Diastereoselective α-Alkylation of Chiral β-Borylated Esters

Michael Thomas Perfetti

Thesis submitted to the faculty of the Virginia Polytechnic Institute and State University

in partial fulfillment of the requirements for the degree of

Master of Science
In
Chemistry

Webster L. Santos, Chairman

Paul R. Carlier

Harry W. Gibson

Wednesday, December 9th, 2009
Blacksburg, Virginia

Keywords: Diastereoselective α-alkylation, β-boronic ester,

boron-"ate", *syn* selective, ^{11}B NMR

Diastereoselective α-Alkylation of Chiral β-Borylated Esters

Michael Thomas Perfetti

ABSTRACT

The use of boron in the synthesis and development of asymmetric methodologies and various biological and medicinal compounds has increased significantly over the last decade. This thesis reports the development of a novel diastereoselective reaction for the α-alkylation of chiral β-borylated esters. We propose that standard deprotonation of chiral β-borylated esters with lithium diisopropylamide (LDA) leads to the formation of a boron-"ate" intermediate that upon treatment with an alkylation reagent collapses to provide chiral α, β-substituted boronic esters with a high degree of diastereoselectivity. This reaction is powerful in that a wide range of chiral β-borylated ester substrates can be employed that possess varying degrees of substitution and steric bulk. Results show that the reaction is *syn*-selective and provides yields of up to 60%, with diastereomeric ratios as high as (9.7:1). Additionally, alkylation products from bulkier *tert*-butyl esters provide higher DR values compared to those of methyl esters that possess the same β-functional groups. Several techniques were utilized to elucidate the mechanism of this reaction including variations of reaction temperature and equivalents of base, and also real-time analysis of the reaction by ^{11}B NMR experiments.

Acknowledgments

I wish to thank my family and friends for their continual love and support during the completion of my Masters degree. I could not have completed this work without them playing such an active role in my life and I cannot thank them enough for all that they have done. In particular, I wish to thank my Mother and Father who inspired me to become a scientist and pursue to my dreams to the fullest of my ability. I also wish to thank, Alexandra, who has been a continual source of love, support, and laughter throughout this work. Thank you!

I would like to sincerely thank my research advisor, Dr. Webster Santos for all of his helpful guidance, support, and understanding throughout the completion of this work. He has mentored me to becoming a more knowledgeable, thorough, patient, and efficient chemist. I have learned an immense amount about both the practice of research and the science of chemistry and cannot thank him enough for his guidance and support. Thank you!

I would like to gratefully acknowledge the support of my Masters advisory committee members, Dr. Harry Gibson and Dr. Paul Carlier. Their helpful and constructive commentary and guidance aided greatly in the overall understanding of the chemistry encountered during this work.

I wish to express my gratitude to all of my research group members for their helpful commentary and support, and to the staff of the Virginia Tech Department of Chemistry Analytical Services for all of their help and assistance with the ^{11}B NMR spectroscopy.

Table of Contents

List of Figures

List of Schemes

List of Tables

List of Abbreviations

TLC	Thin layer chromatography
DR	Diastereomeric ratio
THF	Tetrahydrofuran
DPEPhos	Bis(2-diphenylphosphinophenyl)ether
HRMS	High-resolution mass spectrometry
LDA	Lithium diisopropylamide
GC	Gas chromatography
GC-MS	Gas chromatography-mass spectrometry
NMR	Nuclear magnetic resonance
^{1}H NMR	Proton nuclear magnetic resonance
^{13}C NMR	^{13}Carbon nuclear magnetic resonance
^{11}B NMR	^{11}Boron nuclear magnetic resonance
LiHMDS	Lithium hexamethyldisilazide
KHMDS	Potassium hexamethyldisilazide
DIEA	N,N-Diisopropylethylamine
DCM	Dichloromethane (methylene chloride)
BABE	Benzyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate
MABE	Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate
MCBE	Methyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate
Me_4Si	Tetramethylsilane
PMA	Phosphomolybdic acid

TMSCl	Chlorotrimethylsilane
SAR	Structure activity relationship studies

Preface

The research presented in this thesis details the development and characterization of a new diastereoselective reaction for the α-alkylation of chiral β-borylated esters of varying degrees of substitution and steric bulk. These highly functionalized chiral boryl products can be integrated into biological and medicinal agents, such as transition-state analogues or anticancer agents, and also could be used as intermediates in organic synthesis. In particular, reaction products will be incorporated into N-terminal peptidic boronic acids as transition-state analogue inhibitors for various enzymatic, or protein targets. Funtionalization of the α-carbon of precursor boronic esters allows for exploration of the necessary structural components required to achieve a strong bonding interaction with a target substrate. Further optimization of this reaction will allow for increased yields and determination of the full scope of applicable reaction substrates.

Chapter 1: Use of Boron in Asymmetric Synthesis

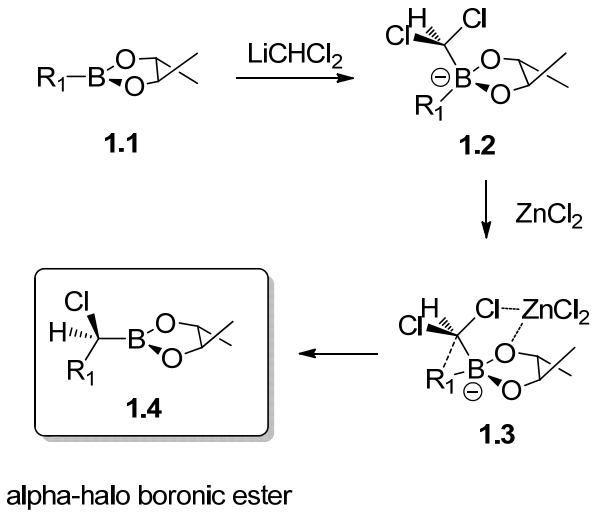
1.1. Introduction

Boron continues to play a unique role in asymmetric synthesis because of its utility as a key structural component of catalysts. Development of several asymmetric catalysts such as oxaborolidines[1] and boronic acid ferrocene derivatives[2] has resulted in a wide range of catalytic syntheses that capitalize on the Lewis acidic nature of boron. Overall, the use of boron in asymmetric synthesis has revolved around boron-containing ligands, where boron is not a component of the original substrate that undergoes modification. The use of boron as a central structural element of the reaction substrate, such as with β-boronic esters, has not been widely researched. Examples present in the literature can be categorized as either intermolecular[3, 4] or intramolecular[5, 6] synthetic methods.

1.2. Intermolecular Catalysis: α-Halo Boronic Esters

The Lewis acidic nature of boron plays a central role in intermolecular asymmetric boryl reactions. The vacant *p*-orbital of boron facilitates the formation of charged boron-"ate" intermediates that upon collapse form new stereogenic centers. Use of this chemical characteristic of boron has resulted in the development of many forms of intermolecular asymmetric syntheses including a homologation technique to provide α-halo boronic esters.[3, 4] The wide-spread use of α-halo boronic esters in asymmetric synthesis has proven of great utility in many areas of chemistry. This strategy was developed by the Matteson group, and its utility has ranged from natural product synthesis, to synthesis of inhibitors in medicinal chemistry, and to the advancement of

asymmetric methodology.[3, 4] α-Halo boronic esters are formed through the insertion of a methylene unit from an alkyllithium species into the boron-carbon bond of the boronic ester substrate, **1.1**, Scheme 1.[7-10] Dichloromethyllithium is typically used as the methylene source and after complexation with boron results in a boron-"ate" intermediate **1.2**. Upon chelation of a metal such as zinc, the intermediate undergoes rearrangement, **1.3**, to provide the α-halo boronic ester **1.4**.

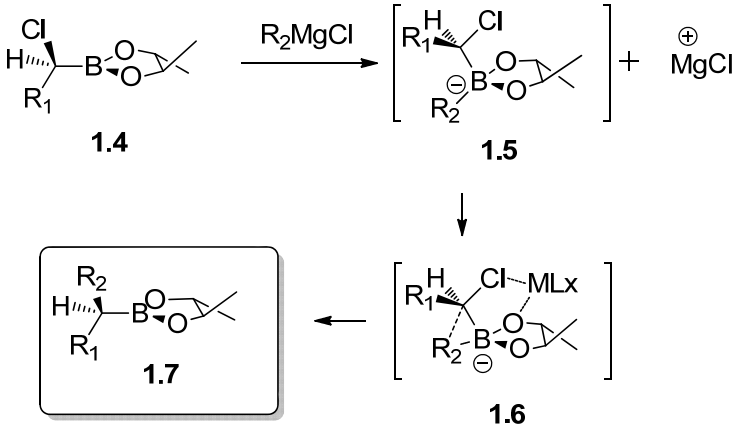


Scheme 1. Formation of α-Halo Boronic Ester

Coordination of the metal to chlorine in **1.2** activates the methylene carbon-chloride bond, allowing the migration of R_1 to displace the chloride in the process. This rearrangement produces a chiral α-halo boronic ester, **1.4**.[11] The use of a C_2-symmetric ligand in the boronic ester provides stereocontrol in the resulting product.[4] C_2-symmetry forces the migration of the R_1 group to a single enantiotopic face of the α-carbon. In addition to acting as a Lewis-acid, zinc chloride provides stereocontrolled coordination by positioning itself in the open coordination site provided by the C_2-symmetric diol. This filled coordination site forces migration to occur on the opposing enantiotopic face of boron.

The α-halo boronic ester can then be further modified in several ways to produce synthetic intermediates used in the synthesis of natural products or inhibitors of proteases such as proteasomes[12-14], phosphatases[15], and chymotrypsin.[16] In addition, modified α-halo boronic esters can be used in the total synthesis of several insect pheromones[11, 17-20] and amino acids. [18] Modifications include additional homologations, addition of various functional groups including carbonyl[17, 18, 20, 21], azido[17], nitrile[22-24], and amide[16] functionalities, or oxidation of the boryl group to provide a secondary alcohol.

Of these techniques, the most common is homologation, Scheme 2. This process consists of treatment of an α-halo boronic ester **1.4**, with an organometallic reagentsuch as a Grignard reagent to form a boron-"ate" **1.5**. The chelation of its respective metal to activate the boron-halogen bond **1.6**, the subsequent R_2 migration, and chloride displacement provides **1.7**. Up to five new chiral centers have been formed using this method.[11, 25]



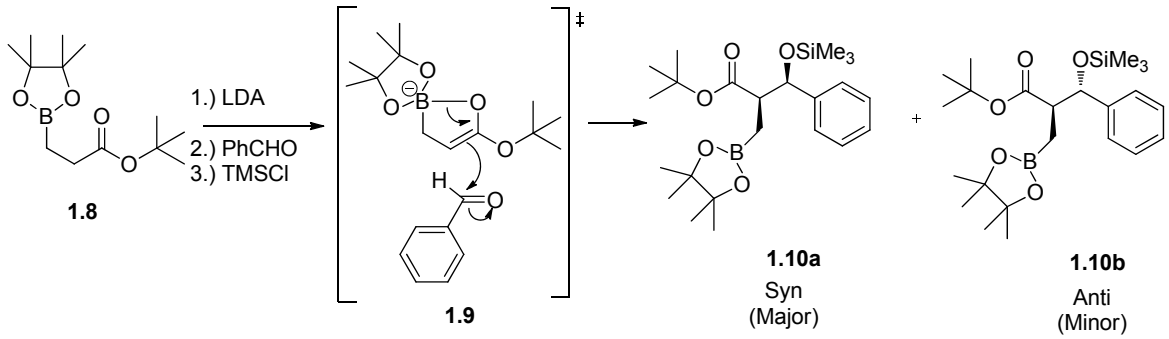
Scheme 2. α-Halo Boronic Ester Chain Extension

1.3 Intramolecular Synthesis

There is little literature on the use of boron as a substrate in intramolecular asymmetric reactions. The need for the development of this form of boron asymmetric methodology is great, as new reactions involving boron-containing substrates will provide more efficient and robust methods that have better atom economy.

1.3.1. Stereoselective Aldol

Application of intramolecular boron chemistry in stereoselective aldol reactions was initially developed by the Whiting group in the early 1990s.[5, 6] Their intramolecular aldol methodology was based on the formation of a cyclic five-membered boron-"ate" intermediate **1.9** derived from **1.8**, Scheme 3. Collapse of this boron-"ate"intermediate, **1.9**, and its subsequent nucleophilic attack on an aldehyde followed by chlorotrimethylsilane (TMSCl) quench resulted in the formation of TMS enol ethers **1.10a** and **1.10b**.



Scheme 3. Stereoselective Intramolecular Aldol

The Whiting group found that the enolate geometry highly influenced the selectivity of the aldol products; *Z*-enolates provided high *syn*-selectivity and *E*-enolates also provided *syn*-selectivity but to a lesser extent. These findings were attributed to chelation enhanced stability of the enolate geometry by the boron-"ate" intermediate.

Overall, asymmetric methodologies incorporating boron have mainly proceeded through intermolecular mechanisms, with only one example of an intramolecular method in the literature. Each of the currently available methods has its individual strengths and weaknesses, but future work in either arena should be aimed at developing new methods that minimize the number of necessary reactions steps and reagents, while also providing acceptable yields, with a high degree of stereocontrol over the resulting products.

Chapter 2: Diastereoselective α-Alkylation of Chiral β-Boronic Esters via a Boron-"ate" Complex

2.1. Synthetic Goals

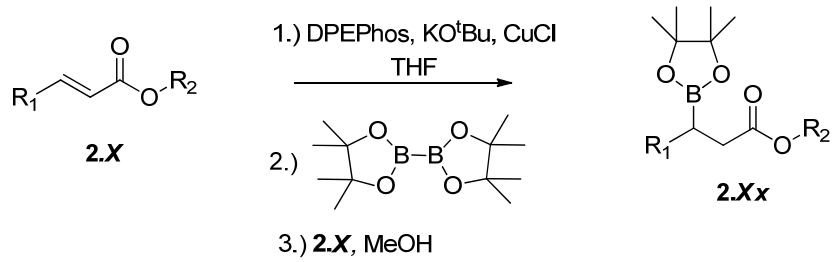
β-Boronic esters are useful functional groups that could be used to synthesize and develop inhibitors and other synthetic intermediates. The incorporation of new functional groups at the α-carbon of esters via alkylation provides access to unique chiral intermediates. These substituted intermediates can then be further modified by saponification or oxidation of the boryl group for use in structure activity relationship studies (SAR). Overall, the synthetic goal of this work is to develop a new diastereoselective method of producing α-carbon functionalized β-boronic esters.

2.2. Chiral β-Boronic Esters

Organoboron compounds have become increasingly more common in the literature and new synthetic methods and techniques have been developed for use in applications as biological agents, functionalized polymers, and synthetic intermediates. [4, 26-30] This work was aimed at developing a new synthetic method to provide highly functionalized β-boronic esters that could later be incorporated into any of the aforementioned applications. In particular, the products of this new intramolecular reaction could be incorporated into transition-state inhibitors of proteases. It is believed that the introduction of substitutents at both the α-, and β-carbons of the boronic ester will provide potent and selective inhibitors.

2.2.1. Synthesis of Chiral β-Boronic Esters

The β-boronic esters used in this study cannot be purchased, and must therefore be synthesized. The β-boronic esters, **2.1a** – **2.5a** were synthesized using a copper catalyzed β-borylation method developed by the Yun Group.[31] The installation of a pinacol boronic ester on various α,β-unsaturated esters was accomplished using bis(pinacolato)diboron (1.1 eq) in the presence of a catalytic amount of CuCl (0.03 eq), bis(2-diphenylphosphinophenyl)ether (DPEPhos, 0.03 eq), $NaOC(CH_3)_3$ (0.09 eq), and MeOH (methanol, 4 eq) at room temperature to provide yields ranging from 9-87%, Scheme 4.

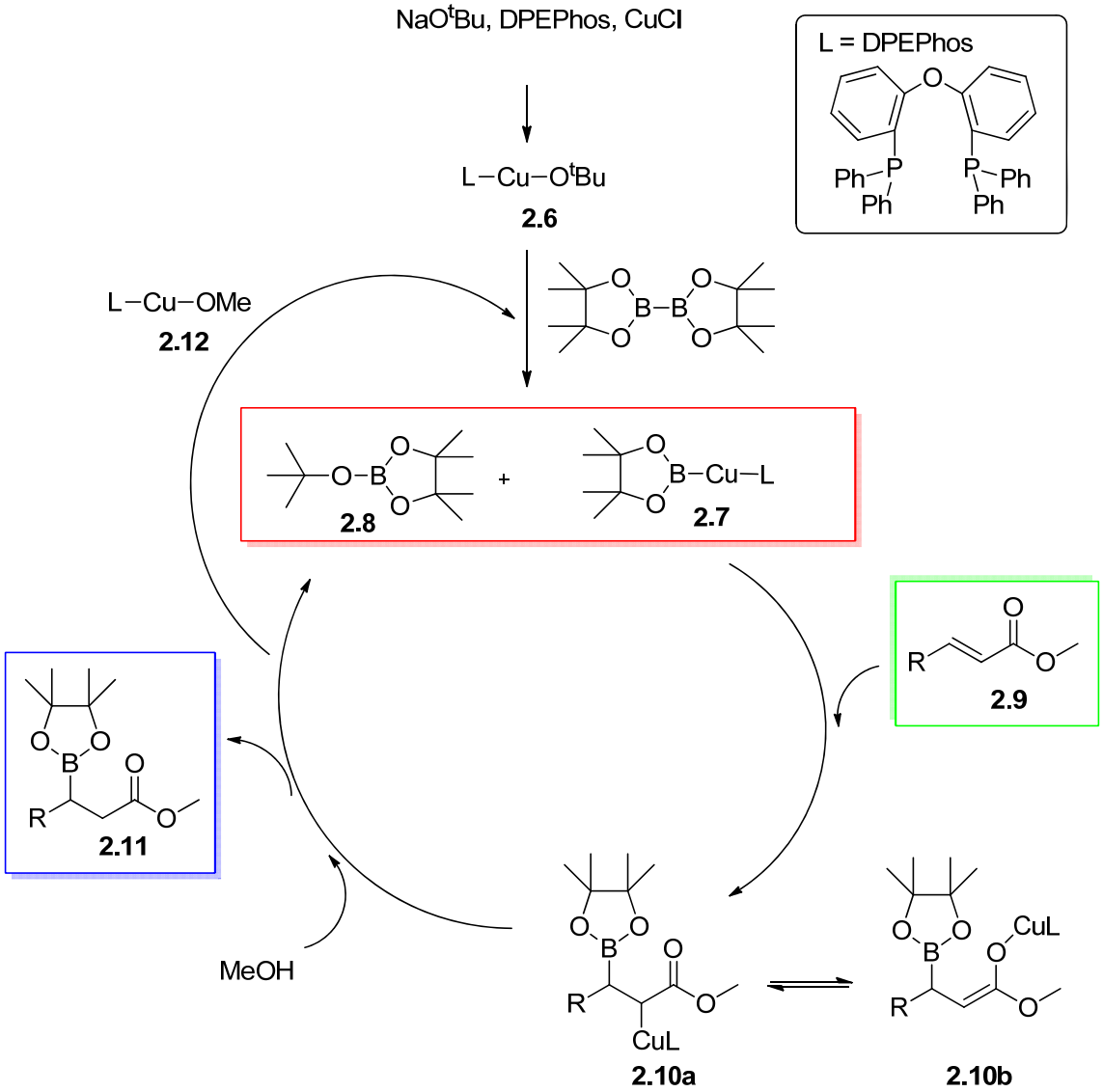


		% Yield
2.1: R_1 = Ph, R_2 = methyl	**2.1a**: R_1 = Ph, R_2 = methyl	87
2.2: R_1 = Methyl, R_2= methyl	**2.2a**: R_1 = Methyl, R_2 = methyl	78
2.3: R_1 = Ph, R_2 = ^{t}Butyl	**2.3a**: R_1 = Ph, R_2= ^{t}Butyl	74
2.4: R_1 = Ethyl, R_2= ^{t}Butyl	**2.4a**: R_1 = Ethyl, R_2 = ^{t}Butyl	28
2.5: R_1 = ^{i}Pr, R_2 = ^{t}Butyl	**2.5a**: R_1 = ^{i}Pr, R_2 = ^{t}Butyl	9

Scheme 4. Synthesis of Chiral β-Boronic Esters.

The proposed catalytic mechanism of this β-borylation works through a phosphine ligand coordinated copper-*tert*-butoxide complex **2.6** that undergoes sigma-bond metathesis with the diboron to produce a boryl-cuprate complex **2.7** and byproduct **2.8**, Scheme 5. Donation of electrons from DPEPhos onto copper activates the copper-boron bond and allows this complex to then react with the α,β-unsaturated ester **2.9** by a 1,4-conjugate addition, resulting in an equilibrium between *C*- and *O*-enolate tautomers

2.10a and **2.10b**. The Yun group found that this reaction will slowly proceed to formation of the β-borylated product, **2.11**, but addition of 4 equivalents of an alcohol such as methanol significantly increased the rate of product formation. The resulting methoxide reforms a phosphine ligand-cuprate-methoxide complex **2.12** that re-enters the catalytic cycle as a surrogate for complex **2.6**.



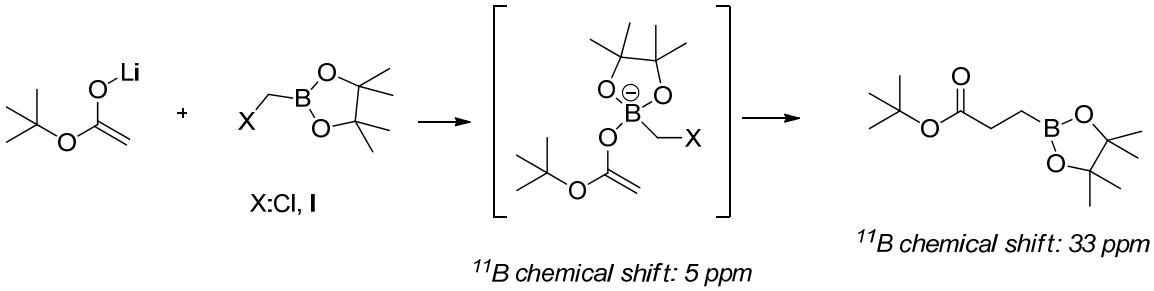
Scheme 5. Catalytic Cycle for the Formation of β-Boronic Esters.

2.3. Diastereoselective α-Alkylation

Current asymmetric synthetic methods often require the use of either external chiral ligands or installation of a chiral auxilary. This project was aimed at using readily available chiral starting materials and taking advantage of the Lewis acidic nature of boron to develop a new diastereoselective α-alkylation reaction.

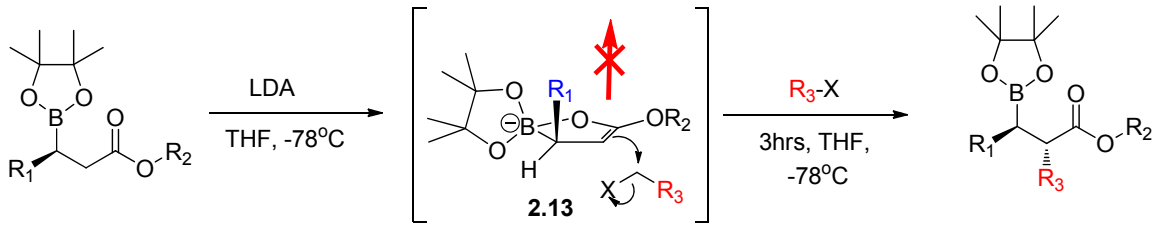
2.3.1. Cyclic Five-Membered Boron-"ate" Intermediate

An acyclic boron-"ate" complex was reported in 1991 by Whiting *et. al.* in the formation of β-boronic *tert*-butyl esters. The tetra coordinate boron-"ate" complex was found to have a chemical shift value of 5 ppm, and the tri-coordinate β-boronic *tert*-butyl ester was found to have a chemical shift of 33 ppm by ^{11}B NMR, Scheme 6.[32]



Scheme 6. Acyclic Boron-"ate" Complex.

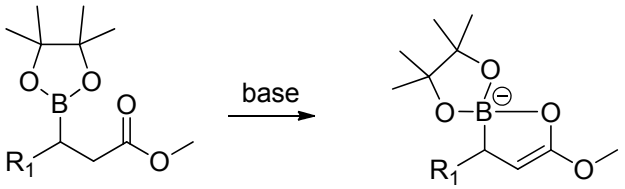
To provide perspective, the ^{11}B NMR chemical shifts of β-boronic esters range from 28- 34 ppm.[4, 32, 33] ^{11}B NMR spectroscopy provides a tool to gain insight on several mechanistic aspects of this proposed diastereoselective reaction. The research and analysis described in this thesis is focused on an intramolecular diastereoselective reaction, Scheme 7, that is based upon the idea of a chelate-stabilized boron-"ate" intermediate **2.13**.



Scheme 7. Intramolecular Chelate-Stabilized Intermediate.

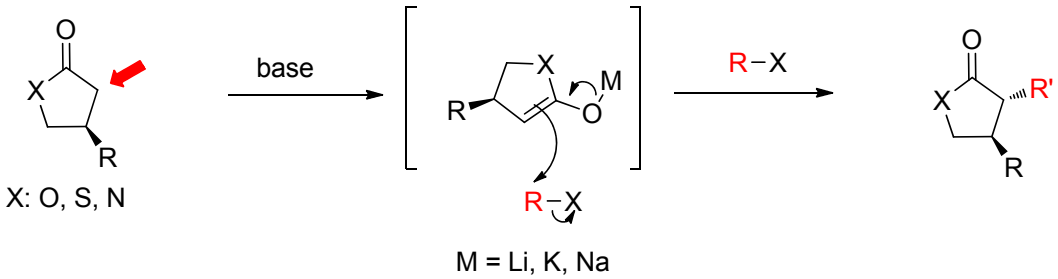
Several factors are proposed to influence the diastereoselectivity of the reaction. The formation of the cyclic five-membered boron-"ate" intermediate will be affected by the geometry of the enolate. The *Z*-enolate is proposed to provide the desired cyclic intermediate, where as the *E*-enolate will not because of unfavorable bond geometry. Upon formation of a cyclic boronate intermediate, the β-functional group will provide control over the facial selectivity of the electrophile; the β-functional group, R_1, will sterically block a single diastereotopic face of the cyclic intermediate. The intermediate needs to be stable to allow the β-functional group to direct the stereochemistry of the resulting product. It is hypothesized that a bulkier ester group will provide the desired *Z*-enolate because of 1,3-allylic strain.

Chiral β-borylated esters were used as substrates for this diastereoselective α-alkylation reaction. The treatment of β-boronic esters with base generates an enolate that is proposed to intramolecularly chelate to boron resulting in a cyclic five-membered boron-"ate" complex **2.14**, Scheme 8.



Scheme 8. Formation of sp^3-Hybridized Boron-"ate" Complex.

The proposed diastereoselective α-alkylation has precedence in the literature.[5, 6] Alkylation of 5-membered heterocyclic compounds proceeds through the deprotonation of the α-carbon to form a lithium enolate that undergoes diastereoselective α-alkylation upon treatment with an alkylating reagent, Scheme 9.



Scheme 9. Cyclic Five-Membered Intermediate.

For example, the diastereoselective alkylation of γ-lactones using iodomethane showed a range of DR values including 4.5:1, [34] 8:1[35], 11:1[36], and 98:2, Figure 1.[37]

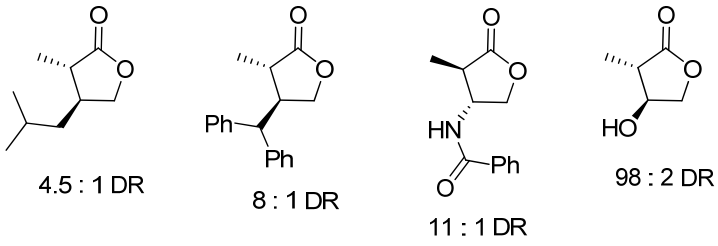


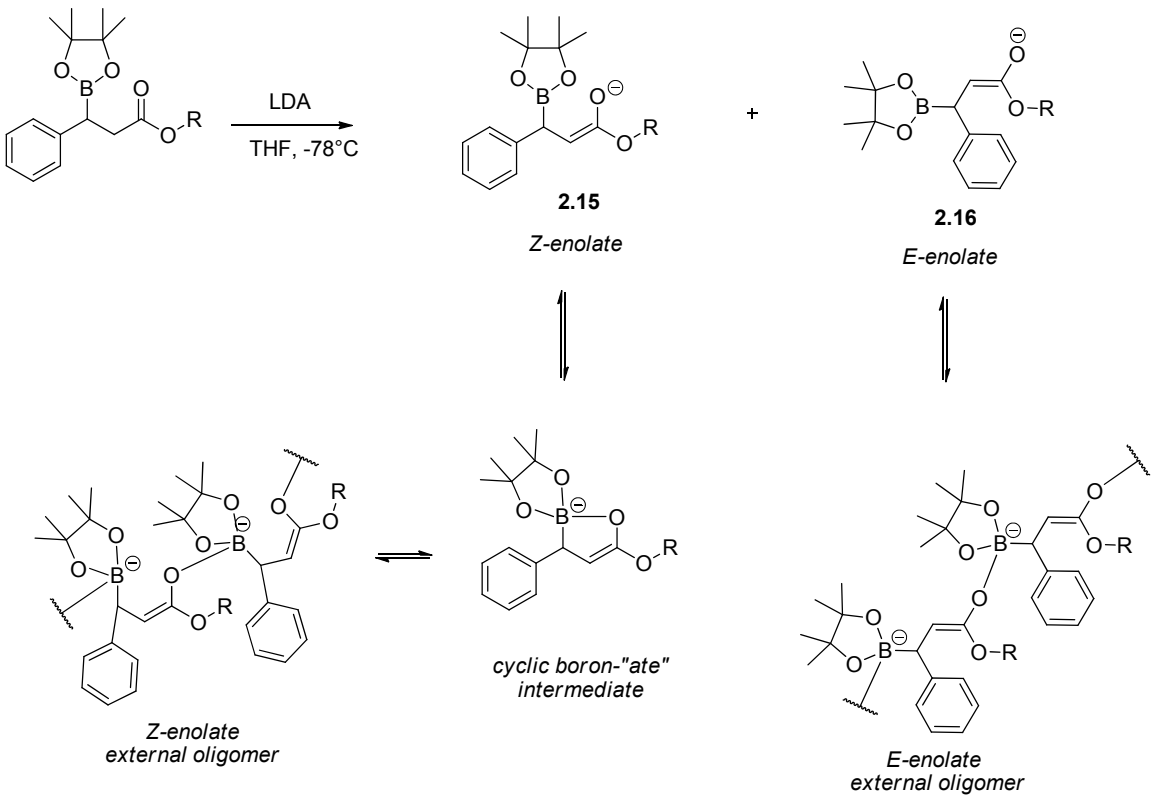
Figure 1. Diastereoselective α-Alkylations of γ-Lactones.

In addition, the diastereoselective alkylation of γ-thiolactones with phenyl selenium bromide provided a DR of 10:1,[38] and γ-lactams with iodomethane provided a

DR of 9:1.[39] These examples of diastereoselective α-alkylations are important because their intermediate structurally and electronically resemble the proposed cyclic intermediate proposed in this study. These preliminary works suggest that the formation of a cyclic boron-"ate" can provide enhanced diastereoselectivity in the resulting alkylation products.

2.3.1.A. Boron-"ate" Structural Analysis

The cyclic five-membered boron-"ate" intermediate is believed to be essential to the diastereoselective process. When the cyclic boron-"ate" intermediate is present, the β-functional group forces the addition to occur on the opposing diastereotopic face of the cyclic five-membered boron-"ate"complex. When the β-boronic ester is deprotonated under kinetic conditions, either the *Z* -, or *E* -enolate are formed, **2.15** and **2.16** respectively; the *Z*-enolate is expected to predominate, Scheme 10. Because these are formed under kinetic conditions, no equilibrium is expected to exist between the two isomers. Additionally, if the ester substituent is bulky, then formation of **2.15** would be preferred because of a 1, 3-allylic strain caused from unfavorable steric interactions between the β-functional group and ester functional group in **2.16**.



Scheme 10. *E*/*Z*-Enolate Formation.

Rotation of the C_2-C_3 bond also plays a role in the stability of the cyclic five-membered boron-"ate" intermediate **2.17** and its ability to influence the resulting DR value (Figure 2). When the reversible covalent B-O bond breaks, the C_2-C_3 bond is then free to rotate. When this bond rotates, all control over the diastereoselectivity of the intermediate is proposed to be lost, since the chiral directing reagent (the β-functional group) is no longer able to sterically block a single diastereotopic face. After B-O bond cleavage, if the C_2-C_3 bond rotation is fast and there is no external *O*-enolate chelation, then there is hypothesized to be little, to no control over the diastereoselectively resulting from the two enolate structures, **2.18** and **2.19**. We hypothesize that this would provide an overall lower diastereoselectivity than from **2.17**. Overall, the stable cyclic five-membered intermediate must be maintained to allow the β-functional group to block a single diastereotopic face and allow for diastereoselectivity.

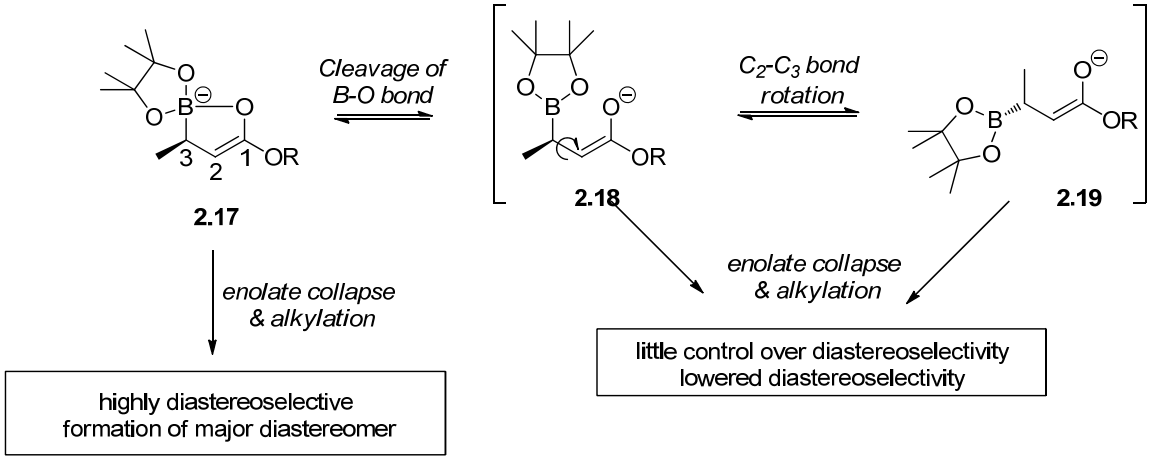
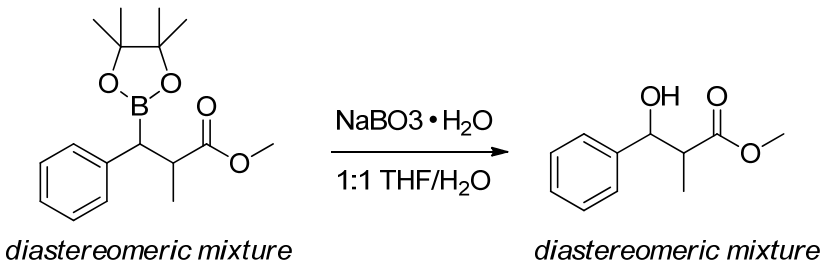


Figure 2. Effects of Cyclic Five-Membered Ring Rigidity.

2.4. Alkylation Results

The results of the α-alkylations are shown in Schemes 11, 12, and 13. The DR values were obtained by analysis of crude reaction mixtures using gas chromatographiy (GC), ^{1}H NMR, HPLC analysis, or GC analysis of crude oxidized product mixtures. Oxidation of the boryl group was performed because of poor resolution of the products using either a standard dimethyl silicone, or 5% phenyl modified dimethyl silicone GC capillary columns under a wide range of conditions. Oxidation of the boryl group using 5 eq of sodium perborate in a 1 to 1 ratio of THF and water provided **2.25** – **2.30, Scheme 11.**

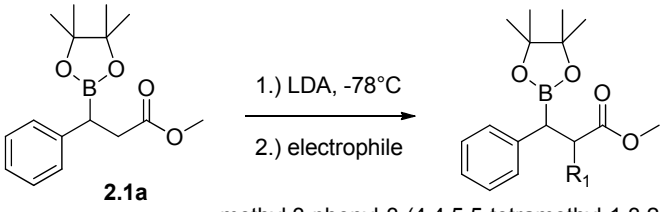


Scheme 11. Boryl Oxidation

After 1 h of reaction time, a small aliquot was analyzed by GC-MS. Increased resolution was believed to occur because of an increased degree of hydrogen bonding between the compounds and stationary media provided by the secondary alcohol moiety.

The proposed diastereoselective α-alkylation was performed with five different β-boronic ester starting materials, **2.1a-2.5a**, to generate 14 α-alkylated diastereomeric products (2.20-2.33). All compounds were found to be oils and their purification proved difficult. Several purification techniques were attempted including column chromatography using silica and alumina, semi-preparative TLC, and distillation; silica column chromatography provided the best results.

Work conducted on methyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoates, **2.1a**, whose β-functional group is a phenyl group showed that there is little diastereoselectivity over the α-alkylation products (Scheme 12).



2.20: R_1 = methyl
2.21: R_1 = allyl
2.22: R_1 = 2-propene
2.23: R_1 = ^{t}butyl acetate

% Yield	DR
49	4[a]
42	2.4[b]
44	1[a]
49	2.4[b]

Scheme 12. Synthesis of α-Alkylated Methyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoates. [a] determined by GC analysis of crude product, [b] determined by ^{1}H NMR of crude alkylation

It was found that as the size of the alkylating reagent increased from methyl to allyl to 2-propene to ^{t}butyl acetate the DR value decreased. These results may be explained by looking at the equilibrium between the "open" and "closed" intermediates, Figure 3. For bulky electrophiles, reaction with the closed intermediate is slow whereas

for small electrophiles such as iodomethane, reaction with the closed intermediate is fast. The loss of diastereoselectivity of the open intermediate was explained in section 2.3.1.A.

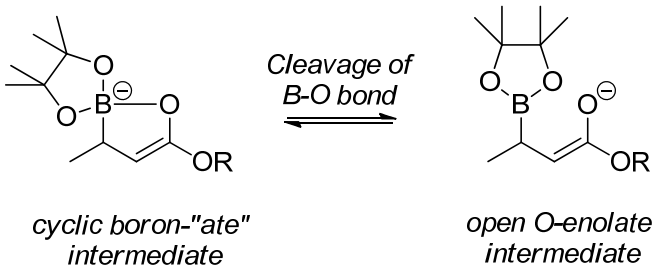
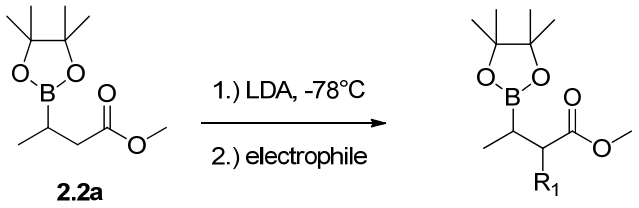


Figure 3. Transition between cyclic and open *O*-enolate intermediate.

Work conducted on methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoates, **2.2a**, in which the β-functional group is a methyl group, showed that there is about the same degree of diastereoselective control over the α-alkylation, as was the case with the methyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate esters, Scheme 13.

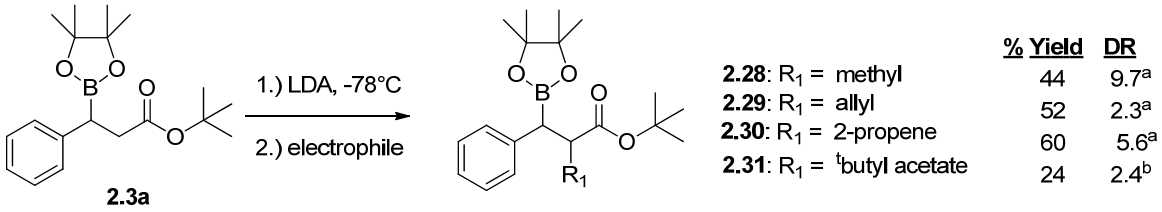


	% Yield	DR
2.24: R_1 = methyl	49	3.6[a]
2.25: R_1 = allyl	43	1.6[b]
2.26: R_1 = 2-propene	20	2[b]
2.27: R_1 = ^{t}butyl acetate	44	1.4[b]

Scheme 13. Synthesis of α-Alkylated Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoates. [a] determined by GC analysis of crude product, [b] determined by GC analysis of crude oxidized product

Again, the bulkier the electrophile became, the lower the DR values that were found. The aforementioned hypothesis of why there is little diastereoselectivity with the alkylation is believed to apply to methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate substrates.

Work conducted on *tert*-butyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoates, **2.3a**, in which the β-functional group is a phenyl group, showed improved DR values only for the smallest electrophile, iodomethane, but no overall change for the other three alkylation reagents, Scheme 14.



Scheme 14. Synthesis of α-Alkylated *tert*-Butyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate Esters. [a] determined by GC analysis of crude oxidized product, [b] determined by HPLC analysis of crude alkylation

The increased diastereoselectivity for the smallest electrophile is believed to come from the more favorable formation of the *Z*-enolate upon deprotonation of the *tert*-butyl ester substrate, in addition to the slowed rate of rotation of the C_2-C_3 bond resulting from the formation and decomposition of a cyclic boron-"ate" intermediate. When the *Z*-enolate predominates, it is believed that the intramolecular cyclic five-membered boron-"ate" intermediate is greatly favored and allows the β-functional group to sterically block a single diastereotopic face. These factors increase the overall DR for the smallest electrophile.

2.5 Relative Configuration of Diastereomeric Products

Determination of which diastereomer was produced in excess would provide insight into the diastereoselectivity of the reaction. However, the relative configurations of the resulting alkylation products were not able to be determined via ^{1}H NMR analysis of the crude reaction mixture because no clearly resolved peaks from the α- or β-protons

from either diastereomer were obtained. From the crude alkylation mixture, a DR value could be calculated based on integration of the methyl ester functional group. To determine the major diastereomer, the β-boronic ester could be oxidized to the secondary alcohol, which can then be compared to the literature values of the well studied aldol reactions (Figure 4).

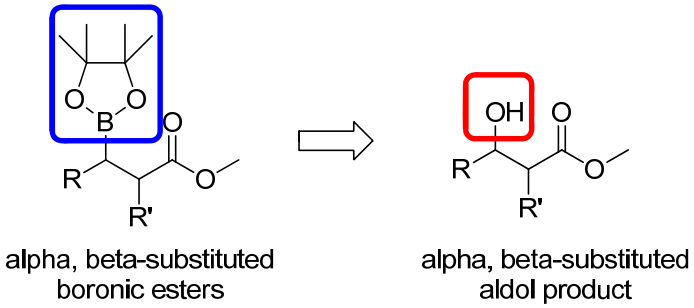
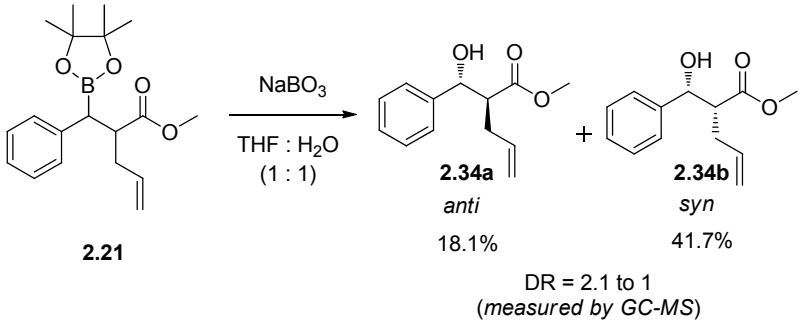


Figure 4. Structural Similarity of α, β-Functionalized Boronic Esters and Aldol Products

Thus, oxidation was conducted by treatment of the crude α-functionalized, β-boronic ester reaction mixture with 5 eq of $NaBO_3 \cdot H_2O$ in a 1 to 1 ratio of THF and water (Scheme 14).



Scheme 15. Formation of Aldol Products from α-Functionalized β-Boronic Esters

Diastereomers **2.34a** and **2.34b** were separable by silica column chromatography and provided an approximate DR value of 2.4 to 1 based upon mass recovery of each diastereomer and this was consistent with the DR values attained by GC-MS. Both *syn* and *anti* assignments were assigned by comparison of the ^{1}H NMR vicinal coupling

constants of the α- and β-protons of each purified diastereomer to known literature shift values of the aldol product, Figure 5.[40] The vicinal coupling values for the *syn* diastereomer are smaller than that for the *anti* diastereomer. Additionally, the chemical shift values of the other protons on each purified diastereomer were compared to the known literature values for verification of proper conformational assignment.

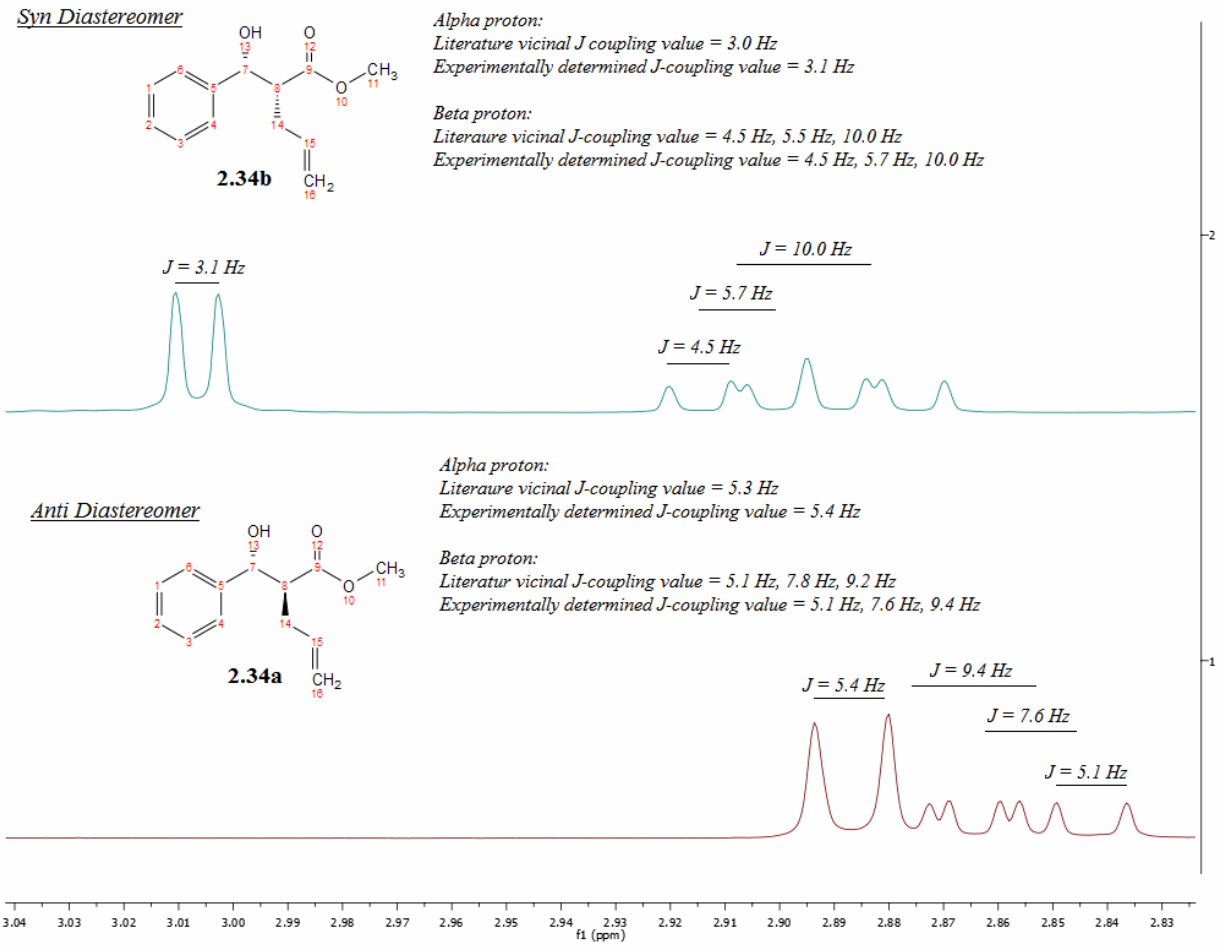


Figure 5. Identification of *Syn* and *Anti* diastereomers from vicinal coupling constants

This finding opposed the initial hypothesis that this reaction proceeded through a closed transition state via a cyclic boron-"ate." If the initial hypothesis were true, then the reaction should be *anti* selective. The *syn* selectivity suggests that this reaction

proceeds through an open transition-state via a *Z*-enolate. An intermolecular oligomeric boron-"ate" could result from the equilibrium shown in Figure 6.

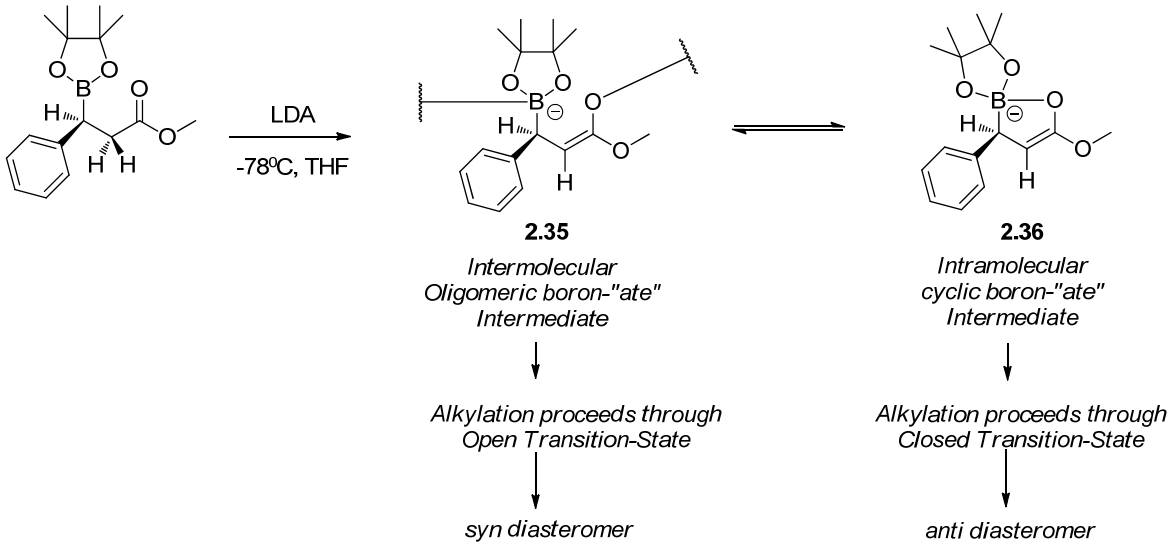


Figure 6. Equilibrium boron-"ates" that may play a role in the diastereoselectivity of the reaction

The application of the Felkin-Ahn model to each boron-"ate" intermediate when viewed in its newman projection shows that the oligomeric intermolecular boron-"ate" intermediate will provide *syn* product **2.35** while the intramolecular cyclic boron-"ate" intermediate will provide *anti* product **2.36**, Figure 7. It is speculated that for the oligomeric intermediate, the largest group (the boronic ester) will be favored to be located on the opposing face of the externally bound *O*-enolate because of unfavorable steric interactions (**2.37**). In the favorable conformation **2.38**, nucleophilic attack will occur between the medium and small groups, phenyl and proton, respectively to provide *syn* product **2.39**. However, when the Felkin-Ahn model is applied to the monomer cyclic boron-"ate" intermediate, the locked five-membered ring is expected to cause the

sterically medium and small groups, phenyl and proton, respectively to be located on the opposite side of the intramolecular chelate (**2.40**) and yield *anti* product **2.41**.

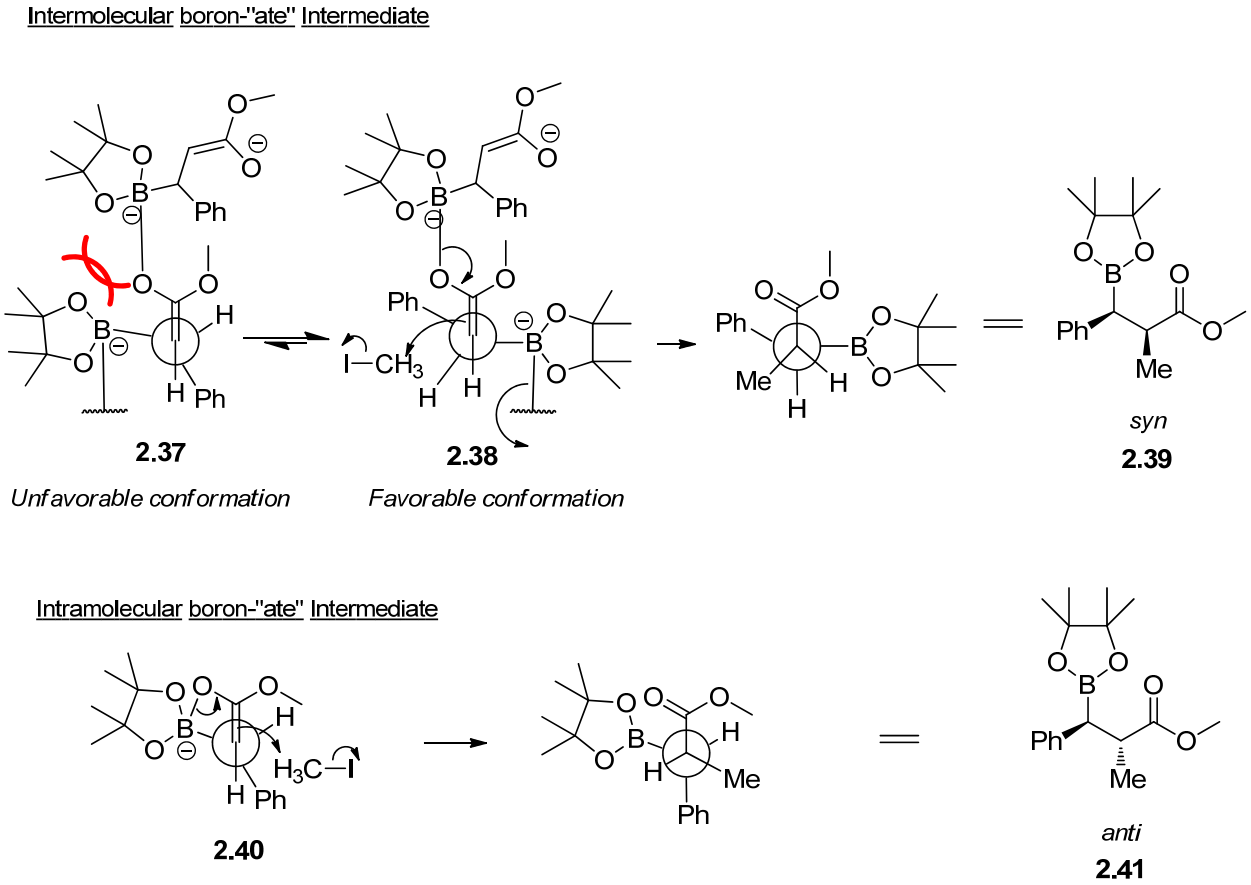


Figure 7. Felkin-Ahn model applied to cyclic and acylic boron-"ate" intermediates

The alkylation results in Schemes 11-13 show that for all substrate families, the smallest electrophile, iodomethane, has the highest DR and that as the steric bulk of the electrophile was increased, the DR of the reaction is lost. This trend of a decreased DR value with increasing steric bulk of the electrophile was found for all three substrate families. There are at least two possible mechanistic concerns that are potentially occurring that influence the diastereoselectivity of this reaction. The first factor influencing the diastereoselectivity is the rate of transition between the two proposed boron-"ate" forms, and how that rate of transition influences the number of resulting *syn*

and *anti* diastereomer products for each substrate. Electrophiles of varying steric bulk may favor one form over the other, but the rate of transition is unknown and therefore it is uncertain whether this transition influences the diastereoselectivity. The other factor is the steric bulk of the electrophile and how that is affected by the form of boron-"ate" present when alkylation occurs. Sterically bulky electrophiles appear to not favor one boron-"ate" form over the other and result in overall decreased DR values for all substrate families tested. The smallest electrophile, iodomethane, appears to favor the proposed open oligomeric boron-"ate" intermediate resulting in an increased DR value, but the reason for this is unknown. Both of these, in addition to other potential factors may work in conjunction to influence the resulting DR values obtained in these experiments, but a definitive explanation for the control of diastereoselectivity of the reaction is uncertain at this time.

2.6 Future Directions

Future application of this diastereoselective reaction on other substrates such as β-borylated ketones, nitriles, and more rigid esters would increase the substrate scope of this reaction. Use of non-carbon electrophiles such as trisyl azide would also increase the range of electrophiles applicable for this reaction and allow for diastereoselective installation of new functional groups.

All of these functionalized compounds will then be saponified to their respective carboxylic acids to allow for incorporation into N-terminal peptidic boronic acids. These highly functionalized peptidic boronic acids will then be utilized in SAR studies for selectivity and inhibition of various enzyme and protein targets.

Chapter 3: *In situ* ^{11}B NMR Analysis of Diastereoselective α-Alkylation Reaction

3.1. Introduction

Findings reported in Chapter 2 show that this diastereoselective reaction was *syn* selective, but provided little insight into the role of the boronic ester functional group. We desired to gain insight into the extent of involvement of the boronic ester and used ^{11}B NMR experiments to elucidate mechanistic aspects of the reaction. ^{11}B NMR spectroscopy is a very useful characterization technique that indicates the coordination state of boryl compounds based on their chemical shift values.

Initial analysis of the starting material showed that sp^2-hybridized boronic esters have a chemical shift value that can vary between 30-34 ppm using an external BF_3-etherate standard. Upon deprotonation, two new signals were detected upfield of the starting material, both below 11 ppm depending upon the β-boronic ester that was deprotonated. These upfield signals indicates the presence of two different tetra-coordinate boron-"ates". Based upon work conducted by Whiting *et al*. that suggested that after deprotonation either a intermolecular or intramolecular boron-"ate" species would be present. It is hypothesize that one of the boron-"ates" possessing the lowest chemical shift is the intramolecular monomeric cyclic five-membered boron-"ate" intermediate and the other unknown boron-"ate" species located downfield of the cyclic five-membered boron-"ate" is an intermolecular oligomeric boron-"ate".[5]

3.2. Effect of Temperature

Initially, experiments were conducted to determine the optimal reaction temperature that provided the greatest amount of boron-"ate". These experiments provided information concerning any potential shift in concentration between the two tetra-coordinate boron-"ates" are a function of temperature. Thus, benzyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (BABE) was treated with 1.5 eq of freshly prepared LDA. This reaction was conducted under inert conditions at -78°C. Immediately after addition of substrate to base, the reaction mixture was quickly transferred to an N_2 flushed, chilled quartz NMR tube maintained at -78°C, then transferred into a previously shimmed NMR spectrometer at -59°C using a BF_3-etherate standard. After the initial scan, the spectrometer temperature was increased to -40°C, and held at that new temperature for 10 min and then scanned. The same process was repeated at -20°C, 0°C, and 25^{o}C. The results are shown in Figure 8. With this experiment, there was unfortunately no means to re-calibrate the spectrometer between each scan as the sample needed to be maintained at a defined temperature, and removal from the unit would have affected the overall experimental findings. That being stated, results showed a slight drift in the chemical shift values for the up-field peaks.

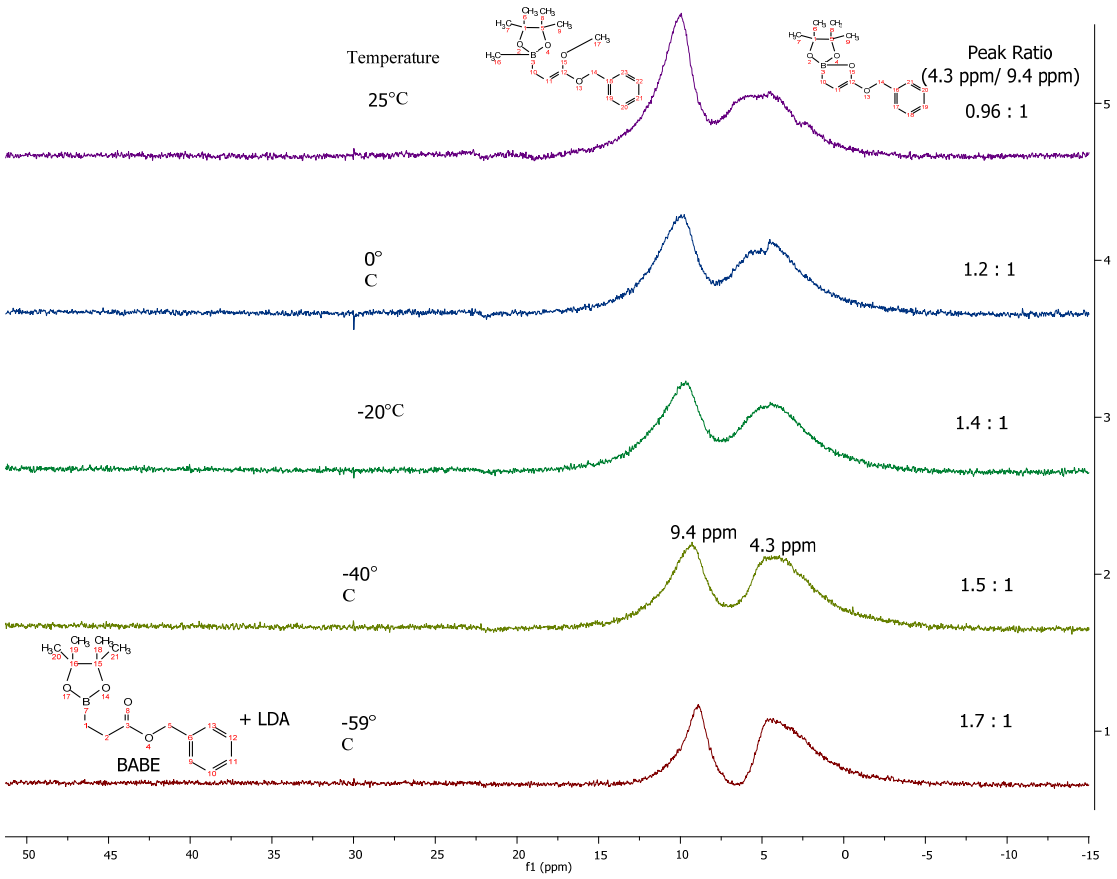


Figure 7. ^{11}B NMR Determination of Optimal Temperature

The approximate area under each of the detected peaks was determined using a deconvolution tool in the TopSpin® NMR analysis software package on the Bruker 600 NMR spectrometer. A Lorentzian fit was used to estimate the area under each peak.

Overall, there were two broad boron-"ate" signals detected. These signals were detected at 4.3 ppm and 9.4 ppm, but were not cleanly separated because of signal overlap particularly as the temperature was increased. From the proposed boron-"ate" identification stated in section 3.1 and the possibility for two different forms of boron-"ate" species suggested by Whiting *et al.*, it is hypothesized that the peak at 4.3 ppm is the intramolecular monomeric cyclic boron-"ate" species and the peak at 9.4 ppm is the intermolecular oligomeric boron-"ate" species.[5] The basis for the proposed identification

is that the intramolecular monomeric cyclic boron-"ate" intermediate is expected to be the more stable of the two boron-"ate" species at lower temperatures because of its closed cyclic nature versus a less stable open intermolecular oligomeric boron-"ate" species. The broadness and overlap of the detected signals partially results from the 3/2 spin state of the ^{11}B nuclei and also from the potential for other boron-"ates" that were present possessing very similar chemical shifts that caused the appeared signal broadness. The data suggest that as the reaction temperature is increased, the ratio of boron-"ate" species decrease to provide equal amounts of each boron-"ate" species. This is possibly caused by some slow transition between the two boron-"ate" species. Additionally, at higher temperatures (between 0° C and 25° C), there appears to be multiple overlapping signals around 4.3 ppm. At lower temperatures (-20° C to -59° C), there appears to be two clearly separated species suggesting that there is no transition between the two boron-"ate" species at those temperatures. A correlation between the temperature and the selectivity of a defined tetra-coordinate boryl species cannot be directly extracted from the findings of this experiment.

3.3. Effect of Base

Experiments were conducted to determine the optimal equivalent of base needed to deprotonate a β-boronic ester, to form a boron-"ate" intermediate. ^{11}B NMR can be used to determine when deprotonation has occurred by monitoring the consumption of the tri-coordinate boron starting material to form the tetra-coordinate boron-"ate." Figure 9 shows that for methyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (MCBE), as the number of equivalents of freshly prepared LDA was

increased from 0.4 to 2.3, the starting material peak at 31.7 ppm was converted to two new upfield peaks at 11.4 ppm and 7.4 ppm. As expected, complete conversion of starting material into the two tetra-coordinate boron-"ates" was found to occur with 1.1 equivalents of LDA suggesting that all of the starting material was deprotonated. Further increase in the equivalency of LDA up to 2.3 showed a slight decrease of the peak at 7.4 ppm, with simultaneous increase of the peak at 11.4 ppm. An explanation for this decreased ratio at higher equivalents of base may be that the excess base may interfere with the formation of the cyclic intermediate and therefore favor the oligomeric species. Additionally, it is speculated that at below 1.1 equivalents of base, there is a slow exchange occurring between the sp^2- and sp^3-hybridized boryl species, as seen with the 0.4 and 0.8 equivalent examples.

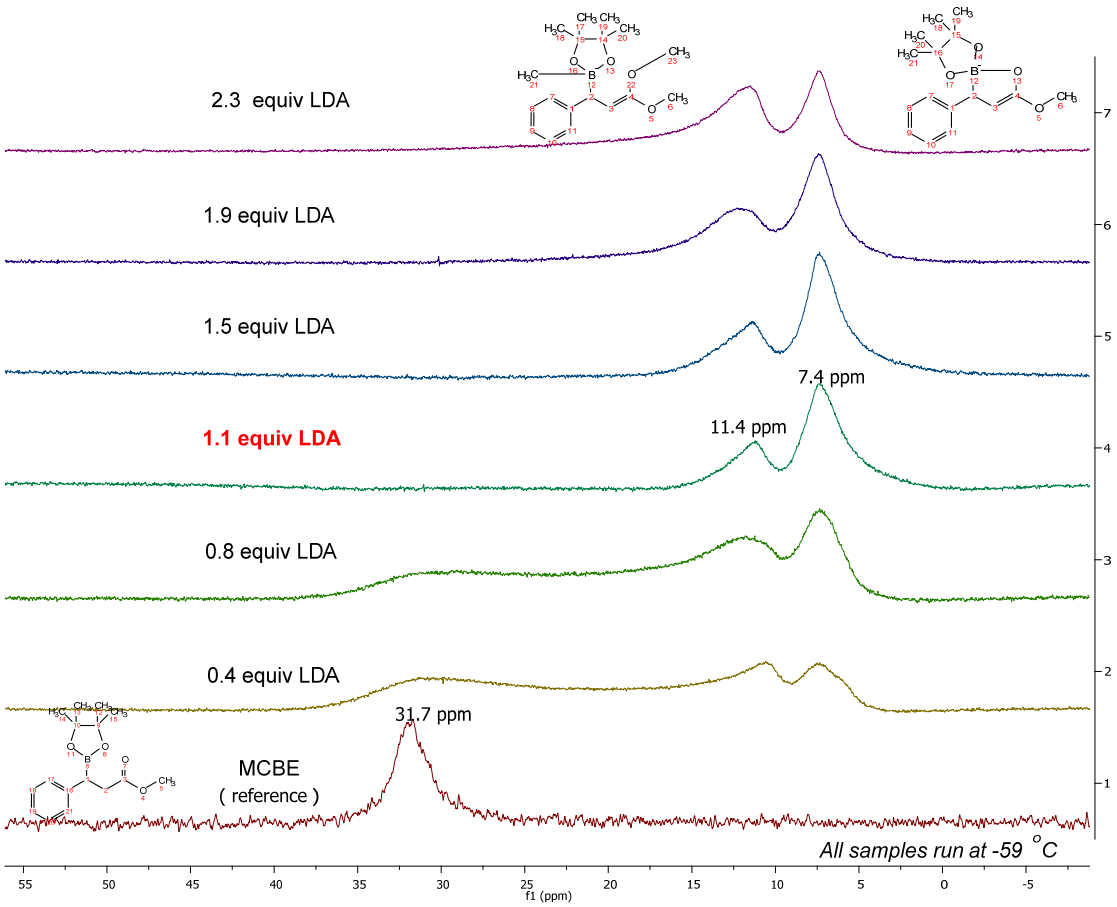


Figure 9. ^{11}B NMR Determination of Optimal Concentration of Base

This experiment shows that two or more boron-"ate" signals were detected depending on the number of equivalents of base that were used. As the number of equivalents increased to above 1, only two broad signals were detected. These findings are similar to those in section 3.2 where boron-"ate" identification was based on Whiting's suggestion that there could be two different types of boron-"ates" formed. It is hypothesized that the two signals are representative of an intramolecular cyclic boron-"ate" species (detected at 7.4 ppm) and an intermolecular oligomeric boron-"ate" species (detected at 11.4 ppm).[5] The difference in chemical shift values for the above proposed boron-"ates" compared to the findings in section 3.2 may be accounted for by the change in the structure of the starting materials used for each experiment where the material in

section 3.2 possessed a different ester functional group and no β-functional group. Overall, it was determined that the optimal number of equivalents of LDA was 1.1 equivalents, which provided the greatest proportion of the desired peak at 7.4 ppm.

3.4. Effect of Concentration

An experiment was devised to analyze whether there was conversion between the proposed monomer and oligomer species depending upon change in overall concentration, Figure 10.

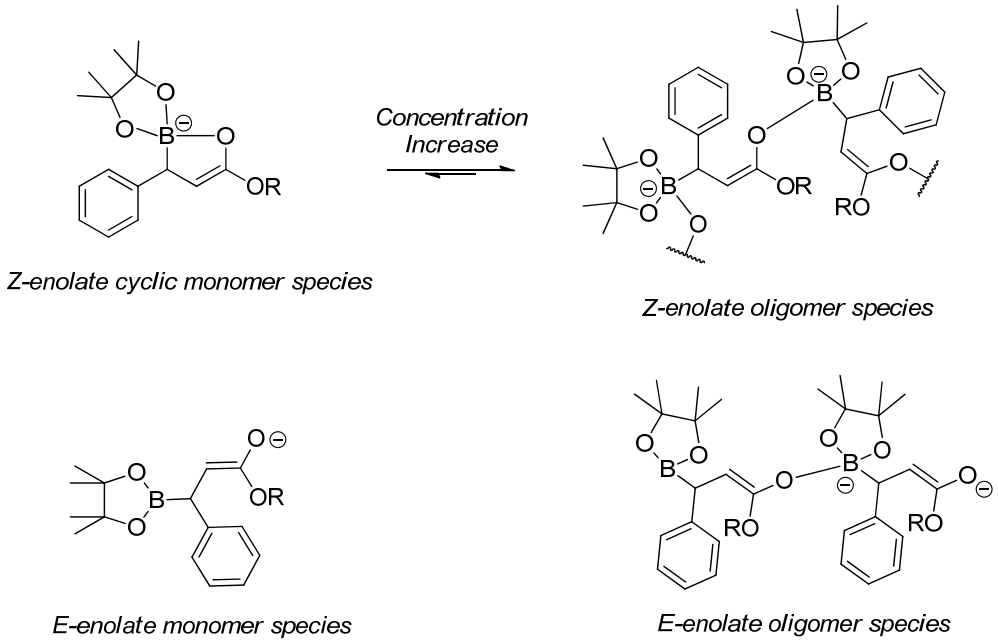


Figure 10. Equilibrium between Cyclic Monomer and Oligomer Boron-"ate" Species

It is hypothesized that as the concentration of the reaction mixture is diluted, oligomeric species would deaggregate into their respective cyclic monomers. This proposal is based on the Ruggli dilution principle that pertains to the concept of how a reaction's effective molarity influences the rate of cyclization vs. oligomerization. Ruggli's dilution principle states that with increasing dilution, the formation of cycles is

favored at the expense of oligomerization.[41] As a result, it is proposed that dilution favors the intramolecular over formation of the intermolecular cyclic five-membered boron-"ate".

As was seen in the NMR tube experiment, preformed at -59°C, both boron-"ate" complexes were formed nearly instantaneously and were thermally stable, Figure 7. With this being stated, the following experiment was conducted to determine whether the Ruggli dilution principle could be applied to this system.

tert-butyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (TCBE) was chosen as the model compound because it was believed to favor *Z*-enolate formation as a result of 1,3-allylic strain. An increase in the peak at 6.8 ppm over that at 11 ppm was thus expected. The experiment was conducted using TCBE added to 1.1 eq of freshly prepared LDA and three different concentrations were prepared by serial dilution. The final concentrations were 0.22, 0.11, and 0.06 M and provided an overall 10-fold change in concentration (Figure 11). Please note that on Figure 10, the listed chemical shift values for the two boron-"ate" peaks are from average of the 4 scans, where the standard deviation of the difference between the two peaks is 0.6 and the relative standard deviation is 14.8%. The error in the precision is greater than 10% because of difficulty in obtaining ^{11}B NMR spectra as sample concentration decreased. It should be noted that the starting material has a chemical shift value of 32.9 ppm with a chemical shift difference of 26.1 ppm against the furthest upfield peak. This again correlates to Whiting's findings. This chemical shift difference therefore provides evidence that the peak at 6.8 ppm is the cyclic five-membered boron-"ate" monomer.

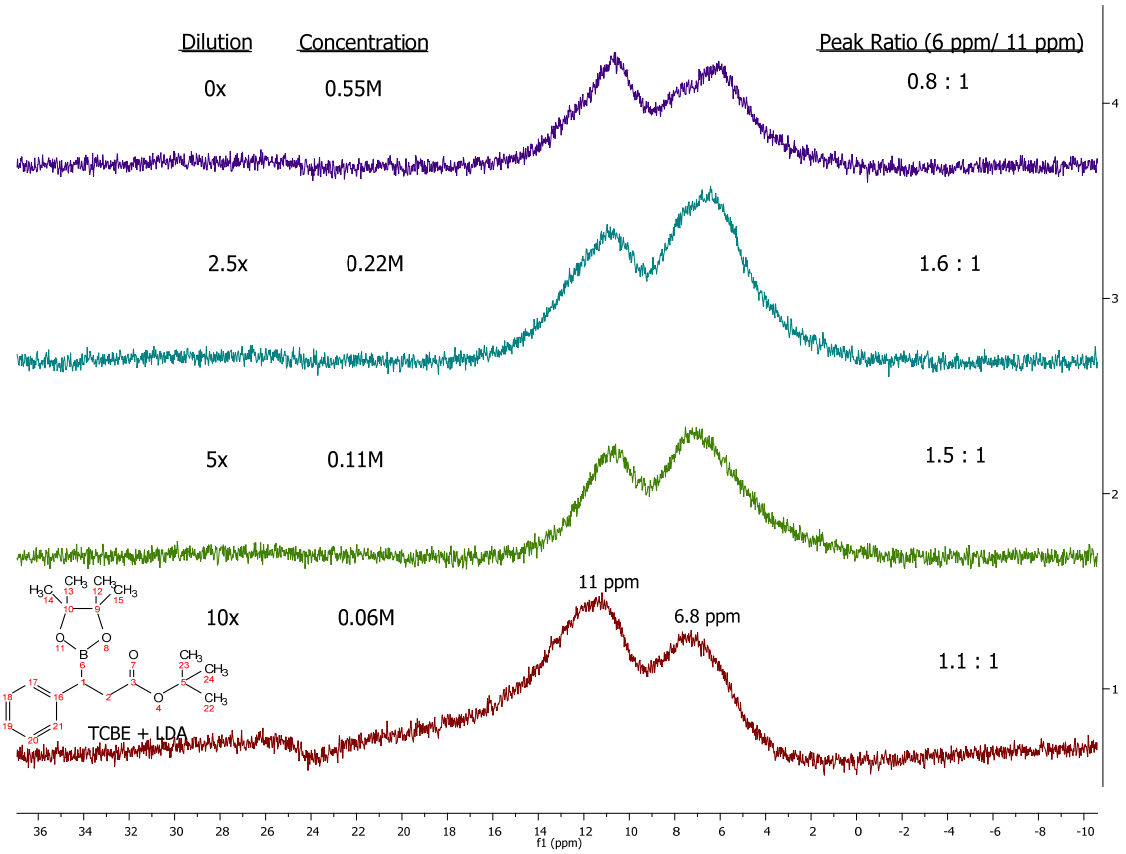


Figure 11. Dilution Experiment for Determination of Equilibrium between Cyclic Monomer and Oligomer Boron-"ates"

For this experiment to be based on Ruggli's principle, at some molar concentration there will be nearly equal amounts of the cyclic and open-chain products present, and at diluted concentration the desired cyclic boron-"ate" intermediate will form predominantly. This experiment showed that a 10-fold change in the concentration caused a small overall change in the approximate ratio between the two boron-"ate" species but that there is no trend. These results do not seem to agree with the proposal of oligomerization. More thorough testing of the proposed affects of dilution upon boron-"ate" structure may provide further insight.

3.5. NMR Tube Reactions

We wanted to investigate whether it is possible to follow the alkylation of the preformed boron enolate using ^{11}B NMR. These experiments included alkylation of the enolate by the addition of *tert*-butyl bromoacetate and quenching the reaction with aqueous saturated ammonium chloride. These NMR experiments allowed us to monitor changes in the coordination state of boron as each reagent is added. It should be noted that these experiments only tell us about the coordination state of boron, but not necessarily what reactions are occurring. However, we hoped to gain useful information so that mechanistic conclusions could be drawn.

The boron-"ate" complex was formed by adding benzyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (BABE) to 1.1 eq of freshly prepared LDA in dry THF at -78°C. This reaction mixture was then quickly transferred to a N_2 flushed quartz NMR tube maintained at -78°C in a transfer dewar, Figure 12.

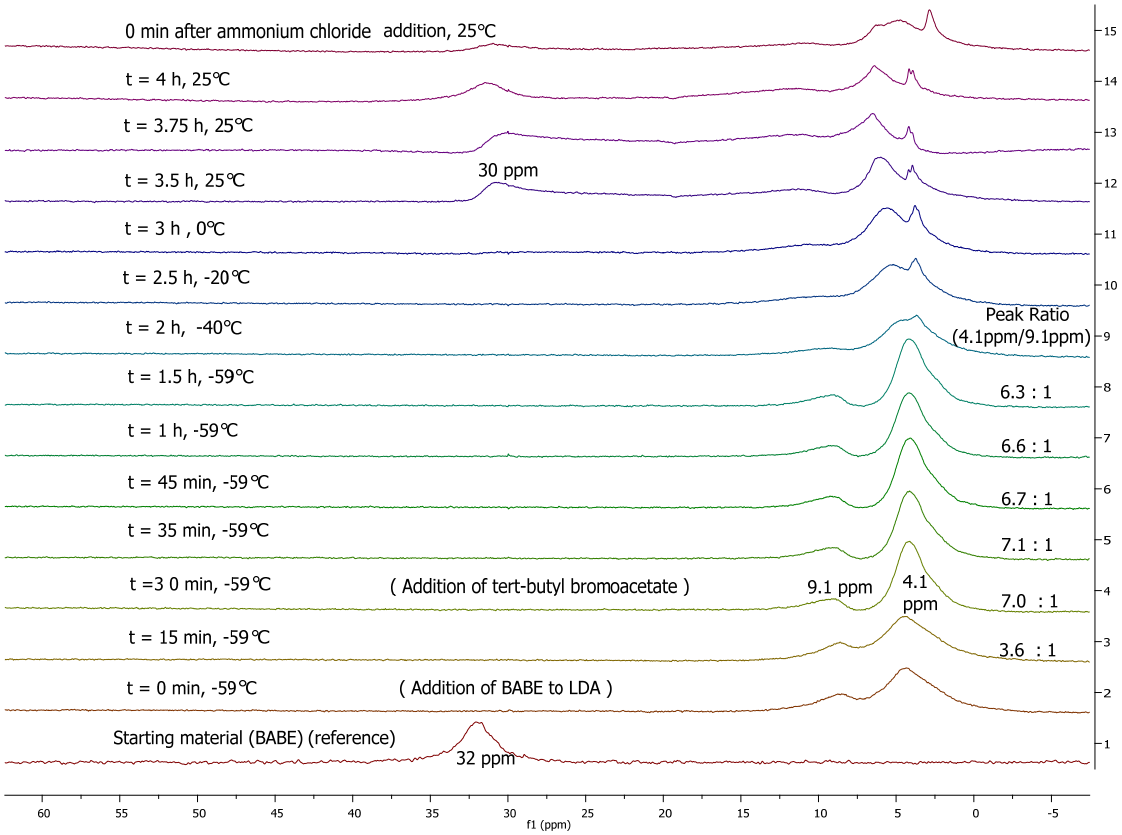


Figure 12. NMR Tube Experiments with Alkylation and Quench

The sample was immediately transferred into a Bruker 600 MHz NMR spectrometer at -59°C that was previously calibrated using BF_3-etherate. The initial ^{11}B NMR scan was started immediately and provided the identification of two tetra-coordinate boron-"ates" (t = 0 min, -59°C) up-field of the starting material, BABE (32 ppm). Being the first NMR tube experiment, we were uncertain whether the newly formed boron-"ates" needed to stabilize, and therefore we obtained an additional spectrum 15 min after the initial scan (t = 15 min, -59°C) and concluded that the reaction had indeed stabilized. It is interesting to note that the purported cyclic five-membered boron-"ate" species is in predominance prior to the addition of the alkylation reagent. After 30 min (t = 30 min, -59°), it was concluded that the two tetra-coordinate boron-"ates" were stable and the tube was quickly ejected from the spectrometer and 4 eq of *tert*-butyl bromoacetate were

added. The tube was re-injected into the NMR spectrometer and scanning immediately began, (t = 35 min, -59°). This scan showed that the approximate ratio of the two tetra-coordinate boron-"ates" changed, almost doubling, to provide more of the peak at 4.1 ppm compared to the peak at 9.1 ppm. The reaction was scanned every 15 min over a 1 h period and the ratio of the two tetra-coordinate boron-"ates" remained constant, Table 1.

Time	**Peak Ratio (4.1 ppm/9.1 ppm)**
Prior to alkylation reagent addition	3.6 : 1
0	7.0 : 1
5	7.1 : 1
15	6.7 : 1
30	6.6 : 1
60	6.3 : 1

Table 1. NMR Tube Experiment Peak Ratios

It was initially assumed that alkylation would occur immediately upon addition of an alkylation reagent, showing an immediate formation of a tri-coordinate boryl peak at ~32 ppm, but this experiment unfortunately provided no direct evidence whether alkylation occurred. After the addition of the *tert*-butyl bromoacetate and a series of four scans over a 1 h period (t = 35 to t = 1.5 h), the reaction mixture was then warmed to -40°C and held there for 30 min and then scanned (t = 2 h, -40°C), allowing the reaction mixture to equilibrate. This process was continued for three additional iterations (-20°C, 0°C, and 25°C). Once at 25°C, ^{11}B NMR showed the formation of a tri-coordinate boryl peak (at ~30 ppm). Since this experiment involved a large temperature change, the magnetic field that the sample was calibrated to at low temperature may have undergone

a small shift; this provides a potential explanation for the slight differences, or drift in the chemical shift of the resulting tri-coordinate peak. After this point, the sample was scanned every 15 min for two iterations to determine if the ratio changed. After 4 h (t = 4 h, 25°C), the reaction was quenched with aqueous saturated ammonium chloride; no changes in the spectrum occurred.

This experiment showed a real time analysis of the coordination states of boron present throughout the overall reaction. Formation of two boron-"ate" species is noted directly after addition of substrate to base and the ratio of those two species appears to be stable. Upon addition of an alkylation reagent, there is a change in the ratio of the two boron-"ate" species favoring the purported intramolecular boron-"ate" species (4.1 ppm) over the intermolecular oligomeric boron-"ate" (9.1 ppm). This ratio remains constant until a temperature change occurs. Upon warming from -40 °C to 0 °C, the boron-"ate" at 9.1 ppm is consumed and additional overlapping boron-"ate" signals are formed. The increase in the reaction temperature caused a change in the form of the boron-"ate" that is present. As the reaction warmed to room temperature a tri-coordinate boronic ester is detected. It is unknown whether this species is the alkylation product or the quenched starting material, but a definitive transition from a tetra-coordinate to a tri-coordinate boryl compound occurred. Overall these experiments showed that the reaction is extremely dynamic. There are multiple forms of tri- and tetra-coordinate boryl compounds present throughout reaction and the presence and ratios of these are directly affected by the addition of alkylation reagent and changes in reaction temperature. True identification of the exact structural forms of theses tri- and tetra-coordinate boryl compounds during these transitions is not possible using ^{11}B NMR, but the experiment

shows that multiple transitions in the coordination states of boron are occurring at various times and temperatures as the reaction process forward.

3.6. Identification of Unknown sp^3-Hybridized Boron-"ate"

Investigation of the identity of the unknown boron-"ate" peak has so far proven unsuccessful. ^{11}B NMR experiments were conducted using the starting material and model compounds under the same *in situ* conditions to determine its identity. We wanted to probe whether a boron-nitrogen (derived from direct attack of the lone electron pair on nitrogen to boron) or a boron-carbon bond (derived from the *C*-enolate) is being formed. The boron-nitrogen bond is hypothesized to occur by attack of non-nucleophilic diisopropyl amine resulting from quenched LDA after deprotonation has occurred.

Free amine base could bond to the vacant *p*-orbital of boron providing a tetra-coordinate boron-"ate." Experiments conducted with methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate, treated with 1.5 eq of N,N-diisopropylethylamine (DIEA), provided no evidence for the formation of a boron-nitrogen bond as all the tri-coordinate starting material was present with no tetra-coordinate boron-"ate" detected, Figure 13.

A *C*-enolate tautomer could hypothetically be present and allow for the formation of a boron-carbon bond by attack of the α-carbon on the empty *p*-orbital of the boronic ester. This hypothesis was tested by treatment of methyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate with 1.1 eq of *n*-butyllithium at -59°C, Figure 13. Results from the ^{11}B NMR experiment show that a boron-carbon bond can form, yielding a chemical shift of 9.4. This chemical shift is close to that of the unknown boron-"ate",

but is not exact and does not provide conclusive proof of the identity of the unknown boron-“ate” peak.

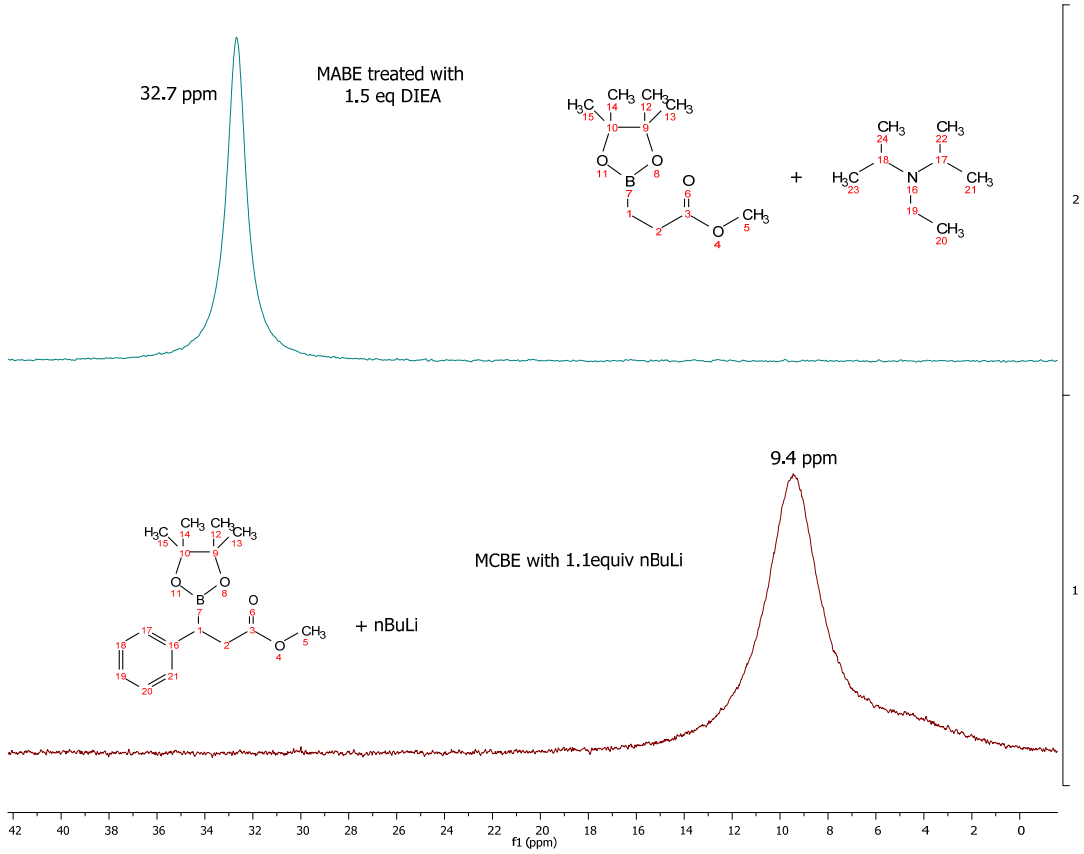


Figure 13. Models of Boron-Nitrogen and Boron-Carbon Bonds

These initial experiments show that a nucleophilic carbon species can bind the vacant *p*-orbital of a β-boronic ester and form a tetra-coordinate boron-“ate” with a chemical shift of 9.4 ppm. Additionally, these experiments show that non-nucleophilic nitrogen species do not bind the open *p*-orbital of a β-boronic ester. Future experiments would include testing whether diisopropylamine would have the potential to bind the *p*-orbital of a β-boronic ester.

3.6.1. ^{11}B NMR Studies of Model Systems

Model systems were utilized in an attempt to confirm the identify of the unknown boron-"ate" peak. Two different boronic esters were tested, a glycol protected phenyl boronic acid **3.1** and an *n*-butyl-pinacol boronic ester **3.2**. These two model systems were used because they did not possess an acidic α-proton and therefore could be treated with LDA to probe the formation of boron-nitrogen bonds. The models were separately treated with 1.5 eq of LDA and provided different results, Figure 14.

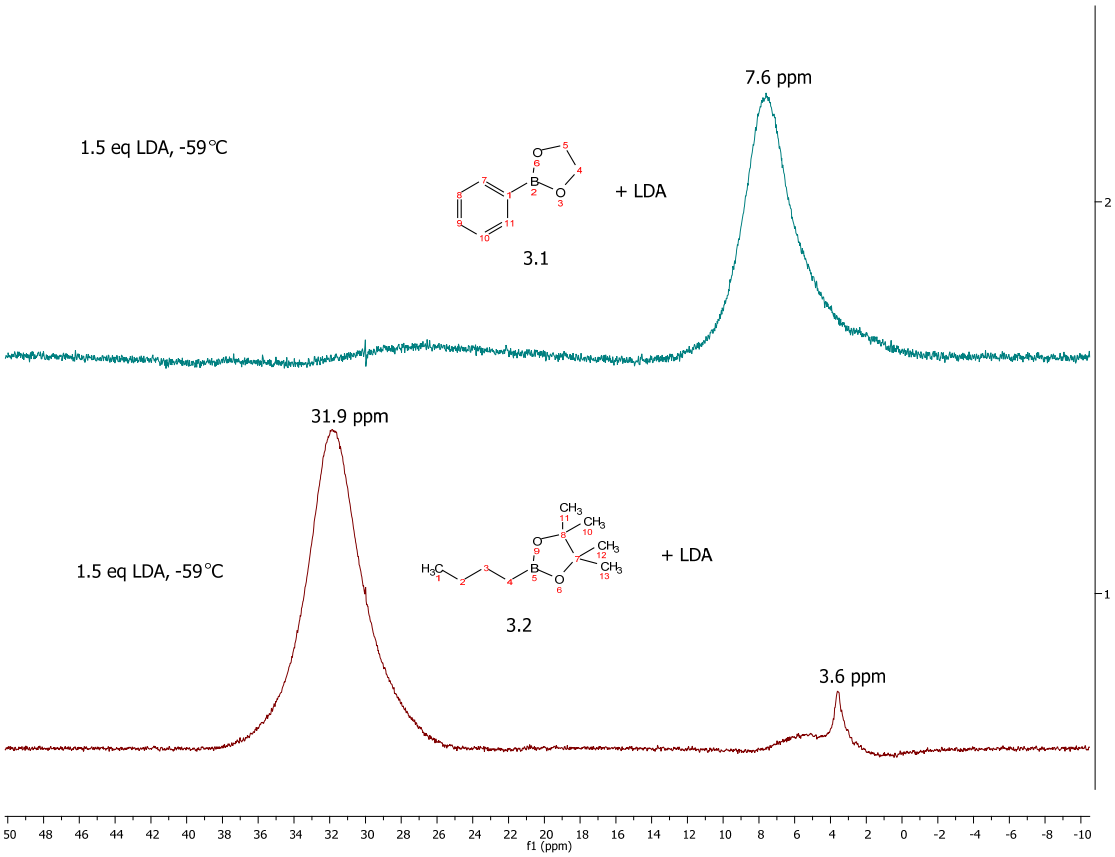


Figure 14. Model System Determination of Boron-Nitrogen Bond Formation

Results from these two experiments show that a boron-nitrogen bond did form with **3.1** to provide a tetra-coordinate boryl species with a chemical shift of 7.6 ppm. In the experiment with **3.2**, no significant tetra-coordinate boryl species was formed,

inferring that no boron-nitrogen bond was formed. Unfortunately, the shift observed for the first model does not match the previous experimental findings; therefore, we cannot confirm that the unknown boron-"ate" peak is a boron-nitrogen bond.

3.7 Future Directions

Future ^{11}B NMR experiments that would provide additional information could entail the use of other model systems to probe identity of the unknown tetra-coordinate boron-"ate." Further experiments should include model substrates that have structural and electronic characteristics similar to the β-boronic ester substrate. An example of this is a β-boronic ketal. Other potential experiments could focus on an external *O*-enolate bound to a different boronic ester in solution to form an extended oligomer. Use of lithium hexamethyldisilazide (LiHMDS) and potassium hexamethyldisilazide (KHMDS) would provide useful information about the chemical shift of a boron-nitrogen bond. These and other experiments would provide further elucidation of the dynamics of this reaction.

Chapter 4: Experimental

4.1. General Information and Instrumentation

Anhydrous tetrahydrofuran solvent and all other chemicals were purchased from Sigma-Aldrich. ^{1}H, ^{13}C, and ^{11}B spectra were recorded on either a JEOL 500, a Varian Inova 400, or a Bruker Advance 600 MHz NMR spectrometer. Chemical shifts (δ) are reported in parts per million with residual solvent protons (^{1}H) or the solvent carbons (^{13}C) as internal standards. Boron NMR spectra were referenced to external $BF_3 \cdot OEt_2$. ^{1}H-NMR data are presented as follows: chemical shift in ppm downfield from Me_4Si (multiplicity, coupling constant, integration). The following abbreviation are used in reporting NMR data: s, singlet; br s, broad singlet; d, doublet; t, triplet; dd, doublet of doublets; dt, doublet of triplets; q, quartet; m, multiplet. Thin layer chromatography (TLC) was performed on EMD silica gel 60 F_{254} aluminum backed TLC plates and spots were visualized with ultraviolet light and $KMnO_{4(aq)}$ or aqueous phosphomolybdic acid (PMA) stain. High resolution mass spectroscopy (HRMS) was performed on an Agilent 6220 LC/MS time-of-flight mass spectrometer using electrospray ionization (ESI). Verification of diastereomeric ratio (DR) was conducted by GC-MS using a Hewlett Packard 6890 Series GC system coupled to a Hewlett Packard 5973 Mass Spectroscopy detector with an Agilent J&W DB-5 GC capillary column.

4.2. Experimental Procedures and Characterization Data

4.2.1 General Preparation Procedures

4.2.1.A. General Procedure A: β-Borylation of α,β-unsaturated Esters

A flame-dried, N_2 flushed round bottom flask was charged with copper(I) chloride (0.03 eq), DPEPhos (0.03 eq), and sodium *tert*-butoxide or potassium *tert*-butoxide (0.09 eq) in dry THF (1 mL). After 0.5 h, bis(pinacolato)diboron (1.1 eq) dissolved in dry THF was added drop-wise to provide a dark red solution. After 0.5 h, the α,β-unsaturated ester (1 eq) and methanol (4 eq) were added simultaneously. This reaction was stirred until all starting material was consumed as followed by TLC (~2-5 h). The reaction mixture was passed through a plug of Celite, concentrated under reduced pressure, and purified by column flash chromatography on silica gel to provide the product.

4.2.1.B. General Procedure B: α-Alkylation of β-Borylated Esters

To a flame-dried, N_2 flushed round bottom flask chilled to -78°C charged with diisoproplyamine (1 eq) in dry THF (0.5 mL) was added 2.5 M *n*-butyllithium in hexane (1.1 eq). After 0.5 h. the β-boronic ester (1 eq) dissolved in 0.5 mL dry THF was added drop-wise. After 0.5 h, the alkylation reagent (1.5 eq) was added drop wise. The mixture was stirred for 3 h. The reaction was quenched at -78°C by the addition of 2 mL of aqueous saturated ammonium chloride and allowed to warm to room temperature and extracted 3 times with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. The reaction mixture was filtered, concentrated under

reduced pressure and purified by flash column chromatography on silica gel to provide the product. Methods for determination of the DR value for all α-alkylated compounds are described in sections **4.2.1.D.**, **4.2.1.E.**, and **4.2.1.F.** Additionally, the total proton count may very slightly from true due to the fact that each described compound is a mixture of two diastereomers possessing slightly different R_f values. There is potential that not all of each separate diastereomer was obtained therefore providing a small fraction of error on the true total number of protons for the diastereomeric mixture.

4.2.1.C. General Procedure C: Preparation of *tert*-Butyl Esters from Corresponding Carboxylic Acids

A round bottom flask was charged with 40 mL of methylene chloride, concentrated sulfuric acid (1 eq) and anhydrous magnesium sulfate (4 eq) was vigorously stirred for 15 min. The carboxylic acid (1 eq) was added to this mixture followed by *t*-butanol (5 eq). After 24 h, the reaction was quenched by the addition of 75 mL of saturated sodium bicarbonate and stirred until all the magnesium sulfate had dissolved. The mixture was transferred to a separatory funnel, the organic layer was separated, washed with brine, and then dried over $MgSO_4$. This crude product mixture was filtered, concentrated, and immediately purified by column flash chromatography on silica gel.

4.2.1.D. General Procedure D: Boryl Ester Functional Group Oxidation to Provide Secondary Alcohols

To a round bottom flask charged with a purified β-borylated boronic ester or a crude α-alkylated, β-boronic ester reaction mixture (1 eq) in dry THF (0.5 mL) was added

sodium perborate monohydrate (5 eq) dissolved in the same volume of water. After 3 h, the reaction mixture was then transferred to a separatory funnel and extracted 3 times with ethyl acetate. The combined organic layers were washed with brine and dried over $MgSO_4$. The reaction mixture was filtered, concentrated under reduced pressure and purified by column flash chromatography on silica gel to provide the product.

4.2.1.E. General Procedure E: Diastereomeric Ratio Determination via Gas Chromatography-Mass Spectroscopy

A small aliquot (<0.5 mL) was taken from the alkylation or oxidation reaction mixture and dissolved in 2 mL ethyl acetate. A 2 μL sample was injected onto an Agilent Technologies J & W Scientific DB-5 capillary gas chromatographic column. The standard GC conditions used to provide peak resolution were a splitless injection (60 : 1), injector port temperature of 250°C, an initial column temperature of 80°C (hold 2 min), a single continuous 10°C/min ramp up to 300°C, and then hold at 300°C for 10 min. The helium carrier gas flow rate was 1 mL/min. These standard GC column conditions may have been varied slightly depending upon the alkylated substrate so as to improve peak resolution. The resulting mass spectrum was analyzed to find two peaks that possessed the correct molecular ion peak and the same fragmentation pattern. These identified peaks were then integrated using the Data Analysis software package to provide a DR value. The parent peak was not always present, but fragments could be identified for all samples.

4.2.1.F. General Procedure F: Diastereomeric Ratio Determination via High Pressure Liquid Chromatography-Mass Spectroscopy

The diastereomeric ratio of crude boryl oxidation mixture was determined using reverse-phase LC separation in conjunction with a TSQ triple quadrapole MS. HPLC runs were performed using an Agilent HPLC 1100 series equipped with a diode array detector and autosampler that injected a 10 μL sample onto a semipreparative Phenomenex Luna C_{18} column (250 x 4.6 mm). Mobile phase A consisted of 1% aqueous formic acid and Mobile phase B consisted of 1% (v/v) formic acid in acetonitrile. The mixture of mobile phases was delivered to the HPLC column at a flow rate of 0.2 ml/min. A gradient elution was used and preceded as follows: time 0-5 min, 5% B to 20% B; time 6-20 min, 20% B to 95% B; time 20-29 min, 95% B; time 29-31 min, 95% B. MS analysis was conducted by pumping HPLC effluent directly into the Thermo Instrument TSQ triple quadrapole MS (Thermo Finnigan, San Jose, CA) equipped with an ESI source. MS parameters for separation and detection were as follows: spray voltage 4000 V, sheath gas pressure 49 psi, auxiliary gas pressure 13 psi, capillary temperature 300°C.

The above HPLC and TSQ MS parameters were modified from literature sources.[42,43] The diastereomers **2.34b** and **2.34a** eluted at 28.83 min and 28.99 min respectively.

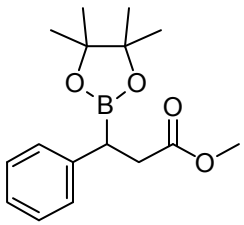
4.2.1.G. General Procedure G: *In situ* ^{11}B NMR Experiments

All *in situ* ^{11}B NMR experiments were conducted using quartz NMR tubes. These *in situ* experiments were performed by preparing individual samples in flame-dried, N_2

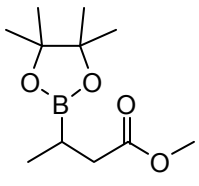
flushed round bottom flask maintained at -78°C using a dry-ice/acetone bath using dry THF as solvent. The β-boronic ester substrate was slowly added to freshly prepared LDA, and then the reaction mixture was quickly transferred to a clean N_2 flushed quartz NMR tube held in a dewar at -78°C using a dry ice/acetone bath. Each individually prepared sample was immediately transported to a cooled NMR unit previously calibrated using a BF_3-etherate external standard, injected into the spectrometer, and NMR analysis for the defined experiment was started immediately.

4.2.2 Characterization Data

4.2.2.A. β-Boronic Esters

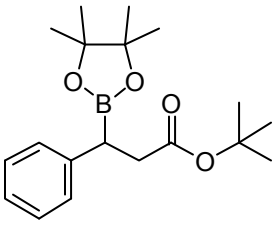


Methyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (2.1a): This product was prepared as described in General Procedure A. White solid, 81% yield; R_f (SiO_2, 9:1 hexane:ethyl acetate) 0.3. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.09 (m, 5H), 3.64 (s, 3H), 2.89 (dd, *J* = 16.2 Hz, 10.1 Hz, 1H), 2.76 – 2.70 (m, 1H), 2.66 (dd, *J* = 16.2 Hz, 5.9 Hz, 1H), 1.19 (d, *J* = 22.6 Hz, 12H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.91, 141.38, 128.58, 128.26, 125.79, 83.65, 51.65, 37.20, 24.65, 24.55. ^{11}B NMR (160 NMR, THF) δ 31.69, MS (+EIC): 313.15 (M+Na+), Calc. 313.15.

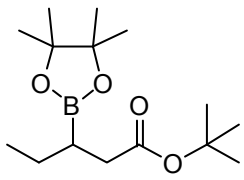


Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (2.2a): This product was prepared as described in General Procedure A. Clear oil, 78% yield; R_f (SiO_2, 9:1 hexane:ethyl acetate) 0.31. ^{1}H NMR

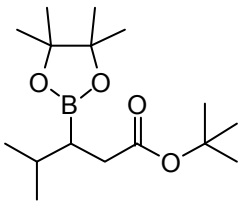
(500 MHz, $CDCl_3$) δ 3.58 (s, 3H), 2.34 (qd, *J* = 7.2 Hz, 16.4 Hz, 2H), 1.35 – 1.24 (m, 1H), 1.17 (d, *J* = 2.4 Hz, 12H), 0.93 (d, *J* = 7.5 Hz, 3H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.30, 83.17, 51.35, 37.47, 24.72, 24.65, 15.10. ^{11}B NMR (160 MHz, THF) δ 33.04. MS (+EIC): 251.14 (M+Na+), Calc. 251.14.



***tert*-Butyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (2.3a)**: This product was prepared as described in General Procedure A. White solid, 74% yield; R_f (SiO_2, 9.5:0.5 hexane:ethyl acetate) 0.31. ^1H NMR (600 MHz, $CDCl_3$) δ 7.30 – 7.11 (m, 5H), 2.81 (dd, *J* = 16.4 Hz, 10.3 Hz, 1H), 2.70 (dd, *J* = 10.1 Hz, 6.4 Hz, 1H), 2.59 (dd, *J* = 16.4 Hz, 6.2 Hz, 1H), 1.41 (s, 9H), 1.20 (d, *J* = 32.8 Hz, 12H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.77, 141.53, 128.35, 128.22, 125.48, 83.44, 80.12, 38.35, 30.89, 28.05, 24.63, 24.47. ^{11}B NMR (193 MHz, THF) δ 32.89. MS (EIC+): 355.21 (M+Na+), Calc. 355.21.

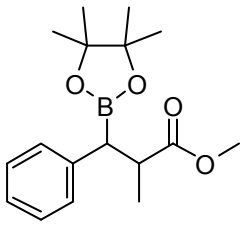


***tert*-Butyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate (2.4a):** This product was prepared as described in General Procedure A. Clear oil, 27.7% yield; R_f (SiO_2, 9.5:0.5 hexane:ethyl acetate) 0.42. ^1H NMR (400 MHz, $CDCl_3$) δ 2.38 – 2.24 (m, 2H), 1.50 – 1.43 (m, 1H), 1.41 (s, 9H), 1.36 (dd, *J* = 14.0 Hz, 6.8 Hz, 1H), 1.22 (m, 13H), 0.90 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.62, 83.19, 79.96, 36.82, 28.31, 25.04, 24.87, 23.62, 13.49. ^{11}B NMR (160 MHz, THF) δ 33.14. MS (ESI +) 307.21(M+Na+), Calc. 307.21.

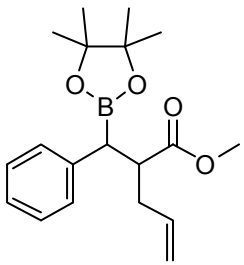


***tert*-Butyl 4-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate (2.5a)**: This product was prepared as described in General Procedure A. Clear oil, 8.9% yield; R_f (SiO_2, 9.5:0.5 hexane:ethyl acetate) 0.44. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.37 (dd, *J* = 16.7 Hz, 10.8 Hz, 1H), 2.28 (dd, *J* = 16.7 Hz, 5.7 Hz, 1H), 1.72 (m, 1H), 1.42 (s, 9H), 1.23 (m, 12H), 0.92 (dd, *J* = 6.8 Hz, 5.3 Hz, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.86, 83.06, 79.79, 34.91, 29.07, 28.20, 25.07, 24.79, 22.13, 21.60. ^{11}B NMR (160 MHz, THF) δ 33.65. MS (ESI +) 321.22 (M+Na+), Calc, 321.22.

4.2.2.B. Methyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate Derivatives:

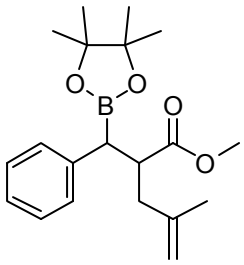


Methyl 2-methyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (2.20): This product was prepared as described in General Procedure B. Clear oil, 49% yield; R_f (SiO_2, 9:1 hexane: ethyl acetate) 0.32. Multiple columns were needed to separate alkylated product from starting material as their R_f values were very similar. DR = 4 : 1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.10 (m, 10H), 3.69 (s, 1.45H, minor diastereomer), 3.42 (s, 4.55H, major diastereomer), 2.99 (dq, *J* = 13.9 Hz, 6.9 Hz, 1.61H, major diastereomer), 2.92 (dd, *J* = 11.5 Hz, 7.1 Hz, 0.39H, minor diastereomer), 2.61 (d, *J* = 10.4 Hz, 1.64H, major diastereomer), 2.41 (d, *J* = 11.5 Hz, 0.36H, minor diastereomer), 1.24 (d, *J* = 6.9 Hz, 4.84H, major diastereomer), 1.21 (s, 6H, major diastereomer), 1.19 (s, 2H, minor diastereomer), 1.18 (s, 6H, major diastereomer), 1.12 (s, 2H, minor diastereomer), 1.00 (d, *J* = 7.1 Hz, 1.16H, minor diastereomer). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.66, 140.32, 129.11, 129.03, 128.52, 128.32, 125.86, 125.83, 83.64, 83.46, 51.78, 51.31, 42.98, 42.21, 24.71, 24.60, 24.58, 24.51, 17.49, 16.81. ^{11}B NMR (160 MHz, THF) δ 30.70. HRMS (EIC+) 327.1708 (M+Na+), Calc. 327.1738.



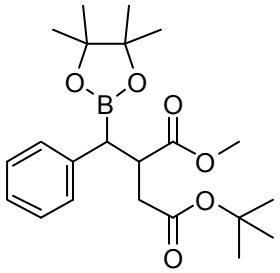
Methyl 2-(phenyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)pent-4-enoate (2.21): This product was prepared as described in General Procedure B. Clear oil, 42% yield; R_f (SiO_2, 9:1 hexane: ethyl acetate) 0.34. DR = 2.4 : 1. ^{1}H NMR (400 MHz,

$CDCl_3$) δ 7.45 – 7.06 (m, 10H), 5.81 (d, *J* = 7.1 Hz, 1.24H, major diastereomer), 5.66 (d, *J* = 7.8 Hz, 0.76H, minor diastereomer), 5.01 (ddd, *J*= 35.0 Hz, 25.2 Hz, 17.0 Hz, 4H), 3.71 (s, 2.3H, minor diastereomer), 3.38 (s, 3.7H, major diastereomer), 3.07 (m, 2H), 2.62 (t, *J* = 1.59 Hz, 1H, major diastereomer), 2.42 (m, 1.27H, major diastereomer), 2.29 (m, 0.45H, minor diastereomer), 2.06 (m, 0.41H, minor diastereomer), 1.23 (m, 2H), 1.19 (s, 6H, major diastereomer), 1.16 (s, 3.37H, minor diastereomer), 1.15 (s, 6H, major diastereomer), 1.09 (s, 3.69H, minor diastereomer). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.13, 175.31, 139.95, 135.66, 134.79, 129.25, 129.08, 128.70, 128.43, 126.04, 126.00, 117.39, 117.02, 83.83, 83.60, 51.67, 51.15, 48.84, 47.54, 37.18, 34.69, 24.81, 24.72, 24.67, 24.61. ^{11}B NMR (160 MHz, THF, ref. ext. BF_3-Et_2Oin $CDCl_3$) δ 31.63, HRMS (ESI+): 331.2059 (M+H+), Calc. 331.2075.



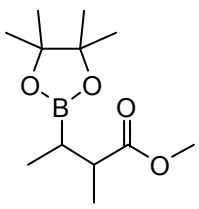
Methyl 4-methyl-2-(phenyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)pent-4-enoate (2.22): This product was prepared as described in General Procedure B. Clear oil, 57% yield; R_f (SiO_2, 9:1 hexane: ethyl acetate) 0.41. DR = 1 : 1. ^1H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.10 (m, 10H), 4.73 (d, *J* = 5.9 Hz, 0.78H, minor diastereomer), 4.63 (d, *J* = 39.3 Hz, 1.22H, major diastereomer), 3.67 (s, 3.85H, major diastereomer), 3.32 (s, 2.15H, minor diastereomer), 3.19 (td, *J* = 10.9 Hz, 4.1 Hz, 0.68H, minor diastereomer), 3.06 (m, 1.32H, major diastereomer), 2.57 (t, *J* = 11.3 Hz, 1.52H, major diastereomer), 2.45 – 2.39 (m, 0.48H, minor diastereomer), 2.26 (s, 0.42H, minor diastereomer), 2.14 – 2.10 (m, 1.58H, major diastereomer), 1.77 (s, 2.23H, minor diastereomer), 1.60 (s, 3.77H, major diastereomer), 1.17 (dd, *J* = 26.8 Hz, 20.3 Hz, 26H).

^{13}C NMR (101 MHz, $CDCl_3$) δ 176.49, 175.51, 175.46, 143.42, 143.29, 140.09, 129.24, 129.09, 128.69, 128.43, 126.06, 126.02, 112.55, 112.51, 83.84, 83.69, 51.51, 51.11, 47.95, 46.73, 41.66, 40.22, 24.88, 24.73, 24.71, 24.59, 22.37, 22.18. ^{11}B NMR (160 MHz, THF) δ 31.70. MS (EIC+): 345.22 (M+H+), Calc. 345.22.



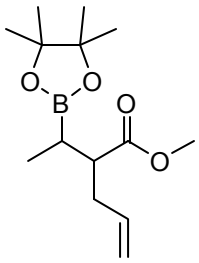
4-*tert*-Butyl 1-methyl 2-(phenyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)succinate (2.23): This product was prepared as described in General Procedure B. Clear oil, 57% yield; R_f (SiO_2, 9:1 hexane: ethyl acetate) 0.16. DR = 2.4 : 1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 7.13 (m, 10H), 3.69 (d, *J* = 9.5 Hz, 1.16H, minor diastereomer), 3.43 (s, 4.84H, major diastereomer), 3.30 – 3.21 (m, 2H), 2.70 (dd, *J* = 16.3 Hz, 10.8, 1H), 2.58 (t, *J* = 10.3 Hz, 1H), 2.41 (td, *J* = 15.9 Hz, 4.0 Hz, 1H), 2.20 (dd, *J* = 16.1 Hz, 8.3 Hz, 0.34H), 1.39 (d, *J* = 11.2 Hz, 18H), 1.19 (dd, *J* = 29.8 Hz, 21.5 Hz, 26H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 175.44, 175.13, 171.31, 171.22, 139.38, 129.63, 129.32, 128.77, 128.51, 126.32, 83.98, 83.64, 80.83, 51.48, 45.07, 37.46, 28.21, 24.90, 24.78, 24.68. ^{11}B NMR (160 MHz, THF) δ 31.43. HRMS (ESI+): 427.2232 (M+Na+), Calc. 427.2262.

4.2.2.C. Methyl 3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate Derivatives:

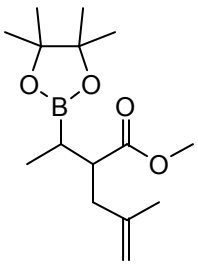


Methyl 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butanoate (2.24): This product was prepared as described in General

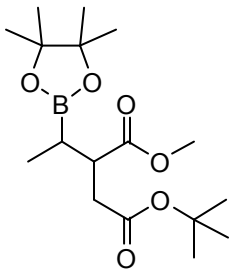
Procedure B. Clear oil, 49% yield; R_f (SiO_2, 9:1 hexane: ethyl acetate) 0.27. DR = 3.6 : 1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.63(d, *J* = 3.9 Hz, 6H), 2.62 (t, *J* = 7.1 Hz, 0.51H, major diastereomer), 2.53 (m, 0.49H, minor diastereomer), 1.26(m, 3H), 1.22 (m, 30H), 1.16 (d, *J* = 1.6 Hz, 1.53H, major diastereomer), 1.15 (d, *J* = 1.5 Hz, 1.47H, minor diastereomer), 0.93 (d, *J* = 7.5 Hz, 1.47H, minor diastereomer), 0.91 (d, *J* = 7.5 Hz, 1.53H, major diastereomer). ^{13}C NMR (151 MHz, $CDCl_3$) δ 206.82, 176.93, 83.09, 83.02, 51.40, 51.23, 41..72, 41.66, 30.88, 24.72, 24.67, 16.21, 15.30, 12..44, 12.35. ^{11}B NMR (193 MHz, THF) δ 33.32, MS (APCI +) 243.18 (M+H+), Calc, 243.18.



Methyl 2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)pent-4-enoate (2.25): This product was prepared as described in General Procedure B. Clear oil, 43 % yield; R_f (SiO_2, 9:1 hexane: ethyl acetate) 0.37. DR = 1.6 : 1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 5.80 – 5.67 (m, 2H), 5.07 – 5.00 (m, 2H), 4.98 (d, *J* = 10.2 Hz, 2H), 3.63 (s, 6H), 2.66 – 2.60 (m, 1H), 2.52 (dd, *J* = 13.0 Hz, 7.5 Hz, 1H), 2.45 – 2.32 (m, 1.56H, major diastereomer), 2.27 – 2.19 (m, 0.44H, minor diastereomer), 1.31 (m, 2H), 1.23 (m, 27H), 0.96 (d, *J* = 7.5 Hz, 3.1H, major diastereomer), 0.90 (d, *J* = 7.4 Hz, 2.9H, minor diastereomer). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.25, 175.81, 136.22, 135.93, 116.65, 116.49, 83.28, 83.14, 51.39, 51.21, 47.84, 47.46, 35.57, 34.44, 24.81, 24.78, 12.99, 12.28. ^{11}B NMR (160 MHz, THF) δ 32.02. MS (EIC+): 269.19 (M+H+), Calc. 269.19.



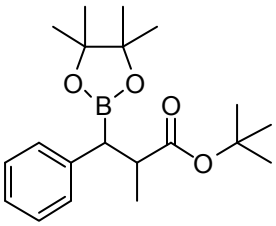
Methyl 4-methyl-2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)pent-4-enoate (2.26): This product was prepared as described in General Procedure B. Clear oil, 44% yield; R_f (SiO_2, 9:1 hexane:ethyl acetate) 0.3. DR = 2 : 1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.74 – 4.68 (m, 4H), 3.63 (d, *J* = 0.8 Hz, 6H), 2.76 (ddd, *J* = 9.5 Hz, 8.1 Hz, 5.7 Hz, 0.8H, minor diastereomer), 2.64 (dt, *J* = 9.2 Hz, 5.8 Hz, 1.2H, major diastereomer), 2.39 (dt, *J* = 13.5 Hz, 10.2 Hz, 2H), 2.28 (dd, *J* = 14.1 Hz, 5.5 Hz, 1.2H, major diastereomer), 2.16 (dd, *J* = 13.9 Hz, 5.5 Hz, 0.8H, minor diastereomer), 1.71 (s, 6H), 1.32 – 1.25 (m, 2H), 1.23 (d, *J* = 4.0 Hz, 24H), 0.98 (d, *J* = 7.5 Hz, 3.4H, major diastereomer), 0.91 (d, *J* = 7.4 Hz, 1.27H, minor diastereomer). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.45, 176.08, 143.68, 143.62, 112.10, 112.00, 83.27, 83.16, 51.31, 51.18, 46.77, 46.26, 39.89, 38.99, 24.87, 24.80, 24.73, 22.35, 22.24, 13.32, 12.52. ^{11}B NMR (160 NMR, THF) δ 32.70, MS (ECI+): 283.21 (M+H+), Calc. 283.21.



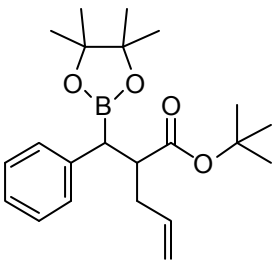
4-*tert*-Butyl 1-methyl 2-(1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)ethyl)succinate (2.27): This product was prepared as described in General Procedure B. Clear oil, 44% yield; R_f (SiO_2, 9:1 hexane: ethyl acetate) 0.24. DR = 1.4 : 1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.66 (d, *J* = 1.0 Hz, 6H), 3.04 (ddd, *J* = 10.5 Hz, 6.1 Hz, 4.6 Hz, 1.06H, major diastereomer), 2.90 (ddd, *J* = 9.6 Hz, 6.4 Hz, 4.5 Hz, 0.94H, minor diastereomer), 2.76 – 2.61 (m, 2H), 2.45 (dd, *J* = 16.3 Hz, 4.5 Hz, 1.06H, major diastereomer), 2.34 (dd, *J* = 16.4 Hz, 4.6 Hz, 0.94H, minor diastereomer), 1.42 (s, 18H), 1.23 (m, 26H), 0.95 (dt, *J*

= 12.6 Hz, 5.2 Hz, 6H). ^{11}B NMR (160 MHz, THF) δ 32.51. HRMS (ESI +) 365.2129 (M+Na+), Calc, 365.2106.

4.2.2.D. *tert*-Butyl 3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate Derivatives:

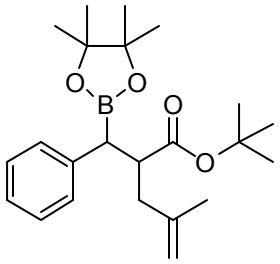


***tert*-Butyl 2-methyl-3-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propanoate (2.28):** This product was prepared as described in General Procedure B. Clear oil, 44% yield; R_f (SiO_2, 9.5:0.5 hexane: ethyl acetate) 0.28. DR = 9.7 : 1. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27 – 7.10 (m, 10H), 2.90 (m, 0.46H), 2.84 – 2.78 (m, 1.54H), 2.54 (d, *J* = 11.3 Hz, 0.46H), 2.34 (d, *J* = 11.5 Hz, 1.41H), 1.47 (s, 6.84H, major diastereomer), 1.40 (s, 2.16H), 1.19 (s, 7.21H, major diastereomer), 1.16 (s, 4.67H, minor diastereomer), 1.14 (s, 3.29H, minor diastereomer), 1.13 (s, 8.35H, major diastereomer), 0.98 (d, *J* = 7.2 Hz, 4.59H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 176.86, 140.65, 129.23, 128.54, 128.43, 128.25, 125.74, 83.65, 83.45, 80.19, 43.36, 28.29, 27.90, 24.84, 24.78, 24.70, 24.64, 17.30. ^{11}B NMR (160 MHz, THF) δ 33.02. HRMS (ESI +) 369.2208 (M+Na+), Calc. 369.2188.

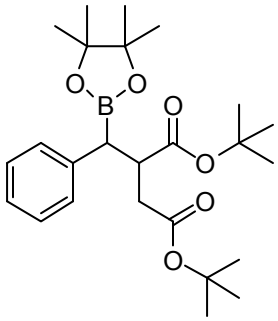


***tert*-Butyl 2-(phenyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)pent-4-enoate (2.29):** This product was prepared as described in General Procedure B. Clear oil, 52% yield; R_f (SiO_2, 9.5:0.5 hexane: ethyl acetate) 0.3. DR = 2.3 : 1. ^{1}H NMR

(500 MHz, $CDCl_3$) δ 7.27 – 7.02 (m, 10H), 5.77 (m, 2H), 5.07 (dd, *J* = 17.1 Hz, 1.5 Hz, 2H), 5.0 (dd, *J* = 10.1 Hz, 1.1 Hz, 2H), 2.91 (ddd, *J* = 11.8 Hz, 9.6 Hz, 4.8 Hz, 0.78H, major diastereomer), 2.74 (d, *J* = 16.2 Hz, 0.22H, minor diastereomer), 2.66 (dd, *J* = 10.1 Hz, 6.1 Hz, 0.18H, minor diastereomer), 2.52 (t, *J* = 17.9 Hz, 0.82H, major diastereomer), 2.31 (dd, *J* = 15.6 Hz, 7.8 Hz, 2H), 1.36 (s, 5.95H, minor diastereomer), 1.14 (dd, *J* = 23.4 Hz, 7.9 Hz, 26H), 1.06 (s, 13.95H, major diastereomer). ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.93, 140.00, 135.75, 129.22, 128.13, 125.73, 116.63, 83.62, 79.81, 48.90, 37.64, 27.79, 24.66, 24.57.^{11}B NMR (160 MHz, THF) δ 30.78. ^{11}B NMR (193 MHz, THF) δ 30.78. MS (ECI +) 395.24 (M+Na+), Calc. 395.24.

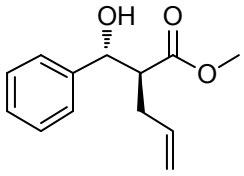


***tert*-Butyl 4-methyl-2-(phenyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)pent-4-enoate (2.30):** This product was prepared as described in General Procedure B. Clear oil, 60% yield; R_f (SiO_2, 9.5:0.5 hexane: ethyl acetate) 0.25. DR = 5.6 : 1. ^1H NMR (400 MHz, $CDCl_3$) δ 7.22 – 7.01 (m, 10H), 4.69 (d, J = 4.73, 3.57H, major diastereomer), 4.57 (d, *J* = 26.5 Hz, 0.42H, minor diastereomer), 3.07 – 2.96 (m, 2H), 2.46 (d, *J* = 11.7 Hz, 1.91H), 2.38 – 2.28 (m, 1.85H), 2.13 (d, *J* = 10.0 Hz, 1.82H), 1.73 (s, 5.26H, major diastereomer), 1.39 (s, 1.93H, minor diastereomer), 1.34 (s, 0.74H, minor diastereomer), 1.18 – 1.05 (m, 26H), 1.01 (s, 16H, major diastereomer). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.11, 143.49, 140.00, 129.37, 128.18, 125.82, 112.38, 83.71, 79.77, 47.82, 42.15, 27.83, 24.81, 24.65, 22.37. ^{11}B NMR (160 MHz, THF) δ 33.00. HRMS (ESI +) 409.2528 (M+Na+), Calc. 409.2521.



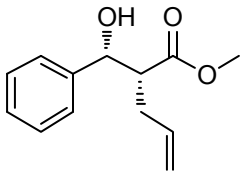
di-*tert*-Butyl 2-(phenyl(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)succinate (2.31): This product was prepared as described in General Procedure B. Clear oil, 24% yield; R_f (SiO_2, 9.5:0.5 hexane: ethyl acetate) 0.45. DR = 2.4 : 1. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 – 7.10 (m, 10H), 3.17 (m, 2H), 2.55 (m, 0.32H), 2.40 (m, 2.35H), 2.16 (dd, *J* = 16.3 Hz, 7.7 Hz, 1.74H), 1.44 (s, 9H, major diastereomer), 1.41 (s, 4H, minor diastereomer), 1.38 (s, 9H, major diastereomer), 1.20 (s, 2.26H, minor diastereomer), 1.18 (s, 5.9H, major diastereomer), 1.16 (s, 2.3H, minor diastereomer), 1.14 (s, 3.2H, minor diastereomer), 1.12 (s, 5.5H major diastereomer). ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.17, 173.79, 171.31, 171.06, 139.79, 139.51, 129.67, 129.27, 128.52, 128.20, 125.98, 125.88, 83.75, 83.36, 80.68, 80.49, 80.30, 80.11, 45.22, 44.77, 37.86, 36.12, 28.16, 28.15, 28.13, 27.75, 24.69, 24.63, 24.59. ^{11}B NMR (160 MHz, THF) δ 31.66. HRMS (ESI +) 447.2924 (M+Na+), Calc. 447.2912.

4.2.2.E. Other α-Alkylation Derivatives

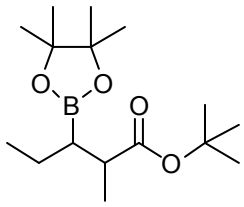


(S)-Methyl 2-((R)-hydroxy(phenyl)methyl)pent-4-enoate (2.34a): This product was prepared as described in General Procedure G. Clear oil, 18.1% yield; R_f (SiO_2, 3:1 hexane: ethyl acetate) 0.13. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.23 (m, 5H), 5.75 – 5.64 (m, 1H), 5.07 – 5.00 (m, 2H), 4.84 (dd, *J* = 7.8 Hz, 5.3 Hz, 1H), 3.71 – 3.69 (m, 3H), 2.90 (d, *J* = 5.4 Hz, 1H), 2.89 – 2.85 (m, 1H), 2.34 – 2.25 (m, 1H), 2.19 – 2.11 (m, 1H). ^{13}C NMR (101 MHz,

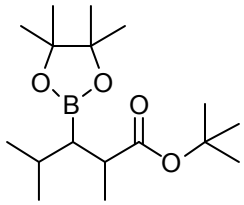
$CDCl_3$) δ 175.12, 141.78, 134.45, 128.73, 128.28, 126.57, 117.49, 75.02, 52.92, 51.89, 33.91. HRMS (ESI +) 220.1102, Calc. 220.1099.



(R)-Methyl 2-((R)-hydroxy(phenyl)methyl)pent-4-enoate (2.34b): This product was prepared as described in General Procedure G. Clear oil, 41.7% yield; R_f (SiO_2, 3:1 hexane: ethyl acetate) 27. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 – 7.13 (m, 5H), 5.83 – 5.71 (m, 1H), 5.11 – 4.98 (m, 3H), 3.61 (s, 3H), 2.98 (d, *J* = 3.1 Hz, 1H), 2.87 (ddd, *J* = 10.1 Hz, 5.7 Hz, 4.6 Hz, 1H), 2.59 – 2.39 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.70, 141.47, 135.46, 128.46, 127.91, 126.23, 116.93, 77.48, 77.16, 76.84, 73.98, 52.92, 51.70, 31.64. HRMS (ESI +) 220.1102, Calc. 220.1099.



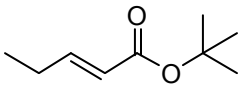
***tert*-Butyl 2-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate (2.32):** This product was prepared as described in General Procedure B. Clear oil, 58% yield; R_f (SiO_2, 9:1 hexane: ethyl acetate) 0.41. ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.50 – 2.39 (m, 1.17H), 2.32 (dd, *J* = 10.8 Hz, 7.8Hz, 1H), 1.51 – 1.33 (m, 22H), 1.23 (dd, *J* = 6.5 Hz, 2.5 Hz, 26H), 1.15 – 1.07 (m, 6H), 0.94 – 0.87 (m, 6H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 176.64, 176.40, 83.08, 83.01, 79.72, 79.67, 41.95, 41.18, 28.20, 28.18, 24.96, 24.92, 24.79, 24.75, 22.52, 21.00, 16.79, 16.15, 13.66, 13.55. ^{11}B NMR (160 MHz, THF) δ 33.91. HRMS (ESI +) 335.2375 (M+Na+), Calc. 335.2364.



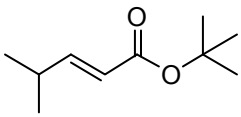
***tert*-Butyl 2,4-dimethyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentanoate (2.33):** This product was prepared as described in General Procedure B. Clear oil, 36% yield; R_f (SiO_2, 9:1 hexane: ethyl acetate) 0.48. ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.54 (dt, *J* = 13.8 Hz, 6.9 Hz, 1H), 2.33 (dd, *J* = 21.2 Hz, 8.2 Hz, 0.4H), 1.72 (dd, *J* = 13.3 Hz, 6.7 Hz, 1.3H), 1.61 (s, 0.5H), 1.42 (s, 18H), 1.25 (s, 26H), 1.09 (d, *J* = 6.9, 3H), 0.93 (dt, *J* = 6.7 Hz, 5.1 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.31, 176.82, 83.23, 79.73, 40.53, 28.24, 28.06, 25.28, 25.15, 25.00, 24.86, 23.16, 22.20, 20.74, 16.90. ^{11}B NMR (160 MHz, THF) δ 33.48. HRMS (ESI +) 321.2216 (M+Na+), Calc. 321.2208.

4.2.2.F. *tert*-Butyl Esters

Compounds **2.1**, **2.2**, and **2.3** were purchased from Sigma-Aldrich.

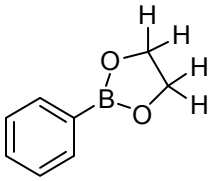


(*E*)-*tert*-Butyl pent-2-enoate (2.4): This product was prepared as described in General Procedure C. Clear oil, 19% yield; R_f (SiO_2, 9.5:0.5 hexane: ethyl acetate) 0.33. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.88 (dt, *J* = 15.6 Hz, 6.3 Hz, 1H), 5.70 (dt, *J* = 15.6 Hz, 1.7 Hz, 1H), 2.21 – 2.12 (m, 2H), 1.45 (s, 9H), 1.03 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.39, 149.50, 122.25, 80.09, 28.32, 25.29, 12.39.



(*E*)-*tert*-Butyl 4-methylpent-2-enoate (2.5): This product was prepared as described in General Procedure C. Clear oil, 44.3%

yield; R_f (SiO_2, 9:1 hexane: ethyl acetate) 0.35. ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.59, 154.32, 120.45, 80.09, 30.92, 28.30, 21.45.



2-Phenyl-1,3,2-dioxaborolane (3.1): This product was prepared by mixing phenylboronic acid (1 eq) with ethylene glycol (1 eq) in pentane for 1 h. A while solid precipitated after 1 h; it was isolated by filtration, and washed 3 times with pentane. The white solid was then dried under vacuum to provide quantitative yield of solid product. ^1H NMR (600 MHz, $CDCl_3$) δ 7.55 (ddd, J = 106.6 Hz, 56.4 Hz, 7.3 Hz, 1H), 4.40 (s, 1H). ^{13}C NMR (151 MHz, $CDCl_3$) δ 134.83, 131.48, 127.85, 66.04. ^{11}B NMR (193 MHz, THF) δ 31.60.

Literature Cited

1. Corey, E. J.; Helal, C. J., Aminoacrylic compounds. Part 31 - Reduction of carbonyl compounds with chiral oxazaborolidine catalysts: A new paradigm for enantioselective catalysis and a powerful new synthetic method. *Angew. Chem. Int. Ed.* **1998,** *37* (15), 1987-2012.

2. Arnold, K.; Davies, B.; Herault, D.; Whiting, A., Asymmetric direct amide synthesis by kinetic amine resolution: A chiral bifunctional aminoboronic acid catalyzed reaction between a racemic amine and an achiral carboxylic acid. *Angew. Chem. Int. Ed.* **2008,** *47* (14), 2673-2676.

3. Matteson, D. S., Asymmetric-Synthesis with Boronic Esters. *Acc. Chem. Res.* **1988,** *21* (8), 294-300.

4. Hall, D., *Boronic acids : preparation and applications in organic synthesis and medicine*. Wiley-VCH ; John Wiley: Weinheim Chichester, 2005; p 549.

5. Curtis, A. D. M.; Whiting, A., Stereoselective Aldol Reactions of Beta-Boronate Carbonyl Derivatives. *Tetrahedron Lett* **1991,** *32* (11), 1507-1510.

6. Curtis, A. D. M.; Mears, R. J.; Whiting, A., The Origin of the Stereoselectivity in the Aldol Reactions of Beta-Boronate Carbonyl Derivatives. *Tetrahedron* **1993,** *49* (1), 187-198.

7. Matteson, D. S.; Majumdar, D., Alpha-Chloro Boronic Esters from Homologation of Boronic Esters. *J. Am. Chem. Soc.* **1980,** *102* (25), 7588-7590.

8. Matteson, D. S.; Ray, R., Directed Chiral Synthesis with Pinanediol Boronic Esters. *J. Am. Chem. Soc.* **1980,** *102* (25), 7590-7591.

9. Matteson, D. S.; Moody, R. J., Homologation of Carbonyl-Compounds to Aldehydes with Lithium Bis(Ethylenedioxyboryl)Methide. *J. Org. Chem.* **1980,** *45* (6), 1091-1095.

10. Matteson, D. S.; Majumdar, D., Homologation of Boronic Esters with Trimethylsilylchloromethyllithium. *J. Organomet. Chem.* **1980,** *184* (2), C41-C43.

11. Tripathy, P. B.; Matteson, D. S., Asymmetric-Synthesis of the 4 Stereoisomers of 4-Methyl-3-Heptanol Via Boronic Esters - Sequential Double Stereodifferentiation Leads to Very High-Purity. *Synthesis-Stuttgart* **1990,** (3), 200-206.

12. Adams, J., The development of proteasome inhibitors as anticancer drugs. *Cancer Cell* **2004,** *5* (5), 417-21.

13. Adams, J., The proteasome: a suitable antineoplastic target. *Nat. Rev. Cancer* **2004,** *4* (5), 349-60.

14. Barlogie, B.; Shaughnessy, J.; Tricot, G.; Jacobson, J.; Zangari, M.; Anaissie, E.; Walker, R.; Crowley, J., Treatment of multiple myeloma. *Blood* **2004,** *103* (1), 20-32.

15. Bauer, S. M.; Armstrong, R. W., Total synthesis of motuporin (nodularin-V). *J. Am. Chem. Soc.* **1999,** *121* (27), 6355-6366.

16. Matteson, D. S.; Sadhu, K. M.; Lienhard, G. E., (R)-1-Acetamido-2-Phenylethaneboronic Acid - a Specific Transition-State Analog for Chymotrypsin. *J. Am. Chem. Soc.* **1981,** *103* (17), 5241-5242.

17. Matteson, D. S.; Sadhu, K. M.; Peterson, M. L., 99-Percent Chirally Selective Syntheses Via Pinanediol Boronic Esters - Insect Pheromones, Diols, and an Amino Alcohol. *J. Am. Chem. Soc.* **1986,** *108* (4), 810-819.

18. Matteson, D. S.; Beedle, E. C., A Directed Chiral Synthesis of Amino-Acids from Boronic Esters. *Tetrahedron Lett.* **1987,** *28* (39), 4499-4502.

19. Matteson, D. S.; Singh, R. P.; Schafman, B.; Yang, J. J., Asymmetric synthesis of serricornin via boronic esters. *J. Org. Chem.* **1998,** *63* (13), 4466-4469.

20. Hiscox, W. C.; Matteson, D. S., Asymmetric synthesis of the Japanese beetle pheromone via boronic esters. *J. Organomet. Chem.* **2000,** *614*, 314-317.

21. Matteson, D. S.; Michnick, T. J., Stereoselective Reaction of an Enolate with Chiral Alpha-Halo Boronic Acid-Esters. *Organometallics* **1990,** *9* (12), 3171-3177.

22. Matteson, D. S.; Lu, J. H., Asymmetric synthesis of 1-acyl-3,4-disubstituted pyrrolidine-2-boronic acid derivatives. *Tetrahedron-Asymmetry* **1998,** *9* (14), 2423-2436.

23. Singh, R. P.; Matteson, D. S., Asymmetric homologation of boronic esters bearing azido and silyloxy substituents. *J. Org. Chem.* **2000,** *65* (20), 6650-6653.

24. Matteson, D. S.; Fernando, D., Bromination of tri(isopropyl)boroxine and asymmetric synthesis of (2-cyano-3,3-dimethylcyclopropyl)boronic esters. *J. Organomet. Chem.* **2003,** *680* (1-2), 100-105.

25. Matteson, D. S.; Peterson, M. L., Synthesis of L-(+)-Ribose Via (S)-Pinanediol (Alpha-S)-Alpha-Bromo Boronic Esters. *J. Org. Chem.* **1987,** *52* (23), 5116-5121.

26. Matteson, D. S., *Stereodirected Synthesis with Organoboranes*. Springer-Verlag: Berlin, 1995; p 405.

27. Matsumi, N.; Naka, K.; Chujo, Y., Extension of pi-conjugation length via the vacant p-orbital of the boron atom. Synthesis of novel electron deficient pi-conjugated systems by hydroboration polymerization and their blue light emission. *J. Am. Chem. Soc.* **1998,** *120* (20), 5112-5113.

28. Entwistle, C. D.; Marder, T. B., Boron chemistry lights the way: Optical properties of molecular and polymeric systems. *Angew. Chem. Int. Ed.* **2002,** *41* (16), 2927-2931.

29. Soloway, A. H.; Tjarks, W.; Barnum, B. A.; Rong, F. G.; Barth, R. F.; Codogni, I. M.; Wilson, J. G., The Chemistry of Neutron Capture Therapy. *Chem. Rev.* **1998,** *98* (4), 1515-1562.

30. Baker, S. J.; Zhang, Y. K.; Akama, T.; Lau, A.; Zhou, H.; Hernandez, V.; Mao, W. M.; Alley, M. R. K.; Sanders, V.; Plattner, J. J., Discovery of a new boron-containing antifungal agent, 5-fluoro-1,3-dihydro-1-hydroxy-2,1-benzoxaborole (AN2690), for the potential treatment of onychomycosis. *J. Med. Chem.* **2006,** *49* (15), 4447-4450.

31. Mun, S.; Lee, J. E.; Yun, J., Copper-catalyzed beta-Boration of alpha,beta-unsaturated carbonyl compounds: rate acceleration by alcohol additives. *Org. Lett.* **2006,** *8* (21), 4887-9.

32. Whiting, A., A Convenient Preparation of Beta-Boronate Carbonyl Derivatives - Evidence for the Intervention of Boronate Ate-Complexes in Enolate Alkylations. *Tetrahedron Lett.* **1991,** *32* (11), 1503-1506.

33. Webb, G. A., *Annual Reports on NMR Spectroscopy*. Academic Press, Inc: San Diego, CA, 1988; Vol. 20.

34. Belliotti, T. R.; Capiris, T.; Ekhato, I. V.; Kinsora, J. J.; Field, M. J.; Heffner, T. G.; Meltzer, L. T.; Schwarz, J. B.; Taylor, C. P.; Thorpe, A. J.; Vartanian, M. G.; Wise, L. D.; Zhi-Su, T.; Weber, M. L.; Wustrow, D. J., Structure-activity relationships of pregabalin and analogues that target the alpha(2)-delta protein. *J. Med. Chem.* **2005,** *48* (7), 2294-307.

35. Sibi, M. P.; Johnson, M. D.; Punniyamurthy, T., Enantioselective synthesis of peperomins A, C, D, and analogs - Examination of diastereoselective cuprate conjugate additions to N-enoyl-4-diphenylmethyl-2-oxazolidinones. *Can. J. Chem.* **2001,** *79* (11), 1546-1555.

36. Mcgarvey, G. J.; Williams, J. M.; Hiner, R. N.; Matsubara, Y.; Oh, T., L-Aspartic Acid in Acyclic Stereoselective Synthesis - Synthetic Studies on Amphotericin-B. *J. Am. Chem. Soc.* **1986,** *108* (16), 4943-4952.

37. Larcheveque, M.; Henrot, S., A Stereospecific Synthesis of Optically Pure (-)-Alpha-Multistriatin. *Tetrahedron* **1987,** *43* (10), 2303-2310.

38. Jeong, L. S.; Kim, H. O.; Moon, H. R.; Hong, J. H.; Yoo, S. J.; Choi, W. J.; Chun, M. W.; Lee, C. K., Syntheses and structure--activity relationships of novel apio and thioapio dideoxydidehydronucleosides as anti-HCMV agents. *J. Med. Chem.* **2001,** *44* (5), 806-13.

39. Balskus, E. P.; Jacobsen, E. N., alpha,beta-unsaturated beta-silyl imide substrates for catalytic, enantioselective conjugate additions: A total synthesis of (+)-lactacystin and the discovery of a new proteasome inhibitor. *J. Am. Chem. Soc.* **2006,** *128* (21), 6810-6812.

40. Tiecco, M.; Testaferri, L.; Marini, F.; Sternativo, S.; Santi, C.; Bagnoli, L.; Temperini, A., Asymmetric aldol reactions from titanium enolates of [alpha]-seleno ketones and esters. *Tetrahedron: Asymmetry* **2004,** *15* (5), 783-791.

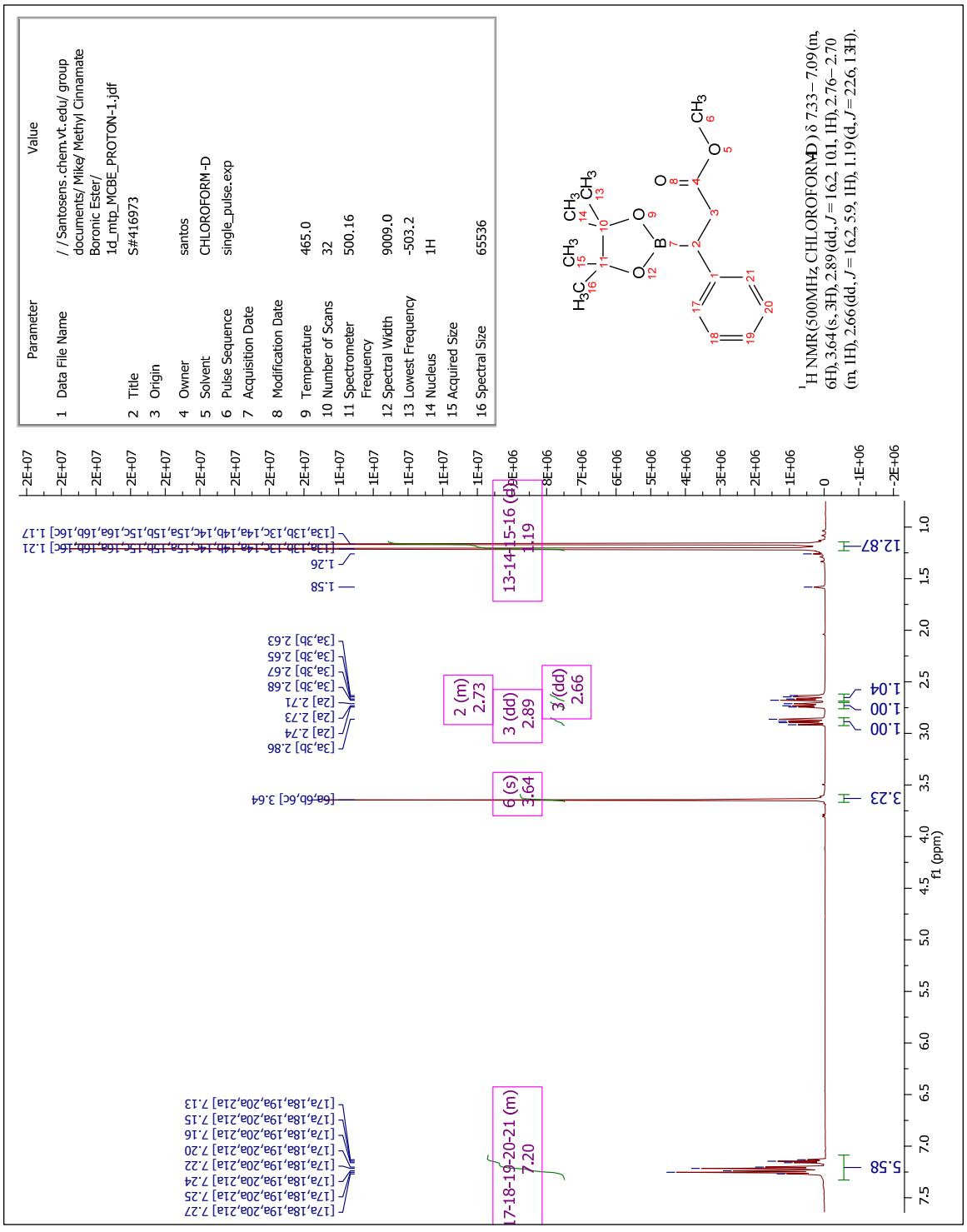
41. Ruggli, P., Über einen Ring mit dreifacher Bindung. *Liebigs Ann. Chem.* **1912,** *392*, 92.

42. Ashraf-Khorassani, M. N., N.; Taylor, L.T.; Coleman III, W.M., Identification and Quantification of Sucrose Esters in Various Turkish Tobaccos. *Beit. Tabakforsch. Int.* **2005,** *21* (8), 441-450.

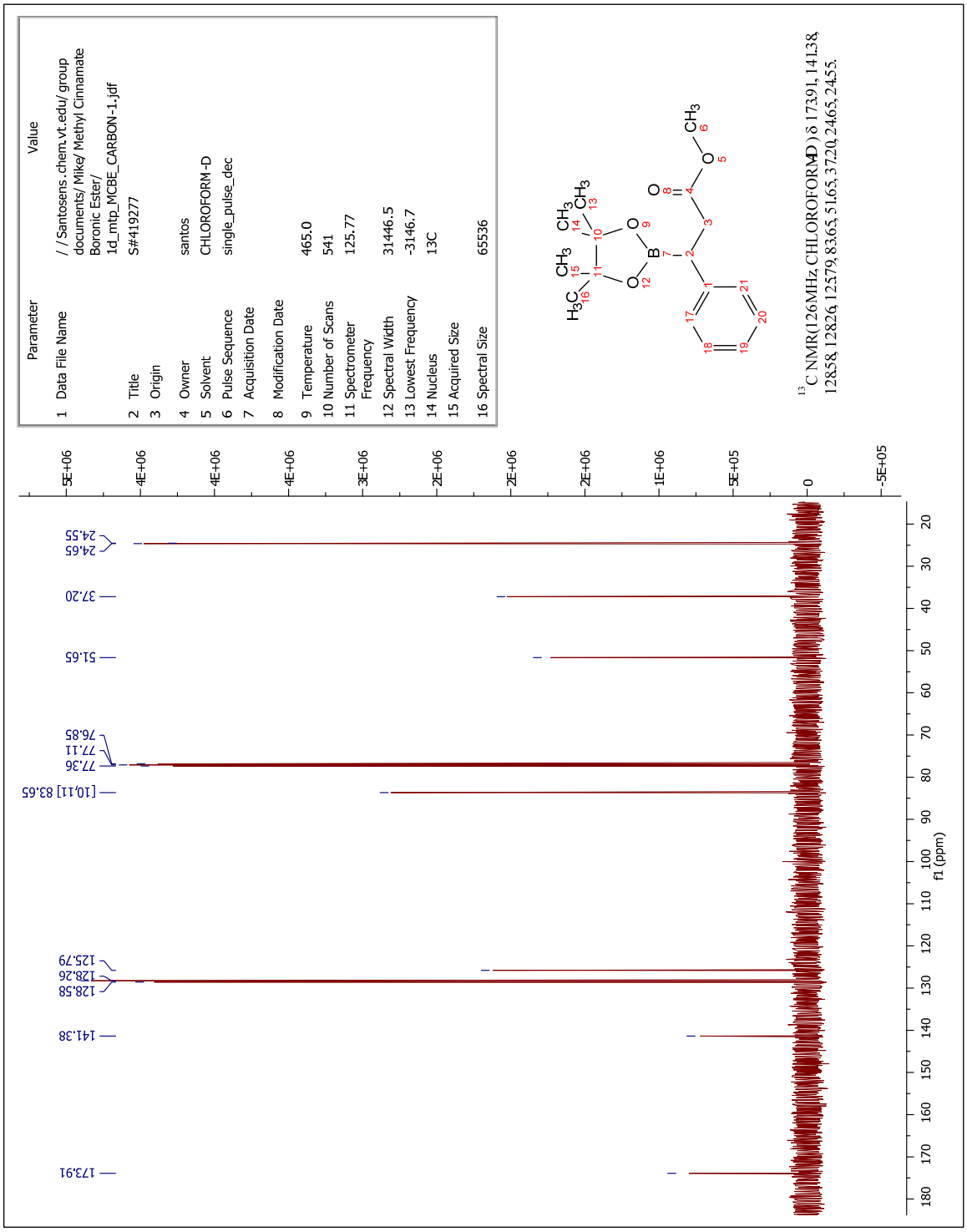
43. Murphy, B. T.; Cao, S.; Brodie, P.; Maharavo, J.; Andriamanantoanina, H.; Ravelonandro, P.; Kingston, D. G. I., Antiproliferative Bistramides from Trididemnum cyclops from Madagascar(1). *J. Nat. Prod.* **2009,** *72* (7), 1338-1340.

Appendix 1

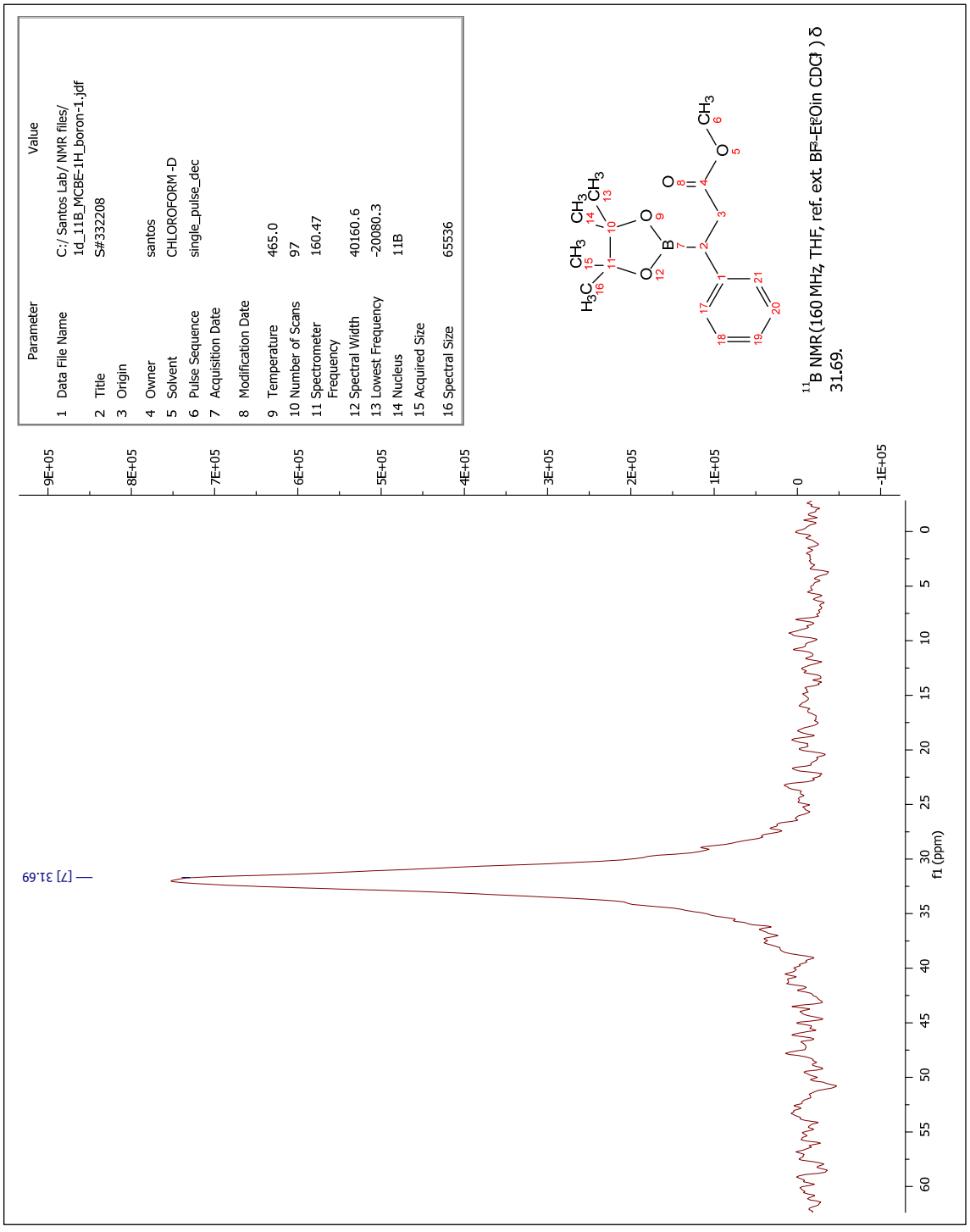
Compound **2.1a**



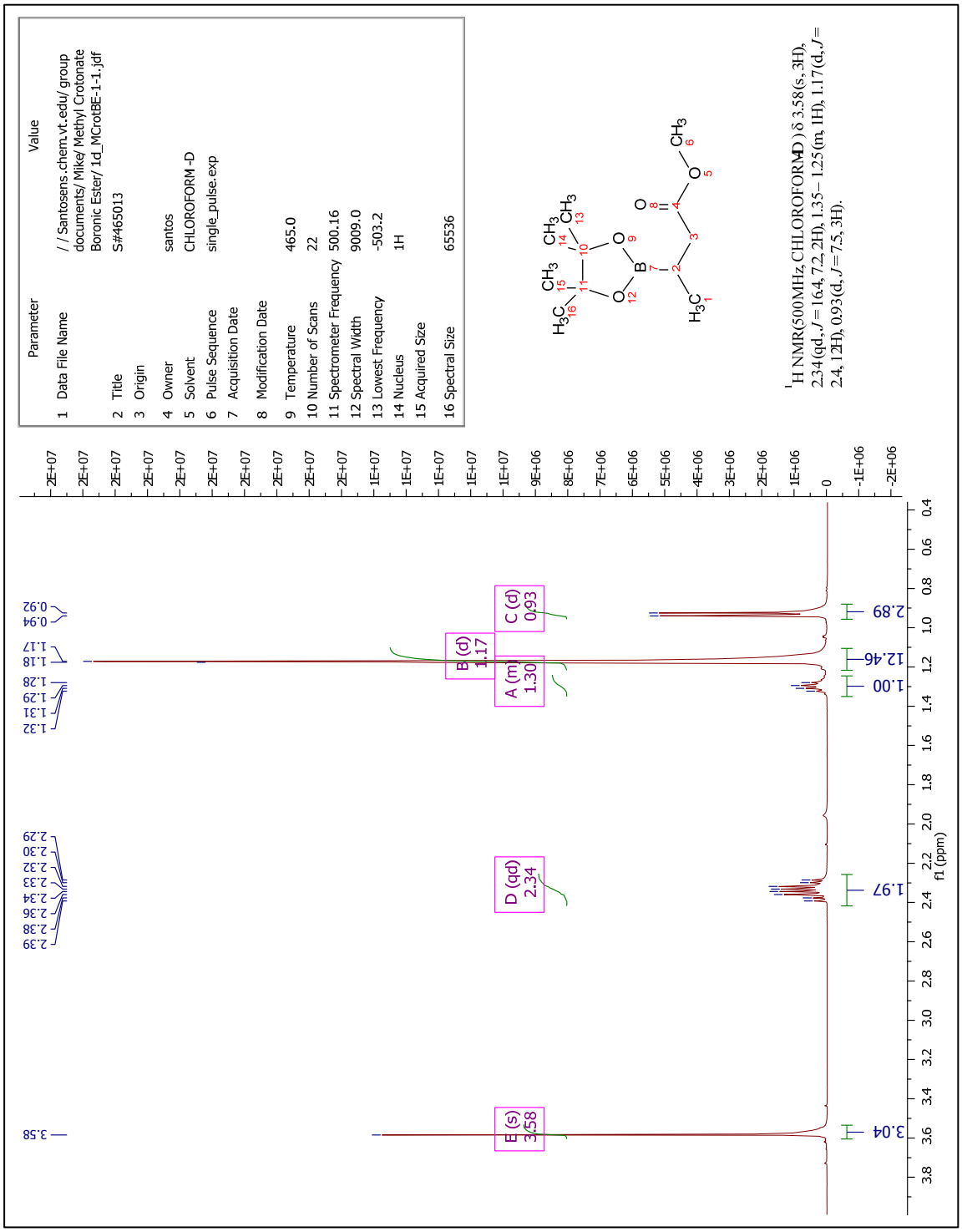
Compound **2.1a**



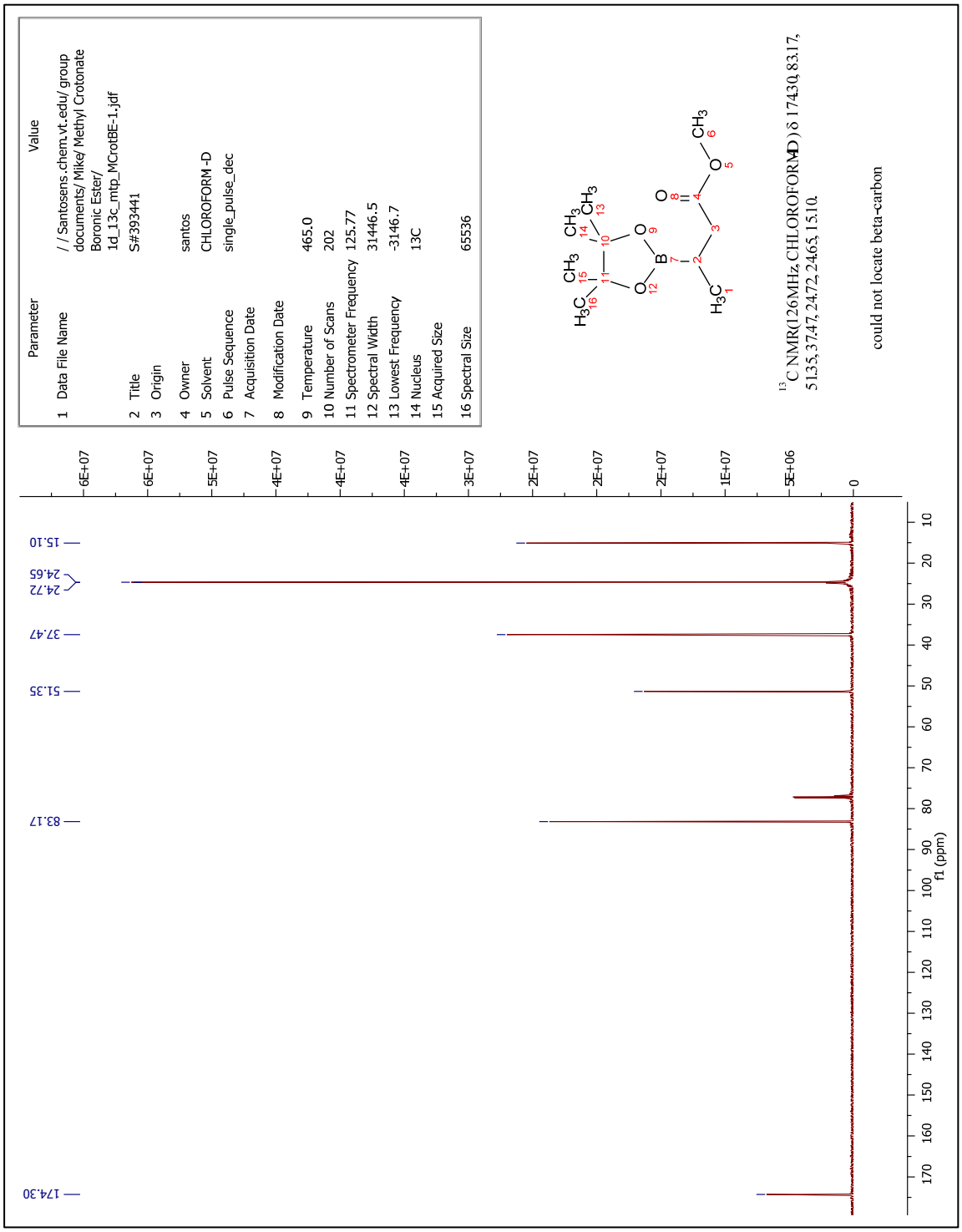
Compound **2.1a**



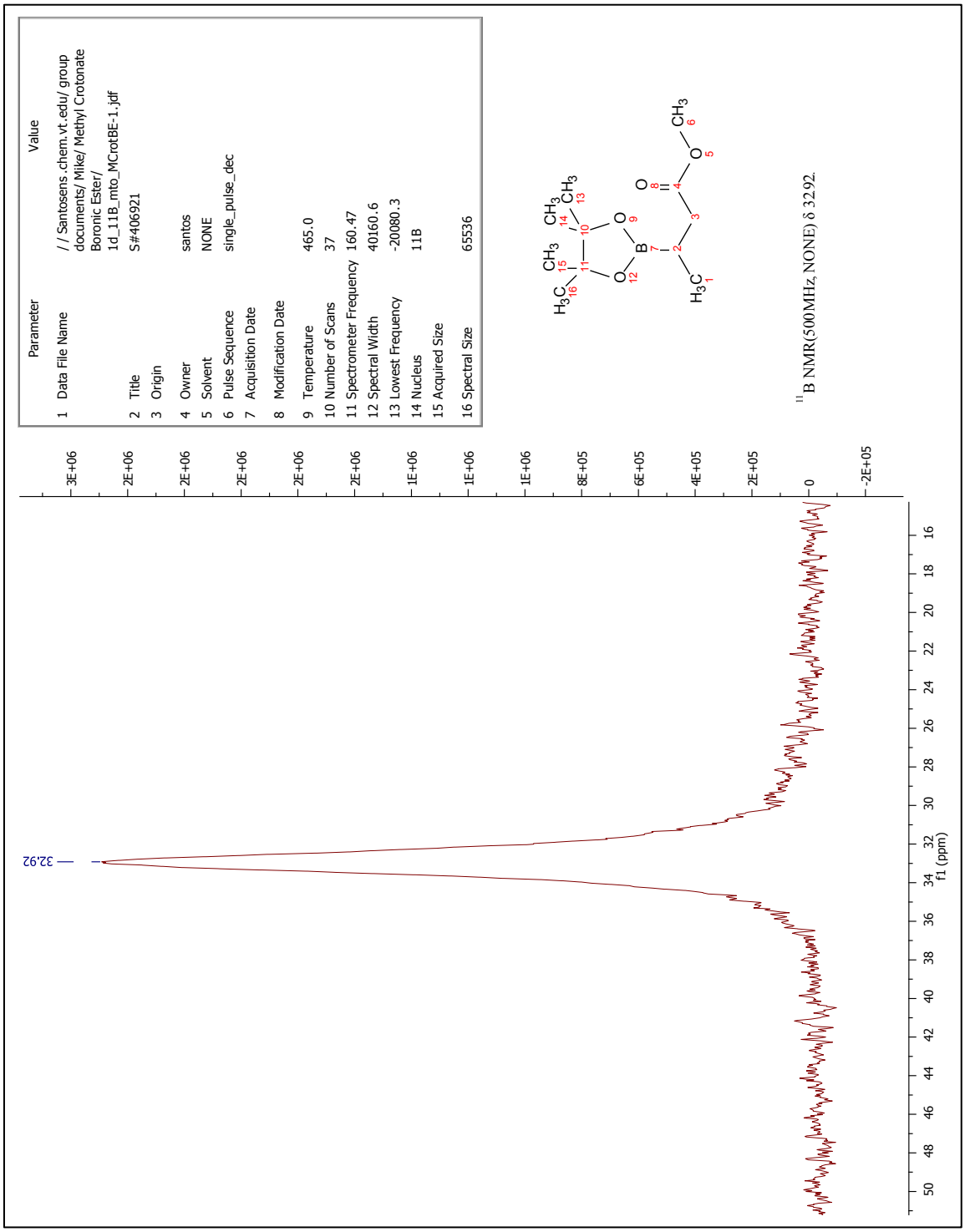
Compound **2.2a**



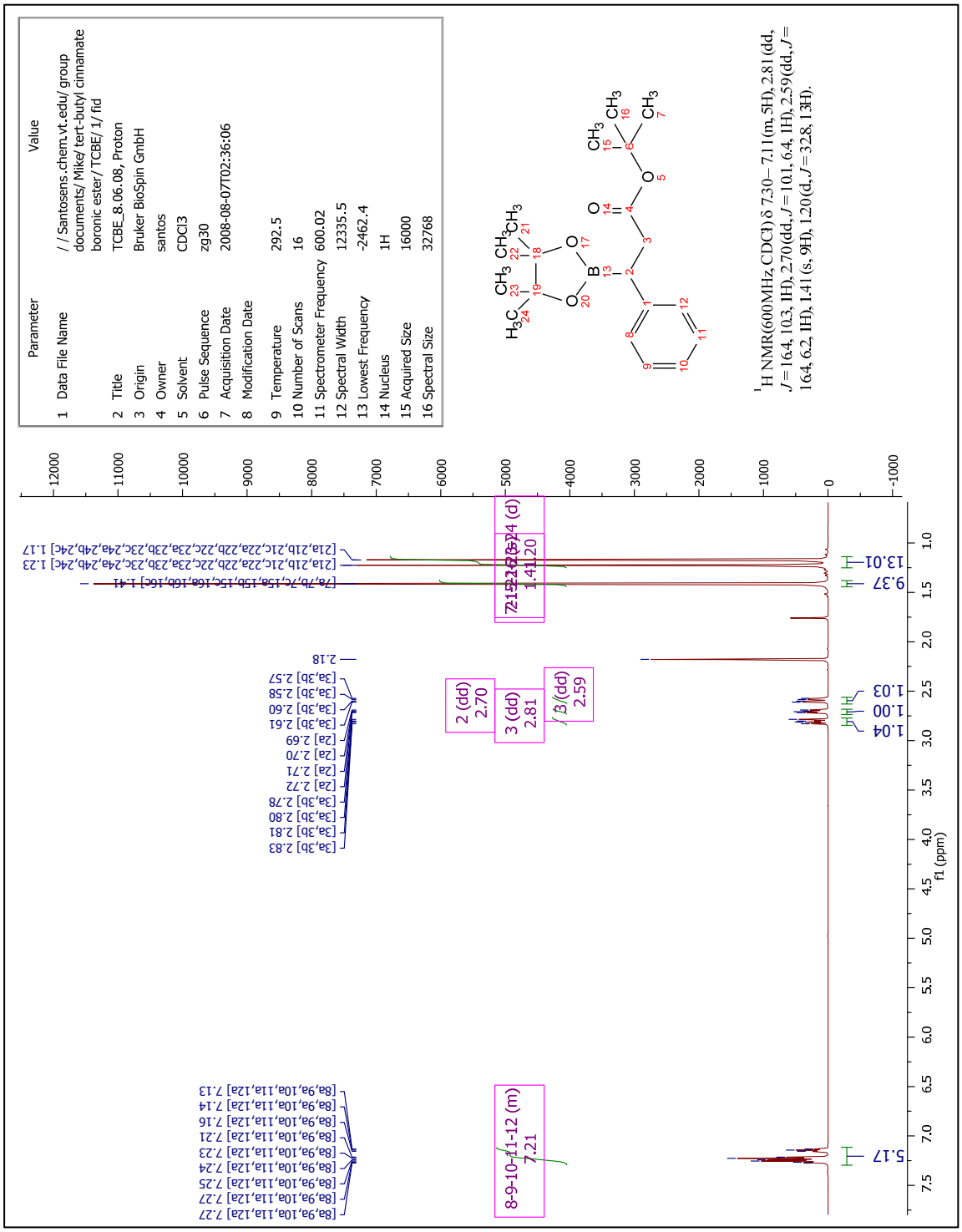
Compound **2.2a**



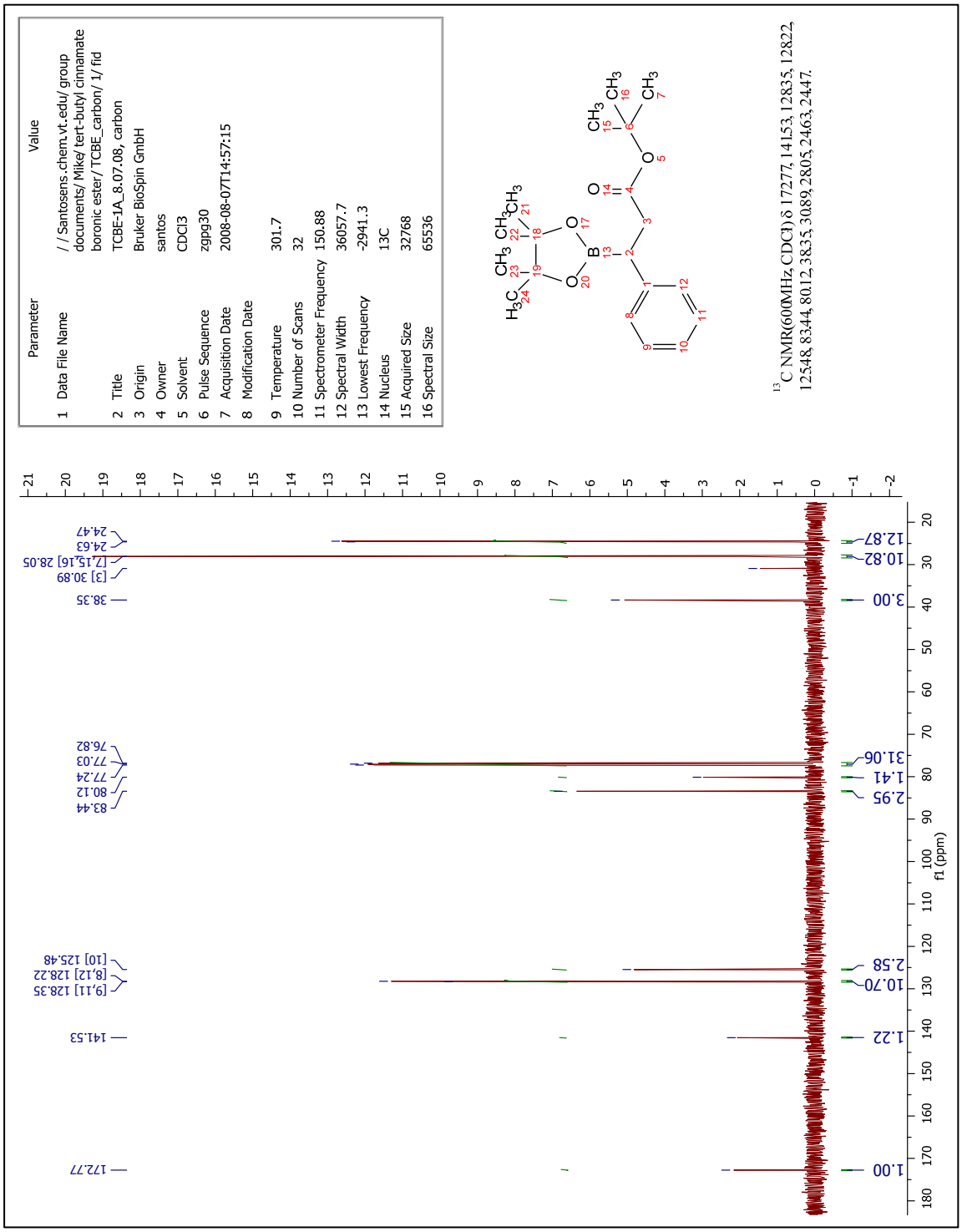
Compound **2.2a**



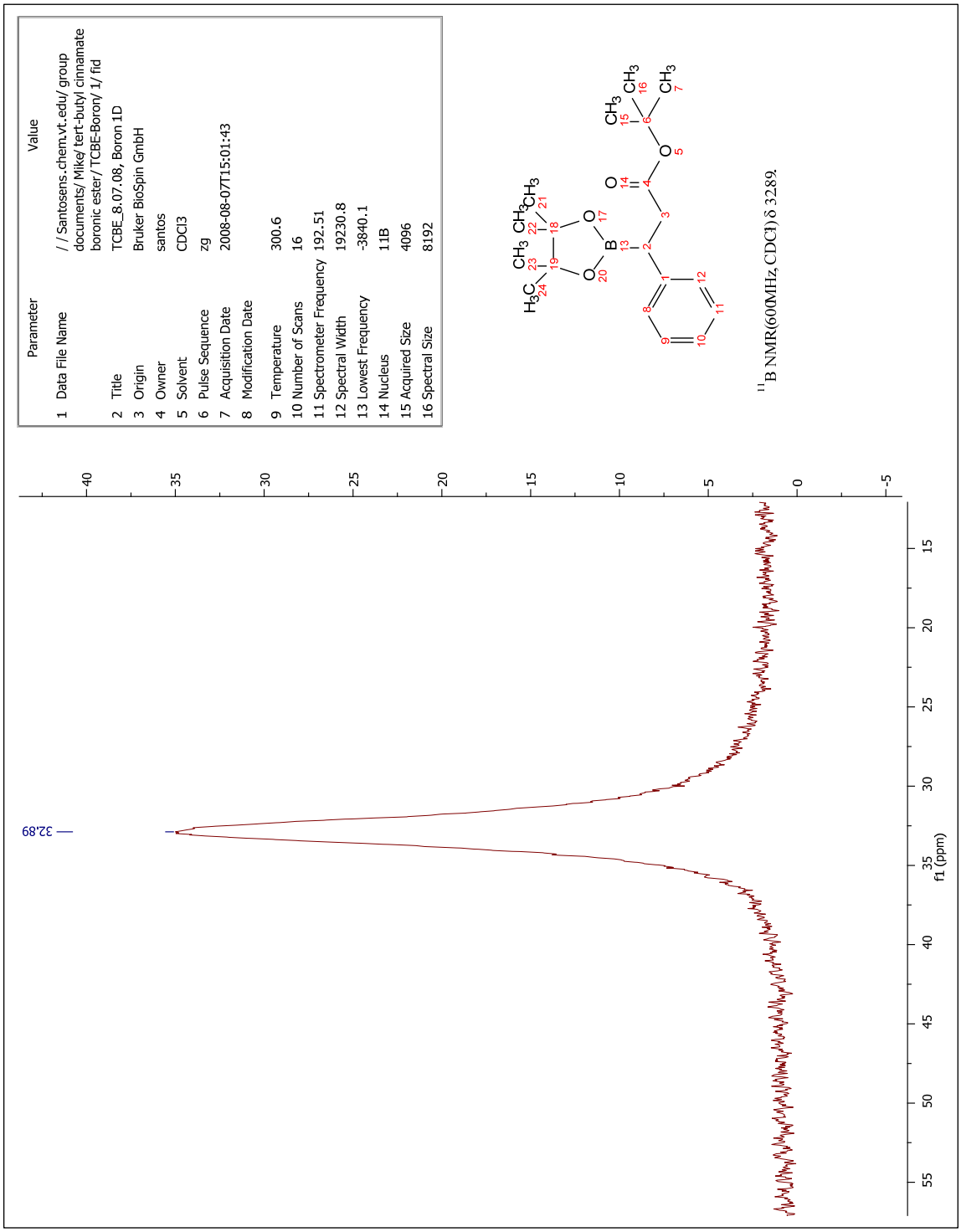
Compound **2.3a**



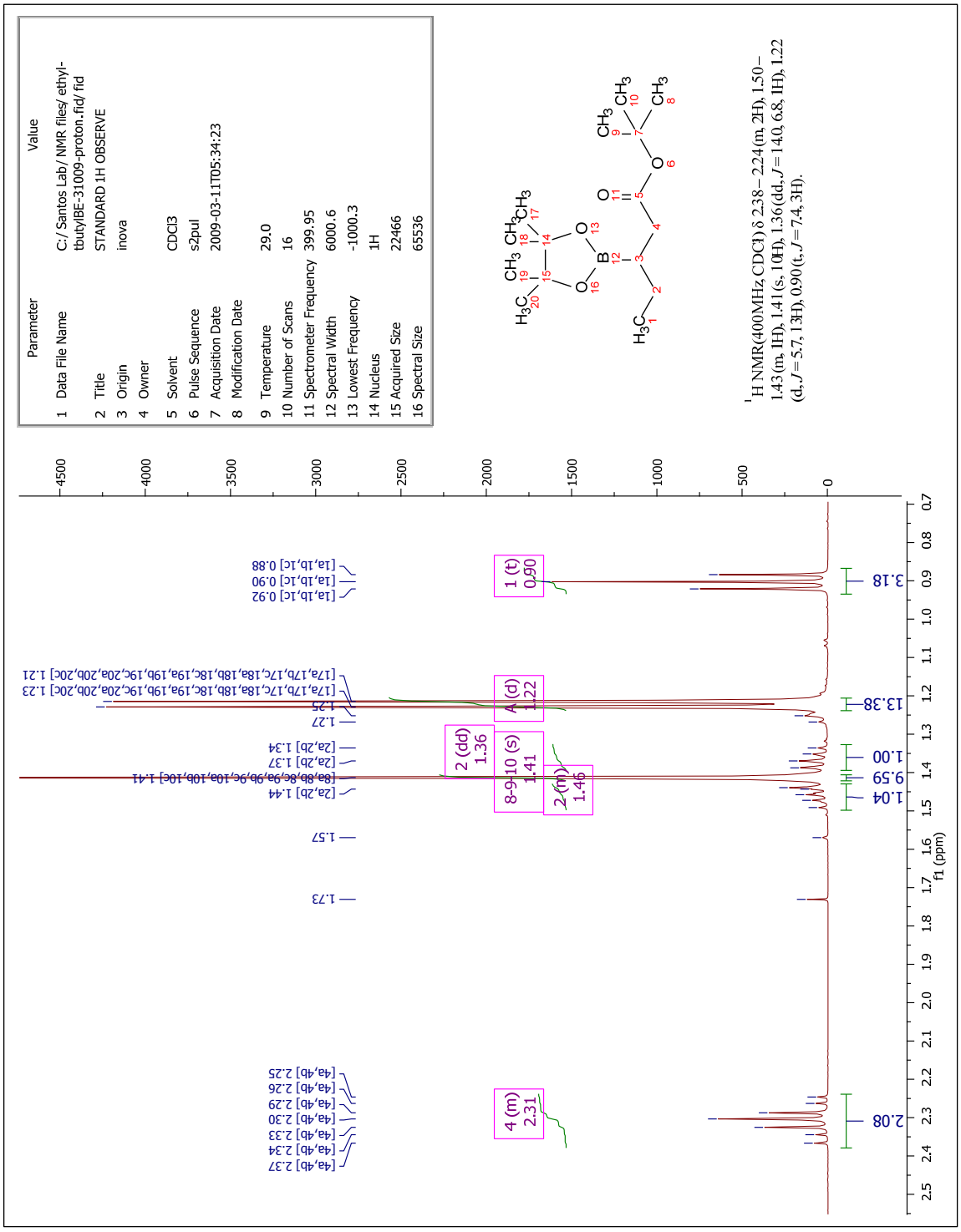
Compound **2.3a**



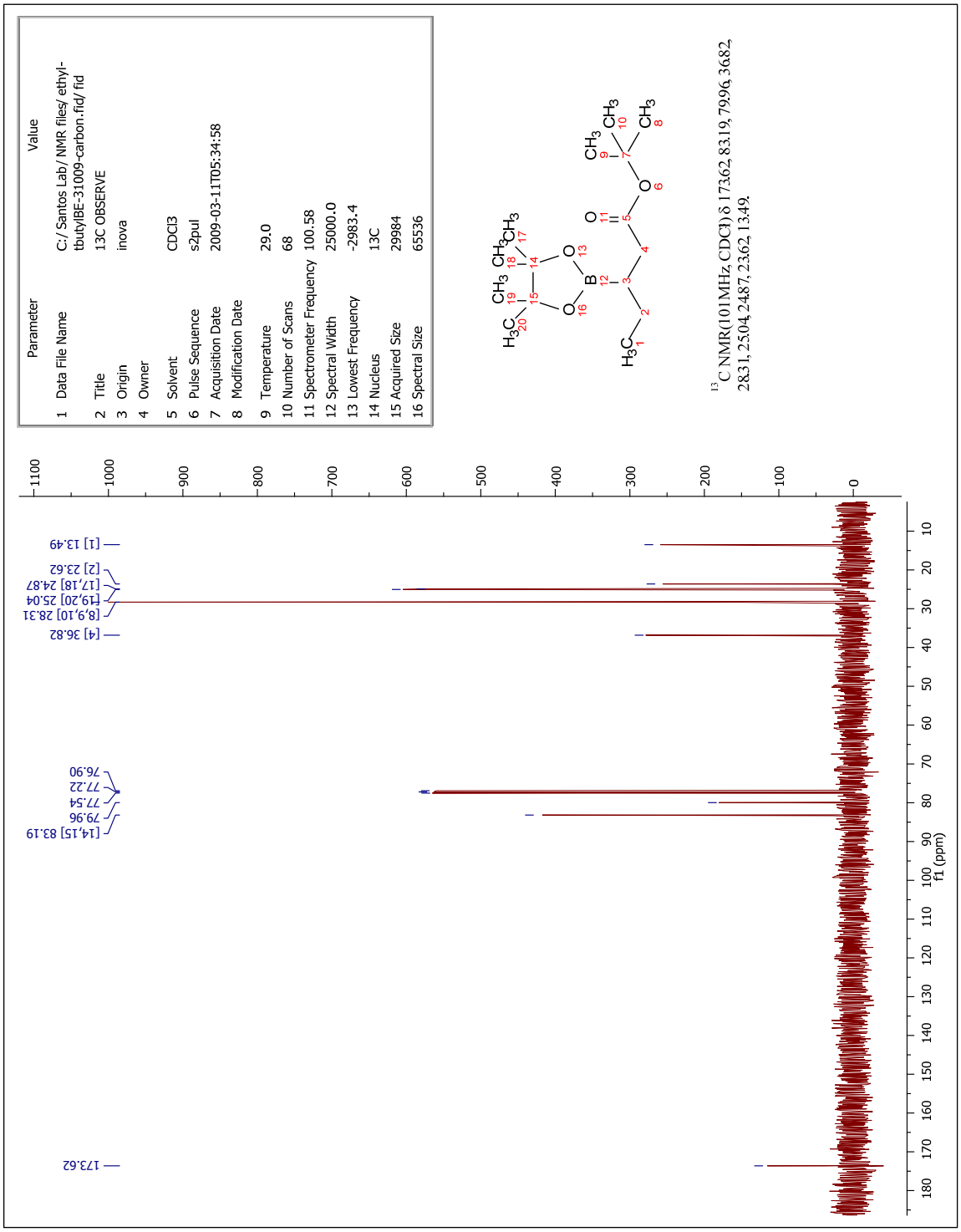
Compound **2.3a**



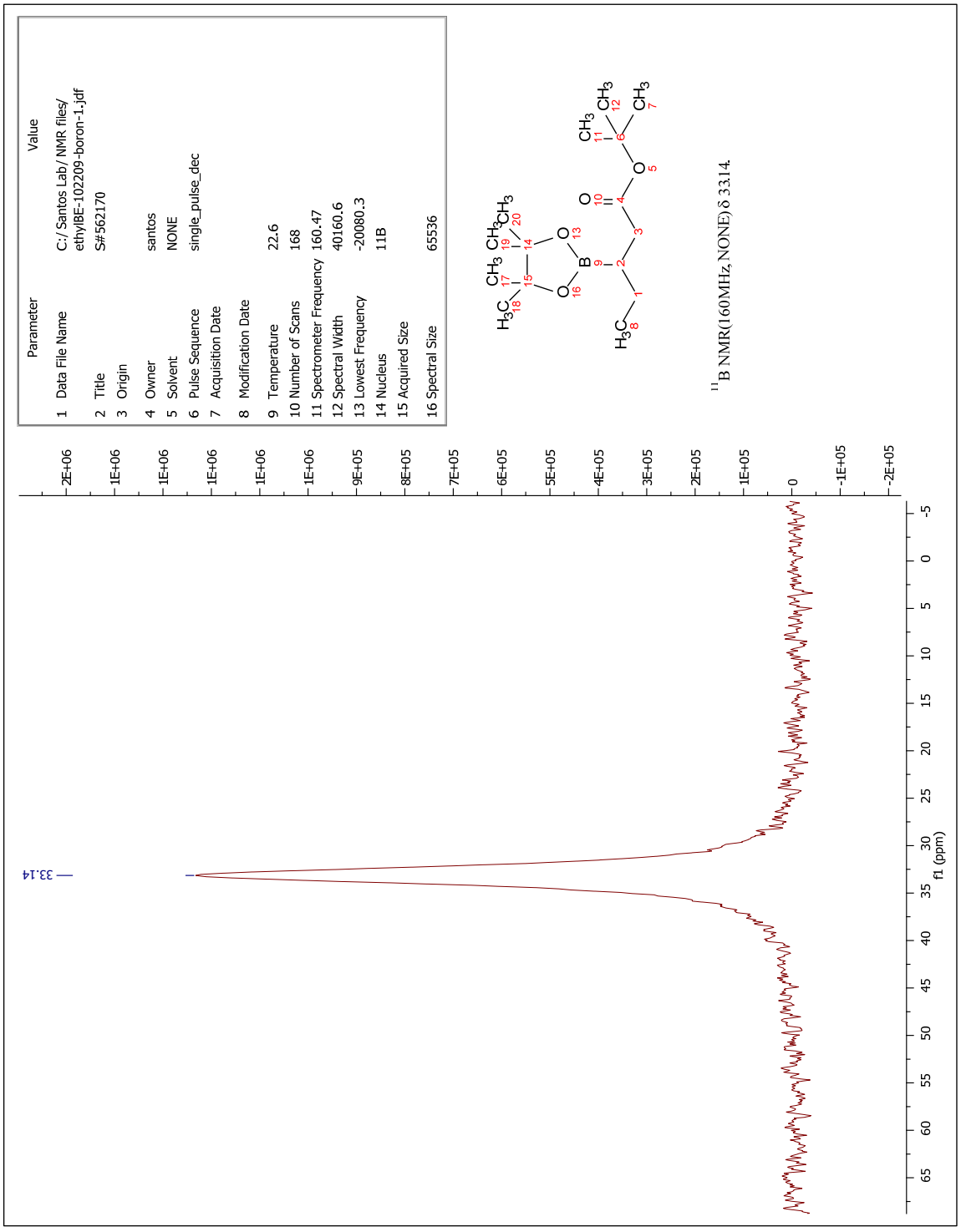
Compound **2.4a**



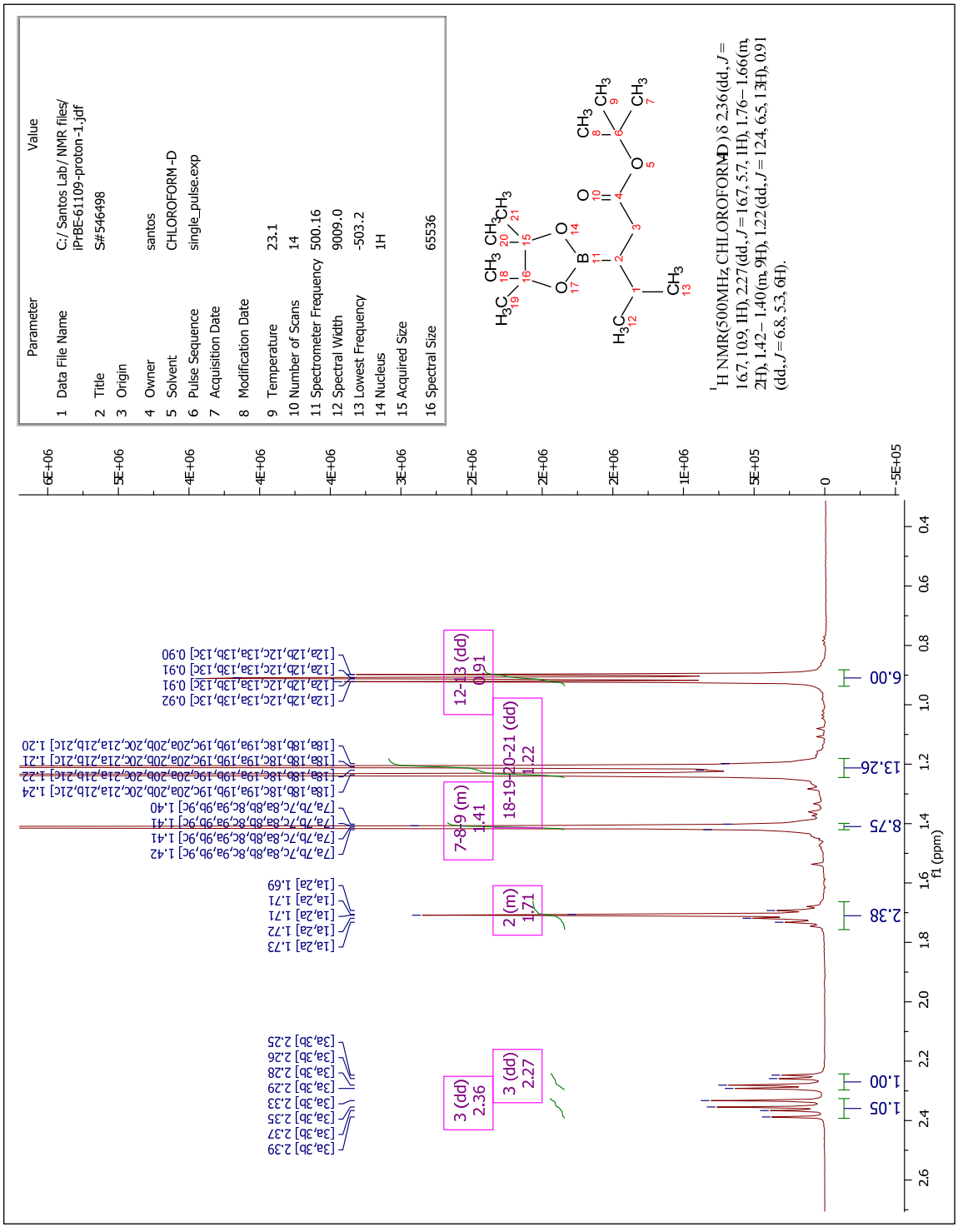
Compound **2.4a**



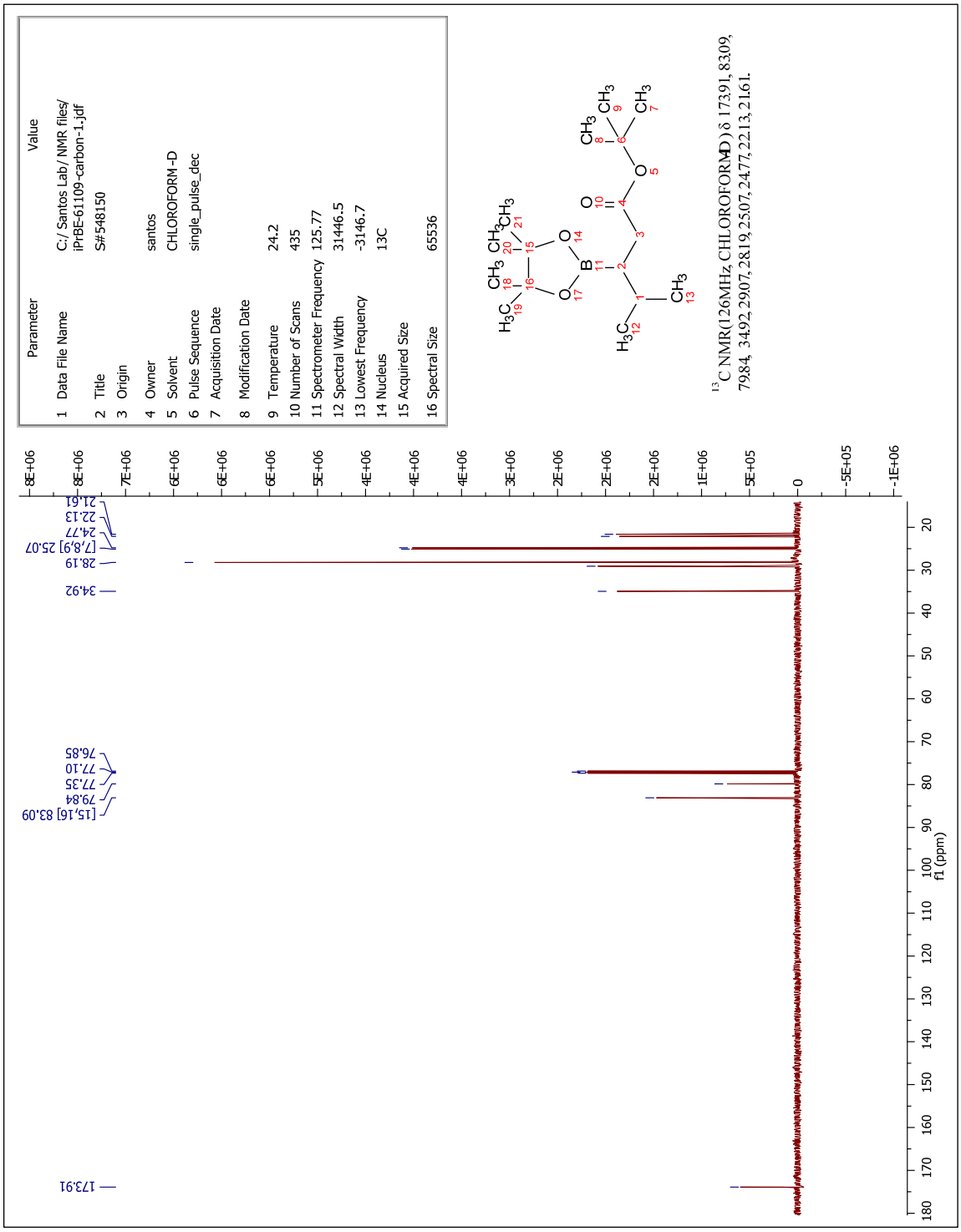
Compound **2.4a**



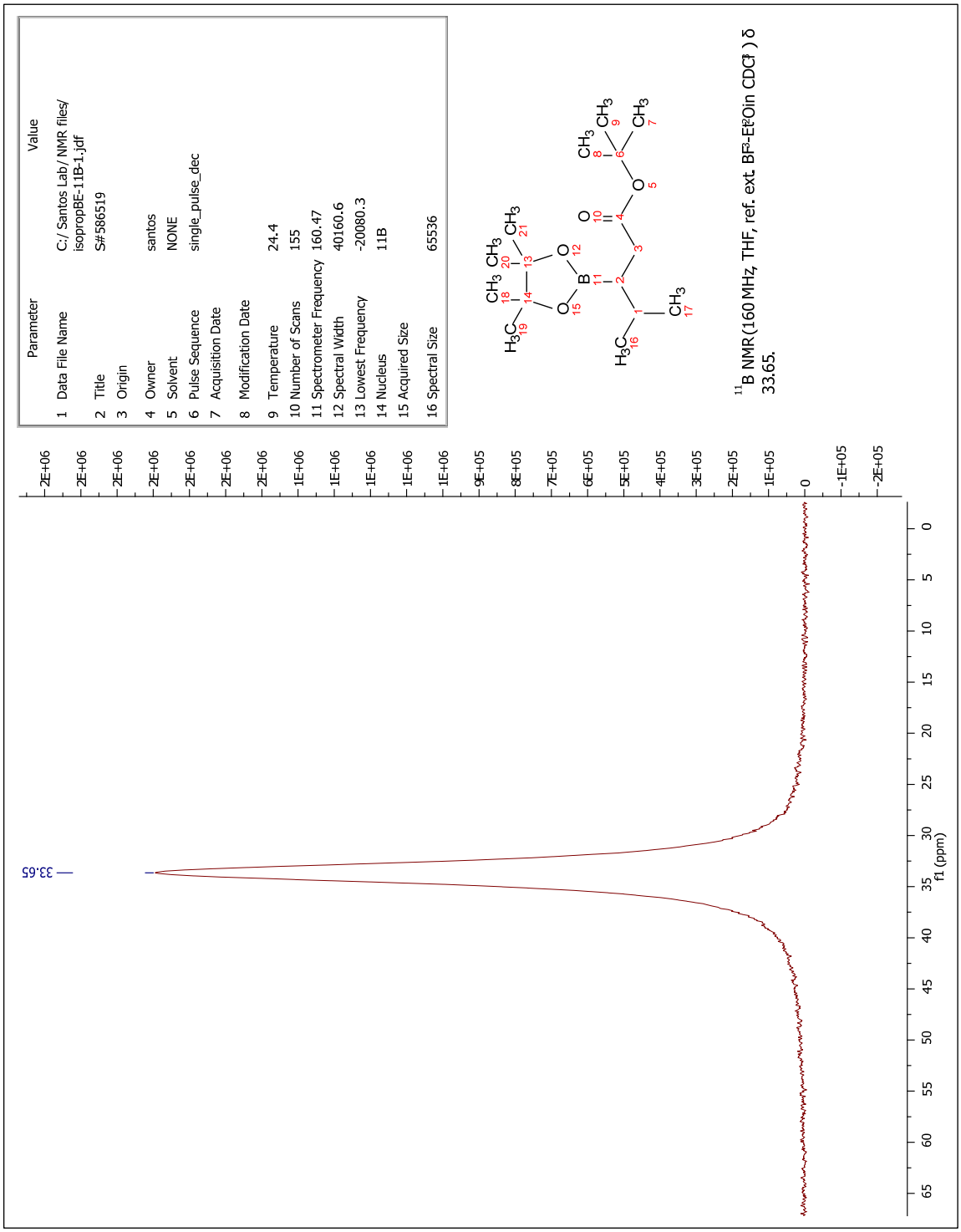
Compound **2.5a**



Compound **2.5a**

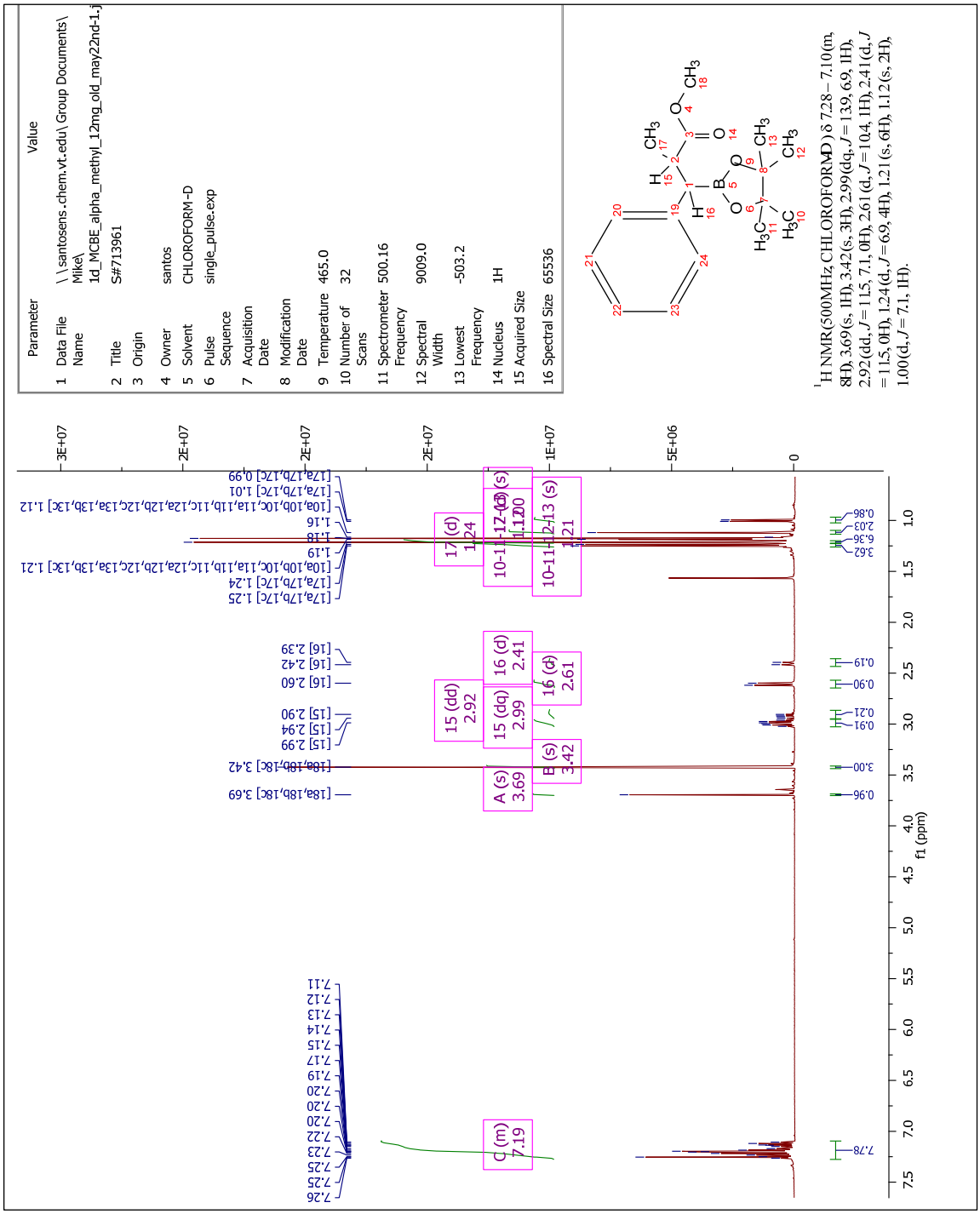


Compound **2.5a**

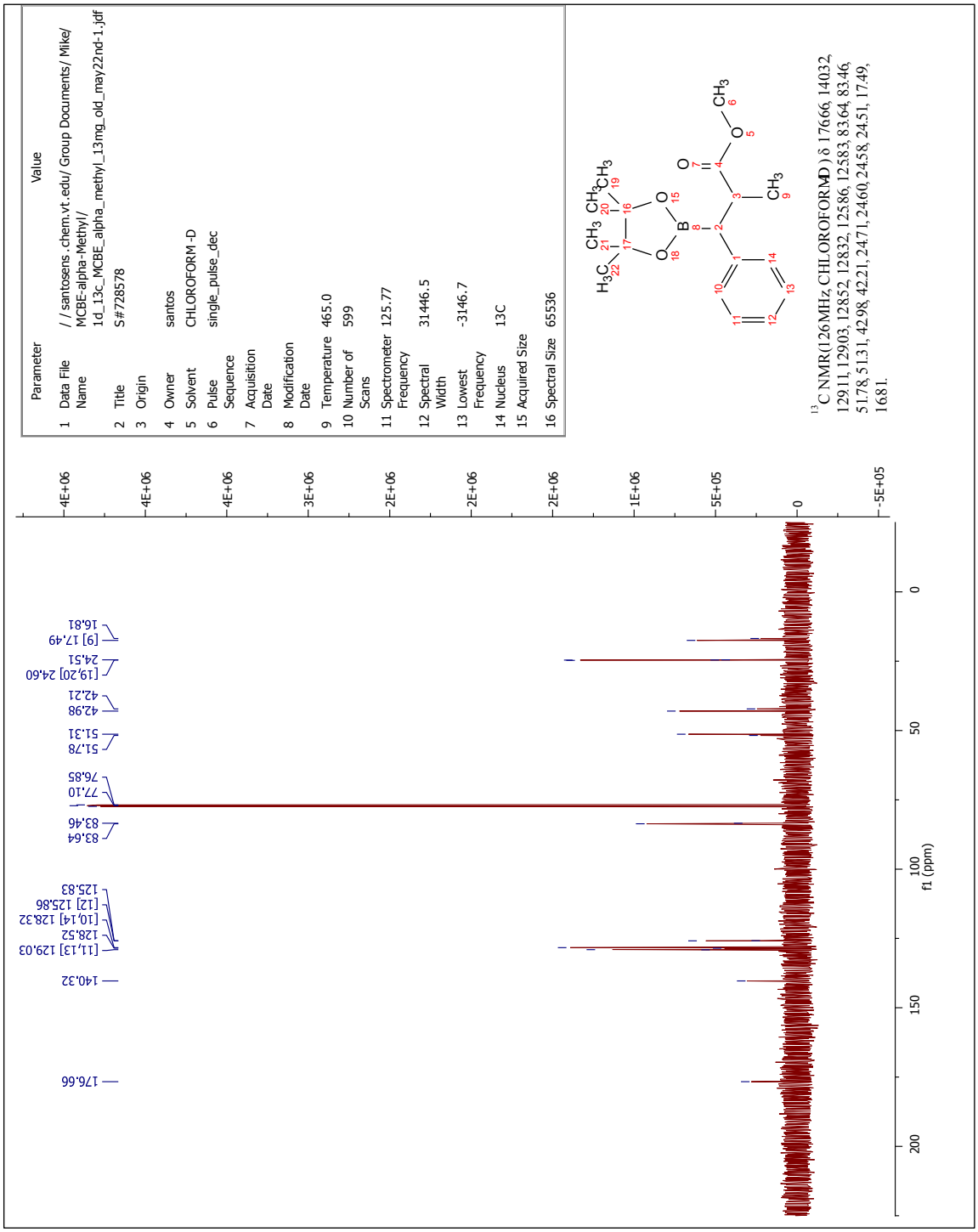


^{11}B NMR (160 MHz, THF, ref. ext. BF_3-Et_2O in $CDCl_3$) δ 33.65.

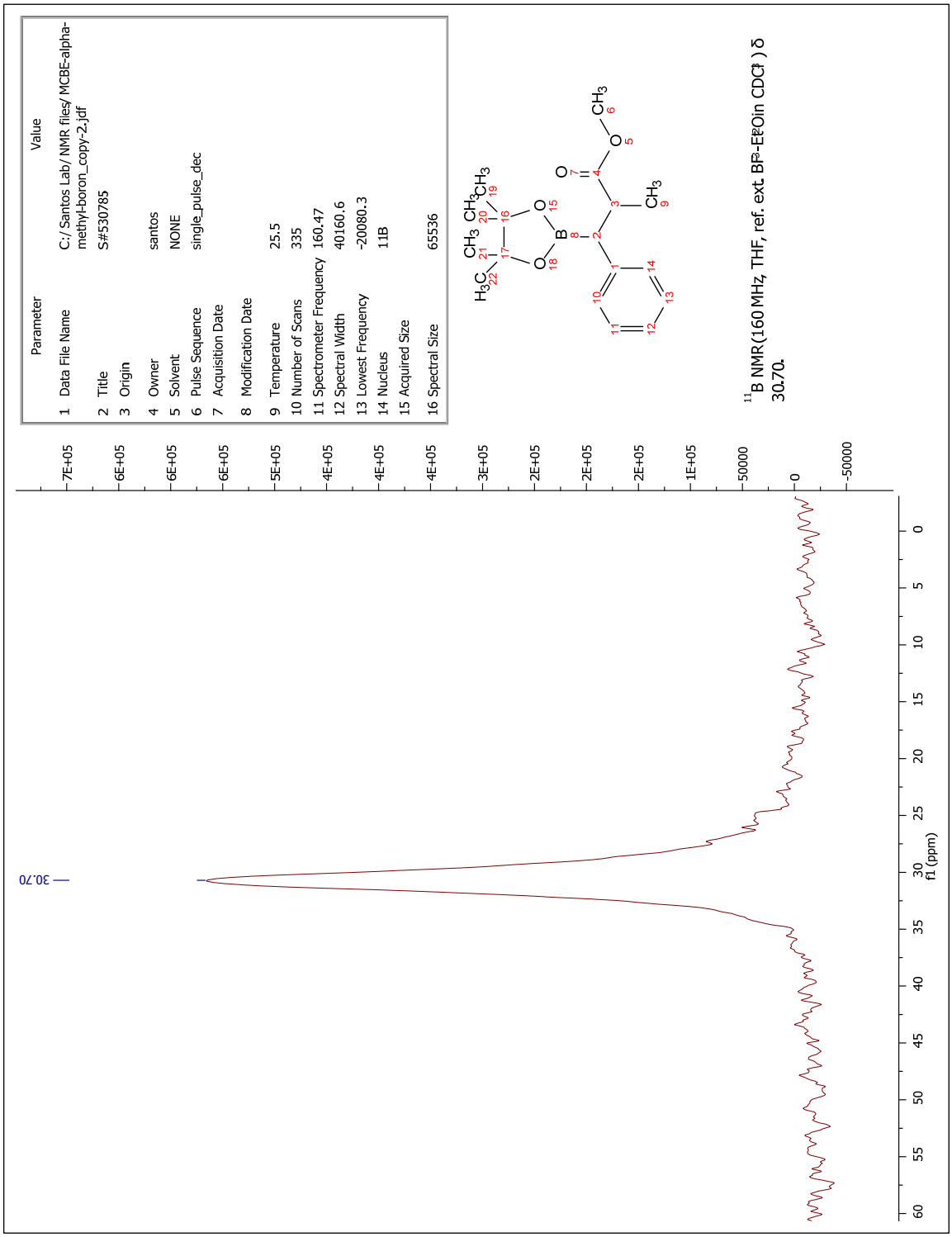
Compound **2.20**



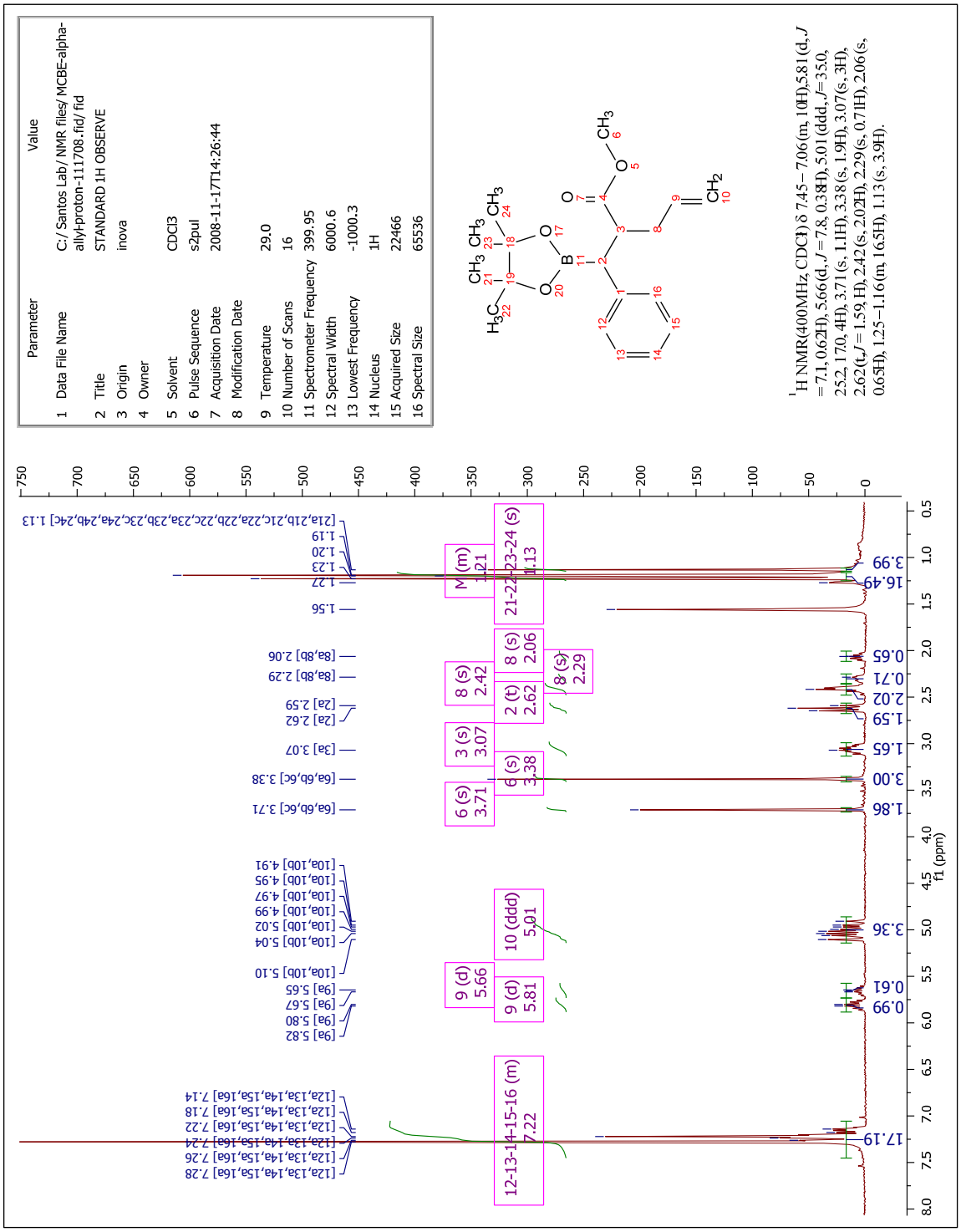
Compound **2.20**



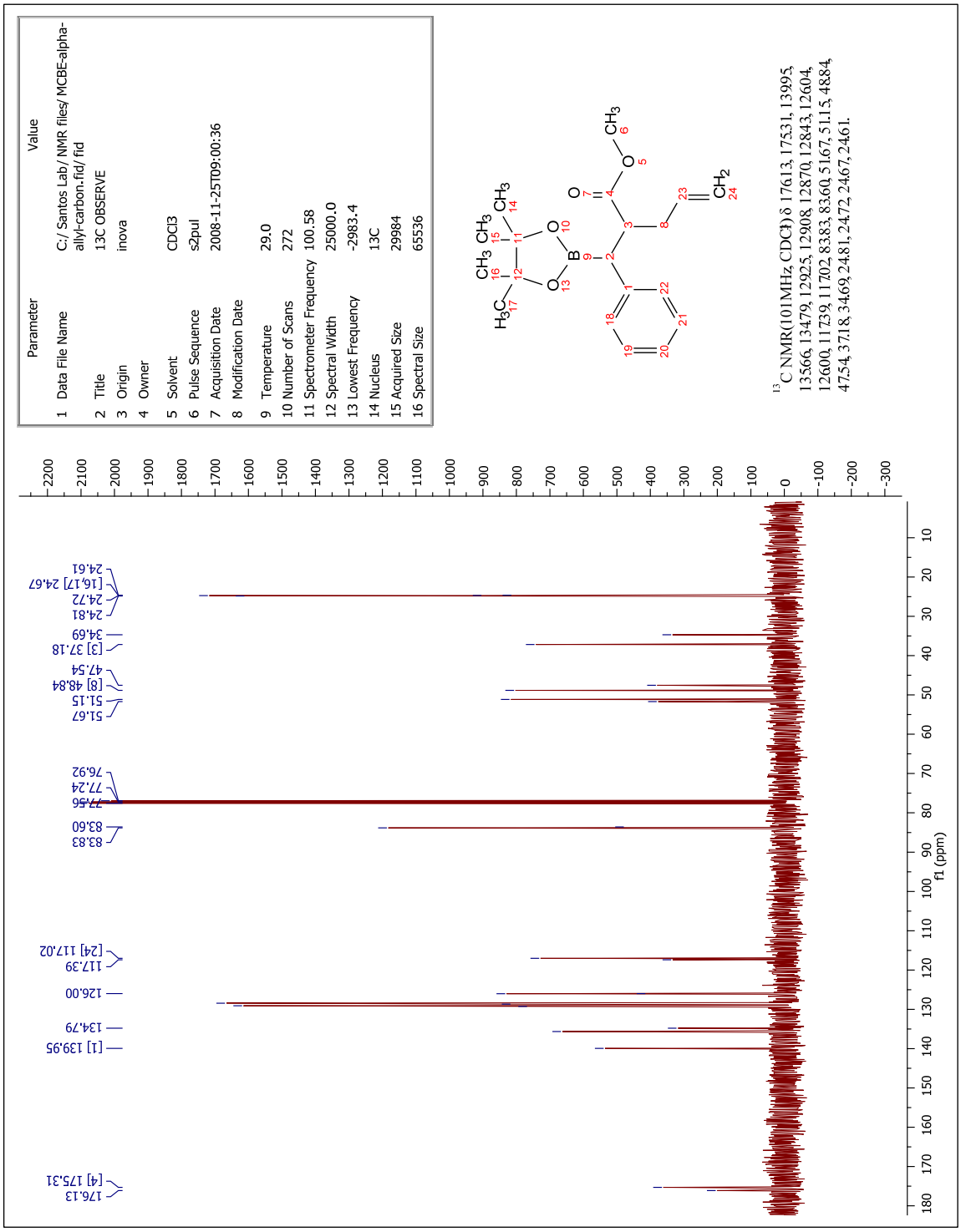
Compound **2.20**



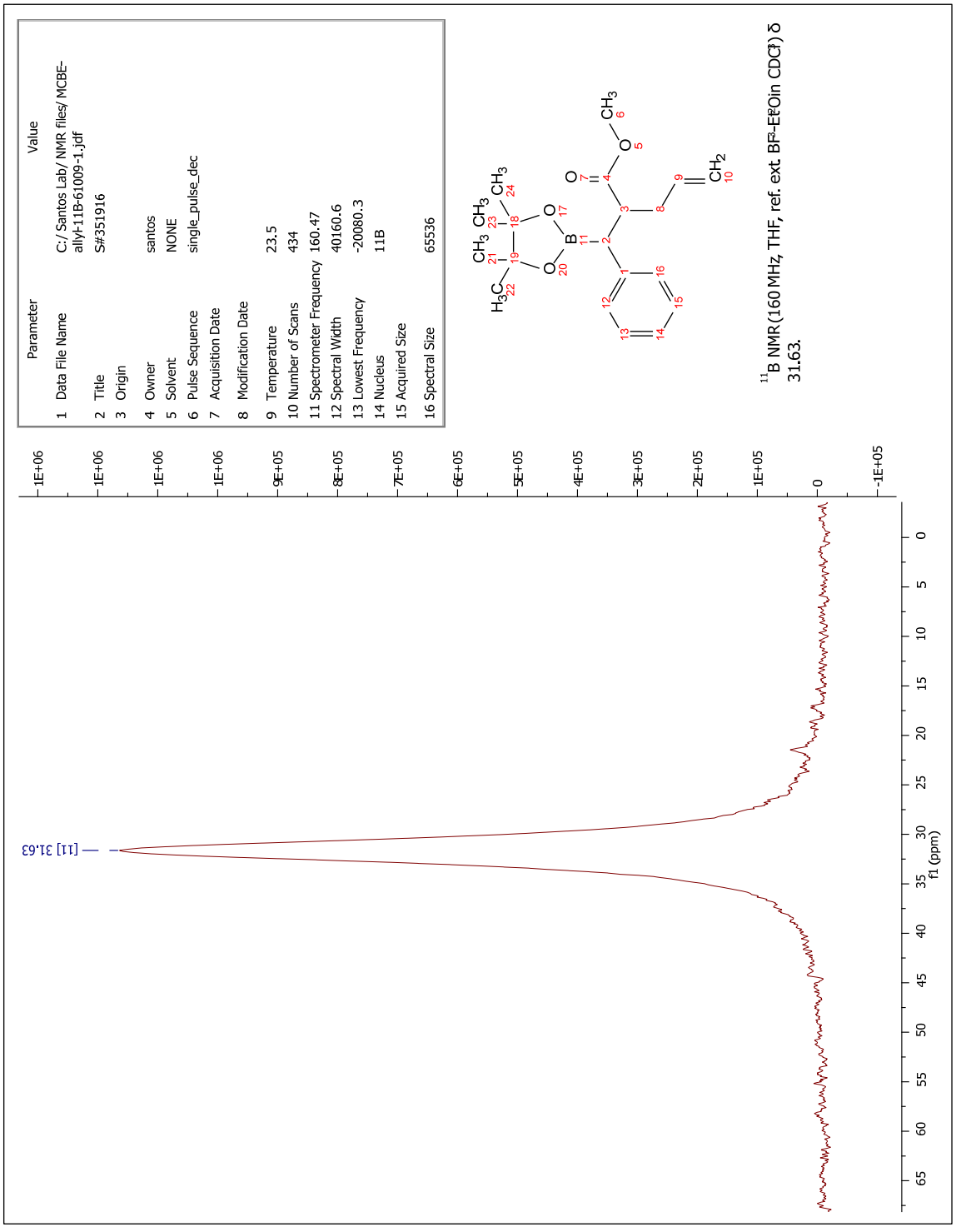
Compound **2.21**



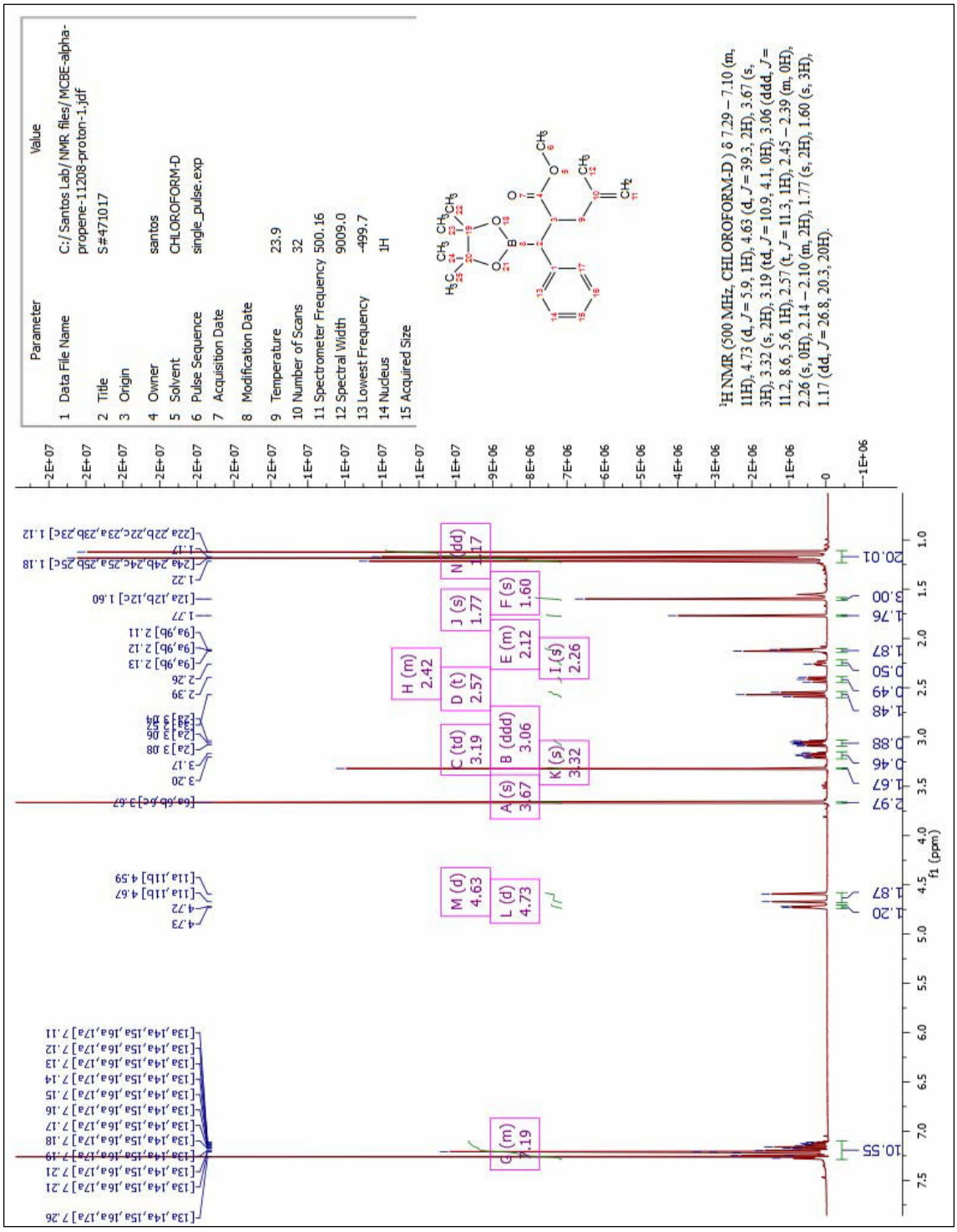
Compound **2.21**



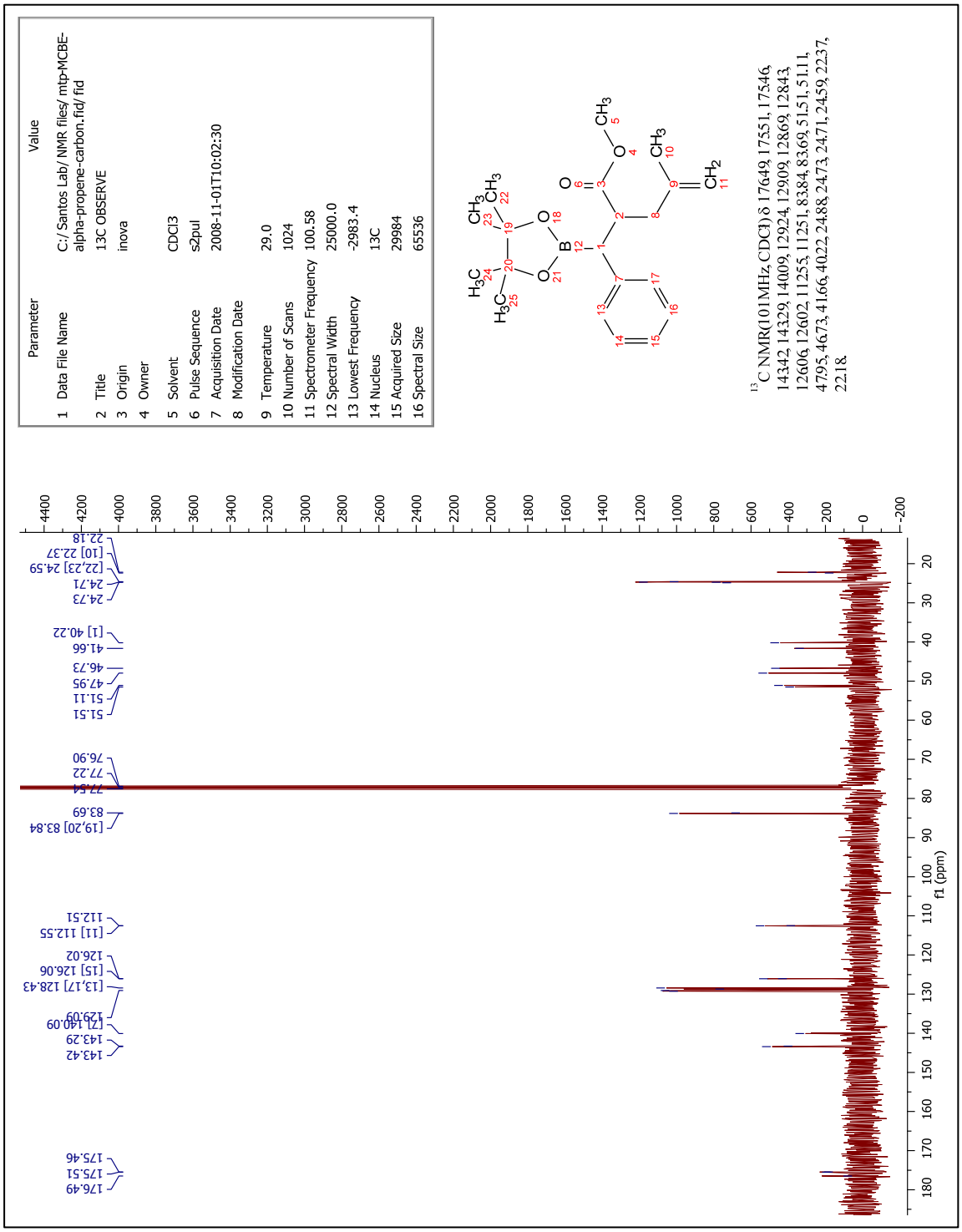
Compound **2.21**



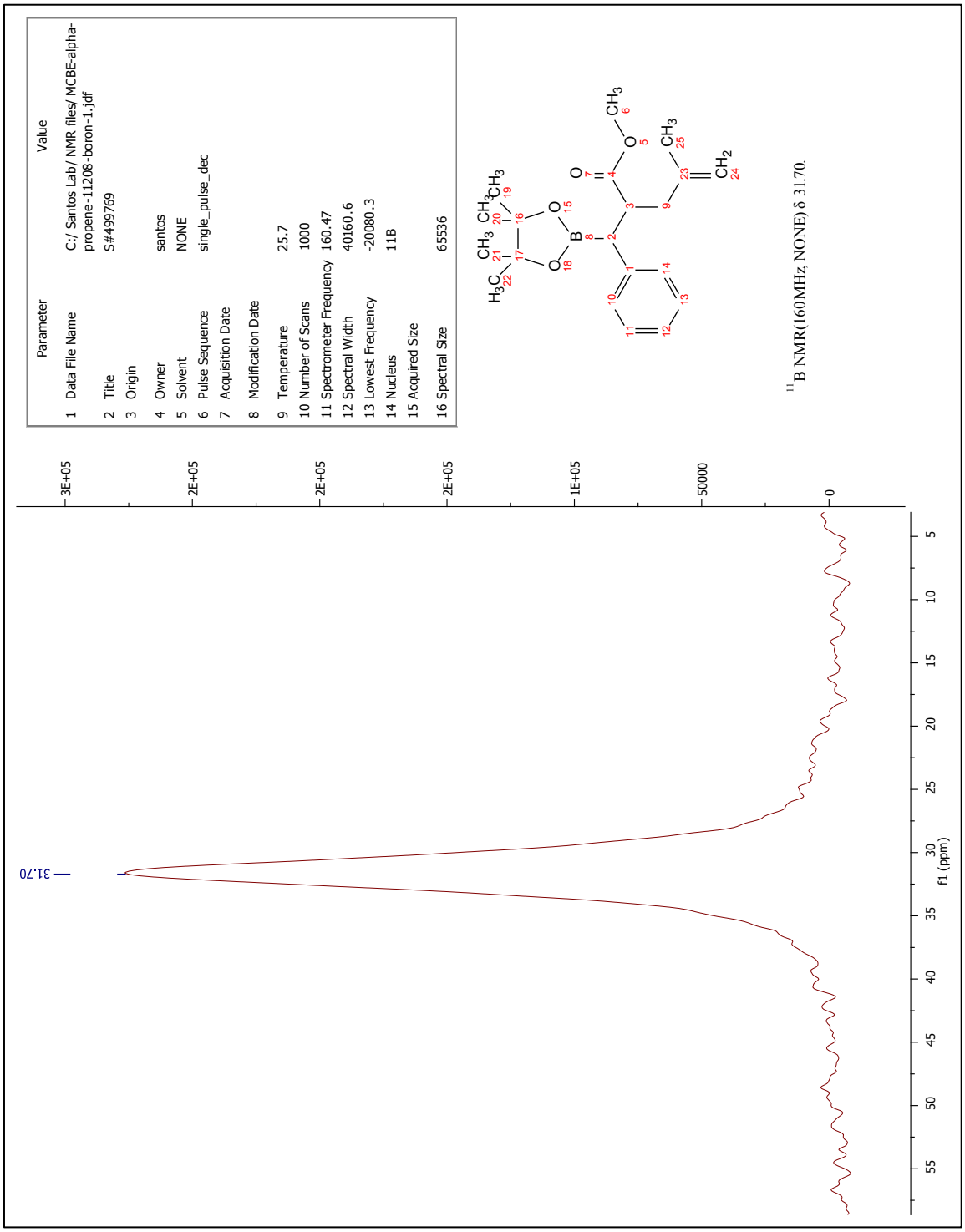
Compound **2.22**



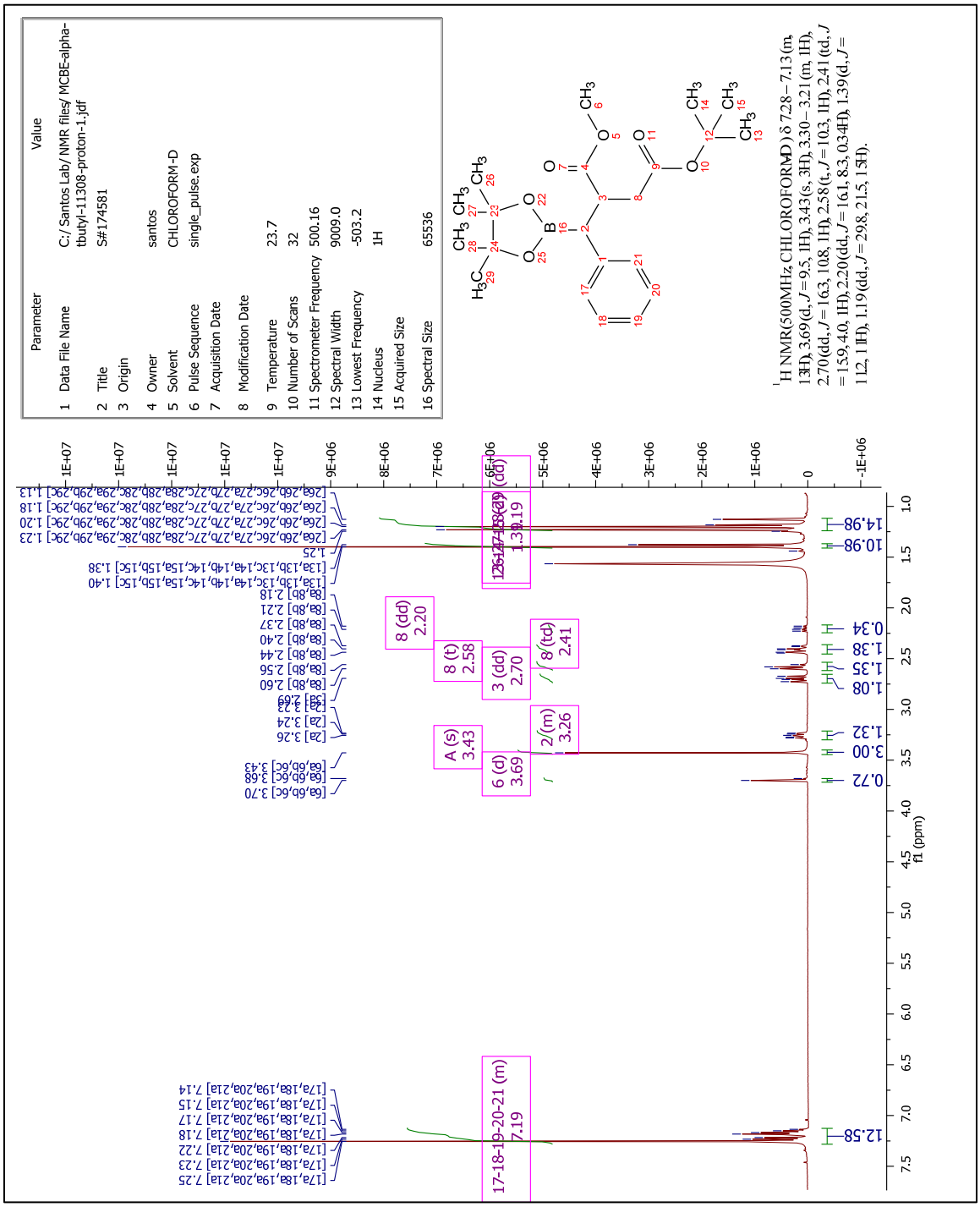
Compound **2.22**



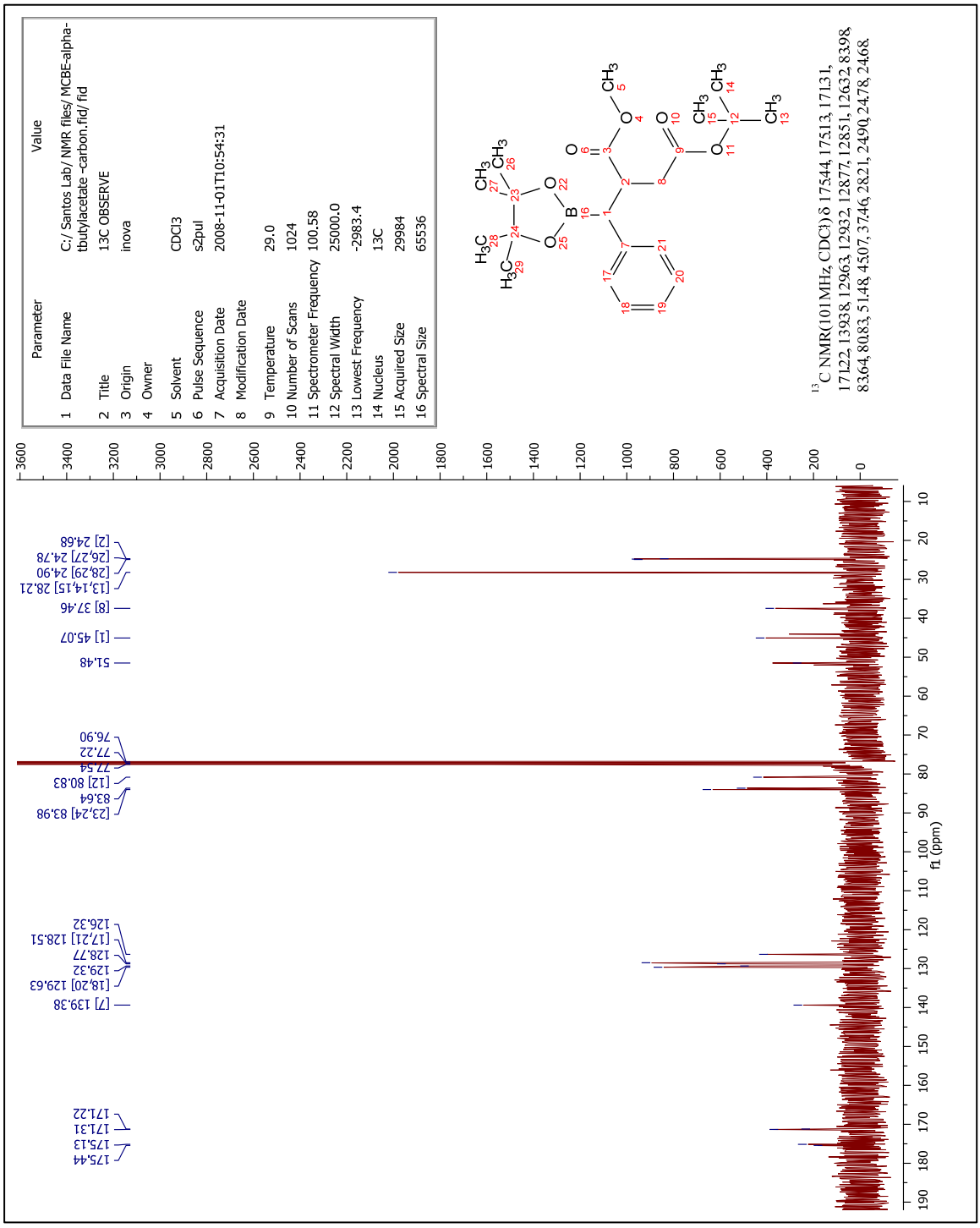
Compound **2.22**



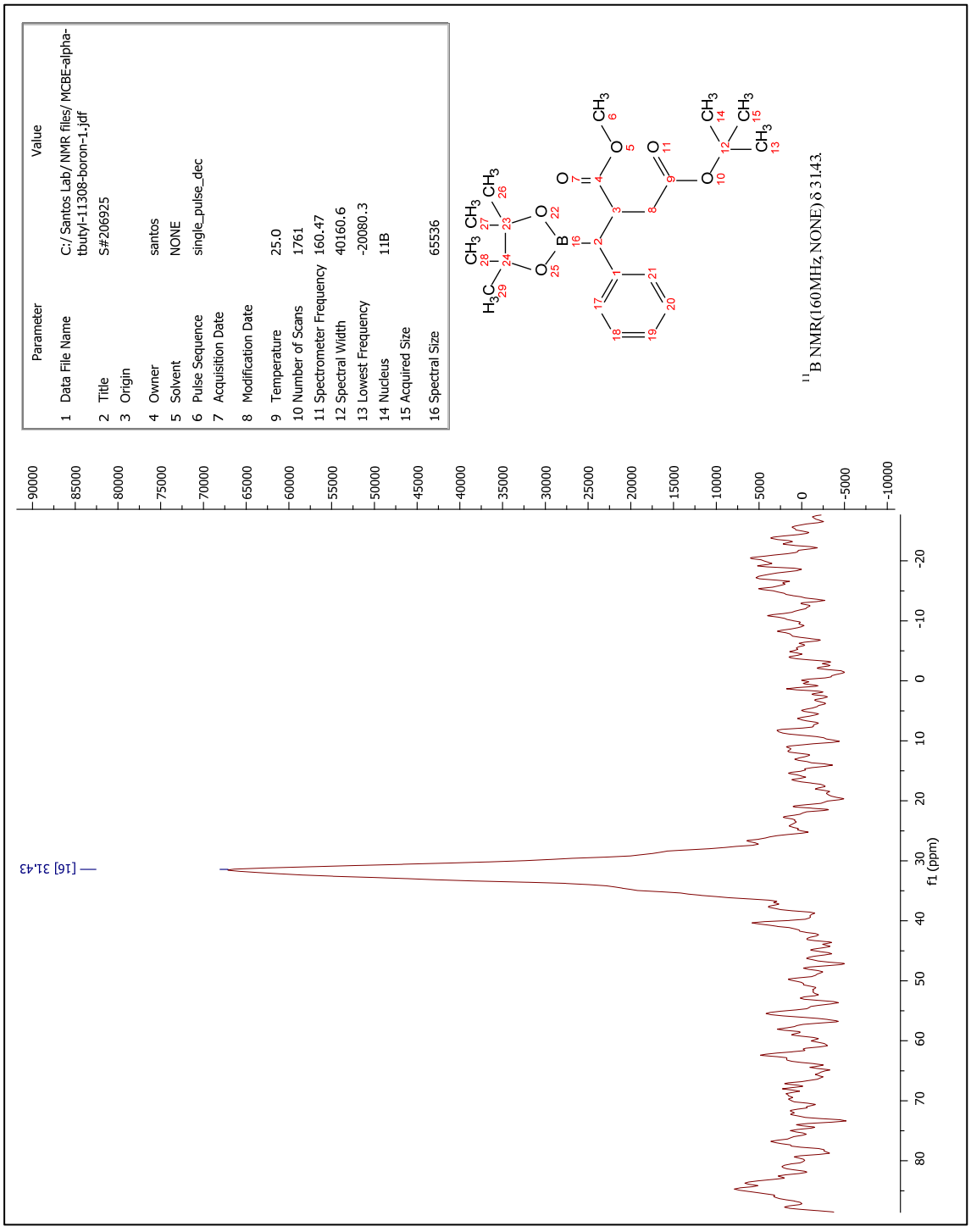
Compound **2.23**



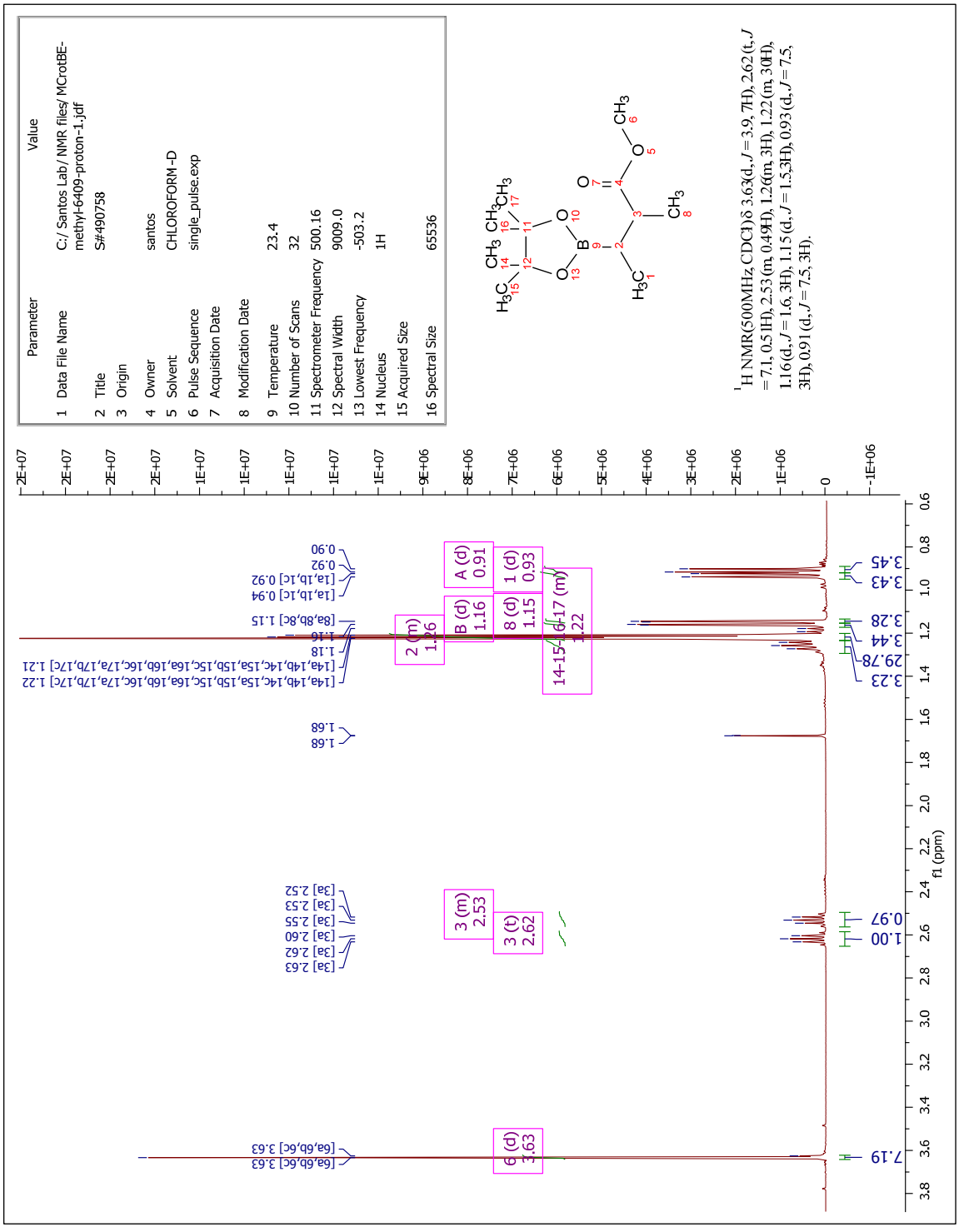
Compound **2.23**



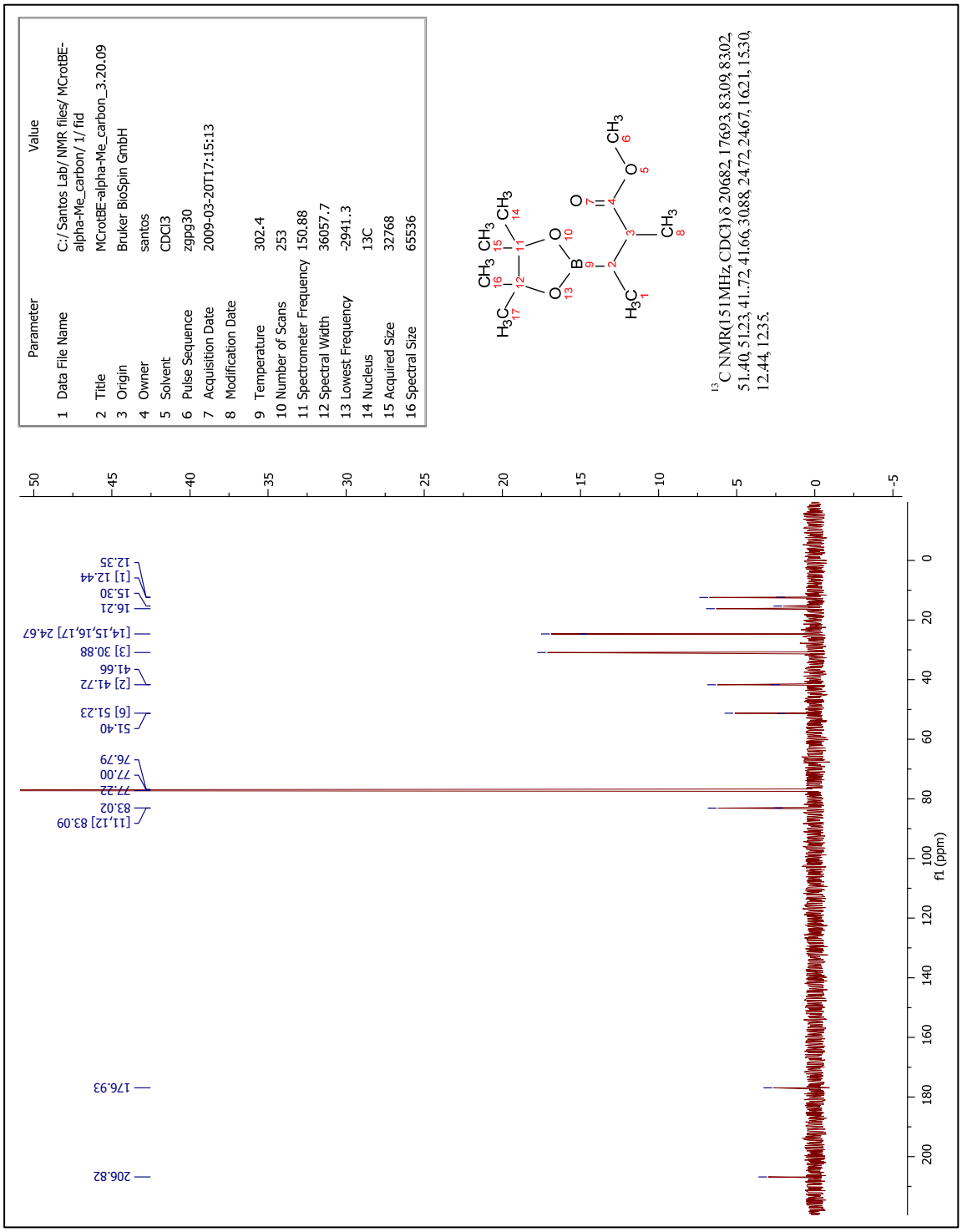
Compound **2.23**



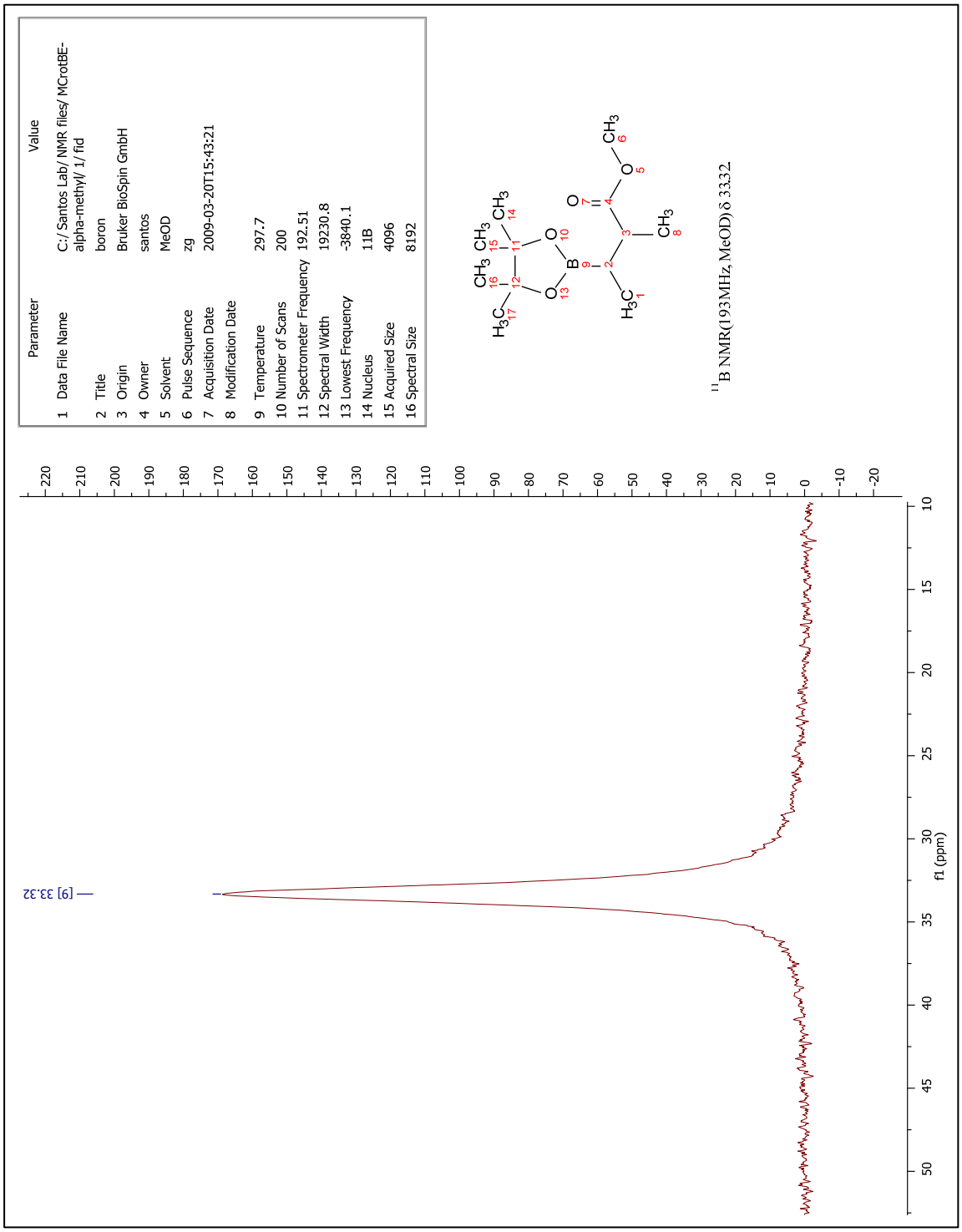
Compound **2.24**



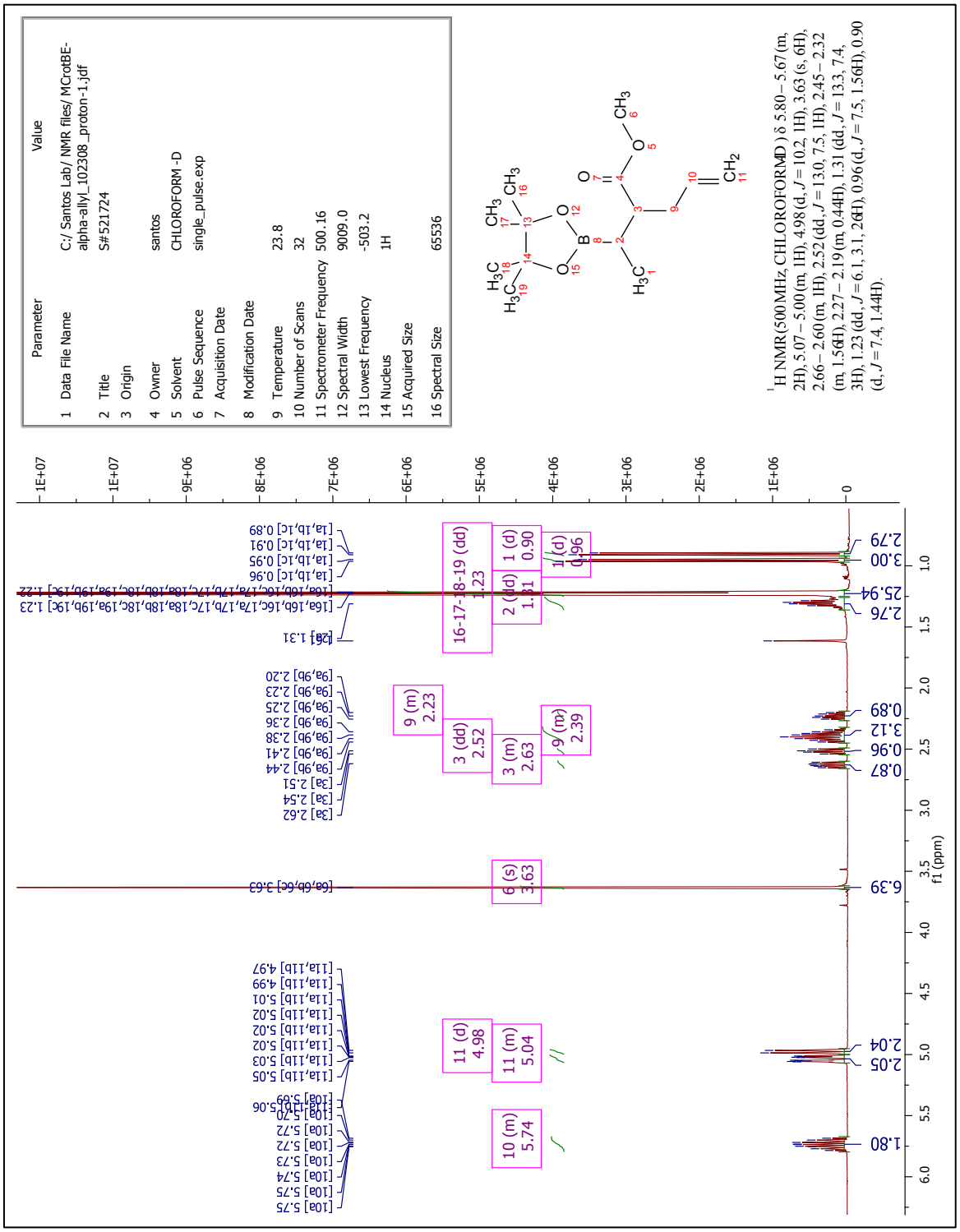
Compound **2.24**



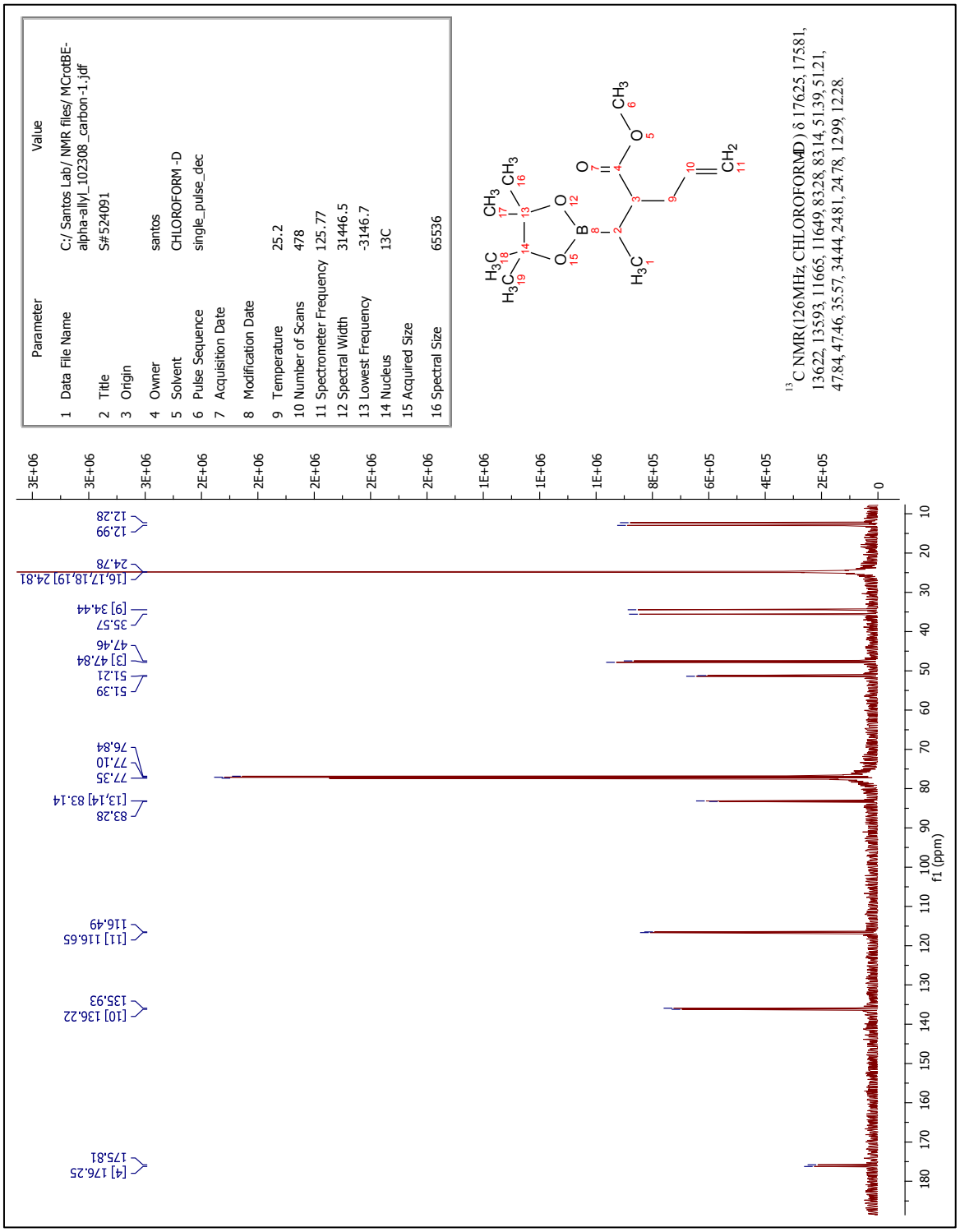
Compound **2.24**



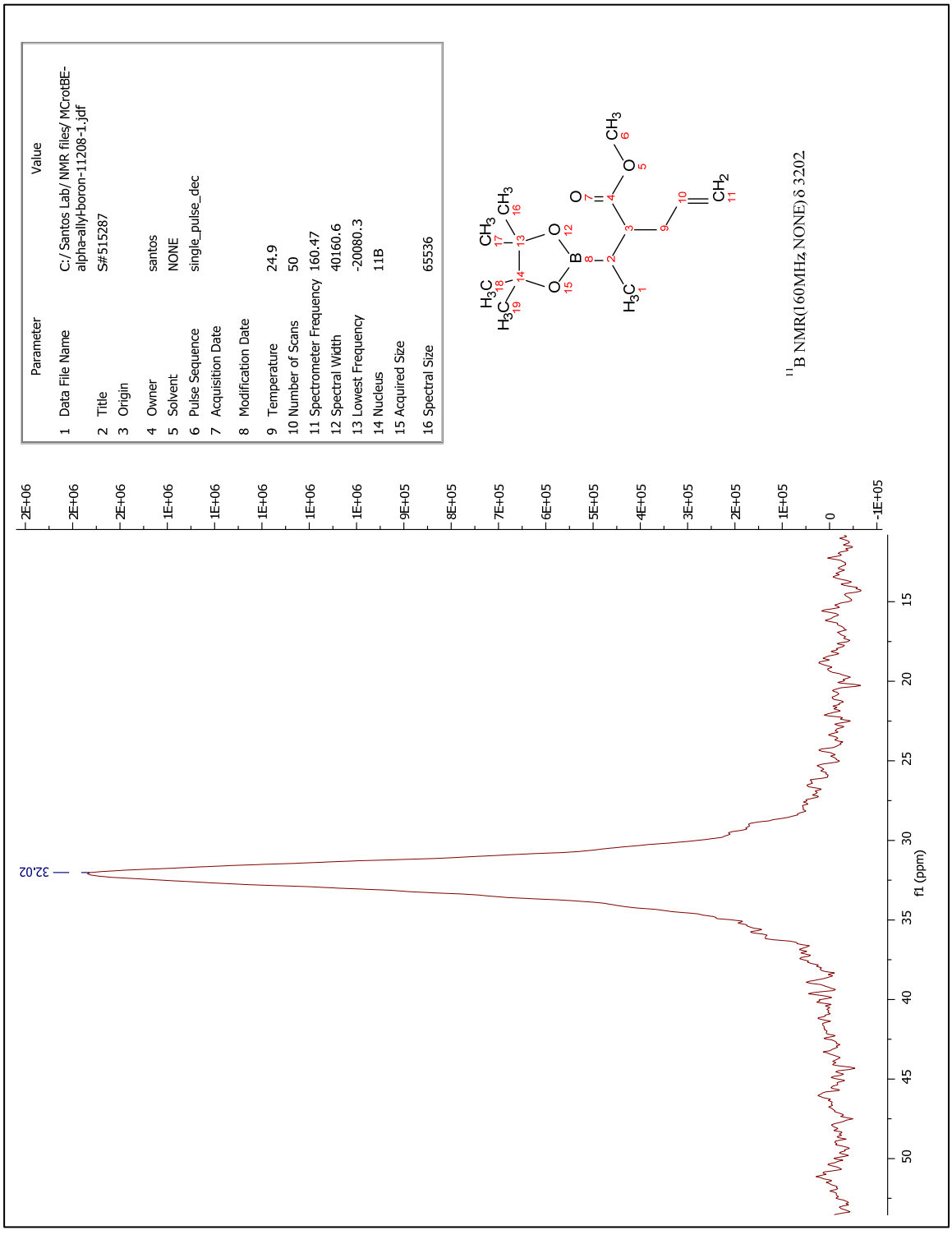
Compound **2.25**



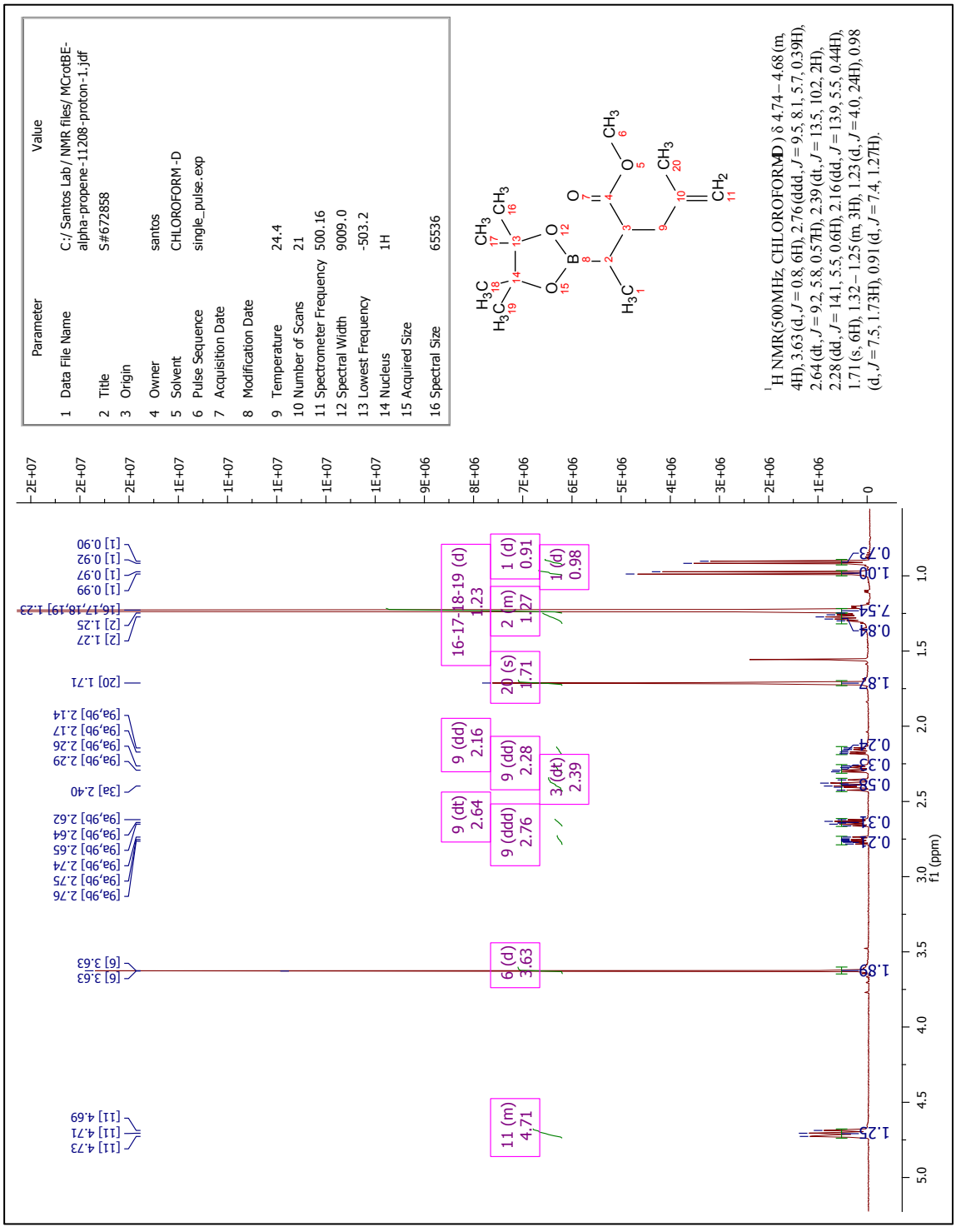
Compound **2.25**



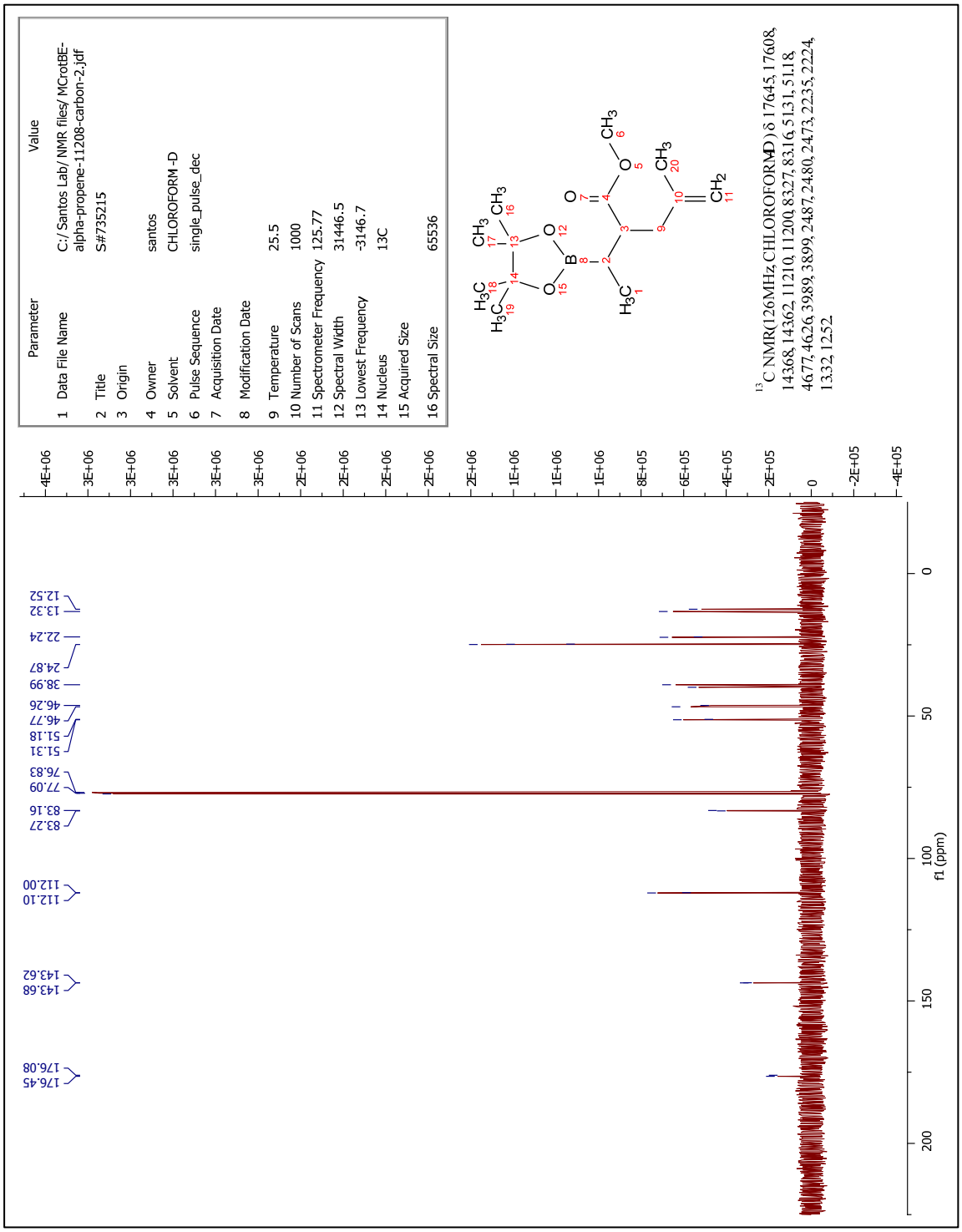
Compound **2.25**



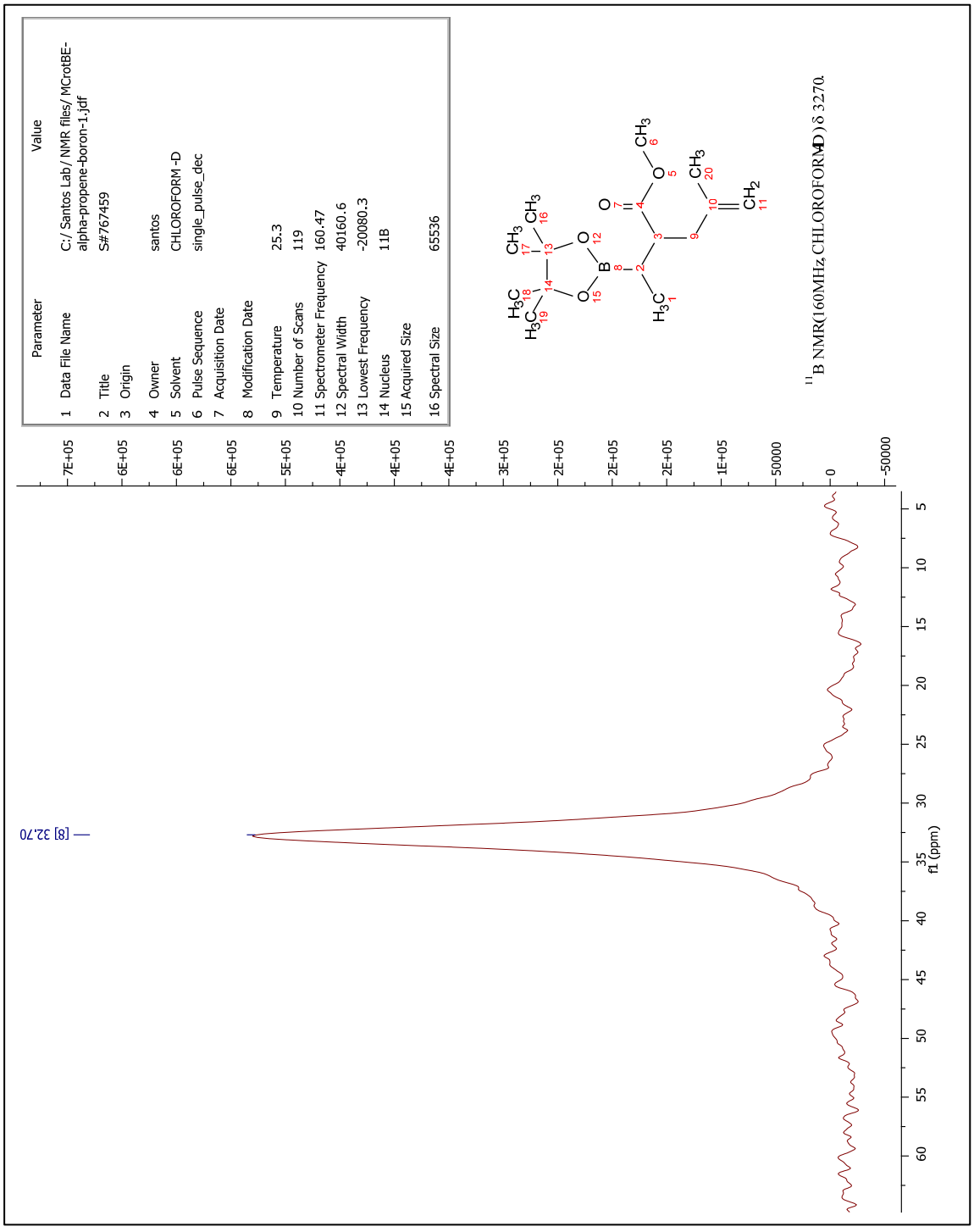
Compound **2.26**



Compound **2.26**

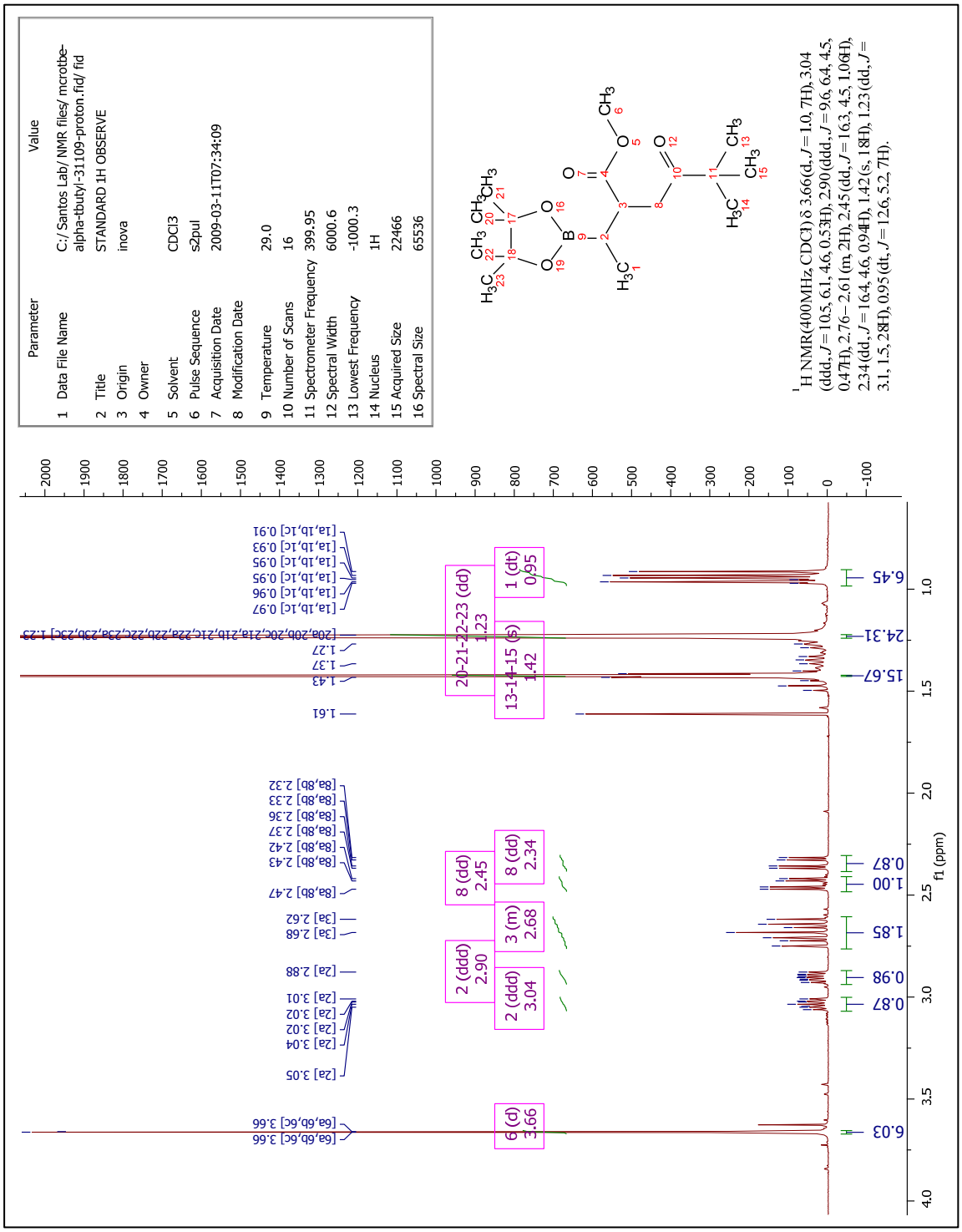


Compound **2.26**

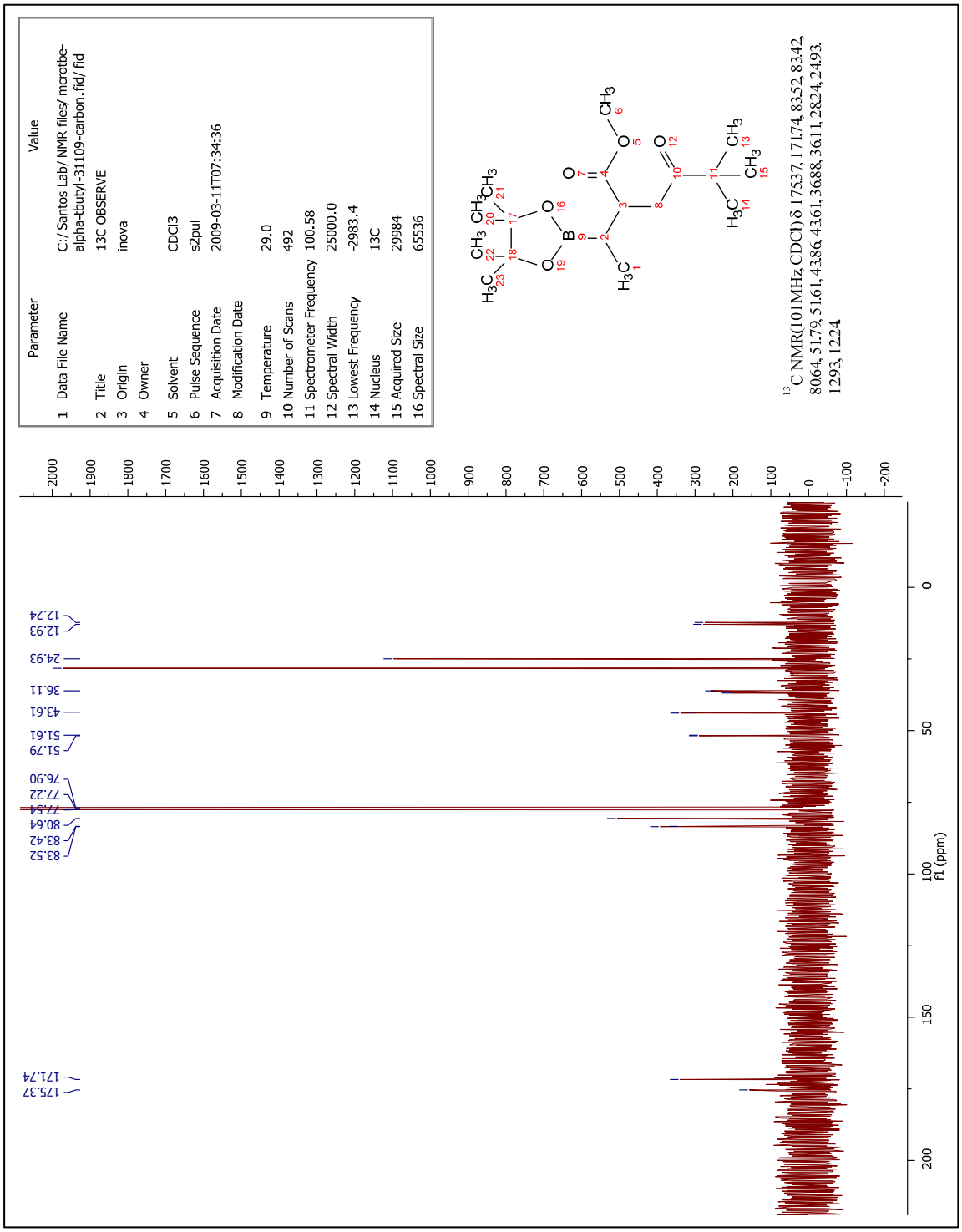


^{11}B NMR(160MHz, CHLOROFORM-D) δ 32.70

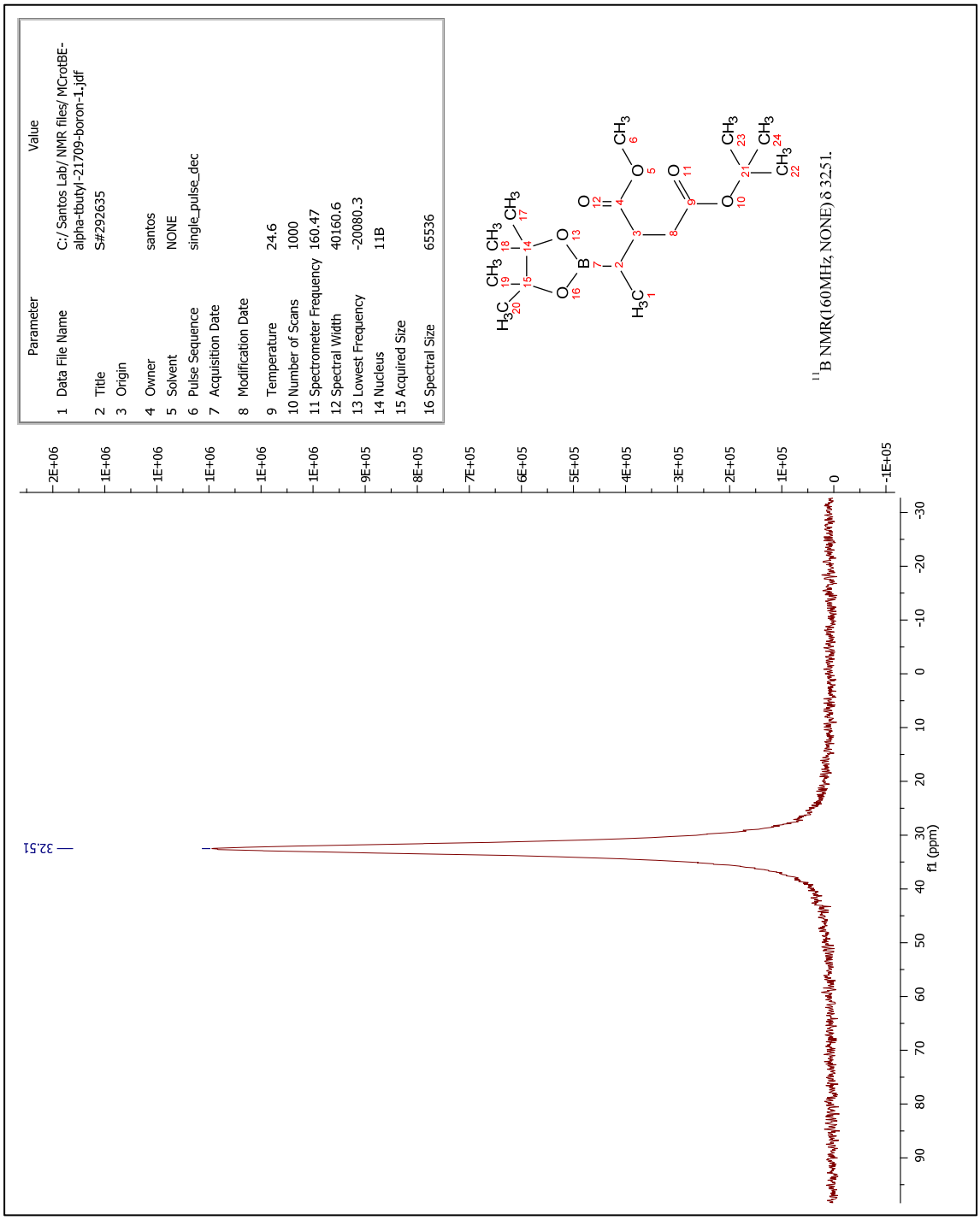
Compound **2.27**



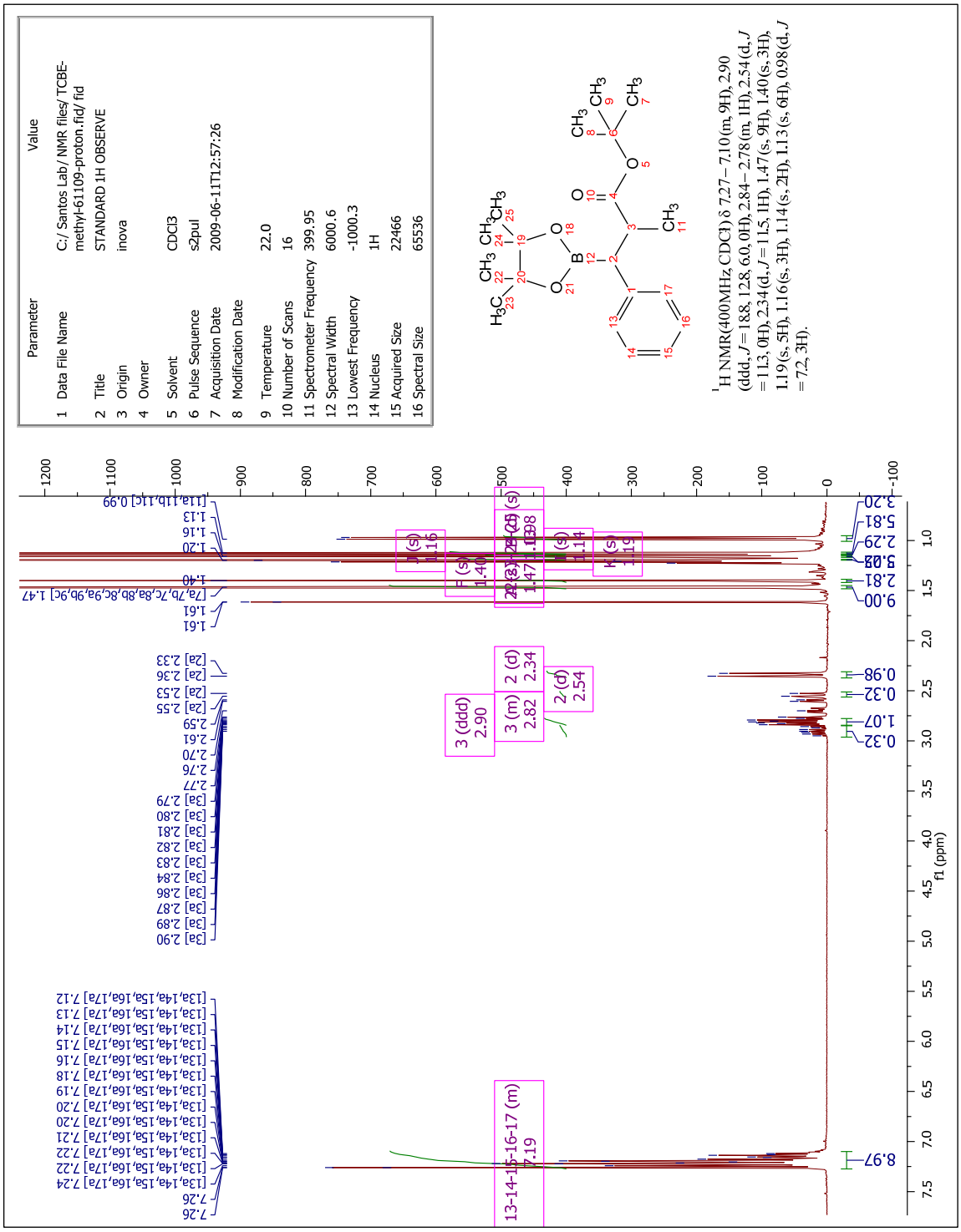
Compound **2.27**



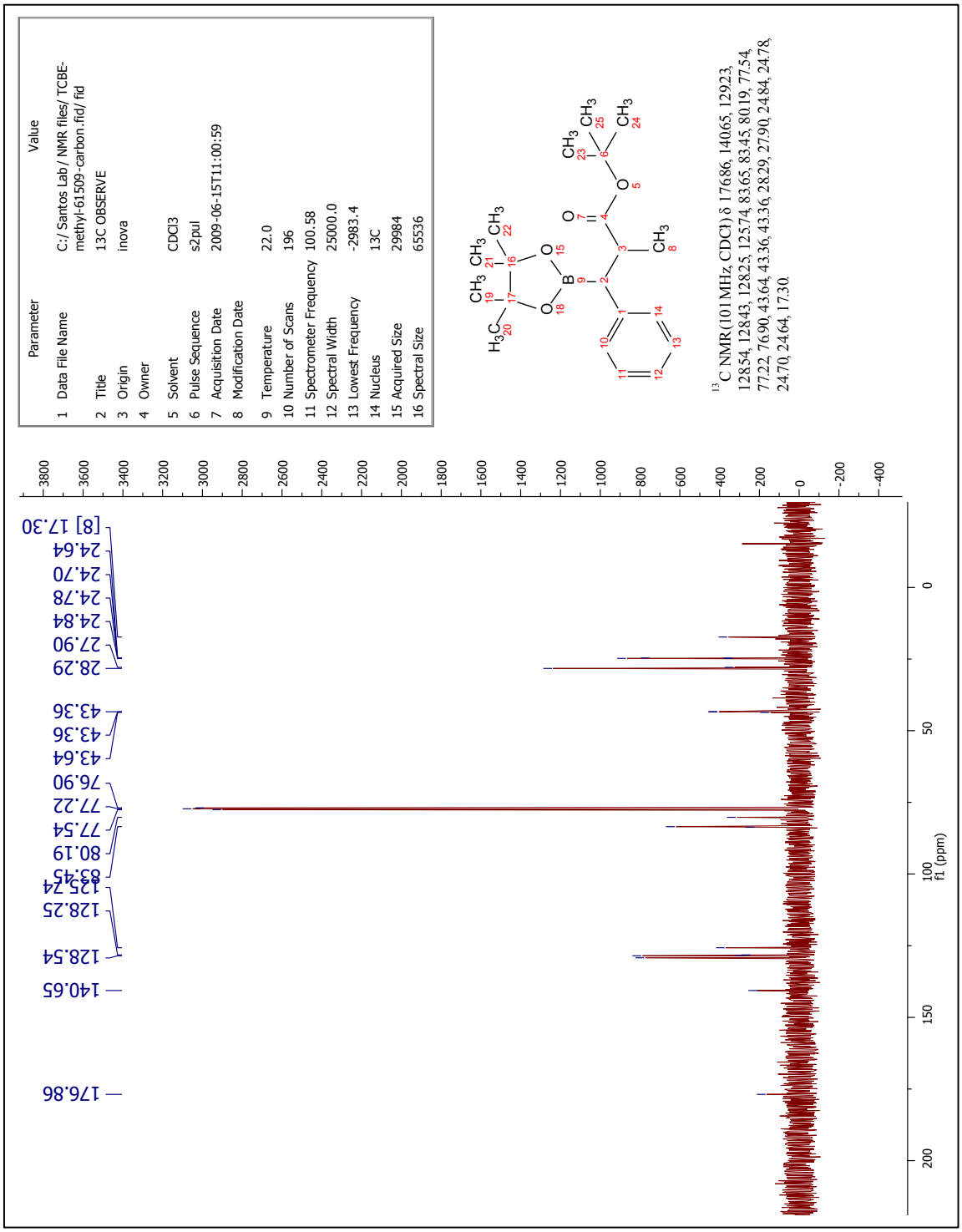
Compound **2.27**



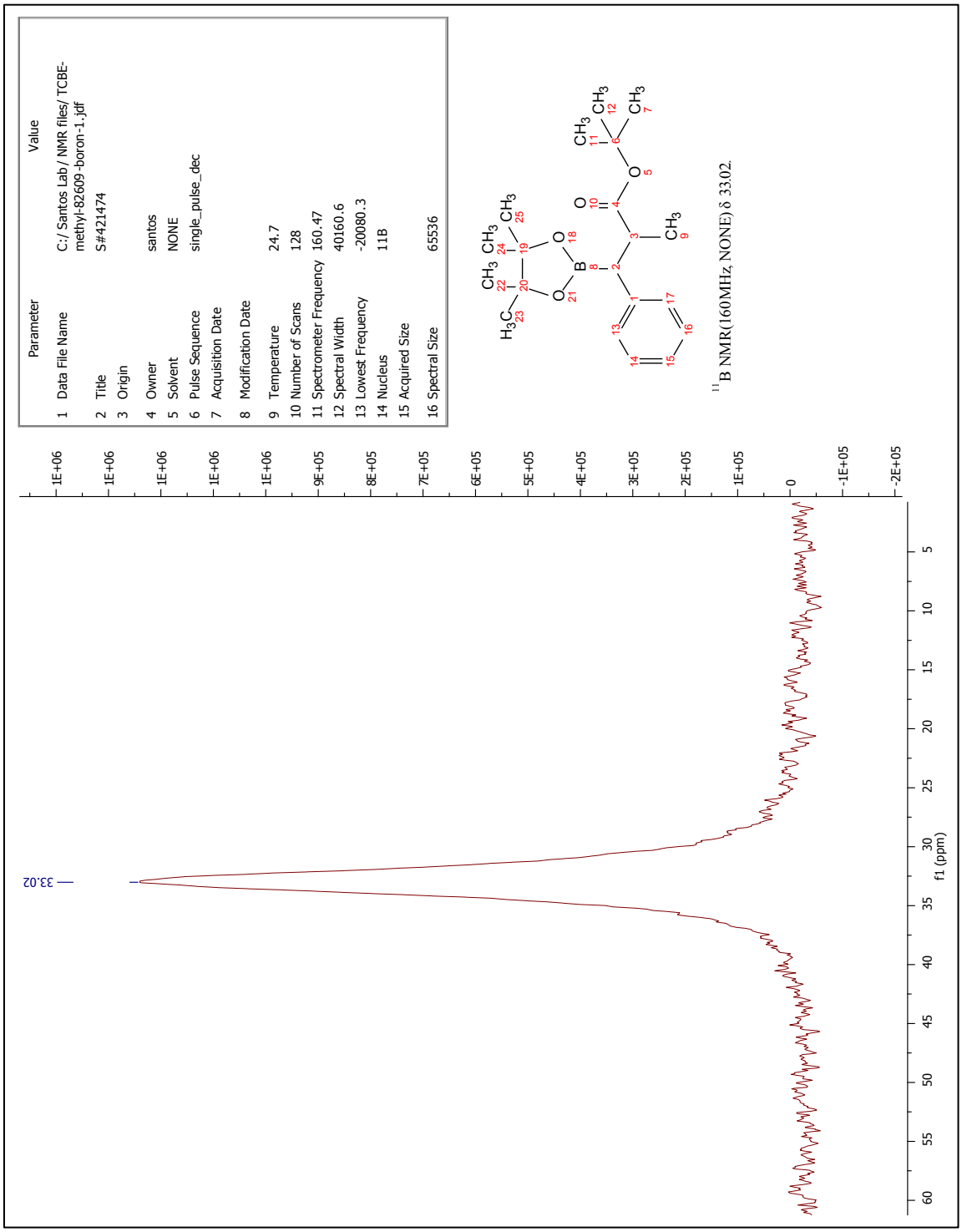
Compound **2.28**



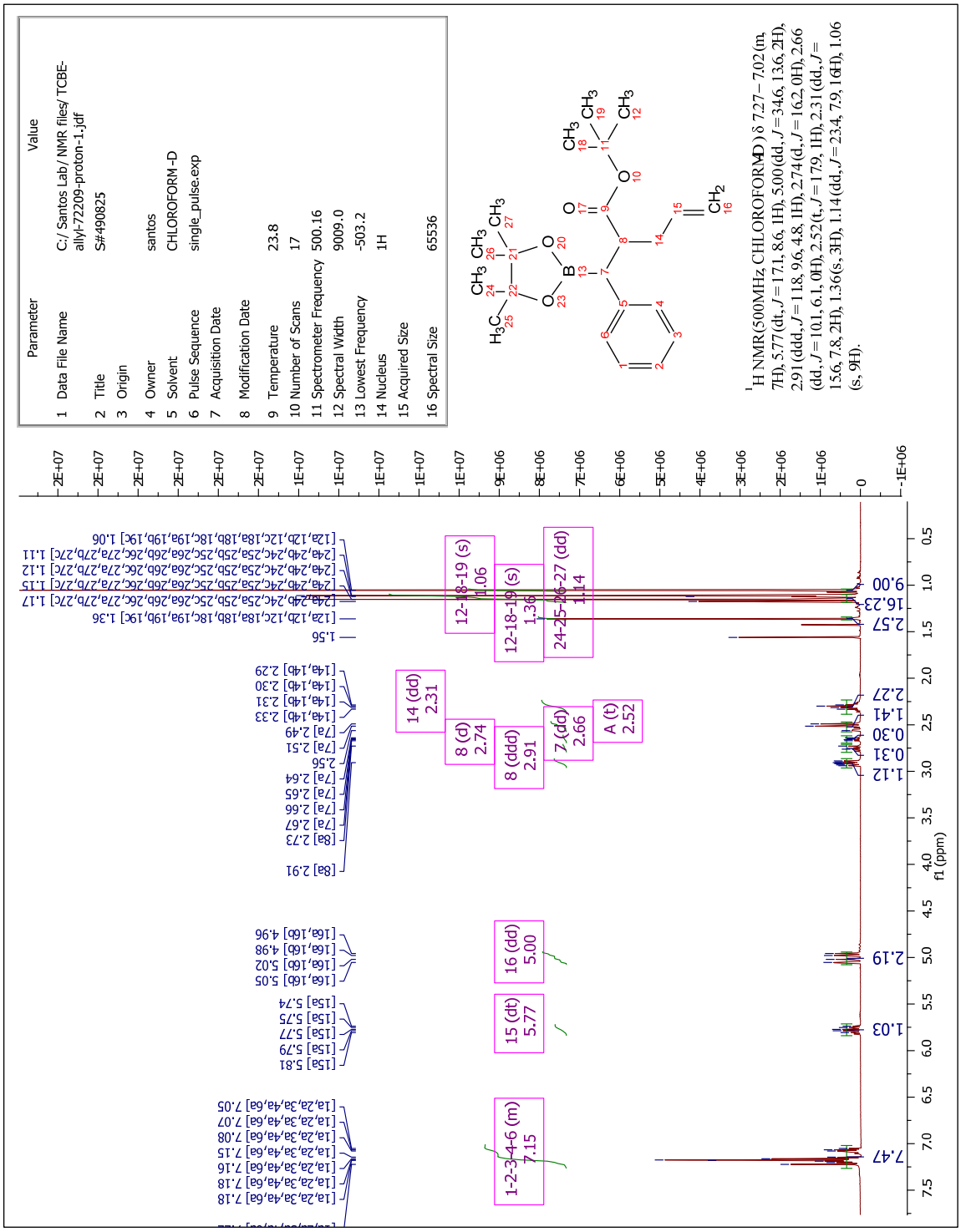
Compound **2.28**



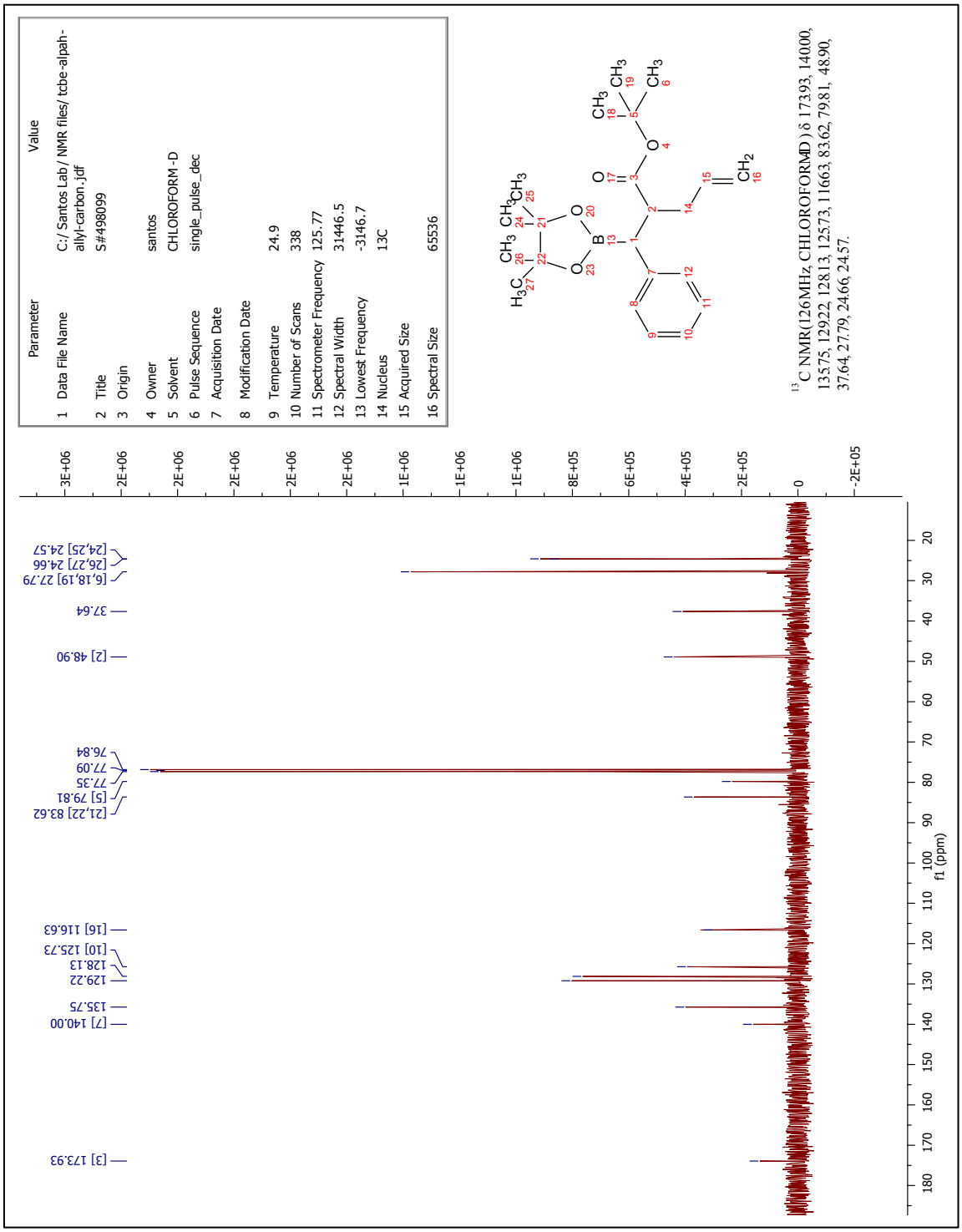
Compound **2.28**



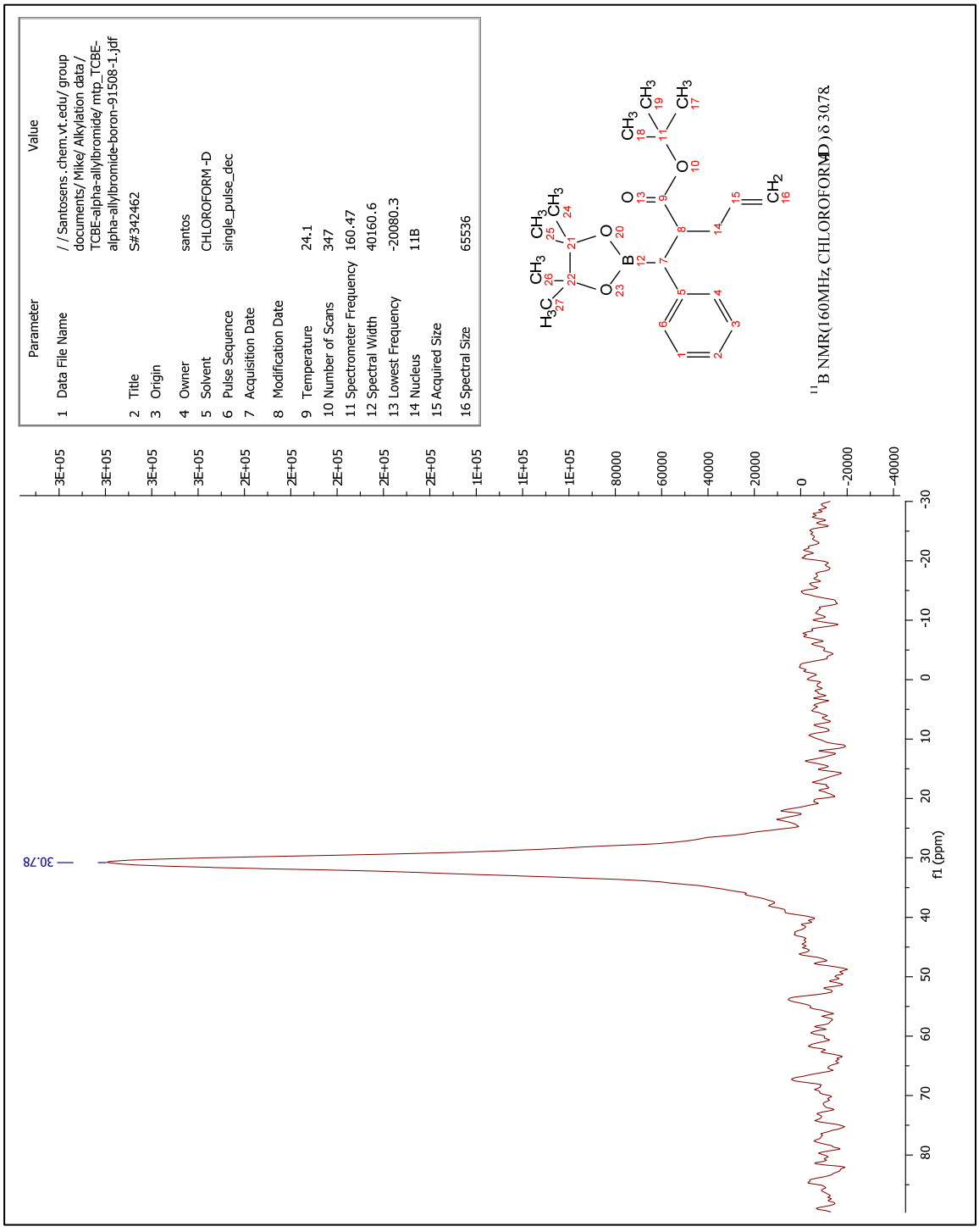
Compound **2.29**



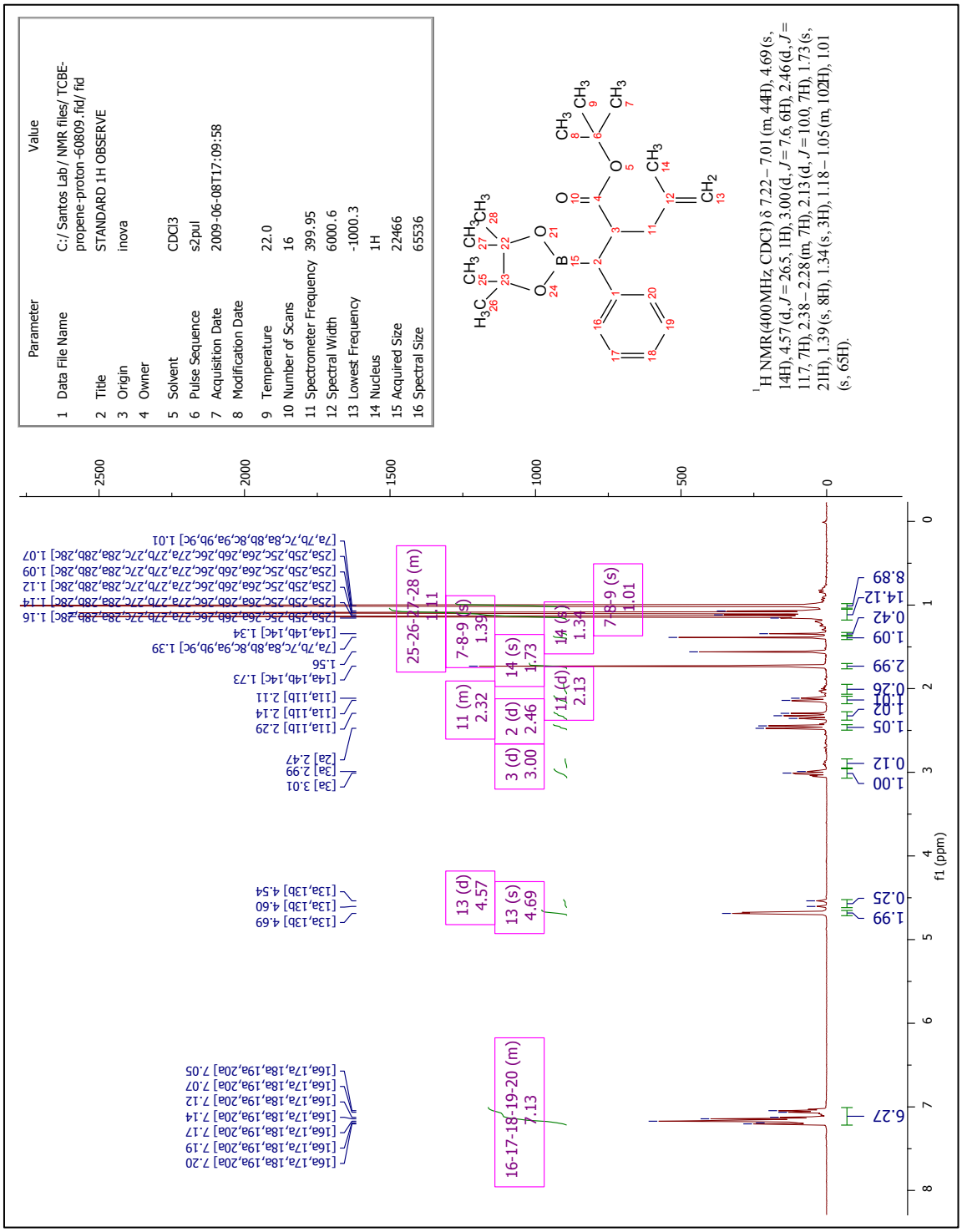
Compound **2.29**



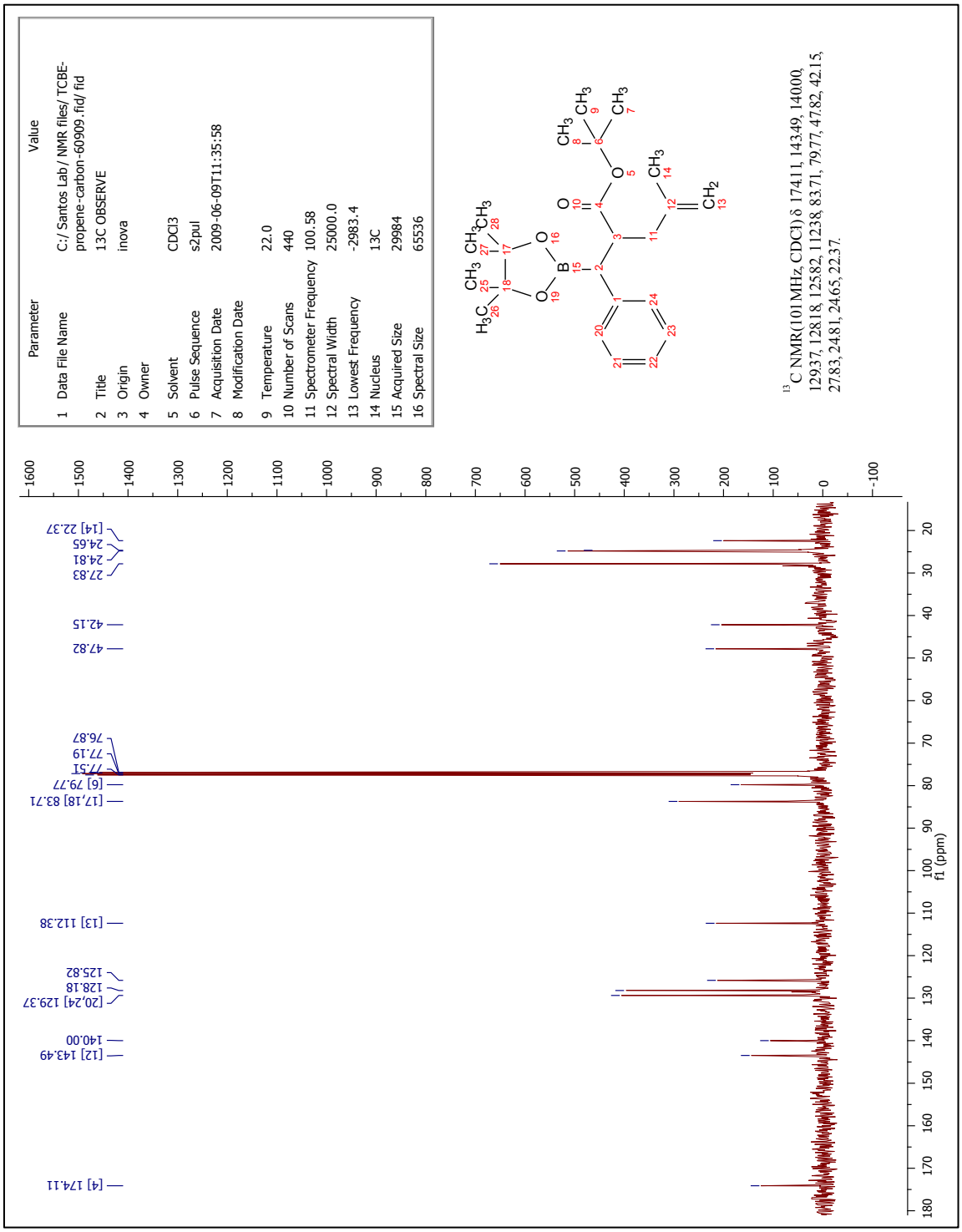
Compound **2.29**



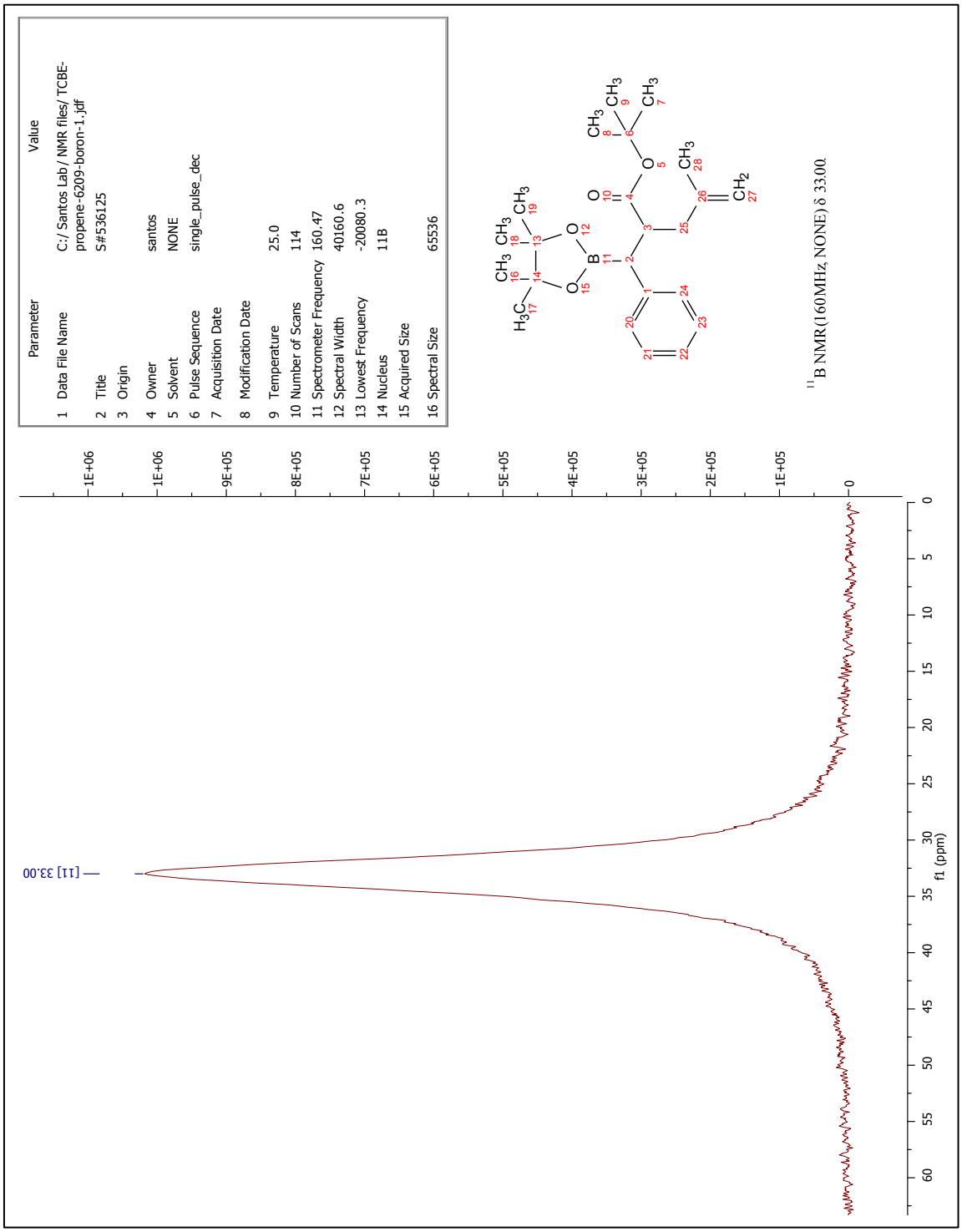
Compound **2.30**



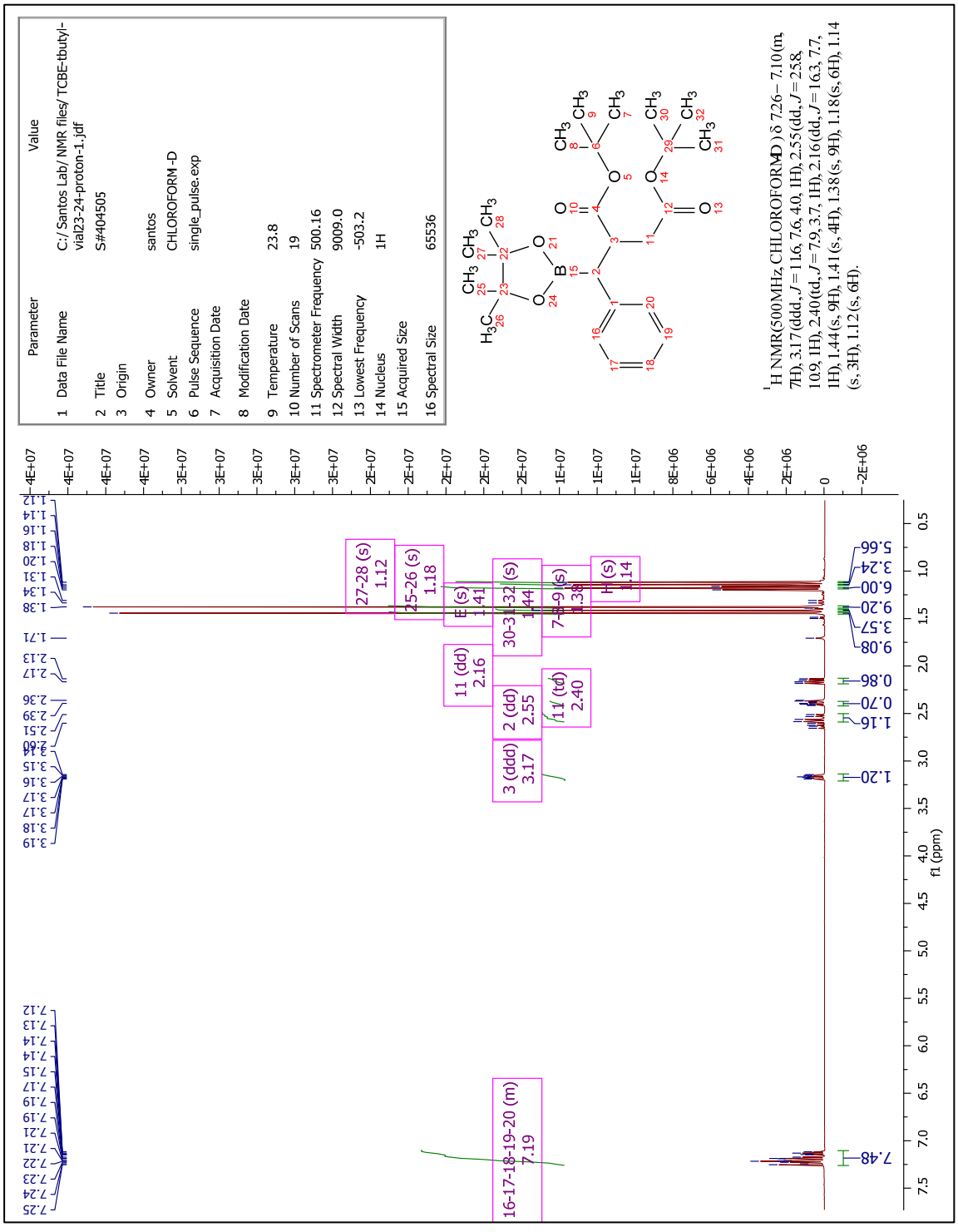
Compound **2.30**



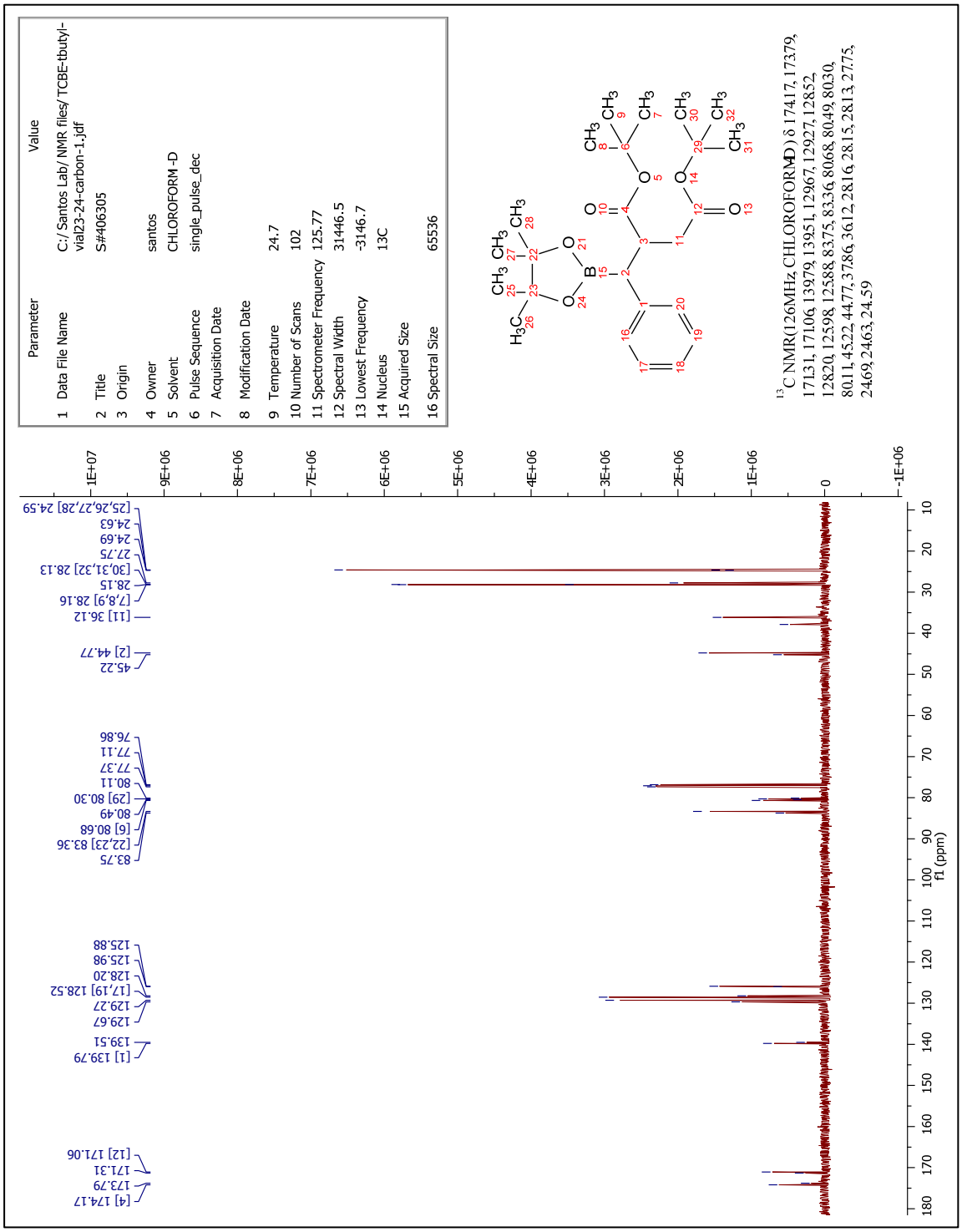
Compound **2.30**



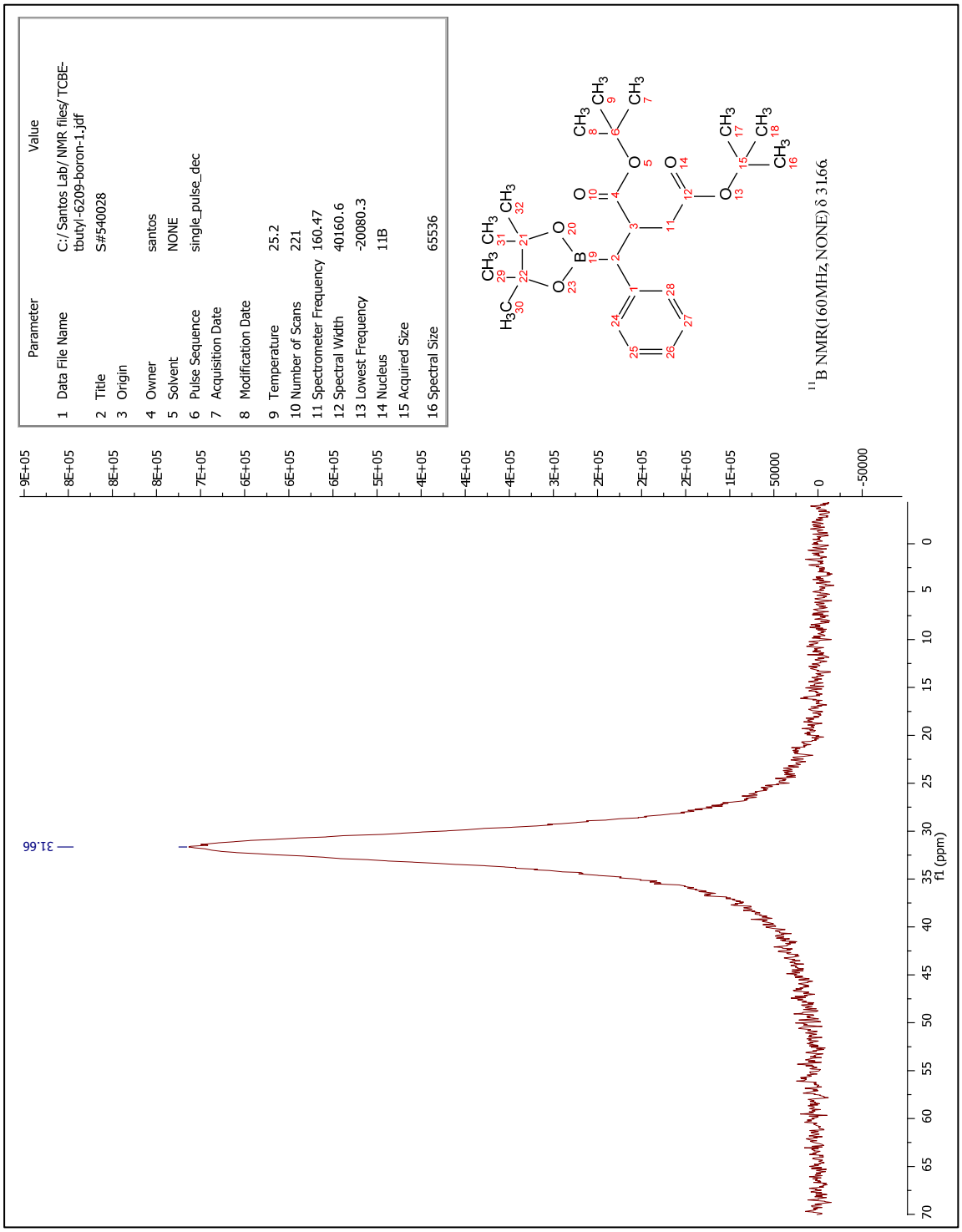
Compound **2.31**



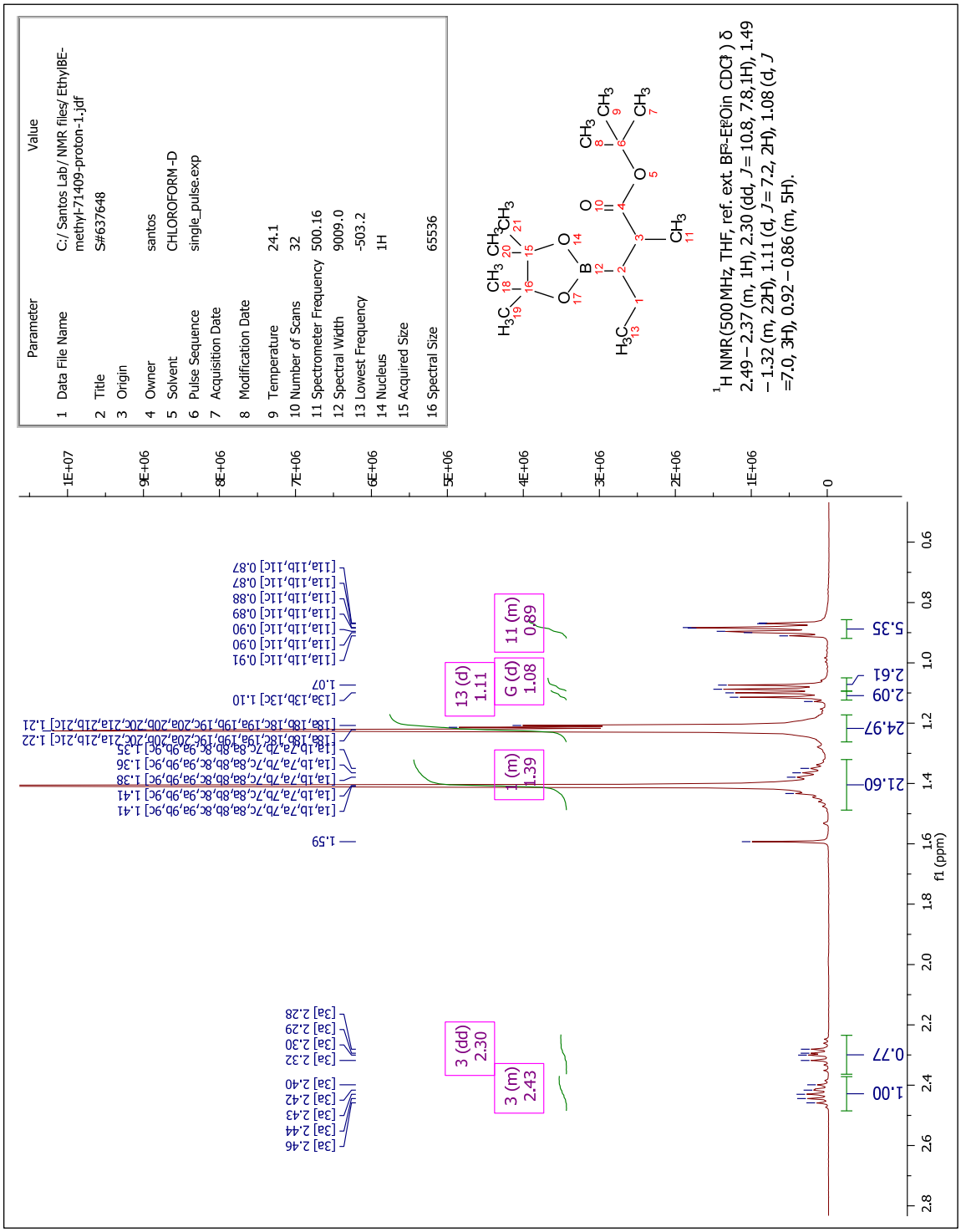
Compound **2.31**



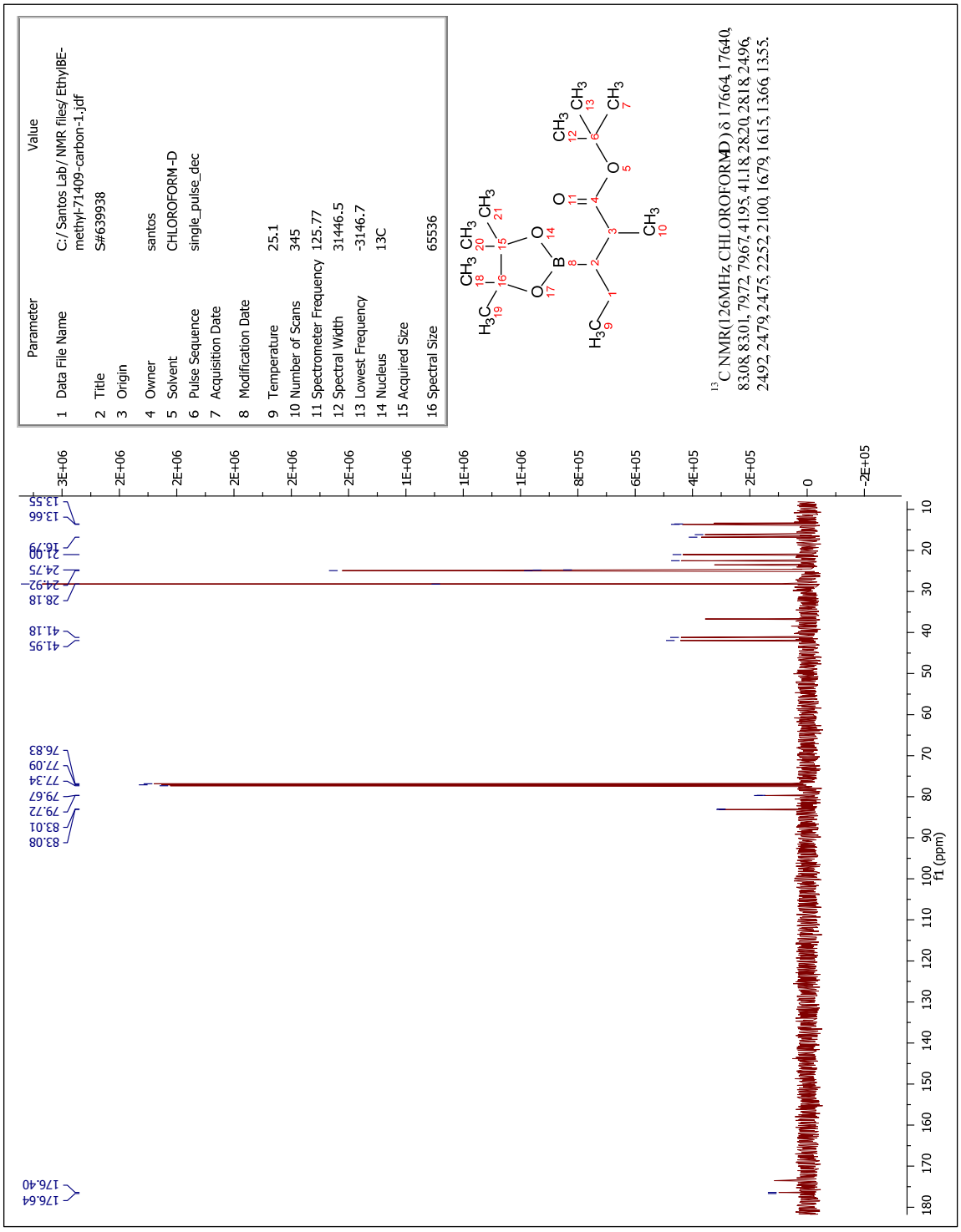
Compound **2.31**



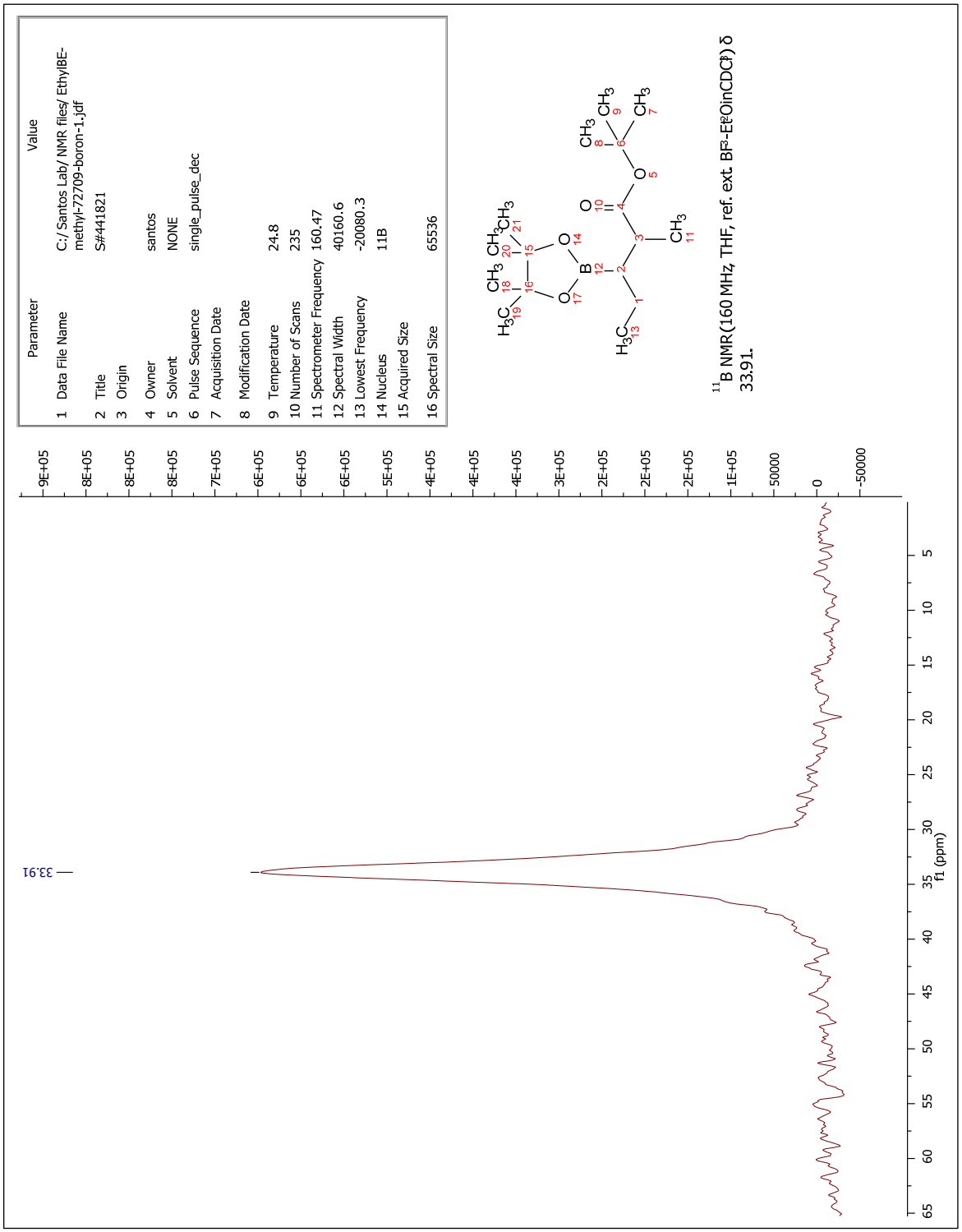
Compound **2.32**



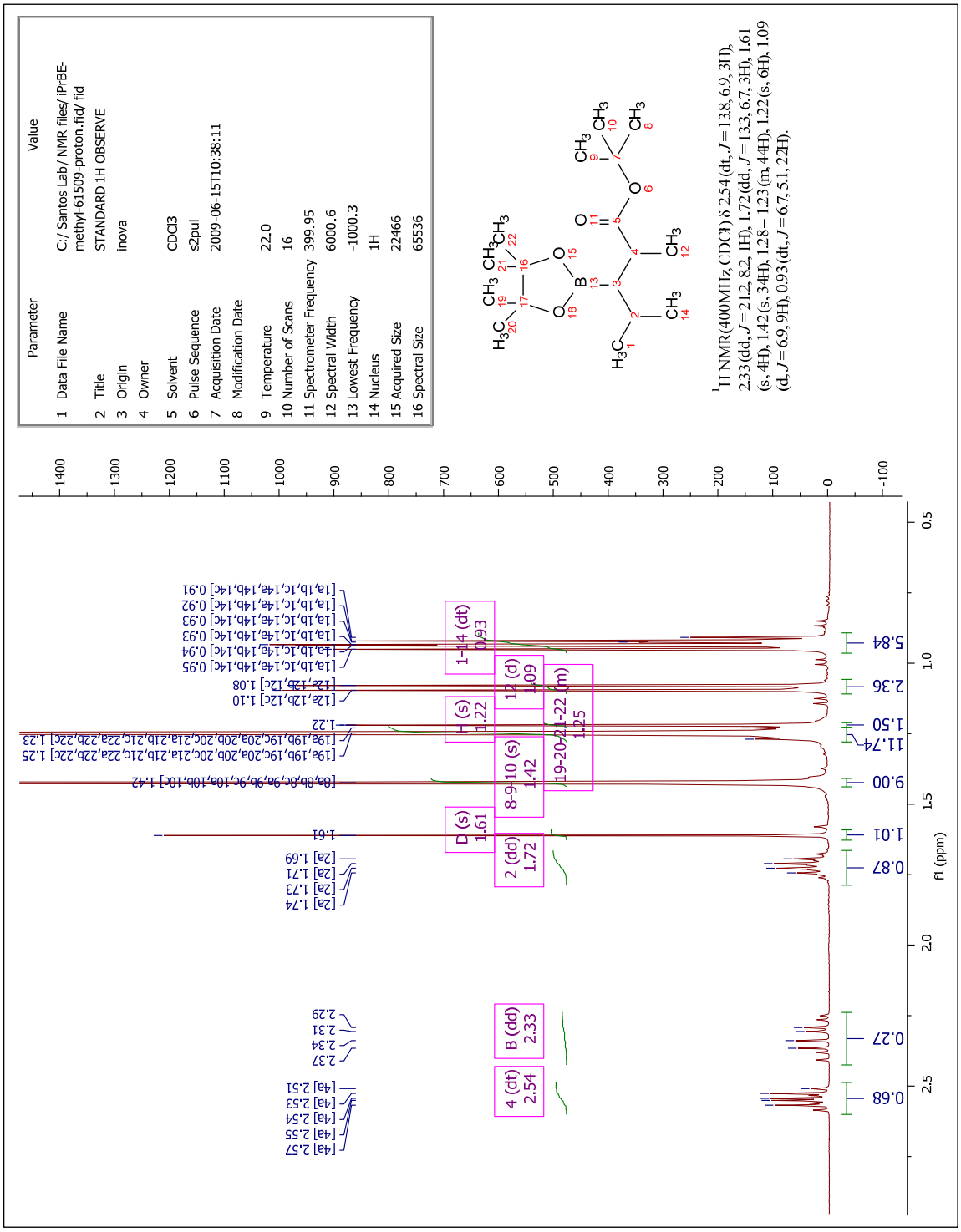
Compound **2.32**



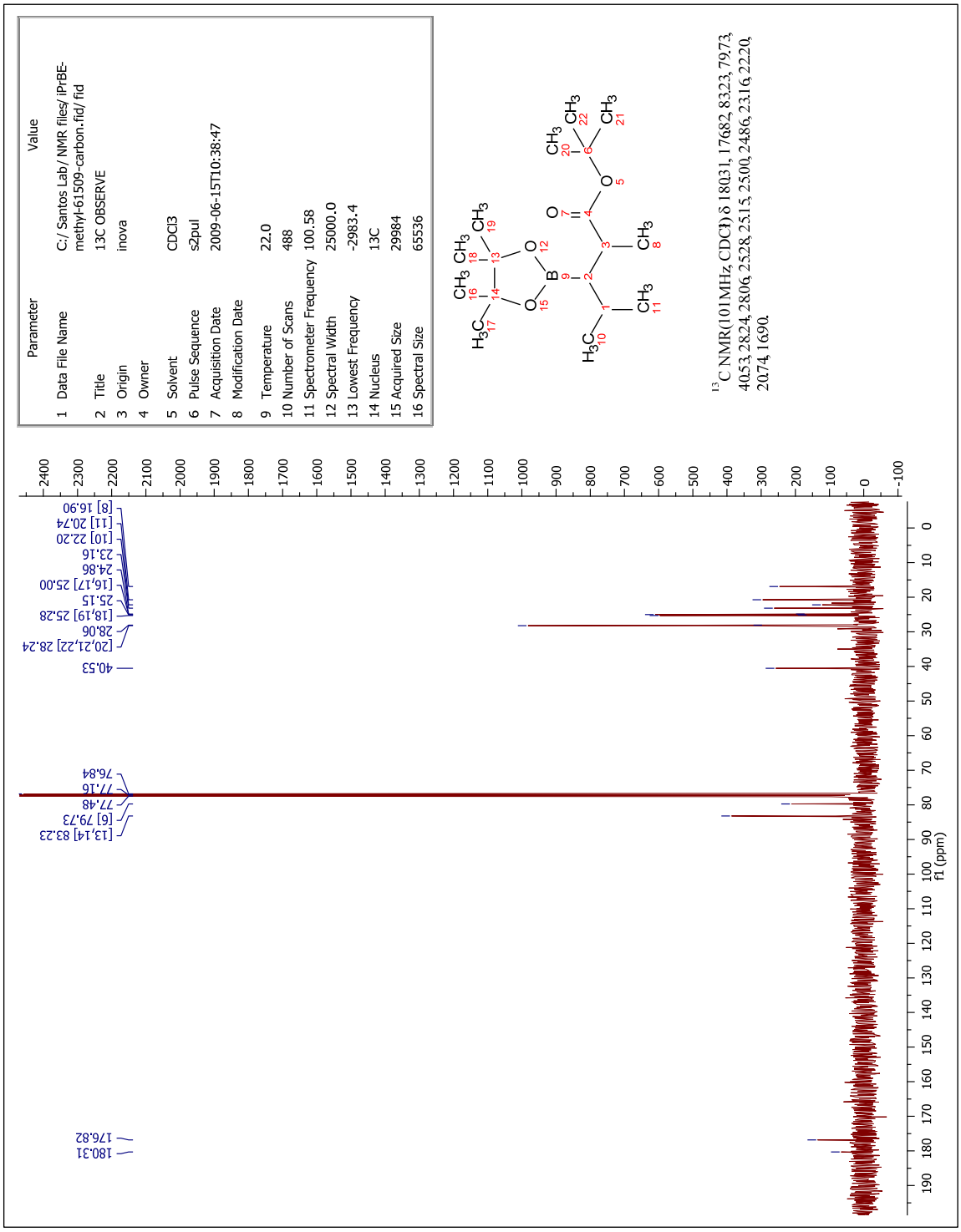
Compound **2.32**



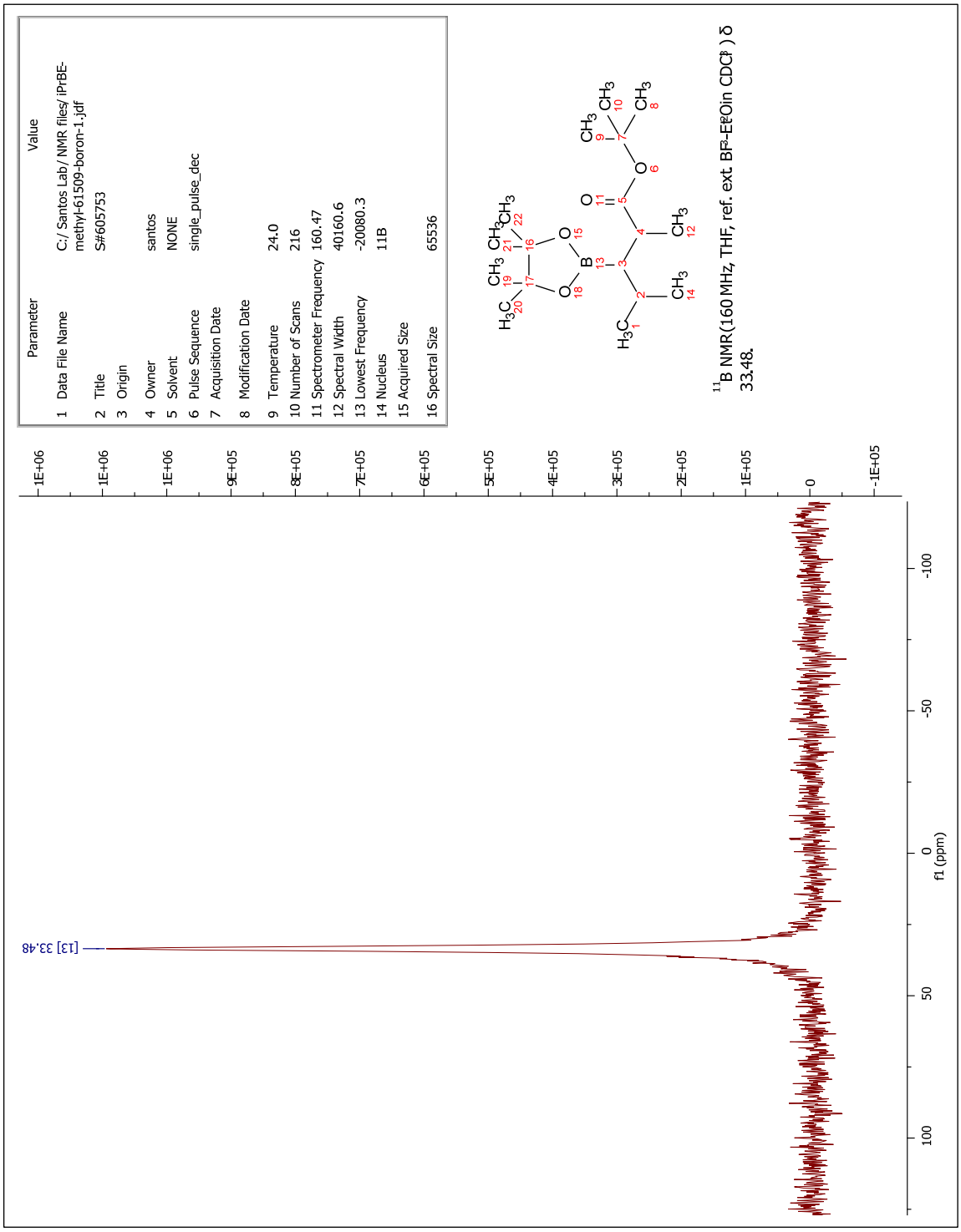
Compound **2.33**



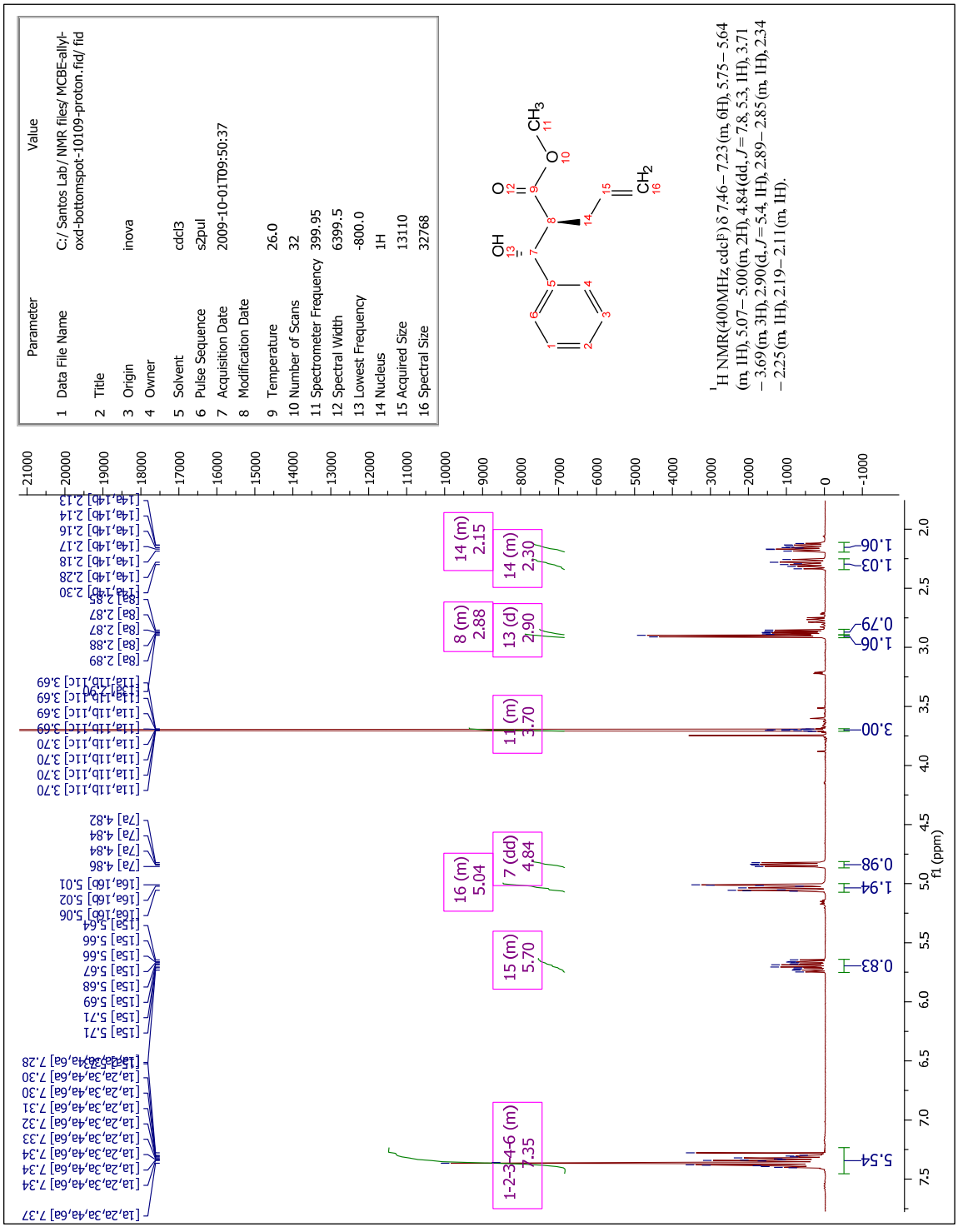
Compound **2.33**



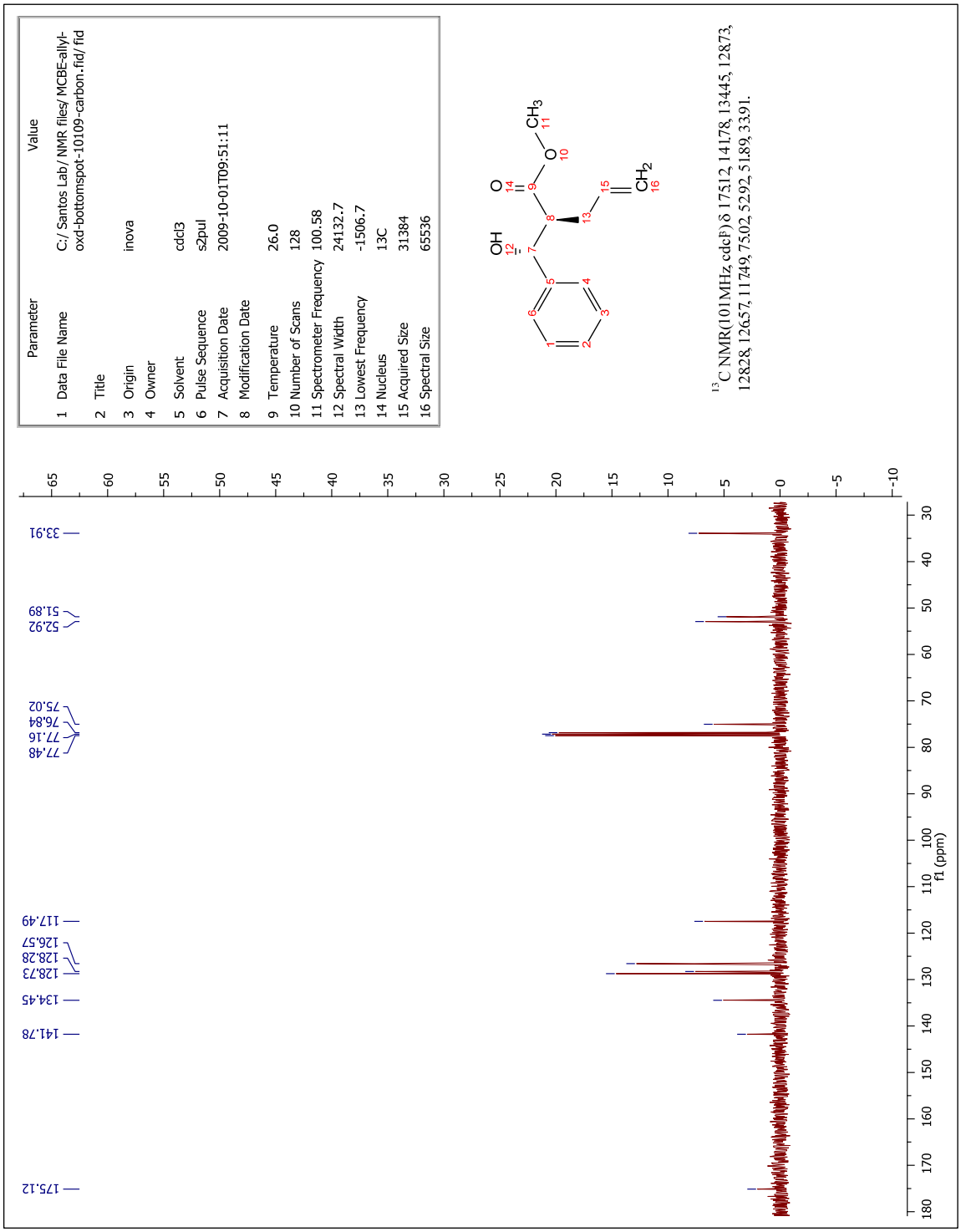
Compound **2.33**



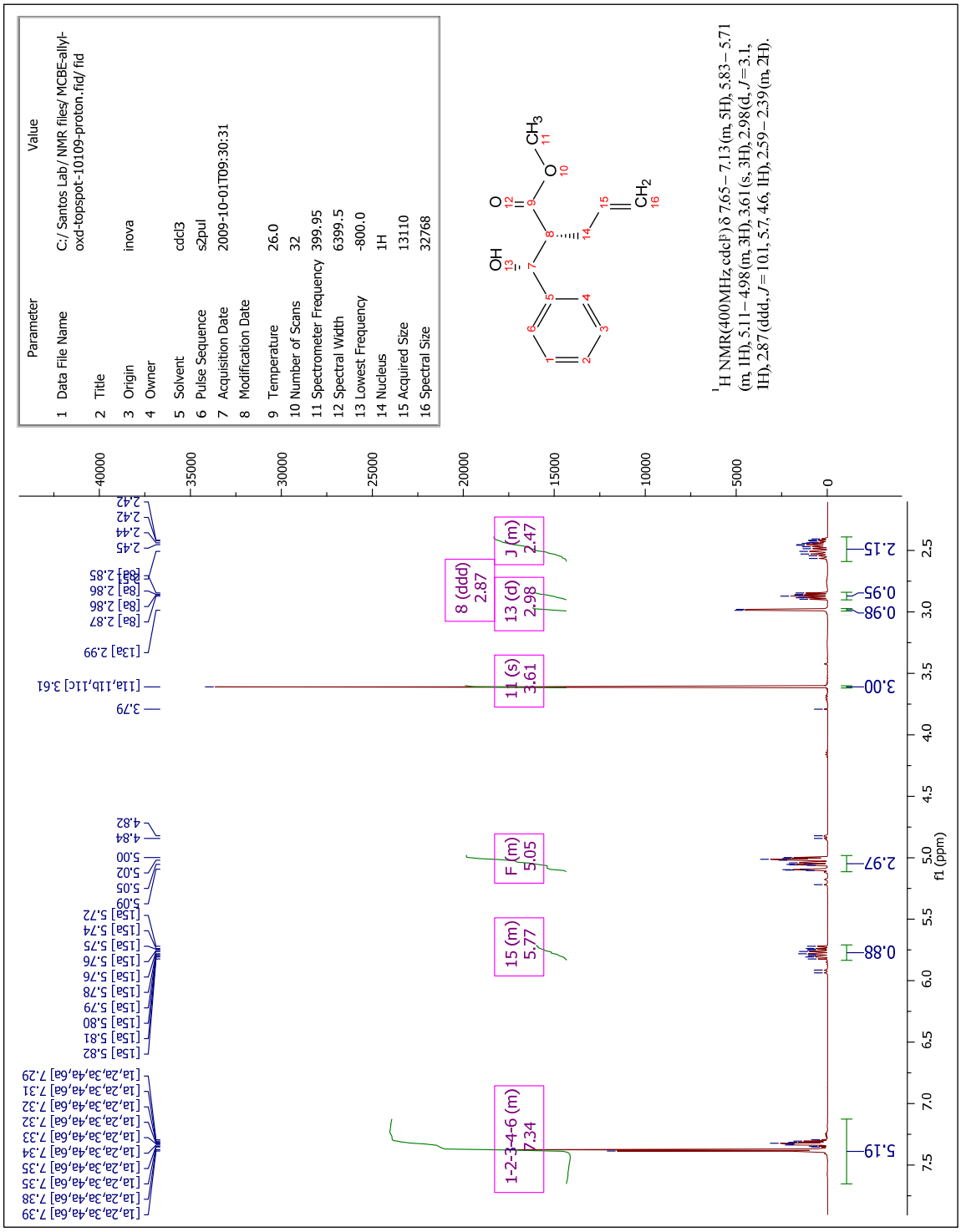
Compound **2X.34a**



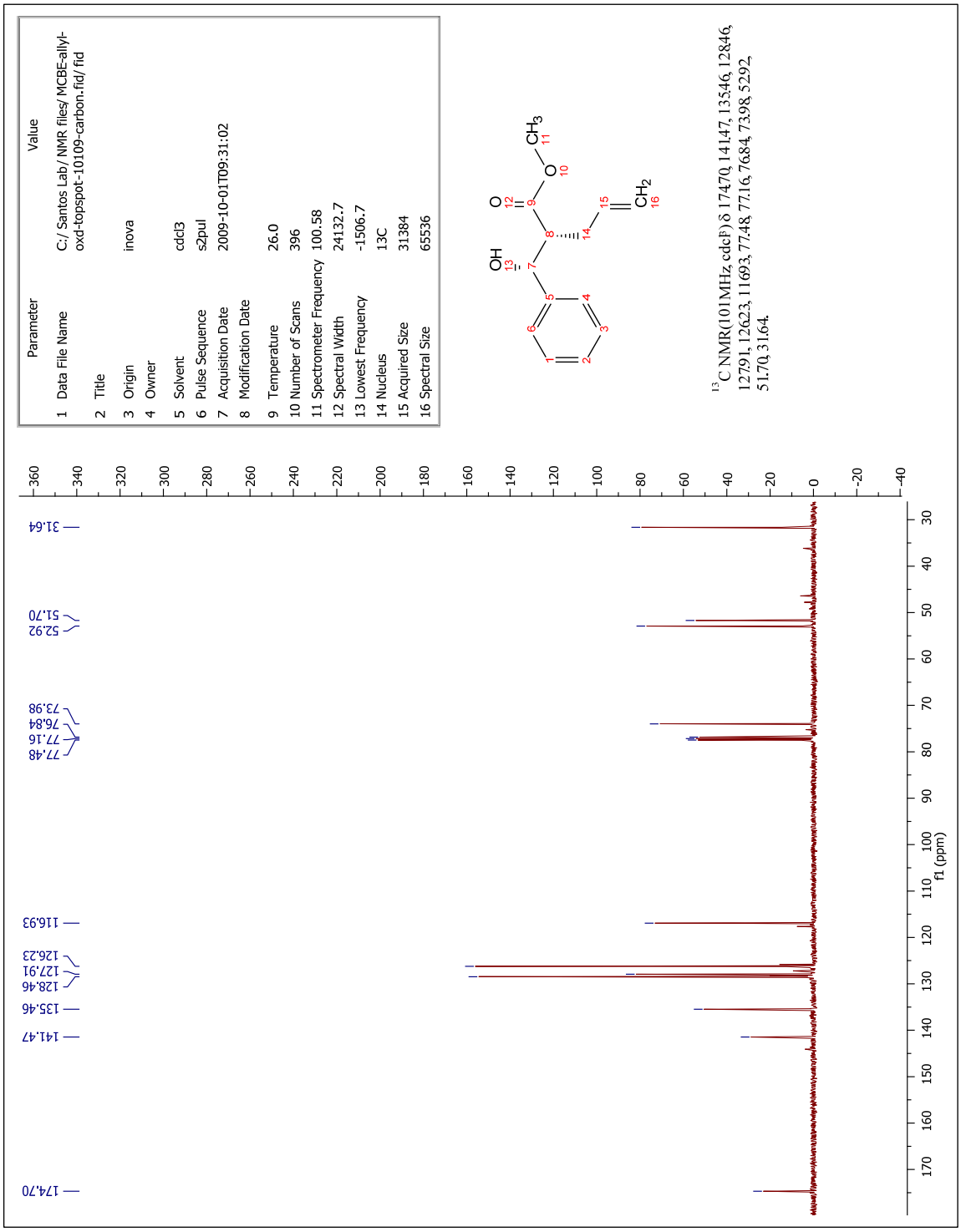
Compound **2.34a**



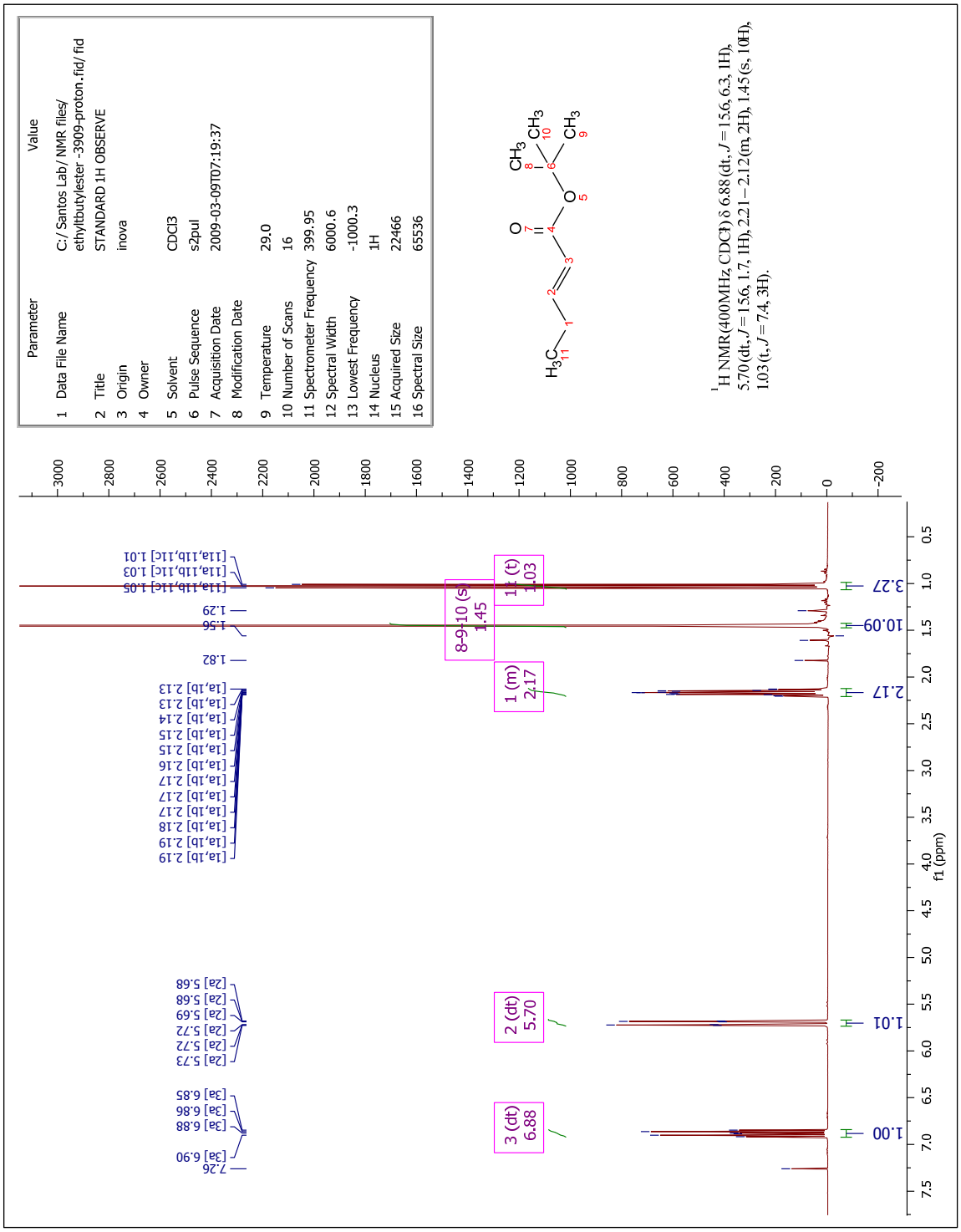
Compound **2.34b**



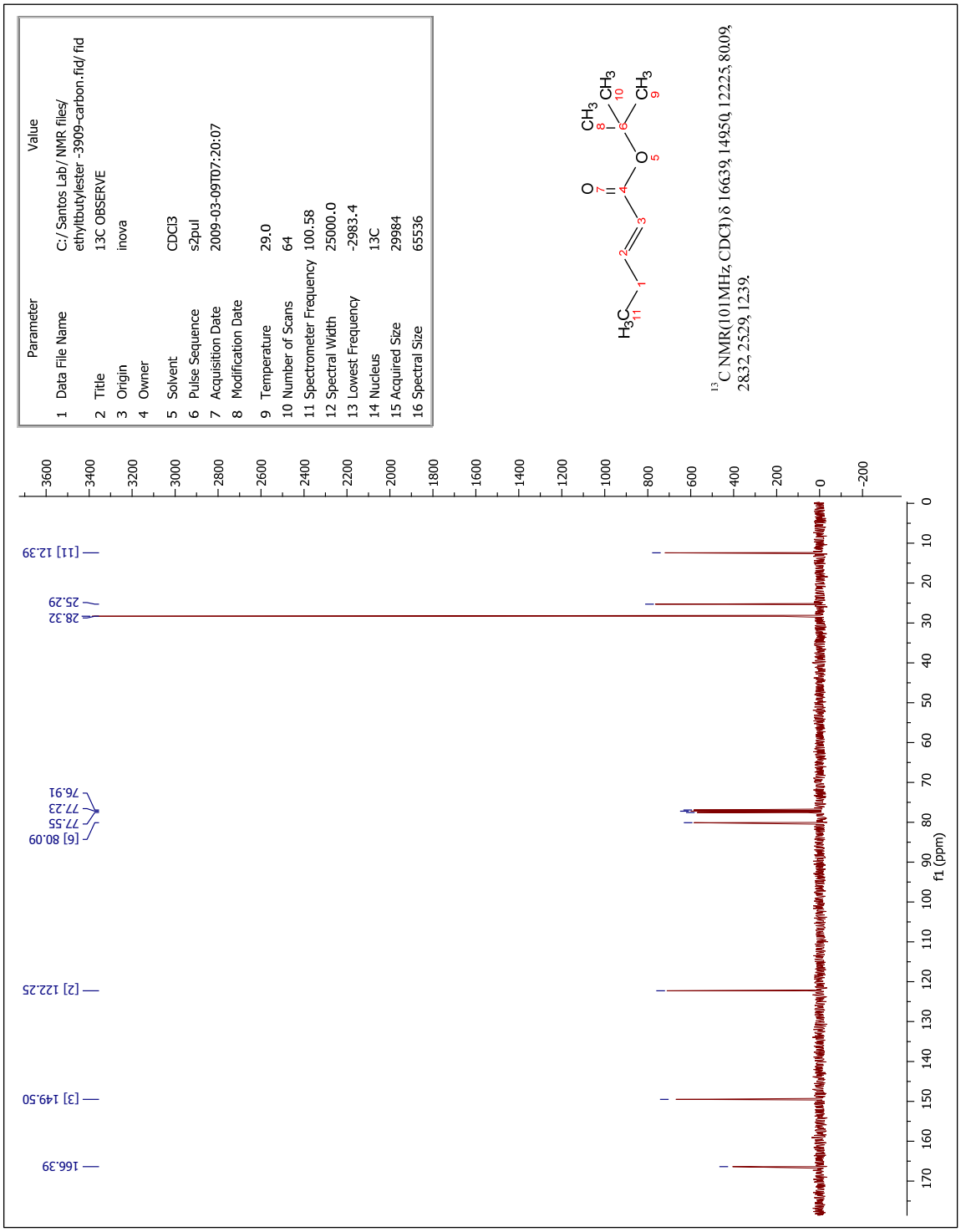
Compound **2.34b**



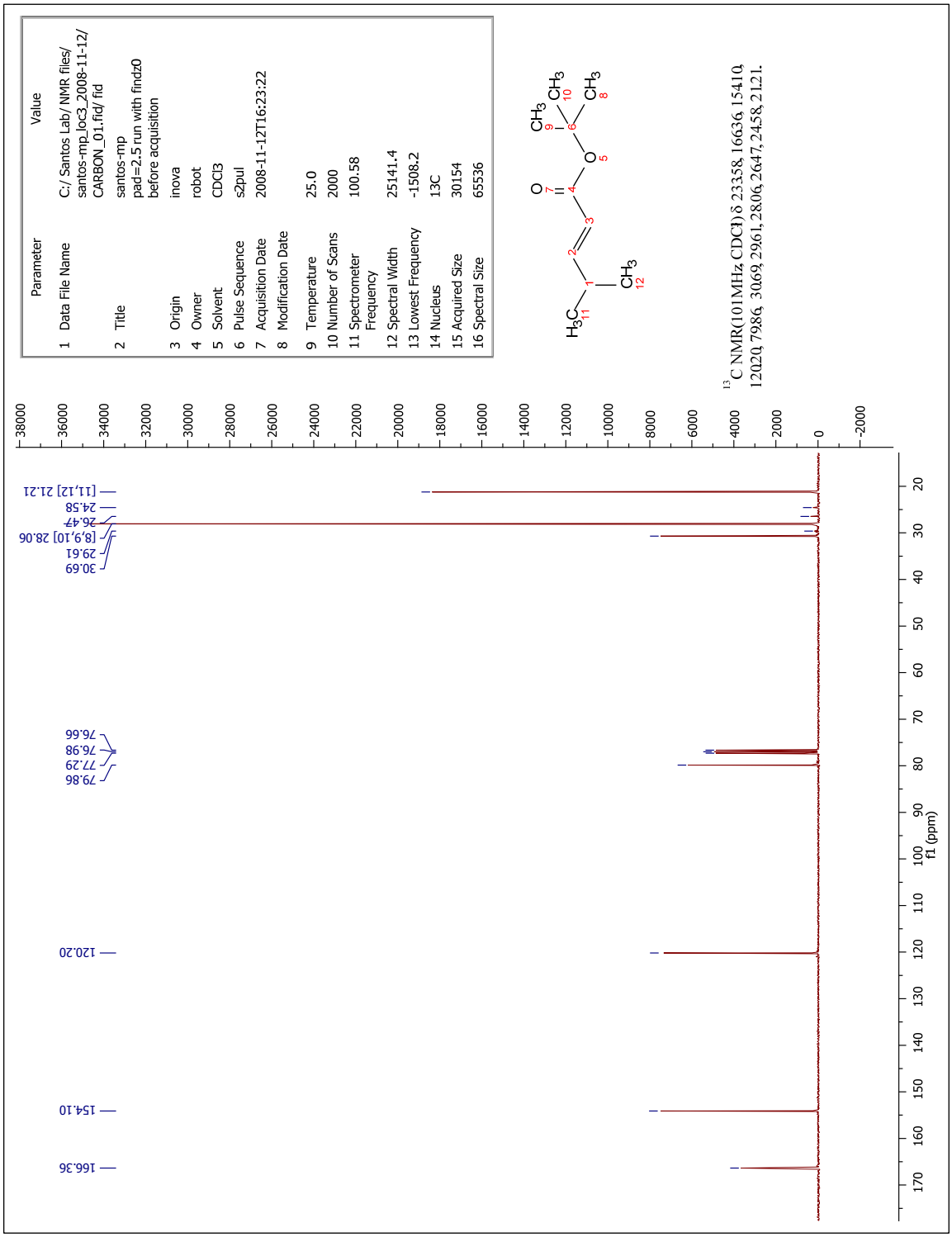
Compound **2.4**


Parameter Value
1 Data File Name C:/ Santos Lab/ NMR files/ ethyltbutylester -3909-proton.fid/ fid
2 Title STANDARD 1H OBSERVE
3 Origin inova
4 Owner
5 Solvent CDCl3
6 Pulse Sequence s2pul
7 Acquisition Date 2009-03-09T07:19:37
8 Modification Date
9 Temperature 29.0
10 Number of Scans 16
11 Spectrometer Frequency 399.95
12 Spectral Width 6000.6
13 Lowest Frequency -1000.3
14 Nucleus 1H
15 Acquired Size 22466
16 Spectral Size 65536
1H NMR (400MHz, CDCl3) δ 6.88 (dt, J = 15.6, 6.3, 1H), 5.70 (dt, J = 15.6, 1.7, 1H), 2.21 – 2.12 (m, 2H), 1.45 (s, 10H), 1.03 (t, J = 7.4, 3H).
f1 (ppm)

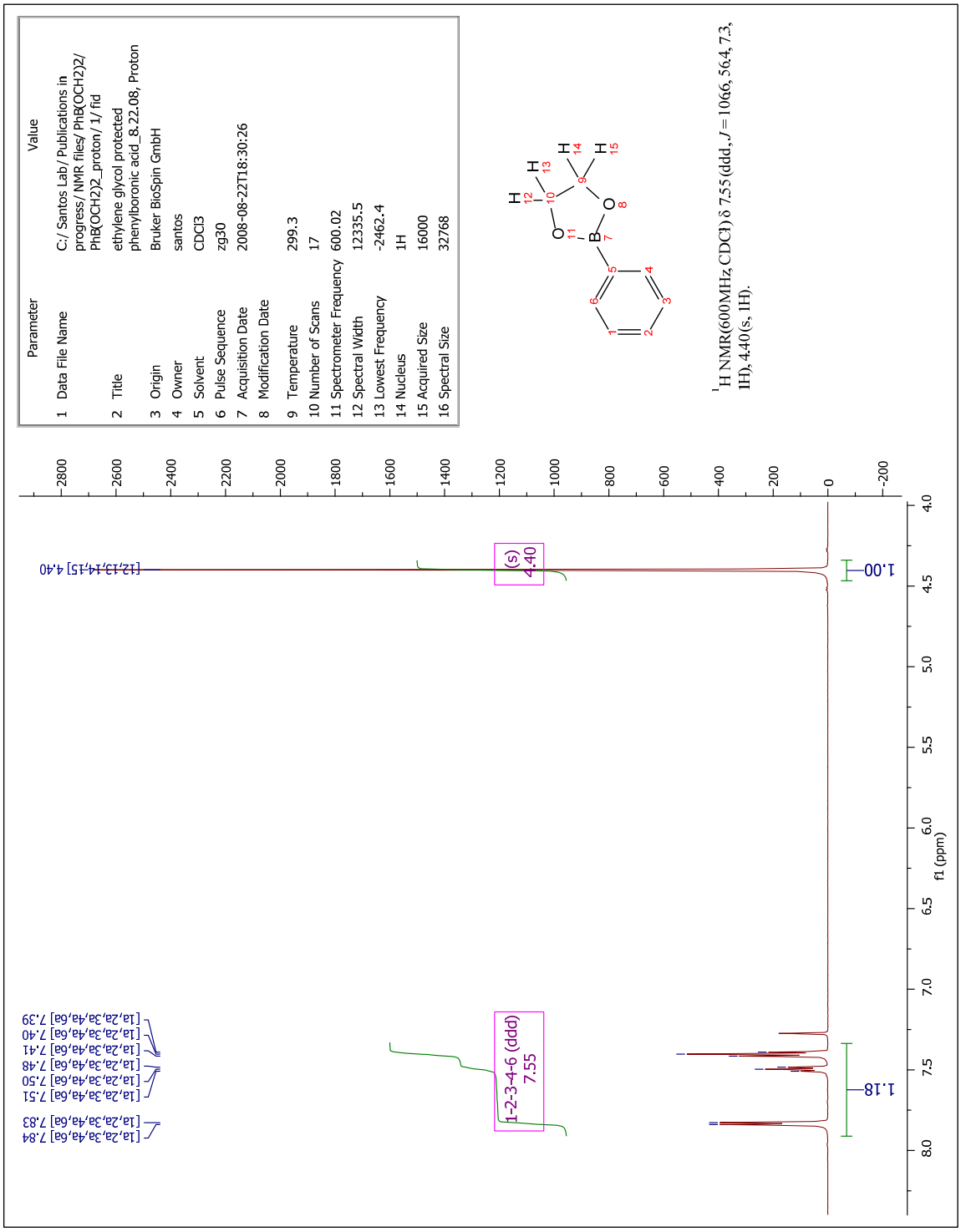
Compound **2.4**


Parameter
Value
1 Data File Name
C:/ Santos Lab/ NMR files/ ethyltbutylester -3909-carbon.fid/ fid
2 Title
13C OBSERVE
3 Origin
inova
4 Owner
5 Solvent
CDCl3
6 Pulse Sequence
s2pul
7 Acquisition Date
2009-03-09T07:20:07
8 Modification Date
9 Temperature
29.0
10 Number of Scans
64
11 Spectrometer Frequency
100.58
12 Spectral Width
25000.0
13 Lowest Frequency
-2983.4
14 Nucleus
13C
15 Acquired Size
29984
16 Spectral Size
65536
13C NMR(101MHz, CDCl) δ 166.39, 149.50, 122.25, 80.09, 28.32, 25.29, 12.39.
[11] 12.39
25.29
28.32
[6] 80.09
77.55
77.23
76.91
[2] 122.25
[3] 149.50
166.39
f1 (ppm)

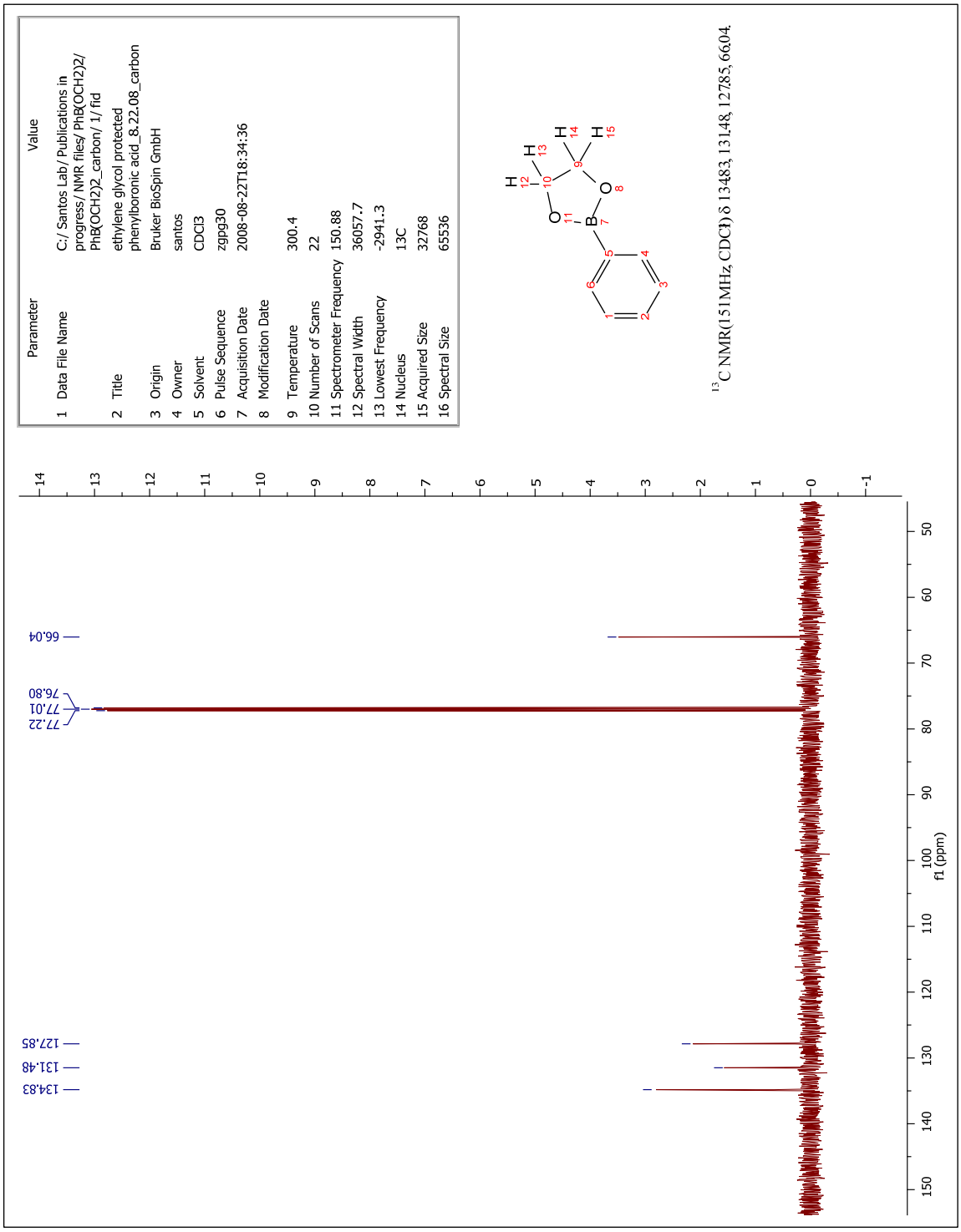
Compound **2.5**


Parameter
Value
1 Data File Name
C:/ Santos Lab/ NMR files/ santos-mp_loc3_2008-11-12/ CARBON_01.fid/ fid
2 Title
santos-mp pad=2.5 run with findz0 before acquisition
3 Origin
inova
4 Owner
robot
5 Solvent
CDCl3
6 Pulse Sequence
s2pul
7 Acquisition Date
2008-11-12T16:23:22
8 Modification Date
9 Temperature
25.0
10 Number of Scans
2000
11 Spectrometer Frequency
100.58
12 Spectral Width
25141.4
13 Lowest Frequency
-1508.2
14 Nucleus
13C
15 Acquired Size
30154
16 Spectral Size
65536
13C NMR(101MHz CDCl3) δ 23358, 16636, 15410, 12020, 7986, 3069, 2961, 2806, 2647, 2458, 2121.
[11,12] 21.21
24.58
26.47
[8,9,10] 28.06
29.61
30.69
76.66
76.98
77.29
79.86
120.20
154.10
166.36
f1 (ppm)

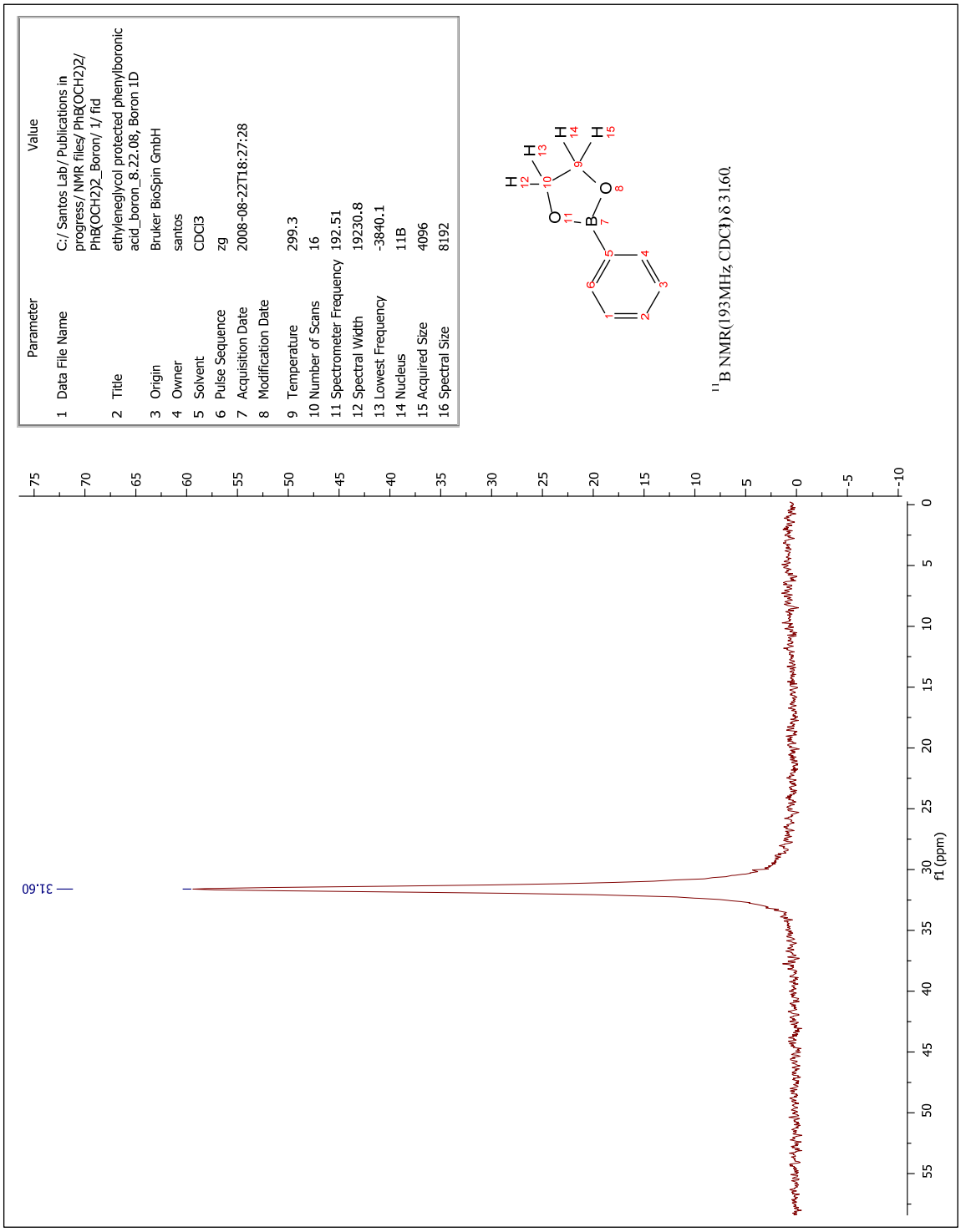
Compound **3.1**


Parameter
Value
1 Data File Name
C:/ Santos Lab/ Publications in progress/ NMR files/ PhB(OCH2)2/ PhB(OCH2)2_proton/ 1/ fid
2 Title
ethylene glycol protected phenylboronic acid_8.22.08, Proton
3 Origin
Bruker BioSpin GmbH
4 Owner
santos
5 Solvent
CDCl3
6 Pulse Sequence
zg30
7 Acquisition Date
2008-08-22T18:30:26
8 Modification Date
9 Temperature
299.3
10 Number of Scans
17
11 Spectrometer Frequency
600.02
12 Spectral Width
12335.5
13 Lowest Frequency
-2462.4
14 Nucleus
1H
15 Acquired Size
16000
16 Spectral Size
32768
^{1}H NMR(600MHz, CDCl) δ 7.55 (ddd, J = 10.6, 5.6, 4.7, 3.3, 1H), 4.40 (s, 1H).
[12,13,14,15] 4.40
(s)
4.40
1-2-3-4-6 (ddd)
7.55
1.00
1.18
[1a,2a,3a,4a,6a] 7.84
[1a,2a,3a,4a,6a] 7.83
[1a,2a,3a,4a,6a] 7.51
[1a,2a,3a,4a,6a] 7.50
[1a,2a,3a,4a,6a] 7.48
[1a,2a,3a,4a,6a] 7.41
[1a,2a,3a,4a,6a] 7.40
[1a,2a,3a,4a,6a] 7.39
f1 (ppm)

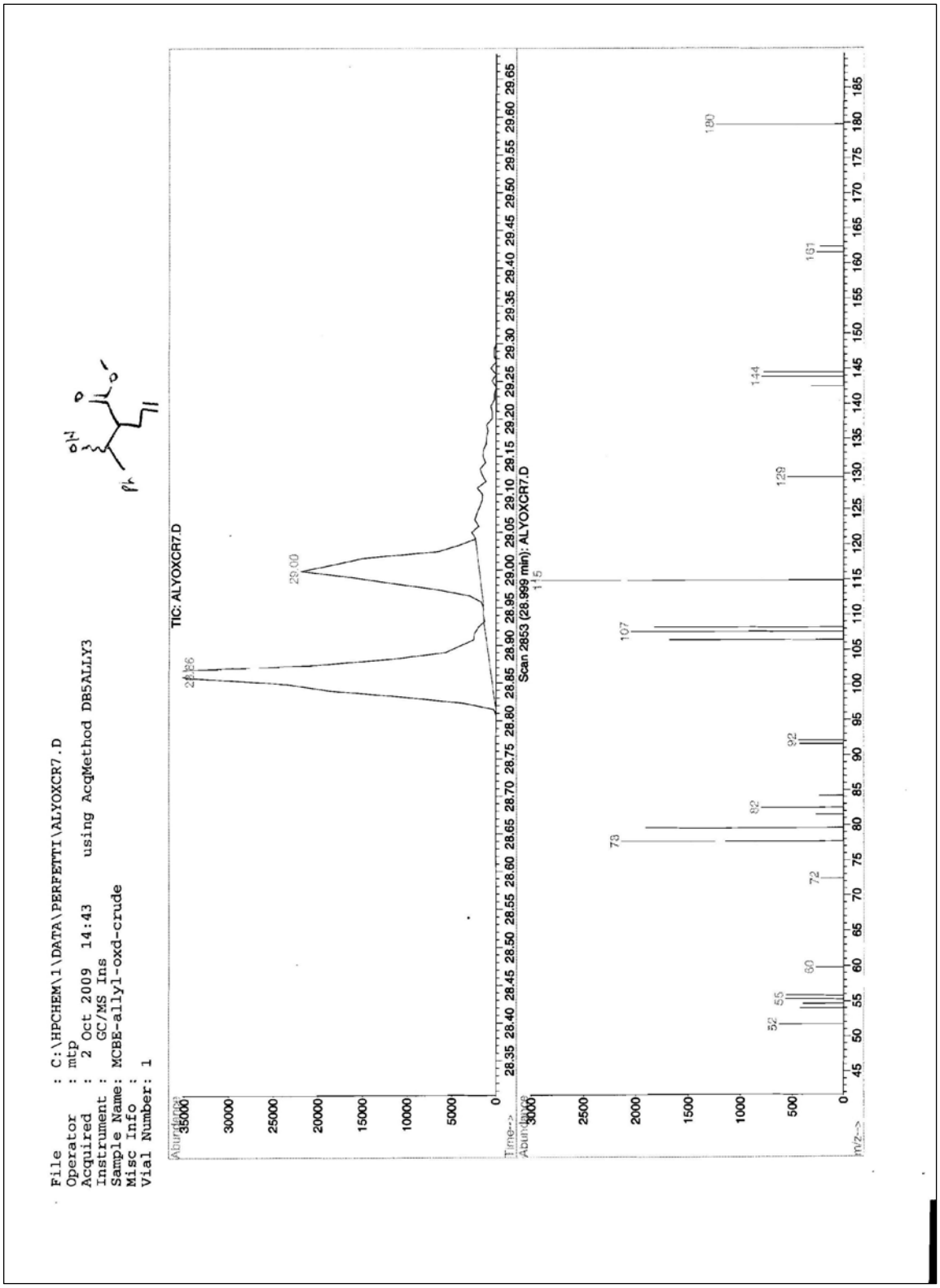
Compound **3.1**


Parameter
Value
1 Data File Name
C:/ Santos Lab/ Publications in progress/ NMR files/ PhB(OCH2)2/ PhB(OCH2)2_carbon/ 1/ fid
2 Title
ethylene glycol protected phenylboronic acid_8.22.08_carbon
3 Origin
Bruker BioSpin GmbH
4 Owner
santos
5 Solvent
CDCl3
6 Pulse Sequence
zgpg30
7 Acquisition Date
2008-08-22T18:34:36
8 Modification Date
9 Temperature
300.4
10 Number of Scans
22
11 Spectrometer Frequency
150.88
12 Spectral Width
36057.7
13 Lowest Frequency
-2941.3
14 Nucleus
13C
15 Acquired Size
32768
16 Spectral Size
65536
13C NMR(151MHz, CDCl3) δ 134.83, 131.48, 127.85, 77.22, 77.01, 76.80, 66.04.
66.04
77.22
77.01
76.80
134.83
131.48
127.85
f1 (ppm)

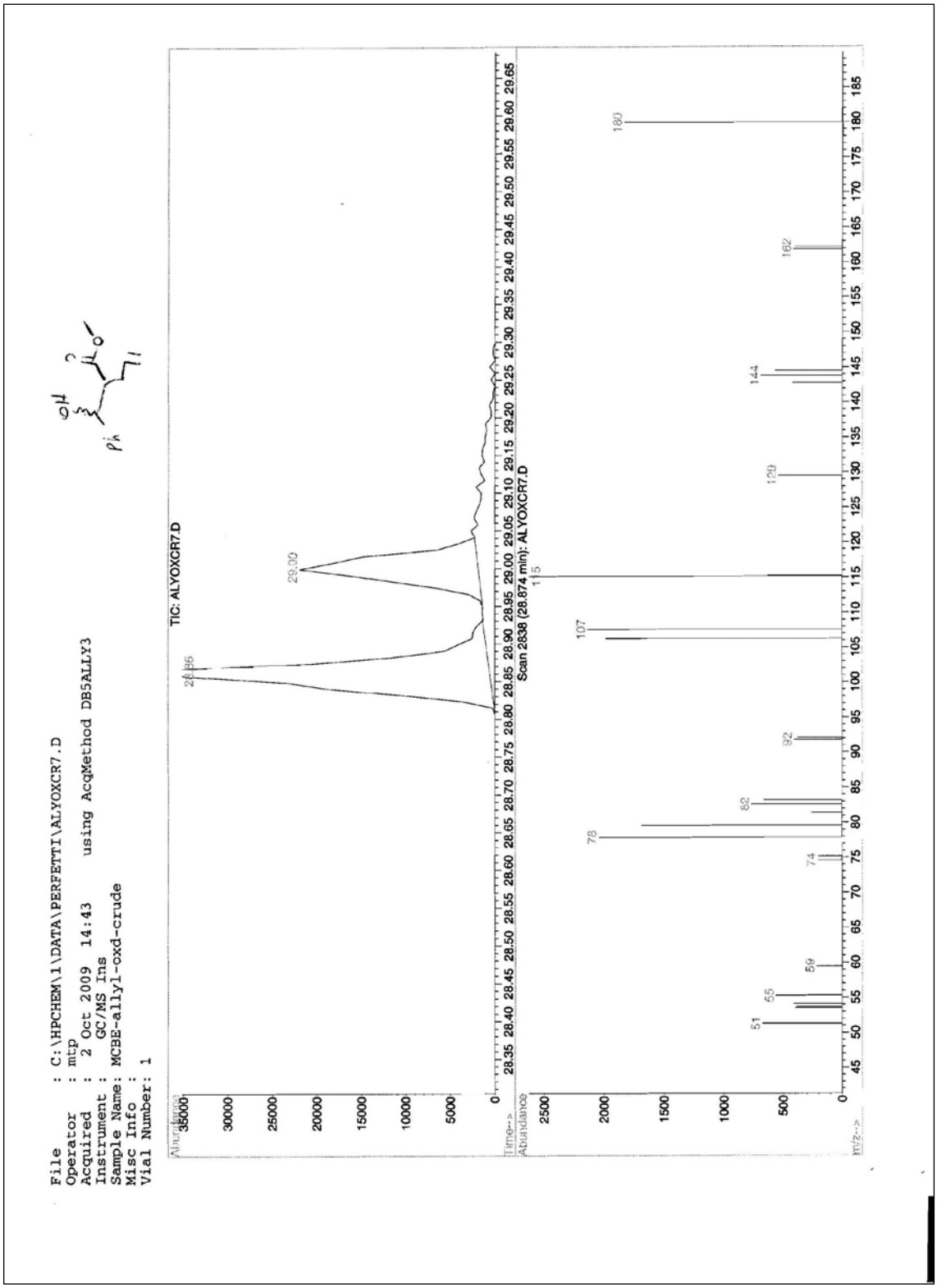
Compound **3.1**


Parameter
Value
1 Data File Name
C:/ Santos Lab/ Publications in progress/ NMR files/ PhB(OCH2)2/ PhB(OCH2)2_Boron/ 1/ fid
2 Title
ethyleneglycol protected phenylboronic acid_boron_8.22.08, Boron 1D
3 Origin
Bruker BioSpin GmbH
4 Owner
santos
5 Solvent
CDCl3
6 Pulse Sequence
zg
7 Acquisition Date
2008-08-22T18:27:28
8 Modification Date
9 Temperature
299.3
10 Number of Scans
16
11 Spectrometer Frequency
192.51
12 Spectral Width
19230.8
13 Lowest Frequency
-3840.1
14 Nucleus
11B
15 Acquired Size
4096
16 Spectral Size
8192
11B NMR(193MHz, CDCl3) δ 31.60.
31.60
f1 (ppm)

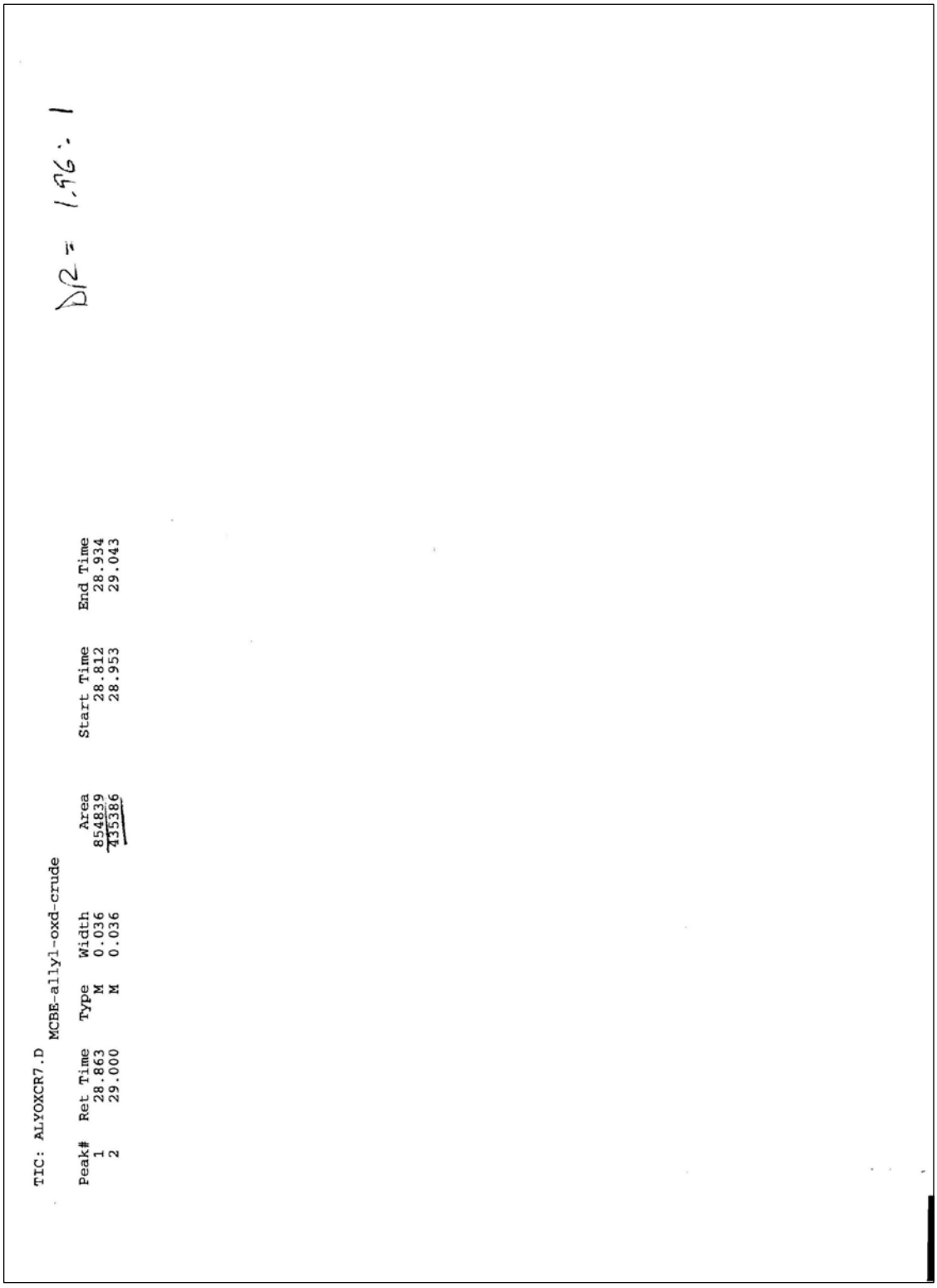
Determination of DR for **2.34a** and **2.34b** by GC-MS (Crude mixture)



Determination of DR for **2.34a** and **2.34b** by GC-MS (Crude mixture)



Determination of DR for **2.34a** and **2.34b** by GC-MS (Crude mixture)

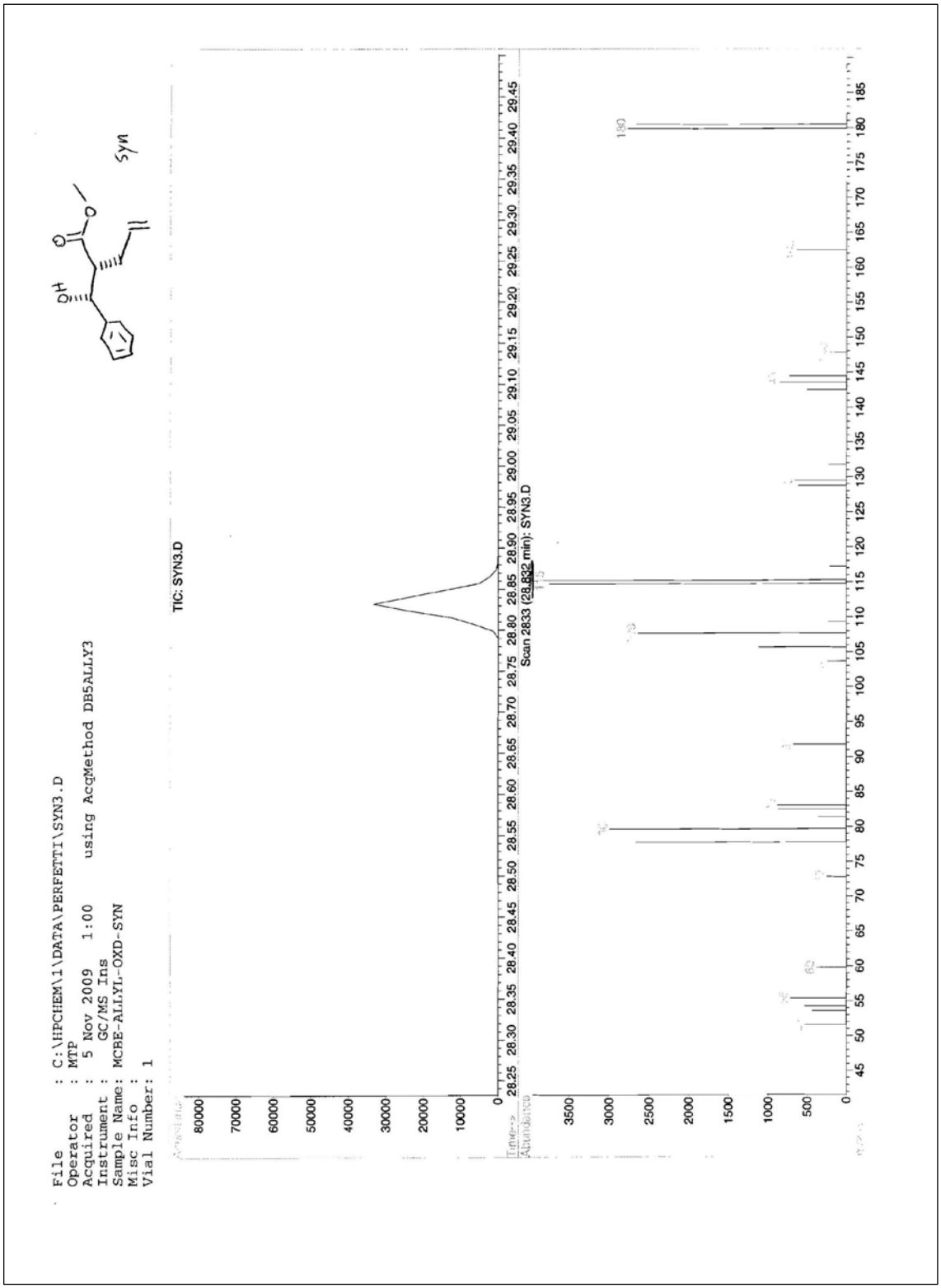


TIC: ALYOXCR7.D
MCBE-allyl-oxd-crude

Peak#	Ret Time	Type	Width	Area	Start Time	End Time
1	28.863	M	0.036	854839	28.812	28.934
2	29.000	M	0.036	435386	28.953	29.043

DR = 1.96 : 1

Determination of DR for **2.34b** by GC-MS (purified *syn* diastereomer)



Determination of DR for **2.34a** by GC-MS (purified *anti* diastereomer)