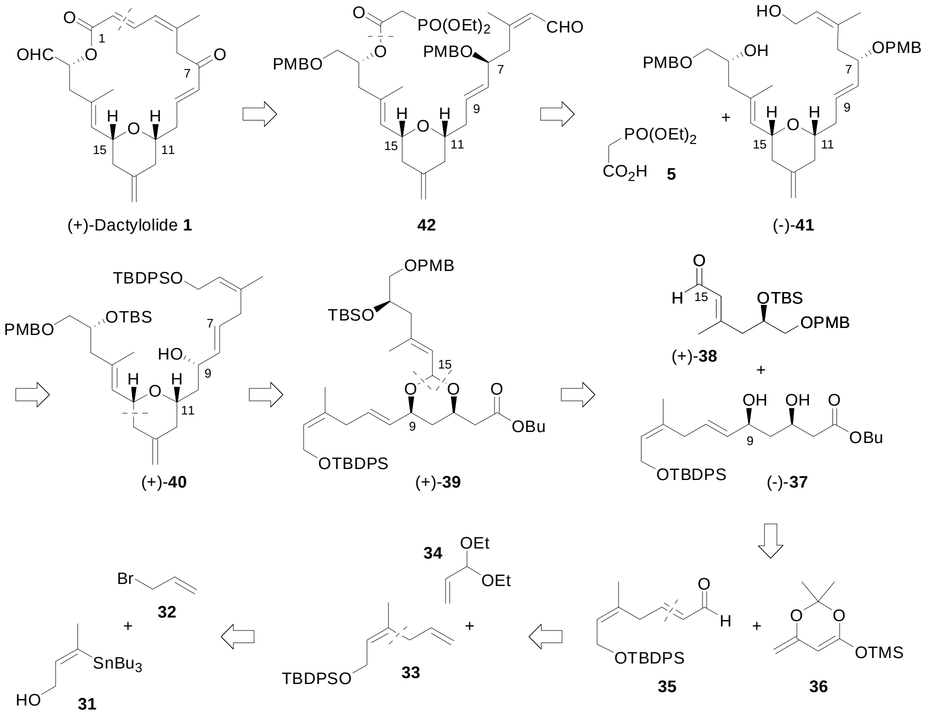

26
27
i. TBSCl, ImH, CH_2Cl_2, 98%
ii. n-BuLi, Et_2O, -78 °C; then
24, Et_2O, 58%
28
1. TBSOTf, 2,6-lutidine, CH_2Cl_2, 90%
2. DIBALH, CH_2Cl_2, 97%
3. i. MnO_2, CH_2Cl_2, 98%, ii. $NaClO_2$, NaH_2PO_4, t-BuOH/H_2O, $Me_2C=CHMe$, 85%, iii. TBAF, THF, 52%
29
$Ti(O^iPr)_4$, CH_2Cl_2, 75 °C, 40%
30
1. TBAF, THF, 85%
2. 4-acetylamino-2,2,6,6-tetramethylpiperdine-1-oxoammonium tetrafluoroborate, SiO_2, CH_2Cl_2, 80%
3. $Pb(OAc)_4$, PhH, 90%
(-)-Dactylolide 20

III. Retrosynthesis

Both Smith and Hoye used convergent strategies focusing on advanced intermediates derived from chiral pool materials as well as asymmetric catalysis that could be applied in unified syntheses of both dactylolide and zampanolide. The bench mark for our synthesis of (+)-dactylolide was set by Smith at a total of thirty-five steps, but more importantly construction of the 2,6-*cis*-4-methylene-tetrahydropyran core in thirteen steps. Given the development of the aqueous Prins cyclization method[89] we believed that the synthesis could be achieved in far fewer steps through a highly convergent route effectively utilizing the Prins cyclization as the key transformation on a late stage synthetic intermediate. The aqueous Prins cyclization method was developed as an efficient and stereoselective entry into 2,6-*cis*-4-methylene-tetrahydropyrans via intramolecular cyclization reaction of a cyclic α,β-unsaturated acetal with a pendent allylsilane. The use of cyclic α,β-unsaturated acetals as cyclization substrates allows for the condensation of two highly functionalized advanced intermediates that can undergo the key transformation, thus dramatically decreasing the number of synthetic manipulations required for completion of the synthesis.

The retrosynthetic analysis is outlined in Figure 3.10. Following in the footsteps of Smith, scission of the C2-C3 olefin provides Horner-Emmons macrocyclization substrate **42.** Disconnection of the C1 acylphoshonate linkage leads to the commercially available diethylphosphonoacetic acid **5** and secondary alcohol (-)-**41**. Reverse allylic transposition of the sencodary alcohol from C9 to C7 provides selenoxide-selenate rearrangement substrate (+)-**40**. Disconnection of the C14-C15 tetrahydropyran bond gives rise to the intramolecular Prins cyclization substrate cyclic α,β-unsaturated acetal (+)-**39**. Cleavage of the cyclic α,β-unsaturated acetal of (+)-**39** yields the known enal (+)-**38**[90] as well as diol (-)-**37**. α,β-unsaturated aldehyde (+)-**38** arises from a copper-pybox catalyzed vinylogous aldol reaction. Diol (-)-**37** also ultimately comes from the vinylogous aldol reaction of enal **35** and silyl ketene acetal **36**. α,β-unsaturated aldehyde **36** can be envisioned to arise from a cross metathesis reaction of the commercially available diethylacrolein acetal with skipped diene **33**. Scission of what will ultimately become the C5-C6 bond gives rise to the starting materials vinyl stannane **31** and allylbromide.

Figure 3.10: Retrosynthetic analysis

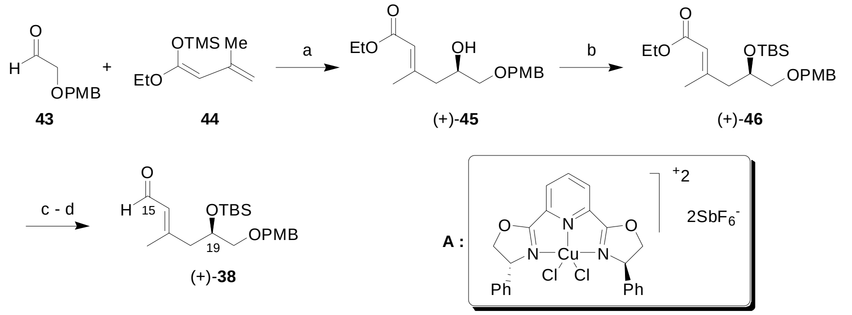

(+)-Dactylolide 1
42
(-)-41
PO(OEt)2
CO2H 5
(+)-40
(+)-39
(+)-38
(-)-37
34
33
32
31
35
36
OHC
PMBO
OPMB
OTBS
TBSO
TBDPSO
OTBDPS
OBu
OTMS
OEt
SnBu3
Br
HO
CHO

3.2. Results and Discussion

The key transformation in our highly convergent route to (+)-dactylolide involves an intramolecular Prins cyclization of a cyclic α,β-unsaturated acetal with a pendent allylsilane. The desired cyclic α,β-unsaturated acetal (+)-**39** results from the condensation of two highly functionalized advanced intermediates enal (+)-**38** and diol (-)-**37**, followed by conversion of the ester to the allylsilane. Both enal (+)-**38** and diol (-)-**37** were synthesized using vinylogous aldol reactions (Figure 3.10).

The synthesis of enal (+)-**38** is shown in Scheme 3.1. *p*-Methoxy benzyloxy acetaldehyde **43** was prepared in three steps from 1,4-butene diol. Protection of 1,4-butene diol as the *bis*-PMB ether followed by Sharpless asymmetric dihydroxylation and silica gel-supported sodium metaperiodate[91] cleavage cleanly provided the aldehyde in good yield. Ozonolysis reactions of either PMB-protected allyl alcohol or the *bis*-PMB-protected 1,4-butene diol were low yielding and difficult to purify. The [Cu((*R*,*R*)PhPyBox)]$(SbF_6)_2$•2Cl catalyzed vinylogous aldol[92] reaction between *p*-methoxy benzyloxy acetaldehyde **43** and enolsilane **44** provided the desired aldol adduct, α,β-unsaturated ester (+)-**45** as a single (*E*)-olefin isomer in good yield and excellent enantioselectivity (82%, 95% ee).

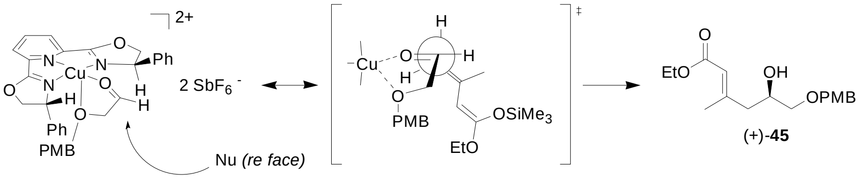
Scheme 3.1: Synthesis of enal (+)-**38**



Reagents: a) **A**, CH_2Cl_2, -78 °C, 82%, 95% ee, b) TBS-Cl, imidazole, DMF, 75%, c) LAH, Et_2O, d) MnO_2, CH_2Cl_2, (80% over two steps)

This vinylogous aldol reaction developed by Evans aptly provides the desired enatio- as well as regioselectivity (through avoidance of unwanted $A_{1,3}$ strain) for the generation of the necessary ε-hydroxy-α,β-unsaturated carbonyl structure. The transition state for the vinylogous aldol is depicted in Figure 3.11, showing *re*-face attack of the diene. No product arising from α-addition of the silylketene acetal was observed, only that of γ-addition.

Figure 3.11: Vinylogous aldol transition state

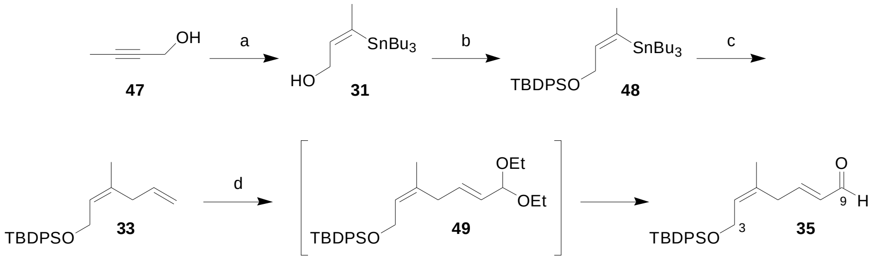


Following the vinylogous aldol reaction, secondary alcohol (+)-**45** (Scheme 3.1) was protected as the *tert*-butyldimethylsilyl ether using *tert*-butyldimethylsilyl chloride and imidazole in DMF. The α,β-unsaturated ester was reduced to the allylic alcohol with lithium aluminum hydride and then oxidized to enal (+)-**38** with manganese dioxide in good yield. Enal (+)-**38**, one major coupling partner needed for cyclic α,β-unsaturated acetal formation, containing what would ultimately become the C19 stereocenter of (+)-dactylolide and bearing the correct geometry for the C16-C17 olefin, was realized in four steps in high yield and excellent enantioselectivity.

A vinylogous aldol reaction was also used in the production of diol (-)-**37**, the second coupling component necessary for cyclic α,β-unsaturated acetal formation. The synthesis of the aldehyde required for the vinylogous aldol reaction, and what would ultimately become the C3-C9 segment, is shown in Scheme 3.2. Preparation of the C4-C5 trisubstituted (*Z*)-olefin started with Red-Al reduction of 2-butyn-1-ol followed by quenching with tributyltin chloride to give (Z)-3-tributylstannyl-but-2-en-1-ol **31** in good yield. The primary alcohol was protected as the *tert*-butyldiphenylsilyl ether to afford vinylstannane **48**. Palladium mediated coupling of vinylstannane **48** and allyl bromide provided the skipped diene **33** in good yield. Cross metathesis[93] between skipped diene **33** and the commercially available diethylacrolein acetal (**34)** using Grubbs 1st generation catalyst, followed by in situ formic acid hydrolysis provided α,β-unstaurated enal **35** in high yield with excellent (*E*)-selectivity. The observed selectivity is proposed to result from the reversibility of the cross metathesis reaction, tending toward the formation of the more thermodynamically stable *E*-isomer. This type of self editing, reversible mechanism was exploited by Smith in his synthesis of (-)-cylindrocyclophanes A and F.[94]

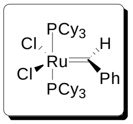
Support for this idea is also provided through the work of Grubbs on ring closing metathesis,[95] as well as by Hoveyda in his work on the total synthesis of fluvirucin B_1.[96]

Scheme 3.2: Synthesis of aldehyde **35**



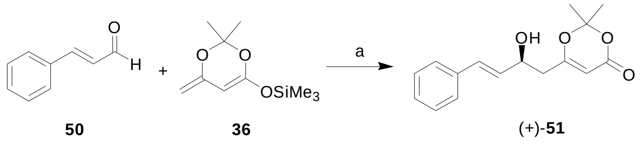
Reagents: a) i. Red-Al, THF, ii. Bu_3SnCl, 83%, b) TBDPS-Cl, imidazole, DMF, 81%, c) **32**, $Pd(PPh_3)_4$, Tol. ↯ 80%, d) i. **34,** Grubbs I (**B**) (2.5 mol%), CH_2Cl_2, ↯, ii. HCO_2H, CH_2Cl_2, 88%.

B:



With aldehyde **35** in hand the stage was set for the second vinylogous aldol reaction. The vinylogous aldol reaction was first examined using the unique chemistry developed by Carreira[97] for the catalytic generation of a chiral Cu(II) dienolate initiated by a (*R*)-Tol-BINAP·Cu(II)-fluoride complex that is generated in situ through the reaction of (*R*)-Tol-BINAP·Cu(II)-triflate with the anhydrous fluoride source $(Bu_4N)Ph_3SiF_2$ (TBAT) as shown in Scheme 3.3. The three salient features of this vinylogous aldol reaction were its application in the total syntheses leucascandrolide A[98] for the formation of a similar dioxenone, combined with the inexpensive, commercially available BINAP ligand, as well as the high yields and enantioselectivities observed by Carreira. However, in test reactions involving cinnamaldehyde and silyl ketene acetal **36** the observed yields and enantioselectivities were considerably less than expected or previously reported in the literature.

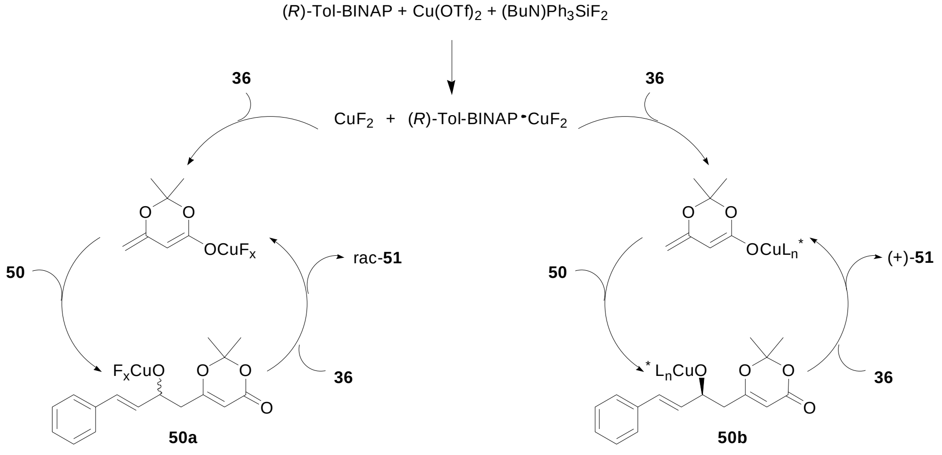
Scheme 3.3: Carreira vinylogous aldol


O
H
+
O
O
OSiMe3
a
OH
O
O
O
50
36
(+)-51

Reagents: a)(R)-Tol-BINAP, $Cu(OTf)_2$, $(Bu_4N)Ph_3SiF_2$, THF, -78°C, 51%, 42% ee

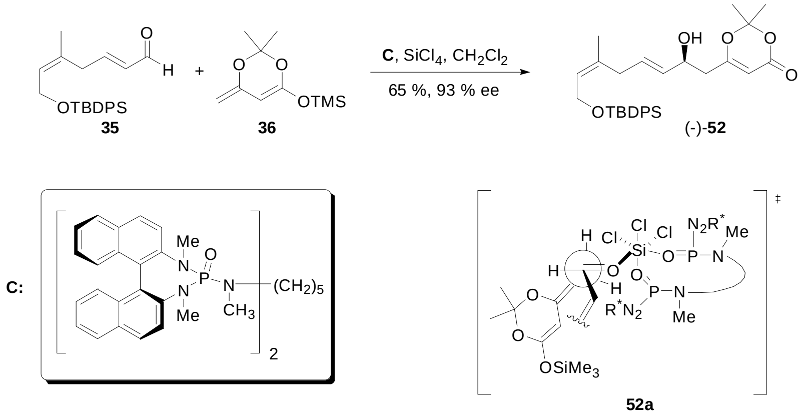
The desired mechanistic pathway involved desilylation by the in situ generated metal fluoride with concomitant generation of a chiral enolate through complexation with the chiral metal complex, as shown in Figure 3.12. The low enantioselectivity was proposed to result from the in situ generation of copper (II) fluoride in competition with the generation of the chiral (R)-Tol-BINAP-Cu(II)-fluoride. Copper (II) fluoride then entered into the catalytic cycle to catalyze the racemic aldol reaction. Given the difficulty in obtaining the desired yields and enantioselectivities, coupled with the success of the alternative Denmark vinylogous aldol, further development of this reaction was not pursued.

Figure 3.12: Carreira vinylogous aldol catalytic cycle


(R)-Tol-BINAP + Cu(OTf)2 + (BuN)Ph3SiF2
36
36
CuF2 + (R)-Tol-BINAP•CuF2
O
O
OCuFx
50
rac-51
O
O
OCuLn*
50
(+)-51
FxCuO
O
O
O
36
*LnCuO
O
O
O
36
50a
50b

Reaction of aldehyde **35** with silyl ketene acetal **36** in the presence of Denmark's chiral bisphosphoramide (*S,S*)-**E**[99] and silicon tetrachloride provided dioxenone (-)-**52** in good yield and excellent enantioselectivity (65%, 93% ee), as shown in Scheme 3.4.

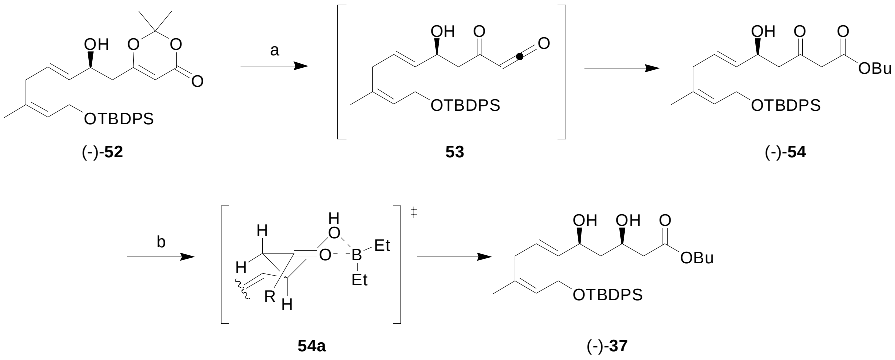
Scheme 3.4: Denmark vinylogous aldol



The reaction is unique in that the active chiral Lewis acid is generated in situ through the coordination of the weak Lewis acid silicon tetrachloride to the strongly Lewis basic bisphosphoramide (*S,S*)-**E** to form a catalytically active pentacoordinate silicon species. Extensive studies by Denmark on solution and solid phase bisphosphoramide•$SnCl_4$ complexes[100] suggest that the reaction proceeds through the hexacoordinate cationic silicon assembly **52a** shown in Scheme 3.4. In allylation as well as aldol reactions higher enantioselectivities were observed using a tethered bisphosphoramide rather than two equivalents of a phosporamide. The restriction provided by a five-methylene unit tether in (*S,S*)-**E** dictates the coordination environment about the reactive silicon center, forcing it to adopt an octahedral geometry. Thus, in the transition structure, the aldehyde would coordinate trans to a chloride at the most Lewis basic site, consequently increasing its electrophilicity. Support for the reaction proceeding through an open transition state was furnished by Denmark's observation that in bisphosphoramide silicon tetrachloride catalyzed aldol[101] reactions the geometrical integrity of the nucleophile had no effect on the enantio- or diastereoselectivity of the products. Denmark further discounted the possibility of a closed Zimmerman-Traxler type transition state[102] through NMR studies on the stability of silyl ketene acetals in the presence of silicon tetrachloride and HMPA, in which no isomerization or metathesis of the silyl ketene acetals was observed.

Following the Denmark vinylogous aldol reaction, synthesis of diol (-)-**37** was completed uneventfully in a total of three steps in high yield an excellent enantioselectivity, as shown in Scheme 3.5. Coversion of dioxenone (-)-**52** to β-hydroxy keto ester (-)-**54** was accomplished through a thermal retro-Diels-Alder reaction leading to intermediate ketene **53** formation through acetone extrusion and subsequent trapping with 1-butanol. β-Hydroxyketone (-)-**54** was subjected to diastereoselective sodium borohydride reduction in the presence of the chelating reagent diethylmethoxyborane[103] to provide 1,3-syn diol (-)-**37** in high yield and 99:1 d.e.

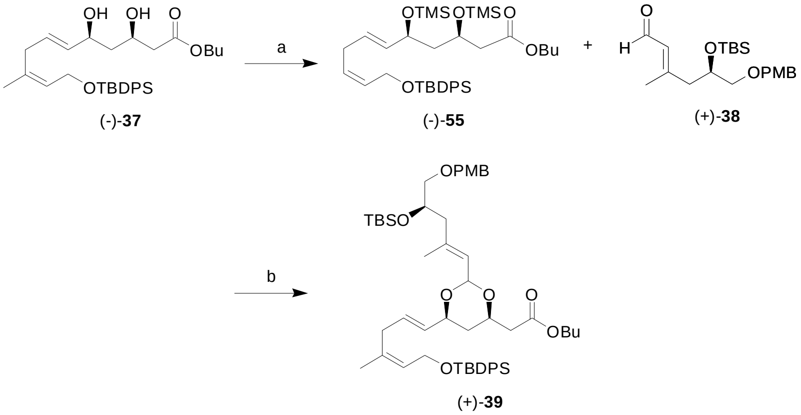
Scheme 3.5: Synthesis of diol (-)-**37**



Reagents: a) *n*BuOH, ⇅, 74%, b) Et_2BOMe, $NaBH_4$, THF, 83%

With the successful synthesis of 1,3-syn diol (-)-**37** and enal (+)-**38**, the focus became formation of the key advanced intermediate, cyclic α,β-unsaturated acetal (+)-**39**. In the development of the aqueous Prins reaction, cyclic acetals were generated under protic conditions either by refluxing with concomitant azeotropic removal of water, or at low temperature utilizing the dehydrating reagent magnesium sulfate. However, all attempts at acetal formation under protic conditions, including the use of Montmorillonite K-10 clay,[104] Amberlyst-15 resin[105] and *trans*-acetalization with the diethylacetal of enal (+)-**38** proved ineffective, and led to *E/Z* isomerization of the aldehyde. Acetalization under Lewis acidic conditions (TMSOTf, WCl_6[106]) was also unproductive. Yet, as shown in Scheme 3.6, successful acetalization was accomplished using conditions developed by Noyori[107] employing catalytic TMSOTf and stoichiometric silyl ethers. Formation of the bis-trimethylsilyl ether (-)-**55** with trimethylsilyl chloride and DMAP in DMF, followed by TMSOTf catalyzed reaction with enal (+)-**38** afforded the desired cyclic α,β-unsaturated acetal (+)-**39** in good yield.

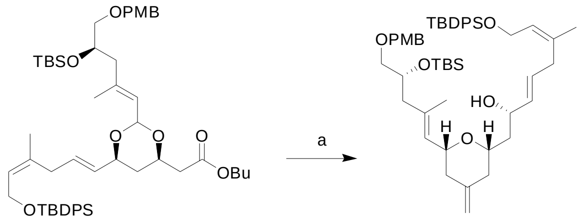
Scheme 3.6: Formation of cyclic α,β-unsaturated acetal (+)-**39**



Reagents: a) Me_3SiCl, inidazole, DMAP, DMF, 80%, b) TMSOTf, CH_2Cl_2, -78°C, 71%

The central transformation in the synthesis involved intramolecular Prins cyclization to form the 2,6-*cis*-4-methylene-tetrahydropyran core of the (+)-dactylolide. The transformation was envisioned to occur upon ionization of the cyclic α,β-unsaturated acetal followed by cyclization with the pendent allylsilane. Therefore, conversion of the butyl ester in cyclic α,β-unsaturated acetal (+)-**39** to the allylsilane was necessary. The literature protocol for the conversion of a functionalized ester to an allylsilane consists of a two step procedure involving the addition of a premixed solution of anhydrous cerium (III) chloride and trimethylsilylmethylmagnesium chloride to the ester to afford the tertiary alcohol. Mild acid treatment of the crude tertiary alcohol with silica gel then initiates Peterson elimination to form the desired allylsilane.[108] When cyclic α,β-unsaturated acetal (+)-**39** was stirred with a premixed solution of anhydrous cerium (III) chloride and trimethylsilylmethylmagnesium chloride followed by quenching with 5% HCl, the product isolated from the reaction mixture was not the expected tertiary alcohol, but rather the 2,6-*cis*-4-methylene-tetrahydropyran core of the molecule (+)-**40**, as shown in Scheme 3.7.

Scheme 3.7: Intramolecular Prins Cyclization

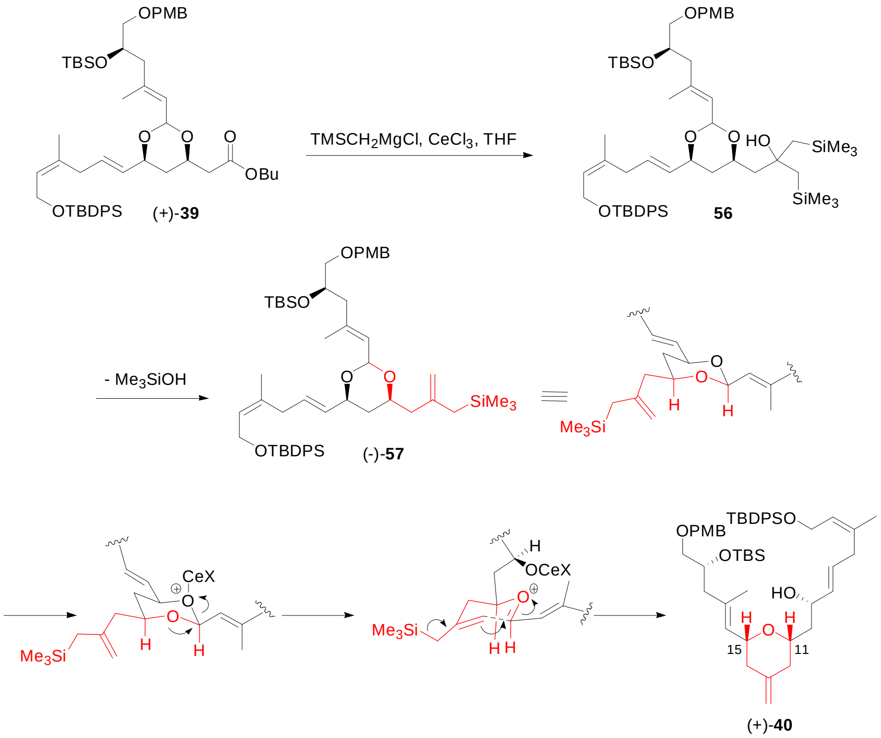


(+)-**39** (+)-**40**

Reagents: a) i.Me$_3$SiCH$_2$MgCl, CeCl$_3$, THF, -78 °C to r.t., ii. 1N HCl, -78 °C to r.t, 42%

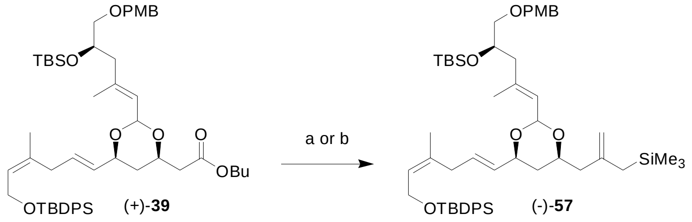
The one pot transformation from cyclic α,β-unsaturated acetal (+)-**39** to the 2,6-*cis*-4-methylene-tetrahydropyran (+)-**40** is shown in Figure 3.13. Under the reaction conditions, the organosilane carries out a double addition into the ester to provide tertiary alcohol **56**. Upon quenching with 5% HCl the tertiary alcohol undergoes Peterson elimination to form the allylsilane (-)-**57**. It is believed that trace amounts of cerium survived the work-up protocol and went on to catalyze the Prins cyclization, because 2,6-*cis*-4-methylene-tetrahydropyran (+)-**40** was only observed following work-up and concentration of the crude reaction mixture.

Figure 3.13: One-pot transformation



In an effort to better understand the results of the one pot ester-to-Prins transformation the quenching and work-up procedures were altered. Repeating the quenching and work-up procedure, followed by allowing the crude product to stand at room temperature overnight led only to decomposition of what appeared to be the desired Prins product by TLC. Refluxing the organic layer obtained after work-up in ether prior to concentration resulted in isolation of only the *E*/*Z* isomerized aldehyde (+)-**38**. As shown in Scheme 3.8, quenching with ethyl acetate followed by basic work-up with saturated NaHCO$_3$ provided tertiary alcohol **56**, which could be converted to allylsilane through stirring with silica gel in CH$_2$Cl$_2$. Quenching with saturated NH$_4$Cl afforded allylsilane (-)-**57**. However, washing allylsilane (-)-**57** with a 1.0 M solution of cerium (III) chloride failed to effect Prins cyclization, as did stirring with silica gel for prolonged periods of time.

Scheme 3.8: Altered quenching method

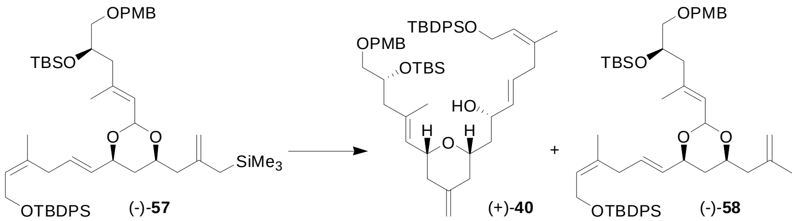


Reagents: a) i. Me_3SiCH_2MgCl, $CeCl_3$, THF, ii. EtOAc, sat. $NaHCO_3$, iii. SiO_2, CH_2Cl_2, 66%
b) i. Me_3SiCH_2MgCl, $CeCl_3$, THF, ii. sat. NH_4Cl, 75%

Given the ability to cleanly isolate allylsilane (-)-**57**, conversion to the Prins cyclization product (+)-**40** was attempted using a variety of Lewis and Brønstead acids as shown in Table 3.2. Prins cyclization could only be affected using both PPTS and the pyridine salt of camphorsulfonic acid (PCSA). Cyclization with PPTS resulted in protodesilylation, as well as the desired tetrahydropyran (+)-**40**. The addition of $MgSO_4$ to PPTS catalyzed Prins cyclization increased reaction yield, and provided only the desired tetrahydropyran (+)-**40**. Subjecting allylsilane (-)-**57** to the reaction conditions developed for the aqueous Prins reaction failed to yield any of the desired tetrahydropyran (+)-**40**, but rather resulted in complete decomposition of the starting material. Under these reaction conditions viable micelle formation was not observed. Neither the critical micelle concentration required was achieved, nor was a surfactant of ideal chain length for viable micelle formation identified. All attempts at performing the Prins cyclization in the presence of a mild Lewis acid at ambient temperature also proved ineffective.

Despite the ability to isolate allysilane (-)-**57** and effect Prins cyclization with PPTS, in terms of overall yield and step count the most synthetically practical route to tetrahydropyran (+)-**40** remains the one pot ester-to-Prins transformation. Isolation of the tertiary alcohol followed by Peterson elimination to give allylsilane (-)-**57** and subsequent Prins cyclization with PPTS is a lengthy, inefficient means for the preparation of the tetrahydropyran (+)-**40.** Protodesilylation is a competitive, unproductive reactive pathway in this route that significantly decreases reaction yield, and affords the side product (-)-**58** that can not be further manipulated for useful synthetic transformations. Therefore, efforts will continue to be focused on optimizing the one pot ester-to-Prins transformation.

Table 3.1: Screening of viable Prins cyclization conditions



Entry	Lewis/Brønstead Acid	Solvent	Product (%)
1	$ScCl_3$•$6H_2O$, SDS	H_2O	Decomposition
2	Me_3Al	CH_2Cl_2	Decomposition
3	$Ce(OTf)_3$	CH_3CN	Decomposition
4	$ScCl_3$•$6H_2O$	CH_3CN	No rxn
5	$Sc(OTf)_3$	CH_3CN	Decomposition
6	$EuCl_3$	CH_3CN	Decomposition
7	$CeCl_3$	EtOAc	No rxn
8	$CeCl_3$, I_2	EtOAc	No rxn
9	$CeCl_3$, SiO_2	EtOAc	No rxn
10	SiO_2	CH_2Cl_2	No rxn
11	$SnCl_4$ on SiO_2	CH_2Cl_2	Decomposition
12	TMSOTf	CH_2Cl_2	Decomposition
13	$MgCl_2$	EtOAc	No rxn

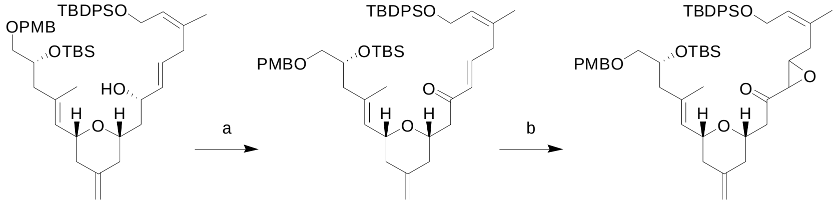
14	Montmorillonite K-10	CH_2Cl_2	No rxn
15	Pyridinium camphorsulfonate	CH_2Cl_2	(+)-**40** (47%)
16	PTSA	CH_2Cl_2	Decomposition
17	PPTS	CH_2Cl_2	(+)-**40** (48%), (-)-**58** (29%)
18	PPTS, $MgSO_4$	CH_2Cl_2	(+)-**40** (66%)

*All reactions conducted at room temperature

In Figure 3.13, the atoms involved in intramolecular Prins cyclization are highlighted in red for clarity. In accord with the observed diastereoselectivity in the development of the aqueous Prins reaction, only a single diastereomer of (+)-**40** was isolated. The *cis* stereochemical relationship between the C11 and C15 protons was conformed through the strong correlation observed in the NOESY spectrum of (-)-**59**. The origin of the *cis* selectivity is understood to be the preference of the two alkyl groups to adopt a pseudoequitorial orientation in the transition state for the Prins reaction. α,β-Unsaturated ketone (-)-**59** was used in spectral studies in preference to (+)-**40** simply for ease of analysis.

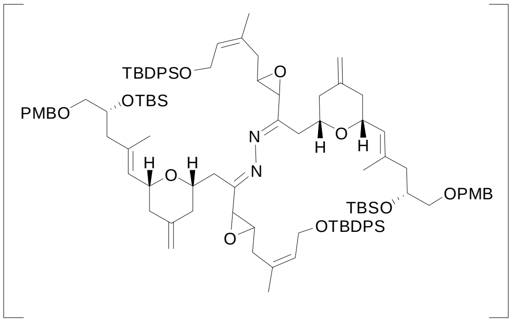
Having successfully constructed the core of the molecule through intramolecular Prins cyclization, the focus shifted to allylic transposition of the C7 alcohol to C9. Initially, the feasibility of allylic transposition via a Wharton epoxy ketone fragmentation[109] was probed. 2,6-*cis*-4-Methylene-tetrahydropyran (+)-**40** was converted to α,β-epoxy ketone (-)-**60**, as shown in Scheme 3.9. However, all attempted to affect the transformation using hydrazine under the conditions developed by Wharton or at low temperature using conditions developed by Luche[110] failed to yield any of the desired transposed allylic alcohol.

Scheme 3.9: Wharton epoxy ketone fragmentation


TBDPSO
OPMB
OTBS
HO
H
O
H
a
TBDPSO
PMBO
OTBS
O
H
O
H
b
TBDPSO
PMBO
OTBS
O
O
H
O
H

(+)-**40** (-)-**59** (-)-**60**

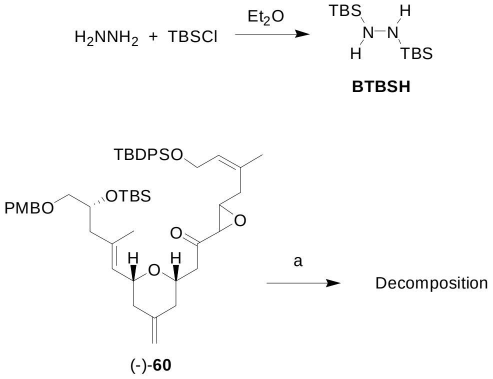
Reagents: a) DMPI, CH_2Cl_2, 95%, b) K_2CO_3, H_2O_2, THF:H_2O, 100%


TBDPSO
PMBO
OTBS
O
N
N
H
O
H
O
H
H
TBSO
OPMB
OTBDPS
O

61

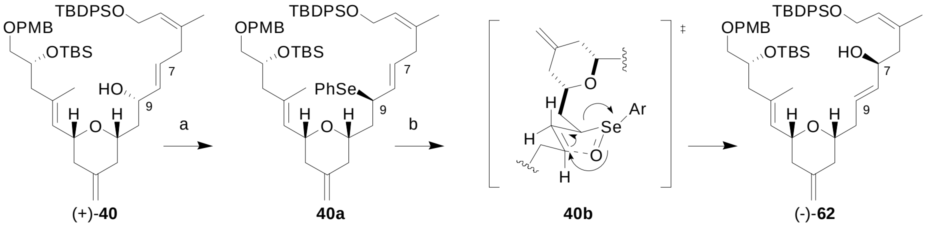
Fearing that facile, self condensation to form azine **61** was inhibiting fragmentation, the reaction was attempted using 1,2-bis(*tert*-butyldimethylsilyl)hydrazine (BTBSH)[111] in the presence of $Sc(OTf)_3$. BTBSH is known to react with ketones and aldehydes in the presence of a Lewis acid, and to date has been employed in Wolff-Kischner-type reduction reactions, Barton vinyl iodide preparation, and the synthesis of *gem*-dihalides.[112] The use of the *N*-silyl hydrazone was expected to enhance stability and prevent azine formation, allowing for isolation of a stable hydrazone which could then be subjected to Wharton fragmentation conditions. However, reaction of BTBSH with epoxy-ketone (-)-**60**, as shown in Scheme 3.10, led only to decomposition of the starting material. No identifiable side products were isolated and no starting material was recovered.

Scheme 3.10: Hydrazone formation with BTBSH



Allylic transposition via the Wharton fragmentation gave way to an allyl selenoxide-selenate [2,3] sigmatropic rearrangement,[113] as all attempts employing hydrazine or BTBSH proved ineffective. The [2,3] sigmatropic rearrangement of selenoxides provides a powerful pathway for allylic transposition of alcohols. Tetrahydropyran (+)-**40** was converted to selenide **40a** with phenylselenocyanate and tributyl phosphine. Selenide **40a** was then treated with peroxide and pyridine to effect oxidation to the selenoxide, followed by [2,3] sigmatropic rearrangement to provide allylic alcohol (-)-**62** (Scheme 3.11). Allylic alcohol (-)-**62** was isolated as a single isomer with complete stereocontrol in the formation of the *trans* C8-C9 olefin. The complete selectivity is attributed to the propensity of the large alkyl groups to preferentially occupy pseudoequitorial positions in the five-membered transition state. This result also is in accord with observations made by Otera in his work on [2,3] sigmatropic rearrangements of allylic sulfoxides, in which rearrangements were found to occur with extremely high *E*-selectivity when a substituent branched at the β position of the sulfinyl group was involved. Thus, formation of the *E*-isomer is thermodynamically, as well as kinetically, favored, so as to avoid $A_{1,3}$ strain that would be imposed by the presence of the THP ring in the *Z*-isomer.

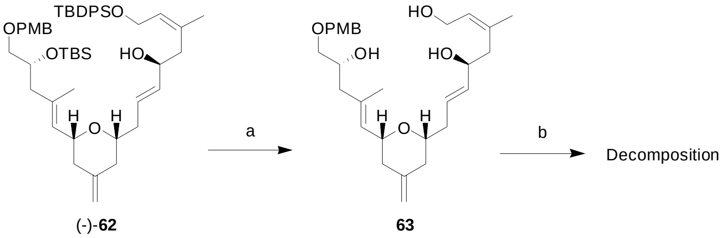
Scheme 3.11: Selenoxide-selenate rearrangement



Reagents: a) C_6H_5SeCn, Bu_3P, THF. b) H_2O_2, pyridine, THF, -30 °C, 65%

Following the selective [2,3]-selenoxide-selenate rearrangement, preparations to close the macrocycle began. Global deprotection of the silyl ethers using TBAF to provide triol **63**, followed by double allylic oxidation with MnO_2 led only to decomposition (Scheme 3.12).

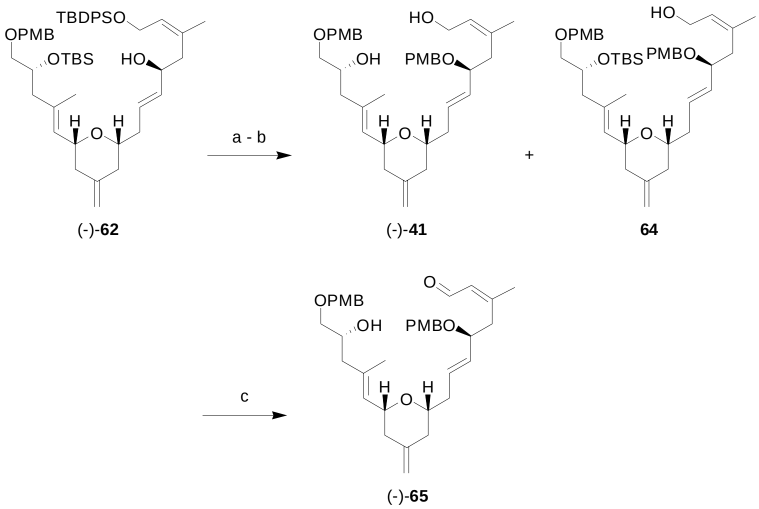
Scheme 3.12: Double allylic oxidation



Reagents: a) TBAF, THF, 95%, b) MnO_2, CH_2Cl_2

Subsequent to the failed double allylic oxidation, the strategy became protection of the C9 alcohol as the PMB ether, followed by global silyl deprotection and selective oxidation of the primary alcohol in the presence of the secondary alcohol. Thus, following acylation with the commercially available diethylphosphonoacetic acid **5** and Horner-Emmons macrocyclization a global deprotection of the PMB ethers followed by a double oxidation would provide the (+)-dactylolide. As shown in Scheme 3.13, the C9 alcohol was protected as the PMB ether using sodium hydride and *p*-methoxybenzyl chloride in DMF. Protection under acidic conditions using *p*-methoxybenzyl trichloroacetimidate failed to yield any of the desired PMB ether. The use of HF-pyridine for global silyl deprotection provided a 40% yield of the desired diol, (-)-**41** and 27% yield of primary alcohol **64**, which could be resubjected to the reaction conditions to provide (-)-**41**. Global silyl deprotection with TBAF proved less favorable, providing only a 27% yield of the desired diol (-)-**41**, with no other isolable products. Selective oxidation of the primary, allylic alcohol in the presence of the secondary alcohol was accomplished using one equivalent of Dess-Martin periodinane to provide aldehyde (-)-**65** in 64% yield.

Scheme 3.13: Selective oxidation



Reagents: a) PMBCl, NaH, TBAI, DMF, b) HF-pyridine, THF, 40%, c) DMPI, CH_2Cl_2, 64%

Precedence for acylation with the commercially available diethylphosphonoacetic acid **5**, followed by Horner-Emmons macrocyclization was established through the work of Smith[3] in the first total synthesis of (+)-dactylolide. An advanced intermediate prepared by Smith differs from (-)-**65** only in that the C9 hydroxyl group is protected as a TBS ether, rather than a PMB ether. Efforts towards the completion of the molecule are on going. However, advanced intermediate (-)-**65** was attained in seventeen total steps, with the longest linear sequence involving seven steps for the preparation of diol (-)-**37**. Thus, this highly convergent route clearly underscores the efforts of Smith who set the bench mark at thirty-five total steps with a longest linear sequence of thirteen steps.

3.3. Conclusion

A highly convergent route towards the total synthesis of the marine macrolide (+)-dactylolide is currently being pursued. The route involves the condensation of two highly functionalized segments of the molecule, an α,β-unsaturated aldehyde and a 1,3-*syn*-diol, to form a cyclic α,β-unsaturated acetal. Both enantiopure segments arise from vinylogous aldol reactions, providing the three necessary stereocenters. The 1,3-*syn*-diol is reached in the longest linear sequence of the synthesis, utilizing only seven steps from commercially available starting materials. The key synthetic transformation involves intramolecular Prins cyclization of a cyclic α,β-unsaturated acetal with a pendent allylsilane to provide the 2,6-*cis*-disubstituted-4-methylenetetrahydropyran core of the molecule efficiently and stereoselectively. The transformation can be achieved either through the in situ generation of the allylsilane in a one pot ester-to-Prins cyclization reaction, or in a lengthier, step-wise manner in which the allylsilane is isolated. Other key transformations include a completely *trans* selective selenoxide-selenate [2,3] sigmatropic rearrangement and the selective oxidation of a primary allylic alcohol in the presence of a secondary alcohol with Dess-Martin periodinane. Thus far the synthesis entails seventeen total steps, with the longest linear sequence involving seven steps, well below the bench mark established by Smith at thirty-five total steps. Precedence for the conversion of the most advanced intermediate attained in this effort to the natural product was also established through the work of Smith.

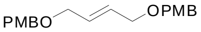
3.4. Experimental

General Procedures. All reactions were performed in oven or flame-dried glassware under a positive pressure of N_2 with magnetic stirring unless otherwise noted.

Materials. Tetrahydrofuran and diethyl ether were dried by passage through an activated alumina column under positive N_2 pressure. Methylene chloride was distilled under N_2 from CaH. Analytical TLC was performed on E. Merck pre-coated (25 mm) silica gel 60F-254 plates. Visualization was done under UV (254 nm). Flash chromatography was done using ICN SiliTech 32-63 60 Å silica gel. Reagent grade ethyl acetate, diethyl ether, pentane and hexanes (commercial mixture) were purchased from EM Science and used as is for chromatography.

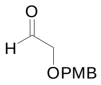
Instrumentation. High resolution and low resolution mass spectra were recorded on a VG 7070 spectrometer. Infrared (IR) spectra were collected on a Mattson Cygnus 100 spectrometer. Samples for IR were prepared as a thin film on a NaCl plate by dissolving the compound in CH_2Cl_2 and then evaporating the CH_2Cl_2. Proton (^1H NMR) and carbon (^{13}C NMR) nuclear magnetic resonance spectra were recorded on Bruker Avance 300 and Bruker Avance 500 spectrometers at 300 MHz and 75 MHz, and 500 MHz and 100 MHz, respectively. The chemical shifts are given in parts per million (ppm) on the delta (δ) scale. The solvent peak was used as a reference value, for ^1H NMR: $CDCl_3$ = 7.27 ppm, for ^{13}C NMR: $CDCl_3$ = 77.23. Data are reported as follows: (s = singlet; d = doublet; t = triplet; q = quartet; dd = doublet of doublets; dt = doublet of triplets; b = broad). HPLC analysis was performed with a HP series 1100 instrument using either a Chiralcel OD-H or OJ or CHIRAPAK AD column.

bis p-Methoxybenzyl ether



To a stirring suspension of sodium hydride (60% dispersion in mineral oil, 1.18 g, 31.12 mmol) under N_2 at 0 ºC in DMF (30 mL) was added but-2-ene-1,4-diol (1.21 g, 13.83 mmol). The reaction was stirred for 30 min. and *p*-methoxybenzyl chloride (4.33 g, 27.66 mmol) was added. The reaction mixture was stirred for 18 h at room temperature, then was quenched by the addition of ice chips, and extracted into hexanes. The organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product (3.37 g, 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 6.5 Hz, 2H), 6.91 (d, *J* = 6.8 Hz, 2H), 5.80 (adt, *J* = 3.8, 1.0 Hz, 1H), 4.48 (s, 2H), 4.07 (dd, *J* = 3.8, 1.0 Hz, 2H), 3.82 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.39, 130.40, 129.69, 113.95, 72.04, 65.62, 55.49.

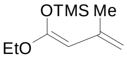
p-methoxy benzyloxy acetaldehyde (43)



43

To a stirring solution of AD-mix-β (1.4g/mmol substrate, 7.00 g) in 1:1 *tert*-butyl alcohol and H_2O (25 mL:25 mL) at 0 ºC was added bis *p*-methoxybenzyl ether (1.64 g, 5.00 mmol). The reaction mixture was warmed to room temperature and stirred for 18 h. The temperature was then decreased to 0 ºC and sodium sulfite (1.5g/mmol substrate, 7.5 g) was added in bulk. The reaction mixture was allowed to stir for 1 h while warming to room temperature, then was extracted into CH_2Cl_2. The aqueous layer was washed with CH_2Cl_2 (2 x 25 mL) and the combined organic layers where dried ($MgSO_4$) and concentrated. The resulting residue was dissolved in CH_2Cl_2 (15 mL) and sodium periodate immobilized on silica gel (2.0g/mmol substrate, 5.52 g) was added. The reaction mixture was stirred vigorously for 30 min., then was filtered. The filter cake was washed with CH_2Cl_2 (2 x 20 mL) and the filtrate was concentrated. The resulting residue was purified by vacuum distillation (bp 120 – 125 ºC, 2 mm Hg) to afford the desired product (1.44 g, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.69 (s, 1H), 7.28 (d, *J* = 8.6 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 4.56 (s, 2H), 4.07 (s, 2H), 3.80 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 200.89, 159.96, 132.21, 129.84, 114.30, 75.27, 73.58, 55.47.

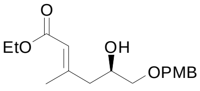
(1-Ethoxy-3-methyl-buta-1,3-dienyloxy)-trimethyl-silane (44)



44

To a solution of diisopropylamine (4.45 g, 44.00 mmol) in THF (50 mL) at 0 ºC under N_2 was added *n*-butyllithium (1.6M in hexanes, 27.5 mL, 44.00 mmol). The reaction mixture was stirred at 0 ºC for 30 min., then the temperature was decreased to -78 ºC. 3-Methyl-but-2-enoic acid ethyl ester (5.12 g, 40.00 mmol) was added and the reaction mixture was stirred for 30 min. before trimethylsilyl chloride (6.52 g, 60.00 mmol) was added. The reaction mixture was stirred for an additional 20 min., then was allowed to warm to room temperature. The reaction mixture was concentrated under reduced pressure and the resulting residue was dissolved in dry pentanes and filtered. The filtrate was concentrated and the resulting residue was purified by distillation (bp 63 – 75 ºC, 2 mm Hg) to afford the desired product (5.95, 74%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.77 (d, *J* = 2.2 Hz, 1H), 4.52 (m, 1H), 4.23 (s, 1H), 3.80 (q, *J* = 6.9 Hz, 2H), 1.93 (s, 1H), 1.30 (t, *J* = 6.9 Hz, 3H), 0.25 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.76, 140.77, 107.28, 81.09, 63.65, 23.92, 14.62, 0.65.

5-Hydroxy-6-(4-methoxybenzyloxy)-3-methyl-hex-2-enoic acid ethyl ester (+)-45

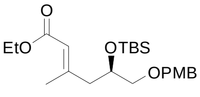


(+)-45

To a solution of (+)-2,6-bis[(4*R*)-4phenyl-2-oxazolin-2-yl]pyridine (0.124 g, 0.337 mmol) in CH_2Cl_2 (13 mL) was added $CuCl_2$ (0.045 g, 0.337 mmol). The reaction mixture was stirred vigorously for 1 h to give a fluorescent green suspension. $AgSbF_6$ (0.232 g, 0.675 mmol, in 10 mL CH_2Cl_2) was added via cannula. The reaction mixture was wrapped in foil and stirred for 3 h. The resulting mixture was filtered directly into the reaction flask through and oven-dried glass pipet, tightly packed with cotton, to remove the white AgCl precipitate, yielding active catalyst (*R,R*)-[Cu(Ph-pybox)]$(SbF_6)_2$ as a clear blue solution. To the solution of active catalyst at -78 ºC was added **43** (2.25 g, 11.21 mmol, in 17 mL CH_2Cl_2). (1-Ethoxy-3-methylbuta-1,3-dienyloxy)trimethylsilane (**44**) (2.69 g, 13.45 mmol) was added drop wise over 30 min. The reaction was stirred at -78 ºC for 4 h, and then was filtered through a pad of silica (1.5 cm thick). The filtrate was concentrated, and the resulting residue was dissolved in THF (20 mL). HCl (1N) was added and the reaction mixture was allowed to stand for 20 min., then was diluted with ether (25 mL) and the two layers were separated. The organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (40% EtOAc in hexanes) to afford the desired product (2.82 g, 82 %); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.29 (d, *J* = 8.6 Hz, 2H), 6.93 (d, *J* = 8.6 Hz, 2H), 5.76 (s, 1H), 4.47 (s, 2H), 4.16 (q, *J* = 7.1 Hz, 2H), 4.04 (m, 1H), 3.83 (s, 3H), 3.51 (dd, *J* = 9.3, 3.3 Hz, 1H), 3.37 (dd, *J* = 7.0, 2.3 Hz, 1H), 2.32 (m, 2H), 2.22 (s, 3H), 1.30 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.63, 159.52, 155.89, 129.99, 129.61, 118.26, 114.03, 73.73, 73.26, 68.44, 59.77, 55.43, 44.79, 19.08, 14.46; $[\alpha]_D^{23}$ 1.25º (CH_2Cl_2 , *c* 9.4).

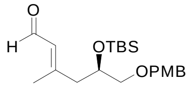
The ee was determined to be 95% by chiral HPLC analysis using a chirapak AD column. Conditions: Hex:*i*-PrOH 95:5, 1.0 mL/min.

5-(tert-Butyldimethylsilanyloxy)-6-(4-methoxybenzyloxy)-3-methylhex-2-enoic acid ethyl ester (+)-46


(+)-46

To a stirring solution of (+)-**45** (4.63 g, 15.04 mmol) in DMF was added imidazole (1.12 g, 16.54 mmol) followed by *tert*-butyldimethylsilyl chloride (2.49 g, 16.54 mmol). The reaction mixture was stirred for 18 h, then was quenched with ice chips and partitioned between water and hexanes. The organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product (5.65 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.6 Hz, 2H), 6.89 (d, *J* = 8.6 Hz, 2H), 5.70 (s, 1H), 4.45 (s, 2H), 4.15 (m, 2H), 3.98 (m, 1H), 3.81 (s, 3H), 3.38 (dd, *J* = 9.5, 5.3 Hz, 1H), 3.32 (dd, *J* = 9.5, 5.8 Hz, 1H), 2.42 (dd, *J* = 13.1, 4.4 Hz, 1H), 2.23 (dd, *J* = 13.1, 7.7 Hz, 1H), 2.18 (d, *J* = 1.2 Hz, 3H), 0.85 (s, 9H), 0.03 (s, 3H), 0.01 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.62, 159.22, 156.40, 130.35, 129.33, 118.56, 113.79, 74.15, 73.07, 69.92, 59.46, 55.32, 46.36, 25.85, 19.51, 18.15, 14.41, -4.40, -4.87; $[\alpha]_D^{23}$ 10.6º (MeOH , *c* 0.64).

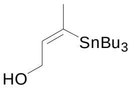
5-(*tert*-Butyl-dimethyl-silanyloxy)-6-(4-methoxybenzyloxy)-3-methyl-hex-2-enal (+)-38


(+)-38

To a solution of lithium aluminum hydride (0.179 g, 4.73 mmol) in ether (15 mL) was added dropwise (+)-**46** (1.00 g, 2.36 mmol, in 5 mL ether). The reaction mixture was stirred for 1 h, then was cooled to 0 ºC and quenched with a saturated solution of sodium potassium tartrate (10 mL). The reaction mixture was warmed to room temperature and stirred for 4 h. The two layers were separated. The water layer was washed with ether (2 x 15 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated. The resulting residue (in 5 mL CH_2Cl_2) was added to a suspension of activated manganese (IV) oxide

(2.00 g, 23.12 mmol) under N_2 in CH_2Cl_2 (10 mL). The reaction mixture was stirred for 18 h, and then was filtered through a pad of celite and was concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford the desired product (0.720 g, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.00 (d, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.6 Hz, 2H), 5.93 (d, *J* = 8.1 Hz, 1H), 4.45 (s, 2H), 4.03 (m, 1H), 3.82 (s, 3H), 3.40 (dd, *J* = 9.4, 5.1 Hz, 1H), 3.32 (dd, *J* = 9.4, 6.2 Hz, 1H), 2.51 (dd, *J* = 13.2, 4.3 Hz, 1H), 2.20 (s, 3H), 0.87 (s, 9H), 0.02 (s, 3H), 0.00 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 191.11, 161.13, 159.42, 130.28, 130.09, 129.51, 113.96, 74.05, 73.24, 70.22, 55.45, 46.14, 25.95, 18.64, 18.26, -4.24, -4.65; $[\alpha]_D^{23}$ 2.05° (CH_2Cl_2 , *c* 0.52).

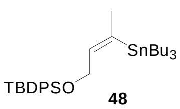
(Z)-3-Tributylstannanylbut-2-en-1-ol (31)



31

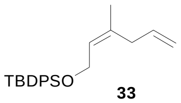
To a solution of 2-butyn-1-ol (4.21 g, 60.0 mmol) in THF (120 mL) at 0 ºC was added Red-Al® (65 % wt solution in toluene, 18.66 g, 60.0 mmol) dropwise over 30 min. After the addition was complete the reaction mixture was warmed to room temperature and stirred for 3 h. Tributyltin chloride (39.05 g, 120 mmol) was added dropwise over a period of ten min. The reaction mixture was stirred for 18 h then was quenched with H_2O and filtered through a pad of Celite. The two layers were separated and the water layer was extracted with Et_2O. The combined organic layers were washed with 10 % KF, dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (gradient from hexanes to 20% EtOAc in hexanes) to afford the desired product (17.95 g, 83 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 6.28 (t, *J* = 6.7, $^3J_{\text{Sn-H}\ trans}$ = 123 Hz, 1H), 4.03 (t, *J* = 5.7 Hz, 2H), 1.96 (s, $^3J_{\text{Sn-H}}$ = 41 Hz, 3H), 1.55 – 1.27 (m, 13H), 0.92 (m, 15H).

tert-Butyldiphenyl(3-tributylstannylbut-2-enyloxy)silane (48)


48

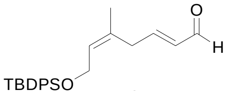
To a stirring solution of **31** (1.00 g, 2.77 mmol) in DMF was added imidazole (0.23 g, 3.32 mmol) followed by *tert*-butyldiphenylsilyl chloride (0.91 g, 3.32 mmol). The reaction mixture was stirred for 3 h, then was quenched with ice chips and partitioned between water and hexanes. The organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford the desired product (1.35 g, 81%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (m, 4H), 7.41 (m, 5H), 6.26 (tq, *J* = 6.5, 1.5 Hz, $^3J_{\text{Sn-H, }\mathit{trans}}$ 127 Hz, 1H), 4.07 (d, *J* = 6.3 Hz, 2H), 1.94 (d, *J* = 0.97 Hz, $^3J_{\text{Sn-H}}$ 41 Hz, 3H), 1.44 – 1.21 (m, 12H), 1.06 (s, 9H), 0.83 (m, 15H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.48, 139.68, 135.73, 134.00, 129.63, 127.70, 66.58, 29.21, 27.45, 26.94, 13.77, 10.00; IR (neat) 3069, 2952, 2923, 2850, 1949, 1890, 1818, 1461, 1425, 1374, 1112, 1083, 1047, 821, 741, 698; HRMS (EI) calcd for $C_{24}H_{43}OSiSn$ (M-C_4H_9) 543.210519, found 543.207774.

tert-Butyl-(3-methylhexa-2,5-dienyloxy)diphenylsilane (33)


33

To a stirring solution of **48** (0.50 g, 0.833 mmol) in toluene (10 mL) was added palladium tetrakistriphenylphosphine (0.048 g, 0.042 mmol) followed by allyl bromide (0.101 g, 0.833 mmol). The reaction mixture was heated to reflux for 18 h, then cooled to room temperature and was partitioned between Et_2O and sat. NH_4Cl. The organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography to afford the desired product (0.234 g, 80%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (m, 4H), 7.41 (m, 5H), 5.62 (m, 1H), 5.48 (t, *J* = 6.3 Hz, 1H), 4.96 (m, 1H), 4.91 (m, 1H), 4.23 (d, *J* = 6.3 Hz, 2H), 2.62 (d, *J* = 6.5 Hz, 2H), 1.70 (s, 3H), 1.06 (s, 9H);); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.91, 135.54, 134.49, 129.74, 127.82, 125.91, 115.59, 61.04, 36.86, 27.28, 22.85, 19.46; IR (neat) 3061, 3040, 2850, 1956, 1890, 1832, 1694, 1636, 1469, 1425, 1105, 1047, 909, 821, 734, 690; HRMS (EI) calcd for $C_{19}H_{21}OSi$ ($M-C_4H_9$) 293.136169, found 293.135677.

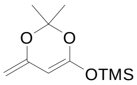
7-(*tert*-Butyldiphenylsilanyloxy)-5-methylhepta-2,5-dienal (35)



35

To a stirring solution of **33** (2.0 g, 5.71 mmol) and acrolein diethylacetal (1.85 g, 14.26 mmol) in CH_2Cl_2 (6 mL) under N_2 was added (Grubbs 1st generation catalyst, 0.117 g, 0.142 mmol). The reaction mixture was heated to reflux for 18 h, then cooled to room temperature and a solution formic acid in CH_2Cl_2 (1:8) (4 mL) was added. The reaction mixture was stirred for 3 h, then was concentrated to one third of its original volume and was purified by flash chromatography (eluting with 100 mL CH_2Cl_2, then 10% EtOAc in hexanes) to afford the desired product (1.92 g, 89%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.45 (d, *J* = 7.8 Hz, 1H), 7.71 (m, 4H), 7.42 (m, 5H), 6.61 (dt, *J* = 15.5, 6.6 Hz, 1H), 6.01 (ddt, *J* = 15.5, 7.8, 1.5 HZ, 1H), 5.60 (t, *J* = 5.9 Hz, 1H), 4.19 (d, *J* = 6.4 Hz, 2H), 2.86 (d, *J* = 6.5 Hz, 2H), 1.72 (d, *J* = 1.2 Hz, 3H), 1.06 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 193.71, 155.18, 135.82, 133.97, 133.68, 133.01, 129.89, 127.89, 127.75, 60.75, 35.74, 27.05, 23.64, 19.37; IR (neat) 3061, 2960, 2923, 2865, 1687, 1469, 1425, 1389, 1112, 1047, 974, 814, 698; HRMS (EI) *m/z* calcd for $C_{20}H_{21}O_2Si$ (M^+) 321.131084, found 321.130751.

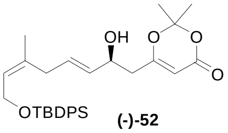
Silyl ketene acetal (36)



36

To a stirring solution of diisopropylamine (2.22 g, 22.00 mmol) in THF (20 mL) at 0 ºC was added *n*-butyllithium (1.6M in hexanes, 13.75 ml, 22.00 mmol) drop wise over 15 min. The reaction was stirred at 0 ºC for 30 min., then the temperature was decreased to -78 ºC. 2,2,6-Trimethyl-[1,3]dioxin-4-one (2.84 g, 20.00 mmol) was added drop wise over 10 min. and the resulting bright orange solution was stirred at -78 ºC for 60 min. Chlorotrimethylsilane (2.61 g, 24.00 mmol) was added over 10 min. and the reaction mixture was stirred for an additional 30 min. at -78 ºC, then was warmed to room temperature. The reaction mixture was then filtered through a pad of oven dried anhydrous Na_2SO_4 and concentrated. The resulting residue was purified by kugelrohr distillation (65 ºC at 0.2 mm Hg, temperature must not exceed 65 ºC in order to avoid decomposition) to afford the desired product as a bright orange liquid (3.76 g, 88%) : ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.65 (s, 1H), 4.08 (s, 1H), 3.98 (s, 1H), 1.56 (s, 6H), 0.26 (s, 9H).

Dioxenone (-)-52



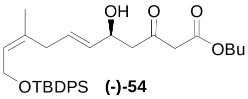
(-)-52

To a stirring solution of (S,S)-N,N'-bis[4,5-dihydro-3,5-dimethyl-4-(3H-dinaphtho[2,1-d:1',2'-f][1,3,2]-2-oxodiazaphosphino)]-N,N'-dimethyl-1,5-pentanediamine (0.04 g, 0.05 mmol) and **35** (1.92 g, 5.07 mmol) in CH_2Cl_2 (20 mL) at -78 ºC was added silicon tetrachloride (0.94 g, 5.57 mmol). The silyl ketene acetal **36** (1.19 g, 5.57 mmol, in 5 mL of CH_2Cl_2) was added via syringe pump over 3h. The reaction mixture was stirred at -78 ºC for 18h, then was added via cannula to a stirring room temperature solution of 1M KH_2PO_4. The resulting biphasic mixture was allowed to warm to room temperature before filtration through a pad of Celite. The filtrate was washed with 10% KF and the organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (40% EtOAc in hexanes) to afford the desired product (1.73 g, 65%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (m, 4H), 7.42 (m, 6H), 5.55–5.53 (m, 3H), 5.28 (s, 1H), 4.31 (m, 1H),

4.19 (d, *J* = 6.4 Hz, 2H), 2.59 (d, *J* = 6.3 Hz, 2H), 2.37 (d, *J* = 3.7 Hz, 1H), 2.34 (d, *J* = 1.8 Hz, 1H), 1.67 (m, 9H), 1.04 (s, 9H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 168.51, 160.92, 135.89, 135.89, 135.10, 134.38, 132.56, 130.26, 129.81, 127.86, 125.20, 106.10, 95.56, 69.71, 60.97, 41.87, 35.15, 27.15, 25.59, 25.15, 23.49, 19.44; IR (neat) 3454, 3069, 3047, 2996, 2923, 2850, 1723, 1629, 1425, 1367, 1280, 1200, 1098, 952, 901, 814, 734, 705 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{27}H_{31}O_5Si$ (M-C_4H_9) 463.194078, found 463.194100.

The ee was determined to be 93% (88.3, 3.2) by chiral HPLC analysis using a chiracel OD-H column. Conditions: Hex:*i*-PrOH 95:5, 0.90 mL/min. Retention time: minor 13.9, major 15.6

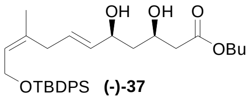
β-hydroxy keto ester (-)-54



(-)-54

The dioxenone (-)-**52** (0.62 g, 1.19 mmol) was dissolved in anhydrous 1-butanol (23 mL). The 1-butanol was degassed by passing a stream of N_2 through for 2h prior to reaction. The reaction mixture was plunged into a preheated oil bath (140 ºC) and allowed to reflux for 1h, then was cooled to room temperature and concentrated under reduced pressure. The resulting residue was purified by flash chromatography (20% EtOAc in hexanes) to afford the desired product (0.47 g, 74%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.70 (m, 4H), 7.42 (m, 6H), 5.49-5.34 (m, 3H), 4.49 (m, 1H), 4.20 (d, *J* = 6.4 Hz, 2H), 4.14 (t, *J* = 6.7 Hz, 2H), 3.45 (s, 2H), 2.68-2.57 (m, 4H), 1.68 (s, 3H), 1.62 (m, 2H), 1.36 (m, 2H), 1.05 (s, 9H), 0.93 (t, *J* = 7.4 Hz, 3H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 202.97, 167.11, 135.78, 135.24, 134.08, 131.75, 129. 75, 129.39, 127.80, 125.92, 68.33, 65. 56, 60.84, 50.10, 49.78, 35.10, 30.65, 27.01, 23.53, 19.34, 19.21, 13.83; IR (neat) 3476, 3127, 3061, 2945, 1956, 1890, 1818, 1738, 1650, 1465, 1419, 1306, 1111, 973, 825, 784, 743, 702, 609 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{32}H_{44}O_5Si$ (M^+) 536.295803, found 536.293564; $[\alpha]_D^{23}$ -9.87º ($CHCl_3$, *c* 1.07).

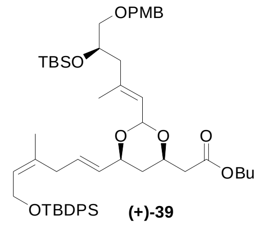
1,3-syn diol (-)-37



(-)-37

To a stirring solution of β-hydroxy keto ester (-)-**54** (1.08 g, 2.02 mmol) in THF (15 mL) at -78 ºC was added diethylmethoxyborane (0.22 g, 2.22 mmol). The reaction mixture was stirred for 30 min. before $NaBH_4$ (0.45 g, 12.14 mmol) was added in bulk. The reaction mixture was stirred at -78 ºC for 18h before being quenched with saturated NH_4Cl (5 mL). The reaction mixture was warmed to room temperature, diluted with Et_2O and acidified to pH 1 by the addition of 1N HCl. The two layers were separated and the aqueous layer was washed with Et_2O (3x20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The resulting residue was azeotroped with MeOH (3x25 mL) and purified by flash chromatography (50% EtOAc in hexanes) to afford the desired product (0.09 g, 83 %): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (m, 4H), 7.41 (m, 6H), 5.44 (m, 3H), 4.29 (m, 2H), 4.21 (d, *J* = 5.5 Hz, 2H), 4.12 (t, *J* = 6.6 Hz, 2H), 2.57 (d, *J* = 6.0 Hz, 2H), 2.47 (d, *J* = 3.6 Hz, 1H), 2.45 (d, *J* = 0.88 Hz, 1H), 1.68 (s, 3H), 1.65-1.50 (m, 4H), 1.35 (m, 4H), 1.05 (s, 9H), 0.94 (t, *J* = 7.3 Hz, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.75, 135.78, 135.50, 134.07, 133.42, 129.74, 128.74, 127.73, 125.77, 72.71, 68.53, 64.85, 60.85, 42.81, 41.76, 35.12, 30.73, 27.01, 23.57, 19.34, 19.28, 13.87; IR (neat) 3403, 3069, 3040, 2734, 1963, 1890, 1818, 1730, 1672, 1592, 1425, 1258, 1112, 814 cm^{-1}; HRMS (EI): *m/z* calcd for $C_{28}H_{35}O_4Si$ ($M–C_4H_9$, H_2O) 463.230463, found 463.231124; $[\alpha]_D^{23}$ -8.57º ($CHCl_3$, *c* 1.08).

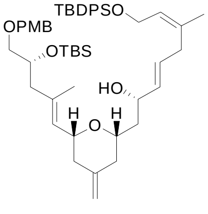
Cyclic α,β-unsaturated acetal (+)-39



(+)-39

To a stirring solution of 1,3-syn diol (-)-**37** (0.77 g, 1.44 mmol) in DMF (10 mL) was added imidazole (0.49 g, 7.23 mmol). The reaction mixture was stirred for 5 min. and chlorotrimethylsilane (0.34 g, 3.18 mmol) was added, followed by DMAP (0.01 g). The reaction mixture was stirred for 18h, then quenched with ice chips. The reaction mixture was extracted into hexanes, and the water layer was washed with hexanes (3x15 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The resulting residue was dissolved CH_2Cl_2 (10 mL) and the temperature was decreased to -78 ºC before 5-(*tert*-butyldimethylsilanyloxy)-6-(4-methoxybenzyloxy)-3-methylhex-2-enal (0.54 g, 1.44 mmol) and TMSOTf (0.03 g, 0.14 mmol) were added. The reaction mixture was stirred for 45 min., then quenched with pyridine (0.01 g, 0.17 mmol), warmed to room temperature and washed with saturated $NaHCO_3$. The organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes) to afford the desired product (0.91 g, 71%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.68 (m, 4H), 7.41 (m, 6H), 7.27 (d, *J* = 8.5 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.51-5.42 (m, 3H), 5.33 (d, *J* = 5.9 Hz, 1H), 5.23 (d, *J* = 6.1 Hz, 1H), 4.44 (s, 2H), 4.20 (d, *J* = 6.3 Hz, 2H), 4.09 (t, *J* = 6.6 Hz, 4H), 3.94 (m, 1H), 3.80 (s, 3H), 3.36 (d, *J* = 5.3 Hz, 2H), 2.66 (dd, *J* = 15.7, 7.0 Hz, 1H), 2.59 (d, *J* = 6.1 Hz, 2H), 2.43 (dd, *J* = 15.6, 6.0 Hz, 1H), 2.26 (dd, *J* = 13.5, 5.3 Hz, 1H), 2.14 (dd, *J* = 13.5, 6.9 Hz, 1H), 1.73 (s, 3H), 1.67 (s, 3H), 1.61 (m, 4H), 1.34 (m, 2H), 1.05 (s, 9H), 0.93 (t, *J* = 7.6 Hz, 3H), 0.86 (s, 9H), 0.03 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.95, 159.21, 139.37, 135.83, 135.44, 134.06, 130.84, 130.75, 129.66, 129.38, 127.79, 125.74, 125.28, 113.82, 98.38, 76.42, 74.46, 73.06, 72.75, 70.49, 64.65, 60.82, 55.40, 44.84, 41.07, 36.65, 35.22, 31.77, 30.76, 27.01, 26.07, 23.54, 22.84, 10.33, 18.32, 18.15, 13.89, -4.32, -4.57; IR (neat) 3061, 2952, 2923, 2850, 1730, 1672, 1607, 1505, 1469, 1381, 1301, 1250, 1120, 1032, 996, 836, 785, 698 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{53}H_{78}O_8NaSi_2$ (M + Na) 921.5133, found 921.5137; $[\alpha]_D^{23}$ -4.25º ($CHCl_3$, *c* 1.00).

2,6-cis-4-methylene-tetrahydropyran (+)-40

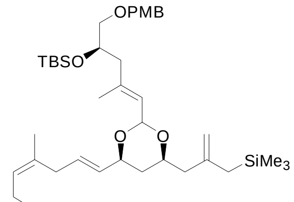


(+)-40

Cerium III chloride (2.46 g, 10.0 mmol) was dried with vigorous stirring under vacuum (0.2 mm Hg) at 150 ºC for 2h, then cooled to room temperature, flushed with N_2 and suspended in THF (15 mL). The suspension was sonicated for 2h, then transferred to a -78 ºC cold bath. Trimethylsilylmethylmagnesium chloride (1.0M in Et_2O, 10.0 mL, 10.0 mmol) was added over 20 min. to form a pale yellow suspension, which stirred for 1h. The cyclic α,β-unsaturated acetal (+)-**39** (0.54 g, 0.60 mmol, in 2 mL THF) was added dropwise, and the reaction mixture was allowed to gradually warm to room temperature and stir for 18h. The temperature was then decreased to -78 ºC and the reaction was quenched by the addition of 5 % HCl (5 mL). The reaction mixture was warmed to room temperature, and the two layers were separated. The aqueous layer was washed with Et_2O (2x25 mL), and the combined organic layers were dried ($MgSO_4$) and concentrated using a 40 ºC water bath. The flask was the placed under vacuum and allowed to stand for 30 min. The resulting residue was purified by flash chromatography (10% → 15% → 20 % → 30% EtOAc in hexanes) to afford the desired product (0.21 g, 42%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 1.4 Hz, 2H), 7.68 (d, *J* = 1.5 Hz, 2H), 7.40 (m, 6H), 7.26 (d, *J* = 8.7 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.46 (m, 2H), 5.38 (dd, *J* = 6.2, 15.6 Hz, 1H), 5.22 (d, *J* = 7.5 Hz, 1H), 4.73 (s, 2H), 4.45 (s, 2H), 4.24 (ddd, *J* = 2.2, 6.2, 9.2 Hz, 1H), 4.20 (d, *J* = 6.4 Hz, 2H), 4.00 (ddd, *J* = 2.5, 7.8, 11.0 Hz, 1H), 3.95 (m, 1H), 3.80 (s, 3H), 3.53 (m, 1H), 3.32 (d, *J* = 5.2 Hz, 2H), 2.57 (d, *J* = 6.0 Hz, 2H), 2.26 (dd, *J* = 6.3, 13.5 Hz, 1H), 2.20 (s, 1H), 2.13 (m, 3H), 2.00 (m, 2H), 1.69 (s, 3H), 1.68

(s, 3H), 1.06 (s, 9H), 0.88 (s, 9H), 0.03 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.17, 143.85, 136.97, 135.72, 135.68, 134.05, 133.63, 130.07, 129.67, 129.35, 127.98, 127.74, 125.51, 113.79, 109.17, 78.82, 75.67, 74.04, 73.03, 72.24, 70.79, 60.82, 55.36, 44.79, 43.35, 40.92, 40.65, 35.13, 26.98, 26.04, 23.52, 19.30, 18.30, 18.04, -4.32, -4.54; IR (neat) 3476, 3076, 2930, 2894, 2850, 1672, 1614, 1585, 1512, 1469, 1425, 1352, 1287, 1250, 1105, 1040, 843, 770, 698 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{51}H_{74}O_6NaSi_2$ (M + Na) 861.4922, found 861.4961; $[\alpha]_D^{23}$ +0.79° ($CHCl_3$, *c* 1.01).

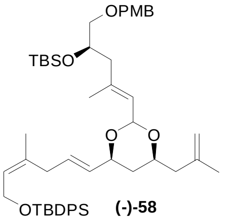
Allylsilane (-)-57



(-)-57

The desired Prins cyclization product could also be obtained in a step-wise manner. Cerium III chloride (2.46 g, 10.0 mmol) was dried with vigorous stirring under vacuum (0.2 mm Hg) at 150 ºC for 2h, then cooled to room temperature, flushed with N_2 and suspended in THF (15 mL). The suspension was sonicated for 2h, then transferred to a -78 ºC cold bath. Trimethylsilylmethylmagnesium chloride (1.0M in Et_2O, 10.0 mL, 10.0 mmol) was added over 20 min. to form a pale yellow suspension, which stirred for 1h. The cyclic α,β-unsaturated acetal (+)-**39** (0.89 g, 1.00 mmol, in 2 mL THF) was added dropwise, and the reaction mixture was allowed to gradually warm to room temperature and stir for 18h. The temperature was then decreased to -78 ºC and the reaction was quenched by the addition of EtOAc (5 mL). The reaction mixture was stirred at -78 ºC for and addition 20 min., then was warmed to room temperature, and washed with saturated $NaHCO_3$ and brine. The organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was dissolved in CH_2Cl_2 (10 mL) and silica gel (1.5 g) was added. The reaction mixture was stirred for 18h, then filtered. The filtrate was concentrated and the resulting residue was purified by flash chromatography (10 % EtOAc in hexanes) to afford the desired product (0.35 g, 66%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.69 (m, 4H), 7.41 (m, 6H), 7.26 (d, *J* = 8.2 Hz, 2H), 6.88 (d, *J* = 8.6 Hz, 2H), 5.55-5.33 (m, 4H), 5.20 (d, *J* = 6.2 Hz, 1H), 4.65 (s, 1H), 4.60 (s, 1H), 4.44 (s, 2H), 4.20 (d, *J* = 6.4 Hz, 2H), 4.07 (m, 1H), 3.95 (m, 1H), 3.81 (s, 4H), 3.36 (d, *J* = 5.3 Hz, 2H), 2.59 (d, *J* = 5.8 Hz, 2H), 2.36 (dd, *J* = 13.9, 5.7 Hz, 1H), 2.26 (dd, *J* = 13.5, 5.5 Hz, 1H), 2.15 (dd, *J* = 13.4, 6.7 Hz, 1H), 2.05 (dd, 15.5, 8.2 Hz, 1H), 1.74 (d, *J* = 0.9 Hz, 3H), 1.67 (s, 3H), 1.27 (s, 2H), 1.05 (s, 9H), 0.86 (s, 9H), 0.04 (s, 15H); ^{13}C NMR (75 MHz, CDCl$_3$) δ 159.40, 143.57, 138.98, 135.90, 135.70, 134.35, 131.50, 131.04, 129.80, 129.45, 129.19, 127.88, 125.84, 114.01, 110.08, 98.51, 75.42, 74.71, 73.22, 70.80, 60.99, 55.54, 45.05, 44.93, 27.56, 27.17, 26.21, 23.59, 19.46, 18.43, 18.29, -1.05, -4.18, -4.46; IR (neat) 3061, 2952, 2850, 2734, 2698, 1949, 1890, 1818, 1738, 1665, 1607, 1585, 1505, 1469, 1425, 1360, 1250, 1112, 843, 778, 734 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{54}H_{82}O_6NaSi_3$ (M + Na) 933.5317, found 933.5359; $[\alpha]_D^{23}$ -5.53° (CHCl$_3$, *c* 0.75).

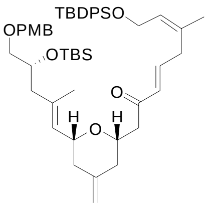
To a solution of PPTS (0.54 g, 1.99 mmol) in CH$_2$Cl$_2$ (2 mL) at room temperature was added allylsilane (0.05 g, 0.05 mmol, in 1 mL CH$_2$Cl$_2$) and MgSO$_4$ (0.26 g, 2.18 mmol). The reaction mixture was stirred at room temperature for 3.5h, then placed directly on a silica gel column. The reaction mixture was purified by flash chromatography (10 % EtOAc in hexanes) to afford the desired Prins cyclization product (0.029 g, 66%).



(-)-58

The proto-desilated acetal was isolated as a by-product of the reaction (0.014g, 29%): ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.67 (m, 4H), 7.42 (m, 6H), 7.23 (d, *J* = 9.8 Hz, 2H), 6.88 (d, *J* = 8.5 Hz, 2H), 5.52-5.33 (m, 4H), 5.20 (d, *J* = 6.2 Hz, 1H), 4.79 (s, 1H), 4.74 (s, 1H), 4.43 (s, 2H), 4.20 (d, *J* = 6.4 Hz, 2H), 4.05 (m, 1H), 3.94 (m, 1H), 3.81 (s, 4H), 3.34 (d, *J* = 5.3 Hz, 2H), 2.59 (d, *J* = 5.8 Hz, 2H), 2.35 (dd, *J* = 7.4, 13.9 Hz, 1H), 2.25 (dd, *J* = 5.5, 13.5 Hz, 1H), 2.12 (dd, *J* = 6.7, 13.8 Hz, 2H), 1.75 (s, 3H), 1.74 (s, 3H), 1.67 (s, 3H), 1.47 (m, 2H), 1.26 (m, 2H), 1.04 (s, 9H), 0.86 (s, 9H), 0.02 (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.49, 142.03, 138.87, 135.89, 134.46, 131.55, 131.13, 129.75, 129.40, 129.11, 127.84, 125.90, 114.07, 112.92, 98.54, 80.12, 75.17, 74.78, 73.23, 70.87, 61.02, 55.53, 45.08, 44.52, 37.14, 35.34, 27.19, 26.20, 23.51, 23.19, 19.45, 18.39, 18.23, -4.19, -4.46; IR (neat) 3069, 2938, 2858, 1607, 1512, 1469, 1425, 1367, 1301, 1243, 1105, 1032, 1003, 829, 770, 698 cm^{-1}; HRMS (ESI) calcd for $C_{51}H_{74}O_6NaSi_2$ (M+Na) 861.4922, found 861.4926.

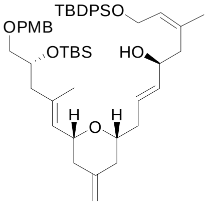
Ketone (-)-59



(-)-59

To a stirring solution of 2,6-*cis*-4-methylene-tetrahydropyran (+)-**40** (0.11 g, 0.12 mmol) in CH_2Cl_2 (5 mL) at 0 ºC was added Des-Martin periodinane (0.06 g, 0.15 mmol). The reaction mixture was stirred at room temperature for 2h, then quenched with a 1:1 mix of saturated $NaHCO_3$ and saturated $Na_2S_2O_3$ (1.5 mL). The resultant biphasic reaction mixture was stirred for 30 min, then the two layers were separated. The aqueous phase was washed with CH_2Cl_2 (10 mL), and the combined organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (10% EtOAc in hexanes) to afford the desired product (0.10 g, 94%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (d, *J* = 4.0 Hz, 4H), 7.45 (m, 5H), 7.29 (d, *J* = 5.0 Hz, 2H), 6.91 (d, *J* = 5.0 Hz, 2H), 6.64 (dt, *J* = 3.9, 9.5 Hz, 1H), 6.02 (d, *J* = 9.5 Hz, 1H), 5.57 (t, *J* = 3.6 Hz, 1H), 5.23 (d, *J* = 4.5 Hz, 1H), 4.77 (s, 1H), 4.76 (s, 1H), 4.47 (s, 2H), 4.20 (d, *J* = 3.7 Hz, 2H), 4.01 (at, *J* = 5.2 Hz, 1H), 3.94 (m, 1H), 3.84 (s, 4H), 3.36 (d, *J* = 3.0 Hz, 2H), 2.90 (dd, *J* = 3.7, 9.6 Hz, 1H), 2.76 (d, *J* = 3.9 Hz, 2H), 2.59 (dd, *J* = 3.7, 9.6 Hz, 1H), 2.32 (d, *J* = 7.8 Hz, 1H), 2.31 (d, *J* = 7.8 Hz, 1H), 2.13 (m, 2H), 2.00 (at, *J* = 7.3 Hz, 1H), 1.93 (at, *J* = 7.4 Hz, 1H), 1.71 (s, 3H), 1.69 (s, 3H), 1.08 (s, 9H), 0.90 (s, 9H), 0.06 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.88, 159.31, 144.71, 144.11, 136.35, 135.81, 133.97, 133.48, 131.61, 130.83, 129.87, 129.41, 128.56, 127.89, 127.30, 113.91, 109.29, 77.23, 75.80, 74.37, 73.13, 70.17, 60.75, 55.47, 46.69, 45.21, 40.78, 40.52, 35.43, 27.05, 26.14, 23.67, 19.38, 18.40, 17.91, -4.25, -4.49; IR (neat) 3069, 2923, 2894, 2843, 1709, 1672, 1614, 1600, 1520, 1469, 1425, 1360, 1250, 1112, 829, 770, 698 cm $^{-1}$; HRMS (ESI): *m/z* calcd for $C_{51}H_{72}O_6NaSi_2$ (M Na) 859.4765, found 859.4805; $[\alpha]_D^{23}$ -8.02º ($CHCl_3$, *c* 1.02).

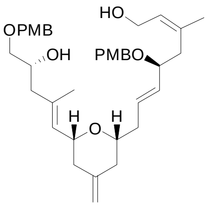
Allylic alcohol (-)-62



(-)-62

To a stirring solution of 2,6-*cis*-4-methylene-tetrahydropyran (+)-**40** (0.13 g, 0.15 mmol) in THF (3 mL) at 0 ºC was added phenylselenocyanate (0.03 g, 0.15 mmol) followed by tributylphosphine (0.03 g, 0.15 mmol). The reaction mixture was stirred at room temperature for 3h, then concentrated. The resulting residue was purified by flash chromatography (CH_2Cl_2) to yield the desired selenide. The selenide was dissolved in CH_2Cl_2 (2 mL) and the temperature was decreased to -30 ºC. Pyridine (0.71 mL) was added, followed by 30% H_2O_2 (1 mL), and the reaction mixture was stirred for 5h, then quenched with saturated NH_4Cl (1 mL). The reaction mixture was warmed to room temperature and extracted into Et_2O. The organic layer was washed with 10% HCl, dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (5% → 20% EtOAc in hexanes) to afford the desired product (0.07 g, 58%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (at, *J* = 7.1 Hz, 4H), 7.44 (m, 6H), 7.28 (d, *J* = 8.3 Hz, 2H), 6.91 (d, *J* = 8.3 Hz, 2H), 5.72 (dt, *J* = 4.1, 15.3 Hz, 1H), 5.63 (t, *J* = 6.5 Hz, 1H), 5.54 (dd, *J* = 6.4, 15.3 Hz, 1H), 5.29 (d, *J* = 7.5 Hz, 1H), 4.75 (s, 2H), 4.48 (s, 2H), 4.23 (m, 1H), 4.16 (m, 1H), 3.98 (m, 2H), 3.84 (s, 3H), 3.38 (d, *J* = 5.2 Hz, 2H), 3.34 (m, 1H), 2.37 (m, 4H), 2.23 (m, 2H), 2.14 (m, 2H), 2.06 (m, 2H), 1.93 (m, 1H), 1.80 (s, 3H), 1.72 (s, 3H), 1.65 (s, 1H), 1.11 (s, 9H), 0.92 (s, 9H), 0.08 (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.28, 144.60, 135.98, 135.62, 133.55, 130.55, 129.63, 129.19, 128.55, 127.66, 127.41, 127.21, 113.64, 108.78, 77.92, 75.82, 74.11, 73.13, 70.49, 70.21, 60.05, 55.23, 45.21, 40.96, 40.74, 40.23, 39.40, 26.77, 25.89, 23.89, 19.07, 18.41, 17.95, -4.24, -4.47; IR (neat) 3461, 3083, 2923, 2894, 2850, 1650, 1607, 1505, 1469, 1425, 1360, 1250, 1120, 836, 770, 741, 705 cm $^{-1}$; HRMS (ESI): *m/z* calcd for $C_{51}H_{74}O_6NaSi_2$ (M + Na) 861.4922, found 861.4948; $[\alpha]_D^{23}$ -2.32º (PhH , *c* 1.82).

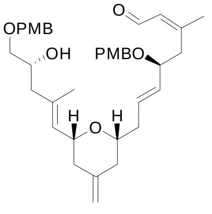
Diol (-)-41



(-)-41

To a stirring solution of allylic alcohol (-)-**62** (0.013 g, 0.015 mmol) in DMF (0.25 mL) at 0 ºC was added 4-methoxybenzyl chloride (0.25 mL), tetrabutylammonium iodide (0.01 g) and sodium hydride (60% dispersion in mineral oil, 0.0009 g, 0.023 mmol). The reaction mixture was stirred for 18h at room temperature, then quenched by the addition of ice chips, and extracted into hexanes. The organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (5% EtOAc in hexanes). The resulting residue was dissolved in THF (0.25 mL) and 3 drops of HF·pyridine were added. The reaction mixture was stirred at room temperature for 18h, then quenched by the careful addition of saturated $NaHCO_3$ (1.5 mL) and extracted into EtOAc (5 mL). The water layer was washed with EtOAc (5 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated. The resulting residue was azeotroped with benzene (3x5 mL) to remove any excess pyridine, and purified by flash chromatography (50% EtOAc in hexanes) to afford the desired product (0.003 g, 40%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (d, *J* = 6.5 Hz, 2H), 7.21 (d, *J* = 8.4 Hz, 2H), 6.89 (d, *J* = 8.4 Hz, 2H), 6.87 (d, *J* = 8.4, 2H), 5.68 (m, 2H), 5.46 (dd, *J* = 8.2, 15.5 Hz, 1H), 5.32 (d, *J* = 7.3 Hz, 1H), 4.75 (s, 2H), 4.54 (d, *J* = 11.5 Hz, 1H), 4.49 (s, 2H), 4.26 (d, *J* = 11.5 Hz, 1H), 4.05 (m, 2H), 3.94 (m, 1H), 3.81 (m, 2H), 3.77 (s, 3H), 3.76 (s, 3H), 3.45 (dd, *J* = 3.7, 9.4 Hz, 1H), 3.40 (m, 1H), 3.35 (dd, *J* = 6.9, 9.3 Hz, 1H), 2.58 (m, 3H), 2.36 (m, 2H), 2.20 (m, 2H), 2.10-1.95 (m, 4H), 1.71 (s, 3H), 1.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.31, 144.27, 136.77, 135.64, 132.59, 130.25, 129.91, 128.62, 127.03, 113.83, 113.77, 108.79, 77.86, 76.75, 75.58, 73.64, 73.04, 69.58, 68.34, 58.04, 55.26, 43.66, 40.66, 40.14, 39.03, 38.54, 23.86, 17.11; IR (neat) 3418, 3076, 2930, 2858, 1650, 1607, 1585, 1512, 1447, 1360, 1294, 1170, 1040, 894, 814 cm^{-1}; HRMS (ESI): *m/z* calcd for $C_{37}H_{50}O_7Na$ (M + Na) 629.3454, found 629.3478 $[\alpha]_D^{23}$ -21.05° (PhH , *c* 0.50).

Aldehyde (-)-65



(-)-**65**

To a stirring solution of diol (-)-**41** (0.004g, 0.006 mmol) in CH_2Cl_2 (0.25 mL) at 0 °C was added Dess-Martin periodinane (0.003 g, 0.006 mmol). The reaction mixture was stirred at 0 °C for 20 min., then warmed to room temperature and stirred for an additional 30 min. The temperature was then decreased to 0 °C and the reaction mixture was quenched with saturated aqueous $NaHCO_3$ (0.5 mL) and saturated aqueous $Na_2S_2O_3$ (0.5 mL). The reaction mixture was stirred for 10 min. before the two layers were separated. The organic layer was dried ($MgSO_4$) and concentrated. The resulting residue was purified by flash chromatography (50% EtOAc in hexanes) to afford the desired product (0.0023 g, 64%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.91 (d, *J* = 8.1 Hz, 1H), 7.27 (d, *J* = 8.0 Hz, 2H), 7.21 (d, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 8.7 Hz, 2H), 6.87 (d, *J* = 8.7 Hz, 2H), 5.93 (d, *J* = 8.1 Hz, 1H), 5.71 (m, 1H), 5.44 (dd, *J* = 15.7, 8.1 Hz, 1H), 5.31 (d, *J* = 7.6 Hz, 1H), 4.77 (s, 2H), 4.51 (m, 3H), 4.25 (d, *J* = 11.5 Hz, 1H), 3.94-3.88 (m, 2H), 8.81 (m, 4H), 3.80 (s 3H), 3.44 (dd, *J* = 9.4, 3.3 Hz, 1H), 3.33 (m, 2H), 2.94 (dd, *J* = 13.3, 7.9 Hz, 1H), 2.64 (dd, *J* = 13.1, 5.4 Hz, 1H), 2.39 (m, 2H), 2.26-1.98 (m, 6H), 1.93 (s, 3H), 1.71 (s,3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.25, 159.91, 144.28, 131.91, 130.90, 130.01, 129.38, 129.26, 128.71, 113.94, 113.87, 109.61, 77.77, 76.75, 75.67, 73.72, 73.10, 69.74, 68.59, 55.30, 43.59, 40.74, 40.15, 39.19, 39.01, 26.02, 17.20; IR (neat) 3461, 3069, 2923, 2850, 1680, 1614, 1595, 1461, 1294, 1243, 1178, 1061, 1032, 821; HRMS (ESI): *m/z* calcd for $C_{37}H_{48}O_7Na$ (M+Na) 627.3298, found 627.3307 $[\alpha]_D^{23}$ -17.95º (PhH , *c* 0.20).

3.5. References

---

[71] Fenical, W. “Chemical studies of marine bacteria: developing a new resource” *Chem. Reviews*, **1993**, *93*, 1673-1683.

[72] Cutignano, A; Bruno, I.; Bifulco, G.; Casapullo, A.; Debitus, C.; Gomez-Paloma, L.; Riccio, R. “Dactylolide, a new cytotoxic macrolide from the Vanuata sponge *Dactylospongia* sp.” *Eur. J. Org. Chem.*, **2001**, 775-778.

[73] Crews, P.; Kakou, Y.; Quinoa, E. “Mycothiozole, a polyketide heterocycle from a marine sponge” *J. Am. Chem. Soc.*, **1988**, *110*, 4365-4368.

[74] Groweiss, A.; Shmueli, U.; Kashman, Y. “Marine toxins of latrunculia magnifica” *J. Org. Chem.*, **1983**, *48*, 3512-3516.

[75] Corely, D. G.; Herb, R.; Moore, R. E.; Scheuer, P. J.; Paul, V. J. “Laulimalides. New potent cytotoxic macrolides from a marine sponge and nudibranch predator” *J. Org. Chem.*, **1988**, *53*, 3644-3646.

[76] Smith, A. B.; Safonov, I. “The total synthesis of (+)-Dactylolide” *Org. Lett.*, **2001**, *4*(4), 635-637.

---

[77] D'Auria, M.; Paloma, L.; Minale, L.; Zampella, A. "Reidispongiolide A and B, two new potent cytotoxic macrolides from the new caleonian sponge *Reidispongia coerulea*" *Tetrahedron,* **1994**, *50*, 4829-4834.

[78] Zhang, X.; Minale, L.; Zampella, A.; Smith, CD. "Microfilament depletion and circumvention of multiple drug resistance by shinxolides" *Cancer Res.*, **1997**, *57*, 3751-3758.

[79] Smith, A.B.; Safonov, I. G.; Corbett, R. "Total synthesis of (+)-zampanolide" *J. Am. Chem. Soc.*, **2001**, 12426-12427.

[80] Petasis, N., A.; Lu, S. "Stereocontrolled synthesis of substituted tetrahydropyrans from 1,3-dioxan-4-ones" *Tet. Lett.*, **1996**, 141-144.

[81] Nicolaou, K. C.; Seitz, S. P.; Pavia, M. R. "Carbohydrates in organic synthesis. Synthesis of 16-membered-ring-macrolide antibiotics. Total synthesis of O-mycinosyltylonolide; coupling key intermediates and macrocyclization" *J. Am. Chem. Soc.*, **1982**, 2030-2031.

[82] Smith, A. B.; Friestad, G. K.; Duan, J. J.; Barbosa, J.; Hull, K. G.; Makoto, I.; Qiu, Y.; Spoors, P. G.; Bertounesque, E.; Salvatore, B. A. "Total synthesis of (+)-Calyculin A and (-)-Calyculin B" *J. Org. Chem.*, **1998**, *63*, 7596-7597.

[83] Blakemore, P. R.; Cole, W. J.; Kocieński, P. J.; Morley, A. "A stereoselective synthesis of *trans*-1,2-disubstituted alkenes based on the condensation of aldehydes with metallated 1-phenyl-1*H*-tetrazol-5-yl sulfones" *Synlett*, **1998**, 26-28.

[84] Brown, H. C.; Jadhav, P. K. "Asymmetric carbon-carbon bond formation via β-allyldiisopinocampheylborane. Simple synthesis of secondary homoallylic alcohols with excellent enantiomeric purities" *J. Am. Chem. Soc.*, **1983**, *105*, 2092.

[85] Petasis, N. A.; Bzowej, E. I. "Titanium-mediated carbonyl olefinations. 1. Methylenations of carbonyl compounds with dimethyltitanocene" *J. Am. Chem. Soc.*, **1990**, *112*, 6392.

[11] Mitsunobu, O. "The use of diethyl azodicarboxylate and triphenylphosphine in synthesis and transformation of natural products" *Synthesis*, **1981**, 1.

[87] Hoye, T. R.; Hu, M. "Macrolactonization via Ti(IV)-mediated epoxy-acid coupling: A total synthesis of (-)-Dactylolide [and Zampanolide]" *J. Am. Chem. Soc.*, **2003**, *125*, 9576-9577.

[88] Sharpless, K., B.; Amberg, W.; Bennani, Y.; Crispino, G.; Hartung, J.; Jeong, K.; Kwong, H.; Morikawa, K.; Wnag, Z.; Xu, D.; Zhang, X. "The osmium-catalyzed asymmetric dihydroxylation: A new ligand class and a process improvement" *J. Org. Chem.*, **1992**, *57*(10), 2768-2771.

[89] Aubele, D. L.; Lee, C. A.; Floreancig, P. E. "The "aqueous" Prins reaction" *Org. Lett.*, **2003**, *5*(23), 4521-4523.

---

[90] Evans, D. A.; Hu, E.; Burch, J. D.; Jaeschke, G. "Enantioselective total synthesis of callipeltoside A", *J. Am. Chem. Soc.*, **2002**, *124*, 5654-5655.

[91] Zhong, Y.; Shing, T. "Efficient and facile glycol cleavage oxidation using improved silica gel-supported sodium metaperiodate", *J. Org. Chem.*, **1997**, *62*, 2622-2624.

[92] Evans, D. A.; Kozlowski, M. C.; Murry, J. A.; Burgey, C. S.; Campos, K. R.; Connell, B. T.; Staples, R. J. "C_2-Symmetric Copper(II) Complexes as Chiral Lewis acids. Scope and Mechanism of catalytic enantioselective aldol additions of enolsilanes to (benzyloxy)acetaldehyde" *J. Am. Chem. Soc.*, **1999**, *121*, 669-685.

[93] O'Leary, D. J.; Blackwell, H. E.; Washenfelder, R. A.; Miura, K.; Grubbs, R. H. "Terminal olefin cross-metathesis with acrolein acetals" *Tet. Lett.*, **1999**, *40*, 1091-1094.

[94] Smith, A. B.; Adams, C. M.; Kozmin, S. A.; Paone, D. V. "Total synthesis of (-)-cylindrocyclophanes A and F exploiting the reversible nature of the olefin cross metathesis reaction" *J. Am. Chem. Soc.*, **2001**, *123*, 5925-5937.

[95] Lee, C. W.; Grubbs, R. H. "Stereoselectivity of macrocyclic ring-closing olefin metathesis" *Org. Lett.*, **2000**, *2*(14), 2145-2147.

[96] Xu, Z.; Johannes, C. W.; Houri, A. F.; La, D. S.; Cogan, D. A.; Hofilena, G. E.; Hoveyda, A. H. "Applications of Zr-catalyzed carbomagnesiation and Mo-catalyzed macrocyclic ring closing metathesis in asymmetric synthesis. Enantioselective total synthesis of Sch 38516 (Fluvirucin B_1)" *J. Am. Chem. Soc.*, **1997**, *119*, 10302-10316.

[97] Krüger, J.; Carreira, E. M. "Apparent catalytic generation of chiral metal enolates: Enatioselective dienolate additions to aldehydes mediated by Tol-BINAP·Cu(II) fluoride complexes" *J. Am. Chem. Soc.*, **1998**, *120*, 837-838.

[98] Fettes, A.; Carreira, E. M. "Leucascandrolide A: Synthesis and related studies" *J. Org. Chem.*, **2003**, *68*, 9274-9283.

[99] Denmark, S. E.; Beutner, G. "Lewis base activation of Lewis acids. Vinylogous aldol reactions" *J. Am. Chem. Soc.*, **2003**, *125*, 7800-7801.

[100] Denmark, S. D.; Fu, J. "Understanding the correlation of structure and selectivity in chiral-phosphoramide-catalyzed enantioselective allylation reactions: Solution and solid-state structural studies of bisphosphoramide•$SnCl_4$ complexes" *J. Am. Chem. Soc.*, **2003**, *125*, 2208-2216.

[101] Denmark, S. E.; Wynn, T. Beutner, G. L. "Lewis base activation of Lewis acids. Addition of silyl ketene acetals to aldehydes" *J. Am. Chem. Soc.*, **2002**, *124*, 13405-13407.

[102] Zimmerman, H. E.; Traxler, M. D. "The stereochemistry of the Ivanov and Reformansky reactions", *J. Am. Chem. Soc.*, **1957**, 1920-1923.

---

[103] Chen, K.; Hardtmann, G. E.; Prasad, K.; Repic, O.; Shapiro, M. J. “1,3-syn diastereoselective reduction of β-hydroxyketones utilizing alkoxydialkylboranes” *Tet. Lett.*, **1987**, *28*, 155-158.

[104] Enev, V. S.; Kaehlig, H.; Mulzer, J. “Macrocyclization via allyl transfer: total synthesis of Laulimalide” *J. Am. Chem. Soc.*, **2001**, 10764-10765.

[105] Wender, P. A.; De Brabander, J.; Harran, P. G.; Jimenez, J.; Koehler, M. F. T.; Lippa, B; Park, C.; Shiozaki, m. “Synthesis of the first members of a new class of biologically active bryostatin analogues” *J. Am. Chem. Soc.*, **1998**, *120*, 4534-4535.

[106] *Syn. Comm.*, **1999**, *29*(13), 2255-.

[107] Noyori, R.; Murata, S.; Suzuki, M. “Trimethylsilyl triflate in organic synthesis” *Tet.*, **1981**, *37*, 3899-3910.

[108] Lee, T. V.; Channon, J. A.; Cregg, C.; Porter, J. R.; Roden, F. S.; Yeoh, H. “The cerium (III) mediated reaction of trimethylsilylmethylmagnesium chloride with esters and lactones: The efficient synthesis of some functionalized allylsilanes of use in annulation reactions” *Tet.*, **1989**, *45*, 5877-5886.

[109] Wharton, P. S.; Bohlen, D. H. “Hydrazine reduction of α,β-epoxy ketones to allylic alcohols” *J. Org. Chem.*, **1961**, *26*, 3615-3616.

[110] Dupuy, C.; Luche, J. L. “New developments of the Wharton transposition” *Tet.*, **1989**, *45*, 3437-3444.

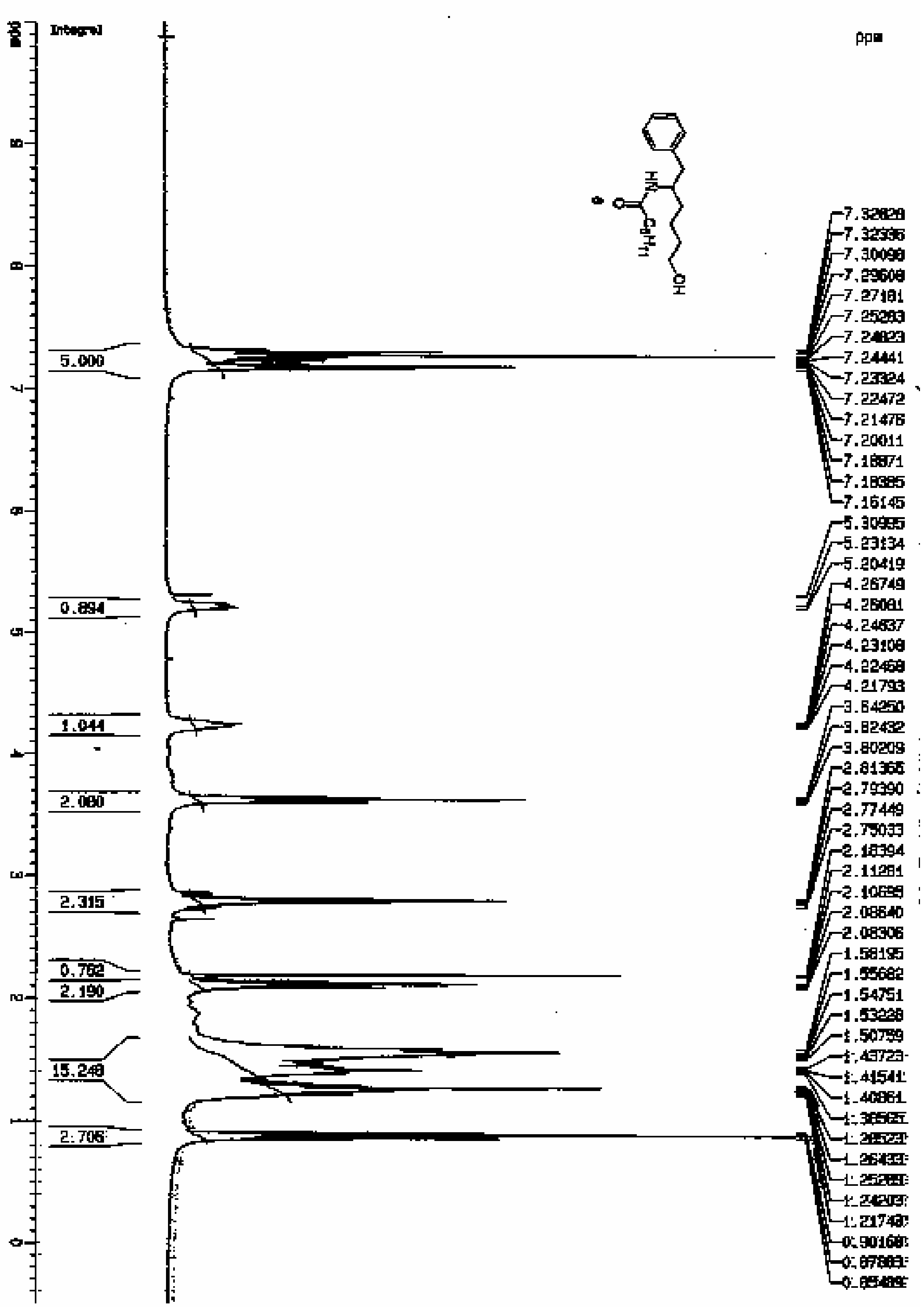
[111] West, R.; Ishikawa, M.; Bailey, R. E. “Anionic Rearrangement of hydrazines. II. Isomers of bis(organosilyl)hydrazines” *J. Am. Chem. Soc.*, **1966**, *88*, 4648-4653.

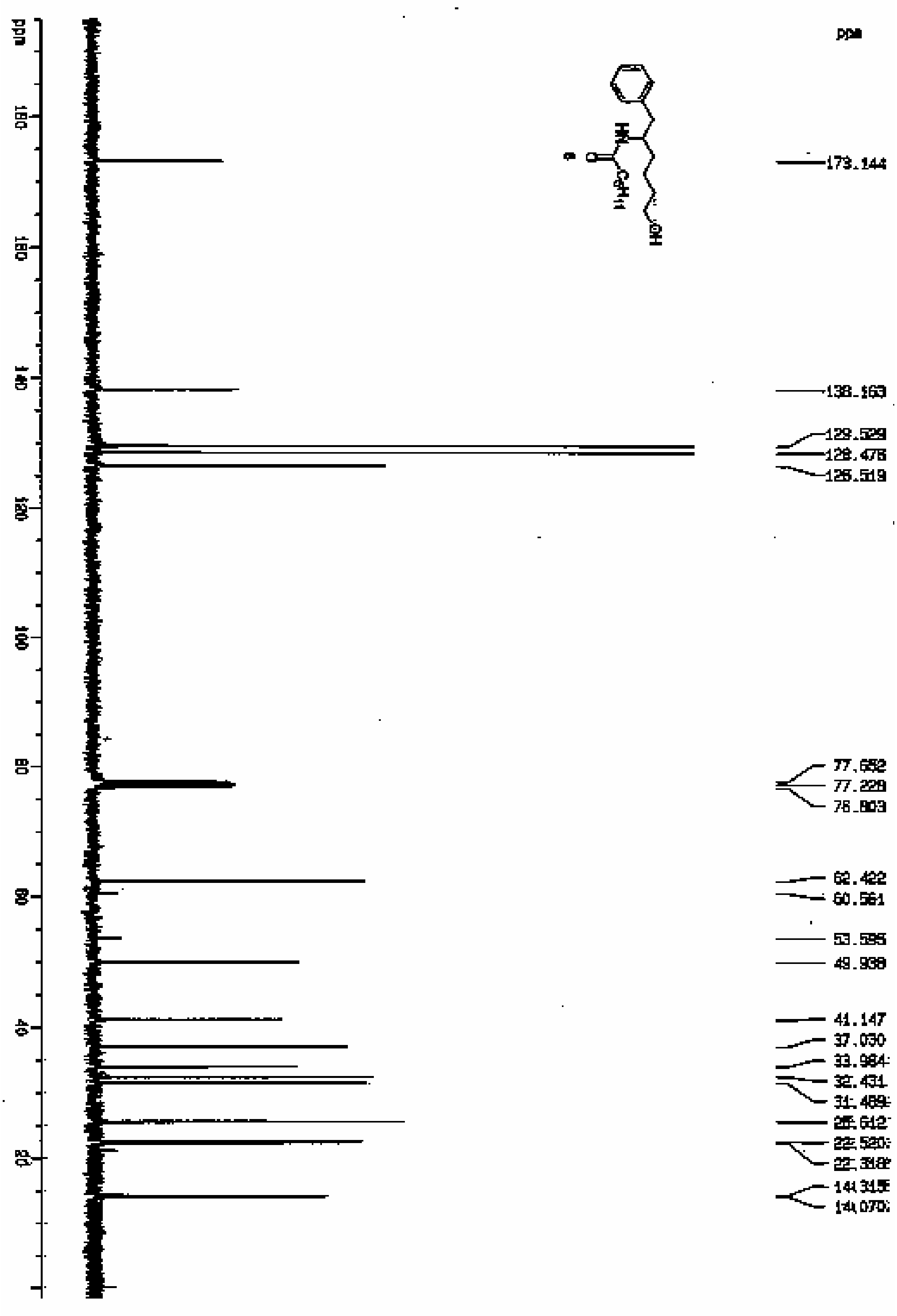
[112] Furrows, M. E.; Myers, A. G. “Practical procedures for the preparation of *N-tert*-butyldimethylsilylhydrazones and their use in modified Wolff-Kischner reductions and in the synthesis of vinyl halides and *gem*-dihalides” *J. Am. Chem. Soc.*, **2004**, *126*, 5436-5445.

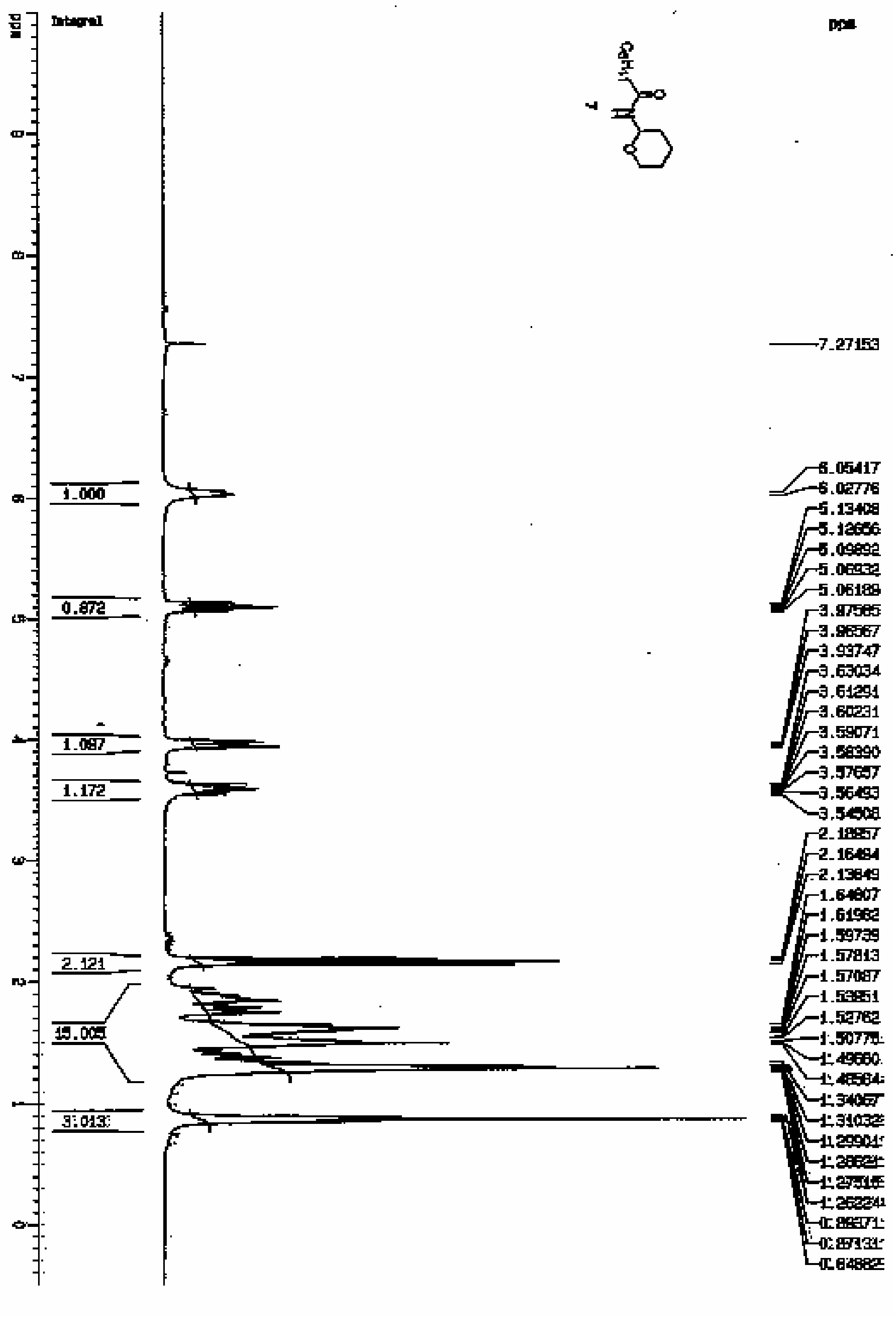
[113] Reich, H. J.; Yelm, K. E.; Wollowitz, S. “Kinetics, thermodynamics, and stereochemistry of the allyl sulfoxide-sulfenate and selenoxide-selenate [2,3] sigmatropic rearrangements” *J. Am. Chem. Soc.*, **1983**, *105*, 2503-2504.

APPENDIX A

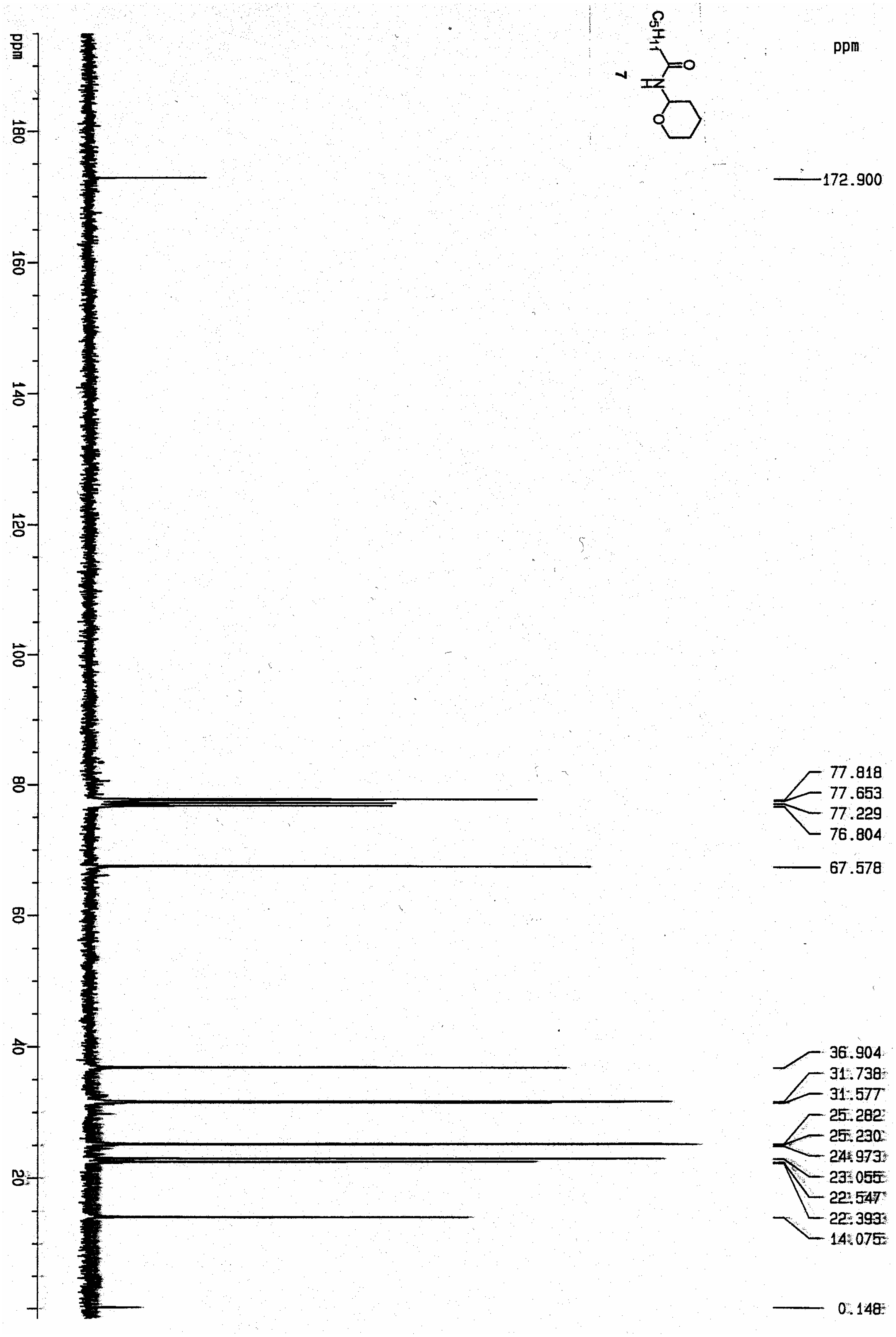
Mechanistic and stereochemical studies of photoinduced electron transfer initiated cyclization reactions: the role of nitrogen (Supporting Information)

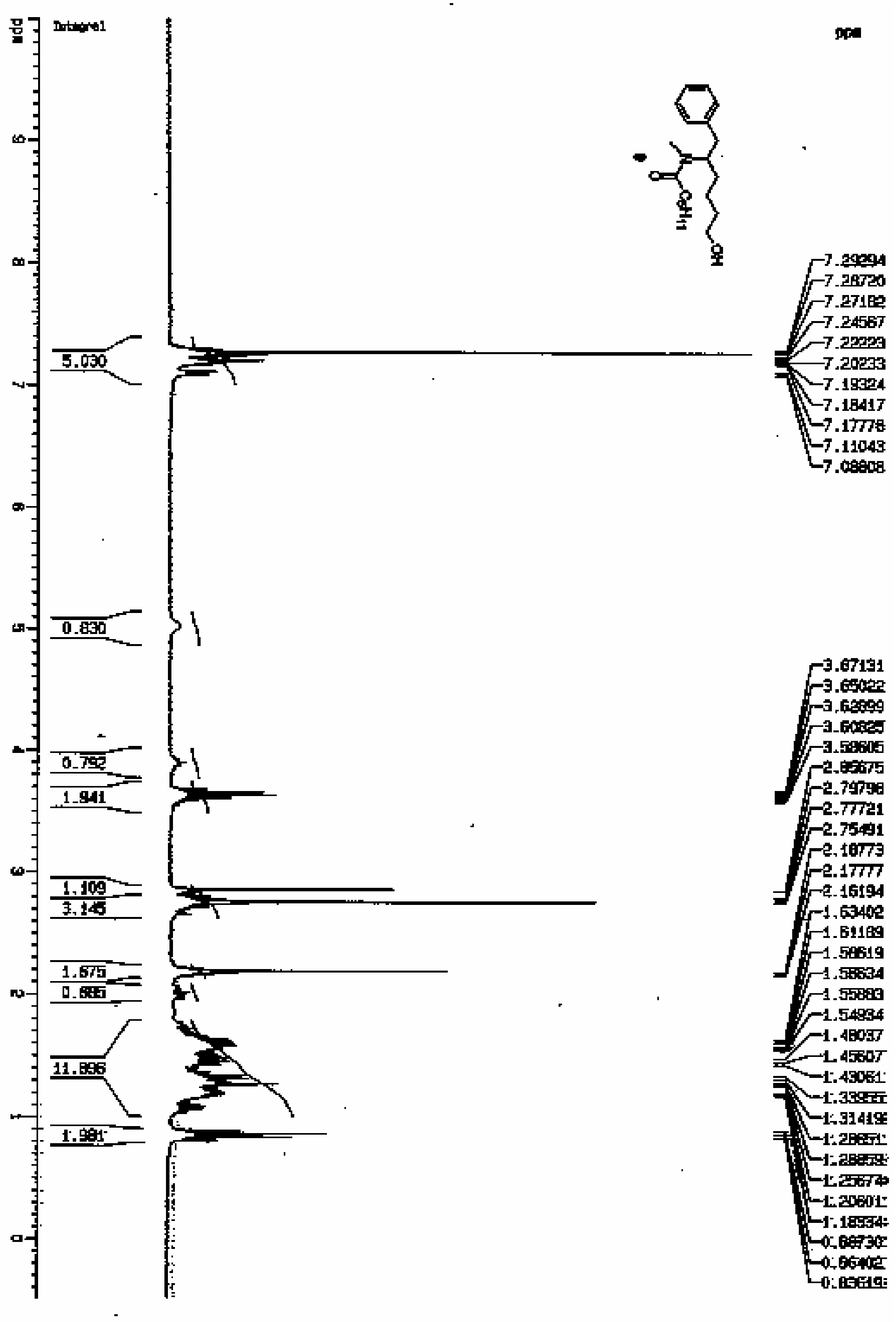

ppm
Integral
5.000
0.894
1.044
2.080
2.315
0.762
2.190
15.240
2.706
OH
HN
O
7.32828
7.32336
7.30098
7.29608
7.27181
7.25283
7.24823
7.24441
7.23324
7.22472
7.21476
7.20011
7.18871
7.18385
7.16145
5.30985
5.23134
5.20419
4.26749
4.26081
4.24637
4.23108
4.22459
4.21793
3.84250
3.82432
3.80209
2.81368
2.79390
2.77449
2.75033
2.16394
2.11261
2.10695
2.08640
2.08306
1.58195
1.55682
1.54751
1.53228
1.50799
1.43723
1.41541
1.40861
1.38565
1.36523
1.26433
1.25280
1.24209
1.21748
0.90168
0.87883
0.85489

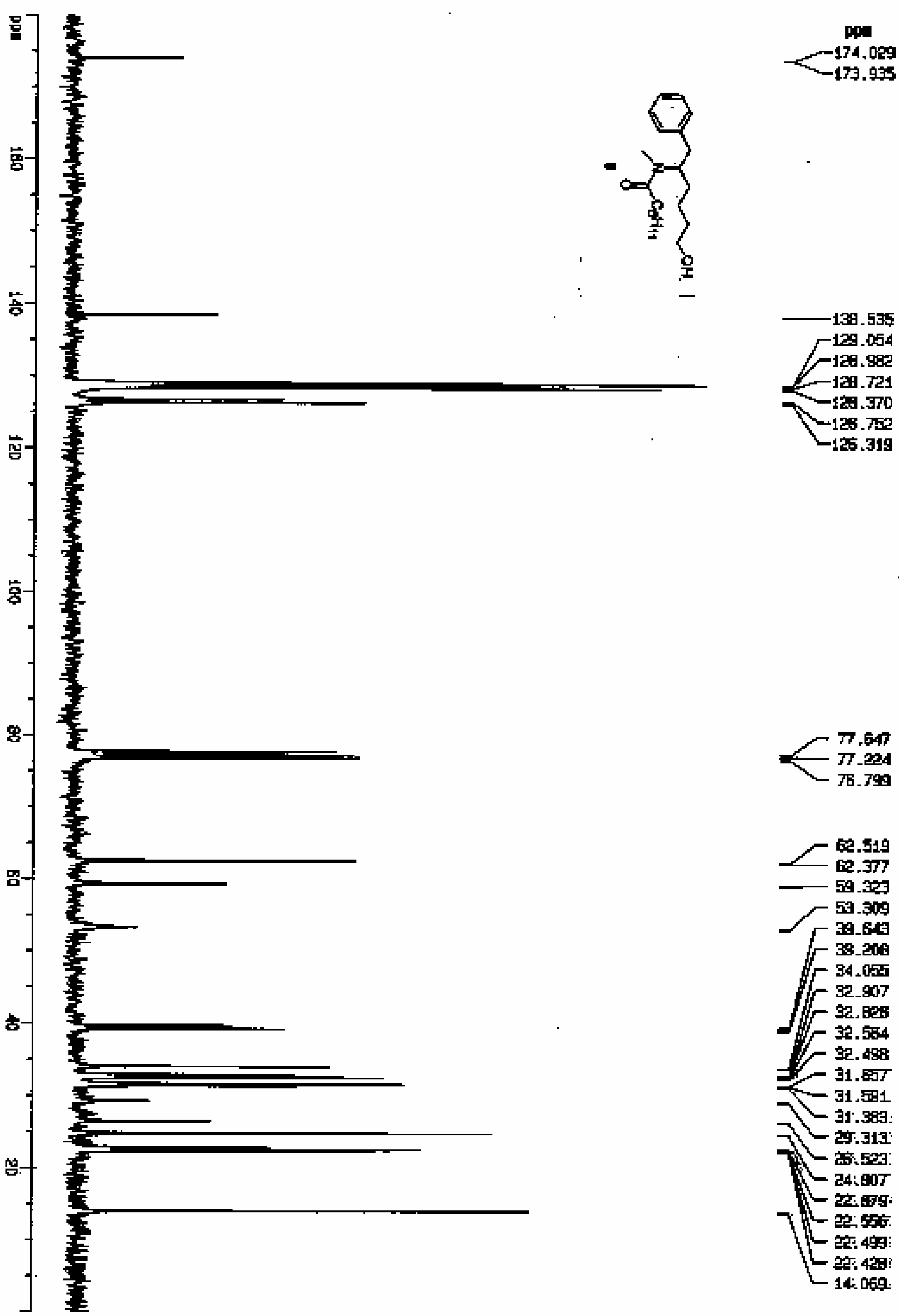

ppm
180
160
140
120
100
80
60
40
20
ppm
HN
O
C5H11
OH
6
173.144
138.163
129.529
128.478
126.519
77.652
77.228
76.803
62.422
60.561
53.595
49.938
41.147
37.030
33.984
32.431
31.489
25.612
22.520
22.318
14.315
14.070

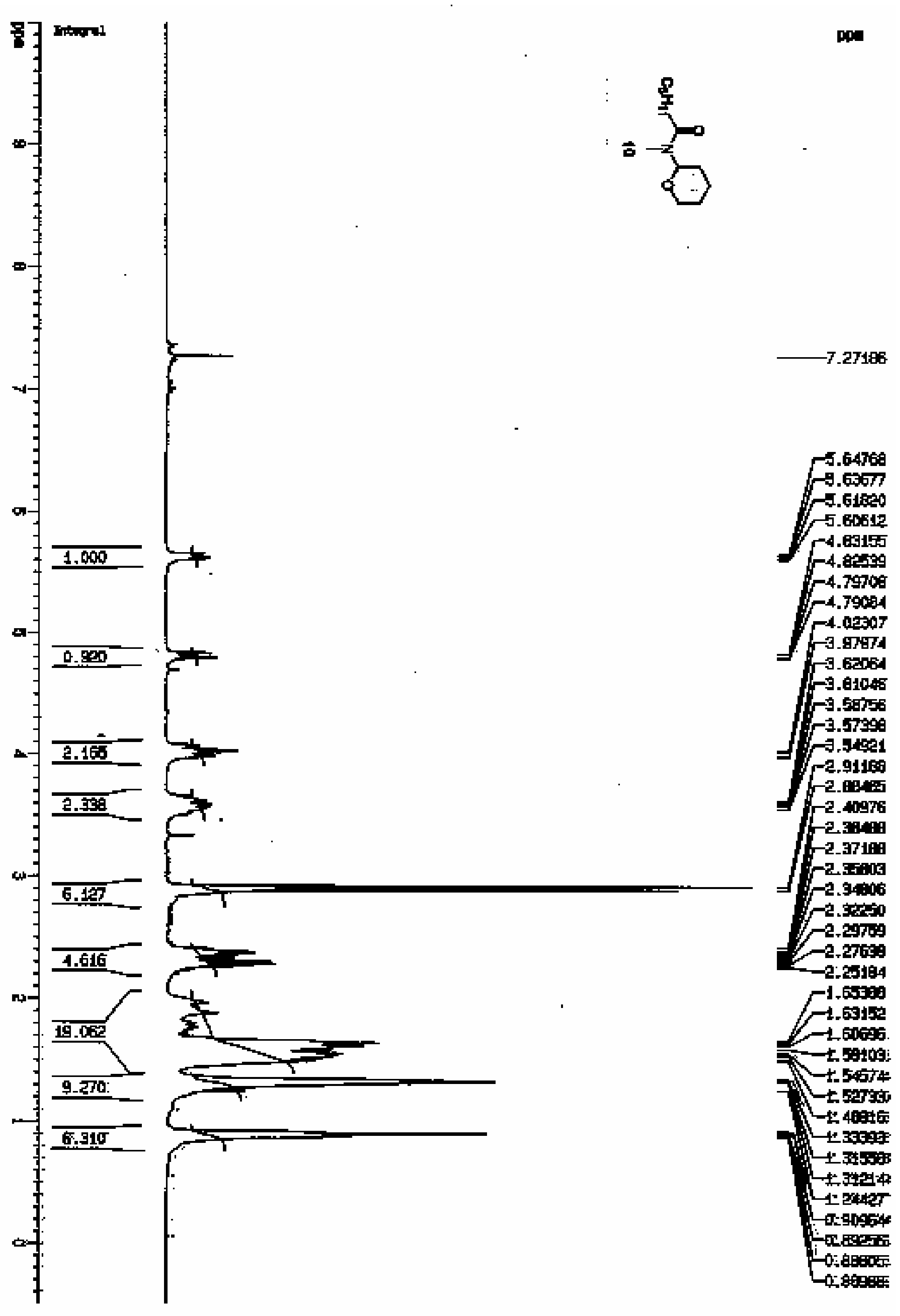


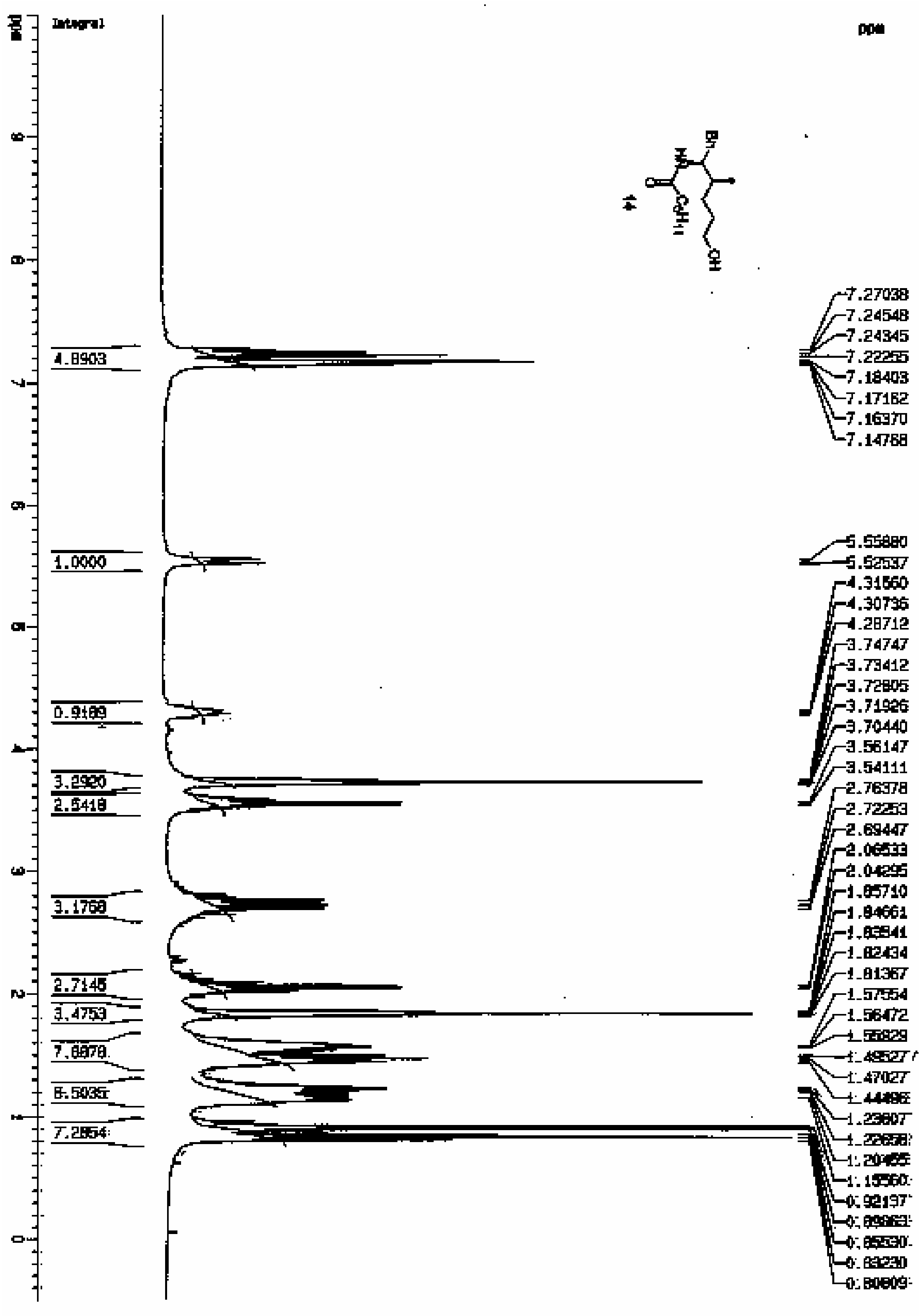
ppm
Integral
7
C_6H_{13}
10
9
8
7
6
5
4
3
2
1
0
1.000
0.872
1.087
1.172
2.121
15.005
3.013
7.27153
6.05417
6.02776
5.13408
5.12656
5.09892
5.06932
5.06188
3.97565
3.96567
3.93747
3.63034
3.61291
3.60231
3.59071
3.58390
3.57657
3.56493
3.54508
2.18857
2.16484
2.13849
1.64807
1.61982
1.59739
1.57813
1.57087
1.53851
1.52762
1.50775
1.49660
1.48564
1.34067
1.31032
1.29904
1.28625
1.27515
1.26224
0.89971
0.87131
0.84882

C5H11
O
N
H
O
7
ppm
172.900
77.818
77.653
77.229
76.804
67.578
36.904
31.738
31.577
25.282
25.230
24.973
23.055
22.547
22.393
14.075
0.148
ppm
180
160
140
120
100
80
60
40
20

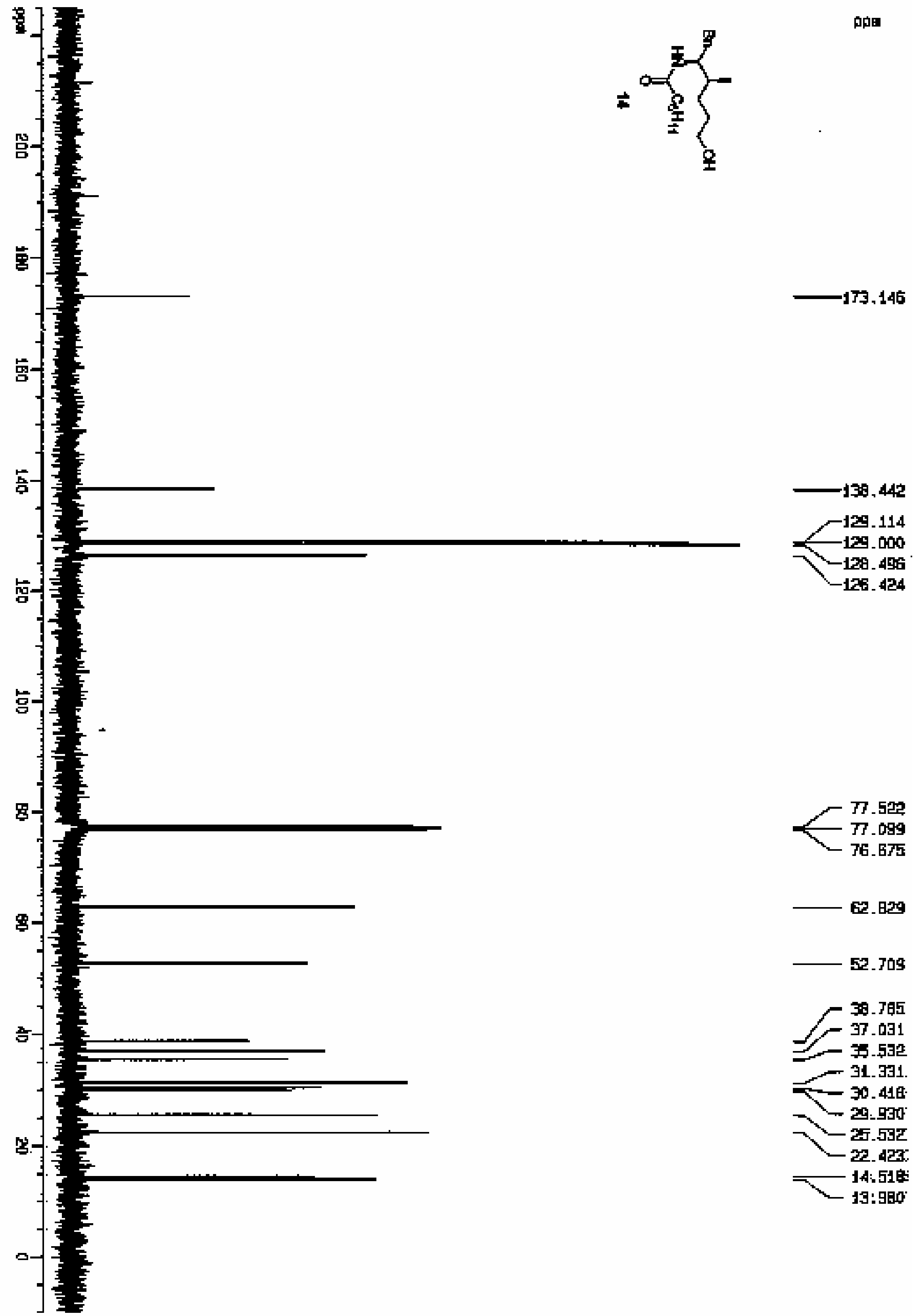

ppm
Integral
ppm
9
8
7
6
5
4
3
2
1
0
5.030
0.830
0.792
1.941
1.109
3.145
1.675
0.885
11.896
1.981
C5H11
O
OH
N
7.29294
7.28720
7.27182
7.24567
7.22223
7.20233
7.19324
7.18417
7.17778
7.11043
7.08808
3.67131
3.65022
3.62899
3.60825
3.59605
2.85675
2.79798
2.77721
2.75491
2.18773
2.17777
2.16194
1.63402
1.61189
1.58619
1.58634
1.55883
1.54934
1.48037
1.45607
1.43061
1.33955
1.31419
1.28851
1.28859
1.25674
1.20601
1.18334
0.88730
0.86402
0.83619

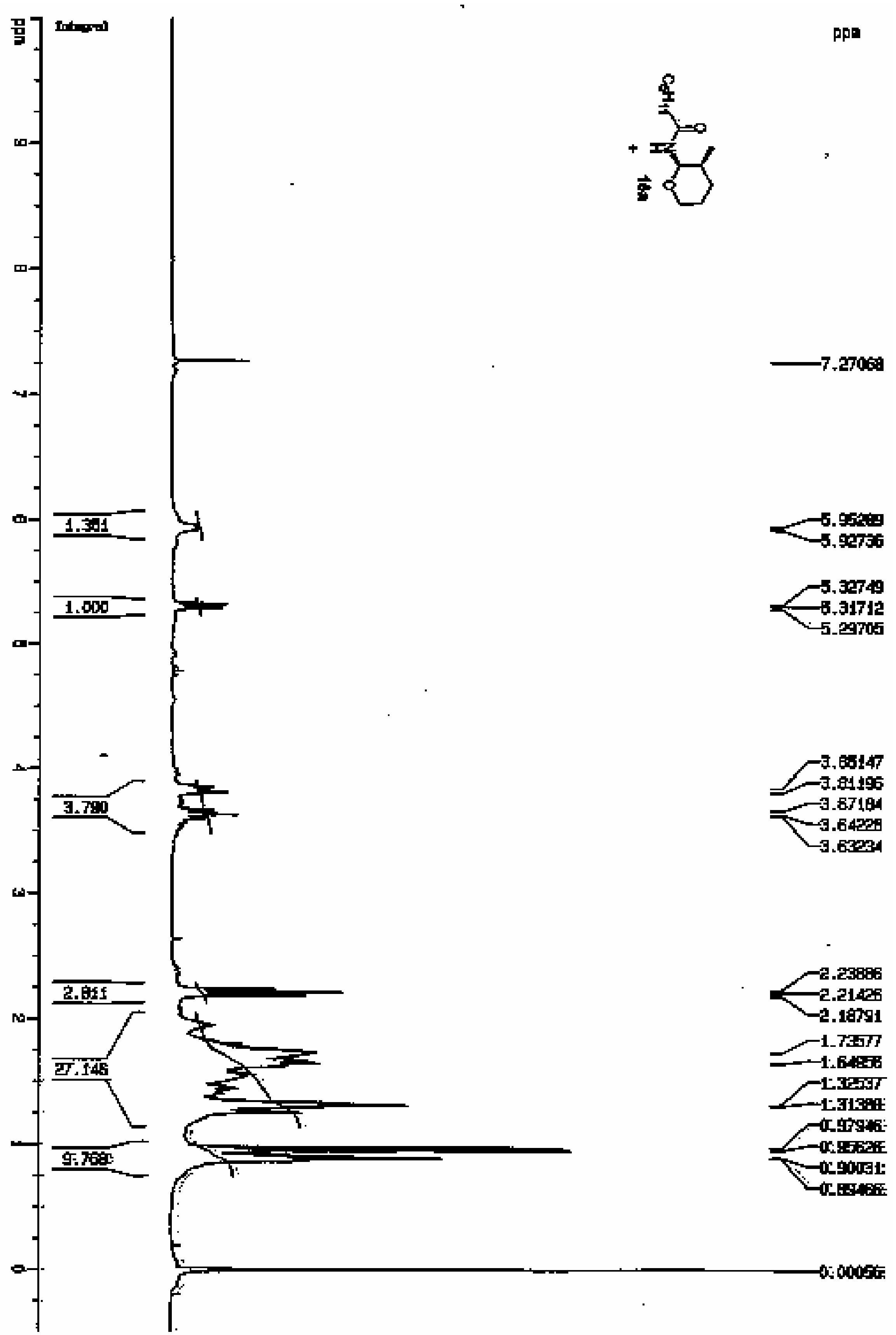

ppm
174.029
173.935
138.535
129.054
128.982
128.721
128.370
126.752
126.319
77.647
77.224
76.799
62.519
62.377
58.323
53.309
38.643
38.208
34.055
32.907
32.828
32.564
32.498
31.857
31.581
31.383
29.313
26.523
24.807
22.679
22.556
22.499
22.428
14.069
OH
N
O
C_5H_{11}
ppm
160
140
120
100
80
60
40
20

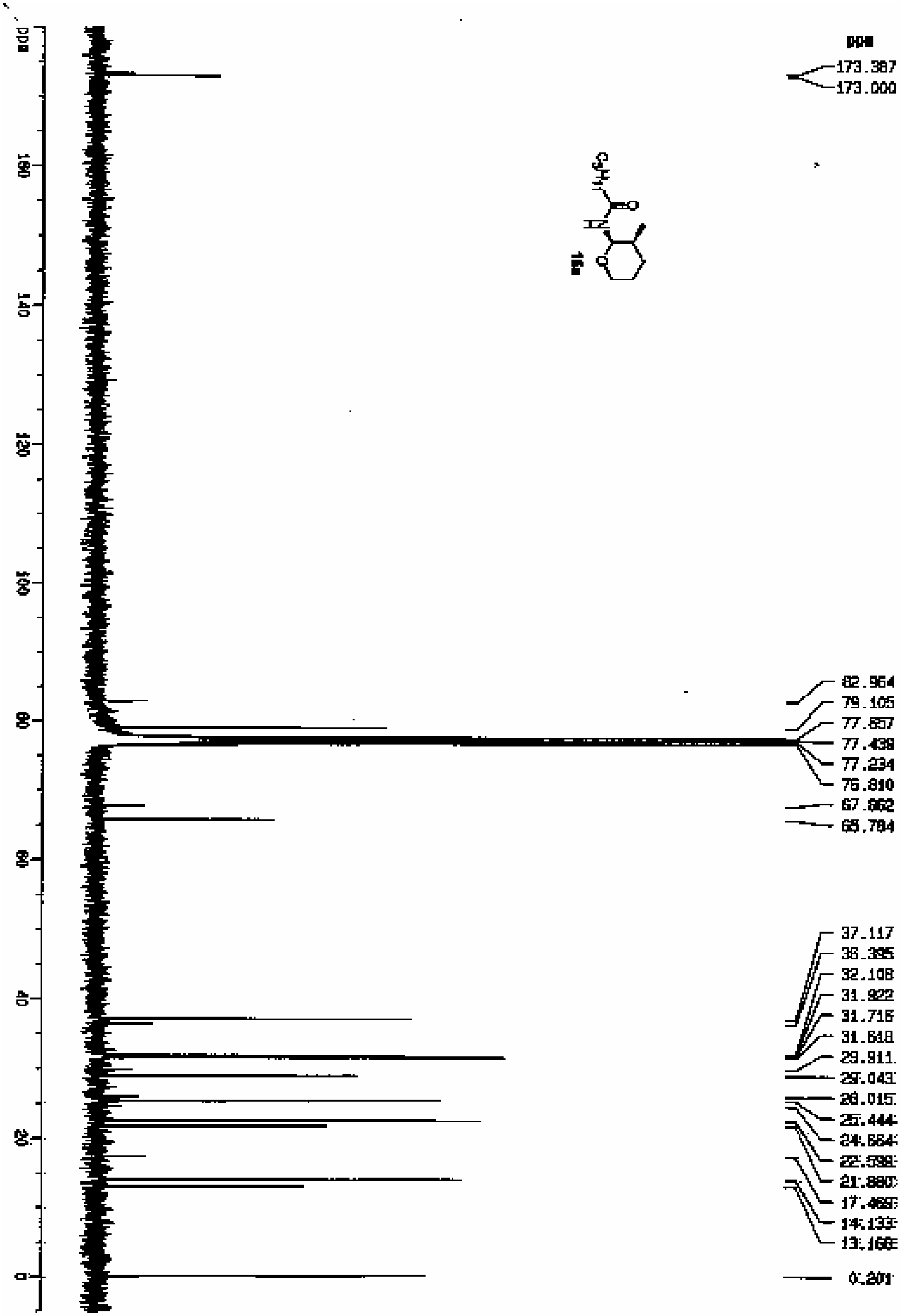

ppm
Integral
1.000
0.920
2.166
2.338
6.127
4.616
19.062
9.270
6.310
9
8
7
6
5
4
3
2
1
0
ppm
10
C7H15
N
O
7.27186
5.64768
5.63677
5.61820
5.60612
4.83155
4.82539
4.79708
4.79084
4.02307
3.97974
3.62064
3.61046
3.58756
3.57398
3.54921
2.91168
2.88485
2.40976
2.38488
2.37188
2.35803
2.34806
2.32250
2.29769
2.27638
2.25184
1.65388
1.63152
1.60696
1.58103
1.54574
1.52733
1.48816
1.33393
1.31558
1.31214
1.24427
0.90964
0.89256
0.88605
0.86988

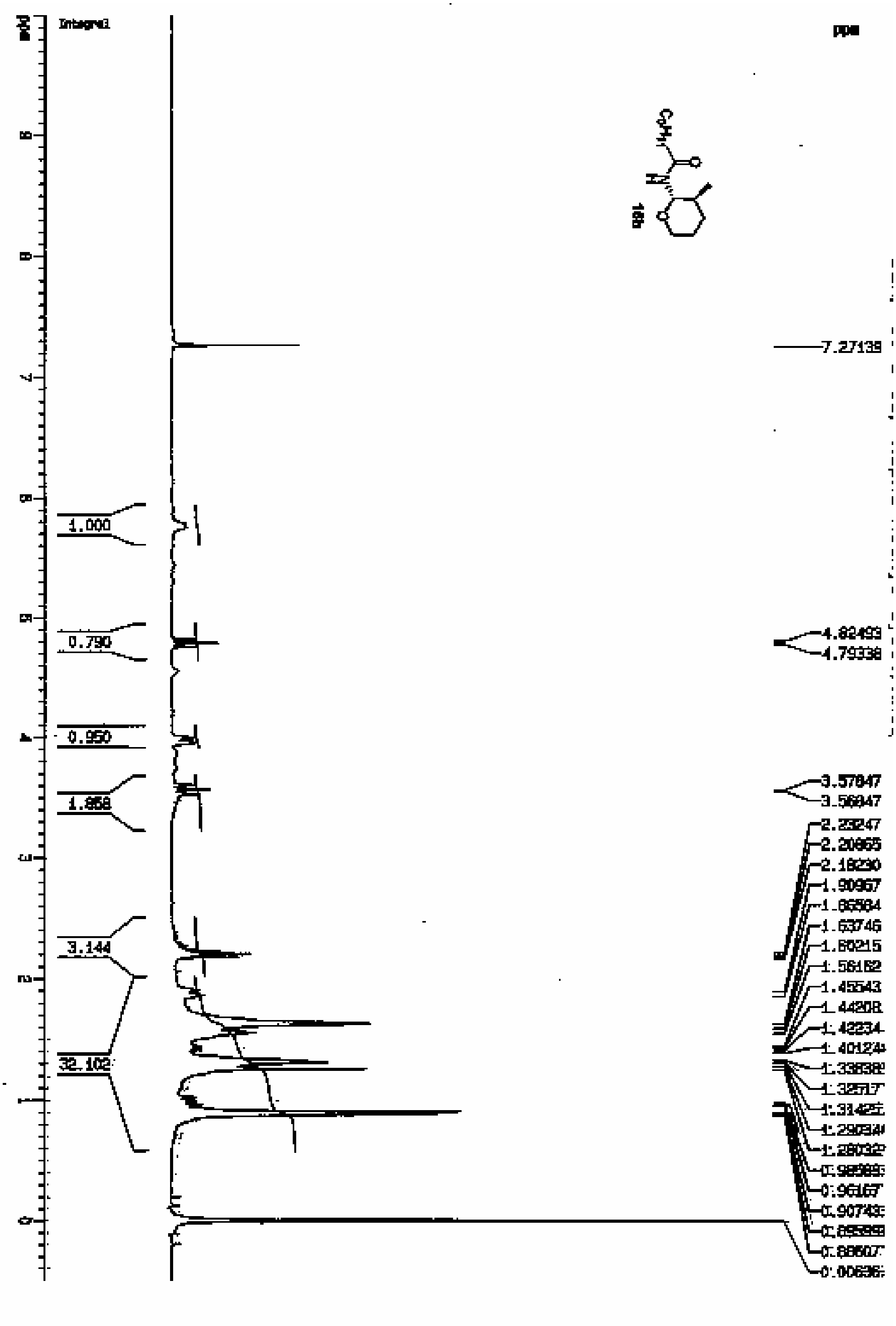


ppm
Integral
ppm
Bn
NH
O
C_5H_{11}
OH
14
4.8903
1.0000
0.9189
3.2920
2.5418
3.1768
2.7146
3.4759
7.6878
8.5035
7.2854
7.27038
7.24548
7.24345
7.22255
7.18403
7.17162
7.16370
7.14768
5.55880
5.52537
4.31560
4.30736
4.28712
3.74747
3.73412
3.72805
3.71926
3.70440
3.56147
3.54111
2.76378
2.72253
2.69447
2.06533
2.04295
1.85710
1.84661
1.83541
1.82434
1.81367
1.57554
1.56472
1.55829
1.49527
1.47027
1.44496
1.23807
1.22658
1.20455
1.15560
0.92137
0.89863
0.85530
0.83230
0.80809


ppm
200
180
160
140
120
100
80
60
40
20
0
ppm
Bn
HN
O
C5H11
OH
14
173.146
138.442
129.114
129.000
128.496
126.424
77.522
77.099
76.675
62.829
52.709
38.765
37.031
35.532
31.331
30.416
29.930
25.532
22.423
14.518
13.980

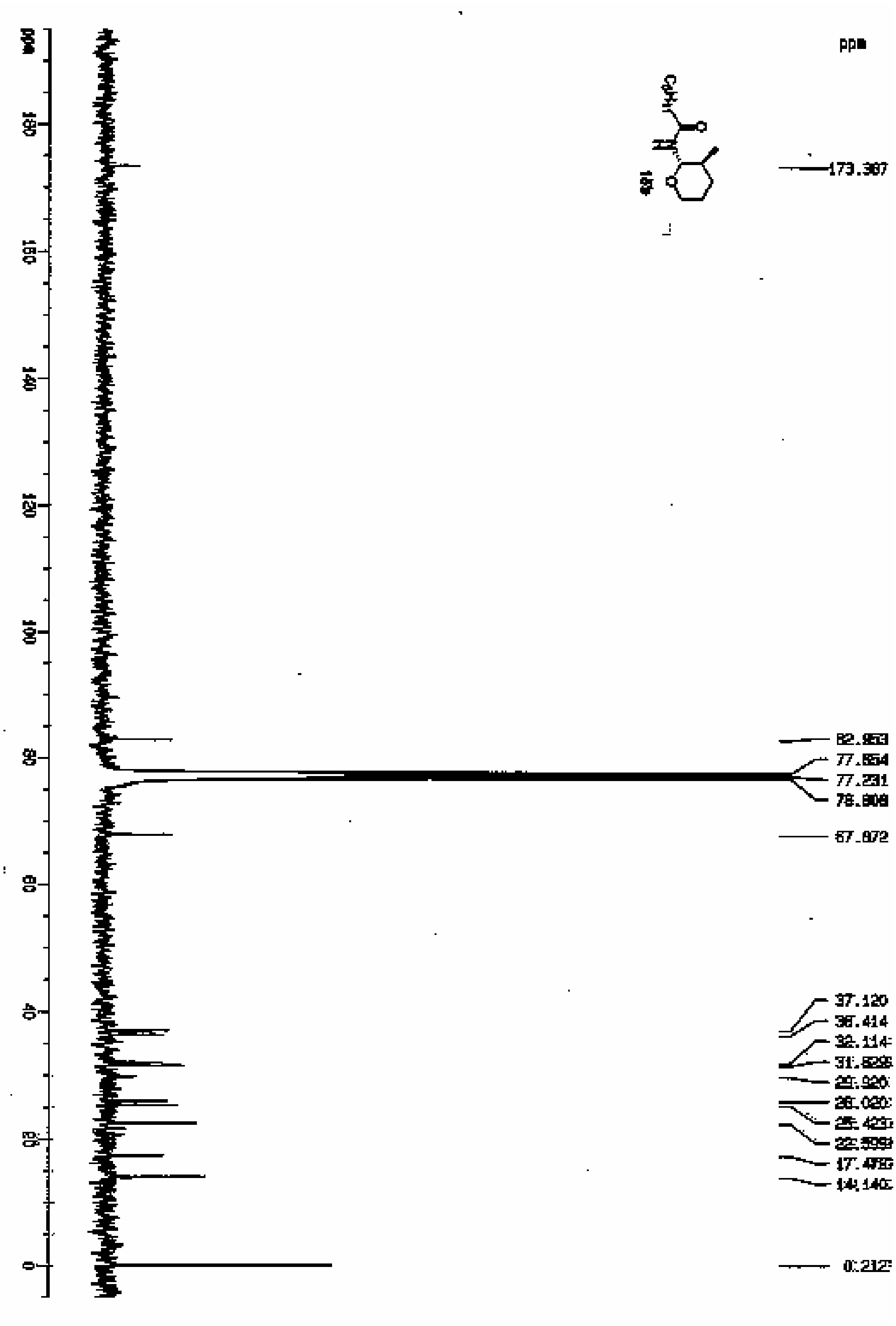

ppm
Integral
ppm
C_8H_{17}
16a
+
7.27068
5.95269
5.92736
5.32749
5.31712
5.29705
3.85147
3.81196
3.67184
3.64228
3.63234
2.23886
2.21426
2.18791
1.73577
1.64858
1.32537
1.31388
0.97946
0.95628
0.90031
0.89466
0.00056
1.361
1.000
3.790
2.811
27.146
9.768
9
8
7
6
5
4
3
2
1
0

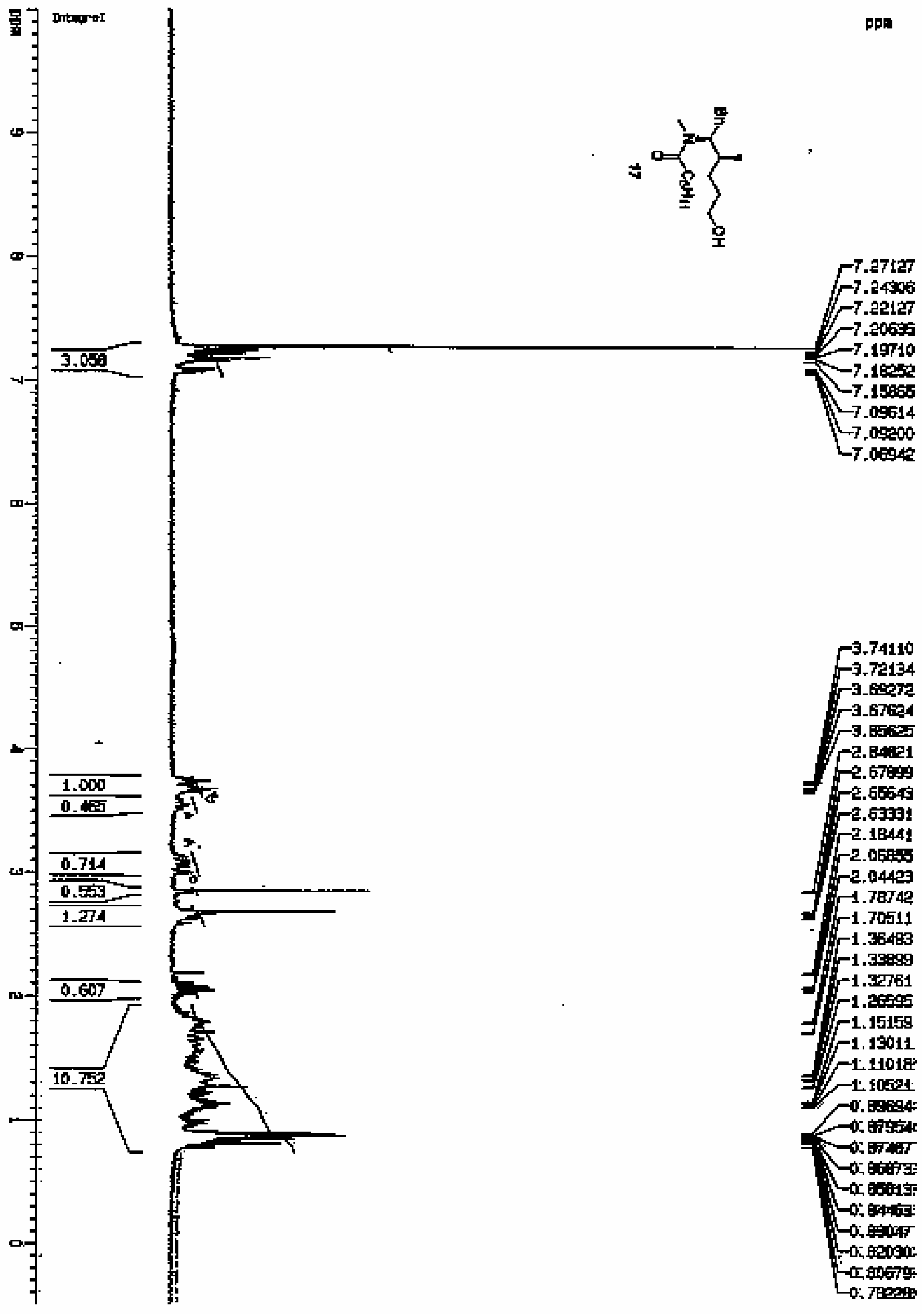

ppm
180
160
140
120
100
80
60
40
20
0
ppm
173.387
173.000
C_9H_{17}
O
N
H
O
16a
82.964
79.105
77.857
77.439
77.234
76.810
67.862
65.784
37.117
36.395
32.108
31.922
31.716
31.618
29.911
29.043
28.015
25.444
24.664
22.598
21.880
17.469
14.133
13.168
0.201

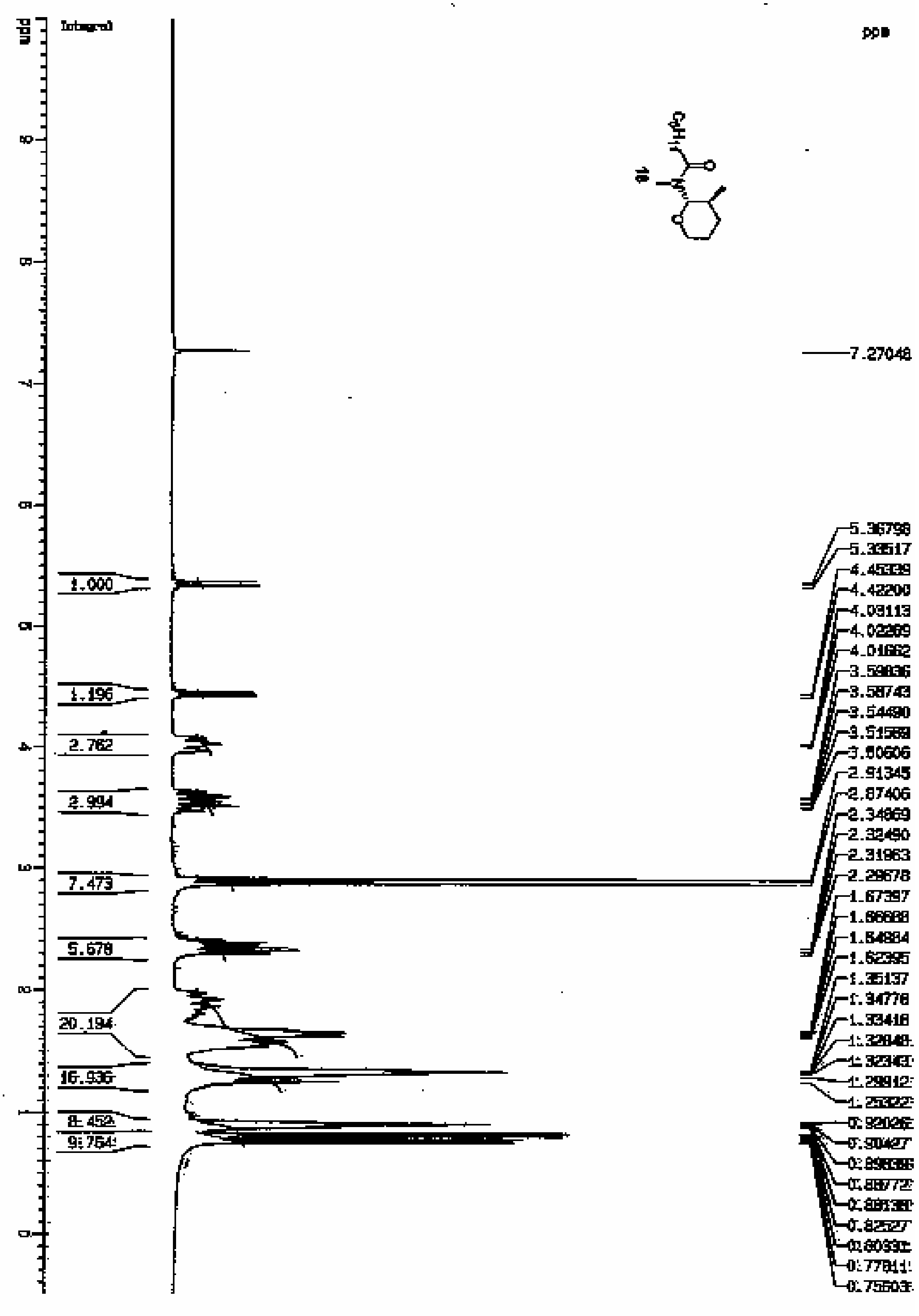


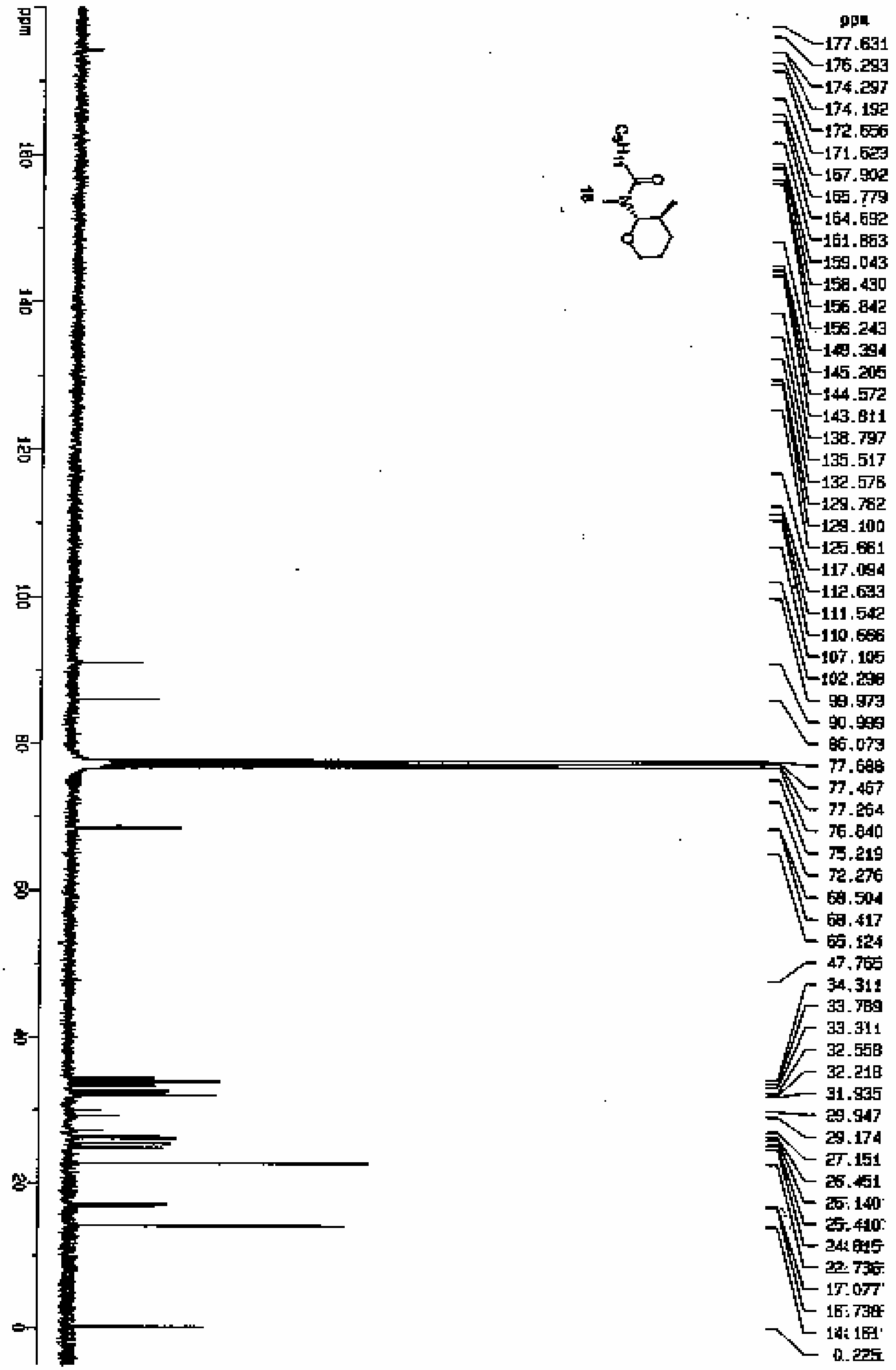
16b

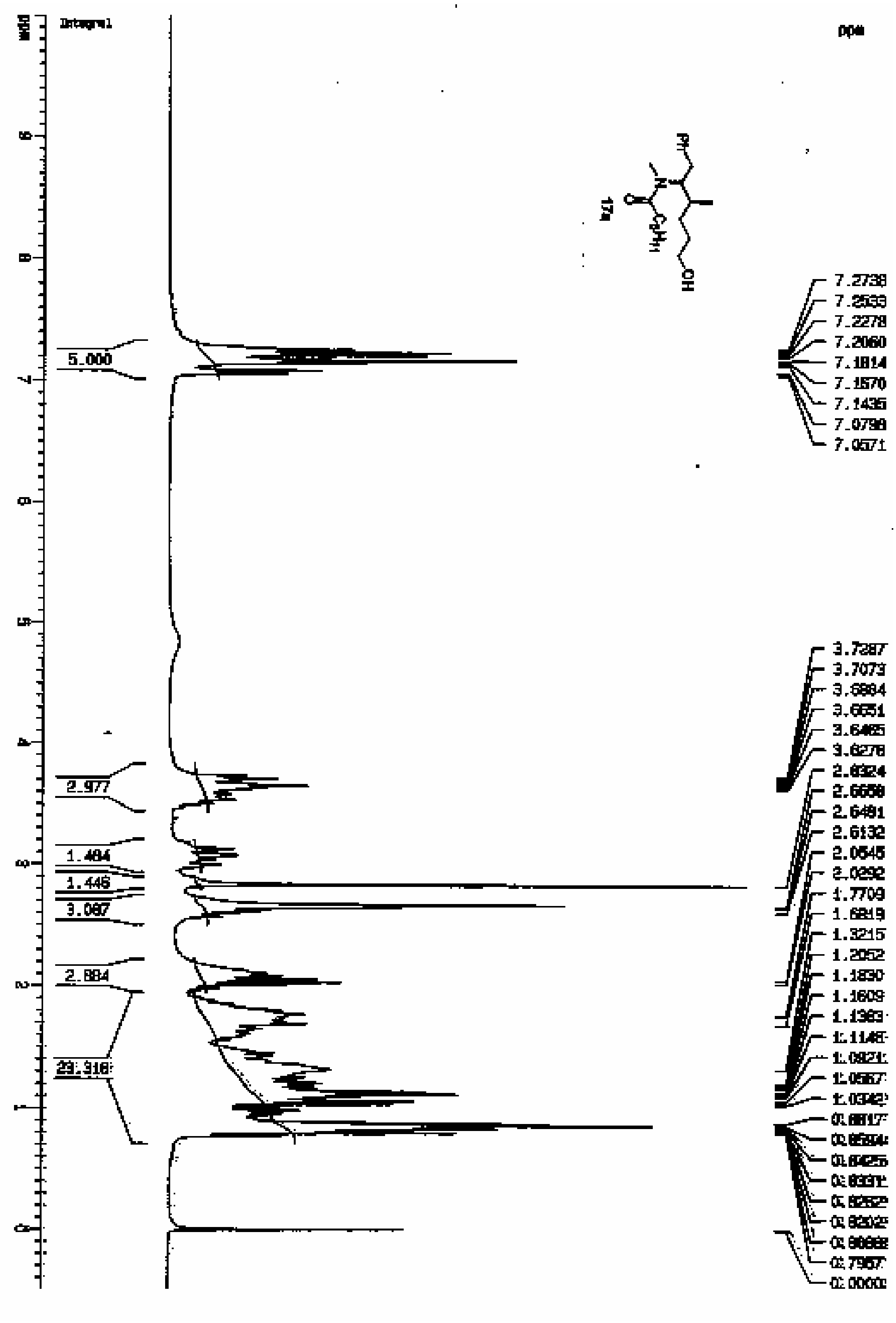
ppm
Integral
1.000
0.790
0.950
1.858
3.144
32.102
7.27139
4.82493
4.79338
3.57847
3.56847
2.23247
2.20865
2.18230
1.90967
1.85584
1.63746
1.60215
1.56182
1.45543
1.44208
1.42234
1.40124
1.33838
1.32517
1.31425
1.29034
1.28032
0.98985
0.96167
0.90743
0.88589
0.86607
0.00636
C_9H_{17}
N
H
O
O


ppm
180
160
140
120
100
80
60
40
20
0
ppm
NH
O
O
173.387
82.953
77.654
77.231
76.808
67.872
37.120
36.414
32.114
31.828
29.920
26.020
25.425
22.599
17.475
14.140
0.212

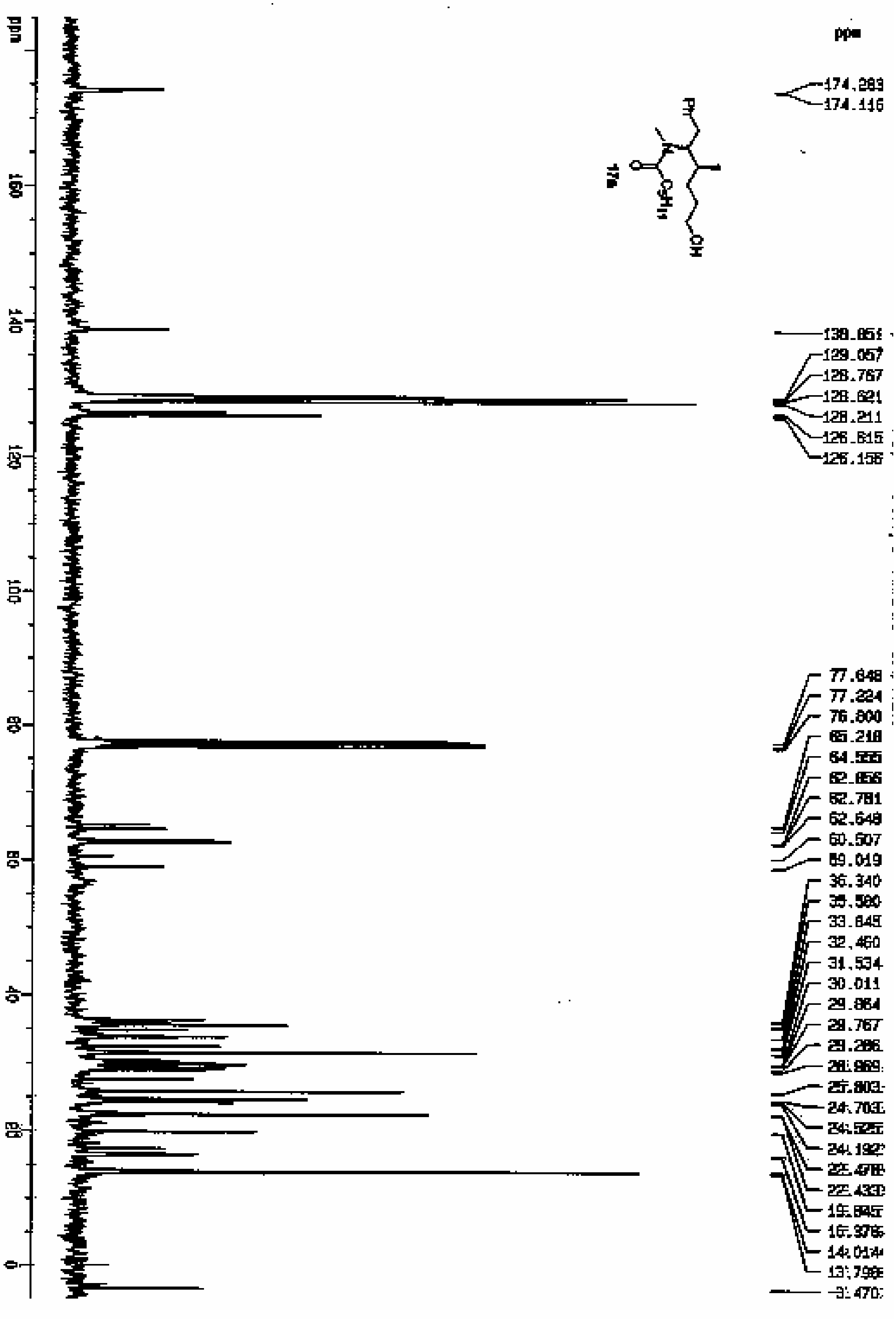

ppm
Integral
ppm
9
8
7
6
5
4
3
2
1
0
3.058
1.000
0.465
0.714
0.553
1.274
0.607
10.752
Bn
N
O
C5H11
OH
17
7.27127
7.24306
7.22127
7.20695
7.19710
7.18252
7.15865
7.09514
7.09200
7.06942
3.74110
3.72134
3.69272
3.67624
3.65625
2.84821
2.67899
2.65643
2.63331
2.18441
2.05855
2.04423
1.78742
1.70511
1.36483
1.33899
1.32761
1.26595
1.15159
1.13011
1.11018
1.10521
0.89694
0.87954
0.87467
0.86873
0.86813
0.84453
0.83047
0.82030
0.80679
0.78228

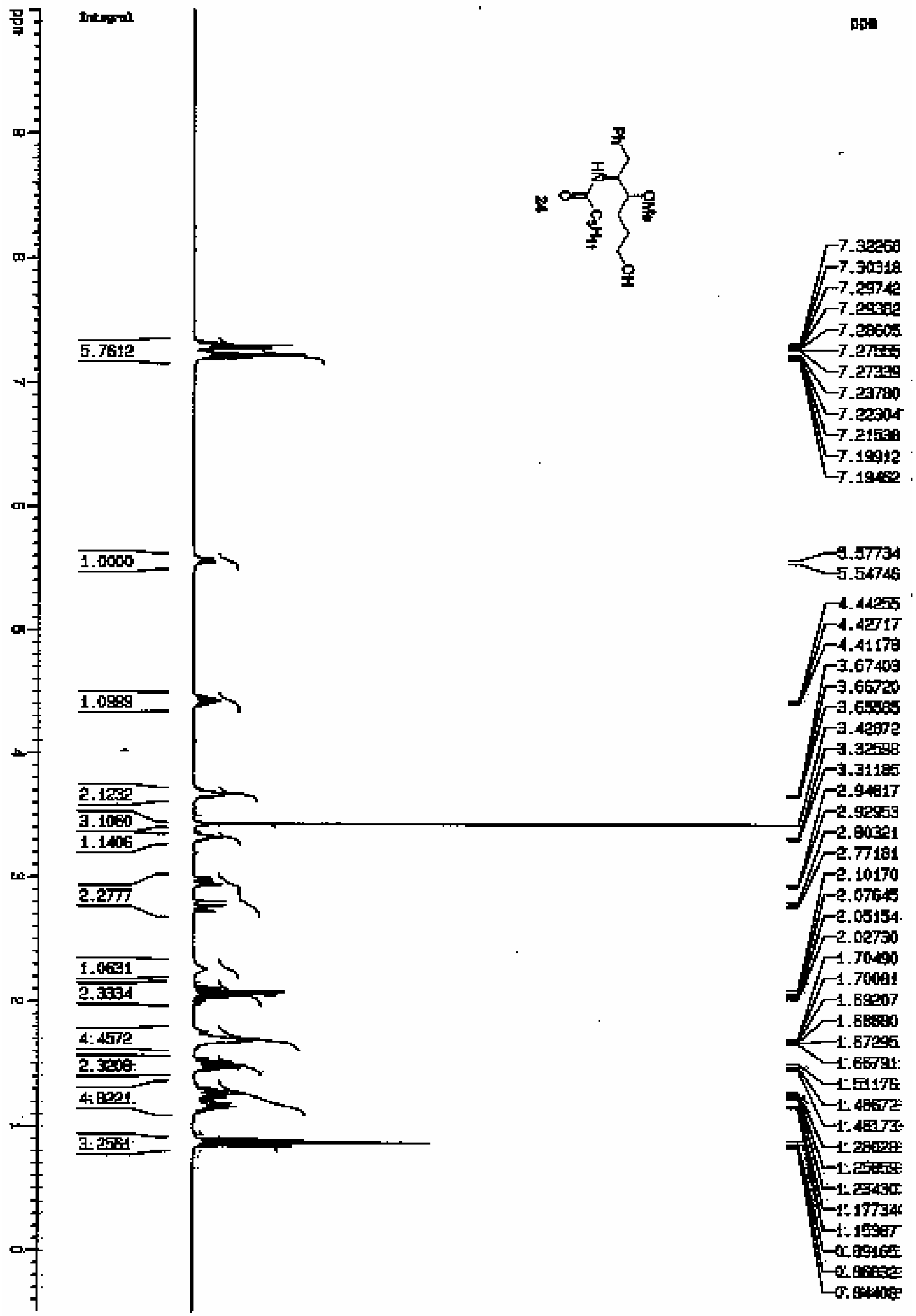
ppm
Integral
ppm
1.000
1.196
2.762
2.994
7.473
5.678
20.194
16.936
8.452
9.754
C9H17
O
O
18
7.27048
5.36798
5.33517
4.45339
4.42200
4.03113
4.02269
4.01662
3.59836
3.58743
3.54490
3.51588
3.50606
2.91345
2.87406
2.34869
2.32490
2.31963
2.29678
1.67397
1.66668
1.64884
1.62395
1.35137
1.34778
1.33418
1.32848
1.32343
1.29812
1.25322
0.92026
0.90427
0.89838
0.88772
0.88138
0.82527
0.80332
0.77811
0.75503


ppm
180
160
140
120
100
80
60
40
20
0
C_7H_{15}
18
177.631
176.293
174.297
174.192
172.656
171.623
167.902
165.779
164.692
161.863
159.043
158.430
156.842
156.243
149.394
145.205
144.572
143.811
138.797
135.517
132.576
129.762
129.100
125.661
117.094
112.633
111.542
110.666
107.105
102.298
99.973
90.999
86.073
77.688
77.467
77.264
76.840
75.219
72.276
68.504
68.417
65.124
47.765
34.311
33.789
33.311
32.558
32.218
31.935
29.947
29.174
27.151
26.451
26.140
25.410
24.815
22.736
17.077
15.738
14.181
0.225

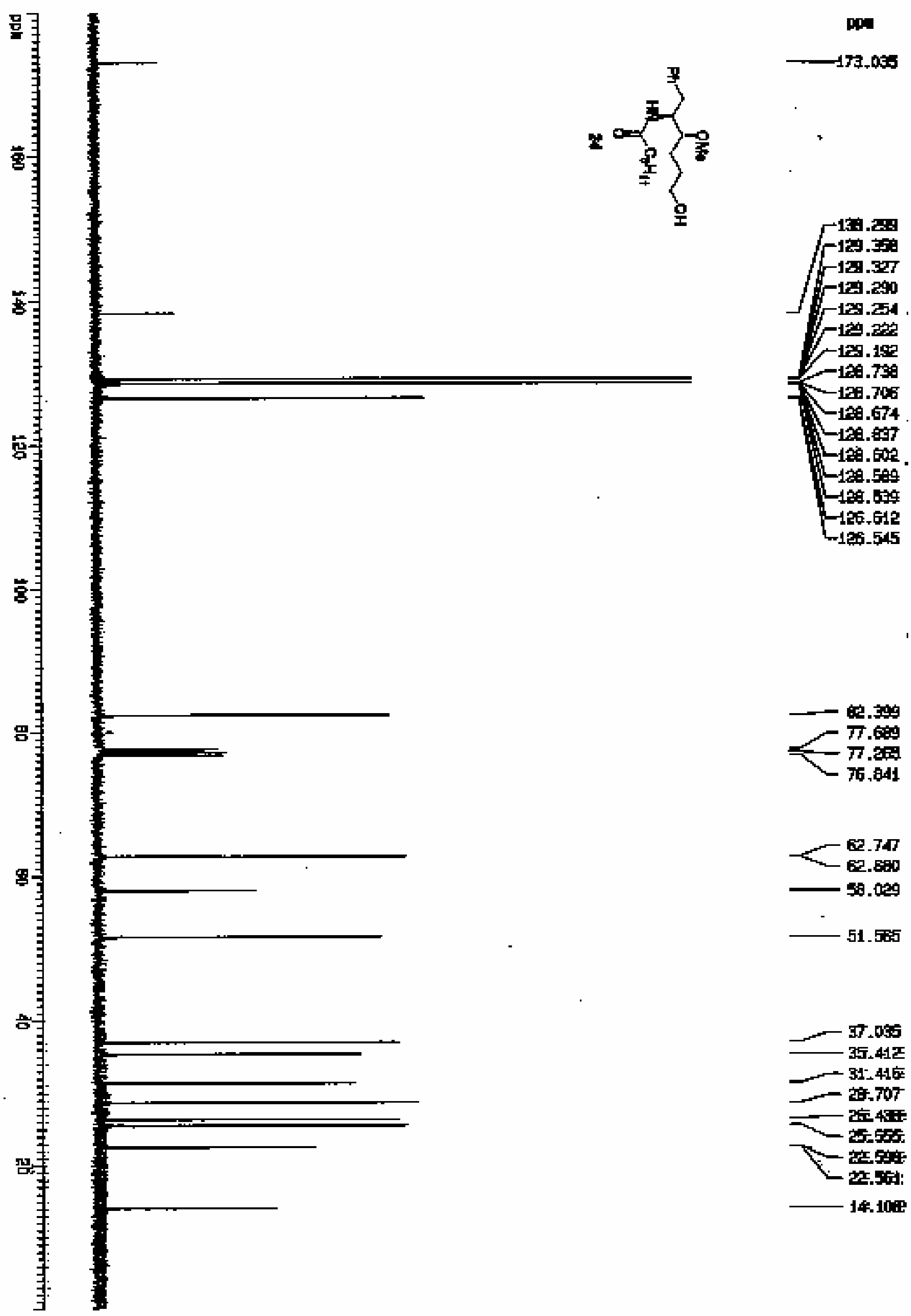


ppm
Integral
17a
Ph
N
O
C9H19
OH
5.000
2.977
1.484
1.446
3.087
2.884
29.318
7.2738
7.2533
7.2278
7.2060
7.1814
7.1570
7.1435
7.0798
7.0571
3.7287
3.7073
3.6864
3.6651
3.6465
3.6276
2.6824
2.6658
2.6491
2.6132
2.0545
2.0292
1.7709
1.6819
1.3215
1.2052
1.1830
1.1609
1.1363
1.1148
1.0821
1.0567
1.0342
0.8817
0.8594
0.8425
0.8371
0.8262
0.8202
0.8068
0.7967
0.0000

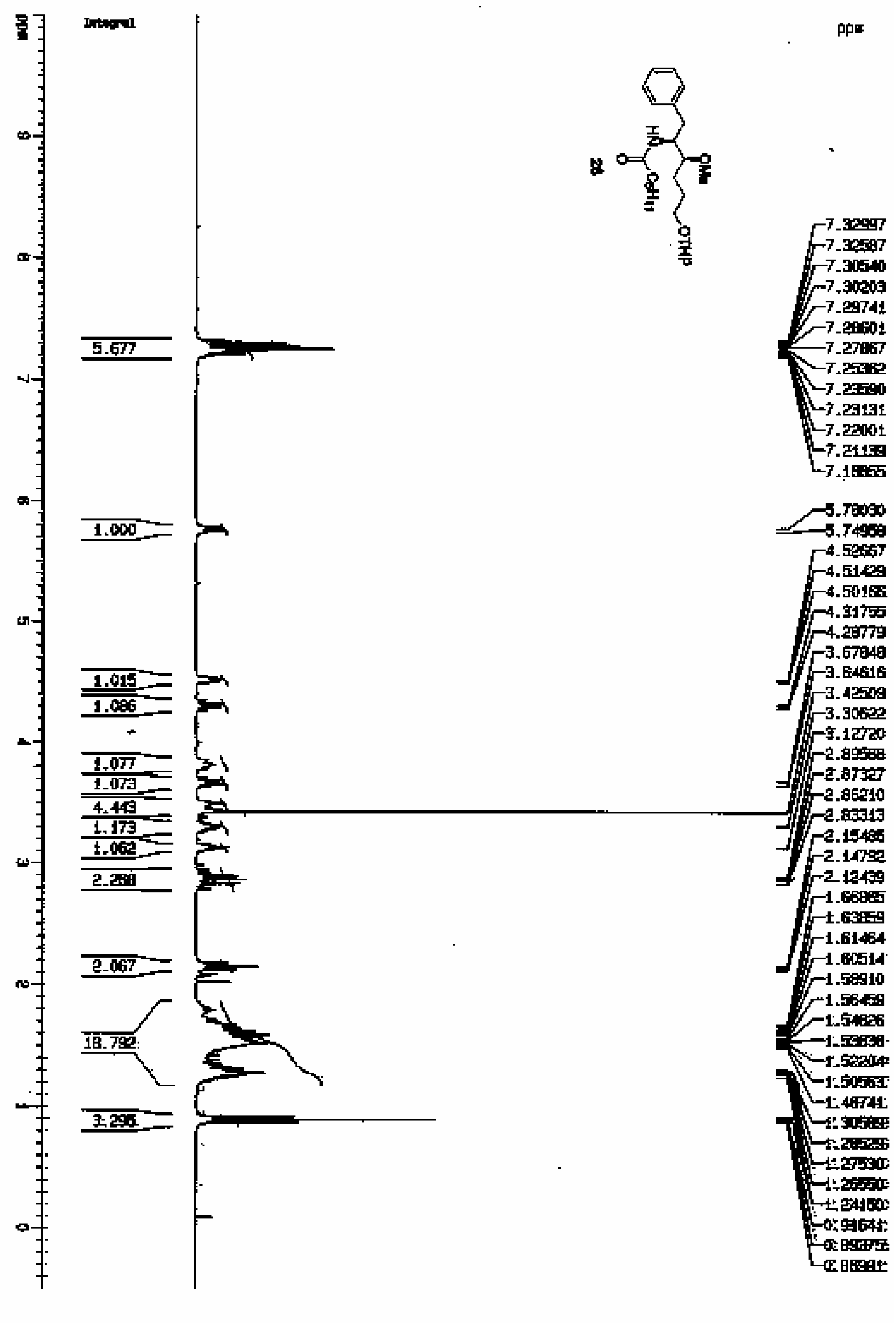

ppm
160
140
120
100
80
60
40
20
0
ppm
Ph
N
O
C5H11
OH
17a
174.283
174.116
138.858
129.057
128.767
128.621
128.211
126.815
126.156
77.648
77.224
76.800
65.218
64.555
62.856
62.781
62.648
60.507
59.019
36.340
35.580
33.645
32.460
31.534
30.011
29.864
29.767
29.286
28.869
25.803
24.703
24.525
24.192
23.478
22.433
19.845
16.376
14.014
13.798
-3.470

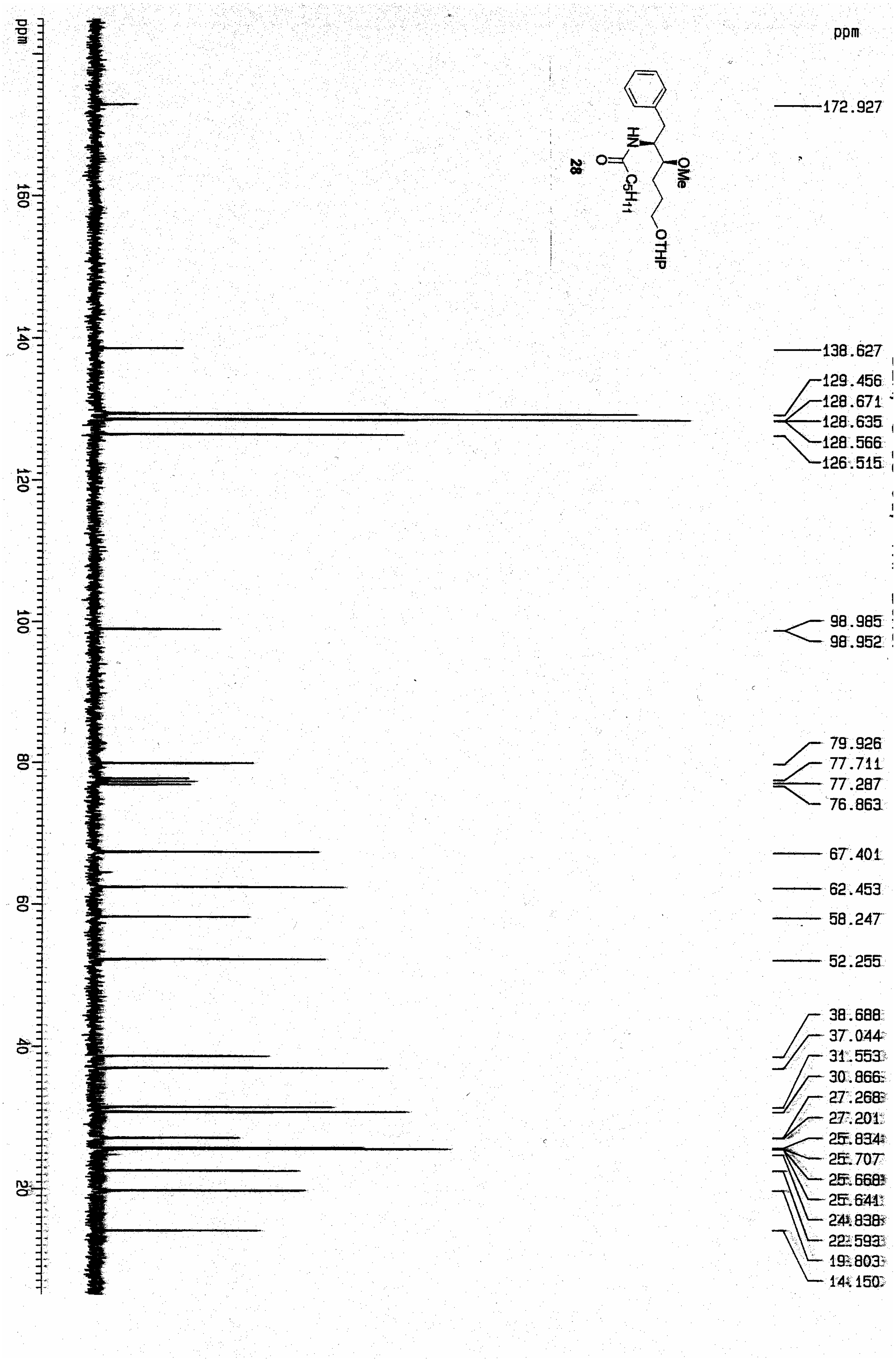


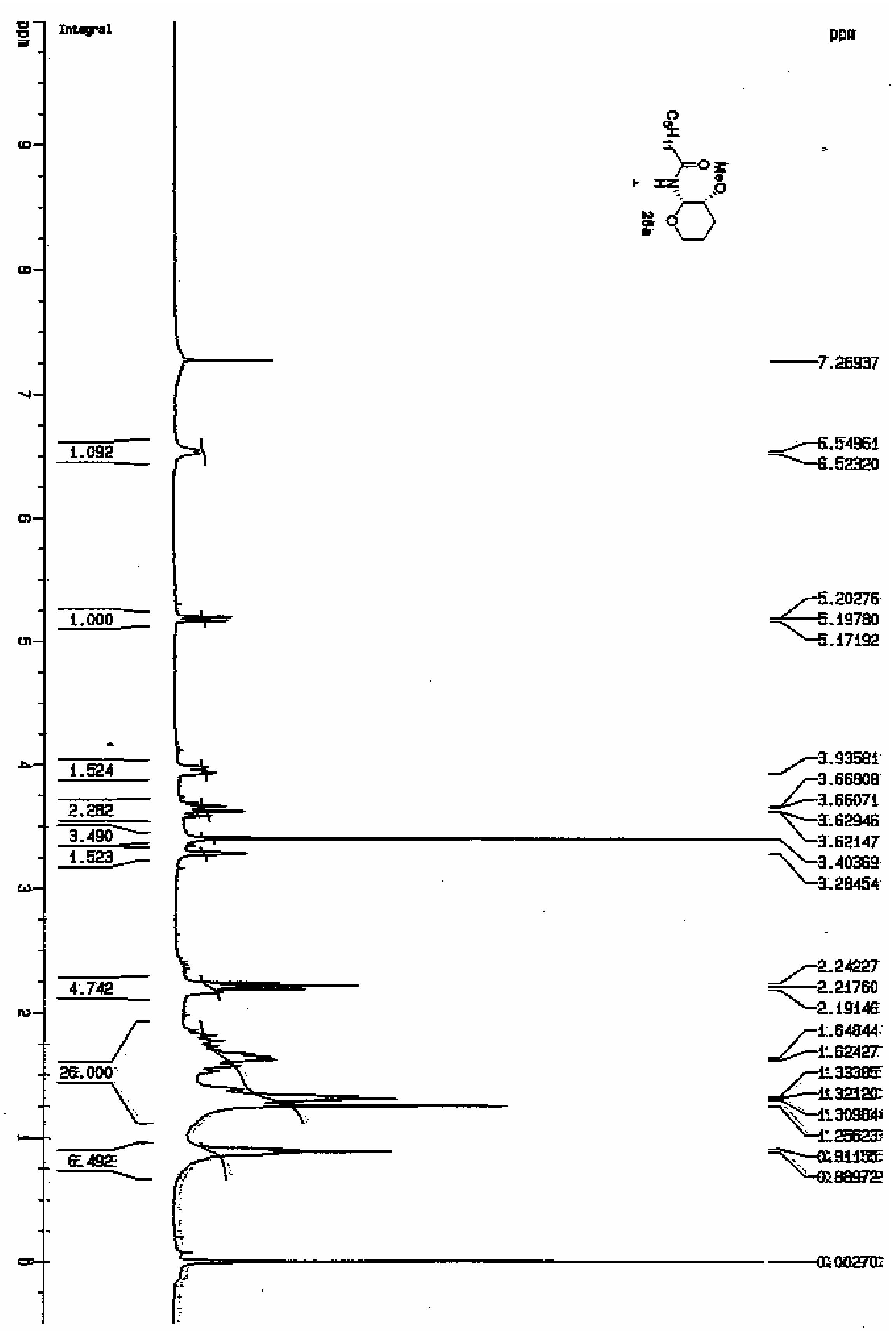
Integral
ppm
ppm
9
8
7
6
5
4
3
2
1
0
Ph
HN
O
OMe
C9H19
OH
24
5.7612
1.0000
1.0989
2.1232
3.1060
1.1406
2.2777
1.0631
2.3334
4.4572
2.3208
4.8221
3.2581
7.32268
7.30318
7.29742
7.29382
7.28605
7.27555
7.27339
7.23780
7.22304
7.21538
7.19912
7.19462
5.57734
5.54746
4.44255
4.42717
4.41179
3.67409
3.66720
3.65565
3.42872
3.32598
3.31185
2.94817
2.92953
2.80321
2.77181
2.10170
2.07645
2.05154
2.02730
1.70490
1.70081
1.69207
1.68880
1.67295
1.66791
1.51175
1.49672
1.48173
1.28028
1.25859
1.23430
1.17734
1.15987
0.89165
0.86832
0.84406

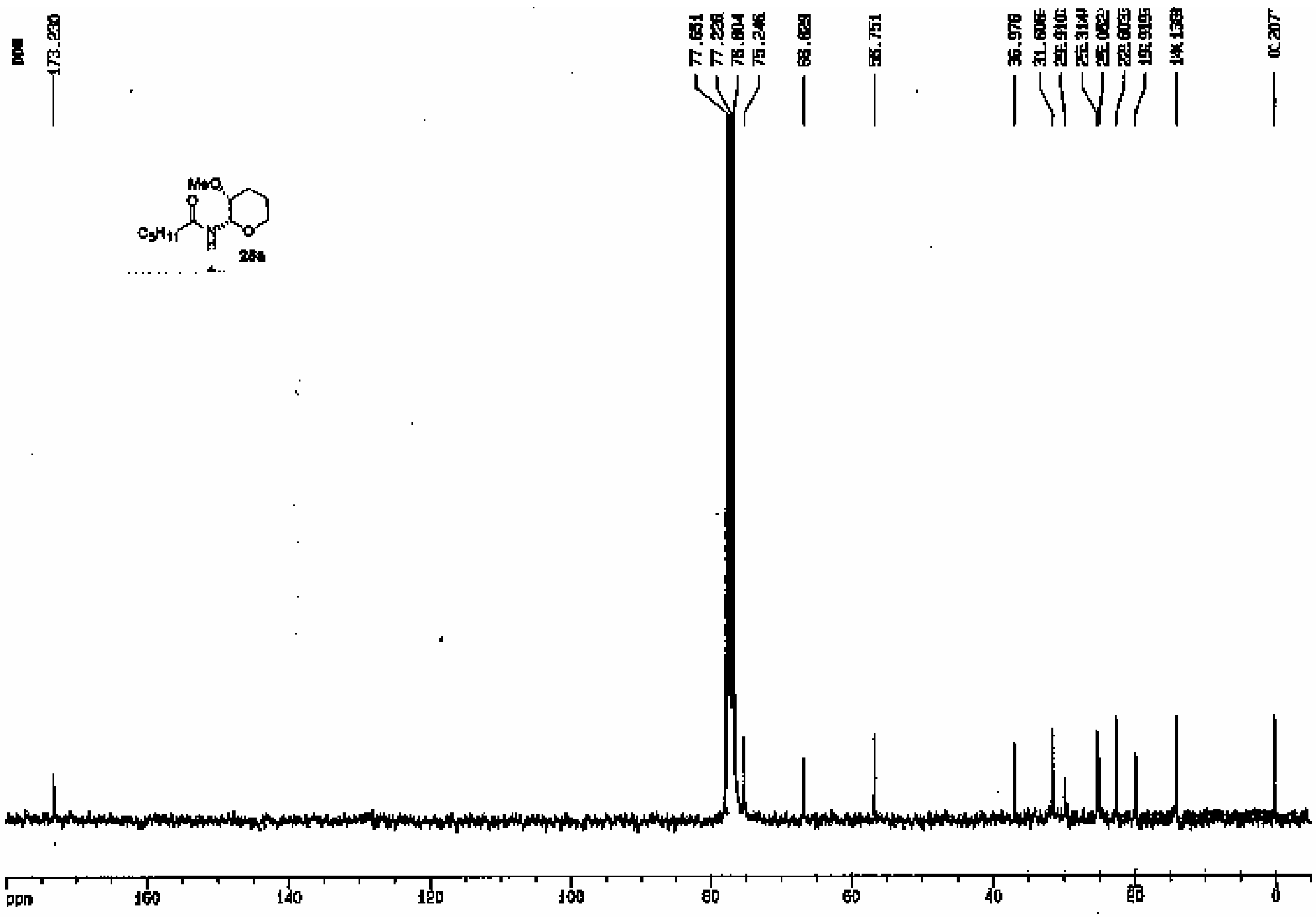


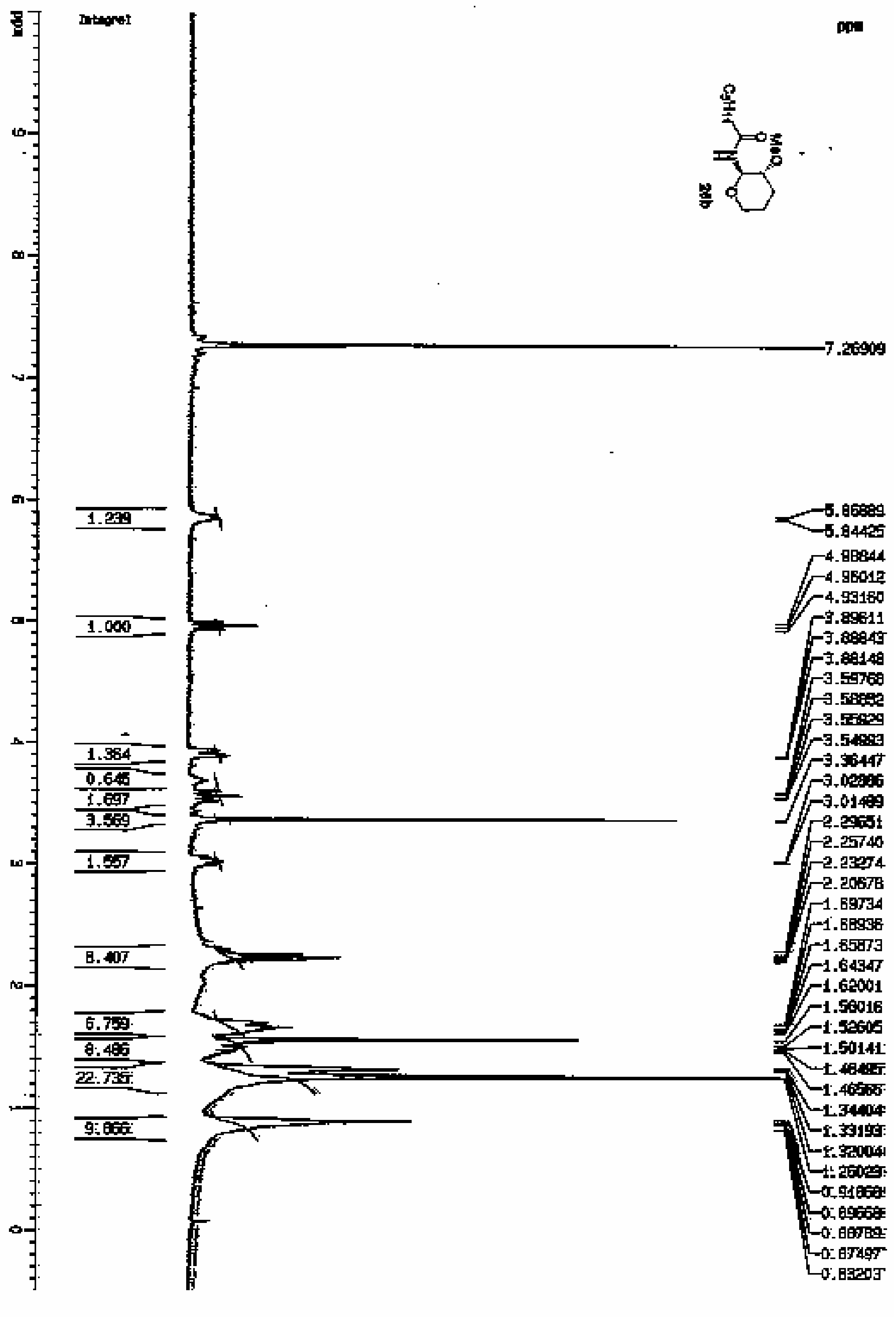
ppm
160
140
120
100
80
60
40
20
Ph
HN
O
C_5H_{11}
OMe
OH
24
ppm
173.035
138.298
129.358
129.327
129.290
129.254
129.222
129.192
128.738
128.706
128.674
128.637
128.602
128.569
128.539
126.612
126.545
82.399
77.689
77.268
76.841
62.747
62.680
58.029
51.565
37.035
35.412
31.416
29.707
26.438
25.555
22.598
22.561
14.108

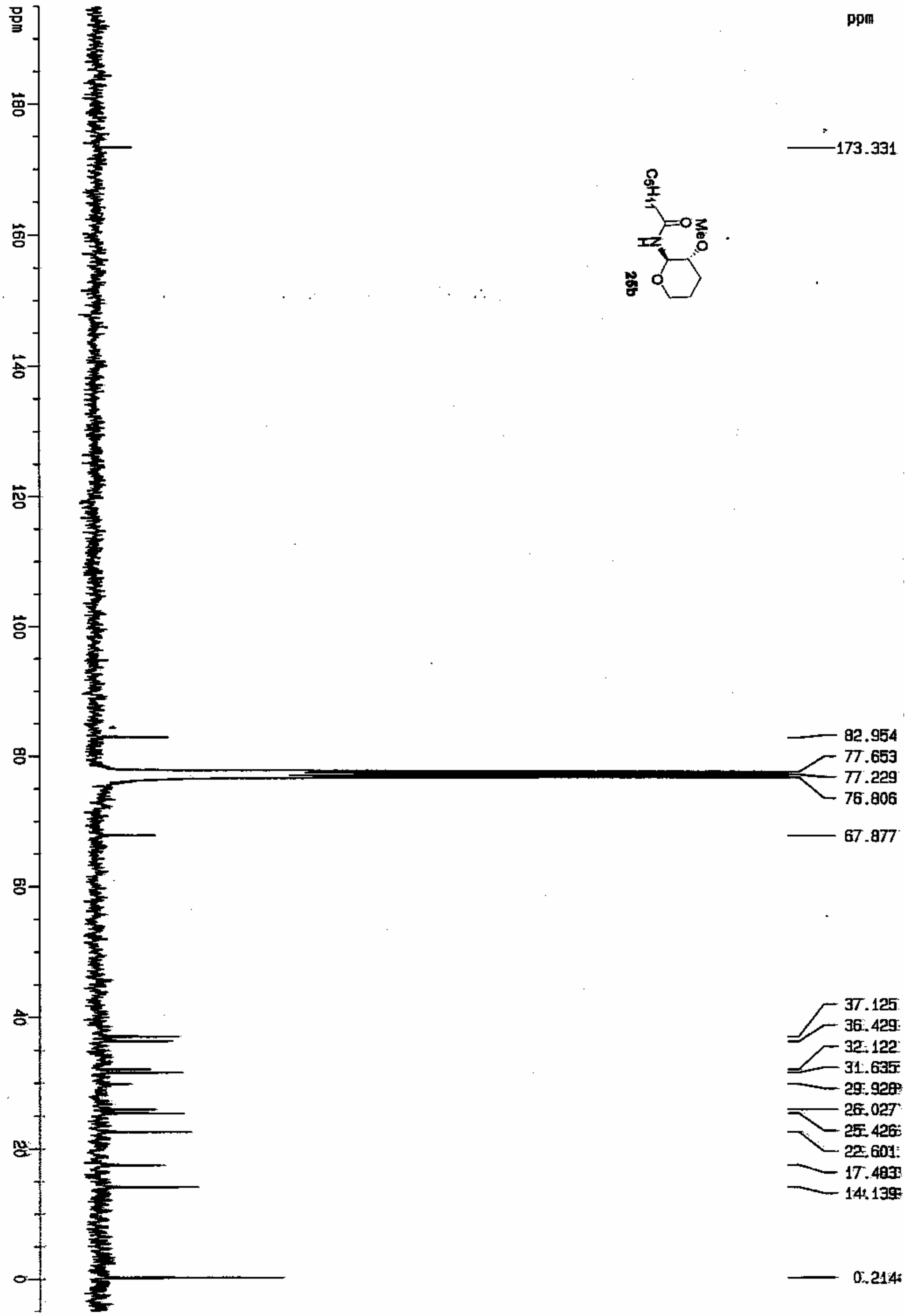

ppm
Integral
ppm
9
8
7
6
5
4
3
2
1
0
OMe
HN
O
C5H11
OTHP
26
5.677
1.000
1.015
1.086
1.077
1.073
4.443
1.173
1.062
2.288
2.067
18.792
3.298
7.32997
7.32587
7.30540
7.30203
7.29741
7.28601
7.27867
7.25362
7.23590
7.23131
7.22001
7.21139
7.18865
5.78030
5.74959
4.52567
4.51429
4.50165
4.31755
4.28779
3.67848
3.64616
3.42509
3.30622
3.12720
2.89568
2.87327
2.85210
2.83313
2.15485
2.14792
2.12439
1.66865
1.63859
1.61464
1.60514
1.58910
1.56459
1.54626
1.53638
1.52204
1.50563
1.48741
1.30588
1.28525
1.27530
1.25550
1.24150
0.91644
0.89675
0.88981

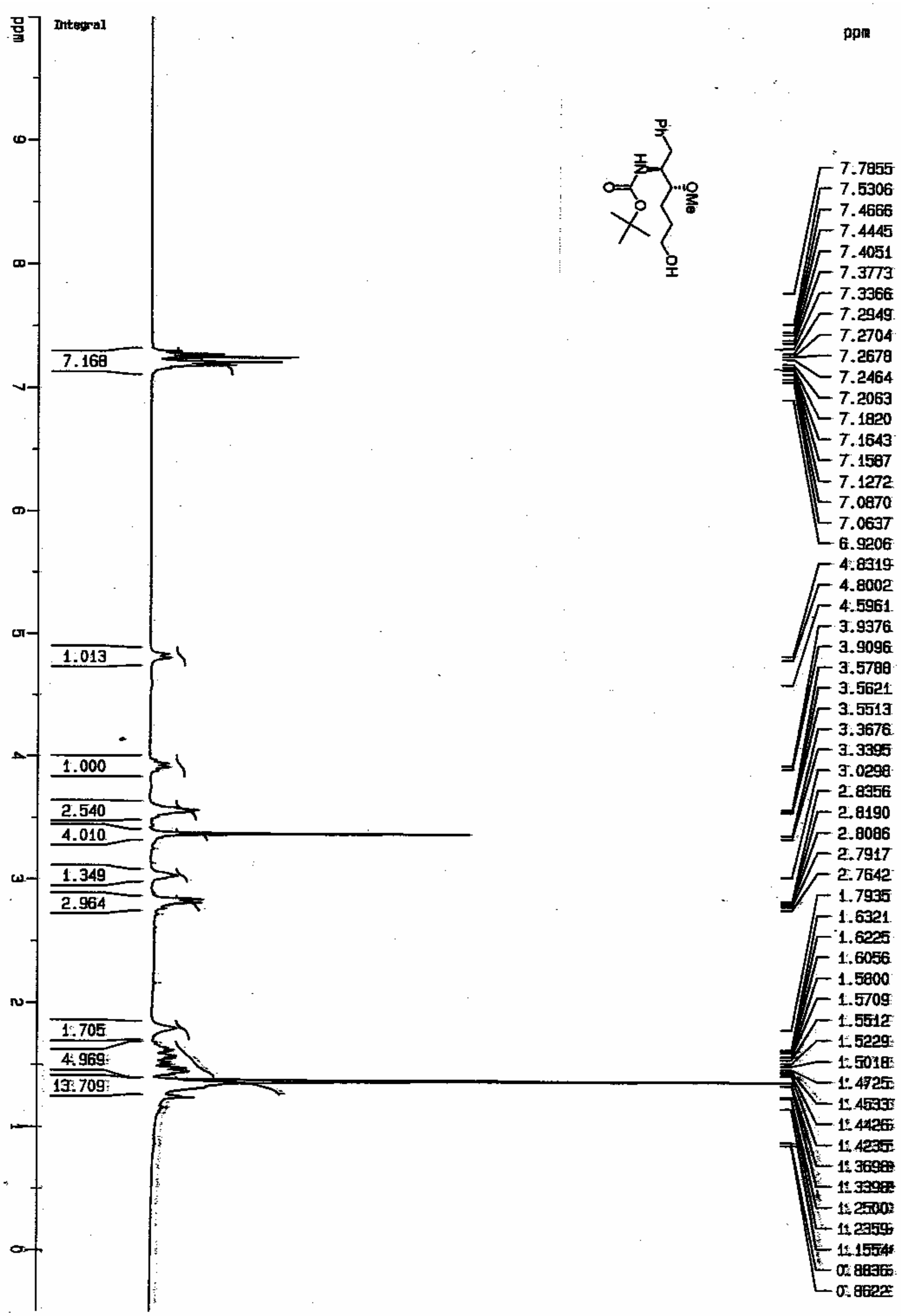

ppm
160
140
120
100
80
60
40
20
ppm
OMe
OTHP
HN
O
C5H11
28
172.927
138.627
129.456
128.671
128.635
128.566
126.515
98.985
98.952
79.926
77.711
77.287
76.863
67.401
62.453
58.247
52.255
38.688
37.044
31.553
30.866
27.268
27.201
25.834
25.707
25.668
25.641
24.838
22.593
19.803
14.150

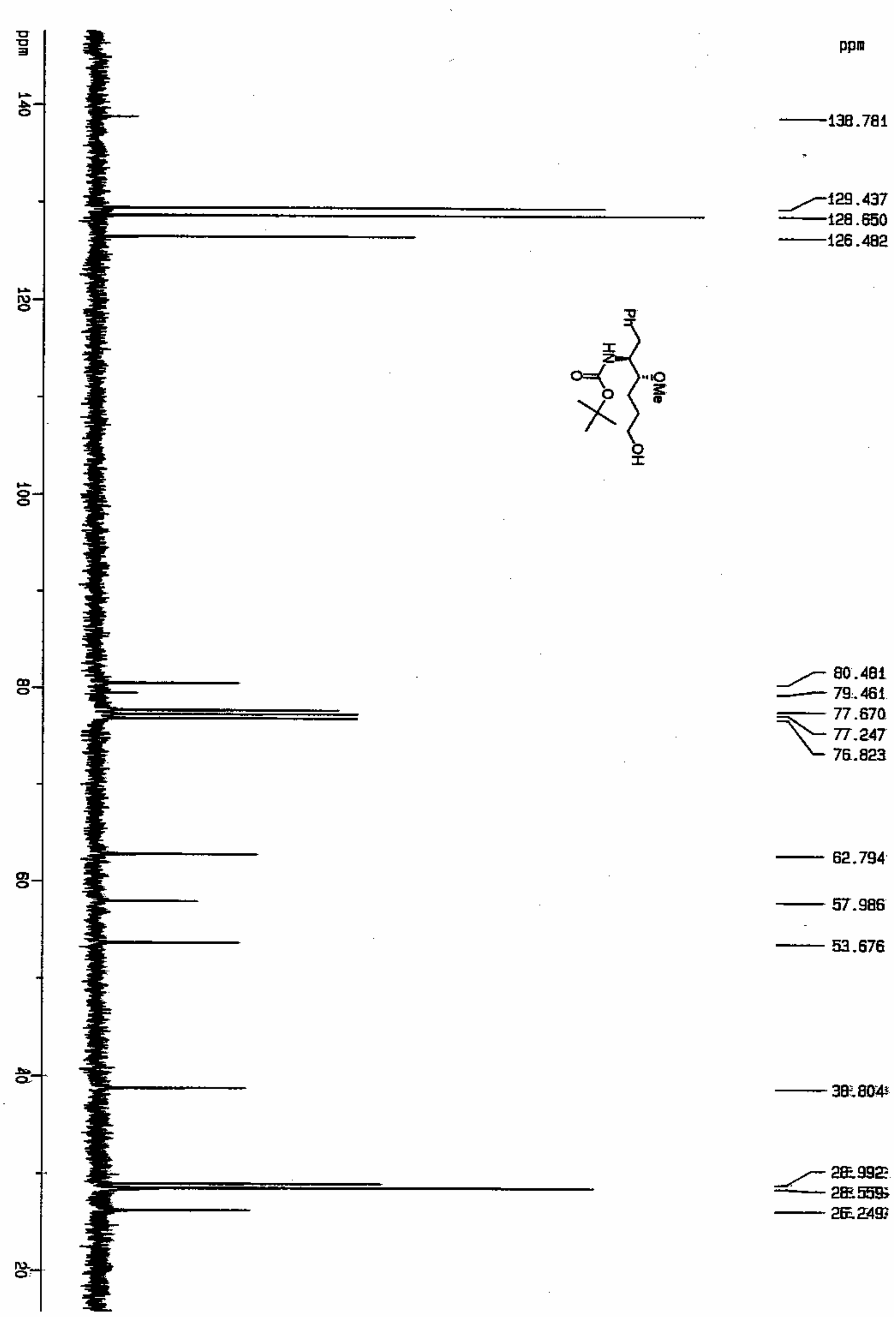

ppm
Integral
ppm
9
8
7
6
5
4
3
2
1
0
MeO
O
O
C8H17
N
H
26a
1.092
1.000
1.524
2.282
3.490
1.523
4.742
26.000
6.492
7.26937
6.54961
6.52320
5.20276
5.19780
5.17192
3.93581
3.66808
3.66071
3.62946
3.62147
3.40369
3.28454
2.24227
2.21760
2.19146
1.64844
1.62427
1.33385
1.32120
1.30984
1.25623
0.91156
0.88972
0.00270

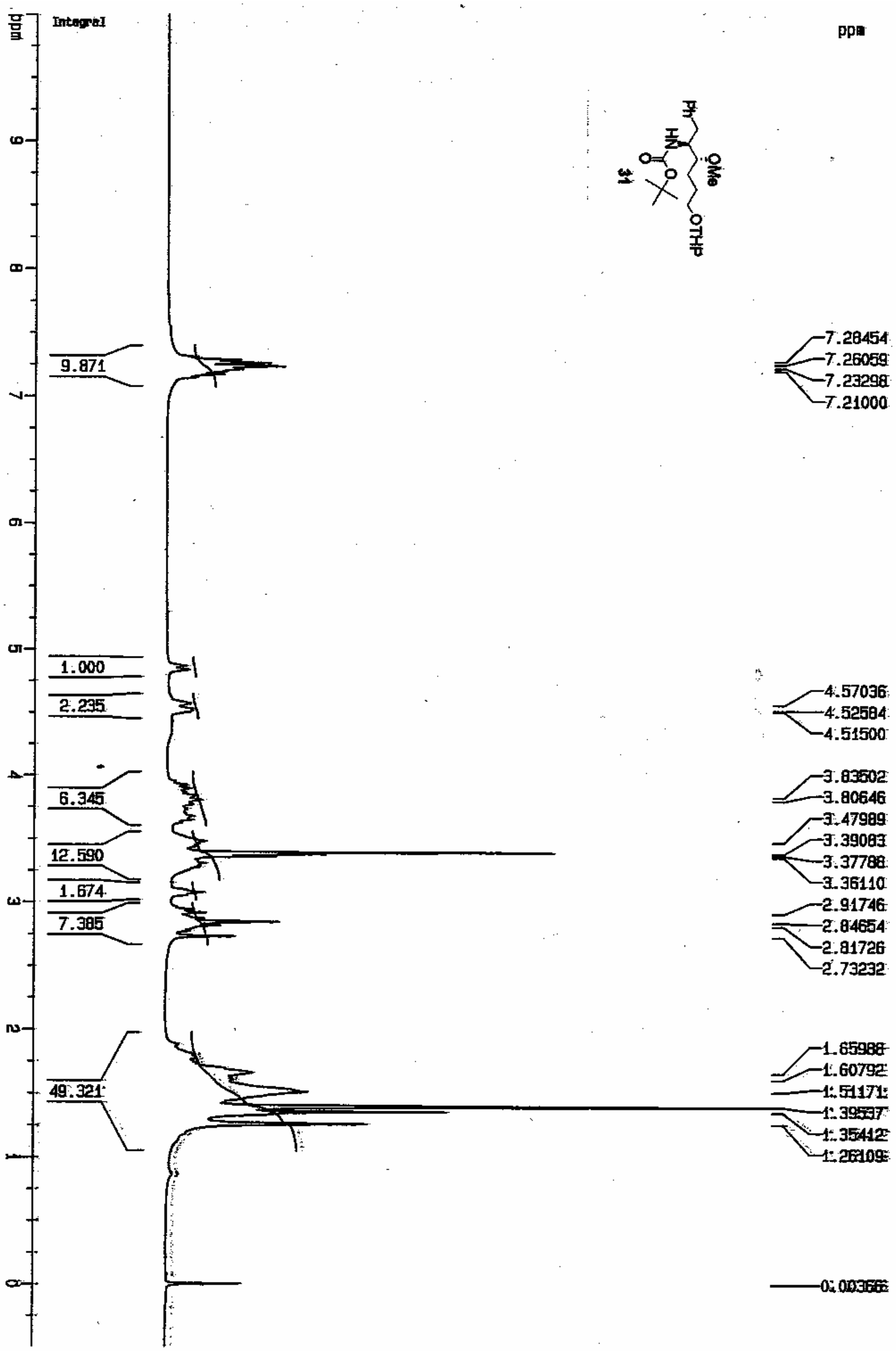

ppm
173.230
77.651
77.228
76.804
75.246
66.629
56.751
36.976
31.606
29.910
25.314
25.052
22.603
19.919
14.138
0.207
MeO
O
C_5H_{11}
N
H
O
28a
ppm
160
140
120
100
80
60
40
20
0

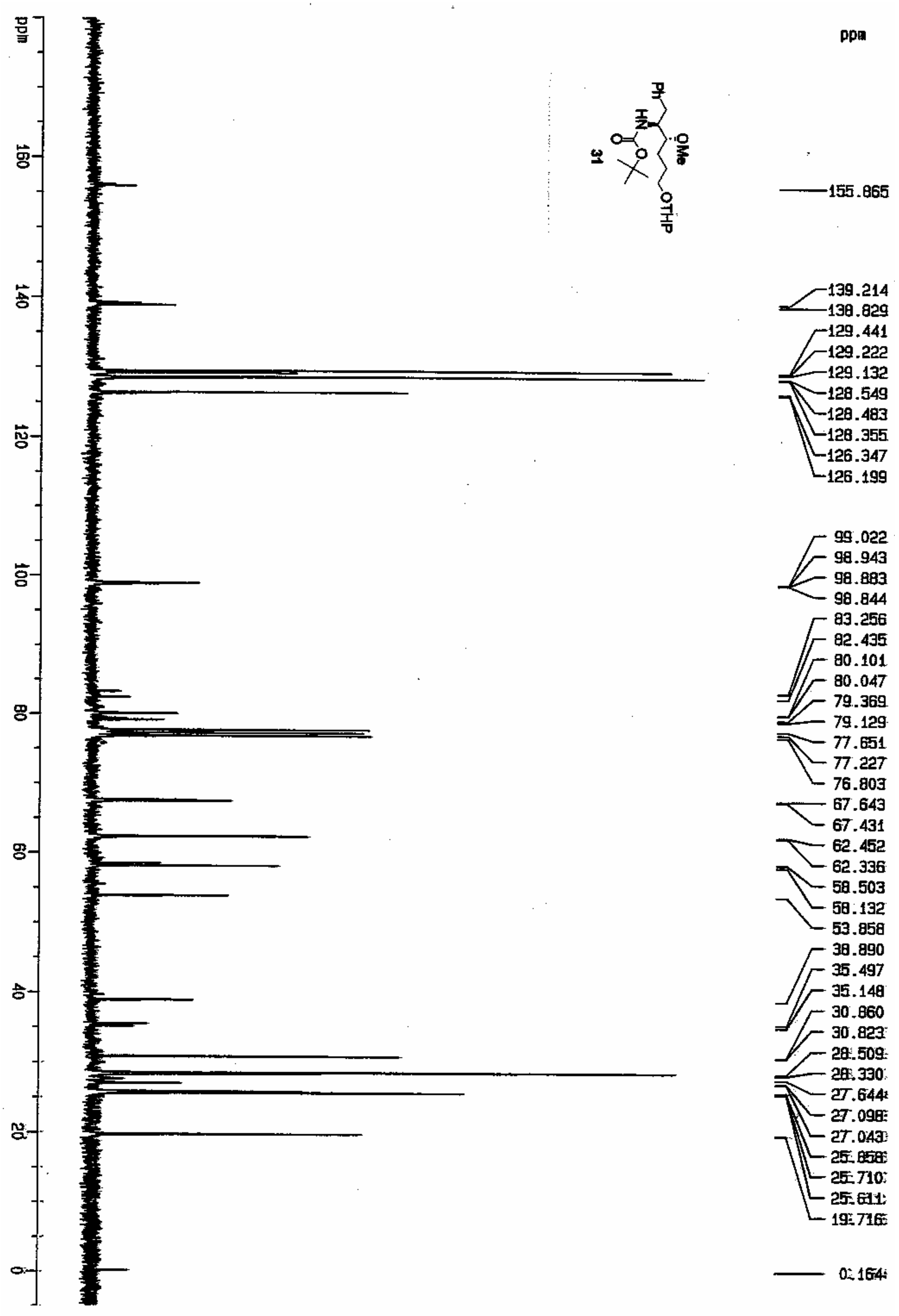

ppm
Integral
ppm
C5H11
MeO
26b
9
8
7
6
5
4
3
2
1
0
1.239
1.000
1.384
0.646
1.697
3.569
1.557
8.407
6.759
8.486
22.735
9.666
7.26909
5.86889
5.84425
4.98844
4.96012
4.93160
3.89611
3.88843
3.88148
3.59768
3.58652
3.55629
3.54883
3.36447
3.02886
3.01499
2.29651
2.25740
2.23274
2.20678
1.69734
1.68936
1.65873
1.64347
1.62001
1.56016
1.52605
1.50141
1.48485
1.46566
1.34404
1.33193
1.32004
1.26029
0.91869
0.89668
0.88789
0.87497
0.83203

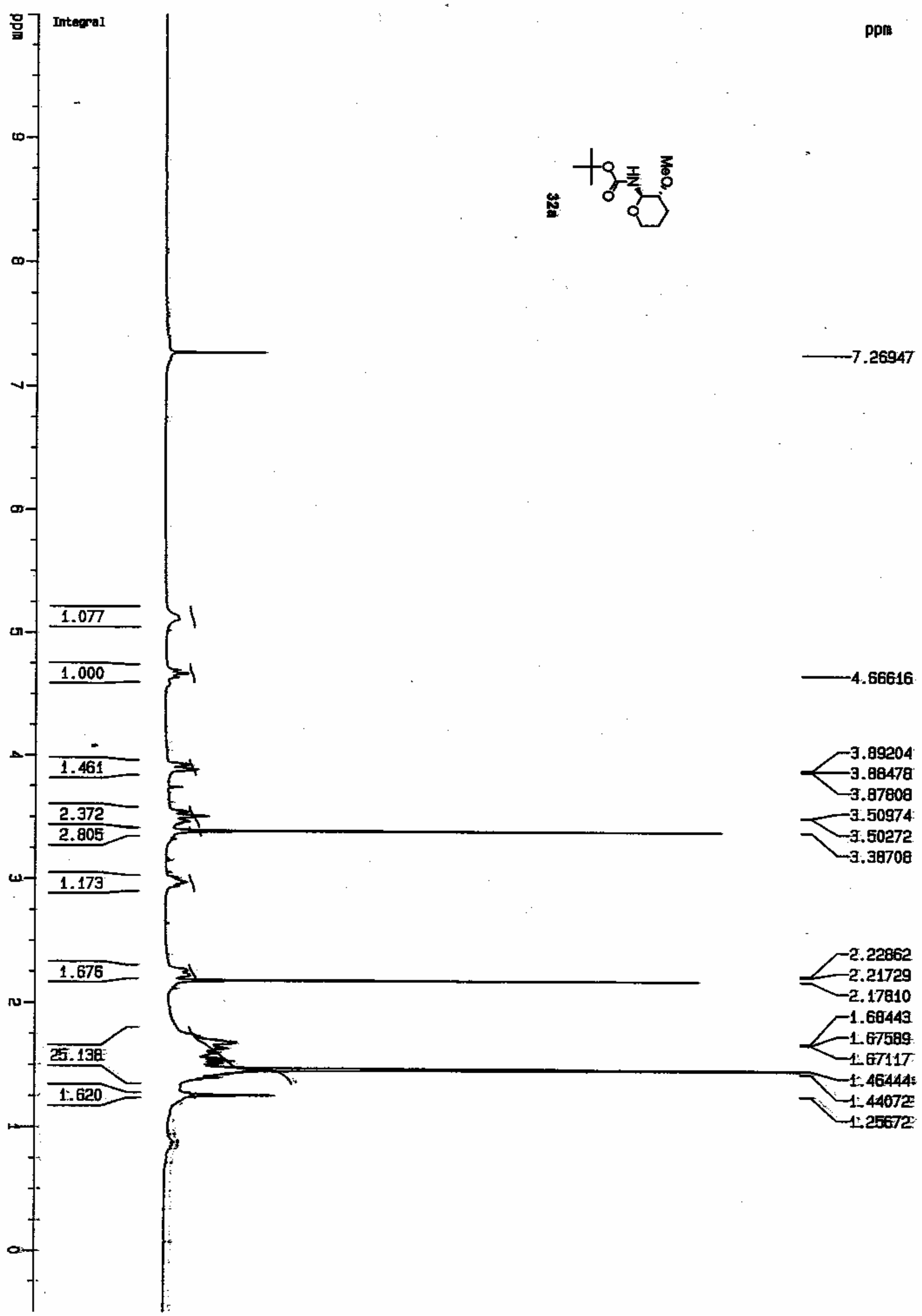

ppm
180
160
140
120
100
80
60
40
20
0
ppm
173.331
82.954
77.653
77.229
76.806
67.877
37.125
36.429
32.122
31.635
29.928
26.027
25.426
22.601
17.483
14.139
0.214
C5H11
O
N
H
MeO
O
25b

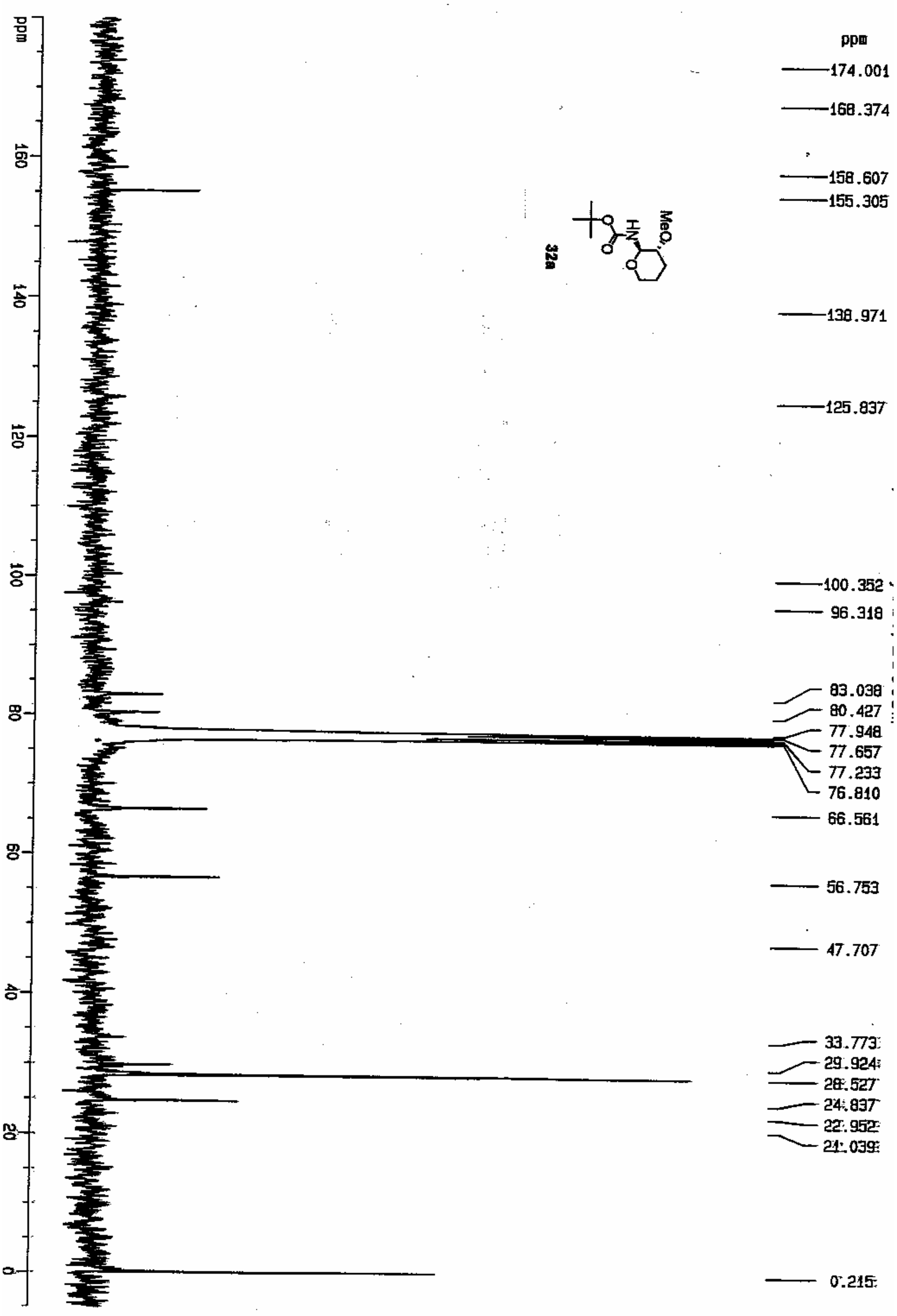

ppm
Integral
ppm
9
8
7
6
5
4
3
2
1
0
7.168
1.013
1.000
2.540
4.010
1.349
2.964
1.705
4.969
13.709
Ph
HN
O
O
OMe
OH
7.7855
7.5306
7.4666
7.4445
7.4051
7.3773
7.3366
7.2949
7.2704
7.2678
7.2464
7.2063
7.1820
7.1643
7.1587
7.1272
7.0870
7.0637
6.9206
4.8319
4.8002
4.5961
3.9376
3.9096
3.5788
3.5621
3.5513
3.3676
3.3395
3.0298
2.8356
2.8190
2.8086
2.7917
2.7642
1.7935
1.6321
1.6225
1.6056
1.5800
1.5709
1.5512
1.5229
1.5018
1.4725
1.4533
1.4426
1.4235
1.3698
1.3398
1.2500
1.2359
1.1554
0.8836
0.8622

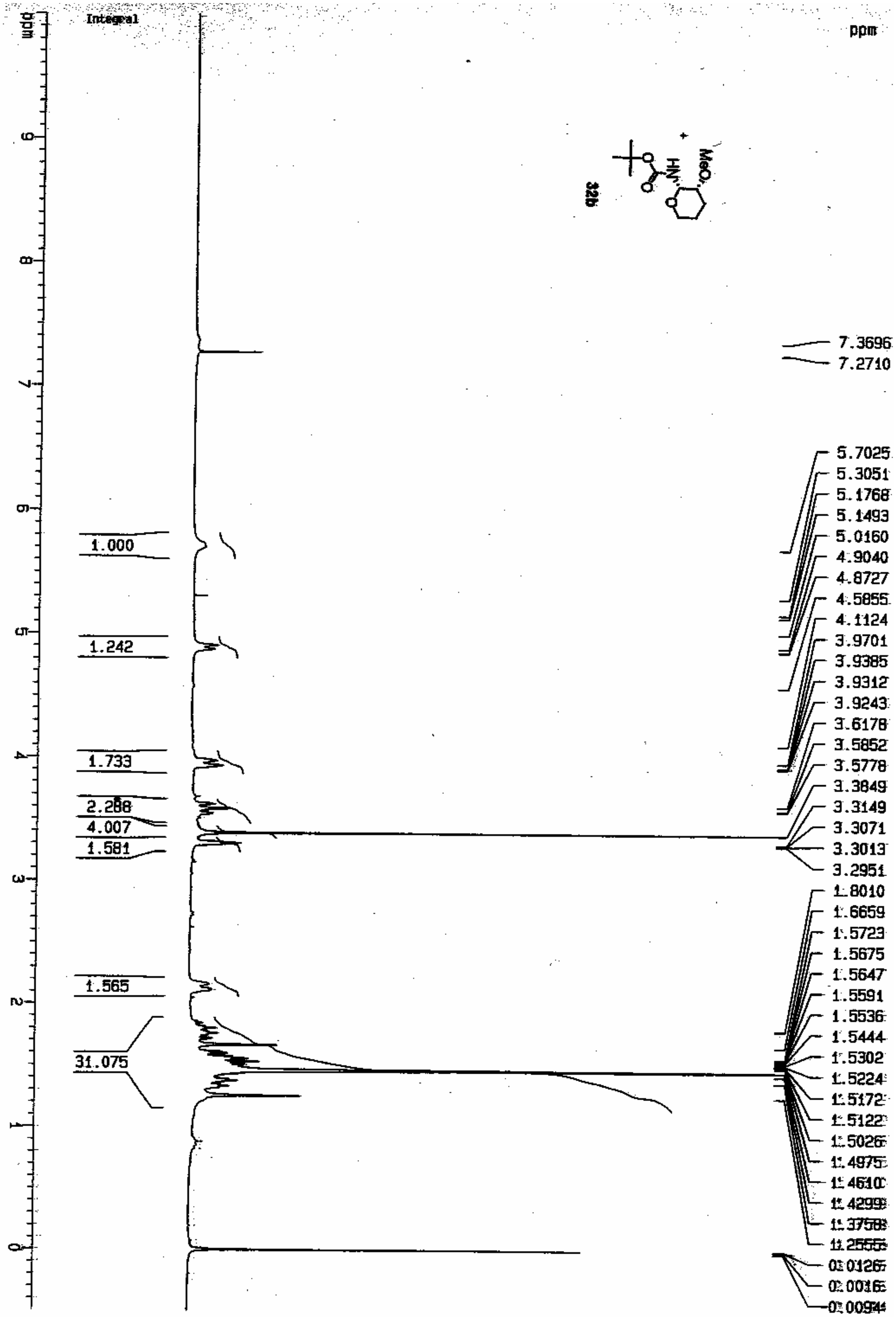

ppm
140
120
100
80
60
40
20
ppm
138.781
129.437
128.650
126.482
80.481
79.461
77.670
77.247
76.823
62.794
57.986
53.676
38.804
28.992
28.559
26.249
Ph
HN
O
O
OMe
OH

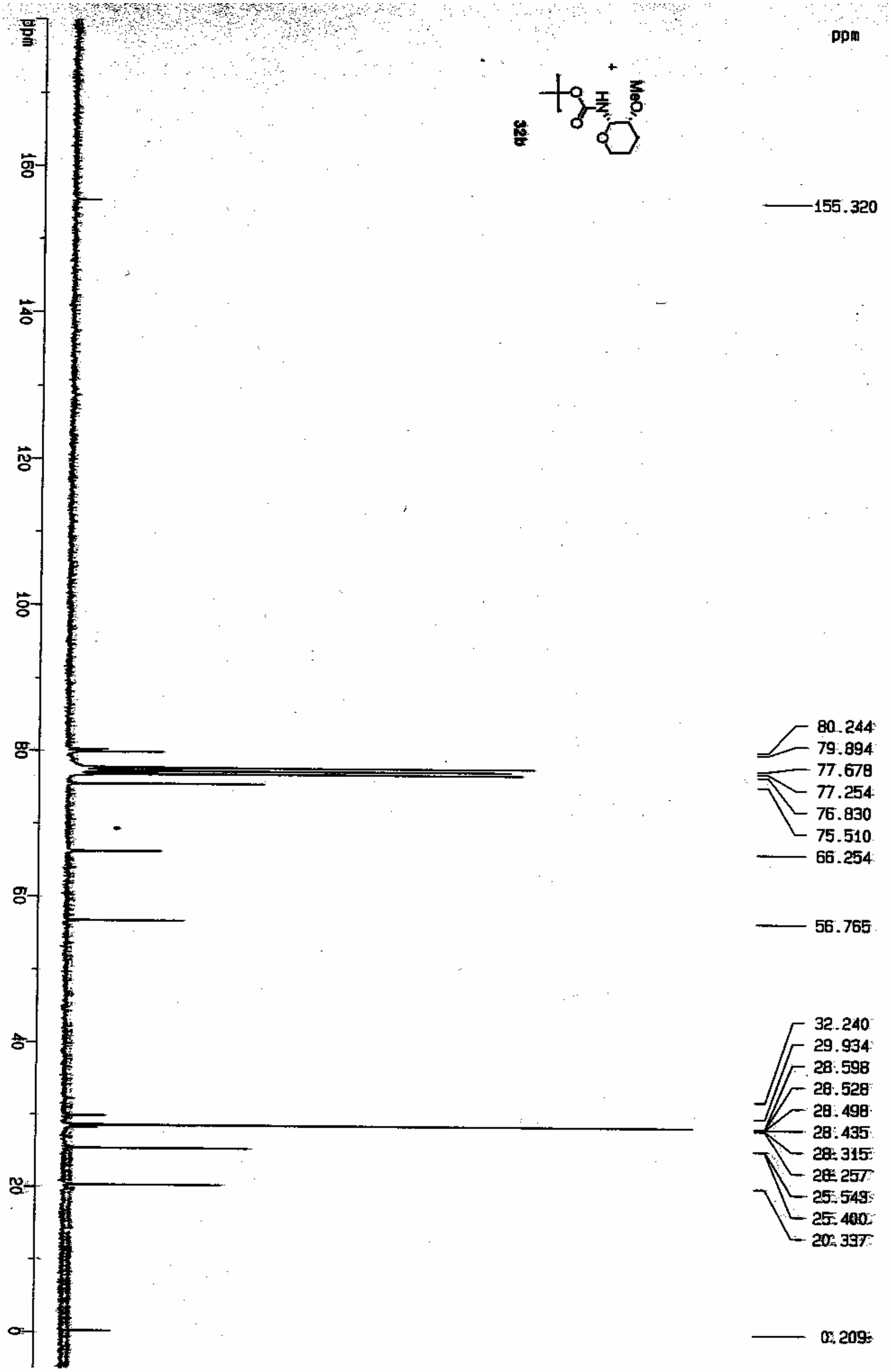

ppm
Integral
ppm
OMe
Ph
HN
O
O
OTHP
31
9.871
1.000
2.235
6.345
12.590
1.674
7.385
49.321
7.28454
7.26059
7.23298
7.21000
4.57036
4.52584
4.51500
3.83502
3.80646
3.47989
3.39083
3.37788
3.36110
2.91746
2.84654
2.81726
2.73232
1.65988
1.60792
1.51171
1.39537
1.35412
1.26109
0.00366
9
8
7
6
5
4
3
2
1
0

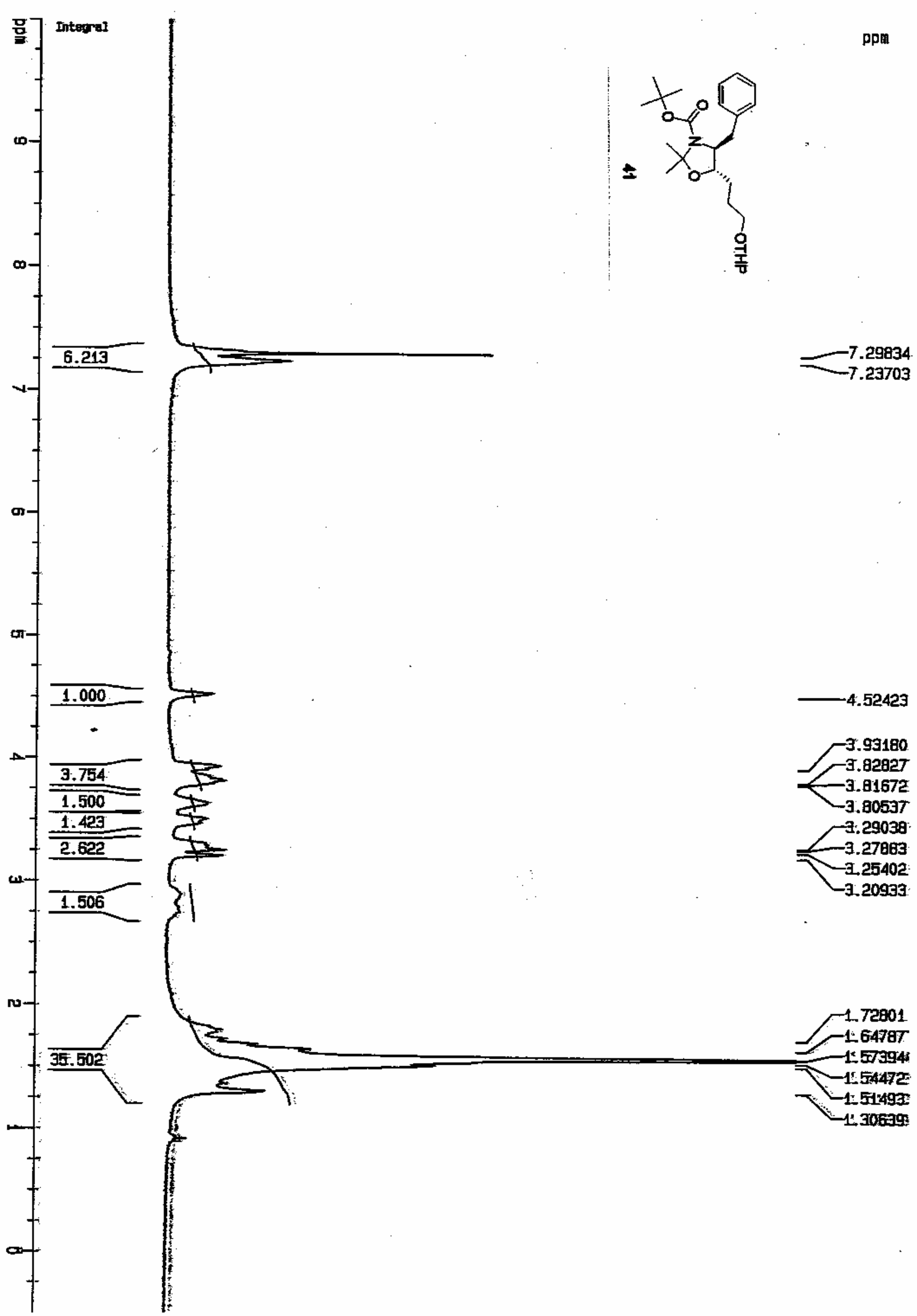

ppm
160
140
120
100
80
60
40
20
0
ppm
Ph
HN
O
O
OMe
OTHP
31
155.865
139.214
138.829
129.441
129.222
129.132
128.549
128.483
128.355
126.347
126.199
99.022
98.943
98.883
98.844
83.256
82.435
80.101
80.047
79.369
79.129
77.651
77.227
76.803
67.643
67.431
62.452
62.336
58.503
58.132
53.858
38.890
35.497
35.148
30.860
30.823
28.509
28.330
27.644
27.098
27.043
25.858
25.710
25.611
19.716
0.164


ppm
Integral
ppm
9
8
7
6
5
4
3
2
1
0
MeO
HN
O
O
O
32a
1.077
1.000
1.461
2.372
2.805
1.173
1.676
25.138
1.620
7.26947
4.66616
3.89204
3.88478
3.87808
3.50974
3.50272
3.38708
2.22862
2.21729
2.17810
1.68443
1.67589
1.67117
1.46444
1.44072
1.25672

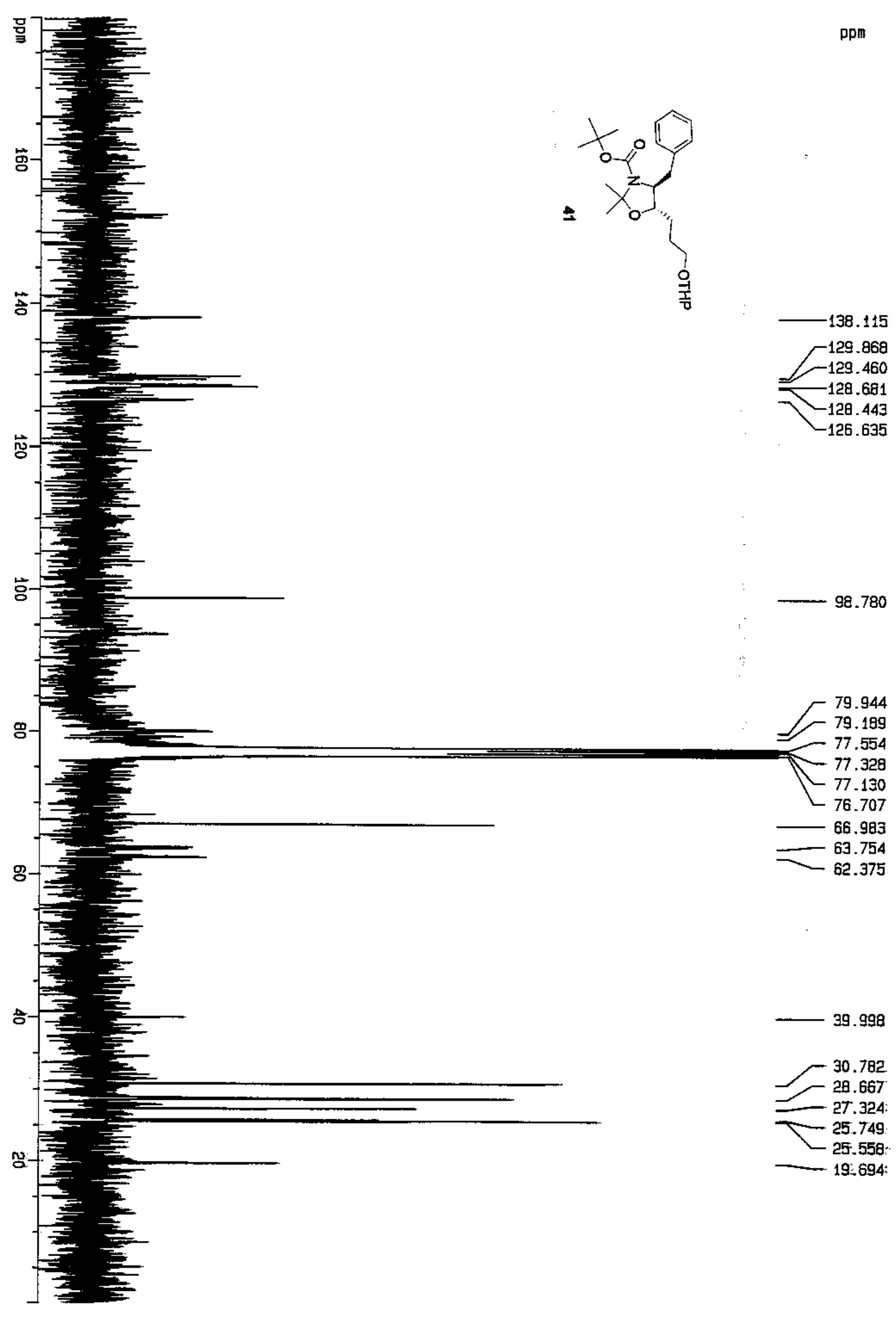

32a
ppm
174.001
168.374
158.607
155.305
138.971
125.837
100.352
96.318
83.038
80.427
77.948
77.657
77.233
76.810
66.561
56.753
47.707
33.773
29.924
28.527
24.837
22.952
21.039
0.215
ppm
160
140
120
100
80
60
40
20
0
MeO
HN
O
O
O

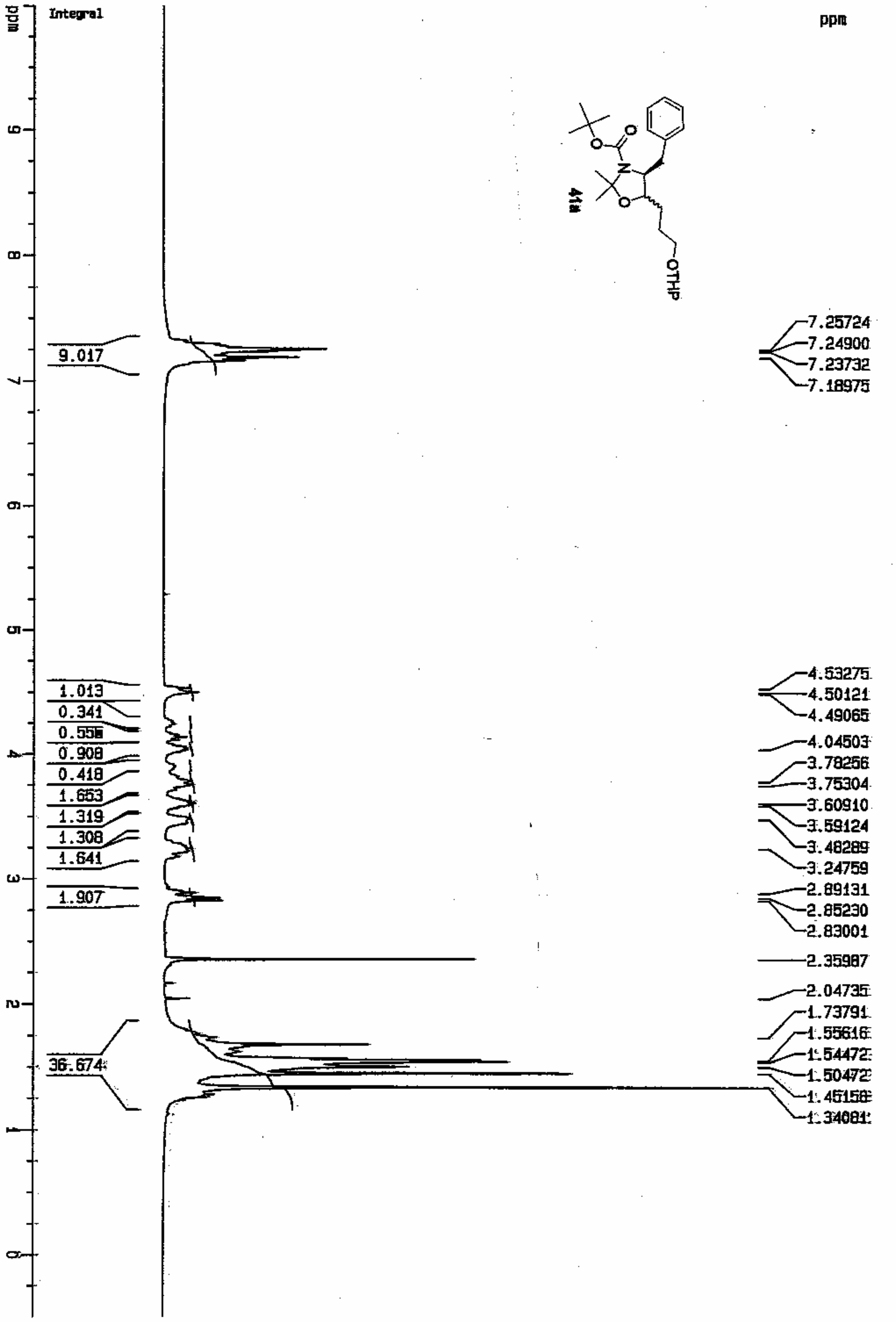

32b
ppm
Integral
ppm
9
8
7
6
5
4
3
2
1
0
MeO
HN
O
O
O
1.000
1.242
1.733
2.288
4.007
1.581
1.565
31.075
7.3696
7.2710
5.7025
5.3051
5.1768
5.1493
5.0160
4.9040
4.8727
4.5855
4.1124
3.9701
3.9385
3.9312
3.9243
3.6178
3.5852
3.5778
3.3849
3.3149
3.3071
3.3013
3.2951
1.8010
1.6659
1.5723
1.5675
1.5647
1.5591
1.5536
1.5444
1.5302
1.5224
1.5172
1.5122
1.5026
1.4975
1.4610
1.4299
1.3758
1.2555
0.0126
0.0016
-0.0094

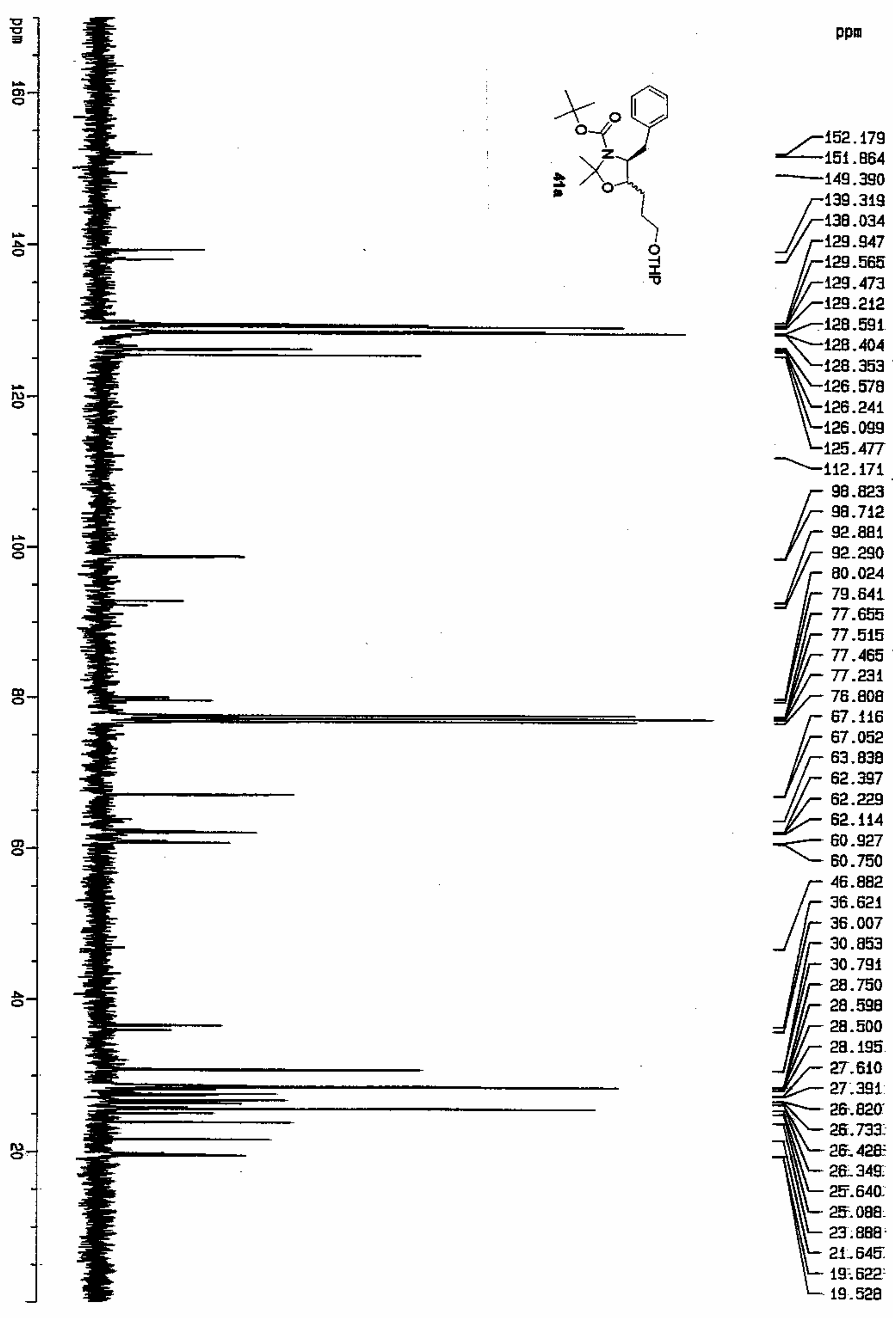

32b
ppm
160
140
120
100
80
60
40
20
0
ppm
MeO
HN
O
155.320
80.244
79.894
77.678
77.254
76.830
75.510
66.254
56.765
32.240
29.934
28.598
28.528
28.498
28.435
28.315
28.257
25.543
25.400
20.337
0.209



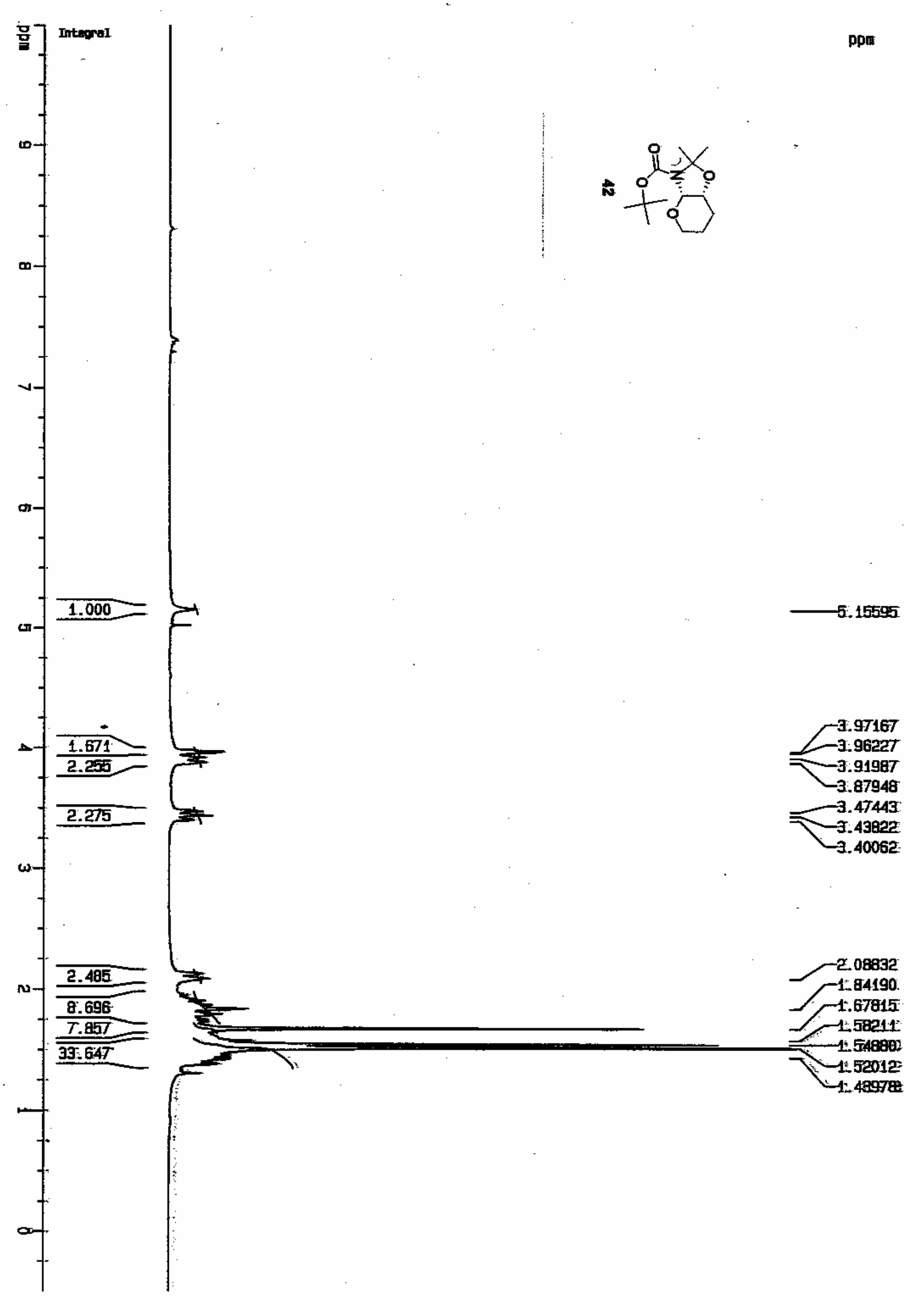
ppm
Integral
9
8
7
6
5
4
3
2
1
0
41
OTHP
N
O
6.213
1.000
3.754
1.500
1.423
2.622
1.506
35.502
7.29834
7.23703
4.52423
3.93180
3.82827
3.81672
3.80537
3.29038
3.27863
3.25402
3.20933
1.72801
1.64787
1.57394
1.54472
1.51493
1.30639

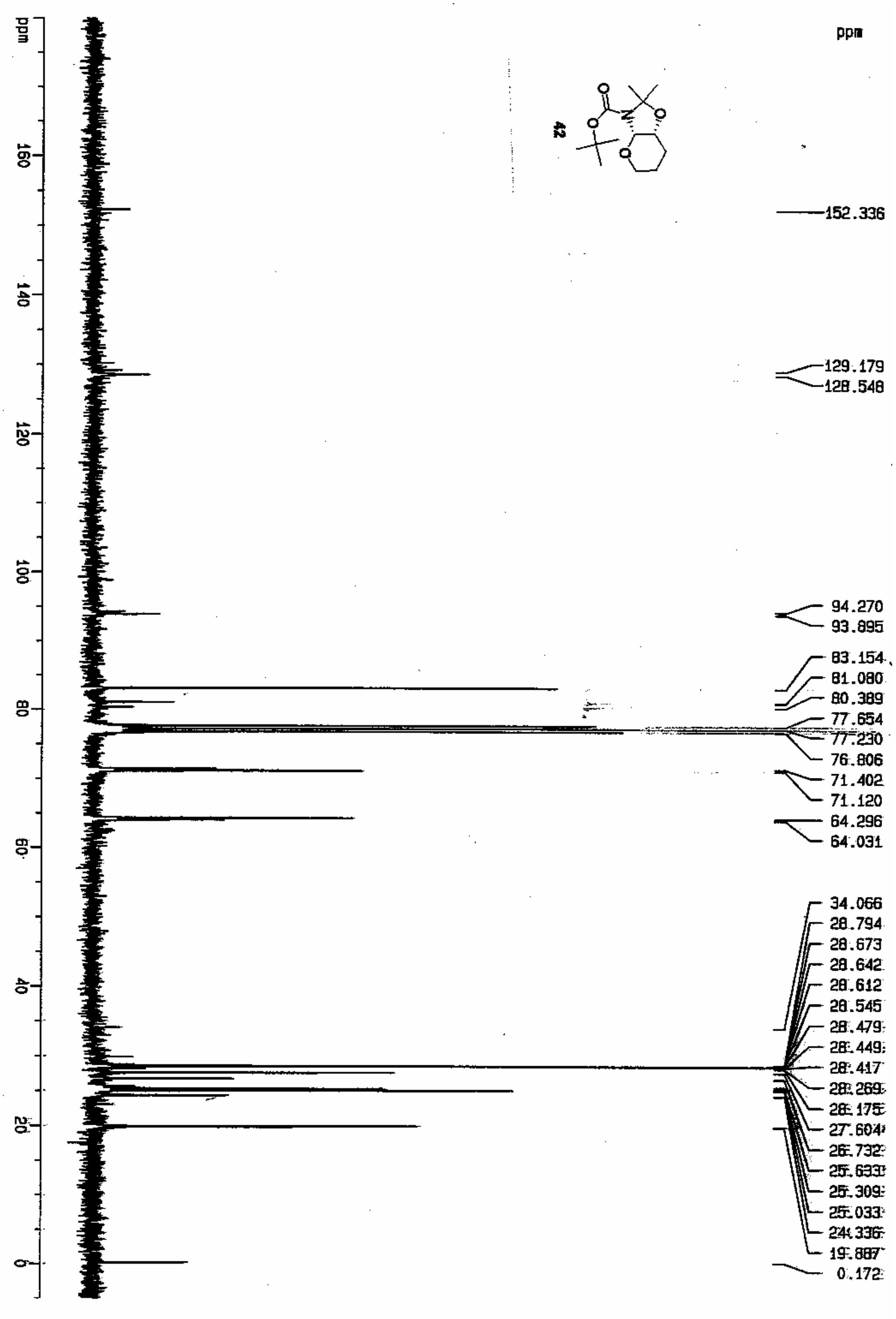

ppm
160
140
120
100
80
60
40
20
ppm
O
O
N
O
OTHP
41
138.115
129.868
129.460
128.681
128.443
126.635
98.780
79.944
79.189
77.554
77.328
77.130
76.707
66.983
63.754
62.375
39.998
30.782
28.667
27.324
25.749
25.558
19.694

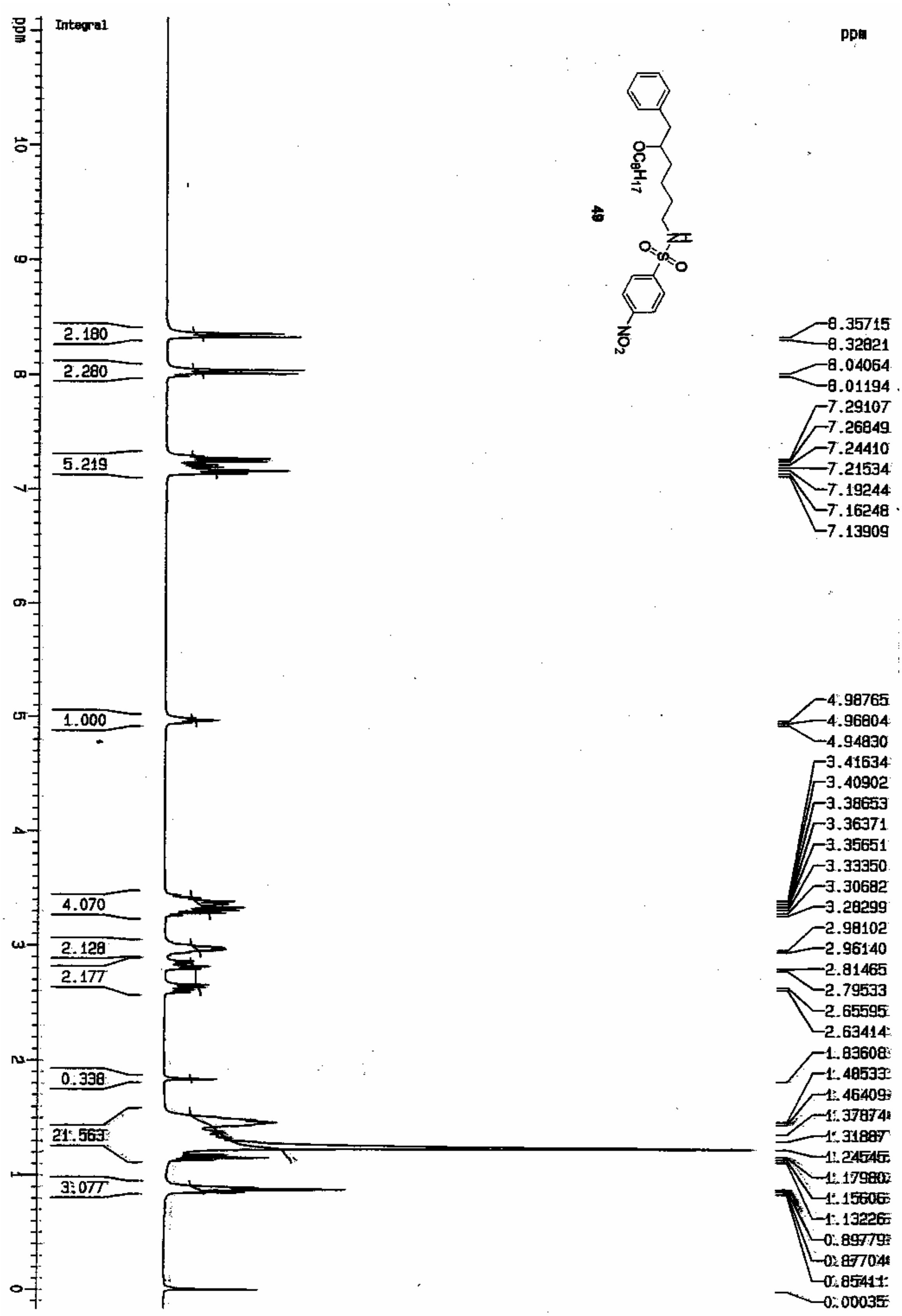

ppm
Integral
ppm
9
8
7
6
5
4
3
2
1
0
9.017
1.013
0.341
0.55
0.908
0.418
1.653
1.319
1.308
1.641
1.907
36.674
7.25724
7.24900
7.23732
7.18975
4.53275
4.50121
4.49065
4.04503
3.78256
3.75304
3.60910
3.59124
3.48289
3.24759
2.89131
2.85230
2.83001
2.35987
2.04735
1.73791
1.55616
1.54472
1.50472
1.45156
1.34081
41a
O
O
N
O
OTHP

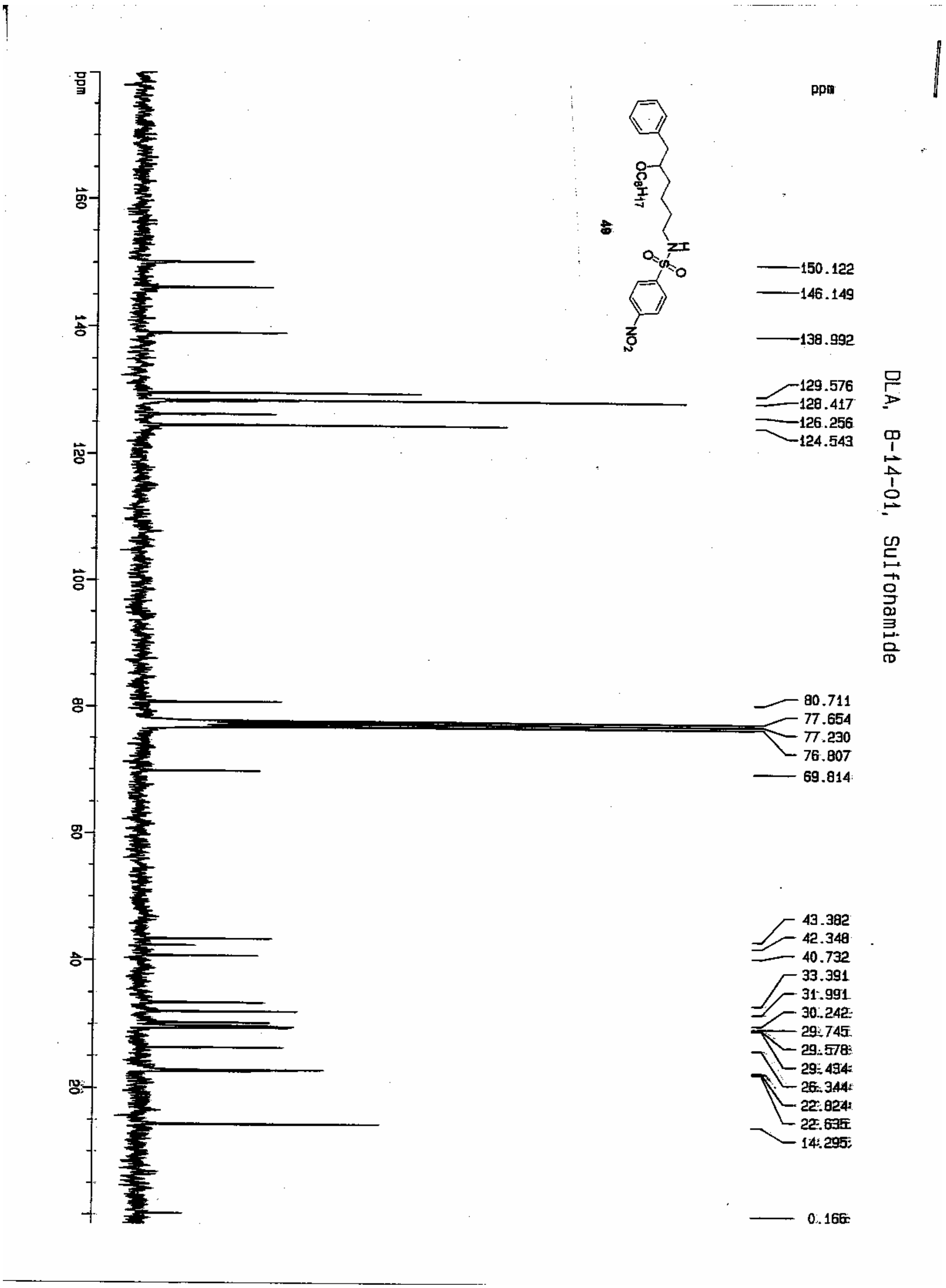


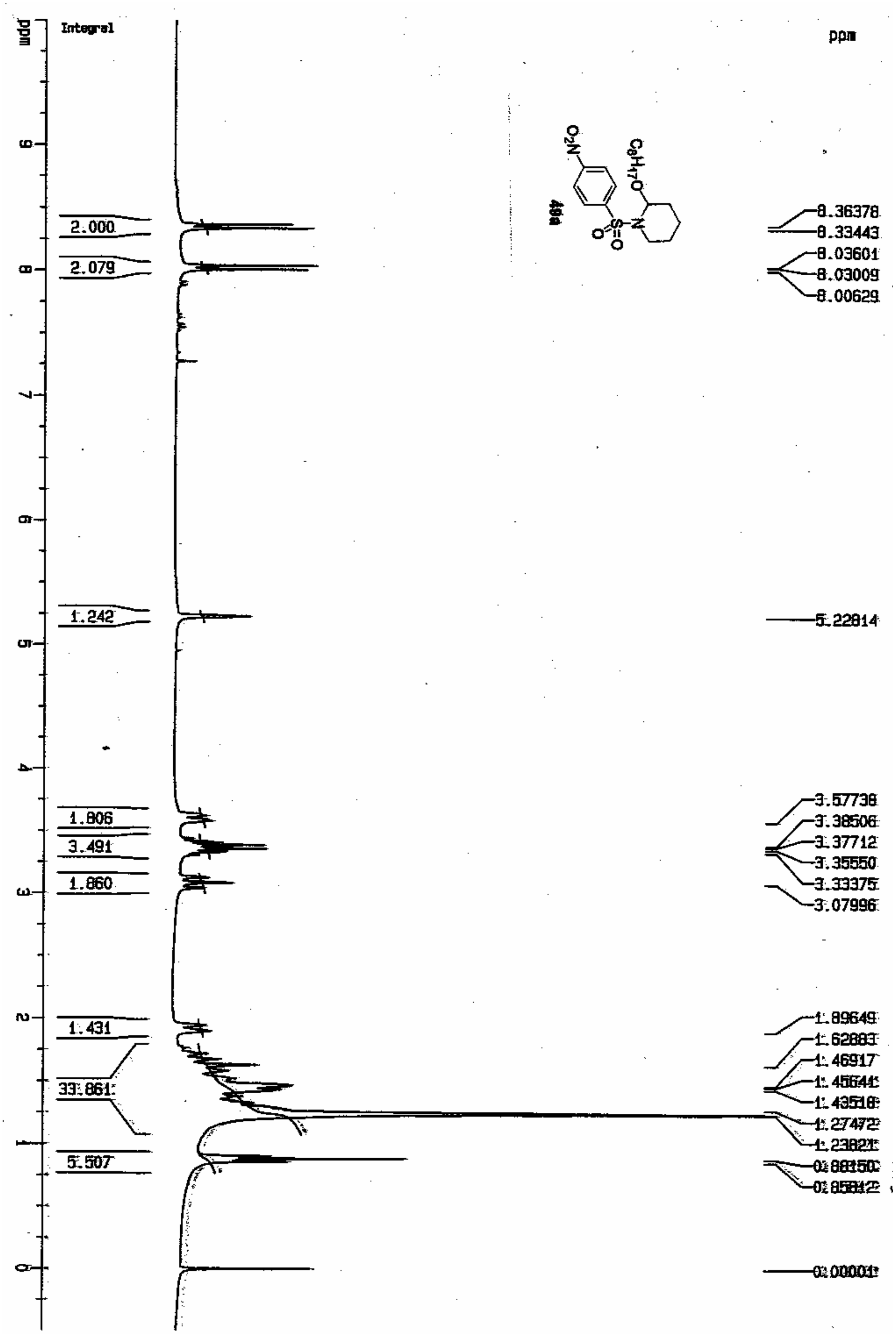
ppm
160
140
120
100
80
60
40
20
OTHP
41a
ppm
152.179
151.864
149.390
139.319
138.034
129.947
129.565
129.473
129.212
128.591
128.404
128.353
126.578
126.241
126.099
125.477
112.171
98.823
98.712
92.881
92.290
80.024
79.641
77.655
77.515
77.465
77.231
76.808
67.116
67.052
63.838
62.397
62.229
62.114
60.927
60.750
46.882
36.621
36.007
30.853
30.791
28.750
28.598
28.500
28.195
27.610
27.391
26.820
26.733
26.428
26.349
25.640
25.088
23.888
21.645
19.622
19.528

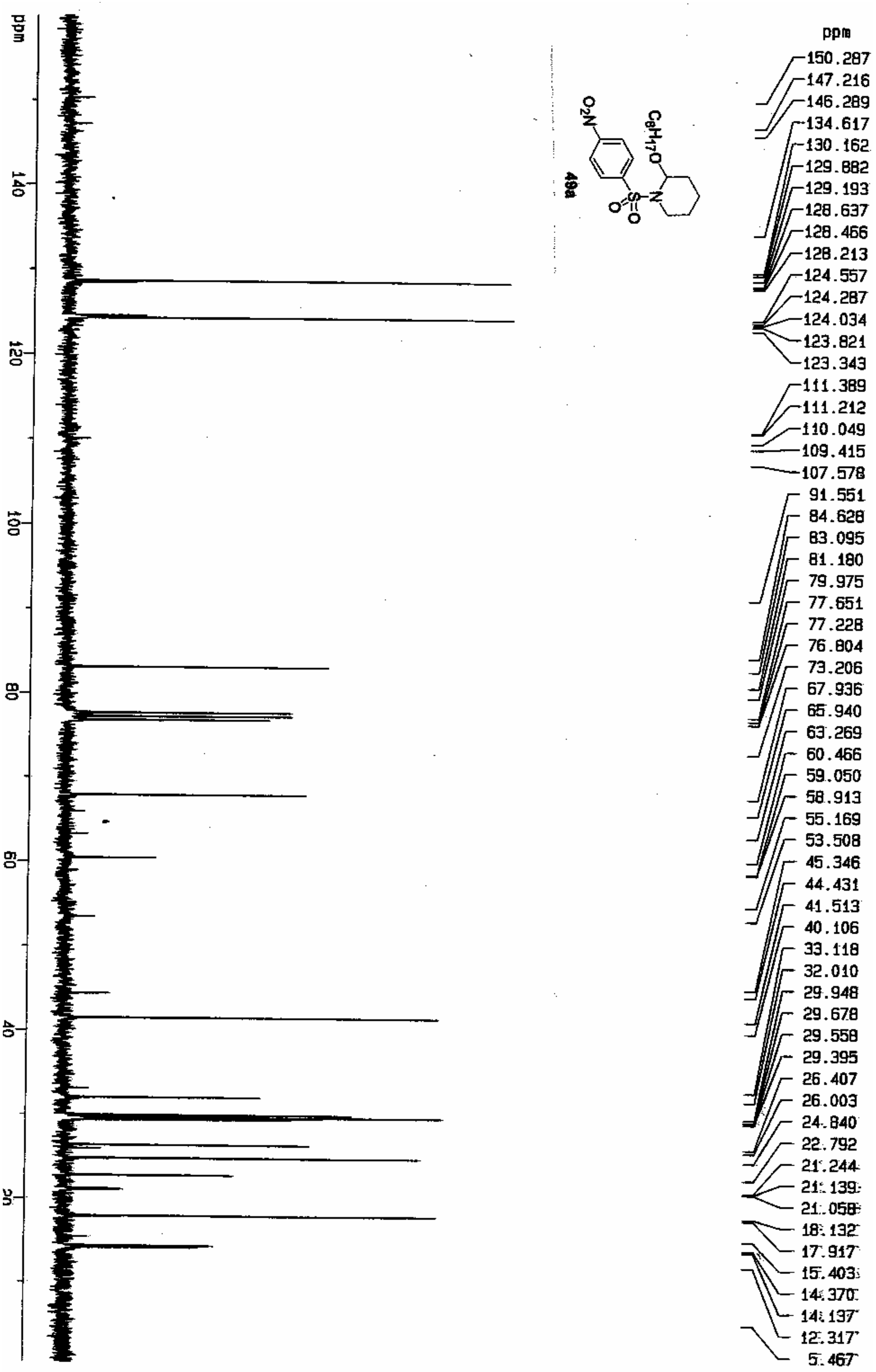

Integral
ppm
42
1.000
1.671
2.255
2.275
2.485
8.696
7.857
33.647
5.15595
3.97167
3.96227
3.91987
3.87948
3.47443
3.43822
3.40062
2.08832
1.84190
1.67815
1.58211
1.54880
1.52012
1.48978
9
8
7
6
5
4
3
2
1
0


ppm
160
140
120
100
80
60
40
20
0
ppm
42
O
O
N
O
O
O
152.336
129.179
128.548
94.270
93.895
83.154
81.080
80.389
77.654
77.230
76.806
71.402
71.120
64.296
64.031
34.066
28.794
28.673
28.642
28.612
28.545
28.479
28.449
28.417
28.269
28.175
27.604
26.732
25.633
25.309
25.033
24.336
19.887
0.172

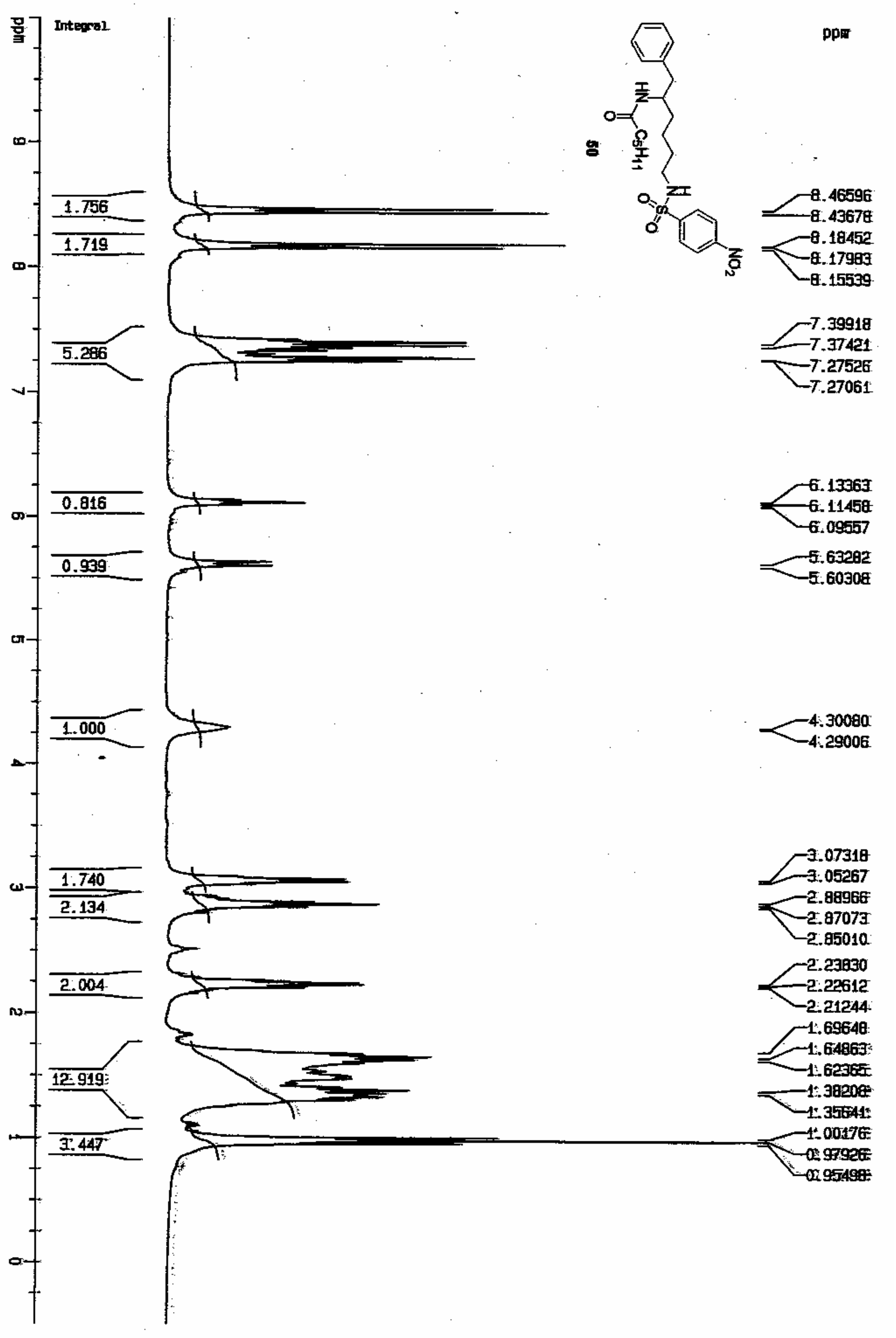

Integral
ppm
OC8H17
49
NO2
2.180
2.280
5.219
1.000
4.070
2.128
2.177
0.338
21.563
3.077
8.35715
8.32821
8.04064
8.01194
7.29107
7.26849
7.24410
7.21534
7.19244
7.16248
7.13909
4.98765
4.96804
4.94830
3.41634
3.40902
3.38653
3.36371
3.35651
3.33350
3.30682
3.28299
2.98102
2.96140
2.81465
2.79533
2.65595
2.63414
1.83608
1.48533
1.46409
1.37874
1.31887
1.24545
1.17980
1.15606
1.13226
0.89779
0.87704
0.85411
0.00035
10
9
8
7
6
5
4
3
2
1
0

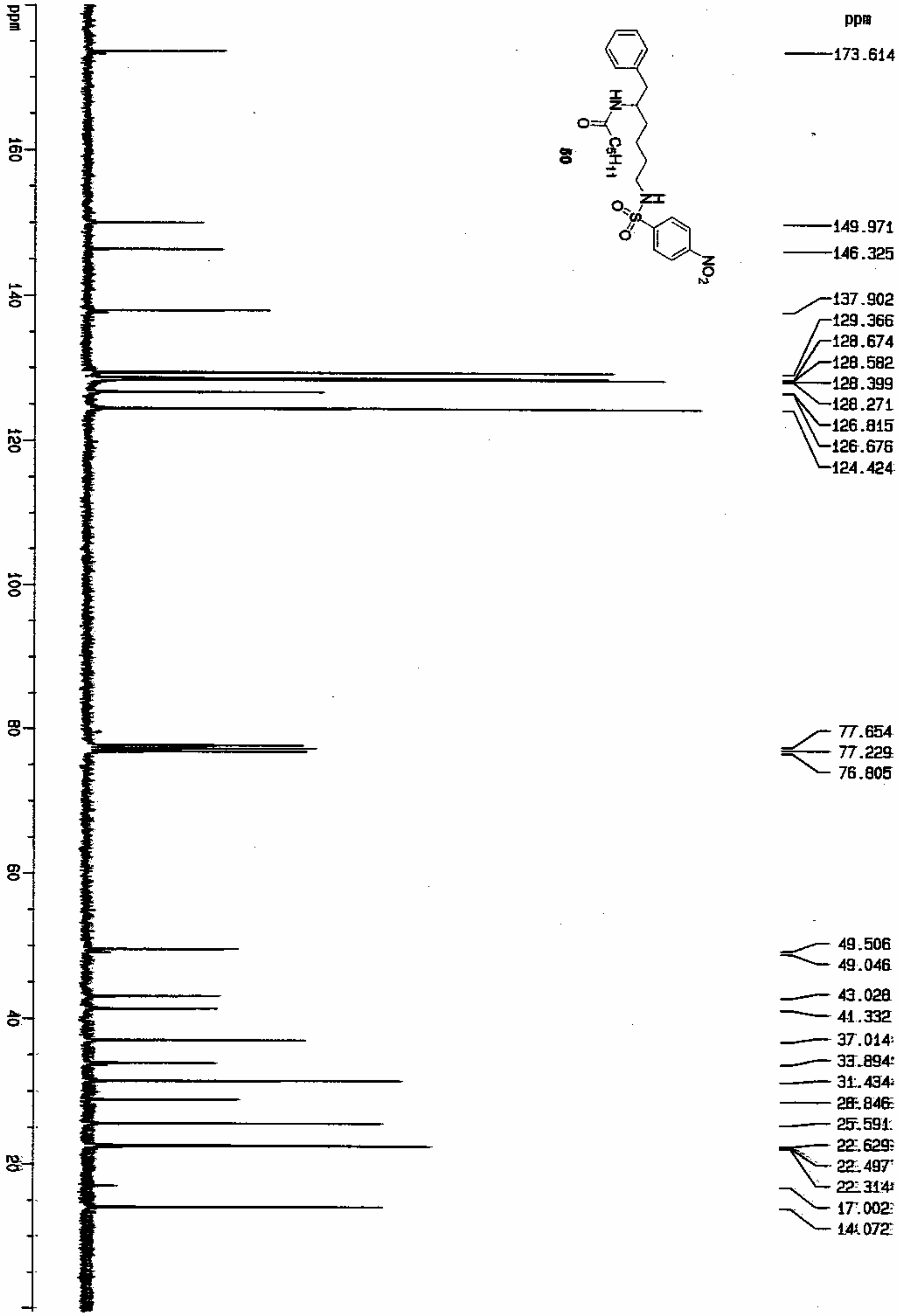

DLA, 8-14-01, Sulfonamide
49
OC$_8$H$_{17}$
H
N
S
O
O
NO$_2$
ppm
150.122
146.149
138.992
129.576
128.417
126.256
124.543
80.711
77.654
77.230
76.807
69.814
43.382
42.348
40.732
33.391
31.991
30.242
29.745
29.578
29.434
26.344
22.824
22.635
14.295
0.166
ppm
160
140
120
100
80
60
40
20

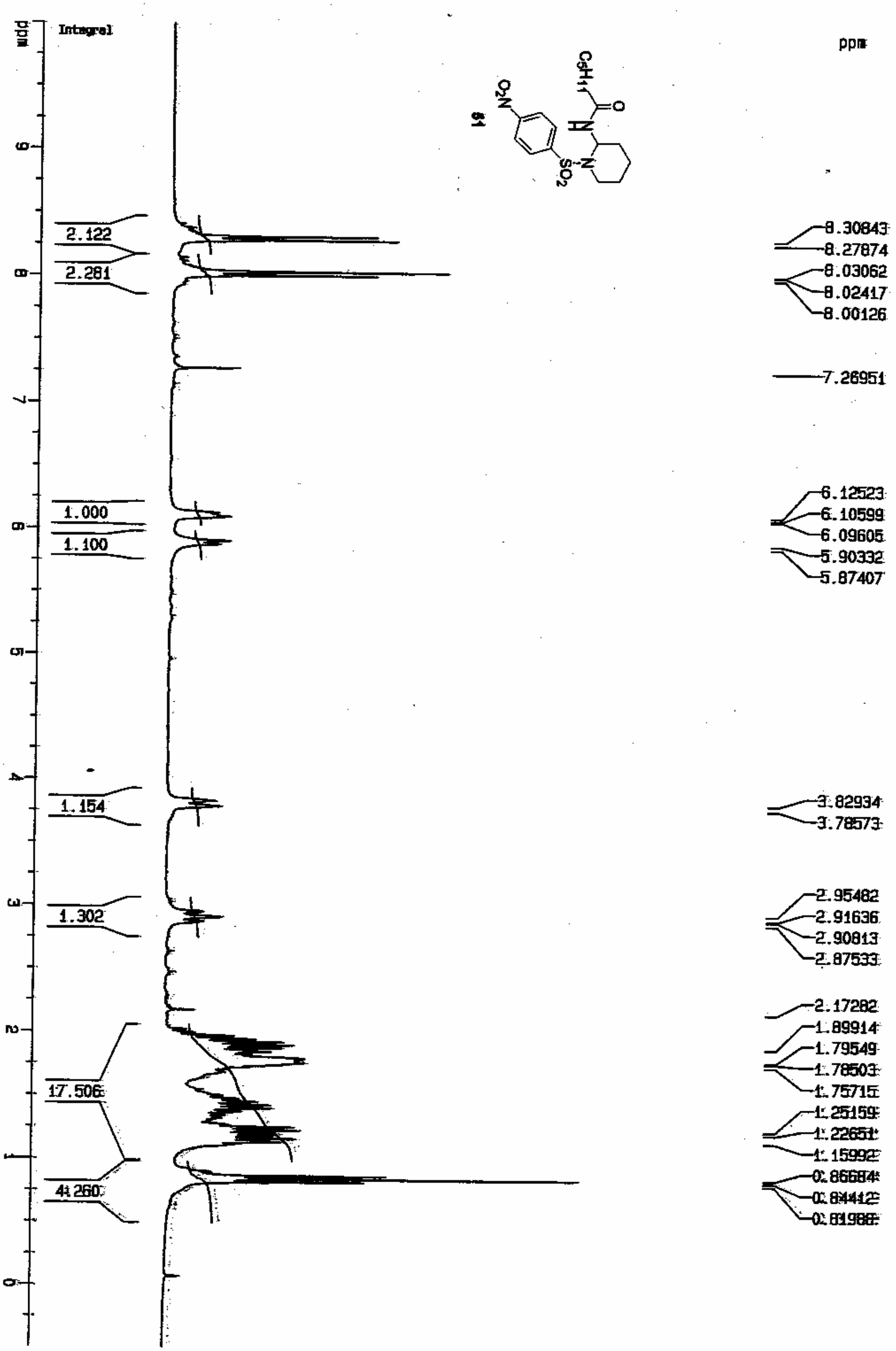

ppm
Integral
ppm
49a
O2N
C8H17O
2.000
2.079
1.242
1.806
3.491
1.860
1.431
33.861
5.507
8.36378
8.33443
8.03601
8.03009
8.00629
5.22814
3.57738
3.38506
3.37712
3.35550
3.33375
3.07996
1.89649
1.62883
1.46917
1.45644
1.43516
1.27472
1.23821
0.88150
0.85812
0.00001
9
8
7
6
5
4
3
2
1
0



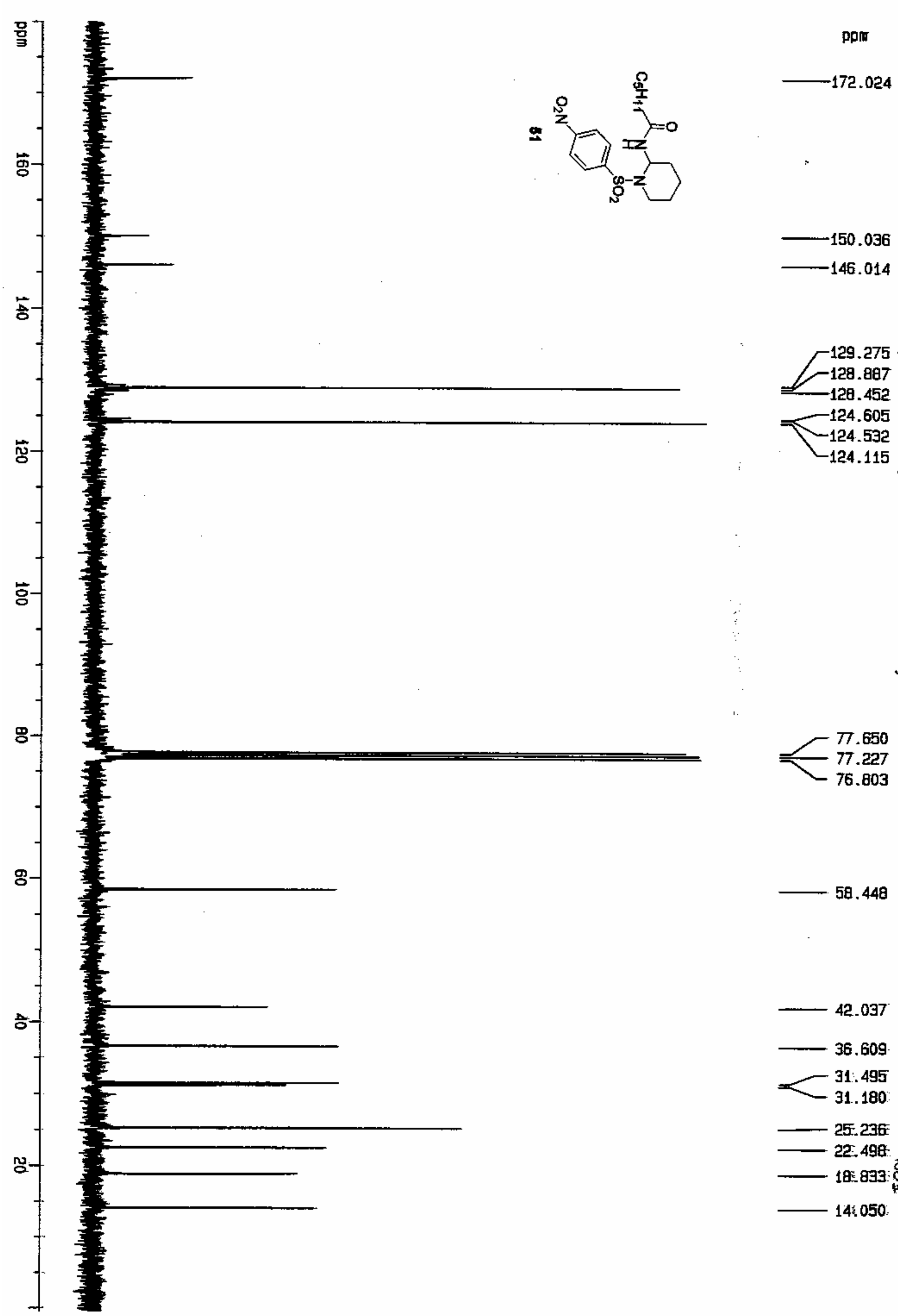
ppm
140
120
100
80
60
40
20
$C_8H_{17}O$
O_2N
N
S
O
O
49a
ppm
150.287
147.216
146.289
134.617
130.162
129.882
129.193
128.637
128.466
128.213
124.557
124.287
124.034
123.821
123.343
111.389
111.212
110.049
109.415
107.578
91.551
84.628
83.095
81.180
79.975
77.651
77.228
76.804
73.206
67.936
65.940
63.269
60.466
59.050
58.913
55.169
53.508
45.346
44.431
41.513
40.106
33.118
32.010
29.948
29.678
29.558
29.395
26.407
26.003
24.840
22.792
21.244
21.139
21.058
18.132
17.917
15.403
14.370
14.137
12.317
5.467

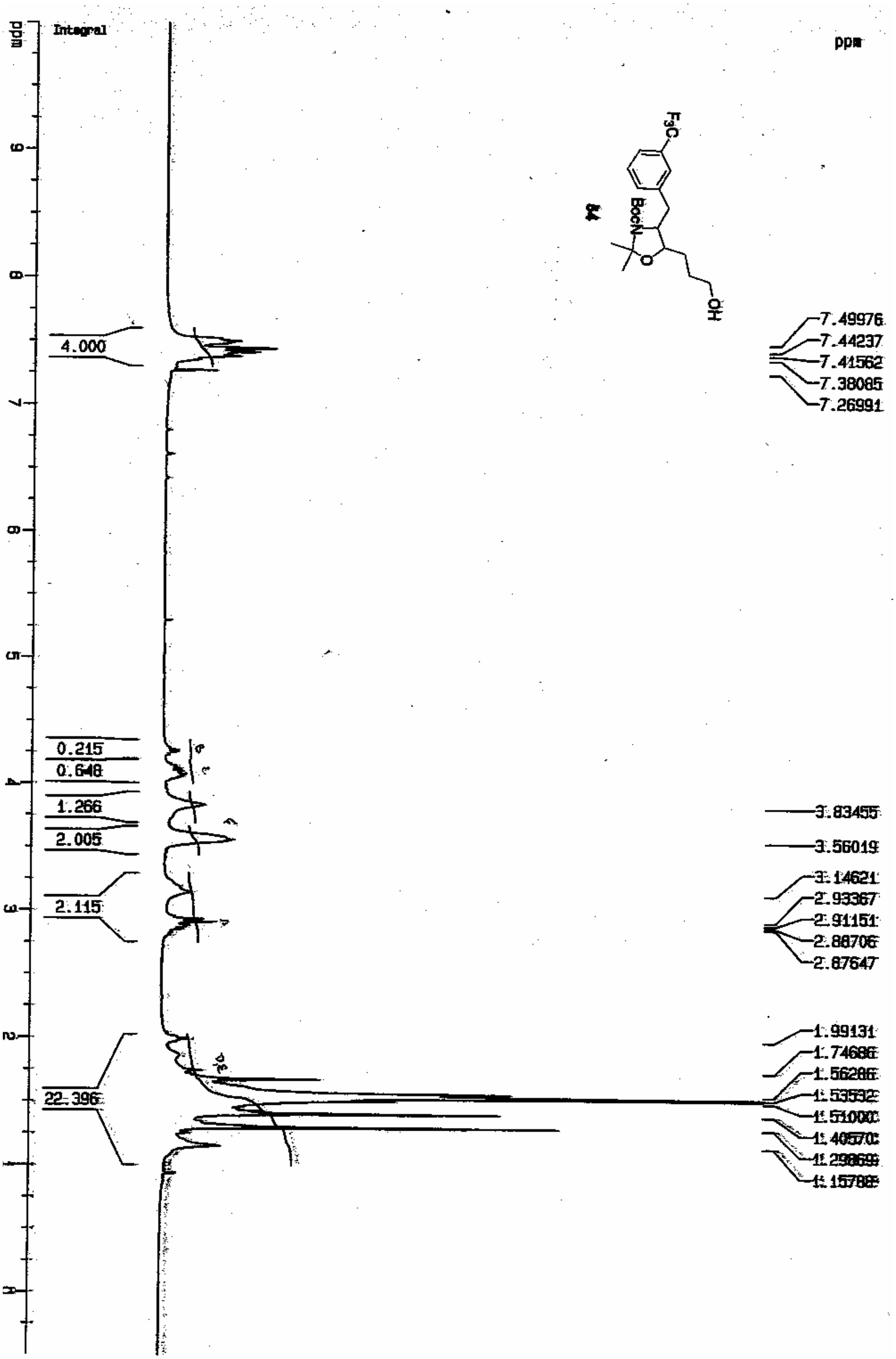

ppm
Integral
1.756
1.719
5.286
0.816
0.939
1.000
1.740
2.134
2.004
12.919
3.447
HN
O
C5H11
50
N
H
S
O
O
NO2
ppm
8.46596
8.43678
8.18452
8.17983
8.15539
7.39918
7.37421
7.27526
7.27061
6.13363
6.11458
6.09557
5.63282
5.60308
4.30080
4.29006
3.07318
3.05267
2.88966
2.87073
2.85010
2.23830
2.22612
2.21244
1.69648
1.64863
1.62365
1.38208
1.35641
1.00176
0.97926
0.95498
9
8
7
6
5
4
3
2
1
0


ppm
160
140
120
100
80
60
40
20
HN
O
C_5H_{11}
60
H
N
O
S
O
NO_2
ppm
173.614
149.971
146.325
137.902
129.366
128.674
128.582
128.399
128.271
126.815
126.676
124.424
77.654
77.229
76.805
49.506
49.046
43.028
41.332
37.014
33.894
31.434
28.846
25.591
22.629
22.497
22.314
17.002
14.072

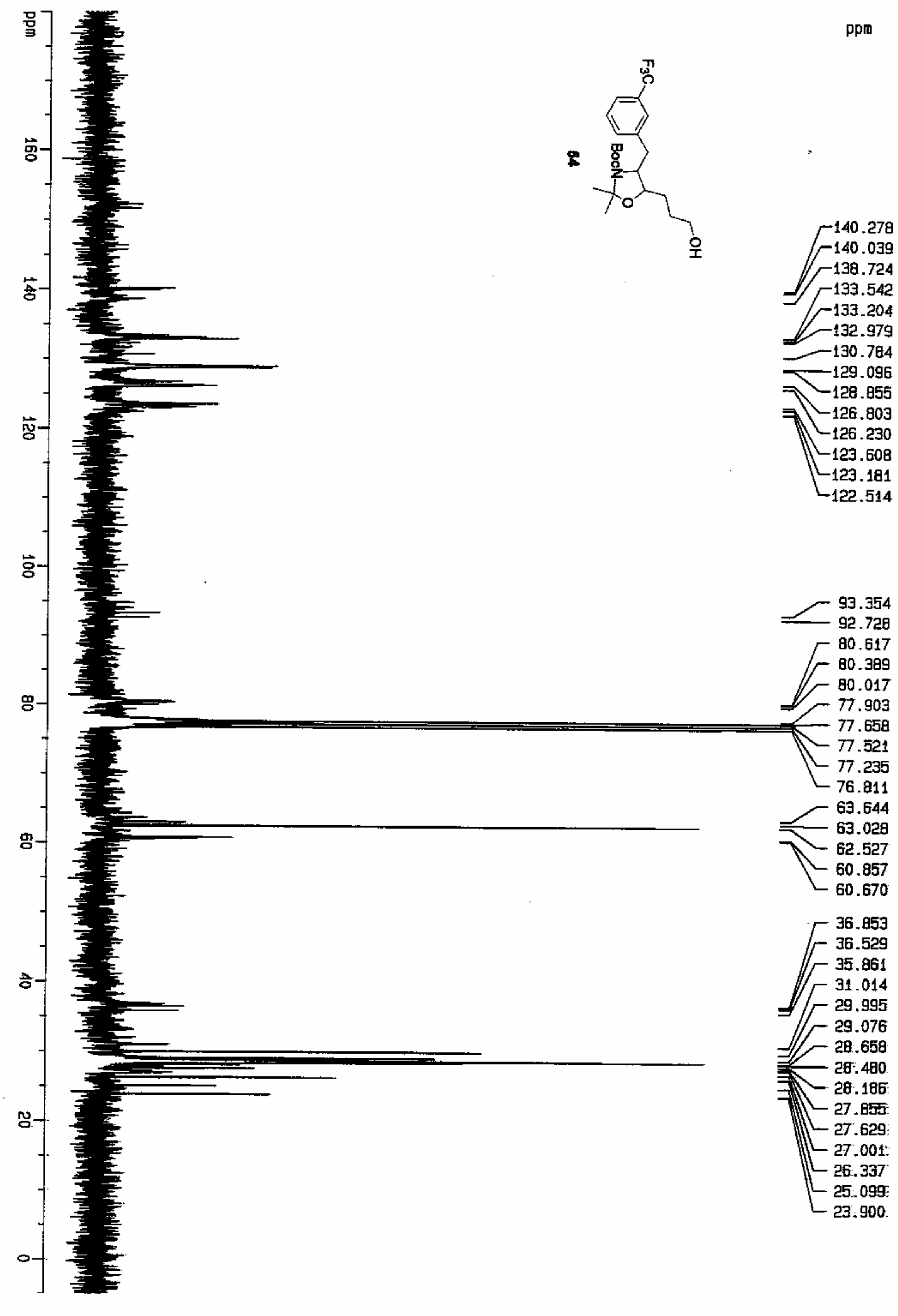

ppm
Integral
9
8
7
6
5
4
3
2
1
0
2.122
2.281
1.000
1.100
1.154
1.302
17.506
4.260
ppm
8.30843
8.27874
8.03062
8.02417
8.00126
7.26951
6.12523
6.10599
6.09605
5.90332
5.87407
3.82934
3.78573
2.95482
2.91636
2.90813
2.87533
2.17282
1.89914
1.79549
1.78503
1.75715
1.25159
1.22651
1.15992
0.86684
0.84412
0.81988
C_5H_{11}
O
N
H
N
SO_2
O_2N

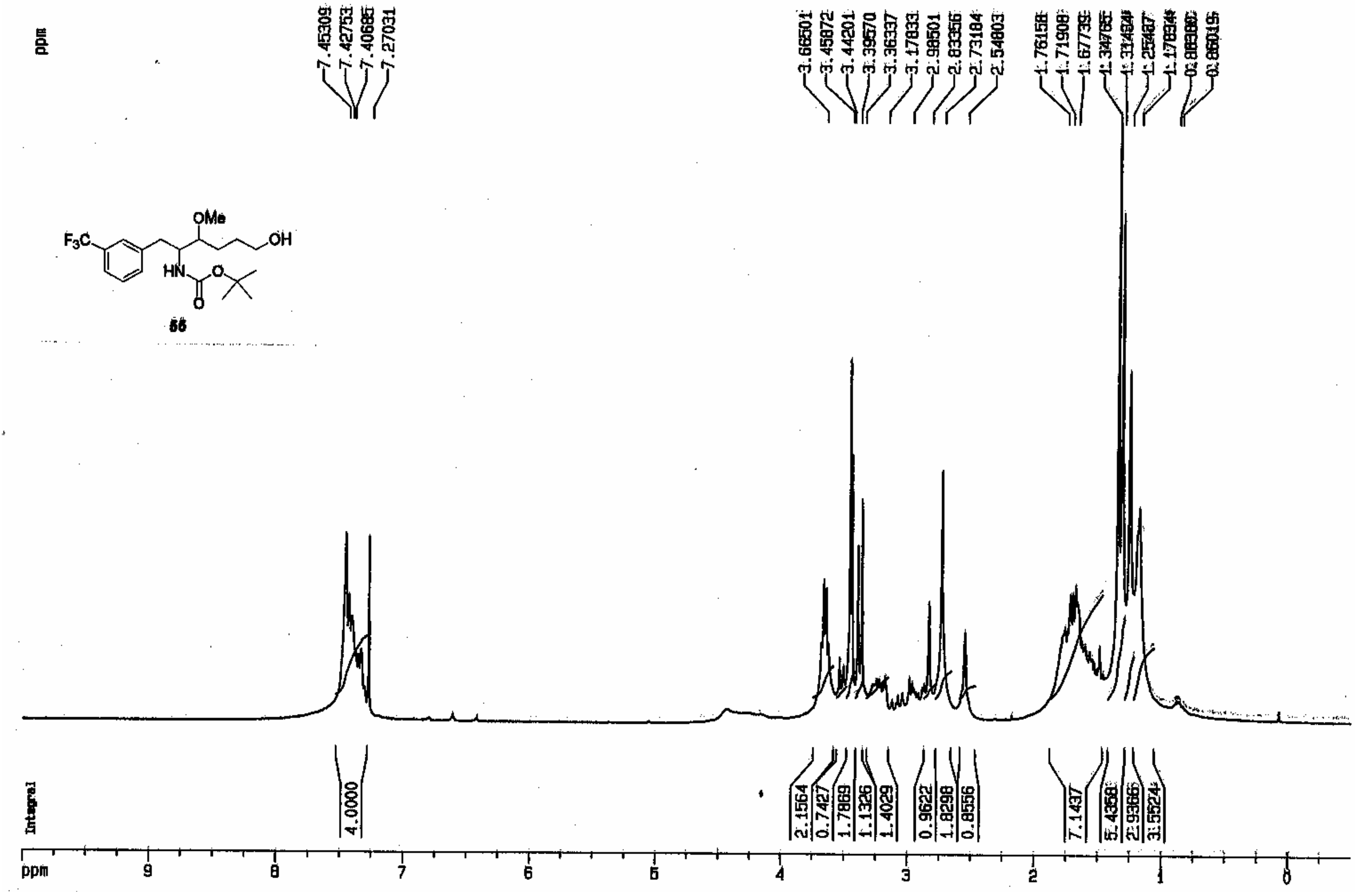
61


ppm
160
140
120
100
80
60
40
20
ppm
172.024
150.036
146.014
129.275
128.887
128.452
124.605
124.532
124.115
77.650
77.227
76.803
58.448
42.037
36.609
31.495
31.180
25.236
22.498
18.833
14.050
C5H11
O
N
H
N
SO2
O2N
51

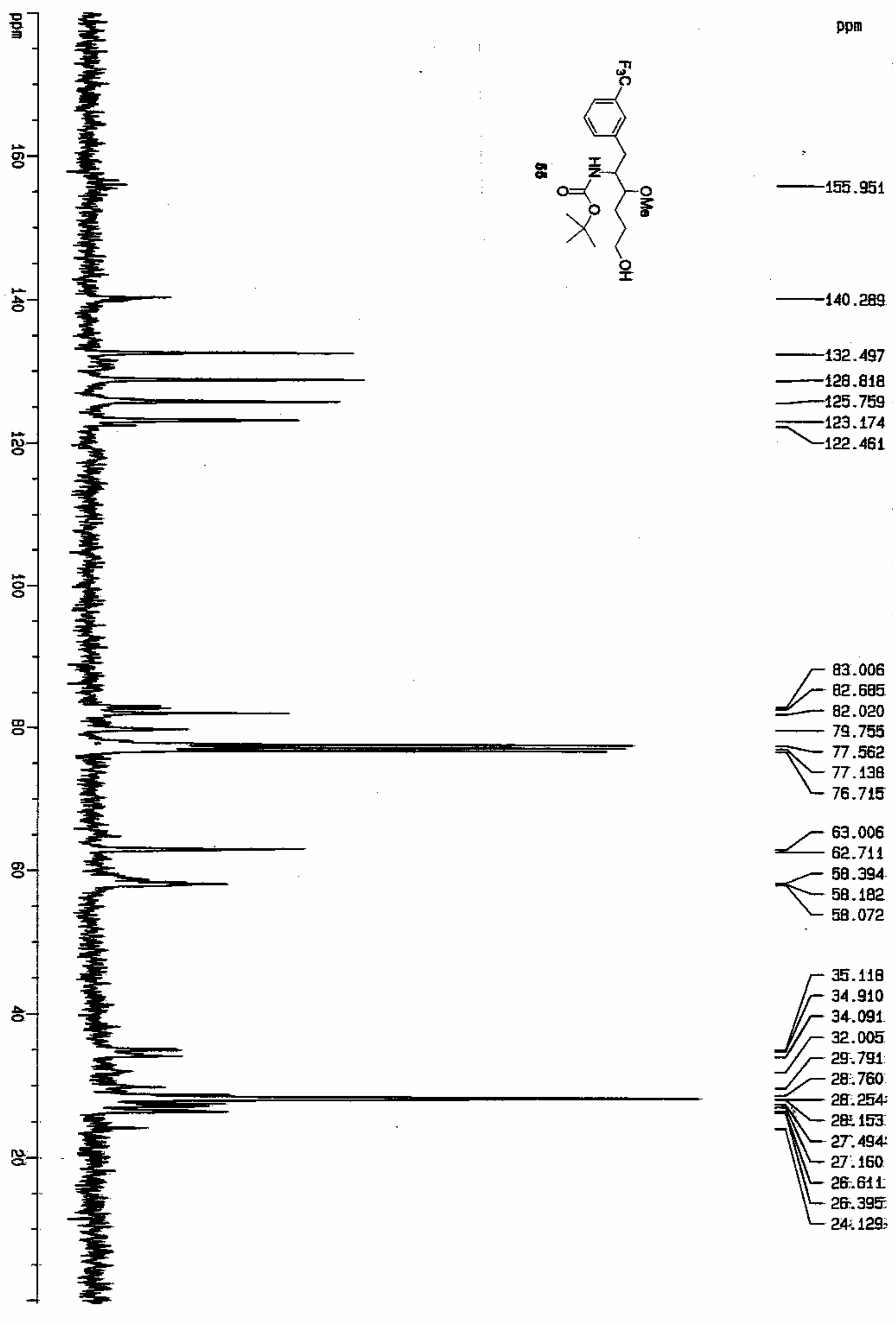


Integral
ppm
ppm
9
8
7
6
5
4
3
2
1
0
F3C
BocN
O
OH
84
4.000
0.215
0.648
1.266
2.005
2.115
22.396
7.49976
7.44237
7.41562
7.38085
7.26991
3.83455
3.56019
3.14621
2.93367
2.91151
2.88706
2.87647
1.99131
1.74686
1.56286
1.53532
1.51000
1.40570
1.29869
1.15788


ppm
160
140
120
100
80
60
40
20
0
ppm
F3C
BocN
O
OH
64
140.278
140.039
138.724
133.542
133.204
132.979
130.784
129.096
128.855
126.803
126.230
123.608
123.181
122.514
93.354
92.728
80.617
80.389
80.017
77.903
77.658
77.521
77.235
76.811
63.644
63.028
62.527
60.857
60.670
36.853
36.529
35.861
31.014
29.995
29.076
28.658
28.480
28.186
27.855
27.629
27.001
26.337
25.099
23.900

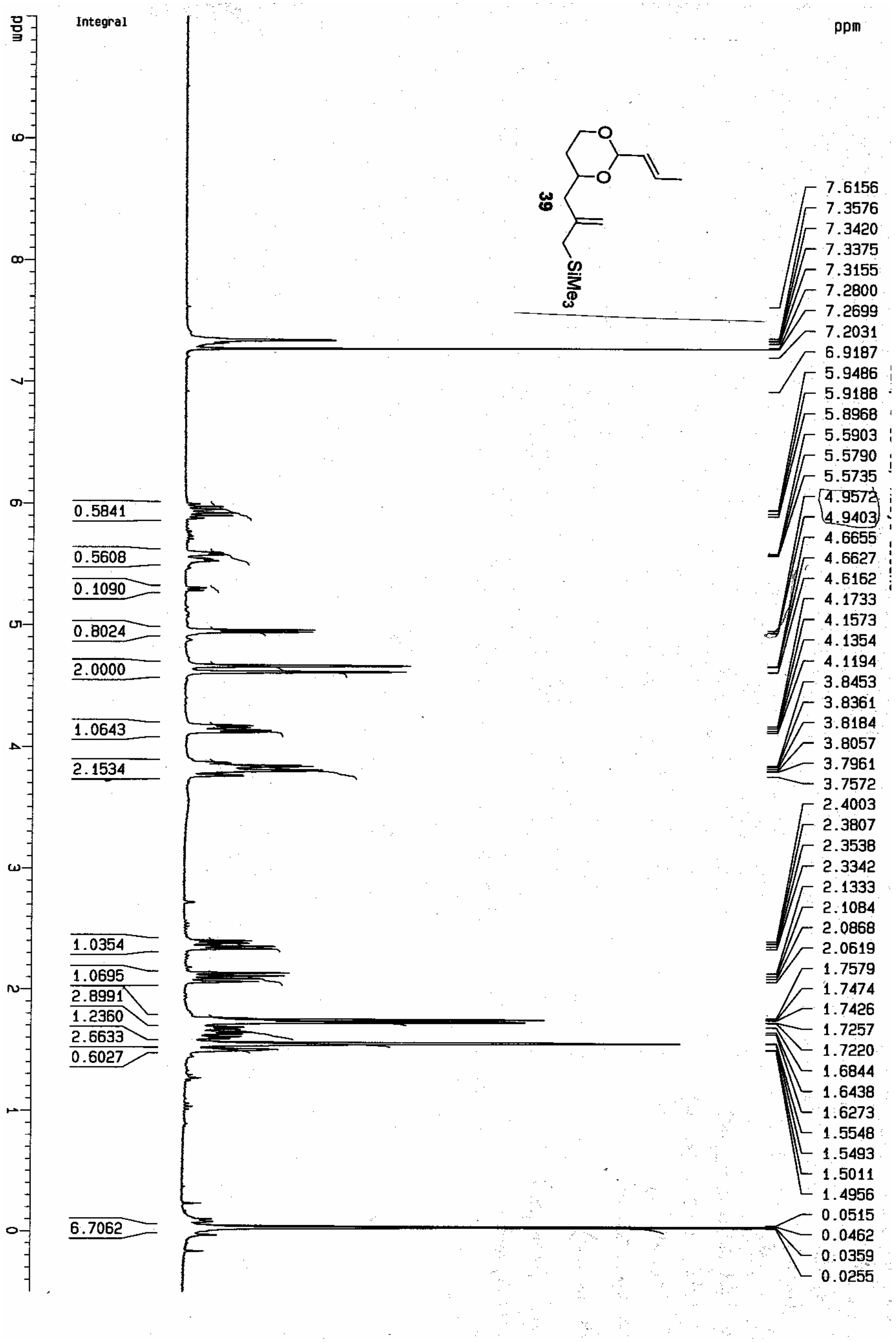

ppm
7.45309
7.42753
7.40685
7.27031
3.66501
3.45872
3.44201
3.39570
3.36337
3.17833
2.98501
2.83356
2.73184
2.54803
1.76158
1.71908
1.67739
1.34765
1.31434
1.25487
1.17834
0.88380
0.86019
F3C
OMe
OH
HN
O
O
Integral
4.0000
2.1564
0.7427
1.7869
1.1326
1.4029
0.9622
1.8298
0.8556
7.1437
5.4358
2.9366
3.5524
ppm
9
8
7
6
5
4
3
2
1
0

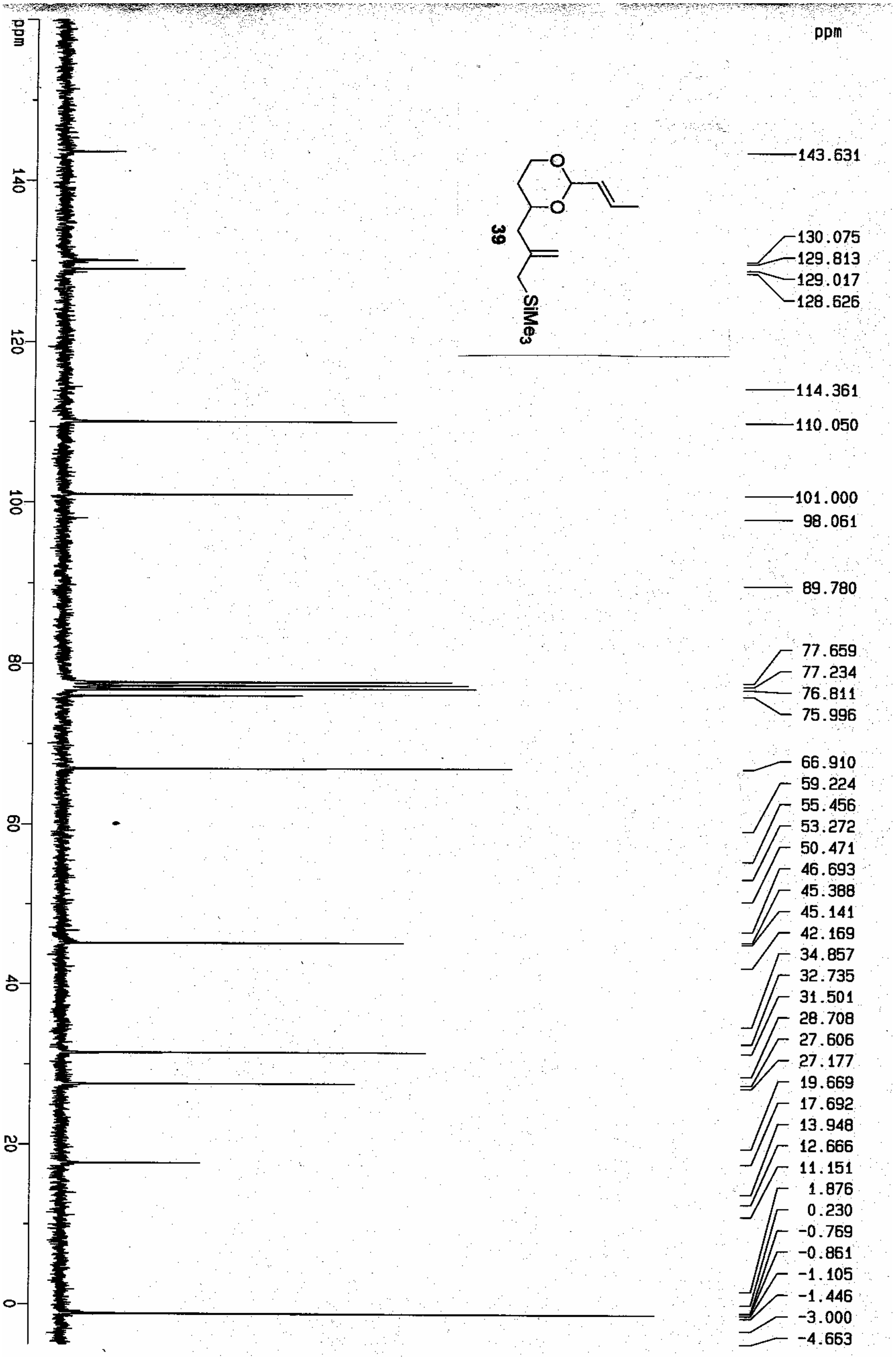
56

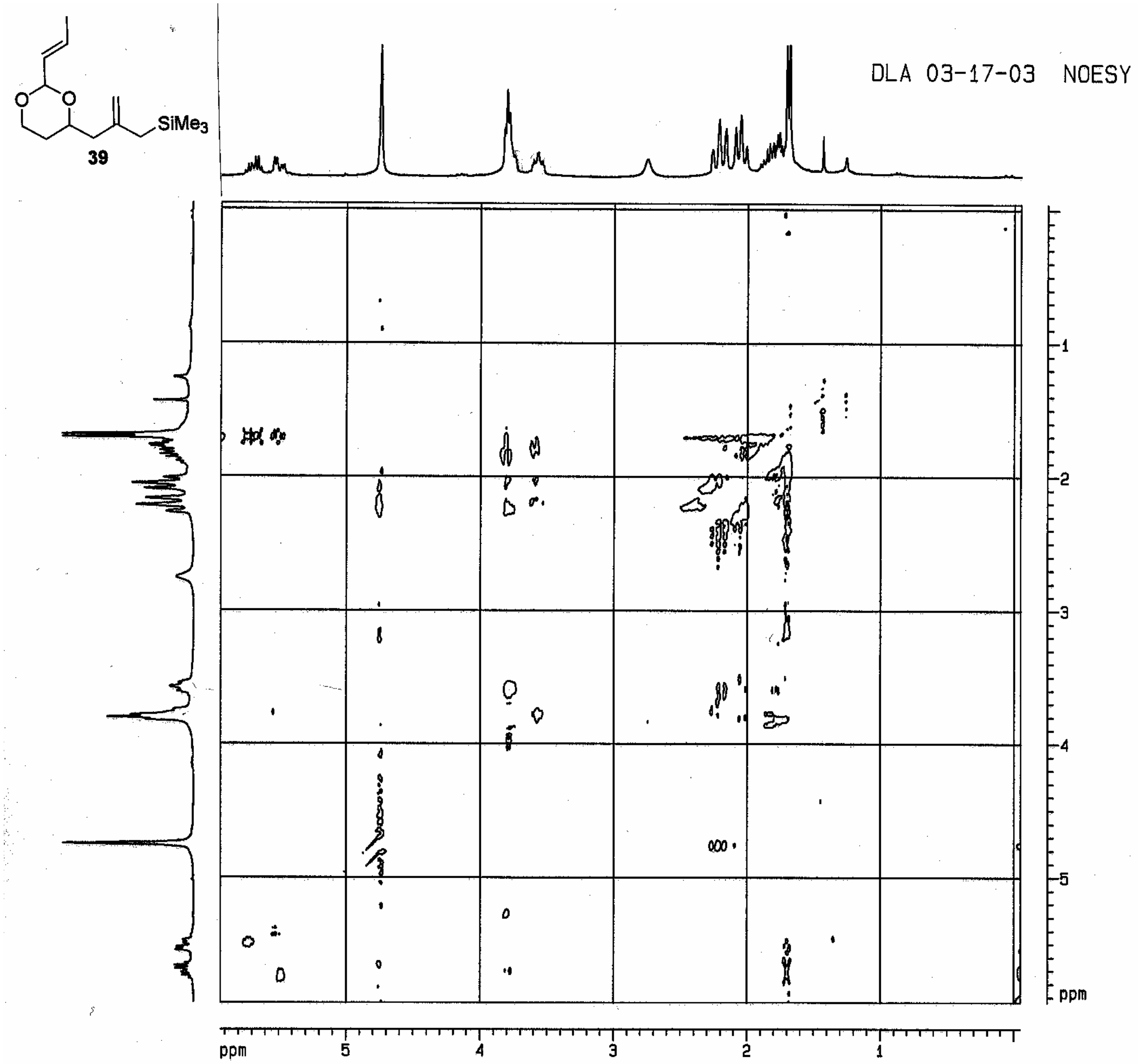
ppm
F3C
HN
OMe
OH
O
O
55
155.951
140.289
132.497
128.818
125.759
123.174
122.461
83.006
82.685
82.020
79.755
77.562
77.138
76.715
63.006
62.711
58.394
58.182
58.072
35.118
34.910
34.091
32.005
29.791
28.760
28.254
28.153
27.494
27.160
26.611
26.395
24.129
160
140
120
100
80
60
40
20
ppm

APPENDIX B

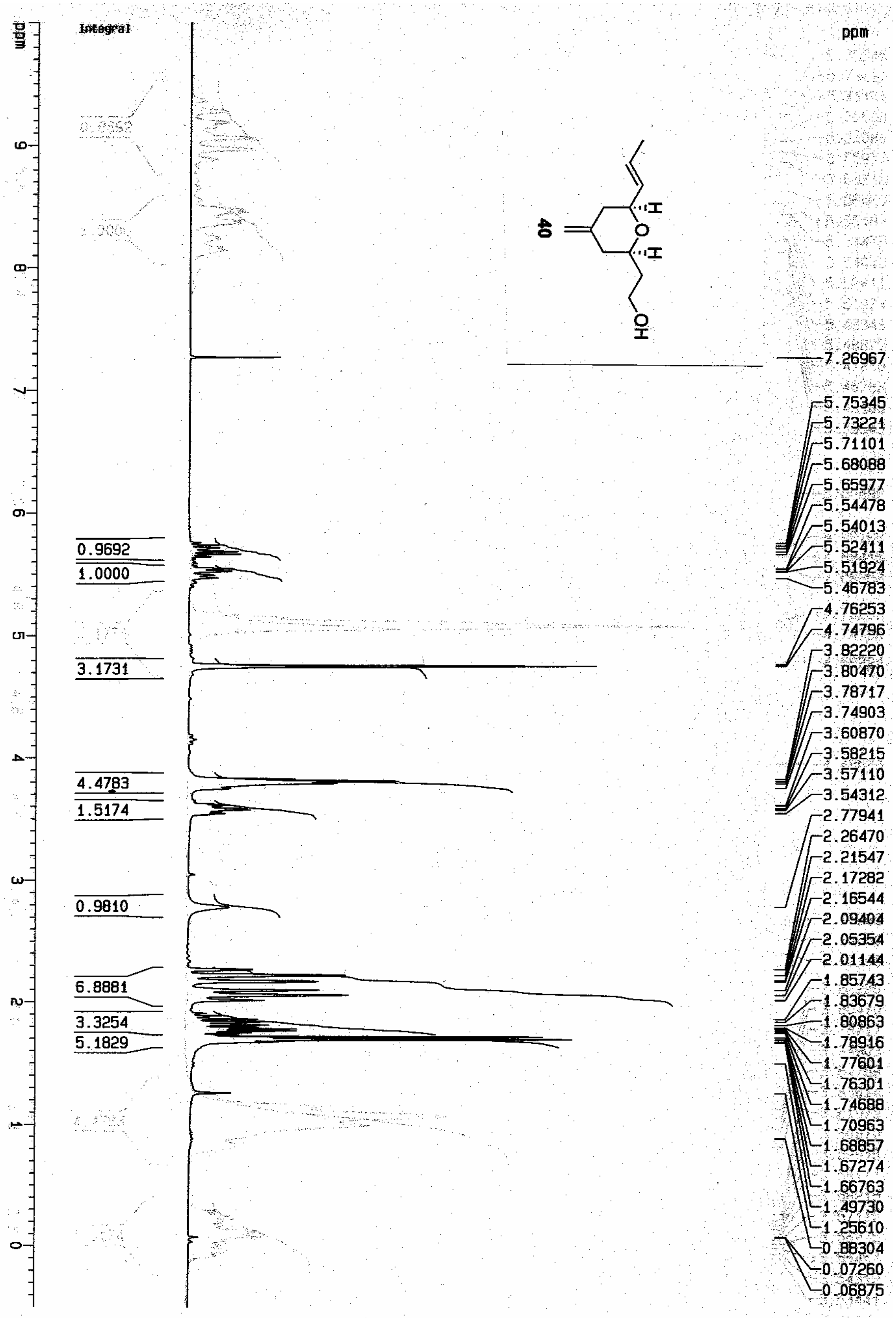
The aqueous Prins reaction (Supporting Information)


ppm
Integral
ppm
39
SiMe3
O
O
0.5841
0.5608
0.1090
0.8024
2.0000
1.0643
2.1534
1.0354
1.0695
2.8991
1.2360
2.6633
0.6027
6.7062
7.6156
7.3576
7.3420
7.3375
7.3155
7.2800
7.2699
7.2031
6.9187
5.9486
5.9188
5.8968
5.5903
5.5790
5.5735
4.9572
4.9403
4.6655
4.6627
4.6162
4.1733
4.1573
4.1354
4.1194
3.8453
3.8361
3.8184
3.8057
3.7961
3.7572
2.4003
2.3807
2.3538
2.3342
2.1333
2.1084
2.0868
2.0619
1.7579
1.7474
1.7426
1.7257
1.7220
1.6844
1.6438
1.6273
1.5548
1.5493
1.5011
1.4956
0.0515
0.0462
0.0359
0.0255
9
8
7
6
5
4
3
2
1
0

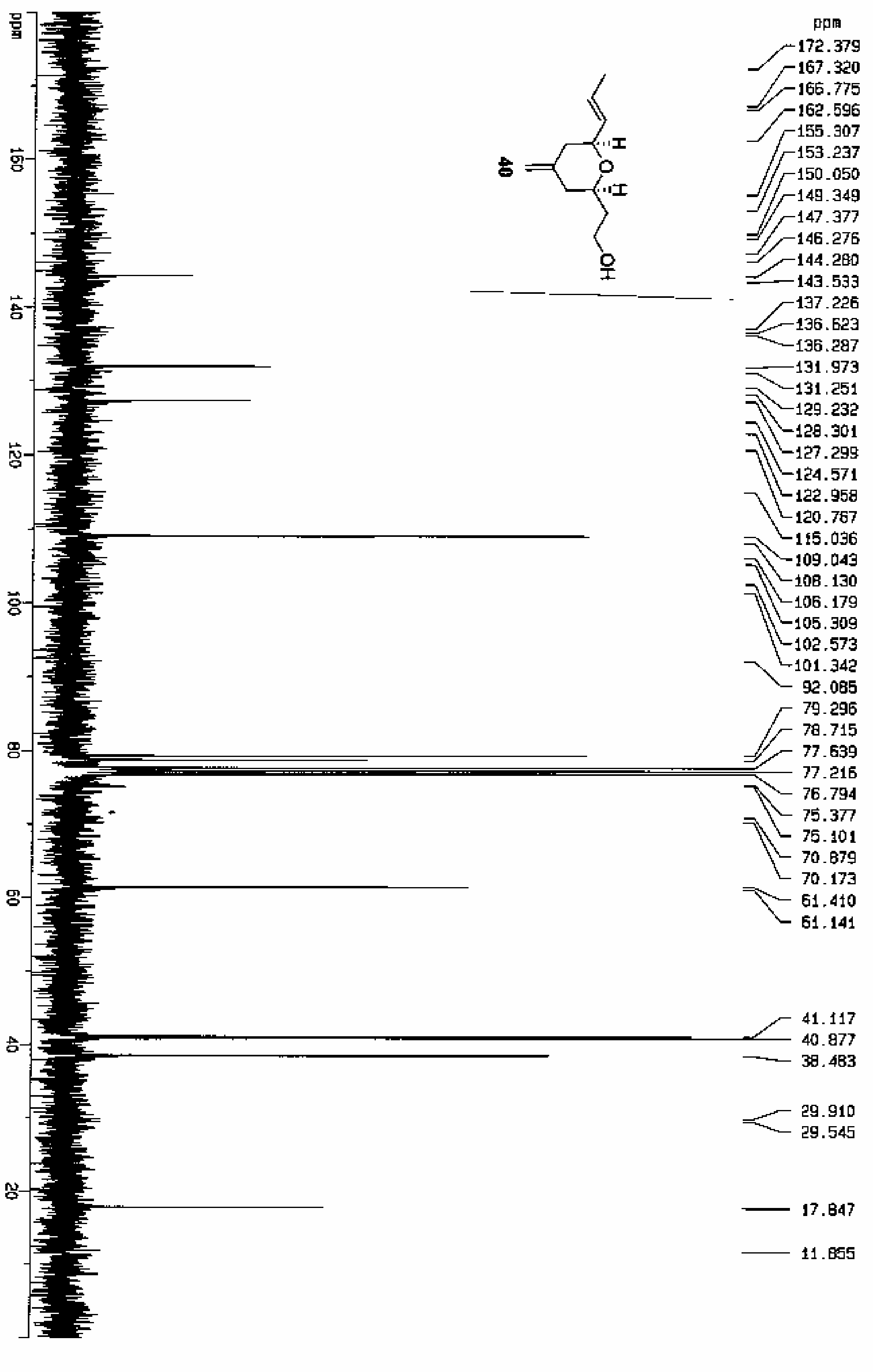
ppm
140
120
100
80
60
40
20
0
ppm
39
SiMe3
143.631
130.075
129.813
129.017
128.626
114.361
110.050
101.000
98.061
89.780
77.659
77.234
76.811
75.996
66.910
59.224
55.456
53.272
50.471
46.693
45.388
45.141
42.169
34.857
32.735
31.501
28.708
27.606
27.177
19.669
17.692
13.948
12.666
11.151
1.876
0.230
-0.769
-0.861
-1.105
-1.446
-3.000
-4.663


39

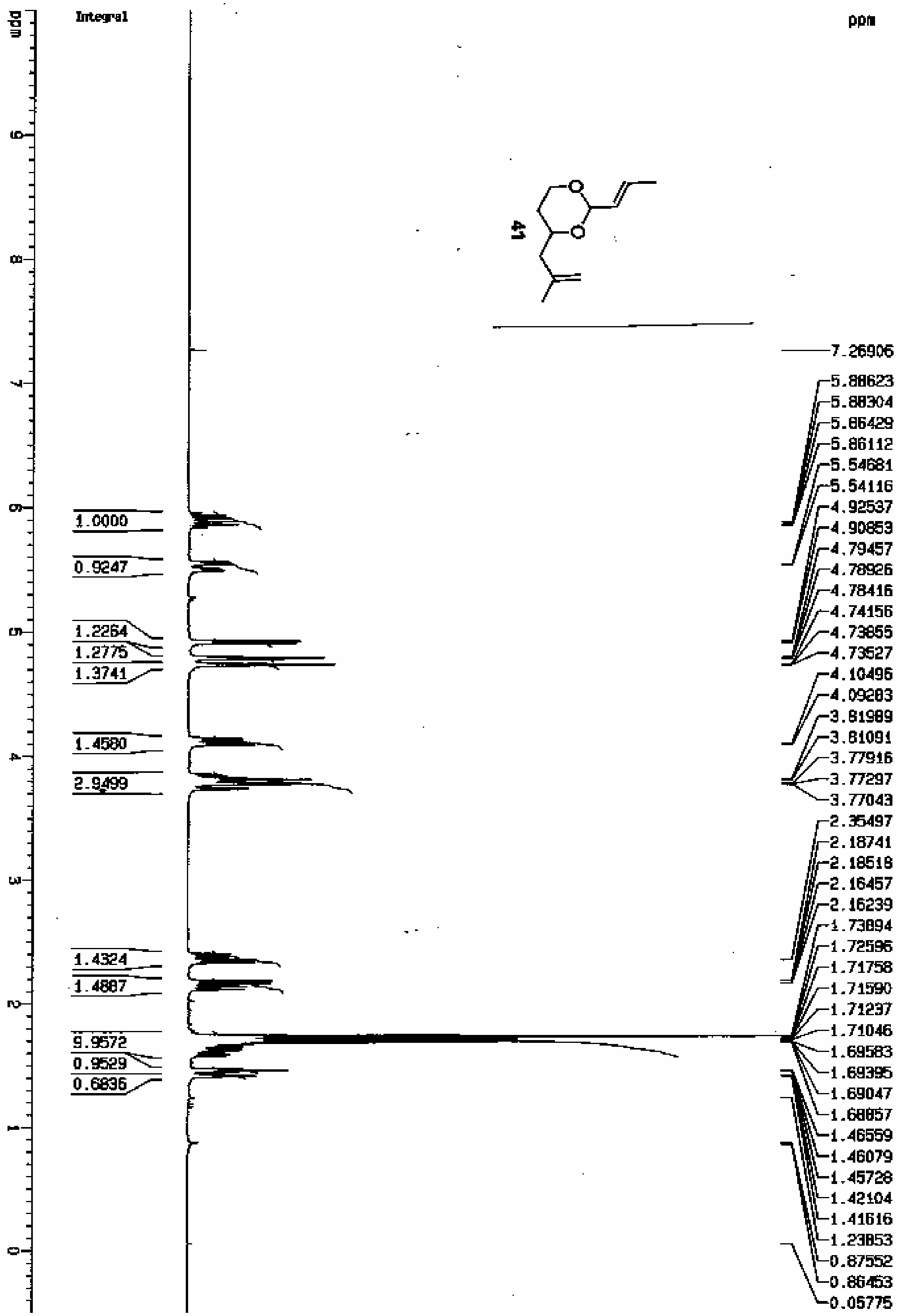
```
          Current Data Parameters
NAME             dla031703
EXPNO                    2
PROCNO                   1

       F2 - Acquisition Parameters
Date_             20030317
Time                 10.16
INSTRUM              spect
PROBHD       5 mm Multinu
PULPROG            noesytp
TD                    1024
SOLVENT              CDCl3
NS                      32
DS                       8
SWH               1795.977 Hz
FIDRES            1.753884 Hz
AQ               0.2851316 sec
RG                     250
DW                 278.400 usec
DE                    6.00 usec
TE                   300.0 K
d0              0.00000300 sec
D1              1.00000000 sec
P1                    8.10 usec
SFO1           300.0859003 MHz
NUC1                    1H
PL1                  -6.00 dB
D8              0.60000002 sec
IN0             0.00027840 sec

       F1 - Acquisition parameters
ND0                      2
TD                     214
SFO1              300.0859 MHz
FIDRES            8.392416 Hz
SW                   5.985 ppm

       F2 - Processing parameters
SI                    1024
SF             300.0850170 MHz
WDW                   SINE
SSB                      2
LB                    0.00 Hz
GB                       0
PC                    0.10

       F1 - Processing parameters
SI                     512
MC2                   TPPI
SF             300.0850155 MHz
WDW                   SINE
SSB                      2
LB                    0.00 Hz
GB                       0

         2D NMR plot parameters
CX2                  15.00 cm
CX1                  15.00 cm
F2PLO                5.936 ppm
F2LO               1781.24 Hz
F2PHI               -0.049 ppm
F2HI                -14.74 Hz
F1PLO                5.941 ppm
F1LO               1782.78 Hz
F1PHI               -0.044 ppm
F1HI                -13.20 Hz
F2PPMCM            0.39899 ppm/cm
F2HZCM           119.73181 Hz/cm
F1PPMCM            0.39899 ppm/cm
F1HZCM           119.73181 Hz/cm
```



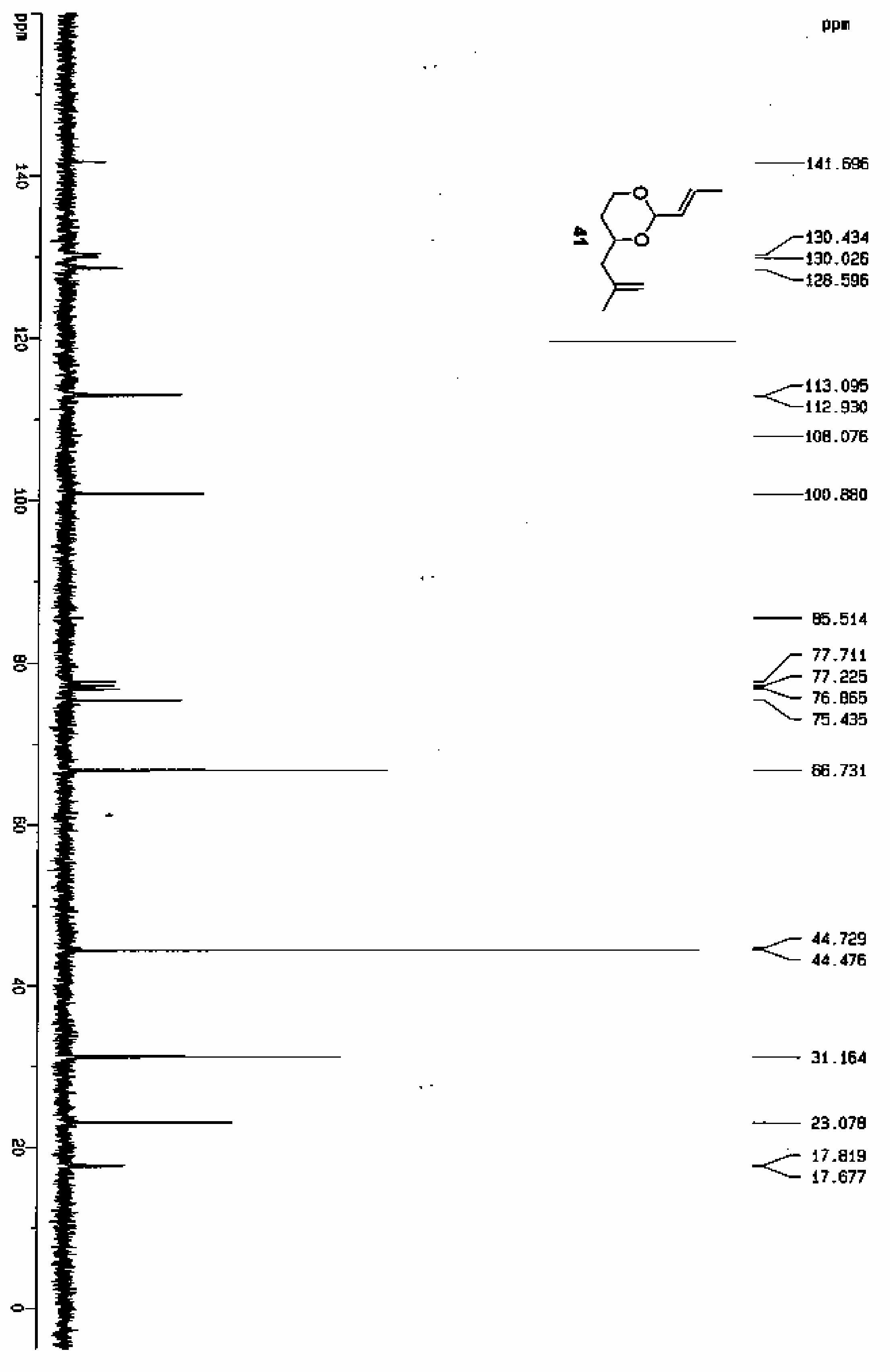
40
OH
H
H
O
ppm
Integral
0.9692
1.0000
3.1731
4.4783
1.5174
0.9810
6.8881
3.3254
5.1829
7.26967
5.75345
5.73221
5.71101
5.68088
5.65977
5.54478
5.54013
5.52411
5.51924
5.46783
4.76253
4.74796
3.82220
3.80470
3.78717
3.74903
3.60870
3.58215
3.57110
3.54312
2.77941
2.26470
2.21547
2.17282
2.16544
2.09404
2.05354
2.01144
1.85743
1.83679
1.80863
1.78916
1.77601
1.76301
1.74688
1.70963
1.68857
1.67274
1.66763
1.49730
1.25610
0.88304
0.07260
0.06875
9
8
7
6
5
4
3
2
1
0

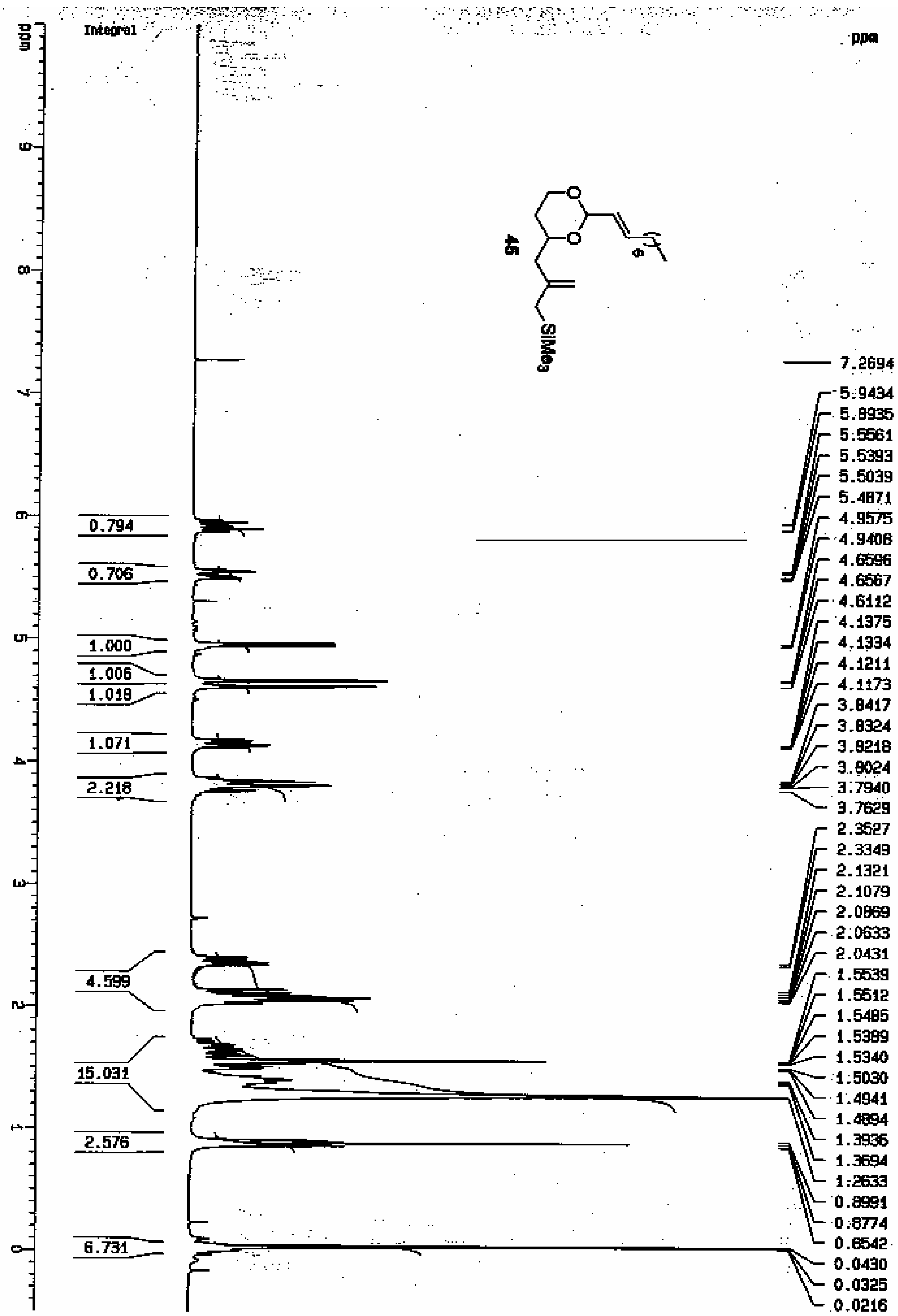

ppm
160
140
120
100
80
60
40
20
ppm
172.379
167.320
166.775
162.596
155.307
153.237
150.050
149.349
147.377
146.276
144.280
143.533
137.226
136.623
136.287
131.973
131.251
129.232
128.301
127.299
124.571
122.958
120.767
115.036
109.043
108.130
106.179
105.309
102.573
101.342
92.085
79.296
78.715
77.639
77.216
76.794
75.377
75.101
70.879
70.173
61.410
61.141
41.117
40.877
38.483
29.910
29.545
17.847
11.855
H
O
H
OH

40

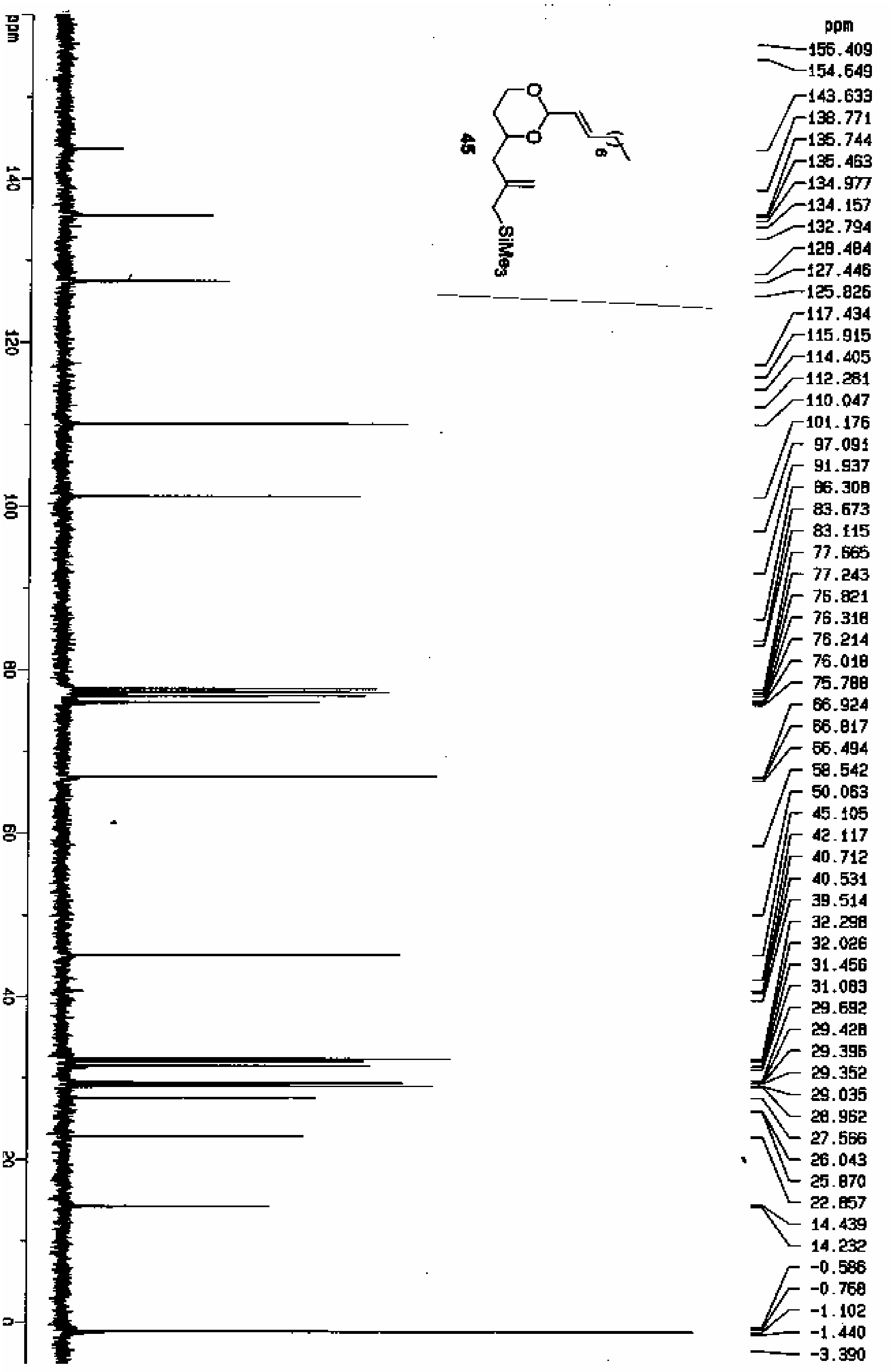


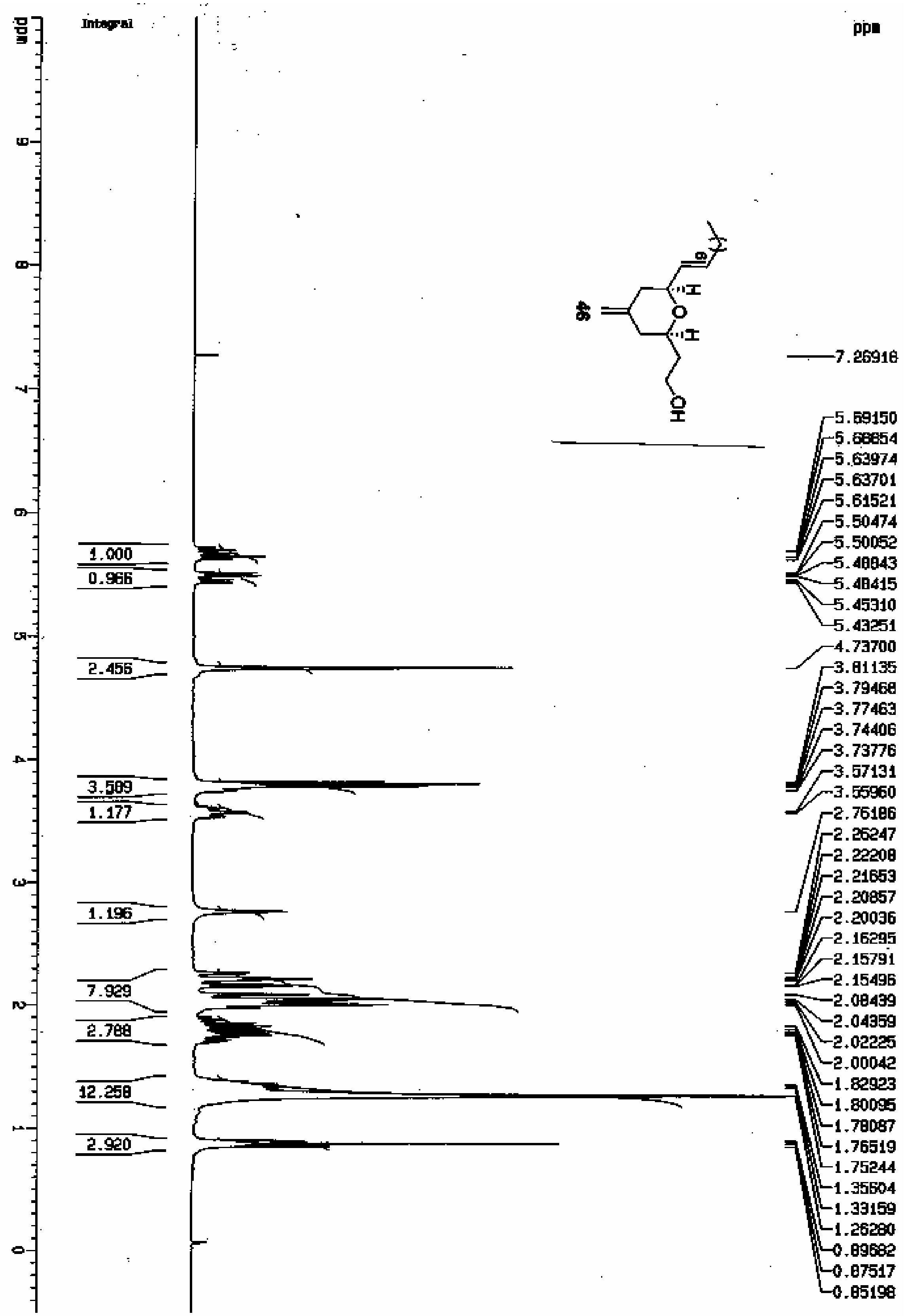
ppm
Integral
ppm
41
7.26906
5.88623
5.88304
5.86429
5.86112
5.54681
5.54116
4.92537
4.90859
4.79457
4.78926
4.78416
4.74156
4.73855
4.73527
4.10496
4.09283
3.81989
3.81091
3.77916
3.77297
3.77043
2.35497
2.18741
2.18518
2.16457
2.16239
1.73894
1.72596
1.71758
1.71590
1.71237
1.71046
1.69583
1.69395
1.69047
1.68857
1.46559
1.46079
1.45728
1.42104
1.41616
1.23853
0.87552
0.86453
0.05775
1.0000
0.9247
1.2264
1.2775
1.3741
1.4580
2.9499
1.4324
1.4887
9.9572
0.9529
0.6836
9
8
7
6
5
4
3
2
1
0


ppm
140
120
100
80
60
40
20
0
ppm
141.696
130.434
130.026
128.596
113.095
112.930
108.076
100.880
85.514
77.711
77.225
76.865
75.435
66.731
44.729
44.476
31.164
23.078
17.819
17.677
O
O
41

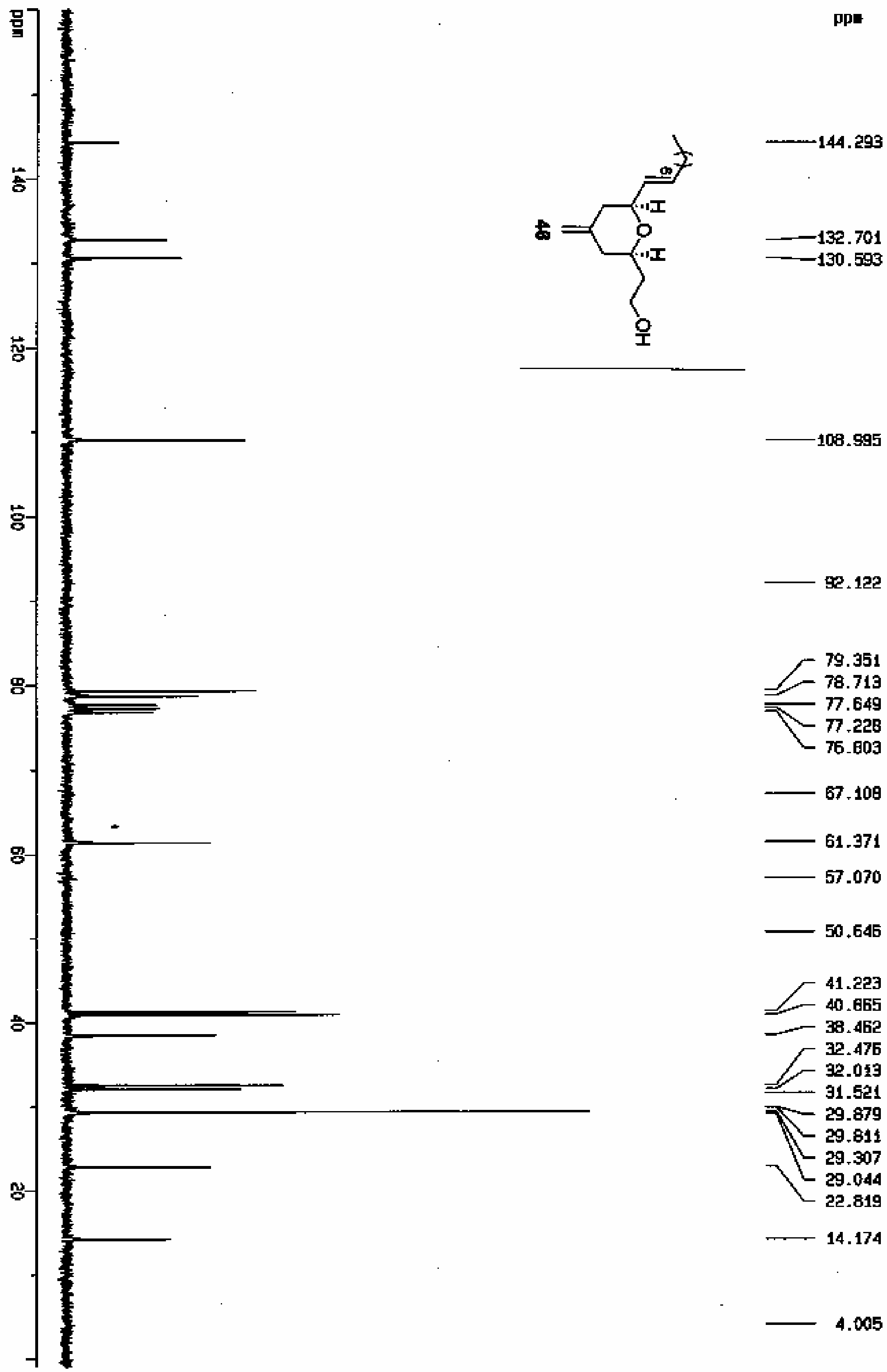

45

ppm
Integral
0.794
0.706
1.000
1.006
1.018
1.071
2.218
4.599
15.031
2.576
6.731
SiMe3
O
O
6
7.2694
5.9434
5.8935
5.5561
5.5393
5.5039
5.4871
4.9575
4.9406
4.6596
4.6567
4.6112
4.1375
4.1334
4.1211
4.1173
3.8417
3.8324
3.8218
3.8024
3.7940
3.7629
2.3527
2.3349
2.1321
2.1079
2.0869
2.0633
2.0431
1.5539
1.5512
1.5485
1.5389
1.5340
1.5030
1.4941
1.4894
1.3936
1.3694
1.2633
0.8991
0.8774
0.8542
0.0430
0.0325
0.0216

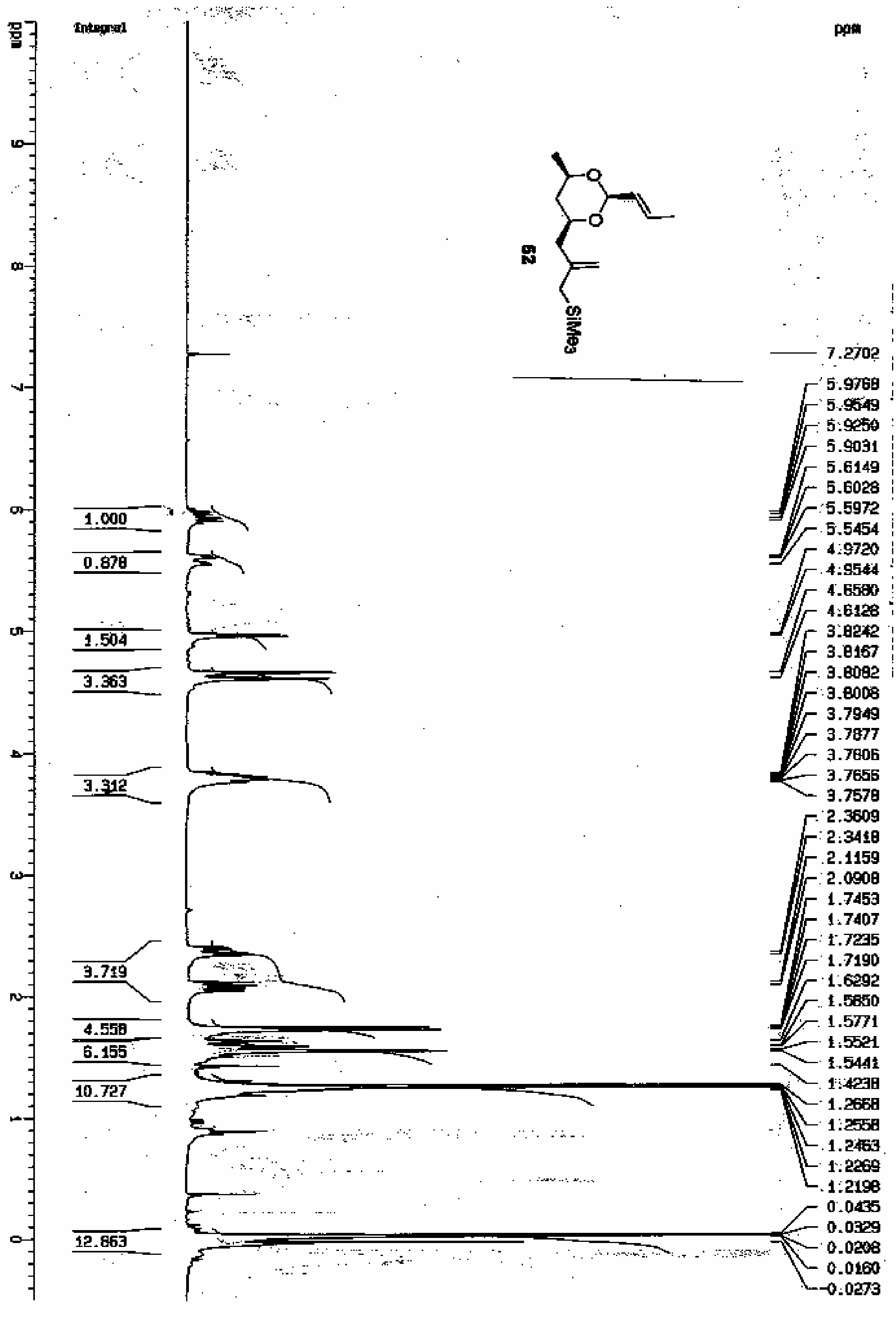

ppm
140
120
100
80
60
40
20
0
O
O
6
45
SiMe3
ppm
156.409
154.649
143.633
138.771
135.744
135.463
134.977
134.157
132.794
128.484
127.446
125.826
117.434
115.915
114.405
112.281
110.047
101.176
97.091
91.937
86.308
83.673
83.115
77.665
77.243
76.821
76.318
76.214
76.018
75.788
66.924
66.817
66.494
58.542
50.063
45.105
42.117
40.712
40.531
39.514
32.298
32.026
31.456
31.083
29.692
29.428
29.396
29.352
29.035
28.962
27.566
26.043
25.870
22.857
14.439
14.232
-0.586
-0.768
-1.102
-1.440
-3.390

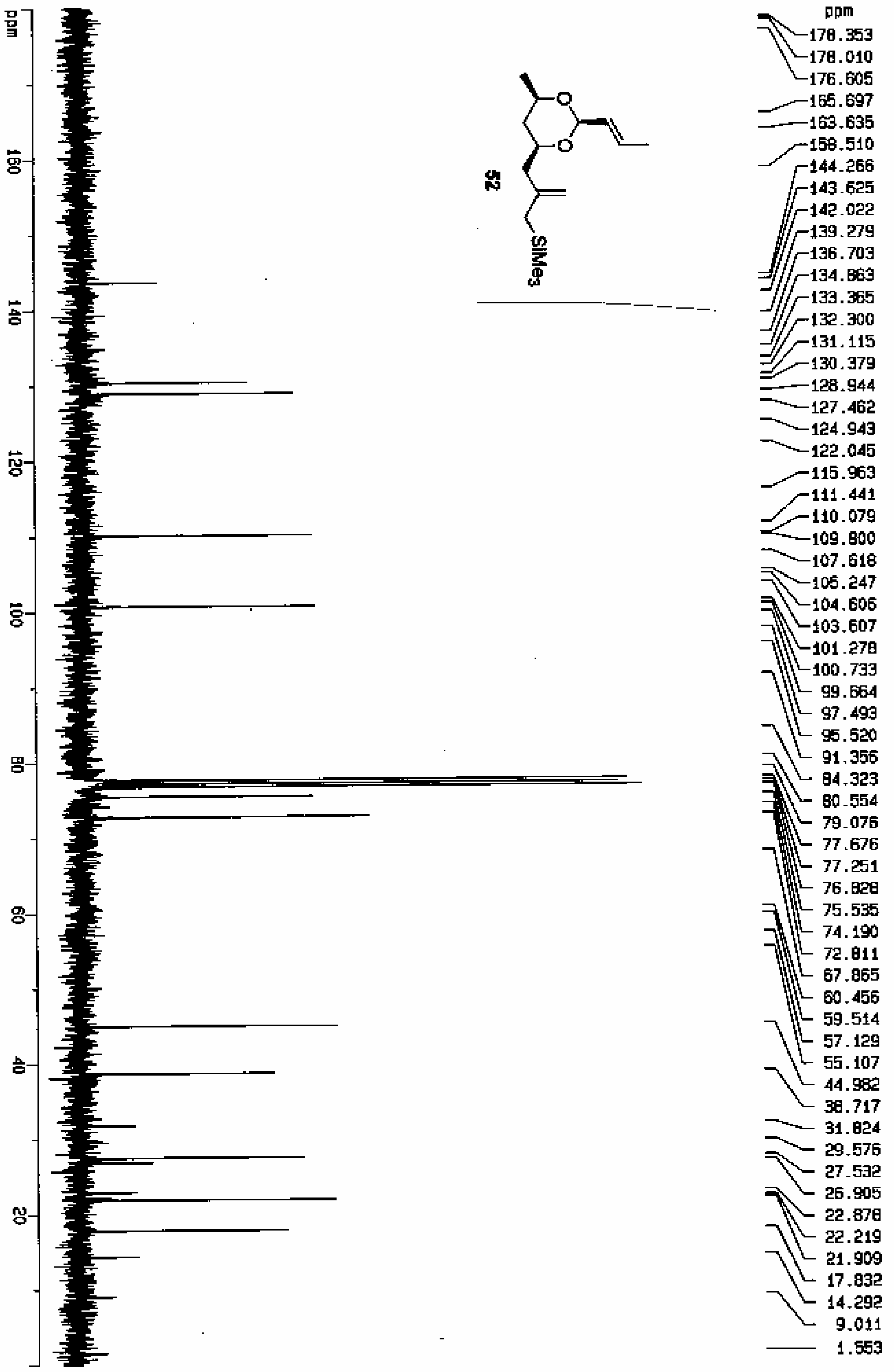

Integral
ppm
1.000
0.966
2.456
3.589
1.177
1.196
7.929
2.788
12.258
2.920
7.26918
5.69150
5.66654
5.63974
5.63701
5.61521
5.50474
5.50052
5.48843
5.48415
5.45310
5.43251
4.73700
3.81135
3.79468
3.77463
3.74406
3.73776
3.57131
3.55960
2.76186
2.26247
2.22208
2.21653
2.20857
2.20036
2.16295
2.15791
2.15496
2.08439
2.04359
2.02225
2.00042
1.82923
1.80095
1.78087
1.76519
1.75244
1.35604
1.33159
1.26280
0.89682
0.87517
0.85198
ppm
9
8
7
6
5
4
3
2
1
0
HO
O
H
H
6

46

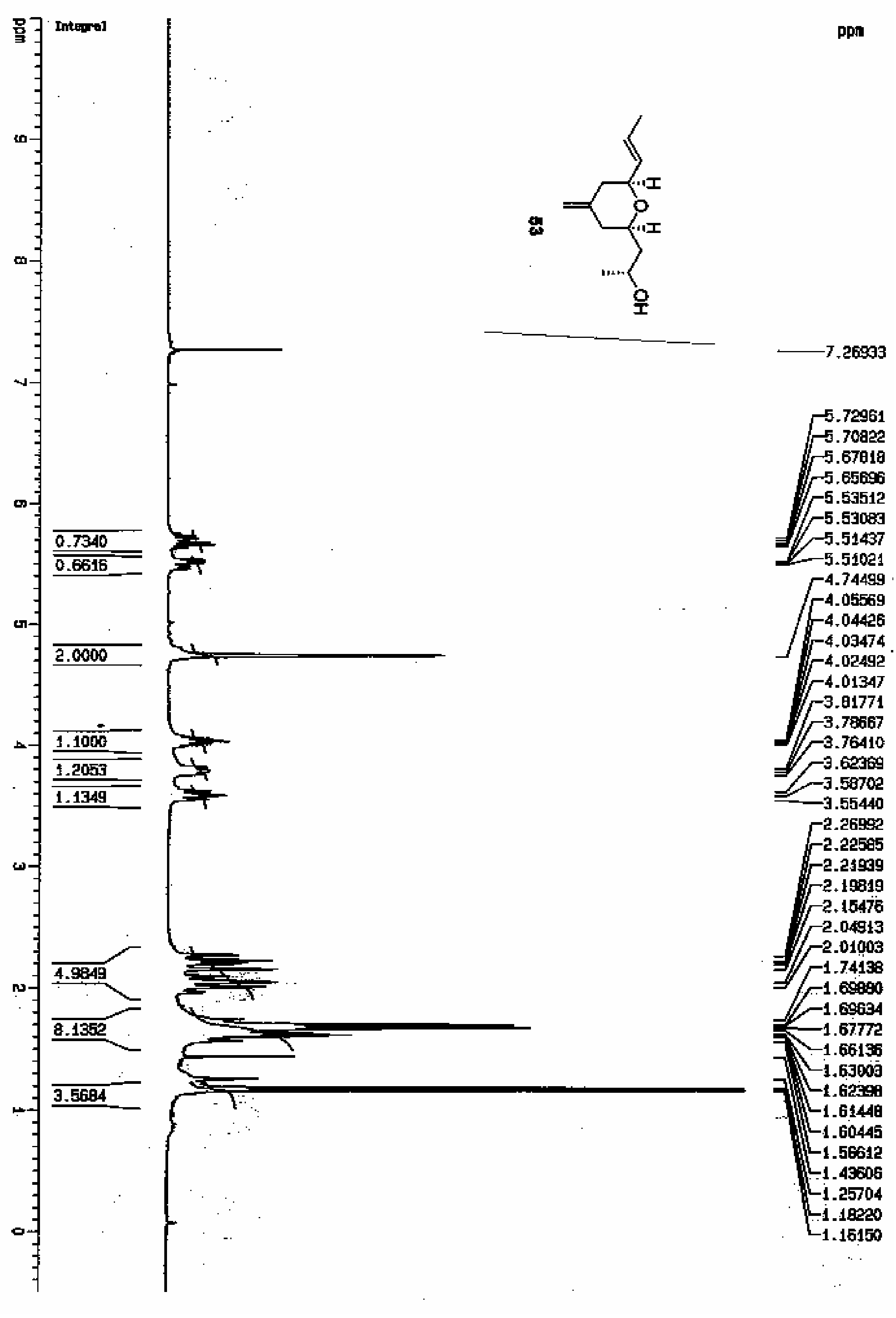

ppm
140
120
100
80
60
40
20
H
O
H
OH
6
ppm
144.293
132.701
130.593
108.995
92.122
79.351
78.713
77.649
77.228
76.803
67.108
61.371
57.070
50.646
41.223
40.665
38.462
32.476
32.019
31.521
29.879
29.811
29.307
29.044
22.819
14.174
4.005

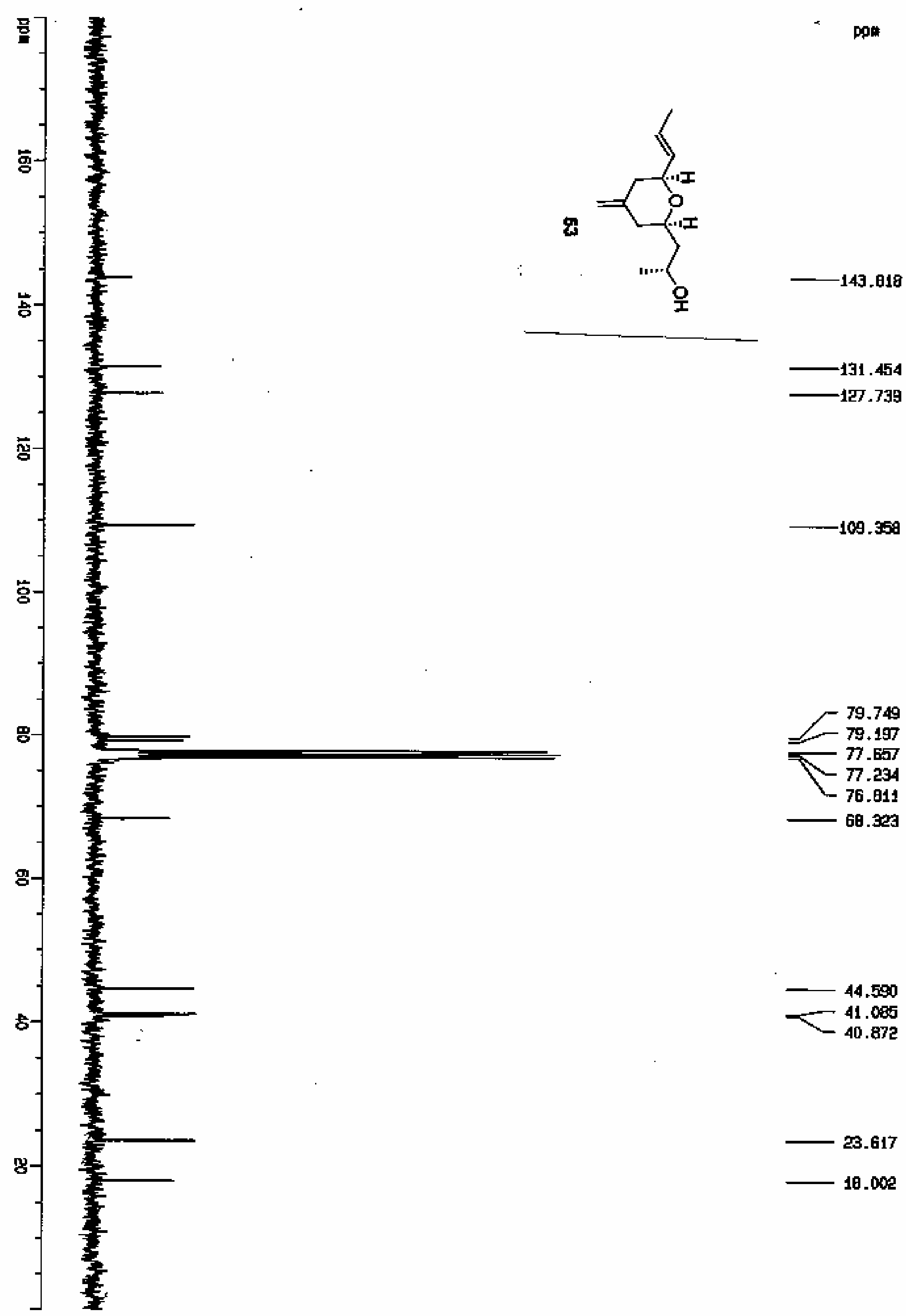
48

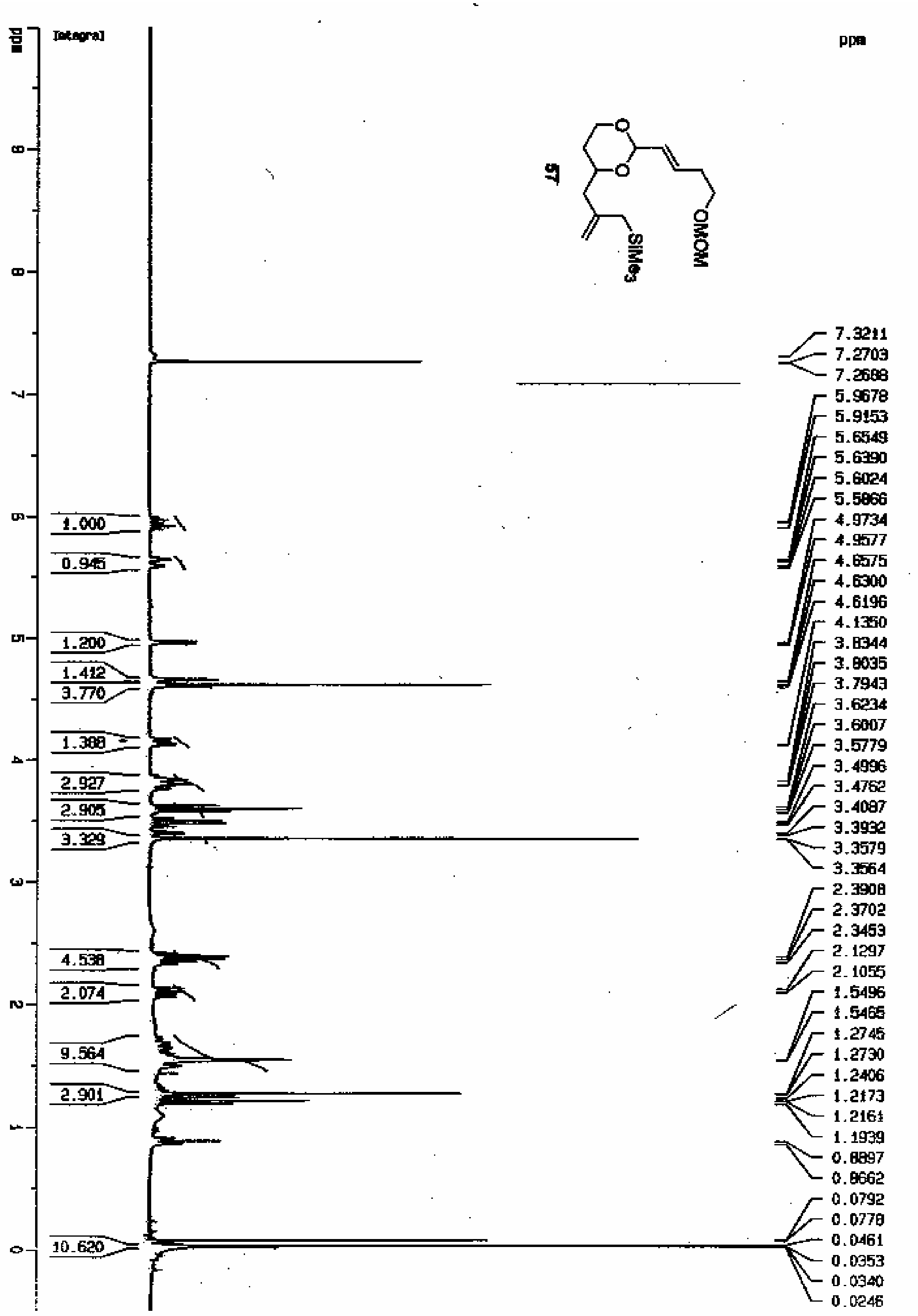

62
SiMe3
Integral
ppm
1.000
0.878
1.504
3.363
3.312
3.719
4.558
6.155
10.727
12.863
7.2702
5.9769
5.9549
5.9250
5.9031
5.6149
5.6028
5.5972
5.5454
4.9720
4.9544
4.6580
4.6128
3.8242
3.8167
3.8092
3.8008
3.7949
3.7877
3.7806
3.7656
3.7579
2.3609
2.3418
2.1159
2.0908
1.7453
1.7407
1.7235
1.7190
1.6292
1.5850
1.5771
1.5521
1.5441
1.4238
1.2668
1.2558
1.2463
1.2269
1.2198
0.0435
0.0329
0.0208
0.0160
-0.0273
9
8
7
6
5
4
3
2
1
0


ppm
160
140
120
100
80
60
40
20
O
O
SiMe3
ppm
178.353
178.010
176.605
165.697
163.635
158.510
144.266
143.625
142.022
139.279
136.703
134.863
133.365
132.300
131.115
130.379
128.944
127.462
124.943
122.045
115.963
111.441
110.079
109.800
107.618
106.247
104.606
103.607
101.278
100.733
99.664
97.493
95.520
91.356
84.323
80.554
79.076
77.676
77.251
76.828
75.535
74.190
72.811
67.865
60.456
59.514
57.129
55.107
44.982
38.717
31.824
29.576
27.532
25.905
22.878
22.219
21.909
17.832
14.292
9.011
1.553

52

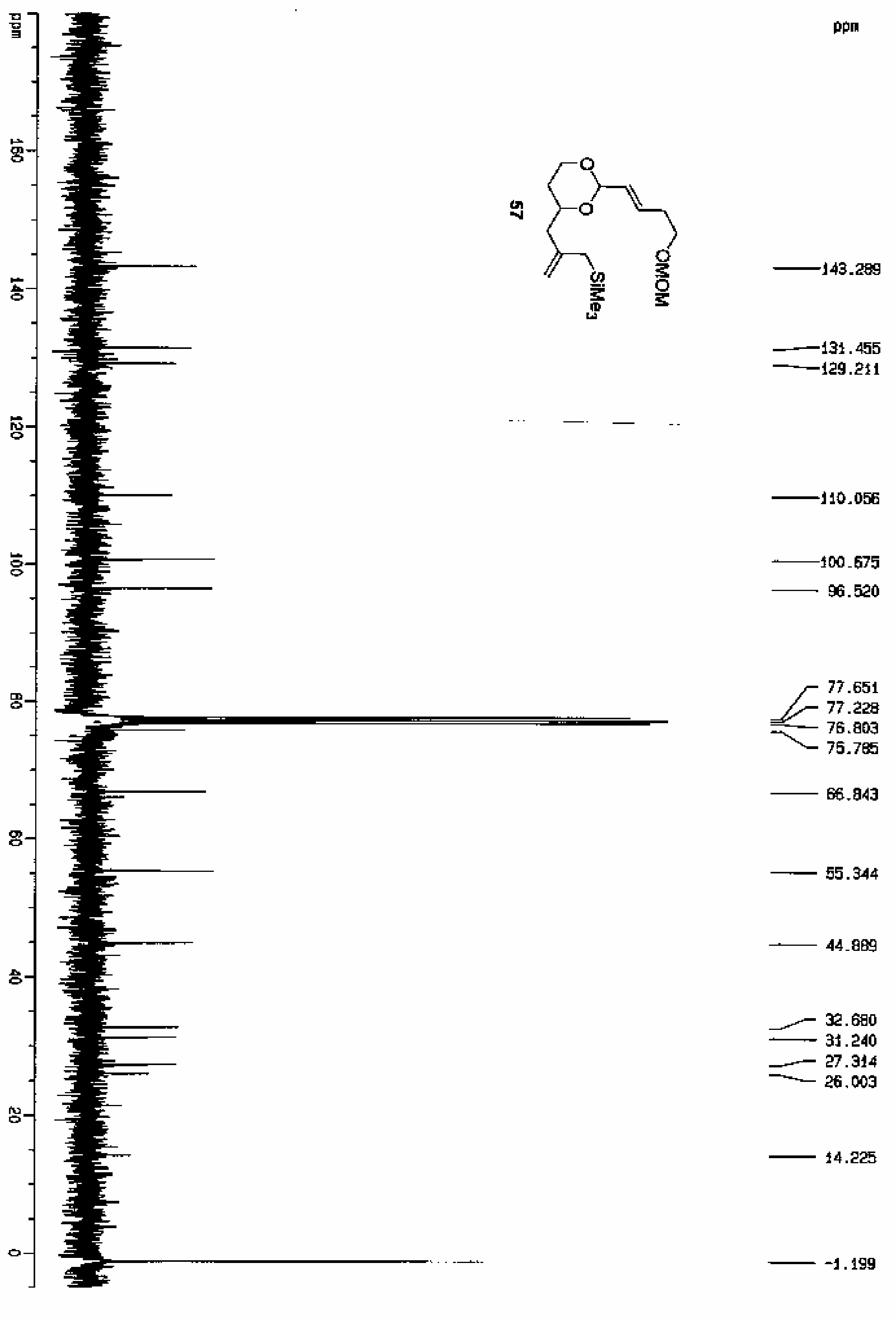

ppm
Integral
ppm
53
OH
H
O
H
9
8
7
6
5
4
3
2
1
0
0.7340
0.6616
2.0000
1.1000
1.2053
1.1349
4.9849
8.1352
3.5684
7.26933
5.72961
5.70822
5.67818
5.65696
5.53512
5.53083
5.51437
5.51021
4.74499
4.05569
4.04426
4.03474
4.02492
4.01347
3.81771
3.78667
3.76410
3.62369
3.58702
3.55440
2.26992
2.22565
2.21939
2.19819
2.15476
2.04913
2.01003
1.74138
1.69880
1.69634
1.67772
1.66136
1.63003
1.62398
1.61448
1.60445
1.56612
1.43606
1.25704
1.18220
1.16150

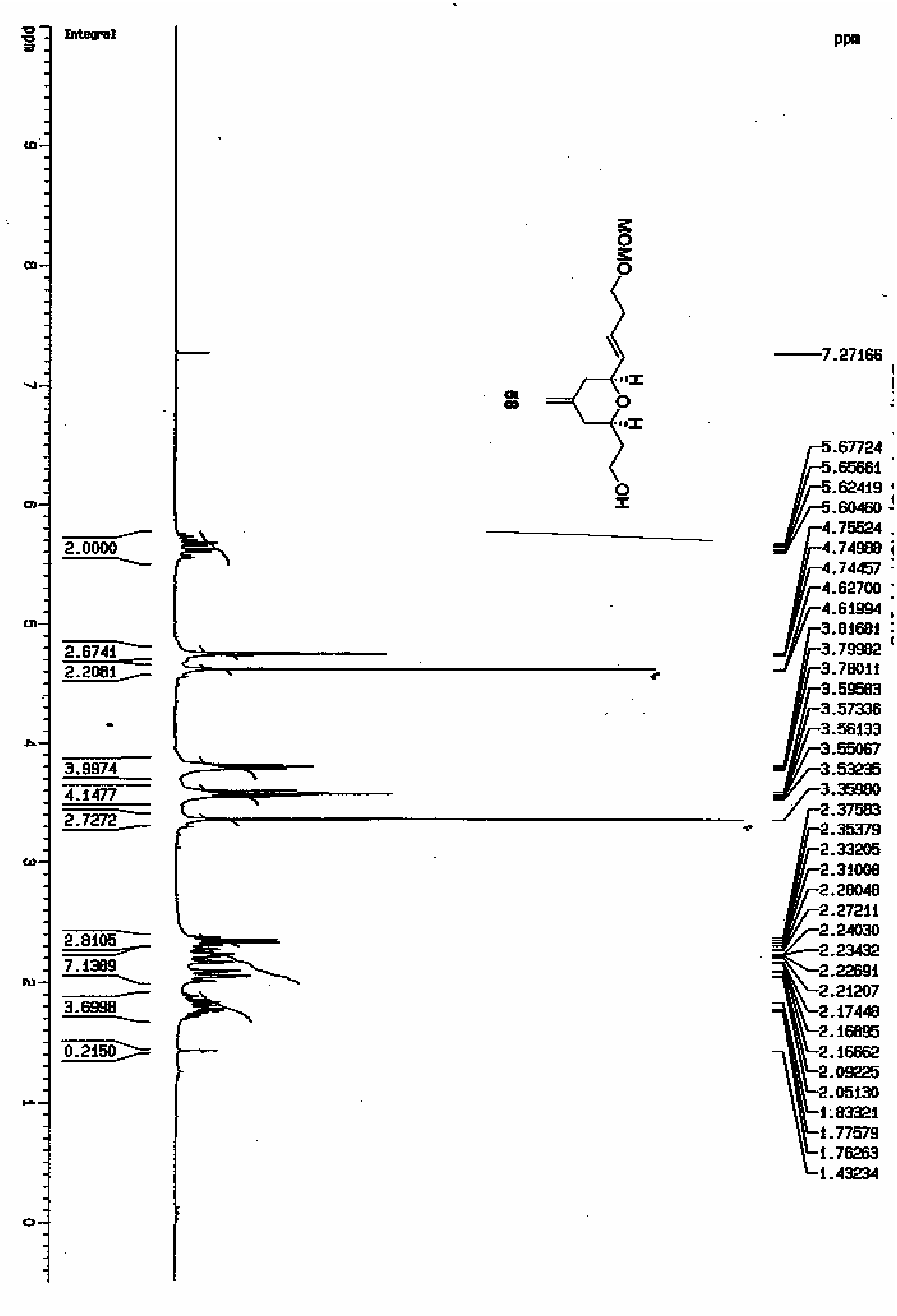

ppm
160
140
120
100
80
60
40
20
ppm
H
O
H
OH
63
143.818
131.454
127.739
109.358
79.749
79.197
77.657
77.234
76.811
68.323
44.590
41.085
40.872
23.617
18.002

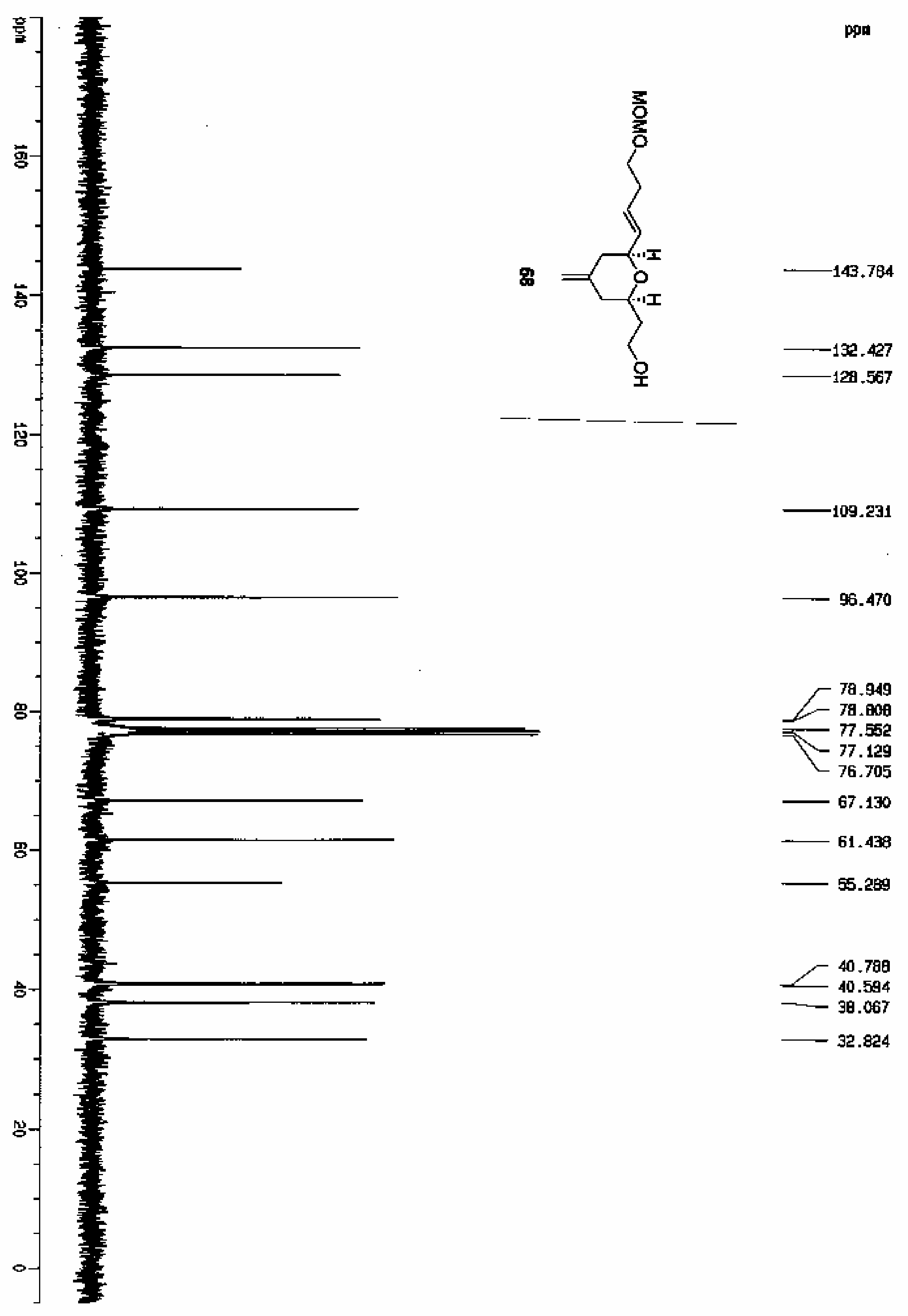


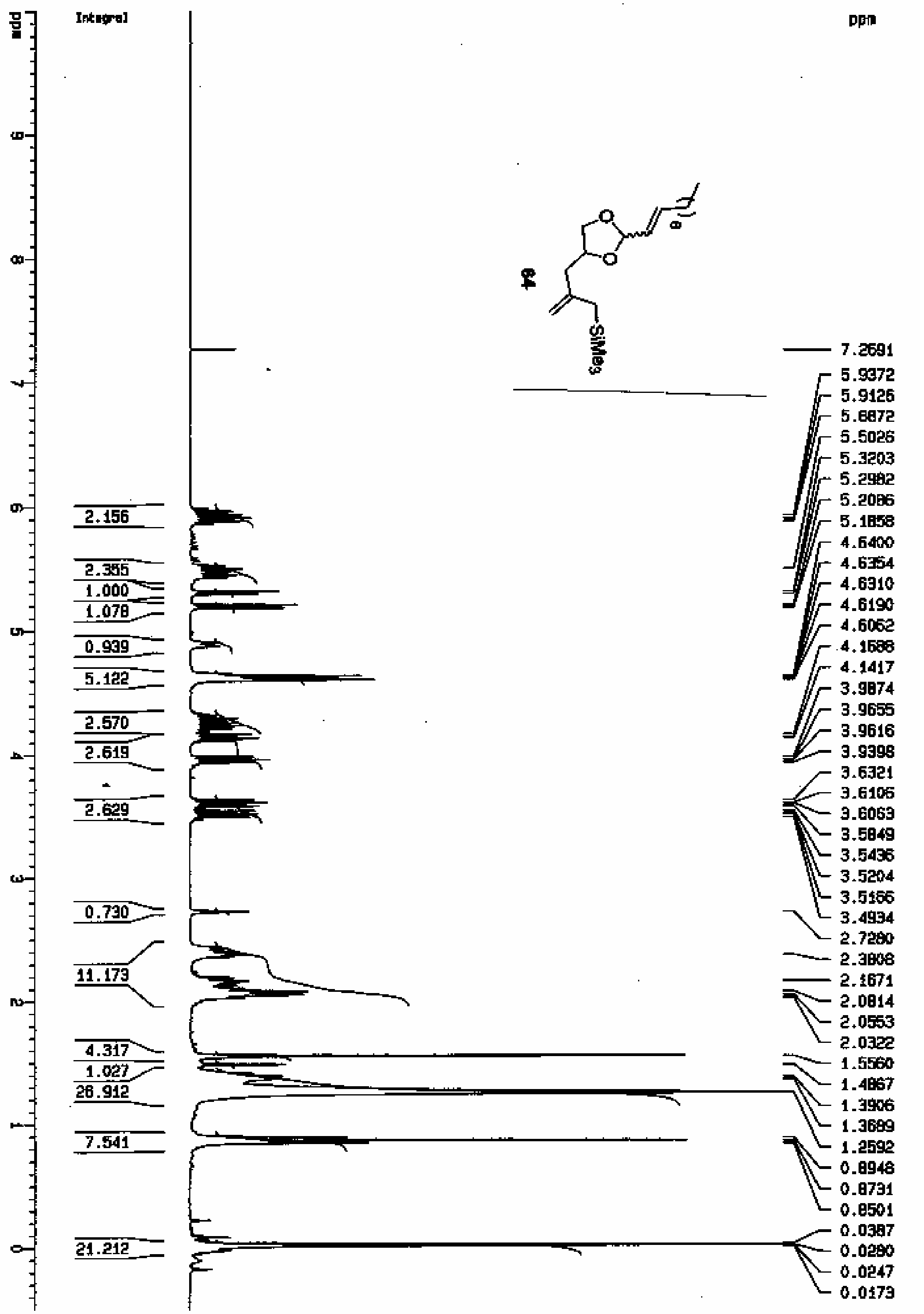
ppm
Integral
9
8
7
6
5
4
3
2
1
0
1.000
0.945
1.200
1.412
3.770
1.388
2.927
2.905
3.329
4.538
2.074
9.564
2.901
10.620
O
O
OMOM
SiMe3
ppm
7.3211
7.2703
7.2688
5.9678
5.9153
5.6549
5.6390
5.6024
5.5866
4.9734
4.9577
4.6575
4.6300
4.6196
4.1350
3.8344
3.8035
3.7943
3.6234
3.6007
3.5779
3.4996
3.4762
3.4087
3.3932
3.3579
3.3564
2.3908
2.3702
2.3453
2.1297
2.1055
1.5496
1.5465
1.2745
1.2730
1.2406
1.2173
1.2161
1.1939
0.8897
0.8662
0.0792
0.0778
0.0461
0.0353
0.0340
0.0246

57

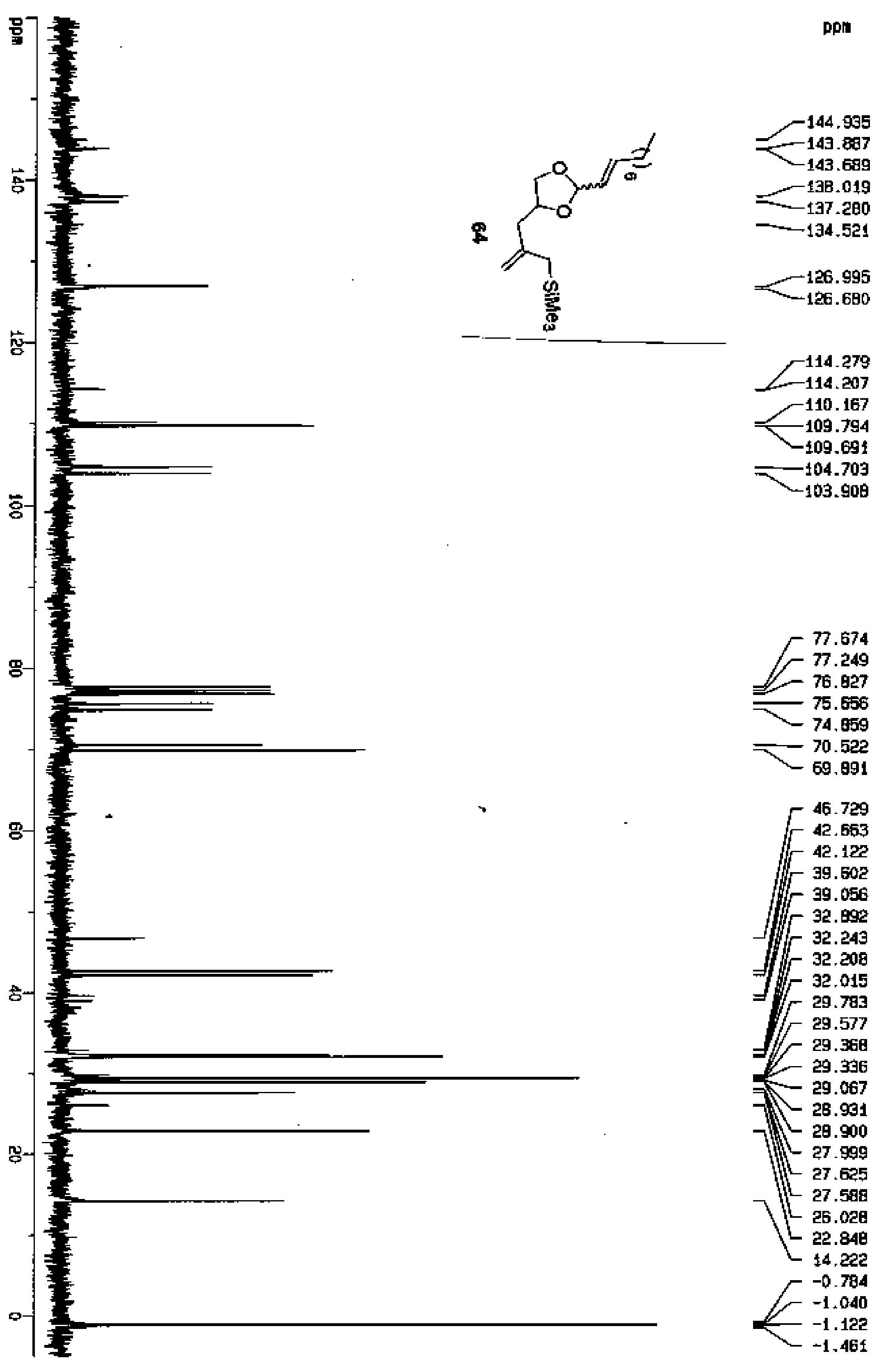

57
OMOM
SiMe3
ppm
160
140
120
100
80
60
40
20
0
ppm
143.289
131.455
129.211
110.056
100.675
96.520
77.651
77.228
76.803
75.785
66.843
55.344
44.889
32.680
31.240
27.314
26.003
14.225
-1.199

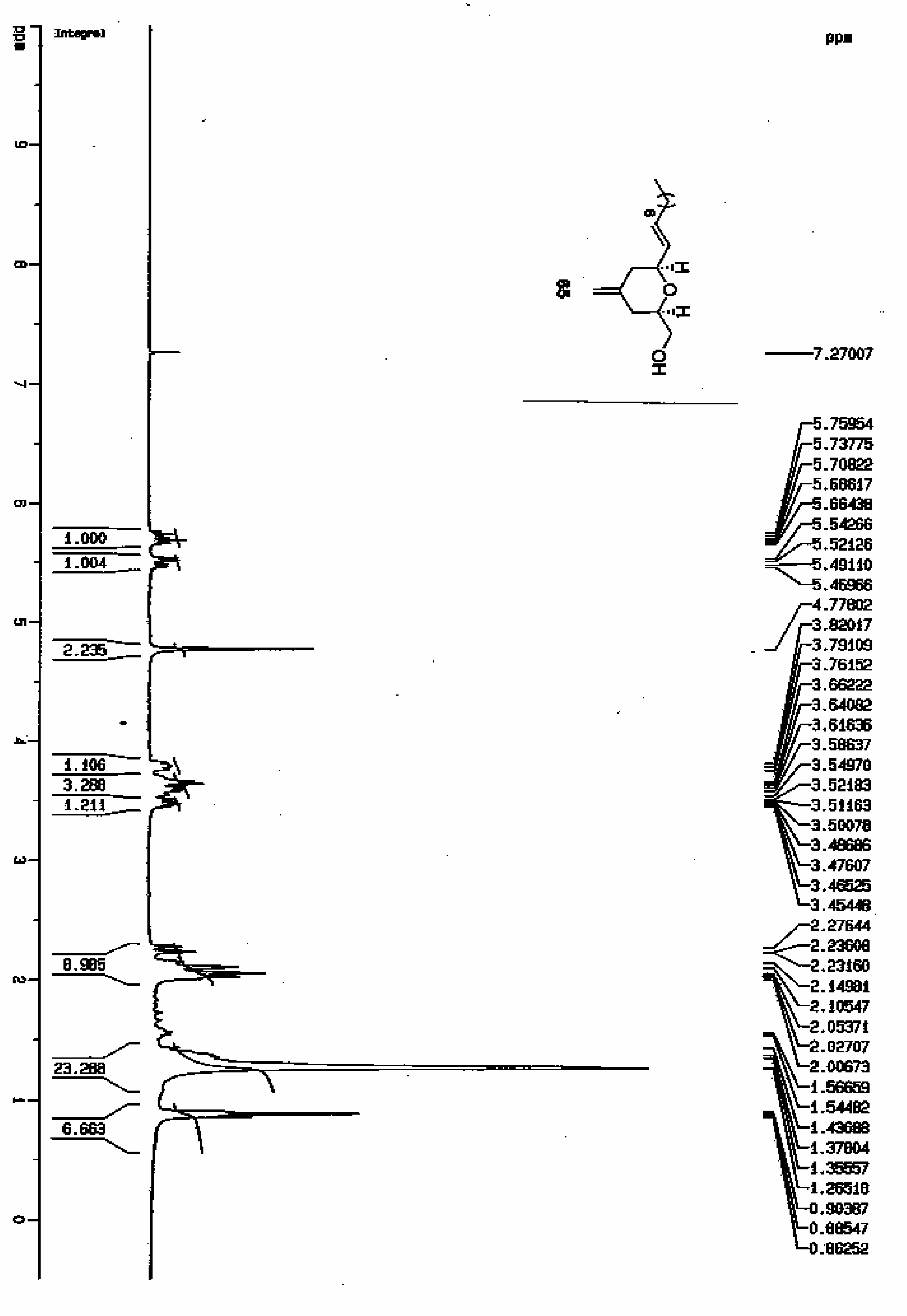

ppm
Integral
ppm
7
6
5
4
3
2
1
0
2.0000
2.6741
2.2081
3.9974
4.1477
2.7272
2.8105
7.1389
3.6988
0.2150
MOMO
H
O
H
OH
88
7.27166
5.67724
5.65661
5.62419
5.60460
4.75524
4.74988
4.74457
4.62700
4.61994
3.81681
3.79982
3.78011
3.59583
3.57336
3.56133
3.55067
3.53235
3.35980
2.37583
2.35379
2.33205
2.31008
2.28048
2.27211
2.24030
2.23432
2.22691
2.21207
2.17448
2.16895
2.16662
2.09225
2.05130
1.83321
1.77579
1.76263
1.43234

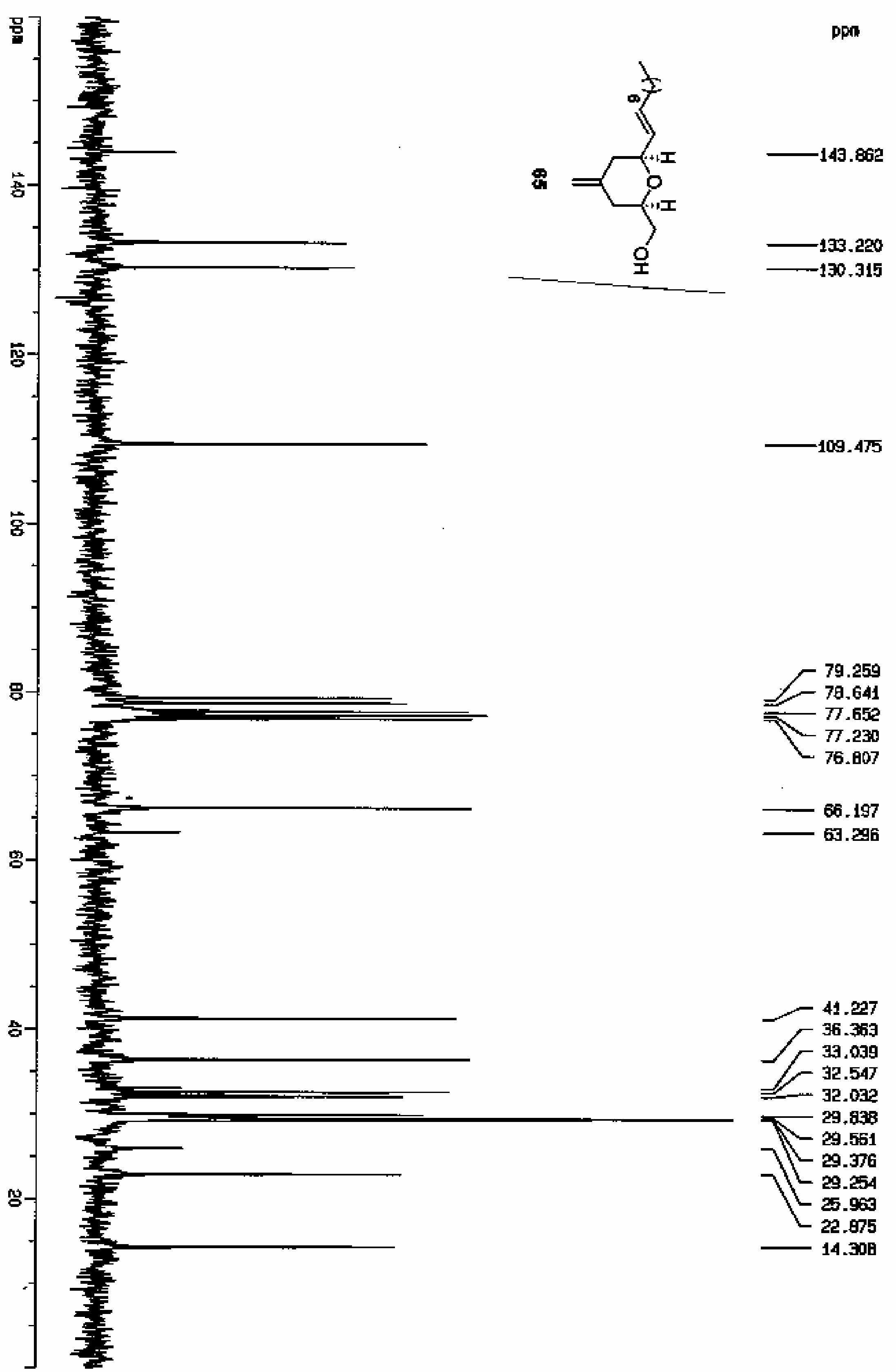

ppm
160
140
120
100
80
60
40
20
0
MOMO
H
O
H
OH
68
ppm
143.784
132.427
128.567
109.231
96.470
78.949
78.808
77.552
77.129
76.705
67.130
61.438
55.289
40.788
40.594
38.067
32.824


64

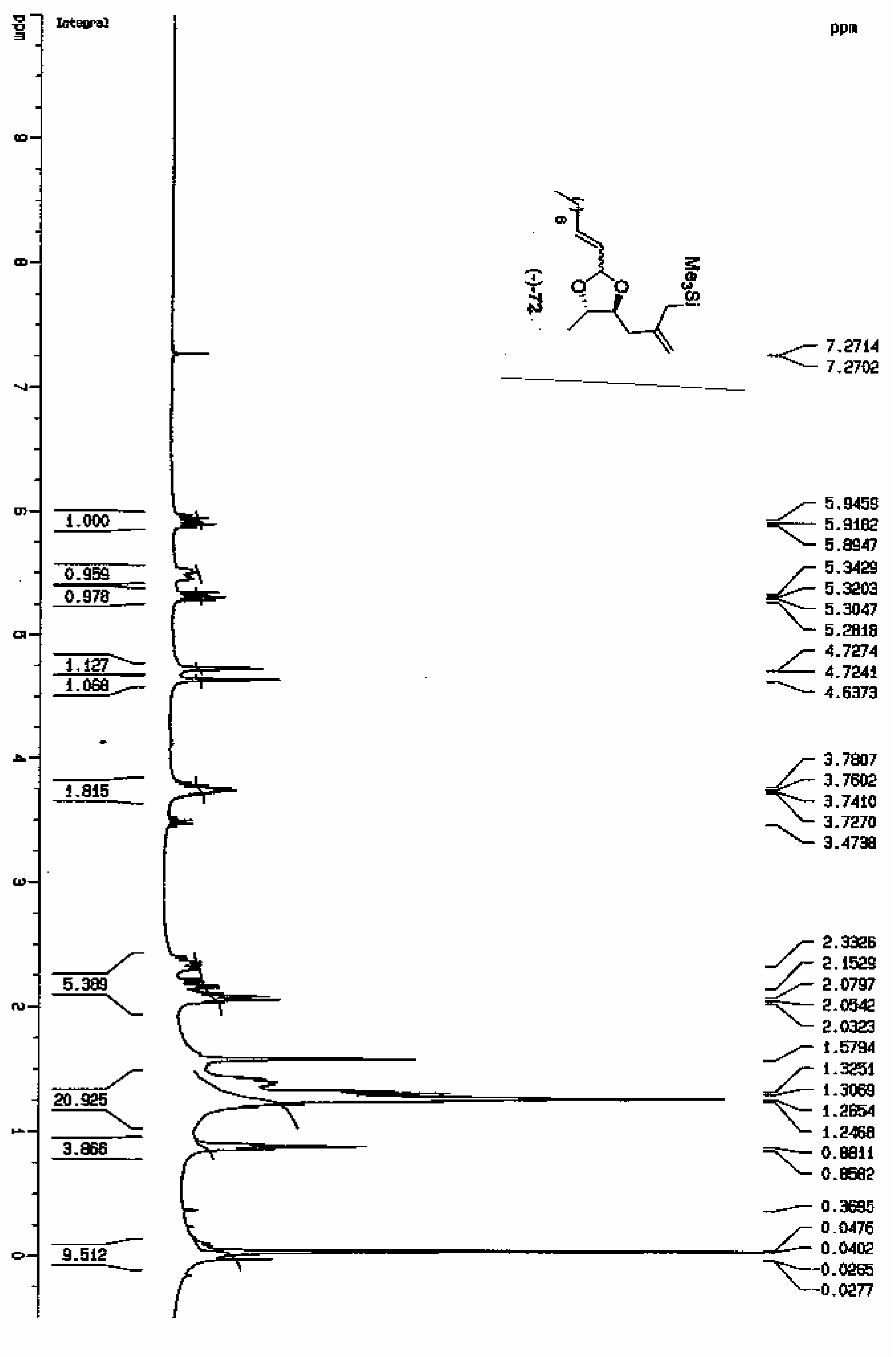
ppm
Integral
2.156
2.355
1.000
1.078
0.939
5.122
2.570
2.619
2.629
0.730
11.179
4.317
1.027
26.912
7.541
21.212
SiMe3
O
O
8
7.2691
5.9372
5.9126
5.6872
5.5026
5.3203
5.2982
5.2086
5.1858
4.6400
4.6354
4.6310
4.6190
4.6062
4.1688
4.1417
3.9874
3.9655
3.9616
3.9398
3.6321
3.6106
3.6063
3.5849
3.5436
3.5204
3.5166
3.4934
2.7280
2.3808
2.1671
2.0814
2.0553
2.0322
1.5560
1.4867
1.3906
1.3689
1.2592
0.8948
0.8731
0.8501
0.0387
0.0280
0.0247
0.0173


ppm
140
120
100
80
60
40
20
0
64
O
O
6
SiMe3
ppm
144.935
143.887
143.689
138.019
137.280
134.521
126.995
126.680
114.279
114.207
110.167
109.794
109.691
104.703
103.908
77.674
77.249
76.827
75.656
74.859
70.522
69.891
46.729
42.663
42.122
39.602
39.056
32.892
32.243
32.208
32.015
29.783
29.577
29.368
29.336
29.067
28.931
28.900
27.999
27.625
27.588
26.028
22.848
14.222
-0.784
-1.040
-1.122
-1.461

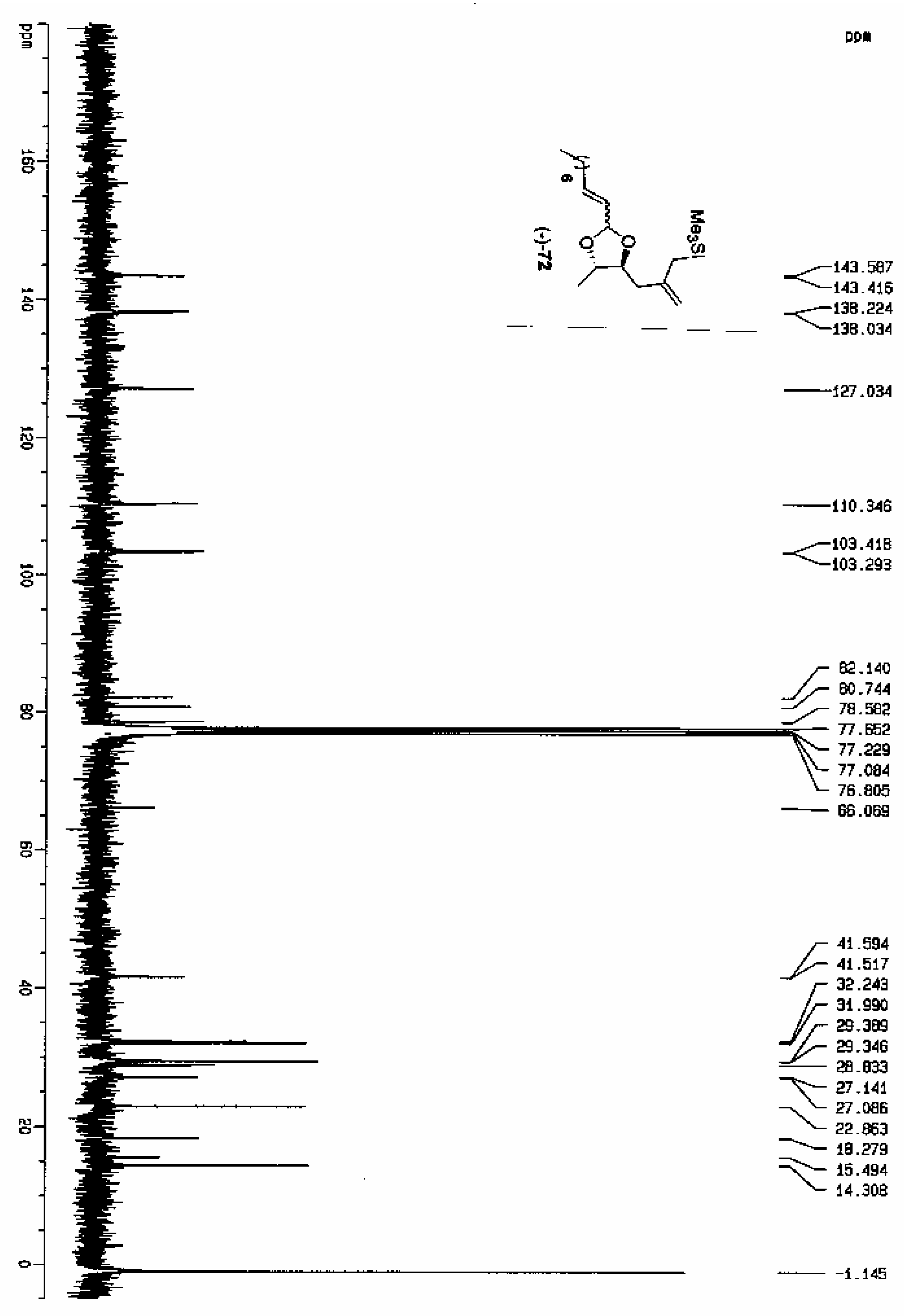

ppm
Integral
1.000
1.004
2.235
1.106
3.288
1.211
8.985
23.288
6.663
ppm
7.27007
5.75954
5.73775
5.70822
5.68617
5.66438
5.54266
5.52126
5.49110
5.46966
4.77802
3.82017
3.79109
3.76152
3.66222
3.64082
3.61636
3.58637
3.54970
3.52183
3.51163
3.50078
3.48686
3.47607
3.46525
3.45448
2.27644
2.23608
2.23160
2.14981
2.10547
2.05371
2.02707
2.00673
1.56659
1.54482
1.43688
1.37804
1.35657
1.26518
0.90387
0.88547
0.86252
65
HO
H
H
O
8

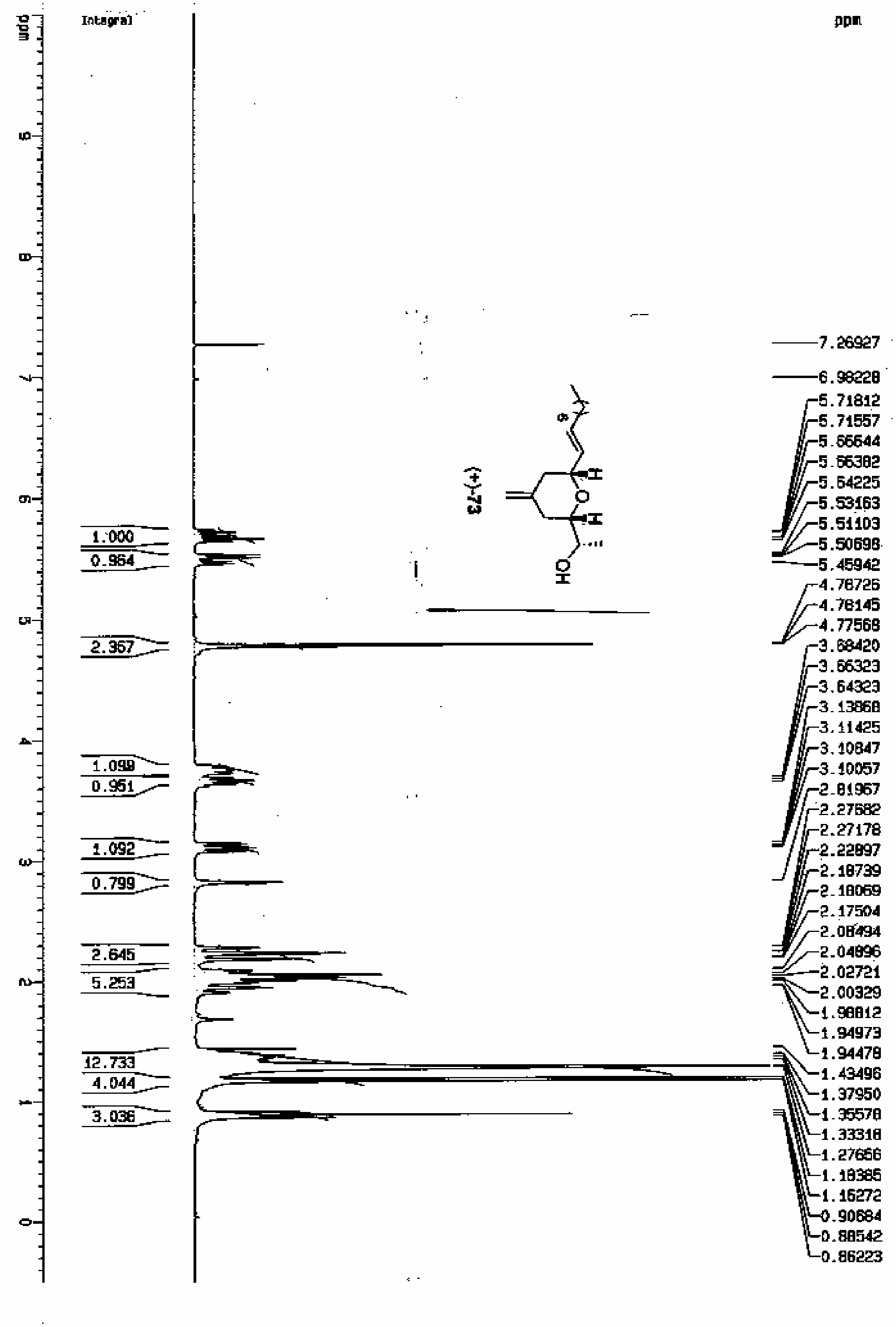

ppm
140
120
100
80
60
40
20
ppm
143.862
133.220
130.315
109.475
79.259
78.641
77.652
77.230
76.807
66.197
63.296
41.227
36.363
33.039
32.547
32.032
29.838
29.551
29.376
29.254
25.963
22.875
14.308
OH
O
H
H
6

65

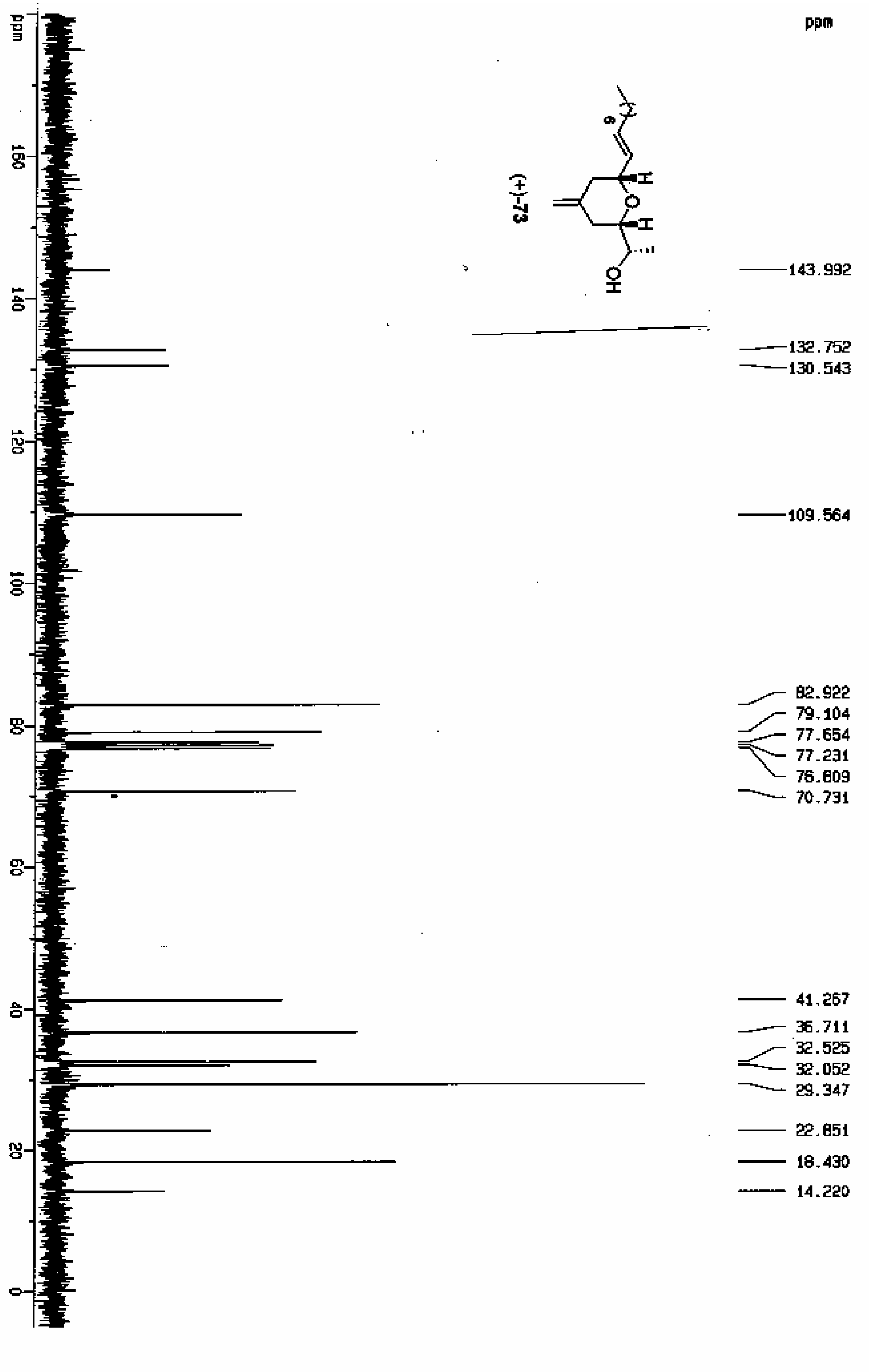


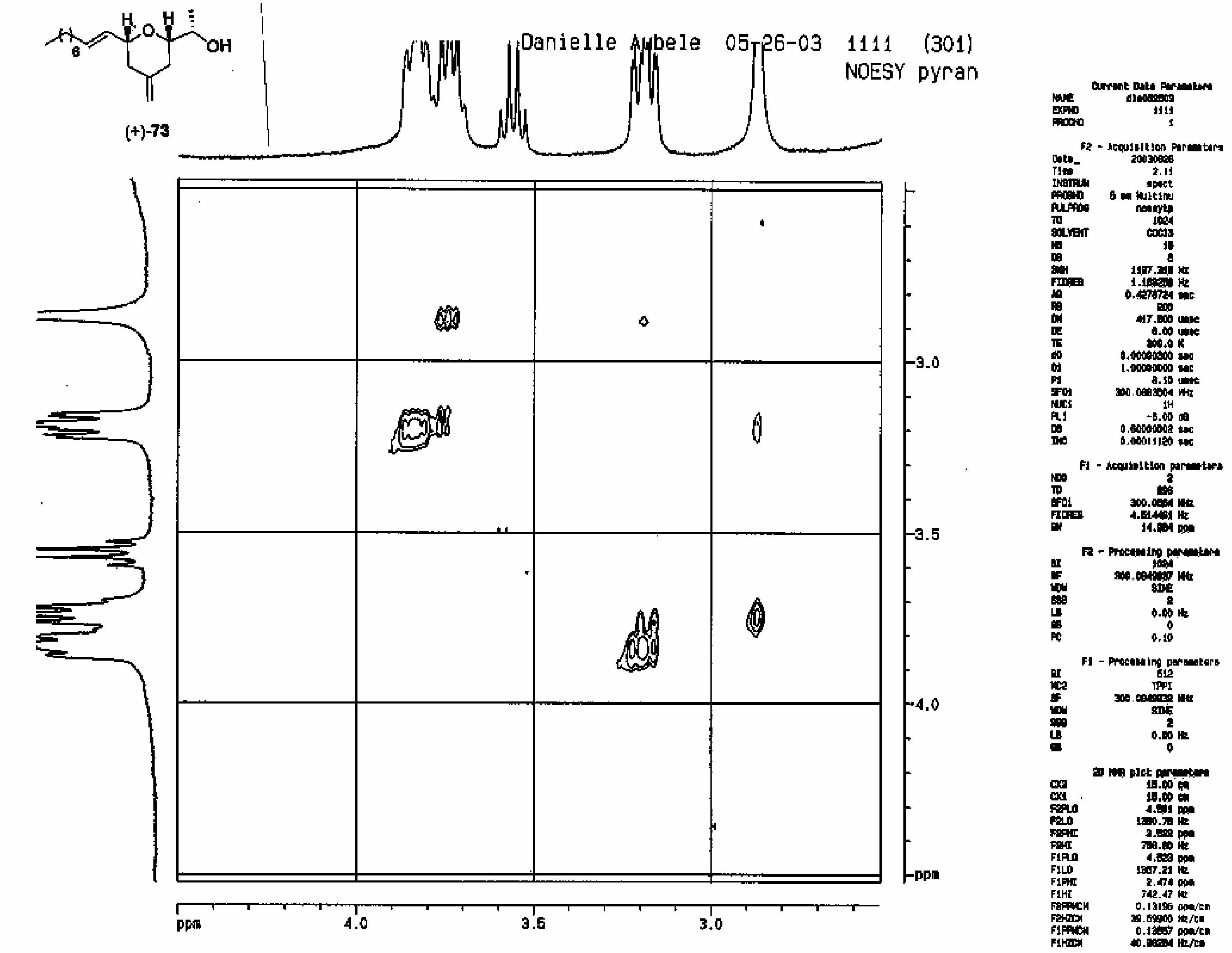
ppm
Integral
ppm
9
8
7
6
5
4
3
2
1
0
1.000
0.959
0.978
1.127
1.068
1.815
5.389
20.925
3.866
9.512
Me3Si
O
O
6
(-)-72
7.2714
7.2702
5.9459
5.9182
5.8947
5.3429
5.3203
5.3047
5.2818
4.7274
4.7241
4.6373
3.7807
3.7602
3.7410
3.7270
3.4738
2.3326
2.1529
2.0797
2.0542
2.0323
1.5794
1.3251
1.3069
1.2654
1.2468
0.8811
0.8582
0.3695
0.0476
0.0402
-0.0265
-0.0277


ppm
160
140
120
100
80
60
40
20
0
ppm
Me3Si
6
(-)-72
143.587
143.416
138.224
138.034
127.034
110.346
103.418
103.293
82.140
80.744
78.582
77.652
77.229
77.084
76.805
66.069
41.594
41.517
32.243
31.990
29.389
29.346
28.833
27.141
27.086
22.863
18.279
15.494
14.308
-1.145



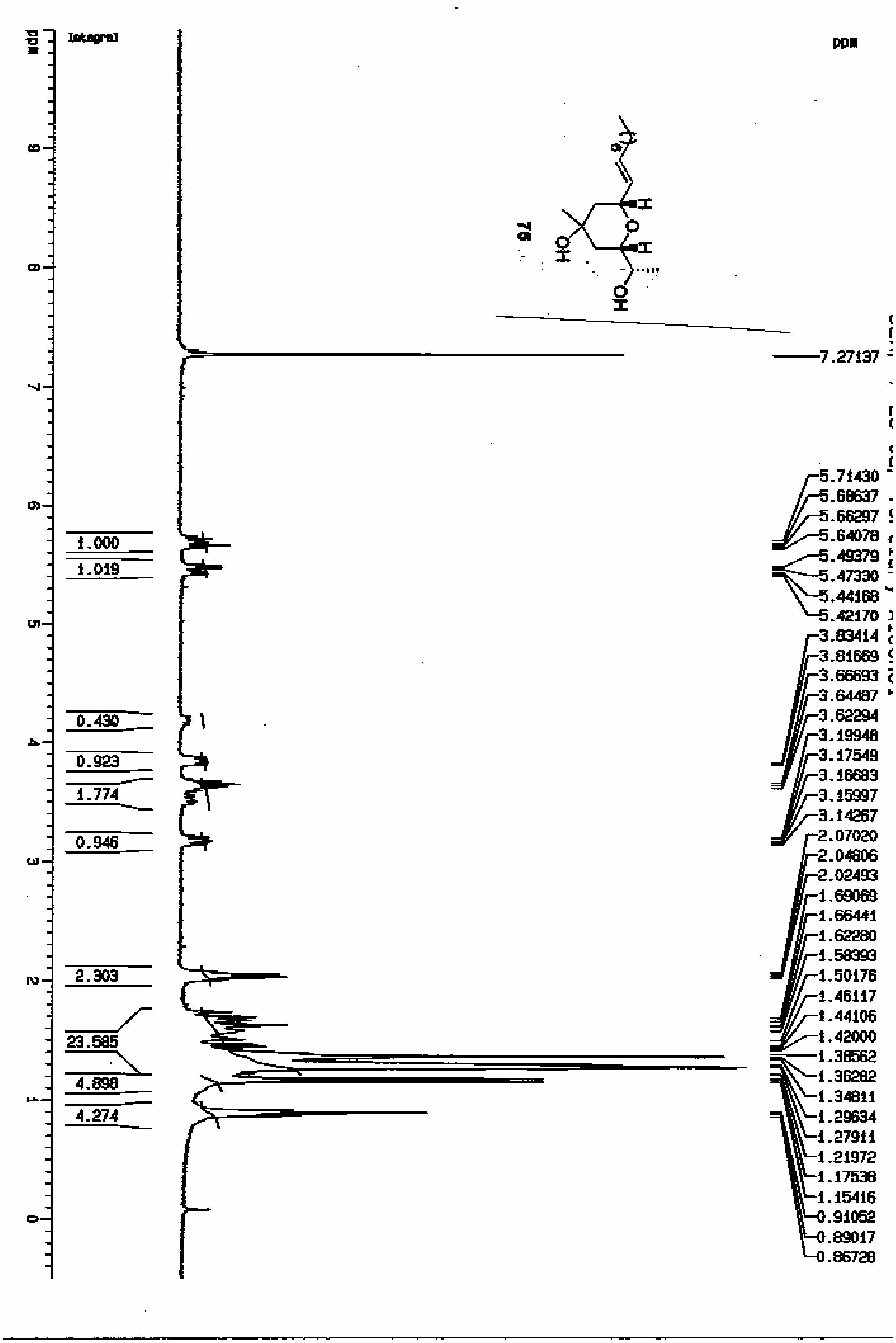
ppm
Integral
9
8
7
6
5
4
3
2
1
0
1.000
0.964
2.367
1.099
0.951
1.092
0.799
2.645
5.253
12.733
4.044
3.036
(+)-73
OH
H
O
H
9
7.26927
6.98228
5.71812
5.71557
5.66644
5.66382
5.64225
5.53163
5.51103
5.50698
5.45942
4.76726
4.76145
4.77568
3.68420
3.66323
3.64323
3.13868
3.11425
3.10847
3.10057
2.81967
2.27682
2.27178
2.22897
2.18739
2.18069
2.17504
2.08494
2.04896
2.02721
2.00329
1.98812
1.94973
1.94478
1.43496
1.37950
1.35578
1.33318
1.27656
1.18385
1.16272
0.90684
0.88542
0.86223

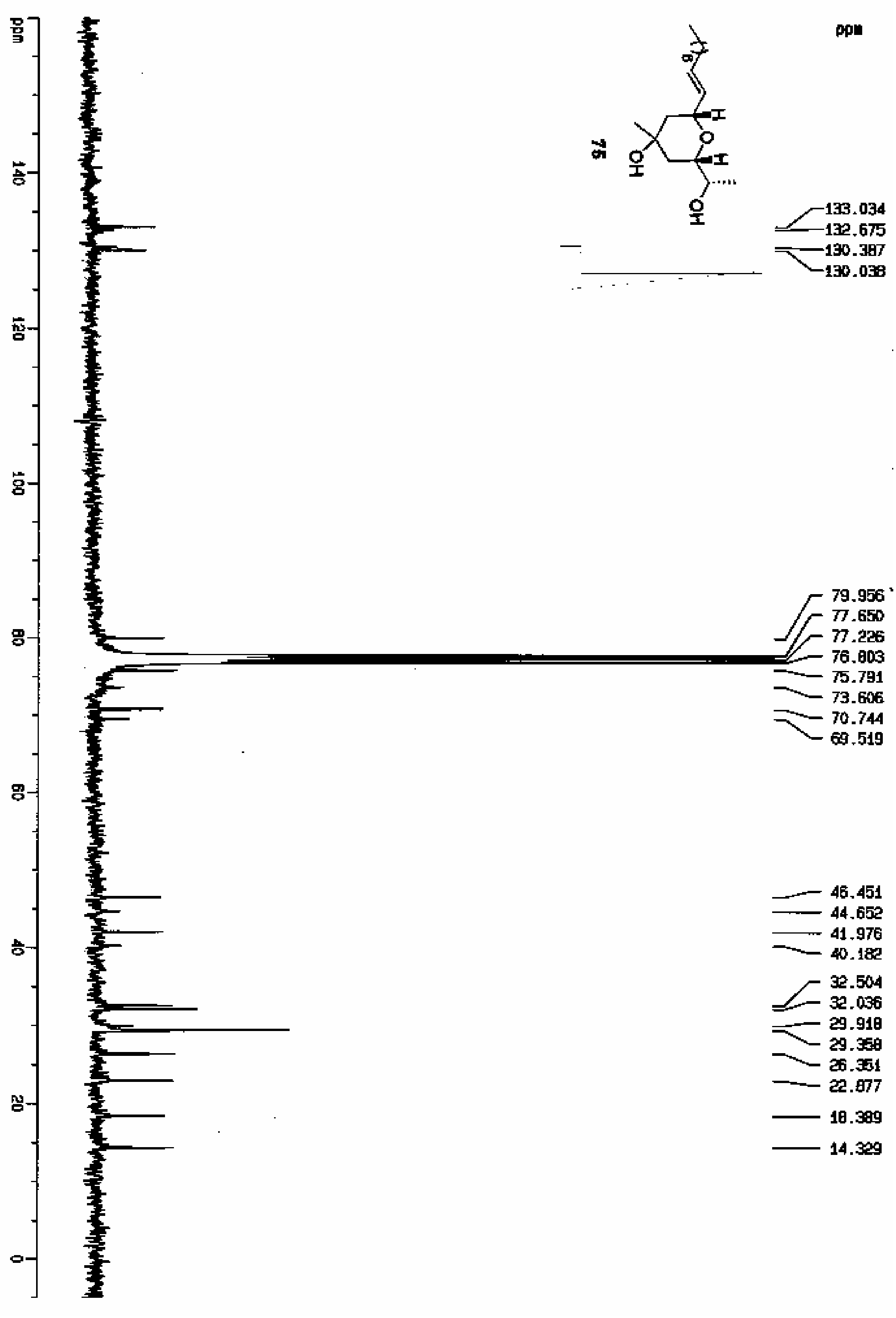

ppm
(+)-73
OH
H
O
H
6
143.992
132.752
130.543
109.564
82.922
79.104
77.654
77.231
76.809
70.731
41.267
36.711
32.525
32.052
29.347
22.851
18.430
14.220
ppm
160
140
120
100
80
60
40
20
0



Danielle Ambele 05-26-03 1111 (301)
NOESY pyran
OH
6
ppm
4.0
3.5
3.0
ppm
3.0
3.5
4.0
Current Data Parameters
F2 - Acquisition Parameters
F1 - Acquisition parameters
F2 - Processing parameters
F1 - Processing parameters
2D NMR plot parameters

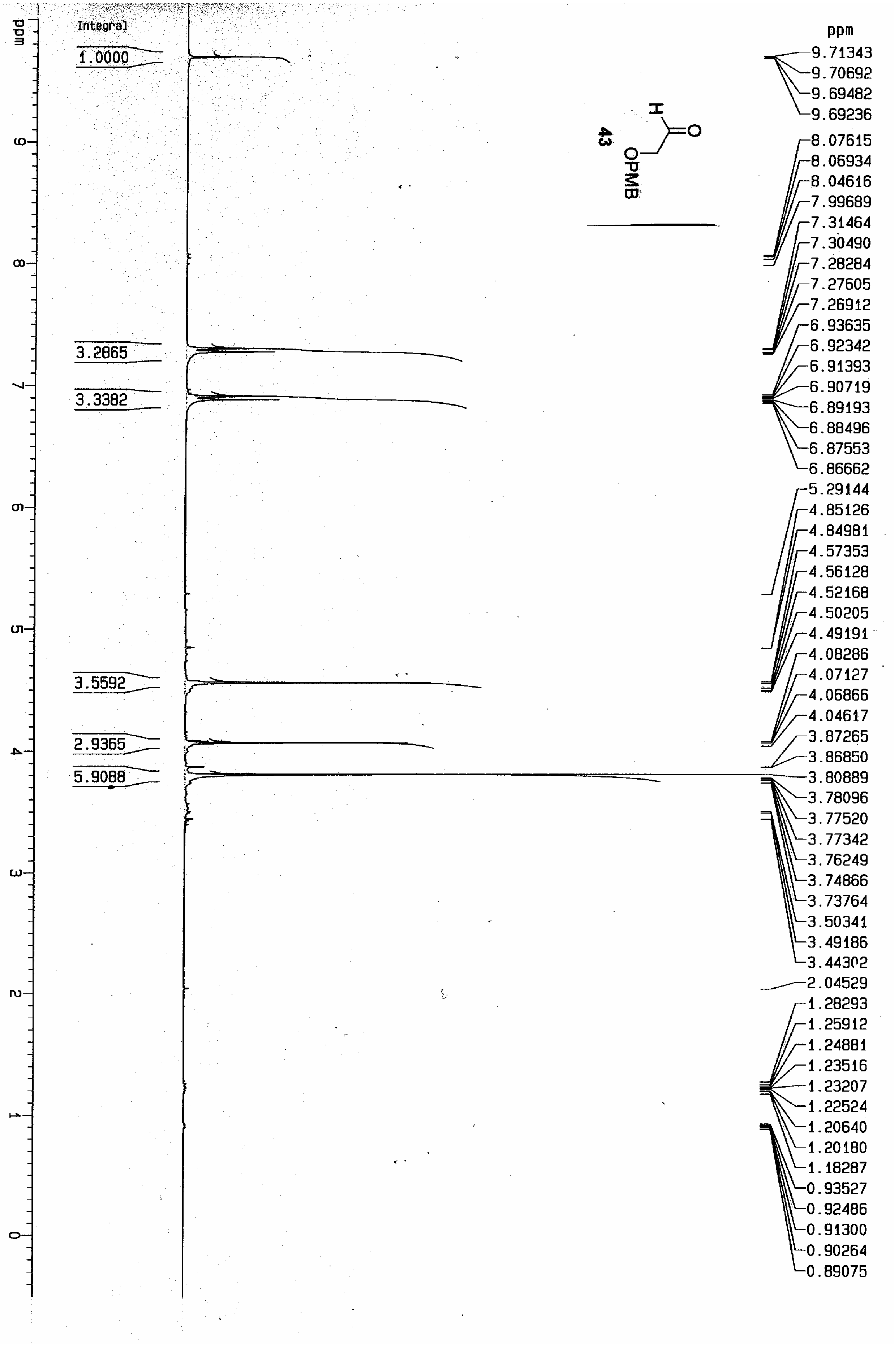
(+)-73

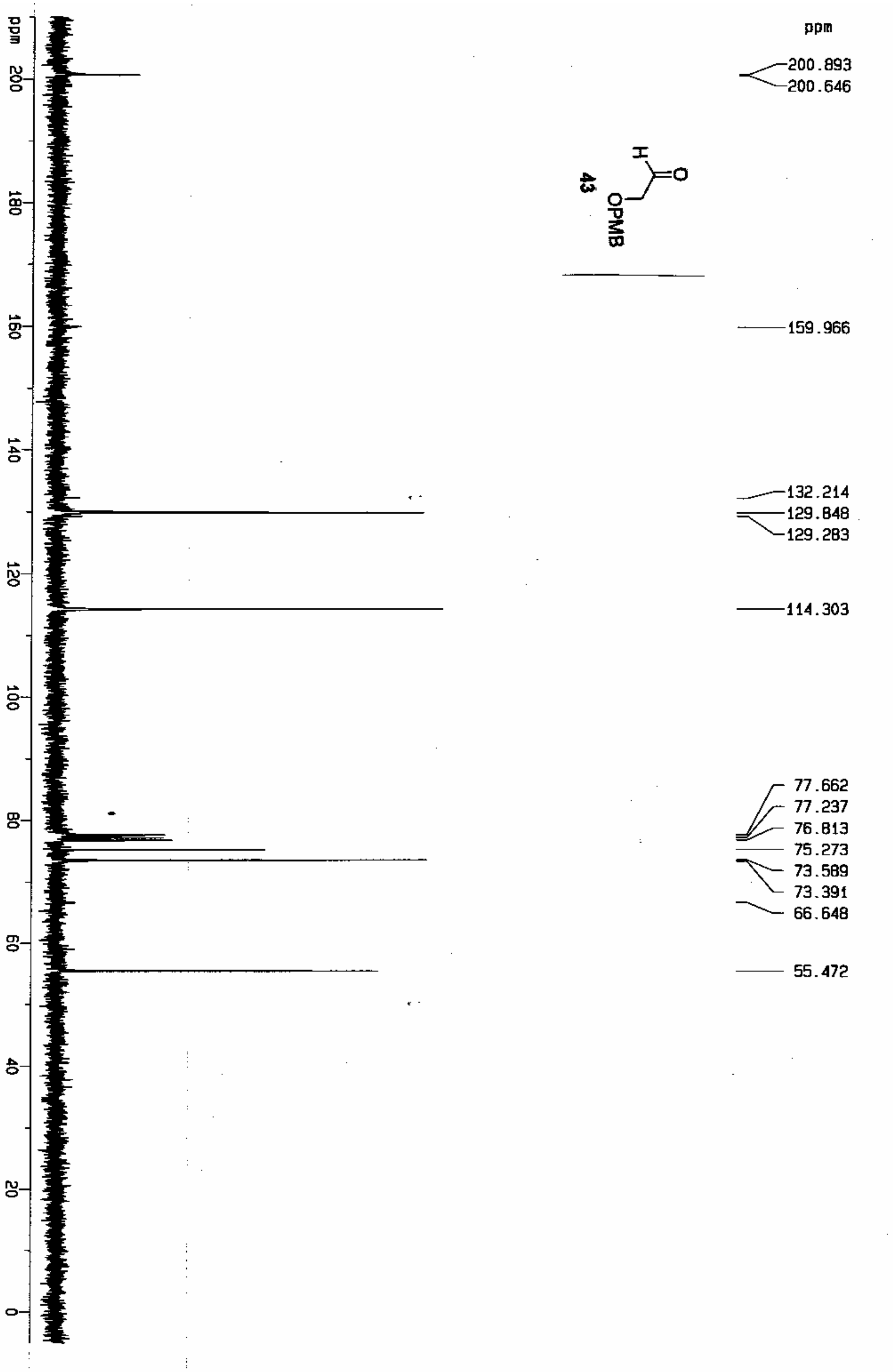

76
ppm
Integral
1.000
1.019
0.430
0.923
1.774
0.946
2.303
23.585
4.898
4.274
7.27137
5.71430
5.68637
5.66297
5.64078
5.49379
5.47330
5.44168
5.42170
3.83414
3.81669
3.66693
3.64487
3.62294
3.19948
3.17549
3.16683
3.15997
3.14267
2.07020
2.04806
2.02493
1.69069
1.66441
1.62280
1.58393
1.50176
1.46117
1.44106
1.42000
1.38562
1.36282
1.34811
1.29634
1.27911
1.21972
1.17538
1.15416
0.91052
0.89017
0.86728

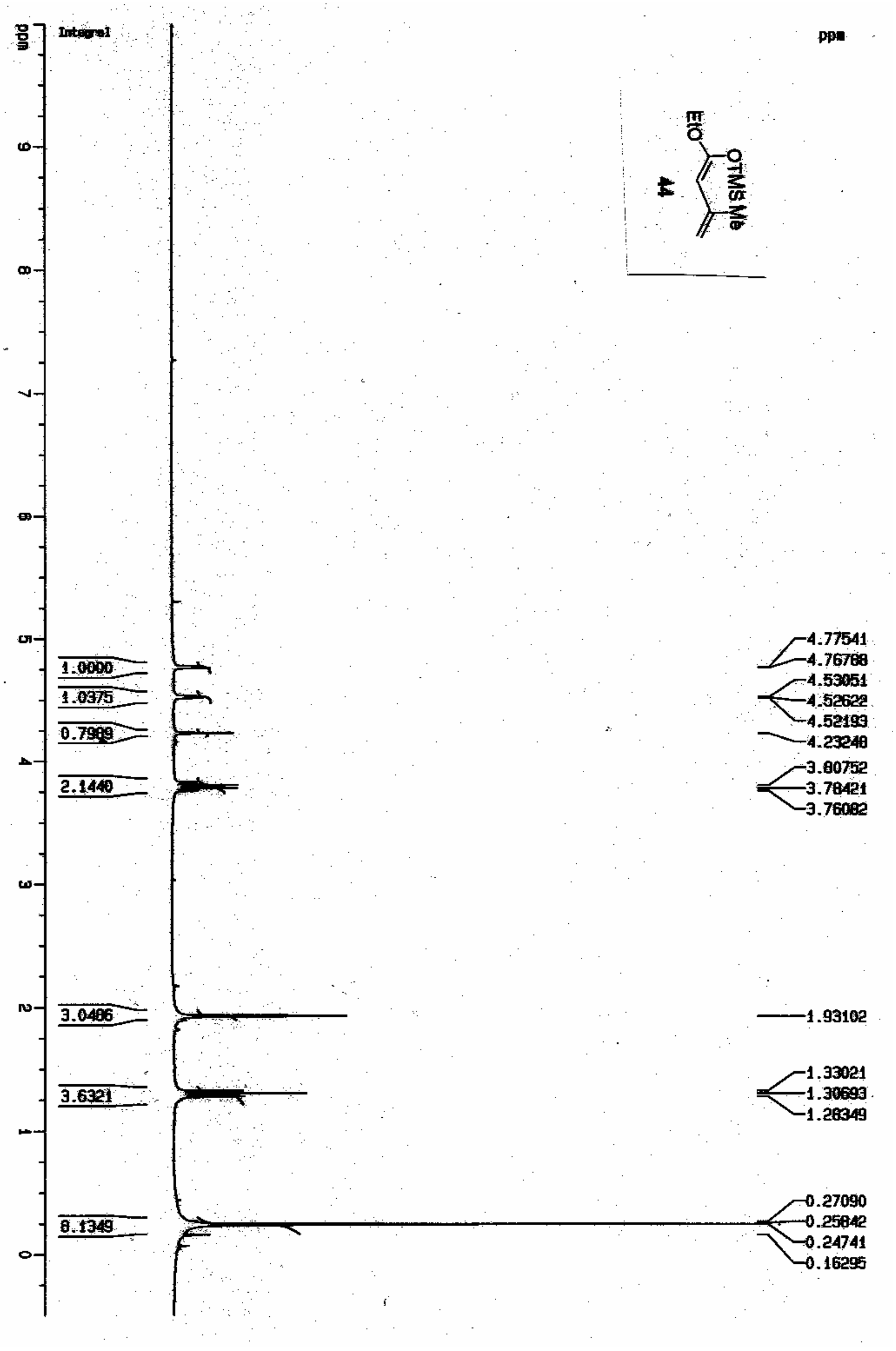

75
ppm
133.034
132.675
130.387
130.038
79.956
77.650
77.226
76.803
75.791
73.606
70.744
69.519
46.451
44.652
41.976
40.182
32.504
32.036
29.918
29.358
26.351
22.877
18.389
14.329
ppm
140
120
100
80
60
40
20
0
OH
OH
H
H
O
6

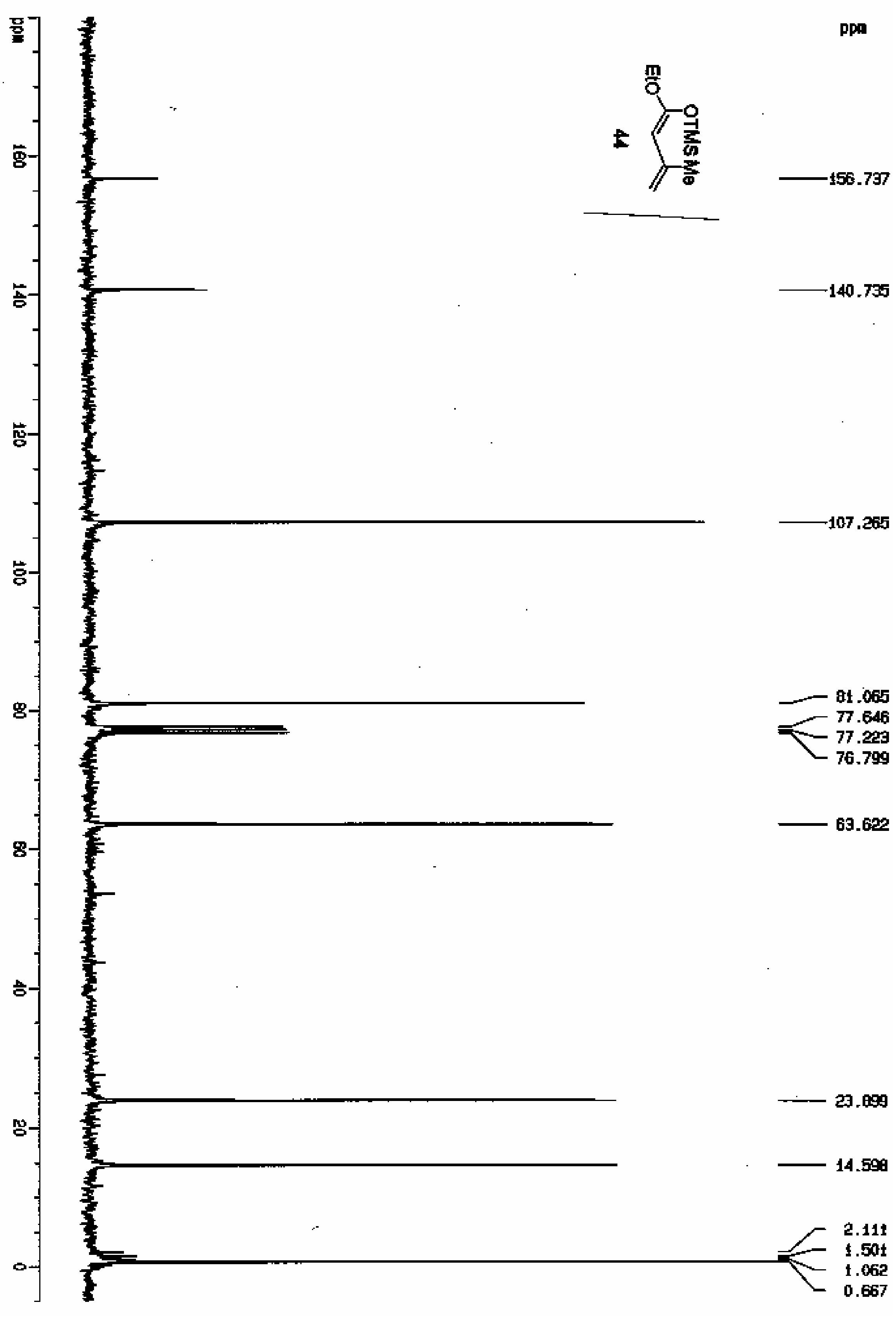
APPEDIX C

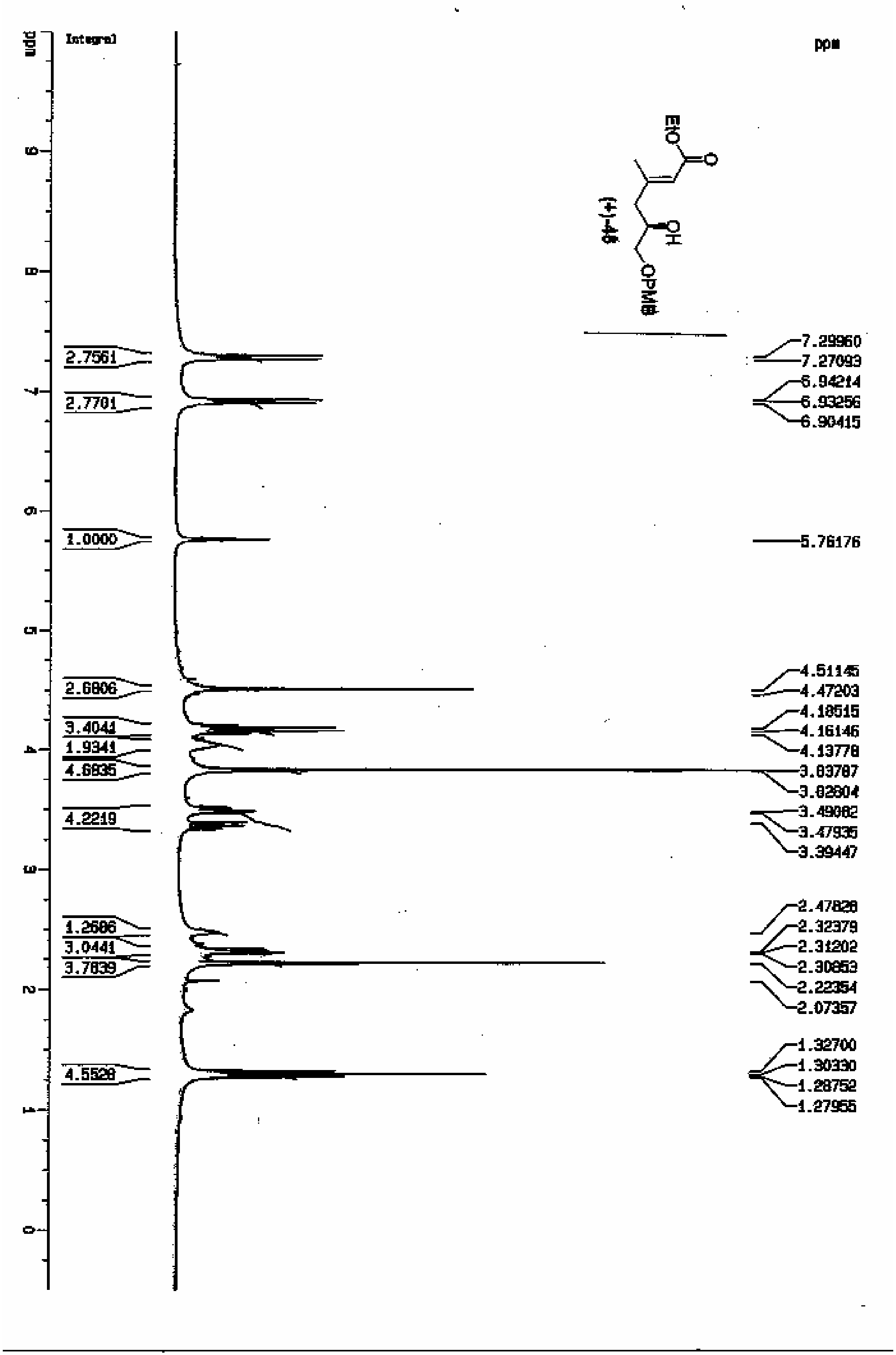
Efforts towards the total synthesis of (+)-Dactylolide (Supporting information)

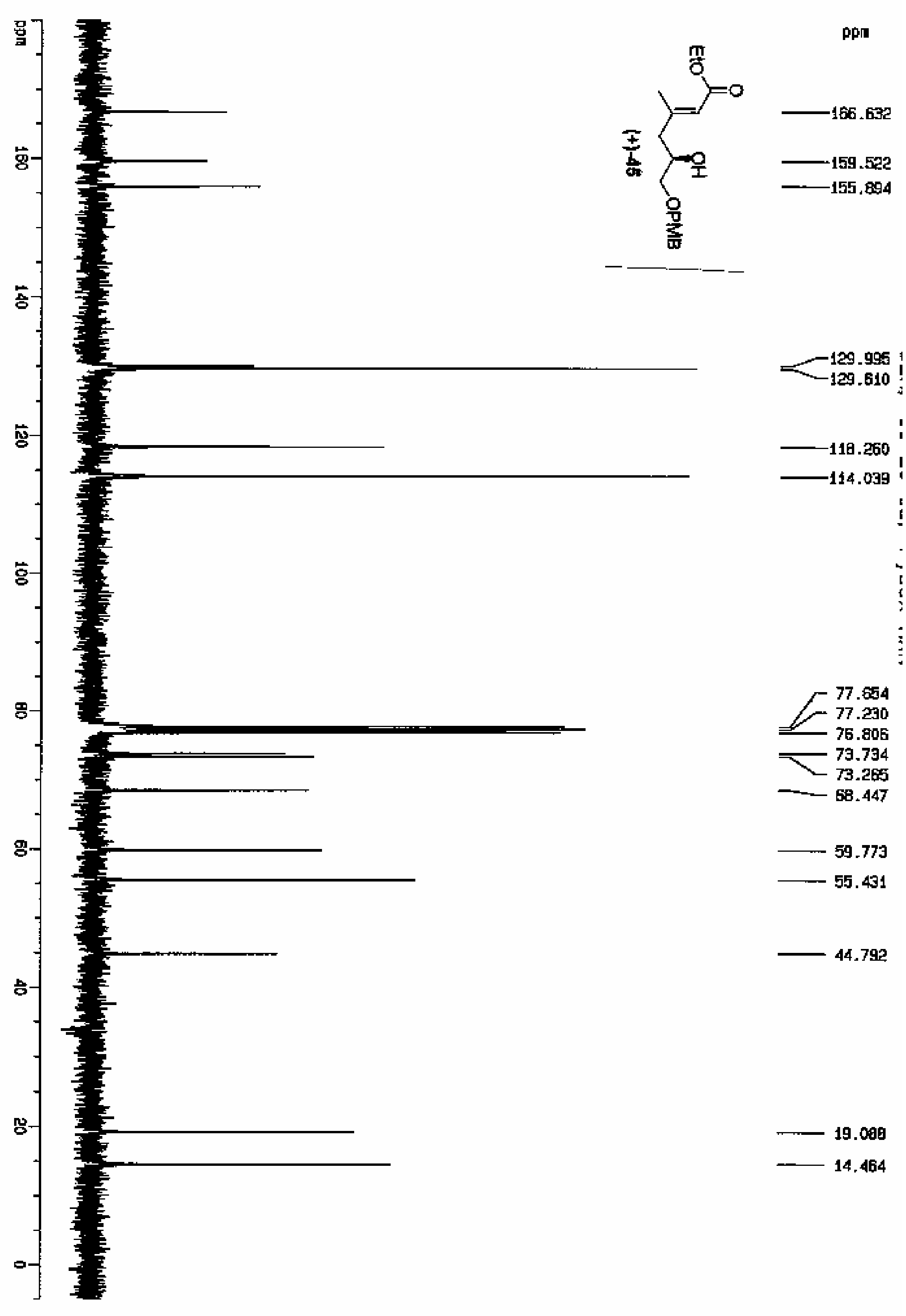

Integral
1.0000
3.2865
3.3382
3.5592
2.9365
5.9088
ppm
9
8
7
6
5
4
3
2
1
0
43
OPMB
H
O
ppm
9.71343
9.70692
9.69482
9.69236
8.07615
8.06934
8.04616
7.99689
7.31464
7.30490
7.28284
7.27605
7.26912
6.93635
6.92342
6.91393
6.90719
6.89193
6.88496
6.87553
6.86662
5.29144
4.85126
4.84981
4.57353
4.56128
4.52168
4.50205
4.49191
4.08286
4.07127
4.06866
4.04617
3.87265
3.86850
3.80889
3.78096
3.77520
3.77342
3.76249
3.74866
3.73764
3.50341
3.49186
3.44302
2.04529
1.28293
1.25912
1.24881
1.23516
1.23207
1.22524
1.20640
1.20180
1.18287
0.93527
0.92486
0.91300
0.90264
0.89075

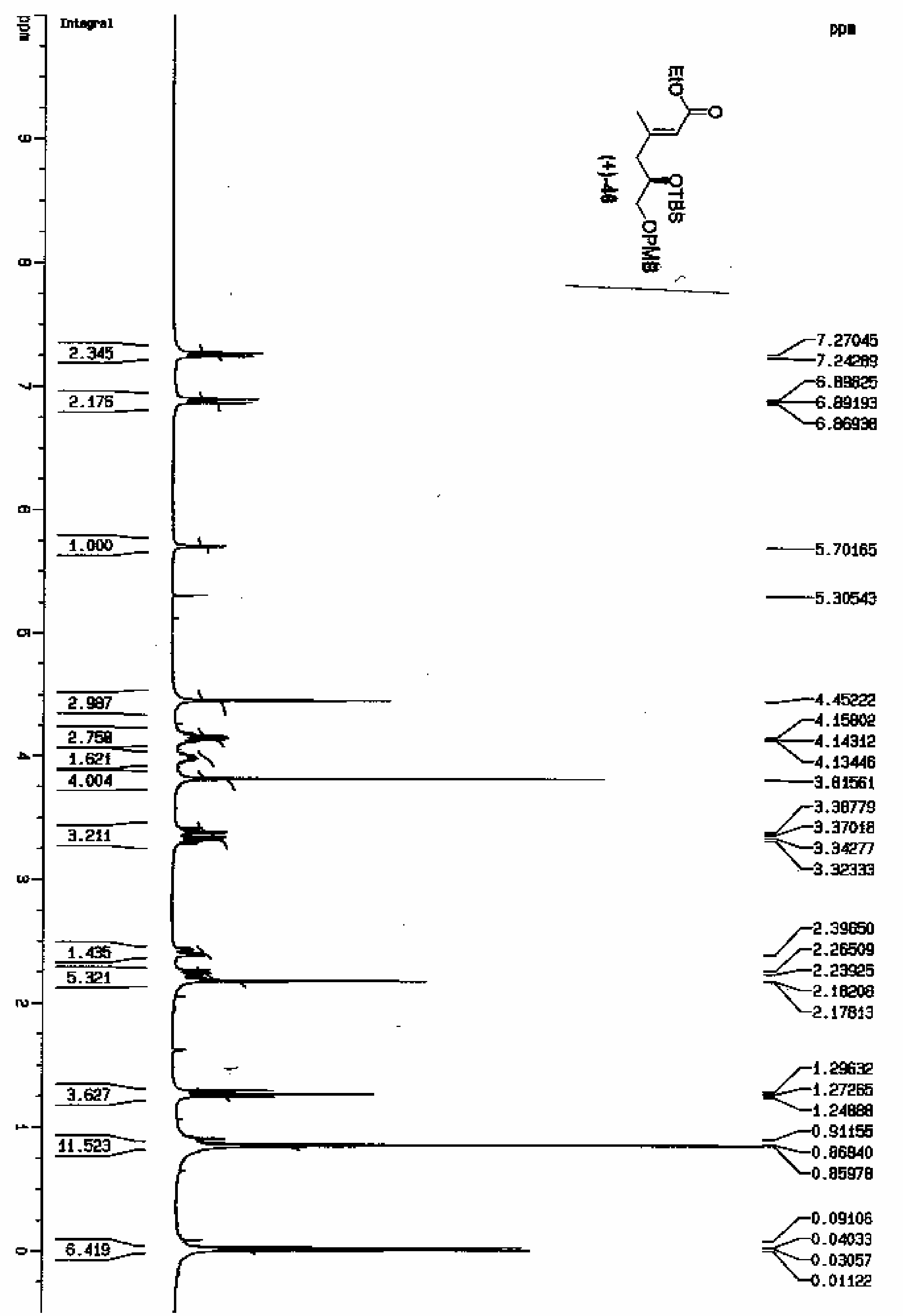

ppm
200.893
200.646
159.966
132.214
129.848
129.283
114.303
77.662
77.237
76.813
75.273
73.589
73.391
66.648
55.472
OPMB
H
O
43
ppm 200
180
160
140
120
100
80
60
40
20
0


ppm
Integral
9
8
7
6
5
4
3
2
1
0
1.0000
1.0375
0.7909
2.1440
3.0486
3.6321
8.1349
EtO
OTMS Me
44
4.77541
4.76788
4.53051
4.52622
4.52193
4.23248
3.80752
3.78421
3.76082
1.93102
1.33021
1.30693
1.28349
0.27090
0.25842
0.24741
0.16295

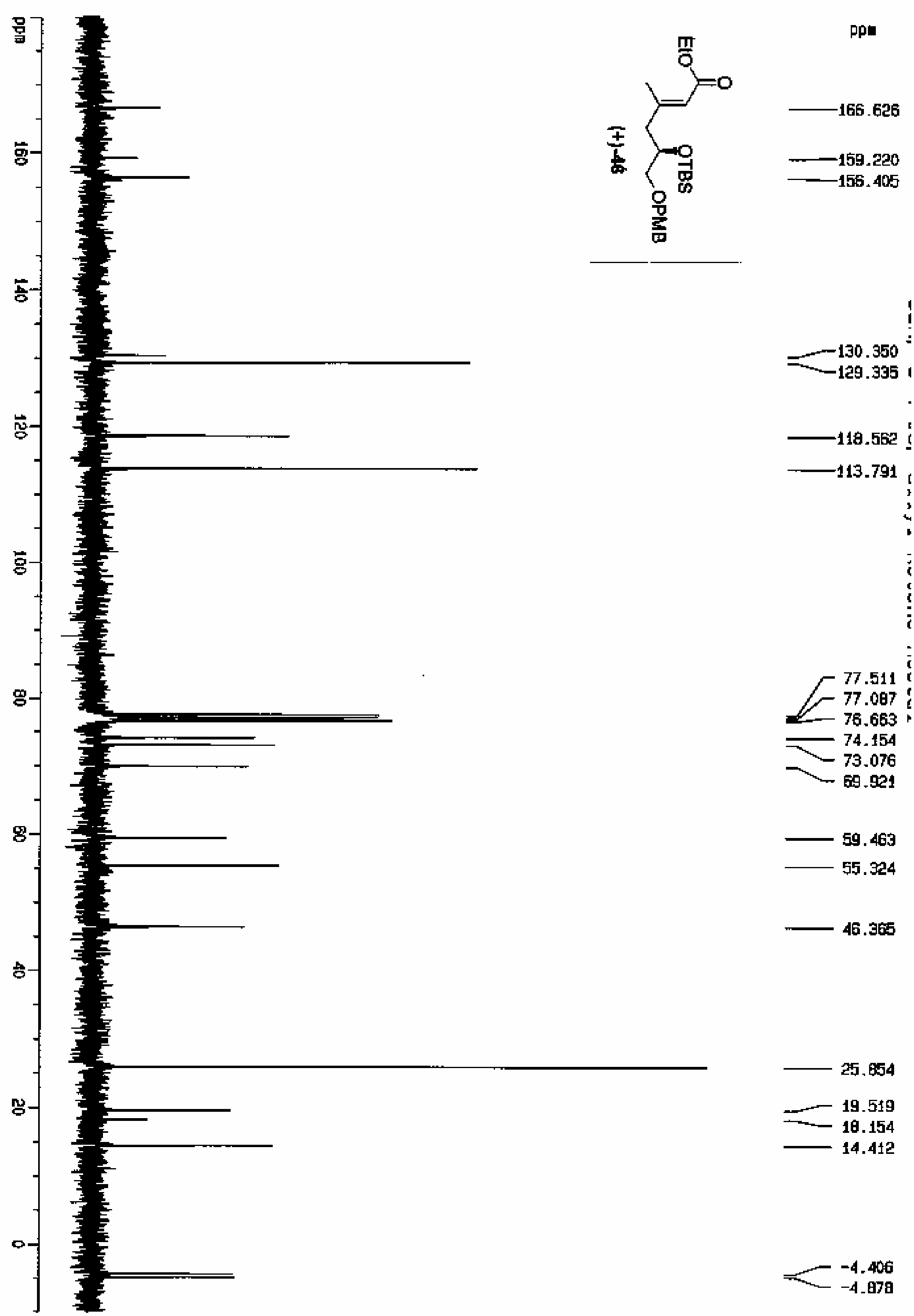

ppm
OTMS Me
EtO
44
156.737
140.735
107.265
81.065
77.646
77.223
76.799
63.622
23.899
14.598
2.111
1.501
1.062
0.667
ppm
160
140
120
100
80
60
40
20
0

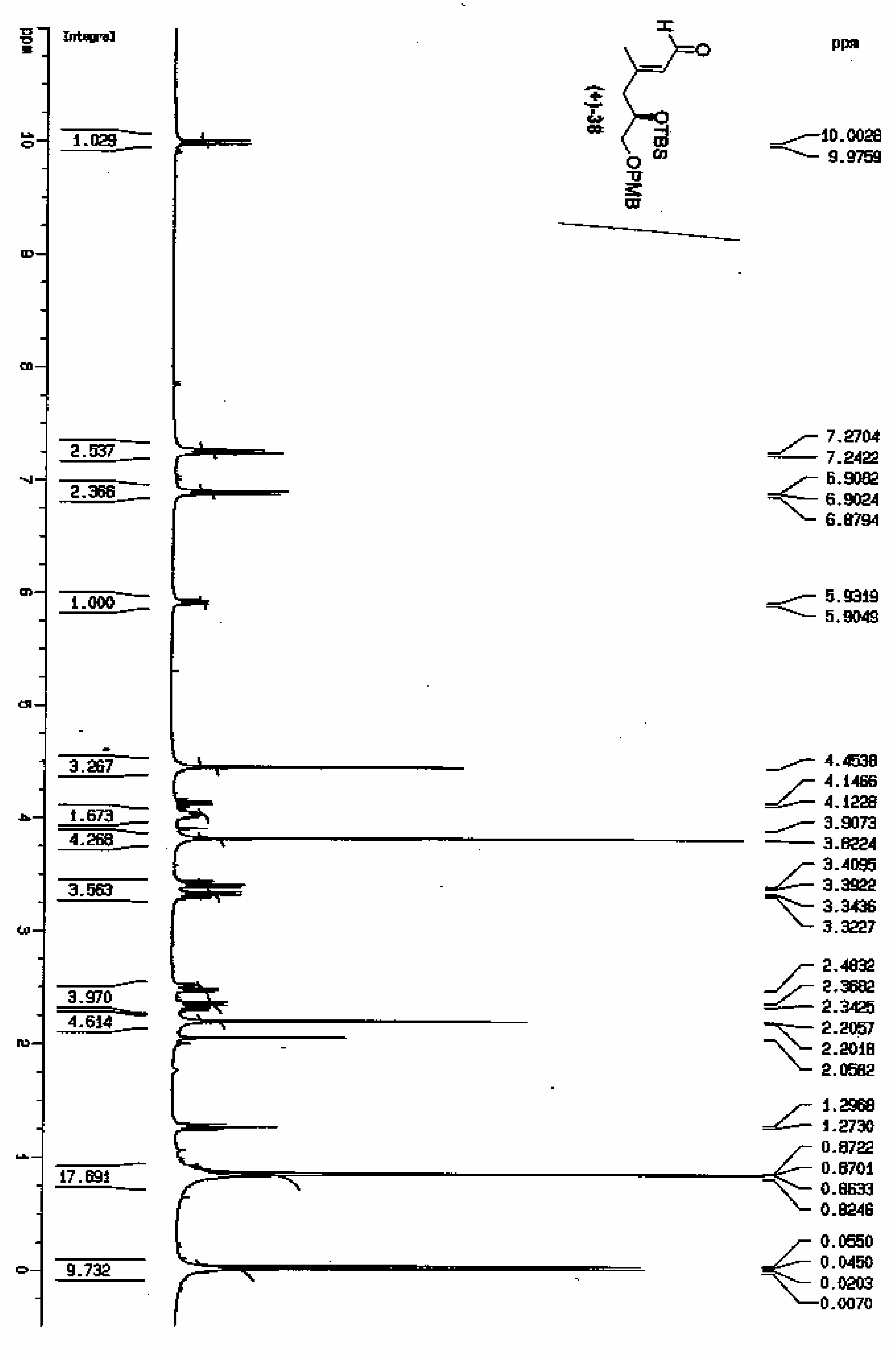

ppm
Integral
ppm
EtO
O
OH
OPMB
(+)-46
2.7561
2.7701
1.0000
2.6806
3.4041
1.9341
4.6835
4.2219
1.2606
3.0441
3.7839
4.5528
7.29960
7.27093
6.94214
6.93256
6.90415
5.76176
4.51145
4.47203
4.18515
4.16146
4.13778
3.83787
3.82804
3.49062
3.47935
3.39447
2.47828
2.32379
2.31202
2.30653
2.22354
2.07357
1.32700
1.30330
1.28752
1.27955
9
8
7
6
5
4
3
2
1
0

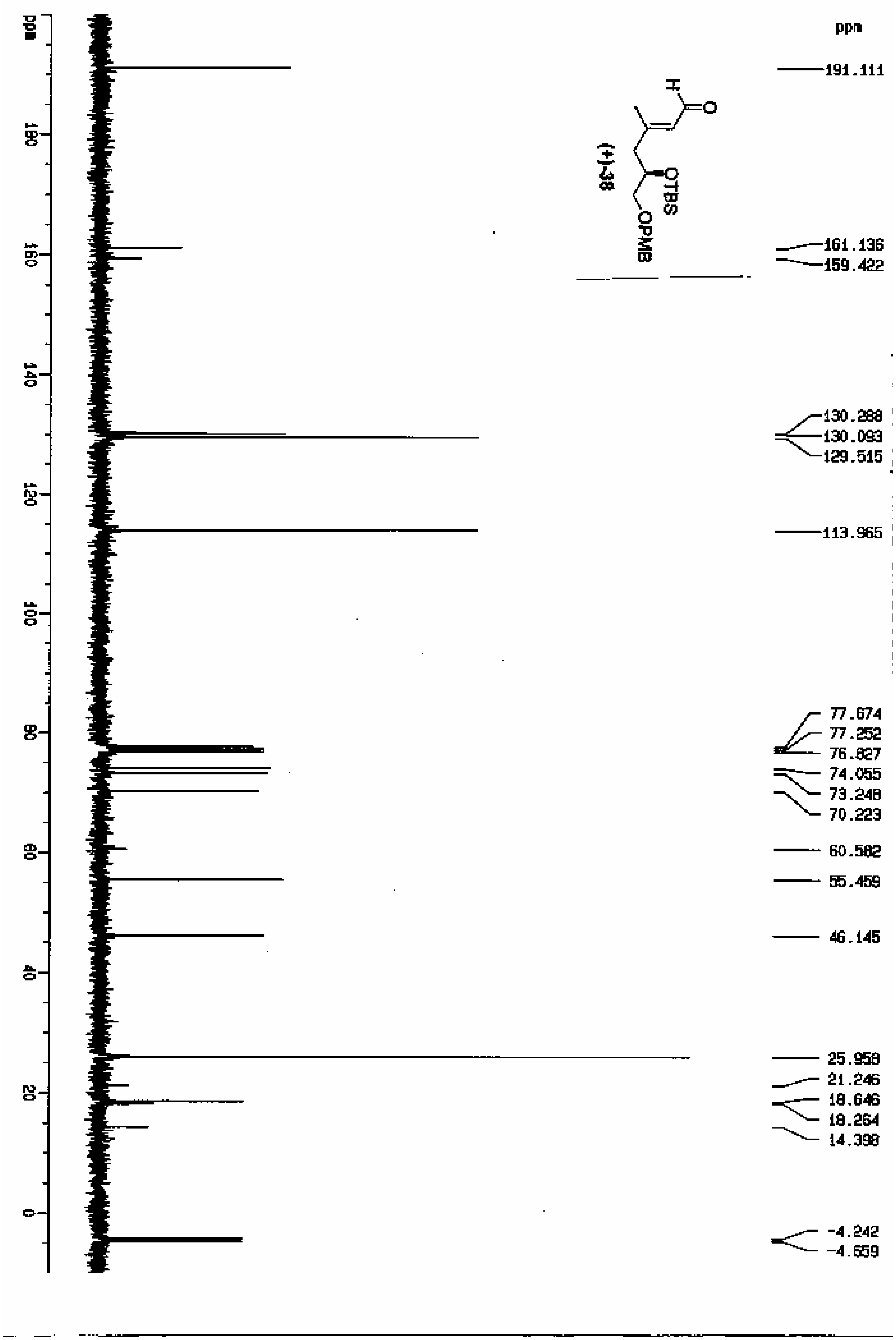

ppm
EtO
O
OH
OPMB
(+)-45
ppm
166.632
159.522
155.894
129.995
129.610
118.260
114.039
77.654
77.230
76.806
73.734
73.265
68.447
59.773
55.431
44.792
19.088
14.464
160
140
120
100
80
60
40
20
0



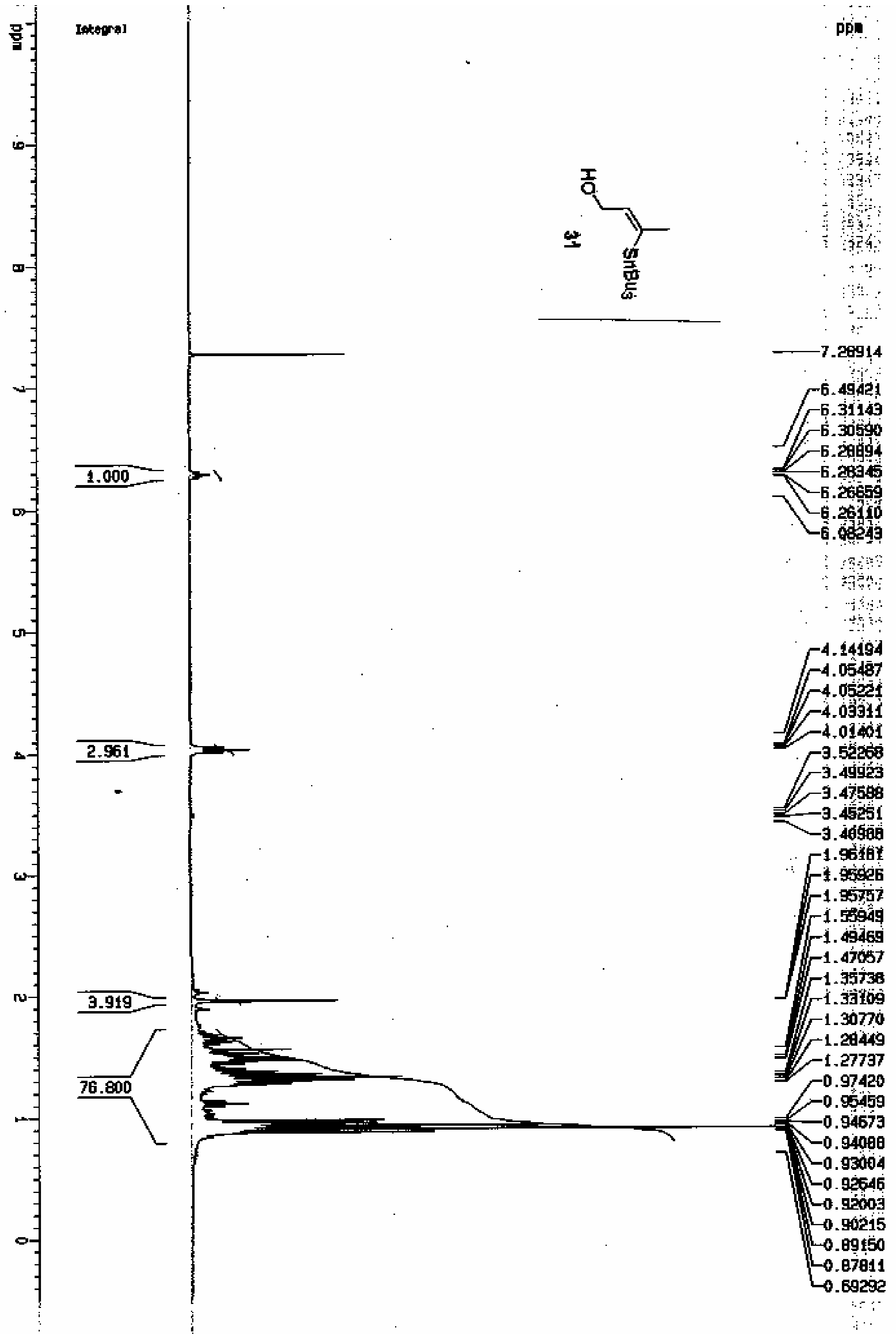
ppm
Integral
ppm
EtO
O
OTBS
OPMB
(+)-46
2.345
2.176
1.000
2.987
2.758
1.621
4.004
3.211
1.435
5.321
3.627
11.523
6.419
7.27045
7.24289
6.89625
6.89193
6.86938
5.70165
5.30543
4.45222
4.15802
4.14312
4.13446
3.81561
3.38779
3.37018
3.34277
3.32333
2.39650
2.26509
2.23925
2.18208
2.17813
1.29632
1.27265
1.24888
0.91155
0.86940
0.85978
0.09106
0.04033
0.03057
0.01122
9
8
7
6
5
4
3
2
1
0

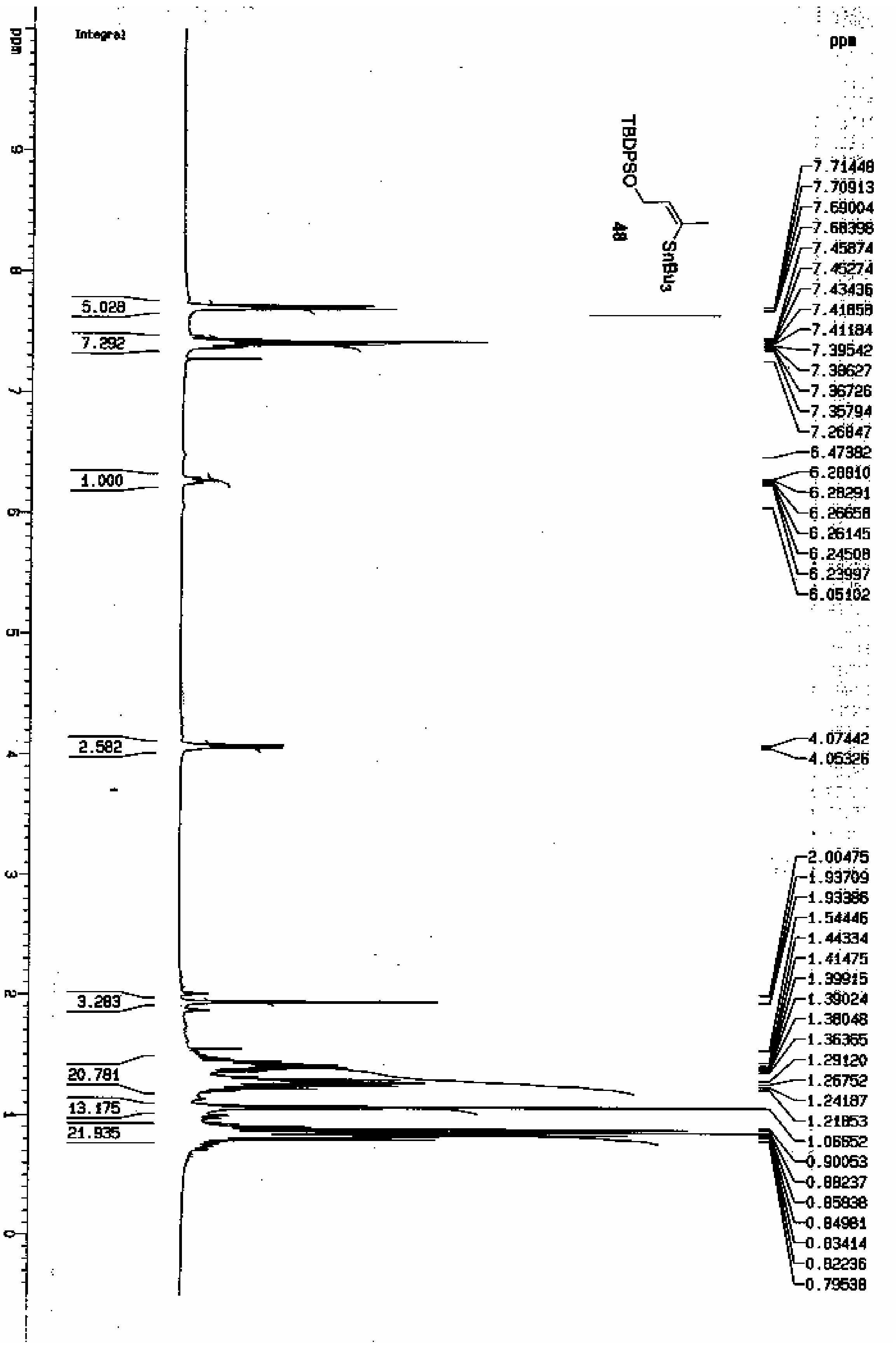

ppm
166.626
159.220
156.405
130.350
129.335
118.562
113.791
77.511
77.087
76.663
74.154
73.076
69.921
59.463
55.324
46.365
25.854
19.519
18.154
14.412
-4.406
-4.878
EtO
O
OTBS
OPMB
(+)-46
160
140
120
100
80
60
40
20
0

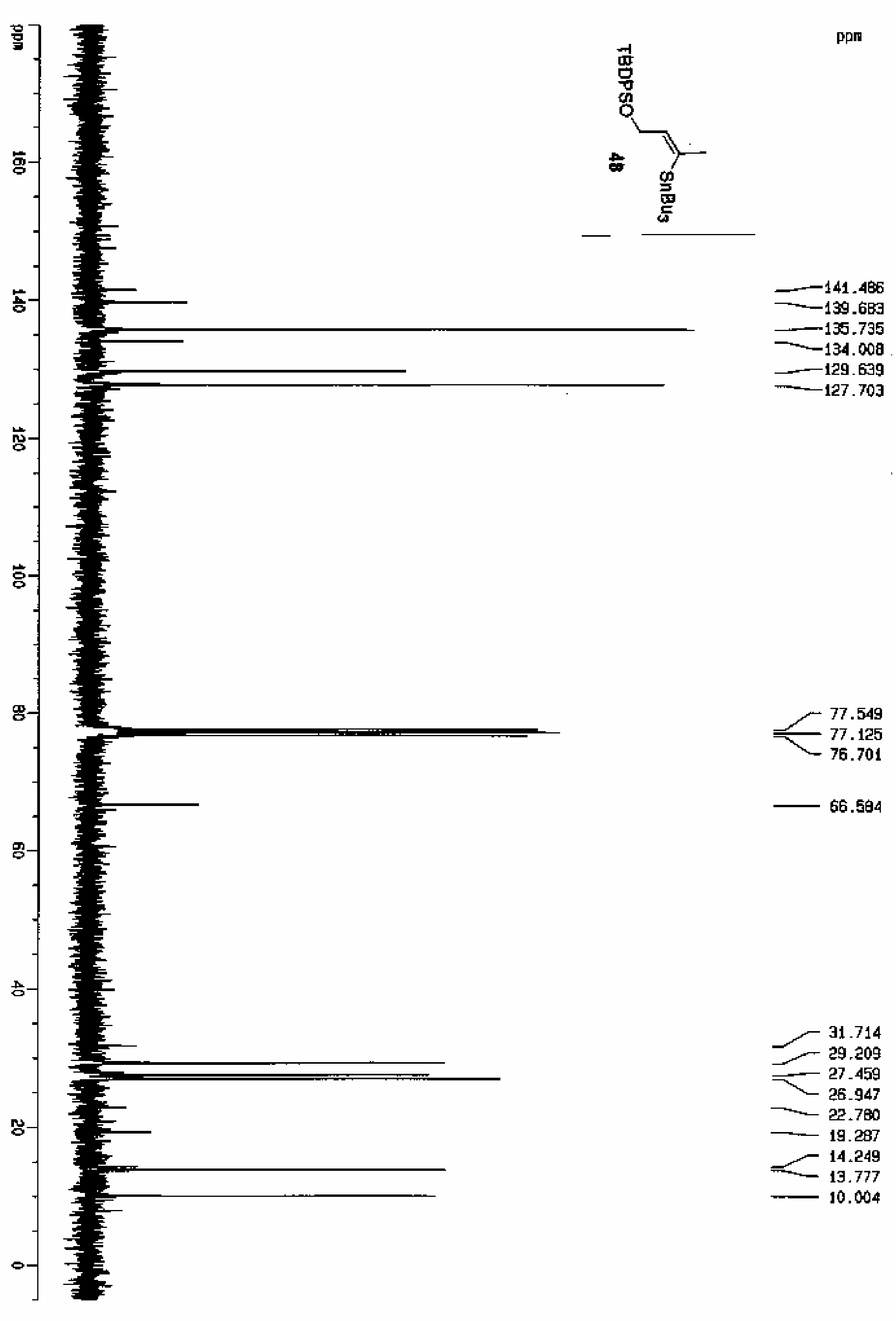

ppm
Integral
10
9
8
7
6
5
4
3
2
1
0
1.029
2.537
2.366
1.000
3.267
1.673
4.268
3.563
3.970
4.614
17.691
9.732
H
O
OTBS
OPMB
(+)-38
ppm
10.0028
9.9759
7.2704
7.2422
6.9082
6.9024
6.8794
5.9319
5.9049
4.4538
4.1466
4.1228
3.9073
3.8224
3.4095
3.3922
3.3436
3.3227
2.4832
2.3682
2.3425
2.2057
2.2018
2.0582
1.2968
1.2730
0.8722
0.8701
0.8633
0.8246
0.0550
0.0450
0.0203
0.0070


ppm
191.111
161.136
159.422
130.288
130.093
129.515
113.965
77.674
77.252
76.827
74.055
73.248
70.223
60.582
55.459
46.145
25.958
21.246
18.646
18.264
14.398
-4.242
-4.659
ppm
180
160
140
120
100
80
60
40
20
0
H
O
OTBS
OPMB

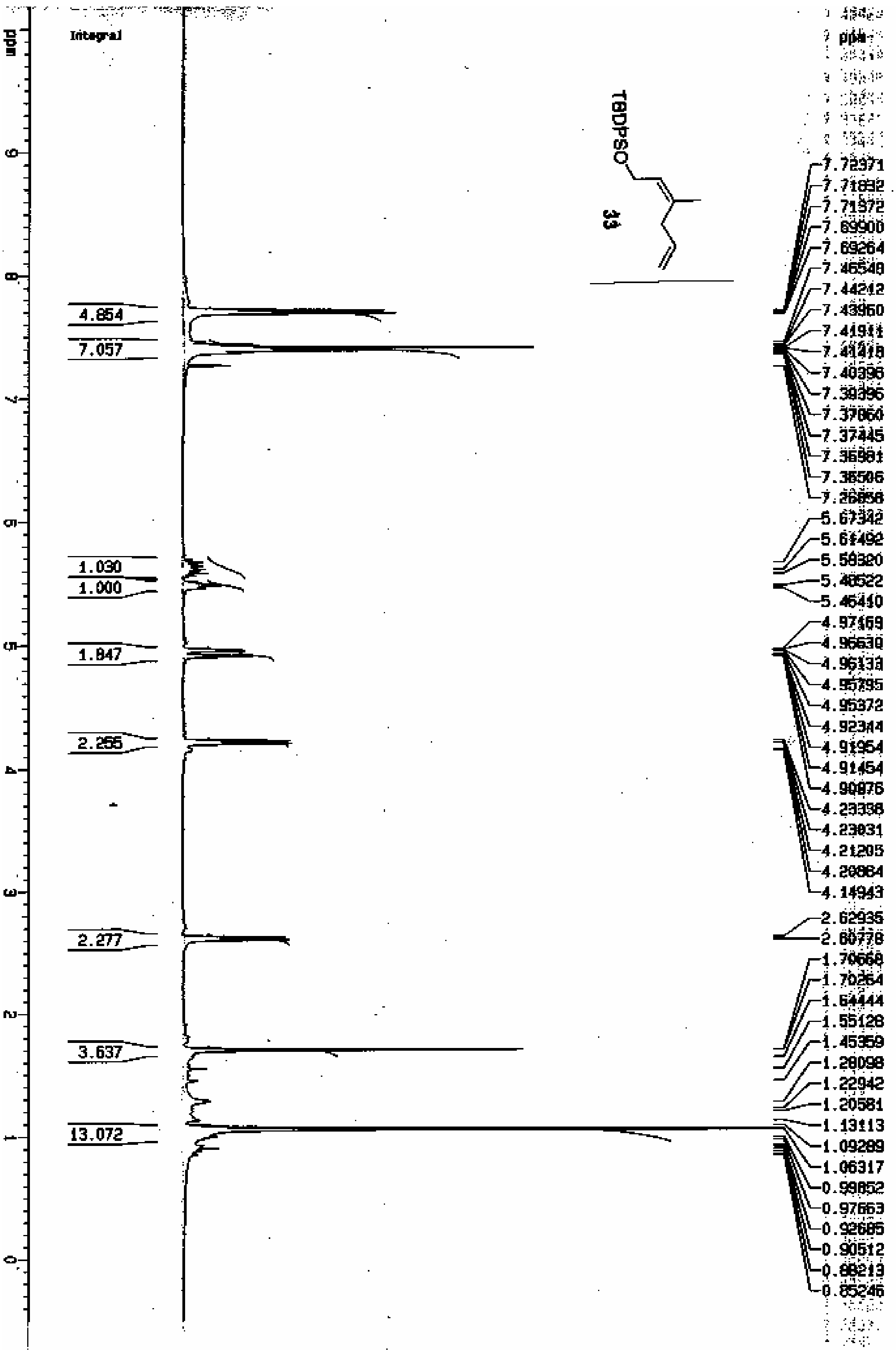
(+)-38

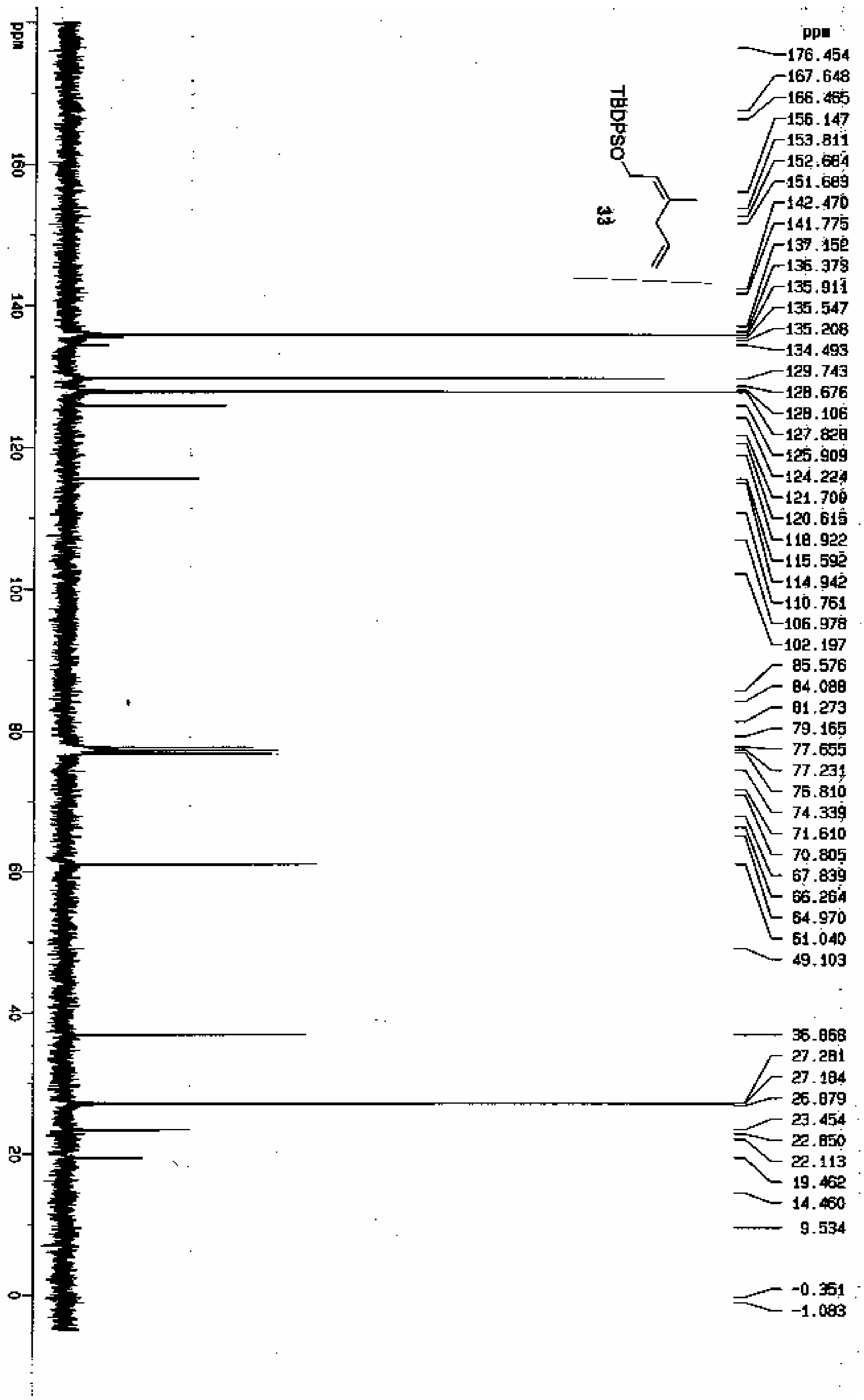

ppm
Integral
1.000
2.961
3.919
76.800
HO
SnBu3
31
7.28914
6.49421
6.31143
6.30590
6.28894
6.28345
6.26659
6.26110
6.08243
4.14194
4.05487
4.05221
4.03311
4.01401
3.52268
3.49923
3.47588
3.45251
3.40968
1.96181
1.95926
1.95757
1.55949
1.49469
1.47057
1.35738
1.33109
1.30770
1.28449
1.27737
0.97420
0.95459
0.94673
0.94088
0.93004
0.92646
0.92003
0.90215
0.89150
0.87811
0.69292
8
7
6
5
4
3
2
1
0

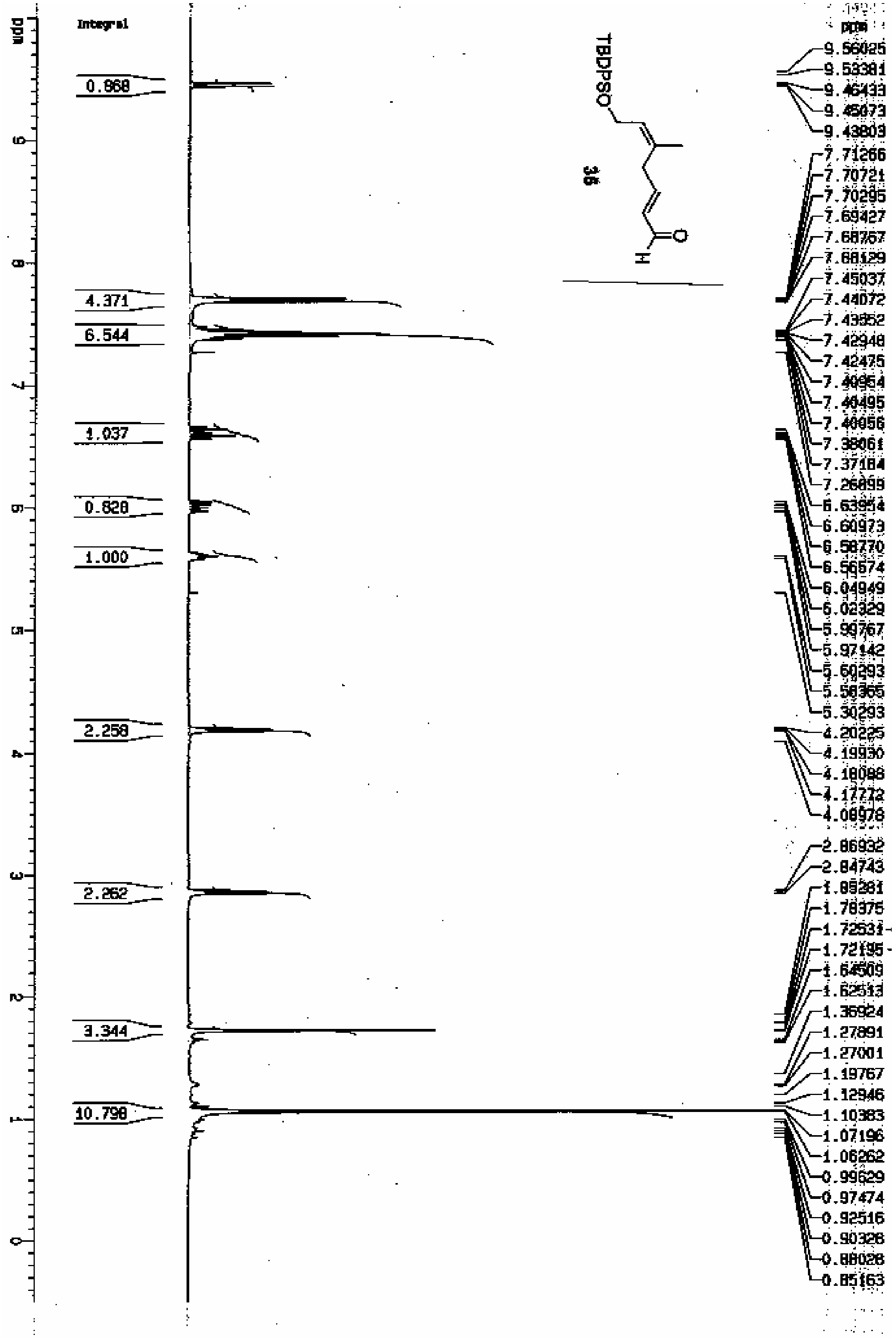

TBDPSO
SnBu3
48
ppm
Integral
5.028
7.292
1.000
2.582
3.283
20.781
13.175
21.835
9
8
7
6
5
4
3
2
1
0
7.71448
7.70913
7.69004
7.68398
7.45874
7.45274
7.43436
7.41858
7.41184
7.39542
7.38627
7.36726
7.35794
7.26847
6.47382
6.28810
6.28291
6.26658
6.26145
6.24508
6.23997
6.05102
4.07442
4.05326
2.00475
1.93709
1.93386
1.54446
1.44334
1.41475
1.39915
1.39024
1.38048
1.36365
1.29120
1.26752
1.24187
1.21853
1.06652
0.90053
0.88237
0.85838
0.84981
0.83414
0.82296
0.79538

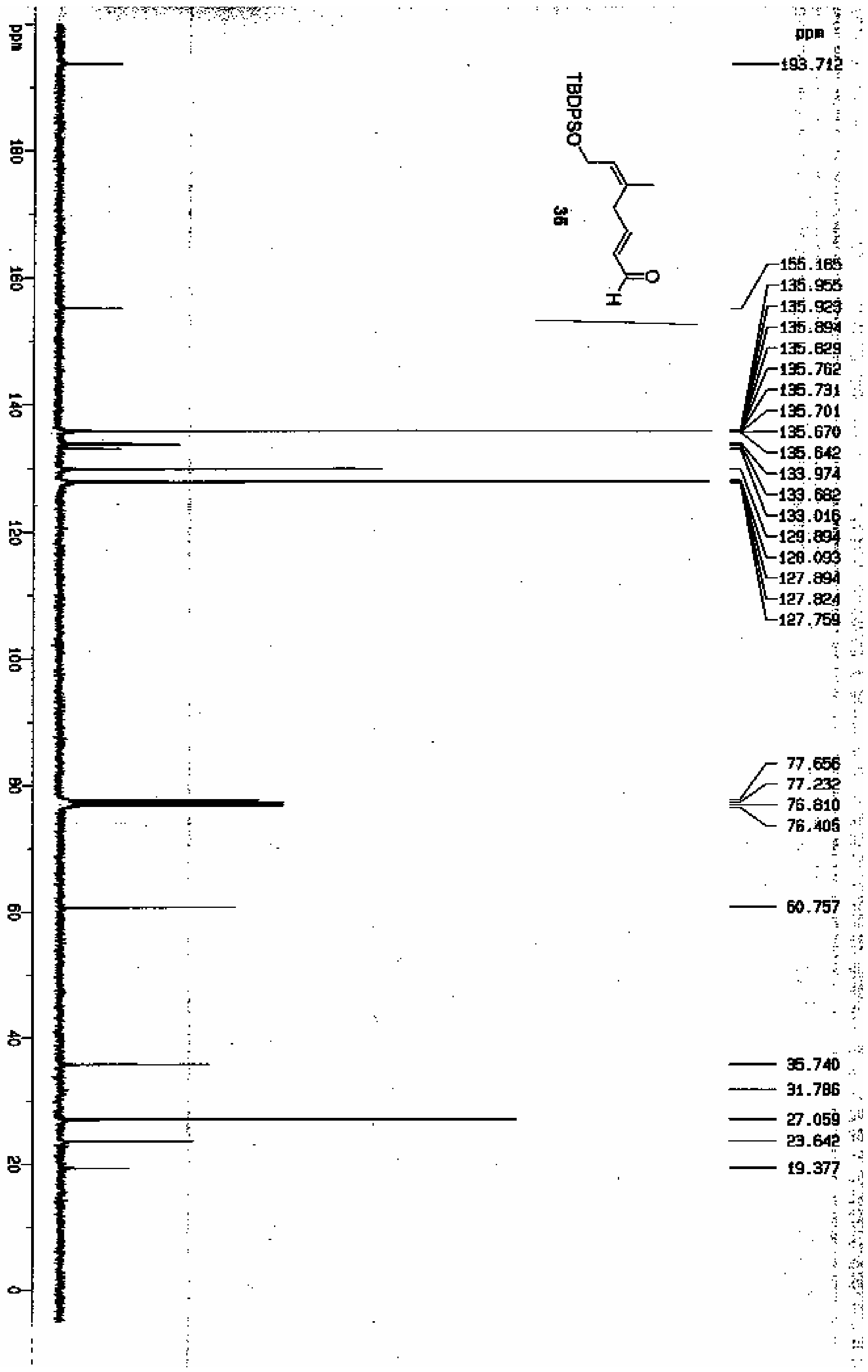

TBDPSO
SnBu3
ppm
160
140
120
100
80
60
40
20
0
ppm
141.486
139.683
135.735
134.008
129.639
127.703
77.549
77.125
76.701
66.584
31.714
29.209
27.459
26.947
22.780
19.287
14.249
13.777
10.004

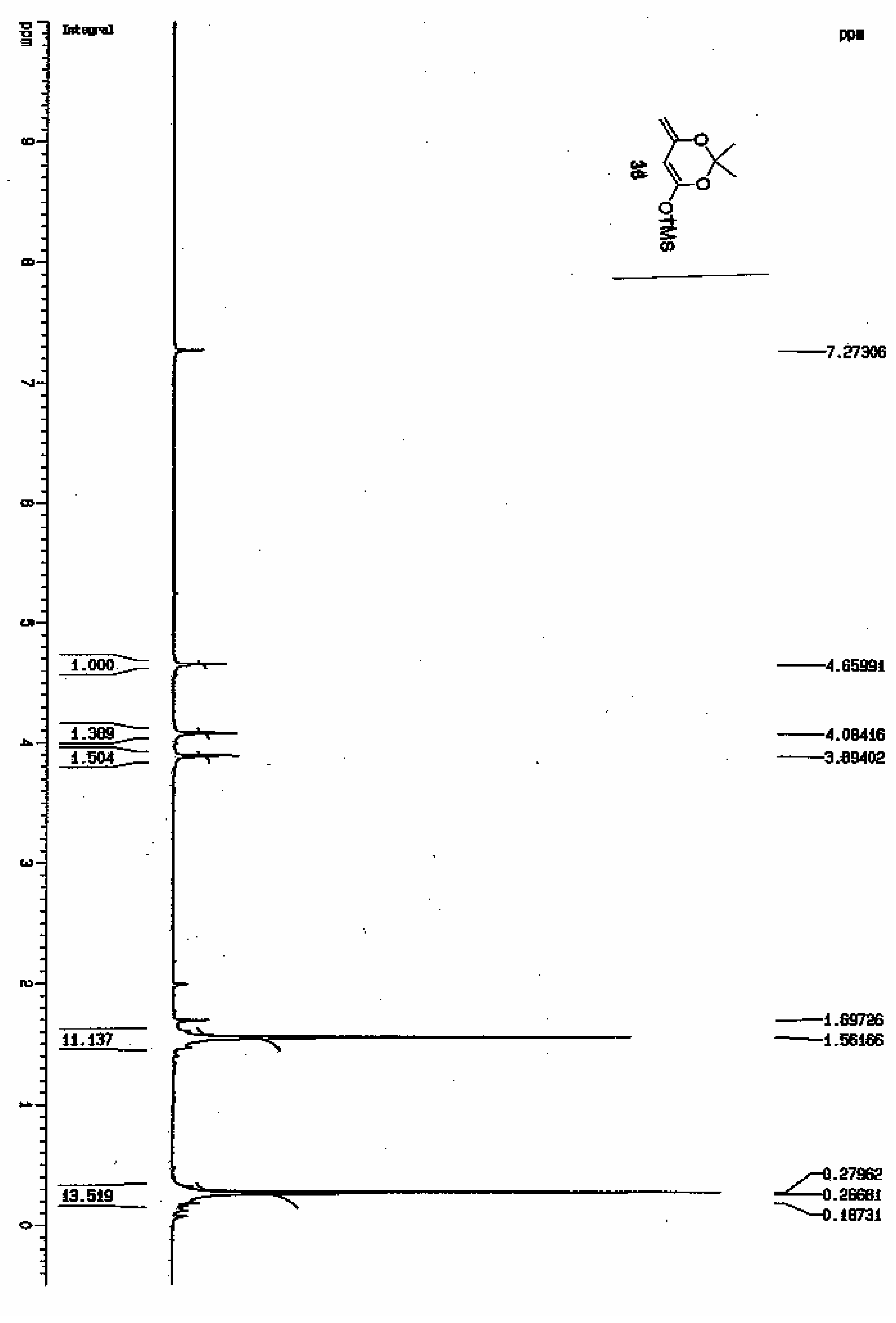
48

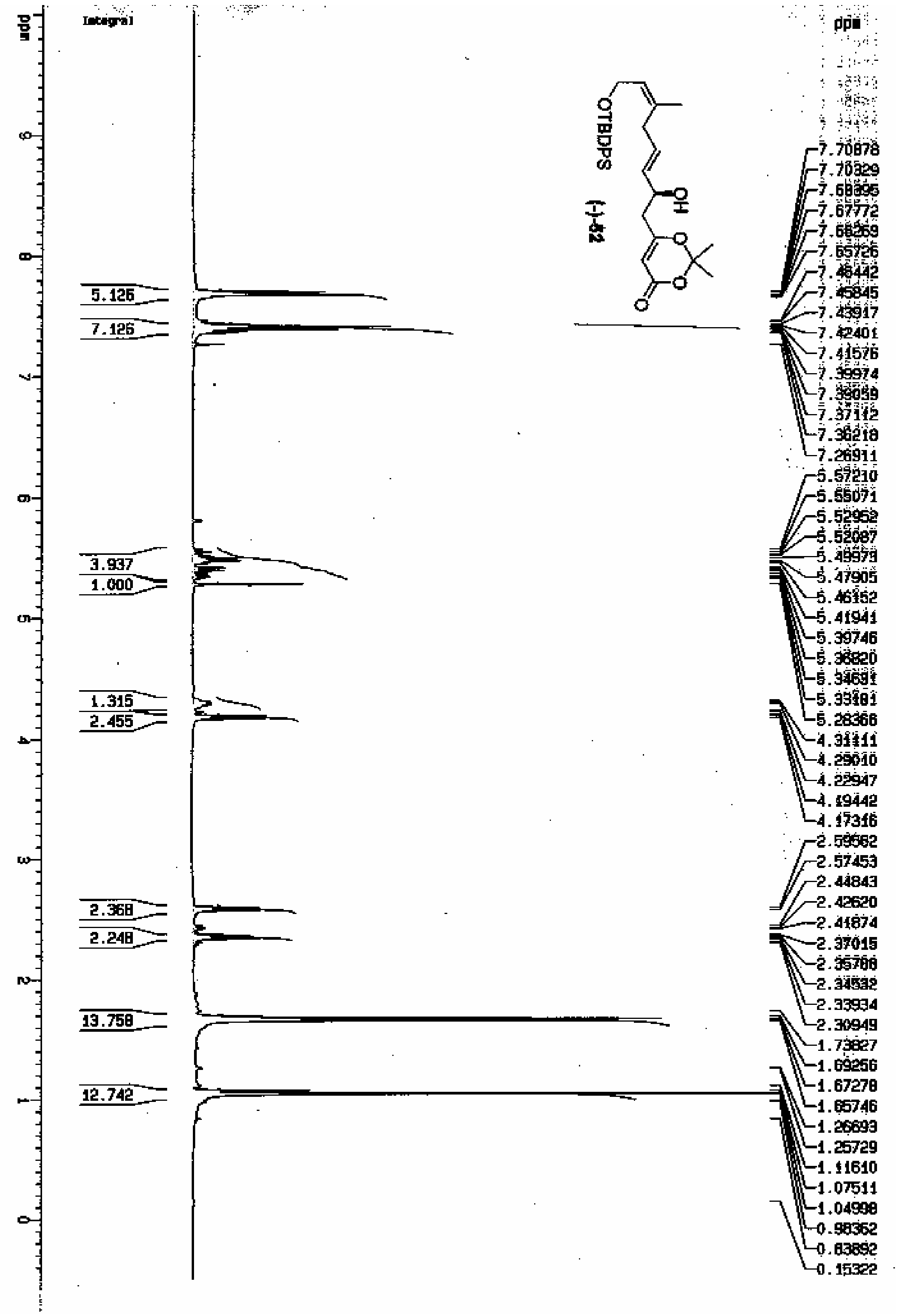

ppm
Integral
9
8
7
6
5
4
3
2
1
0
4.854
7.057
1.030
1.000
1.847
2.265
2.277
3.637
13.072
TBDPSO
33
ppm
7.72371
7.71832
7.71572
7.69900
7.69264
7.46548
7.44212
7.43960
7.41911
7.41418
7.40396
7.39396
7.37860
7.37445
7.36981
7.36506
7.26858
5.67342
5.61492
5.59320
5.48522
5.46440
4.97169
4.96630
4.96133
4.95795
4.95372
4.92344
4.91954
4.91454
4.90876
4.23358
4.23031
4.21205
4.20864
4.14943
2.62935
2.60778
1.70668
1.70264
1.64444
1.55128
1.45359
1.28098
1.22942
1.20581
1.13113
1.09289
1.06317
0.99852
0.97663
0.92685
0.90512
0.88213
0.85246

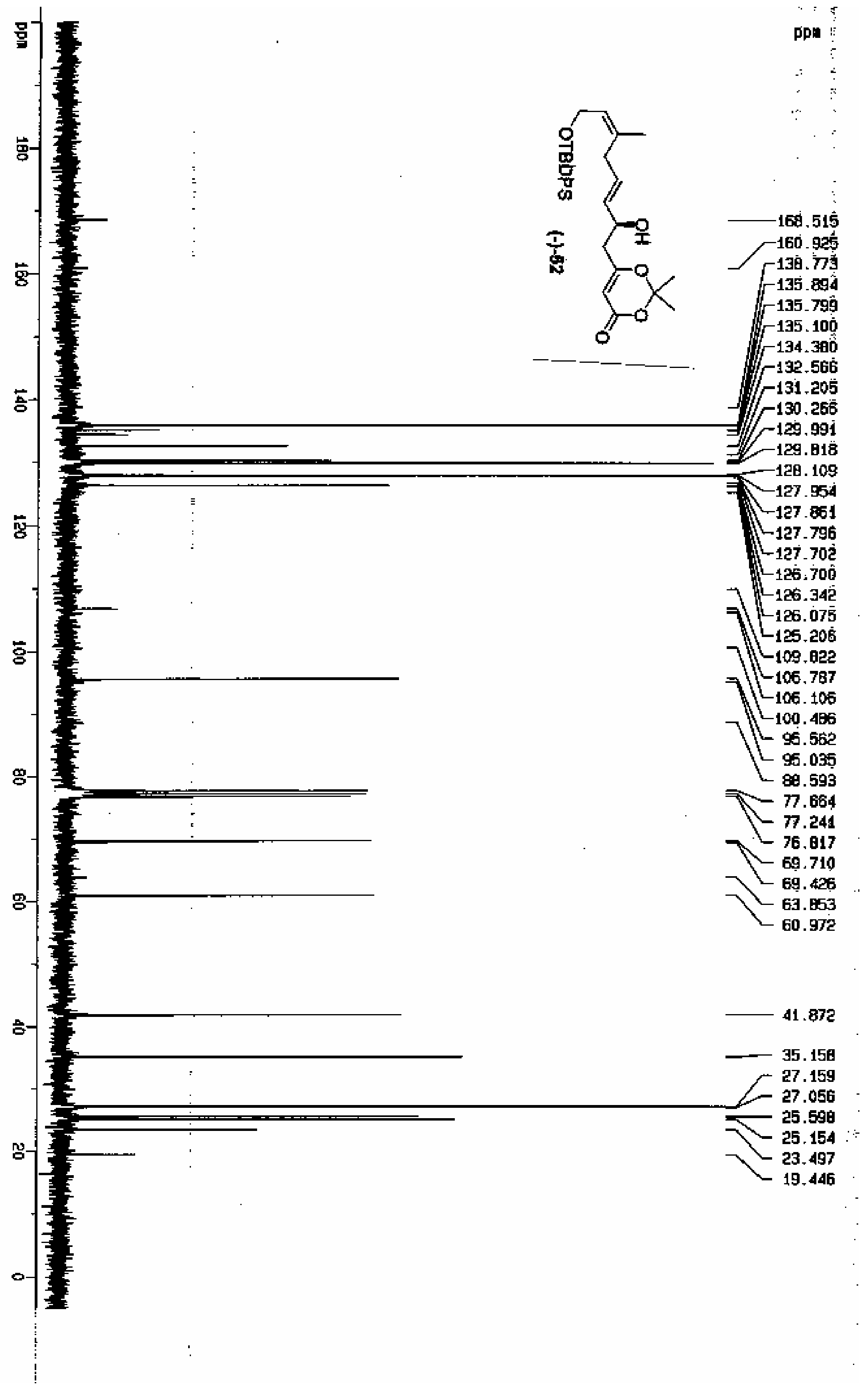

TBDPSO
33
ppm
160
140
120
100
80
60
40
20
0
ppm
176.454
167.648
166.465
156.147
153.811
152.684
151.689
142.470
141.775
137.152
136.378
135.911
135.547
135.208
134.493
129.743
128.676
128.106
127.828
125.909
124.224
121.700
120.615
118.922
115.592
114.942
110.761
106.978
102.197
85.576
84.088
81.273
79.165
77.655
77.231
76.810
74.339
71.610
70.805
67.839
66.264
64.970
61.040
49.103
36.868
27.281
27.184
26.879
23.454
22.850
22.113
19.462
14.460
9.534
-0.351
-1.083

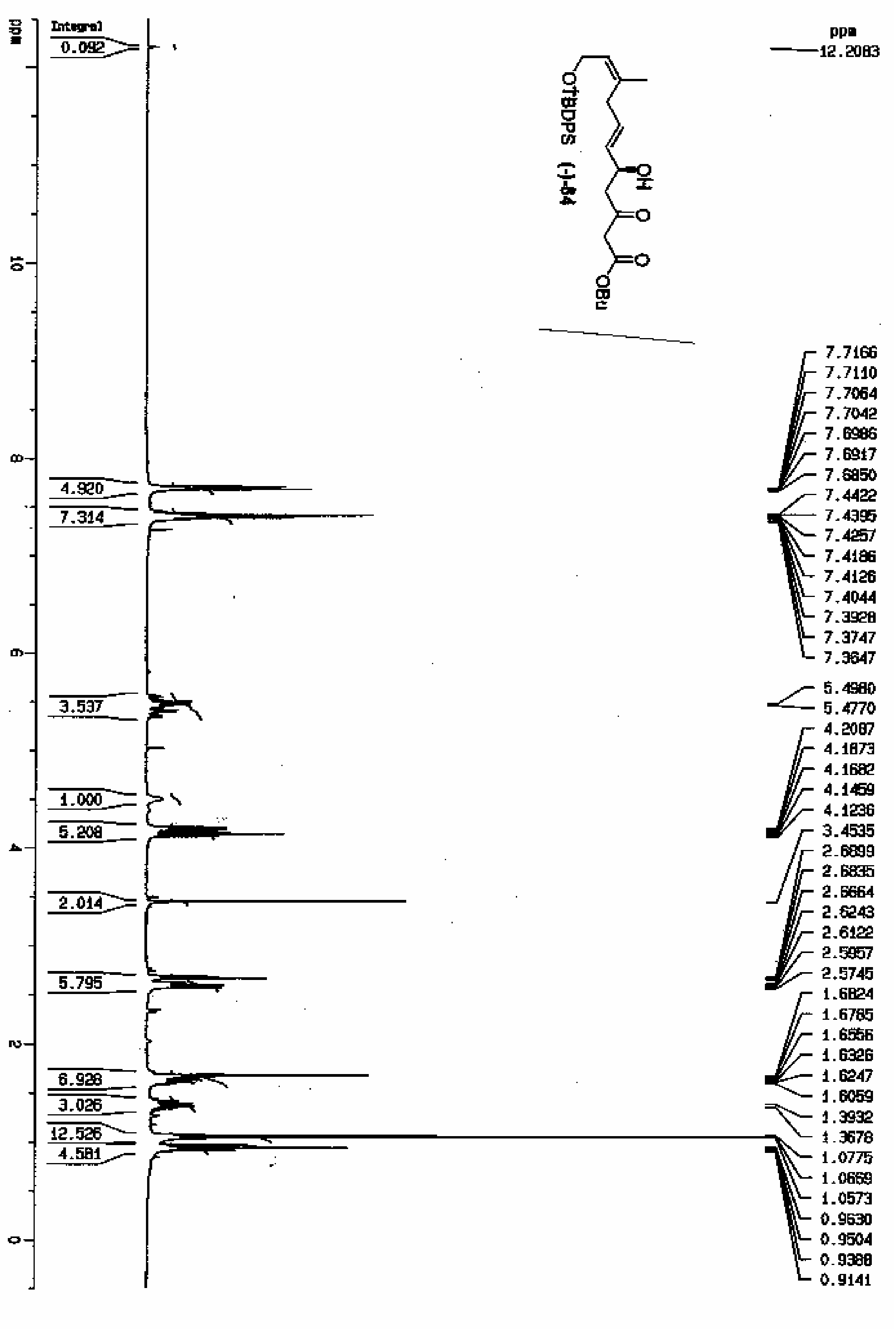

ppm
Integral
0.868
4.371
6.544
1.037
0.828
1.000
2.258
2.262
3.344
10.798
9
8
7
6
5
4
3
2
1
0
TBDPSO
O
H
36
ppm
9.56025
9.53381
9.46433
9.45073
9.43803
7.71266
7.70721
7.70295
7.69427
7.68767
7.68129
7.45037
7.44072
7.43852
7.42948
7.42475
7.40954
7.40495
7.40056
7.38061
7.37184
7.26899
6.63954
6.60973
6.58770
6.56574
6.04949
6.02329
5.99767
5.97142
5.60293
5.58365
5.30293
4.20225
4.19930
4.18088
4.17772
4.08978
2.86932
2.84743
1.89281
1.78376
1.72531
1.72195
1.64509
1.62513
1.36924
1.27891
1.27001
1.19767
1.12946
1.10383
1.07196
1.06262
0.99629
0.97474
0.92516
0.90326
0.88028
0.85163

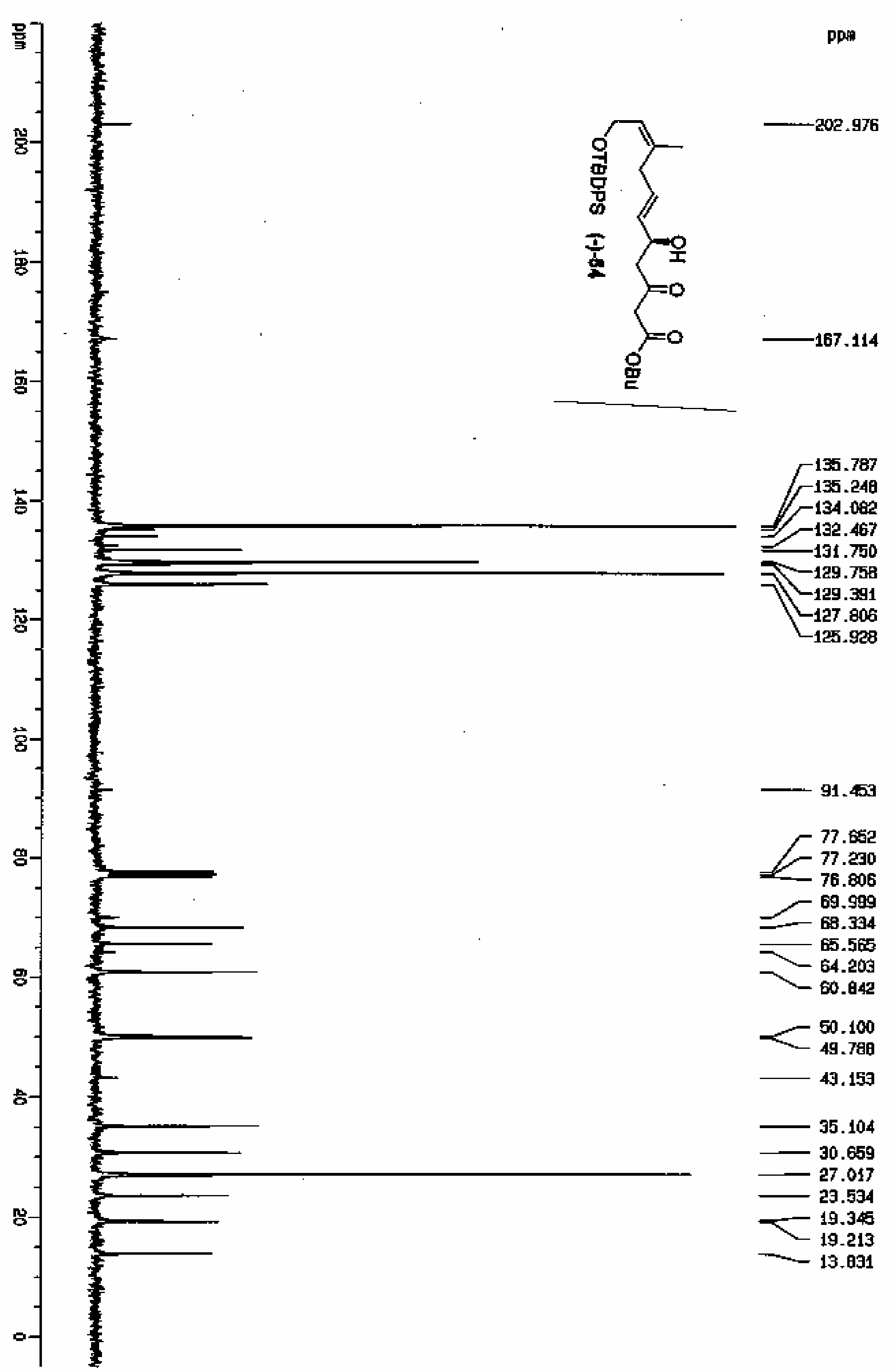

ppm
180
160
140
120
100
80
60
40
20
0
TBDPSO
O
H
35
ppm
193.712
155.165
135.955
135.923
135.894
135.829
135.762
135.731
135.701
135.670
135.642
133.974
133.682
133.016
129.894
128.093
127.894
127.824
127.759
77.656
77.232
76.810
76.405
60.757
35.740
31.786
27.059
23.642
19.377

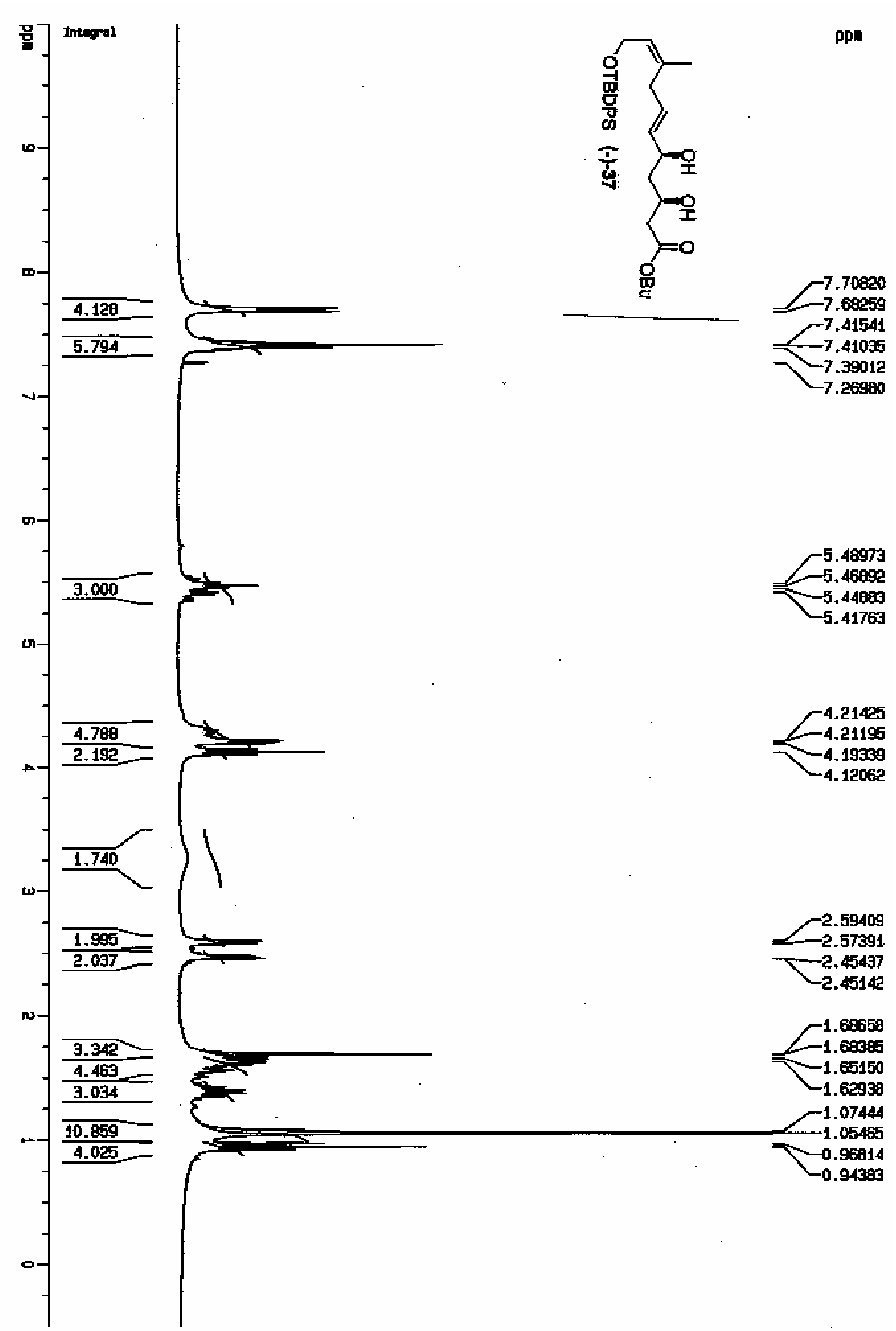

ppm
Integral
ppm
9
8
7
6
5
4
3
2
1
0
1.000
1.389
1.504
11.137
13.519
7.27306
4.65991
4.08416
3.89402
1.69726
1.56166
0.27962
0.26681
0.18731
O
O
OTMS
3d

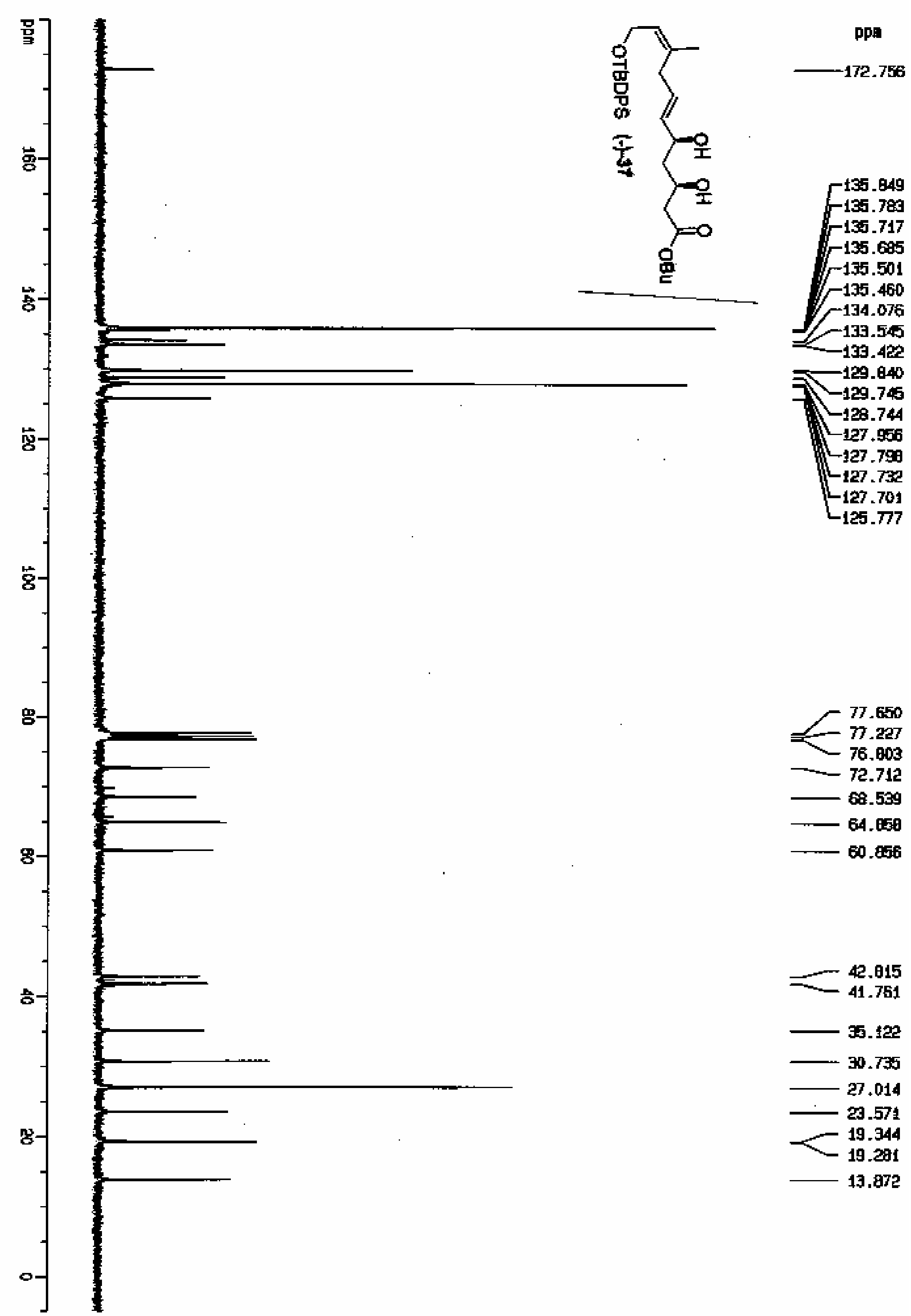

ppm
Integral
OTBDPS
OH
(-)-52
5.126
7.126
3.937
1.000
1.315
2.455
2.368
2.248
13.758
12.742
9
8
7
6
5
4
3
2
1
0
ppm
7.70878
7.70329
7.68895
7.67772
7.66269
7.65726
7.46442
7.45845
7.43917
7.42401
7.41576
7.39974
7.39059
7.37112
7.36218
7.26911
5.57210
5.55071
5.52952
5.52087
5.49979
5.47905
5.46152
5.41941
5.39746
5.36820
5.34691
5.33181
5.28366
4.31111
4.29010
4.22947
4.19442
4.17316
2.59562
2.57453
2.44843
2.42620
2.41874
2.37015
2.35786
2.34532
2.33934
2.30949
1.73827
1.69256
1.67278
1.65746
1.26693
1.25729
1.11610
1.07511
1.04998
0.98362
0.63892
0.15322


ppm
180
160
140
120
100
80
60
40
20
0
ppm
OH
O
O
O
OTBDPS
(-)-62
168.515
160.925
138.773
135.894
135.799
135.100
134.380
132.566
131.205
130.266
129.991
129.818
128.109
127.954
127.861
127.796
127.702
126.700
126.342
126.075
125.206
109.822
106.787
106.106
100.486
95.562
95.035
88.593
77.664
77.241
76.817
69.710
69.426
63.853
60.972
41.872
35.158
27.159
27.056
25.598
25.154
23.497
19.446

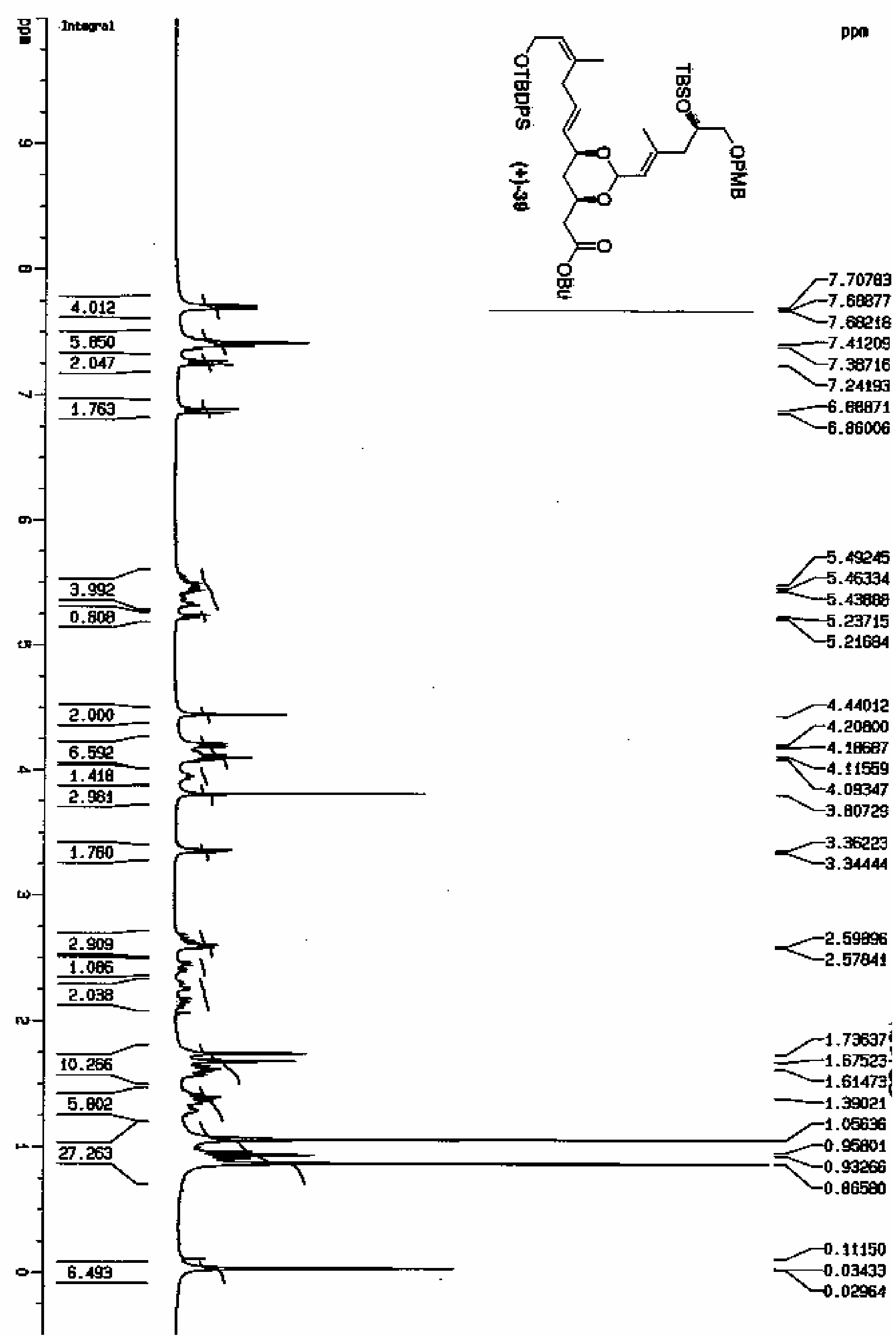

ppm
Integral
0.092
4.920
7.314
3.537
1.000
5.208
2.014
5.795
6.928
3.026
12.526
4.581
10
8
6
4
2
0
OH
O
O
OBu
OTBDPS
(-)-84
ppm
12.2083
7.7166
7.7110
7.7064
7.7042
7.6986
7.6917
7.6850
7.4422
7.4395
7.4257
7.4186
7.4126
7.4044
7.3928
7.3747
7.3647
5.4980
5.4770
4.2087
4.1873
4.1682
4.1459
4.1236
3.4535
2.6899
2.6835
2.6664
2.6243
2.6122
2.5957
2.5745
1.6824
1.6785
1.6556
1.6326
1.6247
1.6059
1.3932
1.3678
1.0775
1.0669
1.0573
0.9630
0.9504
0.9388
0.9141

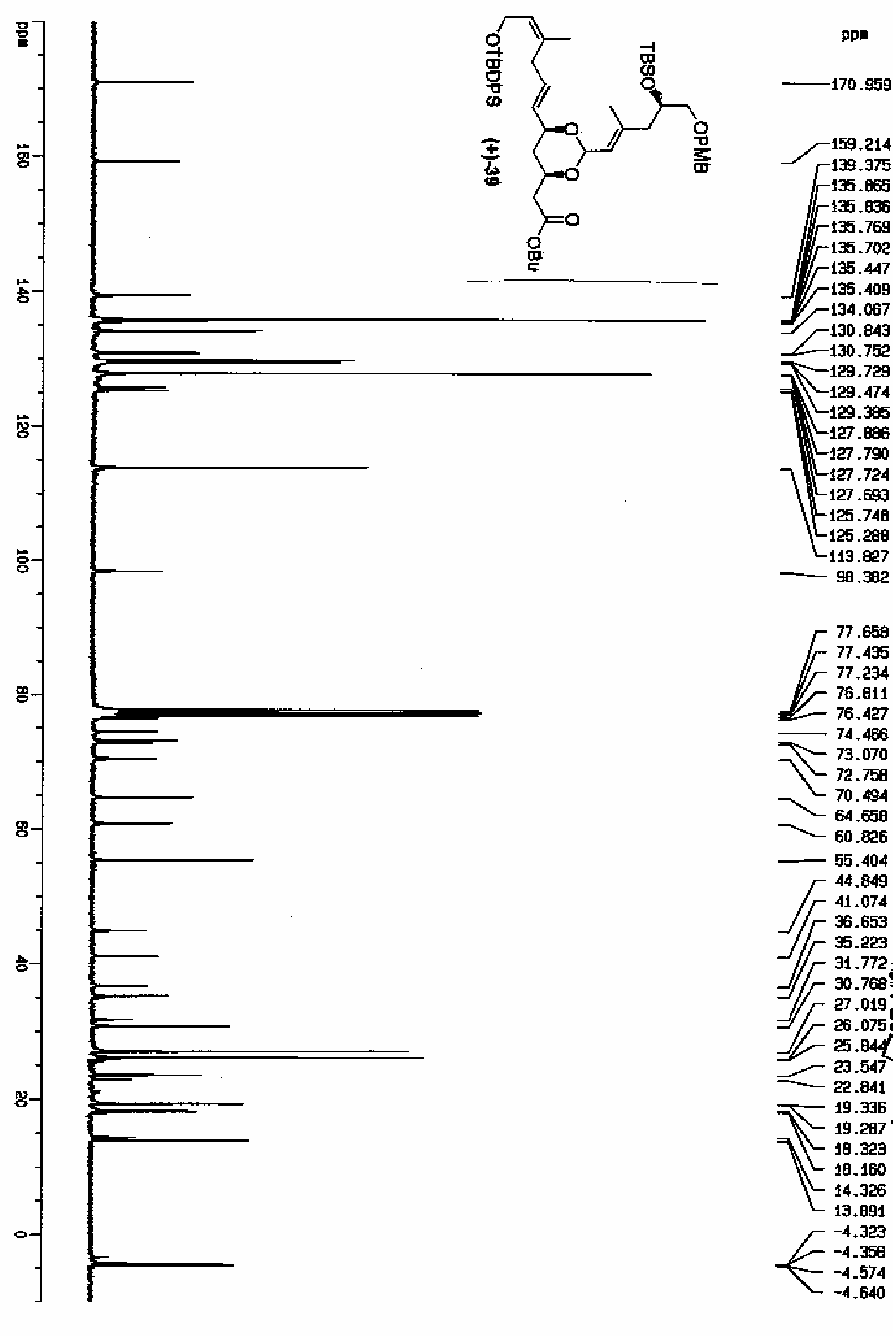

ppm
200
180
160
140
120
100
80
60
40
20
0
ppm
OH
O
O
OBu
OTBDPS
(-)-84
202.976
167.114
135.787
135.248
134.082
132.467
131.750
129.758
129.391
127.806
125.928
91.453
77.652
77.230
76.806
69.999
68.334
65.565
64.203
60.842
50.100
49.788
43.153
35.104
30.659
27.017
23.534
19.345
19.213
13.831


ppm
Integral
OH OH O
OBu
OTBDPS (-)-37
ppm
8
7
6
5
4
3
2
1
0
4.128
5.794
3.000
4.788
2.192
1.740
1.995
2.037
3.342
4.463
3.034
10.859
4.025
7.70820
7.68259
7.41541
7.41035
7.39012
7.26980
5.48973
5.46092
5.44883
5.41763
4.21425
4.21195
4.19339
4.12062
2.59409
2.57391
2.45437
2.45142
1.68658
1.68385
1.65150
1.62938
1.07444
1.05465
0.96814
0.94383

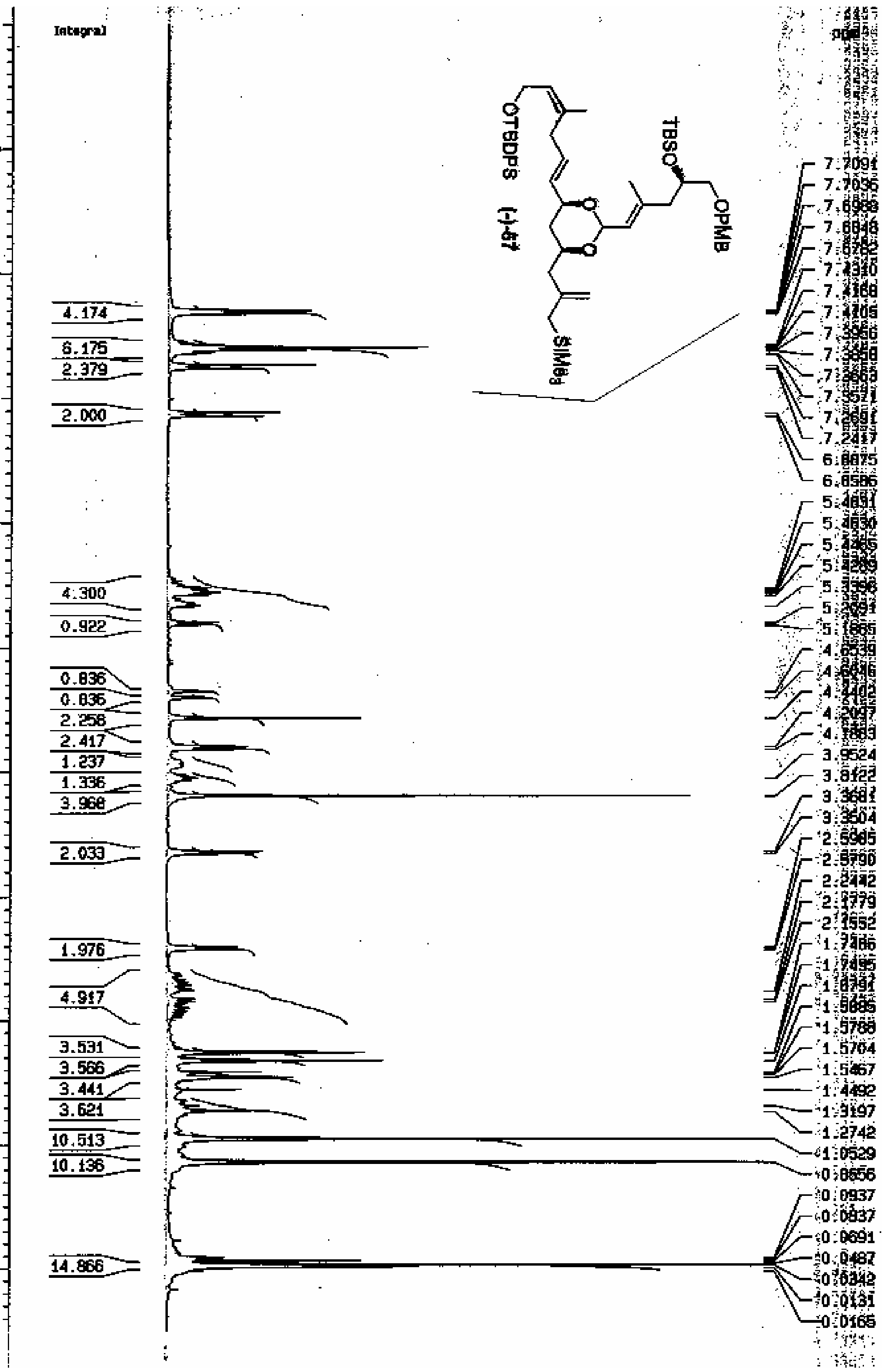

ppm
OH
OH
O
OBu
OTBDPS
172.756
135.849
135.783
135.717
135.685
135.501
135.460
134.076
133.545
133.422
129.840
129.745
128.744
127.956
127.798
127.732
127.701
125.777
77.650
77.227
76.803
72.712
68.539
64.858
60.856
42.815
41.761
35.122
30.735
27.014
23.571
19.344
19.281
13.872
ppm
160
140
120
100
80
60
40
20
0

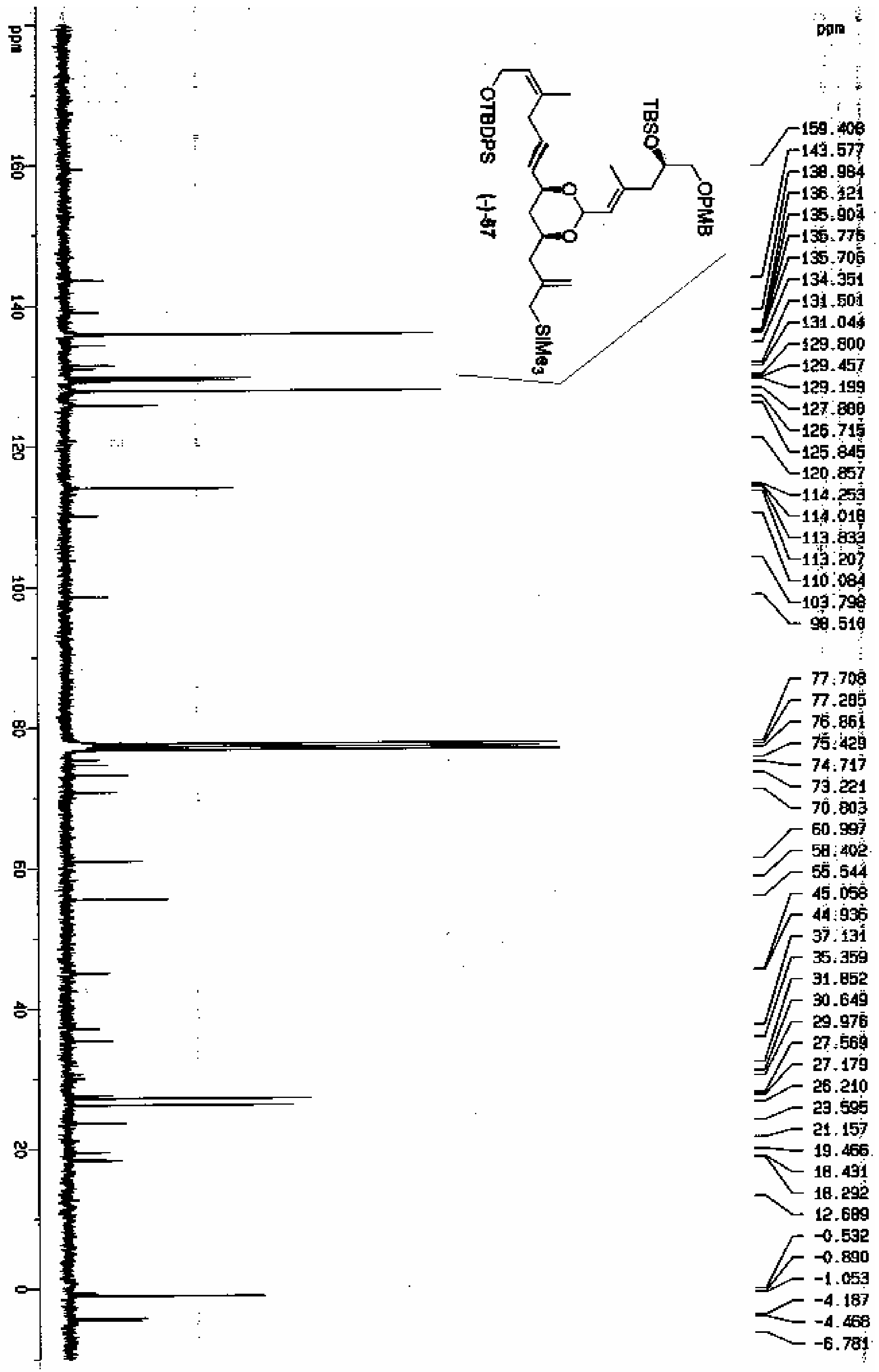
(-)-37

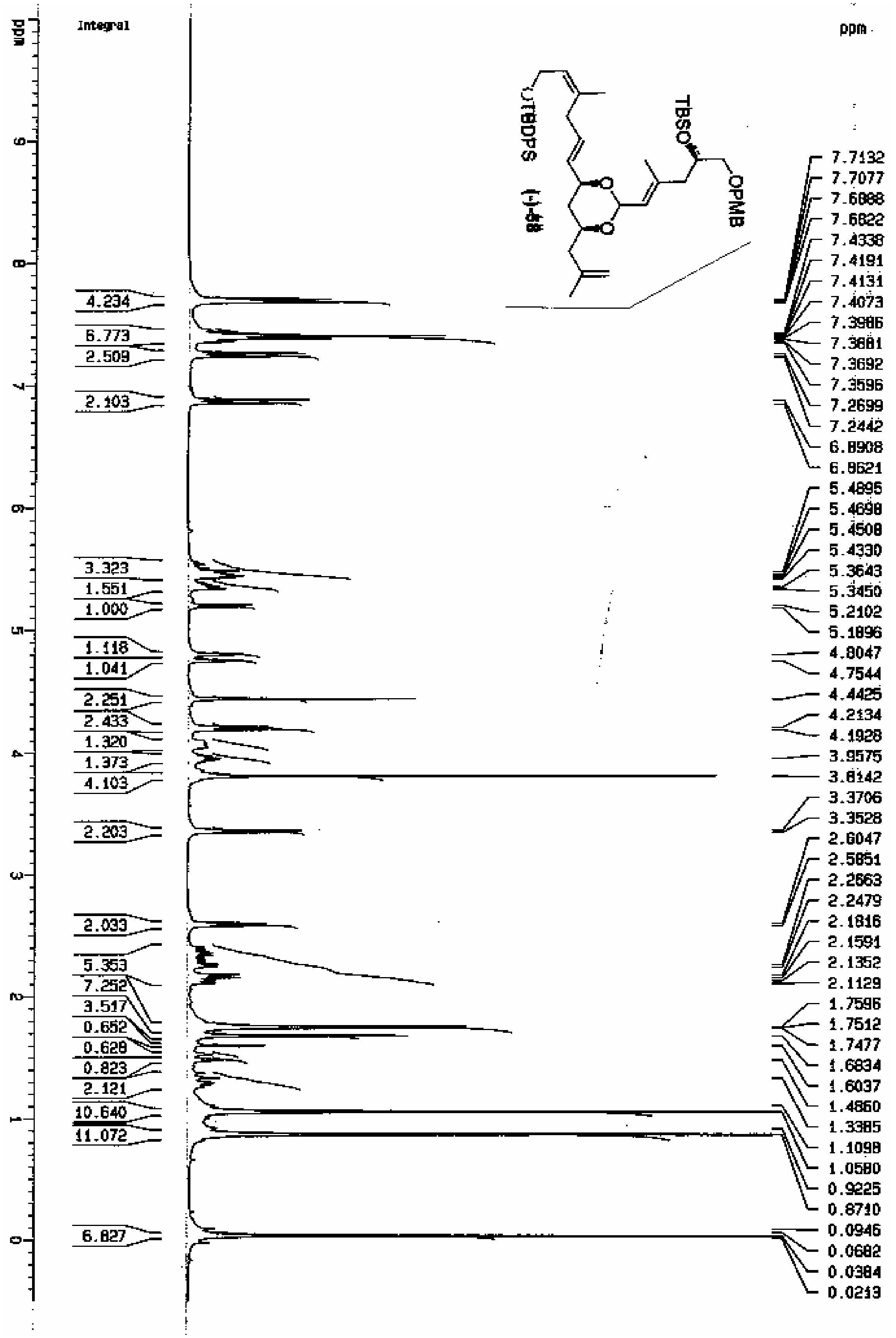

ppm
Integral
9
8
7
6
5
4
3
2
1
0
4.012
5.650
2.047
1.763
3.992
0.808
2.000
6.592
1.418
2.981
1.760
2.909
1.086
2.038
10.256
5.802
27.263
6.493
ppm
7.70783
7.68877
7.68216
7.41209
7.38716
7.24193
6.88871
6.86006
5.49245
5.46334
5.43888
5.23715
5.21684
4.44012
4.20800
4.18687
4.11559
4.09347
3.80729
3.36223
3.34444
2.59896
2.57841
1.73637
1.67523
1.61473
1.39021
1.05636
0.95801
0.93266
0.86580
0.11150
0.03433
0.02964
TBSO
OPMB
O
O
O
OBu^t
OTBDPS
(+)-39

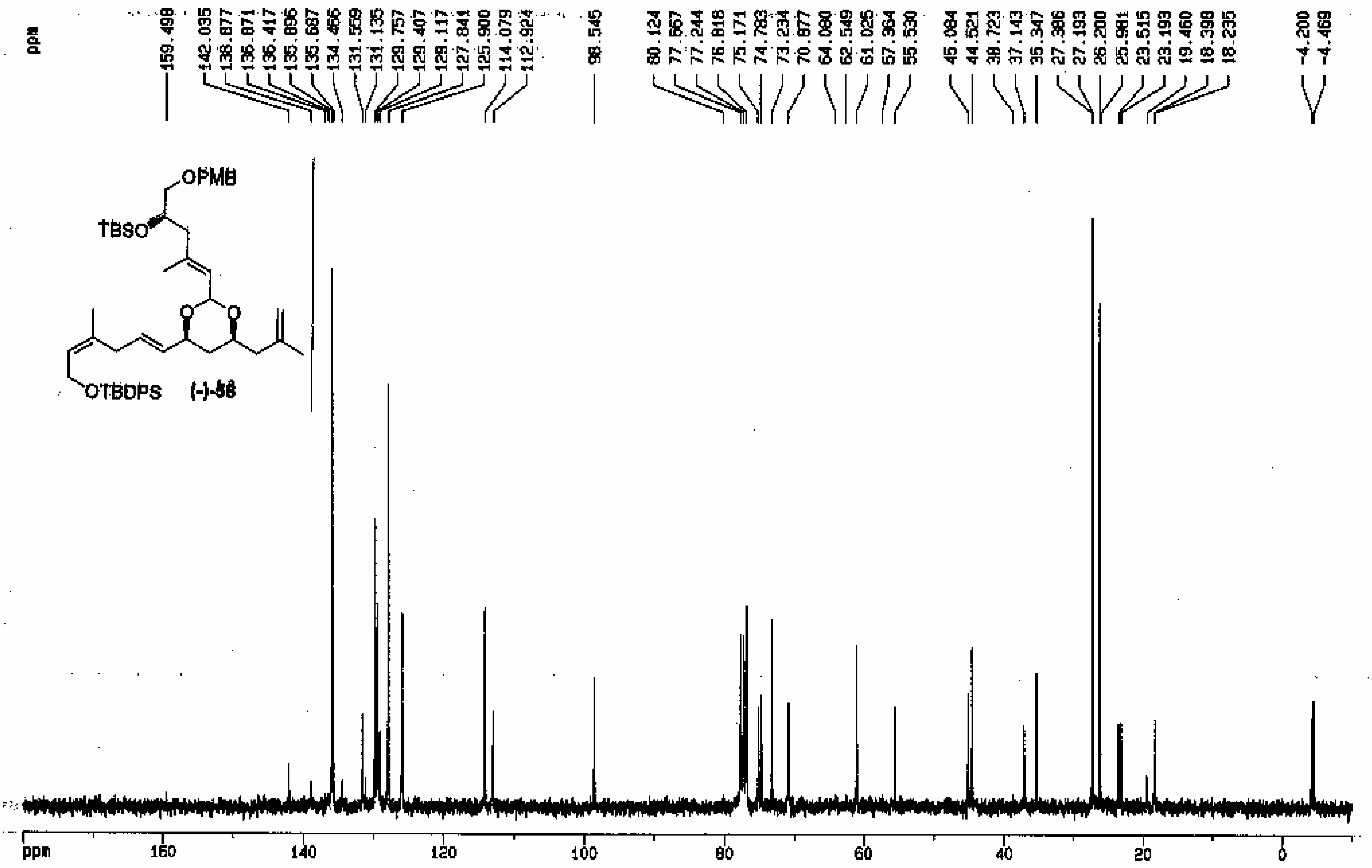

ppm
170.959
159.214
139.375
135.865
135.836
135.769
135.702
135.447
135.409
134.067
130.843
130.752
129.729
129.474
129.385
127.886
127.790
127.724
127.693
125.748
125.288
113.827
98.382
77.658
77.435
77.234
76.811
76.427
74.466
73.070
72.758
70.494
64.658
60.826
55.404
44.849
41.074
36.653
35.223
31.772
30.768
27.019
26.075
25.844
23.547
22.841
19.336
19.287
18.329
18.160
14.326
13.891
-4.323
-4.358
-4.574
-4.640
ppm
160
140
120
100
80
60
40
20
0
TBSO
OPMB
O
O
O
OBu
OTBDPS

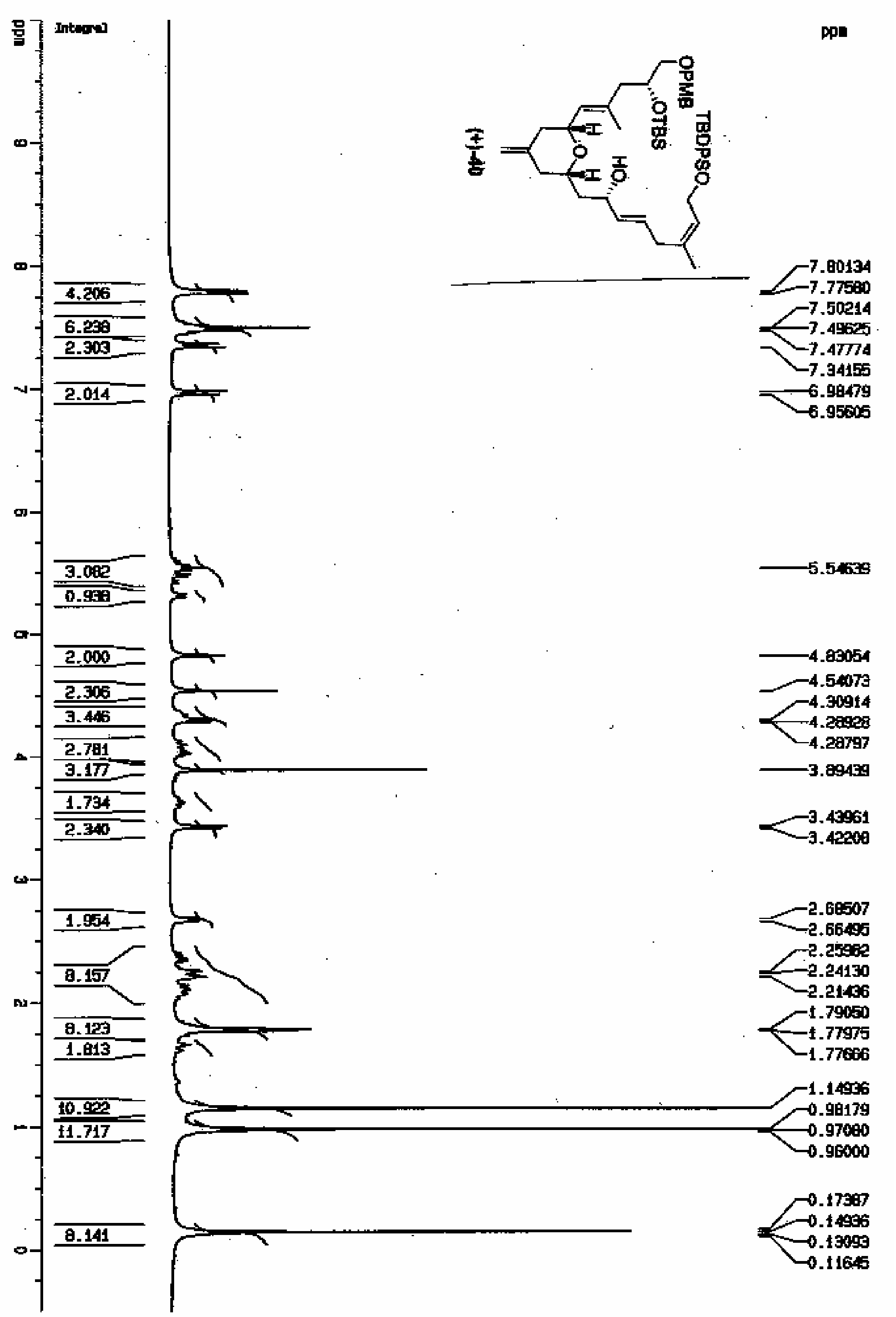
(+)-39

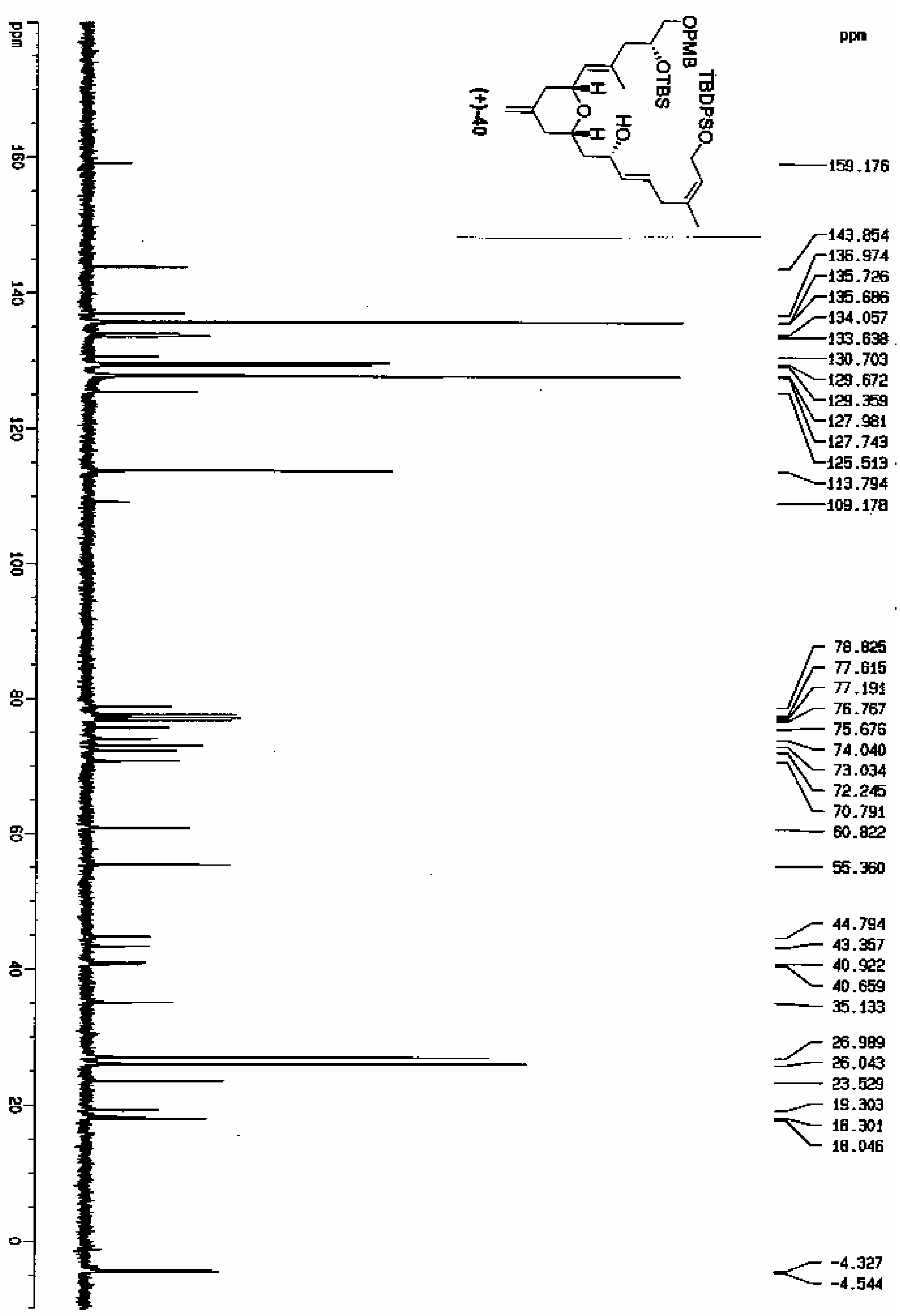

ppm
Integral
TBSO
OPMB
OTBDPS
SiMe3
(-)-67
4.174
6.175
2.379
2.000
4.300
0.922
0.836
0.836
2.256
2.417
1.237
1.336
3.968
2.033
1.976
4.917
3.531
3.566
3.441
3.621
10.513
10.136
14.866


ppm
160
140
120
100
80
60
40
20
0
TBSO
OPMB
O
O
OTBDPS
SiMe3
(-)-87
159.408
143.577
138.984
136.121
135.904
135.776
135.706
134.351
131.501
131.044
129.800
129.457
129.199
127.880
126.715
125.845
120.857
114.253
114.018
113.833
113.207
110.084
103.798
98.510
77.708
77.285
76.861
75.429
74.717
73.221
70.803
60.997
58.402
55.544
45.058
44.936
37.131
35.359
31.852
30.649
29.976
27.569
27.179
26.210
23.595
21.157
19.466
18.431
18.292
12.689
-0.532
-0.890
-1.053
-4.187
-4.468
-6.781

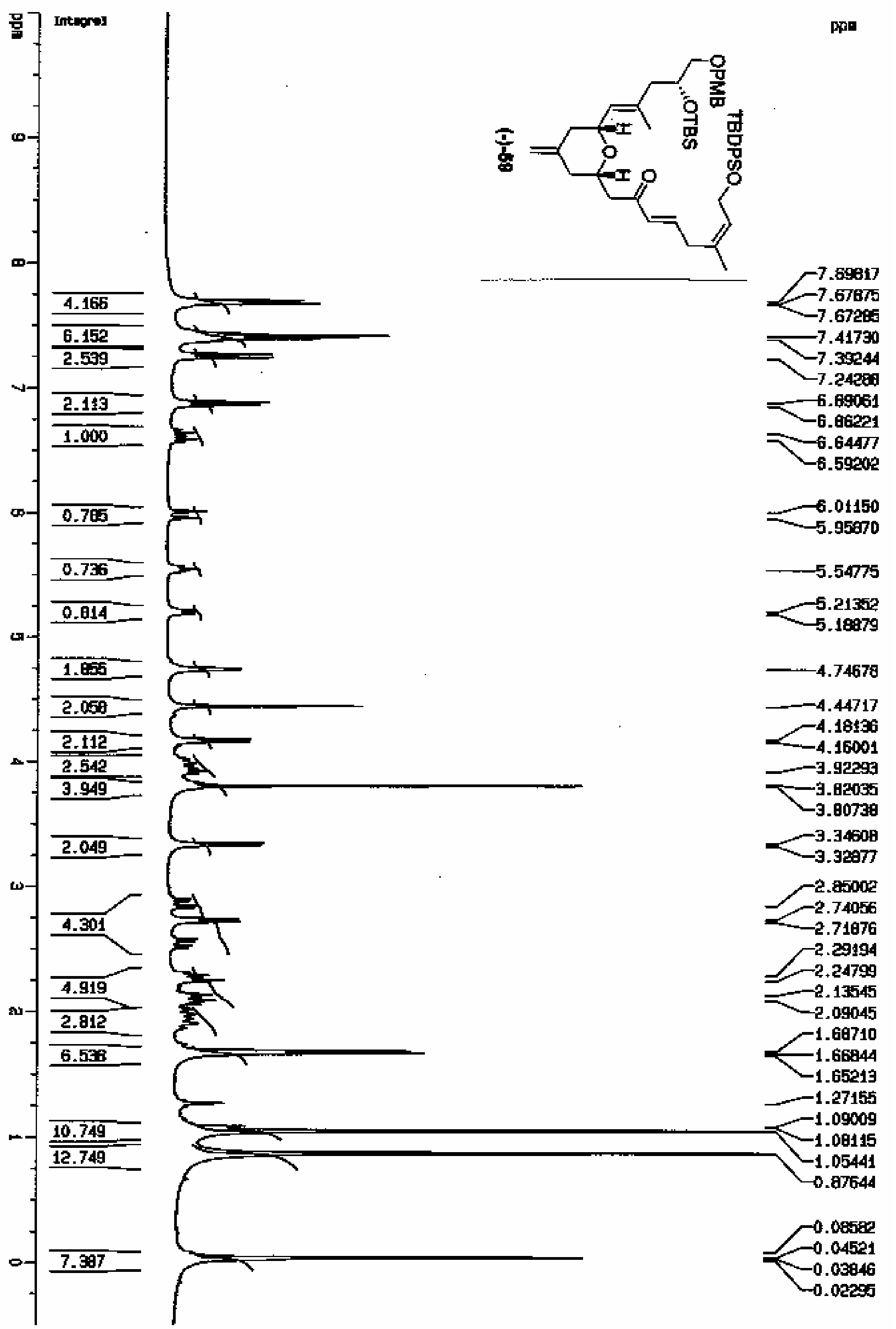

ppm
Integral
TBSO
OPMB
O
O
OTBDPS
(-)-48
9
8
7
6
5
4
3
2
1
0
4.234
6.773
2.509
2.103
3.323
1.551
1.000
1.118
1.041
2.251
2.433
1.320
1.373
4.103
2.203
2.033
5.353
7.252
3.517
0.652
0.628
0.823
2.121
10.640
11.072
6.827
7.7132
7.7077
7.6988
7.6822
7.4338
7.4191
7.4131
7.4073
7.3986
7.3881
7.3692
7.3596
7.2699
7.2442
6.8908
6.8621
5.4895
5.4698
5.4508
5.4330
5.3643
5.3450
5.2102
5.1896
4.8047
4.7544
4.4425
4.2134
4.1928
3.9575
3.8142
3.3706
3.3528
2.6047
2.5851
2.2663
2.2479
2.1816
2.1591
2.1352
2.1129
1.7596
1.7512
1.7477
1.6834
1.6037
1.4860
1.3385
1.1098
1.0580
0.9225
0.8710
0.0946
0.0682
0.0384
0.0213

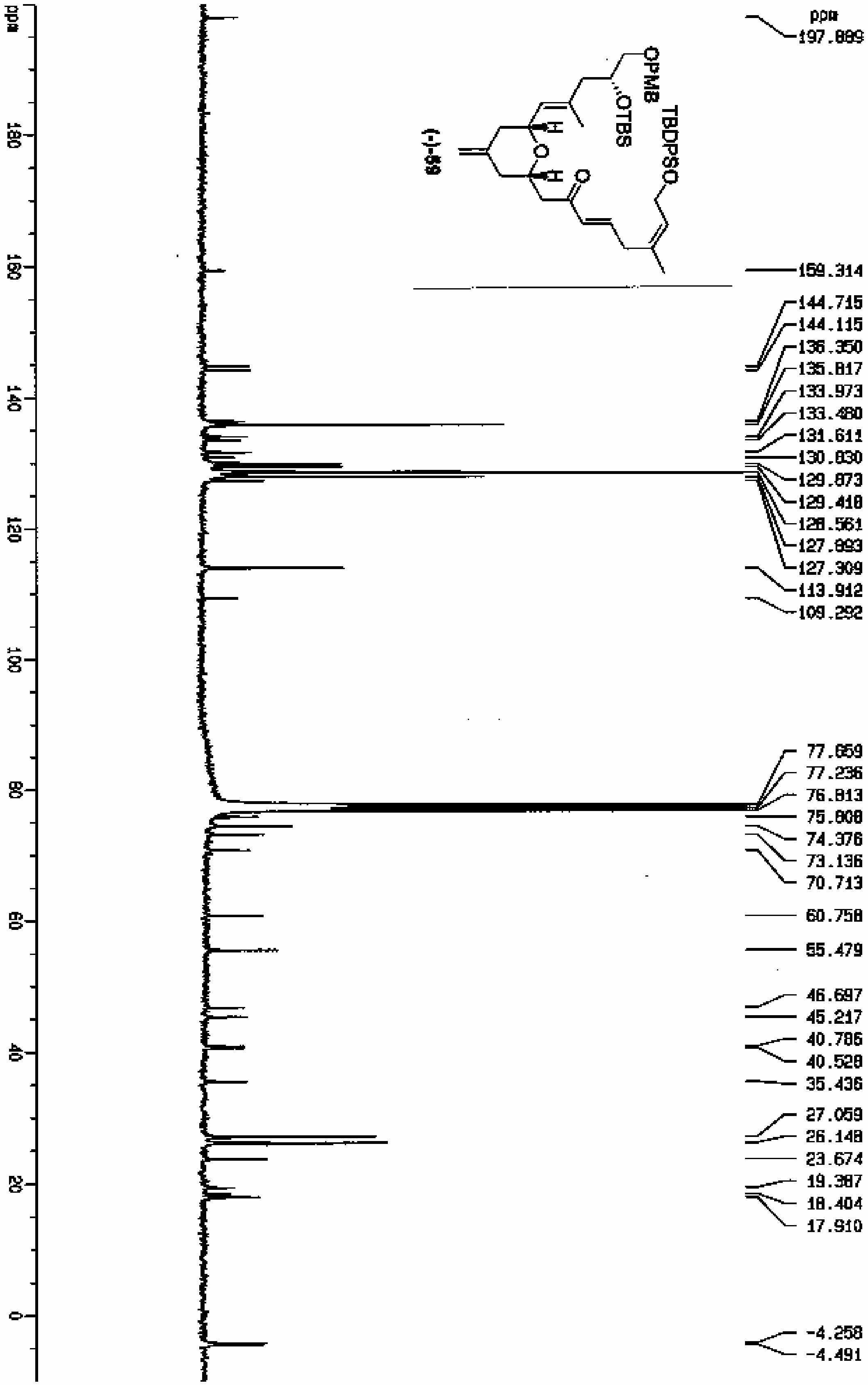

ppm
159.498
142.035
138.877
136.071
136.417
135.896
135.687
134.466
131.559
131.135
129.757
129.407
129.117
127.841
125.900
114.079
112.924
98.545
80.124
77.667
77.244
76.818
75.171
74.783
73.234
70.877
64.080
62.549
61.025
57.364
55.530
45.084
44.521
38.723
37.143
35.347
27.386
27.193
26.200
25.981
23.515
23.193
19.460
18.398
18.235
-4.200
-4.469
OPMB
TBSO
O
O
OTBDPS
(-)-68
ppm
160
140
120
100
80
60
40
20
0

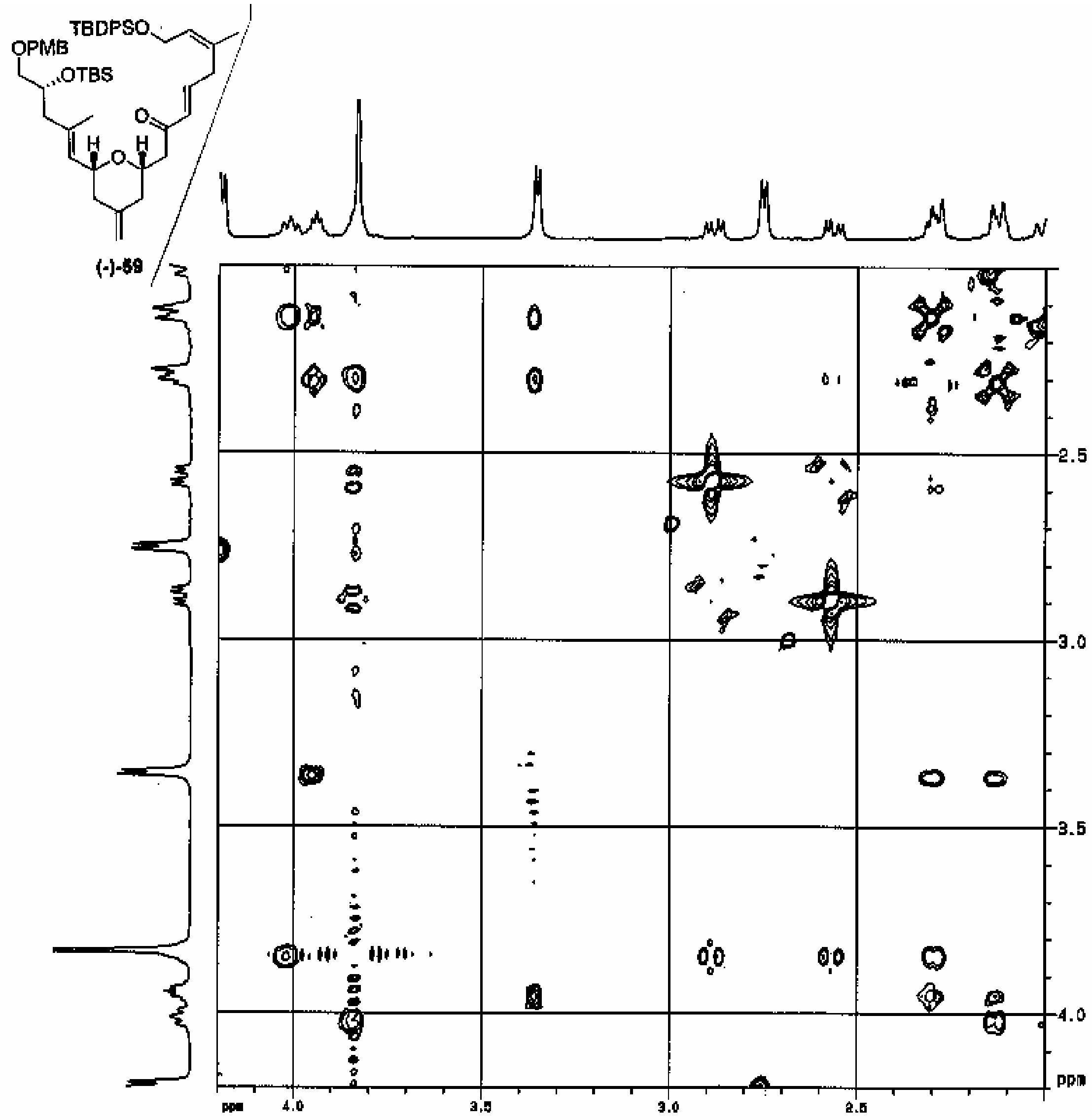

ppm
Integral
ppm
9
8
7
6
5
4
3
2
1
0
4.206
6.238
2.303
2.014
3.082
0.938
2.000
2.306
3.446
2.781
3.177
1.734
2.340
1.954
8.157
8.123
1.813
10.922
11.717
8.141
7.80134
7.77580
7.50214
7.49625
7.47774
7.34155
6.98479
6.95605
5.54639
4.83054
4.54073
4.30914
4.28928
4.28797
3.89439
3.43961
3.42208
2.68507
2.66495
2.25982
2.24130
2.21436
1.79050
1.77975
1.77666
1.14936
0.98179
0.97080
0.96000
0.17387
0.14936
0.13093
0.11645
OPMB
OTBS
TBDPSO
HO
H
O
H
(+)-40


ppm
160
140
120
100
80
60
40
20
0
ppm
TBDPSO
OPMB
OTBS
HO
H
O
H
159.176
143.854
136.974
135.726
135.686
134.057
133.638
130.703
129.672
129.359
127.981
127.743
125.513
113.794
109.178
78.825
77.615
77.191
76.767
75.676
74.040
73.034
72.245
70.791
60.822
55.360
44.794
43.367
40.922
40.659
35.133
26.989
26.043
23.529
19.303
18.301
18.046
-4.327
-4.544

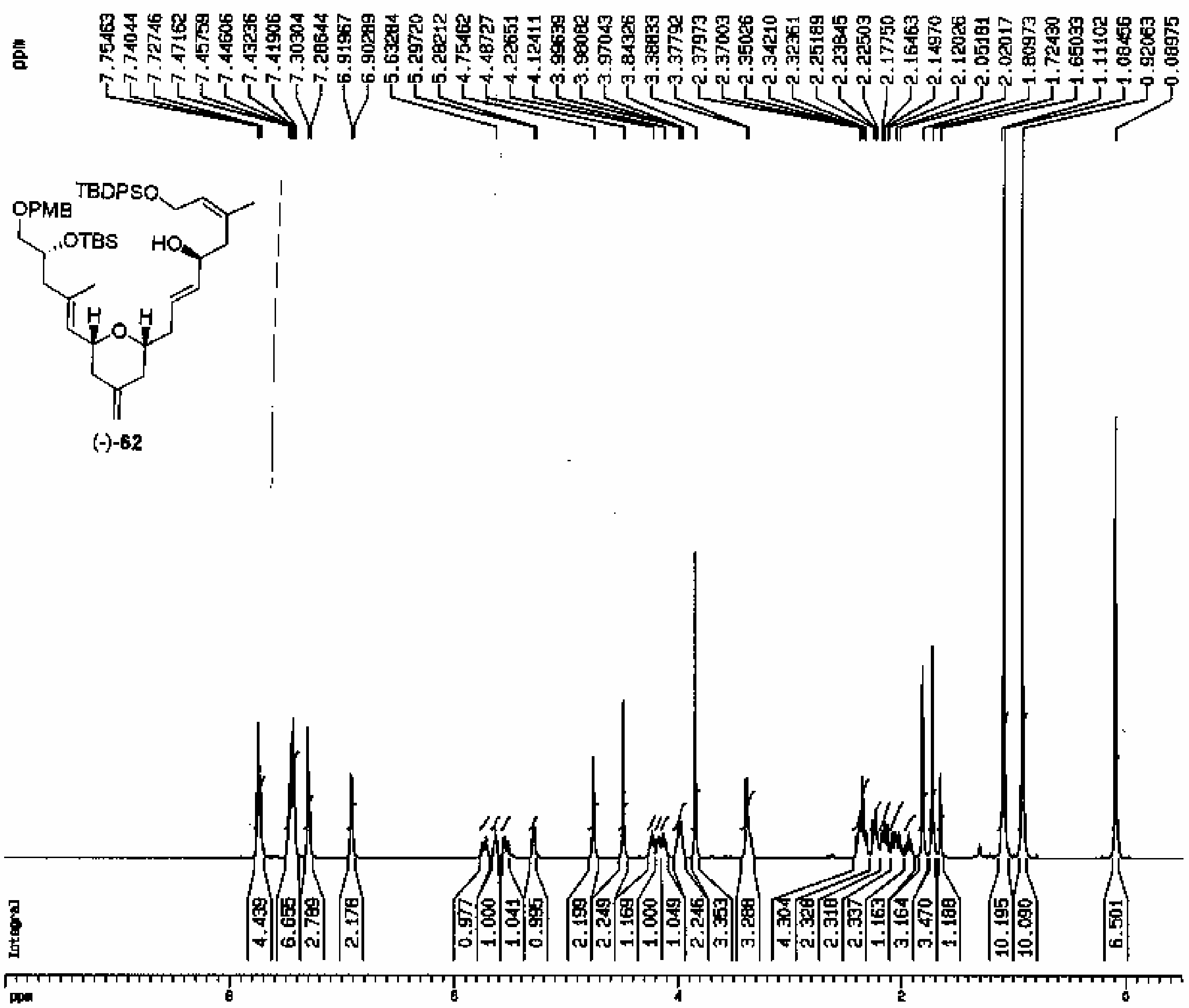
(+)-40


ppm
Integral
ppm
TBDPSO
OPMB
OTBS
H
O
H
O
(-)-59
4.166
6.152
2.539
2.113
1.000
0.785
0.736
0.814
1.855
2.058
2.112
2.542
3.949
2.049
4.301
4.919
2.812
6.536
10.749
12.749
7.387
7.69817
7.67875
7.67295
7.41730
7.39244
7.24288
6.89061
6.86221
6.64477
6.59202
6.01150
5.95870
5.54775
5.21352
5.18879
4.74678
4.44717
4.18136
4.16001
3.92293
3.82035
3.80738
3.34608
3.32877
2.85002
2.74056
2.71876
2.29194
2.24799
2.13545
2.09045
1.68710
1.66844
1.65213
1.27155
1.09009
1.08115
1.05441
0.87644
0.08582
0.04521
0.03846
0.02295
9
8
7
6
5
4
3
2
1
0


ppm
180
160
140
120
100
80
60
40
20
0
ppm
197.889
159.314
144.715
144.115
136.350
135.817
133.973
133.480
131.611
130.830
129.873
129.418
128.561
127.893
127.309
113.912
109.292
77.659
77.236
76.813
75.808
74.376
73.136
70.713
60.758
55.479
46.697
45.217
40.786
40.528
35.436
27.059
26.148
23.674
19.387
18.404
17.910
-4.258
-4.491
TBDPSO
OPMB
OTBS
H
O
H
O
(-)-69

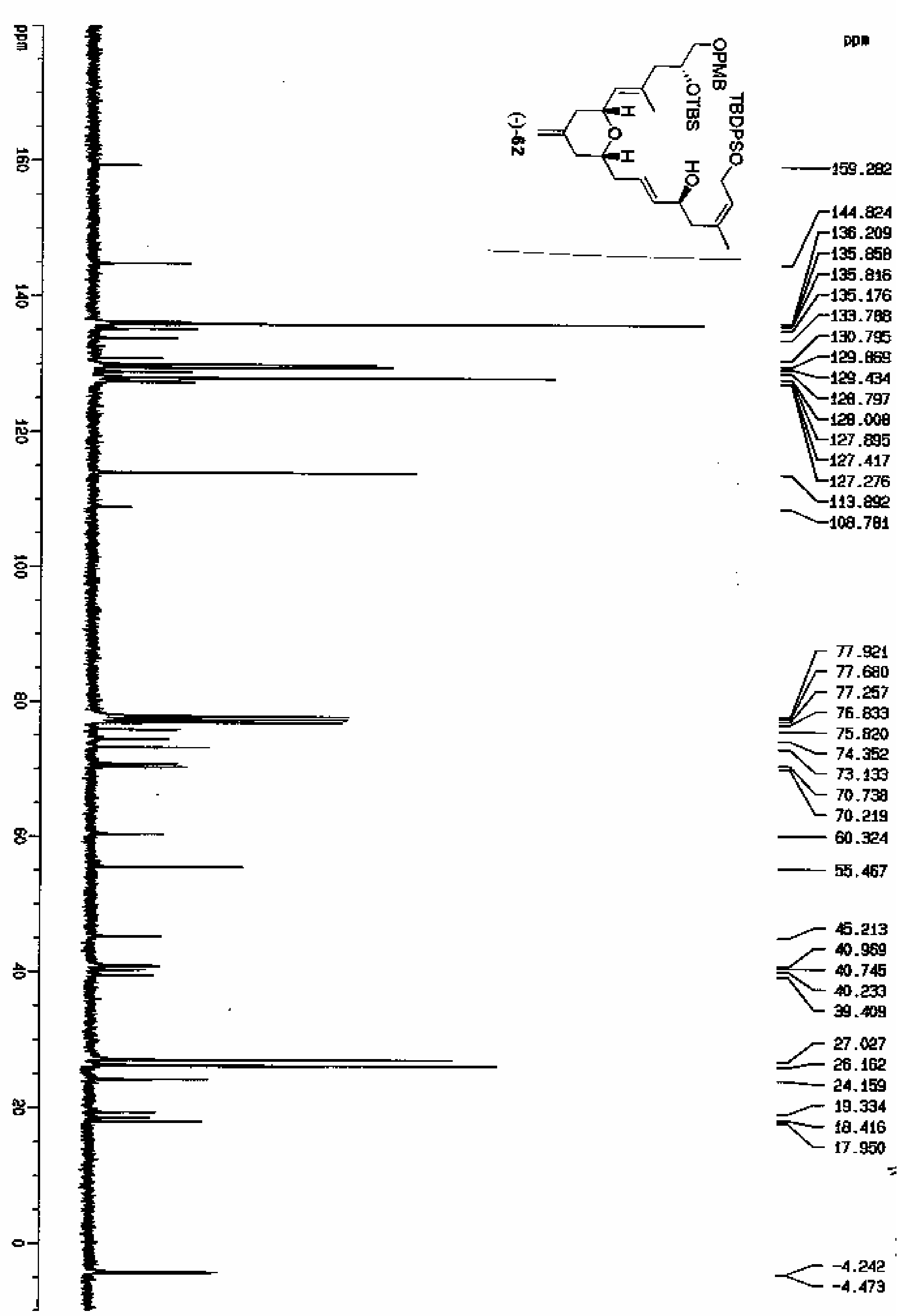


```
         Current Data Parameters
NAME              04041904
EXPNO                 1111 (NOESY)
PROCNO                   1

     F2 - Acquisition Parameters
Date_            [illegible]
Time                 14.01
INSTRUM              spect
PROBHD     5 mm TXI 13C
PULPROG            noesytp
TD                    1024
SOLVENT              CDCl3
NS                      32
DS                       8
SWH               5000.000 Hz
FIDRES            4.882812 Hz
AQ               0.1024000 sec
RG               [illegible]
DW                 100.000 usec
DE                    6.00 usec
TE                   298.0 K
d0             [illegible] sec
D1              1.00000000 sec
P1             [illegible] usec
D8             [illegible] sec
DE                    8.00 usec
SFO1           500.1322500 MHz
NUC1                    1H
PL1                   0.00 dB
IN0             0.00010000 sec

     F1 - Acquisition parameters
ND0                      2
TD             [illegible]
SFO1               500.132 MHz
FIDRES         [illegible] Hz
SW             [illegible] ppm

     F2 - Processing parameters
SI                    1024
SF             500.1300050 MHz
WDW                   SINE
SSB                      2
LB                    0.00 Hz
GB                       0
PC                    1.00

     F1 - Processing parameters
SI                    1024
MC2                   TPPI
SF             [illegible] MHz
WDW                   SINE
SSB                      2
LB                    0.00 Hz
GB                       0

       2D NMR plot parameters
CX2                  15.00 cm
CX1                  15.00 cm
F2PLO                4.200 ppm
F2LO               2100.55 Hz
F2PHI                2.000 ppm
F2HI               1000.26 Hz
F1PLO                4.200 ppm
F1LO               2100.54 Hz
F1PHI                2.000 ppm
F1HI               1000.26 Hz
F2PPMCM            0.14667 ppm/cm
F2HZCM            73.35240 Hz/cm
F1PPMCM            0.14667 ppm/cm
F1HZCM            73.35238 Hz/cm
```

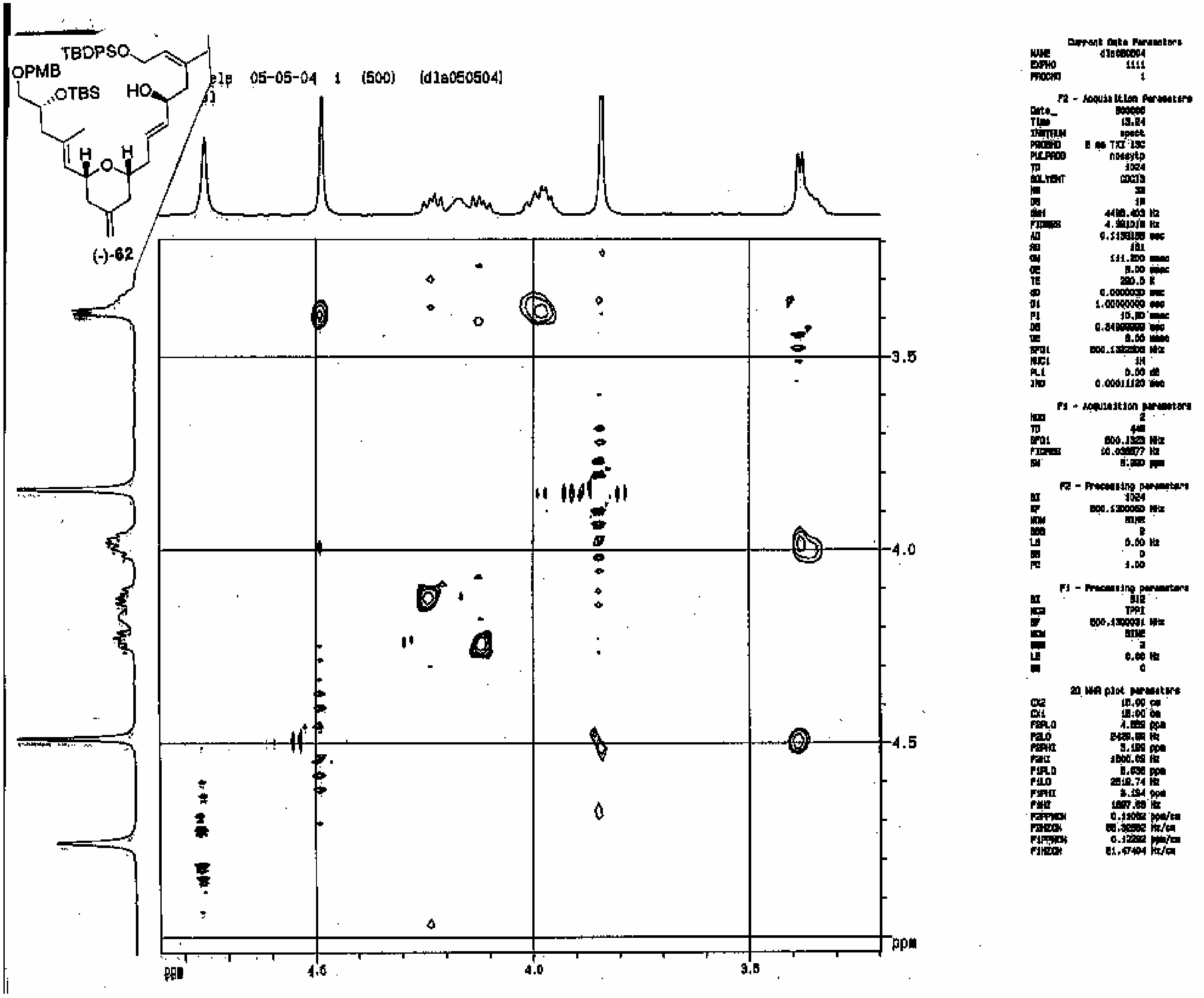


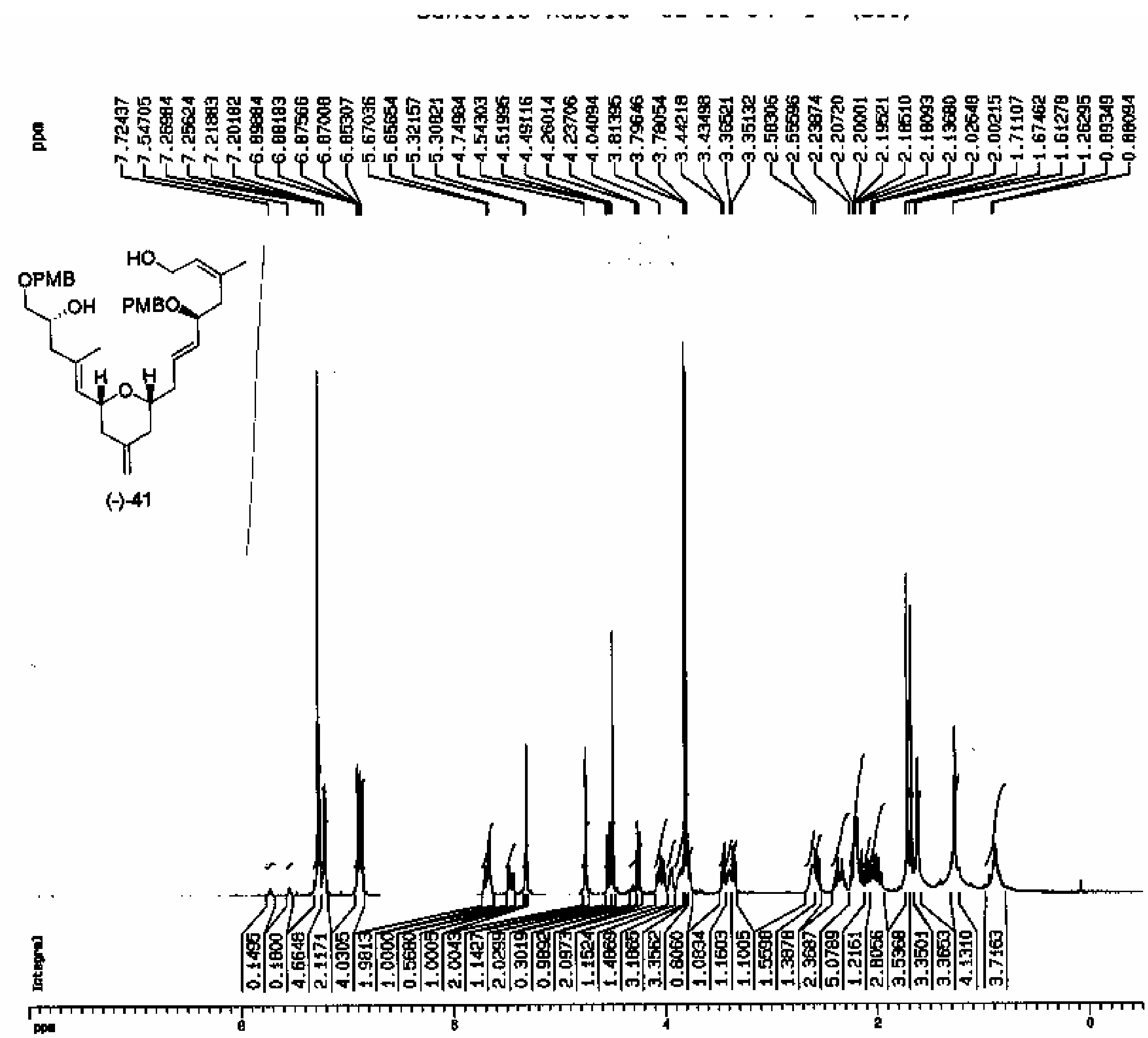
(-)-62

```
NAME              01a050504
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_                500000
Time                  10.33
INSTRUM               spect
PROBHD        5 mm TXI 13C
PULPROG                  zg
TD                    32768
SOLVENT                 D20
NS                       10
DS                        0
SWH                7507.507 Hz
FIDRES             0.229111 Hz
AQ                2.1823988 sec
RG                     20.2
DW                   66.600 usec
DE                     6.00 usec
TE                    290.0 K
D1               6.00000000 sec
P1                    10.60 usec
DE                     6.00 usec
SFO1            500.1330008 MHz
NUC1                     1H
PL1                    0.00 dB

F2 - Processing parameters
SI                    32768
SF              500.1300073 MHz
WDW                      EM
SSB                       0
LB                     0.40 Hz
GB                        0
PC                     1.00

1D NMR plot parameters
CX                    20.00 cm
F1P                  10.000 ppm
F1                  5001.30 Hz
F2P                  -0.500 ppm
F2                  -250.07 Hz
PPMCM               0.52500 ppm/cm
HZCM              262.56824 Hz/cm
```


(-)-62

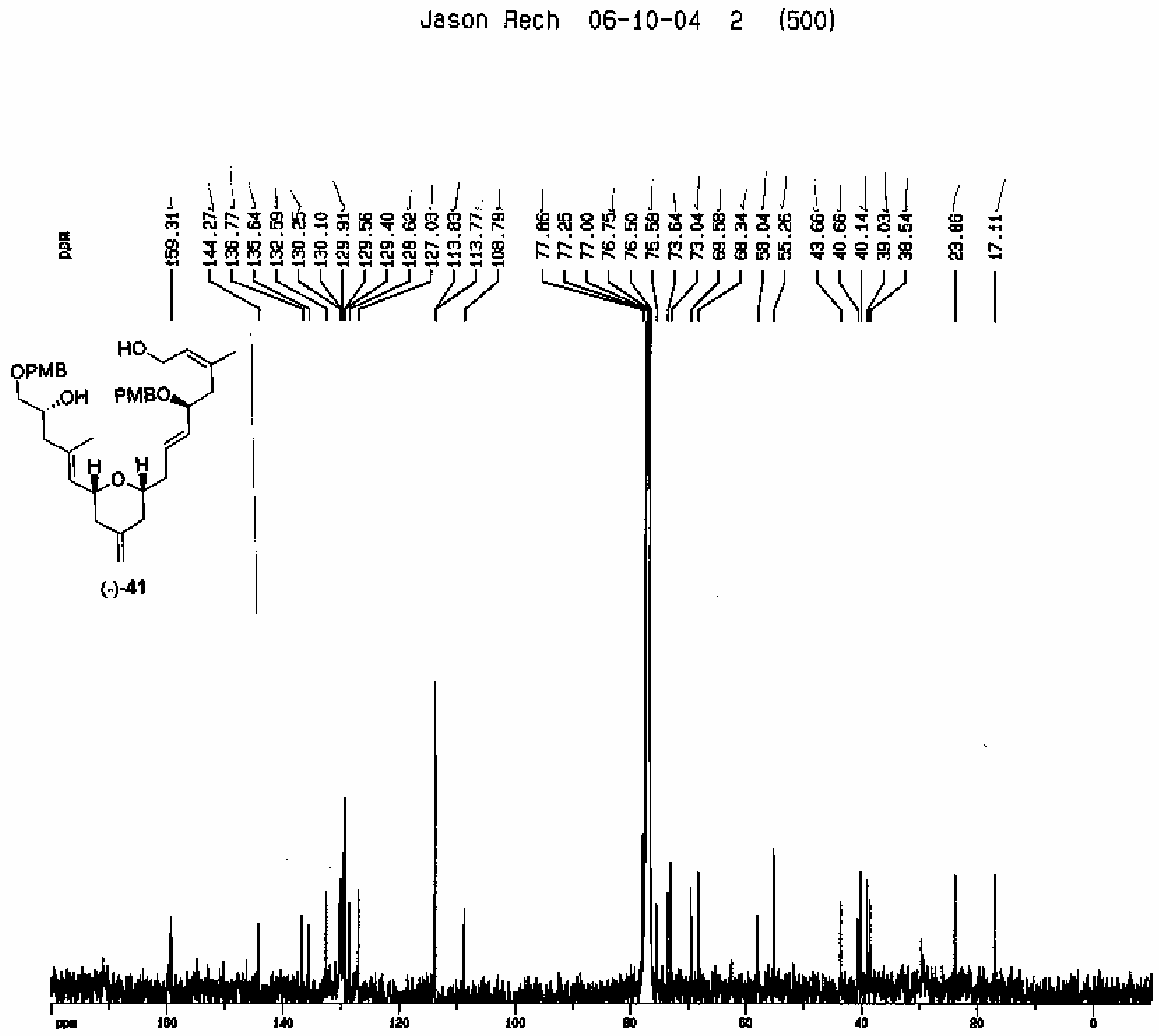
TBDPSO
OPMB
OTBS
HO
H
O
H
ppm
159.282
144.824
136.209
135.858
135.816
135.176
133.788
130.795
129.868
129.434
128.797
128.008
127.895
127.417
127.276
113.892
108.781
77.921
77.680
77.257
76.833
75.820
74.352
73.133
70.738
70.219
60.324
55.467
45.213
40.969
40.745
40.233
39.409
27.027
26.162
24.159
19.334
18.416
17.950
-4.242
-4.473
ppm
160
140
120
100
80
60
40
20
0


TBDPSO
OPMB
OTBS
HO
H
O
H
(-)-62
elg 05-05-04 1 (500) [d1a050504]
ppm
4.5
4.0
3.5
Current Data Parameters
EXPNO 1111
PROCNO 1
F2 - Acquisition Parameters
TD 1024
SOLVENT CDCl3
NUC1 1H
F1 - Acquisition parameters
ND0 2
F2 - Processing parameters
SI 1024
LB 0.00 Hz
PC 1.00
F1 - Processing parameters
MC2 TPPI
LB 0.00 Hz
2D NMR plot parameters

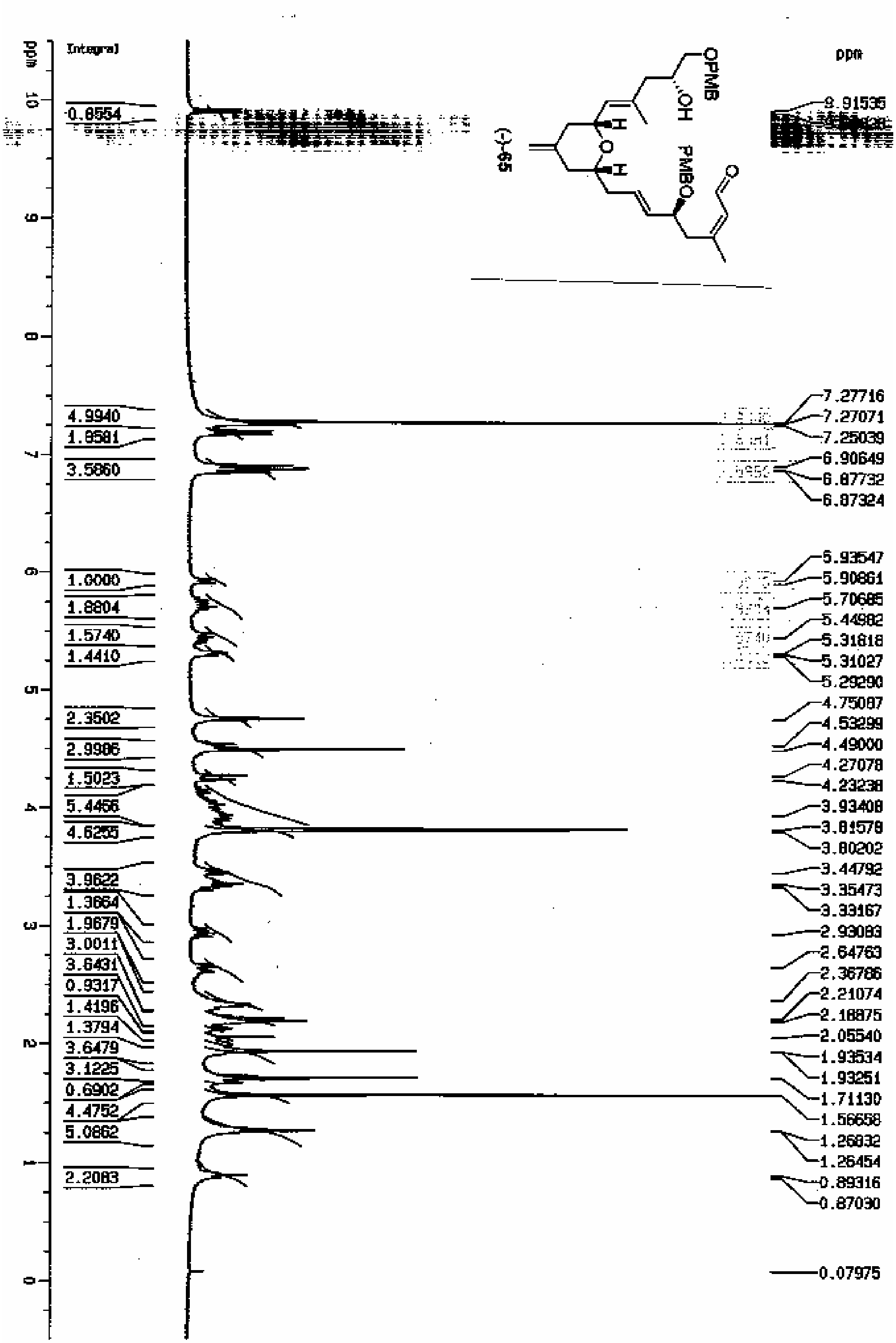


(-)-41

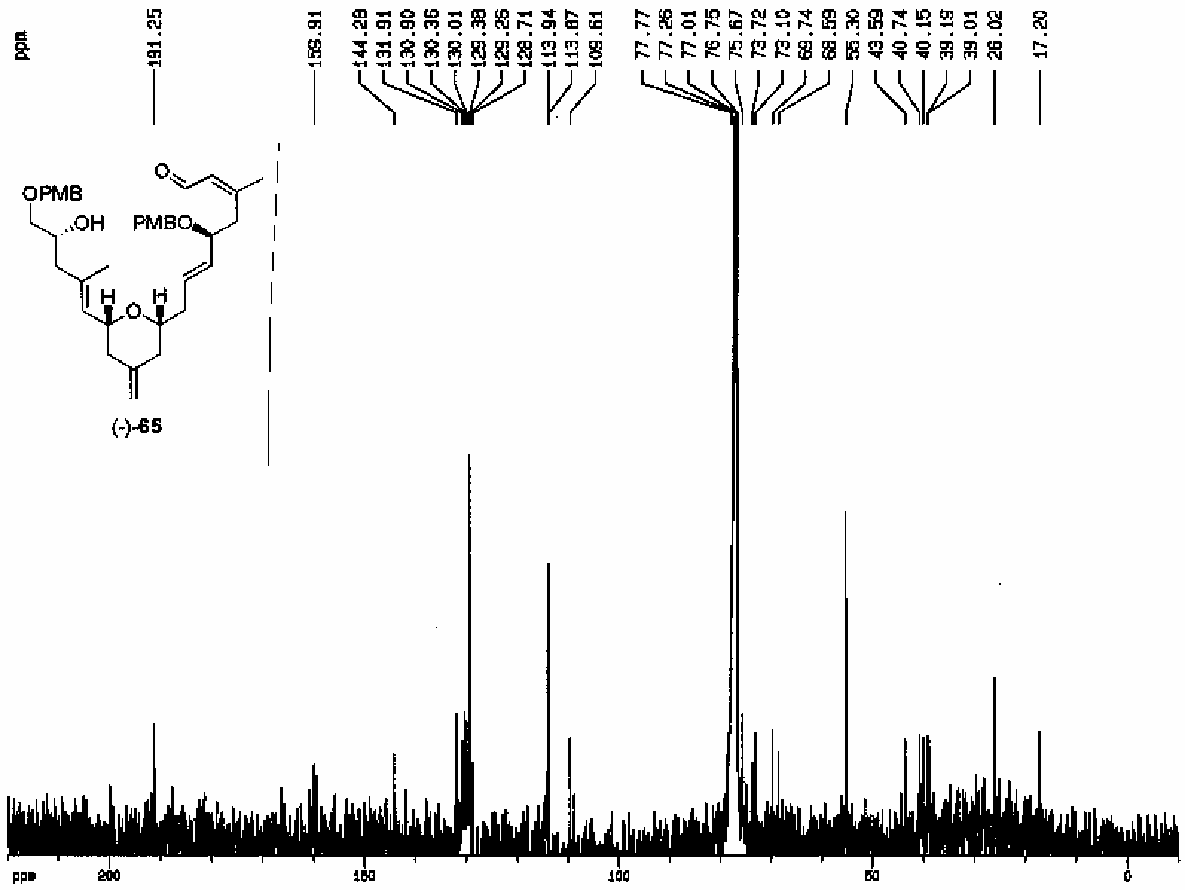
```
Current Data Parameters
NAME           dla061104
EXPNO                  1
PROCNO                 1

F2 - Acquisition Parameters
Date_             500000
Time               10.06
INSTRUM            spect
PROBHD     5 mm TXI 13C
PULPROG               zg
TD                 32768
SOLVENT              D2O
NS                    15
DS                     0
SWH             7507.507 Hz
FIDRES          0.229111 Hz
AQ             2.1823988 sec
RG                  90.5
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           500.1300238 MHz
WDW                   EM
SSB                    0
LB                  0.40 Hz
GB                     0
PC                  1.00

1D NMR plot parameters
CX                 20.00 cm
F1P               10.000 ppm
F1               5001.30 Hz
F2P               -0.500 ppm
F2               -250.07 Hz
PPMCM            0.52500 ppm/cm
HZCM           262.55827 Hz/cm
```



```
Current Data Parameters
NAME            dla061104
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_              500000
Time                10.14
INSTRUM             spect
PROBHD     5 mm TXI 13C
PULPROG          c13wonoe
TD                  32768
SOLVENT             CDC13
NS                  10836
DS                      0
SWH            32679.738 Hz
FIDRES          0.997306 Hz
AQ             0.5014004 sec
RG                  46341
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           weltz16
PCPD2              100.00 usec
SFO2          500.1330008 MHz
NUC2                   1H
PL2                120.00 dB
P1                  21.80 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               160.000 ppm
F1               22636.40 Hz
F2P               -10.000 ppm
F2               -1257.58 Hz
PPMCM             9.50000 ppm/cm
HZCM           1194.69910 Hz/cm
```


(-)-65
OPMB
OH
PMBO
H
O
H
ppm
Integral
10
9
8
7
6
5
4
3
2
1
0
0.8554
4.9940
1.8581
3.5860
1.0000
1.8804
1.5740
1.4410
2.3502
2.9986
1.5023
5.4456
4.6255
3.9622
1.3664
1.9679
3.0011
3.6431
0.9317
1.4196
1.3794
3.6479
3.1225
0.6902
4.4752
5.0862
2.2083
9.91535
7.27716
7.27071
7.25039
6.90649
6.87732
6.87324
5.93547
5.90861
5.70685
5.44982
5.31618
5.31027
5.29290
4.75087
4.53299
4.49000
4.27078
4.23238
3.93408
3.81578
3.80202
3.44792
3.35473
3.33167
2.93083
2.64763
2.36786
2.21074
2.18875
2.05540
1.93534
1.93251
1.71130
1.56658
1.26832
1.26454
0.89316
0.87030
0.07975

DLA 07-12-04 2 (500)



(-)-65

```
Current Data Parameters
NAME             dla071204
EXPNO                    2
PROCNO                   1

F2 - Acquisition Parameters
Date_               500000
Time                 21.28
INSTRUM              spect
PROBHD     5 mm TXI 13C
PULPROG            c13wonoe
TD                   32768
SOLVENT              CDC13
NS                   18571
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              4.00000000 sec
CPDPRG2            waltz16
PCPD2               100.00 usec
SFO2          500.1330008 MHz
NUC2                    1H
PL2                 120.00 dB
P1                   17.00 usec
DE                    6.00 usec
SFO1          125.7715724 MHz
NUC1                   13C
PL1                   0.00 dB

F2 - Processing parameters
SI                    8192
SF            125.7577881 MHz
WDW                     EM
SSB                      0
LB                    4.00 Hz
GB                       0
PC                    1.00

1D NMR plot parameters
CX                   20.00 cm
F1P                220.000 ppm
F1                27666.71 Hz
F2P                -10.000 ppm
F2                -1257.58 Hz
PPMCM             11.50000 ppm/cm
```