UNIVERSITY OF CALIFORNIA,
IRVINE

A Direct Synthesis of Highly Substituted π-Rich Aromatic Heterocycles from Oxetanes

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Synthesis of the AB-Core of the Dihydro-β-agarofurans

&

Methodology and Strategy Development Inspired by the Agarofurans

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Chemistry

by

Ryan Acadia Kozlowski

Dissertation Committee:
Professor Christopher D. Vanderwal, Chair
Professor Scott D. Rychnovsky
Professor Sergey V. Pronin

2022

Portions of Chapter 1 have been adapted with permission from White, A. R.; Kozlowski, R. A.; Tsai, S.-C.; Vanderwal, C. D. *Angew. Chem. Int. Ed.* **2017**, *56*, 10525–10529.

DEDICATION

To

My wife, Anna, my friends, my family, and of course, Steven

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ACKNOWLEDGMENTS

First, I must thank my advisor, Professor Chris Vanderwal, for the opportunity you have given me and for the immense amount of support, both scientifically and personally, that I have received from you. Spending the last five (almost six) years in your lab has been a tremendous experience and I have learned an incredible amount from you. I appreciate the freedom you gave me to explore ideas and for your guidance and frequent meetings when I was struggling. Your mentorship style has always shown how much you care for your students, not just as scientists, but as people as well, and you lead by example as to how one can be both a great scientist and a great person. Thank you for helping me grow and build confidence in myself as an independent scientist.

I would like to thank my thesis committee members, Professors Scott Rychnovsky and Sergey Pronin. Scott, I appreciate the conversations we have had over the past few years, especially the guidance I received from you following my second-year candidacy examination where you served as my committee chair. I have learned a great deal from you and I will miss the fresh perspectives you often brought to my projects. Sergey, I appreciate the enthusiasm you always displayed for my projects whenever we spoke and for the ideas and suggestions you have offered me. I am also grateful for the opportunity to have taken Synth II with you.

I would like to acknowledge Larry Overman and Jennifer Prescher. I am very grateful that Larry and his group would join our group meetings. Having the opportunity to learn from both Larry and his group of incredible post-docs was invaluable. Jenn, I appreciate your guidance following my advancement to candidacy and for the great deal of help you offered me while taking your Chemical Biology class.

I must also acknowledge my undergraduate research advisor, Professor Don Watson, and my high school chemistry teacher, Kevin Harrington, for the instrumental role they played in my chemistry career. To Mr. Harrington, you first sparked my passion for chemistry and I certainly would not be where I am today without the excitement and motivation you first instilled in me. Don, I am grateful that you took me on as an undergraduate student in your lab. I had never done organic synthesis before, but the opportunity you gave me made me realize that I was in the right field. I must also thank Luis Mori-Quiroz who taught me the ropes of organic synthesis when I first joined the Watson lab as a bright-eyed undergrad. To Scott Shuler and Kirk Shimkin, I will be forever grateful for your mentorship and friendship, and for the invaluable guidance you provided me in my graduate school search. To this day, I still miss our Saturday Banh Mi Boy runs.

I would like to acknowledge many former Vanderwal lab members. To Alex White, I am grateful for your mentorship and for the role and impact you allowed me to have on the furan and pyrrole methodology. To Brian Atwood, I appreciate your patience and your willingness to answer my barrage of questions every day. To Glynis Coyne, I appreciate your continued friendship and your presence in lab has been sorely missed. To Michael Lehman, unfortunately we didn't get more time since the pandemic got in the way, but I enjoyed mentoring you and I appreciate the positive demeanor your brought every day. To my many other former lab mates–Jono Chung, Vincenzo Ramella, Daniele Perrotta, Darius Vrubliauskas, Bryan Ellis, Sharon Michalak, Michael Friedberg, Alex Karns, and Zef Könst–I am grateful for the time we spent together and for your guidance and mentorship.

To the current Vanderwal group members–Fabi Hörmann, Riley Mills, Natalie Dwulet, Bonnie Pak, Scott Niman, Joe Capani, Griffin Barnes, Lucas Johnson, Bonnie Park, Jane Supantanapong, Hanh Nguyen, and Phil Lechner–working with you each and every day has been a pleasure, and you have made the Vanderwal lab a great place to be. I will miss our conversations and laughs, and I look forward to crossing paths with each of you in the future. Riley and Bonnie Pak, you two have become some of my closest friends, and I am grateful for all

the jokes, hypotheticals, and conversations that have kept me sane. Fabi, I appreciate your sage advice and calming chats during my final year of graduate school. Hanh, it has been a pleasure to mentor you and I am excited to see where you take our projects.

I must thank all of my friends and family, who have dealt with the struggles and difficulties of graduate school alongside me. To my parents, Paul and Connie, I appreciate your acceptance of my choice to move thousands of miles away and for your support throughout. To my sister, Caitlin, I am grateful for your understanding and compassion, even when I was neglectful at times. To my DnD group–Riley Mills, Alex Lu, Bonnie Pak, Brenna Norton-Baker, Carly Brennan, Megan Rocha, and Robby Dorn–you all have kept me sane more than you likely realize, and our weekly get-togethers always lifted my spirits and kept me going even when things were at their toughest. To my first-year cohort–Anna Love, Eric Touney, Alex Lu, Alex Valdes, and Brenna Norton-Baker–I will never forget our first-year adventures. I am grateful for your friendship and support throughout graduate school. To two of my closest friends, John Edenhofner and Byron Sakiadis, I am immensely grateful for your friendship over the last nine years. Even though I moved thousands of miles away and have often been neglectful of our friendship, I am appreciative of the unwavering support and understanding. Our group chat has provided endless laughs, and I am grateful for the constant updates on our hobbies and interests that I don't have time to keep track of.

Last, but certainly not least, I must thank my wife, Anna Love. Words cannot express how grateful I am for your enduring and steadfast support. Your belief in me, even when my belief in myself wavered, has helped keep me motivated and driven. Graduate school was infinitely better navigating it with you.

Curriculum Vitae

Ryan A. Kozlowski

Education

Ph.D., Organic Chemistry
University of California, Irvine
Research Advisor: Professor Christopher Vanderwal

B.S., Chemistry, Honors Degree with Distinction (June 2016)
University of Delaware
Research Advisor: Professor Donald Watson

Skills

Technical

Proficient in:

- Development and execution of multi-step syntheses.
- Organic synthesis, purification, and characterization, including but not limited to Schlenk/air-free techniques, use of a glovebox, column chromatography, distillation, HPLC, GCMS, and NMR of many nuclei.
- Use of literature searching tools including Reaxys, SciFinder, and Web of Knowledge.

Soft

- Organized and self-motivated
- Works well in teams
- Strong oral and written communication skills
- Accepts and encourages constructive criticism
- Empathetic leadership style
- Calm, open-minded, and friendly

Research Experience

University of California, Irvine (Summer 2016 – current)
Professor Christopher Vanderwal

Synthesis of the AB-ring Core of the Dihydro-β-agarofurans

- Designed and implemented four unique routes towards the agarofurans in pursuit of the first general route focused on synthesizing several members of this family of bioactive natural products.
- Discovered and developed a novel ester-based chiral auxiliary for a diastereoselective Birch reduction/alkylation reaction.
- Synthesized the AB-core of the agarofurans with aims diversify the core into several natural products and related analogs.

Discovery and Development of a Novel Ester-based Chiral Auxiliary for a Diastereoselective Birch Reduction/Alkylation Reaction

- Optimized reaction conditions for use as a general method.

- Empirical data supports hypothesis that a pi-stacking interaction between the chiral auxiliary and intermediate produces the observed diastereoselectivity.
- Previously mentored an undergraduate student and am currently mentoring a second year graduate student on this project.
- To date, 11 substrates have been synthesized in good yield and d.r. with the remaining substrates for publication currently being completed.

Progress Towards the Synthesis of Arcutinidine and Other C_{20}-Diterpene Alkaloids

- In conjunction with another graduate student, we developed a proposed 7-step convergent synthesis of *ent*-arcutinidine using an enzymatic dearomative dihydroxylation.
- Currently, progress has been made on an alternative route as a proof of concept with great success.
- Future work includes engaging a collaborator to perform enzyme evolution to allow access to both enantiomers of the enzymatic dearomative dihydroxylation reaction.
- I am currently mentoring a second year graduate student who is undertaking the synthesis of other diterpene alkaloids using a similar strategy.

Synthesis of PROTACs for Skp2 Degrader

- Collaborated with Professor Xiaolin Zi at the UCI School of Medicine to synthesize thalidomide-based compounds for biological testing against deadly forms of prostate cancer.
- After successful completion of half of the molecule, this project was handed off to a separate graduate student for completion.

Synthesis of Kalihinol Analogues for Biological Testing

- Synthesized several Kalihinol analogues based off of a previously published total synthesis by the Vanderwal lab.
- Compounds were sent to GSK as part of a collaboration in studying the effects and potency of Kalihinol analogues against malaria.

A Direct Synthesis of Highly Substituted π-Rich Aromatic Heterocycles from Oxetanes

- Optimized reaction conditions for a Lewis-acid catalyzed rearrangement of oxetane-bearing α,β-unsaturated carbonyls into furans and pyrroles.
- Developed conditions for a one-pot procedure starting from commercially available starting materials to form highly substituted furans.
- Results published in *Angewandte Chemie International Edition.*

University of Delaware (Winter 2013 – Spring 2016)
Professor Donald Watson

Copper-Catalyzed Amidation of Primary and Secondary Alkyl Boronic Esters

- In conjunction with a post-doctoral researcher, I designed and conducted multi-step syntheses of starting materials and aided in optimization of reaction conditions.
- Results published in *Chemistry – a European Journal*.

Publications

White, A. R.; **Kozlowski, R. A.**; Tsai, S.-C.; Vanderwal, C. D. "A Direct Synthesis of Highly Substituted π-Rich Aromatic Heterocycles from Oxetanes" *Angew. Chem. Int. Ed.* **2017**, *56*, 10525-10529.

Highlighted in *Org. Process Res. Dev.* **2017**, *21*, 1196-1208
Highlighted in *SYNFACTS*, **2017**, *13*, 1025

Mori-Quiroz, L.; Shimkin, K. W.; Rezazadeh, S.; **Kozlowski R. A.**; Watson, D. A. "Copper-Catalyzed Amidation of Primary and Secondary Alkyl Boronic Esters" *Chem. Eur. J.* **2016**, *22*, 15654-15658.

Highlighted in *Org. Chem. Highlights* **2017**, September 11
Highlighted in *SYNFACTS*, **2016**, *12*, 1294

Selected Presentations

"Progress Towards the Dihydro-β-agarofurans Using a Novel Diastereoselective Birch Reduction/Alkylation Sequence"

July 2020 – Applied for and was accepted to present a poster at the ACS DOC Graduate Research Symposium at the University of Albuquerque in New Mexico. This event was cancelled due to the COVID-19 pandemic.

"Progress Towards the Dihydro-β-agarofurans Using a Novel Diastereoselective Birch Reduction/Alkylation Sequence"

August 2019 – Invited poster presentation at AbbVie process and discovery chemistry site in Chicago, Illinois

"Copper-Catalyzed Amidation of Primary Alkylboronic Esters"

May 2016 – Oral defense of written undergraduate honors thesis in front of a panel of three chemistry faculty members.

"Towards the Formation of α-chiral Amides via Palladium-Catalyzed Decarboxylation of O-Acyl Hydroxamates"

August 2015 – Poster presentation at the University of Delaware Undergraduate Research and Service Scholar Celebratory Symposium

"Formation of Secondary Amides via Copper-Catalyzed Amidation of Primary Pinacol Alkylboronates"

August 2014 – Poster presentation at the University of Delaware Undergraduate Research and Service Scholar Celebratory Symposium

Awards

Graduate Dissertation Fellowship, University of California, Irvine (Summer 2021)

Awarded a fellowship to aid in the completion of a doctoral thesis. Award by the department of chemistry to outstanding chemistry students.

Summer Scholar Research Grant, University of Delaware (Summer 2014 and 2015)

Awarded to undergraduate students showing promise as future research scientists to conduct summer research.

Northrup Grumman Scholarship (2012 – 2016)

Awarded to outstanding students whose parent works at Northrup Grumman.

Teaching Experience

Organic Chemistry Teaching Assistant
University of California, Irvine (Spring 2020 and 2021)
Courses Taught: Chem51C

Laboratory Teaching Assistant
University of California, Irvine (Fall 2016 – Winter 2018)
Courses Taught: Chem160, Chem51LB, Chem 51LC, Chem1LC

ABSTRACT OF THE DISSERTATION

A Direct Synthesis of Highly Substituted π-Rich Aromatic Heterocycles from Oxetanes

&

Synthesis of the AB-Core of the Dihydro-β-agarofurans

&

Development of a Diastereoselective Birch Reduction/Alkylation Reaction of Substituted Benzenes Using Ester Chiral Auxiliaries

by

Ryan Acadia Kozlowski

Doctor of Philosophy in Chemistry

University of California, Irvine, 2022

Professor Christopher D. Vanderwal, Chair

The research described herein focuses on the development of novel methods and synthetic sequences to solve problems in organic synthesis. Chapter 1 details our work on an operationally simple method to synthesize furans and pyrroles in high yield from keto-oxetanes, a non-obvious, easily accessible 1,4-dicarbonyl surrogate.

Chapter 2 moves away from synthetic methodologies and is focused on the dihydro-β-agarofuran family of sesquiterpenoid natural products. This chapter begins by detailing the structural features that make this family unique and the diverse array of biological activity that has generated considerable interest in their study. It concludes by discussing the significant amount of synthetic efforts towards the agarofurans, focusing mainly on the most recent examples. Chapter 3 details four strategies towards the synthesis of an easily diversifiable core that could

be used to synthesize several agarofurans and related analogs. Key contributions include the first use of an easter chiral auxiliary in a diastereoselective Birch reduction/alkylation reaction of substituted benzenes, an expedient route towards a fully oxidized A-ring fragment, and the synthesis of the AB-core of the agarofurans using an intramolecular 1,3-dipolar cycloaddition reaction.

Chapter 4 describes the history of the diastereoselective Birch reduction/alkylation reaction and its use in the synthesis of natural products. Chapter 5 details the development of using ester chiral auxiliaries to effect a diastereoselective Birch reduction/alkylation reaction. This method generates quaternary carbons directly from salicylic acid derivatives with good diastereoselectivity using an easily removable (–)-8-phenylmenthol chiral auxiliary.

Chapter 1: A Direct Synthesis of Highly Substituted π-Rich Aromatic Heterocycles from Oxetanes

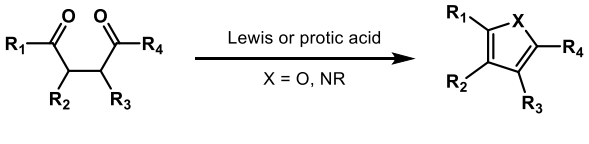
1.1 Introduction

Previous work by Dr. Alex White in the Vanderwal lab uncovered a novel transformation in which β-oxetane-bearing α,β-unsaturated carbonyl compounds can be rapidly transformed into highly substituted furans with protic or Lewis acidic conditions. This reactivity was discovered while Dr. Alex White was working on synthesizing polyketide-inspired chemical probes bearing oxetanes as carbonyl isosteres.[1] Five-membered aromatic heterocycles are prevalent in drug candidates and natural products,[2] which has compelled synthetic chemists to discover novel means of synthesis. Classical synthetic strategies, namely the Paal–Knorr furan and pyrrole synthesis, rely on 1,4-dicarbonyl motifs as these can be directly translated into the oxidation pattern of 5-membered aromatic heterocycles such as furan, pyrroles, and thiophenes. However, 1,4-dicarbonyls are inherently dissonant, and often rely on umpolung strategies or acyl anion chemistry for their synthesis. This is not always applicable to the synthesis of five-membered aromatic hetereocycle precursors, especially when highly unstable 1,4-dicarbonyls containing one or two aldehydes are required. Thus, a 1,4-dicarbonyl surrogate that would obviate the need for the dissonant 1,4-dicarbonyl motif would allow for greater ease of synthesis of five-membered aromatic heterocycles. Herein, we describe the use of a keto-oxetane motif as a non-obvious 1,4-dicarbonyl surrogate. Furthermore, we demonstrate the use of the keto-oxetane motif as a precursor to synthesize highly substituted furans, pyrroles, benzofurans, and indoles. Lastly, we demonstrate this reaction to be operationally simple, scalable, and applicable in further synthetic efforts.

1.2 1,4-Dicarbonyl Compounds as Aromatic Heterocycle Precursors

1.2.1 The Paal–Knorr Furan and Pyrrole Synthesis

The synthesis of furans and pyrroles from 1,4-dicarbonyls was first reported simultaneously by Paal and Knorr in 1884 (Equation 1.1).[3-5] Using this method, most 1,4-dicarbonyls[6] can be transformed into their corresponding furan with acid or pyrrole by treatment with a primary amine or ammonia and acid. Despite the numerous advances in synthetic chemistry since the discovery of the Paal–Knorr furan and pyrrole synthesis, this method remains arguably the most widely used. The major drawback is the synthesis of 1,4-dicarbonyl motifs. This dissonant functionality[7] relies on the use of umpolung strategies or acyl anion chemistry[8-14] to synthesize; however, this is not always directly applicable to the synthesis of furans and pyrroles. As a result of the dissonant 1,4-dicarbonyl motif, unstable precursors are often required, especially those containing aldehydes.[13] Thus, other 1,4-dicarbonyl surrogates have been developed, aimed at removing the need for one or both carbonyls.

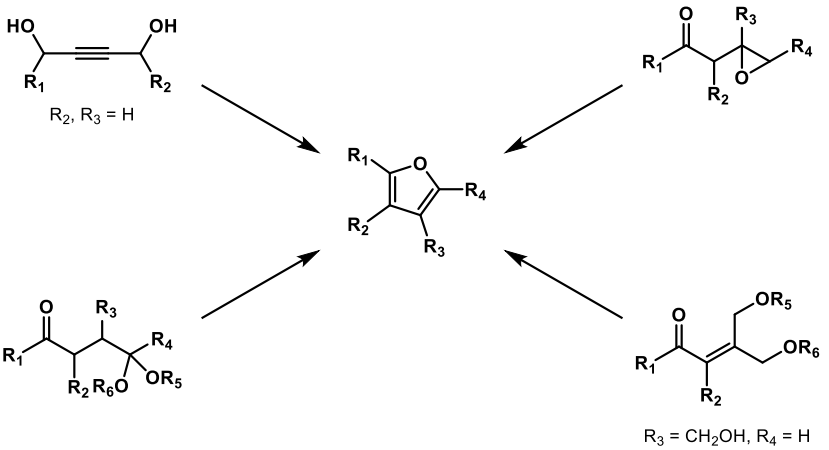


Equation 1.1. The Paal-Knorr furan and pyrrole synthesis

1.2.2 Other 1,4-Dicarbonyl Surrogates

In an effort to find alternatives to the 1,4-dicarbonyl motif, acetals,[15] epoxides,[16] and other functional groups[17-19] have been used as precursors to furans (Scheme 1.1). In general, all of these strategies aim to use a 1,4-dicarbonyl surrogate that replaces the oxidation of one or both of the carbonyls with an appropriate replacement, such as those listed above. However, by replacing the carbonyl with one of these functional groups, several drawbacks are introduced. In these examples, there is often a need for additional manipulations either prior to, or following, the

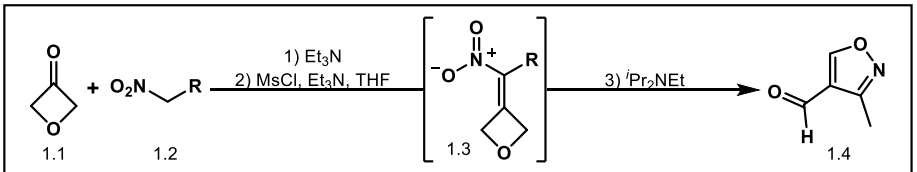
desired transformation, or there is a lack of generality. Lastly, many of these transformations require expensive starting materials, limiting their scalability or use in industrial settings.



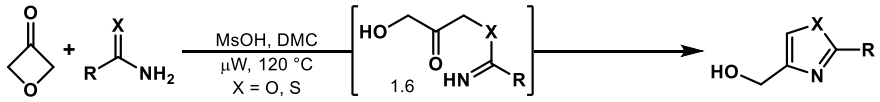
Scheme 1.1. Other 1,4-dicarbonyl surrogates for furan synthesis

1.2.3 Keto-Oxetanes as 1,4-Dicarbonyl Surrogates and Isosteres

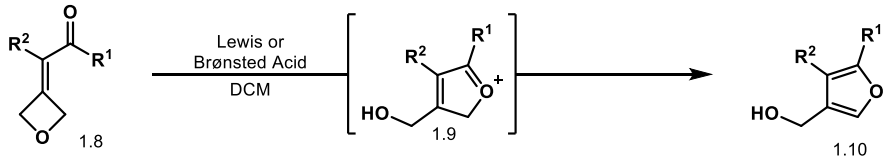
The use of keto-oxetanes offer a solution to the problems faced by 1,4-dicarbonyl motifs. In 2011, Carreira and co-workers synthesized disubstituted isoxazoles, **1.4**, via intramolecular opening of an oxetane ring by a pendant nitro group (Equation 1.2).[20] A Henry reaction, followed by deprotonation and rearrangement afforded 3,4-disubstituted isoxazoles in 58-91% yield from simple nitroalkanes and 3-oxetanone. In 2013, Percy, Harrison, and co-workers reported the synthesis of oxazoles and isoxazoles, **1.7**, starting from 3-oxetanone, giving yields ranging from 13%–64% (Equation 1.3).[21] Although other oxetane ring openings are well-known in the literature,[20-25] furans had yet to be synthesized from keto-oxetanes.[26] Herein we disclose our synthesis of 5-membered aromatic heterocycles from keto-oxetanes (Equation 1.4). Though non-obvious, **1.3**, **1.6**, and **1.8** all bear the same 1,4-oxidation pattern as a 1,4-dicarbonyl; however, replacement of a carbonyl with an oxetane removes many of the problems caused by the 1,4-dicarbonyl motif.



Equation 1.2. Carreira's synthesis of isoxazoles



Equation 1.3. Synthesis of oxazoles and thiazoles



Equation 1.4 Our synthesis of furans

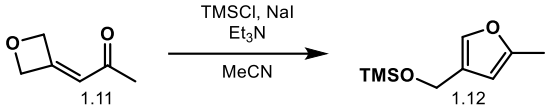
Recently, oxetanes have seen greater use, both as carbonyl isosteres and as a replacement for a *gem*-dimethyl group in medicinal chemistry pursuits. Carreira, Müller, Rogers-Evans, and others have demonstrated the use of oxetanes as carbonyl isosteres for medicinal chemistry purposes.[26-28] As a result, the exploration of oxetane chemistry and the availability of oxetane building blocks has become more widespread, thus leading to their increased use.

1.3 Lewis-Acid-Catalyzed Rearrangement of Oxetanes to Highly Substituted Furans and Benzofurans

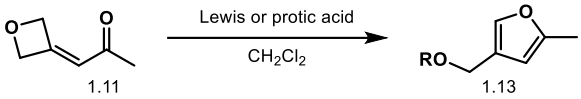
1.3.1 Discovery and Optimization of Reaction Conditions

While Dr. Alex White was synthesizing a polyketide probe containing an oxetane acting as a carbonyl isostere, he discovered the unexpected rearrangement of oxetane-bearing enone **1.11** to furan **1.12** after treatment with soft enolization conditions (Equation 1.5). Following this discovery, I optimized conditions for this transformation, and found that treatment with $BF_3{\cdot}OEt_2$ (1 mol %) in dichloromethane for 1 minute gave 99% yield of furan **1.13** (Table 1.1, Entry 1). Catalyst loadings could be decreased to as low as 0.1 mol % (Entry 2), however this amount could be unwieldy on small scales, so 1 mol % was typically standard. Given that Dr. Alex White had

already demonstrated the use of TMSOTf to effect this transformation (Entry 7), I hypothesized that Lewis and Brønsted acids were likely to do so as well. I found that $AlCl_3$ (99%, Entry 3), $Sc(OTf)_3$ (96%, Entry 4), TFA (84%. Entry 5), and $ZnCl_2$ (93%, Entry 6) all produced the desired transformation. In addition to TMSOTf (84%, Entry 7), Dr. Alex White also demonstrated that $TiCl_4$ (83%, Entry 8) and 1 M $HCl_{(aq.)}$ (95%, Entry 9) caused the desired transformation. $BF_3{\cdot}OEt_2$ was chosen as the reagent to move forward with the substrate scope due to its incredibly fast, clean conversion to furans in exceptionally high yields.



Equation 1.5. Initial discovery of furan cyclization



Entry	*Lewis/Protic Acid*	*Time*	*R =*	*Yield (%)*
1	$BF_3{\cdot}OEt_2$ (1 mol %)	< 1 min	H	99
2	$BF_3{\cdot}OEt_2$ (0.1 mol %)	< 5 min	H	99
3	$AlCl_3$ (1 mol %)	< 1 min	H	99[a]
4	$Sc(OTf)_3$ (1 mol %)	< 1 min	H	96[a]
5	TFA (1.0 equiv.)	< 1 min	H	84
6	$ZnCl_2$ (1.0 mol %)	< 1 min	H	93[a]
7	TMSOTf (1.2 equiv.), NEt_3, MeCN	< 5 min	TMS	84
8	$TiCl_4$ (1.0 mol %)	< 1 min	H	83
9	1 M HCl (1.0 equiv.)	< 10 min	H	95

[a]NMR Yield

Table 1.1. Optimization of reaction conditions

1.3.2 Furan/Benzofuran Substrate Scope

Dr. Alex White conducted much of the substrate scope; however, I prepared substrates **1.14**-**1.19** for use with the optimized conditions (Figure 1.1). The conditions tolerated a variety of functionality. A 3,4-disubstituted furan (**1.24**), using an aldehyde starting material, and 2,4-disubstituted furans (**1.23**, **1.25-1.33**), using ketone or ester starting materials, all competently afforded the corresponding furan in excellent yield (Table 1.2). Most notable of these is the use of an aldehyde-bearing substrate, which forms 3,4-disubstituted furan **1.24**. This substitution pattern would

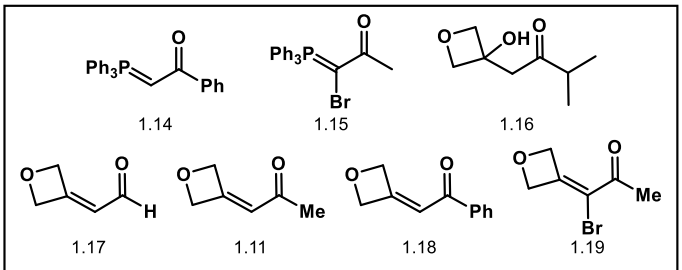


Figure 1.1. Synthesized compounds for substrate scope

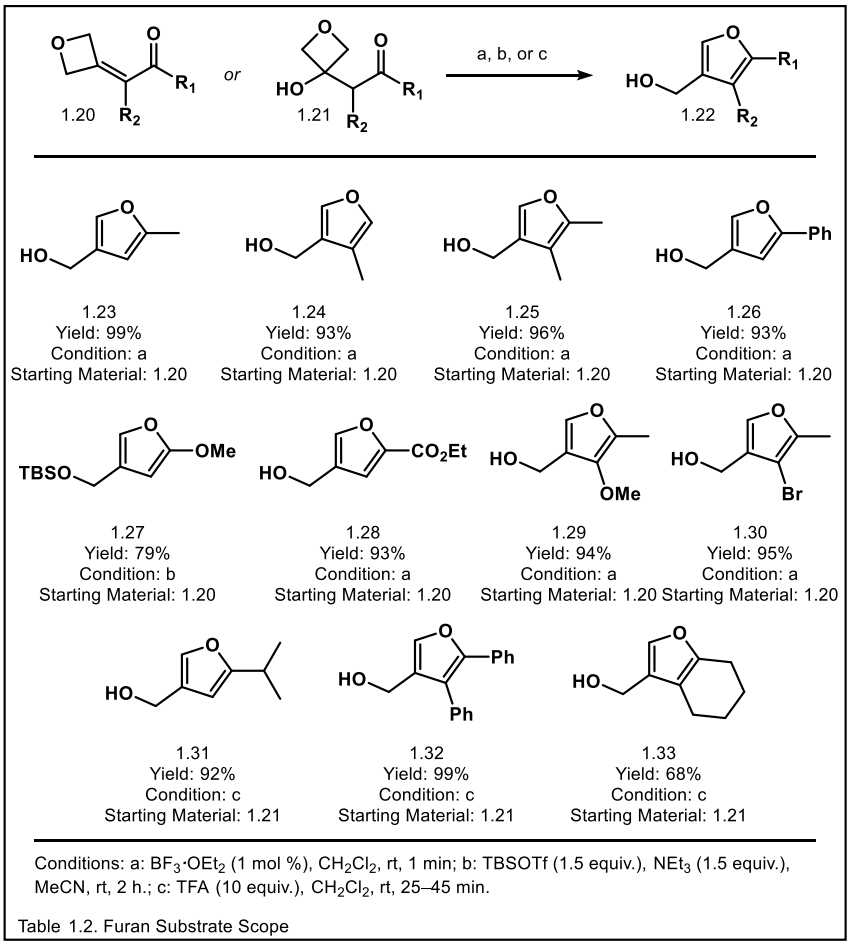
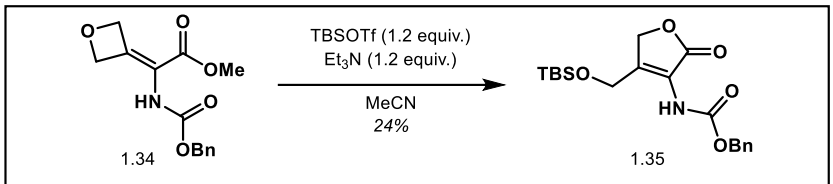
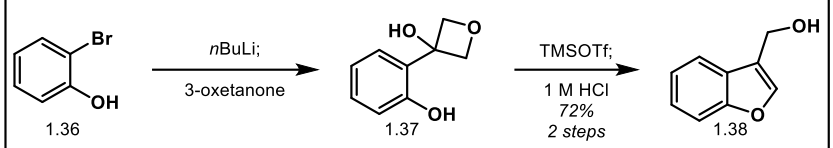


Table 1.2. Furan Substrate Scope

require a highly unstable 1,4-dialdehyde precursor using the Paal-Knorr furan synthesis; however, with this method it can be synthesized in 93% yield from stable starting materials. Tri-substituted furans (**1.25**, **1.29**, **1.32**, and **1.33**) and furans bearing a bromine substitution (**1.30**) were also synthesized this way. β-hydroxy ketones resulting from an aldol addition reaction also performed well, giving the corresponding furan in moderate to excellent yield after treatment with TFA (**1.28**, **1.29**, **1.30**). Interestingly, I treated substrate **1.34** with TBSOTf to observe the effect of a nitrogen substitution on the cyclization. Surprisingly, furanone **1.35** was formed in 24% yield (Equation 1.6). Lastly, benzofuran **1.38** was synthesized in a two-step sequence from 2-bromophenol and 3-oxetanone in 72% yield (Scheme 1.2).[29]



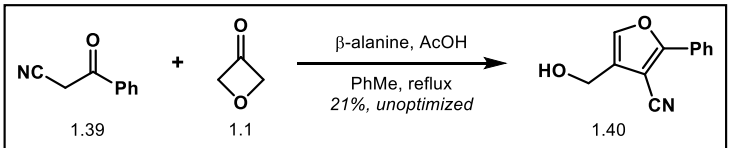
Equation 1.6. Unexpected formation of furanone



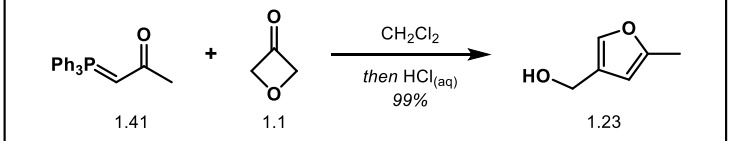
Scheme 1.2. Synthesis of benzofuran

1.3.3 One-Pot Procedure

While this transformation is already operationally very simple, requiring only substrate, catalytic quantities of Lewis acid, and solvent, I developed a one-pot procedure from commercially available 3-oxetanone. While attempting to perform a Knoevenagel condensation between benzoylacetonitrile and 3-oxetanone to afford the desired enone, I instead observed a 21% yield of furan **1.40** (Equation 1.7).[30] The cyclization directly to the furan likely results from the reaction being run under acidic conditions at an elevated temperature. Having observed this result, I hypothesized that a one-pot procedure for our standard substrates could likely be achieved. After performing the Wittig olefination with 3-oxetanone, the reaction mixture was directly treated with aqueous HCl to afford the desired furan in 99% yield (Equation 1.8).



Equation 1.7: Initial hit on one-pot sequence

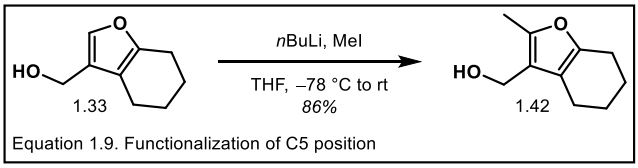


Equation 1.8: Optimized one-pot procedure

1.3.4 Functionalization of C5 Position

Since we already demonstrated formation of di- and tri-substituted furans, we wished to demonstrate formation of fully substituted furans with this method. Functionalization of

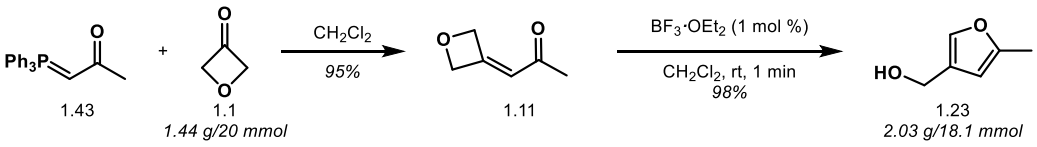
oxetanones is known; however, greater efficiency can be achieved by directly functionalizing the C5 position following cyclization. Functionalization post-cyclization obviates the need to control E/Z selectivity of the Wittig reaction or condensation onto 3-oxetanone or the regioselectivity of the cyclization. Additionally, functionalization at the C2/C5 position of furans is well-documented. Dr. Alex White demonstrated that deprotonation with *n*BuLi and alkylation with MeI works well, giving an 86% yield of the desired fully substituted furan **1.42** (Equation 1.9).



Equation 1.9. Functionalization of C5 position

1.3.5 Scalability

To demonstrate the utility of this method, Dr. Alex White performed this reaction on gram-scale. Using 1.44 g/20 mmol of 3-oxetanone, he obtained cyclization precursor **1.11** in 95% yield after Wittig olefination (Scheme 1.3). Using 2.07 g/18.5 mmol of the isolated material, the cyclization to furan **1.23** was afforded in 98% yield in less than 1 minute. Notably, this reaction was performed at 0 °C since a mild exothermic event was observed.

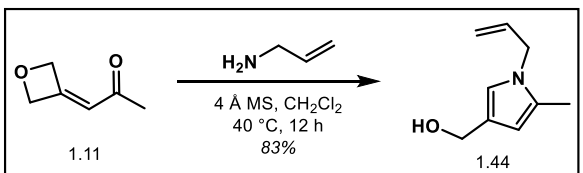


Scheme 1.3. Demonstration of method on gram-scale

1.4 Synthesis of Pyrroles and Indoles

1.4.1 Development of Conditions

We hypothesized that, similar to the Paal–Knorr synthesis, this method could be translated to the synthesis of pyrroles. Dr. Alex White found that treatment of **1.11** with two equivalents of allylamine in the presence of 4 Å molecular sieves for 12 hours resulted in an 83%



Equation 1.10. Initial result for pyrrole formation

yield of pyrrole **1.44** (Equation 1.10). Shorter reaction times, and/or 1 or 4 equivalents of allylamine led to greater quantities of undesired 1,4-addition product. This suggests that 1,4-addition of the amine likely proceeds prior to condensation of a second equivalent of amine. Following cyclization, the first amine is eliminated to aromatize the ring,

1.4.2 Pyrrole/Indole Substrate Scope

Dr. Alex White conducted the entirety of the pyrrole substrate scope. Similar to the furan scope, this method is particularly useful for synthesizing 3,4-disubstituted pyrroles (**1.45**), as these would normally require a difficult-to-access 1,4-dialdehyde precursor Table 1.3). Allyl and alkylamines were both tolerated (**1.45-1.50**), along with alkyl and aryl substitutions (**1.45-1.50**). Both the enones and the β-hydroxy ketones performed well in this reaction to form their corresponding pyrroles (**1.20, 1.21**). Similar to the strategy used to synthesize benzofurans, indoles could also be formed.

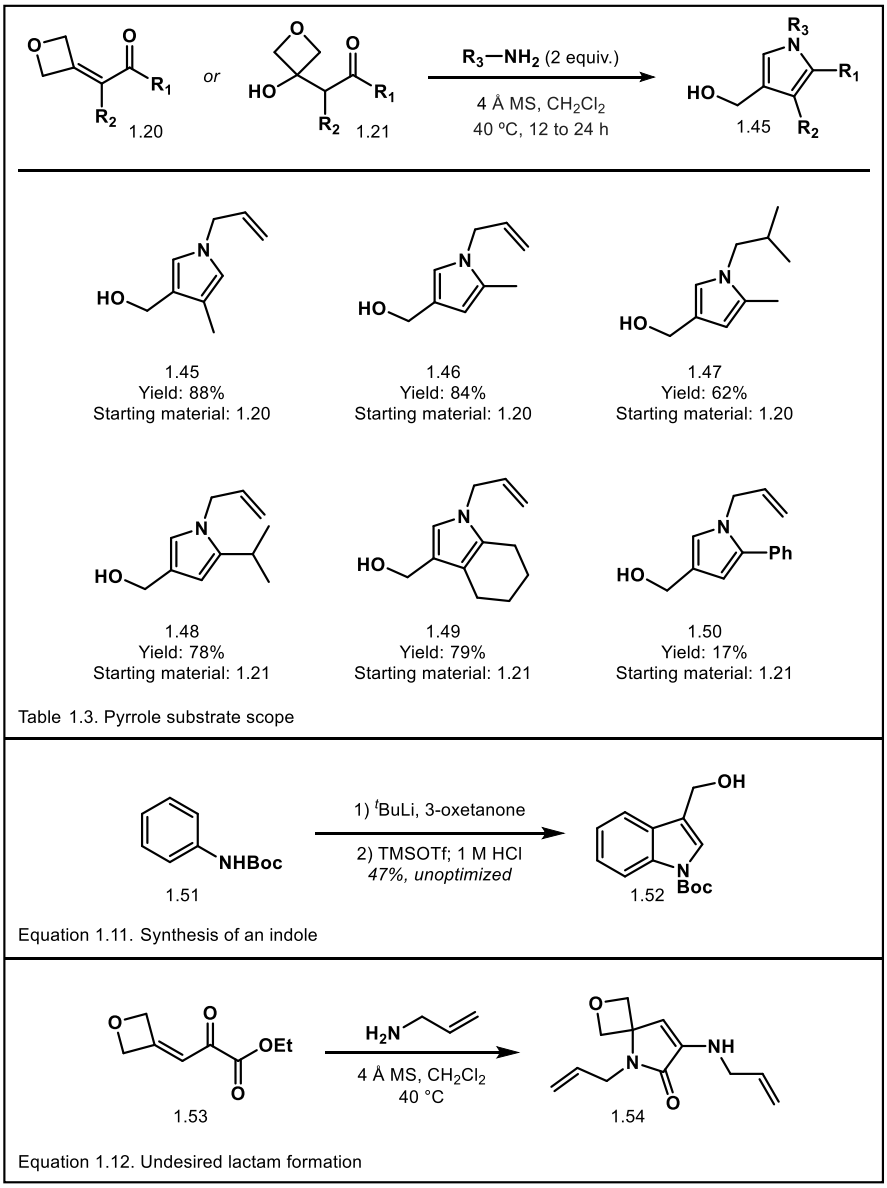


Table 1.3. Pyrrole substrate scope

Equation 1.11. Synthesis of an indole

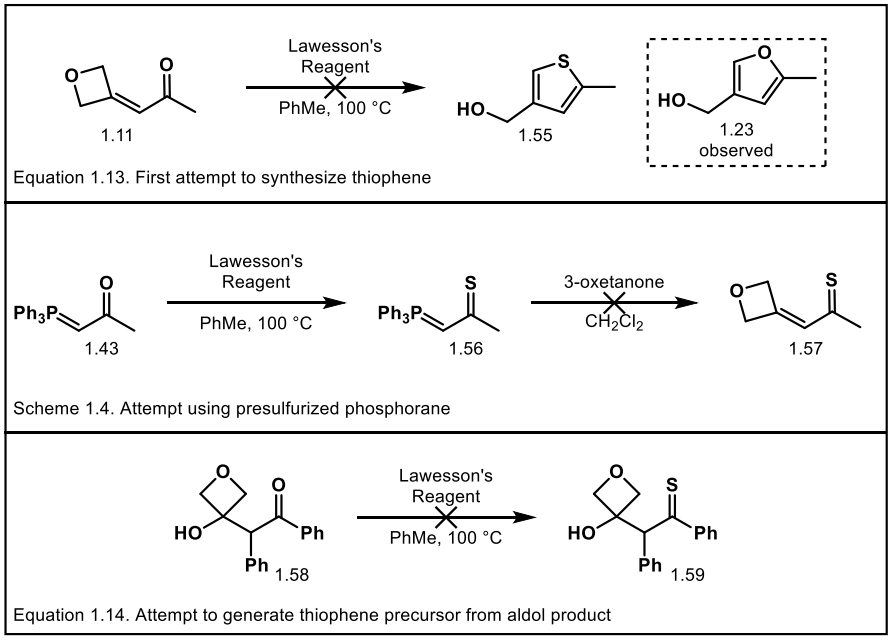
Equation 1.12. Undesired lactam formation

In a two-step procedure beginning with Boc-protected aniline and 3-oxetanone, indole **1.52** was obtained in a 47% unoptimized yield (Equation 1.11).

Unfortunately, there are several limitations to the pyrrole scope. First, attempts to synthesize *N*-aryl pyrroles were met with substitution of the alcohol with another equivalent of aniline. Second, free *N*-H pyrroles have not been synthesized using this method. Lastly, lactam **1.54** was synthesized when attempting to cyclize **1.53** to form a pyrrole with an ester substitution at the 2-position (Equation 1.12). Despite these drawbacks, this method can reliably generate *N*-alkyl pyrroles of varying substitution patterns.

1.4.3 Attempts to Synthesize Thiophenes

In addition to furans and pyrroles, we wanted to explore the expansion of this methodology to thiophenes as well. I treated oxetane-bearing enone **1.11** with Lawesson's reagent attempting to form the thiocarbonyl;[31] however, I only observed conversion to the furan (Equation 1.13). Instead, the thiocarbonyl was synthesized from the corresponding Wittig reagent (Scheme 1.4). When the Wittig olefination was attempted, neither the Wittig product nor the thiophene was produced. Lastly, Dr. Alex White treated β-hydroxy ketone **1.58** with Lawesson's reagent, but this produced an intractable mixture of products (Equation 1.14). Ultimately, thiophenes could not be generated with this method.



Equation 1.13. First attempt to synthesize thiophene

Scheme 1.4. Attempt using presulfurized phosphorane

Equation 1.14. Attempt to generate thiophene precursor from aldol product

1.5 Conclusion

In conclusion, we have developed a highly efficient, scalable, and operationally simple method to synthesize highly substituted furans and pyrroles from keto-oxetanes. The keto-oxetanes function as redox-equivalent 1,4-dicarbonyl surrogates that obviate the need for often unstable, dissonant 1,4-dicarbonyl motifs. Cyclization precursors are stable once synthesized, and can be stored for extended periods of time. They are easily synthesized using simple carbonyl chemistry-based reactions such as Wittig alkenylations, aldol additions, and Knoevenagel condensations. The ease of synthesis of the starting materials and the simple, atom-economical transformation to form the 5-membered aromatic heterocycle make this an ideal method for the synthesis of π-rich aromatic heterocycles.

1.6 Distribution of Credit and Contributions

- **Dr. Alex White** is credited with the genesis of the project and discovery of the initial reactivity. He is acknowledged for performing the reactions for both the furan and pyrrole substrate scopes following optimization of reaction conditions. Additionally, he developed and optimized conditions for the pyrrole syntheses. Lastly, he performed the furan functionalization reactions and the demonstration of scalability.
- Portions of the text and several of the figures, tables, schemes, and equations were adapted from the thesis of **Dr. Alex White**, from the publication of this work, and from the Second Year Report and Orals Report of **Ryan Kozlowski**.

1.7 Experimental Information

1.7.1 Materials and Methods

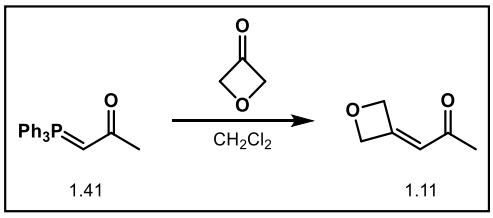
All reactions were carried out in oven-dried (140 °C) or flame-dried glassware under an atmosphere of dry argon unless otherwise noted. Dry dichloromethane (CH_2Cl_2), tetrahydrofuran (THF), diethyl ether (Et_2O), acetonitirile (MeCN), toluene (PhMe), and dimethoxyethane (DME)

were obtained by percolation through columns packed with neutral alumina and columns packed with Q5 reactant, a supported copper catalyst for scavenging oxygen, under a positive pressure of argon. Solvents used for liquid-liquid extraction and chromatography were: Ethyl acetate, (EtOAc, Sigma-Aldrich, ACS grade) hexanes (Sigma-Aldrich, ACS grade), dichloromethane (CH_2Cl_2, Fisher, ACS grade), acetone (Sigma-Aldrich, ACS Grade), diethyl ether (Et_2O, Fisher, ACS grade), and pentane (Sigma-Aldrich, ACS grade). Reactions that were performed open to air utilized solvent dispensed from a wash bottle or solvent bottle, and no precautions were taken to exclude water. Column chromatography was performed using EMD Millipore 60 Å (0.040–0.063 mm) mesh silica gel (SiO_2). Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 TLC plates. Visualization was accomplished with UV (210 nm), and potassium permanganate ($KMnO_4$) or *p*-anisaldehyde staining solutions.

^1H NMR and ^{13}C NMR spectra were recorded at 298 K on Bruker GN500 (500 MHz, ^1H; 125 MHz, ^{13}C) and Bruker CRYO500 (500 MHz, ^1H; 125 MHz, ^{13}C) spectrometers. ^1H and ^{13}C spectra were referenced to residual chloroform (7.26 ppm, ^1H; 77.00 ppm, ^{13}C) or residual methanol (3.31 ppm, ^1H; 49.00, ppm ^{13}C). Chemical shifts are reported in ppm and multiplicities are indicated by: s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), hept (heptet), m (multiplet), and br s (broad singlet). Coupling constants, *J*, are reported in Hertz. The raw fid files were processed into the included NMR spectra using MestReNova 11.0, (Mestrelab Research S. L.). Infrared (IR) spectra were recorded on a Varian 640-IR instrument on NaCl plates and peaks are reported in cm^{-1}. Mass spectrometry data was obtained from the University of California, Irvine Mass Spectrometry Facility. High-resolution mass spectra (HRMS) were recorded on a Waters LCT Premier spectrometer using ESI-TOF (electrospray ionization-time of flight) or a Waters GCT Premier Micromass GC-MS (chemical ionization), and data are reported in the form of (*m/z*).

1.7.2 Experimental Procedures and Characterization Data

Substrate Synthesis



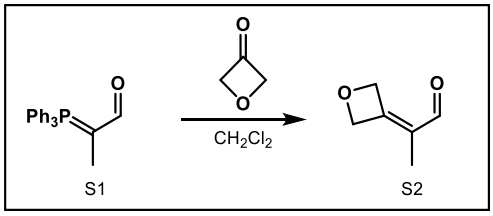
1-(Oxetan-3-ylidene)propan-2-one (1.11)[26] was synthesized according to literature precedent: To a 10 mL round bottom flask were added solid phosphorane **1.41** (891 mg, 2.8 mmol, 1.4 equiv) and dry CH_2Cl_2 (2.6 mL). To the solution was added 3-oxetanone (130 µL, 2.0 mmol, 1.0 equiv) and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was passed through a silica plug using 1:1 Et_2O/pentane as the eluent. Fractions containing the product were pooled and concentrated *in vacuo* to give enone **1.11** (191 mg, 1.7 mmol, 85% yield) as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.01 (p, *J* = 2.4 Hz, 1H), 5.53 (dtd, *J* = 5.2, 2.7, 1.3 Hz, 2H), 5.31 (ddt, *J* = 5.0, 2.2, 1.2 Hz, 2H), 2.18 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 196.6, 158.5, 118.0, 82.0, 78.9, 30.3.

IR (Neat Film NaCl) 2920, 2853, 1708, 1649, 1364, 1197, 952.

HRMS (CI+) *m/z* calc'd for $C_6H_9O_2$ $[M+H]^+$: 113.0603; found 113.0599.



2-(Oxetan-3-ylidene)propanal (S2): To a 10 mL round bottom flask were added solid phosphorane **S1** (891 mg, 2.8 mmol, 1.4 equiv) and dry CH_2Cl_2 (2.6 mL). To the solution was

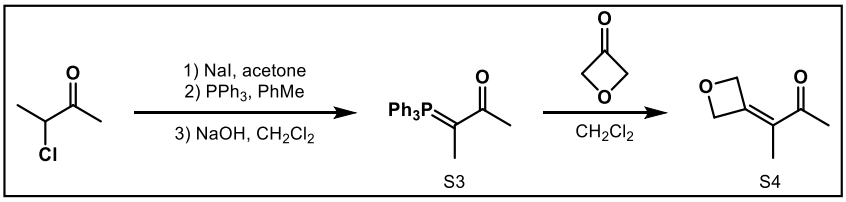
added 3-oxetanone (130 µL, 2.0 mmol, 1.0 equiv) and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was passed through a silica plug using 1:1 Et_2O/pentane as the eluent. Fractions containing the product were pooled and concentrated *in vacuo* to give enone **S2** (147 mg, 1.32 mmol, 66% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.50 (s, 1H), 5.61 (dp, *J* = 5.8, 2.0 Hz, 2H), 5.42 (dp, *J* = 5.1, 1.6 Hz, 2H), 1.63 (p, *J* = 1.8 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 188.5, 157.2, 127.7, 79.2, 78.6, 9.5.

IR (Neat Film NaCl) 2924, 2862, 1708, 1686, 1667, 1292, 1271, 957, 894.

HRMS (CI+) *m/z* calc'd for $C_6H_9O_2$ $[M+H]^+$: 113.0603; found 113.0602.



3-(Triphenylphosphaneylidene)butan-2-one (S3)[32] was synthesized according to literature precedent: To a 50 mL round bottom flask open to air were added solid NaI (1.06 g, 7.07 mmol, 1.01 equiv) and acetone (10 mL). To the solution was added 3-chloro-2-butanone (0.71 mL, 7.0 mmol, 1.00 equiv) and the resulting mixture was stirred at room temperature for 4 h. The reaction mixture was filtered through Celite® and concentrated *in vacuo*. The residue was dissolved in toluene (12 mL) and triphenylphosphine (1.39 g, 7.0 mmol, 1.0 equiv) was added. The mixture was stirred at 80 °C for 16 h. The reaction mixture was cooled to room temperature, concentrated *in vacuo*, filtered through Celite®, and washed with Et_2O. The filtrate was concentrated *in vacuo* and the residue was dissolved in CH_2Cl_2 (47 mL). A solution of aq NaOH (1 M, 14.0 mL) was added and the biphasic mixture was stirred vigorously at room temperature for 2 h. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic

phases were washed with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give phosphorane **S3** as an off-white solid (722 mg). The product was used without further purification.

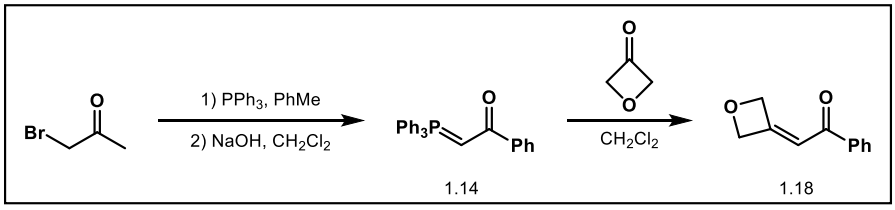
3-(Oxetan-3-ylidene)butan-2-one (S4): To a 5 mL round bottom flask were added solid phosphorane **S3** (408 mg, 1.23 mmol, 1.4 equiv) and dry CH_2Cl_2 (2.4 mL). To the solution was added 3-oxetanone (60 µL, 0.88 mmol, 1.0 equiv) and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was passed through a silica plug using 1:1 Et_2O/pentane as the eluent. Fractions containing the product were pooled and concentrated *in vacuo* to give enone **S4** (100 mg, 0.79 mmol, 90% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.55 – 5.42 (m, 2H), 5.40 – 5.27 (m, 2H), 2.13 (s, 2H), 1.69 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 197.4, 150.7, 126.8, 80.9, 78.6, 28.3, 13.0.

IR (Neat Film NaCl) 2922, 2852, 1666, 1361, 970, 946, 868.

HRMS (CI+) *m/z* calc'd for $C_7H_{10}O_2$ $[M]^+$: 126.068; found 126.0677.



1-Phenyl-2-(triphenylphosphaneylidene)ethan-1-one (1.14)[32] was synthesized according to literature precedent: To a 25 mL round bottom flask open to air were added 2-bromoacetophenone (955 mg, 5.0 mmol, 1.0 equiv), triphenylphosphine (1.31 g, 5.0 mmol, 1.0 equiv), and dry toluene (10 mL). The reaction was stirred at 80 °C for 24 h. The reaction mixture was filtered through Celite®, washed with Et_2O, and concentrated *in vacuo* to obtain a white solid. The residue was dissolved in CH_2Cl_2 (33 mL) and a solution of aq NaOH (1 M, 10 mL) was added. The biphasic mixture was stirred vigorously at room temperature for 2 h. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were washed

with brine, dried over $MgSO_4$, and concentrated *in vacuo* to give phosphorane **1.14** as a white solid (1.90 g). The product was used without further purification.

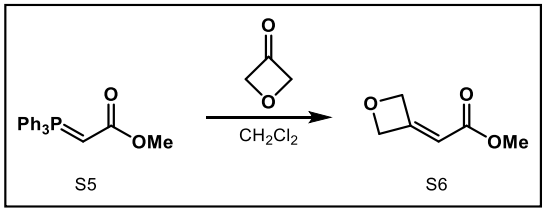
2-(Oxetan-3-ylidene)-1-phenylethan-1-one (1.18): To a 10 mL round bottom flask were added solid phosphorane **1.14** (985 mg, 2.59 mmol, 1.4 equiv) and dry CH_2Cl_2 (2.4 mL). To the solution was added 3-oxetanone (120 µL, 1.85 mmol, 1.0 equiv) and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was passed through a silica plug using 1:1 Et_2O/pentane as the eluent. Fractions containing the product were pooled and concentrated *in vacuo* to give enone **1.18** (319 mg, 1.83 mmol, 99% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 – 7.89 (m, 2H), 7.64 – 7.53 (m, 1H), 7.53 – 7.43 (m, 2H), 6.84 (p, *J* = 2.4 Hz, 1H), 5.75 – 5.65 (m, 2H), 5.50 – 5.35 (m, 2H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 189.0, 161.5, 137.6, 133.1, 128.7, 128.2, 113.4, 82.7, 79.3.

IR (Neat Film NaCl) 2951, 2919, 2844, 1619, 1367, 945, 760, 694.

HRMS (ES+) *m/z* calc'd for $C_{11}H_{11}O_2$ $[M+H]^+$: 175.0759; found 175.0764.



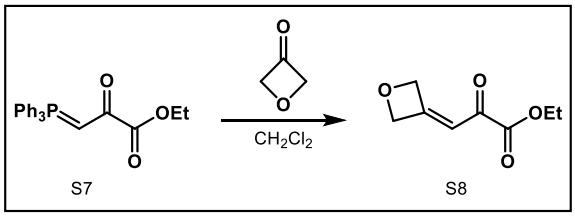
Methyl 2-(oxetan-3-ylidene)acetate (S6): To a 10 mL round bottom flask were added solid phosphorane **S5** (726 mg, 2.17 mmol, 1.4 equiv) and dry CH_2Cl_2 (2.0 mL). To the solution was added 3-oxetanone (100 µL, 1.55 mmol, 1.0 equiv) and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was passed through a silica plug using 1:1 Et_2O/pentane as the eluent. Fractions containing the product were pooled and concentrated *in vacuo* to give enone **S6** (190 mg, 1.47 mmol, 95% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 (p, *J* = 2.4 Hz, 1H), 5.54 – 5.46 (m, 2H), 5.34 – 5.26 (m, 2H), 3.71 (d, *J* = 0.9 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 165.6, 159.5, 110.7, 81.0, 78.4, 51.5.

IR (Neat Film NaCl) 2956, 2852, 1725, 1438, 1352, 1210, 957.

HRMS (CI+) *m/z* calc'd for $C_6H_9O_3$ $[M+H]^+$: 129.0552; found 129.0553.



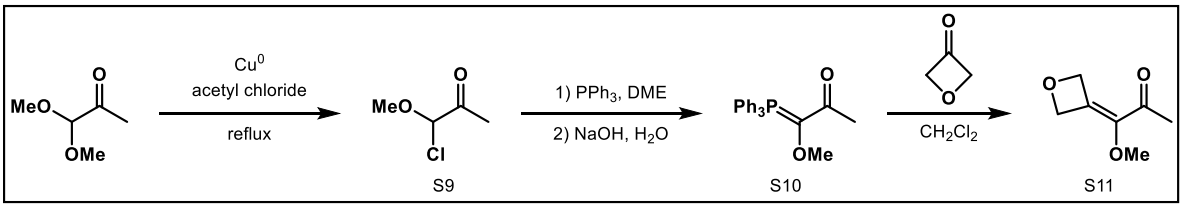
Ethyl 3-(oxetan-3-ylidene)-2-oxopropanoate (S8): To a 10 mL round bottom flask were added solid phosphorane **S7** (1.05 g, 2.80 mmol, 1.4 equiv) and dry CH_2Cl_2 (2.6 mL). To the solution was added 3-oxetanone (130 µL, 2.00 mmol, 1.0 equiv) and the resulting mixture was stirred at room temperature for 16 h. The reaction mixture was passed through a silica plug using 1:1 Et_2O/pentane as the eluent. Fractions containing the product were pooled and concentrated *in vacuo* to give enone **S8** (103 mg, 0.6 mmol, 30% yield) as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.78 (p, *J* = 2.3 Hz, 1H), 5.62 – 5.52 (m, 2H), 5.44 – 5.33 (m, 2H), 4.33 (q, *J* = 7.1 Hz, 2H), 1.37 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 181.1, 166.7, 161.0, 113.2, 82.4, 79.3, 62.7, 14.0.

IR (Neat Film NaCl) 2996, 2938, 2911, 1734, 1703, 1642, 1429, 1297, 1281, 1257, 1144, 949, 920.

HRMS (ES+) *m/z* calc'd for $C_8H_{10}O_4Na$ $[M+Na]^+$: 193.0477; found 193.0467.



1-Chloro-1-methoxypropan-2-one (S9)[33] was synthesized according to literature precedent: To a 50 mL two-neck flask fitted with a reflux condenser were added dimethoxy acetone (12.1 mL, 100 mmol, 1 equiv), acetyl chloride (7.8 mL, 110 mmol, 1.1 equiv), and copper powder (102 mg, 1.60 mmol, 1.6 mol%). The resulting suspension was heated to reflux (~60 °C) for 2 h, changing from a metallic copper color to black as the reaction progressed. The reaction mixture was transferred to a 50 mL round bottom flask and was purified by vacuum distillation (96 °C at 130 torr) to collect **S9** (6.43 g, 0.52 mmol, 52% yield) as pale yellow oil. 1H and 13C NMR spectra were consistent with those previously reported.[3]

1-Methoxy-1-(triphenylphosphaneylidene)propan-2-one (S10)[33] was synthesized according to literature precedent: To a 50 mL round bottom flask open to air were added **S9** (2.82 g, 23.0 mmol, 1 equiv) and DME (17 mL). The mixture was a clear colorless solution. To the stirred mixture was added triphenylphosphine (6.82 g, 26.0 mmol, 1.13 equiv). The reaction mixture was stirred at room temperature for 5 h, at which point a white precipitate had formed. DME was removed *in vacuo*. The resulting residue was suspended in aq NaOH (1 M, 25 mL) and stirred at room temperature for 10 min. The pale yellow suspension was extracted 3 times with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated to give phosphorane **S10** as a pale yellow solid (5.21 g). The product was used without further purification.

1-Methoxy-1-(oxetan-3-ylidene)propan-2-one (S11): To a 50 mL round bottom flask were added solid phosphorane **S10** (4.98 g, 14.3 mmol, 1.4 equiv) and dry CH_2Cl_2 (13 mL). To the solution was added 3-oxetanone (660 µL, 10.2 mmol, 1.0 equiv) and the resulting mixture was

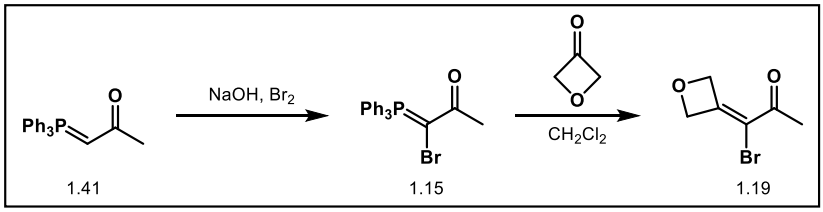
stirred at room temperature for 12 h. The reaction mixture was passed through a silica plug using 1:1 Et_2O/pentane as the eluent. Fractions containing the product were pooled and concentrated *in vacuo* to give enone **S11** (1.35 g, 9.45 mmol, 93% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.57 (t, *J* = 3.8 Hz, 2H), 5.46 (t, *J* = 3.7 Hz, 2H), 3.66 (s, 3H), 2.20 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 196. 7, 142.3, 123.3, 80.6, 77.3, 56.8, 26.7.

IR (Neat Film NaCl) 2923, 2857, 1655, 1358, 1293, 1211, 1177, 1120, 946.

HRMS (ES+) *m/z* calc'd for $C_7H_{10}O_3Na$ $[M+Na]^+$: 165.0528; found 165.0522.



1-Bromo-1-(triphenylphosphaneylidene)propan-2-one (1.15)[33] was synthesized according to literature precedent: To a 100 mL round bottom flask were added **1.41** (1.52 g, 5.0 mmol, 1.0 equiv) and CH_2Cl_2 (34 mL). To this solution, bromine (0.26 mL, 5.0 mmol, 1.0 equiv) was added dropwise followed by a solution of aq NaOH (0.25 M, 22 mL, 1.1 equiv). The biphasic mixture was stirred vigorously at room temperature for 10 min. The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to give phosphorane **1.15** as a tan solid (1.62 g). The product was used without further purification.

1-Bromo-1-(oxetan-3-ylidene)propan-2-one (1.19): To a 10 mL round bottom flask were added solid phosphorane **1.15** (812 mg, 2.04 mmol, 1.4 equiv) and dry CH_2Cl_2 (1.9 mL). To the solution was added 3-oxetanone (94.0 µL, 1.46 mmol, 1.0 equiv) and the resulting mixture was stirred at room temperature for 18 h. The reaction mixture was passed through a silica plug using 1:1

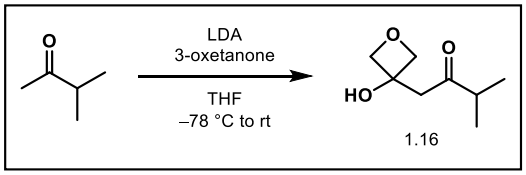
Et_2O/pentane as the eluent. Fractions containing the product were pooled and concentrated *in vacuo* to give enone **1.19** (244 mg, 1.28 mmol, 88% yield) as pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 – 5.30 (m, 2H), 5.23 – 5.10 (m, 2H), 2.40 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 192.5, 155.4, 109.9, 80.4, 79.48, 28.0.

IR (Neat Film NaCl) 2916, 2847, 1693, 1650, 1359, 1231, 953.

HRMS (CI+) *m/z* calc'd for $C_6H_7BrO_2Na$ $[M]^+$: 189.9629; found 189.9627.



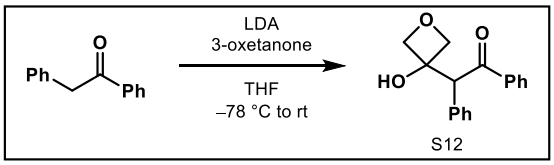
1-(3-Hydroxyoxetan-3-yl)-3-methylbutan-2-one (1.16): To a 10 mL round bottom flask were added *n*-butyllithium (2.38 M in hexanes, 0.84 mL, 2.0 mmol, 1.0 equiv) and dry THF (1.6 mL). The solution was cooled to 0 °C and diisopropylamine (31 µL, 2.2 mmol, 1.1 equiv) was added. The resulting solution was stirred at 0 °C for 10 min then cooled to -78 °C. A solution of 2-methyl-2-butanone (0.22 mL, 2.0 mmol, 1 equiv) in dry THF (4.0 mL) was added dropwise via cannula. The mixture was stirred for 2 h at -78 °C followed by the dropwise addition of 3-oxetanone (120 µL, 2.0 mmol, 1.0 equiv), producing a white precipitate. The reaction mixture was allowed to slowly warm to room temperature and stirred for an additional 12 h. The reaction was quenched with saturated ammonium chloride and extracted three times with Et_2O. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 60% EtOAc in hexanes) to give aldol adduct **1.16** (171 mg, 1.08 mmol, 54% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.69 (d, *J* = 6.9 Hz, 2H), 4.40 – 4.32 (m, 2H), 3.92 (s, 1H), 3.12 (s, 2H), 2.64 (hept, *J* = 7.0 Hz, 1H), 1.14 (d, *J* = 7.0 Hz, 7H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 215.8, 83.2, 72.0, 47.0, 41.5, 17.9.

IR (Neat Film NaCl) 3403, 2970, 2876, 1706, 1468, 1385, 1259, 971.

HRMS (CI+) *m/z* calc'd for $C_8H_{15}O_3$ $[M+H]^+$: 159.1021; found 159.1027.



S12

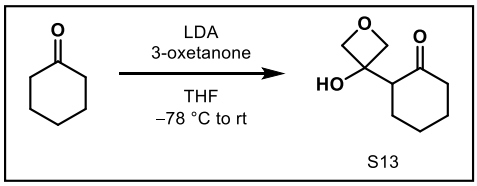
2-(3-Hydroxyoxetan-3-yl)-1,2-diphenylethan-1-one (S12): To a 10 mL round bottom flask were added *n*-butyllithium (2.58 M in hexanes, 0.12 mL, 0.30 mmol, 1.2 equiv) and dry THF (0.2 mL). The solution was cooled to 0 °C and diisopropylamine (40 µL, 0.30 mmol, 1.2 equiv) was added. The resulting solution was stirred at 0 °C for 10 min then cooled to -78 °C. A solution of 2-phenylacetophenone (50 mg, 0.25 mmol, 1 equiv) in dry THF (0.38 mL) was added dropwise via cannula, resulting in a bright yellow solution. The mixture was stirred for 2 h at -78 °C followed by the dropwise addition of a solution of 3-oxetanone (3 M in THF, 100 µL, 0.30 mmol, 1.2 equiv), producing a white precipitate. The reaction mixture was allowed to slowly warm to room temperature and stirred for an additional 12 h. The reaction was quenched with saturated ammonium chloride and extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 30% EtOAc in hexanes) to give aldol adduct **S12** (58 mg, 0.22 mmol, 88% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 – 7.90 (m, 2H), 7.56 – 7.49 (m, 1H), 7.39 (t, *J* = 7.8 Hz, 2H), 7.36 – 7.27 (m, 5H), 5.21 (s, 1H), 4.82 (d, *J* = 6.7 Hz, 1H), 4.61 (d, *J* = 7.1 Hz, 1H), 4.55 (s, 1H), 4.48 (d, *J* = 7.1 Hz, 1H), 4.45 (d, *J* = 6.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 201.4, 135.5, 134.0, 133.7, 129.5, 129.12, 129.05, 128.7, 128.1, 83.9, 80.6, 75.5, 58.5.

IR (Neat Film NaCl) 3477, 3062, 3028, 2951, 2877, 1672, 1597, 1579, 1449, 1323, 1255, 1215, 974, 909, 729, 700, 652.

HRMS (ES+) *m/z* calc'd for $C_{17}H_{16}O_3Na$ $[M+Na]^+$: 291.0997; found 291.0993.



S13

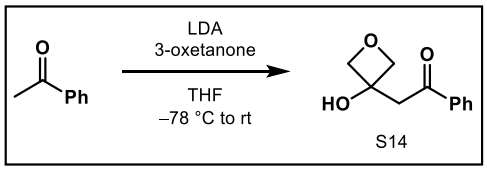
2-(3-Hydroxyoxetan-3-yl)cyclohexan-1-one (S13): To a 25 mL round bottom flask were added *n*-butyllithium (2.44 M in hexanes, 0.82 mL, 2.0 mmol, 1 equiv) and dry THF (1.6 mL). The solution was cooled to 0 °C and diisopropylamine (310 µL, 2.2 mmol, 1.1 equiv) was added. The resulting solution was stirred at 0 °C for 10 min then cooled to -78 °C. A solution of cyclohexanone (210 µL, 2.0 mmol, 1.0 equiv) in dry THF (4.0 mL) was added dropwise via cannula. The mixture was stirred for 2 h at -78 °C followed by the dropwise addition 3-oxetanone (130 µL, 2.0 mmol, 1.0 equiv), producing an off-white precipitate. The reaction mixture was allowed to slowly warm to room temperature and stirred for an additional 2 h. The reaction was quenched with saturated ammonium chloride and extracted three times with Et_2O. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 30% to 50% EtOAc in hexanes) to give aldol adduct **S13** (210 mg, 0.72 mmol, 36% yield) as yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.68 (d, *J* = 7.0 Hz, 1H), 4.58 (d, *J* = 7.0 Hz, 1H), 4.43 (d, *J* = 7.0 Hz, 2H), 3.30 (s, 1H), 3.00 – 2.89 (m, 1H), 2.48 – 2.29 (m, 2H), 2.22 – 2.06 (m, 2H), 2.04 – 1.92 (m, 1H), 1.81 – 1.59 (m, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 214.2, 83.4, 80.6, 74.0, 57.0, 42.6, 27.9, 27.8, 24.8.

IR (Neat Film NaCl) 3422, 2942, 2871, 1702, 1450, 1315, 1237, 1130, 968.

HRMS (ES+) *m/z* calc'd for $C_9H_{14}O_3Na$ $[M+Na]^+$: 193.0841; found 193.0841.



2-(3-Hydroxyoxetan-3-yl)-1-phenylethan-1-one (S14): To a 25 mL round bottom flask were added *n*-butyllithium (2.70 M in hexanes, 0.89 mL, 2.4 mmol, 1.2 equiv) and dry THF (1.7 mL). The solution was cooled to 0 °C and diisopropylamine (340 µL, 2.4 mmol, 1.2 equiv) was added. The resulting solution was stirred at 0 °C for 10 min then cooled to -78 °C. A solution of acetophenone (230 µL, 2.0 mmol, 1.0 equiv) in dry THF (4.0 mL) was added dropwise via cannula producing a bright yellow solution. The mixture was stirred for 2 h at -78 °C followed by the dropwise addition 3-oxetanone (130 µL, 2.0 mmol, 1.0 equiv), producing a white precipitate. The reaction mixture was allowed to slowly warm to room temperature and stirred for an additional 2 h. The reaction was quenched with saturated ammonium chloride and extracted three times with Et_2O. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 30% to 50% to 60% EtOAc in hexanes) to give aldol adduct **S14** (216 mg, 1.12 mmol, 56% yield) as a white solid.

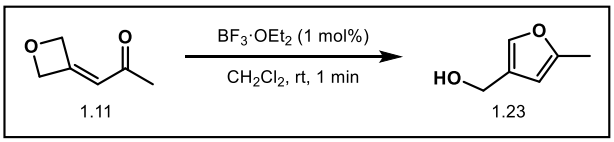
^{1}H NMR (500 MHz, CD_3OD) δ 8.05 – 7.96 (m, 2H), 7.61 (t, *J* = 7.4 Hz, 1H), 7.50 (t, *J* = 7.7 Hz, 2H), 4.70 (q, *J* = 6.8 Hz, 4H), 3.61 (s, 2H).

^{13}C NMR (125 MHz, CD_3OD) δ 199.61, 138.54, 134.50, 129.7, 129.2, 85.1, 73.6, 46.5.

IR (Neat Film NaCl) 3351, 2964, 2886, 2732, 1683, 1216, 1108, 760, 692.

HRMS (ES+) *m/z* calc'd for $C_{11}H_{12}O_3Na$ $[M+Na]^+$: 215.0684; found 215.0695.

Furan Substrate Scope



General Procedure A – for Lewis-acid-catalyzed oxetane rearrangement to produce furans:

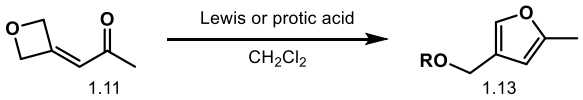
(5-Methylfuran-3-yl)methanol (1.23): To a 1 dram vial were added a solution of enone **1.11** (0.5 M in CH_2Cl_2, 0.40 mL, 0.20 mmol, 1 equiv) and a solution of BF_3OEt_2 (10 mM in CH_2Cl_2, 0.20 mL, 2.0 µmol, 1 mol%). The mixture was stirred at room temperature for 1 min and passed through a plug of silica using Et_2O as the eluent. Fractions containing the product were pooled and concentrated *in vacuo* to give pure furan **1.23** (22.1 mg, 0.197 mmol, 99% yield) as colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (s, 1H), 6.03 (s, 1H), 4.49 (s, 2H), 2.27 (s, 3H), 1.52 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 153.2, 138.1, 125.9, 105.8, 56.9, 13.5.

IR (Neat Film NaCl) 3362, 2922, 2877, 1557, 1122, 1020, 917, 736.

HRMS (ES+) *m/z* calc'd for $C_{12}H_{16}O_4Na$ $[2M+Na]^+$: 247.0946; found 247.0945.



Entry	*Lewis/Protic Acid*	*Time*	*R =*	*Yield (%)*
1	$BF_3·OEt_2$ (1 mol %)	< 1 min	H	99
2	$BF_3·OEt_2$ (0.1 mol %)	< 5 min	H	99
3	$AlCl_3$ (1 mol %)	< 1 min	H	99[a]
4	$Sc(OTf)_3$ (1 mol %)	< 1 min	H	96[a]
5	TFA (1.0 equiv.)	< 1 min	H	84
6	$ZnCl_2$ (1.0 mol %)	< 1 min	H	93[a]
7	TMSOTf (1.2 equiv.), NEt_3, MeCN	< 5 min	TMS	84
8	$TiCl_4$ (1.0 mol %)	< 1 min	H	83
9	1 M HCl (1.0 equiv.)	< 10 min	H	95

[a]NMR Yield

Table #B. Optimization of reaction conditions

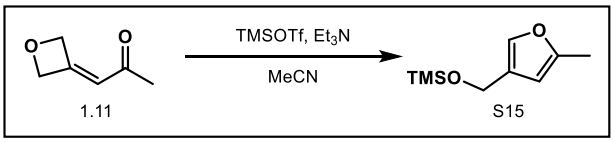
Entry 1: procedure is described above in *General Procedure A*

Entry 2: To a 1 dram vial were added a solution of enone **1.11** (0.5 M in CH_2Cl_2, 0.40 mL, 0.200 mmol, 1 equiv) and a solution of BF_3OEt_2 (1 mM in CH_2Cl_2, 0.20 mL, 0.20 μmol, 0.1 mol%). After stirring at room temperature for 1 min, TLC indicated the presence of starting material. After 5 min, TLC indicated complete conversion. The mixture was passed through a plug of silica using Et_2O as the eluent. Fractions containing the product were pooled and concentrated *in vacuo* to give pure furan **1.23** (22.3 mg, 0.199 mmol, 99% yield) as a colorless oil.

Entries 3, 4, 6: To a 1 dram vial were added a solution of enone **1.11** (0.5 M in CH_2Cl_2, 0.41 mL, 0.207 mmol, 1 equiv) and a solution of the Lewis acid (1 mM in CH_2Cl_2, 0.21 mL, 2.07 μmol, 1.0 mol%). After stirring at room temperature for 1 min, TLC indicated complete conversion. NMR yields were obtained by addition of 1,3,5-trimethoxybenzene as a solution in dichloromethane.

Entry 5: To a 1 dram vial were added a solution of enone **1.11** (0.5 M in CH_2Cl_2, 0.47 mL, 0.234 mmol, 1 equiv) and a solution of $TiCl_4$ (1 mM in CH_2Cl_2, 0.23 mL, 2.34 μmol, 1.0 mol%). After stirring at room temperature for 1 min, TLC indicated complete conversion. The mixture was passed through a plug of silica using Et_2O as the eluent. Fractions containing the product were pooled and concentrated *in vacuo* to give pure furan **1.23** (21.8 mg, 0.194 mmol, 83% yield) as a colorless oil.

Entry 7:



Trimethyl((5-methylfuran-3-yl)methoxy)silane (S15): To a 1 dram vial were added enone **1.11** (50.8 mg, 0.453 mmol, 1 equiv), NEt_3 (0.13 mL, 0.906 mmol, 2 equiv) , and MeCN (1.4 mL). To the solution was added TMSOTf (0.10 mL, 0.544 mmol, 1.2 equiv) and the resulting mixture was stirred at room temperature for 5 min. The reaction was poured over ice water and extracted three times with Et_2O. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 100% pentane) to give furan **S15** (70.3 mg, 0.381 mmol, 84% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (s, 1H), 5.98 (s, 1H), 4.48 (s, 2H), 2.26 (s, 3H), 0.14 (s, 9H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8, 137.8, 125.9, 105.9, 56.64, 13.6, -0.4.

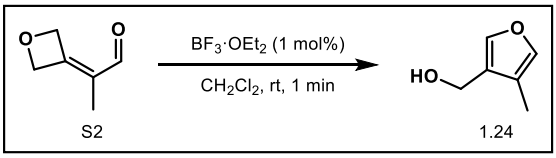
IR (Neat Film NaCl) 2957, 2865, 1559, 1250, 1074, 875, 842.

HRMS (CI+) *m/z* calc'd for $C_9H_{16}O_2SiNa$ $[M+Na]^+$: 207.0817; found 207.0828.

Entry 8: To a 1 dram vial were added a solution of enone **1.11** (0.5 M in CH_2Cl_2, 0.47 mL, 0.234 mmol, 1 equiv) and a solution of $TiCl_4$ (1 mM in CH_2Cl_2, 0.23 mL, 2.34 μmol, 1.0 mol%). After stirring at room temperature for 1 min, TLC indicated complete conversion. The mixture was passed through a plug of silica using Et_2O as the eluent. Fractions containing the product were pooled and concentrated *in vacuo* to give pure furan **1.23** (21.8 mg, 0.194 mmol, 83% yield) as a colorless oil.

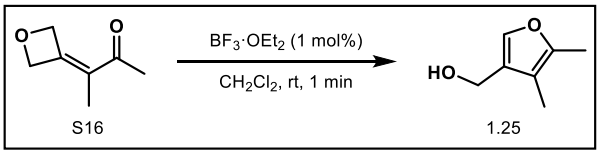
Entry 9: To a 1 dram vial open to air were added enone **1.11** (0.5 M in CH_2Cl_2, 0.40 mL, 0.200 mmol, 1 equiv) and a solution of aq HCl (1 M, 0.20 mL, 0.200 mmol, 1 equiv). After stirring the biphasic mixture vigorously at room temperature for 5 min, TLC indicated the presence of starting

material. After 10 min, TLC indicated complete conversion. The reaction was diluted with CH_2Cl_2 and poured over saturated $NaHCO_3$ (aq). The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to give pure furan **1.23** (21.3 mg, 0.190 mmol, 84% yield) as a colorless oil.



(4-Methylfuran-3-yl)methanol (1.24): Enal **S2** (0.278 mmol) was subjected to *General Procedure A* to give furan **1.24** (28 mg, 0.250 mmol, 93% yield) as a colorless oil.

^{1}H and ^{13}C NMR spectra were consistent with those previously reported.[34]



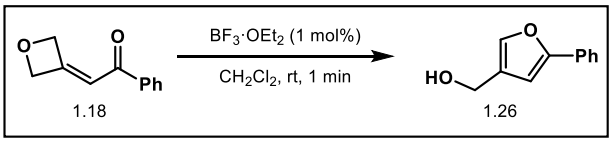
(4,5-Dimethylfuran-3-yl)methanol (1.25): Enone **S16** (0.166 mmol) was subjected to *General Procedure A* to give furan **1.25** (20 mg, 0.159 mmol, 96% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (s, 1H), 4.47 (s, 2H), 2.19 (s, 3H), 1.96 (s, 3H), 1.39 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.5, 137.7, 125.8, 113.5, 55.9, 11.4, 8.0.

IR (Neat Film NaCl) 3346, 2922, 2872, 1569, 1133, 1002, 907, 782, 747.

HRMS (CI+) *m/z* calc'd for $C_7H_{11}O_2$ $[M+H]^+$: 127.0759; found 127.0755.



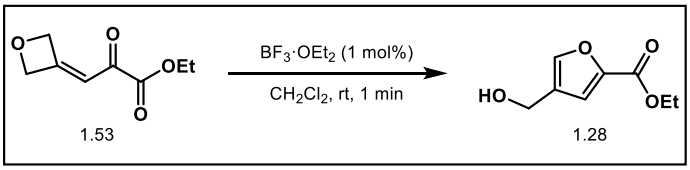
(5-Phenylfuran-3-yl)methanol (1.26): Enone **1.18** (0.161 mmol) was subjected to *General Procedure A* to give furan **1.26** (26 mg, 0.149 mmol, 93% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 – 7.62 (m, 2H), 7.45 (d, *J* = 1.0 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 2H), 7.31 – 7.22 (m, 1H), 6.71 (s, 1H), 4.60 (s, 2H), 1.56 – 1.53 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 154.8, 139.3, 130.6, 128.6, 127.5, 127.2, 123.8, 105.0, 56.9.

IR (Neat Film NaCl) 3233, 3108, 2918, 2850, 1446, 1019, 914, 820, 760, 690.

HRMS (ES+) *m/z* calc'd for $C_{11}H_{10}O_2Na$ $[M+Na]^+$: 197.0578; found 197.0582.



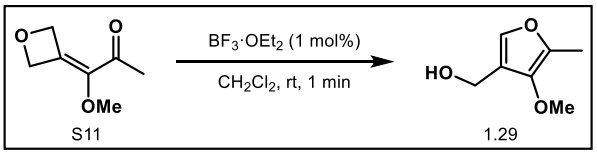
Ethyl 4-(hydroxymethyl)furan-2-carboxylate (1.28): Enone **1.53** (0.229 mmol) was subjected to *General Procedure A* to give furan **1.28** (36 mg, 0.212 mmol, 93% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (s, 1H), 7.19 (s, 1H), 4.58 (s, 2H), 4.35 (q, *J* = 7.1 Hz, 2H), 1.85 (br s, 1H), 1.37 (t, *J* = 7.2 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7, 145.3, 143.3, 127.4, 117.4, 61.1, 56.3, 29.7, 14.3.

IR (Neat Film NaCl) 3414, 3140, 2983, 2921, 1718, 1603, 1511, 1396, 1370, 1315, 1247, 1221, 1191, 1101, 1020, 942, 763.

HRMS (ES+) *m/z* calc'd for $C_8H_{10}O_4Na$ $[M+Na]^+$: 193.0477; found 193.0498



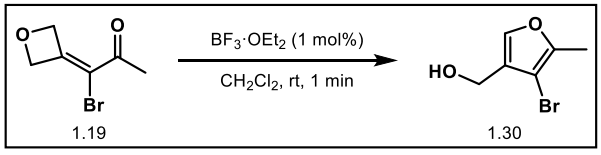
(4-Methoxy-5-methylfuran-3-yl)methanol (1.29): Enone **S11** (0.316 mmol) was subjected to *General Procedure A* to give furan **1.29** (42 mg, 0.295 mmol, 93% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (s, 1H), 4.50 (s, 2H), 3.81 (s, 3H), 2.27 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4, 138.9, 136.7, 120.5, 61.5, 54.9, 11.2.

IR (Neat Film NaCl) 3410, 2937, 2873, 1643, 1571, 1450, 1408, 1284, 1164, 1001.

HRMS (ES+) *m/z* calc'd for $C_7H_{10}O_3Na$ $[M+Na]^+$: 165.0528; found 165.0535.



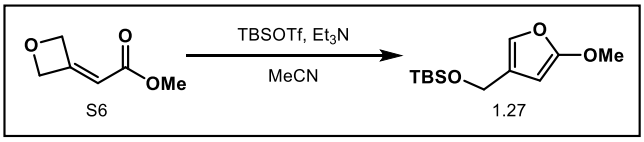
(4-Bromo-5-methylfuran-3-yl)methanol (1.30): Enone **1.19** (0.188 mmol) was subjected to *General Procedure A* to give furan **1.30** (34 mg, 0.178 mmol, 95% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (s, 1H), 4.49 (d, *J* = 1.0 Hz, 2H), 2.27 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$)δ150.1, 138.6, 125.3, 97.4, 55.9, 11.9.

IR (Neat Film NaCl) 3338, 2921, 2876, 1565, 1129, 1074, 994, 925.

HRMS (ES+) *m/z* calc'd for $C_6H_7O_2BrNa$ $[M+Na]^+$: 212.9527; found 212.9536.



***Tert*-butyl((5-methoxyfuran-3-yl)methoxy)dimethylsilane (1.27):** To a 1 dram vial were added enoate **S6** (26 mg, 0.203 mmol, 1 equiv), NEt_3 (40 µL, 0.305 mmol, 1.5 equiv), and MeCN (1.0 mL). To the solution was added TBSOTf (60 µL, 0.305 mmol, 1.5 equiv) and the resulting mixture

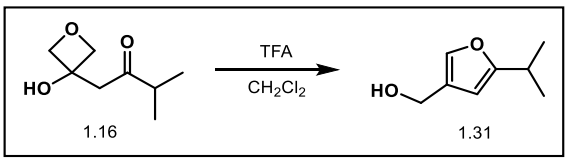
was stirred at room temperature for 2 h. The reaction was poured over ice water and extracted three times with Et_2O. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The amber oil residue was purified by flash column chromatography (SiO_2, 10% Et_2O in pentane) to give furan **1.27** (39 mg, 0.161 mmol, 79% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.80 (d, *J* = 1.3 Hz, 1H), 5.14 (d, *J* = 1.2 Hz, 1H), 4.50 (d, *J* = 1.2 Hz, 2H), 3.82 (s, 3H), 0.92 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 161.9, 129.0, 126.9, 79.5, 58.0, 57.7, 25.9, 18.4, -5.2.

IR (Neat Film NaCl) 2955, 2930, 2885, 2857, 1616, 1579, 1076, 838, 776.

HRMS (ES+) *m/z* calc'd for $C_{12}H_{23}O_3SiNa$ $[M+H]^+$: 243.1416; found 243.1412.



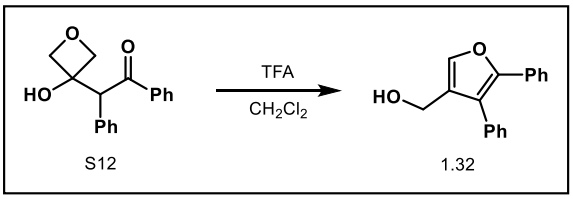
(5-Isopropylfuran-3-yl)methanol (1.31): To a 1 dram vial open to air were added **1.16** (27 mg, 0.171 mmol, 1 equiv) and CH_2Cl_2 (1.7 mL). To the stirred solution, TFA (130 µL, 1.71 mmol, 10 equiv) was added. A bright pink solution resulted, which darkened as the reaction progressed. After stirring at room temperature for 25 min, TLC indicated the complete consumption of starting material. The reaction was poured over saturated $NaHCO_3$ (aq). The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 30% EtOAc in hexanes) to give furan **1.31** (22 mg, 0.157 mmol, 92% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (s, 1H), 6.03 (s, 1H), 4.51 (s, 2H), 2.91 (p, *J* = 6.9 Hz, 1H), 1.47 (s, 1H), 1.23 (d, *J* = 7.0 Hz, 8H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 162.9, 137.9, 125.4, 103.0, 56.9, 29.7, 27.8, 21.0.

IR (Neat Film NaCl) 3334, 2965, 2930, 2874, 1550, 1465, 1018, 981, 934, 810, 729.

HRMS (CI+) *m/z* calc'd for $C_8H_{13}O_2$ $[M+H]^+$: 141.0916; found 141.0914.



S12 1.32

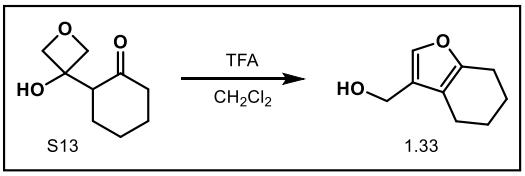
(4,5-Diphenylfuran-3-yl)methanol (1.32): To a 1 dram vial open to air were added **S12** (24 mg, 0.089 mmol, 1 equiv) and CH_2Cl_2 (0.9 mL). To the stirred solution, TFA (70 µL, 1.71 mmol, 10 equiv) was added. A bright pink solution resulted, which darkened as the reaction progressed. After stirring at room temperature for 30 min, TLC indicated the complete consumption of starting material. The reaction was poured over saturated $NaHCO_3$ (aq). The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 20% EtOAc in hexanes) to give furan **1.32** (22 mg, 0.088 mmol, 99% yield) as an off-white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.45 – 7.35 (m, 7H), 7.26 – 7.17 (m, 3H), 4.48 (d, *J* = 4.9 Hz, 2H), 1.40 (t, *J* = 5.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 149.6, 139.6, 133.0, 130.8, 129.8, 128.9, 128.3, 127.6, 127.4, 127.2, 125.7, 121.8, 55.6.

IR (Neat Film NaCl) 3352, 3057, 2923, 1601, 1552, 1503, 1443, 1063, 1016, 986, 933, 767, 695.

HRMS (ES+) *m/z* calc'd for $C_{17}H_{14}O_2Na$ $[M+Na]^+$: 273.0891; found 273.0887.



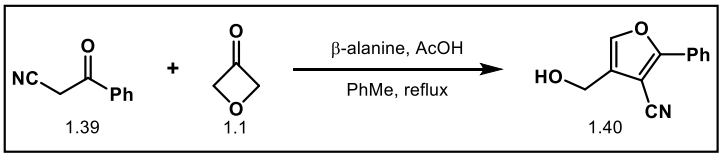
(4,5,6,7-Tetrahydrobenzofuran-3-yl)methanol (1.33): To a 10 mL round bottom flask open to air were added **S13** (93 mg, 0.546 mmol, 1 equiv) and CH_2Cl_2 (5.5 mL). To the stirred solution, TFA (440 µL, 5.46 mmol, 10 equiv) was added. A bright pink solution resulted, turning to dark brown as the reaction progressed. After stirring at room temperature for 45 min, TLC indicated the complete consumption of starting material. The reaction was poured over saturated $NaHCO_3$ (aq). The phases were separated and the aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 20% EtOAc in hexanes) to give furan **1.33** (57 mg, 0.375 mmol, 69% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (s, 1H), 4.49 (s, 2H), 2.56 (t, *J* = 6.2 Hz, 2H), 2.50 – 2.40 (m, 2H), 1.87 – 1.69 (m, 5H), 1.34 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 151.8, 137.8, 124.5, 116.5, 55.9, 23.2, 22.84, 22.81, 20.5.

IR (Neat Film NaCl) 3336, 2928, 2850, 1561, 1444, 1101, 1004, 893.

HRMS (ES+) *m/z* calc'd for $C_9H_{12}O_2Na$ $[M+Na]^+$: 175.0735; found 175.0741.



4-(Hydroxymethyl)-2-phenylfuran-3-carbonitrile (1.40): To a 25 mL round bottom flask open to air were added benzoylacetonitrile (**1.39**, 290 mg, 2.00 mmol, 1 equiv) and toluene (10 mL). To the resulting pale yellow solution were added 3-oxetanone (**1.1**, 190 µL, 3.00 mmol, 1.5 equiv), β-alanine (37 mg, 0.40 mmol, 0.2 equiv), and acetic acid (0.4 mL). The flask was fitted with a Hickman still and a reflux condenser, and the mixture was heated to reflux for 12 h. The reaction

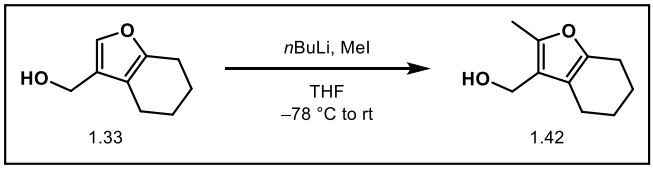
was cooled to room temperature and toluene was removed *in vacuo*. The dark brown residue was purified by flash column chromatography (SiO_2, 30% to 50% EtOAc in hexanes) to give furan **1.40** (82 mg, 0.412 mmol, 21% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.01 – 7.94 (m, 2H), 7.53 – 7.24 (m, 6H), 4.72 (d, *J* = 5.0 Hz, 2H), 1.87 (t, *J* = 5.7 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 160.6, 139.6, 130.3, 129.1, 128.0, 127.9, 125.4, 114.1, 91.7, 55.4.

IR (Neat Film NaCl) 3441, 2917, 2878, 2849, 2227, 1549, 1491, 1447, 1016, 771, 687.

HRMS (ES+) *m/z* calc'd for $C_{12}H_9NO_2Na$ $[M+Na]^+$: 222.0531; found 222.0531.



(2-Methyl-4,5,6,7-tetrahydrobenzofuran-3-yl)methanol (1.42): To a 1 dram vial were added furan **1.33** (19 mg, 0.125 mmol, 1 equiv) and dry THF (0.64 mL). The solution was cooled to -78 °C and a solution of *n*-butyllithium (2.5 M in hexanes, 0.11 mL, 0.269 mmol, 2.1 equiv) was added. The mixture was stirred at -78 °C for 1 h and 0 °C for 1 h. The solution changed from colorless to dark brown upon warming. A solution of iodomethane (1 M in THF, 0.125 mL, 0.125 mmol, 1 equiv) was then added dropwise, resulting in a yellow-orange solution. The reaction mixture was allowed to slowly warm to room temperature and stirred for 16 h. The reaction was quenched with H_2O and extracted 3 times with Et_2O. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 5% acetone in hexanes) to give tetrasubstituted furan **1.42** (18 mg, 0.108 mmol, 86% yield) as a colorless oil. The remainder of the mass balance consisted of unreacted starting material (**5**).

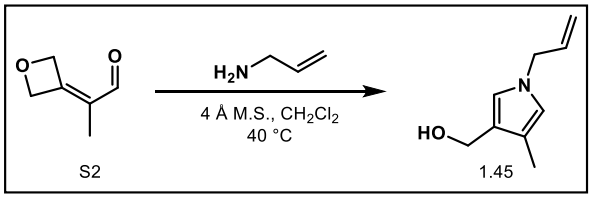
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.42 (s, 2H), 2.52 (t, *J* = 6.2 Hz, 2H), 2.42 (tt, *J* = 6.0, 2.0 Hz, 2H), 2.26 (s, 3H), 1.84 – 1.77 (m, 2H), 1.77 – 1.69 (m, 2H), 1.20 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7, 147.2, 118.2, 117.2, 55.6, 23.0, 22.93, 22.92, 20.6, 11.5.

IR (Neat Film NaCl) 3338, 2930, 2849, 1602, 1443, 1267, 1226, 992.

HRMS (ES+) *m/z* calc'd for $C_{10}H_{14}O_2Na$ $[M+Na]^+$: 166.0994; found 166.0989.

Pyrrole Substrate Scope



General Procedure B – *synthesis of pyrroles from oxetane precursors:*

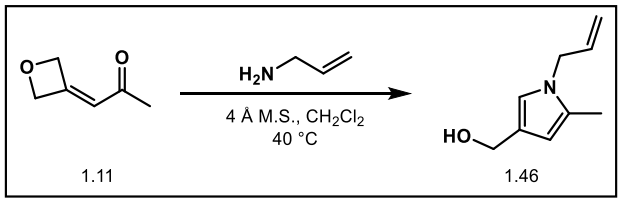
(1-Allyl-4-methyl-1*H*-pyrrol-3-yl)methanol (1.45): To an oven-dried 1 dram vial were added a stir bar and activated 4 Å molecular sieves (250 mg). The vial was flame-dried under vacuum and allowed to cool to room temperature three times. The vial was then evacuated and backfilled with Ar three times. To the vial were added a solution of enal **S2** (38 mg, 0.339 mmol, 1 equiv) in CH_2Cl_2 (0.68 mL) and a solution of allylamine (2 M in CH_2Cl_2, 0.34 mL, 0.678 mmol, 2 equiv). The vial was sealed and heated to 40 °C for 24 h. The reaction mixture was cooled to room temperature and passed through a plug of silica (SiO_2, 50% Et_2O in pentane). Fractions containing the product were pooled and concentrated *in vacuo* to give pyrrole **1.45** (45 mg, 0.298 mmol, 88% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.59 (d, *J* = 2.4 Hz, 1H), 6.41 (dd, *J* = 2.4, 1.1 Hz, 1H), 5.95 (ddt, *J* = 17.1, 10.2, 5.9 Hz, 1H), 5.23 – 5.12 (m, 2H), 4.51 (s, 2H), 4.38 (dt, *J* = 6.0, 1.6 Hz, 2H), 2.11 (s, 3H), 1.31 (br s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 134.3, 122.7, 119.7, 119.4, 117.8, 117.5, 57.2, 51.9, 9.8.

IR (Neat Film NaCl) 3365, 2920, 2866, 1644, 1533, 1367, 1150, 990, 924, 782.

HRMS (ES+) *m/z* calc'd for $C_9H_{13}NONa$ $[M+Na]^+$: 174.0895; found 174.0894.



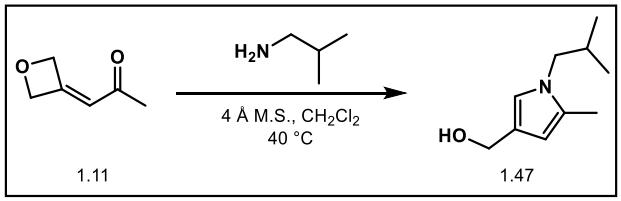
(1-Allyl-5-methyl-1*H*-pyrrol-3-yl)methanol (1.46): Enone **1.11** (30 mg, 0.268 mmol, 1 equiv) was subjected to *General Procedure B* to give pyrrole **1.46** (34 mg, 0.225 mmol, 84% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.57 (s, 1H), 6.01 – 5.81 (m, 2H), 5.17 (dd, *J* = 10.3, 1.8 Hz, 1H), 4.95 (dt, *J* = 17.0, 1.7 Hz, 1H), 4.49 (s, 2H), 4.37 (dd, *J* = 5.1, 1.8 Hz, 2H), 2.18 (s, 3H), 1.47 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 134.1, 129.4, 122.7, 118.7, 116.7, 106.6, 58.8, 49.1, 11.8.

IR (Neat Film NaCl) 3367, 2923, 2863, 1685, 1644, 1518, 1440, 1415, 1352, 1140, 1015, 988, 789.

HRMS (CI+) *m/z* calc'd for $C_9H_{14}NO$ $[M+H]^+$: 152.1075; found 152.1078.



(1-Isobutyl-5-methyl-1*H*-pyrrol-3-yl)methanol (1.47): To an oven-dried 1 dram vial were added a stir bar and activated 4 Å molecular sieves (200 mg). The vial was flame-dried under vacuum and allowed to cool to room temperature three times. The vial was then evacuated and backfilled with Ar three times. To the vial were added a solution of enone **1.11** (28 mg, 0.250 mmol, 1 equiv) in CH_2Cl_2 (0.50 mL) and a solution of isobutylamine (2 M in CH_2Cl_2, 0.25 mL, 0.500 mmol, 2 equiv). The vial was sealed and heated to 40 °C for 24 h. The reaction mixture was cooled to room temperature and passed through a plug of silica (SiO_2, 50% Et_2O in pentane). Fractions

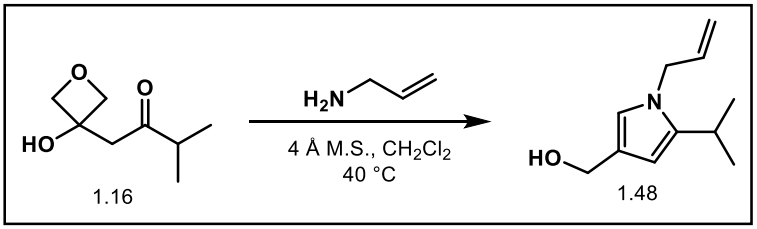
containing the product were pooled and concentrated *in vacuo* to give pyrrole **1.47** (26 mg, 0.155 mmol, 62% yield) as a colorless oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.54 (d, *J* = 2.0 Hz, 1H), 5.89 (s, 1H), 4.49 (s, 2H), 3.54 (d, *J* = 7.4 Hz, 2H), 2.19 (s, 3H), 1.97 (dp, *J* = 13.8, 6.9 Hz, 1H), 1.28 (s, 1H), 0.90 (d, *J* = 6.7 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 129.2, 122.2, 119.2, 106.2, 58.9, 54.1, 30.2, 20.1, 12.1.

IR (Neat Film NaCl) 3374, 2958, 2930, 2871, 1676, 1519, 1468, 1416, 1388, 1142, 1015, 976.

HRMS (CI+) *m/z* calc'd for $C_{10}H_{18}NO$ $[M+H]^+$: 168.1388; found 168.1387.



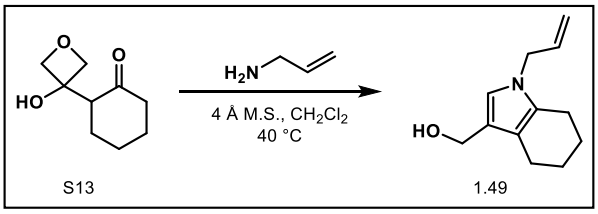
(1-Allyl-5-isopropyl-1*H*-pyrrol-3-yl)methanol (1.48): Aldol adduct **1.16** (35 mg, 0.221 mmol, 1 equiv) was subjected to *General Procedure B* to give pyrrole **1.48** (31 mg, 0.173 mmol, 78% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.55 (s, 1H), 6.01 – 5.87 (m, 2H), 5.17 (dd, *J* = 10.0, 1.8 Hz, 1H), 4.99 (dt, *J* = 17.1, 1.7 Hz, 1H), 4.51 (s, 2H), 4.42 (dt, *J* = 4.4, 1.9 Hz, 2H), 2.84 (hept, *J* = 6.8 Hz, 1H), 1.34 (s, 1H), 1.22 (d, *J* = 6.9 Hz, 6H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5, 134.6, 122.6, 118.5, 116.78, 102.9, 59.0, 48.7, 25.4, 23.2.

IR (Neat Film NaCl) 3369, 2962, 2928, 2869, 1506, 1354, 1147, 1016, 981, 921, 800.

HRMS (ES+) *m/z* calc'd for $C_{11}H_{17}NONa$ $[M+Na]^+$: 202.1208; found 202.1198.



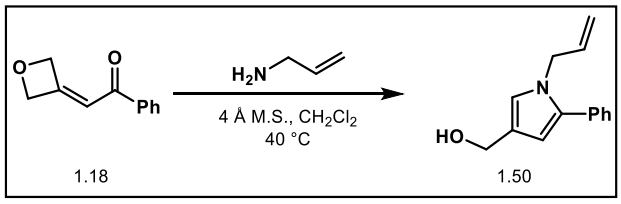
(1-Allyl-4,5,6,7-tetrahydro-1*H*-indol-3-yl)methanol (1.49): Aldol adduct **S13** (19 mg, 0.112 mmol, 1 equiv) was subjected to *General Procedure B* to give pyrrole **1.49** (17 mg, 0.089 mmol, 79% yield) as a pale yellow oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.53 (s, 1H), 5.90 (ddt, *J* = 17.1, 10.5, 5.5 Hz, 1H), 5.16 (dq, *J* = 10.2, 1.4 Hz, 1H), 5.02 (dq, *J* = 17.0, 1.6 Hz, 1H), 4.49 (s, 2H), 4.33 (dt, *J* = 5.6, 1.6 Hz, 2H), 2.53 (tt, *J* = 6.0, 1.5 Hz, 2H), 2.48 (t, *J* = 6.2 Hz, 2H), 1.85 – 1.76 (m, 2H), 1.76 – 1.70 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 134.4, 128.6, 120.6, 117.8, 116.9, 116.5, 57.3, 48.7, 23.3, 23.2, 21.6, 21.3.

IR (Neat Film NaCl) 3394, 2925, 2851, 1712, 1672, 1441, 1393, 991, 921.

HRMS (CI+) *m/z* calc'd for $C_{12}H_{18}NO$ $[M+H]^+$: 192.1388; found 192.1389.



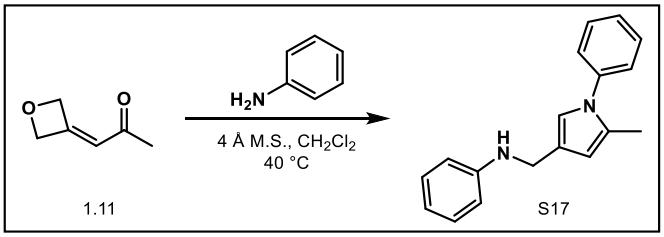
(1-Allyl-5-phenyl-1*H*-pyrrol-3-yl)methanol (1.50): Aldol adduct **1.18** (43 mg, 0.224 mmol, 1 equiv) was subjected to *General Procedure B* to give pyrrole **1.50** (8.3 mg, 0.039 mmol, 17% yield) as a white film.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.35 (m, 5H), 6.77 (d, *J* = 2.0 Hz, 1H), 6.25 (d, *J* = 1.9 Hz, 1H), 5.95 (ddt, *J* = 17.0, 10.3, 5.2 Hz, 1H), 5.20 (dq, *J* = 10.3, 1.5 Hz, 1H), 5.07 (dq, *J* = 17.0, 1.6 Hz, 1H), 4.59 (s, 2H), 4.49 (dt, *J* = 5.3, 1.7 Hz, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 135.1, 134.6, 133.0, 128.7, 128.4, 127.1, 123.8, 120.8, 117.1, 108.2, 58.8, 49.5.

IR (Neat Film NaCl) 3353, 2917, 2849, 1473, 1176, 1138, 1016, 978, 764, 700.

HRMS (ES+) *m/z* calc'd for $C_{14}H_{15}NONa$ $[M+Na]^+$: 236.1051; found 236.1044.



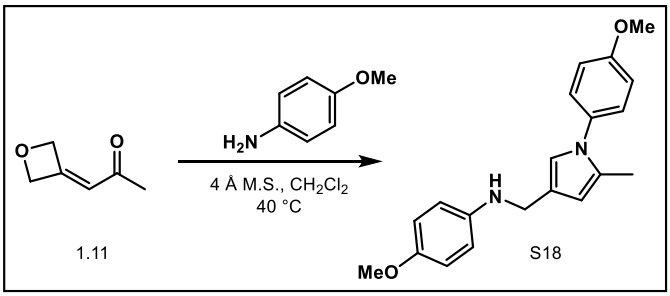
***N*-((5-methyl-1-phenyl-1*H*-pyrrol-3-yl)methyl)aniline (S17):** To an oven-dried 1 dram vial were added a stir bar and activated 4 Å molecular sieves (300 mg). The vial was flame-dried under vacuum and allowed to cool to room temperature three times. The vial was then evacuated and backfilled with Ar three times. To the vial were added a solution of enone **1.11** (34 mg, 0.300 mmol, 1 equiv) in CH_2Cl_2 (0.60 mL) and a solution of aniline (2 M in CH_2Cl_2, 0.30 mL, 0.600 mmol, 2 equiv). The vial was sealed and heated to 40 °C for 24 h. The reaction mixture was cooled to room temperature and purified by flash column chromatography (SiO_2, 30% EtOAc in hexanes). Fractions containing the product were pooled and concentrated *in vacuo* to give pyrrole **S17** (6.0 mg, 0.023 mmol, 8% yield) as a white film.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (t, *J* = 7.8 Hz, 2H), 7.36 – 7.32 (m, 1H), 7.32 – 7.27 (m, 2H), 7.23 – 7.16 (m, 2H), 6.75 (d, *J* = 1.9 Hz, 1H), 6.74 – 6.66 (m, 3H), 6.07 (s, 1H), 4.17 (s, 2H), 3.84 (s, 1H), 2.20 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6, 140.1, 129.5, 129.2, 129.1, 126.8, 125.6, 121.6, 119.5, 117.2, 112.8, 108.2, 41.4, 13.0.

IR (Neat Film NaCl) 3407, 3048, 2920, 2851, 1601, 1499, 1315, 748, 693.

HRMS (ES+) *m/z* calc'd for $C_{18}H_8N_2Na$ $[M+Na]^+$: 285.1368; found 285.1360.



4-Methoxy-*N*-((1-(4-methoxyphenyl)-5-methyl-1*H*-pyrrol-3-yl)methyl)aniline (S18): To an oven-dried 1 dram vial were added a stir bar and activated 4 Å molecular sieves (350 mg). The vial was flame-dried under vacuum and allowed to cool to room temperature three times. The vial was then evacuated and backfilled with Ar three times. To the vial were added a solution of enone **1.11** (40 mg, 0.357 mmol, 1 equiv) in CH_2Cl_2 (0.70 mL) and a solid 4-methoxyaniline (88 mg, 0.714 mmol, 2 equiv). The vial was sealed and heated to 40 °C for 24 h. The reaction mixture was cooled to room temperature and purified by flash column chromatography (SiO_2, 10% EtOAc in hexanes). Fractions containing the product were pooled and concentrated *in vacuo* to give pyrrole **S18** (32 mg, 0.099 mmol, 28% yield) as a white solid.

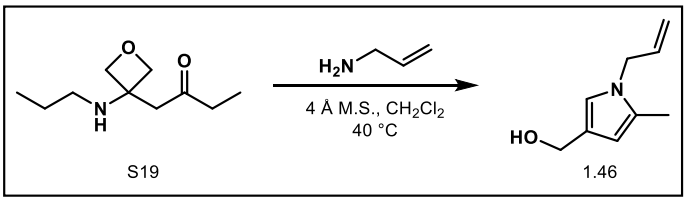
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.8 Hz, 2H), 6.80 (d, *J* = 8.8 Hz, 2H), 6.73 – 6.61 (m, 3H), 6.03 (s, 1H), 4.12 (s, 2H), 3.85 (s, 3H), 3.76 (s, 3H), 2.15 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 158.4, 152.0, 143.0, 133.2, 129.7, 127.0, 121.4, 119.7, 114.8, 114.14, 114.10, 107.6, 55.8, 55.5, 42.3, 12.8.

IR (Neat Film NaCl) 3389, 2919, 2849, 1511, 1463, 1245, 1034, 818.

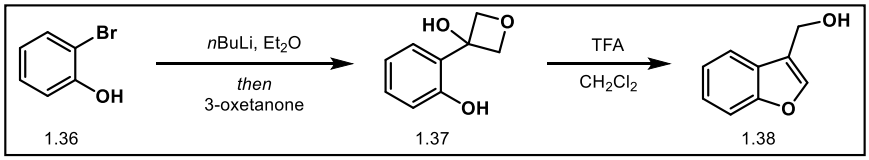
HRMS (ES+) *m/z* calc'd for $C_{20}H_{22}N_2O_2Na$ $[M+Na]^+$: 345.1579; found 345.1596.

*Conversion of 1,4-adduct to pyrrole **1.46**:*



(1-Allyl-5-methyl-1*H*-pyrrol-3-yl)methanol (1.46): 1,4-adduct **S19** (25.0 mg, 0.148 mmol, 1 equiv) was subjected to *General Procedure B* to give pyrrole **1.46** (11.0 mg, 0.074 mmol, 50% yield) as a colorless oil.

Benzofuran and Indole Syntheses



Benzofuran protocol 1:

3-(2-Hydroxyphenyl)oxetan-3-ol (1.38): To a 50 mL round bottom flask were added *n*-butyllithium (2.5 M in hexanes, 1.76 mL, 4.40 mmol, 2.2 equiv) and dry Et_2O (10 mL). The resulting solution was cooled to 0 °C and 2-bromophenol (**1.36**, 0.21 mL, 2.00 mmol, 1 equiv) was added dropwise. The mixture was warmed to room temperature and stirred for 30 min. The mixture was cooled to 0 °C and a solution of 3-oxetanone (0.15 mL, 2.40 mmol, 1.2 equiv) in dry Et_2O (2.7 mL) was added dropwise. A white precipitate was observed. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction was quenched with saturated ammonium chloride (aq) and extracted three times with Et_2O. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 30% EtOAc in hexanes) to give diol **1.37** (247 mg, 1.49 mmol, 75 % yield) as a white solid.

1H and 13C NMR spectra were consistent with those previously reported.[25]

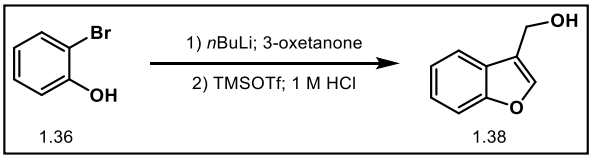
3-Hydroxymethyl benzofuran (1.38): To a 10 mL round bottom flask open to air were added diol **1.37** (187 mg, 1.13 mmol, 1 equiv) and CH_2Cl_2 (4 mL) followed by TFA (0.17 ml, 2.26 mmol, 2 equiv). A bright pink color was observed upon addition of TFA, changing to dark brown as reaction progressed. After stirring at room temperature for 1 h, TLC indicated complete consumption of starting material. The reaction was poured over saturated $NaHCO_3$ (aq) and the phases were separated. The aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 30% EtOAc in hexanes) to give benzofuran **1.38** (85 mg, 0.574 mmol, 51% yield) as a white solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (d, *J* = 7.3 Hz, 1H), 7.61 (s, 1H), 7.50 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.33 (ddd, *J* = 8.3, 7.2, 1.4 Hz, 1H), 7.30 – 7.24 (m, 1H), 4.84 (d, *J* = 3.9 Hz, 2H), 1.76 (t, *J* = 4.8 Hz, 1H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 155.6, 142.3, 126.6, 124.6, 122.7, 120.4, 119.9, 111.6, 55.9.

IR (Neat Film NaCl) 3335, 2926, 2875, 1581, 1452, 1280, 1186, 1099, 1008, 857, 745.

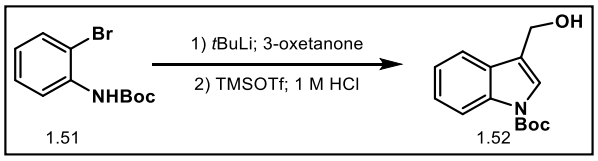
HRMS (ES+) *m/z* calc'd for $C_{18}H_{16}O_4Na$ $[2M+Na]^+$: 319.0946; found 319.0959.



Benzofuran protocol 2:

3-Hydroxymethyl benzofuran (1.38): To a 50 mL round bottom flask were added *n*-butyllithium (2.5 M in hexanes, 1.76 mL, 4.40 mmol, 2.2 equiv) and dry Et_2O (10 mL). The resulting solution was cooled to 0 °C and 2-bromophenol (**1.36**, 0.21 mL, 2.00 mmol, 1 equiv) was added dropwise. The mixture was warmed to room temperature and stirred for 30 min. The mixture was cooled to

0 °C and a solution of 3-oxetanone (0.15 mL, 2.40 mmol, 1.2 equiv) in dry Et_2O (2.7 mL) was added dropwise. A white precipitate was observed. The reaction mixture was allowed to warm to room temperature and stirred for 16 h. The reaction was quenched with saturated ammonium chloride (aq) and extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was transferred to a flame-dried 25 mL round bottom flask under a positive pressure of Ar and dissolved in dry Et_2O (10 mL). To the solution was added NEt_3 (0.84 mL, 6.00 mmol, 3 equiv) followed by TMSOTf (0.76 mL. 4.20 mmol, 2.1 equiv). The reaction mixture was stirred at room temperature for 1 h. To the mixture was added aq HCl (1M, 5 mL) and the biphasic mixture was stirred vigorously for 1 h. The mixture was poured over saturated $NaHCO_3$ and extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 20% to 30% EtOAc in hexanes) to give benzofuran **1.38** (215 mg, 1.45 mmol, 73% yield over two steps) as a white solid.

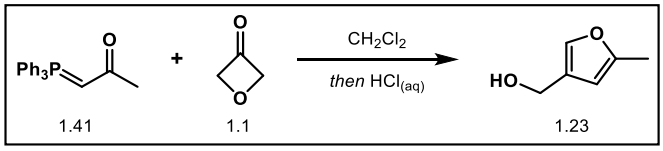


3-Hydroxymethyl-*N*-Boc-indole (1.52): To a 10 mL round bottom flask were added *N*-Boc-aniline (**1.51**, 98 mg, 0.507 mmol, 1 equiv) and dry Et_2O (1 mL). The resulting solution was cooled to -20 °C and *t*-BuLi (0.83 mL, 1.22 mmol, 2.4 equiv) was added dropwise. The mixture was stirred between -20 °C and -10 °C for 3 h, forming a white precipitate. The mixture was then cooled to -78 °C and 3-oxetanone (40 µL, 0.550 mmol, 1.1 equiv) was added. The reaction mixture was allowed to warm to room temperature then placed in a pre-heated oil bath at 35 °C. The mixture was stirred at this temperature for 2 h. After cooling to room temperature, the reaction was quenched with saturated ammonium chloride (aq) and extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was

transferred to a flame-dried 10 mL round bottom flask under a positive pressure of Ar and dissolved in dry Et_2O (2.5 mL). To the solution was added NEt_3 (0.21 mL, 1.52 mmol, 3 equiv) followed by TMSOTf (0.14 mL. 0.761 mmol, 1.5 equiv). The reaction mixture was stirred at room temperature for 1 h. To the mixture was added aq HCl (1M, 1.3 mL) and the biphasic mixture was stirred vigorously for 1 h. The mixture was poured over saturated $NaHCO_3$ and extracted three times with EtOAc. The combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified by flash column chromatography (SiO_2, 30% EtOAc in hexanes) to give indole **1.52** (59 mg, 0.239 mmol, 47% yield over two steps) as a white solid.

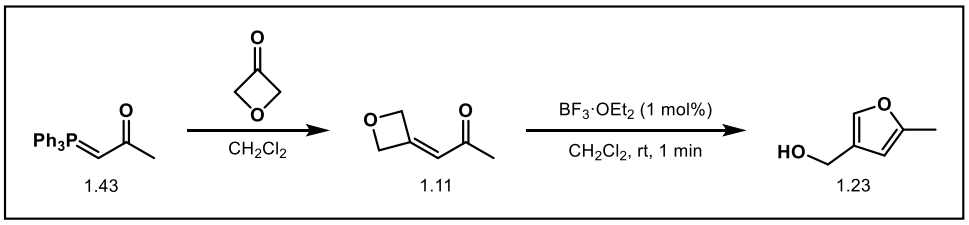
1H and 13C NMR spectra were consistent with those previously reported.[35]

Alternative One-Pot Wittig Olefination/Cylization Procedure



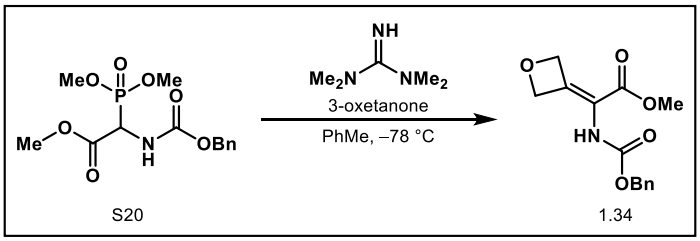
One-pot synthesis of 1.23 from 1.41: To a 10 mL round bottom flask were added phosphorane **1.41** (446 mg, 1.40 mmol, 1.4 equiv) and dry CH_2Cl_2 (1.3 mL). To the solution was added 3-oxetanone (59.0 µL, 1.00 mmol, 1 equiv) and the reaction was stirred at room temperature for 16 h. To the reaction was added aq HCl (1 M, 2.0 mL) and the biphasic mixture was stirred vigorously for 10 min. TLC indicated the complete consumption of enone **1.1**. The reaction was diluted with CH_2Cl_2 and water and the phases were separated. The aqueous phase was extracted twice with CH_2Cl_2. The combined organic phases were dried over Na_sSO_4 and concentrated *in vacuo*. The residue was passed through a silica plug (SiO_2, 50% Et_2O in pentane). Fractions containing the product were pooled and concentrated *in vacuo* to give furan **1.23** (111 mg, 0.989 mmol, 99% yield) as a colorless oil.

Gram-Scale Furan Synthesis



Gram-scale synthesis of 1.11: To a 100 mL round bottom flask were added phosphorane (**1.43**) (8.914 g, 28.0 mmol, 1.4 equiv) and dry CH_2Cl_2 (26 mL). To the solution was added 3-oxetanone (1.29 mL, 20.0 mmol, 1 equiv) and the reaction was stirred at room temperature for 16 h. The solvent was partially removed *in vacuo*. The resulting viscous amber solution was passed through a silica plug (SiO_2, 50% Et_2O in pentane). Fractions containing the product were pooled and concentrated *in vacuo* to give enone **1.11** (2.13 g, 19.0 mmol, 95% yield) as a pale yellow oil.

Gram-scale conversion of 1.11 to 1.23: To a 100 mL round bottom flask were added enone **1.11** (2.07 g, 18.5 mmol, 1 equiv) and CH_2Cl_2 (37 mL) resulting in a clear, colorless solution. The flask was placed in an ice bath.* A solution of BF_3□OEt_2 (1 M in CH_2Cl_2, 0.18 mL, 0.18 mmol, 1 mol%) was added dropwise resulting in an amber solution. The ice bath was removed and the reaction was stirred for 1 min. TLC indicated complete conversion. The reaction mixture was passed through a silica plug (SiO_2, 100% Et_2O). Fractions containing the product were pooled and concentrated *in vacuo* to give furan **1.23** (2.03 g, 18.1 mmol, 98% yield) as a pale yellow oil.
*A slight exotherm is observed upon addition of BF_3OEt_2 at this scale.

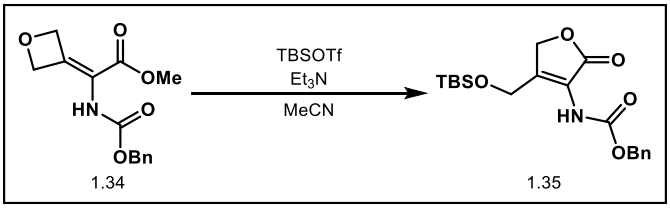


Methyl 2-(((benzyloxy)carbonyl)amino)-2-(oxetan-3-ylidene)acetate (1.34).[36] To a flame dried round bottom flask equipped with a stir bar was added *N*-(benzyloxycarbonyl)phophonoglycine trimethyl ester (**S20**, 0.166 g, 0.50 mmol, 1.0 equiv.) and dry toluene (1.7 mL) under argon. The flask was cooled to -78 °C and N,N,N',N'-tetramethylguanidine was added. After stirring for 30 minutes, a solution of 3-oxetenone (29 µL, 0.50 mmol, 1.0 equiv.) in dry toluene (0.17 mL) was added via syringe. The reaction was allowed to warm to room temperature over 14 hours. The reaction was diluted with H_2O then extracted twice with EtOAc, and then twice with a 20% MeOH in dichloromethane solution. The combined organic phases were dried over $MgSO_4$, filtered through a pad of celite, and concentrated in vacuo. The remaining mixture was purified via flash chromatography (1% MeOH in dichloromethane) to yield **1.34** as a white solid (104 mg, 75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.33 (m, 5H), 6.76 (br s, 1H), 5.45 (s, 2H), 5.41 – 5.39 (m, 2H), 5.11 (s, 2H), 3.79 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 163.8, 152.9, 135.8, 128.8, 128.6, 128.4, 116.0, 78.8, 67.7, 52.9.

HRMS (ESI) calculated for $C_{14}H_{15}NO_5Na$ $[M+Na]^+$: 300.0848 *m*/*z*; found 300.0847 *m*/*z*.



Benzyl-(4-(((*tert*-butyldimethylsilyl)oxy)methyl)-2-oxo-2,5-dihydrofuran-3-yl)carbamate (1.35). To a flame dried vial equipped with a stir bar was added **1.34** (0.0749 g, 0.27 mmol, 1.0 equiv.), dry MeCN (0.675 mL), dry Et_3N (45.2 µL, 0.324 mmol, 1.2 equiv.), and TBSOTf (74.4 µL,

0.324 mmol, 1.2 equiv.). After stirring for two hours, the reaction was poured over a slurry of saturated $NaHCO_3$ in ice. The slurry was extracted twice with Et_2O, dried over $MgSO_4$, filtered through a pad of celite, and concentrated in vacuo to yield **1.35** as a white solid (contains unknown minor impurity):

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (m, 5H), 6.68 (br s, 1H), 5.16 (s, 2H), 4.90 (s, 2H), 4.86 (br s, 2H), 0.90 (s, 9H), 0.09 (s, 6H).

^{13}C NMR (125 mHz, $CDCl_3$) δ 170.8, 153.2, 143.4, 135.4, 128.8, 128.7, 128.4, 118.5, 70.5, 68.1, 60.0, 29.8, 26.0, 5.4.

HRMS (ESI) calculated for $C_{19}H_{27}NO_5SiNa$ $[M+Na]^+$: 400.1556 *m*/*z*; found 400.1543 *m*/*z*.

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Chapter 2: Introduction to the Dihydro-β-Agarofuran Family of Natural Products

2.1 Introduction

The dihydro-β-agarofurans (abbreviated to "agarofurans" for this thesis) are a growing family of sesquiterpenoid natural products, comprising approximately 1000 members to date. These molecules exhibit several similar structural features – a high degree of oxygenation around a conserved tricyclic 5,11-epoxy-5β,10α-eudesman-4-(14)-ene skeleton.[1] Although two different ABC-lettering schemes for the three rings can be found, the most commonly used one is depicted in figure 2.1. The THF-containing, *trans*-decalin agarofuran skeleton is also typically depicted in one of two orientations. Typically, orientation **1** is commonly seen in the *Celestracae* literature; however, orientation **2** corresponds to the traditional presentation of steroid and many other terpenoid structures. In this thesis, orientation **1** will be exclusively employed as it is the most common in the literature. Two numbering schemes have also been used; however, the one denoted in figure 2.1 is most commonly employed.[2]

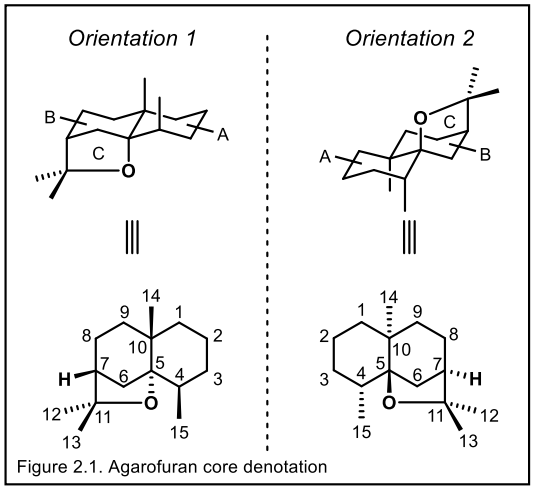


Figure 2.1. Agarofuran core denotation

Although first isolated and characterized in the 1960s, the plants comprising the family *Celastracae*, the most common source of agarofurans, have long been used for medicinal and recreational purposes. The combination of a wide array of biological activity and related, but distinct, structures have led to the agarofurans being considered a "privileged structure." Molecules bearing "privileged structures" possess "a single molecular framework able to provide

ligands for diverse receptors.[3, 4] As a result, they are attractive targets for total synthesis campaigns.

2.2 Structural Diversity

To date, approximately 1000 agarofurans have been isolated and characterized, with new members reported every year. Structurally, the agarofurans are most notable for their highly oxygenated tricyclic core. Two axial methyl groups, C14 and C15, decorate the *trans*-decalin core, while a tetrahydrofuran ring contains carbons 5, 6, 7, and 11. Lastly, carbon 11 of the ring system bears a geminal-dimethyl group. These features are conserved throughout all members of the agarofuran family. The distinguishing characteristics between agarofurans is the type and degree of oxygenation around the core. This diverse family of natural products have been found to contain oxygenation at carbons 1, 2, 3, 4, 6, 8, 9, 13, and/or 14. Typically, oxygenation is found *via* acyloxy functionality; however, free alcohols, and more rarely ketones, can be found in some members. In total, 19 different types of esters have been found decorating the agarofuran core (Figure 2.2).

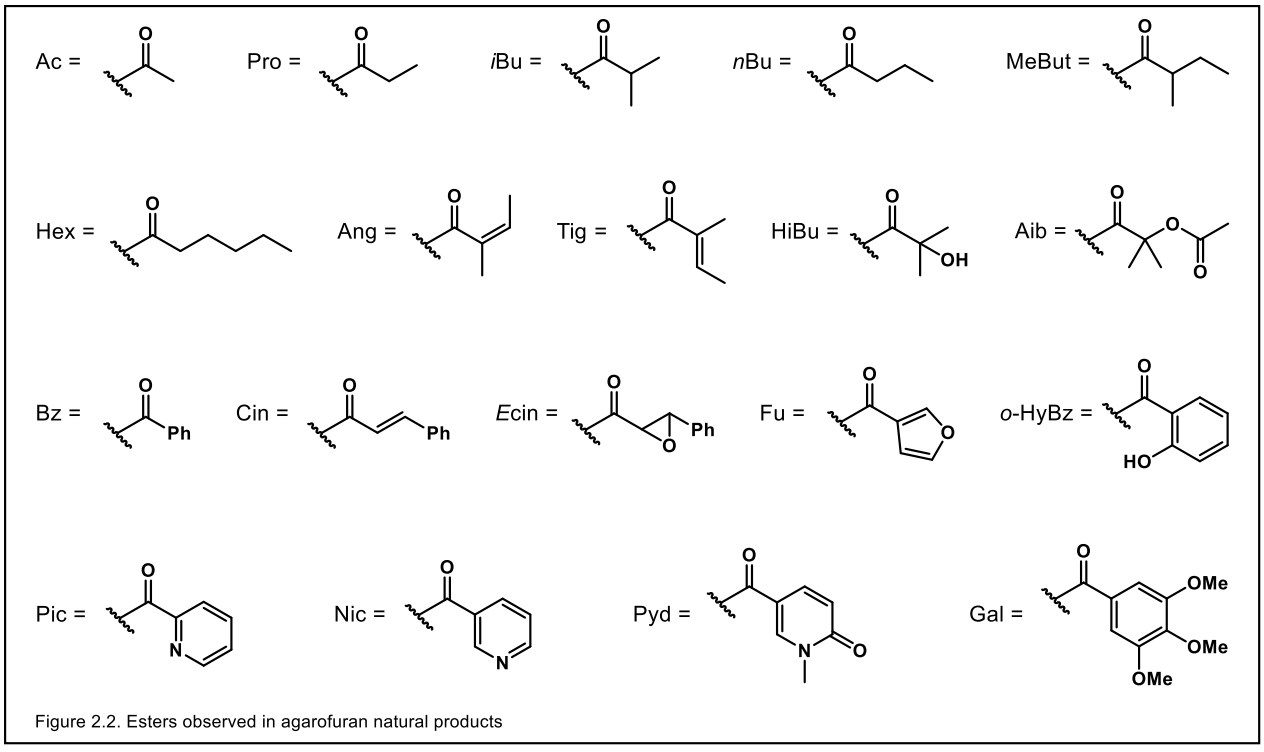
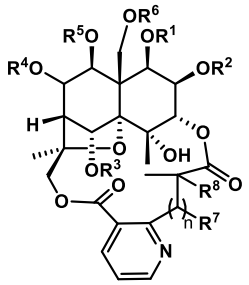


Figure 2.2. Esters observed in agarofuran natural products

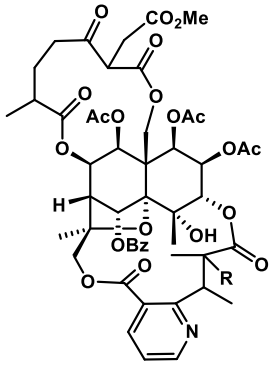
Although acetoxy, benzoyloxy, and furoyloxy are three of the most commonly observed esters, the other 16 still feature prominently.

The first isolated agarofurans contained little oxygenation besides the conserved THF ring; however, as more were isolated, higher degrees of oxygenation were found. To date the most highly oxygenated agarofurans isolated contain nine oxygen substitutions. More common oxygenation patterns include mono- through octa-oxygenated sesquiterpene polyesters, with tetra-, penta-, and hexa-oxygenated agarofurans the most abundant.

Group	*Number of Oxygen Substitutions*
1	2
2	3
3	4
4	5
5	6
6	7
7	8
8	9



Groups 9-14
monomacrolides
R^1-R^6 = esters
R^7 = H, Me
R^8 = H, OH



Group 15
dimacrolides
triptonine A: R = H
triptonine B: R = OH

Figure 2.3. Agarofuran groupings based on degree of oxygenation

The agarofurans can be generally classified into 15 groups based on structural similarities and the amount of oxygenation (Figure 2.3).[1] The di-, tri-, tetra-, penta-, hexa-, hepta-, octa-, and nona-oxygenated sesquiterpene polyesters make up groups 1-8, respectively, while the mono- and dimacrolide sesquiterpene pyridine alkaloids make up groups 9-14 and 15, respectively. The monomacrolide agarofurans typically see the macrocyclic structure connected to the agarofuran core via esters at C3 and C13. The dimacrolide agarofurans have the same macrocyclic bridge as the monomacrolides, but with an additional macrolide connected to the core via esters at C8 and C14. Ultimately, the combination of degree and stereochemistry of oxygenation, along with the type of esters all contribute to the family's diverse array of biological activity.

2.3 Biological Activity

2.3.1 Introduction

The agarofurans are attractive synthetic targets partly due to the wide variety of biological activity that members of this family possess. Different members of the agarofuran family have been found to have potent immunosuppressive, anti-tumor, anti-viral, multidrug resistance (MDR) reversing, intestinal relaxant, anti-inflammatory, insecticidal/antifeedant activity, neuroprotective, anti-microbial, and/or anti-fungal activity (Figure 2.4).[1] The intestinal relaxant,[5] neuroprotective,[6] anti-microbial,[7-9] and anti-fungal activity[10-13] of the agarofurans will not be discussed since the literature reporting this biological activity is minimal. Currently there is not a clear, general pattern between structure and activity, likely because all members of this family have not been comprehensively tested for biological activity. However, some trends between structure and activity exist when studying small subsets of the entire family. In this section, I will mainly discuss the structure-activity relationship (SAR) studies and the most potent agarofurans in each area of biological activity since extensive reviews summarizing the biological activity of the agarofurans have already been published. However, since these reviews[1, 2] were last published, there have been plentiful reports of bioactive agarofurans.[6-30]

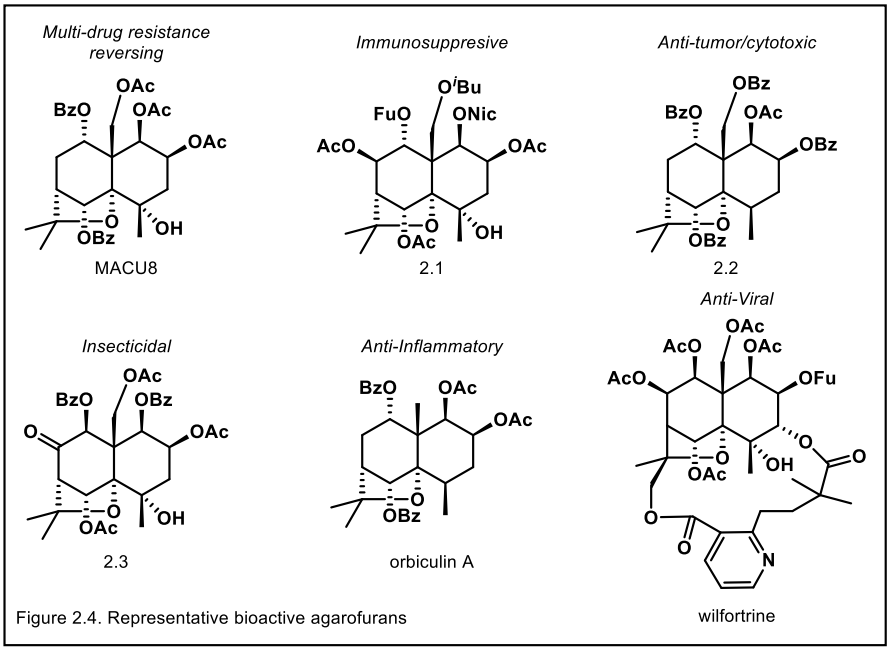
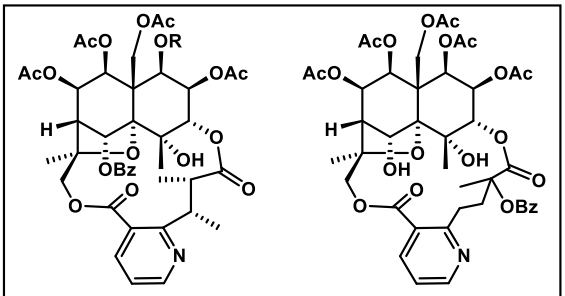


Figure 2.4. Representative bioactive agarofurans

2.3.2 Immunosuppressive Activity

For the natural products exhibiting immunosuppressive activity, most of these are groups 9-14 (monomacrolide-containing) or group 6 (heptahydroxylated) agarofurans. However, there have been limited studies aimed at discovering immunosuppressive activity, and no reported SAR studies. Most notably, the production of interleukin (IL)-2, IL-4, IL-8, interferon (INF)-γ, and tumor necrosis factor (TNF-α) were inhibited by ebenifoline E-II (inhibition: 100%, 100%, 97%, 92%, and 76%, respectively, at 10 μg/mL) and cangorinine E-I (inhibition: 100%, 100%, 84%, 99%, and 37% at 10 μg/mL), while wilfornine B was selective for IL-4 (inhibition: 100%, <22% for all others) (Table 2.1). Notably, ebenifoline E-II and cangorinine E-I only differ by the ester at C1 yet show differences in their activity towards IL-8 (inhibition 97% vs 84%, respectively) and TNF-α (inhibition: 76% vs 37%, respectively). In this report, the authors only studied monomacrocyclic agarofurans.[31] Other reports, albeit with minimal examples, show only moderate to poor immunosuppressive activity or do not report discrete data, noting “remarkable” activity.[1]



	Inhibition %				
Compound	***IL-2***	***IL-4***	***IL-8***	***INF-γ***	***TNF-α***
Ebenifoline E-II	100	100	97	92	76
Cangorinine E-I	100	100	84	99	37
Wilfornine B	22	100	-23	7	-6

Concentration used: 10 μg/mL

Table 2.1. Immunosuppressive activity

2.3.3 Anti-tumor and Cytotoxic Activity

For the natural products exhibiting anti-tumor and cytotoxic activity, a few preliminary studies have shed some light on the impact of various ester substitution patterns. While studying the suppression of the Epstein–Barr virus early antigen (EBV-EA; a primary screening test for anti-tumor promoting agents) in Raji cells, the authors observed inhibition (frequently <40% activation) of the EBV-EA at low doses (1000-5000 mol ratio per TPA (32 pmol; 12-*O*-tetradecanoylphorbol-13-acetate – an EBV-EA inducer)) with minimal toxicity (>70% cell viability

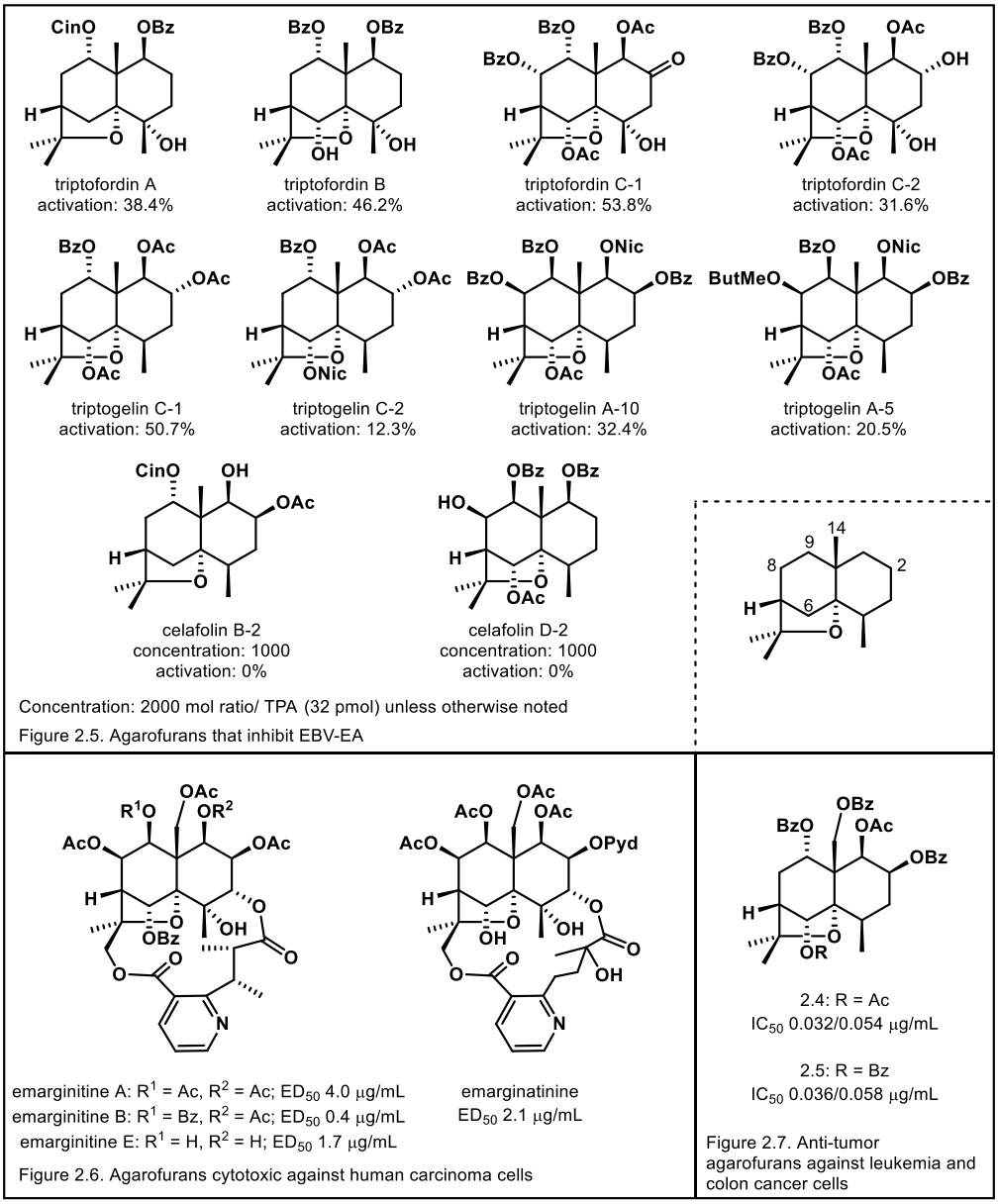


Figure 2.5. Agarofurans that inhibit EBV-EA

Figure 2.6. Agarofurans cytotoxic against human carcinoma cells

Figure 2.7. Anti-tumor agarofurans against leukemia and colon cancer cells

in most cases) to the Raji cells (Figure 2.5).[32] Several trends are noted: 1) A C2 ketone decreases the activity; 2) Changing the ester at C6 from acetoxy (triptogelin C-1) to nicotynoyloxy (triptogelin C-2) increased activity twofold; 3) Changing the ester at C8 from benzoyloxy (triptogelin A-10) to 2-methylbutanoyloxy (triptogelin A-5) increased the activity by about threefold; 4) A macrolide bridge led to a decrease in inhibitory activities; and 5) The configuration of the C9 oxygenation was inconsequential, as seen when comparing triptogelin C-1 to triptogelin A-5. Ultimately, celafolin B-2 and celafolin D-2 were the most potent. In similar experiments, C6 and C9 furoyloxy

groups displayed a tenfold increase in activity over the corresponding benzoyloxy groups. Additionally, C2 substitutions of acetoxy and furoyloxy showed the greatest inhibition; however, benzoyloxy and propionyloxy esters showed significantly less activity when the rest of the structure was conserved.

In a study of nine macrocyle-containing agarofurans, emarginatine A, B, E, and emarginatinine were found to be the most cytotoxic against human epidermoid nasopharynx carcinoma cells (ED_{50} 4.0, 0.4, 1.7, and 2.1 µg/mL, respectively) (Figure 2.6). Ultimately though, they were unable to draw any larger conclusions about the structure activity relationships other than noting the differences between the structures.[33] In a separate report, when studying the inhibitory activity of eighteen agarofurans against liver carcinoma cells the authors found that activity increased as the substitution on C2 changed from acetoxy to furoyloxy to 2-methylbutyroyloxy to *iso*-butyroyloxy.[34]

Two of the most potent anti-tumor/cytotoxic agarofurans to date are **2.4** (IC_{50} 0.032 µg/mL against leukemia neoplasm cells; IC_{50} 0.054 µg/mL against colon cancer cells) and **2.5** (IC_{50} 0.036 µg/mL against leukemia neoplasm cells; IC_{50} 0.058 µg/mL against colon cancer cells) (Figure 2.7). Interestingly, when studying **2.4**, **2.5**, and two other agarofurans, the authors found that agarofurans possessing a C14 benzoyloxy group gave greater cytotoxicity values than those possessing a C14 *iso*-butanoyloxy group.[35] Recent reports corroborate much of what has already been discovered in regards to SAR, namely that polyols suffer from poor activity, thus necessitating the need for ester substitutions, and that acetoxy groups favor greater activity than benzoyloxy and cinnamoyl.[17-20, 26, 28]

2.3.4 Anti-viral Activity

For the natural products exhibiting anti-viral,[23] anti-HIV, and anti-HSV activity, mostly the group 9 and 10 agarofurans are observed, namely in the area of anti-HIV activity. Triptonine B, hypoglaunine B/*iso*-wilfortrine, wilfortrine, and hyponine B all exhibited potent anti-HIV activity (EC_{50} <0.10 µg/mL) with a therapeutic index >1000 (Figure 2.8).[36, 37] Triptofordin C-2 has shown moderate activity against HSV-1, HCMV, measles, and influenza, along with an additive effect with acyclovir, a commonly prescribed antiviral. To shed light on a potential mechanism of action, the authors observed inhibition of HSV-infected cells after addition of triptofordine C-2 at different time points. They noticed that inhibition did not occur when added 4-8 hours post-infection, leading them to conclude that triptofordin C-2 blocks a step of translation and not transcription.[38] Recently isolated **2.6** has displayed 64% inhibition (concentration not reported) against HIV while retaining 96% cell viability.[23] Comparing to the other twelve isolated compounds and seven derivatives that displayed poor activity, they concluded that the C15 acetoxy, the C2 hydroxy group, and the C8 β-acetoxy group were all necessary for activity. Despite these promising results, the anti-viral activity of the agarofurans remains minimally explored.

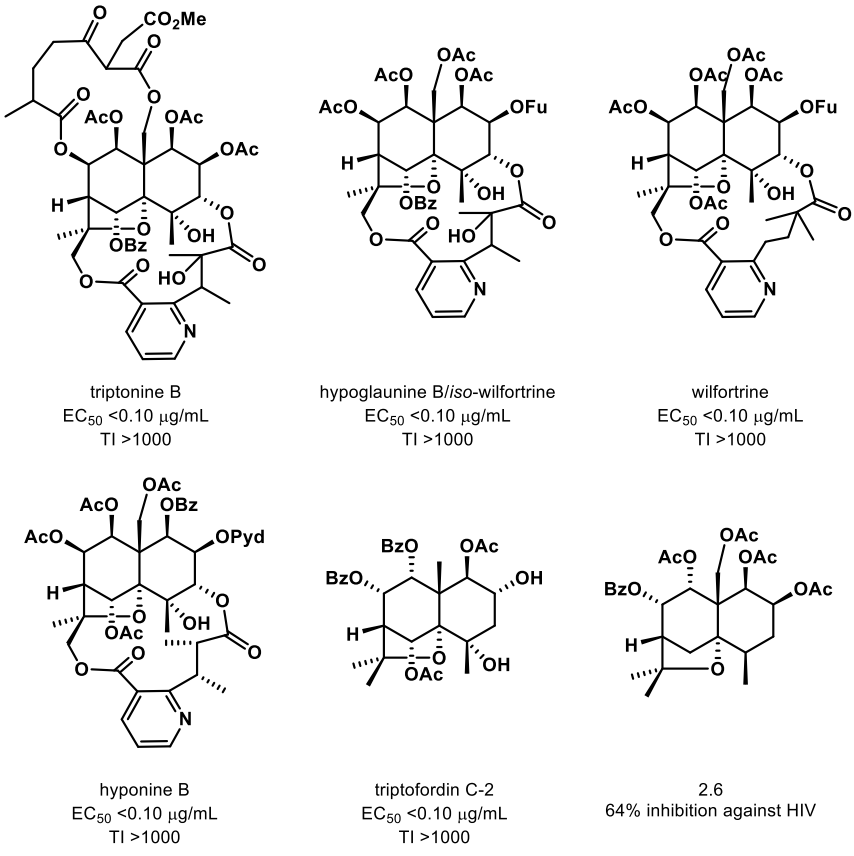
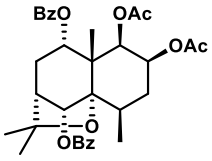


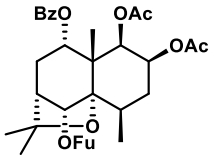
Figure 2.8. Agarofurans that exhibit anti-viral activity

2.3.5 Multidrug Resistance Reversing Activity

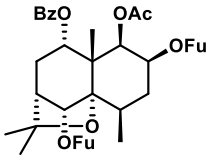
The multidrug resistance reversing activity of the agarofurans is the most well-studied area of agarofuran biological activity. The overexpression of ATP-driven pumps that expel drugs before they can execute their function is a common problem in multidrug resistant diseases, especially various cancers.[39-43] The most potent multidrug resistant reversing members of this family are found to inhibit human P-gp and P-gp-like transporters in cancer and leishmaniasis without being transported themselves. In 1998 and 1999, orbiculins A, E, F, and G, were observed reversing resistance to adriamycin, vinblastine, and paclitaxel in KB-V1 and MCF7/ADR, two human multidrug-resistant cell lines (Figure 2.9).[44, 45] In the first SAR study, orbiculin A, one of the most potent agarofurans studied by the authors, displayed an 80-fold increase (IC_{50} 32.0 to 0.4, Enhancement Factor (EF) of 80.0) in activity when dosed with vinblastine in vinblastine-resistant KB-V1 cells.[45] Interestingly, the authors noted that the introduction of a furoyloxy ester in place of an acetoxy ester decreased the activity (EF of 35.7 for furoyloxy-containing agarofuran vs EF of 66.2 for acetoxy-containing agarofuran). This is in contrast with observations noted in sections 2.3.3, 2.3.6, and 2.3.7 wherein the introduction of a furoyloxy group increased other biological activities over benzoyloxy and acetoxy groups. Unlike other SAR studies done on the agarofurans which focused only on the types of esters on the agarofurans, the authors observed that the tetra- (4 agarofurans; EF of 35.7 to 87.0) and pentaesters (2 agarofurans; EF of 57.2 to 79.4) all significantly outperformed the triesters (5 agarofurans; EF of 6.4 to 17.1). The only instance the triesters were not outperformed was by a tetraester containing 3 benzoyloxy groups (EF of 5.9), the most of any agarofurans the authors studied. Notably, the presence of a C14 acetoxy group led to strong activity (EF of 57.2 and 79.4) regardless of the C2 substitution, leading the authors to conclude that the polarity at the “northern” portion (carbons, 1, 2, 8, 9, 14) of the agarofuran is an important factor in the MDR-reversing activity. When KB-V1 cells (resistant to adriamycin, vinblastine, and paclitaxel) were treated with adriamycin, vinblastine, and paclitaxel and twelve



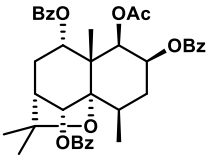
orbiculin A
IC_{50} 0.4
EF 80.0



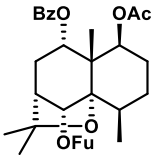
orbiculin E
IC_{50} 0.5
EF 66.2



orbiculin F
IC_{50} 1.1
EF 35.7



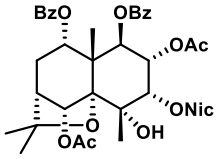
orbiculin G
IC_{50} 4.8
EF 5.9



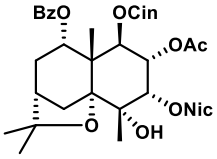
orbiculin B
IC_{50} 19.6
EF 12.5

Concentration: 10 μM; EF = Enhancement factor when dosed with vs. without vinblastine

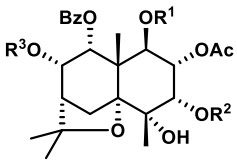
Figure 2.9. Agarofurans that reverse resistance to adriamycin, vinblastine, and paclitaxel in KB-VI and MCF7/ADR cell lines



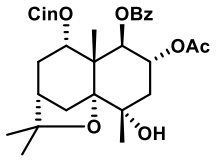
MAMA1
7.5 μM, GI 10.0



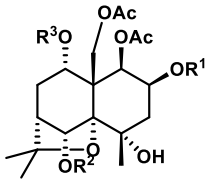
MAMA7
7.5 μM, GI 82.0



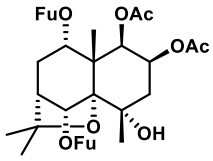
MAMA3: R^1 = Nic, R^2 = Bz, R^3 = Ac; 7.5 μM, GI 21.4
MAMA5: R^1 = Bz, R^2 = Ac, R^3 = Bz; 7.5 μM, GI 48.7
MAMA6: R^1 = Nic, R^2 = Ac, R^3 = Bz; 7.5 μM, GI 23.9



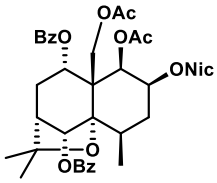
MAMA10
7.5 μM, GI 88.2



MAMA12: R^1 = Nic, R^2 = Bz, R^3 = Bz; 7.5 μM, GI 80.7
MACU7: R^1 = Ac, R^2 = Fu, R^3 = Fu; 3.0 μM, GI >75
MACU8: R^1 = Ac, R^2 = Bz, R^3 = Bz; 3.0 μM, GI >75



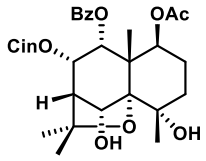
MAMA10
3.0 μM, GI >75



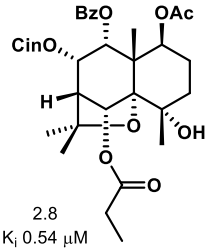
$MACHU_4$
7.5 μM, GI 83.7

GI = Growth Inhibition

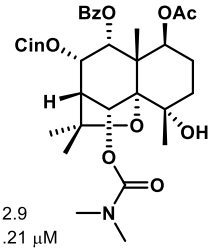
Figure 2.10. Agarofurans that reverse resistance to daunomycin, miltefosine, and phospholipids against MDR *Leishmania tropica*



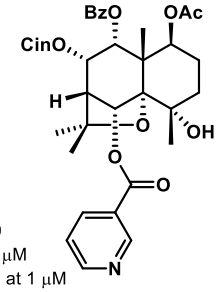
2.7
K_i 0.28 μM
RI 5.6/23.7 at 1 μM
CC_{50} 26.1 μM



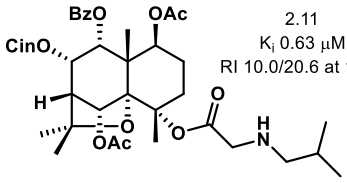
2.8
K_i 0.54 μM
RI 10.8/19.1 at 1 μM



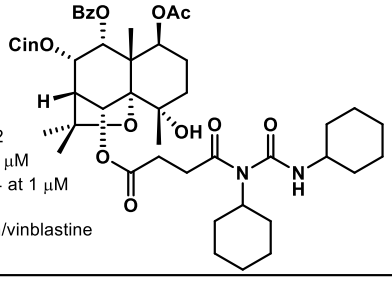
2.9
K_i 1.21 μM
RI 11.8/11.2 at 1 μM



2.10
K_i 0.13 μM
RI 11.8/17.4 at 1 μM



2.11
K_i 0.63 μM
RI 10.0/20.6 at 1 μM



2.12
K_i 0.19 μM
RI 15.8/27.4 at 1 μM

K_i inhibition constant; RI = reversal index (IC_{50} ratio with and without analog) given for daunomycin/vinblastine

Figure 2.11. SAR study done by Bazzocchi and Castanys

different agarofurans, orbiculins A and E were found to restore the activity back to the level of drug sensitive KB-3-1 cells.

In the second SAR study the authors note several observations while studying the resistance to daunomycin, miltefosine, and other alkylphospholipids of an MDR *Leishmania tropica* line overexpressing Pgp (Figure 2.10).[46] MAMA7 (82% growth inhibition (GI), 7.5 μM), lacking a C6 substitution, displayed activity reduced eight-fold compared to MAMA1 which contains a C6 acetoxy group. Conversely, the lack of a substituent at C8 proved to be important since MAMA7 was two- and four-fold more potent than MAMA6 and MAMA3 which both possess a C8 benzoyloxy substitution. Switching the C8 benzoyloxy group for an acetoxy group made no significant change in the activity. MAMA5, possessing a C1 benzoyloxy group was found to have twofold greater activity than MAMA3, possessing a C1 nicotinoyloxy group. The introduction of a C4 tertiary alcohol, as seen in MAMA12 (80.7% GI, 7.5 μM), did not seem to have any impact on the activity when compared to MACHU4 (83.7% GI, 7.5 μM) which lacks a C4 tertiary alcohol. Lastly, they note that agarofurans containing six ester/alcohol substitutions and three bulky ester substituents (cinnamoyloxy, nicotinoyloxy, benzoyloxy) perform significantly worse (two- to ten-fold) than agarofurans containing smaller groups like acetoxy substitutions. However, agarofurans containing six or fewer ester/alcohol substitutions and two or less bulky ester substituents all perform well. This gives rise to the hypothesis that for significant MDR-reversing activity there is a limit to the steric bulk that can be tolerated. Overall, the most potent agarofurans identified were MAMA7, MAMA10, MACU5, MACU7, MACHU4, and MACU8 which all display greater than 75% growth inhibition values at 3.0 μM concentrations. They suggest that these agarofurans are not substrates of Pgp since they do not show significant cross-resistance to MDR cancer cells and MDR *Leishmania*.[4, 44, 45, 47] In a separate report, MAMA5, MAMA12, and MACHU4 were found to be poorly transported by Pgp or other transporters, nor did they display any cross-resistance, suggesting that they would be an excellent scaffold for the design of potent MDR-reversing compounds.[48] More recent studies corroborate much of the previous findings.[14, 27]

Following five successive reports of the isolation of novel agarofurans and their corresponding MDR-reversing activity,[21, 24, 27, 29, 30] the Bazzocchi and Castanys groups reported the most extensive SAR study to date on the agarofurans (Figure 2.11).[49] Noting the significant activity towards MDR cancer strains while retaining low toxicity, the authors believed the agarofuran family could serve as a privileged scaffold upon which to conduct a medicinal chemistry endeavor. The authors conducted their SAR study using **2.7** as their lead compound since it already had potent MDR-reversing activity in MDR1 cells (K_i 0.28 μM; reversal index (RI) 5.6 at 1 μM with daunomycin and RI 23.7 μM with vinblastine), low cytotoxicity (CC_{50} 26.1 μM; verapamil CC_{50} 27.0 μM), and possessed C4 and C6 hydroxylation that could be easily derivatized. A library of 81 compounds were synthesized from lead compound **2.7** by altering seven factors: 1) Types of esters; 2) *Cis* versus *trans*-alkene effects of the cinnamate ester; 3) Anionic character; 4) Introduction of nitrogen atoms; 5) Hydrogen bonding; 6) π-interactions; and 7) Hybrid and dimeric compounds. By studying these factors, five compounds (**2.8**, **2.9**, **2.10**, **2.11**, and **2.12**) were identified as having a superior MDR-reversing activity profile compared to verapamil (VRP), a known Pgp modulator. Through this study they reported the following SAR trends: 1) Types of esters: Aromatic groups, except for nicotinoyl groups, substituted at C6 greatly decreased activity; Steric hinderance at C4 precludes potent activity 2) *Cis* versus *trans*-alkene effects of cinnamate ester: No trend was observed for the *cis*-*trans* isomerization of cinnamoyl esters; 3) Anionic character: Carboxylic acids displayed poor activity, while the respective esters restored activity; 4) Introduction of nitrogen atoms: The presence of nitrogen atoms improved activity, as evidenced by 4 of the 5 most potent analogues containing a nitrogen; 5) Hydrogen bonding: H-bond donors at C6 make little impact, necessitating substitution at this position; loss of a C4 H-bond donor decreases activity; 6) π-interactions: introduction of alkenes at the C4 or C6 positions, or via a cinnamoyl ester decrease activity; and 7) Hybrid and dimeric compounds: formation of hetero- or homodimers results in loss of activity. Ultimately, Bazzocchi and Castanys

illustrate that optimization of the substituents on an agarofuran scaffold can result in a highly potent and non-toxic potential lead compound for MDR-reversibility.

2.3.6 Anti-inflammatory Activity

Six agarofurans have been tested for their ability to inhibit the activation of NF-κB, which has been implicated in numerous inflammatory diseases (Figure 2.12).[50] Three of these, orbiculins D, H, and I, showed moderate activity (IC_{50} 33.5, 61.5, and 36.7 μM, respectively). The other three, orbiculins A, E, and F displayed very poor activity. The authors note that the poor activity can likely be attributed to the conserved C9 benzoyloxy group observed in all three poorly performing orbiculins. Conversely, the three orbiculins exhibiting moderate activity all contain a C9 and C6 furoyloxy group. This pattern of the benzoyloxy-containing natural products performing worse than the furoyloxy-containing natural products was also observed in section 2.3.2 regarding the anti-tumor/cytotoxic activity. However, these patterns were observed only when studying small subsets of agarofurans. Two recent reports note several agarofurans exhibiting similar anti-inflammatory activity (11.9 to 31.0 μM) albeit without any SAR conclusions.[15, 16]

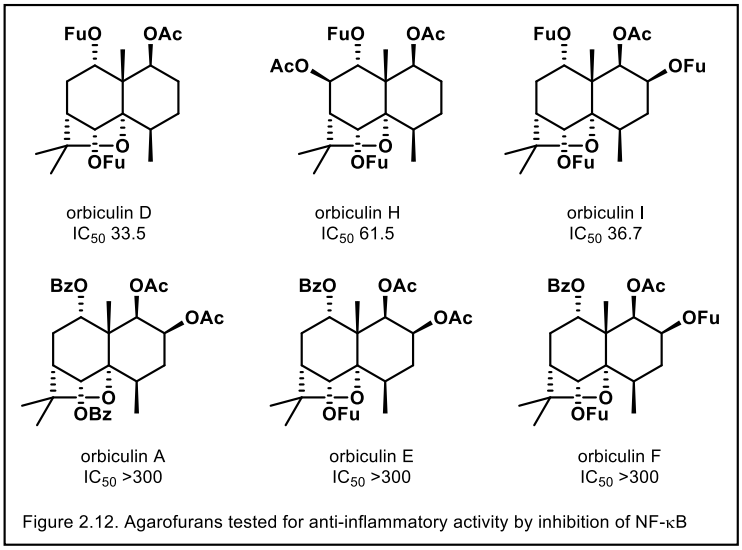


Figure 2.12. Agarofurans tested for anti-inflammatory activity by inhibition of NF-κB

2.3.7 Insecticidal/Anti-feedant Activity

Many agarofurans have been found to have significant insecticidal/anti-feedant activity against several crop pests (Figure 2.13). In fact, the powdered roots of *Celastrus angulatus* and *Tripterygium wilfordii*, two species known for producing agarofurans, have been used to protect crops from pests in China. In a study of about thirty agarofurans, celangulin II (KD_{50} 46 µg of compound/g of larvae), celangulin III (LD_{50} 110 µg/g), **2.13** (KD_{50} 135.3 µg/g), and **2.14** (KD_{50} 73.3 µg/g) were found to have significant insecticidal activity against the armyworm (*Mythimna separata*).[51] Interestingly, the pattern continues where furoyloxy groups improve activity while benzoyloxy groups decrease activity.[52] A study of 54 agarofurans found **2.15** (FR_{50} 0.69 at lowest dose of 0.01 µg/cm^2) to be more potent than triphenyltin acetate (FR_{50} 0.37) and had the most potent insecticidal activity against the Egyptian cotton leaf worm (*Spodoptera littoralis*).[53] The authors noted that the increase in acetoxy esters at the expense of benzoyloxy esters increased the activity (4 OAc, 1 OBz; FR_{50} 0.03 > 3 OAc, 2OBz; FR_{50} 0.24 > 2 OAc, 3 OBz; FR_{50} 0.76). Isolated agarofurans have also been found to possess moderate to potent insecticidal/anti-feedant activity against the pumpkin beetle (*Aulacophora femoralis*; angulatueoid G/triptogelin A-3, 73.2% antifeedant rate, 100 ppm), diamondback moth (*Piutella xylostella*; angulatueoid G/triptogelin A-3, 87.7% antifeedant rate, 100 ppm),[54] cabbage butterfly (*Pieris brassicae*; evonine, 74% mortality. 50-200 µg/larvae),[55] and/or the spotted stalk

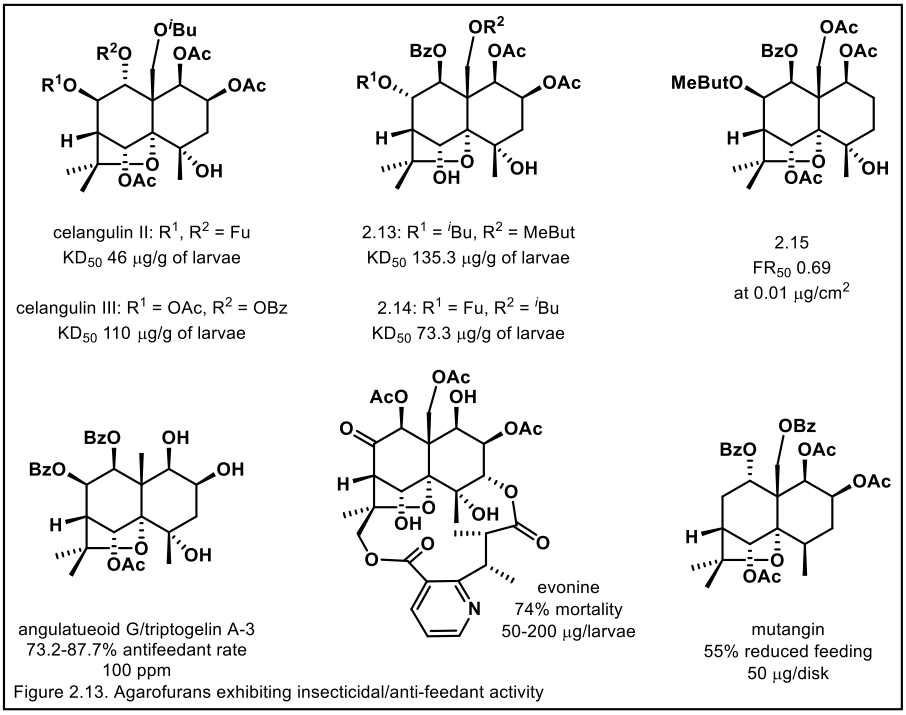


Figure 2.13. Agarofurans exhibiting insecticidal/anti-feedant activity

borer (*Chilo partellus*; mutangin, 55% reduced feeding, 50 µg/disk).[56] However, conclusions regarding the SAR of the agarofurans based on these studies are sparse.

2.3.8 Conclusions and Impacts

Overall, the existing literature focuses only on the biological activity of specific isolated groups of agarofurans. Furthermore, there remains much to be learned regarding the mechanism of action and the structure-activity relationships, despite the preliminary studies already conducted. It is still unclear why certain configurations of esters result in differing biological activities, and therefore likely different targets and mechanisms of action. For example, while several studies across multiple areas of biological activity demonstrate that acetoxy and furoyloxy groups increase potency over benzoyloxy groups, there exist instances where this pattern is inverted. SAR experiments done by Bazzocchi and Castanys prove that careful study and optimization of the substituents decorating the agarofuran core can lead to highly intriguing potential lead compounds. However, due to the immense diversity in both structure and biological activity, these SAR studies have only scraped the tip of the iceberg in regard to understanding the relationship between structure and biological activity. A more comprehensive paradigm of how structure influences observed agarofuran biological activity is critical for their application to human health. To better probe this relationship, the synthesis of agarofuran natural products and appropriate analogs is required. More importantly, a flexible route to access an easily diversifiable core is imperative, as it would allow for significant numbers of agarofurans and agarofuran analogs to be synthesized. In turn, this would support exhaustive SAR and biological studies. To date, there have been several total and semi-synthetic sequences of the agarofurans.

2.4 Previous Syntheses

2.4.1 Introduction

To date, there have been over 30 syntheses of the agarofuran skeleton, agarofuran-like scaffolds, and agarofuran natural products. However, the majority of synthetic efforts target non- or poorly bioactive members of this family (i. e. species containing minimal oxygenation) despite the most highly bioactive members often belonging to group 4 or higher. The recent literature has focused on the most highly oxygenated members of this family, namely euonyminol (nonahydroxylated, group 8); however, in doing so the development of a concise, general route to an easily diversifiable core remains elusive. Additionally, many of the most highly biologically active agarofurans belong to groups 3, 4, and 5. Overall, the lack of a concise route to the core of the highly oxygenated and therefore, most biologically activity agarofurans, precludes generation of these natural products and their analogs for large scale SAR studies.

2.4.2 Early Synthetic Efforts – 1967 to 2005

The synthetic efforts predating 2007 have been reviewed extensively;[1, 2] however, it is worth noting that in the 40 years prior to 2007 the efforts taken to synthesize the agarofurans generally fall into two categories: 1) The cyperone/carvone strategy (most common),[57-68] and 2) Non-cyperone/carvone strategies.[69-74] Readily accessible from carvone, (–)-epi-α-cyperone[75] and its analogs, was an obvious choice for early synthetic efforts since it already contains much of the carbon skeleton that comprises the agarofurans, along with the correct stereochemistry (Figure 2.14). The first synthesis of an agarofuran, (+)-α-agarofuran, was completed by Barrett and Buchi in 1967 using (–)-epi-α-cyperone as their starting material.[57] The carvone-based approaches can be considered in the same category as the cyperone approaches since carvone was frequently used as a precursor to synthesize cyperone-like substrates. However, there were several other approaches that took advantage of other carvone-based strategies, including an RCM-strategy to

furnish the decalin ring system following manipulation of carvone.[66] Several non-cyperone/carvone strategies were employed as well,[69, 70, 72-74] namely those centering around a Diels–Alder reaction,[73] as in White's 1997 20-step synthesis of (±)-euonyminol (Scheme 2.1).[71] Ultimately, a major uniting factor between the cyperone/carvone and non-cyperone/carvone strategies is that these strategies usually focused on building the agarofuran core starting with the B-ring, followed by oxidation of the core. Since the most recent review on the agarofurans,[1] there have been eleven publications detailing synthetic works towards the agarofurans. Of these, reports by Thomas,[76] Barrett,[77] Yu,[78] Mehta,[79] and Ogura[80] are very similar in strategy and/or outcome to previous reports, and thus will not be covered in this thesis. The remaining six reports all focus on synthesis of the most highly oxygenated members of this family, namely euonyminol. However, a flexible route to an easily diversifiable core remains elusive.

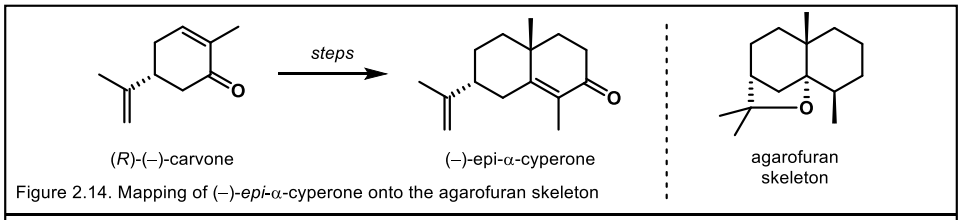
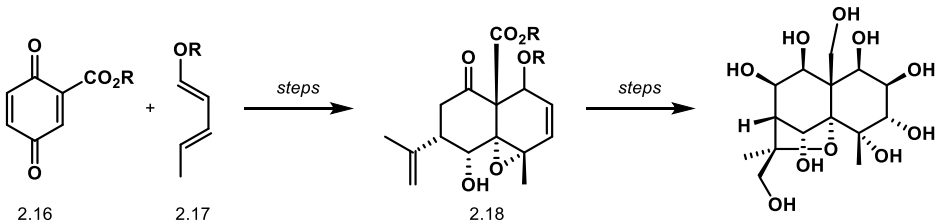


Figure 2.14. Mapping of (–)-*epi*-α-cyperone onto the agarofuran skeleton

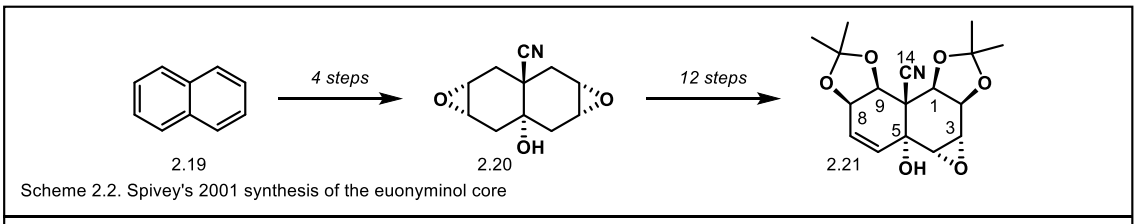


Scheme 2.1. White's synthesis of (±)-euonyminol

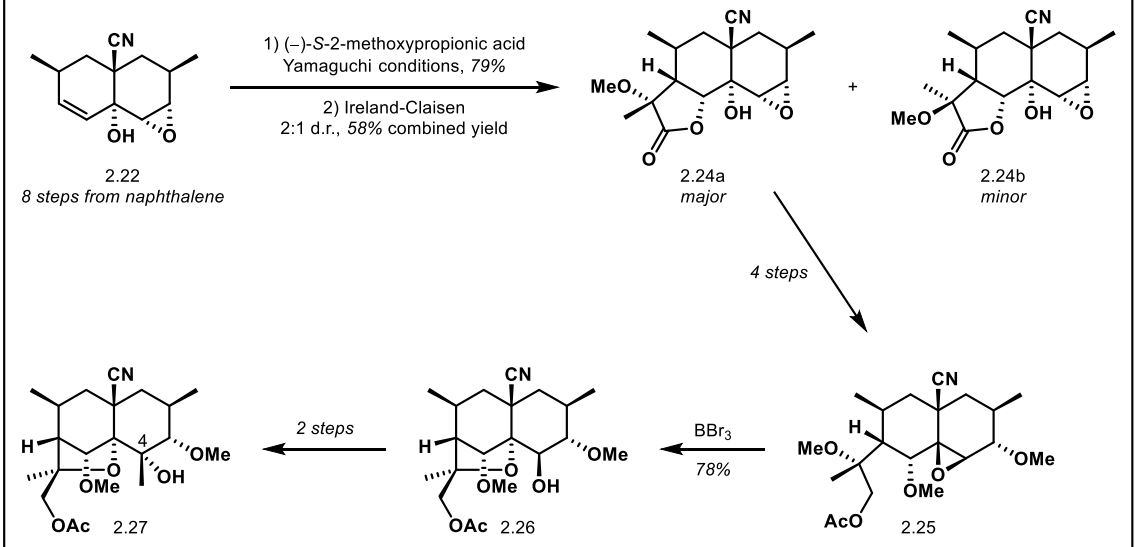
2.4.3 Spivey (2013) – Synthesis of a Fully Functionalized Lower-Rim Model

In 2013, Spivey and coworkers published their work on the synthesis of a fully functionalized lower-rim model, **2.27**.[81] This work builds upon their previous 2001 work where they synthesized a highly oxidized decalin core, **2.21**, in 16 steps from naphthalene with aims to broadly apply this route towards the synthesis of euonyminol and other agarofurans bearing similar oxygenation patterns (Scheme 2.2).[82] This report focused mainly on preparing the

oxidation on the “upper” rim of the agarofuran core, namely at carbons 1, 2, 8, 9, and 14, although they did demonstrate the ability to oxidize carbons 3, 4, and 5 as well. Despite the achievement of synthesizing much of euonyminol’s core, there has been no reports of elaboration of this route to a natural product or analogs. In their 2013 work, the Spivey group aimed to use a similar strategy as in their 2001 publication to fully functionalize the “lower rim,” namely through installation of the required carbons for the C-ring and by oxidation of carbons 3, 4, 6, and 13 (Scheme 2.3). Starting from naphthalene, they synthesized **2.22** in eight steps using a similar route as their 2001 report. Acylation of the tertiary alcohol with a lactic acid derivative set up for an Ireland–Claisen rearrangement to install the required C-ring functionality at C7. The



Scheme 2.2. Spivey's 2001 synthesis of the euonyminol core



Scheme 2.3. Spivey's 2013 synthesis of a fully functionalized lower-rim model

Ireland–Claisen products **2.24a** and **2.24b** were obtained in a 2:1 mixture (58% combined yield) of diastereomers. Methylation, reduction, acylation, and epoxidation set up for closure of the C-ring. Treatment of **2.25** with BBr_3 gave the tricycle **2.26** in 78% yield. Oxidation at C4 and methylation of the resulting ketone gave **2.27** in 19 steps. The authors report that studies towards

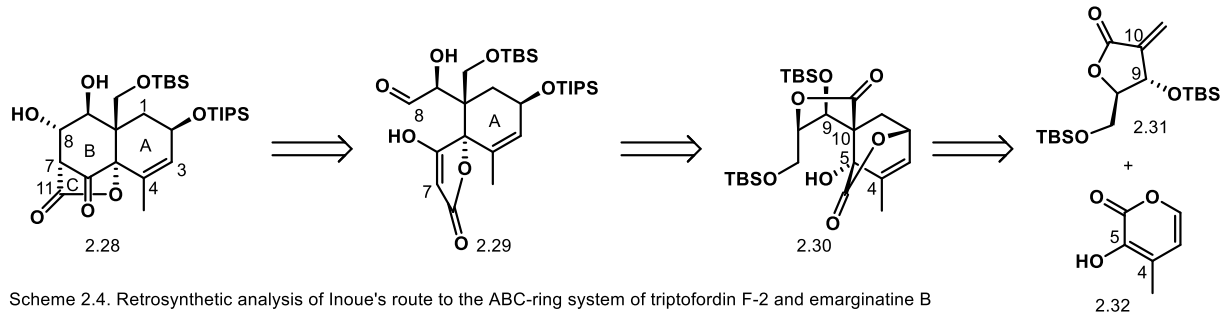
synthesizing euonyminol and the macrolide hypoglaunine B are on-going, though they have yet to be reported.

The Spivey group has disclosed a route towards highly oxygenated decalin scaffolds **2.21** and **2.27** in 16 and 19 steps, respectively, with the end goal of synthesizing the most highly oxygenated members of the agarofuran family. While this goal has yet to come to fruition, Spivey demonstrated the difficulty, in developing a general route towards members of this family. Interestingly, Spivey also demonstrated a novel sequence of installing the C-ring fragment *via* an Ireland–Claisen rearrangement, and then subsequent C-ring closure *via* selective demethylation with BBr_3. However, a major drawback to this route is that it relies on the symmetry observed in the stereochemistry of the oxygenation that decorates euonyminol. As a result, this strategy would only apply towards members possessing this symmetry.

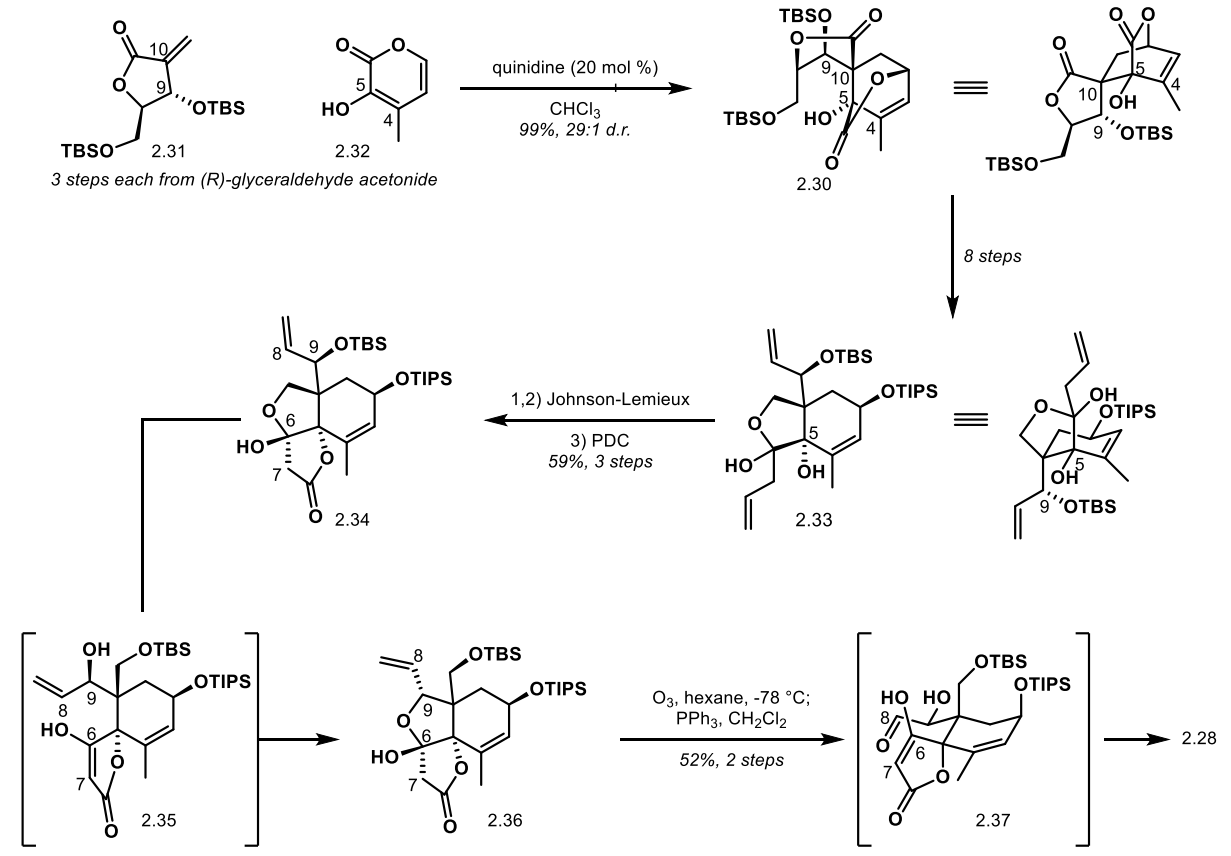
2.4.4 Inoue (2013) – Synthesis of the ABC-Ring System

In an effort to synthesize triptofordin F-2 and emarginatine B, the Inoue group was able to synthesize the ABC-ring system, **2.28**, of these two natural products, containing much of the necessary oxygenation (Scheme 2.4).[83] They developed a novel strategy, hypothesizing that the B-ring could be formed in a final aldol reaction between C7 and C8. The aldol precursor **2.29** could be prepared from A-ring fragment **2.30**, which could result from a stereoselective Diels–Alder reaction between α,β-unsaturated lactone **2.31** and pyrone **2.32**.

Both Diels–Alder precursors **2.31** and **2.32** were prepared in 3 steps from (*R*)-glyceraldehyde acetonide from a known procedure (Scheme 2.5). Attempts at this Diels–Alder reaction by heating in xylenes or by treatment with Et_3N at room temperature led to poor yield (21% of retro-Diels–Alder product) or poor diastereoselectivity (2.4:1), respectively. After screening several bases, they discovered that quinidine was the best base catalyst for the



Scheme 2.4. Retrosynthetic analysis of Inoue's route to the ABC-ring system of triptofordin F-2 and emarginatine B



Scheme 2.5. Forward synthetic route towards the ABC-ring system

Diels–Alder reaction, giving 99% yield and a d.r. of 29:1. Following eight functional group manipulations, **2.33** was prepared from **2.30**. Allyl Grignard addition to the lactone introduced carbons 7 and 11, and following Johnson–Lemieux oxidative cleavage of the alkene and oxidation of the resulting lactol, lactone **2.34** was formed. Though non-intuitive, carbons 6, 7, and 11 of the newly formed lactone would form the corresponding carbons in the C-ring of the agarofuran core. Treatment of lactol **2.34** with *t*-BuOK in *t*-BuOH opened the lactol and promoted silyl transfer

between the C9 silyl ether and the C14 alcohol, forming a new lactol, **2.36** in the process. As a result, C8 is now on the correct face to perform an aldol with C7 following ozonolysis. Ozonolysis of the C8 alkene revealed the aldehyde, and *in situ* generation of the enol resulted in formation of the B-ring, and completion of the ABC-ring system in 17 steps. From here, oxidation of C1 and the C3-C4 alkene would still need to be achieved, along with addition of the *geminal*-dimethyl group at C11 and installation of all the various esters. However, the synthesis of **2.28** proved that new strategies, including those building out from the A-ring, show great potential generating concise and general routes towards the agarofuran core.

Although this strategy has yet to be used to synthesize an agarofuran, Inoue demonstrated an important evolution in the strategy towards synthesizing agarofuran natural products and analogs. Earlier strategies often focused on formation of the carbocyclic skeleton and then subsequent oxidation of the resulting functionality. Inoue instead leveraged the oxidation found in the desired target to promote creative C-C bond forming solutions. The two major key steps, the stereoselective Diels–Alder and the silyl transfer then ozonolysis/*in situ* aldol reaction illustrate this point. Both of these steps are likely not possible without the oxygenation patterns observed in the agarofurans, and taking advantage of the inherent functionality provides new avenues for their synthesis.

2.4.5 Inoue (2017) – Synthesis of a Septahydroxylated ABC-Ring System

Building on their 2013 work, the Inoue group synthesized **2.38**, the enantiomeric structure of the core of euonyminol, missing only the C13 oxygenation.[84] They selected **2.38** as their target due to the difficulty in obtaining the enantiomer of **2.31**, which would be necessary for the synthesis of the natural enantiomer of agarofuran natural products (Figure 2.15). To obtain **2.38**, they envisioned oxidation of the ABC-ring structure of **2.39**. The A-ring of **2.39** would be synthesized from a *6-exo-dig* radical cyclization, and the BC-ring structure of **2.40** could be

synthesized using an alternative application of Diels–Alder product **2.30** synthesized in their 2013 work (Scheme 2.6).

Similar to their 2013 work, α,β-unsaturated lactone **2.31** and pyrone **2.32** underwent a base-mediated Diels–Alder reaction to form bicycle **2.30** (Scheme 2.7). Notably, the α,β-unsaturated lactone was instead synthesized in 5 steps from D-mannitol. Though **2.30** was used in their previous strategy, the newly formed cyclohexene ring now forms the B-ring as opposed to the A-ring. This makes the overall strategy more closely related to much of the earlier agarofuran work where the synthesis started with the B-ring. A five step sequence involving retro-Diels–Alder to extrude CO_2, epoxide formation and opening, 1,4-addition, protection, and addition of TIPS protected acetylene gave **2.41**. Treatment of **2.41** with PhSeCl formed the C-ring, and a four step sequence to reduce the C-Se bond and transform the C3 silyl protected alcohol into a bromide gave radical cyclization precursor **2.42**. Subjecting **2.42** to classical radical conditions resulted in the *6-exo-dig* cyclization to yield the ABC-ring core, **2.43**. Interestingly, they noted that if they used a proton or a TMS group in place of the TIPS group they observed preferential *7-endo-dig* cyclization. Regardless, a six step sequence installed the C8 and C9 oxygenation to give **2.44**. Treatment of the vinylsilane with ozone removed the silyl group to give **2.45**, and then a 7 step sequence removed the C15 oxidation and installed the C3 and C4 oxidation, yielding their desired target **2.38** in 31 steps. Unfortunately, to synthesize euonyminol, C6 oxidation is still required, and synthesis of other highly oxygenated members of this family would require changes in stereochemistry as **2.38** does not directly map onto any known agarofurans.

Inoue and coworkers were able to demonstrate the synthesis of a highly oxygenated ABC core of the agarofurans. The use of their pyrone Diels–Alder reaction in a different application to the agarofurans than their 2013 strategy likely illustrates that the previous strategy ultimately did not produce the results they desired. However, the application of similar starting materials to two separate routes towards highly oxygenated ABC-ring cores of the agarofurans demonstrates the

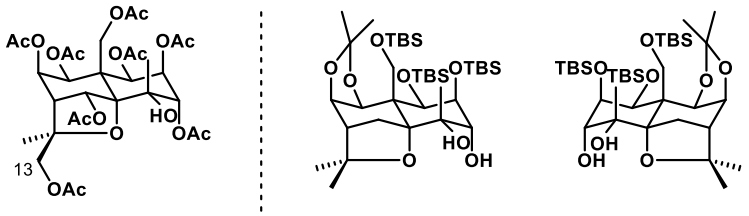
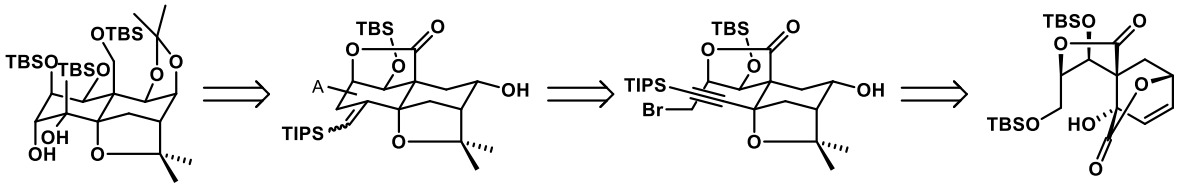
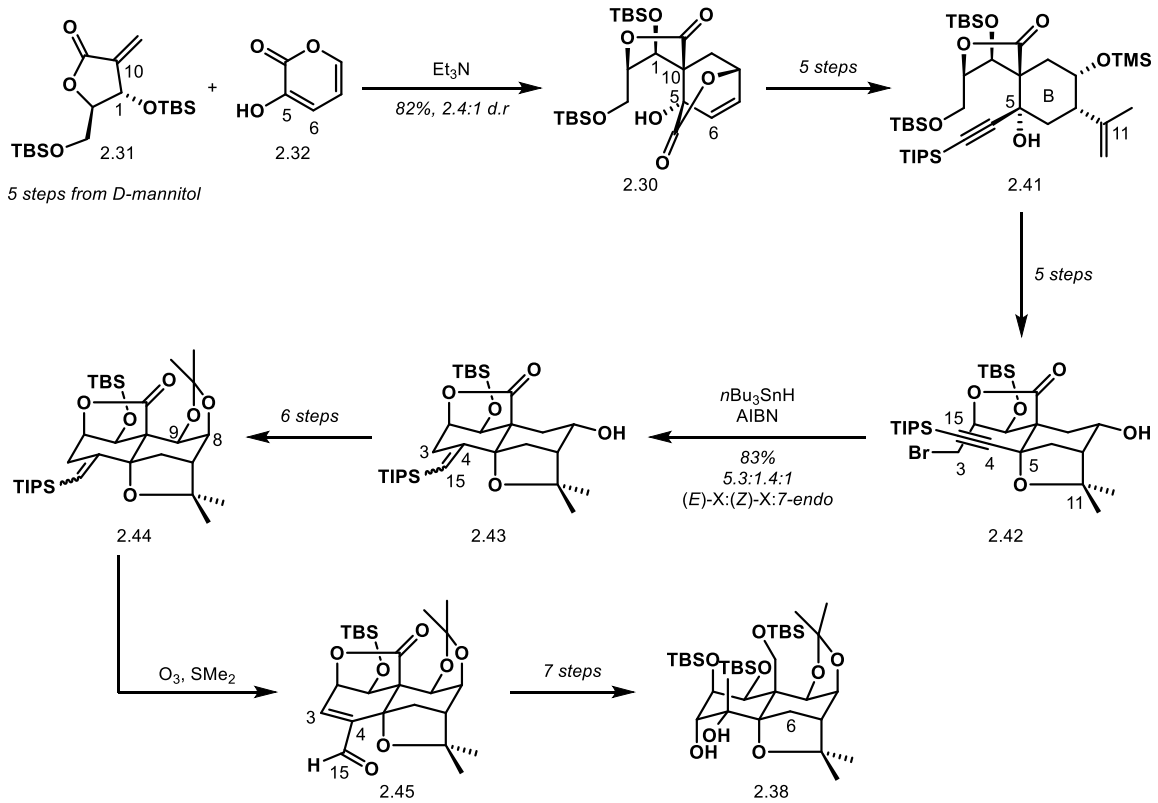


Figure 2.15. Analysis of euonyminol vs. chosen target



Scheme 2.6. Retrosynthetic analysis of septahydroxylated core



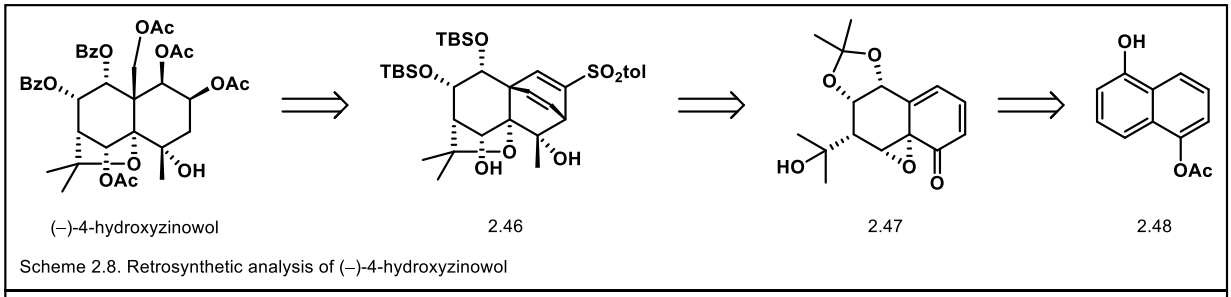
Scheme 2.7. Inoue's synthesis of the septahydroxylated core

flexibility of the overall strategy. Although the synthesis of a natural product has yet to be reported using either the 2013 or 2017 strategy, Inoue has demonstrated the ability to synthesize agarofuran-like cores that could be diversified into several analogs or natural products. The major drawback to these strategies, especially this most recent one which requires 31 steps, is the step count and is what likely led to the potential abandonment of this strategy.

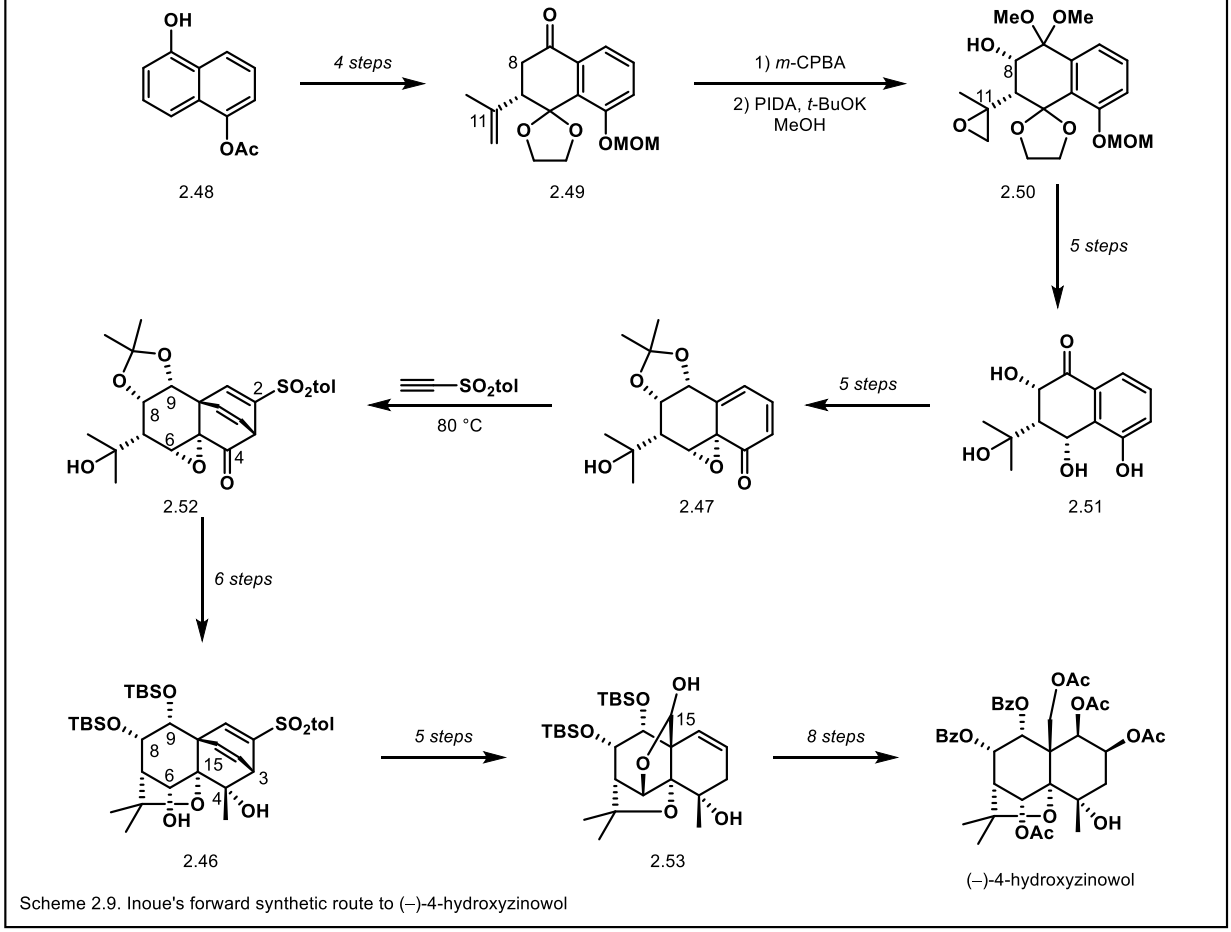
2.4.6 Inoue (2014) – Total Synthesis of (–)-Hydroxyzinowol

In 2014, Inoue and coworkers reported their synthesis of (–)-4-hydroxyzinowol in 36 steps starting from 5-acetoxynaphthalen-1-ol.[85] Prior to this work, White's synthesis of (±)-euonyminol in 1997 was the only synthesis of a highly oxygenated agarofuran. (–)-4-Hydroxyzinowol was chosen as a target due to its potential as a highly effective MDR-reversing agent. Jiménez, Gamarro, and coworkers found that (–)-4-hydroxyzinowol blocked Pgp-mediated transport of daunorubicin at low micromolar concentrations, making it interesting as a potential lead compound. They envisioned a strategy where (–)-4-hydroxyzinowol could result from selective esterification resulting from the oxidation of **2.46** (Scheme 2.8). A Diels–Alder reaction between diene **2.47** and ethynyl *p*-tolyl sulfone and C-ring closure would give **2.46** from **2.47**. The oxidized decalin core of **2.47** can be traced back to dearomatization and oxidation of 5-acetoxynaphthalen-1-ol (**2.48**).

Starting from **2.48**, treatment with PIDA in the presence of ethylene glycol led to the monoprotected quinone (Scheme 2.9). Following hydrolysis of the acetate, enantioselective 1,4-addition installed the isopropenyl group necessary for the C-ring and MOM protection of the phenol prepared **2.49** for oxidation of carbons 8 and 11. Epoxidation with *m*-CPBA afforded the C11 oxidation; however, attempts to directly oxidize C8 gave the wrong β-selectivity. Instead, addition of hypervalent iodine to the β-face, followed by displacement of an *in situ* formed hemiacetal gave **2.50** with the correct stereochemistry at C8. Two reductions, two hydrolyses,



Scheme 2.8. Retrosynthetic analysis of (–)-4-hydroxyzinowol



Scheme 2.9. Inoue's forward synthetic route to (–)-4-hydroxyzinowol

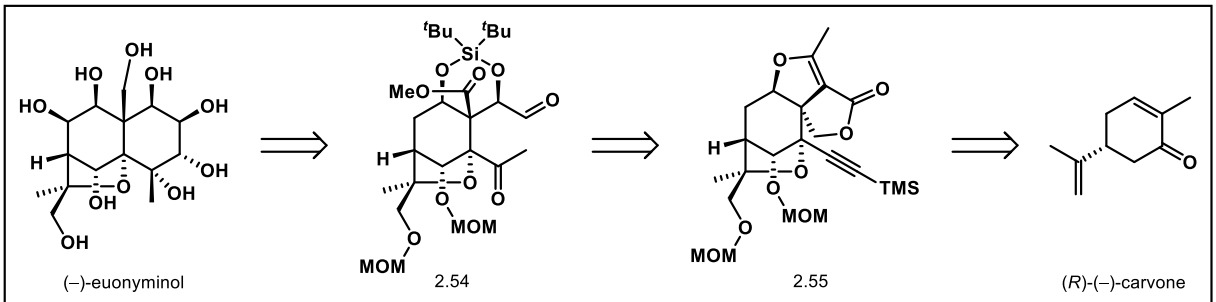
and opening of a persistent acetal gave **2.51** over 5 steps. Two protections, a deprotection, and a reduction, followed by periodate-mediated dearomatization gave Diels–Alder precursor **2.47** over five steps. While the Diels–Alder reaction worked better with methyl acrylate (79%) and methyl propiolate (81%) than with ethynyl *p*-tolyl sulfone (70%), the latter was chosen due to the ease of removal of the sulfone compared to the methyl esters (note the lack of C2 carbon substitutions in the agarofurans). They note that the selectivity of the Diels–Alder reaction results from puckering of the ring, making the α-face the convex face and therefore more sterically

available despite the plethora of functionality on that same face. Deprotection of the acetal, nucleophilic opening of the epoxide, acid-mediated THF ring closure (forms the C-ring), protection of the C8 and C9 alcohols, deprotection of the C6 alcohol, followed by methylation of the C4 ketone gives **2.46**. Ozonolysis at the C15 alkene, liberates C15 with the desired oxygenation, which was trapped as the lactol. A four-step sequence removes the sulfone and the C3 carbon substitution, giving **2.53**. An eight-step sequence to afford the final oxidations and the proper esterifications gives (–)-4-hydroxyzinowol in 36 steps.

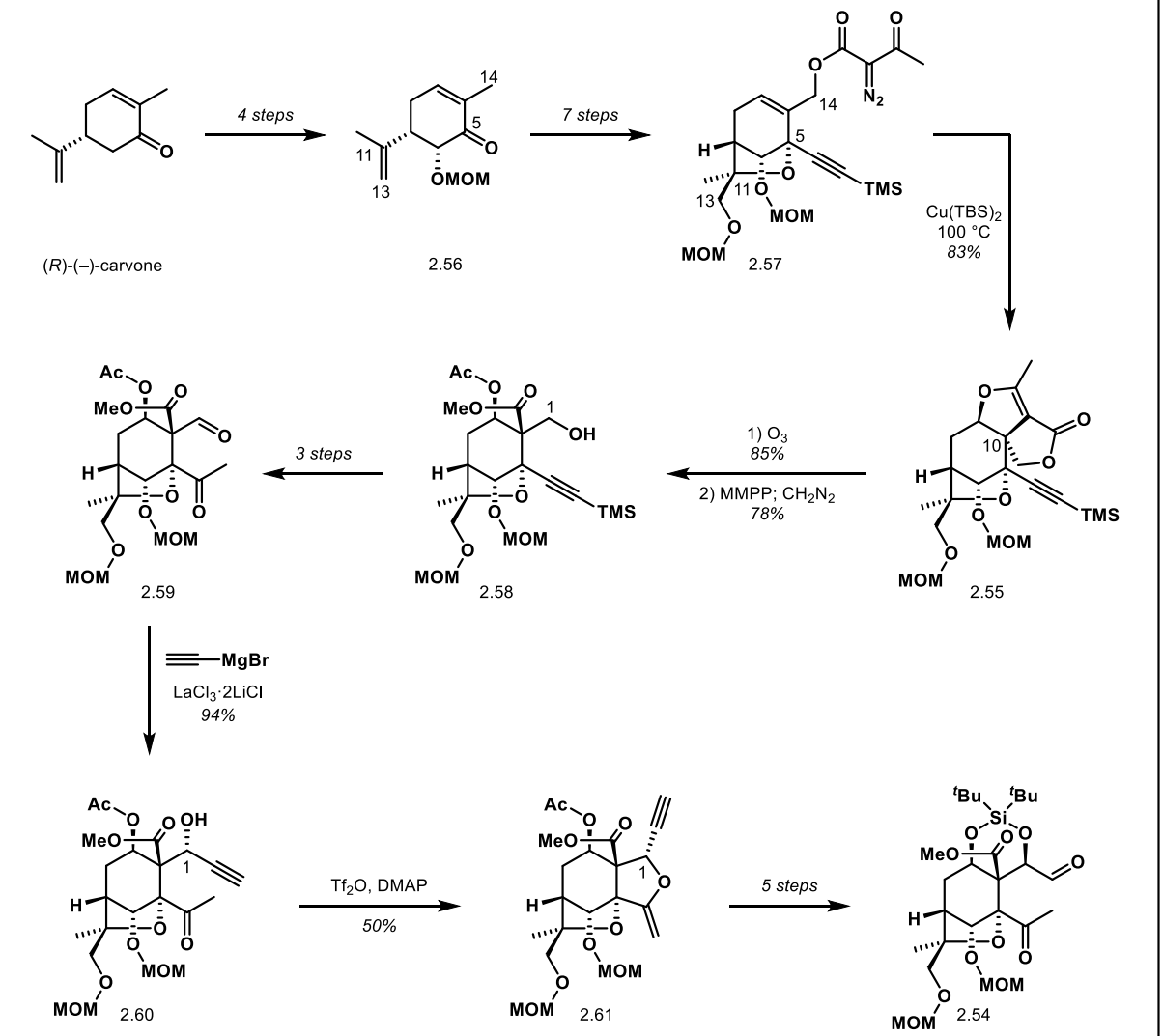
The synthesis of (–)-4-hydroxyzinowol by Inoue and coworkers is a monumental achievement in the area of agarofuran synthesis as it was the first synthesis of a highly oxygenated agarofuran since White's synthesis of (±)-euonyminol almost 20 years prior. It is also arguably the first synthesis of an agarofuran possessing potent bioactivity. Despite this major achievement, the length of the route precludes it from being easily used as a general route for potential SAR and bioactivity studies. Additionally, the route does not lend itself towards being able to make other members of this family. Nonetheless, their accomplishment provides an incredible amount of insight for synthetic chemists aiming to tackle this family of natural products.

2.4.7 Herzon (2021) – Enantioselective Synthesis of (–)-Euonyminol

In 2021, the Herzon group published the first enantioselective synthesis of (–)-euonyminol in 43 steps.[86] Like much of the previous agarofuran work, Herzon started his synthesis with (*R*)-(–)-carvone, though his approach greatly differed from previous routes as he did not pursue a cyperone strategy nor a Diels–Alder-based strategy. They identified that formation of the C10 quaternary carbon would be especially challenging, and their strategy centered around forming C10 stereoselectively. The authors envisioned formation of the A-ring of euonyminol *via* an aldol condensation and oxidation of the resulting alkene from **2.54** (Scheme 2.10). This highly functionalized BC-ring fragment was traced back to **2.55**, the result of an unexpected, but highly



Scheme 2.10. Retrosynthetic analysis of (–)-euonyminol

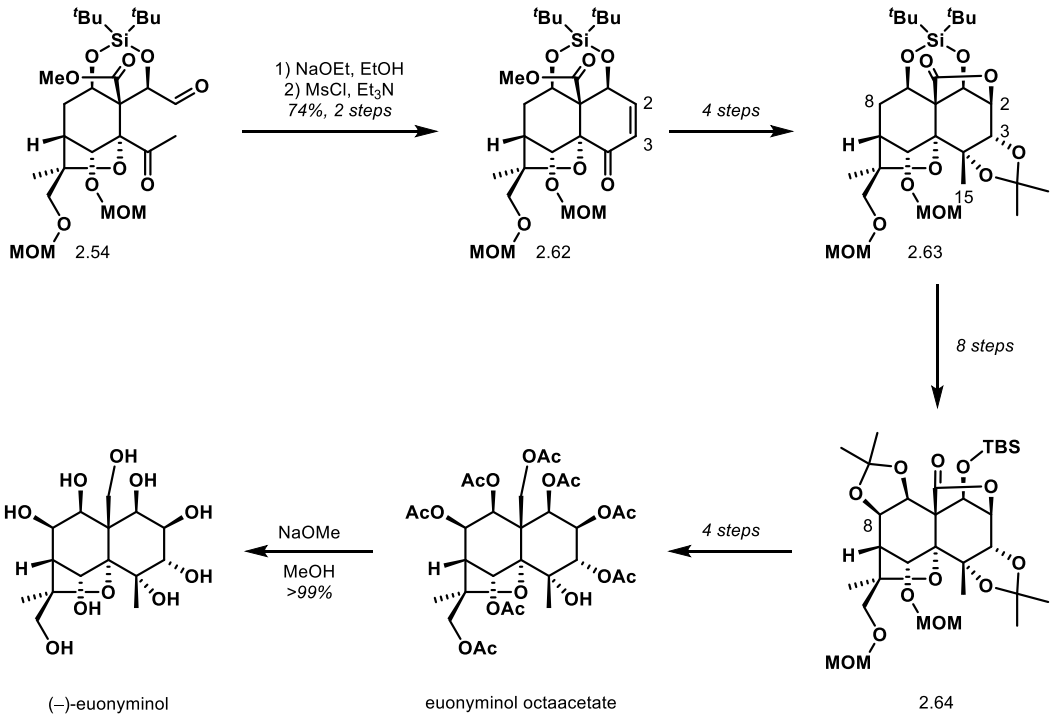


Scheme 2.11. Herzon's forward synthetic route towards the aldol precursor

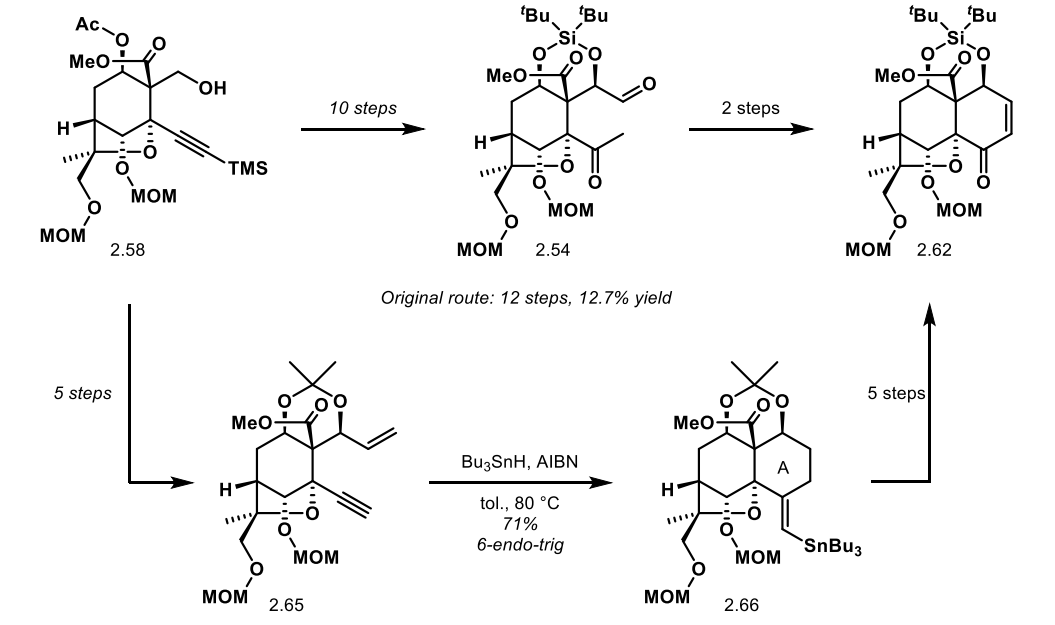
fortuitous, formal [3+2] dipolar cycloaddition to set the C10 quaternary carbon. Following several functionalizations, **2.55** could be formed from (*R*)-(–)-carvone.

To begin the synthesis, **2.56** was synthesized in 4 steps from (*R*)-(–)-carvone via a known route (Scheme 2.11). A seven-step sequence that allowed for oxidation of the C11-C13 alkene, 1,2-addition of lithium trimethylsilylacetylide to the C5 ketone, and oxidation/functionalization of the C14 methyl group to prepare for the [3+2] dipolar cycloaddition, gave **2.57**. Although they expected the cyclopropane after treatment of diazo-containing compound **Yb** with copper, they instead observed formation of tetracycle **2.55**. Realizing that **2.55** was still useful for their forward synthesis since it formed the C10 quaternary center stereoselectively, ozonolysis and Baeyer–Villager oxidation gave β-hydroxy ester **2.58**. A three-step sequence of deprotection, hydration of the alkyne promoted by the neighboring alcohol, and oxidation gave **2.59**. Addition of ethynylmagnesium bromide in the presence of $LaCl_3$ gave the propargylic alcohol with the undesired stereochemistry at C1 in 94% yield. However, they note that these 1,2-addition conditions and use of TMSCN were the only ones they found to add to the C1 aldehyde. Use of various alkenyl metal species in the presence of additives showed no reaction, likely resulting only in α-deprotonation of the ketone. Treatment of **2.60** with triflic anhydride and DMAP inverted the C1 stereochemistry to give **2.61** and a five-step sequence gave aldol precursor **2.54**. The aldol reaction furnished the ABC-ring system in 74% yield over two steps to give **2.62** (Scheme 2.12). A four-step sequence installed the C15 methyl group and oxidized the C2-C3 alkene, forming lactone **2.63** in the process. An eight-step sequence installed the oxidation at C8 and swapped protecting groups. Two deprotections, a reduction, and global acetylation gave euonyminol octaacetate over four steps. Global deacetylation gave (–)-euonyminol in 43 total steps.

Following this publication, Herzon and coworkers published a full article where they go into detail on several of the key steps (Scheme 2.13).[87] Of specific importance to my own work,



Scheme 2.12. Completion of the synthesis of (–)-euonyminol



Scheme 2.13. Herzon's improved A-ring cyclization route

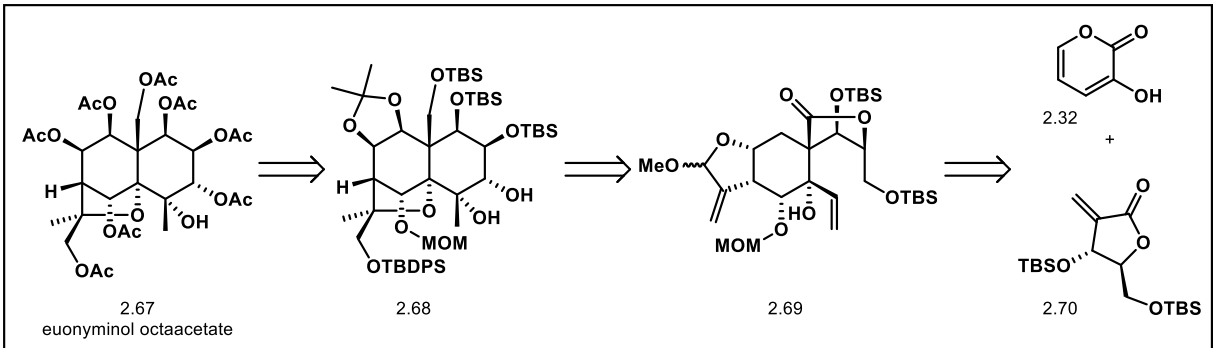
they illustrate the difficulties they found when trying to work with intermediates that could undergo retro-aldol reactions or when attempting to add organometallic reagents to neopentylic aldehydes.

While they also note two alternative routes that ultimately failed, using a semi-pinacol rearrangement or a nickel-catalyzed cyclization, they also include a revised route that improves the overall yield. Previously, they had used a twelve-step sequence centered around an aldol reaction to ultimately form the A-ring (**2.58** to **2.54** to **2.62**). In their revised route, they instead used a *6-endo-trig* radical cyclization to form the A-ring from **2.65**. While this eleven-step sequence only removes one step from the overall route, it does improve the yield in obtaining **2.62** from **2.58** from 12.7% to 21.7%. Interestingly, **2.65** had previously been synthesized in pursuit of their nickel-catalyzed key step; however, it was repurposed later for this key A-ring closure.

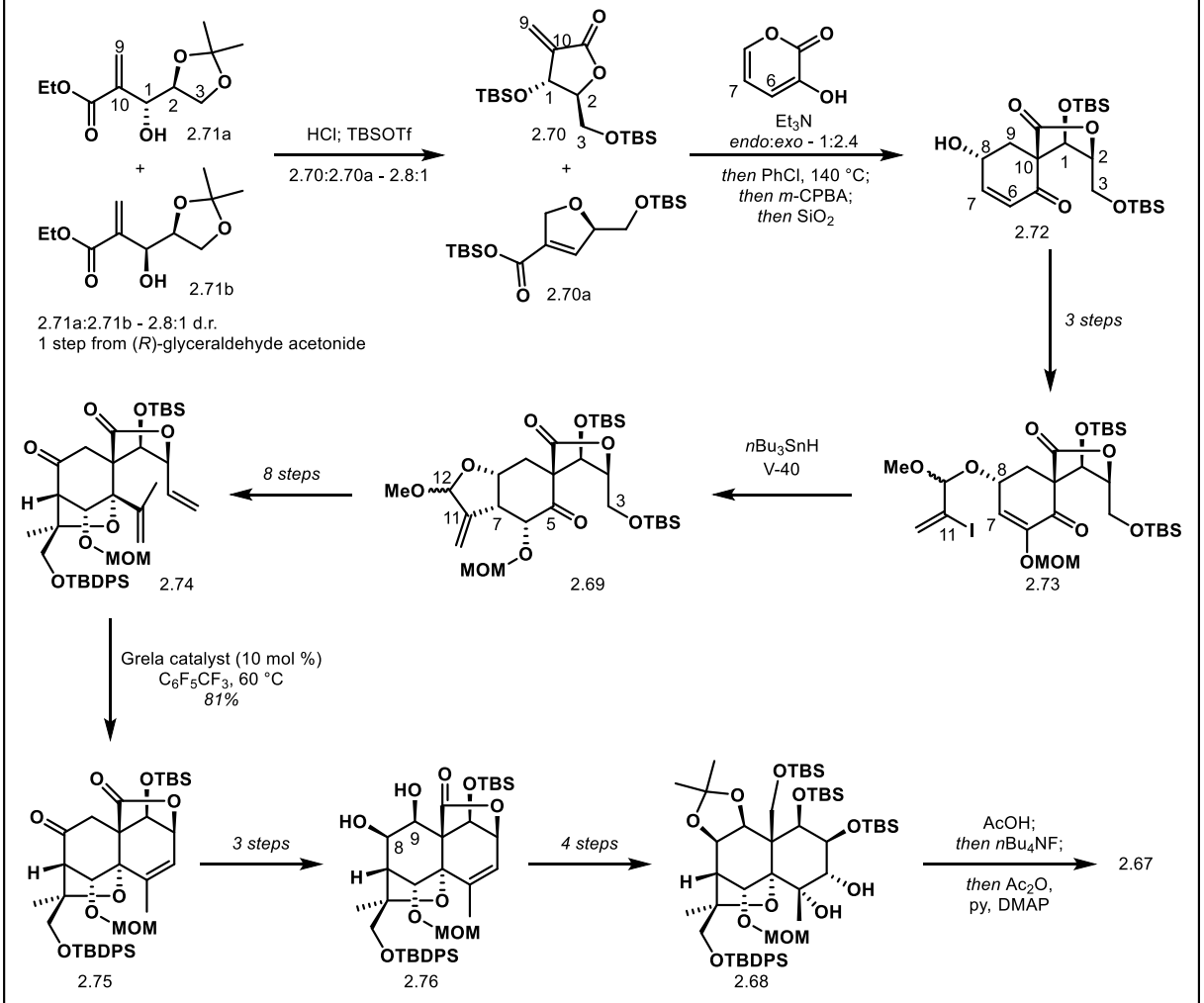
The first enantioselective synthesis of (–)-euonyminol, the most highly oxygenated member of the agarofurans, is a huge achievement. The body of work that Herzon and coworkers demonstrated will be invaluable to future synthetic chemists pursuing the agarofurans both in regard to what was ultimately successful and unsuccessful. Despite this great achievement, the 43 step sequence highlights the difficulty in pursuing the agarofurans and the necessity for a concise route to an easily diversifiable core. The authors note that they aim to use this sequence in pursuit of the dimacrocyclic cathedulins; however, the route is unlikely to produce members of the family or analogs with differing patterns of oxygenation.

2.4.8 Inoue (2021) – Synthesis of Euonymine and Euonyminol Octaacetate

In the same year as Herzon's 43 step enantioselective synthesis of euonyminol, Inoue reported his 24 and 29 step enantioselective syntheses of euonyminol octaacetate and euonymine, respectively.[88] This is the first reported synthesis of euonymine, and the first total synthesis of a macrolide-containing agarofuran. Inoue and coworkers largely built upon their 2013



Scheme 2.14. Retrosynthetic analysis of euonyminol octaacetate



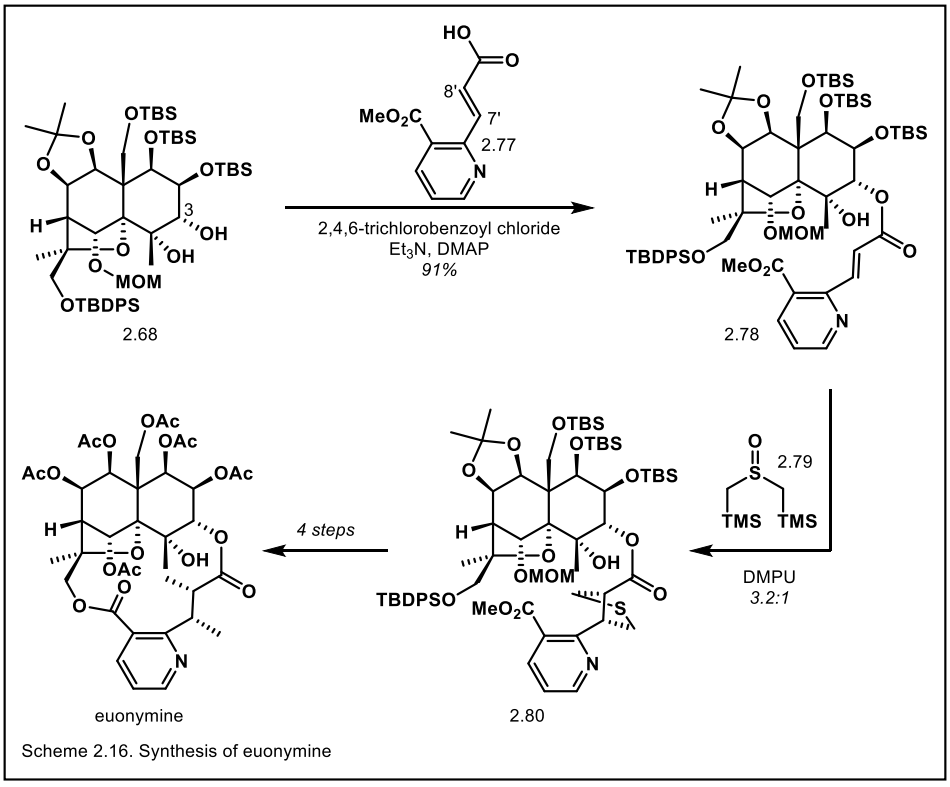
Scheme 2.15. Inoue's synthesis of euonyminol octaacetate

and 2017 work where they used a Diels–Alder reaction between pyrone **2.32** and α,β-unsaturated lactone **2.31** to build either the A- or B-ring of the agarofurans. They traced euonyminol octaacetate (**2.67**) back to a highly oxidized intermediate, **2.68**, that would also be used in the synthesis of euonymine. Tricycle **2.68** could be synthesized from **2.69** via a ring closing metathesis and C-ring closure. **2.69** would come from the aforementioned Diels–Alder reaction. Having learned quite a bit from their extensive work on the agarofurans, the Inoue group produced a highly optimized route to afford these highly oxygenated agarofurans in a much shorter route than their previous synthesis of (–)-(4)-hydroxyzinowol.

To begin the synthesis, they oxidized (*R*)-glyceraldehyde acetonide to form an unstable aldehyde which was immediately treated to Morita–Baylis–Hillman conditions with ethyl acrylate and DABCO to afford **2.71a** and **2.71b** in a 2.8:1 ratio. Interestingly, when treated with acid, **2.71** formed **2.70** while **2.71b** formed **2.70a**. Lactone **2.70** was carried through the telescoped sequence of pyrone Diels–Alder (1:2.4 *endo*:*exo* selectivity that was irrelevant upon retro-Diels–Alder), retro-Diels–Alder expelling CO_2, epoxidation, and elimination to give **2.72**. A three-step sequence to install the C6 oxygenation and append the C11 fragment onto C8 afforded **2.73**. Treatment with *n*Bu_3SnH formed the C7-C11 bond in **2.69**. An eight-step sequence resulted in opening of the mixed acetal, closure of the C-ring, and preparation of C3 and C5 for the ring closing metathesis of **2.74**. Interestingly, the stereochemistry at C12 influenced the addition of isopropenyl Grignard to the C5 ketone. Each diastereomer required separate conditions, with the α-diastereomer requiring only the Grignard reagent in THF at 0 °C (77% yield), but the β-diastereomer requiring the use of $LaCl_3$·LiCl (66% yield). Regardless, they found that **2.74** was unreactive towards standard ring closing metathesis conditions. Ultimately, they found that the Grela catalyst in sparged $C_6F_5CF_3$ gave the desired ring closing metathesis product, **2.75**, in 81% yield. A three-step sequence provided the necessary C8 and C9 oxygenation, and a four step sequence gave **2.68**, which would be used as a common intermediate in the synthesis of

euonymine. Global deprotection and global acetylation gave euonyminol octaacetate, **2.67**, in 24 steps.

To synthesize euonymine, they coupled **2.68** with **2.77** using Yamaguchi esterification conditions to give **2.78**. Unfortunately, they could not do the esterification reaction with the C7' and C8' methyl groups already in place as the *trans*-alkene was necessary to prevent self-addition of the pyridine into the Yamaguchi intermediate, shutting down reactivity with the C3 alcohol of **2.68**. To circumvent this problem, they subjected **2.78** to a [3+2]-cycloaddition using **2.79**, giving the desired **2.80** as the major product in a 3.2:1 mixture of diastereomers at C7' and C8'. They note that if they performed the macrocyclization before the cycloaddition reaction, they preferentially form the undesired diastereomer. To complete the synthesis, selective deprotection of the C13 silyl group with *n*Bu_4NF and AcOH, saponification, macrocyclization using PyBOP and global deprotection and acetylation afford the first synthesis of euonymine in 29 steps.



Scheme 2.16. Synthesis of euonymine

Inoue and coworkers were able to demonstrate the successful implementation of their pyrone Diels–Alder strategy that they have worked on for likely over a decade. They showed that deviating from a carvone-based strategy could drastically lower the step count to synthesize euonyminol and potentially other highly oxygenated agarofurans. However, it must be noted that the strategy lacks flexibility, and it is difficult to envision an adaptation of this route towards analogs and other agarofurans with differing oxygenation patterns. Additionally, they carried unusable diastereomers through multiple steps and greatly decreased their step count by telescoping multiple reactions together without purifications in between, but often with work-up steps. Realistically, in terms of practicality, the number of physical reactions performed is much higher than the step count implies. Nonetheless, the synthesis of euonyminol octaacetate and euonymine by Inoue and coworkers is a monumental achievement in the area of agarofuran synthesis and proves the importance of judicious route planning in pursuit of a concise route towards an easily diversifiable agarofuran core.

2.5 Conclusions

Despite there being over 30 published reports detailing work towards synthesizing agarofurans, the synthesis of the agarofuran family of natural products remains a significant challenge in synthetic chemistry. Unfortunately, many of these reports detail incomplete syntheses of natural products, and until Inoue's and Herzon's groundbreaking syntheses in 2014 and 2021, White's 1997 20-step synthesis of (±)-euonyminol was the only synthesis of a highly oxygenated agarofuran. The other completed total syntheses of agarofurans were usually of the minimally oxygenated members of the family, such as isocelorbicol and α-agarofuran. While interesting in their own right, the less oxygenated/non-ester-containing natural products largely exhibit poor bioactivity, making them less suitable for biological study. Even though Inoue's and Herzon's syntheses of (–)-4-hydroxyzinowol, (–)-euonyminol, and euonymine are monumental

achievements, they still suffer from some significant drawbacks. The step count limits their utility for biological study, and the lack of flexibility in the route to synthesize other members of this family in addition to potential analogs. Overall, the vast majority of syntheses begin with carvone since this chiral pool building block contains: 1) the isopropenyl group necessary for synthesis of the C-ring, 2) the entire core structure of the B-ring, 3) the necessary C10 methyl group, and 4) additional functionality capable of being transformed into the rest of the natural product. However, the use of carvone as a starting material is not without its drawbacks, namely: 1) the lack of oxidation and the lack of functional groups in key locations on the ring, requiring significant functional group manipulations, 2) it forces a strategy originating from the B-ring and building outwards, and 3) despite the numerous syntheses beginning with carvone, this strategy has yet to provide successful routes to more complex members of the family with the exception of Herzon's 43-step synthesis of (–)-euonyminol. Conscious of the extensive literature on the agarofurans, it is clear that a new strategy for developing a synthetic route is required, especially with the goal of brevity and generality in mind. Access to a concise and general route to the core of the agarofuran family of natural products would allow for easy diversification into many natural products and their appropriate analogs, thus setting the stage for synthesis fueling the understanding and application of the agarofurans and their extensive, potent biological activity.

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Chapter 3: Synthesis of the AB-Core of the Dihydro-β-agarofurans

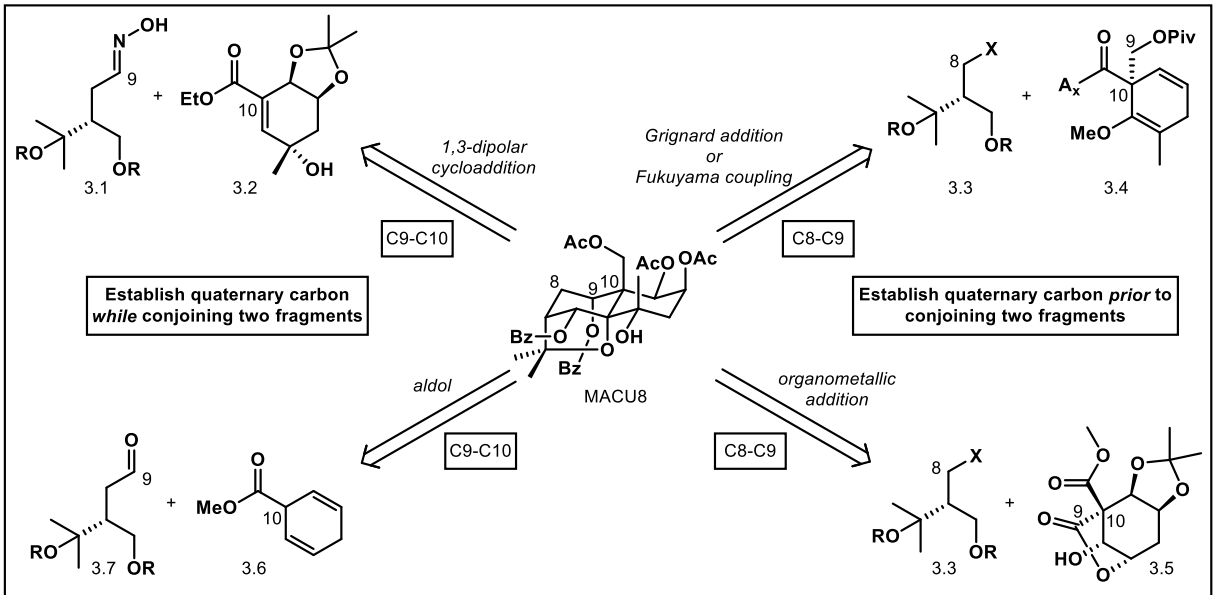
3.1 Introduction and Motivation

The agarofurans have long been highly sought-after synthetic targets; however, many of the strategies used to approach them have remained relatively similar over the last fifty years. In general, the most common approach starts with (*R*)-(–)-carvone, which functionally serves as the platform for the B-ring, and builds out the A-ring often through the synthesis of cyperone scaffolds or some other annulation strategy. While this strategy has been successful for the synthesis of less complex agarofurans like isocelorbicol and α-agarofuran, this approach has been exhaustively studied and has ultimately proven to be unconducive towards generating a synthetic route to target several highly potent and highly oxygenated members of this family (see Chapter 2, section 2.4.2). Recently, Herzon and co-workers have demonstrated that the carvone strategy could be successfully applied to the synthesis of the most highly oxygenated of all agarofurans, (–)-euonyminol, albeit in 43 steps (see Chapter 2, section 2.4.7). However, recent work by Herzon and Inoue (see Chapter 2, sections 2.4.6 and 2.4.8) highlights the need for access to an easily diversifiable core. Currently, there is no general route to access numerous agarofurans and appropriate analogs for biological and SAR study. Conscious of the plethora of work already done on this family of natural products, we aimed to take a different approach focused on starting from the A-ring and building out the B-ring, essentially working in the opposite direction from most of the reports in the literature. While carvone seems like an advantageous starting point because of its auspiciously placed isopropenyl group, we hypothesized that a more expedient route could be developed by moving away from this precursor, thus allowing greater flexibility in the strategy. Ultimately, MACU8[1] was chosen as a target for generating a concise, general route towards an easily diversifiable agarofuran core. Synthesis of such a core would allow for rapid expansion into

several natural products and analogs, thus allowing for significant biological studies to be undertaken.

3.1.1 General Retrosynthetic Analysis and Strategy

I identified MACU8[1] as an ideal initial target for two reasons: 1) it has highly potent multidrug resistance reversing biological activity (see section 2.3.5), which is the area of agarofuran biological activity that is the most studied and 2) its oxygenation pattern is conducive towards generating a synthetic route that would likely allow for the synthesis of several highly potent members of this natural product family. To develop such a route, I identified C10, the central quaternary carbon, as the key to this synthesis. Being able to generate that quaternary carbon stereoselectively is crucial since the remaining stereochemistry could likely be relayed from that single stereocenter (Scheme 3.1). Additionally, I envisioned conjoining two separate



Scheme 3.1. General retrosynthetic analysis of MACU8

fragments, with the first fragment being the A-ring scaffold and the second fragment being the piece that would eventually become the B-ring. To achieve these two goals of: 1) stereoselectively generating quaternary carbon C10 and 2) producing a convergent synthesis, I foresaw four potential strategies stemming from two general bond disconnections. The first of these general

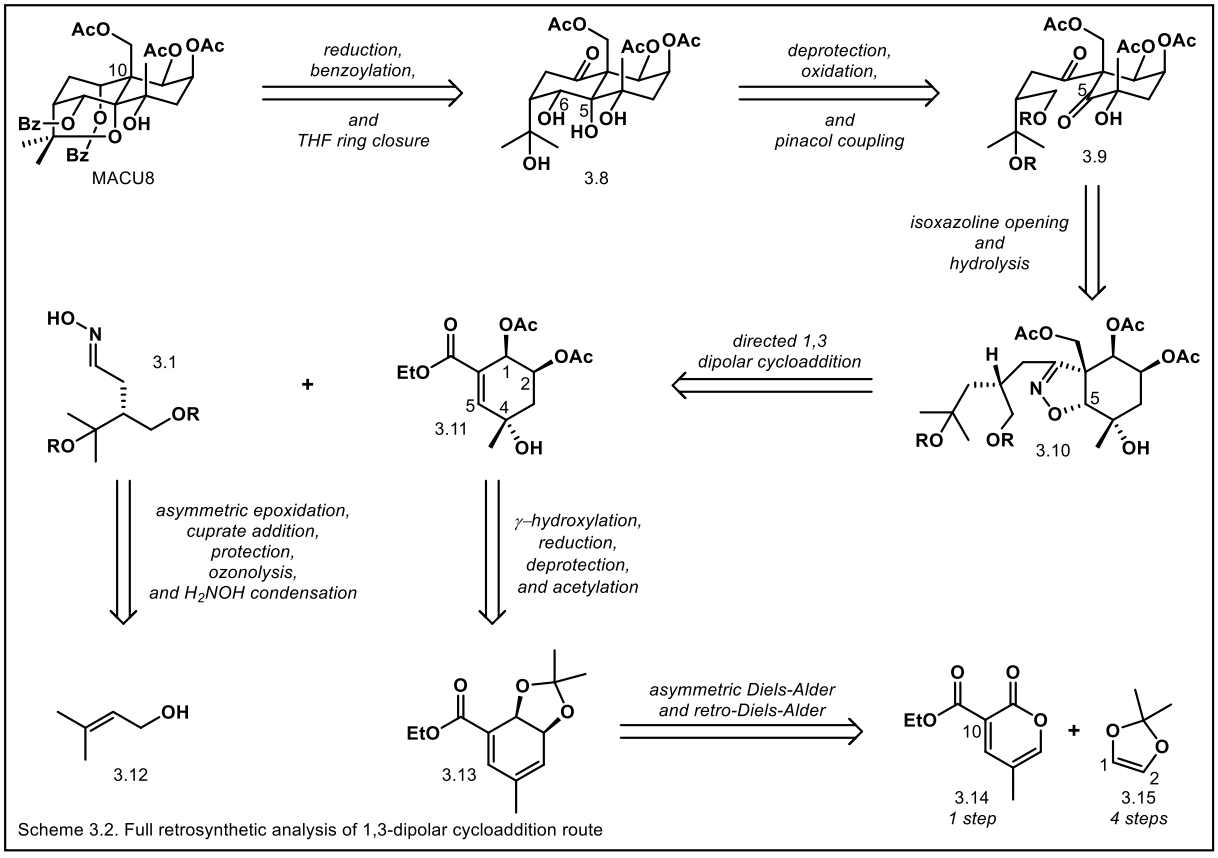
bond disconnections (C9–C10) involves concurrent conjoining of the two fragments and formation of quaternary carbon C10. I envisioned two potential ways of achieving this: 1) A 1,3-dipolar cycloaddition between nitrile oxide precursor **3.1** and alkene **3.2**; or 2) An aldol reaction between aldehyde **3.7** and ester **3.6**. The second bond disconnection (C8–C9) involves formation of quaternary carbon C10 prior to conjoining the two fragments. I also considered two possible ways of achieving this pathway: 1) A Fukuyama coupling[2] or Grignard addition of B-ring fragment **3.3** to a C9 carbonyl on **3.4** following an oxidation event; or 2) An organometallic addition of B-ring fragment **3.3** to the C9 lactone of **3.5**. For both the concurrent formation of C10 and the prior formation of C10 strategies, each had a possible route in which the oxygenation of the A-ring was either established before or after the key step bringing the two fragments together. Additionally, convergence of the A- and B-ring fragments would not only help shorten the synthetic route, but would also allow great flexibility in adapting the route towards numerous agarofurans and analogs.

3.2 Concurrent Conjoining of Fragments and Formation of the Quaternary Carbon at C10: 1,3-Dipolar Cycloaddition Strategy

3.2.1 Retrosynthetic Analysis

This strategy involves a 1,3-dipolar cycloaddition to form the central quaternary carbon, C10, in the same step that the A- and B-ring fragments are conjoined. This disconnection would allow for stereoselective formation of the quaternary carbon both by direction from the C4 allylic alcohol and the steric encumbrance of the C1 and C2 acetates, along with formation of the necessary C5 oxygenation in the same step. Other than the required functional group manipulations to place the correct esters on each alcohol, pinacol coupling of **3.9** would furnish the B-ring, closing the decalin ring system (Scheme 3.2). Closure of the C-ring, which is well-precedented in the literature,[3-9] would give the desired natural product MACU8. Following the 1,3-dipolar cycloaddition of fragments **3.1** and **3.11**, isooxazoline **3.10** could be reductively cleaved[10]

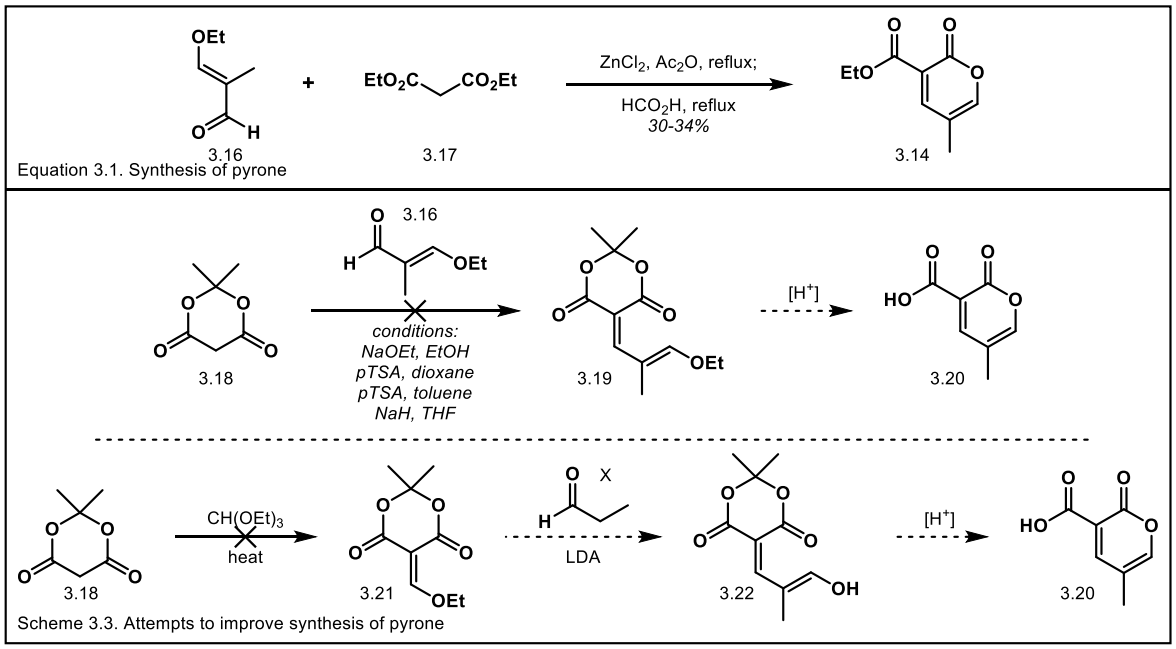
to give diketone **3.9**. A-ring fragment **3.11** would be synthesized via a Mukaiyama hydration[11] of diene **3.13**, which can be synthesized enantioselectively from pyrone **3.14** and dienophile **3.15** in an asymmetric Diels–Alder/retro-Diels–Alder sequence previously reported in the literature.[12] Fragment **3.1** could be synthesized in five steps from allylic alcohol **3.12**, following a sequence of asymmetric epoxidation, organometallic addition, protection of the diol, ozonolysis, and lastly oxime formation.



Scheme 3.2. Full retrosynthetic analysis of 1,3-dipolar cycloaddition route

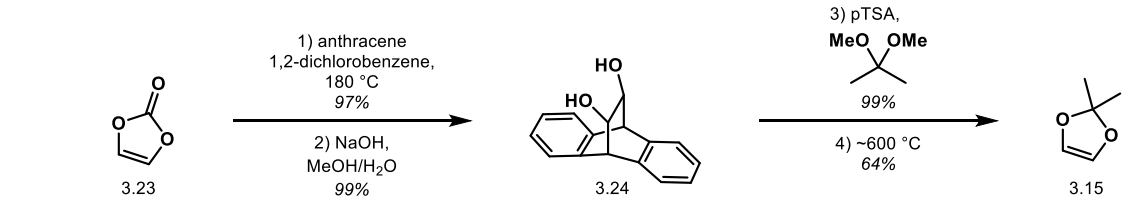
3.2.2 Asymmetric Diels–Alder/Retro-Diels–Alder Sequence

The synthesis of pyrone[12] **3.14** and dienophile[13] **3.15** are both known in the literature. I synthesized pyrone **3.14** in 30-34% yield, comparable to that observed in previous reports (Equation 3.1). However, I did attempt to find an alternative, hopefully higher yielding route. (Scheme 3.3). Using Meldrum's acid, **3.18**, I envisioned two potential routes. The first was condensation and subsequent cyclization using aldehyde **3.16**, the same aldehyde used in the

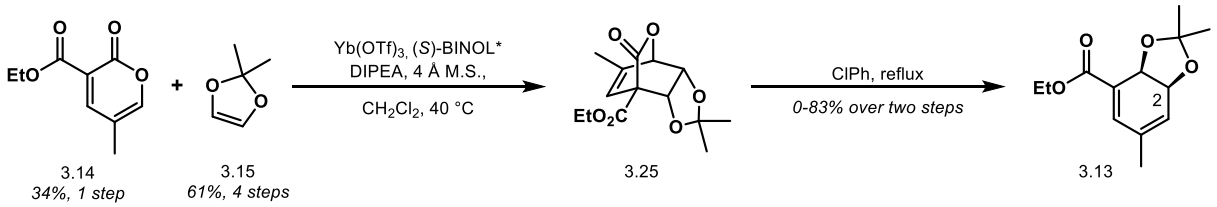


previous route. Unfortunately, I found that attempts to perform this condensation using a variety of acid and basic conditions led to decomposition of either Meldrum's acid or of the aldehyde. The second would use a more stepwise route, first by formation of β-ethoxy-α,β-unsaturated diester **3.21**, then by cyclization following a 1,4-addition of an enolate formed from propanal. Despite a similar sequence being known in the literature,[14] attempts to condense Meldrum's acid with triethyl orthoformate were ultimately unsuccessful, usually leading to decomposition of Meldrum's acid with no appreciable product formation. Ultimately, the previously disclosed route using diethyl malonate and aldehyde **3.16** was used. Dienophile **3.15** could easily be synthesized using a known procedure from the literature (Scheme 3.4).[13] Starting with vinylene carbonate, **3.23**, a Diels–Alder reaction with anthracene was performed to protect the alkene. Cleavage of the carbonate, followed by protection as the acetal went smoothly to prepare for the retro-Diels–Alder reaction to unveil the dienophile. The retro-Diels–Alder reaction was performed by heating the neat solid using a propane torch until the retro-Diels–Alder reaction occurred and the dienophile was distilled in the same process, giving **3.15** in 64% yield.

Initial attempts to perform the asymmetric Diels–Alder reaction between pyrone **3.14** and dienophile **3.15** were ultimately unsuccessful, leading to no observable conversion (Scheme 3.5).

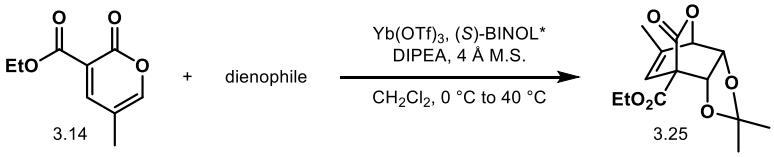


Scheme 3.4. Synthesis of dienophile



Scheme 3.5. Replication of Diels-Alder/retro-Diels-Alder sequence

After contacting the authors of the asymmetric Diels–Alder paper, I was made aware of further purification steps that were used for pyrone **3.14**, namely recrystallization following column chromatography. After subjecting pyrone **3.14** to column chromatography, it was recovered as a viscous orange oil, deemed pure by ^{1}H NMR and ^{13}C NMR. After screening a number of solvents, I found that use of hexanes with dichloromethane as a cosolvent was sufficient for recrystallization of pyrone **3.14** to yield a pale yellow to white solid. When subjecting this material to the asymmetric Diels–Alder conditions, I observed irreproducible results. I synthesized bicycle **3.25** twice in 95% and 97% yield on small scale (<20 mg) (Scheme 3.5); however, I found that in every other attempt I would see little to no observable conversion despite using the exact same materials in each attempt and following the exact same protocol. Looking to further purify pyrone **3.14**, I developed



Entry	*Dienophile*	*Notes*	*Yield*
1	3.15	first time using distilled pyrone	9%
2	3.15	distilled dienophile directly before use	26%
3	3.15	larger scale (50 mg)	14%
4	3.26	-	97%
5	3.23	-	0%

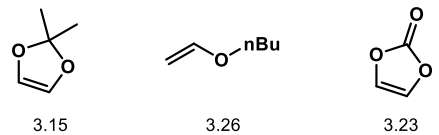
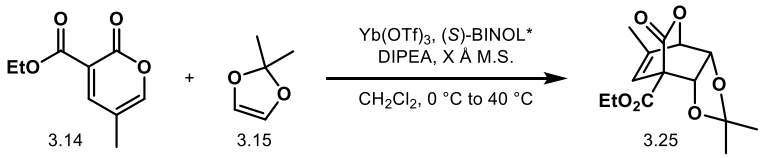


Table 3.1. Attempts to reproduce asymmetric Diels–Alder reaction

conditions to distill it, obtaining a pure white solid in the process. Unfortunately, I found that this made no difference in the outcome of the asymmetric Diels–Alder reaction (Table 3.1, Entry 1). Despite numerous attempts, further purification of dienophile **3.15** never led to yields greater than 26% (Entry 2). Attempts to increase the scale of the of the reaction that gave a 26% yield also resulted in a decreased 14% yield (Entry 3). Switching to a more reactive dienophile, **3.26**, led to a 97% yield of bicycle **3.25** (Entry 4); however, use of vinylene carbonate, **3.23**, gave none of the desired Diels–Alder adduct (Entry 5). In previous reports, molecular sieves were found to have a dramatic impact on the enantiomeric excess of an enantioselective pyrone Diels–Alder reaction.[15, 16] Although nothing is mentioned about the impact on the yield of the reaction, one could deduce that the molecular sieves could potentially have an impact on the yield as well as the enantioselectivity. Three types of molecular sieves were used in the asymmetric Diels–Alder reaction (Table 3.2). Using 4 Å pellets gave a 10% yield, while the 4 Å powder gave an improved 34% yield. A decrease to a 26% yield was observed when using the 3 Å pellets. Unfortunately, further improvements were never observed.

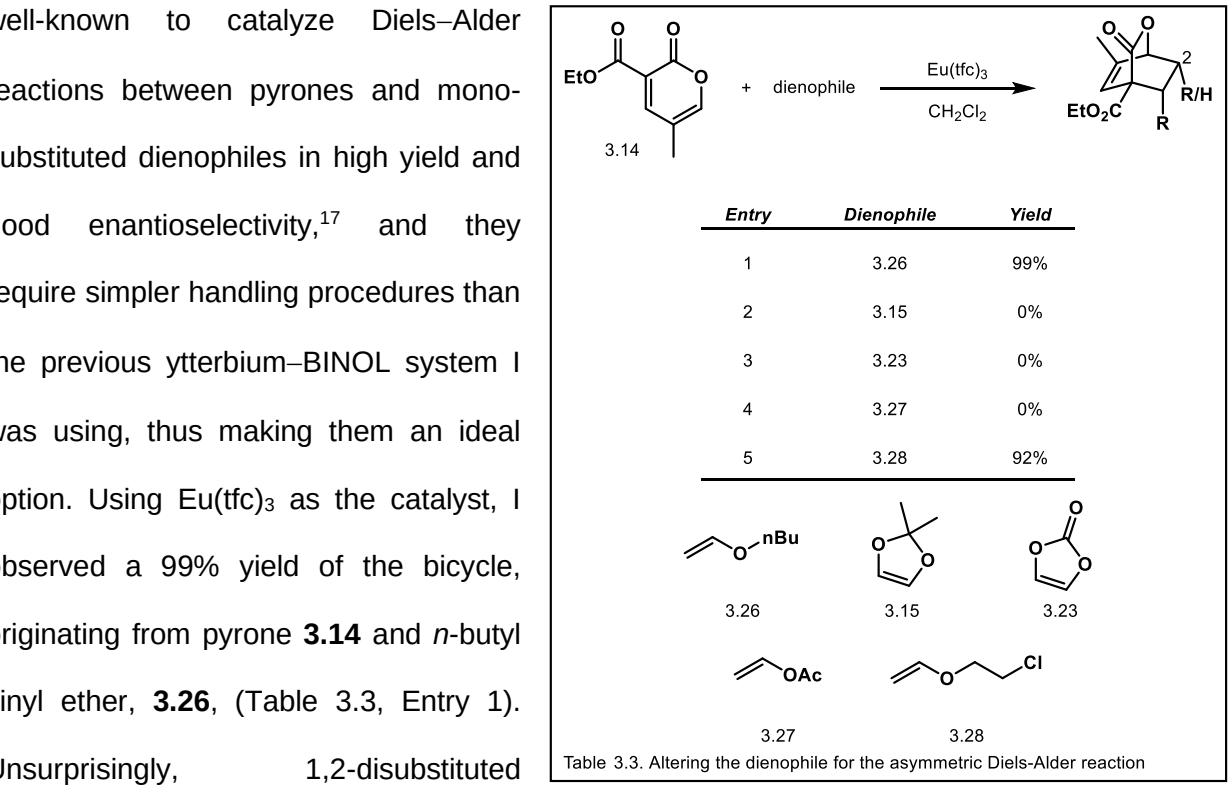


Entry	*Type of Mol. Sieves*	*Yield*
1	4 Å pellets	10%
2	4 Å powdered	34%
3	3 Å pellets	26%

Table 3.2. Effect of molecular sieves on yield

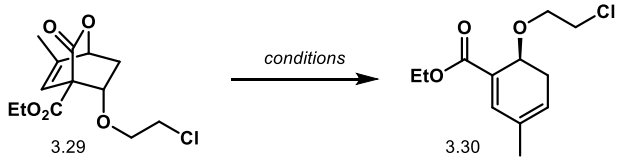
Since accessing diene **3.13** in usable quantities was proving to be prohibitive, I looked to synthesize a simpler diene, namely one that is missing oxygenation at C2. For the Diels–Alder reaction between a pyrone and a dienophile, monosubstituted dienophiles perform well while 1,2-disubstituted dienophiles offer poor to no reactivity in almost all cases.[17, 18] Instead of using dienophile **3.15**, I turned to a monosubstituted dienophile to help promote the desired Diels–Alder transformation since **3.26** was already demonstrated to give high yields. Europium catalysts are

well-known to catalyze Diels–Alder reactions between pyrones and mono-substituted dienophiles in high yield and good enantioselectivity,[17] and they require simpler handling procedures than the previous ytterbium–BINOL system I was using, thus making them an ideal option. Using $Eu(tfc)_3$ as the catalyst, I observed a 99% yield of the bicycle, originating from pyrone **3.14** and *n*-butyl vinyl ether, **3.26**, (Table 3.3, Entry 1). Unsurprisingly, 1,2-disubstituted dienophiles such as **3.15** and **3.23** did not work, showing no observable conversion (Entries 2, 3). From the bicycle formed using **3.26**, it was apparent that removal of the *n*-butyl group to unveil the alcohol would likely be non-trivial, so vinyl acetate, **3.27**, and chloromethyl vinyl ether, **3.28**, were also used as dienophiles since they both contained more easily removable functionality. Vinyl acetate gave no observable conversion (Entry 4); however, chloromethyl vinyl ether gave a 92% yield of the corresponding bicycle (Entry 5). Next, a retro-Diels–Alder reaction, liberating CO_2, was required to reveal the dienoate. Using the same conditions as had been previously used for dienoate **3.13** unfortunately only gave aromatized products (Table 3.4, Entry 1). Changing the solvent from chlorobenzene to 1,2-dichlorobenzene



Entry	*Dienophile*	*Yield*
1	3.26	99%
2	3.15	0%
3	3.23	0%
4	3.27	0%
5	3.28	92%

Table 3.3. Altering the dienophile for the asymmetric Diels-Alder reaction



Entry	*Conditions*	*Scale*	*Result*
1	ClPh, reflux	40 mg	0%, aromatized
2	1,2-dichlorobenzene, 140 °C	20 mg	0%, aromatized
3	DCE, 140 °C, μw, 1 hr	10 mg	93%
4	DCE, 140 °C, μw, 1 hr	97 mg	53%
5	DCE, 140 °C, μw, 1 hr	20 mg	10%

Table 3.4. Retro-Diels-Alder

gave the same result (Entry 2). Hypothesizing that heating for an extended period of time led to aromatization, I attempted the use of microwave conditions to shorten the reaction time. Heating 10 mg of **3.29** to 140 °C in dichloroethane for 1 hour gave a 93% yield of dienoate **3.30** (Entry 3). However, when increasing the scale from 10 mg to 97 mg led to a sharp decrease in yield to 53% (Entry 4). Unfortunately, attempting this reaction on scales larger than 10 mg were incredibly inconsistent and often led to decomposition of the starting material, usually to aromatic products (Entry 5). However, enough dienoate **3.30** was produced to proceed forward with the key 1,3-dipolar cycloaddition step. This is discussed in section 3.2.4.

3.2.3 1,3-Dipolar Cycloaddition Model Systems

3.2.3.1 Intermolecular Model Systems

In an attempt to understand the potential limitations of the key 1,3-dipolar cycloaddition, several model systems were developed based on the desired dienophile, **3.1** (Table 3.5). Ideally, a Mukaiyama hydration reaction would install oxidation on the face opposite the acetal, and the subsequent dipolar cycloaddition could be directed to the α-face by the adjacent alcohol as demonstrated by work of Kanemasa and co-workers.[19] Since the substitution at C15 adjacent to the alkene

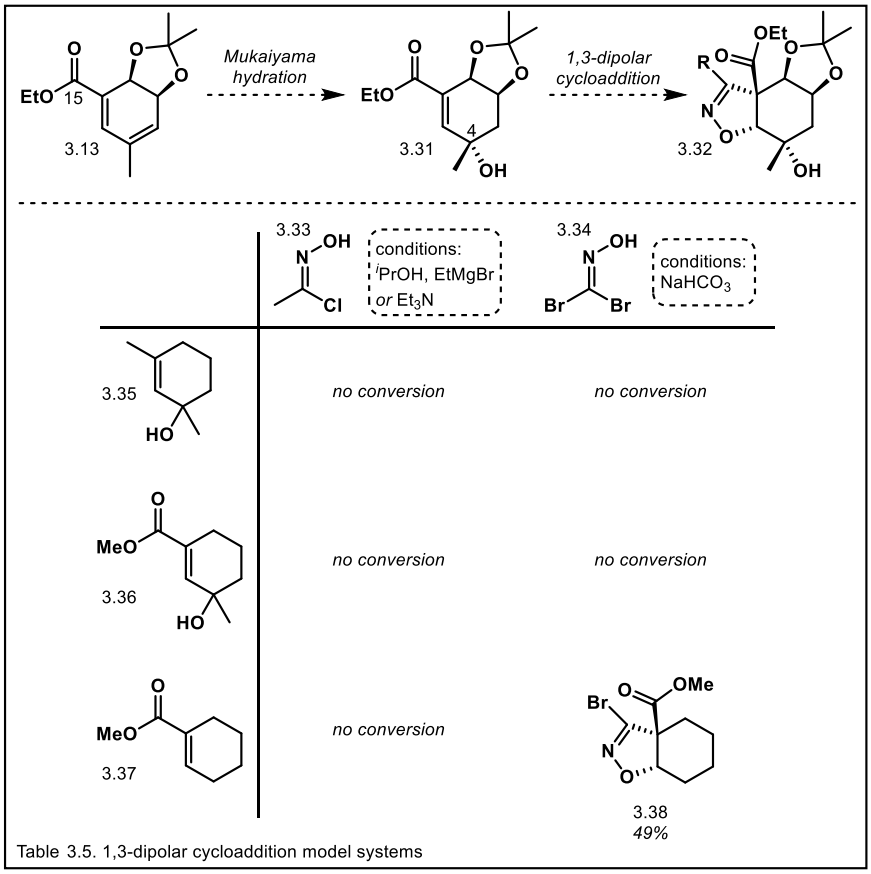


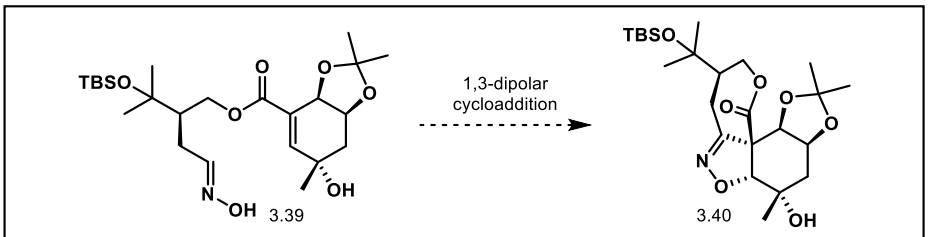
Table 3.5. 1,3-dipolar cycloaddition model systems

could be either an ester or an alkyl group, model systems **3.35** and **3.36** were synthesized. Using acetaldoxime **3.33** or dibromoaldoxime **3.34** as nitrile oxide precursors gave no conversion regardless of conditions. Given that tertiary alcohols had never been demonstrated in the literature as suitable directing groups for nitrile oxides,[19] model system **3.37** was also prepared, which was missing additional substitution adjacent to the alkene. While attempts to react this alkene with acetaldoxime **3.33** once again resulted in no reactivity, using dibromoaldoxime **3.34** gave a promising 49% yield, although the regioselectivity is unconfirmed. These results demonstrated that dienophile **3.31** is likely an unsuitable dipolar cycloaddition partner and that installation of the C4 hydroxyl group likely needs to take place after the dipolar cycloaddition. These results also demonstrated that alkyl nitrile oxides were too unreactive and that the more reactive bromo nitrile oxide was required for this system.

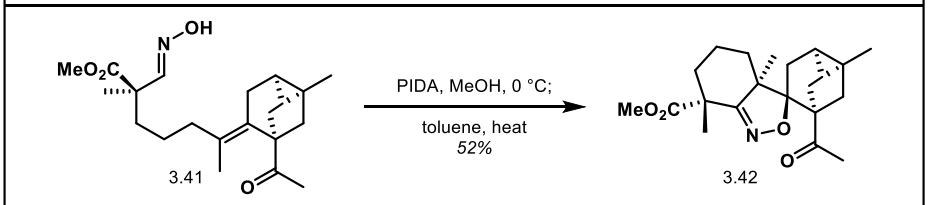
3.2.3.2 Intramolecular Model Systems

In light of the poor reactivity observed in the intermolecular dipolar cycloaddition model systems, model systems to study an intramolecular variant were also developed. I envisioned that B-ring fragment **3.1** could be previously conjoined with A-ring fragment **3.2** which would allow for an intramolecular dipolar cycloaddition to form **3.40** (Equation 3.2). While intermolecular dipolar cycloadditions have frequently found use in only relatively simple settings, intramolecular dipolar cycloadditions have been used in numerous complex examples, although formation of a seven-membered ring has yet to be disclosed. A recent example was disclosed by Carreira and coworkers where they used an intramolecular dipolar cycloaddition *en route* to (–)-mitrephorone A (Equation 3.3).[20] To determine whether this idea was likely to be met with success, model system **3.43** was synthesized since nitrile oxides can be easily generated from both oximes and nitro groups (Scheme 3.6). Starting from the nitro group, instead of cyclization, nucleophilic addition to the nitrile oxide was observed. Starting from the oxime in place of the nitro group resulted in no reactivity towards cyclization products. Given that intermolecular addition of a

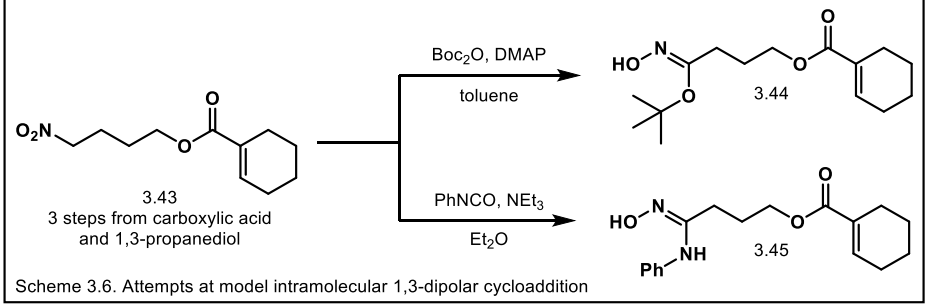
nucleophile was preferential to intramolecular cyclization, this demonstrated that attempting a dipolar cycloaddition of substrate **3.39** was unlikely to be effective.



Equation 3.2. Proposed intramolecular 1,3-dipolar cycloaddition



Equation 3.3. Carreira's use of an intramolecular dipolar cycloaddition *en route* to (–)-mitrephorone A



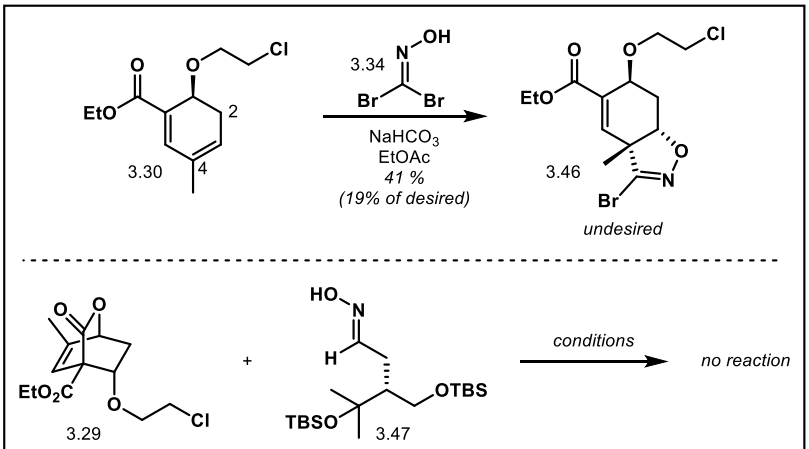
Scheme 3.6. Attempts at model intramolecular 1,3-dipolar cycloaddition

3.2.4 1,3-Dipolar Cycloaddition Attempts

The model systems provided four major details in pursuit of the dipolar cycloaddition reaction: 1) A fully substituted carbon at C4 impeded reactivity at the adjacent alkene. 2) Alkyl nitriles oxides were unreactive towards cyclohexene scaffolds. 3) Intramolecular dipolar cycloadditions were unfavorable compared to nucleophilic addition to the nitrile oxide. 4) Bromo nitrile oxide was able to react with cyclohexene scaffolds without substitution at C4 adjacent to the alkene. Armed with this knowledge, I aimed to use dienoate **3.13** and **3.34** as the dienophile, hypothesizing that by planarizing C4 there would be the possibility of reactivity with bromo nitrile oxide. Using dienoate **3.30** due to the poor access to dienoate **3.13**, I observed a 2:1 mixture of

products **3.46** and its regioisomer in a 60% combined yield, giving the undesired regioselectivity (Scheme 3.7). While this may be the result of a lack of substitution at C2, the issues in obtaining usable quantities of dienoates **3.13** and **3.30** led me to believe that this synthetic pathway was unlikely to be successful.

I also envisioned that bicycle **3.29** could potentially be a competent dienophile for a dipolar cycloaddition. Reacting nitrile oxide precursor **3.47** with norbornadiene showed promising reactivity; however, when switching to bicycle **3.29** I observed no conversion. Using the more reactive dibromoaldoxime instead, I only observed trace amounts of cycloadduct. Additionally, attempts using nitrones instead of nitrile oxides were unsuccessful. Given the lack of success with potential inter- and intramolecular dipolar cycloadditions, in addition to the reproducibility issues in accessing **3.13** and **3.30**, I decided to take an alternative approach to forging the key central quaternary carbon and bringing together the A- and B-ring fragments.



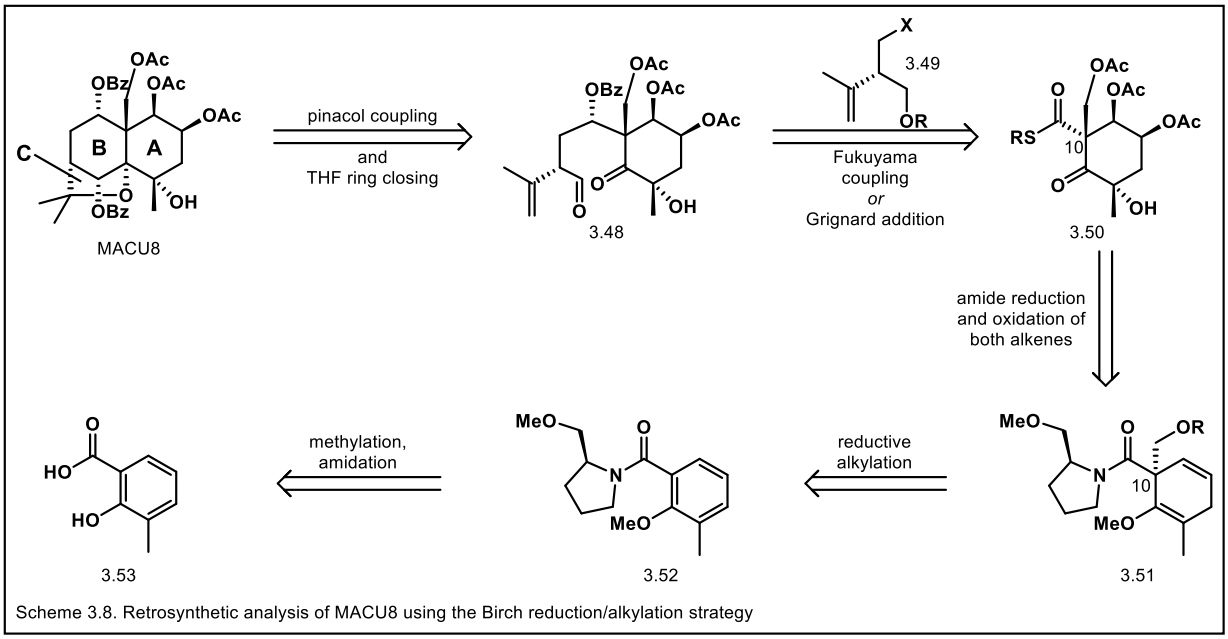
Scheme 3.7. Dipolar cycloaddition attempts

3.3 Formation of the Quaternary Carbon Stereogenic Center Prior to Conjoining of Fragments: Diastereoselective Birch Reduction/Alkylation Strategy

3.3.1 Retrosynthetic Analysis

For this strategy, I envisioned a similar endgame to that which was detailed in section 3.2.1, which aimed to use a pinacol coupling to close the B-ring and acid-catalyzed ring closure to furnish the C-ring, giving MACU8 from **3.48** (Scheme 3.8). Here the strategy deviates quite starkly from the previously described 1,3-dipolar cycloaddition route. Instead of forming the key

C10 quaternary carbon in the same step that fragment **3.49** is installed, I proposed that the C10 stereocenter could already be in place prior to installation of fragment **3.49**, either via a Fukuyama coupling[2] or a Grignard addition. Sequential oxidations of diene **3.51** would lead to full oxidized A-ring fragment **3.50**. The quaternary carbon stereocenter at C10 in fragment **3.51** could be installed via a diastereoselective Birch reduction/alkylation reaction using a proline-derived chiral auxiliary. Arene **3.52** could be synthesized in only a few steps from 3-methylsalicylic acid.

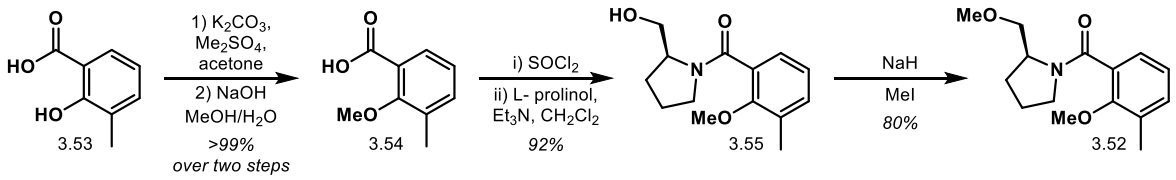


Scheme 3.8. Retrosynthetic analysis of MACU8 using the Birch reduction/alkylation strategy

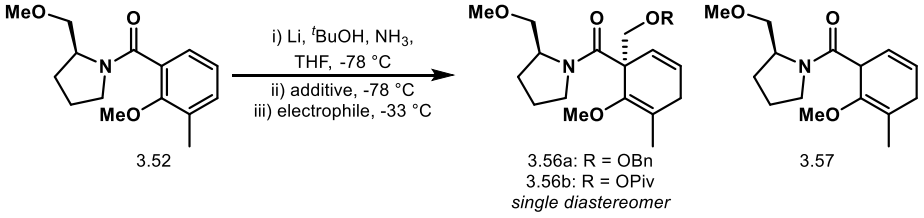
3.3.2 Diastereoselective Birch Reduction/Alkylation Route Using a Proline-Derived Chiral Auxiliary

Starting from 3-methylsalicylic acid, Birch reduction precursor, **3.52**, was synthesized in four steps (Scheme 3.9). First, dimethylation of 3-methylsalicylic acid was achieved with Me_2SO_4 and K_2CO_3 in acetone. The methylation of the phenolic alcohol proved difficult, likely because of the ortho electron withdrawing group decreasing the nucleophilicity of the oxygen combined with the steric encumbrance afforded by the di-*ortho*-substitution. While many conditions easily methylated the carboxylic acid, most were insufficient to methylate the phenolic alcohol. Using methyl iodide, stoichiometric amounts of Me_2SO_4, different solvents, or non-concentrated

conditions led to low yields of the dimethylated product, even after heating to reflux. Ultimately, the conditions I developed to dimethylate 3-methylsalicylic acid used a large excess of Me_2SO_4, K_2CO_3, and as little acetone as possible to allow the reaction to effectively stir. Following methylation, saponification of the ester with NaOH in a mixture of MeOH and H_2O gave **3.54** in 99% yield. The saponification step served the dual purpose of not only forming the desired carboxylic acid, but also removed any remaining Me_2SO_4 since a large excess was necessary for the methylation. Treatment of carboxylic acid **3.54** with $SOCl_2$ formed the corresponding acid chloride, which was then transformed into amide **3.55** after addition of prolinol in 92% yield. Following methylation with NaH and MeI, Birch reduction precursor **3.52** was obtained in a 73% yield over four steps.

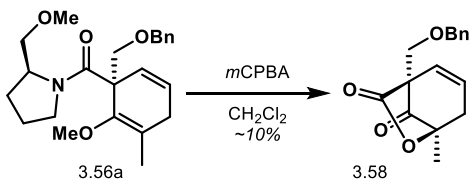


Scheme 3.9. Synthesis of Birch reduction/alkylation precursor

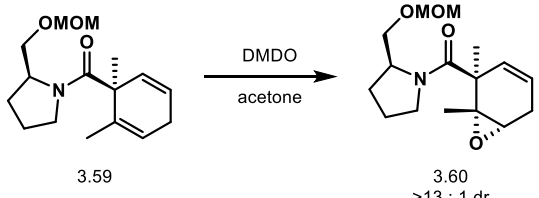


Electrophile	*Additive*	*3.56a/b*	*Yd*
BOMCl	-	36%	55%
$ClCH_2OPiv$	-	0%	99%
ICH_2OPiv	piperylene	84%	0%

Table 3.6. Optimization of Birch reduction/alkylation



Equation 3.4. Removal of chiral auxiliary and lactonization

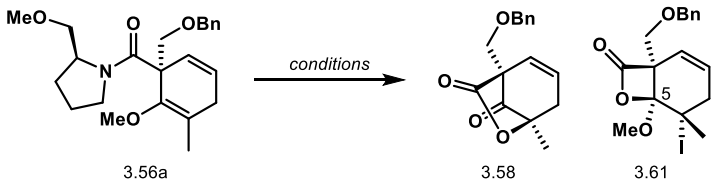


Equation 3.5. Schultz's epoxidation using DMDO

Arene **3.52** has already been previously used in a diastereoselective Birch reduction/alkylation reaction by Schultz, giving a 5:1 d.r. with MeI as the electrophile.[21, 22] However, a methyl group at the 3-position gives the opposite diastereomer than when a methyl group is located at the 4-, 5-, or 6-position, or when it is missing entirely. Regardless, an advantage to this Birch reduction/alkylation strategy is that either diastereomer is useful for the synthesis, as C9 and C14 can be differentiated by their oxidation states following the Birch reduction/alkylation reaction. Thus, this makes C9 and C14 effectively interchangeable. Initially, using BOMCl as the electrophile gave only a 36% yield of the desired product **3.56a**, while the reduced but unalkylated product, **3.57**, was isolated in 55% yield (Table 3.6). Switching to iodomethylpivalate as the electrophile in the Birch reduction/alkylation reaction, which is easily synthesized in one step from its chlorinated precursor, gave an 84% yield of the desired product **3.56b** as a single diastereomer. Unsurprisingly, chloromethylpivalate gave a 99% yield of the reduced, but unalkylated product **3.57** because it is less electrophilic than BOMCl. Before I had found that iodomethylpivalate gave higher yields, I explored the potential reactivity of the alkenes on the benzyl ether substrate. Treatment of **3.56a** with [$VO(acac)_2$] and *tert*-butyl hydroperoxide led to a quantitative yield of aromatized product **3.52**. Switching to mCPBA in dichloromethane gave a 10% yield of lactone **3.58** (Equation 3.4). After formation of the epoxide, the amide cyclized, opening the epoxide and the auxiliary was removed through hydrolysis upon workup. However, reactivity was poor, with most of the starting material remaining unreacted likely resulting from the adjacent quaternary carbon containing two large functional groups. In work by Schultz and coworkers from 1992, they demonstrated that they were able to effectively epoxidize substrate **3.59** using DMDO (Equation 3.5).[23] Notably though, the methyl group attached to the quaternary carbon is much smaller than a CH_2OBn group, and their alkene is only tri-substituted as opposed to tetra-substituted. Despite this precedent, treatment of **3.56a** with DMDO displayed poor conversion overall and no conversion to bicycle **3.58**.

Attempts to replicate this reactivity using halolactonization conditions were largely ineffective. Use of I_2 with and without the presence of $NaHCO_3$ or use of iodobis(collidine)PF_6 resulted in no reaction (Table 3.7). Treatment with PIDA in the presence of I_2 gave a 10% yield of β-lactone **3.58** and a 27% yield of aromatized product **3.52**. Use of NBS led to a 25% yield of aromatized product **3.52**. Despite the low yield of **3.61** using PIDA, I wanted to explore the use of work from the Romo group in which they form γ-lactones from the β-lactones using a Lewis acid-mediated formal dyotropic rearrangement (Scheme 3.10). I envisioned that activation of the β-lactone would be facile given the donation from the C5 methoxy group. Ideally, following activation of the β-lactone with a Lewis acid, the C5 methoxy group could eject the carboxylate which could subsequently substitute the iodide at C4. Unfortunately, treatment of **3.61** with $Zn(OTf)_2$, $MgBr_2{\cdot}OEt_2$, or TMSOTf resulted in poor reactivity or decomposition of the starting material (Table 3.8). The use of phenylselenium halides or diphenyl diselenide also resulted in no reactivity (Table 3.9). Diphenyl disulfide in the presence of $Mn(OAc)_3$ gave trace yields of **3.58** and a 70% yield of aromatized product **3.52**. Attempts to dihydroxylate led to poor reactivity and trace yields of aromatized product **3.52**. Given the poor reactivity of both alkenes, and the inability to remove the benzyl protecting group, I aimed to change the protecting group on the C9 oxygen, allowing for its removal. Following its removal, the resulting alcohol could be used as a directing group for oxidation and the reduced steric encumbrance would likely increase reactivity.

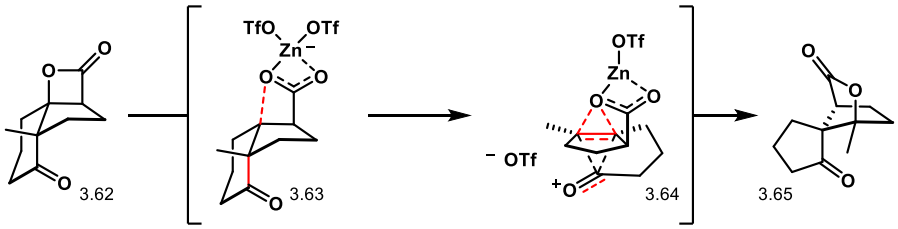
Since the benzyl ether was unable to be cleaved in the presence of alkenes, I switched to the pivalate ester substrate, **3.56b**. Removal of the pivalate ester with MeLi afforded β-hydroxy amide **3.66** in 66% yield (Scheme 3.11). Attempts to remove the pivalate ester with hydrolysis led only to rearomatization to **3.52**, likely resulting from a retro-aldol reaction. Additionally, attempts to functionalize the alkenes before removal of the pivalate group were unsuccessful. Dihydroxylation using OsO_4 or epoxidation with mCPBA both gave no conversion, while treatment with I_2 or Ph_2Se_2 to promote lactonization gave only rearomatized **3.52**.



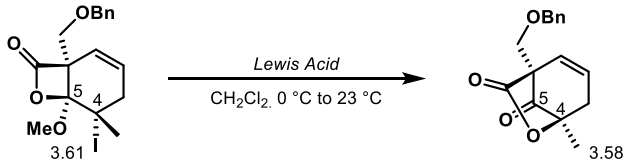
3.56a 3.58 3.61

Conditions	*3.58*	*3.61*
$NaHCO_3$, I_2, THF	-	-
I_2, THF/H_2O	-	-
iodobis(collidine)PF_6, CH_2Cl_2	-	-
PIDA, I_2, MeCN	-	10%
NBS, AcOH, H_2O/THF	-	-

Table 3.7. Attempts at halolactonization

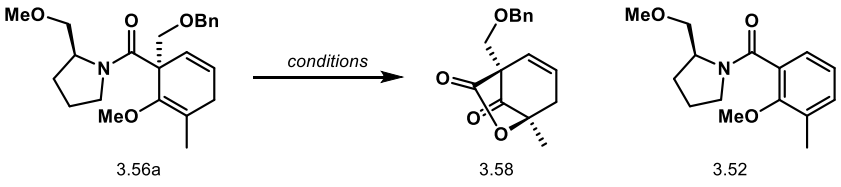


Scheme 3.10. Romo's dyotropic rearrangement



Lewis Acid	*Result*
$Zn(OTf)_2$	no reaction
$MgBr_2 \cdot OEt_2$	no reaction
TMSOTf	decomposition

Table 3.8. Attempts to rearrange lactone

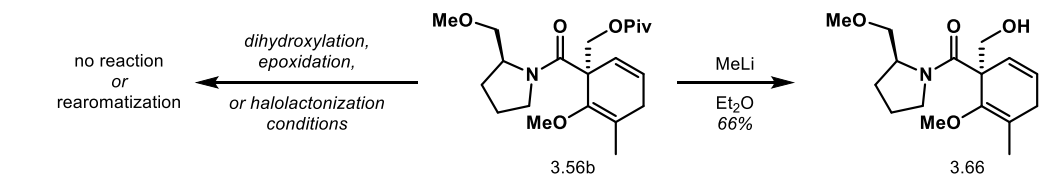


3.56a 3.58 3.52

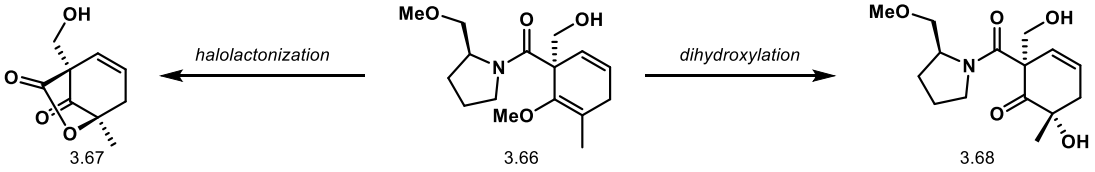
Conditions	*3.58*	*3.52*
PhSeCl, MeCN	no reaction	
PhSeBr, MeCN	no reaction	
Ph_2Se_2, $(NH_4)_2S_2O_8$, MeCN, 70 °C	no reaction	
PhSSPh, $Mn(OAc)_3 \cdot 2\ H_2O$, TFA, CH_2Cl_2	<10%	70%

Table 3.9. Other attempts at lactonization

After removal of the pivalate group, I aimed to use the directing ability of the unveiled primary alcohol and/or the decreased steric bulk to functionalize both alkenes. Dihydroxylation of the more electron-rich alkene to give the α-hydroxy ketone was unsuccessful, resulting from a lack of reactivity (Table 3.10). Addition of TMEDA to direct the oxidation with the homoallylic alcohol did not improve the reactivity.[24] In an attempt to remove the chiral auxiliary and oxidize the methoxy-substituted alkene concurrently, halolactonization conditions were employed. Treatment of diene **3.66** with I_2 in a mixture of THF and H_2O gave a 78% yield of rearomatized product **3.52**. Switching to NIS and acetic acid in the same solvent system increased the yield of **3.52** to 95%. While dihydroxylation and halolactonization conditions were largely unproductive, attempts to epoxidize were met with greater success (Table 3.11). While treatment with $VO(acac)_2$ in the presence of TBHP led to no reaction, use of $Ti(O^iPr)_4$ led to a 39% yield of **3.69**, albeit with a 43% yield of rearomatized **3.52**. Despite the epoxidation conditions, no epoxide was isolated. Instead, oxetane acetal **3.69** was isolated. This likely forms by alcohol-directed epoxidation of the alkene, followed by opening of the epoxide by the methoxy group, and lastly addition of the primary alcohol to the intermediate oxocarbenium ion. Use of oxone/acetone with $NaHCO_3$ gave trace yields of **3.69**, but gave a 22% yield of the corresponding aldehyde, displaying preferential oxidation of the primary alcohol over the tetrasubstituted alkene. Encouragingly, treatment with mCPBA gave a 24% yield of **3.69** without formation of side products. Switching the solvent to MeOH resulted in no reactivity, but the inclusion of Na_2HPO_4 increased the yield to 10%. Use of DMF as solvent shut down the reactivity, even in the presence of base. Excitingly, switching to MeCN as solvent and Na_2HPO_4 as base, an 84% yield of **3.69** was observed, which was confirmed via X-ray crystallographic analysis.[25] Without the use of base, lower yields and poor mass recovery was observed.

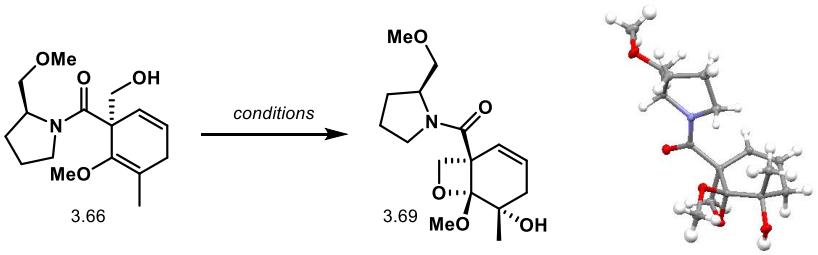


Scheme 3.11. Selective removal of pivalate ester and attempts to functionalize before pivalate ester removal



Conditions	*Result*	*Side Products*
$K_2OsO_4 \cdot 2\ H_2O$	0%	-
OsO_4 solution in *t*BuOH	0%	trace rearomatization and aldehyde
OsO_4, TMEDA	0%	trace rearomatization and aldehyde
I_2, THF/H_2O	0%	78% rearomatized
NIS, AcOH, H_2O, THF	0%	95% rearomatized

Table 3.10. Attempts at dihydroxylaion and halolactonization



Conditions	*Result*	*Side Products*
$VO(acac)_2$ TBHP, CH_2Cl_2	no reaction	-
$Ti(O^iPr)_4$, TBHP, CH_2Cl_2	39%	43% rearomatized
oxone, $NaHCO_3$, acetone/H_2O	<5%	22% aldehyde
mCPBA, CH_2Cl_2	24%	-
mCPBA, Na_2HPO_4, MeOH	10%	-
mCPBA, Na_2HPO_4, DMF	no reaction	-
mCPBA, Na_2HPO_4, MeCN	84%	-

Table 3.11. Epoxidation of electron-rich alkene

To move forward with the synthesis, the alkene would need to be oxidized, the chiral auxiliary removed, and the oxetane acetal opened and oxidized to prepare for attachment of the B-ring fragment **3.49** (Figure 3.1). Following these steps, the endgame described in section 3.3.1 would be applied. Attempts to dihydroxylate the remaining alkene were unsuccessful. Similar my to attempts to dihydroxylate **3.66**, treatment of **3.69** with a variety of dihydroxylation conditions resulted in no reactivity. Without the ability to functionalize the alkene, it became clear that the chiral auxiliary must be removed first.

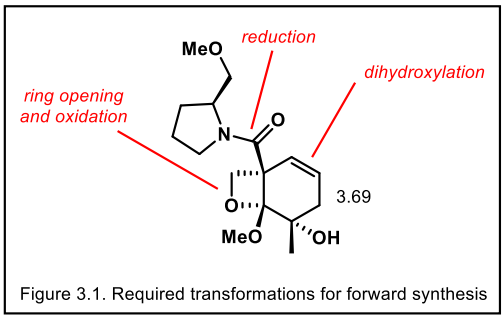
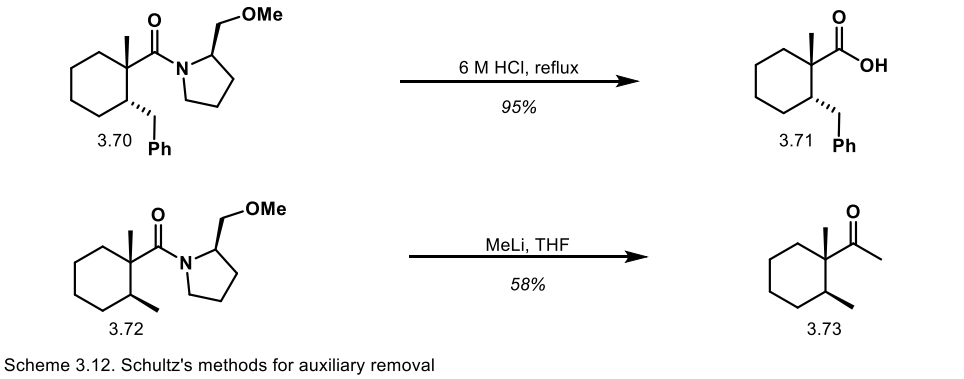
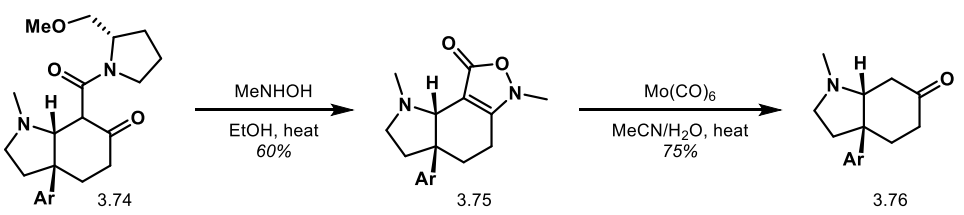


Figure 3.1. Required transformations for forward synthesis

Although the Schultz amide auxiliary has seen frequent use, including several recent examples (see Chapter 4, section 4.4.2.3), the methods to remove the auxiliary remain limited (see Chapter 4, section 4.4.2.2). In Schultz's early reports the auxiliary was removed either by treatment with 6M HCl at reflux to form carboxylic acid **3.71** or with MeLi to form ketone **3.73** (Scheme 3.12).[21, 26] Unfortunately, neither of these conditions are applicable to the current synthetic route. More recently, the Malachowski group has developed a two-step protocol for



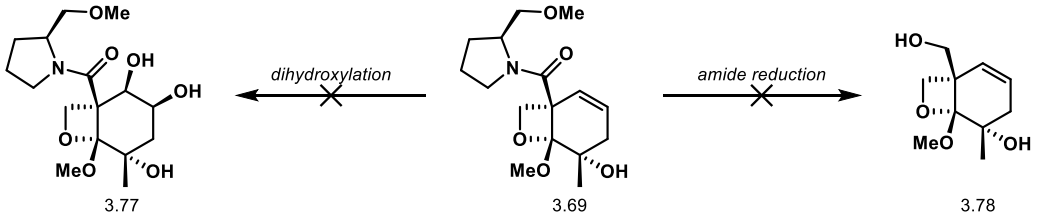
Scheme 3.12. Schultz's methods for auxiliary removal



Scheme 3.13. Malachowski's protocol for auxiliary removal

auxiliary removal.[27-30] Following the diastereoselective Birch reduction/alkylation reaction, they use a four-step sequence to afford **3.74** (Scheme 3.13). *N*-methylhydroxylamine is then condensed with the ketone and cyclizes, removing the auxiliary in the process to give **3.75**. Treatment with $Mo(CO)_6$ then decarboxylates and hydrolyzes the isoxazolone tautomer to reveal the ketone, giving **3.76**. While Malachowski and coworkers found a creative approach to remove the chiral auxiliary, their method would remove the carbon that would become C14 in MACU8 and requires formation of the C5 ketone prior to removal, both of which are unamenable to the synthesis of MACU8. As a result, I turned to other methods to attempt removal of the chiral auxiliary.

Attempting to oxidize the remaining alkene in **3.69**, I found that use of OsO_4 in the presence of TMEDA led to poor conversion (Table 3.12). Treatment of amide **3.69** with $LiAlH_4$ unsurprisingly gave evidence of only amine formation. Treatment with DIBAL-H in toluene led to rearomatizatized product **3.52**. Prior activation of the amide with either Comin's reagent or Meerwein's salt also led only to rearomatized product **3.52**. Use of lithium



Conditions	*Results*
OsO_4, TMEDA, H_2O/acetone	poor conversion; mixture of diol and osmate ester
$LiAlH_4$, THF	reduction to amine
Comin's reagent *or* Me_3OBF_4, THF *or toluene* *then* DIBAL-H, toluene	rearomatization
Comin's reagent *or* Me_3OBF_4, THF *or* toluene	rearomatization

Conditions	*Results*
Cp_2ZrHCl, MeCN, reflux	trace conversion
N—BH_3Li or Me_2NBH_3Li	trace conversion
NaH, ZnI_2, NaI, THF, reflux	no conversion
DIBAL-H, toluene –78 °C	rearomatization
$LiEt_3BH$ (1.0 M in THF), reflux	poor conversion; decomposition upon work-up

Table 3.12. Attempts to remove the amide chiral auxiliary or functionalize alkene to prevent rearomatization

dimethylaminoborohydride or lithium pyrrolidinoborohydride led to only trace conversion to an unknown product. Similar results were observed when treating with Schwartz's reagent in refluxing MeCN or with NaH, ZnI_2, and NaI in refluxing THF. Only when using a 1.0 M solution of $LiEt_3BH$ in THF as solvent and refluxing was any notable conversion to desired product **3.78** observed. However, the conversion never exceeded 10% and the product decomposed upon workup to cleave the boron-oxygen bond. All attempts to remove the chiral auxiliary led to either poor reactivity, likely due to hindered access to the carbonyl, or rearomatization to **3.52**, resulting from elimination of the tertiary alcohol and deformylation. While functionalizing the alkene would minimize the possibility of aromatization, attempts to functionalize the alkene were thwarted by the adjacent quaternary carbon and the large chiral auxiliary. Given that the alkene precluded removal of the chiral auxiliary and the chiral auxiliary precluded functionalization of the alkene, I turned my attention towards modifying the chiral auxiliary for easier removal.

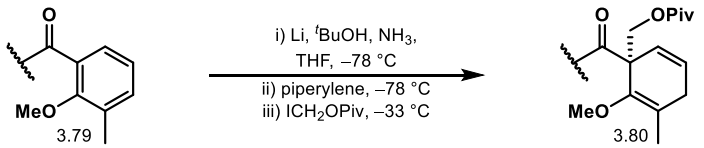
3.3.3 Development of an Ester Chiral Auxiliary

In an attempt to solve the issues caused by the amide chiral auxiliary, I aimed to develop a chiral auxiliary unprecedented in a diastereoselective Birch reduction/alkylation reaction of substituted benzene rings. Given the inherent stability of amides relative to other types of carbonyls, I expected that if I were able to develop an ester chiral auxiliary, it should be more labile than its amide counterpart and thus more easily removed. However, since the ester is more electrophilic than the amide, this also increases the possibility of retro-aldol reactivity.

Initially, I synthesized substrates with borneol, menthol, and isomenthol as chiral auxiliaries. These sterically-based chiral auxiliaries provided poor selectivity, likely owing to the degrees of freedom upon which the alkyl C–O ester bond can rotate thus rendering the auxiliary unable to remain fixed in a specific conformation to impart good selectivity (Table 3.13). Several groups have found great success taking advantage of π-stacking interactions between their substrates and an aromatic ring on their chiral auxiliary. In 1975, Corey and coworkers used (–)-

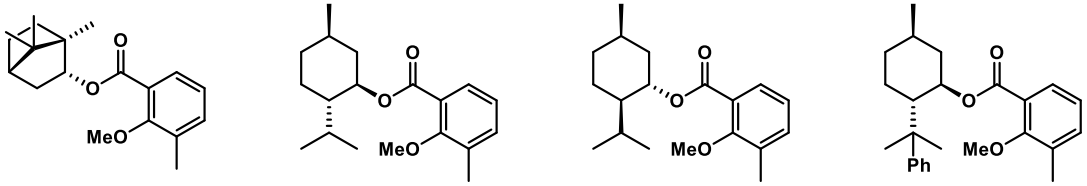
8-phenylmenthol as a chiral auxiliary to perform a diastereoselective Diels–Alder reaction en route to the prostaglandins.[31] Corey later expanded on this work, using **3.85** containing a hydroxysulfone auxiliary to perform a similar transformation (Scheme 3.14).[32] In addition to the diastereoselective Diels–Alder reaction, Corey also demonstrated that his hydroxysulfone auxiliary could be used for enolate alkylations of α-phenyl esters, producing one of **3.88**, **3.89**, or **3.90** from **3.87**. In 1999, Donohoe and coworkers demonstrated use of (–)-8-phenylmenthol as an auxiliary in a stereoselective Birch-type reduction of pyrroles (Equation 3.6).[33] However, they turn to trans-2-(α-cumyl)cyclohexanol as their chiral auxiliary of choice since both enantiomers of the cyclohexanol-based chiral auxiliary were more readily accessible at the time. They are accessed in two to three steps from cyclohexene oxide. Fortunately, in 2016 Shenvi and coworkers developed a simple two-step procedure to synthesize (–)-8-phenylmenthol from isopulegol.[34] Additionally, this method allows for the synthesis of menthol derivatives containing different aromatic functionality at the C8 position.

Using Corey's hydroxysulfone chiral auxiliary, I observed reduction of the carbon–sulfur bond in the chiral auxiliary under Birch conditions. When using the thioether instead, I observed similar results. Switching to (–)-8-phenylmenthol as the chiral auxiliary gave a promising 46% yield and 4:1 d.r. using iodomethylpivalate as the electrophile (Table 3.13). After addition of the substrate to a solution of *tert*-butanol in 5:1 NH_3:THF at –78 °C the solution became milky white, likely due to the formation of a suspension resulting from the substrate being poorly soluble in NH_3. To increase the solubility, the amount of THF was increased to a ratio of 2:1 NH_3:THF. Excitingly, this resulted in an increase in both yield and d.r. to 66% and 7:1, respectively. Increasing the amount of THF further, to 1:1 NH_3:THF kept the d.r. the same at 7:1, but further increased the yield to 80%. Further increases in the amount of THF were not attempted due to the poor solubility of lithium metal in THF. At a 1:1 ratio the time required to solubilize the lithium was greatly extended from ratios of 2:1 and 5:1, sometimes upwards of 30 minutes. I found that



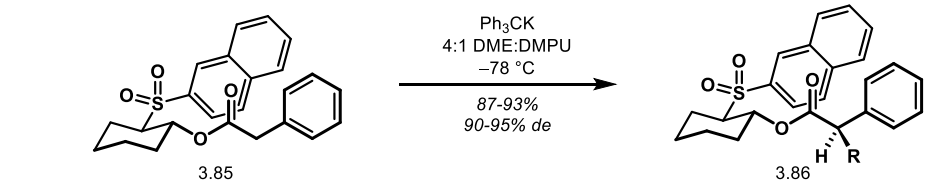
3.79 3.80

Chiral Auxiliary	*NH_3:THF*	*Yield*	*d.r.*
(–)-borneol	5:1	61%	1.2:1
(–)-menthol	5:1	28%	1.1:1
(+)-isomenthol	5:1	82%	1.2:1
(–)-8-phenylmenthol	5:1	46%	4:1
(–)-8-phenylmenthol	2:1	66%	7:1
(–)-8-phenylmenthol	1:1	80%	7:1

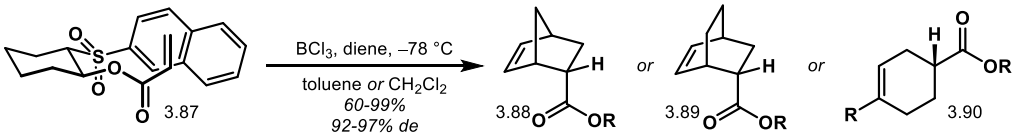


3.81 (–)-borneol | 3.82 (–)-menthol | 3.83 (+)-isomenthol | 3.84 (–)-8-phenylmenthol

Table 3.13. Optimzation of ester chiral auxiliary

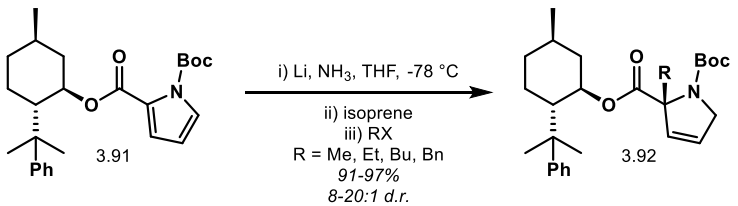


3.85 3.86



3.87 3.88 3.89 3.90

Scheme 3.14. Corey's use of a hydroxy sulfone auxiliary



3.91 3.92

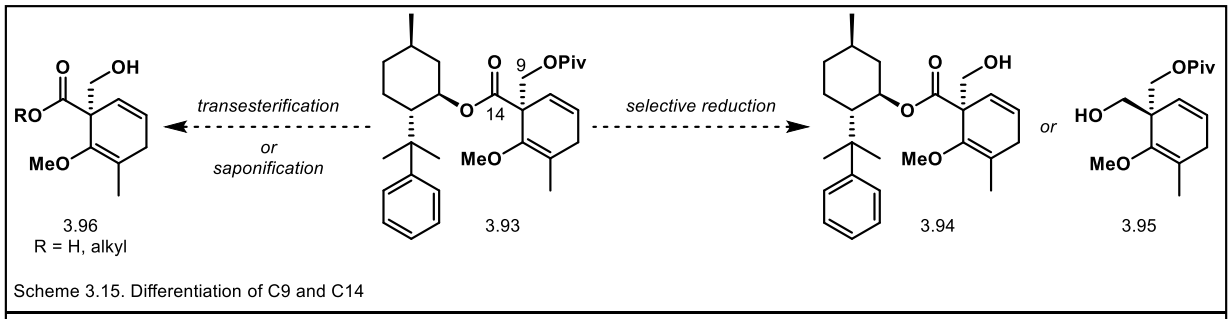
Equation 3.6. Donohoe's reductive alkylation of pyrroles

diligent removal of salts formed on the surface of the lithium metal and slicing the metal into small pieces were crucial to solubilizing the lithium effectively. This is the first example of an ester chiral auxiliary being used in a diastereoselective Birch reduction/alkylation reaction of benzene derivatives, and as such we looked to develop this chemistry into a general method. The development of this method is expanded upon in greater detail in chapters four and five.

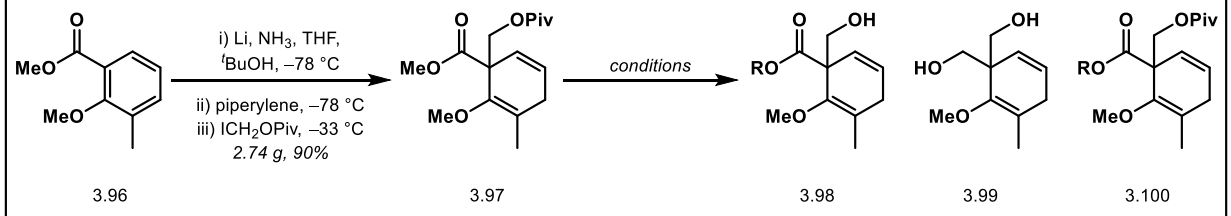
3.3.4 Attempts to Remove the Ester Chiral Auxiliary

With optimized conditions in hand, the next step was to differentiate C9 and C14 via either selective reduction of one of the two esters, or saponification/transesterification (Scheme 3.15). I aimed to mimic the strategy previously used with the amide chiral auxiliary where, following removal of the pivalate group, I was able to oxidize the more electron-rich alkene. Now, by having an ester chiral auxiliary in place instead of the amide, the ester should be more easily reduced.

I had previously synthesized model system **3.97** while investigating the ester chiral auxiliaries to determine conditions for potential pivalate/chiral auxiliary removal (Table 3.14). Use of Na^0 in methanol to form NaOMe *in situ* resulted in partial isomerization of the alkene into conjugation with the other alkene, with no evidence of transesterification. Treatment with K_2CO_3 in methanol at reflux resulted in no reaction. Moving to reductive conditions, I found that 1.0 equivalent of DIBAL-H in toluene at −78 °C led to a 36% yield of alcohol **3.98**, showcasing preferential reactivity at the pivalate ester. However, when increasing the amount of reductant to 2.0 equivalents, I obtained a ~2:1 mixture of achiral diol **3.99** and alcohol **3.98**. Promisingly though, when I moved to saponification conditions, I observed a 95% yield of carboxylic acid **3.100** when treating with Bu_4NOH in a mixture of dioxane and H_2O. Repeating those same conditions but at reflux to try to remove the pivalate group concurrently led only to decomposition. Decreasing the temperature to 50 °C led to a 90% yield of β-hydroxy carboxylic acid **3.98**.



Scheme 3.15. Differentiation of C9 and C14

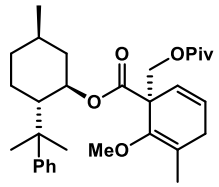


Conditions	*Results*
Na^0, MeOH	isomerized alkene into conjugation
K_2CO_3, MeOH, reflux	no conversion
DIBAL-H (1.0 equiv.), toluene, –78 °C	36% yield of 3.98; R = Me
DIBAL-H (2.0 equiv.), toluene, –78 °C	25% of 3.98; 45% of 3.99; R = Me
Bu_4NOH, dioxane/H_2O, rt	95% of 3.100; R = H
Bu_4NOH, dioxane/H_2O, reflux	complete decomposition
Bu_4NOH, dioxane/H_2O, 50 °C	90% of 3.98; R = H

Table 3.14. Model system optimization for C9 and C14 differentiation

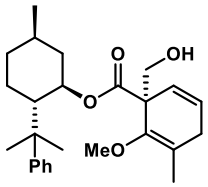
With optimized auxiliary removal conditions in hand, I aimed to apply these to the desired system (Table 3.15). Treatment of **3.93** with Bu_4NOH in dioxane/H_2O at 50 °C unfortunately led to full conversion to aromatized product **3.84**. In the model system, saponification of the methyl ester occurred prior to removal of the pivalate group. Formation of the carboxylate before the removal of the pivalate group likely shut down the retro-aldol reaction necessary for aromatization due to the poor electrophilicity of the carboxylate anion. However, when the methyl ester was exchanged for an (–)-8-phenylmenthol ester, the change in steric encumbrance was likely enough to promote preferential removal of the pivalate group prior to removal of the chiral auxiliary. Once

the alkoxide is formed, it can undergo a retro-aldol reaction since the ester is much more electrophilic than the carboxylate, thus leading to aromatized product **3.84**. Use of a variety of metal triflates and Lewis acids in methanol at reflux gave no observable conversion. The more nucleophilic potassium superoxide with 18-crown-6 also resulted in no reactivity. DBU and LiBr in methanol displayed full conversion to rearomatized **3.84**, likely meaning there was selective removal of the pivalate ester. Using conditions to form sodium telluride to remove the ester in an S_N2 reaction also proved unsuccessful. However, elimination conditions using potassium *tert*-

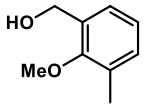


3.93

conditions



3.94



3.101

Conditions	***Results***	***Conditions***	***Results***
nBu$_4$NOH, dioxane, 50 °C	rearomatization	KO_2, 18-crown-6, PhH	trace conversion
La/In/Ti/Zn/Yb/Sc/Sn triflates and other Lewis acid salts, MeOH, reflux	no conversion	Te, $NaBH_4$, ^{t}BuOH, DMF, 80 °C	no conversion
DBU, LiBr, MeOH	rearomatization	Et_2AlCl, MeONHMe·HCl, CH_2Cl_2	no conversion
KO^{t}Bu, DMSO, 80 °C	65% of benzyl alcohol, 3.101; 94% of phenylmenthol	$AlMe_3$, EtSH, 1.5:1 toluene:CH_2Cl_2	70% of 3.94

Table 3.15. Attempts to remove chiral auxiliary

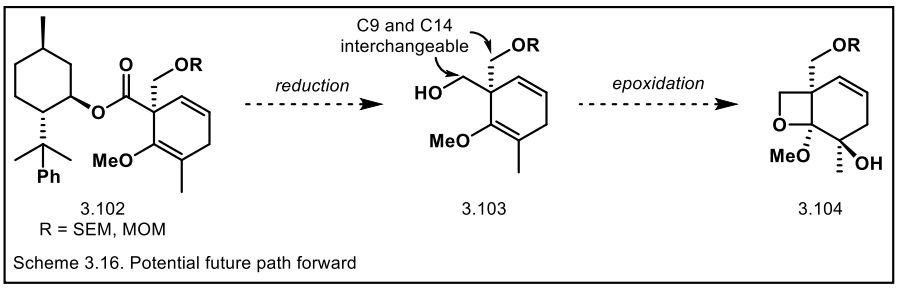
butoxide in DMSO at 80 °C led to a 65% yield of benzyl alcohol **3.101** and a 94% yield of (–)-8-phenylmenthol. Attempts to form the Weinreb amide instead, also led to no observable conversion. The only conditions found that did not lead to aromatization or a lack of reactivity were with $AlMe_3$ and ethanethiol in a 1.5:1 mixture of toluene and dichloromethane, which led to a 70% yield of alcohol **3.94**. Changing dichloromethane to dichloroethane and increasing the temperature to reflux in an attempt to also remove the chiral auxiliary still led to a 70% yield of alcohol **3.94**. Interestingly, despite the preferential removal of the pivalate group, there was no

retro-aldol and subsequent aromatization, I attribute this to the formation of the oxygen-aluminum bond, preventing the retro-aldol reaction until protonation upon workup.

With conditions in hand to selectively remove the pivalate ester, I aimed to apply the same conditions used with the amide auxiliary system to oxidize the more electron-rich alkene. However, due to the increased electrophilicity of an ester over an amide, I found that treatment with mCPBA and Na_2HPO_4 in MeCN led to rearomatization and decomposition. Reactions without base gave similar results. Ultimately, given the difficulty in effective differentiation of the two esters in **3.93** and the preponderance for **3.94** to retro-aldol and rearomatize, I aimed to develop an improved route with the aim to saturate the A-ring quickly and use a 1,3-diester in place of a β-hydroxy ester to prevent the retro-aldol/aromatization pathway.

3.3.5 Future Directions

While the 1,3-oxygenation pattern at the C9/C14 positions has hindered progress of the synthesis of MACU8, there is a pathway worth potential future exploration. The idea is to perform the diastereoselective Birch reduction/alkylation reaction with an electrophile such as SEMCl or MOMCl that incorporates a reduction-tolerant protecting group (Scheme 3.16). Following alkylation, the chiral auxiliary could be removed with a highly reactive reducing agent like $LiAlH_4$. Since both enantiomers of isopulegol are available commercially, both enantiomers of (–)-8-phenylmenthol can be synthesized, and therefore both enantiomers of **3.103** can be synthesized. This makes the strategy flexible since the oxidation at C9 and C14 can be differentiated as needed. Once the chiral auxiliary is removed, oxidation should proceed similarly to the oxidation of **3.66**. Without the possibility of a retro-aldol reaction, rearomatization should be mitigated. After formation of **3.104**,



Scheme 3.16. Potential future path forward

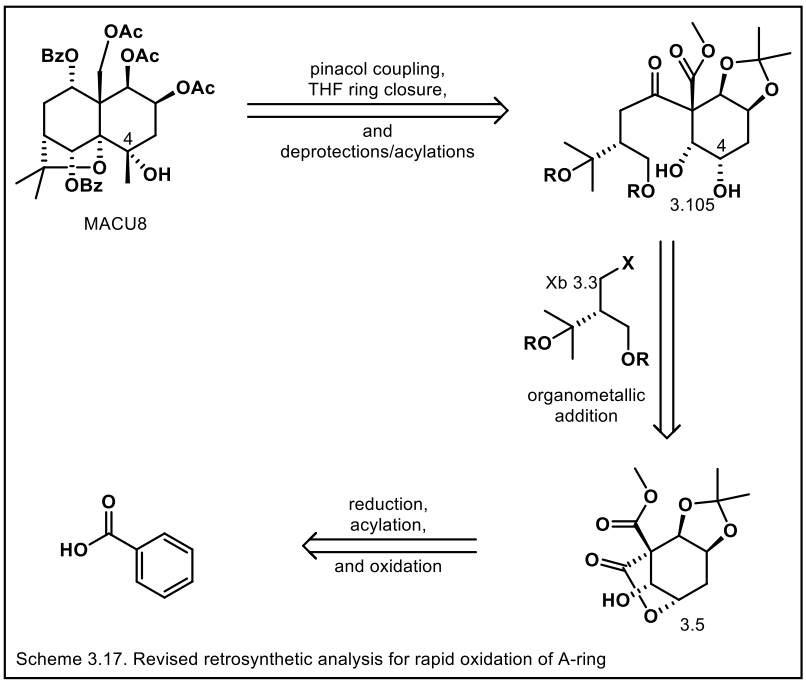
a similar strategy to complete the synthesis of MACU8 could be used as previously detailed in section 3.3.1.

3.4 Formation of the Quaternary Carbon Stereogenic Center Prior to Conjoining of Fragments: Early Oxidation Strategy

3.4.1 Retrosynthetic Analysis

The Birch reduction/alkylation route was unfortunately plagued by a facile retro-aldol reaction, which ultimately led to aromatization, thus destroying the newly formed quaternary carbon and reverting back to the pre-Birch reduction/alkylation substrate. To mitigate this pervasive issue, I envisioned making two alterations to the global strategy: 1) increase the oxidation state from a β-hydroxy amide/ester to that of a 1,3-dicarbonyl to eliminate the retro-aldol pathway and 2) swiftly saturate the A-ring fragment to make aromatization unfavorable.

To this end, I envisioned a reasonably similar endgame to that detailed in sections 3.2 and 3.3, where a pinacol coupling and acid-catalyzed THF ring-closure would generate the B- and C-rings, giving MACU8 (Scheme 3.17). The C4 methyl group could be stereoselectively installed following C-ring formation, as demonstrated in Herzon's synthesis of (–)-euonyminol.[9] I could trace **3.105** back to **3.5** following several functional group manipulations. A Grignard reagent generated from **3.3** could add to lactone **3.5** to bring the A- and B-ring fragments together. The fully oxidized A-ring fragment **3.5**

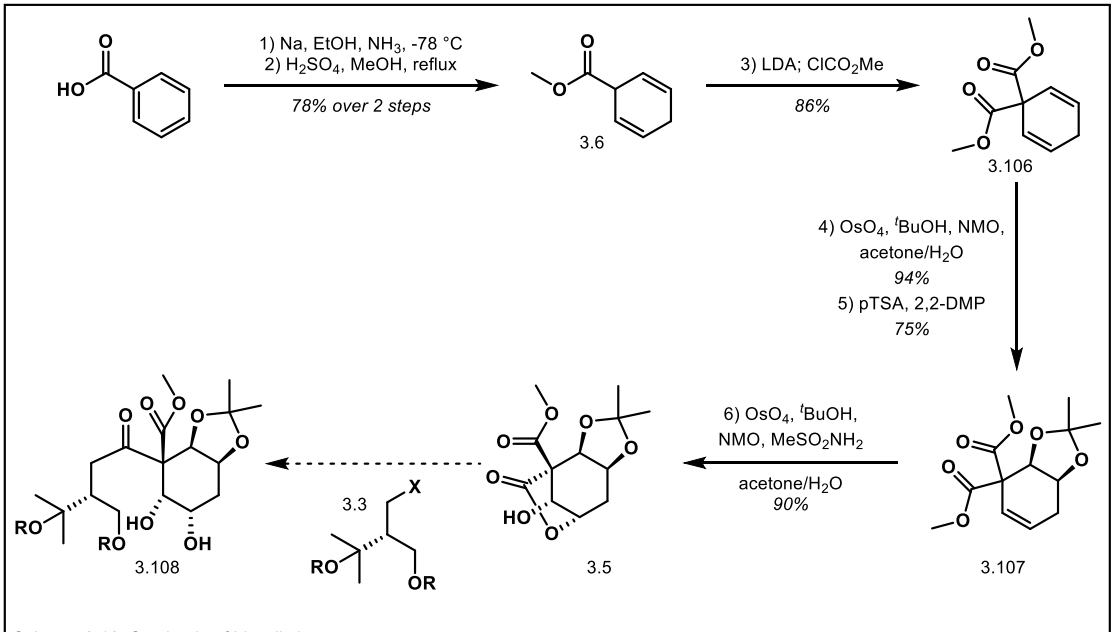


Scheme 3.17. Revised retrosynthetic analysis for rapid oxidation of A-ring

could be generated by sequential dihydroxylations following Birch reduction and acylation of benzoic acid.

3.4.2 Synthesis of Bicyclic Lactone

Birch reduction of benzoic acid and esterification to form methyl ester **3.6** proceeded in 78% over two steps. Treatment of ester **3.6** with LDA and methyl chloroformate gave 1,3-diester **3.106** in 86% yield. The first dihydroxylation with OsO_4 and NMO gave an 94% yield of diol. Use of the $K_2OsO_4 \cdot H_2O$ gave lower yields and some undesired side products. When using excess NMO, no conversion was observed to the tetra-hydroxylated product. Protection of the diol with catalytic pTSA in 2,2-dimethyoxypropane gave a 75% yield of acetal **3.107**. Treatment of acetal **3.107** with the same dihydroxylation conditions as used for the first dihydroxylation led to only a 30% yield of **3.5** over seven days, with the remaining mass being entirely starting material. Addition of methane sulfonamide or citric acid greatly increased the rate of the reaction, leading to full conversion after only two hours.[35] However, the *tert*-butyl esters of citric acid co-eluted with lactone **3.5** when purifying via column chromatography. Use of methane sulfonamide removed this possibility and a 90% yield of **3.5** was obtained. Having synthesized lactone **3.5** in only six



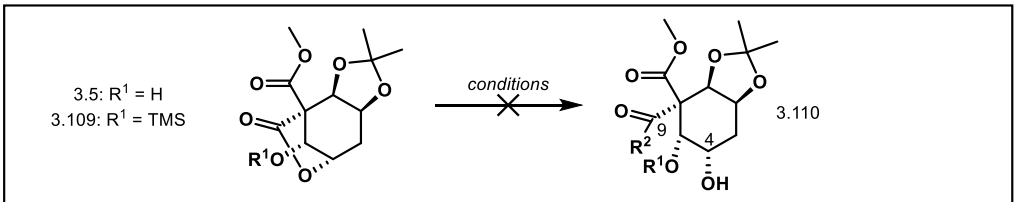
Scheme 3.18. Synthesis of bicyclic lactone

steps and 33% overall yield, I had not only achieved the goal of accessing a fully oxidized A-ring fragment but have done so in a swift and scalable manner. The use of the 1,3-diester had removed the retro-aldol pathway, allowing for oxidation of the A-ring without observable aromatization. When compared to the natural product, lactone **3.5** contains all of the necessary oxidation except for the C6 oxidation located on the B-ring fragment.

3.4.3 Attempts to Incorporate the B-Ring Fragment

With lactone **3.5** in hand, I wanted to explore potential conditions to incorporate B-ring fragment **3.3**. Initially, I envisioned nucleophilic addition to the lactone with a Grignard or alkyllithium reagent synthesized from **3.3**. Since the lactone carbonyl is neopentylic, I wanted to see whether the addition could be potentially stopped after a single addition due to the high degree of steric encumbrance surrounding the carbonyl, as well as the wealth of oxygen atoms that could stabilize metalated tetrahedral intermediates. After protecting the secondary alcohol with a TMS group, I treated lactone **3.109** with 1.0 equivalent of MeLi and MeMgBr at −78 °C (Entries 1 and 2). After gradually warming to 0 °C, I observed desilylation with MeLi and no conversion with MeMgBr. Since Grignard reagents were clearly not strong enough nucleophiles to add to the lactone, I moved strictly to trying alkyllithiums. Without the TMS protecting group, I treated lactone **3.5** with 2.0 equivalents of MeLi at −78 °C (Entry 3). After warming to 0 °C and room temperature, I observed no conversion (Entry 4). In an effort to increase the reactivity of the alkyllithium towards the lactone, I added either $LiClO_4$ or HMPA (Entries 5 and 6). Unfortunately, both instances recorded only trace conversion. Using EtSH and $AlMe_3$ to attempt to make the thioester, again no conversion was observed (Entry 7). Treatment with DIBAL-H led to only trace amounts of the lactol (Entry 8). Use of the TMS protected alcohol with 2.0 equivalents of DIBAL-H to attempt to obtain the alcohol also led to only trace conversion to the lactol (Entry 9). The inability to reduce the small amounts of lactol to the primary alcohol can likely be attributed to the C4 alkoxide and

the C9 aldehyde both sitting diaxial, therefore situated well to form the lactol preferentially. To take advantage of the free secondary alcohol, I attempted using $AlMe_3$ and MeLi to form the aluminate species which could deliver a methyl group in an intramolecular fashion. While this forms a potential chair-like transition state with both the ester and the lactone, I hypothesized that the more reactive lactone could react preferentially. Unfortunately, I observed a 35% yield of **3.111**, the product of dimethyl addition to the ester (Entry 10). Thus, it must have favored the *trans*-decalin transition structure over the *cis*-decalin transition structure. Formation of the alkylcerium with MeLi and $CeCl_3$ also gave preferential reactivity with the ester, giving a 21% yield of **3.112** (Entry 11). The remaining mass balance in entries 10 and 11 was unreacted starting material. The poor reactivity of the lactone can likely be attributed to the poor accessibility of the π* orbital of the lactone carbonyl. To solve this issue, perhaps the B-ring fragment could be



Entry	*R^1 =*	*R^2 =*	*Conditions*	*Additive*	*°C*	*Result*
1	TMS	Me	MeLi (1.0 equiv.), THF	-	–78 to 0	desilylation
2	TMS	Me	MeMgBr (1.0 equiv.), THF	-	–78 to 0	no conversion
3	H	Me	MeLi (2.0 equiv.), THF	-	–78 to 0	no conversion
4	H	Me	MeLi (2.0 equiv.), THF	-	–78 to rt	no conversion
5	H	Me	MeLi (2.0 equiv.), Et_2O	$LiClO_4$	–78 to rt	mostly starting material
6	H	Me	MeLi (2.0 equiv.), Et_2O	HMPA	–78 to rt	mostly starting material
7	H	SEt	EtSH, $AlMe_3$, CH_2Cl_2	-	0 to rt	no conversion
8	H	H	DIBAL-H (2.0 equiv.), toluene	-	–78 to rt	trace lactol
9	TMS	H	DIBAL-H (2.0 equiv.), toluene	-	0 to rt	trace lactol
10	H	Me	MeLi, $AlMe_3$, 1:1 tol:THF	-	–78 °C to rt	35% of 3.111
11	H	Me	MeLi, $CeCl_3$, THF	-	–78 °C to rt	21% of 3.112

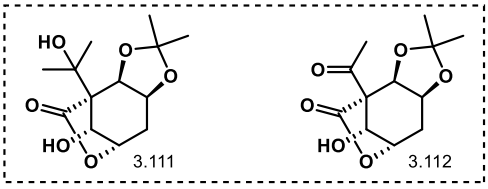
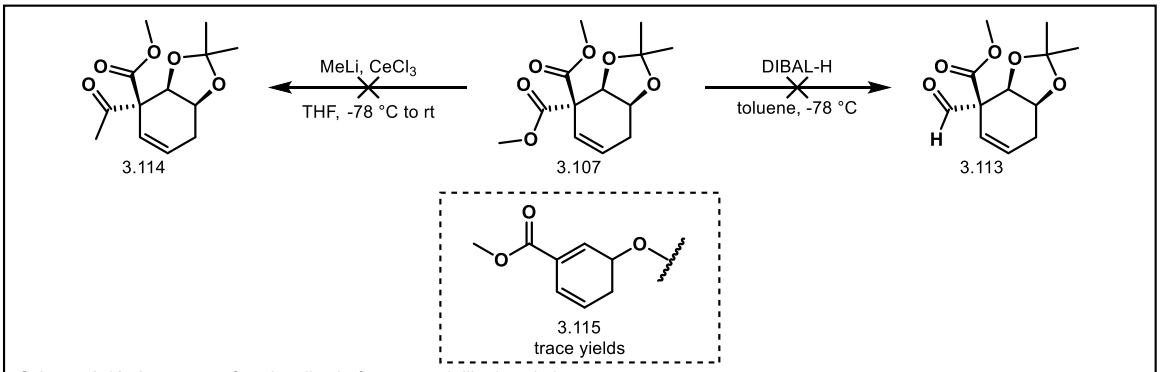


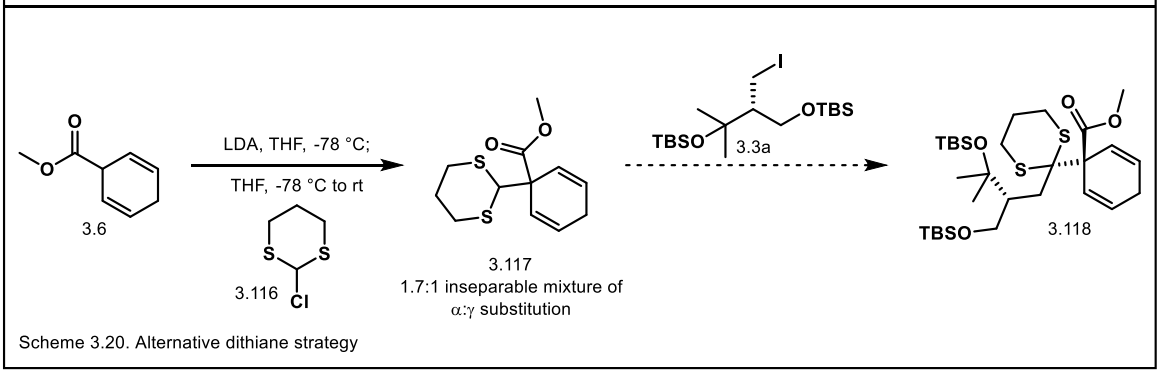
Table 3.16. Attempts to functionalize lactone

incorporated a step earlier, prior to the second dihydroxylation and spontaneous lactone formation.

Interestingly, treatment of 1,3-diester **3.107** with either DIBAL-H or MeLi led to trace yields of an undetermined side product containing fragment **3.115** (Scheme 3.19). This likely means that following addition to the ester, there is a retro-Claisen reaction and the resulting enolate eliminates one of the acetal oxygens. Additionally, the mass balance was mainly starting material, demonstrating poor reactivity. Given the poor reactivity of nucleophiles toward the neopentylic carbonyl groups, a potential work-around was developed. Chlorinated dithiane **3.116** could be used as a lynchpin between the A-ring and B-ring fragments (Scheme 3.20). After alkylation, the dithiane can be lithiated and used as a nucleophile to displace a leaving group on the B-ring fragment, thus conjoining both fragments. However, alkylation of ester **3.6** with chlorinated dithiane **3.116** led to a 1.7:1 inseparable mixture of α:γ substitution.



Scheme 3.19. Attempts to functionalize before second dihydroxylation

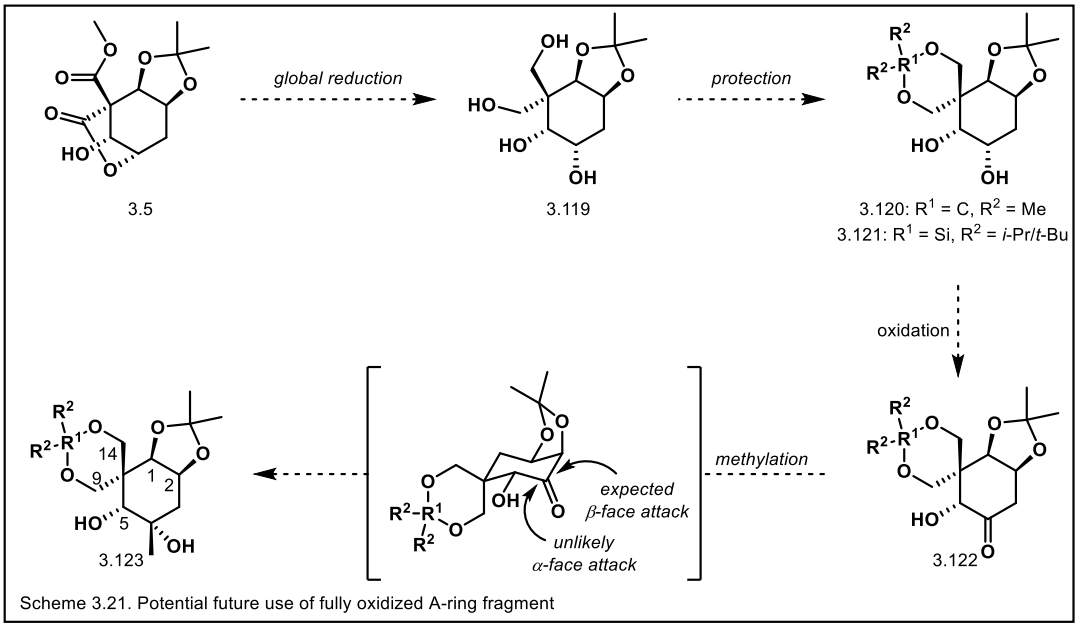


Scheme 3.20. Alternative dithiane strategy

While lactone **3.5** could be synthesized in an efficient manner, the ability to incorporate the B-ring fragment was hampered by the high degree of functionality and steric encumbrance around the A-ring. However, I was able to introduce all the oxidation found in the natural product except for the C6 oxidation. This route also demonstrated the effectiveness of the C9/C14 1,3-dicarbonyl mitigating retro-aldol and aromatization pathways. As a result, the diene could be effectively oxidized. While there are still some potential pathways forward using this route, I refocused my efforts towards a strategy that would incorporate the B-ring fragment earlier in the sequence and then take advantage of the bis-dihydroxylation sequence.

3.4.4 Future Directions

While this route stalled when attempting to incorporate the B-ring fragment, there are still a couple potential avenues to explore use of lactone **3.5** in the synthesis of the agarofurans. The first is by performing a global reduction of lactone **3.5** to tetraol **3.119**, likely with a strong reducing agent like $LiAlH_4$ or $LiEt_3BH$. A carefully planned protecting group strategy could then be applied in several possible pathways forward. The two secondary alcohols could be protected as the acetal or silacycle, allowing the secondary alcohols to be differentiated based on their different steric environments. Oxidation of the less sterically hindered alcohol would give ketone **3.122**. Stereochemical analysis reveals that methylation should occur selectively from the β-face, installing the C4 methyl group in the correct orientation. Moving forward with the synthesis would require, in no particular order, oxidation of the C5 alcohol, deprotection and acylation of the C1/C2 diol, and deprotection of the C9/C14 diol. Incorporation of the B-ring fragment would follow differentiation of the C9/C14 diol, which could likely be accomplished by taking advantage of the differing steric environments. Once the A- and B-ring fragments are joined, a similar endgame as described in previous sections could be employed.



Scheme 3.21. Potential future use of fully oxidized A-ring fragment

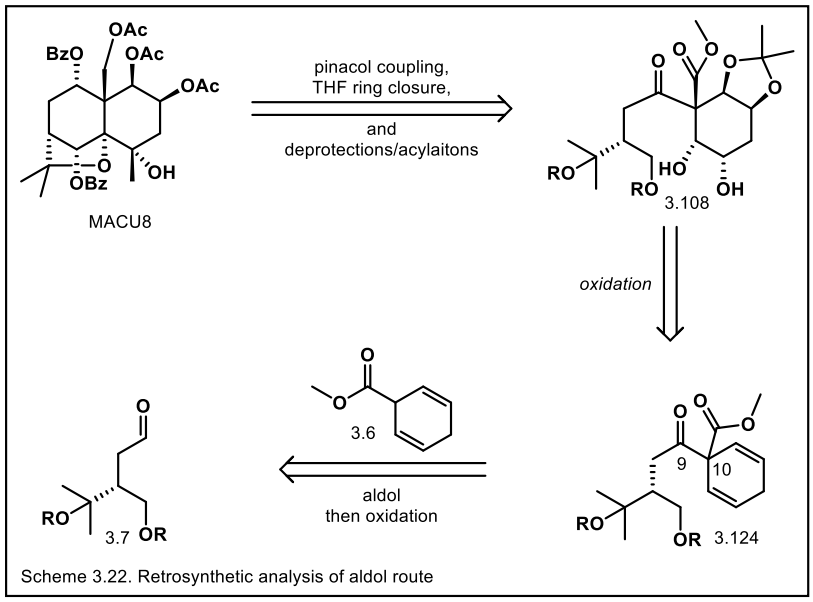
The second idea is to take advantage of the dithiane reactivity. While a 1.7:1 mixture of α:γ substitution was observed, it's possible that this reaction could be optimized to give better selectivity. Additives such as TMEDA, DMPU, HMPA, or others could potentially improve the selectivity. If that's the case, the dithiane could then be lithiated to perform an S_N2 reaction with alkyl iodide **3.3a**, which I have previously synthesized. This sequence would remove the need to do an organometallic addition to a neopentylic carbonyl, which could lead to better reactivity. Following conjoining of the A- and B-ring fragments, a similar endgame as described in previous sections could be employed.

3.5 Concurrent Conjoining of Fragments and Formation of the Quaternary Carbon at C10: Aldol Strategy

3.5.1 Retrosynthetic Analysis

As described in sections 3.4.2 and 3.4.3, the success of oxidizing the A-ring fragment combined with the difficulties incorporating the B-ring fragment led to a reevaluation of strategy. Since the double dihydroxylation of 1,3-dicarbonyl-containing diene **3.106** (previous section)

proceeded with great success and lactone **3.5** was relatively inert towards addition of organometallic reagents, I envisioned installing the B-ring fragment prior to oxidation of the diene.

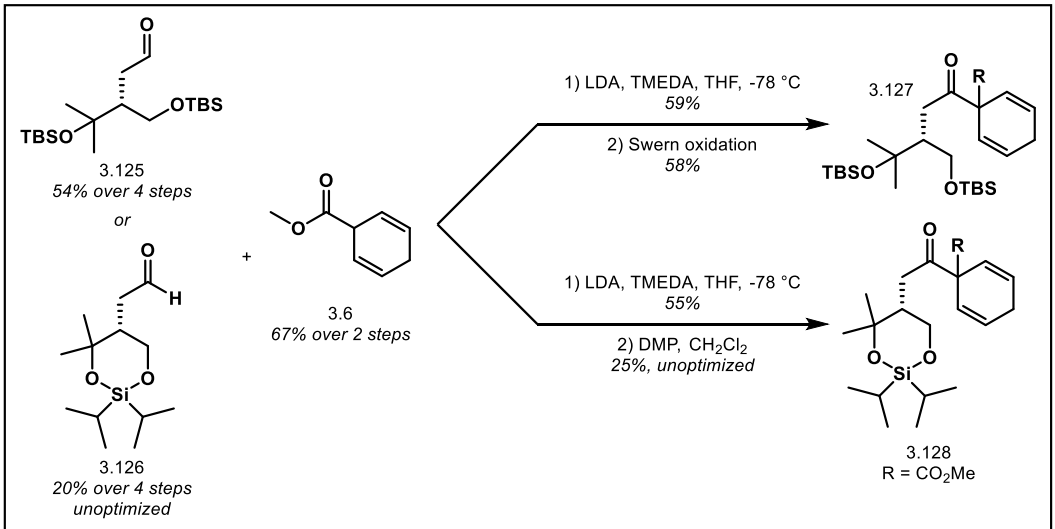


Scheme 3.22. Retrosynthetic analysis of aldol route

To complete the synthesis, a similar endgame as was previously envisioned in section 3.4.1 could be applied. Instead of performing the double dihydroxylation prior to incorporation of the B-ring fragment, I could instead have the B-ring fragment already installed, and perform the same double dihydroxylation sequence, albeit with important stereochemical implications resulting from the prochiral center at C10 (Scheme 3.22). Given the previous success of this oxidation sequence on **3.106** (previous section), I anticipated a similar strategy would be successful with **3.124**. The 1,4-diene substrate, **3.124**, could be synthesized by an aldol reaction between ester **3.6** and aldehyde **3.7** followed by oxidation at C9 to afford the β-keto ester. Both **3.6** and **3.7** have been synthesized in previous routes.

3.5.2 Initial Aldol Studies

Aldehyde **3.125** was synthesized in a 54% yield over four steps using the same sequence as used in the synthesis of **3.47** (See SI). Ester **3.6** was synthesized in a 67% yield over two steps using the same sequence described in Scheme 3.18, section 3.4.2. Treatment of ester **3.6** with LDA, followed by addition of aldehyde **3.125** as a solution in TMEDA at −78 °C excitingly led to a 59% yield of β-hydroxy ester (Scheme 3.23). Allowing the reaction mixture to warm to 0 °C or room temperature led to low yield and good recovery of the starting material. This can likely be attributed to the retro-aldol reaction becoming more favorable at warmer temperatures.



Scheme 3.23. Aldol reaction to conjoin the A- and B-ring fragments

Quenching the reaction with saturated aqueous NH_4Cl at −78 °C and then warming to room temperature allowed for recovery of aldol product. Use of HMPA in place of TMEDA led to greater conversions but poor purity of product following column chromatography. Swern oxidation to form β-keto ester **3.127** proceeded in a 58% yield. In an attempt to further increase the yield of the aldol reaction, I hypothesized that tying back the 1,3-diol as the acetal or silacycle could make the aldehyde's π* more accessible for nucleophilic attack. Attempts to protect the 1,3-diol as the acetal resulted in an inseparable mixture of product and an undetermined byproduct. Silacycle **3.126** was synthesized in an unoptimized 20% yield over four steps using the same sequence to synthesize **3.125**. When subjecting **3.126** to the aldol conditions, a 55% yield of β-hydroxy ester was observed, comparable to the 59% yield for the bis-TBS protected diol. Seeing no significant difference in yield, and with bis-TBS compound **3.127** allowing for differentiation of the 1,3-diol, I proceeded with **3.127** as the dihydroxylation substrate.

3.5.3 Diene Double Dihydroxylation

3.5.3.1 Stereochemical Analysis

Given the similarities between diene **3.127** and diene **3.106** I envisioned using a similar strategy to dihydroxylate as had been previously described in section 3.4.2. However, in substrate

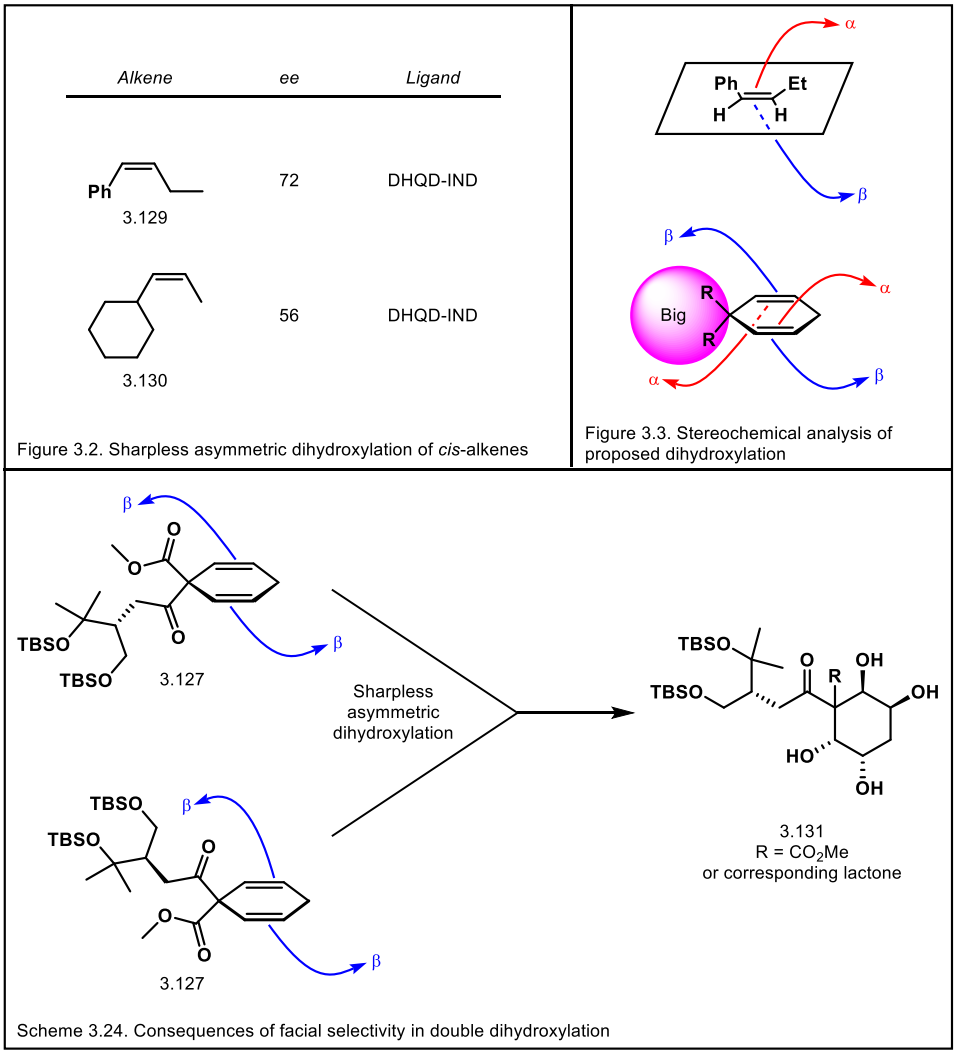


Figure 3.2. Sharpless asymmetric dihydroxylation of *cis*-alkenes

Figure 3.3. Stereochemical analysis of proposed dihydroxylation

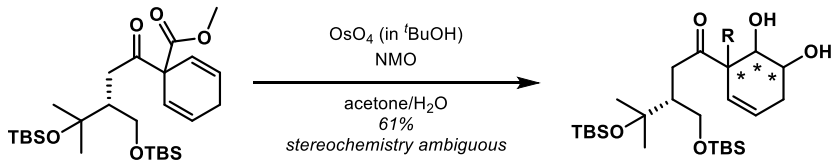
Scheme 3.24. Consequences of facial selectivity in double dihydroxylation

3.127, C10 is now prochiral so the dihydroxylations must be stereoselective. I hypothesized that a Sharpless asymmetric dihydroxylation could be used to afford the desired diastereoselectivity. Sharpless has reported the asymmetric dihydroxylation of *cis*-alkenes; however, it is notable that *cis*-alkenes are generally poor substrates for asymmetric dihydroxylations and in this report only moderate enantioselectivity was observed (Figure 3.2).[36] From Sharpless's report, substrates **3.129** and **3.130** were most similar to the system I wished to employ, and they gave ee's of 72% and 56%, respectively, when using the DHQD-IND ligand. However, no cyclic alkenes were reported and no alkenes with adjacent quaternary carbons were reported. In practice, although Sharpless reported that the specialized IND ligands were best for *cis*-alkenes, the Carter and

Oberthür groups reported that in their respective syntheses of mandelalide A[37] and echinocandin C[38] that the IND ligands performed poorly and the more traditional PHAL ligands performed better. When applying this knowledge to the dihydroxylation of **3.127**, I hypothesized that the large quaternary carbon, when compared to the adjacent methylene, could aid in the selectivity (Figure 3.3). Additionally, since I aimed for dihydroxylation of both alkenes, facial selectivity was inconsequential. Since the second dihydroxylation should proceed from the face opposite the first dihydroxylation, if the first dihydroxylation proceeds with good diastereoselectivity then the correct diastereomer of tetraol **3.131** should be generated (Scheme 3.24). The mnemonic developed by Sharpless suggests that the correct diastereoselectivity should be achieved regardless of the facial selectivity, thus the facial selectivity is ultimately unimportant.

3.5.3.2 Dihydroxylation Attempts

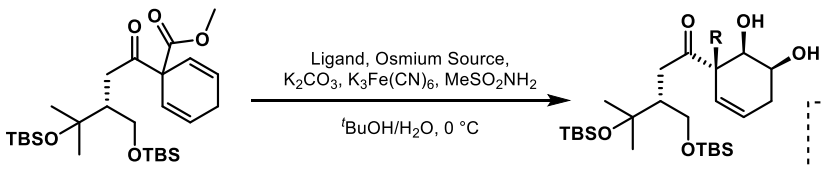
Initially, to test the reactivity of substrate **3.127**, it was subjected to the same dihydroxylation conditions as described in section 3.4.2. Treatment with OsO_4 and NMO gave a 61% yield of diol **3.132** (Equation 3.7). Notably, this yield is significantly lower than the yield observed in the dihydroxylation of the 1,3-diester, implying that that the larger ketone fragment is hindering reactivity. Unfortunately, the stereochemistry of the three contiguous stereocenters could not be assigned as NMR and nOE analysis was inconclusive. Treatment with standard Sharpless asymmetric dihydroxylation conditions gave only trace conversion (Table 3.17). Switching the osmium source to an OsO_4 solution in *tert*-butanol increased the yield to 18%. Warming the reaction to room temperature showed no improvement in conversion or yield. The DHQ-IND ligand was synthesized in 98% yield in two steps; however, when used as the ligand I observed only trace conversion. To probe whether the reactivity was the major issue, diol **3.132** was protected as the acetal and treated with the same dihydroxylation conditions that were successful in conducting the second dihydroxylation in section 3.4.2 (Scheme 3.25). Unfortunately, no conversion was observed. Additionally, treatment of diol **3.132** with the same



3.127

3.132
R = CO_2Me

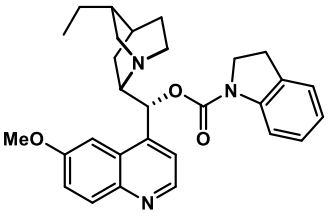
Equation 3.7. Non-asymmetric dihydroxylation



3.127

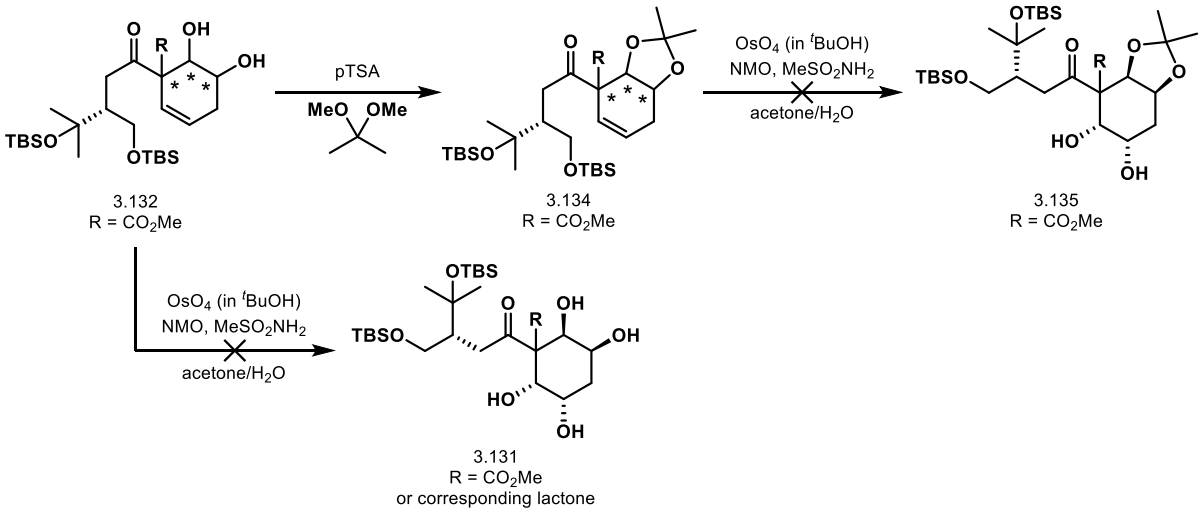
3.132
R = CO_2Me

Entry	*Osmium Source*	*Ligand*	*Result*
1	$K_2OsO_4 \cdot 2H_2O$	$(DHQD)_2PHAL$	trace conversion
2	OsO_4 (in ^{t}BuOH)	$(DHQD)_2PHAL$	18%
3	OsO_4 (in ^{t}BuOH)	DHQ-IND	trace conversion



3.133
DHQ-IND
98%, 2 steps

Table 3.17. Attempts at asymmetric dihydroxylation



3.132
R = CO_2Me

3.134
R = CO_2Me

3.135
R = CO_2Me

3.131
R = CO_2Me
or corresponding lactone

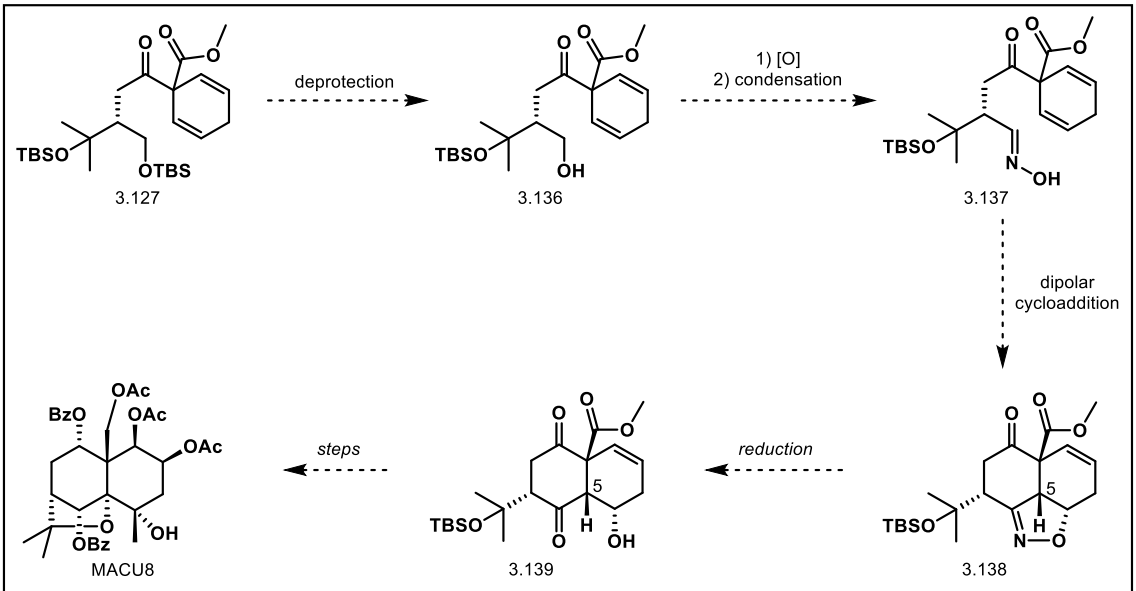
Scheme 3.25. Proof of poor reactivity in dihydroxylation reaction

dihydroxylation conditions displayed no conversion. Ultimately, the change from the methyl ester to a β-branched ketone was a large enough change in the steric environment to disrupt the dihydroxylation sequence.

Despite the poor reactivity of the β-keto ester-containing diene towards dihydroxylation conditions, I had successfully conjoined the A- and B-ring fragments. Using an aldol reaction to bring these two fragments together I had successfully installed all of the carbon atoms present in the core of the agarofurans except for the C4 methyl group and the esters. Additionally, I had synthesized an intermediate that contains all the necessary functional group handles to install the remaining oxygenation. From intermediate **3.127**, I envisioned an alternative route inspired by my previous 1,3-dipolar cycloaddition work.

3.5.4 Revised Forward Route

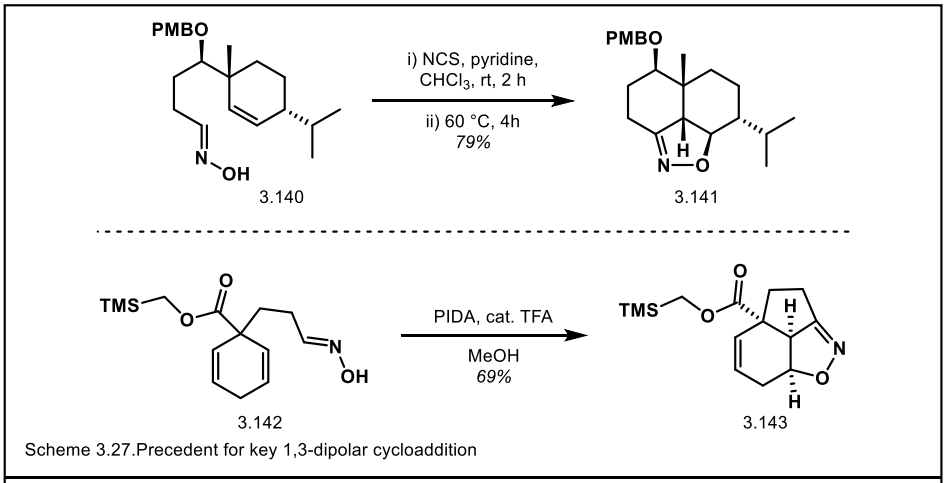
Since I observed poor reactivity of diene **3.127** towards dihydroxylation conditions, I developed an alternative route starting from the same intermediate (Scheme 3.26). Deprotection of the silyl protected alcohol would give me **3.136**. Oxidation of the primary alcohol to the aldehyde and condensation of hydroxylamine would give oxime **3.137**. Oxidation of the oxime to the nitrile



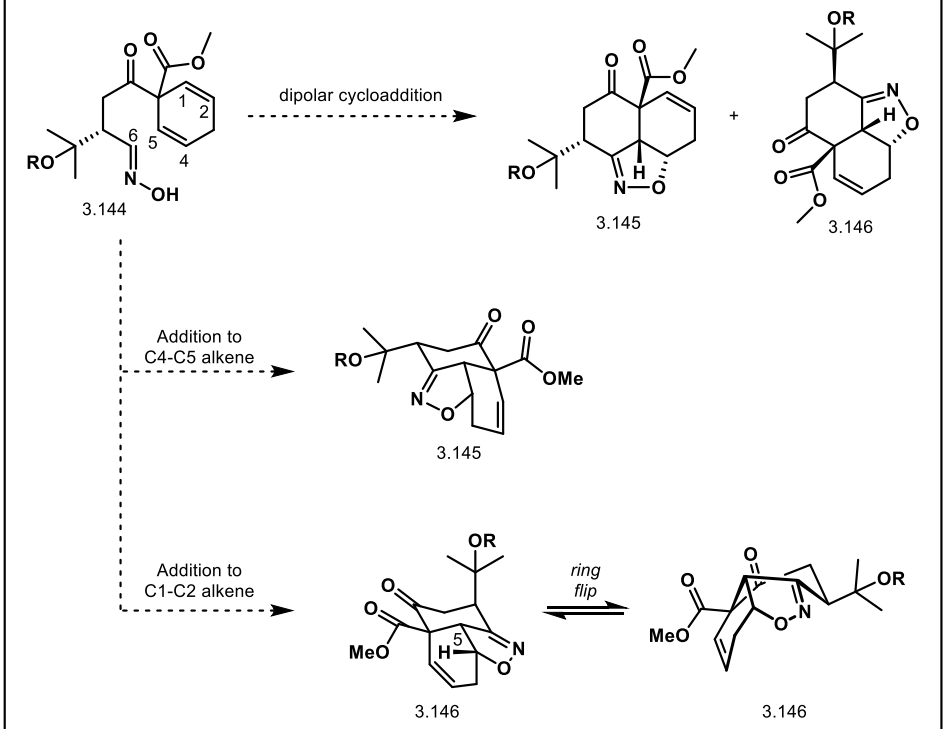
Scheme 3.26. Revised forward route using a 1,3-dipolar cycloaddition

oxide could lead to a spontaneous 1,3-dipolar cycloaddition with one of the alkenes, forging the final carbon-carbon bond to form the B-ring while also oxidizing the same alkene. The isoxazoline can be reductively cleaved, yielding β-hydroxy ketone **3.139**. From here, dihydroxylation of the remaining alkene, epimerization at C5, and several functional group manipulations would yield the natural product. This route is particularly intriguing since formation of the core structure, **3.138**, would allow for the synthesis of many agarofuran natural products due to the flexibility in manipulating the remaining functionality.

Fortunately, the key 1,3-dipolar cycloaddition step is well-precedented in two similar situations. In 2012, the synthesis of a rare *cis*-fused agarofuran, (+)-5-epi-eudesm-4(15)-ene-1β,6β-diol, was reported wherein the authors took advantage of an intramolecular nitrile oxide dipolar cycloaddition to forge the A-ring (instead of the B-ring in my proposed example) and form the desired *cis*-ring fusion (Scheme 3.27).[39] Having synthesized oxime **3.140** in nine steps from (–)-*cis*-piperitol, they subjected the oxime to NCS and pyridine to form the nitrile oxide and perform the desired 1,3-dipolar cycloaddition in 79% yield over two steps (condensation and cyclization). However, it must be noted that there was not a second alkene to contend with in this example. Isoxazoline **3.141** was elaborated to the natural product in an additional four steps. In a 2009 report wherein the authors disclose conditions to form nitrile oxides from oximes using hypervalent iodine, they include a particularly relevant example to demonstrate their conditions.[40] Using cyclic 1,4-diene **3.142** containing an oxime, they perform the 1,3-dipolar cycloaddition to give tricycle **3.143** in 69% yield. However, it must be noted that although this is encouraging given the presence of the 1,4-diene, they are forming two 5-membered rings instead of the six- and five-membered rings I propose. While neither of these examples exactly match my desired system, they demonstrate that a nitrile oxide dipolar cycloaddition is plausible. However, it's imperative to determine if the sole C6 stereocenter could impart any degree of chemoselectivity between the two alkenes. When I examined a potential cycloaddition reaction between the C6 nitrile oxide and the desired C4-C5 alkene, I was pleased to find that the newly formed six-membered ring could



Scheme 3.27.Precedent for key 1,3-dipolar cycloaddition



Scheme 3.28. Stereochemical analysis of 1,3-dipolar cycloaddition

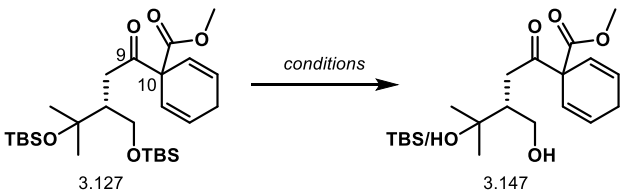
sit in a pseudo-chair conformation with the bulky protected tertiary alcohol in a pseudo-equatorial position (**3.145**, Scheme 3.28). When I examined the potential cycloaddition with the undesired C1-C2 alkene I was gratified to see a much more unfavorable interaction. To place the newly formed six-membered ring in a pseudo-chair conformation, the bulky protected tertiary alcohol group would have to be placed pseudo-axial, clashing with the C5 axial hydrogen (**3.146**). To avoid this unfavorable steric interaction and place the protected tertiary alcohol in a pseudo-

equatorial position, the newly formed 6-membered ring must adopt an unfavorable twist-boat conformation. Given the results of this analysis, I was confident that good chemoselectivity could be achieved in the 1,3-dipolar cycloaddition reaction.

3.5.5 Synthesis of the AB-Core of the Agarofurans

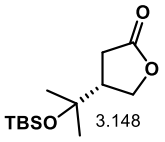
First, the primary alcohol must be unveiled by removal of the TBS group. Treatment with TBAF at 0 °C led to a complex mixture of multiple products (Entry 1, Table 3.18). Use of HF or HF·pyridine in MeCN led to an unknown side product resulting from cleavage of the C9-C10 bond (Entries 2 and 3). Unfortunately, I observed a 79% of lactone **3.148** when using $HCl_{(aq.)}$ in THF (Entry 4). This product likely results from an intramolecular retro-Claisen reaction once the alcohol is revealed. $BF_3{\cdot}OEt_2$ and CsF also resulted in selective formation of lactone **3.148** (Entries 5 and 6). Since revealing the alcohol/alkoxide *in situ* resulted in a facile and unproductive retro-Claisen reaction, I looked to directly oxidize the silyl-protected alcohol to the aldehyde. Both the tetrafluoroborate and perchorlate salts of Bobbitt's salt have been demonstrated to directly oxidize TBS protected alcohols directly to the aldehyde.[41] While most deprotection/oxidation conditions go through a sequence wherein the alcohol is first deprotected, revealing the alcohol or alkoxide, and then oxidizing to the carbonyl, Bobbitt's salt has been hypothesized to oxidize the carbon-oxygen bond first, followed by removal of the silyl group. Since deprotection would simply lead to the retro-Claisen reaction, the use of Bobbitt's salt seemed particularly suited for my specific substrate. However, treatment of **3.127** with both the tetrafluoroborate and perchlorate salts of Bobbitt's salt led exclusively to lactone **3.148**, implying that the carbon-oxygen bond is not oxidized prior to silyl removal (Table 3.19).

While it is known that -OTMS and -OTES bonds can be oxidized directly to the carbonyl with more traditional oxidation conditions, I believed these would be unlikely to work. For example, after formation of aldehyde **3.125** containing TES-protected alcohols, I could perform a similar aldol reaction. At this stage I could doubly oxidize the C9 alcohol and the C6 -OTES group.



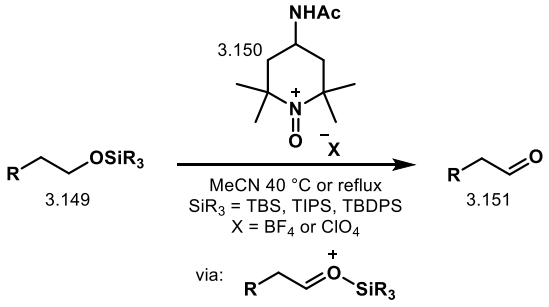
3.127 3.147

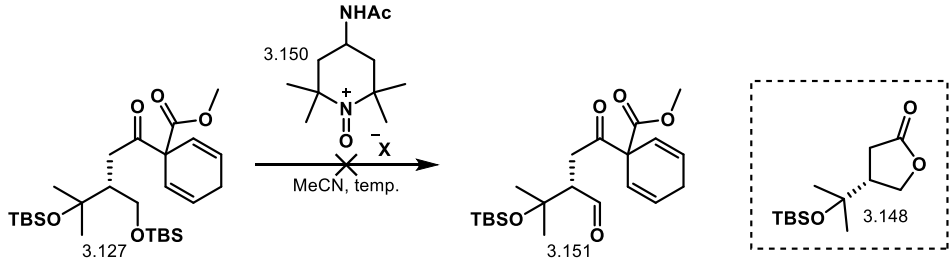
Entry	Conditions	Result
1	TBAF, THF, 0 °C	indiscernable mixture
2	HF·pyridine, MeCN	cleaved molecule to unknown side product
3	HF, MeCN	cleaved molecule to unknown side product
4	HCl, THF	79% of **3.148**
5	$BF_3{\cdot}OEt_2$, CH_2Cl_2	produced only **3.148**
6	CsF, $MeCN/H_2O$	produced only **3.148**



3.148

Table 3.18. Attempts to deprotect primary silyl-protected alcohol



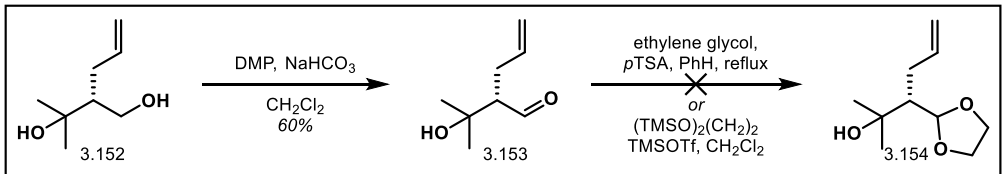


Entry	X^-	°C	Result
1	BF_4	reflux	3.148
2	ClO_4	40	3.148

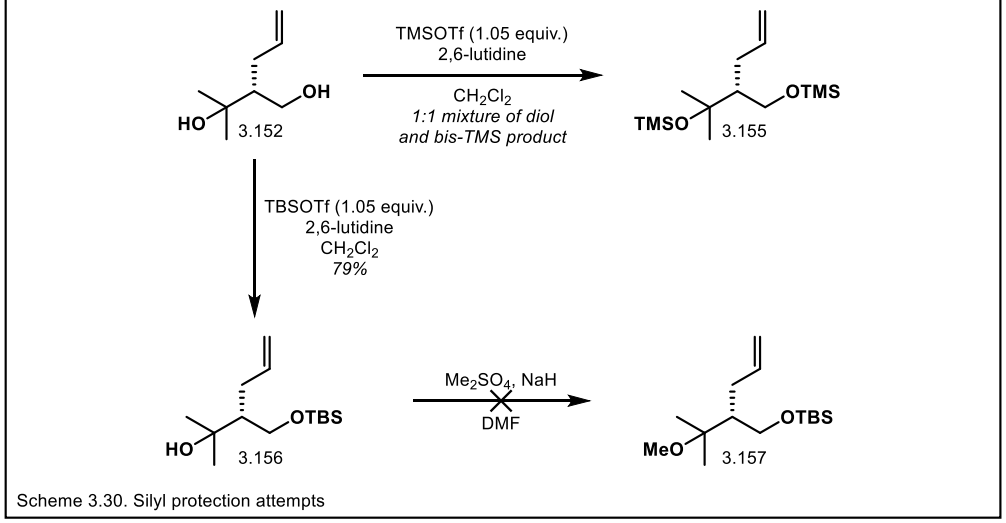
Table 3.19. Attempts to oxidize directly to the aldehyde using Bobbitt's salt

However, for this to be successful, the C9 alcohol must be oxidized first, followed by oxidation of the C6 -OTES group without prior removal of the TES group. If the -OTES group is oxidized first, the C9 alcohol can simply form the lactol, followed by oxidation to the lactone which is unproductive for the forward route. Additionally, if the C9 alcohol is oxidized first, but the TES group is removed prior to oxidation, then lactone **3.148** would be formed again. Ultimately, this route was deemed unlikely to succeed and was not pursued. From these results, it became clear that C6 must be brought in at an oxidation state higher than an alcohol to prevent the facile retro-Claisen reaction.

To bring in the B-ring fragment at a higher oxidation state, I first treated diol **3.152** with DMP to form aldehyde **3.153**. To form the acetal, I subjected aldehyde **3.153** to standard protection conditions using ethylene glycol, catalytic pTSA, in benzene at reflux (Scheme 3.29). While full conversion was observed, there was no mass recovered likely due to a retro-aldol reaction resulting in volatile products. Use of $TMSO(CH_2)_2OTMS$ in the presence of catalytic



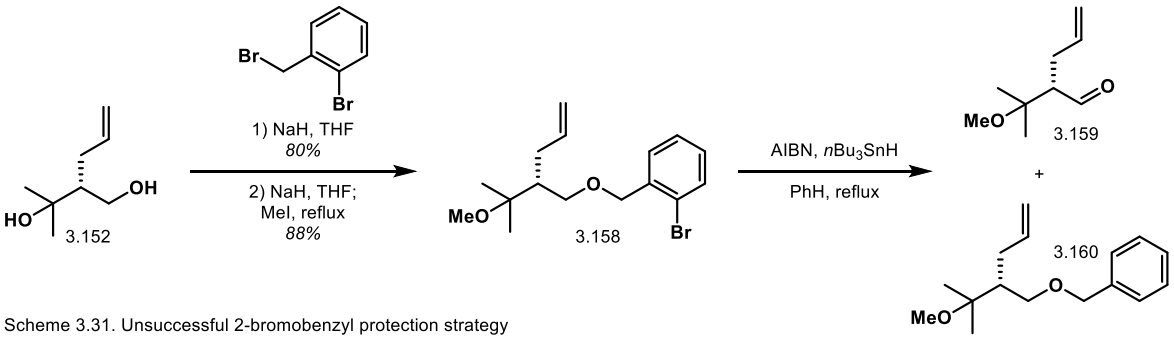
Scheme 3.29. Attempts to protect β-hydroxy aldehyde



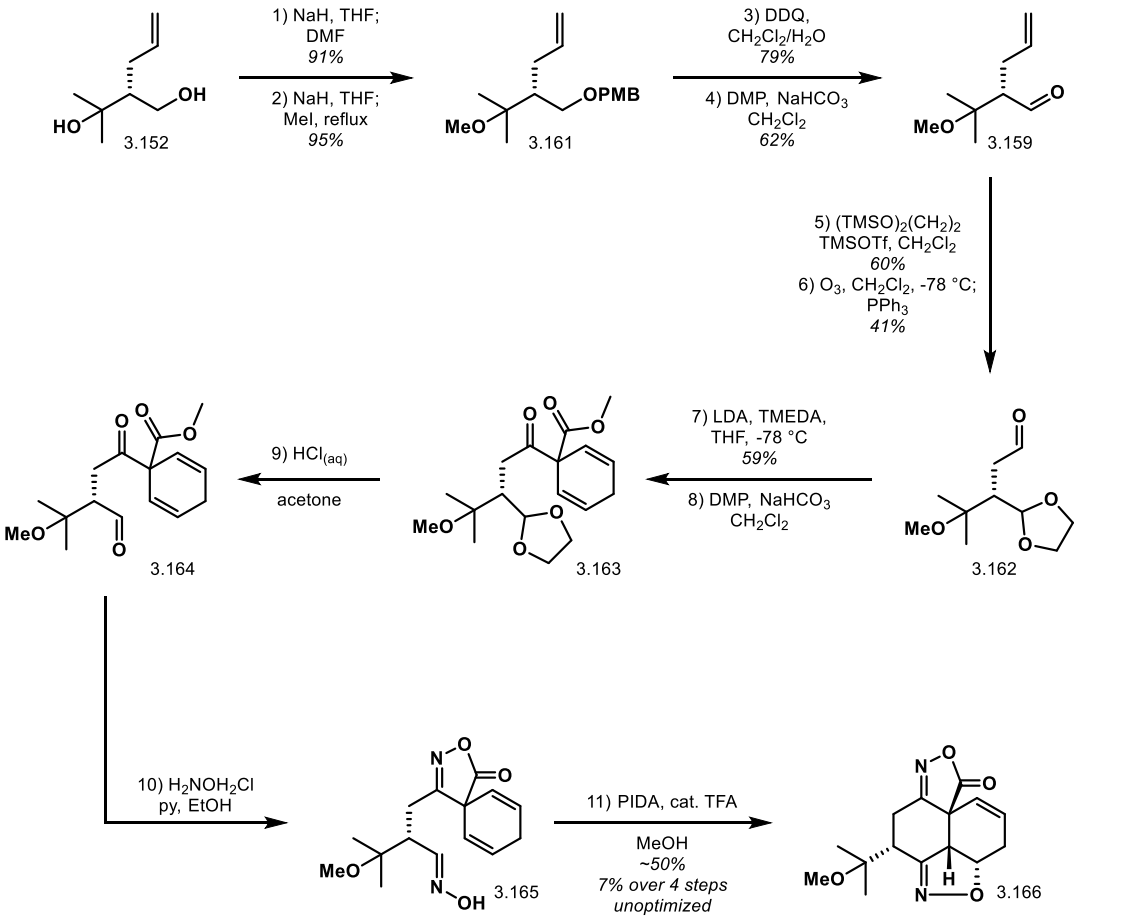
Scheme 3.30. Silyl protection attempts

TMSOTf also resulted in no mass recovery. Attempts to protect the tertiary alcohol at this stage also led to no mass recovery.

Realizing that the tertiary alcohol must be protected prior to oxidation of the primary alcohol to the aldehyde to prevent a possible retro-aldol reaction, I subjected diol **3.152** to 1.05 equivalents of TMSOTf in the presence of 2,6-lutidine to selectively protect the primary alcohol. Surprisingly, this led to a 1:1 mixture of the bis-protected product and the diol starting material (Scheme 3.30). When subjecting diol **3.152** to 1.05 equivalents of TBSOTf mono-protection of the primary alcohol was obtained in 79% yield. However, when the tertiary alcohol was subjected to NaH and Me_2SO_4 in DMF, five new products were formed swiftly, likely resulting from potential silyl transfer and the possible mixtures of methylations. Since silyl protecting groups were proving problematic, I switched my focus to other protecting groups, namely PMB and 2-bromobenzyl. 2-Bromobenzyl ether was synthesized in 80% yield from diol **3.152** by subjecting to NaH in THF followed by 2-bromobenzyl bromide (Scheme 3.31). The resulting tertiary alcohol was then methylated in 88% yield after treating with NaH in THF, followed by MeI and heating to reflux to afford **3.158**. The 2-bromobenzyl protecting group was chosen because upon deprotection under reductive conditions it directly affords the aldehyde, which would streamline the synthetic route. When subjecting bromide **3.158** to excess *n*-Bu_3SnH and stoichiometric AIBN in refluxing benzene, only debromination to **3.160** was observed. Treatment with a catalytic quantity of AIBN and a slight excess of *n*-Bu_3SnH gave a 1:1 mixture of debromination and the desired aldehyde, **3.159**. The debromination pathway ultimately led me to opt for the PMB protection route. Treatment of diol **3.152** with NaH in DMF followed by PMBCl gave a 91% yield of the PMB-protected primary alcohol (Scheme 3.32). The use of THF as solvent instead of DMF led to incomplete conversion. Then, methylation of the tertiary alcohol proceeded in 95% yield by subjecting the tertiary alcohol to NaH in THF, followed by MeI and heating to reflux to give **3.161**. Interestingly, this methylation proceeded poorly when using DMF as the solvent, resulting in mostly starting material remaining. The primary alcohol can be revealed by treating PMB



Scheme 3.31. Unsuccessful 2-bromobenzyl protection strategy



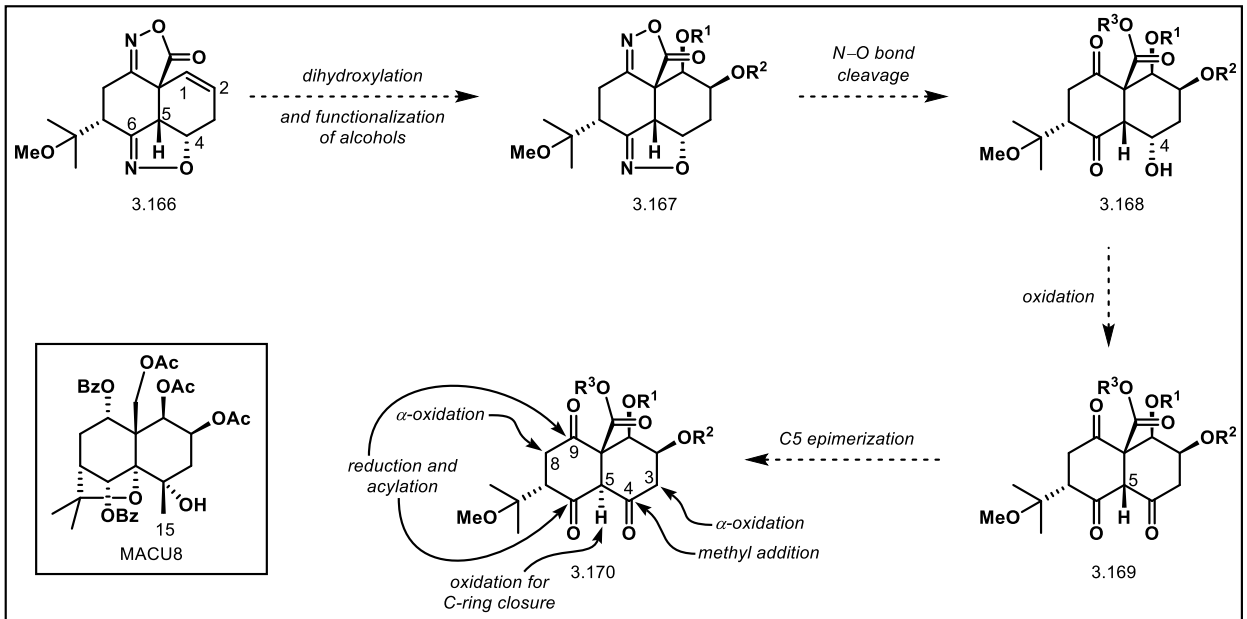
Scheme 3.32. Successful synthesis of the AB-core of the agarofurans

protected alcohol **3.161** with DDQ, giving the desired alcohol in 79% yield. The alcohol can be oxidized to aldehyde **3.159** in 62% yield with DMP. This four-step procedure can also be done on multigram scale, giving a 43% yield of aldehyde **3.159** (81% average yield for each step), without any purifications until the aldehyde. Now that the tertiary alcohol is protected, the retro-aldol reaction should be unfavorable and the aldehyde can be protected as the acetal. This proved true, and the acetal was formed in 60% yield. Ozonolysis provided the aldehyde **3.162** in 41% yield and the B-ring fragment was now prepared for the aldol reaction to bring the two fragments together. Using the same aldol conditions I developed previously, the β-hydroxy ester was formed in 56% yield, with 42% recovery of the starting aldehyde. Oxidation to β-keto ester **3.163** with DMP followed by deprotection of the acetal to the aldehyde with 1 M aqueous HCl and acetone gave **3.164**. The resulting products of both of these steps were used in the next step without extensive purification. Treatment of aldehyde **3.164** with hydroxylamine gave an unexpected side product. It was initially indeterminable what this side product was, however, it was clear that an oxime was formed. The structure was unable to be assigned as a result of a byproduct that co-eluted with the product during purification via column chromatography. This byproduct gave integrations by ^{1}H NMR that were proportional to the integrations of peaks I had assigned to the product. As a result, I was unable to properly assign the structure of the product at that time. However, since I knew that the product had an oxime present (as determined by ^{13}C NMR analysis) I subjected the unknown side product to oxidative conditions intending to trigger a dipolar cycloaddition, treating with PIDA and catalytic TFA. Excitingly, tetracycle **3.166** was isolated in a 50% yield, forming the AB-ring system of the agarofuran skeleton.

3.5.6 Future Directions and Conclusion

The AB-ring system of the agarofurans was synthesized by formation of the C5-C6 bond via a 1,3-dipolar cycloaddition. This intermediate, **3.166**, contains all of the carbon atoms found in MACU8 except for the C15 methyl group which can be installed via an organometallic addition

to a C4 ketone following oxidation (Scheme 3.33). This also installed the C4 oxidation found in many agarofuran natural products. Dihydroxylation of the C1-C2 alkene should proceed on the convex, β-face, thus resulting in **3.167**, which contains all the oxygenation contained in MACU8. More importantly **3.166** is a scaffold that can likely be used to synthesize several agarofuran natural products and appropriate analogs. Following dihydroxylation and protection, both N–O bonds can be reduced using known protocols, revealing diketone **3.168**. Oxidation of the C4 alcohol sets up for epimerization to the *trans*-decalin at C5. From **3.169**, differentiation of the three ketones will be determined by experimentation. Formation of the C-ring can likely be done *via* a Hoffmann–Löffler–Freytag-type process or *via* a C-H functionalization. Following C-ring formation, stereoselective installation of the C15 methyl group to the C4 ketone is known. Additionally, the C4 and C9 ketones would allow for introduction of C3 and C8 oxygenation, should it be so desired. Alternatively, to synthesize agarofurans with different stereochemistry at C1 and C2, dihydroxylation could be performed following epimerization instead of before to establish C1 and C2 oxygenation on the α-face, or epoxidation could allow for C1/C2 *trans*-oxygenation. Overall, **3.166** provides a diversifiable scaffold that could be applied to an incredible number of

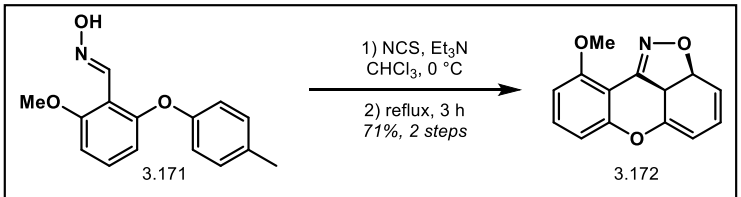


Scheme 3.33. Future directions and possible diversification routes to other agarofurans and analogs

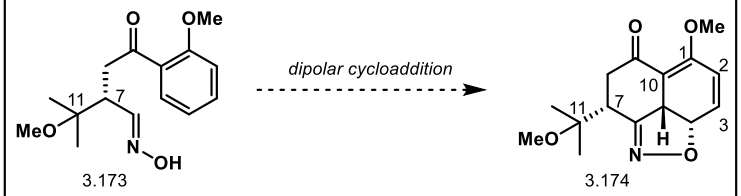
agarofuran natural products and analogs for biological studies. This concise, general, and operationally simple route sets the stage for a new era of agarofuran syntheses focused on generating libraries of compounds to further understand this extensive family of natural products.

3.5.7 Other Ideas

In 2012, the intramolecular 1,3-dipolar cycloaddition between nitrile oxides and aromatic rings was disclosed.[42] Starting with oxime **3.171**, the authors form the nitrile oxide using NCS and Et_3N. After heating in $CHCl_3$ to reflux, product **3.172** resulting from the dearomative 1,3-dipolar cycloaddition is formed. Of particular note is that electron-withdrawing groups, such as esters, can be incorporated, albeit reforming the aromatic ring after a net oxidative event. I hypothesized that substrate **3.173** could undergo a similar dearomative 1,3-dipolar cycloaddition reaction. The authors note that use of 2,6-dimethyl substitution impedes the cycloaddition reaction, thus I would expect cycloaddition of **3.173** to form product **3.174**. Similar to the proposed dipolar cycloaddition in section 3.5.5, I expect the C7 stereocenter to impart some facial selectivity in the dipolar cycloaddition. Addition from the β-face would result in the C11 fully substituted carbon being placed in the pseudo-axial position. Addition from the α-face would instead place that same group in a pseudo-equatorial position, thus I expect this stereoisomer should predominate.



Equation 3.8. Precedented dearomative 1,3-dipolar cycloaddition



Equation 3.9. Proposed dearomative 1,3-dipolar cycloaddition

Tricycle **3.174** could be used in a similar endgame as described in section 3.5.6, although it would require introduction of C14 *via* formation of the C10 quaternary carbon. However, this route would allow for easier introduction of C3 oxygenation. Lastly, different methoxy substitution patterns could be used on the aromatic ring to modulate reactivity and to open up hydrogenation as a

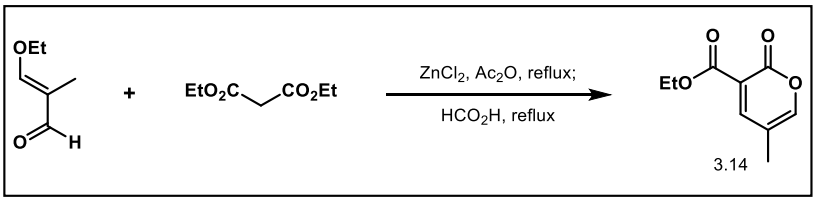
pathway for introducing the C1, C2, and/or the C3 stereochemistry. While perhaps worth pursuing, **3.166** is a more intriguing candidate since the C10 quaternary carbon is already set.

3.6 Experimental Information

3.6.1 Materials and Methods

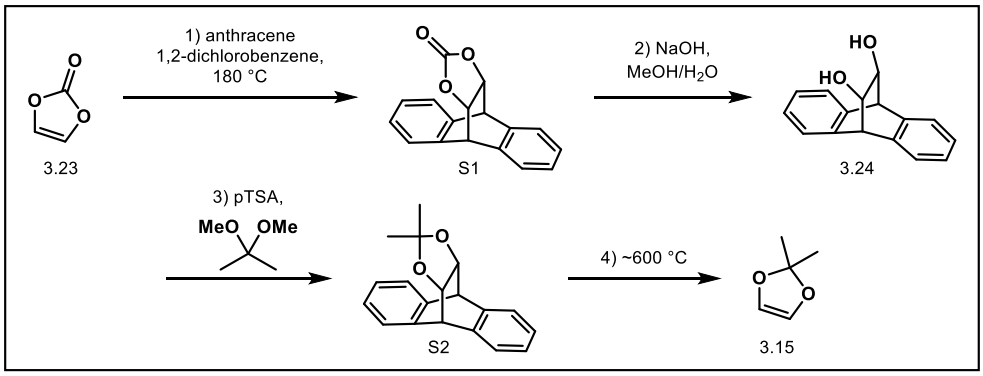
All reactions were carried out in flame dried glassware under an argon atmosphere with a Teflon® coated stir bar, unless otherwise noted. Dry DCM, THF, MeCN, Et_2O, PhH, PhMe were obtained by percolation through columns packed with neutral alumina and columns packed with Q5 reactant under argon. All solvents used for extraction and flash chromatography were purchased from either Sigma-Aldrich or Fischer and used with no further purification. All amine bases were distilled from calcium hydride before use, unless otherwise noted. All reagents were used as received from commercial sources or prepared according to literature procedures, unless otherwise noted. Flash chromatography was performed using Geduran® Silica Gel 60 (0.040 – 0.063 mm) mesh silica gel, and eluent mixtures are reported as %v/v. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 TLC plates, using UV (254 nm), $KMnO_4$ in K_2CO_3/NaOH/H_2O with heat, or *p*-anisaldehyde in ethanol/$H_2SO_{4(aq)}$/$AcOH_{(aq)}$ with heat to visualize. ^1H NMR and ^{13}C NMR spectra were recorded on a Bruker CRYO500 or AVANCE600 spectrometer equipped with a CRYO500 probe at 298 K, unless otherwise noted. Chemical shifts are reported in parts per million, using residual solvent ($CHCl_3$) as internal calibration (7.26 ppm for ^1H) or $CDCl_3$ as internal calibration (77.16 ppm for ^{13}C). Couplings are reported using the following designations: s = singlet, d= doublet, t = triplet, q = quartet, quin = quintet, hept = heptet, m = multiplet. Coupling constants are reported in Hertz measured at the reported field strengths. High-resolution mass spectra were obtained on a Waters LCT Premier spectrometer using ESI-TOF and values are reported as [*m*/*z*].

3.6.2 Experimental Procedures and Characterization Data



Pyrone 3.14. A flame-dried 500 mL round bottom flask equipped with a stir bar was charged with anhydrous $ZnCl_2$ (0.812 g, 5.96 mmol), acetic anhydride (120 mL), diethyl malonate (21.05 g, 131.41 mmol), and 3-ethoxymethacrolein (10.0 g, 87.61 mmol). The reaction mixture was stirred at reflux for 4 hours. The reaction mixture was cooled to room temperature and acetic anhydride was removed *in vacuo* and the resulting residue was dissolved in formic acid (120 mL). After stirring at reflux for 15 minutes, the reaction mixture was cooled to room temperature and the formic acid was removed *in vacuo*. The resulting residue was dissolved in dichloromethane (300 mL) and washed with a saturated aqueous solution of $NaHCO_3$ (3 x 50 mL). The volatiles were removed *in vacuo* and the resulting residue was subjected to column chromatography (25% EtOAc in hexanes) to afford **3.14** as a vicous orange oil. **3.14** was then recrystallized from hexanes using dichloromethane as a co-solvent to yield a pale yellow-white solid. Lastly, **3.14** (Melting point: ~64 °C; Distillation: bath temperature 135 °C, pressure 0.66 Torr) was distilled to yield a white solid (4.79 g, 30%).

^{1}H and ^{13}C NMR spectra were consistent with those previously reported.[12]



Carbonate S1. A flame-dried 250 mL round bottom flask equipped with a stir bar was charged with anthracene (24.44 g, 137.1 mmol), vinylene carbonate (11.80 g, 137.1 mmol) and 1,2-dichlorobenzene (45 mL). The reaction mixture was stirred at reflux overnight, then cooled to room temperature. Hexanes (300 mL) was added and a solid precipitated. The solid was filtered and collected to yield a yellow powder (35.15 g, 97%). **S1** was used in the next step without further purification. (Tetrahedron 1990, 46, 4573)

^{1}H and ^{13}C NMR spectra were consistent with those previously reported.[13]

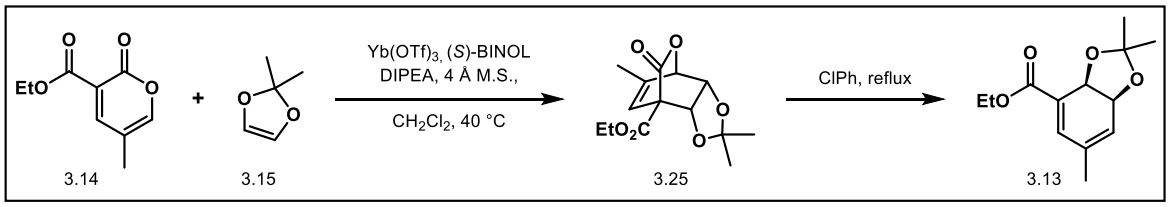
Diol 3.24. A flame-dried 1 L round bottom flask equipped with a stir bar was charged with **S1** (26.10 g, 98.76 mmol), NaOH (7.90 g, 197.5 mmol), H_2O (57 mL), and MeOH (380 mL). The reaction mixture was stirred at reflux overnight, then cooled to room temperature. The reaction mixture was acidified, then filtered to yield a yellow powder (23.30 g, 99%) **3.24** was used in the next step without further purification.

^{1}H and ^{13}C NMR spectra were consistent with those previously reported.[13]

Acetal S2. A 500 mL flame-dried round bottom flask equipped with a stir bar was charged with **3.24** (23.30 g, 97.77 mmol), pTSA (1.0 g), and 2,2-dimethoxypropane (150 mL). The reaction mixture was stirred overnight. The reaction mixture was diluted with dichloromethane (1 L), washed with a saturated aqueous solution of $NaHCO_3$ (3 x 100 mL), washed with H_2O (100 mL),

then the organic phase was dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo* to afford a yellow powder (26.94 g, 99%). **S2** was used in the next step without further purification. ^1H and ^{13}C NMR spectra were consistent with those previously reported.[13]

Acetonide 3.15. A flame-dried 25 mL tapered flask was charged with **S2** (10.0 g, 35.93 mmol) and a few crystals of BHT. A Vigreux column was attached to the flask, followed by attachment of a short-path distillation apparatus to the column. Lastly, a four-pronged glass distribution apparatus with four 25 mL tapered flasks was attached. The distillation set-up was evacuated and back-filled with argon three times. Using a propane torch, the solid **S2** was melted then cracked, being careful not to allow vaporized anthracene to travel up the Vigreux column by gently heating/removing the heat as needed. Once distillation was complete, the first yellow fraction was discarded and then second clear fraction was collected and stored under argon (2.32 g, 64%). ^1H and ^{13}C NMR spectra were consistent with those previously reported.[13]

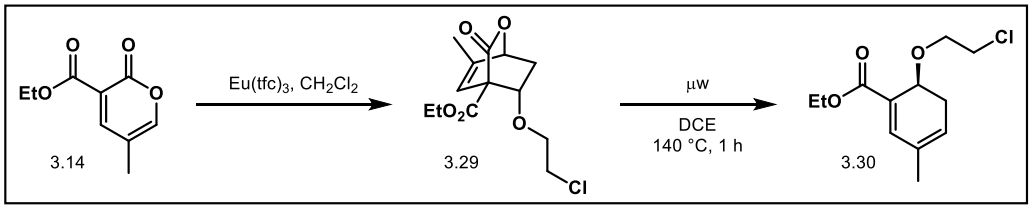


General Asymmetric Diels-Alder Procedure A.[12] A flame-dried 1 dram vial equipped with a stir bar was charged with $Yb(OTf)_3$ (113 mg, 0.182 mmol) and flame-dried. Oven/flame-dried 4 Å molecular sieves (0.474 g) were added to the vial followed by the **S27** (135 mg, 0.218 mmol), dichloromethane (4.55 mL), and DIPEA (0.076 mL). The mixture was stirred at 0 °C for 30 minutes. Pyrone **3.14** (332 mg, 1.82 mmol) was added to the reaction mixture and stirred for 10 minutes at 0 °C. Lastly, **3.15** (547 mg, 5.46 mmol) was added and the reaction mixture was stirred at 40 °C overnight. The reaction mixture was cooled to room temperature, concentrated *in vacuo*,

and purified by column chromatography (10% EtOAc in hexanes) to afford **3.25** as a white solid (128 mg, 25%). The yields for this reaction varied wildly, ranging from 0–97%, but typically <30%. ^{1}H and ^{13}C NMR spectra were consistent with those previously reported.[12]

Dienoate 3.13. A flame-dried 100 mL round bottom flask equipped with a stir bar was charged with **3.25** (125 mg, 0.443 mmol) and chlorobenzene (44 mL). The reaction mixture was stirred at reflux until the reaction was deemed complete by TLC, then cooled to room temperature and concentrated *in vacuo*. The resulting residue was purified by column chromatography (20% EtOAc in hexanes) to afford **3.13** as a white solid (93 mg, 88%).

^{1}H and ^{13}C NMR spectra were consistent with those previously reported.[12]



General Asymmetric Diels–Alder Procedure B.[17] A flame-dried 25 mL round bottom flask equipped with a stir bar was charged with **3.14** (300 mg, 1.65 mmol), $Eu(tfc)_3$ (79 mg, 0.089 mmol), dichloromethane (8 mL), and chloromethyl vinyl ether (1.30 mL, 12.77 mmol). The reaction mixture was stirred at room temperature until judged complete by TLC, then concentrated *in vacuo*, and purified by column chromatography (10% EtOAc in hexanes) to afford **3.29** as a white solid (438 mg, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.35 (s, 1H), 4.95 (s, 1H), 4.44 – 4.33 (m, 3H), 3.72 (dd, *J* = 7.1, 5.3 Hz, 2H), 3.51 (t, *J* = 5.6 Hz, 2H), 2.66 – 2.58 (m, 1H), 1.98 (s, 3H), 1.70 (d, *J* = 14.0 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR data not obtained due to time constraints resulting from COVID-19 shift work and this substrate not being used in the current forward route.

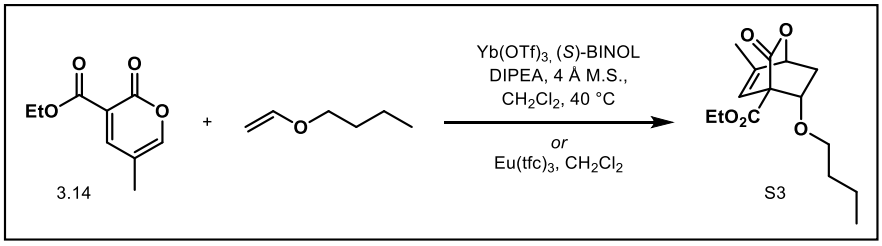
HRMS (ES+) *m/z* calculated for $C_{13}H_{17}ClO_5Na$ $[M+Na]^+$: 311.0662, 313.0638; found 311.0648, 313.0633.

X-Ray Crystal Structure: See Appendix D.

Dienoate 3.30. A microwave vial equipped with a stir bar was charged with **3.29** (10 mg, 0.035 mmol), a crystal of BHT (< 1 mg), and dichloroethane (3.5 mL). The reaction mixture was placed in a microwave and heated to 140 °C for 1 hour. The dichloroethane was removed *in vacuo* and the resulting residue was purified by column chromatography (20% EtOAc in hexanes) to afford a thin film (8 mg, 93%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.15 (s, 1H), 5.90 (d, *J* = 3.4 Hz, 1H), 4.42 (d, *J* = 6.8 Hz, 1H), 4.26 (qd, *J* = 7.1, 3.8 Hz, 2H), 3.78 – 3.70 (m, 2H), 3.61 – 3.51 (m, 2H), 2.76 (dd, *J* = 19.5, 5.7 Hz, 1H), 2.46 – 2.36 (m, 1H), 1.90 (s, 3H), 1.33 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR data not obtained due to time constraints resulting from COVID-19 shift work and this substrate not being used in the current forward route.

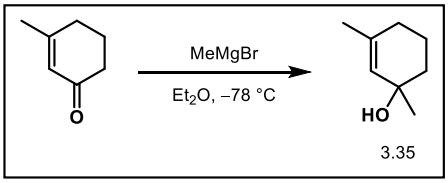


Bicycle S3. Pyrone **3.14** (10 mg, 0.055 mmol) was subjected to general asymmetric Diels–Alder procedure A to afford bicycle **S3** as a white solid (15 mg, 97%).

Bicycle S3. Pyrone **3.14** (5 mg, 0.027 mmol) was subjected to general asymmetric Diels–Alder procedure B to afford bicycle **S3** as a white solid (8 mg, 99%).

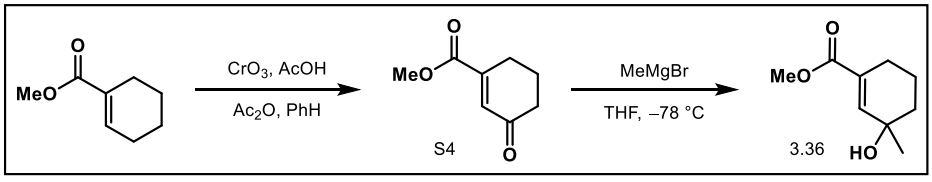
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.39 (s, 1H), 4.94 (s, 1H), 4.37 (dd, *J* = 12.9, 7.0 Hz, 3H), 3.48 (dt, *J* = 12.8, 6.5 Hz, 1H), 3.37 (dd, *J* = 15.9, 6.8 Hz, 1H), 2.60 – 2.52 (m, 1H), 1.97 (s, 3H), 1.63 (d, *J* = 13.8 Hz, 1H), 1.44 (d, *J* = 6.1 Hz, 2H), 1.36 (t, *J* = 7.1 Hz, 3H), 1.28 (dd, *J* = 14.6, 7.3 Hz, 2H), 0.87 (t, *J* = 7.4 Hz, 3H).

^{13}C NMR data not obtained due to time constraints resulting from COVID-19 shift work and this substrate not being used in the current forward route.



1,3-Dimethylcyclohex-2-en-1-ol 3.35. A flame-dried 250 mL round bottom flask equipped with a stir bar was charged with 3-methylcyclohexenone (2.00 g, 18.16 mmol) and diethyl ether (91 mL), then cooled to -78 °C. MeMgBr (3.0 M in diethyl ether, 7.26 mL) was added dropwise. After 1 hour, the reaction mixture was quenched with methanol (5 mL) then diluted with H_2O (100 mL). The organic phase was separated, and the aqueous phase was extracted with diethyl ether (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo* to yield a yellow oil (2.27 g, 99%).

^{1}H and ^{13}C NMR spectra were consistent with those previously reported.[43]



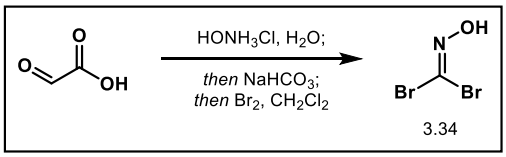
Methyl 3-oxocyclohex-1-ene-1-carboxylate S4. A 50 mL round bottom flask equipped with a stir bar was charged with methyl cyclohex-1-ene-1-carboxylate (500 mg, 3.57 mmol), benzene (5 mL), acetic acid (5.5 mL), acetic anhydride (2.75 mL), and chromium trioxide (1.11 g). When the

reaction was judged complete by TLC, it was quenched with 1 M NaOH, then extracted with diethyl ether (3 x 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (2 x 50 mL), dried over $MgSO_4$, then concentrated *in vacuo*. The resulting residue was purified by column chromatography (20% EtOAc in hexanes) to afford a yellow oil (213 mg, 39%). ^1H and ^{13}C NMR spectra were consistent with those previously reported.[44]

Methyl 3-hydroxy-3-methylcyclohex-1-ene-1-carboxylate 3.36. A 25 mL flame-dried round bottom flask equipped with a stir bar was charged with **S4** (213 mg, 1.38 mmol) and THF (7 mL), then cooled to −78 °C. MeMgBr (3.0 M in diethyl ether, 0.46 mL) was added dropwise. After 1 hour, the reaction mixture was quenched with methanol (1 mL) then diluted with H_2O (20 mL). The organic phase was separated, and the aqueous phase was extracted with diethyl ether (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (30% EtOAc in hexanes) to afford a clear oil (88 mg, 37%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.74 (s, 1H), 3.75 (s, 3H), 2.33 (dt, *J* = 18.2, 5.0 Hz, 1H), 2.17 (dt, *J* = 18.0, 5.7 Hz, 1H), 1.79 – 1.63 (m, 4H), 1.58 (s, 1H), 1.35 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.0, 142.9, 131.3, 68.4, 51.9, 37.2, 28.9, 24.5, 19.6.

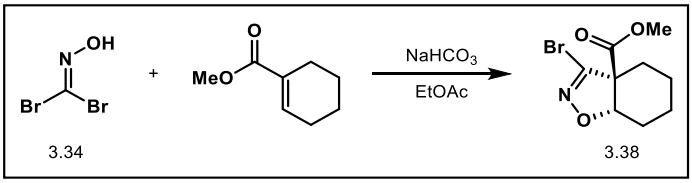


3.34

Dibromoaldoxime S-15. A 1 L round bottom flask was charged with glyoxalic acid (5.00 g, 54.32 mmol), hydroxylamine hydrochloride (3.77 g, 54.32 mmol), and H_2O (272 mL). The reaction mixture was stirred overnight, then $NaHCO_3$ (9.13 g, 108.64 mmol) was added carefully portionwise over 30 minutes. Dichloromethane (320 mL) was added, followed by Br_2 (5.43 mL). After vigorously stirring for an additional 3 hours, the reaction mixture was separated and the

aqueous phase was extracted with dichloromethane (3 x 300 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo* to afford a yellow-white solid (5.89 g, 53%).

^{1}H and ^{13}C NMR spectra were consistent with those previously reported.[45]

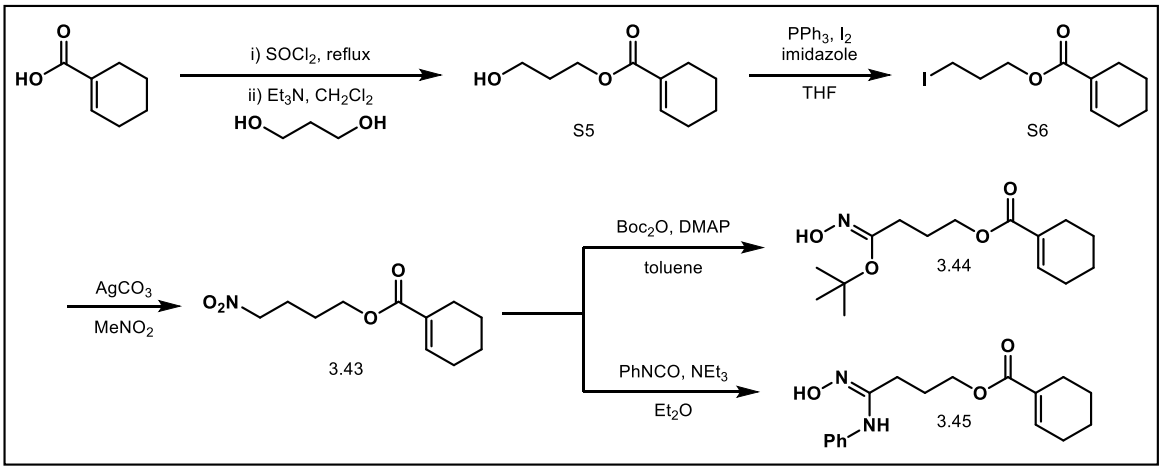


Bromoisoxazoline 3.38.[46] A flame-dried 1-dram vial equipped with a stir bar was charged with methyl cyclohex-1-ene-1-carboxylate (41 mg, 0.296 mmol), **3.34** (30 mg, 0.148 mmol), EtOAc (0.60 mL), then $NaHCO_3$ (25 mg, 0.296 mmol). Once the reaction was judged complete by TLC, the reaction mixture was diluted with H_2O (1 mL) and extracted with EtOAc (4 x 2 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (30% EtOAc in hexanes) to afford a clear oil (19 mg, 49%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 3.80 (s, 3H), 3.61 (t, *J* = 6.5 Hz, 1H), 2.03 (dd, *J* = 12.7, 7.5 Hz, 1H), 2.00 – 1.88 (m, 2H), 1.65 – 1.55 (m, 3H), 1.53 – 1.41 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.3, 144.9, 87.7, 77.4, 76.9, 53.2, 52.4, 28.2, 23.5, 19.6, 18.8.

HRMS (ES+) *m/z* calculated for $C_9H_{12}BrNO_3Na$ $[M+Na]^+$: 283.9898, 285.9879; found 283.9911, 285.9904.



3-Hydroxypropyl cyclohex-1-ene-1-carboxylate S5. A flame-dried 25 mL round bottom flask equipped with a stir bar was charged with cyclohex-1-ene-1-carboxylic acid (200 mg, 1.56 mmol) and $SOCl_2$ (2.28 mL) and stirred at reflux for 2 hours. After cooling to room temperature, the reaction mixture was diluted with benzene and concentrated *in vacuo*. This process was repeated twice more. The resulting residue was dissolved in dichloromethane (8 mL), then 1,3-propanediol (0.564 mL, 7.80 mmol) and Et_3N (0.239 mL, 1.72 mmol) were added by syringe. After stirring for 4 hours, the reaction was quenched with methanol (1 mL) and diluted with H_2O (20 mL). The phases were separated and the aqueous phase was extracted with dichloromethane (3 x 40 mL). The combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (40% EtOAc in hexanes) to afford a clear oil (230 mg, 50%).

^{1}H NMR (499 MHz, $CDCl_3$) δ 7.00 (s, 1H), 4.30 (t, *J* = 6.0 Hz, 2H), 3.71 (t, *J* = 6.0 Hz, 2H), 2.25 (d, *J* = 2.3 Hz, 2H), 2.19 (dd, *J* = 6.0, 2.9 Hz, 2H), 1.93 – 1.87 (m, 2H), 1.65 (dd, *J* = 11.8, 5.9 Hz, 2H), 1.60 (dd, *J* = 11.5, 5.7 Hz, 2H).

^{13}C NMR data not obtained due to time constraints resulting from COVID-19 shift work and this substrate not being used in the current forward route.

HRMS (ES+) *m/z* calculated for $C_{10}H_{16}O_3Na$ $[M+Na]^+$: 207.0997; found 207.0999.

3-Iodopropyl cyclohex-1-ene-1-carboxylate S6. A flame-dried 25 mL round bottom flask equipped with a stir bar was charged with **S5** (220 mg, 0.748 mmol), THF (5 mL), imidazole (102 mg, 1.50 mmol), triphenylphosphine (443 mg, 1.69 mmol), and I_2 (353 mg, 1.39 mmol), and the reaction mixture was stirred at room temperature. When deemed complete by TLC, the reaction was quenched with a saturated aqueous solution of sodium thiosulfate, and extracted with diethyl ether (3 x 30 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was filtered through a pad of silica (5% EtOAc in hexanes) and used in the next step without further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 4.20 (t, *J* = 6.0 Hz, 2H), 3.24 (t, *J* = 6.9 Hz, 2H), 2.25 (d, *J* = 1.9 Hz, 2H), 2.22 – 2.13 (m, 4H), 1.63 (ddd, *J* = 10.4, 9.2, 5.2 Hz, 4H).

^{13}C NMR data not obtained due to time constraints resulting from COVID-19 shift work and this substrate not being used in the current forward route.

HRMS (ES+) *m/z* calculated for $C_{10}H_{15}O_2INa$ $[M+Na]^+$: 317.0015; found 317.0027.

4-Nitrobutyl cyclohex-1-ene-1-carboxylate 3.43. A flame-dried 2-dram vial equipped with a stir bar was charged with **S6** (100 mg, 0.340 mmol), $MeNO_2$ (1.7 mL) and $AgCO_3$ (112 mg, 0.340 mmol) and stirred at room temperature. When the reaction was deemed complete by TLC, the reaction mixture was diluted with H_2O (10 mL) and extracted with dichloromethane (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (10% EtOAc in hexanes) to afford a yellow oil (57 mg, 74%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (s, 1H), 4.28 (t, *J* = 6.0 Hz, 2H), 3.69 (t, *J* = 5.9 Hz, 2H), 2.24 (s, 2H), 2.18 (d, *J* = 2.4 Hz, 2H), 1.92 – 1.86 (m, 2H), 1.67 – 1.55 (m, 4H), 1.25 (d, *J* = 7.5 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.1, 140.3, 130.3, 61.3, 59.4, 32.0, 25.9, 24.3, 22.2, 21.5.

4-(Tert-butoxy)-4-(hydroxyimino)butyl cyclohex-1-ene-1-carboxylate 3.44. A flame-dried 1-dram vial equipped with a stir bar was charged with **3.43** (19 mg, 0.084 mmol), toluene (0.7 mL), di-*tert*-butyl decarbonate (29 mg, 0.134 mmol), and DMAP (1 mg, 0.0084 mmol), and stirred for 4 hours. The reaction mixture was diluted with H_2O (2 mL) and extracted with EtOAc (4 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (20% EtOAc in hexanes) to afford a clear oil (17 mg, 71%).

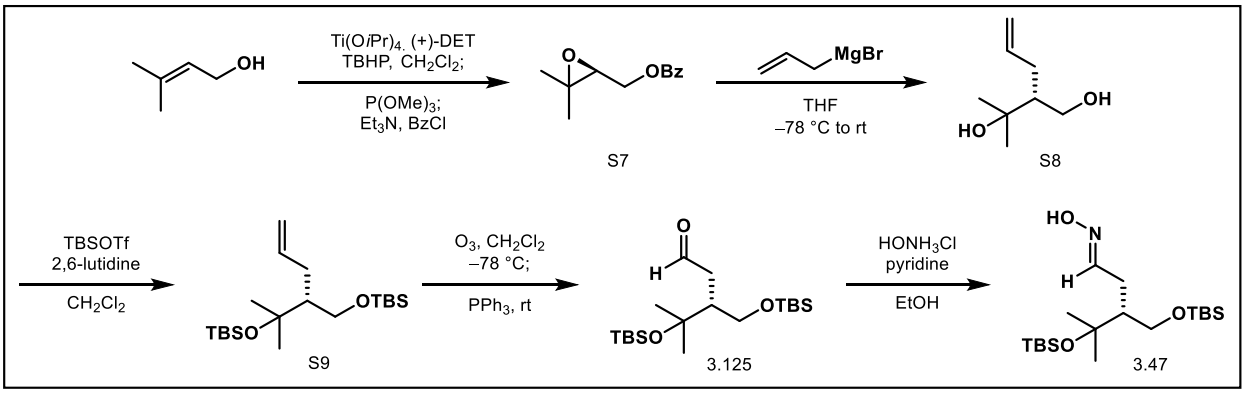
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.98 (s, 1H), 4.21 (t, *J* = 6.2 Hz, 2H), 4.16 (t, *J* = 6.4 Hz, 2H), 2.24 (d, *J* = 1.9 Hz, 2H), 2.18 (dd, *J* = 5.9, 2.7 Hz, 2H), 2.05 – 1.98 (m, 2H), 1.67 – 1.62 (m, 2H), 1.61 – 1.56 (m, 2H), 1.48 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 167.6, 153.6, 140.1, 130.3, 82.2, 64.0, 60.9, 28.3, 27.9, 25.9, 24.2, 22.2, 21.6.

4-(Hydroxyimino)-4-(phenylamino)butyl cyclohex-1-ene-1-carboxylate 3.45. A flame-dried 1-dram vial equipped with a stir bar was charged with **3.43** (10 mg, 0.044 mmol), phenyl isocyanate (0.005 mL, 0.044 mmol), Et_3N (0.006 mL, 0.044 mmol) and Et_2O (0.3 mL), and stirred for 4 hours. The reaction mixture was diluted with H_2O (2 mL) and extracted with EtOAc (4 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (30% EtOAc in hexanes) to afford a clear oil (9 mg, 68%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.38 (d, *J* = 7.2 Hz, 2H), 7.30 (t, *J* = 7.8 Hz, 2H), 7.06 (t, *J* = 7.3 Hz, 1H), 7.00 (s, 1H), 6.66 (br s, 1H), 4.30 – 4.22 (m, 4H), 2.29 – 2.22 (m, 2H), 2.20 – 2.14 (m, 2H), 2.08 – 2.02 (m, 2H), 1.67 – 1.62 (m, 2H), 1.62 – 1.56 (m, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 167.6, 140.2, 137.9, 130.3, 129.2, 123.6, 118.7, 60.9, 28.5, 25.9, 24.2, 22.2, 21.5.



Epoxide S7.[47] A flame-dried 1 L round bottom flask equipped with a stir bar was charged with oven-dried 4 Å molecular sieves (powder, 3.60 g) and flame-dried. Dichloromethane (240 mL) was added and the suspension was cooled to −40 °C. Next, $Ti(O^iPr)_4$ (3.54 mL, 12.0 mmol) (+)-diethyl tartrate (2.47 mL, 14.4 mmol), and *tert*-butyl hydroperoxide (22.4 mL of a 5.5 M solution in nonane) were added. After stirring for 45 minutes, 3-methylbut-2-en-1-ol (12.20 mL, 120.0 mmol) was added and the reaction mixture was stirred for 3 hours at −40 °C. Trimethyl phosphite (28.32 mL, 240 mmol) was added slowly to quench the reaction and the reaction mixture was warmed to −20 °C. Triethylamine (20.08 mL, 144.0 mmol) and benzoyl chloride (13.92 mL, 120 mmol) were added successively and the reaction mixture was allowed to warm to room temperature overnight. The reaction mixture was filtered through a pad of celite, and the fitrate was washed with a 10% aqueous solution of tartaric acid (100 mL), a saturated aqueous $NaHCO_3$ solution (100 mL), and a brine solution (100 mL). The organic phase was dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (5% EtOAc in hexanes) to afford a yellow oil (18.30 g, 74%).

^1H and ^{13}C NMR spectra were consistent with those previously reported.[47]

(*R*)-2-Allyl-3-methylbutane-1,3-diol 3.152. A flame-dried 1 L round bottom flask equipped with a stir bar was charged with **S7** (10.31 g, 50.0 mmol) and THF (200 mL) then cooled to −78 °C. Allylmagnesium bromide (200.0 mL of a 1.0 M solution in diethyl ether) was added dropwise *via*

addition funnel. After addition was complete, the reaction mixture was allowed to slowly warm to room temperature over 4 hours. The reaction was quenched with methanol (50 mL), then diluted with H_2O (200 mL) and extracted with EtOAc (4 x 200 mL). The combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (30 to 50% EtOAc in hexanes) to afford a clear oil (5.96 g, 83%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.85 – 5.76 (m, 1H), 5.04 (t, *J* = 14.5 Hz, 2H), 3.83 (dd, *J* = 11.3, 3.4 Hz, 1H), 3.74 (dd, *J* = 11.3, 7.2 Hz, 1H), 2.72 (s, 2H), 2.25 – 2.18 (m, 1H), 1.95 – 1.87 (m, 1H), 1.67 (ddd, *J* = 10.5, 7.1, 3.5 Hz, 1H), 1.32 (s, 3H), 1.22 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.5, 116.5, 74.7, 63.3, 49.0, 32.2, 30.0, 25.7.

HRMS (ES+) *m/z* calculated for $C_8H_{16}O_2Na$ $[M+Na]^+$: 167.1048; found 167.1045.

Silyl ether S8. A flame-dried 50 mL round bottom flask equipped with a stir bar was charged with **3.152** (575 mg, 3.99 mmol), dichloromethane (13 mL), and 2,6-lutidine (1.63 mL, 13.97 mmol), and cooled to 0 °C. TBSOTf (2.29 mL, 9.98 mmol) was added dropwise. When the reaction was deemed complete by TLC, the reaction was quenched with MeOH (2 mL), diluted with H_2O (50 mL) and extracted with diethyl ether (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting clear oil was purified by column chromatography (100% hexanes) to afford a clear oil (1.37 g, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 – 5.77 (m, 1H), 5.04 – 4.93 (m, 2H), 3.66 (d, *J* = 4.5 Hz, 2H), 2.34 – 2.27 (m, 1H), 2.08 (dt, *J* = 14.1, 8.8 Hz, 1H), 1.46 (td, *J* = 8.1, 4.3 Hz, 1H), 1.24 (s, 3H), 1.21 (s, 3H), 0.88 (s, 9H), 0.86 (s, 9H), 0.08 (s, 6H), 0.02 (s, 6H).

^{13}C NMR data not obtained due to time constraints resulting from COVID-19 shift work and this substrate not being used in the current forward route.

HRMS (ES+) *m/z* calculated for $C_{20}H_{44}O_2Si_2H$ $[M+H]^+$: 373.2958; found 373.2943.

Aldehyde 3.125. A 100 mL round bottom flask equipped with a stir bar was charged with **S8** (500 mg, 1.34 mmol) and dichloromethane (13 mL), then cooled to −78 °C. Ozone was bubbled through the solution until the solution turned blue, then bubbled for an additional 10 minutes. The solution was sparged with O_2 to remove any remaining dissolved ozone, then triphenylphosphine (422 mg, 1.61 mmol) was added. The reaction mixture was allowed to warm to room temperature overnight, then the reaction mixture was concentrated *in vacuo*. The resulting white solid was purified by column chromatography (1 to 2% EtOAc in hexanes) to afford a clear oil (487 mg, 97%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.73 (dd, *J* = 3.2, 1.2 Hz, 1H), 3.85 (dd, *J* = 9.8, 4.5 Hz, 1H), 3.49 (dd, *J* = 9.6, 8.8 Hz, 1H), 2.55 (ddd, *J* = 16.3, 4.0, 1.2 Hz, 1H), 2.40 (ddd, *J* = 16.3, 8.6, 3.3 Hz, 1H), 2.24 (dt, *J* = 8.6, 4.3 Hz, 1H), 1.23 (s, 3H), 1.20 (s, 3H), 0.86 (d, *J* = 8.1 Hz, 18H), 0.09 (d, *J* = 2.6 Hz, 6H), 0.02 (s, 6H).

^{13}C NMR data not obtained due to time constraints resulting from COVID-19 shift work and this substrate not being used in the current forward route.

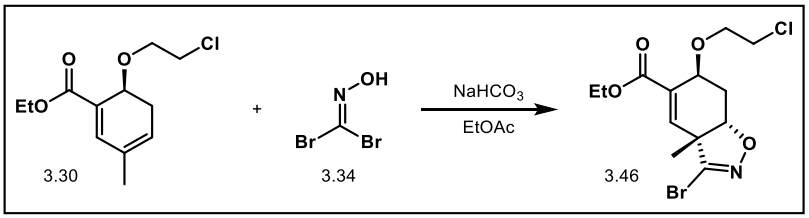
HRMS (ES+) *m/z* calculated for $C_{19}H_{42}O_3Si_2Na$ $[M+Na]^+$: 397.2570; found 397.2560.

Oxime 3.47.[20] A flame-dried 1-dram vial equipped with a stir bar was charged with **3.125** (93 mg, 0.248 mmol), hydroxylamine hydrochloride (22 mg, 0.323 mmol), pyridine (0.564 mL), and EtOH (1.5 mL). After stirring overnight, the reaction mixture was diluted with H_2O (2 mL) and extracted with EtOAc (4 x 2 mL). The combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (5 to 10% EtOAc in hexanes) to afford a clear oil (19 mg, 98%, 1:1 *Z*:*E*-*oxime*).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (t, *J* = 6.3 Hz, 0.5H), 6.88 (s, 0.5H), 3.79 (ddd, *J* = 27.4, 10.2, 4.4 Hz, 1H), 3.60 (ddd, *J* = 17.1, 10.2, 6.6 Hz, 1H), 2.66 – 2.57 (m, 0.5H), 2.45 (ddd, *J* = 11.7, 9.9, 6.1 Hz, 1H), 2.30 – 2.21 (m, 0.5H), 1.77 – 1.66 (m, 1H), 1.25 – 1.22 (m, 6H), 0.87 (d, *J* = 12.8 Hz, 18H), 0.08 (s, 6H), 0.04 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 153.3, 75.3, 63.3, 62.5, 50.1, 50.9, 29.9, 28.5, 28.4, 28.3, 28.3, 27.9, 26.1, 25.10, 18.3, 18.3, -1.9, -5.4, -5.4, -5.4.

HRMS (ES+) *m/z* calculated for $C_{19}H_{43}NO_3Si_2Na$ $[M+Na]^+$: 412.2679; found 412.2675.

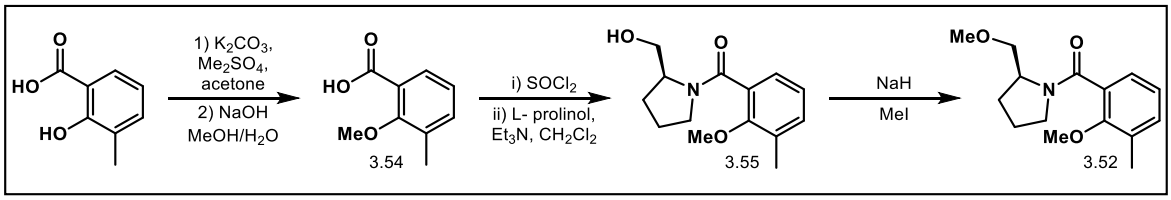


Bromoisoxazoline 3.46.[46] A flame-dried 1-dram vial equipped with a stir bar was charged with **3.30** (36 mg, 0.147 mmol), **3.34** (60 mg, 0.294 mmol), $NaHCO_3$ (49 mg, 0.588 mmol), and EtOAc (0.6 mL). Once the reaction was deemed complete by TLC, the reaction mixture was diluted with H_2O (2 mL) and extracted with EtOAc (5 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (10 to 20% EtOAc in hexanes) to afford a thin film (22 mg, 41%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.75 (s, 1H), 4.36 – 4.31 (m, 1H), 4.24 (q, *J* = 7.1 Hz, 2H), 3.88 (dt, *J* = 10.1, 6.8 Hz, 1H), 3.75 – 3.67 (m, 1H), 3.65 – 3.54 (m, 2H), 3.23 (dd, *J* = 5.6, 2.4 Hz, 1H), 2.57 (dd, *J* = 15.3, 2.2 Hz, 1H), 1.73 (ddd, *J* = 15.3, 5.5, 3.7 Hz, 1H), 1.62 (s, 3H), 1.32 (t, *J* = 7.1 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 165.6, 143.6, 138.6, 131.4, 82.8, 70.9, 67.4, 61.4, 52.5, 42.0, 25.4, 25.2, 14.3.

HRMS (ES+) *m/z* calculated for $C_{13}H_{17}$ $BrClNO_4Na$ $[M+Na]^+$: 366.0108, 368.0086; found 366.0114, 368.0082.



2-Methoxy-3-methylbenzoic acid 3.54. A flame-dried 250 mL round bottom flask equipped with a stir bar was charged with 3-methylsalicylic acid (1.00 g, 6.57 mmol), and freshly ground K_2CO_3 (3.63 g, 26.29 mmol). The minimum amount of acetone necessary to allow for stirring was added (~75 mL) and the slurry was stirred. Me_2SO_4 was added dropwise (2.49 mL, 26.28 mL) and the reaction was stirred until deemed complete by aliquot ^{1}H NMR. The reaction mixture was diluted with H_2O (200 mL) and extracted with diethyl ether (3 x 200 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting clear oil was dissolved in methanol (13 mL) and added dropwise to a stirred solution of NaOH (2.63 g, 65.7 mmol) in H_2O (5.5 mL). After full consumption of starting material was judged by TLC, the reaction mixture was acidified to pH 1, and extracted with EtOAc (3 x 200 mL). The combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo* to afford a white solid (1.08 g, 99%).

^{1}H and ^{13}C NMR spectra were consistent with those previously reported.[48]

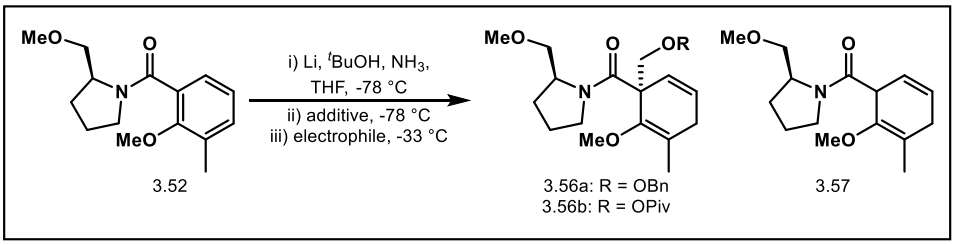
General Amidation/Esterification Procedure A. A flame-dried 250 mL round bottom flask equipped with a stir bar was charged with **3.54** (11.53 g, 69.38) and $SOCl_2$ (50 mL). The flask was equipped with a reflux condenser and the reaction mixture was heated to reflux for 3 hours. After cooling to room temperature, the reaction mixture was diluted with benzene (75 mL) and concentrated *in vacuo*. This process was repeated two more times. The resulting yellow oil was dissolved in benzene (30 mL) and added dropwise to a stirred solution of prolinol (13.55 ml, 138.8 mmol) and Et_3N (19.35 mL, 138.8 mmol) in dichloromethane (150 mL) at 0 °C. After stirring overnight, the reaction mixture was diluted with dichloromethane (150 mL) and washed with H_2O

(100 mL) and a brine solution (100 mL), then the phases were separated and the organic phase was dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (50 to 100% EtOAc in hexanes) to afford **3.55** as a viscous yellow oil (16.02 g, 92%).

3.55: ^{1}H and ^{13}C NMR spectra were consistent with those previously reported.[21]

(S)-(2-Methoxy-3-methylphenyl)(2-(methoxymethyl)pyrrolidin-1-yl)methanone 3.52. A flame-dried 100 mL round bottom flask equipped with a stir bar was charged with **3.55** (3.49 g, 14.0 mmol), MeI (15 mL), and cooled to 0 °C. NaH (645 mg, 16.8 mmol) was added in small portions. After full consumption of starting material as judged by TLC, the reaction was quenched with isopropylamine (15 mL), then acidified with 6 M HCl until pH <7.0 and extracted with EtOAc (3 x 200 mL). The combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (30 to 40% EtOAc in hexanes) to afford a yellow oil (2.93 g, 80%).

^{1}H and ^{13}C NMR spectra were consistent with those previously reported.[21]



Birch reduction/alkylation product 3.56A.[21] A flame-dried 100 mL round bottom flask equipped with a stir bar and cold-finger condenser was cooled to −78 °C and charged with ammonia (13 mL) followed by a solution of **3.52** (600 mg, 2.28 mmol) and *tert*-butanol (0.218 mL, 2.28 mmol) in THF (3.0 mL). Lithium metal (40 mg, 5.69 mmol) was added portionwise as small chunks. The reaction mixture was stirred for 10 minutes after turning blue, then BOMCl (0.951 mL, 6.84 mmol)

was added dropwise and the solution turned yellow rapidly. The reaction mixture was allowed to warm to reflux and was stirred for an additional 2 hours. The reaction was quenched with solid NH_4Cl (500 mg) and following evaporation of the ammonia, brine solution was added (50 mL) and it was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (15 to 30% EtOAc in hexanes) to afford **3.56A** as a clear oil (306 mg, 36%) and **3.57** as a clear oil (333 mg, 55%).

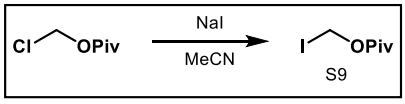
3.56A:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.28 (m, 4H), 7.24 – 7.22 (m, 1H), 5.88 (dt, *J* = 9.8, 3.4 Hz, 1H), 5.50 (dt, *J* = 9.8, 1.8 Hz, 1H), 4.56 (s, 2H), 4.30 – 4.27 (m, 1H), 4.03 (d, *J* = 9.7 Hz, 1H), 3.74 (d, *J* = 9.8 Hz, 1H), 3.57, (s, 3H), 3.54 (d, *J* = 3.2 Hz, 1H), 3.44 (t, *J* = 6.7 Hz, 2H), 3.33 (s, 3H), 3.31 – 3.30 (m, 1H), 3.29 (d, *J* = 5.3 Hz, 1H), 2.92 (d, *J* = 22.2 Hz, 1H), 2.62 (d, *J* = 22.3 Hz, 1H) 1.90 – 1.73 (m, 3H), 1.73 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 169.9, 145.9, 139.2, 128.2, 127.4, 127.3, 127.1, 126.4, 118.2, 73.2, 72.2, 60.6, 59.1, 58.0, 54.5, 46.0, 33.8, 26.6, 24.9, 16.1.

HRMS (ES+) calculated for $[M+Na]^+$: 408.2151 *m*/*z*; found 408.2141 *m*/*z*.

3.57: ^{1}H and ^{13}C NMR spectra were consistent with those previously reported.[21]



S9

Iodomethyl pivalate S9. A flame-dried 250 mL round bottom flask equipped with a stir bar was charged with MeCN (40 mL), chloromethyl pivalate (9.57 mL, 66.4 mmol), and NaI (11.94 g, 79.68 mmol) and stirred for 5 hours. The reaction mixture was filtered through a pad of celite (EtOAc as eluent) and concentrated *in vacuo*. The resulting mixture was taken up in dichloromethane (500 mL) and washed with a saturated aqueous solution of $Na_2S_2O_3$ (100 mL), then H_2O (100 mL),

then the organic phase was separated, dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo* to afford a yellow-orange oil (15.35 g, 96%). This material was used without further purification.

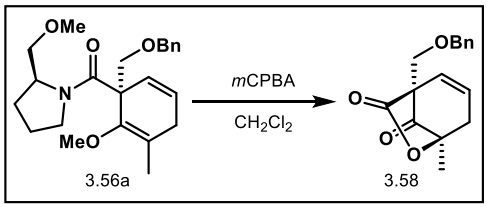
^1H and ^{13}C NMR spectra were consistent with those previously reported.[49]

General Birch reduction/alkylation procedure A.[21] A flame-dried 50 mL round bottom flask equipped with a stir bar and cold-finger condenser was cooled to −78 °C and charged with ammonia (2.4 mL) followed by a solution of **3.52** (100 mg, 0.380 mmol) and *tert*-butanol (0.036 mL, 0.380 mmol) in THF (0.5 mL). Lithium metal (7 mg, 0.95 mmol) was added portionwise as small chunks. The reaction mixture was stirred for 10 minutes after turning blue, then 1,3-pentadiene (0.075 mL, 0.76 mmol) was added until the reaction mixture turned from blue to yellow. Then, **S9** (276 mg, 1.14 mmol) was added dropwise. The reaction mixture was allowed to warm to reflux and was stirred for an additional 2 hours. The reaction was quenched with solid NH_4Cl (100 mg) and following evaporation of the ammonia, brine solution was added (20 mL) and it was extracted with EtOAc (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (15 to 30% EtOAc in hexanes) to afford **3.56B** as a clear oil (121 mg, 84%, >20:1 d.r.).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (dt, *J* = 9.9, 3.3 Hz, 1H), 5.45 (dt, *J* = 9.8, 1.8 Hz, 1H), 4.58 (d, *J* = 11.2 Hz, 1H), 4.42 (d, *J* = 11.2 Hz, 1H), 4.30 (dt, *J* = 10.8, 3.7 Hz, 1H), 3.61 (s, 3H), 3.54 (dd, *J* = 9.4, 3.1 Hz, 1H), 3.44 – 3.38 (m, 2H), 3.33 (s, 3H), 2.84 (d, *J* = 22.7 Hz, 1H), 2.66 (d, *J* = 22.6 Hz, 1H), 1.93 – 1.84 (m, 2H), 1.84 – 1.78 (m, 1H), 1.73 (s, 3H), 1.24 (s, 1H), 1.13 (s, 9H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 169.1, 145.3, 126.6, 126.3, 118.4, 72.2, 65.8, 60.8, 59.1, 58.1, 53.8, 46.0, 39.0, 33.8, 27.3, 27.2, 26.6, 25.0, 16.0.

HRMS (ES+) m/z calc'd for $C_{25}H_{32}O_3$ $[M + Na]^+$: 403.2249, found 403.2237.

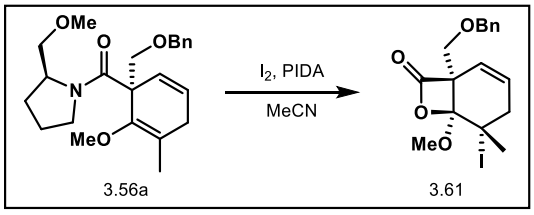


Lactone 3.58. A flame-dried 1-dram vial equipped with a stir bar was charged with **3.56A** (10 mg, 0.026 mmol), dichloromethane (0.3 mL), and *m*CPBA (7 mg, 0.029 mmol). After stirring for 4 hours, the reaction mixture was diluted with dichloromethane (10 mL), washed with H_2O (2 x 5 mL), then the organic phase was separated and dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (30% Et_2O in hexanes) to afford a thin film (1 mg, 10%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.36 (m, 4H), 7.32 – 7.29 (m, 1H), 6.06 – 6.02 (m, 2H), 4.74 (dd, *J* = 12.2, 9.3Hz, 1H), 4.65 (dd, *J* = 12.1, 9.7 Hz, 1H), 3.99 – 3.93 (m, 2H), 2.77 (s, 2H), 1.74 (s, 3H).

^{13}C NMR (125 MHz, $CDCl_3$) δ 168.5, 165.4, 137.4, 134.0, 128.7, 128.1, 128.1, 125.1, 81.1, 74.3, 69.9, 38.2, 23.9.

HRMS (ES+) calculated for hemiacetal of methanol $[M+Na]^+$: 327.1208 *m*/*z*; found 327.1207 *m*/*z*.

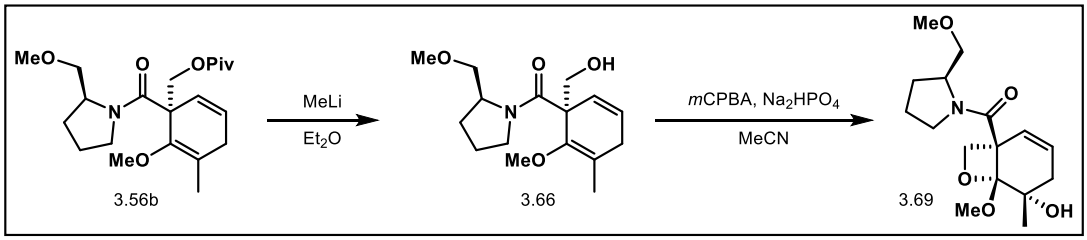


Iodide 3.61. A flame-dried 1-dram vial equipped with a stir bar was charged with **3.56A** (10 mg, 0.026 mmol), MeCN (0.2 mL), PIDA (10 mg, 0.026 mmol), and I_2 (8 mg, 0.026 mmol). After stirring for 10 hours, the reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$ and extracted with EtOAc (4 x 3 mL). The combined organic phases were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column

chromatography (10 to 100% EtOAc in hexanes in 10% increments) to afford a thin film (1 mg, 10%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (s, 14H), 4.90 (d, *J* = 5.1 Hz, 3H), 4.73 – 4.63 (m, 7H), 4.56 (d, *J* = 11.9 Hz, 3H), 4.06 (d, *J* = 10.2 Hz, 3H), 3.68 (d, *J* = 10.2 Hz, 3H), 3.56 (s, 9H), 2.73 (d, *J* = 18.8 Hz, 3H), 2.50 (d, *J* = 18.5 Hz, 3H), 1.68 (s, 9H).

^{13}C NMR data not obtained due to this substrate not being used in the current forward route.



Alcohol 3.66. A flame-dried 1-dram vial equipped with a stir bar was charged with **3.56B** (31 mg, 0.082 mmol) and Et_2O (0.8 mL), then cooled to 0 °C. Then, MeLi (0.103 mL of a 1.6 M solution in Et_2O) was added dropwise. After stirring for 2 hours, the reaction was quenched with MeOH (0.2 mL), diluted with H_2O (1.0 mL), and extracted with EtOAc (4 x 2 mL). The combined organic phases were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (40 to 50 to 100% EtOAc in hexanes) to afford a clear oil (16 mg, 66%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (dt, *J* = 9.9, 3.4 Hz, 1H), 5.75 (dt, *J* = 9.9, 1.9 Hz, 1H), 4.35 – 4.28 (m, 1H), 4.20 (d, *J* = 10.6 Hz, 1H), 3.60 (s, 3H), 3.58 – 3.53 (m, 2H), 3.45 – 3.36 (m, 3H), 3.34 (s, 3H), 2.87 (d, *J* = 22.6 Hz, 1H), 2.66 (d, *J* = 21.7 Hz, 1H), 1.94 – 1.86 (m, 2H), 1.86 – 1.80 (m, 1H), 1.80 – 1.74 (m, 1H), 1.72 (s, 3H).

^{13}C NMR data not obtained due to this substrate not being used in the current forward route.

HRMS (ES+) *m/z* calculated for $C_{16}H_{25}NO_4Na$ $[M+Na]^+$: 318.1681; found 318.1696.

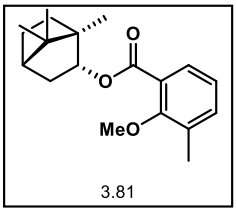
Bicycle 3.69.[25] A flame-dried 25 mL round bottom flask equipped with a stir bar was charged with **3.66** (200 mg, 0.677 mmol), MeCN (7 mL), Na_2HPO_4 (384 mg, 2.71 mmol), and *m*CPBA (184 mg, 1.064 mmol). After stirring overnight, the reaction mixture was filtered through a pad of celite and concentrated *in vacuo*. The resulting residue was dissolved in EtOAc (100 mL), washed with a saturated solution of $NaHSO_3$ (50 mL), and the phases were separated. The aqueous phase was extracted with EtOAc (2 x 100 mL), then the combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (50% EtOAc in hexanes) to afford a white solid (174 mg, 84%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.92 (dd, *J* = 10.1, 3.3 Hz, 1H), 5.81 – 5.72 (m, 1H), 4.57 (d, *J* = 5.0 Hz, 1H), 4.05 – 3.97 (m, 1H), 3.63 (d, *J* = 5.0 Hz, 3H), 3.37 – 3.30 (m, 4H), 3.23 (dd, *J* = 9.3, 6.2 Hz, 1H), 3.18 (d, *J* = 13.5 Hz, 1H), 2.96 (dt, *J* = 9.9, 5.0 Hz, 1H), 2.74 – 2.65 (m, 1H), 2.61 (d, *J* = 13.5 Hz, 2H), 2.34 – 2.28 (m, 1H), 2.19 (dd, *J* = 16.1, 6.8 Hz, 1H), 1.90 – 1.82 (m, 1H), 1.72 – 1.65 (m, 2H), 1.14 (s, 3H).

^{13}C NMR data not obtained due to this substrate not being used in the current forward route.

HRMS (ES+) *m/z* calculated for $C_{16}H_{25}NO_5Na$ $[M+Na]^+$: 312.1811; found 312.1802.

X-Ray Crystal Structure: See Appendix D.



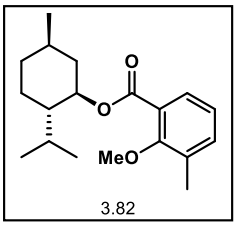
3.81

(–)-Borneol ester 3.81. Carboxylic acid **3.54** (100 mg, 0.602 mmol) was subjected to general esterification procedure A to afford ester **3.81** as a clear oil (175 mg, 96%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.07 (ddd, *J* = 7.7, 4.7, 1.7 Hz, 1H), 5.14 (d, *J* = 9.6 Hz, 1H), 3.88 – 3.80 (m, 3H), 2.50 (td, *J* = 10.2, 5.1 Hz, 1H), 2.34 (s, 3H), 2.12 (td, *J* = 9.7, 4.7 Hz, 1H), 1.85 – 1.76 (m, 1H), 1.74 (t, *J* = 3.6 Hz, 1H), 1.43 – 1.34 (m, 1H), 1.30 (ddd, *J* = 14.7, 10.8, 3.7 Hz, 2H), 1.15 (s, 1H), 0.98 (s, 3H), 0.95 – 0.90 (m, 6H).

^{13}C NMR data not obtained due to this substrate not being used in the current forward route.

HRMS (ES+) *m/z* calculated for $C_{19}H_{26}O_3Na$ $[M+Na]^+$: 325.1780; found 325.1794.



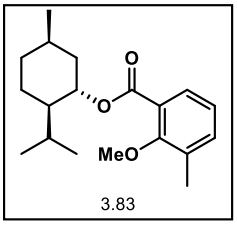
3.82

(–)-Menthol ester 3.82. Carboxylic acid **3.54** (100 mg, 0.602 mmol) was subjected to general esterification procedure A to afford ester **3.82** as a clear oil (180 mg, 98%).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.32 (d, *J* = 6.7 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 4.96 (td, *J* = 10.9, 4.4 Hz, 1H), 3.83 (d, *J* = 3.5 Hz, 3H), 2.32 (s, 3H), 2.21 – 2.11 (m, 1H), 2.04 (dtd, *J* = 13.9, 7.0, 2.7 Hz, 1H), 1.77 – 1.68 (m, 2H), 1.50 (dd, *J* = 8.6, 5.7 Hz, 1H), 1.20 – 1.03 (m, 2H), 0.93 (t, *J* = 6.8 Hz, 5H), 0.82 (d, *J* = 6.9 Hz, 3H).

^{13}C NMR data not obtained due to this substrate not being used in the current forward route.

HRMS (ES+) *m/z* calculated for $C_{19}H_{28}O_3Na$ $[M+Na]^+$: 327.1936; found 327.1933.



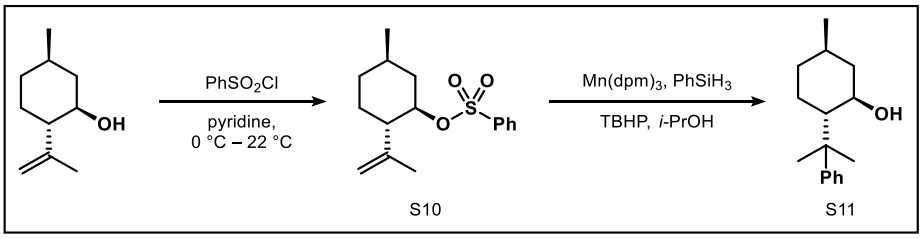
3.83

(+)-Isomenthol ester 3.83. Carboxylic acid **3.54** (100 mg, 0.602 mmol) was subjected to general esterification procedure A to afford ester **3.83** as a clear oil (182 mg, 99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 5.31 (dd, *J* = 6.5, 3.1 Hz, 1H), 3.83 (s, 3H), 2.32 (s, 3H), 1.97 (ddd, *J* = 10.8, 7.2, 3.3 Hz, 1H), 1.86 (dd, *J* = 13.6, 6.8 Hz, 1H), 1.78 – 1.67 (m, 2H), 1.66 – 1.55 (m, 2H), 1.54 (s, 2H), 1.49 (d, *J* = 4.1 Hz, 2H), 1.28 (ddd, *J* = 13.2, 8.5, 3.5 Hz, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR data not obtained due to this substrate not being used in the current forward route.

HRMS (ES+) *m/z* calculated for $C_{19}H_{28}O_3Na$ $[M+Na]^+$: 327.1936; found 327.1953.

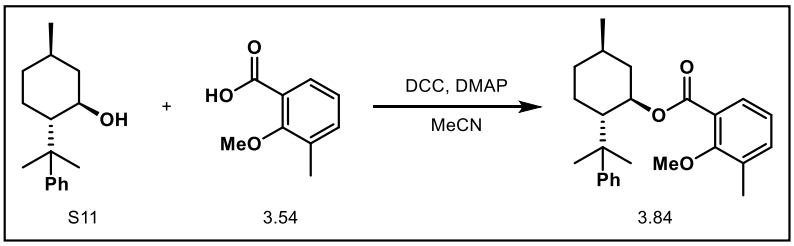


Sulfonate S10. (–)-8-phenylmenthol was prepared according to the procedure developed by Shenvi and coworkers. A flame-dried 100 mL round bottom flask equipped with a stir bar was charged with (–)-isopulegol (2.54 mL, 15.00 mmol) and pyridine (19 mL), then cooled to 0 °C. $PhSO_2Cl$ (2.30 mL, 18.00 mmol) was added dropwise to the stirring solution. After stirring overnight, the reaction mixture was diluted with ice water and the precipitate was collected by filtration to afford **S10** as a pink-white solid (4.36 g, 99%).

^1H and ^{13}C NMR spectra were consistent with those previously reported.[34]

(–)-8-Phenylmenthol S11. A flame-dried 500 mL round bottom flask equipped with a stir bar was charged with **S10** (4.36 g, 14.81 mmol) and $Mn(OAc)_3{\cdot}H_2O$ (3.97 g, 14.81 mmol) and evacuated/back-filled with argon (3x). Degassed isopropanol (150 mL), 2,2,6,6-tetramethylheptane-3,5-dione (0.620 mL, 2.96 mmol), TBHP (5.39 mL of a 5.5 M solution in nonane), and $PhSiH_3$ (1.92 mL) were added in succession. After stirring for 24 hours, the reaction mixture was diluted with H_2O (300 mL), extracted with EtOAc (4 x 300 mL), and the combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (10% EtOAc in hexanes) to afford a viscous clear oil (2.37 g, 69%).

^1H and ^{13}C NMR spectra were consistent with those previously reported.[34]

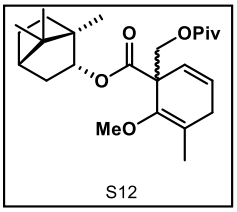


(–)-8-Phenylmenthol ester 3.84. A flame-dried 25 mL round bottom flask equipped with a stir bar was charged with **3.54** (668 mg, 4.02 mmol), MeCN (5 mL), (–)-8-phenylmenthol (467 mg, 2.01 mmol), DMAP (368 mg, 3.02 mmol), and DCC (622 mg, 3.02 mmol). After stirring for 24 hours, the reaction mixture was filtered through a pad of celite (using EtOAc as eluent) and concentrated *in vacuo*. The resulting residue was purified by column chromatography (5% EtOAc in hexanes to afford a clear oil (658 mg, 86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, *J* = 4.1 Hz, 3H), 7.15 (t, *J* = 7.7 Hz, 2H), 7.09 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.00 (t, *J* = 7.3 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 5.09 (td, *J* = 10.7, 4.4 Hz, 1H), 3.79 (s, 3H), 2.29 (s, 3H), 2.15 – 2.02 (m, 2H), 1.68 – 1.58 (m, 2H), 1.53 (ddd, *J* = 8.4, 6.1, 3.0 Hz, 1H), 1.34 (s, 3H), 1.26 (s, 3H), 1.18 – 1.05 (m, 2H), 0.88 (dd, *J* = 6.8, 4.8 Hz, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 158.6, 151.4, 134.9, 132.6, 129.3, 128.1, 125.6, 125.2, 125.1, 123.3, 75.1, 61.6, 50.7, 42.0, 40.1, 34.8, 31.5, 27.1, 26.9, 26.8, 22.0, 16.1.

HRMS (ES+) m/z calc'd for $C_{25}H_{32}O_3$ $[M + Na]^+$: 403.2249, found 403.2237.

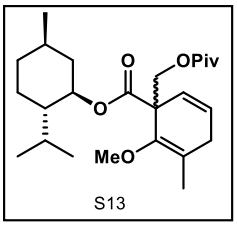


Birch reduction/alkylation product S12. Ester **3.81** (90 mg, 0.296 mmol) was subjected to general Birch reduction/alkylation procedure A to afford **S12** as a clear oil (76 mg, 61%, 1.2:1 d.r.).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dq, *J* = 10.0, 3.4 Hz, 1H), 5.51 (ddt, *J* = 9.8, 3.7, 1.9 Hz, 1H), 4.91 – 4.84 (m, 1H), 4.62 (dd, *J* = 10.9, 4.9 Hz, 1H), 4.32 (dd, *J* = 10.8, 7.3 Hz, 1H), 3.63 (d, *J* = 4.7 Hz, 3H), 2.82 (d, *J* = 22.2 Hz, 1H), 2.70 (d, *J* = 22.2 Hz, 1H), 2.34 (dt, *J* = 13.8, 4.1 Hz, 1H), 1.93 – 1.85 (m, 1H), 1.76 (d, *J* = 3.2 Hz, 3H), 1.75 – 1.69 (m, 1H), 1.67 (t, *J*

= 4.5 Hz, 1H), 1.27 (dt, *J* = 22.0, 13.4 Hz, 3H), 1.14 (s, 9H), 0.89 (d, *J* = 1.3 Hz, 3H), 0.86 (s, 3H), 0.81 (d, *J* = 3.1 Hz, 3H).

^{13}C NMR data not obtained due to this substrate not being used in the current forward route.

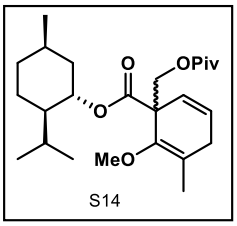


S13

Birch reduction/alkylation product S13. Ester **3.82** (90 mg, 0.296 mmol) was subjected to general Birch reduction/alkylation procedure A to afford **S13** as a clear oil (35 mg, 28%, 1.1:1 d.r.).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 9.2, 6.2, 3.3 Hz, 1H), 5.48 (d, *J* = 9.8 Hz, 1H), 4.71 – 4.62 (m, 1H), 4.58 (dd, *J* = 19.7, 10.9 Hz, 1H), 4.28 (dd, *J* = 18.2, 10.9 Hz, 1H), 3.64 (s, 3H), 2.80 (d, *J* = 22.4 Hz, 1H), 2.68 (d, *J* = 22.8 Hz, 1H), 1.99 (d, *J* = 12.0 Hz, 1H), 1.93 – 1.83 (m, 1H), 1.75 (d, *J* = 4.0 Hz, 3H), 1.67 (d, *J* = 11.3 Hz, 2H), 1.52 – 1.45 (m, 1H), 1.41 (dd, *J* = 20.0, 7.1 Hz, 2H), 1.13 (d, *J* = 2.2 Hz, 9H), 0.99 (ddd, *J* = 18.8, 16.3, 9.8 Hz, 2H), 0.89 (dd, *J* = 11.6, 4.8 Hz, 6H), 0.76 – 0.70 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.11, 178.08, 171.3, 171.2, 146.4, 146.3, 127.3, 127.1, 125.83, 125.81, 118.1, 117.9, 75.53, 75.52, 66.0, 64.6, 61.2, 61.1, 54.2, 54.1, 47.1, 40.8, 40.7, 38.9, 34.37, 34.35, 33.53, 33.49, 31.52, 31.50, 27.2, 26.2, 26.2, 23.5, 22.1, 20.9, 20.9, 16.3, 16.3, 15.4.

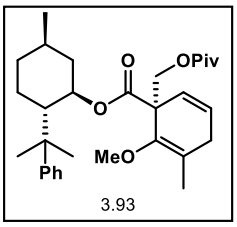


S14

Birch reduction/alkylation product S14. Ester **3.83** (90 mg, 0.296 mmol) was subjected to general Birch reduction/alkylation procedure A to afford **S14** as a clear oil (102 mg, 82%, 1.2:1 d.r.).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 – 5.82 (m, 1H), 5.50 (dd, *J* = 9.8, 2.0 Hz, 1H), 5.09 – 5.02 (m, 1H), 4.61 (dd, *J* = 10.8, 6.3 Hz, 1H), 4.31 (dd, *J* = 10.8, 8.3 Hz, 1H), 3.63 (s, 3H), 2.81 (d, *J* = 22.4 Hz, 1H), 2.69 (d, *J* = 21.6 Hz, 1H), 1.83 (dd, *J* = 11.0, 6.9 Hz, 1H), 1.76 (s, 3H), 1.75 – 1.69 (m, 1H), 1.44 (ddd, *J* = 13.3, 6.9, 3.8 Hz, 3H), 1.37 – 1.25 (m, 3H), 1.13 (s, 9H), 0.94 – 0.89 (m, 6H), 0.85 (d, *J* = 6.7 Hz, 3H).

^{13}C NMR data not obtained due to this substrate not being used in the current forward route.



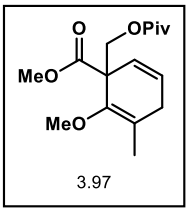
3.93

Birch reduction/alkylation product 3.93. A flame-dried 100 mL round bottom flask equipped with a stir bar and cold-finger condenser was cooled to −78 °C and charged with ammonia (7.5 mL) followed by a solution of **3.84** (250 mg, 0.657 mmol) and *tert*-butanol (0.063 mL, 0.657 mmol) in THF (7.5 mL). Lithium metal (11 mg, 1.64 mmol) was added portionwise as small chunks. The reaction mixture was stirred for 10 minutes after turning blue, then 1,3-pentadiene (0.129 mL, 1.31 mmol) was added until the reaction mixture turned from blue to yellow. Then, **S9** (477 mg, 1.97 mmol) was added dropwise. The reaction mixture was allowed to warm to reflux and was stirred for an additional 2 hours. The reaction was quenched with solid NH_4Cl (250 mg) and following evaporation of the ammonia, brine solution was added (50 mL) and it was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (5% EtOAc in hexanes) to afford **3.84** as a clear oil (259 mg, 80%, 7:1 d.r.).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 6.4 Hz, 4H), 7.11 (tt, *J* = 5.5, 2.2 Hz, 1H), 5.91 (dt, *J* = 9.9, 3.6 Hz, 1H), 5.39 (dt, *J* = 9.9, 2.1 Hz, 1H), 4.84 – 4.73 (m, 2H), 4.38 (d, *J* = 10.7 Hz, 1H), 4.18 (d, *J* = 10.7 Hz, 1H), 3.44 (s, 3H), 2.90 – 2.72 (m, 2H), 1.92 – 1.79 (m, 2H), 1.44 (dt, *J* = 12.8, 3.3 Hz, 1H), 1.36 (td, *J* = 13.1, 6.7 Hz, 1H), 1.26 (s, 3H), 1.20 (s, 3H), 1.09 (s, 9H), 0.93 – 0.82 (m, 3H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.68 (qd, *J* = 12.8, 3.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 170.6, 150.62, 150.59, 128.2, 127.6, 126.0, 125.5, 124.7, 94.5, 77.4, 76.6, 64.9, 54.2, 52.4, 50.4, 41.6, 40.4, 38.9, 34.6, 31.4, 30.0, 27.5, 27.3, 26.6, 23.6, 21.9.

HRMS (ES+) m/z calc'd for $C_{30}H_{42}O_5Na$ $[M + Na]^+$: 483.3110, found 483.3108.

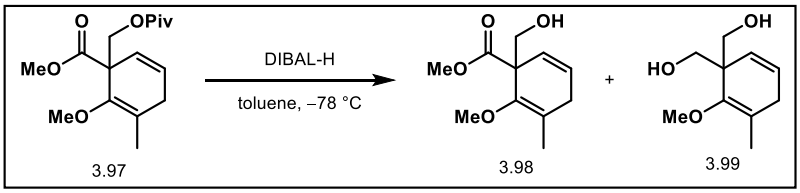


3.97

Birch reduction/alkylation product 3.97. Methyl 2-methoxy-3-methylbenzoate (1.85 g, 10.27 mmol) was subjected to general Birch reduction/alkylation procedure A to afford **3.97** as a clear oil (2.74 g, 90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.87 (dd, *J* = 8.3, 4.9 Hz, 1H), 5.51 (dt, *J* = 9.8, 1.9 Hz, 1H), 4.58 (d, *J* = 10.9 Hz, 1H), 4.28 (d, *J* = 10.9 Hz, 1H), 3.72 (s, 3H), 3.62 (s, 3H), 2.82 (d, *J* = 22.3 Hz, 1H), 2.71 (d, *J* = 22.3 Hz, 1H), 1.76 (s, 3H), 1.13 (s, 9H).

^{13}C NMR data not obtained due to this substrate not being used in the current forward route.



3.97 3.98 3.99

Reduction of 3.97. A flame-dried 1-dram vial equipped with a stir bar was charged with **3.97** (50 mg, 0.170 mmol) and toluene (0.85 mL), then cooled to –78 °C. Then, DIBAL-H (0.061 mL, 0.340 mmol) was added dropwise. After stirring for 3.5 hours, the reaction was quenched with MeOH (0.2 mL) and stirred with a saturated aqueous solution of Rochelle's salt (3 mL) for 30 minutes. The reaction mixture was diluted with EtOAc (10 mL), separated, and the aqueous phase was extracted with EtOAc (3 x 10 mL). The combined organic extracts were then dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (10 to 30 to 50% EtOAc in hexanes) to afford **3.98** as a clear oil (9 mg, 25%) and **3.99** as a clear oil (14 mg, 45%).

3.99:

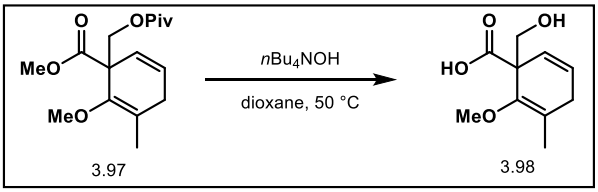
^{1}H NMR (500 MHz, $CDCl_3$) δ 5.93 (dt, *J* = 9.7, 3.3 Hz, 1H), 5.60 (d, *J* = 9.8 Hz, 1H), 3.92 (d, *J* = 10.9 Hz, 1H), 3.85 (d, *J* = 10.0 Hz, 1H), 3.73 (s, 3H), 3.66 (s, 3H), 2.84 (d, *J* = 22.4 Hz, 1H), 2.74 (d, *J* = 22.0 Hz, 1H), 1.77 (s, 3H).

^{13}C NMR data not obtained due to this substrate not being used in the current forward route.

3.99:

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.00 (dt, *J* = 9.9, 3.3 Hz, 1H), 5.37 (d, *J* = 9.9 Hz, 1H), 3.73 (d, *J* = 8.9 Hz, 5H), 3.50 (d, *J* = 10.7 Hz, 2H), 2.76 (s, 2H), 1.76 (s, 3H).

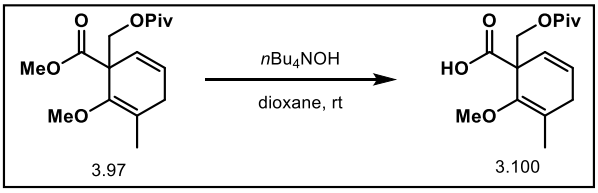
^{13}C NMR data not obtained due to this substrate not being used in the current forward route.



Carboxylic acid 3.98. A 1-dram vial equipped with a stir-bar was charged with **3.97** (20 mg, 0.067 mmol), dioxane (0.3 mL), and *n*Bu_4NOH (0.232 mL of a 40% w/w solution in H_2O) and was stirred at 50 °C for 12 hours. The reaction mixture was acidified to pH 1, extracted with EtOAc (4 x 3 mL), and the combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting white powder was purified by column chromatography (50% EtOAc, 1% AcOH in hexanes) to afford a white powder (12 mg, 90%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (dd, *J* = 6.8, 2.9 Hz, 1H), 5.63 (d, *J* = 9.8 Hz, 1H), 3.94 – 3.85 (m, 2H), 3.72 (d, *J* = 1.7 Hz, 3H), 2.79 (dd, *J* = 52.1, 22.5 Hz, 2H), 1.77 (s, 3H).

^{13}C NMR data not obtained due to this substrate not being used in the current forward route.

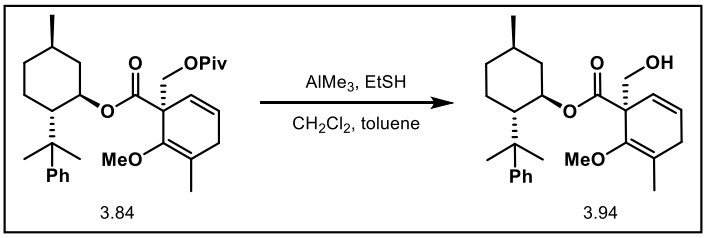


Carboxylic acid 3.100. A 1-dram vial equipped with a stir-bar was charged with **3.97** (23 mg, 0.067 mmol), dioxane (0.3 mL), and nBu_4NOH (0.232 mL of a 40% w/w solution in H_2O) and was stirred at room temperature for 12 hours. The reaction mixture was acidified to pH 1, extracted with EtOAc (4 x 3 mL), and the combined organic extracts were dried over Na_2SO_4, filtered

through cotton, and concentrated *in vacuo*. The resulting white powder was purified by column chromatography (50% EtOAc, 1% AcOH in hexanes) to afford a white powder (21 mg, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (dd, *J* = 6.5, 3.2 Hz, 1H), 5.56 (d, *J* = 9.6 Hz, 1H), 4.57 (d, *J* = 10.7 Hz, 1H), 4.27 (d, *J* = 10.9 Hz, 1H), 3.68 (s, 3H), 2.77 (q, *J* = 22.5 Hz, 2H), 1.14 (s, 9H).

^{13}C NMR data not obtained due to this substrate not being used in the current forward route.

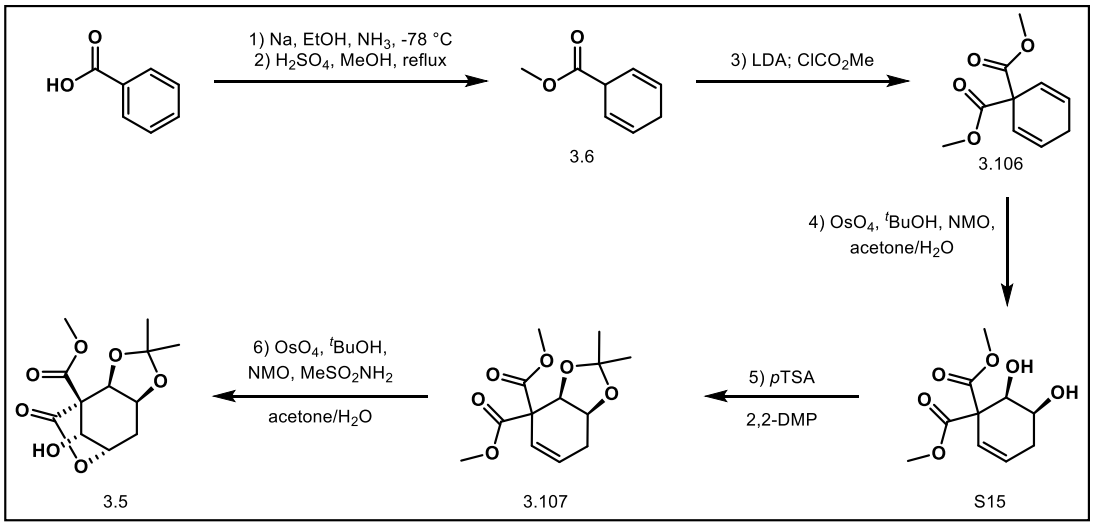


3.84 3.94

Alcohol 3.94.[50] A flame-dried 1-dram vial equipped with a stir bar was charged with dichloromethane (0.1 mL), toluene (0.2 mL), and $AlMe_3$ (0.026 mL, 0.272 mmol) and cooled to 0 °C. EtSH (0.020 mL, 0.272 mmol) was added dropwise and gas evolution was observed. A solution of **3.84** (45 mg, 0.091 mmol) in dichloromethane (0.1 mL) and toluene (0.1 mL) was added dropwise. After stirring for 4.5 hours, the reaction was quenched with MeOH (0.1 mL), then diluted with a saturated aqueous solution of Rochelle's salt (0.3 mL) and extracted with EtOAc (4 x 3 mL). The combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography to afford a clear oil (26 mg, 70%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (t, *J* = 5.7 Hz, 4H), 7.17 (d, *J* = 3.8 Hz, 1H), 5.95 – 5.88 (m, 1H), 5.40 (d, *J* = 9.9 Hz, 1H), 4.81 (td, *J* = 10.5, 3.9 Hz, 1H), 3.76 (d, *J* = 15.1 Hz, 1H), 3.69 (s, 3H), 3.63 (d, *J* = 10.8 Hz, 1H), 2.76 (q, *J* = 22.2 Hz, 2H), 2.04 – 1.91 (m, 3H), 1.73 (s, 3H), 1.63 – 1.47 (m, 3H), 1.31 (s, 3H), 1.23 (s, 3H), 0.97 (dd, *J* = 20.4, 12.7 Hz, 3H), 0.85 (d, *J* = 6.4 Hz, 3H).

^{13}C NMR data not obtained due to this substrate not being used in the current forward route.



Methyl cyclohexa-2,5-diene-1-carboxylate 3.6.[51, 52] A flame-dried 3-necked 1 L round bottom flask was equipped with a cold-finger condenser and a mechanical stirring apparatus. NH_3 was condensed (~200 mL) followed by addition of benzoic acid (5.24 g, 43.0 mmol) and EtOH (30 mL). Sodium metal (3.68 g, 160 mmol) was added portionwise over 1 hour. After stirring for 6 hours, the reaction was quenched with solid NH_4Cl (8.20 g, 153.3 mmol) added portionwise over 30 minutes. Following evaporation of the ammonia by gentle warming in an ice bath, the resulting suspension was poured into ice, acidified to pH 1, and extracted with Et_2O (4 x 300 mL). The combined organic extracts were washed with brine (200 mL), dried over Na_2SO_4, filtered through cotton and concentrated *in vacuo*. The resulting residue was then dissolved in MeOH (30 mL) and concentrated H_2SO_4 was added slowly (2.4 mL). After stirring for 4 hours, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with Et_2O (3 x 200 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (1 to 5 % EtOAc in hexanes) to afford a clear oil (4.65 g, 78%).

^1H and ^{13}C NMR spectra were consistent with those previously reported.[51]

Dimethyl cyclohexa-2,5-diene-1,1-dicarboxylate 3.106. A flame-dried 50 mL round bottom flask equipped with a stir bar was charged with THF (7 mL) and DIPA (0.507 mL, 3.62 mmol), and cooled to −78 °C. Then, *n*BuLi (1.45 mL of a 2.5 M solution in THF) was added dropwise and the reaction mixture was stirred for 15 minutes at −78 °C. A solution of **3.6** (500 mg, 3.62 mmol) in THF (2 mL) was added dropwise and the reaction mixture was stirred for 15 minutes. Methyl chloroformate (0.308 mL, 3.98 mmol) was added dropwise at −78 °C. After stirring for 15 minutes, the reaction was quenched with saturated aqueous NH_4Cl (5 mL), then diluted with H_2O (50 mL) and extracted with Et_2O (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (0 to 2 % EtOAc in hexanes) to afford a clear oil (610 mg, 86%).

^1H and ^{13}C NMR spectra were consistent with those previously reported.[53]

Diol S15. A 1-dram vial equipped with a stir bar was charged with **3.106** (100 mg, 0.510 mmol), acetone (1.3 mL), H_2O (0.4 mL), OsO_4 (518 mg of a 2.5 wt% solution in *tert*-butanol), and NMO (131 mg, 1.12 mmol). After stirring for 2 hours, the reaction was quenched with saturated aqueous $NaHSO_3$ (5 mL), diluted with H_2O (20 mL) and extracted with EtOAc (5 x 50 mL). The combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (70% EtOAc in hexanes) to afford a clear oil (110 mg, 94%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 5.93 – 5.86 (m, 1H), 5.82 (d, *J* = 10.5 Hz, 1H), 4.52 (s, 1H), 4.15 (s, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 2.38 (dt, *J* = 17.7, 5.2 Hz, 1H), 2.28 – 2.21 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 170.1, 169.4, 128.6, 121.6, 71.6, 67.2, 60.7, 53.3, 53.2, 29.6.

Acetal 3.107. A flame-dried 1-dram vial equipped with a stir bar was charged with **S15** (110 mg, 0.478 mmol), 2,2-dimethoxypropane (0.7 mL), and *p*TSA (5 mg, 0.026 mmol). After stirring

overnight, the reaction was quenched with saturated aqueous $NaHCO_3$ (5 mL) and extracted with Et_2O (5 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (5 to 10% EtOAc in hexanes) to afford a clear oil (97 mg, 75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.21 (ddd, *J* = 9.7, 3.0, 1.1 Hz, 1H), 5.99 (ddd, *J* = 9.4, 7.1, 1.9 Hz, 1H), 5.05 (dd, *J* = 7.0, 1.1 Hz, 1H), 4.77 – 4.71 (m, 1H), 3.80 (s, 3H), 3.67 (s, 3H), 2.36 (ddd, *J* = 17.1, 7.0, 1.6 Hz, 1H), 2.27 – 2.17 (m, 1H), 1.31 (s, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 168.6, 168.1, 128.9, 123.8, 108.6, 76.6, 72.6, 57.3, 52.9, 52.89, 27.4, 26.2, 24.5.

HRMS (ES+) *m/z* calculated for $C_{13}H_{18}O_6Na$ $[M+Na]^+$: 293.1001; found 293.1012.

Lactone 3.5. A 1-dram vial equipped with a stir bar was charged with **3.107** (5 mg, 0.0184 mmol), *tert*-butanol (0.2 mL), H_2O (0.2 mL), OsO_4 (19 mg of a 2.5 wt% solution in *tert*-butanol), NMO (5 mg, 0.040 mmol), and $MeSO_2NH_2$ (2 mg, 0.0184 mmol). After stirring for 5 hours, the reaction was quenched with saturated aqueous $NaHSO_3$ (0.2 mL), diluted with H_2O (2 mL) and extracted with EtOAc (5 x 3 mL). The combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (20 to 40% EtOAc in hexanes) to afford a white solid (5 mg, 90%).

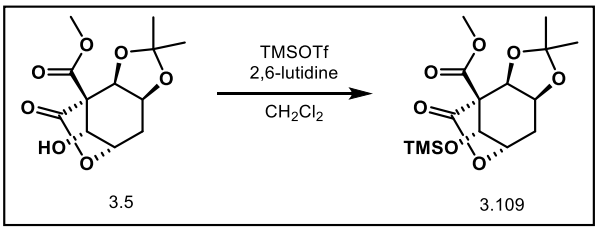
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.82 (s, 1H), 4.71 (d, *J* = 6.3 Hz, 2H), 4.44 (t, *J* = 6.8 Hz, 1H), 4.22 (s, 1H), 3.93 (s, 3H), 2.47 (dd, *J* = 15.9, 7.5 Hz, 1H), 2.09 (d, *J* = 15.9 Hz, 1H), 1.47 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.0, 168.3, 109.5, 81.2, 75.9, 71.8, 70.7, 61.1, 53.6, 32.2, 27.0, 24.6.

IR (thin film) 3518, 2945, 1772, 1726 cm^{-1}

HRMS (ES+) *m/z* calculated for $C_{12}H_{16}O_7Na$ $[M+Na]^+$: 295.0794; found 295.0808.

X-Ray Crystal Structure: See Appendix D.

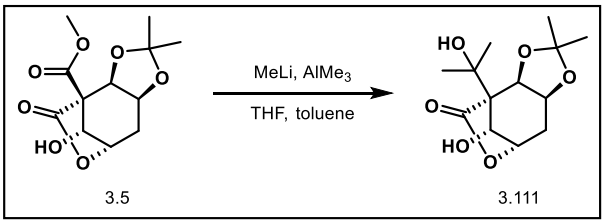


Trimethylsilyl ether 3.109. A flame-dried 2-dram vial equipped with a stir bar was charged with **3.5** (100 mg, 0.367 mmol), dichloromethane (1.2 mL), and 2,6-lutidine (0.085 mL, 0.734 mmol), and cooled to 0 °C. TMSOTf (0.100 mL, 0.551 mmol) was added dropwise. After stirring overnight, starting material remained, so additional 2,6-lutidine (0.085 mL, 0.734 mmol) and TMSOTf (0.100 mL, 0.551 mmol) were added successively. After stirring overnight, the reaction was quenched with MeOH (0.5 mL), diluted with H_2O (10 mL), and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (2 to 5% EtOAc in hexanes) to afford a clear oil (116 mg, 92%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.80 (s, 1H), 4.56 (d, *J* = 5.8 Hz, 1H), 4.44 (s, 1H), 4.39 (d, *J* = 4.7 Hz, 1H), 3.82 (d, *J* = 0.7 Hz, 3H), 2.42 (dd, *J* = 15.9, 7.2 Hz, 1H), 2.17 – 2.03 (m, 1H), 1.50 (s, 3H), 1.30 (s, 3H), 0.16 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 169.6, 165.2, 109.5, 81.8, 76.8, 71.8, 70.9, 61.6, 52.5, 32.0, 27.0, 25.1, 0.1.

HRMS (ES+) *m/z* calculated for $C_{15}H_{24}O_7SiH$ $[M+H]^+$: 345.1370; found 345.1377.

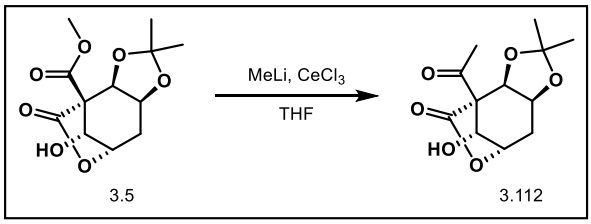


Diol 3.111. A flame-dried 1-dram vial equipped with a stir bar was charged with **3.5** (10 mg, 0.0367 mmol) and THF (0.2 mL), and cooled to 0 °C. A solution of $AlMe_3$ (0.004 mL, 0.0404 mmol) in toluene (0.1 mL) was added dropwise, and gas evolution was observed. This solution was added to a solution of MeLi (0.054 mL of a 1.5 M solution in Et_2O) in 0.1 mL toluene at −78 °C. After stirring for 3 hours, the reaction was quenched with MeOH (0.2 mL), diluted with H_2O (2 mL) and extracted with Et_2O (5 x 2 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (20 to 40% EtOAc in hexanes) to afford a thin film (7 mg, 35%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.72 (s, 1H), 4.62 (dd, *J* = 4.9, 3.6 Hz, 2H), 4.36 (d, *J* = 6.1 Hz, 1H), 4.31 (dd, *J* = 13.9, 6.1 Hz, 1H), 2.86 (s, 1H), 2.54 (ddd, *J* = 14.8, 8.0, 4.1 Hz, 1H), 1.81 (dd, *J* = 14.9, 5.8 Hz, 1H), 1.65 (s, 3H), 1.57 (s, 3H), 1.51 (s, 3H), 1.31 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 175.0, 110.5, 83.1, 75.5, 74.4, 74.3, 71.9, 59.3, 33.1, 27.7, 27.0, 25.8, 25.3.

HRMS (ES+) *m/z* calculated for $C_{13}H_{20}O_6Na$ $[M+Na]^+$: 295.1158; found 295.1161.



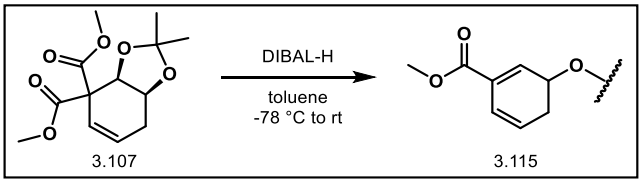
Ketone 3.112. A flame-dried 1-dram vial equipped with a stir bar was charged with anhydrous $CeCl_3$ (20 mg, 0.081 mmol) and THF (0.35 mL). The suspension was stirred vigorously for 1 hour, then placed in a sonicator for 1 hour. The suspension was then cooled to −78 °C and MeLi (0.049

mL of a 1.5 M solution in Et_2O) was added dropwise, upon which the suspension turned a pale yellow. After vigorously stirring for 2 hours at this temperature, a solution of **3.5** (10 mg, 0.0367 mmol) in THF (0.1 mL) was added dropwise and the reaction mixture was allowed to gradually warm to room temperature. After stirring for 3.5 hours, the reaction was quenched with H_2O (0.3 mL) then diluted with brine (1 mL) and extracted with EtOAc (4 x 3 mL). The combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (20 to 40% EtOAc in hexanes) to afford a 1:1.2 mixture of **3.112** (1 mg, 10%). and **3.5**.

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.89 (s, 1H), 4.73 (s, 1H), 4.64 (d, *J* = 2.0 Hz, 1H), 4.50 (t, *J* = 6.8 Hz, 1H), 4.12 (d, *J* = 7.2 Hz, 1H), 4.01 (s, 1H), 2.56 (s, 3H), 2.40 (dd, *J* = 16.2, 7.1 Hz, 1H), 2.21 (dd, *J* = 16.4, 2.3 Hz, 1H), 2.04 (s, 1H), 1.57 (s, 3H), 1.44 (s, 3H).

^{13}C NMR data not obtained due to this substrate not being used in the current forward route.

HRMS (ES+) *m/z* calculated for $C_{12}H_{16}O_6Na$ $[M+Na]^+$: 279.0845; found 279.0840.

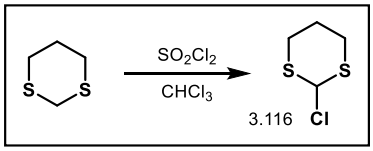


Unknown side product 3.115. A flame-dried 1-dram vial equipped with a stir bar was charged with **3.107** (40 mg, 0.148 mmol) and toluene (0.5 mL), and was cooled to −78 °C. DIBAL-H (0.026 mL, 0.148 mmol) was added dropwise and the reaction mixture was gradually warmed to room temperature over 4 hours. The reaction was diluted with Et_2O (1 mL) and H_2O (0.05 mL), followed by 0.05 mL 1 M NaOH and 0.1 mL H_2O. After stirring for 15 minutes, $MgSO_4$ was added, and after stirring an additional 15 minutes the reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by column chromatography (5 to 10% EtOAc in hexanes) to afford a clear oil (3 mg).

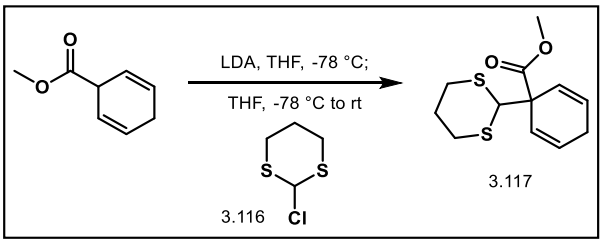
^{1}H NMR (500 MHz, $CDCl_3$) δ 6.94 (s, 1H), 6.48 (d, *J* = 9.7 Hz, 1H), 5.99 (dd, *J* = 8.9, 3.6 Hz, 1H), 4.47 (d, *J* = 4.0 Hz, 1H), 3.80 (s, 3H), 2.53 (s, 2H), 1.57 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.3, 135.3, 129.1, 126.6, 121.4, 63.9, 52.2, 31.8, 29.9.

COSY spectra can be located in Appendix B



2-Chloro-1,3-dithiane 3.116.[54] A flame-dried 25 mL round bottom flask equipped with a stir bar was charged with 1,3-dithiane (200 mg, 1.66 mmol) and chloroform (0.5 mL), and was cooled to −40 °C. Sulfuryl chloride (0.148 mL, 1.83 mmol) was added dropwise over 15 minutes, and the reaction was gradually warmed to room temperature over 2 hours. The solution was concentrated *in vacuo* at 0 °C, then stirred at 0 °C in THF (1.0 mL) for 1 hour until its use in the next step.

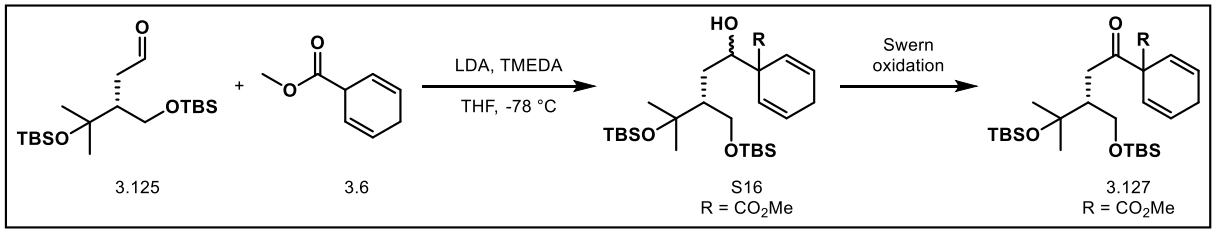


Dithiane 3.117. A flame-dried 2-dram vial equipped with a stir bar was charged with THF (0.7 mL) and DIPA (0.051 mL, 0.362 mmol), and cooled to −78 °C. *n*BuLi (0.145 mL of a 2.5 M solution in THF) was added dropwise and the reaction mixture was stirred for 15 minutes at −78 °C. A solution of **3.6** (50 mg, 0.362 mmol) in THF (0.3 mL) was added dropwise and the reaction mixture was stirred for 15 minutes. The solution of **3.116** in THF (1.0 mL) was added dropwise at −78 °C, and the reaction mixture was allowed to gradually warm to room temperature. After stirring for 2 hours, the reaction was quenched with saturated aqueous NH_4Cl (0.5 mL), then diluted with H_2O

(10 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (5% EtOAc in hexanes) to afford **3.117** as a clear oil (1.7:1 mixture of α:γ substitution) with a small amount of aldehyde.

^{1}H NMR (500 MHz, $CDCl_3$) δ 10.14 (s, 0.1H), 6.95 (s, 0.3H), 6.40 (d, *J* = 9.5 Hz, 0.3H), 6.10 – 6.03 (m, 1H), 5.95 (dd, *J* = 9.2, 4.1 Hz, 0.3H), 5.87 (d, *J* = 9.3 Hz, 1H), 4.90 (s), 4.54 (s), 4.21 (d, *J* = 5.6 Hz), 3.77 (s), 3.74 (s), 3.26 (dd, *J* = 16.3, 6.9 Hz), 3.14 – 3.07 (m), 2.97 – 2.84 (m), 2.82 – 2.61 (m), 2.47 (dd, *J* = 17.5, 14.7 Hz), 2.37 – 2.27 (m), 2.16 – 2.06 (m), 1.98 – 1.76 (m).

^{13}C NMR data not obtained due to this substrate not being used in the current forward route.



General aldol procedure A. A flame-dried 100 mL round bottom flask equipped with a stir bar was charged with THF (16 mL) and DIPA (0.562 mL, 4.01 mmol), and cooled to −78 °C. *n*BuLi (1.60 mL of a 2.5 M solution in THF) was added dropwise and the reaction mixture was stirred for 30 minutes at this temperature. A solution of **3.6** (553 mg, 4.01 mmol) in TMEDA (4.01 mL) was added dropwise at −78 °C, and the reaction mixture was stirred for 30 minutes at this temperature. A solution of **3.125** (300 mg, 0.801 mmol) in THF (1.0 mL) was added at −78 °C. After stirring at this temperature for 4 hours, the reaction was quenched at −78 °C with saturated aqueous NH_4Cl (3 mL), warmed to room temperature, diluted with H_2O (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (10 to 30% EtOAc in hexanes) to afford **S16** as a clear oil (243 mg, 59%, 2:1 d.r.).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.97 (qd, *J* = 10.4, 5.5 Hz, 2H), 5.90 (d, *J* = 10.1 Hz, 1H), 5.69 (dt, *J* = 10.2, 5.3 Hz, 1H), 4.21 (d, *J* = 3.2 Hz, 0.4H), 4.16 (dd, *J* = 7.6, 5.5 Hz, 0.6H), 3.96 (dd, *J* = 9.1, 4.1 Hz, 0.5H), 3.91 – 3.84 (m, 1H), 3.75 (s, 0.4H), 3.72 (s, 1H), 3.70 (s, 2H), 3.54 (dd, *J* = 10.0, 6.9 Hz, 0.7H), 3.37 (t, *J* = 9.8 Hz, 0.4H), 2.93 (d, *J* = 4.6 Hz, 0.6H), 2.67 (dd, *J* = 27.5, 12.7 Hz, 2H), 1.83 (d, *J* = 15.2 Hz, 0.5H), 1.72 (ddd, *J* = 15.1, 7.6, 4.2 Hz, 1.4H), 1.63 – 1.53 (m, 2H), 1.19 – 1.14 (m, 6H), 0.90 (d, *J* = 4.7 Hz, 9H), 0.84 (dd, *J* = 7.9, 4.4 Hz, 9H), 0.07 (dd, *J* = 11.0, 4.6 Hz, 18H).

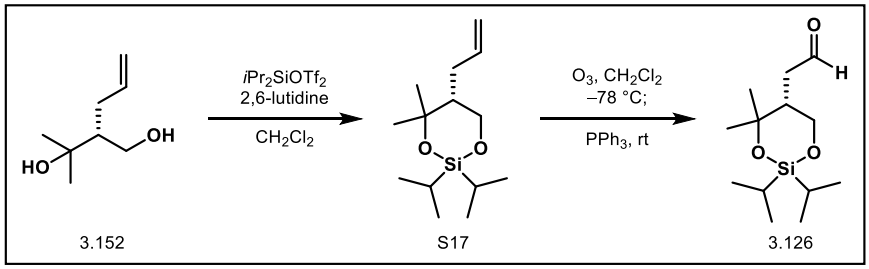
^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 174.5, 127.7, 127.6, 126.7, 126.1, 126.0, 125.6, 124.3, 124.0, 77.2, 75.6, 75.4, 74.1, 65.2, 64.0, 54.2, 53.8, 52.3, 50.6, 48.6, 32.0, 30.9, 28.49, 28.45, 28.0, 27.8, 26.9, 26.7, 26.1, 26.0, 25.9, 18.5, 18.30, 18.28, 18.2, -1.9, -1.99, -2.01, -5.3, -5.4, -5.47, -5.51.

β-Keto ester 3.127. A flame-dried 2-dram vial equipped with a stir bar was charged with dichloromethane (1.20 mL), and DMSO (0.133 mL, 0.468 mmol) and cooled to −78 °C. Oxalyl chloride (0.119 mL, 1.40 mmol) was added dropwise and the reaction mixture was stirred at this temperature for 15 minutes. A solution of **S16** (240 mg, 0.468 mmol) in dichloromethane (0.5 mL) was added dropwise at −78 °C. After stirring for 30 minutes, Et_3N (0.587 mL, 4.21 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature over 30 minutes. The reaction mixture was diluted with H_2O (5 mL) and the phases were separated. The aqueous phase was extracted with dichloromethane (3 x 20 mL) and the combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (2 to 5% EtOAc in hexanes) to afford a clear oil (138 mg, 58%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 – 5.97 (m, 4H), 3.73 (s, 3H), 3.71 – 3.65 (m, 1H), 3.51 (dd, *J* = 10.2, 5.8 Hz, 1H), 2.79 – 2.75 (m, 3H), 2.17 – 2.11 (m, 1H), 1.17 (d, *J* = 10.3 Hz, 6H), 0.85 (s, 9H), 0.83 (s, 9H), 0.08 – 0.03 (m, 9H), 0.01 – -0.01 (m, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 206.0, 171.2, 127.8, 127.7, 123.64, 123.61, 75.1, 62.9, 62.1, 52.6, 46.2, 36.3, 29.2, 28.2, 26.2, 26.02, 25.95, 18.30, 18.27, 1.2, -1.99, -2.02, -5.4.

HRMS (ES+) *m/z* calculated for $C_{27}H_{50}O_5Si_2Na$ $[M+Na]^+$: 533.3094; found 533.3079.



Silacycle S17. A flame-dried 1-dram vial equipped with a stir bar was charged with **3.152** (35 mg, 0.243 mmol), dichloromethane (1.0 mL), and 2,6-lutidine (0.085 mL, 0.729 mmol), and cooled to 0 °C. Diisopropylsilyl ditriflate (0.086 mL, 0.291 mmol) was added dropwise. After stirring overnight, the reaction was quenched with MeOH (0.5 mL), diluted with H_2O (5.0 mL) and extracted with dichloromethane (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (2% EtOAc in hexanes) to afford a clear oil (26 mg, 42%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.75 (tdd, *J* = 14.0, 8.2, 5.8 Hz, 1H), 5.05 – 4.97 (m, 2H), 3.89 (dd, *J* = 11.4, 3.8 Hz, 1H), 3.79 (t, *J* = 11.1 Hz, 1H), 2.13 – 2.05 (m, 1H), 1.87 (tt, *J* = 10.6, 3.4 Hz, 1H), 1.68 – 1.60 (m, 1H), 1.31 (s, 3H), 1.19 (s, 3H), 1.04 – 0.98 (m, 12H), 0.95 – 0.84 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 136.9, 116.5, 75.6, 64.1, 49.3, 33.1, 30.8, 24.0, 17.14, 17.09, 17.0, 13.6, 13.1.

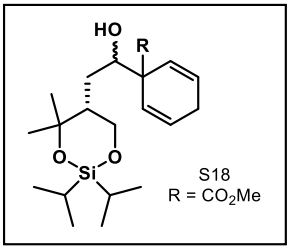
HRMS (ES+) *m/z* calculated for $C_{14}H_{28}O_2SiH$ $[M+H]^+$: 257.1937; found 257.1925.

Aldehyde 3.126. A 20 mL scintillation vial equipped with a stir bar was charged with **S17** (25 mg, 0.098 mmol) and dichloromethane (5 mL), then cooled to −78 °C. Ozone was bubbled through the solution until the solution turned blue, then bubbled for an additional 10 minutes. The solution was sparged with O_2 to remove any remaining dissolved ozone, then triphenyl phosphine (31 mg, 0.117 mmol) was added. The reaction mixture was allowed to warm to room temperature overnight, then the reaction mixture was concentrated *in vacuo*. The resulting white solid was purified by column chromatography (1 to 2% EtOAc in hexanes) to afford a clear oil (17 mg, 75%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.75 (s, 1H), 3.88 – 3.78 (m, 2H), 2.47 (td, *J* = 9.2, 4.7 Hz, 1H), 2.43 – 2.36 (m, 1H), 2.12 (ddd, *J* = 17.4, 9.1, 1.5 Hz, 1H), 1.30 (s, 3H), 1.20 (s, 3H), 1.02 (td, *J* = 7.6, 3.4 Hz, 12H), 0.97 – 0.90 (m, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 200.3, 74.8, 64.4, 43.17, 43.15, 30.7, 24.6, 17.13, 17.11, 17.05, 17.0, 13.5, 13.2.

HRMS was unable to validate the parent mass.

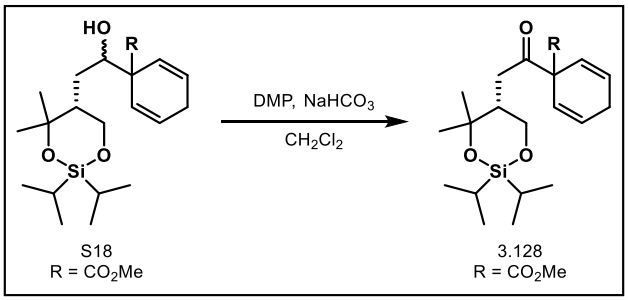


β-Hydroxy ester S18. Aldehyde **3.126** (17 mg, 0.074 mmol) was subjected to general aldol procedure A to afford **S18** as a clear oil (16 mg, 55%, 1:1 d.r.).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.06 – 5.96 (m, 2H), 5.83 (dd, *J* = 10.3, 1.8 Hz, 1H), 5.61 (ddd, *J* = 25.7, 10.2, 1.9 Hz, 1H), 4.09 (dd, *J* = 11.4, 3.9 Hz, 0.5H), 3.99 – 3.94 (m, 0.5H), 3.92 – 3.86 (m, 1.5H), 3.82 – 3.76 (m, 1.5H), 3.72 (d, *J* = 1.5 Hz, 3H), 2.78 – 2.61 (m, 2H), 2.48 (dd, *J* = 24.4, 4.4 Hz, 1H), 2.12 – 2.03 (m, 1H), 1.93 (ddd, *J* = 10.6, 7.4, 3.6 Hz, 0.5H), 1.63 (s, 1H), 1.29 (s, 2H), 1.24 (s, 1H), 1.14 (d, *J* = 9.1 Hz, 3H), 1.00 (dd, *J* = 7.1, 2.7 Hz, 12H), 0.89 (dd, *J* = 9.8, 4.8 Hz, 2H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 174.6, 128.5, 128.0, 127.9, 124.3, 124.2, 123.5, 76.8, 75.8, 75.7, 73.7, 65.6, 63.9, 54.5, 54.0, 52.7, 48.6, 45.6, 31.0, 30.7, 30.6, 30.5, 26.70, 26.69, 24.3, 24.1, 20.9, 17.20, 17.19, 17.17, 17.15, 17.1, 17.0, 13.6, 13.3.

HRMS (ES+) *m/z* calculated for $C_{21}H_{36}O_5SiNa$ $[M+Na]^+$: 419.2230; found 419.2233.

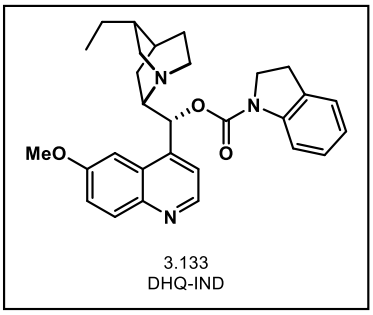


β-Keto ester 3.128. A 1-dram vial equipped with a stir bar was charged with **S18** (16 mg, 0.041 mmol), dichloromethane (0.4 mL), $NaHCO_3$ (17 mg, 0.210 mmol), and Dess-Martin periodinane (27 mg, 0.065 mmol). After stirring for 2 hours, the reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (0.5 mL) and a saturated aqueous solution of $NaHCO_3$ (0.5 mL) then diluted with H_2O (1 mL) and extracted with Et_2O (4 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (2 to 5% EtOAc in hexanes) to afford a clear oil (4 mg, 25%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.11 – 6.05 (m, 2H), 6.00 – 5.92 (m, 2H), 3.83 – 3.80 (m, 1H), 3.76 (s, 3H), 3.72 (s, 1H), 3.68 (d, *J* = 11.1 Hz, 1H), 2.77 (ddd, *J* = 26.0, 13.5, 11.5 Hz, 2H), 2.51 – 2.44 (m, 2H), 2.31 – 2.26 (m, 1H), 1.26 (s, 3H), 1.15 (s, 3H), 1.03 – 1.00 (m, 12H), 0.91 (dd, *J* = 11.6, 4.9 Hz, 2H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 204.2, 170.7, 128.6, 128.5, 122.82, 122.75, 74.8, 64.4, 63.1, 52.8, 43.5, 37.5, 30.5, 26.2, 25.0, 17.2, 17.13, 17.07, 17.0, 13.41, 13.37.

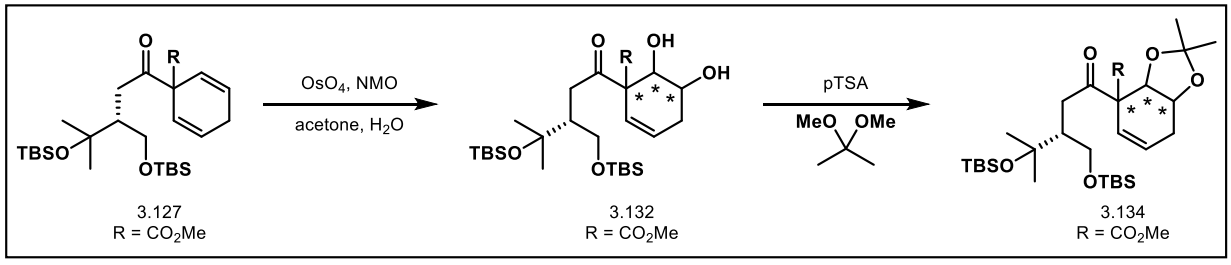
HRMS (ES+) *m/z* calculated for $C_{21}H_{34}O_5SiNa$ $[M+Na]^+$: 417.2073; found 417.2055.



3.133
DHQ-IND

DHQ-IND 3.133. A flame-dried 2-dram vial equipped with a stir bar was charged with indoline (0.131 mL, 1.17 mmol) and Et_3N (0.326 mL, 2.34 mmol). A solution of triphosgene (104 mg, 0.350 mmol) in THF (1.33 mL) was added at 0 °C. After stirring for 2 hours, the reaction mixture was diluted in hexanes and the resulting precipitate was filtered, collected, and dissolved in dichloromethane (0.6 mL). To that solution was added Et_3N (0.085 mL, 0.612 mmol) and hydroquinine (54 mg, 0.165 mmol). After stirring for 1 hour, the reaction mixture was diluted in dichloromethane (30 mL) and washed with brine (3 x 10 mL). The combined aqueous phase was extracted with dichloromethane (3 x 30 mL) and the combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo* to afford a yellow-white solid (76 mg, 98%).

^1H and ^{13}C NMR spectra were consistent with those previously reported.[36]



3.127
R = CO_2Me

3.132
R = CO_2Me

3.134
R = CO_2Me

Diol 3.132. A 1-dram vial equipped with a stir bar was charged with **3.127** (9 mg, 0.018 mmol), acetone (0.3 mL), H_2O (0.1 mL), OsO_4 (18 mg of a 2.5 wt% solution in *tert*-butanol), and NMO (5 mg, 0.040 mmol). After stirring overnight, the reaction was quenched with saturated aqueous $NaHSO_3$ (0.5 mL), diluted with H_2O (2 mL) and extracted with EtOAc (5 x 5 mL). The combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (20 to 40% EtOAc in hexanes) to afford a clear oil (6 mg, 61%) as an indeterminable mixture of diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.98 (d, *J* = 8.7 Hz, 1H), 5.90 (dd, *J* = 6.9, 3.3 Hz, 1H), 5.30 (d, *J* = 1.9 Hz, 1H), 4.57 (d, *J* = 2.6 Hz, 1H), 4.01 (d, *J* = 7.0 Hz, 1H), 3.78 (s, 3H), 3.68 – 3.64 (m, 1H), 3.51 (dd, *J* = 9.1, 4.7 Hz, 1H), 2.82 (dd, *J* = 19.1, 8.8 Hz, 1H), 2.70 – 2.61 (m, 1H), 2.36 (dd, *J* = 12.4, 5.2 Hz, 1H), 2.28 – 2.13 (m, 2H), 1.18 – 1.15 (m, 6H), 0.87 – 0.82 (m, 18H), 0.07 – -0.04 (m, 12H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 203.6, 203.5, 170.8, 170.7, 128.9, 128.8, 128.5, 122.3, 122.0, 75.1, 75.0, 71.9, 71.8, 67.5, 67.3, 67.2, 67.2, 62.2, 62.0, 53.2, 53.1, 46.3, 46.2, 37.5, 37.4, 30.1, 29.9, 29.3, 29.0, 28.1, 28.0, 26.03, 25.98, 25.95, 25.9, 18.32, 18.26, 18.2, -1.97, -1.99, -2.01, -5.4, -5.45, -5.46.

COSY spectra in Appendix B

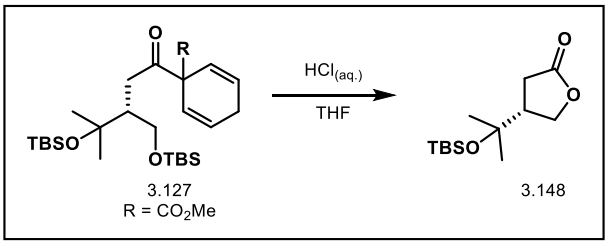
HRMS (ES+) *m/z* calculated for $C_{27}H_{52}O_7Si_2Na$ $[M+Na]^+$: 567.3149; found 567.3143.

Acetal 3.134. A flame-dried 1-dram vial equipped with a stir bar was charged with **3.132** (4 mg, 0.007 mmol), 2,2-dimethoxypropane (0.3 mL), and a crystal of *p*TSA. After stirring for 4 hours, the reaction was quenched with saturated aqueous $NaHCO_3$ (0.5 mL), diluted with H_2O (2 mL) and extracted with Et_2O (5 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (0 to 5% EtOAc in hexanes) to afford a thin film (<1 mg, <25%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.32 (dd, *J* = 27.2, 8.7 Hz, 1H), 6.00 (t, *J* = 7.7 Hz, 1H), 5.06 (d, *J* = 7.6 Hz, 1H), 4.75 – 4.68 (m, 1H), 3.80 (d, *J* = 2.8 Hz, 3H), 3.56 – 3.40 (m, 2H), 2.75 – 2.64 (m, 1H), 2.46 (ddd, *J* = 25.1, 19.0, 4.9 Hz, 1H), 2.32 – 2.27 (m, 1H), 1.30 (d, *J* = 4.4 Hz, 6H), 1.16 (d, *J* = 9.1 Hz, 6H), 0.86 – 0.81 (m, 18H), 0.06 – -0.05 (m, 12H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 200.5, 130.1, 123.7, 108.2, 75.0, 73.1, 64.8, 61.9, 52.9, 46.1, 36.6, 31.7, 29.0, 28.0, 27.6, 26.2, 26.03, 25.99, 25.95, 24.3, 22.8, 18.6, 14.3, -2.0, -5.36, -5.43, -5.5.

ESIMS (ES+) *m/z* calculated for $C_{30}H_{56}O_7Si_2Na$ $[M+Na]^+$: 607.36; found 607.5.

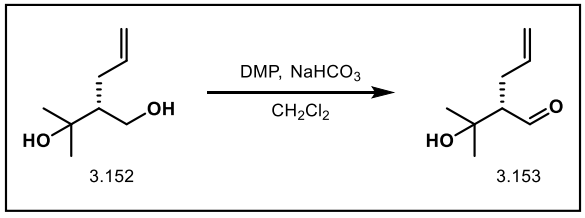


Deprotection of 3.127. A 1-dram vial equipped with a stir bar was charged with **3.127** (10 mg, 0.0195 mmol), THF (0.4 mL), and a drop of concentrated aqueous HCl. After stirring for 3 hours, the reaction was quenched with saturated aqueous $NaHCO_3$ (0.2 mL), diluted with H_2O (1 mL), and extracted with Et_2O (5 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (5 to 10% EtOAc in hexanes) to afford **3.148** as a thin film (4 mg, 79%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.33 (t, *J* = 8.3 Hz, 1H), 4.26 (t, *J* = 8.3 Hz, 1H), 2.63 – 2.49 (m, 2H), 2.44 (dd, *J* = 16.0, 8.0 Hz, 1H), 1.22 (d, *J* = 8.9 Hz, 6H), 0.86 (d, *J* = 1.0 Hz, 9H), 0.11 (s, 6H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 177.6, 72.5, 69.5, 47.6, 29.7, 28.7, 28.0, 25.94, 25.90, 18.3, -2.06, -2.09.

HRMS (ES+) *m/z* calculated for $C_{13}H_{26}O_3SiNa$ $[M+Na]^+$: 281.1549; found 281.1542.



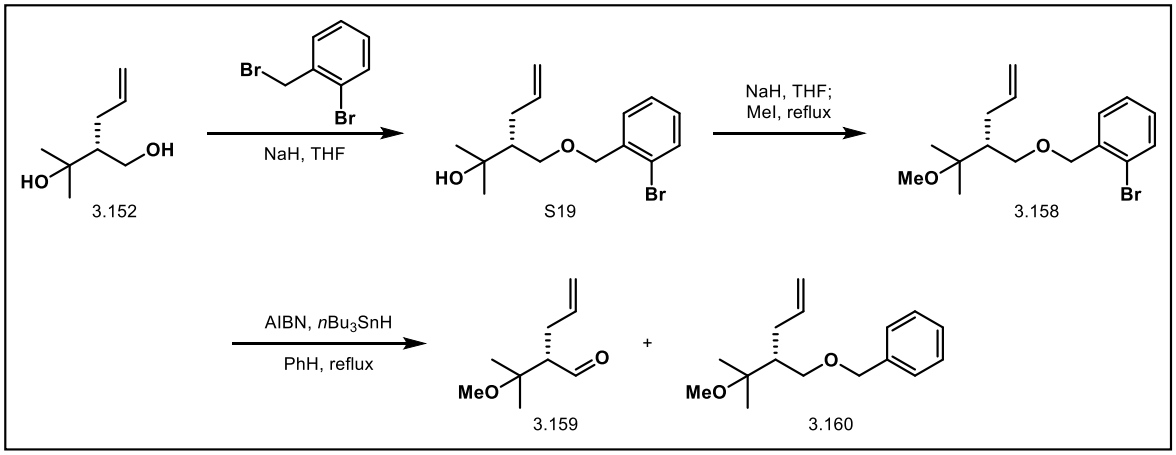
β-Hydroxy aldehyde 3.153. A 2-dram vial equipped with a stir bar was charged with **3.152** (90 mg, 0.624 mmol), dichloromethane (3.0 mL), $NaHCO_3$ (262 mg, 3.12 mmol), and Dess-Martin periodinane (423 mg, 0.998 mmol). After stirring for 2 hours, the reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (2 mL) and a saturated aqueous solution of $NaHCO_3$ (2 mL) then diluted with H_2O (10 mL) and extracted with EtOAc (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting

residue was purified by column chromatography (30% EtOAc in hexanes) to afford a clear oil (53 mg, 60%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.77 (d, *J* = 2.6 Hz, 1H), 5.78 (ddt, *J* = 17.1, 10.1, 6.6 Hz, 1H), 5.13 – 5.03 (m, 2H), 2.54 – 2.38 (m, 3H), 1.29 (d, *J* = 5.5 Hz, 6H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 205.7, 135.7, 117.2, 72.4, 61.1, 30.0, 28.8, 27.8.

HRMS was unable to validate the parent mass.



2-Bromobenzyl protection of 3.152.[55] A flame-dried 2-dram vial equipped with a stir bar was charged with **3.152** (50 mg, 0.347 mmol), THF (1.7 mL), and NaH (35 mg, 0.867 mmol) at 0 °C. After stirring for 30 minutes, 2-bromobenzyl bromide was added in one portion (260 mg, 1.04 mmol). After stirring for 2 hours, the reaction was quenched with MeOH (0.5 mL), diluted with H_2O (10 mL), and extracted with Et_2O (3 x 20 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (15% EtOAc in hexanes) to afford **S19** as a clear oil (87 mg, 80%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.0 Hz, 1H), 7.40 (d, *J* = 7.6 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 5.78 (ddd, *J* = 16.0, 9.3, 5.7 Hz, 1H), 5.02 (dd, *J* = 12.3, 10.4 Hz, 2H), 4.61 – 4.51 (m, 2H), 3.77 (dd, *J* = 9.6, 3.6 Hz, 1H), 3.64 (dd, *J* = 9.5, 6.5 Hz, 1H), 2.33 (dd,

J = 11.9, 2.4 Hz, 1H), 2.05 (dt, *J* = 14.4, 9.5 Hz, 1H), 1.75 (ddt, *J* = 10.1, 6.9, 3.6 Hz, 1H), 1.27 (s, 3H), 1.20 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 137.6, 137.1, 132.8, 129.5, 129.4, 127.6, 123.1, 116.4, 73.07, 73.06, 71.2, 47.8, 32.1, 29.3, 26.3.

HRMS (ES+) *m/z* calculated for $C_{15}H_{21}BrO_2Na$ $[M+Na]^+$: 335.0623, 337.0604; found 335.0623, 337.0614.

Methylation of S19. A flame-dried 1-dram vial equipped with a stir bar was charged with **S19** (30 mg, 0.096 mmol), THF (0.5 mL), and NaH (11 mg, 0.287 mmol) at 0 °C. After stirring for 30 minutes, Me_2SO_4 (0.045 mL, 0.218 mmol) was added. After stirring overnight, the reaction was diluted with H_2O (1 mL) and extracted with Et_2O (4 x 5 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (5% EtOAc in hexanes) to afford **3.158** as a clear oil (33 mg, 99%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.52 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.50 – 7.47 (m, 1H), 7.31 (td, *J* = 7.6, 0.9 Hz, 1H), 7.13 (td, *J* = 7.9, 1.6 Hz, 1H), 5.93 – 5.84 (m, 1H), 5.07 – 4.96 (m, 2H), 4.50 (s, 2H), 3.63 (dd, *J* = 9.6, 4.6 Hz, 1H), 3.55 (dd, *J* = 9.6, 4.7 Hz, 1H), 3.19 (s, 3H), 2.38 – 2.32 (m, 1H), 2.17 – 2.09 (m, 1H), 1.89 (td, *J* = 8.4, 4.5 Hz, 1H), 1.21 (s, 3H), 1.18 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 138.5, 138.2, 132.5, 129.0, 128.8, 127.4, 122.5, 115.7, 76.7, 72.5, 70.5, 48.9, 46.3, 32.1, 23.5, 23.3.

HRMS (ES+) *m/z* calculated for $C_{16}H_{23}BrO_2Na$ $[M+Na]^+$: 349.0779, 351.0760; found 349.0777, 351.0767.

Deprotection of 3.158.[55] A flame-dried 100 mL round bottom flask equipped with a stir and reflux condenser was charged with degassed benzene (31 mL), **3.158** (10 mg, 0.031 mmol), AIBN (0.5 mg, 0.003 mmol), and *n*Bu_3SnH (0.010 mL, 0.036 mmol), then heated to reflux for 2 hours. After

cooling to room temperature the reaction mixture was concentrated *in vacuo*. The resulting residue was purified by column chromatography to afford a 1:1 mixture of **3.159** (2 mg, 42%) and **3.160** (3.7 mg, 48%).

3.159:

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (d, *J* = 2.7 Hz, 1H), 5.76 – 5.66 (m, 1H), 5.02 (dd, *J* = 23.7, 13.6 Hz, 2H), 3.21 (s, 3H), 2.57 – 2.47 (m, 2H), 2.28 (dd, *J* = 11.5, 6.4 Hz, 1H), 1.24 (s, 3H), 1.21 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 204.8, 136.0, 116.7, 76.3, 59.7, 49.2, 29.1, 23.7, 23.1.

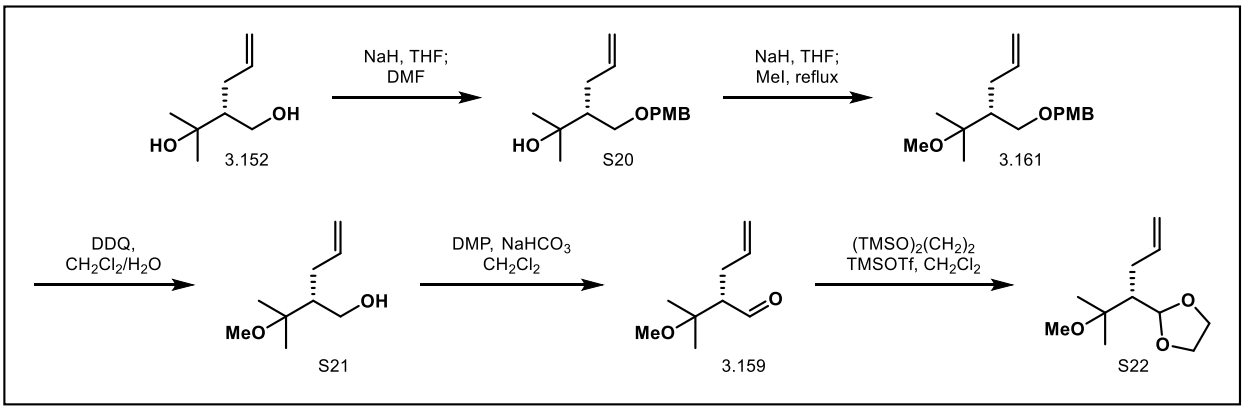
HRMS was unable to validate the parent mass.

3.160:

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, *J* = 5.7 Hz, 5H), 5.92 – 5.80 (m, 1H), 5.00 (dd, *J* = 26.5, 13.5 Hz, 2H), 4.46 (s, 2H), 3.55 (dd, *J* = 9.6, 4.6 Hz, 1H), 3.45 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.17 (d, *J* = 6.3 Hz, 3H), 2.36 – 2.27 (m, 1H), 2.09 (dt, *J* = 14.2, 8.9 Hz, 1H), 1.89 – 1.81 (m, 1H), 1.18 (s, 3H), 1.15 (s, 3H).

^{13}C NMR data not obtained due to this substrate not being used in the current forward route.

HRMS (ES+) *m/z* calculated for $C_{16}H_{24}O_2Na$ $[M+Na]^+$: 271.1674; found 271.1665.



PMB protection of 3.152. A flame-dried 50 mL round bottom flask equipped with a stir bar was charged with **3.152** (500 mg, 3.47 mmol), DMF (14 mL), and NaH (347 mg, 8.68 mmol) at 0 °C. After stirring for 30 minutes, PMBCl (0.520 mL, 3.82 mmol) was added. After stirring for 2 hours, the reaction was quenched with MeOH (2 mL), diluted with H_2O (100 mL), and extracted with Et_2O (4 x 200 mL). The combined organic extracts were washed with brine (3 x 200 mL), dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (15% EtOAc in hexanes) to afford **S20** as a clear oil (824 mg, 91%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.75 (dddd, *J* = 16.7, 10.0, 8.6, 5.7 Hz, 1H), 5.04 – 4.97 (m, 2H), 4.42 (dd, *J* = 26.8, 11.5 Hz, 2H), 3.80 (s, 3H), 3.66 (dd, *J* = 9.6, 3.7 Hz, 1H), 3.53 (dd, *J* = 9.6, 6.8 Hz, 1H), 2.32 – 2.25 (m, 1H), 2.02 – 1.93 (m, 1H), 1.71 (ddt, *J* = 10.4, 7.0, 3.6 Hz, 1H), 1.24 (s, 3H), 1.16 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.4, 137.7, 129.9, 129.5, 116.3, 114.0, 73.3, 73.1, 70.5, 55.4, 47.5, 32.2, 29.3, 26.1.

HRMS (ES+) *m/z* calculated for $C_{16}H_{24}O_3Na$ $[M+Na]^+$: 287.1623, found 287.1633.

Methylation of S20. A flame-dried 50 mL round bottom flask equipped with a stir bar was charged with **S20** (790 mg, 2.99 mmol), THF (15 mL), and NaH (359 mg, 8.96 mmol) at 0 °C. After stirring for 30 minutes, MeI (3.72 mL, 59.8 mmol) was added. After stirring overnight, the reaction was quenched and diluted with H_2O (50 mL), extracted with Et_2O (3 x 100 mL), and the combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (5% EtOAc in hexanes) to afford **3.161** as a clear oil (788 mg, 95%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 8.5 Hz, 2H), 6.87 (d, *J* = 8.6 Hz, 2H), 5.91 – 5.81 (m, 1H), 5.00 (ddd, *J* = 13.6, 10.9, 1.0 Hz, 2H), 4.38 (s, 2H), 3.80 (s, 3H), 3.51 (dd, *J* = 9.6, 4.6 Hz, 1H), 3.41 (dd, *J* = 9.6, 4.8 Hz, 1H), 3.17 (s, 3H), 2.35 – 2.27 (m, 1H), 2.06 (dt, *J* = 14.2, 8.7 Hz, 1H), 1.84 (td, *J* = 8.9, 4.5 Hz, 1H), 1.17 (s, 3H), 1.14 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 159.1, 138.6, 131.0, 129.2, 115.5, 113.8, 76.7, 72.8, 69.8, 66.0, 55.4, 48.9, 46.1, 32.2, 23.6, 23.3, 15.4.

HRMS (ES+) *m/z* calculated for $C_{17}H_{26}O_3Na$ $[M+Na]^+$: 301.1780; found 301.1768.

PMB deprotection of 3.161. A 50 mL round bottom flask equipped with a stir bar was charged with **3.161** (750 mg, 2.69 mmol), dichloromethane (10 mL), H_2O (0.5 mL), then DDQ (669 mg, 2.95 mmol). After stirring for 2 hours, the reaction was diluted with saturated aqueous $NaHCO_3$ (30 mL) and extracted with dichloromethane (3 x 50 mL). The combined organic extracts were washed with saturated aqueous $NaHCO_3$ (30 mL) and brine (30 mL), then dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (5 to 10 to 20% EtOAc in hexanes) to afford **S21** as an orange oil (339 mg, 79%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.81 (tdd, *J* = 8.2, 6.9, 2.0 Hz, 1H), 5.11 – 4.97 (m, 2H), 3.74 – 3.64 (m, 2H), 3.23 (d, *J* = 2.0 Hz, 3H), 2.17 (dd, *J* = 14.3, 1.8 Hz, 1H), 1.95 – 1.84 (m, 1H), 1.74 (ddd, *J* = 10.1, 6.8, 3.0 Hz, 1H), 1.25 (d, *J* = 1.7 Hz, 3H), 1.17 (d, *J* = 1.7 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 137.7, 116.3, 79.8, 63.1, 48.9, 48.5, 32.1, 23.9, 20.5.

HRMS (ES+) *m/z* calculated for $C_9H_{18}O_2Na$ $[M+Na]^+$: 181.1205; found 181.1201.

Oxidation of S21. A 25 mL round bottom flask equipped with a stir bar was charged with **S21** (325 mg, 2.05 mmol), dichloromethane (8.0 mL), $NaHCO_3$ (861 mg, 10.25 mmol), and Dess-Martin periodinane (1.31 g, 3.08 mmol). After stirring for 2 hours, the reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (10 mL) and a saturated aqueous solution of $NaHCO_3$ (10 mL) then diluted with H_2O (50 mL) and extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (5 to 10% EtOAc in hexanes) to afford **3.159** as a yellow oil (198 mg, 62%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.70 (d, *J* = 2.7 Hz, 1H), 5.76 – 5.66 (m, 1H), 5.02 (dd, *J* = 23.7, 13.6 Hz, 2H), 3.21 (s, 3H), 2.57 – 2.47 (m, 2H), 2.28 (dd, *J* = 11.5, 6.4 Hz, 1H), 1.24 (s, 3H), 1.21 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 204.8, 136.0, 116.7, 76.3, 59.7, 49.2, 29.1, 23.7, 23.1.

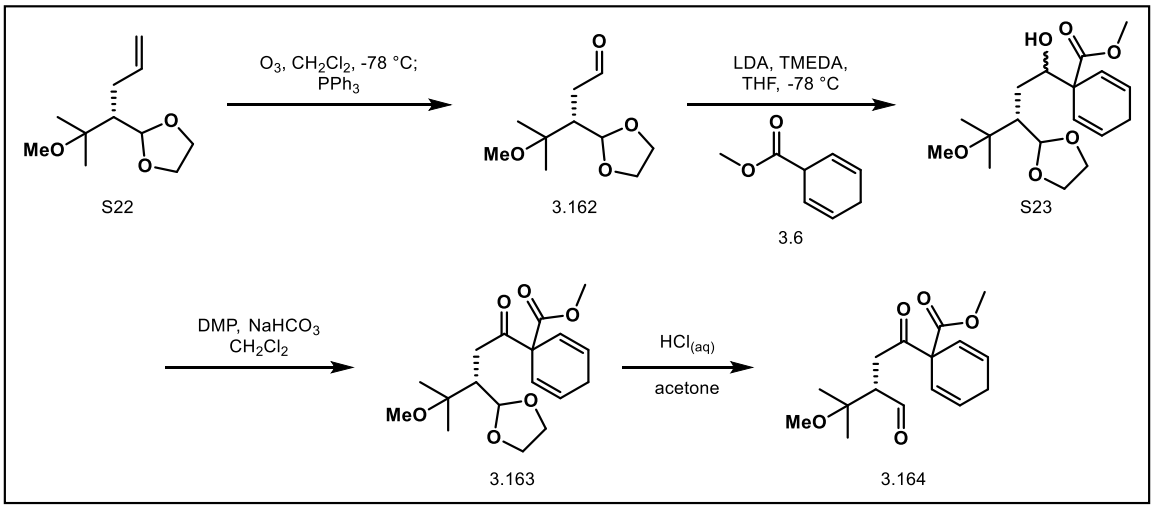
HRMS was unable to validate the parent mass.

Acetal protection of 3.159. A flame-dried 25 mL round bottom flask equipped with a stir bar was charged with **3.159** (170 mg, 1.09 mmol), dichloromethane (5.5 mL), and 1,2-bis(trimethylsiloxy)ethane (0.534 mL, 2.18 mmol) and was cooled to 0 °C. TMSOTf (0.020 mL, 0.109 mmol) was added. After stirring overnight, the reaction was quenched with MeOH (2 mL), diluted with H_2O (30 mL), and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (5% EtOAc in hexanes) to afford **S22** as a yellow oil (131 mg, 60%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.91 (ddt, *J* = 17.1, 10.0, 6.8 Hz, 1H), 5.04 (s, 1H), 5.02 – 4.95 (m, 1H), 4.90 (d, *J* = 10.1 Hz, 1H), 3.99 – 3.95 (m, 1H), 3.87 (tt, *J* = 12.9, 6.3 Hz, 2H), 3.79 – 3.75 (m, 1H), 3.18 (s, 3H), 2.30 (dd, *J* = 14.5, 8.2 Hz, 1H), 2.17 – 2.10 (m, 2H), 1.20 (s, 3H), 1.18 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 140.1, 114.0, 104.2, 76.3, 65.6, 64.1, 48.9, 48.5, 29.0, 23.8, 23.4.

HRMS (ES+) *m/z* calculated for $C_{10}H_{18}O_4Na$ $[M+Na]^+$: 225.1103; found 225.1093



Ozonolysis of S22. A 20 mL scintillation vial equipped with a stir bar was charged with **S22** (131 mg, 0.654 mmol) and dichloromethane (5 mL), then cooled to −78 °C. Ozone was bubbled through the solution until the solution turned blue, then bubbled for an additional 10 minutes. The solution was sparged with O_2 to remove any remaining dissolved ozone, then triphenyl phosphine (206 mg, 0.785 mmol) was added. The reaction mixture was allowed to warm to room temperature overnight, then the reaction mixture was concentrated *in vacuo*. The resulting white solid was purified by column chromatography (15 to 25% EtOAc in hexanes) to afford **3.162** as a clear oil (54 mg, 41%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.64 – 9.59 (m, 1H), 5.00 (d, *J* = 2.0 Hz, 1H), 3.95 (dd, *J* = 13.1, 6.6 Hz, 1H), 3.86 – 3.74 (m, 3H), 3.17 (s, 3H), 2.70 – 2.63 (m, 1H), 2.47 (ddd, *J* = 16.0, 8.3, 3.4 Hz, 1H), 2.38 (dd, *J* = 16.0, 4.8 Hz, 1H), 1.24 (s, 3H), 1.16 (s, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 202.0, 103.2, 75.3, 65.7, 64.1, 48.8, 45.9, 38.7, 23.5, 22.4.

HRMS was unable to validate the parent mass.

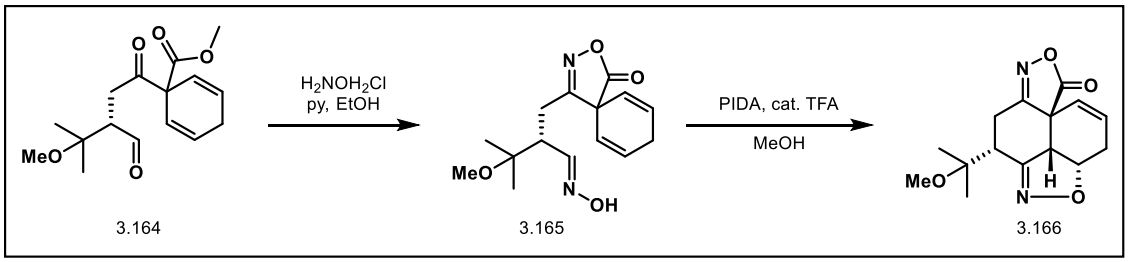
Aldol reaction with 3.162 and 3.6. Aldehyde **3.162** (50 mg, 0.247 mmol) was subjected to general aldol procedure A to afford **S23** as a clear oil (47 mg, 56%, 3:1 d.r.).

^{1}H NMR (600 MHz, $CDCl_3$) δ 6.02 – 5.90 (m, 3H), 5.70 (td, *J* = 9.8, 1.8 Hz, 1H), 5.00 (d, *J* = 2.3 Hz, 0.25H), 4.96 (d, *J* = 1.8 Hz, 0.75H), 4.03 (dd, *J* = 13.1, 3.9 Hz, 1H), 4.01 – 3.96 (m, 1H), 3.89 (dd, *J* = 7.5, 5.0 Hz, 1H), 3.85 (dd, *J* = 13.0, 6.7 Hz, 1H), 3.82 – 3.78 (m, 1H), 3.73 (s, 0.75H), 3.72 (s, 2.25H), 3.20 (s, 2.25H), 3.19 (s, 0.75H), 2.68 (t, *J* = 13.1 Hz, 2H), 2.23 – 2.19 (m, 0.75H), 2.14 (dd, *J* = 5.4, 2.6 Hz, 0.25H), 1.64 (ddd, *J* = 14.7, 6.7, 1.7 Hz, 1H), 1.56 – 1.50 (m, 1H), 1.21 (s, 2.25H), 1.17 (s, 0.75H), 1.15 (s, 0.75H), 1.13 (s, 2.25H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 174.7, 128.0, 127.5, 126.6, 126.5, 125.7, 125.6, 124.1, 123.8, 104.4, 103.5, 76.4, 76.2, 65.7, 65.5, 64.3, 64.2, 54.0, 52.38, 52.35, 49.2, 48.6, 47.3, 26.83, 26.78, 26.5, 26.3, 23.70, 23.5, 23.0, 21.6.

Oxidation of S23. A 1-dram vial equipped with a stir bar was charged with **S23** (43 mg, 0.126 mmol), dichloromethane (0.6 mL), $NaHCO_3$ (53 mg, 0.630 mmol), and Dess-Martin periodinane (86 mg, 0.202 mmol). After stirring for 2 hours, the reaction was quenched with a saturated aqueous solution of $Na_2S_2O_3$ (0.5 mL) and a saturated aqueous solution of $NaHCO_3$ (0.5 mL) then diluted with H_2O (1 mL) and extracted with Et_2O (4 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was passed through a silica plug (10 to 20% EtOAc in hexanes) to afford **3.163** as an impure mixture (28 mg). **3.163** was used in the next step without further purification.

Deprotection of 3.163. A 1-dram vial equipped with a stir bar was charged with **3.163** (25 mg, 0.074 mmol), acetone, (0.62 mL) and 1 M $HCl_{(aq)}$ (0.74 mL) and was stirred overnight. The reaction mixture was diluted with H_2O (3 mL) and extracted with EtOAc (5 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was passed through a silica plug (10 to 20% EtOAc in hexanes) to afford **3.164** as an impure mixture (10 mg). **3.164** was used in the next step without further purification.



Oxime formation from 3.164.[20] A flame-dried 1-dram vial equipped with a stir bar was charged with **3.164** (10 mg, 0.034 mmol), EtOH (0.56 mL), pyridine (0.07 mL), and hydroxylamine hydrochloride (3 mg, 0.044 mmol). The reaction was stirred for 6 hours, then concentrated, diluted with H_2O (3 mL) and extracted with EtOAc (5 x 3 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was passed through a silica plug (15 to 25 to 40% EtOAc in hexanes) to afford **3.165** as an impure mixture (4 mg). **3.165** was used in the next step without further purification.

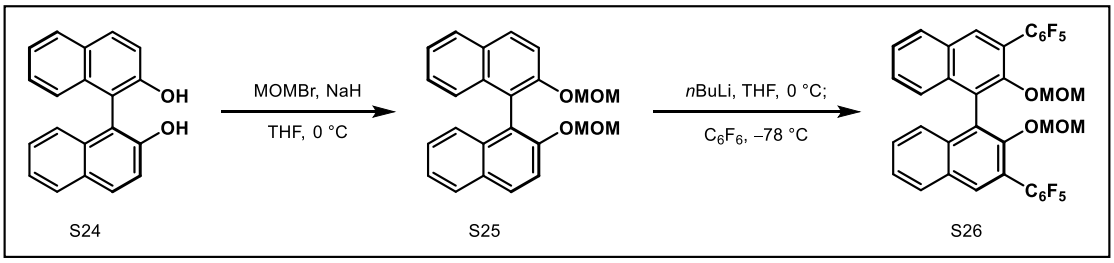
Cyclization of 3.165.[40] A flame-dried 1-dram vial equipped with a stir bar was charged with **3.165** (4 mg, 0.0136 mmol), MeOH (0.10 mL), TFA (0.6 µL), and PIDA (6 mg, 0.0173 mmol). After stirring for 5 hours, the reaction was quenched with a 5% aqueous solution of $NaHCO_3$ (1 mL) and a 10% aqueous solution of $NaHSO_3$ (1 mL), then extracted with Et_2O (5 x 4 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (30% EtOAc in hexanes) to afford **3.166** as a thin film (2 mg, 50%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 6.45 (ddd, *J* = 9.6, 7.2, 2.4 Hz, 1H), 5.51 (dd, *J* = 9.6, 3.2 Hz, 1H), 5.13 (dd, *J* = 11.1, 3.0 Hz, 1H), 3.72 (d, *J* = 11.1 Hz, 1H), 3.22 (s, 3H), 3.18 (dd, *J* = 13.6, 5.0 Hz, 1H), 2.85 (ddd, *J* = 17.1, 7.1, 3.0 Hz, 1H), 2.74 – 2.64 (m, 2H), 2.31 (t, *J* = 13.0 Hz, 1H), 1.41 (s, 3H), 1.35 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 176.4, 169.4, 152.7, 135.5, 120.6, 75.9, 75.3, 54.9, 49.9, 48.9, 46.6, 27.8, 26.6, 23.5, 20.7.

COSY, **HMQC**, and **NOESY** spectra in Appendix B.

LCMS (ES+) *m*/*z* calculated for $C_{15}H_{18}N_2O_4H$ $[M+H]^+$: 291.13; found 291.1156.

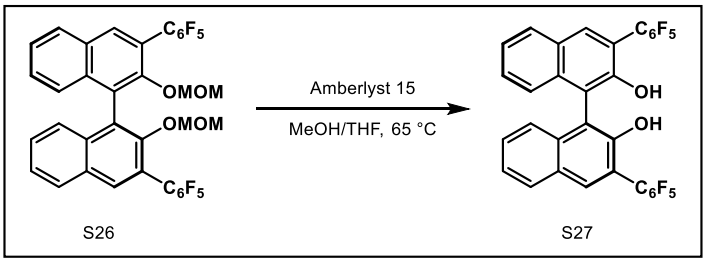


S24 S25 S26

MOM Protection of (*S*)-BINOL S24. A flame-dried 50 mL round bottom flask equipped with a stir bar was charged with **S24** (1.00 g, 3.49 mmol), THF (15 mL), and NaH (419 mg, 0.470 mmol) at 0 °C. After stirring for 30 minutes, MOMBr (0.627 mL, 7.68 mmol) was added dropwise. After stirring an additional 2 hours, saturated aqueous NH_4Cl (10 mL) was added and the aqueous phase was extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting white solid was purified by column chromatography (15% EtOAc in hexanes) to afford **S25** as a white solid (1.22 g, 93%). ^1H and ^{13}C NMR spectra were consistent with those previously reported.[56]

Arylation of S25. A flame-dried 100 mL round bottom flask equipped with a stir bar was charged with **S25** (1.22 g, 3.26 mmol) and THF (19 mL) and cooled to −78 °C. *n*BuLi (3.91 mL of a 2.5 M solution in hexanes) was added dropwise. After stirring for 30 minutes at this temperature, C_6F_6 (2.63 mL, 22.82 mmol) was added dropwise. After stirring for 3 hours, allowing the reaction mixture to warm to room temperature, the reaction was quenched with a saturated aqueous solution of NH_4Cl (10 mL) and extracted with Et_2O (3 x 50 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (10% EtOAc in hexanes) to afford **S26** as an off-white solid (2.07 g, 90%).

^{1}H and ^{13}C NMR spectra were consistent with those previously reported.[56]



Deprotection of S26. A flame-dried 100 mL round bottom flask equipped with a stir bar was charged with **S26** (2.07 g, 2.93 mmol), MeOH (12 mL), THF (12 mL), and Amberlyst 15 (4.14 g), and heated to 65 °C. Once the reaction as judged completed by TLC, the reaction mixture was filtered through a pad of celite (Et_2O) and the resulting filtrate was concentrated *in vacuo*. The resulting solid was purified by column chromatography (20% EtOAc in hexanes) to afford **S27** as a yellow-white solid (1.621 g, 89%).

^{1}H and ^{13}C NMR spectra were consistent with those previously reported.[56]

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Chapter 4: Introduction to Diastereoselective Birch Reduction/Alkylation Reactions

4.1 Introduction and Motivations

The Birch reduction has been known for over 80 years,[1] and it remains an important reaction for the synthesis of complex molecules, with few changes to the original conditions. The ability to use ubiquitous aromatic rings as key synthons has proved immensely powerful. The Birch reduction still sees use in complex settings as evidenced by a recent publication by our own lab where it serves a pivotal role in the synthesis of 7,20-diisocyanoadociane.[2] When an electron withdrawing group, such as a ketone, ester, or carboxylic acid, is placed on the aromatic ring, the resulting stabilized carbanion formed from reduction of the arene can be trapped with an electrophile. As a result, arenes appended with carbonyl functionality are retrons to 1,4-cyclohexadienes bearing a newly formed quaternary carbon, which can be stereogenic depending upon the substitution pattern of the arene. The ability to control the stereochemistry of the newly formed quaternary carbon has significant importance for the synthesis of complex cyclohexane scaffolds.

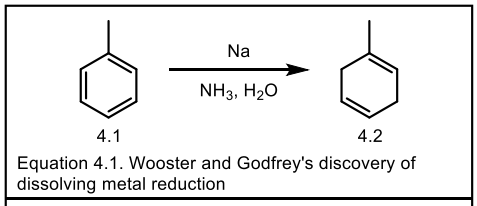
During the course of my work on the synthesis of the core of the agarofurans, I aimed to develop a diastereoselective Birch reduction/alkylation reaction using a non-amide-based chiral auxiliary. In section 3.3.3 of this thesis, I detailed the discovery of the use of (–)-8-phenylmenthol as a chiral auxiliary for the diastereoselective Birch reduction/alkylation reaction of benzene derivatives. This was the first example using a non-amide chiral auxiliary on benzene derivatives and I aimed to develop this into a general method. The use of an ester chiral auxiliary has advantages over the current amide chiral auxiliary technology, namely in its ease of removal. Thus, this method fills a gap in the current scientific literature wherein complex cyclohexane

scaffolds can be synthesized stereoselectively starting from simple, and widely available, aromatic building blocks.

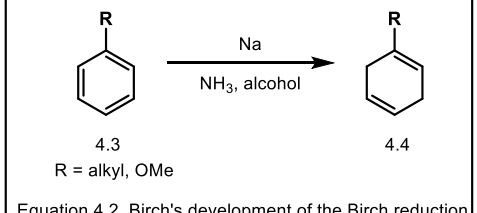
4.2 The Birch Reduction

4.2.1 Introduction

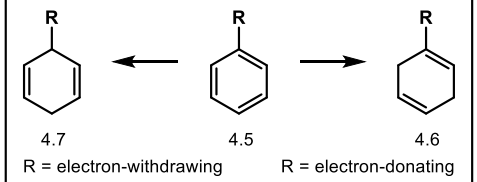
The venerable Birch reduction reaction was originally discovered by Wooster and Godfrey in 1937.[3] In their seminal work, they describe the reduction of toluene to diene **4.2** using sodium metal dissolved in a mixture of ammonia and water (Equation 4.1). However, Arthur Birch has been recognized for much of the development of this reaction. In 1944, Arthur Birch reported his findings on the reduction of various anisoles and alkylbenzenes using sodium in ammonia and an alcoholic co-solvent (Equation 4.2).[1] Birch was the first to suggest that the reduction went through an anionic process, forming a carbanion that is protonated by the alcoholic co-solvent. This mechanistic hypothesis was corroborated by the inability to reduce phenols and the slower reductions of more electron-rich substrates. Birch also demonstrated that alcohols performed better than water as a proton source. Most significantly, Birch also discovered and developed the rules that govern the selectivity of the protonation of the resultant anions (Scheme 4.1). He noted that the reduction of aromatic rings substituted with electron-donating groups resulted in 1,4-dienes, forming the most highly substituted alkenes (**4.6**). Although the most highly substituted alkenes are formed, the reasoning for the observed selectivity is to localize the electron density on the carbons where it is most stable. As a result, protonation almost always occurs on a secondary carbon, thus forming the most highly substituted alkenes, giving ortho and meta protonation. When an aromatic ring containing an



Equation 4.1. Wooster and Godfrey's discovery of dissolving metal reduction



Equation 4.2. Birch's development of the Birch reduction



Scheme 4.1. Birch's rules for reduction selectivity

electron-withdrawing substituent is subjected to dissolving metal conditions, similar reasoning can be applied. The most stable concentration of electron density is on the carbon adjacent to the electron withdrawing group. Thus, protonation occurs at the para and ipso positions (**4.7**). The formation of the carbanion adjacent to the electron-withdrawing group results in an enolate intermediate. This enolate can be functionalized with an electrophile, leading to a newly formed quaternary carbon.[4]

4.2.2 Common Conditions

Though the Birch reduction was originally discovered using sodium metal, lithium metal is typically used due to its higher reduction potential (–2.99 V for Li vs. –2.59 V for Na in NH_3); however, if lithium results in overreduction, sodium can often be substituted with greater success.[5] Reductions of aromatic ketones with lithium or sodium can often result in competitive carbonyl reduction or dimerization, in which case potassium can be used. Despite potassium (–2.73 V in NH_3) having a higher reduction potential than sodium, it has been demonstrated to mitigate competitive carbonyl reduction in aromatic ketones. In terms of co-solvents and proton sources, diethyl ether and THF are the most common co-solvents while *tert*-butyl alcohol and ethanol are the most common proton sources. However, glymes have also been reported as co-solvents, along with the use of methanol or other aliphatic alcohols as proton sources. Although the Birch reduction was initially disclosed using water, it is now rarely used as a proton source. The co-solvent is frequently used in lower amounts than the ammonia, and the reaction is typically run dilute. Additionally, there are traditionally two modes commonly employed for order of addition: 1) Substrate is dissolved in a co-solvent and then added to a solution of metal in ammonia and alcohol; or 2) Metal is added directly to a solution of substrate, ammonia, and co-solvent. In some cases, the proton source is added last. For quenching, typically solid ammonium chloride is added, followed by work-up *via* evaporation of ammonia, addition of a saturated brine solution

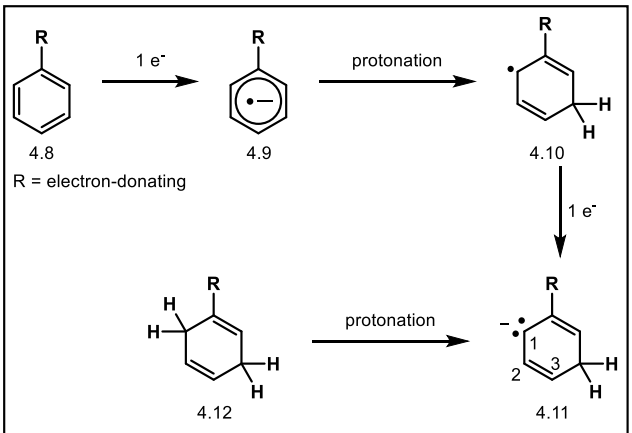
and extraction with an appropriate organic solvent. If a reductive alkylation is desired, quenching is done with the electrophile, although the lithium may be quenched prior to the addition of an electrophile with a diene such as 1,3-pentadiene, isoprene, or 1,3-cyclohexadiene.[4]

Ammonia-free conditions have also been developed; however, these tend to be less commonly used for several reasons, namely the propensity of overreduction, lack of substrate tolerance, and ease of use. Benkeser conditions replace ammonia with primary and/or secondary amines; however, these conditions are more reducing than standard ammonia-based conditions and frequently result in overreduction,[6] though recent work by Koide and coworkers has limited this overreduction.[7] The increased reduction power can be useful for difficult to reduce substrates. Electrochemical conditions were originally reported by Birch in 1946 using a copper cathode to reduce 1,3-dimethylbenzene.[8] Since then, there has been intense interest in developing electrochemical conditions,[9-14] along with photochemical conditions.[15, 16] However, despite these advances, the classic Birch reduction conditions still find frequent use.

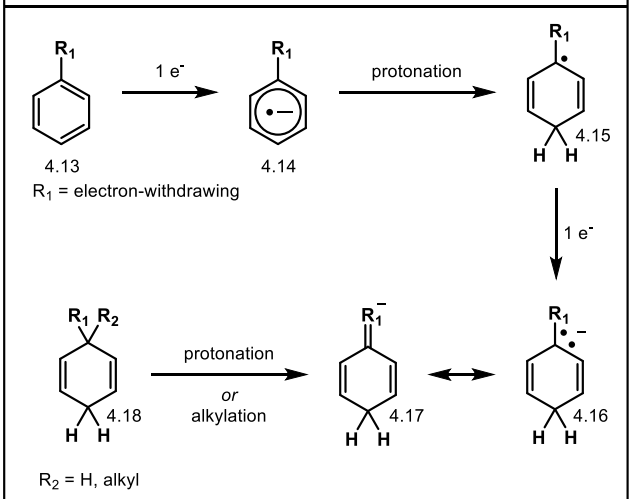
4.2.3 Mechanism of the Birch Reduction

Through empirical evidence, Birch concluded that the mechanism of the arene reduction must go through anionic intermediates.[1] He proposed that the aromatic ring accepts an electron from sodium, forming radical anion **4.9** (Scheme 4.2). This radical anion is then protonated at the *meta* position, followed by a second single-electron reduction, forming carbanion **4.11**. The second protonation then occurs *para* to the first protonation to give the 1,4-diene product **4.12**. Birch hypothesized that protonation would occur at the *meta* position first to reduce electronic repulsions. However, in 1961, Zimmerman demonstrated that molecular orbital theory was more appropriate to describe the protonation of the radical anion intermediate[17] than valence bond theory, as Birch had proposed. As such, Zimmerman indicated that the first protonation likely occurred at the *ortho* position, followed the second protonation occurring *para* to the first protonation (*meta* to the substituent). During the 1950s and 60s there was much debate regarding

the order of protonation; however, these arguments were usually made qualitatively.[18-20] In 1980 Birch and Radom published two reports detailing computational studies they performed to elucidate the order of protonation.[21, 22] Ultimately, they concluded that there was a slight preference for *ortho*-protonation although mixtures of *ortho*- and *meta*-protonation were likely to occur. Despite this, Birch asserted in the 1990s that *meta*-protonation is preferable.[23, 24] Also in the 1990s, Zimmerman aimed to elucidate the order of protonation using the kinetic isotope effect by deuterating the radical anion.[25, 26] He states that the radical anion should be more basic than the anion formed after the second reduction, and therefore deuteration should be conclusive. They observed greater deuterium incorporation at the *meta* site than the *ortho* site. Computations that they performed agreed with their findings. Despite these experiments, it is still ambiguous which site is protonated first in the Birch reduction mechanism and thus it can be typically depicted in either fashion without any detriment to the understanding of the reaction.



Scheme 4.2. Mechanism for reduction of electron-rich arenes



Scheme 4.3. Mechanism for reduction of electron-poor arenes

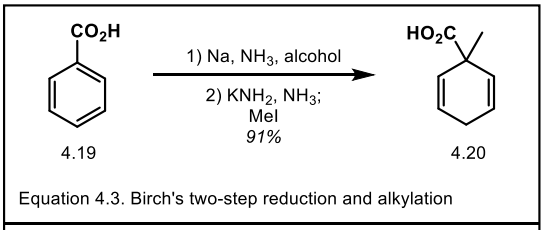
The second protonation step also requires mechanistic inquiries, since protonation could theoretically occur *ortho* or *para* to the first protonation. Computations have shown that electron density is greatest at the position *para* to the initial protonation, and therefore protonation is favored at that position.[25, 26] Additionally, the bond order between C1 and C2 has been calculated to be significantly lower than that between C2 and C3, which corresponds to the observed

selectivity.[17] Most importantly, *para*-protonation to the initial protonation site is almost exclusively observed in isolated products.

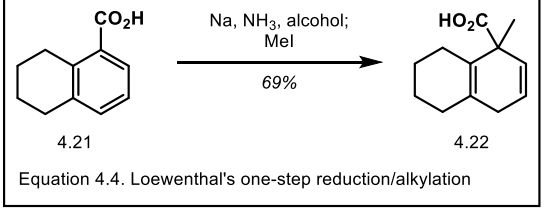
The mechanism of the Birch reduction of an aromatic ring bearing an electron-withdrawing substituent is much more clear (Scheme 4.3).[27, 28] A single electron reduction event produces radical anion **4.14** which is subsequently protonated. A second single electron reduction forms stabilized anion **4.16**. This anion can then be protonated or reacted with an electrophile, such as an alkyl halide, to give **4.18**.

4.3 The Birch Reduction/Alkylation Reaction

When the reduction of aromatic rings was first discovered, it was believed to go through an anionic intermediate as discussed in the previous section. As a result, it did not take long to see that this carbanion could be used advantageously in a synthetic setting. In 1950, Birch reported the alkylation of 1,4-dihydrobenzoic acid with methyl iodide; however, he did so in a two-step sequence of reduction then deprotonation and alkylation (Equation 4.3).[29] The first example of a single step procedure was reported in 1969 by Loewenthal and coworkers (J Org Chem 1969, 34, 126-135), wherein they disclose the reduction of **4.21** with sodium and ammonia, followed by alkylation with methyl iodide *en route* to gibberellic acid analogs (Equation 4.4).[28] Since this discovery, reductive alkylations have been reported for aromatic esters, amides, ketones, and nitriles, and have found extensive use in complex molecule synthesis.[4] While alkyl iodides are the most common electrophile, alkyl bromides, formaldehyde, α,β-unsaturated esters, and epoxides have all been used as electrophiles. Naturally, after discovery of the reductive alkylation procedure, ways to render this reaction stereoselective were pursued.



Equation 4.3. Birch's two-step reduction and alkylation



Equation 4.4. Loewenthal's one-step reduction/alkylation

4.4 Chiral Auxiliaries in the Birch Reduction/Alkylation Reaction

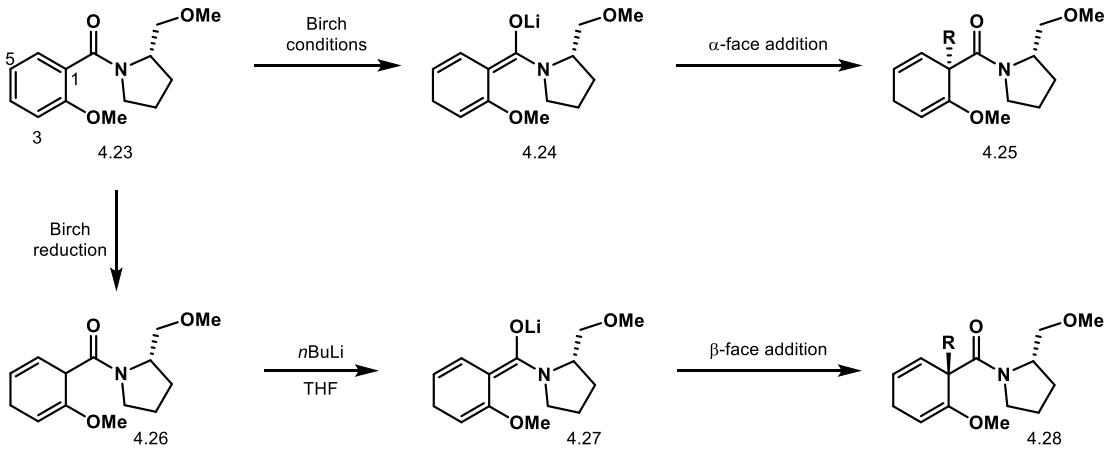
4.4.1 Introduction

In the 1980s and 90s, Arthur Schultz pioneered the diastereoselective Birch reduction/alkylation reaction.[30, 31] Similar to classical acyclic enolate alkylation chemistry wherein chiral auxiliaries were developed to render these reactions diastereoselective and therefore obtain enantiopure materials following cleavage of the auxiliary, Schultz applied the same concept to the Birch reduction/alkylation reaction. The Birch reduction of an arene bearing an electron-withdrawing group produces a stabilized carbanion, as described in the previous section, thus it can effectively be treated as a classical enolate. As such, Schultz developed a proline-derived chiral auxiliary to control the diastereoselectivity of the alkylation step. More recently, Donohoe and coworkers disclosed the use of trans-2-(α-cumyl)cyclohexanol and (–)-phenylmenthol as chiral auxiliaries in the reductive alkylation of pyrroles.[32]

4.4.2 Proline-Derived Chiral Auxiliaries

4.4.2.1 Introduction and Utility

Using proline as a scaffold, Schultz has developed two different chiral auxiliary systems.[30, 31] The first, and the most commonly employed, is **4.23** where the auxiliary is connected to the rest of the molecule solely through the amide bond (Scheme 4.4). The second, **4.31**, forms a seven membered ring with the substrate. For **4.23**, Schultz proposes a dimeric transition state, resulting in β-face addition of the electrophile (Figure 4.1).[33] To demonstrate the influence that the ammonia and the metal species are likely having on the stereochemical outcome, Schultz showed that if you deprotonate to form **4.27** under traditional enolate alkylation conditions, β-face attack of the electrophile is preferred as opposed to α-face attack under Birch conditions (Scheme 4.4).



Scheme 4.4. Difference in selectivity between Birch conditions and standard enolate conditions

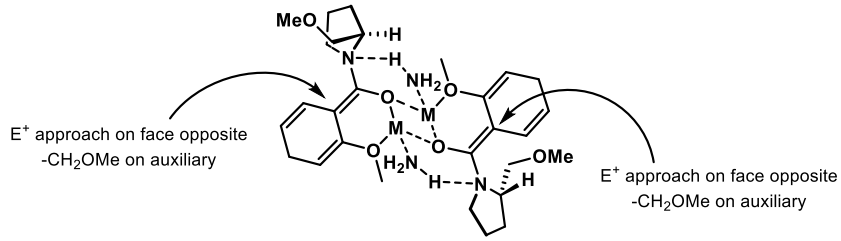
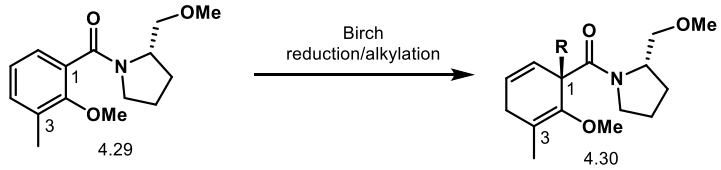
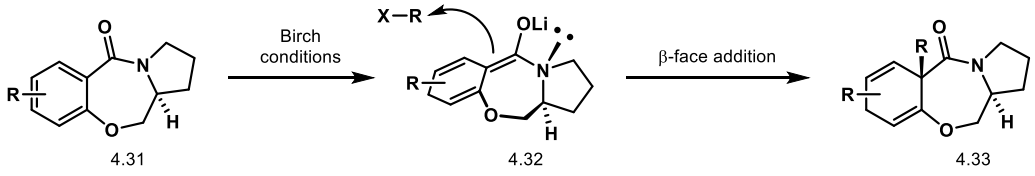


Figure 4.1. Schultz's proposed stereochemical model



Scheme 4.5. Change in alkylation selectivity with substitution at the 3-position



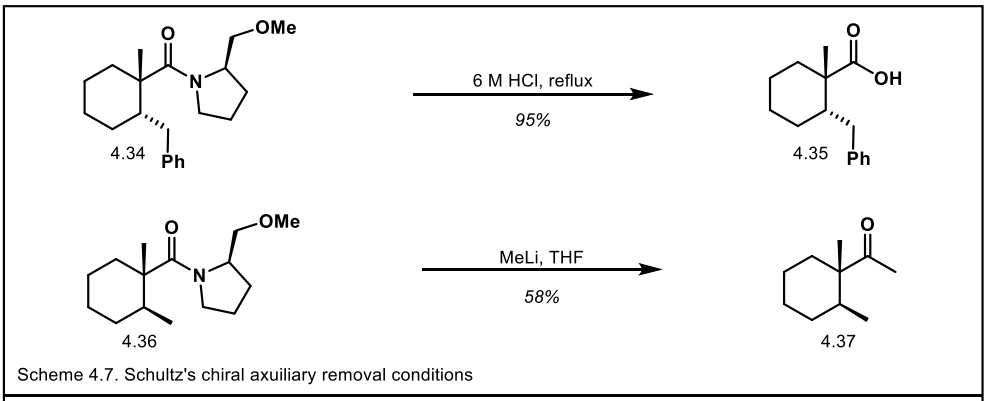
Scheme 4.6. Alkylation of seven-membered ring auxiliary

Interestingly, when a 3-methyl group is placed on the aromatic ring, once again β-face attack is observed; however, if the methyl group is placed at the 4-, 5-, or 6-positions, the standard α-face attack is observed (Scheme 4.5). This is likely explained by the pseudo-$A_{1,3}$ strain resulting from the 3-methyl and 2-methoxy substituents in the dimeric enolate aggregate. Interestingly, **4.23** and **4.31** give opposite selectivity, with **4.23** alkylating from the α-face and **4.31** alkylating from the β-face (Scheme 4.6). For **4.31**, Schultz proposes a convex attack onto enolate **4.32**. Regarding the substituents on the aromatic ring, the proline-derived auxiliary requires substitution at the 2-position. Typically, this is a methoxy group, although methyl, benzyl, allyl, along with several other aliphatic chains have also been used. Substrates typically give yields ranging from 60-90% with excellent diastereoselectivity (>20:1) using various alkyl iodides and bromides. Notably, substrates with 2-methoxy substitution alkylate from the α-face, while substrates with 2-alkyl substitution alkylate from the β-face. This lends credence to the hypothesis that the 2-methoxy substitution is providing a coordination effect in the active enolate species. Overall, Birch reduction/alkylation reactions using the proline-derived chiral auxiliaries give great yields, exceptional d.r., and can use a variety of alkylating agents. However, their main issue is how difficult they are to remove.

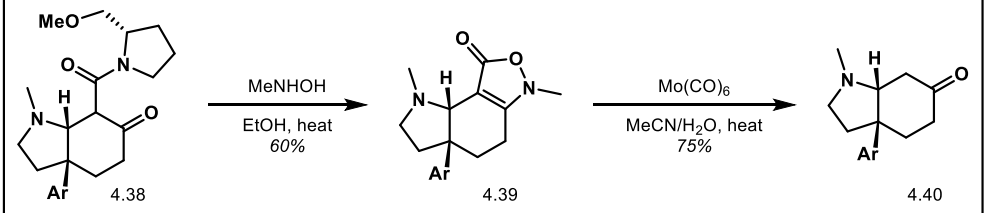
4.4.2.2 Removal Conditions

There are three direct ways to remove these proline-derived chiral auxiliaries.[30, 31] The first is to treat with aqueous HCl, often at reflux (Scheme 4.7). Chiral auxiliaries of type **4.31** are only known to be removed with acid, giving the carboxylic acid. The second is addition of methyllithium to afford the methyl ketone. These methods were developed and used by Schultz. The third is a recent protocol developed by Malachowski and coworkers wherein they require a β-ketone to the amide (Scheme 4.8).[34-37] Condensation of *N*-methylhydroxylamine with the ketone and subsequent displacement of the chiral auxiliary gives **4.39**. Treatment with $Mo(CO)_6$ returns the keto-acid after hydrolysis, which formally decarboxylates to give **4.40**. Additionally, Schultz has

demonstrated situations in which the auxiliary can be removed via iodolactonization; however, these examples are substrate specific.



Scheme 4.7. Schultz's chiral axuiliary removal conditions

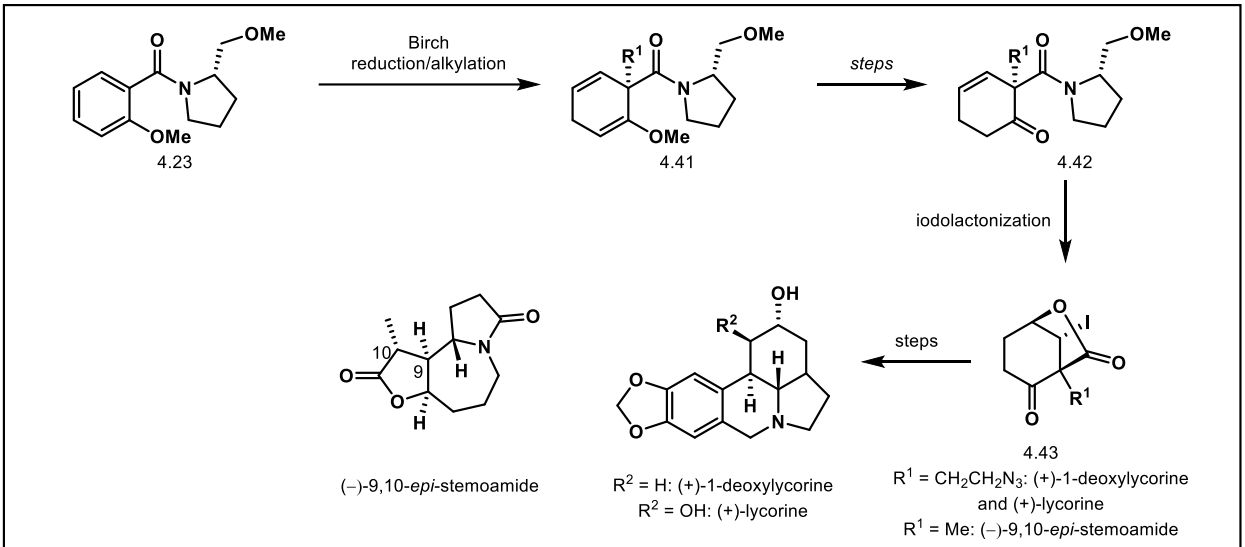


Scheme 4.8. Malchowski's two-step protocol for auxiliary removal

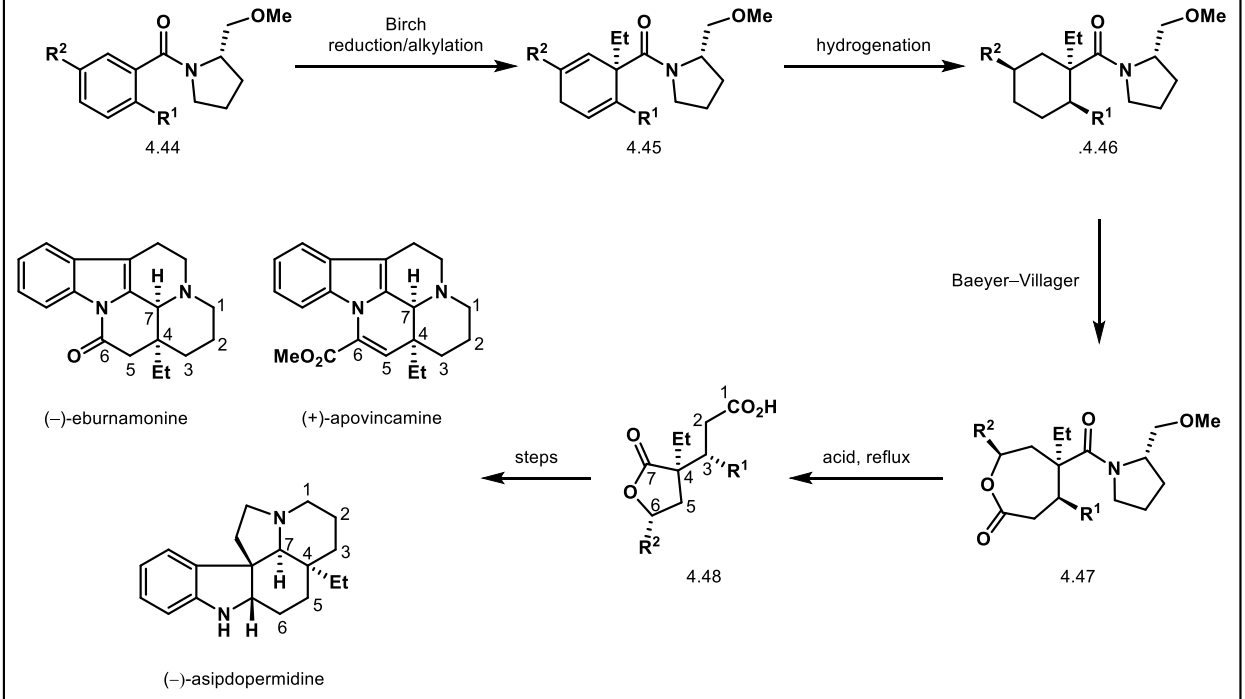
Given that these are the only known methods to remove the chiral auxiliary, this has become prohibitive towards its use in many settings. The chiral auxiliary is frequently carried through several steps until reaching a point at which the substrate is stable to hot acid; however, that is often not practical in complex settings. Addition of an organolithium to give a ketone cannot be typically relied on, and syntheses that do not require a ketone functionality at that position do not benefit from this strategy. Lastly, Malachowski's protocol is only helpful in the specific situation where a synthesis can accommodate a β-ketone, and also requires removal of the chiral auxiliary carbonyl as well.

4.4.2.3 Applications in Complex Synthesis

In the last 25 years there have been several examples of Schultz's proline-derived chiral auxiliary finding use in the synthesis of complex molecules. Many of the early examples were by Schultz himself; however, several other groups have found use for the auxiliary. In 1996 and



Scheme 4.9. Schultz's general strategy towards the synthesis of (+)-1-deoxylycorine, (+)-lycorine, and (–)-9,10-*epi*-stemoamide



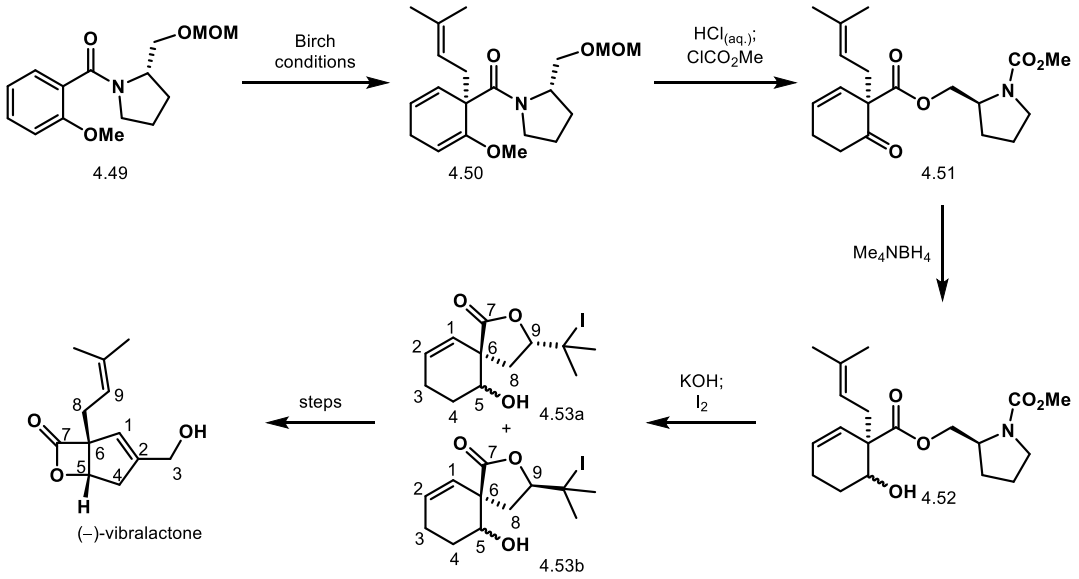
Scheme 4.10. Schultz's general strategy towards (+)-apovincamine, (–)-eburnamonine, and (–)-asipdopermidine

2004, Schultz published syntheses of (+)-lycorine/(+)-1-deoxylycorine[38] and (–)-9,10-*epi*-stemoamide[39] using his chiral auxiliary to set the stereochemistry at the quaternary carbon (Scheme 4.9). In both syntheses, a similar strategy is used regarding the diastereoselective Birch reduction/alkylation reaction. After formation of amide **4.23** the Birch reduction/alkylation reaction is performed with one of two electrophiles. After cleavage of the methyl alkenyl ether with acid to unveil the ketone, treatment with iodolactonization conditions forms lactone **4.43** and removes the chiral auxiliary. From here, the desired natural products are synthesized over several steps. A separate strategy was employed by Schultz in 1997 in his synthesis of (+)-apovincamine (Scheme 4.10).[40] After the Birch reduction/alkylation of **4.44** to form **4.45**, hydrogenation gives fully saturated cyclohexane **4.46**. Baeyer–Villager oxidation gives the ε-lactone, and treatment with acid at reflux forms the γ-lactone **4.48** and removes the chiral auxiliary. In several additional steps they were able to afford (+)-apovincamine and a formal synthesis of (+)-vincamine. This same strategy was also used in Schultz's synthesis of (–)-eburnamonine and (–)-aspidospermidine albeit with different substitutions on the aromatic ring.[41]

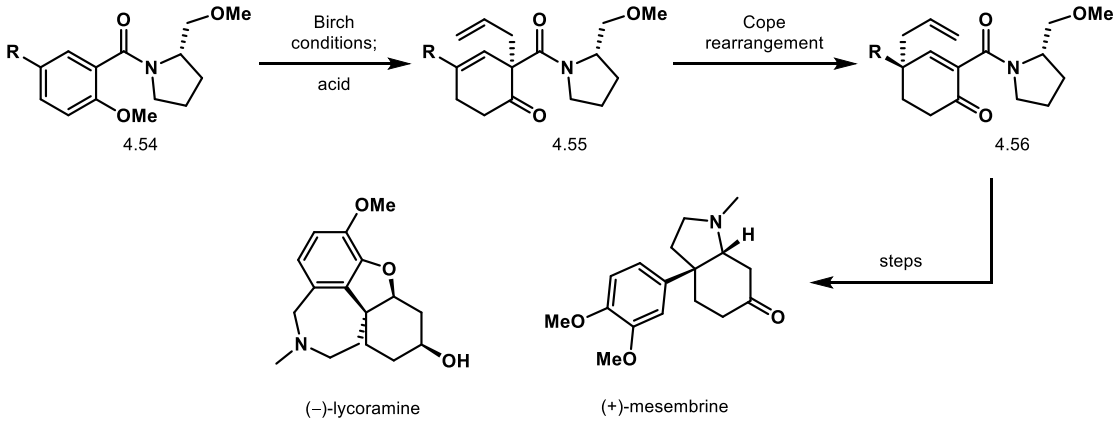
In 2008, Snider and coworkers reported a synthesis of (–)-vibralactone using a diastereoselective Birch reduction/alkylation as a key step (Scheme 4.11).[42] Starting from arene **4.49** and using prenyl bromide as the electrophile, they formed **4.50**. They used the methoxymethyl ether (MOM)-protected auxiliary instead of the methyl-protected because they found all attempts at hydrolysis of the methyl-protected auxiliary unsuccessful. Treatment of **4.50** with acid deprotected the MOM group and resulted in formation of ester **4.51**, which could later be removed *via* saponification then iodolactonization to afford lactones **4.53a** and **4.53b**. Several additional steps yielded (–)-vibralactone.

The Malachowski group has published a series of reports on an enantioselective Birch/Cope sequence that they have used in the synthesis of several natural products and natural product scaffolds (Scheme 4.12).[34-37] Following the Birch reduction/alkylation reaction of **4.54**,

using an allylic electrophile, they hydrolyze the alkenyl ether with acid to reveal the β-keto amide **4.55**. They perform the Cope rearrangement to afford substrates such as **4.56**. The Malachowski group has used this strategy in the synthesis of (+)-mesembrine,[37] (–)-lycoramine,[36] and of diterpene scaffolds.[34, 35] Their means of removal is described in section 4.4.2.2 wherein treatment of the β-keto amide with *N*-methylhydroxylamine forms the 5-isoxazoline and reduction with $Mo(CO)_6$ cleaves the N-O bond and formally decarboxylates.



Scheme 4.11. Snider's synthesis of (–)-vibralactone

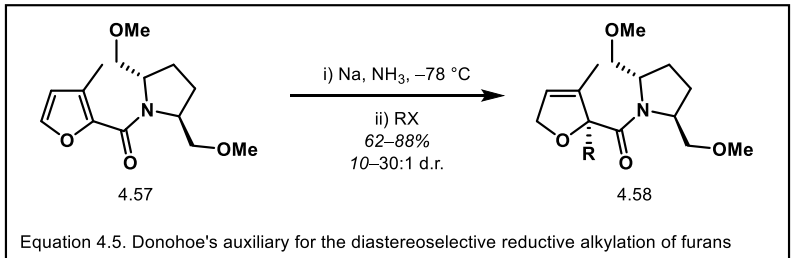


Scheme 4.12. Malachowski's syntheses of (–)-lycoramine and (+)-mesembrine

There have been several other reports of Schultz's proline-derived chiral auxiliary; however, these are not discussed in this thesis since their use is similar to the reports previously mentioned.[43-53]

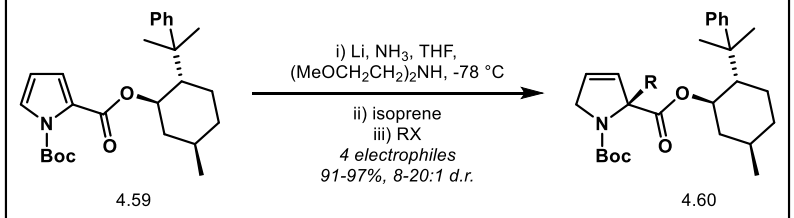
4.4.3 Other Chiral Auxiliaries

To date, two other chiral auxiliaries have been used in a reductive alkylation reaction of aromatic systems. In 1998, Donohoe and coworkers reported the reductive alkylation of pyrroles.[32] Previously, they had disclosed the reductive alkylation of furans, using an altered version of Schultz's proline-derived chiral auxiliary (Equation 4.5).[54] In this report they note that Schult'z proline-derived chiral auxiliary gave poor diastereoselectivity (1.5:1 d.r.) with furans, leading them to try alternative auxiliaries. They also report the use of (–)-8-phenylmenthol (Equation 4.6) and trans-2-(α-cumyl)cyclohexanol (Equation 4.7) as chiral auxiliaries in the reductive alkylation of pyrrole-2-carboxylic acid derivatives.[32] Using (–)-8-phenylmenthol they used MeI, EtI, *n*BuI, and BnBr as electrophiles, observing yields of 91–97% and diastereomeric ratios of 8–20:1. However, they note that they moved away from (–)-8-phenylmenthol as a chiral auxiliary due to its difficult access. At the time, the procedure to synthesize it was lengthy, and access to the other enantiomer was impractical. Using trans-2-(α-cumyl)cyclohexanol instead and



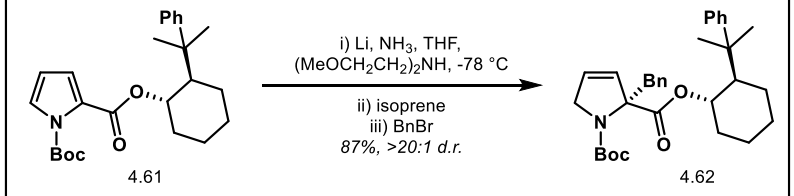
4.57 4.58

Equation 4.5. Donohoe's auxiliary for the diastereoselective reductive alkylation of furans



4.59 4.60

Equation 4.6. Donohoe's use of (–)-8-phenylmenthol as a chiral auxiliary



4.61 4.62

Equation 4.7. Donohoe's use of *trans*-2-(α-cumyl)cyclohexanol as a chiral auxiliary

benzyl bromide as the electrophile, they observed an 87% yield and >20:1 d.r. of **4.62**. To the best of my knowledge, this single example is the only report of a reductive alkylation using a chiral auxiliary other than Schultz's proline-derived example.

4.5 Conclusions

The Birch reduction of aromatic rings has been a widely used synthetic transformation to access cyclohexadiene and therefore cyclohexane scaffolds from aromatic rings. Furthermore, the Birch reduction/alkylation reaction has proven to be an extremely powerful transformation in organic chemistry. The ability to form a stereogenic quaternary carbon directly from abundant chemical feedstocks like substituted benzenes has resulted in its widespread use in organic synthesis. Despite the importance of this transformation, there has been little advancement in the area of diastereoselective Birch reduction/alkylation reactions since Schultz developed the proline-derived chiral auxiliary in the late 1980s/early 1990s. While this auxiliary has been used extensively, its use also been greatly restricted by the harsh or very specific and substrate-dependent conditions required to remove it. As a result, many syntheses that could benefit from the generation of 1,4-cyclohexadienes bearing stereogenic quaternary carbons must look towards other strategies. Thus, development of a method that allows for the diastereoselective Birch reduction/alkylation of substituted benzenes using an easily removable chiral auxiliary would be of great utility to the synthetic community.

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Chapter 5: Development of a Diastereoselective Birch Reduction/Alkylation Reaction of Substituted Benzenes Using Ester Chiral Auxiliaries

5.1 Introduction and Motivations

While working on a general and concise route towards a synthesis of several members of the agarofuran family of natural products (see Chapter 3), I found that the use of Schultz's proline-derived chiral auxiliary prevented progress in the synthetic route (Chapter 3, section 3.3.2). The auxiliary provided enough steric hinderance to prevent productive reactivity at other sites on the molecule; furthermore the chiral auxiliary could not be removed in the presence of the other functionality, namely the 1,4-cyclohexadiene that would frequently aromatize. Since the inability to remove the auxiliary precluded any advancement of the synthesis, I hypothesized that a more labile auxiliary would solve this issue. As a result, I looked to exchange the amide chiral auxiliary for an ester chiral auxiliary. However, as mentioned in chapter 4, the only example using an ester chiral auxiliary in a reductive alkylation was Donohoe's reductive alkylation of pyrroles.[1] Since there had never been an example of a diastereoselective Birch reduction/alkylation reaction on benzene derivatives that did not use an amide chiral auxiliary, I saw an opportunity to develop conditions using an ester chiral auxiliary. If this were to be successful, this work could be generalized as a new method that would allow for greater utility of this powerful Birch reduction/alkylation transformation. A more labile chiral auxiliary is more easily removed, and thus has wider applicability. This, in turn, would hopefully spur increased interest in the use of diastereoselective Birch reduction/alkylation reactions in the synthesis of complex molecules.

5.2 Development of the Chiral Auxiliary

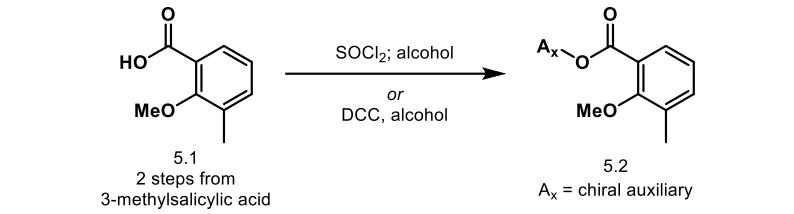
5.2.1 Introduction

Schultz had proposed models for the diastereoselectivity observed for both his acyclic and cyclic chiral auxiliaries.[2] As described in chapter 4, the acyclic chiral auxiliary is hypothesized to form a dimeric intermediate which results in electrophile addition from the α-face. When a 3-methyl group is present, such as in my substrate, the opposite selectivity is observed, as described in the previous chapter. The cyclic chiral auxiliary is hypothesized to adopt a puckered conformation, allowing alkylation from the β-face.[3, 4] These models are inapplicable when changing from an amide chiral auxiliary to an ester chiral auxiliary. The decreased basicity of oxygen compared to nitrogen likely impedes formation of the dimeric intermediate. Additionally, nitrogen forms an extra bond that oxygen cannot, therefore providing greater rigidity in the auxiliary structure which can aid in maintaining a specific conformation to provide the desired diastereoselectivity. As a result, alternative approaches to delivering the desired diastereoselectivity must be considered when using an ester chiral auxiliary.

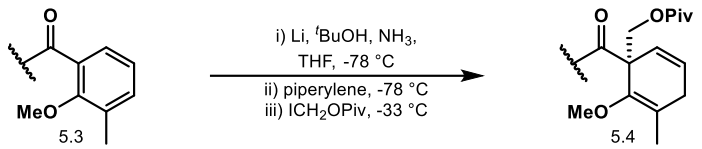
5.2.2 Optimization of Chiral Auxiliary

To test different chiral auxiliaries in the diastereoselective Birch reduction/alkylation reaction, I used the same arene and electrophile that I had used with the proline-derived chiral auxiliary. The Birch reduction substrates were all synthesized from 3-methyl-2-methoxybenzoic acid (Equation 5.1). Appending the chiral auxiliary was done either through addition of the alcohol into the acid chloride formed from 3-methyl-2-methoxybenzoic acid, or using a carboxylic acid activating reagent such as DCC. Iodomethylpivalate, synthesized *via* a Finkelstein reaction from chloromethylpivalate, was chosen as the electrophile since the resulting product, **5.4**, had potential utility in the synthesis of the agarofurans.

Initially, to observe the role of the chiral auxiliary's steric environment on the observed diastereoselectivity, (–)-borneol, (–)-menthol, and (–)-isomenthol were all chosen as potential chiral auxiliaries. Since they all are saturated hydrocarbons, they would test what level of influence only the steric environment has on the diastereoselectivity of the Birch reduction/alkylation reaction. Unsurprisingly, they displayed nearly no selectivity (Table 5.1). This illustrated that the freedom of rotation around the C–O bond in the auxiliary was likely not allowing any particular reactive conformation to take precedence, thus imparting no significant selectivity. As a result, to deliver good selectivity, an intramolecular interaction would need to be harnessed to restrict the conformation and enable the auxiliary to control facial selectivity.



Equation 5.1. Synthesis of substrates for optimization studies



Chiral Auxiliary	*Yield*	*d.r.*
(–)-borneol	61%	1.2:1
(–)-menthol	28%	1.1:1
(+)-isomenthol	82%	1.2:1

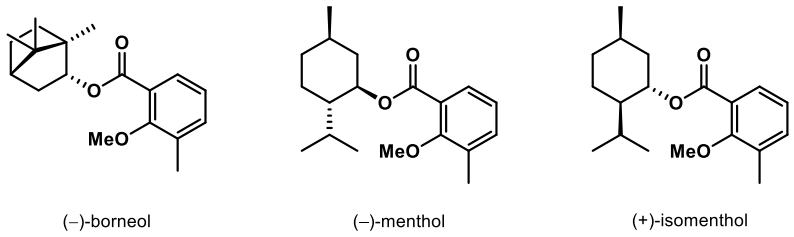
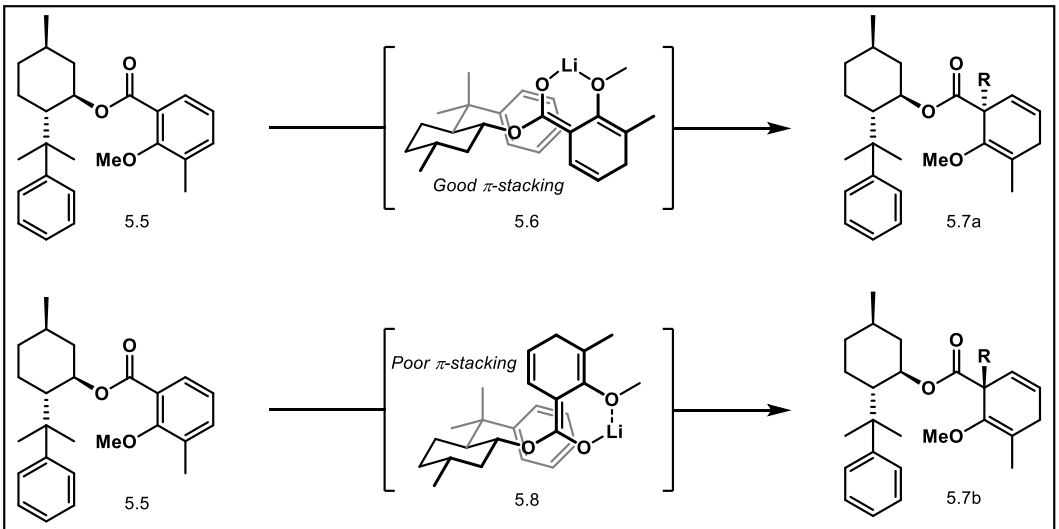


Table 5.1. Chiral auxiliary optimization: examination of the effect of the steric environment

Since the lithium ions in solution likely coordinate with the methoxy group and the ester carbonyl, thus holding the ester carbonyl in one conformation, the main problem to solve is how to keep the remainder of the ester chiral auxiliary in one conformation that blocks one face of the substrate. Following the reduction of the aromatic ring, a very electron-rich triene is formed. I

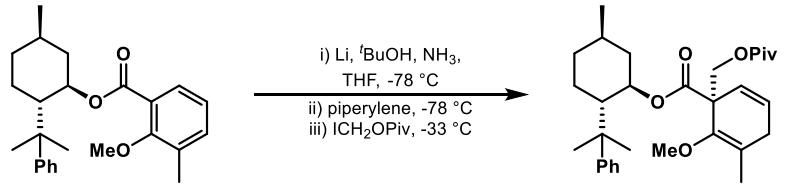
hypothesized that if an aromatic group existed on the chiral auxiliary, it could participate in a π-stacking interaction with the electron-rich triene (Scheme 5.1). However, there are two potential conformations. I hypothesize that reactive conformation **5.6** would predominate over **5.8** due to the phenyl ring and the triene being in greater proximity than with **5.8**. As a result, this could impart the desired selectivity. To date, there have been several chiral auxiliaries developed to take advantage of π-stacking interactions. As discussed in chapter 3, Corey and coworkers have



Scheme 5.1. Potential stereochemical models for a π-stacking chiral auxiliary

developed a hydroxy sulfone auxiliary for diastereoselective enolate alkylations and Diels–Alder reactions.[5] (–)-8-Phenylmenthol has been used as a chiral auxiliary in several different transformations;[6-9] however, the most relevant of these is Donohoe's reductive alkylation of pyrroles. Donohoe also demonstrated the use of *trans*-2-(α-cumyl)cyclohexanol since (–)-8-phenylmenthol was arduous to synthesize at that time.[1] However, Shenvi and coworkers have since developed a simple two-step protocol to synthesize (–)-8-phenylmenthol and related analogs.[10] Switching to (–)-8-phenylmenthol as the chiral auxiliary, I observed a 46% yield and a promising 4:1 d.r., thus providing support that the π-stacking hypothesis might be viable (Table 5.2). While setting up this reaction, I noticed that the solution turned an opaque white before the addition of lithium. I interpreted this to mean that my largely non-polar substrate was likely only

moderately soluble in the 5:1 ammonia:THF mixture at –78 °C. In an effort to increase the solubility of the substrate, I increased the amount of THF to a 2:1 ratio of ammonia:THF. With the improved solubility, I observed an increase in the yield and d.r. to 66% and 7:1, respectively. Increasing the amount of THF even further, to a ratio of 1:1, I observed a further increase in the yield to 80% and the d.r. remained constant at 7:1. Further increases in the amount of THF were never attempted since at a ratio of 1:1 ammonia:THF, the amount of time required to solubilize the lithium was significant, taking upwards of 30 minutes. While this was not problematic for the overall transformation, increasing the amount of THF further would be disadvantageous to the protocol. Since Shenvi and coworkers' 2 step protocol to synthesize (–)-8-phenylmenthol also allows for other aromatic substitutions, the (–)-8-(4-fluorophenyl)menthol (**5.10**), (–)-8-bis(3,5-trifluoromethyl)phenylmenthol (**5.11**), (–)-8-(1-naphthyl)menthol (**5.12**), and (–)-8-(2-

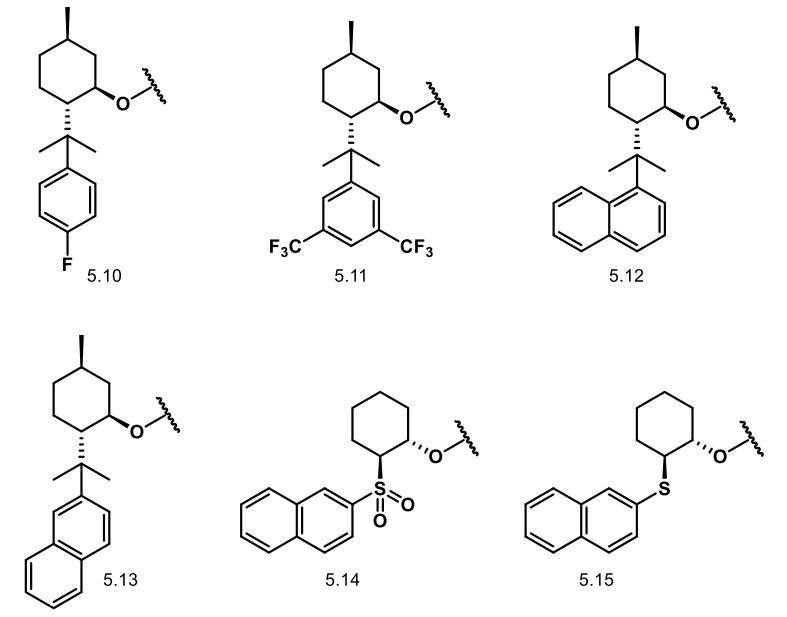


5.5
(–)-8-phenylmenthol

5.9

NH_3:THF	Yield	d.r.
5:1	46%	4:1
2:1	66%	7:1
1:1	80%	7:1

Table 5.2. Final optimization of chiral axuiliary



5.10 5.11 5.12

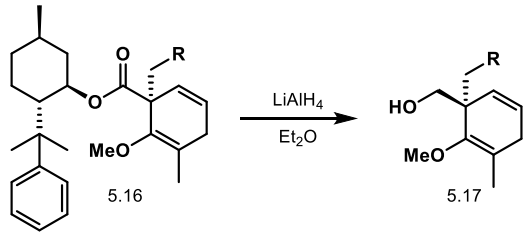
5.13 5.14 5.15

Figure 5.1. Other auxiliaries examined during optimization

naphthyl)menthol (**5.13**) auxiliaries were synthesized and evaluated in the Birch reduction/alkylation reaction by an undergraduate student, Michael Lehman (Figure 5.1).[10] I hypothesized that the electron-poor auxiliaries (**5.10** and **5.11**) could improve the diastereoselectivity by electronically matching with the electron-rich triene following Birch reduction of the arene. Matching the electron-poor auxiliary with the electron-rich substrate could improve the electrostatic interactions between them, thus creating a much stronger interaction and providing greater selectivity. However, by making the auxiliary more electron-poor, it could be competitively reduced and unfortunately, this is exactly what was observed. For the naphthyl-containing auxiliaries (**5.12** and **5.13**), I hypothesized that extension of the π-system would increase the strength of the π-stacking interaction; however, they were competitively reduced. Use of Corey's hydroxy sulfone auxiliary, **5.14**, along with the thioether version, **5.15**, resulted only in reduction of the carbon–sulfur bond. Since none of these additional menthol-derived auxiliaries proved advantageous, the substrate scope was developed using (–)-8-phenylmenthol. With optimized reaction conditions in hand, a method to remove the auxiliary were explored and a substrate scope was developed.

5.3 Removal of Chiral Auxiliary

As discussed in chapter 3, attempts to remove the chiral auxiliary from diester substrate **5.9** were largely unsuccessful. Most attempts led to aromatization back to the Birch reduction precursor, **5.5**, or showed little to no conversion. However, removal of the chiral auxiliary when an aliphatic or ethereal electrophile was used was simple and straightforward. Treatment of **5.16a** or **5.16b** with $LiAlH_4$ in Et_2O gave 71% and 88% yield of the desired alcohol, respectively, and 90% recovery of the chiral auxiliary, respectively



5.16 5.17

5.17a: R = Ph: 71% yield of alcohol

5.17b: R = $O(CH_2)_2TMS$: 88% yield of alcohol; 90% yield of phenylmenthol

Equation 5.2. Removal of chiral auxiliary

(Equation 5.2). This demonstrated that when electrophiles other than iodomethylpivalate were used that the chiral auxiliary could be easily removed.

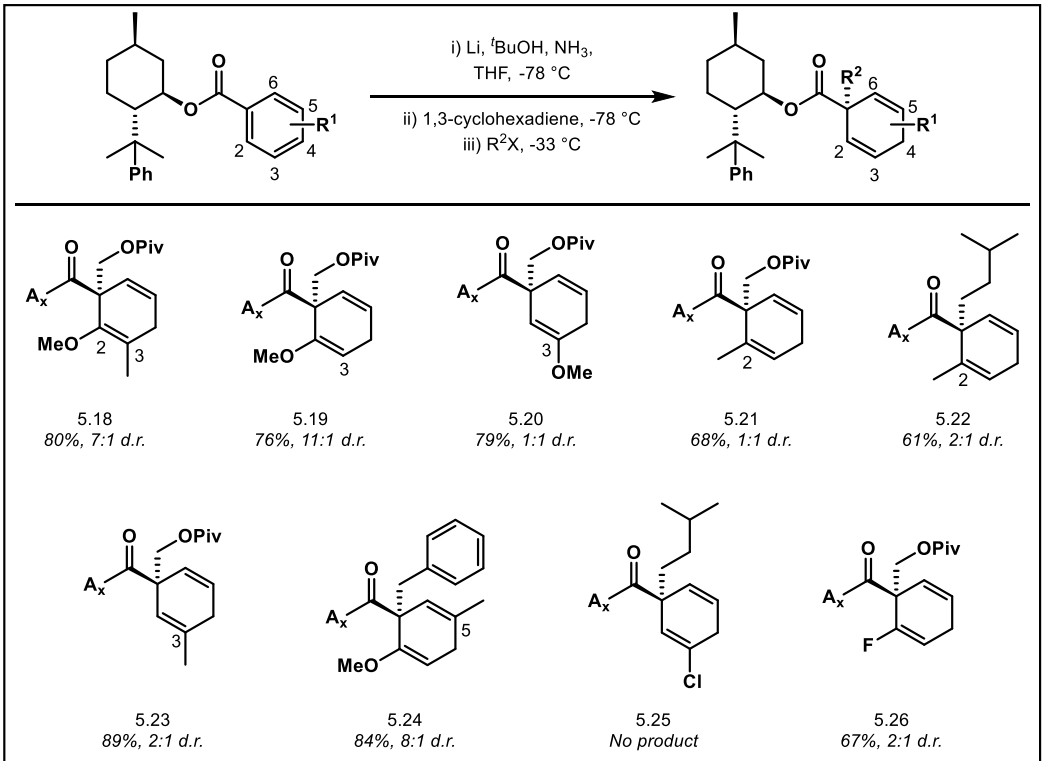
5.4 Substrate Scope

5.4.1 Introduction

My fellow graduate student, Hanh Nguyen, produced most of the results for the substrate scope though we collaborated on the arenes and electrophiles chosen for the scope. We identified the two major factors we wished to explore: 1) The impact of differing substituents and substitution patterns on the aromatic ring; and 2) The impact of different electrophiles and the range of tolerance for different functional groups. In particular, we wished to see whether the 2-methoxy substituent on the aromatic ring was necessary for the observed diasteroselectivity, and more broadly, if substitution at the 2-position was necessary at all. Additionally, we aimed to see if halogen substitution was tolerated. For the electrophiles, we wanted to explore the use of alkyl iodides, bromides, and activated alkyl chlorides. We also wished to observe the tolerance towards several functional groups including, but not limited to, nitriles, Boc-protected amines, and protected alcohols.

5.4.2 Arene Substrate Scope

In the optimization of the reaction conditions, the 3-methyl-2-methoxy substrate/iodomethyl pivalate combination gave an 80% yield and a 7:1 diastereomeric ratio (**5.18**, Table 5.3). Swapping the 3-methyl group for a hydrogen gave a similar yield, but increased the d.r. to 11:1 (**5.19**). This increase in selectivity likely results from the removal of potential $A^{1,3}$-type strain between the methyl and methoxy groups, which could result in the methoxy-methyl group disrupting the π-stacking interaction. Moving the methoxy group to the 3-position gave a comparable yield, but there was no selectivity (**5.20**). This shows that 2-substitution is necessary for selectivity. Exchanging the 2-methoxy group for a 2-methyl group also results in complete loss



5.18 *80%, 7:1 d.r.* | 5.19 *76%, 11:1 d.r.* | 5.20 *79%, 1:1 d.r.* | 5.21 *68%, 1:1 d.r.* | 5.22 *61%, 2:1 d.r.*

5.23 *89%, 2:1 d.r.* | 5.24 *84%, 8:1 d.r.* | 5.25 *No product* | 5.26 *67%, 2:1 d.r.*

A_x = (–)-8-phenylmenthol

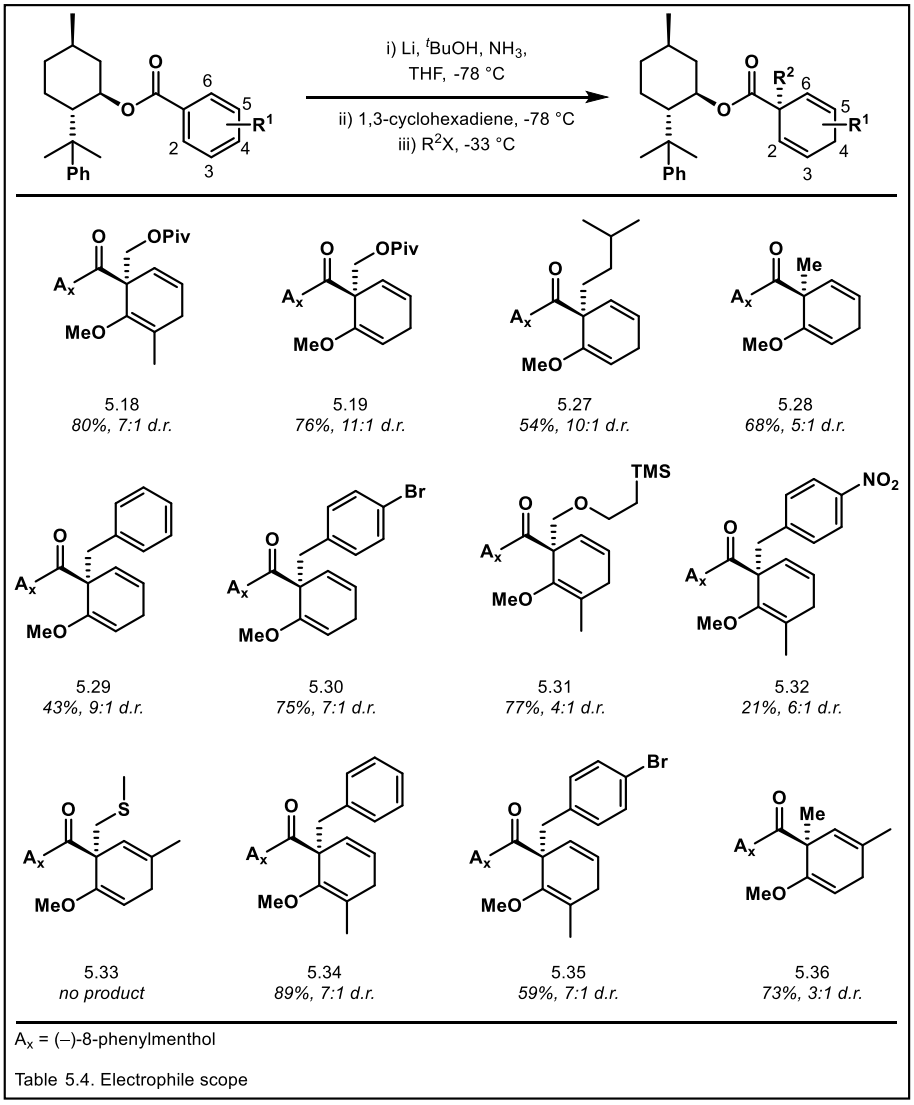
Table 5.3. Arene substrate scope

of selectivity (**5.21**). This same trend is observed with alkyl electrophiles (**5.22**) and with a 3-methyl substitution (**5.23**). Thus, we concluded that a 2-alkoxyoxy substitution is required for selectivity. Keeping the 2-methoxy substitution constant, the methyl group was now moved to the 5-position. Using benzyl bromide as the electrophile, an 84% yield and 8:1 d.r is observed (**5.24**). As of this writing, experiments to test 2-methoxy-6-methyl substrates are underway.

Halogen substitution on the aromatic ring was also tested. A 3-chloro substitution resulted in none of the desired product, likely due to reduction of the carbon–chlorine bond (**5.25**). As a result, bromine and iodine substitution would likely give similar results; however, a carbon-fluorine bond was unlikely to be reduced. A substrate containing 2-fluoro substitution gave a 67% yield; however, the d.r. was poor at 2:1, likely due to poor coordination of the fluorine to lithium (**5.26**).

5.4.3 Electrophile Scope

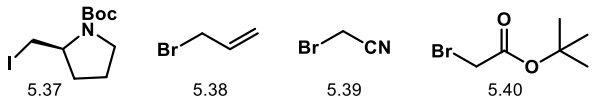
To explore the electrophile scope, we wanted to examine electrophiles with a range of electronic differences and steric environments (Table 5.4). Iodomethylpivalate was demonstrated in the previous section to give good yield and diastereoselectivity (**5.18, 5.19**). Using a simple akyl iodide gave moderate yield and good diastereoselectivity, of 54% and 10:1, respectively (**5.27**). Methyl iodide, however, gave reduced selectivity (5:1), likely owing to its smaller size (**5.28**). Benzyl bromide (43%, 9:1) and 4-bromobenzyl bromide (75%, 7:1) gave moderate to good yields and good diastereoselectivity (**5.29, 5.30**). Using SEMCl gave good yield (77%) although modest selectivity (4:1, **5.31**). A very low yield, although with moderate diastereoselectivity was



A_x = (–)-8-phenylmenthol

Table 5.4. Electrophile scope

obtained using 4-nitrobenzyl bromide (21%, 6:1, **5.32**). This low yield can likely be attributed to the reduction of the nitro group by the reduced arene since starting arene was recovered despite full conversion after the Birch reduction step. Lastly, no product was observed when using chloromethyl methyl sulfide (**5.33**). Use of benzyl bromide (89%, 7:1) and 4-bromobenzyl bromide (59%, 7:1) with the 2-methoxy-3-methyl substrate also gave moderate to good yield and good diastereoselectivity (**5.34, 5.35**). To complete the electrophile substrate scope, we plan to examine the following electrophiles: **5.37**, **5.38**, **5.39**, and **5.40** (Figure 5.2).



5.37 5.38 5.39 5.40

Figure 5.2. Remaining electrophiles to complete substrate scope

5.5 Conclusions and Future Directions

I have developed a novel diastereoselective Birch reduction/alkylation reaction of salicylic acid derivatives using an ester chiral auxiliary. The diastereoselectivity is presumably imparted through a π-stacking interaction between the phenyl group on the (–)-8-phenylmenthol chiral auxiliary and the triene resulting from reduction of the aromatic substrate. Competitive reduction of the chiral auxiliary is not observed. When electrophiles other than iodomethylpivalate are used, the chiral auxiliary can be easily removed *via* $LiAlH_4$ reduction. To date, the aromatic ring has been shown to tolerate substitution at positions 2-5, and experiments to examine the 6-methyl substitution are underway. Most importantly, a 2-methoxy substitution has been demonstrated to be necessary for diastereoselectivity, as removal or replacement of the 2-methoxy group results in steep erosion of the diastereoselectivity. The reaction is not tolerant of chlorine substitution and in one case fluorine substitution gives poor diastereoselectivity. The electrophile scope has shown that several alkyl iodides and bromides and one activated alkyl chloride proceed in moderate to excellent yield and diastereoselectivity. The reaction has proven tolerant of aromatic bromides, esters, aromatic rings, and SEM-protected alcohols, although it is intolerant of nitrobenzenes and

thioethers. To complete the electrophile scope, a BOC-protected amine, allyl bromide, bromoacetonitrile, and *tert*-butyl bromoacetate will be examined.

5.6 Distribution of Credit and Contributions

- Undergraduate Student **Michael Lehman** is acknowledged for his help in substrate synthesis and for the synthesis and testing of several chiral auxiliaries. He was specifically responsible for determining that chiral auxiliaries **5.10**-**5.15** were reduced under the reaction conditions.
- Graduate student **Hanh Nguyen** is acknowledged for her great deal of effort in working towards the completion of the substrate scope. She is specifically responsible for the synthesis and characterization of all products in the substrate scope and their corresponding starting materials except for **5.18**, **5.27**, and **5.31**. She is also responsible for confirmation of the diastereoselectivity by removal of the chiral auxiliary and determination of the enantioselectivity of the resulting compound by SFC. Lastly, she is acknowledged for her continued hard work on this project and seeing it through to completion and ultimately to publication.

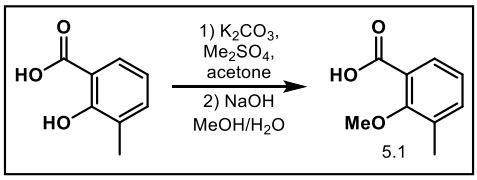
5.7 Experimental Information

5.7.1 Materials and Methods

All reactions were carried out in flame dried glassware under an argon atmosphere with a Teflon® coated stir bar, unless otherwise noted. Dry DCM, THF, MeCN, Et_2O, PhH, PhMe were obtained by percolation through columns packed with neutral alumina and columns packed with Q5 reactant under argon. All solvents used for extraction and flash chromatography were purchased from either Sigma-Aldrich or Fischer and used with no further purification. All amine bases were distilled from calcium hydride before use, unless otherwise noted. All reagents were used as received from commercial sources or prepared according to literature procedures, unless

otherwise noted. Flash chromatography was performed using Geduran® Silica Gel 60 (0.040 – 0.063 mm) mesh silica gel, and eluent mixtures are reported as %v/v. Analytical thin-layer chromatography (TLC) was performed on Merck silica gel 60 F254 TLC plates, using UV (254 nm), $KMnO_4$ in K_2CO_3/NaOH/H_2O with heat, or *p*-anisaldehyde in ethanol/$H_2SO_{4(aq)}$/$AcOH_{(aq)}$ with heat to visualize. ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker CRYO500 or AVANCE600 spectrometer equipped with a CRYO500 probe at 298 K, unless otherwise noted. Chemical shifts are reported in parts per million, using residual solvent ($CHCl_3$) as internal calibration (7.26 ppm for ^{1}H) or $CDCl_3$ as internal calibration (77.16 ppm for ^{13}C). Couplings are reported using the following designations: s = singlet, d= doublet, t = triplet, q = quartet, quin = quintet, hept = heptet, m = multiplet. Coupling constants are reported in Hertz measured at the reported field strengths. High-resolution mass spectra were obtained on a Waters LCT Premier spectrometer using ESI-TOF and values are reported as [*m*/*z*]. Enantiomeric ratio for reduction product after diastereoselective Birch reduction/alkylation reactions was determined by chiral SFC analysis using an Agilent Technologies HPLC (1200 series) system and Aurora A5 Fusion.

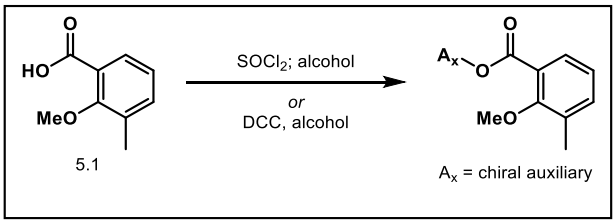
5.7.2 Experimental Procedures and Characterization Data



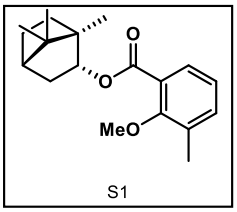
2-methoxy-3-methylbenzoic acid 5.1. A flame-dried 250 mL round bottom flask equipped with a stir bar was charged with 3-methylsalicylic acid (1.00 g, 6.57 mmol), and freshly ground K_2CO_3 (3.63 g, 26.29 mmol). The minimum amount of acetone necessary to allow for stirring was added (~75 mL) and the slurry was allowed the stir. Me_2SO_4 was added dropwise (2.49 mL, 26.28 mL) and the reaction was stirred until deemed complete by aliquot ^{1}HNMR. The reaction mixture was diluted with H_2O (200 mL) and extracted with diethyl ether (3 x 200 mL). The combined organic

extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting clear oil was dissolved in methanol (13 mL) and added dropwise to a stirred solution of NaOH (2.63 g, 65.7 mmol) in H_2O (5.5 mL). After full consumption of starting material was judged by TLC, the reaction mixture was acidified to pH 1, and extracted with EtOAc (3 x 200 mL). The combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo* to afford a white solid (1.08 g, 99%).

^1H and ^{13}C NMR spectra were consistent with those previously reported.[11]



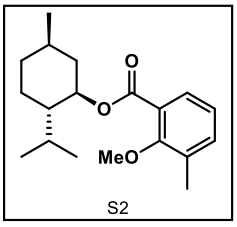
General esterification procedure A. A flame-dried 250 mL round bottom flask equipped with a stir bar was charged with **5.1** (1 equiv.) and $SOCl_2$ (1.4 M). The flask was equipped with a reflux condenser and the reaction mixture was heated to reflux for 3 hours. After cooling to room temperature, the reaction mixture was diluted with benzene (0.93 M) and concentrated *in vacuo*. This process was repeated two more times. The resulting yellow oil was dissolved in benzene (2.3 M) and added dropwise to a stirred solution of alcohol (2.0 equiv.) and Et_3N (2.0 equiv.) in dichloromethane (0.46 M) at 0 °C. After stirring overnight, the reaction mixture was diluted with dichloromethane and washed with H_2O and a brine solution, then the phases were separated and the organic phase was dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (5% EtOAc in hexanes) to afford the product as a clear oil.



S1

(–)-borneol ester S1. Carboxylic acid **5.1** (100 mg, 0.602 mmol) was subjected to general esterification procedure A to afford ester **S1** as a clear oil (175 mg, 96%).

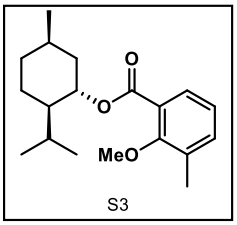
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.07 (ddd, *J* = 7.7, 4.7, 1.7 Hz, 1H), 5.14 (d, *J* = 9.6 Hz, 1H), 3.88 – 3.80 (m, 3H), 2.50 (td, *J* = 10.2, 5.1 Hz, 1H), 2.34 (s, 3H), 2.12 (td, *J* = 9.7, 4.7 Hz, 1H), 1.85 – 1.76 (m, 1H), 1.74 (t, *J* = 3.6 Hz, 1H), 1.43 – 1.34 (m, 1H), 1.30 (ddd, *J* = 14.7, 10.8, 3.7 Hz, 2H), 1.15 (s, 1H), 0.98 (s, 3H), 0.95 – 0.90 (m, 6H).



S2

(–)-menthol ester S2. Carboxylic acid **5.1** (100 mg, 0.602 mmol) was subjected to general esterification procedure A to afford ester **S2** as a clear oil (180 mg, 98%).

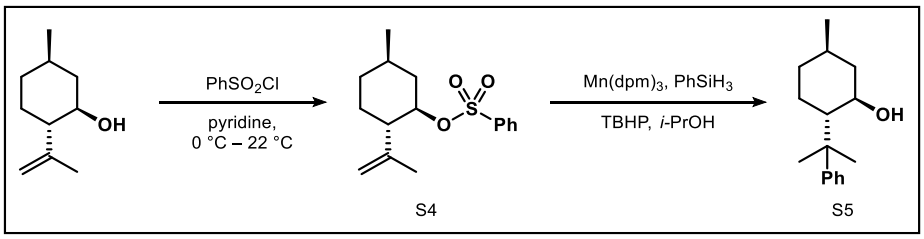
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.32 (d, *J* = 6.7 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 4.96 (td, *J* = 10.9, 4.4 Hz, 1H), 3.83 (d, *J* = 3.5 Hz, 3H), 2.32 (s, 3H), 2.21 – 2.11 (m, 1H), 2.04 (dtd, *J* = 13.9, 7.0, 2.7 Hz, 1H), 1.77 – 1.68 (m, 2H), 1.50 (dd, *J* = 8.6, 5.7 Hz, 1H), 1.20 – 1.03 (m, 2H), 0.93 (t, *J* = 6.8 Hz, 5H), 0.82 (d, *J* = 6.9 Hz, 3H).



S3

(+)-isomenthol ester S3. Carboxylic acid **5.1** (100 mg, 0.602 mmol) was subjected to general esterification procedure A to afford ester **S3** as a clear oil (182 mg, 99%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.62 (dd, *J* = 7.7, 1.3 Hz, 1H), 7.34 – 7.30 (m, 1H), 7.05 (t, *J* = 7.6 Hz, 1H), 5.31 (dd, *J* = 6.5, 3.1 Hz, 1H), 3.83 (s, 3H), 2.32 (s, 3H), 1.97 (ddd, *J* = 10.8, 7.2, 3.3 Hz, 1H), 1.86 (dd, *J* = 13.6, 6.8 Hz, 1H), 1.78 – 1.67 (m, 2H), 1.66 – 1.55 (m, 2H), 1.54 (s, 2H), 1.49 (d, *J* = 4.1 Hz, 2H), 1.28 (ddd, *J* = 13.2, 8.5, 3.5 Hz, 1H), 0.99 (d, *J* = 6.8 Hz, 3H), 0.97 (d, *J* = 6.9 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H).

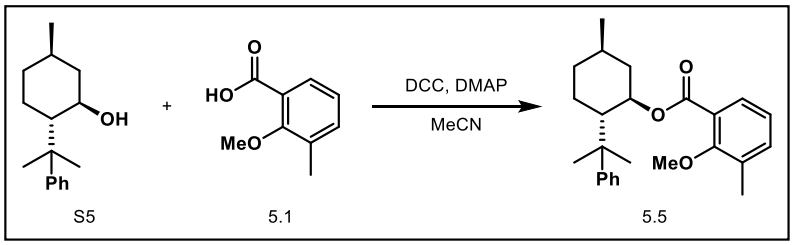


Sulfonate S4. (–)-8-phenylmenthol was prepared according to the procedure developed by Shenvi and coworkers. A flame-dried 100 mL round bottom flask equipped with a stir bar was charged with (–)-isopulegol (2.54 mL, 15.00 mmol) and pyridine (19 mL), then cooled to 0 °C. $PhSO_2Cl$ (2.30 mL, 18.00 mmol) was added dropwise to the stirring solution. After stirring overnight, the reaction mixture was diluted with ice water and the precipitate was collected by filtration to afford **S4** as a pink-white solid (4.36 g, 99%).

^1H and ^{13}C NMR spectra were consistent with those previously reported.[10]

(–)-8-phenylmenthol S5. A flame-dried 500 mL round bottom flask equipped with a stir bar was charged with **S4** (4.36 g, 14.81 mmol) and $Mn(OAc)_3{\cdot}H_2O$ (3.97 g, 14.81 mmol) and evacuated/back-filled with argon (3x). Then, degassed isopropanol (150 mL), 2,2,6,6-tetramethylheptane-3,5-dione (0.620 mL, 2.96 mmol), TBHP (5.39 mL of a 5.5 M solution in nonane), and $PhSiH_3$ (1.92 mL) were added in succession. After stirring for 24 hours, the reaction mixture was diluted with H_2O (300 mL), extracted with EtOAc (4 x 300 mL), and the combined organic extracts were dried over Na_2SO_4, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (10% EtOAc in hexanes) to afford a viscous clear oil (2.37 g, 69%).

^1H and ^{13}C NMR spectra were consistent with those previously reported.[10]



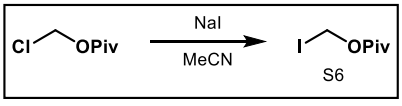
General Esterification Procedure B[12]

(–)-8-Phenylmenthol ester 5.5. A flame-dried 25 mL round bottom flask equipped with a stir bar was charged with **5.1** (668 mg, 4.02 mmol), MeCN (5 mL), (–)-8-phenylmenthol (467 mg, 2.01 mmol), DMAP (368 mg, 3.02 mmol), and DCC (622 mg, 3.02 mmol). After stirring for 24 hours, the reaction mixture was filtered through a pad of celite (using EtOAc as eluent) and concentrated *in vacuo*. The resulting residue was purified by column chromatography (5% EtOAc in hexanes to afford a clear oil (658 mg, 86%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, *J* = 4.1 Hz, 3H), 7.15 (t, *J* = 7.7 Hz, 2H), 7.09 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.00 (t, *J* = 7.3 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 5.09 (td, *J* = 10.7, 4.4 Hz, 1H), 3.79 (s, 3H), 2.29 (s, 3H), 2.15 – 2.02 (m, 2H), 1.68 – 1.58 (m, 2H), 1.53 (ddd, *J* = 8.4, 6.1, 3.0 Hz, 1H), 1.34 (s, 3H), 1.26 (s, 3H), 1.18 – 1.05 (m, 2H), 0.88 (dd, *J* = 6.8, 4.8 Hz, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 158.6, 151.4, 134.9, 132.6, 129.3, 128.1, 125.6, 125.2, 125.1, 123.3, 75.1, 61.6, 50.7, 42.0, 40.1, 34.8, 31.5, 27.1, 26.9, 26.8, 22.0, 16.1.

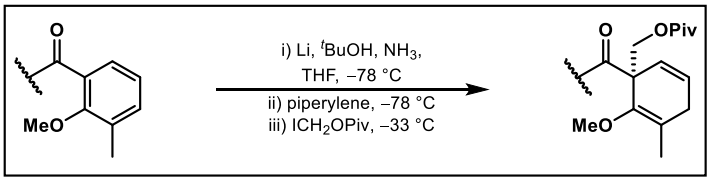
HRMS (ES+) m/z calc'd for $C_{25}H_{32}O_3$ $[M + Na]^+$: 403.2249, found 403.2237.



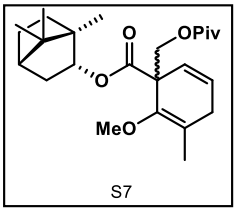
Iodomethylpivalate S6. A flame-dried 250 mL round bottom flask equipped with a stir bar was charged with MeCN (40 mL), chloromethylpivalate (9.57 mL, 66.4 mmol), and NaI (11.94 g, 79.68 mmol) and stirred for 5 hours. The reaction mixture was filtered through a pad of celite (EtOAc as eluent) and concentrated *in vacuo*. The resulting mixture was taken up in dichloromethane (500

mL) and washed with a saturated aqueous solution of $Na_2S_2O_3$ (100 mL), then H_2O (100 mL), then the organic phase was separated, dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo* to afford a yellow-orange oil (15.35 g, 96%). This material was used without further purification.

^1H and ^{13}C NMR spectra were consistent with those previously reported.[13]

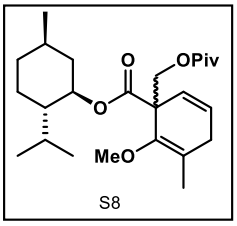


General Birch reduction/alkylation procedure A. A flame-dried 50 mL round bottom flask equipped with a stir bar and cold-finger condenser was cooled to -78 °C and charged with ammonia (0.16 M) followed by a solution of **SI-30** (100 mg, 0.380 mmol) and *tert*-butanol (1.0 equiv.) in THF (0.76 mL). Lithium metal (2.5 equiv.) was added in portion as small chunks. The reaction mixture was stirred for 10 minutes after turning blue, then 1,3-pentadiene (2.0 equiv.) was added until the reaction mixture turned from blue to yellow. **S6** (3 equiv.) was added dropwise. The reaction mixture was allowed to warm to reflux and was stirred for an additional 2 hours. The reaction was quenched with solid NH_4Cl and following evaporation of the ammonia, brine solution was added and it was extracted with EtOAc. The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (5 to 10% EtOAc in hexanes) to afford a clear oil.



Birch reduction/alkylation product S7. Ester **S1** (90 mg, 0.296 mmol) was subjected to general Birch reduction/alkylation procedure A to afford **S7** as a clear oil (76 mg, 61%, 1.2:1 d.r.).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.86 (dq, *J* = 10.0, 3.4 Hz, 1H), 5.51 (ddt, *J* = 9.8, 3.7, 1.9 Hz, 1H), 4.91 – 4.84 (m, 1H), 4.62 (dd, *J* = 10.9, 4.9 Hz, 1H), 4.32 (dd, *J* = 10.8, 7.3 Hz, 1H), 3.63 (d, *J* = 4.7 Hz, 3H), 2.82 (d, *J* = 22.2 Hz, 1H), 2.70 (d, *J* = 22.2 Hz, 1H), 2.34 (dt, *J* = 13.8, 4.1 Hz, 1H), 1.93 – 1.85 (m, 1H), 1.76 (d, *J* = 3.2 Hz, 3H), 1.75 – 1.69 (m, 1H), 1.67 (t, *J* = 4.5 Hz, 1H), 1.27 (dt, *J* = 22.0, 13.4 Hz, 3H), 1.14 (s, 9H), 0.89 (d, *J* = 1.3 Hz, 3H), 0.86 (s, 3H), 0.81 (d, *J* = 3.1 Hz, 3H).

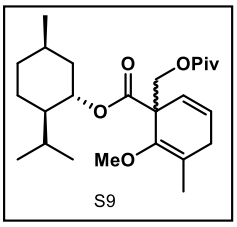


S8

Birch reduction/alkylation product S8. Ester **S1** (90 mg, 0.296 mmol) was subjected to general Birch reduction/alkylation procedure A to afford **S8** as a clear oil (35 mg, 28%, 1.1:1 d.r.).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.84 (ddt, *J* = 9.2, 6.2, 3.3 Hz, 1H), 5.48 (d, *J* = 9.8 Hz, 1H), 4.71 – 4.62 (m, 1H), 4.58 (dd, *J* = 19.7, 10.9 Hz, 1H), 4.28 (dd, *J* = 18.2, 10.9 Hz, 1H), 3.64 (s, 3H), 2.80 (d, *J* = 22.4 Hz, 1H), 2.68 (d, *J* = 22.8 Hz, 1H), 1.99 (d, *J* = 12.0 Hz, 1H), 1.93 – 1.83 (m, 1H), 1.75 (d, *J* = 4.0 Hz, 3H), 1.67 (d, *J* = 11.3 Hz, 2H), 1.52 – 1.45 (m, 1H), 1.41 (dd, *J* = 20.0, 7.1 Hz, 2H), 1.13 (d, *J* = 2.2 Hz, 9H), 0.99 (ddd, *J* = 18.8, 16.3, 9.8 Hz, 2H), 0.89 (dd, *J* = 11.6, 4.8 Hz, 6H), 0.76 – 0.70 (m, 3H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.11, 178.08, 171.3, 171.2, 146.4, 146.3, 127.3, 127.1, 125.83, 125.81, 118.1, 117.9, 75.53, 75.52, 66.0, 64.6, 61.2, 61.1, 54.2, 54.1, 47.1, 40.8, 40.7, 38.9, 34.37, 34.35, 33.53, 33.49, 31.52, 31.50, 27.2, 26.2, 26.2, 23.5, 22.1, 20.9, 20.9, 16.3, 16.3, 15.4.

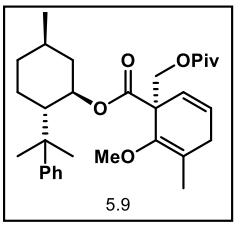


S9

Birch reduction/alkylation product S9. Ester **S3** (90 mg, 0.296 mmol) was subjected to general Birch reduction/alkylation procedure A to afford **S9** as a clear oil (102 mg, 82%, 1.2:1 d.r.).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.88 – 5.82 (m, 1H), 5.50 (dd, *J* = 9.8, 2.0 Hz, 1H), 5.09 – 5.02 (m, 1H), 4.61 (dd, *J* = 10.8, 6.3 Hz, 1H), 4.31 (dd, *J* = 10.8, 8.3 Hz, 1H), 3.63 (s, 3H), 2.81 (d, *J* = 22.4 Hz, 1H), 2.69 (d, *J* = 21.6 Hz, 1H), 1.83 (dd, *J* = 11.0, 6.9 Hz, 1H), 1.76 (s,

3H), 1.75 – 1.69 (m, 1H), 1.44 (ddd, *J* = 13.3, 6.9, 3.8 Hz, 3H), 1.37 – 1.25 (m, 3H), 1.13 (s, 9H), 0.94 – 0.89 (m, 6H), 0.85 (d, *J* = 6.7 Hz, 3H).



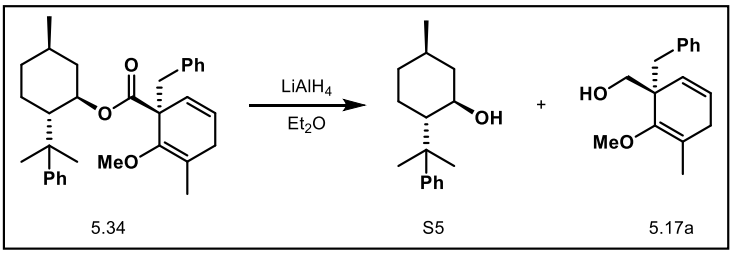
5.9

Birch reduction/alkylation product 5.9. A flame-dried 100 mL round bottom flask equipped with a stir bar and cold-finger condenser was cooled to −78 °C and charged with ammonia (7.5 mL) followed by a solution of **5.5** (250 mg, 0.657 mmol) and *tert*-butanol (0.063 mL, 0.657 mmol) in THF (7.5 mL). Lithium metal (11 mg, 1.64 mmol) was added in portion as small chunks. The reaction mixture was stirred for 10 minutes after turning blue, then 1,3-pentadiene (0.129 mL, 1.31 mmol) was added until the reaction mixture turned from blue to yellow. **S6** (477 mg, 1.97 mmol) was added dropwise. The reaction mixture was allowed to warm to reflux and was stirred for an additional 2 hours. The reaction was quenched with solid NH_4Cl (250 mg) and following evaporation of the ammonia, brine solution was added (50 mL) and it was extracted with EtOAc (3 x 100 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting yellow oil was purified by column chromatography (5% EtOAc in hexanes) to afford **5.9** as a clear oil (259 mg, 80%, 7:1 d.r.).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 6.4 Hz, 4H), 7.11 (tt, *J* = 5.5, 2.2 Hz, 1H), 5.91 (dt, *J* = 9.9, 3.6 Hz, 1H), 5.39 (dt, *J* = 9.9, 2.1 Hz, 1H), 4.84 – 4.73 (m, 2H), 4.38 (d, *J* = 10.7 Hz, 1H), 4.18 (d, *J* = 10.7 Hz, 1H), 3.44 (s, 3H), 2.90 – 2.72 (m, 2H), 1.92 – 1.79 (m, 2H), 1.44 (dt, *J* = 12.8, 3.3 Hz, 1H), 1.36 (td, *J* = 13.1, 6.7 Hz, 1H), 1.26 (s, 3H), 1.20 (s, 3H), 1.09 (s, 9H), 0.93 – 0.82 (m, 3H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.68 (qd, *J* = 12.8, 3.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 170.6, 150.62, 150.59, 128.2, 127.6, 126.0, 125.5, 124.7, 94.5, 77.4, 76.6, 64.9, 54.2, 52.4, 50.4, 41.6, 40.4, 38.9, 34.6, 31.4, 30.0, 27.5, 27.3, 26.6, 23.6, 21.9.

HRMS (ES+) m/z calc'd for $C_{30}H_{42}O_5Na$ $[M + Na]^+$: 483.3110, found 483.3108.



General Chiral Auxiliary Removal Procedure A. A flame-dried 50 mL round bottom flask equipped with a stir bar was charged with **5.34** (135 mg, 0.29 mmol) and Et_20 (3 mL) and was cooled to 0 °C. The, lithium aluminum hydride (16.3 mg, 0.43 mmol) was added portionwise and allowed to warm to room temperature. After 1 hour, the reaction mixture was diluted with Et_2O (10 mL) and a saturated aqueous solution of Rochelle's salt (10 mL) was added. After stirring an additional 15 minutes, the phases were separated and the aqueous phase was extracted with Et_2O (3 x 10 mL). The combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting residue was purified by column chromatography (5% EtOAc in hexanes) to afford **5.17a** as a clear oil (48 mg, 71%).

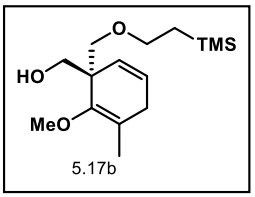
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (dd, *J* = 8.0, 6.3 Hz, 2H), 7.17 – 7.13 (m, 1H), 7.12 – 7.06 (m, 2H), 5.75 (dt, *J* = 10.0, 3.4 Hz, 1H), 5.29 (dd, *J* = 9.9, 2.3 Hz, 1H), 3.81 – 3.76 (m, 1H), 3.76 (d, *J* = 0.9 Hz, 3H), 3.40 (dd, *J* = 10.4, 3.1 Hz, 1H), 2.88 (d, *J* = 13.0 Hz, 1H), 2.57 – 2.47 (m, 2H), 2.21 – 2.13 (m, 1H), 1.68 (dd, *J* = 8.8, 3.5 Hz, 1H), 1.63 (s, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 149.45, 137.67, 130.67, 129.59, 127.90, 125.95, 118.89, 68.05, 61.29, 49.35, 40.76, 33.48, 16.21.

HRMS (ES+) m/z calc'd for $C_{16}H_{20}O_2Na$ $[M + Na]^+$: 267.1361, found 267.1353.

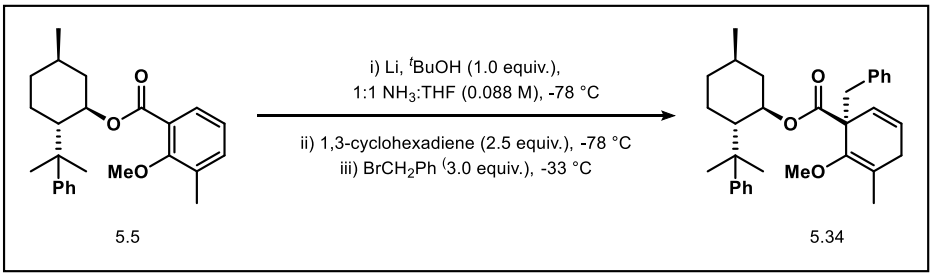
Chiral SFC: 100 mm CHIRALCEL OD-H, 2% ^{i}PrOH, 2.0 mL/min, 220 nm, 44 °C, nozzle pressure = 200 bar CO2, t_{R1} (major) = 4.5, t_{R2} (minor) = 5.1 min.

(R)-(2-methoxy-3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)cyclohexa-2,5-dien-1-yl)methanol 5.17b. Alcohol **5.17b** was prepared from the corresponding ester (20 mg, 0.039 mmol) via general chiral auxiliary removal procedure A to afford **5.17b** as a clear oil (10 mg, 88%) and (–)-8-phenylmenthol as a clear oil (8 mg, 90%).



5.17b

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.89 – 5.83 (m, 1H), 5.58 (d, *J* = 10.0 Hz, 1H), 3.66 (s, 3H), 3.62 (d, *J* = 10.4 Hz, 1H), 3.56 – 3.48 (m, 4H), 3.43 (d, *J* = 8.8 Hz, 1H), 2.79 – 2.65 (m, 2H), 1.72 (s, 3H), -0.01 (s, 9H).

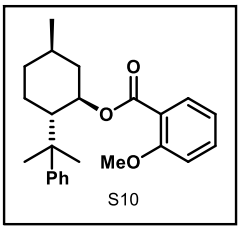


5.5 5.34

General Birch Reduction/Alkylation Procedure B. A flame-dried 25 mL three-necked round bottom flask equipped with a glass-encased stir bar and a cold finger condenser was cooled to −78 °C and charged with ammonia (4 mL), then **5.5** (147 mg, 0.39 mmol) as a solution in THF (4 mL) and *tert*-butanol (0.39 mL, 0.39 mmol, 1 M in THF). Lithium metal (13 mg, 1.94 mmol) was added portionwise over 10 minutes and the reaction mixture turned a deep blue. After stirring for 30 minutes at −78 °C, the remaining lithium was quenched with 1,3-cyclohexadiene (0.093 mL, 0.97 mmol) and the reaction mixture turned from blue to yellow. After stirring an additional 30 minutes, benzyl bromide (0.140 mL, 1.16 mmol) was added dropwise and the reaction mixture was allowed to slowly warm to reflux. After stirring for 3 hours, the reaction was quenched with solid NH_4Cl (62 mg, 1.16 mmol) and the ammonia was allowed to evaporate. The reaction mixture was diluted with brine (10 mL), then extracted with hexanes (3 x 10 mL), and the combined organic extracts were dried over $MgSO_4$, filtered through cotton, and concentrated *in vacuo*. The resulting

yellow oil was purified by column chromatography (2% EtOAc in hexanes) to afford **5.34** (162 mg, 89%) as a clear oil.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-methoxybenzoate (S10)



S10

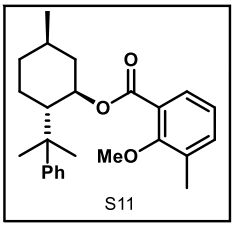
Prepared according to **general esterification procedure B**, using (–)-8-phenylmenthol (950 mg, 4.1 mmol)and 2-methoxybenzoic acid (1.25 g, 8.2 mmol) to afford **S10** as a clear oil (1.4 g, 3.8 mmol, 93% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.95 (m, 2H), 7.38 – 7.32 (m, 4H), 7.19 (td, *J* = 6.9, 1.8 Hz, 1H), 7.15 – 7.09 (m, 2H), 5.60 (dd, *J* = 10.0, 3.4 Hz, 1H), 5.19 (dd, *J* = 10.0, 2.0 Hz, 1H), 4.92 (td, *J* = 10.7, 4.2 Hz, 1H), 3.69 (d, *J* = 1.5 Hz, 3H), 3.16 (d, *J* = 12.9 Hz, 1H), 2.54 – 2.42 (m, 1H), 2.32 (dd, *J* = 13.0, 2.1 Hz, 1H), 2.21 – 2.11 (m, 1H), 2.00 (d, *J* = 12.0 Hz, 1H), 1.86 – 1.77 (m, 1H), 1.67 – 1.57 (m, 3H), 1.51 (s, 3H), 1.36 (s, 3H), 1.21 (s, 3H), 1.12 – 1.03 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 151.8, 146.6, 146.5, 146.1, 131.7, 128.4, 126.8, 126.1, 125.7, 125.5, 122.2, 118.0, 76.4, 61.3, 54.8, 49.8, 41.9, 40.1, 39.3, 34.7, 33.0, 31.5, 27.3, 27.1, 26.7, 22.0, 16.0.

HRMS (ES+) m/z calc'd for $C_{24}H_{30}O_3$ $[M + Na]^+$: 389.2093, found 389.2094.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-2-methoxy-3-methylbenzoate (S11).



S11

Prepared according to **general esterification procedure B**, using (–)-8-phenylmenthol (1.9 g, 8.2 mmol) and 3-methyl-2-methoxybenzoic acid (2.1 g, 12 mmol) to afford **S11** as a clear oil (2.9 g, 94% yield).

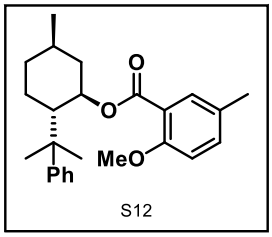
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (t, *J* = 4.1 Hz, 3H), 7.15 (t, *J* = 7.7 Hz, 2H), 7.09 (dd, *J* = 7.9, 1.8 Hz, 1H), 7.00 (t, *J* = 7.3 Hz, 1H), 6.90 (t, *J* = 7.6 Hz, 1H), 5.09 (td, *J* = 10.7, 4.4 Hz, 1H), 3.79

(s, 3H), 2.29 (s, 3H), 2.15 – 2.02 (m, 2H), 1.68 – 1.58 (m, 2H), 1.53 (ddd, *J* = 8.4, 6.1, 3.0 Hz, 1H), 1.34 (s, 3H), 1.26 (s, 3H), 1.18 – 1.05 (m, 2H), 0.88 (dd, *J* = 6.8, 4.8 Hz, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 165.2, 158.6, 151.4, 134.9, 132.6, 129.3, 128.1, 125.6, 125.2, 125.1, 123.3, 75.1, 61.6, 50.7, 42.0, 40.1, 34.8, 31.5, 27.1, 26.9, 26.8, 22.0, 16.1.

HRMS (ES+) m/z calc'd for $C_{25}H_{32}O_3$ $[M + Na]^+$: 403.2249, found 403.2237.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-methoxy-5-methylbenzoate (S12)



S12

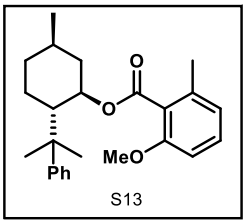
Prepared according to **general esterification procedure B**, using (–)-8-phenylmenthol (700 mg, 3.0 mmol, 1.0 equiv.) and 5-methyl-2-methoxybenzoic acid (750 mg, 4.5 mmol, 1.5 equiv.) to afford **S12** as a clear oil (1.1 g, 96% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.26 (m, 2H), 7.21 – 7.12 (m, 3H), 7.03 – 6.95 (m, 2H), 6.80 (d, J = 8.5 Hz, 1H), 5.10 (td, J = 10.7, 4.4 Hz, 1H), 3.85 (s, 3H), 2.22 (s, 3H), 2.13 (ddd, J = 12.2, 10.5, 3.3 Hz, 1H), 2.02 (dd, J = 11.1, 5.4 Hz, 1H), 1.69 – 1.61 (m, 2H), 1.52 (ddp, J = 8.9, 5.9, 3.1 Hz, 1H), 1.36 (s, 3H), 1.26 (s, 3H), 1.19 – 1.03 (m, 2H), 0.88 (d, J = 6.6 Hz, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 164.9, 157.6, 133.9, 132.0, 129.0, 127.9, 125.6, 125.0, 119.8, 111.9, 74.6, 56.2, 50.7, 42.1, 40.0, 34.8, 31.5, 27.2, 27.0, 26.3, 22.0, 20.4.

HRMS (ES+) m/z calc'd for $C_{25}H_{32}O_3$ $[M + Na]^+$: 403.2249, found 403.2235.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-2-methoxy-6-methylbenzoate (S13)



S13

A flame-dried 50 mL round bottom flask equipped with a magnetic stir bar was charged with 6-methyl-2-methoxybenzoic acid (698 mg, 4.2 mmol) and benzene (20 mL). Then, thionyl chloride (0.377 mL, 5.2 mmol) was added dropwise, followed by DMF (0.150 ml). The reaction was stirred at 70 °C

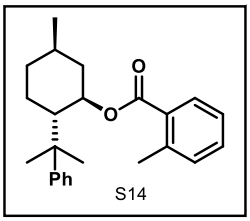
overnight. Once the reaction was judged complete by aliquot NMR, the reaction mixture was concentrated *in vacuo*. A separate flame-dried 50 mL round bottom flask was charged with NaH (180 mg, 4.5 mmol), (–)-8-phenylmenthol, and dichloroethane (10 mL). A solution of the acid chloride dissolved in dichloroethane (5 mL) was added to the solution of (–)-8-phenylmenthol and the reaction was stirred at 65-70 °C for 5 days. The reaction mixture was diluted with dichloromethane (20 mL) and filtered through a pad of celite. The resulting filtrate was concentrated *in vacuo*, and the resulting residue was purified by column chromatography (5% EtOAc in hexanes) to afford **S13** as a clear oil (1.2 g, 90% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 – 7.26 (m, 2H), 7.24 – 7.18 (m, 3H), 7.08 (t, *J* = 7.2 Hz, 1H), 6.76 (dd, *J* = 17.2, 8.0 Hz, 2H), 5.05 (td, *J* = 10.6, 4.2 Hz, 1H), 2.30 (s, 4H), 2.00 – 1.87 (m, 1H), 1.58 – 1.45 (m, 3H), 1.37 (d, *J* = 2.5 Hz, 6H), 1.32 – 1.19 (m, 2H), 1.12 (q, *J* = 11.6 Hz, 1H), 1.00 – 0.92 (m, 1H), 0.90 (d, *J* = 6.3 Hz, 4H), 0.77 (qd, *J* = 13.0, 3.3 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 168.1, 156.2, 150.9, 136.1, 130.0, 128.0, 125.9, 125.3, 124.7, 122.5, 108.5, 76.8, 55.7, 50.9, 41.7, 40.6, 34.7, 31.6, 30.1, 27.7, 23.0, 22.0, 19.3.

HRMS (ES+) m/z calc'd for $C_{24}H_{30}O_3Na$ $[M + Na]^+$: 403.2249, found 403.2260.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-methylbenzoate (S14)



S14

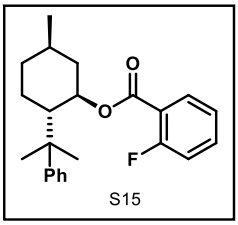
Prepared according to **general esterification procedure B**, using (–)-8-phenylmenthol (538 mg, 2.3 mmol) and 2-methylbenzoic acid (630 mg, 4.6 mmol) to afford **S14** as a clear oil (778 mg, 95% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (ddd, *J* = 7.3, 5.8, 1.7 Hz, 2H), 7.26 – 7.23 (m, 2H), 7.18 – 7.10 (m, 3H), 7.08 (td, *J* = 7.6, 1.3 Hz, 1H), 6.98 (tt, *J* = 7.3, 1.2 Hz, 1H), 5.06 (td, *J* = 10.7, 4.4 Hz, 1H), 2.53 (s, 3H), 2.15 (ddd, *J* = 12.3, 10.5, 3.5 Hz, 1H), 2.03 (dtd, *J* = 12.3, 3.9, 2.1 Hz, 1H), 1.71 – 1.63 (m, 2H), 1.60 – 1.49 (m, 1H), 1.34 (s, 3H), 1.20 – 1.06 (m, 2H), 0.96 – 0.85 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.7, 151.5, 140.3, 131.7, 131.5, 130.8, 129.9, 128.1, 125.51, 125.46, 125.1, 74.8, 50.8, 42.1, 40.0, 34.8, 31.6, 27.4, 27.0, 26.3, 22.03, 21.97.

HRMS (ES+) m/z calc'd for $C_{24}H_{30}O_2Na$ $[M + Na]^+$: 461.3032, found 461.3011.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 2-fluorobenzoate (S15)



S15

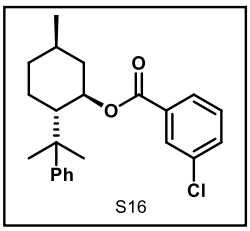
Prepared according to **general esterification procedure B**, using (–)-8-phenylmenthol (200 mg, 0.86 mmol) and 2-fluorobenzoic acid (241 mg, 1.7 mmol) to afford **S15** as a clear oil (252 mg, 83% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (dddd, *J* = 8.3, 7.3, 4.8, 1.9 Hz, 1H), 7.33 (td, *J* = 7.7, 1.9 Hz, 1H), 7.28 – 7.25 (m, 2H), 7.14 – 7.10 (m, 2H), 7.05 – 7.00 (m, 2H), 6.94 (tt, *J* = 7.3, 1.2 Hz, 1H), 5.12 (td, *J* = 10.7, 4.5 Hz, 1H), 2.17 (ddd, *J* = 12.3, 10.6, 3.6 Hz, 1H), 2.06 – 2.00 (m, 1H), 1.73 (dq, *J* = 13.5, 3.5 Hz, 1H), 1.68 (dtd, *J* = 13.2, 3.5, 2.3 Hz, 1H), 1.59 – 1.49 (m, 1H), 1.35 (s, 3H), 1.26 (s, 3H), 1.21 – 1.08 (m, 2H), 0.97 – 0.88 (m, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 163.21, 163.18, 163.0, 161.3, 151.5, 134.1, 134.0, 132.2, 128.0, 125.4, 125.0, 123.6, 123.5, 119.09, 119.03, 116.8, 116.7, 75.2, 50.6, 41.9, 39.9, 31.5, 27.8, 26.8, 25.6, 21.9.

HRMS (ES+) m/z calc'd for $C_{23}H_{27}FO_2Na$ $[M +]^+$: 354.1995, found 354.1987.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 3-chlorobenzoate (S16)



S16

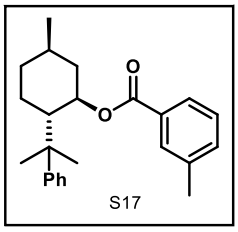
Prepared according to **general esterification procedure B**, using (–)-8-phenylmenthol (494 mg, 2.1 mmol) and 3-chlorobenzoic acid (666 mg, 4.3 mmol) to afford **S16** as a white solid (471 mg, 70% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.45 – 7.40 (m, 2H), 7.33 (t, *J* = 1.9 Hz, 1H), 7.26 – 7.22 (m, 2H), 7.21 (t, *J* = 7.8 Hz, 1H), 7.13 – 7.09 (m, 2H), 7.00 – 6.96 (m, 1H), 5.08 (td, *J* = 10.7, 4.4 Hz, 1H), 2.22 (ddd, *J* = 12.3, 10.5, 3.6 Hz, 1H), 1.95 (dtd, *J* = 12.3, 3.9, 2.2 Hz, 1H), 1.85 (dq, *J* = 13.6, 3.5 Hz, 1H), 1.76 – 1.68 (m, 1H), 1.55 (dddp, *J* = 12.8, 9.8, 6.6, 3.2 Hz, 1H), 1.32 (s, 3H), 1.21 (s,

4H), 1.07 (td, *J* = 12.2, 10.8 Hz, 1H), 0.95 (tdd, *J* = 13.2, 11.8, 3.7 Hz, 1H), 0.90 (d, *J* = 6.5 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 164.6, 151.8, 134.1, 132.6, 132.2, 129.6, 129.2, 128.1, 127.8, 125.3, 125.2, 75.5, 50.6, 41.9, 39.7, 34.8, 31.5, 29.1, 26.9, 24.1, 21.9.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 3-methylbenzoate (S17)



S17

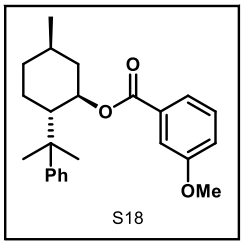
Prepared according to **general esterification procedure B**, using (–)-8-phenylmenthol (500 mg, 2.2 mmol) and 3-methylbenzoic acid (586 mg, 4.3 mmol) to afford **S17** as a white solid (651 mg, 86% yield).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 7.8, 1.6 Hz, 1H), 7.35 (d, *J* = 1.9 Hz, 1H), 7.30 – 7.26 (m, 3H), 7.21 – 7.12 (m, 3H), 7.04 – 6.99 (m, 1H), 5.08 (td, *J* = 10.7, 4.4 Hz, 1H), 2.33 (s, 3H), 2.19 (ddd, *J* = 12.3, 10.5, 3.5 Hz, 1H), 1.99 (dtd, *J* = 12.3, 4.0, 2.2 Hz, 1H), 1.76 – 1.64 (m, 2H), 1.55 (dddd, *J* = 12.0, 8.5, 5.8, 3.1 Hz, 1H), 1.34 (s, 3H), 1.24 (s, 3H), 1.16 (qd, *J* = 13.1, 3.4 Hz, 1H), 1.07 (td, *J* = 12.2, 10.8 Hz, 1H), 0.97 – 0.89 (m, 1H), 0.88 (d, *J* = 6.6 Hz, 3H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 166.0, 151.8, 137.7, 133.4, 130.6, 130.2, 128.1, 128.0, 126.9, 125.5, 125.1, 75.1, 50.7, 41.9, 39.9, 34.8, 31.5, 27.9, 26.9, 25.7, 22.0, 21.4.

HRMS (ES+) m/z calc'd for $C_{24}H_{30}O_2Na$ $[M + Na]^+$: 350.2246, found 350.2253.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl 3-methoxybenzoate (S18)



S18

Prepared according to **general esterification procedure B**, using (–)-8-phenylmenthol (480 mg, 2.1 mmol) and 3-methoxybenzoic acid (629 mg, 4.1 mmol) to afford **S18** as a clear oil (626 mg, 83% yield).

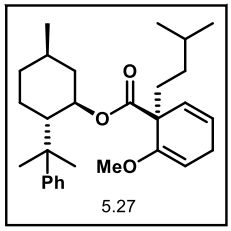
^{1}H NMR (600 MHz, $CDCl_3$) δ 7.99 (d, *J* = 8.4 Hz, 2H), 7.38 – 7.31 (m, 4H), 7.19 (t, *J* = 6.9 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 2H), 5.60 (dt, *J* = 10.0, 3.4 Hz, 1H), 5.19 (dd, *J* = 9.9, 2.3 Hz, 1H), 4.92 (td, *J* = 10.6, 4.3 Hz, 1H), 3.69 (s, 3H), 3.15 (d, *J* = 13.0 Hz, 1H), 2.53 – 2.43 (m, 1H), 2.30 (d, *J* = 12.8 Hz, 1H), 2.20 – 2.12 (m, 1H), 1.99 (dd, *J* = 11.9, 5.3 Hz, 1H), 1.84 –

1.77 (m, 1H), 1.66 – 1.58 (m, 2H), 1.51 (s, 3H), 1.35 (s, 3H), 1.21 (s, 3H), 1.12 – 1.03 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 4H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.8, 151.8, 146.6, 146.5, 146.1, 131.7, 128.4, 126.8, 126.1, 125.7, 125.5, 122.2, 118.0, 76.4, 61.3, 54.8, 49.8, 41.9, 40.1, 39.3, 33.0, 31.7, 31.5, 27.4, 27.1, 26.7, 22.8, 22.0, 16.0, 14.3.

HRMS (ES+) m/z calc'd for $C_{24}H_{30}O_3Na$ $[M + Na]^+$: 389.2093, found 389.2094.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-(S)-1-isopentyl-2-methoxycyclohexa-2,5-diene-1-carboxylate (15a)



5.27

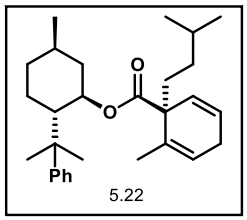
Prepared according to **general Birch reduction/alkylation procedure B**, using ester **S10** (100 mg, 0.27 mmol) and 1-iodo-3-methylbutane (162 mg, 0.82 mmol) to afford **5.27** as a clear oil (64.7 mg, 54% yield, 10:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 4.6 Hz, 4H), 7.18 – 7.12 (m, 1H), 5.91 – 5.85 (m, 1H), 5.29 (dd, *J* = 9.9, 2.3 Hz, 1H), 4.84 – 4.74 (m, 2H), 3.47 (s, 3H), 2.93 – 2.75 (m, 2H), 2.05 (td, *J* = 12.9, 4.7 Hz, 1H), 1.91 (d, *J* = 12.9 Hz, 1H), 1.88 – 1.81 (m, 1H), 1.52 – 1.46 (m, 2H), 1.30 (s, 3H), 1.24 (s, 4H), 0.87 – 0.85 (m, 6H), 0.82 (d, *J* = 6.4 Hz, 3H), 0.77 – 0.65 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.3, 152.4, 150.8, 128.1, 127.7, 126.3, 126.0, 125.4, 93.7, 76.1, 54.0, 52.2, 50.5, 41.6, 40.5, 34.7, 33.4, 32.0, 31.7, 31.5, 30.5, 28.4, 27.7, 26.7, 23.1, 22.94, 22.85, 21.9, 14.3.

HRMS (ES+) m/z calc'd for $C_{29}H_{42}O_3Na$ $[M + Na]^+$: 461.3032, found 461.3011.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-(S)-1-isopentyl-2-methylcyclohexa-2,5-diene-1-carboxylate (5.22)



5.22

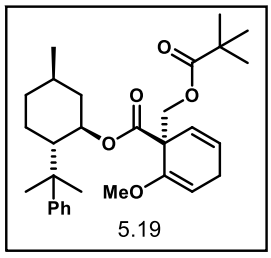
Prepared according to **general Birch reduction/alkylation procedure B**, using ester **S14** (85 mg, 0.24 mmol) and 1-iodo-3-methylbutane (140 mg, 0.73 mmol) to afford **5.22** as a clear oil (63 mg, 61% yield, 2:1 dr).

^{1}H NMR (500 MHz, C_6D_6) δ 7.29 – 7.19 (m, 4H), 7.11 – 7.02 (m, 1H), 5.86 – 5.71 (m, 1H), 5.61 – 5.46 (m, 2H), 4.99 (ddt, *J* = 14.9, 10.5, 5.2 Hz, 1H), 2.64 – 2.41 (m, 2H), 2.30 – 2.04 (m, 2H), 2.03 – 1.69 (m, 5H), 1.53 (dp, *J* = 13.6, 6.6 Hz, 1H), 1.44 (d, *J* = 10.3 Hz, 3H), 1.33 – 1.22 (m, 7H), 1.00 – 0.81 (m, 9H), 0.70 (t, *J* = 6.4 Hz, 3H), 0.62 – 0.47 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.9, 172.7, 150.5, 150.3, 131.5, 130.8, 128.4, 128.2, 126.2, 125.9, 125.4, 125.2, 123.9, 123.0, 75.5, 51.9, 50.4, 41.7, 40.3, 34.4, 33.8 – 32.2 (m), 31.8 – 30.0 (m), 28.9 – 26.5 (m), 24.1 – 19.4 (m), 14.0.

HRMS (ES+) m/z calc'd for $C_{29}H_{42}O_2Na$ $[M + Na]^+$: 445.3083, found 445.3091.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-(R)-2-methoxy-1-((pivaloyloxy)methyl)cyclohexa-2,5-diene-1-carboxylate (5.19)



5.19

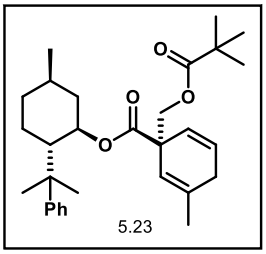
Prepared according to **general Birch reduction/alkylation procedure B**, using ester **S10** (93 mg, 0.25 mmol) and iodomethylpivalate (184 mg, 0.76 mmol) to afford **5.19** as a clear oil (93 mg, 76% yield, 11:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (d, *J* = 6.4 Hz, 4H), 7.11 (tt, *J* = 5.5, 2.2 Hz, 1H), 5.91 (dt, *J* = 9.9, 3.6 Hz, 1H), 5.39 (dt, *J* = 9.9, 2.1 Hz, 1H), 4.84 – 4.73 (m, 2H), 4.38 (d, *J* = 10.7 Hz, 1H), 4.18 (d, *J* = 10.7 Hz, 1H), 3.44 (s, 3H), 2.90 – 2.72 (m, 2H), 1.92 – 1.79 (m, 2H), 1.44 (dt, *J* = 12.8, 3.3 Hz, 1H), 1.36 (td, *J* = 13.1, 6.7 Hz, 1H), 1.26 (s, 3H), 1.20 (s, 3H), 1.09 (s, 9H), 0.93 – 0.82 (m, 3H), 0.79 (d, *J* = 6.6 Hz, 3H), 0.68 (qd, *J* = 12.8, 3.4 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 170.6, 150.62, 150.59, 128.2, 127.6, 126.0, 125.5, 124.7, 94.5, 77.4, 76.6, 64.9, 54.2, 52.4, 50.4, 41.6, 40.4, 38.9, 34.6, 31.4, 30.0, 27.5, 27.3, 26.6, 23.6, 21.9.

HRMS (ES+) m/z calc'd for $C_{30}H_{42}O_5Na$ [M + Na]$^+$: 483.3110, found 483.3108.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-(S)-3-methyl-1-((pivaloyloxy)methyl)cyclohexa-2,5-diene-1-carboxylate (5.23)



5.23

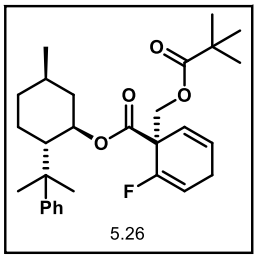
Prepared according to **general Birch reduction/alkylation procedure B**, using ester **S17** (93 mg, 0.27 mmol) and iodomethylpivalate (192 mg, 0.80 mmol) to afford **5.23** as a clear oil (110 mg, 89% yield, 2:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 4H), 7.15 (dtd, *J* = 7.2, 3.9, 1.5 Hz, 1H), 5.91 (ddt, *J* = 16.9, 10.1, 3.4 Hz, 1H), 5.74 – 5.60 (m, 1H), 5.38 (dp, *J* = 5.3, 1.7 Hz, 1H), 4.83 (tdd, *J* = 10.8, 6.8, 4.4 Hz, 1H), 4.15 – 4.00 (m, 2H), 2.61 – 2.50 (m, 2H), 1.94 (dddd, *J* = 14.2, 11.9, 6.3, 3.7 Hz, 2H), 1.79 – 1.71 (m, 3H), 1.55 – 1.47 (m, 1H), 1.42 (dddd, *J* = 15.3, 8.4, 6.5, 3.4 Hz, 1H), 1.31 (d, *J* = 8.8 Hz, 4H), 1.24 (d, *J* = 3.6 Hz, 3H), 1.22 – 1.12 (m, 9H), 1.01 – 0.87 (m, 3H), 0.83 (d, *J* = 6.7 Hz, 3H), 0.75 (tdd, *J* = 13.0, 11.5, 3.5 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.0, 172.0, 150.5, 135.0, 128.1, 127.2, 126.8, 125.8, 125.5, 124.2, 124.0, 118.6, 118.5, 76.2, 69.2, 50.3, 49.8, 41.9, 40.4, 39.0, 34.6, 31.7, 31.4, 31.2, 30.1, 29.9, 27.4, 27.3, 24.3, 23.3, 22.8, 21.8, 14.2.

HRMS (ES+) m/z calc'd for $C_{30}H_{42}O_4Na$ [M + Na]$^+$: 467.3161, found 467.3156.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-(S)-2-fluoro-1-((pivaloyloxy)methyl)cyclohexa-2,5-diene-1-carboxylate (5.26)



5.26

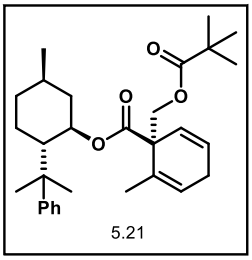
Prepared according to **general Birch reduction/alkylation procedure B**, using ester **S15** (85 mg, 0.24 mmol) and iodomethylpivalate (175 mg, 0.72 mmol) to afford **5.26** as a clear oil (76 mg, 67% yield, 2:1 dr).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 – 7.25 (m, 4H), 7.19 – 7.13 (m, 1H), 5.98 – 5.87 (m, 2H), 5.71 – 5.45 (m, 2H), 4.86 (tdd, *J* = 10.6, 8.5, 4.4 Hz, 1H), 4.23 – 4.09 (m, 1H), 2.85 – 2.63 (m, 2H), 2.01 – 1.88 (m, 2H), 1.56 – 1.47 (m, 1H), 1.42 (tdd, *J* = 9.7, 3.6, 1.7 Hz, 1H), 1.32 – 1.30 (s, 3H), 1.25 – 1.24 (s, 3H), 1.18 – 1.16 (s, 9H), 1.02 – 0.90 (m, 2H), 0.84 (dd, *J* = 6.6, 5.4 Hz, 3H), 0.81 – 0.70 (m, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 178.0, 177.87, 177.86, 171.7, 168.92, 168.90, 155.9, 154.2, 150.7, 150.6, 150.3, 128.20, 128.16, 127.88, 127.86, 127.4, 127.1, 125.84, 125.79, 125.53, 125.51, 125.47, 124.3, 124.2, 124.1, 103.9, 103.8, 103.5, 103.4, 77.1, 76.3, 69.0, 63.8, 63.7, 52.1, 51.9, 50.4, 50.2, 50.1, 48.5, 41.9, 41.6, 41.43, 40.43, 40.39, 40.3, 39.0, 38.9, 34.49, 34.47, 31.4, 30.2, 29.8, 29.2, 27.4, 27.34, 27.27, 27.2, 26.51, 26.47, 26.4, 26.3, 24.8, 24.6, 23.9, 22.8, 22.7, 21.8, 21.8, 14.2.

HRMS (ES+) m/z calc'd for $C_{29}H_{39}FO_4Na$ $[M + Na]^+$: 493.2730, found 493.2731.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-(S)-2-methyl-1-((pivaloyloxy)methyl)cyclohexa-2,5-diene-1-carboxylate (5.21)



5.21

Prepared according to **general Birch reduction/alkylation procedure B**, using ester **S14** (130 mg, 0.37 mmol) and iodomethylpivalate (450 mg, 1.8 mmol) to afford **5.21** as a clear oil (118 mg, 68% yield, 1:1 dr).

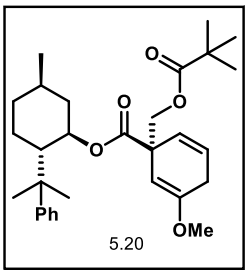
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.26 (m, 4H), 7.15 (tdd, *J* = 6.5, 4.1, 2.1 Hz, 1H), 5.93 (tq, *J* = 6.8, 2.7 Hz, 1H), 5.72 (s, 1H), 5.50 (ddd, *J* = 10.1, 8.1, 2.0 Hz, 1H), 4.83 (tt, *J* = 9.3, 4.8 Hz, 1H), 4.40 – 4.24 (m, 1H), 4.24 – 4.06 (m, 1H), 2.77 – 2.59 (m, 2H), 2.01 – 1.84

(m, 2H), 1.77 – 1.69 (m, 3H), 1.31 (d, *J* = 8.6 Hz, 4H), 1.23 (d, *J* = 9.7 Hz, 3H), 1.14 (d, *J* = 1.6 Hz, 9H), 1.06 – 0.86 (m, 4H), 0.84 (dd, *J* = 6.6, 3.2 Hz, 3H), 0.81 – 0.67 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 178.2, 171.2, 171.1, 150.7, 150.5, 129.5, 128.8, 128.2, 128.2, 127.7, 126.8, 125.9, 125.8, 125.52, 125.49, 125.3, 125.2, 124.9, 124.0, 76.7, 76.3, 65.5, 65.3, 52.4, 52.2, 50.4, 50.3, 41.8, 41.5, 40.5, 40.4, 38.9, 34.6, 31.7, 31.43, 31.42, 30.6, 29.8, 27.5, 27.4, 27.22, 27.16, 27.1, 24.3, 23.8, 22.8, 21.9, 20.0, 19.9, 14.3.

HRMS (ES+) m/z calc'd for $C_{30}H_{42}O_4Na$ $[M + Na]^+$: 489.2981, found 489.2781.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-(S)-3-methoxy-1-((pivaloyloxy)methyl)cyclohexa-2,5-diene-1-carboxylate (5.20)



5.20

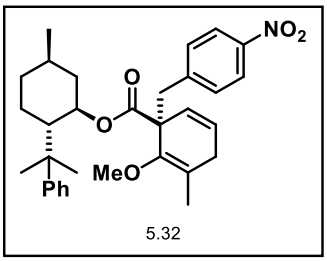
Prepared according to **general Birch reduction/alkylation procedure B**, using ester **S18** (100 mg, 0.27 mmol) and iodomethylpivalate (199 mg, 0.82 mmol) to afford **5.20** as a clear oil (105 mg, 79% yield, 1:1 dr).

^{1}H NMR (500 MHz, C_6D_6) δ 7.21 (dd, *J* = 6.4, 3.0 Hz, 4H), 7.08 (dddd, *J* = 8.4, 6.2, 3.8, 2.3 Hz, 1H), 5.86 (tq, *J* = 9.9, 2.1 Hz, 1H), 5.59 (dq, *J* = 9.8, 3.3 Hz, 1H), 5.03 (qd, *J* = 10.8, 4.4 Hz, 1H), 4.85 – 4.72 (m, 1H), 4.49 – 4.37 (m, 2H), 3.27 (d, *J* = 17.4 Hz, 3H), 2.70 – 2.53 (m, 2H), 2.09 (dddd, *J* = 13.9, 7.8, 6.2, 3.9 Hz, 1H), 1.86 (dddd, *J* = 12.2, 10.6, 4.5, 3.4 Hz, 1H), 1.39 (d, *J* = 17.5 Hz, 4H), 1.25 (s, 5H), 1.21 (d, *J* = 3.2 Hz, 9H), 1.16 – 1.05 (m, 1H), 0.96 (tdd, *J* = 12.2, 10.6, 4.3 Hz, 1H), 0.82 – 0.71 (m, 2H), 0.71 (dd, *J* = 6.5, 4.4 Hz, 3H), 0.61 – 0.49 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 177.4, 177.3, 172.1, 172.0, 156.1, 156.0, 150.7, 150.6, 128.5, 128.4, 128.3, 128.1, 127.9, 126.13, 126.11, 125.82, 125.79, 125.7, 125.5, 125.3, 125.2, 92.5, 76.12, 76.09, 70.1, 70.0, 53.84, 53.78, 51.2, 50.61, 50.57, 42.2, 42.1, 40.62, 40.58, 39.0, 34.7, 34.6, 31.41, 31.39, 30.8, 30.4, 29.30, 29.27, 27.7, 27.6, 27.4, 27.4, 24.4, 24.3, 21.9.

HRMS (ES+) m/z calc'd for $C_{30}H_{42}O_5Na$ $[M + Na]^+$: 505.2930, found 505.2915.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-(S)-2-methoxy-3-methyl-1-(4-nitrobenzyl)cyclohexa-2,5-diene-1-carboxylate (5.32)



5.32

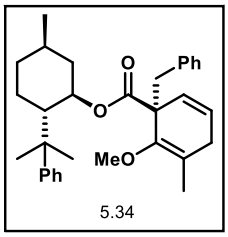
Prepared according to **general Birch reduction/alkylation procedure B**, using ester **S11** (143 mg, 0.38 mmol) and 4-nitrobenzyl bromide (245 mg, 1.1 mmol) to afford **5.32** as a clear oil (42 mg, 21% yield, 6:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 – 7.97 (m, 2H), 7.39 – 7.31 (m, 4H), 7.19 (tt, *J* = 6.8, 1.7 Hz, 1H), 7.13 (d, *J* = 8.3 Hz, 2H), 5.60 (dt, *J* = 9.9, 3.4 Hz, 1H), 5.19 (dt, *J* = 9.9, 1.9 Hz, 1H), 4.92 (td, *J* = 10.7, 4.3 Hz, 1H), 3.69 (s, 3H), 3.16 (d, *J* = 13.0 Hz, 1H), 2.54 – 2.44 (m, 1H), 2.31 (d, *J* = 12.9 Hz, 1H), 2.21 – 2.12 (m, 1H), 2.04 – 1.96 (m, 1H), 1.86 – 1.76 (m, 1H), 1.68 – 1.60 (m, 2H), 1.51 (s, 3H), 1.36 (s, 3H), 1.26 (d, *J* = 4.7 Hz, 1H), 1.21 (s, 3H), 1.12 – 1.01 (m, 2H), 0.90 (t, *J* = 6.7 Hz, 4H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.8, 151.8, 146.6, 146.5, 146.1, 131.7, 128.4, 126.8, 126.1, 125.7, 125.5, 122.2, 118.0, 76.4, 61.3, 54.8, 49.8, 41.9, 40.1, 39.3, 34.7, 33.0, 31.5, 27.3, 27.1, 26.7, 22.0, 16.0.

HRMS (ES+) m/z calc'd for $C_{32}H_{39}NO_5Na$ $[M + Na]^+$: 540.2726, found 540.2732.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-(S)-1-benzyl-2-methoxy-3-methylcyclohexa-2,5-diene-1-carboxylate (5.34)



5.34

Prepared according to **general Birch reduction/alkylation procedure B**, using ester **S11** (147 mg, 0.39 mmol) and benzyl bromide (198 mg, 1.2 mmol) to afford **5.34** as a clear oil (162 mg, 89% yield, 7:1 dr).

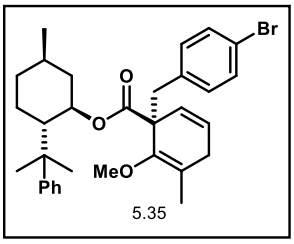
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36 – 7.29 (m, 4H), 7.22 – 7.17 (m, 1H), 7.17 – 7.11 (m, 3H), 7.04 – 7.00 (m, 2H), 5.58 (dq, *J* = 9.3, 2.9 Hz, 1H), 5.27 (dq, *J* = 9.9, 2.2 Hz, 1H), 4.92 (td, *J* = 10.6, 4.3 Hz, 1H), 3.71 (d, *J* = 2.7 Hz, 3H), 3.10 (dd, *J* = 13.2, 2.4 Hz, 1H), 2.52 (dd, *J* = 13.2, 2.5 Hz, 1H), 2.49 – 2.40 (m, 1H), 2.08 (ddd, *J* = 12.3, 10.4, 3.6 Hz, 1H), 2.00 (dtd, *J* =

12.1, 3.9, 2.2 Hz, 1H), 1.90 – 1.80 (m, 1H), 1.61 – 1.45 (m, 7H), 1.36 (d, *J* = 2.2 Hz, 3H), 1.24 (d, *J* = 2.3 Hz, 3H), 1.04 (dtd, *J* = 15.0, 12.6, 10.1 Hz, 2H), 0.88 (dd, *J* = 6.4, 2.6 Hz, 3H), 0.83 (td, *J* = 12.4, 3.3 Hz, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.4, 151.5, 147.4, 137.7, 131.1, 131.0, 128.3, 127.11, 127.07, 126.9, 126.0, 125.9, 125.8, 125.5, 117.5, 76.1, 61.3, 54.9, 50.1, 42.0, 40.3, 39.9, 33.1, 28.1, 27.3, 26.0, 22.0, 16.2.

HRMS (ES+) m/z calc'd for $C_{32}H_{40}O_3Na$ $[M + Na]^+$: 495.2875, found 495.2864.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-(S)-1-(4-bromobenzyl)-2-methoxy-3-methylcyclohexa-2,5-diene-1-carboxylate (5.35)



5.35

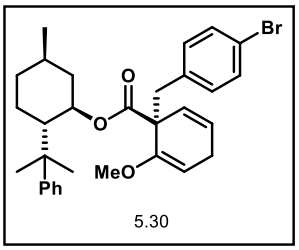
Prepared according to **general Birch reduction/alkylation procedure B**, using ester **S11** (97 mg, 0.25 mmol) and 4-bromobenzylbromide (190 mg, 0.76 mmol) to afford **5.35** as a clear oil (83 mg, 59% yield, 7:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.29 (m, 4H), 7.28 – 7.25 (m, 2H), 7.18 (tt, *J* = 6.5, 2.0 Hz, 1H), 6.90 – 6.85 (m, 2H), 5.60 (dt, *J* = 9.9, 3.4 Hz, 1H), 5.22 (dt, *J* = 9.9, 2.0 Hz, 1H), 4.91 (td, *J* = 10.6, 4.3 Hz, 1H), 3.69 (s, 3H), 3.04 (d, *J* = 13.3 Hz, 1H), 2.54 – 2.43 (m, 1H), 2.35 (d, *J* = 13.3 Hz, 1H), 2.11 (ddd, *J* = 12.2, 10.5, 3.5 Hz, 1H), 2.03 – 1.96 (m, 1H), 1.94 – 1.85 (m, 1H), 1.56 – 1.49 (m, 5H), 1.36 (s, 3H), 1.23 (s, 3H), 1.10 – 1.01 (m, 2H), 0.89 (dd, *J* = 6.7, 4.2 Hz, 5H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.1, 151.5, 147.0, 136.8, 132.7, 130.1, 128.3, 126.5, 126.4, 125.7, 125.4, 119.9, 117.7, 77.4, 76.9, 76.2, 61.2, 54.8, 49.9, 42.0, 41.9, 40.2, 39.1, 34.7, 33.1, 31.4, 27.5, 27.2, 26.5, 21.97, 21.95, 16.1.

HRMS (ES+) m/z calc'd for $C_{32}H_{39}BrO_3Na$ $[M + Na]^+$: 573.1980, found 573.2001.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-(S)-1-(4-bromobenzyl)-2-methoxycyclohexa-2,5-diene-1-carboxylate (5.30)



5.30

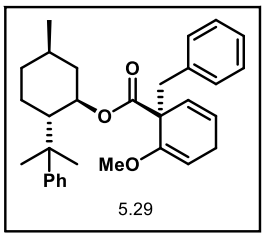
Prepared according to **general Birch reduction/alkylation procedure B**, using ester **S10** (158 mg, 0.43 mmol) and benzyl bromide (324 mg, 1.3 mmol) to afford **5.30** as a clear oil (175 mg, 75% yield, 7:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 – 7.28 (m, 6H), 7.17 (h, *J* = 4.1 Hz, 1H), 6.90 (dd, *J* = 8.9, 2.3 Hz, 2H), 5.81 – 5.74 (m, 1H), 5.35 (dt, *J* = 9.8, 2.0 Hz, 1H), 4.84 (td, *J* = 10.5, 4.2 Hz, 1H), 4.60 (t, *J* = 3.6 Hz, 1H), 3.49 (d, *J* = 4.5 Hz, 1H), 3.47 (s, 3H), 3.31 (d, *J* = 13.4 Hz, 1H), 2.69 – 2.58 (m, 2H), 2.28 – 2.18 (m, 1H), 1.98 – 1.87 (m, 2H), 1.50 (dt, *J* = 12.9, 2.9 Hz, 1H), 1.47 – 1.37 (m, 1H), 1.31 (s, 3H), 1.26 (d, *J* = 2.4 Hz, 3H), 1.01 – 0.91 (m, 2H), 0.85 (d, *J* = 6.4 Hz, 4H), 0.80 – 0.68 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 172.7, 151.0, 150.9, 136.9, 132.4, 132.4, 132.0, 130.5, 128.2, 128.1, 127.2, 126.2, 126.0, 125.5, 120.1, 94.8, 76.6, 53.7, 50.4, 41.6, 40.4, 39.7, 34.7, 31.5, 29.7, 27.6, 26.3, 23.8, 21.9.

HRMS (ES+) m/z calc'd for $C_{31}H_{37}BrO_3Na$ $[M + Na]^+$: 559.1824, found 559.1844.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl (S)-1-benzyl-2-methoxycyclohexa-2,5-diene-1-carboxylate (5.29)



5.29

Prepared according to **general Birch reduction/alkylation procedure B**, using ester **S10** (90 mg, 0.24 mmol) and benzylbromide (125 mg, 0.73 mmol) to afford **5.29** as a clear oil (65 mg, 43% yield, 9:1 dr).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.30 (d, *J* = 4.3 Hz, 4H), 7.16 (dddd, *J* = 8.8, 6.5, 4.8, 2.4 Hz, 4H), 7.05 – 7.00 (m, 2H), 5.79 – 5.73 (m, 1H), 5.40 (dt, *J* = 9.8, 2.1 Hz, 1H), 4.85 (td, *J* = 10.6, 4.2 Hz, 1H), 4.59 (t, *J* = 3.7 Hz, 1H), 3.48 (s, 3H), 3.38 (d, *J* = 13.3 Hz, 1H), 2.74 (d, *J* = 13.4 Hz, 1H), 2.64 – 2.56 (m, 1H), 2.21 – 2.13 (m, 1H), 1.97 (d, *J* = 12.6 Hz, 1H), 1.94 – 1.87

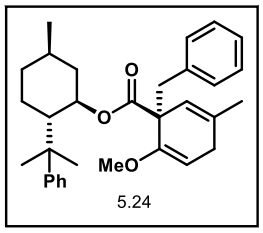
(m, 1H), 1.49 (dd, *J* = 13.0, 2.9 Hz, 1H), 1.44 (d, *J* = 6.5 Hz, 1H), 1.32 (s, 3H), 1.27 (s, 4H), 1.02 – 0.94 (m, 1H), 0.93 – 0.87 (m, 1H), 0.85 (d, *J* = 6.4 Hz, 3H), 0.74 (qd, *J* = 12.7, 3.5 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 172.9, 151.3, 150.9, 137.83, 130.79, 128.14, 128.08, 127.4, 126.8, 126.5, 126.02, 125.98, 125.5, 76.5, 53.64, 53.57, 50.4, 41.6, 40.4, 40.3, 34.7, 29.9, 27.6, 26.3, 23.6, 21.9.

HRMS (ES+) m/z calc'd for $C_{31}H_{38}O_3$ $[M]^+$: 458.2821, found 458.2808.

X-Ray Crystal Structure: See Appendix D.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-(S)-1-benzyl-2-methoxy-5-methylcyclohexa-2,5-diene-1-carboxylate (5.24)



5.24

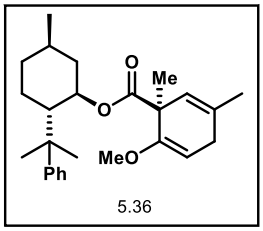
Prepared according to **general Birch reduction/alkylation procedure B**, using ester **S12** (82 mg, 0.22 mmol) and benzyl bromide (110 mg, 0.65 mmol) to afford **5.24** as a clear oil (86 mg, 84% yield, 8:1 dr).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.31 (dd, *J* = 4.3, 1.7 Hz, 4H), 7.20 – 7.13 (m, 4H), 7.00 (dd, *J* = 7.1, 1.8 Hz, 2H), 5.11 (t, *J* = 1.4 Hz, 1H), 4.85 (td, *J* = 10.6, 4.2 Hz, 1H), 4.54 (t, *J* = 3.6 Hz, 1H), 3.48 (s, 3H), 3.32 (d, *J* = 13.2 Hz, 1H), 2.70 (d, *J* = 13.2 Hz, 1H), 2.50 – 2.41 (m, 1H), 2.02 – 1.96 (m, 2H), 1.93 (ddd, *J* = 13.1, 10.3, 3.2 Hz, 1H), 1.66 (s, 3H), 1.51 (dq, *J* = 13.3, 2.8 Hz, 1H), 1.45 (pd, *J* = 7.2, 4.8 Hz, 1H), 1.33 (s, 3H), 1.27 (d, *J* = 3.0 Hz, 4H), 1.02 – 0.90 (m, 2H), 0.87 (d, *J* = 6.4 Hz, 3H), 0.76 (qd, *J* = 12.7, 3.5 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.3, 151.4, 151.0, 138.0, 130.7, 127.2, 126.0, 125.8, 125.4, 121.4, 94.5, 76.4, 54.3, 53.8, 50.4, 41.6, 40.6, 40.4, 34.7, 31.5, 30.9, 29.8, 27.6, 23.7, 22.5, 21.9.

HRMS (ES+) m/z calc'd for $C_{32}H_{40}O_3Na$ $[M + Na]^+$: 495.2875, found 495.2862.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl-(S)-2-methoxy-1,5-dimethylcyclohexa-2,5-diene-1-carboxylate (5.36)



5.36

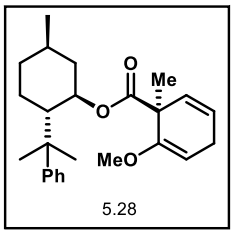
Prepared according to **general Birch reduction/alkylation procedure B**, using ester **S12** (74 mg, 0.19 mmol) and methyl iodide (83 mg, 0.58 mmol) to afford **5.36** as a clear oil (56 mg, 73% yield, 3:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 4.4 Hz, 4H), 7.16 (h, *J* = 4.4 Hz, 1H), 5.14 (q, *J* = 1.6 Hz, 1H), 4.78 (td, *J* = 10.6, 4.2 Hz, 1H), 4.70 (t, *J* = 3.6 Hz, 1H), 3.49 (s, 3H), 2.84 – 2.66 (m, 3H), 1.95 – 1.80 (m, 2H), 1.74 (d, *J* = 1.5 Hz, 3H), 1.50 – 1.45 (m, 1H), 1.43 – 1.39 (m, 1H), 1.33 (s, 3H), 1.31 (s, 3H), 1.25 (s, 4H), 0.97 – 0.87 (m, 2H), 0.84 – 0.82 (m, 3H), 0.76 – 0.68 (m, 1H).

^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 154.9, 150.8, 132.4, 128.1, 128.0, 126.04, 126.00, 125.43, 125.40, 123.9, 123.6, 91.8, 91.6, 76.1, 76.0, 54.2, 50.5, 41.6, 40.5, 34.7, 31.5, 31.4, 30.4, 27.6, 23.5, 23.1, 22.6, 21.9.

HRMS (ES+) m/z calc'd for $C_{26}H_{36}O_3Na$ $[M + Na]^+$: 419.2562, found 419.2556.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl (S)-2-methoxy-1-methylcyclohexa-2,5-diene-1-carboxylate (5.28)



5.28

Prepared according to **general Birch reduction/alkylation procedure B**, using ester **S10** (87 mg, 0.24 mmol) and methyl iodide (101 mg, 0.72 mmol) to afford **5.28** as a clear oil (62 mg, 68% yield, 5:1 dr).

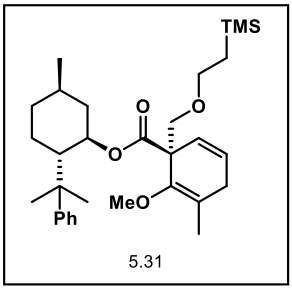
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, *J* = 1.5 Hz, 3H), 7.25 (d, *J* = 2.4 Hz, 1H), 7.14 (dddd, *J* = 8.8, 5.1, 3.1, 1.7 Hz, 1H), 5.78 (dtd, *J* = 9.8, 3.4, 1.1 Hz, 1H), 5.42 (dt, *J* = 9.8, 2.0 Hz, 1H), 4.77 (td, *J* = 10.6, 4.3 Hz, 1H), 4.70 (td, *J* = 3.6, 1.1 Hz, 1H), 3.47 (s, 3H), 2.93 – 2.75 (m, 2H), 1.90 (dtd, *J* = 12.2, 4.0, 2.3 Hz, 1H), 1.84 (ddd, *J* = 12.2, 10.5, 3.5 Hz, 1H), 1.49 – 1.42 (m, 1H), 1.41 – 1.37 (m, 1H), 1.34 (s, 3H), 1.29 (s, 3H), 1.23 (d, *J* = 2.0 Hz, 3H), 1.19 (ddd,

J = 10.3, 5.2, 2.4 Hz, 1H), 0.97 – 0.84 (m, 2H), 0.81 (d, *J* = 6.5 Hz, 3H), 0.70 (tdd, *J* = 12.9, 11.3, 3.4 Hz, 1H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 173.4, 173.4, 154.6, 150.8, 129.1, 128.1, 126.0, 125.4, 124.7, 91.8, 76.3, 54.0, 50.5, 48.1, 41.6, 40.5, 34.7, 31.5, 30.4, 27.6, 26.6, 23.5, 23.1, 21.9.

HRMS (ES+) m/z calc'd for $C_{25}H_{34}O_3Na$ $[M + Na]^+$: 405.2406, found 405.2395.

(1R,2S,5R)-5-methyl-2-(2-phenylpropan-2-yl)cyclohexyl (R)-2-methoxy-3-methyl-1-((2-(trimethylsilyl)ethoxy)methyl)cyclohexa-2,5-diene-1-carboxylate (5.13)



5.31

Prepared according to **general Birch reduction/alkylation procedure B**, using ester **S11** (80 mg, 0.210 mmol) and SEMCl (0.112 mL, 0.630 mmol) to afford **5.31** as a clear oil (83 mg, 77% yield, 4:1 dr).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.26 (d, *J* = 4.1 Hz, 4H), 7.16 – 7.11 (m, 1H), 5.82 (dd, *J* = 9.6, 3.2 Hz, 1H), 5.46 (d, *J* = 9.6 Hz, 1H), 4.74 (td, *J* = 10.3, 3.9 Hz, 1H), 3.70 (d, *J* = 9.2 Hz, 1H), 3.64 (d, *J* = 17.3 Hz, 3H), 3.51 (t, *J* = 8.0 Hz, 2H), 3.40 (d, *J* = 9.1 Hz, 1H), 2.71 (d, *J* = 8.4 Hz, 2H), 1.95 – 1.85 (m, 2H), 1.68 (s, 3H), 1.30 (d, *J* = 14.5 Hz, 4H), 1.24 – 1.17 (m, 4H), 0.96 – 0.84 (m, 5H), 0.82 (d, *J* = 6.3 Hz, 3H), -0.03 (s, 9H).

^{13}C NMR (151 MHz, $CDCl_3$) δ 171.6, 151.0, 146.7, 128.1, 127.1, 126.4, 125.9, 125.4, 118.4, 76.3, 71.7, 68.7, 61.0, 54.7, 50.5, 41.6, 40.4, 34.7, 33.5, 31.7, 31.5, 31.4, 29.6, 27.5, 24.2, 22.8, 21.9, 18.1, 16.4, 14.3, -1.2.

HRMS (ES+) m/z calc'd for $C_{31}H_{48}O_4SiNa$ $[M + Na]^+$: 513.3400, found 513.3392.

5.8 References

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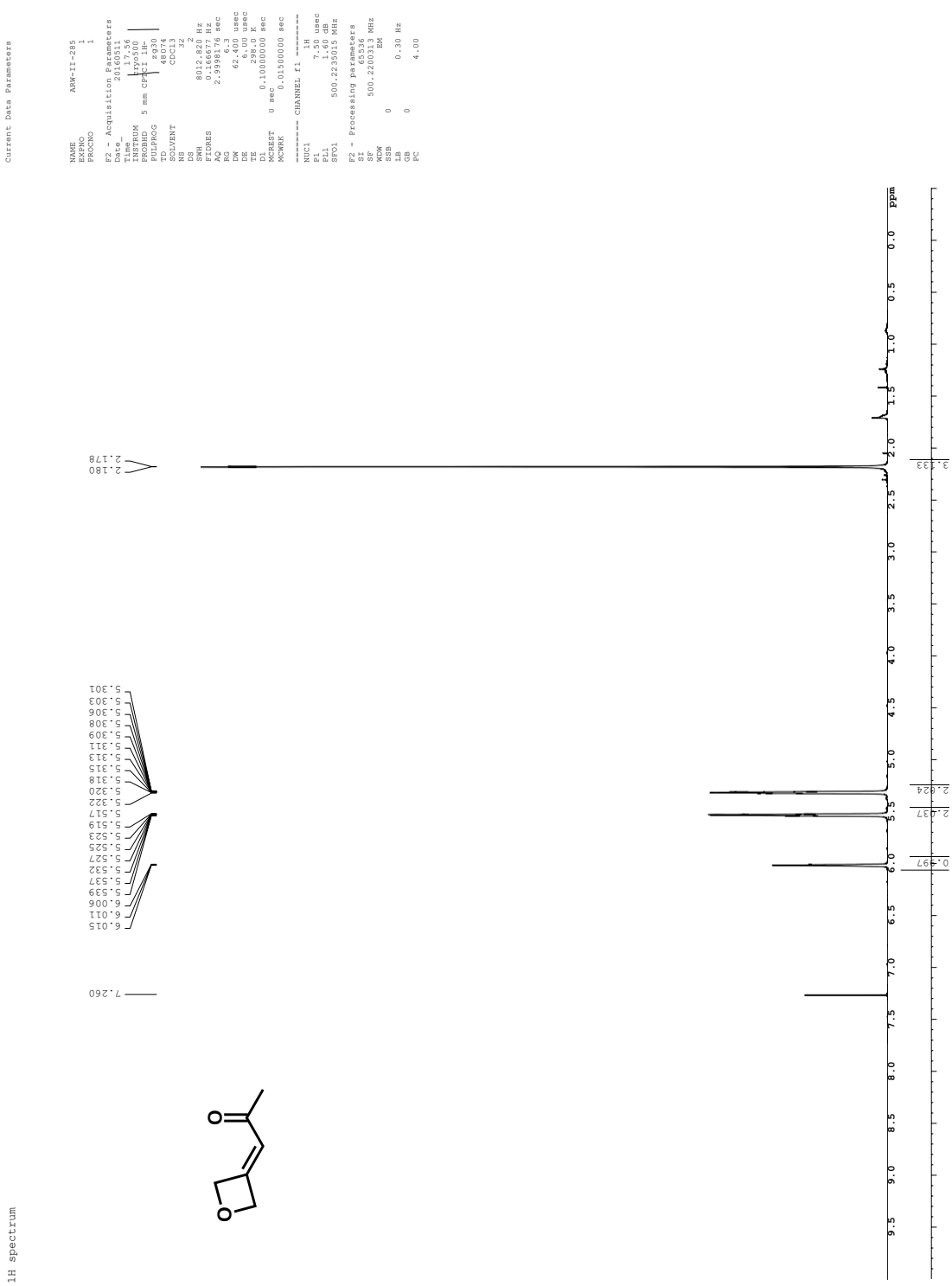
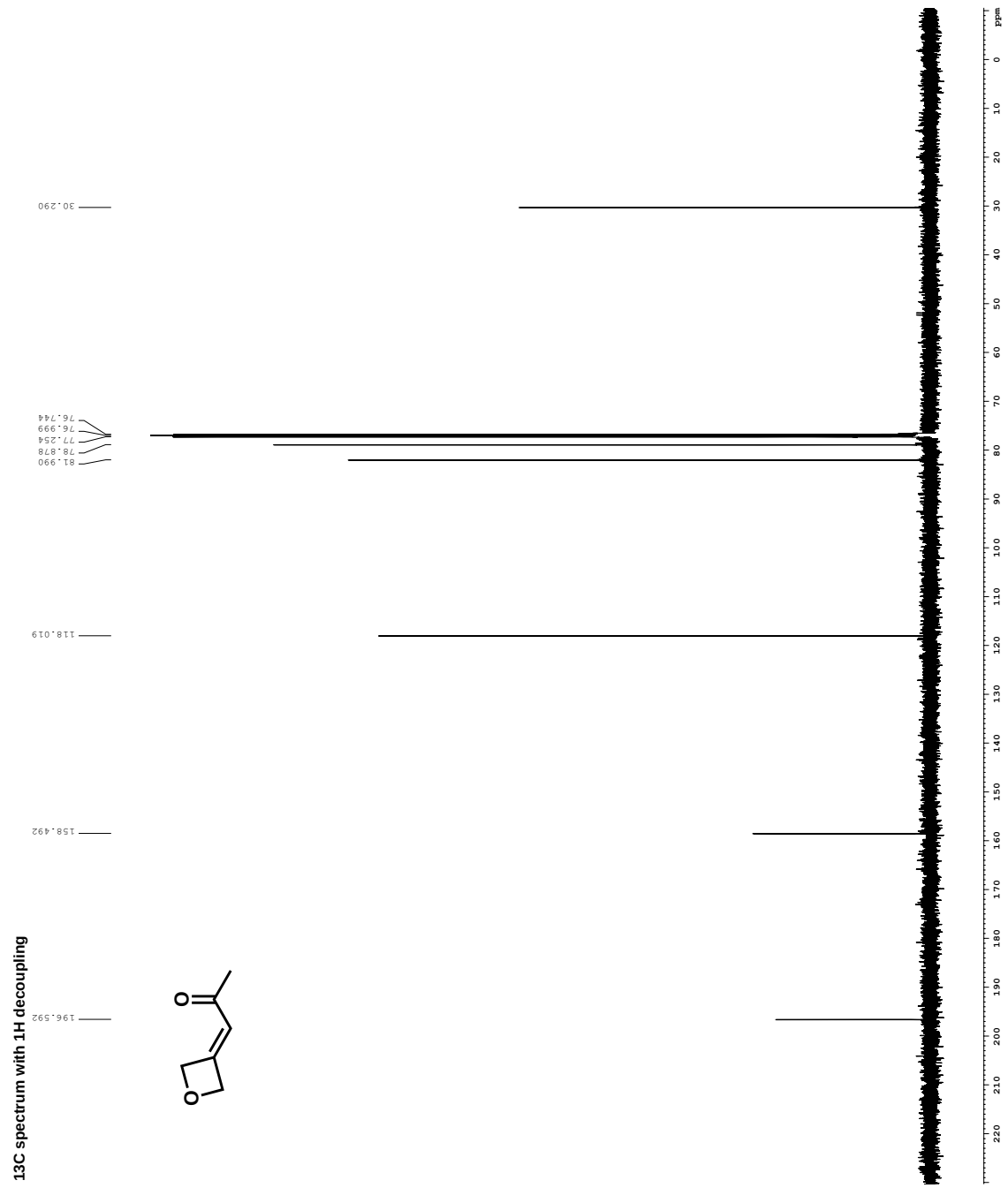
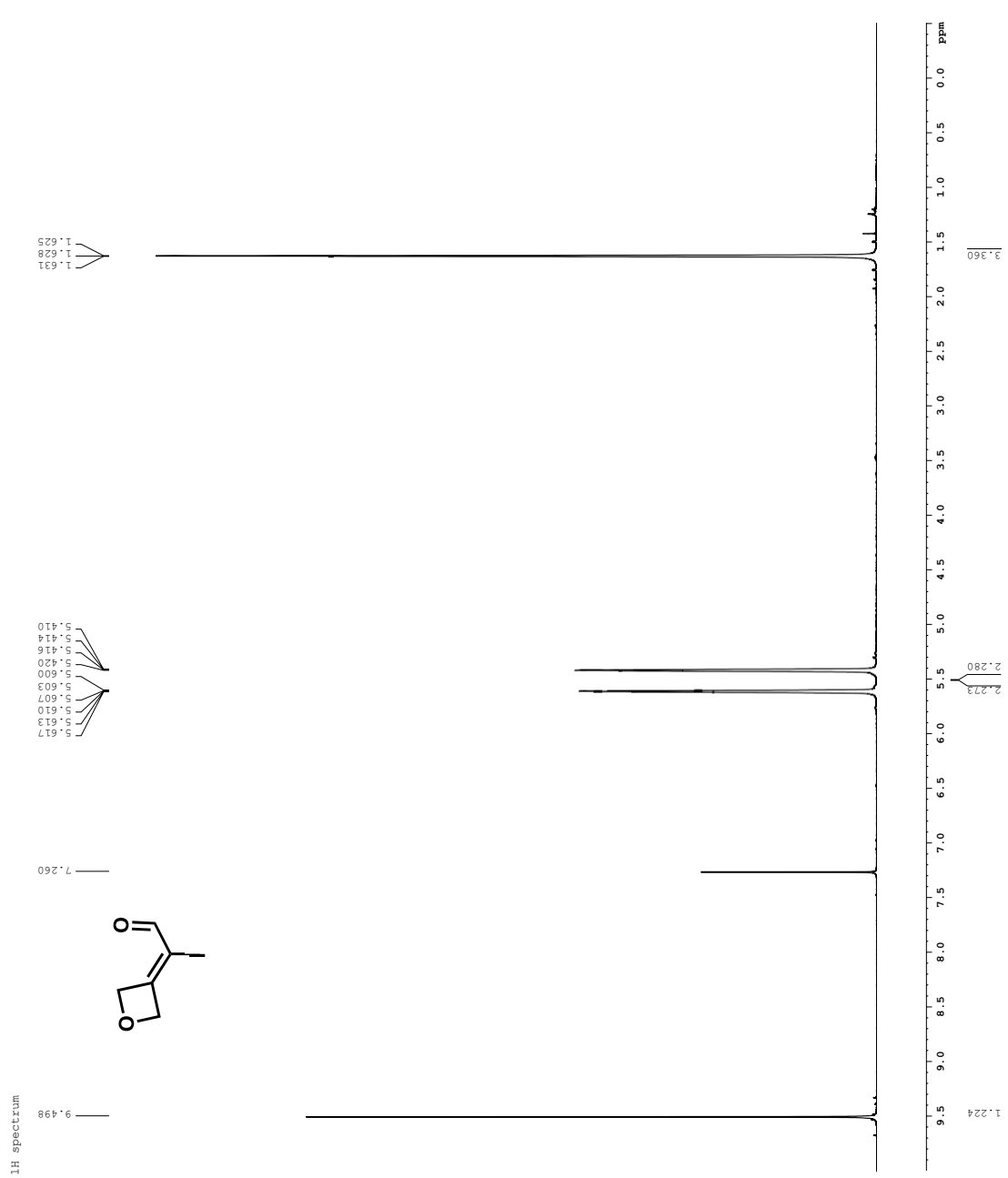
Appendix A: Spectra





13C spectrum with 1H decoupling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PROCNO 1
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Date_ 20160905
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INSTRUM spect600
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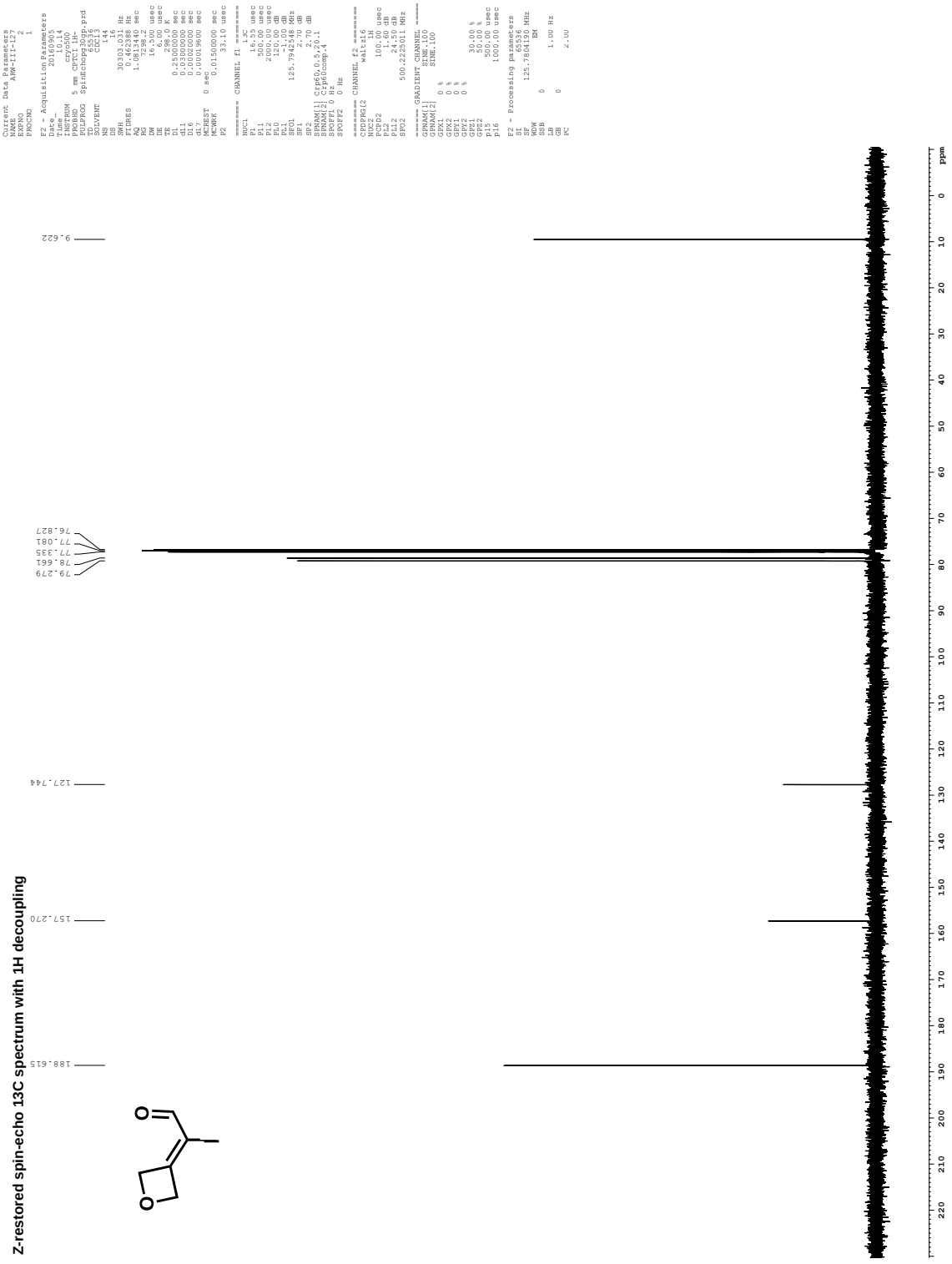
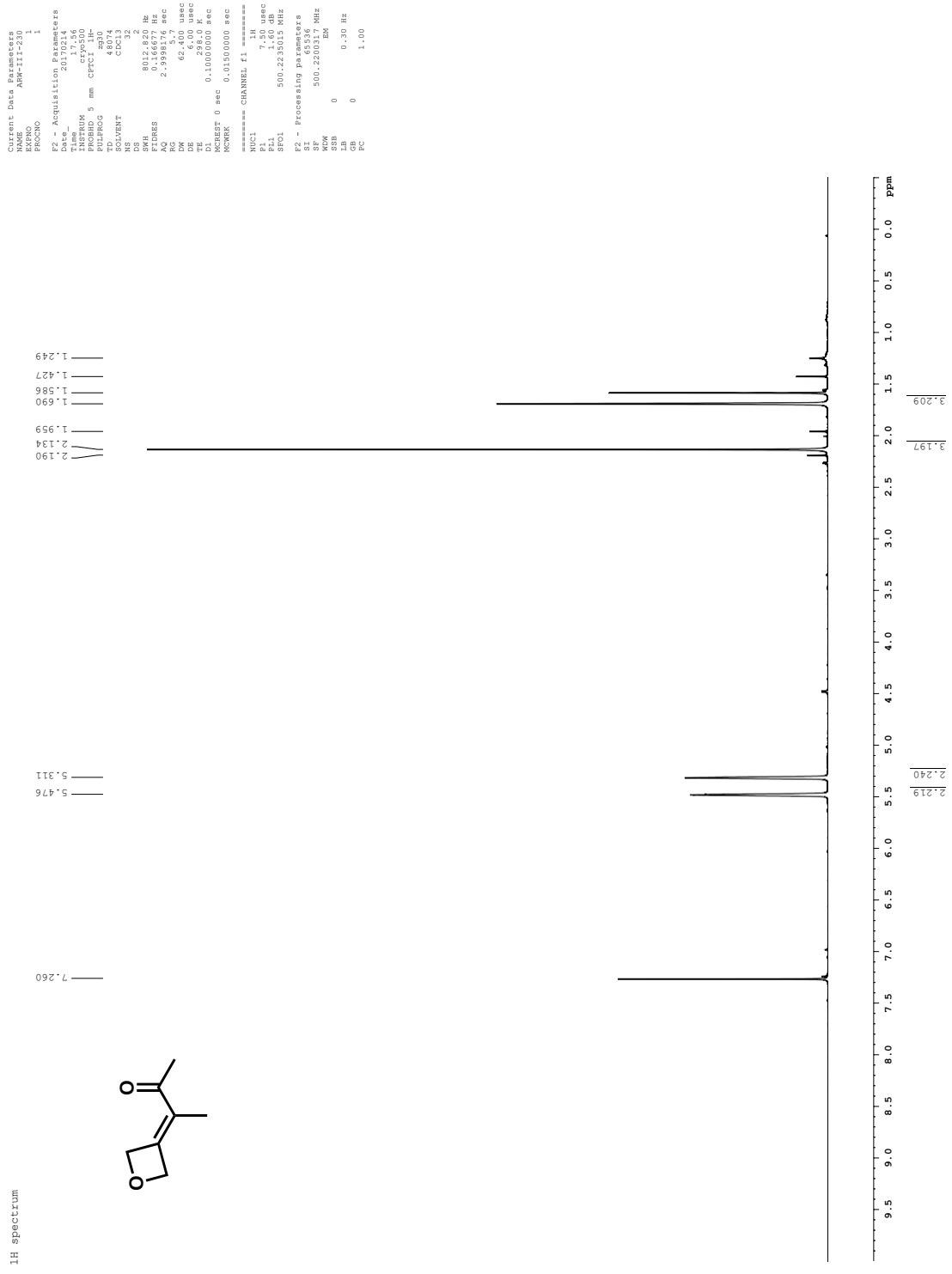
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998273 sec
RG 4.5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
WCPKEST 0 sec
WCWRK 0.01500000 sec
CHANNEL f1 1H
NUC1
P1 7.50 usec
PL1 1.00 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200312 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
1H spectrum
9.498
7.260
5.617
5.613
5.610
5.607
5.603
5.600
5.420
5.416
5.414
5.410
1.631
1.628
1.625
3.360
2.280
2.273
1.224
ppm

Z-restored spin-echo 13C spectrum with 1H decoupling




1H spectrum
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PROCNO 1
F2 - Acquisition Parameters
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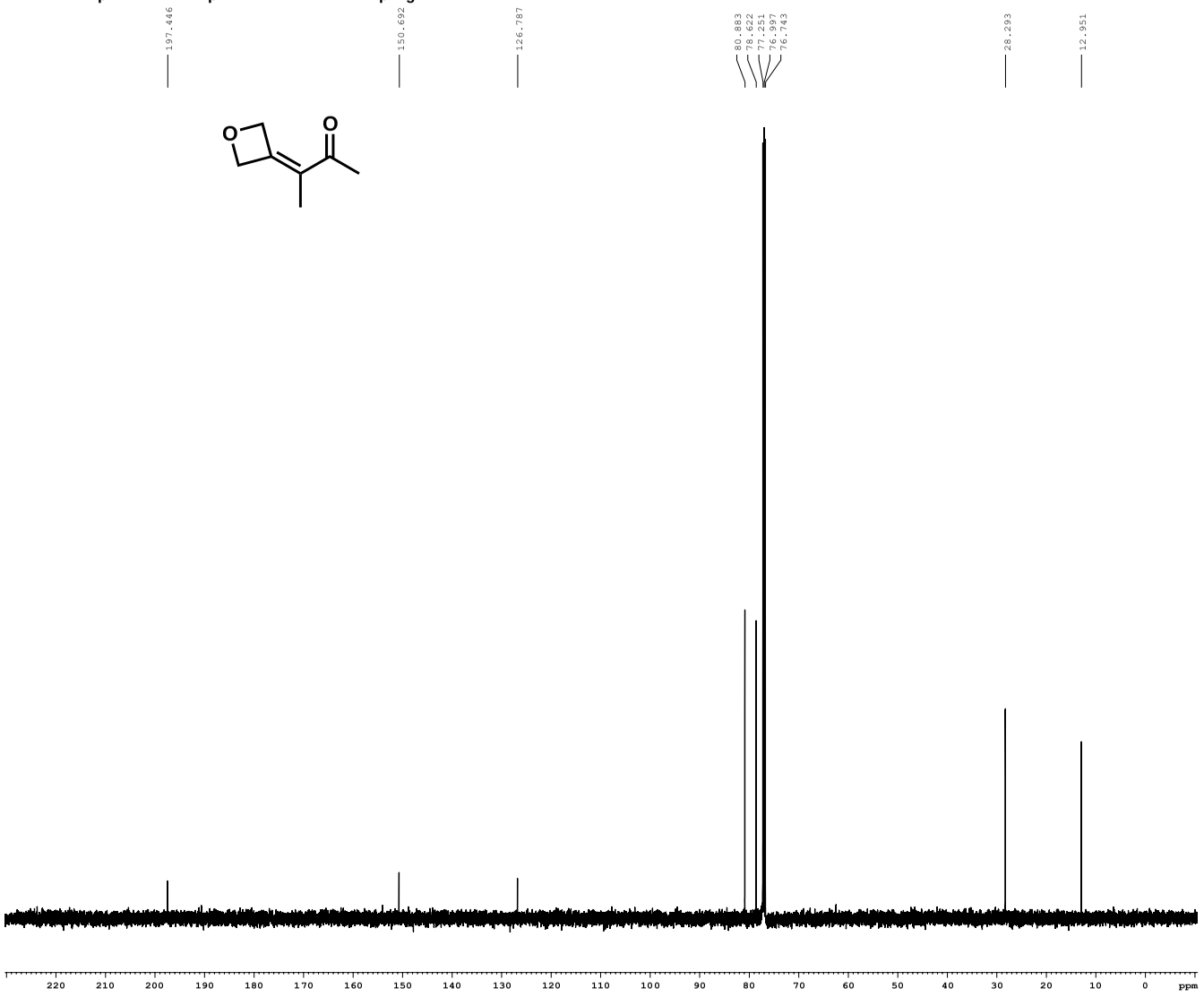
Time 17.56
INSTRUM spect
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 48074
SOLVENT CDCl3
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.166677 Hz
AQ 2.9998176 sec
RG 5.7
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200317 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.260
5.476
5.311
2.190
2.134
1.959
1.690
1.586
1.427
1.249
3.209
3.197
2.219
2.240
ppm

Z-restored spin-echo 13C spectrum with 1H decoupling

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EXPNO                   2
PROCNO                  1

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PULPROG  SpinEchopg30gp.prd
TD                65536
SOLVENT           CDCl3
NS                  400
DS                   16
SWH           30303.031 Hz
FIDRES        0.462388 Hz
AQ            1.0813440 sec
RG               5160.6
DW               16.500 usec
DE                6.00 usec
TE               298.0 K
D1            0.25000000 sec
d11           0.03000000 sec
D16           0.00020000 sec
d17           0.00019600 sec
MCREST   0 sec
MCWRK         0.01500000 sec
P2               33.10 usec

======= CHANNEL f1 ========
NUC1                  1H
P1                16.55 usec
P11              500.00 usec
P12             2000.00 usec
PL0               120.00 dB
PL1                -1.00 dB
SFO1         125.7942548 MHz
SP1                2.70 dB
SP2                2.70 dB
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SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

======= CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12              24.50 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
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GPNAM[2]         SINE.100
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GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1              30.00 %
GPZ2              50.00 %
p15              500.00 usec
p16             1000.00 usec

F2 - Processing parameters
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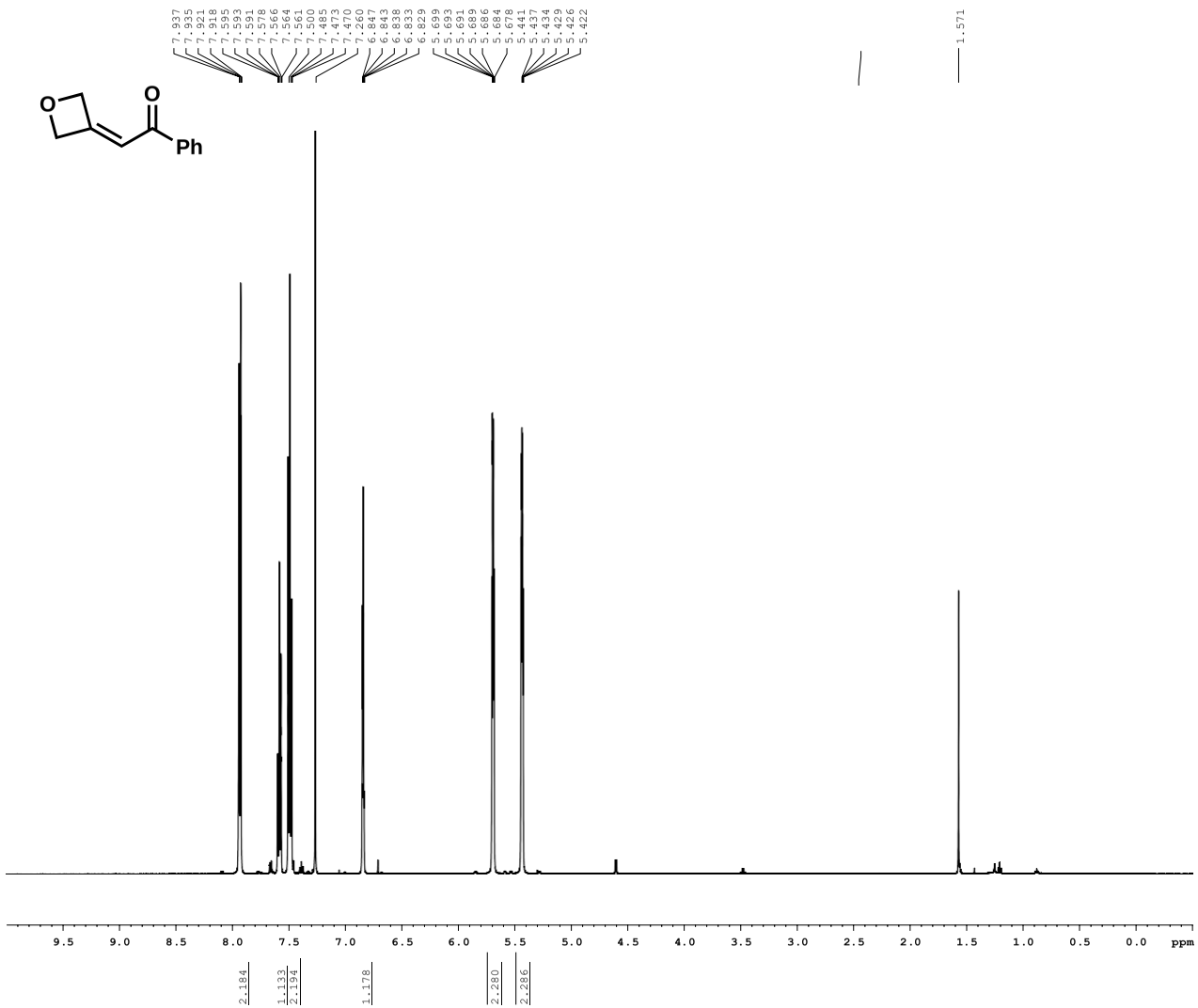
SF           125.7804282 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 2.00
```

1H spectrum

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PROCNO                  1

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PULPROG             zg30
TD                 48074
SOLVENT            CDCl3
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FIDRES             0.166677 Hz
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RG                     5
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
D1              0.10000000 sec
MCREST    0 sec
MCWRK           0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  7.50 usec
PL1                 1.60 dB
SFO1          500.2235015 MHz

F2 - Processing parameters
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SSB          0
LB                   0.30 Hz
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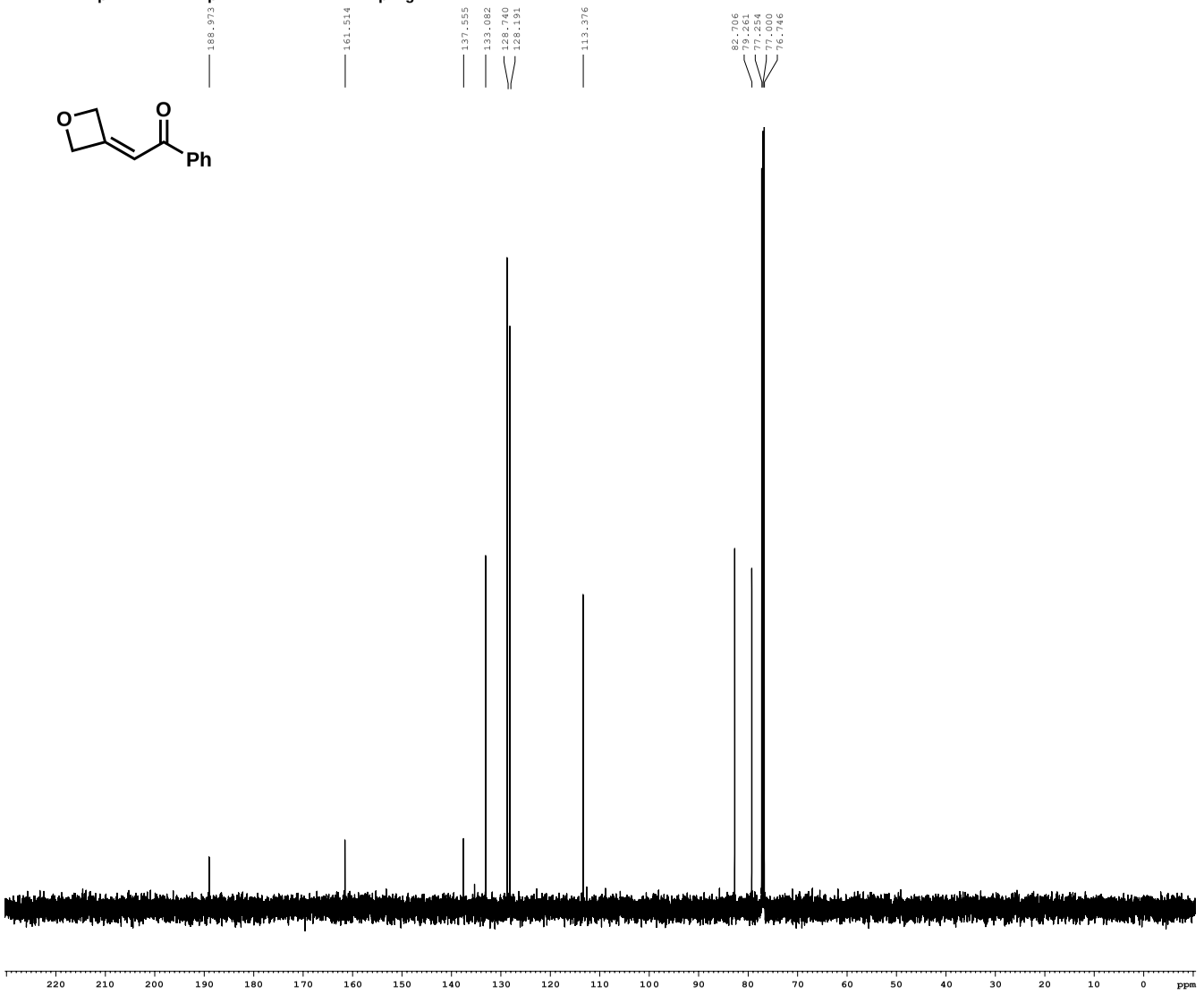
Z-restored spin-echo 13C spectrum with 1H decoupling

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PULPROG  SpinEchopg30gp.prd
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SOLVENT           CDCl3
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DS                   16
SWH           30303.031 Hz
FIDRES        0.462388 Hz
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DE                6.00 usec
TE               298.0 K
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d11           0.03000000 sec
D16           0.00020000 sec
d17           0.00019600 sec
MCREST   0 sec
MCWRK         0.01500000 sec
P2               33.10 usec

======= CHANNEL f1 ========
NUC1                  1H
P1                16.55 usec
P11              500.00 usec
P12             2000.00 usec
PL0               120.00 dB
PL1                -1.00 dB
SFO1         125.7942548 MHz
SP1                2.70 dB
SP2                2.70 dB
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SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

======= CHANNEL f2 ========
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NUC2                  1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12              24.50 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
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GPNAM[2]        SINE.100
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GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1             30.00 %
GPZ2             50.00 %
p15             500.00 usec
p16            1000.00 usec

F2 - Processing parameters
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PC                2.00
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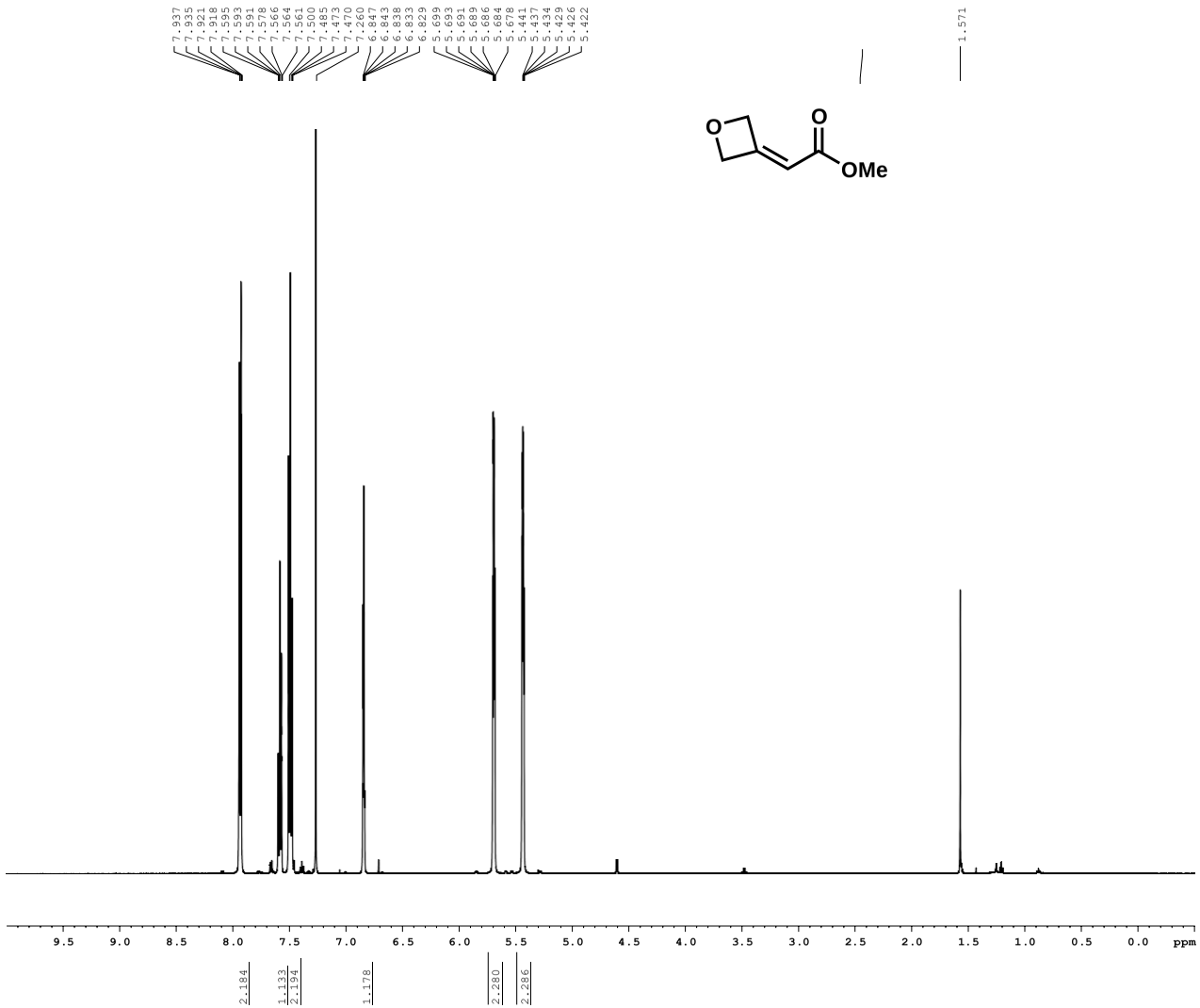
1H spectrum

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PROCNO                  1

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TD                 48074
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DS                     2
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FIDRES           0.166677 Hz
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RG                     5
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
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MCREST 0 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
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PL1                 1.60 dB
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F2 - Processing parameters
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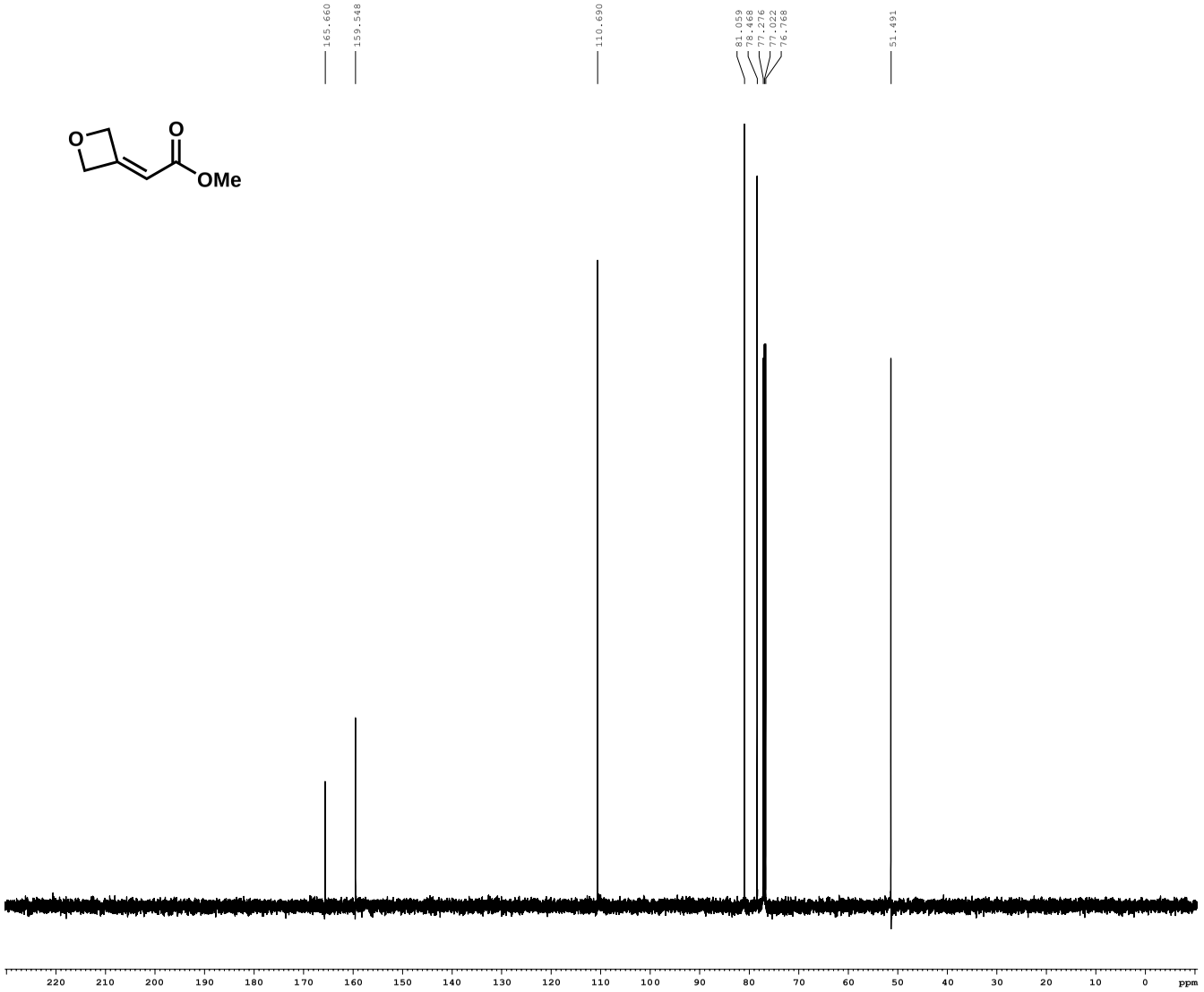
```

Z-restored spin-echo 13C spectrum with 1H decoupling

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NS                    112
DS                     16
SWH             30303.031 Hz
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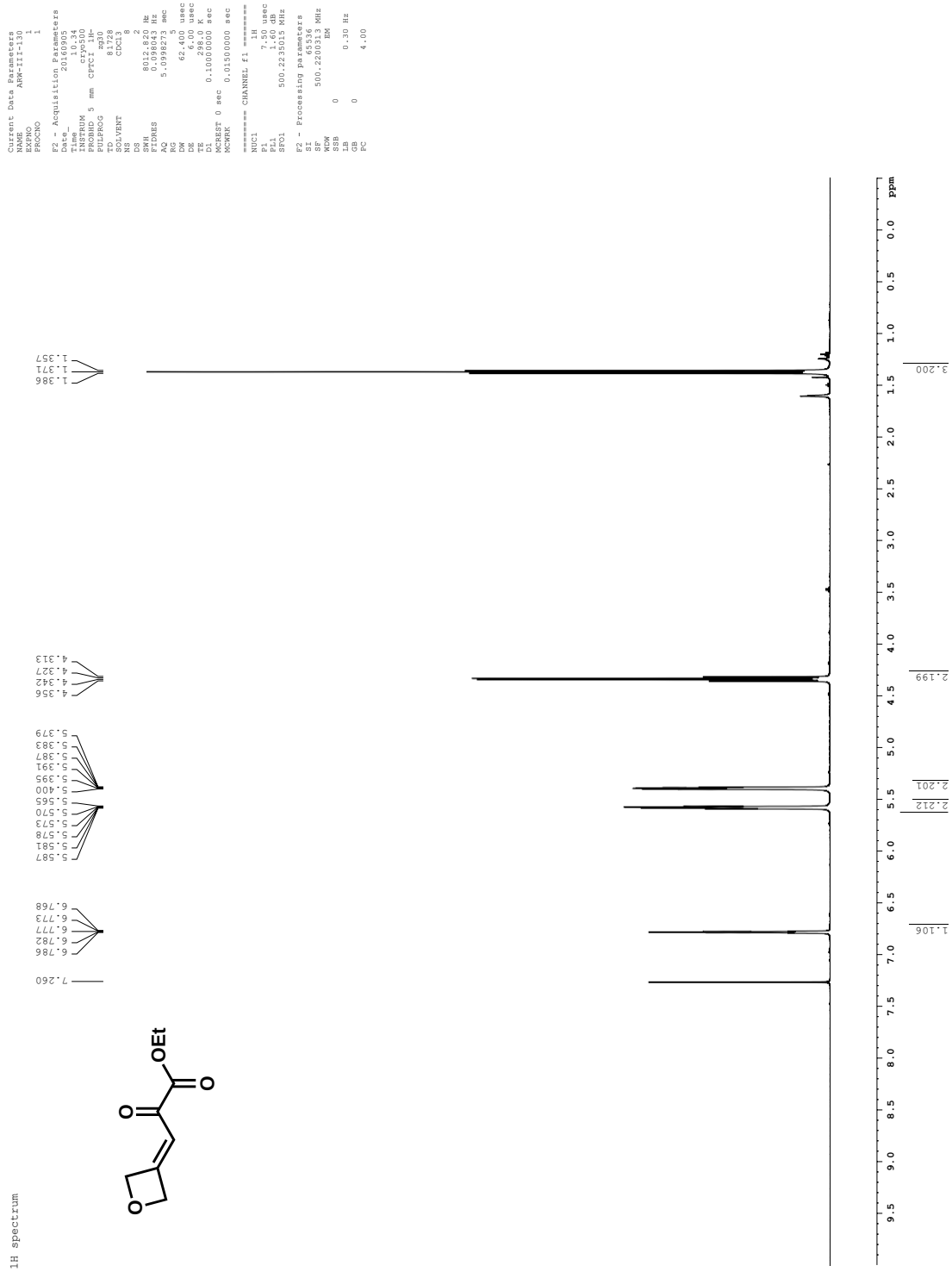
AQ              1.081248U sec
RG                 5792.6
DW                 16.500 usec
DE                  6.00 usec
TE                298.0 K
D1              0.25000000 sec
d11             0.03000000 sec
D16             0.00020000 sec
d17             0.00019600 sec
MCREST   0 sec
MCWRK           0.01500000 sec
P2                 33.10 usec

======= CHANNEL f1 =======
NUC1                  13C
P1                  16.55 usec
P11                500.00 usec
P12               2000.00 usec
PL0                120.00 dB
PL1                 -1.00 dB
SFO1         125.7942548 MHz
SP1                 2.70 dB
SP2                 2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

======= CHANNEL f2 =======
CPDPRG[2          waltz16
NUC2                  1H
PCPD2              100.00 usec
PL2                 1.60 dB
PL12               24.50 dB
SFO2         500.2225011 MHz

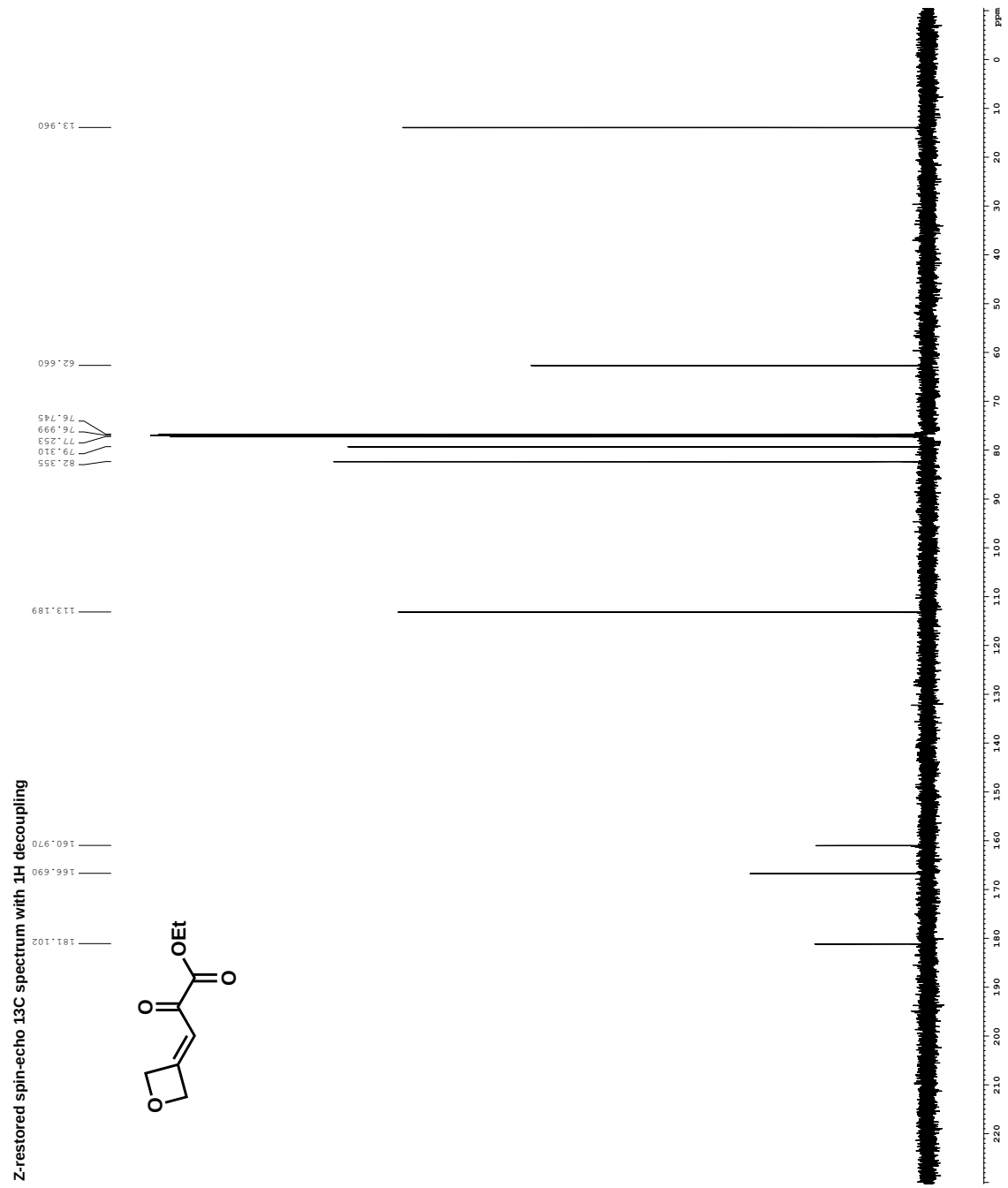
===== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1               30.00 %
GPZ2               50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                 65536
SF          125.7804129 MHz
WDW                   EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  2.00
```

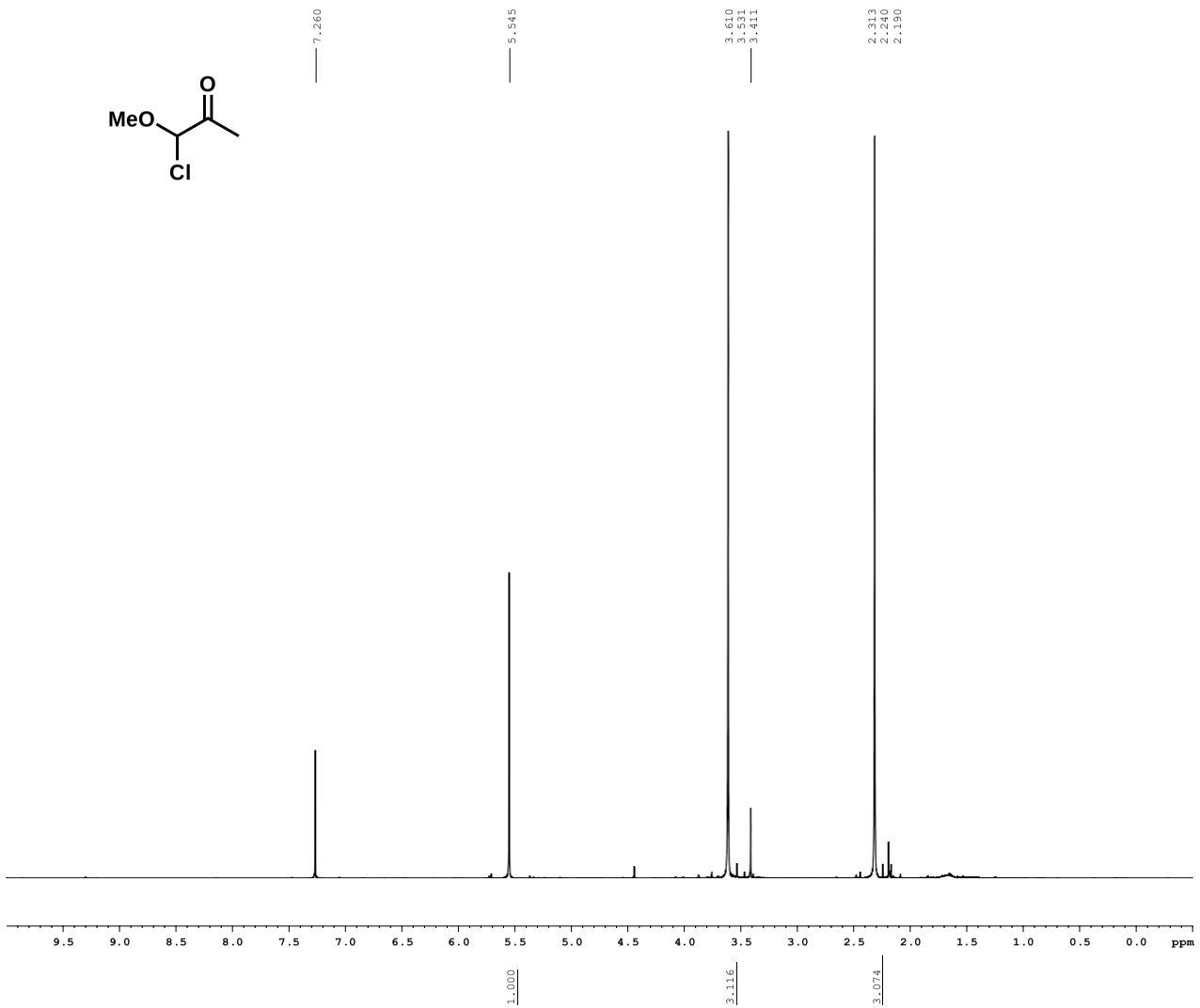

Current Data Parameters
NAME AWK-IT-130
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160905
Time 10.34
INSTRUM spect
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 2
DS 2
SWH 8012.820 Hz
FIDRES 0.098643 Hz
AQ 5.0998273 sec
RG 5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.00 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200313 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
1.357
1.371
1.386
4.313
4.327
4.342
4.356
5.379
5.383
5.387
5.391
5.395
5.400
5.565
5.570
5.573
5.578
5.581
5.587
6.768
6.773
6.777
6.782
6.786
7.260
OEt
O
O
O
1.106
2.212
2.201
1.199
3.200
ppm

1H spectrum

Z-restored spin-echo 13C spectrum with 1H decoupling



1H spectrum



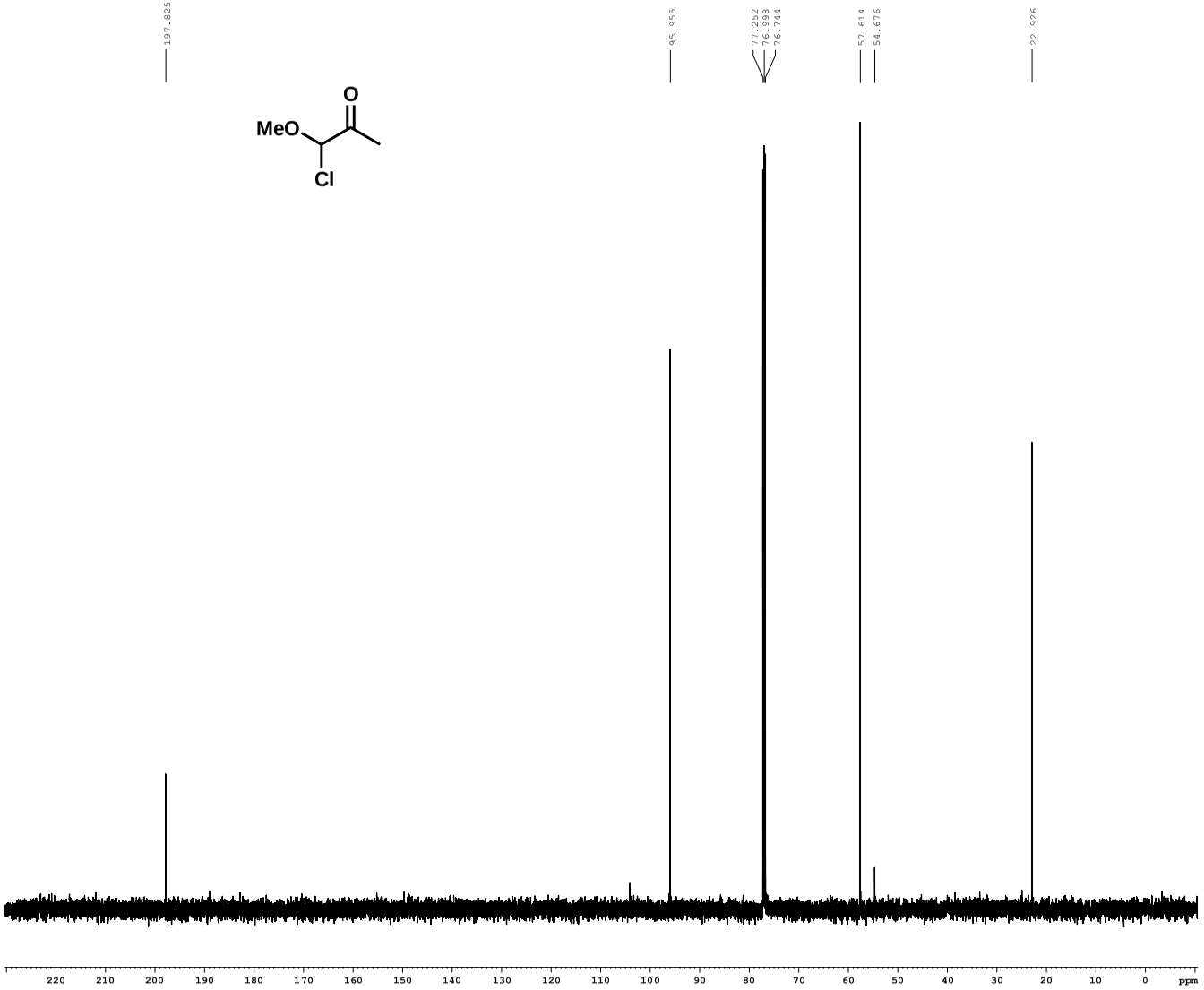

```
Current Data Parameters
NAME      ARW-III-204cryo
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_             20170315
Time                13.33
INSTRUM           cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 48074
SOLVENT             CDCl3
NS                     12
DS                      2
SWH              8012.820 Hz
FIDRES           0.166677 Hz
AQ               2.9998176 sec
RG                    5.7
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
D1           0.10000000 sec
MCREST 0 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  7.50 usec
PL1                 1.60 dB
SFO1         500.2235015 MHz

F2 - Processing parameters
SI                  65536
SF           500.2200315 MHz
WDW                    EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME        ARW-III-204cryo
EXPNO                    2
PROCNO                   1

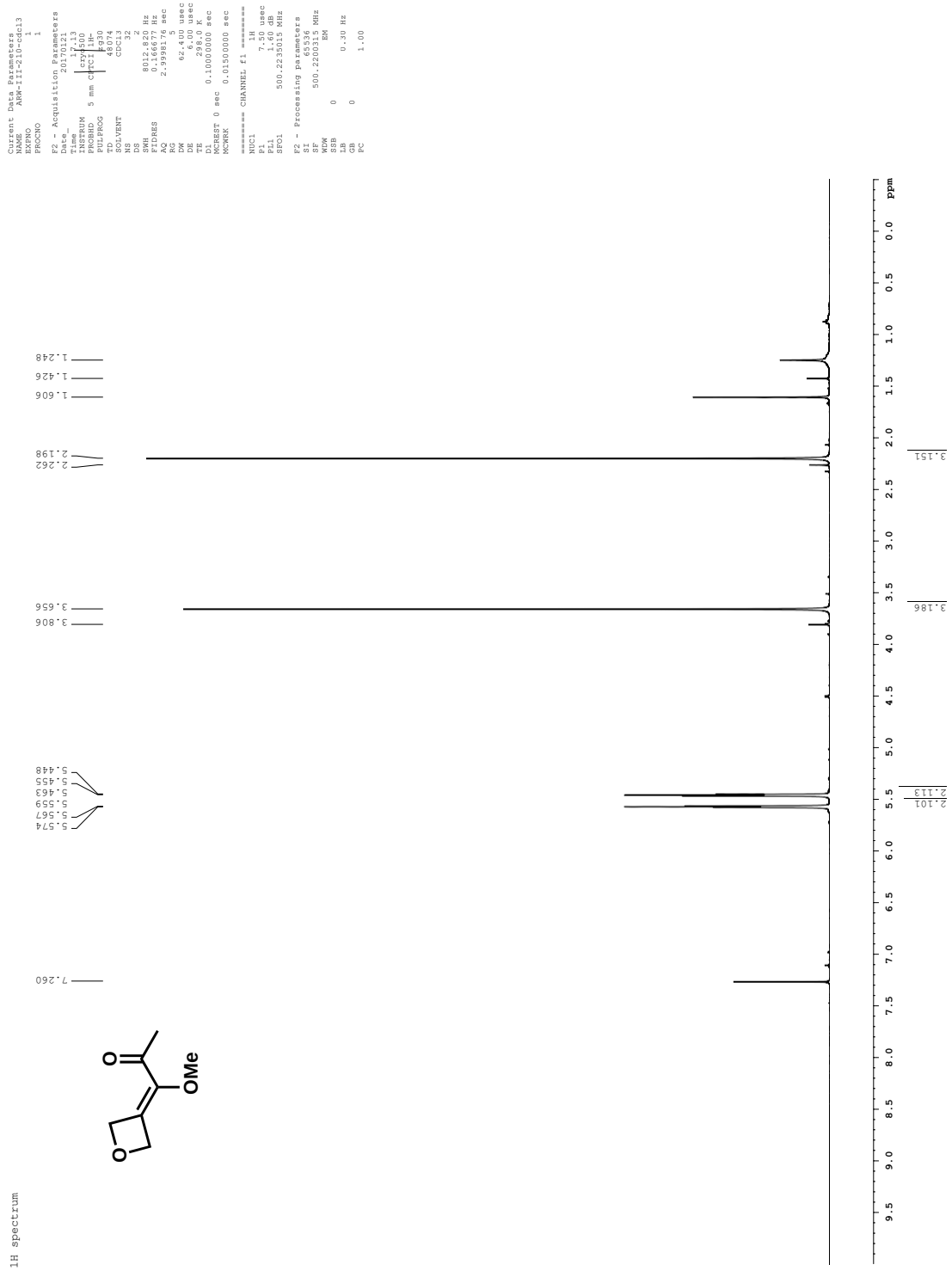
F2 - Acquisition Parameters
Date_           20170315
Time              13.35
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD                65536
SOLVENT             CDCl3
NS                   120
DS                    16
SWH             30303.031 Hz
FIDRES          0.462388 Hz
AQ              1.081344U sec
RG                7298.2
DW                16.500 usec
DE                 6.00 usec
TE                298.0 K
D1              0.25000000 sec
d11             0.03000000 sec
D16             0.00020000 sec
d17             0.00019600 sec
MCREST 0 sec
MCWRK           0.01500000 sec
P2                33.10 usec

======= CHANNEL f1 =======
NUC1                 13C
P1                 16.55 usec
P11               500.00 usec
P12              2000.00 usec
PL0                 120.00 dB
PL1                  -1.00 dB
SFO1          125.7942548 MHz
SP1                  2.70 dB
SP2                  2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

======= CHANNEL f2 =======
CPDPRG[2          waltz16
NUC2                 1H
PCPD2              100.00 usec
PL2                  1.60 dB
PL12                24.50 dB
SFO2          500.2225011 MHz

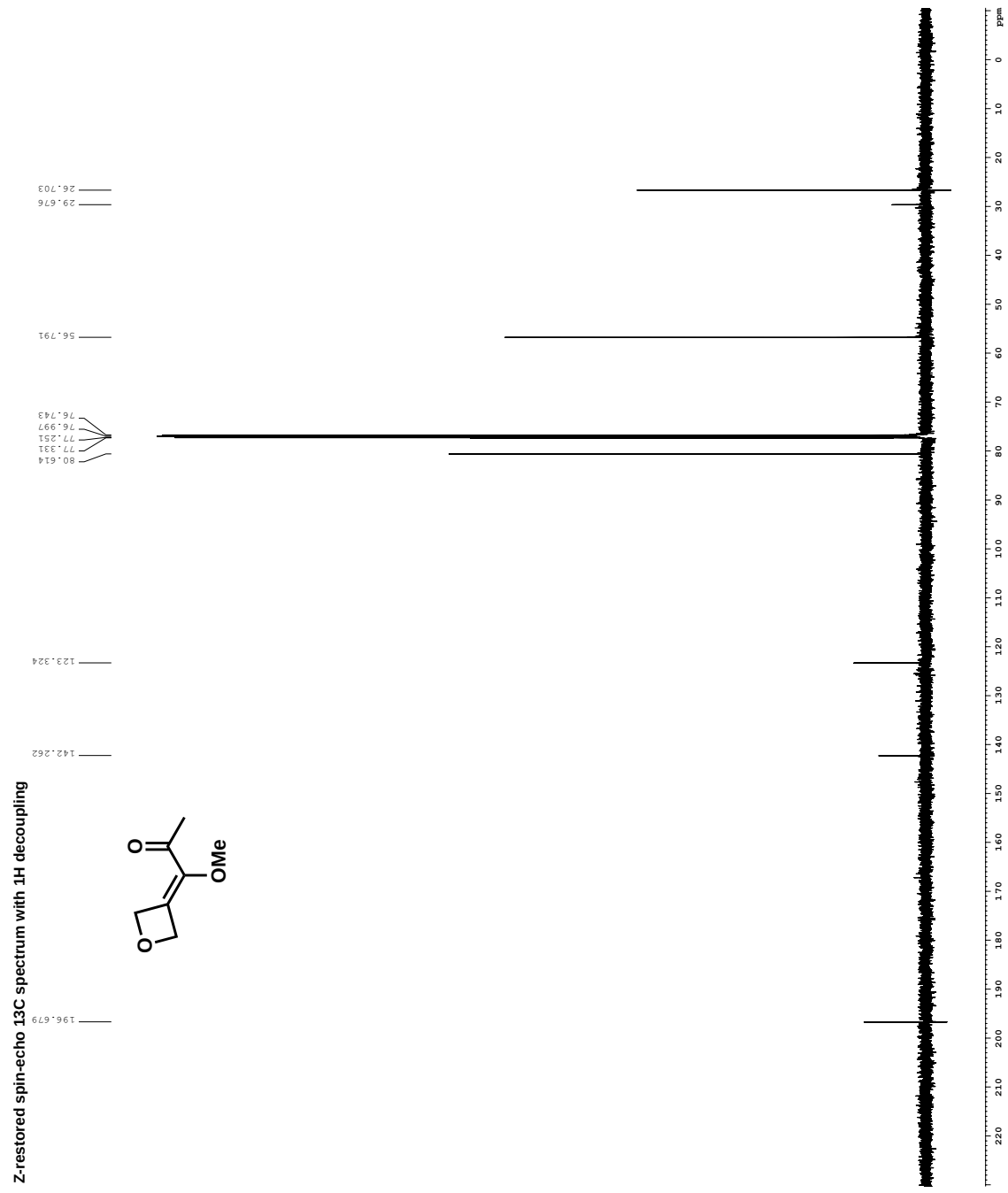
====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1                30.00 %
GPZ2                50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                  65536
SF            125.7804291 MHz
WDW                    EM
SSB       0
LB                   1.00 Hz
GB        0
PC                   2.00
```

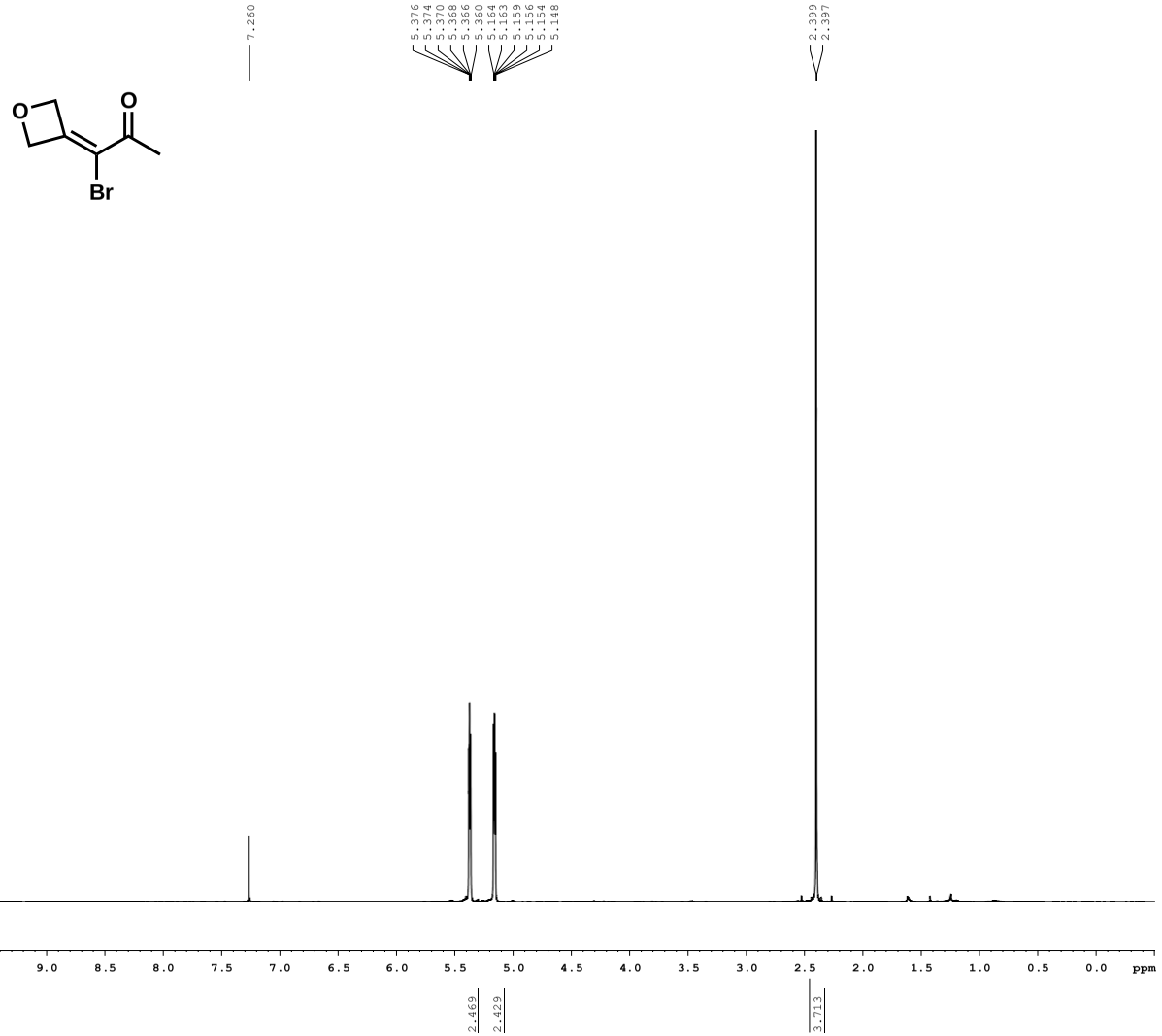

Current Data Parameters
NAME AKM-II-210-cdcl3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170121
Time 17.13
INSTRUM spect600
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 48074
SOLVENT CDCl3
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.166677 Hz
AQ 2.9998176 sec
RG 5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200315 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB
PC 1.00
1.248
1.426
1.606
2.198
2.262
3.656
3.806
5.448
5.455
5.463
5.559
5.567
5.574
7.260
3.151
3.186
2.101
2.113
O
OMe
O
ppm

1H spectrum

Z-restored spin-echo 13C spectrum with 1H decoupling



1H spectrum



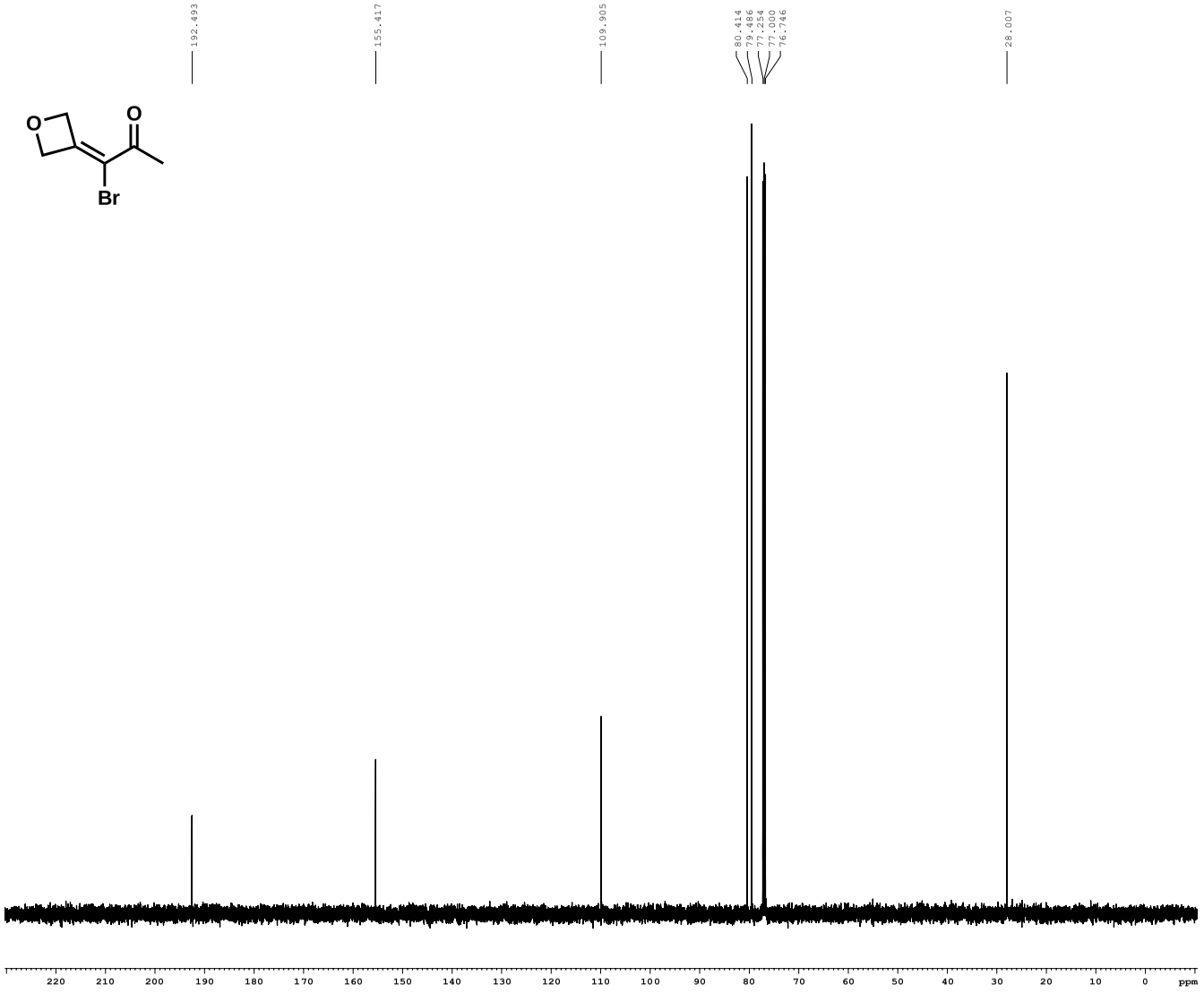

```
Current Data Parameters
NAME          ARW-III-163
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20161022
Time              18.30
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 48074
SOLVENT            CDCl3
NS                    24
DS                     2
SWH             8012.820 Hz
FIDRES             0.166677 Hz
AQ              2.9998176 sec
RG                     5
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
D1             0.10000000 sec
MCREST    0 sec
MCWRK          0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  7.50 usec
PL1                 1.60 dB
SFO1          500.2235015 MHz

F2 - Processing parameters
SI                    65536
SF            500.2200306 MHz
WDW                     EM
SSB          0
LB                  0.30 Hz
GB           0
PC                  4.00
```

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME          ARW-III-163
EXPNO                   2
PROCNO                  1

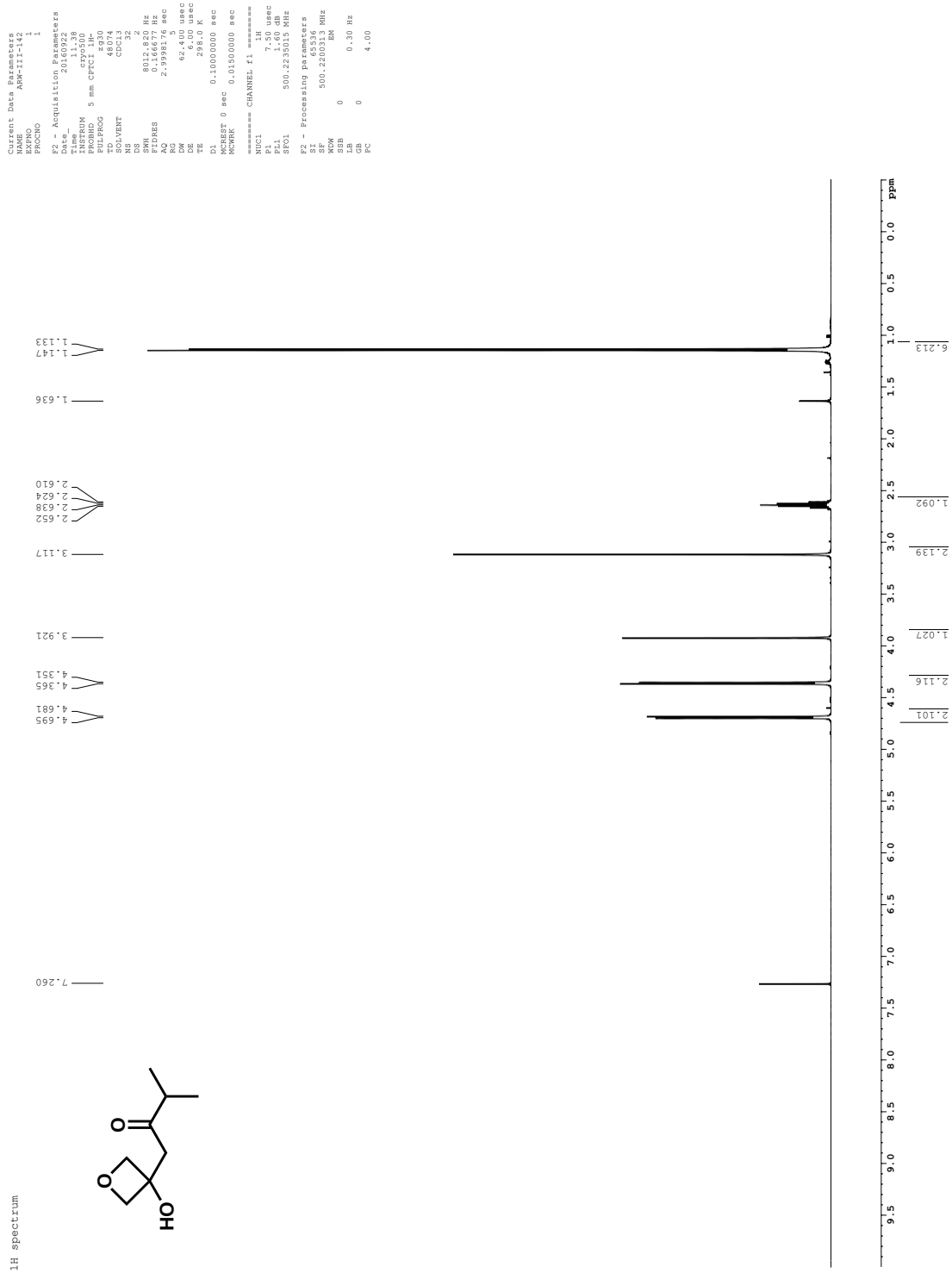
F2 - Acquisition Parameters
Date_           20161022
Time              18.33
INSTRUM           cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                65536
SOLVENT           CDCl3
NS                  128
DS                   16
SWH           30303.031 Hz
FIDRES        0.462388 Hz
AQ            1.0813440 sec
RG               5160.6
DW               16.500 usec
DE                6.00 usec
TE              298.0 K
D1            0.25000000 sec
d11           0.03000000 sec
D16           0.00020000 sec
d17           0.00019600 sec
MCREST   0 sec
MCWRK         0.01500000 sec
P2               33.10 usec

======= CHANNEL f1 ========
NUC1                1H
P1               16.55 usec
P11             500.00 usec
P12            2000.00 usec
PL0             120.00 dB
PL1              -1.00 dB
SFO1         125.7942548 MHz
SP1              2.70 dB
SP2              2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

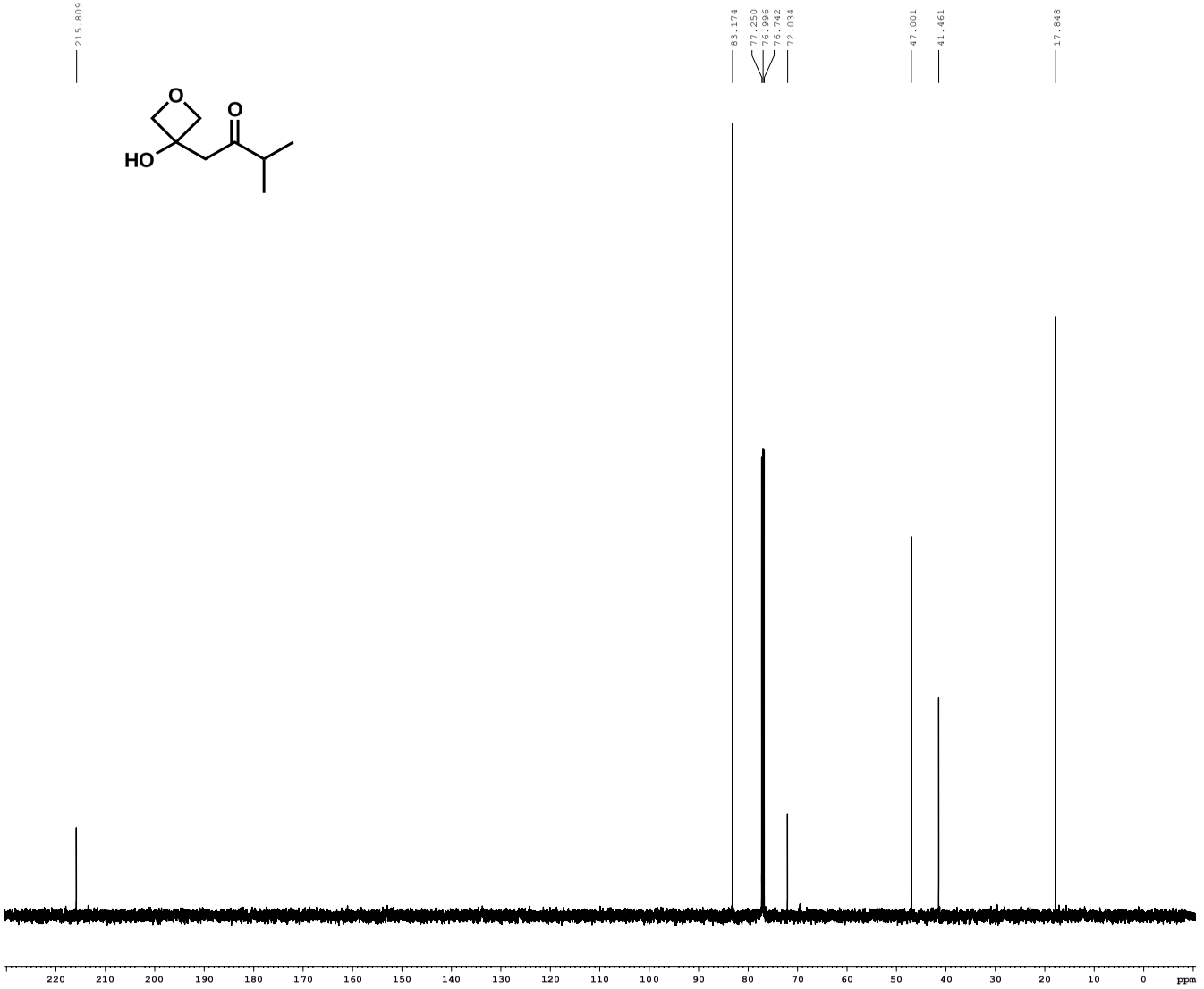
======= CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                13C
PCPD2           100.00 usec
PL2               1.60 dB
PL12             24.50 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]        SINE.100
GPNAM[2]        SINE.100
GPX1     0 %
GPX2     0 %
GPY1     0 %
GPY2     0 %
GPZ1            30.00 %
GPZ2            50.00 %
p15            500.00 usec
p16           1000.00 usec

F2 - Processing parameters
SI                65536
SF           125.7804291 MHz
WDW                  EM
SSB      0
LB                1.00 Hz
GB       0
PC                2.00
```


Current Data Parameters
NAME AWK1F142
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160922
Time 11.38
INSTRUM spect600
PROBHD 5 mm CPTCI 1H
PULPROG zg30
TD 48074
SOLVENT CDCl3
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.166677 Hz
AQ 2.9998176 sec
RG 5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200013 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
1H spectrum
7.260
4.695
4.681
4.365
4.351
3.921
3.117
2.652
2.638
2.624
2.610
1.636
1.147
1.133
6.213
2.101
2.116
1.027
2.139
1.092
ppm
O
O
HO

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME          ARW-III-142
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_           20160922
Time              11.40
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD                65536
SOLVENT             CDCl3
NS                    112
DS                     16
SWH             30303.031 Hz
FIDRES          0.462388 Hz
AQ              1.0912480 sec
RG                 7298.2
DW                16.500 usec
DE                 6.00 usec
TE                298.0 K
D1              0.25000000 sec
d11             0.03000000 sec
D16             0.00020000 sec
d17             0.00019600 sec
MCREST   0 sec
MCWRK           0.01500000 sec
P2                33.10 usec

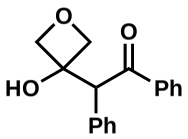
======= CHANNEL f1 =======
NUC1                  13C
P1                  16.55 usec
P11                500.00 usec
P12               2000.00 usec
PL0                120.00 dB
PL1                 -1.00 dB
SFO1          125.7942548 MHz
SP1                 2.70 dB
SP2                 2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

======= CHANNEL f2 =======
CPDPRG[2          waltz16
NUC2                  1H
PCPD2              100.00 usec
PL2                 1.60 dB
PL12               24.50 dB
SFO2          500.2225011 MHz

===== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1               30.00 %
GPZ2               50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                  65536
SF          125.7804291 MHz
WDW                    EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  2.00
```

1H spectrum



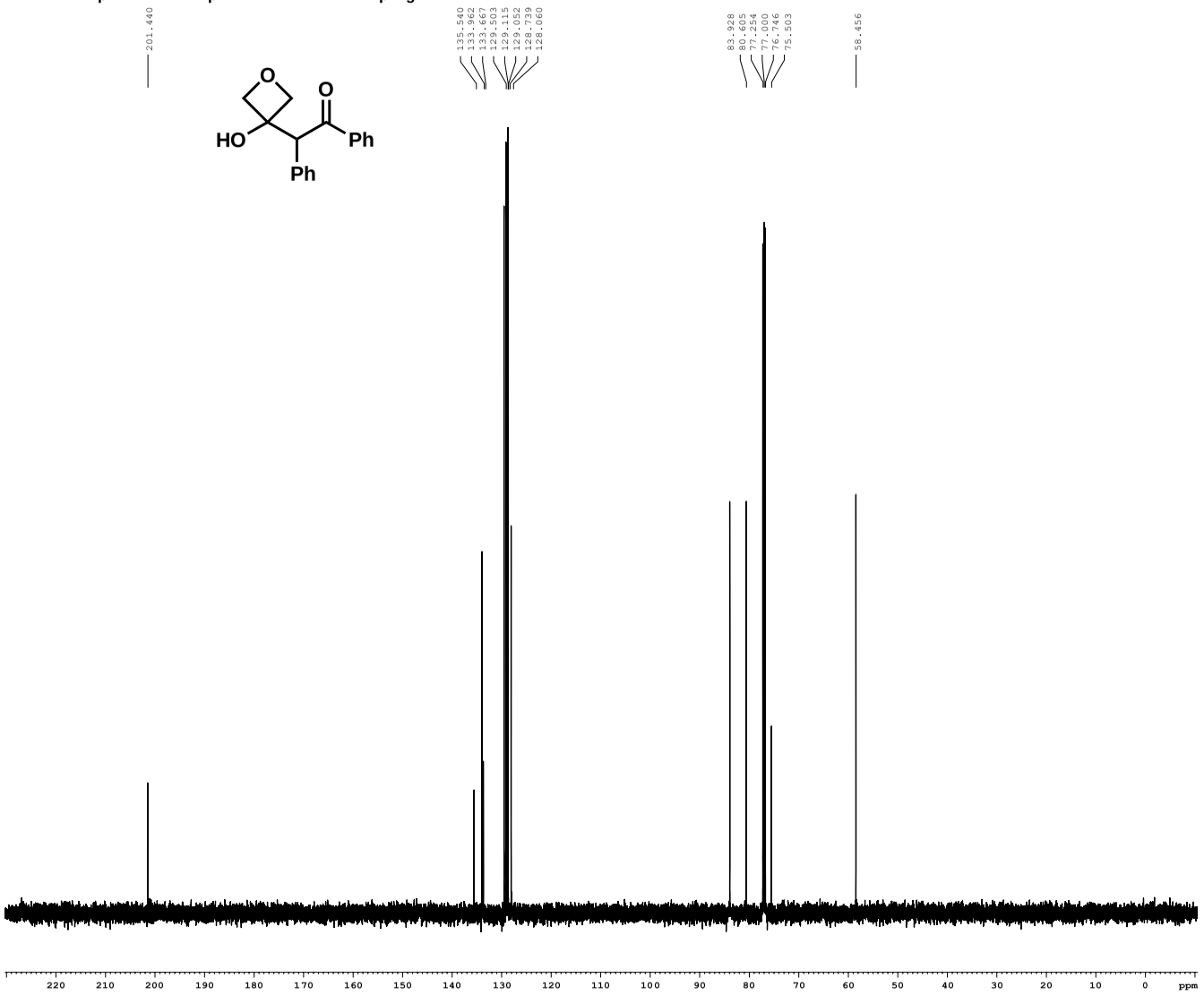

```
Current Data Parameters
NAME          ARW-III-148p3
EXPNO                     1
PROCNO                    1

F2 - Acquisition Parameters
Date_              20161004
Time                 19.04
INSTRUM              cryo500
PROBHD 5  mm  CPTCI  1H-
PULPROG                zg30
TD                    48074
SOLVENT               CDCl3
NS                       10
DS                        2
SWH                8012.820 Hz
FIDRES                0.166677 Hz
AQ                 2.9998176 sec
RG                        5.7
DW                   62.400 usec
DE                    6.00 usec
TE                   298.0 K
D1                 0.10000000 sec
MCREST 0 sec
MCWRK              0.01500000 sec

======== CHANNEL f1 ========
NUC1                      1H
P1                     7.50 usec
PL1                    1.60 dB
SFO1           500.2235015 MHz

F2 - Processing parameters
SI                        65536
SF             500.2200312 MHz
WDW                       EM
SSB          0
LB                     0.30 Hz
GB           0
PC                     4.00
```

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME        ARW-III-148p3
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_           20161004
Time              19.06
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD                65536
SOLVENT             CDCl3
NS                    112
DS                     16
SWH             30303.031 Hz
FIDRES          0.462388 Hz
AQ              1.081344U sec
RG                10321.3
DW                16.500 usec
DE                 6.00 usec
TE                298.0 K
D1          0.25000000 sec
d11         0.03000000 sec
D16         0.00020000 sec
d17         0.00019600 sec
MCREST 0 sec
MCWRK       0.01500000 sec
P2                33.10 usec

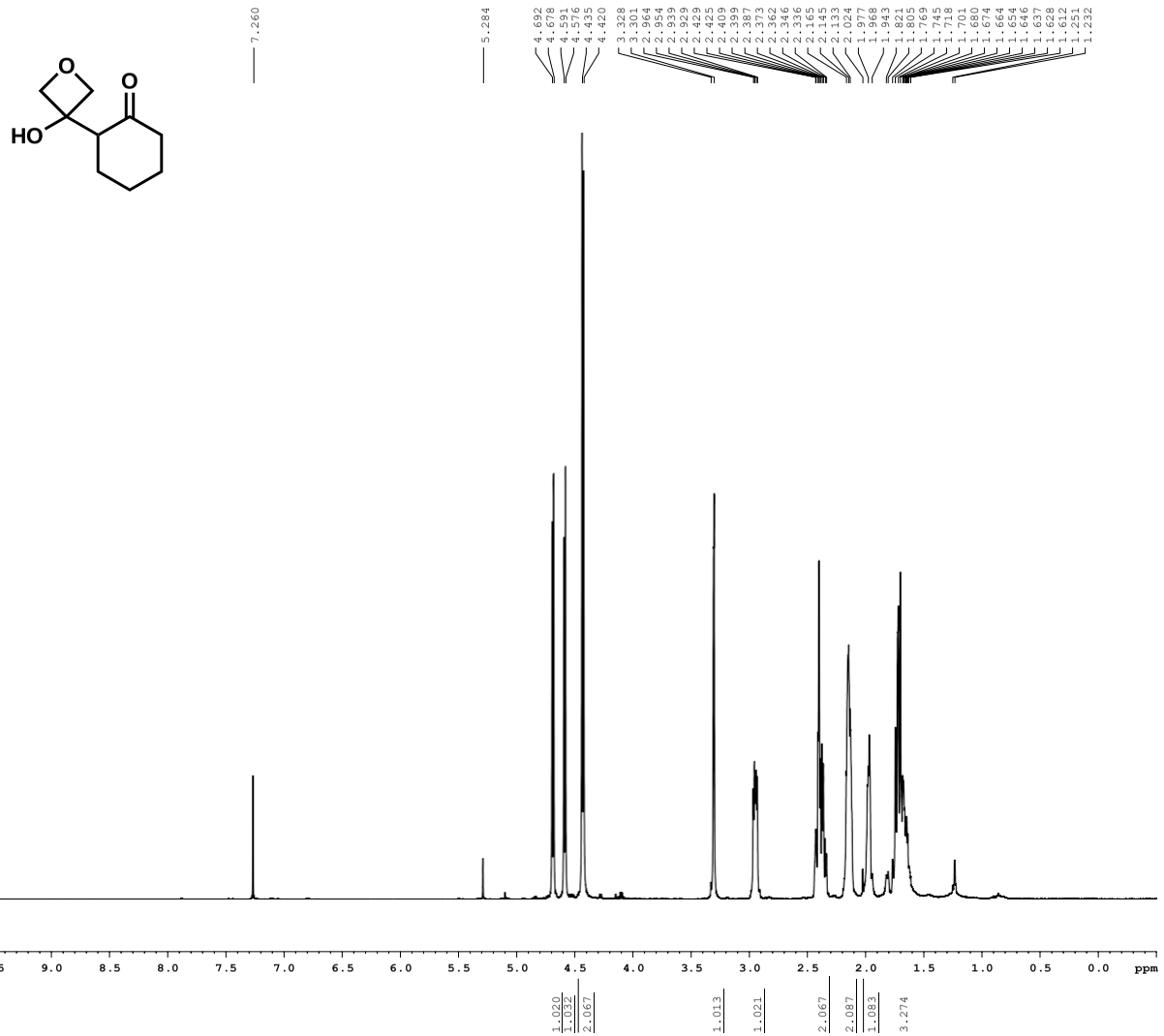
======= CHANNEL f1 =======
NUC1                  13C
P1                 16.55 usec
P11               500.00 usec
P12              2000.00 usec
PL0                120.00 dB
PL1                 -1.00 dB
SFO1         125.7942698 MHz
SP1                 2.70 dB
SP2                 2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

======= CHANNEL f2 =======
CPDPRG[2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                 1.60 dB
PL12               24.50 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPX1     0 %
GPX2     0 %
GPY1     0 %
GPY2     0 %
GPZ1                30.00 %
GPZ2                50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                  65536
SF          125.7804291 MHz
WDW                    EM
SSB      0
LB                  1.00 Hz
GB       0
PC                  2.00
```

1H spectrum



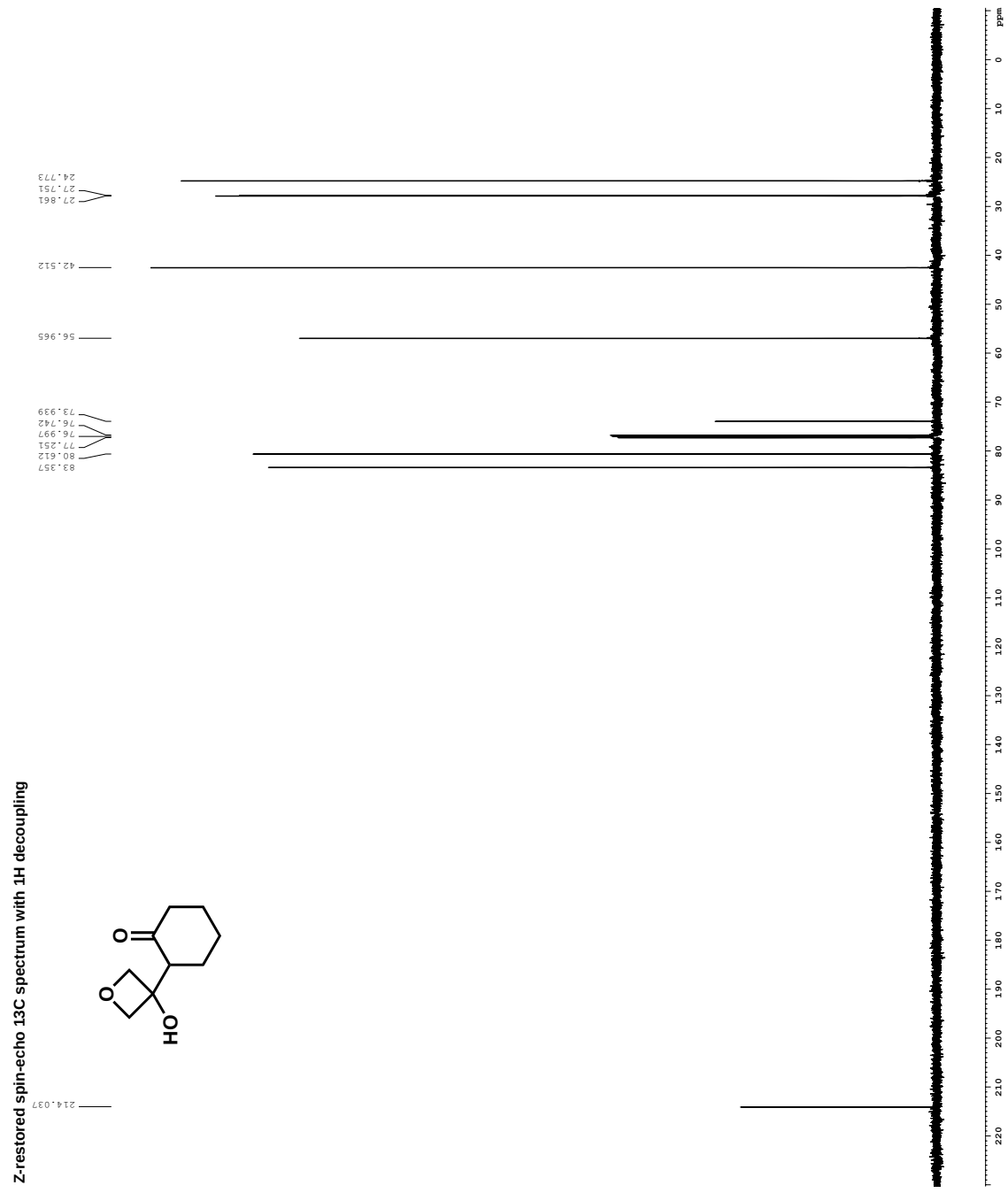

```
Current Data Parameters
NAME          ARW-III-221
EXPNO                   1
PROCNO                  1

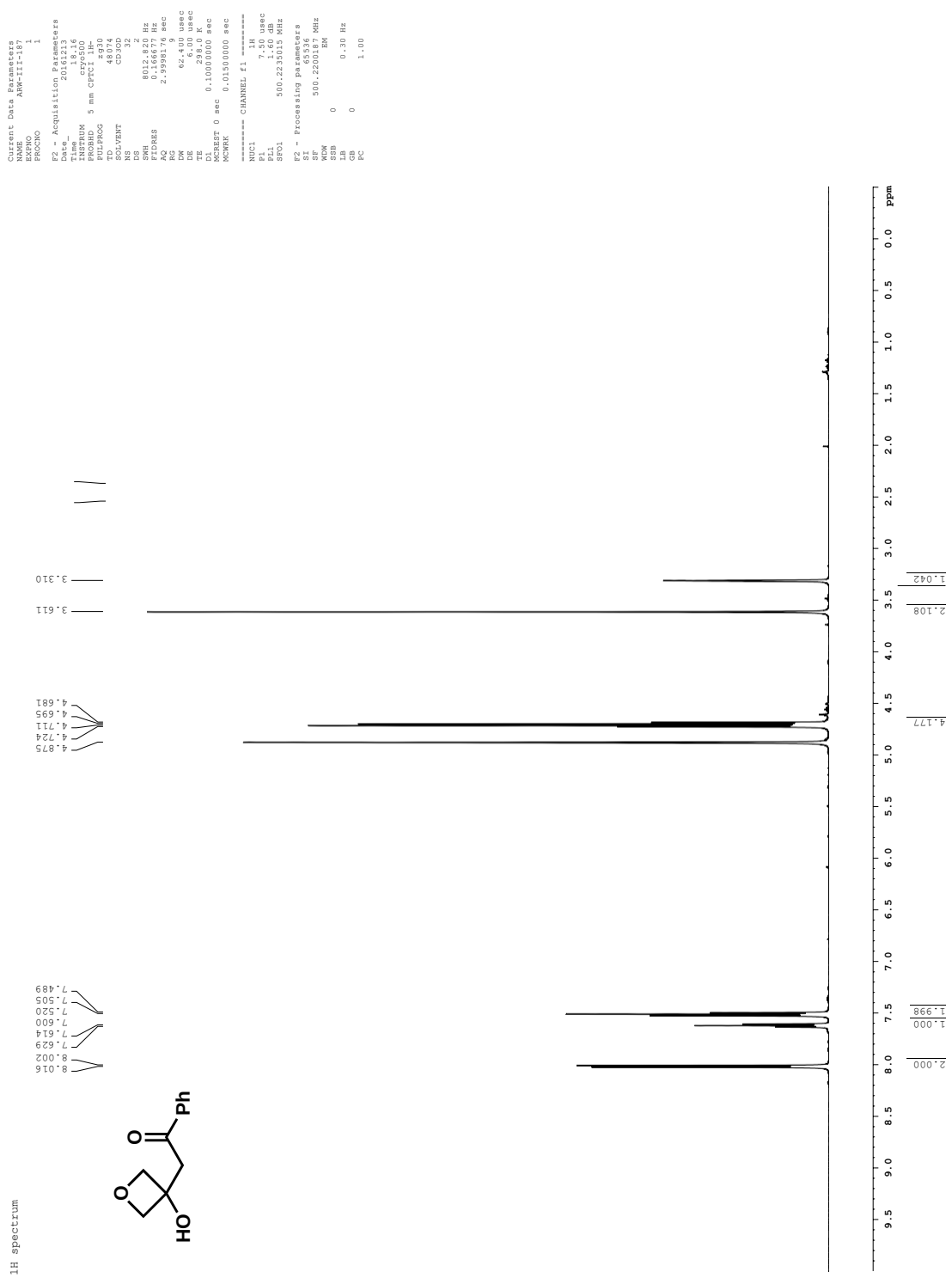
F2 - Acquisition Parameters
Date_              20170209
Time                  12.15
INSTRUM             cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG                zg30
TD                    48074
SOLVENT               CDCl3
NS                       24
DS                        2
SWH                8012.820 Hz
FIDRES            0.166677 Hz
AQ                2.9998176 sec
RG                      4.5
DW                   62.400 usec
DE                    6.00 usec
TE                   298.0 K
D1                0.10000000 sec
MCREST 0 sec
MCWRK             0.01500000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    7.50 usec
PL1                   1.60 dB
SFO1          500.2235015 MHz

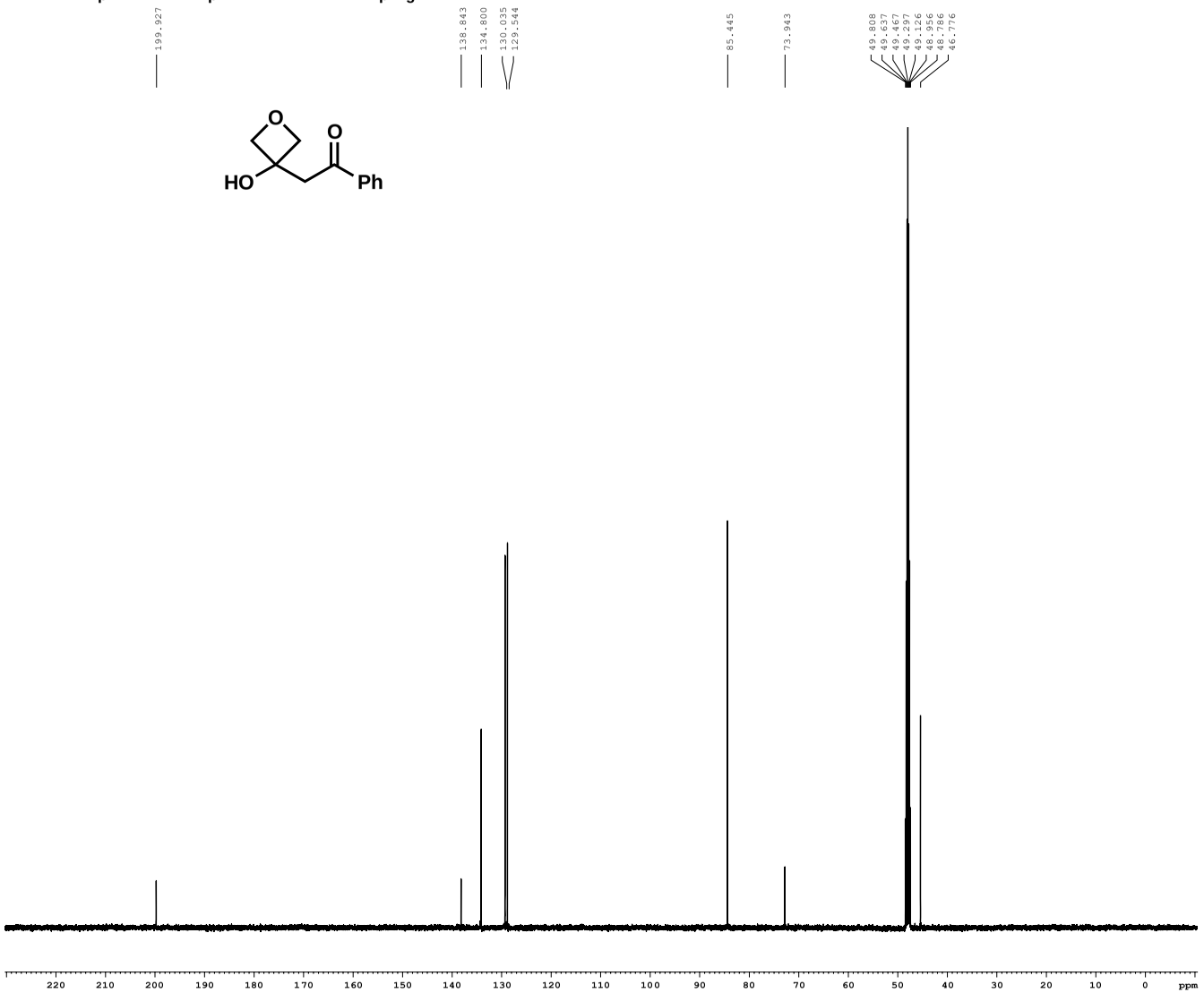
F2 - Processing parameters
SI                     65536
SF            500.2200313 MHz
WDW                       EM
SSB          0
LB                    0.30 Hz
GB           0
PC                    1.00
```

Z-restored spin-echo 13C spectrum with 1H decoupling




Current Data Parameters
NAME AWK-II-187
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161213
Time 18.16
INSTRUM spect600
PROBHD 5 mm CPTCI 1H
PULPROG zg30
TD 48074
SOLVENT CDCl3
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.166677 Hz
AQ 2.9998176 sec
RG 9
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200187 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB
PC 1.00
1H spectrum
8.016
8.002
7.629
7.614
7.600
7.520
7.505
7.489
4.875
4.724
4.711
4.695
4.681
3.611
3.310
2.000
1.000
1.998
4.177
2.108
1.042
O
Ph
O
HO
ppm

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME          ARW-III-187
EXPNO                   2
PROCNO                  1

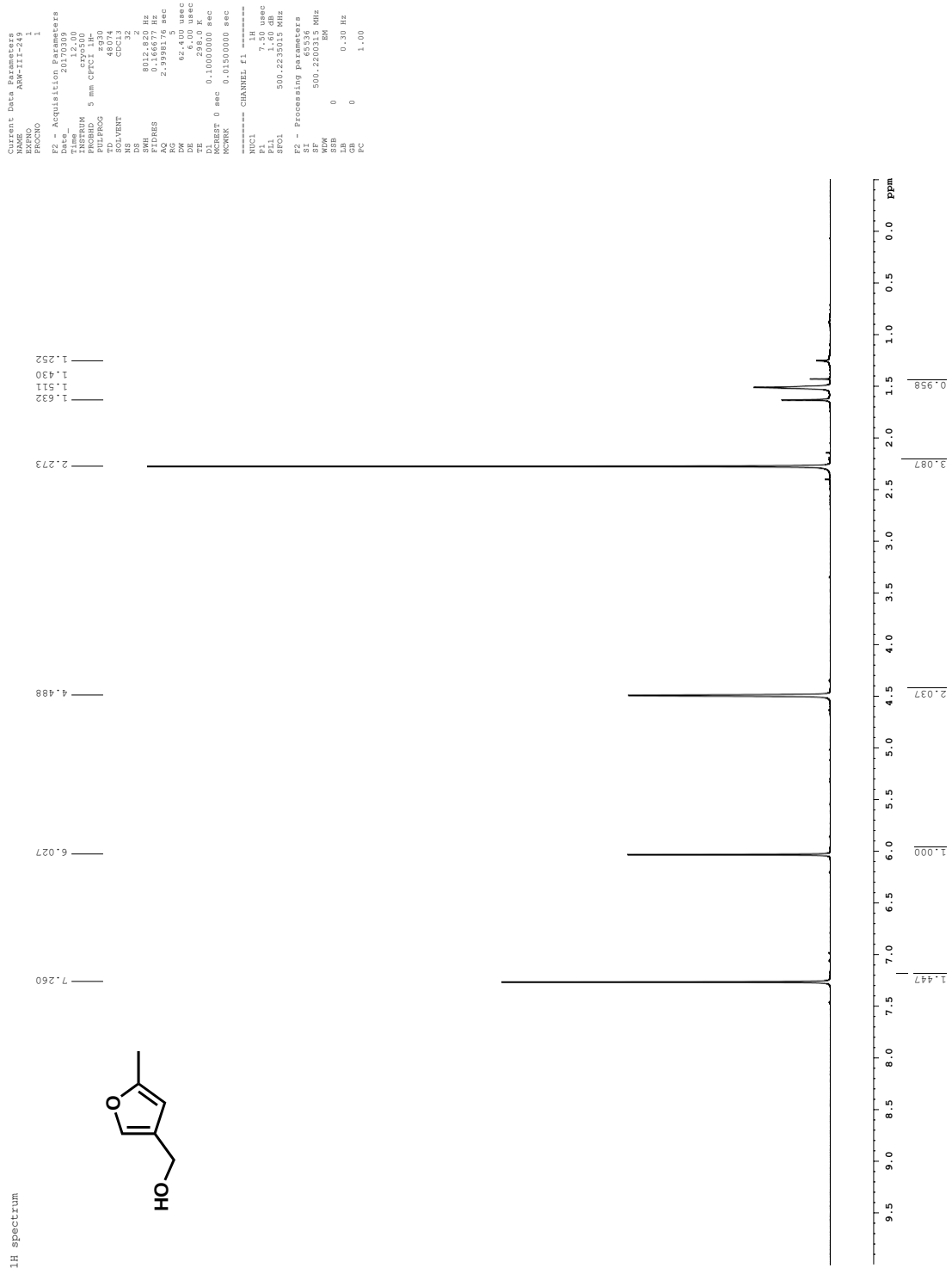
F2 - Acquisition Parameters
Date_           20161213
Time              18.19
INSTRUM           cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD                65536
SOLVENT             CDCl3
NS                    176
DS                     16
SWH           30303.031 Hz
FIDRES        0.462388 Hz
AQ            1.081248U sec
RG                 4597.6
DW                16.500 usec
DE                 6.00 usec
TE                298.0 K
D1            0.25000000 sec
d11           0.03000000 sec
D16           0.00020000 sec
d17           0.00019600 sec
MCREST   0 sec
MCWRK         0.01500000 sec
P2                33.10 usec

======= CHANNEL f1 =======
NUC1                  13C
P1                  16.55 usec
P11                500.00 usec
P12               2000.00 usec
PL0                 120.00 dB
PL1                  -1.00 dB
SFO1         125.7942548 MHz
SP1                  2.70 dB
SP2                  2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

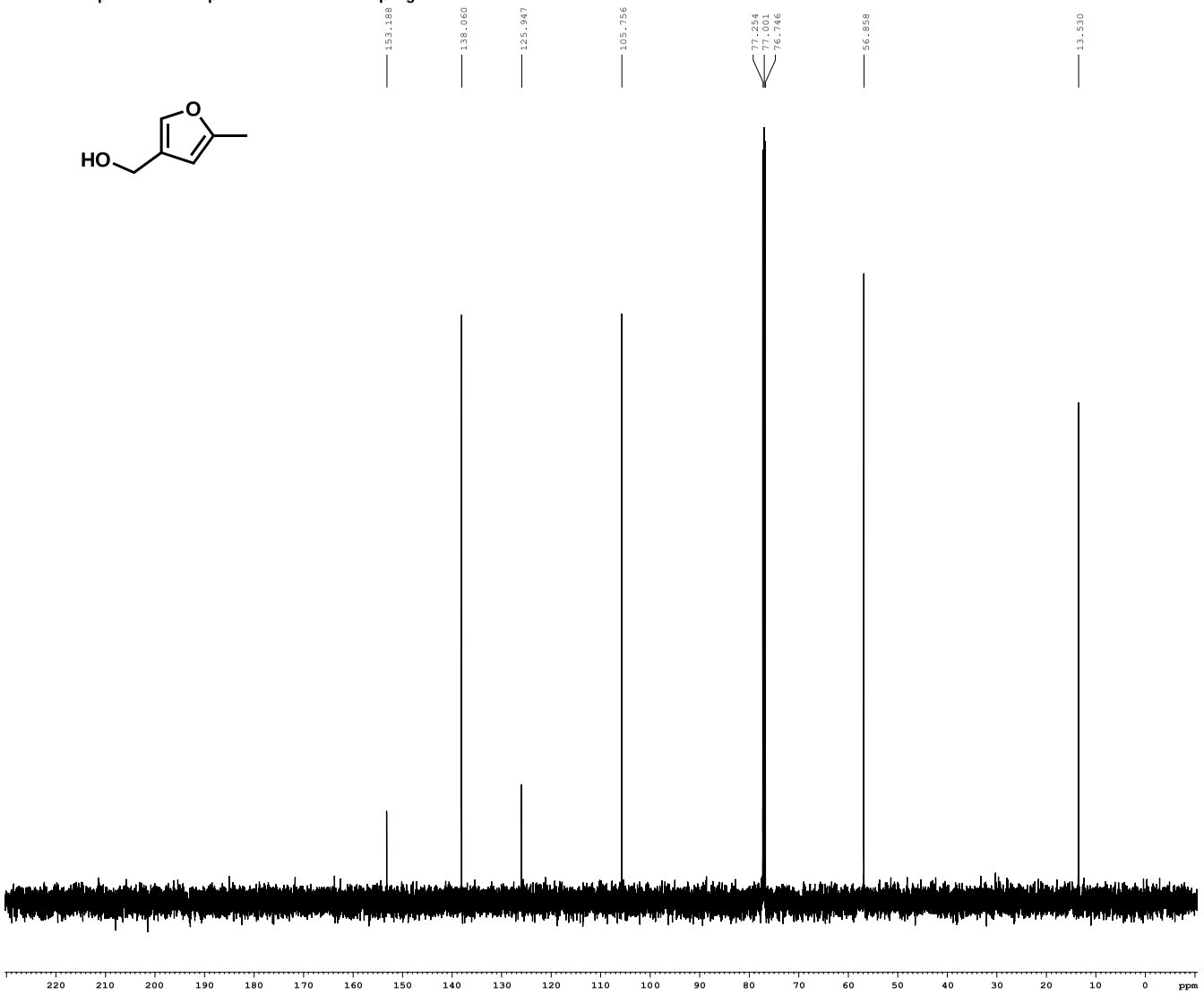
======= CHANNEL f2 =======
CPDPRG[2          waltz16
NUC2                  1H
PCPD2              100.00 usec
PL2                  1.60 dB
PL12                24.50 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1                30.00 %
GPZ2                50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                  65536
SF           125.7802086 MHz
WDW                    EM
SSB       0
LB                   1.00 Hz
GB        0
PC                   2.00
```


Current Data Parameters
NAME AKM-IF-249
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170309
Time 12.00
INSTRUM spect600
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 48074
SOLVENT CDCl3
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.166677 Hz
AQ 2.9998176 sec
RG 5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200315 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB
PC 1.00
1H spectrum
7.260
6.027
4.488
2.273
1.632
1.511
1.430
1.252
1.447
1.000
2.037
3.087
0.958
ppm
HO

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME          ARW-III-249
EXPNO                   2
PROCNO                  1

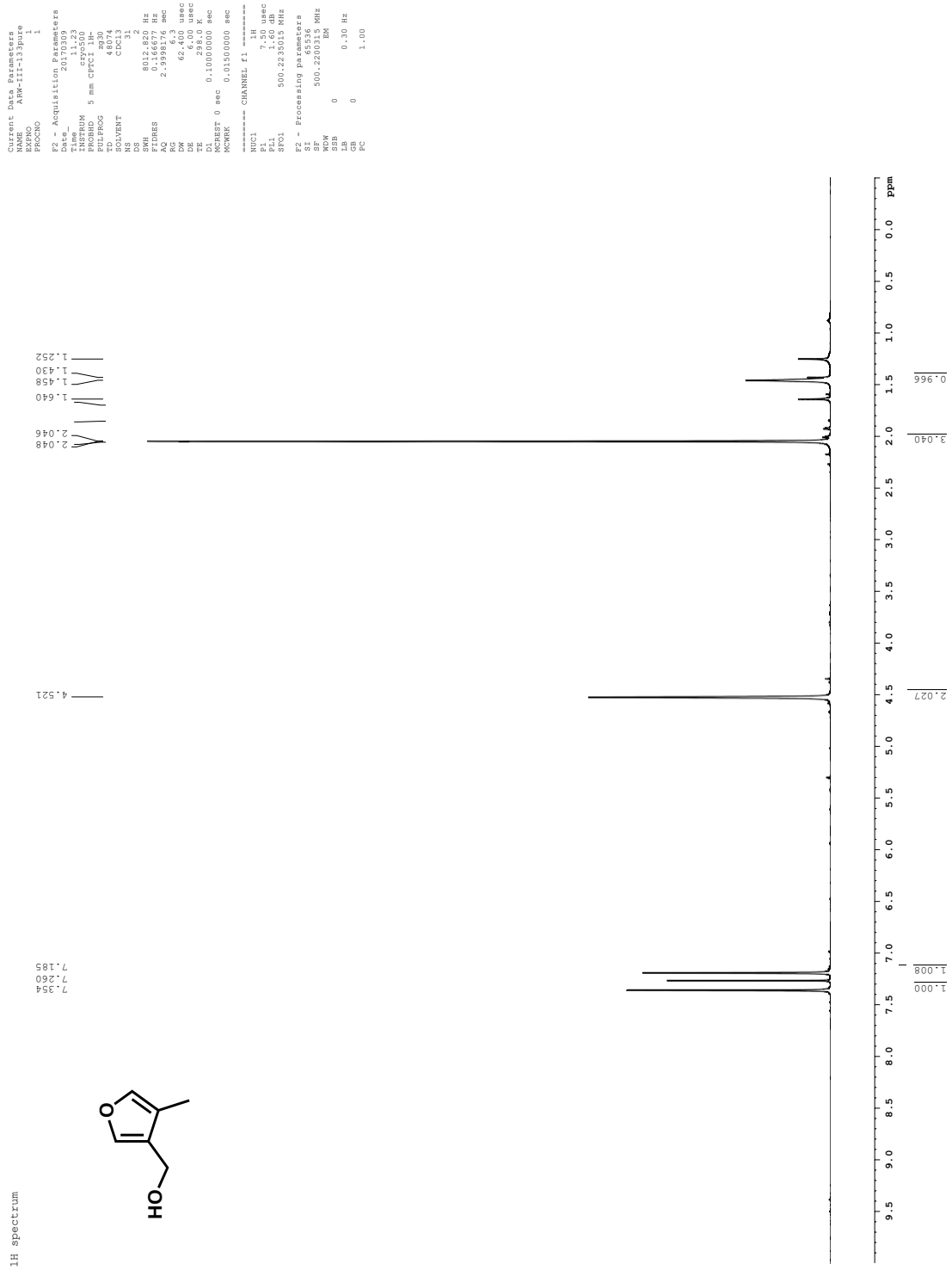
F2 - Acquisition Parameters
Date_           20170309
Time              12.04
INSTRUM           cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                65536
SOLVENT             CDCl3
NS                     96
DS                     16
SWH           30303.031 Hz
FIDRES        0.462388 Hz
AQ            1.0813440 sec
RG                7298.2
DW               16.500 usec
DE                6.00 usec
TE                298.0 K
D1            0.25000000 sec
d11           0.03000000 sec
D16           0.00020000 sec
d17           0.00019600 sec
MCREST   0 sec
MCWRK         0.01500000 sec
P2               33.10 usec

======= CHANNEL f1 ========
NUC1                  1C
P1                16.55 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1         125.7942548 MHz
SP1                2.70 dB
SP2                2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

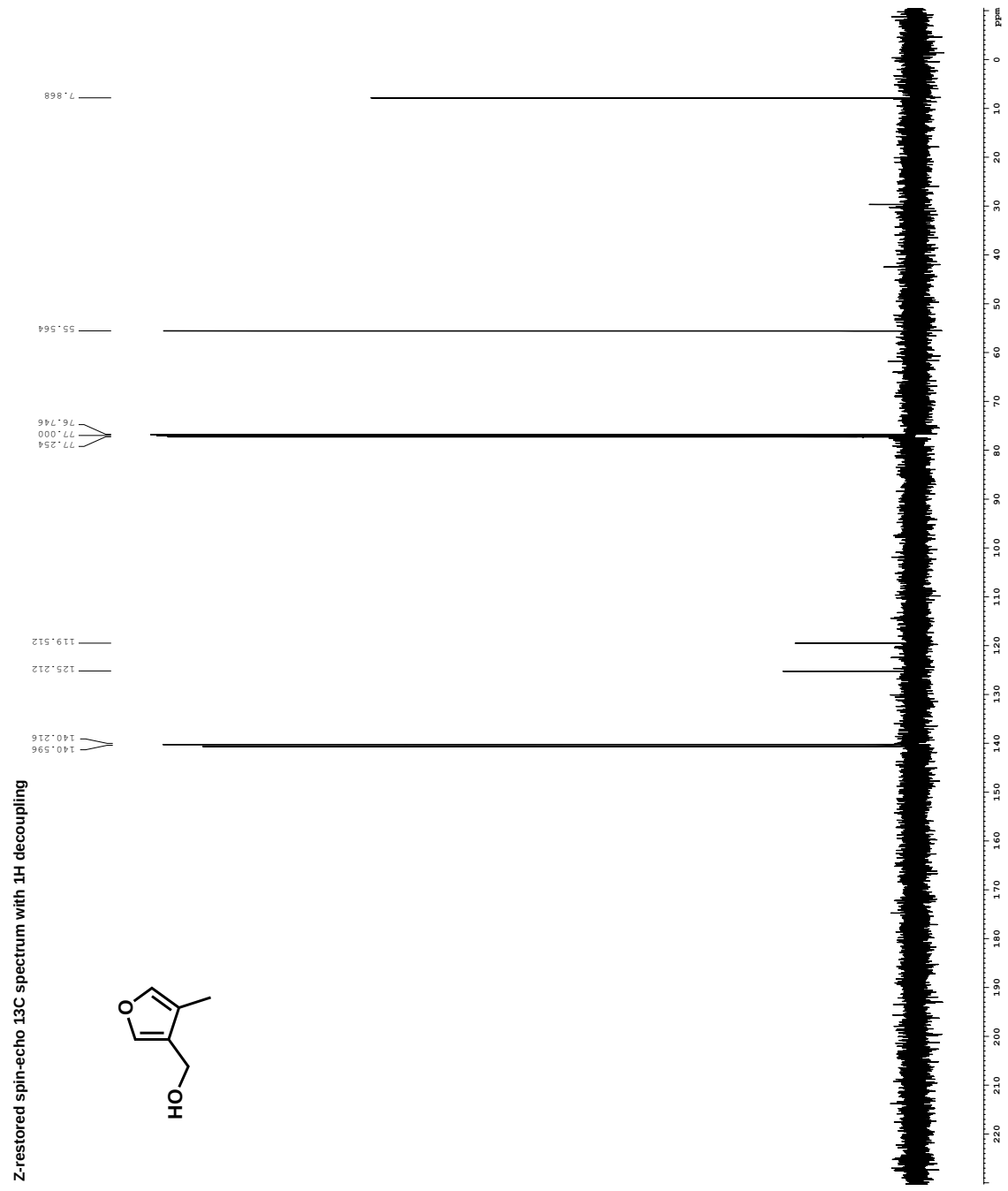
======= CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                  1H
PCPD2            100.00 usec
PL2               1.60 dB
PL12             24.50 dB
SFO2         500.2225011 MHz

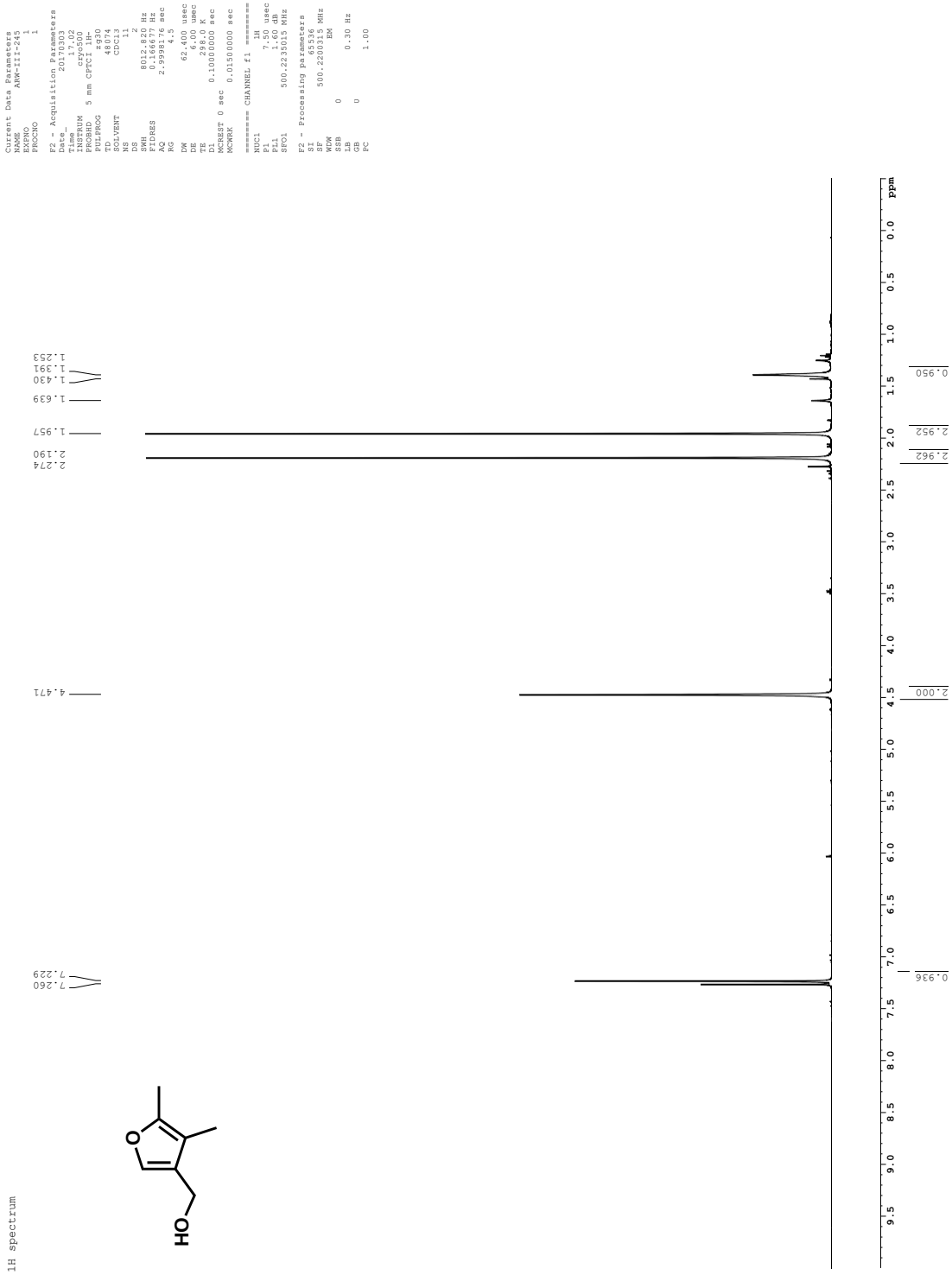
====== GRADIENT CHANNEL =====
GPNAM[1]        SINE.100
GPNAM[2]        SINE.100
GPX1     0 %
GPX2     0 %
GPY1     0 %
GPY2     0 %
GPZ1              30.00 %
GPZ2              50.00 %
p15              500.00 usec
p16             1000.00 usec

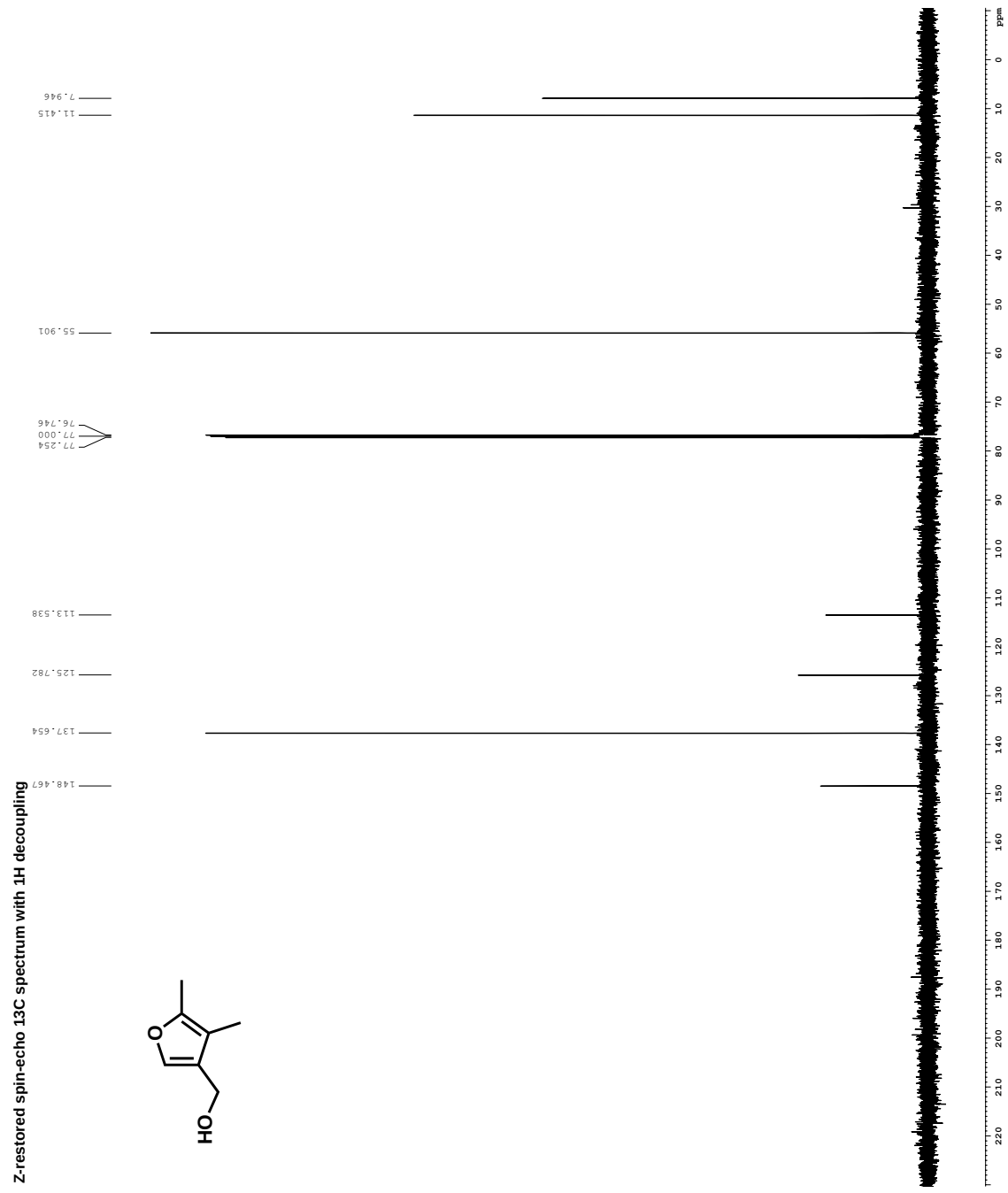
F2 - Processing parameters
SI                 65536
SF           125.7804291 MHz
WDW                   EM
SSB      0
LB                 1.00 Hz
GB       0
PC                 2.00
```


Current Data Parameters
NAME AKW-III-43pure
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170309
Time 11:23
INSTRUM spect600
PROBHD 5 mm CPTCI 1H
PULPROG zg30
TD 40074
SOLVENT CDCl3
NS 2
DS 2
SWH 8012.820 Hz
FIDRES 0.199677 Hz
AQ 2.9998176 sec
RG 6.3
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.00 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200315 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.354
7.260
7.185
4.521
2.048
2.046
1.640
1.458
1.430
1.252
1.000
1.008
2.027
3.040
0.966
ppm
HO
1H spectrum

Z-restored spin-echo 13C spectrum with 1H decoupling

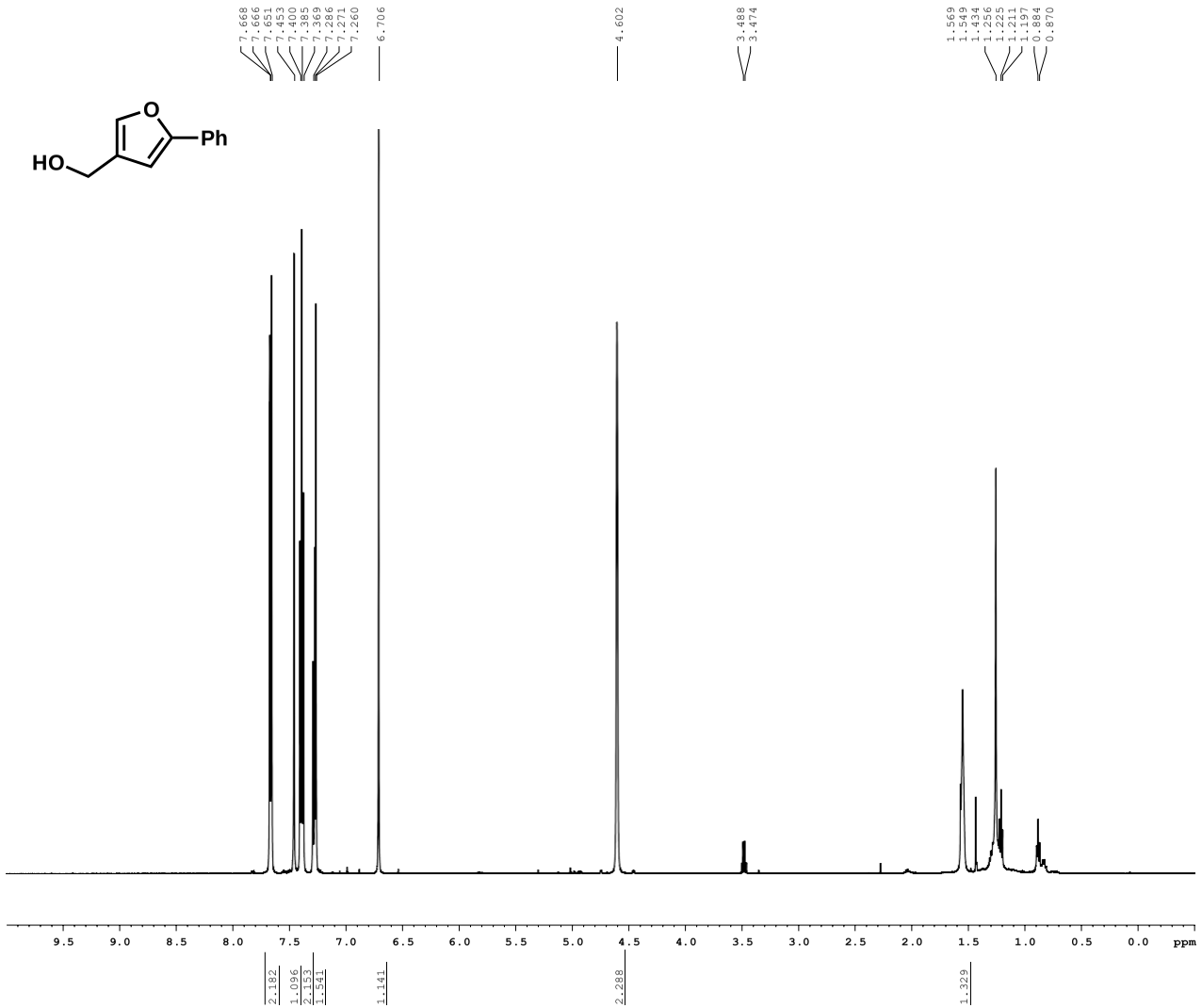



Current Data Parameters
NAME AWK1F245
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170303
Time 17.02
INSTRUM spect600
PROBHD 5 mm CPTCI 1H
PULPROG zg30
TD 48074
SOLVENT CDCl3
NS 2
DS 2
SWH 8012.820 Hz
FIDRES 0.166677 Hz
AQ 2.9998176 sec
RG 4.5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200015 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
7.260
7.229
4.471
2.274
2.190
1.957
1.639
1.430
1.391
1.253
0.950
2.952
2.962
2.000
0.936
ppm
1H spectrum
HO



Z-restored spin-echo 13C spectrum with 1H decoupling

1H spectrum



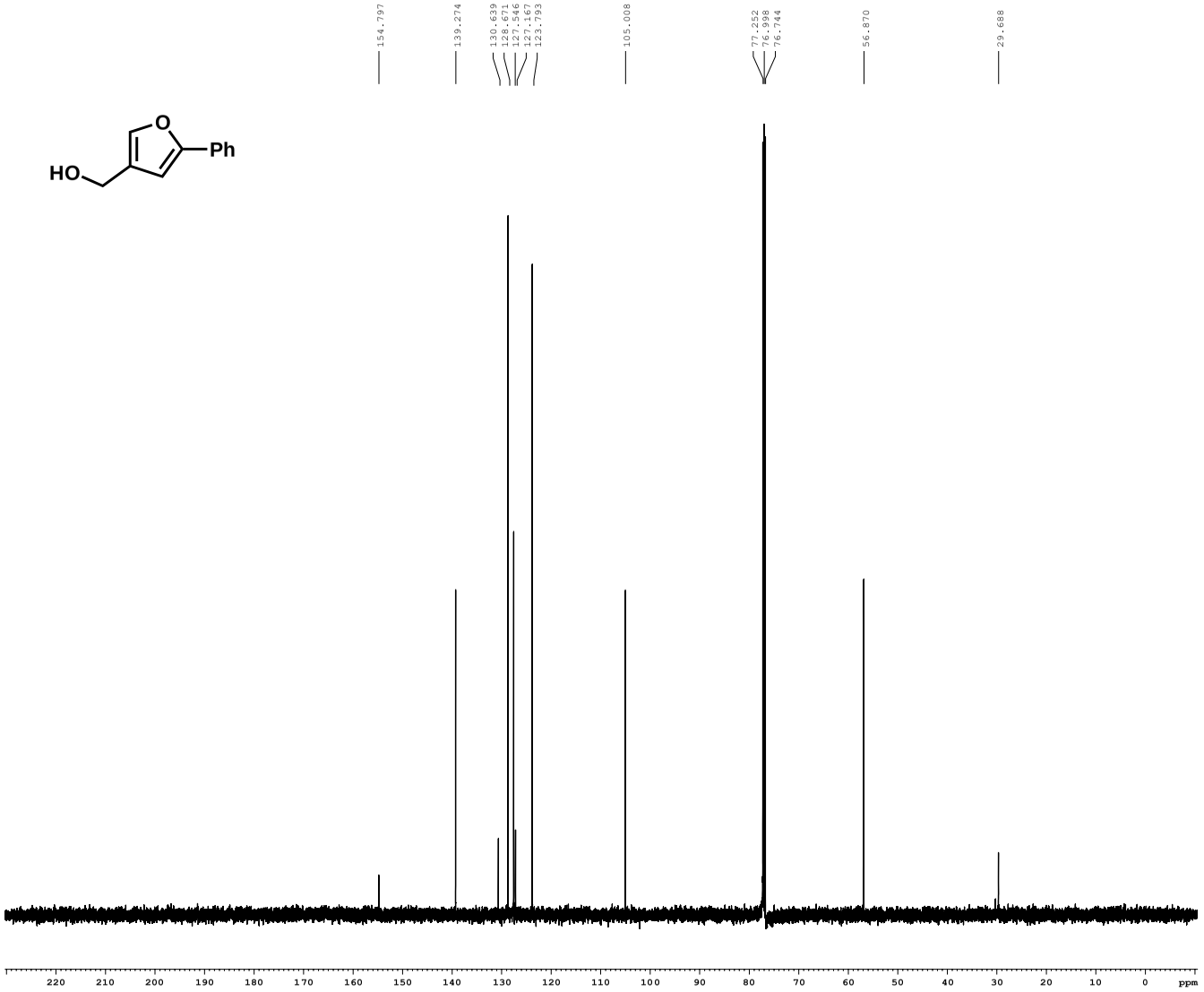

```
Current Data Parameters
NAME          ARW-III-160
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20161020
Time              21.31
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG             zg30
TD                 48074
SOLVENT           CDCl3
NS                    32
DS                     2
SWH            8012.820 Hz
FIDRES        0.166677 Hz
AQ            2.9998176 sec
RG                     5
DW               62.400 usec
DE                6.00 usec
TE                298.0 K
D1           0.10000000 sec
MCREST 0 sec
MCWRK        0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                 7.50 usec
PL1                1.60 dB
SFO1         500.2235015 MHz

F2 - Processing parameters
SI                 65536
SF           500.2200306 MHz
WDW                   EM
SSB       0
LB                 0.30 Hz
GB        0
PC                 4.00
```

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME          ARW-III-160
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_           20161020
Time              21.33
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD                65536
SOLVENT             CDCl3
NS                    344
DS                     16
SWH             30303.031 Hz
FIDRES          0.462388 Hz
AQ              1.081344U sec
RG                 7298.2
DW                 16.500 usec
DE                  6.00 usec
TE                298.0 K
D1              0.25000000 sec
d11             0.03000000 sec
D16             0.00020000 sec
d17             0.00019600 sec
MCREST   0 sec
MCWRK           0.01500000 sec
P2                 33.10 usec

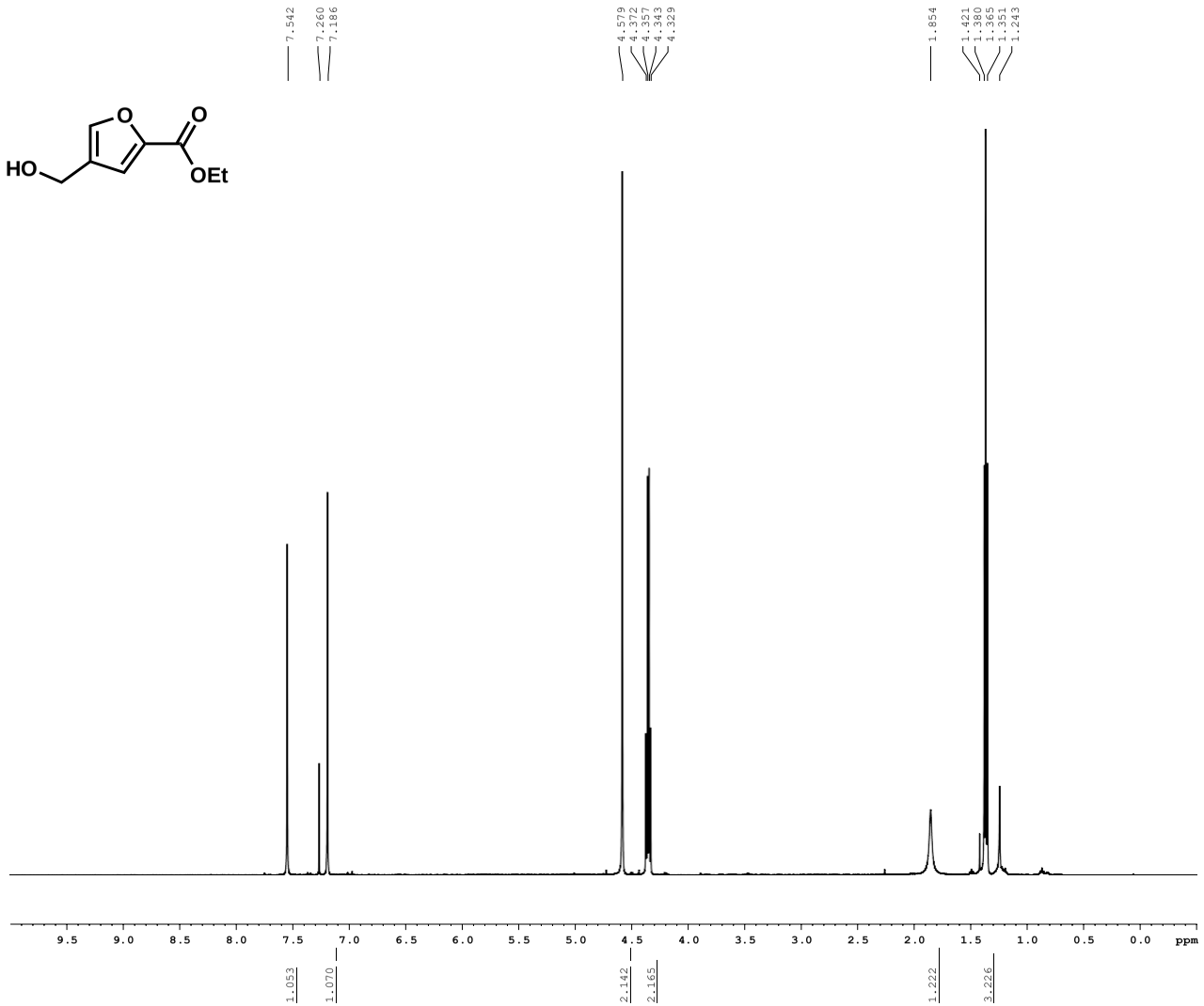
======= CHANNEL f1 =======
NUC1                  13C
P1                  16.55 usec
P11                500.00 usec
P12               2000.00 usec
PL0                120.00 dB
PL1                 -1.00 dB
SFO1          125.7942648 MHz
SP1                 2.70 dB
SP2                 2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

======= CHANNEL f2 =======
CPDPRG[2          waltz16
NUC2                  1H
PCPD2              100.00 usec
PL2                 1.60 dB
PL12               24.50 dB
SFO2          500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1               30.00 %
GPZ2               50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                 65536
SF          125.7804282 MHz
WDW                   EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  2.00
```

1H spectrum

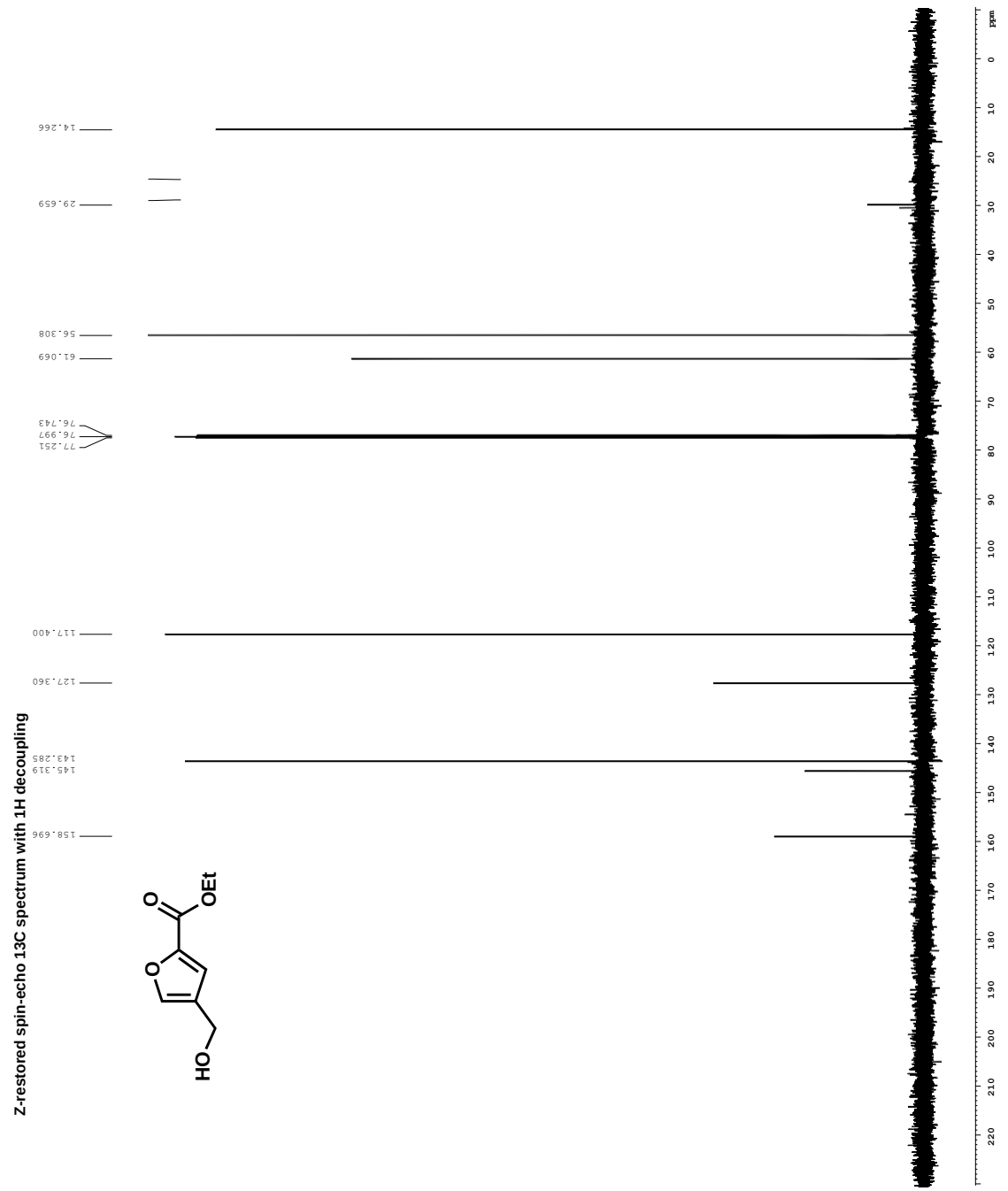


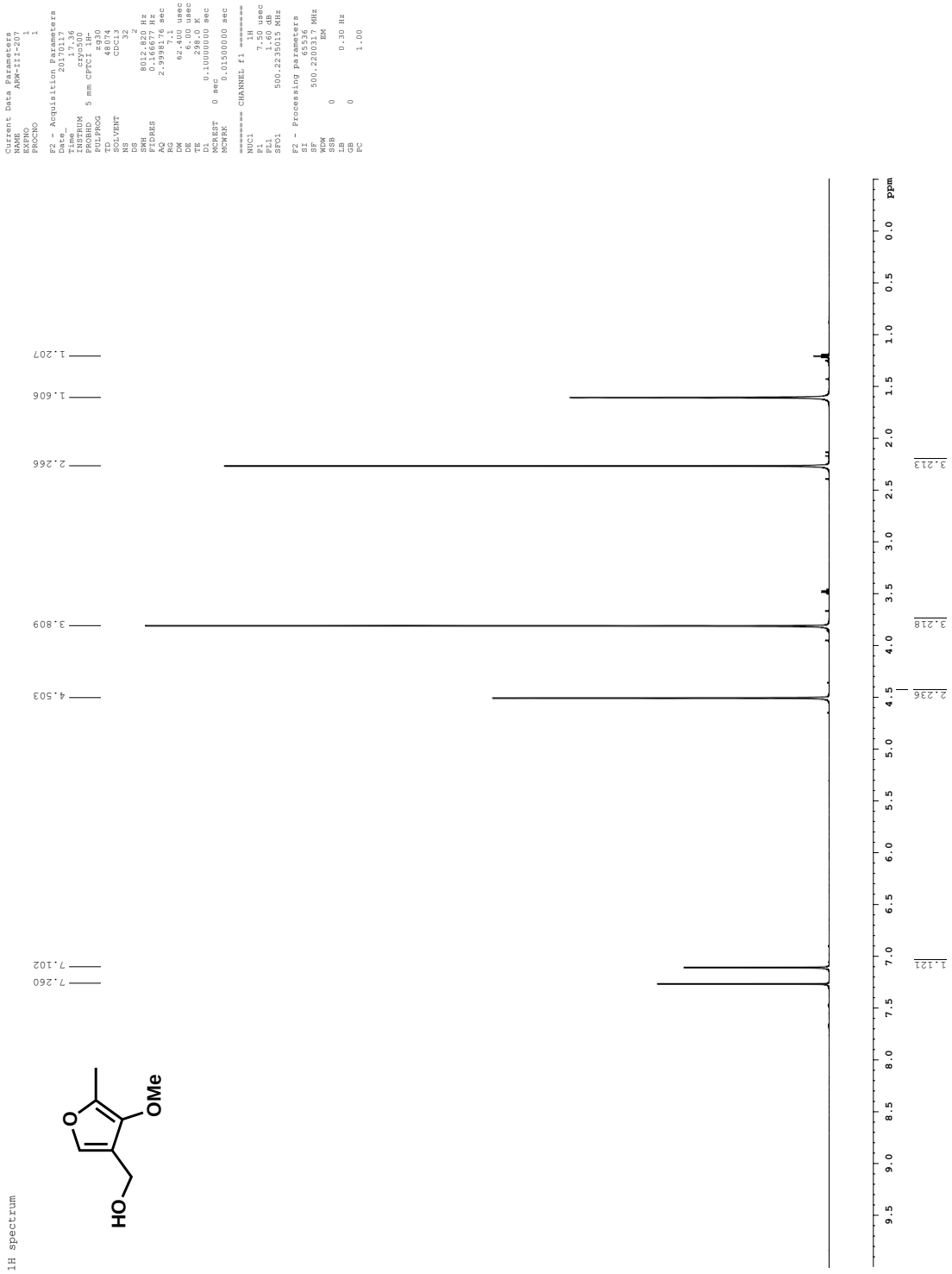

```
Current Data Parameters
NAME          ARW-III-135
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_            20160907
Time                11.52
INSTRUM           cryo500
PROBHD 5  mm  CPTCI  1H-
PULPROG              zg30
TD                  81728
SOLVENT             CDCl3
NS                      8
DS                      2
SWH              8012.820  Hz
FIDRES           0.098043  Hz
AQ               5.0998273  sec
RG                    4.5
DW                 62.400  usec
DE                  6.00  usec
TE                298.0  K
D1             0.10000000  sec
MCREST 0 sec
MCWRK          0.01500000  sec

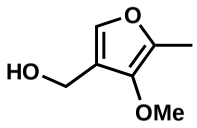
======== CHANNEL f1 ========
NUC1                   1H
P1                  7.50  usec
PL1                 1.60  dB
SFO1          500.2235015  MHz

F2 - Processing parameters
SI                  65536
SF            500.2200311  MHz
WDW                    EM
SSB       0
LB                  0.30  Hz
GB        0
PC                  4.00
```


Z-restored spin-echo 13C spectrum with 1H decoupling
158.696
145.319
143.285
127.360
117.400
77.251
76.997
76.743
61.069
56.308
29.659
14.266
OEt
O
O
HO
ppm


Current Data Parameters
NAME AWK1F207
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170117
Time 17.36
INSTRUM spect600
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 48074
SOLVENT CDCl3
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.166677 Hz
AQ 2.9998176 sec
RG 7.1
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200317 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB
PC 1.00
1H spectrum
HO
OMe
7.260
7.102
4.503
3.809
2.266
1.606
1.207
1.121
2.236
3.218
3.213
ppm

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME          ARW-III-207
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_           20170117
Time              17.39
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD                65536
SOLVENT             CDCl3
NS                    504
DS                     16
SWH             30303.031 Hz
FIDRES          0.462388 Hz
AQ              1.081248U sec
RG                 2298.8
DW                16.500 usec
DE                 6.00 usec
TE                298.0 K
D1           0.25000000 sec
d11          0.03000000 sec
D16          0.00020000 sec
d17          0.00019600 sec
MCREST 0 sec
MCWRK        0.01500000 sec
P2                33.10 usec

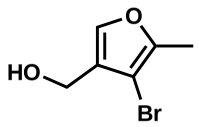
======= CHANNEL f1 ========
NUC1                  13C
P1                  16.55 usec
P11                500.00 usec
P12               2000.00 usec
PL0                 120.00 dB
PL1                  -1.00 dB
SFO1          125.7942548 MHz
SP1                  2.70 dB
SP2                  2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

======= CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                  1H
PCPD2              100.00 usec
PL2                  1.60 dB
PL12                24.50 dB
SFO2          500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1                30.00 %
GPZ2                50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                  65536
SF            125.7804282 MHz
WDW                    EM
SSB       0
LB                   1.00 Hz
GB        0
PC                   2.00
```

1H spectrum



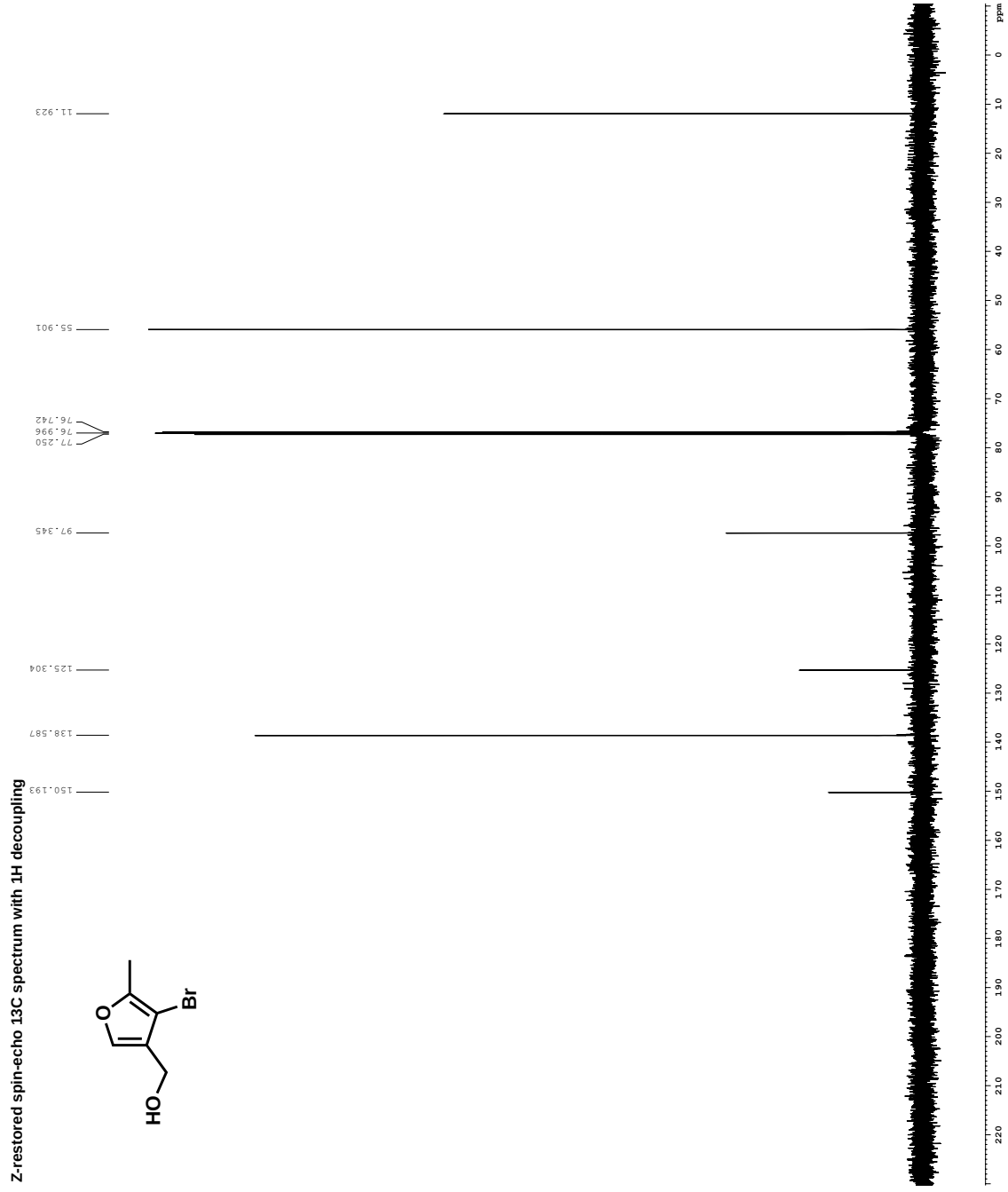

```
Current Data Parameters
NAME          ARW-III-199
EXPNO                   1
PROCNO                  1

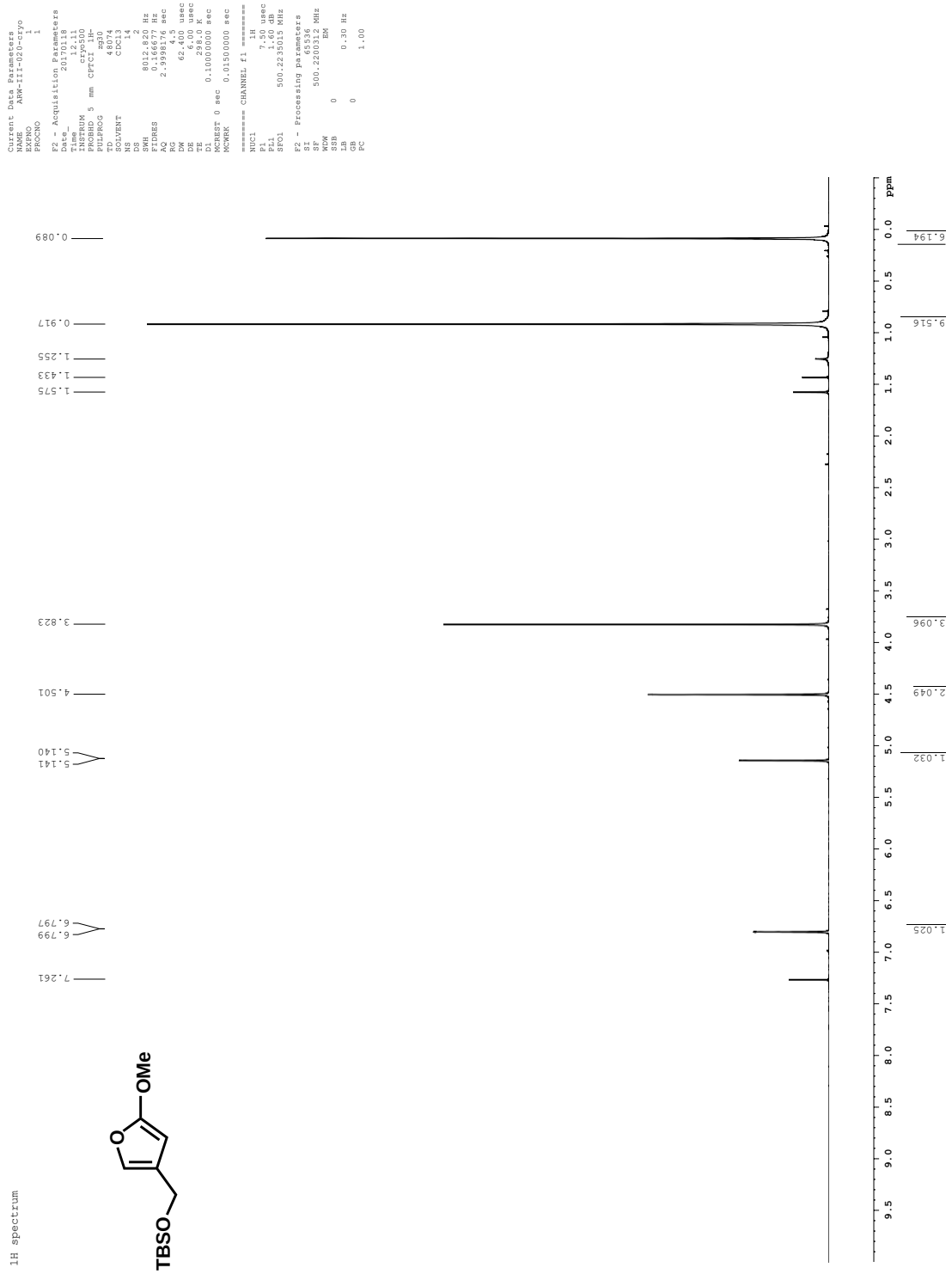
F2 - Acquisition Parameters
Date_              20170110
Time                 17.33
INSTRUM            cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG                zg30
TD                    48074
SOLVENT               CDCl3
NS                       32
DS                        2
SWH                8012.820 Hz
FIDRES            0.166677 Hz
AQ                2.9998176 sec
RG                      5.7
DW                   62.400 usec
DE                    6.00 usec
TE                   298.0 K
D1                0.10000000 sec
MCREST    0 sec
MCWRK             0.01500000 sec

======== CHANNEL f1 ========
NUC1                    1H
P1                    7.50 usec
PL1                   1.60 dB
SFO1          500.2235015 MHz

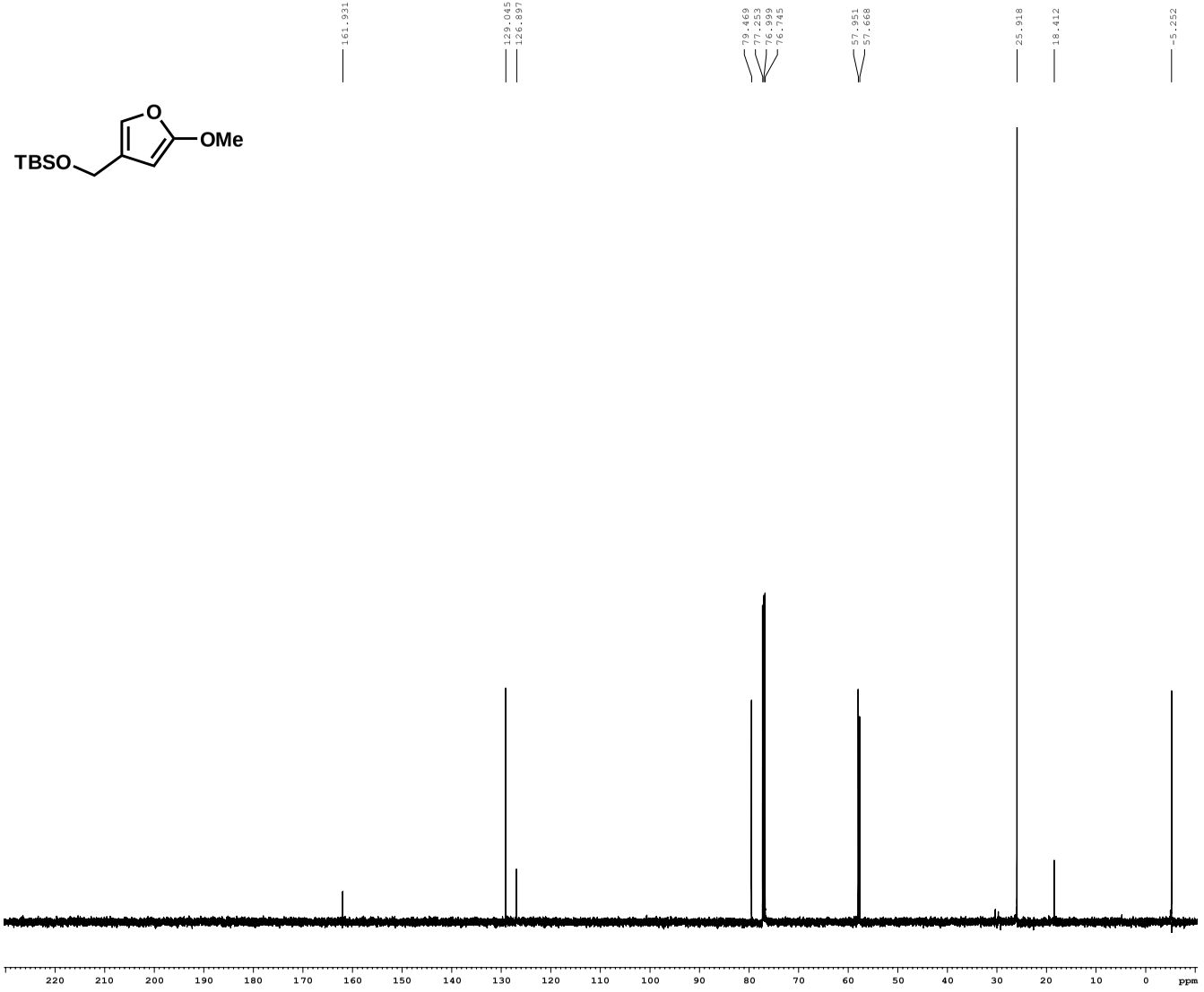
F2 - Processing parameters
SI                     65536
SF            500.2200315 MHz
WDW                       EM
SSB       0
LB                    0.30 Hz
GB        0
PC                    1.00
```

Z-restored spin-echo 13C spectrum with 1H decoupling




Current Data Parameters
NAME AEM-II-067-cryo
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170118
Time 12.11
INSTRUM spect
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 48074
SOLVENT CDCl3
NS 2
DS 2
SWH 8012.820 Hz
FIDRES 0.166677 Hz
AQ 2.9998176 sec
RG 4.5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200312 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB
PC 1.00
0.089
0.917
1.255
1.433
1.575
3.823
4.501
5.141
5.140
6.799
6.797
7.261
6.194
9.516
3.096
2.049
1.032
1.025
ppm
1H spectrum
OMe
O
TBSO

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME      ARW-III-020-cryo
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_           20170118
Time              12.14
INSTRUM         cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD                65536
SOLVENT             CDCl3
NS                   128
DS                    16
SWH           30303.031 Hz
FIDRES        0.462388 Hz
AQ            1.081344U sec
RG                 7298.2
DW               16.500 usec
DE                6.00 usec
TE                298.0 K
D1            0.25000000 sec
d11           0.03000000 sec
D16           0.00020000 sec
d17           0.00019600 sec
MCREST 0 sec
MCWRK         0.01500000 sec
P2               33.10 usec

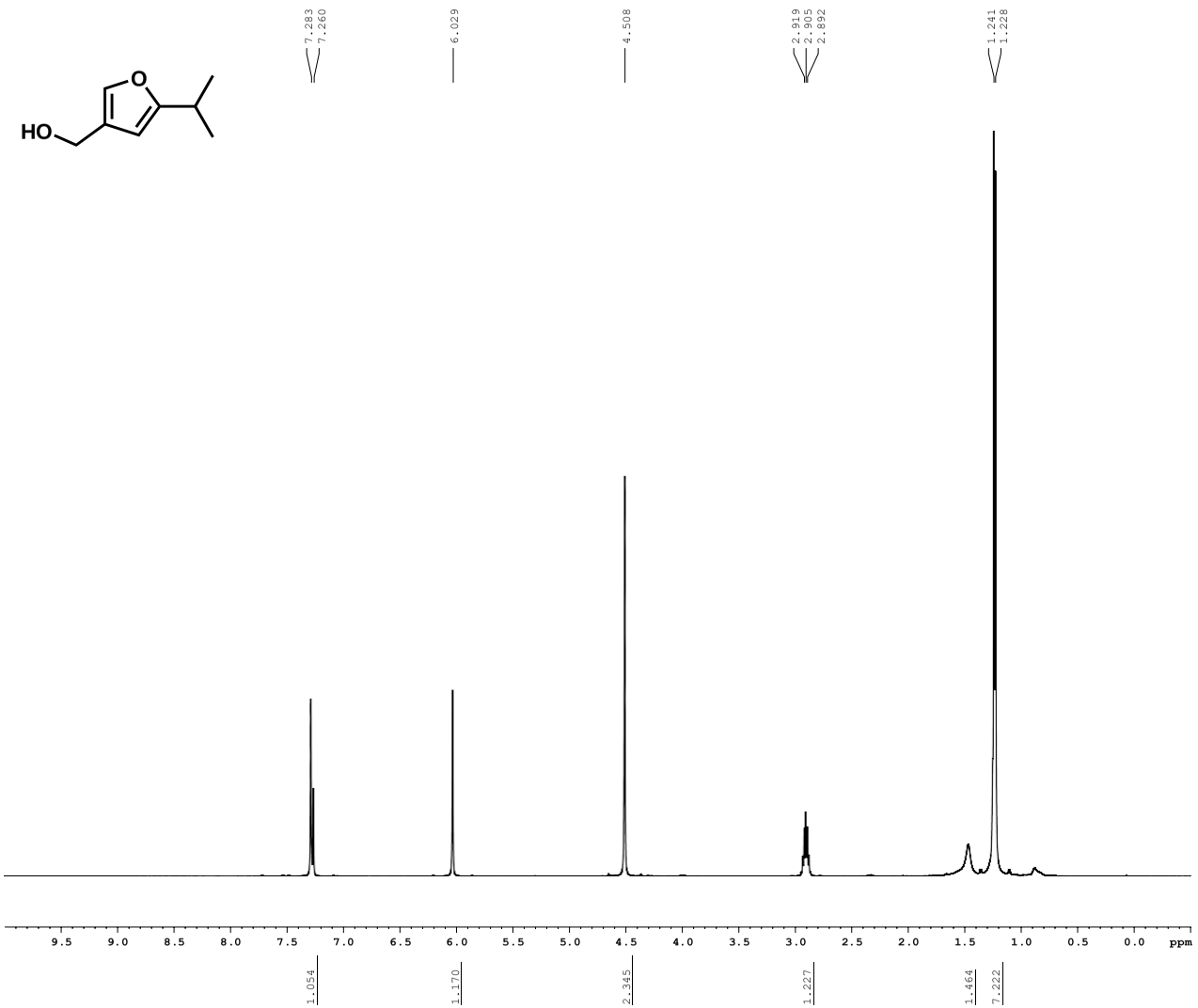
======= CHANNEL f1 ========
NUC1                  13C
P1                  16.55 usec
P11                500.00 usec
P12               2000.00 usec
PL0                120.00 dB
PL1                 -1.00 dB
SFO1         125.7942548 MHz
SP1                 2.70 dB
SP2                 2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

======= CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                  1H
PCPD2              100.00 usec
PL2                 1.60 dB
PL12               24.50 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1               30.00 %
GPZ2               50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                  65536
SF           125.7804282 MHz
WDW                    EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  2.00
```

1H spectrum



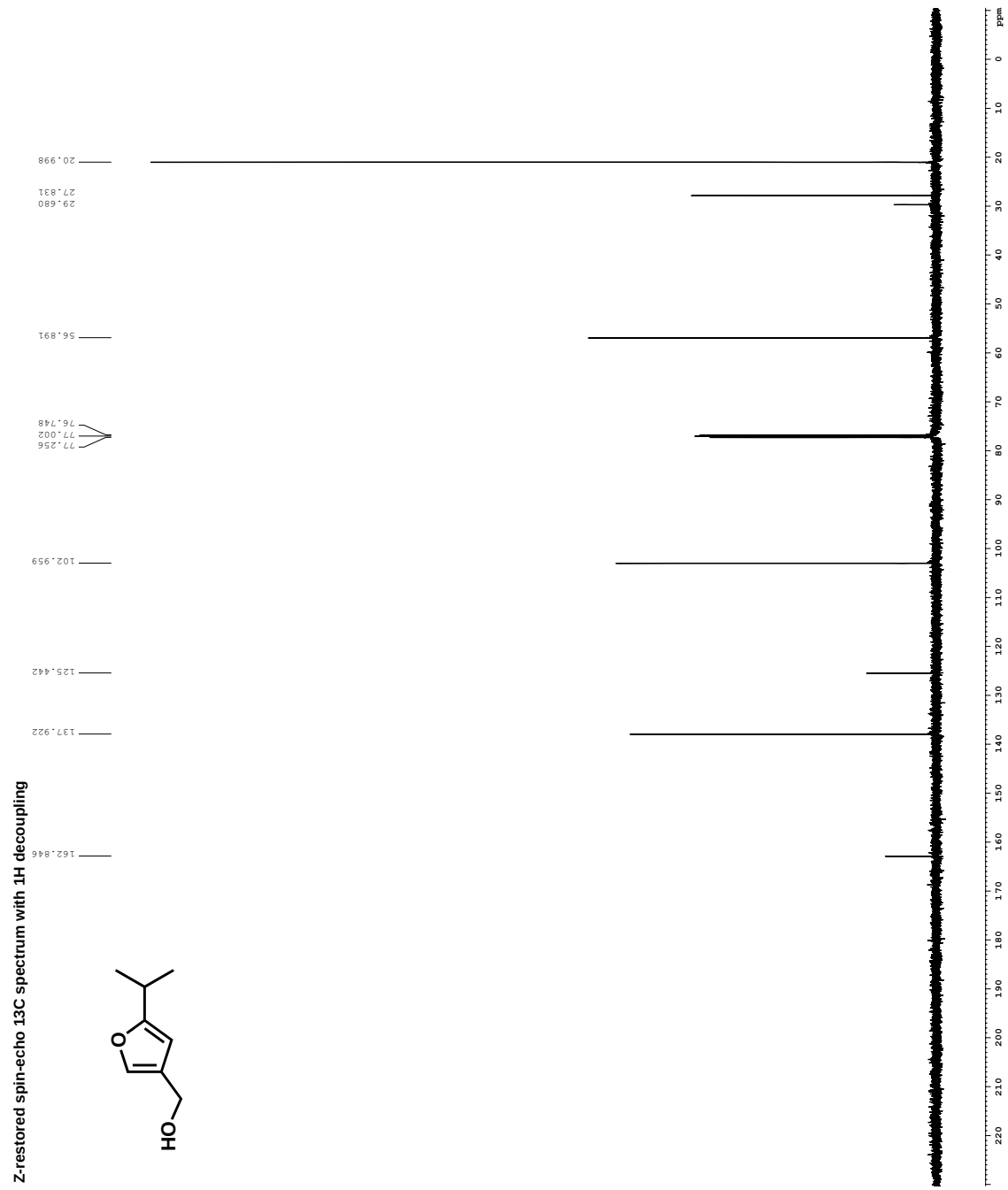

```
Current Data Parameters
NAME          ARW-III-144
EXPNO                   1
PROCNO                  1

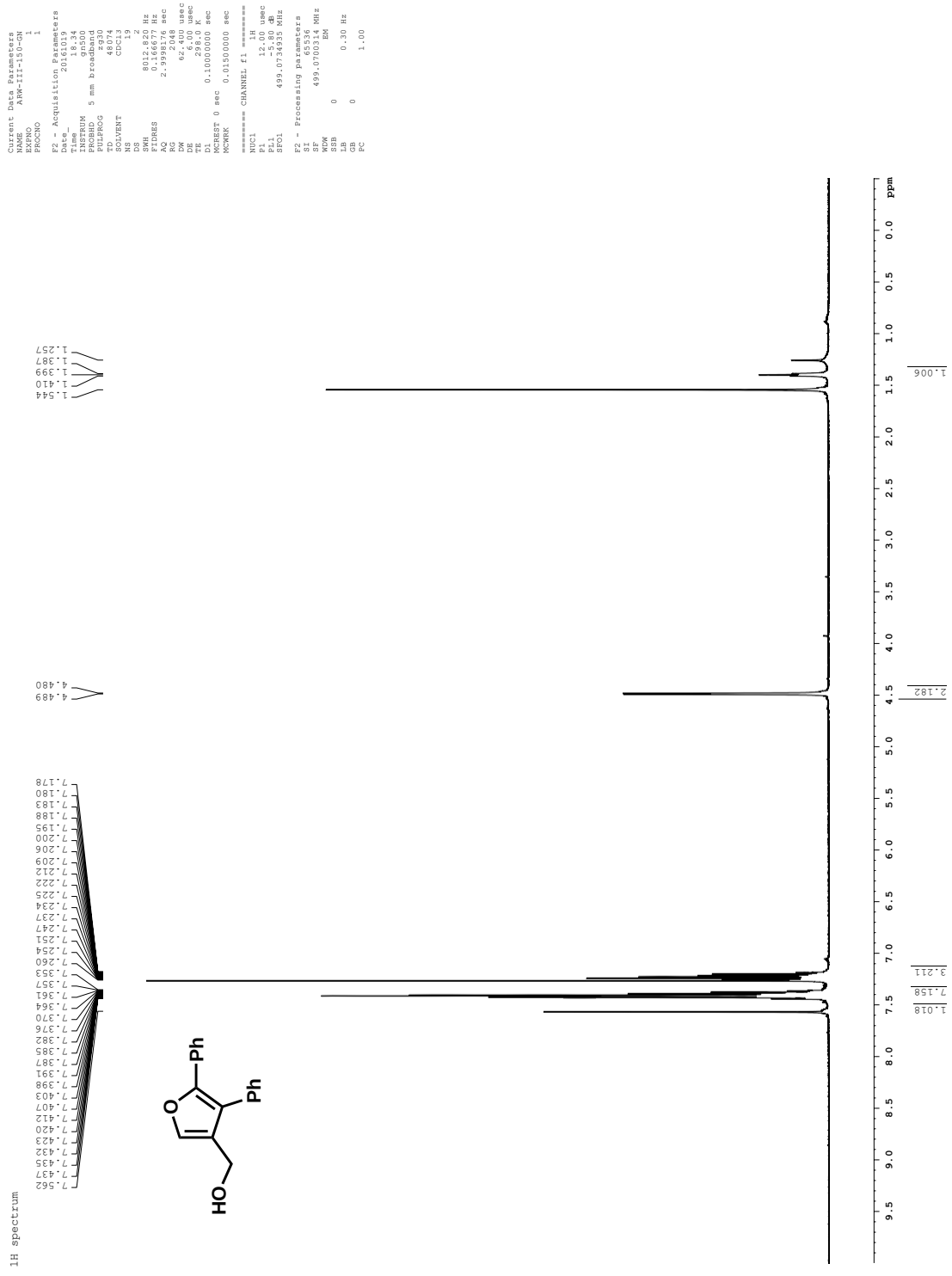
F2 - Acquisition Parameters
Date_           20160923
Time               16.34
INSTRUM          cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG             zg30
TD                 48074
SOLVENT            CDCl3
NS                    31
DS                     2
SWH             8012.820 Hz
FIDRES             0.166677 Hz
AQ              2.9998176 sec
RG                   5.7
DW                62.400 usec
DE                 6.00 usec
TE                298.0 K
D1              0.10000000 sec
MCREST 0 sec
MCWRK           0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                  7.50 usec
PL1                 1.60 dB
SFO1          500.2235015 MHz

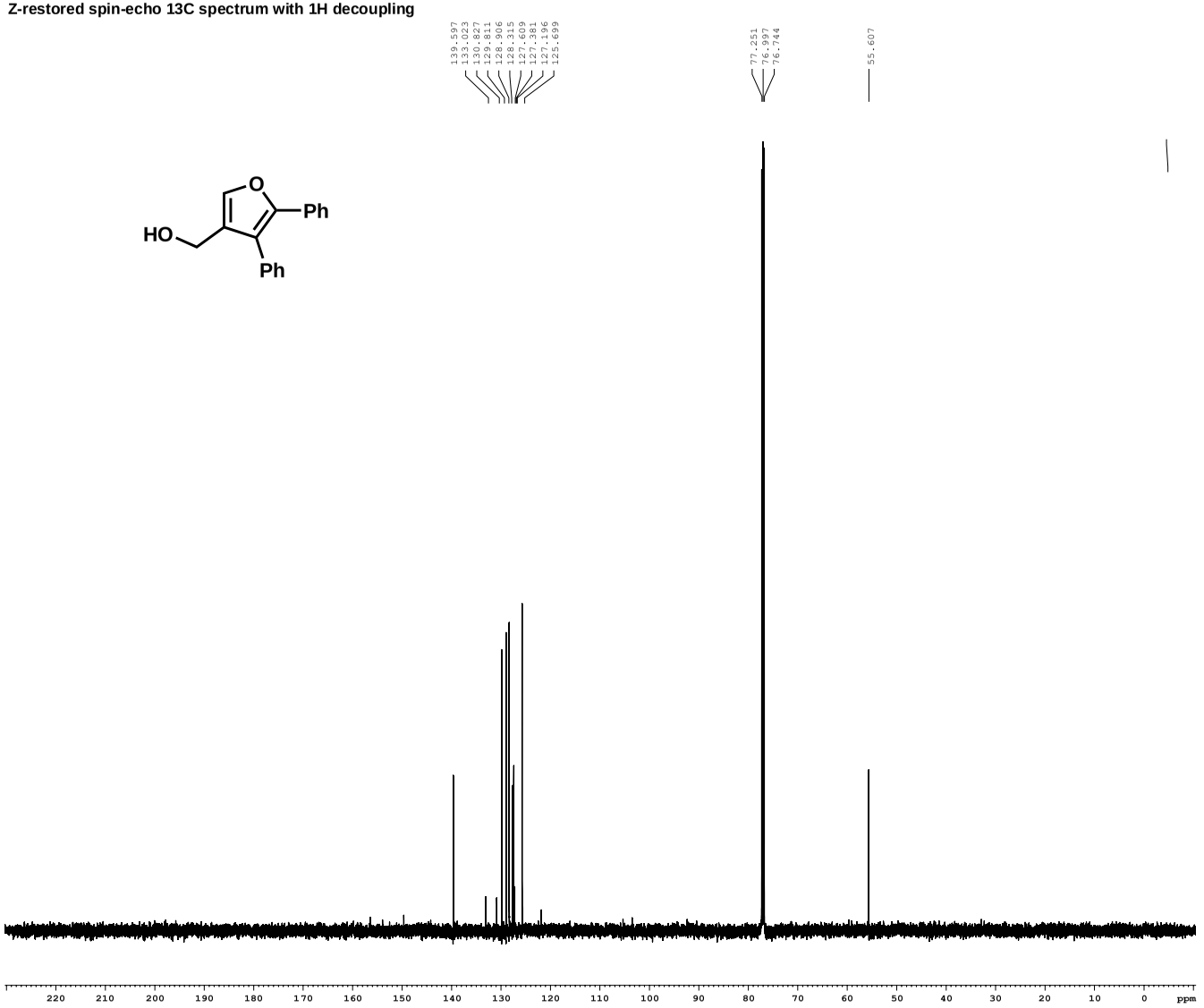
F2 - Processing parameters
SI                  65536
SF            500.2200312 MHz
WDW                    EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  4.00
```

Z-restored spin-echo 13C spectrum with 1H decoupling




Current Data Parameters
NAME AKW-III-210-CDCl3
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161019
Time 18.34
INSTRUM spect
PROBHD 5 mm broadband
PULPROG zg30
TD 48074
SOLVENT CDCl3
NS 2
DS 2
SWH 8012.820 Hz
FIDRES 0.166677 Hz
AQ 2.9998176 sec
RG 2.048
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK 0.01500000 sec
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 -5.80 dB
SFO1 499.0734935 MHz
F2 - Processing parameters
SI 65536
SF 499.0700314 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H spectrum
Ph
Ph
HO
7.562
7.437
7.435
7.432
7.423
7.420
7.412
7.403
7.407
7.398
7.391
7.387
7.385
7.382
7.376
7.370
7.364
7.361
7.357
7.353
7.260
7.254
7.251
7.247
7.237
7.234
7.225
7.222
7.212
7.209
7.206
7.200
7.195
7.188
7.183
7.180
7.178
4.489
4.480
1.544
1.410
1.399
1.387
1.257
1.018
7.158
3.211
2.182
1.006
ppm

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME        ARW-III-150cryo
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_           20161019
Time              18.58
INSTRUM         cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD                65536
SOLVENT           CDCl3
NS                  608
DS                   16
SWH           30303.031 Hz
FIDRES        0.462388 Hz
AQ            1.0813440 sec
RG                5160.6
DW               16.500 usec
DE                6.00 usec
TE               298.0 K
D1            0.25000000 sec
d11           0.03000000 sec
D16           0.00020000 sec
d17           0.00019600 sec
MCREST 0 sec
MCWRK         0.01500000 sec
P2               33.10 usec

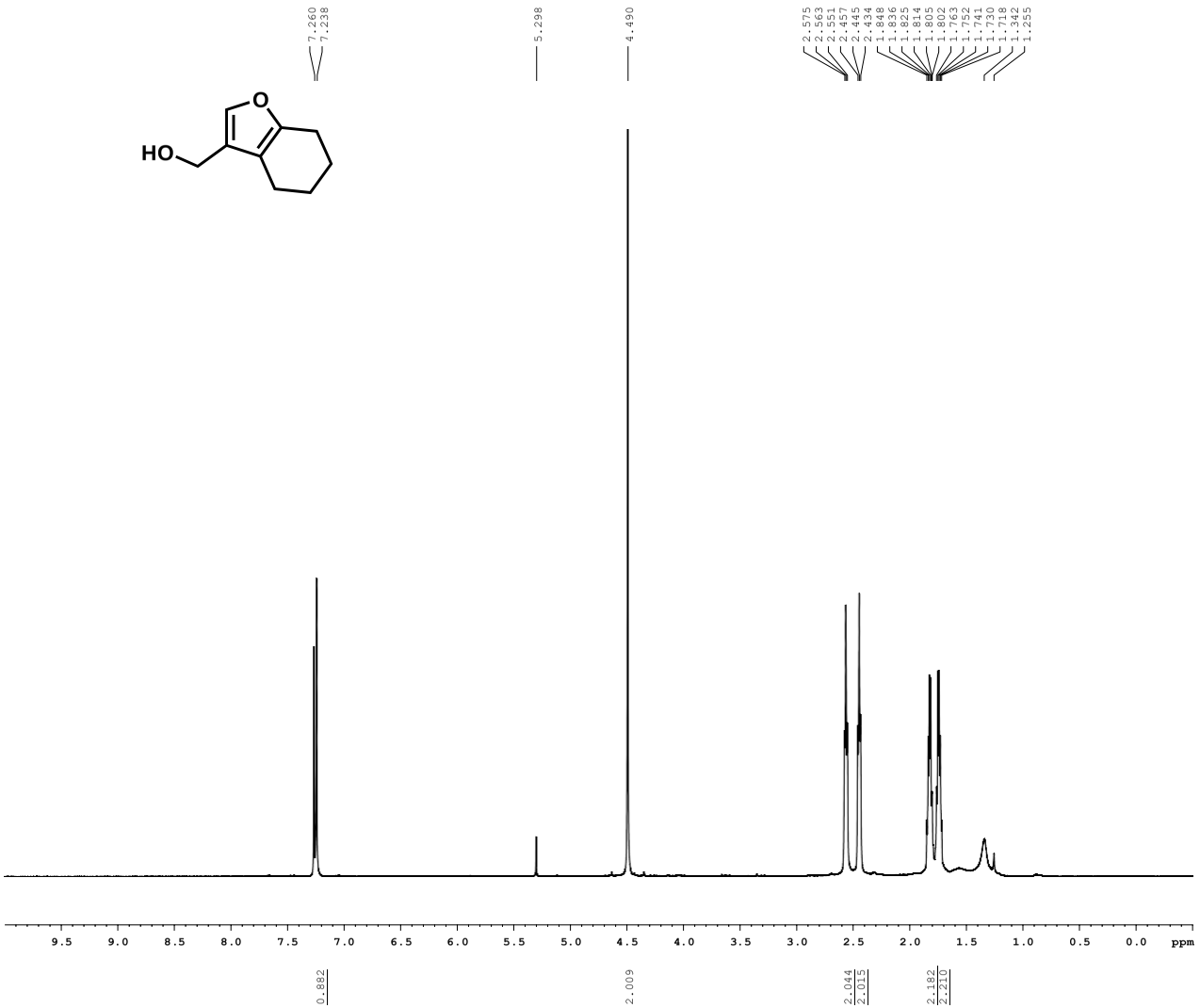
======= CHANNEL f1 =======
NUC1                13C
P1                16.55 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1         125.7942548 MHz
SP1               2.70 dB
SP2               2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

======= CHANNEL f2 =======
CPDPRG[2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12              24.50 dB
SFO2         500.2225011 MHz

===== GRADIENT CHANNEL =====
GPNAM[1]        SINE.100
GPNAM[2]        SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1             30.00 %
GPZ2             50.00 %
p15             500.00 usec
p16            1000.00 usec

F2 - Processing parameters
SI                65536
SF           125.7804277 MHz
WDW                  EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 2.00
```

1H spectrum

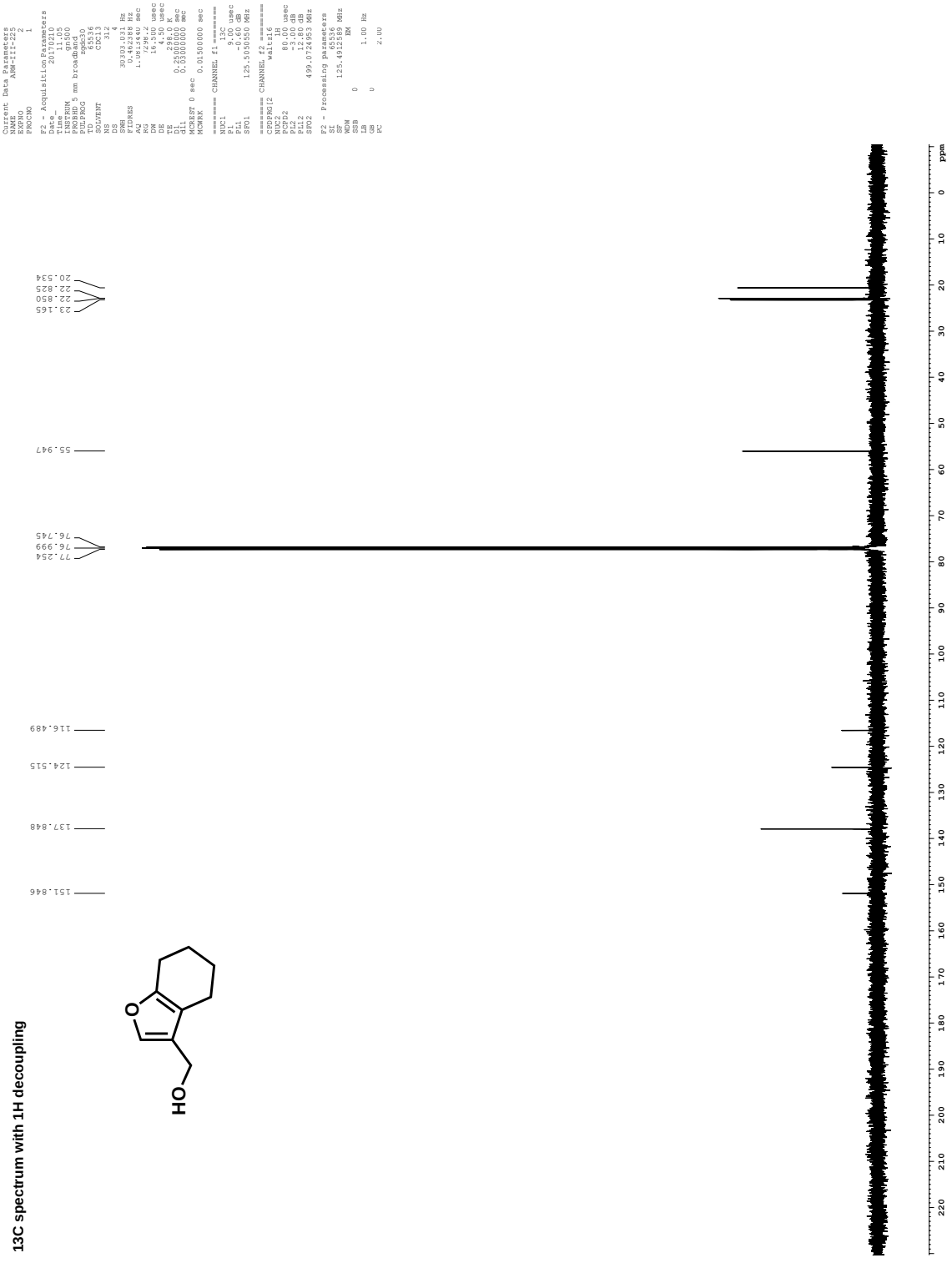



```
Current Data Parameters
NAME          ARW-III-225
EXPNO                   1
PROCNO                  1

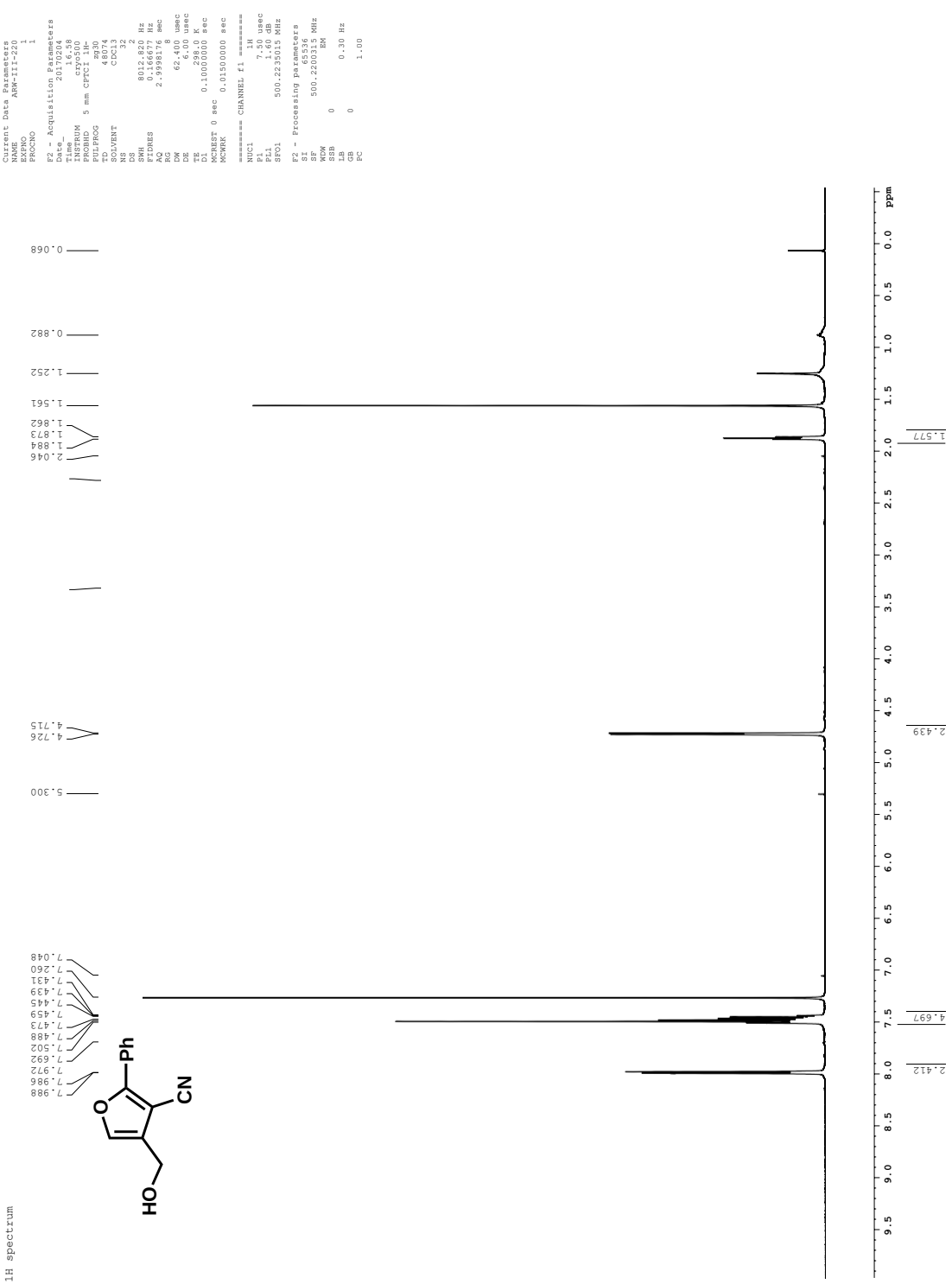
F2 - Acquisition Parameters
Date_            20170210
Time                11.01
INSTRUM             gn500
PROBHD   5 mm broadband
PULPROG              zg30
TD                  48074
SOLVENT             CDCl3
NS                     22
DS                      2
SWH              8012.820 Hz
FIDRES           0.166677 Hz
AQ               2.9998176 sec
RG                   1024
DW                 62.400 usec
DE                  6.00 usec
TE                 298.0 K
D1              0.10000000 sec
MCREST    0 sec
MCWRK           0.01500000 sec

======== CHANNEL f1 ========
NUC1                   1H
P1                 12.00 usec
PL1                -5.80 dB
SFO1         499.0734935 MHz

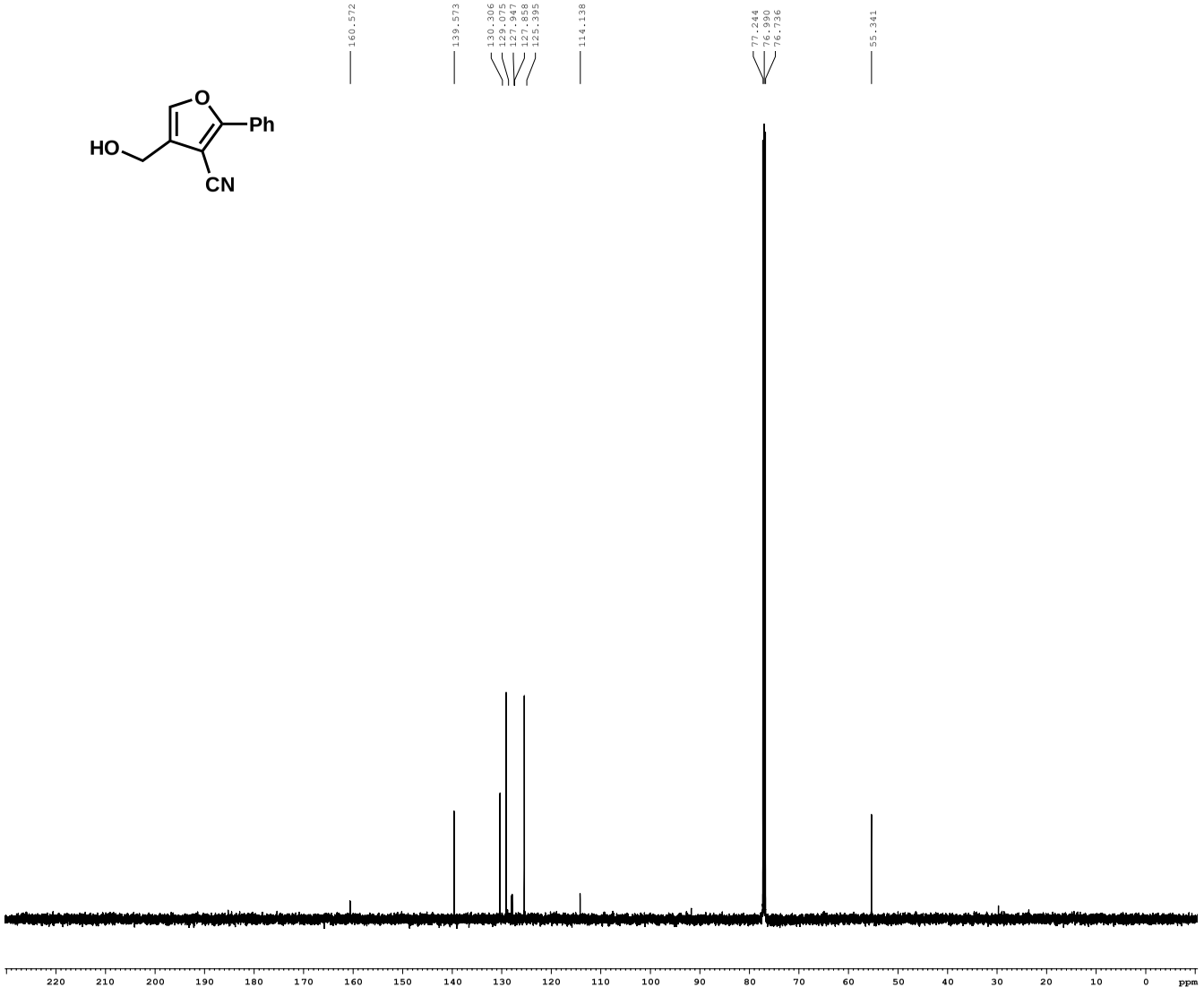
F2 - Processing parameters
SI                    65536
SF           499.0700316 MHz
WDW                     EM
SSB       0
LB                  0.30 Hz
GB        0
PC                  1.00
```



13C spectrum with 1H decoupling


Current Data Parameters
NAME AWK-II-220
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170204
Time 16.58
INSTRUM spect600
PROBHD 5 mm CPTCI 1H
PULPROG zg30
TD 40074
SOLVENT CDCl3
NS 2
DS 2
SWH 8012.820 Hz
FIDRES 0.199977 Hz
AQ 2.9998176 sec
RG 8
DW 62.400 usec
DE 6.50 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.00 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200315 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
0.068
0.882
1.252
1.561
1.862
1.873
1.884
2.046
4.715
4.726
5.300
7.048
7.260
7.431
7.439
7.445
7.459
7.473
7.488
7.502
7.692
7.972
7.986
7.988
Ph
CN
O
HO
1.577
2.439
4.697
2.412
ppm
1H spectrum

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME          ARW-III-220
EXPNO                   2
PROCNO                  1

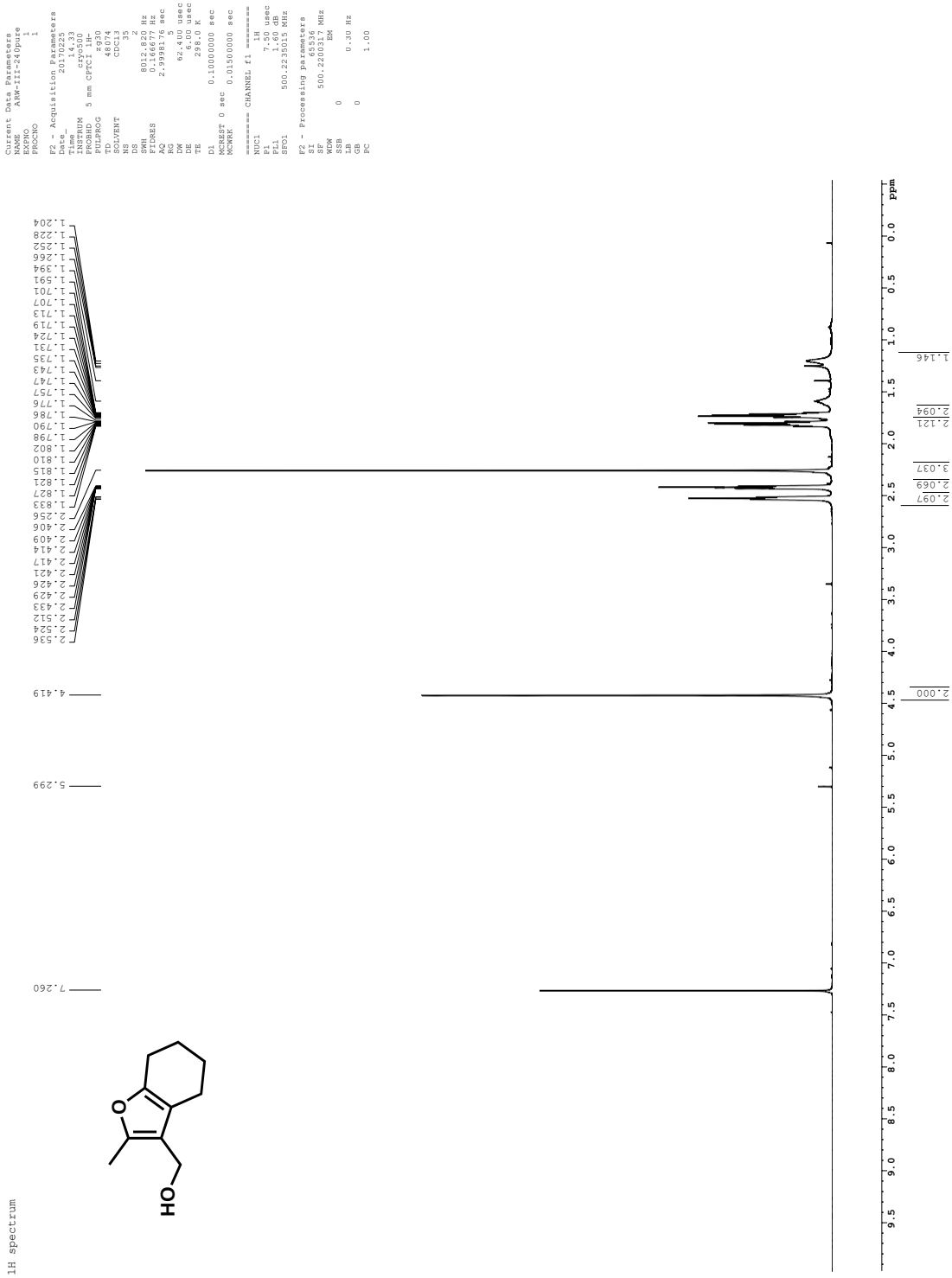
F2 - Acquisition Parameters
Date_           20170204
Time              17.02
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                65536
SOLVENT           CDCl3
NS                  808
DS                   16
SWH           30303.031 Hz
FIDRES        0.462388 Hz
AQ            1.0813440 sec
RG               7298.2
DW              16.500 usec
DE               6.00 usec
TE              298.0 K
D1          0.25000000 sec
d11         0.03000000 sec
D16         0.00020000 sec
d17         0.00019600 sec
MCREST   0 sec
MCWRK       0.01500000 sec
P2             33.10 usec

======= CHANNEL f1 ========
NUC1                1H
P1             16.55 usec
P11           500.00 usec
P12          2000.00 usec
PL0           120.00 dB
PL1            -1.00 dB
SFO1       125.7942548 MHz
SP1            2.70 dB
SP2            2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

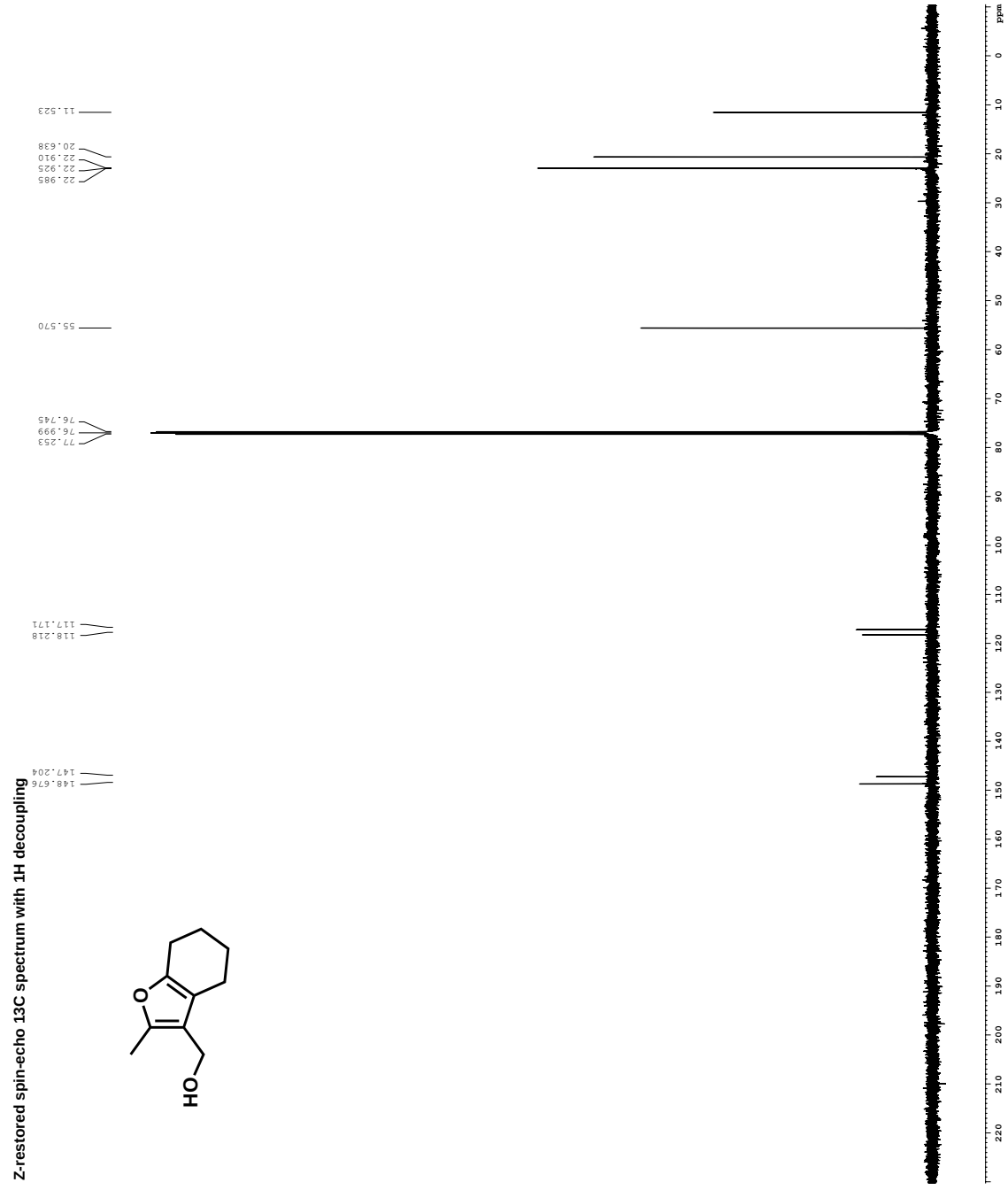
======= CHANNEL f2 ========
CPDPRG[2         waltz16
NUC2                1H
PCPD2          100.00 usec
PL2             1.60 dB
PL12           24.50 dB
SFO2       500.2225011 MHz

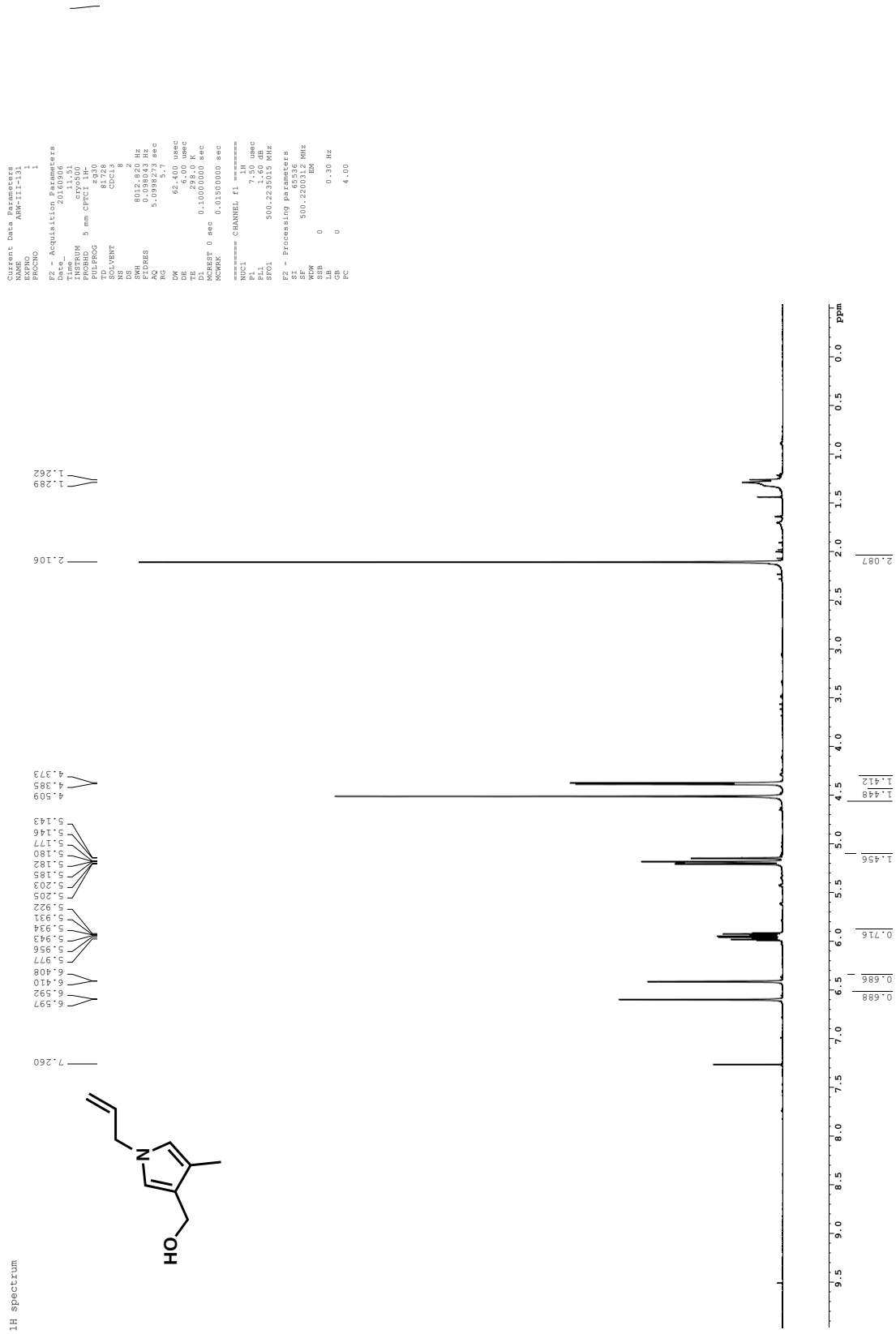
====== GRADIENT CHANNEL =====
GPNAM[1]        SINE.100
GPNAM[2]        SINE.100
GPX1     0 %
GPX2     0 %
GPY1     0 %
GPY2     0 %
GPZ1           30.00 %
GPZ2           50.00 %
p15           500.00 usec
p16          1000.00 usec

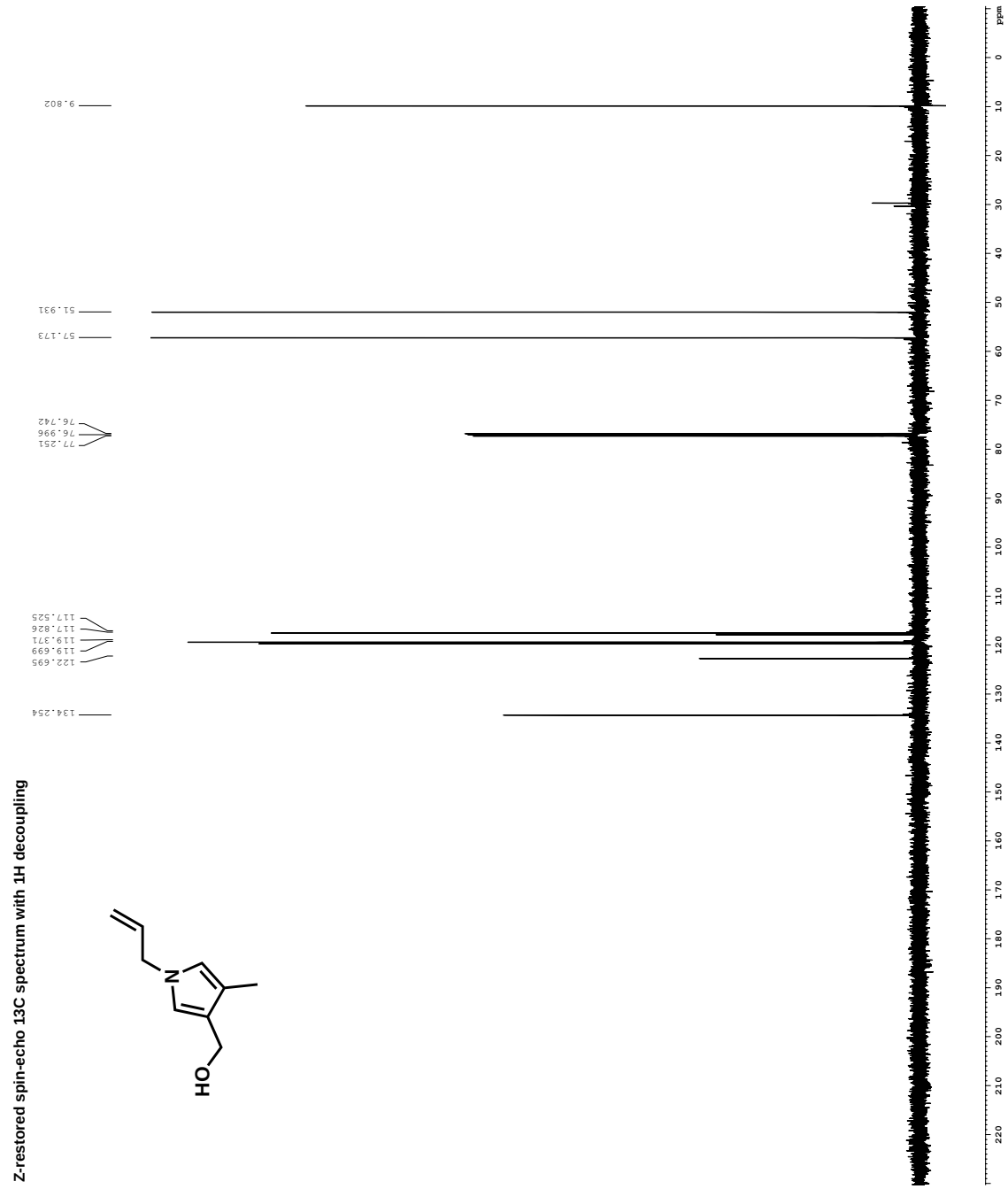
F2 - Processing parameters
SI                65536
SF          125.7804291 MHz
WDW                   EM
SSB      0
LB               1.00 Hz
GB       0
PC               2.00
```


Current Data Parameters
NAME AKW-IR-240pure
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170225
Time 14.33
INSTRUM spect
PROBHD 5 mm CPTCI 1H
PULPROG zg30
TD 48074
SOLVENT CDCl3
NS 2
DS 2
SWH 8012.820 Hz
FIDRES 0.166677 Hz
AQ 2.9998176 sec
RG 5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200317 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H spectrum
HO
7.260
5.299
4.419
2.536
2.524
2.512
2.433
2.429
2.426
2.421
2.417
2.414
2.409
2.406
2.256
1.833
1.827
1.821
1.815
1.810
1.802
1.798
1.790
1.786
1.776
1.757
1.747
1.743
1.735
1.731
1.724
1.719
1.713
1.707
1.701
1.591
1.394
1.266
1.252
1.228
1.204
2.000
2.097
2.069
3.037
2.094
2.121
1.146
ppm

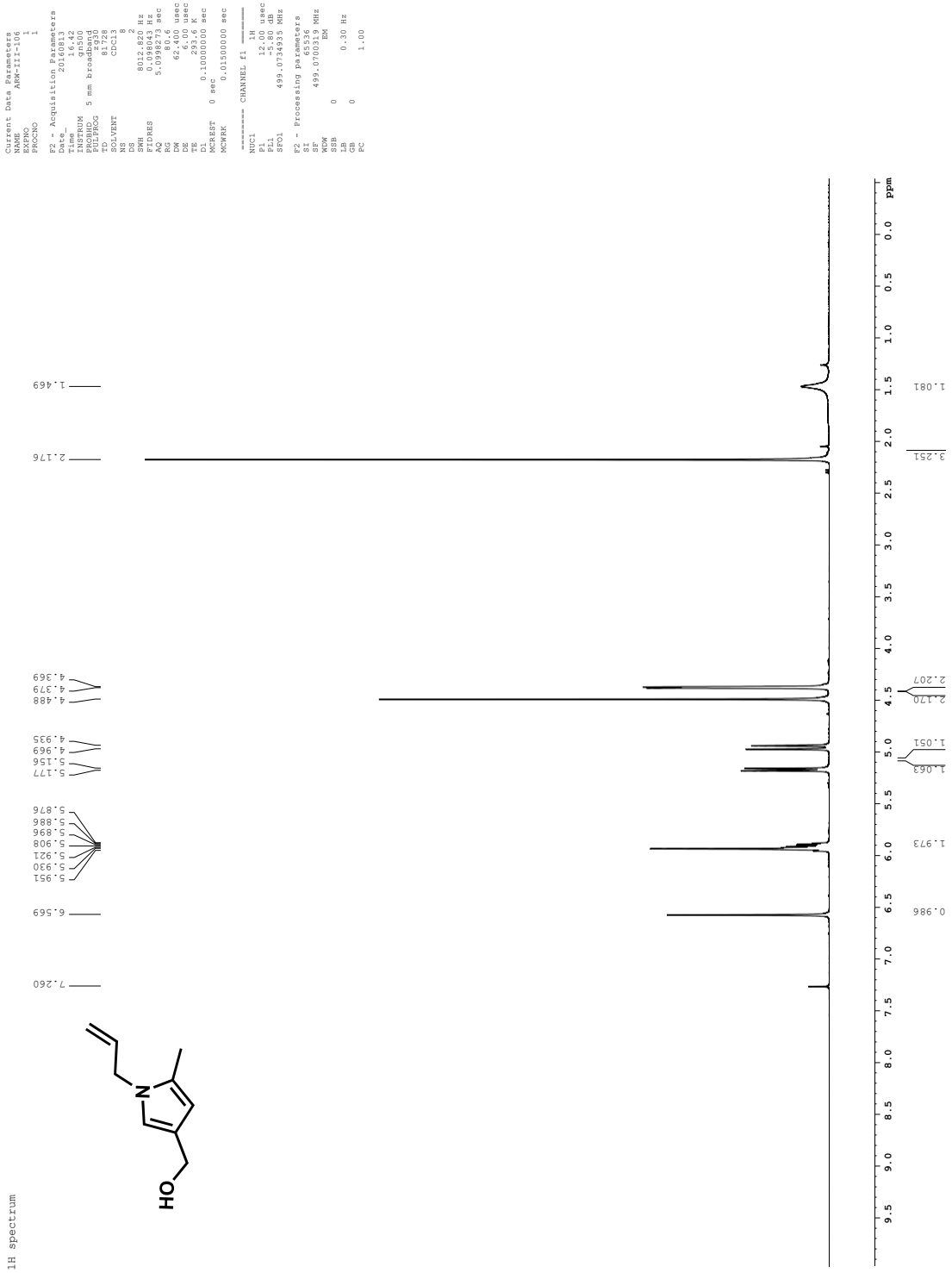
Z-restored spin-echo 13C spectrum with 1H decoupling



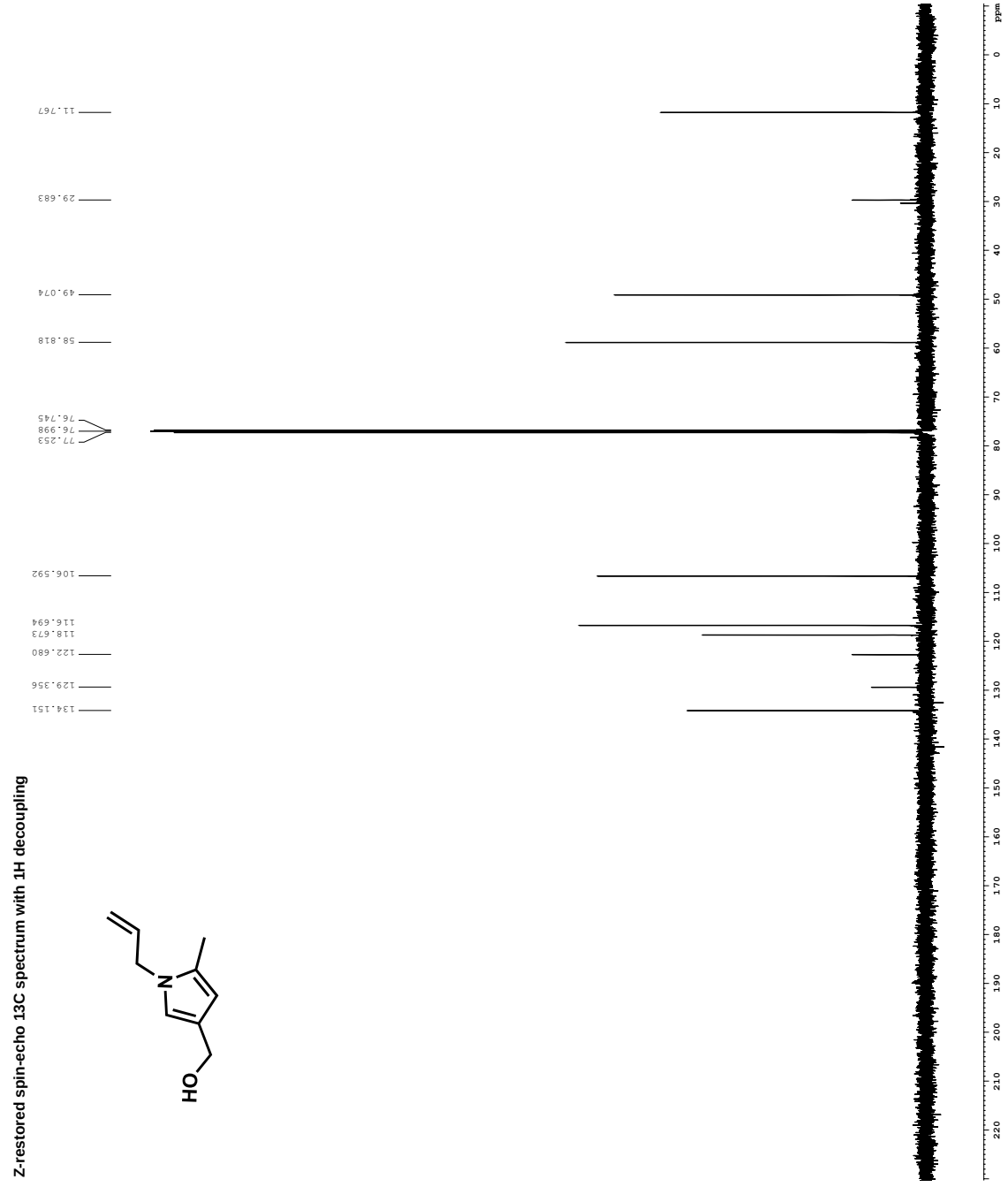

1H spectrum
Current Data Parameters
NAME AM-IT-131
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160906
Time 11.51
INSTRUM spect600
PROBHD 5 mm CPTCI 1H
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098273 Hz
AQ 5.0998273 sec
RG 5.7
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200132 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
7.260
6.597
6.592
6.410
6.408
5.977
5.956
5.943
5.934
5.931
5.922
5.205
5.203
5.185
5.182
5.180
5.177
5.146
5.143
4.509
4.385
4.373
2.106
1.289
1.262
HO
N
2.087
1.448
1.412
1.456
0.716
0.686
0.688
ppm

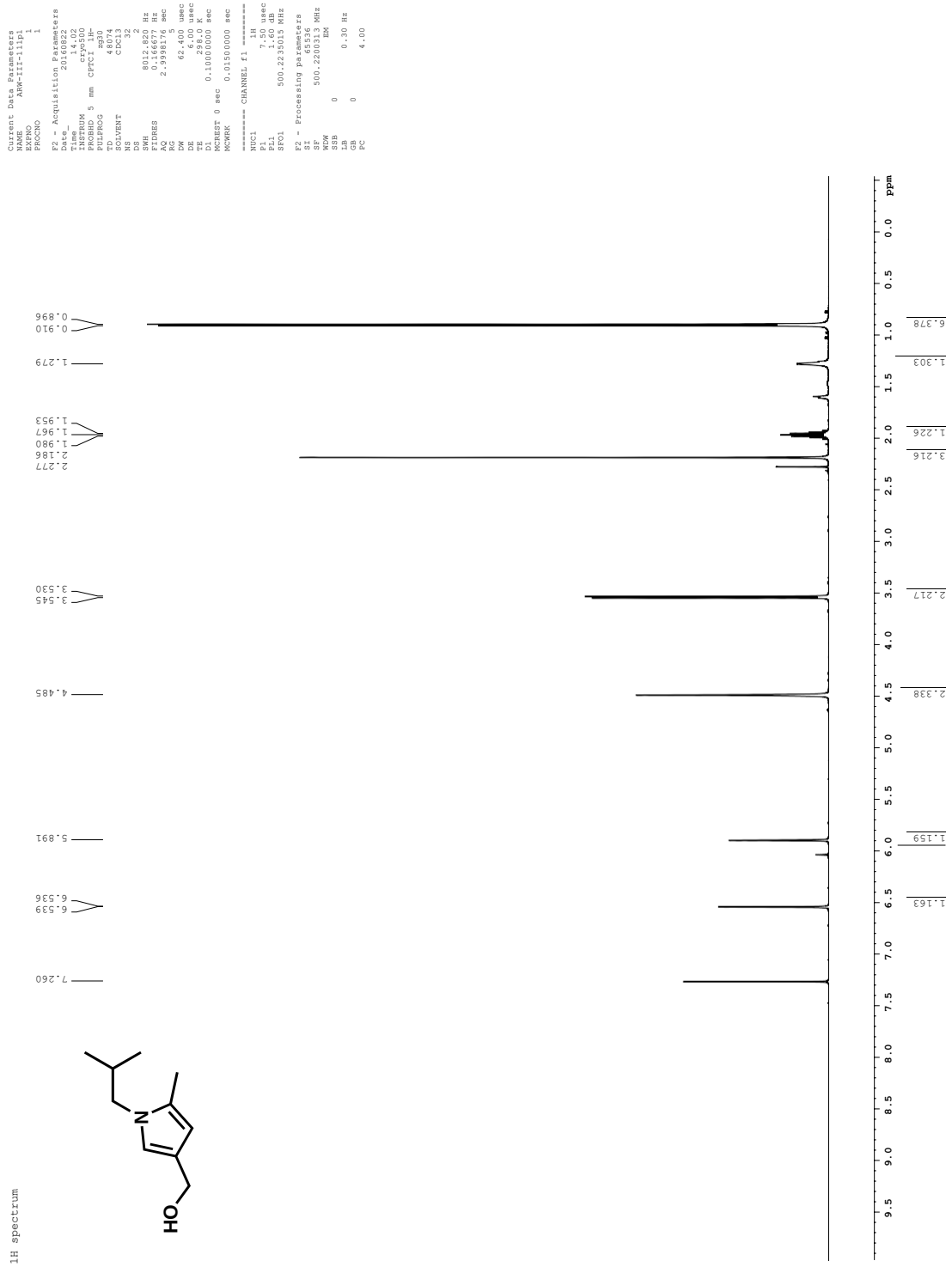


Z-restored spin-echo 13C spectrum with 1H decoupling

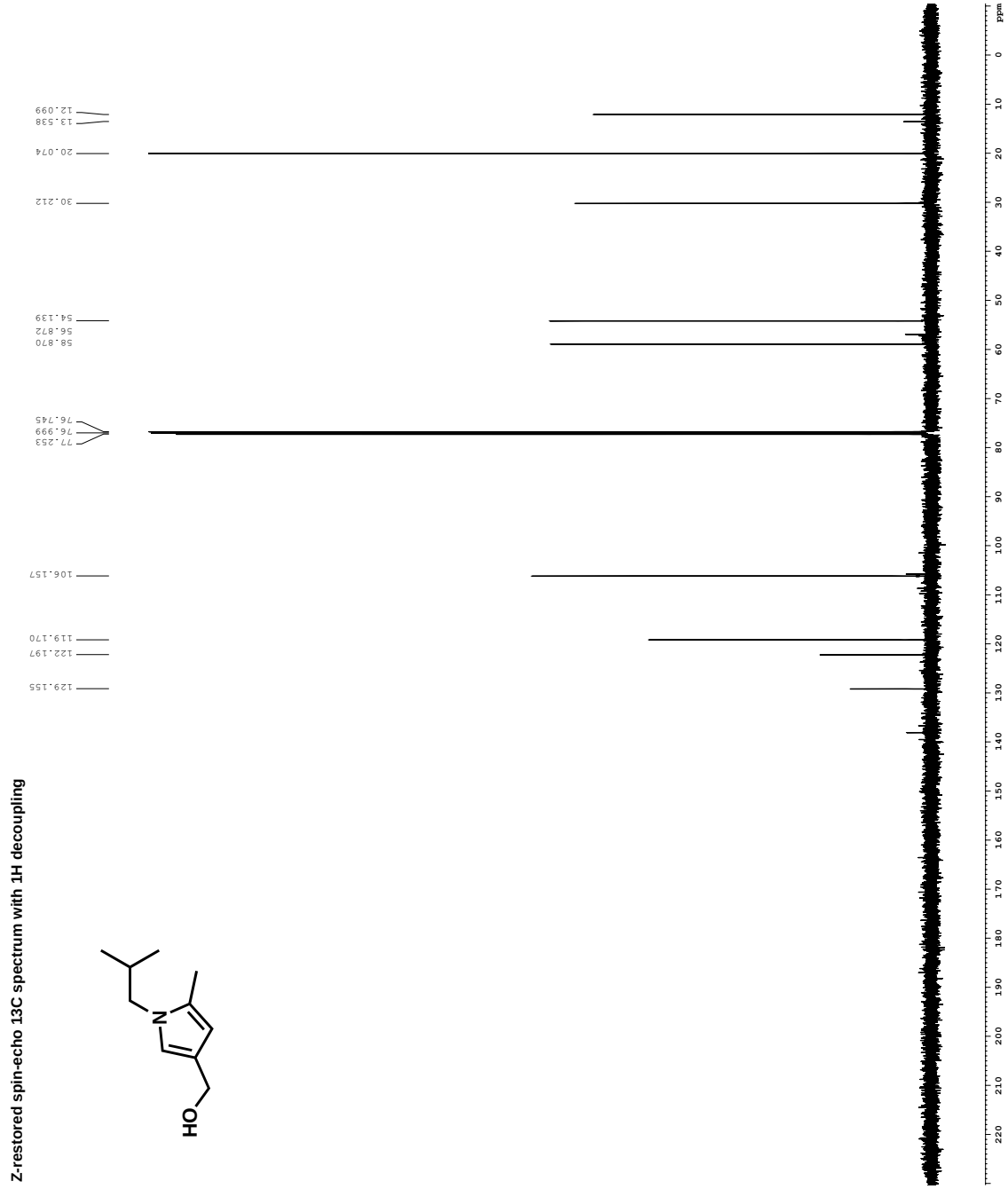

Current Data Parameters
NAME AWK-II-106
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160813
Time 16.42
INSTRUM spect
PROBHD 5 mm broadband
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 8
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998273 sec
RG 80.6
DW 62.400 usec
DE 6.00 usec
TE 293.6 K
D1 0.10000000 sec
MCREST 0 sec
MCWRK 0.01500000 sec
NUC1 1H
P1 12.00 usec
PL1 -2.00 dB
SFO1 499.0734935 MHz
F2 - Processing parameters
SI 65536
SF 499.0700319 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H spectrum
HO
N
7.260
6.569
5.951
5.930
5.921
5.908
5.896
5.886
5.876
5.177
5.156
4.969
4.935
4.488
4.379
4.369
2.176
1.469
ppm
0.986
1.973
1.063
1.051
2.207
2.170
3.251
1.081

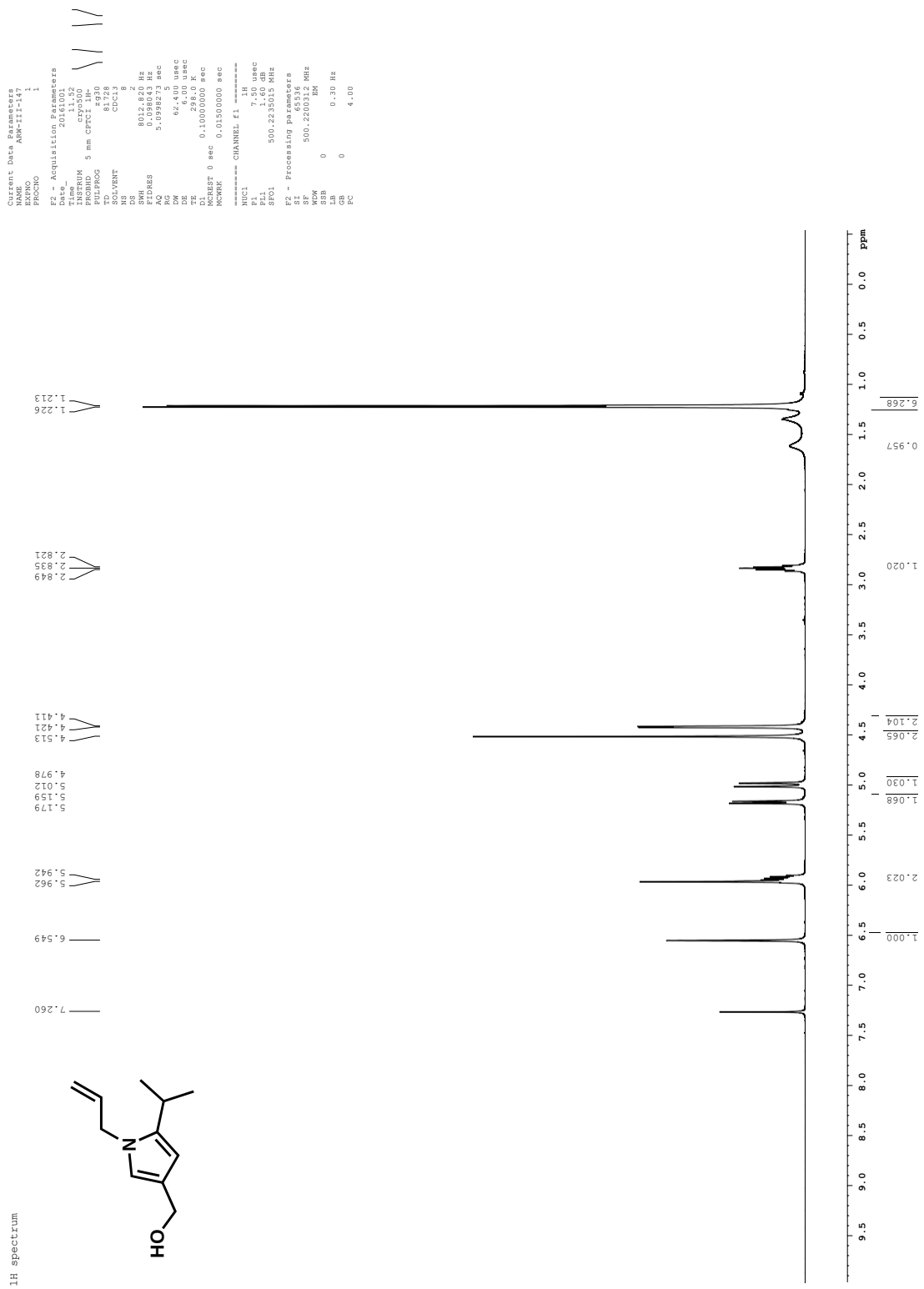
Z-restored spin-echo 13C spectrum with 1H decoupling



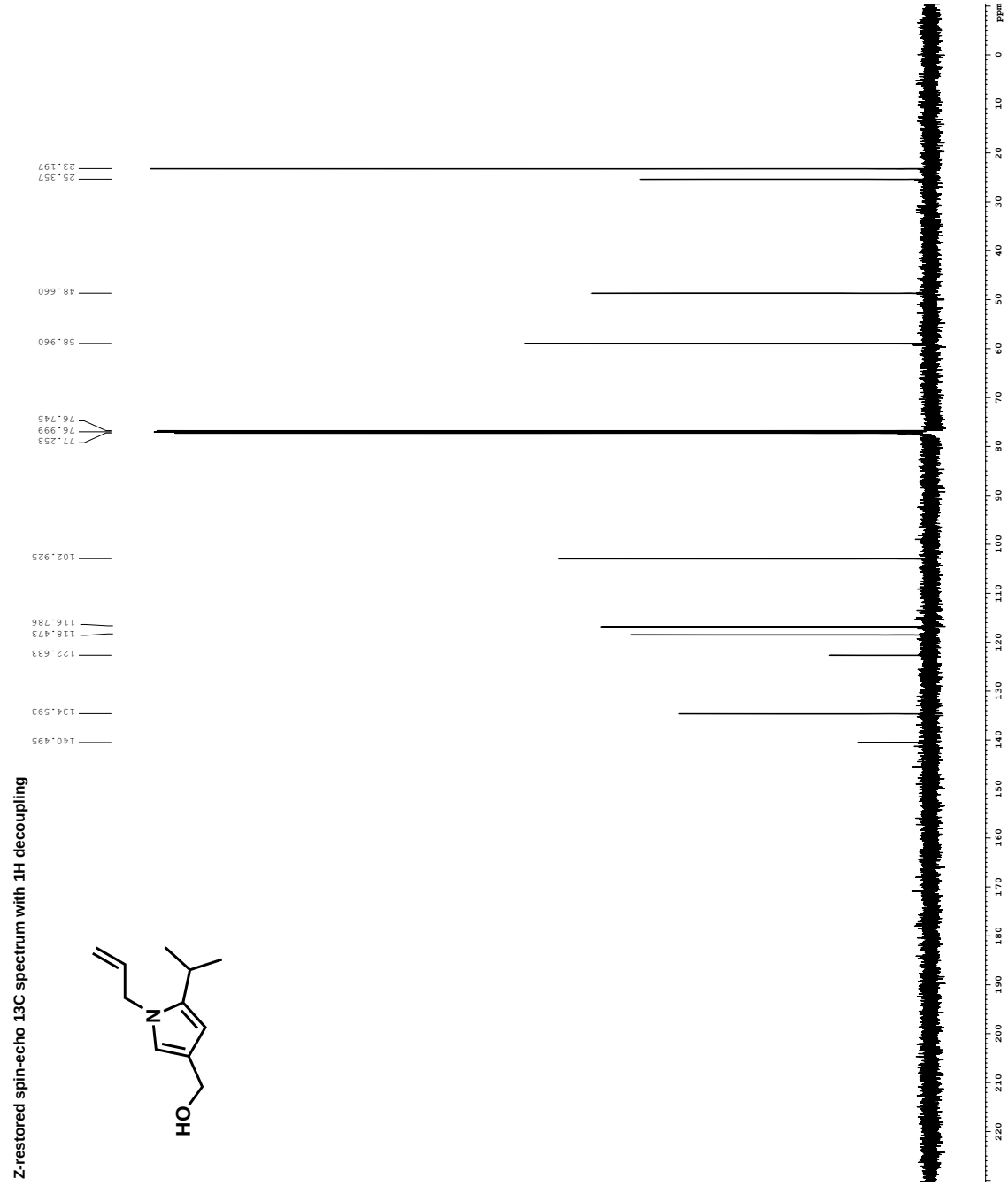

Current Data Parameters
NAME AWK-III-ip1
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160822
Time 14.02
INSTRUM spect
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 48074
SOLVENT CDCl3
NS 32
DS 2
SWH 8012.820 Hz
FIDRES 0.166677 Hz
AQ 2.9998176 sec
RG 5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.00 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200313 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
0.896
0.910
1.279
1.953
1.967
1.980
2.186
2.277
3.530
3.545
4.485
5.891
6.536
6.539
7.260
6.378
1.303
1.226
3.216
2.217
2.338
1.159
1.163
ppm
1H spectrum

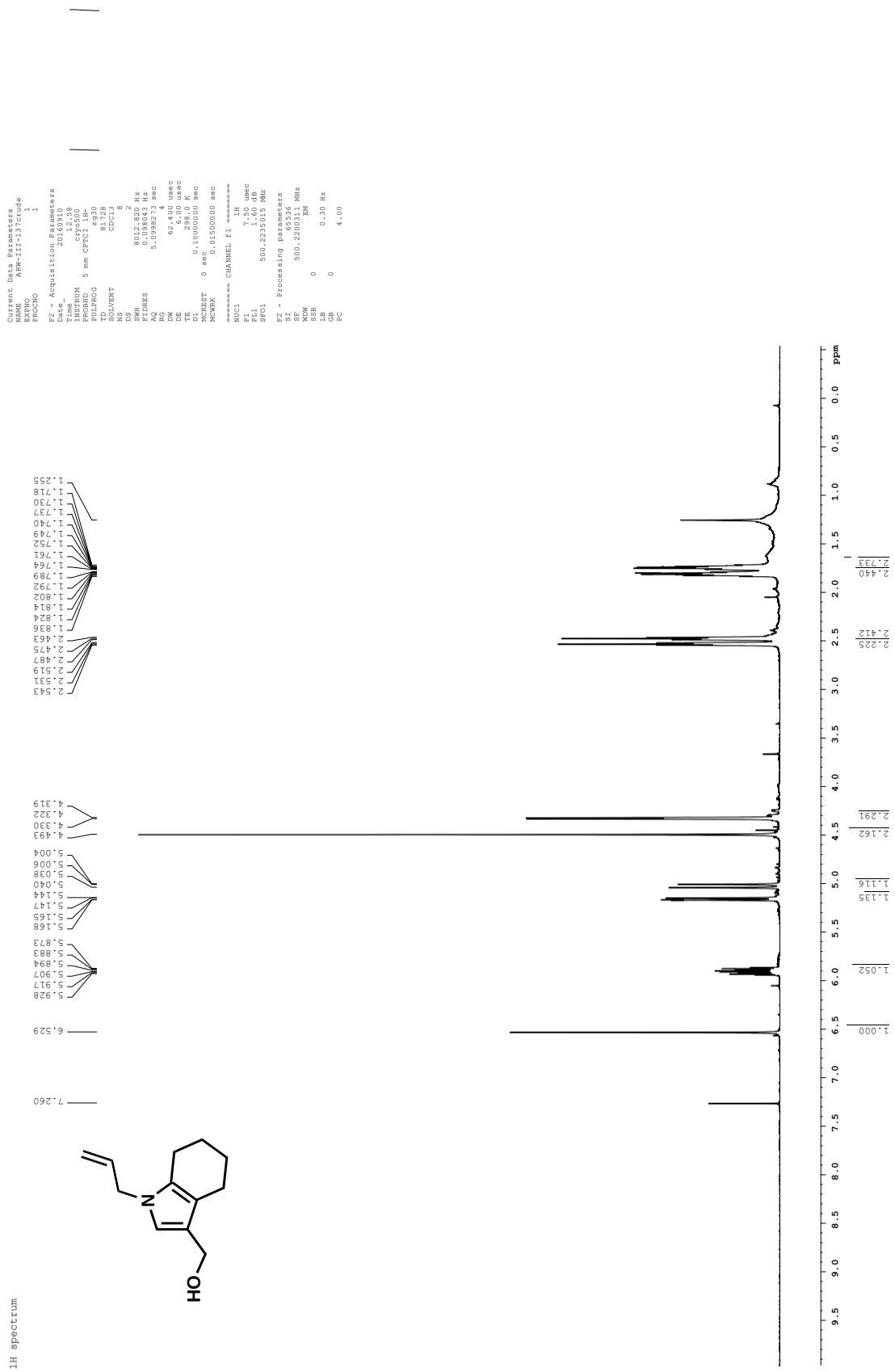
Z-restored spin-echo 13C spectrum with 1H decoupling



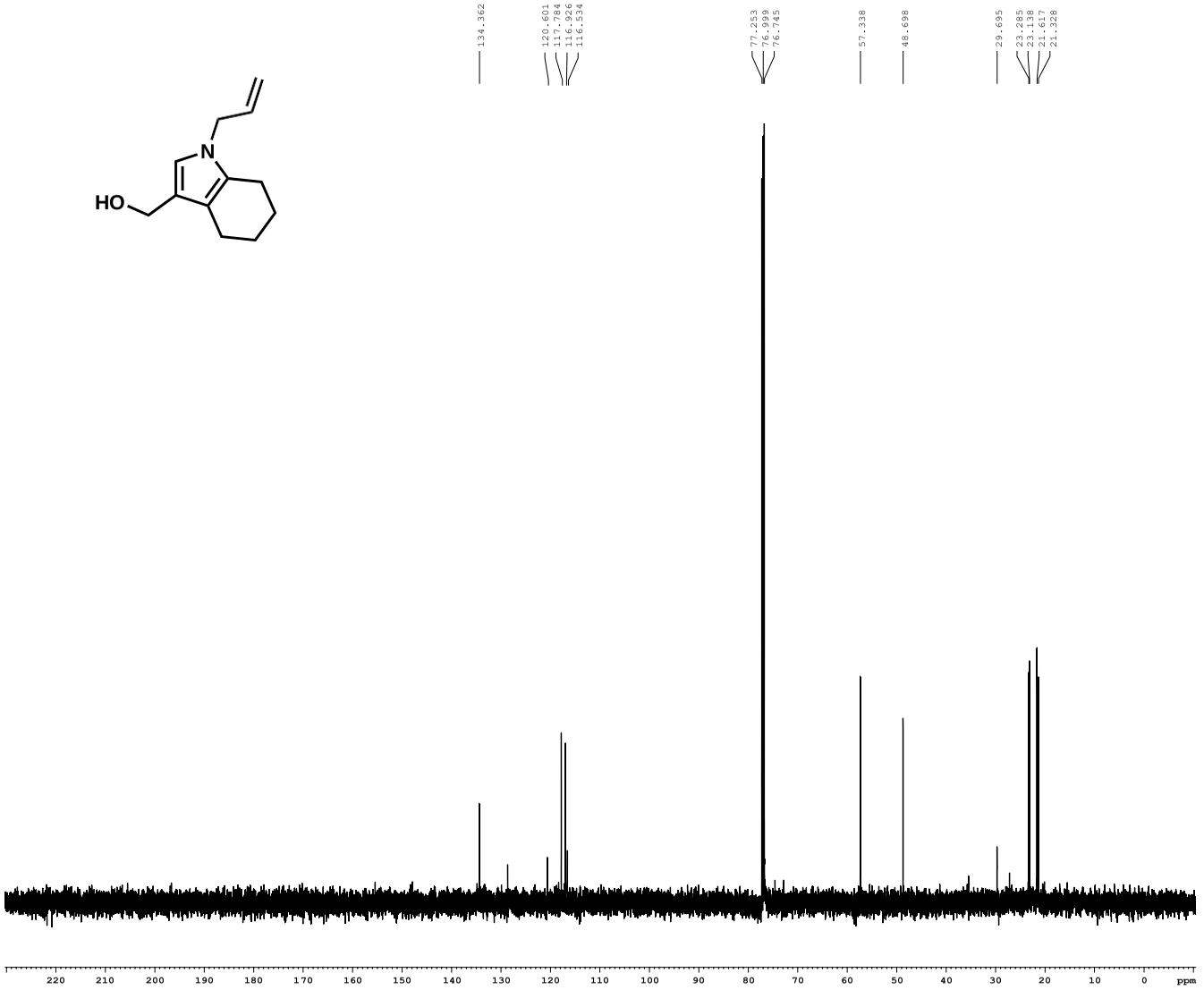

1H spectrum
Current Data Parameters
NAME AM-IT-147
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20161001
Time 11.52
INSTRUM spect600
PROBHD 5 mm CPTCI 1H
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 2
DS 8
SWH 8012.820 Hz
FIDRES 0.098013 Hz
AQ 5.0982173 sec
RG 5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200312 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 4.00
7.260
6.549
5.962
5.942
5.179
5.159
5.012
4.978
4.513
4.421
4.411
2.849
2.835
2.821
1.226
1.213
HO
N
1.000
2.023
1.068
1.030
2.065
2.104
6.268
0.957
1.020
ppm

Z-restored spin-echo 13C spectrum with 1H decoupling




1H spectrum
HO
ppm

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME          ARW-III-137
EXPNO                   2
PROCNO                  1

F2 - Acquisition Parameters
Date_           20160910
Time              17.13
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD                65536
SOLVENT             CDCl3
NS                    512
DS                     16
SWH             30303.031 Hz
FIDRES          0.462388 Hz
AQ              1.081344U sec
RG                 7298.2
DW                16.500 usec
DE                 6.00 usec
TE                 298.0 K
D1           0.25000000 sec
d11          0.03000000 sec
D16          0.00020000 sec
d17          0.00019600 sec
MCREST 0 sec
MCWRK        0.01500000 sec
P2                33.10 usec

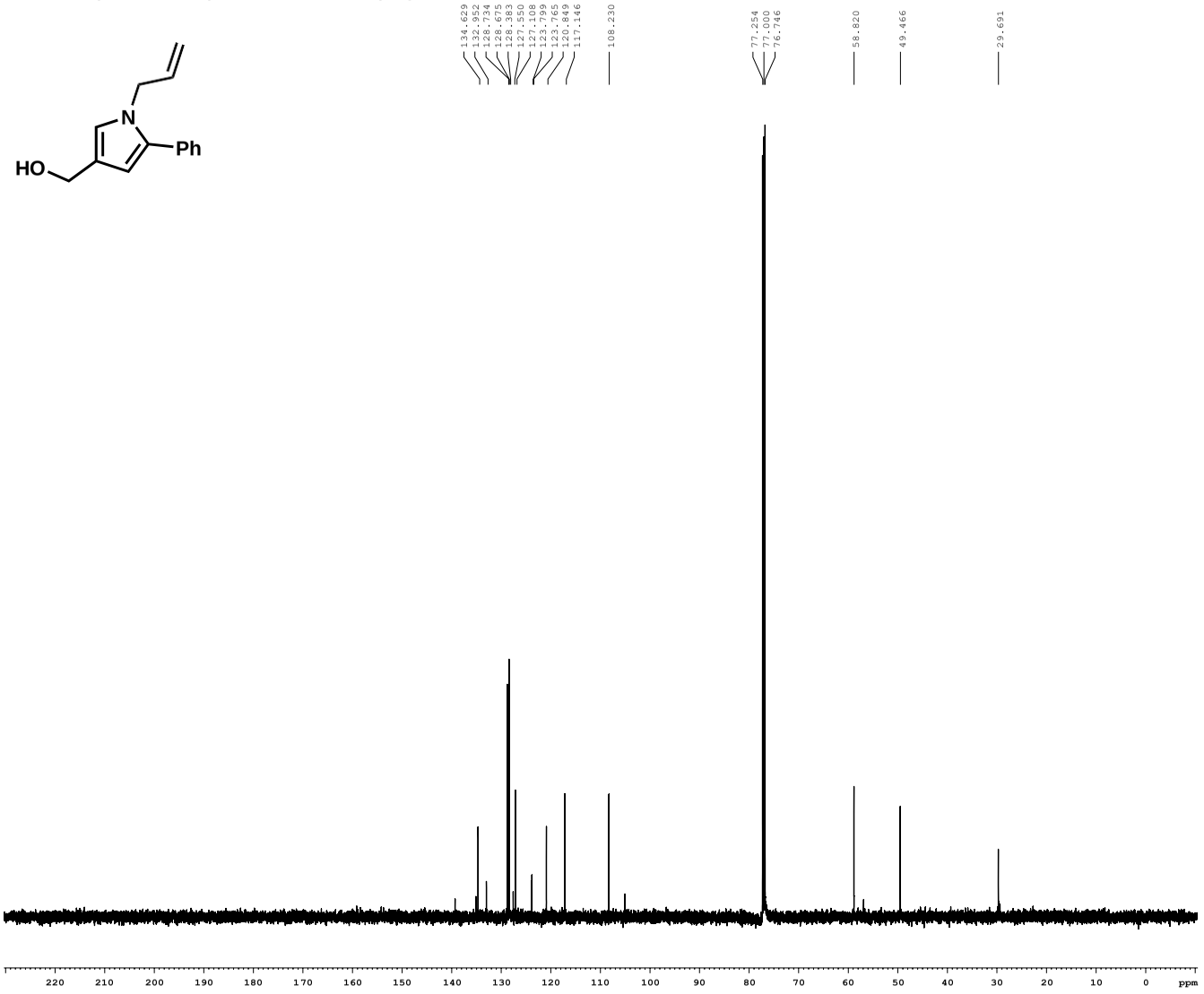
======= CHANNEL f1 =======
NUC1                  13C
P1                  16.55 usec
P11                500.00 usec
P12               2000.00 usec
PL0                 120.00 dB
PL1                  -1.00 dB
SFO1         125.7942548 MHz
SP1                  2.70 dB
SP2                  2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

======= CHANNEL f2 =======
CPDPRG[2          waltz16
NUC2                   1H
PCPD2              100.00 usec
PL2                  1.60 dB
PL12                24.50 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1                30.00 %
GPZ2                50.00 %
p15                500.00 usec
p16               1000.00 usec

F2 - Processing parameters
SI                    65536
SF          125.7804263 MHz
WDW                     EM
SSB       0
LB                   1.00 Hz
GB        0
PC                   2.00
```

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME            ARW-III-190
EXPNO                     2
PROCNO                    1

F2 - Acquisition Parameters
Date_          20161215
Time              13.30
INSTRUM           cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD                65536
SOLVENT             CDCl3
NS                    440
DS                     16
SWH           30303.031 Hz
FIDRES        0.462388 Hz
AQ            1.081344 sec
RG              10321.3
DW               16.500 usec
DE                6.00 usec
TE                298.0 K
D1            0.25000000 sec
d11           0.03000000 sec
D16           0.00020000 sec
d17           0.00019600 sec
MCREST   0 sec
MCWRK         0.01500000 sec
PZ                33.10 usec

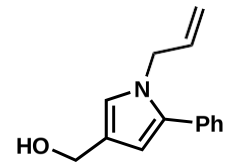
====== CHANNEL f1 ======
NUC1                 13C
P1                 16.55 usec
P11               500.00 usec
PL2              2000.00 usec
PL0               120.00 dB
PL1                -1.00 dB
SFO1         125.7942548 MHz
SP1                 2.70 dB
SP2                 2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2    0 Hz

====== CHANNEL f2 ======
CPDPRG[2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12              24.50 dB
SFO2         500.2225011 MHz

===== GRADIENT CHANNEL =====
GPNAM[1]        SINE.100
GPNAM[2]        SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1                30.00 %
GPZ2                50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                  65536
SF           125.7804272 MHz
WDW                    EM
SSB       0
LB                  1.00 Hz
GB        0
PC                  2.00
```

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME          ARW-III-190
EXPNO                   2
PROCNO                  1

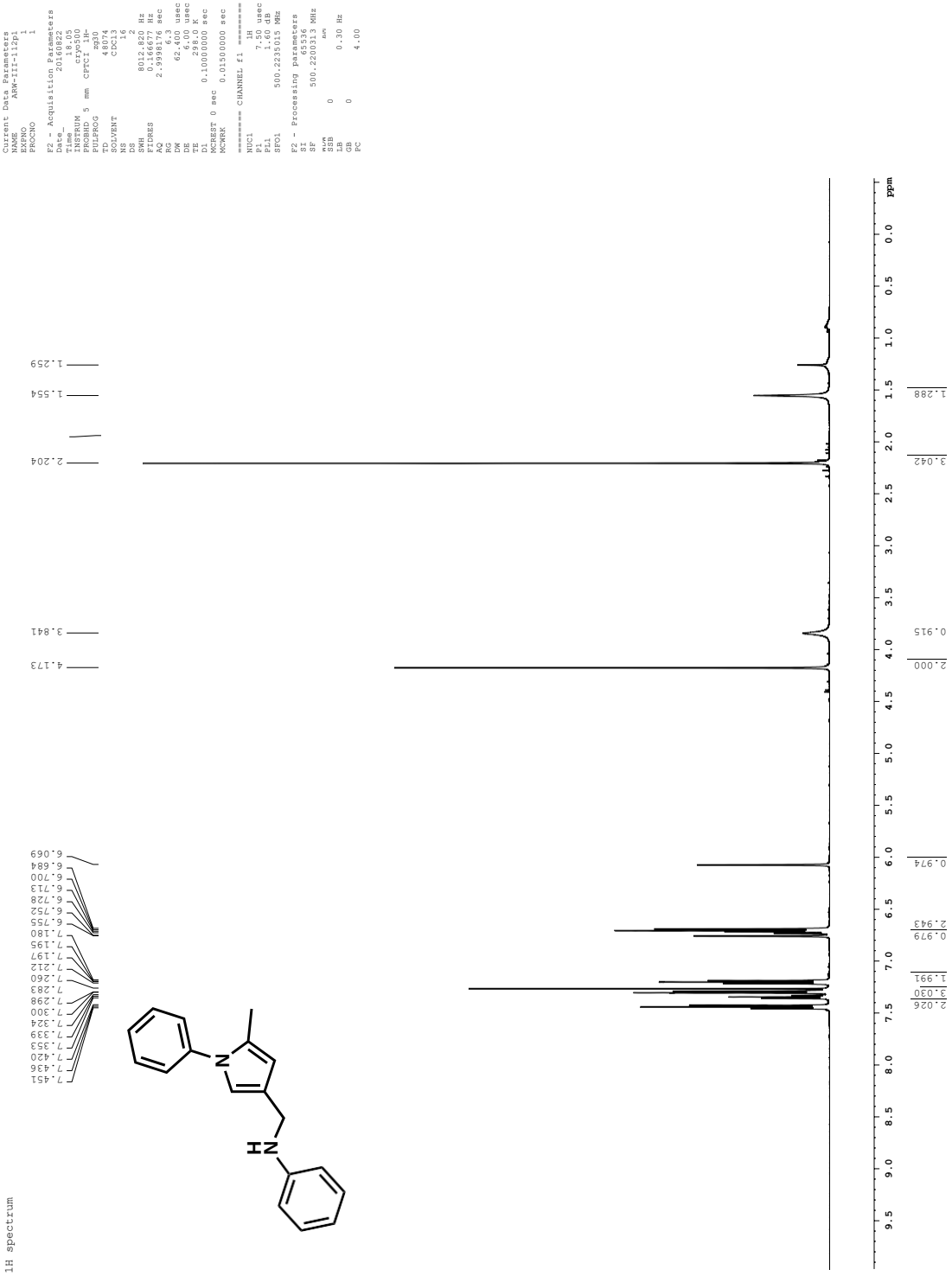
F2 - Acquisition Parameters
Date_           20161215
Time              13.30
INSTRUM           cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD                65536
SOLVENT             CDCl3
NS                    440
DS                     16
SWH            30303.031 Hz
FIDRES         0.462388 Hz
AQ             1.081344U sec
RG               10321.3
DW                16.500 usec
DE                 6.00 usec
TE                298.0 K
D1             0.25000000 sec
d11            0.03000000 sec
D16            0.00020000 sec
d17            0.00019600 sec
MCREST    0 sec
MCWRK          0.01500000 sec
P2                33.10 usec

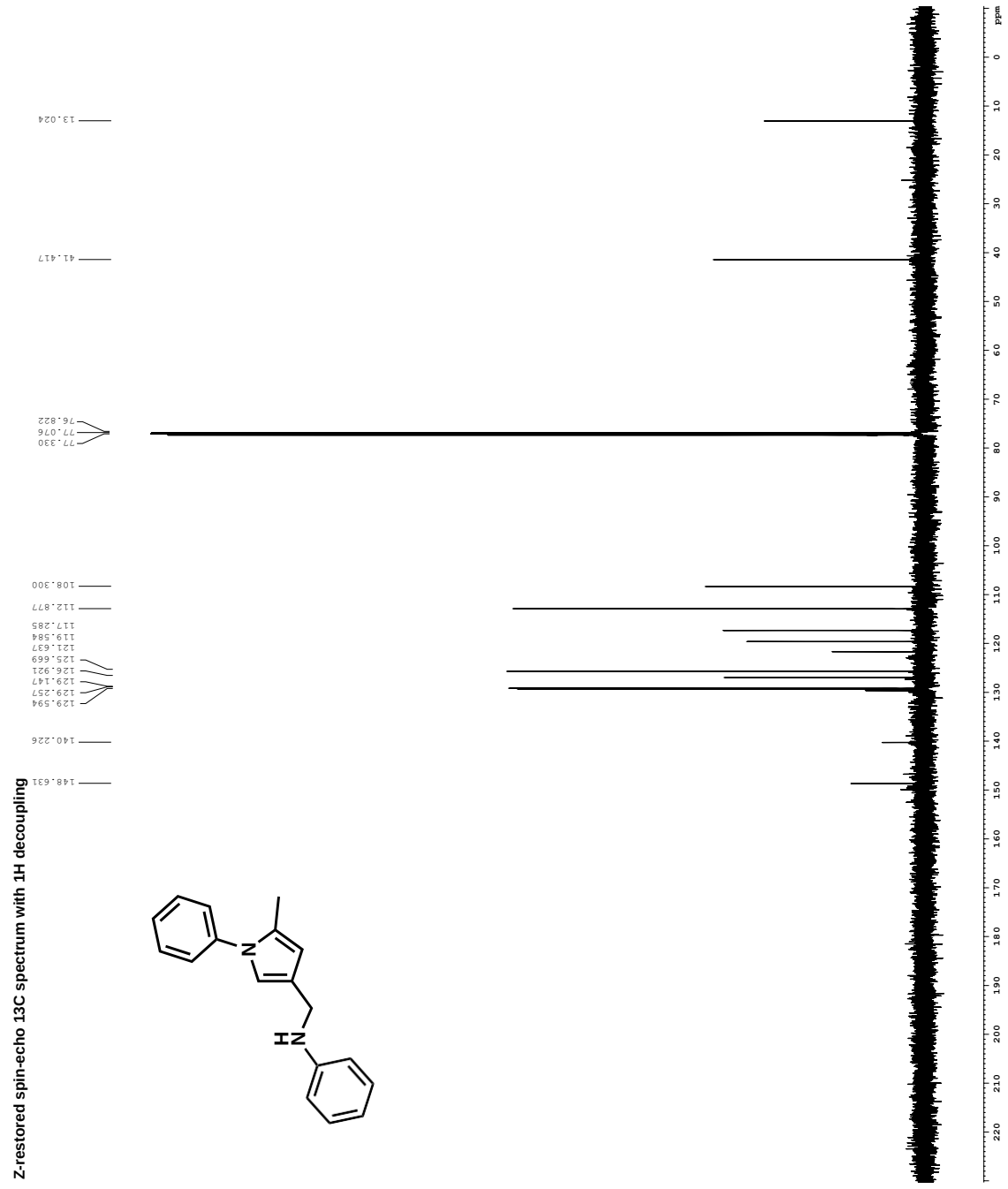
======= CHANNEL f1 =======
NUC1                  13C
P1                  16.55 usec
P11                500.00 usec
P12               2000.00 usec
PL0                 120.00 dB
PL1                  -1.00 dB
SFO1         125.7942548 MHz
SP1                  2.70 dB
SP2                  2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

======= CHANNEL f2 =======
CPDPRG[2          waltz16
NUC2                  1H
PCPD2              100.00 usec
PL2                  1.60 dB
PL12                24.50 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1                30.00 %
GPZ2                50.00 %
p15               500.00 usec
p16              1000.00 usec

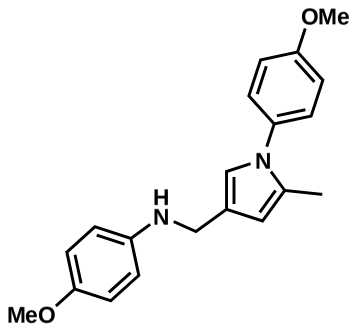
F2 - Processing parameters
SI                  65536
SF           125.7804272 MHz
WDW                    EM
SSB       0
LB                   1.00 Hz
GB        0
PC                   2.00
```


1H spectrum
Current Data Parameters
NAME AWK-III-Lip1
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160822
Time 18.05
INSTRUM spect
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 48074
SOLVENT CDCl3
NS 2
DS 2
SWH 8012.820 Hz
FIDRES 0.166677 Hz
AQ 2.9998176 sec
RG 6.3
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200313 MHz
WDW
SSB 0
LB 0.30 Hz
GB
PC 4.00
1.259
1.554
2.204
3.841
4.173
6.069
6.684
6.700
6.713
6.728
6.752
6.755
7.180
7.195
7.197
7.212
7.260
7.283
7.298
7.300
7.324
7.339
7.353
7.420
7.436
7.451
2.026
3.030
1.991
0.979
2.943
0.974
2.000
0.915
3.042
1.288
ppm



Z-restored spin-echo 13C spectrum with 1H decoupling

1H spectrum

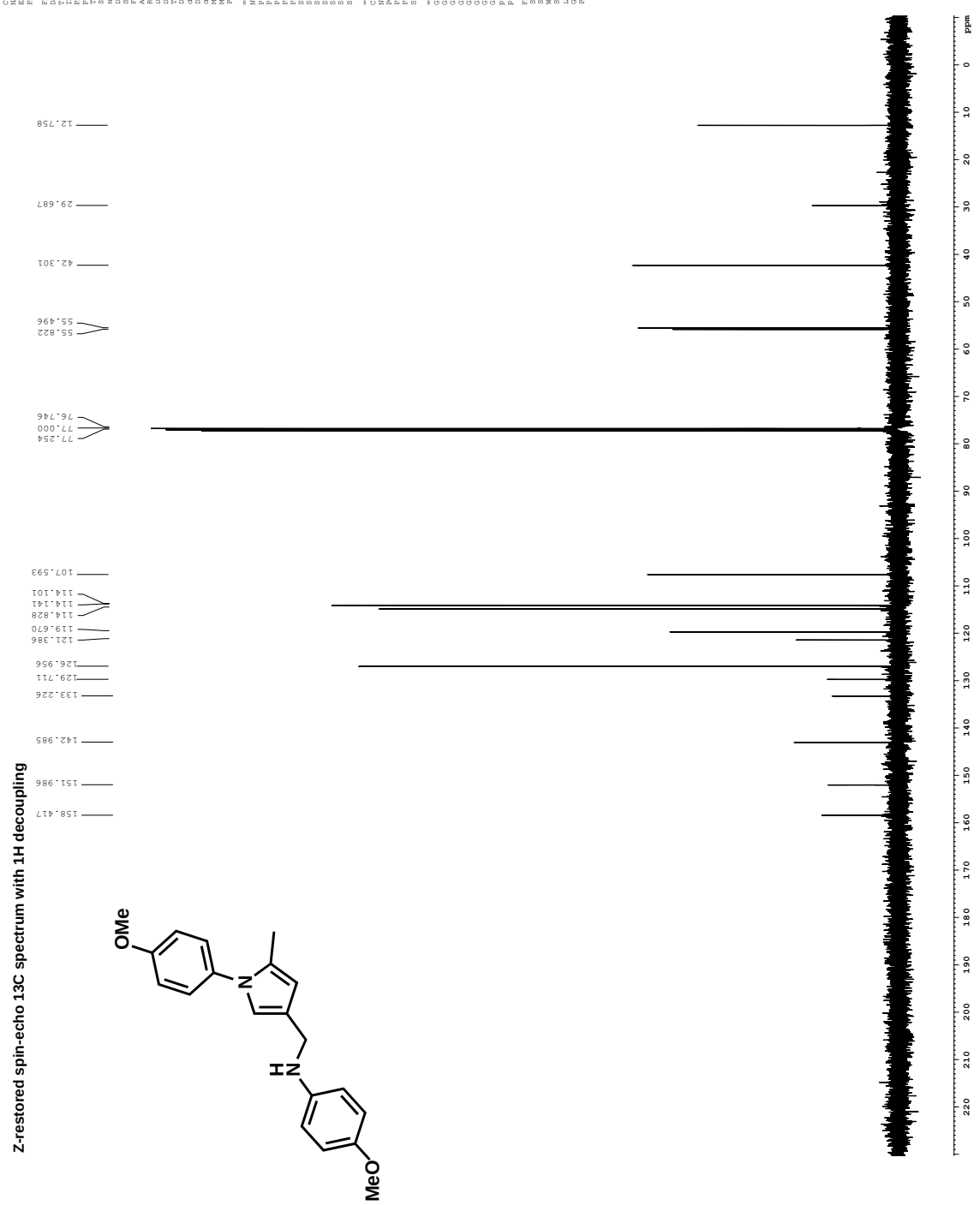


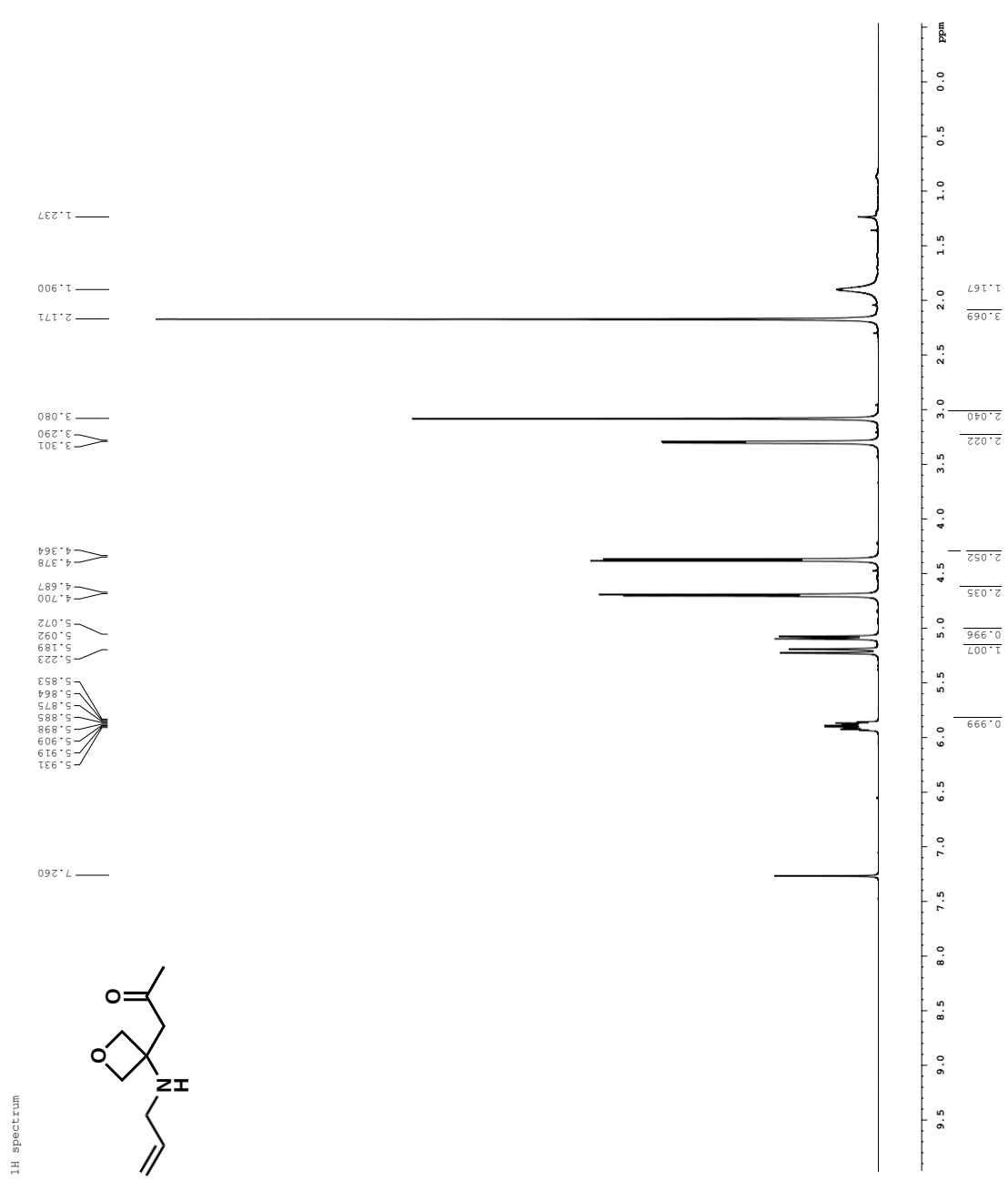

```
Current Data Parameters
NAME          ARW-III-155
EXPNO                   1
PROCNO                  1

F2 - Acquisition Parameters
Date_           20161018
Time              17.52
INSTRUM          cryo500
PROBHD 5  mm  CPTCI  1H-
PULPROG             zg30
TD                 48074
SOLVENT            CDCl3
NS                    25
DS                     2
SWH            8012.820  Hz
FIDRES            0.166677  Hz
AQ             2.9998176  sec
RG                   5.7
DW                62.400  usec
DE                 6.00  usec
TE                298.0  K
D1             0.10000000  sec
MCREST 0 sec
MCWRK          0.01500000  sec

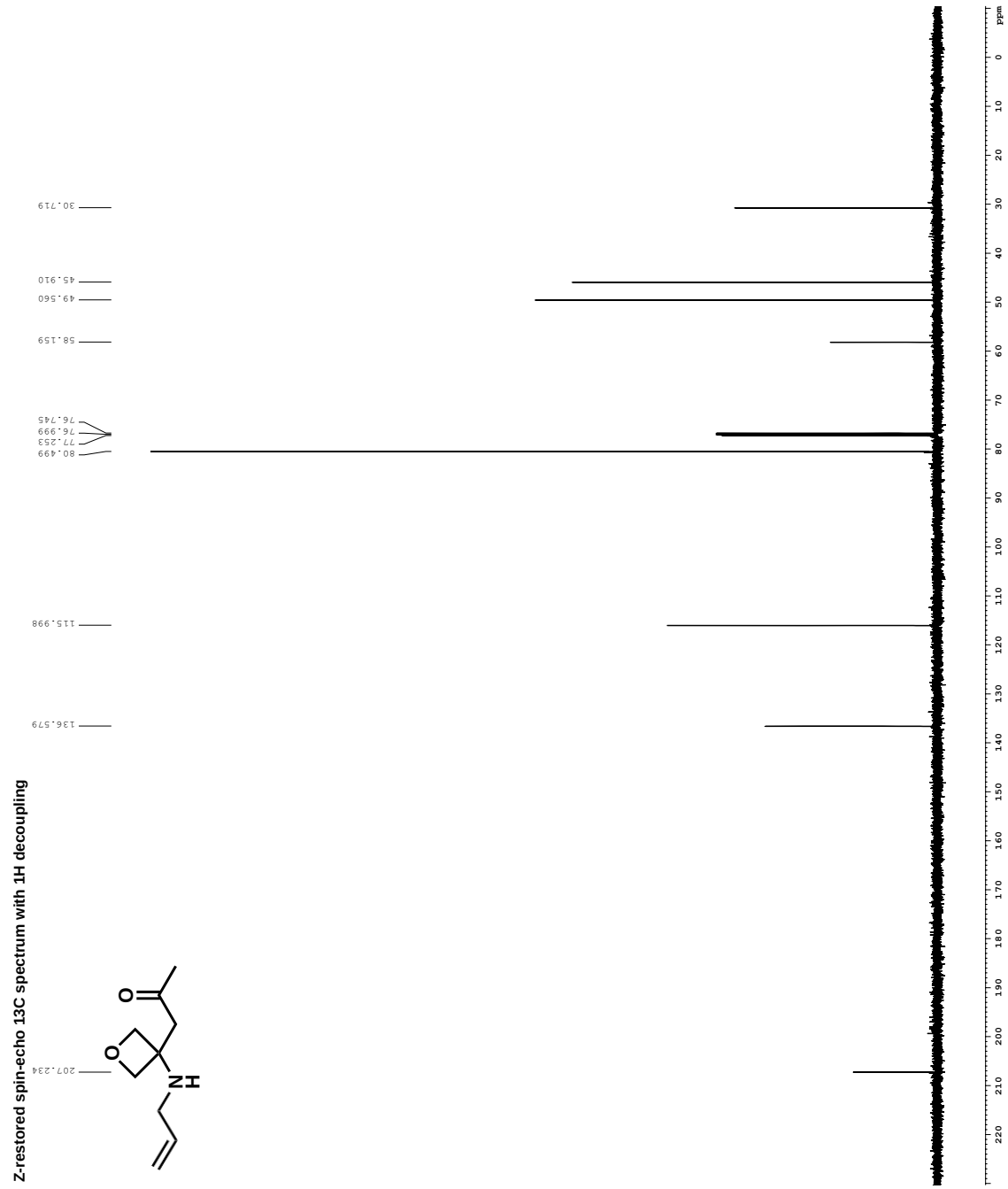
======== CHANNEL f1 ========
NUC1                   1H
P1                  7.50  usec
PL1                 1.60  dB
SFO1          500.2235015  MHz

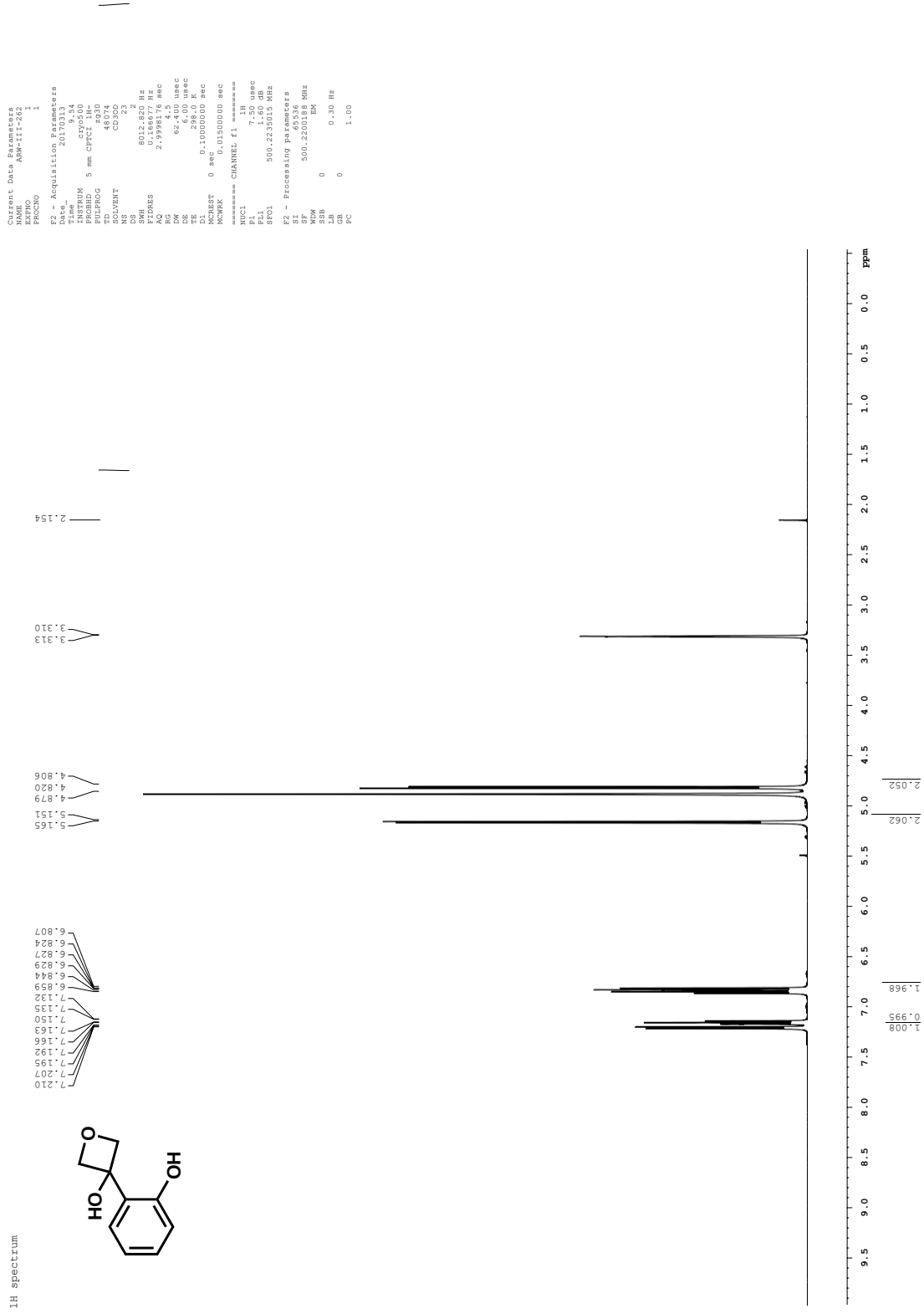
F2 - Processing parameters
SI                  65536
SF            500.2200304  MHz
WDW                    EM
SSB       0
LB                  0.30  Hz
GB        0
PC                  4.00
```


Z-restored spin-echo 13C spectrum with 1H decoupling
OMe
MeO
N
H
158.417
151.986
142.985
133.226
129.711
126.956
121.386
119.670
114.828
114.141
114.101
107.593
77.254
77.000
76.746
55.822
55.496
42.301
29.687
12.758
ppm

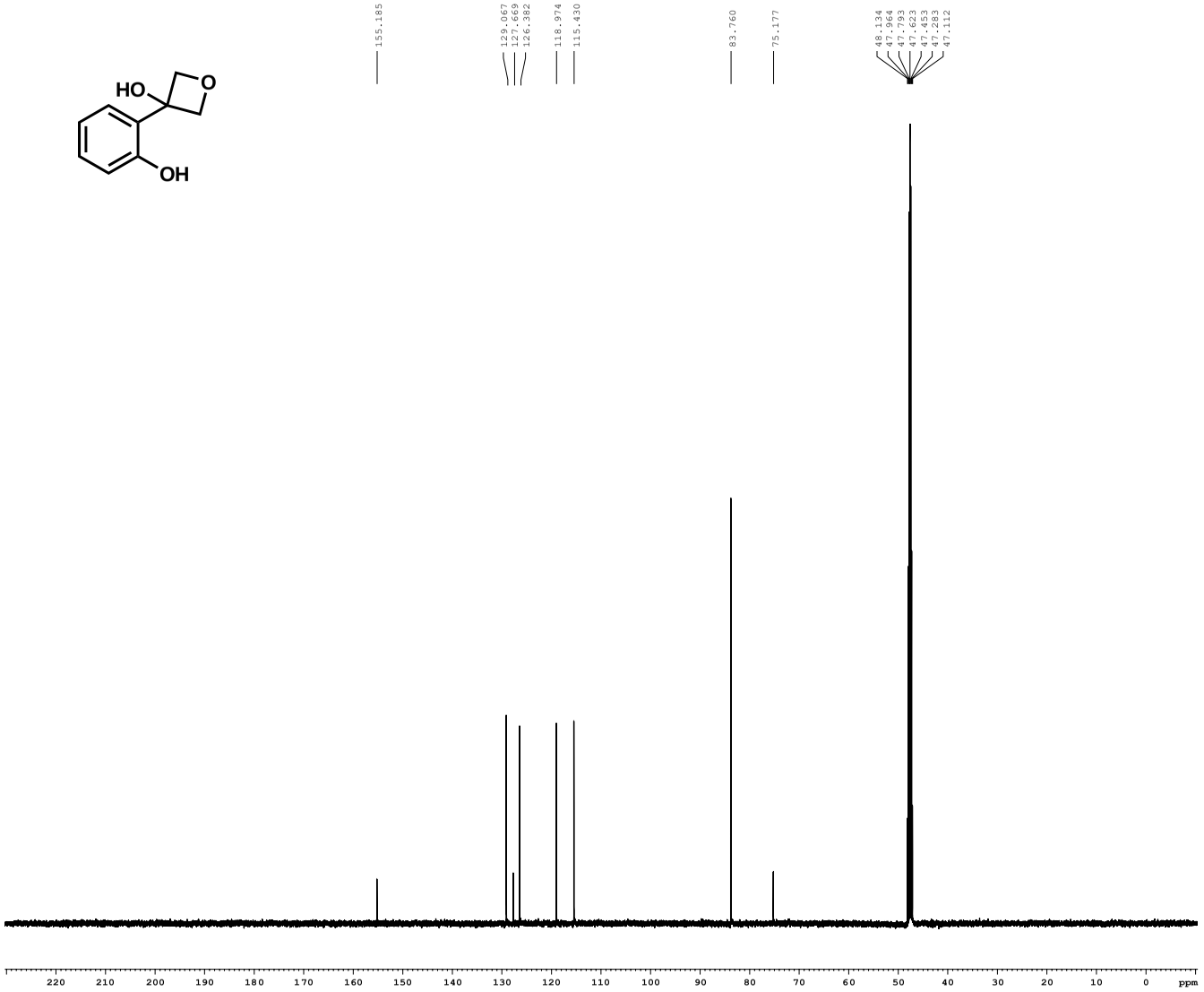

Current Data Parameters
NAME AM-II-260
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170309
Time 20.24
INSTRUM cryo500
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 48074
SOLVENT CDCl3
NS 1
DS 2
SWH 8012.820 Hz
FIDRES 0.166677 Hz
AQ 2.9998176 sec
RG 5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200315 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB
PC 1.00
1H spectrum
7.260
5.931
5.919
5.909
5.898
5.885
5.875
5.864
5.853
5.223
5.189
5.092
5.072
4.700
4.687
4.378
4.364
3.301
3.290
3.080
2.171
1.900
1.237
0.999
1.007
0.996
2.035
2.052
2.022
2.040
3.069
1.167
ppm

Z-restored spin-echo 13C spectrum with 1H decoupling




Current Data Parameters
NAME AWK1F562
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170313
Time 9.54
INSTRUM spect
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 48074
SOLVENT CDCl3
NS 2
DS 2
SWH 8012.820 Hz
FIDRES 0.166677 Hz
AQ 2.9998176 sec
RG 4.5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200188 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H spectrum
7.210
7.207
7.195
7.192
7.166
7.163
7.150
7.135
7.132
6.859
6.844
6.829
6.827
6.824
6.807
5.165
5.151
4.879
4.820
4.806
3.313
3.310
2.154
2.062
2.052
1.968
1.008
0.995
ppm

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME          ARW-III-262
EXPNO                   2
PROCNO                  1

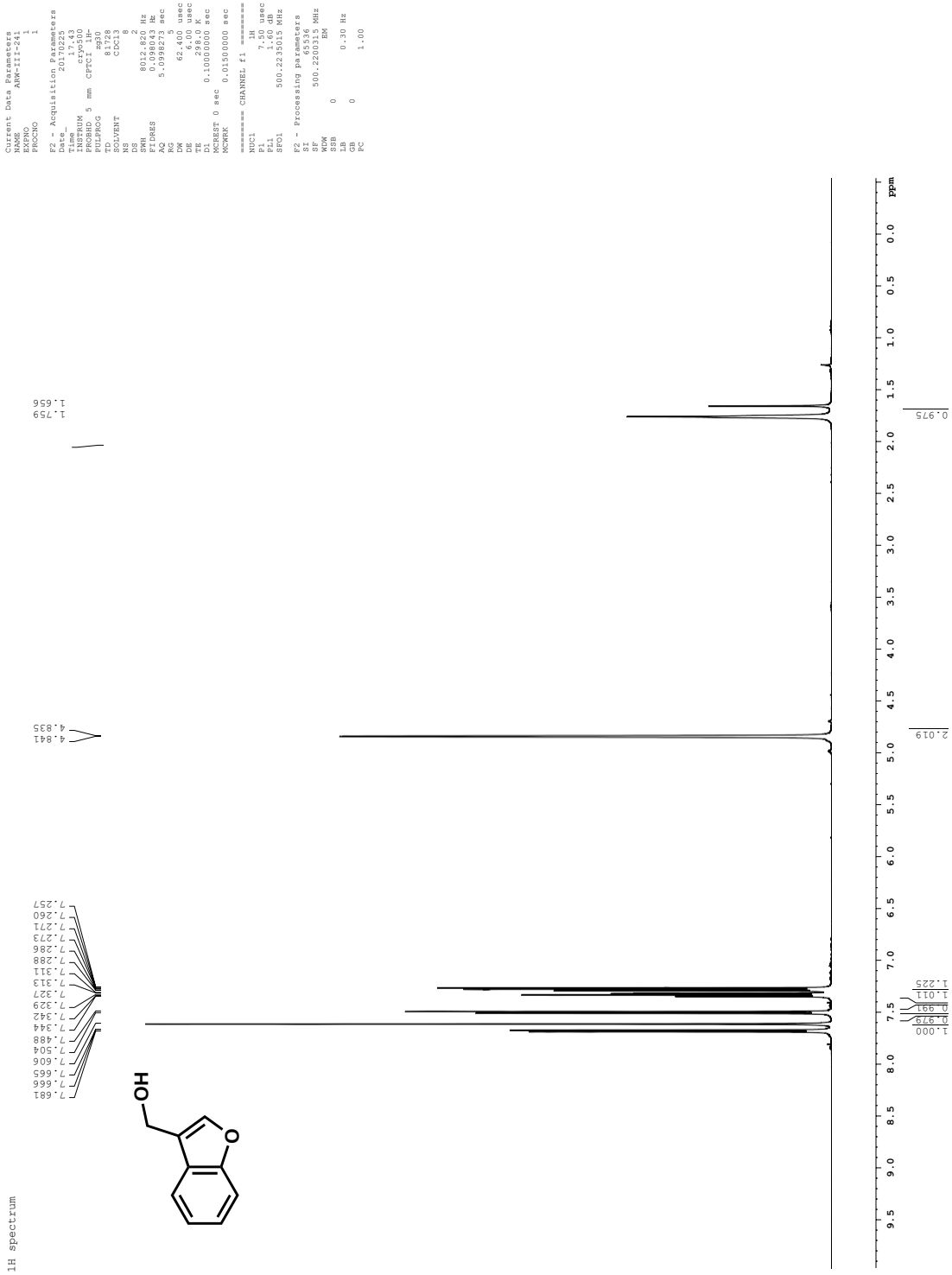
F2 - Acquisition Parameters
Date_           20170313
Time                9.56
INSTRUM          cry500
PROBHD   5 mm CPTCI 1H-
PULPROG  SpinEchopg30gp.prd
TD                 65536
SOLVENT             CDCl3
NS                    120
DS                     16
SWH              30303.031 Hz
FIDRES           0.462388 Hz
AQ               1.0813440 sec
RG                  6502
DW                16.500 usec
DE                 6.00 usec
TE                298.0 K
D1             0.25000000 sec
d11            0.03000000 sec
D16            0.00020000 sec
d17            0.00019600 sec
MCREST    0 sec
MCWRK          0.01500000 sec
P2                33.10 usec

======= CHANNEL f1 ========
NUC1                  1C
P1                 16.55 usec
P11               500.00 usec
P12              2000.00 usec
PL0               120.00 dB
PL1                -1.00 dB
SFO1         125.7942548 MHz
SP1                2.70 dB
SP2                2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2    0 Hz

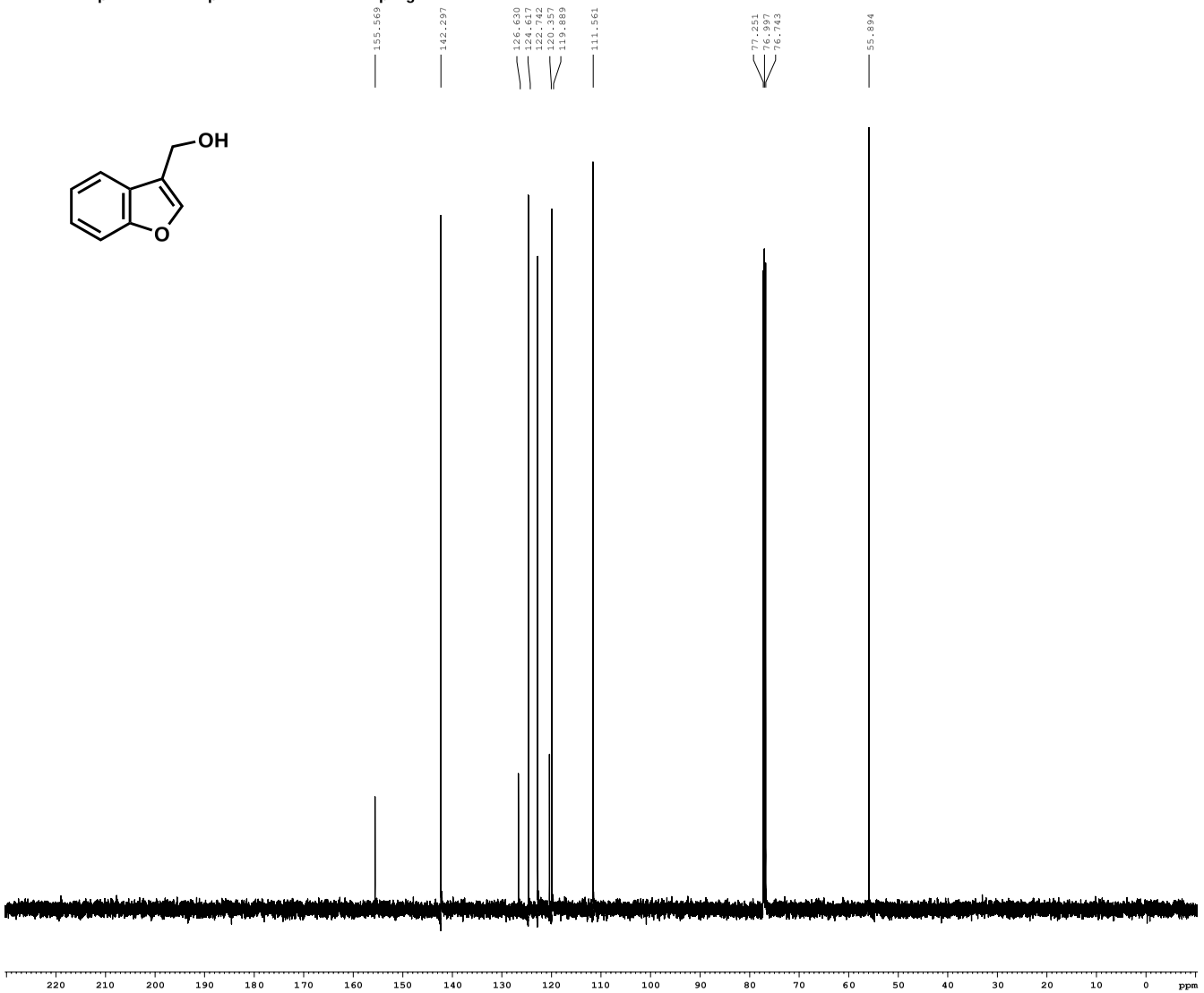
======= CHANNEL f2 ========
CPDPRG[2          waltz16
NUC2                  1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12              24.50 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1              30.00 %
GPZ2              50.00 %
p15              500.00 usec
p16             1000.00 usec

F2 - Processing parameters
SI                 65536
SF           125.7804190 MHz
WDW                   EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 2.00
```


Current Data Parameters
NAME AWK-II-241
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170225
Time 17.43
INSTRUM spect
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 2
DS 2
SWH 8012.820 Hz
FIDRES 0.098043 Hz
AQ 5.0998273 sec
RG 5
DW 62.400 usec
DE 64.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200315 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H spectrum
ppm
OH
O

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME          ARW-III-241
EXPNO                   2
PROCNO                  1

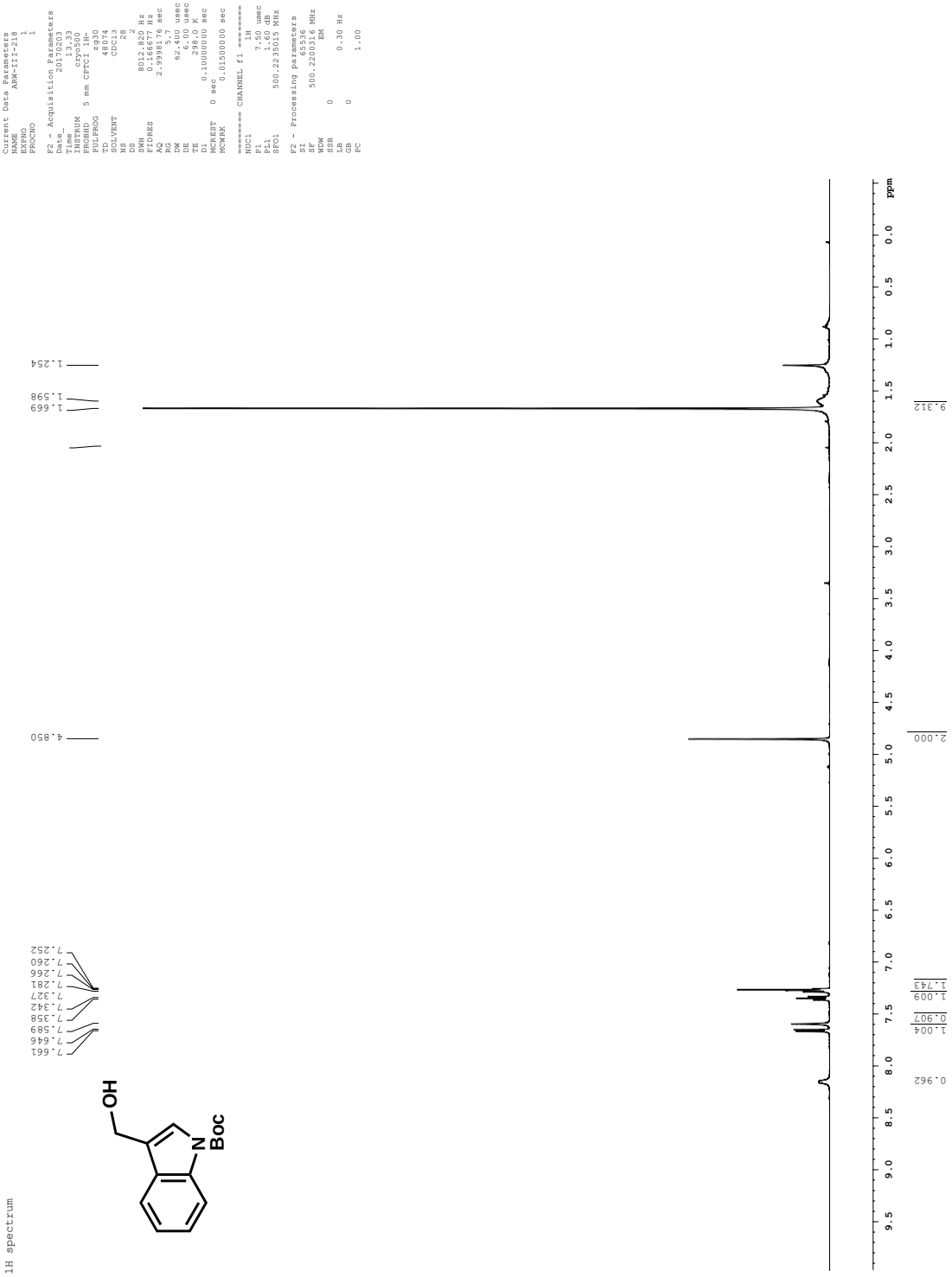
F2 - Acquisition Parameters
Date_           20170225
Time              17.45
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD                65536
SOLVENT           CDCl3
NS                   96
DS                   16
SWH           30303.031 Hz
FIDRES        0.462388 Hz
AQ            1.0813440 sec
RG                 3251
DW               16.500 usec
DE                6.00 usec
TE              298.0 K
D1            0.25000000 sec
d11           0.03000000 sec
D16           0.00020000 sec
d17           0.00019600 sec
MCREST 0 sec
MCWRK         0.01500000 sec
P2               33.10 usec

======= CHANNEL f1 =======
NUC1                13C
P1                16.55 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1         125.7942548 MHz
SP1               2.70 dB
SP2               2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

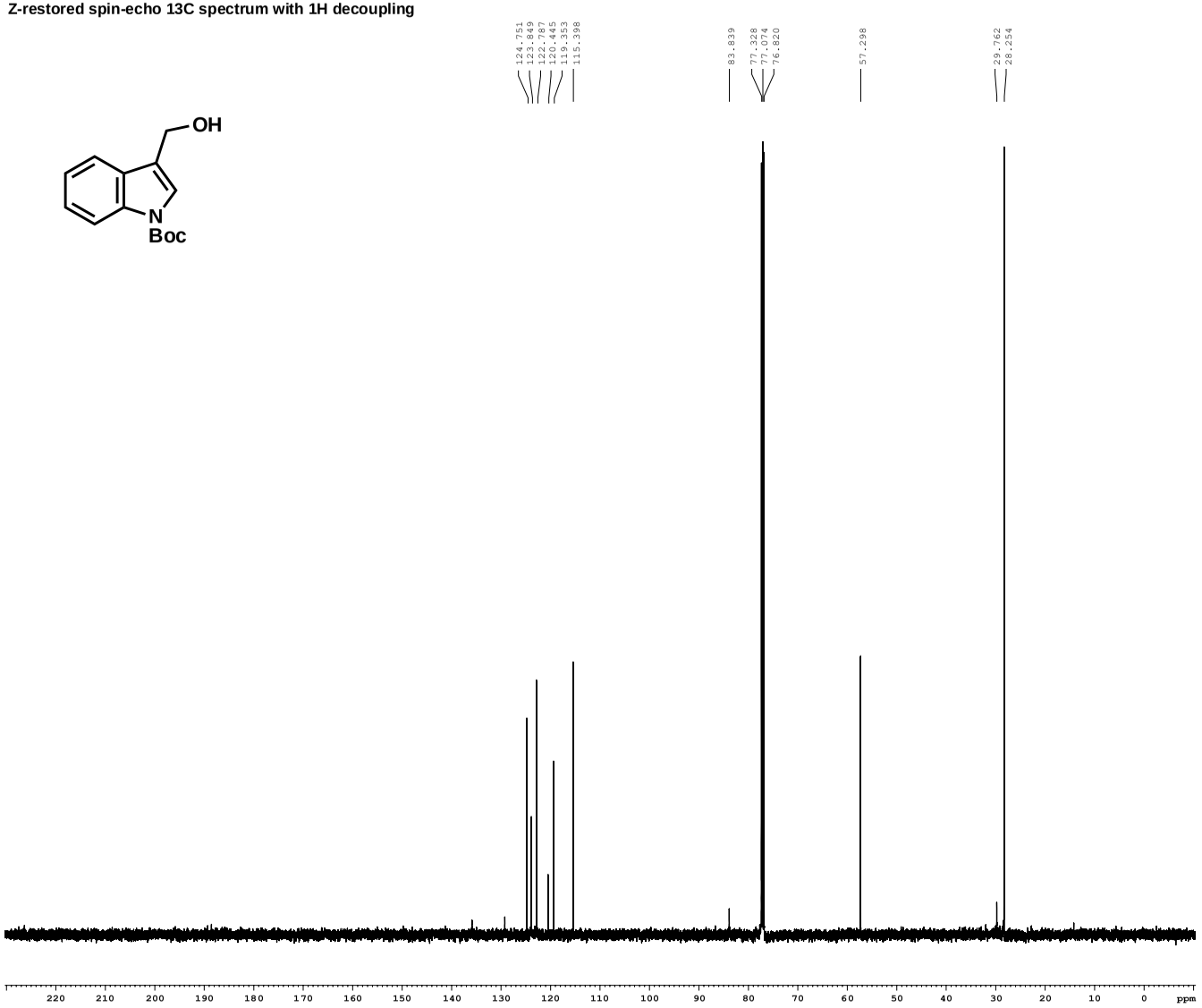
======= CHANNEL f2 =======
CPDPRG[2          waltz16
NUC2                 1H
PCPD2             100.00 usec
PL2                1.60 dB
PL12              24.50 dB
SFO2         500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]        SINE.100
GPNAM[2]        SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1             30.00 %
GPZ2             50.00 %
p15             500.00 usec
p16            1000.00 usec

F2 - Processing parameters
SI                  65536
SF           125.7804314 MHz
WDW                    EM
SSB       0
LB                 1.00 Hz
GB        0
PC                 2.00
```


1H spectrum
Current Data Parameters
NAME AWK-IT-218
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170203
Time 13.33
INSTRUM spect600
PROBHD 5 mm CPTCI 1H
PULPROG zg30
TD 48074
SOLVENT CDCl3
NS 2
DS 2
SWH 8012.820 Hz
FIDRES 0.166677 Hz
AQ 2.9998176 sec
RG 5.7
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200316 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB
PC 1.00
1.254
1.598
1.669
4.850
7.252
7.260
7.266
7.281
7.327
7.342
7.358
7.589
7.646
7.661
OH
N
Boc
0.962
1.004
0.907
1.009
1.743
2.000
9.312
ppm

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME          ARW-III-218
EXPNO                   2
PROCNO                  1

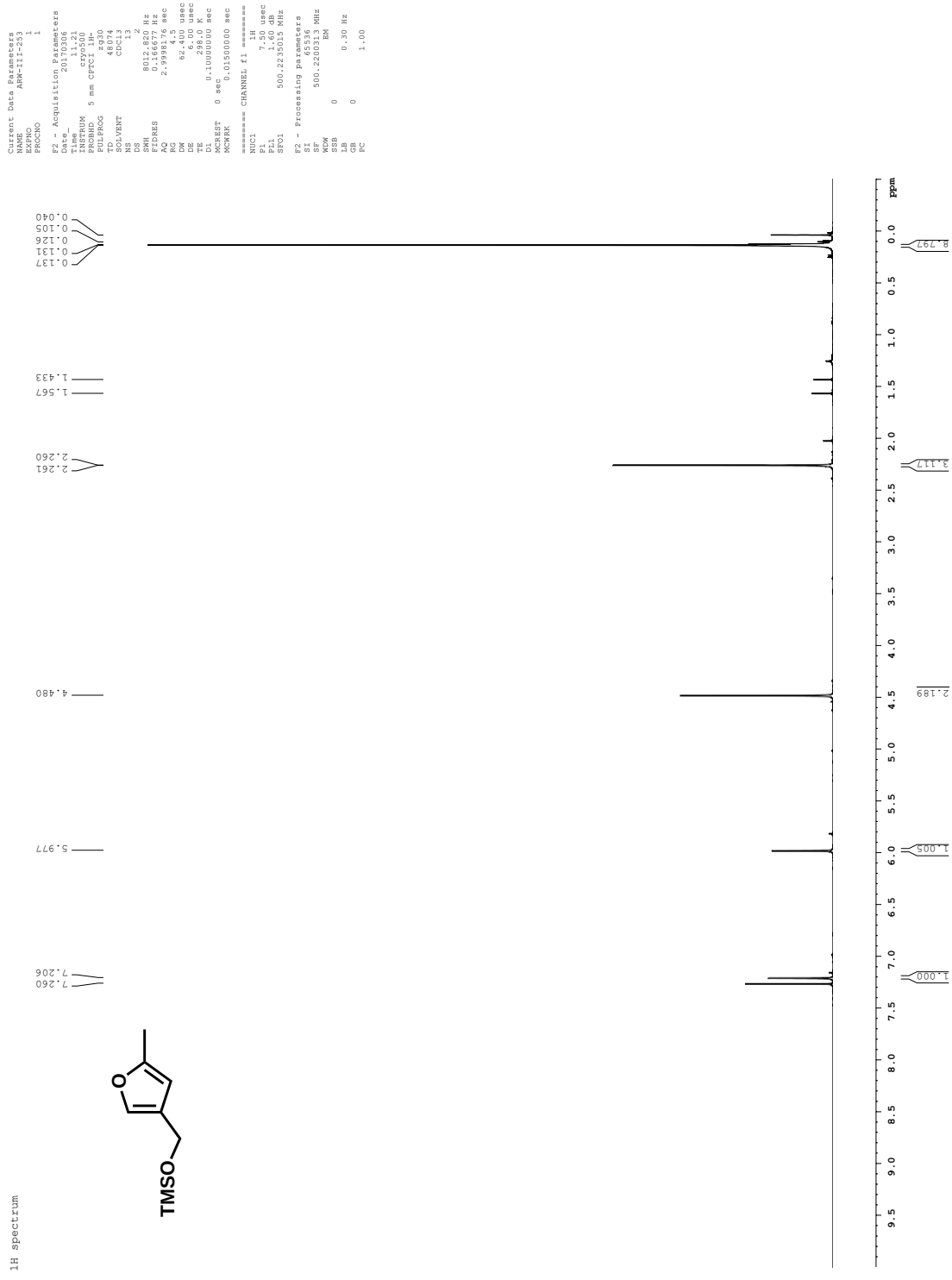
F2 - Acquisition Parameters
Date_           20170203
Time              13.39
INSTRUM          cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD                65536
SOLVENT             CDCl3
NS                    632
DS                     16
SWH            30303.031 Hz
FIDRES         0.462388 Hz
AQ             1.081344U sec
RG                3649.1
DW               16.500 usec
DE                6.00 usec
TE                298.0 K
D1             0.25000000 sec
d11            0.03000000 sec
D16            0.00020000 sec
d17            0.00019600 sec
MCREST 0 sec
MCWRK          0.01500000 sec
P2                33.10 usec

======= CHANNEL f1 =======
NUC1                  13C
P1                  16.55 usec
P11                500.00 usec
P12               2000.00 usec
PL0                 120.00 dB
PL1                  -1.00 dB
SFO1          125.7942548 MHz
SP1                  2.70 dB
SP2                  2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

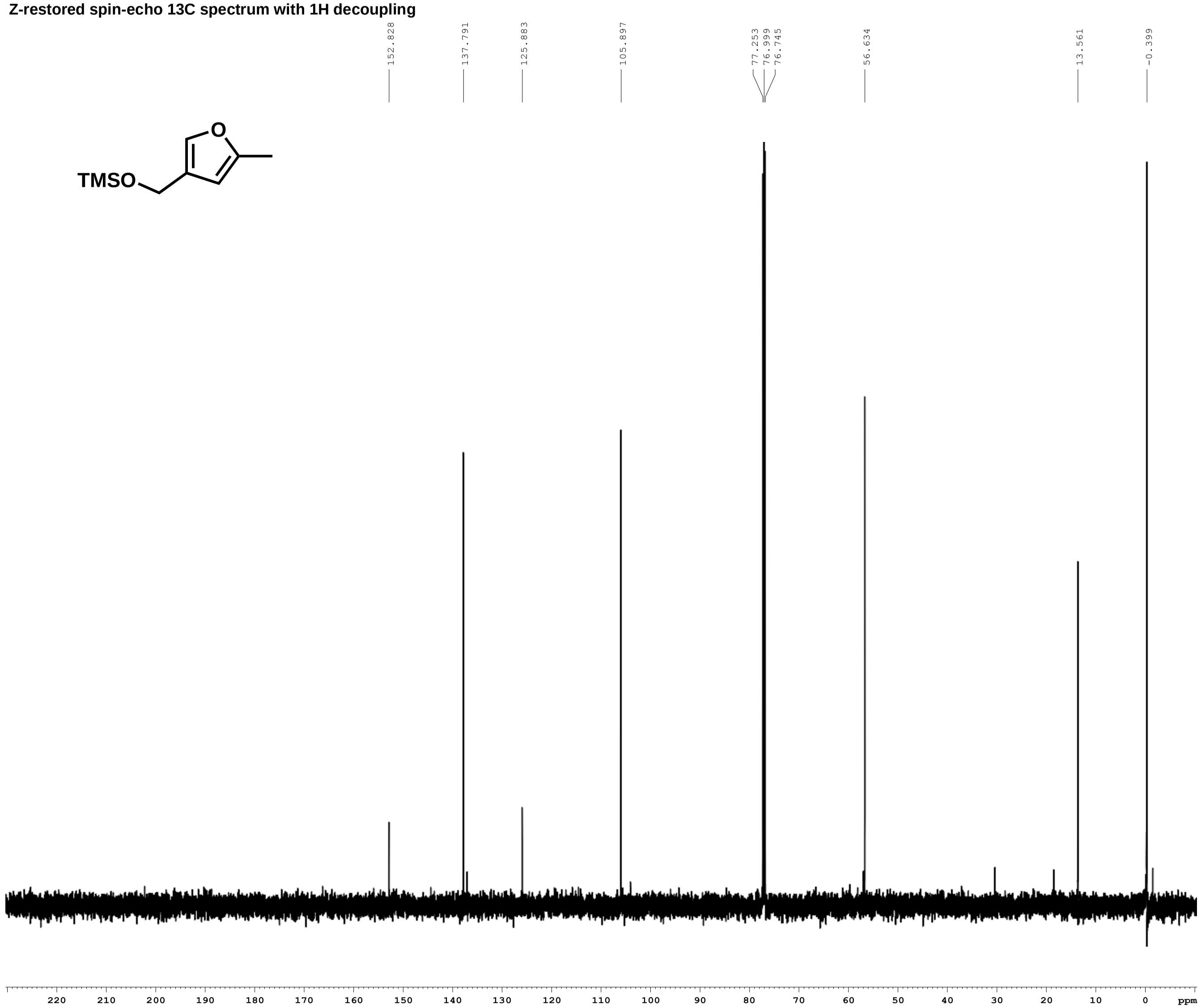
======= CHANNEL f2 =======
CPDPRG[2          waltz16
NUC2                  1H
PCPD2              100.00 usec
PL2                  1.60 dB
PL12                24.50 dB
SFO2          500.2225011 MHz

====== GRADIENT CHANNEL =====
GPNAM[1]         SINE.100
GPNAM[2]         SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1                30.00 %
GPZ2                50.00 %
p15               500.00 usec
p16              1000.00 usec

F2 - Processing parameters
SI                  65536
SF            125.7804190 MHz
WDW                    EM
SSB       0
LB                   1.00 Hz
GB        0
PC                   2.00
```


Current Data Parameters
NAME AWK1F255
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20170306
Time 11.21
INSTRUM spect600
PROBHD 5 mm CPTCI 1H-
PULPROG zg30
TD 48074
SOLVENT CDCl3
NS 2
DS 2
SWH 8012.820 Hz
FIDRES 0.166677 Hz
AQ 2.9998176 sec
RG 4.5
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 7.50 usec
PL1 1.60 dB
SFO1 500.2235015 MHz
F2 - Processing parameters
SI 65536
SF 500.2200313 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB
PC 1.00
TMSO
1H spectrum
ppm
0.040
0.105
0.126
0.131
0.137
1.433
1.567
2.260
2.261
4.480
5.977
7.206
7.260
8.797
3.117
2.189
1.005
1.000

Z-restored spin-echo 13C spectrum with 1H decoupling




```
Current Data Parameters
NAME        ARW-III-253
EXPNO                 2
PROCNO                1

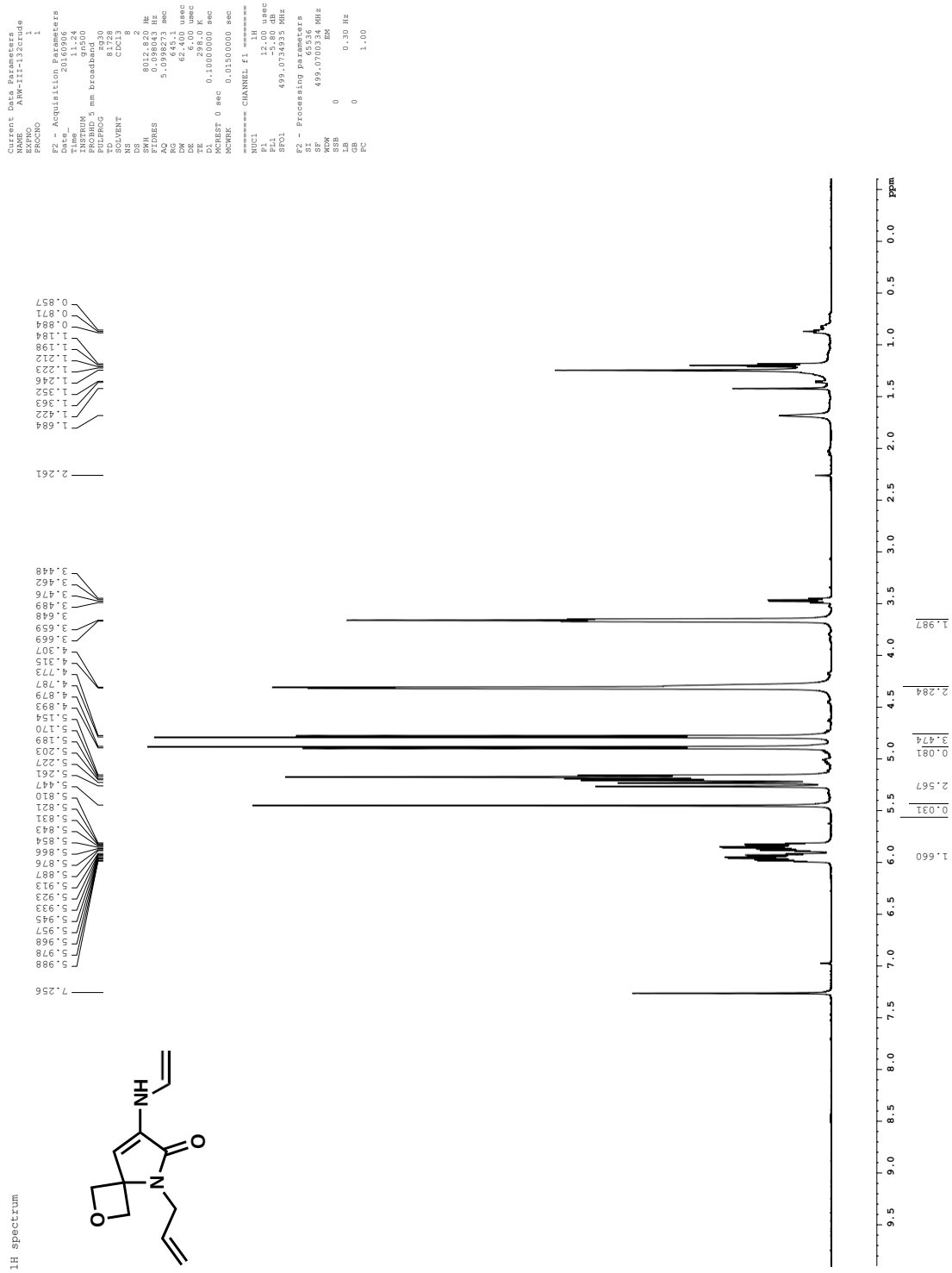
F2 - Acquisition Parameters
Date_          20170306
Time              11.25
INSTRUM         cryo500
PROBHD   5 mm CPTCI 1H-
PULPROG SpinEchopg30gp.prd
TD                65536
SOLVENT           CDCl3
NS                  120
DS                   16
SWH           30303.031 Hz
FIDRES         0.462388 Hz
AQ            1.0813440 sec
RG                 3251
DW               16.500 usec
DE                 6.00 usec
TE                298.0 K
D1           0.25000000 sec
d11          0.03000000 sec
D16          0.00020000 sec
d17          0.00019600 sec
MCREST 0 sec
MCWRK        0.01500000 sec
P2                33.10 usec

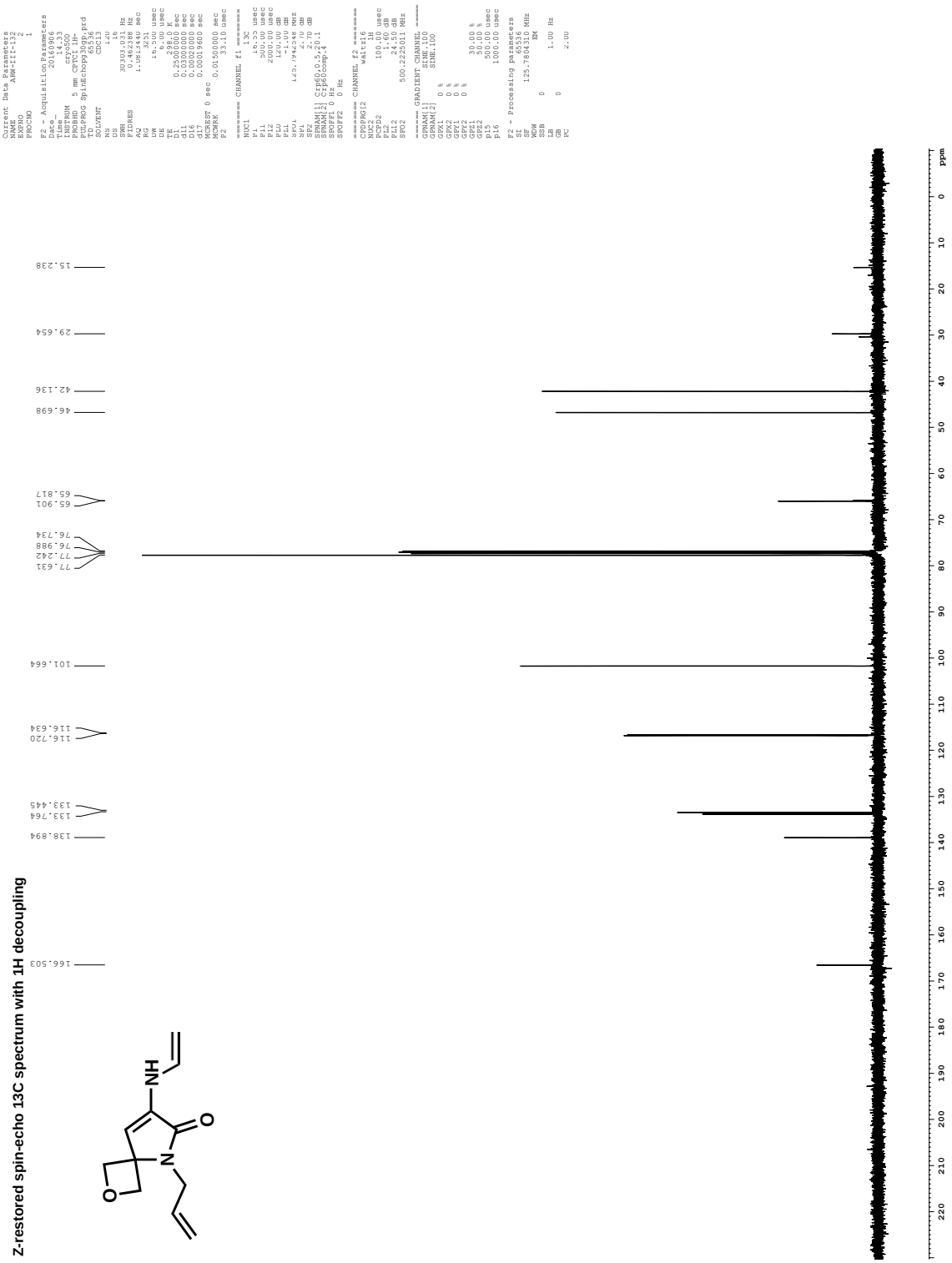
======== CHANNEL f1 ========
NUC1                13C
P1                16.55 usec
P11              500.00 usec
P12             2000.00 usec
PL0              120.00 dB
PL1               -1.00 dB
SFO1        125.7942548 MHz
SP1                2.70 dB
SP2                2.70 dB
SPNAM[1] Crp60,0.5,20.1
SPNAM[2] Crp60comp.4
SPOFF1 0 Hz
SPOFF2   0 Hz

======== CHANNEL f2 ========
CPDPRG[2        waltz16
NUC2                 1H
PCPD2            100.00 usec
PL2                1.60 dB
PL12              24.50 dB
SFO2        500.2225011 MHz

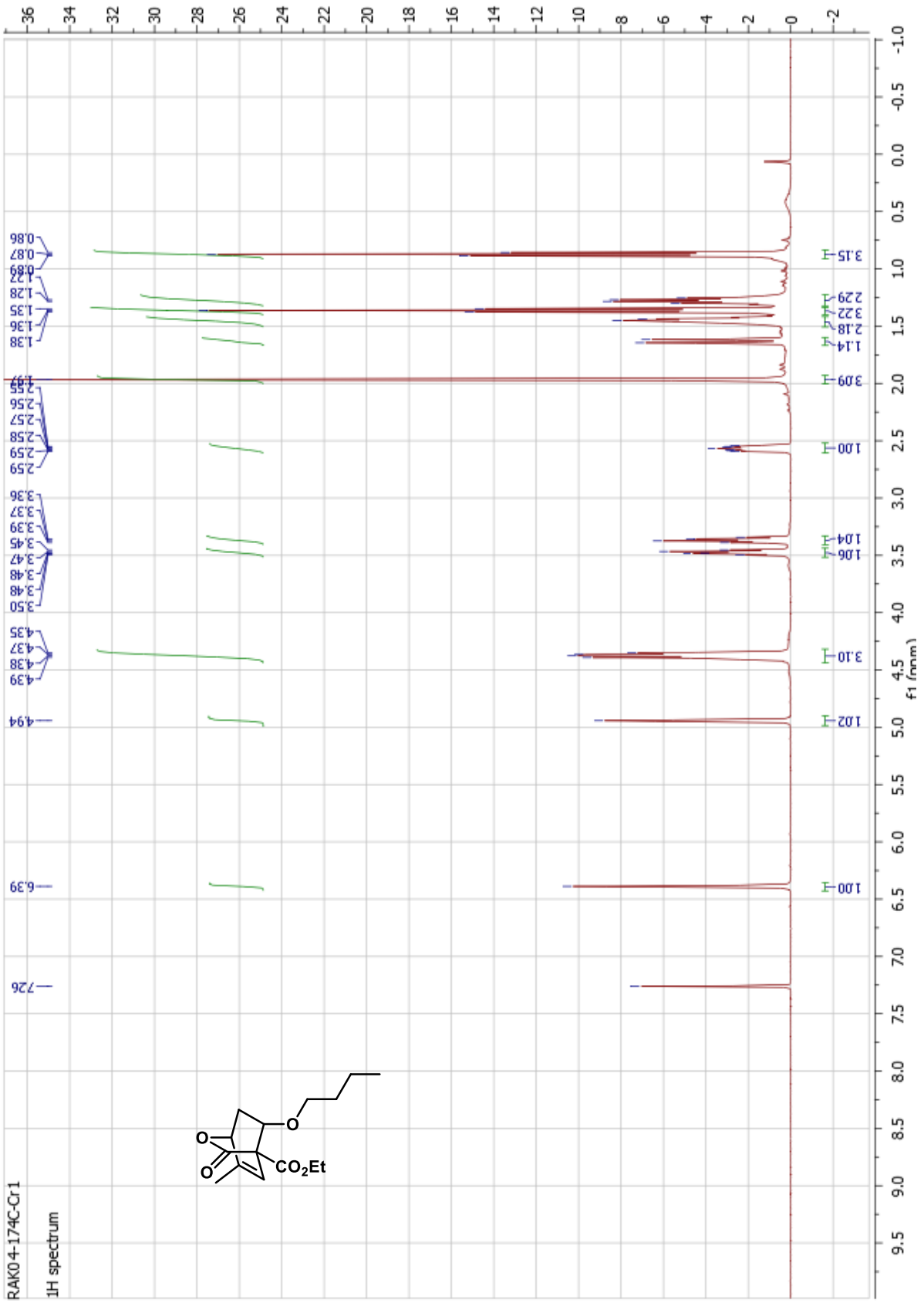
====== GRADIENT CHANNEL =====
GPNAM[1]       SINE.100
GPNAM[2]       SINE.100
GPX1      0 %
GPX2      0 %
GPY1      0 %
GPY2      0 %
GPZ1              30.00 %
GPZ2              50.00 %
p15              500.00 usec
p16             1000.00 usec

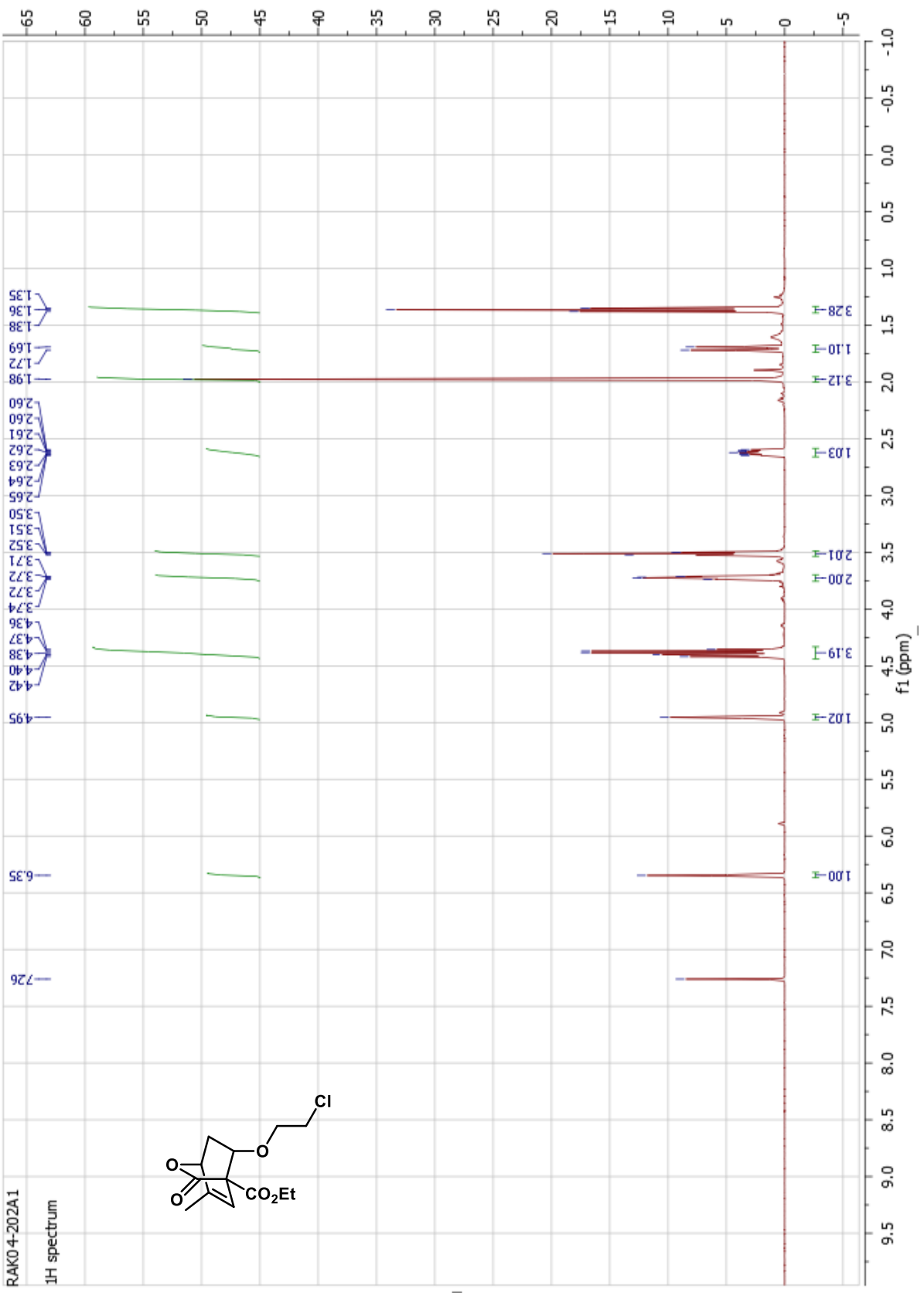
F2 - Processing parameters
SI                65536
SF          125.7804277 MHz
WDW                  EM
SSB      0
LB                 1.00 Hz
GB       0
PC                 2.00
```

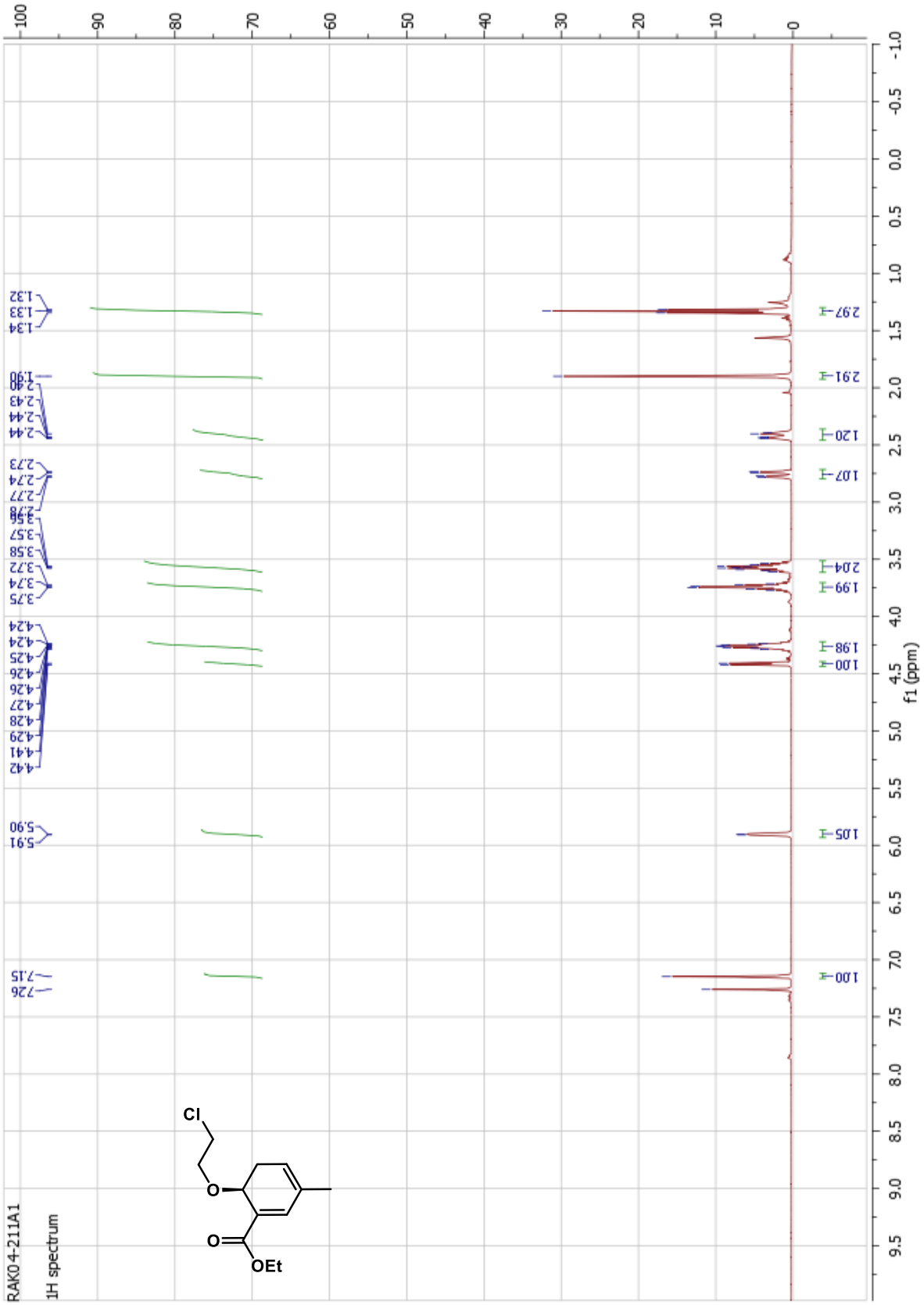

Current Data Parameters
NAME AKW-III-42Oxide
EXPNO 1
PROCNO 1
F2 - Acquisition Parameters
Date_ 20160906
Time 11.24
INSTRUM spect
PROBHD 5 mm broadband
PULPROG zg30
TD 81728
SOLVENT CDCl3
NS 2
DS 2
SWH 8012.820 Hz
FIDRES 0.098067 Hz
AQ 5.0998273 sec
RG 645.1
DW 62.400 usec
DE 6.00 usec
TE 298.0 K
D1 0.10000000 sec
MCREST 0 sec 0.01500000 sec
MCWRK
======== CHANNEL f1 ========
NUC1 1H
P1 12.00 usec
PL1 -2.00 dB
SFO1 499.0734935 MHz
F2 - Processing parameters
SI 65536
SF 499.0700334 MHz
WDW EM
SSB 0
LB 0.30 Hz
GB 0
PC 1.00
1H spectrum
ppm
7.256
5.988
5.978
5.968
5.957
5.945
5.933
5.923
5.913
5.897
5.876
5.866
5.854
5.843
5.831
5.821
5.810
5.447
5.261
5.227
5.203
5.189
5.170
5.154
4.893
4.879
4.787
4.773
4.315
4.307
3.669
3.659
3.648
3.489
3.476
3.462
3.448
2.261
1.684
1.422
1.363
1.352
1.246
1.223
1.212
1.198
1.184
0.884
0.871
0.857
1.660
0.031
2.567
0.081
3.474
2.284
1.987

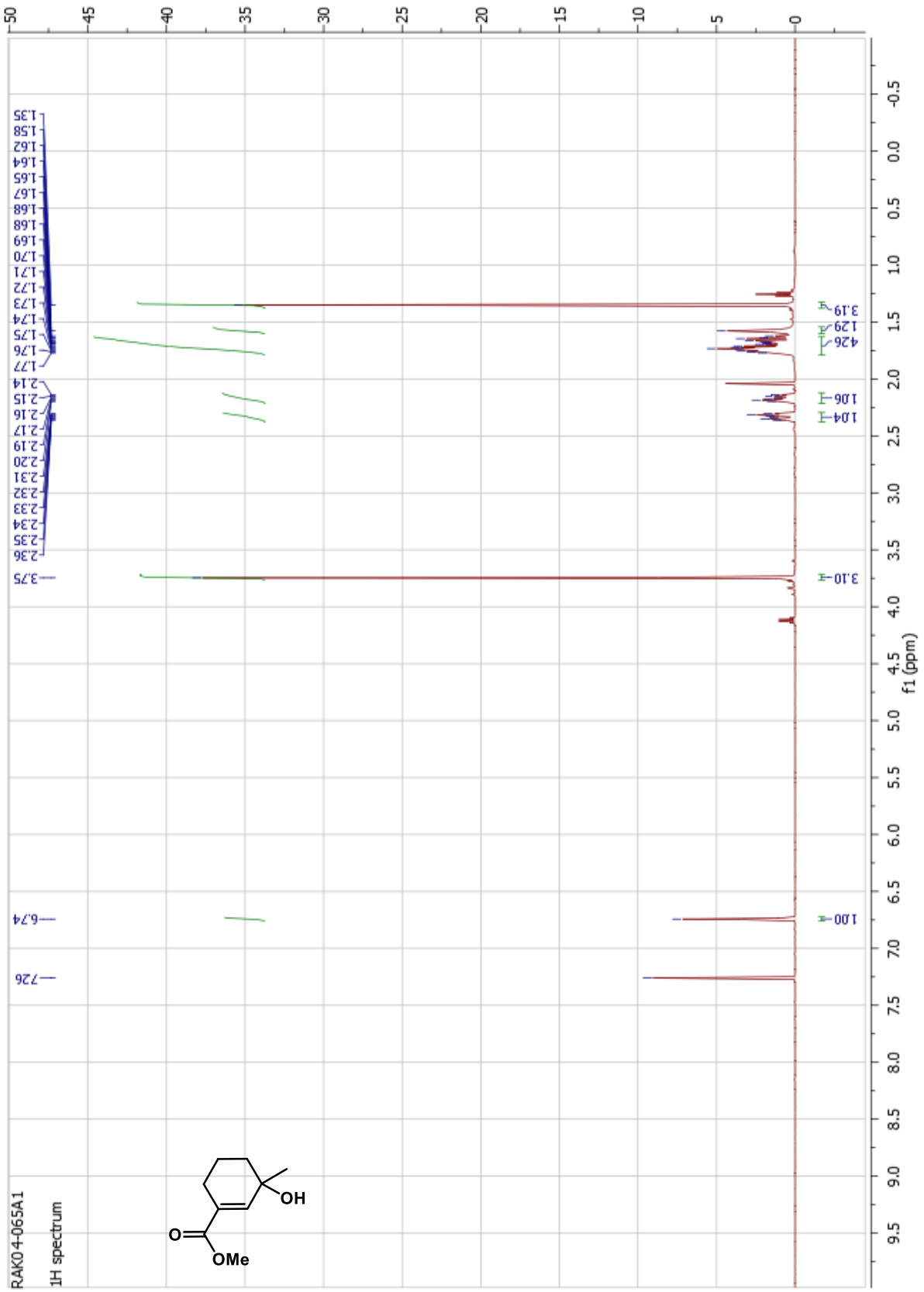

Z-restored spin-echo 13C spectrum with 1H decoupling
166.503
138.894
133.764
133.445
116.720
116.634
101.664
77.631
77.242
76.988
76.734
65.901
65.817
46.698
42.136
29.654
15.238
NH
O
N
O
ppm

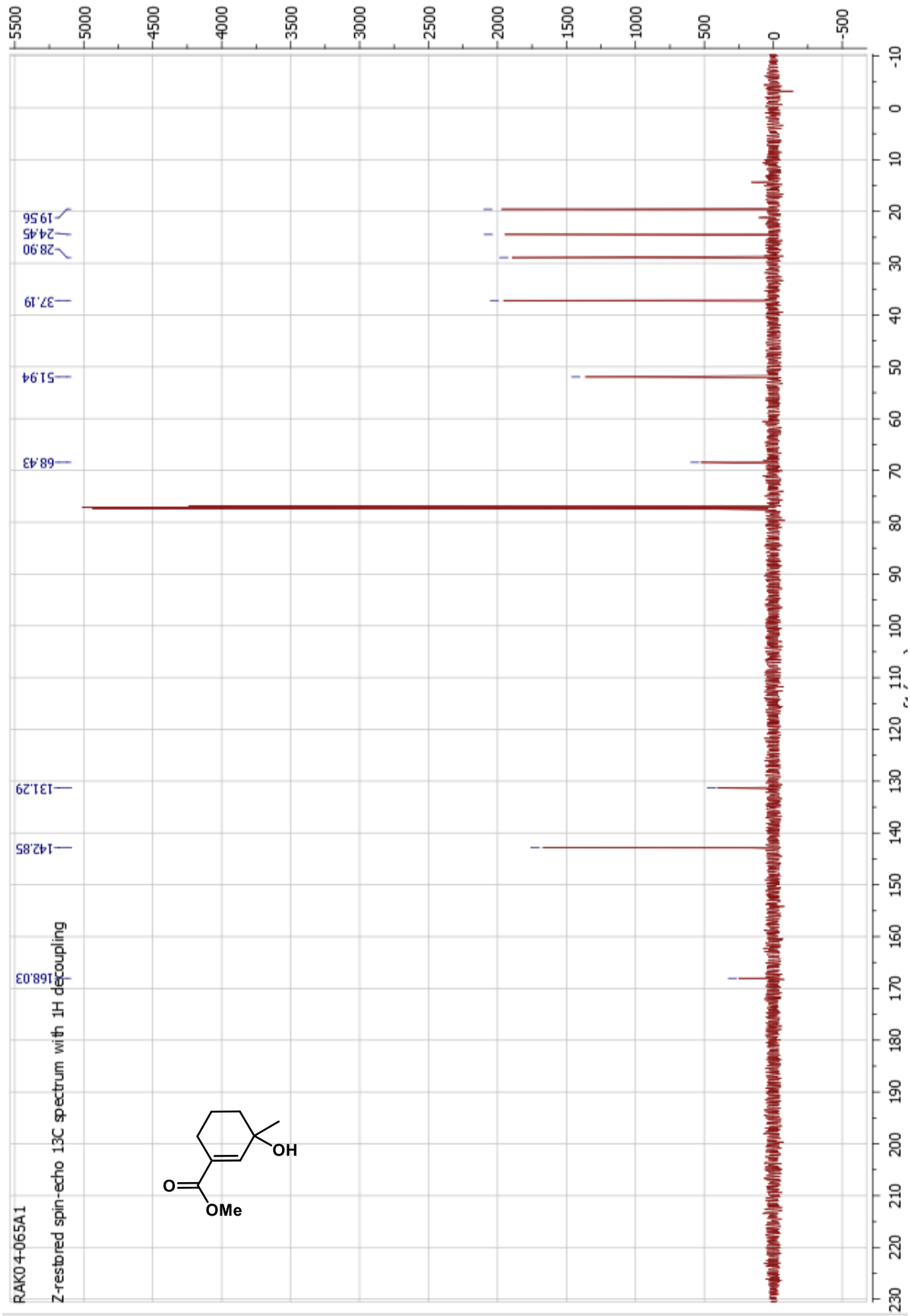
Appendix B: Agarofuran Spectra

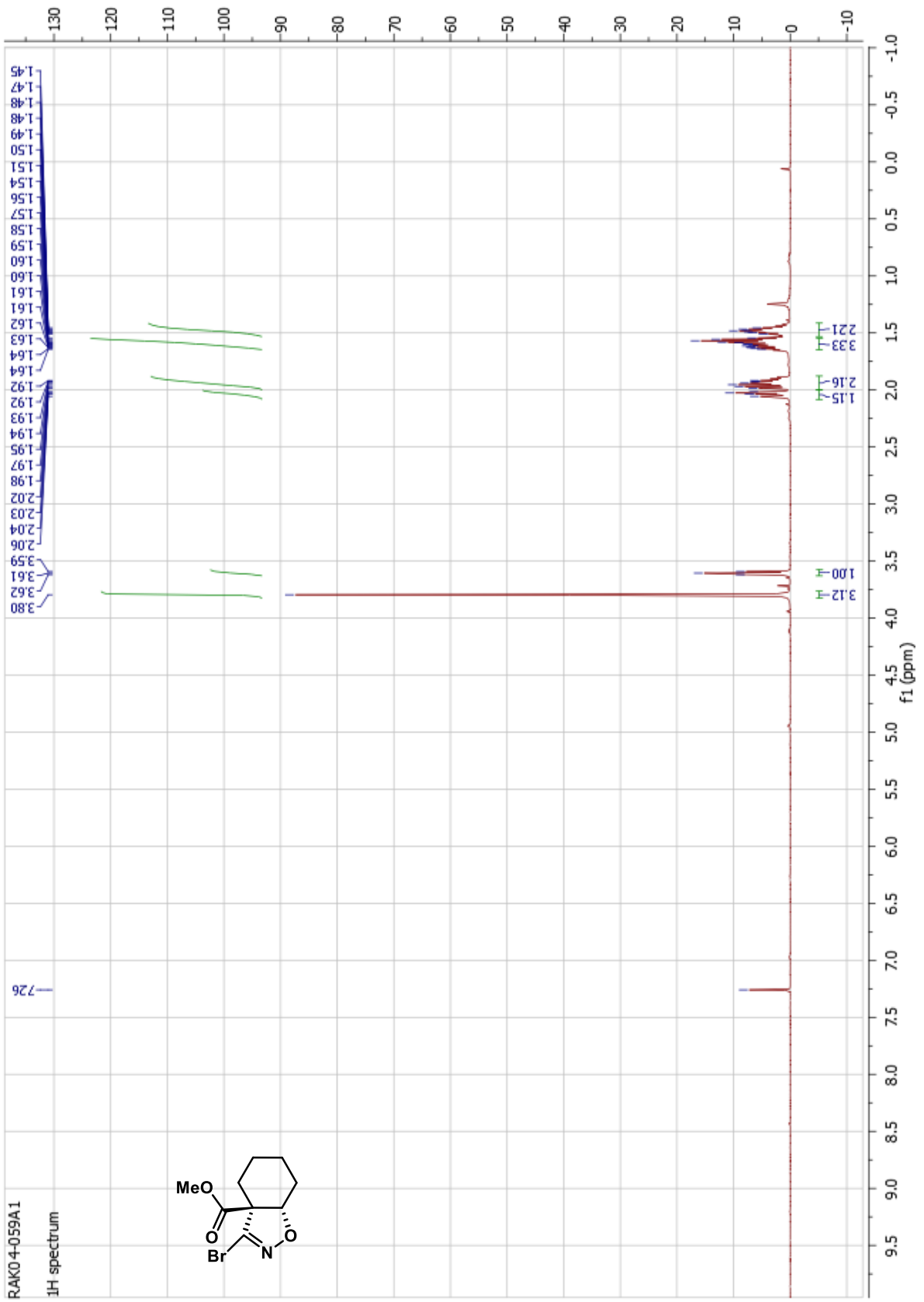


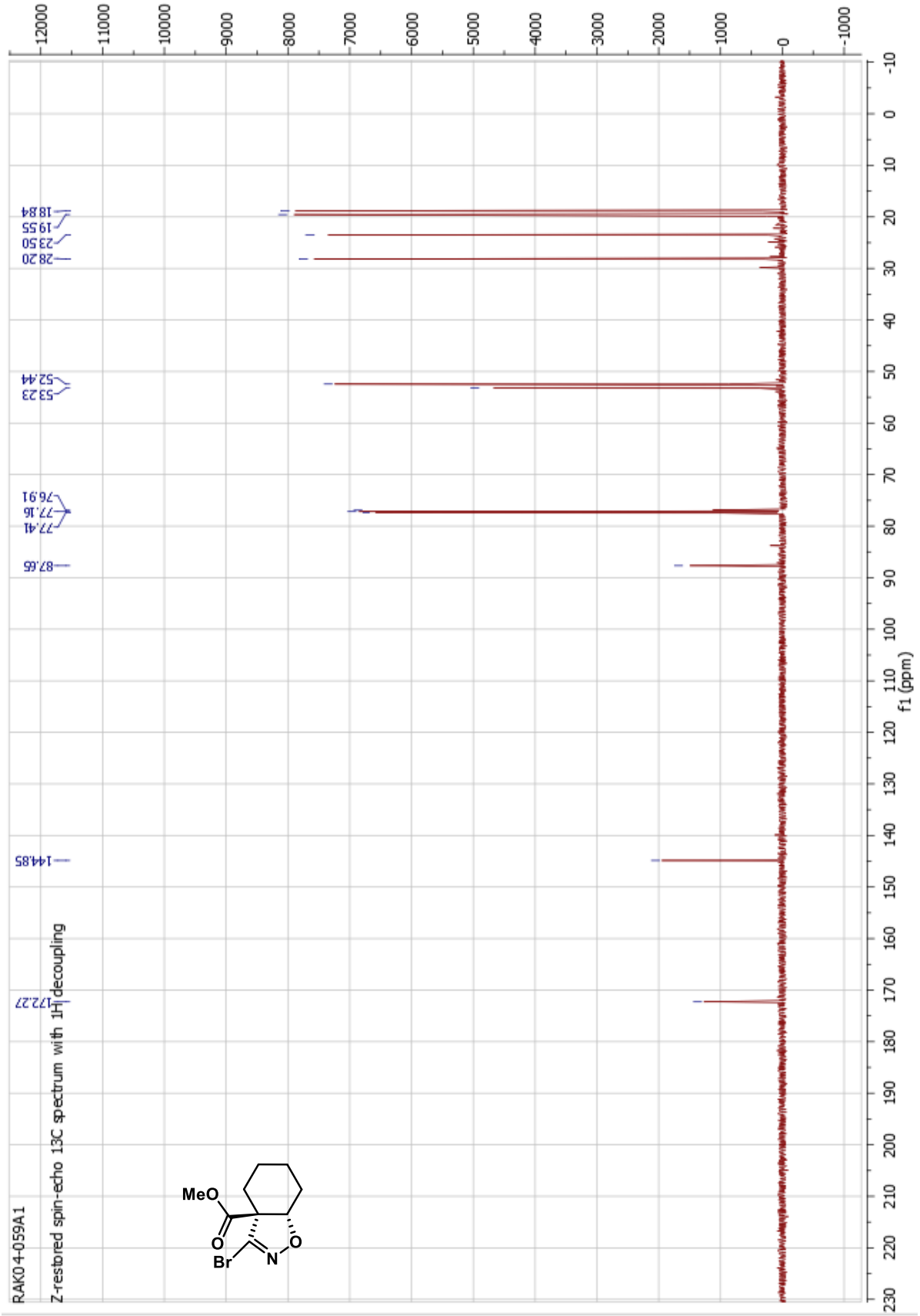

RAK04-202A1
1H spectrum
f1 (ppm)
Cl
O
O
O
O
CO2Et

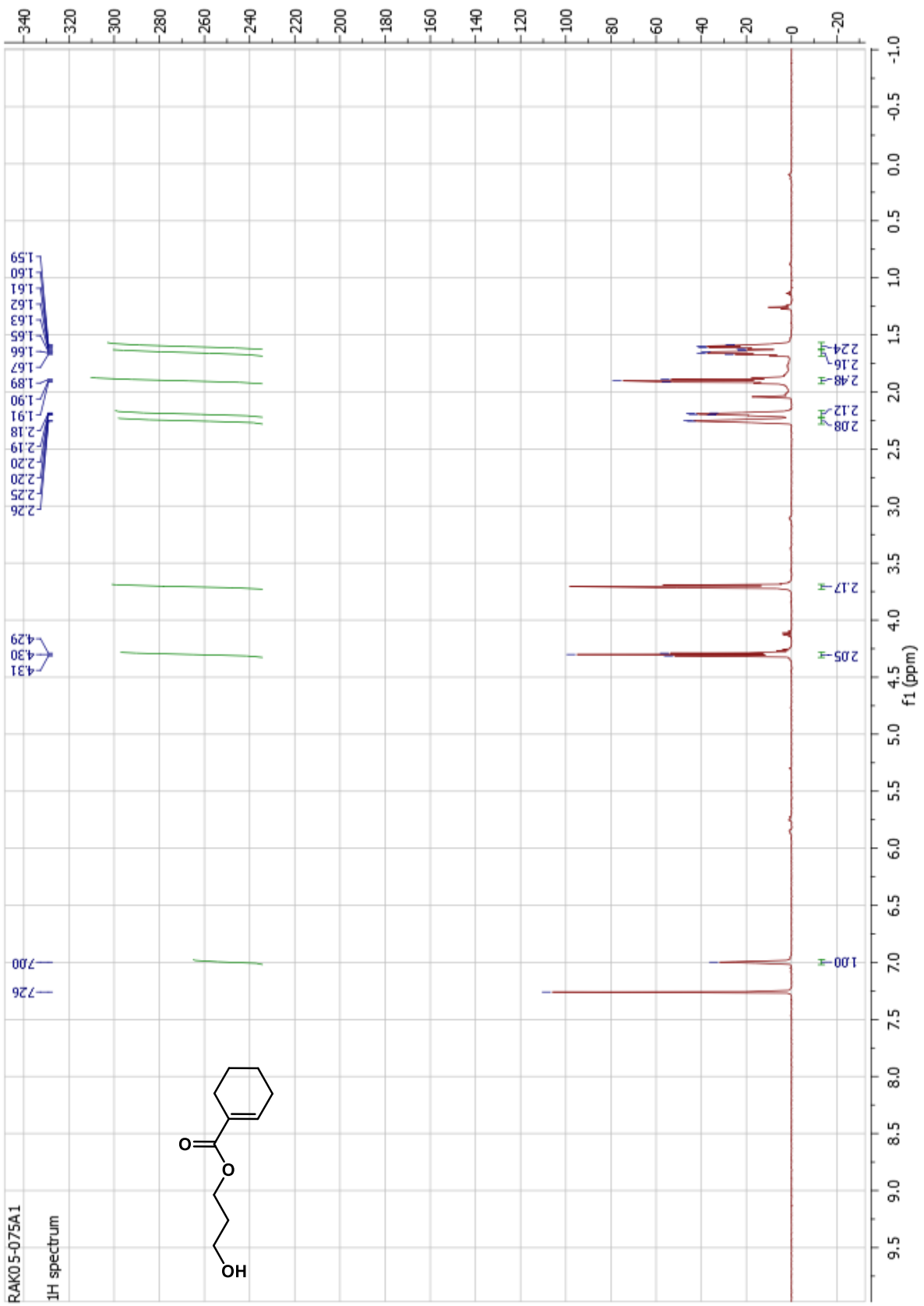

RAK04-211A1
1H spectrum
Cl
O
O
OEt
f1 (ppm)

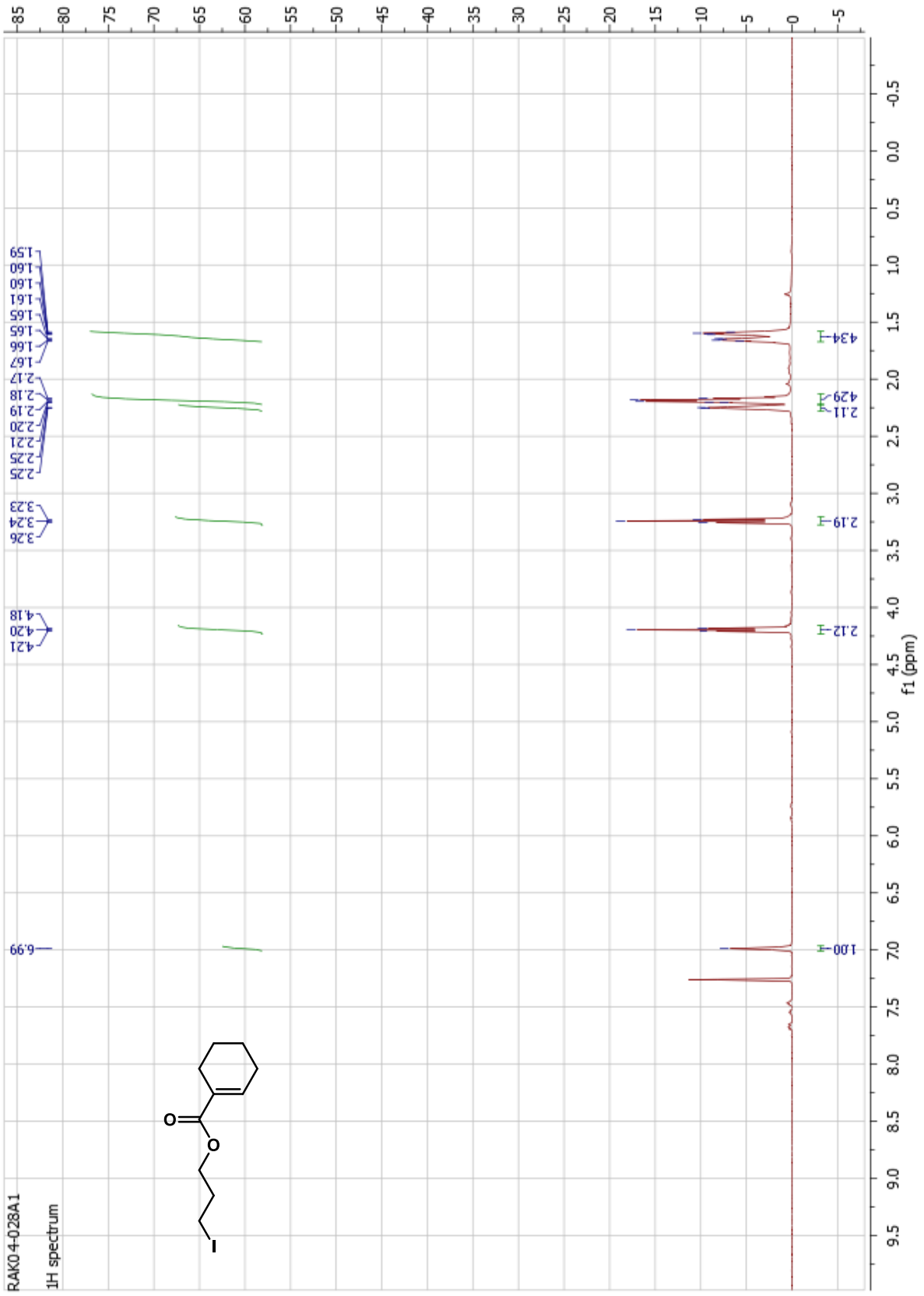

RAK04-065A1
1H spectrum
OH
O
OMe
f1 (ppm)

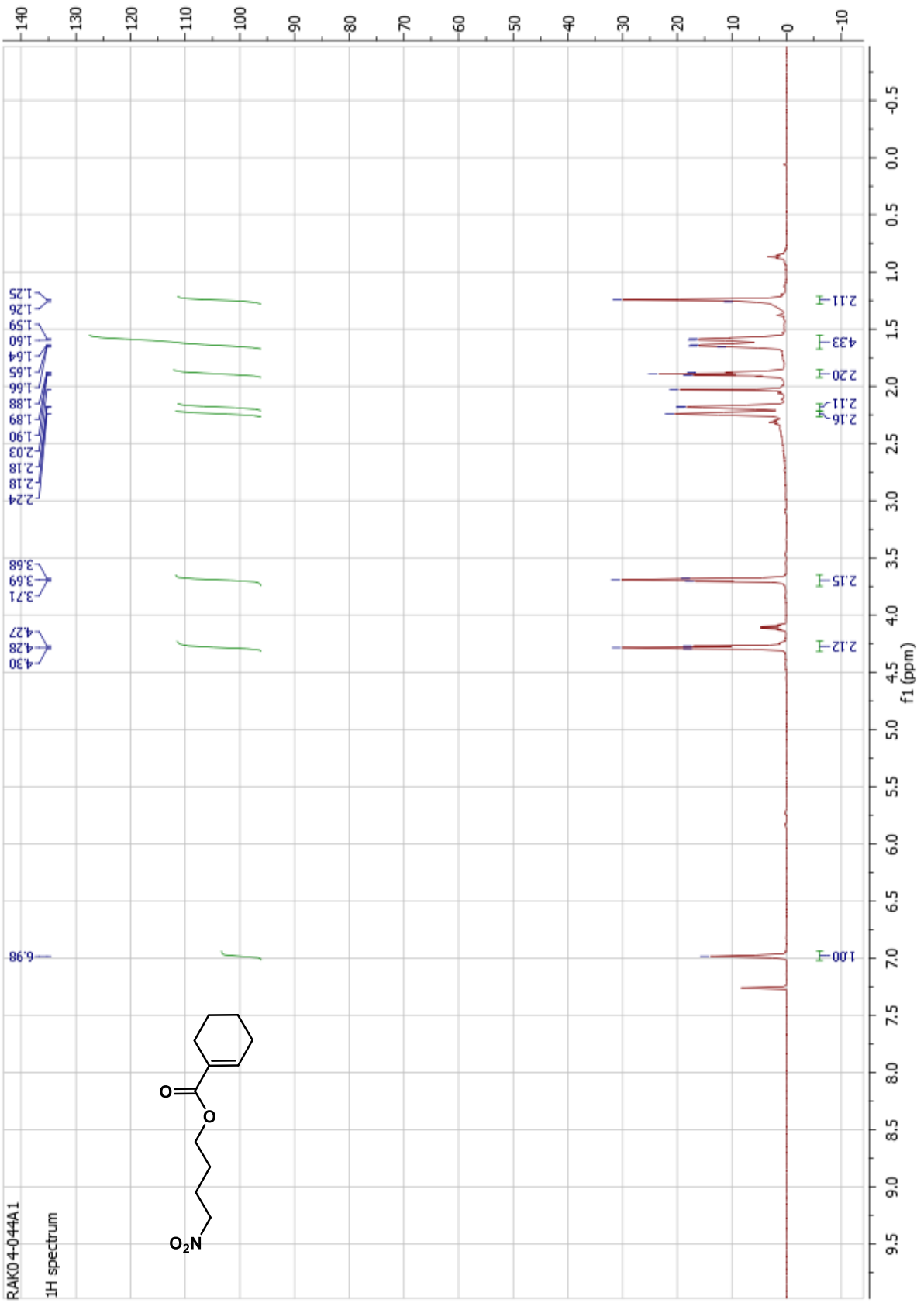

RAK04-065A1
Z-restored spin-echo 13C spectrum with 1H decoupling
168.03
142.85
131.29
68.43
51.94
37.19
28.90
24.45
19.56
OH
O
OMe

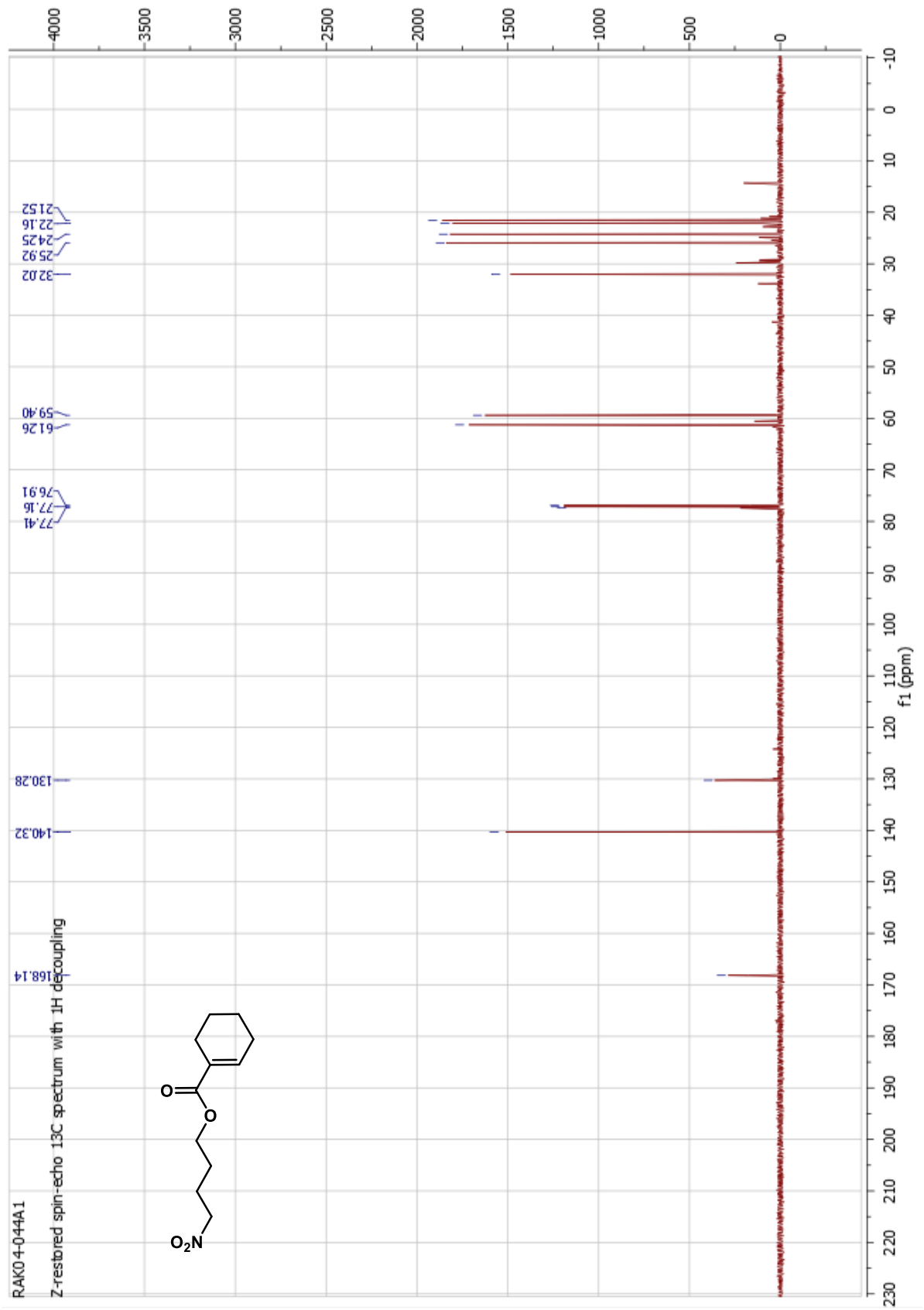

RAK04-059A1
1H spectrum
MeO
O
Br
N
O
f1 (ppm)

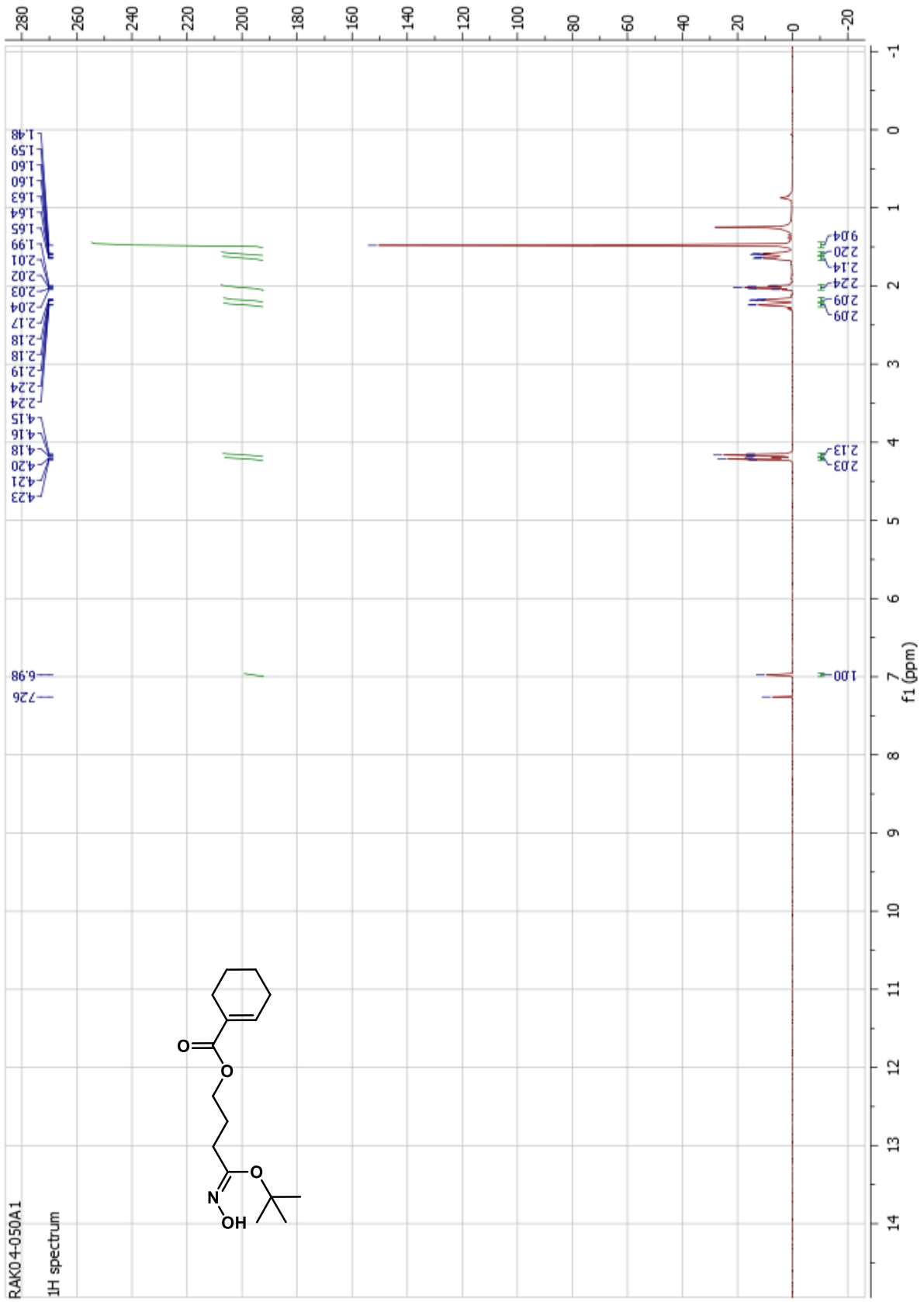

RAK04-059A1
Z-restored spin-echo 13C spectrum with 1H decoupling
f1 (ppm)
18.84
19.55
23.50
28.20
52.44
53.23
76.91
77.16
77.41
87.65
144.85
172.27
MeO
O
Br
N
O

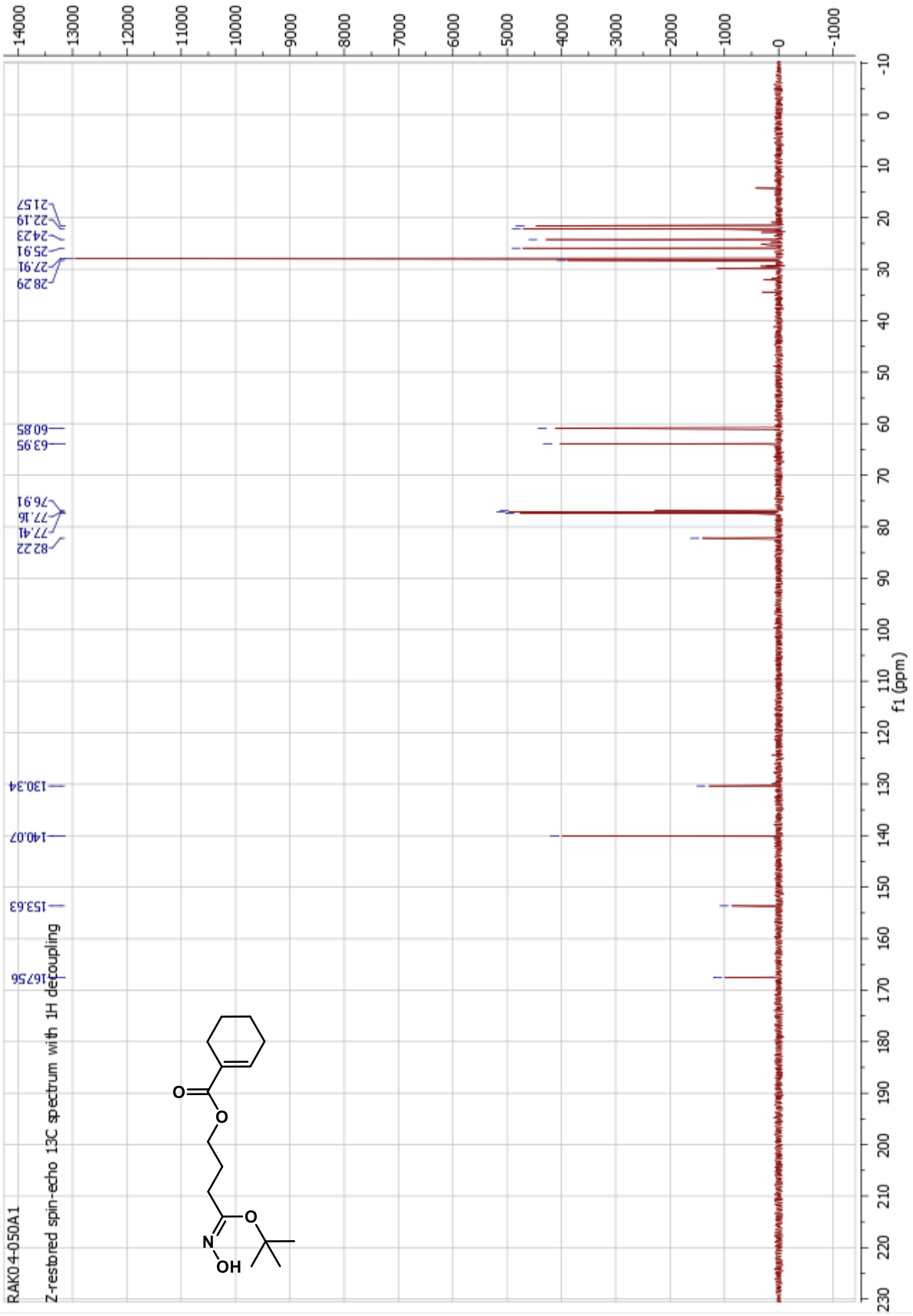

RAK05-075A1
1H spectrum
O
O
OH
f1 (ppm)

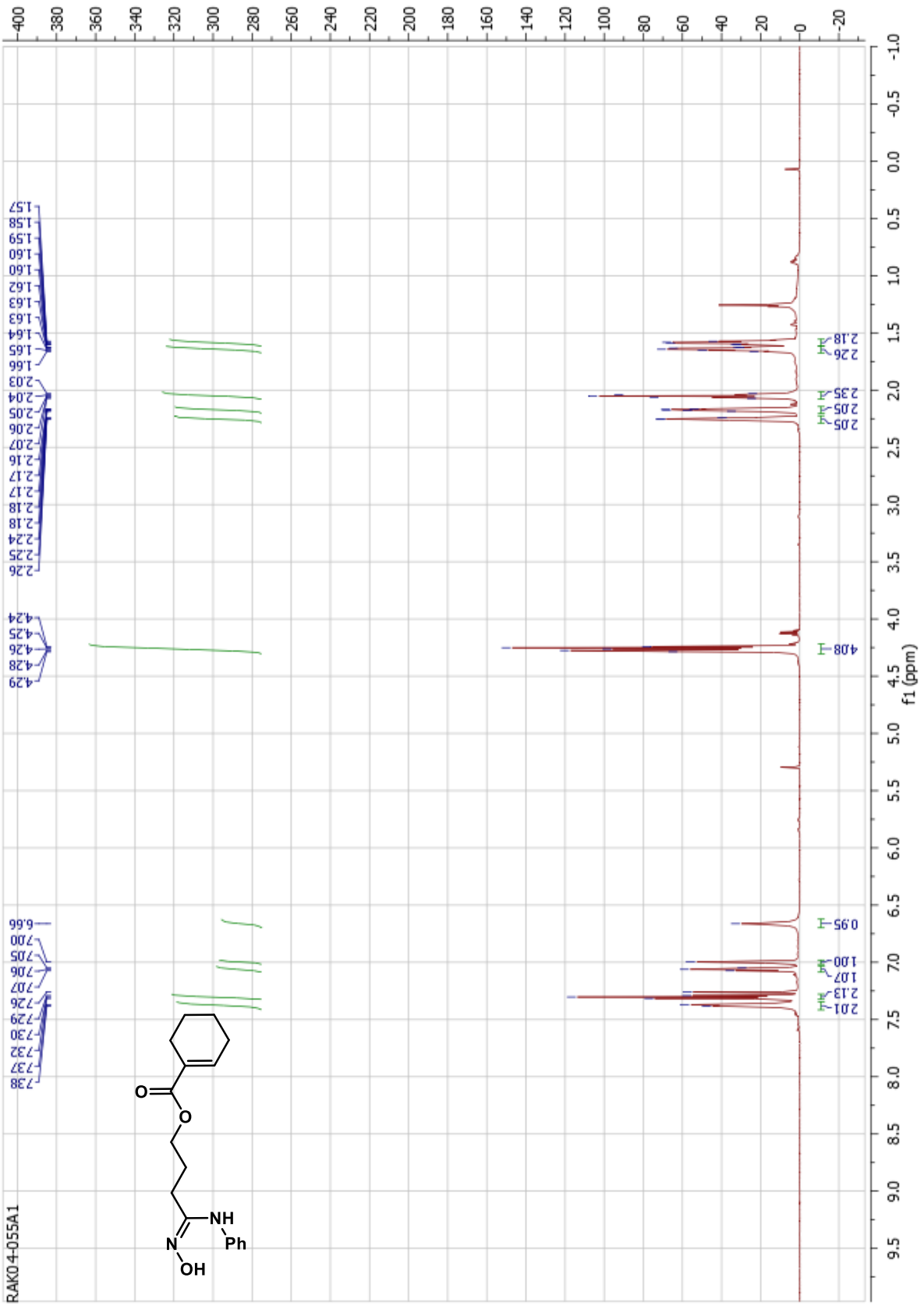

RAK04-028A1
1H spectrum
f1 (ppm)
O
O
I

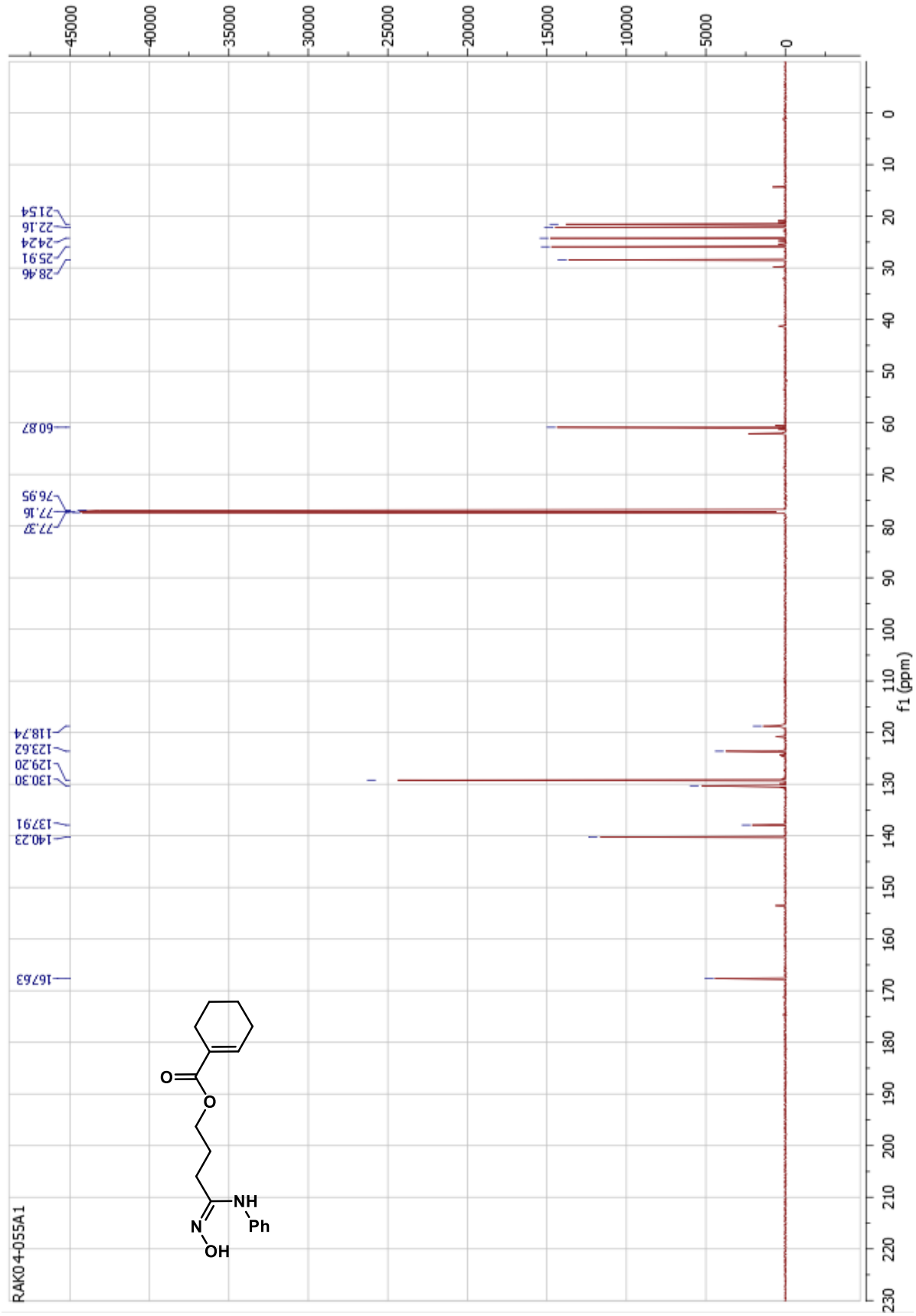

RAK04-044A1
1H spectrum
f1 (ppm)
O
O
O2N

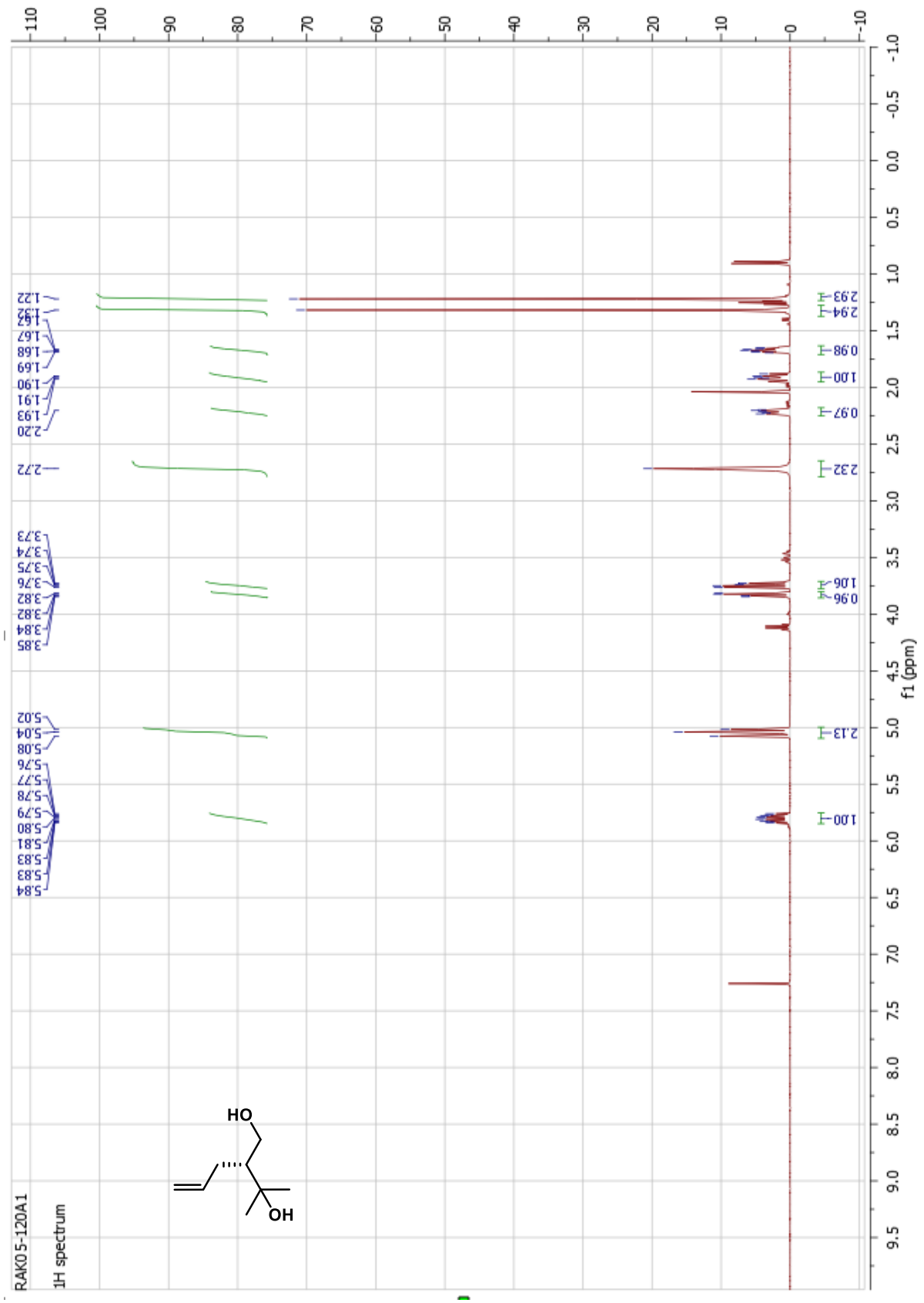

RAK04-044A1
Z-restored spin-echo 13C spectrum with 1H decoupling
168.14
140.32
130.28
77.41
77.16
76.91
61.26
59.40
32.02
25.92
24.25
22.16
21.52
f1 (ppm)
O
O
O2N

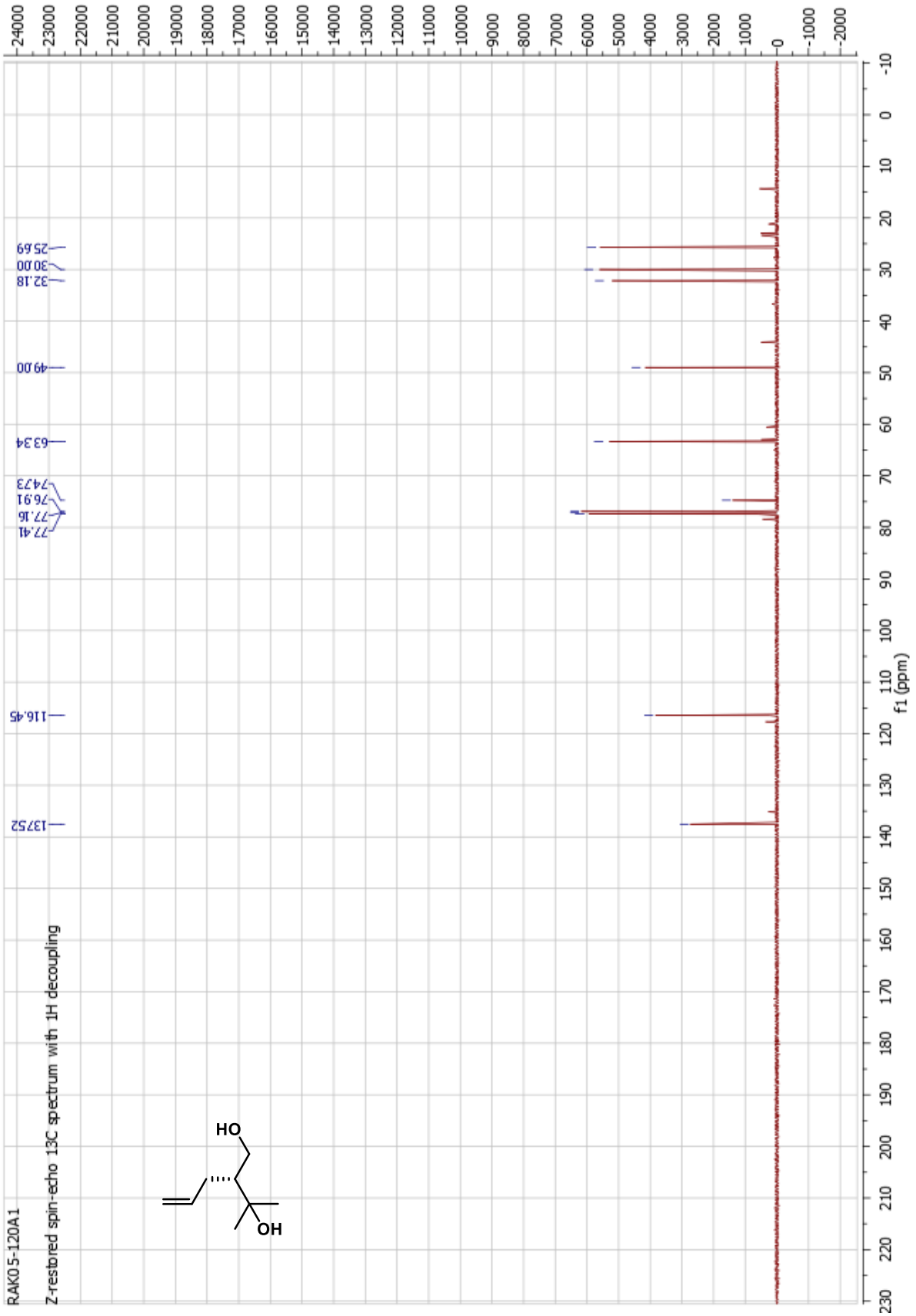

RAK04-050A1
1H spectrum
f1 (ppm)
O
O
N
OH
O

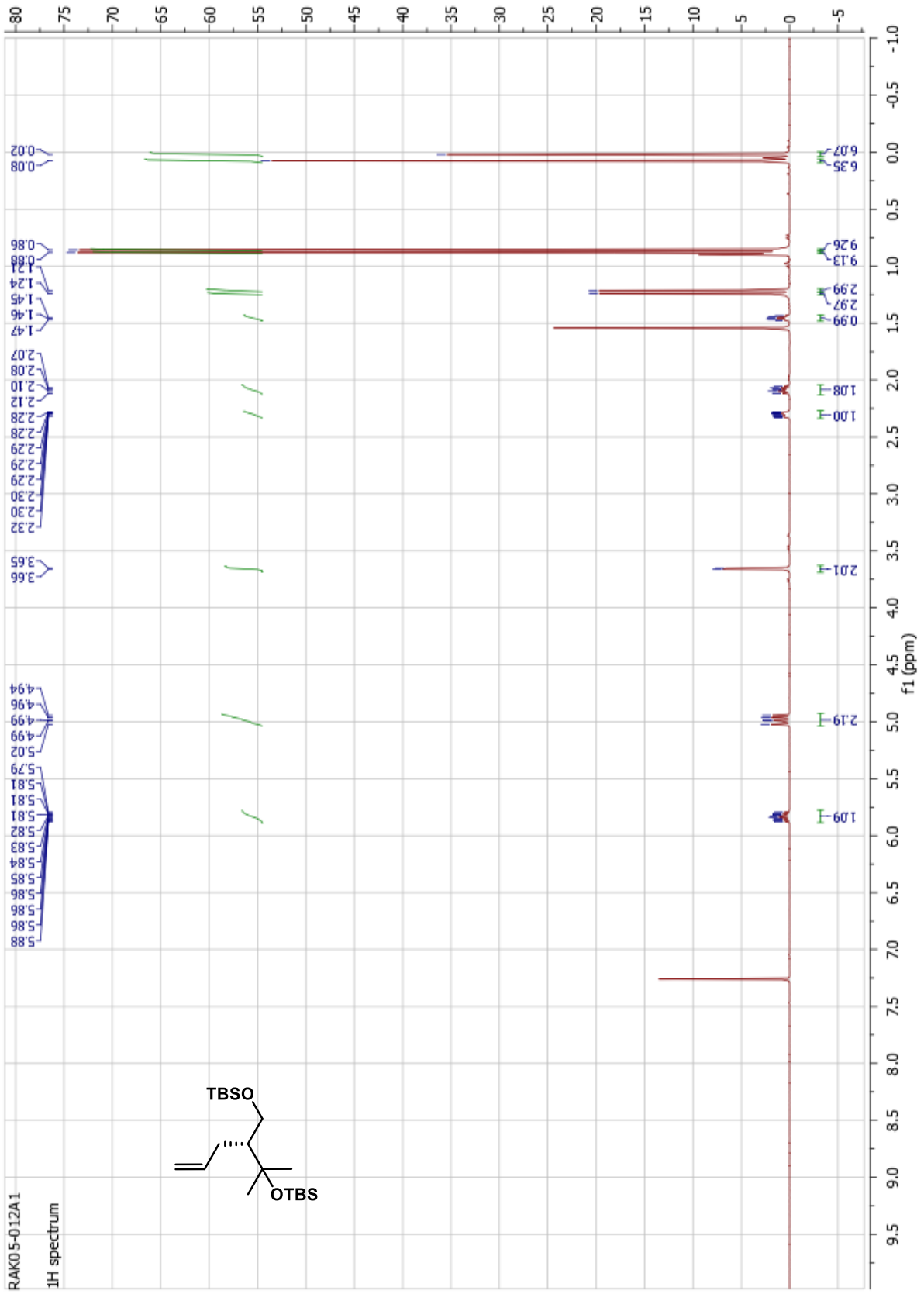

RAK04-050A1
Z-restored spin-echo 13C spectrum with 1H decoupling
167.56
153.63
140.07
130.34
82.22
77.41
77.16
76.91
63.95
60.85
28.29
27.91
25.91
24.23
22.19
21.57
f1 (ppm)
O
O
N
OH
O

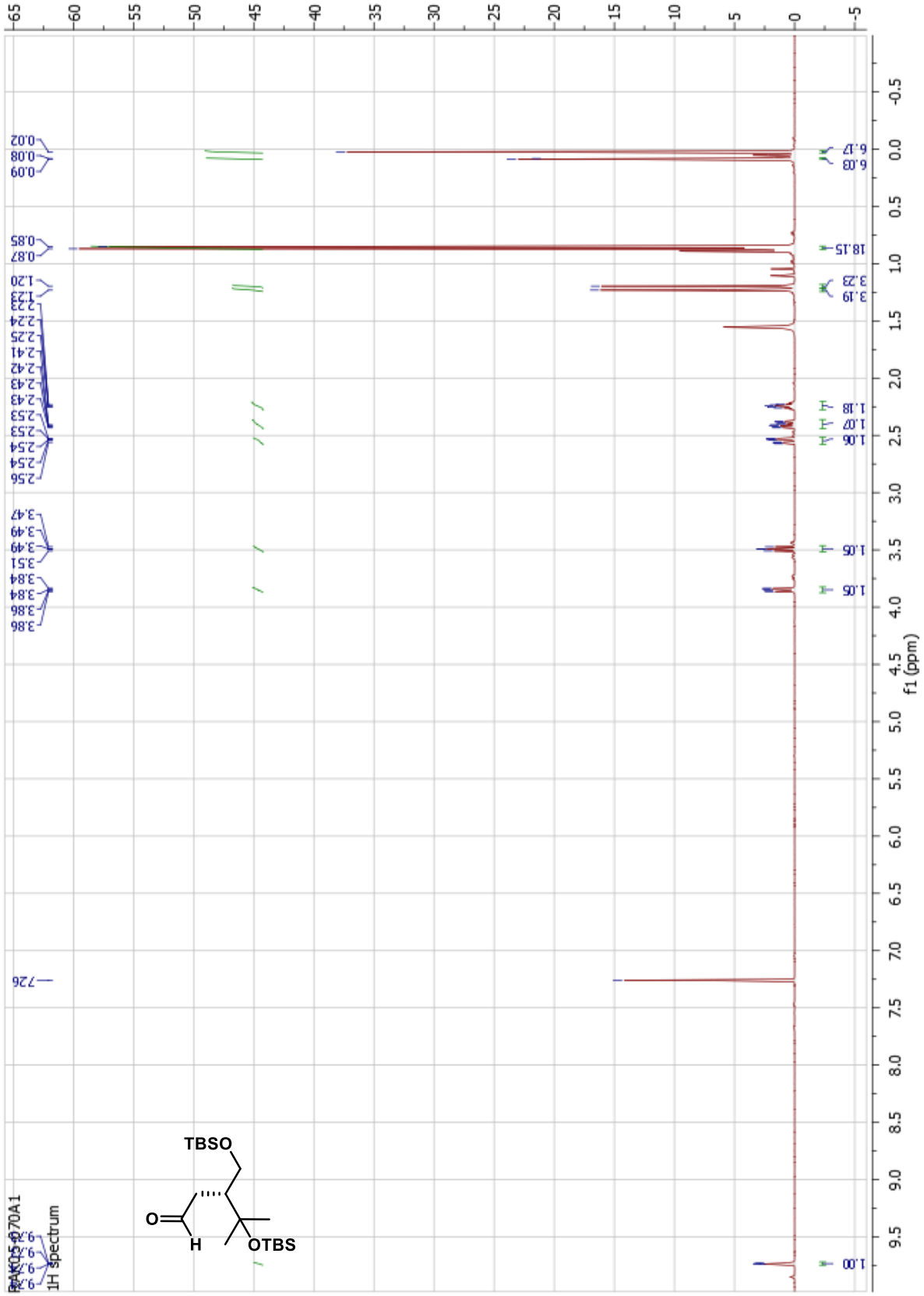

RAK04-055A1
O
O
NH
Ph
N
OH
f1 (ppm)

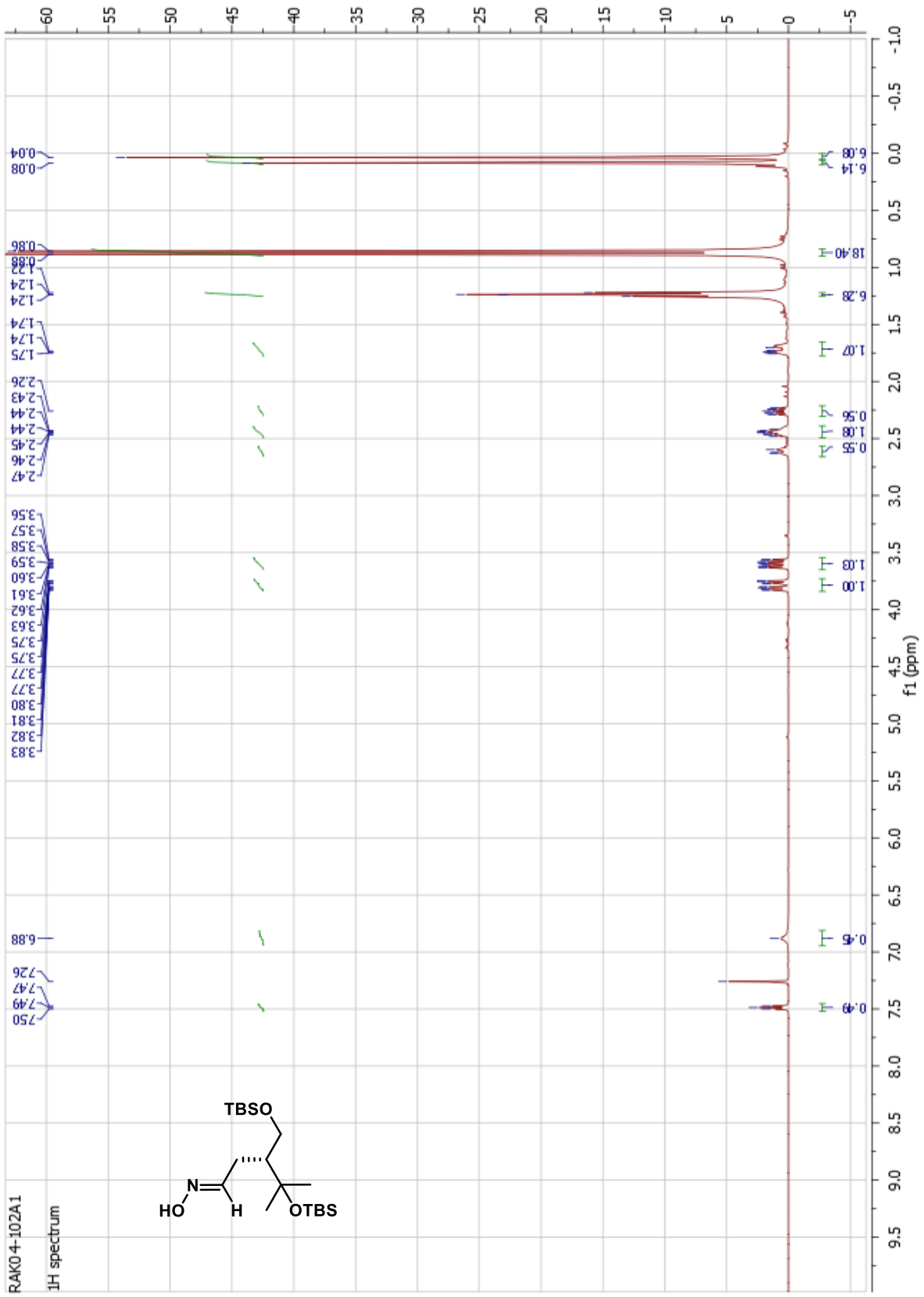

RAK04-055A1
f1 (ppm)
215.4
22.16
24.24
25.91
28.46
60.87
76.95
77.16
77.37
118.74
123.62
129.20
130.30
137.91
140.23
167.63
O
O
NH
Ph
N
OH

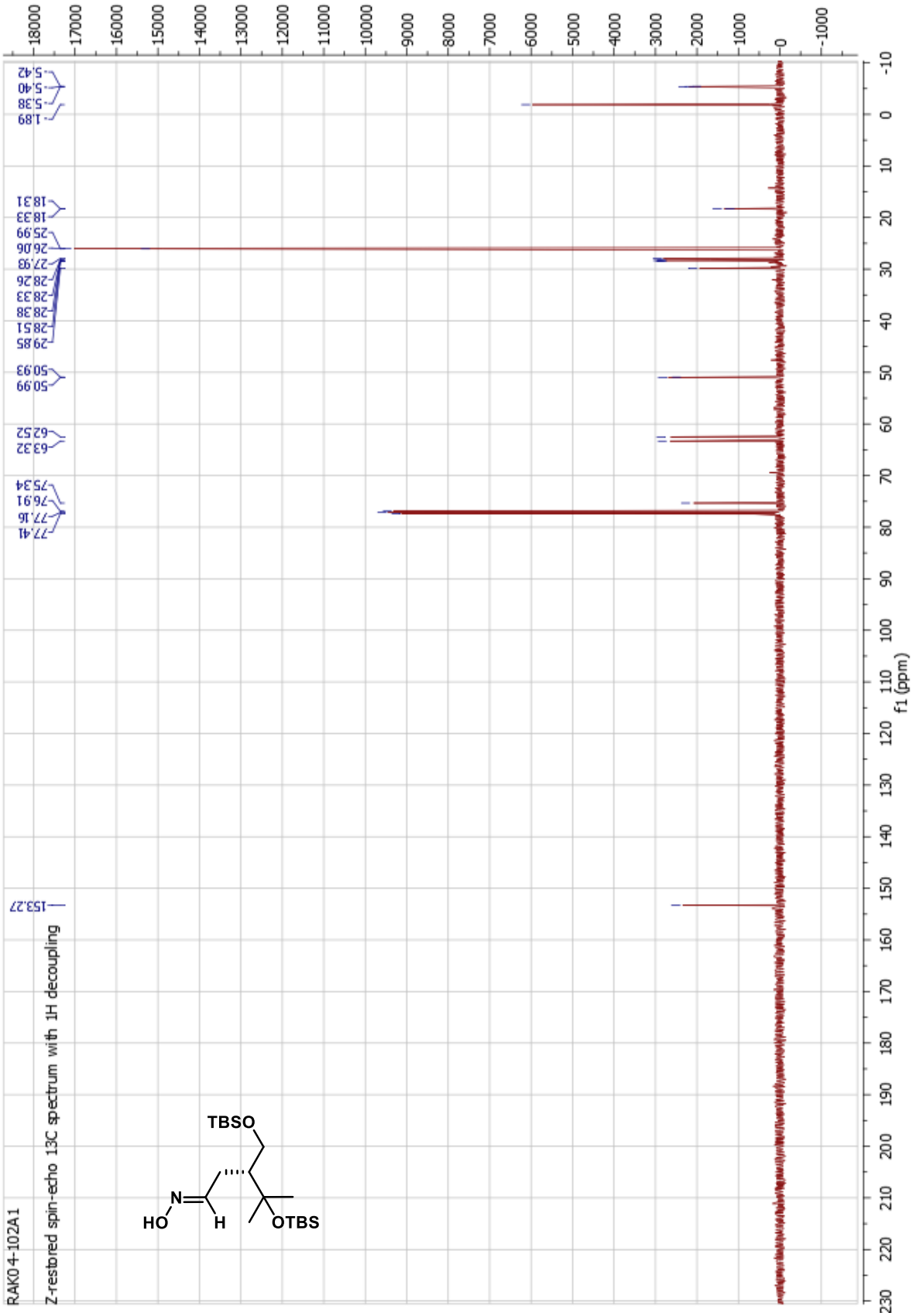

RAK05-120A1
1H spectrum
HO
OH
f1 (ppm)

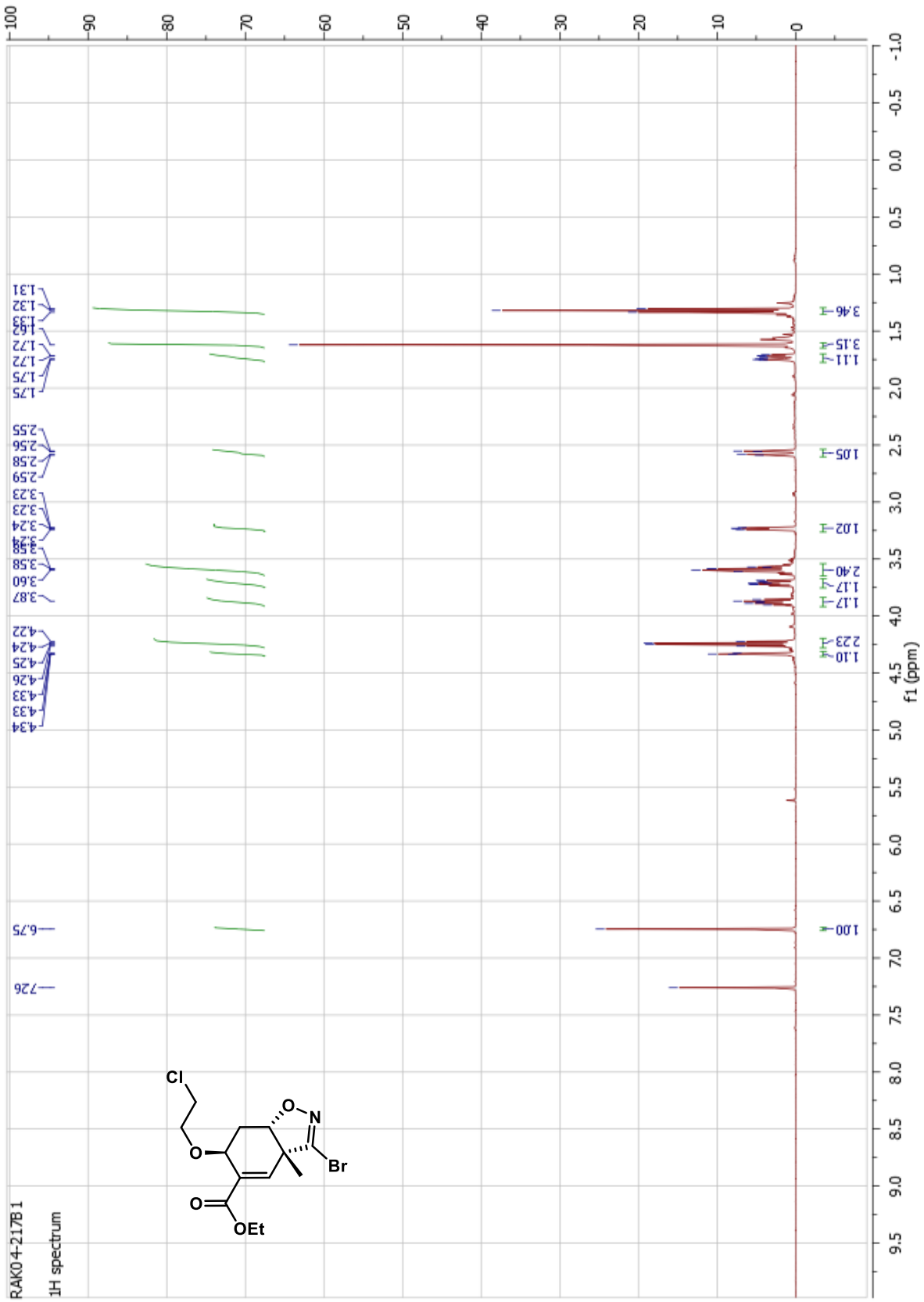

RAK05-120A1
Z-restored spin-echo 13C spectrum with 1H decoupling
HO
OH
137.52
116.45
77.41
77.16
76.91
74.73
63.34
49.00
32.18
30.00
25.69
f1 (ppm)

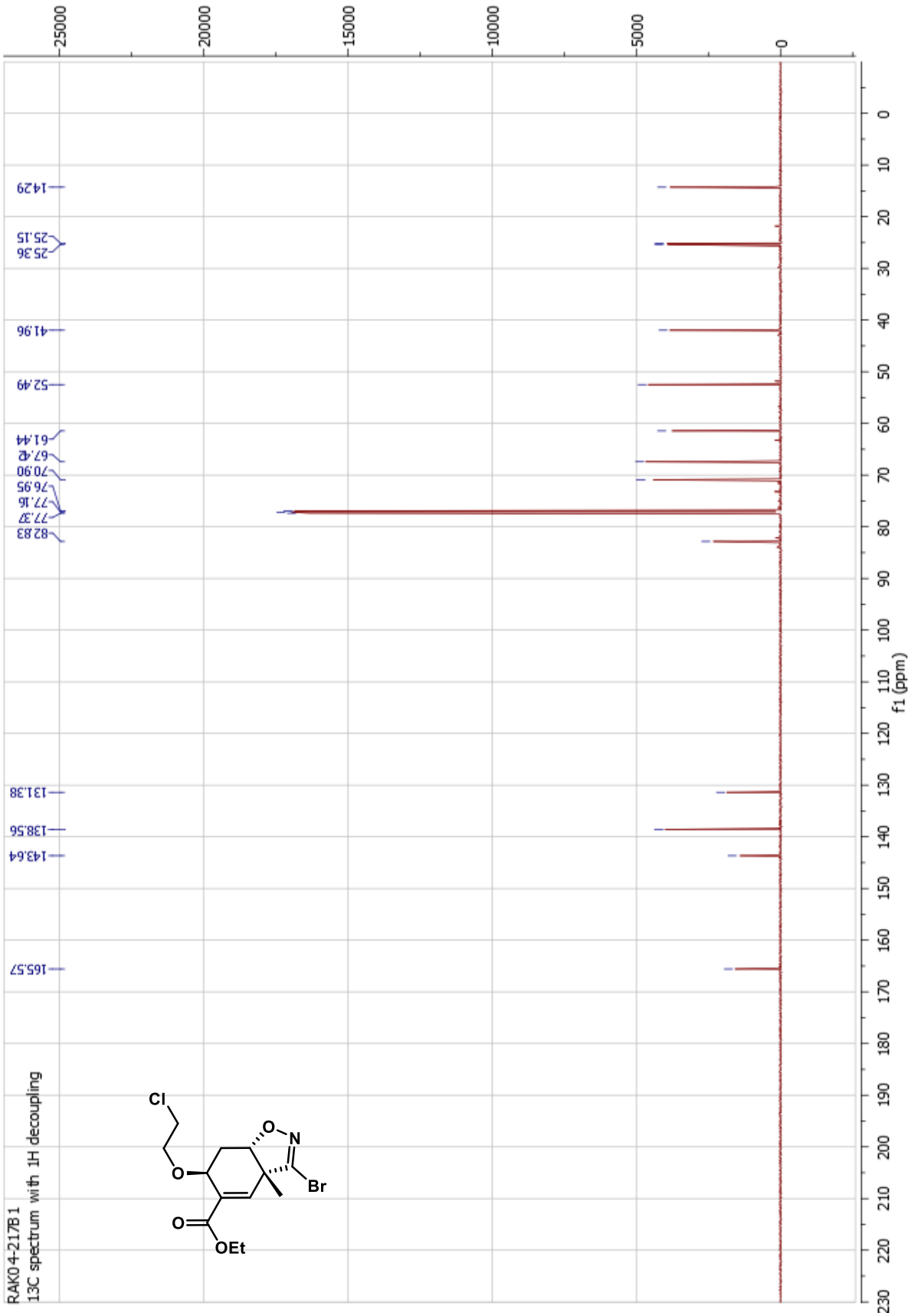

TBSO
OTBS
RAK05-012A1
1H spectrum
f1 (ppm)

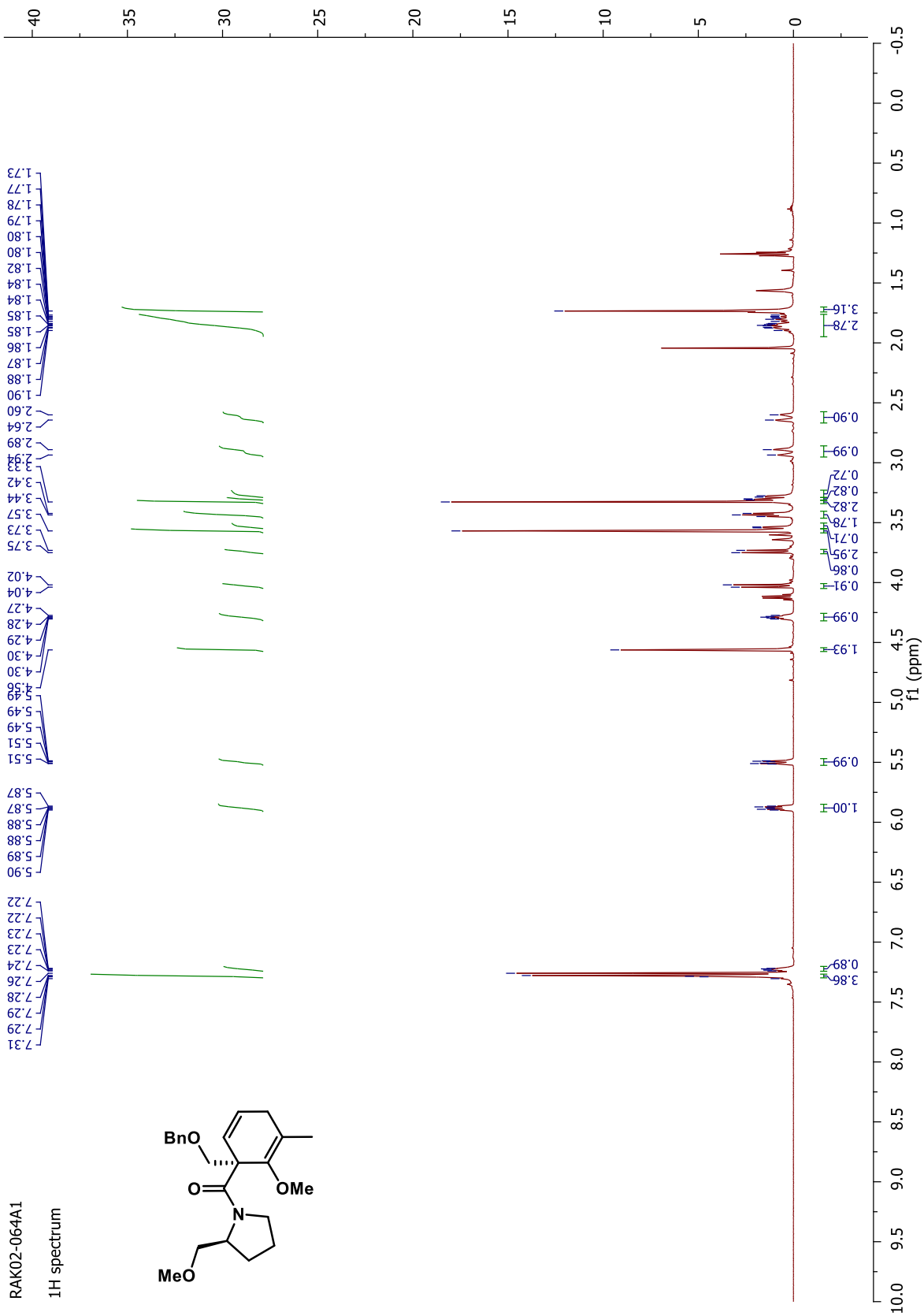

TBSO
O
H
OTBS
f1 (ppm)

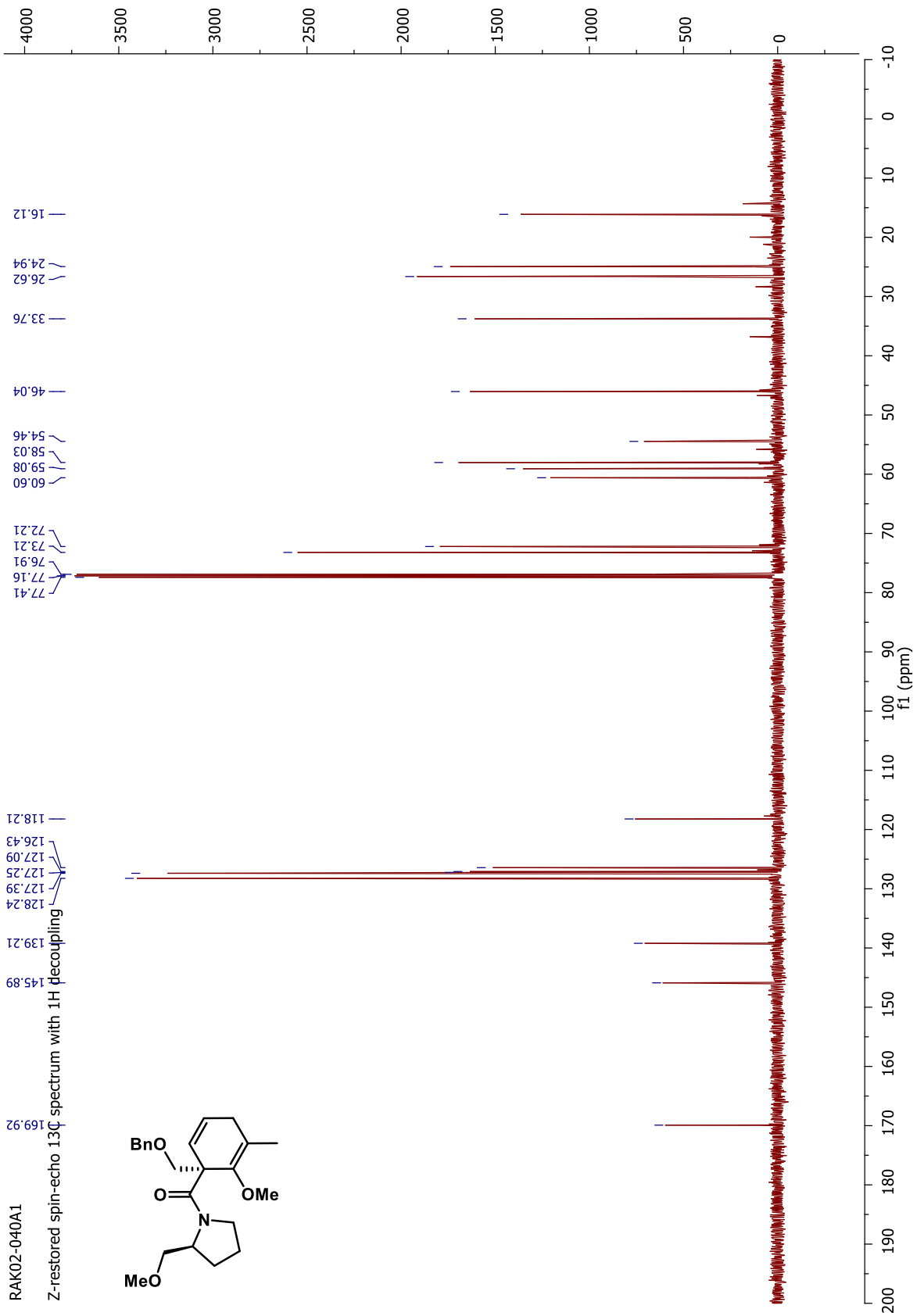

RAK04-102A1
1H spectrum
f1 (ppm)
TBSO
N
HO
H
OTBS

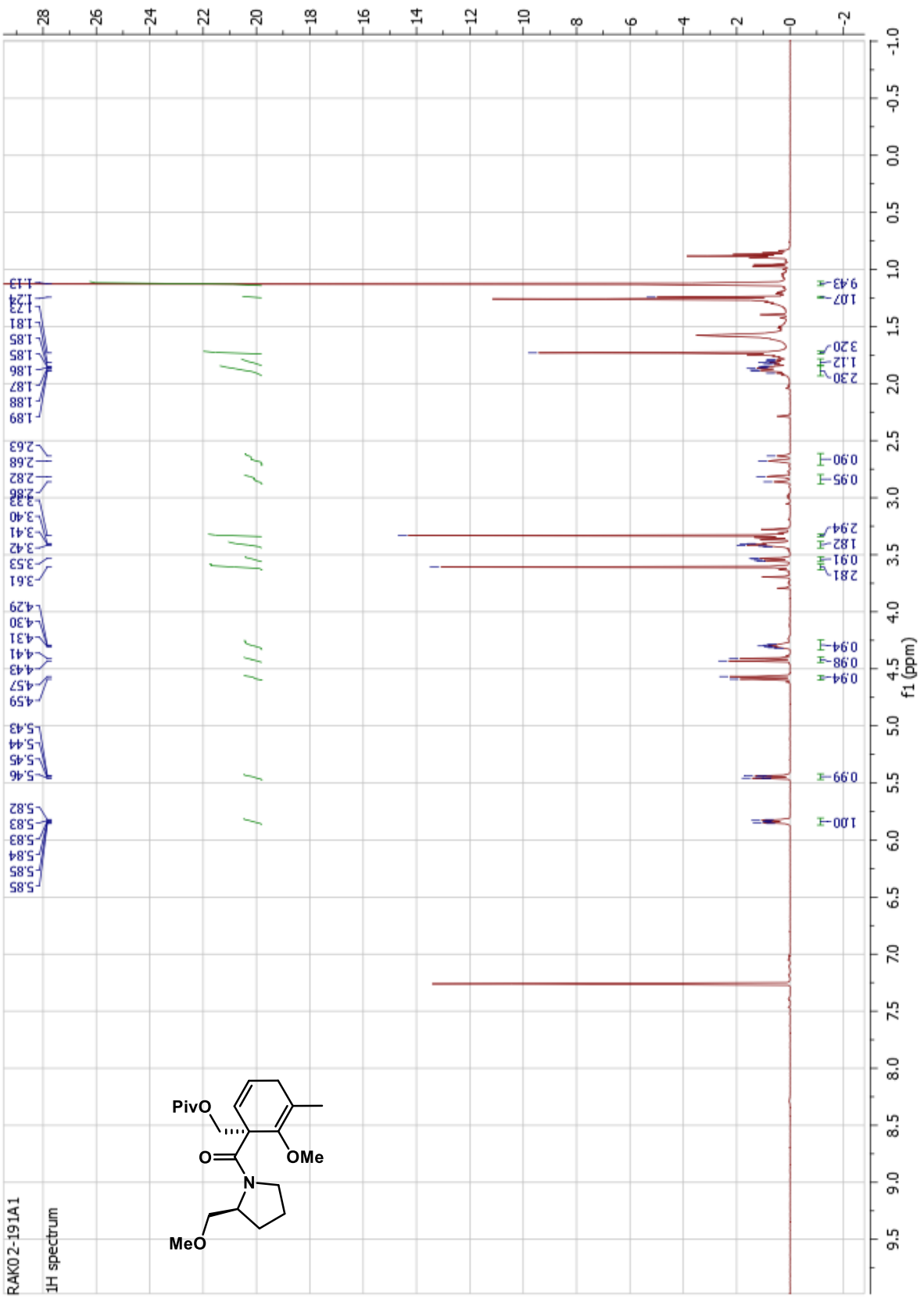

RAK04-102A1
Z-restored spin-echo 13C spectrum with 1H decoupling
153.27
77.41
77.16
76.91
75.34
63.32
62.52
50.99
50.93
29.85
28.51
28.38
28.33
28.26
27.99
26.06
25.99
18.33
18.31
5.42
5.40
5.38
1.89
TBSO
N
HO
H
OTBS
f1 (ppm)

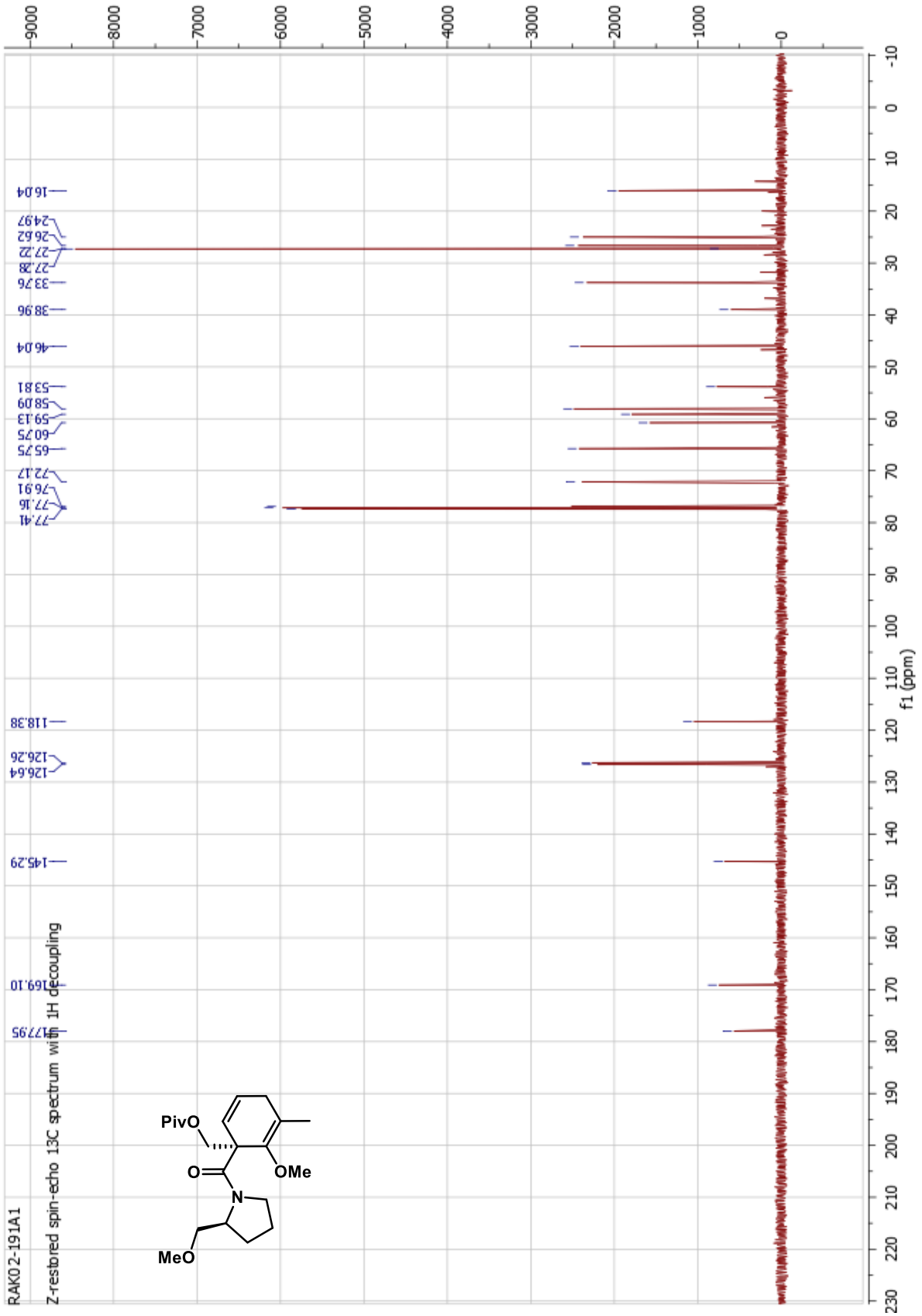

RAK04-217B1
1H spectrum
f1 (ppm)
Cl
O
N
Br
O
O
OEt

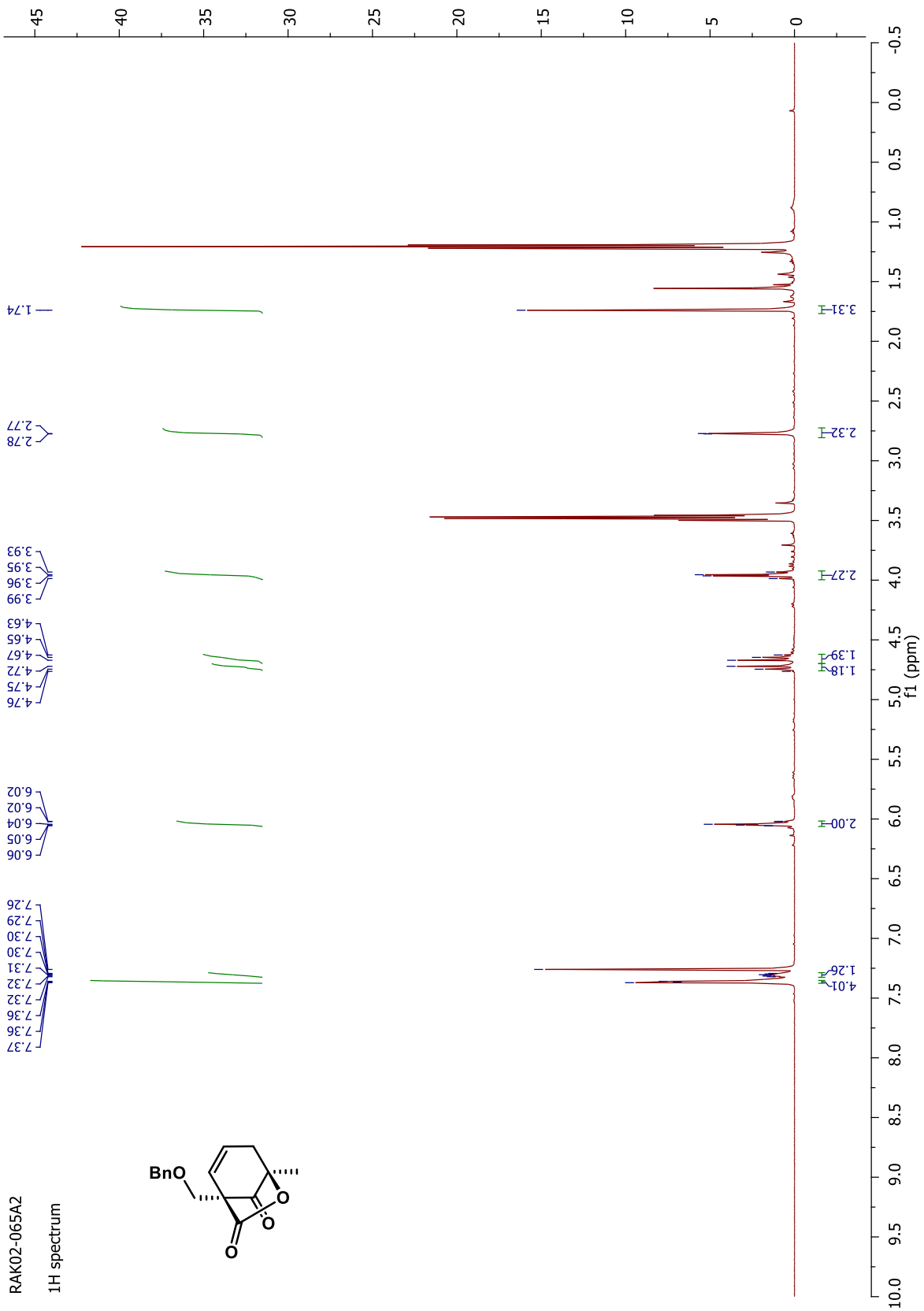

RAK04-217B1
13C spectrum with 1H decoupling
f1 (ppm)
14.29
25.15
25.36
41.96
52.49
61.44
67.42
70.90
76.95
77.16
77.37
82.83
131.38
138.56
143.64
165.57
Cl
O
O
N
Br
O
OEt

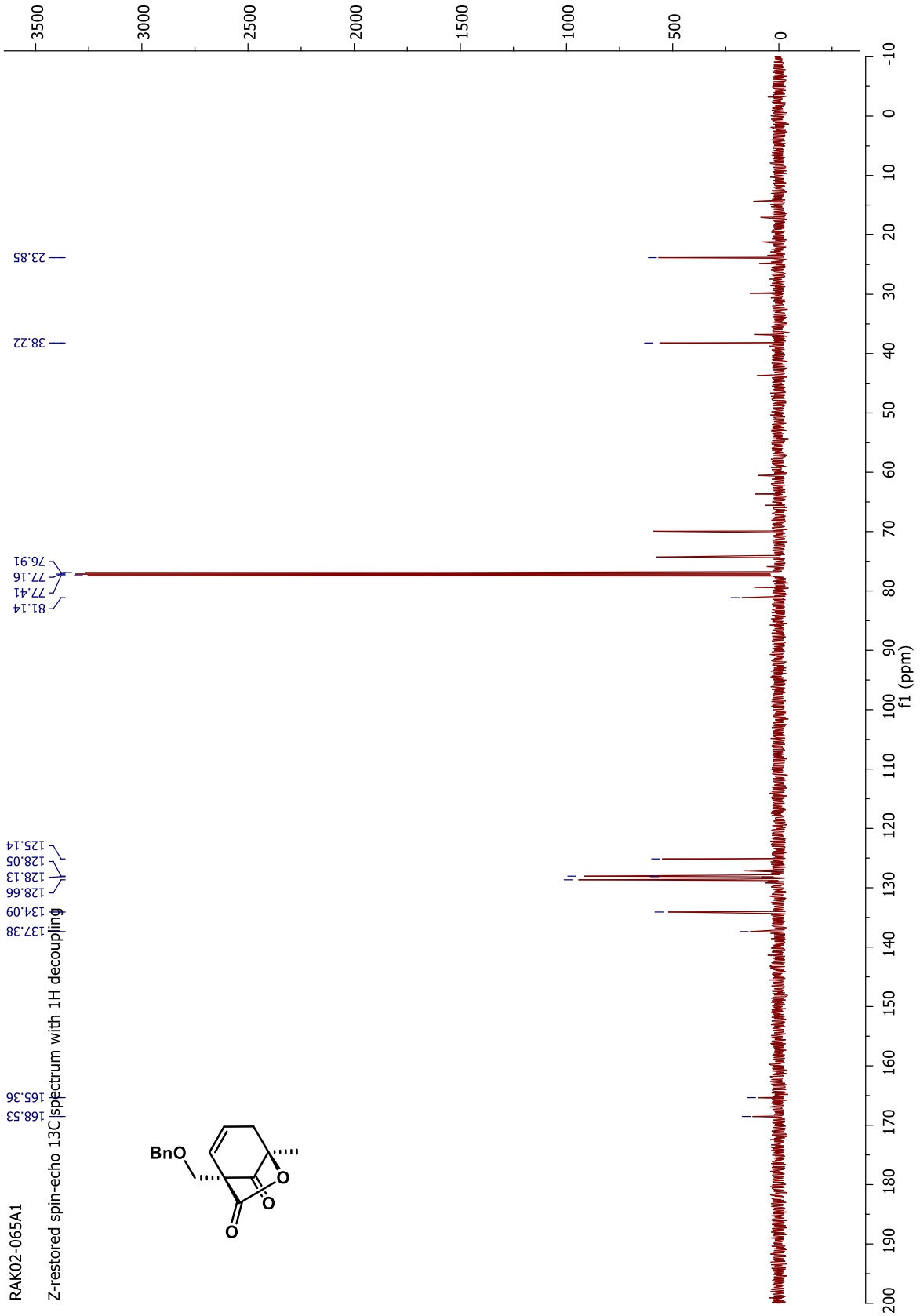

RAK02-064A1
1H spectrum
BnO
O
N
OMe
MeO
f1 (ppm)

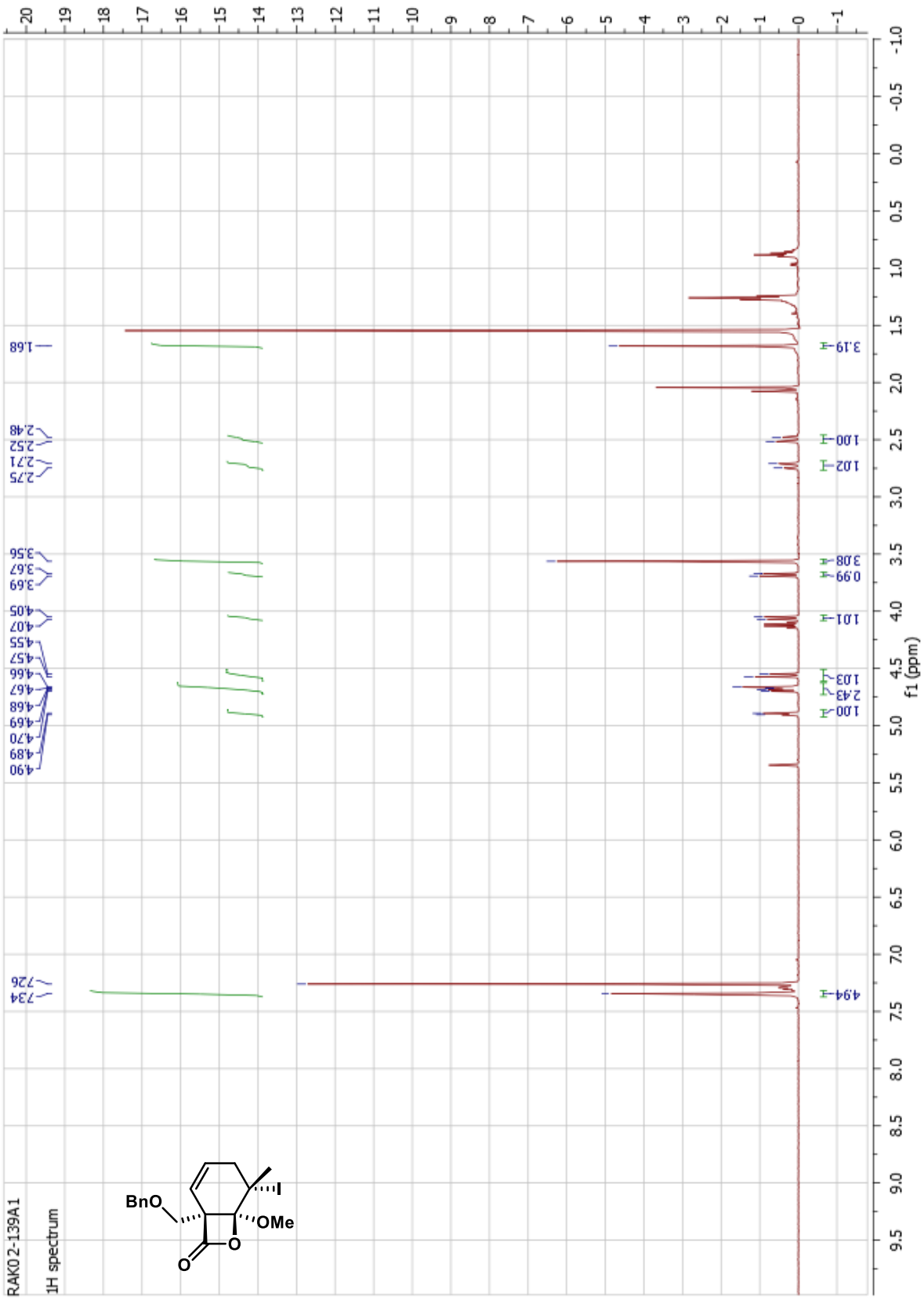

RAK02-040A1
Z-restored spin-echo 13C spectrum with 1H decoupling
f1 (ppm)
BnO
OMe
O
N
MeO

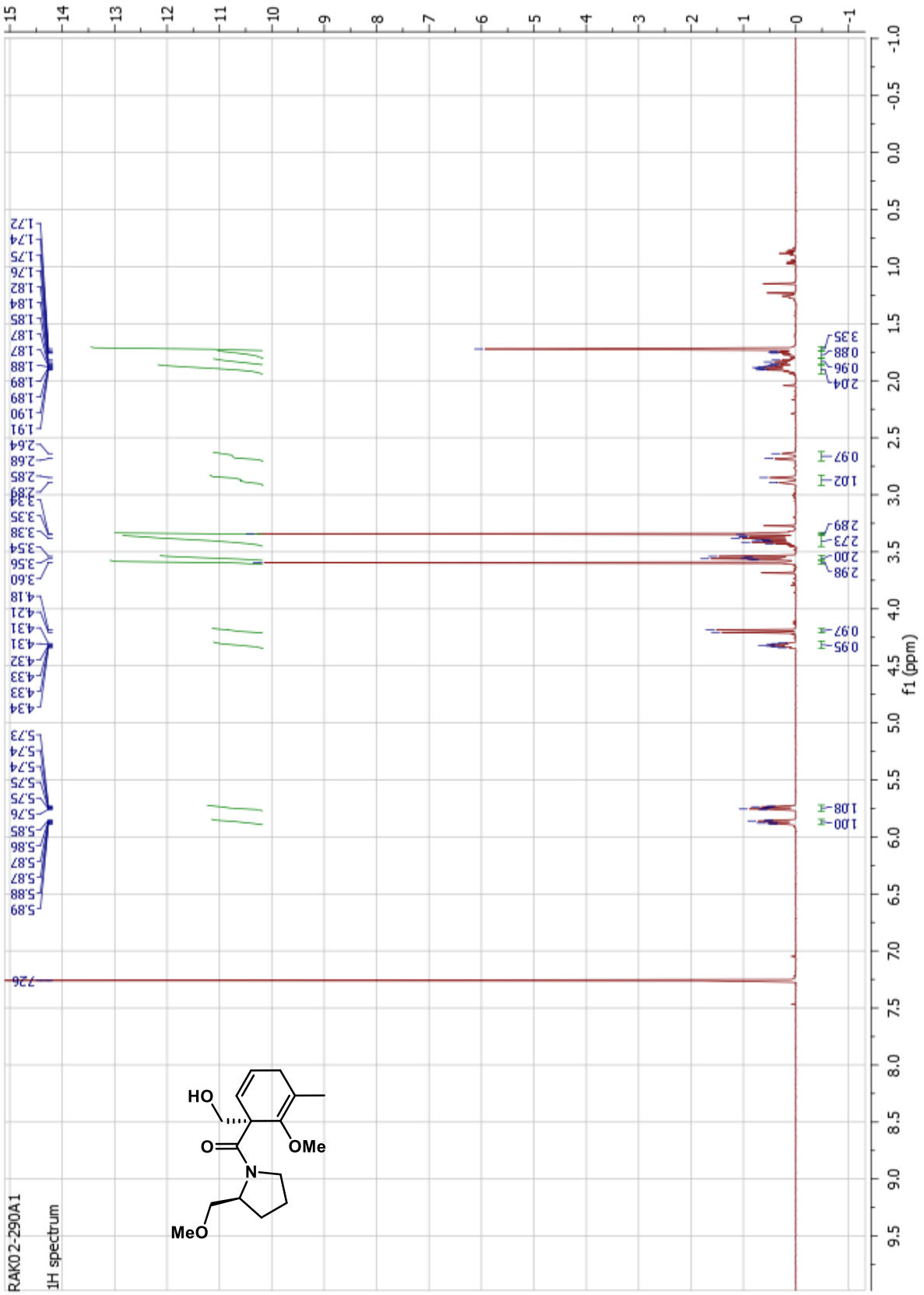

RAK02-191A1
1H spectrum
PivO
O
N
OMe
MeO
f1 (ppm)

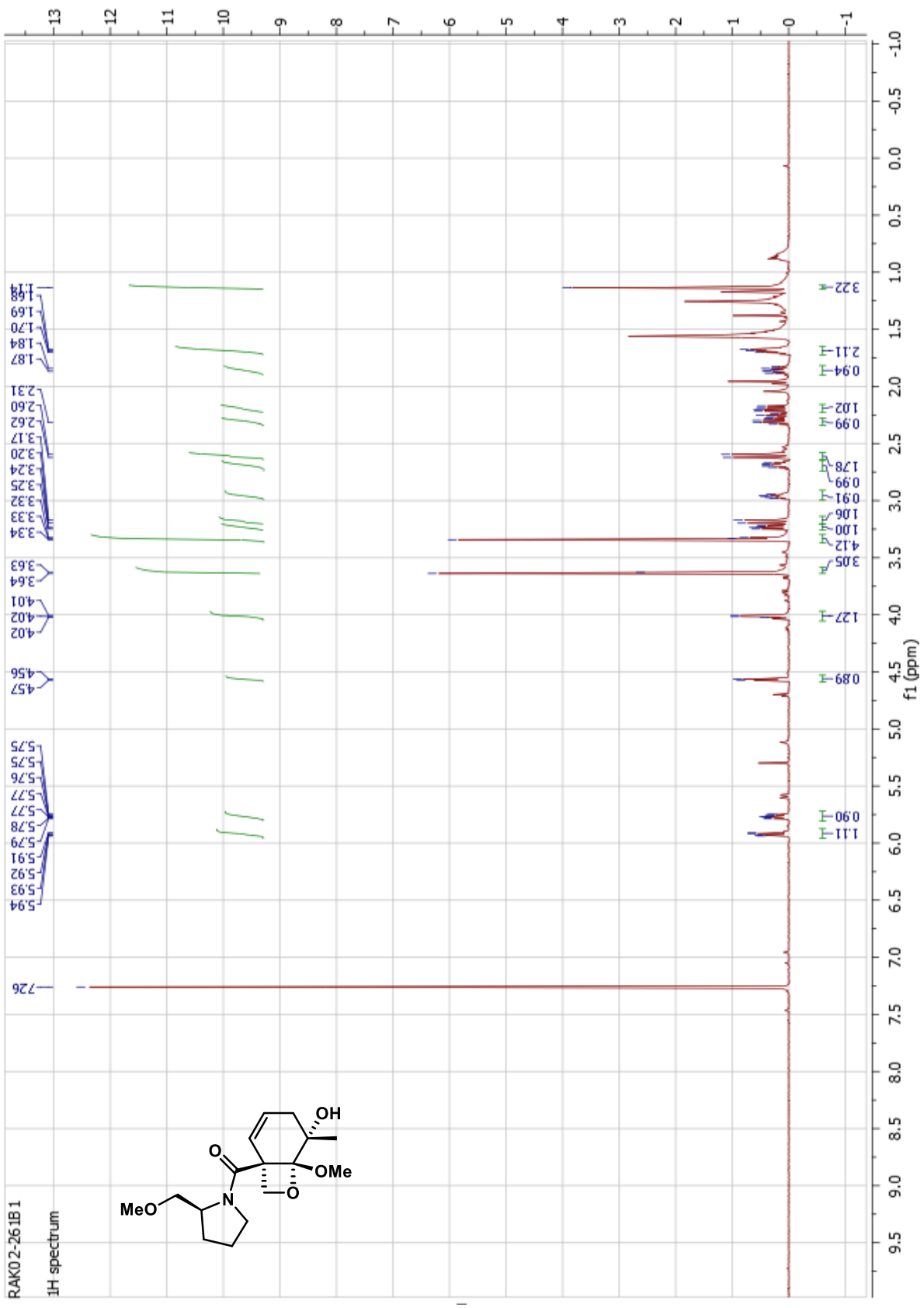

RAK02-191A1
Z-restored spin-echo 13C spectrum with 1H decoupling
f1 (ppm)
PivO
OMe
O
N
MeO

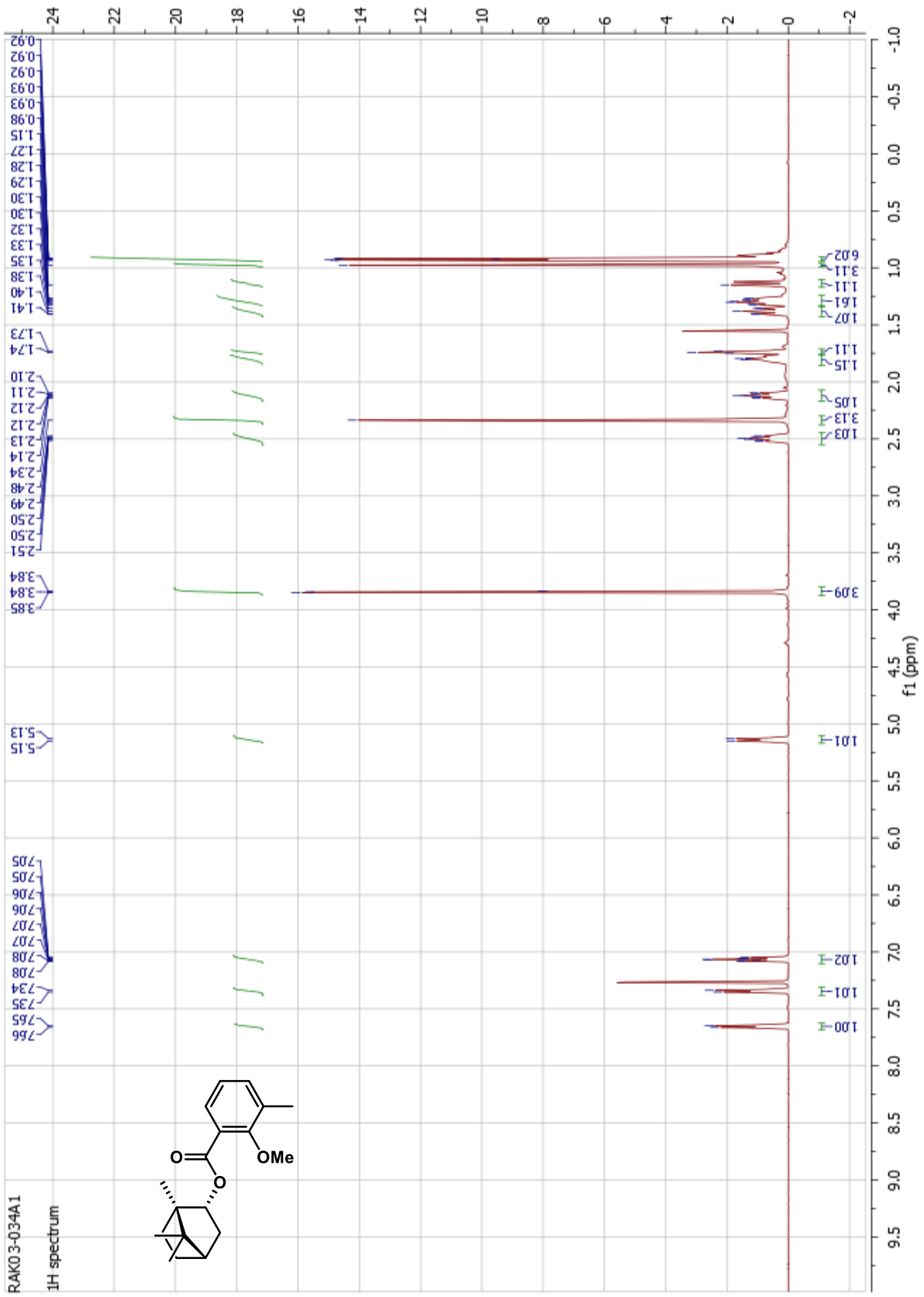

RAK02-065A2
1H spectrum
BnO
O
O
O
f1 (ppm)
1.74
2.78
2.77
3.99
3.96
3.95
3.93
4.76
4.75
4.72
4.67
4.65
4.63
6.06
6.05
6.04
6.02
6.02
7.37
7.36
7.36
7.32
7.32
7.31
7.30
7.30
7.29
7.26
4.01
1.26
2.00
1.39
1.18
2.27
2.32
3.31

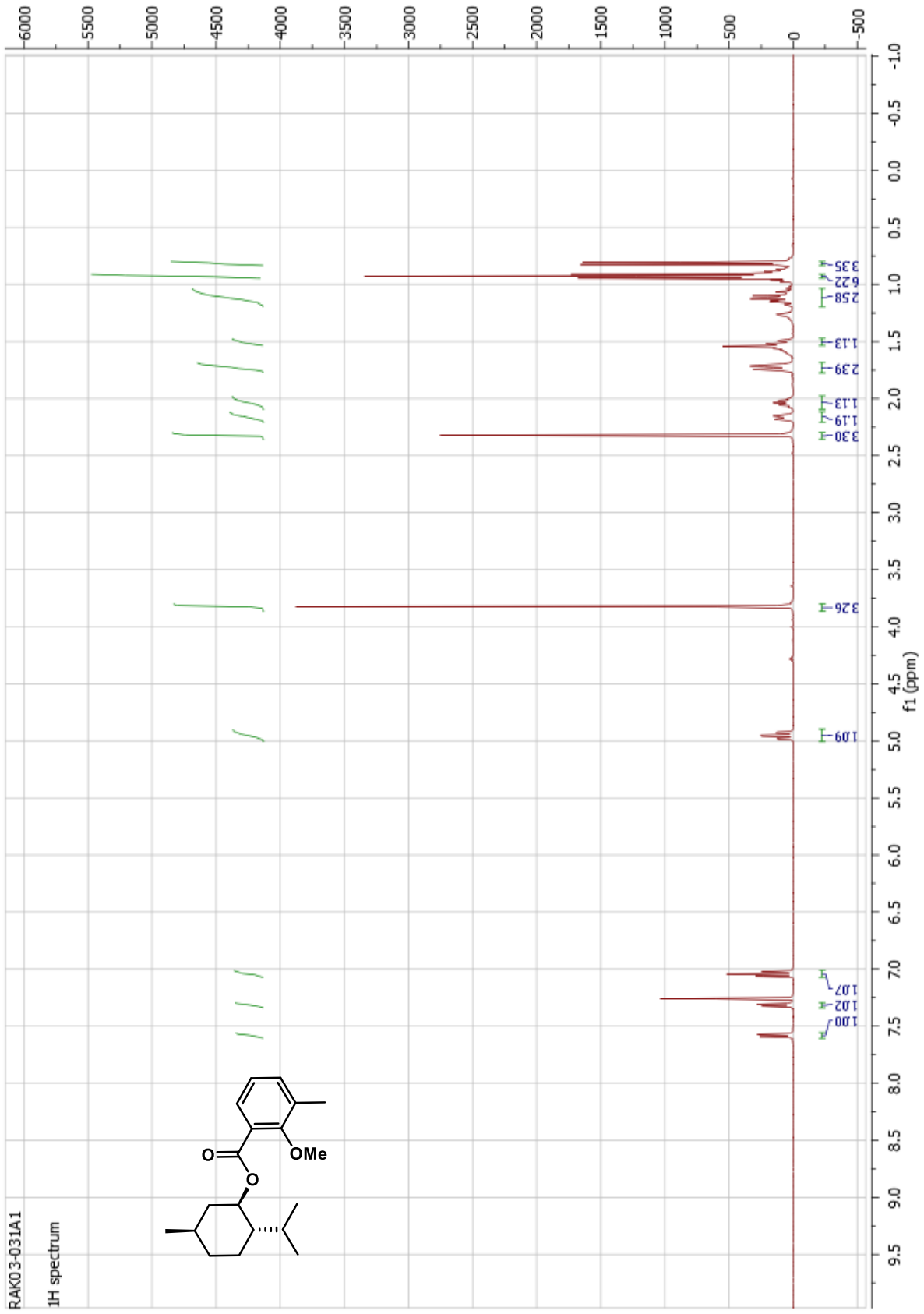

RAK02-065A1
Z-restored spin-echo 13C spectrum with 1H decoupling
168.53
165.36
137.38
134.09
128.66
128.13
128.05
125.14
81.14
77.41
77.16
76.91
38.22
23.85
BnO
O
O
O
f1 (ppm)

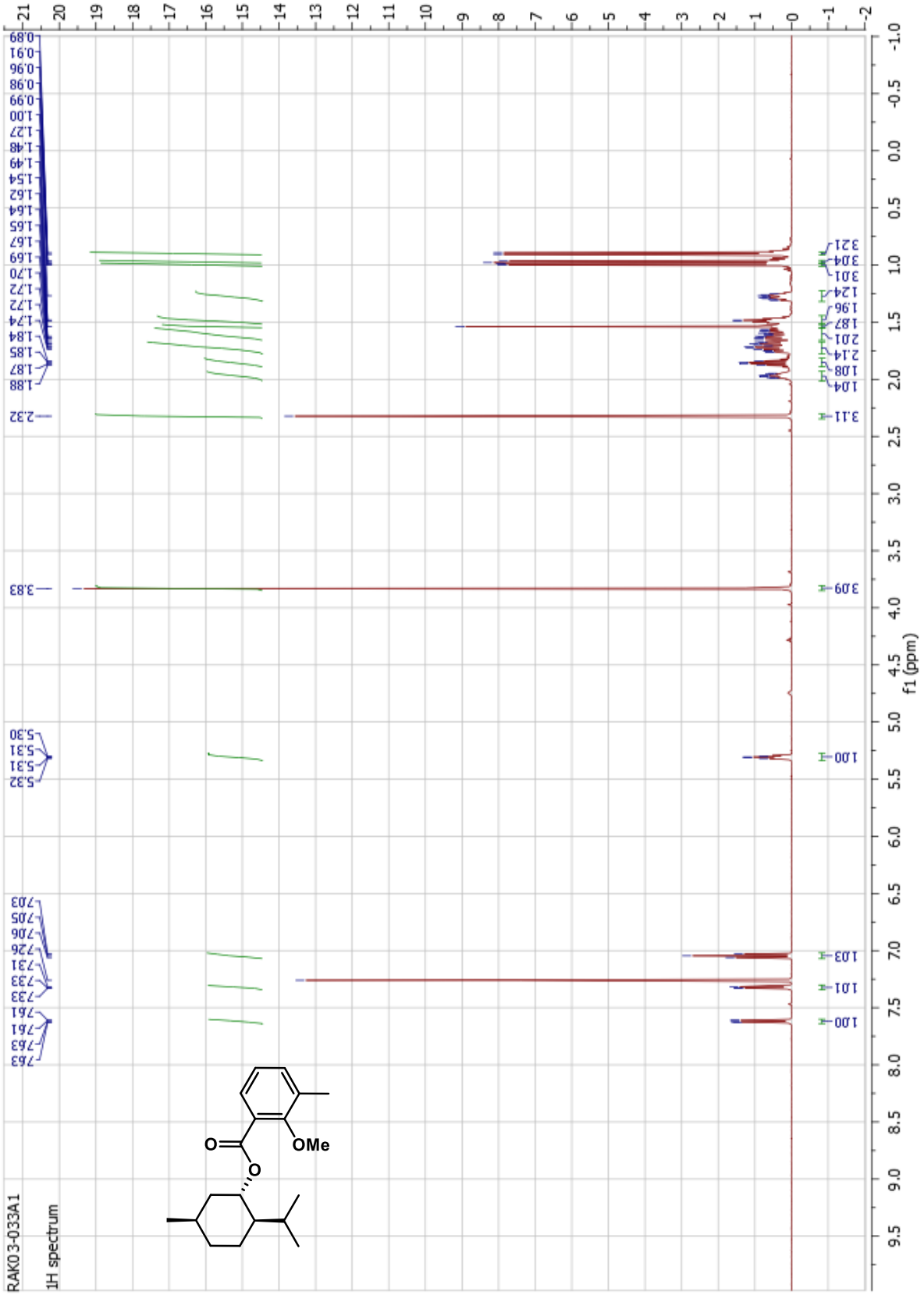

RAK02-139A1
1H spectrum
f1 (ppm)
BnO
OMe
O
O
1.68
2.48
2.52
2.71
2.75
3.56
3.67
3.69
4.05
4.07
4.55
4.57
4.66
4.67
4.68
4.69
4.70
4.89
4.90
7.26
7.34
3.19
1.00
1.02
3.08
0.99
1.01
1.03
2.43
1.00
4.94

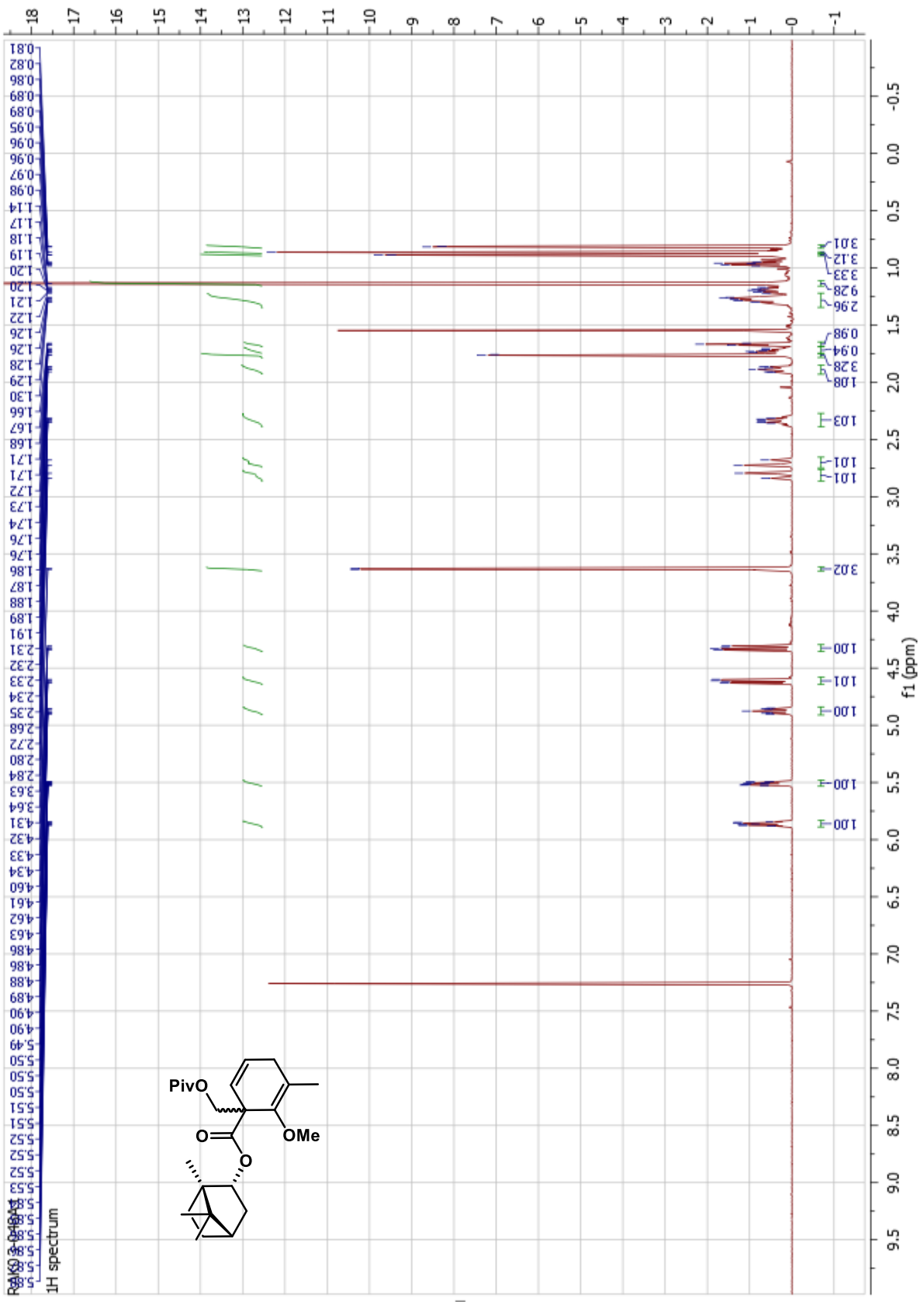

RAK02-290A1
1H spectrum
HO
O
OMe
N
MeO
f1 (ppm)

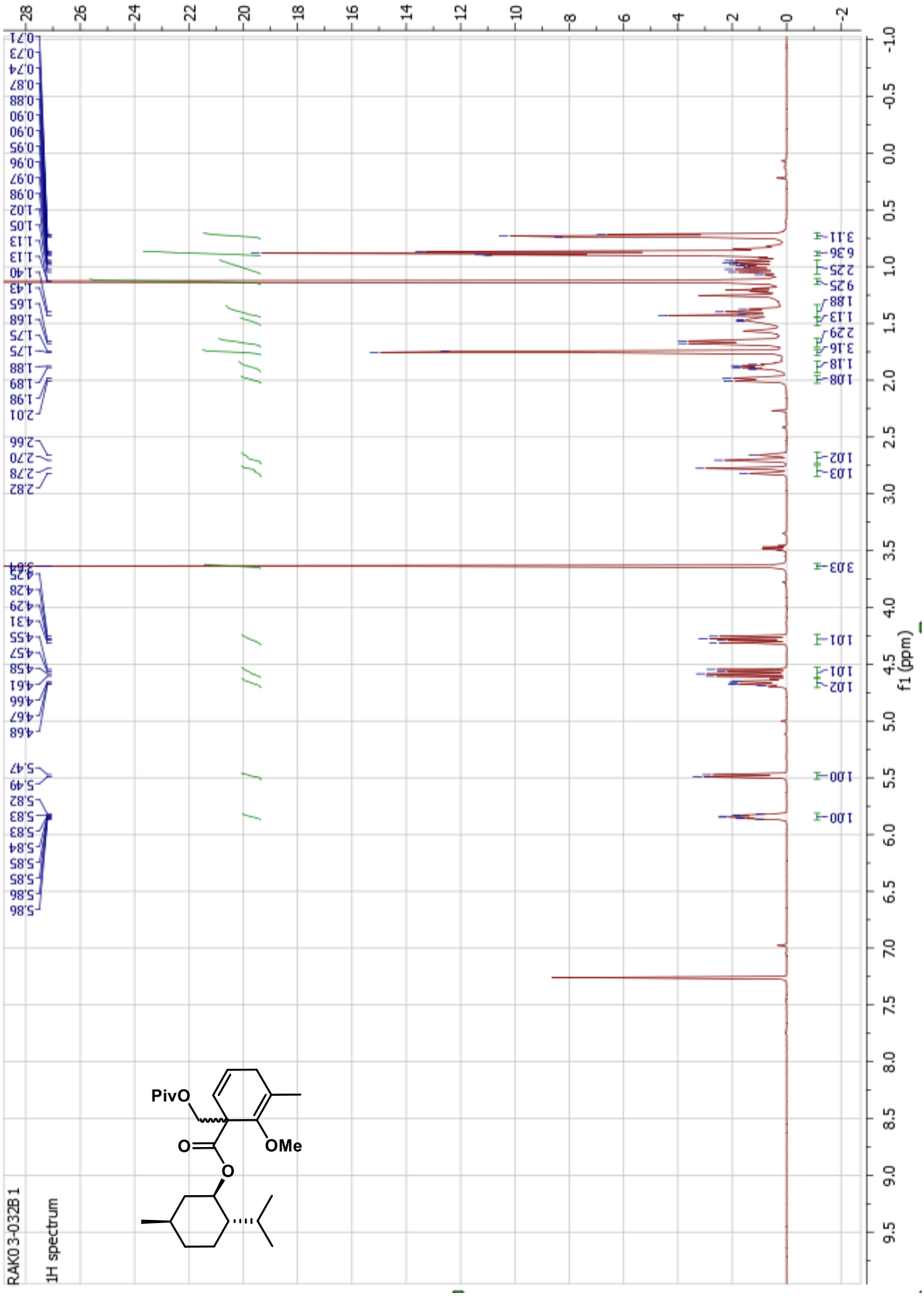

RAK02-261B1
1H spectrum
f1 (ppm)
OH
OMe
O
N
MeO

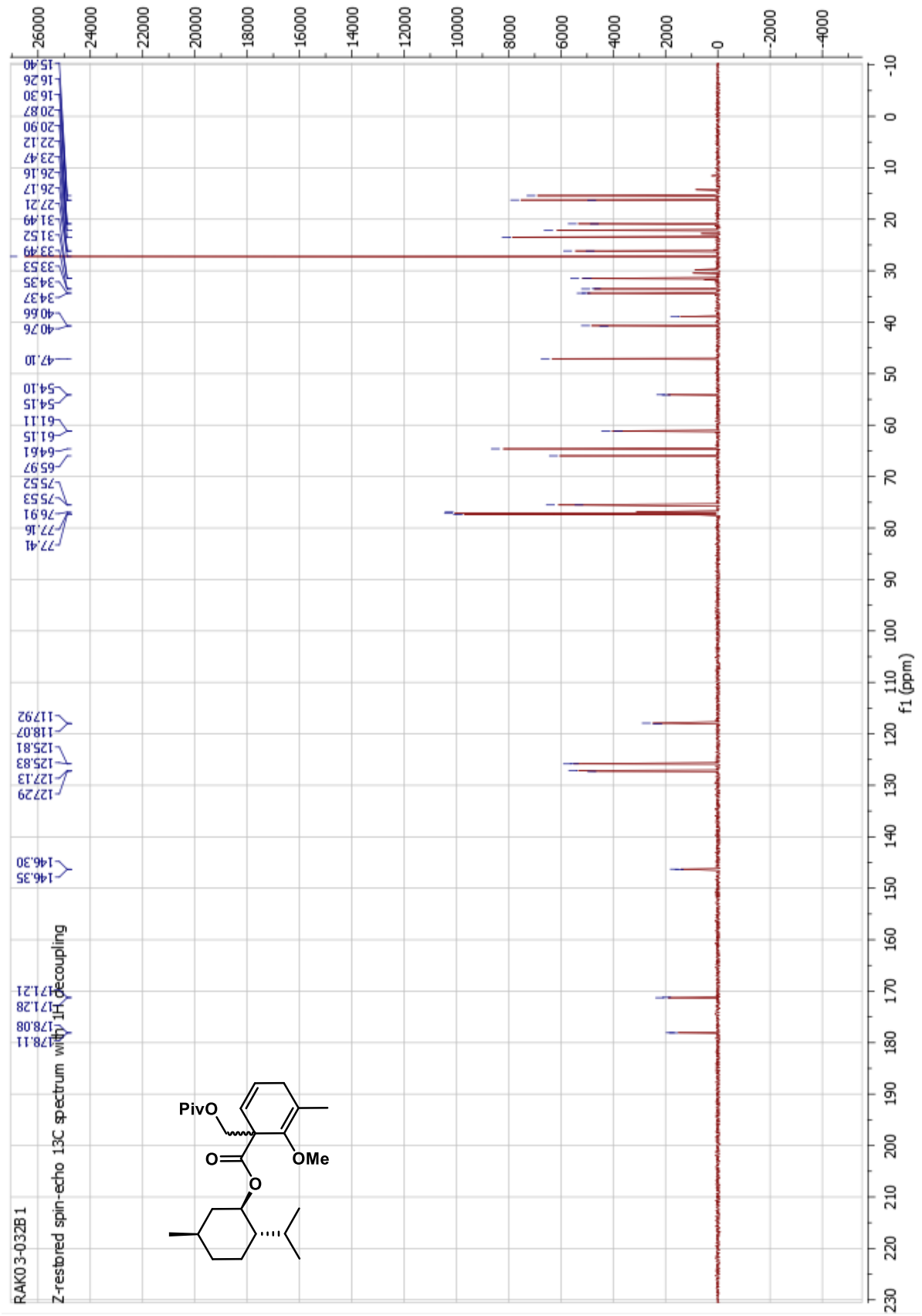

RAK03-034A1
1H spectrum
f1 (ppm)
O
O
OMe

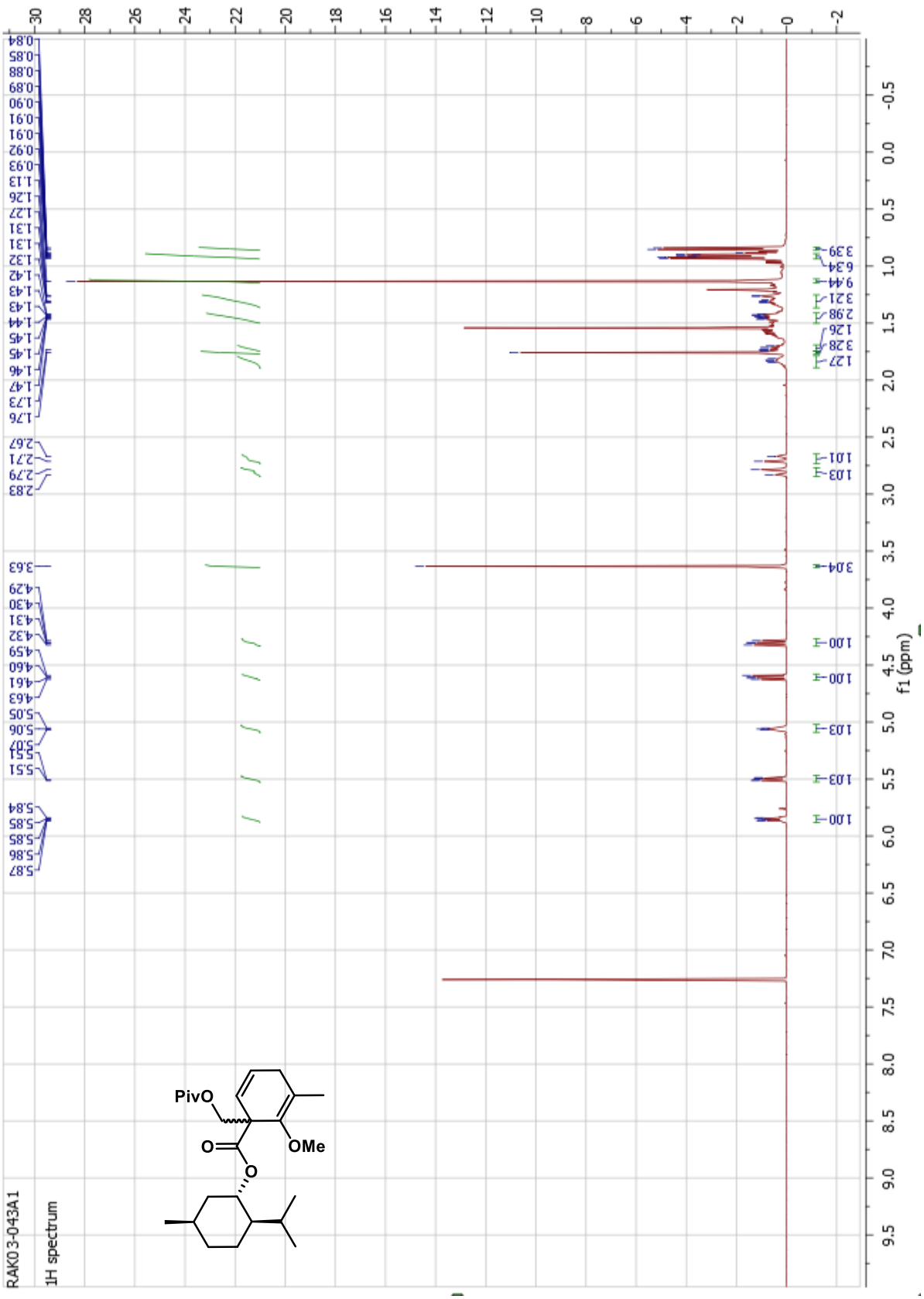

RAK03-031A1
1H spectrum
O
O
OMe
f1 (ppm)

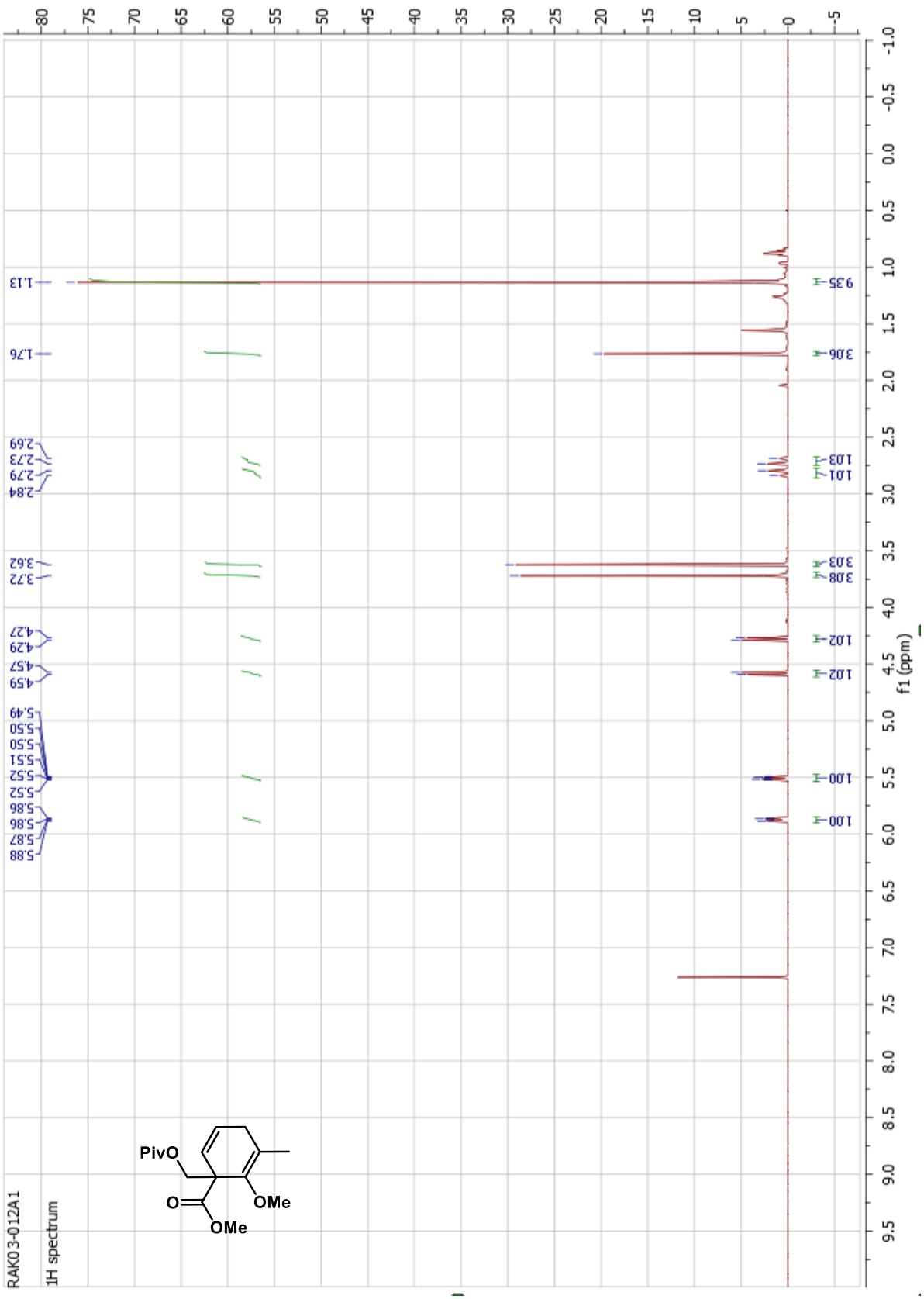

RAK03-033A1
1H spectrum
O
O
OMe
f1 (ppm)

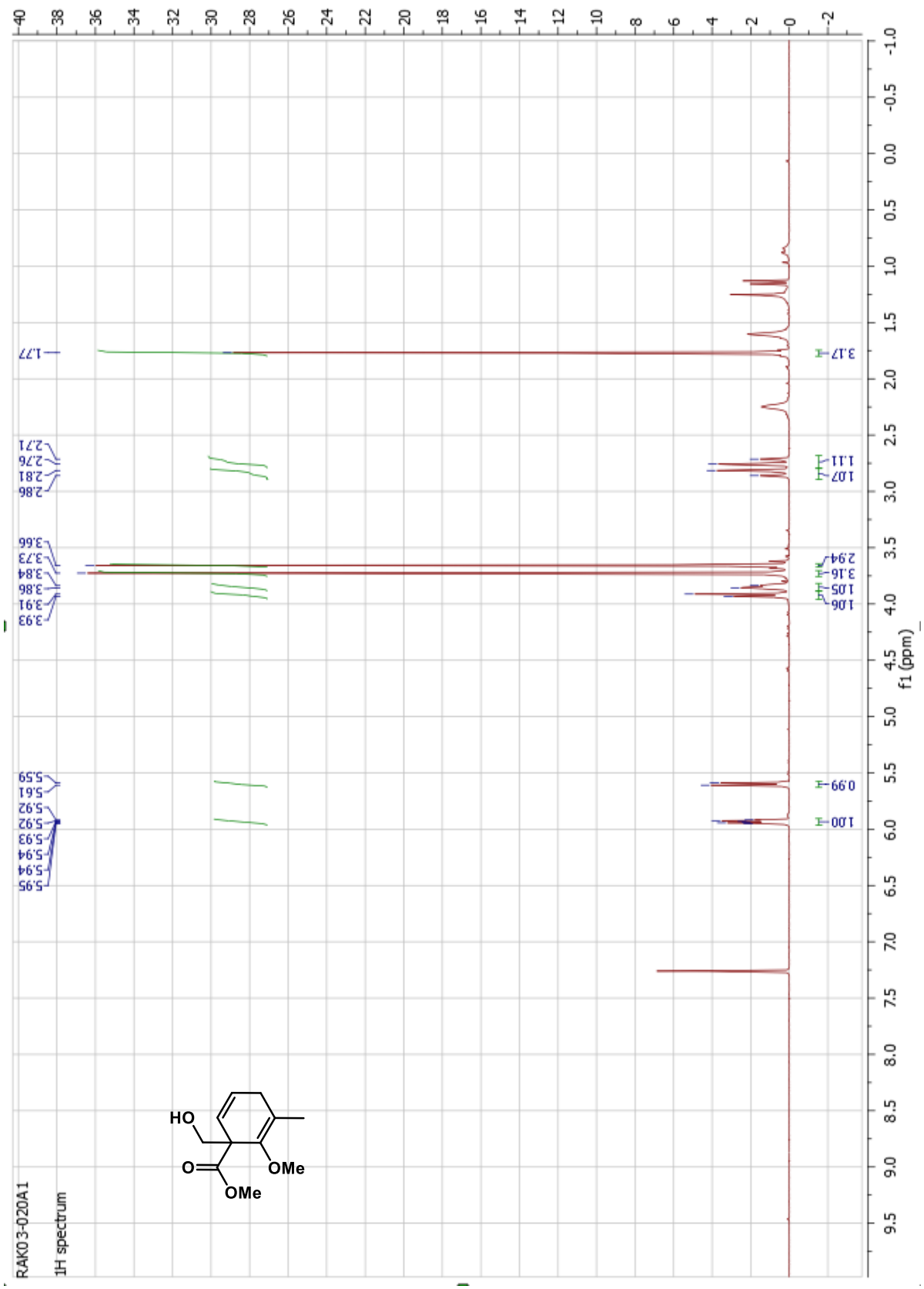

PivO
O
O
OMe
f1 (ppm)
1H spectrum

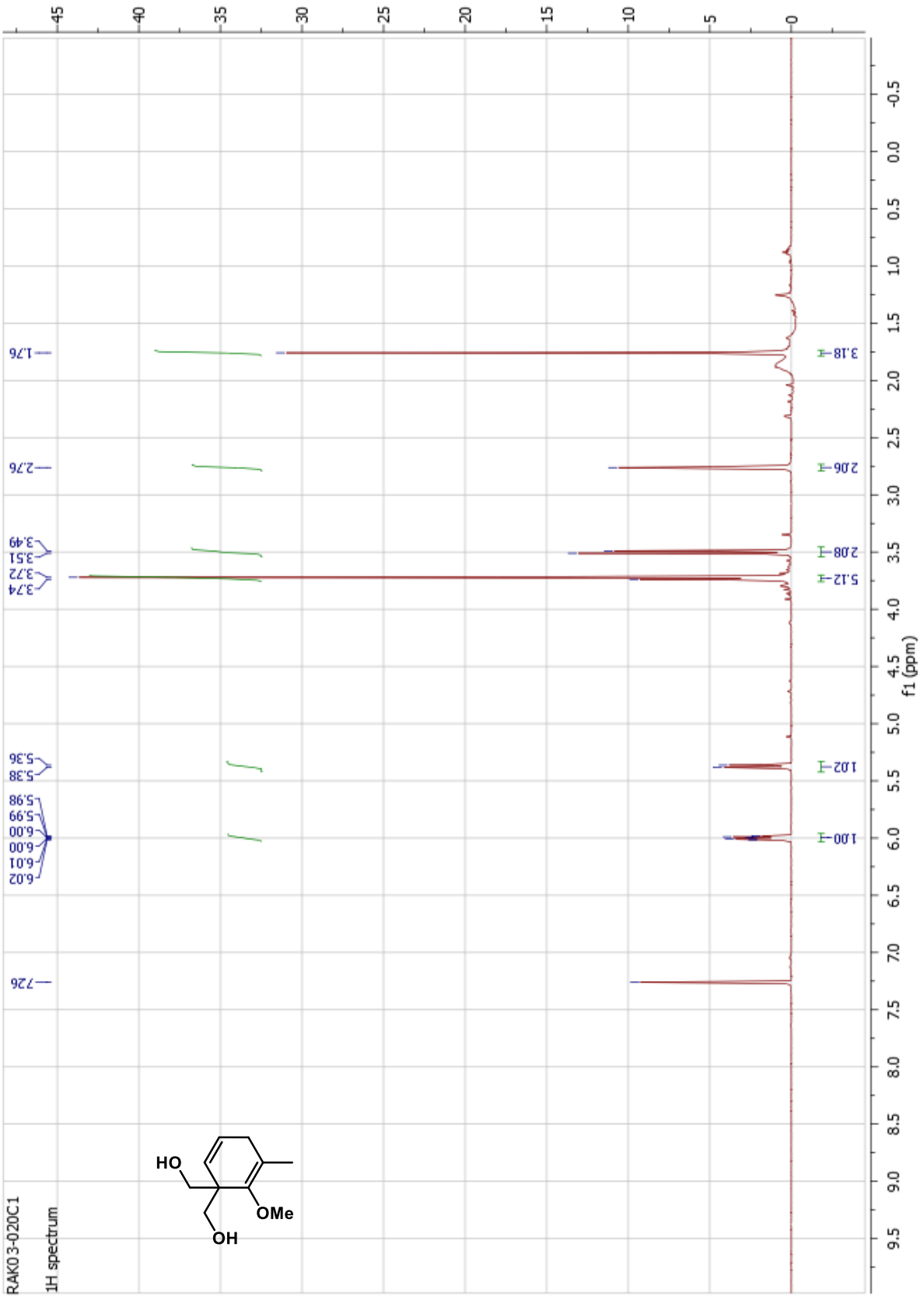

PivO
O
OMe
O
RAK03-032B1
1H spectrum
f1 (ppm)

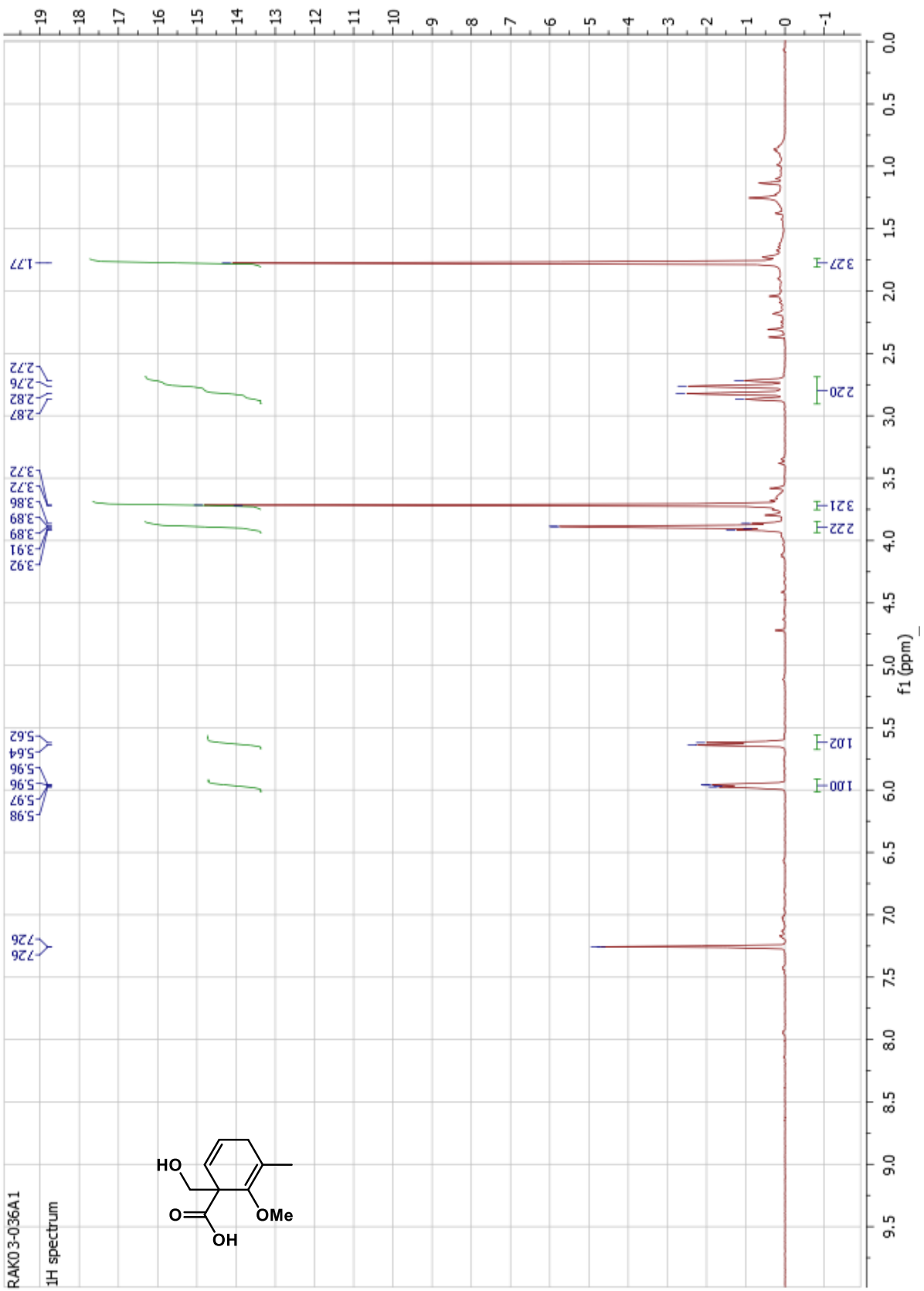

RAK03-032B1
Z-restored spin-echo 13C spectrum with 1H decoupling
PivO
O
O
OMe
f1 (ppm)

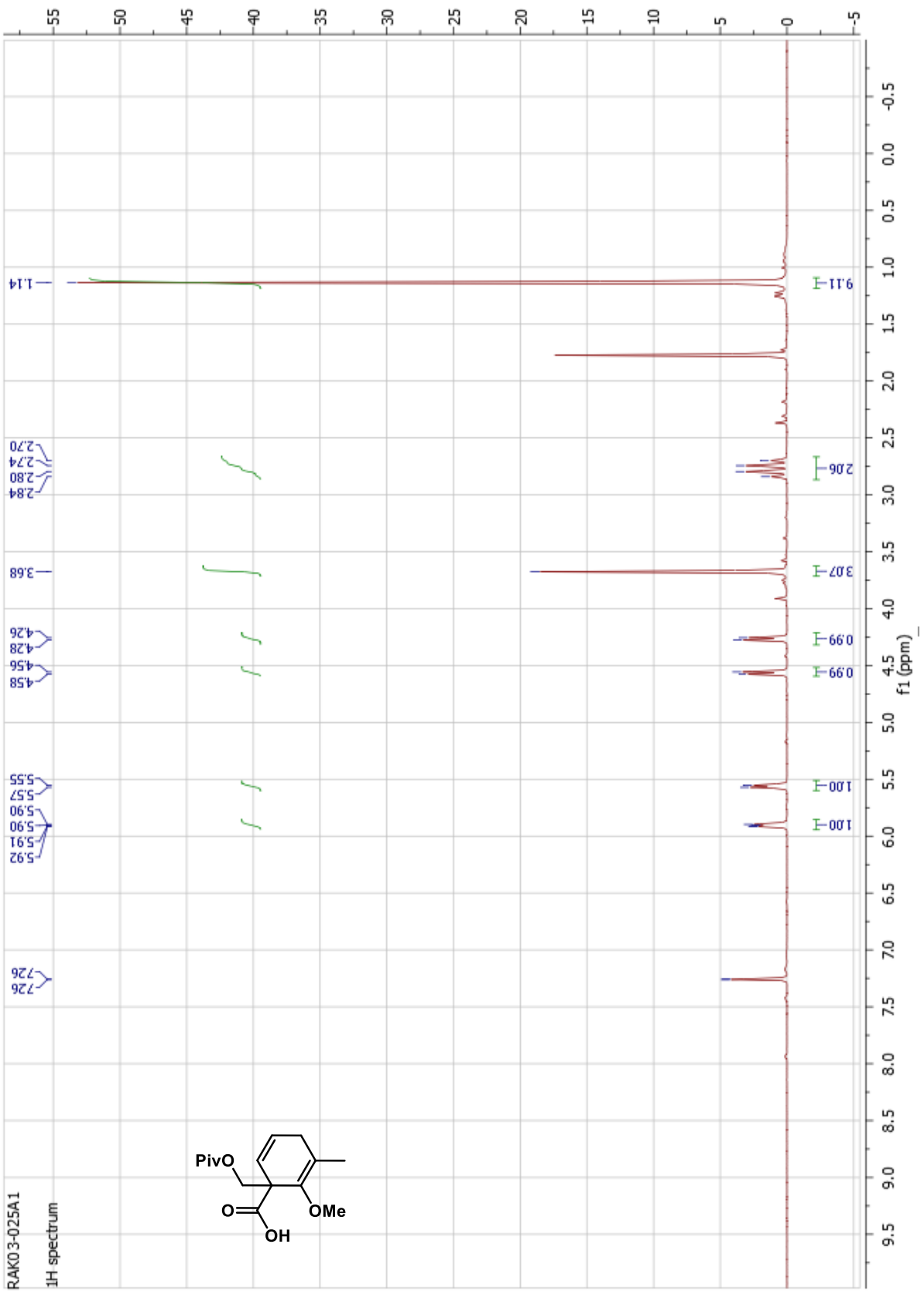

RAK03-043A1
1H spectrum
PivO
O
OMe
O
f1 (ppm)

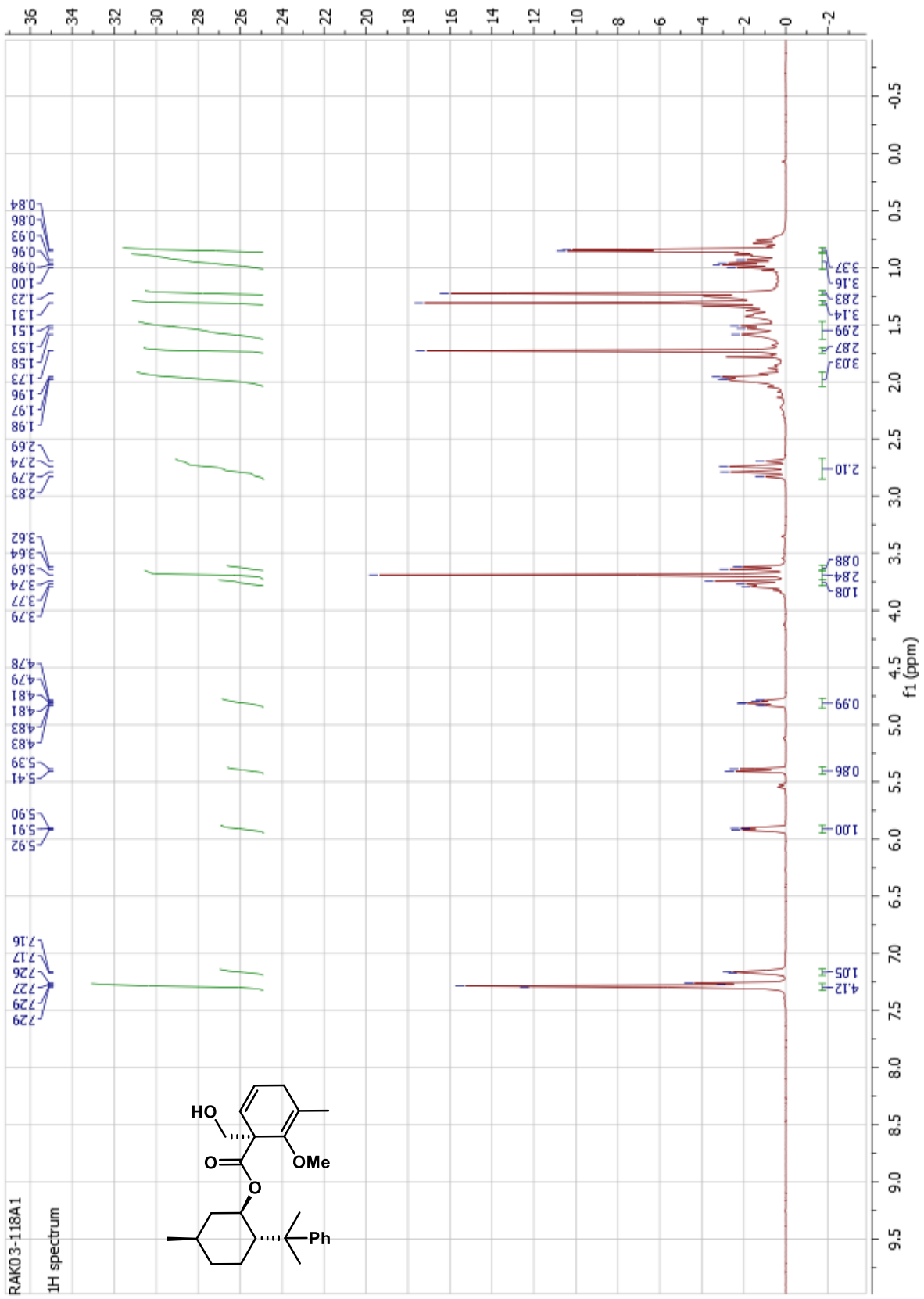

RAK03-012A1
1H spectrum
PivO
O
OMe
OMe
f1 (ppm)

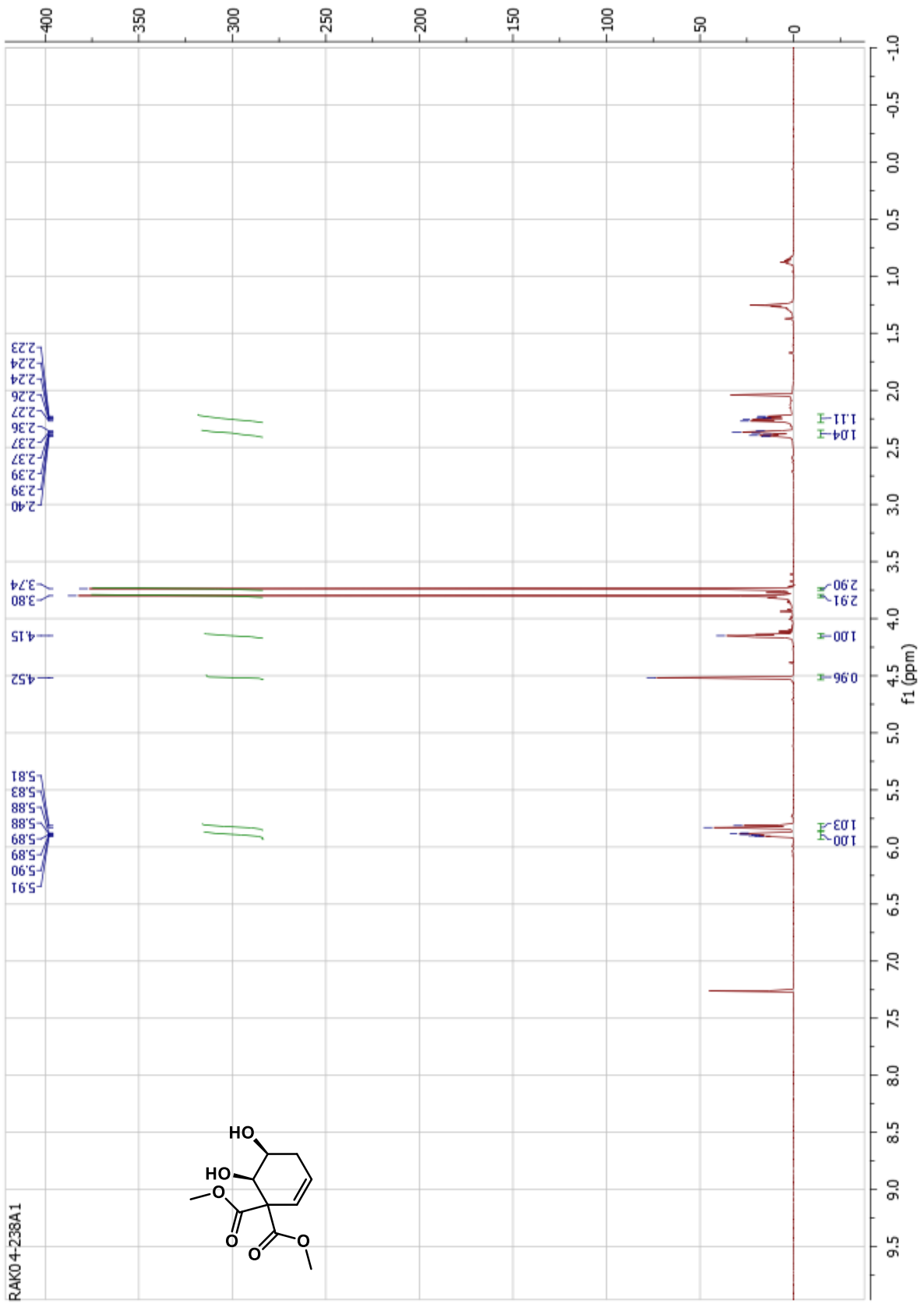

RAK03-020A1
1H spectrum
HO
O
OMe
OMe
f1 (ppm)

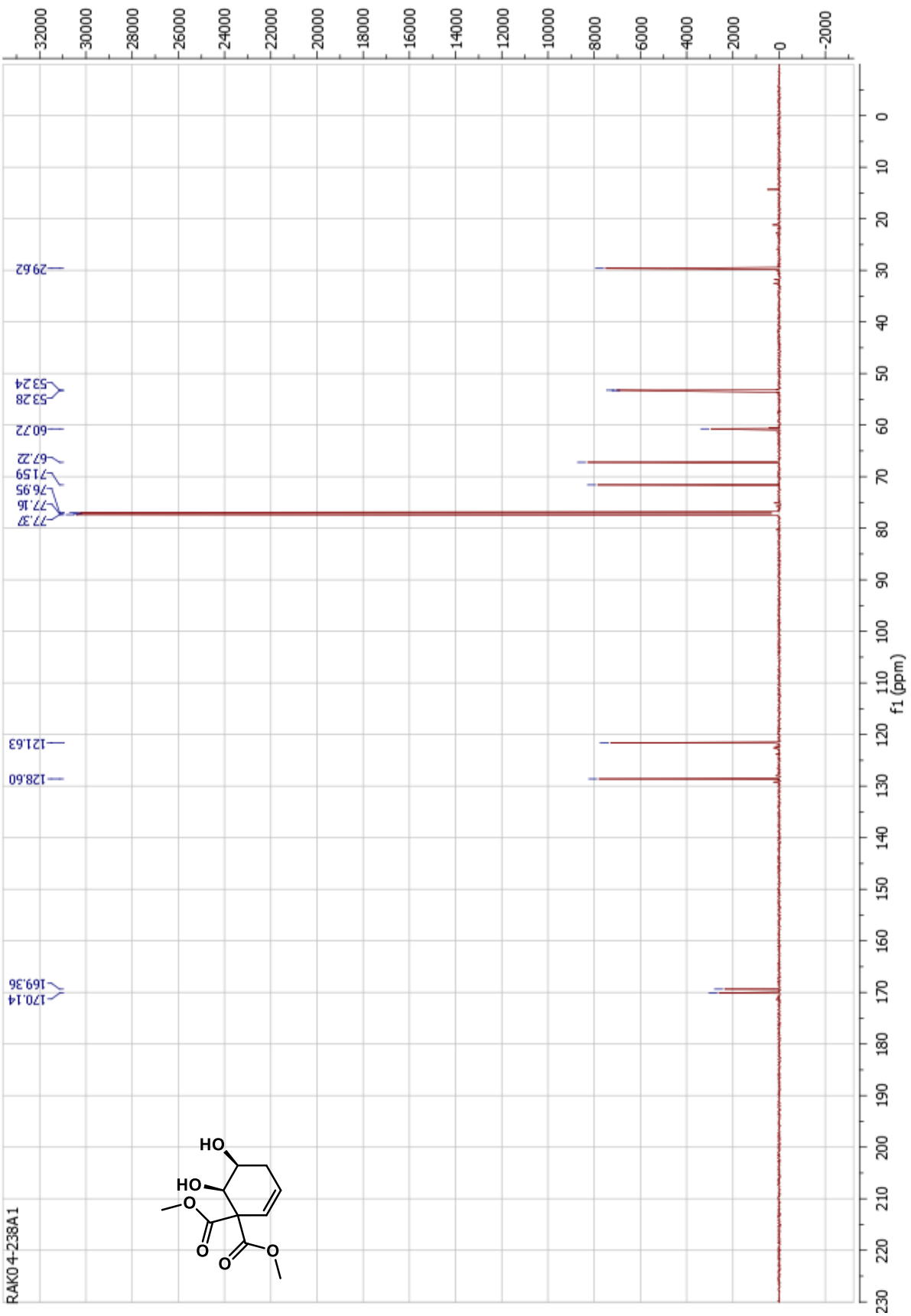

RAK03-020C1
1H spectrum
HO
OMe
OH
f1 (ppm)
1.76
2.76
3.49
3.51
3.72
3.74
5.36
5.38
5.98
5.99
6.00
6.00
6.01
6.02
7.26
3.18
2.06
2.08
5.12
1.02
1.00

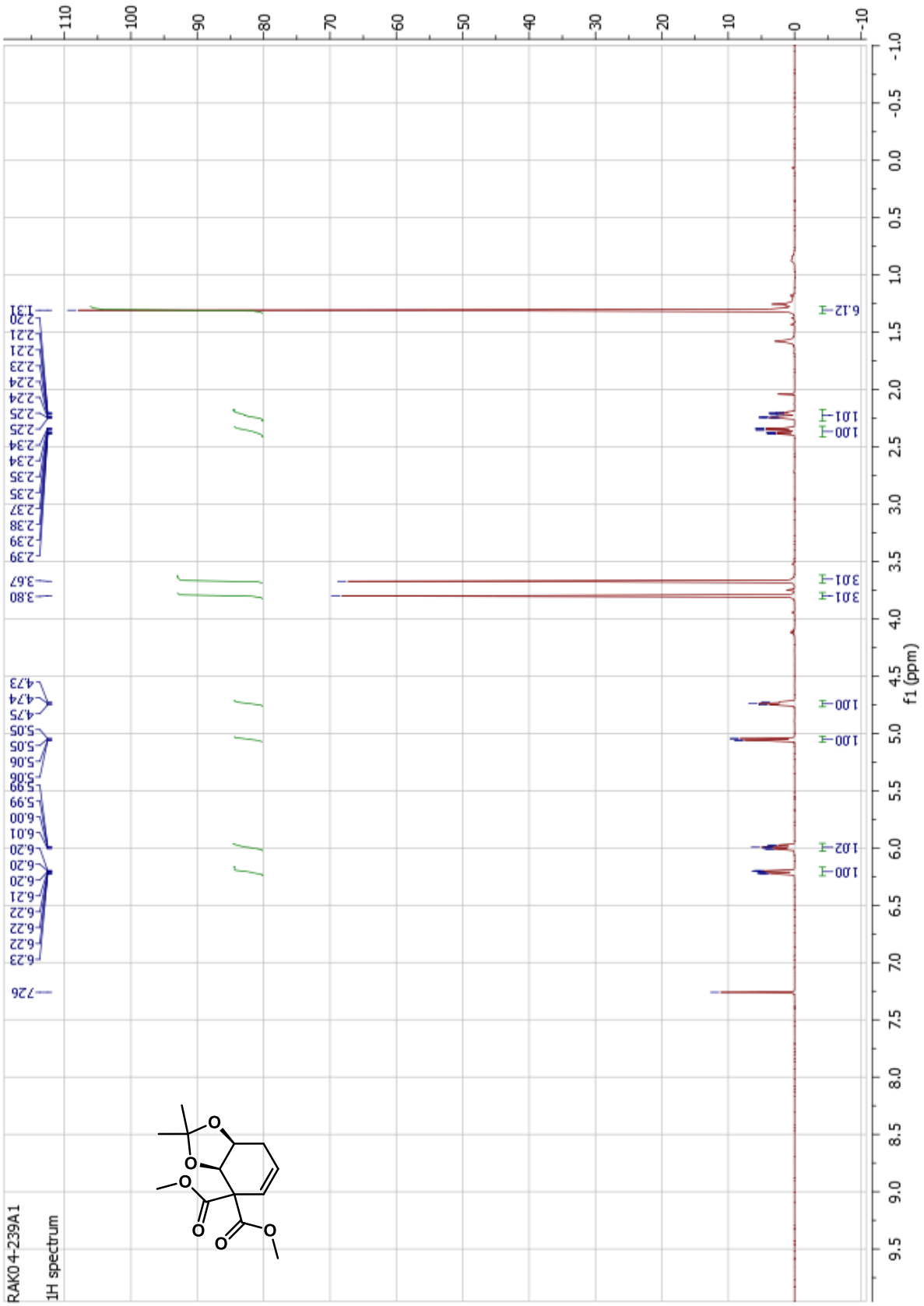

RAK03-036A1
1H spectrum
HO
O
OH
OMe
f1 (ppm)
1.77
3.27
2.87
2.82
2.76
2.72
2.20
3.92
3.91
3.89
3.86
3.72
3.72
3.21
2.22
5.98
5.97
5.96
5.96
5.64
5.62
1.02
1.00
7.26
7.26

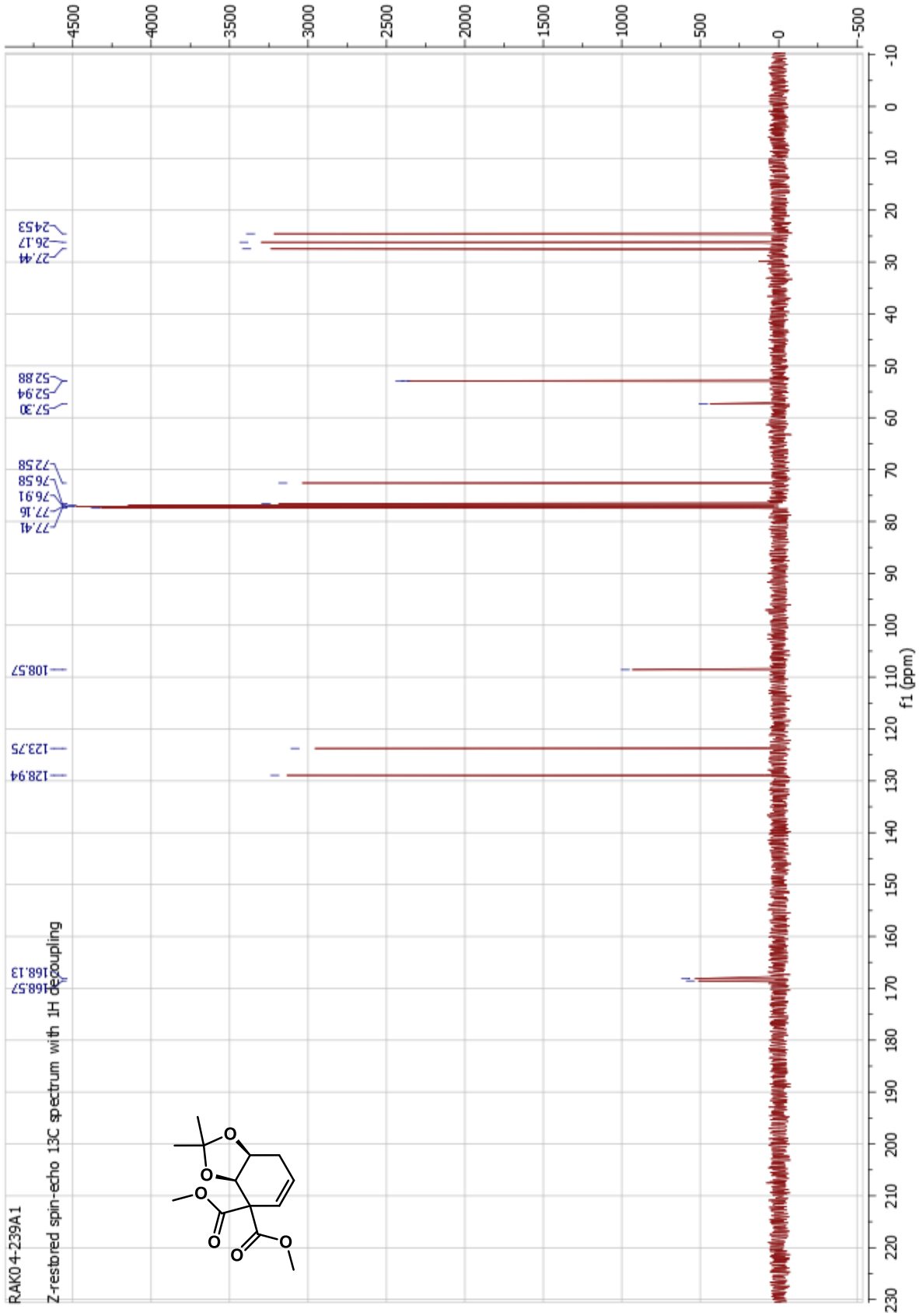

RAK03-025A1
1H spectrum
PivO
O
OH
OMe
f1 (ppm)
1.14
9.11
2.84
2.80
2.74
2.70
2.06
3.68
3.07
4.58
4.56
4.28
4.26
0.99
0.99
5.92
5.91
5.90
5.90
5.57
5.55
1.00
1.00
7.26
7.26

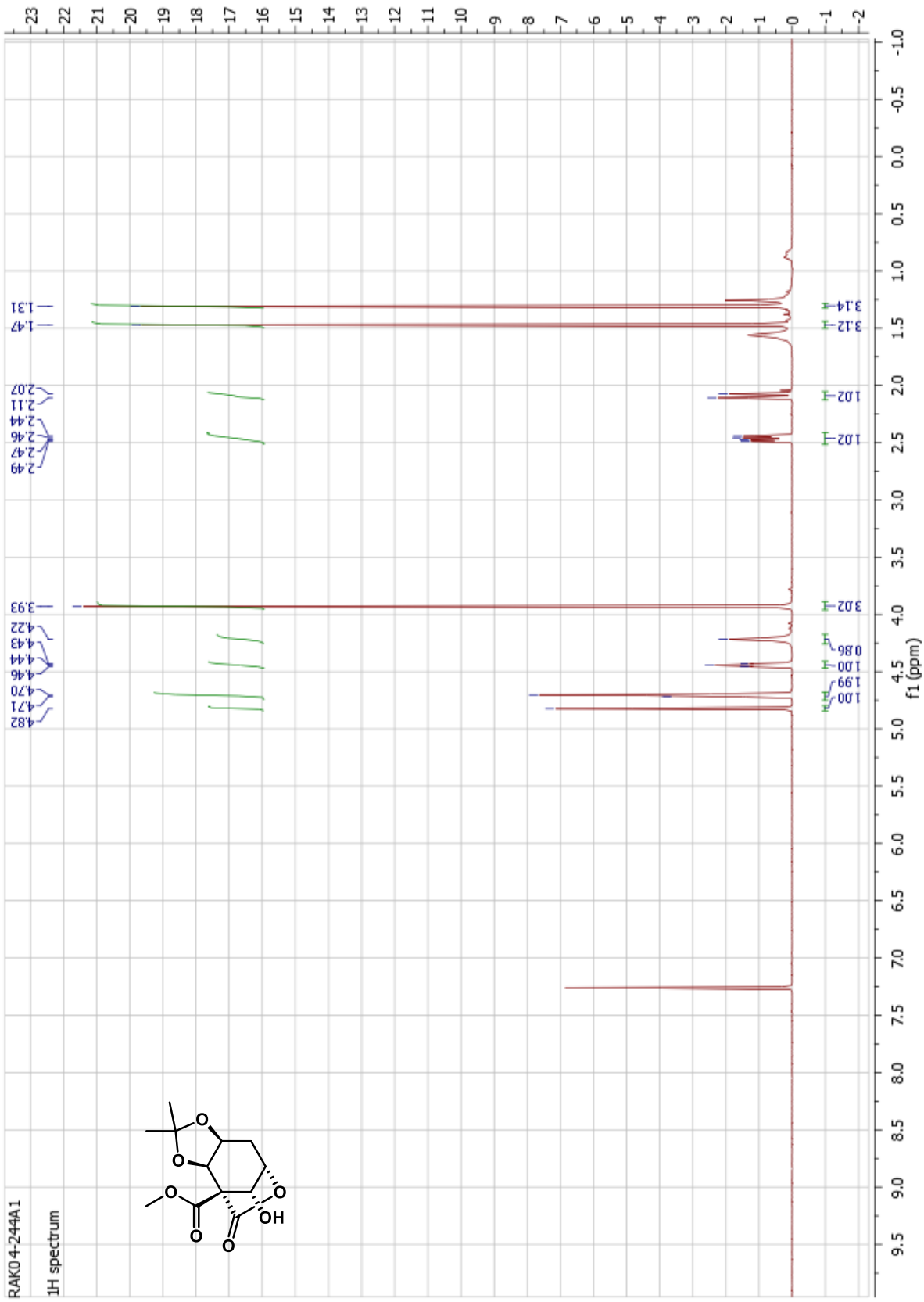

RAK03-118A1
1H spectrum
HO
O
OMe
O
Ph
f1 (ppm)

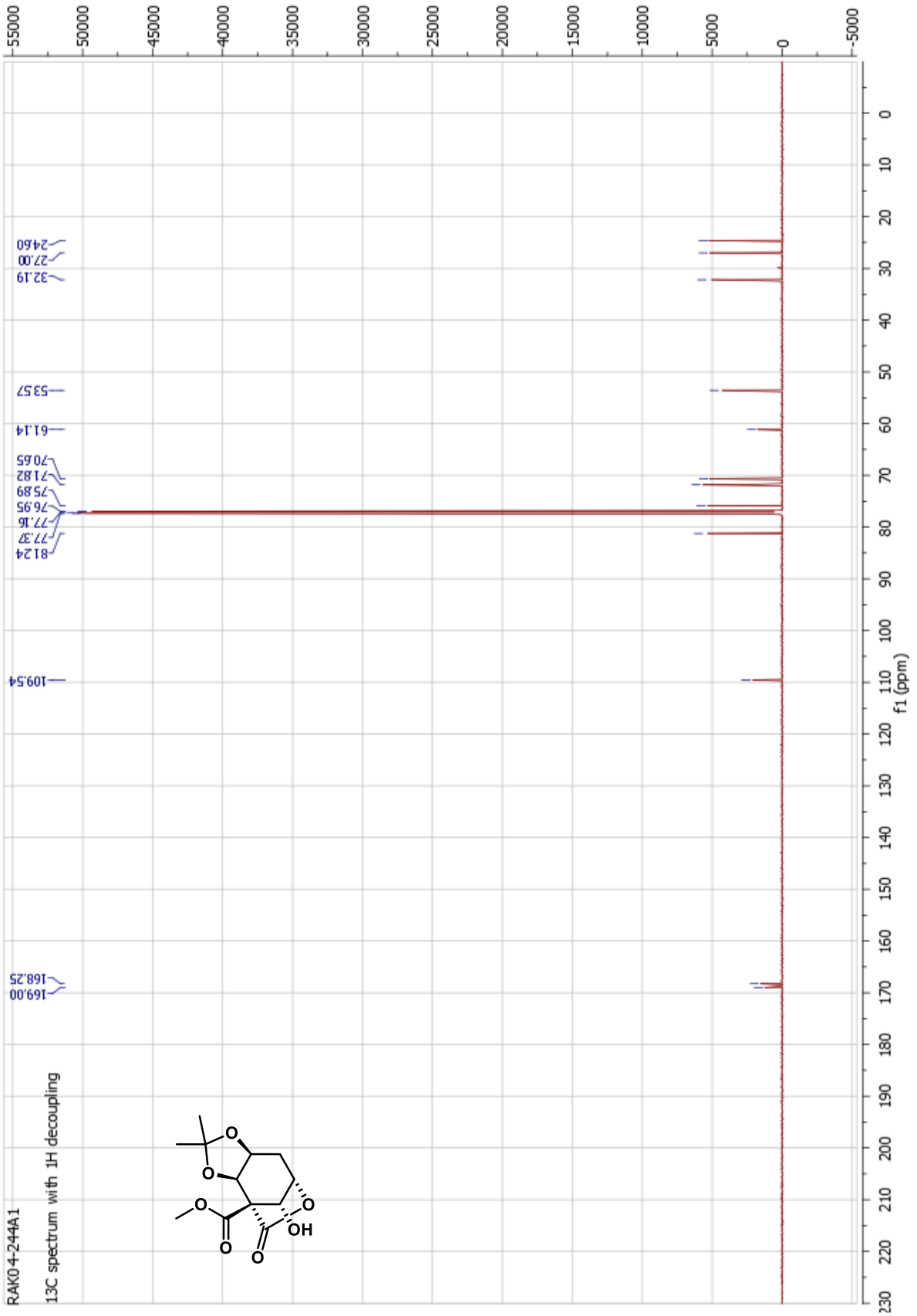

RAK04-238A1
f1 (ppm)
HO
HO
O
O
O
O

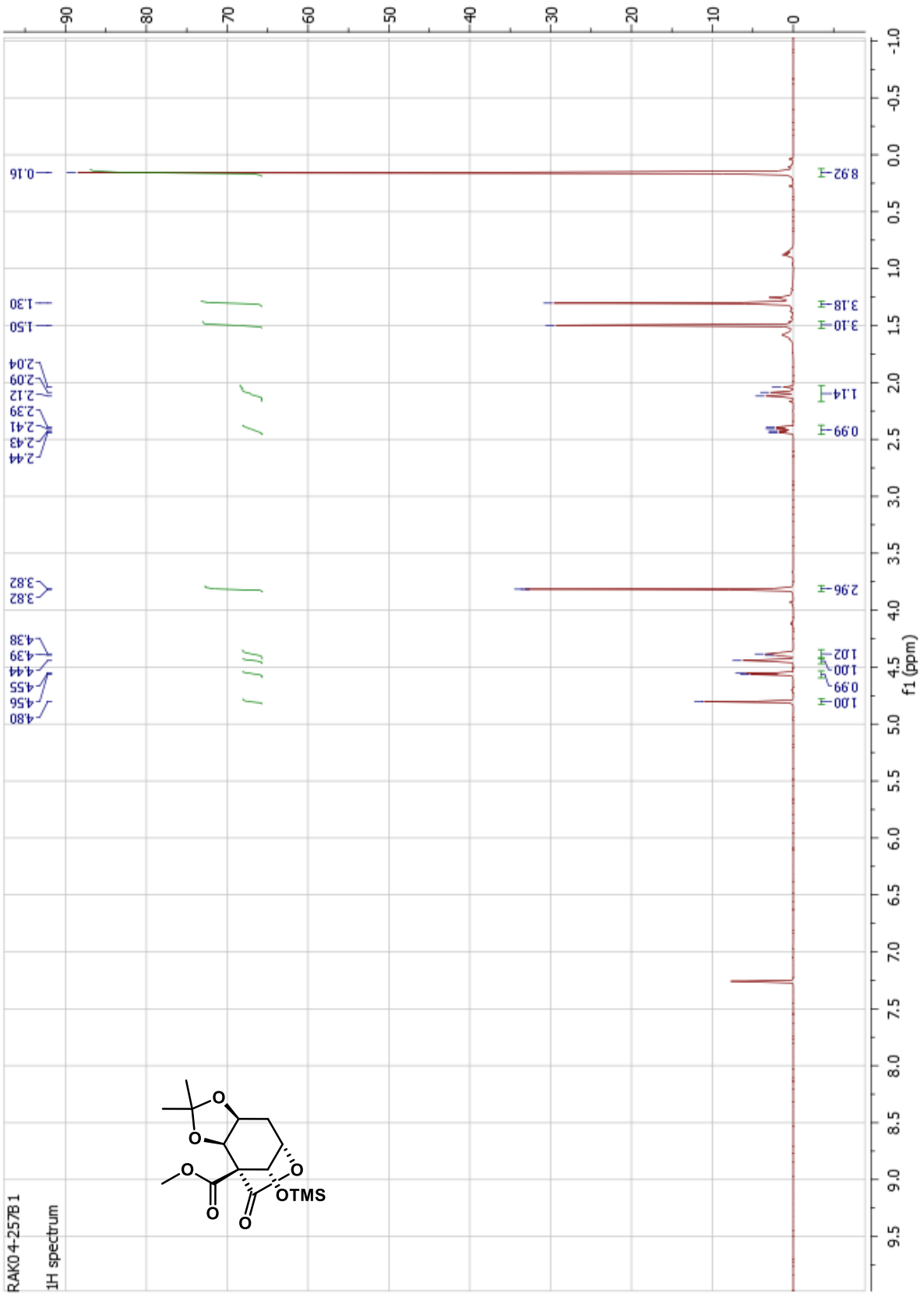

RAK04-238A1
f1 (ppm)
29.62
53.24
53.28
60.72
67.22
71.59
76.95
77.16
77.37
121.63
128.60
169.36
170.14
HO
HO
O
O
O
O

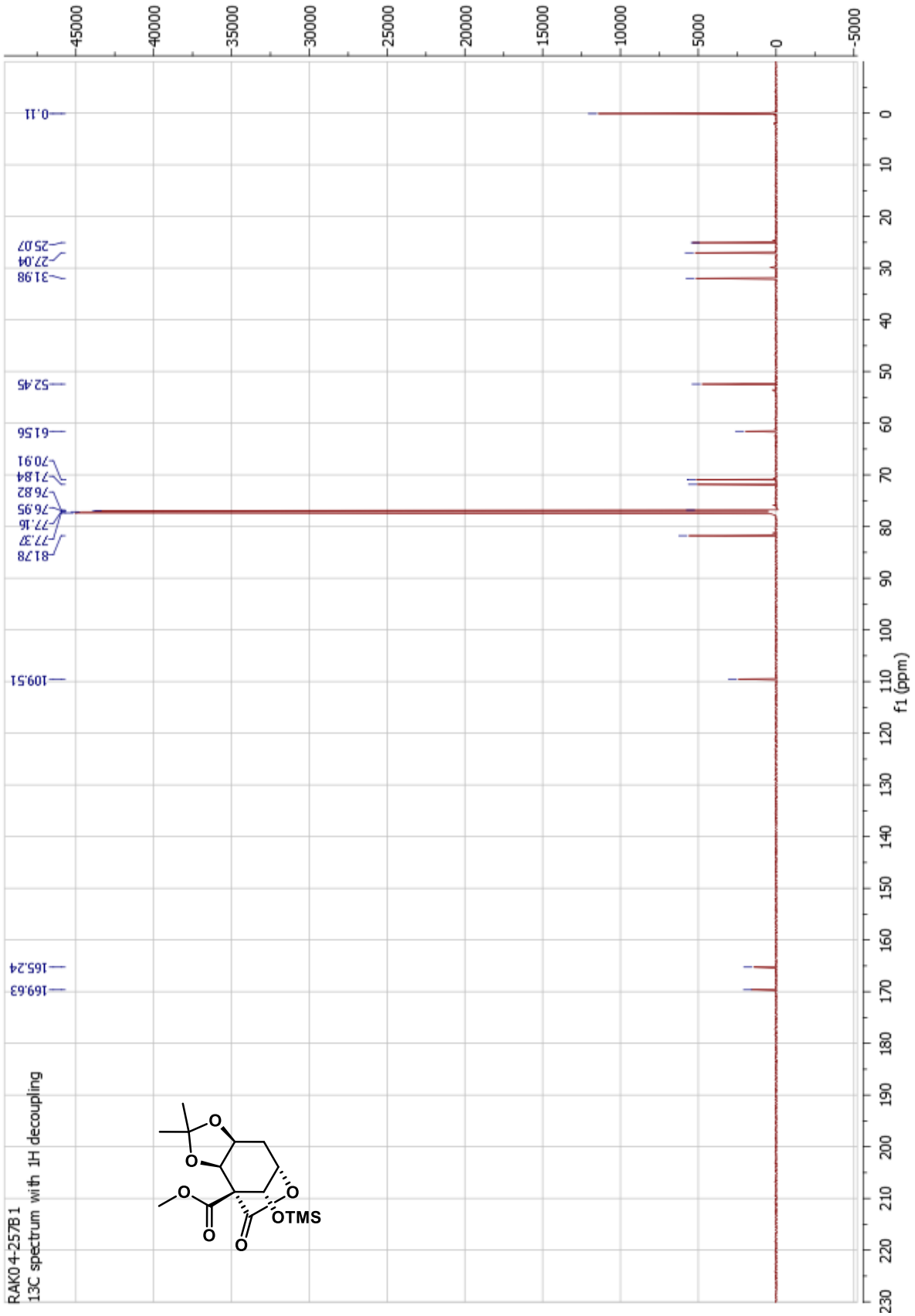

RAK04-239A1
1H spectrum
f1 (ppm)

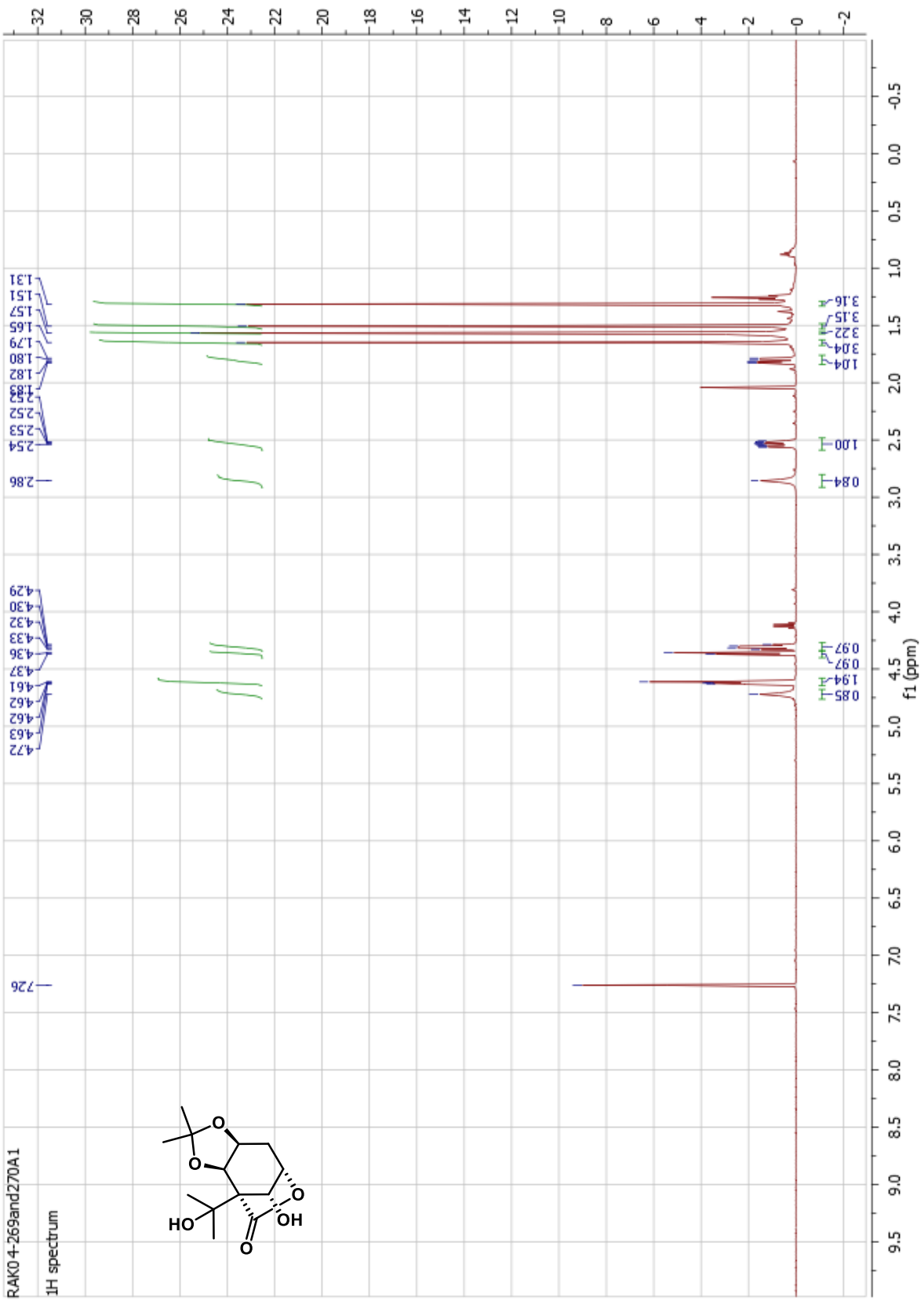

RAK04-239A1
Z-restored spin-echo 13C spectrum with 1H decoupling
168.57
168.13
128.94
123.75
108.57
77.41
77.16
76.91
76.58
72.58
57.30
52.94
52.88
27.44
26.17
24.53
f1 (ppm)

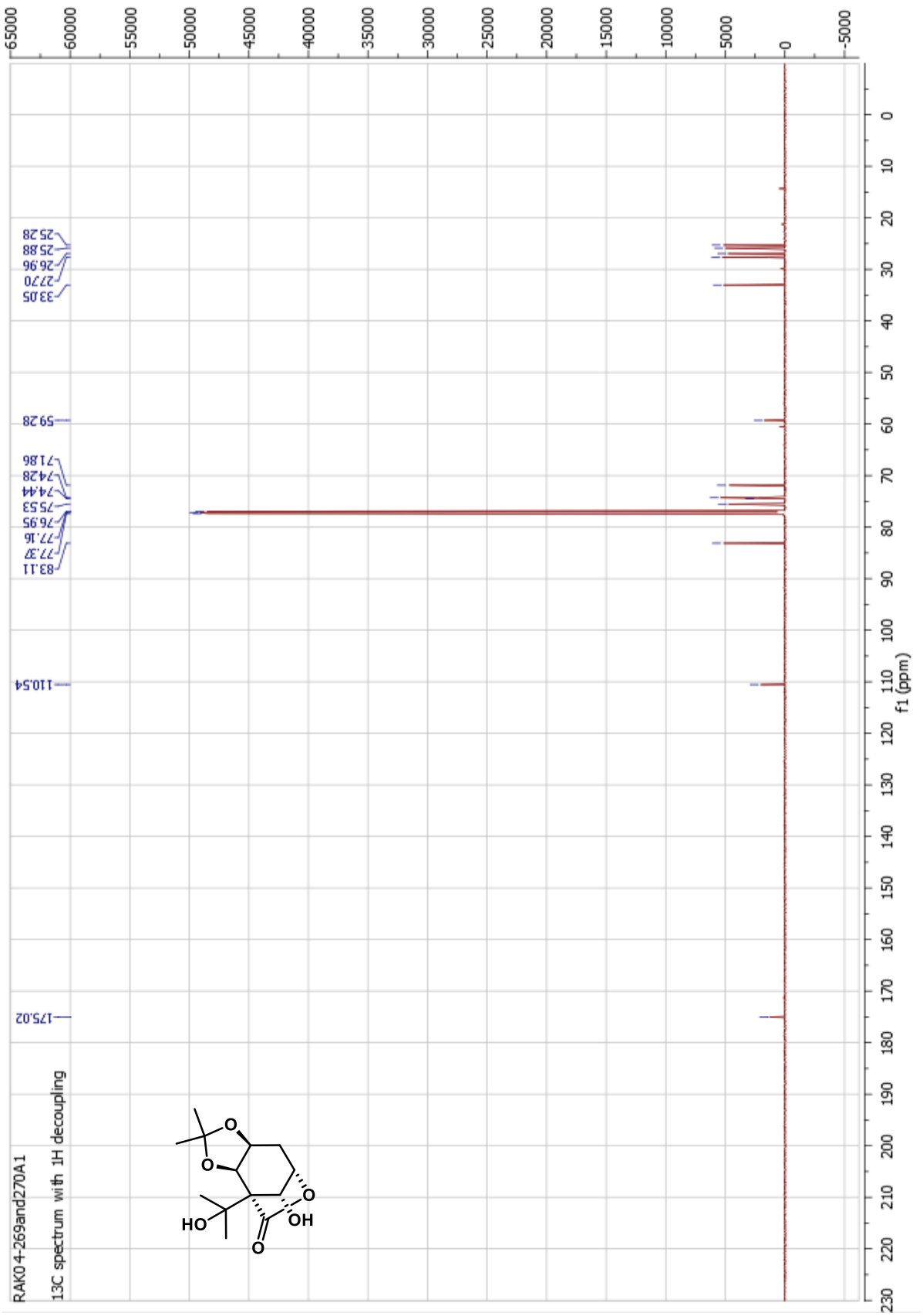

RAK04-244A1
1H spectrum
f1 (ppm)
OH

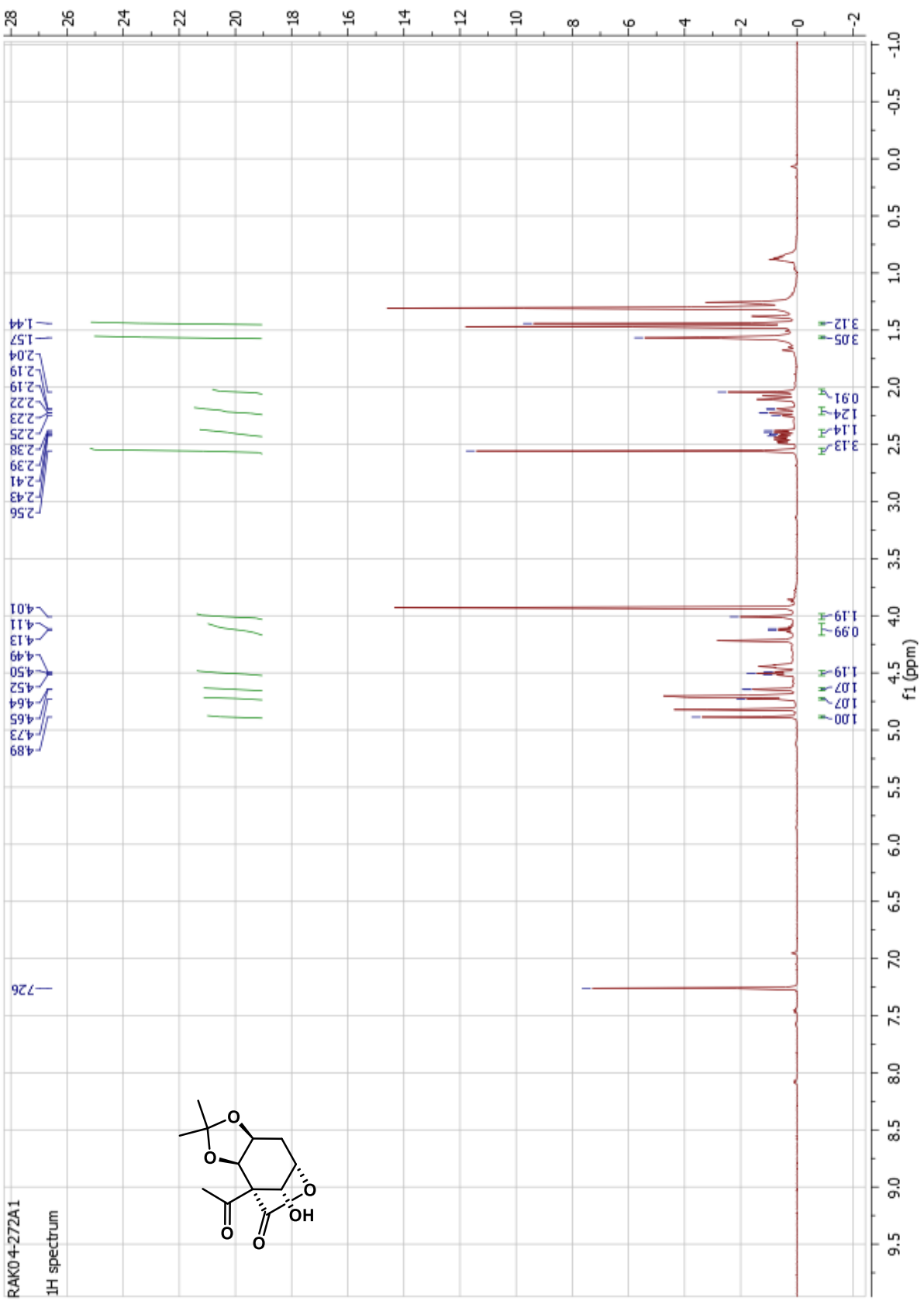

RAK04-244A1
13C spectrum with 1H decoupling
f1 (ppm)
24.60
27.00
32.19
53.57
61.14
70.65
71.82
75.89
76.95
77.16
77.37
81.24
109.54
169.00
168.25
OH

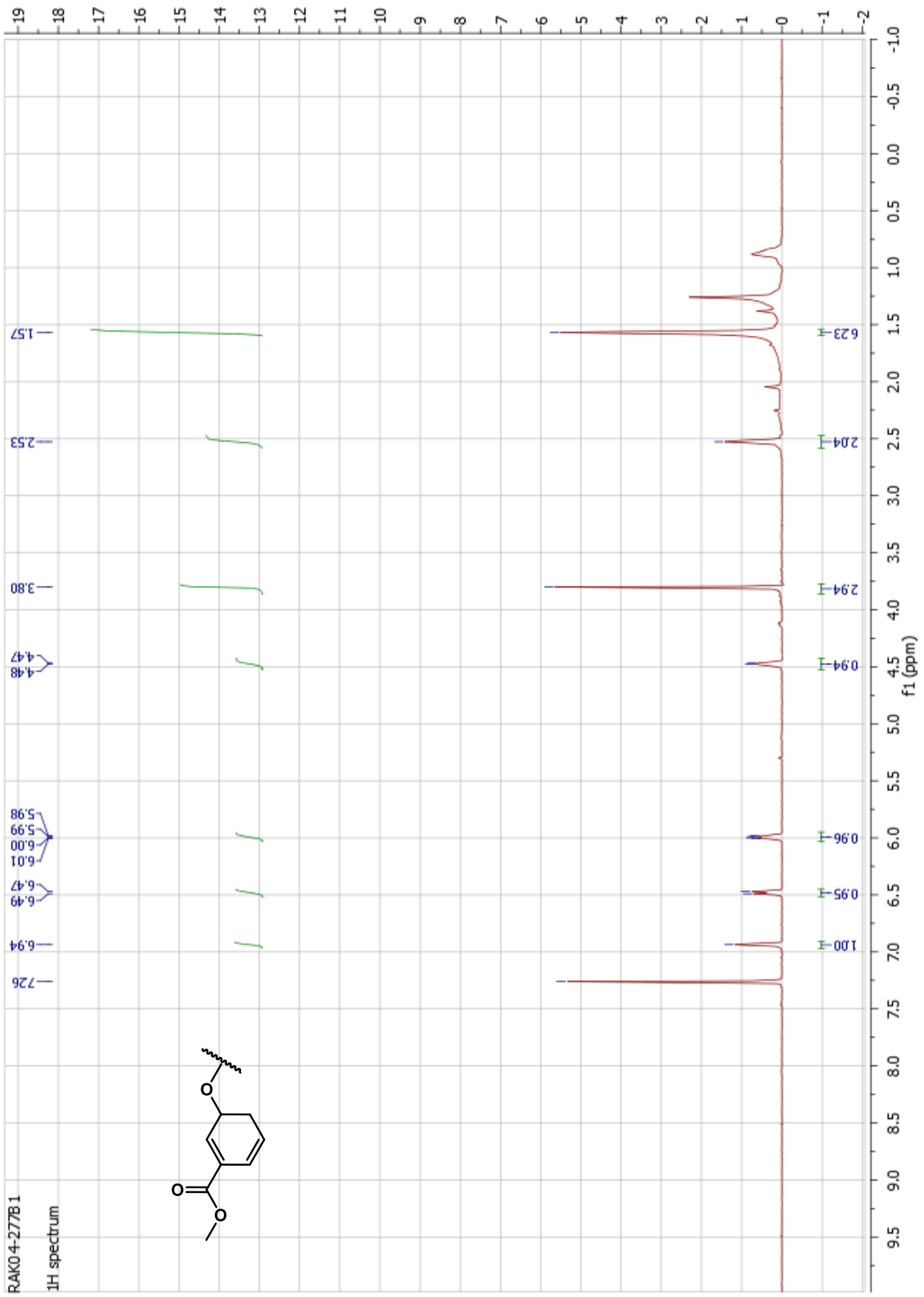

RAK04-257B1
1H spectrum
OTMS
f1 (ppm)

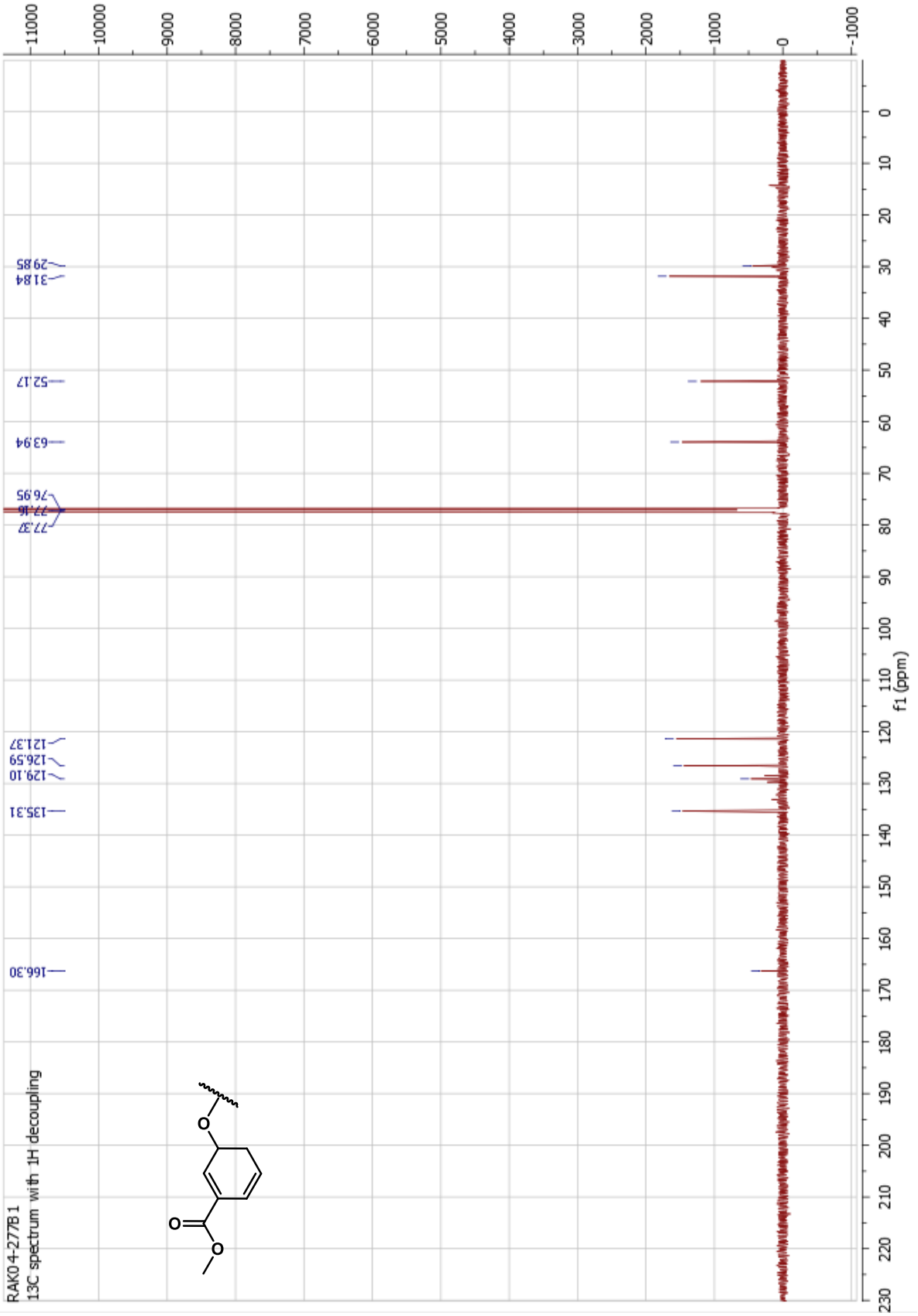

RAK04-257B1
13C spectrum with 1H decoupling
0.11
25.07
27.04
31.98
52.45
61.56
70.91
71.84
76.82
76.95
77.16
77.37
81.78
109.51
165.24
169.63
OTMS
f1 (ppm)

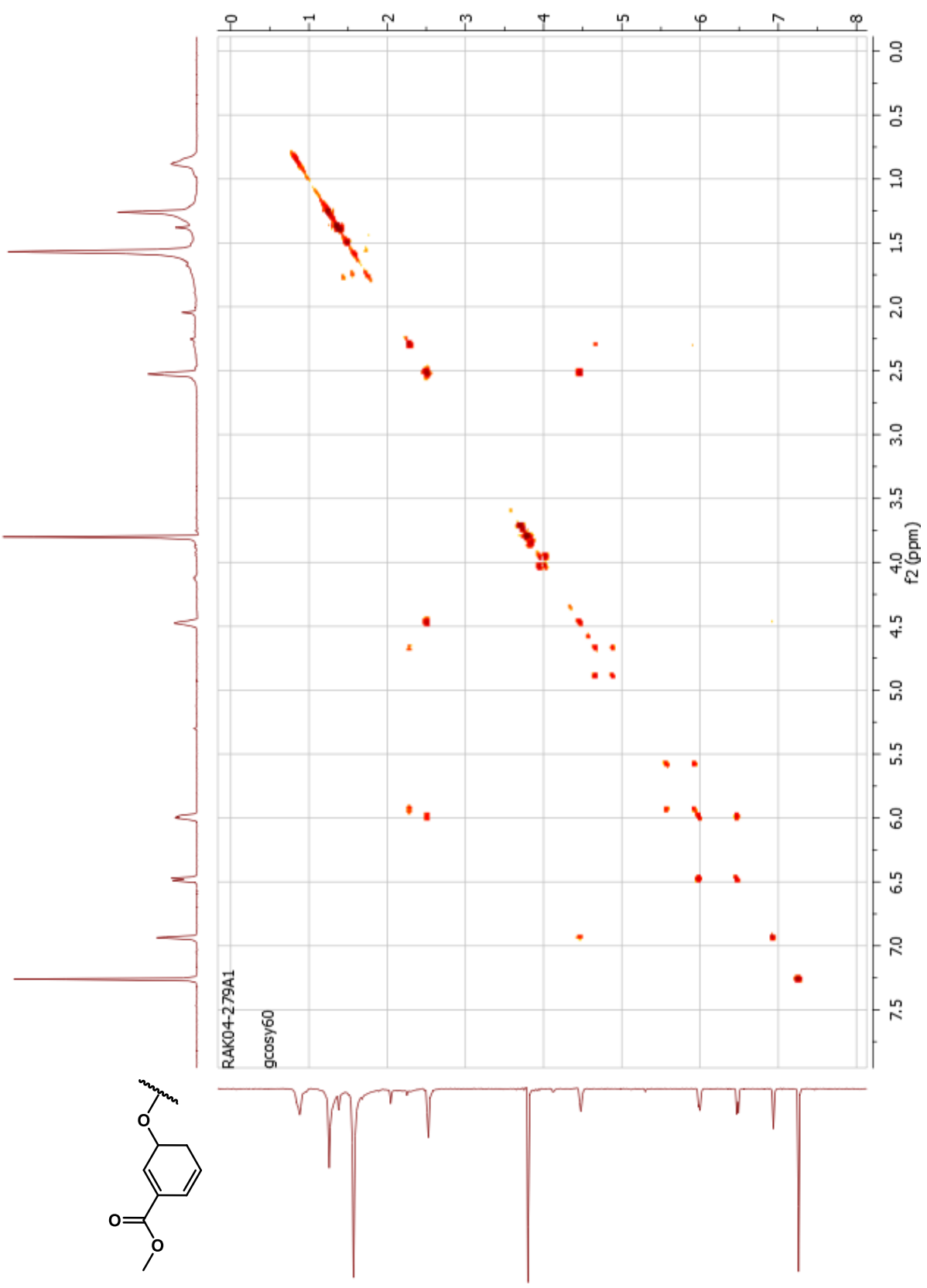

RAK04-269and270A1
1H spectrum
f1 (ppm)
HO
OH
O
O
O
O

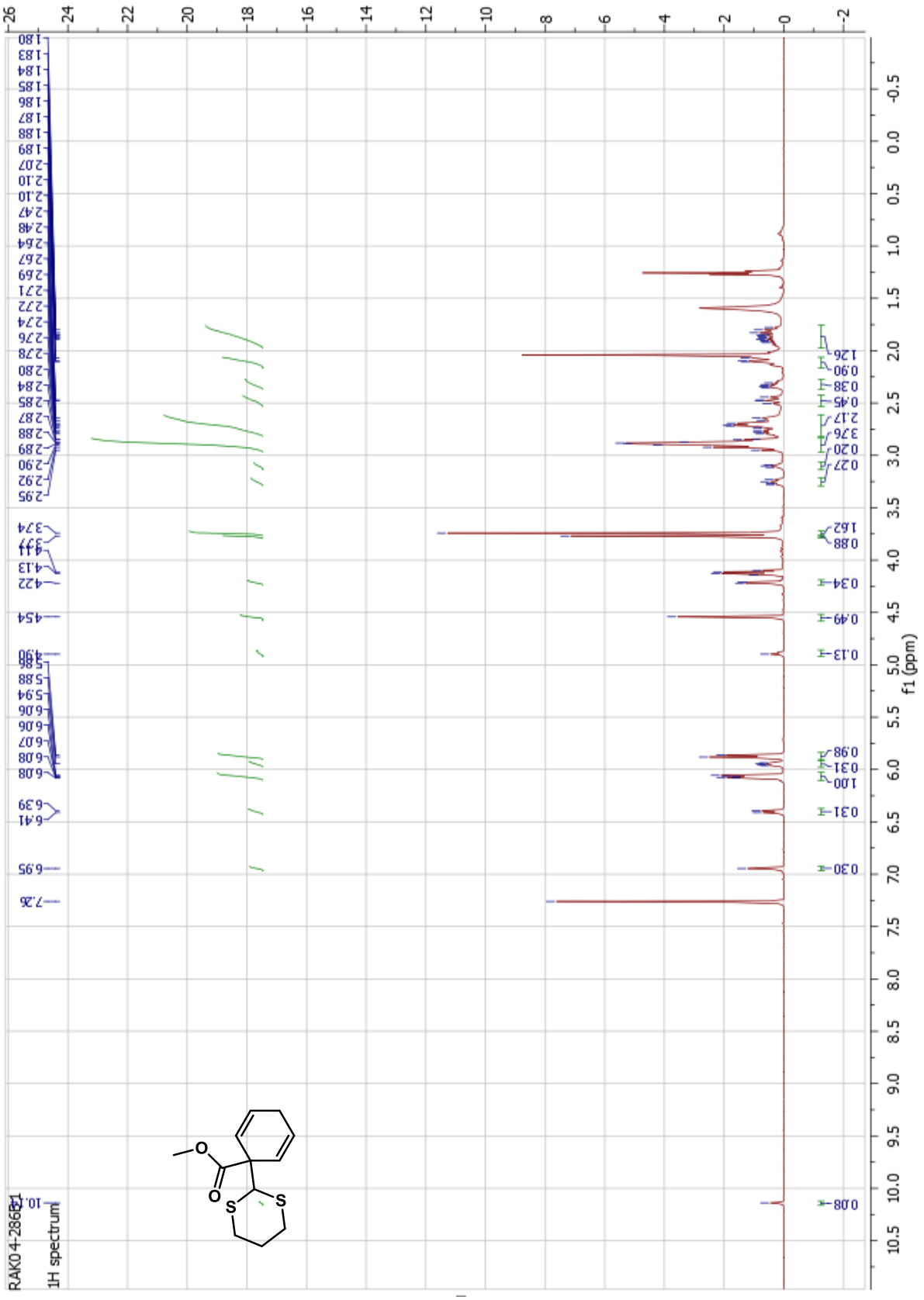

RAK04-269and270A1
13C spectrum with 1H decoupling
175.02
110.54
83.11
77.37
77.16
76.95
75.53
74.44
74.28
71.86
59.28
33.05
27.70
26.96
25.88
25.28
HO
OH
O
f1 (ppm)

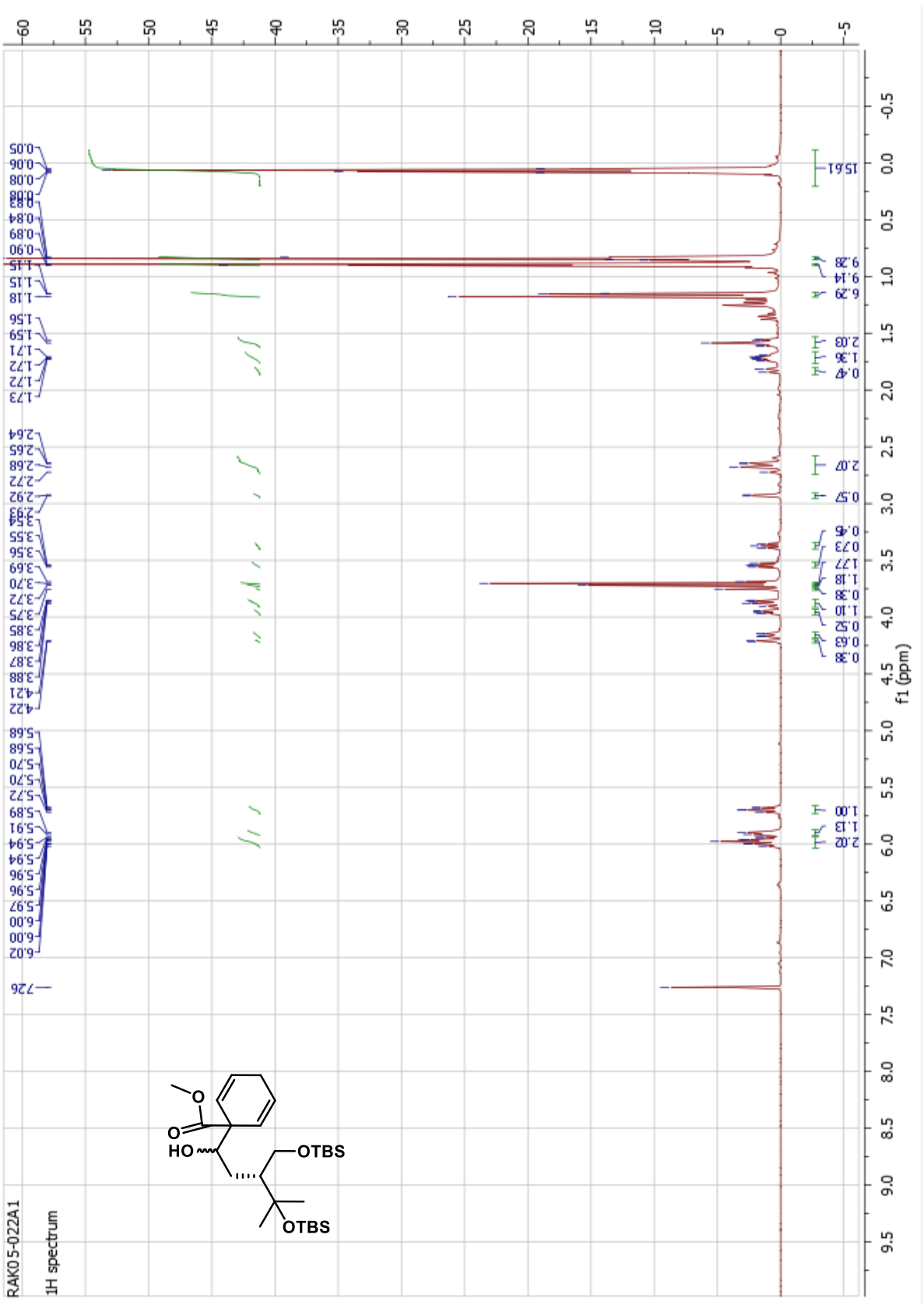

RAK04-272A1
1H spectrum
f1 (ppm)
OH
O

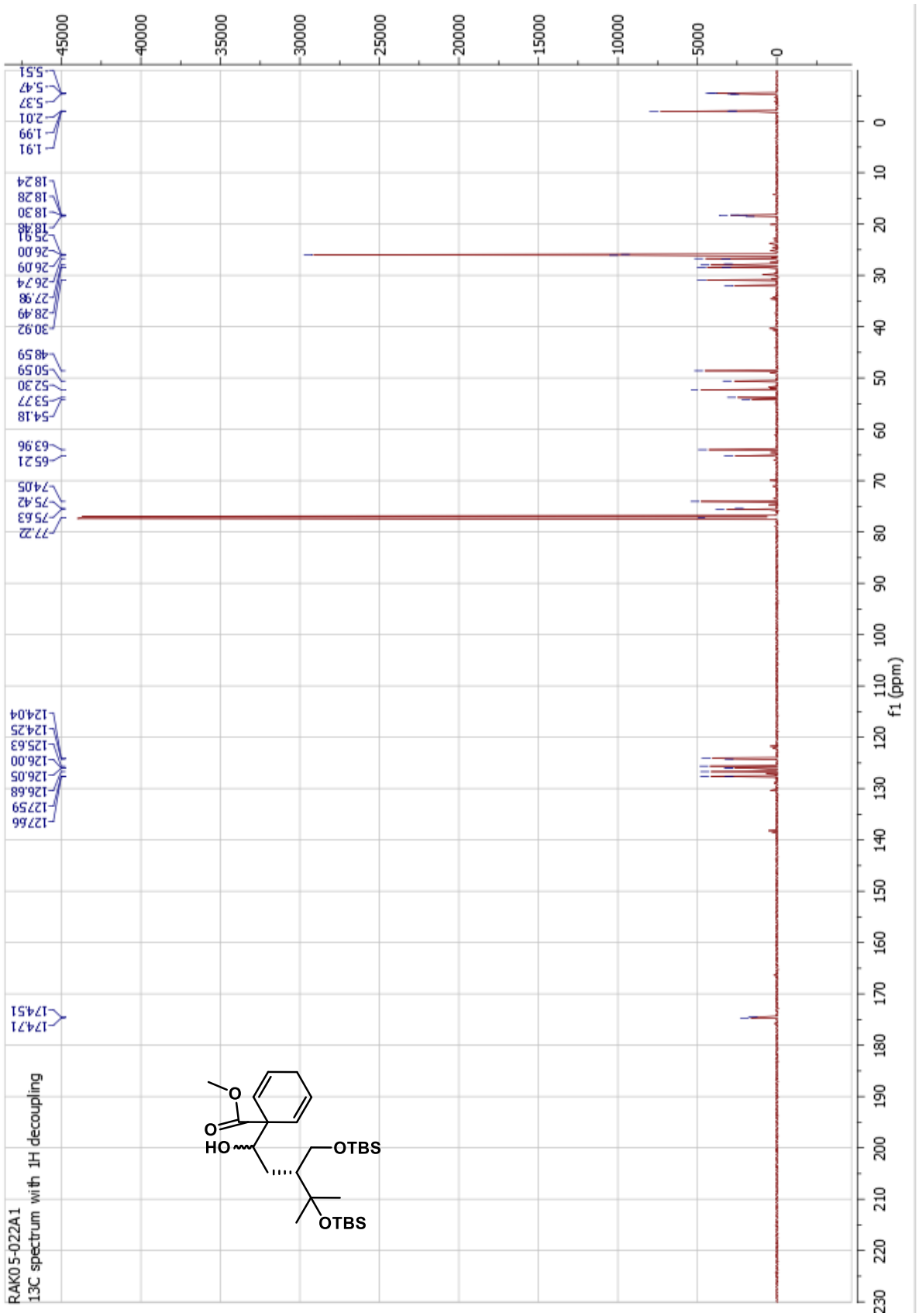

RAK04-277B1
1H spectrum
f1 (ppm)
7.26
6.94
6.49
6.47
6.01
6.00
5.99
5.98
4.48
4.47
3.80
2.53
1.57
1.00
0.95
0.96
0.94
2.94
2.04
6.23

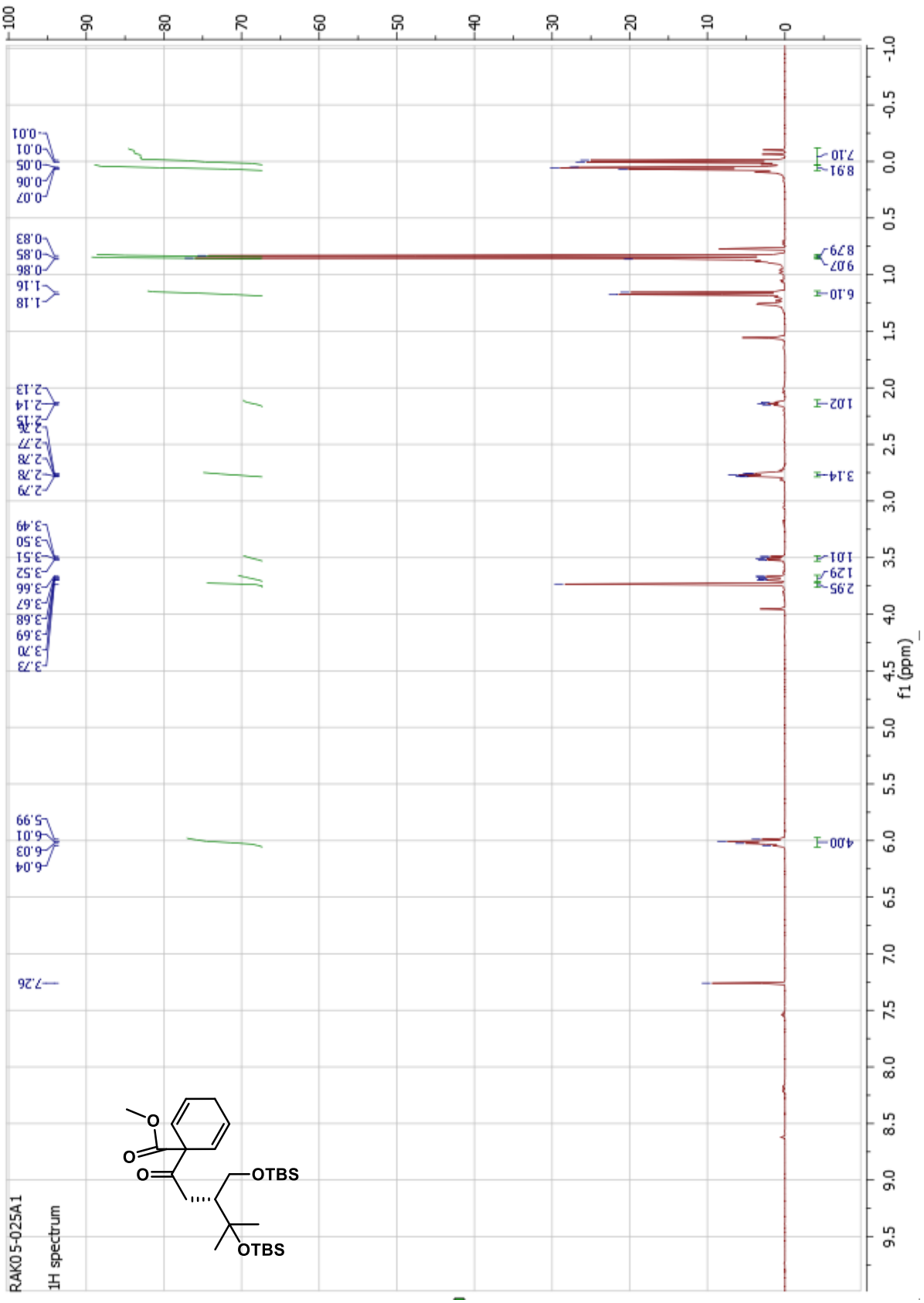

RAK04-277B1
13C spectrum with 1H decoupling
166.30
135.31
129.10
126.59
121.37
77.37
77.16
76.95
63.94
52.17
31.84
29.85
f1 (ppm)

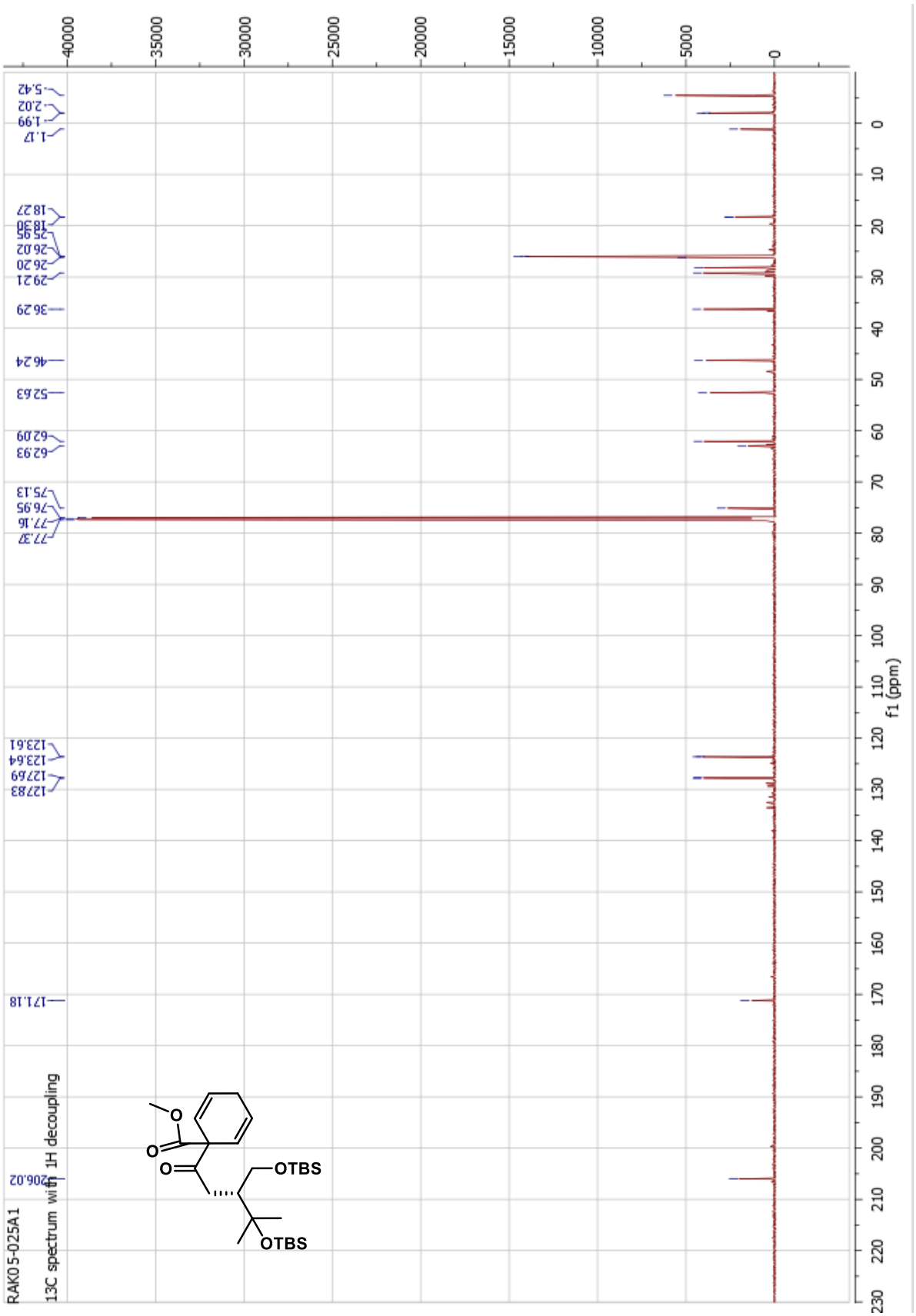

RAK04-279A1
gcosy60
f2 (ppm)
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
0
1
2
3
4
5
6
7
8
O
O
O
O

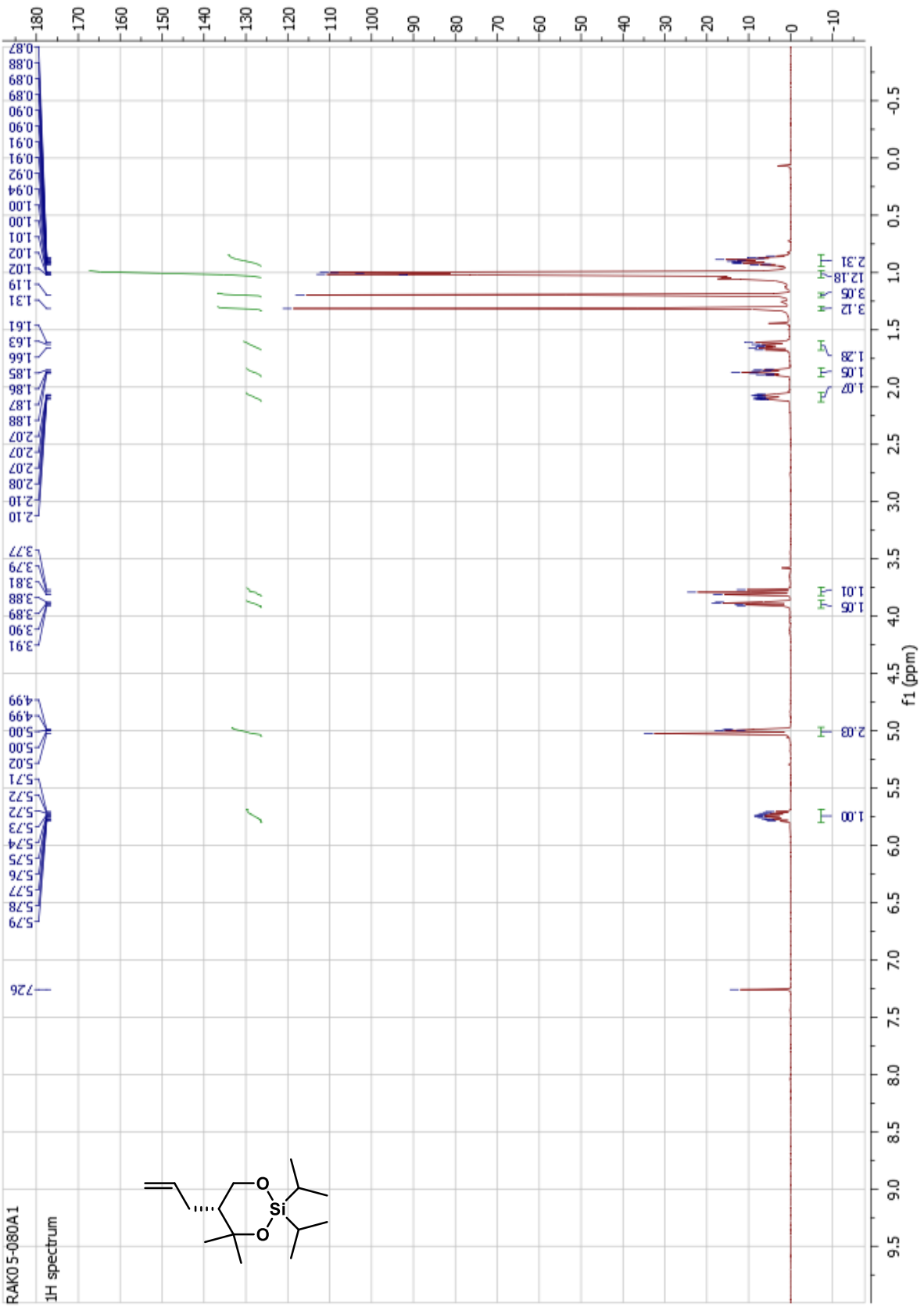

RAK04-286-P1
1H spectrum
f1 (ppm)

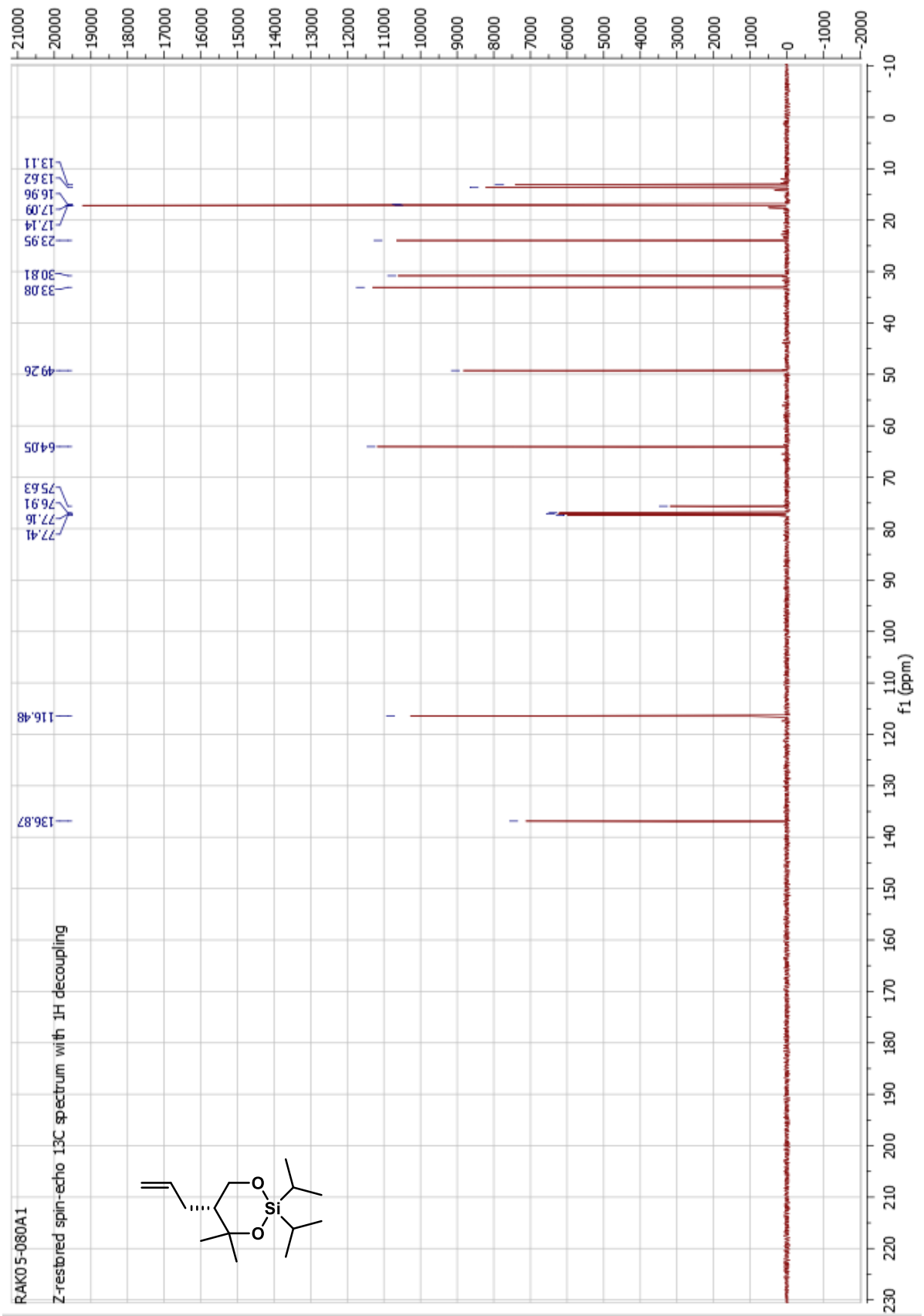

RAK05-022A1
1H spectrum
f1 (ppm)
HO
O
O
OTBS
OTBS

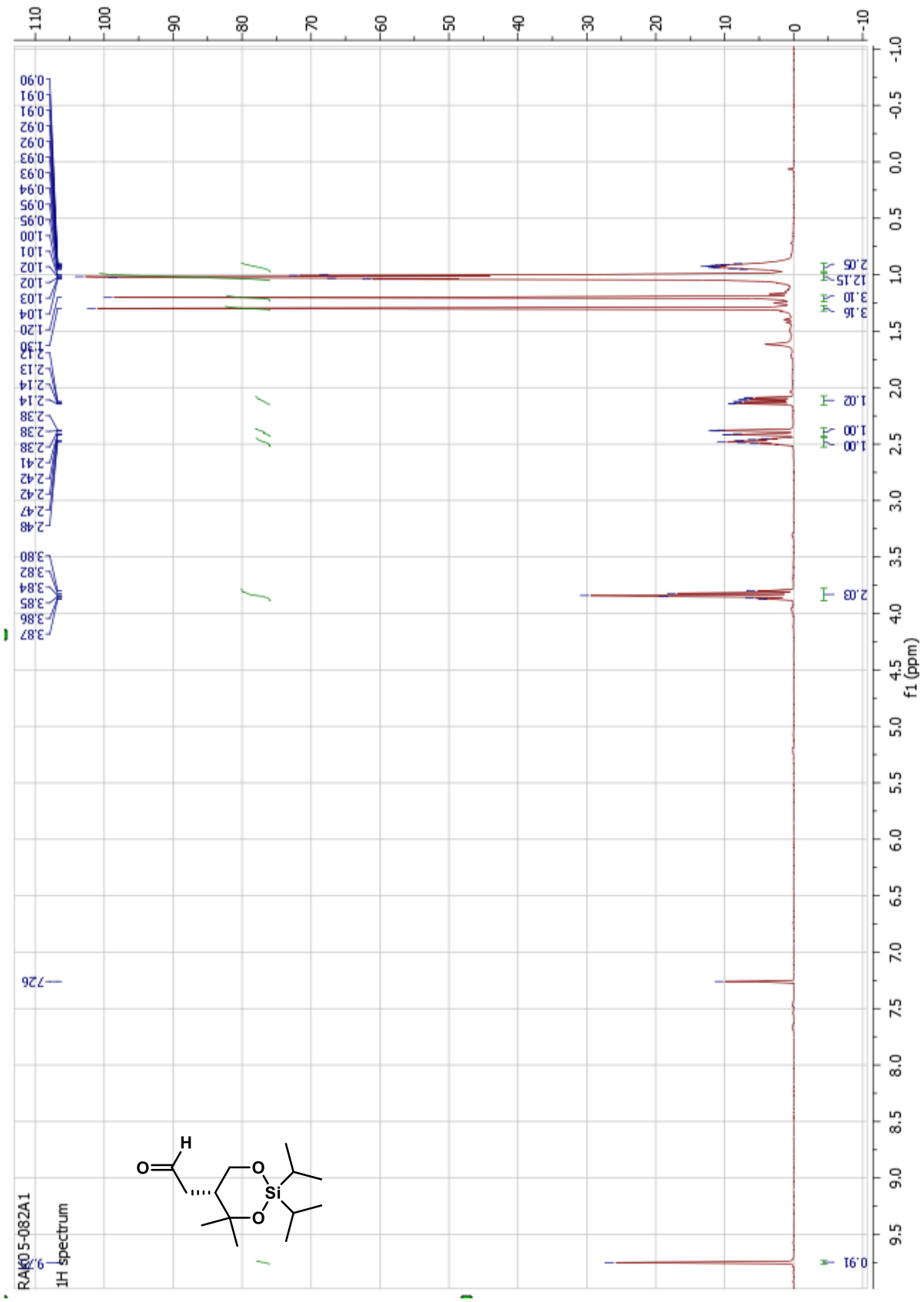

RAK05-022A1
13C spectrum with 1H decoupling
f1 (ppm)
O
O
HO
OTBS
OTBS

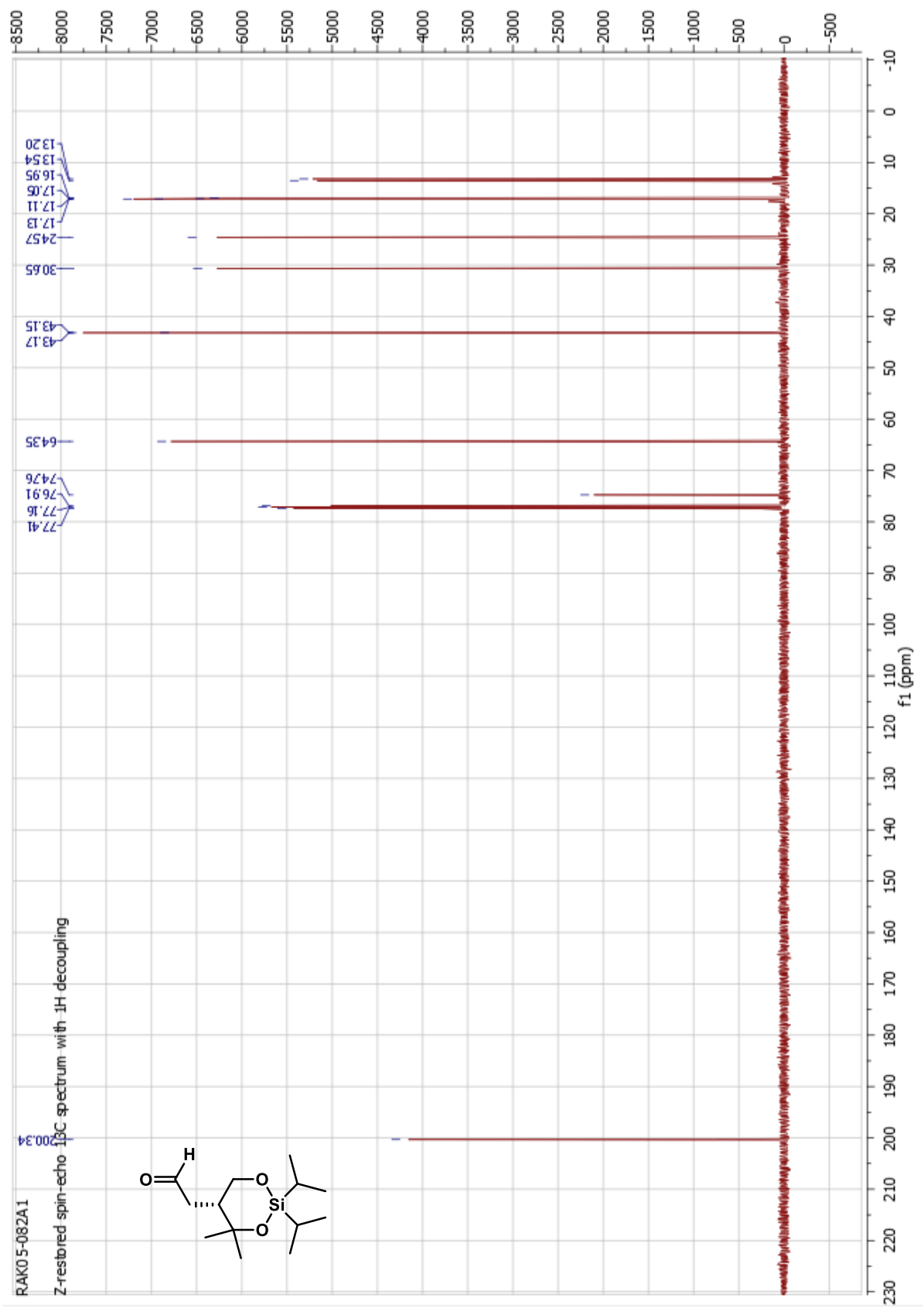

RAK05-025A1
1H spectrum
OTBS
OTBS
f1 (ppm)

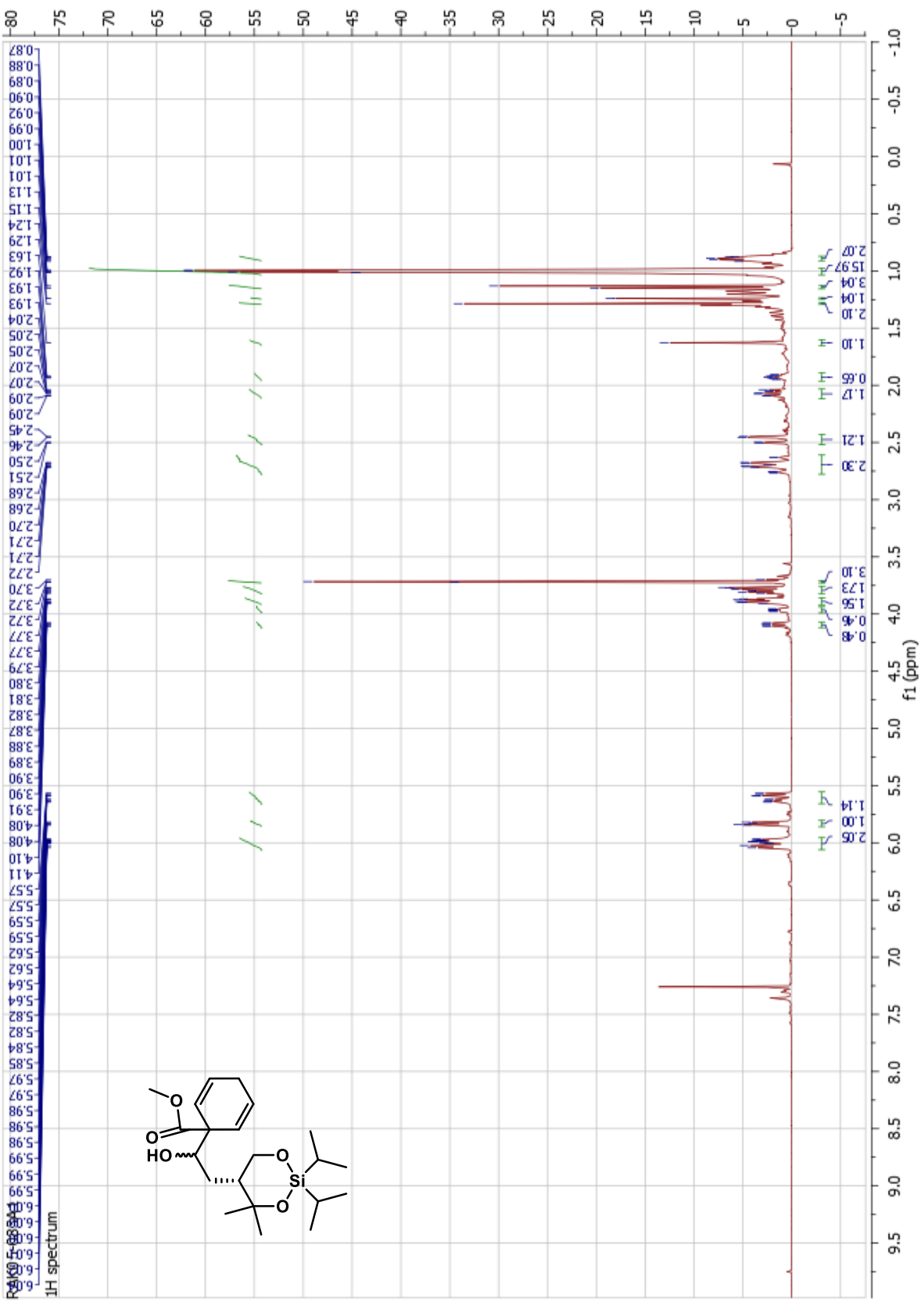

RAK05-025A1
13C spectrum with 1H decoupling
206.02
171.18
127.83
127.69
123.64
123.61
77.37
77.16
76.95
75.13
62.93
62.09
52.63
46.24
36.29
29.21
26.20
26.02
25.95
18.30
18.27
1.99
2.02
5.42
OTBS
OTBS
f1 (ppm)

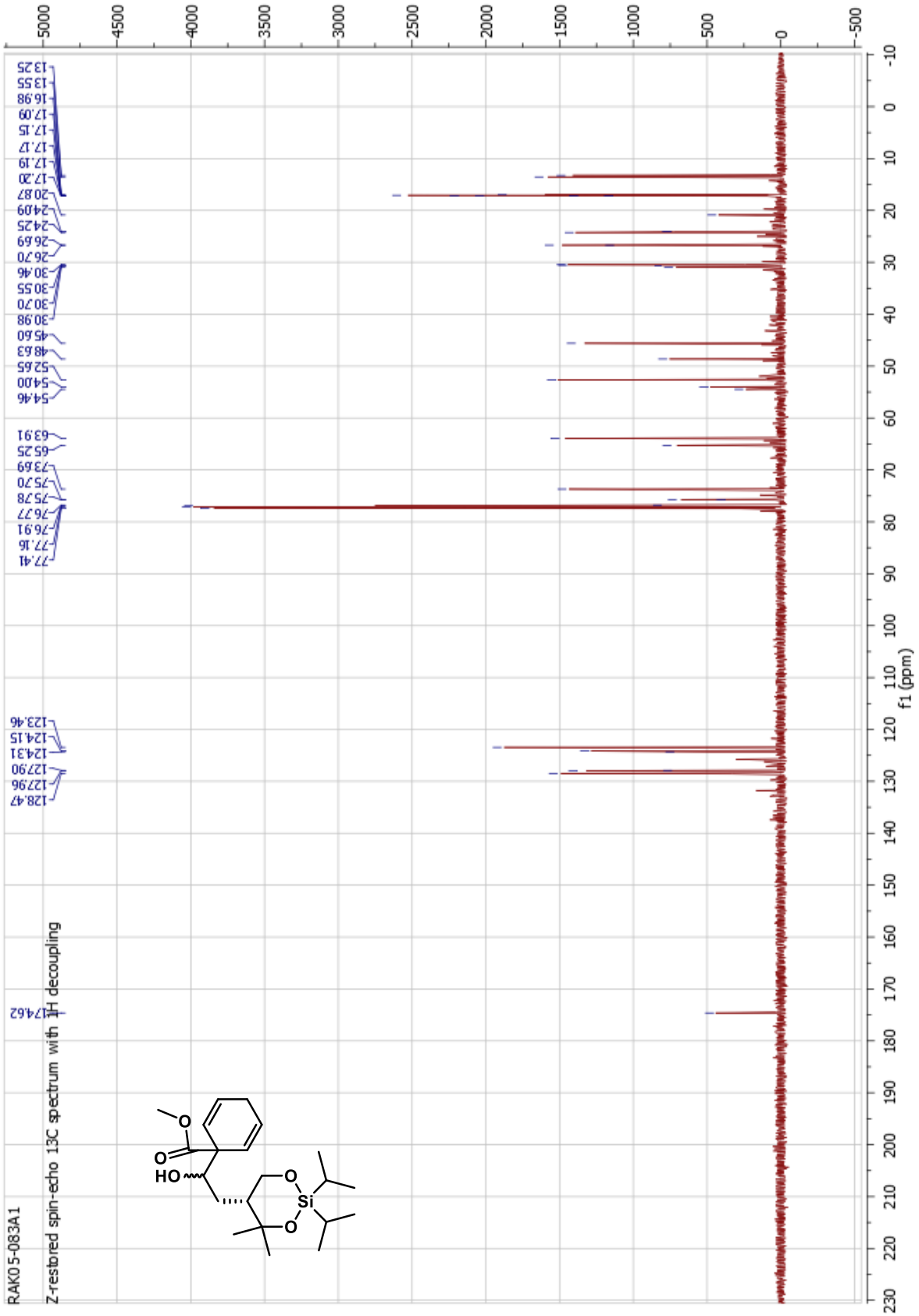

RAK05-080A1
1H spectrum
f1 (ppm)
Si
O
O

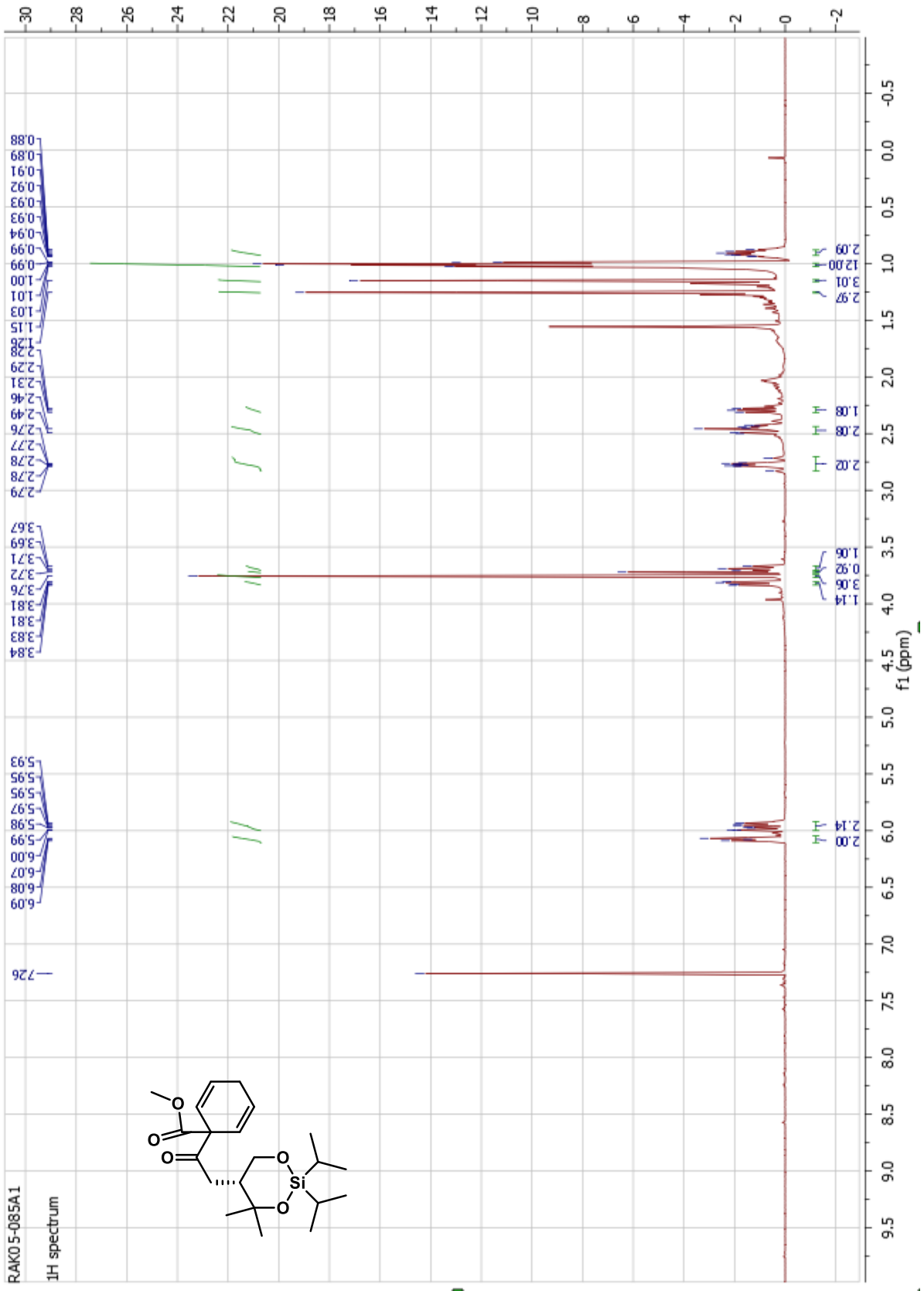

RAK05-080A1
Z-restored spin-echo 13C spectrum with 1H decoupling
f1 (ppm)
13.11
13.62
16.96
17.09
17.14
23.95
30.81
33.08
49.26
64.05
75.63
76.91
77.16
77.41
116.48
136.87
Si
O
O

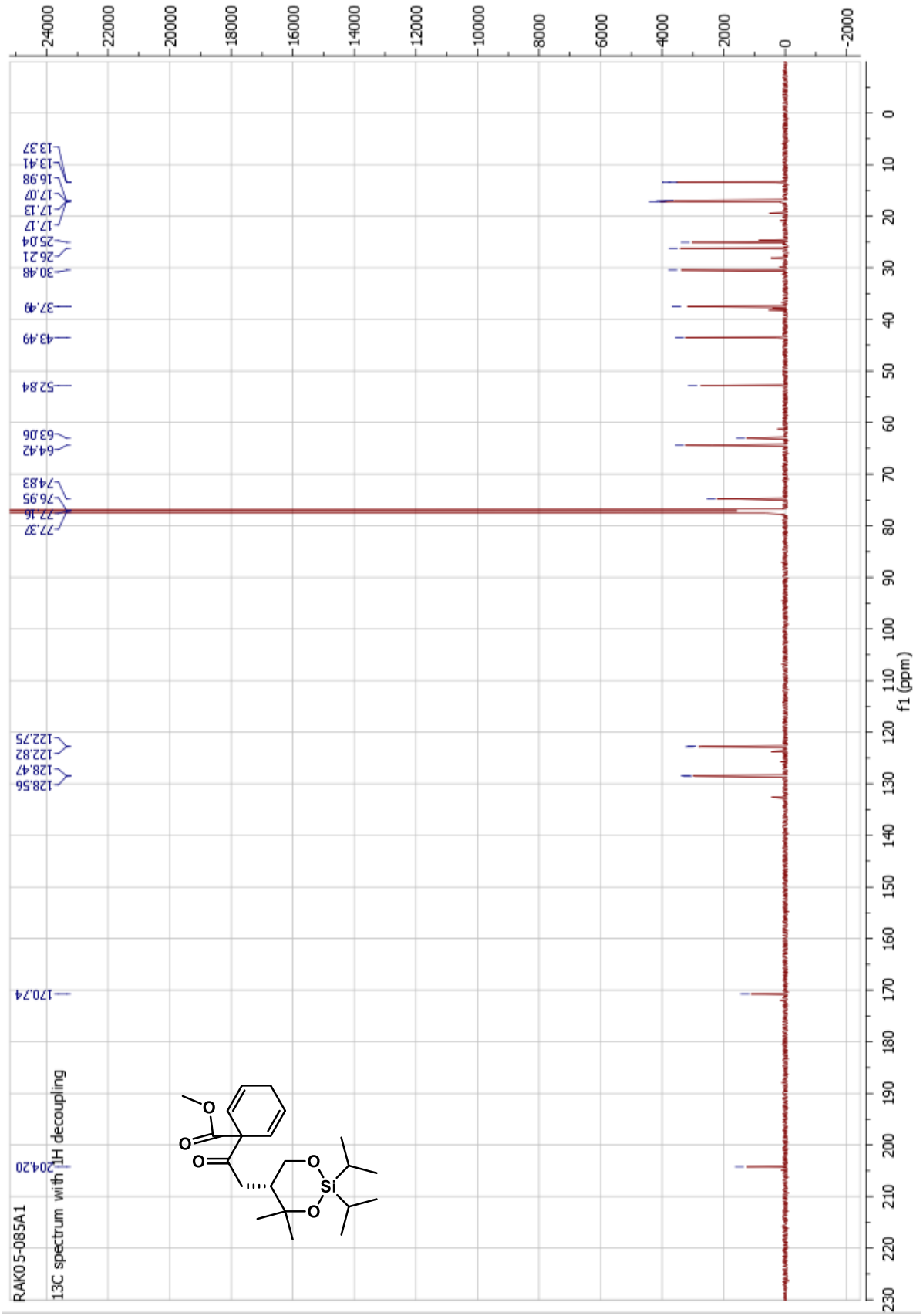

RAK05-082A1
1H spectrum
f1 (ppm)
H
O
O
Si
O

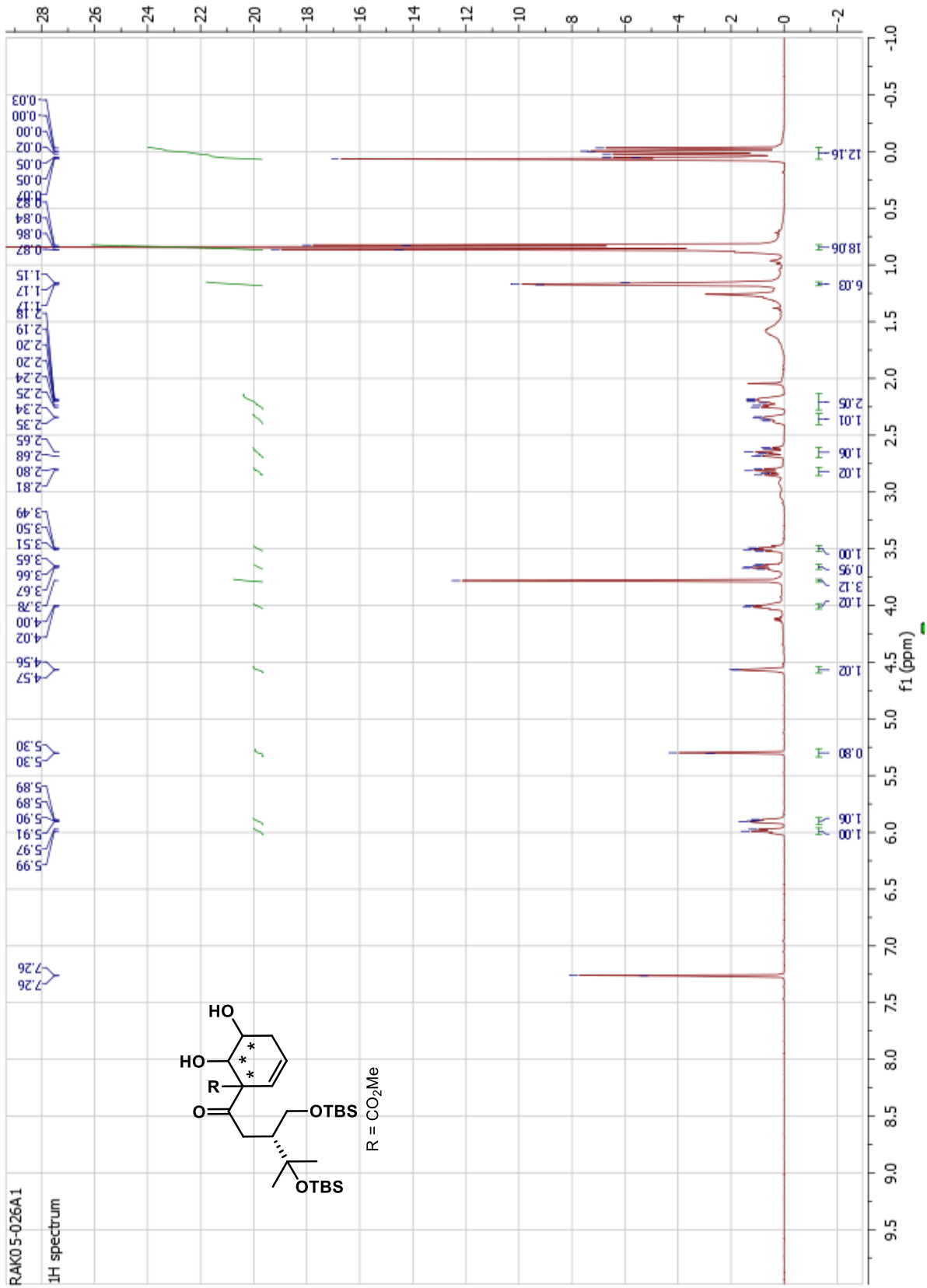

RAK05-082A1
Z-restored spin-echo 13C spectrum with 1H decoupling
f1 (ppm)
13.20
13.54
16.95
17.05
17.11
17.13
24.57
30.65
43.17
43.15
64.35
74.76
76.91
77.16
77.41
200.34
H
O
O
Si
O

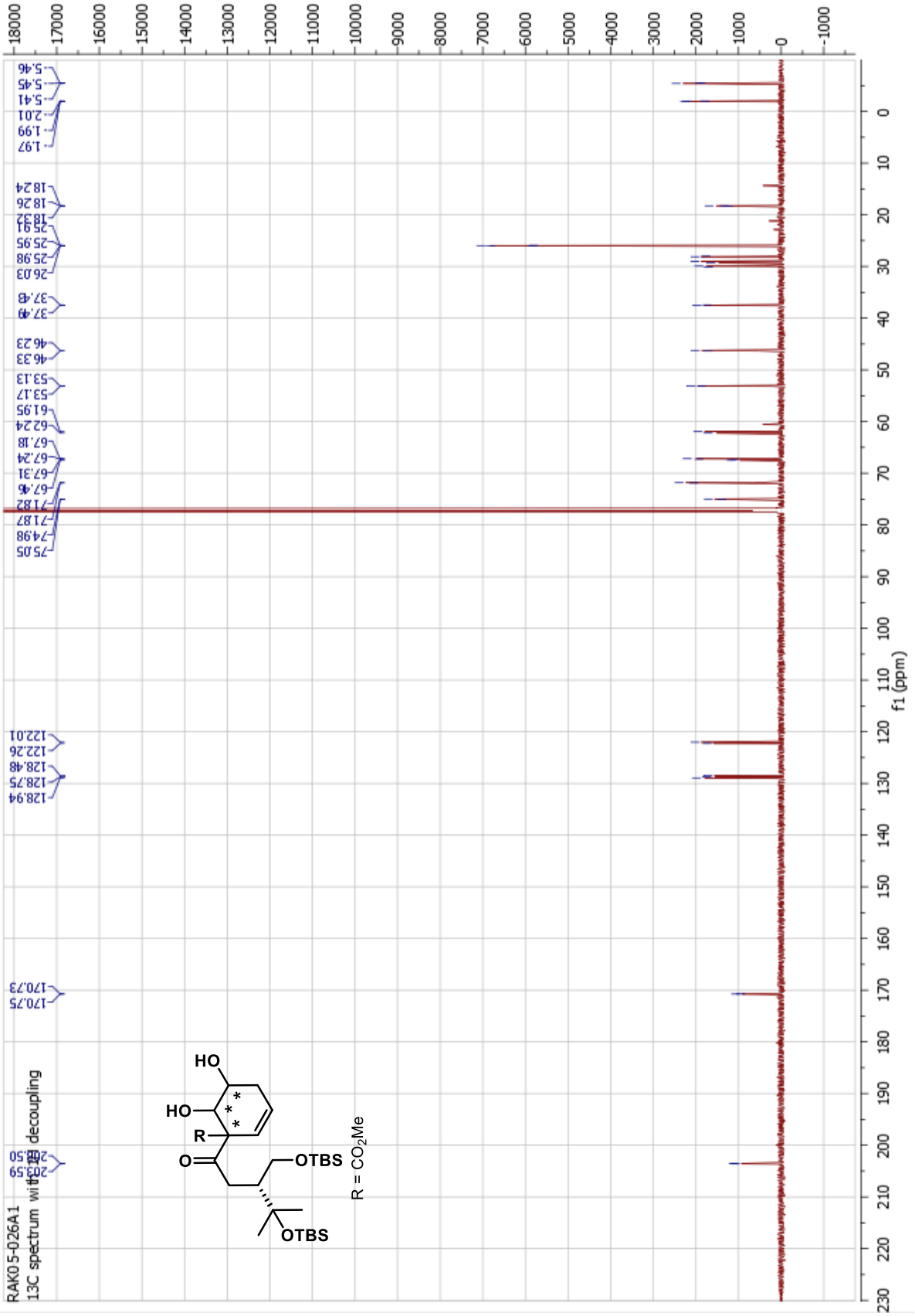

1H spectrum
f1 (ppm)
HO
O
O
O
Si
O

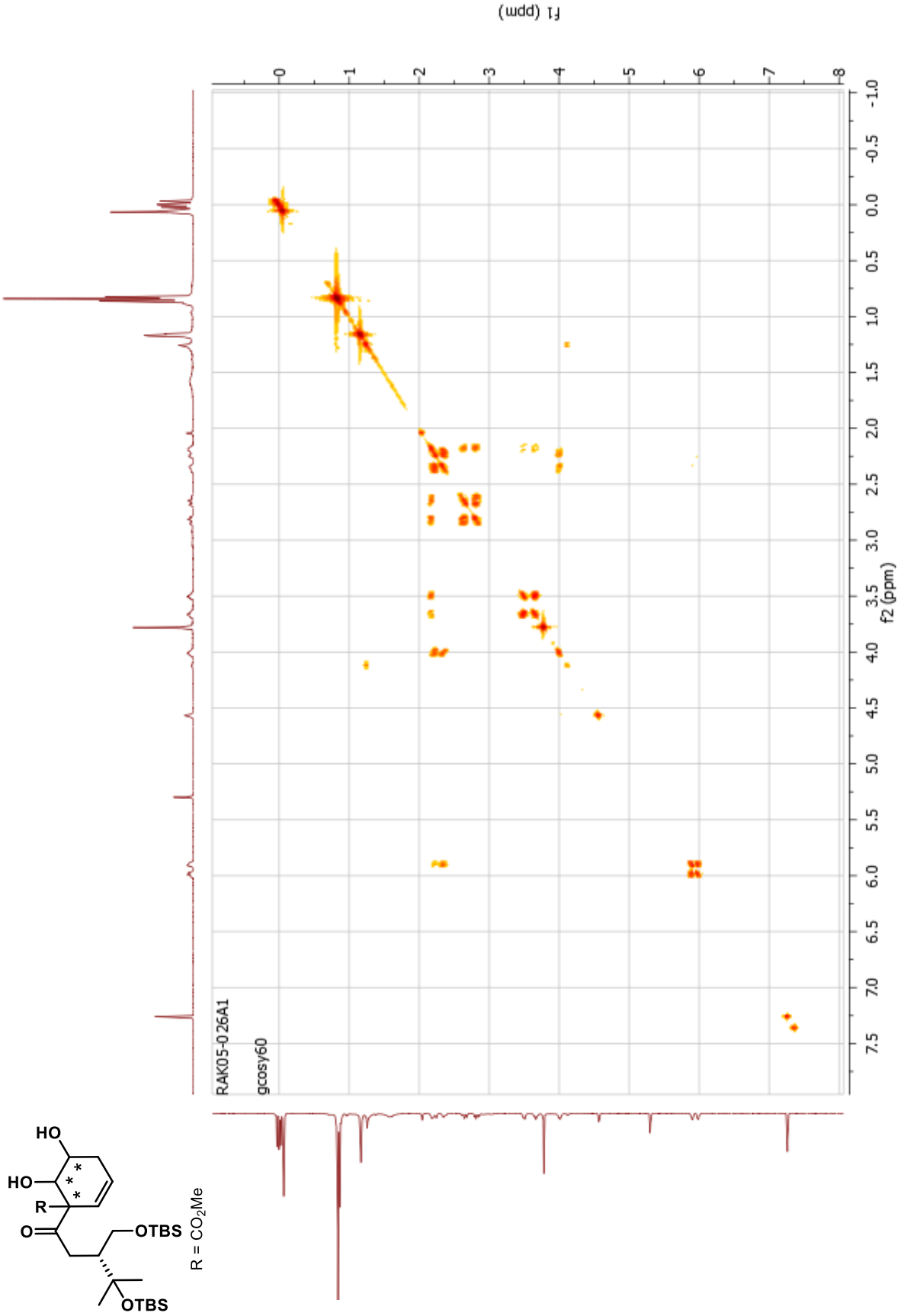

RAK05-083A1
Z-restored spin-echo 13C spectrum with 1H decoupling
f1 (ppm)
HO
O
Si

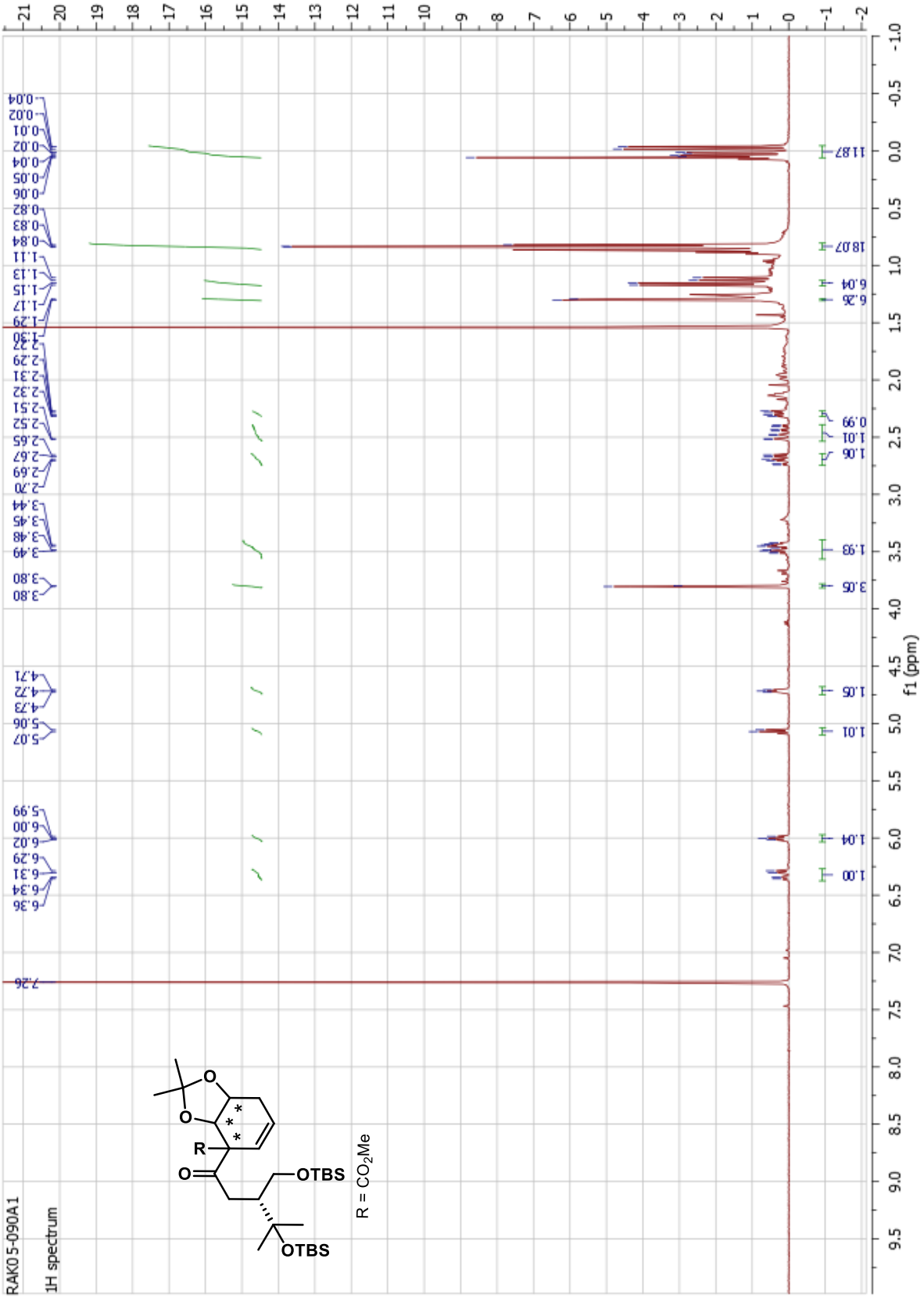

RAK05-085A1
1H spectrum
f1 (ppm)
O
O
O
O
Si

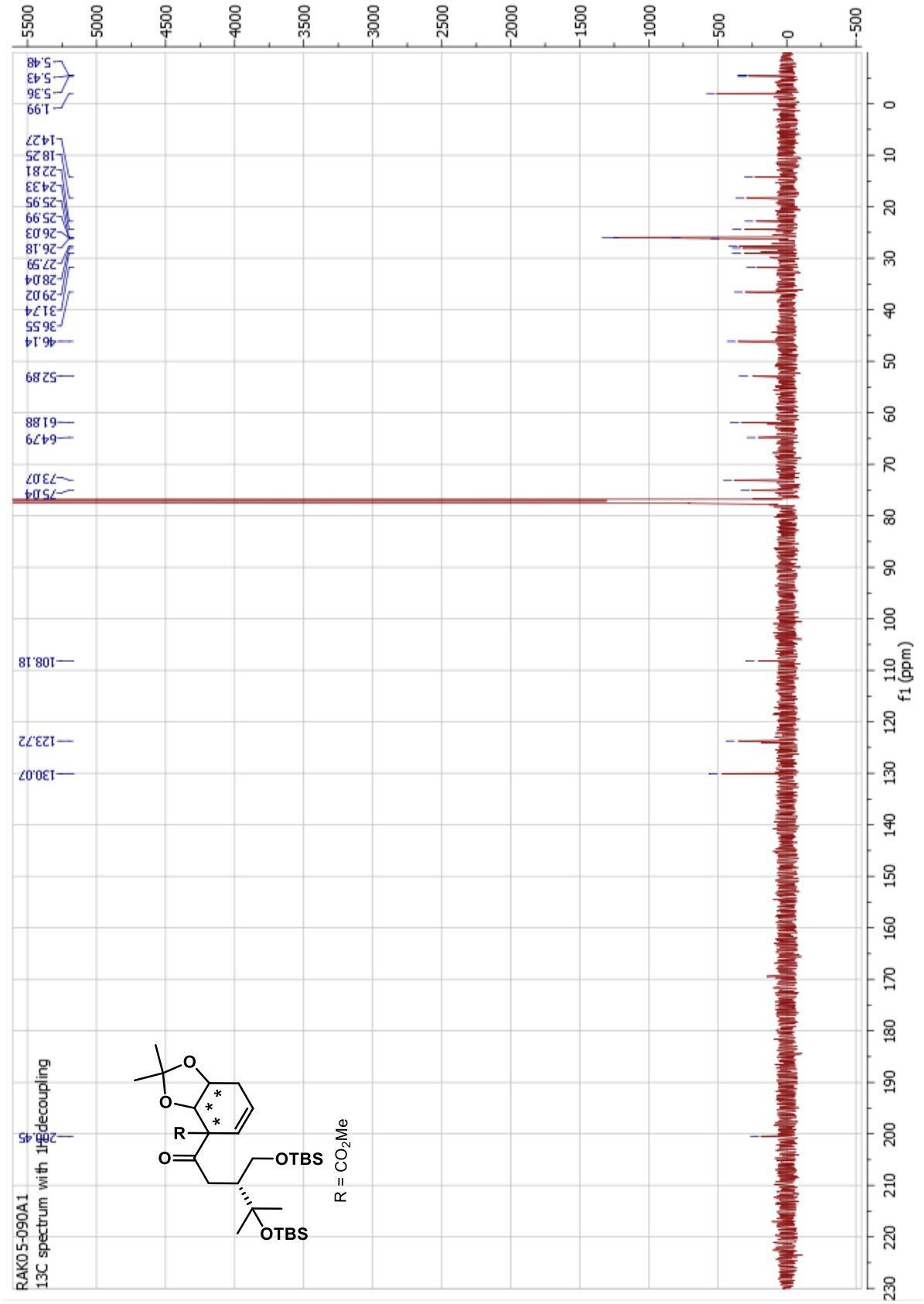

RAK05-085A1
13C spectrum with 1H decoupling
f1 (ppm)
Si

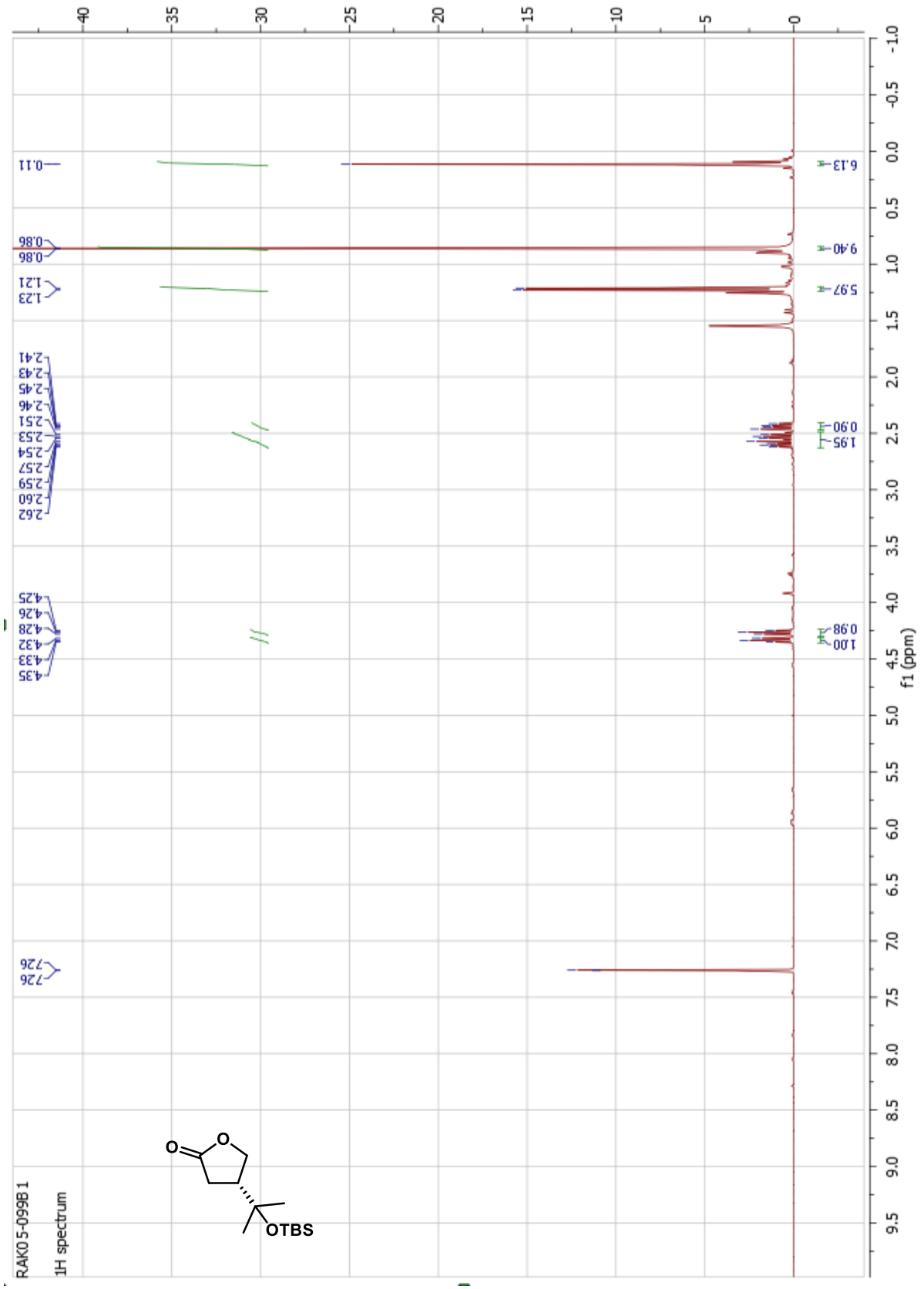

RAK05-026A1
1H spectrum
f1 (ppm)
HO
HO
R
O
OTBS
OTBS
R = CO2Me

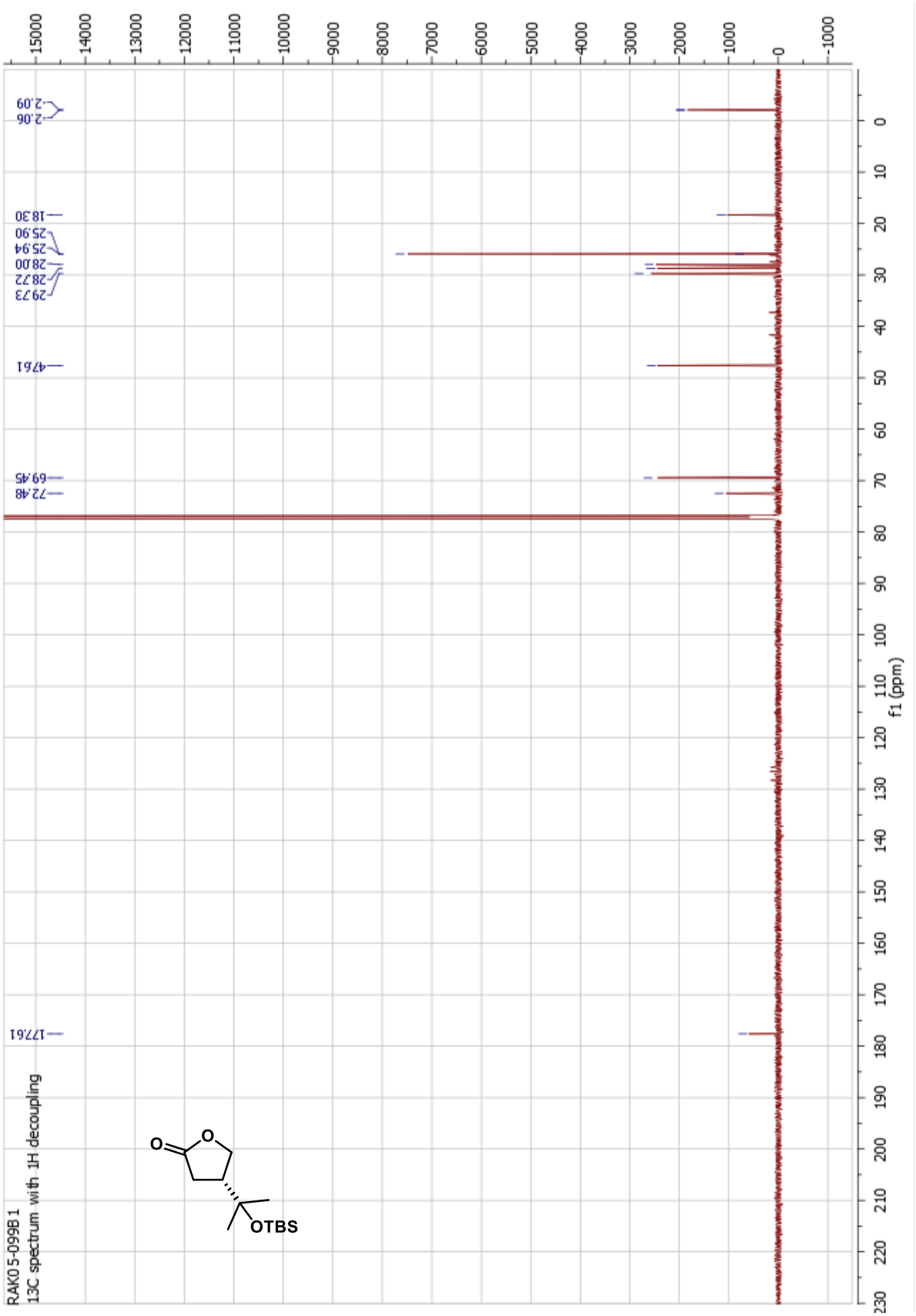

RAK05-026A1
13C spectrum with decoupling
HO
HO
R
O
OTBS
OTBS
R = CO2Me
f1 (ppm)

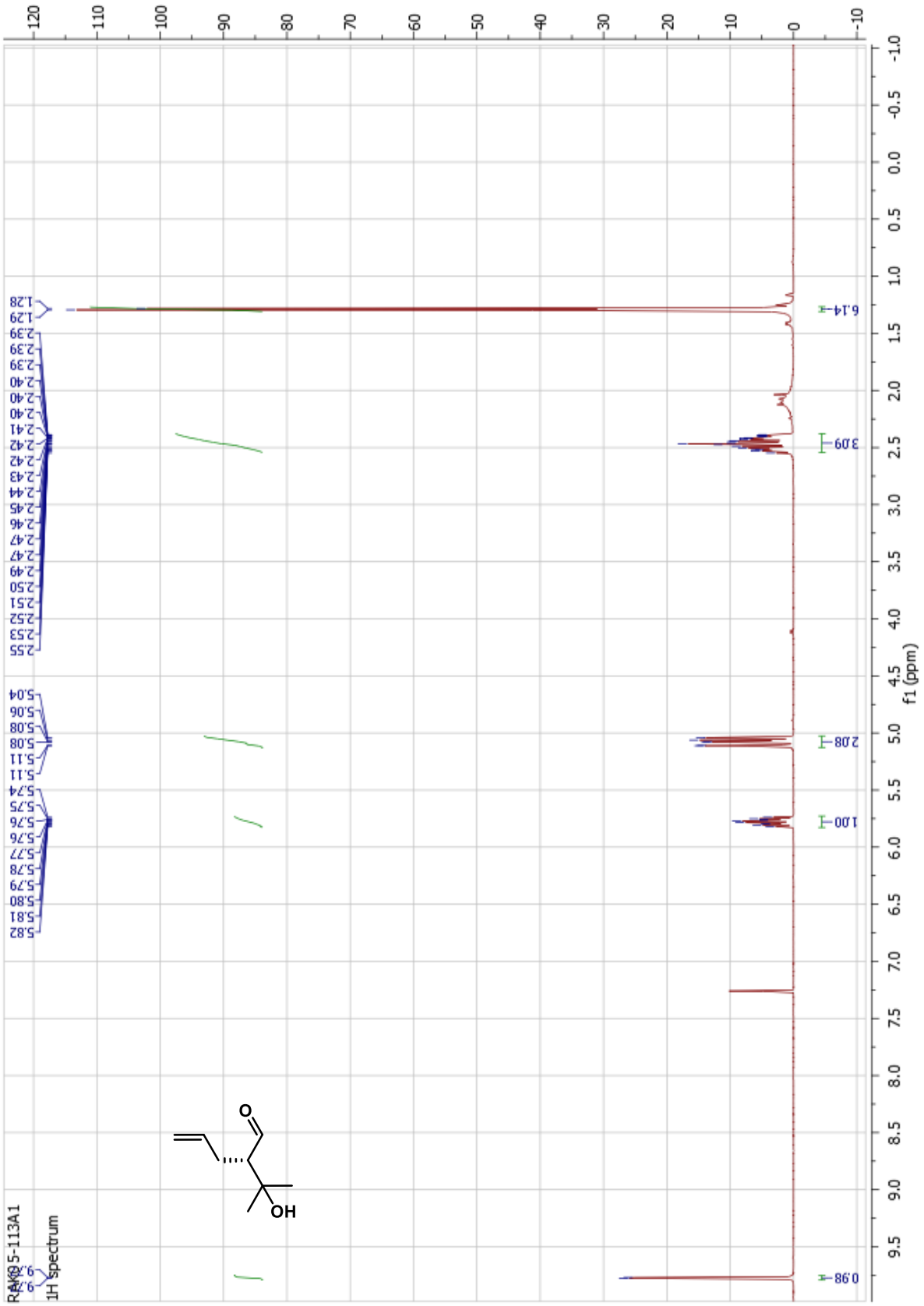

f1 (ppm)
f2 (ppm)
RAK05-026A1
gcosy60
HO
HO
R
O
OTBS
OTBS
R = CO2Me

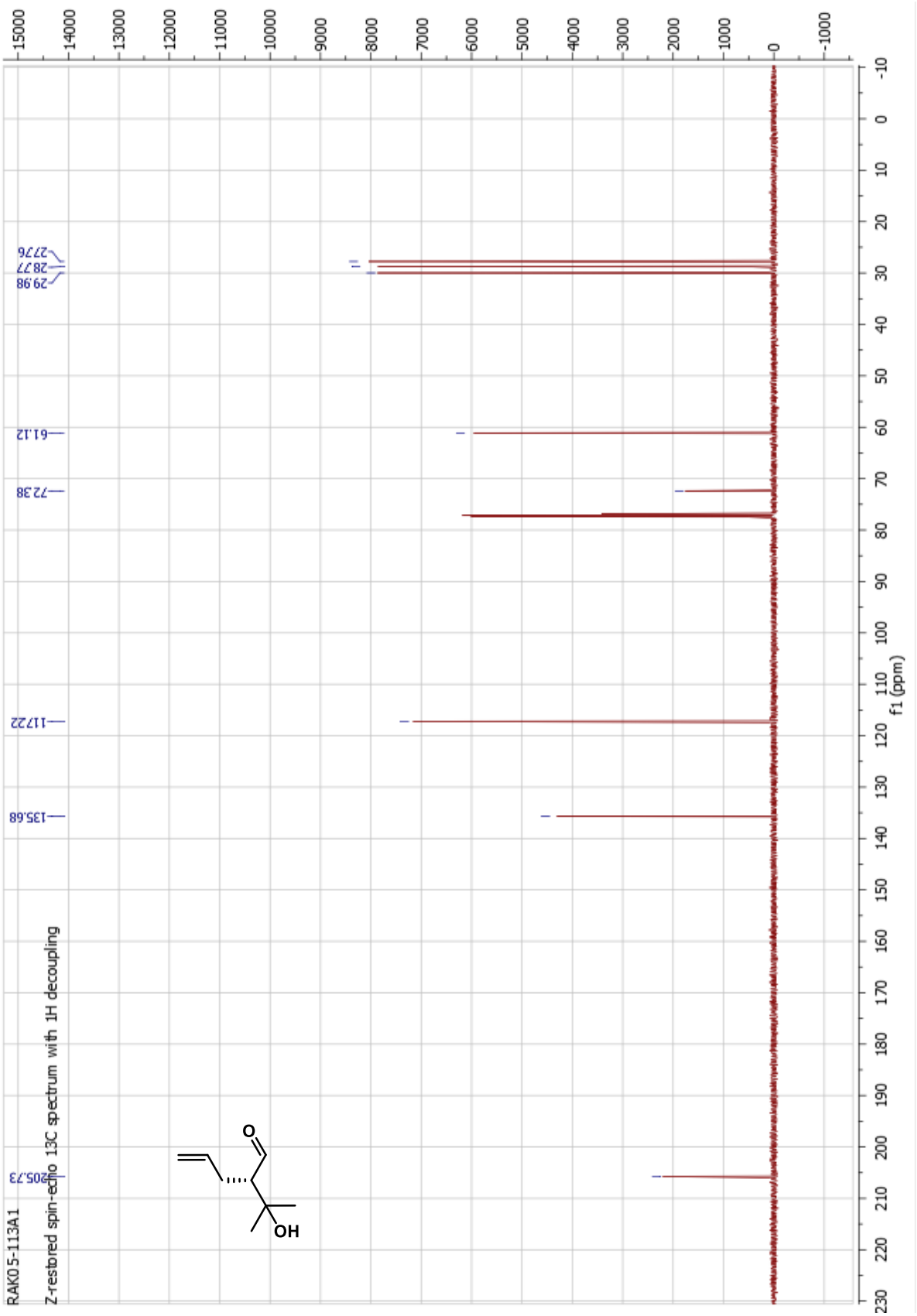

RAK05-090A1
1H spectrum
R = CO2Me
OTBS
OTBS
f1 (ppm)

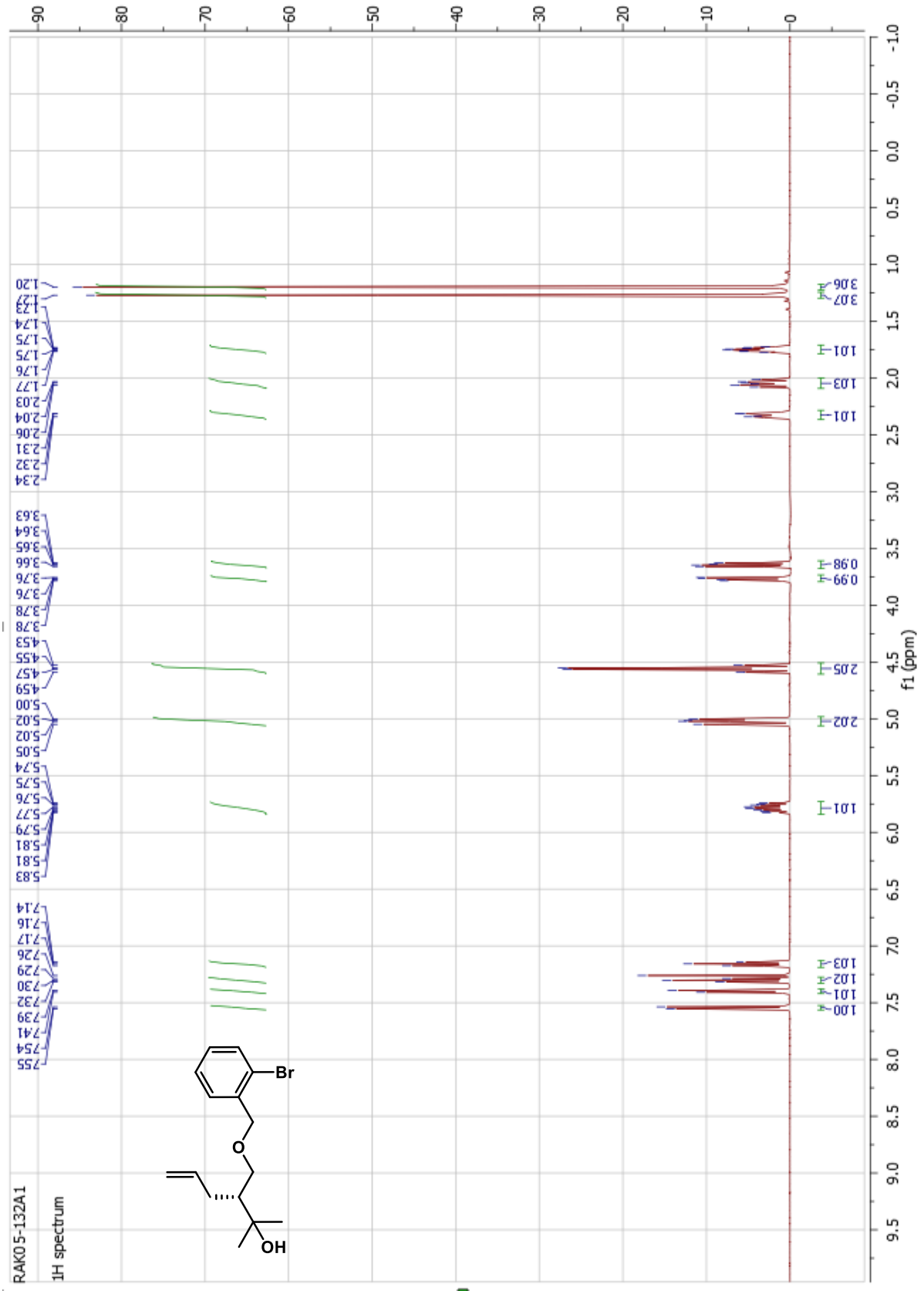

RAK05-090A1
13C spectrum with 1H decoupling
R = CO2Me
OTBS
OTBS
f1 (ppm)

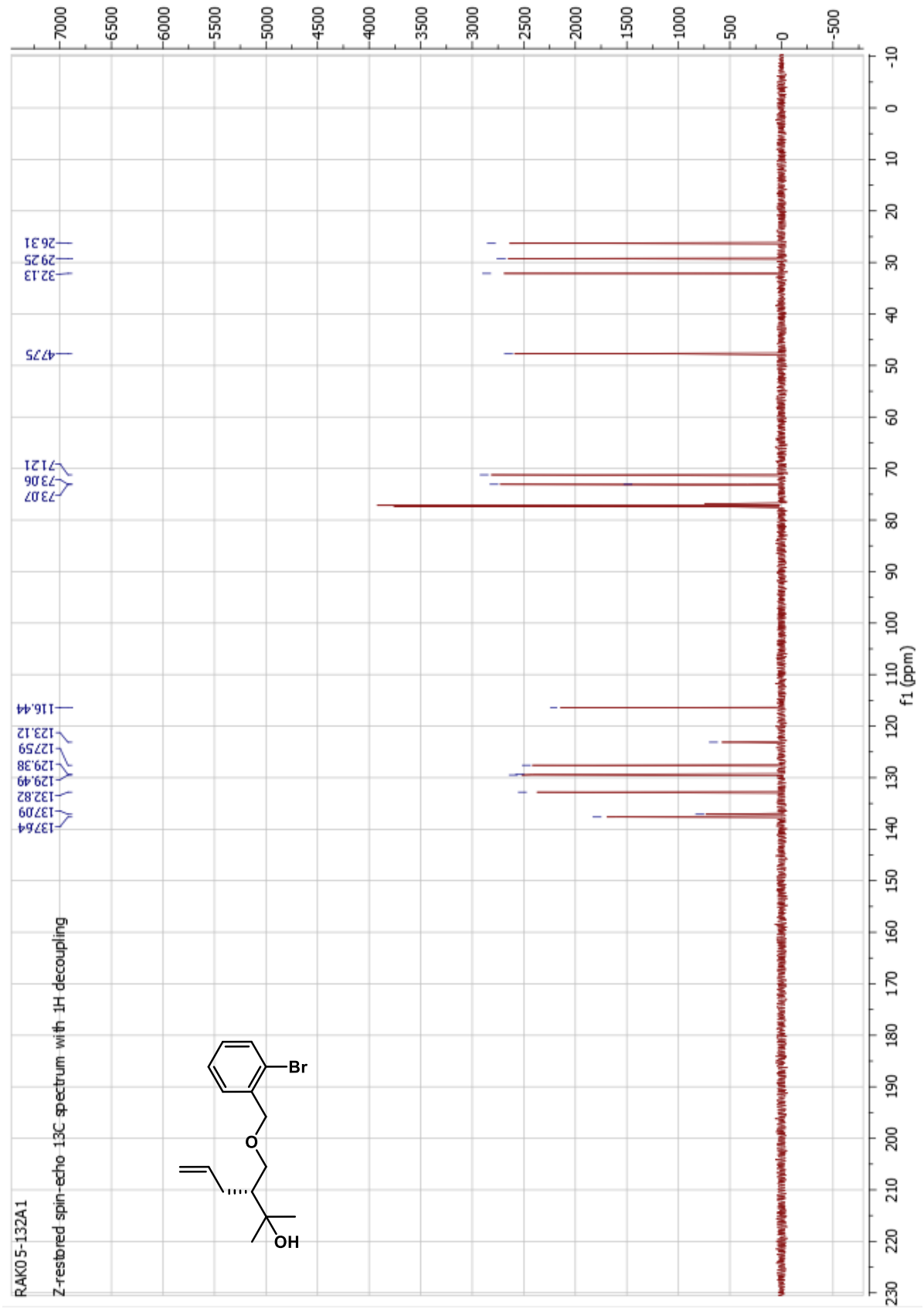

RAK05-099B 1
1H spectrum
OTBS
f1 (ppm)

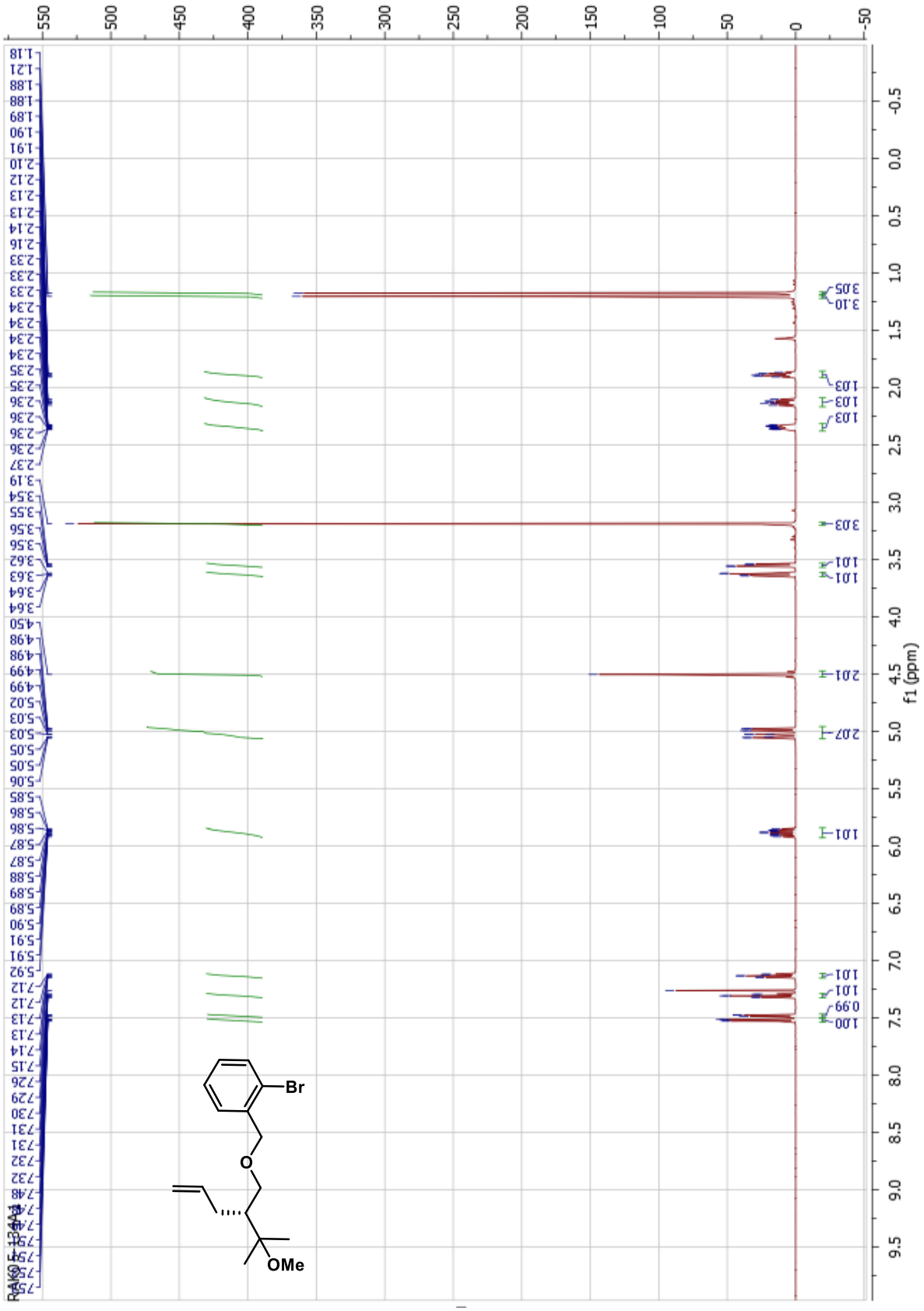

RAK05-099B1
13C spectrum with 1H decoupling
177.61
72.48
69.45
47.61
29.73
28.72
28.00
25.94
25.90
18.30
-2.06
-2.09
OTBS
f1 (ppm)

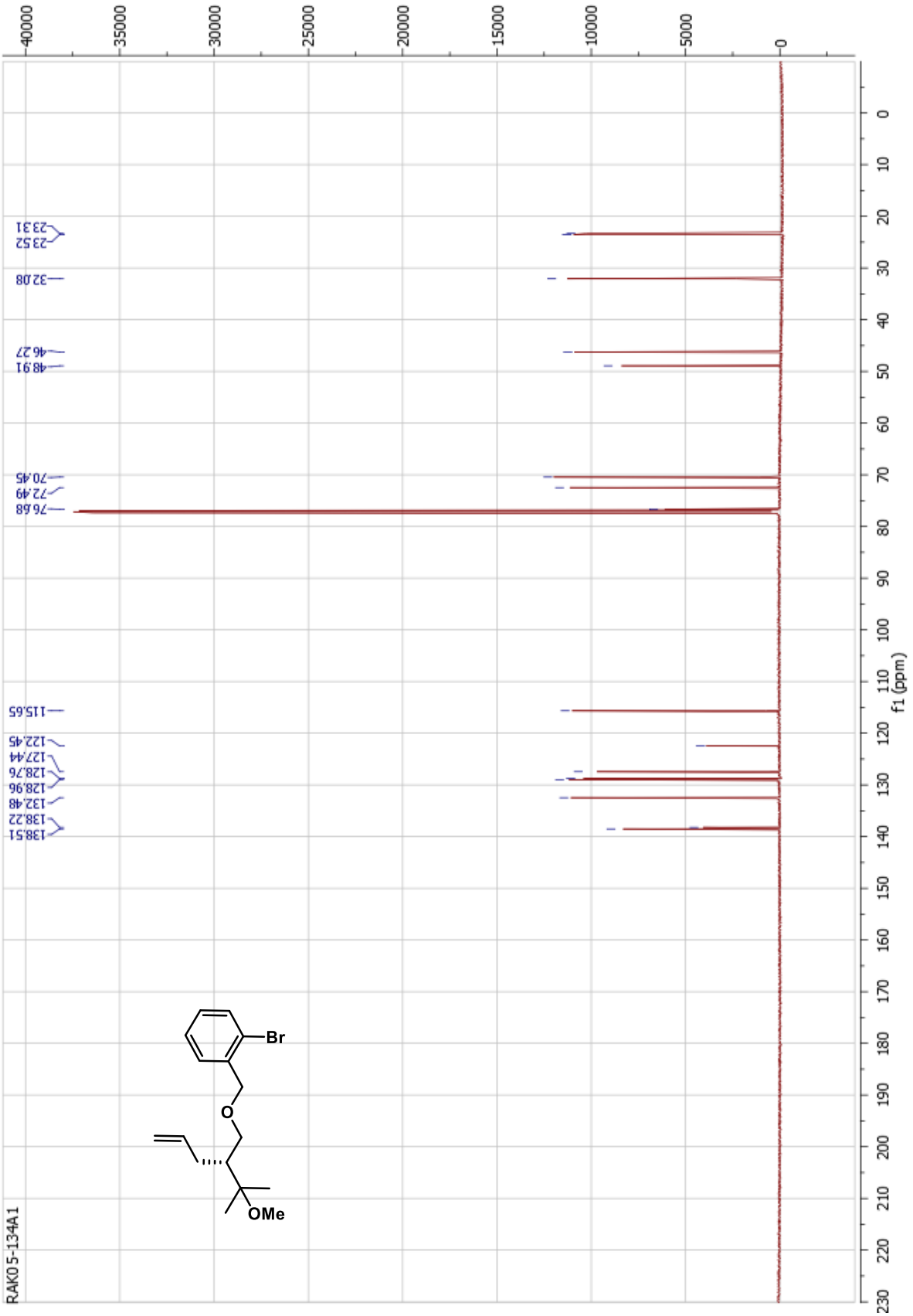

RAM-05-113A1
1H spectrum
f1 (ppm)
6.14
3.09
2.08
1.00
0.98
O
OH

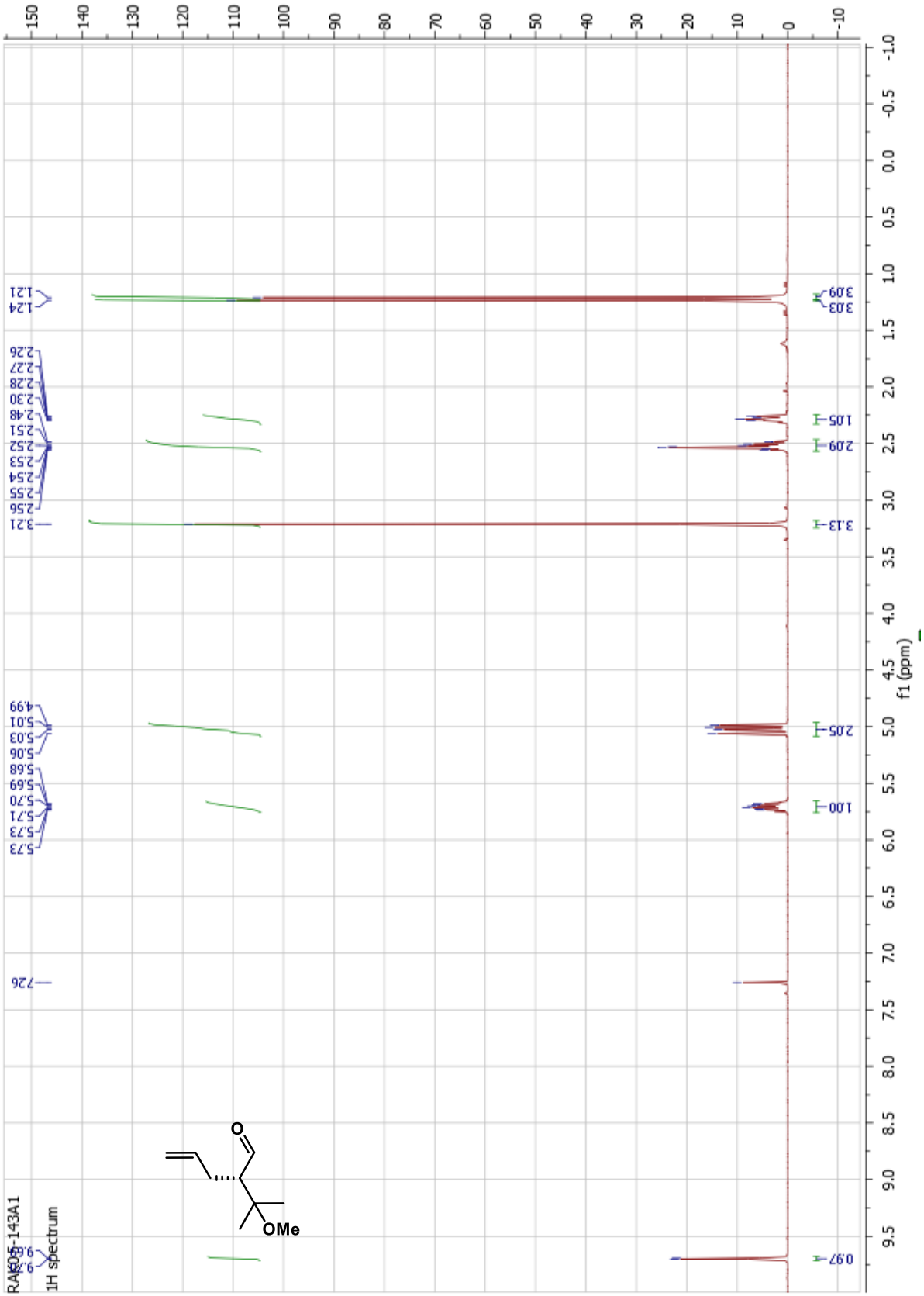

RAK05-113A1
Z-restored spin-echo 13C spectrum with 1H decoupling
205.73
135.68
117.22
72.38
61.12
29.98
28.77
27.76
f1 (ppm)
O
OH

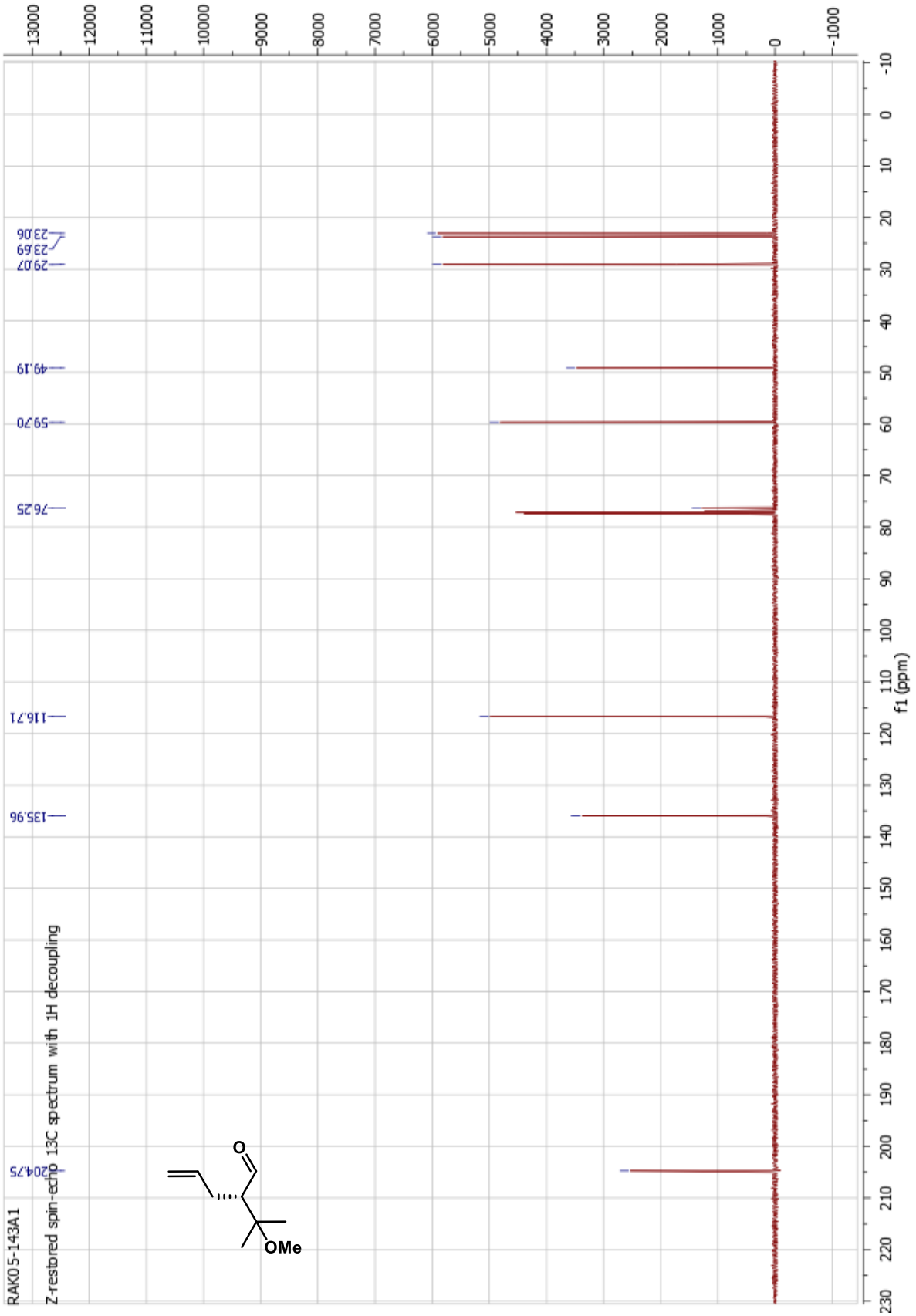

RAK05-132A1
1H spectrum
f1 (ppm)
Br
O
OH

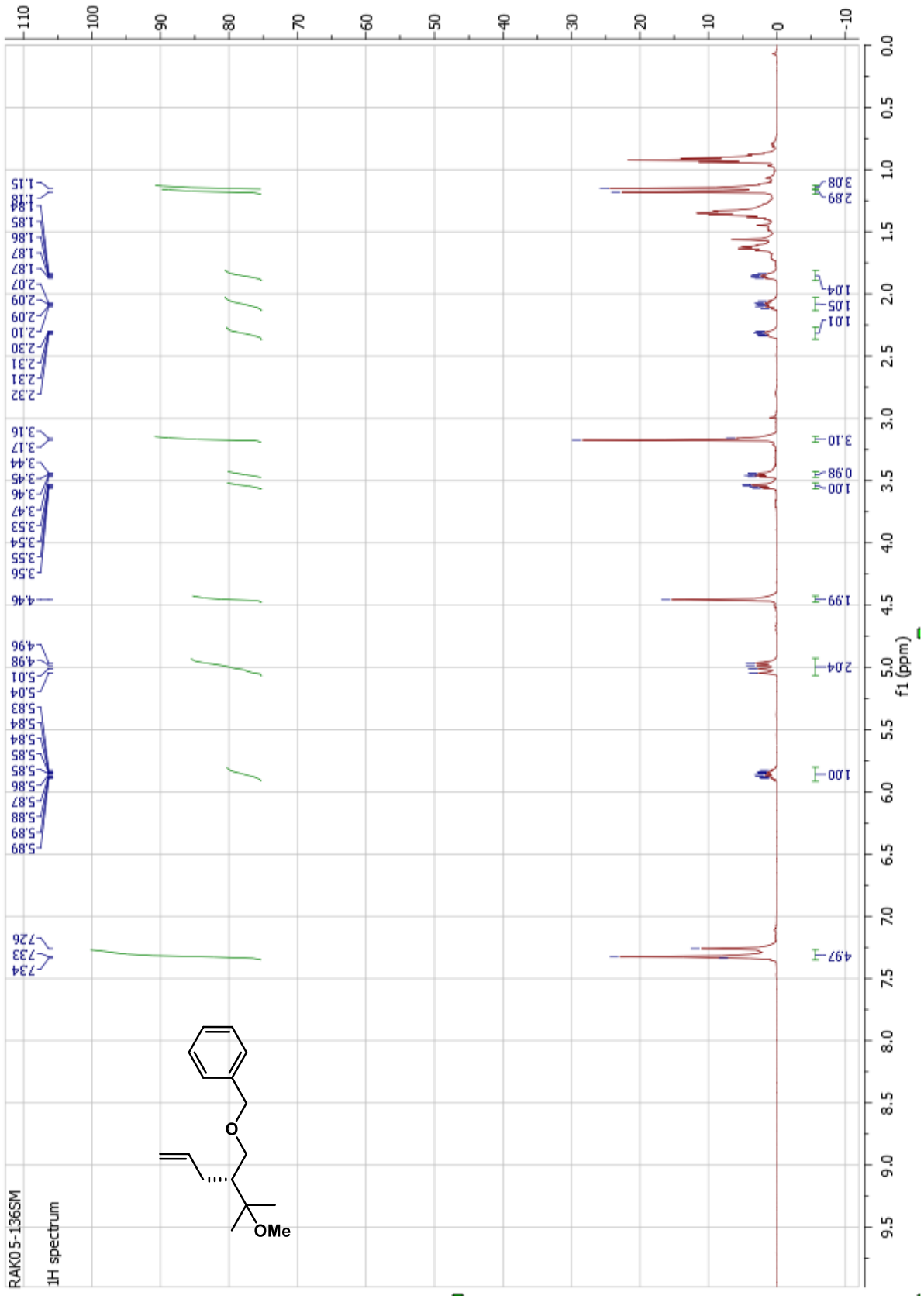

RAK05-132A1
Z-restored spin-echo 13C spectrum with 1H decoupling
f1 (ppm)
Br
O
OH

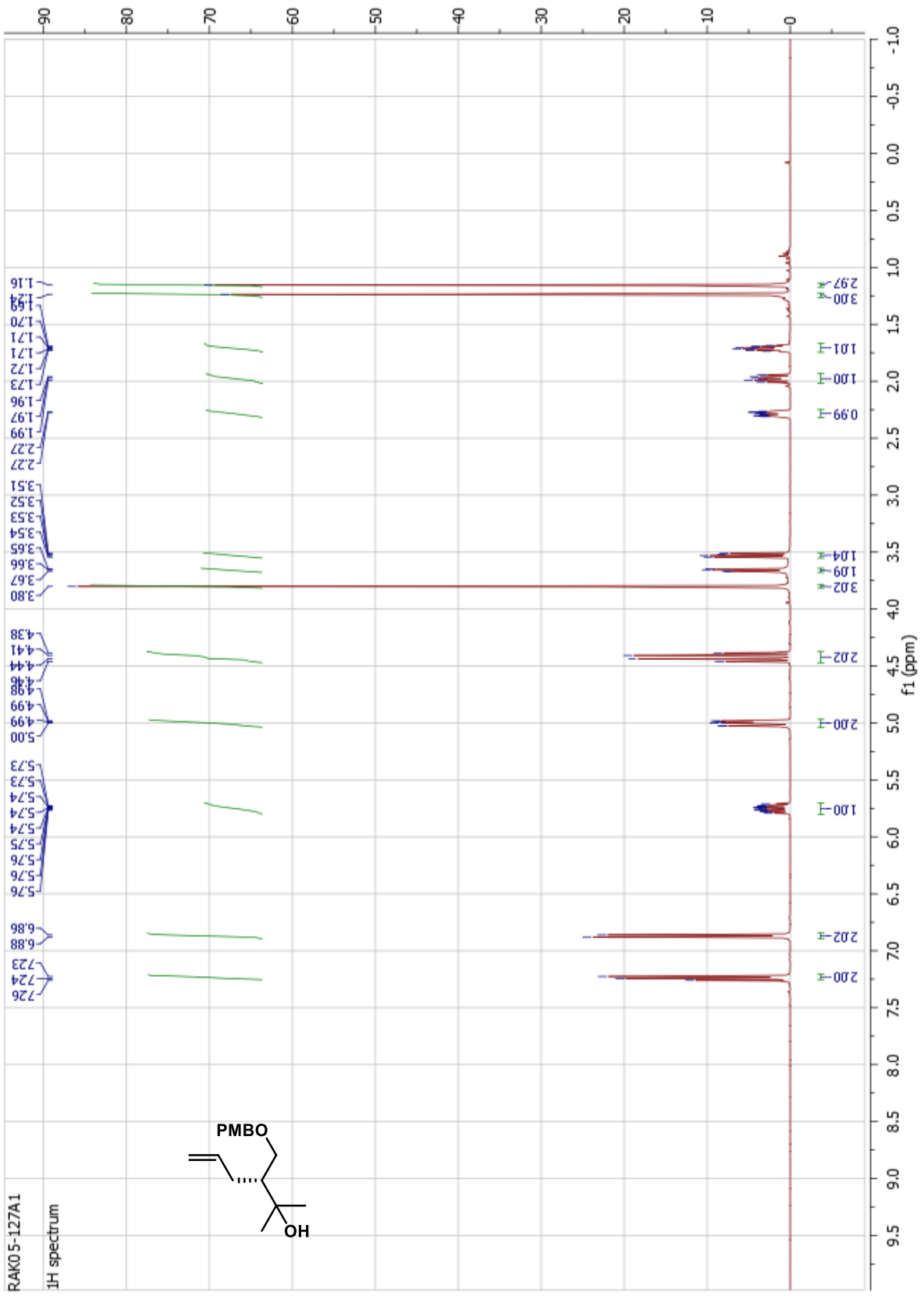

Br
O
OMe
f1 (ppm)

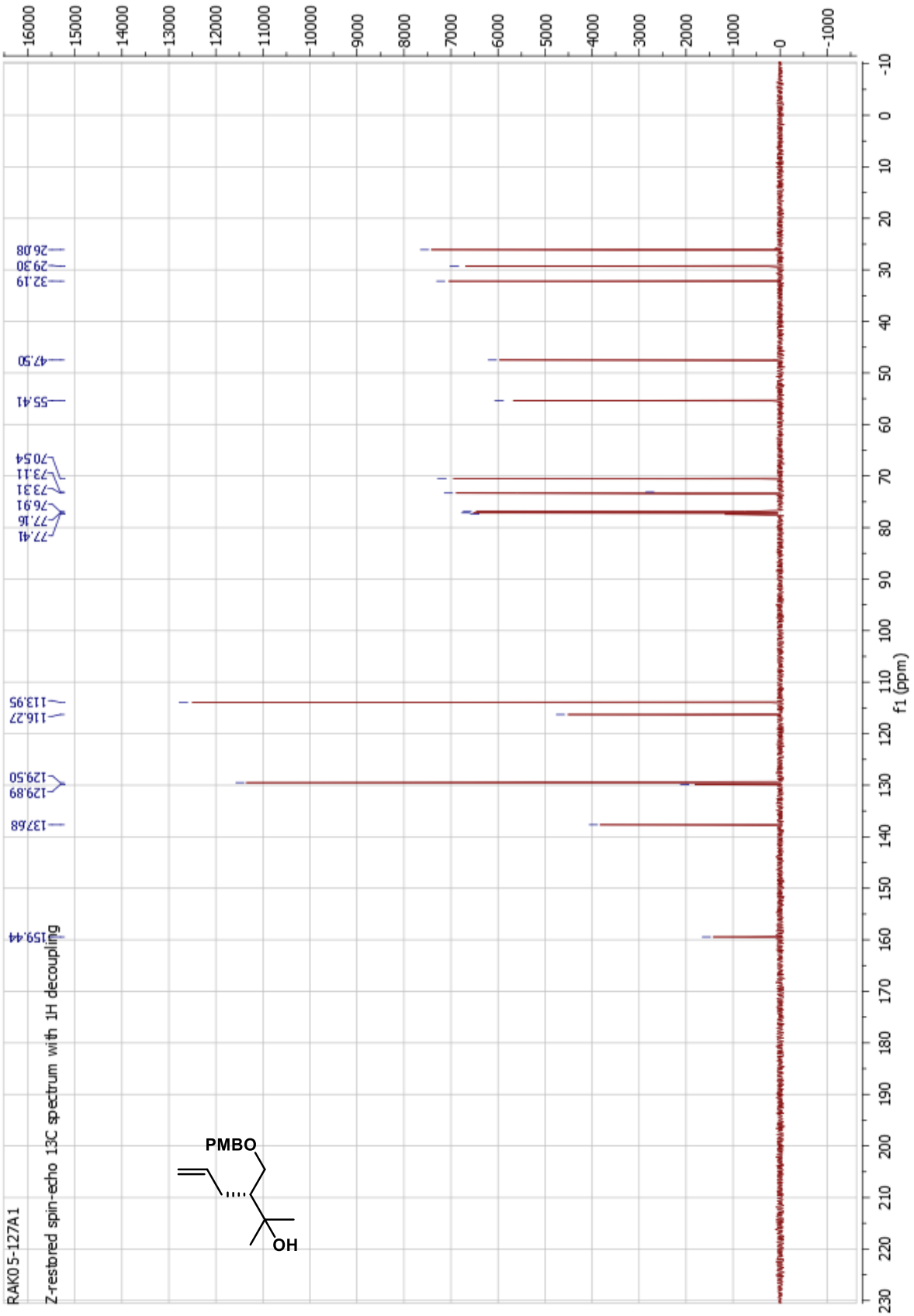

RAK05-134A1
f1 (ppm)
Br
O
OMe

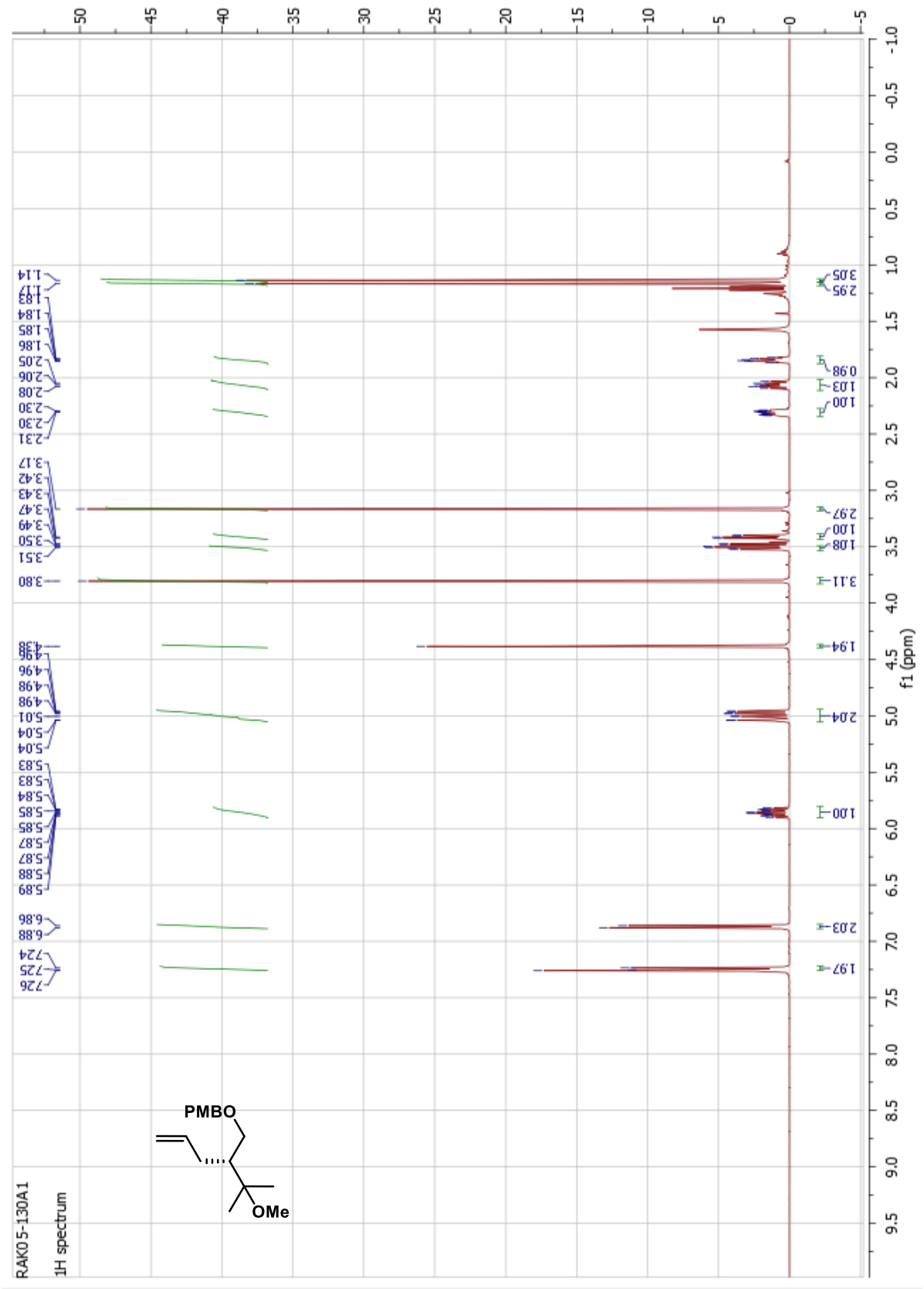

RAK05-143A1
1H spectrum
O
OMe
f1 (ppm)

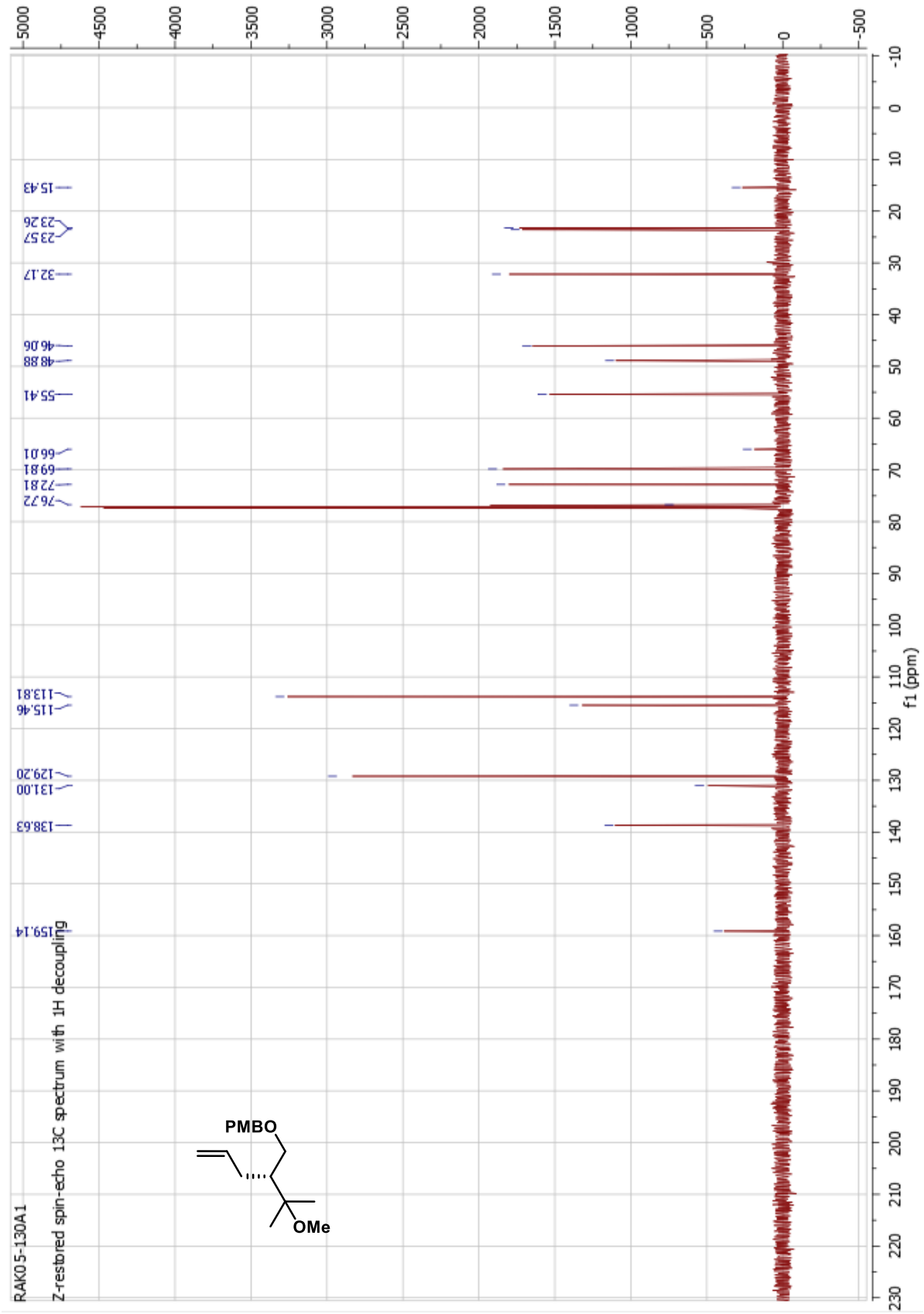

RAK05-143A1
Z-restored spin-echo 13C spectrum with 1H decoupling
204.75
135.96
116.71
76.25
59.70
49.19
29.07
23.69
23.06
O
OMe
f1 (ppm)

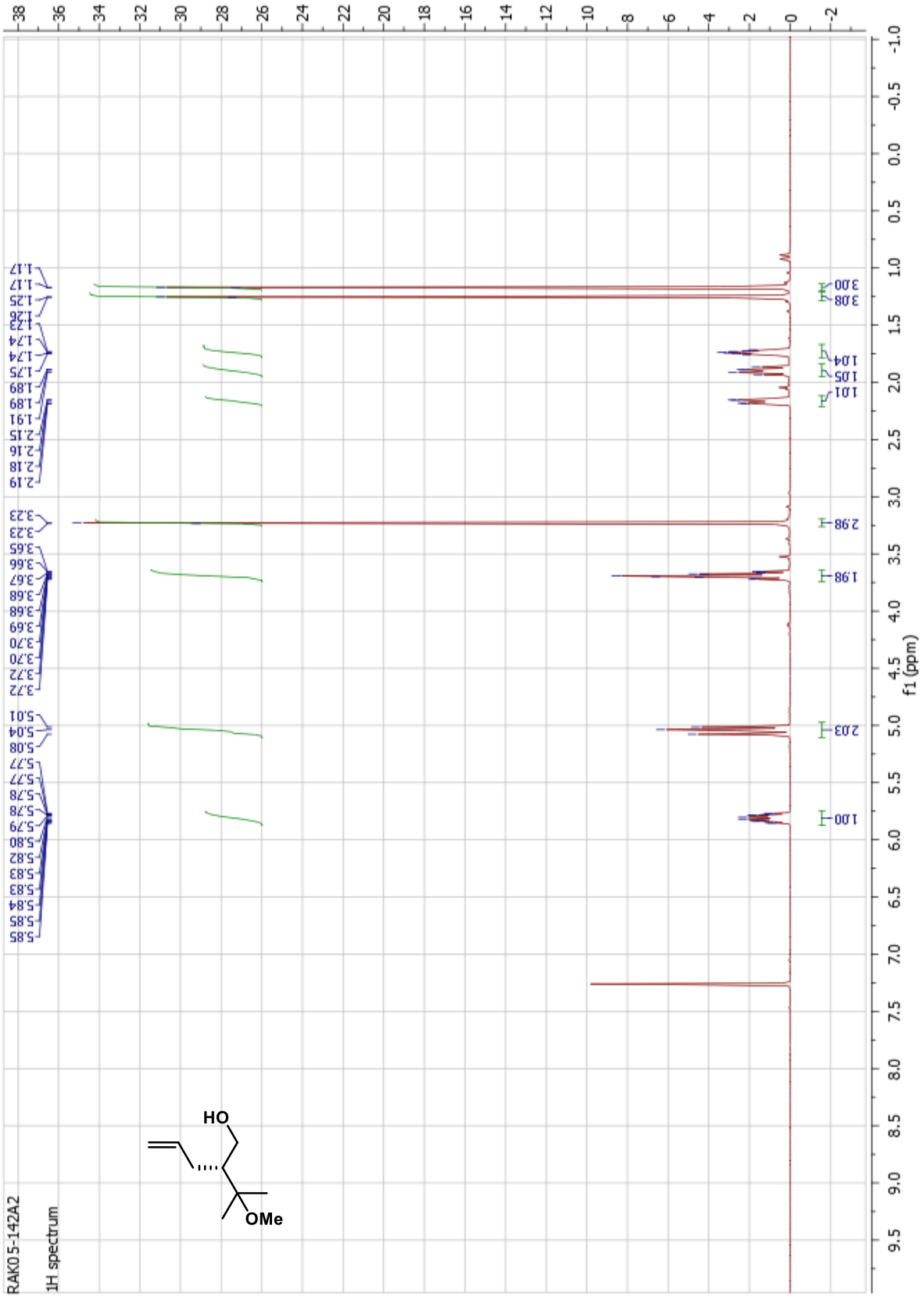

RAK05-136SM
1H spectrum
OMe
f1 (ppm)

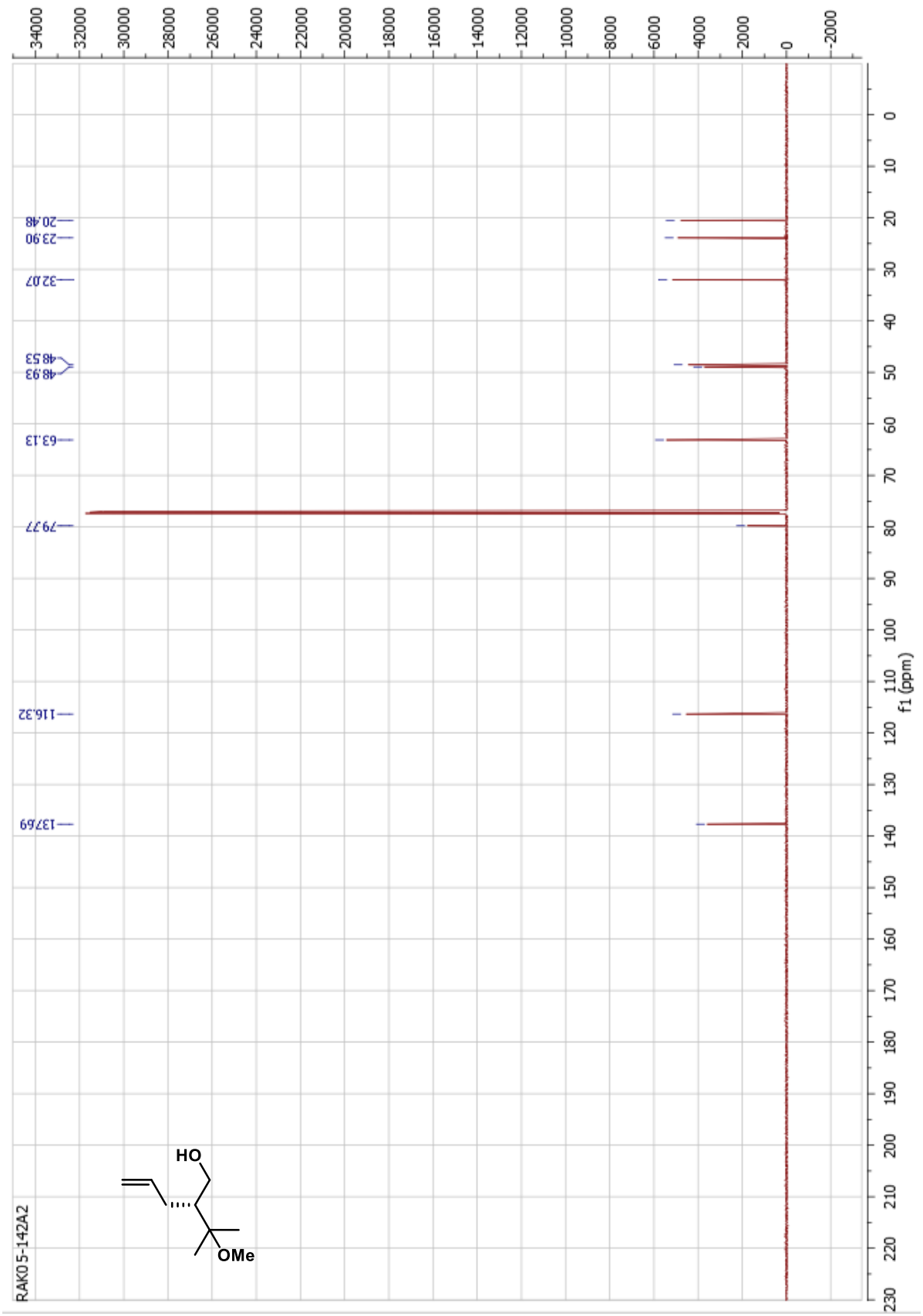

PMBO
OH
RAK05-127A1
1H spectrum
f1 (ppm)

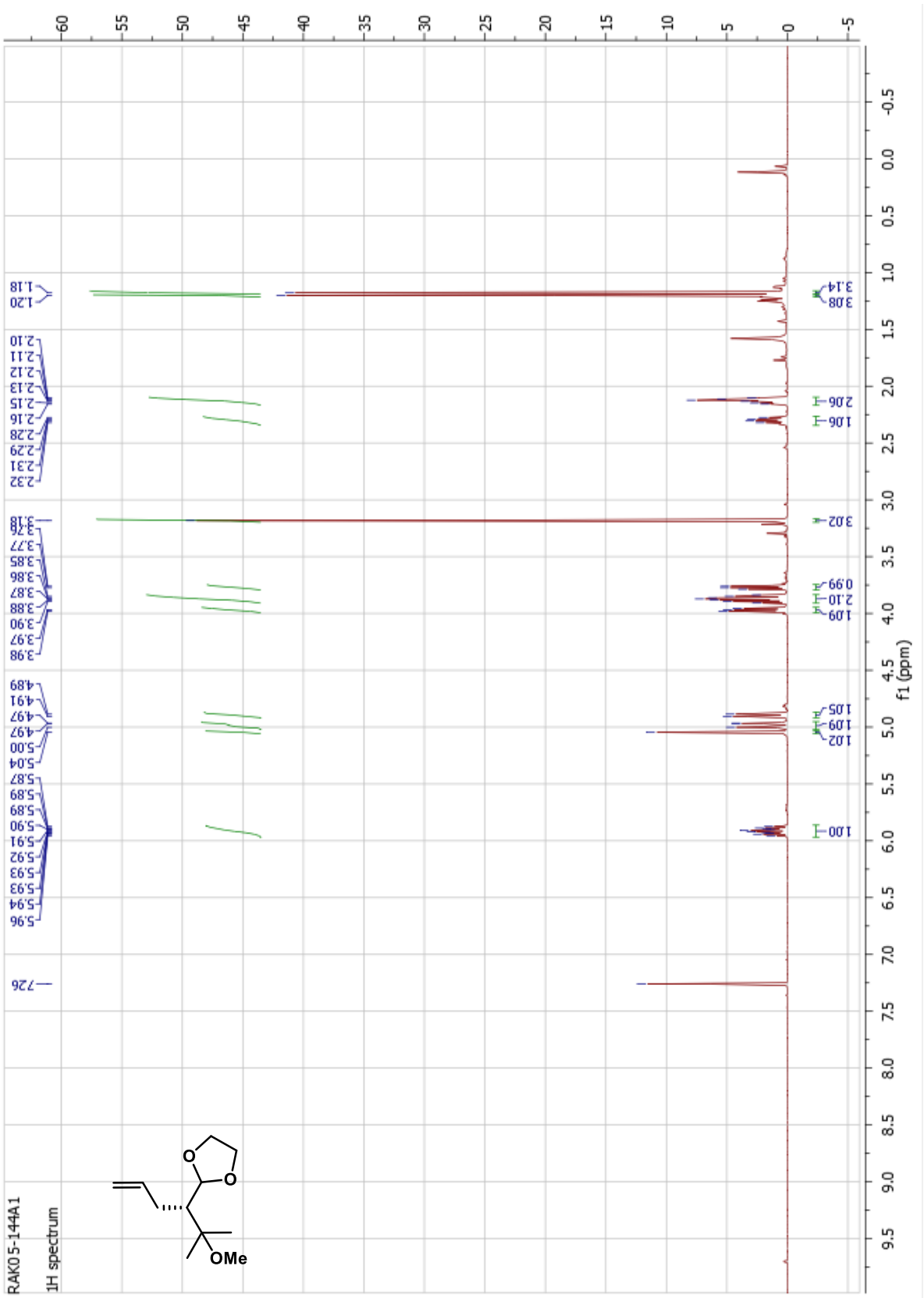

RAK05-127A1
Z-restored spin-echo 13C spectrum with 1H decoupling
f1 (ppm)
PMBO
OH
159.44
137.68
129.89
129.50
116.27
113.95
77.41
77.16
76.91
73.31
73.11
70.54
55.41
47.50
32.19
29.30
26.08

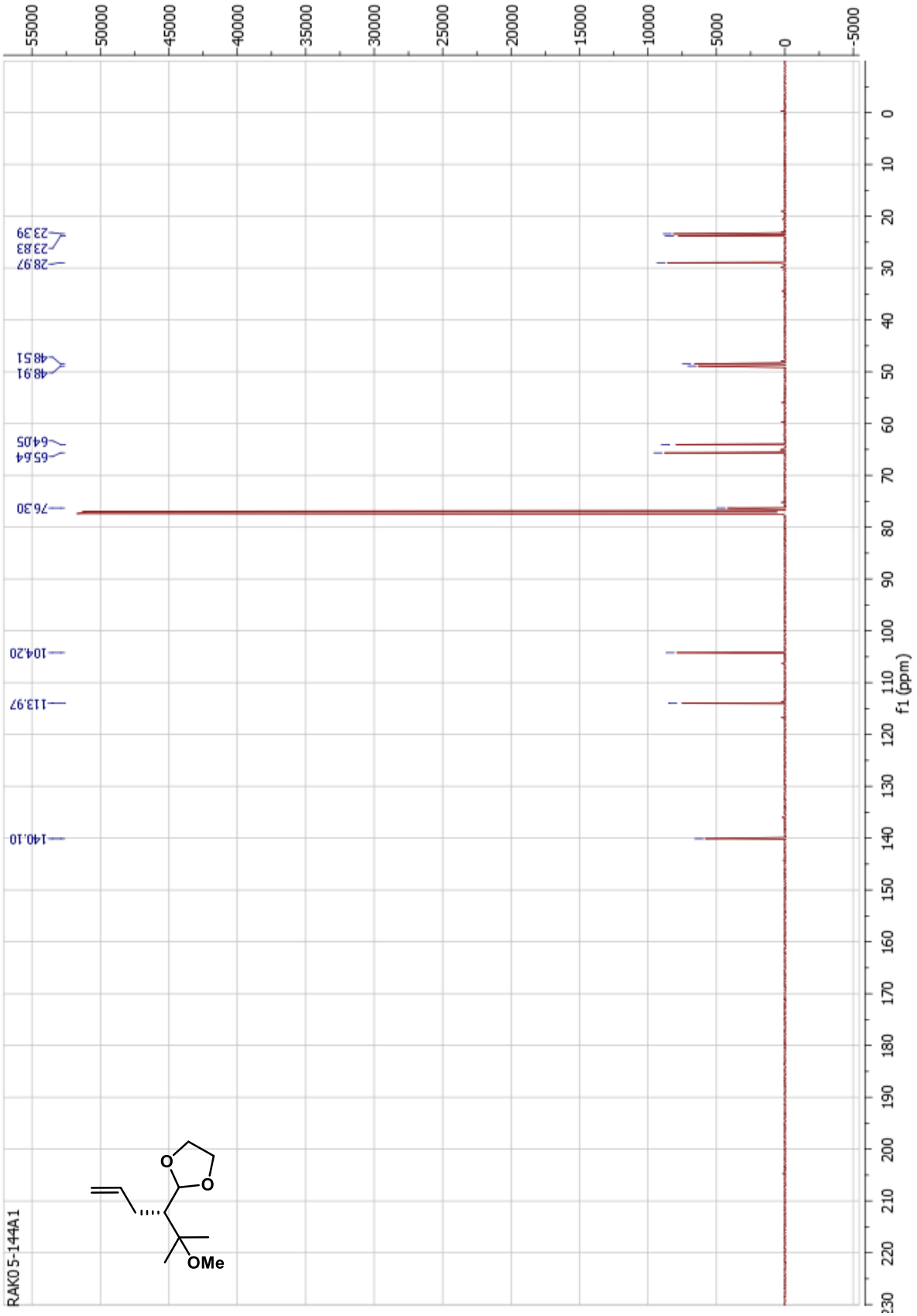

PMBO
OMe
RAK05-130A1
1H spectrum
f1 (ppm)

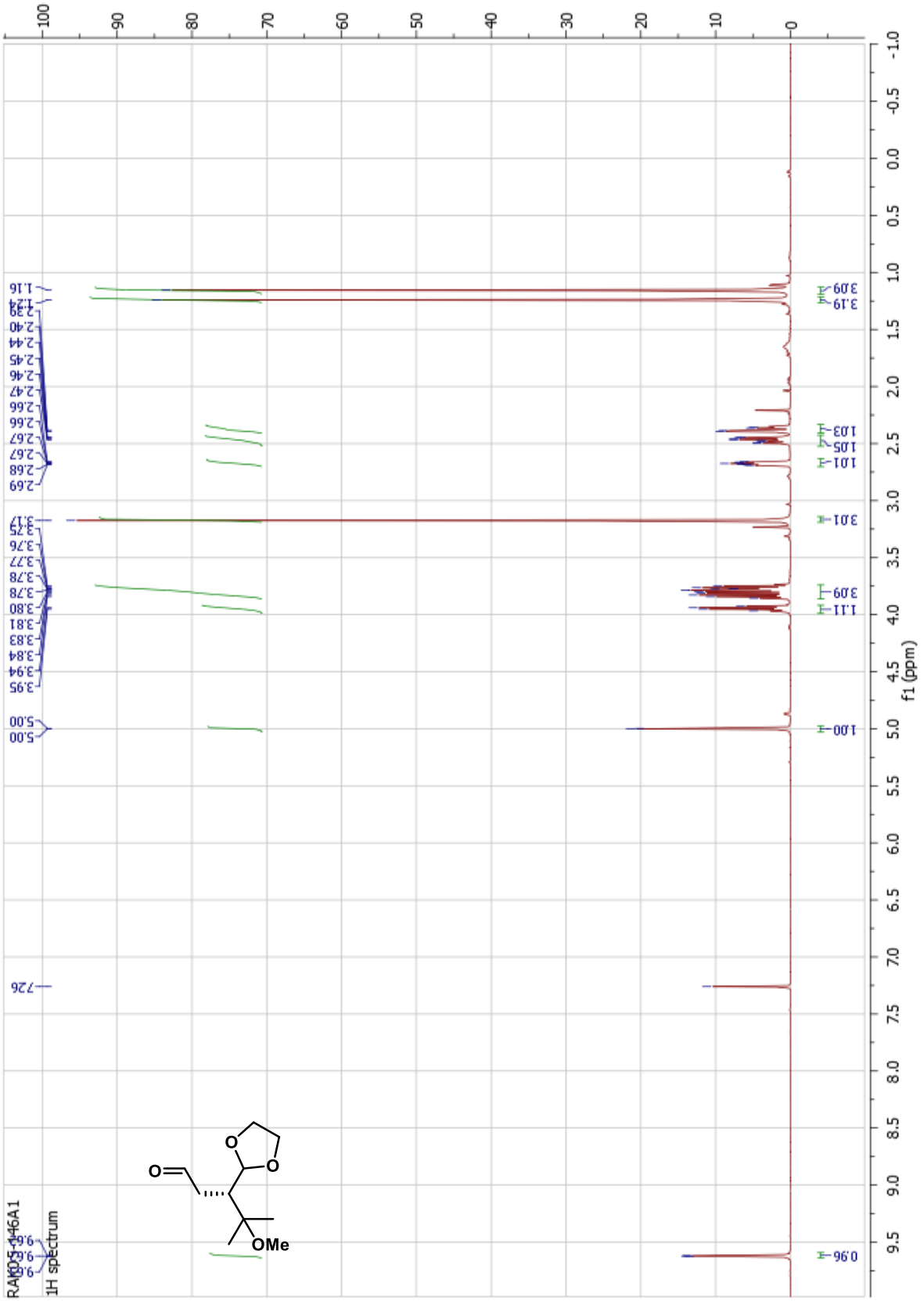

RAK05-130A1
Z-restored spin-echo 13C spectrum with 1H decoupling
159.14
138.63
131.00
129.20
115.46
113.81
76.72
72.81
69.81
66.01
55.41
48.88
46.06
32.17
23.57
23.26
15.43
PMBO
OMe
f1 (ppm)

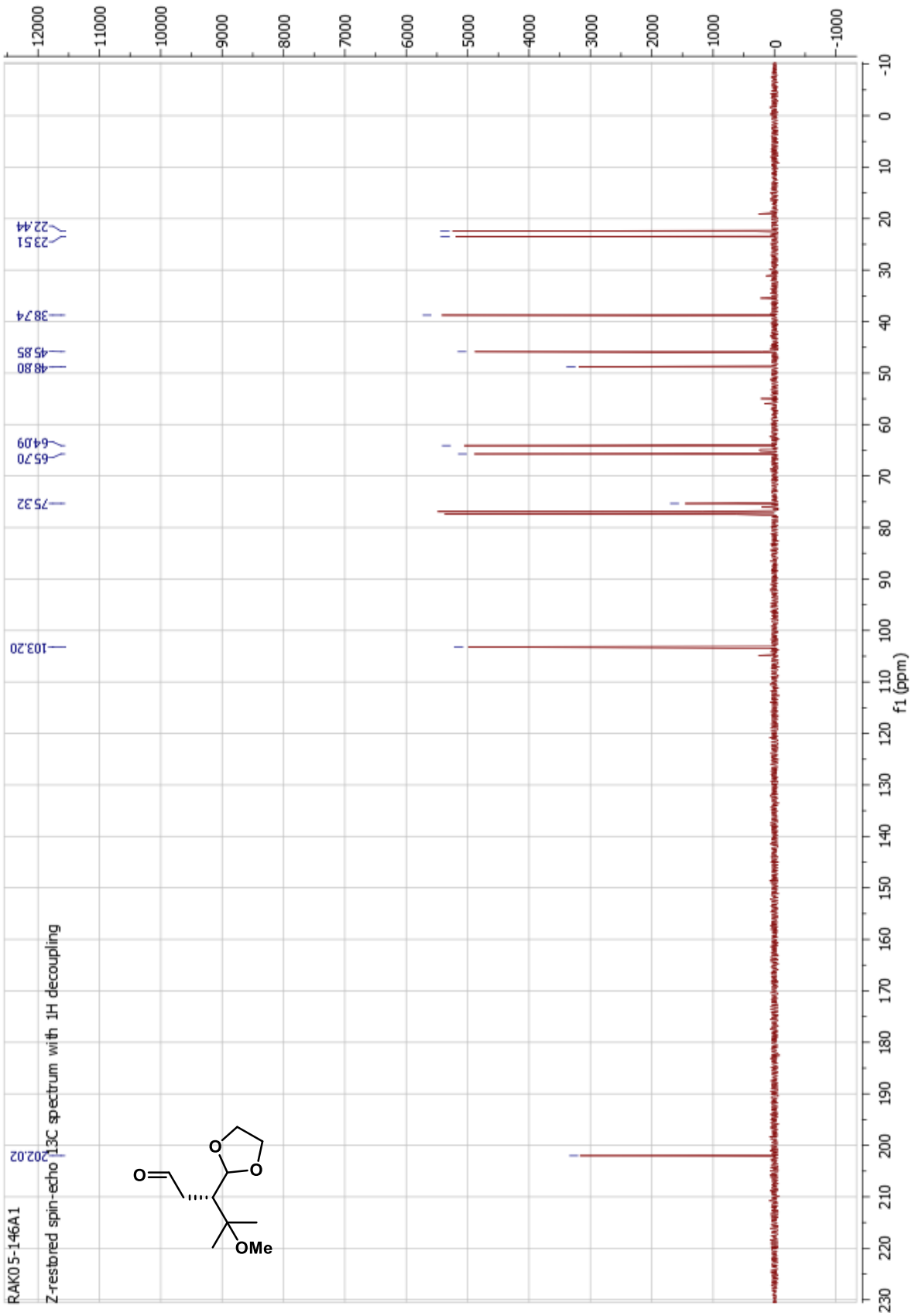

RAK05-142A2
1H spectrum
HO
OMe
f1 (ppm)

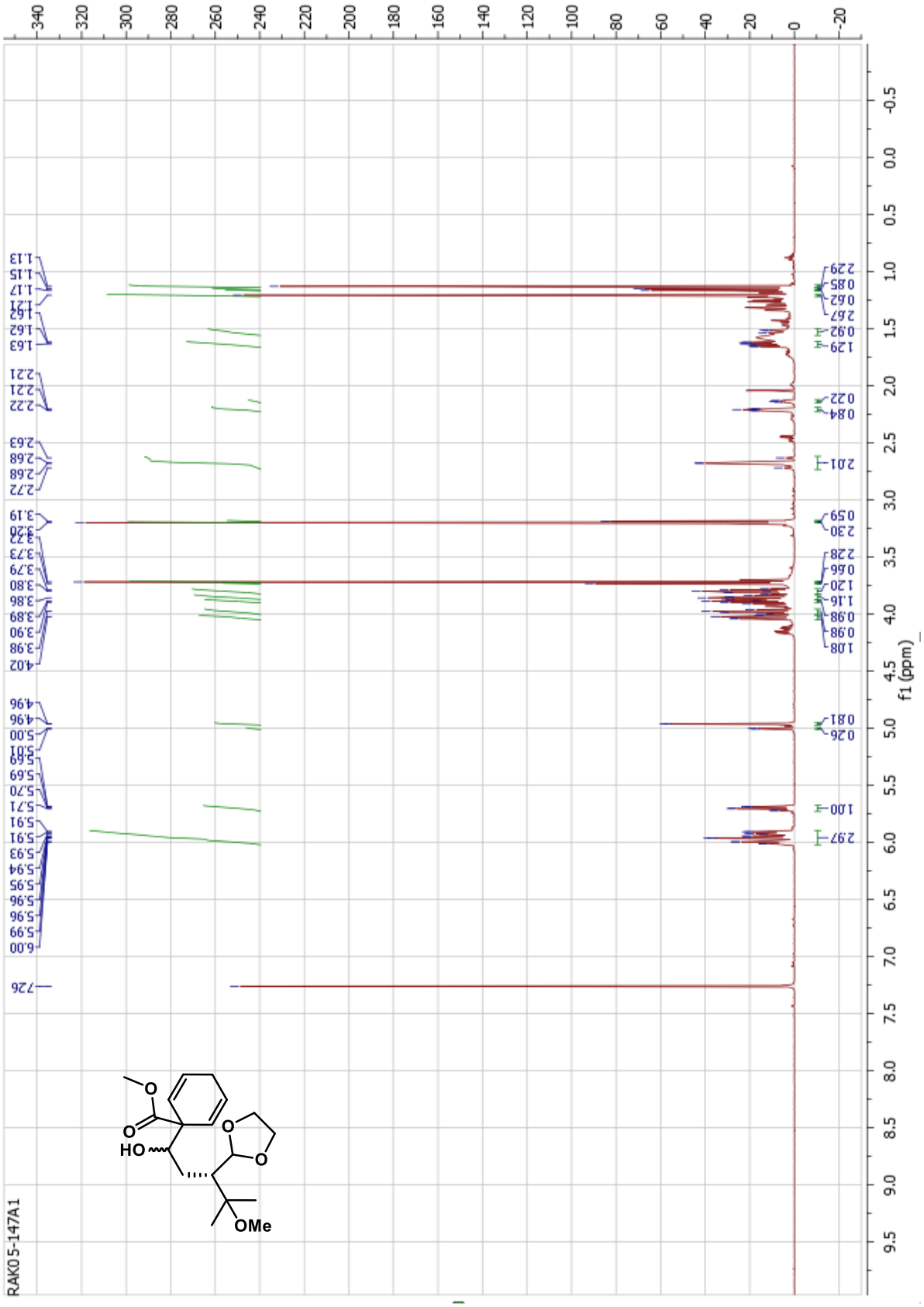

20.48
23.90
32.07
48.53
48.93
63.13
79.27
116.32
137.69
HO
OMe
RAK05-142A2
f1 (ppm)

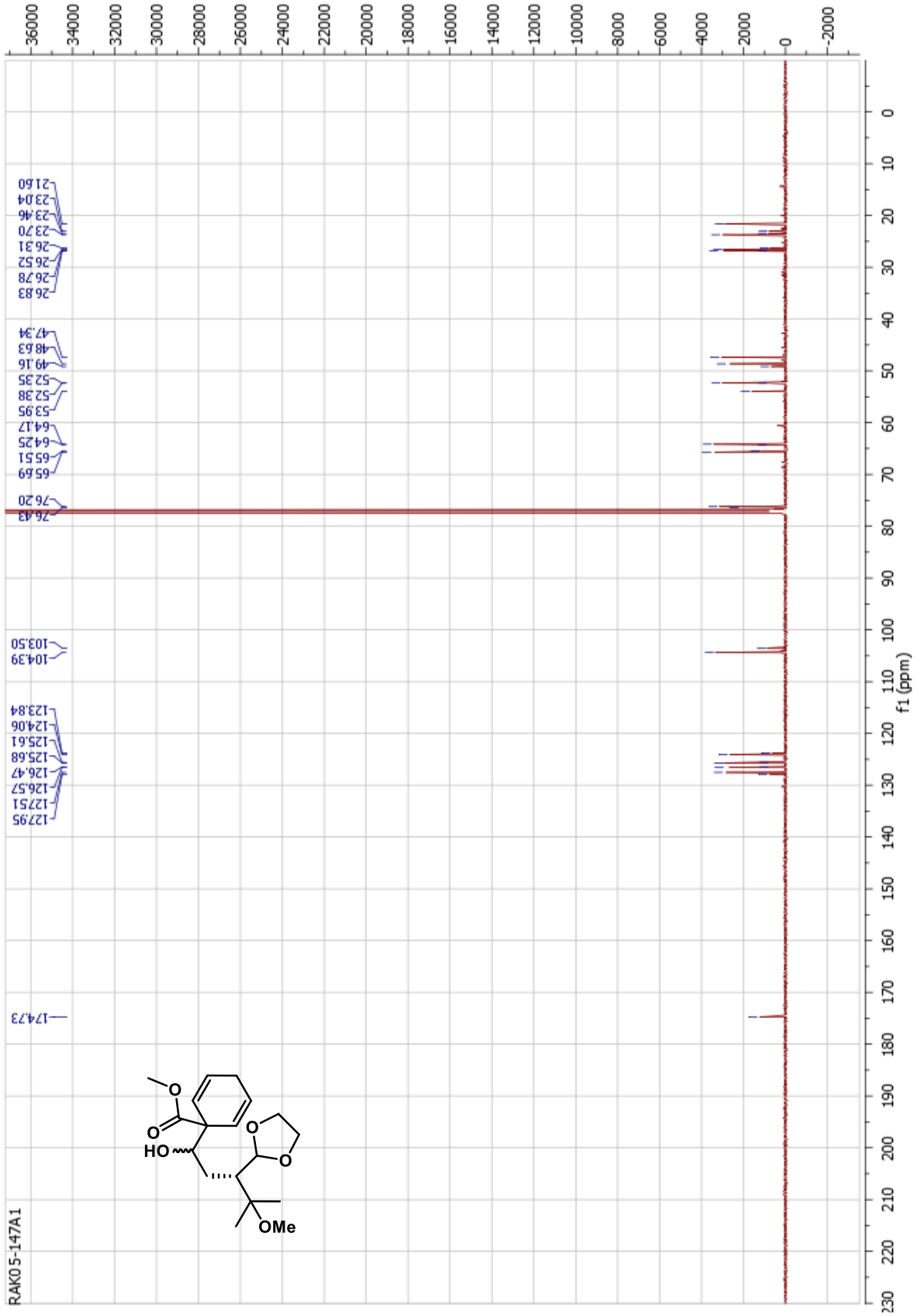

RAK05-144A1
1H spectrum
OMe
f1 (ppm)

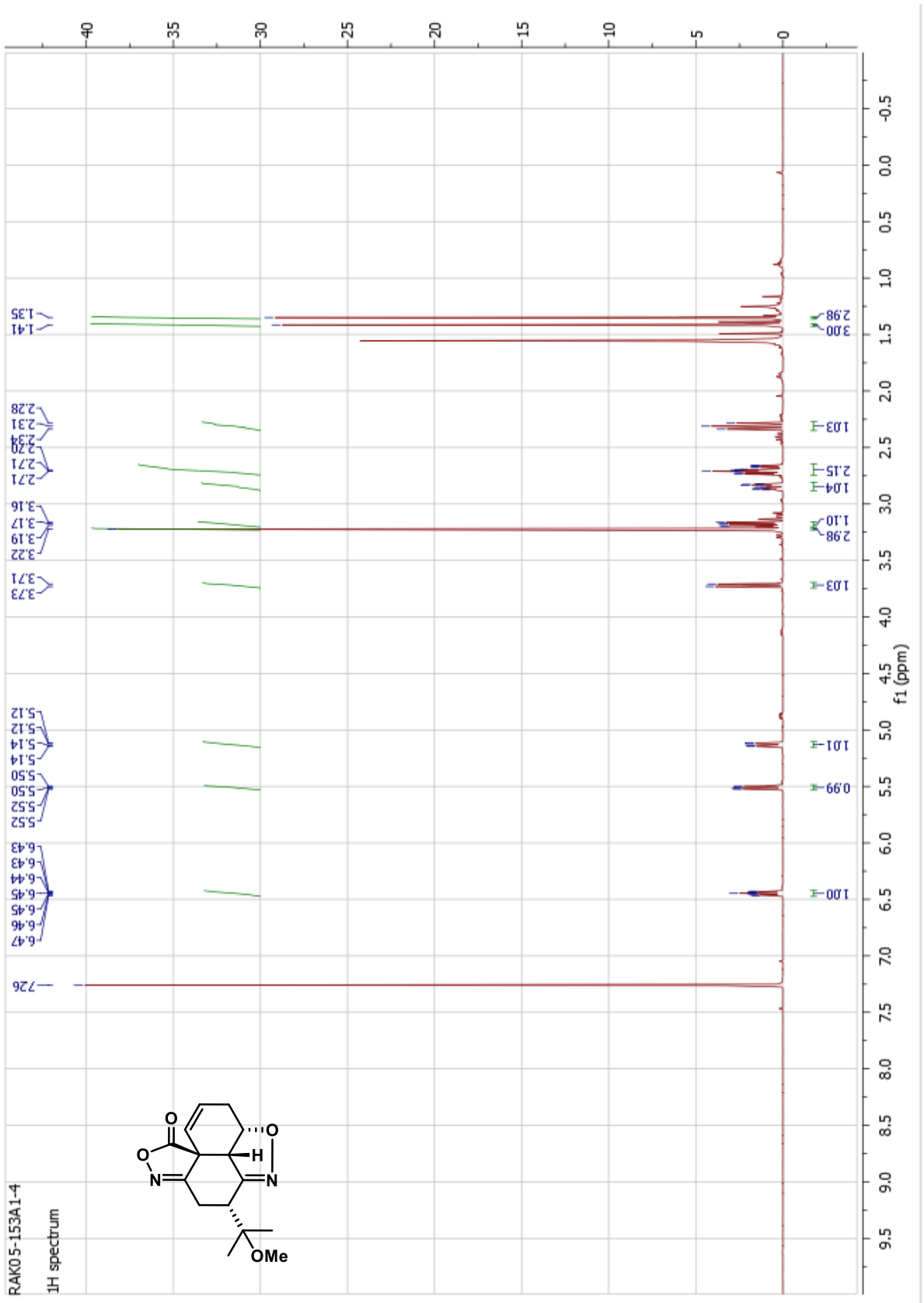

23.39
23.83
28.97
48.51
48.91
64.05
65.64
76.30
104.20
113.97
140.10
f1 (ppm)
RAK05-144A1
OMe

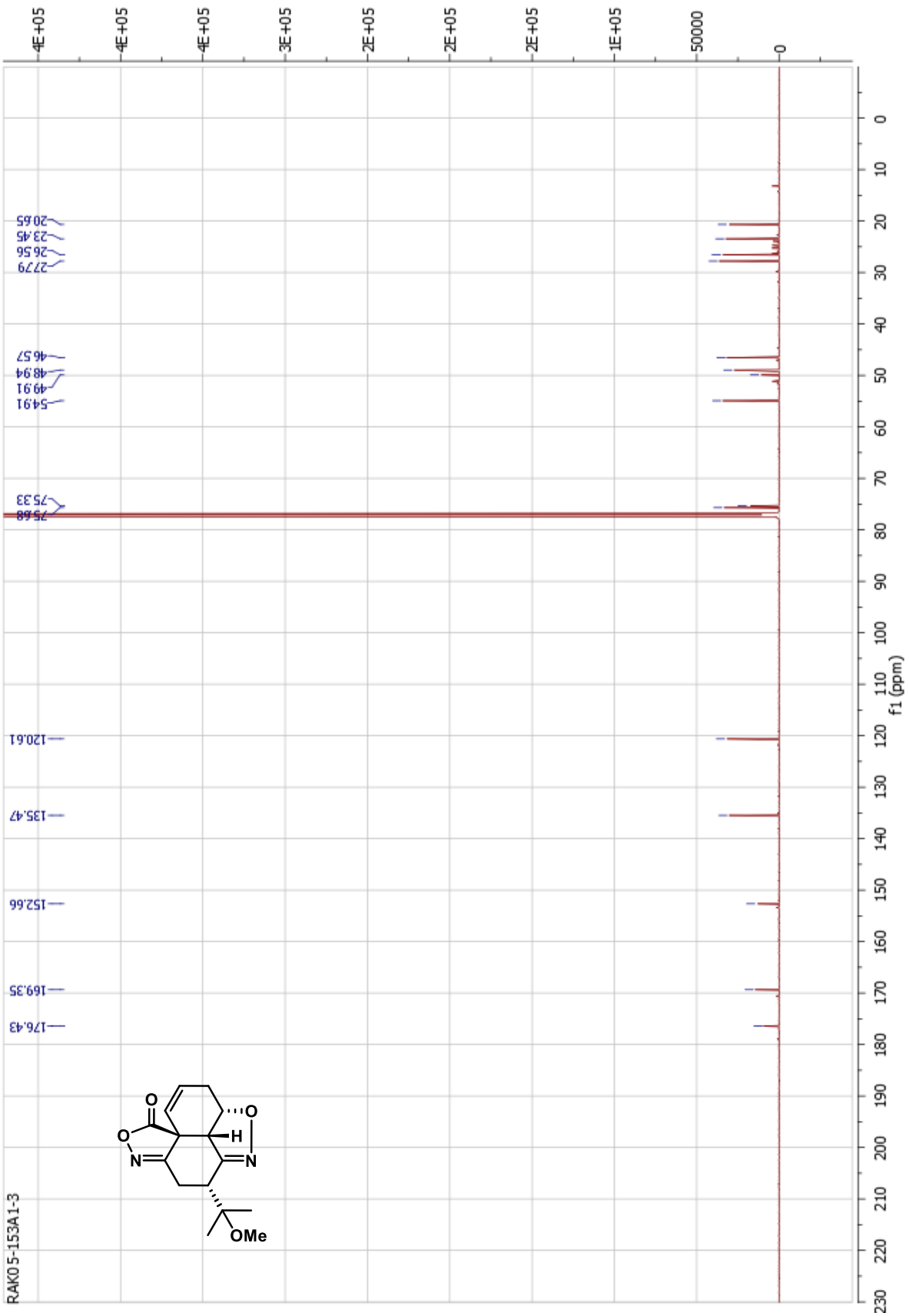

RAK05-146A1
1H spectrum
O
O
O
OMe
f1 (ppm)

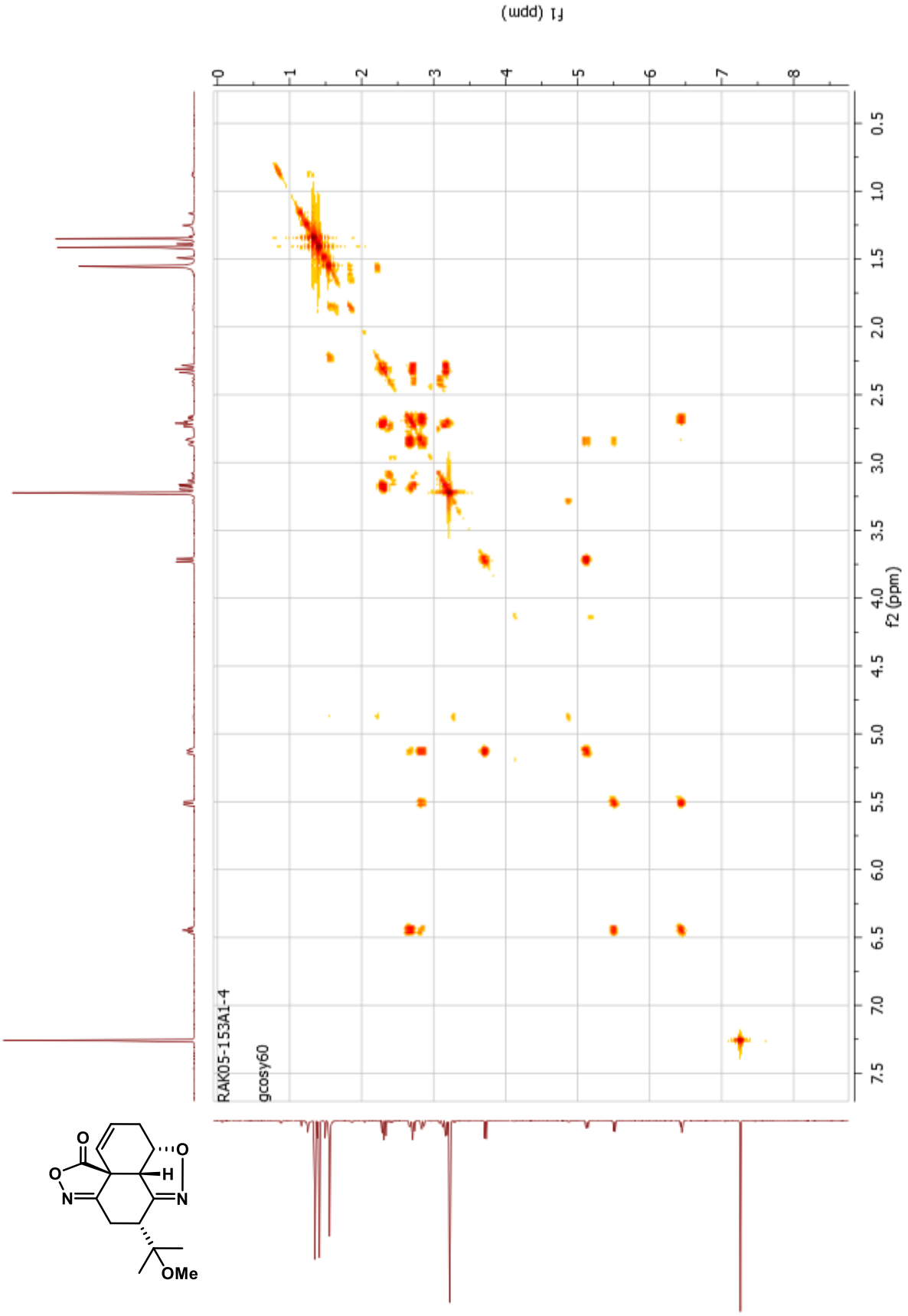

RAK05-146A1
Z-restored spin-echo 13C spectrum with 1H decoupling
202.02
103.20
75.32
65.70
64.09
48.80
45.85
38.74
23.51
22.44
O
O
O
OMe
f1 (ppm)

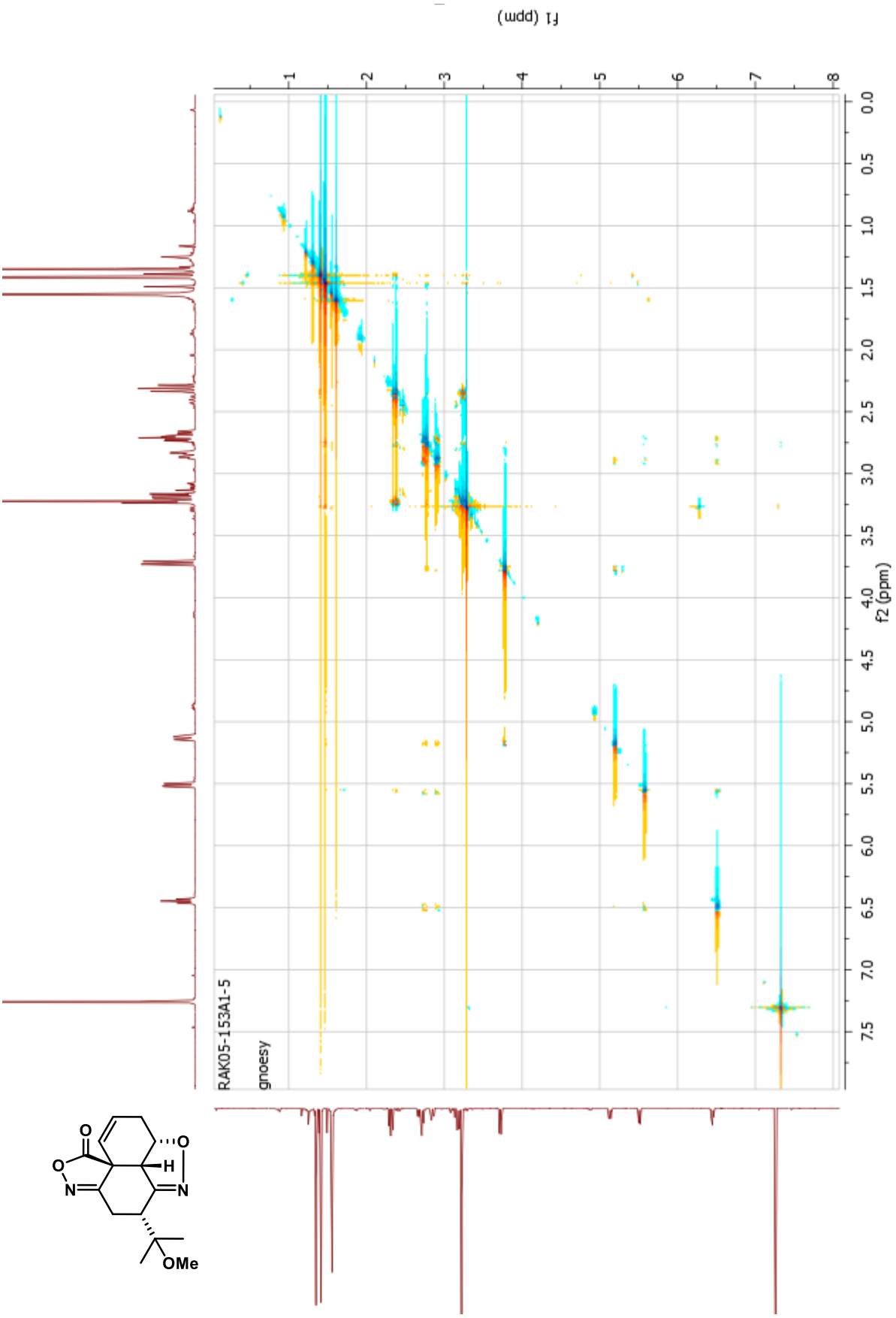

RAK05-147A1
f1 (ppm)
HO
OMe

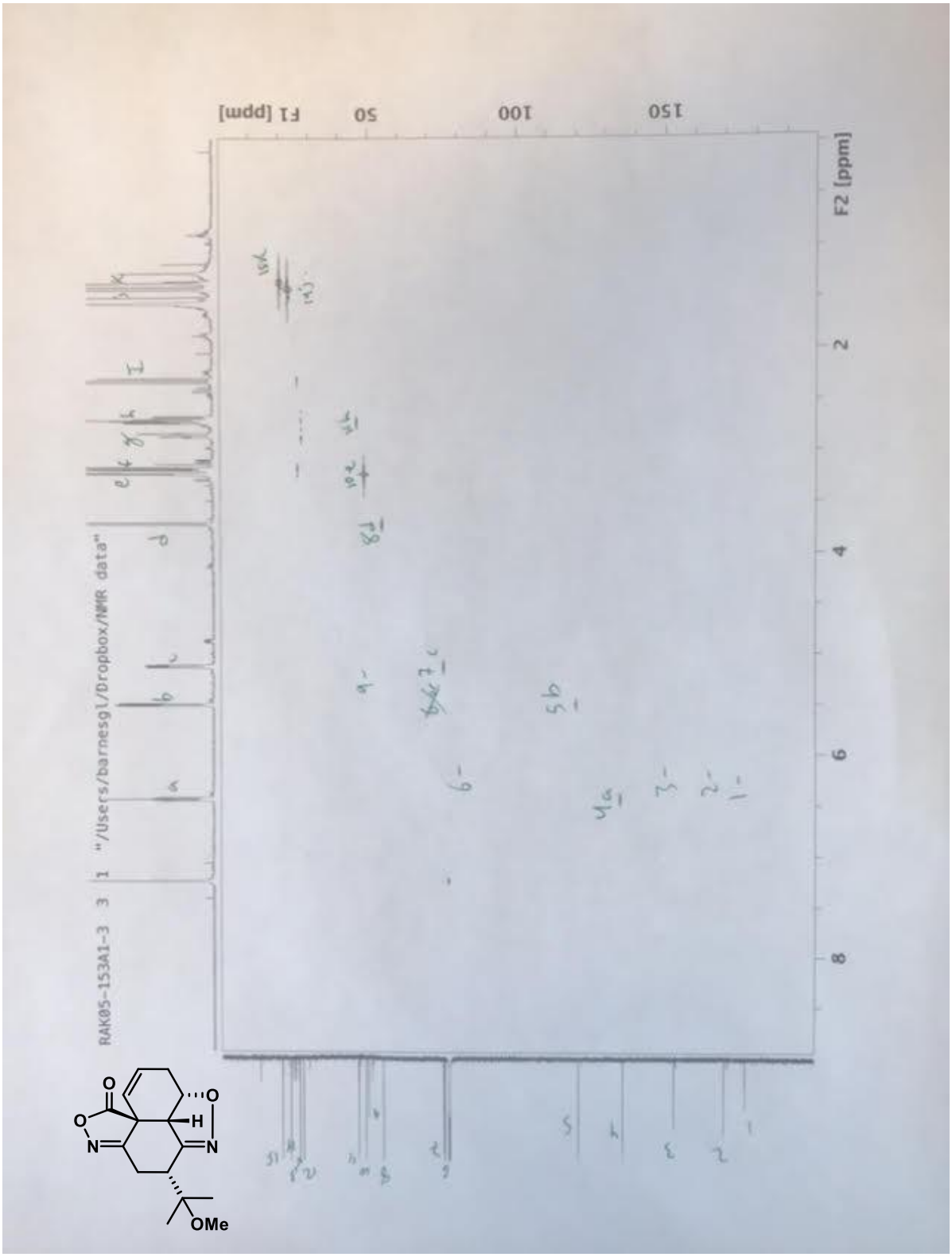

RAK05-147A1
f1 (ppm)
174.73
103.50
104.39
127.95
127.51
126.57
126.47
125.68
125.61
124.06
123.84
76.20
76.43
65.69
65.51
64.25
64.17
53.95
52.38
52.35
49.16
48.63
47.34
26.83
26.78
26.52
26.31
23.70
23.46
23.04
21.60
HO
O
O
O
O
OMe


RAK05-153A1-4
1H spectrum
f1 (ppm)
OMe

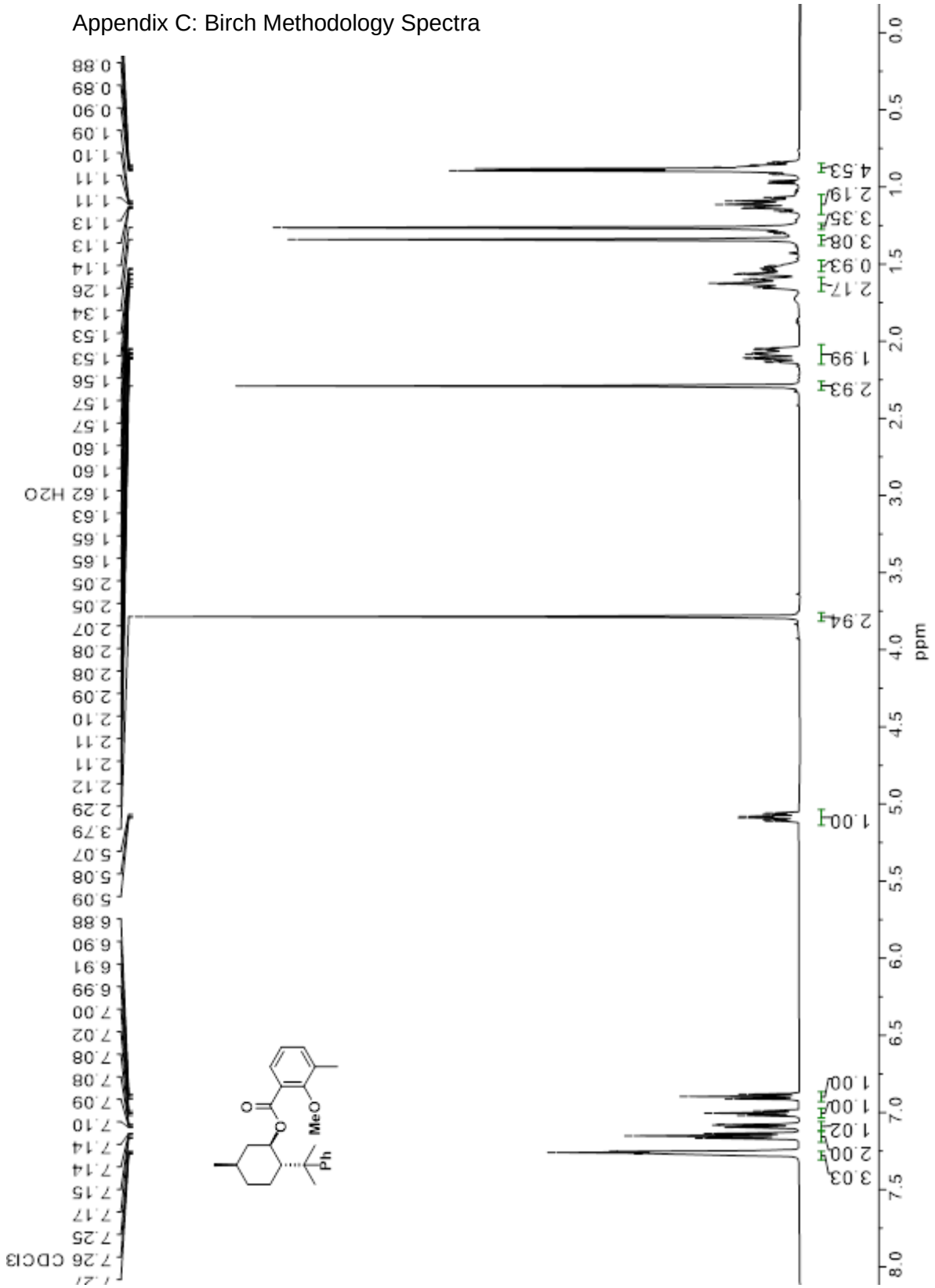

RAK05-153A1-3
f1 (ppm)
20.65
23.45
26.56
27.79
46.57
48.94
49.91
54.91
75.33
75.68
120.61
135.47
152.66
169.35
176.43
O
O
N
H
O
N
OMe


f1 (ppm)
f2 (ppm)
RAK05-153A1-4
gcosy60
OMe


f1 (ppm)
RAK05-153A1-5
gnoesy
f2 (ppm)
OMe


RAK05-153A1-3 3 1 "/Users/barnesgl/Dropbox/NMR data"
F1 [ppm]
F2 [ppm]
150
100
50
2
4
6
8
O
O
O
H
N
N
OMe

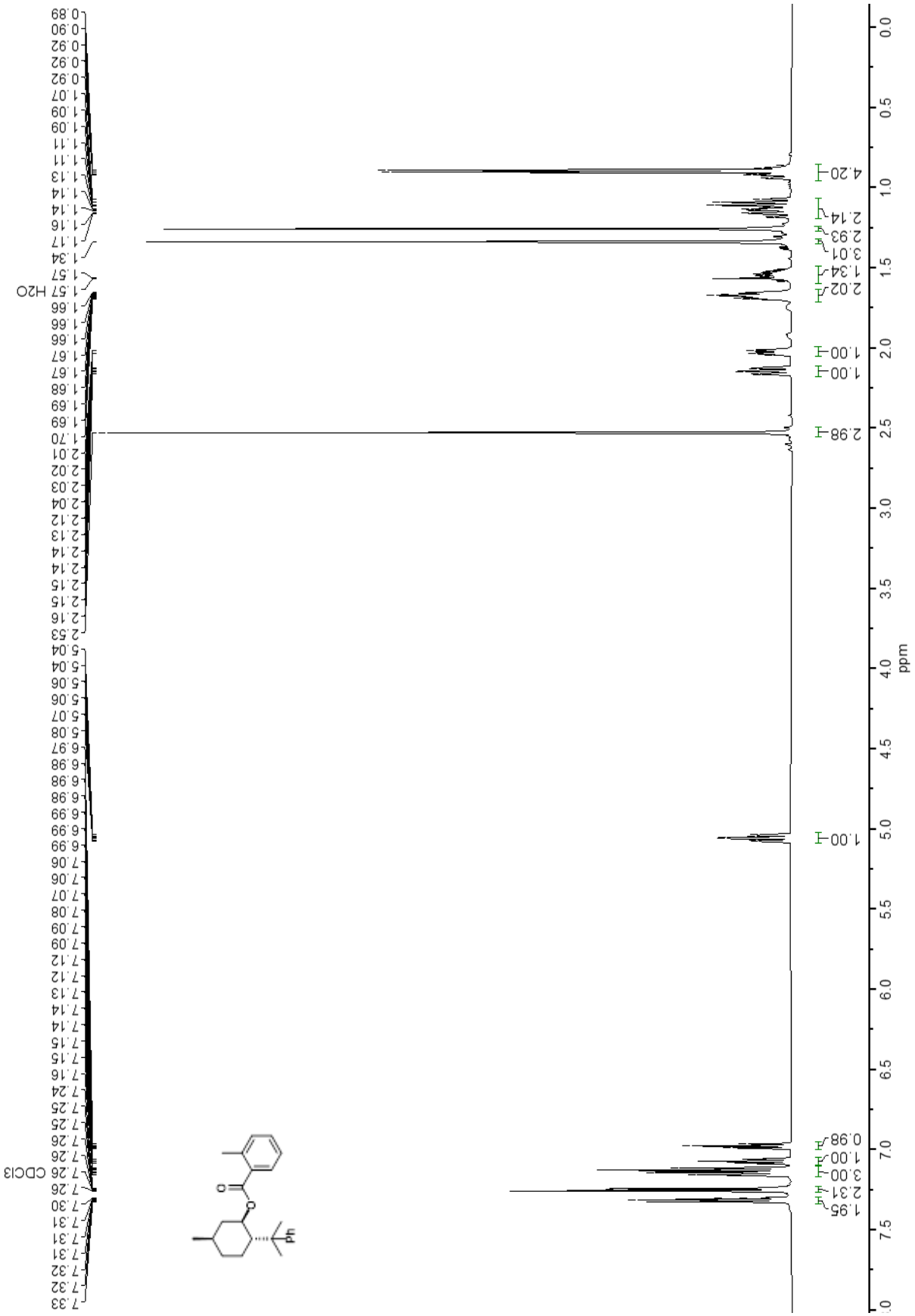
Appendix C: Birch Methodology Spectra



165.2
158.6
151.4
134.9
132.5
129.2
128.1
125.6
125.2
125.1
123.3
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
75.1
61.5
50.7
42.0
40.1
34.8
31.5
27.1
26.9
26.8
22.0
16.1
MeO
Ph
ppm

0.88
0.90
0.91
0.92
1.06
1.07
1.08
1.09
1.10
1.21
1.36
1.51
1.58
1.59
1.61
1.62
1.65
1.79
1.83
2.15
2.16
2.30
2.30
2.33
2.33
2.46
2.46
2.47
2.51
3.15
3.17
3.69
3.69
4.91
4.92
5.18
5.19
5.20
5.21
5.59
5.61
7.12
7.12
7.14
7.19
7.19
7.20
7.26 CDCl3
7.32
7.33
7.35
7.35
7.36
7.37
7.98
7.99
1.99
3.76
1.10
2.00
1.03
1.04
1.00
3.04
1.00
1.02
1.05
1.06
1.09
1.13
3.03
3.34
3.15
3.20
2.28
4.38
MeO
Ph
ppm

172.8
151.8
146.6
146.5
146.1
131.7
128.3
126.8
126.1
125.7
125.4
122.2
118.0
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
76.4
61.3
54.8
54.3
49.8
41.9
40.1
39.3
34.7
33.0
31.5
27.3
27.1
26.7
22.0
16.0
O
O
MeO
Ph
ppm


CDCl3
H2O
ppm

166.7
151.5
140.3
131.7
131.5
130.8
129.9
128.0
125.5
125.5
125.1
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
74.8
50.8
42.1
40.0
34.8
31.6
27.4
27.0
26.3
22.0
22.0
ppm

0.91
0.91
0.92
0.94
1.11
1.11
1.13
1.13
1.15
1.15
1.26
1.35
1.71
1.72
1.73
1.74
2.17
2.17
5.11
5.12
6.93
6.94
6.94
6.94
6.95
7.01
7.01
7.01
7.01
7.02
7.02
7.02
7.03
7.03
7.03
7.03
7.04
7.04
7.11
7.11
7.12
7.12
7.13
7.14
7.26
7.26 CDCl3
7.26
7.26
7.26
7.27
7.27
7.28
7.32
7.32
7.33
7.33
0.95
0.96
2.00
1.93
1.89
0.96
0.96
4.00
2.02
2.92
2.87
1.05
2.01
0.99
0.99
0.96
O
O
F
Ph
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
ppm

163.2
163.2
163.0
161.3
151.5
134.1
134.0
132.2
128.0
125.4
125.0
123.6
123.5
119.1
119.0
116.8
116.6
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
75.1
50.6
41.9
39.9
31.5
27.8
26.8
25.6
21.9
O
O
F
Ph
ppm

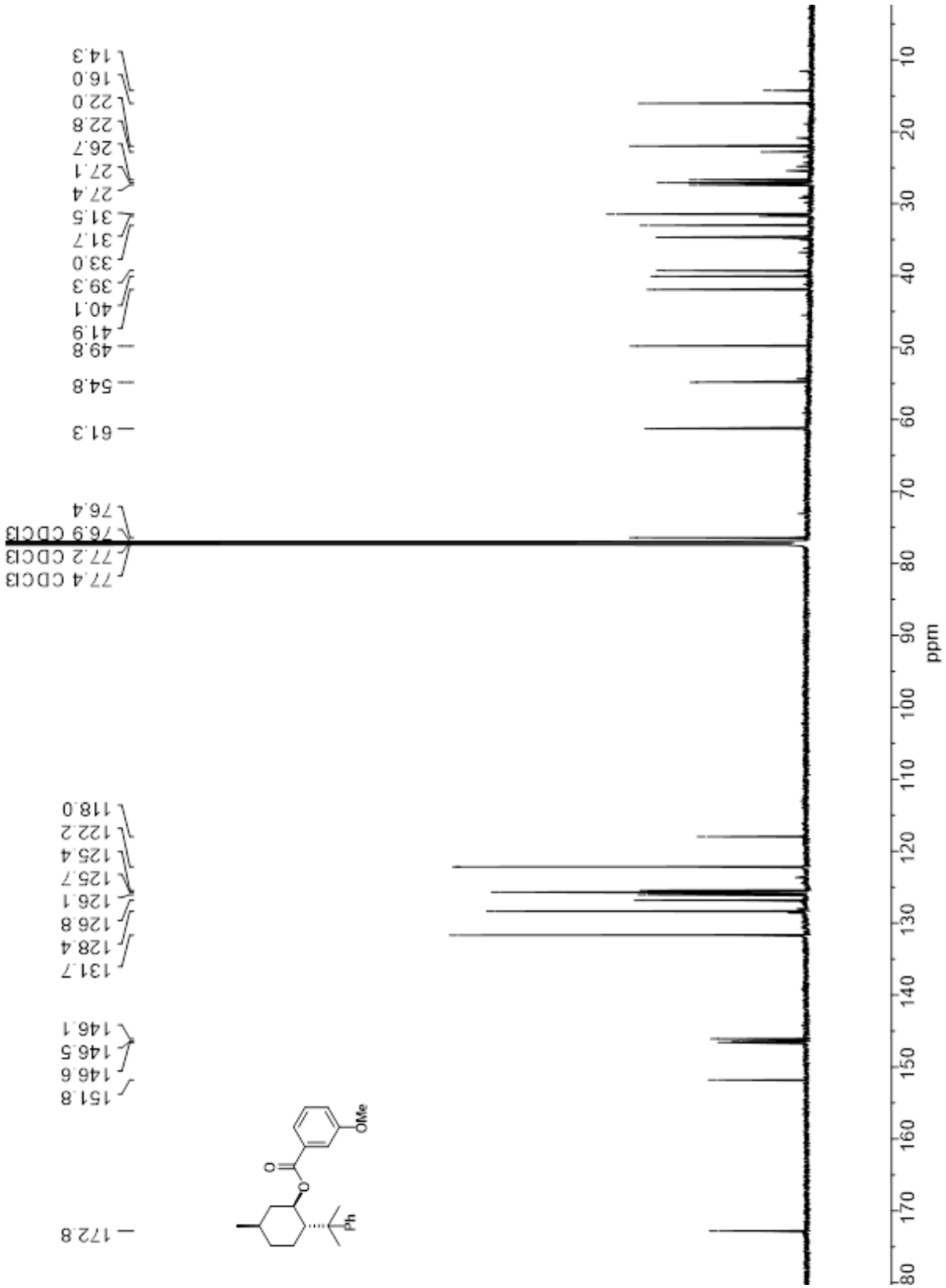
0.90
0.97
1.06
1.06
1.08
1.08
1.21
1.32
1.55
1.55
1.56
1.83
1.84
1.85
1.86
2.22
2.22
2.22
5.08
5.08
6.97
6.98
6.98
6.98
6.99
6.99
7.10
7.10
7.11
7.12
7.12
7.19
7.21
7.22
7.23
7.23
7.24
7.25
7.25
7.26 CDCl3
7.33
7.33
7.34
7.40
7.41
7.41
7.41
7.42
7.42
7.42
7.42
7.43
7.43
7.43
7.44
7.44
1.95
0.94
2.09
1.01
1.98
0.98
1.00
1.00
3.11
1.15
1.08
3.93
3.08
1.43
1.04
1.00
0.99
1.00
ppm
Cl
O
O
Ph

164.6
151.8
134.0
132.6
132.2
129.6
129.2
128.1
127.8
125.3
125.2
77.4 CDCl3
77.2 CDCl3
77.0 CDCl3
75.4
50.6
41.9
39.7
34.8
31.5
29.1
26.7
24.1
21.9
Cl
O
O
Ph
ppm

0.88
0.89
0.91
0.93
1.06
1.07
1.08
1.09
1.15
1.15
1.17
1.24
1.34
1.55
1.55
1.56
1.71
1.71
1.73
1.74
2.19
2.19
2.33
5.08
5.09
7.00
7.01
7.01
7.02
7.03
7.03
7.14
7.14
7.15
7.15
7.16
7.16
7.17
7.18
7.20
7.26
7.26 CDCl3
7.26
7.27
7.27
7.27
7.28
7.28
7.28
7.35
7.35
7.35
7.41
7.41
7.41
7.42
O
O
Ph
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
0.97
0.98
3.32
3.02
1.00
1.00
2.94
1.02
1.00
2.06
1.39
2.96
2.94
1.06
1.03
1.04
3.05

166.0
151.8
137.7
133.4
130.5
130.1
128.1
128.0
126.9
125.5
125.1
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
75.1
50.7
41.9
39.9
34.8
31.5
27.9
26.9
25.7
22.0
21.4
O
O
Ph
ppm

0.91
0.92
1.06
1.07
1.07
1.08
1.09
1.10
1.10
1.21
1.35
1.51
1.57 H2O
1.59
1.59
1.61
1.62
1.62
1.63
1.65
1.65
1.78
1.82
1.98
2.01
2.16
2.16
2.16
2.29
2.31
2.46
2.46
2.50
3.14
3.16
3.69
4.91
4.92
5.18
5.20
5.20
5.59
5.61
7.12
7.13
7.18
7.19
7.20
7.26 CDCl3
7.32
7.33
7.35
7.35
7.36
7.37
7.98
OMe
O
O
Ph
1.93
3.96
1.05
1.93
0.98
0.96
1.00
2.94
0.97
0.98
1.02
1.02
1.05
1.03
2.39
3.31
2.97
3.01
2.30
4.13
ppm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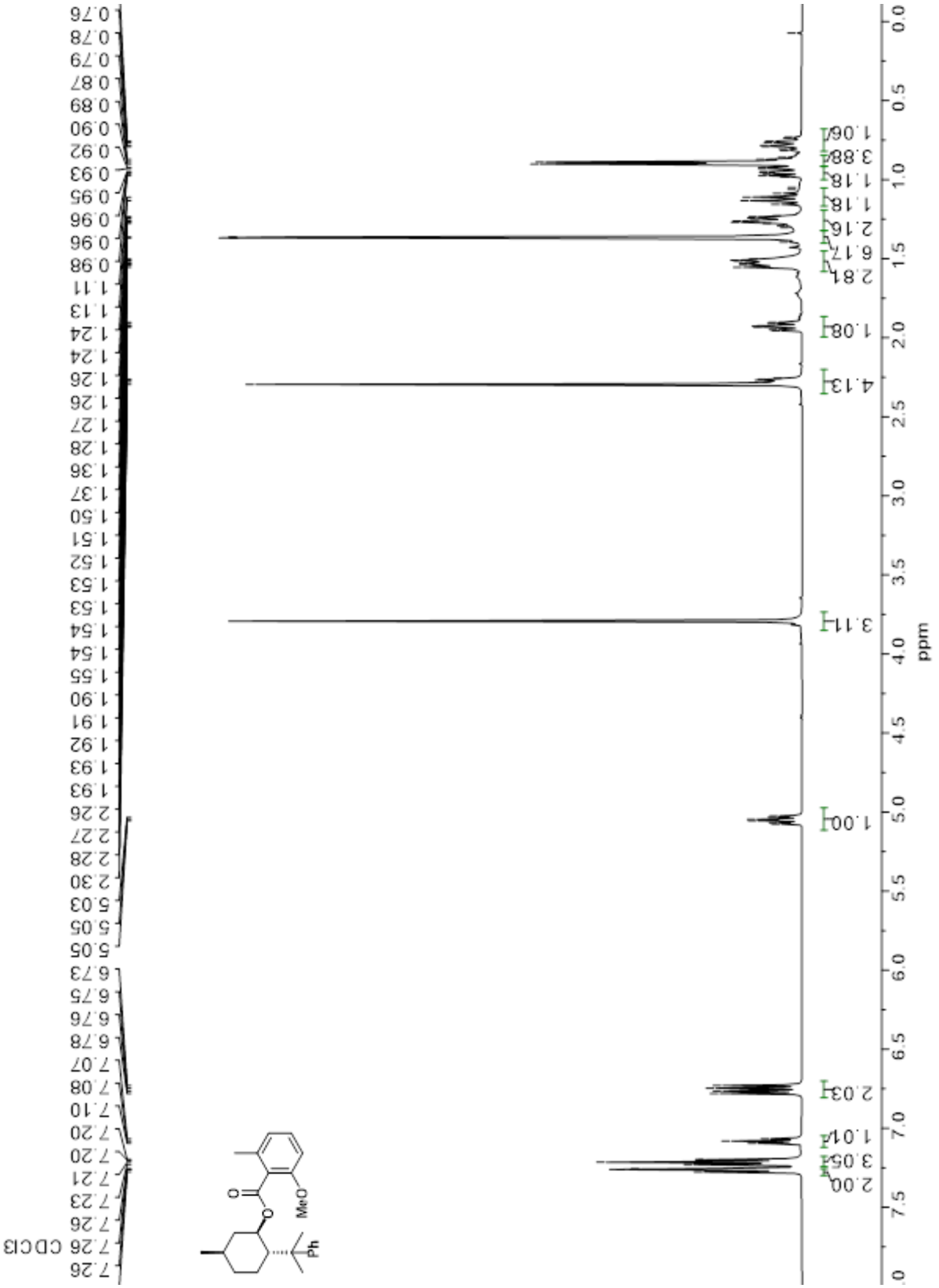
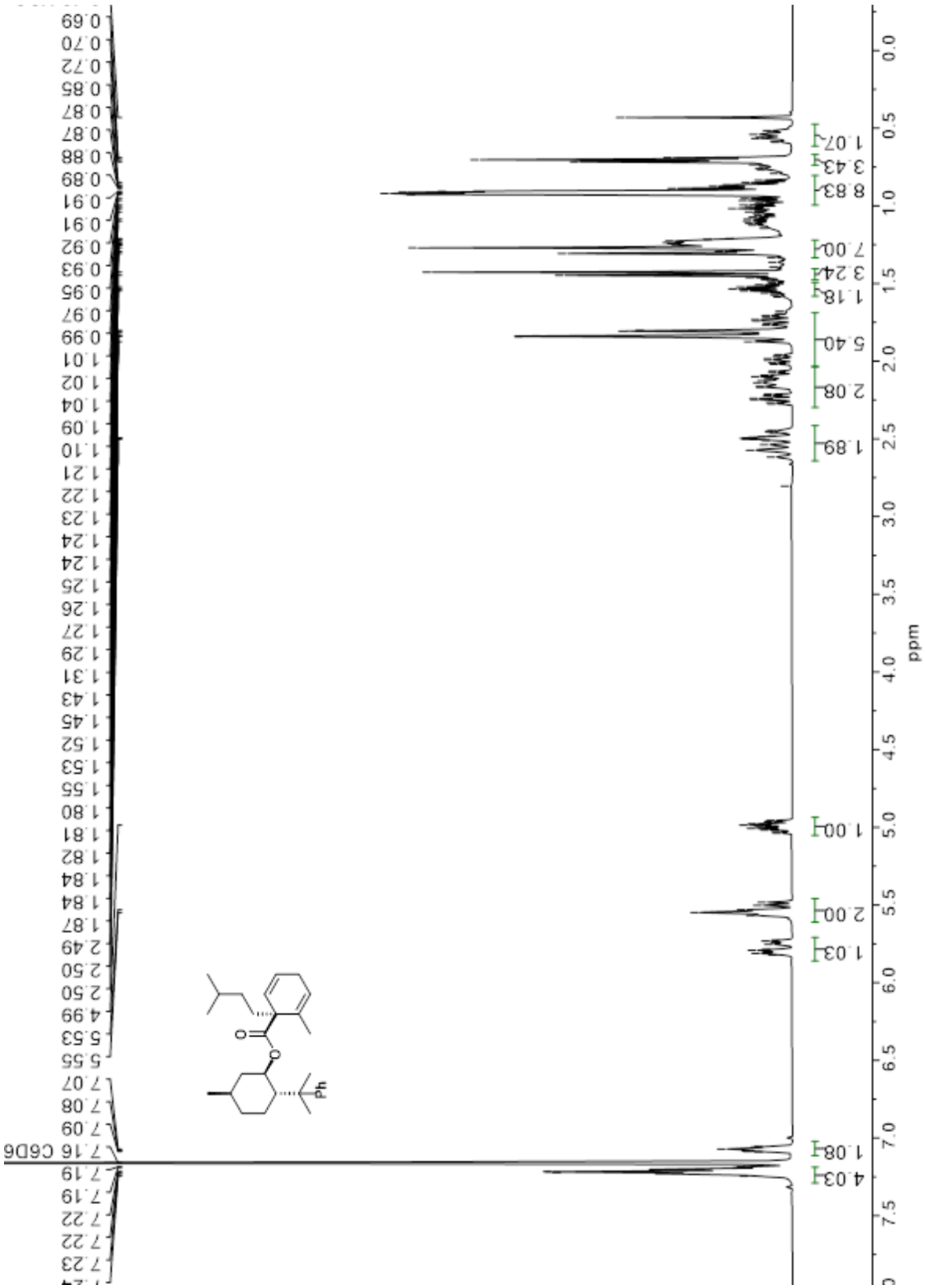
151.8
146.6
146.5
146.1
131.7
128.4
126.8
126.1
125.7
125.4
122.2
118.0
77.4 CDCl3
77.2 CDCl3
76.9 CDCl3
76.4
61.3
54.8
49.8
41.9
40.1
39.3
33.0
31.7
31.5
27.4
27.1
26.7
22.8
22.0
16.0
14.3
OMe
Ph
ppm


MeO
Ph
CDCl3
ppm

168.1
156.2
150.9
136.1
130.0
128.0
125.9
125.3
124.7
122.5
108.5
77.4 CDCl3
77.3
77.2 CDCl3
77.1
76.9 CDCl3
76.7
55.7
50.9
41.7
40.6
34.7
31.6
30.1
27.7
23.1
22.0
19.3
MeO
Ph
O
O
ppm

0.70
0.72
0.73
0.82
0.83
0.86
0.86
0.87
0.88
1.24
1.30
1.47
1.48
1.49
1.50
1.50
1.51
1.54 H2O
1.82
1.83
1.85
1.87
1.89
1.92
2.02
2.03
2.05
2.06
2.82
2.82
2.85
2.86
2.87
3.47
4.76
4.77
4.78
4.79
4.80
5.28
5.29
5.30
5.31
5.86
5.87
5.88
5.89
7.14
7.14
7.15
7.16
7.17
7.26
7.26 CDCl3
7.27
7.28
O
O
MeO
Ph
3.87
1.03
1.00
1.03
2.06
2.04
3.12
0.95
1.01
1.04
9.27
2.32
3.21
3.29
5.53
3.46
1.22
ppm

173.3
152.4
150.8
128.1
127.7
126.3
126.0
125.4
110.1
93.7
77.4 CDCl3
77.2 CDCl3
77.2 CDCl3
76.9 CDCl3
76.1
54.0
52.2
50.5
41.6
40.5
34.7
33.4
32.0
31.7
31.5
30.5
28.4
27.7
26.7
23.1
22.9
22.8
21.9
MeO
Ph
O
O
ppm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0.72
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0.87
0.87
0.88
0.89
0.91
0.91
0.92
0.93
0.95
0.97
0.99
1.01
1.02
1.04
1.09
1.10
1.21
1.22
1.23
1.24
1.24
1.25
1.26
1.27
1.29
1.31
1.43
1.45
1.52
1.53
1.55
1.80
1.81
1.82
1.84
1.84
1.87
2.49
2.50
2.50
4.99
5.53
5.55
7.07
7.08
7.09
7.16 C6D6
7.19
7.19
7.22
7.22
7.23
1.07
3.43
8.83
7.00
3.24
1.18
5.40
2.08
1.89
1.00
2.00
1.03
1.08
4.03
O
O
Ph
0.0
0.5
1.0
1.5
2.0
2.5
3.0
3.5
4.0
4.5
5.0
5.5
6.0
6.5
7.0
7.5
ppm

173.0
150.8
150.7
131.9
131.2
128.8
128.6
128.1
C6D6
126.6
126.3
126.2
125.8
125.7
125.5
124.2
123.3
76.1
75.7
52.3
50.8
50.7
42.1
42.0
40.7
40.6
34.8
34.7
33.7
33.6
33.2
33.0
32.0
31.5
31.4
31.2
31.0
28.8
28.8
27.9
27.8
27.5
27.4
23.8
23.6
23.1
23.1
23.1
22.9
22.8
22.0
22.0
20.2
20.2
O
O
Ph
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160
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77.2 CDCl3
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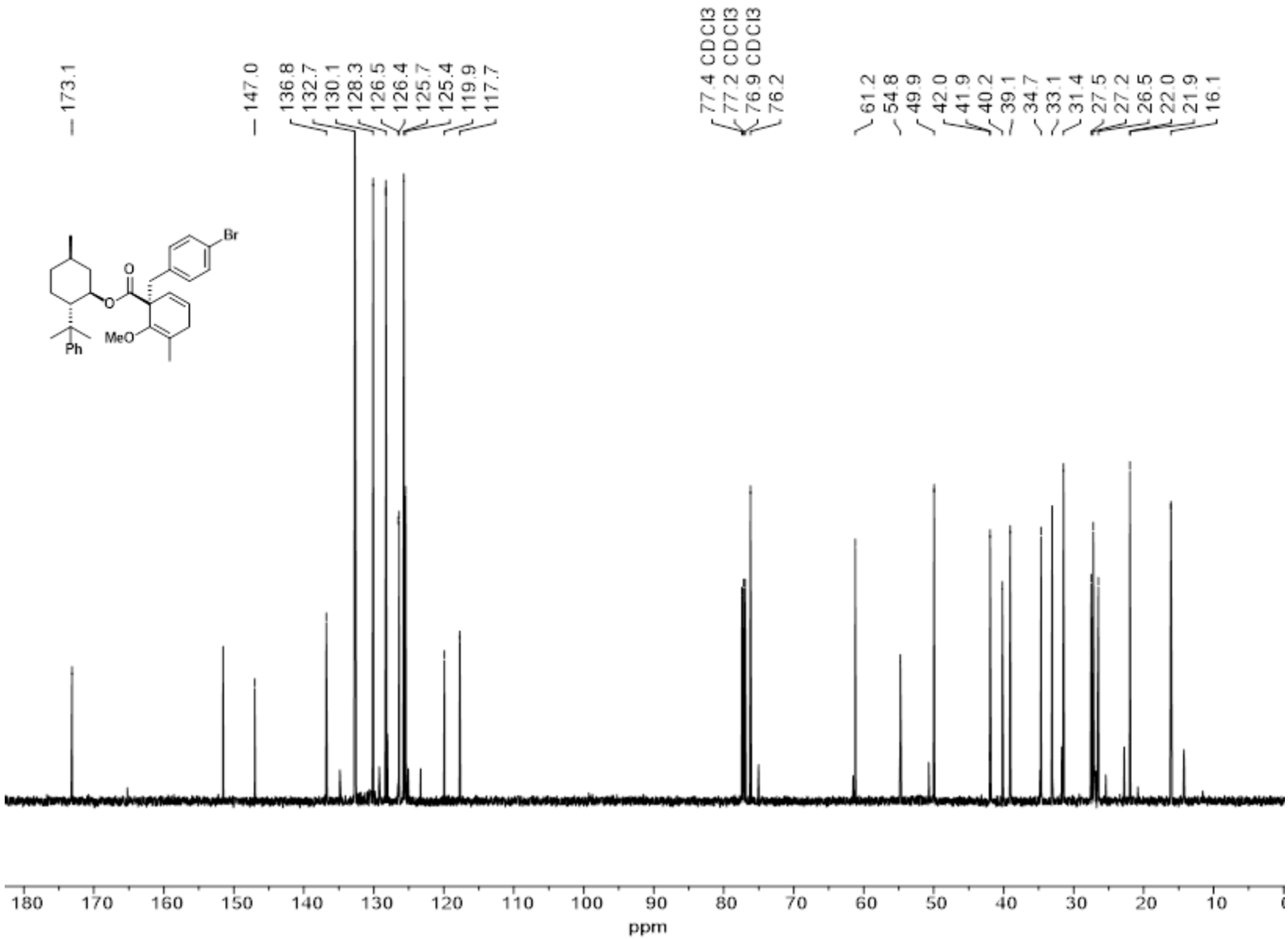
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MeO
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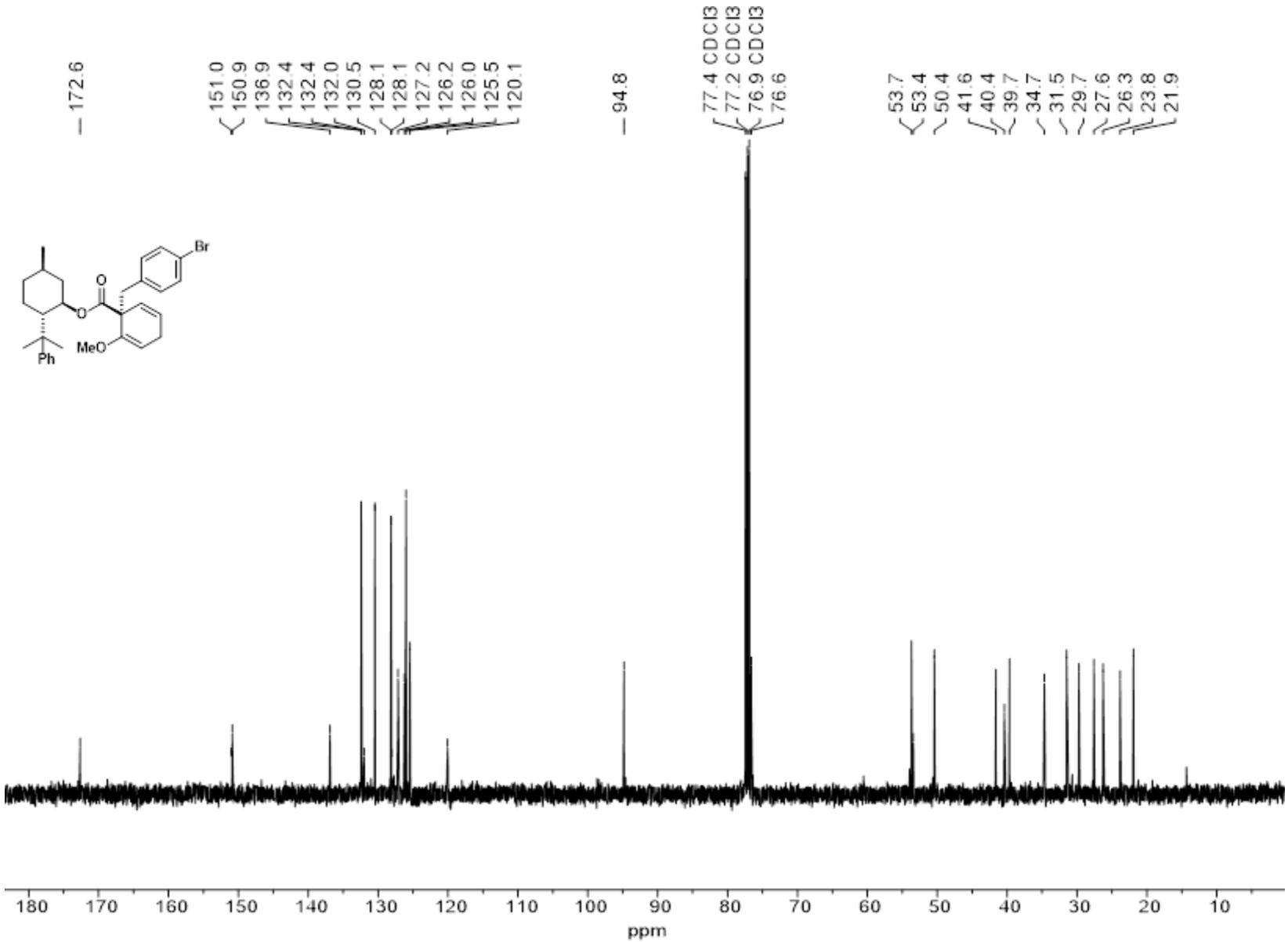
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76.9 CDCl3
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23.8
21.9
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MeO
Ph
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20
10
ppm

MeO
Ph
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Ph
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53.8
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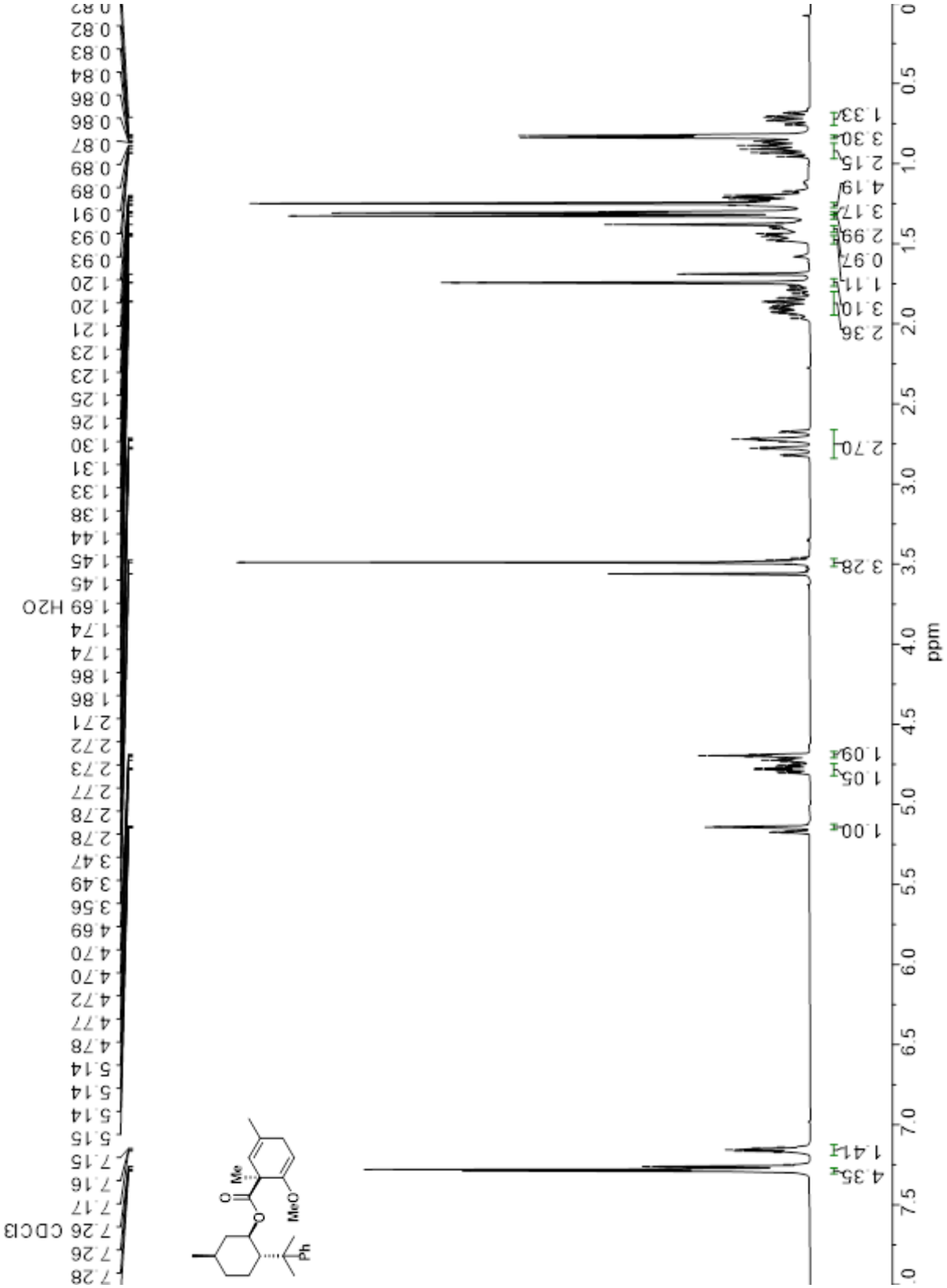
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HO
MeO
ppm

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7.16
7.16
7.15
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7.10
7.09
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7.09
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5.68
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5.53
5.53
5.52
5.52
5.51
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3.03
3.02
3.01
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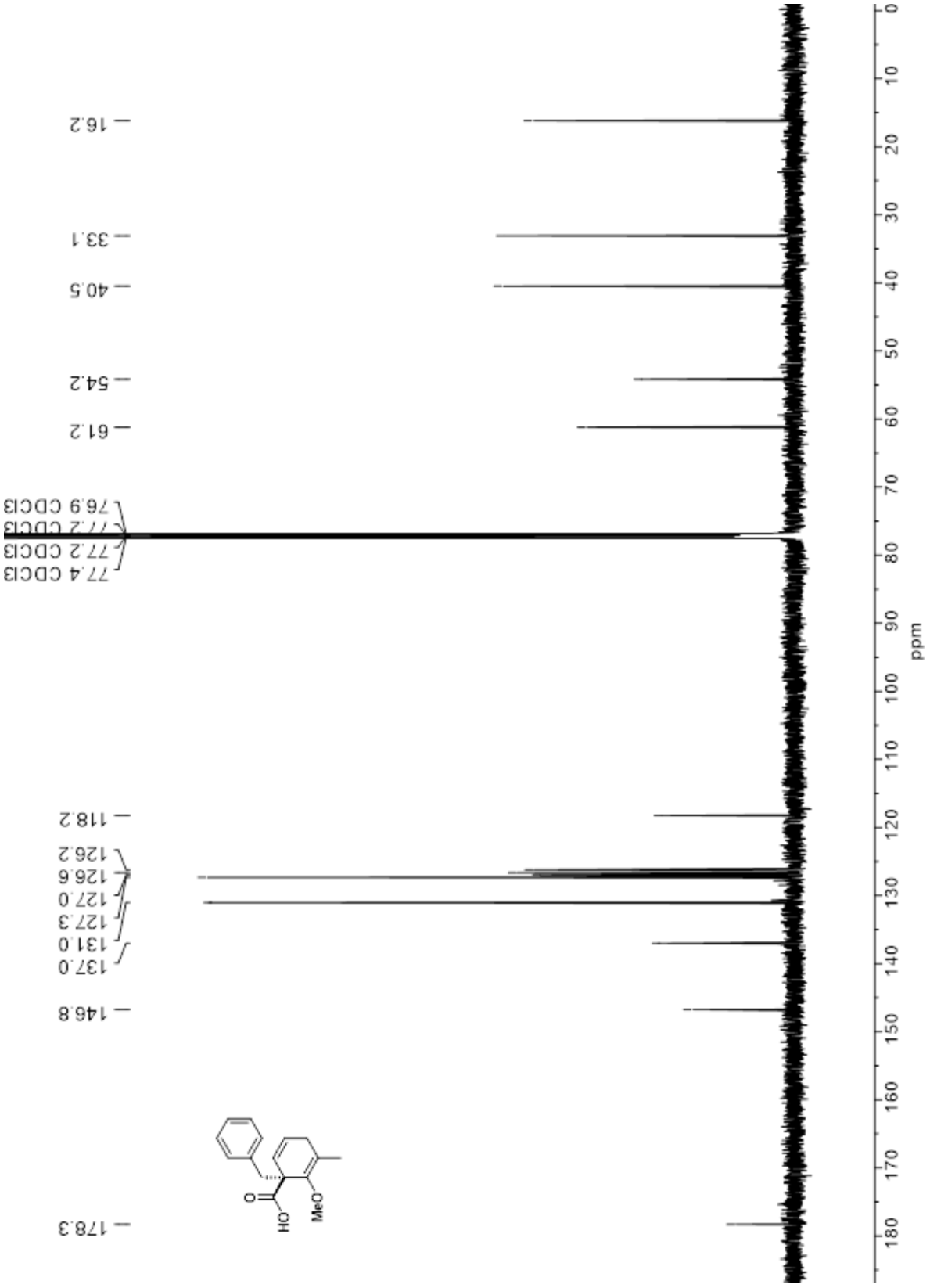
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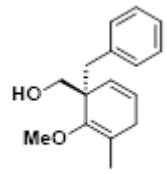
HO
MeO
ppm



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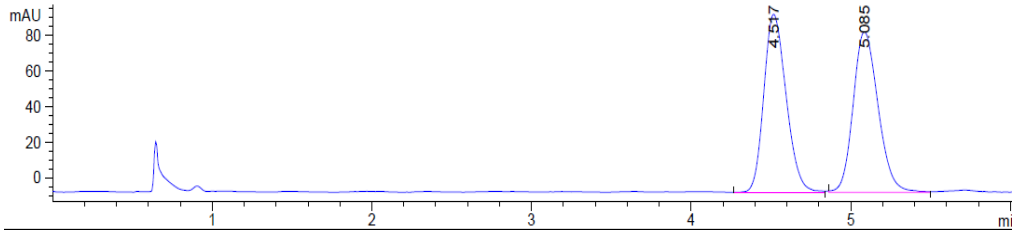
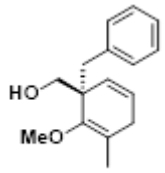
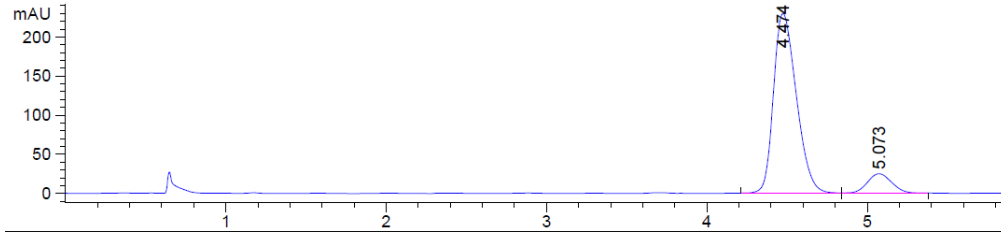


Peak #	Area %
1	49.8588
2	50.1412



enantiopure



Peak #	Area %
1	89.0636
2	10.9364

Appendix D: X-Ray Crystallographic Data

X-ray Data Collection, Structure Solution and Refinement for **3.29** *(cdv74).*

A colorless crystal of approximate dimensions 0.111 x 0.206 x 0.325 mm was mounted on a glass fiber and transferred to a Bruker SMART APEX II diffractometer system. The APEX2[1] program package was used to determine the unit-cell parameters and for data collection (10 sec/frame scan time). The raw frame data was processed using SAINT[2] and SADABS[3] to yield the reflection data file. Subsequent calculations were carried out using the SHELXTL[4] program package. There were no systematic absences nor any diffraction symmetry other than the Friedel condition. The centrosymmetric triclinic space group $P\bar{1}$ was assigned and later determined to be correct.

The structure was solved by direct methods and refined on F^2 by full-matrix least-squares techniques. The analytical scattering factors[5] for neutral atoms were used throughout the analysis. Hydrogen atoms were included using a riding model.

Least-squares analysis yielded wR2 = 0.0864 and Goof = 1.050 for 174 variables refined against 4222 data (0.68 Å), R1 = 0.0404 for those 3411 data with $I > 2.0\sigma(I)$.

References.

1. APEX2 Version 2014.11-0, Bruker AXS, Inc.; Madison, WI 2014.

2. SAINT Version 8.34a, Bruker AXS, Inc.; Madison, WI 2013.

3. Sheldrick, G. M. SADABS, Version 2014/5, Bruker AXS, Inc.; Madison, WI 2014.

4. Sheldrick, G. M. SHELXTL, Version 2014/7, Bruker AXS, Inc.; Madison, WI 2014.

5. International Tables for Crystallography 1992, Vol. C., Dordrecht: Kluwer Academic Publishers.

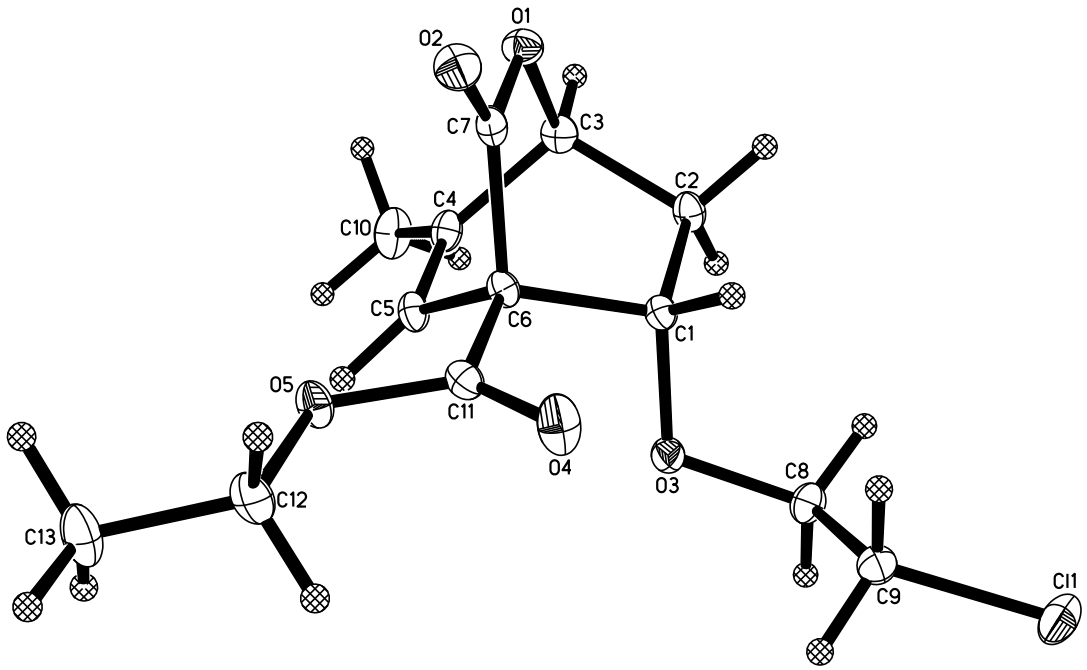
Definitions:

$wR2 = [\Sigma[w(F_o^2-F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

$R1 = \Sigma||F_o|-|F_c|| / \Sigma|F_o|$

$Goof = S = [\Sigma[w(F_o^2-F_c^2)^2] / (n-p)]^{1/2}$ where n is the number of reflections and p is the total number of parameters refined.

The thermal ellipsoid plot is shown at the 50% probability level.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C2
C4
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C5
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C11
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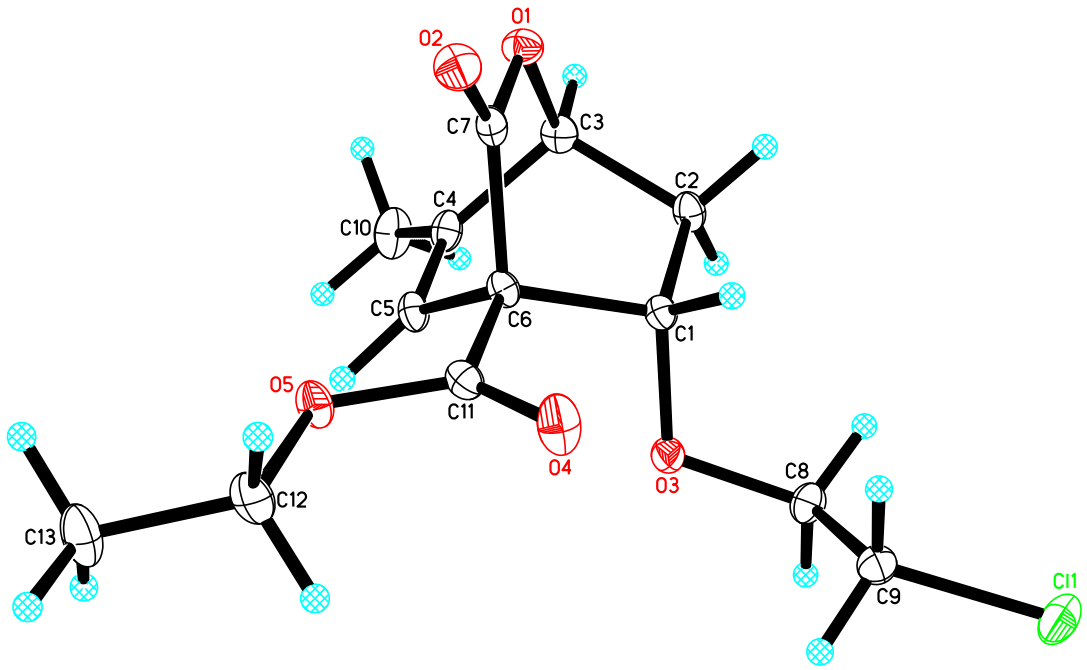
O3
C8
C12
C13
C9
Cl1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C11
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O3
C8
C12
C13
C9
Cl1

Table 1. Crystal data and structure refinement for cdv74.

Identification code	cdv74 (Ryan Kozlowski)	
Empirical formula	C_{13} H_{17} Cl O_5	
Formula weight	288.71	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 6.9777(3) Å	a = 86.6775(8)°.
	b = 9.6883(4) Å	b = 79.1836(7)°.
	c = 10.7935(5) Å	g = 71.2456(7)°.
Volume	678.64(5) $Å^3$	
Z	2	
Density (calculated)	1.413 Mg/m^3	
Absorption coefficient	0.295 mm^{-1}	
F(000)	304	
Crystal color	colorless	
Crystal size	0.325 x 0.206 x 0.111 mm^3	
Theta range for data collection	1.921 to 31.546°	
Index ranges	$-10 \le h \le 10$, $-13 \le k \le 14$, $-15 \le l \le 15$	
Reflections collected	17510	
Independent reflections	4222 [R(int) = 0.0314]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8623 and 0.8327	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4222 / 0 / 174	
Goodness-of-fit on F^2	1.050	
Final R indices [I>2sigma(I) = 3411 data]	R1 = 0.0404, wR2 = 0.0790	
R indices (all data, 0.68 Å)	R1 = 0.0563, wR2 = 0.0864	
Largest diff. peak and hole	0.488 and -0.316 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for cdv74. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cl(1)	7781(1)	8625(1)	-2930(1)	21(1)
O(1)	5230(1)	4233(1)	2504(1)	14(1)
O(2)	2024(1)	5031(1)	2130(1)	17(1)
O(3)	6157(1)	7910(1)	735(1)	13(1)
O(4)	1631(2)	8125(1)	632(1)	20(1)
O(5)	650(1)	8451(1)	2735(1)	14(1)
C(1)	5739(2)	6555(1)	882(1)	10(1)
C(2)	7584(2)	5289(1)	1194(1)	13(1)
C(3)	6991(2)	4763(1)	2532(1)	13(1)
C(4)	6285(2)	6026(2)	3449(1)	13(1)
C(5)	4647(2)	7079(1)	3179(1)	12(1)
C(6)	3919(2)	6772(1)	2012(1)	10(1)
C(7)	3579(2)	5288(1)	2218(1)	12(1)
C(8)	7425(2)	8029(2)	-451(1)	14(1)
C(9)	6113(2)	8559(2)	-1460(1)	14(1)
C(10)	7471(2)	6003(2)	4473(1)	19(1)
C(11)	1957(2)	7867(1)	1692(1)	12(1)
C(12)	-1316(2)	9496(2)	2536(1)	16(1)
C(13)	-2397(2)	10203(2)	3795(1)	22(1)

Table 3. Bond lengths [Å] and angles [°] for cdv74.

Cl(1)-C(9)	1.7952(13)
O(1)-C(7)	1.3436(15)
O(1)-C(3)	1.4820(15)
O(2)-C(7)	1.2100(15)
O(3)-C(1)	1.4271(15)
O(3)-C(8)	1.4347(15)
O(4)-C(11)	1.2040(16)
O(5)-C(11)	1.3329(15)
O(5)-C(12)	1.4645(15)
C(1)-C(2)	1.5414(17)
C(1)-C(6)	1.5561(16)
C(2)-C(3)	1.5299(18)
C(3)-C(4)	1.5133(18)
C(4)-C(5)	1.3319(18)
C(4)-C(10)	1.4953(18)
C(5)-C(6)	1.5215(17)
C(6)-C(11)	1.5230(17)
C(6)-C(7)	1.5289(18)
C(8)-C(9)	1.5144(18)
C(12)-C(13)	1.5088(19)

C(7)-O(1)-C(3)	112.78(10)
C(1)-O(3)-C(8)	113.09(9)
C(11)-O(5)-C(12)	115.54(10)
O(3)-C(1)-C(2)	112.55(10)
O(3)-C(1)-C(6)	105.92(9)
C(2)-C(1)-C(6)	108.54(10)
C(3)-C(2)-C(1)	108.30(10)
O(1)-C(3)-C(4)	108.50(10)
O(1)-C(3)-C(2)	105.98(10)
C(4)-C(3)-C(2)	109.99(11)
C(5)-C(4)-C(10)	128.04(13)
C(5)-C(4)-C(3)	112.28(11)
C(10)-C(4)-C(3)	119.63(12)

C(4)-C(5)-C(6)	113.73(11)
C(5)-C(6)-C(11)	117.19(10)
C(5)-C(6)-C(7)	106.50(10)
C(11)-C(6)-C(7)	108.13(10)
C(5)-C(6)-C(1)	107.68(10)
C(11)-C(6)-C(1)	111.15(10)
C(7)-C(6)-C(1)	105.49(10)
O(2)-C(7)-O(1)	121.23(12)
O(2)-C(7)-C(6)	125.65(12)
O(1)-C(7)-C(6)	113.12(10)
O(3)-C(8)-C(9)	110.15(10)
C(8)-C(9)-Cl(1)	108.26(9)
O(4)-C(11)-O(5)	125.27(12)
O(4)-C(11)-C(6)	123.70(11)
O(5)-C(11)-C(6)	111.00(10)
O(5)-C(12)-C(13)	106.85(11)

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for cdv74. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cl(1)	26(1)	26(1)	13(1)	4(1)	-4(1)	-13(1)
O(1)	13(1)	12(1)	17(1)	1(1)	-3(1)	-4(1)
O(2)	15(1)	19(1)	19(1)	-2(1)	-3(1)	-8(1)
O(3)	14(1)	13(1)	12(1)	-2(1)	0(1)	-6(1)
O(4)	15(1)	26(1)	13(1)	-1(1)	-5(1)	1(1)
O(5)	9(1)	16(1)	14(1)	-2(1)	-2(1)	1(1)
C(1)	10(1)	11(1)	10(1)	-1(1)	-2(1)	-3(1)
C(2)	10(1)	14(1)	12(1)	-1(1)	-2(1)	-1(1)
C(3)	10(1)	15(1)	14(1)	0(1)	-3(1)	-2(1)
C(4)	12(1)	18(1)	10(1)	0(1)	-2(1)	-6(1)
C(5)	11(1)	15(1)	10(1)	-3(1)	-1(1)	-5(1)
C(6)	8(1)	11(1)	11(1)	-2(1)	-2(1)	-2(1)
C(7)	13(1)	14(1)	9(1)	-2(1)	0(1)	-3(1)
C(8)	12(1)	17(1)	12(1)	1(1)	-2(1)	-6(1)
C(9)	15(1)	14(1)	13(1)	1(1)	-3(1)	-4(1)
C(10)	15(1)	30(1)	13(1)	0(1)	-6(1)	-6(1)
C(11)	9(1)	12(1)	14(1)	-2(1)	-2(1)	-3(1)
C(12)	9(1)	17(1)	18(1)	-2(1)	-3(1)	2(1)
C(13)	13(1)	26(1)	19(1)	-5(1)	0(1)	2(1)

Table 5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2\ x\ 10^3$) for cdv74.

	x	y	z	U(eq)
H(1A)	5327	6324	100	13
H(2A)	7939	4482	584	15
H(2B)	8798	5623	1140	15
H(3A)	8170	3963	2782	16
H(5A)	3994	7942	3670	14
H(8A)	8452	7067	-696	16
H(8B)	8174	8722	-369	16
H(9A)	5122	9540	-1238	17
H(9B)	5329	7886	-1529	17
H(10A)	6776	6867	5010	29
H(10B)	8862	6006	4098	29
H(10C)	7552	5123	4983	29
H(12A)	-2157	8990	2221	19
H(12B)	-1081	10239	1910	19
H(13A)	-3707	10936	3698	32
H(13B)	-1529	10674	4108	32
H(13C)	-2658	9460	4398	32

Table 6. Torsion angles [°] for cdv74.

C(8)-O(3)-C(1)-C(2)	76.56(12)
C(8)-O(3)-C(1)-C(6)	-164.99(10)
O(3)-C(1)-C(2)-C(3)	113.78(11)
C(6)-C(1)-C(2)-C(3)	-3.12(14)
C(7)-O(1)-C(3)-C(4)	55.85(13)
C(7)-O(1)-C(3)-C(2)	-62.25(12)
C(1)-C(2)-C(3)-O(1)	61.97(12)
C(1)-C(2)-C(3)-C(4)	-55.13(13)
O(1)-C(3)-C(4)-C(5)	-55.04(14)
C(2)-C(3)-C(4)-C(5)	60.48(14)
O(1)-C(3)-C(4)-C(10)	127.48(12)
C(2)-C(3)-C(4)-C(10)	-117.01(13)
C(10)-C(4)-C(5)-C(6)	176.11(12)
C(3)-C(4)-C(5)-C(6)	-1.11(15)
C(4)-C(5)-C(6)-C(11)	175.47(11)
C(4)-C(5)-C(6)-C(7)	54.34(13)
C(4)-C(5)-C(6)-C(1)	-58.41(14)
O(3)-C(1)-C(6)-C(5)	-62.85(12)
C(2)-C(1)-C(6)-C(5)	58.23(13)
O(3)-C(1)-C(6)-C(11)	66.75(12)
C(2)-C(1)-C(6)-C(11)	-172.17(10)
O(3)-C(1)-C(6)-C(7)	-176.28(9)
C(2)-C(1)-C(6)-C(7)	-55.20(12)
C(3)-O(1)-C(7)-O(2)	178.42(11)
C(3)-O(1)-C(7)-C(6)	-0.80(14)
C(5)-C(6)-C(7)-O(2)	127.36(13)
C(11)-C(6)-C(7)-O(2)	0.60(17)
C(1)-C(6)-C(7)-O(2)	-118.39(13)
C(5)-C(6)-C(7)-O(1)	-53.47(13)
C(11)-C(6)-C(7)-O(1)	179.78(10)
C(1)-C(6)-C(7)-O(1)	60.79(13)
C(1)-O(3)-C(8)-C(9)	84.73(13)
O(3)-C(8)-C(9)-Cl(1)	-177.95(9)
C(12)-O(5)-C(11)-O(4)	-0.60(19)

C(12)-O(5)-C(11)-C(6)	-178.58(10)
C(5)-C(6)-C(11)-O(4)	149.04(13)
C(7)-C(6)-C(11)-O(4)	-90.69(15)
C(1)-C(6)-C(11)-O(4)	24.66(17)
C(5)-C(6)-C(11)-O(5)	-32.94(15)
C(7)-C(6)-C(11)-O(5)	87.33(12)
C(1)-C(6)-C(11)-O(5)	-157.33(10)
C(11)-O(5)-C(12)-C(13)	-170.72(11)

X-ray Data Collection, Structure Solution and Refinement for **3.69** *(cdv55)*.

A colorless crystal of approximate dimensions 0.171 x 0.344 x 0.375 mm was mounted in a cryoloop and transferred to a Bruker SMART APEX II diffractometer system. The APEX2[1] program package was used to determine the unit-cell parameters and for data collection (45 sec/frame scan time). The raw frame data was processed using SAINT[2] and SADABS[3] to yield the reflection data file. Subsequent calculations were carried out using the SHELXTL[4] program package. The diffraction symmetry was *mmm* and the systematic absences were consistent with the orthorhombic space group $P2_12_12_1$ that was later determined to be correct.

The structure was solved by direct methods and refined on F^2 by full-matrix least-squares techniques. The analytical scattering factors[5] for neutral atoms were used throughout the analysis. Hydrogen atoms were located from a difference-Fourier map and refined (x,y,z and U_{iso}).

Least-squares analysis yielded wR2 = 0.0737 and Goof = 1.041 for 299 variables refined against 3819 data (0.74 Å), R1 = 0.0277 for those 3697 with $I > 2.0\sigma(I)$. The absolute structure could not be assigned by refinement of the Flack[6] parameter. The assignment was based on the synthetic method.

References.

6. APEX2 Version 2014.11-0, Bruker AXS, Inc.; Madison, WI 2014.

7. SAINT Version 8.34a, Bruker AXS, Inc.; Madison, WI 2013.

8. Sheldrick, G. M. SADABS, Version 2014/5, Bruker AXS, Inc.; Madison, WI 2014.

9. Sheldrick, G. M. SHELXTL, Version 2014/7, Bruker AXS, Inc.; Madison, WI 2014.

10. International Tables for Crystallography 1992, Vol. C., Dordrecht: Kluwer Academic Publishers.

1. Parsons, S., Flack, H. D., Wagner, T. Acta. Cryst. B69, 249-259, 2013.

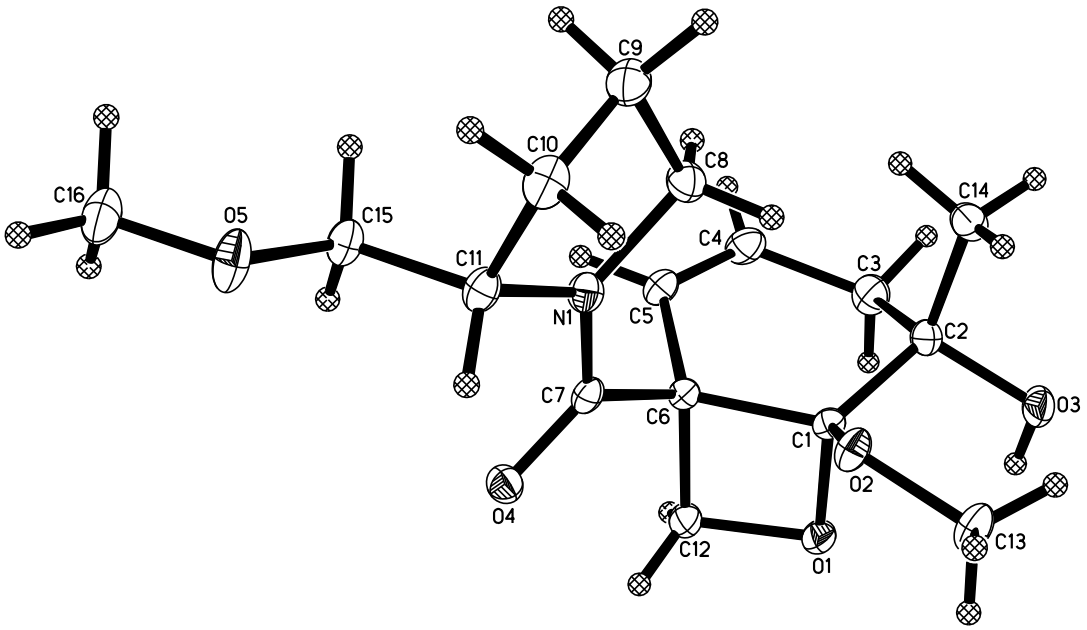
Definitions:

$wR2 = [\Sigma[w(F_o^2-F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

$R1 = \Sigma||F_o|-|F_c|| / \Sigma|F_o|$

$Goof = S = [\Sigma[w(F_o^2-F_c^2)^2] / (n-p)]^{1/2}$ where n is the number of reflections and p is the total number of parameters refined.

The thermal ellipsoid plot is shown at the 50% probability level.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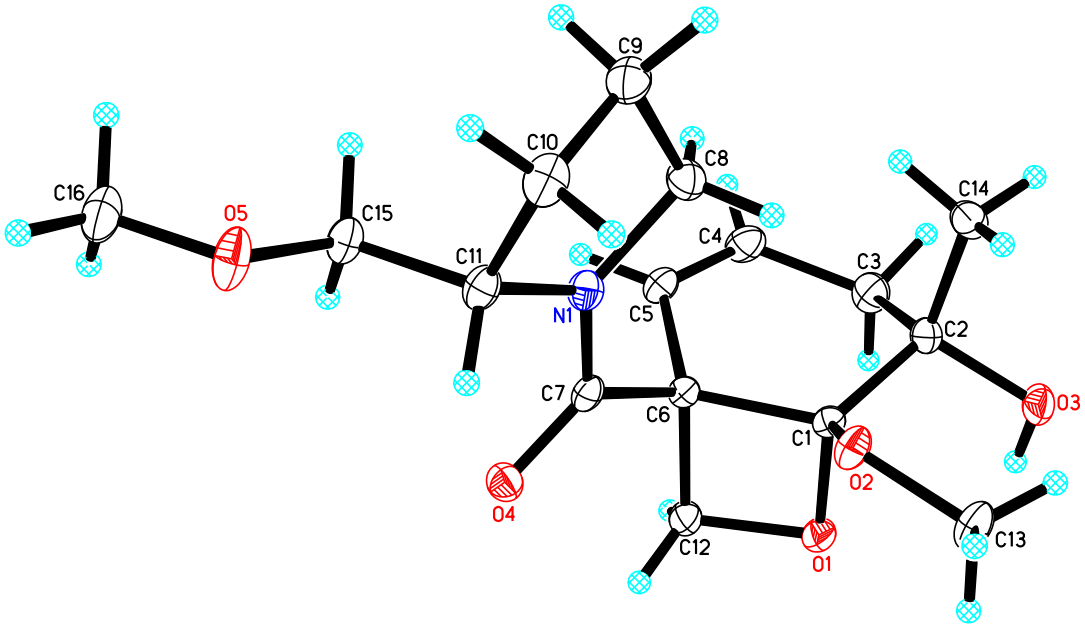
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Table 1. Crystal data and structure refinement for cdv55.

Identification code	cdv55 (Ryan Kozlowski)	
Empirical formula	C_{16} H_{25} N O_5	
Formula weight	311.37	
Temperature	133(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	$P2_12_12_1$	
Unit cell dimensions	a = 7.7631(9) Å	a = 90°.
	b = 11.3468(13) Å	b = 90°.
	c = 17.712(2) Å	g = 90°.
Volume	1560.2(3) $Å^3$	
Z	4	
Density (calculated)	1.326 Mg/m^3	
Absorption coefficient	0.098 mm^{-1}	
F(000)	672	
Crystal color	colorless	
Crystal size	0.375 x 0.344 x 0.171 mm^3	
Theta range for data collection	2.132 to 28.884°	
Index ranges	$-10 \le h \le 10$, $-15 \le k \le 15$, $-23 \le l \le 23$	
Reflections collected	18832	
Independent reflections	3819 [R(int) = 0.0268]	
Completeness to theta = 25.500°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.7458 and 0.6832	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3819 / 0 / 299	
Goodness-of-fit on F^2	1.041	
Final R indices [I>2sigma(I) = 3697 data]	R1 = 0.0277, wR2 = 0.0729	
R indices (all data, 0.74 Å)	R1 = 0.0287, wR2 = 0.0737	
Largest diff. peak and hole	0.333 and -0.138 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for cdv55. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	5244(1)	668(1)	2506(1)	16(1)
O(2)	6644(1)	807(1)	3685(1)	16(1)
O(3)	8285(1)	-536(1)	2367(1)	19(1)
O(4)	4028(1)	3358(1)	3632(1)	16(1)
O(5)	5139(2)	6001(1)	5109(1)	23(1)
N(1)	6770(2)	3492(1)	4019(1)	15(1)
C(1)	6718(2)	1103(1)	2921(1)	13(1)
C(2)	8371(2)	703(1)	2504(1)	16(1)
C(3)	8533(2)	1364(1)	1751(1)	20(1)
C(4)	8278(2)	2675(1)	1818(1)	19(1)
C(5)	7192(2)	3149(1)	2312(1)	16(1)
C(6)	6103(2)	2412(1)	2828(1)	12(1)
C(7)	5560(2)	3104(1)	3537(1)	13(1)
C(8)	8621(2)	3192(1)	4027(1)	18(1)
C(9)	9321(2)	3920(1)	4685(1)	20(1)
C(10)	7789(2)	4010(1)	5226(1)	20(1)
C(11)	6248(2)	4159(1)	4699(1)	15(1)
C(12)	4522(2)	1847(1)	2441(1)	16(1)
C(13)	6545(2)	-426(1)	3861(1)	21(1)
C(14)	9995(2)	886(1)	2971(1)	21(1)
C(15)	5898(2)	5431(1)	4478(1)	16(1)
C(16)	4798(2)	7202(1)	4959(1)	24(1)

Table 3. Bond lengths [Å] and angles [°] for cdv55.

O(1)-C(1)	1.4468(16)
O(1)-C(12)	1.4555(16)
O(2)-C(1)	1.3959(16)
O(2)-C(13)	1.4355(16)
O(3)-C(2)	1.4284(16)
O(4)-C(7)	1.2352(17)
O(5)-C(16)	1.4130(18)
O(5)-C(15)	1.4188(17)
N(1)-C(7)	1.3434(18)
N(1)-C(8)	1.4766(18)
N(1)-C(11)	1.4785(17)
C(1)-C(2)	1.5485(19)
C(1)-C(6)	1.5692(18)
C(2)-C(14)	1.522(2)
C(2)-C(3)	1.5366(19)
C(3)-C(4)	1.505(2)
C(4)-C(5)	1.329(2)
C(5)-C(6)	1.4997(19)
C(6)-C(7)	1.5396(18)
C(6)-C(12)	1.5457(19)
C(8)-C(9)	1.528(2)
C(9)-C(10)	1.531(2)
C(10)-C(11)	1.528(2)
C(11)-C(15)	1.5194(18)

C(1)-O(1)-C(12)	91.77(9)
C(1)-O(2)-C(13)	116.54(10)
C(16)-O(5)-C(15)	111.69(12)
C(7)-N(1)-C(8)	127.69(11)
C(7)-N(1)-C(11)	119.53(11)
C(8)-N(1)-C(11)	112.15(11)
O(2)-C(1)-O(1)	112.25(11)
O(2)-C(1)-C(2)	115.19(11)
O(1)-C(1)-C(2)	108.25(10)

O(2)-C(1)-C(6)	108.45(10)
O(1)-C(1)-C(6)	91.70(10)
C(2)-C(1)-C(6)	118.66(11)
O(3)-C(2)-C(14)	105.41(11)
O(3)-C(2)-C(3)	109.70(11)
C(14)-C(2)-C(3)	109.69(12)
O(3)-C(2)-C(1)	109.34(11)
C(14)-C(2)-C(1)	112.82(11)
C(3)-C(2)-C(1)	109.78(11)
C(4)-C(3)-C(2)	113.80(12)
C(5)-C(4)-C(3)	122.37(13)
C(4)-C(5)-C(6)	122.24(12)
C(5)-C(6)-C(7)	111.57(11)
C(5)-C(6)-C(12)	114.08(12)
C(7)-C(6)-C(12)	110.86(11)
C(5)-C(6)-C(1)	114.85(11)
C(7)-C(6)-C(1)	118.73(11)
C(12)-C(6)-C(1)	83.97(10)
O(4)-C(7)-N(1)	120.71(12)
O(4)-C(7)-C(6)	119.57(12)
N(1)-C(7)-C(6)	119.57(12)
N(1)-C(8)-C(9)	103.24(11)
C(8)-C(9)-C(10)	103.73(12)
C(11)-C(10)-C(9)	103.44(11)
N(1)-C(11)-C(15)	109.06(11)
N(1)-C(11)-C(10)	103.08(11)
C(15)-C(11)-C(10)	113.69(12)
O(1)-C(12)-C(6)	92.33(9)
O(5)-C(15)-C(11)	107.78(11)

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for cdv55. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	15(1)	12(1)	22(1)	-2(1)	-3(1)	-1(1)
O(2)	23(1)	11(1)	15(1)	2(1)	1(1)	0(1)
O(3)	19(1)	13(1)	25(1)	-5(1)	-3(1)	3(1)
O(4)	15(1)	16(1)	18(1)	1(1)	2(1)	1(1)
O(5)	38(1)	14(1)	17(1)	-2(1)	5(1)	5(1)
N(1)	17(1)	14(1)	14(1)	-2(1)	0(1)	1(1)
C(1)	13(1)	11(1)	15(1)	-1(1)	-1(1)	-1(1)
C(2)	14(1)	13(1)	19(1)	-3(1)	1(1)	2(1)
C(3)	21(1)	19(1)	18(1)	-2(1)	6(1)	1(1)
C(4)	22(1)	18(1)	18(1)	2(1)	4(1)	-4(1)
C(5)	19(1)	12(1)	16(1)	2(1)	0(1)	-2(1)
C(6)	12(1)	11(1)	14(1)	0(1)	-1(1)	0(1)
C(7)	17(1)	9(1)	13(1)	2(1)	1(1)	-1(1)
C(8)	16(1)	18(1)	19(1)	-3(1)	-2(1)	2(1)
C(9)	22(1)	19(1)	20(1)	-2(1)	-5(1)	1(1)
C(10)	27(1)	18(1)	15(1)	0(1)	-4(1)	1(1)
C(11)	21(1)	13(1)	12(1)	-1(1)	1(1)	0(1)
C(12)	15(1)	14(1)	21(1)	-4(1)	-3(1)	0(1)
C(13)	28(1)	12(1)	22(1)	4(1)	1(1)	0(1)
C(14)	14(1)	19(1)	30(1)	-6(1)	-2(1)	2(1)
C(15)	23(1)	13(1)	14(1)	0(1)	2(1)	1(1)
C(16)	30(1)	16(1)	26(1)	-3(1)	-5(1)	5(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for cdv55.

	x	y	z	U(eq)
H(3)	7430(30)	-640(20)	2060(14)	36(6)
H(3A)	9670(30)	1171(17)	1557(11)	22(5)
H(3B)	7660(30)	1064(18)	1399(12)	23(5)
H(4)	8910(30)	3156(17)	1482(11)	21(5)
H(5)	7030(20)	3973(16)	2331(10)	15(4)
H(8A)	9140(20)	3389(16)	3552(10)	14(4)
H(8B)	8740(20)	2386(15)	4132(10)	10(4)
H(9A)	9610(30)	4716(19)	4510(11)	22(5)
H(9B)	10370(30)	3569(18)	4903(12)	27(5)
H(10A)	7620(30)	3293(18)	5515(11)	21(5)
H(10B)	7900(30)	4669(18)	5558(11)	21(5)
H(11)	5180(20)	3847(16)	4899(10)	15(4)
H(12A)	3500(30)	1921(16)	2712(10)	16(4)
H(12B)	4390(30)	2047(18)	1885(12)	28(5)
H(13A)	5530(30)	-770(20)	3641(13)	36(6)
H(13B)	6390(30)	-460(20)	4394(13)	29(5)
H(13C)	7510(30)	-868(17)	3715(11)	21(5)
H(14A)	9860(30)	529(19)	3484(13)	30(5)
H(14B)	10230(30)	1690(20)	3023(11)	24(5)
H(14C)	10960(30)	549(19)	2692(12)	27(5)
H(15A)	6960(20)	5837(16)	4334(10)	15(4)
H(15B)	5090(20)	5457(17)	4032(11)	18(4)
H(16A)	4070(30)	7280(20)	4509(13)	28(5)
H(16B)	5870(30)	7620(20)	4852(14)	39(6)
H(16C)	4220(30)	7546(18)	5405(12)	24(5)

Table 6. Torsion angles [°] for cdv55.

C(13)-O(2)-C(1)-O(1)	58.40(16)
C(13)-O(2)-C(1)-C(2)	-66.10(16)
C(13)-O(2)-C(1)-C(6)	158.20(12)
C(12)-O(1)-C(1)-O(2)	106.98(11)
C(12)-O(1)-C(1)-C(2)	-124.76(11)
C(12)-O(1)-C(1)-C(6)	-3.76(10)
O(2)-C(1)-C(2)-O(3)	75.47(14)
O(1)-C(1)-C(2)-O(3)	-51.10(13)
C(6)-C(1)-C(2)-O(3)	-153.56(11)
O(2)-C(1)-C(2)-C(14)	-41.47(15)
O(1)-C(1)-C(2)-C(14)	-168.04(11)
C(6)-C(1)-C(2)-C(14)	89.50(15)
O(2)-C(1)-C(2)-C(3)	-164.14(11)
O(1)-C(1)-C(2)-C(3)	69.29(13)
C(6)-C(1)-C(2)-C(3)	-33.18(16)
O(3)-C(2)-C(3)-C(4)	168.45(12)
C(14)-C(2)-C(3)-C(4)	-76.22(15)
C(1)-C(2)-C(3)-C(4)	48.28(16)
C(2)-C(3)-C(4)-C(5)	-33.8(2)
C(3)-C(4)-C(5)-C(6)	-1.6(2)
C(4)-C(5)-C(6)-C(7)	156.47(13)
C(4)-C(5)-C(6)-C(12)	-76.95(17)
C(4)-C(5)-C(6)-C(1)	17.65(19)
O(2)-C(1)-C(6)-C(5)	135.63(12)
O(1)-C(1)-C(6)-C(5)	-110.21(12)
C(2)-C(1)-C(6)-C(5)	1.70(17)
O(2)-C(1)-C(6)-C(7)	-0.09(16)
O(1)-C(1)-C(6)-C(7)	114.07(12)
C(2)-C(1)-C(6)-C(7)	-134.01(12)
O(2)-C(1)-C(6)-C(12)	-110.60(11)
O(1)-C(1)-C(6)-C(12)	3.56(10)
C(2)-C(1)-C(6)-C(12)	115.48(12)
C(8)-N(1)-C(7)-O(4)	174.40(13)
C(11)-N(1)-C(7)-O(4)	4.33(19)

C(8)-N(1)-C(7)-C(6)	-10.1(2)
C(11)-N(1)-C(7)-C(6)	179.81(11)
C(5)-C(6)-C(7)-O(4)	112.82(14)
C(12)-C(6)-C(7)-O(4)	-15.50(17)
C(1)-C(6)-C(7)-O(4)	-110.12(14)
C(5)-C(6)-C(7)-N(1)	-62.71(16)
C(12)-C(6)-C(7)-N(1)	168.96(11)
C(1)-C(6)-C(7)-N(1)	74.34(16)
C(7)-N(1)-C(8)-C(9)	178.66(13)
C(11)-N(1)-C(8)-C(9)	-10.65(15)
N(1)-C(8)-C(9)-C(10)	29.97(14)
C(8)-C(9)-C(10)-C(11)	-38.42(14)
C(7)-N(1)-C(11)-C(15)	-80.38(15)
C(8)-N(1)-C(11)-C(15)	108.09(13)
C(7)-N(1)-C(11)-C(10)	158.52(12)
C(8)-N(1)-C(11)-C(10)	-13.01(15)
C(9)-C(10)-C(11)-N(1)	31.27(14)
C(9)-C(10)-C(11)-C(15)	-86.63(14)
C(1)-O(1)-C(12)-C(6)	3.82(10)
C(5)-C(6)-C(12)-O(1)	111.02(12)
C(7)-C(6)-C(12)-O(1)	-122.02(11)
C(1)-C(6)-C(12)-O(1)	-3.54(10)
C(16)-O(5)-C(15)-C(11)	178.91(12)
N(1)-C(11)-C(15)-O(5)	170.79(11)
C(10)-C(11)-C(15)-O(5)	-74.81(15)

Table 7. Hydrogen bonds for cdv55 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(3)-H(3)...O(4)#1	0.87(3)	2.02(3)	2.8160(15)	153(2)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y-1/2,-z+1/2

X-ray Data Collection, Structure Solution and Refinement for **3.5** *(cdv76*).

A colorless crystal of approximate dimensions 0.144 x 0.266 x 0.304 mm was mounted on a glass fiber and transferred to a Bruker SMART APEX II diffractometer system. The APEX2[1] program package was used to determine the unit-cell parameters and for data collection (20 sec/frame scan time). The raw frame data was processed using SAINT[2] and SADABS[3] to yield the reflection data file. Subsequent calculations were carried out using the SHELXTL[4] program package. There were no systematic absences nor any diffraction symmetry other than the Friedel condition. The centrosymmetric triclinic space group $P\bar{1}$ was assigned and later determined to be correct.

The structure was solved by direct methods and refined on F^2 by full-matrix least-squares techniques. The analytical scattering factors[5] for neutral atoms were used throughout the analysis. Hydrogen atoms were included using a riding model. There were two molecules of the formula-unit present (Z = 4).

Least-squares analysis yielded wR2 = 0.0937 and Goof = 1.026 for 349 variables refined against 7482 data (0.68 Å), R1 = 0.0358 for those 6448 data with $I > 2.0\sigma(I)$.

References.

2. APEX2 Version 2014.11-0, Bruker AXS, Inc.; Madison, WI 2014.

3. SAINT Version 8.34a, Bruker AXS, Inc.; Madison, WI 2013.

4. Sheldrick, G. M. SADABS, Version 2014/5, Bruker AXS, Inc.; Madison, WI 2014.

5. Sheldrick, G. M. SHELXTL, Version 2014/7, Bruker AXS, Inc.; Madison, WI 2014.

6. International Tables for Crystallography 1992, Vol. C., Dordrecht: Kluwer Academic Publishers.

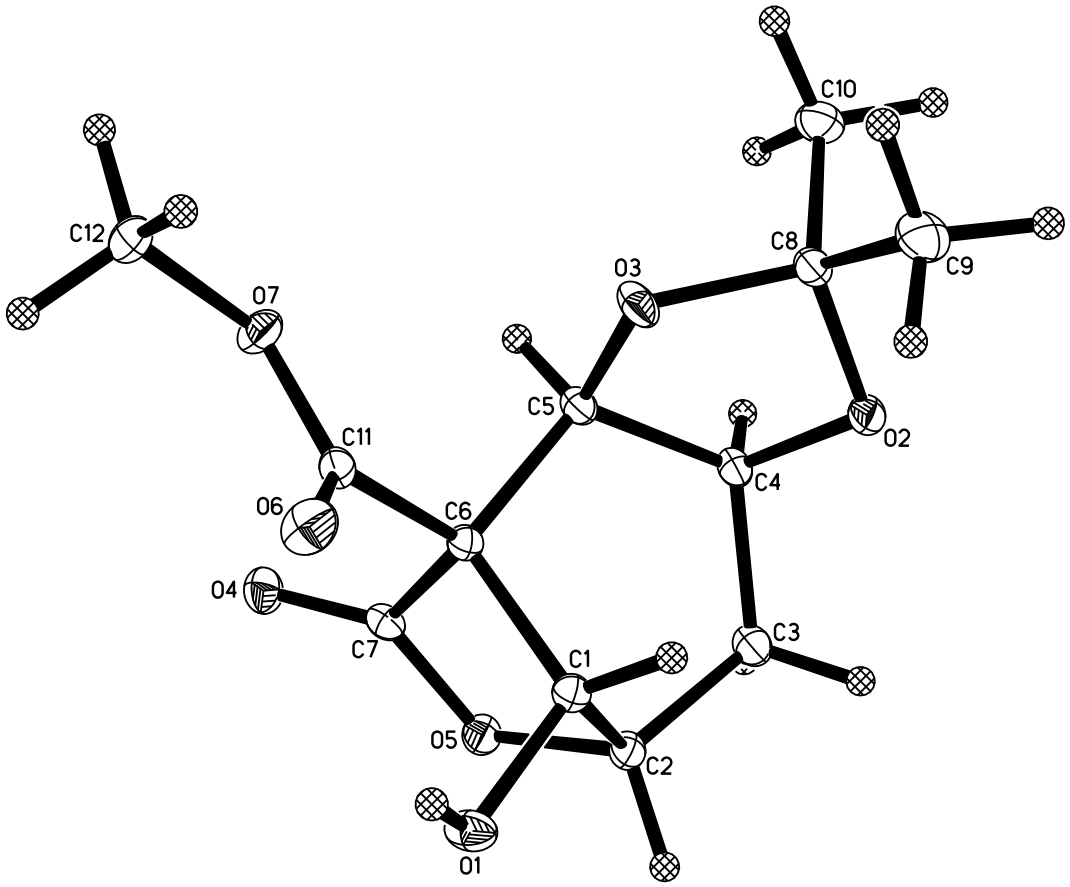
Definitions:

$wR2 = [\Sigma[w(F_o^2-F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

$R1 = \Sigma||F_o|-|F_c|| / \Sigma|F_o|$

$Goof = S = [\Sigma[w(F_o^2-F_c^2)^2] / (n-p)]^{1/2}$ where n is the number of reflections and p is the total number of parameters refined.

The thermal ellipsoid plot is shown at the 50% probability level.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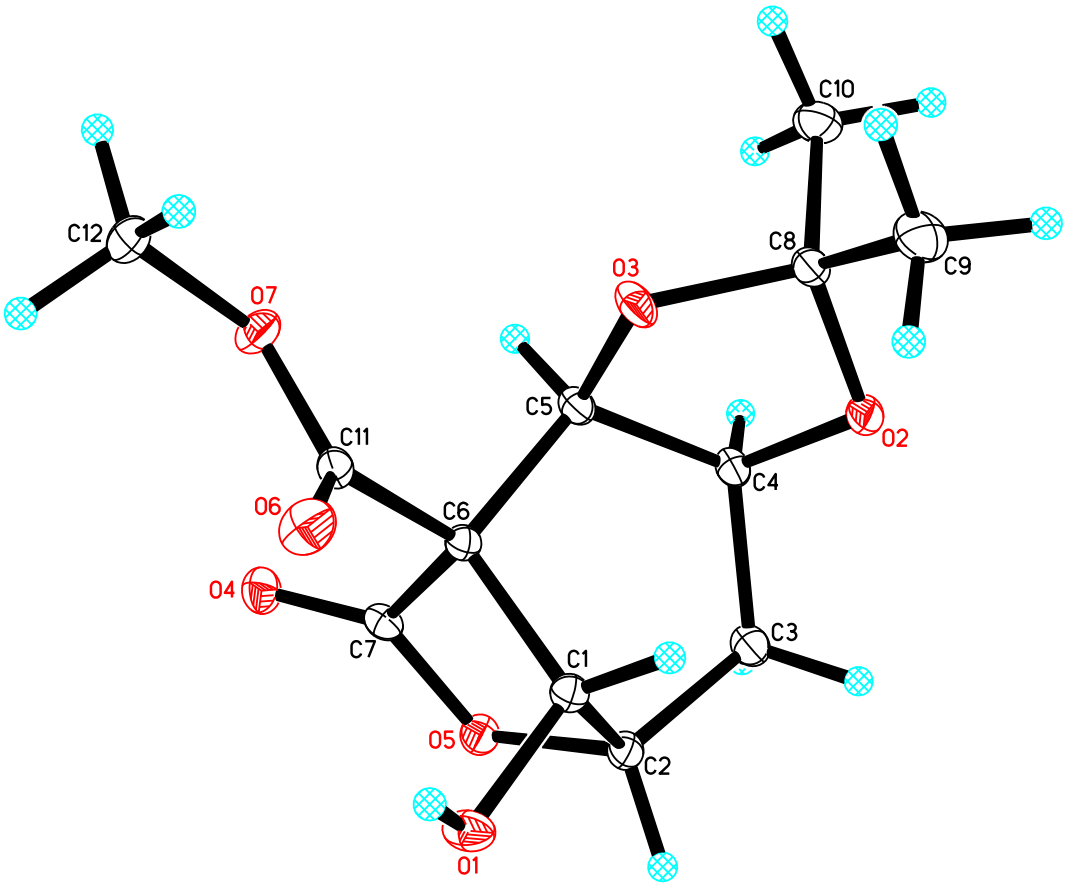
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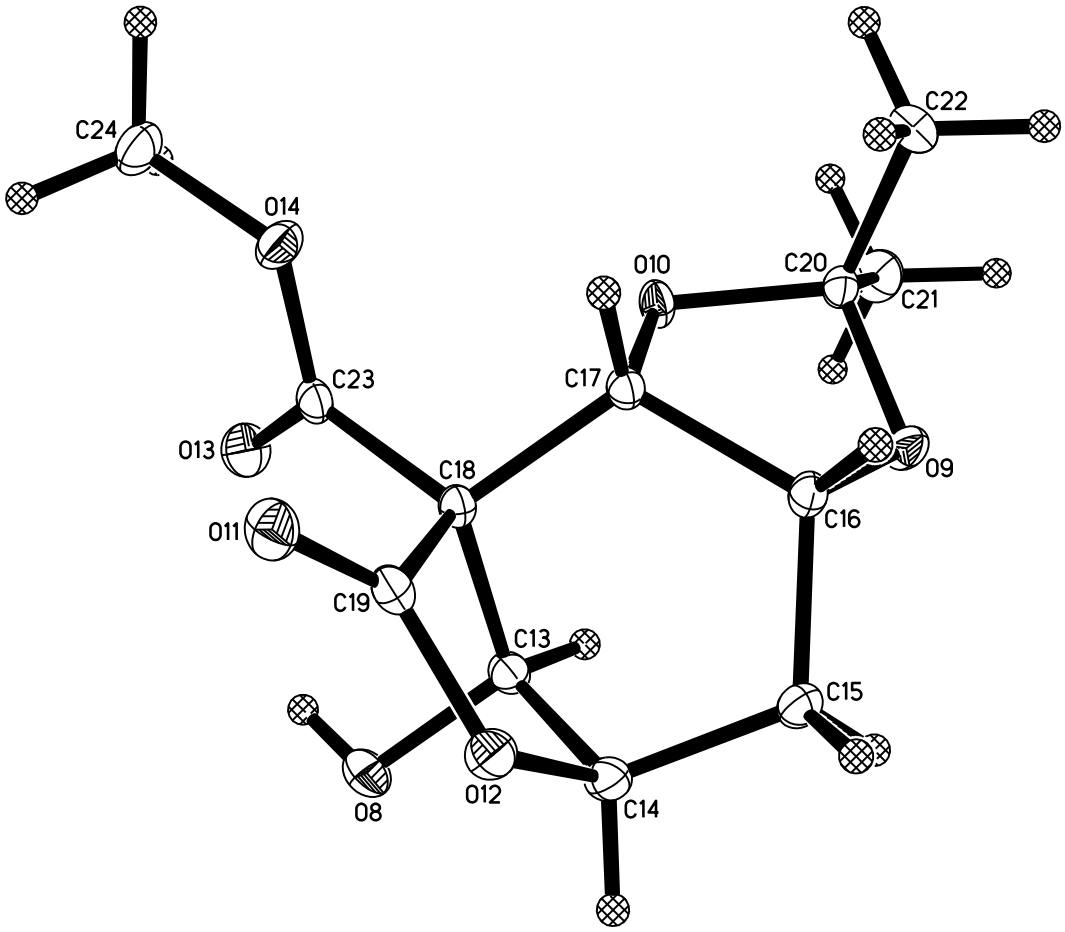
C2
O1


C24
O14
C22
O10
C20
C21
C23
C17
O13
C18
O9
O11
C16
C19
C13
C15
O8
O12
C14

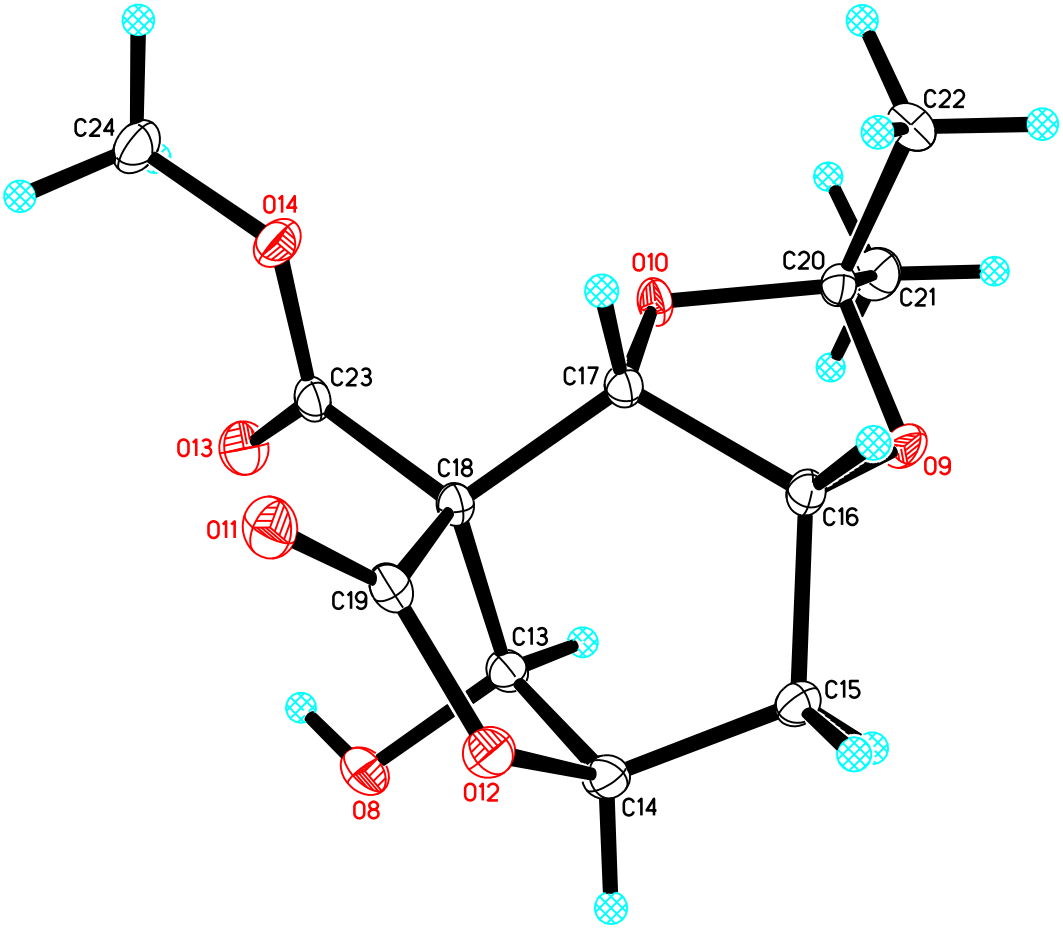

C24
O14
C22
O10
C20
C21
C23
C17
O13
C18
O9
O11
C16
C19
C13
C15
O8
O12
C14

Table 1. Crystal data and structure refinement for cdv76.

Identification code	cdv76 (Ryan Kozlowski)	
Empirical formula	C_{12} H_{16} O_7	
Formula weight	272.25	
Temperature	93(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	$P\bar{1}$	
Unit cell dimensions	a = 9.1261(4) Å	a = 69.6875(6)°.
	b = 10.9200(4) Å	b = 89.1330(7)°.
	c = 12.8872(5) Å	g = 84.5574(7)°.
Volume	1198.79(8) $Å^3$	
Z	4	
Density (calculated)	1.508 Mg/m^3	
Absorption coefficient	0.125 mm^{-1}	
F(000)	576	
Crystal color	colorless	
Crystal size	0.304 x 0.266 x 0.144 mm^3	
Theta range for data collection	1.685 to 31.584°	
Index ranges	$-13 \le h \le 13$, $-16 \le k \le 15$, $-18 \le l \le 18$	
Reflections collected	31548	
Independent reflections	7482 [R(int) = 0.0233]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8623 and 0.8379	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7482 / 0 / 349	
Goodness-of-fit on F^2	1.026	
Final R indices [I>2sigma(I) = 6448 data]	R1 = 0.0358, wR2 = 0.0879	
R indices (all data, 0.68 Å)	R1 = 0.0442, wR2 = 0.0937	
Largest diff. peak and hole	0.433 and -0.287 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for cdv76. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	7343(1)	5121(1)	247(1)	14(1)
O(2)	6519(1)	3549(1)	4119(1)	12(1)
O(3)	8654(1)	2767(1)	3589(1)	13(1)
O(4)	7115(1)	1488(1)	865(1)	15(1)
O(5)	5471(1)	3078(1)	1003(1)	12(1)
O(6)	10085(1)	3790(1)	1018(1)	17(1)
O(7)	10017(1)	1639(1)	1969(1)	13(1)
C(1)	7076(1)	4434(1)	1374(1)	10(1)
C(2)	5462(1)	4155(1)	1448(1)	11(1)
C(3)	4907(1)	3681(1)	2622(1)	13(1)
C(4)	6061(1)	2802(1)	3481(1)	10(1)
C(5)	7553(1)	2353(1)	3041(1)	10(1)
C(6)	7788(1)	3012(1)	1781(1)	9(1)
C(7)	6811(1)	2406(1)	1166(1)	11(1)
C(8)	7975(1)	3032(1)	4513(1)	11(1)
C(9)	8731(1)	4080(1)	4747(1)	17(1)
C(10)	7989(1)	1773(1)	5513(1)	16(1)
C(11)	9418(1)	2874(1)	1531(1)	11(1)
C(12)	11591(1)	1460(1)	1798(1)	15(1)
O(8)	5446(1)	3457(1)	6471(1)	16(1)
O(9)	1280(1)	2525(1)	8968(1)	13(1)
O(10)	985(1)	2539(1)	7241(1)	12(1)
O(11)	4948(1)	-142(1)	6994(1)	16(1)
O(12)	5516(1)	901(1)	8136(1)	14(1)
O(13)	3381(1)	3258(1)	5001(1)	17(1)
O(14)	2318(1)	1368(1)	5567(1)	15(1)
C(13)	4282(1)	2979(1)	7195(1)	12(1)
C(14)	4979(1)	2133(1)	8313(1)	13(1)
C(15)	3876(1)	1846(1)	9236(1)	13(1)

C(16)	2385(1)	1524(1)	8904(1)	11(1)
C(17)	2176(1)	1547(1)	7691(1)	10(1)
C(18)	3514(1)	1925(1)	6935(1)	10(1)
C(19)	4713(1)	761(1)	7320(1)	12(1)
C(20)	161(1)	2624(1)	8178(1)	12(1)
C(21)	-702(1)	3955(1)	7878(1)	18(1)
C(22)	-814(1)	1504(1)	8598(1)	17(1)
C(23)	3073(1)	2277(1)	5728(1)	12(1)
C(24)	1954(1)	1596(1)	4417(1)	17(1)

Table 3. Bond lengths [Å] and angles [°] for cdv76.

O(1)-C(1)	1.4145(11)
O(2)-C(8)	1.4218(11)
O(2)-C(4)	1.4345(11)
O(3)-C(5)	1.4294(11)
O(3)-C(8)	1.4385(11)
O(4)-C(7)	1.2035(12)
O(5)-C(7)	1.3447(11)
O(5)-C(2)	1.4761(11)
O(6)-C(11)	1.2051(12)
O(7)-C(11)	1.3332(12)
O(7)-C(12)	1.4553(11)
C(1)-C(2)	1.5266(12)
C(1)-C(6)	1.5369(13)
C(2)-C(3)	1.5164(13)
C(3)-C(4)	1.5366(13)
C(4)-C(5)	1.5688(13)
C(5)-C(6)	1.5513(13)
C(6)-C(11)	1.5215(12)
C(6)-C(7)	1.5353(12)
C(8)-C(9)	1.5077(13)
C(8)-C(10)	1.5220(14)
O(8)-C(13)	1.4173(11)
O(9)-C(20)	1.4227(11)
O(9)-C(16)	1.4390(11)
O(10)-C(17)	1.4319(11)
O(10)-C(20)	1.4387(11)
O(11)-C(19)	1.2011(12)
O(12)-C(19)	1.3492(12)
O(12)-C(14)	1.4780(12)
O(13)-C(23)	1.2071(12)
O(14)-C(23)	1.3350(12)
O(14)-C(24)	1.4527(12)
C(13)-C(14)	1.5253(14)
C(13)-C(18)	1.5353(13)

C(14)-C(15)	1.5133(14)
C(15)-C(16)	1.5394(13)
C(16)-C(17)	1.5686(13)
C(17)-C(18)	1.5468(12)
C(18)-C(23)	1.5177(13)
C(18)-C(19)	1.5406(13)
C(20)-C(21)	1.5109(14)
C(20)-C(22)	1.5218(14)

C(8)-O(2)-C(4)	106.96(7)
C(5)-O(3)-C(8)	107.56(7)
C(7)-O(5)-C(2)	109.54(7)
C(11)-O(7)-C(12)	114.57(8)
O(1)-C(1)-C(2)	106.86(7)
O(1)-C(1)-C(6)	113.05(7)
C(2)-C(1)-C(6)	98.69(7)
O(5)-C(2)-C(3)	108.71(8)
O(5)-C(2)-C(1)	102.58(7)
C(3)-C(2)-C(1)	113.49(7)
C(2)-C(3)-C(4)	113.92(7)
O(2)-C(4)-C(3)	107.71(8)
O(2)-C(4)-C(5)	102.80(7)
C(3)-C(4)-C(5)	117.65(7)
O(3)-C(5)-C(6)	106.46(7)
O(3)-C(5)-C(4)	104.29(7)
C(6)-C(5)-C(4)	115.37(7)
C(11)-C(6)-C(7)	114.00(7)
C(11)-C(6)-C(1)	114.20(7)
C(7)-C(6)-C(1)	100.11(7)
C(11)-C(6)-C(5)	109.79(7)
C(7)-C(6)-C(5)	108.05(7)
C(1)-C(6)-C(5)	110.23(7)
O(4)-C(7)-O(5)	122.79(9)
O(4)-C(7)-C(6)	128.81(8)
O(5)-C(7)-C(6)	108.39(8)
O(2)-C(8)-O(3)	103.43(7)

O(2)-C(8)-C(9)	108.59(8)
O(3)-C(8)-C(9)	109.57(8)
O(2)-C(8)-C(10)	111.84(8)
O(3)-C(8)-C(10)	110.31(8)
C(9)-C(8)-C(10)	112.68(8)
O(6)-C(11)-O(7)	124.49(9)
O(6)-C(11)-C(6)	123.25(9)
O(7)-C(11)-C(6)	112.24(8)
C(20)-O(9)-C(16)	106.44(7)
C(17)-O(10)-C(20)	105.55(7)
C(19)-O(12)-C(14)	109.63(7)
C(23)-O(14)-C(24)	114.80(8)
O(8)-C(13)-C(14)	107.20(7)
O(8)-C(13)-C(18)	113.49(8)
C(14)-C(13)-C(18)	98.81(7)
O(12)-C(14)-C(15)	109.52(8)
O(12)-C(14)-C(13)	103.10(7)
C(15)-C(14)-C(13)	112.53(8)
C(14)-C(15)-C(16)	113.48(8)
O(9)-C(16)-C(15)	107.81(7)
O(9)-C(16)-C(17)	102.76(7)
C(15)-C(16)-C(17)	118.26(8)
O(10)-C(17)-C(18)	107.76(7)
O(10)-C(17)-C(16)	104.30(7)
C(18)-C(17)-C(16)	115.29(7)
C(23)-C(18)-C(13)	114.73(8)
C(23)-C(18)-C(19)	112.36(8)
C(13)-C(18)-C(19)	100.54(7)
C(23)-C(18)-C(17)	110.86(7)
C(13)-C(18)-C(17)	110.22(7)
C(19)-C(18)-C(17)	107.52(7)
O(11)-C(19)-O(12)	123.09(9)
O(11)-C(19)-C(18)	128.90(9)
O(12)-C(19)-C(18)	108.01(8)
O(9)-C(20)-O(10)	103.05(7)
O(9)-C(20)-C(21)	108.91(8)

O(10)-C(20)-C(21)	109.79(8)
O(9)-C(20)-C(22)	111.51(8)
O(10)-C(20)-C(22)	110.58(8)
C(21)-C(20)-C(22)	112.56(8)
O(13)-C(23)-O(14)	124.20(9)
O(13)-C(23)-C(18)	123.85(9)
O(14)-C(23)-C(18)	111.95(8)

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for cdv76. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	12(1)	15(1)	11(1)	0(1)	1(1)	-2(1)
O(2)	11(1)	16(1)	13(1)	-8(1)	-2(1)	1(1)
O(3)	9(1)	24(1)	10(1)	-9(1)	0(1)	-3(1)
O(4)	18(1)	14(1)	15(1)	-8(1)	1(1)	-1(1)
O(5)	11(1)	14(1)	13(1)	-7(1)	-2(1)	0(1)
O(6)	13(1)	15(1)	20(1)	-3(1)	4(1)	-2(1)
O(7)	10(1)	13(1)	16(1)	-4(1)	1(1)	2(1)
C(1)	10(1)	11(1)	10(1)	-4(1)	0(1)	0(1)
C(2)	10(1)	12(1)	11(1)	-6(1)	-1(1)	0(1)
C(3)	9(1)	19(1)	11(1)	-6(1)	0(1)	0(1)
C(4)	10(1)	13(1)	9(1)	-5(1)	1(1)	-2(1)
C(5)	9(1)	13(1)	9(1)	-4(1)	0(1)	-2(1)
C(6)	9(1)	10(1)	9(1)	-4(1)	0(1)	-1(1)
C(7)	12(1)	12(1)	8(1)	-2(1)	1(1)	-2(1)
C(8)	10(1)	14(1)	9(1)	-5(1)	0(1)	0(1)
C(9)	18(1)	17(1)	17(1)	-8(1)	-4(1)	-3(1)
C(10)	17(1)	17(1)	12(1)	-2(1)	-1(1)	0(1)
C(11)	10(1)	13(1)	9(1)	-5(1)	0(1)	0(1)
C(12)	10(1)	20(1)	16(1)	-7(1)	0(1)	3(1)
O(8)	14(1)	18(1)	16(1)	-4(1)	4(1)	-6(1)
O(9)	11(1)	18(1)	14(1)	-10(1)	-2(1)	2(1)
O(10)	10(1)	15(1)	9(1)	-4(1)	1(1)	2(1)
O(11)	16(1)	14(1)	20(1)	-9(1)	2(1)	1(1)
O(12)	12(1)	15(1)	16(1)	-7(1)	-2(1)	3(1)
O(13)	20(1)	18(1)	13(1)	-2(1)	2(1)	-4(1)
O(14)	18(1)	17(1)	11(1)	-6(1)	-1(1)	-4(1)
C(13)	10(1)	12(1)	13(1)	-5(1)	2(1)	-2(1)
C(14)	11(1)	14(1)	15(1)	-7(1)	-1(1)	0(1)
C(15)	12(1)	17(1)	11(1)	-6(1)	-2(1)	0(1)
C(16)	11(1)	12(1)	10(1)	-5(1)	1(1)	0(1)
C(17)	9(1)	11(1)	10(1)	-4(1)	1(1)	0(1)

C(18)	10(1)	10(1)	10(1)	-4(1)	1(1)	0(1)
C(19)	10(1)	13(1)	12(1)	-3(1)	2(1)	-1(1)
C(20)	10(1)	16(1)	10(1)	-7(1)	1(1)	-1(1)
C(21)	15(1)	19(1)	20(1)	-10(1)	-2(1)	5(1)
C(22)	13(1)	22(1)	17(1)	-7(1)	4(1)	-5(1)
C(23)	10(1)	15(1)	11(1)	-6(1)	2(1)	1(1)
C(24)	18(1)	23(1)	13(1)	-9(1)	-2(1)	0(1)

Table 5. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for cdv76.

	x	y	z	U(eq)
H(1)	8213	5288	180	20
H(1A)	7326	4924	1865	12
H(2A)	4826	4943	975	13
H(3A)	4044	3187	2647	15
H(3B)	4572	4453	2829	15
H(4A)	5607	2015	3980	13
H(5A)	7671	1376	3252	12
H(9A)	9746	3744	5000	25
H(9B)	8202	4327	5323	25
H(9C)	8737	4851	4070	25
H(10A)	9009	1413	5729	24
H(10B)	7468	1132	5323	24
H(10C)	7499	1962	6129	24
H(12A)	11982	575	2265	23
H(12B)	12087	2108	1996	23
H(12C)	11765	1576	1019	23
H(8)	5110	3761	5810	24
H(13A)	3567	3704	7253	14
H(14A)	5819	2553	8495	15
H(15A)	3710	2616	9474	16
H(15B)	4297	1095	9876	16
H(16A)	2150	655	9437	13
H(17A)	1890	679	7707	12
H(21A)	-1431	4055	7297	27
H(21B)	-29	4642	7608	27
H(21C)	-1205	4031	8533	27
H(22A)	-1570	1599	8035	25
H(22B)	-1289	1524	9280	25

H(22C)	-213	666	8748	25
H(24A)	1185	1042	4382	26
H(24B)	2834	1378	4046	26
H(24C)	1598	2520	4048	26

Table 6. Torsion angles [°] for cdv76.

C(7)-O(5)-C(2)-C(3)	-93.91(8)
C(7)-O(5)-C(2)-C(1)	26.53(9)
O(1)-C(1)-C(2)-O(5)	75.19(8)
C(6)-C(1)-C(2)-O(5)	-42.20(8)
O(1)-C(1)-C(2)-C(3)	-167.72(8)
C(6)-C(1)-C(2)-C(3)	74.88(9)
O(5)-C(2)-C(3)-C(4)	77.94(9)
C(1)-C(2)-C(3)-C(4)	-35.50(11)
C(8)-O(2)-C(4)-C(3)	-153.19(7)
C(8)-O(2)-C(4)-C(5)	-28.29(9)
C(2)-C(3)-C(4)-O(2)	107.42(9)
C(2)-C(3)-C(4)-C(5)	-8.05(12)
C(8)-O(3)-C(5)-C(6)	139.47(7)
C(8)-O(3)-C(5)-C(4)	17.05(9)
O(2)-C(4)-C(5)-O(3)	6.61(9)
C(3)-C(4)-C(5)-O(3)	124.73(8)
O(2)-C(4)-C(5)-C(6)	-109.76(8)
C(3)-C(4)-C(5)-C(6)	8.35(12)
O(1)-C(1)-C(6)-C(11)	51.53(10)
C(2)-C(1)-C(6)-C(11)	164.10(7)
O(1)-C(1)-C(6)-C(7)	-70.68(8)
C(2)-C(1)-C(6)-C(7)	41.89(8)
O(1)-C(1)-C(6)-C(5)	175.67(7)
C(2)-C(1)-C(6)-C(5)	-71.76(8)
O(3)-C(5)-C(6)-C(11)	45.31(9)
C(4)-C(5)-C(6)-C(11)	160.45(7)
O(3)-C(5)-C(6)-C(7)	170.20(7)
C(4)-C(5)-C(6)-C(7)	-74.66(9)
O(3)-C(5)-C(6)-C(1)	-81.33(8)
C(4)-C(5)-C(6)-C(1)	33.81(10)
C(2)-O(5)-C(7)-O(4)	-178.94(9)
C(2)-O(5)-C(7)-C(6)	1.45(9)
C(11)-C(6)-C(7)-O(4)	29.67(14)
C(1)-C(6)-C(7)-O(4)	152.02(10)

C(5)-C(6)-C(7)-O(4)	-92.67(11)
C(11)-C(6)-C(7)-O(5)	-150.75(8)
C(1)-C(6)-C(7)-O(5)	-28.40(9)
C(5)-C(6)-C(7)-O(5)	86.91(9)
C(4)-O(2)-C(8)-O(3)	39.62(9)
C(4)-O(2)-C(8)-C(9)	155.96(8)
C(4)-O(2)-C(8)-C(10)	-79.08(9)
C(5)-O(3)-C(8)-O(2)	-34.87(9)
C(5)-O(3)-C(8)-C(9)	-150.51(8)
C(5)-O(3)-C(8)-C(10)	84.88(9)
C(12)-O(7)-C(11)-O(6)	0.91(13)
C(12)-O(7)-C(11)-C(6)	-177.35(7)
C(7)-C(6)-C(11)-O(6)	111.25(10)
C(1)-C(6)-C(11)-O(6)	-3.00(13)
C(5)-C(6)-C(11)-O(6)	-127.38(10)
C(7)-C(6)-C(11)-O(7)	-70.47(10)
C(1)-C(6)-C(11)-O(7)	175.28(7)
C(5)-C(6)-C(11)-O(7)	50.90(10)
C(19)-O(12)-C(14)-C(15)	94.59(9)
C(19)-O(12)-C(14)-C(13)	-25.40(9)
O(8)-C(13)-C(14)-O(12)	-76.82(8)
C(18)-C(13)-C(14)-O(12)	41.23(8)
O(8)-C(13)-C(14)-C(15)	165.28(8)
C(18)-C(13)-C(14)-C(15)	-76.67(9)
O(12)-C(14)-C(15)-C(16)	-72.47(10)
C(13)-C(14)-C(15)-C(16)	41.57(11)
C(20)-O(9)-C(16)-C(15)	151.21(8)
C(20)-O(9)-C(16)-C(17)	25.57(9)
C(14)-C(15)-C(16)-O(9)	-116.66(9)
C(14)-C(15)-C(16)-C(17)	-0.80(12)
C(20)-O(10)-C(17)-C(18)	-147.32(7)
C(20)-O(10)-C(17)-C(16)	-24.32(9)
O(9)-C(16)-C(17)-O(10)	-0.50(9)
C(15)-C(16)-C(17)-O(10)	-119.04(8)
O(9)-C(16)-C(17)-C(18)	117.45(8)
C(15)-C(16)-C(17)-C(18)	-1.09(12)

O(8)-C(13)-C(18)-C(23)	-48.98(11)
C(14)-C(13)-C(18)-C(23)	-162.15(7)
O(8)-C(13)-C(18)-C(19)	71.80(9)
C(14)-C(13)-C(18)-C(19)	-41.38(8)
O(8)-C(13)-C(18)-C(17)	-174.95(7)
C(14)-C(13)-C(18)-C(17)	71.87(8)
O(10)-C(17)-C(18)-C(23)	-48.63(10)
C(16)-C(17)-C(18)-C(23)	-164.62(8)
O(10)-C(17)-C(18)-C(13)	79.49(9)
C(16)-C(17)-C(18)-C(13)	-36.50(10)
O(10)-C(17)-C(18)-C(19)	-171.81(7)
C(16)-C(17)-C(18)-C(19)	72.20(10)
C(14)-O(12)-C(19)-O(11)	178.06(9)
C(14)-O(12)-C(19)-C(18)	-2.23(10)
C(23)-C(18)-C(19)-O(11)	-29.33(14)
C(13)-C(18)-C(19)-O(11)	-151.78(10)
C(17)-C(18)-C(19)-O(11)	92.92(11)
C(23)-C(18)-C(19)-O(12)	150.98(8)
C(13)-C(18)-C(19)-O(12)	28.53(9)
C(17)-C(18)-C(19)-O(12)	-86.77(9)
C(16)-O(9)-C(20)-O(10)	-41.60(9)
C(16)-O(9)-C(20)-C(21)	-158.13(8)
C(16)-O(9)-C(20)-C(22)	77.04(9)
C(17)-O(10)-C(20)-O(9)	40.86(9)
C(17)-O(10)-C(20)-C(21)	156.78(8)
C(17)-O(10)-C(20)-C(22)	-78.42(9)
C(24)-O(14)-C(23)-O(13)	3.75(13)
C(24)-O(14)-C(23)-C(18)	-175.69(8)
C(13)-C(18)-C(23)-O(13)	5.08(13)
C(19)-C(18)-C(23)-O(13)	-108.94(10)
C(17)-C(18)-C(23)-O(13)	130.72(10)
C(13)-C(18)-C(23)-O(14)	-175.48(7)
C(19)-C(18)-C(23)-O(14)	70.50(10)
C(17)-C(18)-C(23)-O(14)	-49.83(10)

Table 7. Hydrogen bonds for cdv76 [Å and °].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)
O(1)-H(1)...O(6)	0.83	2.25	2.7831(10)	122.5
O(1)-H(1)...O(6)#1	0.83	2.23	2.9407(10)	144.7
O(8)-H(8)...O(2)	0.85	2.58	3.1419(10)	124.5
O(8)-H(8)...O(13)	0.85	2.12	2.7675(11)	132.8

Symmetry transformations used to generate equivalent atoms:

#1 -x+2,-y+1,-z

X-ray Data Collection, Structure Solution and Refinement for **5.29** *(cdv84)*.

A colorless crystal of approximate dimensions 0.362 x 0.382 x 0.432 mm was mounted on a glass fiber and transferred to a Bruker SMART APEX II diffractometer system. The APEX2[1] program package was used to determine the unit-cell parameters and for data collection (10 sec/frame scan time). The raw frame data was processed using SAINT[2] and SADABS[3] to yield the reflection data file. Subsequent calculations were carried out using the SHELXTL[4] program package. The diffraction symmetry was 2/*m* and the systematic absences were consistent with the monoclinic space groups $P2_1$ and $P2_1/m$. It was later determined that space group $P2_1$ was correct.

The structure was solved by direct methods and refined on F^2 by full-matrix least-squares techniques. The analytical scattering factors[5] for neutral atoms were used throughout the analysis. Hydrogen atoms were located from a difference-Fourier map and refined (x,y,z and U_{iso}).

Least-squares analysis yielded wR2 = 0.0965 and Goof = 1.039 for 459 variables refined against 7789 data (0.69 Å), R1 = 0.0375 for those 7183 data with $I > 2.0\sigma(I)$. The absolute structure could not be assigned by refinement of the Flack[6] parameter. The assignment was based on the synthetic method.

References.

7. APEX2 Version 2014.11-0, Bruker AXS, Inc.; Madison, WI 2014.

8. SAINT Version 8.34a, Bruker AXS, Inc.; Madison, WI 2013.

9. Sheldrick, G. M. SADABS, Version 2014/5, Bruker AXS, Inc.; Madison, WI 2014.

10. Sheldrick, G. M. SHELXTL, Version 2014/7, Bruker AXS, Inc.; Madison, WI 2014.

11. International Tables for Crystallography 1992, Vol. C., Dordrecht: Kluwer Academic Publishers.

12. Parsons, S., Flack, H. D., Wagner, T. Acta. Cryst. B69, 249-259, 2013.

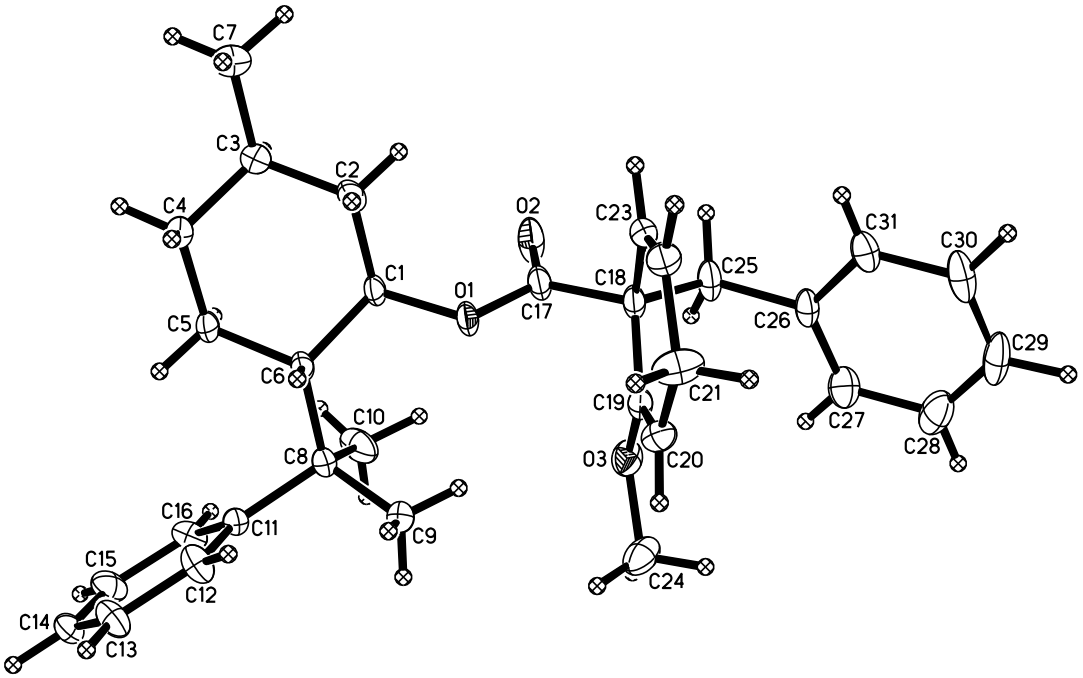
Definitions:

$wR2 = [\Sigma[w(F_o^2-F_c^2)^2] / \Sigma[w(F_o^2)^2]]^{1/2}$

$R1 = \Sigma||F_o|-|F_c|| / \Sigma|F_o|$

$Goof = S = [\Sigma[w(F_o^2-F_c^2)^2] / (n-p)]^{1/2}$ where n is the number of reflections and p is the total number of parameters refined.

The thermal ellipsoid plot is shown at the 50% probability level.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C3
C2
C4
C1
O2
C23
C31
C30
O1
C17
C18
C25
C5
C26
C29
C6
C19
C21
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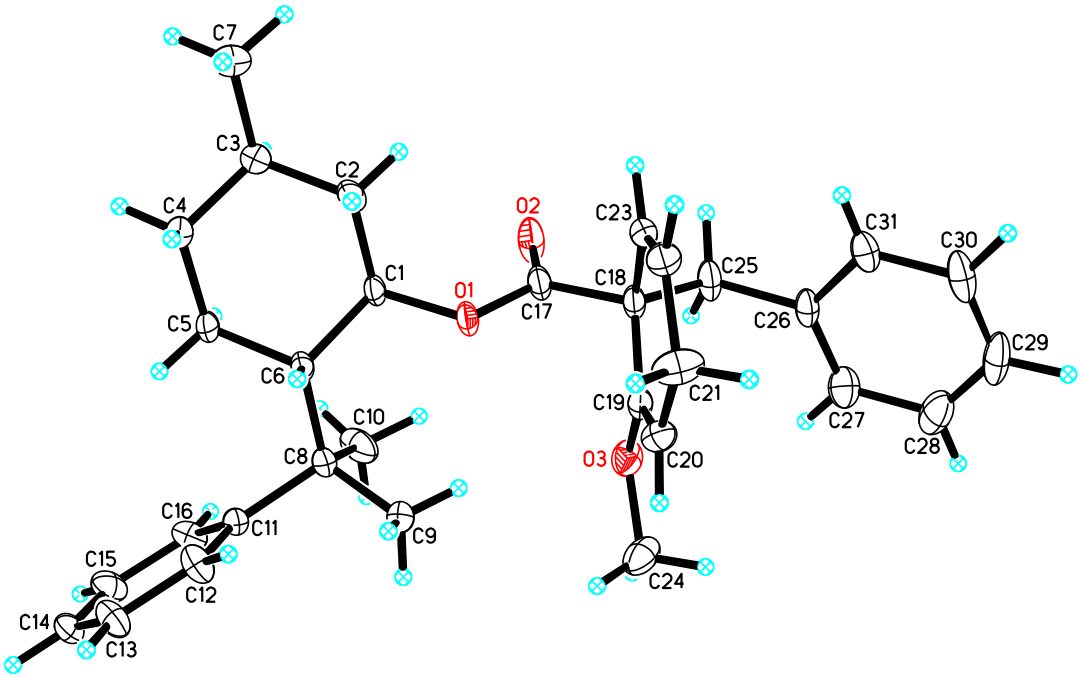
C8
O3
C20
C28
C16
C11
C9
C15
C12
C24
C14
C13


C7
C3
C2
C4
C1
O2
C23
C31
C30
O1
C17
C18
C25
C5
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C29
C6
C19
C21
C10
C27
C8
O3
C20
C28
C16
C11
C9
C15
C12
C24
C14
C13

Table 1. Crystal data and structure refinement for cdv84.

Identification code	cdv84 (Hanh Nguyen)	
Empirical formula	C_{31} H_{38} O_3	
Formula weight	458.61	
Temperature	133(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	$P2_1$	
Unit cell dimensions	a = 10.8664(5) Å	□ = 90°.
	b = 9.8173(4) Å	□ = 100.7809(7)°.
	c = 12.4405(6) Å	□ = 90°.
Volume	1303.71(10) $Å^3$	
Z	2	
Density (calculated)	1.168 Mg/m^3	
Absorption coefficient	0.073 mm^{-1}	
F(000)	496	
Crystal color	colorless	
Crystal size	0.432 x 0.382 x 0.362 mm^3	
Theta range for data collection	1.666 to 31.055°	
Index ranges	$-15 \le h \le 15$, $-14 \le k \le 14$, $-18 \le l \le 17$	
Reflections collected	32572	
Independent reflections	7789 [R(int) = 0.0327]	
Completeness to theta = 25.242°	100.0 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.8622 and 0.8201	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	7789 / 1 / 459	
Goodness-of-fit on F^2	1.039	
Final R indices [I>2sigma(I) = 7183 data]	R1 = 0.0375, wR2 = 0.0931	
R indices (all data, 0.69 Å)	R1 = 0.0425, wR2 = 0.0965	
Largest diff. peak and hole	0.294 and -0.181 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for cdv84. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(1)	4466(1)	366(1)	7566(1)	21(1)
O(2)	3410(1)	-1601(1)	7174(1)	33(1)
O(3)	4304(1)	484(1)	5034(1)	24(1)
C(1)	5182(1)	-231(2)	8567(1)	17(1)
C(2)	4425(1)	6(2)	9463(1)	21(1)
C(3)	5076(1)	-564(2)	10567(1)	22(1)
C(4)	6387(1)	48(2)	10858(1)	25(1)
C(5)	7127(1)	-173(2)	9943(1)	21(1)
C(6)	6485(1)	416(2)	8831(1)	16(1)
C(7)	4302(2)	-301(3)	11450(2)	36(1)
C(8)	7307(1)	229(2)	7925(1)	22(1)
C(9)	6882(2)	1222(3)	6967(2)	40(1)
C(10)	7176(2)	-1224(2)	7469(2)	36(1)
C(11)	8676(1)	560(2)	8422(1)	19(1)
C(12)	9039(1)	1899(2)	8684(1)	25(1)
C(13)	10264(1)	2225(2)	9154(2)	26(1)
C(14)	11158(1)	1207(2)	9385(1)	23(1)
C(15)	10820(1)	-122(2)	9128(2)	26(1)
C(16)	9589(1)	-444(2)	8643(1)	24(1)
C(17)	3566(1)	-418(2)	6987(1)	22(1)
C(18)	2723(1)	413(2)	6088(1)	20(1)
C(19)	3506(1)	1294(2)	5492(1)	18(1)
C(20)	3411(2)	2635(2)	5402(1)	22(1)
C(21)	2486(2)	3446(2)	5897(2)	32(1)
C(22)	1768(1)	2604(2)	6562(1)	24(1)
C(23)	1876(1)	1273(2)	6657(1)	21(1)
C(24)	5010(2)	1163(2)	4331(2)	33(1)
C(25)	1921(2)	-613(2)	5291(1)	25(1)
C(26)	1170(1)	45(2)	4280(1)	21(1)

C(27)	1583(2)	-28(2)	3288(2)	30(1)
C(28)	874(2)	521(2)	2341(2)	36(1)
C(29)	-253(2)	1160(2)	2371(2)	35(1)
C(30)	-672(2)	1255(2)	3350(2)	32(1)
C(31)	37(2)	706(2)	4302(2)	26(1)

Table 3. Bond lengths [Å] and angles [°] for cdv84.

O(1)-C(17)	1.3436(18)
O(1)-C(1)	1.4617(16)
O(2)-C(17)	1.203(2)
O(3)-C(19)	1.3765(18)
O(3)-C(24)	1.431(2)
C(1)-C(2)	1.522(2)
C(1)-C(6)	1.5308(18)
C(1)-H(1A)	0.97(2)
C(2)-C(3)	1.528(2)
C(2)-H(2A)	0.95(2)
C(2)-H(2B)	0.97(3)
C(3)-C(7)	1.526(2)
C(3)-C(4)	1.526(2)
C(3)-H(3A)	0.97(2)
C(4)-C(5)	1.527(2)
C(4)-H(4A)	0.99(3)
C(4)-H(4B)	0.99(3)
C(5)-C(6)	1.541(2)
C(5)-H(5A)	0.95(2)
C(5)-H(5B)	0.94(2)
C(6)-C(8)	1.574(2)
C(6)-H(6A)	1.02(2)
C(7)-H(7A)	0.97(3)
C(7)-H(7B)	1.01(2)
C(7)-H(7C)	1.02(3)
C(8)-C(10)	1.532(3)
C(8)-C(11)	1.5355(19)
C(8)-C(9)	1.542(3)
C(9)-H(9A)	0.91(3)
C(9)-H(9B)	1.06(4)
C(9)-H(9C)	0.93(3)
C(10)-H(10A)	0.91(3)
C(10)-H(10B)	1.01(3)
C(10)-H(10C)	0.97(3)

C(11)-C(16)	1.389(2)
C(11)-C(12)	1.393(2)
C(12)-C(13)	1.387(2)
C(12)-H(12A)	0.94(3)
C(13)-C(14)	1.386(2)
C(13)-H(13A)	0.92(2)
C(14)-C(15)	1.378(3)
C(14)-H(14A)	0.94(2)
C(15)-C(16)	1.397(2)
C(15)-H(15A)	0.95(3)
C(16)-H(16A)	0.94(3)
C(17)-C(18)	1.540(2)
C(18)-C(19)	1.502(2)
C(18)-C(23)	1.518(2)
C(18)-C(25)	1.560(2)
C(19)-C(20)	1.324(2)
C(20)-C(21)	1.502(2)
C(20)-H(20A)	0.91(2)
C(21)-C(22)	1.490(2)
C(21)-H(21A)	0.96(3)
C(21)-H(21B)	0.98(3)
C(22)-C(23)	1.315(2)
C(22)-H(22A)	0.95(2)
C(23)-H(23A)	0.98(3)
C(24)-H(24A)	0.97(3)
C(24)-H(24B)	1.02(3)
C(24)-H(24C)	0.96(2)
C(25)-C(26)	1.511(2)
C(25)-H(25A)	0.96(3)
C(25)-H(25B)	1.01(2)
C(26)-C(27)	1.390(3)
C(26)-C(31)	1.396(2)
C(27)-C(28)	1.390(3)
C(27)-H(27A)	0.95(3)
C(28)-C(29)	1.384(3)
C(28)-H(28A)	0.93(3)

C(29)-C(30)	1.381(3)
C(29)-H(29A)	1.02(3)
C(30)-C(31)	1.394(2)
C(30)-H(30A)	1.00(3)
C(31)-H(31A)	0.90(2)

C(17)-O(1)-C(1)	116.39(11)
C(19)-O(3)-C(24)	115.83(14)
O(1)-C(1)-C(2)	106.80(11)
O(1)-C(1)-C(6)	109.84(11)
C(2)-C(1)-C(6)	112.60(12)
O(1)-C(1)-H(1A)	109.1(12)
C(2)-C(1)-H(1A)	110.7(12)
C(6)-C(1)-H(1A)	107.8(11)
C(1)-C(2)-C(3)	112.30(12)
C(1)-C(2)-H(2A)	109.3(12)
C(3)-C(2)-H(2A)	108.8(12)
C(1)-C(2)-H(2B)	108.8(13)
C(3)-C(2)-H(2B)	109.4(13)
H(2A)-C(2)-H(2B)	108.2(18)
C(7)-C(3)-C(4)	112.27(14)
C(7)-C(3)-C(2)	111.11(14)
C(4)-C(3)-C(2)	108.88(13)
C(7)-C(3)-H(3A)	107.2(12)
C(4)-C(3)-H(3A)	110.9(12)
C(2)-C(3)-H(3A)	106.3(12)
C(3)-C(4)-C(5)	111.48(13)
C(3)-C(4)-H(4A)	106.7(15)
C(5)-C(4)-H(4A)	108.8(16)
C(3)-C(4)-H(4B)	106.6(14)
C(5)-C(4)-H(4B)	114.3(14)
H(4A)-C(4)-H(4B)	109(2)
C(4)-C(5)-C(6)	113.75(12)
C(4)-C(5)-H(5A)	106.6(13)
C(6)-C(5)-H(5A)	108.5(13)
C(4)-C(5)-H(5B)	109.8(12)

C(6)-C(5)-H(5B)	109.5(13)
H(5A)-C(5)-H(5B)	108.5(18)
C(1)-C(6)-C(5)	106.40(11)
C(1)-C(6)-C(8)	115.12(12)
C(5)-C(6)-C(8)	112.11(11)
C(1)-C(6)-H(6A)	109.6(12)
C(5)-C(6)-H(6A)	107.4(12)
C(8)-C(6)-H(6A)	106.0(12)
C(3)-C(7)-H(7A)	110.8(15)
C(3)-C(7)-H(7B)	111.0(14)
H(7A)-C(7)-H(7B)	108(2)
C(3)-C(7)-H(7C)	111.4(15)
H(7A)-C(7)-H(7C)	109(2)
H(7B)-C(7)-H(7C)	106(2)
C(10)-C(8)-C(11)	111.24(14)
C(10)-C(8)-C(9)	107.98(16)
C(11)-C(8)-C(9)	107.77(13)
C(10)-C(8)-C(6)	110.33(13)
C(11)-C(8)-C(6)	108.91(11)
C(9)-C(8)-C(6)	110.58(14)
C(8)-C(9)-H(9A)	111.0(18)
C(8)-C(9)-H(9B)	116.0(18)
H(9A)-C(9)-H(9B)	99(2)
C(8)-C(9)-H(9C)	112.2(18)
H(9A)-C(9)-H(9C)	111(2)
H(9B)-C(9)-H(9C)	107(3)
C(8)-C(10)-H(10A)	112.4(19)
C(8)-C(10)-H(10B)	111.2(16)
H(10A)-C(10)-H(10B)	105(2)
C(8)-C(10)-H(10C)	112.2(16)
H(10A)-C(10)-H(10C)	108(2)
H(10B)-C(10)-H(10C)	107(2)
C(16)-C(11)-C(12)	117.58(13)
C(16)-C(11)-C(8)	122.14(14)
C(12)-C(11)-C(8)	120.28(14)
C(13)-C(12)-C(11)	121.57(15)

C(13)-C(12)-H(12A)	119.3(16)
C(11)-C(12)-H(12A)	119.1(16)
C(14)-C(13)-C(12)	120.08(16)
C(14)-C(13)-H(13A)	120.0(15)
C(12)-C(13)-H(13A)	119.9(15)
C(15)-C(14)-C(13)	119.24(14)
C(15)-C(14)-H(14A)	120.6(15)
C(13)-C(14)-H(14A)	120.1(16)
C(14)-C(15)-C(16)	120.44(15)
C(14)-C(15)-H(15A)	118.5(16)
C(16)-C(15)-H(15A)	121.0(16)
C(11)-C(16)-C(15)	121.07(16)
C(11)-C(16)-H(16A)	122.4(14)
C(15)-C(16)-H(16A)	116.5(14)
O(2)-C(17)-O(1)	124.38(14)
O(2)-C(17)-C(18)	124.45(13)
O(1)-C(17)-C(18)	111.11(13)
C(19)-C(18)-C(23)	111.01(14)
C(19)-C(18)-C(17)	110.35(11)
C(23)-C(18)-C(17)	106.67(12)
C(19)-C(18)-C(25)	111.00(13)
C(23)-C(18)-C(25)	109.90(12)
C(17)-C(18)-C(25)	107.77(13)
C(20)-C(19)-O(3)	125.74(14)
C(20)-C(19)-C(18)	124.90(14)
O(3)-C(19)-C(18)	109.34(13)
C(19)-C(20)-C(21)	122.67(15)
C(19)-C(20)-H(20A)	117.5(14)
C(21)-C(20)-H(20A)	119.9(14)
C(22)-C(21)-C(20)	113.21(15)
C(22)-C(21)-H(21A)	109.5(15)
C(20)-C(21)-H(21A)	111.8(14)
C(22)-C(21)-H(21B)	110.5(18)
C(20)-C(21)-H(21B)	107.2(18)
H(21A)-C(21)-H(21B)	104(2)
C(23)-C(22)-C(21)	123.62(15)

C(23)-C(22)-H(22A)	116.0(14)
C(21)-C(22)-H(22A)	120.2(14)
C(22)-C(23)-C(18)	124.24(14)
C(22)-C(23)-H(23A)	120.9(15)
C(18)-C(23)-H(23A)	114.9(15)
O(3)-C(24)-H(24A)	99.3(18)
O(3)-C(24)-H(24B)	111.7(15)
H(24A)-C(24)-H(24B)	117(2)
O(3)-C(24)-H(24C)	108.3(13)
H(24A)-C(24)-H(24C)	110(2)
H(24B)-C(24)-H(24C)	110(2)
C(26)-C(25)-C(18)	113.83(13)
C(26)-C(25)-H(25A)	108.7(15)
C(18)-C(25)-H(25A)	104.5(15)
C(26)-C(25)-H(25B)	110.7(13)
C(18)-C(25)-H(25B)	106.8(13)
H(25A)-C(25)-H(25B)	112(2)
C(27)-C(26)-C(31)	118.24(15)
C(27)-C(26)-C(25)	120.23(15)
C(31)-C(26)-C(25)	121.51(15)
C(26)-C(27)-C(28)	120.87(17)
C(26)-C(27)-H(27A)	117.4(16)
C(28)-C(27)-H(27A)	121.7(16)
C(29)-C(28)-C(27)	120.33(18)
C(29)-C(28)-H(28A)	121.1(18)
C(27)-C(28)-H(28A)	118.5(19)
C(30)-C(29)-C(28)	119.64(16)
C(30)-C(29)-H(29A)	118.5(15)
C(28)-C(29)-H(29A)	121.8(15)
C(29)-C(30)-C(31)	120.08(17)
C(29)-C(30)-H(30A)	119.5(15)
C(31)-C(30)-H(30A)	120.5(15)
C(30)-C(31)-C(26)	120.82(17)
C(30)-C(31)-H(31A)	121.1(14)
C(26)-C(31)-H(31A)	117.8(14)

Table 4. Anisotropic displacement parameters ($Å^2 \times 10^3$) for cdv84. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(1)	16(1)	21(1)	21(1)	7(1)	-7(1)	-4(1)
O(2)	32(1)	23(1)	35(1)	10(1)	-16(1)	-10(1)
O(3)	24(1)	26(1)	23(1)	2(1)	3(1)	8(1)
C(1)	13(1)	18(1)	17(1)	4(1)	-4(1)	0(1)
C(2)	14(1)	23(1)	24(1)	3(1)	1(1)	0(1)
C(3)	19(1)	28(1)	21(1)	2(1)	4(1)	-1(1)
C(4)	19(1)	39(1)	17(1)	-1(1)	1(1)	-2(1)
C(5)	14(1)	30(1)	16(1)	1(1)	-2(1)	1(1)
C(6)	13(1)	19(1)	16(1)	1(1)	-2(1)	-1(1)
C(7)	28(1)	56(1)	28(1)	-2(1)	12(1)	-5(1)
C(8)	16(1)	33(1)	16(1)	-2(1)	0(1)	-6(1)
C(9)	22(1)	71(2)	24(1)	20(1)	-5(1)	-15(1)
C(10)	27(1)	50(1)	33(1)	-23(1)	11(1)	-15(1)
C(11)	16(1)	26(1)	15(1)	-2(1)	2(1)	-4(1)
C(12)	18(1)	24(1)	32(1)	-4(1)	0(1)	1(1)
C(13)	18(1)	26(1)	32(1)	-9(1)	3(1)	-4(1)
C(14)	14(1)	33(1)	23(1)	-2(1)	3(1)	-3(1)
C(15)	17(1)	28(1)	35(1)	4(1)	7(1)	2(1)
C(16)	20(1)	22(1)	30(1)	-2(1)	9(1)	-3(1)
C(17)	17(1)	23(1)	22(1)	5(1)	-6(1)	-4(1)
C(18)	17(1)	19(1)	19(1)	4(1)	-6(1)	-3(1)
C(19)	17(1)	22(1)	15(1)	1(1)	-1(1)	1(1)
C(20)	25(1)	21(1)	21(1)	1(1)	6(1)	-2(1)
C(21)	44(1)	21(1)	36(1)	1(1)	21(1)	2(1)
C(22)	22(1)	30(1)	21(1)	-1(1)	5(1)	1(1)
C(23)	16(1)	28(1)	18(1)	4(1)	0(1)	-4(1)
C(24)	34(1)	44(1)	23(1)	7(1)	11(1)	16(1)
C(25)	24(1)	20(1)	26(1)	3(1)	-11(1)	-4(1)
C(26)	21(1)	17(1)	22(1)	1(1)	-7(1)	-2(1)
C(27)	30(1)	31(1)	26(1)	-4(1)	-2(1)	1(1)
C(28)	46(1)	36(1)	21(1)	-1(1)	-4(1)	-8(1)

C(29)	43(1)	22(1)	30(1)	4(1)	-20(1)	-7(1)
C(30)	26(1)	23(1)	40(1)	-3(1)	-15(1)	1(1)
C(31)	20(1)	26(1)	28(1)	-3(1)	-5(1)	-2(1)

Table 5. Hydrogen coordinates ($x\ 10^4$) and isotropic displacement parameters ($Å^2\ x\ 10^3$) for cdv84.

	x	y	z	U(eq)
H(1A)	5289(18)	-1190(20)	8454(16)	17(4)
H(2A)	3630(18)	-420(20)	9263(16)	16(4)
H(2B)	4300(20)	980(30)	9531(18)	27(5)
H(3A)	5117(19)	-1540(20)	10475(17)	22(5)
H(4A)	6280(20)	1040(30)	10950(20)	42(7)
H(4B)	6780(20)	-350(30)	11570(20)	35(6)
H(5A)	7208(19)	-1120(30)	9868(17)	24(5)
H(5B)	7936(19)	210(20)	10145(16)	20(5)
H(6A)	6400(20)	1450(20)	8928(18)	24(5)
H(7A)	4690(20)	-720(30)	12140(20)	40(6)
H(7B)	3430(20)	-680(30)	11230(20)	34(6)
H(7C)	4200(20)	710(30)	11570(20)	43(7)
H(9A)	7460(30)	1260(30)	6520(20)	45(7)
H(9B)	6860(30)	2260(40)	7180(30)	61(9)
H(9C)	6100(30)	1000(30)	6570(20)	49(7)
H(10A)	7690(30)	-1390(30)	6990(20)	49(7)
H(10B)	6300(20)	-1400(30)	7050(20)	40(6)
H(10C)	7340(20)	-1900(30)	8040(20)	38(7)
H(12A)	8430(20)	2590(30)	8560(20)	40(6)
H(13A)	10480(20)	3110(20)	9309(19)	29(5)
H(14A)	11990(20)	1430(30)	9700(20)	35(6)
H(15A)	11440(20)	-810(30)	9280(20)	40(6)
H(16A)	9420(20)	-1370(30)	8484(18)	25(5)
H(20A)	3950(20)	3070(20)	5041(19)	23(5)
H(21A)	2880(20)	4190(30)	6330(20)	34(6)
H(21B)	1910(30)	3890(30)	5290(30)	56(8)
H(22A)	1150(20)	3010(20)	6910(19)	30(6)
H(23A)	1390(20)	760(30)	7110(20)	38(6)

H(24A)	5430(30)	380(30)	4090(20)	51(7)
H(24B)	5560(20)	1910(30)	4730(20)	39(6)
H(24C)	4430(20)	1550(20)	3728(19)	27(5)
H(25A)	2530(20)	-1220(30)	5070(20)	35(6)
H(25B)	1350(20)	-1090(30)	5722(18)	30(5)
H(27A)	2350(20)	-480(30)	3280(20)	43(7)
H(28A)	1160(30)	410(30)	1690(20)	51(7)
H(29A)	-810(20)	1540(30)	1680(20)	45(7)
H(30A)	-1500(20)	1700(30)	3370(20)	41(7)
H(31A)	-250(20)	690(20)	4930(20)	28(6)

Table 6. Torsion angles [°] for cdv84.

C(17)-O(1)-C(1)-C(2)	-84.20(15)
C(17)-O(1)-C(1)-C(6)	153.41(13)
O(1)-C(1)-C(2)-C(3)	-179.57(12)
C(6)-C(1)-C(2)-C(3)	-58.94(17)
C(1)-C(2)-C(3)-C(7)	179.54(15)
C(1)-C(2)-C(3)-C(4)	55.39(18)
C(7)-C(3)-C(4)-C(5)	-177.56(16)
C(2)-C(3)-C(4)-C(5)	-54.10(19)
C(3)-C(4)-C(5)-C(6)	57.42(19)
O(1)-C(1)-C(6)-C(5)	175.06(12)
C(2)-C(1)-C(6)-C(5)	56.19(16)
O(1)-C(1)-C(6)-C(8)	-60.10(16)
C(2)-C(1)-C(6)-C(8)	-178.98(13)
C(4)-C(5)-C(6)-C(1)	-56.06(17)
C(4)-C(5)-C(6)-C(8)	177.28(14)
C(1)-C(6)-C(8)-C(10)	-41.93(18)
C(5)-C(6)-C(8)-C(10)	79.87(16)
C(1)-C(6)-C(8)-C(11)	-164.30(13)
C(5)-C(6)-C(8)-C(11)	-42.50(18)
C(1)-C(6)-C(8)-C(9)	77.45(17)
C(5)-C(6)-C(8)-C(9)	-160.75(14)
C(10)-C(8)-C(11)-C(16)	-13.7(2)
C(9)-C(8)-C(11)-C(16)	-131.88(18)
C(6)-C(8)-C(11)-C(16)	108.11(16)
C(10)-C(8)-C(11)-C(12)	167.30(15)
C(9)-C(8)-C(11)-C(12)	49.1(2)
C(6)-C(8)-C(11)-C(12)	-70.89(18)
C(16)-C(11)-C(12)-C(13)	-0.3(2)
C(8)-C(11)-C(12)-C(13)	178.75(15)
C(11)-C(12)-C(13)-C(14)	-0.8(3)
C(12)-C(13)-C(14)-C(15)	1.1(3)
C(13)-C(14)-C(15)-C(16)	-0.3(3)
C(12)-C(11)-C(16)-C(15)	1.1(2)
C(8)-C(11)-C(16)-C(15)	-177.94(14)

C(14)-C(15)-C(16)-C(11)	-0.8(3)
C(1)-O(1)-C(17)-O(2)	-8.3(2)
C(1)-O(1)-C(17)-C(18)	168.94(12)
O(2)-C(17)-C(18)-C(19)	-137.26(18)
O(1)-C(17)-C(18)-C(19)	45.48(18)
O(2)-C(17)-C(18)-C(23)	102.1(2)
O(1)-C(17)-C(18)-C(23)	-75.20(15)
O(2)-C(17)-C(18)-C(25)	-15.9(2)
O(1)-C(17)-C(18)-C(25)	166.82(13)
C(24)-O(3)-C(19)-C(20)	-5.3(2)
C(24)-O(3)-C(19)-C(18)	173.00(13)
C(23)-C(18)-C(19)-C(20)	-4.7(2)
C(17)-C(18)-C(19)-C(20)	-122.70(16)
C(25)-C(18)-C(19)-C(20)	117.89(17)
C(23)-C(18)-C(19)-O(3)	177.03(11)
C(17)-C(18)-C(19)-O(3)	58.98(16)
C(25)-C(18)-C(19)-O(3)	-60.43(15)
O(3)-C(19)-C(20)-C(21)	177.92(15)
C(18)-C(19)-C(20)-C(21)	-0.1(3)
C(19)-C(20)-C(21)-C(22)	4.5(3)
C(20)-C(21)-C(22)-C(23)	-3.8(3)
C(21)-C(22)-C(23)-C(18)	-1.2(3)
C(19)-C(18)-C(23)-C(22)	5.3(2)
C(17)-C(18)-C(23)-C(22)	125.58(16)
C(25)-C(18)-C(23)-C(22)	-117.85(16)
C(19)-C(18)-C(25)-C(26)	-51.25(19)
C(23)-C(18)-C(25)-C(26)	71.93(17)
C(17)-C(18)-C(25)-C(26)	-172.20(14)
C(18)-C(25)-C(26)-C(27)	101.61(18)
C(18)-C(25)-C(26)-C(31)	-80.11(19)
C(31)-C(26)-C(27)-C(28)	-1.2(3)
C(25)-C(26)-C(27)-C(28)	177.14(17)
C(26)-C(27)-C(28)-C(29)	0.5(3)
C(27)-C(28)-C(29)-C(30)	0.1(3)
C(28)-C(29)-C(30)-C(31)	-0.1(3)
C(29)-C(30)-C(31)-C(26)	-0.6(3)

C(27)-C(26)-C(31)-C(30)	1.2(2)
C(25)-C(26)-C(31)-C(30)	-177.09(15)