Title

Steps Away from (–)-Azaspirene: Synthesis of the Core Spirocycle Chemical Studies in Copper(I) Iodide Dimethyl Sulfide Catalyzed Asymmetric Conjugate Addition Wittig Chemistry in the Teaching Laboratory: A Novel Water-Organic Interface Reaction

Author

Kelly, Michael John Barker

Publication Date

2019

Peer reviewed|Thesis/dissertation

UNIVERSITY OF CALIFORNIA SAN DIEGO

SAN DIEGO STATE UNIVERSITY

Steps Away from (–)-Azaspirene: Synthesis of the Core Spirocycle

Chemical Studies in Copper(I) Iodide Dimethyl Sulfide Catalyzed Asymmetric Conjugate Addition

Wittig Chemistry in the Teaching Laboratory: A Novel Water-Organic Interface Reaction

A dissertation submitted in partial satisfaction of the requirements for the degree

Doctor of Philosophy

in

Chemistry

by

Michael John Barker Kelly

Committee in Charge:

University of California San Diego

Professor Joseph Noel
Professor Emmanuel Theodorakis

San Diego State University

Professor Bernt Mikael Bergdahl, Chair
Professor Thomas Cole
Professor Roland Wolkowicz

2019

The dissertation of Michael John Barker Kelly is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

_____

_____

_____

_____

_____

Chair

University of California San Diego

San Diego State University

2019

DEDICATION

This dissertation is dedicated to my wonderful and long-suffering husband, Tom, and my old Boston terrier, Agador Spartacus, who was a puppy when this work began.

EPIGRAPH

“Leave this world a little better than you found it.”

-Robert Baden-Powell

“One may smile, and smile, and be a villain!”

-Hamlet

“Research is always incomplete.”

-Mark Pattison

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF TABLES

LIST OF ABBREVIATIONS

Ac	Acetyl
acac	Acetylacetone
ACN	Acetonitrile
aq	Aqueous
Bn	Benzyl
BuLi	n-Butyllithium
BOC	*tert*-Butoxycarbonyl
BSA	N,O-bis(trimethylsilyl)acetamide
Bu	Butyl
Bz	Benzoyl
cat	Catalytic
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
Cy	Cyclohexyl
DABCO	1,4-Diazabicyclo[2.2.2]octane
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCA	Dichloroacetic acid
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane

DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
de	Diastereomeric Excess
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminum hydride
DIPEA	N,N-Diisopropylethylamine, “Hünig’s base”
DMAP	4-N,N-Dimethylaminopyridine
DMDO	Dimethyldioxirane
DMF	N,N-Dimethylformamide
DMP	Dess-Martin Periodinane
DMS	Dimethyl Sulfide
DMSO	Dimethyl Sulfoxide
dr	Diastereomeric Ratio
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
ee	Enantiomeric Excess
equiv	Equivalents
Et	Ethyl
Et_2O	Diethyl Ether
EtOH	Ethanol
HMDS	Hexamethyldisilazane
HMPA	Hexamethylphosphoramide
HWE	Horner-Wadsworth-Emmons reaction

imid.	Imidazole
IPA	Isopropyl Alcohol (Isopropanol)
i-Pr	Isopropyl
i-PrOH	Isopropyl Alcohol (Isopropanol)
KHMDS	Potassium hexamethyldisilazide
LAH	Lithium aluminum hydride
LDA	Lithium diisopropylamide
MCPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
MeOH	Methanol
MMPP	Magnesium monoperoxyphthalate
MMT	*para*-Monomethoxytrityl
MOM	Methoxymethyl
Ms	Methanesulfonyl
MTBE	Methyl *tert*-butyl ether
NaHMDS	Sodium hexamethyldisilazide
NIS	N-Iodosuccinimide
NMO	4-Methylmorpholine N-oxide
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
Ph	Phenyl

pin	Pinacol
PMB	*para*-Methoxybenzyl
PPTS	Pyridinium *para*-toluenesulfonate
pyr	Pyridine
rt	Room temperature
sat	Saturated
SEM	2-(Trimethylsilyl)ethoxymethyl
SM	Starting material
TBAF	Tetrabutylammonium fluoride
TBAI	Tetrabutylammonium iodide
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
TBSOTf	*tert*-Butyldimethylsilyltriflate
TES	Triethylsilyl
TEMPO	2,2,6,6-Tetramethyl-1-piperidinyloxidanyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TLC	Thin Layer Chromatography

TMS	Trimethylsilyl
TPAP	Tetrapropylammonium perruthenate
Tr	Trityl
tol	Toluene
Ts	Toluenesulfonyl or Tosyl

ACKNOWLEDGMENTS

I'd like to thank Dr. Mike Bergdahl for his mentorship and care. I will always be humbled and grateful that I had the opportunity to work with him and be a part of his lab, and pick his brain about projects large and small. I'm grateful to my committee for their counsel, and for helping me progress, especially Dr. Thomas Cole. I'd like to thank Dr. Matt Parker for his help and advice.

I'm grateful to all of the graduate students I had the pleasure of working with at SDSU and UCSD; especially Dave Schmit, Tim Montgomery, Lee Wang, Scott Burley and Brent Banasik. It was a long journey and it was a true pleasure to take it with you. Melissa Lokensgard-Allen, Aaron Nash, Jayneil Kamdar, Caline Abadjian and so many more; thank you for everything and for being the wonderful people that you are. Keep on keeping on. I hope to see many of you again along the way.

Parts I (chapter 3) and II (chapter 6), in part, include material being prepared for publication. I would like to thank Dr. Tim Montgomery, Dr. David Schmit, Paul Smith, and Kevin Walsworth for their permission to use this material. The dissertation author was a primary investigator and author of this material.

Part III (chapter 7), in part, is a reprint of material as it appears in the *Journal of Chemical Education.* Reprinted with permission from: Kelly, M.; Fallot, L.; Gustafson, J.; Bergdahl, M. *J. Chem. Ed.* **2016**, *93* (9), 1631-1636. Copyright 2016 American Chemical Society. I would like to acknowledge Major Lucas Fallot and Dr. Jeffrey Gustafson, for allowing me to use this material. The dissertation author was a primary investigator and author on this paper.

To the undergraduates in my classes and under my care in the Bergdahl lab, especially

Yamilette Mendez, Andrew Valiere and Sean Najjar, thank you. I learned something from all of you.

Thank you to my San Diego and Seattle friends and my family. You kept me sane at the craziest points, and kept me more entertained than I had any right to be. Thanks particularly to Andrew Rudolph, Eric Mercer, Erica Wollerman Bischeri, Michelle Tontz, Vinny Cicero, Court Lani, Andy Markham, and Kate Sowell Ueland; but so many people helped me along the way. Tommy Kelly, Glenda and Stephen Barker, Carol and Kenneth Kelly, Rebekah Barker, Darcie Merrill, my Meda. Thanks aren't enough.

VITA

2019 PhD, Chemistry, University of California San Diego and San Diego State University Joint Doctoral Program, San Diego, CA

2010 Teaching Assistant, Department of Chemistry and Biochemistry, University of California San Diego, San Diego, CA

2009-2016 Teaching Assistant, Department of Chemistry and Biochemistry, San Diego State University, San Diego, CA

2009 BS, Chemistry, University of Washington, Seattle, WA

2006 AS, Seattle Central College, Seattle, WA

PUBLICATIONS

Kelly, Michael J. B.; Fallot, Lucas B.; Gustafson, Jeffrey L.; Bergdahl, B. Mikael. "Water Mediated Wittig Reactions of Aldehydes in the Teaching Laboratory: Using Sodium Bicarbonate for the in Situ Formation of Stabilized Ylides." *Journal of Chemical Education*. **2016**, *93* (9), 1631-1636.

Kelly, Michael J. B.; Montgomery, Timothy R.; Bergdahl, B. Mikael. "Copper-Promoted and Copper-Free Asymmetric Conjugate Addition of Different Silylzinc Reagents to various N-Enoyl-2-Oxazolidinones." Manuscript in Preparation for Submission.

Montgomery, Timothy R.; Kelly, Michael J. B.; Schmit, David; Smith, Paul; Walsworth, Kevin; Bergdahl, B. Mikael. "An Efficient Total Synthesis of the Angiogenesis Inhibitor Azaspirene." Manuscript in Preparation for Submission.

FIELDS OF STUDY

Synthetic Organic Chemistry (Graduate Study):
- Natural Products Synthesis
- Medicinal Chemistry
- Professor B. Mikael Bergdahl

Inorganic Synthesis (Undergraduate):
- Catalytic Hydrogen Storage
- Professor Karen Goldberg

ABSTRACT OF THE DISSERTATION

Steps Away from (–)-Azaspirene: A Novel Synthesis of the Core Spirocycle

Chemical Studies in Copper(I) Iodide Dimethyl Sulfide Catalyzed Asymmetric Conjugate Addition

Wittig Chemistry in the Teaching Laboratory: A Novel Water-Organic Interface Reaction

Michael John Barker Kelly

Doctor of Philosophy in Chemistry

University of California San Diego 2019

San Diego State University 2019

Professor Bernt Mikael Bergdahl, Chair

(–)-Azaspirene is a fungal metabolite isolated by the Osada[1] group in 2002 from the soil fungus *Neosartorya sp*. that has been shown to have promising inhibition of angiogenesis[1,2] *in vitro* and *in vivo*, and which may be the key to the synthesis and elucidation of the structurally-similar pseurotin family of compounds. This family of compounds is interesting because its members have been shown to have a wide range of interesting therapeutic effects, which will be discussed in detail. Unfortunately, it is impractical to isolate sufficient quantities of azaspirene from its natural

source (85 mg were obtained from a 15 liter culture[1]). In addition, the previous synthetic routes to azaspirene, discussed within, are notoriously difficult and low-yielding. Because of these issues, sufficient material has been difficult to obtain to satisfy the twin goals of thorough biological testing to confirm the anti-angiogenic effects of azaspirene and the synthesis and elucidation of its derivatives. The overarching goal in part I has been to find a simpler, more accessible route to azaspirene, and through it the pseurotin family.

Silyl groups have been used extensively in organic synthesis as valuable protecting groups, bulky directing groups, and masked hydroxyl groups.[3] In 2002, the Bergdahl lab published new methodology for asymmetric silyl conjugate addition reactions with monosilylcopper reagents and oxazolidinones.[4] This methodology was expanded further in 2005 with the introduction of a novel stoichiometric copper iodide-dimethyl sulfide complex.[5] Combining the two approaches, and with further development that allows the catalytic use of the copper complex, it was possible to probe the scope of the technique and show its utility in Part II.

The Wittig reaction is a fundamental synthetic organic reaction which has been extensively used for more than fifty years to build organic frameworks through its robust creation of carbon-carbon double bonds.[6] However, for most of its history relatively harsh conditions have been employed to push the reaction forward. In 2007, the Bergdahl lab was able to conceive an alternative[7] which used aqueous sodium bicarbonate and stabilized ylides to effect the same change in high yields. In Part III, this important methodology has been expanded. An efficient lab protocol was developed for use in teaching the reaction to undergraduates in a lab setting.[8]

Chapter 1: General Introduction

The modern drug discovery process is focused on the treatment of disease through the discovery and modification of novel molecules that have a therapeutic effect.[9] In this vein, the problem of drug design is often approached from three distinct areas of discovery: first, biochemistry and the study of the molecular origins of disease in the human body; second, computational and combinatorial chemistry and the design of drugs which are similar to existing successful drugs; and third, natural products chemistry and the discovery of bioactive compounds found in nature. In the biochemical vein of drug discovery, the body is studied in an attempt to understand its processes on a molecular level. In this way, a disease pathway is discovered or the structure-activity relationship between a particular molecular signal and receptor is identified, and this information is used as a jumping-off point to drug design. Conversely, in natural products chemistry, a mixture is discovered in nature that has a particular therapeutic effect, and the identification and structural elucidation of the active species in the mixture is used as a jumping-off point to drug design. Applied biochemistry and natural products chemistry can, in this way, be considered to be working on drug design from opposite ends of the problem—biochemistry from the human body out, and natural products chemistry from the outside in.

Nature is an amazing source of molecular diversity,[10] developed over millions of years. Important small molecules from aspirin to penicillin to ziconotide which treat human disease and improve the human condition were first found in nature (in willow trees, mold, and sea snails, respectively) and have been adapted to great effect by chemists and doctors for use in humans (as a pain killer and blood thinner, a potent antibiotic, and treatment of severe chronic pain). Natural

products chemistry is the discipline concerned with mining these molecular gems from nature and determining their biological activity and their physical structure. Synthetic organic chemists are the next link in this chain, responsible for creating the identified molecules and their derivatives, and continuing their testing for biological activity. Once a target molecule is synthesized and is shown to be biologically effective, it can then be analyzed by medicinal chemists, biologists and others, before they are finally tested by a government agency or drug company. If this testing shows the potential drug to be beneficial, cost-effective and relatively harmless in its application, it can finally be put on the market with Food and Drug Administration approval. It is an expensive and lengthy process, but it ensures that any drugs that come to market have the expected therapeutic effect, and that the danger of any side effect does not overshadow the treatment.

In Part I, the main focus of this dissertation, a part of this drug discovery process is explored through the synthesis of a potential anti-tumor drug, the angiogenesis inhibitor azaspirene. A novel approach to the synthesis of the core spirocyclic structure of azaspirene is outlined, and each step documented fully and characterized by H-NMR and HRMS.

Conjugate addition reactions and Wittig reactions are two important sources of carbon-carbon bond formation in synthetic organic chemistry. Both are widely used in the synthesis of important molecules which help improve the human condition. In Part II, a novel approach to asymmetric conjugate addition involving a twist on Evans' chiral auxiliary chemistry is outlined, and a new methodology is explored. In Part III, an improved method for creating carbon-carbon double bonds through Wittig reactions with stabilized ylides and sodium bicarbonate are adapted for use in the undergraduate teaching laboratory.

PART I: Steps Away from (–)-Azaspirene: A Novel Synthesis of the Core Spirocycle

Chapter 2: (–)-Azaspirene and the Pseurotin Family

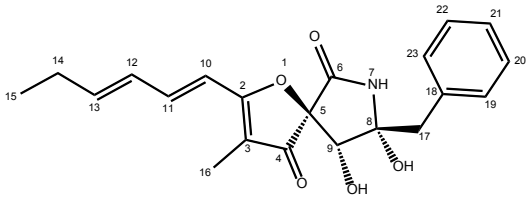


Figure 2.1: (–)-Azaspirene

2.1 Introduction and Significance of Research

The Bergdahl group has been focused for several years on the synthesis of the spirocyclic soil fungus metabolite azaspirene, a member of the pseurotin family of compounds, isolated by Osada and coworkers[1] in 2002 from a broth of *Neosartorya sp*. Throughout the several iterations of the synthetic route that have been pursued, two goals have remained constant: first a concise, asymmetric route which improves upon the methods used in prior syntheses; and second a route which provides for the simple introduction of diversity in the structure of the molecule. The achievement of both goals will provide sufficient material for effective biological testing, structure-activity relationship (SAR) determination and, perhaps most importantly, the synthesis of analogs of azaspirene and its sister molecules from the pseurotin family. Further study of the pseurotin family of compounds with their diverse range of biological activities holds promise for the treatment of several critical human diseases, from bacterial and fungal infections to cancer. In the pursuit of the synthetic route to azaspirene, novel chemistry was developed. This includes the selective conjugate addition of alkenes made from alkynes using Schwartz's Reagent and a

copper-dimethyl sulfide catalyst, the stereoselective conjugate addition of silyl groups to alkenes using Evans' chiral auxiliaries in old chemistry with a new twist, and the use of chiral malimides as stereo-directing frameworks in a way never done before to build up the spirocycle at the heart of azaspirene and the larger pseurotin family.

2.2 Synthesis of the Pseurotins

The path toward the synthesis of azaspirene began with the discovery of pseurotin A in 1976 by Peter Bloch, Christoph Tamm and coworkers.[11] The pseurotin family of compounds (Figure 2.2) is so named because pseurotin A, as the first member of the family identified, was isolated from the Argentinean soil fungus *Pseudeurotium ovalis* Stolk by Tamm's group. The pseurotin family, including azaspirene, is defined by the same distinctive spirocyclic core structure with differences in two main areas: first, only azaspirene has a hydroxyl group and a benzyl group on C-8 in the spirocyclic core—all others have a methoxy group and a benzoyl group on C-8; second, the "tail" carbon chain on C-2 of the spirocycle is different for each family compound (see Figure 2.2 for examples). The pseurotin family lends itself to study because despite the similarities among their structures, the biological effects of the members of the family are diverse, so it is likely that small changes in structure will lead to large differences in biological activity. The study of and path to the synthesis of these compounds is an extensive one. However, the study of these prior syntheses is important because it led to the methodology which was pursued in the Bergdahl lab effort in synthesizing azaspirene.

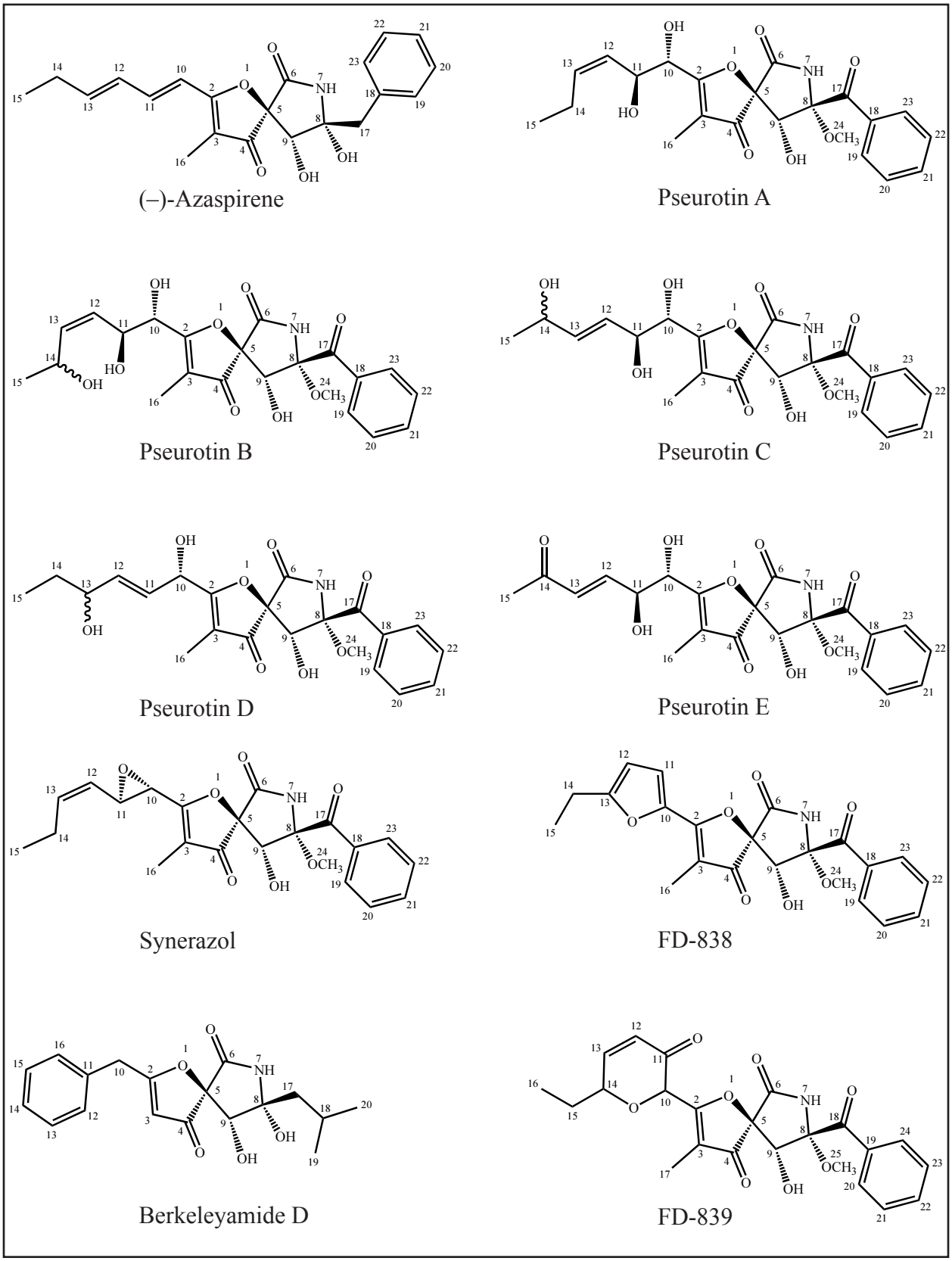


Figure 2.2: The Pseurotins

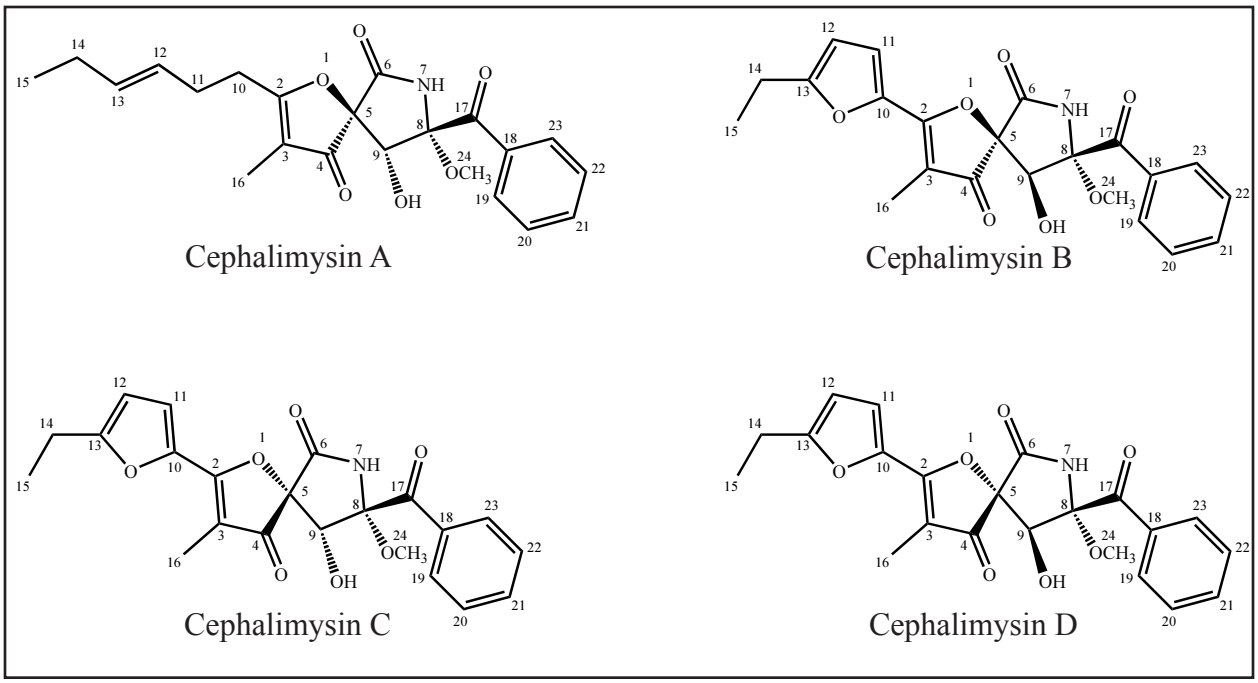


Figure 2.2: The Pseurotins (continued)

2.2.1 Pseurotin A

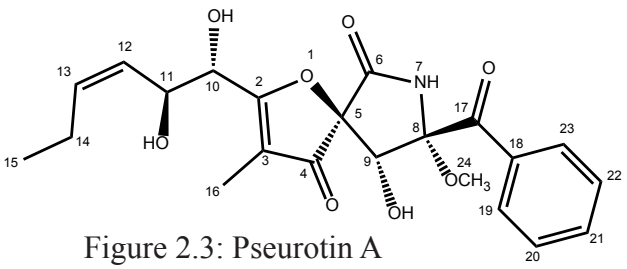


Figure 2.3: Pseurotin A

Pseurotin A was the first member of the pseurotin family discovered, in 1976, by Tamm[11] and coworkers and was named after the Argentinean soil fungus *Pseudeurotium ovalis* Stolk from which it was isolated. It was selected as a molecule of study not because it showed any biological activity initially (Tamm reported specifically that it was neither antifungal nor antibiotic in his testing), but because of its "novel, highly substituted and functionalized spirocyclic system." Its structure was elucidated in 1976 by chemical tests and x-ray analysis of its dibromo derivative. The discovery was soon followed by Tamm's study of its biosynthesis[12] in 1981 and the isolation of its sister compounds pseurotins B, C, D and E from the same soil fungus, which structurally only differ in the "tail" attached to C-2 of the spirocycle (see Figure 2.2). Notably, it was reported by Tamm that none of the compounds showed significant biological activity in his tests. Nevertheless, in 1990[13] and 1991,[14] Tamm and coworkers took initial steps toward synthesizing the new compounds.

Tamm's initial results were not the last word on the biological activity of pseurotin A, however. In 1993, Sterner[15] and coworkers published the first indication that pseurotin A was biologically active in the inhibition of chitin synthase, but reported that this did not translate to antifungal activity. In 1996, Fujita[17] and coworkers discovered that pseurotin A had neuritogenic

activity, including possible neuroprotective properties which they reported may be useful in the treatment of some forms of dementia and Alzheimer's disease. They also reported that pseurotin A had an IC_{50} of 12 μg/mL in A2780 human ovarian carcinoma cells, which indicates that it may be an effective treatment for some kinds of cancer.

In 2004, Oki's[18] group published an account of the directed biosynthesis of a fluorinated derivative of pseurotin A (and of its sister pseurotin synerazol) by the fungus *Aspergillus fumigatus* by feeding it fluorinated phenylalanine. In addition to providing new information about the biosynthesis of the molecule, they also reported that pseurotin A showed no antibiotic or antifungal activity, and they also reported that it did not inhibit angiogenesis, which supports prior reports.

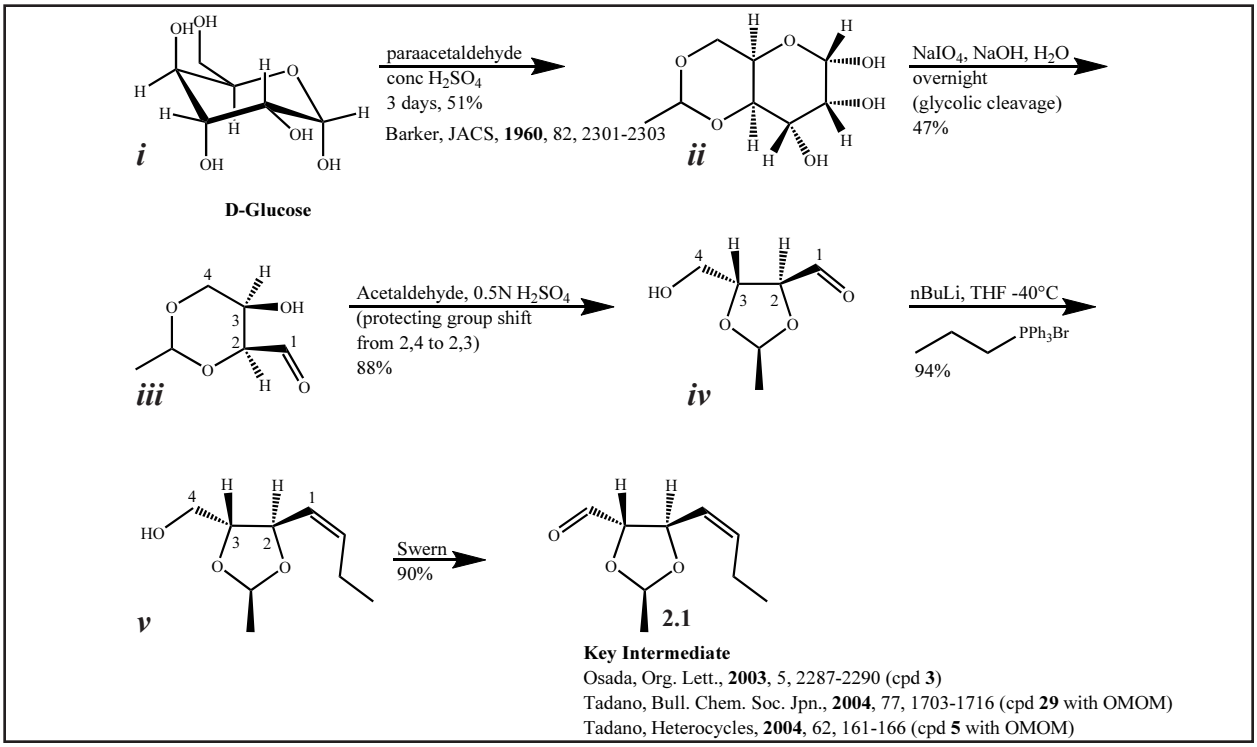
In 2009, Murata[19] and coworkers described the inhibition of immunoglobulin E by pseurotin A and suggested that structure-activity relationships could explain this behavior. In 2010, Chowdhury[20] and his group reported that pseurotin A did show "selective antibiotic activity" against *Bacillus cereus* and *Shigella shiga* at 64 μg/mL, in contrast to Tamm's prior reports. They additionally reported that pseurotin A showed no activity against cancer cells nor against fungi. However, in 2011, Gu[21] and colleagues found that pseurotin A and some of its diastereomers were cytotoxic against HL 60 cell lines *in vitro*, with an IC_{50} of 67.0 μmol/L. In 2013, Marinho[22] and colleagues also reported an antibiotic effect from pseurotin A, with a minimum inhibitory concentration of 15.62 μg/mL against *Bacillus subtilis* and *Staphylococcus aureus*. Finally, in 2016, Yamada[23] and Yang[24] both published structural elucidations of diastereomers of pseurotin A.

2.2.1.1 The Tamm Route Toward Pseurotin A

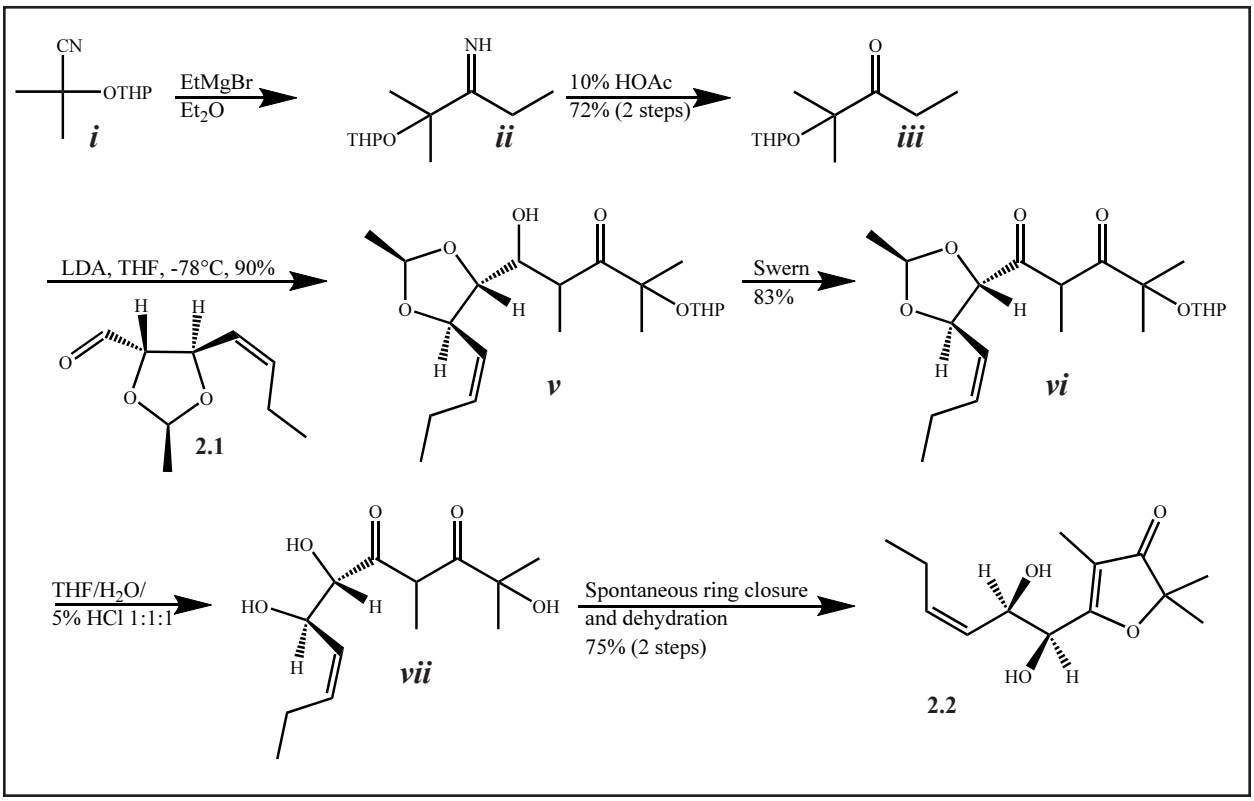
Tamm's approach did not result in the synthesis of the target molecule, pseurotin A, but it utilized several novel schemes that are worthy of closer study, not only because they were the first efforts toward any of the pseurotins, but because they were adapted by some of the later routes to synthesizing the family of molecules; particularly the other approaches to pseurotin A (discussed later this chapter). As shown in scheme 2.1, Tamm's use of D-glucose[13a] as a starting material and its transformation to the key chiral creating block **2.1** indicated is particularly important because the same approach was used by both Osada[32] and Tadano[25] in their syntheses of pseurotin A. As shown in Tamm's route in scheme 2.1, the application of catalytic acid and paraformaldehyde formed the acetal ***ii*** selectively, and glycolic cleavage with sodium periodate yielded ***iii***. A shift of the acetal protecting group from 2,4 to 2,3 gave ***iv***, a selective Wittig reaction gave ***v***, and a Swern oxidation changed the primary alcohol into an aldehyde to give **2.1**.

Tamm intended that the chiral chain of **2.1** would form the "tail" of pseurotin A, and its framework could be used to build up the spirocyclic system in a stereoselective fashion. In their first attempt, shown in scheme 2.2, they were largely successful. An acetone cyanohydrin ***i*** was subjected to Grignard conditions to give ***ii***, and hydrolysis of the imine to the ketone gave ***iii***. Chiral synthon **2.1** was then coupled to ***iii*** give ***v***. Next, with a Swern oxidation and acetal deprotection they were able to spontaneously close the molecule to a five-member ring and synthesize **2.2**, which resembles the western ring of pseurotin A with the correct stereochemistry (scheme 2.2).

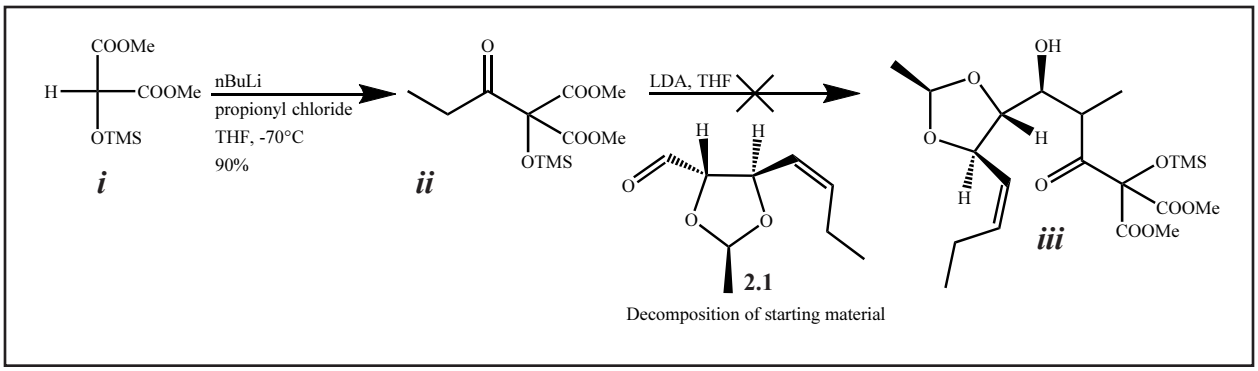
Next, Tamm's group made their first attempt at creating a structure that would provide the



Scheme 2.1: Tamm Pseurotin A Tail Synthesis (**2.1**)

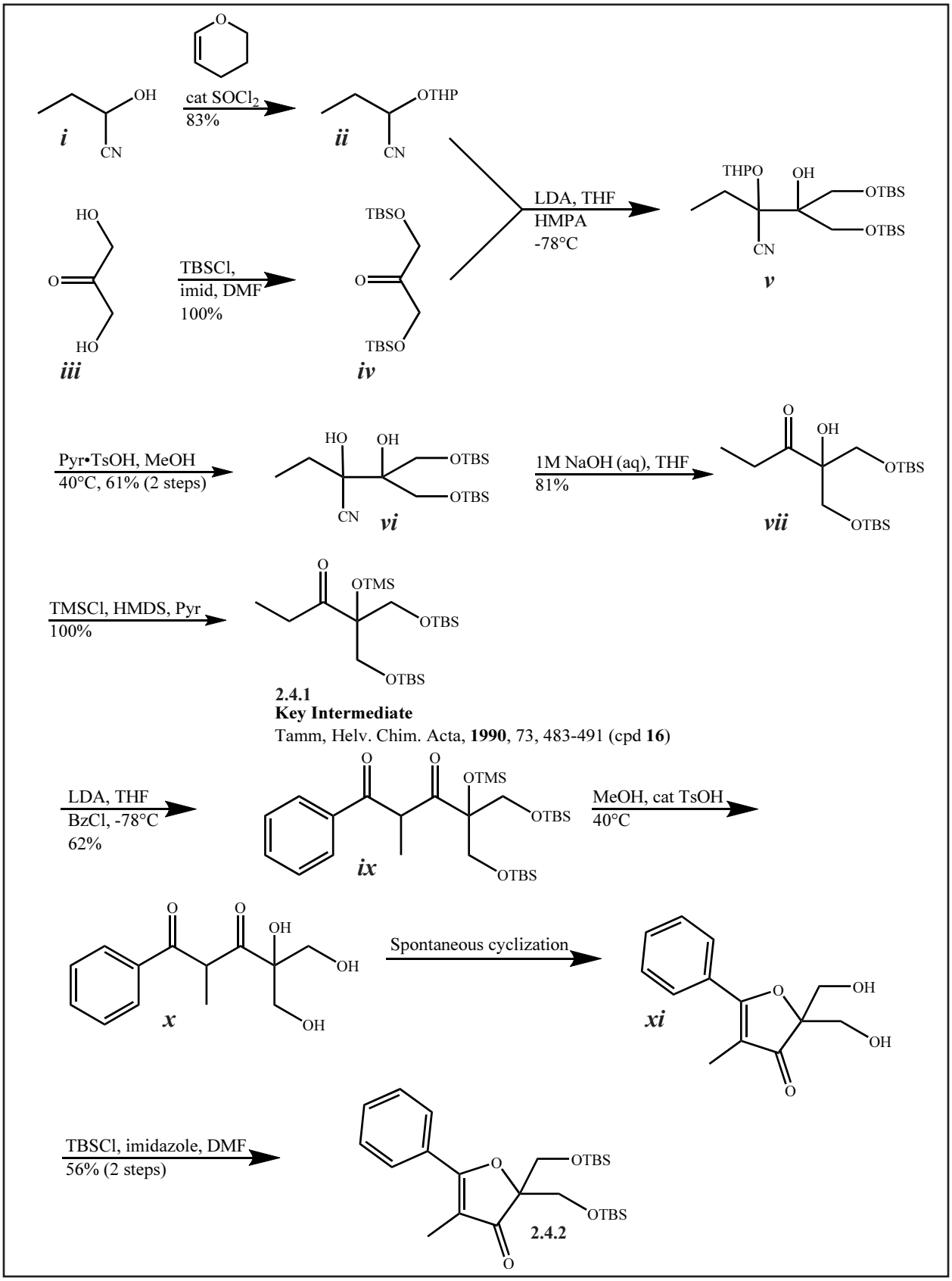


Scheme 2.2: Tamm Synthesis of a β-oxygenated enone plus tail

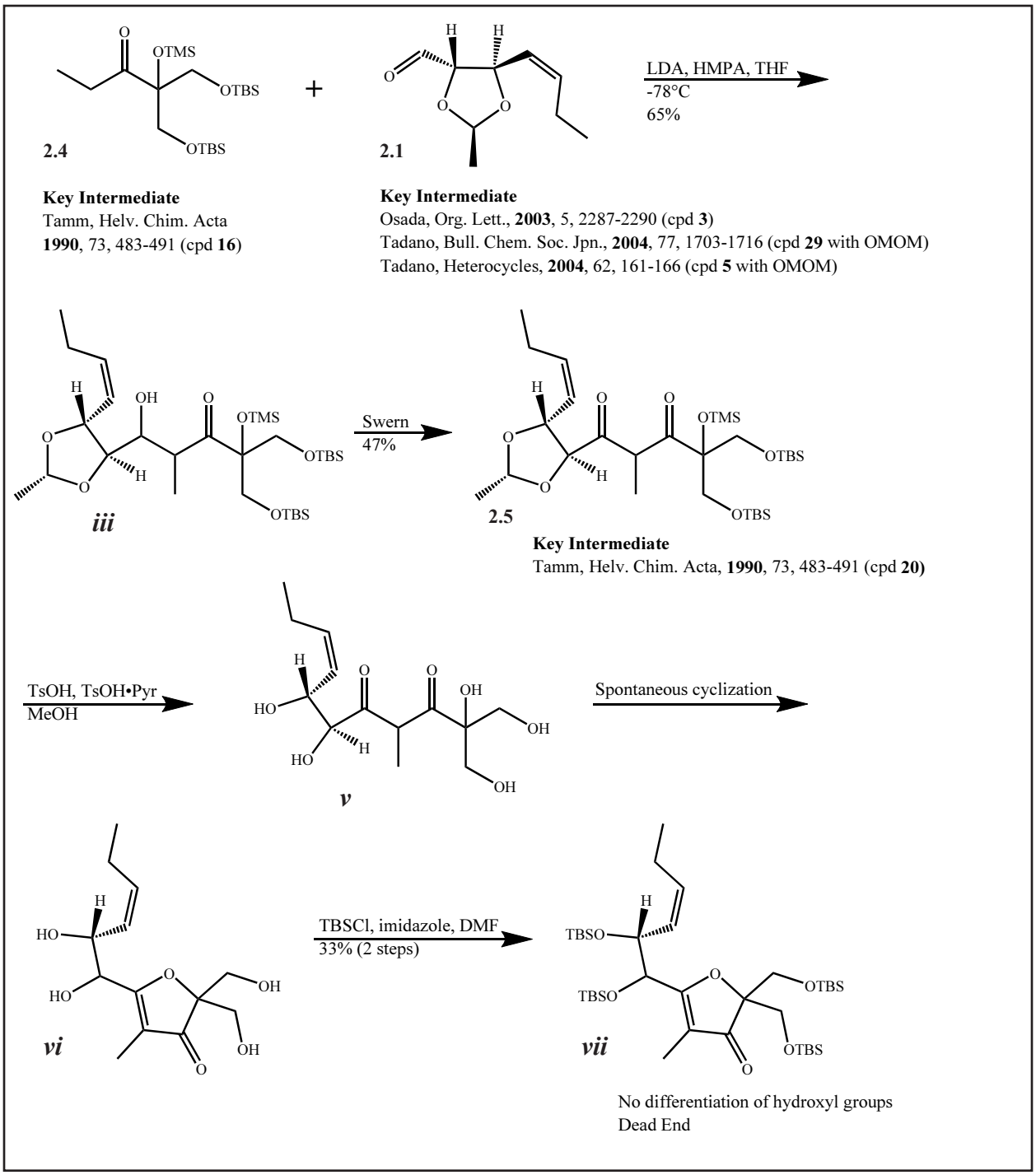


Scheme 2.3: Tamm's unsuccessful coupling of the tail aldehyde

necessary chemical "handles" to construct the eastern ring of the spirocycle of pseurotin A onto the western ring, which is illustrated in scheme 2.3. They attempted to functionalize the methyl groups of the acetone cyanohydrin from scheme 2.2 by substituting TMS-protected dimethyl-2-hydroxymalonate (***i***, scheme 2.3).[13b] The enolate coupling with propionyl chloride gave ***ii***, but unfortunately ***ii*** decomposed upon formation of the enolate necessary for coupling with **2.1**. To get around this problem, as shown in scheme 2.4, they used a second cyanohydrin, a THP-protected propionyl cyanohydrin, ***ii***, and were able to successfully couple it to a protected dihydroxyacetone, ***iv***. In this way, it was possible to retain the hydroxyl functionality needed as a synthetic handle to create the right ring of the molecule, with different protecting groups allowing differentiation among the three hydroxyl groups (scheme 2.4, **2.4.1**).[13b] They successfully tested the utility of the scheme by coupling the new molecule with benzoyl chloride and closing the left ring, yielding **2.4.2**.[13a] With their success in hand, as shown in scheme 2.5, **2.4.2** was coupled with the protected tail portion, **2.1** (scheme 2.1), and the result was subjected to the same cyclization conditions (scheme 2.5, ***v*** to ***vi***). Unfortunately, it was discovered that the acidic TMS deprotection conditions they had used previously to accomplish the cyclization would not work. Under these conditions, all protecting groups were removed and it became impossible to differentiate among

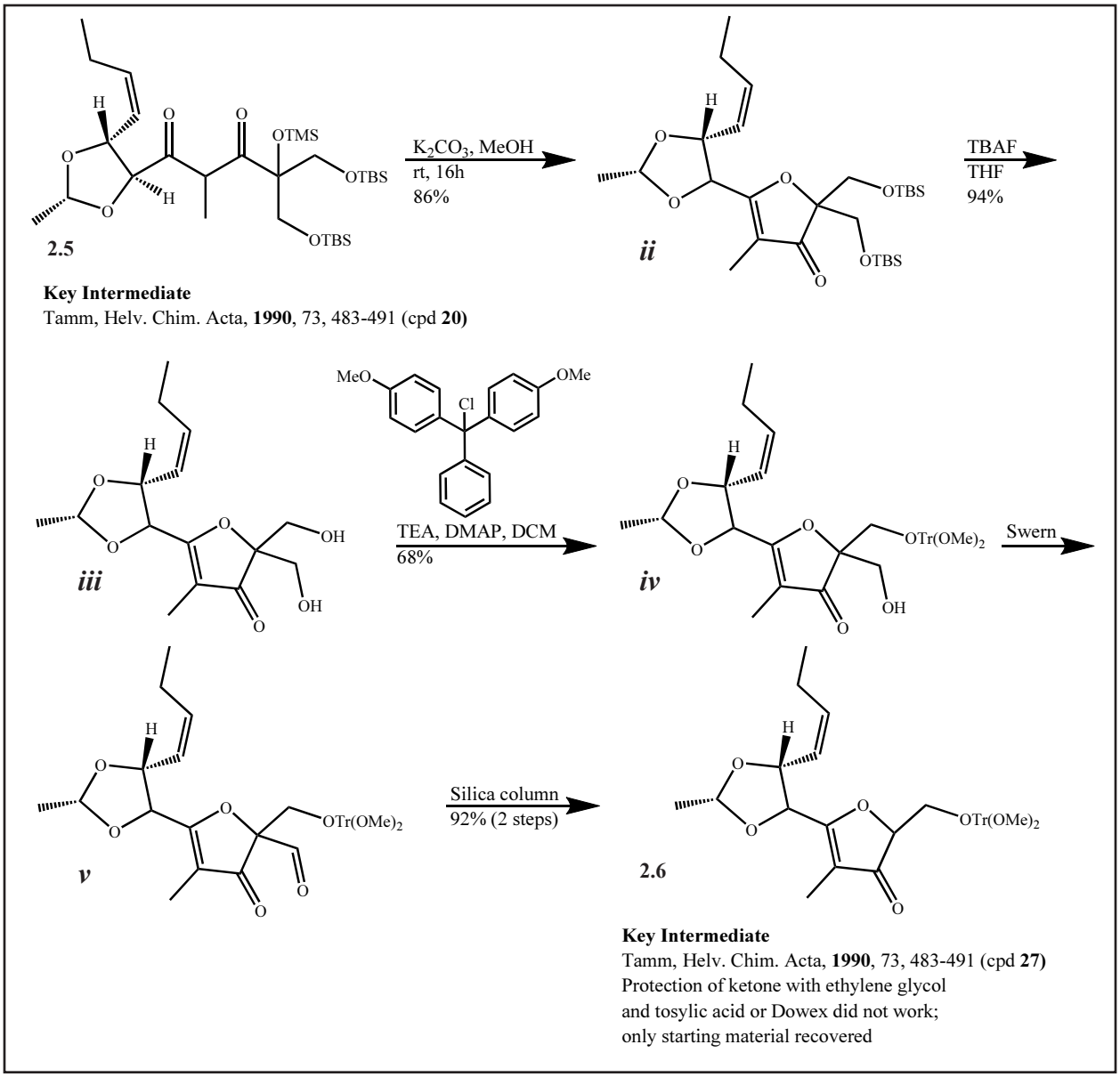


Scheme 2.4: Tamm synthesis of an alternative starting enone

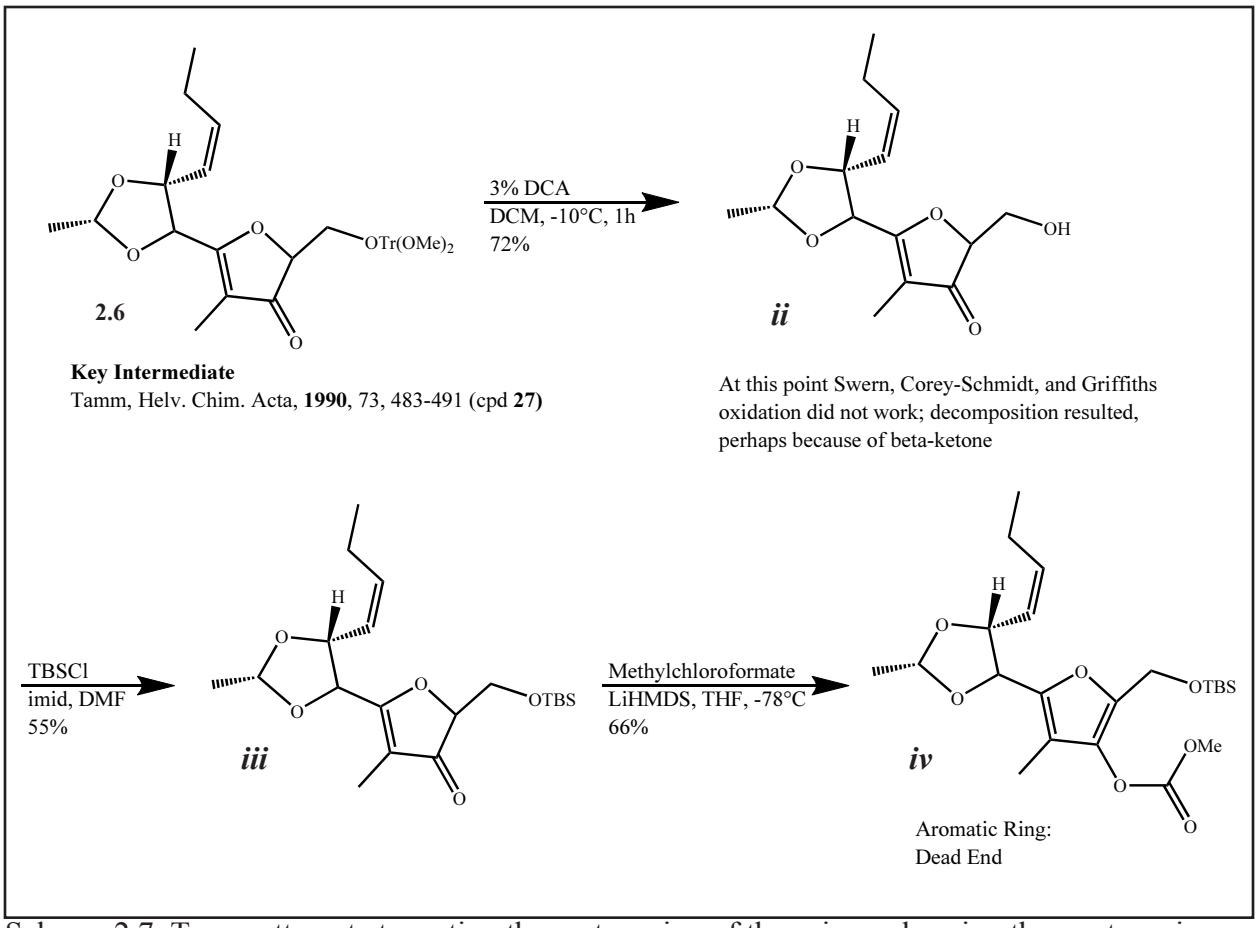


Scheme 2.5: Tamm synthesis of a functionalized enone plus tail

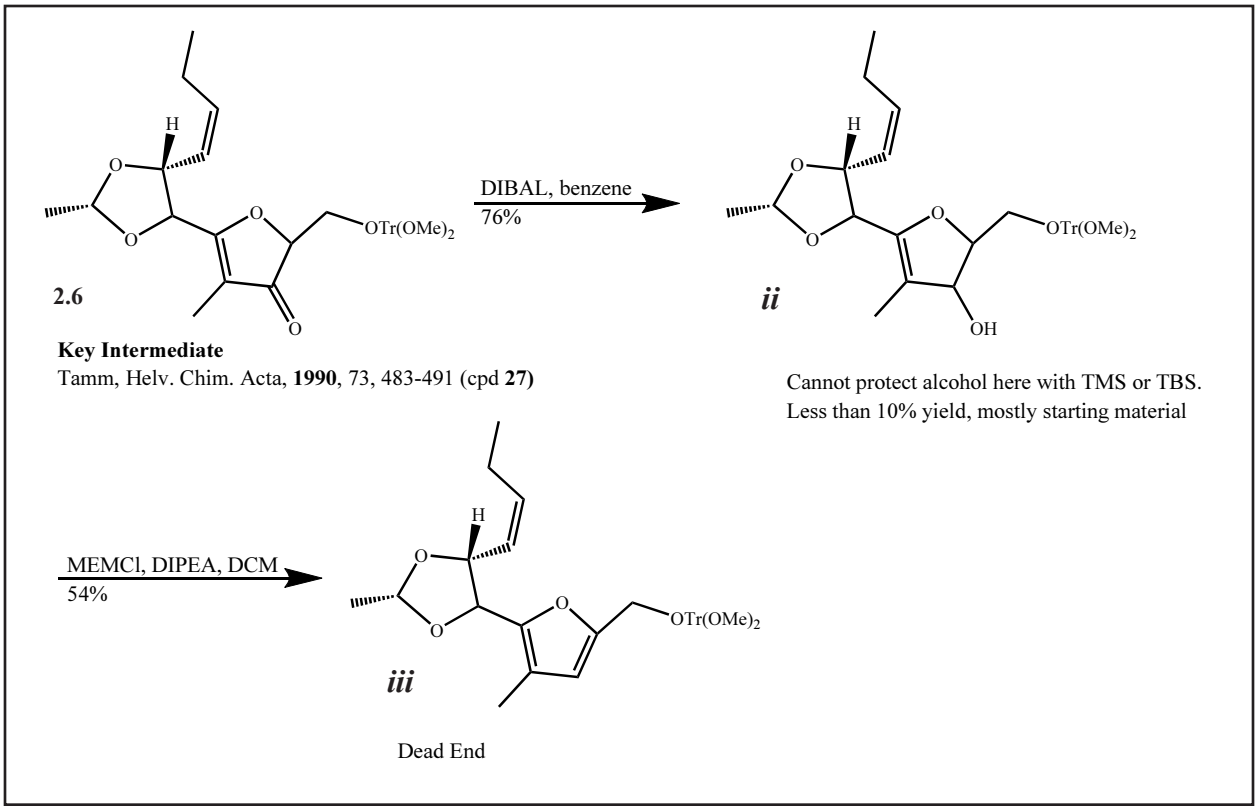
the hydroxyl groups (scheme 2.5, ***vii***). In the process of correcting the problem, it was discovered that deprotecting the TMS group under mildly basic conditions would allow the cyclization to proceed without removing the other protecting groups (scheme 2.6). The removal of the TBS groups with TBAF and subsequent monoprotection using the large trityl protecting group shown in ***iv*** (scheme 2.6), allowed for sufficient differentiation to move forward, and it was envisioned that oxidation of the primary alcohol would provide a further handle for constructing the second ring. Unfortunately, an unwanted decarboxylation was the result (**2.6**). Nevertheless, a semblance of the left ring and tail of the molecule **2.6** was achieved (scheme 2.6). Unfortunately, several different attempts to protect the ketone of the ring and deprotect and oxidize the remaining hydroxyl group to begin constructing the second ring were also unsuccessful (schemes 2.7 and 2.8). Still, in 1991,[14] Tamm published a paper outlining the utility of the ring-closing step discovered (scheme 2.9).



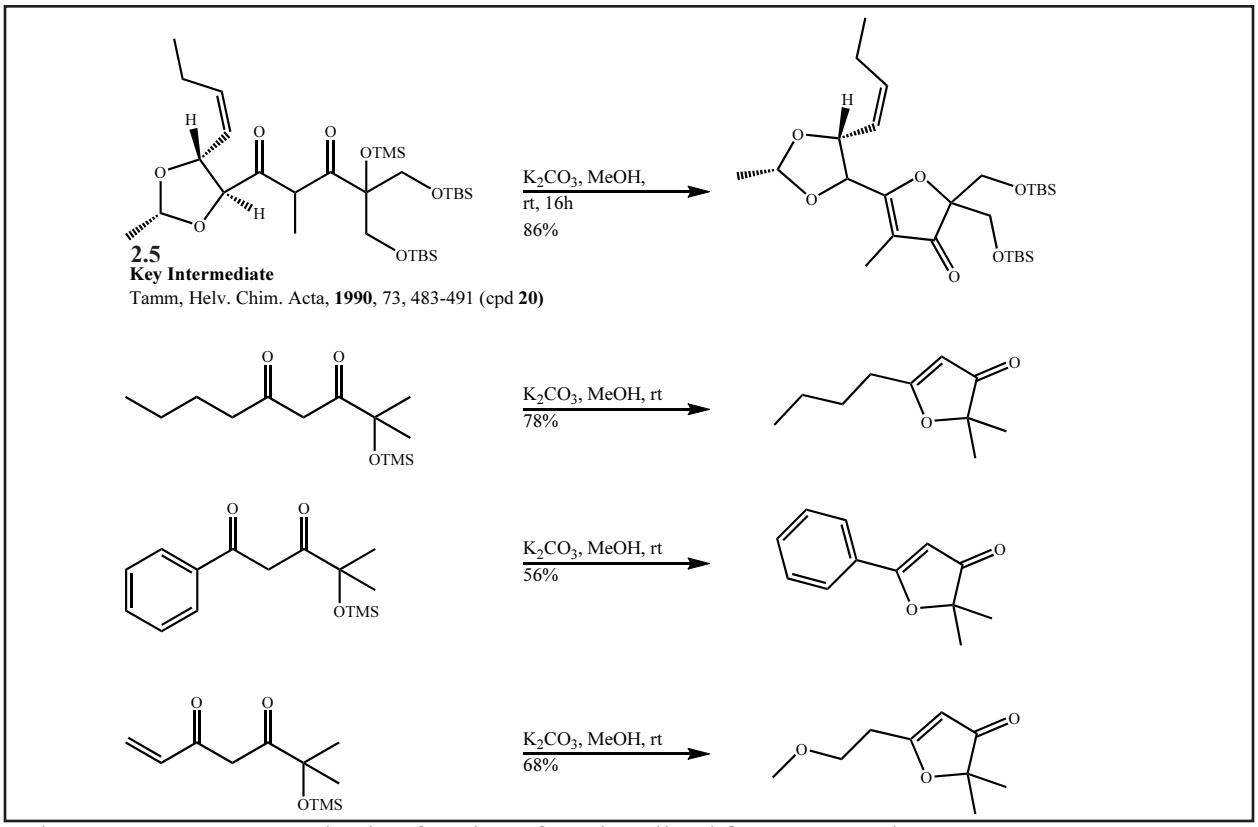
Scheme 2.6: Tamm synthesis of the western ring of the spirocycle plus tail (**2.6**)



Scheme 2.7: Tamm attempt at creating the eastern ring of the spirocycle using the western ring

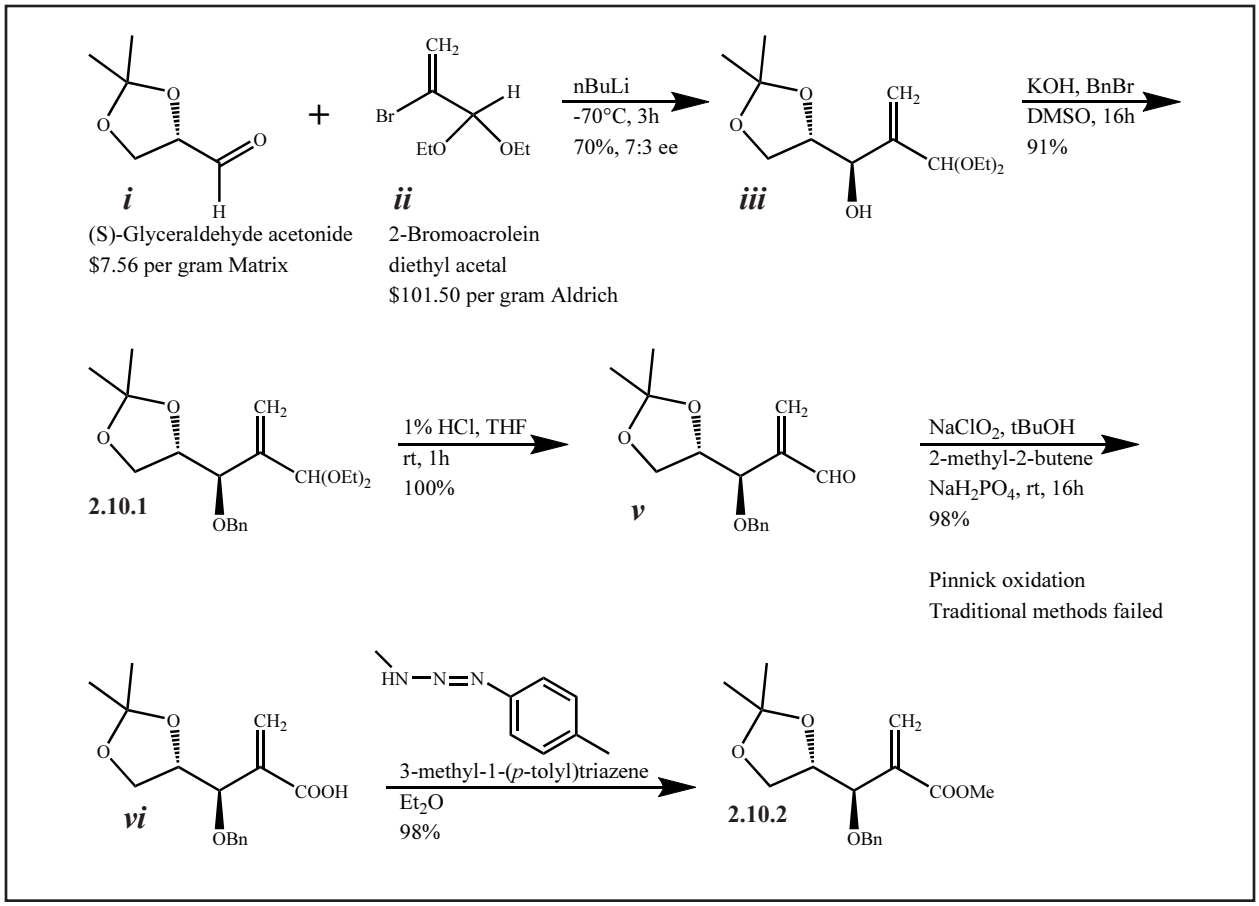


Scheme 2.8: Tamm attempt at creating the eastern ring of the spirocycle using the western ring

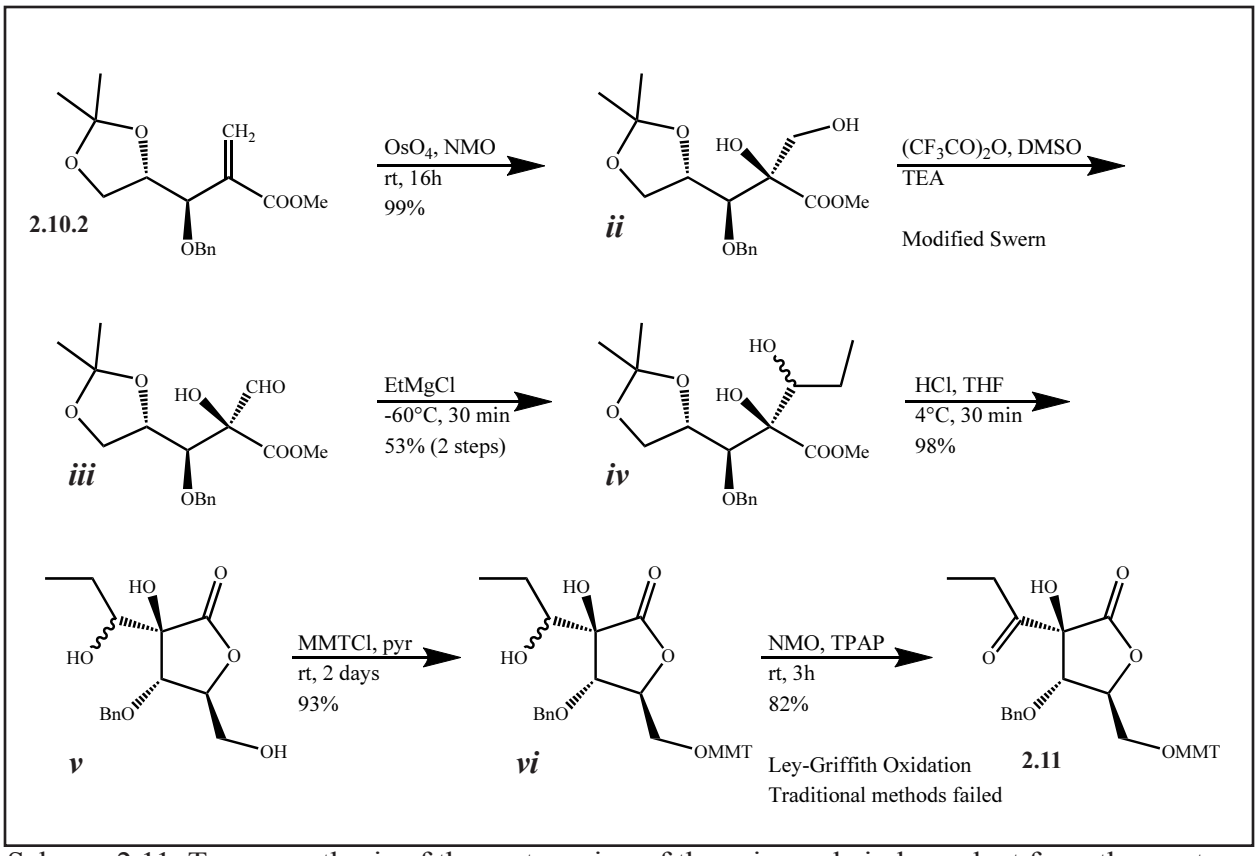


Scheme 2.9: Tamm synthesis of various functionalized β-oxygenated enones

In 1995,[16] Tamm's group published an updated progress report on their efforts to synthesize the psuerotins, focusing on the eastern ring of the molecule (schemes 2.10, 2.11 and 2.12). In their first attempt,[16a] illustrated in schemes 2.10 and 2.11, Tamm's group started by coupling two relatively expensive materials: an acetonide protected unnatural enantiomer of glyceraldehyde ***i*** and an acetal protected bromoacrolein ***ii***, to create a framework with the proper stereochemistry. The chiral framework was built into a semblance of the eastern ring of pseurotin A with several protection/deprotection and oxidation steps. In scheme 2.10, some notable techniques were used; for example, oxidation of an aldehyde, ***v***, to a carboxylic acid, ***vi***, (the mild Pinnick oxidation, which was used because other methods were troublesome) and an unusual methylation reagent



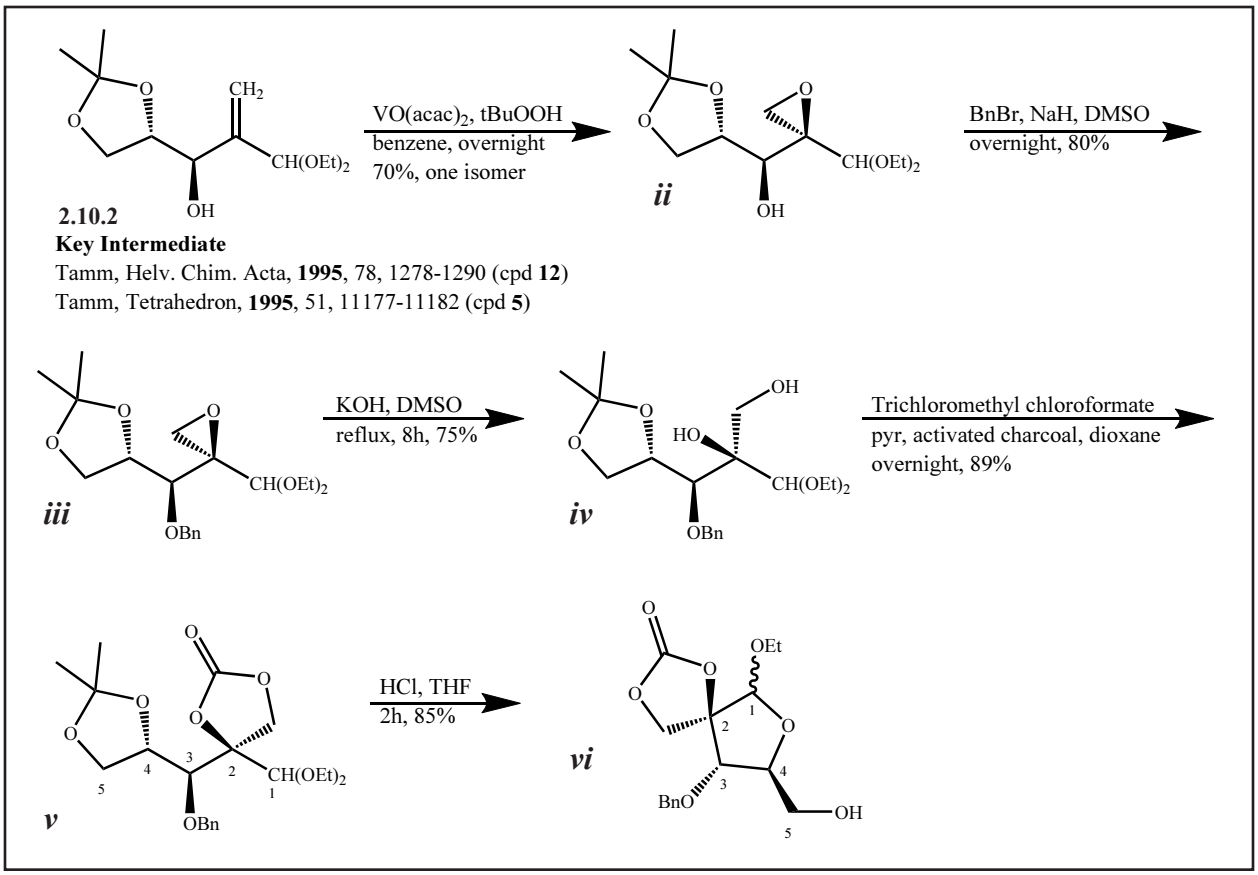
Scheme 2.10: Tamm toward the synthesis the eastern ring of the spirocycle independent from the western ring



Scheme 2.11: Tamm synthesis of the eastern ring of the spirocycle independent from the western ring

to change a carboxylic acid ***vi*** to an ester **2.10.2**. Notable reactions include an asymmetric dihydroxylation to **2.10.2** to yield ***ii*** followed by a modified Swern using trifluoroacetic anhydride to give ***iii*** (scheme 2.11). A large substituted trityl group protected the primary alcohol in ***v*** to give ***vi***, and a Ley-Griffith oxidation transformed the secondary alcohol into the necessary ketone **2.11** (scheme 2.11). The yields in each step were excellent, except for a troublesome Grignard reaction used to transform ***iii*** to ***iv***. The difficulty with the Grignard addition seemed to derive from problems with the stability of the aldehyde starting material ***iii***. Despite their success, they next adjusted their approach in an attempt to improve their overall yield.

In their second paper published in 1995,[16b] reflected in scheme 2.12, the same chiral



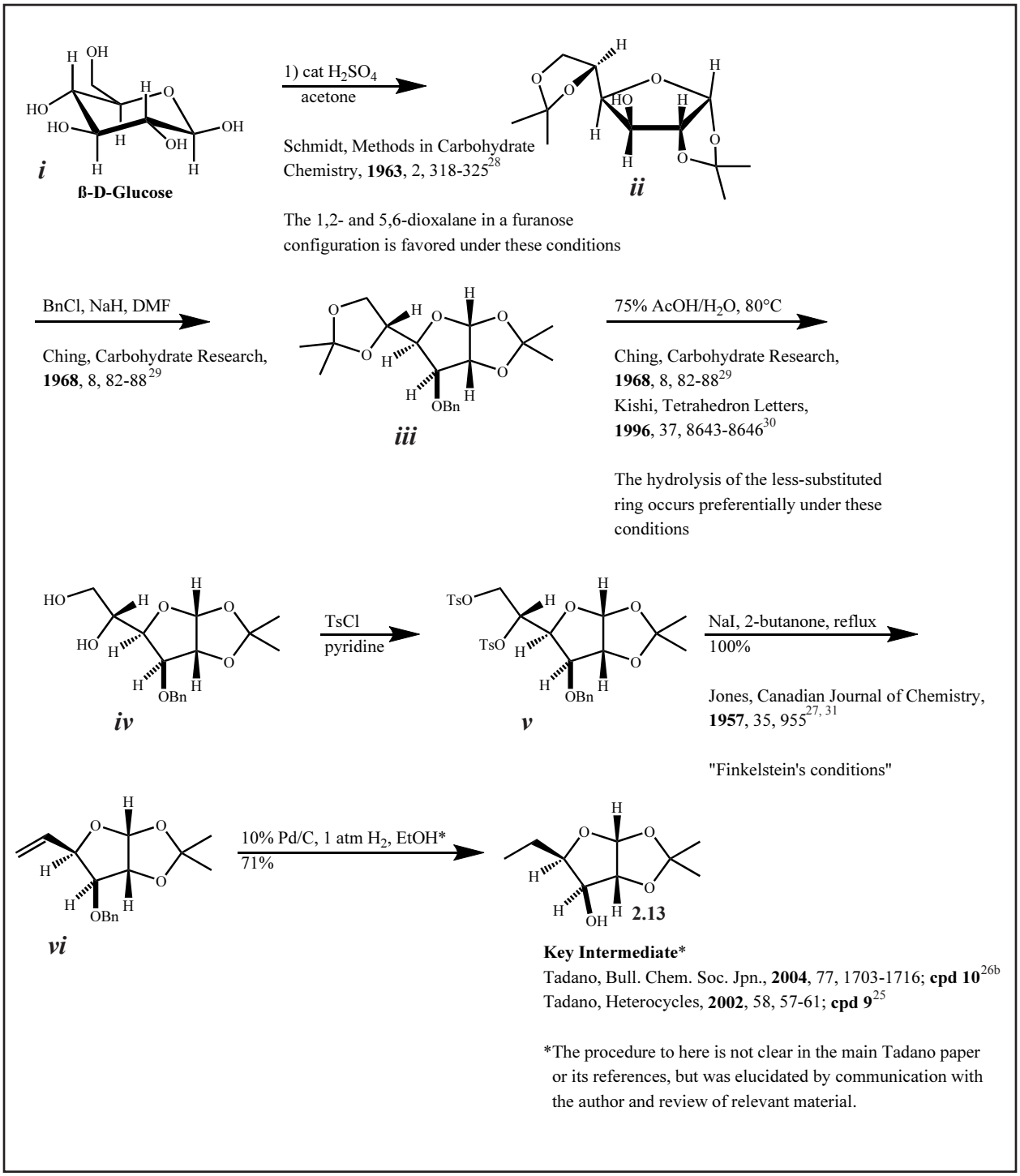
Scheme 2.12: Tamm alternative synthesis of an eastern ring analog

starting material **2.10.2** was used, this time in an asymmetric epoxidation to change **2.10.2** to ***ii***, a feat that several other pseurotin routes[48,50,51] were not able to achieve. The secondary alcohol was protected yielding ***iii***, and the epoxide selectively opened with base to yield ***iv***. The new hydroxyl groups were protected as a carbonate derivative (***v***), and the ring was finally closed via an acetonide rearrangement to form acetal ***vi*** (scheme 2.12). While this approach utilized some novel techniques, the result seems further afield than the previous attempt, in that the resulting molecule is less similar to the target eastern ring of pseurotin A.

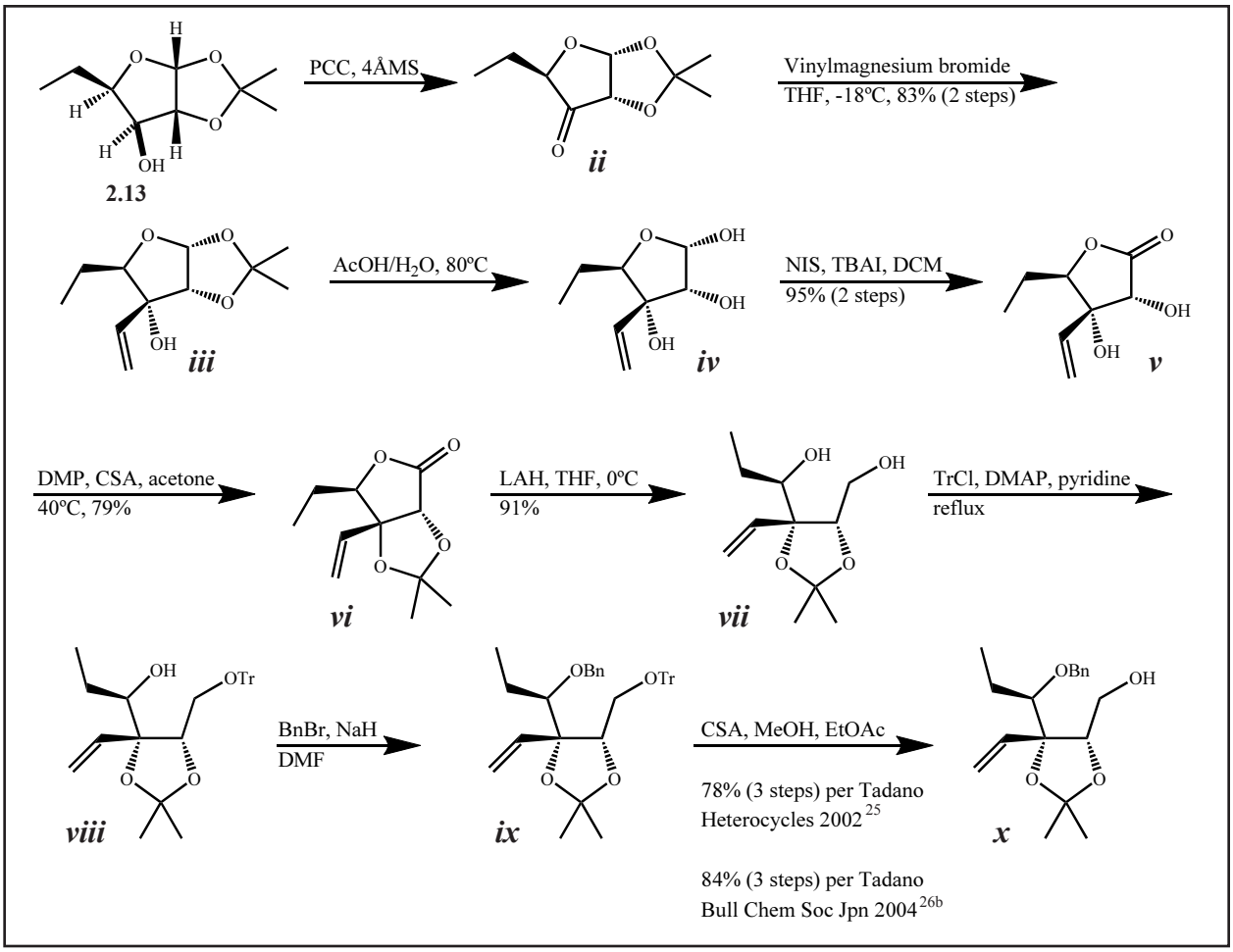
2.2.1.2: The Tadano Route to Pseurotin A

In 2002 Tadano's group published[25] their first attempt toward the synthesis of pseurotin A (see Tadano's first four schemes, 2.13-2.14.3). Tadano's route, like Tamm's,[13] used D-glucose for the (S,Z)-3-hexenyl-1,2-diol tail. Tadano's effort diverges from Tamm's in its use of D-glucose as the chiral template to build up the eastern ring of the spirocycle. The Tadano route toward the eastern ring of the spirocycle of pseurotin A was initiated with a series of vague transformations, referred to as "known 5 steps" and later, "6 convenient steps[26]" to transform D-glucose into the necessary chiral director starting material (scheme 2.13). The experimental procedure for this transformation is not listed; instead Tadano referenced a 1957 *Canadian Journal of Chemistry* paper[27] that seems to be inadequate. Upon communication with Tadano, however, the route shown in scheme 2.13 was outlined. Using Schmidt's[28] method, D-glucose ***i*** was protected as its di-acetonide in a procedure which favored the furanose conformation in ***ii***, and the unprotected alcohol was benzylated[29] to give ***iii***. The less-substituted ring was hydrolyzed,[29,30] and the resulting diol ***iv*** reprotected as the tosylate ***v***. Using Finkelstein's conditions,[27,31] an iodine replaced the tosylated alcohols to form the vicinal diiodide, one of which reacted with another iodide ion, eliminating the remaining iodide and leaving the double bond ***vi*** (see scheme 2.43a on page 77 for a proposed mechanism). Finally the double bond was reduced and the benzyl protecting group was removed via hydrogenation to form the chiral key intermediate product **2.13** from scheme 2.13.

Tadano's synthesis of the eastern ring of pseurotin A continued in scheme 2.14.1 with the oxidation of the unprotected alcohol of the chiral key intermediate **2.13** with pyridinium chlorochromate, which gave β-oxygenated ketone ***ii***. This ketone was subjected to a stereodirected

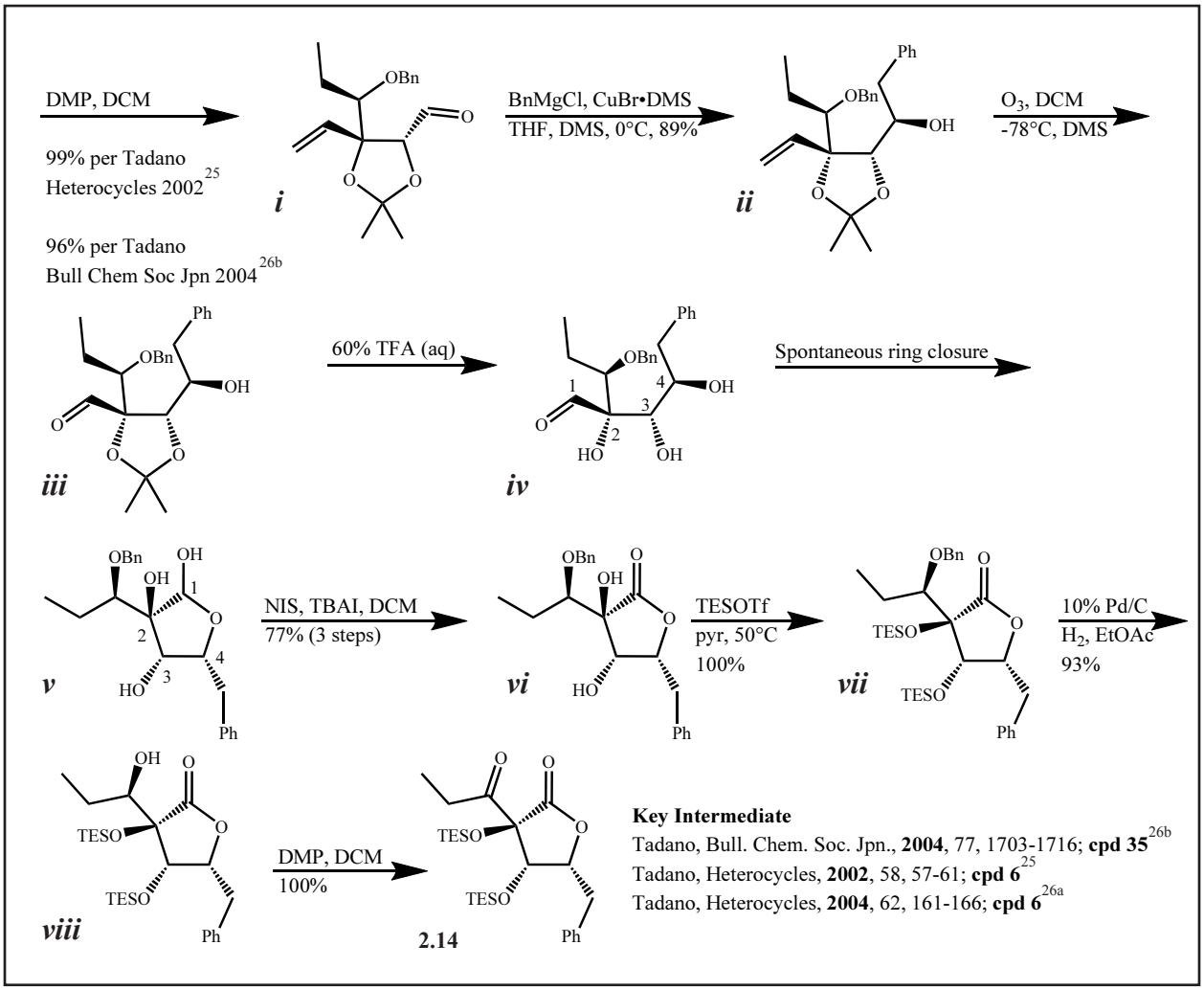


Scheme 2.13: Tadano synthesis of a chiral intermediate toward the eastern ring of pseurotin A



Scheme 2.14.1: Tadano further work toward the synthesis of the eastern ring of the spirocycle of pseurotin A

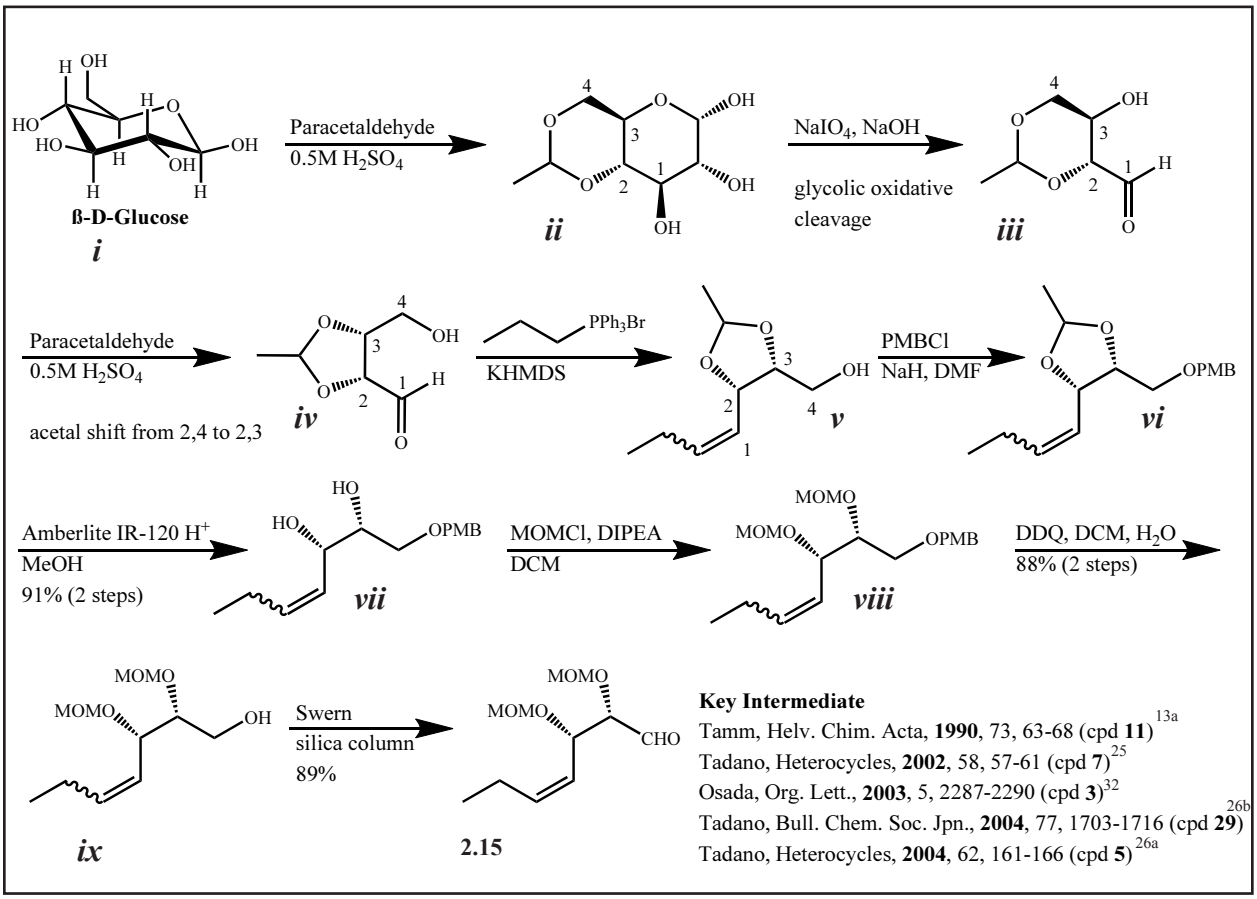
Grignard reaction with vinylmagnesium bromide to give ***iii*** in an excellent 83% yield over 2 steps. The acetonide protecting group was removed, and the hemiacetal ***iv*** was selectively oxidized with via a radical reaction with NIS to give the lactone ***v*** in a 95% yield over two steps. The diol was then reprotected using dimethoxypropane to form the acetonide ***vi***, and the lactone was opened with LAH to give ***vii***, all with excellent yields. The resulting primary alcohol was next protected selectively with a bulky trityl group to give ***viii***, the secondary alcohol was protected as a benzyl ether for ***ix***, then the trityl was removed to give ***x*** (concluding scheme 2.14.1). Next, in scheme 2.14.2, a Dess-Martin oxidation yielded aldehyde ***i***, which was subjected to a stereocontrolled



Scheme 2.14.2: Tadano synthesis of a key intermediate toward the eastern ring of pseurotin A

Grignard reagent addition using benzylmagnesium chloride to give ***ii***. The vinyl group was transformed into an aldehyde ***iii*** by ozonolysis, the acetonide removed to give ***iv*** which rearranged to ***v***, and the hemiacetal was selectively oxidized via another radical reaction with NIS to give ***vi***. A TES protecting group was added to give ***vii***, the benzyl protecting group removed to give ***viii***, and the alcohol oxidized with Dess-Martin periodinane to give the dicarbonyl **2.14**. This key intermediate, which forms much of the eastern ring of pseurotin A, is markedly similar to Tamm's **2.11**, though the route to the molecule was very different.

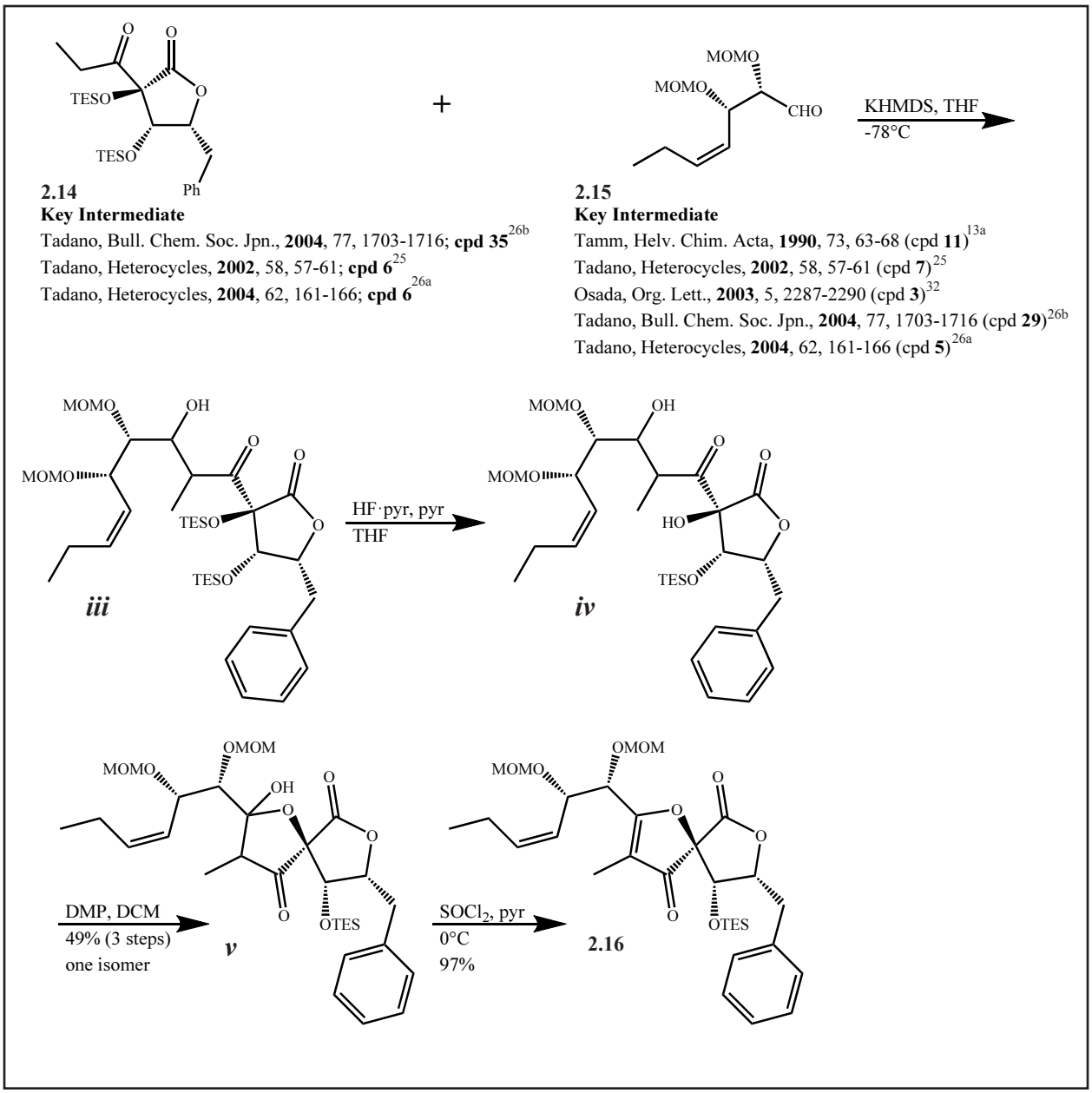
With the eastern ring of pseurotin A mostly completed (scheme 2.14.2, compound **2.14**),



Scheme 2.15: Tadano synthesis of the tail of pseurotin A

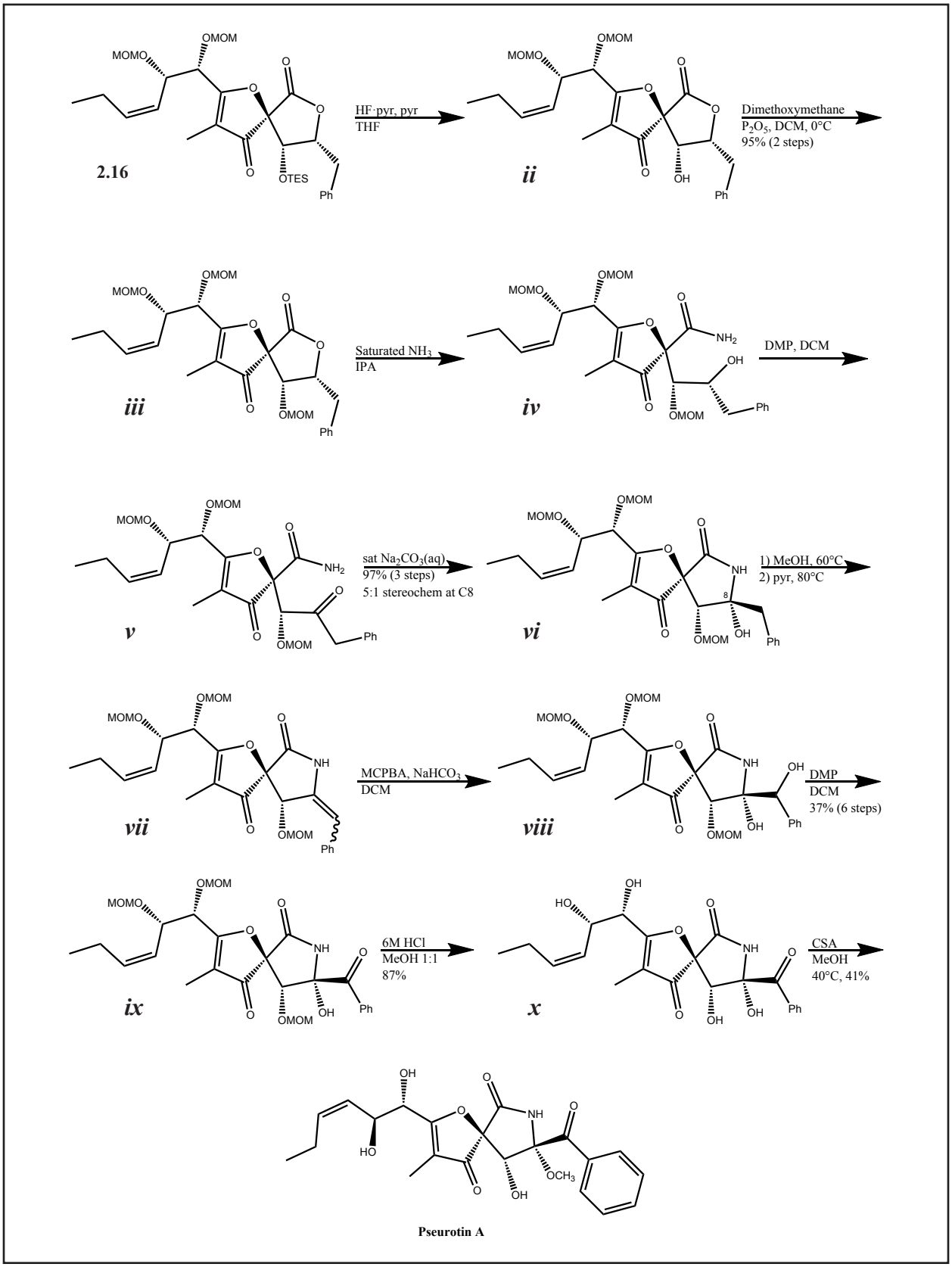
Tadano moved on to create the tail of the molecule from D-glucose (scheme 2.15, compound **2.15**) in a stereoselective fashion in nearly the same way reported by Tamm[13a] (scheme 2.1), with the difference only in the protecting groups.

The two chiral pieces (**2.14 and 2.15**) were successfully coupled to give ***iii***, and a deprotection to give ***iv*** followed by a Dess-Martin oxidation caused the western ring to spontaneously cyclize to give ***v***, which after dehydration provided the spirocycle **2.16** (scheme 2.16). Tadano's group published their progress to **2.16** in 2002, and did not publish the synthesis of their target molecule, pseurotin A, until 2004.[26] In two papers that year, they finished the synthesis of both pseurotin A and azaspirene.



Scheme 2.16: Tadano closing the spirocycle of pseurotin A (end of 2002 effort)

Tadano's 2004 route[26] completed the synthesis of pseurotin A (scheme 2.17). It was initiated with **2.16**, but the protecting group was changed from TES to MOM in ***ii*** and ***iii***. This was done because the TES group was not stable enough in the aminolysis conditions that followed. By introducing ammonia in isopropanol, Tadano was able to open the lactone and form the amide ***iv***, which upon oxidation to give ***v*** and with the application of mild base closed to the desired lactam



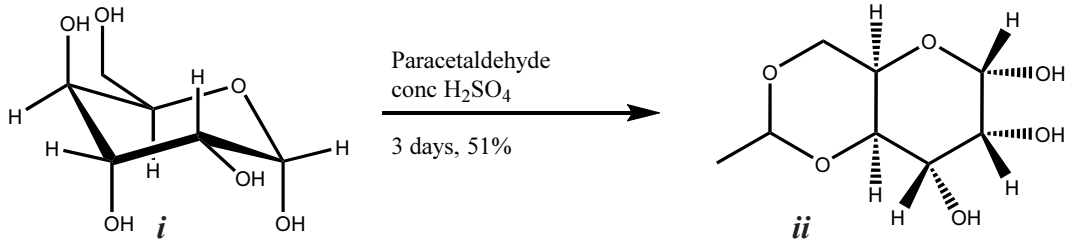
Scheme 2.17: Tadano completion of pseurotin A

vi with a five-fold preference for the desired stereochemistry. However, the stereochemistry was not critical in ***vi***, because in the next step the stereocenter was destroyed by eliminating the labile hydroxyl group to give ***vii***. The necessary stereocenter was reintroduced in a stereoselective fashion creating an epoxide that was opened in a stereoselective fashion to form diol ***viii***. The secondary alcohol was oxidized to form the desired benzoyl group ***ix***, the MOM protecting groups were removed with HCl to give ***x***. The hydroxy group at C-8 was then selectively replaced with a methoxy group to give pseurotin A, but with a low yield for the last step. The total yield for pseurotin A, excluding the steps for which there is no yield information (the first few steps), is 1.2% over 37 steps. Though the synthetic scheme is novel and uses cheap and common D-glucose, it is not an efficient route.

2.2.1.3 The Osada Route to Pseurotin A

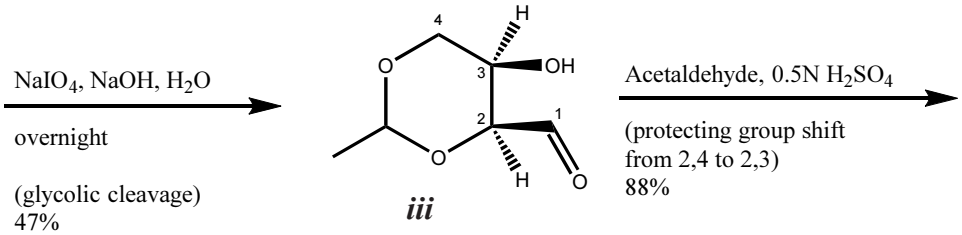
Osada and coworkers published[32] their synthesis of pseurotin A in 2003, and were the first to achieve the total synthesis of the molecule. Osada's route is derived from his group's 2002 synthesis of azaspirene.[33] Their strategy began with the synthesis of the (S,Z)-3-hexenyl-1,2-diol tail portion of pseurotin A from D-glucose using Tamm's[13] method (scheme 2.18, **2.1**).

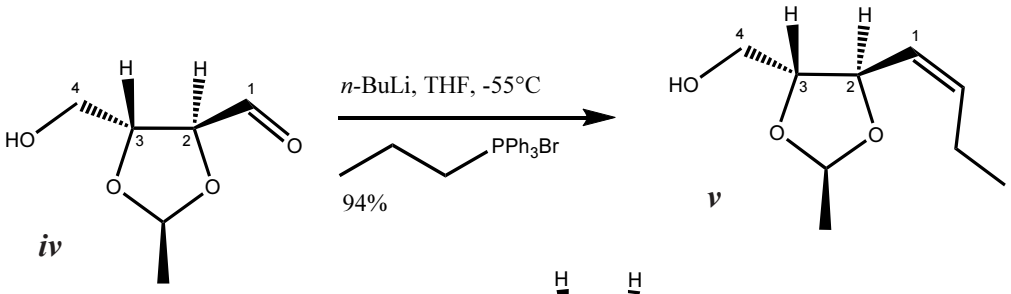
Next, Osada's group employed a Sharpless asymmetric dihydroxylation with methyl (E)-pent-2-enoate (***i***) to install a vicinal diol in a stereoselective fashion, providing ***ii*** (scheme 2.19). The vicinal diol was protected as the acetonide to give ***iii***, and an aldol condensation was completed

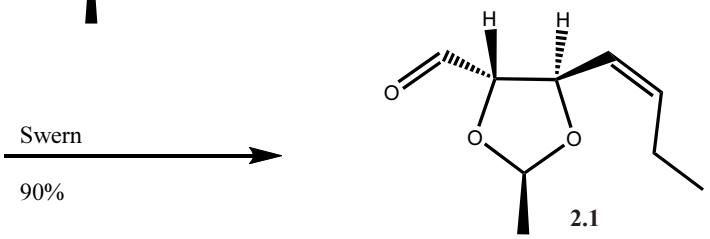


D-Glucose

This part is entirely from one paper:
Dolder, Helv. Chim. Acta, **1990**, 73, 63-68[13a]







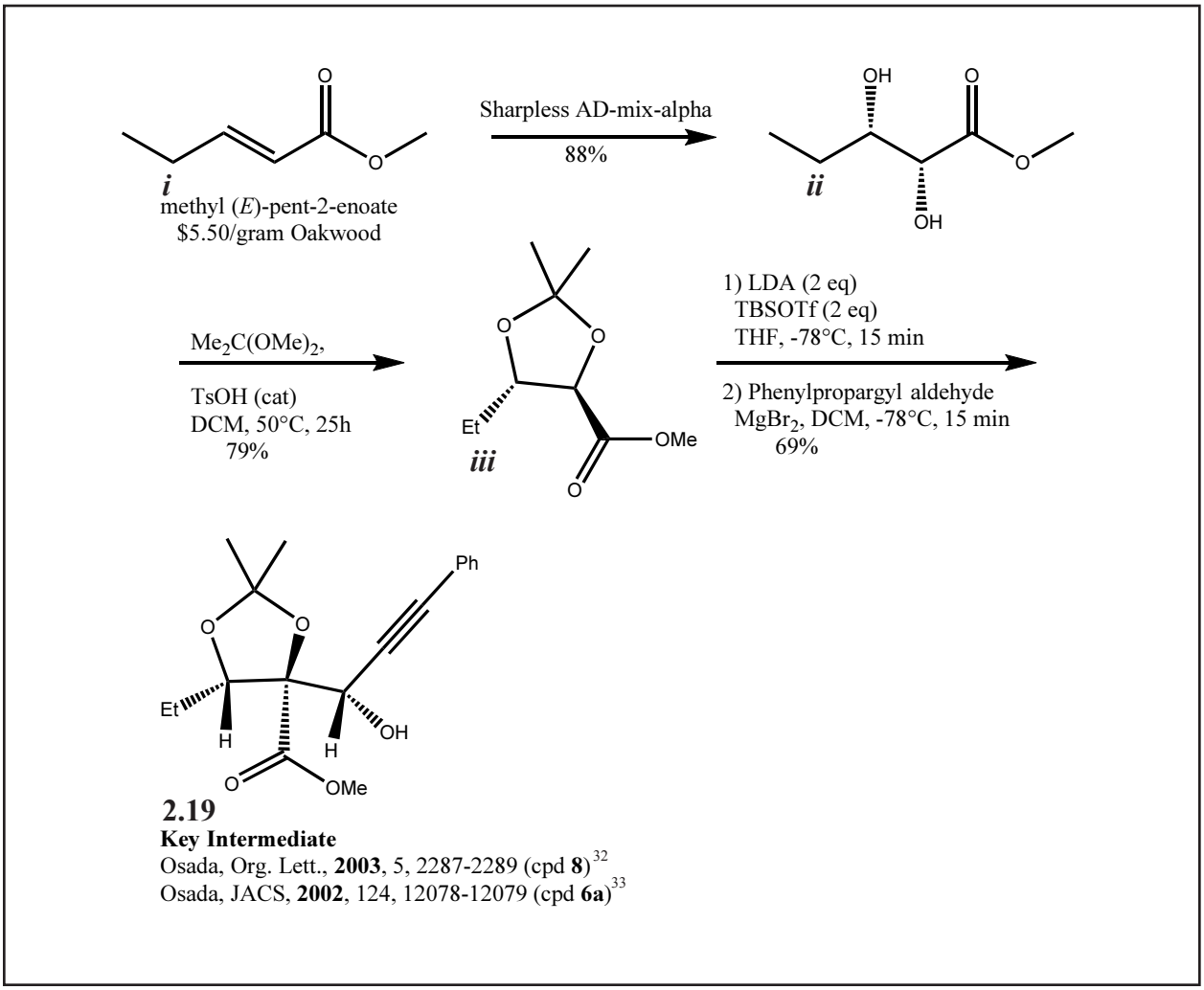
Key Intermediate

Tamm, Helv. Chim. Acta, **1990**, 73, 63-68 (cpd **11**)[13a]
Tadano, Heterocycles, **2002**, 58, 57-61 (cpd **7**)[25]
Osada, Org. Lett., **2003**, 5, 2287-2290 (cpd **3**)[32]
Tadano, Bull. Chem. Soc. Jpn., **2004**, 77, 1703-1716 (cpd **29**)[26b]
Tadano, Heterocycles, **2004**, 62, 161-166 (cpd **5**)[26a]

Scheme 2.18: Osada's synthesis of the tail of pseurotin A using Tamm's method

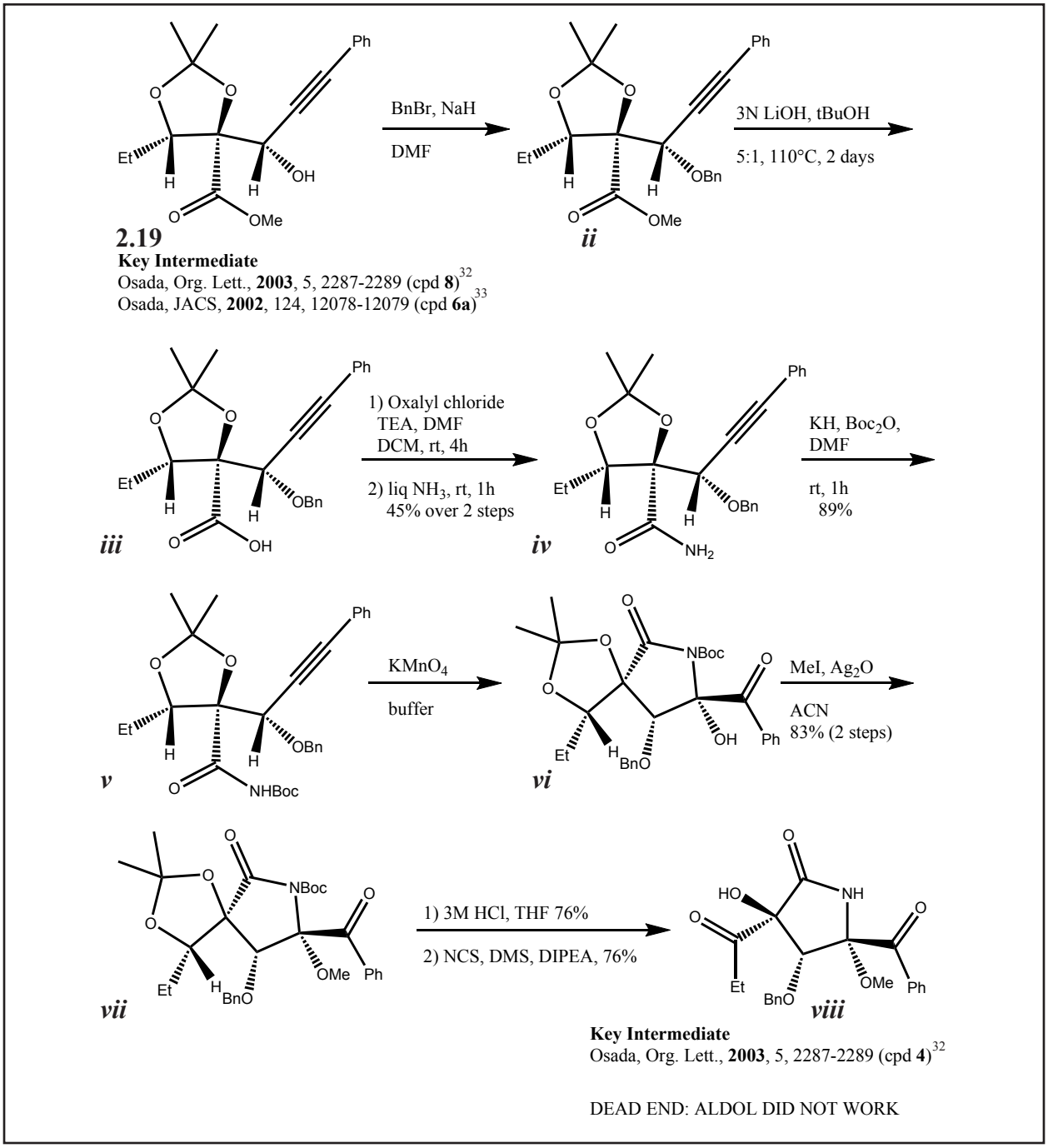
with phenylpropargyl aldehyde in modest yields to give **2.19** (scheme 2.19).

Next, the benzylation of the secondary alcohol gave ***ii*** (scheme 2.20). The ester was hydrolyzed yielding ***iii***, converted to an acid chloride with oxalyl chloride, then turned into an amide (***iv***) with liquid ammonia. This amide was BOC-protected to give ***v***, and then treated with potassium permanganate to give the diol. As the diol formed, it was oxidized to the dione by potassium permanganate, and the dione cyclized to form the desired lactam (***vi***) with the benzoyl group in the desired position (but with ambiguous stereochemistry). The hydroxyl group was methylated to give ***vii***, the acetal protecting group removed, and the secondary alcohol successfully



Scheme 2.19: Osada synthesis of a chiral intermediate toward the eastern ring of pseurotin A

and selectively oxidized with NCS yielding ***viii*** (scheme 2.20). The product of this scheme (***viii***) closely resembles the protected eastern ring of pseurotin A, and therefore appears to be a good target that was achieved in an elegant and fairly efficient synthesis. Unfortunately, the necessary aldol reaction between the tail and the eastern ring analog could not be accomplished despite

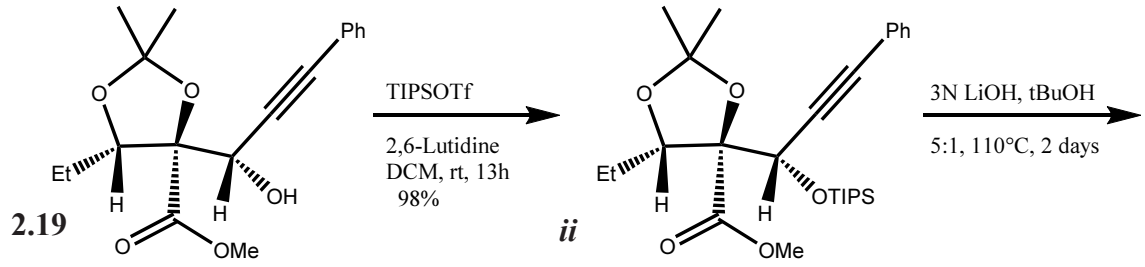


Scheme 2.20: Osada unsuccessful attempt toward the eastern ring of pseurotin A

several efforts, and so the route had to be adjusted.

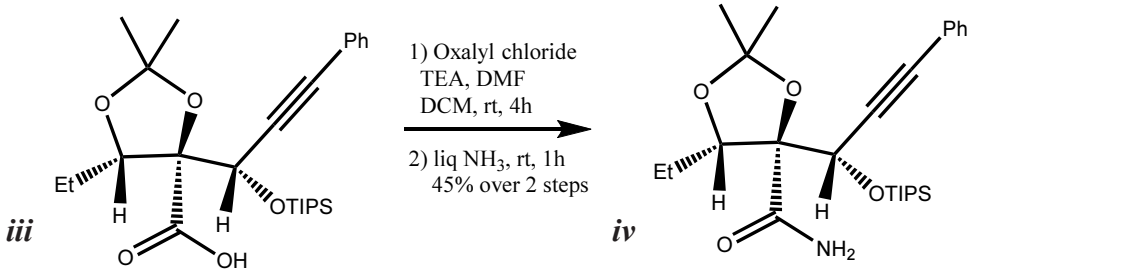
The next attempt began with the same intermediate, **2.19**, which was protected as its TIPS ether to give ***ii***, and then put through a similar sequence of steps; thus ester hydrolysis to give ***iii***, and acid chloride formation and amidation with liquid ammonia to produce ***iv*** (scheme 2.21). Then in deviation from the first attempt, the amide was treated with sodium hydride. The Osada group discovered when they used sodium hydride in an adaptation of the BOC protection step from scheme 2.20 (***iv*** to ***v***), it gave a promising side product which was further optimized to yield lactam ***v*** as shown in scheme 2.21. This lactam (***v***) was obtained from a nucleophilic attack on the triple bond under sonication, with the Z alkene as the predominant product. The acetonide protecting group was removed with TFA to give ***vi***, and the secondary alcohol oxidized with Dess-Martin periodinane, to give **2.21**. The structure of **2.21** is similar to Tadano's[25] compound **2.14** and Tamm's[13] compound **2.11**; all which are similar to the eastern ring of pseurotin A.

With the successful creation of **2.21**, an aldol reaction was successfully conducted between **2.21** and Tamm's[13] tail portion, **2.1**, resulting in ***iii*** (scheme 2.22.1). The reaction proceeded in modest yield, and the resulting secondary alcohol was oxidized with Dess-Martin periodinane to give ***iv***. Upon preparative TLC purification, the compound spontaneously cyclized and dehydrated to give spirocycle ***v***, a structure that is similar to the spirocyclic framework of pseurotin A. The exocyclic double bond on the lactam was then oxidized with DMDO to give the epoxide which was selectively opened to give ***i*** (scheme 2.22.2), and the secondary alcohol was oxidized with Dess-Martin periodinane to give ***ii***. The TIPS protecting group was successfully removed with TBAF to yield ***iii***. Finally, when the compound was treated with acetyl chloride and methanol, the

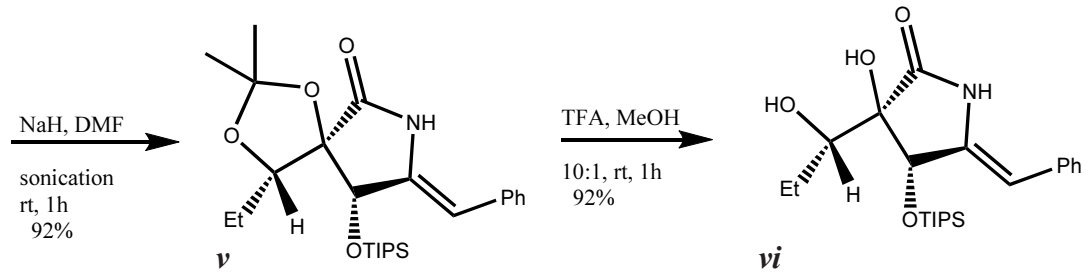


2.19 *ii*

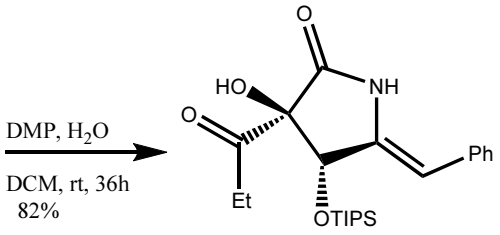
Key Intermediate
Osada, Org. Lett., **2003**, 5, 2287-2289 (cpd **8**)[32]
Osada, JACS, **2002**, 124, 12078-12079 (cpd **6a**)[33]



iii *iv*



v *vi*



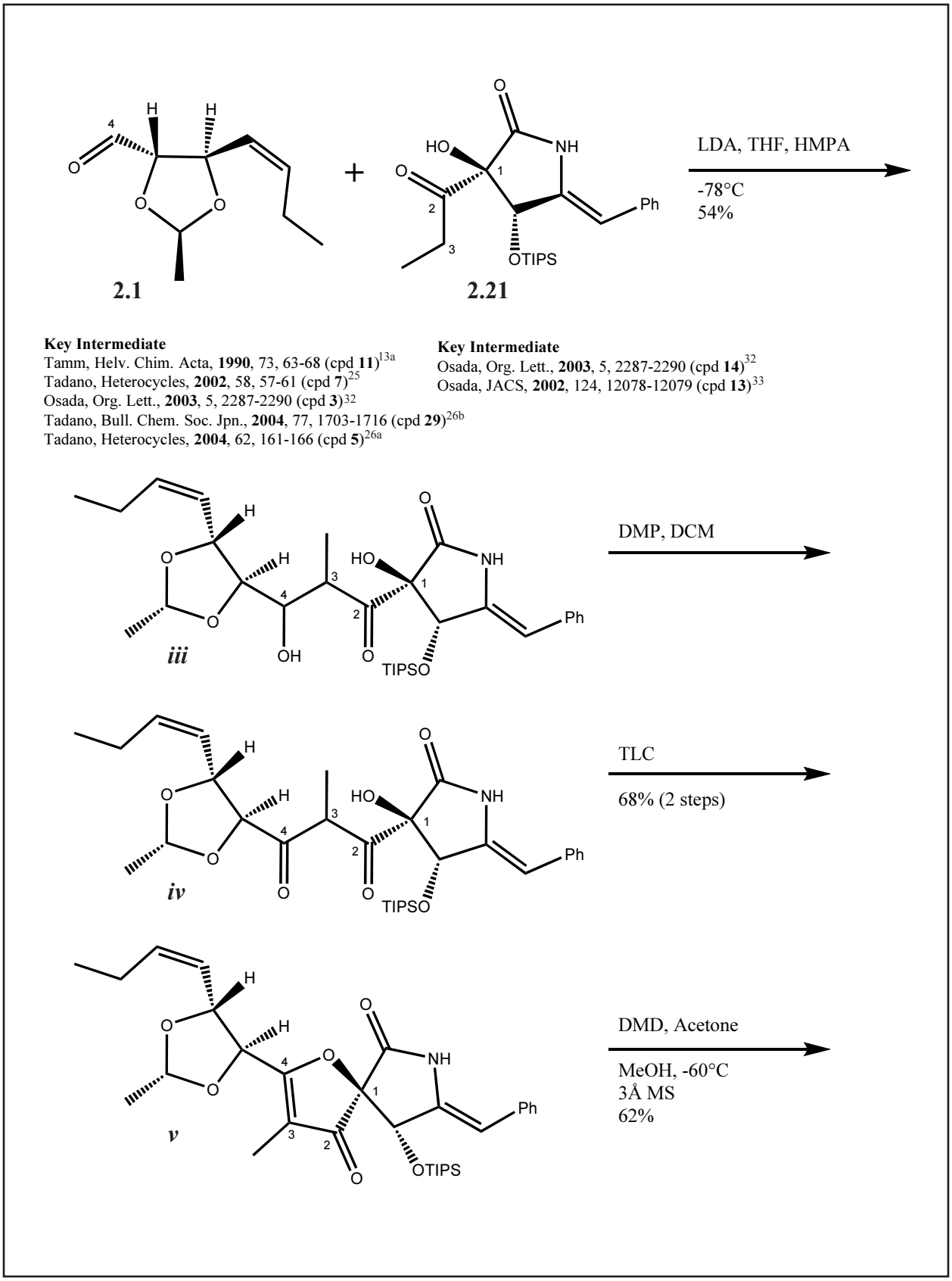
2.21

Key Intermediate
Osada, Org. Lett., **2003**, 5, 2287-2290 (cpd **14**)[32]
Osada, JACS, **2002**, 124, 12078-12079 (cpd **13**)[33]

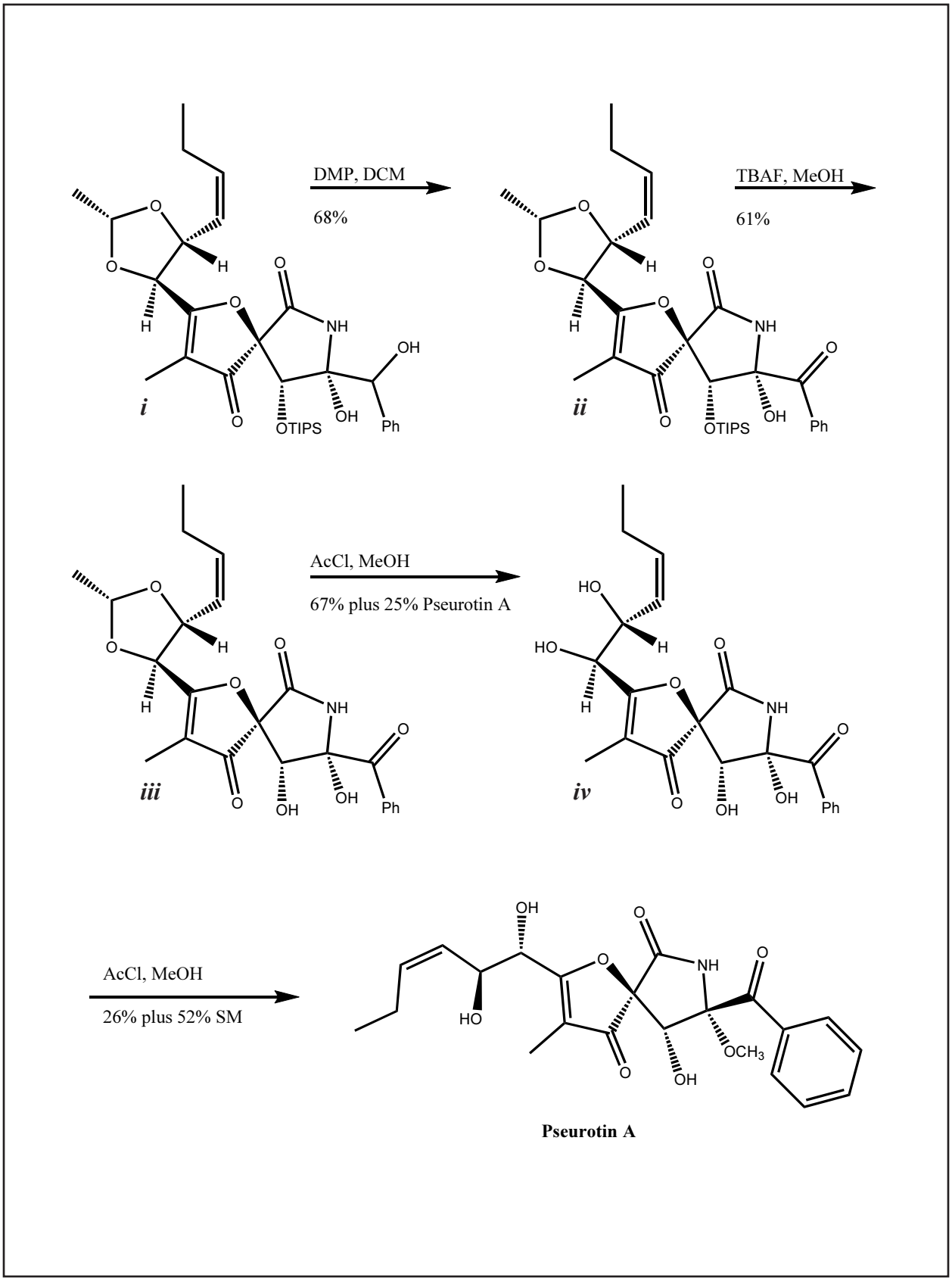
Scheme 2.21: Osada synthesis of a chiral intermediate toward the eastern ring of pseurotin A

acetal protecting group was removed to give ***iv***, and some of the product was methylated to give pseurotin A. The unmethylated product was subjected to the same conditions to give additional pseurotin A (scheme 2.22.2).

Osada's synthetic scheme illustrates the first complete synthesis of any pseurotin. It is, compared to the Tadano[25] scheme, relatively concise, and achieved pseurotin A in 19 steps in a 0.3% overall yield. This overall yield is lower than Tadano's, and the relatively costly starting material makes the route impractical for scale-up.



Scheme 2.22.1: Osada synthesis of pseurotin A, part 1



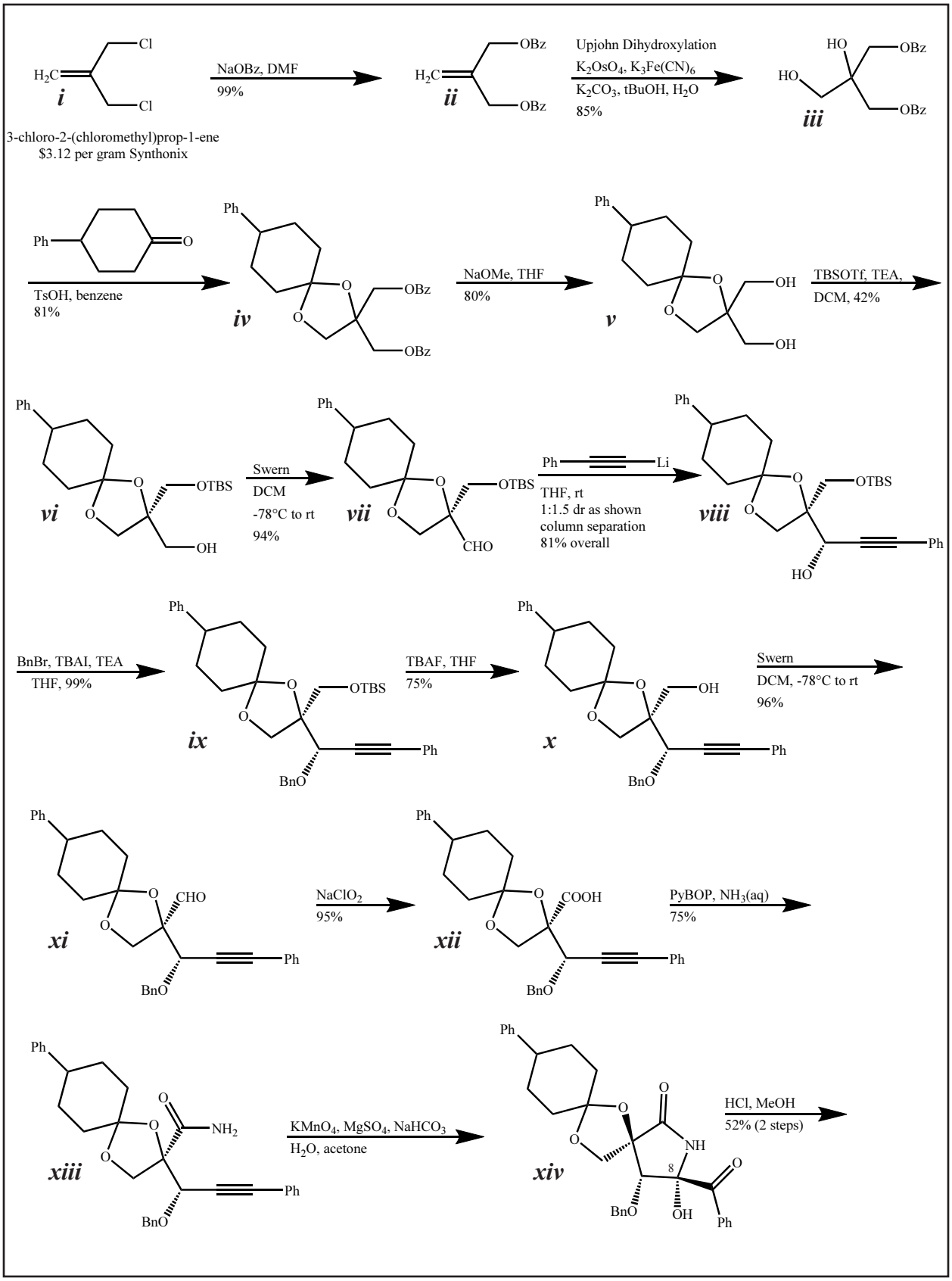
Scheme 2.22.2: Osada synthesis of pseurotin A, part 2

2.2.1.4 The Finney Scheme Toward Pseurotin A

In 2005, Mitchell and Finney published[34] their synthesis toward pseurotin A. Their research was focused on antifungal drug targets, and despite the previous reports of pseurotin A's lack of antifungal activity, because it was reported to be active against chitin synthase,[15] they decided to investigate an approach to construct it to further study its potential as an antifungal compound.

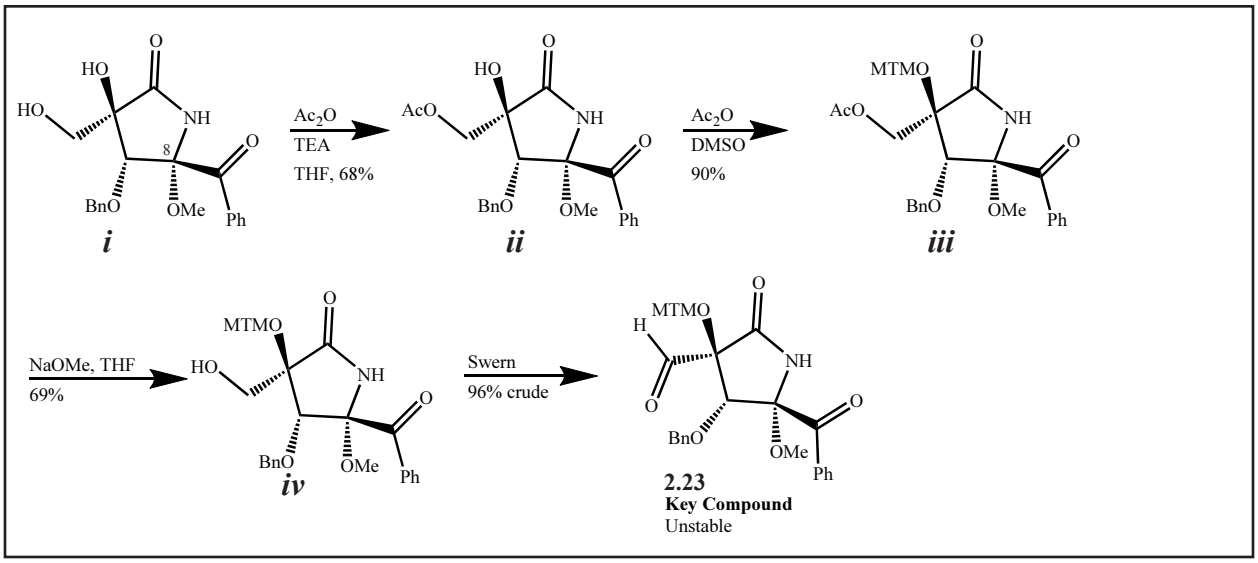
Their route was similar to the published approaches in that they synthesized the chiral tail using Tamm's strategy from D-glucose (scheme 2.1), and they created a lactam which closely resembled the eastern ring of the spirocycle. Similar to previous routes, they attempted to couple the tail and the lactam via an aldol reaction before closing the western ring of the spirocycle. However, their approach used a different nucleophile and electrophile for the aldol reaction (schemes 2.23.1 and 2.23.2). They envisioned a synthetic scheme which used an electrophilic aldehyde on the lactam portion of the molecule and a nucleophilic enolate created from a ketone on the tail; an electronic situation that is opposite of previous approaches. If those two pieces were coupled, it was expected that the cyclization of the western ring of the spirocycle would be relatively straightforward and the completion of the synthesis would allow further investigation of the biological activity of the molecule and its derivatives. However, the aldehyde portion of the molecule was unstable and was an ineffective electrophile. The enolate portion of the molecule would not couple, even with very simple aldehydes. Instead the enolate decomposed, evidently due to the lactam functionality.

Their approach began with the relatively expensive starting material ***i***, which when coupled



Scheme 2.23.1: Finney's first attempt toward pseurotin A

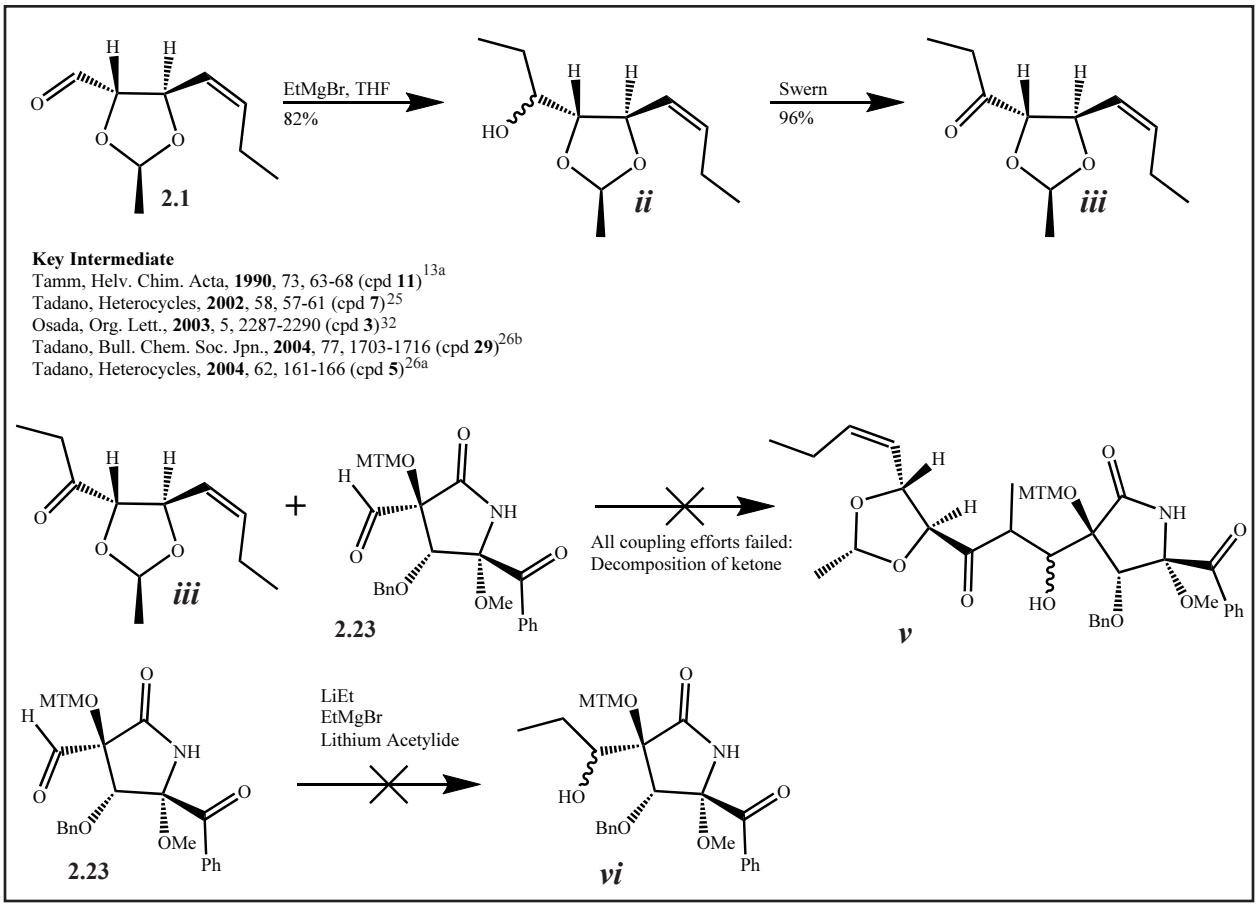
with sodium benzoate via a substitution reaction gave ***ii***, which was then dihydroxylated to give ***iii***. The newly-created diol was protected as an acetal (***iv***), and the benzoyl group was removed with sodium methoxide to give ***v***. They selectively TBS protected only one of the hydroxyl groups to give ***vi***, which aided in their isolation of ***vi*** from ***v***, albeit in relatively low yield. Oxidation to the aldehyde (***vii***) and addition of phenylacetylene yielded alcohol ***viii***. After shuffling protecting groups, ***viii*** was oxidized to aldehyde ***xi*** then carboxylic acid ***xii***. Next, the amide was created through a peptide coupling reaction between ammonia and ***xii***, to give ***xiii***. They accomplished a ring closing very similar to the Osada approach (scheme 2.20, ***v*** to ***vi***), with a dihydroxylation of the triple bond and its subsequent oxidation to the diketone with potassium permanganate. This spontaneously cyclized to yield the lactam with the desired stereochemistry (***xiv***), but purification failed at this point, presumably because of the reversibility of the ring closing in silica. In an attempt to resolve the difficulty with the purification of ***xiv***, acid and methanol were added to the crude material of ***xiv*** (scheme 2.23.1) to remove the acetal protecting group. These conditions also effected selective dehydration of the hydroxyl on C-8. The subsequent replacement of the dehydrated hydroxyl group by a methoxy group on C-8 occurred with the desired stereochemistry yielding ***i*** (scheme 2.23.2). This stereochemical change was possible because the eastern ring opened and the methoxy group on C-8 was labile. Because selective oxidation of the primary alcohol failed, the protecting group strategy had to be altered. Thus, the tertiary alcohol was protected as a methyl-thio-methyl group, and the successful Swern oxidation of the deprotected primary alcohol to the aldehyde was accomplished to give **2.23**, a compound which unfortunately turned out to be unstable.



Scheme 2.23.2: Finney's first attempt toward pseurotin A

To synthesize the tail for the molecule the authors followed the procedure first reported by Tamm[13] and his group in the 1990s. Once the Finney group had synthesized Tamm's key intermediate, **2.1** (the same intermediate used by every other synthesis of pseurotin A; see Tamm's scheme 2.1 for the synthetic steps), they then converted it to a ketone ***ii*** by the addition of ethylmagnesium bromide and then oxidized the secondary alcohol to give ***iii*** in excellent yield (scheme 2.24).

With their two advanced intermediates in-hand, they were unsuccessful in coupling the molecules, despite several different attempts. In fact, they report that any attempt at an addition reaction to lactam aldehyde **2.23** was unsuccessful.



Scheme 2.24: Finney second attempt toward pseurotin A

2.2.1.5 Summary of the Efforts Toward Pseurotin A

Though pseurotin A was discovered in 1976, it is still a relevant topic of research. The different reported results from the biological testing of the molecule demonstrate that different testing methodologies can have dramatically different results, and that subjecting complicated mixtures to purification, structural elucidation and biological testing is difficult. Furthermore, the range of biological activity attributed to pseurotin A underscores the promise in the further study of the pseurotins.

2.2.2 Synerazol

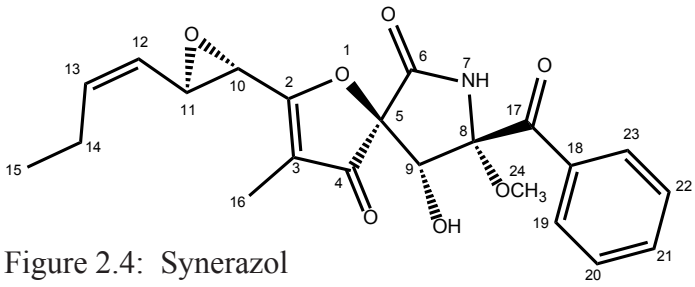
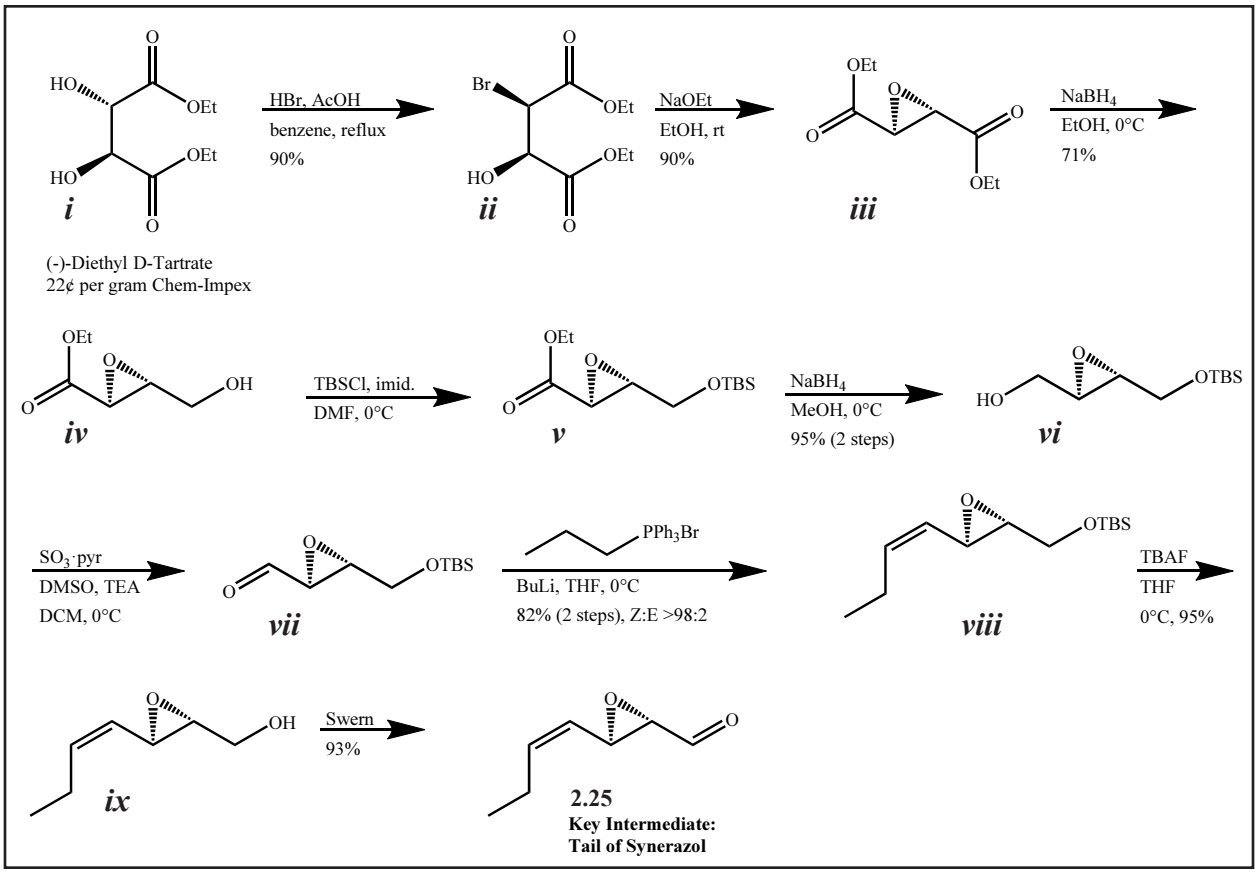


Figure 2.4: Synerazol

In 1991, Haneishi and coworkers isolated[35] the antifungal antibiotic synerazol from a broth of the Thai soil fungus *Aspergillus fumigatus*, the first time such a spirocyclic compound was isolated from an organism besides *Pseudeurotium ovalis* Stolk. In 2004, Igarashi[36] and coworkers published the absolute configuration of synerazol. In the same year, Oki[18] and colleagues discussed fluorinated derivatives of synerazol, and suggested that synerazol and pseurotin A were related in their biosynthesis; a hypothesis that seems likely given the similarities in their structures. Oki[18] reported that synerazol was not an antibiotic, but was antifungal and inhibited angiogenesis in chicken CAM assays. In 2009, Murata[19] and coworkers described the immunosuppresive activity of synerazol.

2.2.2.1 Osada Synthesis of Synerazol

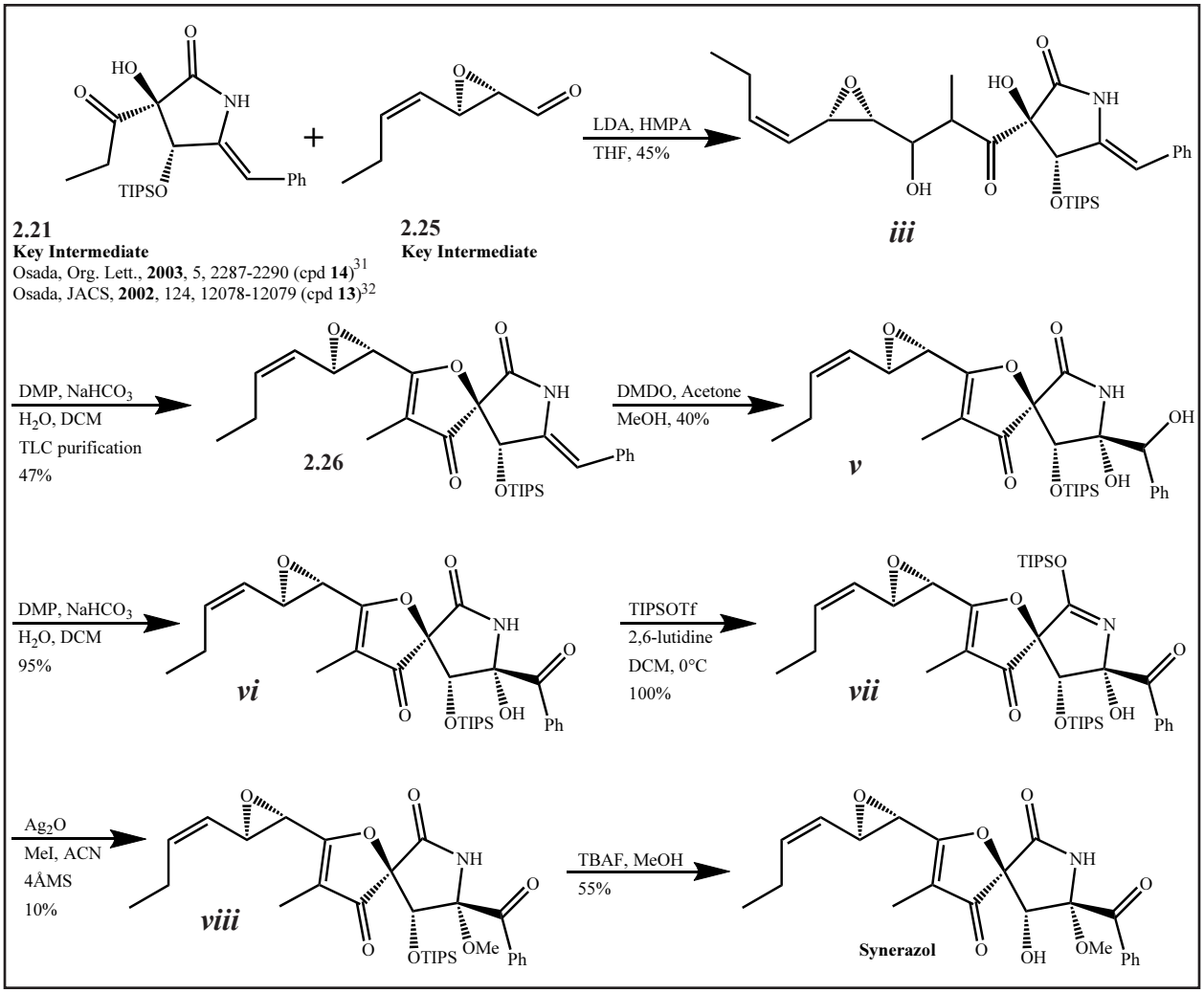
In 2005, Osada's[37] group published the first total synthesis of synerazol. In their first approach, they took advantage of the same chiral template, **2.21**, which they utilized for pseurotin A[32] and azaspirene[33] (see scheme 2.21 for details on the synthetic steps). The tail portion of the molecule was synthesized in a novel procedure from diethyl D-tartrate (scheme 2.25). This



Scheme 2.25: Osada synthesis of the tail of synerazol

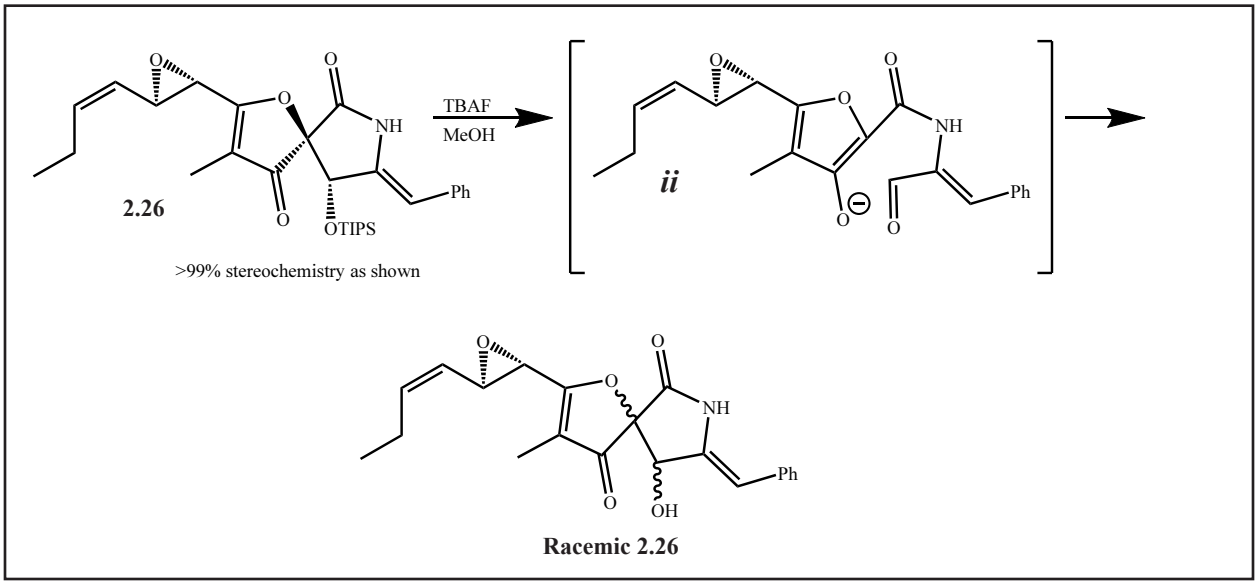
starting material, though it is the unnatural isomer, is relatively inexpensive and readily available. A standard selective bromination to give ***ii*** and an epoxidation to give ***iii*** was followed by the differentiation of the ester ends of the molecule through a single reduction to give ***iv***. A protection followed to give ***v***, and a reduction to give ***vi***. The unprotected hydroxy group was subjected to a Swern oxidation to provide the aldehyde (***vii***). A subsequent Wittig reaction formed the necessary Z-double bond and extended the carbon chain to give ***viii***. The deprotection of the other hydroxy group followed by another Swern oxidation finished the tail fragment **2.25** (scheme 2.25).

The new tail fragment was successfully coupled with the eastern spirocycle fragment, **2.21**, to yield ***iii*** (the synthesis of 2.21 can be found in scheme 2.21; the current procedure is reflected

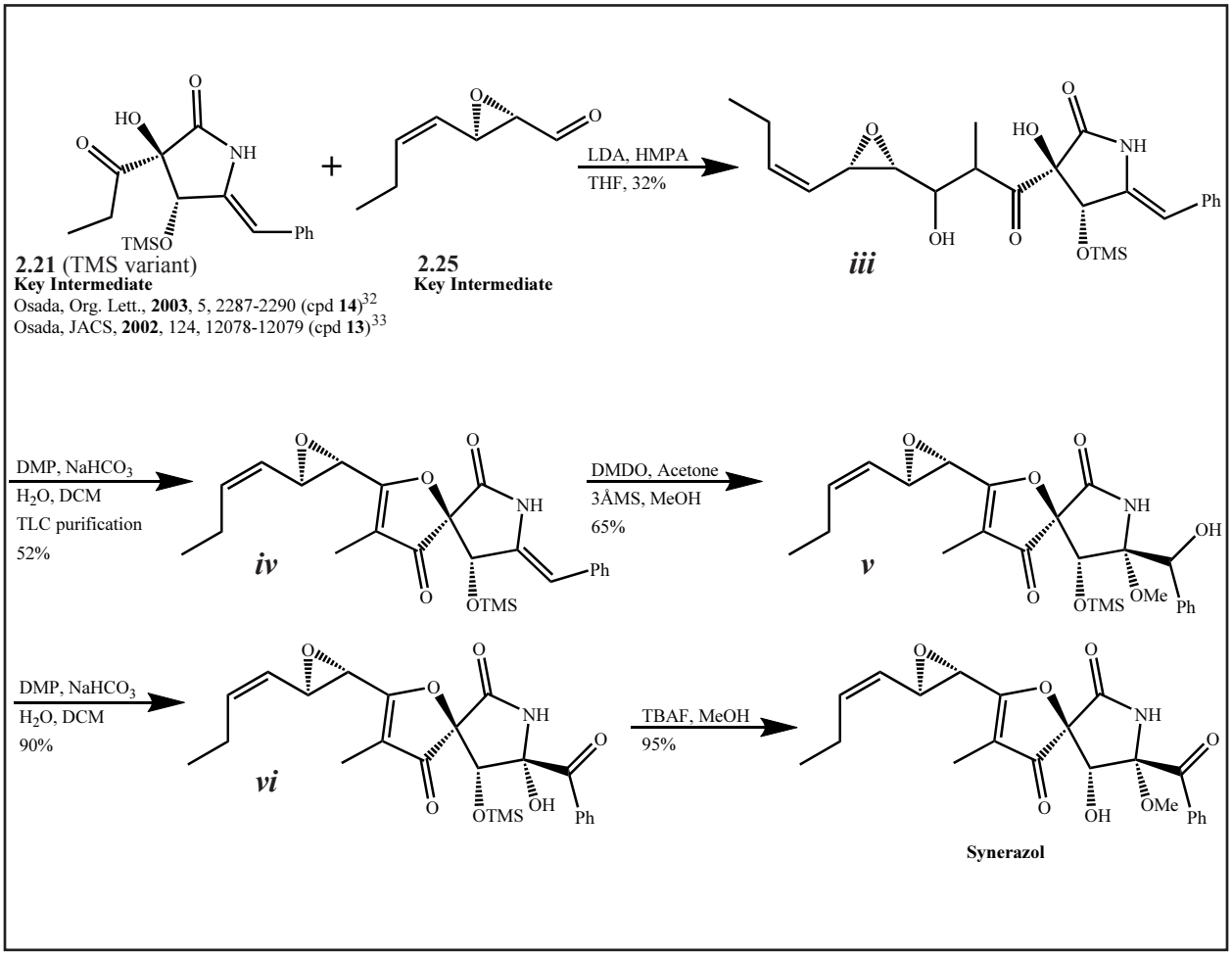


Scheme 2.26: Osada's first synthesis of synerazol

in scheme 2.26). A Dess-Martin oxidation of ***iii*** underwent a cyclization to the hemiacetal, which dehydrated to give **2.26** (scheme 2.26). The exocyclic double bond in the eastern lactam was selectively dihydroxylated with DMDO and water via the formation of an epoxide to give ***v***. An attempt to open the epoxide with methanol instead of water to create the methyl ether and provide ***viii*** in one step was unsuccessful. Instead, the benzoyl group was created by oxidation to give ***vi***, and efforts were made to methylate the remaining hydroxyl group. Since the carbonyl position was consistently methylated instead, its enol analog was first protected as a TIPS ether to give



Scheme 2.27: Osada's removal of a TIPS protecting group scrambled the stereochemistry of the spirocycle

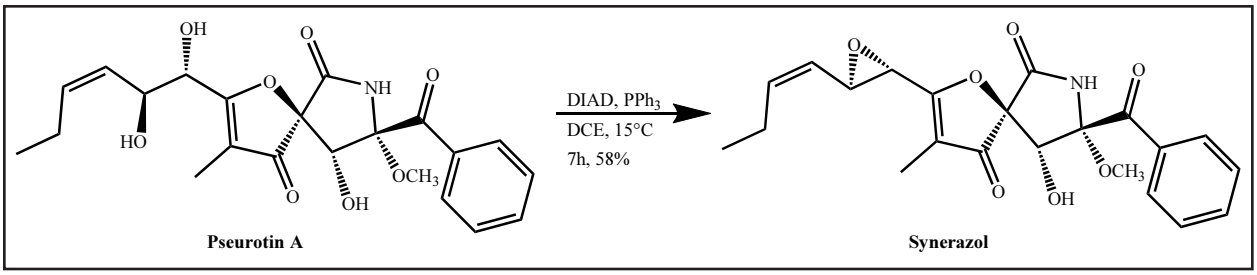


Scheme 2.28: Osada second synthesis of synerazol

vii. The yield of the methylation to give ***viii*** was low, presumably because the TIPS group was too sterically demanding. Final deprotection gave synerazol in a 0.6% overall yield over 17 steps (scheme 2.26).

The authors theorized that changing the TIPS protecting group to a smaller group would improve the yield by making substitution with methanol at the epoxide opening step possible, but removing the TIPS group on the advanced spirocyclic intermediate **2.26** proved impossible: the eastern ring instead opened to the conjugated aldehyde and furan moiety as shown in scheme 2.27, which as a consequence scrambled several stereocenters. To fix this dilemma, as shown in scheme 2.28, the authors backtracked to the original lactam intermediate **2.21**, and tested both a TES and TMS ether of **2.21** as a replacement. While both protecting groups were adequate, the TMS ether of **2.21** proceeded with higher yields overall. Opening of the epoxide with methanol proved successful in modest yields (scheme 2.28, ***iv*** to ***v***). With the problem solved, a Dess-Martin oxidation to give ***vi*** followed by a deprotection yielded synerazol, with a 1.3% overall yield over 15 steps (scheme 2.28).

The Osada route to synerazol demonstrated the importance of an approach toward the general spirocyclic core of the pseurotins, which can be applied to the synthesis of other pseurotins. Osada's group was able to apply their approach in the syntheses of pseurotin A[32] and azaspirene[33] to the synthesis of synerazol, which is proof of the general utility of their approach. Unfortunately, their overall yield is still too low for scale-up or adequate testing.



Scheme 2.29: Ninomiya synthesis of synerazol from pseurotin A via a Mitsunobu reaction

2.2.2.2 Ninomiya Synthesis of Synerazol

In 2008, Ishikawa and Ninomiya[38] synthesized synerazol and pseurotin E in a one-pot procedure from pseurotin A. Pseurotin A was chosen as their starting material because it is the most available pseurotin from its natural source, and because of its similarity to the intended products. Their approach shows the utility in transforming one pseurotin to another via chemical manipulation. Thus, with a simple Mitsunobu reaction the authors were able to create an epoxide from the diol of pseurotin A with the proper stereochemistry to give synerazol. The scarcity of the starting material makes this approach generally impractical. An efficient total synthesis is still necessary for further study of synerazol.

2.2.3 FD-838

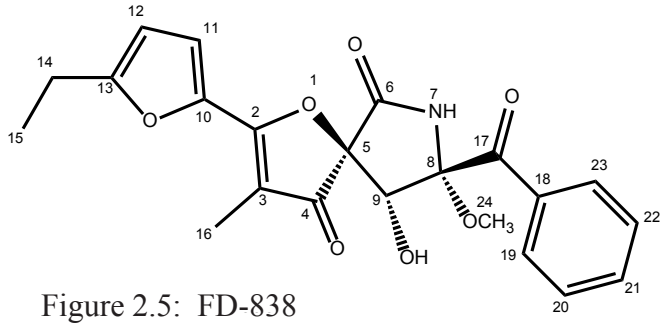


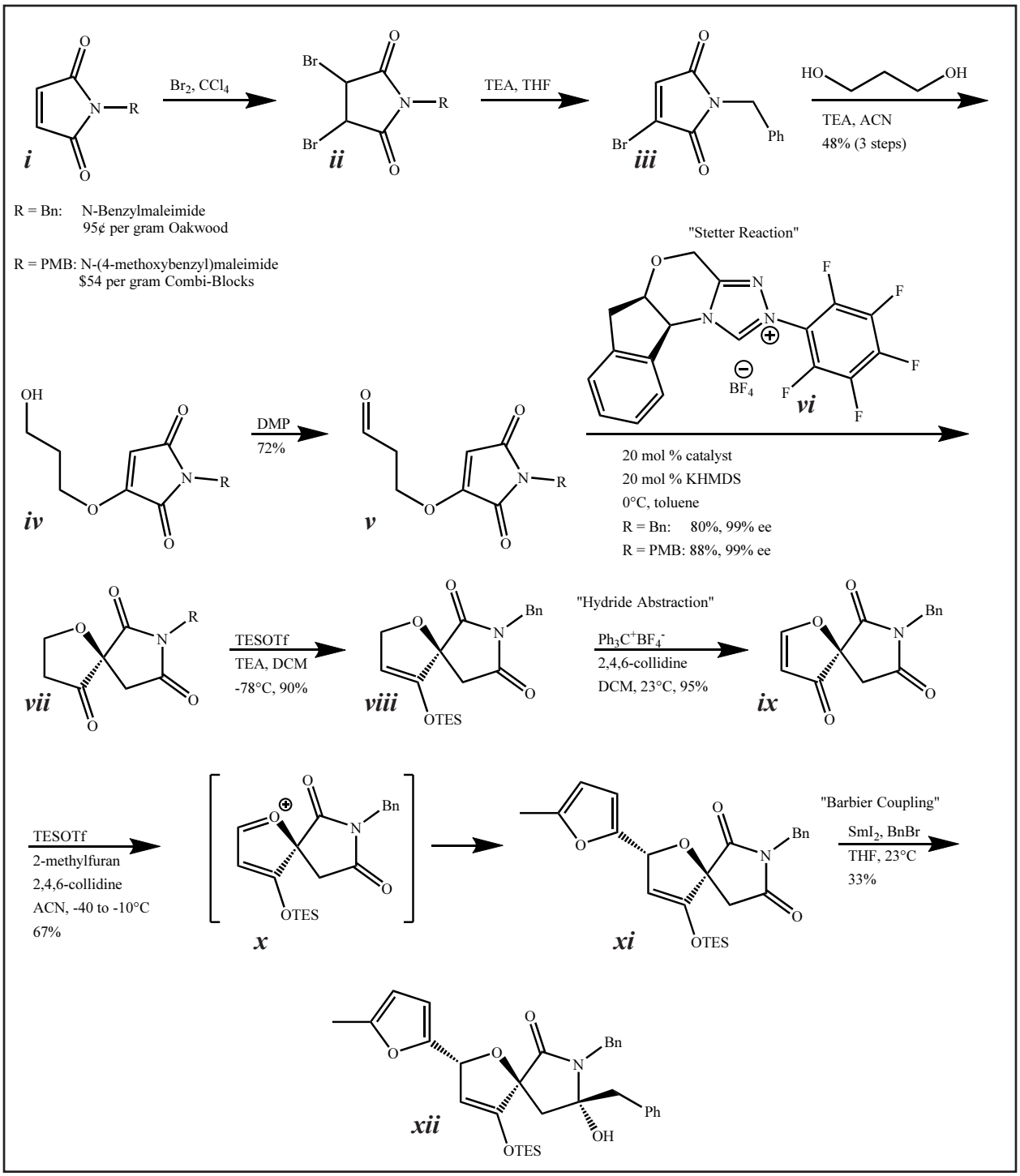
Figure 2.5: FD-838

Omura[39] and coworkers reported the isolation of FD-838 and its antibiotic effects in a patent application from 1987. It was not until 2008, however, that Orellana and Rovis[40] attempted further study of FD-838.

2.2.3.1 The Rovis Route Toward FD-838

The Rovis[40] route toward FD-838, completed in 2008, is different from previous pseurotin syntheses in that a common maleimide precursor was used. This precursor was manipulated into a spirocyclic core similar to FD-838 in 7 steps and a 24% overall yield. The key to Rovis' approach was a catalytic Stetter reaction which, with the use of an organocatalyst, proceeded with high selectivity and provided the desired chiral framework. However, though this in itself was an accomplishment, their compound lacked the necessary functional groups to complete the target, FD-838.

The route was initiated by dibrominating the N-protected maleimide ***i*** to give ***ii*** (scheme

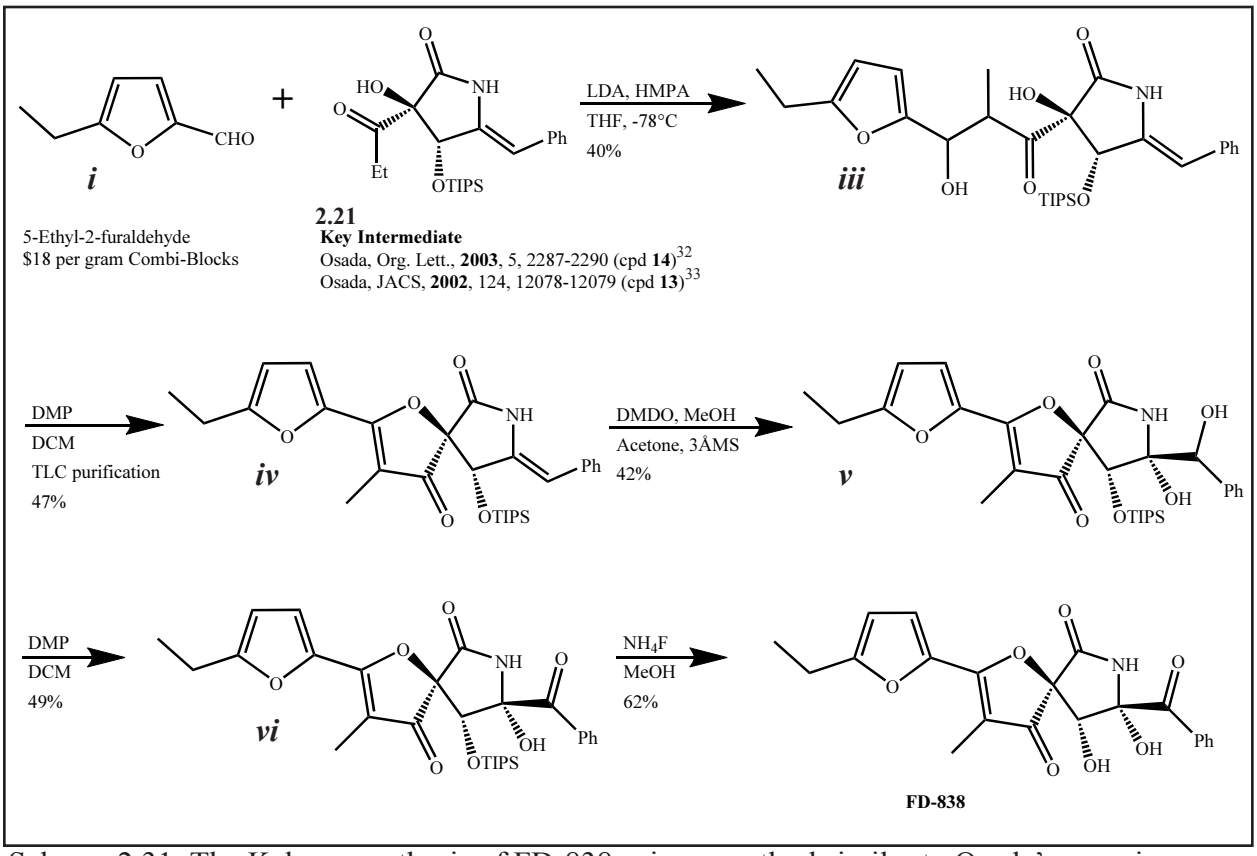


Scheme 2.30: The Rovis approach toward FD-838

2.30). The double bond was reintroduced by elimination under basic conditions to give ***iii***. Bomine was replaced with 1,3-propanediol to give ***iv***, in 48% yield from ***i***. The alcohol was successfully oxidized to the aldehyde (***v***) using Dess-Martin reagent. When ***v*** was subjected to Stetter conditions using the N-heterocyclic carbene organocatalyst ***vi*** (scheme 2.30), the spirocycle spontaneously closed with the proper stereochemistry to give ***vii***. Formation of the O-protected enolate ***viii*** with triethylsilyl triflate followed by a "hydride abstraction" with trityl and a bulky base formed the necessary double bond to give ***ix*** in excellent yield. In a similar fashion a resonance stabilized positive charge was induced with triethylsilyl triflate to give ***x***. This allowed 2-methylfuran to be added in a stereoselective fashion to give ***xi***. The final step in Rovis' scheme added a benzyl group selectively to the imide using "Barbier-type alkylation of succinimides," yielding ***xii***. While this effort did not result in successful synthesis of the target molecule, the authors did use what they learned from this effort in a synthesis of diastereomers of another pseurotin, cephalimysin A, which is discussed later.

2.2.3.2 The Kakeya Synthesis of FD-838

Soon after Rovis, in 2009, Kakeya,[41] Hayashi and coworkers published their total synthesis of FD-838. Using the Osada[32] route previously applied to azaspirene,[1,2,33] pseurotin A,[32] and synerazol,[37] they created the main chiral lactam **2.21** (scheme 2.21). Compound **2.21** was coupled with commercially available 5-ethyl-2-furaldehyde (***i***) via an aldol reaction to yield ***iii*** in modest yield (scheme 2.31). A Dess-Martin oxidation and purification by TLC on silica gel spontaneously



Scheme 2.31: The Kakeya synthesis of FD-838 using a method similar to Osada's azaspirene, pseurotin A and synerazol syntheses

closed the spirocycle to give ***iv***. A subsequent DMDO epoxidation of the exocyclic lactam double bond and opening of the epoxide with methanol gave ***v***. In contrast to their synthesis of synerazol, they retain the TIPS protecting group for the synthesis of FD-838. A further Dess-Martin oxidation gave ***vi*** and a deprotection gave FD-838 in 0.7% yield, over 12 steps.

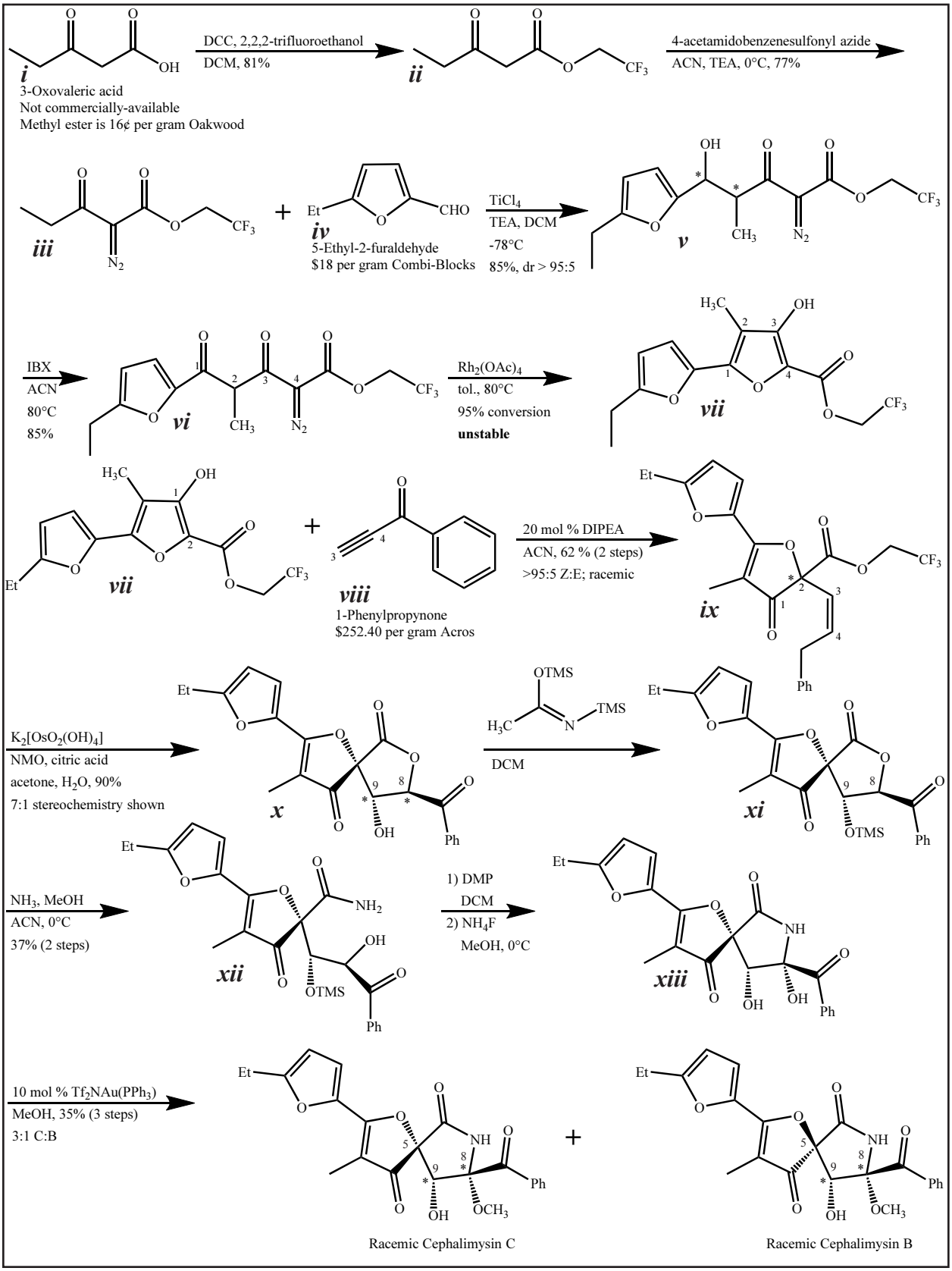
The success in utilizing the Osada route in creating multiple pseurotins demonstrates once again the general utility of their approach. Their yields, however, make the route unsuitable for scale-up.

2.2.3.3 The Svenda Route to Cephalimysins B and C (Epimers of FD-838)

In 2010, FD-838 and three of its epimers, cephalimysins B-D, were isolated from the fungus *Aspergillus fumigatus* extracted from a fish, *Mugil cephalus*, and characterized by the Yamada[42] group. Yamada reported that FD-838 had an IC_{50} of 56.0 μM against murine P388, 60.8 μM against HL-60, 70.5 μM against L1210 and 73.0 against KB cancer cell lines. Additionally, the Yamada group reported that cephalimysin B was not effective against any cell line, and cephalimysins C and D were not effective against the L1210 or KB cell lines, but each was effective against the other cell lines similarly to FD-838: Cephalimysin C had an IC_{50} of 53.5 μM against P388 and 58.4 μM against HL-60; Cephalimysin D had an IC_{50} of 51.1 μM against P388 and 48.7 μM against HL-60.

In 2017, Svenda[43] and coworkers published their synthesis of racemic cephalimysins B and C, which are epimers of FD-838 (scheme 2.32). Their route contains novel chemistry, but it is unselective, and therefore the stereochemistry is mixed at carbons 5, 8 and 9 in their products. However, this gave the authors a way to synthesize cephalimysins B and C, because they differ in their stereochemistry at C-5, which is the spirocenter of the molecule, as well as C-8 and C-9 as compared to FD-838.

Svenda's group started by creating the western ring of cephalimysins B and C, beginning with 3-oxovaleric acid ***i*** (scheme 2.32), which is not readily commercially available, but which presumably can be created from an ester that is available (for example, the methyl ester). They next made the trifluoroethyl ester ***ii*** from the acid ***i***. A diazo group was introduced to give ***iii***, in



Scheme 2.32: The Svenda route to racemic cephalimysin B and C

order to facilitate the future ring closing step that would give ***vii***. Compound ***iii*** was coupled with an expensive ethyl furfural ***iv*** via a Mukaiyama type aldol reaction to give ***v***. After an oxidation with IBX to give ***vi***, Svenda's group was able to close the ring with a rhodium catalyst to give ***vii***, similar to the methods described by Park.[44] A conjugate addition of the furan ring on the triple bond of expensive 1-phenylpropynone ***viii*** formed a racemic spirocenter ***ix***, and left the exocyclic double bond in Z-formation. A dihydroxylation of the double bond with potassium osmate(VI) dihydrate spontaneously caused the eastern ring of the spirocycle to close to form lactone ***x***, with the stereochemistry shown at C-8 and C-9 favored in a ratio of 7:1. After a TMS protection of the secondary alcohol to give ***xi***, a ring opening was accomplished with ammonia to give ***xii***. After oxidation with Dess-Martin reagent, the ring closed to form lactam ***xiii***. The hydroxyl group at C-8 was then replaced with a methoxy group using a gold catalyst, providing cephalimysin C in a 2.4% overall yield and cephalimysin B in a 0.8% overall yield over 12 steps; both racemic around C-8 and C-9. The authors were also able to synthesize six derivatives, also racemic, with substitutions in the benzoyl group at C- 8 and at the tail of the molecule (Figure 2.6). It is an approach with useful features as discussed, but the reported route is not stereoselective.

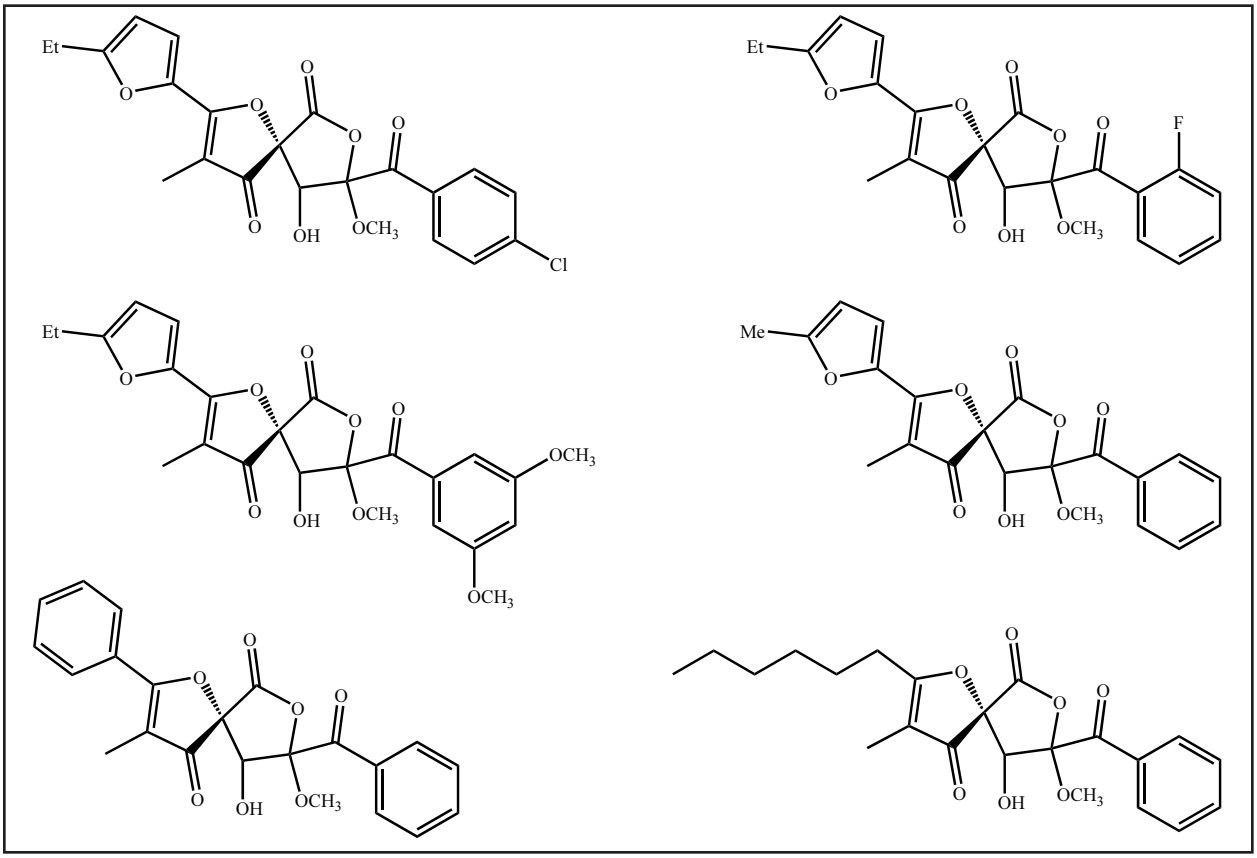


Figure 2.6: Svenda derivatives of Cephalimysins A, B and C

2.2.4 Cephalimysin A

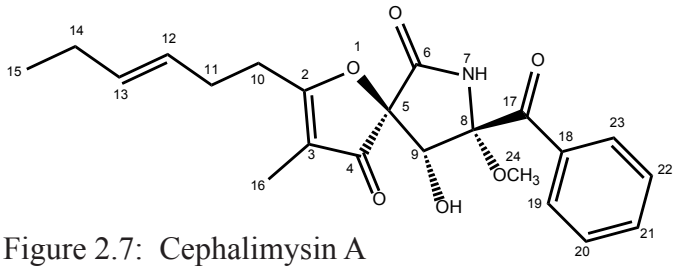
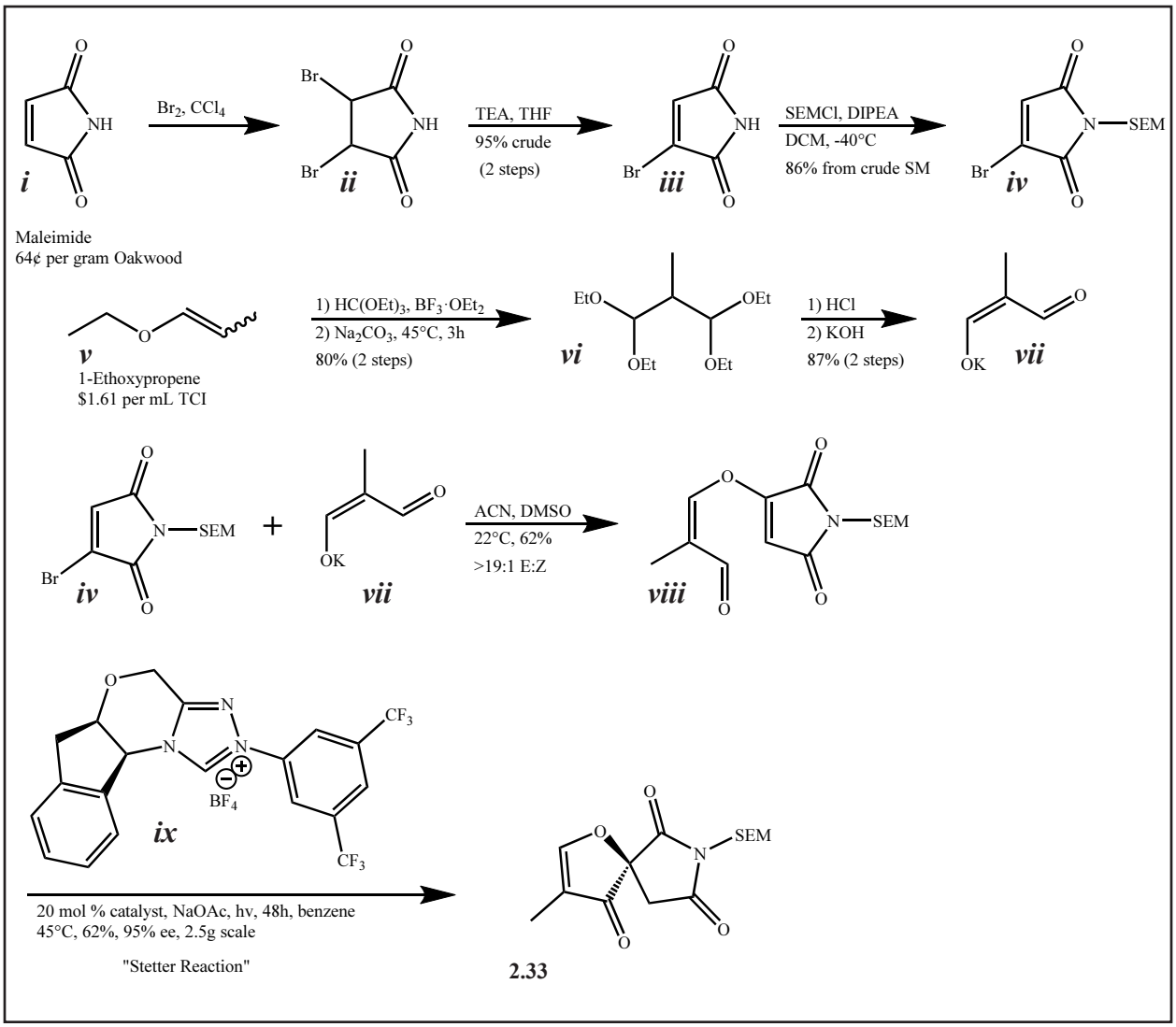


Figure 2.7: Cephalimysin A

In 2007, cephalimysin A was isolated[45] from the fungus *Aspergillus fumigatus* extracted from a fish, *Mugil cephalus*, and structurally characterized by the Yamada group. They found it to have cytotoxic activity against the murine P388 leukemia cell line and the human HL 60 leukemia cell line, with an IC_{50} of 15.0 and 9.5 nM respectively.

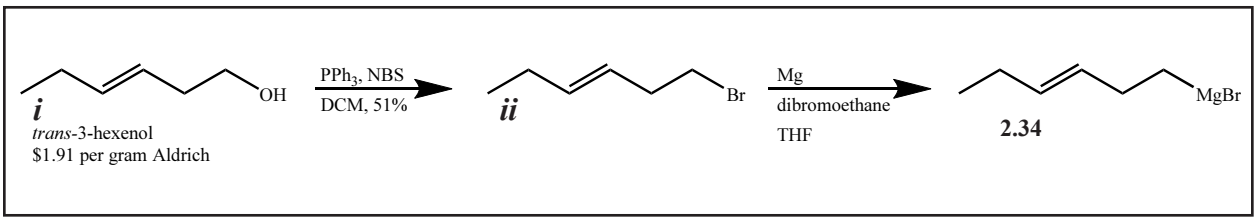
2.2.4.1: The Rovis Synthesis of Three Epimers of Cephalimysin A

In 2013, Lathrop and Rovis[46] published their synthesis of several diastereomers of cephalimysin A, using the same novel Stetter reaction technique they used in their effort toward FD-838.[39] They were not successful in synthesizing cephalimysin A itself, but they did confirm the structure of cephalimysin A by analyzing the spectra of their synthesized epimers as compared to the natural product. Their approach is also important because it builds upon the work they did toward the synthesis of FD-838, and demonstrates the utility of their catalytic Stetter reaction, as well as a "Barbier-type" coupling which introduces the benzoyl group to the molecule in a unique way.



Scheme 2.33: Rovis effort toward Cephalimysin A, Part 1

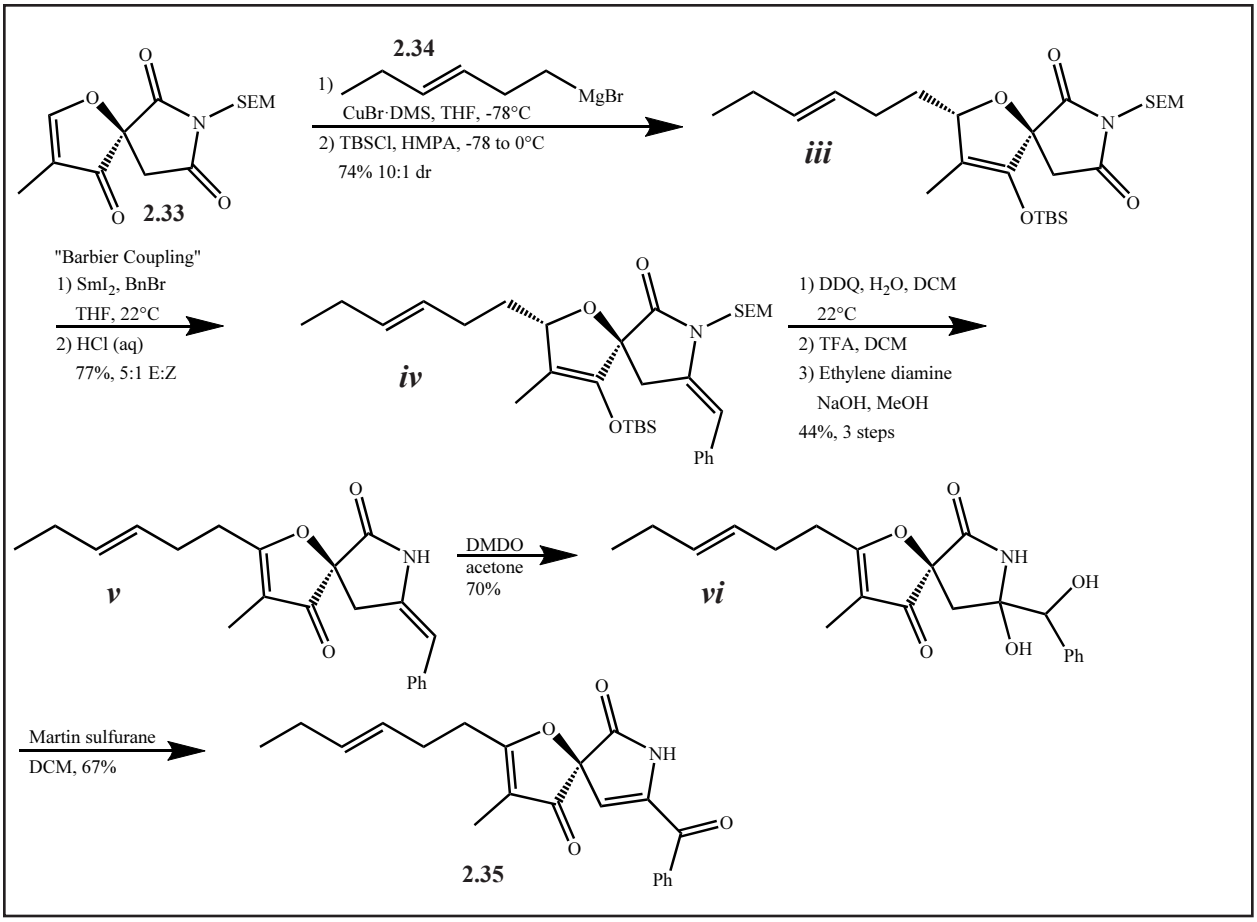
The Rovis effort toward cephalimysin A began similarly to their effort toward FD-838[40] (scheme 2.30), with the bromination of cheap, readily-available maleimide ***i*** and its O-coupling with a 1,3-dialdehyde enolate ***vii*** created efficiently from 1-ethoxypropene to yield ***viii*** (scheme 2.33). With their Stetter substrate ***viii*** in hand, they successfully screened a number of catalysts and conditions to optimize a N-heterocyclic carbene catalyzed reaction which coupled the aldehyde carbon with the spirocyclic carbon to close the spirocycle and form the framework of the molecule **2.33** (scheme 2.33).



Scheme 2.34: Rovis Cephalimysin A, Part 2

As a first effort in adding the necessary functional groups to the spirocyclic framework of **2.33**, Rovis created a Grignard reagent by replacing the hydroxyl group of *trans*-3-hexenol with a bromine to form **2.34** (scheme 2.34).

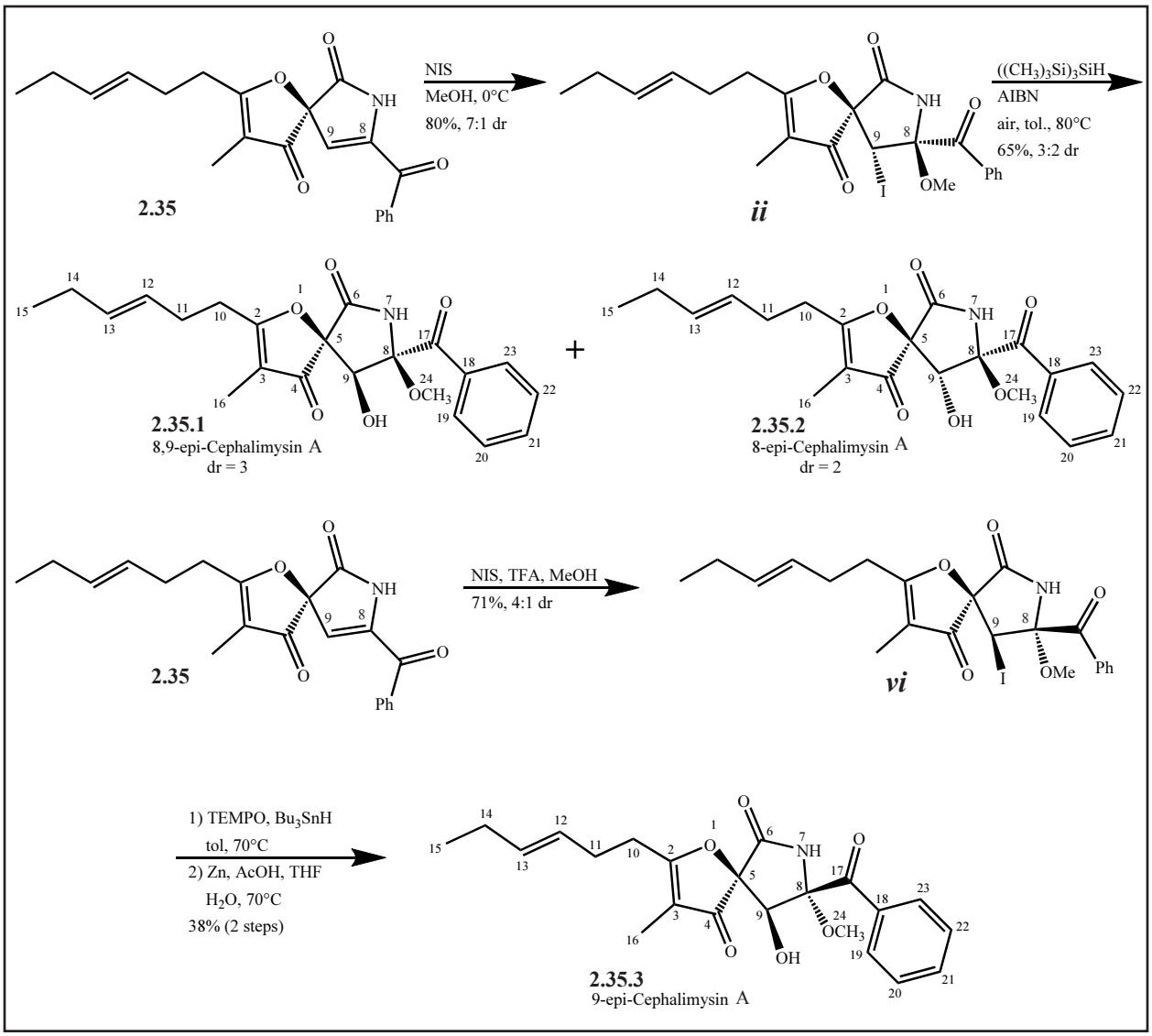
The Grignard reagent **2.34** was coupled with **2.33** in a conjugate addition reaction, which was trapped in its enolate form by the addition of TBSCl to give ***iii*** (scheme 2.35). In the next step, a "Barbier-type" coupling selectively replaced the necessary imide carbonyl with an unsaturated



Scheme 2.35: Rovis Cephalimysin A, Part 3

benzyl group to give ***iv***, with excellent yield and selectivity. The authors reported that had the ketone in ***iii*** not been protected as the TBS enolate, the Barbier-type coupling would have proceeded with reduced selectivity. In the coupling, the samarium chelated between the halogen and the benzyl group, and this reactive species immediately added selectively to the desired imide carbonyl, presumably via the least-hindered π-face. The addition of HCl in the second step dehydrated the resulting alcohol to form the exocyclic double bond seen in ***iv***. Once the protecting groups were removed to form ***v***, the vicinal diol ***vi*** was introduced via an epoxide with DMDO, which then opened to the corresponding diol with water. The tertiary alcohol in ***vi*** was then dehydrated to form a double bond and the secondary alcohol oxidized in good yields with Martin sulfurane, to provide **2.35** (scheme 2.35).

Subsequent epoxidation of the double bond in lactam **2.35** was invariably unsuccessful (scheme 2.36). Instead, **2.35** decomposed, or its tail was oxidized. To resolve this problem, the double bond was instead treated with NIS to create the iodonium ion, which was then easily opened with methanol to form the desired iodo-substituted compound ***ii*** with the proper stereochemistry. Nakamura type dehalogenative hydroxylation of ***ii*** yielded two epimers of cephalimysin A in a 60/40 ratio (**2.35.1** and **2.35.2**), over 20 steps with an overall yield of 0.8% and 0.5%, respectively. As shown in scheme 2.36, the final epimer, **2.35.3**, was synthesized from **2.35** by changing the conditions of the iodination reaction. TFA was introduced in an effort to reverse the stereochemistry of the epoxide and as a consequence reverse the stereochemistry at C-8 and C-9 compared to the previous two epimers. The opposite stereochemistry was selectively introduced in this way to provide ***vi***, but when the iodine was replaced with a hydroxyl group to yield **2.35.3**



Scheme 2.36: Rovis Cephalimysin A Scheme 4

the stereochemistry at C-8 was still incorrect as compared to the natural form of cephalimysin A, creating epimer **2.35.3** in 20 steps with an overall yield of 0.7%.

Despite that cephalimysin A was not synthesized with correct stereochemistry, Rovis' route is still quite a useful illustration because it demonstrates the utility of their Stetter reaction protocol in its ability to form the required spirocycle in a stereoselective fashion. Additionally, several creative ways of introducing the necessary functional groups are presented, in relatively high yields.

2.2.5 Berkeleyamide D

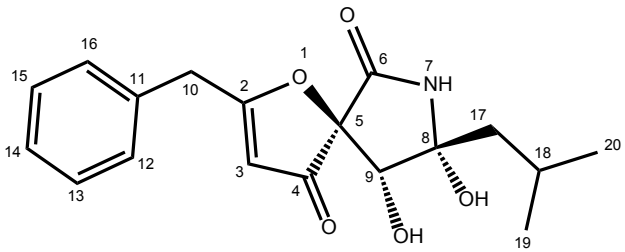


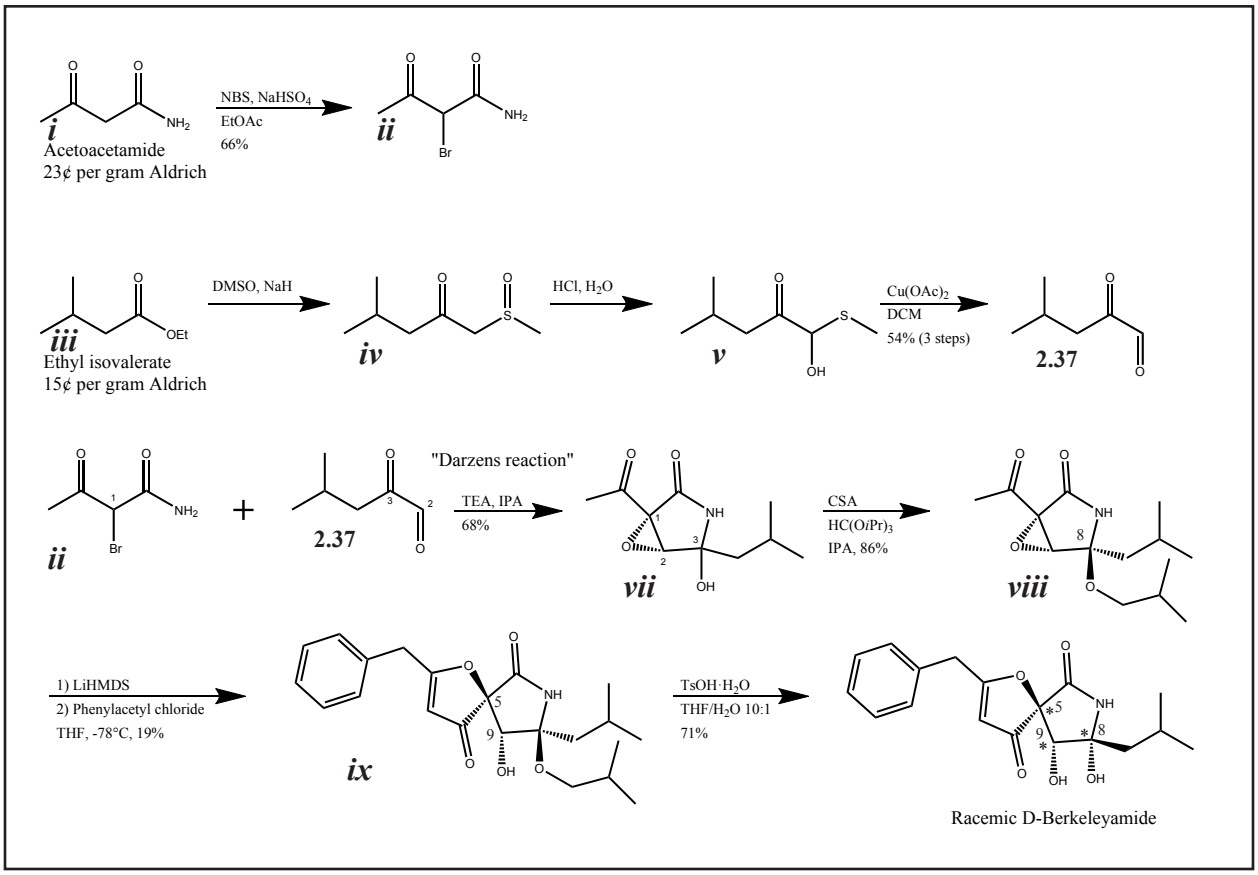
Figure 2.8: Berkeleyamide D

In 2008, Patacini[47] and coworkers isolated several novel amide compounds from the fungus *Penicillium rubrum* Stoll, which they found in the Berkeley Pit Lake System superfund site near Butte, Montana. Berkeleyamide D was reported to inhibit MMP-3 and caspase-1, which Patacini reports may inhibit tumor growth.

2.2.5.1 The Tsubaki Route to Racemic Berkeleyamide D

In 2014, Tsubaki[48] and coworkers synthesized racemic berkeleyamide D, and updated their synthetic strategy in 2016.[49] In their approach, they adapt some classic chemistry to create their starting materials, and bring the resulting two molecules together in a "Darzens reaction," to form the eastern lactam of berkeleyamide D with the proper functional groups and in good yield, but not in a stereoselective fashion.

Tsubaki's first approach,[48] (scheme 2.37), began with acetoacetamide ***i***, which was brominated with NBS to give ***ii***. Next, ethyl isovalerate ***iii*** was subjected to a set of reactions which the authors neglect to cover in great detail, but which involve the deprotonation of DMSO,

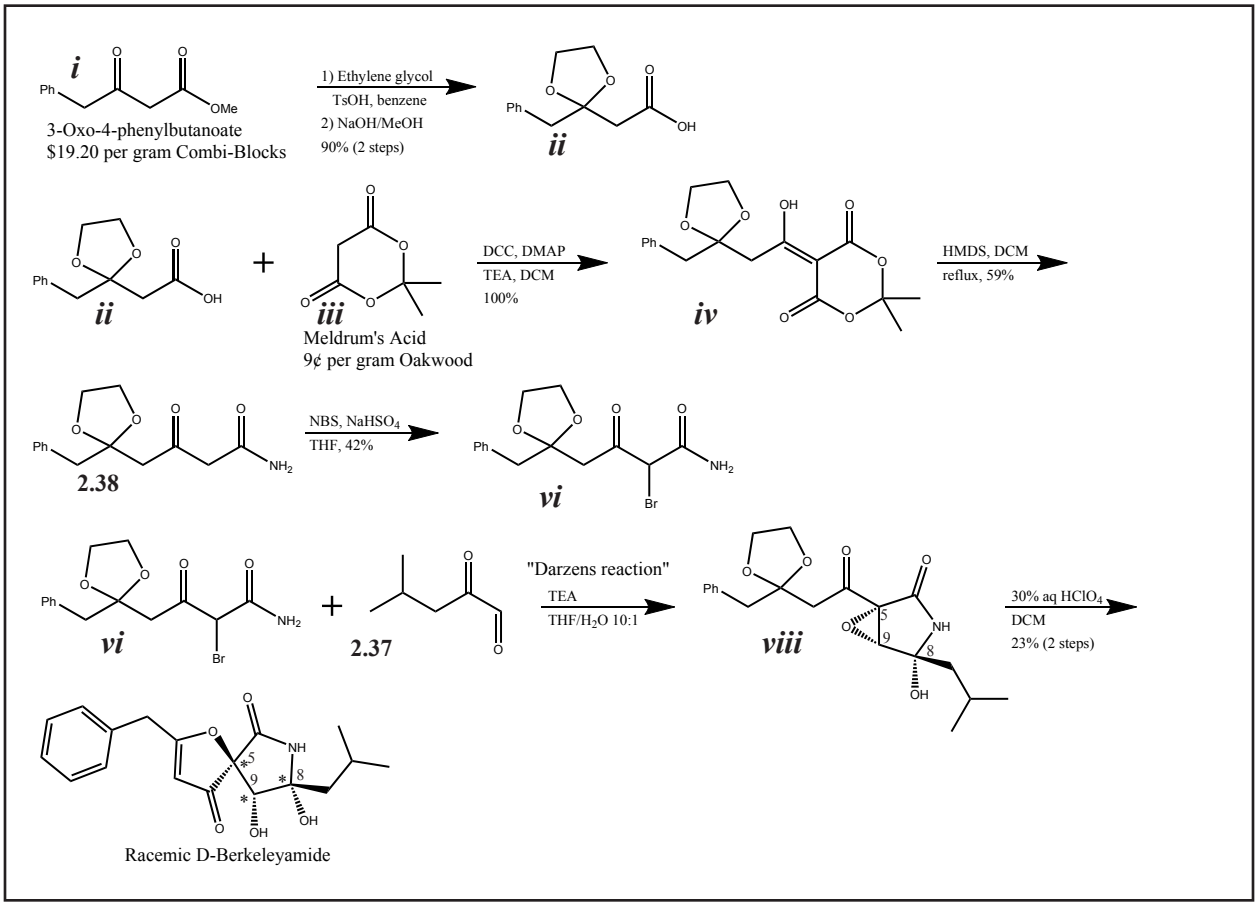


Scheme 2.37: The first Tsubaki route to racemic Berkeleyamide D (2014)

its attack on and displacement of the ester group ***iv***, and then a transfer in strong aqueous acid of the oxygen from the sulfur to the adjacent carbon to give ***v***. Copper removed the sulfur atom to form aldehyde **2.37**.

With their two starting materials, **2.37** and ***ii*** in hand, Tsubaki's group subjected both to weak base to zip the two molecules together in a "Darzens reaction," starting with the deprotonation of the relatively acidic middle carbon of the 1,3-dicarbonyl, and its attack on the aldehyde of the 1,2-dicarbonyl. The negatively charged oxygen from the addition then attacked the center carbon of the 1,3-dicarbonyl to displace the bromine and to form a racemic epoxide. The amide nitrogen then attacked the ketone of the 1,2-dicarbonyl, resulting in a lactam (***vii***) that is very similar to

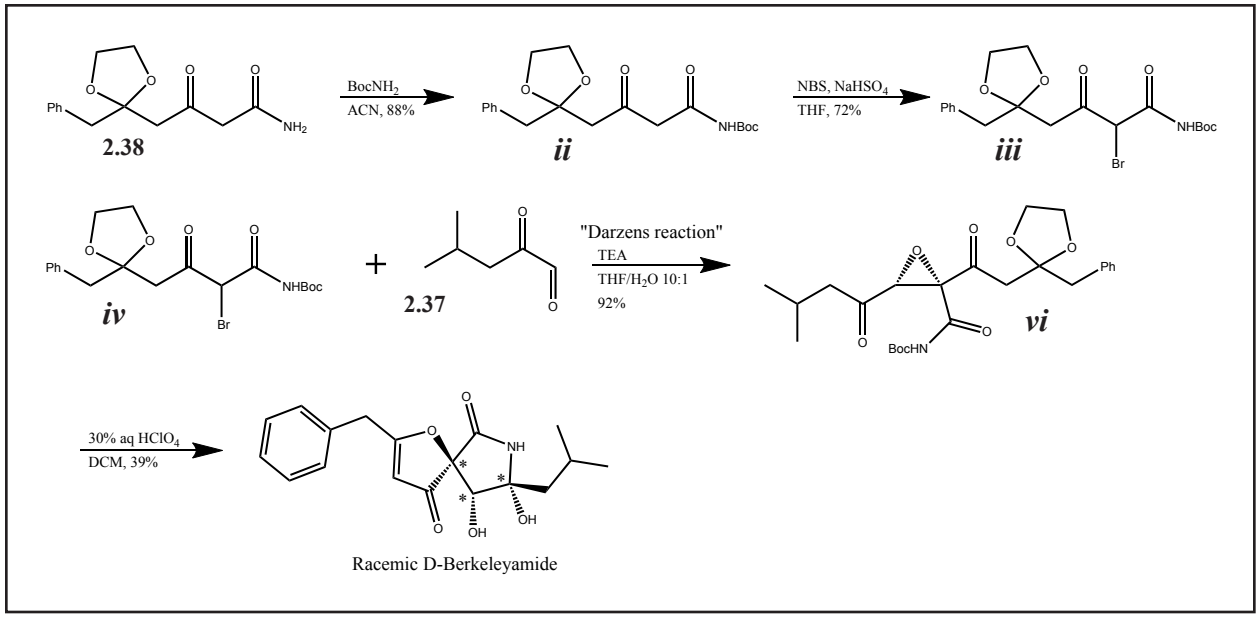
the eastern lactam structure of the berkeleyamide spirocycle. The alcohol was replaced by an isobutyl ether via dehydration to give ***viii***, racemic around C-8. The exocyclic ketone α-carbon was deprotonated and coupled with phenylacetyl chloride. The resulting 1,3-dicarbonyl was immediately deprotonated to form a negatively charged oxygen which then opened the epoxide, and closed the western ring of the spirocycle yielding ***ix*** as shown, with the stereochemistry at C-5 and C-9 determined by the stereochemistry of the original epoxide. The manipulation in this step might be a useful adaptation in routes toward other pseurotins, and was somewhat similar to the Margaretha[69] ring closing step, which will be discussed in the Bergdahl strategy to azaspirene. Finally, the isobutyl ether was replaced with a hydroxy group in a non-selective fashion, to form racemic D-berkeleyamide in 8 steps with a 2.8% overall yield.



Scheme 2.38: The second Tsubaki route to racemic Berkeleyamide D (2016)

Tsubaki's second attempt in the synthesis of berkeleyamide D in 2016,[49] (scheme 2.38), was an effort at improving the overall yield compared to their original strategy. The starting material was changed to include a phenylacetyl group (***i***), and the ketone was masked as a ketal (***ii***). The carboxylic acid in ***ii*** was coupled to Meldrum's acid (***iii***) to form ***iv***. An amidation was then performed with hexamethyldisilazane to give **2.38**, and subsequent bromination with NBS gave ***vi***. Compound ***vi*** was then coupled with **2.37** in a Darzens reaction, to form unstable epoxide ***viii***, racemic at C-5, C-8 and C-9. The final step removed the ketal to form the enol with perchloric acid in water, which cyclized to form the western ring of the spirocycle and produce berkeleyamide D. Tsubaki's second attempt yielded racemic berkeleyamide D in a 3% overall yield over 8 steps. This second approach did not significantly improve the overall yield, nor reduce the number of steps.

In their final effort[49] (scheme 2.39), Tsubaki's group used the same starting material **2.38**,

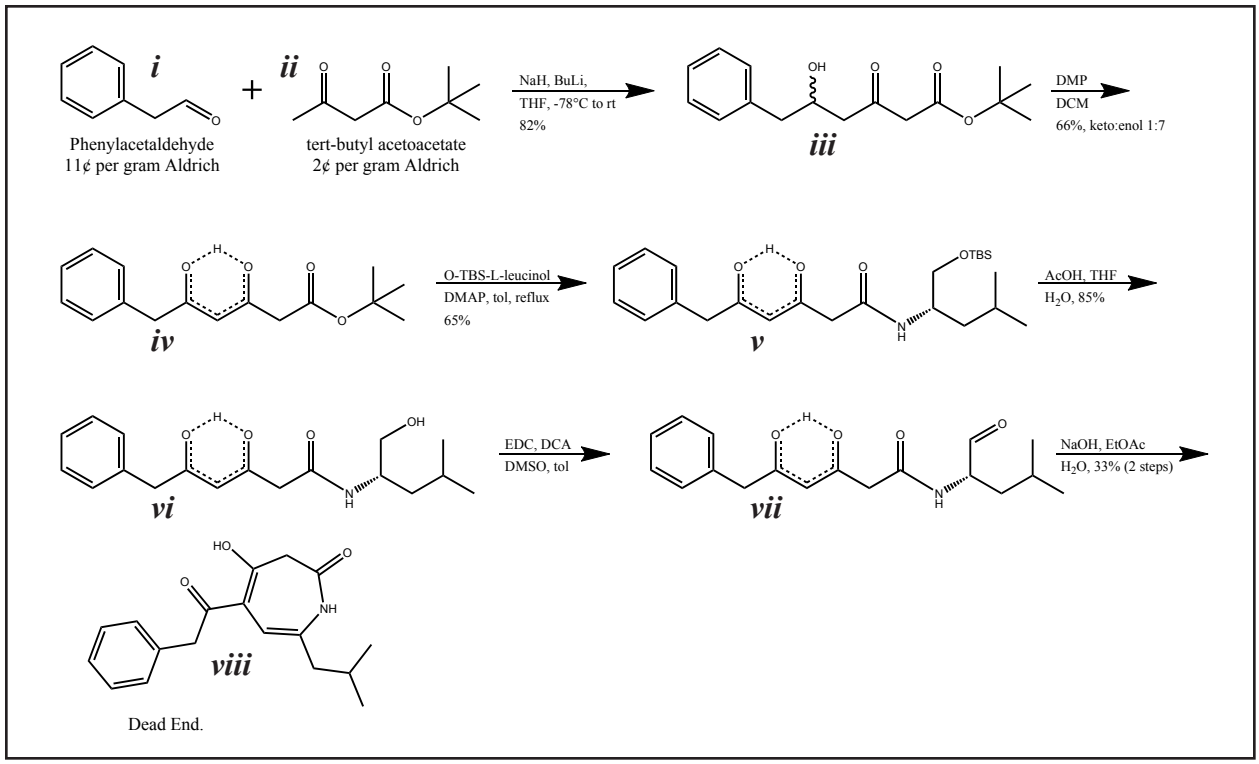


Scheme 2.39: The third Tsubaki route to racemic Berkeleyamide D (2016)

but the amide was BOC-protected in an effort to improve the yield of the bromination and the Darzens reaction. In addition, the compound was expected to cyclize once the BOC group was removed.

The BOC-protection proceeded smoothly to give ***ii***, and the bromination yield of ***iii*** increased from 42% to 72% (scheme 2.39). The Darzens reaction product ***vi*** proved relatively stable, and was purified in a 92% yield, instead of the 23% yield over 2 steps in their second attempt. An acetal and BOC-deprotection with 30% perchloric acid in water formed the spirocycle, and the final product, racemic berkeleyamide D, was achieved over 9 steps in a 7% overall yield.

The use of the Darzens reaction to bring the molecule together was an unusual and effective approach to achieve the spirocycle in few steps and good yields. However, the product was unfortunately racemic.



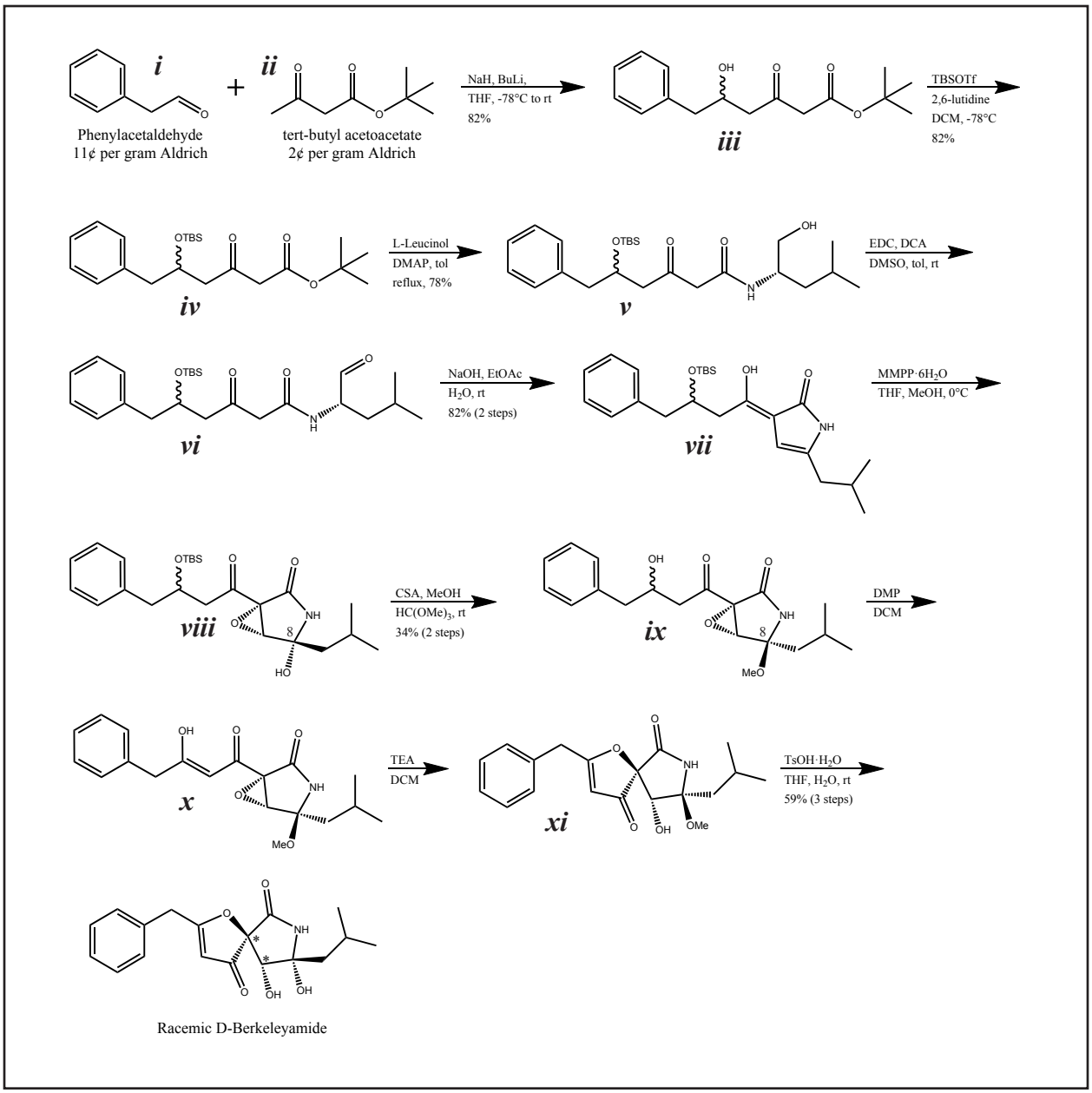
Scheme 2.40: The first Han route toward racemic Berkeleyamide D

2.2.5.2 The Han Route to Berkeleyamide D

In 2017, Han published a synthesis of both racemic Berkeleyamide D[50] and azaspirene,[51] by taking advantage of novel biomimetic approaches. In the synthesis of berkeleyamide D, the strategy was to create a linear structure via biomimetic chemistry, and cyclize at the end.

Han's first attempt (scheme 2.40), was initiated with phenylacetaldehyde (***i***) and *tert*-butyl acetoacetate (***ii***), which formed the aldol product ***iii***. Subsequent Dess Martin oxidation provided ***iv***, and the *tert*-butyl ester was transformed to the chiral amide ***v*** using O-TBS-protected L-leucinol. Removal of the TBS group with acid gave ***vi***, and a modified Pfitzner-Moffat[50] oxidation provided aldehyde ***vii***, which was used directly in the next step. Deprotonation of ***vii*** with sodium hydroxide invariably yielded a 7-membered ring (***viii***) rather than the desired 5-membered ring.

Han's second attempt[50] (scheme 2.41), was initiated using the same starting materials, which were brought together via an aldol reaction to give ***iii***. In an effort to prevent the formation of the 7-membered ring, the aldol product (***iii***) was first protected as its TBS ether (***iv***), and the oxidation of ***iii*** to the ketone was avoided. Ester ***iv*** was reacted with unprotected L-leucinol to give amide ***v***, and the primary alcohol was oxidized using a modified Pfitzner-Moffat method to give aldehyde ***vi***. When the aldehyde (***vi***) was exposed to sodium hydroxide, the desired 5-membered lactam (***vii***) was obtained in good yields. The subsequent installation of an epoxide with MMPP proceeded to give ***viii***, though not in a stereoselective fashion. Camphorsulfonic acid in methanol then removed the TBS protecting group and installed a methyl ether at C-8 to provide ***ix*** with



Scheme 2.41: The second Han route toward racemic Berkeleyamide D

inversion of stereochemistry. Subsequent oxidation of the unprotected alcohol to the enol (***x***) and application of triethylamine caused the hydroxy group of the enol to open the epoxide, closing the western ring to form the spirocycle (***xi***). Tosic acid in water then replaced the methoxy group with a hydroxy group, to give racemic berkeleyamide D, in 10 steps and an 8.6% overall yield.

Han's biomimetic approach to conceive the total synthesis of berkeleyamide D has several interesting features. For instance, the use of L-leucinol to create the eastern ring of the spirocycle may provide a handle for future asymmetric syntheses. It is notable that, just like the Tsubaki[47,48] strategy, the non-asymmetrical creation of an epoxide was an additional key step which caused the final result to be racemic. Overall, the fact that the Han group was able to build even the racemic molecule with a high overall yield is an accomplishment.

2.3 A Summary of the Synthesis of the Pseurotins

If one was able to find an overall efficient way to build the novel spirocyclic framework of the pseurotin family, it would offer relatively simple access to the other structures within the family. Thus the study of the pseurotin molecular family is very important. Because the different substances in the molecular family are reported to have very different biological activities, the opportunity for finding useful drugs among them remains very strong. With a few adjustments to the tail portion of the molecule and the attachments on C-8 of the spirocycle, it should be possible to create a facile synthesis of many of these potential drug targets. The exploration of the synthetic strategies, outlined in the previous schemes, has illustrated this in detail. Many of the groups

which have successfully synthesized members of this structural family have used variations on their initial procedure to access sister molecules in subsequent papers.

All of this brings us forward to the syntheses of the main target molecule for the work that was accomplished in the Bergdahl laboratory and described herein: the synthesis of azaspirene. First, the existing synthetic routes toward azaspirene must be conveyed in detail.

2.4 (–)-Azaspirene

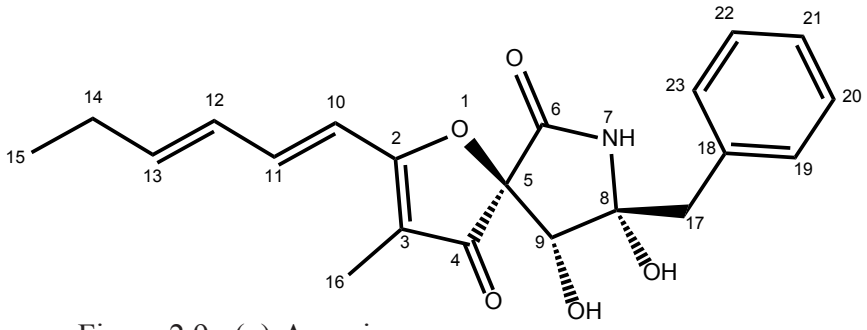


Figure 2.9: (–)-Azaspirene

(–)-Azaspirene was isolated from a broth of *Neosartorya* sp. and characterized by Osada and coworkers in 2002.[1] The research of the Osada group had been specifically focused on angiogenesis inhibitors, and they reported azaspirene showed promise in this area. Azaspirene caused complete inhibition of vascular ethothelial growth factor (VEGF) induced cell migration in human umbilical vein endothelial cells (HUVECs) at a concentration of 27 μM *in vitro*. This result was later supported by more extensive *in vivo* testing by the Osada[2] group in 2008, using chicken CAM assays and a mouse study.

In Osada's mouse study[2] (Figure 2.10), BALB/c mice were inoculated with RENCA tumor cells, and received either paclitaxel, used as a positive control because it is known to

Figure 2.10: Photographs from Osada's *Cancer Science* paper of tumor-induced blood vessel formation in their mouse study

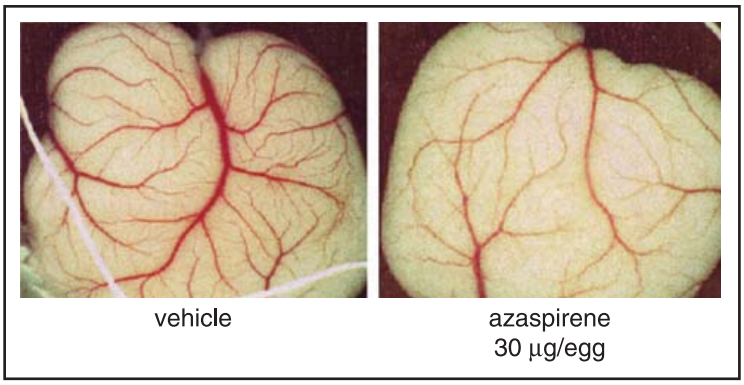


Figure 2.11: Photographs from Osada's *Cancer Science* paper of chicken CAM assay results

inhibit angiogenesis, at a dose of 6 or 20 mg/kg; asazpirene, at a dose of 31.6 or 100 mg/kg; or dimethylsulfoxide vehicle as a negative control. After one week, each dose of both drugs showed significantly fewer blood vessels oriented toward the tumor as compared to the vehicle, and the azaspirene mice seemed to be in generally better health than the paclitaxel mice. Unfortunately, the authors are unclear on the number of mice used for the study.

In the chicken CAM assay[2] (Figure 2.11), 30 μg azaspirene was dosed per fertilized Dekalb chicken egg, and the eggs were incubated for 2 days. Finally a fat emulsion was injected, and the blood vessel growth analyzed. According to the authors, the azaspirene eggs showed an anti-angiogenic response compared to the control.

In 2015, Emoto[52] reported that an analog of azaspirene with an ethyl group on C-2 of the spirocycle showed anti-angiogenic activity. Both enantiomers of their analog were tested *in vivo* using a mouse study. Compared to thalidomide as a positive control, they reported that both enantiomers of their ethyl analog showed anti-angiogenic activity with VEGF inhibition in HUVECs with an IC_{50} of 10 μg per mL, without the body mass loss seen in the mice treated with thalidomide. This data not only support that azaspirene has an anti-angiogenic effect as reported

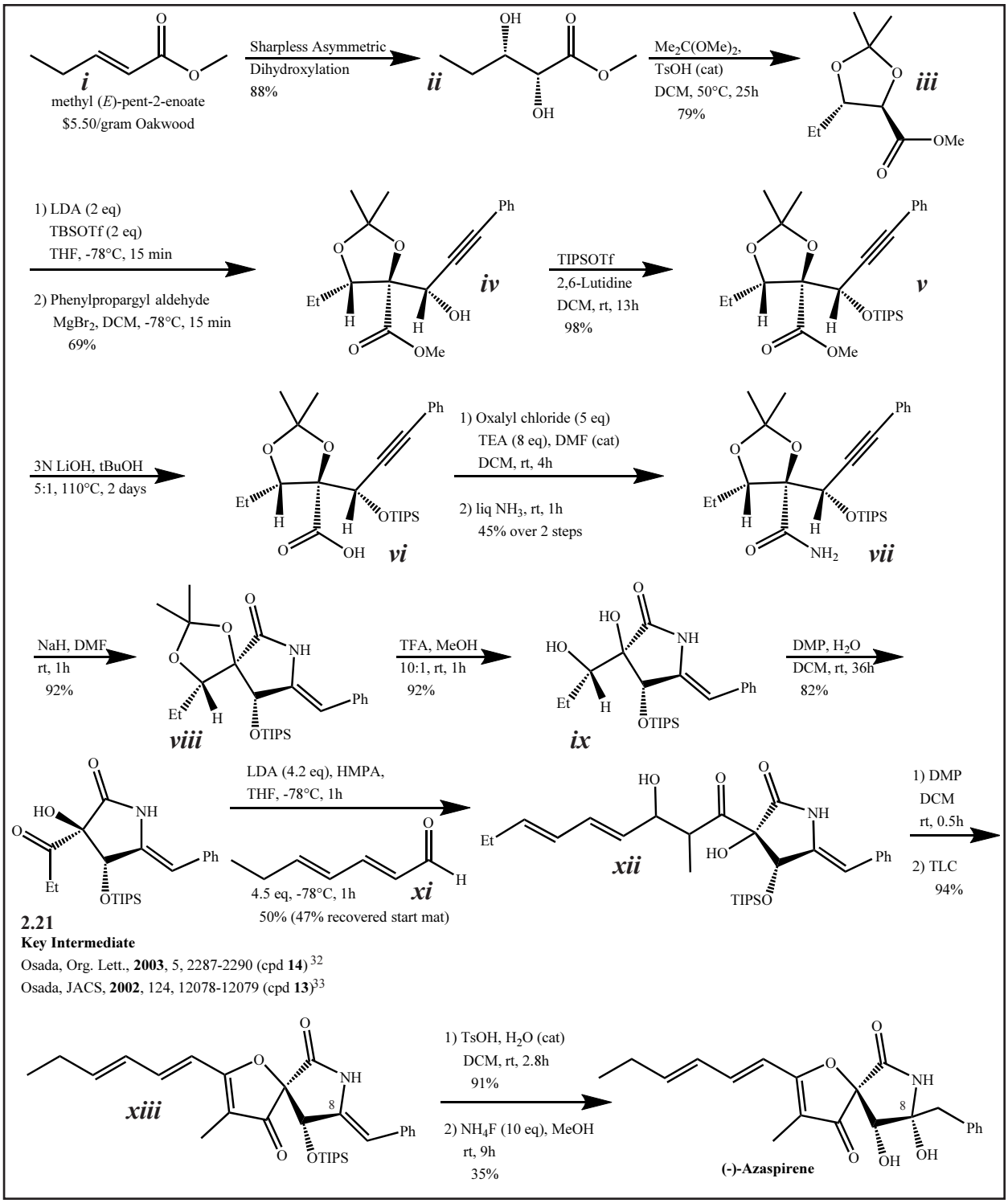
by Osada, but also suggest that the hexadienyl tail contributes less in the overall anti-angiogenic properties of the molecule. Importantly, the synthesis of Emoto's analog has not yet been reported.

In view of the potential of azaspirene as an anti-tumor drug, and the difficulty in isolating the molecule from its natural sources, it became an interesting synthetic target. Four total syntheses of azaspirene have followed.

2.4.1 The Osada Route to (–)-Azaspirene

Osada's[33] route to (–)-azaspirene was published in July of 2002, a year prior to their total synthesis of pseurotin A,[32] and three years prior to their synthesis of synerazol.[37] At this point, there had been no reports which completed the synthesis of any of the pseurotins, though Tamm was more than a decade into his attempts toward pseurotin A.[11-14,16] In addition, Tadano's[25] group had just published their work toward pseurotin A and azaspirene in March 2002, but would not complete the synthesis of either molecule until 2004.[26]

The Osada[33] route to azaspirene is shown in scheme 2.42. They began by creating the eastern ring of azaspirene with an achiral enone (***i***), which was transformed via a stereocontrolled Sharpless asymmetric dihydroxylation to give ***ii***. The diol was protected as its acetonide to provide ***iii***, and propargyl aldehyde was installed via an aldol reaction to form ***iv***. After a TIPS protection of the resulting secondary alcohol to give ***v***, the ester was hydrolyzed to the carboxylic acid (***vi***), which was then transformed to its acid chloride with oxalyl chloride. Ammonia was added to form amide ***vii***, and the lactam was closed via addition to the triple bond to produce ***viii***. The acetonide

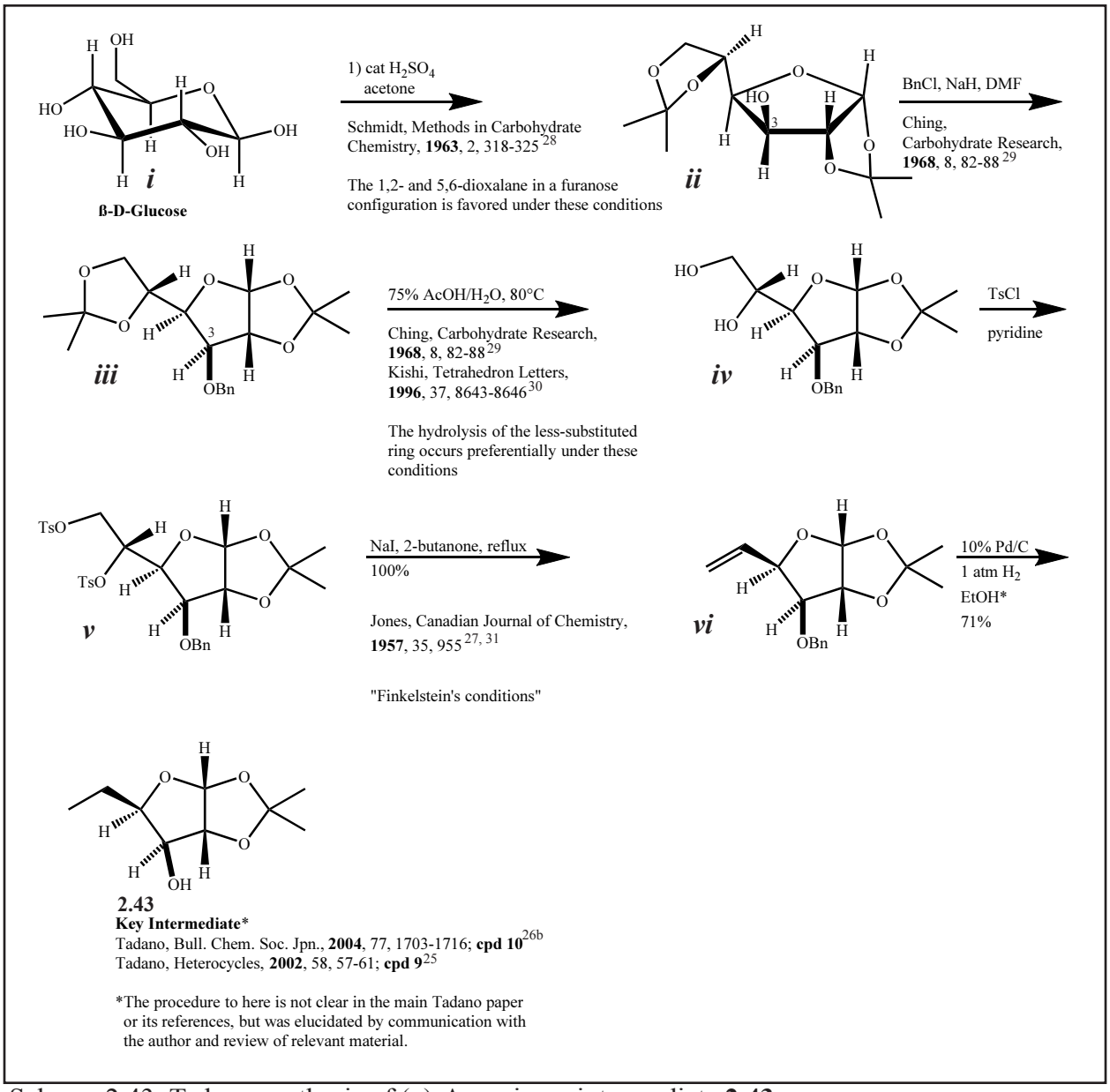


Scheme 2.42: Osada synthesis of (–)-Azaspirene

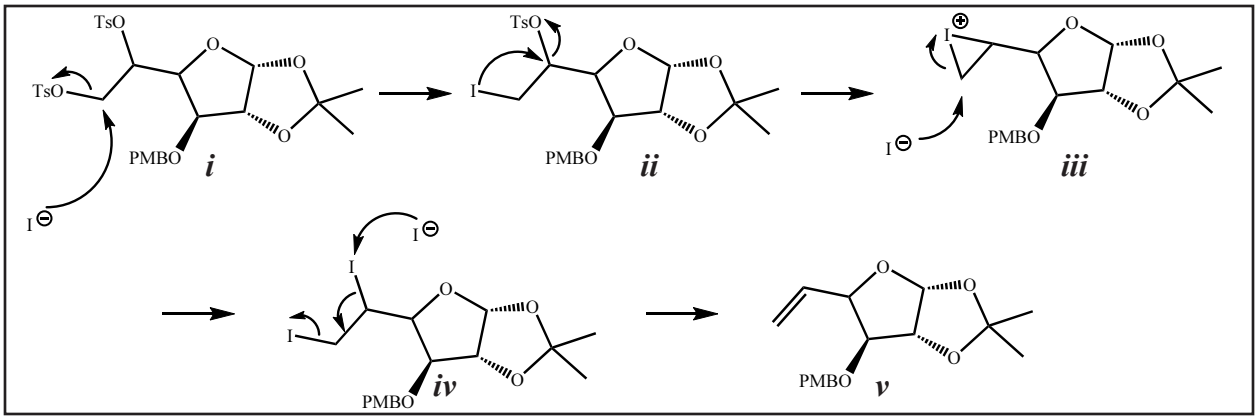
was next removed to form diol ***ix***, and the secondary alcohol oxidized with Dess-Martin reagent to give **2.21**. Compound **2.21** is the same key intermediate used in the Osada synthesis of pseurotin A[32] and synerazol,[37] and the Kakeya synthesis of FD-838.[41]

The common intermediate (**2.21**) was subjected to an aldol reaction with commercially available 2,4-heptadienal (***xi***), which added the tail of the molecule to the framework to give ***xii***. Next, an additional Dess-Martin oxidation was performed, which upon purification with silica gel thin layer chromatography caused the closure of the western ring of the spirocycle to provide ***xiii***. The stereocontrol of the TIPS-protected alcohol allowed the necessary hydroxyl group to be introduced in a stereoselective fashion to C-8 of the spirocycle across the exocyclic double bond. This was accomplished by employing a mixture of tosic acid and water. The TIPS group was then removed with ammonium fluoride to yield (–)-azaspirene over 13 steps in an overall yield of 2.2%.

The Osada group has demonstrated through the synthesis of azaspirene, pseurotin A[32] and synerazol;[37] and Kakeya through the synthesis of FD-838,[41] that their inventive approach is useful for accessing many of the pseurotins. Their common intermediate (**2.21**) can be used to access the pseurotins and their analogs. The overall yield and the relatively low number of steps is also very good, especially as compared to the Tadano[25,26] route. However, the Osada route is still challenging due to its scalability, especially in their use of preparative TLC to close the western ring of the spirocycle. Moreover, the yield of the last step is painfully low. However, theirs was the first complete, relatively efficient, asymmetric synthetic strategy published.



Scheme 2.43: Tadano synthesis of (–)-Azaspirene intermediate **2.43**



Scheme 2.43.a: Mechanism for the Finkelstein reaction

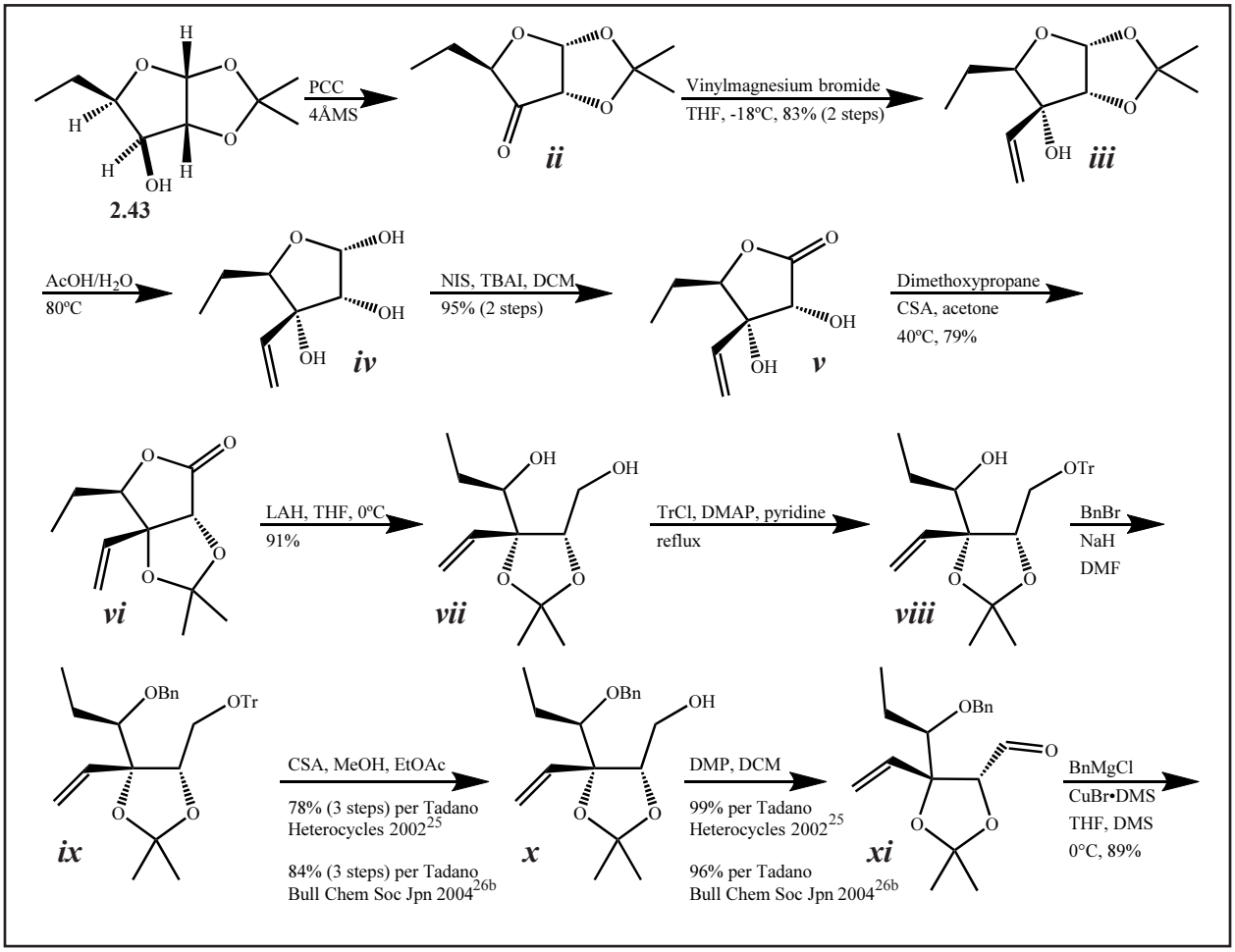
2.4.2 The Tadano Route to (–)-Azaspirene

Tadano's group was the first to describe a workable version of the spirocyclic core of the psuerotins, reported in 2002.[25] However, their strategy did not produce a complete synthetic scheme until azaspirene and pseurotin A were reported in 2004.[26] Tadano was able to use D-glucose to achieve the tail of pseurotin A using Tamm's[13a] method. In addition, Tadano used D-glucose as a chiral template for the spirocyclic core of azaspirene, pseurotin A and pseurotin F_2. Unfortunately, Tadano's route is comparatively long, and some steps– especially the first "six convenient steps" employed to transform D-glucose to their starting material (**2.43**)– are not explicitly listed anywhere in their procedure, and the references[27] provided are also inadequate. Thankfully, Tadano was gracious enough to give insight into their methods, and the Tadano synthesis is shown in schemes 2.43 to 2.44.

Tadano's route to azaspirene (scheme 2.43), was initiated with β-D-glucose (***i***), which when subjected to Schmidt's[28] acetonide formation conditions rearranged to form the 1,2- and 5,6-dioxalane ***ii***. Next, benzyl protection of the free hydroxyl group at C-3 gave ***iii*** using Ching's[29] method. Subsequently, using Ching's[29] and Kishi's[30] methods, the selective removal of the less-substituted 5,6-dioxolane was effected by 75% acetic acid in water to give ***iv***. The addition of tosyl groups to the diol gave ***v***, which provided good leaving groups for a subsequent iodination/ elimination reaction to give ***vi***. This Finkelstein reaction,[27,31] which plausible mechanism is shown (scheme 2.43.a), transformed the diol to an alkene. This alkene was hydrogenated to form **2.43**. It should be noted that no yields are available for these reactions, except for the iodination/ elimination and hydrogenation, which were provided[26c] by Tadano. The missing yields therefore

are not included in the overall yield calculation attributed to this route.

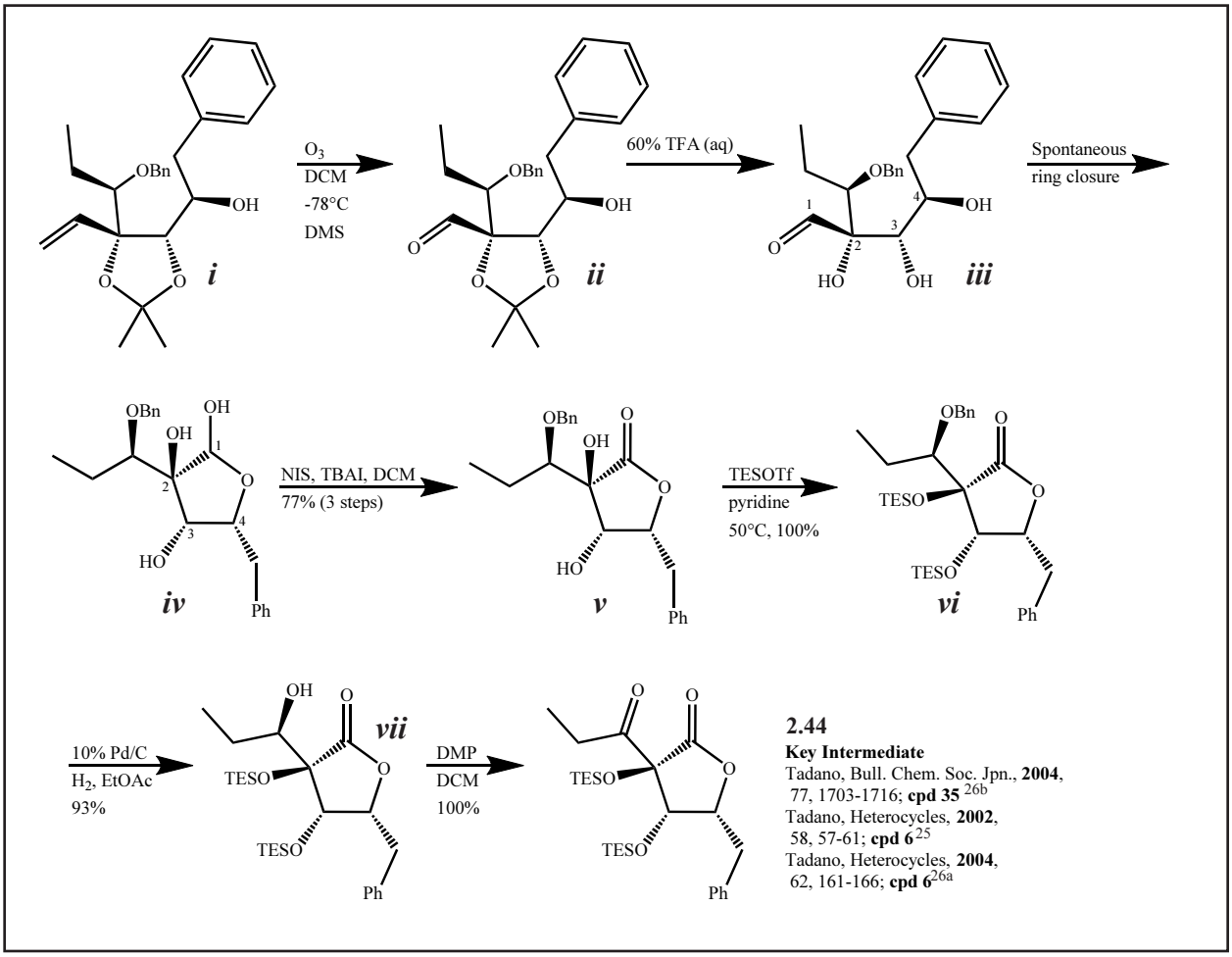
As illustrated in scheme 2.44.1, secondary alcohol **2.43** was oxidized with PCC to give the β-oxygenated ketone ***ii***, which upon exposure to a vinyl Grignard reagent formed ***iii*** in a stereoselective fashion. Removal of the acetonide with acetic acid and water gave ***iv*** and a radical oxidation selectively formed the corresponding lactone ***v***, from the triol. Dimethoxypropane was used to reintroduce the acetonide (***vi***), and the lactone was reduced with lithium aluminum hydride to give ***vii***. The primary alcohol was then selectively protected as a bulky trityl ether (***viii***) and the secondary alcohol protected as its benzyl ether providing ***ix***. Selective deprotection of the trityl ether to give ***x*** and subsequent oxidation of the primary alcohol provided aldehyde ***xi***. Exposure



Scheme 2.44.1: Tadano synthesis of (–)-Azaspirene intermediate 2.44 part 1

of ***xi*** to a benzyl Grignard reagent introduced the benzyl group in a stereoselective fashion, to give compound ***i*** (scheme 2.44.2).

Alkene ***i*** was subjected to ozonolysis conditions to form aldehyde ***ii*** (scheme 2.44.2). Removal of the acetonide group with trifluoroacetic acid gave ***iii***, and caused formation of hemiacetal ***iv***. A subsequent radical oxidation yielded lactone ***v***. After triethylsilyl protection of ***vi***, hydrogenation conditions removed the benzyl protecting group to form ***vii***. This secondary alcohol was subsequently oxidized to give **2.44**. Compound **2.44** resembles the eastern ring of the spirocycle and is a key sub-unit which Tadano's group used to access the three pseurotins for which they report syntheses: azaspirene, pseurotin A and pseurotin F_2. This sub-unit is similar to

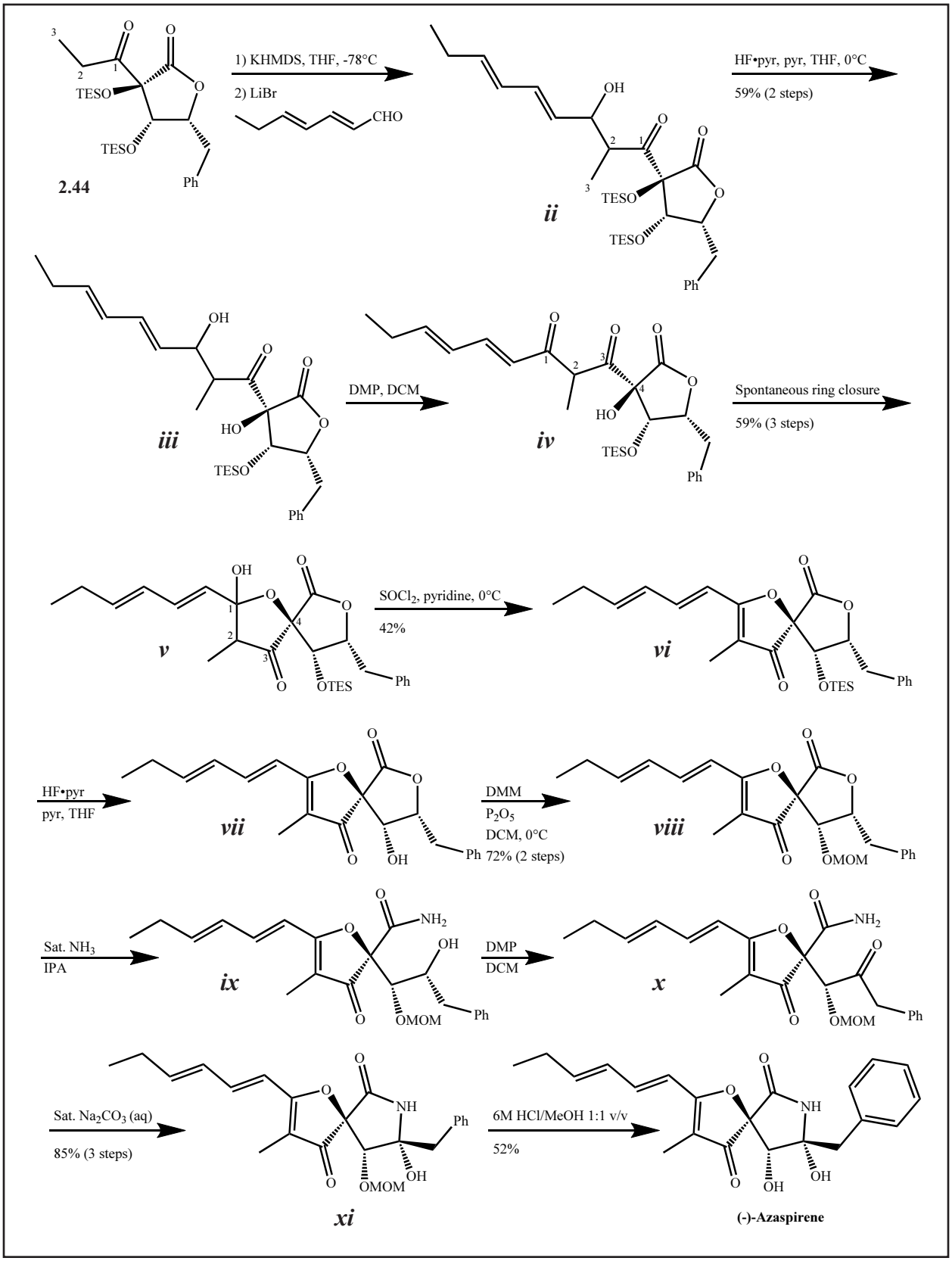


Scheme 2.44.2: Tadano synthesis of (–)-Azaspirene intermediate 2.44 part 2

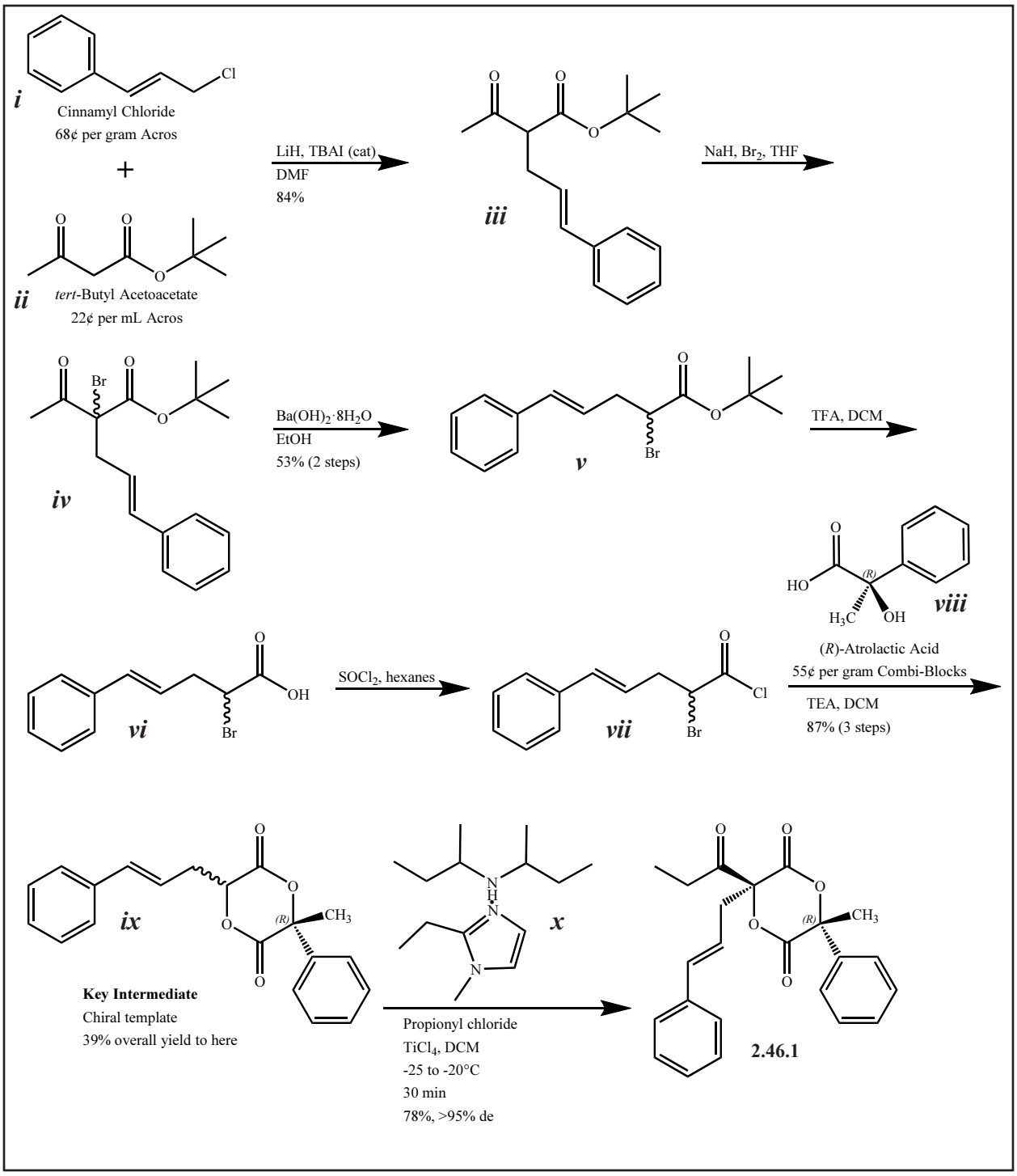
Tamm's[13] compound **2.11**.

Tadano next used 2,4-heptadienal (scheme 2.45), also used by Osada[33] (scheme 2.42), in an aldol reaction to introduce the tail of the molecule and to start creating the western ring of the spirocycle (***ii***). As shown, hydrofluoric acid selectively removed the tertiary TES group to provide ***iii***. Subsequent oxidation to ketone ***iv*** caused the western ring of the spirocycle to spontaneously cyclize to form hemiacetal ***v***. This hemiacetal was next exposed to thionyl chloride, and the subsequent E2-type elimination reaction with pyridine formed the double bond in the western ring to create ***vi***. Due to difficulty with the subsequent aminolysis step, the problematic TES group was exchanged for a more suitable MOM group (***vii*** to ***viii***). Ammonia in isopropanol converted the lactone to the corresponding amide and secondary alcohol ***ix***. This alcohol was oxidized to ketone ***x*** using Dess-Martin reagent. Weak base caused the eastern ring to close as the corresponding lactam with the correct stereochemistry (***xi***). Removal of the MOM group with strong acid gave azaspirene, over 33 steps with less than a 1% overall yield, not including the first four steps for which yields are not documented.

The Tadano strategy is important because of its novel use of common and very inexpensive D-glucose as a chiral template. The use of ozonolysis and radical oxidation to bring the synthesis forward is elegant, and the achievement of an asymmetric synthesis which can access multiple pseurotins is admirable. However, the strategy suffers from a large number of steps, and therefore the overall yield is low. Additionally, the lack of clarity with which the first few steps are reported in the literature is problematic. For all of these reasons, the Tadano route is impractical for scale-up.



Scheme 2.45: Tadano synthesis of (–)-Azaspirene



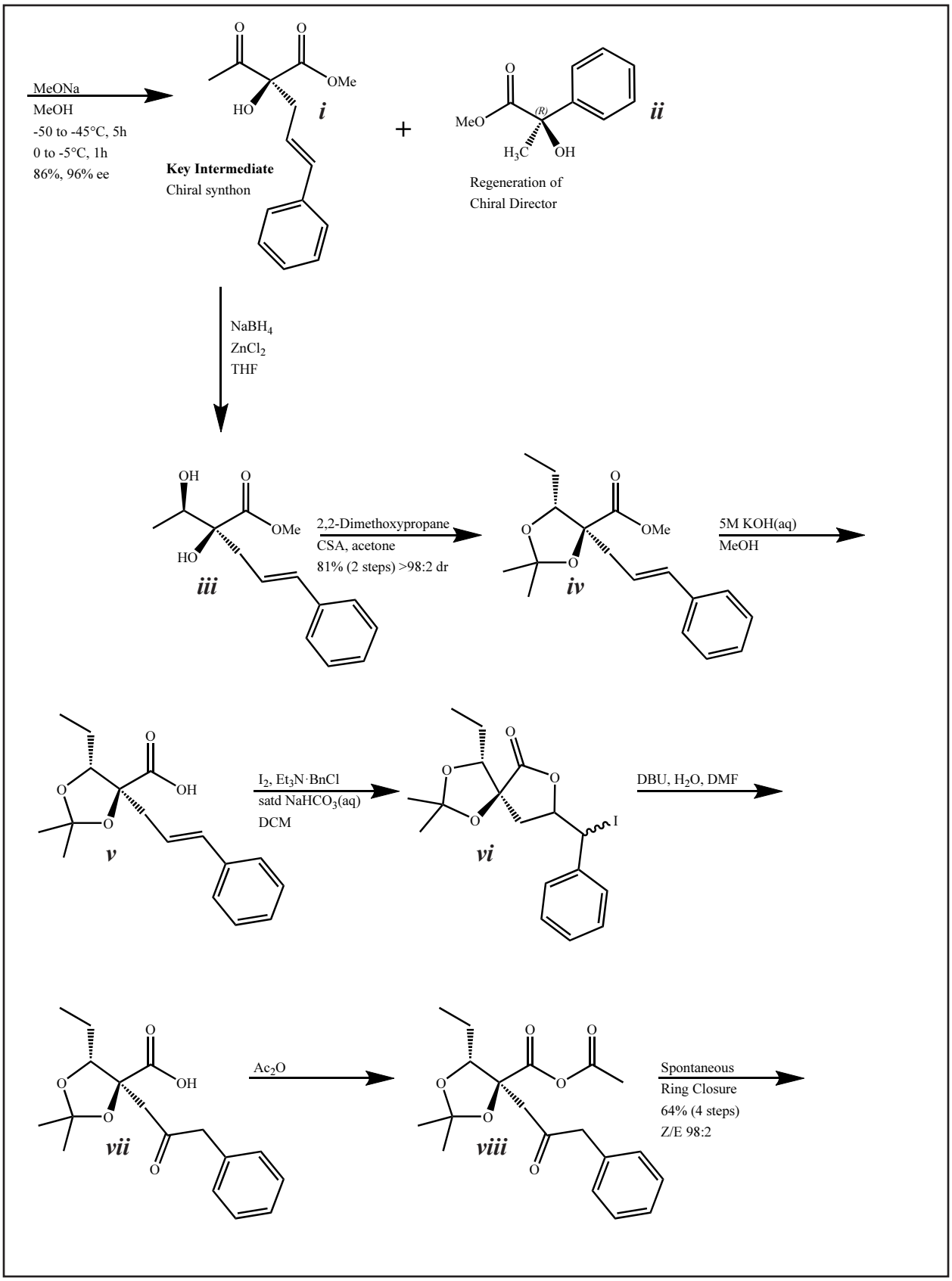
Scheme 2.46.1: Tanabe synthesis of (–)-Azaspirene part 1

2.4.3 The Tanabe Synthesis of (–)-Azaspirene

A major focus of research in the Tanabe[53] group was a unique protocol they had developed for titanium-directed aldol and claisen condensation reactions. Considering the challenges faced by previous syntheses of the pseurotins in the use of key aldol reactions in their respective approaches, the Tanabe aldol adaptation seemed to be a promising way to solve some of these problems. To demonstrate the efficacy of their approach, they published a protocol for the asymmetric synthesis of (–)-azaspirene.

The Tanabe approach was initiated with cinnamyl chloride (***i***) and *tert*-butyl acetoacetate (***ii***), both readily available starting materials (scheme 2.46.1). A standard coupling between the diketone and the alkenyl chloride to give ***iii*** was followed by a bromination to yield ***iv***. Decarboxylation with barium hydroxide to give ***v*** was followed by an ester hydrolysis with TFA to give ***vi***. The resulting carboxylic acid ***vi*** was converted to the acid chloride with thionyl chloride yielding ***vii***. When exposed to (R)-atrolactic acid (***viii***), the acid chloride (***vii***) yielded the ester and subsequently displaced the α-bromide with the carboxylate group as the nucleophile to form dilactone ring ***ix***. The addition of this chiral (R)-atrolactic acid auxiliary would serve to direct the stereochemistry of the Mukayiama Claisen reaction that followed.

Next, the Tanabe group's selective crossed Claisen reaction was employed. Propionyl chloride was added to ***ix*** in a stereoselective fashion, using titanium tetrachloride and a special di-*sec*-butylamine/2-ethyl-1-methylimidazole complex (***x***), to yield **2.46.1** in high yield and with a large diastereomeric excess.

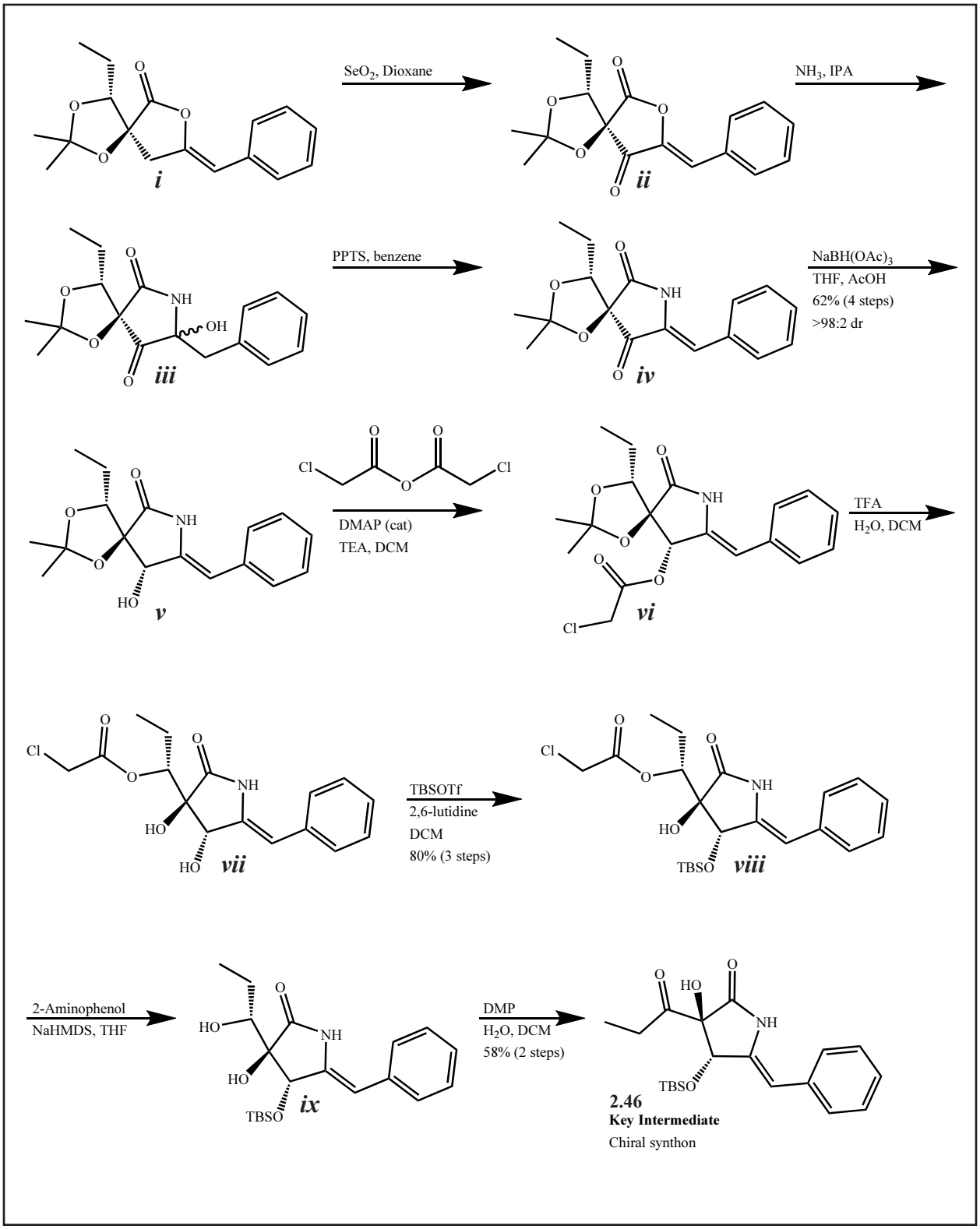


Scheme 2.46.2: Tanabe synthesis of (–)-Azaspirene part 2

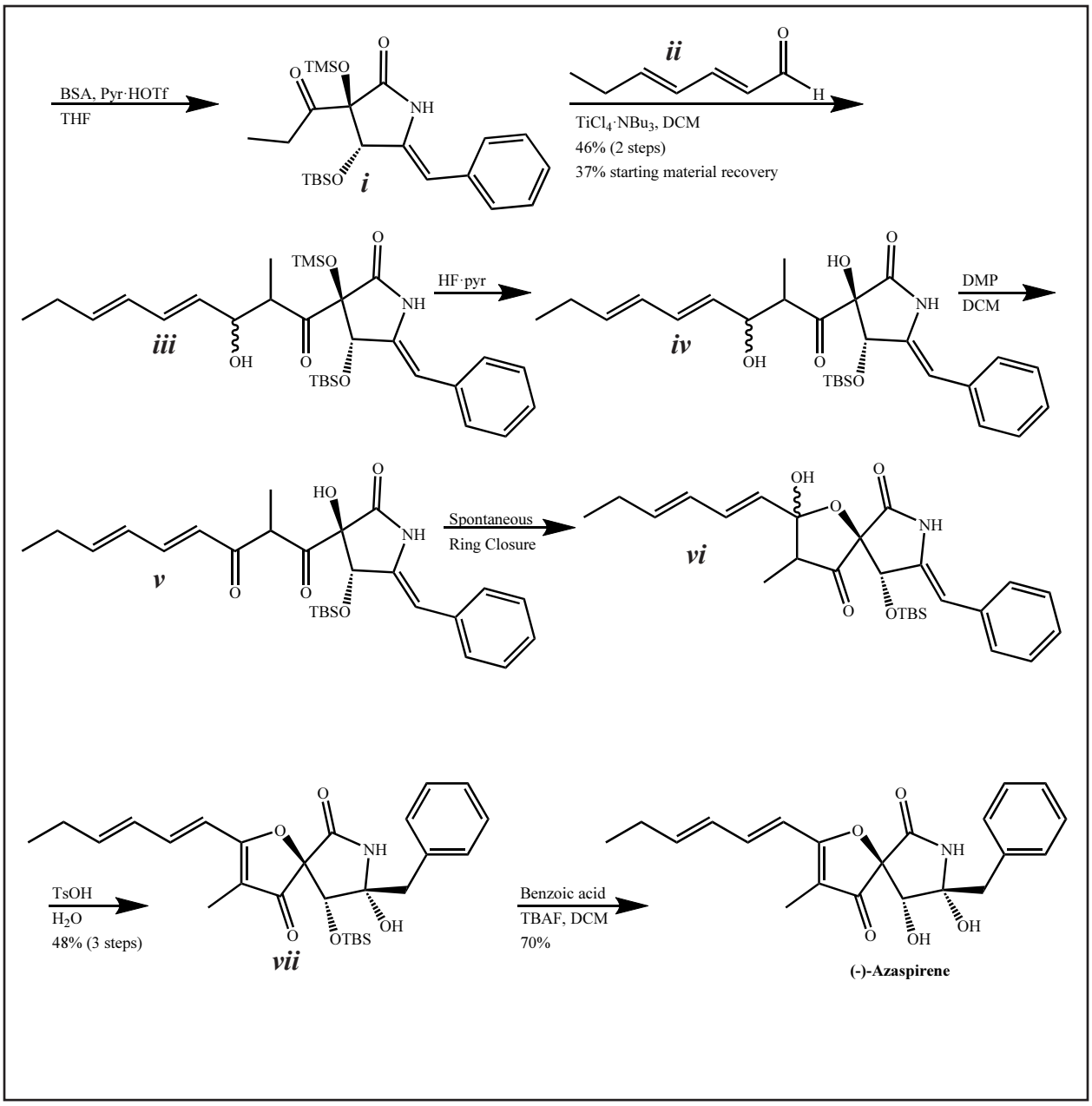
The route continues in scheme 2.46.2, which illustrates the removal of the atrolactic acid chiral auxiliary with sodium methoxide to give ***i***, and a reduction with sodium borohydride and zinc chloride to give the vicinal diol (***iii***). After ***iii*** was protected through the formation of an acetonide to give ***iv***, the ester was hydrolyzed to the acid to give ***v***. The iodinium ion was formed through the addition of I_2, and an iodolactonization formed lactone ***vi***. Since dry DBU proved ineffective, a DBU/water mixture was added to give ***vii***. A mixed anhydride activation gave ***viii***, and a subsequent ring closing was accomplished with acetic anhydride, to give chiral lactone ***i*** (scheme 2.46.3).

Chiral lactone ***i*** was oxidized with selenium dioxide to give ***ii*** (scheme 2.46.3). The lactone was next transformed to the corresponding lactam (***iii***) by the addition of ammonia in isopropanol. After dehydration of the racemic alcohol to give ***iv***, the ketone was reduced in a stereoselective fashion with sodium triacetoxyborohydride to form ***v***. The alcohol was then protected as the chloroacetate (***vi***). The acetonide was removed with acid, which also caused the transfer of the chloroacetyl group to give diol ***vii***. The secondary alcohol was protected over the tertiary alcohol to give the TBS ether (***viii***), and the chloroacetyl protecting group was removed with 2-aminophenol and strong base to provide ***ix***. Oxidation of the secondary alcohol gave **2.46**, which is structurally similar to Osada[33] **2.21**, Tamm[13] **2.11**, and Tadano[25, 26] compound **2.44**.

In completion of the synthesis of (–)-azaspirene (scheme 2.46.4), the tertiary alcohol of **2.46** was protected as its TMS-ether to give compound ***i***. 2,4-heptadienal (***ii***) was added via a modified Mukaiyama aldol reaction to give ***iii***, in a strategy similar to that of Osada[32] and Tadano.[26] The TMS group was removed to provide alcohol ***iv*** and the secondary alcohol was oxidized to



Scheme 2.46.3: Tanabe synthesis of azaspirene part 3



Scheme 2.46.4: Tanabe synthesis of (–)-azaspirene part 4 and completion

ketone ***v***, which spontaneously formed spirocycle ***vi***. A double bond was installed by dehydration using tosic acid to give ***vii***. Then a mixture of benzoic acid and TBAF removed the TBS protecting group to give (–)-azaspirene, in a 0.6% overall yield and 29 steps.

The Tanabe route shows the utility of their novel titanium Claisen condensation procedure, and their signature reaction proceeds with a 78% yield and diastereomeric excess greater than 95%. While it is commendable that an asymmetric synthesis was achieved, their route has large number of steps, and the overall yield is lower than previously published routes. Because of the low yield and the number of steps, this route is impractical for scale-up.

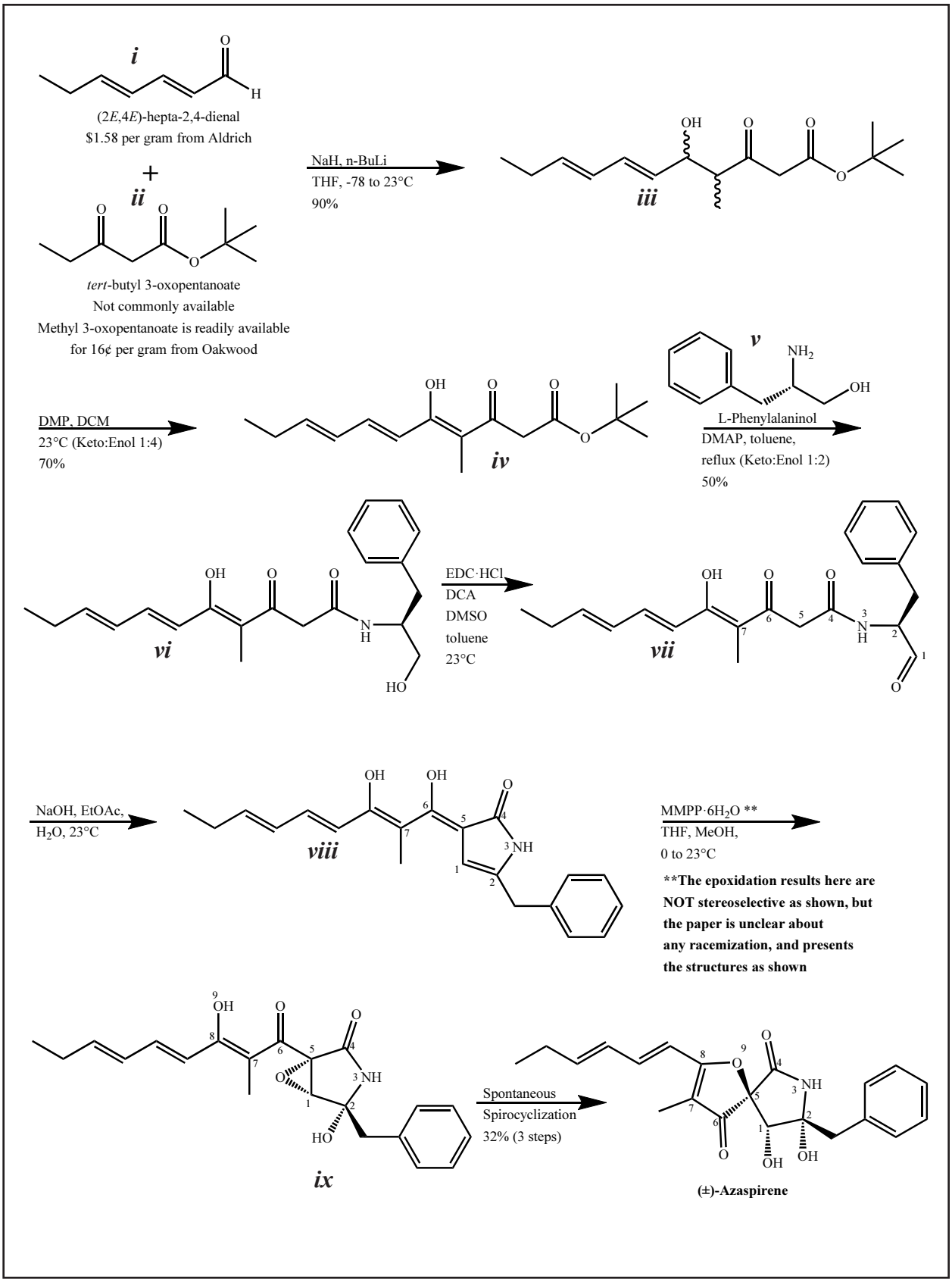
2.4.4 The Han Synthesis of Racemic Azaspirene

In July 2017, the Han[51] group published the most recent synthesis of azaspirene, which is similar to their 2017 synthesis of berkeleyamide D.[50] Their approach involved using biomimetic starting materials and transformations to approximate the biosynthesis of azaspirene by its native fungus, *Neosartorya sp.* Han's group took a linear approach to the synthesis of the molecule. In addition, Han's strategy had the fewest steps by far, at six total, than any of the other routes. Their product is unfortunately racemic, however.

The Han group initiated their synthesis with the same 2,4-heptadienal (***i***) that is seen in the Tadano and Osada routes, and *tert*-butyl 3-oxopentanoate (***ii***, scheme 2.47). The diketone (***ii***) was subjected to strong base to form the dienolate, which was then added to aldehyde ***i***. The resulting compound ***iii*** was oxidized to the enol (***iv***), and the amino group of chiral L-phenylalaninol (***v***) replaced the *tert*-butoxy group to form amide ***vi***. The alcohol on the phenylalaninol moiety was then oxidized with a modified Swern protocol to form aldehyde ***vii***. Formation of an enolate with NaOH allowed addition to the aldehyde to close the lactam, and subsequent dehydration gave ***viii***. Epoxide formation was accomplished using MMPP in a non-stereospecific fashion to give ***ix***. This racemic expoxide was opened with the enol oxygen to form the racemic spirocycle and azaspirene in an impressive 10% yield over six steps.

The Han synthesis is notable because of its simplicity, high yield, and few steps. Using techniques inspired by nature to develop a synthetic scheme as Han described is an elegant approach. It is unfortunate, however, that the result of this synthetic strategy is racemic, due to the

lack of stereospecificity in the epoxidation step. More importantly, it has not been demonstrated that the Han strategy will work to access the other pseurotin compounds. If this route proves generally applicable to the pseurotins, the Han strategy could be of practical use to access the family of compounds and to further study its analogs.



Scheme 2.47: Han synthesis of racemic azaspirene

Chapter 3: The Bergdahl Synthesis of (–)-Azaspirene

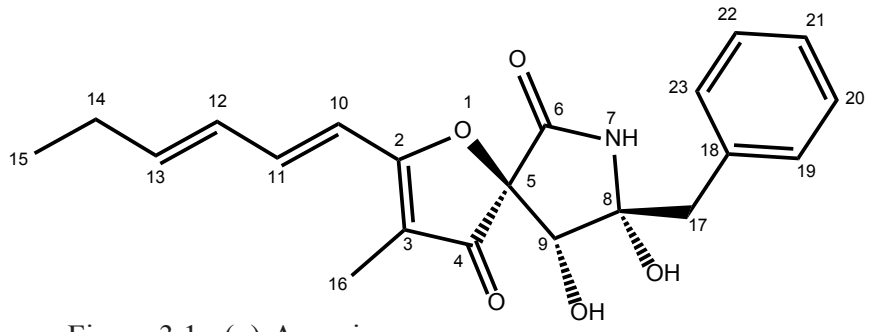


Figure 3.1: (–)-Azaspirene

3.1: The First Effort Toward (–)-Azaspirene

From its inception, a major goal of the synthesis of (–)-azaspirene in the Bergdahl group was to achieve a synthetic process which improved on the overall yield of the molecule and also allowed the introduction of diversity in key areas of its structure. In this way it should be possible to use one versatile synthetic route to create derivatives of azaspirene and to access the other pseurotin structures for study (figure 2.2). Because the main areas of structural difference in the pseurotin family are with the tail on C-2 and various groups on C-8 of the same basic spirocyclic framework, it was expected that focusing on a synthesis of this basic framework while allowing diversity in these areas would be the best way to achieve this major goal, and access the pseurotin family of compounds (figure 2.2).

D-Malic acid, the unnatural enantiomer of malic acid, was chosen as the starting material for the synthetic route, both because its stereochemistry matches the eastern ring of azaspirene well, and because it is easily created from very inexpensive D-aspartic acid through a diazotization reaction.[55]

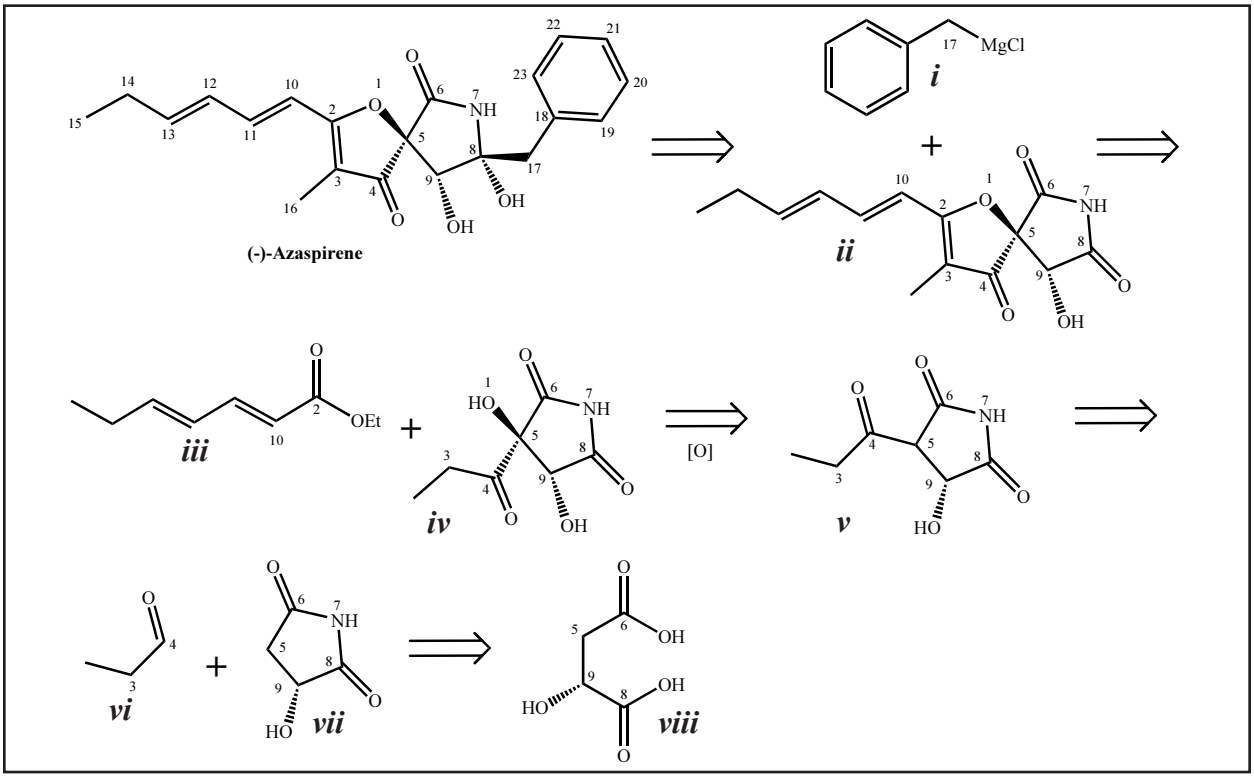
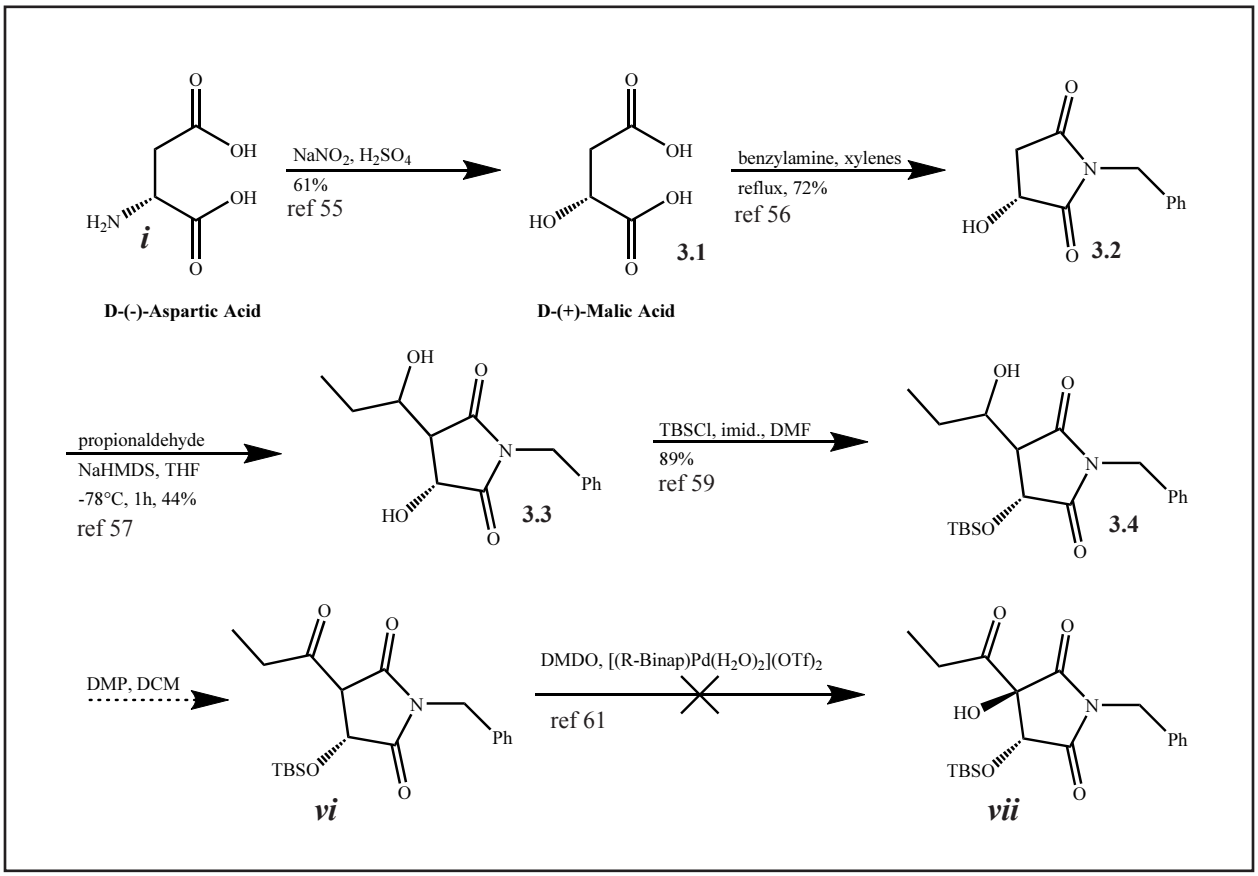


Figure 3.2: First Kelly Retrosynthetic Analysis



Scheme 3.1: The First Kelly Synthetic Attempt

As shown in figure 3.2, it was expected that this iteration of the route could be concluded with a benzyl addition to C-8 of spirocycle ***ii***, presumably with a Grignard reagent. In addition, the tail diene portion ***iii*** on C-2 of the imide framework ***iv*** could also be added relatively late, through a consecutive trans-esterification and enolate addition. An alternative zirconocene-based conjugate addition reaction was also explored, but was discarded (see scheme and compound 8.1 in the appendix). Since C-8 and the C-2 tail portion are the major points of diversity among the pseurotin family, adding both as late as possible was expected to be advantageous. The necessary tertiary hydroxyl group to give ***iv*** may be added in a stereoselective manner with a special palladium catalyst[61] to 1,3-dicarbonyl ***v***. Compound ***v***, in turn, could be the result from the oxidation of a the aldol product of aldehyde ***vi*** and malimide ***vii***. Finally, the malimide ***vii*** may be easily created from D-malic acid ***viii*** in an imidation[56] reaction with benzyl amine. An alternative tartarimide-based route was also explored, but was discarded (see compounds 8.2 through 8.4 in the appendix).

3.1.1: The Aldol Condensation

In initiation of the route to azaspirene, D-aspartic acid was transformed to crude D-malic acid via a diazotization[55] procedure (scheme 3.1). This crude malic acid proceeded smoothly through an imidation[56] reaction with benzylamine to give N-benzyl-D-malimide (**3.2**) in multi-gram quantities (ca. 70% yield, scheme 3.1). The next step in the sequence to azaspirene required an aldol reaction[57] with propanal to give **3.3**, to provide the beginning of the western ring of azaspirene. After exhaustive optimization, the aldol reaction proceeded with the modest yields

expected based on literature[57] precedent. Multiple attempts with different bases and conditions were attempted, and often the result was decomposition of the starting material. The small successes achieved, however, as well as the examples which claimed success from literature,[57] provided hope that the reaction could be optimized to improve the result.

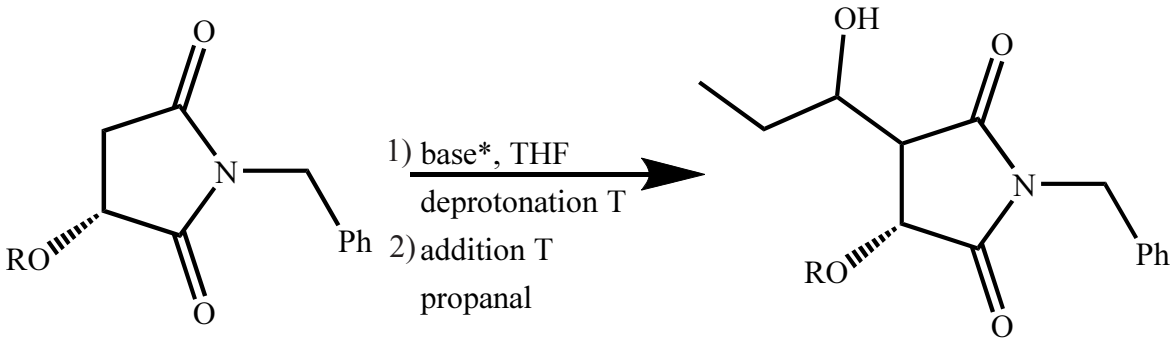
As shown in table 3.1, to begin, it was necessary to find a base that would deprotonate the imide substrate **3.2** without decomposition. Despite the suggestion of literature protocols,[57] standard conditions with lithium diisopropyl amide (LDA) were unsuccessful. Even deprotonating the substrate with LDA for subsequent deuteration was unsuccessful. The use of stronger alkyllithium bases was attempted to see whether complete and immediate deprotonation of the substrate would block possible side reactions, like coupling, that could be destroying the substrate. Unfortunately, the use of *n*-butyllithium resulted in decomposition of the starting material. However, there was some small success with *tert*-butyllithium (less than 5% yield, with no starting material recovery). Initial tests with a slighly weaker bulky amide base, lithium hexamethyldisilazide (HMDS), made *in-situ* with hexamethyldisilazane and *n*-butyllithium were more successful, with just under a 10% yield, but with minimal recovery of starting material. Following this improvement, further tests were done to see whether the reactivity of the base could be tuned by changing the metal cation. Tests with potassium HMDS were slightly more effective than the lithium counterpart, with just over a 10% yield, but with minimal starting material recovery. Finally, the most improved yields, at between 10% and 20% yield with ca. 10% starting material recovery, were achieved with sodium HMDS.

With the most effective base, sodium hexamethyldizilazide, in hand, protection of the

malimide hydroxyl group was tested to see whether any protection would improve the yield (table 3.1). Though these protections were usually quite successful, the protected starting material decomposed when subjected to strong base for the aldol reaction. After several attempts, it became clear that the best result would be obtained if the hydroxyl group remained as is (see compounds 8.5 through 8.13 for further examples). Thus, deprotonation of **3.2** would require creating a dianion, both at the hydroxyl position and at the α-carbon. Other attempts at improving the aldol reaction included the replacement of the N-benzyl protecting group with an (S)-methylbenzyl protecting group, and reduction of the bottom carbonyl of the imide to an ethoxy group.[58] These modifications did not improve the product yield for the aldol reaction, however. Thus, the original N-benzylmalimide **3.2** was retained. Next the reaction was further optimized by modification of the reaction temperature.

Initially, the aldol condensation reaction was attempted at -78 °C throughout, as suggested by much of the literature,[57,58] resulting in the 10-20% yields discussed. Other sources[57a] suggested conducting the deprotonation reaction at 0 °C and then cooling to -78 °C for the aldehyde addition. In order to determine which temperature combination was the best in terms of yield with the desired substrate, several reactions at different temperatures were run in series (see table 3.1). This was done with the expectation that a warmer temperature could allow full and faster double-deprotonation of the malimide. Conversely, it was important to maintain a cool temperature to allow selective deprotonation and prevent side reactions like coupling. The reaction run at 0 °C then cooled to -78 °C achieved a 38% yield, which was the highest yield achieved yet. This result suggested that the formation of the enolate at 0 °C followed by cooling to -78 °C for the aldehyde

Table 3.1: A Selection of Aldol Condensation Conditions Attempted



Starting Material Cpd #	R	Base*	Deprotonation Temperature (°C)	Addition Temperature (°C)	% Yield
3.2.1.A	H	NaHMDS	0	-78	44
3.2.1.A	H	LDA	0	-78	0
3.2.1.A	H	tBuLi	0	-78	<5
3.2.1.A	H	nBuLi	0	-78	0
3.2.1.A	H	LiHMDS	0	-78	<10
3.2.1.A	H	KHMDS	0	-78	10
3.2.1.B	TBS	NaHMDS	0	-78	0
3.2.1.C	MOM	NaHMDS	0	-78	0
3.2.1.D	TIPS	NaHMDS	0	-78	0
3.2.1.E	Me	NaHMDS	0	-78	0
3.2.1.F	Allyl	NaHMDS	0	-78	0
3.2.1.G	Benzyl	NaHMDS	0	-78	0
3.2.1.H	tBu	NaHMDS	0	-78	0
3.2.1.A	H	NaHMDS	-30	-78	23
3.2.1.A	H	NaHMDS	0	-30	0
3.2.1.A	H	NaHMDS	-78	-78	10-20

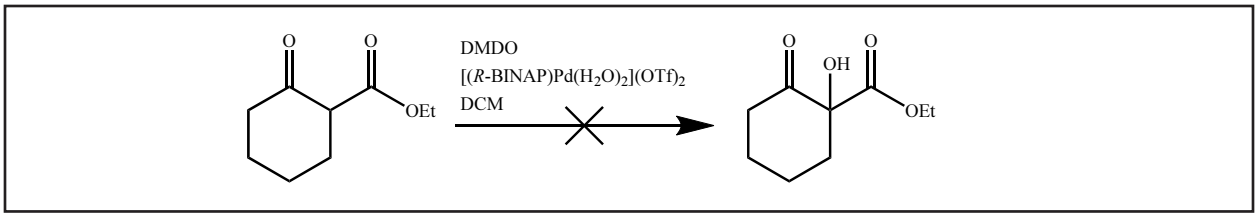
*2.1 eq of base were used for R=H. All other reactions used 1.2 eq of base

addition was optimal.

A variety of changes were attempted to improve the result of the aldol reaction, including the variations shown in table 3.1, but also additional modifications. Among these, attempts with acid chlorides and esters instead of aldehydes, attempts with several different solvents, and attempts where the substrate was changed from an imide to an ester were notable, but did not improve the yield of the reaction. Finally, a 44% yield was achieved, which is similar to published routes.[57] With reproducible results in the aldol condensation, it was finally possible to move on to the next step.

As shown in scheme 3.1, the selective creation of a TBS-ether[59] at the ring hydroxyl gave **3.4**. Notably, the mono-protection reaction was conducted at room temperature for only one hour, because longer times favored the double-protection. The selective protection was possible because of the relative rigidity of the 5-member ring and the relative ease with which the 1,3-chain hydroxyl can hydrogen bond as compared with the 1,2-ring hydroxyl.[60] The yield of the protection reaction was consistently in the high 70% range.

Next, a Dess-Martin oxidation to the diketone was envisioned. This would have allowed a subsequent stereoselective DMDO hydroxylation[61,62] to give ***vii***. However, the DMDO reaction did

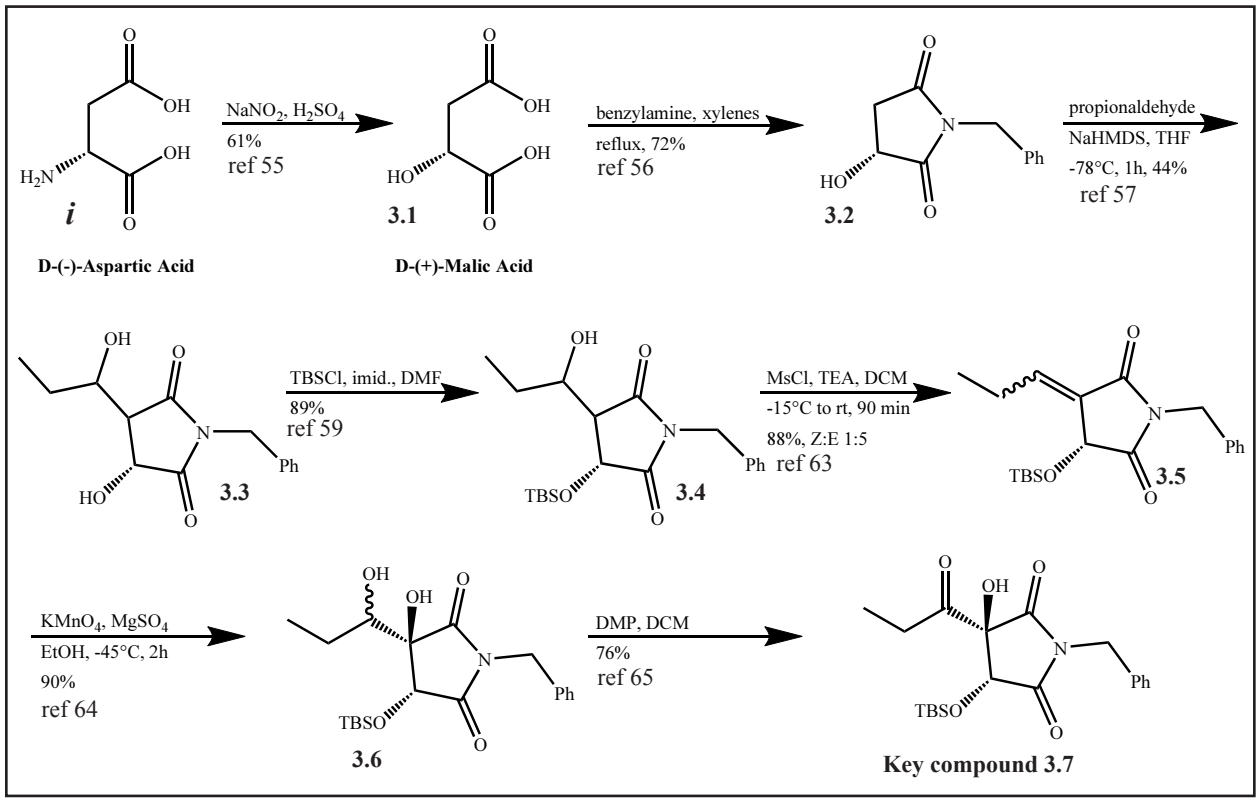


Scheme 3.2: An unsuccessful DMDO hydroxyl installation with a test substrate

not produce the desired result in the preliminary reactions studied (schemes 3.1 and 3.2). While it should be possible to install a hydroxyl group in a stereoselective fashion between two carbonyl groups with a palladium catalyst according to Hii[61] et al., their result could not be duplicated.

3.2: The Second Effort Toward (–)-Azaspirene

To obtain the necessary tertiary hydroxyl in **3.6** (schemes 3.1 and 3.3), a dehydration and subsequent dihydroxylation were considered as an alternative to the palladium-catalyzed hydroxylation thus far attempted (schemes 3.1 and 3.2). If the secondary hydroxyl group in **3.4** could be dehydrated, the resulting double bond could be dihydroxylated in a stereoselective fashion to give **3.6**. In practice, the dehydration of **3.4** in the method of Procter[63] with triethylamine and methanesulfonyl chloride resulted in product **3.5** with a ratio of 1:5 Z:E, with a total yield often

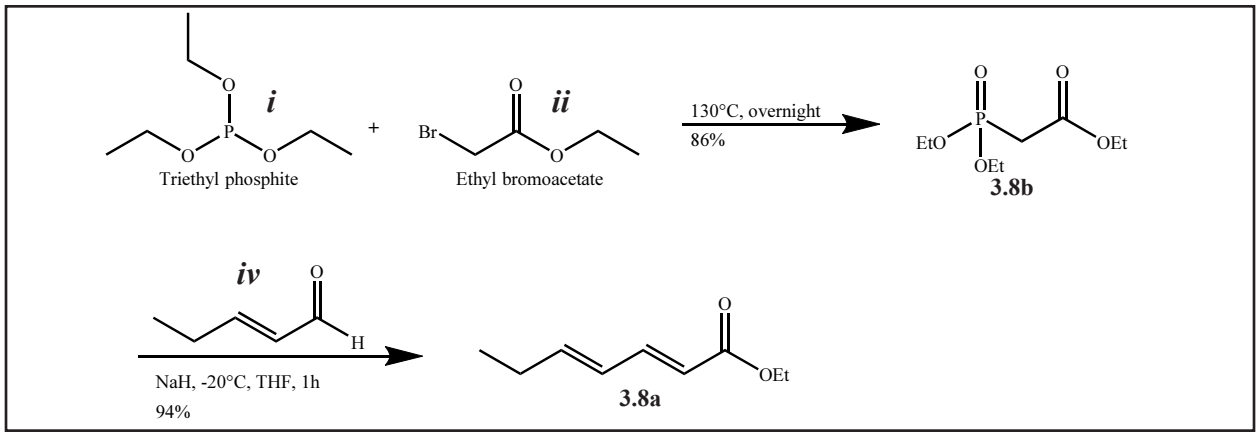


Scheme 3.3: The Bergdahl-Kelly Second Synthetic Attempt

over 90% (scheme 3.3). Dihydroxylation in a stereoselective manner was necessary, and Sharpless asymmetric dihydroxylation was an obvious choice. However, in an attempt to avoid the use of osmium reagents, it was expected that the bulky TBS ether could direct a hydroxylation with potassium permanganate in the method of Reissig.[64] Reissig's process proceeded smoothly to give **3.6**, with the addition anti to the TBS-ether. This provided the tertiary hydroxyl group with the correct stereochemistry, and the secondary alcohol in the same 1:5 ratio as the Z:E isomers, in total yields approaching 90%. The secondary alcohol in **3.6** was successfully oxidized in yields in the mid-70% range with Dess-Martin periodinane[65] to give **key compound 3.7**. However, occasionally the minor dihydroxylated product of the Z isomer would be slow to oxidize. In those cases, Jones[66] oxidation was used, and consistently provided comparable results. The product (**key compound 3.7**) was substantially similar to key intermediates in each of the major prior schemes (Tamm **2.11**, Tadano **2.14**, Osada **2.21** and Tanabe **2.46**). This structure resembles the eastern ring of the spirocycle closely, including the crucial components to begin creating the western portion of azaspirene (scheme 3.3).

3.2.1: Adding the Tail

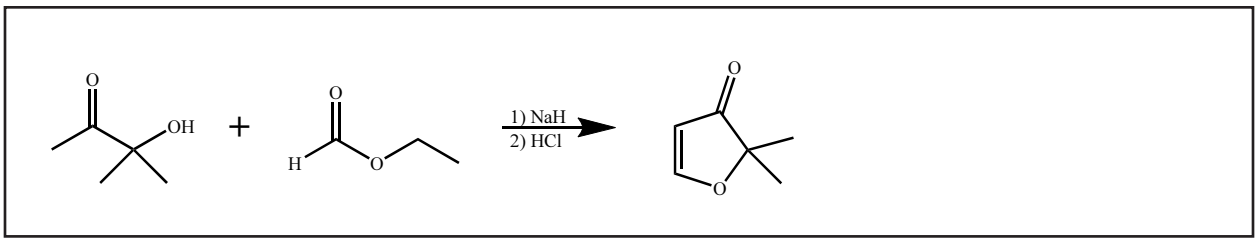
With **key compound 3.7** (scheme 3.3) in hand, it was necessary to incorporate the unsaturated "tail" of the molecule. Employing Watanabe's[67] method (scheme 3.4), using triethyl phosphite (***i***) and ethyl bromoacetate (***ii***), triethyl phosphonoacetate (**3.8b**) was formed in an overnight reaction. Compound **3.8b** was then subjected to a Horner-Wadsworth-Emmons reaction with 2-pentenal



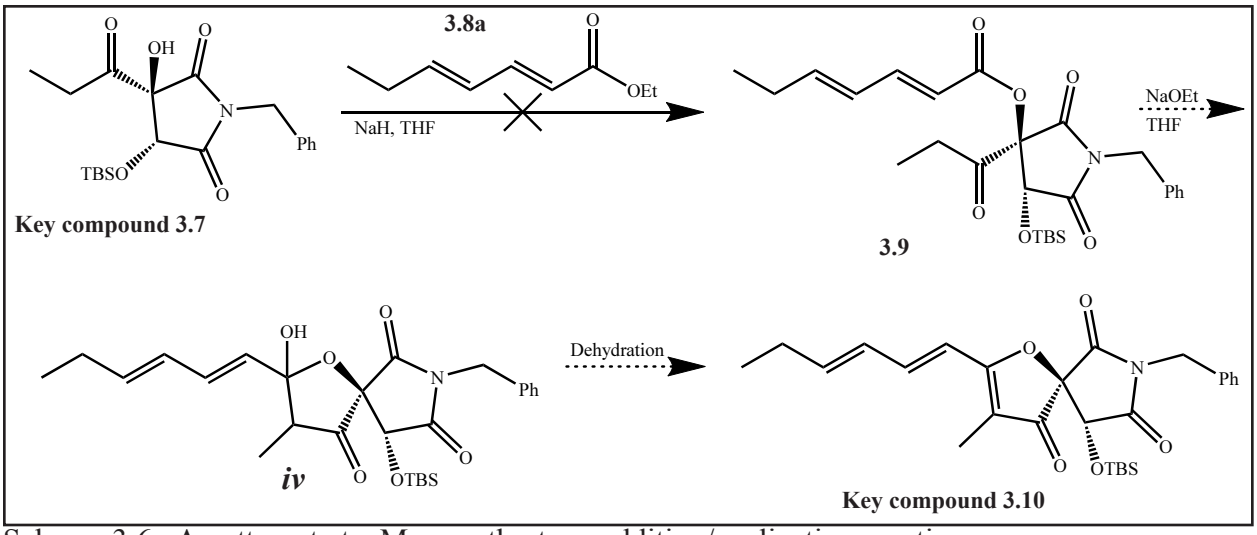
Scheme 3.4: Synthesis of the tail of (–)-azaspirene

(***iv***) using Marquet's method[68] to obtain the doubly-unsaturated ethyl heptadienoate (**3.8a**). A very small amount of inseparable *cis-trans* product was a common side-product, which can be seen in the H-NMR as a very small peak next to the CH=CHCH_2CH$_3$ peak, at 2.34 ppm, once the tail has been added to spirocycle **3.7**.

The first approach envisioned employing a tandem trans esterification-cyclization similar to the method of Margaretha[69] (scheme 3.5) to add the tail ester **3.8a** to **key compound 3.7** (scheme 3.6). The Margaretha approach was attractive because an ester was added to a tertiary alcohol to form a β-oxygenated enone similar to the western ring of azaspirene in a one-pot process. The relative steric bulk of the imide substrate and the less electrophilic unsaturated ester necessary for azaspirene made this approach unworkable, however. Instead, a two-step approach was applied (scheme 3.7)– a standard DCC coupling[70] reaction followed by a ring-closing aldol reaction.

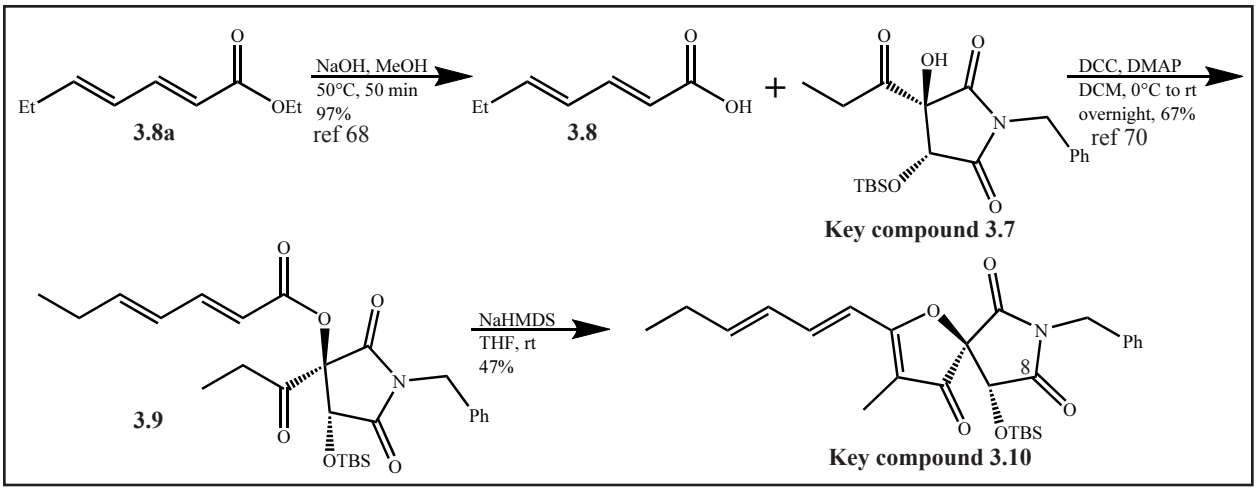


Scheme 3.5: An Example of the Margaretha Method

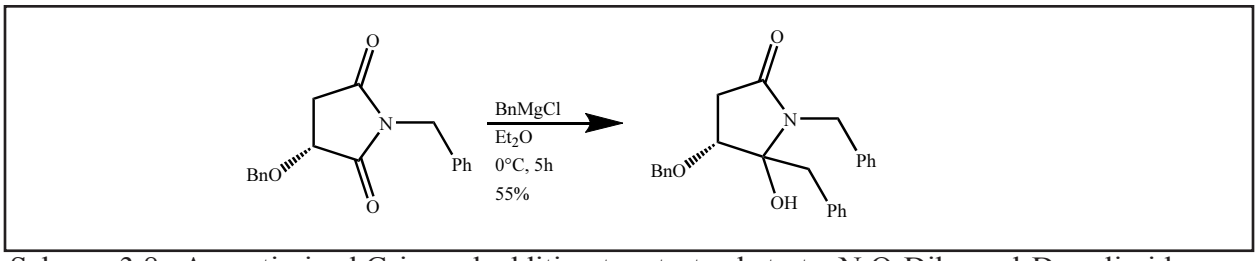


Scheme 3.6: An attempt at a Margaretha-type addition/cyclization reaction

First, the unsaturated ester (**3.8a**) was hydrolyzed[68] to acid **3.8**. The acid was coupled to **3.7** using a Steglich esterification[70] to form **3.9** (scheme 3.7). Finally, the western ring of the spirocycle was formed with strong base. The elimination of the hemiacetal hydroxyl formed the necessary double bond during workup, to give **key compound 3.10**, which completed the main spirocyclic framework of (–)-azaspirene in 8 steps from D-(+)-malic acid, in a 5.3% overall yield. In order to complete (–)-azaspirene, a benzyl group needed to be incorporated in not only a regiospecific, but also in a stereospecific way to C-8 of spirocycle **3.10**, which was expected to be complicated in a molecule with three carbonyls available. The product of the benzyl addition would additionally



Scheme 3.7: Tail hydrolysis and coupling, closing the western ring



Scheme 3.8: An optimized Grignard addition to a test substrate, N,O-Dibenzyl-D-malimide

need to be deprotected by the removal of the TBS-ether and the N-benzyl protecting groups.

3.2.2: The Benzyl Grignard

As the final step prior to deprotection in the route to (–)-azaspirene, it was necessary to incorporate a benzyl group in a stereoselective fashion to C-8 of **key compound 3.10** (scheme 3.7). A few options were considered, but the most straightforward seemed to be the addition of a benzyl Grignard to compound **3.10**. The benzyl Grignard reaction was studied with the starting malimide substrate with various protecting groups on the alcohol group (scheme 3.8). Under the right conditions[72] the addition was reported to be selective[71,72] at the desired imide carbonyl. In the case of **key compound 3.10**, it was expected that the TBS-ether would shield the back face of the ring, and that the top imide carbonyl and ketone would be too sterically congested to allow any addition. Support for this hypothesis included literature reports that in the malimide substrate the addition at the desired imide carbonyl is favored.[71] The benzyl Grignard addition was selective to the malimide substrate under relatively warm conditions (0 °C) and with a benzyl ether protecting the chiral alcohol (scheme 3.8). A TBS-ether in the same position proved nonselective, resulting in addition at both imide carbonyls, presumably due to a reduced chelation effect with the silyl

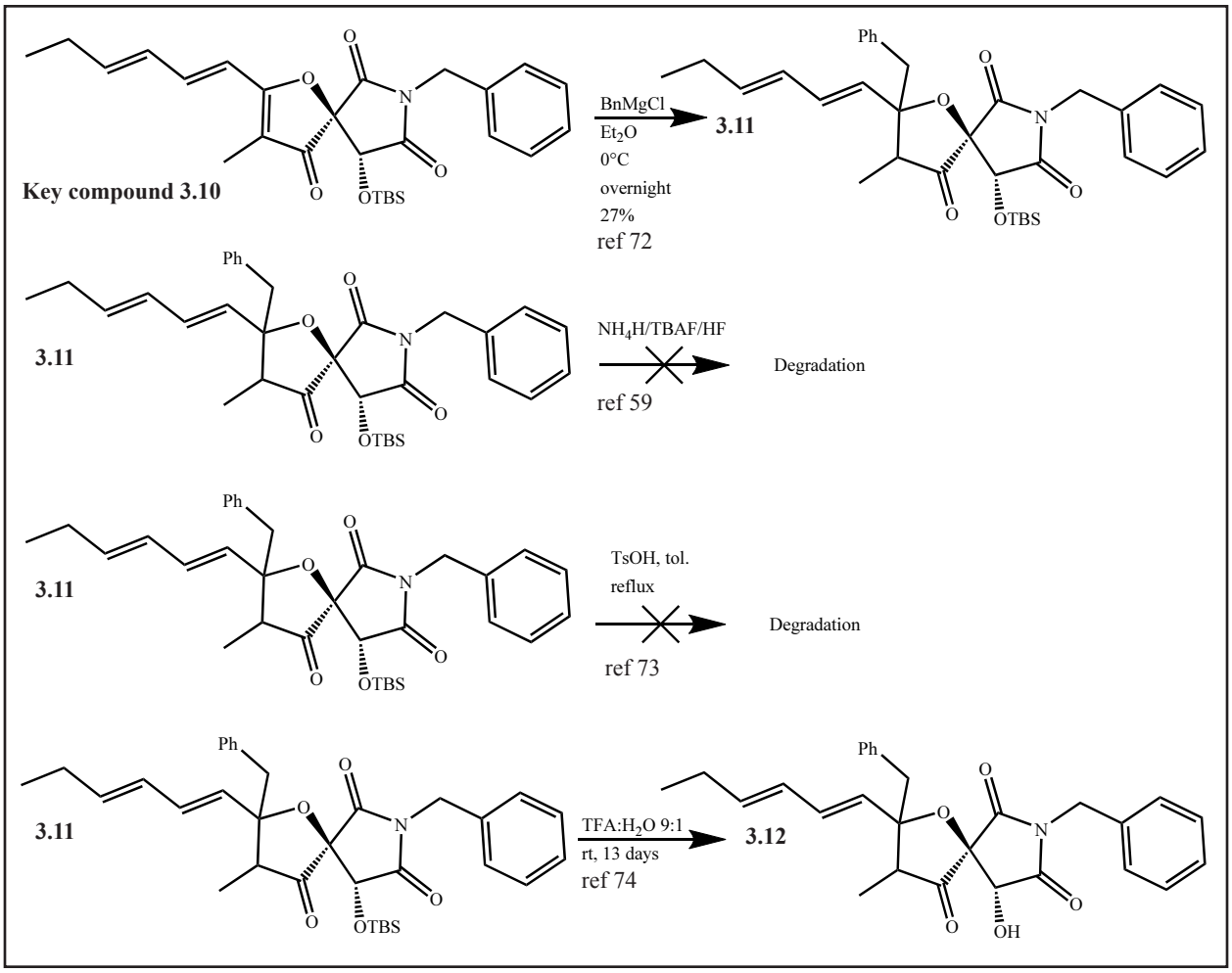
ether. Diethyl ether as the solvent was selective for the desired imide carbonyl, and THF was non-selective, presumably for the same reason. At reaction temperatures warmer or cooler than 0 °C, the yields for the benzyl addition decreased. The optimized conditions using the malimide substrate are shown in scheme 3.8.

Given the appropriate conditions for adding a benzyl Grignard to the malimide substrate, these conditions could be applied to **key compound 3.10**. Unfortunately, the benzyl Grignard reagent added to none of the three carbonyls in the molecule– they were all evidently too sterically congested. Instead, the benzyl group added to the double bond in the western ring of the spirocycle to yield **3.11** in a 27% yield (scheme 3.9). The conjugate addition was supported by the following evidence: in the H-NMR spectrum, the appearance of a quartet at 2.70 ppm represented the H installed at C-3 on the spirocycle, which was split by the three hydrogens on C-16. The signal from the three protons on C-16, in turn, changed from a singlet at 1.74 ppm in the starting material to a doublet at 0.98 ppm. In the IR, the loss of a peak at 1619.89 cm^{-1} from the starting material to the product indicated the absence of the conjugated ketone. In the C-NMR spectrum, the signal at 207 ppm indicated the ketone was still present, though it was shifted upfield from the starting material, which is an indication of the loss of the double bond. However, the C-NMR evidence is ambiguous on its own, given that the signals change from 4 signals in the range of 166-194 ppm (the carbonyl range) in the starting material, which represent the three carbonyls and the conjugated C-2 of the spirocycle, to instead 3 signals for the product, as would be expected for any 1,4-addition product. Given the NMR and IR spectral evidence together, however, the loss of the double bond at C-2 is certain (see the appendix for the NMR and IR data).

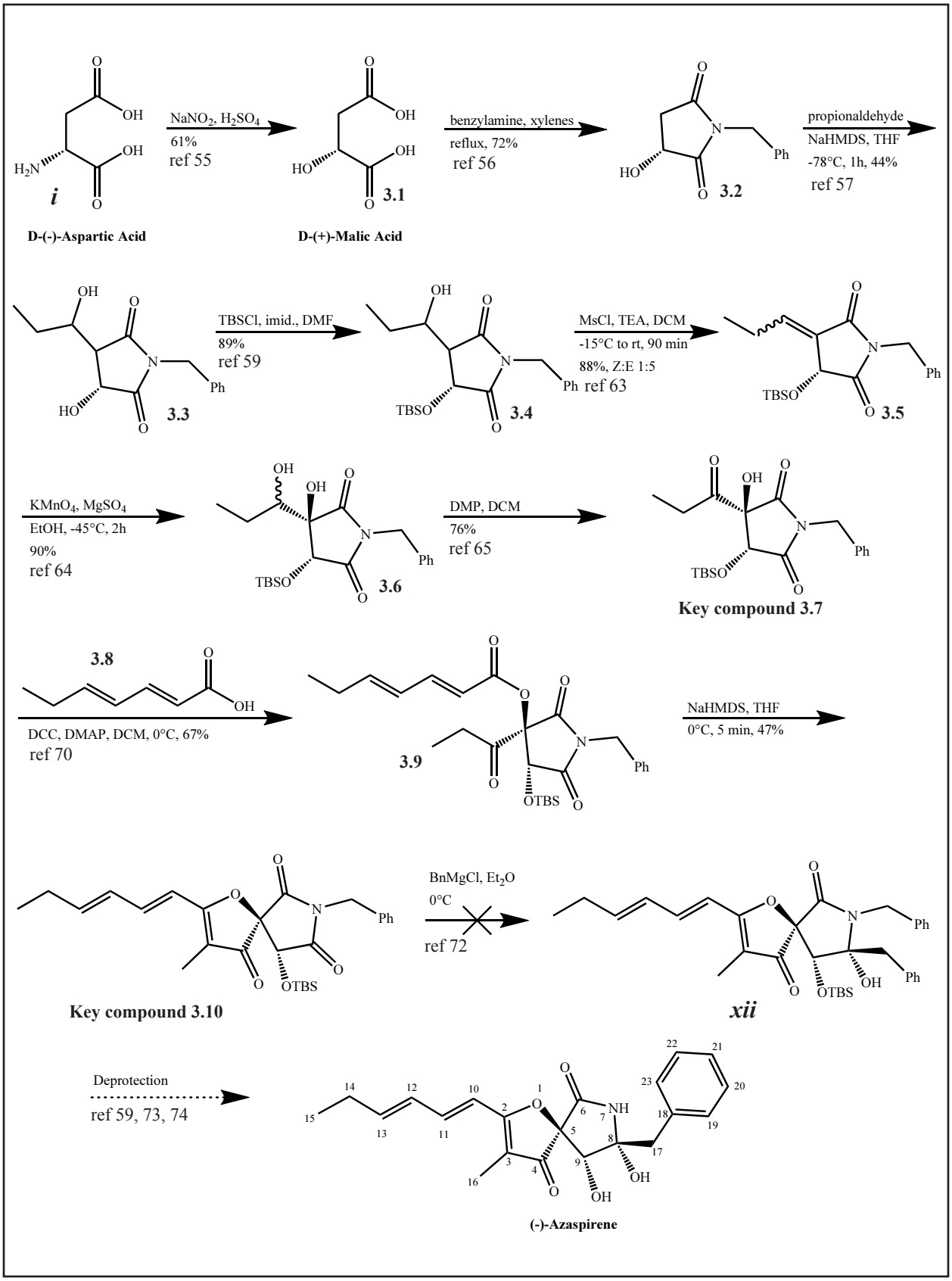
In an effort to block the conjugate addition, different versions of an acetal protection of the ketone were attempted, both acidic and basic, using the smallest substrates available (a methanol/ methoxy and an ethylene glycol protection were both attempted). Unfortunately, the starting material was reclaimed without any reaction, presumably because of the same steric congestion that prevented the Grignard addition in the first place. It became clear that another adjustment in the approach was necessary.

3.3: Conclusion of the Route

The investigation described has provided a way to reliably build the spirocyclic core of azaspirene, and may provide a new way to access the pseurotin family of compounds. However, there are still two issues that must be resolved before the synthesis of the target molecule can be achieved: the N-benzyl group must be substituted for a protecting group that is more easily removed, and additional strategies for adding the benzyl group to C-8 in a stereoselective manner need to be investigated. Despite this ongoing process, however, another successful synthesis of azaspirene was achieved in the Bergdahl lab, in part based on the successes and problems of the initial described approach.



Scheme 3.9: Grignard conjugate addition and removal of TBS group



Scheme 3.10: Summary of the route to Key Compound 3.10 in the pursuit of azaspirene

3.4: The Montgomery Route to (–)-Azaspirene

In 2016, Dr. Timothy Montgomery completed an alternative route to (–)-azaspirene in which a chiral lactone was used as the starting material, thereby circumventing some of the problems associated with the previously discussed effort initiated with malimide. The advantage of substituting an oxygen for the nitrogen in the heterocyclic starting material was evidenced by simpler purification and elucidation throughout the route without the troublesome imide group.

The Montgomery synthesis was initiated with a chiral lactone (***vii***), which serves as a chiral template for creating the eastern ring of azaspirene (scheme 3.11). Unfortunately, the benzyl-substituted chiral lactone (***vii***) is difficult to find commercially. Therefore, the starting material was made from L-phenylalanine (***i***): a process which adds 5 steps to the synthesis and produces ***vii*** in a 65% overall yield.

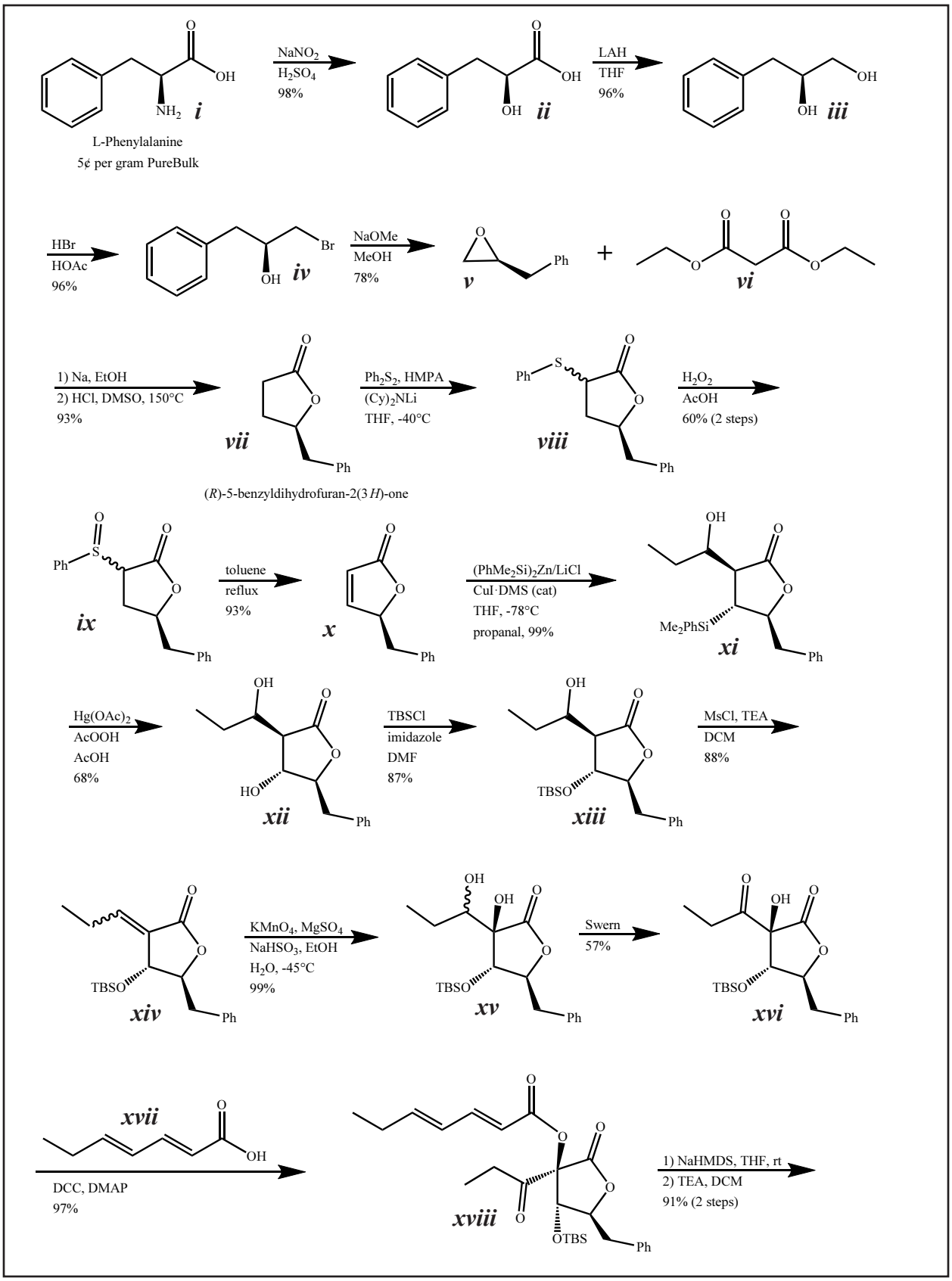
L-Phenylalanine (***i***) was subjected to a diazotization to give ***ii***, and reduced to the diol to give ***iii*** with LAH (scheme 3.11). A bromination of ***iii*** gave ***iv*** and an epoxidation of ***iv*** yielded (phenylmethyl)oxirane (***v***). The epoxide (***v***) was opened under basic conditions while exposed to diethyl malonate (***vi***). A subsequent decarboxylation yielded the chiral lactone (***vii***).

Next, a double bond was introduced with diphenyldisulfide to give ***x*** over three steps (though phenylselenide compounds work as well in just two steps). Then a novel stereoselective conjugate addition was performed with catalytic copper iodide-dimethylsulfide complex and a novel silyl zinc reagent, which in a one-pot reaction was coupled in a stereoselective fashion with propanal to give ***xi***. A Tamao-Fleming oxidation was employed next to give ***xii***. After TBS

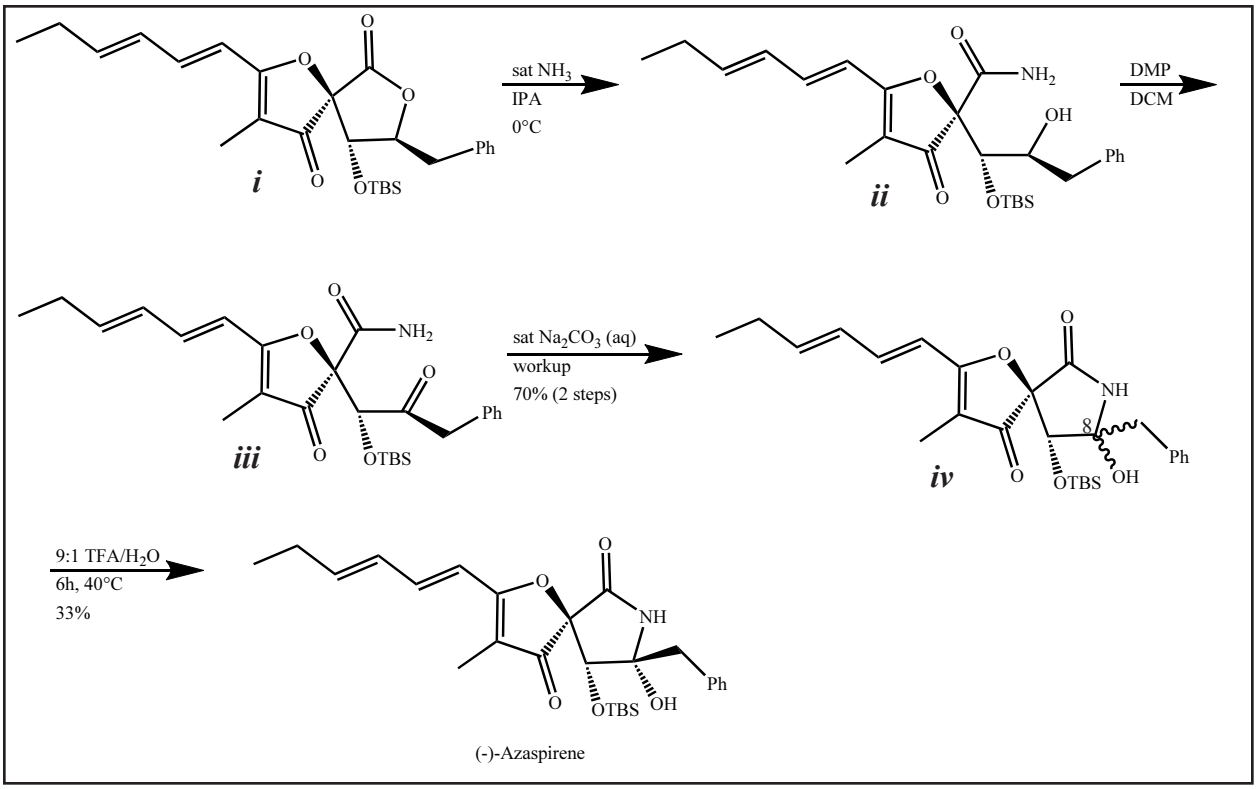
protection of the chiral ring alcohol to give ***xiii***, the chain alcohol was subjected to E2 dehydration conditions to install the double bond (***xiv***). Next, a diol was introduced in a stereoselective fashion anti to the TBS-ether with potassium permanganate to give ***xv***. Dess-Martin oxidation failed at this point, but a Swern oxidation succeeded to give ***xvi*** in acceptable yields. This was followed by a DCC coupling which paired 2,4-heptadienoic acid (***xvii***) to the tertiary alcohol of ***xvi*** to yield ***xviii***. The application of strong base to ***xviii*** (scheme 3.11) resulted in formation of the spirocycle moiety and provided ***i*** (scheme 3.12).

The addition of saturated ammonia in isopropanol transformed the lactone ***i*** to lactam ***iv*** over three steps, a process which scrambled the stereochemistry at C-8 (scheme 3.12). Gratifyingly, when exposed to TFA, the stereochemistry was corrected to form the more thermodynamically favorable diastereomer via the opening and closing of the amide ring. The TBS group was also removed by TFA, yielding (–)-azaspirene, in 11 steps from the lactone with an overall yield of 6% (though as shown, 15 steps from the lactone with a yield of 3%).

Chapter 3 contains material being prepared for submission for publication where the dissertation author is a principal researcher and co-author on the manuscript. I'd like to thank Dr. Timothy Montgomery, Dr. David Schmit, Paul Smith, and Kevin Walsworth for their permission to use this material.



Scheme 3.11: The Montgomery synthesis of (–)-Azaspirene part 1



Scheme 3.12: The Montgomery synthesis of (–)-Azaspirene part 2

Chapter 4: Conclusion

Natural products synthesis is not a trivial task. There are many approaches to chemical transformations. There are also many resources available for help along the way, not the least of which is the experience of those scientists who attempted similar transformations previously. The route to (–)-azaspirene has been a process in studying previous syntheses of the pseurotins and their drawbacks, with a constant imperative to improve on past efforts. An efficient, high yielding, generally applicable synthesis of the pseurotin family of compounds will allow further study of these biologically active molecules, and could help yield compounds which will improve the human condition through the treatment of disease.

The Tamm route to pseurotin A is notable because it was the first attempt toward the synthesis of this family of potentially useful compounds. It failed in its main task of actually synthesizing a pseurotin, however. The Osada-Kakeya and Tadano routes are notable because their strategies are both asymmetric and have been used to synthesize multiple members of the pseurotin family of compounds. Their routes are too low yielding to be practical, however. Each of the strategies takes a different approach which broadens the knowledge of the chemistry and biological activity of the pseurotins, but does not improve on the main problem of the Osada-Kakeya and Tadano routes: their low yields.

Of all the asymmetric routes, it is again notable that the first, the Osada route, is still the most viable, at least as measured by the number of pseurotins they have produced with it. But it is interesting that the new Han racemic route achieved an overall yield nearly 10 times higher than

the Osada route, though it is racemic. It is also worth noting again that so many of the more recent published routes to the pseurotins were not improvements at all, but still contained interesting chemistry that was worth studying.

Our route to (–)-azaspirene in this context is still a work in progress. There are many improvements currently being investigated which could lead to more efficient asymmetric syntheses of the pseurotins.

Chapter 5: Future Work

Both the current effort and the Montgomery route are worthy of study because of their potential for fewer steps and higher yields in the synthesis of the pseurotin family of compounds than their competitors. The primary work needed to improve the malimide strategy, which is in one sense the most economical in terms of steps and potential stereocontrol, is selecting workable protecting groups, and the addition of the final benzyl group on C-8 of compound **3.10** (scheme 3.10).

In order to add the troublesome benzyl group to C-8, it may be possible to incorporate Rovis's[40,46] Barbier-type samarium or a benzyl zinc coupling instead of the Grignard addition on C-8 of the advanced spirocycle. Rovis' trapped enolate method to protect the ketone is also worth further study in the context of the benzyl addition.

Finally, taking the best aspects of each of the routes discussed and combining them, a new path to azaspirene should be possible. By having a concise record of the other routes to the psuerotins, more of these ideas will be more accessible for future study.

Part II: Chemical Studies in Copper(I) Iodide Dimethyl Sulfide Catalyzed Asymmetric Conjugate Addition

Chapter 6: Copper Catalyzed Silyl Conjugate Addition Chemistry

6.1: Introduction: Disilylzinc/copper and Oxazolidinone Chemistry

Silicon-carbon bond creation through conjugate addition chemistry is a classic approach which has been used in organic synthesis for decades.[3] Silicon groups are often used as bulky directing groups or "masked" hydroxyls since they can be easily oxidized through Fleming-Tamao[75] chemistry with retention of stereochemistry to form the corresponding alcohol groups.

6.2: The Bergdahl Oxazolidinone Methodology

In 2002 our laboratory devised[76] a method for adapting Evans' chiral auxiliary to create carbon-carbon bonds via asymmetric conjugate addition of lithium monoorganocopper reagents with stoichiometric copper.[75,77]

In 2003, this method was expanded[78] by adding silyl groups via conjugate addition with a special copper iodide-dimethyl sulfide catalyst, with close to quantitative yields of the β-silyl addition product. Additionally, the Bergdahl group verified that the inclusion of Evans' chiral

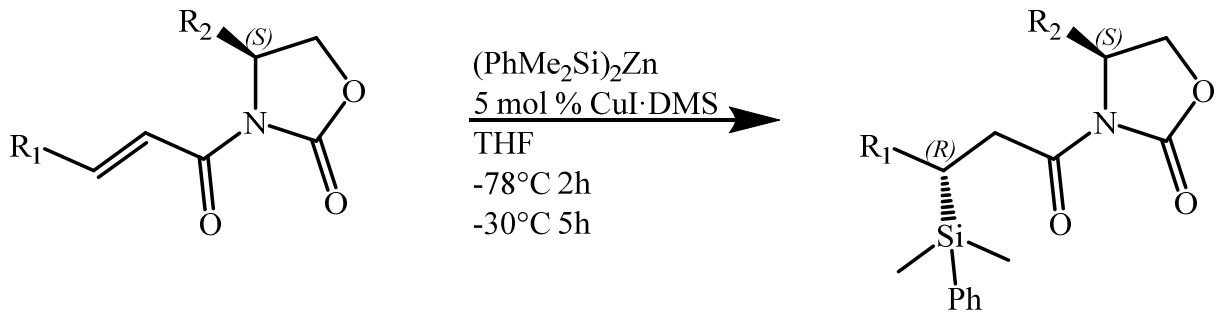
auxiliary would selectively direct the conjugate addition reaction to form a masked asymmetric aldol fragment product.[78,79] However, the reaction still required the presence of stoichiometric amounts of copper. In 2005 this method was again expanded[80] to include the use of dimethyl sulfide as a solvent, which was more efficient for some substrates with congested β-carbons.

In 2004, Oestreich and Weiner[81] published their approach to silyl conjugate addition via a disilyl zinc reagent using a variety of catalytic copper reagents. Their method employed zinc chloride instead of the more common pyrophoric dialkyl zinc reagents, and was performed on a variety of substrates, with racemic products. They updated their work with three papers in 2006, the first[82] of which expanded their methodology to incorporate additions to substituted acetylenes, 1,3-dienes and styrenes. The second[83] paper detailed their efforts in adapting their approach to provide asymmetric products, which were not ultimately successful. The third[84] paper outlined the enantioselective addition of silanes to special chiral alkenyl substrates. However, the copper-catalyzed silyl conjugate addition reactions as outlined in the first two papers were not successfully adapted to provide asymmetric products.

Our laboratory combined the prior effort in enantioselective silyl conjugate additions with Oestreich's method[81] in creating disilyl zinc reagents with zinc chloride, and developed a protocol for adding silyl groups in a stereocontrolled fashion to these substrates. The results are shown in the schemes that follow (see table 6.1).

This method improves on prior work because it was successful in creating silicon-carbon bonds through conjugate addition in a stereoselective fashion using catalytic copper and Evans'

Table 6.1: Yield and dr of asymmetric conjugate addition reactions on various substrates

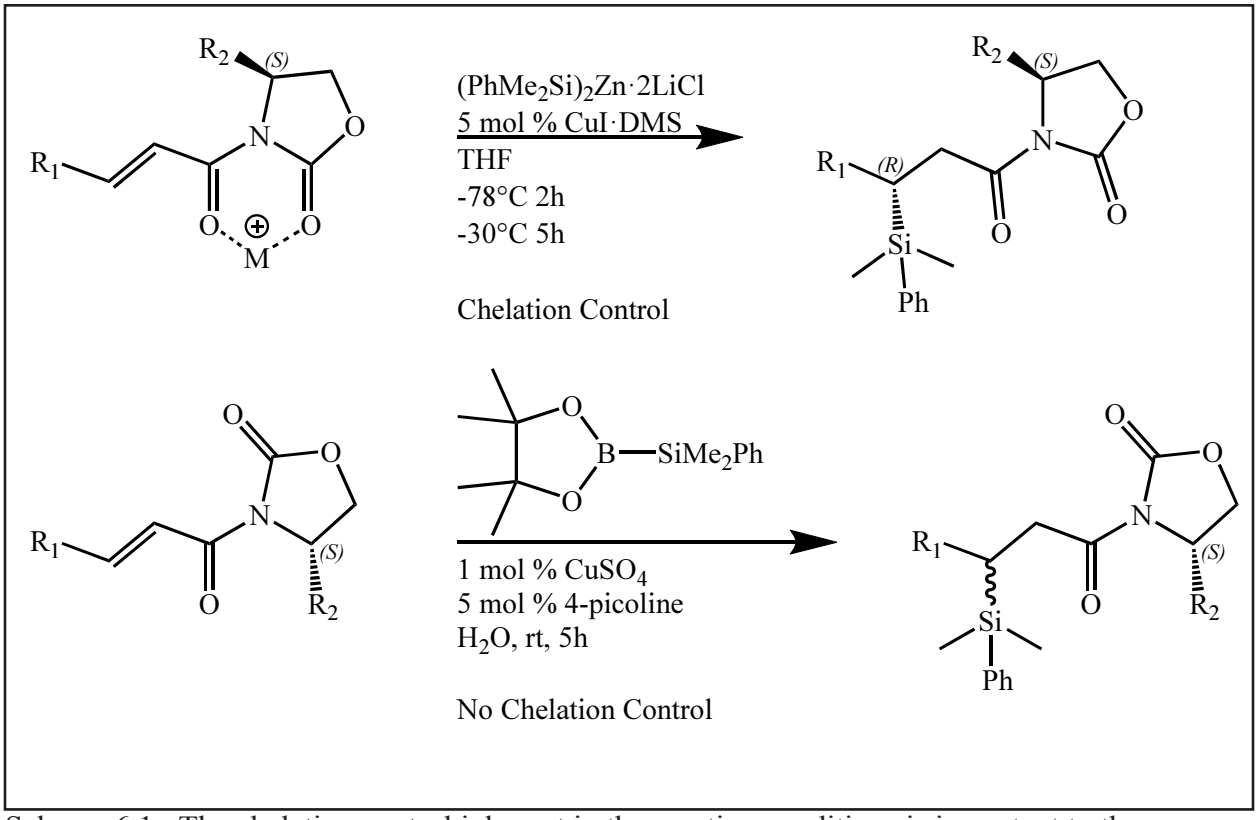


Cpd #	R_1	R_2	% Yield	dr
6.1	Me	iPr	91	87:13
6.2	Ph	iPr	90	87:13
6.3	n-Pr	iPr	80	87:13
6.4	Me	t-Bu	95	95:5
6.5	Ph	t-Bu	82	96:4
6.6	n-Pr	t-Bu	80	97:3
6.7	Me	Bn	91	92:8
6.8	Ph	Bn	87	84:16
6.9	n-Pr	Bn	93	91:9
6.10*	Me	Ph*	95	95:5
6.11*	Ph	Ph*	89	97:3
6.12*	n-Pr	Ph*	82	98:2

*These reactions have stereochemistry opposite to that shown in the figure: the stereochemistry for the silyl group is *(S)* and R_2 is *(R)*.

chiral auxiliary. It has been shown that disilylzinc reagents can be utilized in conjugate addition reactions in a stereoselective fashion with high yields and diastereomeric ratios, without pyrophoric alkyl zincs or any other additives. This approach has also been shown to be generally applicable to unsaturated carbonyl compounds, and is stereocontrolled when our conditions are applied.

While the asymmetric nature of the reaction was preserved at the temperature indicated, increasing the reaction temperature resulted in a drastic reduction in diastereomeric ratio, and approached a racemic mixture. When a similar reaction was run in more polar solvents, like water, the result was also racemic, likely due to the inhibition of the chelation effect of the metal ion (either lithium or zinc) between the two carbonyls of the substrate, allowing the chiral oxazolidinone group to freely rotate (see scheme 6.1). The larger substituents on the oxazolidinone group also



Scheme 6.1: The chelation control inherent in the reaction conditions is important to the asymmetric nature of the reaction

produced higher diastereomeric ratios, and the differences in the alkenyl R group proved to be less important to the result.

In developing the conditions for the reaction, several variables were important. First, the silyllithium reagent must be freshly prepared and used within a few days. Silyl anion reagent solutions kept under argon in the freezer for longer periods caused reduced yields. Second, the temperature of the reaction must be monitored closely, especially for the disilyl zinc reagent itself: once it is made it is better to transfer it via cannula than syringe, especially for large reactions. The yield and the stereoselectivity of the addition suffered with increased reaction temperature for oxazolidinone imides. However, for non-oxazolidinone substrates that contain double bonds which are particularly electron-poor or held in a favorable s-cis conformation, the conjugate addition reaction proceeded nicely at -78 °C without warming to -30 °C. Conversely, for those substrates with bulky groups near the double bond or relatively electron-rich double bonds, the reaction may need to be warmed to as much as 0 °C for the reaction to proceed, or may not react at all.

6.2.1: A proposed catalytic cycle for silylzinc conjugate addition

The conjugate addition reaction as outlined with catalytic copper allowed for improvements in atom economy and simplification of product workup and purification. It is expected that the reaction follows a catalytic cycle similar to the one proposed by Oestreich and Weiner[81] (Figure 6.1). In the catalytic cycle, copper(I) iodide accepts a silyl anion from zinc, producing a negative charge at the copper that is balanced by the positive charge at the zinc. Once the enone substrate is

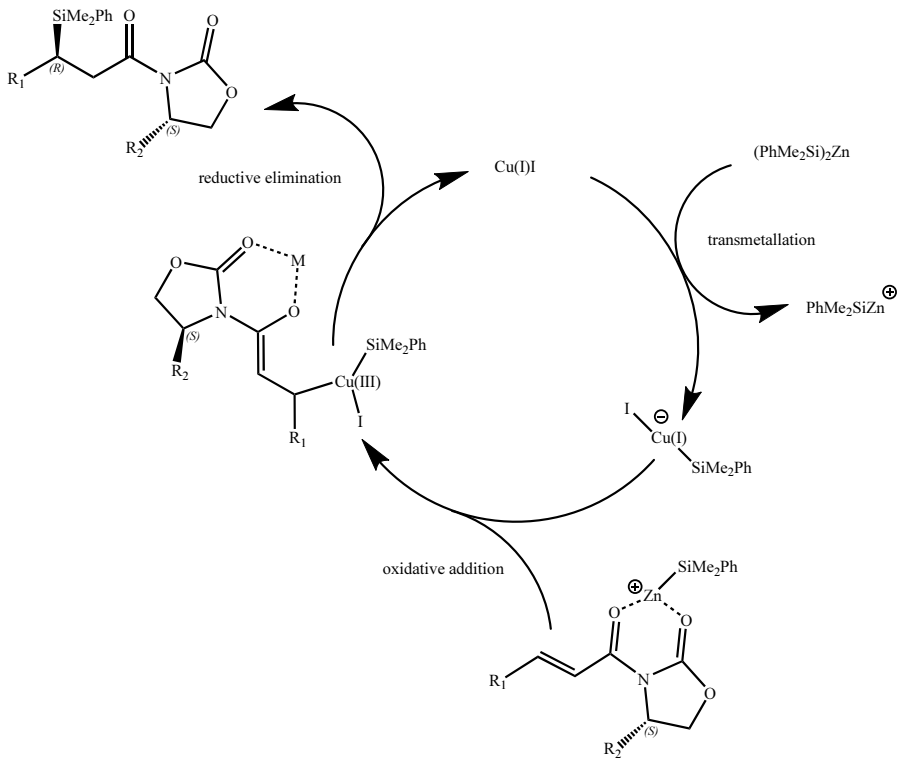


Figure 6.1: A proposed catalytic cycle

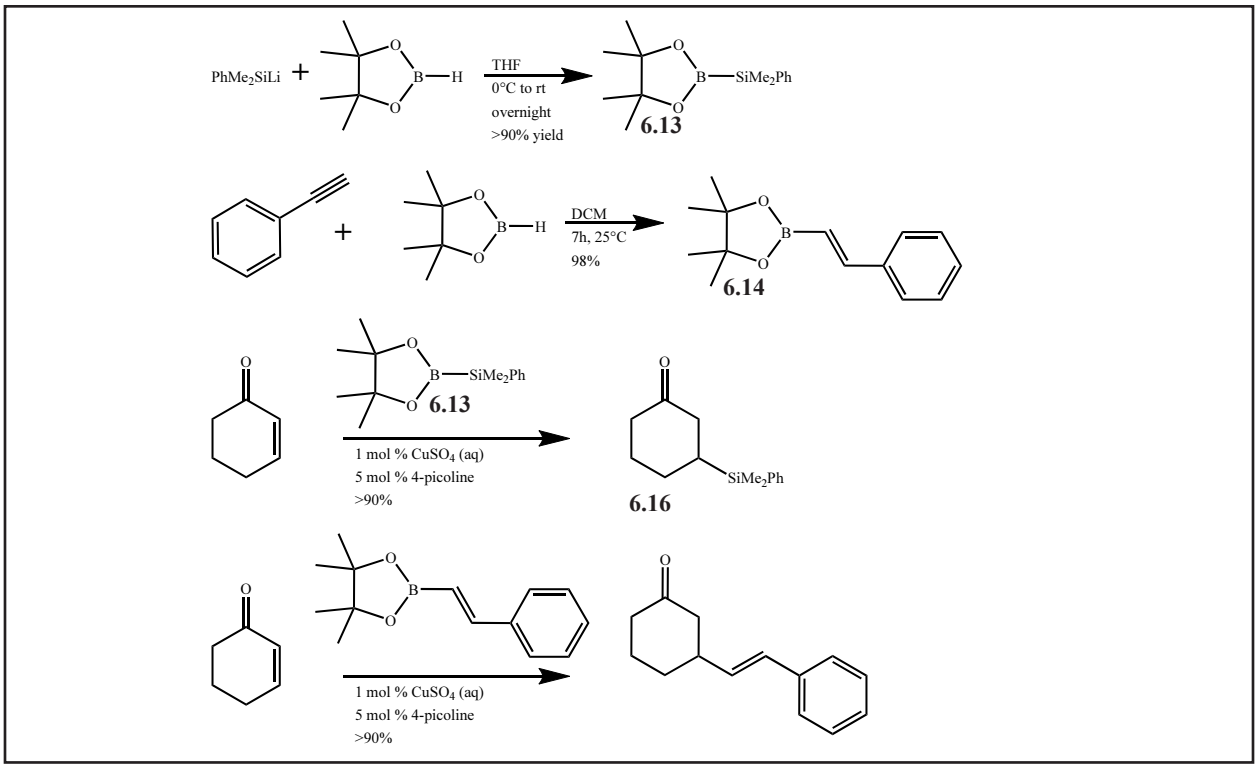
introduced to the reaction the zinc likely chelates to the carbonyl, especially given the 1,3-dicarbonyl available in the main oxazolidinone substrate. The anionic copper adds to the double bond on the enone by oxidative addition on the π-face opposite to the oxazolidinone R_2 group. Finally, by reductive elimination a bond is formed between the silicon and the β-carbon, with stereochemistry opposite to the oxazolidinone R_2 group, and copper(I) iodide is regenerated. Notably, the second equivalent of silyl anion in the cycle, shown attached to the zinc, was never observed to add.

Given the high yields and high stereoselectivity of these reactions, accessing chiral silyl addition products is a simpler, more efficient process. The β-silane products can be used to access chiral alcohols that mimic aldol condensation fragments by utilizing the Fleming-Tamao[75] oxidation technique to convert the silyl group to a β-hydroxy group with retention of stereochemistry. The

oxazolidinone chiral auxiliary can easily be removed from most target substrates with mild sodium methoxide/dimethylcarbonate[85] to give a substrate methyl ester, or with hydroxides to give a substrate carboxylic acid. With stronger reducing agents like, for example, lithium aluminum hydride, access can be provided to a substrate alcohol. The chiral auxiliary can then be retained and reused.

6.3: Racemic conjugate addition of silyl groups in water with boron-silicon reagents.

In 2012, Calderone and Santos[86] published an account of their addition of silyl groups to enones in water using a pinacolboron-dimethylphenylsilyl reagent. Given their success in adding similar silyl anions in a stereoselective fashion to enones in organic solutions, it seemed potentially

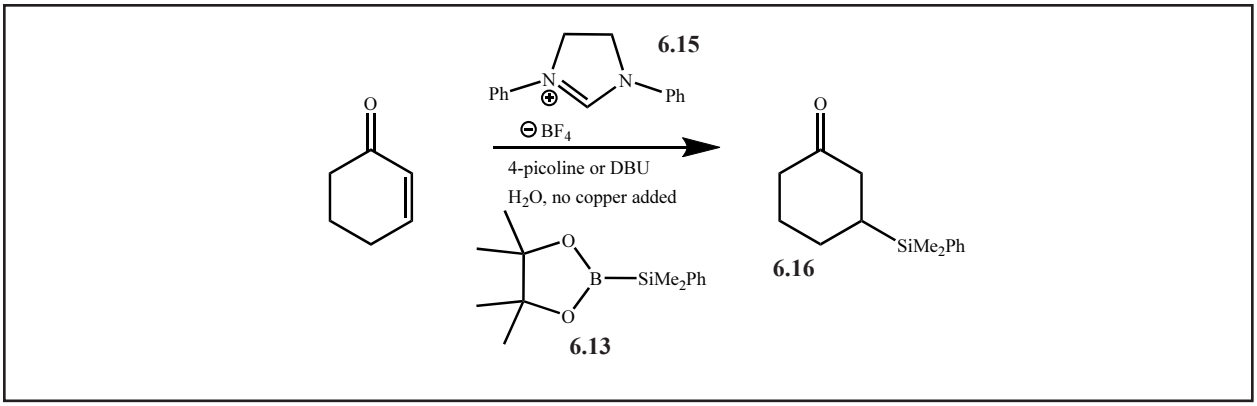


Scheme 6.2: Synthesis of boron reagents. Aqueous conjugate addition reactions with boron reagents

fruitful to investigate whether the Calderone and Santos protocol could be expanded using our oxazolidinone method, using water as a medium and utilizing their silyl-boron reagent and catalytic copper(II) sulfate. The pinacolboron-dimethylphenylsilyl reagent was easily prepared from pinacolborane and an identical silyl anion reagent as we used previously, by using lithium metal and dimethylphenylsilyl chloride following Calderone and Santos's protocol.

With the boron-silicon reagent in hand, the silyl group was added to α,β-unsaturated carbonyl compounds in conjugate addition reactions in water in an adapted Calerone and Santos protocol. A vinyl-boron complex produced in a similar way to their silyl-boron protocol showed that a carbon-based approach was also effective using the Calderone-Santos technique (scheme 6.2). When applied to chiral substrates including the oxazolidinones used in our prior procedures, the products were racemic. This was most likely because there is a significantly reduced chelation effect in the presence of water, which allowed the oxazolidinone to freely rotate along the carbon-nitrogen bond (scheme 6.1).

In an attempt to adapt the Calderone-Santos protocol to obtain a stereoselective product, a chiral catalyst framework was envisioned. An N-heterocyclic carbene (NHC), that would become



Scheme 6.3: NHC catalyzed addition of silyl groups to cyclohexenone

a chiral ligand for the copper and direct the conjugate addition reaction to produce products in a stereoselective fashion. As an initial step toward this approach, a simple NHC compound, a symmetrical, N,N-diphenyl-NHC tetrafluoroborate salt, created following the protocol of Lee and Hoveyda,[87] was employed. We combined the approaches of Calderone and Santos and Hoveyda by substituting Hoveyda's NHC for Calderone and Santos's boron complex. The NHC was expected to act as a tunable chiral delivery device for a variety of nucleophilic substrates in conjugate addition reactions, with a focus on the carbon- and silicon-based nucleophiles we used previously, and employing achiral α,β-unsaturated substrates. This approach using catalytic (5 mol %) NHC without added copper was promising, with conjugate addition products approaching 90% yields (scheme 6.3). The reaction did not proceed with the addition of the copper sulfate when utilized with catalytic NHC, however.

Subsequently, Sawamura's[88] group published a procedure for the stereoselective addition of carbon-based groups to α,β-unsaturated carbonyls using NHC complexes and copper(I) chloride, which may provide additional information for the adjustment of our approach. Specifically, adapting the Sawamura approach to allow conjugate addition reactions in an aqueous environment is a potential avenue for further study in this area.

6.4: Summary and Future Work

Copper conjugate addition reactions are important carbon-silicon and carbon-carbon bond formation reactions that have been used widely in organic synthesis, and can be particularly

valuable when stereoselective. The first part of this work improves on prior methods with a new protocol which uses a copper iodide-dimethylsulfide catalyst and silylzinc reagents to add silyl groups in a stereoselective fashion to α,β-unsaturated carbonyl compounds with oxazolidinone chiral auxiliaries in high yields and high stereoselectivity. It may be possible to further expand this protocol by performing the addition on new substrates, investigating other ways to make the addition stereoselective besides the use of oxazolidinones, and using silylzinc reagents that, once they are added, are more easily oxidized. The Montgomery work on azaspirene also suggests that a tandem conjugate addition-aldol reaction protocol may be a fruitful method to explore.

The second part of this chapter focuses on two distinct yet related approaches to silyl conjugate addition reactions. The first approach utilizes copper sulfate and either boron-silicon reagents or boron-carbon reagents in water to achieve respective racemic silyl or carbon-based conjugate addition to a variety of α,β-unsaturated carbonyl compounds. The second approach utilizes catalytic N-heterocyclic carbenes (NHCs) and silyl or carbon-based nucleophiles to achieve addition to similar α,β-unsaturated carbonyl compounds. While both approaches were successful, there is significant opportunity to expand the method; particularly with their potential for adding nucleophilic groups to α,β-unsaturated carbonyl compounds in a stereoselective fashion in an aqueous environment.

Chapter 6 contains material being prepared for submission for publication where the dissertation author is a principal researcher and author on the manuscript. I'd like to thank Dr. Timothy Montgomery for his permission to use this material.

Part III: Wittig Chemistry in the Teaching Laboratory: A Novel Water-Organic Interface Reaction

Chapter 7: Aqueous Wittig Chemistry

Since its discovery in the 50s by Georg Wittig,[89] the reaction that bears his name has been used extensively in organic synthesis to create carbon-carbon double bonds from carbonyl compounds and ylides,[90] and has been a subject of much research. Simply, the Wittig reaction is an energetically favorable reaction because of the special stability of the phosphonium oxides which are the main byproduct. Traditional Wittig reactions often use strong bases to deprotonate the Wittig salt to form the ylide, and most take place under inert atmosphere in organic solvents.

In 2005,[91] and expanded in 2007,[7] our lab published an adaptation of the classic Wittig procedure that takes advantage of the special properties of stabilized ylides to run Wittig reactions in heterogeneous aqueous sodium bicarbonate solution, an improvement which reduces the use of strong bases and organic solvents which are normally used for such reactions. This is not only an improvement in green chemistry methodology, because it virtually eliminates the use of organic solvents for the reaction, but it also simplifies the reaction remarkably: there is no need to keep the reaction anhydrous, and the need for potentially dangerous chemicals is reduced. Our protocol, therefore, made a tempting target for adaptation for the teaching laboratory.

Because the classic Wittig reaction has wide application in synthesis and a relatively simple procedure, it is one of the major reactions taught to undergraduates in general organic chemistry laboratories. In 2016, the Bergdahl lab optimized[8] a few of the procedures outlined in the 2007

paper for use in an undergraduate teaching laboratory. The adaptation scales the reactions up to make them easier for students to deal with, and includes full procedures and spectra analysis as appropriate. Additionally, this method has been used in the teaching lab at San Diego State University for the last few years, with great success. The paper, originally published in *Journal of Chemical Education,* follows.

Chapter 7 contains material being prepared for submission for publication where the dissertation author is a principal researcher and author on the manuscript. I'd like to thank Major Lucas Fallot, Dr. Jeffrey Gustafson and the American Chemical Society for their permission to use this material.

JOURNAL OF CHEMICAL EDUCATION

Laboratory Experiment

pubs.acs.org/jchemeduc

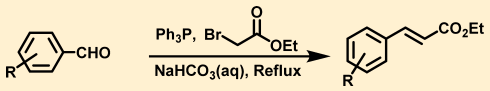
Water Mediated Wittig Reactions of Aldehydes in the Teaching Laboratory: Using Sodium Bicarbonate for the in Situ Formation of Stabilized Ylides

Michael J. B. Kelly, Lucas B. Fallot, Jeffrey L. Gustafson, and B. Mikael Bergdahl*

Department of Chemistry and Biochemistry, San Diego State University, San Diego, California 92182-1030, United States

Supporting Information

ABSTRACT: The synthesis of alkenes using the Wittig reaction is a traditional part of many undergraduate organic chemistry teaching laboratory curricula. The aqueous medium version of the Wittig reaction presented is a reliable adaptation of this alkene formation reaction as a very safe alternative in the introductory organic chemistry laboratory. The specific aqueous Wittig reactions discussed use a *one-pot* reagent setup and *greener* methods that the students can complete within 30 min with partial workup in one laboratory period. The aqueous Wittig reactions presented have been implemented to various aldehydes and take advantage of dilute sodium bicarbonate ("baking soda") as the only base needed for in the *in situ* formation of stabilized ylides. Outcomes from the implementation of the proposed aqueous Wittig procedure into the organic chemistry teaching laboratory curriculum are presented. Described also are reaction workup, purification, and analysis of products using ^{1}H NMR and IR spectroscopy.



KEYWORDS: *Second-Year Undergraduate, Aqueous Solution Chemistry, Organic Chemistry, Alkenes, Synthesis, Water/Water Chemistry, Green Chemistry, Hands-On Learning/Manipulatives, Laboratory Instruction*

Ever since the first report of alkene synthesis from aldehydes in the 1950s by Wittig,[1] the reaction has remained a powerful tool in the organic chemistry community for the construction of unsaturated carbon−carbon bonds. Since then the Wittig reaction has become one of the most commonly used instruments in synthetic organic chemistry to generate excess of either the *E*- or *Z*-geometrical isomers of alkenes, and even though the reaction has been known for over six decades, it is still under intense mechanistic investigation.[2] Conventional reaction conditions for the selective formation of *E*-alkenes use stabilized ylides and aldehydes, most of the time paired with organic solvents like toluene, DMF, or DMSO.

As a consequence of its wide use, the Wittig methodology has been included in the organic chemistry curriculum for quite some time,[3] but unfortunately the Wittig protocol has historically involved dangerous reagents and relatively complicated procedures less suitable for a teaching laboratory. However, with modern laboratory techniques, the chemistry can be made much easier and safer, while still demonstrating to students the important concepts of the reaction, especially the formation of the ylide and its characteristic reaction with aldehydes to form unsaturated carbon−carbon bonds.[3k,4]

In the early 1980s, Breslow[5] and Grieco[6] disclosed that the interaction of hydrophobic moieties in aqueous media can have a tremendous effect on the rate of organic reactions. However, it was not until relatively recently that the prospect of water as a medium for organic reactions gained widespread attention,[7] and significant advances have been made in achieving organic reactions in water by utilizing this favorable hydrophobic interaction of the reactants.[8] Such a "hydrophobic effect"[9] fits well with the concepts learned early in the chemistry curriculum, and is especially well-designed for the organic chemistry laboratory where chemistry experiments commonly are conducted using conventional organic solvents.

In order to increase yield or selectivity in the Wittig reaction, many modified condition alternatives have been reported, such as increasing temperature[10] or pressure,[11] using additives,[12] sonication,[13] silica gel,[14] ionic solvents,[15] irradiation with microwaves[16] or light,[17] and quite recently neat water.[4a,b] Some reports describing the influence of aqueous LiCl[18] and surfactant[19] on the Wittig reaction have also emerged. Advances also include the *in situ* formation of the phosphorus ylide in solid state reactions employing the corresponding phosphonium salt with anhydrous K_2CO_3, and then subsequent Wittig reaction in a solvent-free setting.[20]

The experiment disclosed is intended to expose students to alkene synthesis via the aqueous Wittig reaction conducted under very mild basic aqueous conditions, and in this way teach a novel version of an important class of reactions in organic chemistry experimentally. Instrumental analysis and group discussions are then integrated for assessment of the laboratory experience. Since water is inexpensive and extremely easy to handle and represents few environmental concerns, the illustrated laboratory experiment should help students see water as a possible medium for organic reactions, and its potential for wider adoption.

Received: March 23, 2016
Revised: June 18, 2016
Published: July 18, 2016

DOI: 10.1021/acs.jchemed.6b00206
J. Chem. Educ. 2016, 93, 1631−1636

THE AQUEOUS WITTIG REACTION

Water has previously been used as a solvent for Wittig reactions utilizing modified water-soluble phosphonium salts,[21] but the application of water as a crucial medium for conducting Wittig reactions employing poorly water-soluble stabilized ylides is limited. In this paper we present suitable solutions from our original report[4b] on aqueous promoted Wittig reactions fitting for a second semester organic chemistry laboratory experiment. Apart from the application of the illustrated student experiments to *greener chemistry*,[22] these proposed reactions contribute a valuable methodology for carbon−carbon double bond creation in water in synthetic organic chemistry.

The *in situ* formation of ylides during the Wittig reaction employing water as a medium and sodium bicarbonate as a base along with triphenylphosphine and α-bromo esters recently has been a particularly fruitful area of study. We have had seven of these aqueous Wittig reactions tailor-made and adopted in the organic teaching laboratories for over two years, during which they have been tested by a total of roughly 500 students during a three week laboratory period. The first week incorporates the examination of the importance of water as a medium in various types of organic reactions, the reaction setup and execution, and the partial workup of the Wittig product. The second week includes purification and isolation of the Wittig product using silica gel column chromatography or recrystallization and the use of a rotary evaporator. The third week is used for analysis with a discussion around the product structure and completion of ^{1}H NMR and IR spectroscopy.[23]

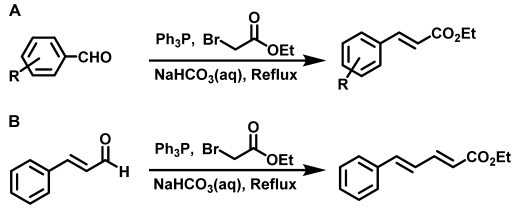
THE LABORATORY EXPERIMENTS

The aqueous Wittig reactions presented herein demonstrate optimized examples of laboratory experiments that can be adopted in second semester organic chemistry laboratory course. The aqueous Wittig reactions exemplified are simple, safe, and an example of a *greener one-pot* setup that the students can complete within 30 min with partial workup in one laboratory period. They take advantage of dilute sodium bicarbonate as the only base needed for in the *in situ* formation of stabilized ylides required for alkene formation.

Examples of the reaction are found in general organic chemistry textbooks[24] and in numerous published synthetic procedures,[1−22] and, therefore, the reaction is often covered specifically in introductory organic chemistry classes and their corresponding laboratories. Many of the literature procedures reported for conducting a Wittig reaction use problematic or hazardous reagents which make them unsuitable in an organic chemistry teaching laboratory. To circumvent such problems *greener* alternatives to the traditional Wittig reaction have been reported[3k] using semistabilized ylide substrates and the use of sodium bicarbonate as a base.[4b] Greener chemistry is an increasingly important lesson for young scientists for the critical analysis and simplification of laboratory procedures. The Wittig reactions described herein are summarized in Scheme 1.

While several stabilized ylides are commercially available, many can easily be prepared in the teaching laboratory *in situ* during the Wittig reaction using the less expensive reagents triphenylphosphine, ethyl bromoacetate, and sodium bicarbonate. Implementing a more contemporary aqueous Wittig reaction in the organic chemistry teaching laboratory creates a constructive experience and provides an opportunity for group discussions for the students when comparing the reaction to the classic Wittig reaction developed many years ago. An organic solvent is not used in the aqueous Wittig reaction itself but is required in the workup procedure and during the purification step using either a semi-microscale silica gel column chromatography technique or recrystallization. The students will also learn how to use a rotary evaporator in order to quickly remove solvent from their product. The learning experience is also enhanced by the characterization of the Wittig products using ^{1}H NMR and IR spectroscopy.

Scheme 1. Aqueous Wittig Reactions with Ethyl Bromoacetate and Triphenylphosphine to Substituted Benzaldehydes (A) and Cinnamaldehyde (B)



The aqueous medium is mild, inexpensive, and especially safe for conducting the Wittig reaction in the teaching laboratory. The laboratory experiment can be completed in two lab periods (generally, one lab period for the reaction and one lab period for the purification), and a third week can be used for analysis with a discussion around the product structure and completion of ^{1}H NMR and IR spectroscopy.

EXPERIMENTAL OVERVIEW

The students work individually and can choose or be assigned any of the seven suggested aldehydes (see Table 1). Alternatively the aldehydes can be provided as "unknowns" for students and they can determine the structure of their original aldehyde from the ^{1}H NMR spectra obtained of their product after conducting the Wittig reaction.

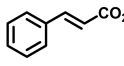
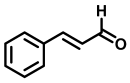
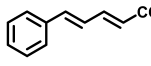
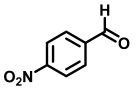
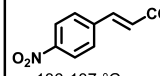
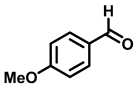
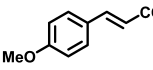
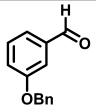
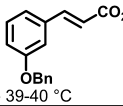
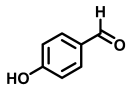
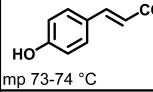
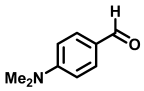
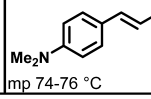
The aldehydes used in the experiment are benzaldehyde, cinnamaldehyde, *p*-nitrobenzaldehyde, *p*-methoxybenzaldehyde, *m*-benzyloxybenzaldehyde, *p*-hydroxybenzaldehyde, and *p*-dimethylaminobenzaldehyde. Each student mixes the appropriate aldehyde (1 equiv), triphenylphosphine (1.5 equiv), ethyl bromoacetate (2 equiv), and saturated sodium bicarbonate (20 mL) in a 100 mL single-neck round-bottom flask fitted with a reflux condenser. The heterogeneous solution is refluxed with rapid stirring for 30 min. After cooling, the solution is extracted with 4−5 portions of ethyl acetate (total solvent volume: 20−30 mL). The organic solvent is evaporated to give a mixture of the product and triphenylphosphine oxide byproduct. The product is either a white to yellow solid or oil that is purified by a simple recrystallization or by silica gel chromatography. The product is characterized by IR and ^{1}H NMR spectroscopy and by melting point if the product is crystalline. Detailed instructions can be found in the Supporting Information.

HAZARDS

Ethyl bromoacetate is a potent lachrymator and should be used with caution in a ventilated hood. Each of the aldehydes and triphenylphosphine are irritants and should be used with caution. Do not inhale silica dust; use with caution in a well-ventilated hood. Both the olefin products and 10% aqueous sodium bisulfite are harmful if swallowed. The products are considered skin and eye irritants and should not be swallowed.

DOI: 10.1021/acs.jchemed.6b00206
J. Chem. Educ. 2016, 93, 1631−1636

Table 1. Summary of Product Yields and NMR Data

Aldehyde	Product[a,b] (1-7)	Yield Range[c], %	^{1}H NMR[d], $CDCl_3$
	 (1) liquid	60 - 93	7.68 (d, *J* = 16.0 Hz, 1H), 7.52-7.46 (m, 2H), 7.37-7.33 (m, 3H), 6.43 (d, *J* = 16.0 Hz, 1H), 4.25 (q, *J* = 7.1 Hz, 2H), 1.32 (t, *J* = 7.1 Hz, 3H)
	 (2) mp 25-26 °C	60 - 88	7.55-7.25 (m, 6H), 6.92-6.80 (m, 2H), 5.99 (d, *J* = 15.3 Hz, 1H), 4.23 (q, *J* = 7.1 Hz, 2H), 1.31 (t, *J* = 7.1 Hz, 3H)
	 (3) mp 136-137 °C	40 - 94[e]	8.25 (m, 2H), 7.70 (d, *J* = 15.4 Hz, 1H), 7.66 (m, 2H), 6.55 (d, *J* = 15.4 Hz, 1H), 4.30 (q, *J* = 7.1 Hz, 2H), 1.35 (t, *J* = 7.1 Hz, 3H)
	 (4) mp 48-51 °C	50 - 94	7.62 (d, *J* = 16.0 Hz, 1H), 7.44 (m, 2H), 6.88 (m, 2H), 6.29 (d, *J* = 16.0 Hz, 1H), 4.18 (q, *J* = 7.1 Hz, 2H), 3.80 (s, CH3CO, 3H), 1.29 (t, *J* = 7.1 Hz, 3H)
	 (5) mp 39-40 °C	60 - 90	7.64 (d, *J* = 16.0 Hz, 1H), 7.45-7.25 (m, 6H), 7.15-7.11 (m, 2H), 7.00 (m, 1H), 6.40 (d, *J* = 16.0 Hz, 1H), 5.09 (s, 2H), 4.25 (q, *J* = 7.0 Hz, 2H), 1.37 (t, *J* = 7.0 Hz, 3H)
	 (6) mp 73-74 °C	44 - 64	7.64 (d, *J* = 16.0 Hz, 1H), 7.42 (m, 2H), 6.86 (m, 2H), 6.29 (d, *J* = 16.0 Hz, 1H), 6.25 (bs, 1H), 4.26 (q, *J* = 7.0 Hz, 2H), 1.34 (t, *J* = 7.0 Hz, 3H)
	 (7) mp 74-76 °C	36 - 64	7.62 (d, *J* = 16.0 Hz, 1H), 7.42 (m, 2H), 6.66 (m, 2H), 6.22 (d, *J* = 16.0 Hz, 1H), 4.24 (q, *J* = 7.0 Hz, 2H), 3.02 (s, 6H), 1.32 (t, *J* = 7.0 Hz, 3H)

[a]Major *E*-isomer. [b]Literature mp for the pure *E*-isomer. [c]Yield range of major *E*-isomer after column chromatography purification. [d]400 MHz NMR data of major *E*-isomer. [e]Highest yield was obtained from simple recrystallization from 95% ethanol.

Ethyl acetate is an eye irritant and is highly flammable. Hexanes are highly flammable and a neurotoxin. Deuterated chloroform is an irritant, is harmful if swallowed, and is a suspected carcinogen. Consult safety data sheets for all reagents prior to conducting the laboratory experiment.

RESULTS AND DISCUSSION

The aqueous Wittig laboratory experiment has been completed during five consecutive semesters by roughly 500 second year undergraduate students enrolled in a second semester organic chemistry course. A typical student product yield was 36% to 80% depending on the aldehyde the student used. In general, the product yield is quite high, but it is dependent on how well the student accomplishes the recrystallization and the column chromatography. Typically, students obtained a solid Wittig product after purification (except for products **1** and **2**) and the melting point was determined as a way to check for relative purity and compare it to the reported literature melting point (see Table 1). It is expected that a decrease in melting point will occur as a consequence of a low *E*/*Z* ratio. For instance, Wittig product **2** never solidified even though the pure *E*,*E*-isomer has been reported as a low melting point solid. The corresponding *E*-isomer is the major constitutional isomer relative to the minor *Z*-isomer (Figure 1).

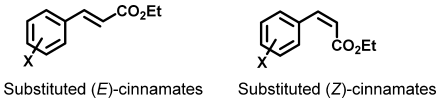


Figure 1. Illustration of *E* and *Z* isomers that form.

Even though the ratio of the *E*- and *Z*-isomers is clearly visible in the ^{1}H NMR spectrum, the students need to have a firm knowledge of NMR spectroscopy in order to interpret the data fully, for example by identifying the coupling constants for the *E*- and the *Z*-isomers. However, the students can still accomplish a simple analysis of their Wittig products with less ^{1}H NMR comprehension, for instance by the identification the alkene protons in the ^{1}H NMR spectrum and the determination of the *E*/*Z* ratio.

The students' NMR spectra were obtained by the students themselves using our 80 MHz picoSpin NMR spectrometer located on the benchtop in the laboratory. Even with this relatively low field strength instrument, sufficient spectroscopic information can be obtained in order to characterize the Wittig products. At 80 MHz it is possible to determine the coupling constant for the alkene protons. The product composition was also analyzed by 400 MHz ^{1}H NMR spectroscopy (see Supporting Information). In this case, the students did not

DOI: 10.1021/acs.jchemed.6b00206
J. Chem. Educ. 2016, 93, 1631−1636

collect the NMR data themselves but instead an autosampler with the Varian 400 MHz NMR spectrometer was used, which allowed for 20 students' NMR samples to be collected overnight. Although an error analysis of the spectroscopic data can be done, it was not introduced as a requirement in the laboratory course. If the students are able to obtain a low resolution NMR (80 MHz), they will be able to compare these data with the 400 MHz spectra found in the Supporting Information and thereby analyze the difference between high and low field resolution. The students analyzed the NMR spectra and measured the *E*/*Z* ratio by comparing the integration of the olefin peaks for each isomer of the Wittig products, and relating the different coupling constants of alkene protons. The *E*-isomer was the major product at a ratio greater than 5:1, though the exact ratio varies by aldehyde. The loss of the aldehyde signal in the ^{1}H NMR spectrum (usually found at 9.5−10.5 ppm) is one indication of the consumption of the starting material. Students can compare their product NMR spectra with the spectra of the starting material (see Supporting Information). Remaining triphenylphosphine is the only major contaminant in the product after column chromatography, but made up <1% of the product. It is expected that the triphenylphosphine contamination will affect a slight decrease in melting point of the Wittig product. The student yield ranges and NMR data for the *E*-isomer of each product are summarized in Table 1.

The students also used the IR spectrometer as a tool to confirm the chemical structure of the products, with the shift of the carbonyl peak from the aldehyde range to the ester range, the appearance of the ester C−O stretches, and the appearance of alkene and phenyl groups (see Supporting Information).

The reaction takes roughly 30 min to conduct, but the majority of the time in lab was spent on reaction setup, workup, and the purification followed by the evaporation of the solvent. Thus, it is recommended to conduct at least the spectroscopic analysis during a different 3 h laboratory session. The students will then have additional time available to analyze and compare their individual spectra with the ^{1}H NMR and IR spectra (Supporting Information). The scope of analysis is dependent on time available in the laboratory session and the instrumentation accessible. There are several benefits to the proposed instructional water based Wittig reaction with various levels of instrumentation or various academic goals.

CONCLUSION

A mild aqueous sodium bicarbonate based Wittig reaction that works with different aldehydes has been created as a suitable experiment for a second semester organic chemistry laboratory. The simple procedures included allow for simple reaction setup, purification, and characterization of products using ^{1}H NMR and IR spectroscopy. The large number of students who participated in this study were exposed to a number of laboratory and spectroscopic techniques required for analysis of their products.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.6b00206.

Laboratory materials (PDF, DOCX)

Student instructions, instructor notes, and IR and ^{1}NMR spectra for reaction using *m*-benzyloxybenzaldehyde (PDF, DOCX)

Student instructions, instructor notes, and IR and ^{1}NMR spectra for reaction using *p*-(dimethylamino)-benzaldehyde (PDF, DOCX)

Student instructions, instructor notes, and IR and ^{1}NMR spectra for reaction using *p*-anisaldehyde (PDF, DOCX)

Student instructions, instructor notes, and IR and ^{1}NMR spectra for reaction using *p*-nitrobenzaldehyde (PDF, DOCX)

Student instructions, instructor notes, and IR and ^{1}NMR spectra for reaction using cinnamaldehyde (PDF, DOCX)

Student instructions, instructor notes, and IR and ^{1}NMR spectra for reaction using benzaldehyde (PDF, DOCX)

Student instructions, instructor notes, and IR and ^{1}NMR spectra for reaction using *p*-hydroxybenzaldehyde (PDF, DOCX)

AUTHOR INFORMATION

Corresponding Author

*E-mail: bbergdahl@mail.sdsu.edu.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

The authors wish to thank San Diego State University for the University Grant Program in support of the development of this experiment. We also would like to thank organic chemistry faculty and the chemistry students at SDSU for their effort and comments in incorporating this laboratory experiment into our undergraduate organic chemistry laboratory curriculum.

REFERENCES

(1) (a) Wittig, G.; Geissler, G. Zur Reaktionsweise des Pentaphenyl-phosphors und einiger Derivate. *Liebigs Ann. Chem.* **1953**, *580*, 44−68. (b) Wittig, G.; Schöllkopf, U. Über Triphenyl-phosphin-methylene als Olefinbildende Reagenzien (1. Mitteil.). *Chem. Ber.* **1954**, *87* (9), 1318−1330. (c) Wittig, G. From Diyls to Ylides to My Idyll. *Science* **1980**, *210* (4470), 600−604 and references therein.

(2) (a) Bangerter, F.; Karpf, M.; Meier, L. A.; Rys, P.; Skrabal, P. Observation of Pseudorotamers of Two Unconstrained Wittig Intermediates, (3*RS*,4*SR*)- and (3*RS*,4*RS*)-4-Cyclohexyl-2-ethyl-3,4-dimethyl-2,2-diphenyl-1,2λ^5-oxaphosphetane, by Dynamic ^{31}P NMR Spectroscopy: Line-Shape Analyses, Conformations, and Decomposition Kinetics. *J. Am. Chem. Soc.* **1998**, *120* (41), 10653−10659. (b) Robiette, R.; Richardson, J.; Aggarwal, V. K.; Harvey, J. N. Reactivity and Selectivity in the Wittig Reaction: A Computational Study. *J. Am. Chem. Soc.* **2006**, *128* (7), 2394−2409. (c) Byrne, P. A.; Gilheany, D. G. The Modern Interpretation of the Wittig Reaction Mechanism. *Chem. Soc. Rev.* **2013**, *42* (16), 6670−6696. (d) Ayub, K.; Ludwig, R. Gas Hydrates Model for the Mechanistic Investigation of the Wittig Reaction "on Water. *RSC Adv.* **2016**, *6* (28), 23448−23458.

(3) (a) Broos, R.; Tavernier, D.; Anteunis, M. *p*-Carboxystyrene: A Wittig Procedure in Aqueous Medium. *J. Chem. Educ.* **1978**, *55* (12), 813. (b) Warner, J. C.; Anastas, P. T.; Anselme, J. The Wittig Reaction in the Undergraduate Organic Laboratory. *J. Chem. Educ.* **1985**, *62* (4), 346. (c) Silversmith, E. F. A Wittig Reaction that Gives Only One Stereoisomer. *J. Chem. Educ.* **1986**, *63* (7), 645. (d) Pike, R. M.; Mayo, D. W.; Butcher, S. S.; Butcher, D. J.; Hinkle, R. J. Microscale Organic Laboratory IV. A Simple and Rapid Procedure for Carrying Out Wittig Reactions. *J. Chem. Educ.* **1986**, *63* (10), 917−918. (e) Breuer, S. W. The Wittig Synthesis of Alkenes by Phase-Transfer Catalysis: The

DOI: 10.1021/acs.jchemed.6b00206
J. Chem. Educ. 2016, 93, 1631−1636

Syntheses of 4,4′-Dichlorostilbenes and of *E,E*-1,4-Diphenylbutadiene. *J. Chem. Educ.* **1991**, *68* (3), A58−A60. (f) Breton, G. W. The Wittig Reaction: Generation, Observation and Reactivity of a Phosphorous Ylide Intermediate. An Experiment for the Advanced Organic Chemistry Laboratory. *J. Chem. Educ.* **1997**, *74* (1), 114−115. (g) Jaworek, C.; Iacobucci, S. Wittig Reaction: The Synthesis of *trans*-9-(2-Phenylethenyl)anthracene Revisited. *J. Chem. Educ.* **2002**, *79* (1), 111. (h) Speed, T. J.; McIntyre, J. P.; Thamattoor, D. M. Wittig Reaction Using a Stabilized Phosphorus Ylid: An Efficient and Stereoselective Synthesis of Ethyl *trans*-Cinnamate. *J. Chem. Educ.* **2004**, *81* (9), 1355−1356. (i) Cheung, L. L. W.; Lin, R. J.; McIntee, J. W.; Dicks, A. P. Expeditious Horner-Wadsworth−Emmons Synthesis of Methyl Cinnamate Esters under Aqueous Conditions. *Chem. Educ.* **2005**, *10* (4), 300−302. (j) Nguyen, K.; Weizman, H. Greening Wittig Reactions: Solvent-Free Synthesis of Ethyl trans-Cinnamate and *trans*-3-(9-Anthryl)-2-Propenoic Acid Ethyl Ester. *J. Chem. Educ.* **2007**, *84* (1), 119−121. (k) Morsch, L. A.; Deak, L.; Tiburzi, D.; Schuster, H.; Meyer, B. Green Aqueous Wittig Reaction: Teaching Green Chemistry in Organic Teaching Laboratories. *J. Chem. Educ.* **2014**, *91* (4), 611−614.

(4) (a) Dambacher, J.; Zhao, W.; El-Batta, A.; Anness, R.; Jiang, C.; Bergdahl, M. Water is an Efficient Medium for Wittig Reactions Employing Stabilized Ylides and Aldehydes. *Tetrahedron Lett.* **2005**, *46* (26), 4473−4477. (b) El-Batta, A.; Jiang, C.; Zhao, W.; Anness, R.; Cooksy, A. L.; Bergdahl, M. Wittig Reactions in Water Media Employing Stabilized Ylides with Aldehydes. Synthesis of α,β-Unsaturated Esters from Mixing Aldehydes, α-Bromoesters, and Ph_3P in Aqueous $NaHCO_3$. *J. Org. Chem.* **2007**, *72* (14), 5244−5259. (c) Leung, S. H.; Angel, S. A. Solvent-Free Wittig Reaction: A Green Organic Chemistry Laboratory Experiment. *J. Chem. Educ.* **2004**, *81* (10), 1492−1493. (d) Texier-Boullet, F.; Villemin, D.; Ricard, M.; Moison, H.; Foucaud, A. Reactions de Wittig, Wittig-Horner et Knoevenagel par Activation Anionique avec L'Alumine ou le Fluorure de Potassium Depose sur L'Alumine, sans Solvent. *Tetrahedron* **1985**, *41* (7), 1259−1266. (e) Martin, E.; Kellen-Yuen, C. Microwave Assisted Organic Synthesis in the Organic Lab: A Simple, Greener Wittig Reaction. *J. Chem. Educ.* **2007**, *84* (12), 2004−2006. (f) Baar, M. R.; Falcone, D.; Gordon, C. Microwave-Enhanced Organic Syntheses for the Undergraduate Laboratory: Diels-Alder Cycloaddition, Wittig Reaction, and Williamson Ether Synthesis. *J. Chem. Educ.* **2010**, *87* (1), 84−86. (g) Wu, J.; Li, D.; Zhang, D. Aqueous Wittig Reactions of Aldehydes with In Situ Formed Semistabilized Phosphorus Ylides. *Synth. Commun.* **2005**, *35* (19), 2543−2551. (h) McNulty, J.; Das, P. Aqueous Wittig Reactions of Semi-Stabilized Ylides. A Straightforward Synthesis of 1,3-Dienes and 1,3,5-Trienes. *Tetrahedron Lett.* **2009**, *50* (41), 5737−5740.

(5) (a) Rideout, D. C.; Breslow, R. Hydrophobic Acceleration of Diels-Alder Reactions. *J. Am. Chem. Soc.* **1980**, *102* (26), 7816−7817. (b) Breslow, R.; Maitra, U.; Rideout, D. C. Selective Diels-Alder Reactions in Aqueous Solutions and Suspensions. *Tetrahedron Lett.* **1983**, *24* (18), 1901−1904. (c) Breslow, R.; Maitra, U. On the Origin of Product Selectivity in Aqueous Diels-Alder Reactions. *Tetrahedron Lett.* **1984**, *25* (12), 1239−1240.

(6) Grieco, P. A.; Garner, P.; He, Z. Micellar" Catalysis in the Aqueous Intermolecular Diels-Alder Reaction: Rate Acceleration and Enhanced Selectivity. *Tetrahedron Lett.* **1983**, *24* (18), 1897−1900.

(7) (a) Lindström, U. M.; Andersson, F. Hydrophobically Directed Organic Synthesis. *Angew. Chem., Int. Ed.* **2006**, *45* (4), 548−551. (b) Li, C.-J.; Chen, L. Organic Chemistry in Water. *Chem. Soc. Rev.* **2006**, *35* (1), 68−82. (c) Lindström, U. M. Stereoselective Organic Reactions in Water. *Chem. Rev.* **2002**, *102* (8), 2751−2772.

(8) Narayan, S.; Muldoon, J.; Finn, M. G.; Fokin, V. V.; Kolb, H. C.; Sharpless, K. B. On Water": Unique Reactivity of Organic Compounds in Aqueous Suspension. *Angew. Chem., Int. Ed.* **2005**, *44* (21), 3275−3279.

(9) (a) Otto, S.; Engberts, J. B. F. N. Hydrophobic Interactions and Chemical Reactivity. *Org. Biomol. Chem.* **2003**, *1* (16), 2809−2820. (b) Breslow, R.; Groves, K.; Mayer, M. U. The Hydrophobic Effect as a Mechanistic Tool. *Pure Appl. Chem.* **1998**, *70* (10), 1933−1938. (c) Breslow, R. Hydrophobic Effects on Simple Organic Reactions in Water. *Acc. Chem. Res.* **1991**, *24* (6), 159−164.

(10) Fodor, G.; Tömösközi, I. The Reaction of Carbethoxymethylenetriphenyl-phosphorane with Ketones. *Tetrahedron Lett.* **1961**, *2* (16), 579−582.

(11) (a) Nonnenmacher, A.; Mayer, R.; Plieninger, H. Hochdruckversuche, XII. Über die Anwendung von Hohem Druck bei Wittig-Reaktionen mit Resonanzstabilisierten Yliden. *Liebigs Ann. Chem.* **1983**, *1983* (12), 2135−2140. (b) Isaacs, N. S.; El-Din, G. N. The Application of High Pressure to Some Difficult Wittig Reactions. *Tetrahedron Lett.* **1987**, *28* (19), 2191−2192.

(12) Lithium salts: (a) House, H. O.; Jones, V. K.; Frank, G. A. The Chemistry of Carbanions. VI. Stereochemistry of the Wittig Reaction with Stabilized Ylids. *J. Org. Chem.* **1964**, *29* (11), 3327−3333. (b) Hooper, D. L.; Garagan, S.; Kayser, M. M. Lithium Cation-Catalyzed Wittig Reactions. *J. Org. Chem.* **1994**, *59* (5), 1126−1128. Benzoic acid: (c) Fliszár, S.; Hudson, R. F.; Salvadori, G. Note sur la Catalyse Acide de la Réaction des Phosphobétaïnes avec le Benzaldéhyde. *Helv. Chim. Acta* **1964**, *47* (1), 159−162. (d) Rüchardt, C.; Panse, P.; Eichler, S. Zum Mechanismus der Wittig-Reaktion mit Triaryl-alkoxycarbonylmethylen-phosphoranen. *Chem. Ber.* **1967**, *100* (4), 1144−1164. (e) Corey, E. J.; Clark, D. A.; Goto, G.; Marfat, A.; Mioskowski, C.; Samuelsson, B.; Hammarström, S. Stereospecific Total Synthesis of a "Slow Reacting Substance" of Anaphylaxis, Leukotriene C-1. *J. Am. Chem. Soc.* **1980**, *102* (4), 1436−1439. (f) Marriott, D. P.; Bantick, J. R. 5(S),6(R)-5,7-Dibenzoyloxy-6-hydroxyheptanoate ester: Improved Synthesis of a Leukotriene Intermediate. *Tetrahedron Lett.* **1981**, *22* (37), 3657−3658. (g) Thiemann, T.; Thiemann, C.; Sasaki, S.; Vill, V.; Mataka, S.; Tashiro, M. Synthesis and Photochemical Behaviour of 3-(Estran-16-yl)acrylates and 2-(Estran-16-yl)vinyl Ketones. *J. Chem. Res., Synop.* **1997**, No. 7, 248−249. Phase transfer catalyst: (h) Stafford, J. A.; McMurry, J. E. An Efficient Method for the Preparation of Alkylidenecyclopropanes. *Tetrahedron Lett.* **1988**, *29* (21), 2531−2534. Cyclodextrins: (i) Westman, G.; Wennerström, O.; Raston, I. On the Effect of Cyclodextrin on the *Z/E*-Selectivity of Wittig Reactions with Semistabilized Ylides. *Tetrahedron* **1993**, *49* (2), 483−488.

(13) Silveira, C. C.; Perin, G.; Braga, A. L. Synthesis of Vinylic Chalcogenides Under Sonication. *J. Chem. Res., Synop.* **1994**, No. 12, 492−493.

(14) Patil, V. J.; Mävers, U. Wittig Reactions in the Presence of Silica Gel. *Tetrahedron Lett.* **1996**, *37* (8), 1281−1284.

(15) Le Boulaire, V.; Grée, R. Wittig Reactions in the Ionic Solvent [bmim][BF_4]. *Chem. Commun.* **2000**, No. 22, 2195−2196.

(16) (a) Xu, C.; Chen, G.; Fu, C.; Huang, X. The Wittig Reaction of Stable Ylide with Aldehyde Under Microwave Irradiation: Synthesis of Ethyl Cinnamates. *Synth. Commun.* **1995**, *25* (15), 2229−2233. (b) Spinella, A.; Fortunati, T.; Soriente, A. Microwave Accelerated Wittig Reactions of Stabilized Phosphorus Ylides with Ketones under Solvent-Free Conditions. *Synlett* **1997**, *1997* (1), 93−94. (c) Wu, J.; Wu, H.; Wei, S.; Dai, W.-M. Highly Regioselective Wittig Reactions of Cyclic Ketones with a Stabilized Phosphorus Ylide under Controlled Microwave Heating. *Tetrahedron Lett.* **2004**, *45* (22), 4401−4404.

(17) Matikainen, J. K.; Kaltia, S.; Hase, T. Wittig Reactions under Daylight Lamp Irradiation: Maximizing the Yields of (*E*)-Alkenes. *Synlett* **1994**, *1994* (10), 817−818.

(18) Wu, J.; Zhang, D.; Wei, S. Wittig Reactions of Stabilized Phosphorus Ylides with Aldehydes in Water. *Synth. Commun.* **2005**, *35* (9), 1213−1222 See also ref 4g.

(19) Orsini, F.; Sello, G.; Fumagalli, T. One-Pot Wittig Reactions in Water and in the Presence of a Surfactant. *Synlett* **2006**, *2006* (11), 1717−1718.

(20) Balema, V. P.; Wiench, J. W.; Pruski, M.; Pecharsky, V. K. Mechanically Induced Solid-State Generation of Phosphorus Ylides and the Solvent-Free Wittig Reaction. *J. Am. Chem. Soc.* **2002**, *124* (22), 6244−6245.

(21) (a) Russell, M. G.; Warren, S. Synthesis of New Water-Soluble Phosphonium Salts and Their Wittig Reactions in Water. *J. Chem. Soc.*

DOI: 10.1021/acs.jchemed.6b00206
J. Chem. Educ. 2016, 93, 1631−1636

Perkin Trans. I. **2000**, No. 4, 505−513. Using phosphonates in Wittig−Horner reactions in aqueous media, see: (b) Villieras, J.; Rambaud, M. Wittig-Horner Reactions in Heterogeneous Media; 2. A Convenient Synthesis of α,β-Unsaturated Esters and Ketones using Weak Bases in Water. *Synthesis* **1983**, *1983* (4), 300−303. (c) Rambaud, M.; Vecchio, A.; Villieras, J. Wittig-Horner Reaction in Heterogenous Media: V. An Efficient Synthesis of Alkene-Phosphonates and αL-Hydroxymethyl-α-Vinyl Phosphonate in Water in the Presence of Potassium Carbonate. *Synth. Commun.* **1984**, *14* (9), 833−841. (d) Villieras, J.; Rambaud, M.; Graff, M. La reaction de Wittig-Horner en Milieu Heterogene VI. Selectivite de la Reaction sur des Composes Bifonctionnels. *Tetrahedron Lett.* **1985**, *26* (1), 53−56. (e) Mouloungui, Z.; Delmas, M.; Gaset, A. The Wittig-Horner Reaction in Weakly Hydrated Solid/Liquid Media: Structure and Reactivity of Carbanionic Species Formed from Ethyl (diethyl phosphono)acetate by Adsorption on Solid Inorganic Bases. *J. Org. Chem.* **1989**, *54* (16), 3936−3941.

(22) (a) Tucker, J. L. Green Chemistry, a Pharmaceutical Perspective. *Org. Process Res. Dev.* **2006**, *10* (2), 315−319. (b) Clark, J. H.; Tavener, S. Alternative Solvents: Shades of Green. *Org. Process Res. Dev.* **2007**, *11* (1), 149−155.

(23) For ^{1}H NMR and IR spectra of starting materials and products, see Supporting Information.

(24) For some examples, see: (a) Solomons, T.; Fryhle, C.; Snyder, S. *Organic Chemistry*, 12th ed.; Wiley: Hoboken, NJ, 2016; pp 737−739. (b) Carey, F.; Sundberg, R. *Advanced Organic Chemistry Part B: Reactions and Synthesis*, 5th ed.; Springer: New York, 2007; pp 157−164. (c) Anslyn, E.; Dougherty, D. *Modern Physical Organic Chemistry*; University Science Books: Sausalito, CA, 2006; p 599.

DOI: 10.1021/acs.jchemed.6b00206
J. Chem. Educ. 2016, 93, 1631−1636

Part III, in part, is a reprint of the material as it appears in the *Journal of Chemical Education.* Reprinted with permission from: Kelly, M.; Fallot, L.; Gustafson, J.; Bergdahl, M. *J. Chem. Ed.* **2016**, *93* (9), 1631-1636. Copyright 2016 American Chemical Society.

I would like to acknowledge Major Lucas Fallot and Dr. Jeffrey Gustafson, for allowing me to use this material. The dissertation author was a primary investigator and author of this paper.

Chapter 8: Experimental Section

8.1 Chemicals and Instruments

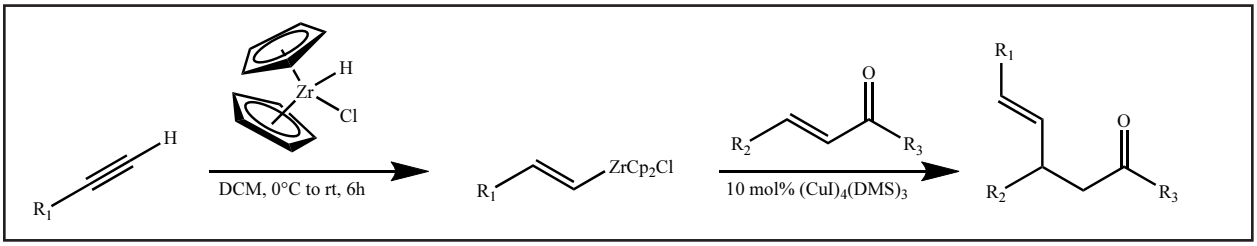
General: All reactions were conducted in septum-sealed, oven-dry glassware under inert positive-pressure argon atmosphere unless otherwise specified. All reagents and solvents were obtained commercially from companies like Aldrich, Fisher Scientific, Combi-Blocks, Oakwood Chemical, Chem-Impex, and PureBulk Supplements. Thin-layer chromatography was conducted using glass-backed SiliCycle 250 micron, 60Å particle size TLC plates. NMR spectra were taken on Varian 400 or 500 MHz instruments using deuterated chloroform with tetramethylsilane as an internal standard, deuterated dimethylsulfoxide, or D_2O. Column chromatography was performed either manually using glass columns or with a Biotage Isolera with refillable Biotage snap columns, filled with SorbTech 60Å silica gel, 230-400 mesh.

8.2 Experimental Procedures

Copper Iodide-Dimethyl Sulfide Complex, $(CuI)_4(DMS)_3$:[51b] Copper iodide (5 grams, 5.23 mmol) was dissolved in 15 mL of diethyl ether in a 125 mL Erlenmeyer flask, and 20 mL of dimethylsulfide was added. The reaction mixture was filtered to remove any insoluble material, then 50 mL cold hexanes was added slowly. The solution was kept in the freezer overnight, and pure white crystals were separated by filtration the next morning and washed with cold hexanes.

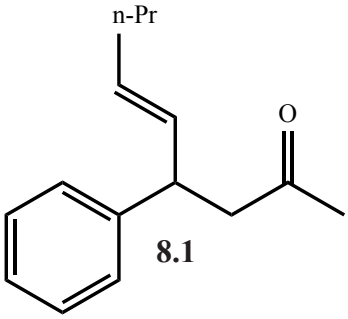
The crystals were held in a vacuum desiccator in the dark until their mass remained constant. 60% yield.

Schwartz's Reagent, $Cp_2Zr(H)Cl$:[51a, 92] Zirconocene dichloride (5 grams, 17 mmol) was dissolved in 100 mL of anhydrous THF in a 200 mL round bottom flask under argon, and 1.5 mL of 4.0 M (6 mmol, 0.34 eq) lithium aluminum hydride solution in diethyl ether was added dropwise over 45 minutes. The solution was stirred at room temperature for 90 minutes, then the apparatus was equipped with an oven-dry Schlenk filter and a 500 mL oven-dry round bottom flask, and the solid was separated by inverting the apparatus and pulling the liquid into the 500 mL flask, being careful not to expose the solid to atmosphere. Under argon, the solid was washed with 25 mL of anhydrous THF four times, then 25 mL of DCM twice, and 25 mL of diethyl ether four times; the solid was agitated with a magnetic stir bar and a magnet in between each wash. The dichloromethane washes are particularly important, because they convert any over-reduced dihydride product to the desired hydride-chloride product. The white solid was collected and dried in a vacuum desiccator in the dark. 90% yield.



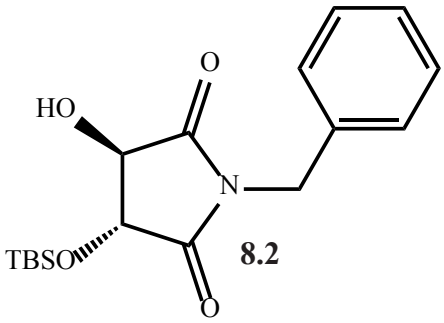
Scheme 8.1: Zirconocene vinyl conjugate addition

General procedure for zirconocene vinyl conjugate additions[51a] (scheme 8.1): Freshly prepared Schwartz's reagent (1.3 grams, 5 mmol, 1.1 eq) was added to an oven-dry, 2-neck round bottom flask equipped with a stir bar, condenser, and septum, under argon. The flask was cooled in an ice bath, and 20 mL anhydrous THF was added through the septum, then 5 mmol (1.1 eq) of the alkyne was added. The solution was stirred for 5 minutes at ice bath temperature, then heated in an oil bath at 40 °C for 6 hours, then cooled to room temperature. 4.5 mmol (1 eq) of the anhydrous enone was then added through the septum (make a solution in anhydrous THF if necessary), and after 5 minutes 0.47 grams (0.5 mmol, 0.1 eq) of freshly prepared copper iodide-dimethyl sulfide was added by removing the septum temporarily. The solution was stirred at 40 °C for 12 hours. After 12 hours, the solution was cooled to room temperature in a water bath, and quenched with 20 mL of wet diethyl ether. After stirring for 10 minutes, the solution was filtered through a celite pad, which was rinsed three times with 100 mL of ether each time. The combined organics were transferred to a separatory funnel, and washed twice with 20 mL of saturated sodium bicarbonate, then dried over anhydrous sodium sulfate. The dry organic layer was filtered through celite again, and again the celite pad was washed with ether. Volatiles were removed on the rotovap, and the residue purified on a silica column. 70-95% yield.



8.1

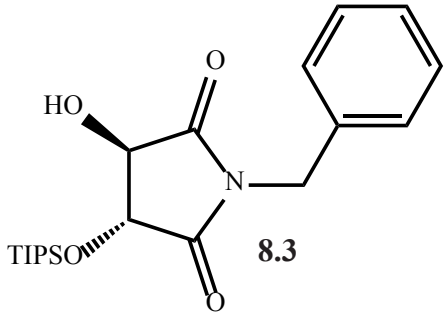
4-phenyl-*trans*-5-decen-2-one[1] (8.1): Synthesized using the general zirconocene conjugate addition procedure above. Product: 68% yield, yellow oil, Rf 0.5 10% ethyl acetate/hexanes. 1H NMR (400 MHz, CDCl3) δ: 1H NMR (400 MHz, Chloroform-d) δ 7.33 – 7.14 (m, 5H), 5.59 – 5.39 (m, 2H), 3.84 (q, J = 7.2 Hz, 1H), 2.80 (dd, J = 7.4, 3.6 Hz, 2H), 2.07 (s, 3H), 1.98 (q, J = 7.0 Hz, 2H), 1.29 (dd, J = 7.4, 3.7 Hz, 4H), 0.87 (t, J = 7.1 Hz, 3H).



8.2

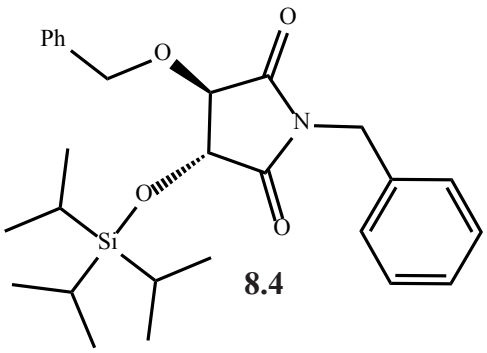
N-Benzyl-mono-O-*tert*-butyldimethylsilyl-L-tartarimide:[59] To a 50 mL oven-dry round bottom flask under argon added 6.6 grams (30 mmol) tartarimide, 5.07 grams (75 mmol, 2.5 eq) imidazole and 5.4 grams (36 mmol, 1.2 eq) TBSCl. Added 13 mL of DMF through the septum by syringe. Stirred at room temperature overnight. The next morning, transferred to a separatory funnel with ca 50 mL of diethyl ether. Washed the organic layer 5x with water, then once with saturated brine. Dry over anhydrous sodium sulfate. Silica column, 0-15% MeOH/DCM. 87% yield, offwhite

solid. 1H NMR (400 MHz, Chloroform-d) δ 7.42 – 7.28 (m, 4H), 4.65 (s, 2H), 4.55 – 4.41 (m, 2H), 2.72 (s, 1H), 0.95 (s, 9H), 0.21 (s, 3H), 0.18 (s, 3H).



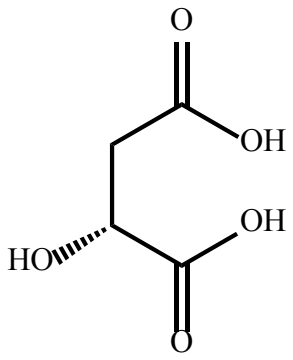
8.3

N-Benzyl-mono-O-Triisopropylsilyl-L-Tartarimide:[59] N-benzyl-L-tartarimide (0.2 grams, 0.91 mmol) and imidazole (0.154 grams, 2.26 mmol, 2.5 eq) were added to an oven-dry 25 mL round bottom flask under argon. Anhydrous DMF (4 mL) was added via syringe, then TIPSCl (0.178 mL, 0.83 mmol, 0.9 eq) was added dropwise over 5 min. The reaction was stirred for 3 days at room temperature. Transferred to separatory funnel with 25 mL of DCM, washed organic layer 5x with water, then once with brine. Dried over sodium sulfate. Rotovap. Silica column, 0-50% EtOAc/Hexanes. 78% yield. Yellow oil. 1H NMR (400 MHz, Chloroform-d) δ 7.45 – 7.18 (m, 6H), 4.72 – 4.56 (m, 3H), 4.49 (t, J = 4.5 Hz, 1H), 4.06 (d, J = 5.5 Hz, 1H), 1.36 – 1.15 (m, 3H), 1.15 – 1.05 (m, 19H).



8.4

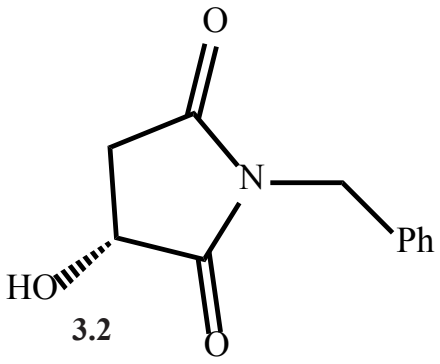
N,O-Dibenzyl-O-Triisopropylsilyl-L-Tartarimide:[59] Dry N-benzyl-mono-O-triisopropylsilyl-L-tartarimide (1.97 grams, 5.22 mmol) and freshly-prepared silver oxide (5 grams, 22 mmol, 4 eq) were added to a 250 mL oven-dry round bottom flask under argon, and anhydrous diethyl ether (100 mL) was added. Once the substrate was dissolved, and while stirring rapidly, benzyl bromide (2.0 mL, 16.8 mmol, 3 eq) was added slowly. The flask was wrapped in foil to protect it from light, the argon flow was removed, and the solution was stirred for 7 days. After 7 days, the solution was poured through celite with more anhydrous ether, and the volatiles were removed on a rotovap. 100 gram silica column, 0-20% EtOAc/hexanes, hold at 20% for 3 column volumes, then increase to 60% EtOAc/hexanes over 5 column volumes. Product comes out with benzyl alcohol in the middle isocratic portion, then alone in the higher gradient. 62% yield. Yellow oil. 1H NMR (400 MHz, Chloroform-d) δ 7.47 – 7.19 (m, 10H), 5.15 (d, J = 11.1 Hz, 1H), 4.82 (d, J = 11.0 Hz, 1H), 4.66 (d, J = 5.0 Hz, 1H), 4.64 (s, 2H), 4.29 (d, J = 4.9 Hz, 1H), 1.28 – 1.11 (m, 3H), 1.07 (d, J = 5.8 Hz, 18H).



3.1

D-(+)-Malic Acid (3.1):[55] D-aspartic acid (50 grams, 376 mmol) was dissolved in 0.5M H_2SO_4 (2 liters, 1 mol, 2.5 eq) in a 5-liter 3-neck round bottom flask equipped with a 1-liter addition funnel and a large stir bar; one neck was connected to a gentle stream of air and one neck left open to vent. $NaNO_2$ (169 grams, 2.44 mol, 6.5 eq) was dissolved in 394 mL water to make a 30% solution, then transferred to the addition funnel and added to the acid solution dropwise at room temperature while stirring rapidly, with the stream of air evacuating the resulting brown NO_2 gas from the flask out of the open neck. Significant nitrogen gas emission and nitrogen dioxide gas emission was observed (the solution became translucent blue-green and effervescent). The solution was stirred at room temperature overnight. The next morning the reaction was heated to a simmer for 30 minutes to push it to completion and evacuate any residual gases, and the water was removed under reduced pressure on a rotary evaporator. The product was taken up from the remaining white to yellow solid by washing several times with boiling acetone, breaking up any chunks and filtering each wash through a silica plug, until the bright white residual salts were persistent and no significant product mass was collected with further washes. The acetone was removed on a rotary evaporator, and the resulting clear to yellow syrup was rinsed twice with toluene and rotovapped to

remove residual water, then finally put under vacuum while heated at 50 °C in an oil bath overnight to remove any remaining solvent. The next morning a light yellow to off-white solid remained, which is pure D-(+)-malic acid by NMR. The product is very water soluble, but mostly insoluble in organics, and may be further purified by Soxhlet[55b] with diethyl ether if desired. Product: 86% yield, light tan solid, mp 98-101 °C. 1H NMR (400 MHz, Deuterium Oxide) δ 4.62 (dd, C*H*OH, J = 6.7, 4.6 Hz, 1H), 2.91 (ddd, CH_2CHOH, J = 16.6, 6.8, 4.6 Hz, 2H).



3.2

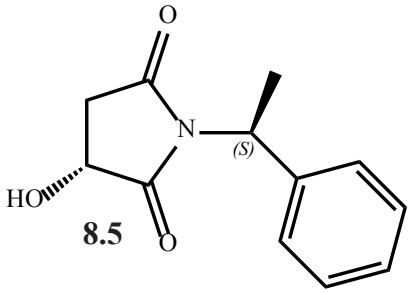
D-(+)-N-Benzylmalimide (3.2): Method A:[56b] D-(+)-malic acid (50 grams, 373 mmol) was suspended in 50 mL methanol in a 1000 mL round bottom flask to make a clear to light yellow heterogeneous solution. While stirring rapidly, benzylamine (40.0 mL, 366 mmol, 0.98 eq), previously distilled from calcium hydride, was added in a slow stream. Once the addition was complete, the solution was stirred at room temperature for one hour, and the methanol was removed under reduced pressure on a rotary evaporator leaving a white to yellow solid. The flask was equipped with a bump trap without drain holes as a crude water trap and heated in an oil bath at 140 °C for 8 hours. The solid melted within the first hour resulting in about 100 mL of a clear to light

yellow syrup which became orange to brown as the reaction proceeded. Significant condensation was observed on the sides of the flask and about 10-20 mL of water was collected in the bump trap. After 8 hours (or overnight) about 500 mL of toluene was added to the syrup, and the heterogenous solution was boiled with rapid stirring, becoming less heterogenous as it warmed. Any solids that did not dissolve in boiling toluene were removed by hot filtration through a large glass-fritted funnel. Finally the solution was allowed to cool to room temperature and put in the fridge overnight. The next morning crude solid D-malimide was separated by vacuum filtration and washed with cold toluene. The mother liquor was collected and rotovapped, the residue boiled with toluene again and put in the fridge to affect further crops of product. Each time the crude solid was collected, but if it was still very brown then toluene was added to it and the process was repeated to obtain light brown to yellow crude product. This crude product was dissolved in minimum dichloromethane and hexanes were added until fluffy white crystals formed. The crystals were collected by filtration, the mother liquor rotovapped and the process repeated to obtain additional product. Once crystallization failed the residual brown syrup was further purified on a silica column with 100% ethyl acetate. Note that any of the main (+)-N,N'-Dibenzyl-D-malic diamide byproduct must be removed from the final product, if present, by further purification with a silica plug and 50% ethyl acetate-hexanes, monitoring the eluent by TLC (Rf of product is 0.5, Rf of byproduct is 0.1; potassium permanganate stain). The product is usually completely separated from the byproduct which should begin to appear as a faint spot near the baseline. See the product and byproduct NMRs in the appendix. Product: 72% yield, fluffy white solid.

Method B:[56a] D-(+)-malic acid (50 grams, 373 mmol) was dissolved in 25 mL water and 25 mL

methanol in a 2-liter single-neck round bottom flask to make a clear to light yellow homogenous syrup. While stirring rapidly, benzylamine (40 mL, 366 mmol, 0.98 equiv), previously distilled from calcium hydride, was added in a slow stream by syringe. Once the addition was complete, and while continuing to stir, the solution was heated for 30 minutes at 50 °C, then the methanol was removed under reduced pressure on a rotary evaporator. 1 liter of xylenes was added, a Dean-Stark trap and condenser were equipped, and the solution was slowly brought to boiling. The heterogeneous solution became homogenous as it heated. The reaction was monitored for the first two hours for excessive foaming, to ensure homogeneity, and to empty the Dean-Stark trap; then refluxed overnight. The solution became homogenous and well-behaved within the first two hours, but the product syrup can burn or foam can climb the condenser if the reaction is not properly monitored. The next morning the xylenes solution was cooled to room temperature, then put in the fridge overnight to effect crystallization of the product. The product was separated by vacuum filtration and washed with a minimum of cold xylenes. The mother liquor was rotovapped and the residue saved if its volume was significant. The crude solid and any residue were recrystallized from boiling toluene, with any insoluble material removed by hot filtration. Often, it was necessary to leave the solution in the fridge overnight to achieve complete recrystallization, and the mother liquor was always saved and rotovapped to reclaim impure product and to repeat the process. The recrystallization from toluene was repeated until the product solid was light tan to yellow. Then it was dissolved in a minimum amount of dichloromethane, and hexanes were added until pure D-(+)-malimide crystallized as a fluffy white solid. The crystals were collected by filtration, the mother liquor rotovapped and the process repeated to obtain additional product. Once crystallization failed

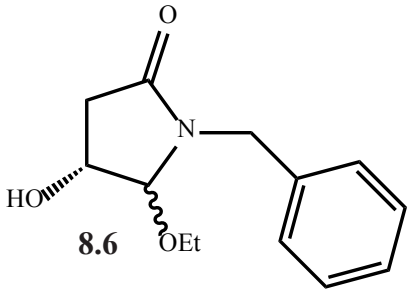
the residual brown syrup was further purified on a silica column with 100% ethyl acetate. Note that any of the main (+)-N,N'-Dibenzyl-D-malic diamide byproduct must be removed from the final product, if present, by further purification with a silica plug and 50% ethyl acetate-hexanes, monitoring the eluent by TLC (Rf of product is 0.5, Rf of byproduct is 0.1; potassium permanganate stain). The product is usually completely separated from the byproduct which should begin to appear as a faint spot near the baseline. See the product and byproduct NMRs in the appendix. Product: 60% yield, white solid, mp 107 °C. 1H NMR (400 MHz, Chloroform-d) δ 7.51 – 7.12 (m, Ar*H*, 5H), 4.67 (d, NC*HH*Ph, J = 1.6 Hz, 2H), 4.62 (ABXddd, $CH_AH_BC\mathit{H}_XOH$, J = 8.4, 4.8, 2.7 Hz, 1H), 3.07 (ABXdd, $C\mathit{H}_AH_BCH_XOH$, J = 18.2, 8.4 Hz, 1H), 2.89 (d, $CH_AH_BCH_XO\mathit{H}$, J = 2.7 Hz, 1H), 2.68 (ABXdd, $CH_A\mathit{H}_BCH_XOH$ J = 18.2, 4.8 Hz, 1H). 13C NMR (125.7 MHz, Chloroform-d) δ 177.78, 173.65, 135.19, 128.83, 128.74, 128.17, 67.01, 42.53, 37.13. FTIR (neat, diamond ATR, cm^{-1}) 3358, 1690. MS (ASAP): calcd for ($[M+H]^+$, $C_{11}H_{12}NO_3^+$) 206.08, found 206.0.



8.5

N-(*S*)-Methylbenzyl-D-Malimide:[56a] The same procedure was used as **3.2**, method B, except (*S*)-Methylbenzylamine was used instead of benzylamine. Purified on a silica column, 20-50% EtOAc/Hexanes. Offwhite solid. 47% yield. 1H NMR (400 MHz, DMSO-d6) δ 7.36 – 7.20 (m, 5H), 6.05 (d, J = 6.6 Hz, 1H), 5.25 (q, J = 7.2 Hz, 1H), 4.54 – 4.42 (m, 1H), 2.99 (dd, J = 17.7, 8.4

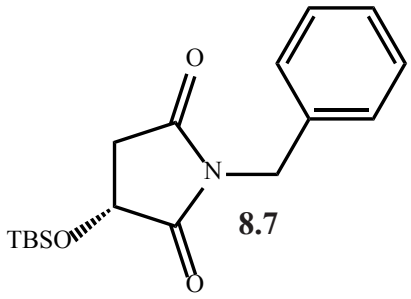
Hz, 1H), 2.39 (dd, J = 17.7, 4.5 Hz, 1H), 1.69 (d, J = 7.3 Hz, 3H).



8.6

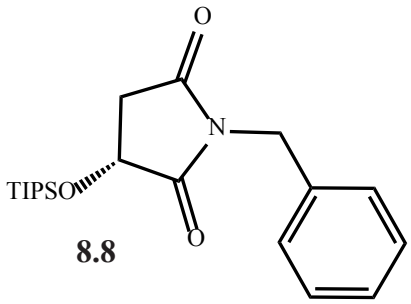
(4R)-1-benzyl-5-ethoxy-4-hydroxypyrrolidin-2-one:[58] N-Benzyl-D-Malimide (2 grams, 9.7 mmol) was dissolved in 100 mL of anhydrous THF in an oven-dry 250 mL round bottom flask equipped with a 25 mL addition funnel under argon. The solution was cooled to -20 °C. $LiBH_4$ (12.5 mL of 2.0M in THF, 25 mmol, 2.5 eq) was transferred to the addition funnel, and added dropwise to the malimide solution over 30 minutes. After the addition was complete, the solution was stirred for 90 minutes. The reaction was quenched by adding just enough 2M sulfuric acid in ethanol to bring the solution to a neutral pH (wet pH paper was used to get a reading on the organic solution). The solution was rotovapped to remove the THF, and the residue was dissolved in enough ethanol to fill the flask halfway. The pH was reduced to about 3 by the addition of more 2M sulfuric acid in ethanol, and the solution was stirred at room temperature overnight. The yellow-grey solution was cloudy white the next morning. The solution was refluxed for 8 hours, and became cloudier as it boiled. After 8 hours the solution was neutralized with about 1 mL of hot NaOH in ethanol (a few pellets of NaOH in ethanol was sufficient; a 5% solution could be used for larger scales). After the solution had cooled, it was filtered through celite with lots of ethanol. Rotovap. The residue was heated at 40 °C under hi-vac to remove the rest of the solvent. Yellow

solid, insoluble in DCM and chloroform. Silica column, 3-20% EtOH/DCM. 70% yield. 1H NMR (400 MHz, DMSO-d6) δ 7.42 – 7.16 (m, 5H), 5.37 (d, J = 3.7 Hz, 1H), 4.67 (d, J = 15.4 Hz, 1H), 4.44 (s, 1H), 4.07 (d, J = 15.5 Hz, 1H), 4.04 (dd, J = 9.9, 5.2 Hz, 1H), 3.52 – 3.35 (m, 2H), 2.69 (dd, J = 17.3, 6.1 Hz, 1H), 2.05 (dd, J = 17.3, 1.3 Hz, 1H), 1.05 (t, J = 7.0 Hz, 3H).



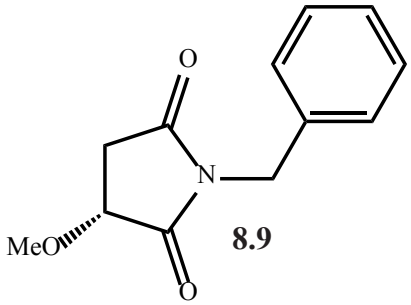
8.7

N-Benzyl-O-*tert*-Butyldimethylsilyl-D-Malimide:[59] Dry D-malimide (1 gram, 4.9 mmol), imidazole (1.0 gram, 14.7 mmol, 3 eq), and TBSCl (2.2 grams, 14.7 mmol, 3 eq) were added to a 50 mL oven-dry round bottom flask under argon, and 20 mL anhydrous DMF was added through a septum. The solution was stirred overnight at room temperature under argon. The next morning, diethyl ether was added, and the solution was transferred to a separatory funnel with more ether. The combined ether layer was washed 5x with water, then once with saturated brine, then dried over anhydrous sodium sulfate. The volatiles were removed on a rotovap and the yellow oil purified on a silica column, 0-10% EtOAc/Hexanes. 90% yield, yellow oil. 1H NMR (400 MHz, Chloroform-d) δ 7.41 – 7.23 (m, 5H), 4.65 (dd, J = 21.7, 15.2 Hz, 2H), 4.57 (dd, J = 8.1, 4.5 Hz, 1H), 2.99 (dd, J = 18.0, 8.1 Hz, 1H), 2.60 (dd, J = 18.0, 4.4 Hz, 1H), 0.90 (s, 9H), 0.16 (d, J = 3.9 Hz, 6H).



8.8

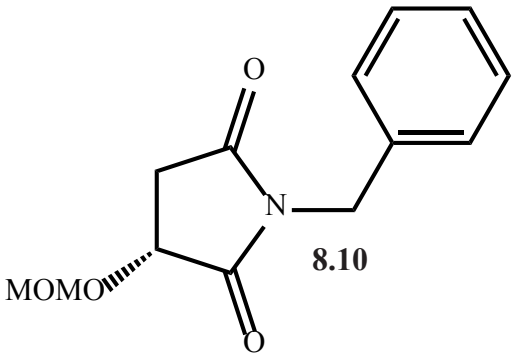
N-Benzyl-O-Triisopropylsilyl-D-Malimide:[59] N-benzyl-D-malimide (0.5 grams, 2.44 mmol) and imidazole (0.85 grams, 12.5 mmol, 5 eq) were added to an oven-dry 25 mL round bottom flask under argon. The solids were dissolved in 3 mL of anhydrous DMF, then TIPSCl (2.7 mL, 12.6 mmol, 5 eq) was added. The solution was stirred at room temperature overnight. The next day the reaction was poured into 25 mL of water in a separatory funnel with the aid of 50 mL of diethyl ether. The ether layer was washed 5 times with water, then brine once, then dried over anhydrous sodium sulfate. Rotovap. Silica column, 0-30% EtOAc/hexanes. Yellow syrup. Quantitative yield. 1H NMR (400 MHz, Chloroform-d) δ 7.45 – 7.19 (m, 5H), 4.74 – 4.57 (m, 1H), 4.73 – 4.59 (m, 2H), 3.03 (dd, J = 17.9, 8.1 Hz, 1H), 2.63 (dd, J = 17.8, 4.4 Hz, 1H), 1.23 – 1.07 (m, 3H), 1.05 (d, J = 1.0 Hz, 18H).



8.9

N-Benzyl-O-Methyl-D-Malimide:[93] Dry N-benzyl-D-malimide (0.188 grams, 0.916 mmol) and freshly-prepared silver oxide (0.639 grams, 2.76 mmol, 3 eq) were added to a 25 mL oven-dry round

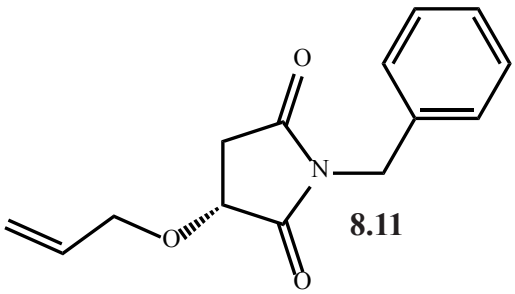
bottom flask under argon, 10 mL of anhydrous diethyl ether was added, and the heterogeneous black solution was stirred for a few minutes, then the flask was covered in foil to keep out the light. Methyl iodide was added through the septum, and the solution was stirred under argon for an hour. Then triethyl amine (0.5 mL) was added. After another hour the flow of argon was removed to preserve the solvent (a balloon may be used). The solution was stirred overnight. The next morning, the solution was filtered through celite with more ether, then the combined organics were washed with 10% HCl twice, then saturated sodium bicarbonate once, then saturated brine. Dried over anhydrous sodium sulfate. Yellow oil, 20% yield. 1H NMR (400 MHz, Chloroform-d) δ 7.43 – 7.22 (m, 5H), 4.66 (d, J = 2.2 Hz, 2H), 4.20 (dd, J = 8.2, 4.2 Hz, 1H), 3.61 (s, 3H), 2.99 (dd, J = 18.2, 8.2 Hz, 1H), 2.62 (dd, J = 18.2, 4.1 Hz, 1H).



8.10

N-Benzyl-O-Methoxymethyl-D-Malimide:[94] A 25 mL 2-neck oven-dry round bottom flask was equipped with a thermometer in one neck, placed under argon. Freshly distilled dimethoxymethane (DMM, 0.22 mL, 2.5 mmol, 1.0 eq), and 3x the volume of toluene as compared to DMM (0.6 mL) were added. A spatula tip of zinc bromide (0.01 mol % was necessary) was added by removing the septum briefly, then acetyl chloride (0.18 mL, 2.5 mmol, 1.0 eq) was added dropwise. The reaction spontaneously warmed to 40-45 °C and then cooled, indicating that the MOMCl

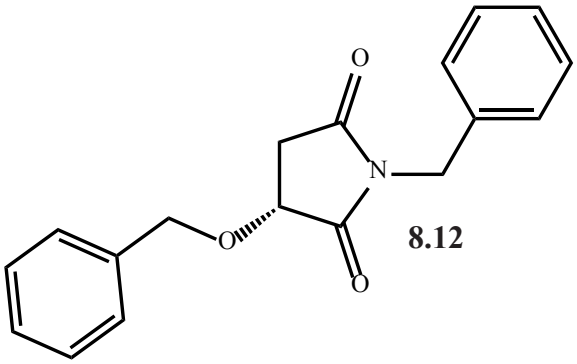
producing reaction was proceeding. The solution was cooled in an ice bath, 0.5 grams (2.4 mmol) of dry D-malimide were added in one portion by removing the septum briefly, and the solution was stirred for a few minutes. DIPEA (0.53 mL, 3 mmol, 1.25 eq) was added dropwise, while maintaining the temperature of the reaction below 25 °C. After the addition was complete, the ice was allowed to melt, and the solution was stirred 2 days at room temperature. After 2 days, the solution was poured carefully into 50 mL each of EtOAc and saturated ammonium chloride. Let stir 30 min to quench any remaining MOMCl. The solution was poured into a separatory funnel, and the layers separated. The organic layer was washed with water twice, brine once, then dried over anhydrous sodium sulfate. The volatiles were removed on a rotovap. Yellow solid. Purified on a silica column, 0-30% EtOAc/Hexanes. The main byproducts are starting material (ca 40%) and acetylated D-Malimide (ca 30%). 20% yield, light yellow solid. 1H NMR (400 MHz, Chloroform-d) δ 7.44 – 7.23 (m, 5H), 5.44 (dd, J = 8.7, 4.8 Hz, 1H), 4.99 (d, J = 6.8 Hz, 1H), 4.78 – 4.63 (m, 2H), 4.58 (dd, J = 8.4, 4.5 Hz, 1H), 3.41 (s, 3H), 3.04 (dd, J = 18.2, 8.4 Hz, 1H), 2.74 – 2.61 (m, 1H).



8.11

N-Benzyl-O-Allyl-D-Malimide:[95] D-malimide (0.5 grams, 2.4 mmol) were dissolved in 4 mL of DCM in a 25 mL oven-dry round bottom flask. Allyl bromide (0.5 grams, 2.4 mmol) and 50%

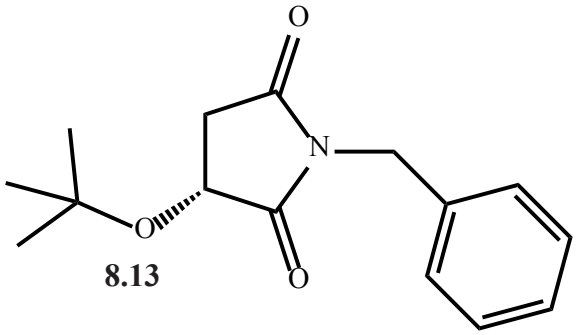
aqueous KOH (1.8 mL, 40 mmol, 16 eq) were added, and the heterogeneous mixture was stirred vigorously for 4 hours. The mixture was diluted with 10 mL water, and stirred for 5 minutes. The reaction was poured into a separatory funnel with more DCM, the layers separated, and the organic layer washed with 10% aqueous NaBr once, then the organic layer was dried over sodium sulfate. The volatiles were removed on a rotovap, and the yellow syrup was purified on a silica column, 0-20% MeOH/DCM. 11% yield, yellow solid. 1H NMR (400 MHz, Chloroform-d) δ 7.42 – 7.15 (m, 5H), 5.83 (ddt, J = 17.0, 10.2, 5.9 Hz, 1H), 5.28 – 5.15 (m, 2H), 4.55 – 4.35 (m, 2H), 4.31 (dd, J = 7.0, 4.6 Hz, 1H), 4.19 – 4.01 (m, 2H), 2.86 (dd, J = 14.9, 4.6 Hz, 1H), 2.59 (dd, J = 15.0, 7.0 Hz, 1H).



8.12

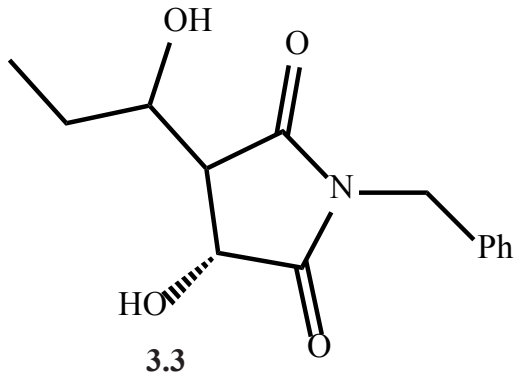
N-Benzyl-O-Benzyl-D-Malimide:[96] D-malimide (0.48 grams, 2.3 mmol) and freshly-prepared silver oxide (1.6 grams, 6.9 mmol, 3 eq) were added to a 50 mL oven-dry round bottom flask under argon. 20 mL of ether were added, then freshly-distilled benzyl bromide (0.83 mL, 6.9 mmol, 3 eq). After a few hours removed the argon flow to preserve the solvent. Stirred at room temperature, flask covered in aluminum foil, for 5 days. After 5 days, the reaction solution was filtered through celite with more ether. Rotovap, brown oil. Silica column, 0-40% EtOAc/Hexanes. 96% yield, clear oil turns to white solid on standing. 1H NMR (400 MHz, Chloroform-d) δ 7.41 – 7.24 (m,

10H), 4.99 (d, J = 11.7 Hz, 1H), 4.78 (d, J = 11.7 Hz, 1H), 4.66 (d, J = 2.4 Hz, 2H), 4.36 (dd, J = 8.2, 4.2 Hz, 1H), 2.95 (dd, J = 18.3, 8.3 Hz, 1H), 2.66 (dd, J = 18.2, 4.2 Hz, 1H).



8.13

N-Benzyl-O-*tert*-butyl-D-Malimide:[97] $MgSO_4$ (0.48 grams, 4 mmol, 4 eq) was added to 3 mL of cyclohexane in a 25 mL round bottom flask, and the suspension was stirred vigorously while 3 drops (ca 0.06 mL, 1 mmol, 1 eq) of concentrated sulfuric acid was added. The mixture was stirred for 15 minutes. Separately, *tert*-butanol (0.5 mL, 5 mmol, 5 eq) and N-benzyl-D-malimide (0.2 grams, 1 mmol, 1 eq) were dissolved in 1 mL of 1:1 DCM/cyclohexane, and the solution was added to the magnesium sulfate solution via syringe. The flask was sealed with a glass stopper, and stirred at room temperature overnight. The next morning, the solution was transferred to a separatory funnel with 25 mL of diethyl ether, and the organic layer was washed with saturated sodium bicarbonate, then brine, then dried over anhydrous sodium sulfate. Rotovap. Product has Rf of 0.4 in 20% EtOAc/Hexanes. Silica column, 15-70% EtOAc/Hexanes. White solid. 68% yield. 1H NMR (400 MHz, Chloroform-d) δ 7.42 – 7.24 (m, 5H), 4.65 (dd, J = 18.4, 14.1 Hz, 2H), 4.45 (dd, J = 8.3, 4.8 Hz, 1H), 2.98 (dd, J = 18.0, 8.4 Hz, 1H), 2.59 (dd, J = 18.0, 4.8 Hz, 1H), 1.27 (s, 9H).

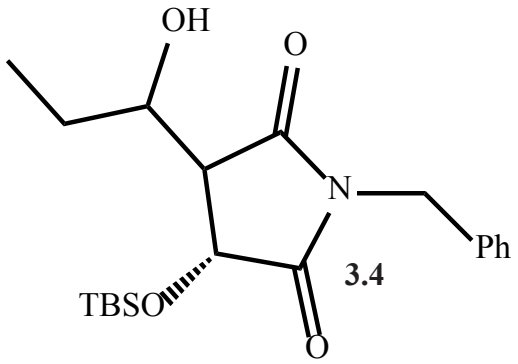


3.3

(3*R*)-1-benzyl-3-hydroxy-4-(1-hydroxypropyl)pyrrolidine-2,5-dione (3.3):[57] Very pure white D-(+)-N-Benzylmalimide (5 grams, 24.4 mmol) was added to a 250 mL 24/40 single-neck round bottom flask. The malimide was thoroughly dried by adding toluene and removing it three times with a rotary evaporator; and finally by placing it in a vacuum desiccator overnight. The next morning, an oven-dry 1-liter 2-neck round bottom flask (at least one neck was 29/42 to accommodate a large-sized stir bar) was equipped with a large stir bar, an interior thermometer through the side neck, and an oven-dry 500-milliliter addition funnel through the top neck. The setup was evacuated and refilled with argon three times. Separately, the malimide in its flask was removed from the desiccator and also setup under argon. 100 mL anhydrous THF was added to the malimide flask, swirling to dissolve, and 200 mL anhydrous THF was added to the 1-liter flask. NaHMDS (48.75 mL, 1.0M, 48.8 mmol, 2.0 eq) was added to the 1-liter flask all at once, and both flasks were cooled to 0 °C. The cooled malimide solution was transferred to the closed addition funnel by cannula, and was added dropwise to the cooled base solution, at such a rate to maintain the internal temperature at 0 °C throughout the addition, while stirring thoroughly. The solution went from clear to cloudy yellow or tan to pinkish as the addition progressed, and

became increasingly heterogeneous. It is critical that it does not stop stirring. Once the addition of the malimide to the base solution was complete, it was stirred for an additional 5 minutes at 0 °C. Meanwhile, the addition funnel was replaced by a septum, and the flask was cooled to -78 °C. Propanal (1.76 mL, 24.4 mmol, 1.0 eq), previously distilled from calcium hydride, was added in a slow stream to the base solution by syringe, maintaining the temperature at -78 °C. There was no change in the appearance of the solution throughout the aldehyde addition. Once the addition was complete, the solution was stirred at -78 °C for 90 minutes. After 90 minutes at -78 °C the flask was removed from the dewar and poured into a 2-liter separatory funnel containing 300 milliliters of saturated aqueous ammonium chloride, using 600 mL of 25% dichloromethane in diethyl ether to aid the transfer. After shaking, a minimum amount of distilled water was added and the funnel shaken again to break up any solids. The organic layer was washed twice more with 100 mL of saturated aqueous ammonium chloride and finally with 100 mL of saturated brine solution, and dried over anhydrous sodium sulfate. The volatiles were removed on a rotary evaporator, and the yellow to orange syrup was purified on a 100-gram silica column with 60-100% diethyl ether-hexanes, resulting in two separable diastereomers as yellow solids. Often, leftover starting material coelutes with the more polar isomer, and some may be separated with another 100-gram silica column and 90-100% diethyl ether-hexanes, but in practice some starting material always contaminates the more polar sample. TLC: in 100% diethyl ether and permanganate stain, the less polar product isomer had an Rf of about 0.7, and the more polar product isomer had an Rf of about 0.6, and was usually mixed with starting material. The nonpolar yellow oil with an Rf of about 0.9 was a mess by NMR that contained no phenyl group, and the brown solid with an

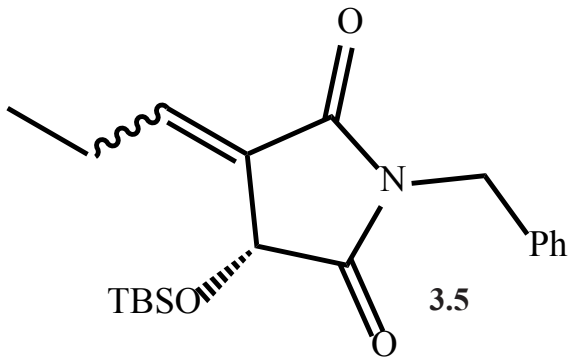
Rf of about 0.1 was a mess by NMR that was unidentifiable. Product: 44% yield, yellow solid, mp 98-101 °C. 1H NMR (400 MHz, Chloroform-d) less polar isomer 1: δ 7.35 – 7.21 (m, Ar*H*, 5H), 4.73 (d, COC*H*OH, J = 5.3 Hz, 1H), 4.64 (ABdd, NCH_AH_BPh, J = 19.0, 14.3 Hz, 2H), 4.26 (td, C*H*(OH)CH_2CH_3, J = 6.7, 3.7 Hz, 1H), 3.76 (s, CH(O*H*)CH_2CH_3, 1H), 2.82 (dd, C*H*CH(OH) CH_2CH_3, J = 5.4, 2.6 Hz, 1H), 2.39 (d, COCHO*H*, J = 4.0 Hz, 1H), 1.67 (dq, CH(OH)CH_2CH_3, J = 14.7, 7.3 Hz, 2H), 0.99 (t, CH(OH)CH_2CH_3, J = 7.4 Hz, 3H). more polar isomer 2: δ 7.37 – 7.16 (m, Ar*H*, 5H), 4.61 (ABdd, NCH_AH_BPh, J = 20.6, 14.3 Hz, 2H), 4.47 (d, COC*H*OH, J = 5.6 Hz, 1H), 3.88 (dt, C*H*(OH)CH_2CH_3, J = 11.7, 5.8 Hz, 1H), 2.82 (t, C*H*CH(OH)CH_2CH_3, J = 5.5 Hz, 1H), 1.73 (p, CH(OH)CH_2CH_3, J = 7.3 Hz, 2H), 0.98 (t, CH(OH)CH_2CH_3, J = 7.4 Hz, 3H). 13C NMR (125.7 MHz, Chloroform-d) δ 177.93, 175.59, 135.16, 128.70, 128.34, 127.99, 69.82, 67.26, 53.77, 42.54, 27.84, 10.16. FTIR (neat, diamond ATR, cm^{-1}) 3464, 3320, 1678. HR-ESI-TOFMS: calcd for ($[M+H]^+$, $C_{14}H_{18}NO_4^+$) 264.1230, found 264.1234.



3.4

(3R)-1-benzyl-3-((*tert*-butyldimethylsilyl)oxy)-4-(1-hydroxypropyl)pyrrolidine-2,5-dione (3.4):[59] Dry yellow solid (3R)-1-benzyl-3-hydroxy-4-(1-hydroxypropyl)pyrrolidine-2,5-dione (5.0 grams, 19 mmol) was placed under argon and dissolved in 20.0 mL anhydrous N,N-

dimethylformamide. *tert*-Butyldimethylsilyl chloride (8.6 grams, 57 mmol, 3 eq) and imidazole (3.9 grams, 57 mmol, 3 eq) were added by removing the septum briefly, and the mixture was stirred at room temperature for exactly one hour (exactly one equivalent of each reagent may be used, but yields will be reduced unless it is very fresh). Any additional time will result in more of the di-protected product, any less time results in extra starting material. After an hour passed, the argon was removed and water was added to quench the reaction. The reaction mixture was poured into about 50 mL of water in a separatory funnel with the aid of about 50 mL of diethyl ether. The organic layer was washed five times with water and once with brine, then dried over anhydrous sodium sulfate. The yellow solution was rotovapped, and the yellow residue taken up in hexanes and injected onto a 100 gram silica column with 0-30% ethyl acetate-hexanes. TLC: in 30% ethyl acetate-hexanes with KMnO4 stain the product had an R¬f of about 0.3; the double-protected product and extra TBS reagent came off early with an Rf near 0.9. Starting material, when present, comes off with an Rf of about 0.6. Product: 89% yield, light yellow oil. 1H NMR (400 MHz, Chloroform-d) δ 7.37 – 7.21 (m, Ar*H*, 5H), 4.70 (d, C*H*OTBS, J = 4.7 Hz, 1H), 4.64 (ABdd, CH_AH_BPh, J = 27.1, 14.3 Hz, 2H), 4.24 (tdd, C*H*(OH)CH_2CH_3, J = 7.1, 4.5, 2.4 Hz, 1H), 2.81 (dd, C*H*CH(OH)CH_2CH_3, J = 4.7, 2.4 Hz, 1H), 1.96 (d, CH(O*H*)CH_2CH_3, J = 4.8 Hz, 1H), 1.62 (pd, CH(OH)CH_2CH_3, J = 7.4, 1.9 Hz, 2H), 0.99 (t, CH(OH)CH_2CH_3 J = 7.4 Hz, 3H), 0.89 (s, OSi*tBu*, 9H), 0.23 (s, OSiCH_3, 3H), 0.19 (s, OSiCH_3, 3H). 13C NMR (125.7 MHz, Chloroform-d) δ 175.58, 175.50, 135.37, 128.67, 128.60, 127.95, 72.20, 71.46, 54.20, 42.27, 27.96, 25.65, 18.13, 9.92, -4.13, -5.19. FTIR (neat, diamond ATR, cm^{-1}) 3482, 2929, 1702.

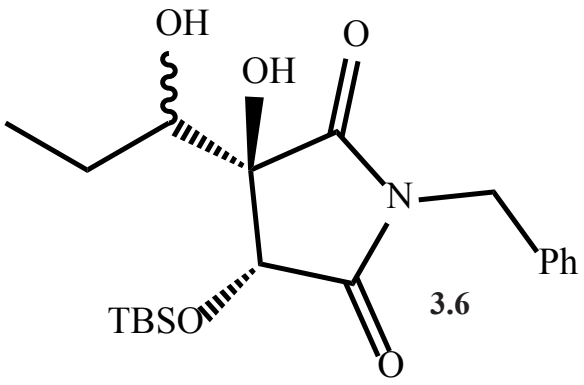


3.5

(R)-1-benzyl-3-((*tert*-butyldimethylsilyl)oxy)-4-propylidenepyrrolidine-2,5-dione (3.5):[63]

(3R)-1-benzyl-3-((*tert*-butyldimethylsilyl)oxy)-4-(1-hydroxypropyl)pyrrolidine-2,5-dione (5.0 grams, 13 mmol) was dissolved in dichloromethane and 28 mL (199 mmol, 15 eq) of triethylamine was added. The solution was cooled to -45 °C under argon, and methanesulfonyl chloride (5.1 mL, 66 mmol, 5 eq) was added via syringe. The heterogeneous brown solution was stirred at -45 °C for one hour, then was allowed to warm to room temperature for one hour. Saturated ammonium chloride was added to quench, and the solution was poured into about 50 mL of saturated ammonium chloride in a separatory funnel with the aid of about 50 mL of dichloromethane. The aqueous layer was extracted with dichloromethane 3 times, and the combined organic layers were passed through a 2 to 3-inch silica plug with more dichloromethane. The solvent was removed by evaporation, and purified in 1-gram portions on a 100 gram silica column with 0-20% ethyl acetate/hexanes (Rf about 0.5 in 10% ethyl acetate/hexanes, permanganate stain, two isomers). The product must be purified the same day it is prepared to preserve the yield. Product: 88% yield, light yellow oil. 1H NMR (400 MHz, Chloroform-d) trans isomer: δ 7.43 – 7.15 (m, Ar*H*, 5H), 6.89 (td, C=C*H*CH_2CH_3, J = 7.8, 2.0 Hz, 1H), 4.89 (dt, C*H*OTBS, J = 2.0, 1.0 Hz, 1H), 4.67 (ABq, CH_AH_BPh, J = 14.0 Hz, 2H), 2.34 (ddq, CHC=CHCH_2CH_3, J = 7.8, 7.5, 1.0 Hz, 2H),

1.07 (t, $CHCH_2CH_3$, J = 7.5 Hz, 3H), 0.86 (s, OSi*tBu*, 9H), 0.18 (d, $OSi(CH_3)_2$, J = 1.9 Hz, 6H).. cis isomer: δ 7.43 – 7.26 (m, Ar*H*, 5H), 6.29 (td, $C{=}CHCH_2CH_3$, J = 7.8, 1.9 Hz, 1H), 4.78 (dt, $CHC{=}CHCH_2CH_3$, J = 1.9, 1.6 Hz, 1H), 4.67 (ABdd, NCH_AH_BPh, J = 21.6, 14.0 Hz, 2H), 2.81 (pt, $C{=}CHCH_2CH_3$, 7.5, 1.6 Hz, 2H), 1.09 (t, $C{=}CHCH_2CH_3$, J = 7.5 Hz, 3H), 0.94 (s, OSi*tBu*, 9H), 0.20 (d, $OSi(CH_3)_2$, J = 6.6 Hz, 6H). 13C NMR (125.7 MHz, Chloroform-d) δ 174.22, 168.17, 144.84, 135.67, 128.79, 128.59, 127.87, 67.50, 42.09, 25.73, 25.39, 22.65, 18.24, 12.88, -3.82, -5.05. FTIR (neat, diamond ATR, cm^{-1}) 3034, 2930, 1711, 1677. HR-ESI-TOFMS: calcd for ($[M+H]^+$, $C_{20}H_{30}NO_3Si^+$) 360.1989, found 360.1988.

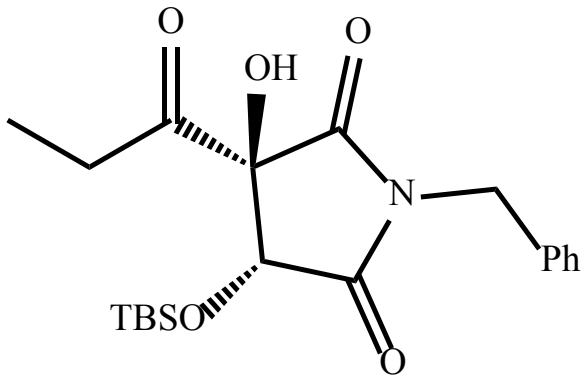


3.6

(3R,4R)-1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-3-(1-hydroxypropyl) pyrrolidine-2,5-dione (3.6):[64] (R)-1-benzyl-3-((*tert*-butyldimethylsilyl)oxy)-4-propylidenepyrrolidine-2,5-dione (5.0 grams, 14 mmol) was dissolved in 100 mL of 95% ethanol, and the solution was cooled to -15 °C. Separately, potassium permanganate (11 g, 70 mmol, 5 eq) and magnesium sulfate (8.4 g, 70 mmol, 5 eq) were dissolved in 20 mL of water and added with rapid stirring to the ethanol solution dropwise with a large pipet. It was important that the ratio of alcohol to water remained around 3:1 to avoid freezing. Once the addition was complete, the

solution was stirred at -15 °C for 30 minutes, then allowed to warm to room temperature for at least one hour. Sodium bisulfite (100 mL of 40% w/v) was added to quench the permanganate, and the solution was stirred overnight. The purple to brown opaque solution became a white solid suspended in a clear solution by the morning. The solution was filtered through celite with ethyl acetate, the volatiles were evaporated and the aqueous layer extracted 3 times with ethyl acetate. The combined organic layers were washed once with brine and dried over sodium sulfate. The diastereomers were separated and purified in about 1 gram portions on a 100 gram silica column with 20-40% ethyl acetate hexanes. Often, at least a quarter of the product yield is the over-oxidized (3S,4R)-1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-3-propionylpyrrolidine-2,5-dione. Rf in 20% ethyl acetate/hexanes with permanganate stain is about 0.8 for the starting material, 0.4 for the over-oxidized product, and 0.3 for the product. Product: 79% yield, white solid, mp 91 °C for the less polar diastereomer and 106-107 °C for the more polar diastereomer. 1H NMR (400 MHz, Chloroform-d) syn diol: δ 7.42 – 7.15 (m, Ar*H*, 5H), 4.68 (s, NCH_2Ph, 2H), 4.54 (s, C*H*OSi, 1H), 3.77 (ddd, C*H*(OH)CH_2CH_3, J = 10.9, 5.2, 2.2 Hz, 1H), 3.22 (s, 3°O*H*, 1H), 2.70 (dd, CH(O*H*)CH_2CH_3, J = 5.2, 1.6 Hz, 1H), 1.70 – 1.30 (m, CH(OH)CH_2CH_3 2H), 0.98 (t, J = 7.3 Hz, 3H), 0.97 (s, 9H), 0.25 (s, 3H), 0.20 (s, 3H). Anti diol: 1H NMR (400 MHz, Chloroform-d) δ 7.46 – 7.20 (m, Ar*H*, 5H), 4.64 (ABq, NCH_AH_BPh, J = 14.0 Hz, 2H), 4.63 (s, C*H*OSi, 1H), 4.01 (s, 3°OH, 1H), 3.66 (t, C*H*(OH)CH_2CH_3, J = 10.0 Hz, 1H), 2.01 (d, CH(O*H*)CH_2CH_3, J = 10.3 Hz, 1H), 1.49 – 0.68 (m, CH(OH)CH_2CH_3, 2H), 0.94 (s, 9H), 0.90 (t, CH(OH)CH_2CH_3, J = 7.2 Hz, 3H), 0.22 (s, 3H), 0.17 (s, 3H). 13C NMR (125.7 MHz, Chloroform-d) δ 175.03, 173.26, 134.93, 128.63, 128.46, 127.94, 81.38, 77.55, 75.61, 42.64, 25.62, 22.72, 18.28, 10.91, -4.74, -5.27. FTIR

(neat, diamond ATR, cm^{-1}) 3551, 3472, 2930, 2857, 1703. HR-ESI-TOFMS: calcd for ($[M+Na]^+$, $C_{20}H_{29}NO_5SiNa^+$) 416.1864, found 416.1868.



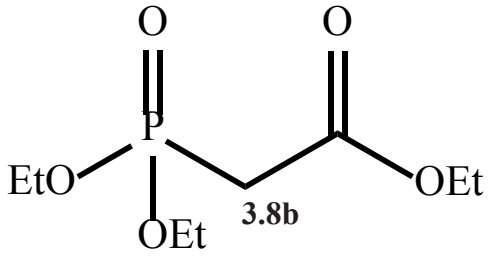
Key compound 3.7

(3S,4R)-1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-3-propionylpyrrolidine-2,5-dione (key compound 3.7): Method A:[65] (3R,4R)-1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-3-(1-hydroxypropyl)pyrrolidine-2,5-dione (5.0 grams, 13 mmol) was dissolved in dichloromethane at room temperature under argon and Dess-Martin periodinane (16.1 g, 38 mmol, 3 eq) was added. The argon inlet was removed from the tightly-sealed system and the reaction was stirred overnight. The next morning 100 mL of a 1:1 saturated sodium thiosulfate and sodium bicarbonate solution was added and the solution was stirred until homogenous. The solution was transferred to a separatory funnel, and the aqueous layer was extracted three times with dichloromethane. The combined organic layers were washed once with saturated brine and dried over sodium sulfate. The product was purified in 1 gram portions on a 100 gram silica column with 15-20% ethyl acetate hexanes. Rf of about 0.5 in 20% ethyl acetate/hexanes with permanganate stain. 76% yield, white solid, mp 109-111 °C. Often, one isomer of the starting material is very

slow to oxidize with DMP, but is successfully oxidized with Jones reagent according to method B, which seems to be most successful on a smaller scale.

Method B: Jones reagent creation;[66b] oxidation procedure.[66a] (3R,4R)-1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-3-(1-hydroxypropyl)pyrrolidine-2,5-dione (100 mg, 0.254 mmol) was dissolved in 5 mL of acetone in a 25 mL Erlenmeyer flask equipped with a stir bar. Separately, chromium trioxide (130 mg, 1.30 mmol, 5 eq) was dissolved in 2 mL of water in a small vial, and concentrated 18M sulfuric acid (0.10 mL, 1.9 mmol, 7.5 eq) was added slowly, and additional water was added dropwise to dissolve any resulting solid salts to form a translucent, homogenous orange Jones reagent solution. Both solutions were cooled to 0 °C in an ice bath and, while stirring, the Jones reagent was added to the acetone solution dropwise with a Pasteur pipet. The clear acetone solution turned green and then orange-green as the addition progressed, and a dark green goo precipitated. Once the addition was complete the ice bath was removed, and the reaction was stirred to room temperature for 1-2 hours, while monitoring its progress via TLC (product Rf of about 0.5 in 20% ethyl acetate/hexanes with permanganate stain, starting material Rf of about 0.3). Once the reaction was complete, added a solution of 10 mL diethyl ether and 3 mL isopropanol to the reaction to quench the Jones reagent, then passed the mixture through a 2-inch celite pad with about 250 mL more ether to separate most of the green precipitate from the product. It's important to break up the green goo as much as possible, and disperse it in the ether to maximize the product yield. The greenish solution was transferred to 250 mL of water in a separatory funnel, and the organic layer was washed once and separated. The aqueous layer was extracted with ether two more times. The combined organics were washed with saturated sodium

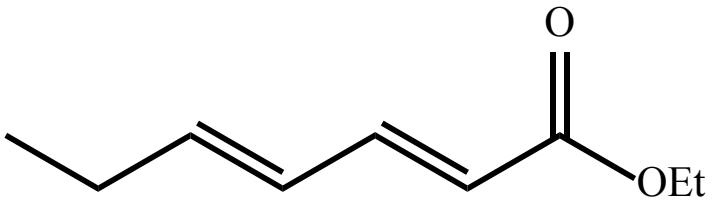
bicarbonate once, then dried over sodium sulfate. The volatiles were rotovapped away, and the crude yellow to light green solid was applied to a 50 g silica column, with a gradient of 15-20% ethyl acetate/hexanes. The product has an R¬f of about 0.5 in 20% ethyl acetate/hexanes with a permanganate stain. 74% yield, white solid, mp 109-111 °C. 1H NMR (500 MHz, Chloroform-d) δ 7.47 – 7.28 (m, Ar*H*, 5H), 4.75 (ABdd, NCH_AH_BPh, J = 31.9, 13.8 Hz, 2H), 4.74 (s, C*H*OSi, 1H), 4.66 (s, 3°O*H*, 1H), 2.08 (ddq, COCH_2CH$_3$, J = 275.3, 18.5, 7.1 Hz, 2H), 0.90 (t, COCH$_2$CH_3, J = 7.1 Hz, 3H), 0.85 (s, 9H), 0.17 (s, 3H), 0.08 (s, 3H). 13C NMR (125.7 MHz, Chloroform-d) δ 201.90, 172.78, 170.46, 134.39, 129.34, 128.84, 128.50, 86.54, 77.42, 43.21, 31.92, 25.41, 18.08, 6.93, -4.92, -5.39. FTIR (neat, diamond ATR, cm^{-1}) 3434, 2930, 1714. HR-ESI-TOFMS: calcd for ([M+Na]$^+$, $C_{20}H_{29}NO_5SiNa^+$) 414.1707, found 414.1709.



3.8b

Triethyl phosphonoacetate:[67] Ethyl bromoacetate (11.0 mL, 99 mmol) and triethyl phosphite (18.0 mL, 105 mmol, 1.1 eq) were added a round bottom flask equipped with a large bump trap without drainage holes under argon. The solution was heated at 140 °C overnight. Ethyl bromide boiled off rapidly once the solution hit 140 °C, and collected in the bump trap. The next morning the yellowish oil was cooled to 60 °C and placed under high vacuum to remove residual ethyl bromide. The result is pure enough to use in the next step, but may be purified on a silica column

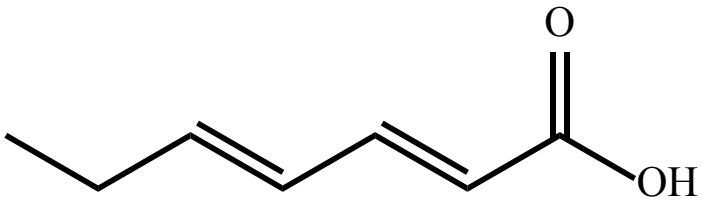
with 0-10% ethyl acetate hexanes. Product: 85% yield, clear to light yellow oil. 1H NMR (400 MHz, Chloroform-d) δ 4.19 (dq, J = 14.6, 7.1 Hz, 6H), 2.96 (d, J = 21.6 Hz, 2H), 1.35 (t, J = 7.1 Hz, 6H), 1.29 (t, J = 7.1 Hz, 3H).



3.8a

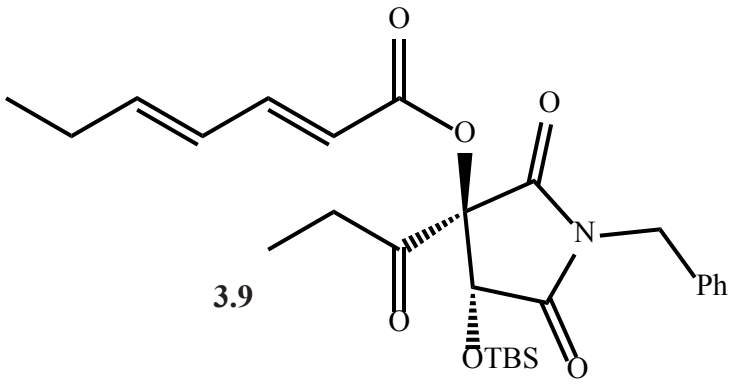
Ethyl (2E,4E)-hepta-2,4-dienoate (3.8a):[68] Sodium hydride (60% dispersion in mineral oil, 4.0 grams, 100 mmol, 3 eq) were added to a 100 mL oven-dry round bottom flask under argon, and dry hexanes were added and withdrawn once to remove excess mineral oil. The grey solid was suspended in 40 mL of anhydrous THF and cooled to -20 °C. Triethyl phosphonoacetate (11.5 mL, 58 mmol, 1.8 eq) was added dropwise, maintaining the temperature at -20 °C. Once the addition was complete, 2-pentenal (3.2 mL, 33 mmol) was added in a slow stream, and the solution was stirred for 30 minutes at -20 °C. The solution was warmed to room temperature and stirred for another 30 minutes. Finally, it was quenched with a minimum amount of water, and transferred to a separatory funnel with about 300 mL of diethyl ether. The organic layer was washed with saturated ammonium chloride once, then saturated sodium carbonate twice and saturated brine once, before being dried over anhydrous magnesium sulfate. The bright yellow oil was purified on a 100 g silica column with 0-15% ethyl acetate/hexanes. Rf of about 0.5 in 10% ethyl acetate/ hexanes with permanganate stain. Product: 94% yield, light yellow oil. 1H NMR (400 MHz,

Chloroform-d) δ 7.31 – 7.19 (m, 1H), 6.26 – 6.04 (m, 2H), 5.77 (d, J = 15.4 Hz, 1H), 4.18 (q, J = 7.1 Hz, 2H), 2.27 – 2.11 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H), 1.03 (t, J = 7.4 Hz, 3H). 13C NMR (101 MHz, Chloroform-d) δ 167.19 , 145.82 , 145.01 , 127.37 , 119.20 , 60.06 , 25.96 , 14.25 , 12.83 .



3.8

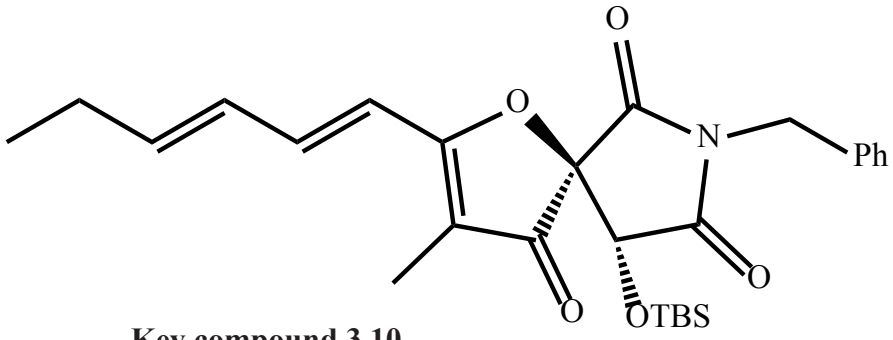
(2E,4E)-hepta-2,4-dienoic acid (3.8):[68] Ethyl (2E,4E)-hepta-2,4-dienoate (3.9 grams, 25 mmol) was dissolved in 65 mL methanol, and sodium hydroxide (2M, 65 mL, 130 mmol, 5 eq) was added. The solution was heated at 40 °C for one hour, then the methanol was removed under reduced pressure and the resulting solution was washed once with diethyl ether, which was discarded. The aqueous solution was acidified to pH 1 with concentrated HCl, then extracted three times with dichloromethane. The solution was dried over anhydrous magnesium sulfate, then filtered and the solvent was evaporated, leaving pure white solid product. The product can be further purified, if necessary, by silica column with 0-10% methanol dichloromethane. Product: 97% yield, white solid, mp 38-39 °C. 1H NMR (400 MHz, Chloroform-d) δ 11.28 (s, 1H), 7.41 – 7.30 (m, 1H), 6.36 – 6.09 (m, 2H), 5.80 (d, J = 15.3 Hz, 1H), 2.22 (qd, J = 7.4, 4.9 Hz, 2H), 1.06 (t, J = 7.4 Hz, 3H). 13C NMR (126 MHz, Chloroform-d) δ 172.72, 147.57, 147.48, 127.30, 118.28, 26.10, 12.79.



3.9

(3S,4R)-1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-2,5-dioxo-3-propionylpyrrolidin-3-yl (2E,4E)-hepta-2,4-dienoate (3.9):[70] (2E,4E)-hepta-2,4-dienoic acid (335 mg, 2.66 mmol, 2 eq) and 4-(dimethylamino)pyridine (DMAP, 740 mg, 6.11 mmol, 5 eq) were added to an oven-dry 100 mL round bottom flask with a stir bar under argon. 20 mL anhydrous dichloromethane was added and the solution was cooled to 0 °C in an ice bath. Separately, (3S,4R)-1-benzyl-4-((*tert*-butyldimethylsilyl)oxy)-3-hydroxy-3-propionylpyrrolidine-2,5-dione (450 mg, 1.15 mmol) was dissolved in 5 mL anhydrous dichloromethane, and added to the cooled solution slowly, while monitoring its temperature. The solution was stirred 10 minutes at 0 °C, then solid dicyclohexylcarbodiimide (DCC, 720 mg, 3.49 mmol, 3 eq) was added by opening the system briefly. Let the solution stir overnight to room temperature. The next morning the brown solution was passed through a 1-inch celite plug with more dichloromethane to remove precipitated dicyclohexylurea, the volatiles were removed via rotovap, and the residue was again passed through a 1-inch celite plug with dichloromethane. The brown solution was washed with 10% HCl twice, saturated bicarbonate solution twice, then saturated brine solution once. Dried over sodium sulfate. After removing volatiles again on a rotovap, the brown residue was purified on a 100 g silica column with a 0-20% ethylacetate/hexanes gradient (product Rf of about 0.5 in 10% ethyl

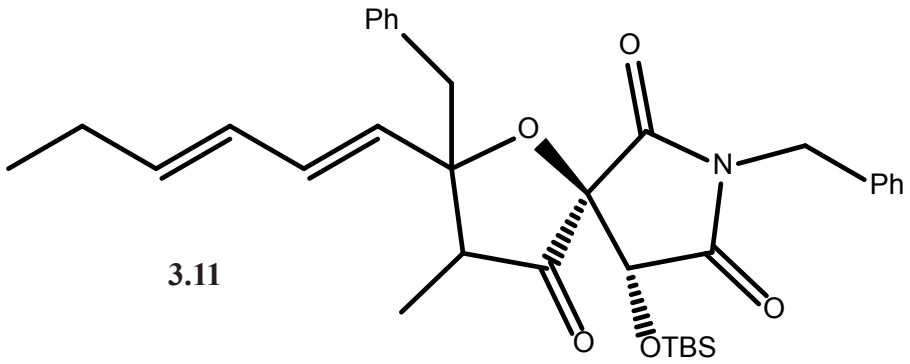
acetate/hexanes with permanganate stain). The main byproduct seems to be the substrate coupled with DCC. Product: 76% yield, white solid, mp 64-65 °C. 1H NMR (400 MHz, Chloroform-d) δ 7.47 – 7.23 (m, ArH, CH=C*H*CH=CHCH$_2$CH$_3$, 6H), 6.36 – 6.17 (m, CH=CHC*H*=C*H*CH$_2$CH$_3$, 2H), 5.92 (d, C*H*=CHCH=CHCH$_2$CH$_3$, J = 15.4 Hz, 1H), 5.12 (s, C*H*OSi, 1H), 4.77 (ABq, NC$H_A H_B$Ph, J = 32.8, 14.7 Hz, 2H), 2.70 (ddq, COCH_2CH$_3$, J = 71.9, 19.3, 7.1 Hz, 2H), 2.25 (p, CH=CHCH_2CH$_3$, J = 7.1 Hz, 2H), 1.08 (t, COCH$_2$CH_3, J = 7.1 Hz, 3H), 1.05 (t, CH=CHCH$_2$CH_3, J = 7.1 Hz, 3H), 0.86 (s, 9H), 0.14 (s, 3H), 0.07 (s, 3H). 13C NMR (125.7 MHz, Chloroform-d) δ 201.34, 171.90, 168.36, 165.72, 149.17, 148.87, 134.90, 128.75, 128.30, 127.96, 127.25, 116.60, 89.62, 74.49, 43.12, 34.05, 26.35, 25.63, 18.30, 12.85, 6.79, -4.62, -5.12. FTIR (neat, diamond ATR, cm^{-1}) 3034, 2931, 2857, 1714, 1637. HR-ESI-TOFMS: calcd for ([M+H]$^+$, $C_{27}H_{38}NO_6Si^+$) 500.2463, found 500.2467.



Key compound 3.10

(5S,9R)-7-benzyl-9-((*tert*-butyldimethylsilyl)oxy)-2-((1E,3E)-hexa-1,3-dien-1-yl)-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6,8-trione (3.10): Sodium hexamethyldisilazane (1.0M, 0.50 mL, 0.50 mmol) was added to 10 mL of anhydrous THF in a 50 mL oven-dry round bottom flask under argon, and cooled to 0 °C in an ice bath. Separately, the yellow oil substrate (250 mg, 0.50

mmol) was dissolved in 10 mL anhydrous THF, cooled to 0 °C, and the substrate solution was added dropwise to the base solution, maintaining the temperature at 0 °C. The solution was stirred for 5 minutes after addition was complete, and then quenched with 10 mL of 1.0 M HCl. About 20 mL of ethyl acetate was added to the solution, and the aqueous layer was extracted 3 times with more ethyl acetate, the combined organic layers were washed once with saturated brine, then dried over anhydrous sodium sulfate. The volatiles were removed, and the yellow oil was purified on a 50 g silica column with 0-20% ethyl acetate/hexanes. The product has an Rf of about 0.3 in 10% ethyl acetate/hexanes with permanganate stain. Product: 72% yield, yellow syrup. 1H NMR (400 MHz, Chloroform-d) δ 7.49 – 7.23 (m, Ar*H*, 5H), 7.18 (dd, CCH=C*H*CH=CHCH$_2$CH$_3$, J = 14.9, 10.0 Hz, 1H), 6.33 (d, CC*H*=CHCH=CHCH$_2$CH$_3$, J = 15.4 Hz, 1H), 6.29 – 6.14 (m, CCH=CHC*H*=C*H*CH$_2$CH$_3$, 2H), 4.84 (s, C*H*OSi, 1H), 4.74 (ABdd, NCH_AH_BPh, J = 20.9, 14.5 Hz, 2H), 2.24 (p, CCH=CHCH=CHCH_2CH$_3$, J = 7.3 Hz, 2H), 1.74 (s, CH_3C=CCH=CH, 3H), 1.07 (t, CCH=CHCH=CHCH$_2$CH_3, J = 7.4 Hz, 3H), 0.80 (s, 9H), 0.14 (s, 3H), 0.01 (s, 3H). 13C NMR (125.7 MHz, Chloroform-d) δ 193.68, 179.79, 171.41, 166.58, 146.95, 139.97, 134.78, 128.69, 128.52, 128.44, 128.01, 114.71, 110.27, 90.99, 74.08, 42.99, 29.68, 26.22, 25.26, 18.03, 12.81, 5.61, -4.83, -5.58. FTIR (neat, diamond ATR, cm^{-1}) 3034, 2929, 2857, 1728, 1620. HR-ESI-TOFMS: calcd for ([M+H]$^+$, $C_{27}H_{35}NO_5Si^+$) 482.2357, found 482.2357.

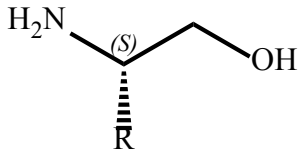


3.11

(5S,9R)-2,7-dibenzyl-9-((*tert*-butyldimethylsilyl)oxy)-2-((1E,3E)-hexa-1,3-dien-1-yl)-3-methyl-1-oxa-7-azaspiro[4.4]nonane-4,6,8-trione (3.11):[72] (5S,9R)-7-benzyl-9-((*tert*-butyldimethylsilyl)oxy)-2-((1E,3E)-hexa-1,3-dien-1-yl)-3-methyl-1-oxa-7-azaspiro[4.4]non-2-ene-4,6,8-trione (**3.1.G**, 50 mg, 0.1038 mmol) was dissolved in 5 mL anhydrous diethyl ether in an oven-dry round bottom flask. under argon. Separately, benzylmagnesium chloride (1.0M, 0.32 mL, 3 eq) was added to an oven-dry round bottom flask under argon. Both flasks were cooled to 0 °C, and the substrate solution was transferred by syringe to the Grignard solution dropwise. The mixture was stirred overnight to room temperature, then stirred for three days until the starting material spot was gone (silica gel TLC, 10% EtOAc/hexanes, UV light, R_f of starting material is about 0.3, R_f of product is about 0.5). The reaction was quenched with 10 mL saturated ammonium chloride, extract with 10 mL ethyl acetate three times. Dry over sodium sulfate. Rotovap. 5 gram silica column, 10% ethyl acetate hexanes. Product R_f at about 0.5. 16 mg yellow oil. 27% yield. Only conjugate addition product isolated, no addition to any carbonyl. 1H NMR (400 MHz, Chloroform-d) δ 7.36 – 7.21 (m, 2 x Ar*H*, 10H), 6.27 (dd, CH=C*H*CH=CHCH$_2$CH$_3$, J = 15.3, 10.4 Hz, 1H), 6.00 (dd, CH=CHC*H*=CHCH$_2$CH$_3$, J = 15.2, 10.4 Hz, 1H), 5.70 (dt, CH=CHCH=C*H*CH$_2$CH$_3$, J = 15.1, 6.4 Hz, 1H), 5.54 (d, C*H*=CHCH=CHCH$_2$CH$_3$, J = 15.4 Hz,

1H), 4.71 (ABd, NCH_AH_BPh, J = 10.5 Hz, 2H), 3.26 (ABdd, CHCCH_AH_BPh, J = 47.1, 13.4 Hz, 2H), 2.70 (q, CH_3CHCO, J = 7.5 Hz, 1H), 2.09 (p, CH=CHCH=CHCH_2CH_3, J = 6.8 Hz, 2H), 1.00 (t, CH=CHCH=CHCH$_2$CH_3, J = 7.4 Hz, 3H), 0.98 (d, CH_3CHCO, J = 7.5 Hz, 3H), 0.86 (s, 9H), 0.20 (s, 3H), 0.10 (s, 3H). 13C NMR (125.7 MHz, Chloroform-d) δ 207.06, 171.89, 169.42, 137.67, 135.76, 134.82, 131.44, 131.04, 129.55, 128.68, 128.26, 128.16, 127.96, 127.94, 126.70, 90.04, 87.17, 75.58, 49.51, 47.45, 42.72, 29.69, 25.78, 25.65, 18.25, 13.31, 11.40, -4.14, -4.48. FTIR (neat, diamond ATR, cm^{-1}) 3031, 2927, 2855, 1724. HR-ESI-TOFMS: calcd for ($[M+H]^+$, $C_{34}H_{44}NO_5Si^+$) 574.2983, found 574.2984.

Part II: Synthesis of oxazolidinones:

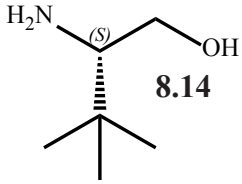


Reduction of an amino acid to an amino alcohol, general procedure. Method A,[98] $NaBH_4/I_2$ reduction: Amino acid (30 mmol) was added to a 500 mL 3-neck round bottom flask under argon with a stir bar; a thermometer equipped on one neck, a 200 mL addition funnel with a septum on the center neck, and a glass stopper on the third neck. Around 100 mL of anhydrous THF was added, and the solution was cooled to between 0 and 4 °C (internal temperature). Sodium borohydride (2.84 grams, 75 mmol, 2.5 eq) was added in one portion by removing the glass stopper briefly. Separately, 50 mL of anhydrous THF was added to a 100 mL oven-dry round bottom flask with a

stir bar under argon, and iodine (8.38 grams, 33 mmol, 1.1 eq) was added by removing the septum briefly. The solution was stirred for a few minutes to dissolve the iodine. The iodine solution was then transferred to the addition funnel via cannula, and the iodine solution was added to the amino acid solution at a slow drip, slowing the addition to keep the internal temperature below 10 °C (the addition takes about 40 min). The brown heterogeneous solution turned white as the iodine reacted, with significant hydrogen gas emission. Once the iodine addition was complete, the solution was stirred for 20 minutes more before removing the cooling bath, thermometer and addition funnel (replacing those with septa or glass stoppers, keeping the system under argon). The solution was then heated in an oil bath to 85 °C (oil bath temperature) for 18 hours. After 18 hours, the reaction was quenched by the slow addition of methanol, and the solution turns from heterogeneous white to homogenous tan. The solution was transferred to a single-neck round bottom flask with more methanol, and stirred for 30 min to ensure a full quench. The volatiles were removed on a rotovap, leaving a white slurry. The slurry was dissolved in 200 mL 20% aqueous KOH, and the solution was stirred 5 hours at room temperature. After 5 hours, the solution was transferred to a separatory funnel, and the aqueous layer was extracted 6 times with dichloromethane. The combined organics were dried over anhydrous sodium sulfate, and rotovapped to leave a white solid. The solid was further purified by vacuum distillation. Product is a white solid. 70-90% yield.

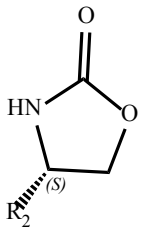
Method B,[99] LAH reduction: About 350 mL of anhydrous THF was added to a 1-liter 3-neck flask with a stir bar under argon (one neck covered with septum, one with a glass stopper, and one with a thermometer), and grey lithium aluminum hydride powder (4.5 grams, 118 mmol, ca 4 eq) was added carefully (if the LAH is white, it's gone bad). The septum was removed and the

flask was equipped with a condenser with an argon inflow at the top. The solution was cooled to 0 to 4 °C internal temperature in an ice bath, and 30 mmol of amino acid was carefully added in *small* portions by removing the glass stopper, keeping the additions small enough to prevent the internal temperature from exceeding 10 °C. Once the addition was complete, the solution was allowed to slowly increase to room temperature before the thermometer was removed and replaced with another glass stopper (let it stir for at least one hour). It was checked that the stoppers and condenser were greased to form a tight seal, then the solution was heated to reflux for 16 hours. After 16 hours the solution was cooled to 0 °C, and the reaction was carefully quenched by the *slow* addition of 20 mL water, then 20 mL of 15% NaOH, then 60 mL of water. There will be much gas emitted! Go slow. The reaction was stirred to room temperature (at least one hour), and turned from grey to white. Then the solution was filtered through celite, and the cake washed with 400 mL of ethyl acetate. The combined organics were washed with brine, then dried over sodium sulfate. Removal of the solvent by rotovap left a tan solid, which may be purified by vacuum distillation. Product is a white solid. 70-90% yield.

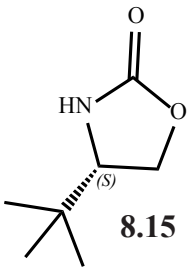


8.14

(L)-*tert*-Leucinol. Product: white solid, 86 % yield. 1H NMR (500 MHz, DMSO-d6) δ 3.04 (ABXdd, CH_XCH_AH$_B$OH, J = 10.2, 9.3 Hz, 1H), 2.95 (ABXddd, CH$_X$C$H_A$$H_B$OH J = 583.1, 9.7, 3.2 Hz, 2H), 0.83 (s, 9H).

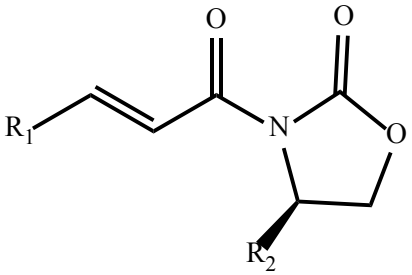


Synthesis of an oxozolidinone from an amino alcohol, general procedure:[100] The purified amino alcohol (30 mmol) was added to a 25 mL oven-dry round bottom flask with a stir bar and an oven-dry short-path distillation apparatus under argon. 0.83 grams (6 mmol, 0.2 eq) anhydrous potassium carbonate was added and 11 mL (90 mmol, 3 eq) of diethyl carbonate. The heterogeneous solution was heated in an oil bath at 100 °C for 20 minutes then 120 °C for 5 hours. The amino alcohol melted and the potassium carbonate dispersed, making a homogenous cloudy white solution. Additional insulation on the short-path distillation apparatus is advised to remove most of the ethanol byproduct. After 5 hours, the solution was cooled briefly (to at least 80 °C), and placed under vacuum to remove more ethanol, then heated again at 100 °C for one hour. Cooled to room temperature, transferred the pot solution to a separatory funnel with dichloromethane. Washed the organic layer with brine, then dried over anhydrous sodium sulfate. Rotovapped. White fluffy solid was contaminated with diethyl carbonate. Stirred the crystals in diethyl ether for 30 min, then collected them by filtration. Saved the ether washes. Rotovapped again. Continued the process to collect more product. 80-95% yield. White solid. Note that most oxazolidinones can be purchased relatively cheaply from Combi-Blocks.



8.15

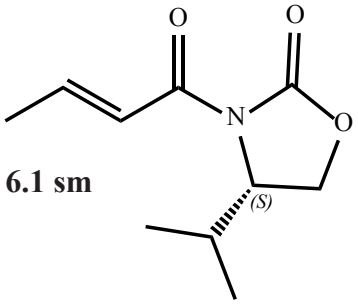
(S)-4-(*tert*-butyl)oxazolidin-2-one. Obtained following the general procedure using L-*tert*-leucinol. Product: white solid. 85% yield. 1H NMR (400 MHz, Chloroform-d) δ 5.99 (s, N*H*, 1H), 4.37 (ABXtd, CH_XCH$_A$H$_B$O, J = 9.0, 0.4 Hz, 1H), 4.20 (ABXdd, CH$_X$CH_AH$_B$O, J = 9.0, 5.8 Hz, 1H), 3.59 (ABXddd, CH$_X$CH$_A$$H_B$O, J = 9.0, 5.8, 1.1 Hz, 1H), 0.91 (s, 9H).



General Procedure for coupling α,β-unsaturated carbonyl compounds and oxazolidinones:[101]

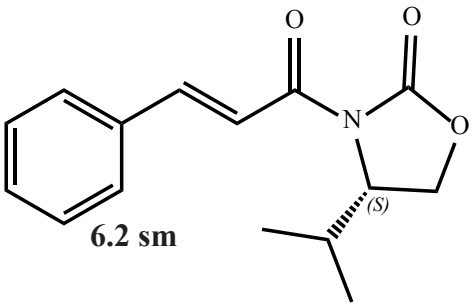
30 mmol of very pure oxazolidinone was thoroughly dried by adding toluene three times and rotovapping it off, then setup under argon in an oven-dry 100 mL round bottom flask. The oxazolidinone was dissolved in ca 50 mL of anhydrous THF, and cooled to -78 °C in a dry ice-IPA bath. 15.6 mL (35 mmol, 1.3 eq) of n-butyllithium was added dropwise, let stir for 30 min at -78 °C, then warmed to 0 °C. 39 mmol (1.3 eq) of very pure (often recently distilled) acid chloride was added in three portions by removing the septum briefly. Let stir to room temperature overnight. The next morning carefully poured the reaction into 50 mL of saturated sodium bicarbonate carefully to

quench, and rotovap off the THF. Transferred the heterogeneous solution to a separatory funnel with ca 100 mL of diethyl ether, then washed the aqueous layer three times with more ether. The combined organic layers were washed with saturated sodium bicarbonate three times, then dried over anhydrous sodium sulfate. Dissolved the crude crystals in dichloromethane, and precipitated pure crystals by adding hexanes. The final crop can be purified on a silica column. White solid. 60-95% yield.



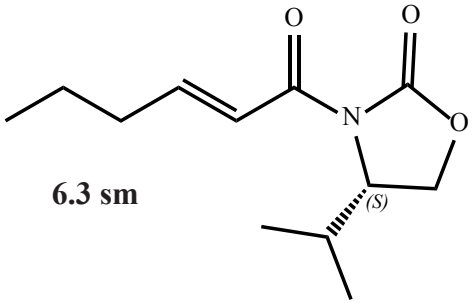
6.1 sm

(S)-3-(crotonoyl)-4-isopropyloxazolidin-2-one (6.1 sm). Used 4S-isopropyl-oxazolidin-2-one (0.30 g, 2.32 mmol) with (E)-crotonyl chloride in the general protocol. The crude product was purified using flash chromatography (30% ether in pentane, R*f* 0.14). Product: 93%; 1H NMR (500 MHz, CDCl3) δ 7.28 (dq, CH_3CH=CH, J = 15.5, 1.5 Hz, 1H), 7.15 (dq, CH_3CH=CH, J = 15.5, 7.0 Hz, 1H), 4.49 (m, OCH_2CHN, 1H), 4.28 (dd, OCH_2CHN, J = 9.0, 8.0 Hz, 1H), 4.22 (dd, OCH_2CHN, J = 9.0, 3.5 Hz, 1H), 2.41 (m, $CH(CH_3)_2$, 1H), 1.96 (d, CH_3CH=CH, J = 7.0 Hz, 3H), 0.93, 0.88 (2d, $CH(CH_3)_2$, J = 7 Hz, 3H each); 13C NMR (125.7 MHz, $CDCl_3$) δ 165.0, 154.0, 146.6, 121.9, 63.3, 58.5, 28.5, 18.4, 18.0, 14.7.



6.2 sm

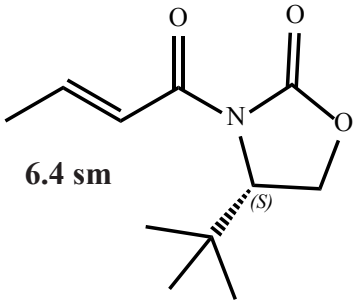
(S)-3-cinnamoyl-4-isopropyloxazolidin-2-one (6.2 sm): Obtained from the acylation of S-4-isopropyl-oxazolidin-2-one (0.30 g, 2.32 mmol) with (E)-cinnamoyl chloride according to the general protocol detailed above. The crude product was purified using flash chromatography (50% Et2O in pentane, R*f* 0.25) to give 85% (510 mg) of product; 1H NMR (500 MHz, CDCl3) δ 7.95 (d, PhCH=CH, J = 15.6 Hz, 1H), 7.84 (d, PhCH=CH, J = 15.6 Hz, 1H), 7.63–7.60 (m, 2 H), 7.40–7.37 (m, 3H), 4.55 (m, OCH2CHN, 1H), 4.30 (dd, OCH2CHN, J = 9.0, 8.0 Hz, 1H), 4.24 (dd, OCH2CHN, J = 8.0, 3.0 Hz, 1H), 2.46 (m, CH(CH3)2, 1H), 0.94, 0.91 (2d, J = 7.0 Hz, CH(CH3)2, 3H each); 13C (125.7 MHz, CDCl3) δ 165.1, 154.1, 146.1, 134.6, 130.5, 128.8, 128.5, 117.1, 63.4, 58.6, 28.5, 18.0, 14.7.



6.3 sm

(S,E)-3-(hex-2-enoyl)-4-isopropyloxazolidin-2-one (6.3 sm): Obtained from the acylation of S-4-isopropyl-oxazolidin-2-one (1.29 g, 10.02 mmol) with 2(E)-hexenoyl chloride according to

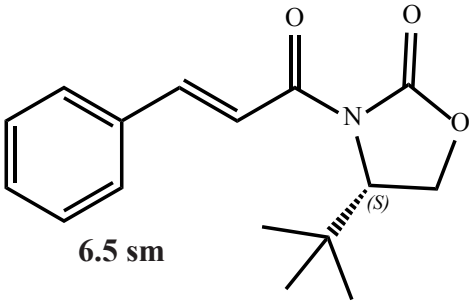
the general protocol detailed above. The crude product was purified using flash chromatography (0–30% EtOAc in hexanes) to give 27% (602 mg) of product as a clear gel, [α]D^{20} +82.0º (c=1.0, CHCl3). {Lit.[105] [α]D^{25} +89.7º (c=1.0, CHCl3}. 1H NMR (400 MHz, CDCl3) δ 7.27 (dt, CH2CH=CH, J = 15.3, 1.4 Hz, 1H), 7.14 (dt, CH2CH=CH, J = 15.3, 6.9 Hz, 1H), 4.49 (m, OCH2CHN, 1H), 4.27 (dd, OCH2CHN, J = 9.1, 9.1 Hz, 1H), 4.21 (dd, OCH2CHN, J = 9.1, 3.1 Hz, 1H), 2.41 (m, CH(CH3)2, 1H), 2.26 (ddd, CH2CH2CH=CH, J = 7.4, 6.9, 1.4 Hz, 2H), 1.53 (sext, CH3CH2CH2, J = 7.4 Hz, 2H), 0.95 (t, CH3CH2, J = 7.3 Hz, 3H), 0.96–0.88 (2d, CHCH3, J = 7.0 Hz, 3H each); 13C NMR (125.7 MHz, DMSO-d6) δ 164.6, 154.4, 150.2, 121.1, 63.9, 58.5, 34.4, 28.7, 21.3, 18.0, 15.0, 13.9; FTIR (cm-1) 1776, 1685, 1636, 1367, 1203, 712. LCMS [C12H20NO3]+ (MH+) 226.1, found 226.0.



6.4 sm

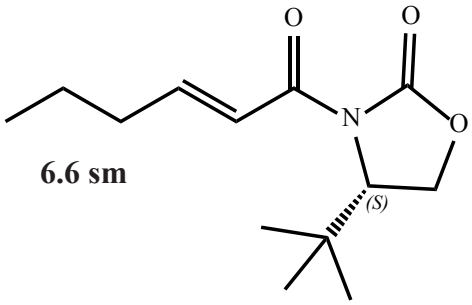
(S)-3-(crotonoyl)-4-(*tert*-butyl)oxazolidin-2-one (6.4 sm): Obtained from the acylation of 4S-*tert*-butyl-oxazolidin-2-one (0.30 g, 2.10 mmol) with (E)-crotonyl chloride according to the general protocol detailed above. The crude product was purified using flash chromatography (30% Et2O in pentane, R*f* 0.50) to give 70% (310 mg) of product as a clear oil; 1H NMR (500 MHz, CDCl3) δ 7.28 (dq, COCH=CH, J = 15.5, 1.5 Hz, 1H), 7.15 (dq, COCH=CH, J = 15.5, 7.0 Hz, 1H), 4.53 (dd, NCHCH2O, J = 7.4, 1.5 Hz, 1H), 4.28 (dd, NCHCH2O, J = 9.2, 1.5 Hz, 1H), 4.24

(dd, NCHCH2O, J = 9.2, 7.4 Hz, 1H), 1.96 (dd, CH3CH, J = 7.0, 1.5 Hz, 3H), 0.94 (s, t-Bu, 9H); 13C NMR (125.7 MHz, CDCl3) δ 165.0, 154.5, 146.4, 121.8, 65.0, 60.6, 35.7, 25.4, 18.2.



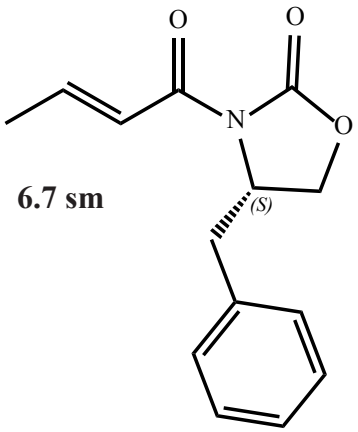
6.5 sm

(S)-4-(*tert*-butyl)-3-cinnamoyloxazolidin-2-one (6.5 sm): Obtained from the acylation of S-4-*tert*-butyl-oxazolidin-2-one (0.30 g, 2.10 mmol) with (E)-cinnamoyl chloride according to the general protocol detailed above. The crude product was purified using flash chromatography (50% Et2O in pentane, R*f* 0.50) to give 85% (480 mg) of product as a clear syrup; 1H NMR (500 MHz, CDCl3) δ 7.95 (d, J = 15.6 Hz, 1H), 7.85 (d, J = 15.6 Hz, 1H), 7.62 (m, 2H), 7.39 (m, 3H), 4.59 (dd, NCHOCH2, J = 7.4, 1.8 Hz, 1H), 4.33 (dd, NCHCH2O, J = 9.2, 1.8 Hz, 1H), 4.28 (dd, NCHCH2O, J = 9.2, 7.4 Hz, 1H), 0.98 (s, t-Bu, 9H); 13C NMR (125.7 MHz, CDCl3) δ 165.5, 154.7, 146.4, 134.6, 130.6, 128.9, 128.6, 117.2, 65.3, 61.0, 36.0, 25.7.



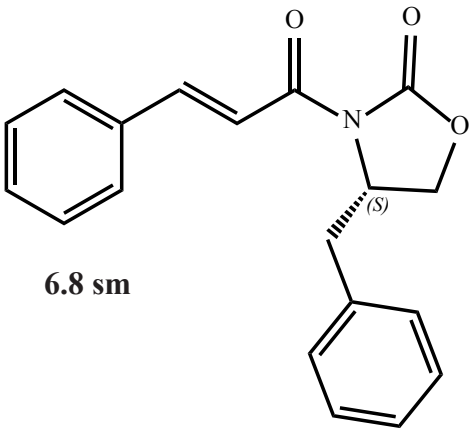
6.6 sm

(S,E)-4-(tert-butyl)-3-(hex-2-enoyl)oxazolidin-2-one (6.6 sm): Obtained from the acylation of S-4-*tert*-butyl-oxazolidin-2-one (1.254 g, 8.76 mmol) with 2(E)-hexenoyl chloride according to the general protocol detailed above. The crude product was purified using flash chromatography (0–30% EtOAc in hexanes) to give 17% (359 mg) of product as a clear syrup, $[\alpha]D^{20}$ +88.0º (c=1.0, CHCl3). 1H NMR (400 MHz, DMSO-d6) δ 7.17 (dt, CH2CH=CH, J = 15.2, 1.3 Hz, 1H), 6.98 (dt, CH2CH=CH, J = 15.2, 6.6 Hz, 1H), 4.41–4.37 (m, OCH2CHN and ½OCH2CHN, 2H), 4.33 (dd, ½OCH2CHN, J = 9.1, 8.8 Hz, 1H), 2.22 (ddd, CH2CH2CH=CH, J = 7.1, 6.6, 1.3 Hz, 2H), 1.46 (sext, CH3CH2CH2, J = 7.1 Hz, 2H), 0.91 (t, CH3CH2, J = 7.1 Hz, 3H), 0.85 (s, *tert*-Bu, 9H); 13C NMR (125.7 MHz, DMSO-d6) δ 164.9, 155.1, 150.1, 121.2, 65.6, 60.9, 35.9, 34.4, 25.8, 21.3, 14.0; FTIR (cm-1) 1777, 1689, 1657, 1340, 1186, 715. LCMS [C13H22NO3]+ (MH+) 240.2, found 240.0.



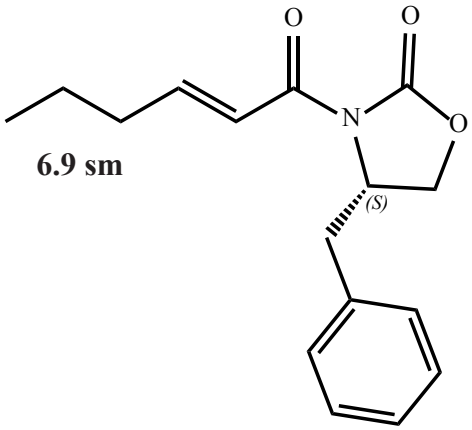
6.7 sm

(S)-4-benzyl-3-(crotonoyl)oxazolidin-2-one (6.7 sm): Obtained from the acylation of S-4-benzyl-oxazolidin-2-one with (E)-crotonyl chloride according to the general protocol detailed above. The crude product was purified using flash chromatography (50% Et2O in pentane, R*f* 0.50) to give 91% of 3 as a white solid; 1H NMR (500 MHz, CDCl3) δ 7.35–7.31 (m, aromatic, 2H), 7.30–7.18 (m, aromatic and olefinic, 5H), 4.73 (m, NCHCH2O, 1H), 4.21–4.17 (m, NCHCH2O, 2H), 3.33 (dd, CH2Ph, J = 13.4, 3.2 Hz, 1H), 2.80 (dd, CH2Ph, J = 13.4, 9.5 Hz, 1H), 1.98 (d, CH3CH, J = 6.0 Hz, 3H); 13C NMR (125.7 MHz, CDCl3) δ 165.0, 153.4, 146.9, 135.4, 129.5, 129.90, 127.3, 122.0, 66.1, 55.3, 37.9, 18.5.



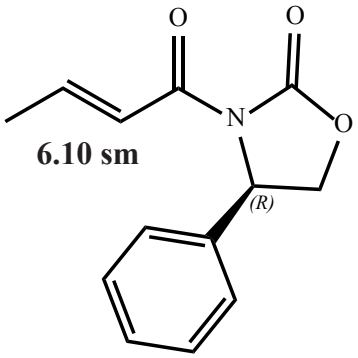
6.8 sm

(S)-4-benzyl-3-cinnamoyloxazolidin-2-one (6.8 sm): Obtained from the acylation of S-4-benzyl-oxazolidin-2-one (0.40 g, 2.16 mmol) with (E)-cinnamoyl chloride according to the general protocol detailed above. The crude product was purified using flash chromatography (40% Et2O in pentane, R*f* 0.30) to give 88% (580 mg) of product as a white solid; 1H NMR (500 MHz, CDCl3) δ 7.92 (2d, J = 15.0 Hz, 2H), 7.64 (4m, 2H), 7.42-7.23 (4m, 8H), 4.81 (m, NCHCH2O, 1H), 4.26–4.21 (m, NCHCH2O, 2H), 3.38 (dd, CH2Ph, J = 12.4, 2.9 Hz, 1H), 2.86 (dd, CH2Ph, J = 12.4, 8.3 Hz, 1H); 13C NMR (125.7 MHz, CDCl3) δ 165.2, 153.6, 146.5, 135.4, 134.6, 130.7, 129.5, 129.0, 128.9, 128.7, 127.4, 117.1, 66.2, 55.5, 38.0.



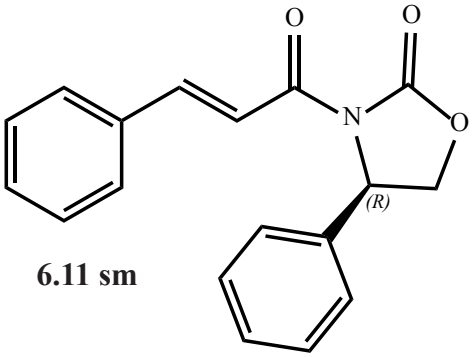
6.9 sm

(S,E)-4-benzyl-3-(hex-2-enoyl)oxazolidin-2-one (6.9 sm): Obtained from the acylation of S-4-benzyl-oxazolidin-2-one (1.77 g, 10.01 mmol) with 2(E)-hexenoyl chloride according to the general protocol detailed above. The crude product was purified using flash chromatography (0–30% EtOAc in hexanes) to give 47% (1.294 mg) of product as a white solid, mp 52.0–53.1 ºC, [α]D20 +64.6º (c=1.1, CHCl3). {Lit.[106] [α]D25 +65.5º (c=1.1, CHCl3)}. 1H NMR (400 MHz, DMSO-d6) δ 7.34–7.29 (m, PhH, 2H), 7.28–7.23 (m, PhH, 1H), 7.21–7.18 (m, PhH, 2H), 7.14 (d, olefinic, CH2CH=CH, J = 15.2 Hz, 1H), 7.06 (dt, CH2CH=CH, J = 15.2, 6.6 Hz, 1H), 4.74–4.68 (m, NCH, 1H), 4.35 (dd, OCH2CHN, J = 8.6, 8.6 Hz, 1H), 4.19 (dd, OCH2CHN, J = 8.6, 3.0 Hz, 1H), 3.05 (dd, PhCH2CH, J = 13.3, 3.2 Hz, 1H), 2.96 (dd, PhCH2CH, J = 13.3, 7.8 Hz, 1H), 2.25 (bq, CH2CH2CH=CH, J = 6.9 Hz, 2H), 1.46 (sext, CH3CH2CH2, J = 7.0 Hz, 2H), 0.92 (t, CH3CH2, J = 7.0 Hz, 3H); 13C NMR (125.7 MHz, CDCl3) δ 165.1, 153.4, 151.7, 135.4, 129.4, 128.9, 127.3, 120.5, 66.1, 55.3, 37.9, 34.7, 21.4, 13.7; FTIR (cm-1) 1781, 1678, 1635, 1352, 1200, 705. LCMS [C16H20NO3]+ (MH+) 274.1, found 273.9.



6.10 sm

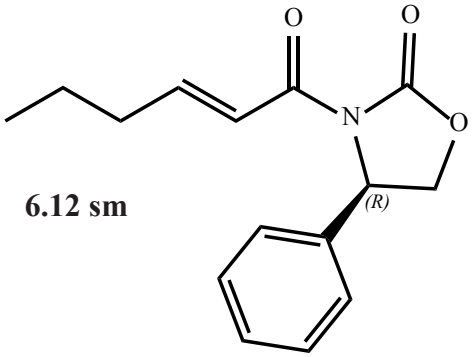
(R)-3-(crotonoyl)-4-phenyloxazolidin-2-one (6.10 sm): Obtained from the acylation of R-4-phenyl-oxazolidin-2-one with (E)-crotonyl chloride according to the general protocol detailed above. The crude product was purified using flash chromatography (30% Et2O in pentane, R*f* 0.40) to give 76% of 4 as a white solid; 1H NMR (500 MHz, CDCl3) δ 7.40–7.29 (m, aromatic, 5H), 7.28 (dq, COCH=CH, J = 15.3, 1.6 Hz, 1H), 7.09 (dq, COCH=CH, J = 15.3, 7.0 Hz, 1 H), 5.48 (dd, NCHCH2O, J = 8.8, 3.9 Hz, 1H), 4.69 (dd, NCHOCH2, J = 8.8, 8.8 Hz, 1H), 4.27 (dd, NCHOCH2, J = 8.8, 3.9 Hz, 1H), 1.93 (dd, CH3CH=CH, J = 7.0, 1.7 Hz, 3H); 13C NMR (125.7 MHz, CDCl3) δ 164.5, 153.7, 147.3, 139.1, 129.2, 128.6, 125.9, 121.7, 69.9, 57.7, 18.5.



6.11 sm

(R)-3-cinnamoyl-4-phenyloxazolidin-2-one (6.11 sm): Obtained from the acylation of R-4-phenyl-oxazolidin-2-one (0.30 g, 1.84 mmol) with (E)-cinnamoyl chloride according to the general

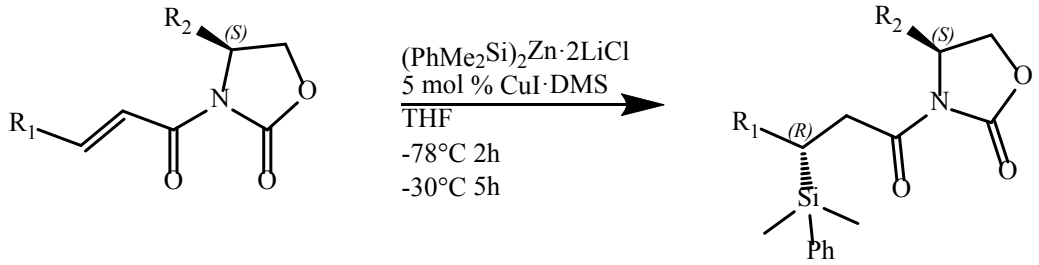
protocol detailed above. The crude product was purified using flash chromatography (15% EtOAc in petroleum ether, R*f* 0.40) to give 88% (470 mg) of product as a white solid; 1H NMR (500 MHz, CDCl3) δ 7.96 (d, PhCH=CH, J = 15.5 Hz, 1 H), 7.80 (d, PhCH=CH, J = 15.5 Hz, 1H), 7.60 (m, 2H), 7.42–7.32 (2m, 8H), 5.56 (dd, NCHOCH2, J = 8.7, 3.8 Hz, 1H), 4.71 (dd, NCHOCH2, J = 8.7, 8.7 Hz, 1H), 4.29 (dd, NCHOCH2, J = 8.7, 3.8 Hz, 1H); 13C NMR (125.7 MHz, CDCl3) δ 164.6, 153.7, 146.5, 139.0, 134.4, 130.6, 129.0, 128.8, 128.5, 128.5, 125.9, 116.8, 69.9, 57.7.



6.12 sm

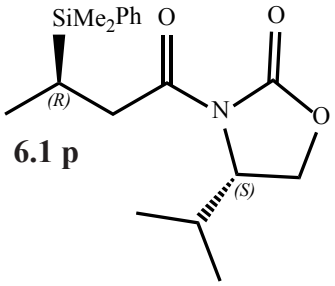
(R,E)-3-(hex-2-enoyl)-4-phenyloxazolidin-2-one (6.12 sm): Obtained from the acylation of R-4-phenyl-oxazolidin-2-one (1.63 g, 10.00 mmol) with 2(E)-hexenoyl chloride according to the general protocol detailed above. The crude product was purified using flash chromatography (0–30% EtOAc in hexanes) to give 28% (721 mg) of product as a white solid, mp 76.0–77.2 ºC, [α]D20 –101.1º (c=1.5, CHCl3). {Lit.[107] [α]D25 –95.0º (c=1.5, CHCl3)}. 1H NMR (400 MHz, DMSO-d6) δ 7.41–7.36 (m, PhH, 2H), 7.34–7.27 (m, PhH, 3H), 7.17 (d, CH2CH=CH, J = 15.0 Hz, 1H), 6.92 (dt, CH2CH=CH, J = 15.0, 7.0 Hz, 1H), 5.50 (dd, NCH, J = 8.6, 3.3 Hz, 1H), 4.76 (dd, OCH2CHN, J = 8.6, 8.6 Hz, 1H), 4.17 (dd, OCH2CHN, J = 8.6, 3.3 Hz, 1H), 2.21 (dq, CH2CH2CH=CH, J = 6.9 Hz, 2H), 1.44 (sext, CH3CH2CH2, J = 7.5 Hz, 2H), 0.92 (t, CH3CH2, J

= 7.5 Hz, 3H); 13C NMR (125.7 MHz, CDCl3) δ 164.7, 153.7, 152.0, 139.2, 129.2, 128.6, 126.0, 120.4, 69.9, 57.8, 34.7, 21.3, 13.7; FTIR (cm-1) 1775, 1683, 1635, 1327, 1205, 707. LCMS [C15H18NO3]+ (MH+) 260.1, found 259.9.



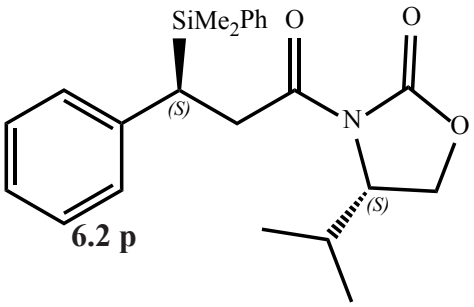
General procedure for adding phenyldimethylsilyl zinc reagents in conjugate addition reactions to enones. $PhMe_2SiLi$ was first prepared by adding $PhMe_2SiCl$ (0.420 mL, 2.5 mmol, 2.5 eq) to lithium metal (70 mg, 10 mmol, 10 eq) in 5 mL of anhydrous THF in a 10 mL oven-dry strawberry-shaped flask, under argon. The solution was stirred at 0 °C for 5 hours, then a new, unpierced septum was switched in, and the solution was stored in the freezer at least overnight. The opaque red solution must be prepared fresh (within a few days of the main reaction) for consistent results. $(PhMe2Si)_2Zn/LiCl$ was prepared by adding the entire red silyl anion solution, $PhMe_2SiLi/LiCl$ (2.50 mmol, 2.50 eq) to $ZnCl_2$ (0.5 M in THF, 2.5 mL, 1.25 mmol, 1.25 eq) via syringe under argon to at -78 °C. The resulting grey to yellow slurry was stirred for 10 min at -78 °C and then stirred for exactly 10 min at 0 °C. It is often easier to leave the silyl anion syringe hanging in the zinc solution round bottom septum to reuse to withdraw the silyl zinc solution once it is done. In a separate 25 mL oven-dry round bottom flask containing a stir-bar, the appropriate dry enone substrate (1.0 mmol, 1.0 eq) was added along with recently prepared and dry

CuI•0.75DMS (47 mg, 0.05 mmol, 0.05 eq, 5 mol%), under argon, and the substrate was dissolved in 5 mL anhydrous THF (the copper does not dissolve). The temperature of the flask was then lowered to -78 °C and the silylzinc reagent was added slowly using a syringe while maintaining the temperature at -78 °C. The reaction mixture should turn opaque black after a few minutes. The reaction mixture was stirred for 2h at -78 °C. After increasing the reaction temperature to -30 °C by switching the cooling bath, the reaction was stirred over the next 5h, maintaining the temperature at -30 °C by adding dry ice to the bath every once in awhile. After 5h, the reaction was quenched by removing the argon and septum and adding a saturated solution of NH_4Cl/NH_3 (10 mL, pH = 10). The resulting mixture was stirred until a homogeneous deep blue solution was obtained. The solution was then poured out into a mixture of Et_2O (25 mL) and water (25 mL) and transferred to a separatory funnel. After the aqueous phase was extracted with Et_2O (3 x 25 mL), the combined organic layers were dried over anhydrous Na_2SO_4. The organic solvent was then removed under reduced pressure and the diasteromeric ratio of the crude product was analyzed using 1H NMR spectroscopy. The crude product was then purified using flash chromatography on silica gel twice: once with a gradient of ethyl acetate/hexanes, then again with dichloromethane. The first column purification removed all of the impurities except for extra silyl byproduct. The dichloromethane column separated the silyl byproduct from the product. Note that the temperature required for selective addition is dependent on the reactivity of the enone substrate: reactive enones can be run at -78 °C the whole time, while very unreactive enones may need to be warmed further. For oxazolidinone substrates, the procedure as listed is optimum.



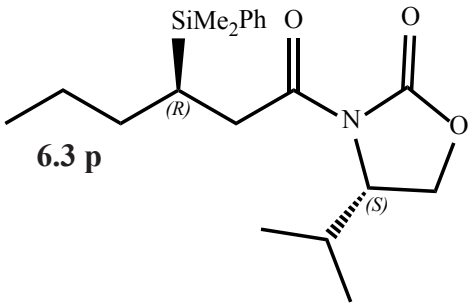
6.1 p

(S)-3-((R)-3-(dimethyl(phenyl)silyl)butanoyl)-4-isopropyloxazolidin-2-one (6.1 p): Created following the general procedure with (S)-3-(crotonoyl)-4-isopropyloxazolidin-2-one. The crude product was purified using flash chromatography (0-20% EtOAc in hexane, R_f 0.4 in 10% EtOAc/ hexanes) and (100% DCM, R_f 0.9) to give 91% (91 mg, 87:13 d.r.) of product as a white solid. 1H NMR (500 MHz, CDCl3) δ 7.53-7.50 (m, Ar-H, 2H), 7.38-7.33 (m, Ar-H, 3H), 4.39 (m, NCHCH2O 1H), 4.26 (dd, NCHCH2O, J = 9.2, 1.6 Hz, 1H), 4.20 (dd, NCHCH2O, J = 9.2, 7.6 Hz, 1H), 3.10 (dd, COCH2, J = 15.5, 3.5 Hz, 1H), 2.63 (dd, COCH2, J = 15.5, 11.0 Hz, 1H), 2.33 (m, (CH3)2CH, 1H), 1.56 (m, SiCH, 1H), 0.97 (d, CH3CH, J = 7.5, 3H), 0.90 (d, CH3CH, J = 7.5, 3H), 0.85 (d, CH3CH, J = 7.0, 3H), 0.34, 0.33 (2s, Si(CH3)2, 3H each); 13C NMR (125.7 MHz, CDCl3) δ 173.33, 153.94, 137.42, 134.02, 129.00, 127.73, 63.16, 58.30, 37.87, 28.31, 17.96, 15.78, 14.52, 14.28, −5.01, −5.09; FTIR (cm-1) 1782, 1698; HRMS (ESI) calcd for [C18H27NO3SiNa]+ (MNa+) 356.1657, found 356.1654.



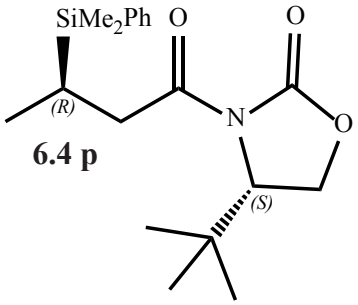
6.2 p

(S)-3-(dimethylphenyl)silyl-(S)-3-phenylpropanoyl-4-isopropyloxazolidin-2-one (6.2 p): Obtained following the general procedure for the disilylzinc reaction, using (S)-3-cinnamoyl-4-isopropyloxazolidin-2-one. The product was purified using flash chromatography (0-20% EtOAc in hexanes, R_f 0.4 in 10% EtOAc/hexanes) and 100% DCM (R_f 0.9) to give 90% product as a clear oil. 1H NMR (500 MHz, CDCl3) δ 7.31-7.45 (2m, 5H), 7.19 (dd, J = 7.5 Hz, 2H), 7.08 (dd, J = 7.5 Hz, 1H), 6.97 (d, J = 7.5 Hz, 2H), 4.18 (m, NCHOCH2, 1H), 4.12-4.05 (dd, NCHOCH2, 2H), 3.58 (dd, SiCH, J = 17.0, 12.0 Hz, 1H), 3.16 (dd, COCH2, J = 17.0, 4.0 Hz, 1H), 3.01 (dd, COCH2, J = 12.0, 4.0 Hz, 1H), 2.09 (m, (CH3)2CH, 1H), 0.79, 0.73 (2d, (CH3)2CH, J = 7.5, 3H each), 0.31, 0.26 (2s, Si(CH3)2, 3H each); 13C NMR (125.7 MHz, CDCl3) δ 172.49, 154.10, 141.59, 136.5, 134.18, 129.24, 128.01, 127.78, 127.68, 124.90, 63.31, 58.31, 35.67, 31.87, 28.26, 17.84, 14.58, -4.15, -5.27; FTIR (cm-1) 1780, 1701; MS m/z 319 (M-C6H5, 23%), 135 (C8H10Si, 100%). HRMS (ESI) calcd for [C23H29NO3SiNa]+ (MNa+) 418.1814, found 418.1811.



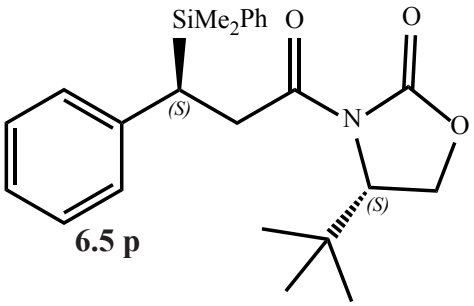
6.3 p

(S)-3-((R)-3-(dimethyl(phenyl)silyl)hexanoyl)-4-isopropyloxazolidin-2-one (6.3 p): Created using the general procedure and (S,E)-3-(hex-2-enoyl)-4-isopropyloxazolidin-2-one. The product was purified using flash chromatography (0-20% EtOAc in hexane, R_f 0.4 in 10% EtOAc/Hex) and (100% DCM, R_f 0.9) to give 80% (80 mg, 87:13 d.r.) of product as a clear oil. 1H NMR (500 MHz, CDCl3) δ 7.55-7.49 (m, 2H), 7.36-7.31 (m, 3H), 4.30 (ddd, NCH, J = 7.9, 3.5, 3.4 Hz, 1H), 4.17 (dd, NCHCH2O, J = 9.1, 7.9 Hz, 1H), 4.14 (dd, NHCH2O, J = 9.1, 3.4 Hz 1H), 3.00 (dd, COCH2, J = 17.2, 5.9 Hz, 1H), 2.86 (dd, COCH2, J = 17.2, 7.9 Hz, 1H), 2.33-2.20 (m, (CH3)2CH, 1H), 1.64-1.56 (m, SiCH, 1H), 1.49-1.39 (m, CH2, 1H), 1.34-1.16 (m, CH2, 3H), 0.87 (d, CH3CH, J = 7.1 Hz, 3H), 0.81 (t, CH3CH2, J = 7.0 Hz, 3H), 0.80 (d, CH3CH, J = 7.1 Hz, 3H), 0.31 (s, Si(CH3)2, 6H); 13C NMR (125.7 MHz, CDCl3) δ 173.68, 154.11, 138.42, 134.10, 128.99, 127.79, 63.23, 58.55, 36.40, 32.78, 28.33, 22.29, 20.52, 18.12, 14.63, 14.39, -3.80, -4.00; FTIR 1778, 1700 (cm-1)



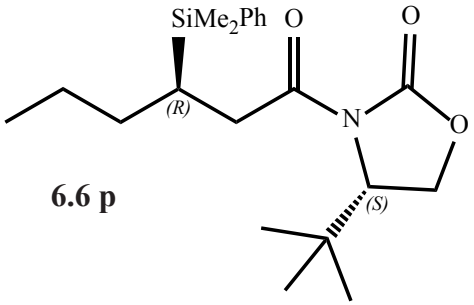
6.4 p

(S)-4-(tert-butyl)-3-((R)-3-(dimethyl(phenyl)silyl)butanoyl)oxazolidin-2-one (6.4 p): Obtained from the general procedure using (S)-3-(crotonoyl)-4-(tert-butyl)oxazolidin-2-one. The product was purified using flash chromatography (0-20% EtOAc in hexane, R_f 0.4 in 10% EtOAc/ Hex) and (100% DCM, R_f 0.9) to give 95% (95 mg, 95:5 d.r.) of product as a white solid. 1H NMR (500 MHz, CDCl3) δ 7.52 (m, Ar-H, 2H), 7.35 (m, Ar-H, 3H), 4.39 (dd, NCH, J = 7.6, 1.6 Hz, 1H), 4.24 (dd, OCH2, J = 9.2, 1.6 Hz, 1H), 4.16 (dd, OCH2, J = 9.2, 7.6 Hz, 1H), 3.02 (dd, COCH2, J = 15.8, 3.2 Hz, 1H), 2.69 (dd, COCH2, J = 15.8, 11.3 Hz, 1H), 1.57 (m, SiCH, 1H), 0.97 (d, CH3CH, J = 7.5 Hz, 3H), 0.90 (s, t-Bu, 9H), 0.33, 0.32 (2s, Si(CH3)2, 3H each); 13C NMR (125 MHz, CDCl3) δ 173.47, 154.70, 137.49, 134.04, 129.05, 127.76, 65.33, 61.01, 37.60, 35.68, 25.71, 16.09, 14.41, −4.90, −5.08; FTIR (cm-1) 1782, 1703; HRMS (EI, DCI/NH3) calcd for [C19H30NO3Si]+ (MH+) 348.1995, found 348.1985.



6.5 p

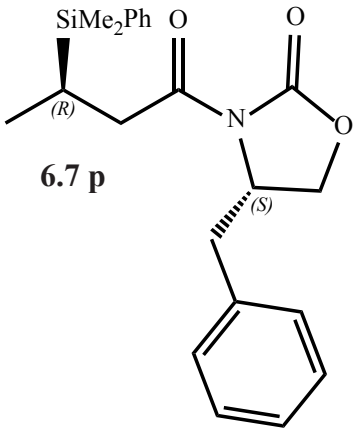
(S)-4-(tert-butyl)-3-((S)-3-(dimethyl(phenyl)silyl)-3-phenylpropanoyl)oxazolidin-2-one (6.5 p): Created using the general procedure and (S)-4-(tert-butyl)-3-cinnamoyloxazolidin-2-one. The product was purified using flash chromatography (0-20% EtOAc in hexane, R_f 0.4 in 10% EtOAc/ hexanes) and (100% DCM, R_f 0.90) to give 82% (82 mg, 96:4 d.r.) of product as a white solid. 1H NMR (500 MHz, CDCl3) δ 7.42-7.30 (m, 5H), 7.15 (m, 2H), 7.05 (m, 1H), 6.94 (m, 2H), 4.18 (dd, NCH, J = 7.8, 1.6 Hz, 1H), 4.14 (dd, OCH2, J = 9.2, 1.6 Hz, 1H), 3.97 (dd, OCH2, J = 9.2, 7.8 Hz, 1H), 3.58 (dd, PhCH, J = 16.1, 12.2 Hz, 1H), 3.09 (dd, COCH2, J = 16.1, 3.6 Hz, 1H), 3.05 (dd, COCH2, J = 12.2, 3.6 Hz, 1H), 0.72 (s, t-Bu, 9H), 0.30, 0.24 (2s, Si(CH3)2, 3H each); 13C NMR (125.7 MHz, CDCl3) δ 173.00, 155.00, 141.62, 136.69, 134.42, 129.49, 128.29, 128.15, 127.92, 125.19, 65.53, 61.20, 35.75, 35.70, 32.69, 25.63, −3.97, −5.01; FTIR (cm-1) 1774, 1701



6.6 p

(S)-4-(tert-butyl)-3-((R)-3-(dimethyl(phenyl)silyl)hexanoyl)oxazolidin-2-one (6.6 p): Created using the general procedure and (S,E)-4-(tert-butyl)-3-(hex-2-enoyl)oxazolidin-2-one. The

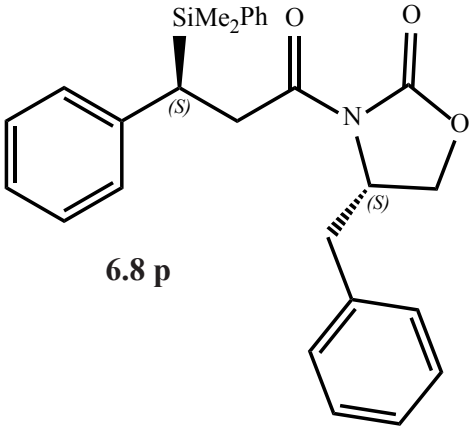
product was purified using flash chromatography (0-20% EtOAc in hexane, R_f 0.4 in 10% EtOAc/ Hex) and (100% DCM, R_f 0.9) to give 80% (80 mg, 97:3 d.r.) of product as a clear viscous oil. 1H NMR (400 MHz, CDCl3) δ 7.56-7.49 (m, 2H), 7.37-7.32 (m, 3H), 4.35 (dd, NCH, J = 7.6, 1.6 Hz, 1H), 4.22 (dd, NCHCH2O, J = 9.2, 1.6 Hz, 1H), 4.13 (NCHCH2O, J = 9.2, 7.6 Hz, 1H), 2.94 (d, COCH2, J = 6.5 Hz, 2H), 1.62 (m, SiCH, 1H), 1.50-1.39 (m, CH2, 1H), 1.34-1.14 (m, CH2, 3H), 0.87 (s, tert-Bu, 9H), 0.80 (t, CH3CH2, J = 7.1 Hz, 3H), 0.32 (2s, Si(CH3)2, 3H each); 13C NMR (125.7 MHz, CDCl3) δ 173.79, 154.80, 138.49, 134.07, 129.00, 127.82, 65.36, 61.20, 36.14, 35.79, 32.90, 25.78, 22.34, 20.68, 14.38, -3.70, -3.90; FTIR (cm-1) 1779, 1701.



6.7 p

(S)-4-benzyl-3-((R)-3-(dimethyl(phenyl)silyl)butanoyl)oxazolidin-2-one (6.7 p): Created using the general procedure and (S)-4-benzyl-3-(crotonoyl)oxazolidin-2-one. The product was purified using flash chromatography (0-20% EtOAc in hexanes, R_f 0.4 in 10% EtOAc/hexanes) and (100% DCM, R_f 0.9) to give 91% (91 mg, 92:8 d.r.) of product as a white solid; mp 87-90 °C. 1H NMR (500 MHz, CDCl3) δ 7.53-7.42 (m, Ar-H, 2H), 7.38-7.23 (m, Ar-H, 6H), 7.18 (m, Ar-H, 2H), 4.59 (m, NCH, 1H), 4.14-4.08 (m, NHCH2O, 2H), 3.25 (dd, PhCH2, J = 13.3, 3.4

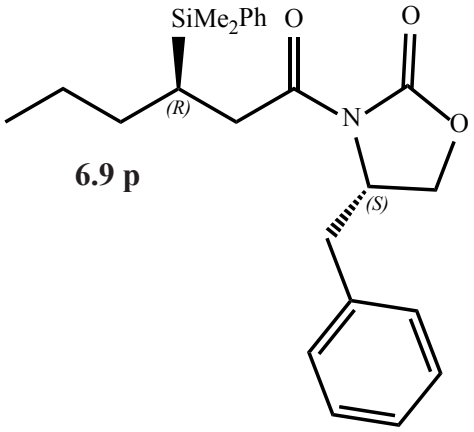
Hz, 1H), 3.03 (dd, NHCH2O, J= 16.1, 3.8 Hz, 1H), 2.74 (dd, NHCH2O, J = 16.1, 10.8 Hz, 1H), 2.66 (dd, PhCH2, J = 13.3, 9.8 Hz, 1H), 1.60 (m, SiCH, 1H), 1.00 (d, CH3CH, J = 7.3 Hz, 3H), 0.34, 0.33 (2s, Si(CH3)2, 3H each); 13C NMR (125.7 MHz, CDCl3) δ 173.30, 153.35, 137.46, 135.39, 134.03, 129.38, 129.06, 128.91, 127.76, 127.27, 66.13, 55.15, 37.97, 37.85, 15.50, 14.51, −4.96, −5.16; FTIR (cm-1) 1790, 1697; HRMS (EI) calcd for [C22H27NO3Si] 381.1760, found 381.1756.



6.8 p

(S)-4-benzyl-3-((S)-3-(dimethyl(phenyl)silyl)-3-phenylpropanoyl)oxazolidin-2-one (6.8 p): Created using the general procedure and (S)-4-benzyl-3-cinnamoyloxazolidin-2-one. The product was purified using flash chromatography (0-20% EtOAc in hexanes, R_f 0.4 in 10% EtOAc/hexanes) and (100% DCM, R_f 0.9) to give 87% (87 mg, 84:16 d.r.) of product as a white solid. 1H NMR (500 MHz, CDCl3) δ 7.46-7.43 (m, Ar-H, 2H), 7.38-7.31 (m, Ar-H, 3H), 7.27-7.16 (m, Ar-H, 5H), 7.09-7.04 (m, Ar-H, 3H), 7.01-6.98 (m, Ar-H, 2H), 4.41 (m, NCH, 1H), 4.02 (dd, OCH2, J = 3.0, 9.0 Hz, 1H), 3.96 (dd, OCH2, J = 8.0, 9.0 Hz, 1H), 3.60 (dd, SiCH, J = 17.0, 11.5 Hz, 1H), 3.12 (dd, COCH2, J = 17.0, 4.0 Hz, 1H), 3.02 (dd, COCH2, J = 11.5, 4.0 Hz, 1H), 3.02 (m, PhCH2,

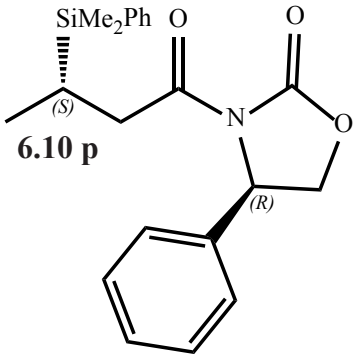
1H), 2.48 (dd, PhCH2, J = 13.5, 10.0 Hz, 1H), 0.31, 0.24 (2s, Si(CH3)2, 3H each); 13C NMR (125.7 MHz, CDCl3) δ 172.54, 153.49, 141.79, 136.59, 135.36, 134.2, 134.2, 129.30, 129.29, 128.84, 128.13, 127.76, 127.19, 125.00, 66.14, 55.08, 37.68, 35.82, 31.67, -4.04, -5.39; FTIR (cm-1) 1778, 1701. HRMS (ESI) calcd for [C27H29NO3SiNa]+ (MNa+) 466.1814, found 466.1806.



6.9 p

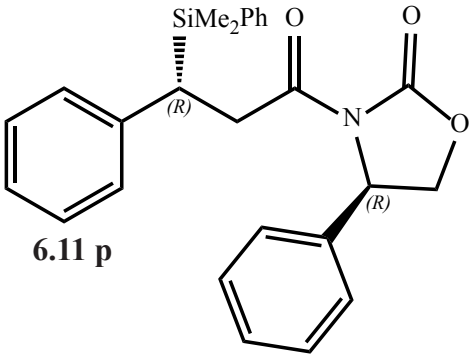
(S)-4-benzyl-3-((R)-3-(dimethyl(phenyl)silyl)hexanoyl)oxazolidin-2-one (6.9 p): Created with the general procedure and (S,E)-4-benzyl-3-(hex-2-enoyl)oxazolidin-2-one. The product was purified using flash chromatography (0-20% EtOAc in hexane, R_f 0.4 in 10% EtOAc/hexanes) and (100% DCM, R_f 0.9) to give 93% (93 mg, 91:9 d.r.) of product as a white solid. 1H NMR (400 MHz, CDCl3) δ 7.57-7.50 (m, Ar-H, 2H), 7.36-7.23 (m, Ar-H, 6H), 7.17-7.13 (m, Ar-H, 2H), 4.50 (m, NCH, 1H), 4.08 (d, NCHCH2O, J = 5.0 Hz, 2H), 3.17 (dd, PhCH2, J = 13.3, 3.3 Hz, 1H), 2.99 (dd, COCH2, J = 17.3, 6.0 Hz, 1H), 2.90 (dd, COCH2, J = 17.3, 7.6 Hz, 1H), 2.58 (dd, PhCH2, J = 13.3, 9.9 Hz, 1H), 1.65 (m, SiCH, 1H), 1.53-1.44 (m, CH2, 1H), 1.38-1.18 (m, CH2, 3H), 0.84 (t, CH3CH2, J = 6.9 Hz, 3H), 0.34, 0.33 (2s, Si(CH3)2, 3H each); 13C NMR (125.7 MHz, CDCl3) δ 173.70, 153.50, 138.41, 135.55, 134.16, 129.48, 129.06, 129.04, 127.83, 127.38, 66.20, 55.36,

37.95, 36.36, 32.91, 22.31, 20.43, 14.42, -3.65, 4.23; FTIR (cm-1) 1779, 1696.



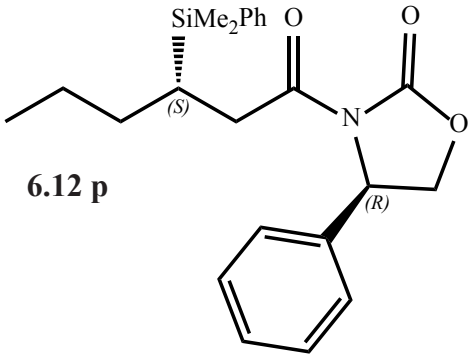
6.10 p

(R)-3-((S)-3-(dimethyl(phenyl)silyl)butanoyl)-4-phenyloxazolidin-2-one (6.10 p): Created using the general procedure with (R)-3-(crotonoyl)-4-phenyloxazolidin-2-one. The product was purified using flash chromatography (0-20% EtOAc in hexanes, R_f 0.4 in 10% EtOAc/hexanes) and (100% DCM, R_f 0.9) to give 95% (95 mg, 95:5 d.r.) of product as a white solid; mp 73-75 °C. 1H NMR (500 MHz, CDCl3) δ 7.52 (m, Ar-H, 2H), 7.40-7.29 (m, Ar-H, 8H), 5.36 (dd, NCH, J = 8.7, 3.7 Hz, 1H), 4.64 (dd, OCH2, J = 8.9, 8.7 Hz, 1H), 4.25 (dd, OCH2, J = 8.9, 3.7 Hz, 1H), 3.05 (dd, COCH2, J = 15.8, 3.7 Hz, 1H), 2.70 (dd, COCH2, J = 15.8, 11.2 Hz, 1H), 1.54 (m, SiCH, 1H), 0.86 (d, CH3CH, J= 7.3 Hz, 3H), 0.31, 0.30 (2s, SiCH3, 3H each); 13C NMR (125.7 MHz, CDCl3) δ 172.81, 153.56, 139.24, 137.34, 133.98, 129.07, 129.01, 128.61, 127.70, 125.96, 69.83, 57.51, 37.84, 15.59, 14.12, −5.11, −5.14; FTIR (cm-1) 1785, 1703.



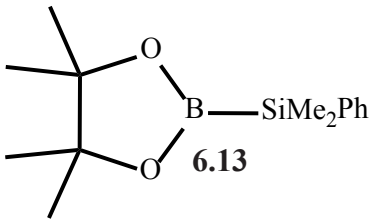
6.11 p

(R)-3-((R)-3-(dimethyl(phenyl)silyl)-3-phenylpropanoyl)-4-phenyloxazolidin-2-one (6.11 p): Created using the general procedure and (R)-3-cinnamoyl-4-phenyloxazolidin-2-one. The crude product was purified using flash chromatography (0-20% EtOAc in hexane, R_f 0.4 in 10% EtOAc/ hexanes) and (100% DCM, R_f 0.9) to give 89% (89 mg, 97:3 d.r.) of product as a white solid. 1H NMR (500 MHz, CDCl3) δ 7.43-7.26 (m, Ar-H, 8H), 7.21-7.07 (m, Ar-H, 5H), 6.97 (d, Ar-H, J = 7.5 Hz, 2H), 5.16 (dd, NCH, J = 8.5, 4.0 Hz, 1H), 4.47 (dd, OCH2, J = 9.0, 8.5 Hz, 1H), 4.14 (dd, OCH2, J = 9.0, 4.0 Hz, 1H), 3.73 (dd, PhCH, J = 17.0, 12.0 Hz, 1H), 3.09 (dd, COCH2, J = 17.0, 4.0 Hz, 1H), 3.00 (dd, COCH2, J = 12.0, 4.0 Hz, 1H), 0.31, 0.24 (2s, SiCH3, 3H each); 13C NMR (125.7 MHz, CDCl3) δ 172.06, 153.79, 141.66, 138.84, 136.49, 134.16, 129.26, 129.03, 128.48, 128.07, 127.73, 127.70, 125.83, 124.91, 69.90, 57.54, 35.71, 31.50, -4.14, -5.29; FTIR (cm-1) 1779, 1705; MS m/z 319 (35%), 265 (100%). HRMS (ESI) calcd for [C26H27NO3SiNa]+ (MNa+) 452.1657, found 452.1652.



6.12 p

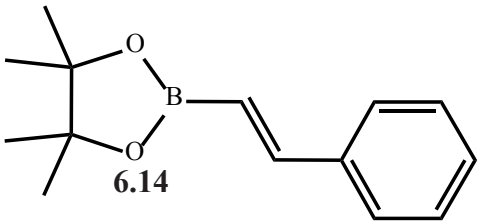
(R)-3-((S)-3-(dimethyl(phenyl)silyl)hexanoyl)-4-phenyloxazolidin-2-one (6.12 p): Created using the general procedure and (R,E)-3-(hex-2-enoyl)-4-phenyloxazolidin-2-one. The product was purified using flash chromatography (0-20% EtOAc in hexanes, R_f 0.4 in 10% EtOAc/hexanes) and (100% DCM, R_f 0.9) to give 82% (82 mg, 98:2 d.r.) of product as a clear oil. 1H NMR (400 MHz, CDCl3) δ 7.49-7.45 (m, Ar-H, 2H), 7.38-7.27 (m, Ar-H, 6H), 7.26-7.22 (m, Ar-H, 2H), 5.27 (dd, NCH, J = 8.8, 3.7 Hz, 1H), 4.58 (dd, NCHCH2O, J = 8.8, 8.8 Hz, 1H), 4.22 (dd, NCHCH2O, J = 8.8, 3.7 Hz, 1H), 2.94 (dd, COCH2, J = 16.8, 5.8 Hz, 1H), 2.88 (dd, COCH2, J = 16.8, 8.2 Hz, 1H), 1.54 (m, SiCH, 1H), 1.40-1.27 (m, CH2, 1H), 1.22-1.06 (m, CH2, 3H), 0.73 (t, CH3CH2, J = 6.9 Hz, 3H), 0.23, 0.22 (2s, Si(CH3)2, 3H each); 13C NMR (125.7 MHz, CDCl3) δ 173.24, 153.72, 139.25, 138.35, 134.06, 129.19, 128.99, 128.73, 127.80, 126.16, 69.97, 57.73, 36.59, 32.68, 22.25, 20.60, 14.35, -3.90, -4.08; FTIR (cm-1) 1780, 1702



6.13

(Dimethylphenylsilyl)boronic acid pinacol ester (6.13):[102] To a 25 mL oven-dry round bottom

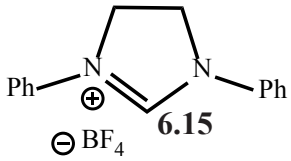
flask was added lithium metal (0.21 grams, 30 mmol, 4 eq) under argon, then 10 mL of anhydrous THF. The mixture was cooled to 0 °C, then 1.28 mL of dimethylphenylsilyl chloride was added by syringe. The solution was stirred at 0 °C for 5 hours, then put in freezer overnight. It should turn dark, opaque red within a few minutes of adding the silyl chloride. The next morning, 2.21 mL (15 mmol, 2 eq) of a clear liquid pinacolborane were added to 10 mL of hexanes in a 100 mL oven-dry round bottom flask under argon. The solution was cooled to 0 °C, then the whole red liquid solution of dimethylphenylsilyllithium was added to the borane solution dropwise over 30 min. The solution was stirred an additional 30 min at 0 °C, then the ice bath was removed and the solution was stirred at room temperature overnight. The next day the solution was cloudy white. The volatiles were removed on a rotovap, 40 mL hexanes were added to the residue, and the solution was filtered under argon using a Schlenk filter to remove the solids. The hexanes were removed in vacuo, leaving ca 2 grams of a clear yellow gel product. >90% yield, product is used as is, with some borane contaminant.



6.14

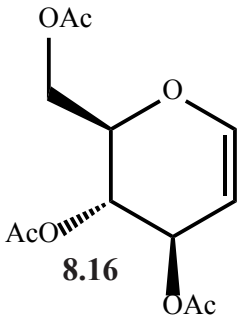
trans-2-Phenylvinylboronic acid pinacol ester (6.14):[103] 2.5 mL (17 mmol, 2 eq) of pinacolborane were added to 2 mL of dichloromethane in a 25 mL oven-dry round bottom flask under argon, and cooled to 0 °C. 0.95 mL (8.65 mmol, 1 eq) of phenylacetylene was added by syringe slowly, and the solution was warmed to 25 °C and stirred for an hour. After an hour, the solution was

cooled to 0 °C again, and 0.112 grams (0.434 mmol, 5 mol %) of Schwartz's reagent was added by removing the septum briefly (the Schwartz's reagent catalyzes the reaction, which is slow otherwise). The solution was stirred at room temperature for 48h, then quenched the reaction by adding 10 mL diethyl ether and 10 mL water. Transferred to a separatory funnel. Extract the aqueous layer 3x with more ether, then washed the combined organics 5x with water. Dry over anhydrous magnesium sulfate. Rotovap. Clear yellow syrup. >90% yield, used as is with some borane contaminant.



6.15

1,3-diphenyl-4,5-dihydroimidazolium tetrafluoroborate (6.15):[87] A 25 mL oven-dry round bottom flask with a condenser was setup under argon. N,N-diphenylethylenediamine was added, then triethylorthoformate, then ammonium tetrafluoroborate. The heterogeneous solution was heated at 115 °C for 3h. After 3h, the solution was cooled, the resulting solid was dissolved in a minimum amount of DMSO, and an equal volume of dichloromethane was added. The pure product will precipitate as it stands. 30% yield. 1H NMR (400 MHz, DMSO-d6) δ 9.94 (s, 1H), 7.68 – 7.34 (m, 10H), 4.60 (s, 4H).

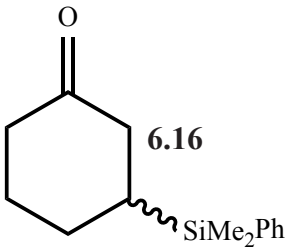


8.16

Tri-O-Acetyl-D-Glucal:[104] 30 grams of D-glucose pentaacetate (77 mmol) was cooled in an ice bath in a 250 mL Erlenmeyer flask equipped with a stir bar. 18 mL (308 mmol, 4 eq) of acetic acid and 15 mL (159 mmol, 2 eq) of acetic anhydride were added, and stirred until the solution had cooled to ice bath temperature, and the glucose was dissolved. 63 mL (360 mmol, 4.7 eq) of ice cold 33% wt HBr in acetic acid was added dropwise with an addition funnel over 30 minutes. Once the addition was complete, the solution was stirred at ice bath temperature for 10 minutes, then for 2 hours at room temperature. Separately, 75 grams (550 mmol, 7 eq) of sodium acetate was dissolved in 250 mL of 50 % v/v acetic acid/water in a 1 liter Erlenmeyer flask, and cooled to -10 °C in a dry ice/isopropanol bath. 54 grams (833 mmol, 11 eq) of zinc powder were added carefully, maintaining the reaction temperature and keeping the solution stirring. A solution of 5.4 grams of copper sulfate (22 mmol, 0.28 eq) in 18 mL of water was added, and formation of hydrogen gas bubbles was observed and the solution was stirred until it turned clear. Keeping the solution temperature around -10 °C, the HBr solution was added to the zinc solution dropwise. The HBr addition took about 30 minutes. The solution was stirred at between -10 °C and 10 °C for two hours. The solution was filtered through celite, and washed with a 50% v/v solution of acetic acid in water. It is important that the filter cake does not dry out– it can start a fire. The filtrate was diluted with about 200 grams of ice, 200 mL of dichloromethane were added, and the mixture

was transferred to a separatory funnel. The layers were separated, and the aqueous layer extracted once with 200 mL more of dichloromethane. The combined organics were washed with 200 mL of water once, then saturated sodium bicarbonate, then water again. The organic layer was dried over anhydrous magnesium sulfate, and the volatiles removed. The residue was purified on a silica column with isocratic 30% EtOAc/Hexanes gave 5.34 g (64%) of product as a white, crystalline solid. TLC (25% EtOAc/hexanes) R_f = 0.2. 1H NMR (400 MHz, CDCl3) δ 6.47 (dd, OCH=CH, J = 6.1, 1.4 Hz, 1H), 5.35 (ddd, OCH=CHCHOAc, J = 5.6, 3.3, 1.4 Hz, 1H), 5.23 (dd, OCHCHOAc, J = 7.6, 5.6 Hz, 1H), 4.85 (dd, OCH=CH, J = 6.1, 3.3 Hz, 1H), 4.40 (dd, CH2OAc, J = 12.0, 5.6 Hz, 1H), 4.29 - 4.23 (m, CHCH2OAc, 1H), 4.20 (dd, CH2OAc, J = 12.0, 3.1 Hz, 1H), 2.10 (s, OCOCH3, 3H), 2.08 (s, OCOCH3, 3H), 2.05 (s, OCOCH3, 3H).

General Procedure for Copper-Conjugate Additions with Silyl-Boranes in Water:[86] 0.8 μL (8.3 μmol, 0.05 eq) of 4-picoline, 0.165 mmol of enone, and 0.198 mmol (1.2 eq) of borane reagent was added to a very small vial equipped with a stir bar, and 1.0 mL of 1.66 mM (1.66 μmol, 0.01 eq) copper sulfate in degassed water was added. With vigorous stirring, the heterogeneous solution turned opaque black after a few minutes. Let stir overnight at room temperature. The next morning, 1 mL of extractive solvent (ether or hexanes are common) was added along with 1 mL of pH 10 ammonia/ammonium chloride buffer. After stirring for 30 minutes to quench, the whole mixture was transferred to a separatory funnel with ca 5 mL more solvent and ca 5 mL more water. The aqueous layer was extracted 3 times with more solvent, then the combined organics were washed 2 times with water. Dried over sodium sulfate, rotovap. Silica column.

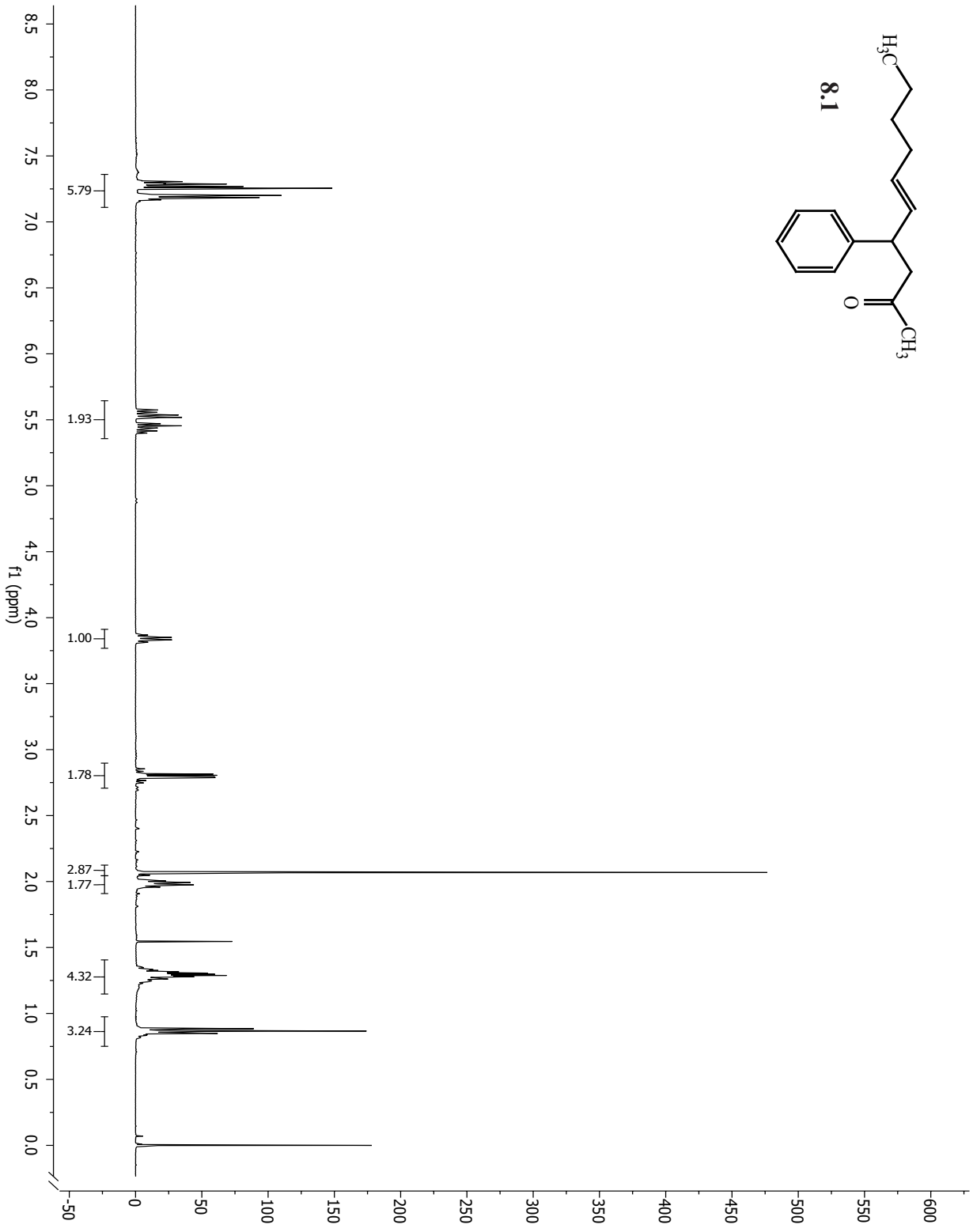


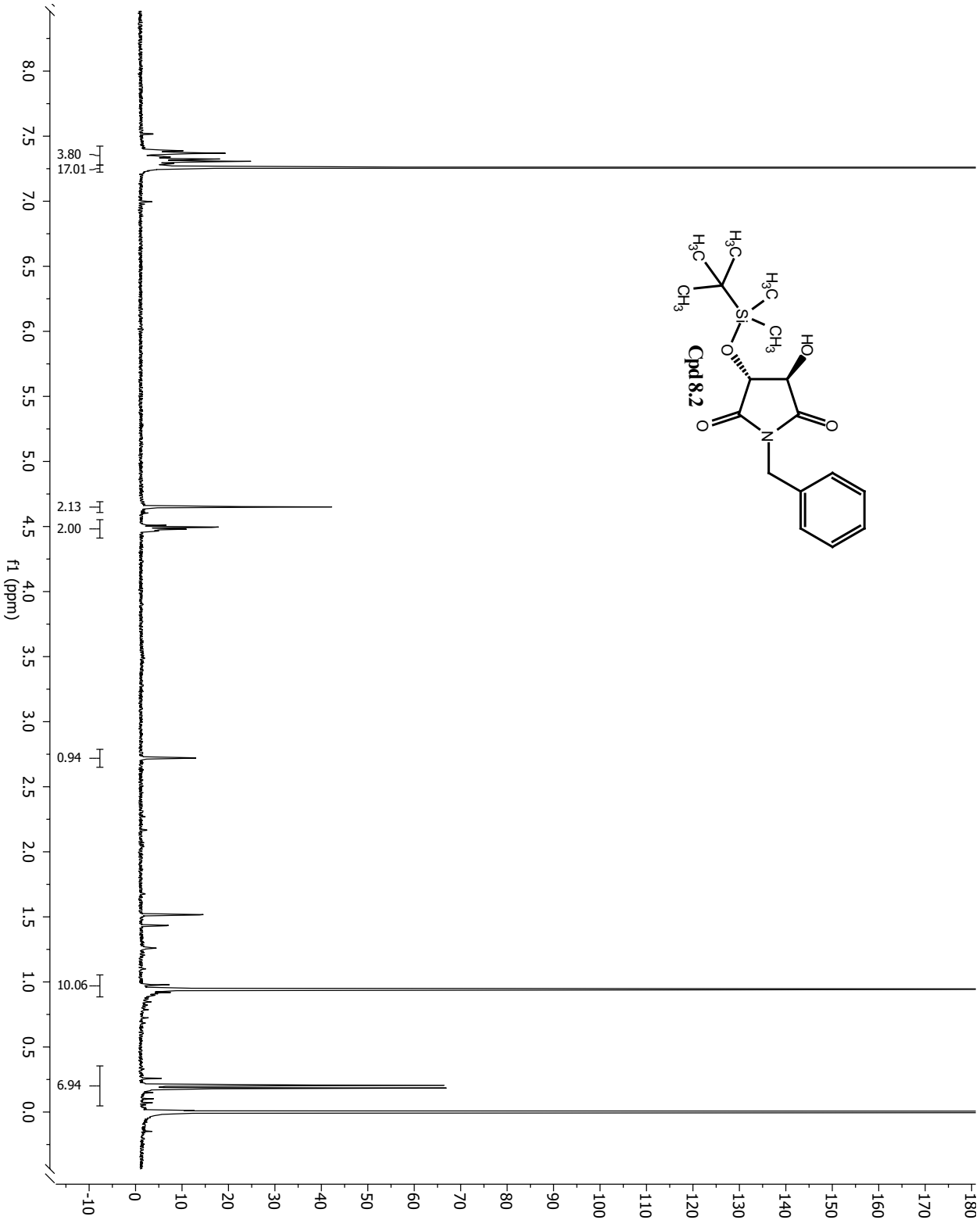
6.16

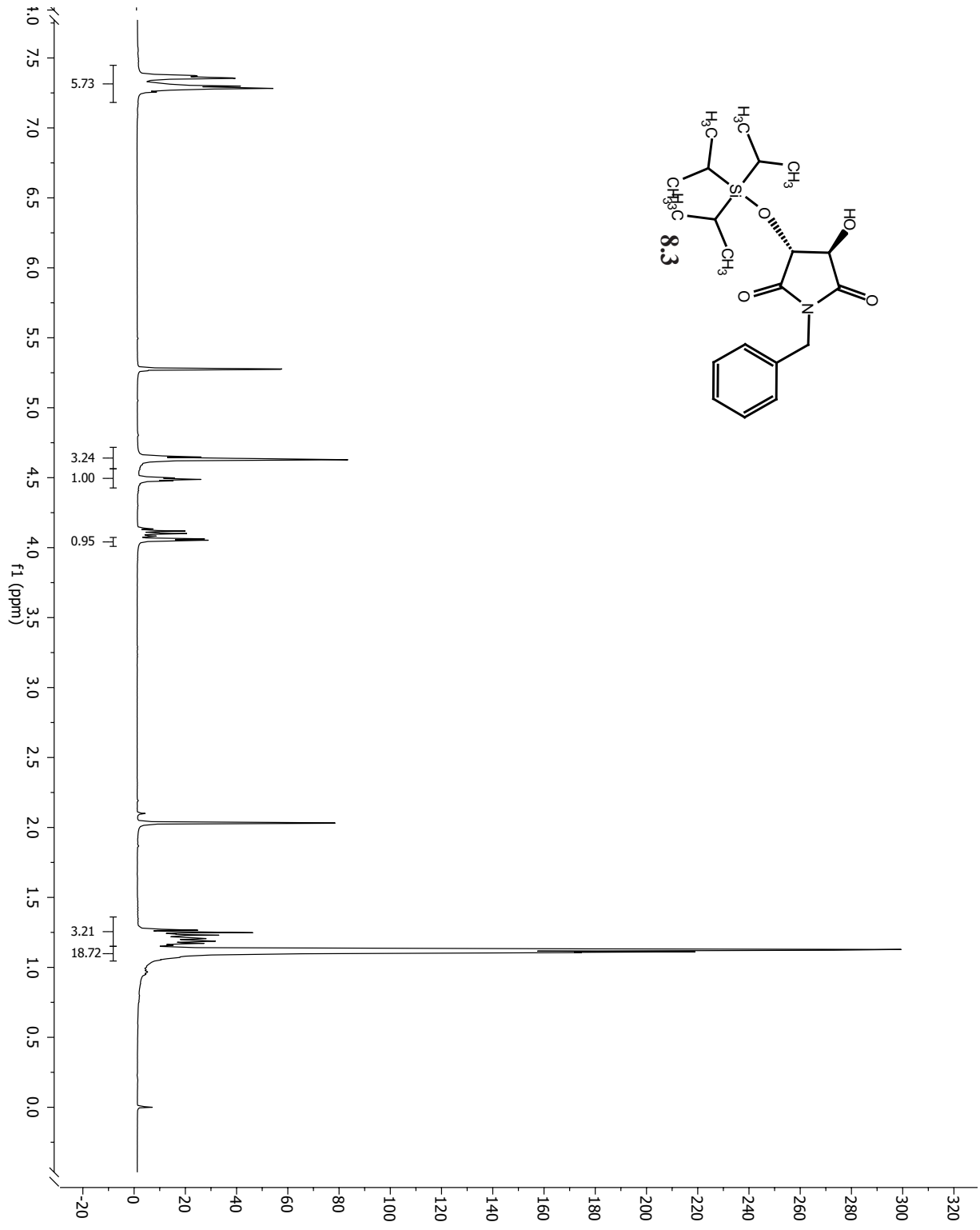
3-(dimethyl(phenyl)silyl)cyclohexan-1-one (6.16): Prepared according to the general procedure. The enone used was 2-cyclohexenone, the borane reagent was (dimethylphenylsilyl)boronic acid pinacol ester, the workup solvent used was hexanes. The column was run with 0-10% diethyl ether/hexanes. 89% yield, yellow oil. 1H NMR (500 MHz, CDCl3) δ 7.52–7.46 (m, Ar-H, 2H), 7.40–7.33 (m, Ar-H, 3H), 2.40–2.23 (m, CH, 3H), 2.18–2.09 (m, CH, 2H), 1.86–1.80 (m, CH, 1H), 1.76–1.65 (m, CH, 1H), 1.48–1.39 (m, CH, 1H), 1.35–1.28 (m, CH, 1H), 0.32, 0.32 (2s, Si(CH3)2, 3H each); 13C NMR (500 MHz, CDCl3) δ 212.4, 136.6, 133.9, 129.2, 127.8, 42.3, 41.8, 29.7, 27.6, 26.0, -5.3, -5.5. MS m/z 232 (M+, 3%), 156 (M – C6H5, 27%), 135(M – C6H9O, 100%). Anal. Calcd for C14H20OSi: C, 72.36; H, 8.67. Found: C, 72.28; H, 8.65

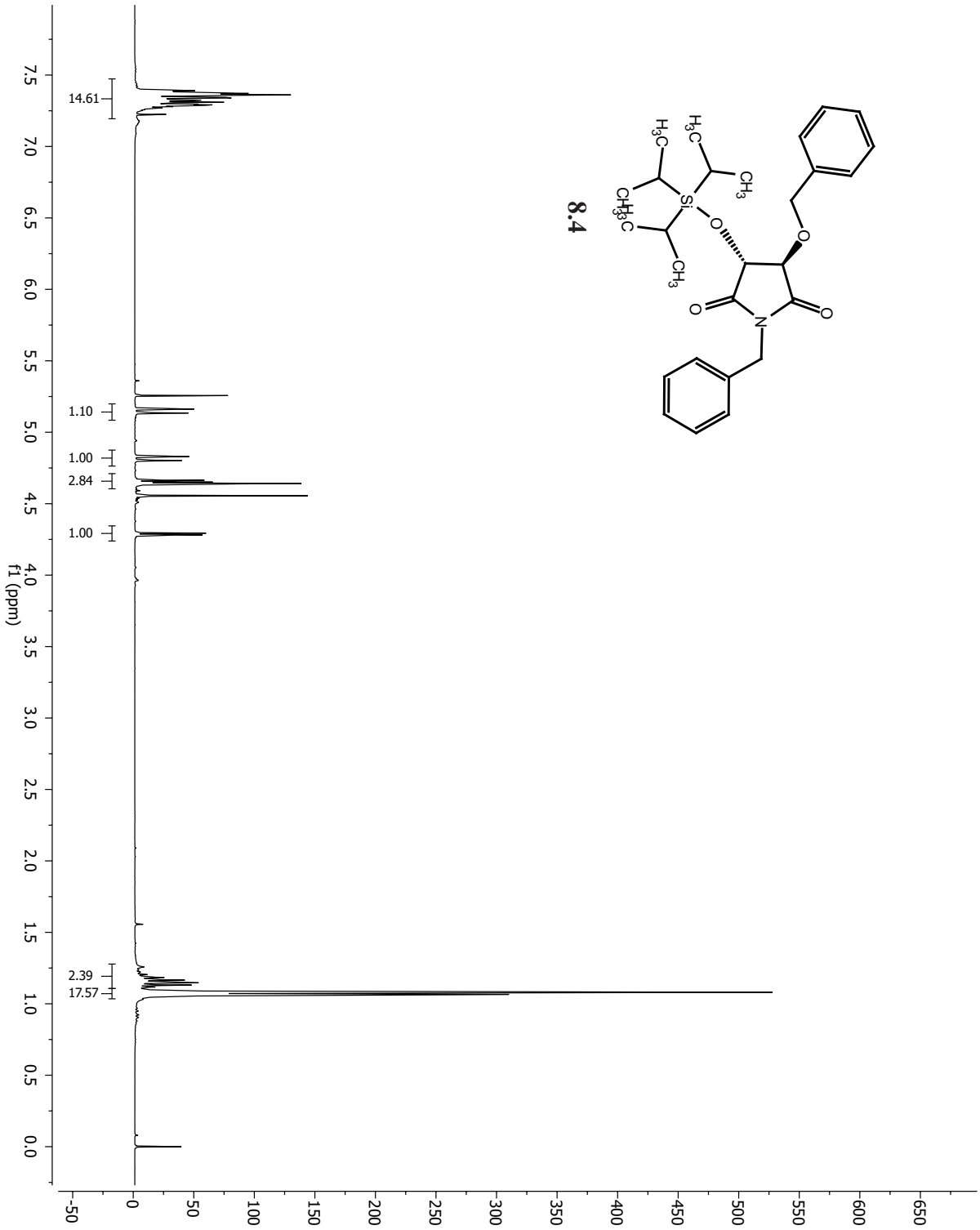
APPENDIX

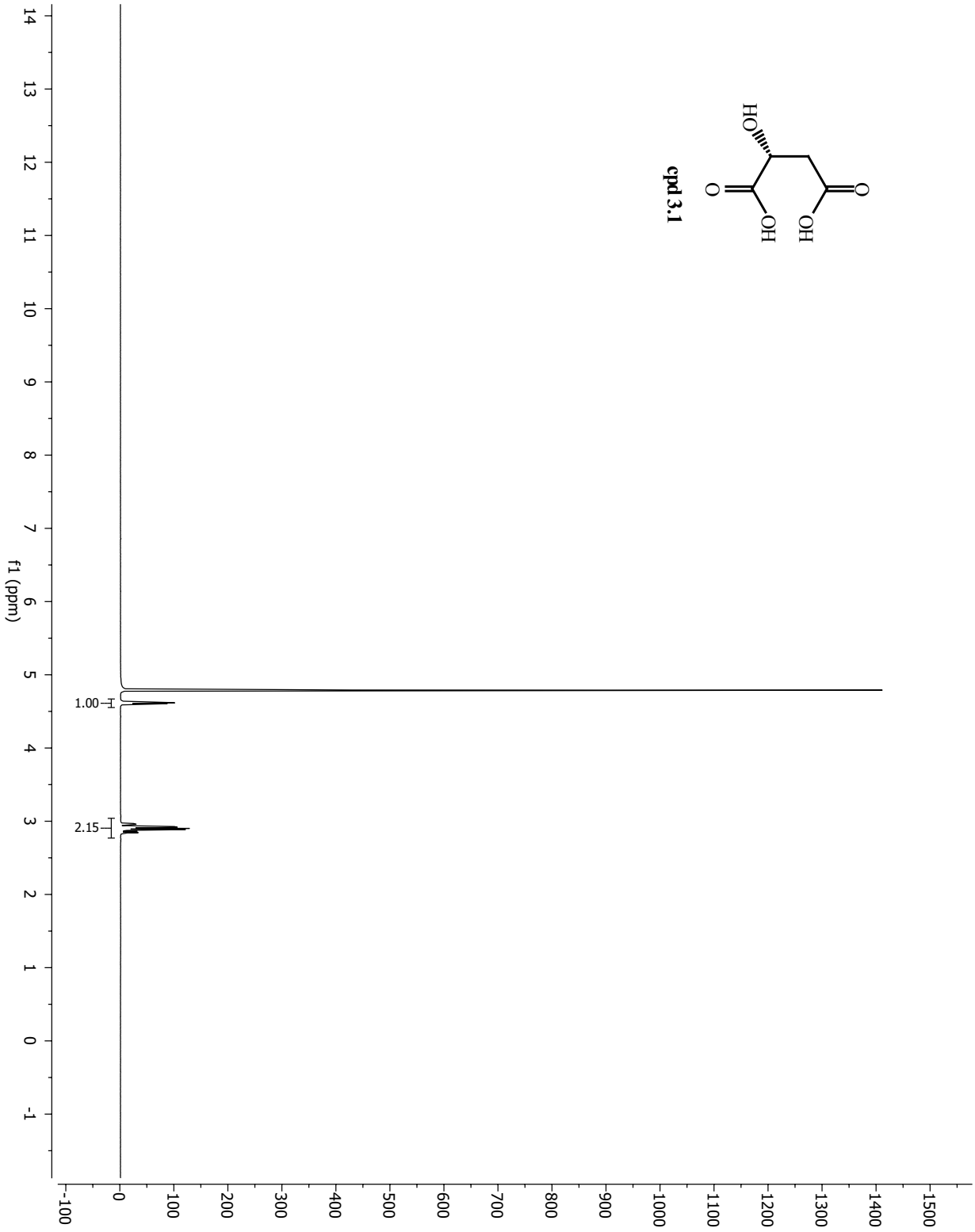
Spectra: H-NMR, C-NMR, Mass Spec, HRMS, IR

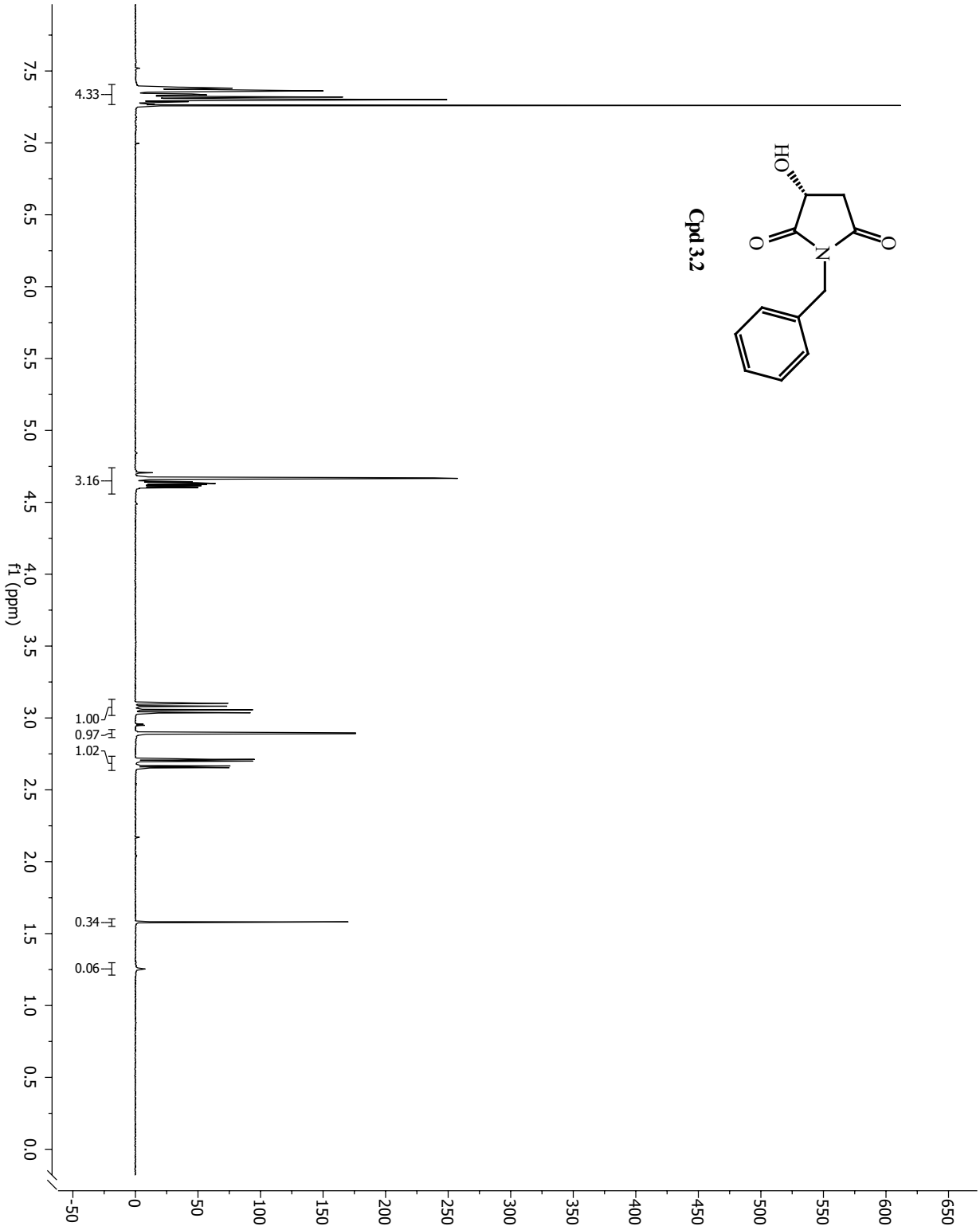

8.1
H3C
O
CH3
f1 (ppm)
5.79
1.93
1.00
1.78
2.87
1.77
4.32
3.24

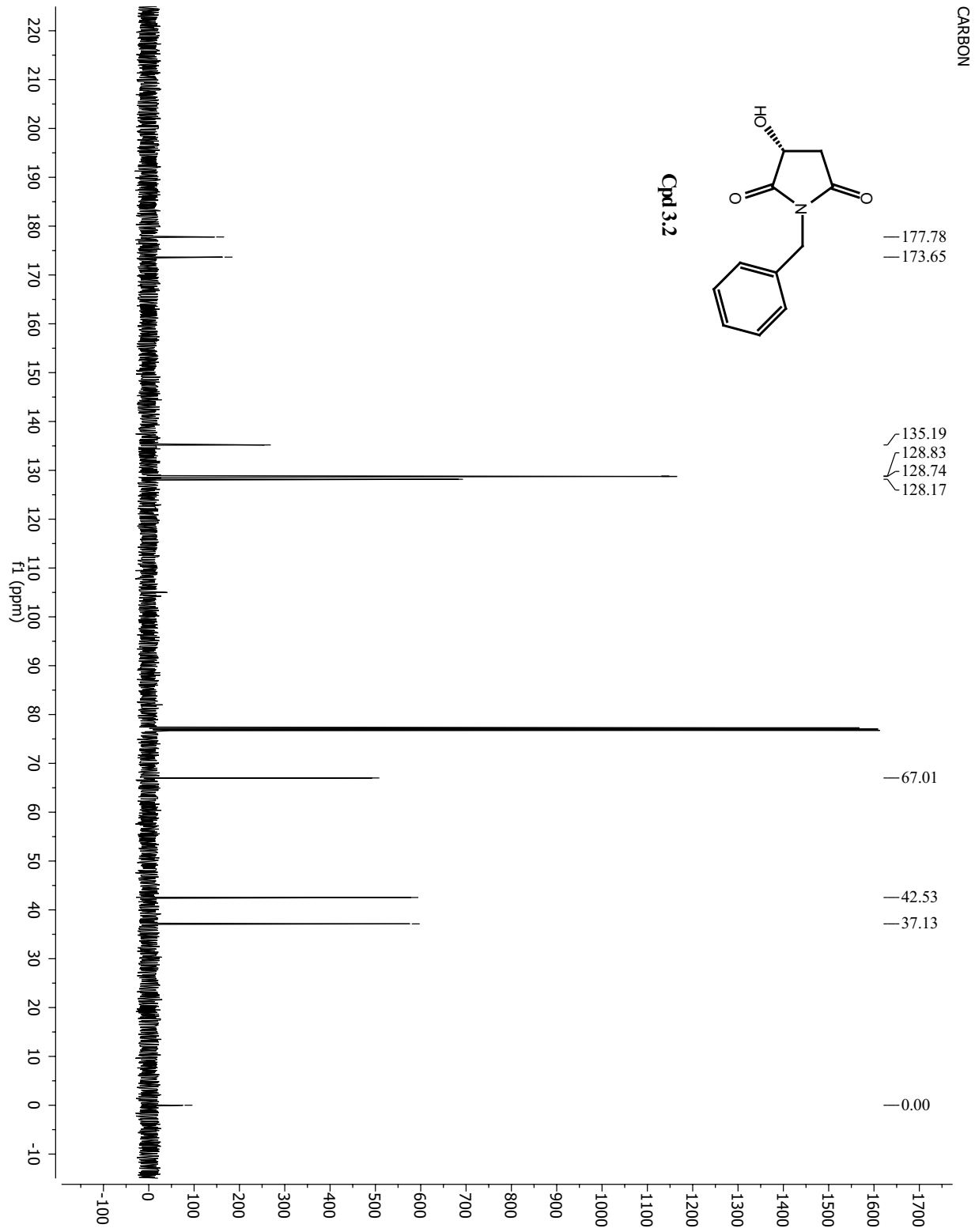

3.80
17.01
2.13
2.00
0.94
10.06
6.94
f1 (ppm)
Cpd 8.2

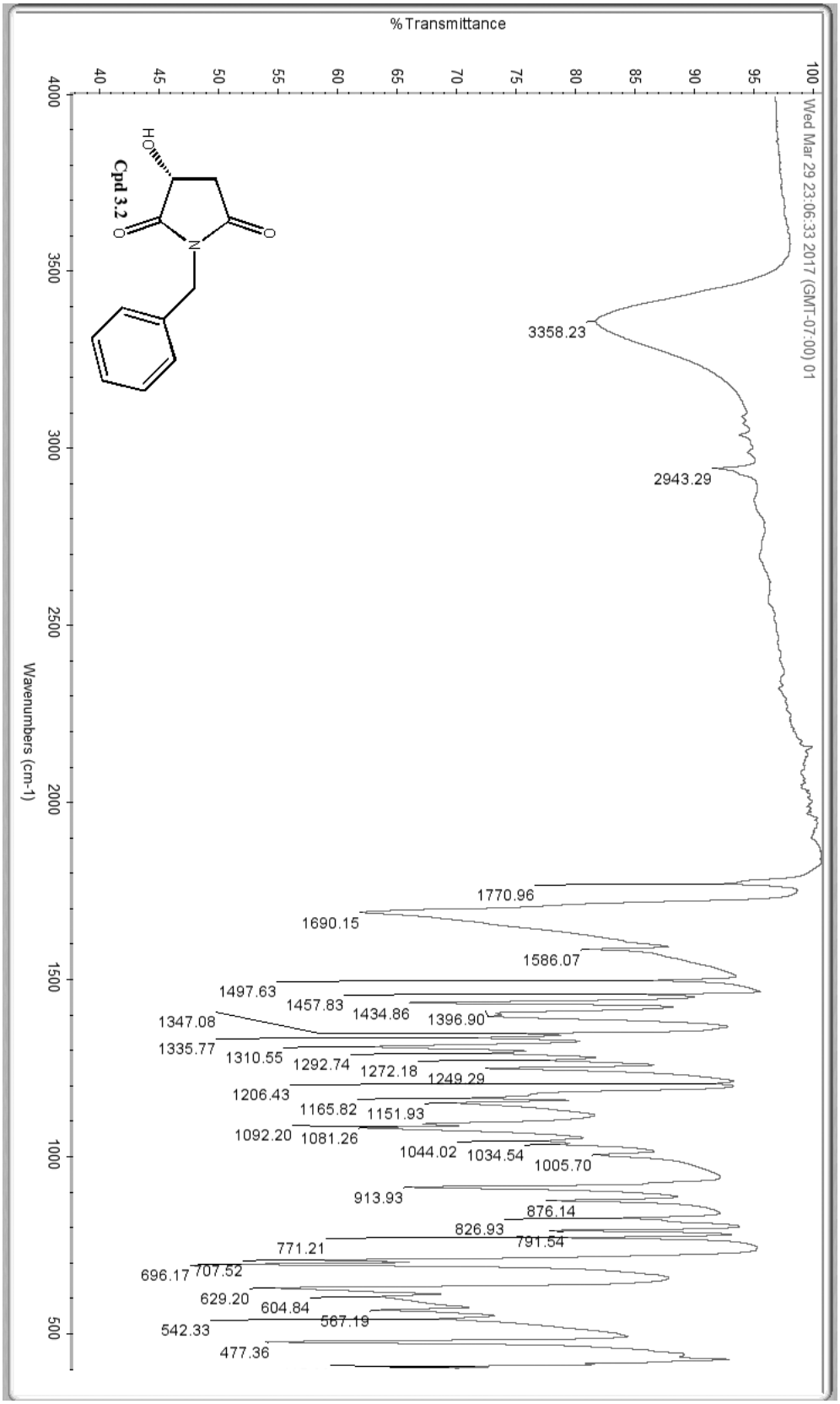

8.3
5.73
3.24
1.00
0.95
3.21
18.72
f1 (ppm)


14.61
1.10
1.00
2.84
1.00
2.39
17.57
f1 (ppm)
8.4

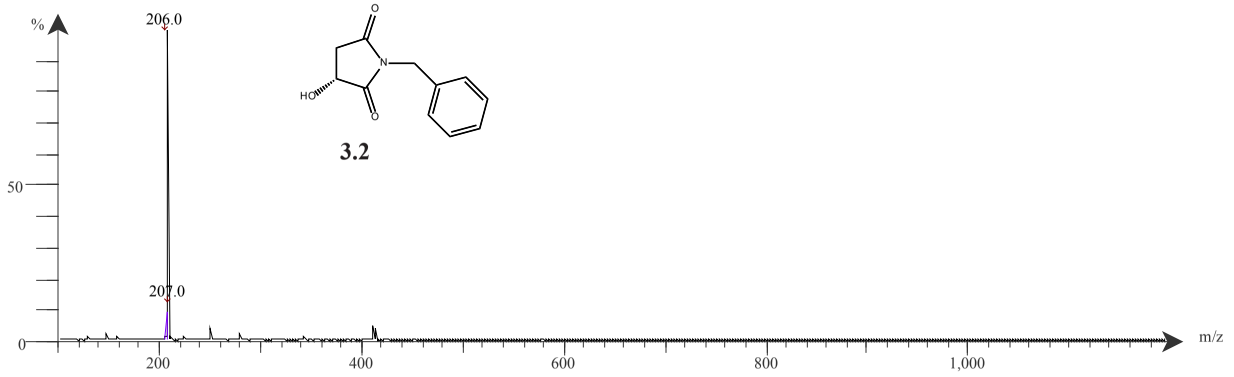

cpd 3.1
HO
O
OH
OH
O
f1 (ppm)
1.00
2.15


Cpd 3.2
HO
O
O
N
O
4.33
3.16
1.00
0.97
1.02
0.34
0.06
f1 (ppm)

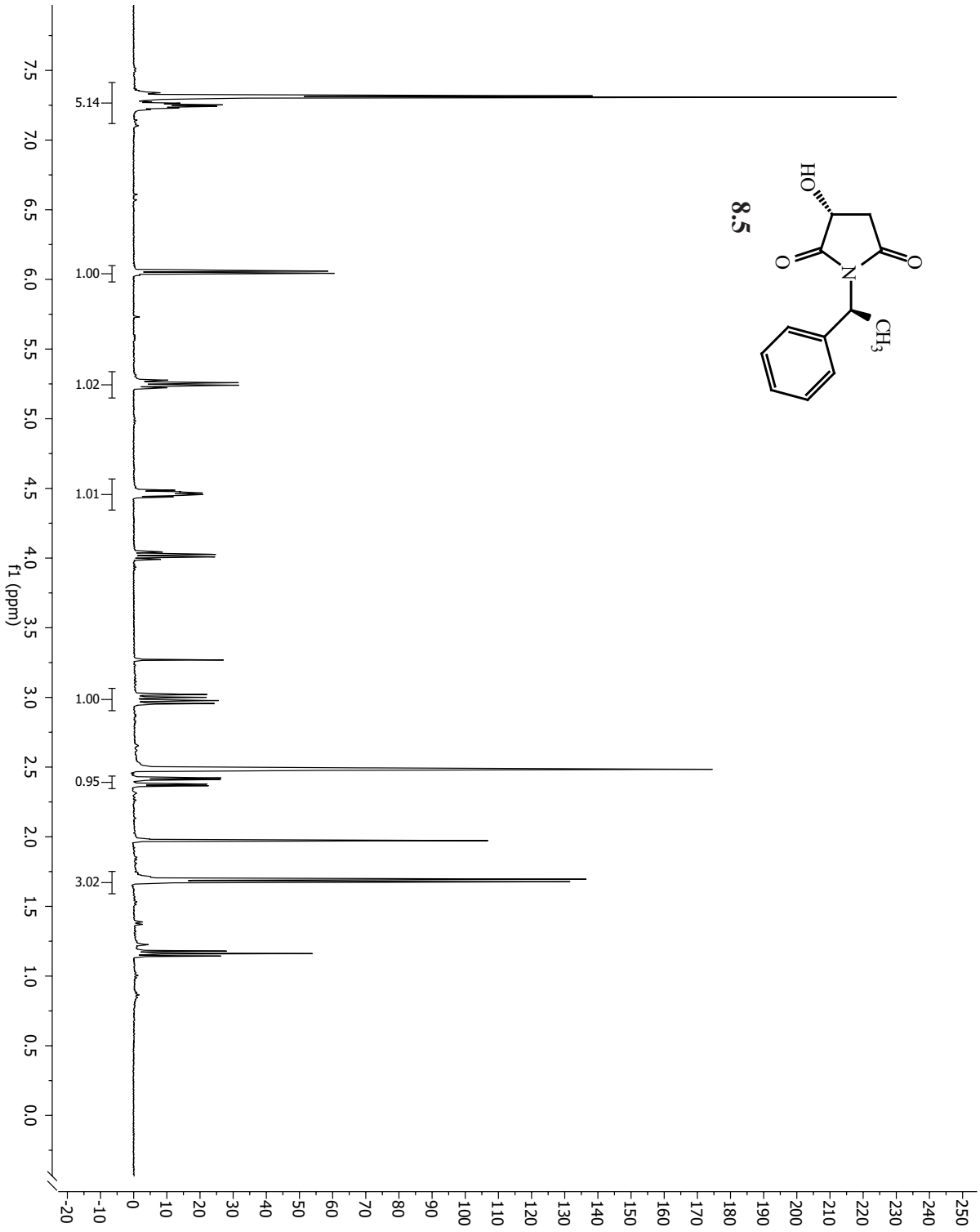

CARBON
Cpd 3.2
HO
O
N
O
177.78
173.65
135.19
128.83
128.74
128.17
67.01
42.53
37.13
0.00
f1 (ppm)

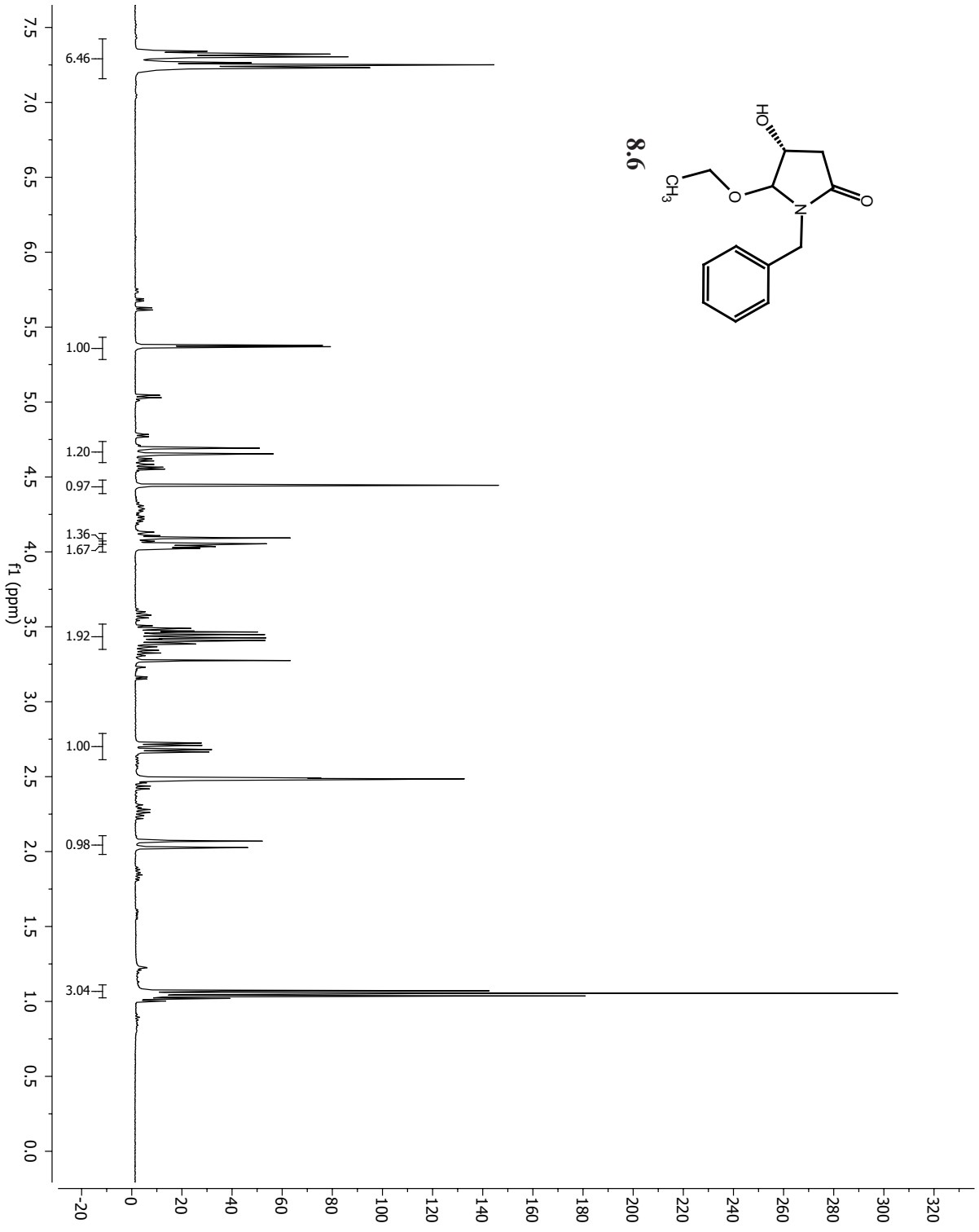

%Transmittance
Wavenumbers (cm-1)
Wed Mar 29 23:06:33 2017 (GMT-07:00) 01
Cpd 3.2
HO
O
O
N
3358.23
2943.29
1770.96
1690.15
1586.07
1497.63
1457.83
1434.86
1396.90
1347.08
1335.77
1310.55
1292.74
1272.18
1249.29
1206.43
1165.82
1151.93
1092.20
1081.26
1044.02
1034.54
1005.70
913.93
876.14
826.93
791.54
771.21
696.17
707.52
629.20
604.84
567.19
542.33
477.36

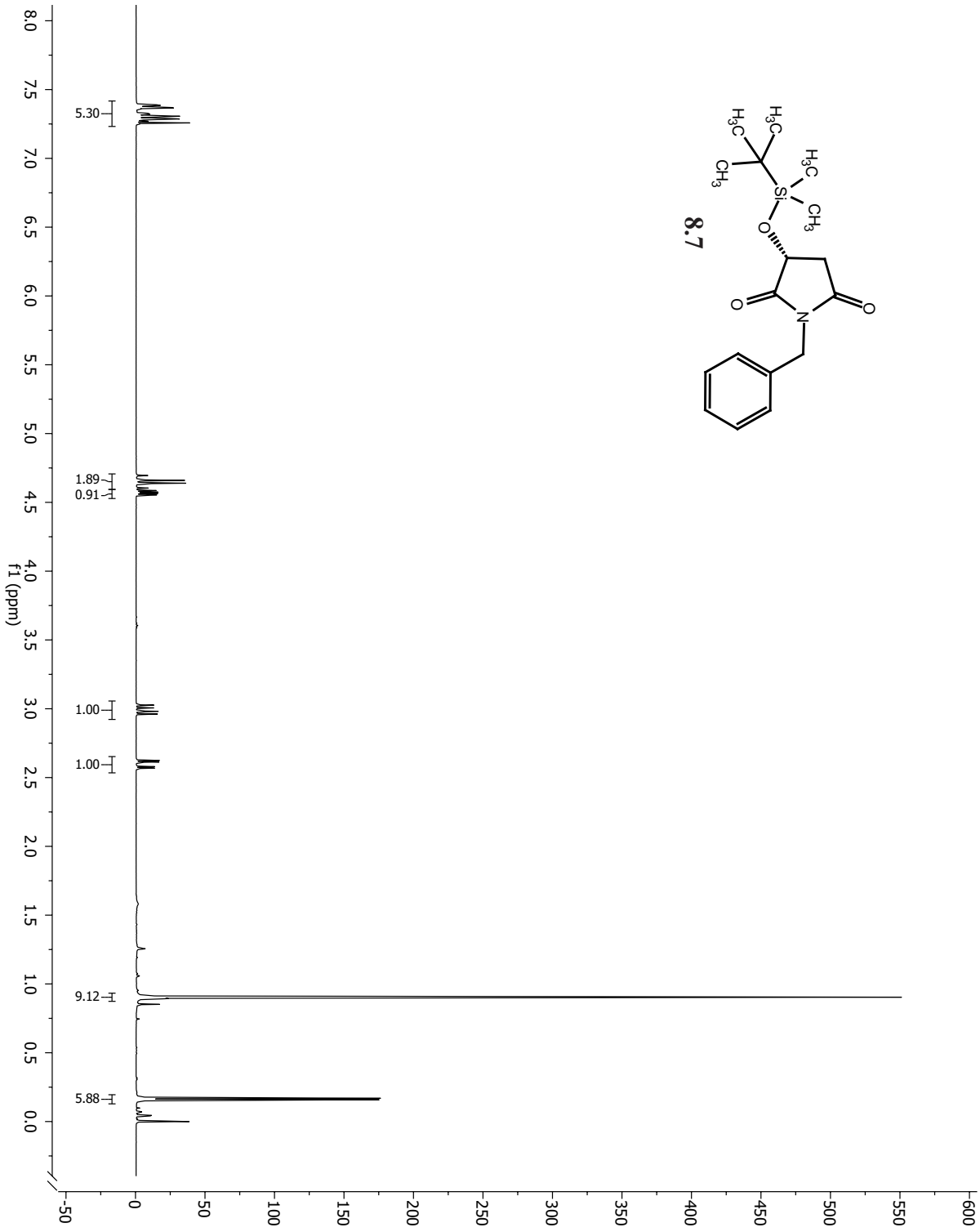
Spectrum RT 2.75 - 3.07 {19 scans}
mjb N-Benzyl D-Malimide_is1 2017.03.10 09:50:35 ;
Intensity APCI + Max: 2.1E9

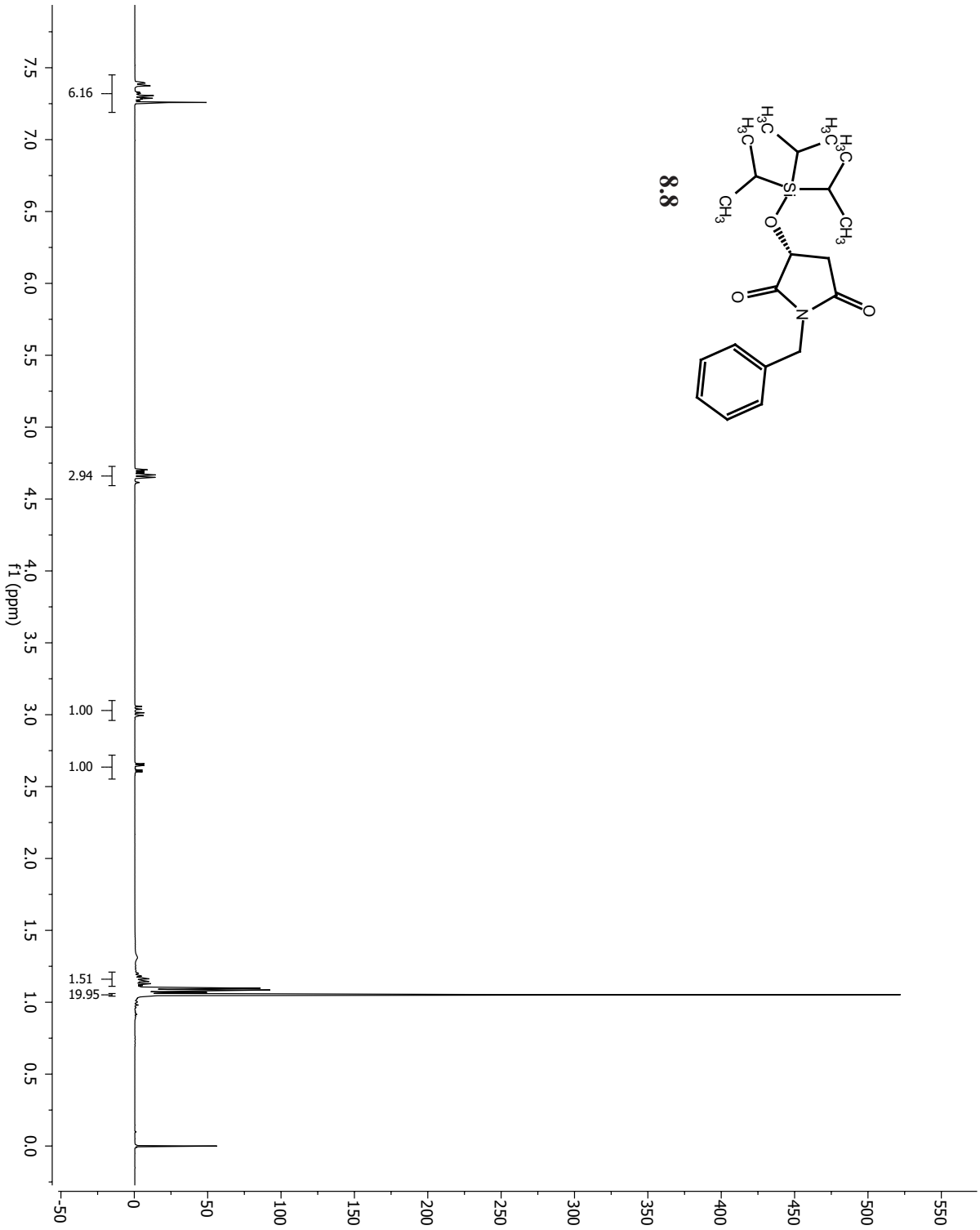


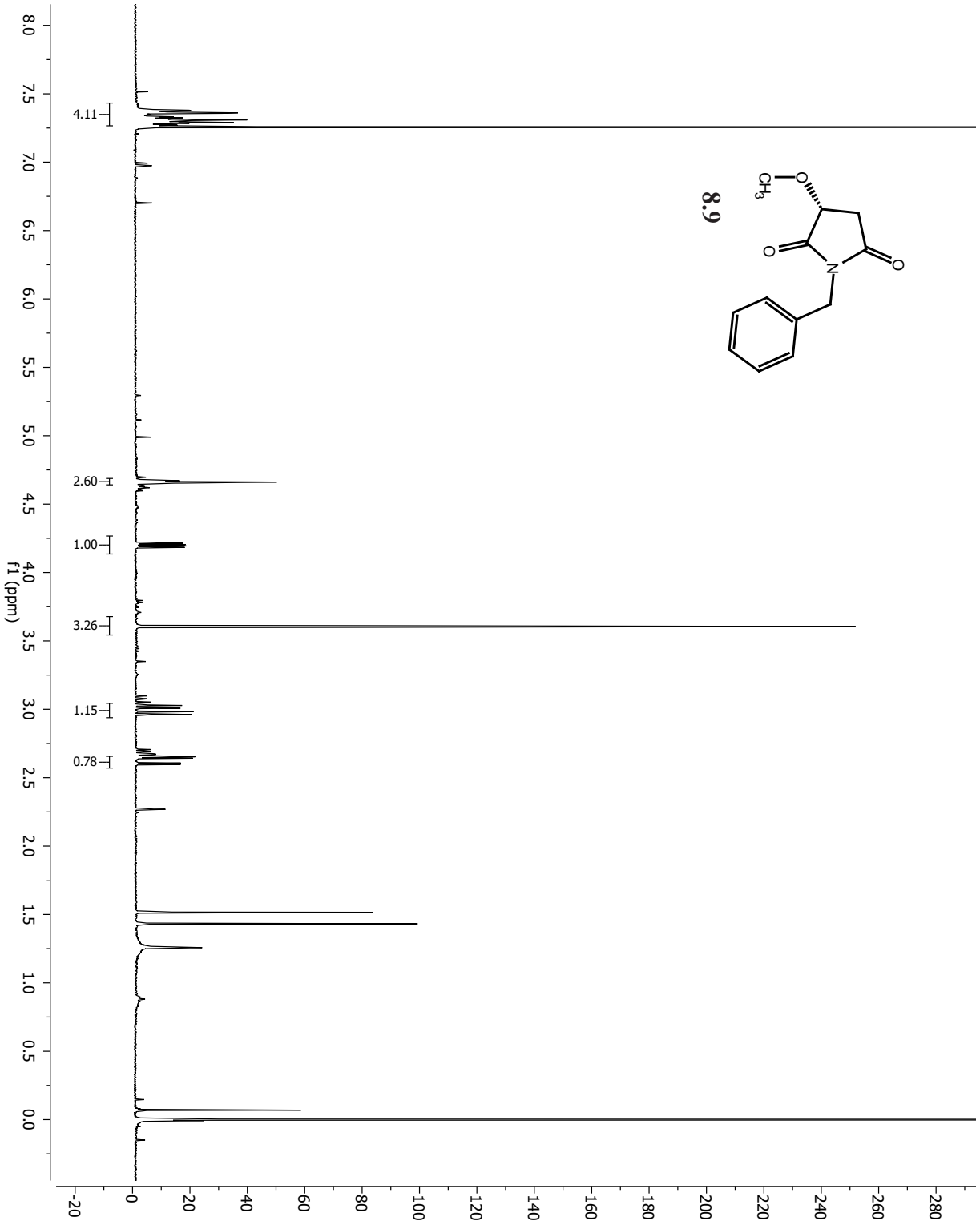
3.2

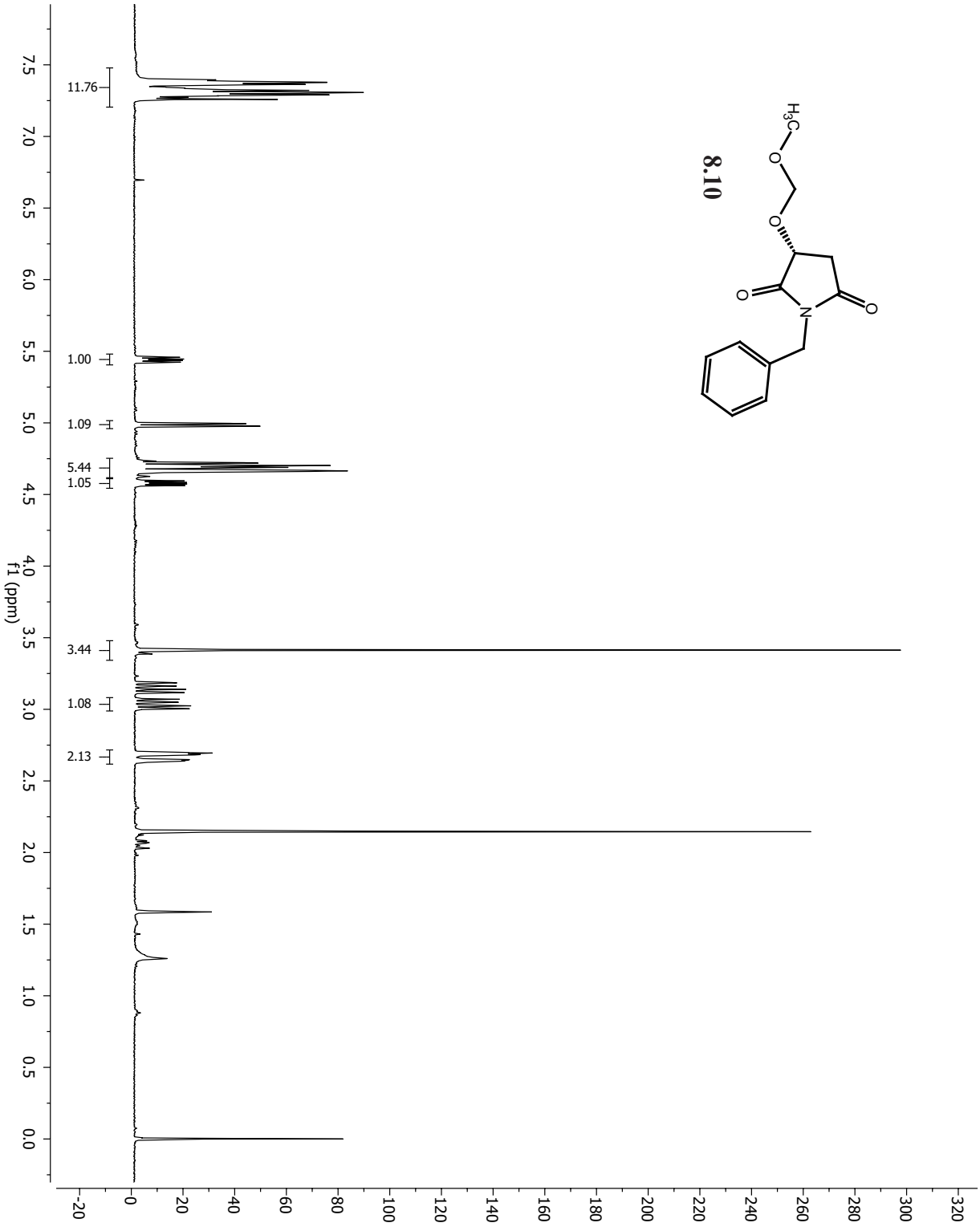

8.5
HO
O
O
N
CH3
5.14
1.00
1.02
1.01
1.00
0.95
3.02
f1 (ppm)

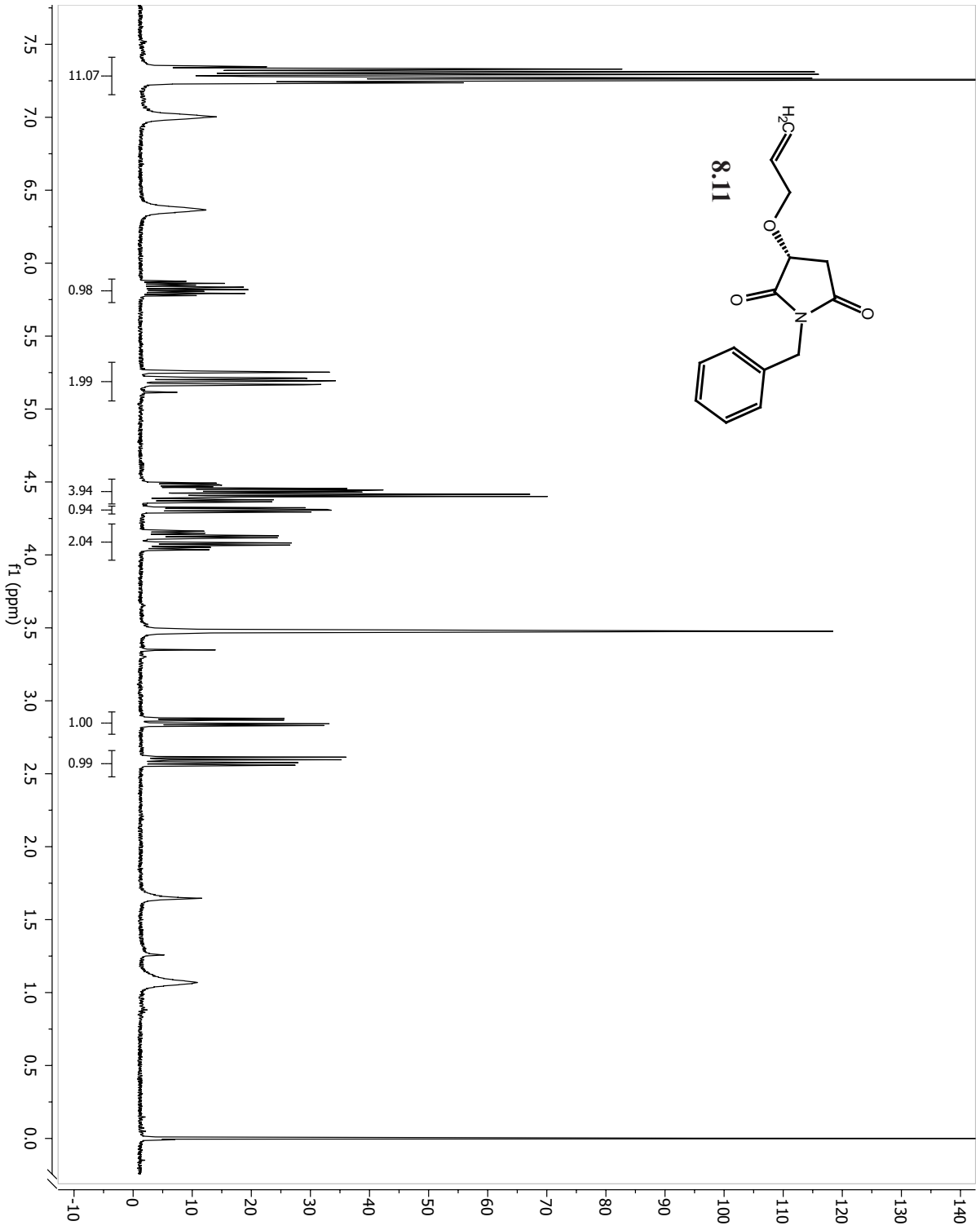

8.6
HO
O
CH3
N
O
6.46
1.00
1.20
0.97
1.36
1.67
1.92
1.00
0.98
3.04
f1 (ppm)

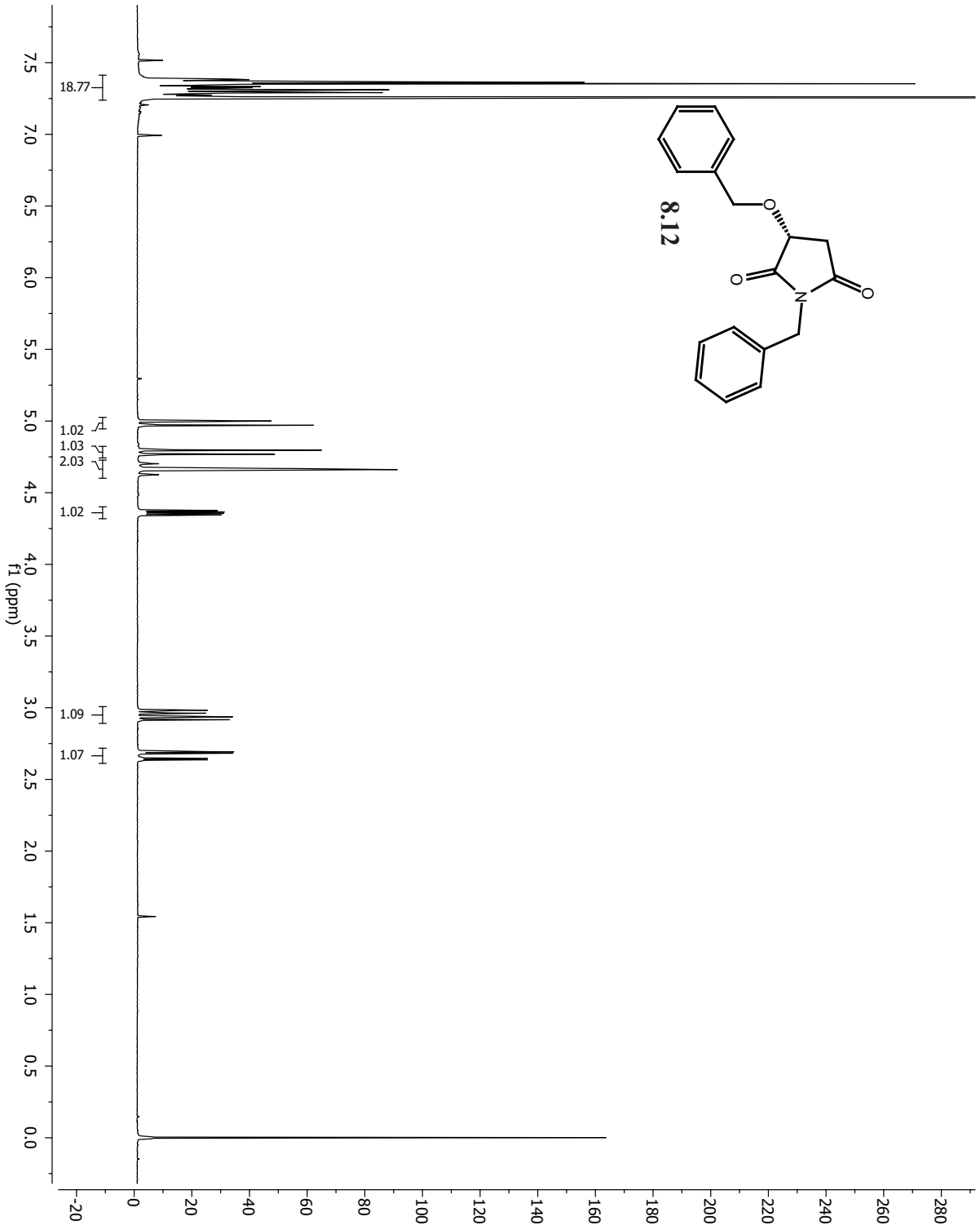

8.7
5.30
1.89
0.91
1.00
1.00
9.12
5.88
f1 (ppm)

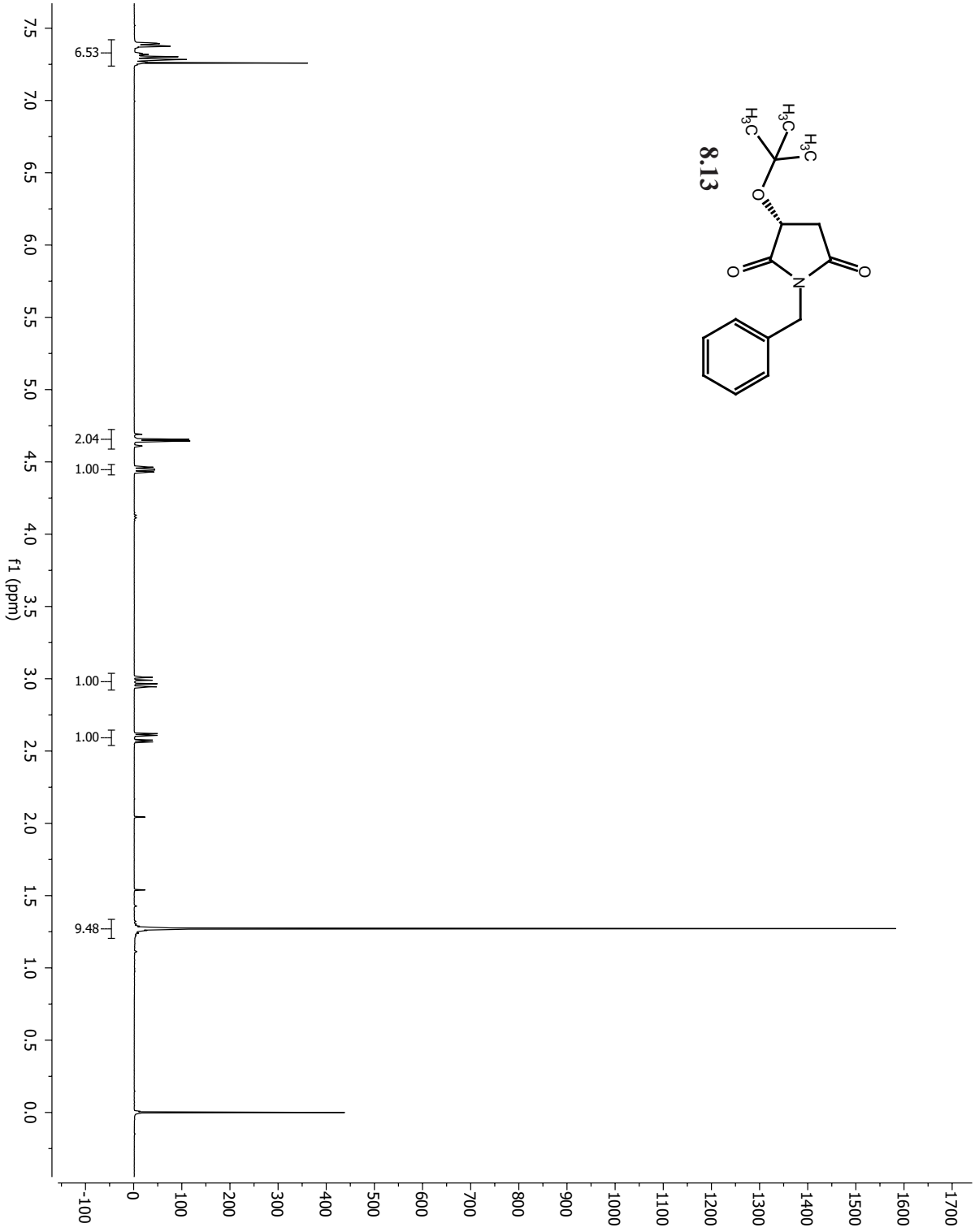

6.16
2.94
1.00
1.00
1.51
19.95
f1 (ppm)
8.8

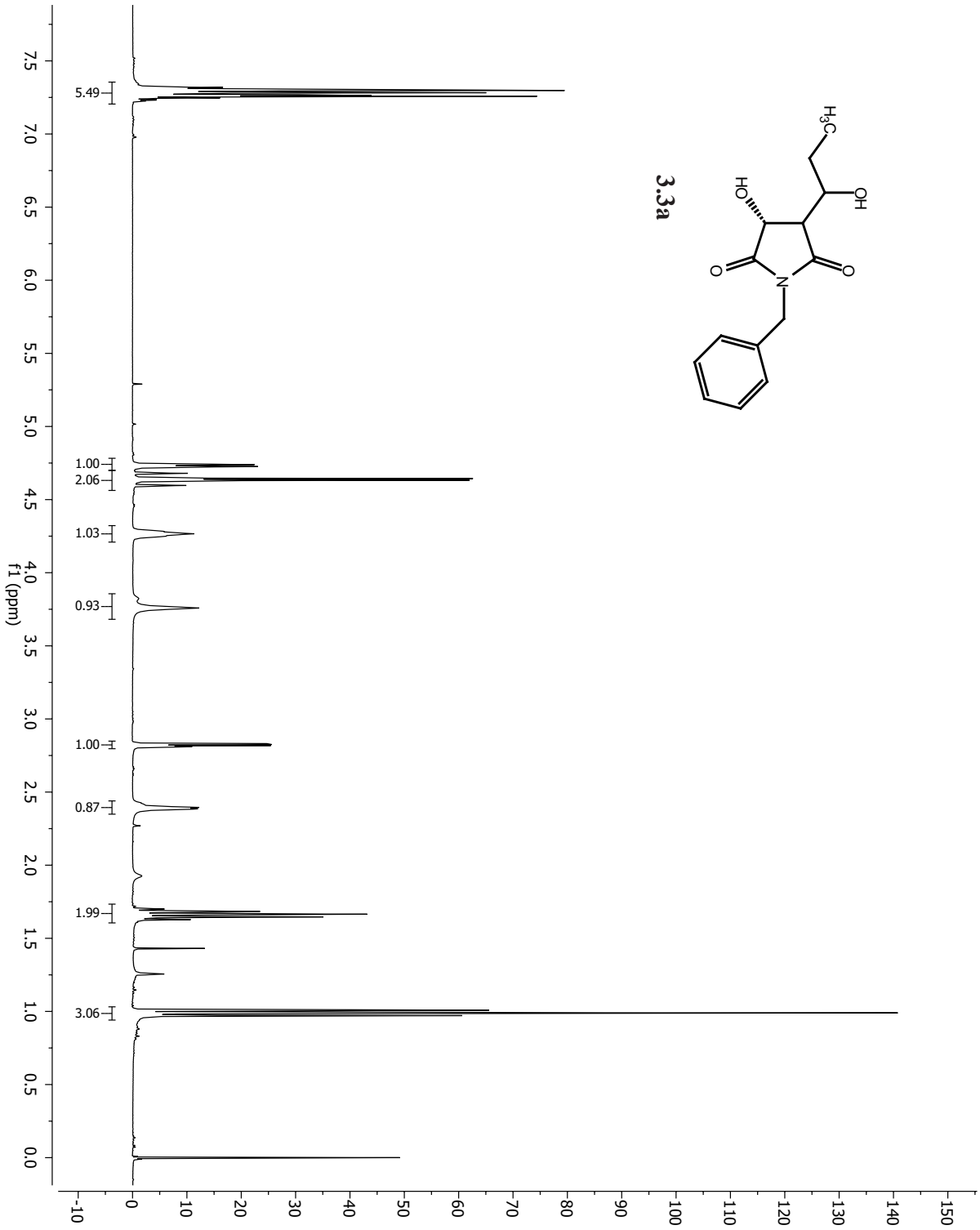

8.9
4.11
2.60
1.00
3.26
1.15
0.78
f1 (ppm)

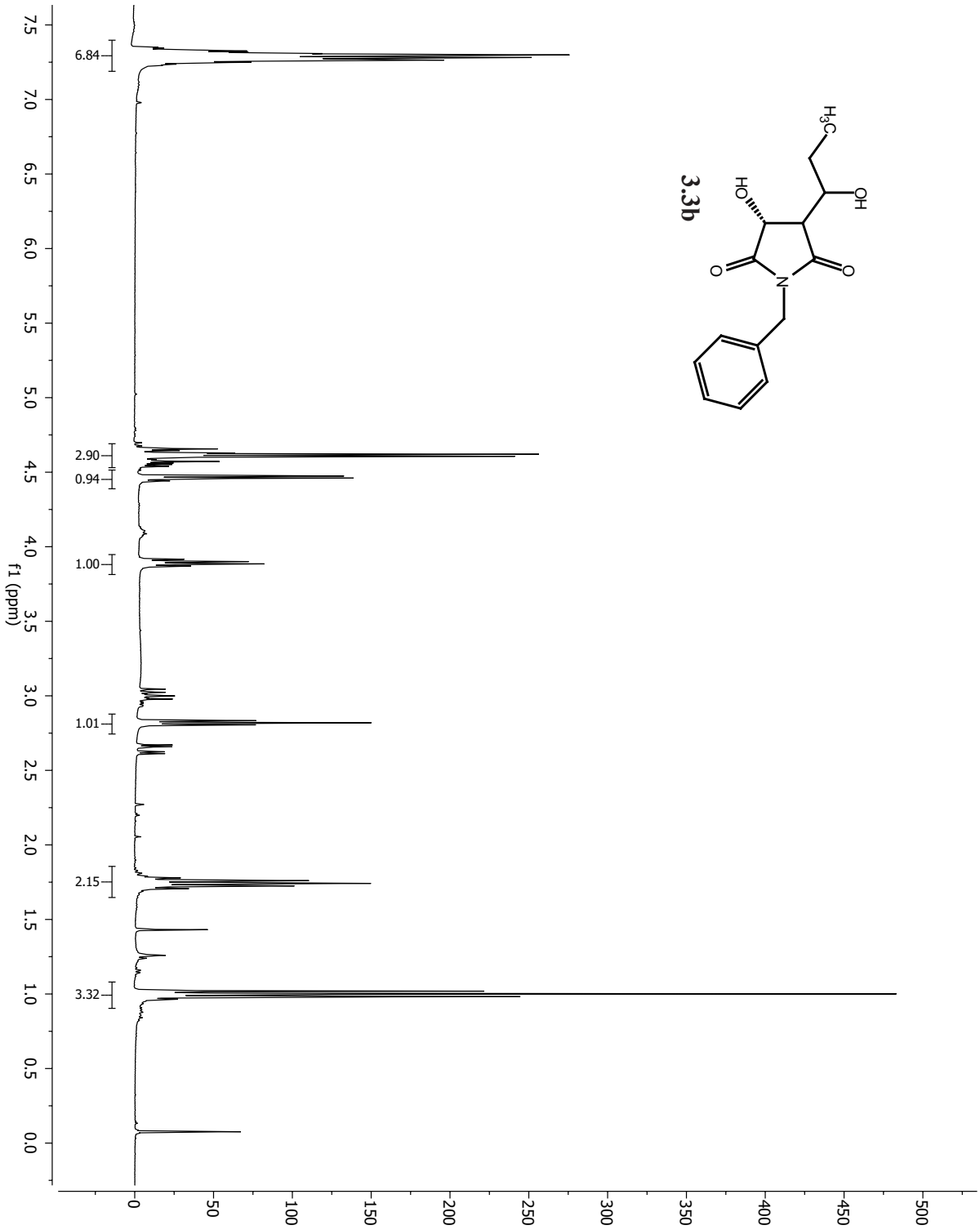

8.10
11.76
1.00
1.09
5.44
1.05
3.44
1.08
2.13
f1 (ppm)

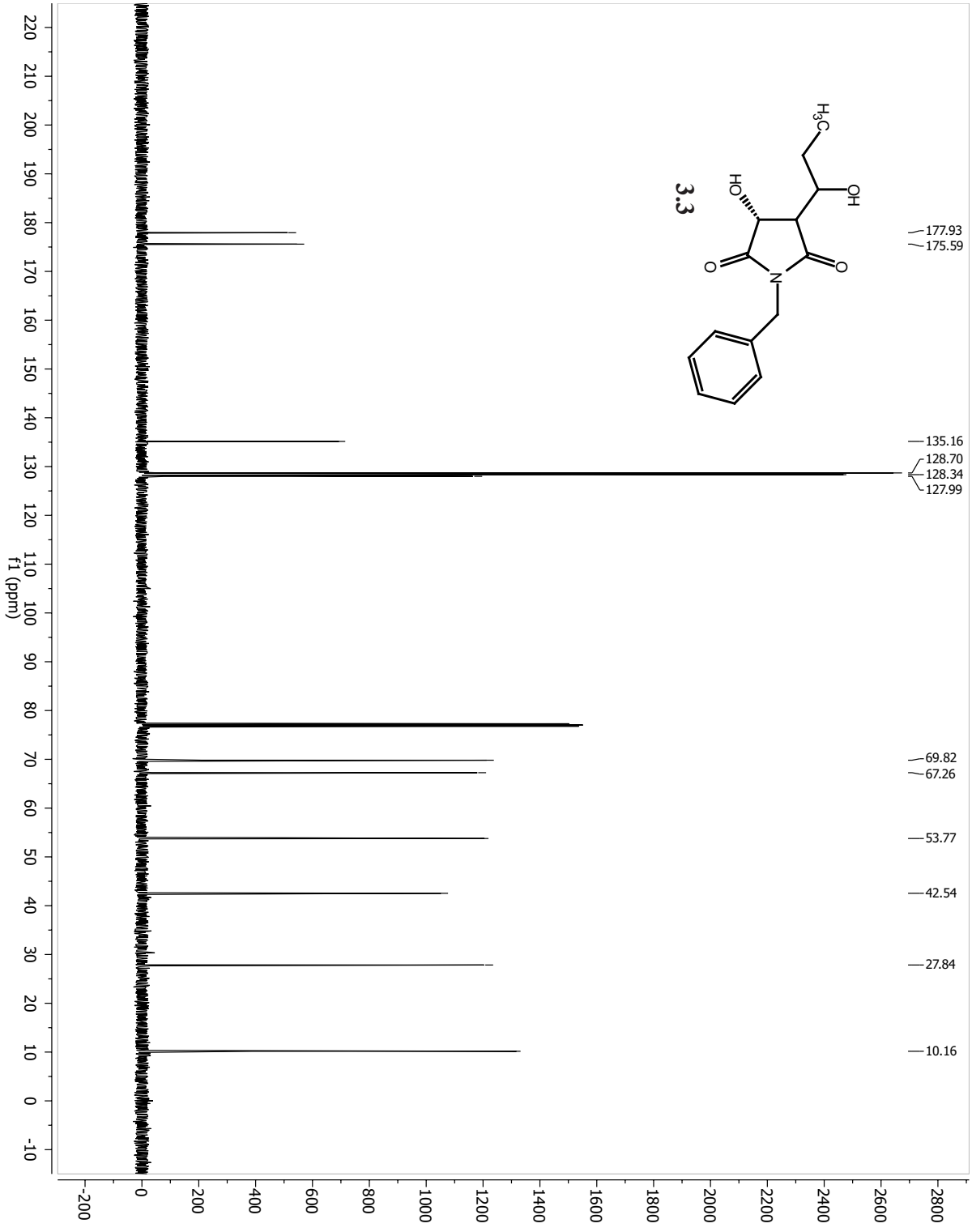

8.11
11.07
0.98
1.99
3.94
0.94
2.04
1.00
0.99
f1 (ppm)

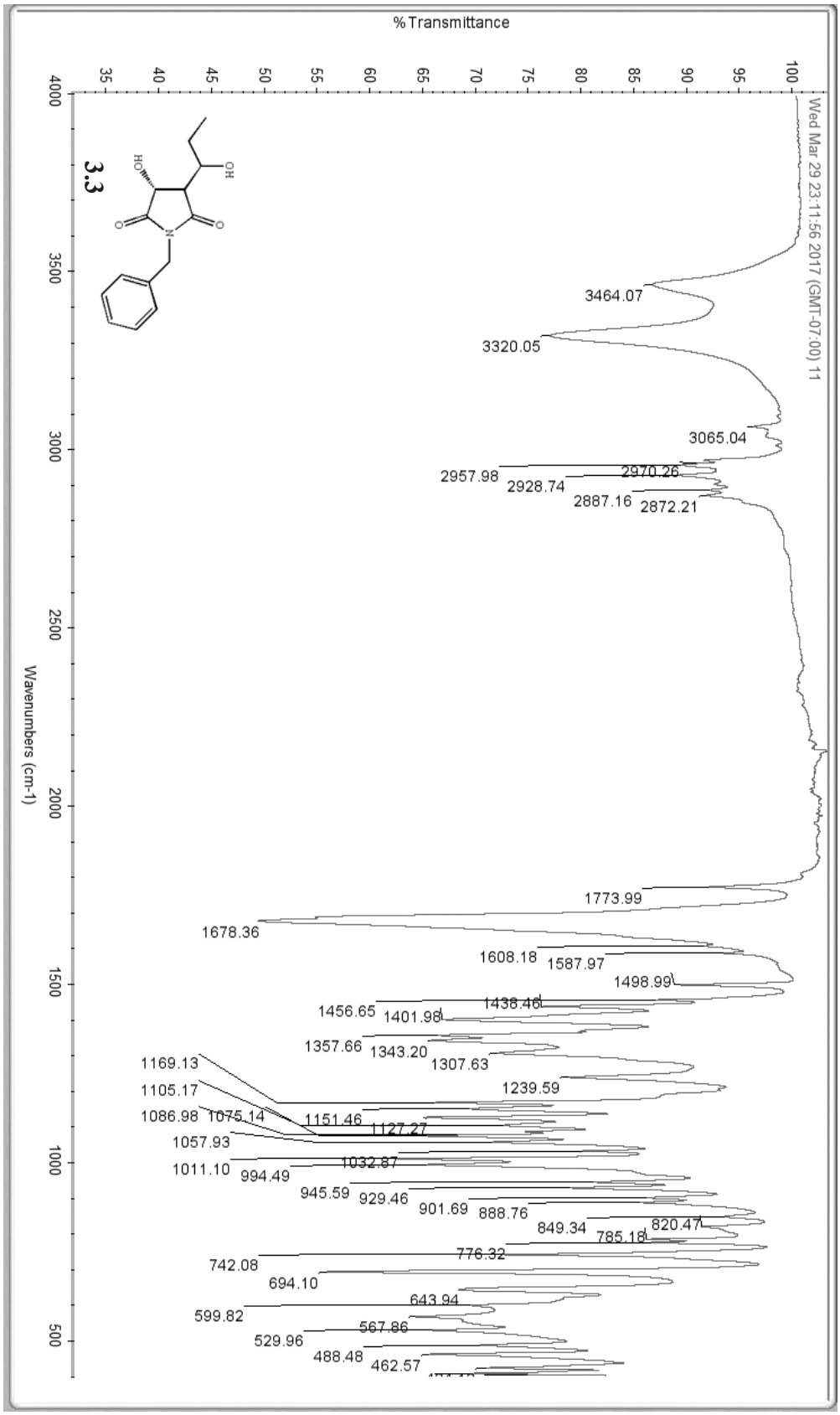

8.12
18.77
1.02
1.03
2.03
1.02
1.09
1.07
f1 (ppm)

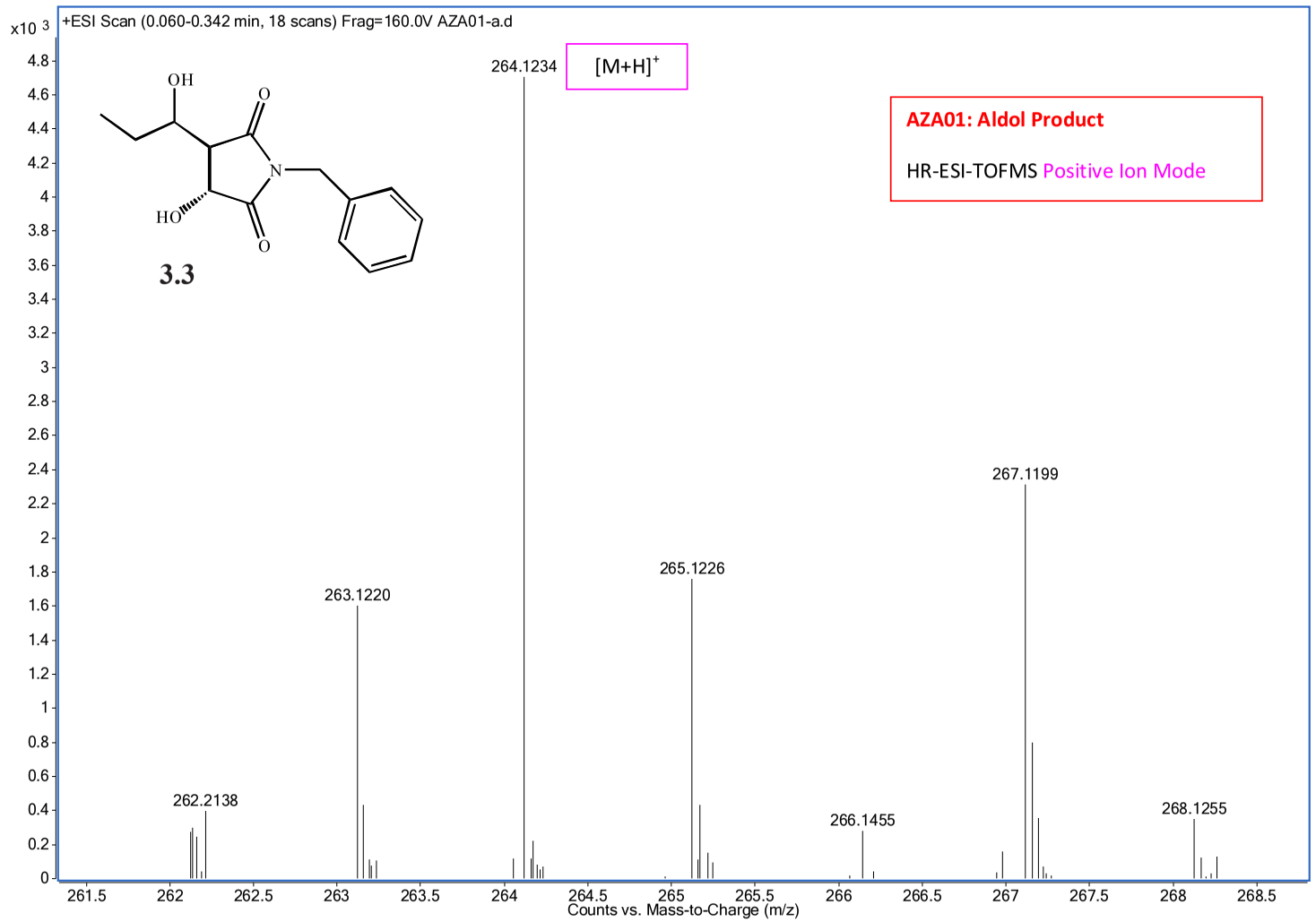

8.13
6.53
2.04
1.00
1.00
1.00
9.48
f1 (ppm)


3.3a
HO
OH
H3C
O
O
N
5.49
1.00
2.06
1.03
0.93
1.00
0.87
1.99
3.06
f1 (ppm)


6.84
2.90
0.94
1.00
1.01
2.15
3.32
f1 (ppm)
3.3b
HO
OH
H3C
O
O
N

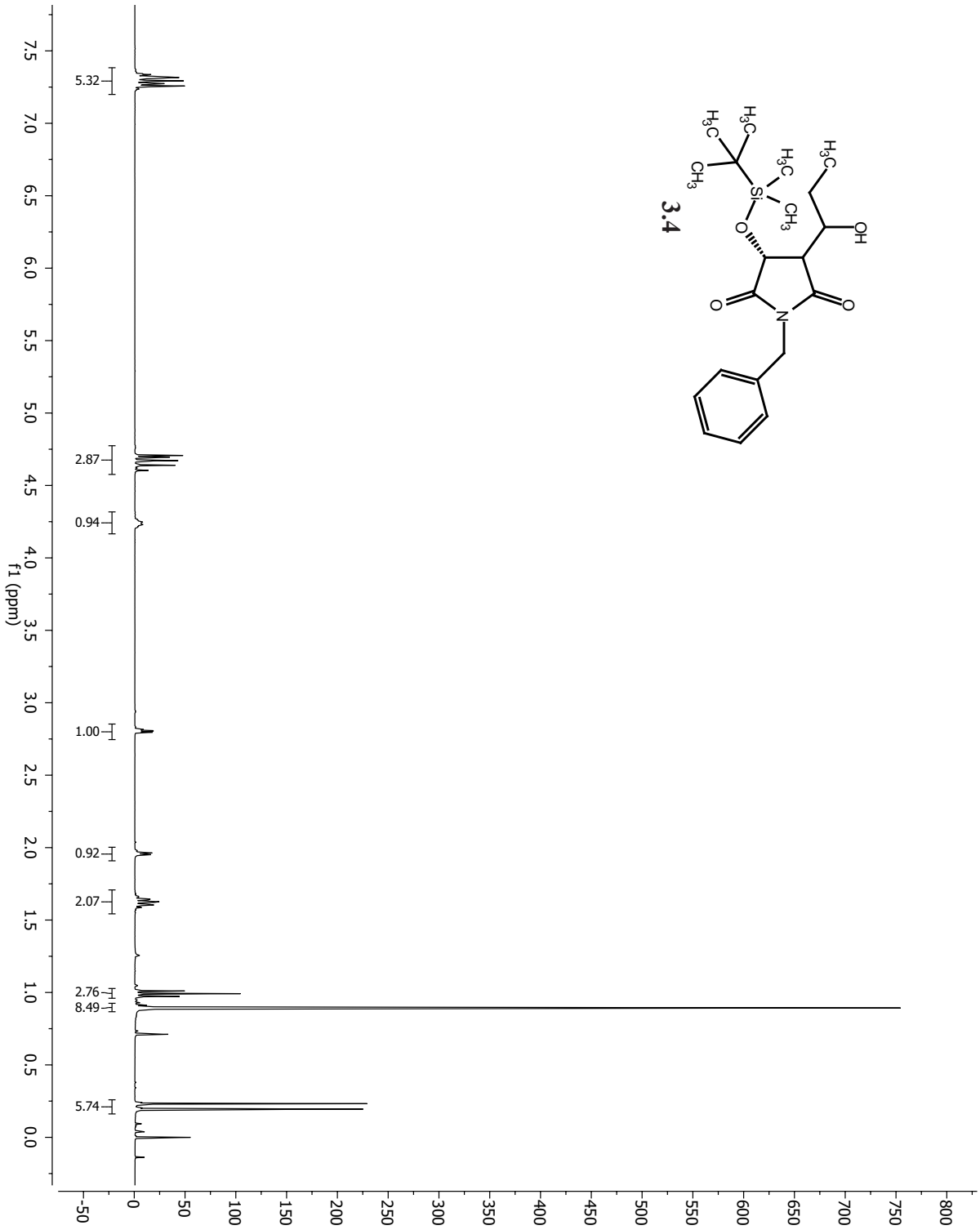

3.3
177.93
175.59
135.16
128.70
128.34
127.99
69.82
67.26
53.77
42.54
27.84
10.16
f1 (ppm)

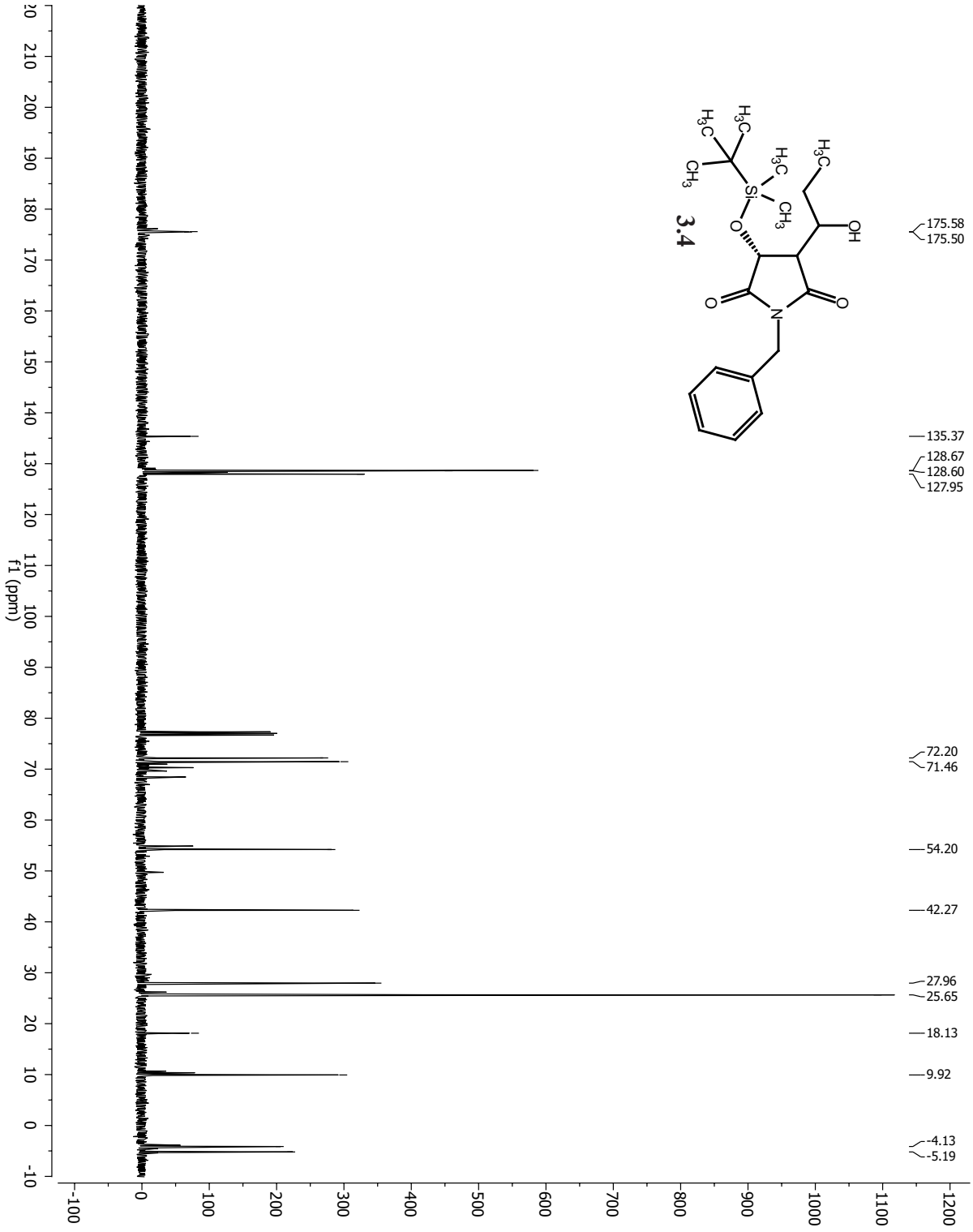

% Transmittance
Wavenumbers (cm-1)
Wed Mar 29 23:11:56 2017 (GMT-07:00) 11
3.3
3464.07
3320.05
3065.04
2957.98
2928.74
2970.26
2887.16
2872.21
1773.99
1678.36
1608.18
1587.97
1498.99
1456.65
1438.46
1401.98
1357.66
1343.20
1307.63
1239.59
1169.13
1105.17
1086.98
1075.14
1151.46
1127.27
1057.93
1011.10
1032.87
994.49
945.59
929.46
901.69
888.76
849.34
820.47
785.18
776.32
742.08
694.10
643.94
599.82
567.86
529.96
488.48
462.57

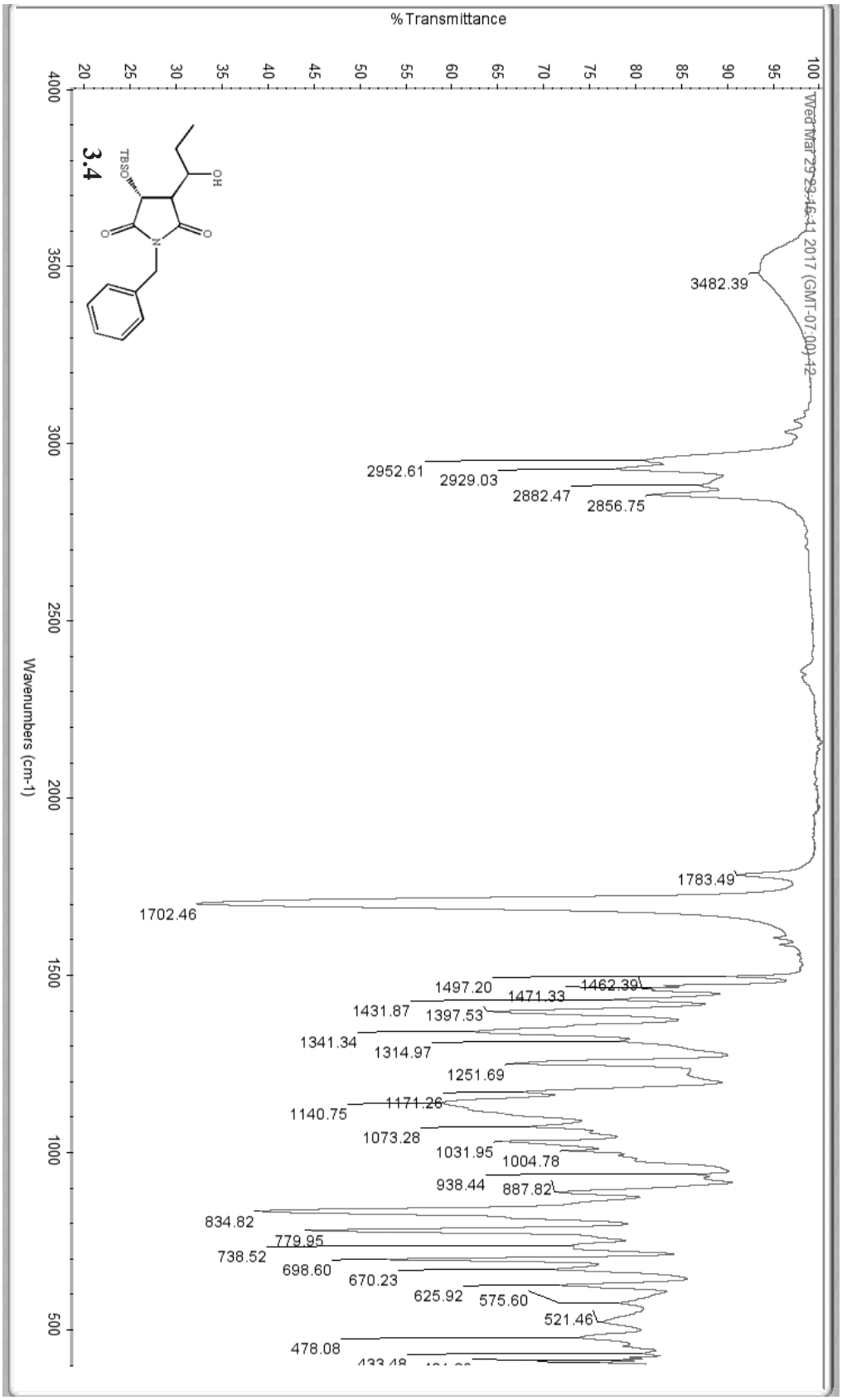


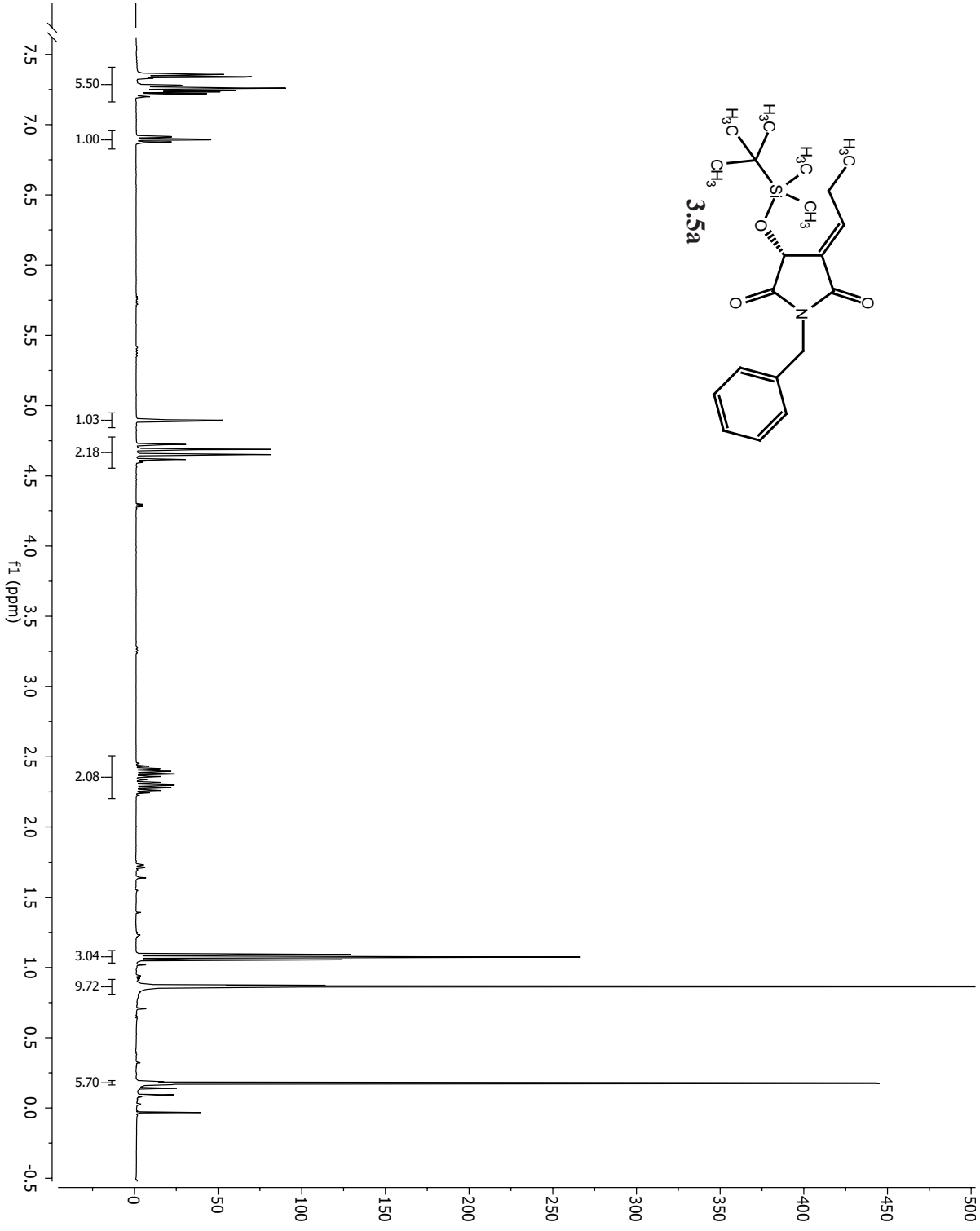
Search Results: **Sample AZA01: Aldol Product**

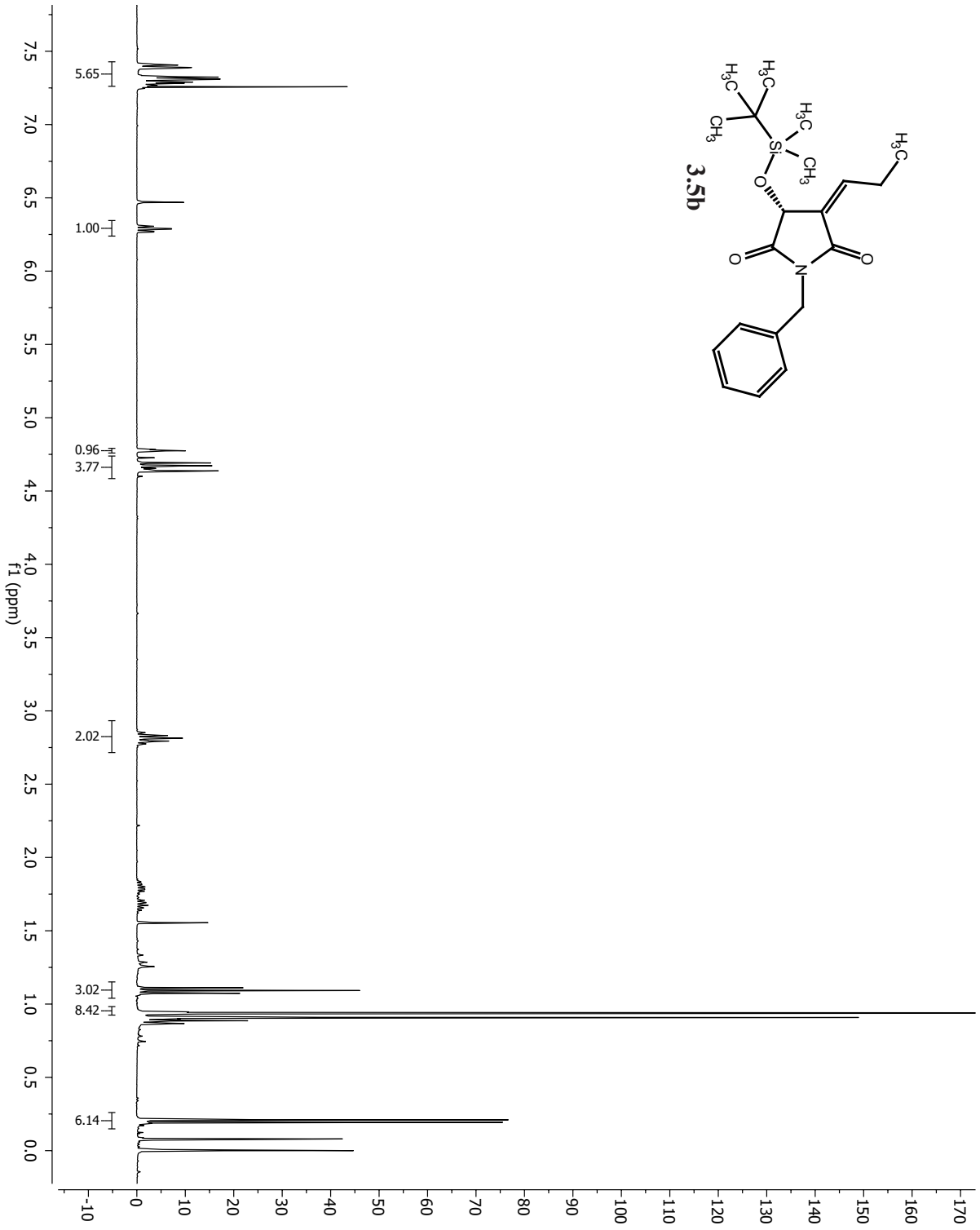
Mass Measured	Theo. Mass	Delta (ppm)	Composition
264.1234	264.1230	1.7	$[C_{14}H_{18}NO_4]^+$

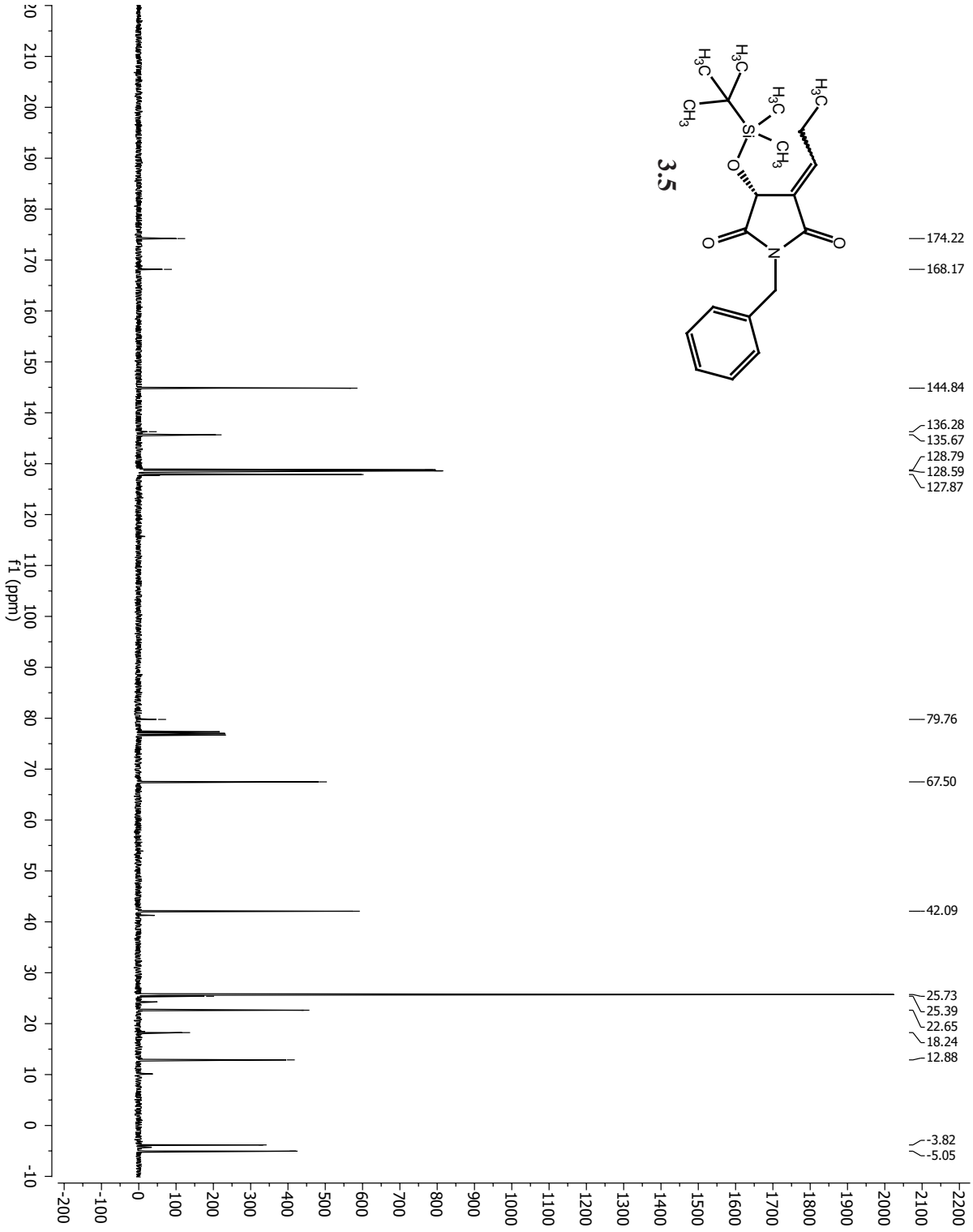

5.32
2.87
0.94
1.00
0.92
2.07
2.76
8.49
5.74
f1 (ppm)
3.4
H3C
CH3
Si
O
OH
N

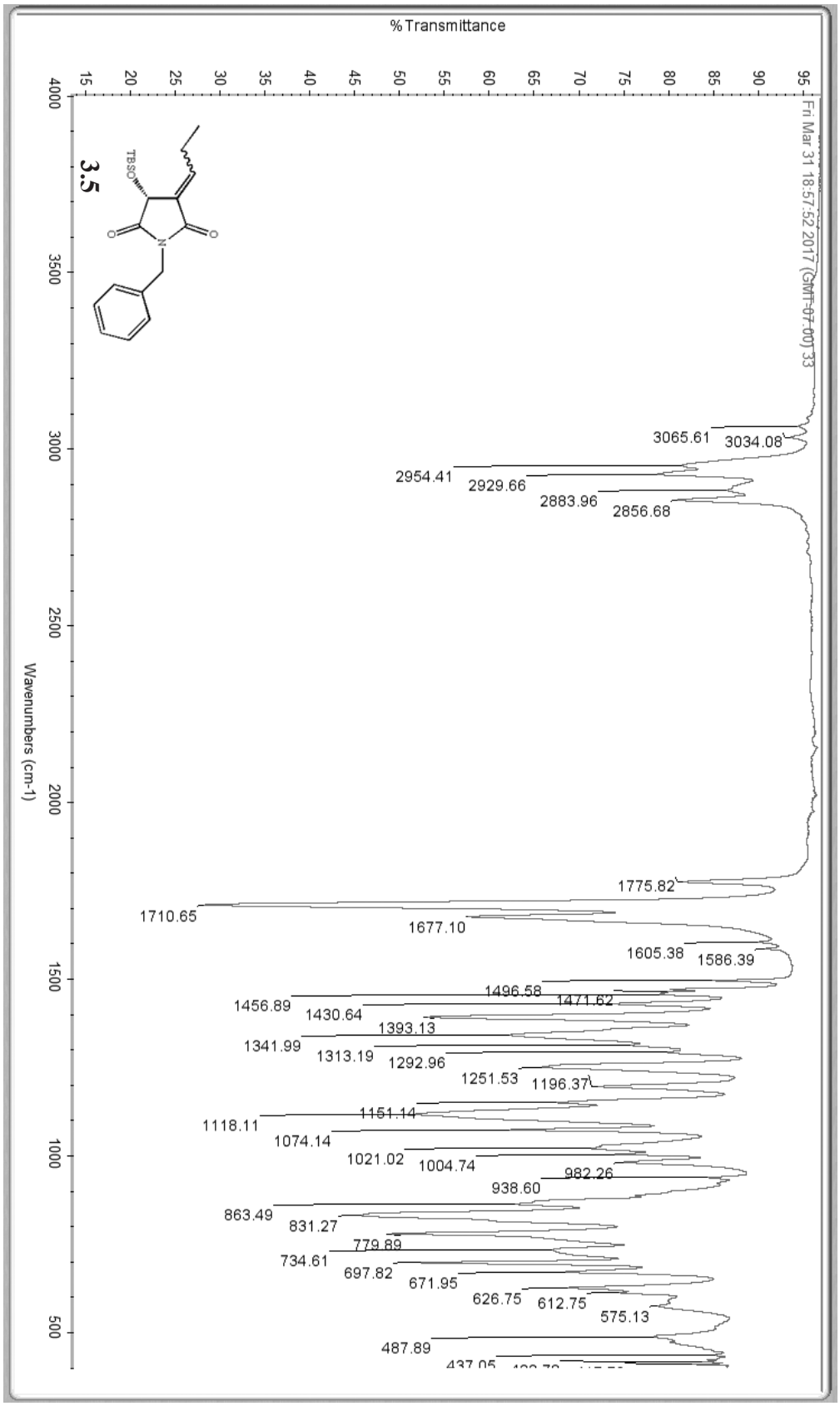

3.4
175.58
175.50
135.37
128.67
128.60
127.95
72.20
71.46
54.20
42.27
27.96
25.65
18.13
9.92
-4.13
-5.19
f1 (ppm)

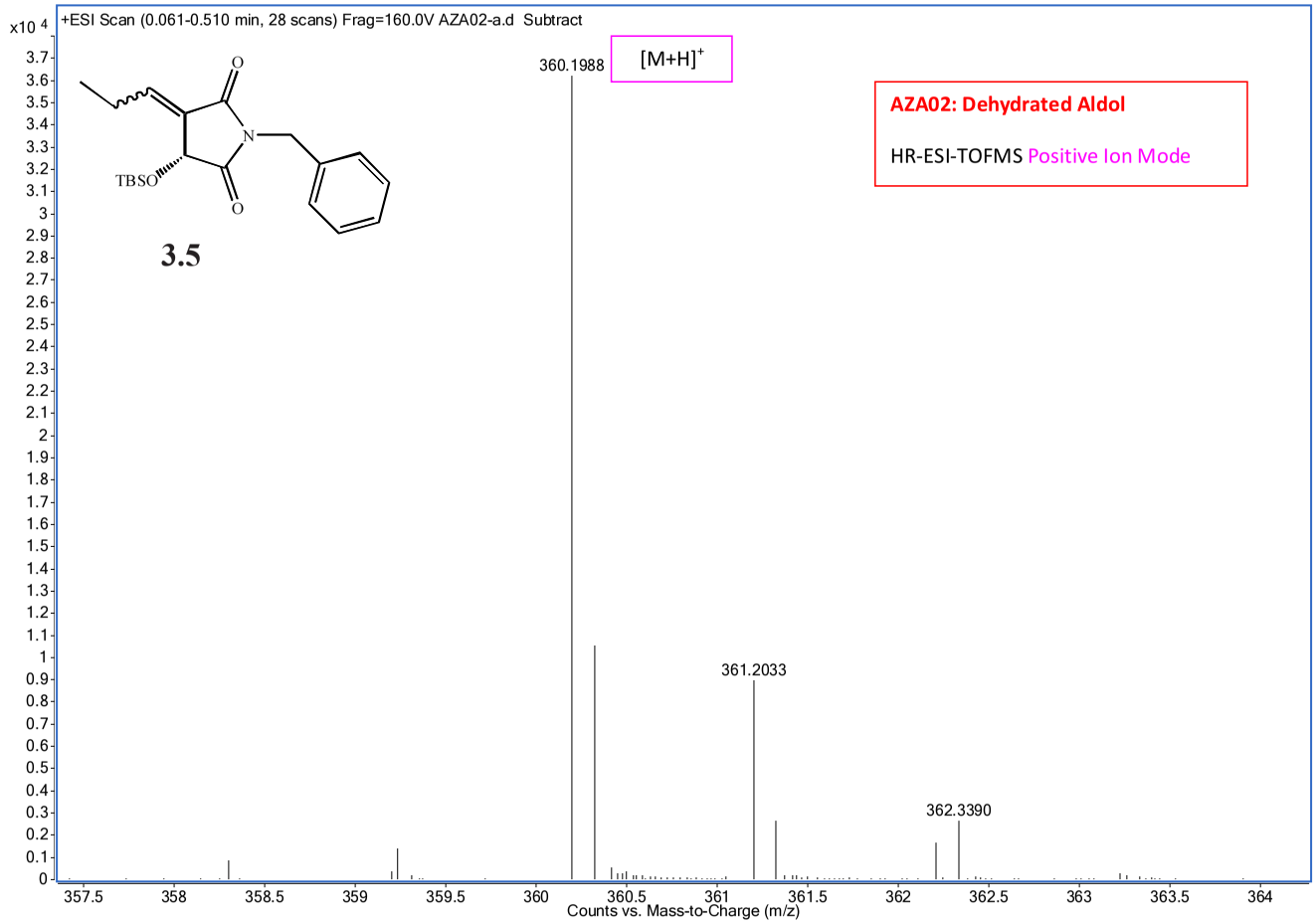

% Transmittance
Wavenumbers (cm-1)
3.4
TBSO
OH
Wed Mar 29 23:16:11 2017 (GMT-07:00) 42
3482.39
2952.61
2929.03
2882.47
2856.75
1783.49
1702.46
1497.20
1462.39
1471.33
1431.87
1397.53
1341.34
1314.97
1251.69
1171.26
1140.75
1073.28
1031.95
1004.78
938.44
887.82
834.82
779.95
738.52
698.60
670.23
625.92
575.60
521.46
478.08


5.50
1.00
1.03
2.18
2.08
3.04
9.72
5.70
f1 (ppm)
3.5a


3.5b
5.65
1.00
0.96
3.77
2.02
3.02
8.42
6.14
f1 (ppm)

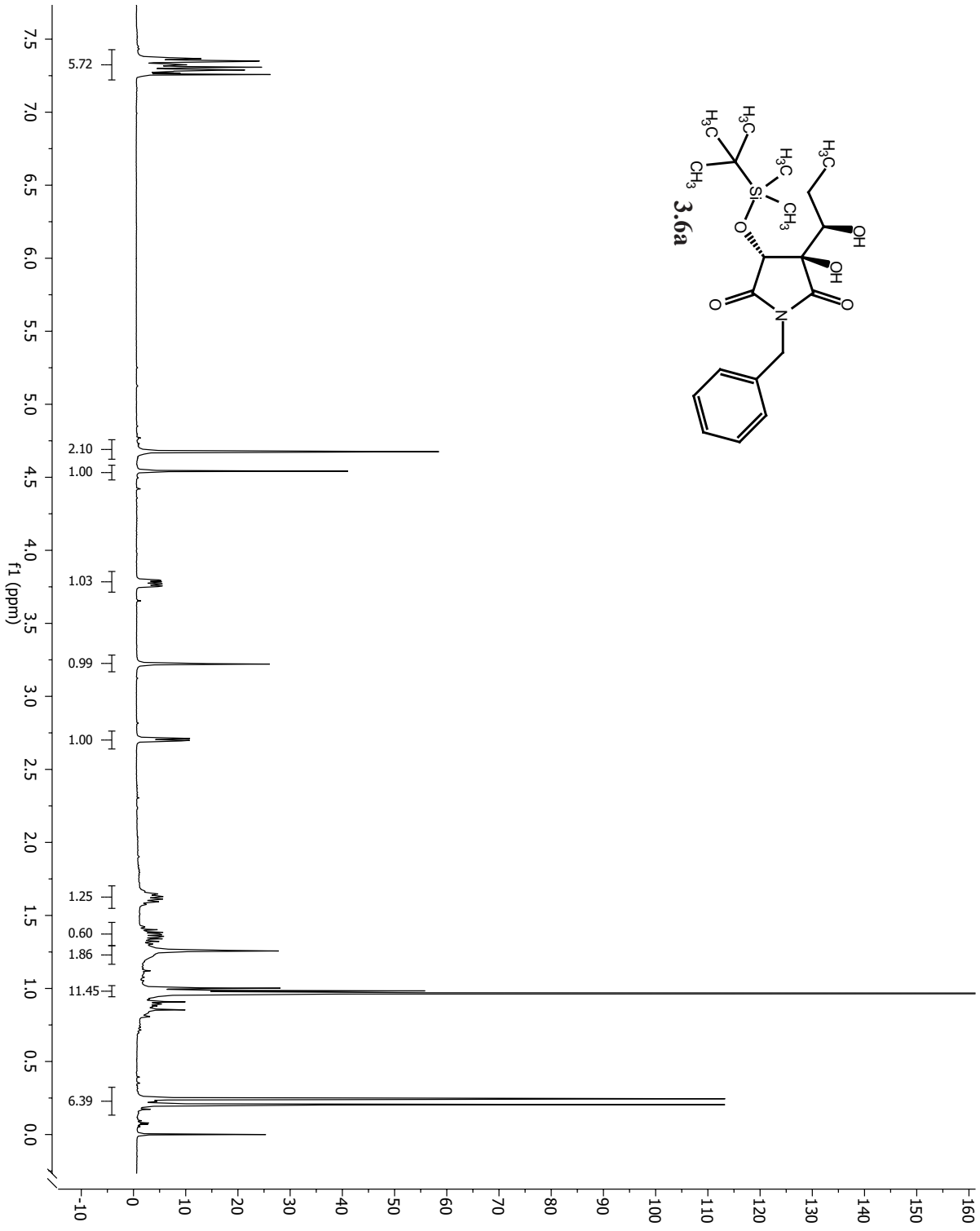

3.5
174.22
168.17
144.84
136.28
135.67
128.79
128.59
127.87
79.76
67.50
42.09
25.73
25.39
22.65
18.24
12.88
-3.82
-5.05
f1 (ppm)

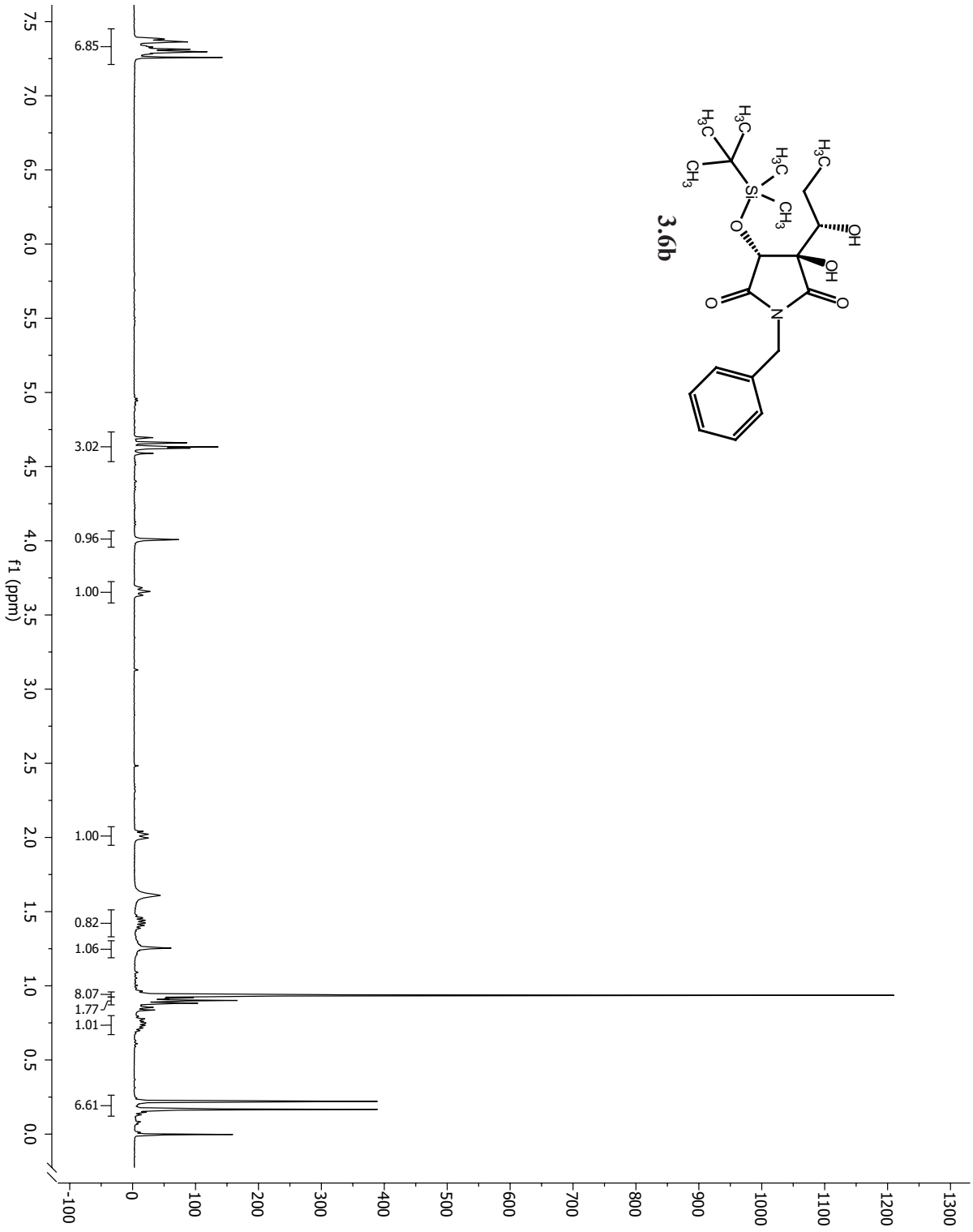

% Transmittance
Wavenumbers (cm-1)
3.5
TBSO
3065.61
3034.08
2954.41
2929.66
2883.96
2856.68
1775.82
1710.65
1677.10
1605.38
1586.39
1496.58
1471.62
1456.89
1430.64
1393.13
1341.99
1313.19
1292.96
1251.53
1196.37
1151.14
1118.11
1074.14
1021.02
1004.74
982.26
938.60
863.49
831.27
779.89
734.61
697.82
671.95
626.75
612.75
575.13
487.89

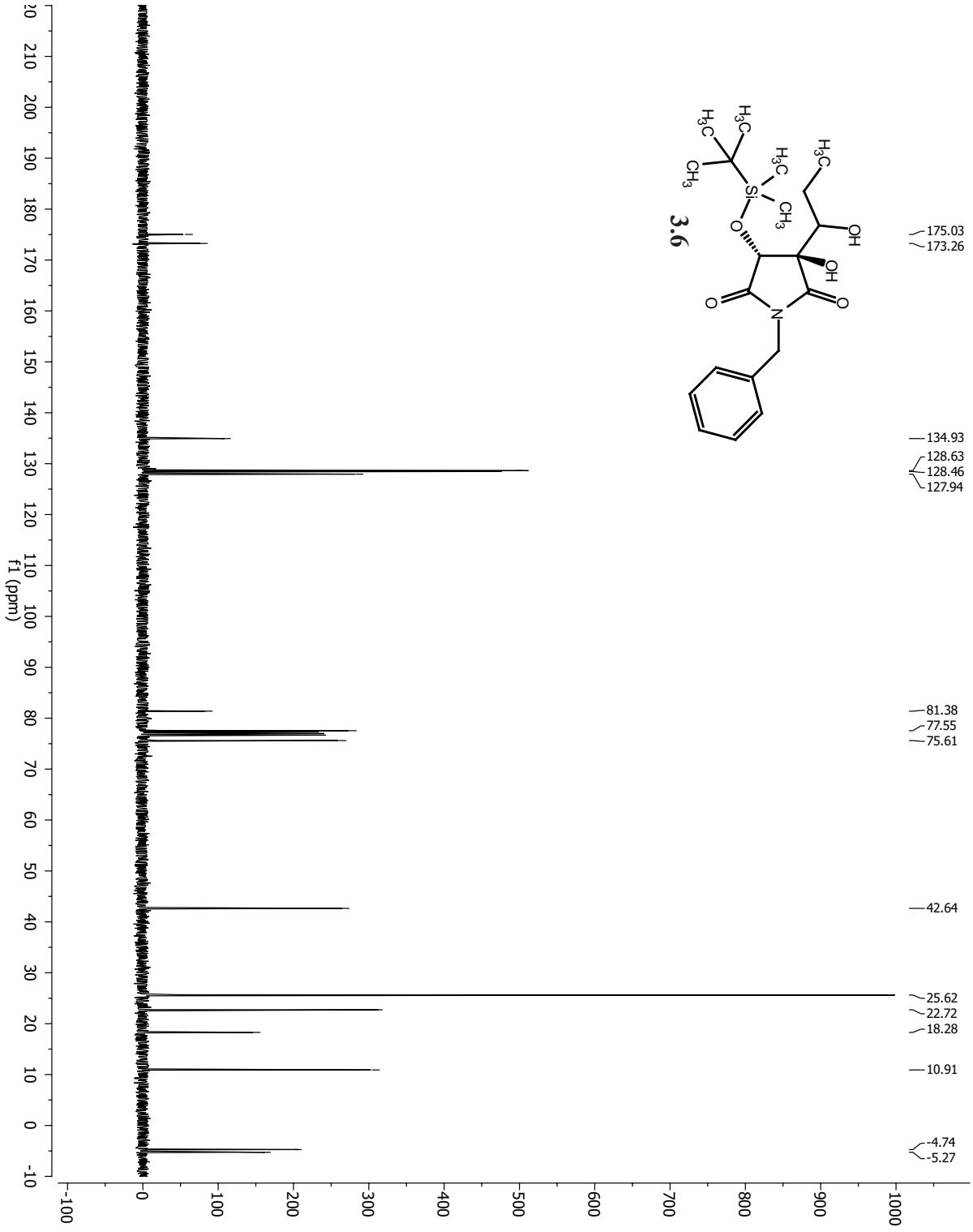


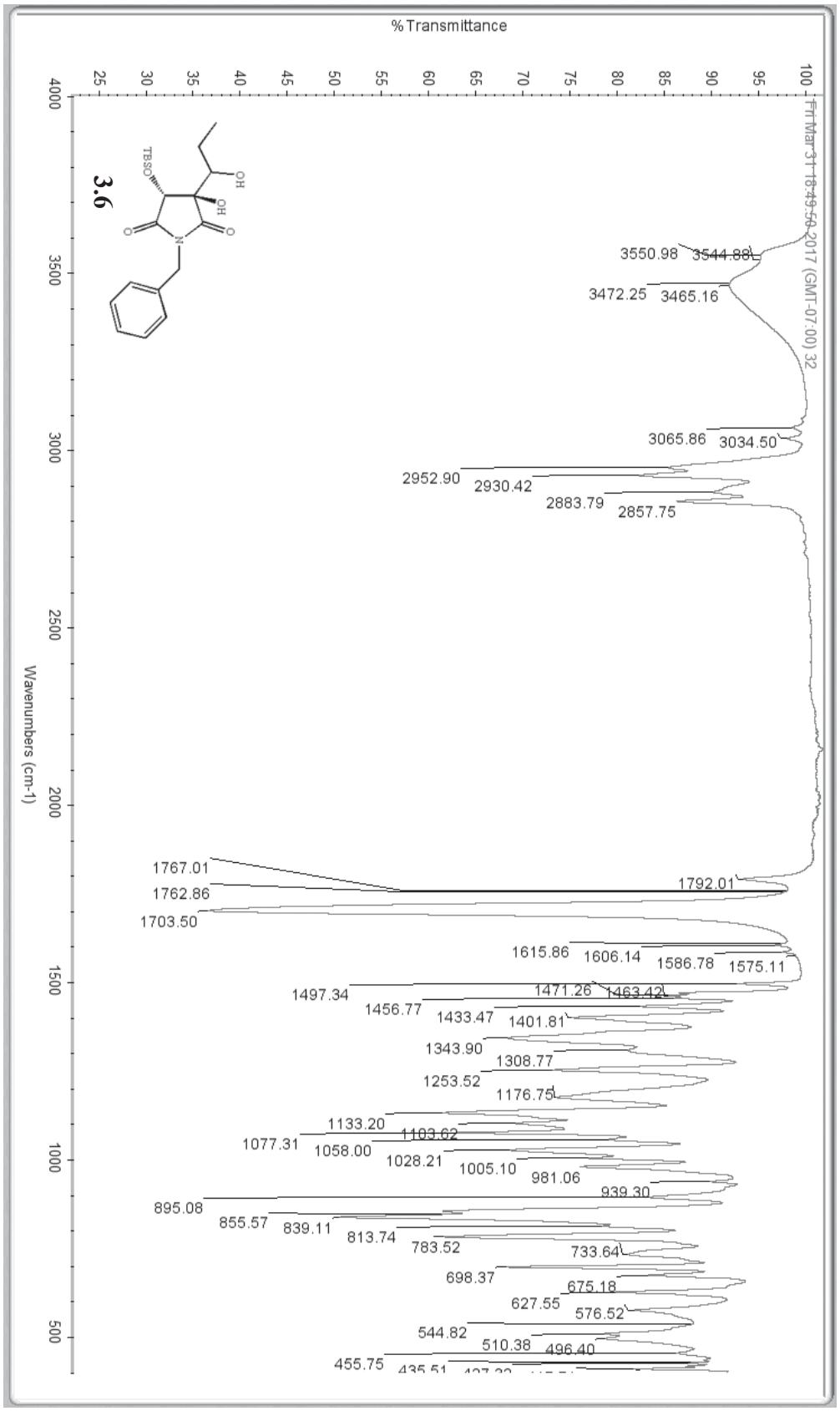
Search Results: **Sample AZA02: Dehydrated Aldol**

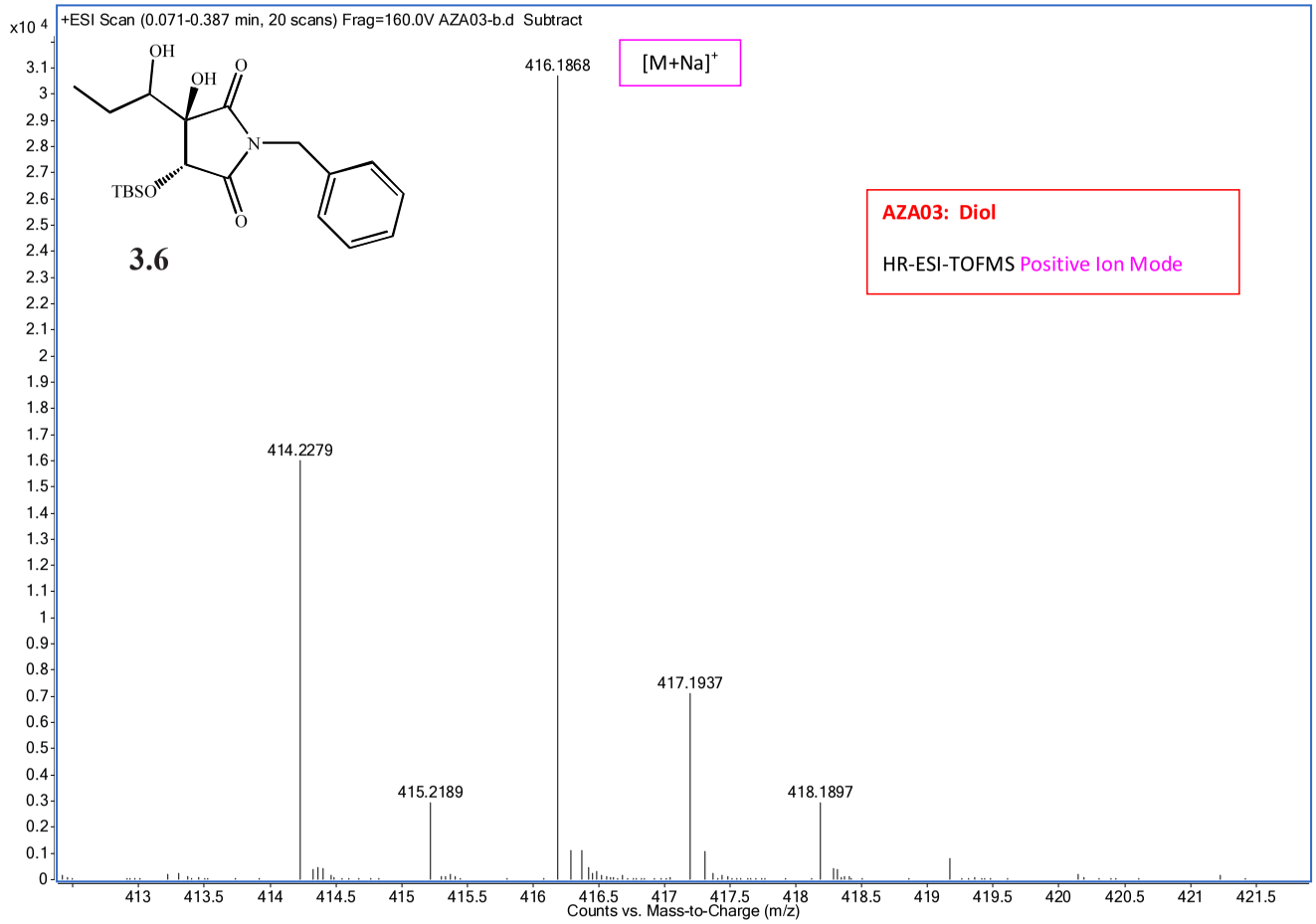
Mass Measured	Theo. Mass	Delta (ppm)	Composition
360.1988	360.1989	-0.3	$[C_{20}H_{30}NO_3Si]^+$


5.72
2.10
1.00
1.03
0.99
1.00
1.25
0.60
1.86
11.45
6.39
f1 (ppm)
3.6a


6.85
3.02
0.96
1.00
1.00
0.82
1.06
8.07
1.77
1.01
6.61
f1 (ppm)
3.6b

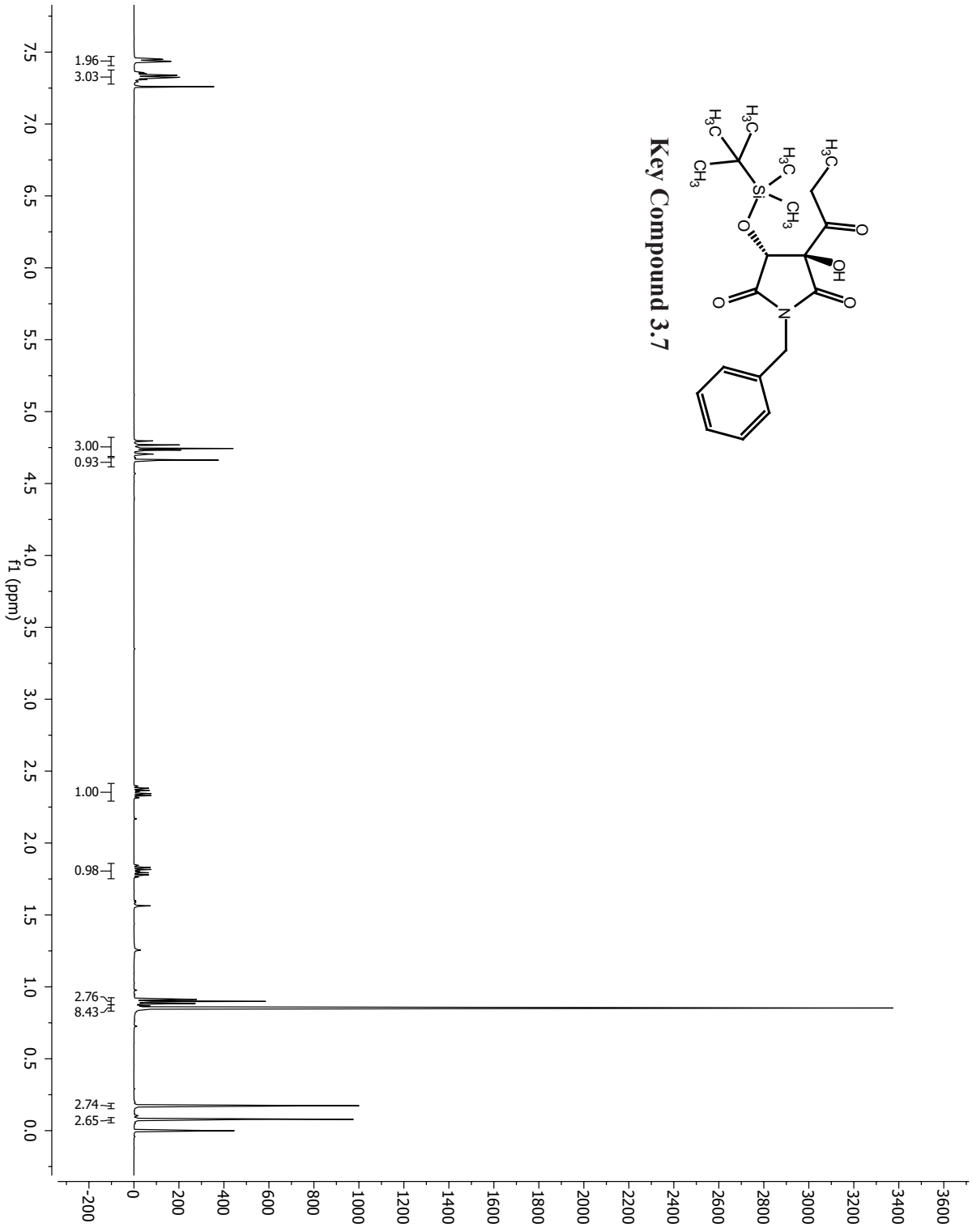

3.6
175.03
173.26
134.93
128.63
128.46
127.94
81.38
77.55
75.61
42.64
25.62
22.72
18.28
10.91
-4.74
-5.27
f1 (ppm)

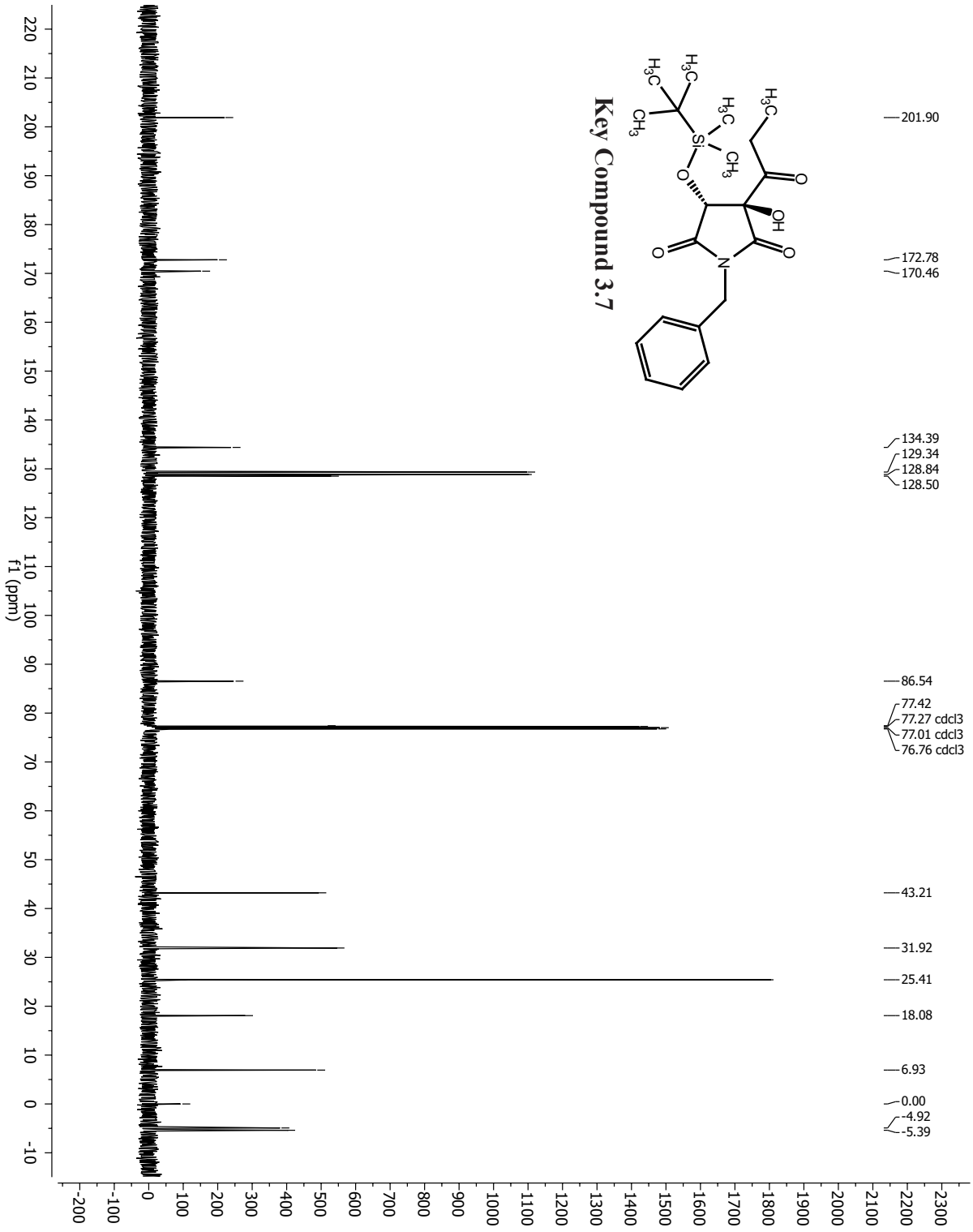

% Transmittance
Wavenumbers (cm-1)
Fri Mar 31 18:49:50 2017 (GMT-07:00) 32
3.6
TBSO
OH
OH
O
O
N
3550.98
3544.88
3472.25
3465.16
3065.86
3034.50
2952.90
2930.42
2883.79
2857.75
1792.01
1767.01
1762.86
1703.50
1615.86
1606.14
1586.78
1575.11
1497.34
1471.26
1463.42
1456.77
1433.47
1401.81
1343.90
1308.77
1253.52
1176.75
1133.20
1103.62
1077.31
1058.00
1028.21
1005.10
981.06
939.30
895.08
855.57
839.11
813.74
783.52
733.64
698.37
675.18
627.55
576.52
544.82
510.38
496.40
455.75

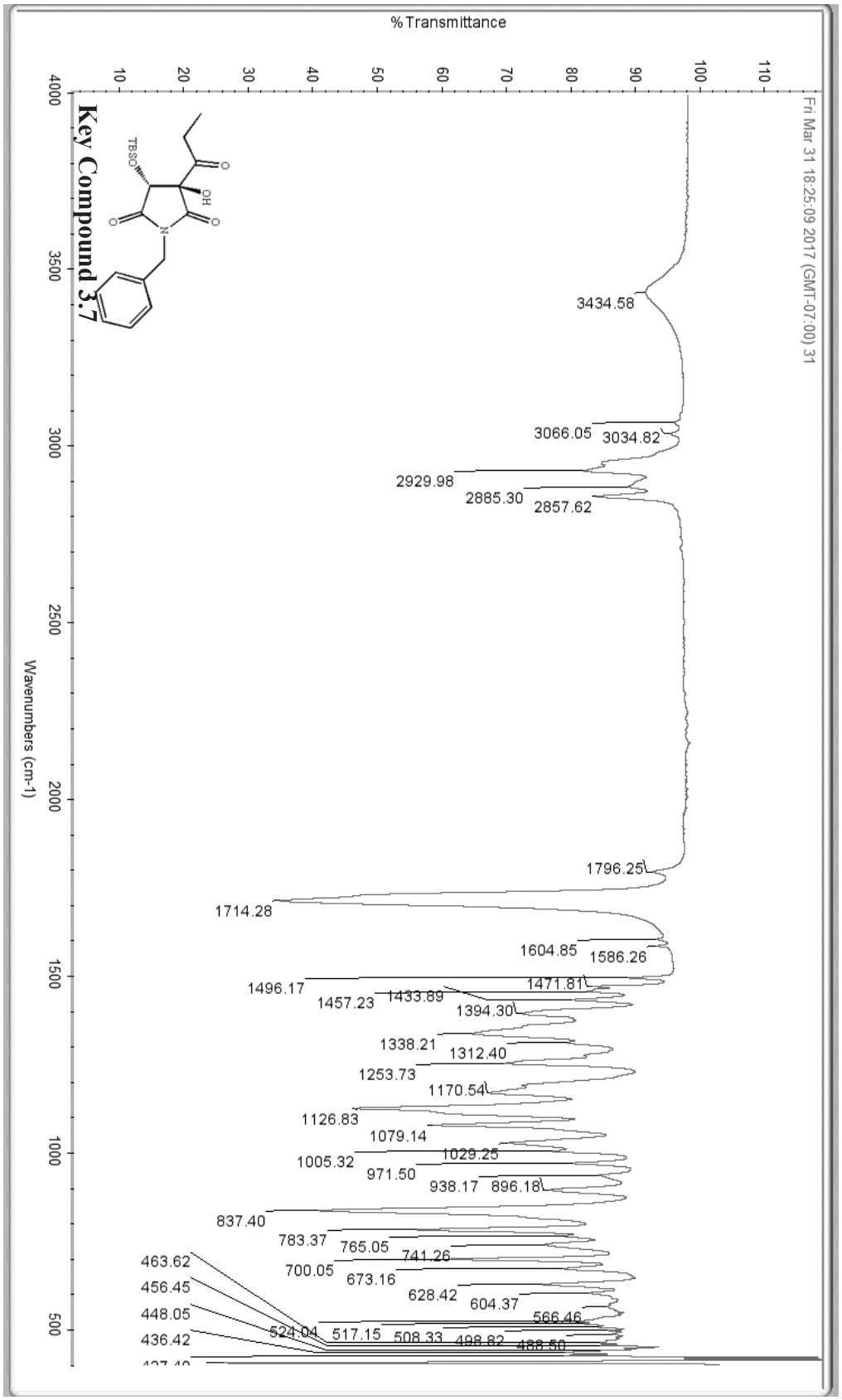


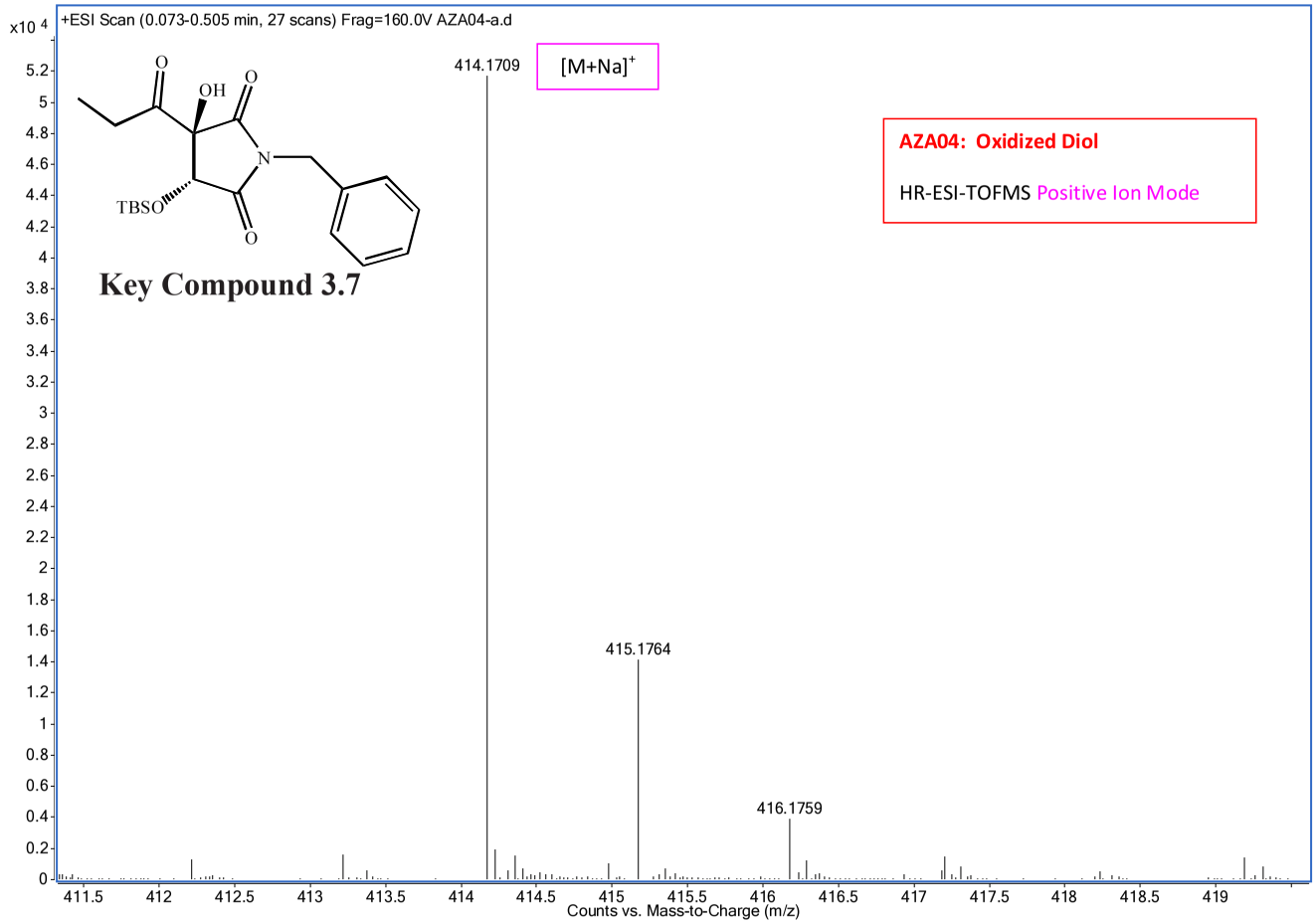
Search Results: **Sample AZA03: Diol**

Mass Measured	Theo. Mass	Delta (ppm)	Composition
416.1868	416.1864	1.0	$[C_{20}H_{31}NO_5SiNa]^+$


Key Compound 3.7
1.96
3.03
3.00
0.93
1.00
0.98
2.76
8.43
2.74
2.65
f1 (ppm)

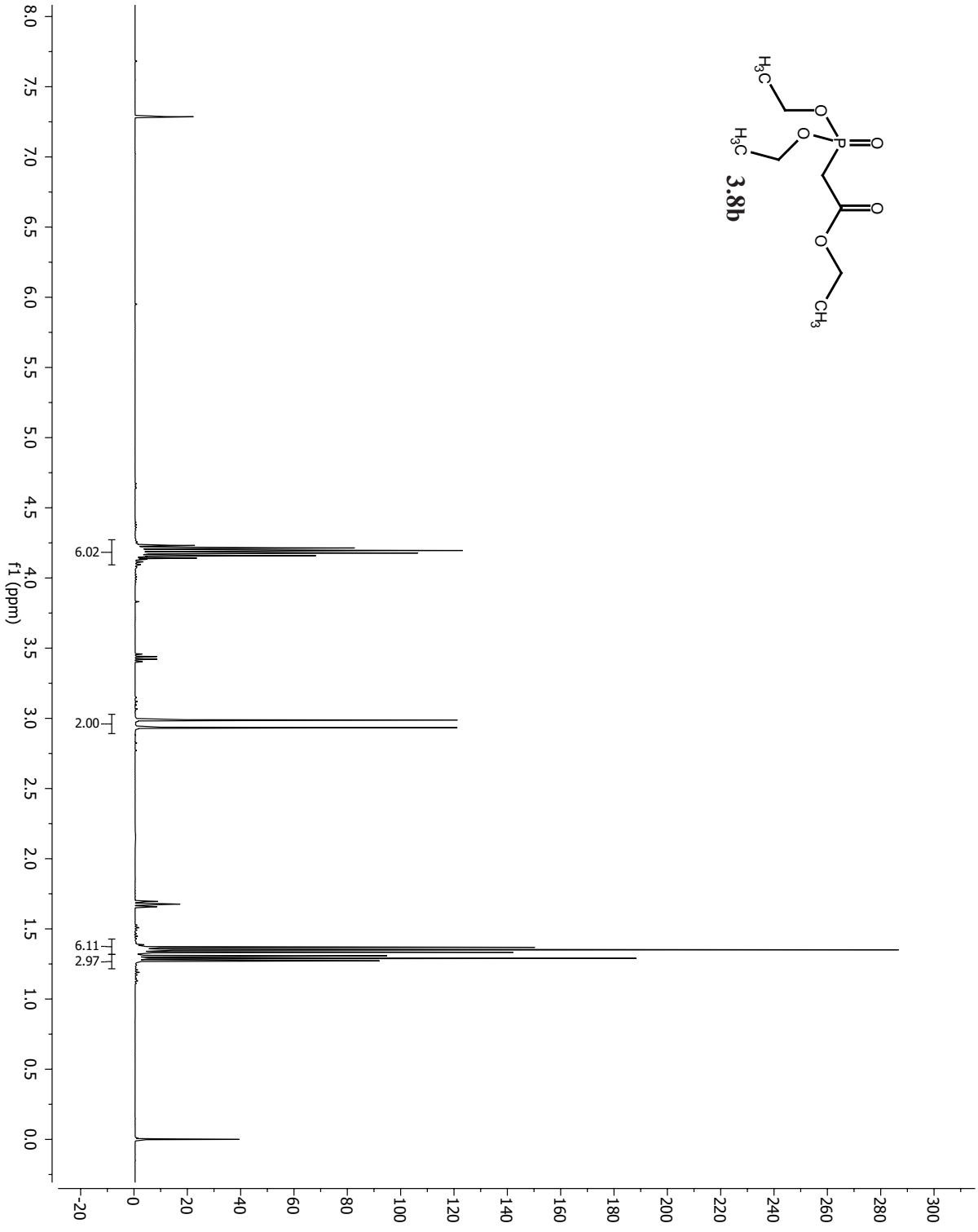

Key Compound 3.7
f1 (ppm)
201.90
172.78
170.46
134.39
129.34
128.84
128.50
86.54
77.42
77.27 cdcl3
77.01 cdcl3
76.76 cdcl3
43.21
31.92
25.41
18.08
6.93
0.00
-4.92
-5.39

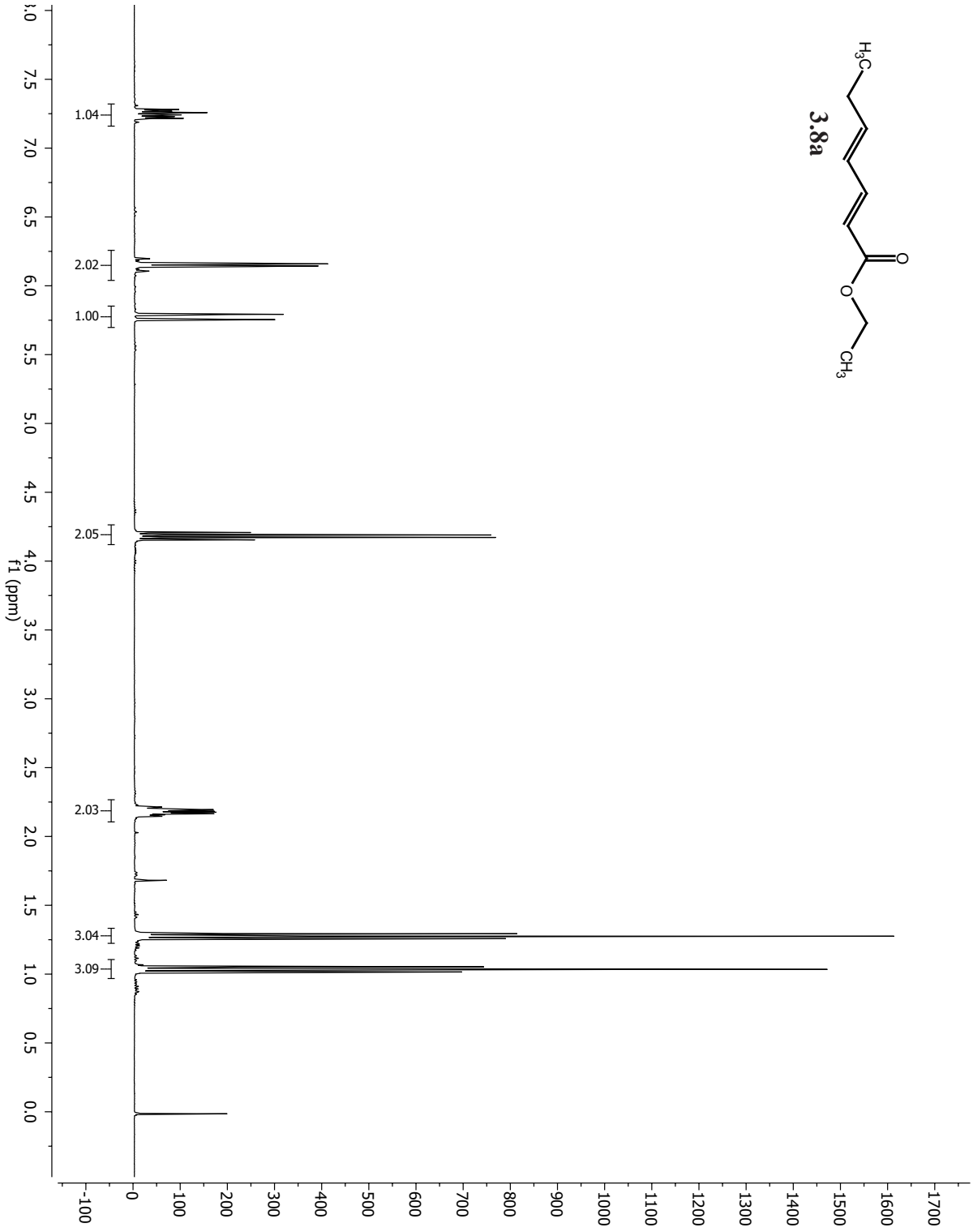

Key Compound 3.7
% Transmittance
Wavenumbers (cm-1)
Fri Mar 31 18:25:09 2017 (GMT-07:00) 31
3434.58
3066.05
3034.82
2929.98
2885.30
2857.62
1796.25
1714.28
1604.85
1586.26
1496.17
1471.81
1457.23
1433.89
1394.30
1338.21
1312.40
1253.73
1170.54
1126.83
1079.14
1005.32
1029.25
971.50
938.17
896.18
837.40
783.37
765.05
741.26
700.05
673.16
628.42
604.37
566.46
463.62
456.45
448.05
436.42
524.04
517.15
508.33
498.82
488.50

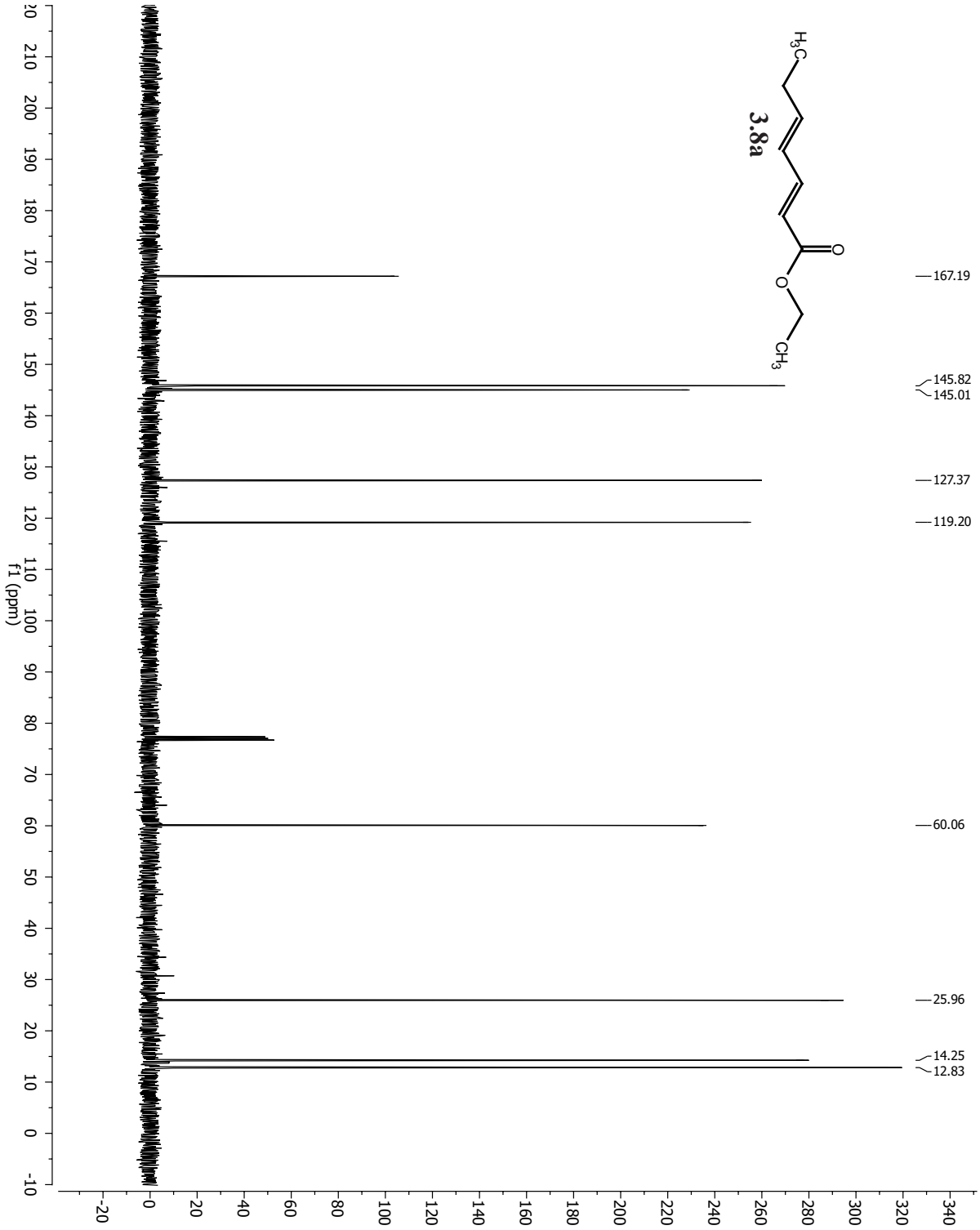


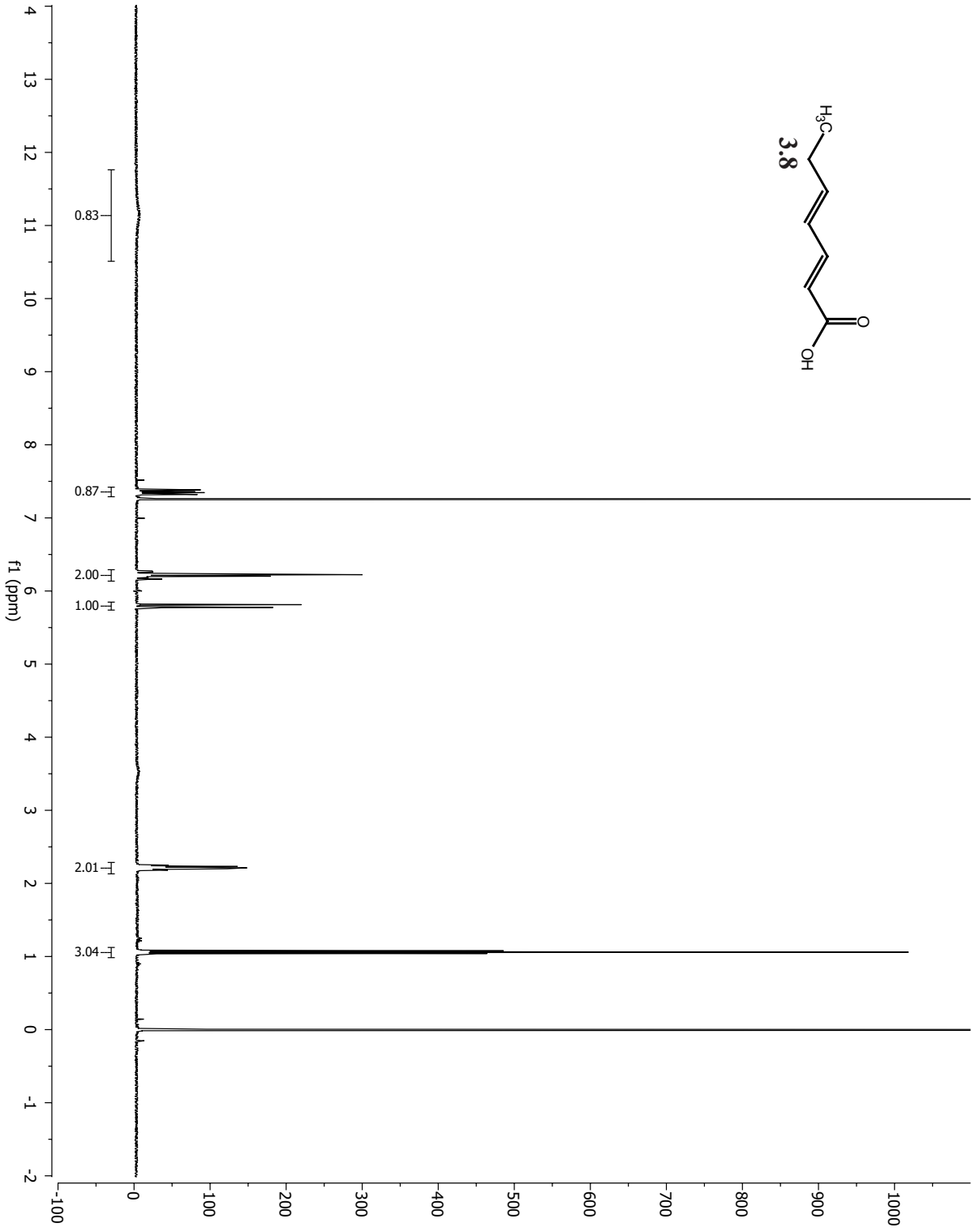
Search Results: **Sample AZA04: Oxidized Diol**

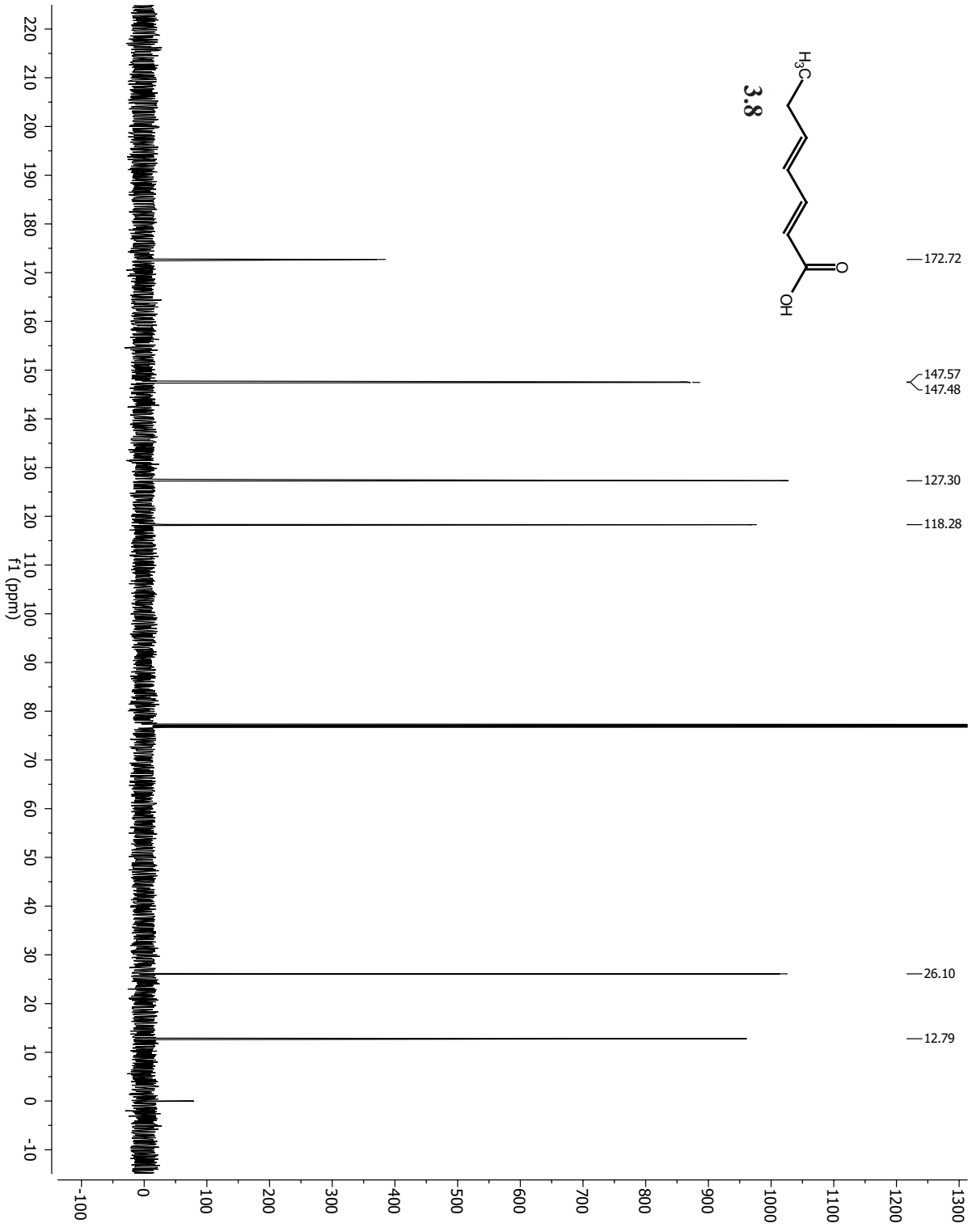
Mass Measured	Theo. Mass	Delta (ppm)	Composition
414.1709	414.1707	0.5	$[C_{20}H_{29}NO_5SiNa]^+$

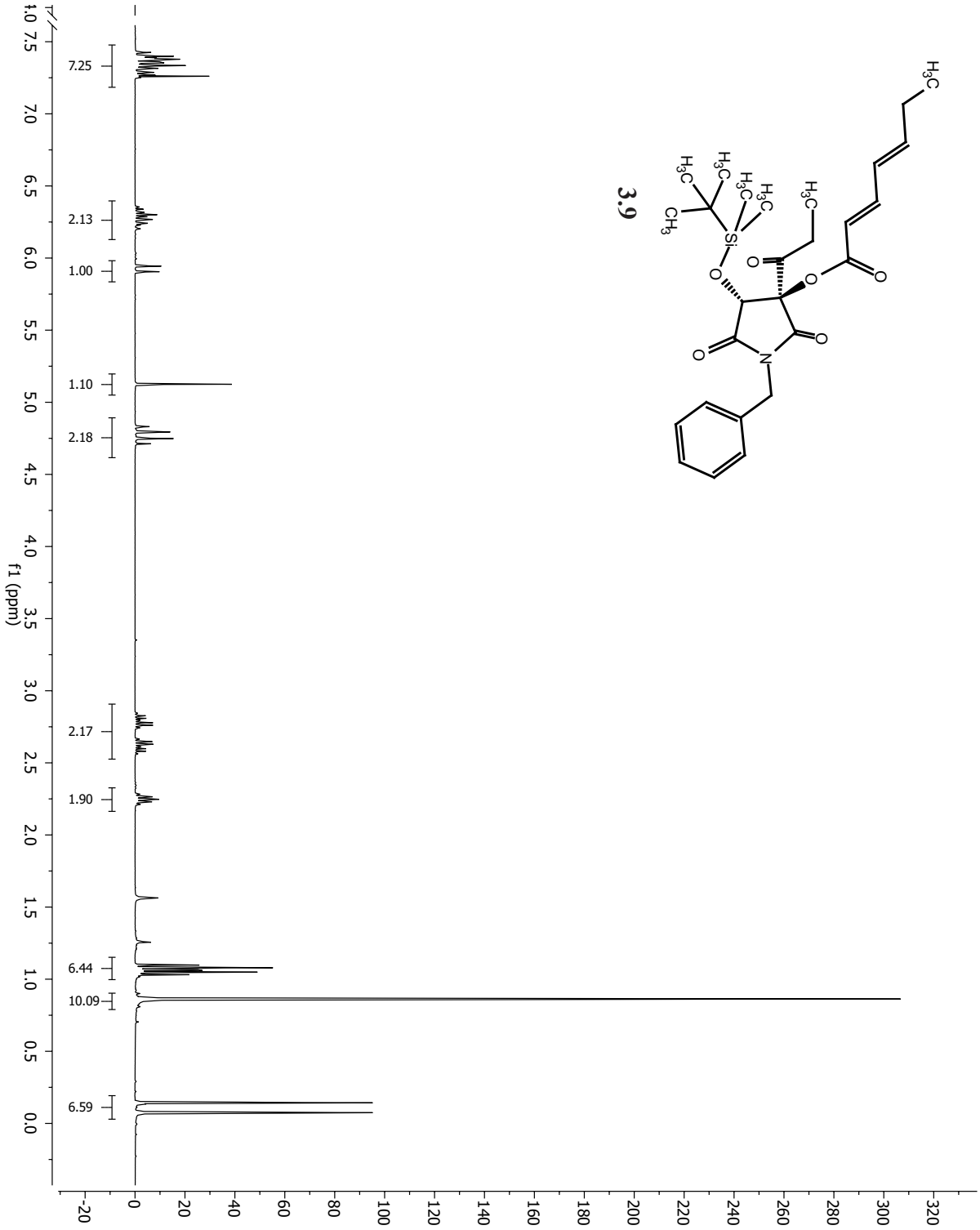

3.8b
6.02
2.00
6.11
2.97
f1 (ppm)

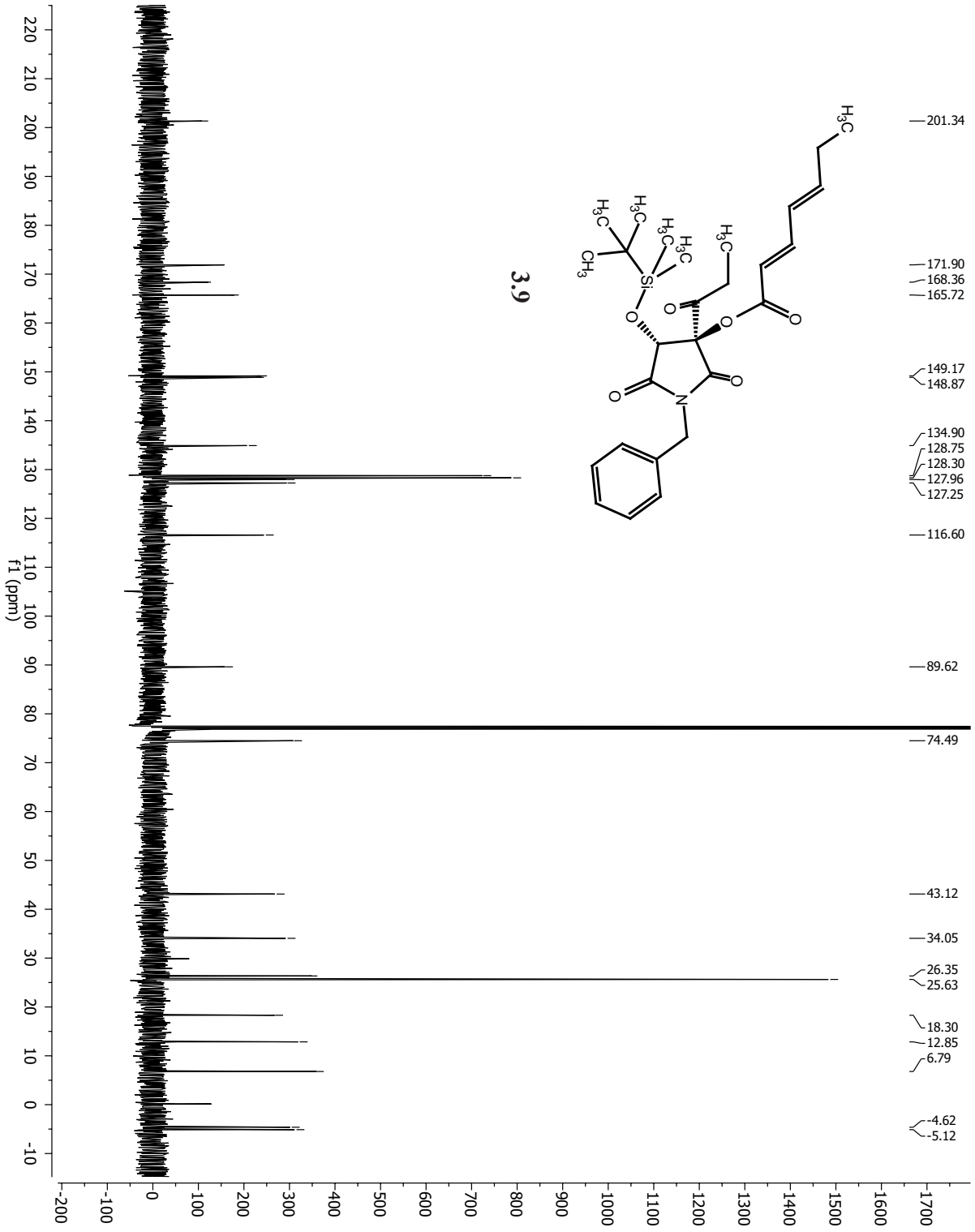

3.8a
1.04
2.02
1.00
2.05
2.03
3.04
3.09
f1 (ppm)

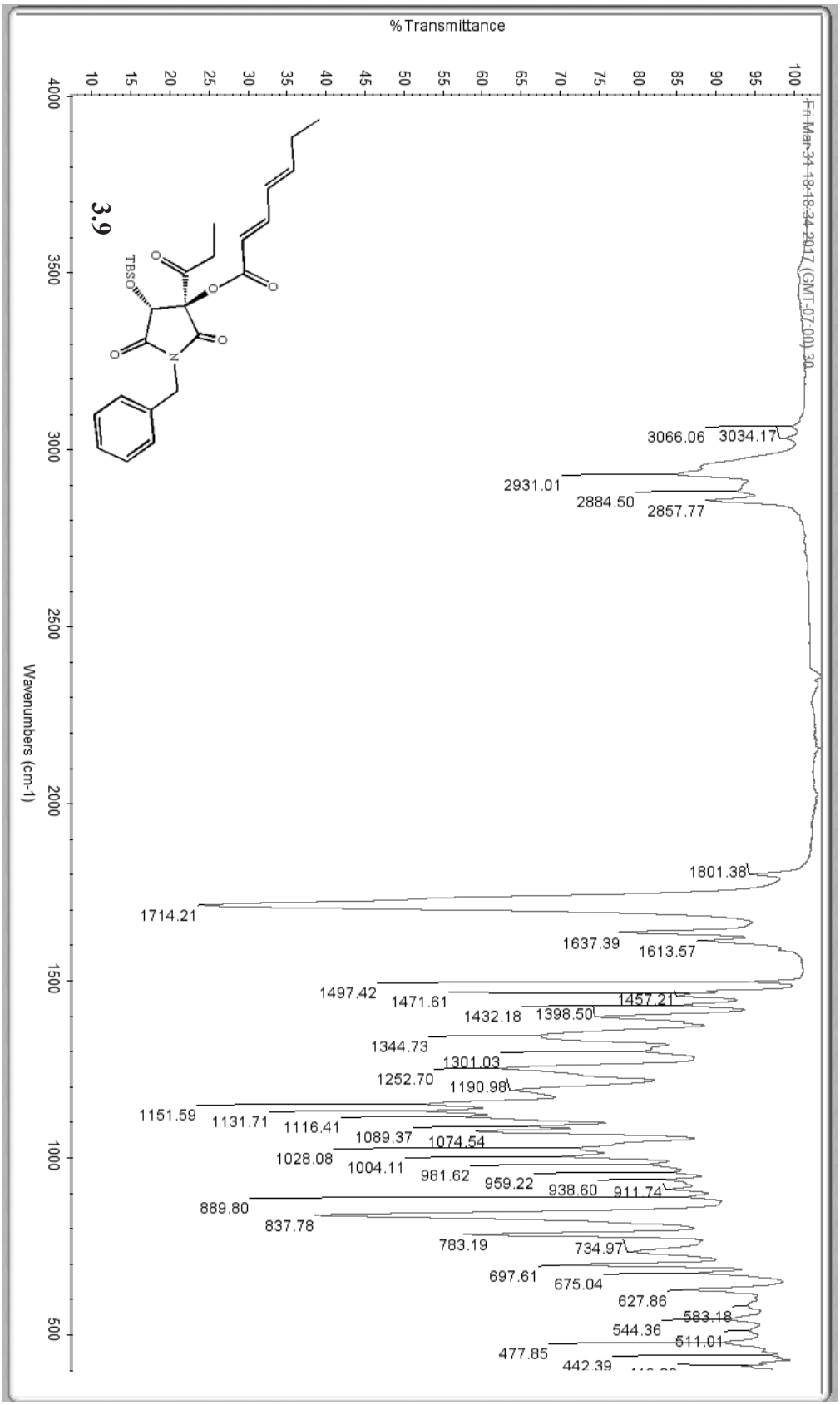

3.8a
167.19
145.82
145.01
127.37
119.20
60.06
25.96
14.25
12.83
f1 (ppm)

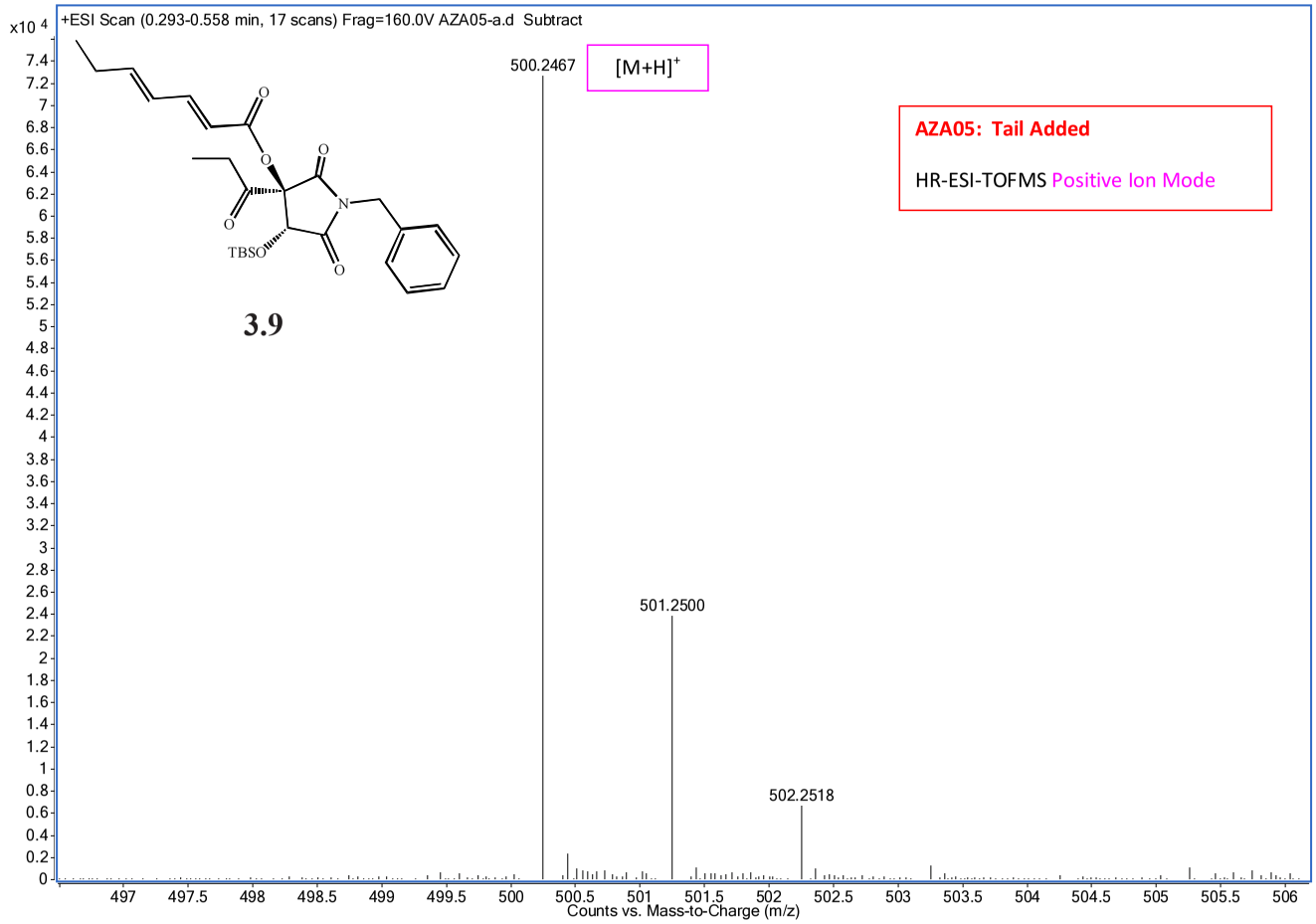

3.8
H3C
O
OH
0.83
0.87
2.00
1.00
2.01
3.04
f1 (ppm)


3.8
H3C
O
OH
172.72
147.57
147.48
127.30
118.28
26.10
12.79
f1 (ppm)


7.25
2.13
1.00
1.10
2.18
2.17
1.90
6.44
10.09
6.59
f1 (ppm)
3.9

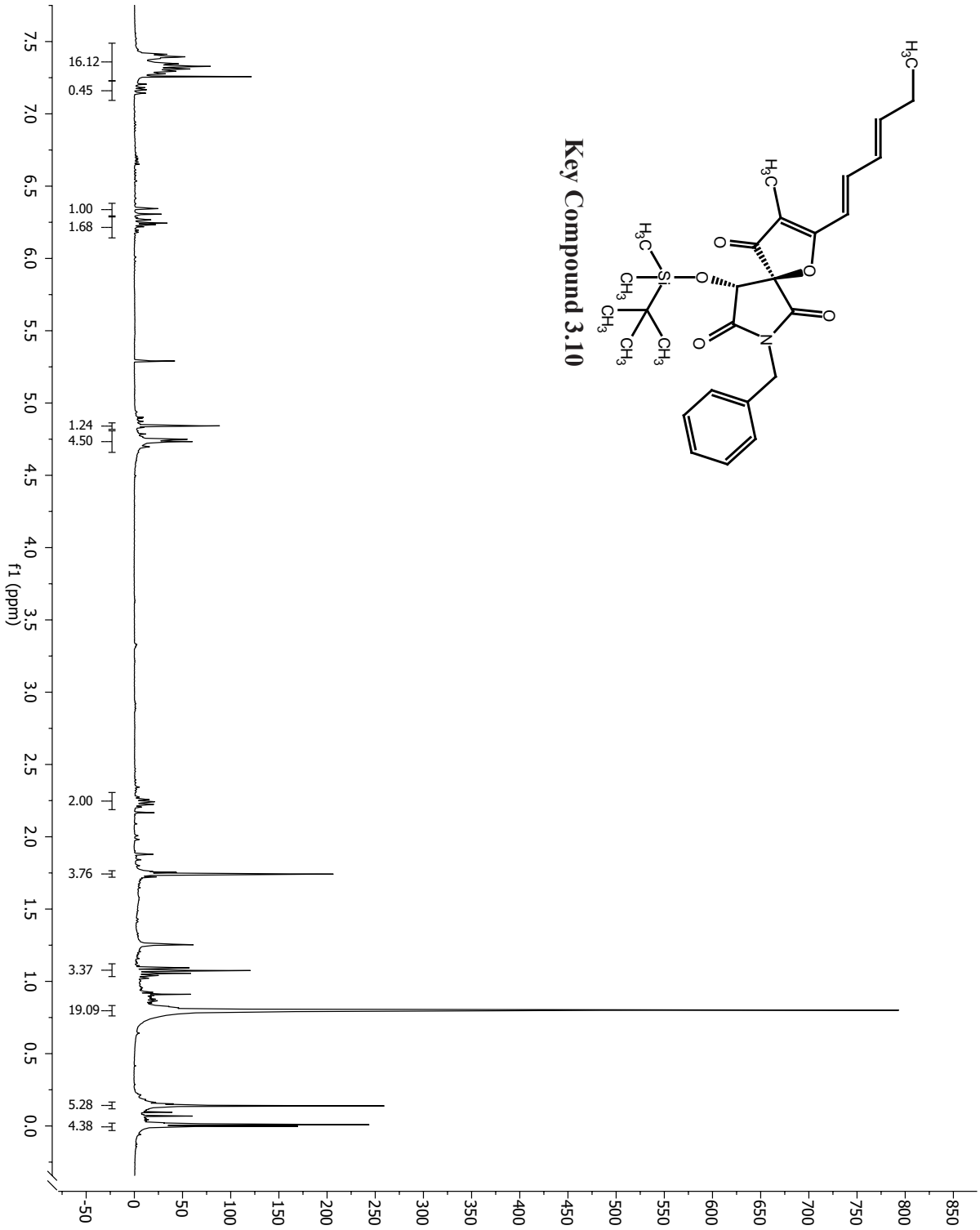

3.9
201.34
171.90
168.36
165.72
149.17
148.87
134.90
128.75
128.30
127.96
127.25
116.60
89.62
74.49
43.12
34.05
26.35
25.63
18.30
12.85
6.79
-4.62
-5.12
f1 (ppm)

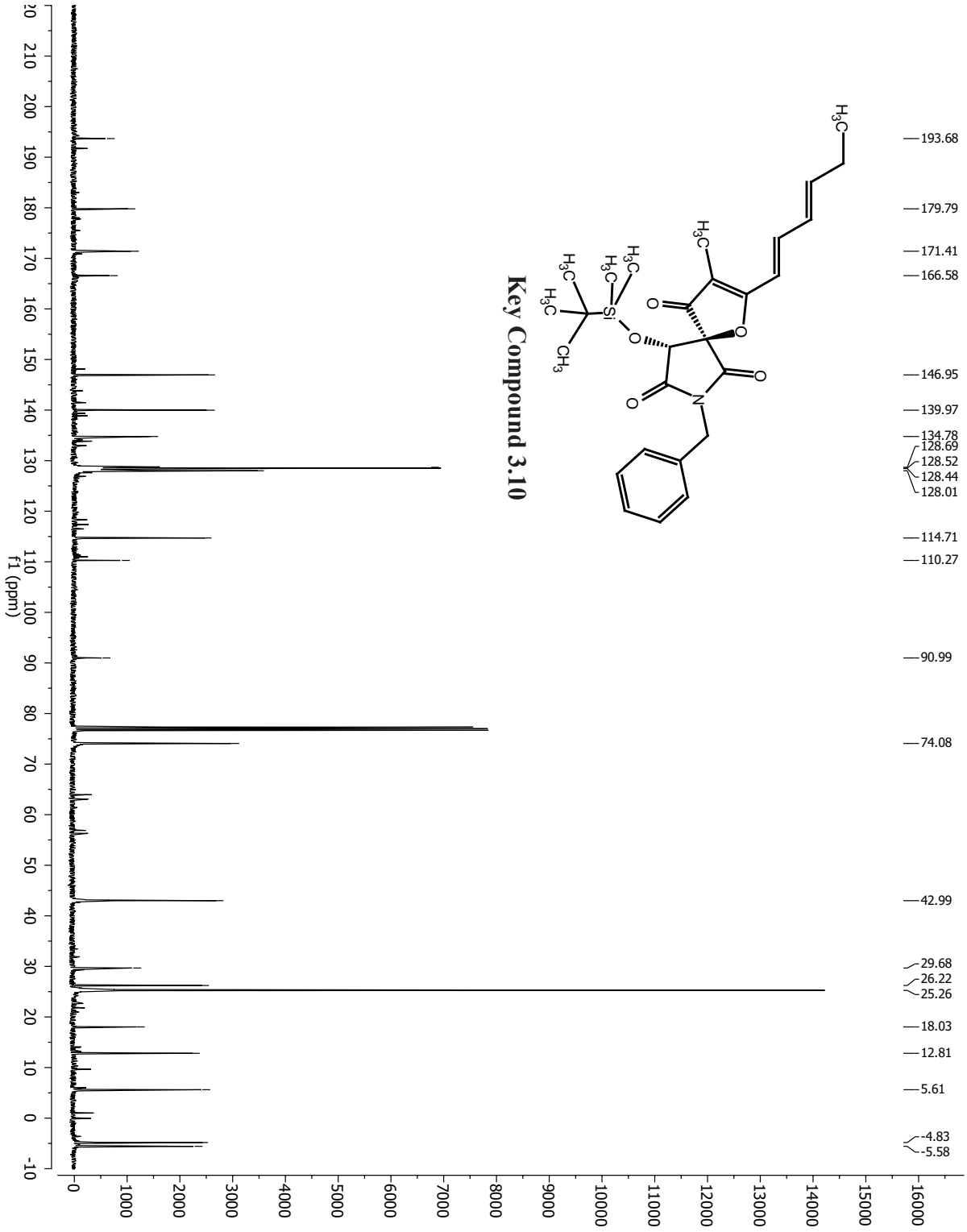

% Transmittance
Wavenumbers (cm-1)
3.9
TBSO
Fri Mar 31 18:18:34 2017 (GMT-07:00) 30
3066.06
3034.17
2931.01
2884.50
2857.77
1801.38
1714.21
1637.39
1613.57
1497.42
1471.61
1457.21
1432.18
1398.50
1344.73
1301.03
1252.70
1190.98
1151.59
1131.71
1116.41
1089.37
1074.54
1028.08
1004.11
981.62
959.22
938.60
911.74
889.80
837.78
783.19
734.97
697.61
675.04
627.86
583.18
544.36
511.01
477.85
442.39

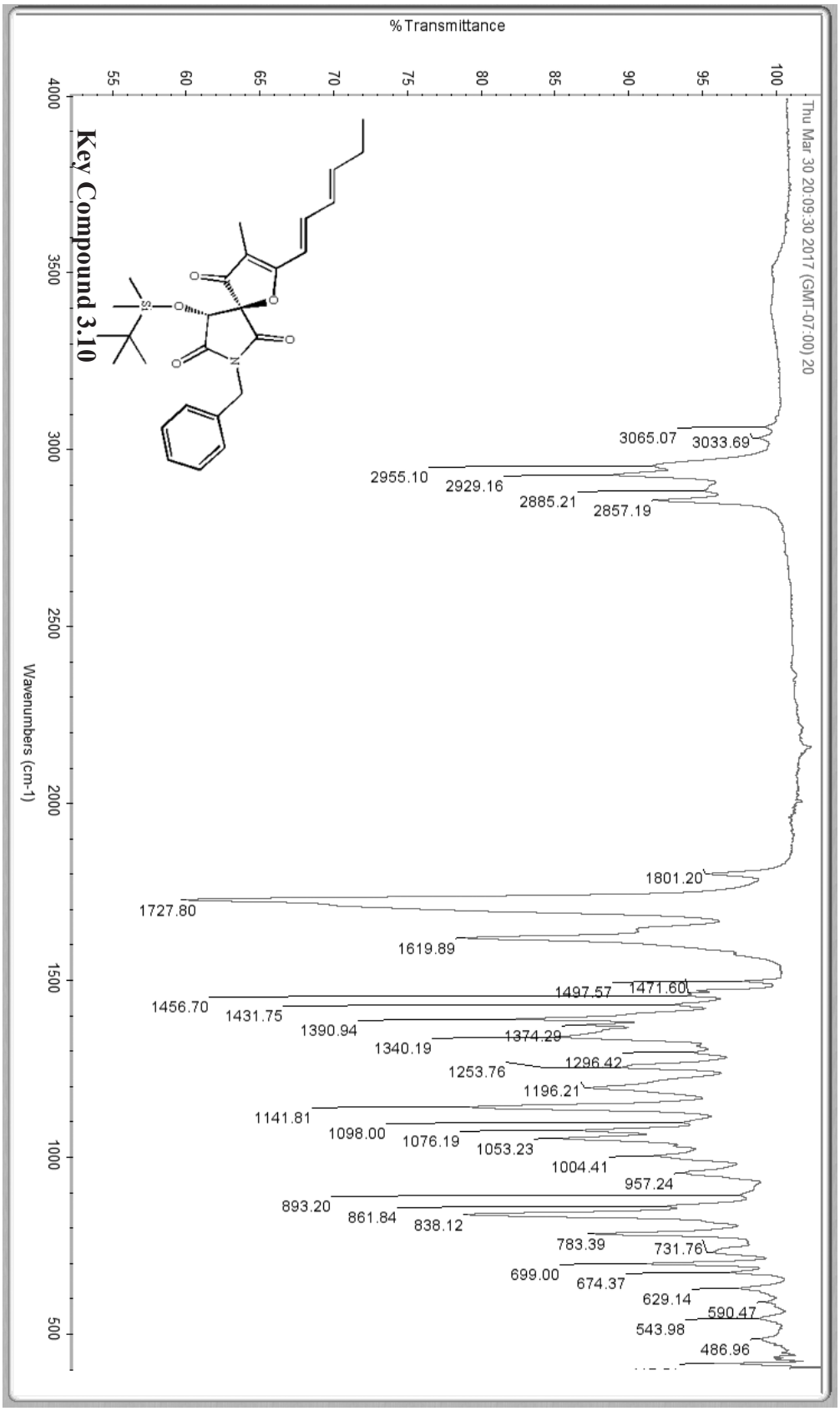


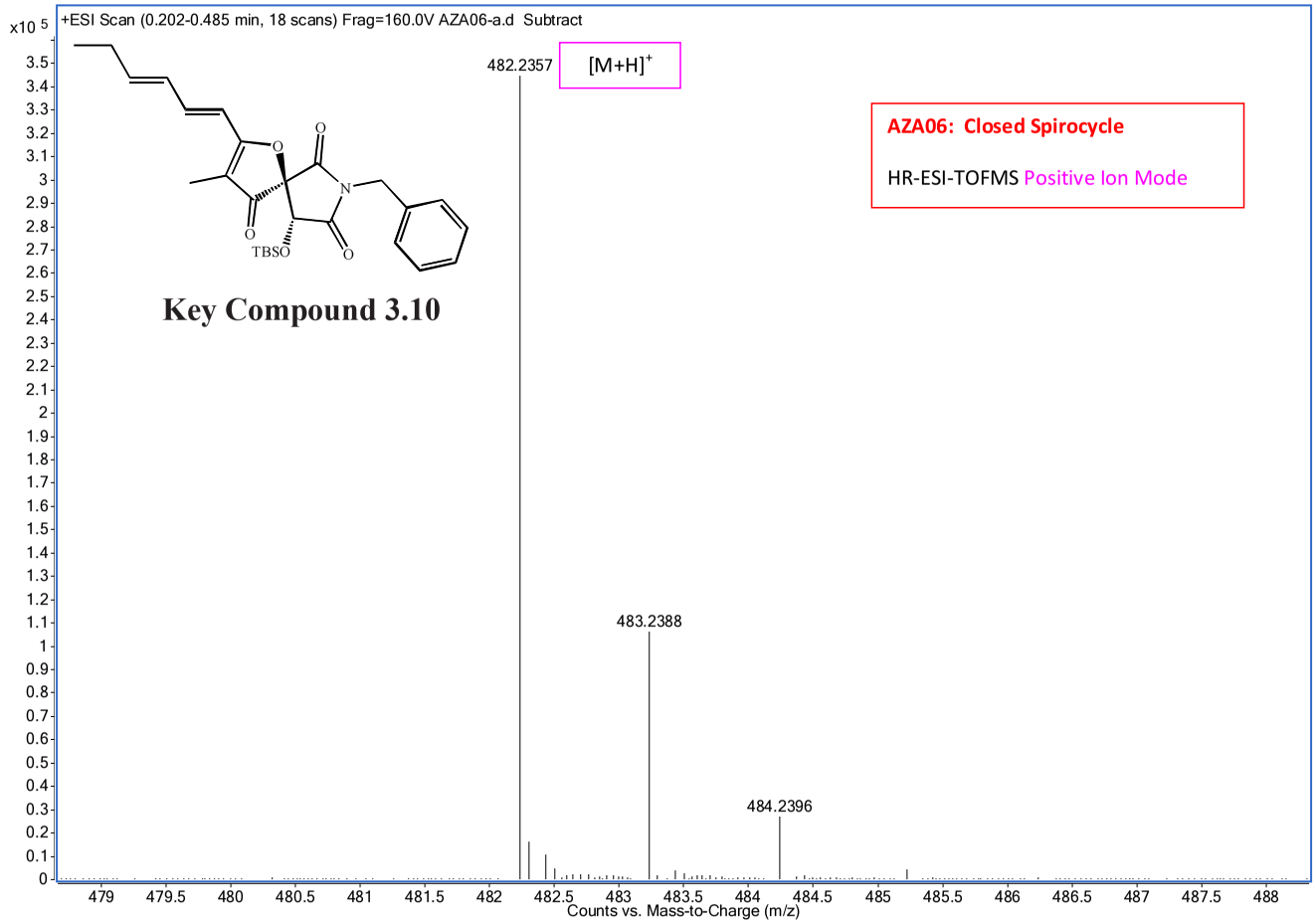
Search Results: Sample AZA05: Tail Added

Mass Measured	Theo. Mass	Delta (ppm)	Composition
500.2467	500.2463	0.8	$[C_{27}H_{38}NO_6Si]^+$


Key Compound 3.10
16.12
0.45
1.00
1.68
1.24
4.50
2.00
3.76
3.37
19.09
5.28
4.38
f1 (ppm)

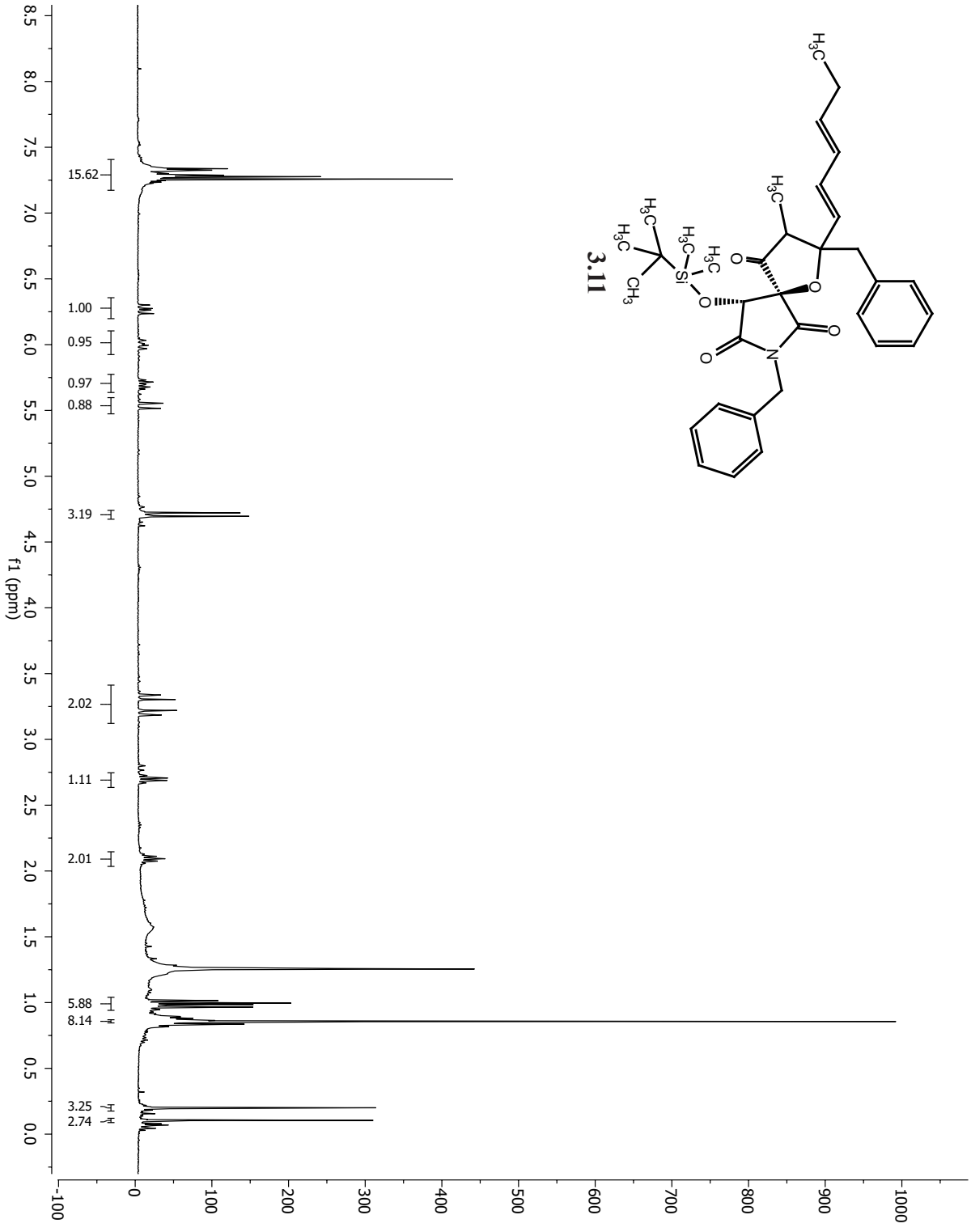

Key Compound 3.10
f1 (ppm)
193.68
179.79
171.41
166.58
146.95
139.97
134.78
128.69
128.52
128.44
128.01
114.71
110.27
90.99
74.08
42.99
29.68
26.22
25.26
18.03
12.81
5.61
-4.83
-5.58

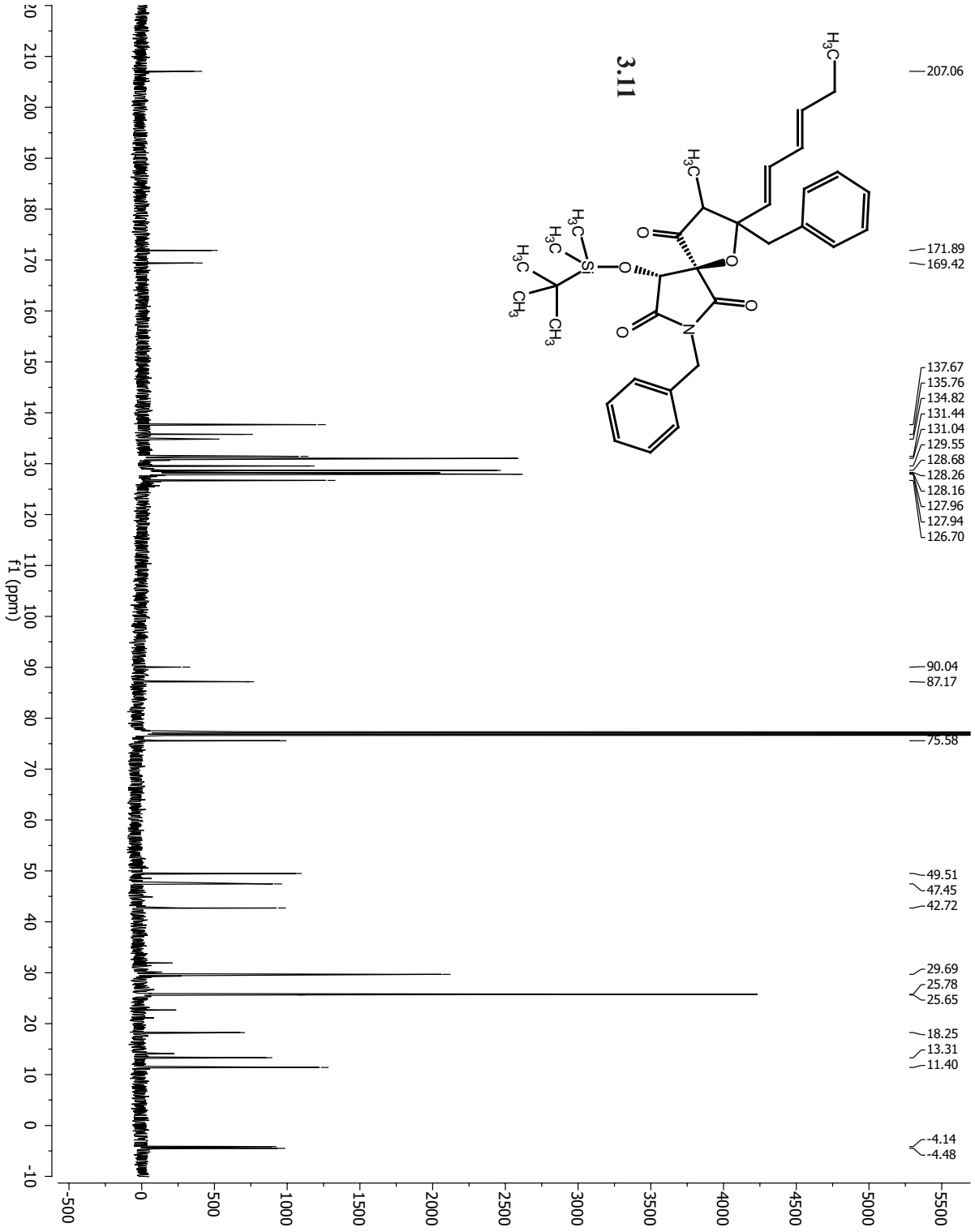

% Transmittance
Wavenumbers (cm-1)
Thu Mar 30 20:09:30 2017 (GMT-07:00) 20
Key Compound 3.10
3065.07
3033.69
2955.10
2929.16
2885.21
2857.19
1801.20
1727.80
1619.89
1497.57
1471.60
1456.70
1431.75
1390.94
1374.29
1340.19
1296.42
1253.76
1196.21
1141.81
1098.00
1076.19
1053.23
1004.41
957.24
893.20
861.84
838.12
783.39
731.76
699.00
674.37
629.14
590.47
543.98
486.96

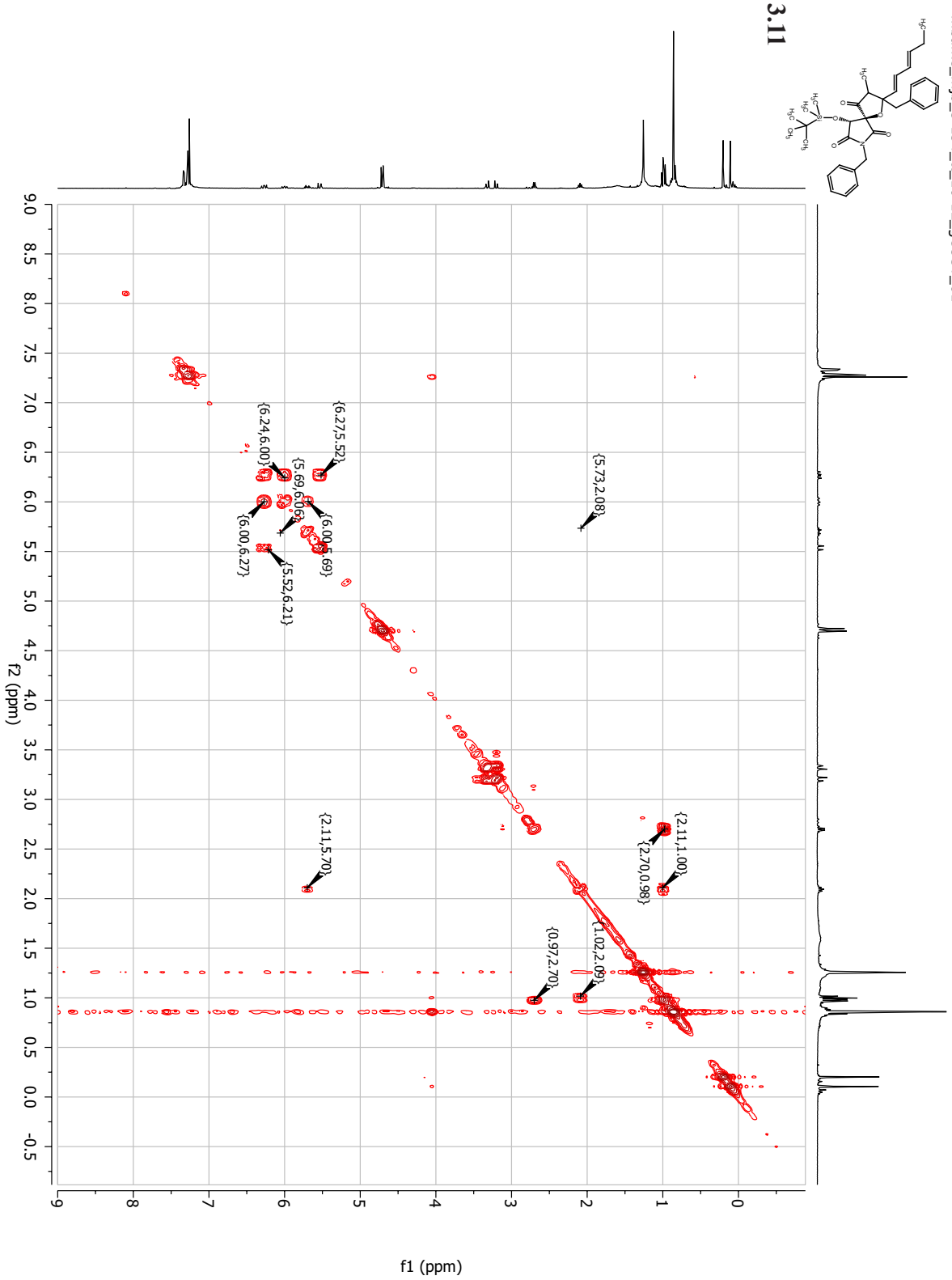


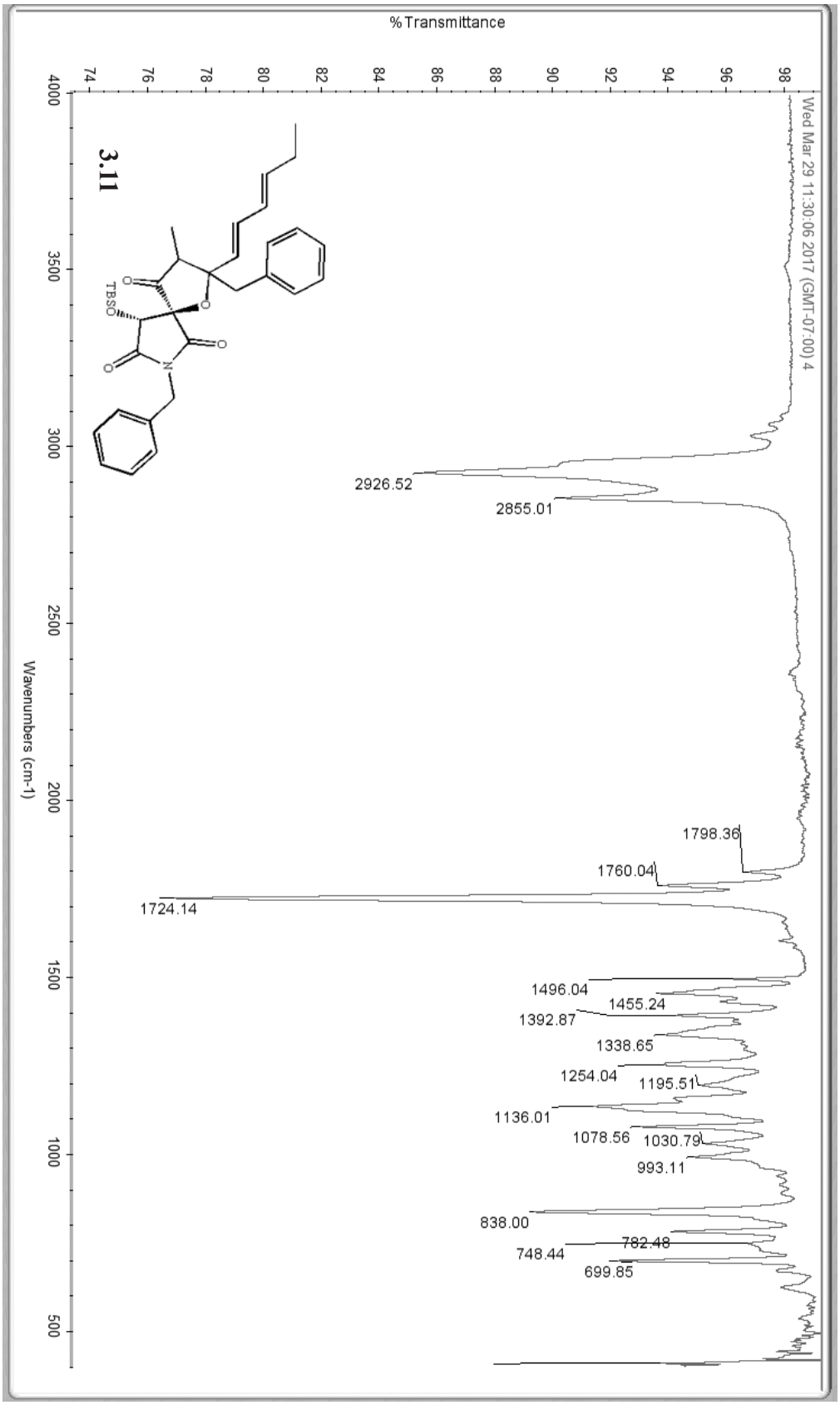
Search Results: **Sample** **AZA06: Closed Spirocycle**

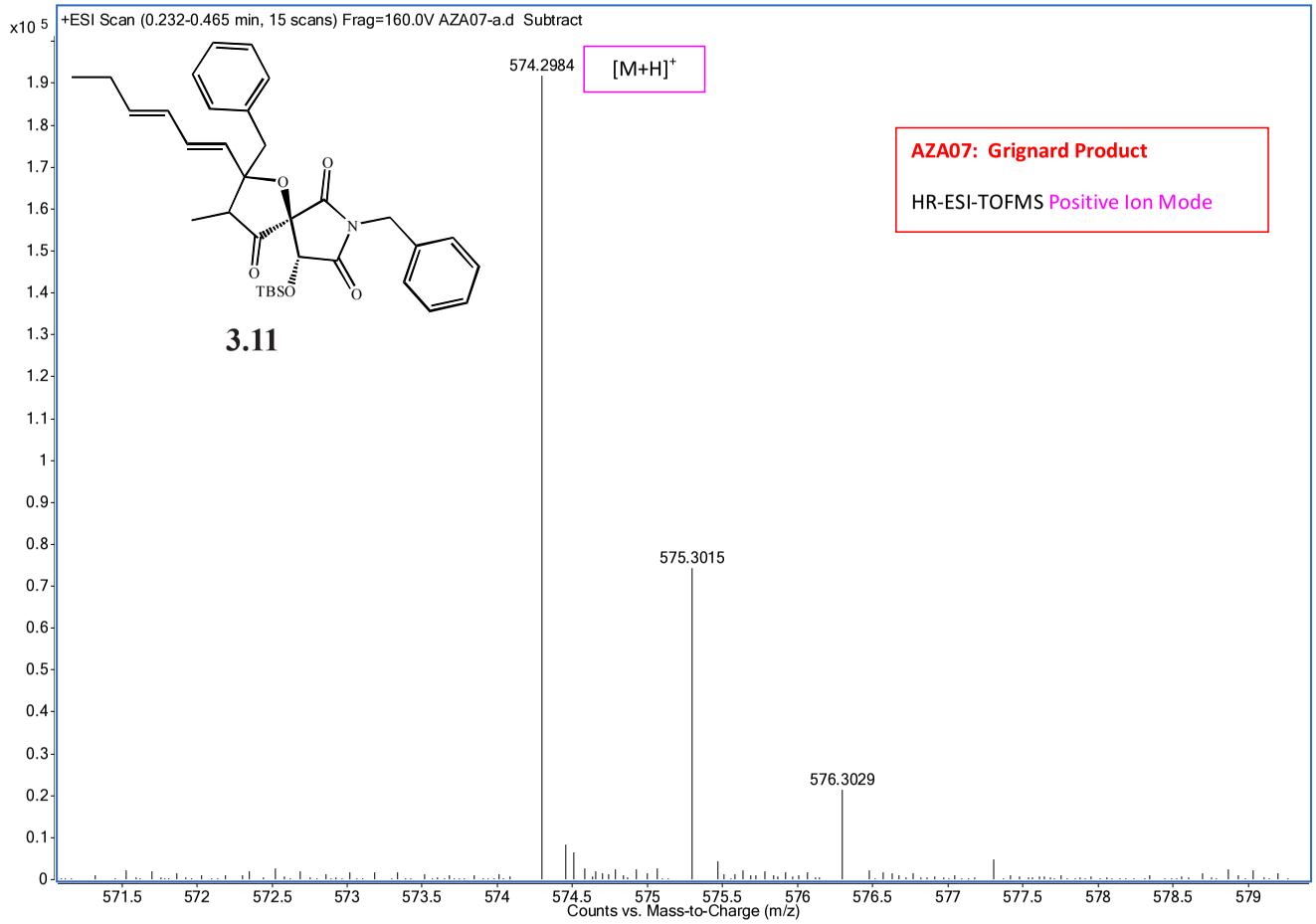
Mass Measured	Theo. Mass	Delta (ppm)	Composition
482.2357	482.2357	0.0	$[C_{27}H_{36}NO_5Si]^+$


15.62
1.00
0.95
0.97
0.88
3.19
2.02
1.11
2.01
5.88
8.14
3.25
2.74
f1 (ppm)
3.11


3.11
207.06
171.89
169.42
137.67
135.76
134.82
131.44
131.04
129.55
128.68
128.26
128.16
127.96
127.94
126.70
90.04
87.17
75.58
49.51
47.45
42.72
29.69
25.78
25.65
18.25
13.31
11.40
-4.14
-4.48
f1 (ppm)

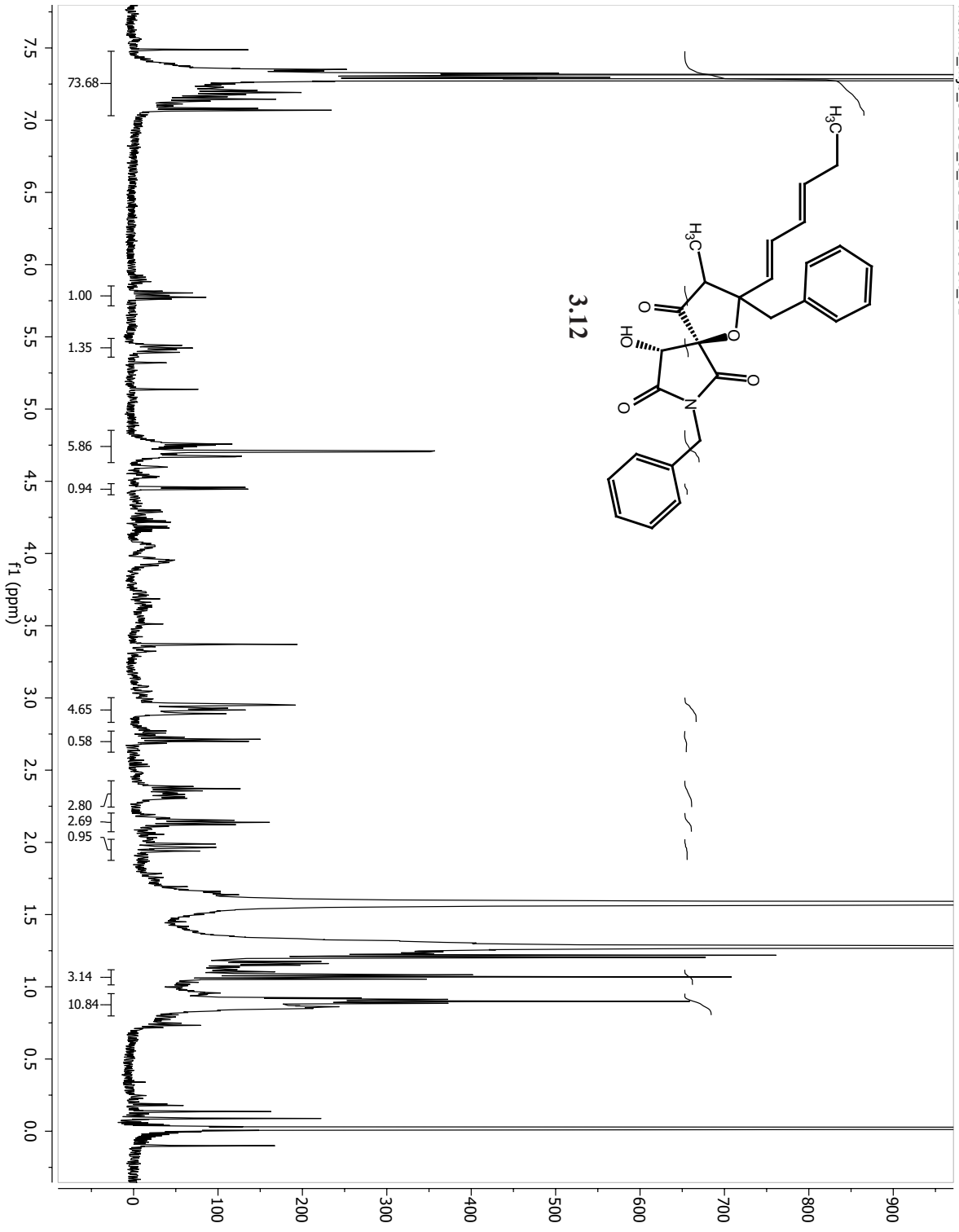

mbarke_mjb_3-134_tt_10-12_gCOSY_01 —
3.11
{6.27,5.52}
{6.24,6.00}
{5.69,6.06}
{6.00,5.69}
{6.00,6.27}
{5.52,6.21}
{5.73,2.08}
{2.11,1.00}
{2.70,0.98}
{1.02,2.09}
{0.97,2.70}
{2.11,5.70}
f2 (ppm)
f1 (ppm)

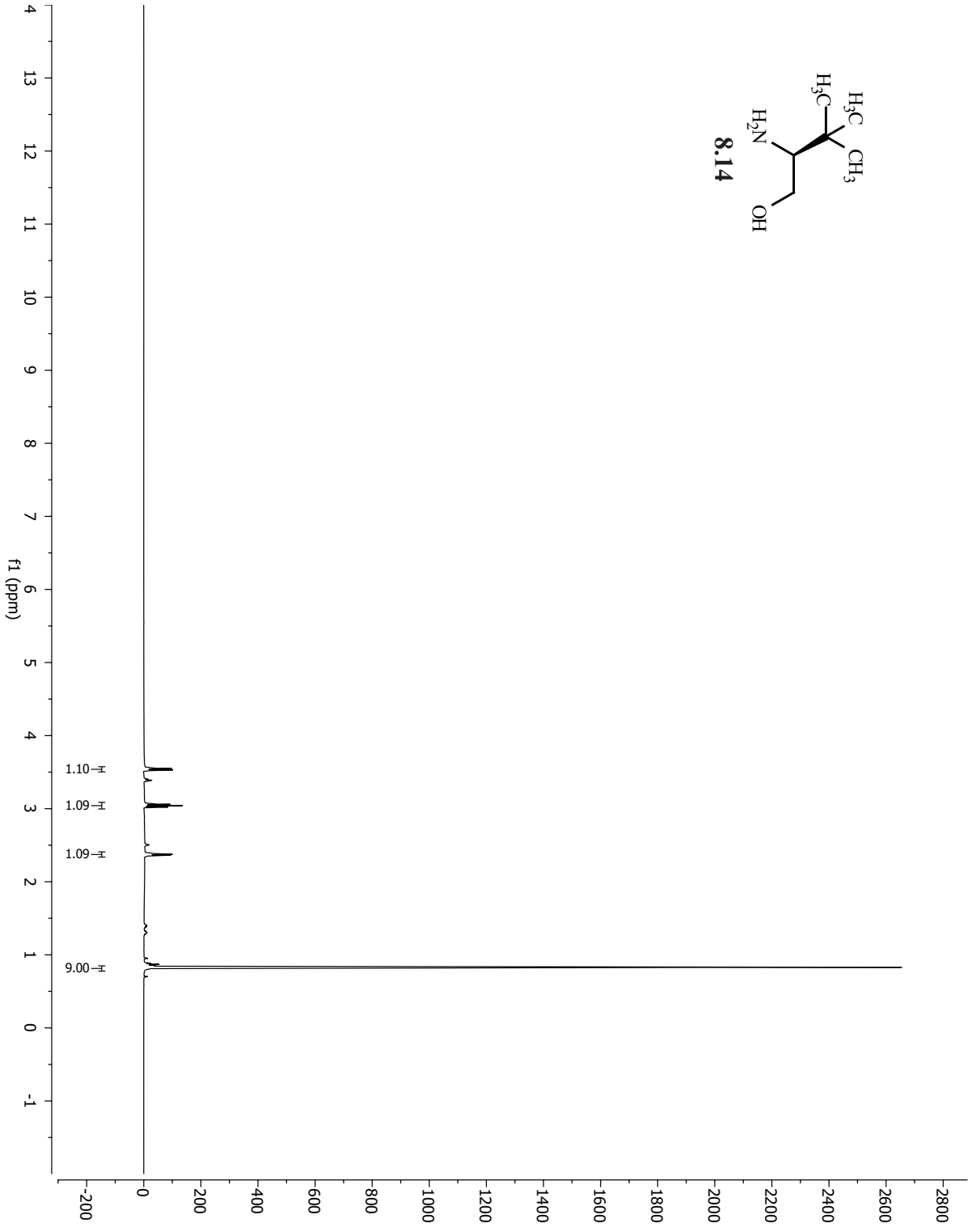

% Transmittance
Wavenumbers (cm-1)
Wed Mar 29 11:30:06 2017 (GMT-07:00) 4
3.11
TBSO
2926.52
2855.01
1798.36
1760.04
1724.14
1496.04
1455.24
1392.87
1338.65
1254.04
1195.51
1136.01
1078.56
1030.79
993.11
838.00
782.48
748.44
699.85

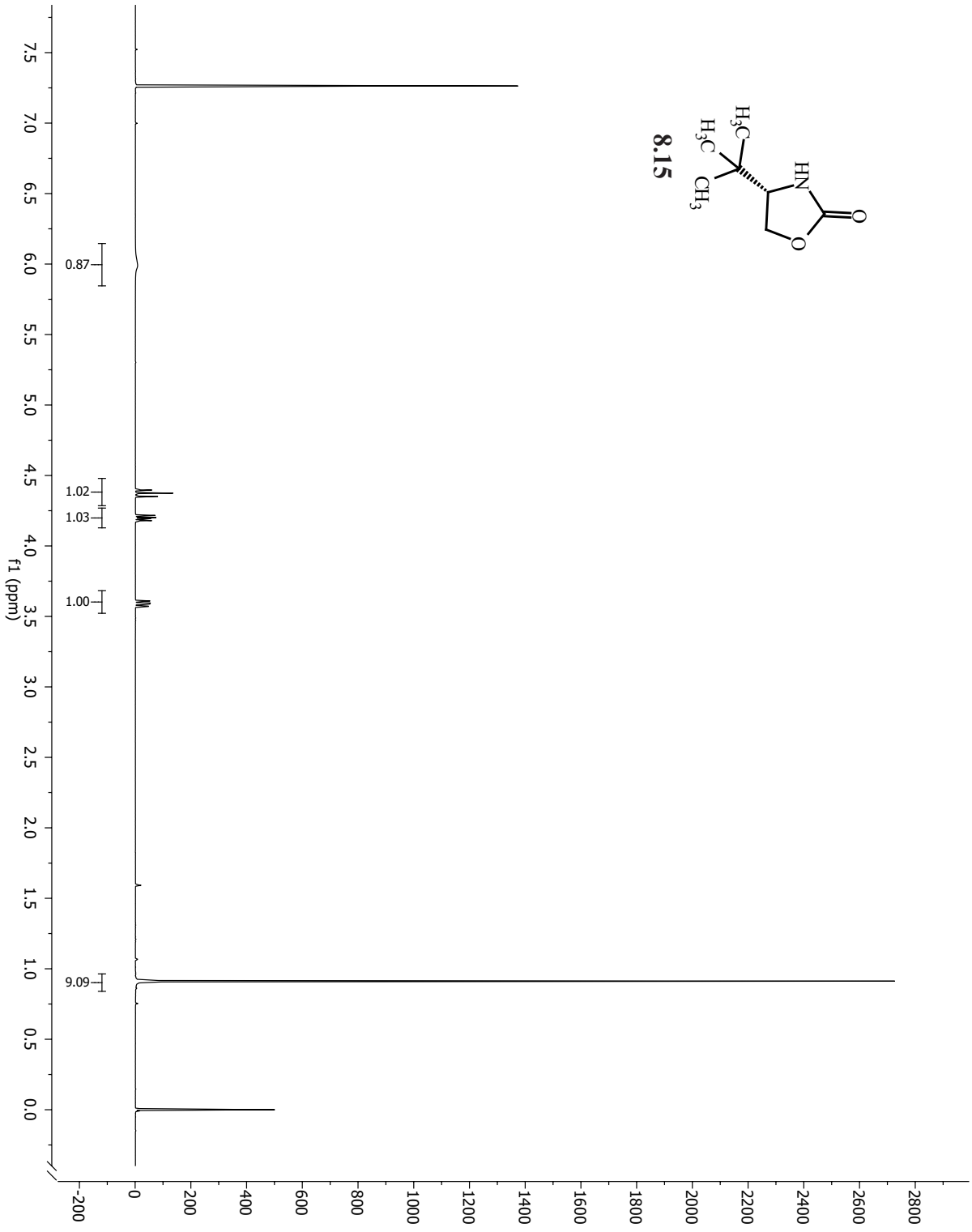


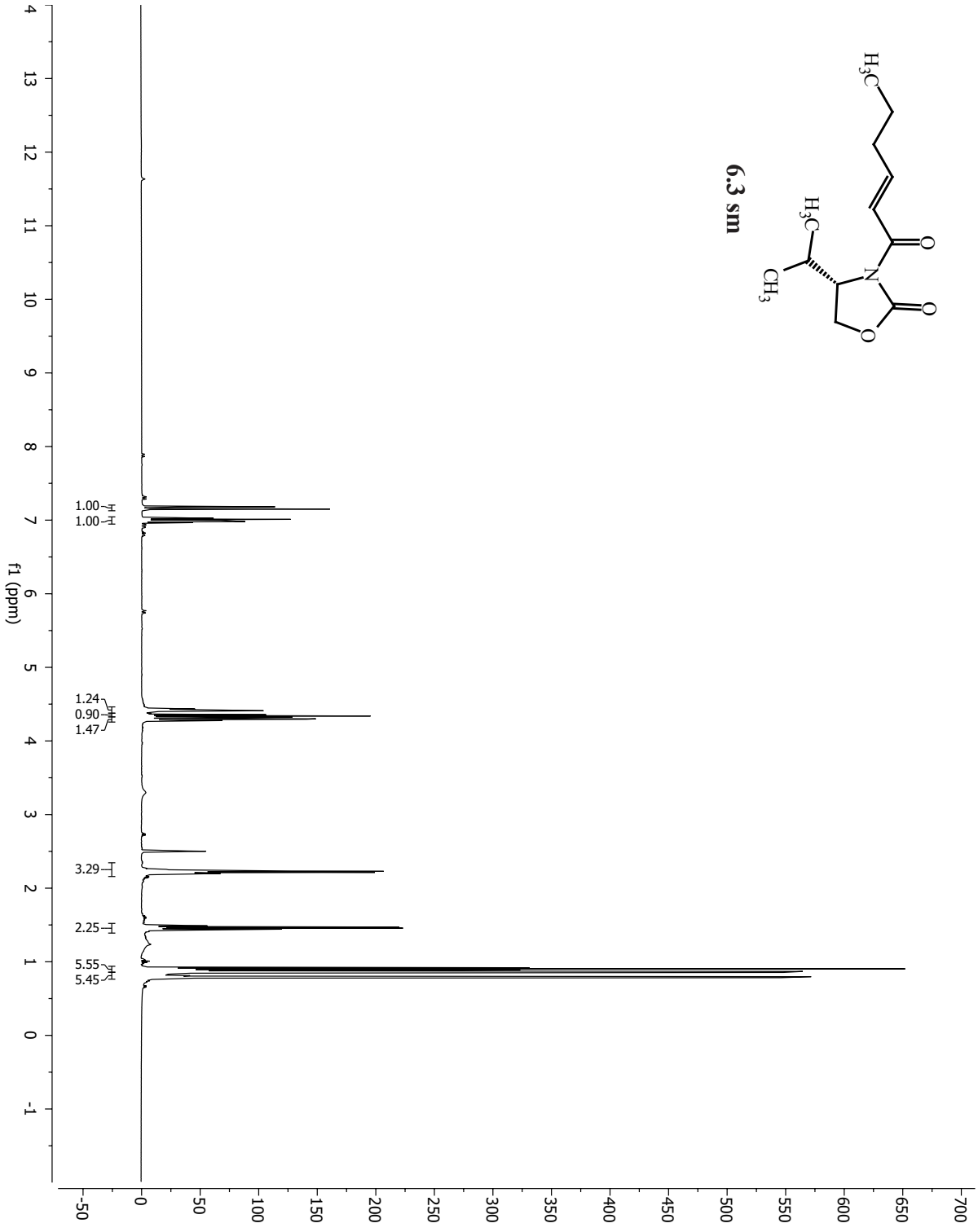
Search Results: **Sample AZA07: Grignard Product**

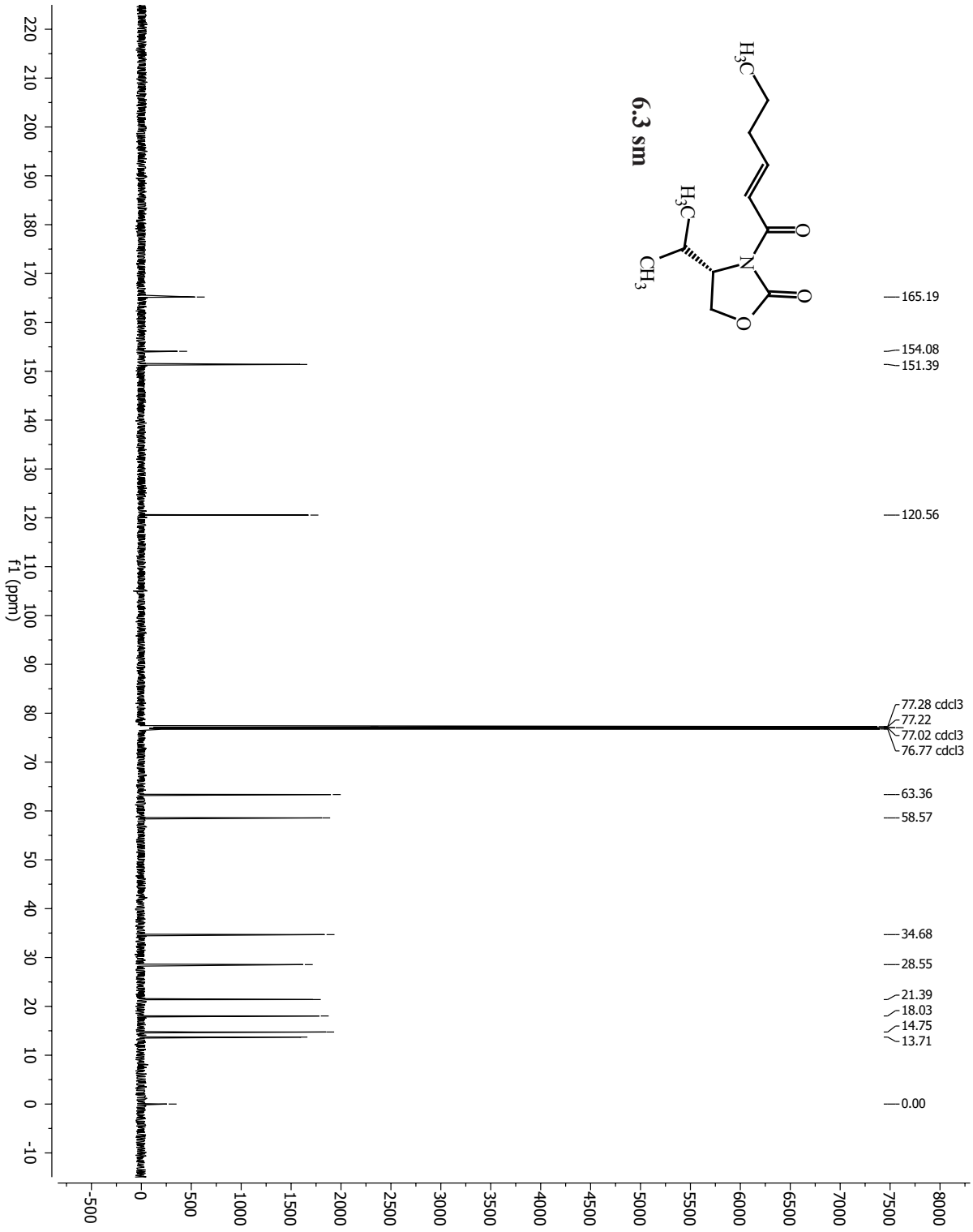
Mass Measured	Theo. Mass	Delta (ppm)	Composition
574.2984	574.2983	0.2	$[C_{34}H_{44}NO_5Si]^+$

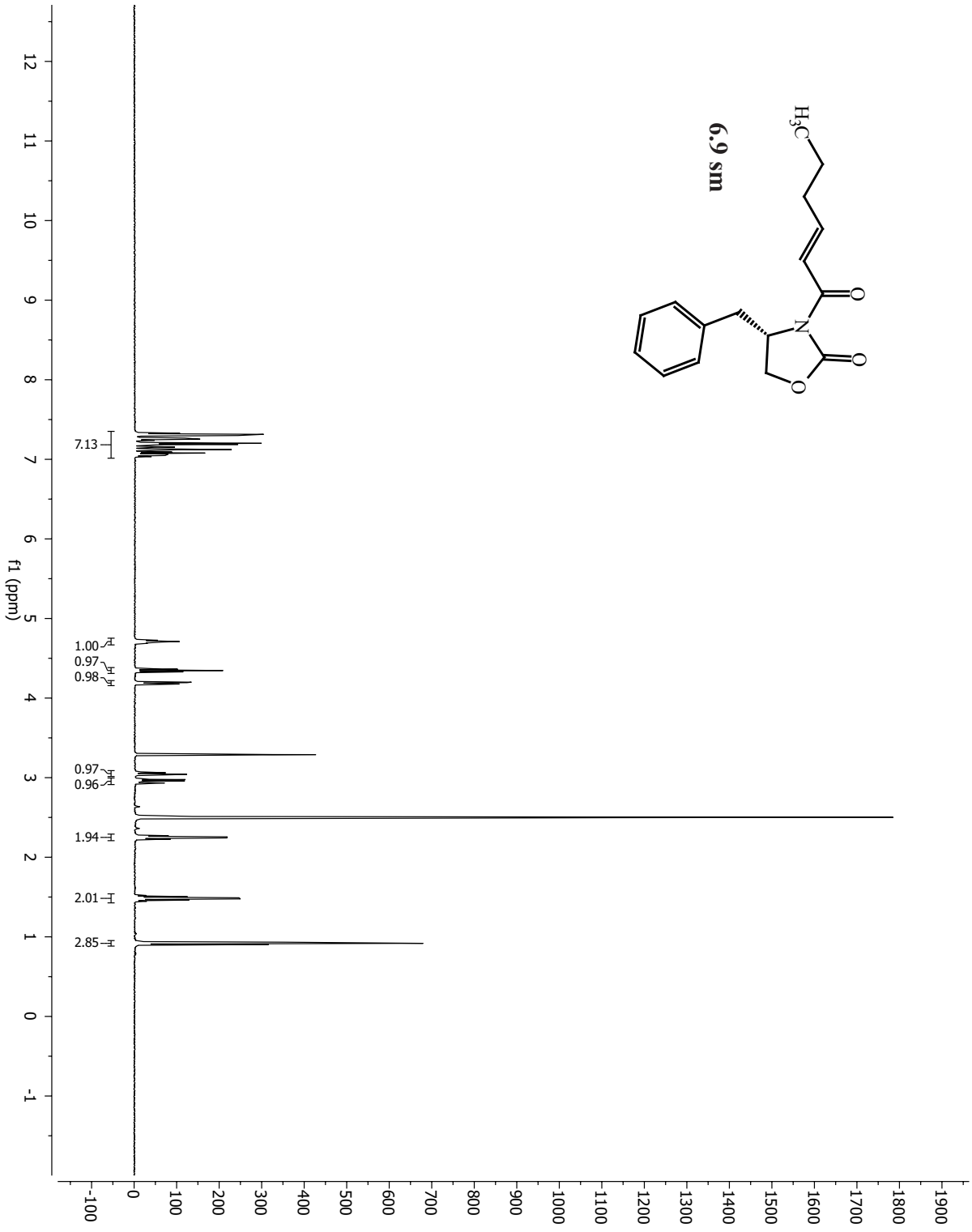

mbarke_mjb_3-135B_tt_15-21_PROTON_01
3.12
f1 (ppm)
73.68
1.00
1.35
5.86
0.94
4.65
0.58
2.80
2.69
0.95
3.14
10.84

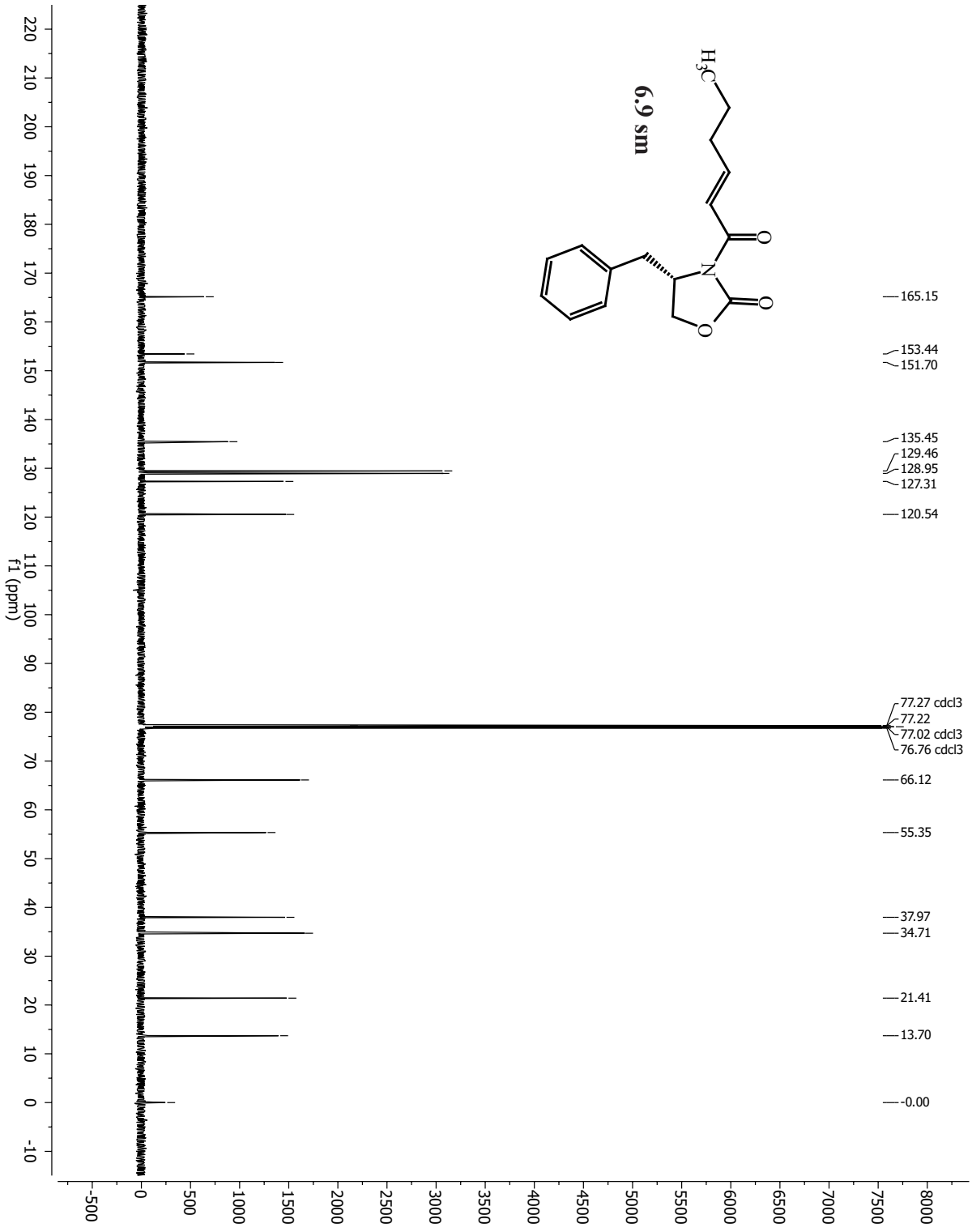

8.14
H3C
H3C
CH3
H2N
OH
f1 (ppm)
1.10
1.09
1.09
9.00

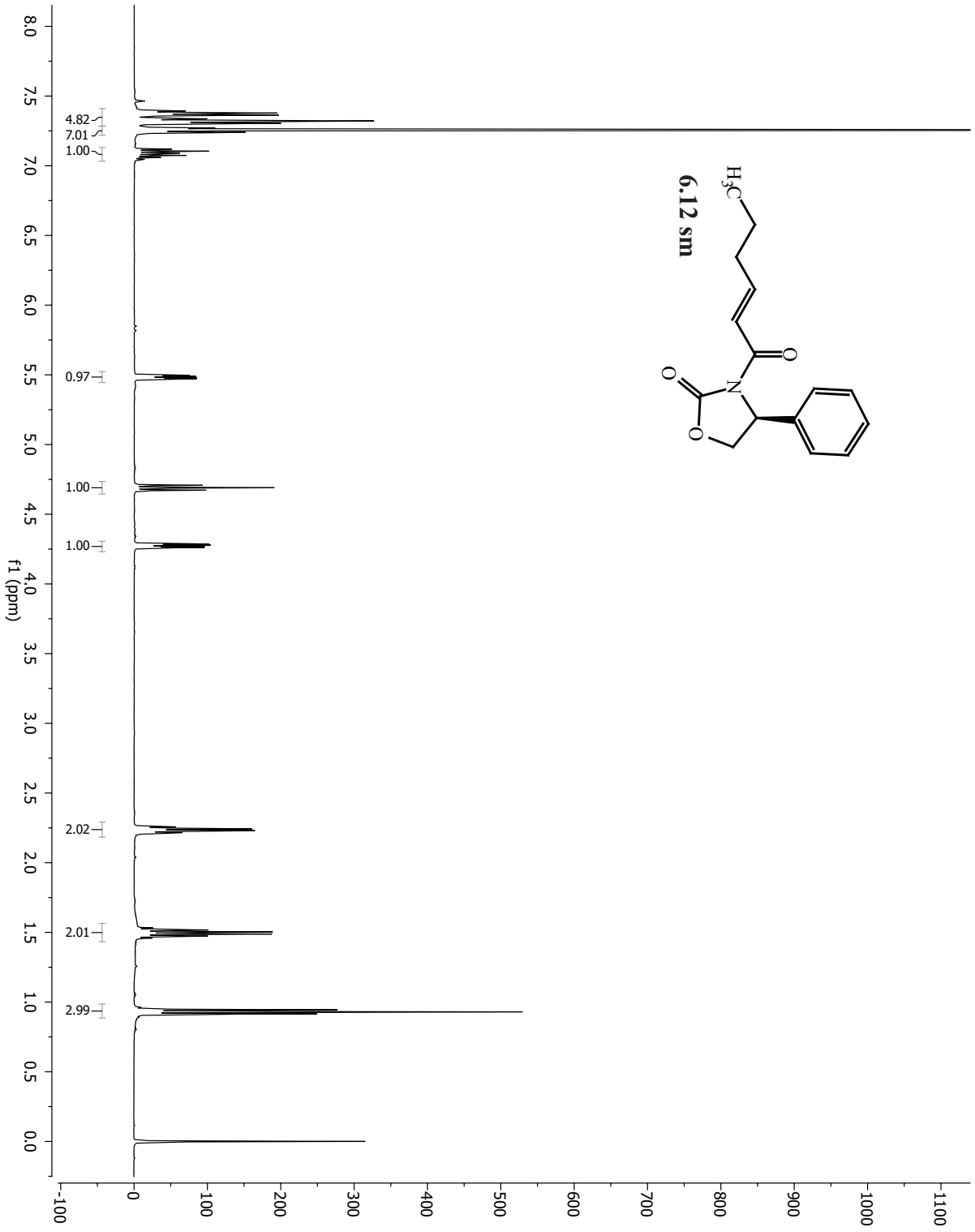

8.15
0.87
1.02
1.03
1.00
9.09
f1 (ppm)

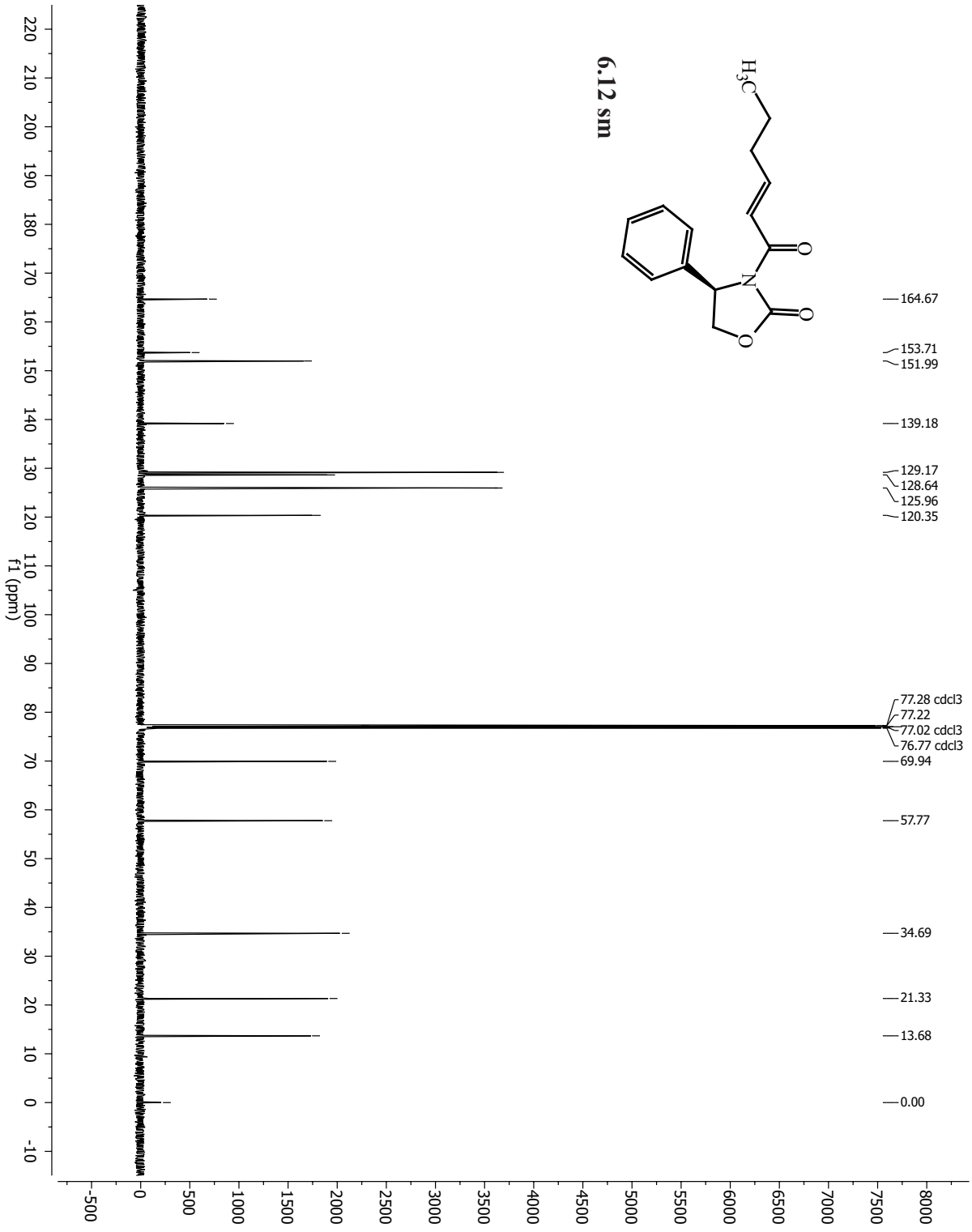

6.3 sm
f1 (ppm)
1.00
1.00
1.24
0.90
1.47
3.29
2.25
5.55
5.45

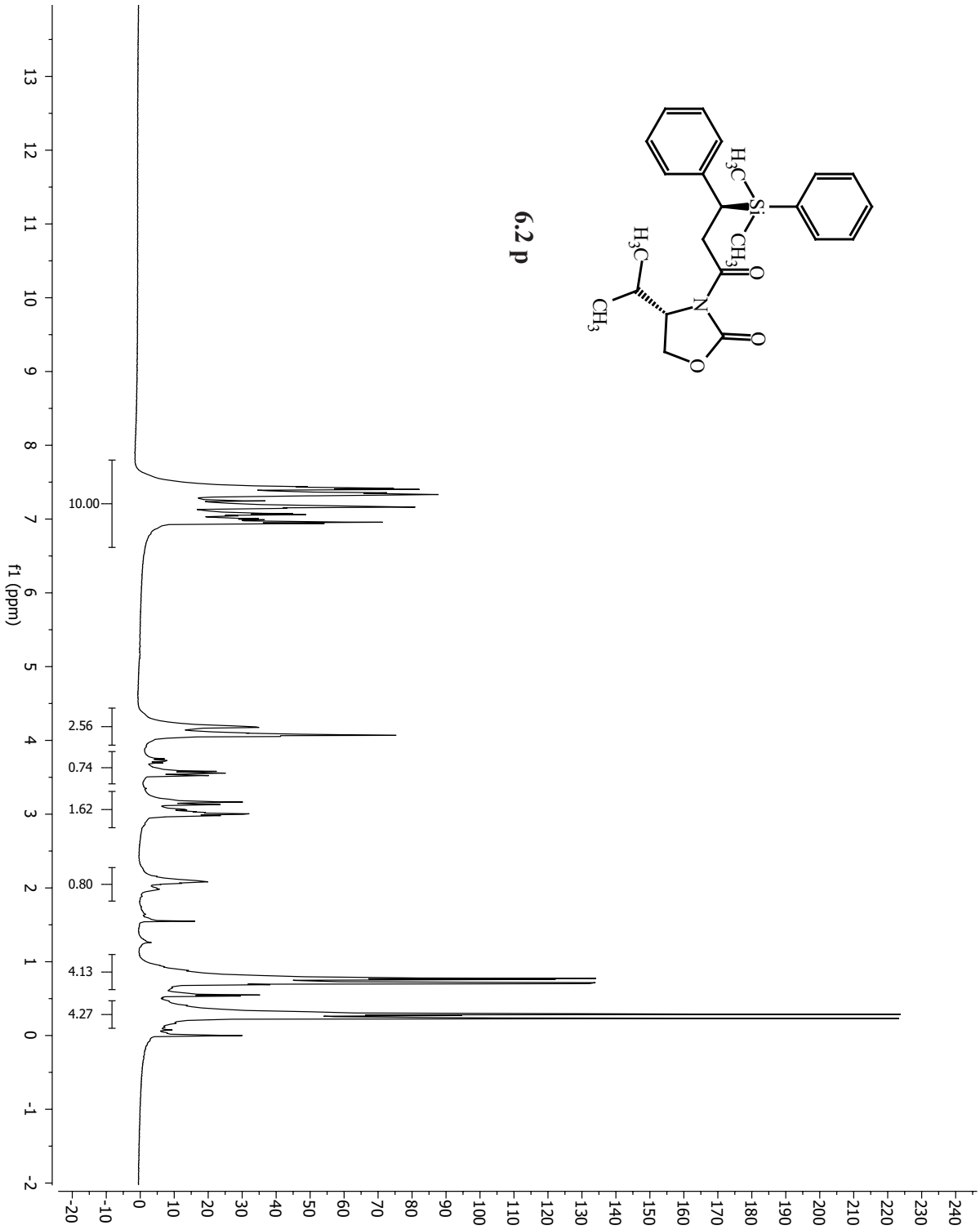

6.3 sm
165.19
154.08
151.39
120.56
77.28 cdcl3
77.22
77.02 cdcl3
76.77 cdcl3
63.36
58.57
34.68
28.55
21.39
18.03
14.75
13.71
0.00
f1 (ppm)

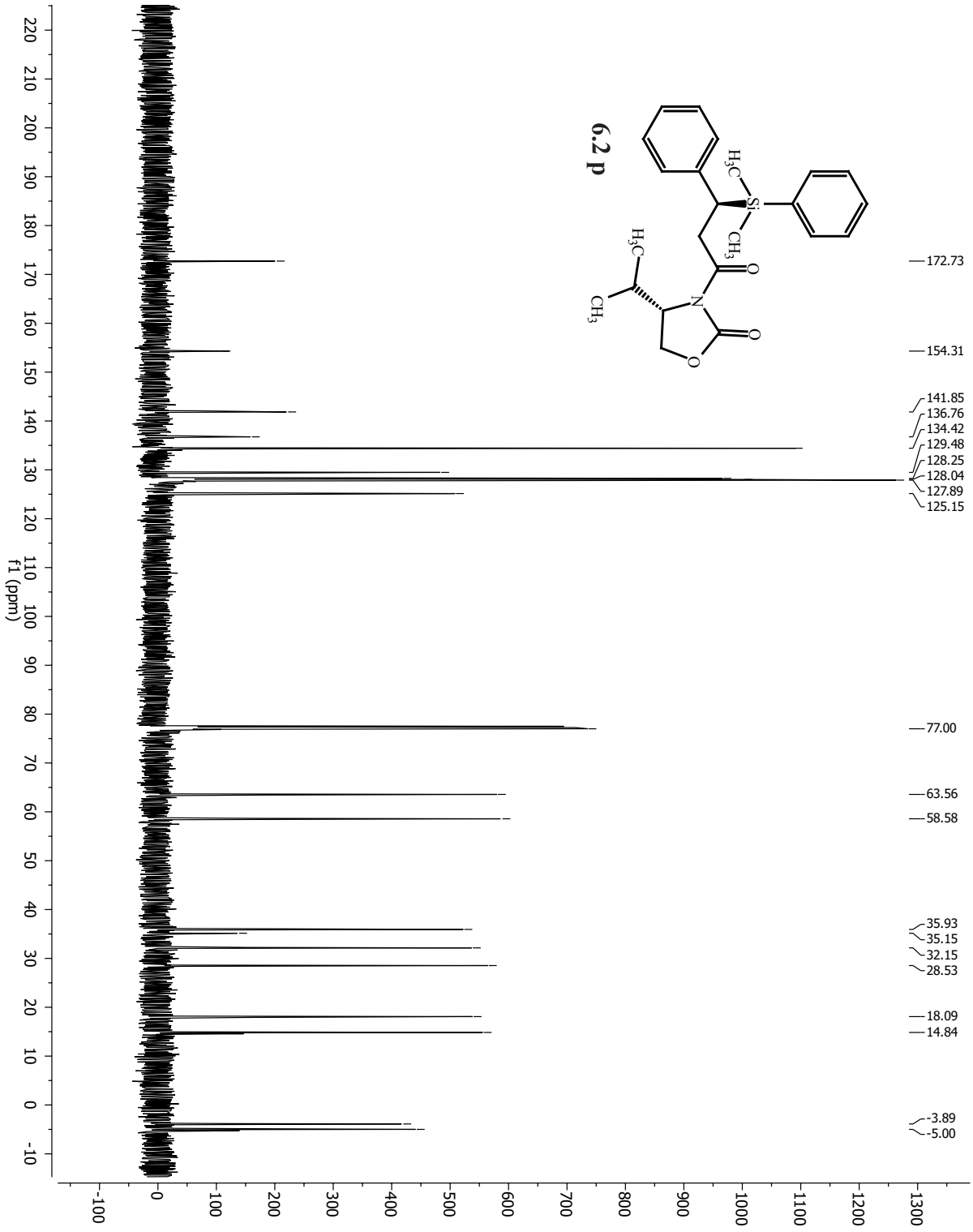

6.9 sm
7.13
1.00
0.97
0.98
0.97
0.96
1.94
2.01
2.85
f1 (ppm)

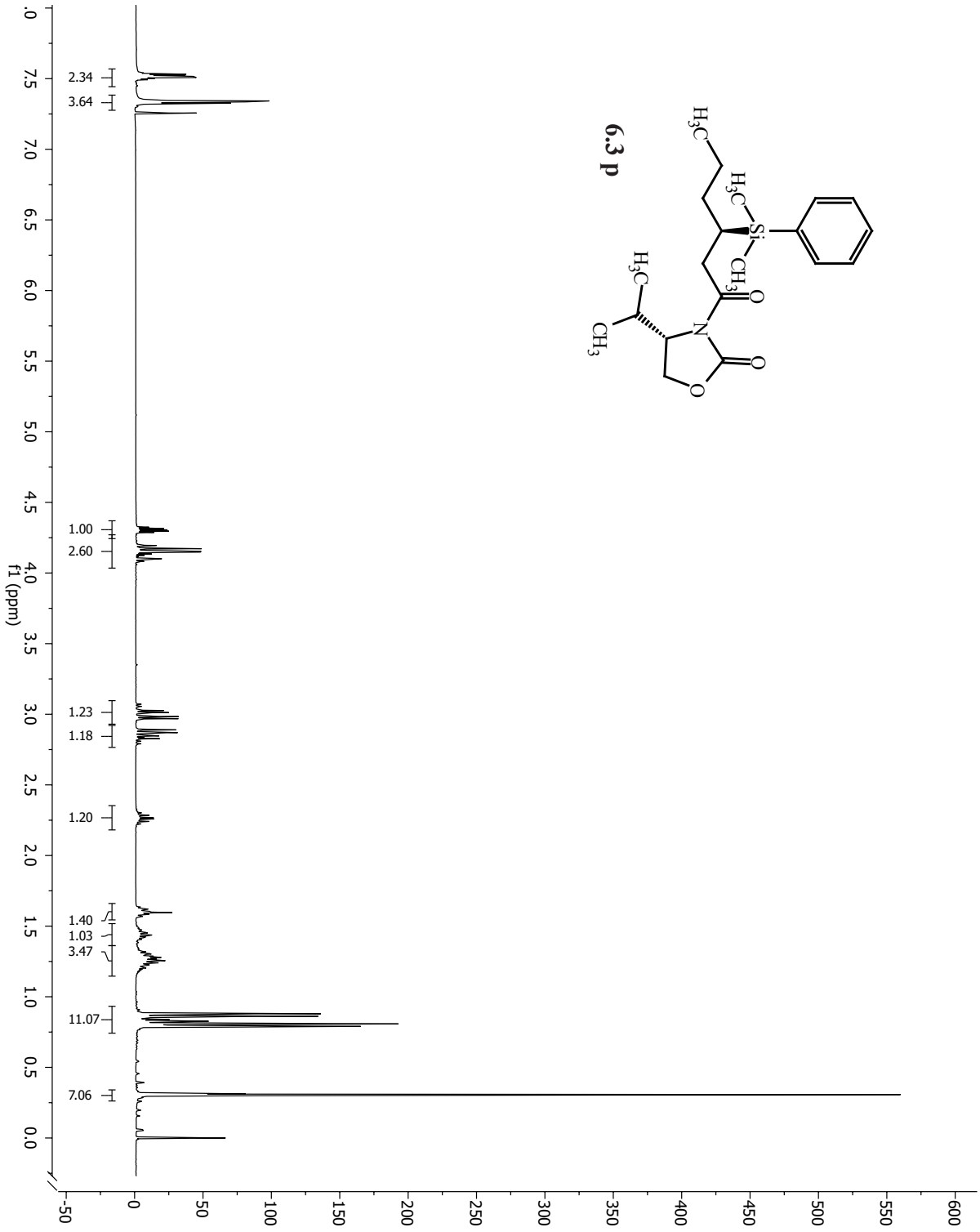

6.9 sm
165.15
153.44
151.70
135.45
129.46
128.95
127.31
120.54
77.27 cdcl3
77.22
77.02 cdcl3
76.76 cdcl3
66.12
55.35
37.97
34.71
21.41
13.70
-0.00
f1 (ppm)

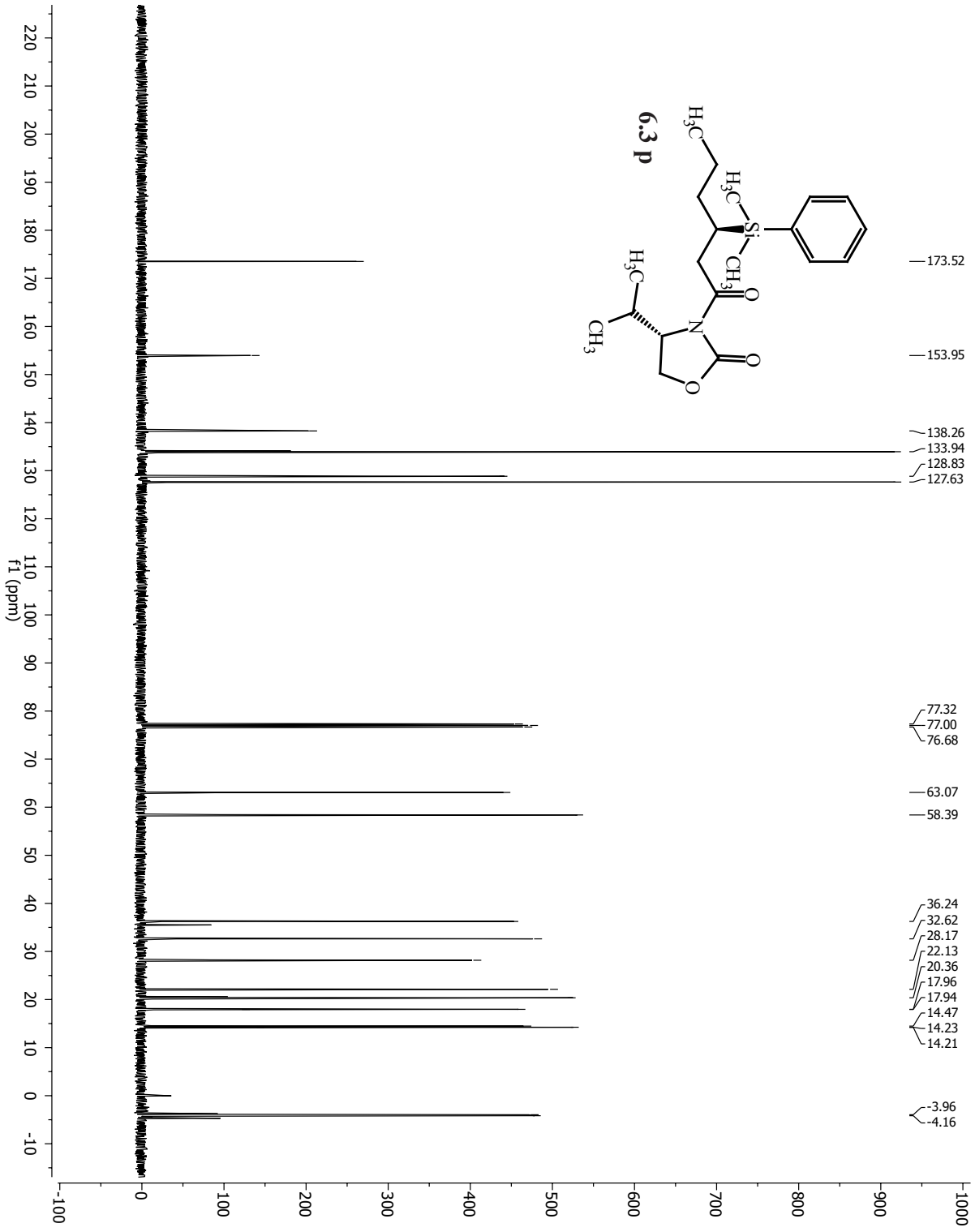

6.12 sm
4.82
7.01
1.00
0.97
1.00
1.00
2.02
2.01
2.99
f1 (ppm)

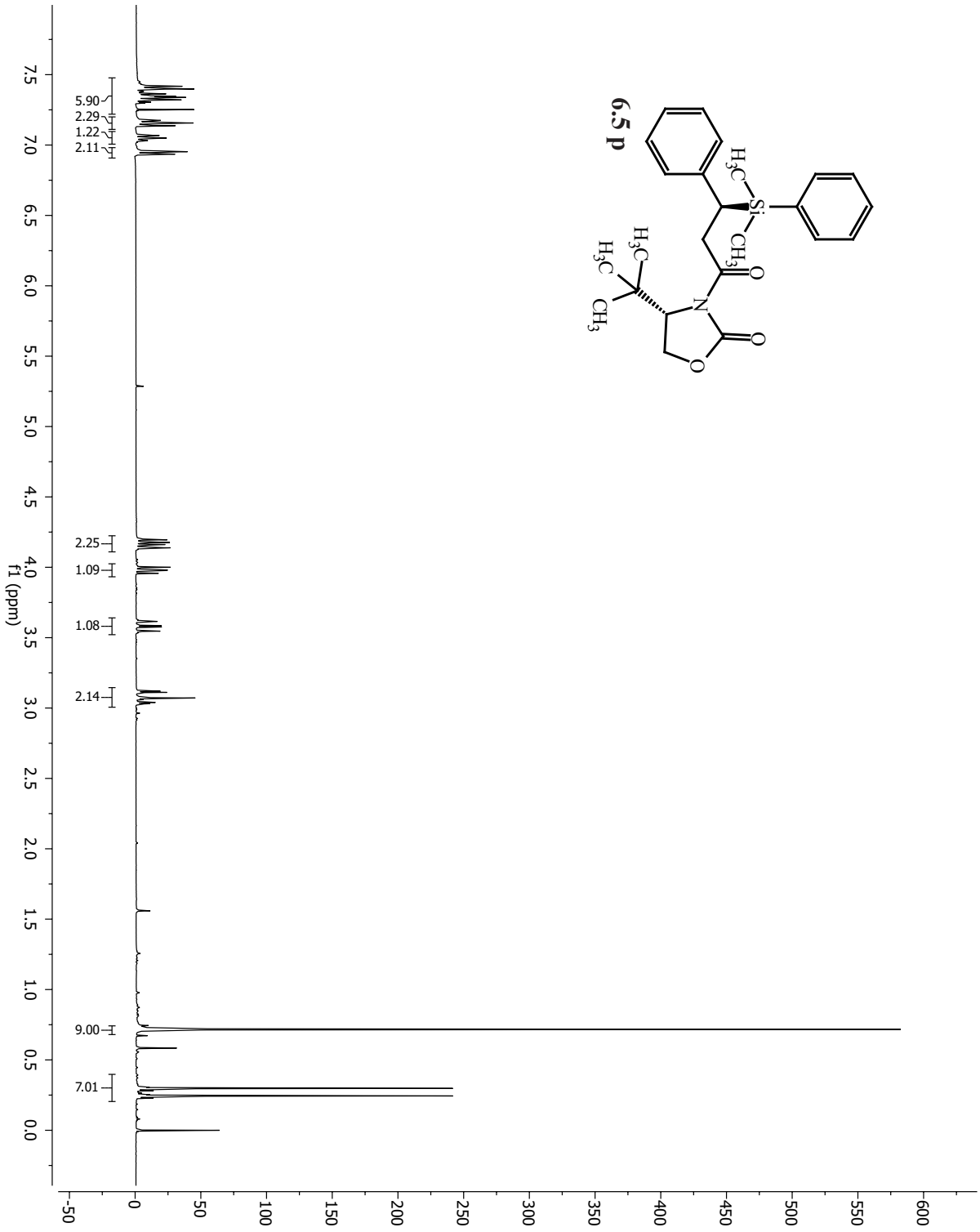

6.12 sm
H3C
O
N
O
O
164.67
153.71
151.99
139.18
129.17
128.64
125.96
120.35
77.28 cdcl3
77.22
77.02 cdcl3
76.77 cdcl3
69.94
57.77
34.69
21.33
13.68
0.00
f1 (ppm)

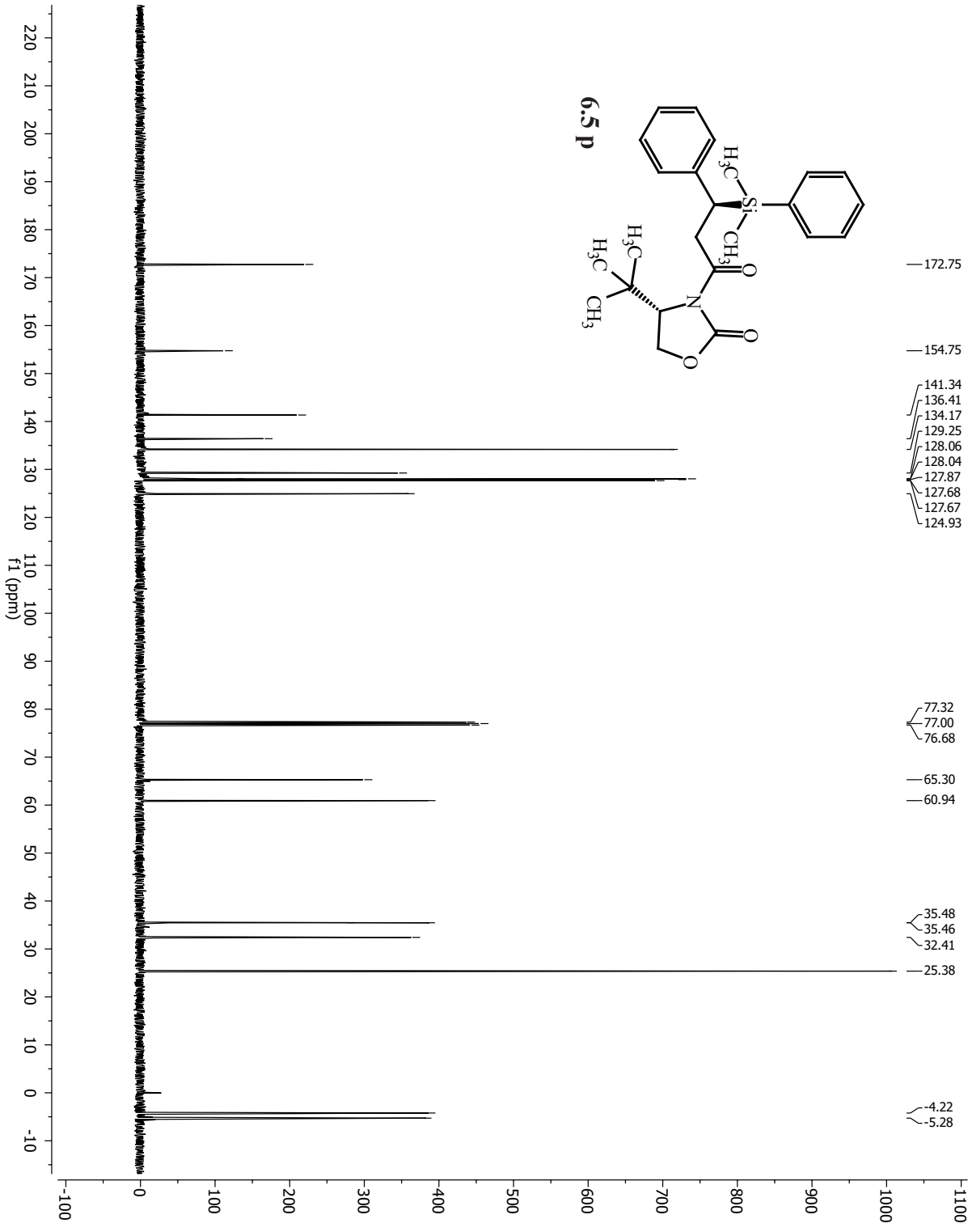

6.2 p
10.00
2.56
0.74
1.62
0.80
4.13
4.27
f1 (ppm)

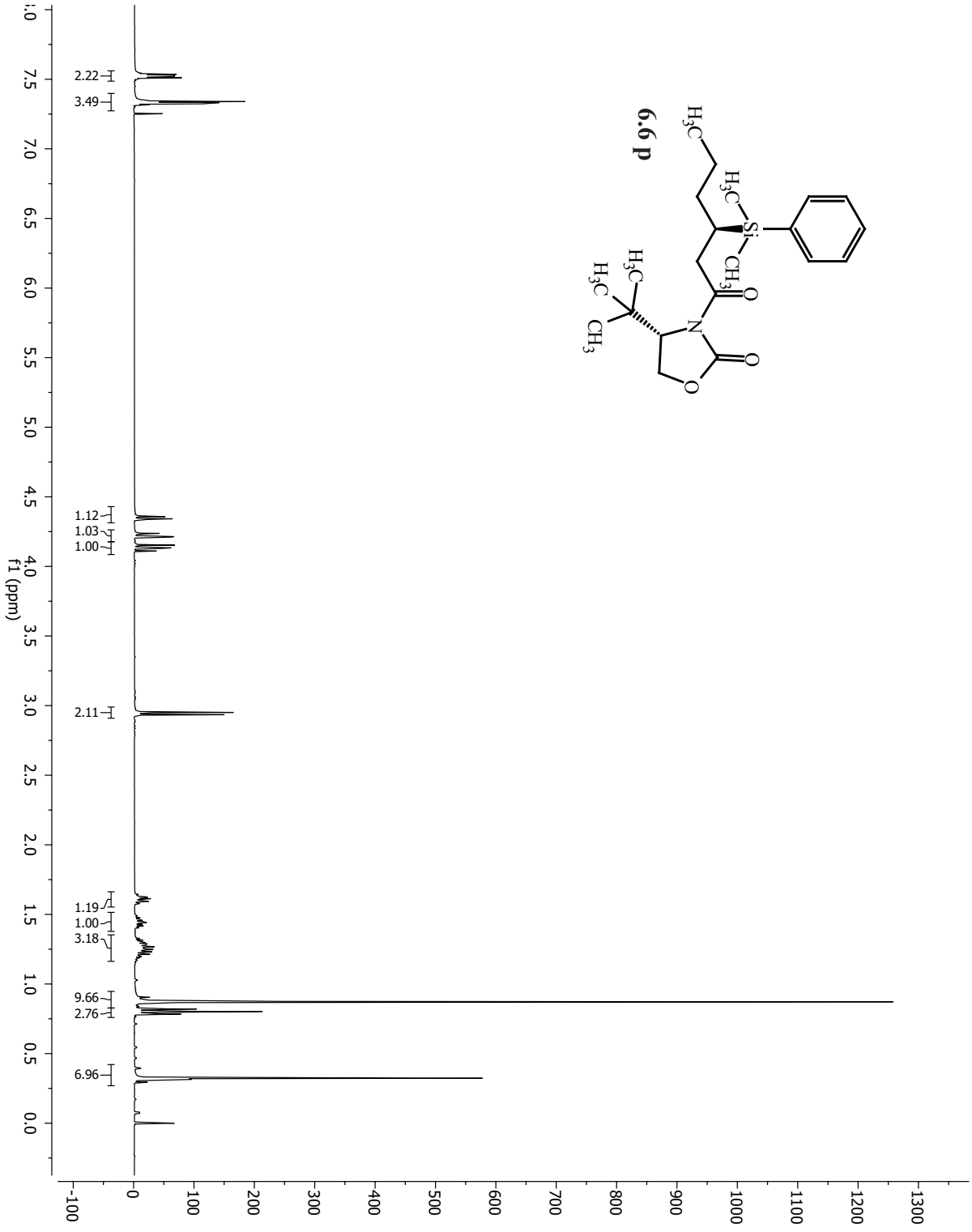

6.2 p
172.73
154.31
141.85
136.76
134.42
129.48
128.25
128.04
127.89
125.15
77.00
63.56
58.58
35.93
35.15
32.15
28.53
18.09
14.84
-3.89
-5.00
f1 (ppm)

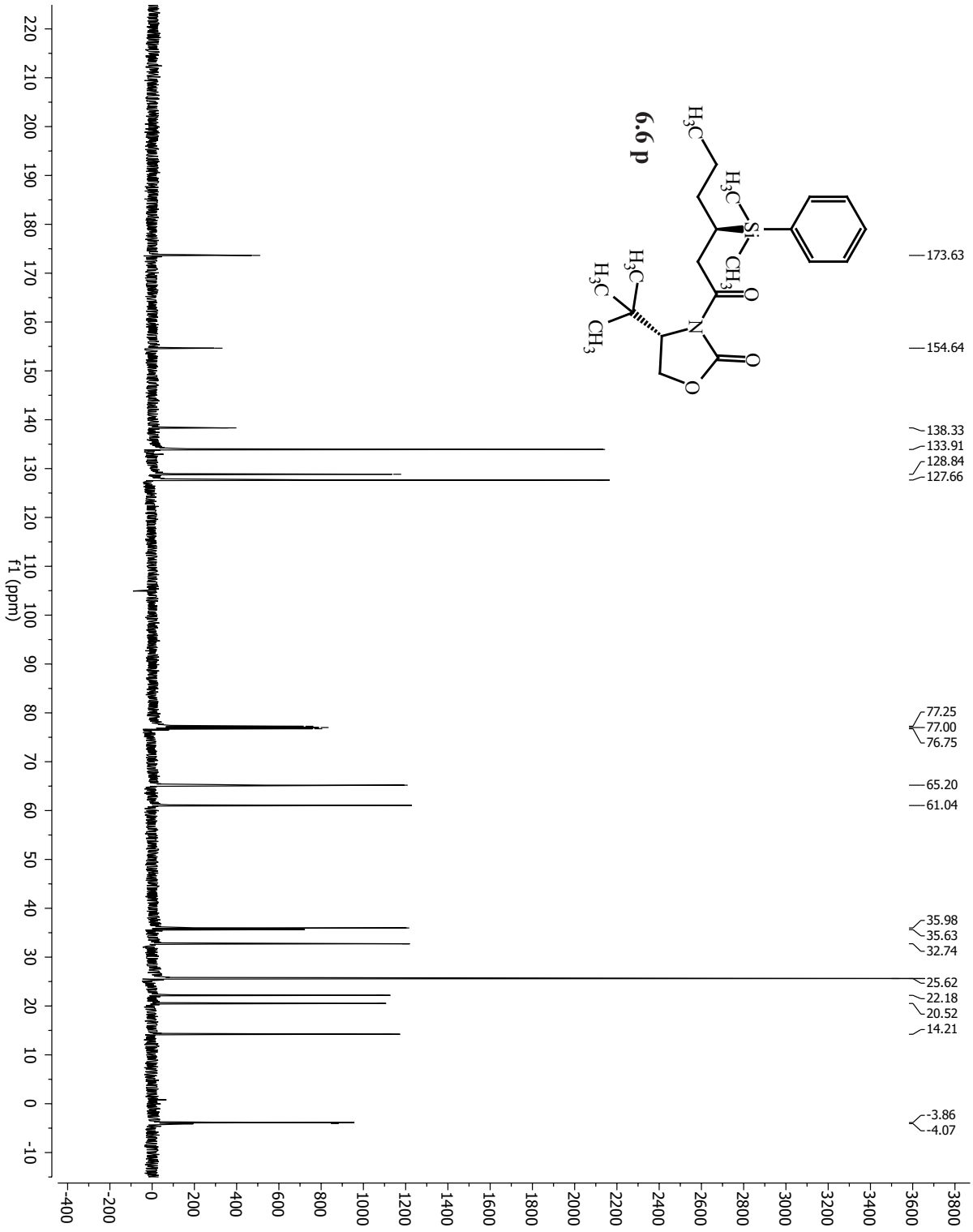

6.3 p
f1 (ppm)
2.34
3.64
1.00
2.60
1.23
1.18
1.20
1.40
1.03
3.47
11.07
7.06

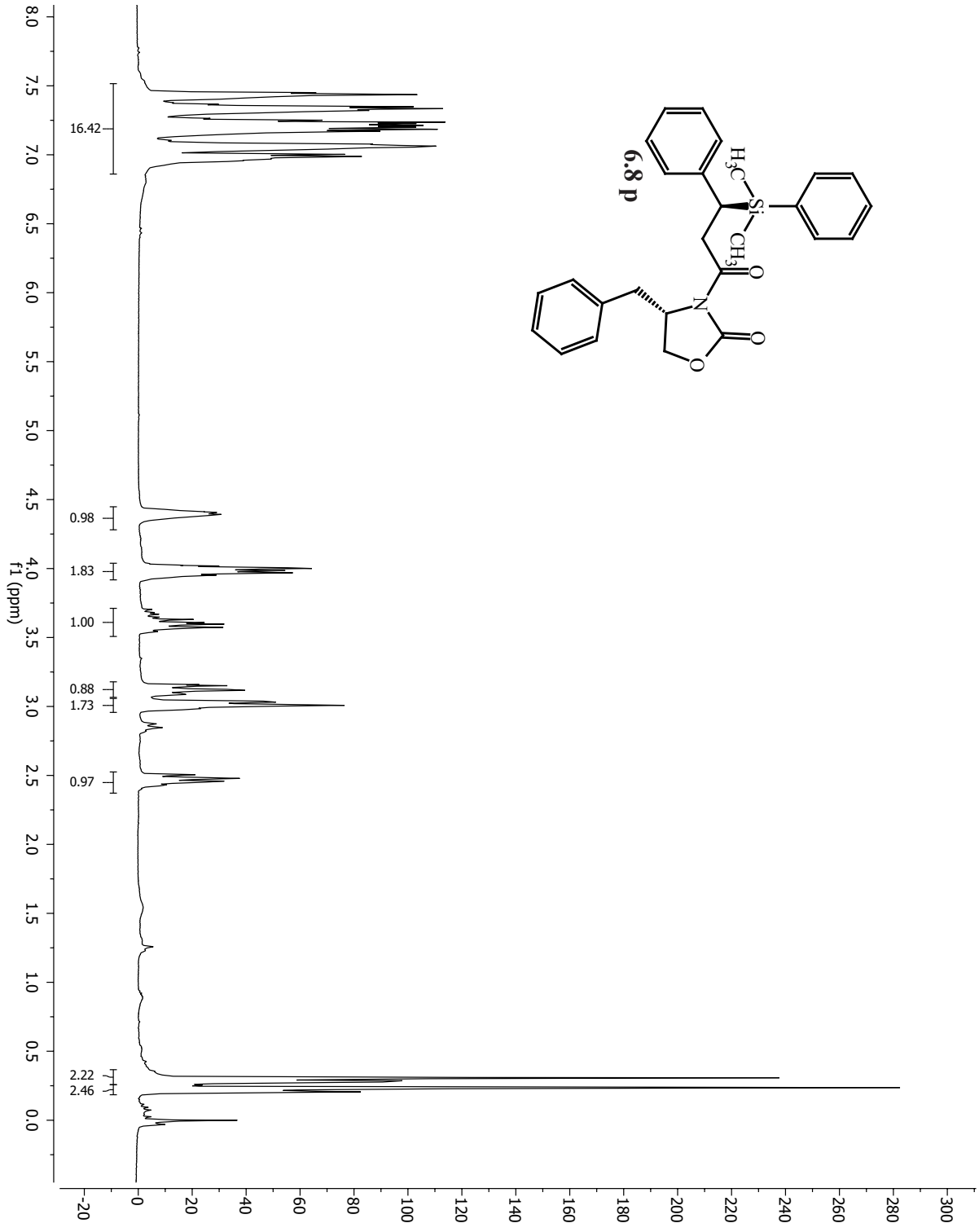

6.3 p
173.52
153.95
138.26
133.94
128.83
127.63
77.32
77.00
76.68
63.07
58.39
36.24
32.62
28.17
22.13
20.36
17.96
17.94
14.47
14.23
14.21
-3.96
-4.16
f1 (ppm)

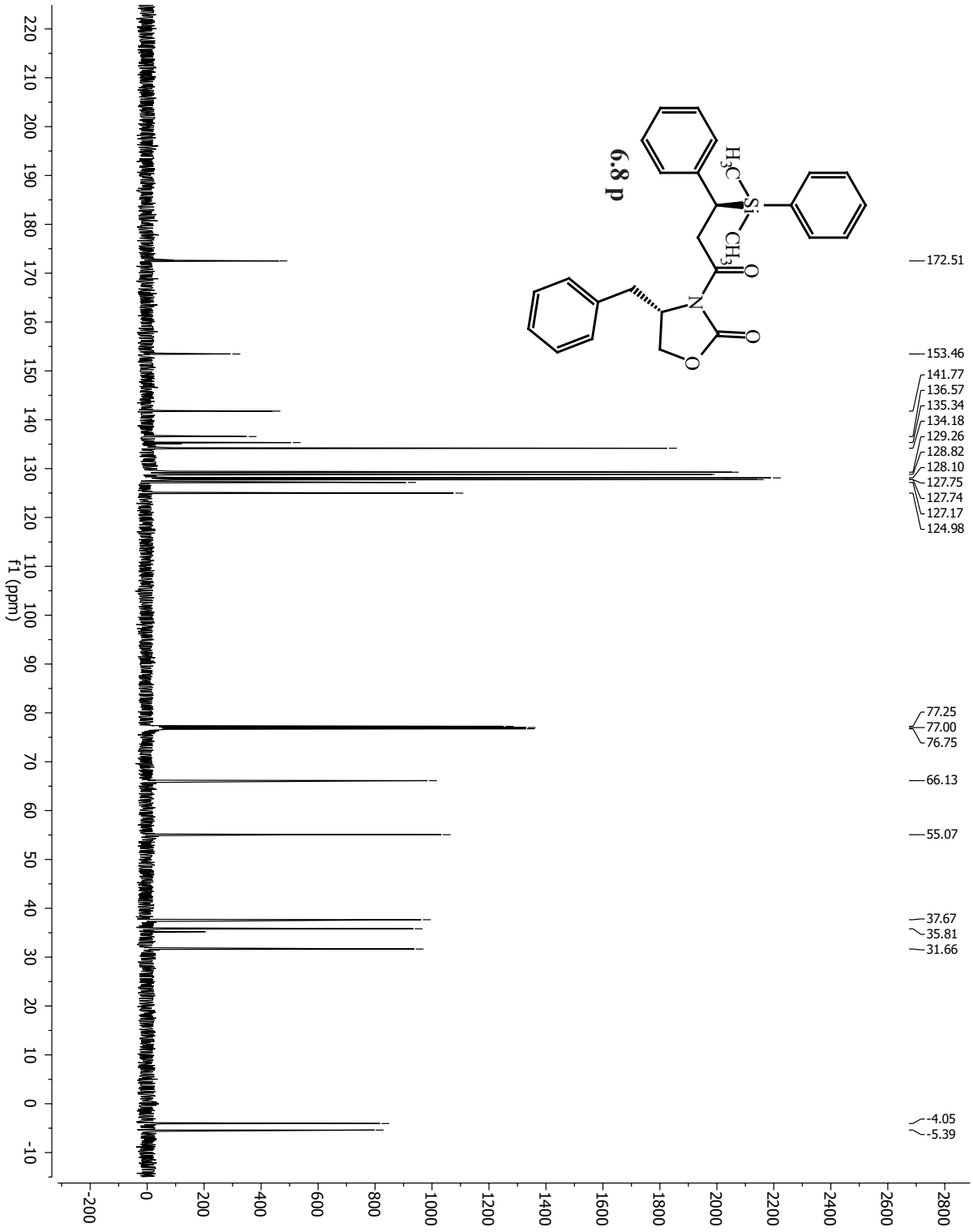

6.5 p
5.90
2.29
1.22
2.11
2.25
1.09
1.08
2.14
9.00
7.01
f1 (ppm)

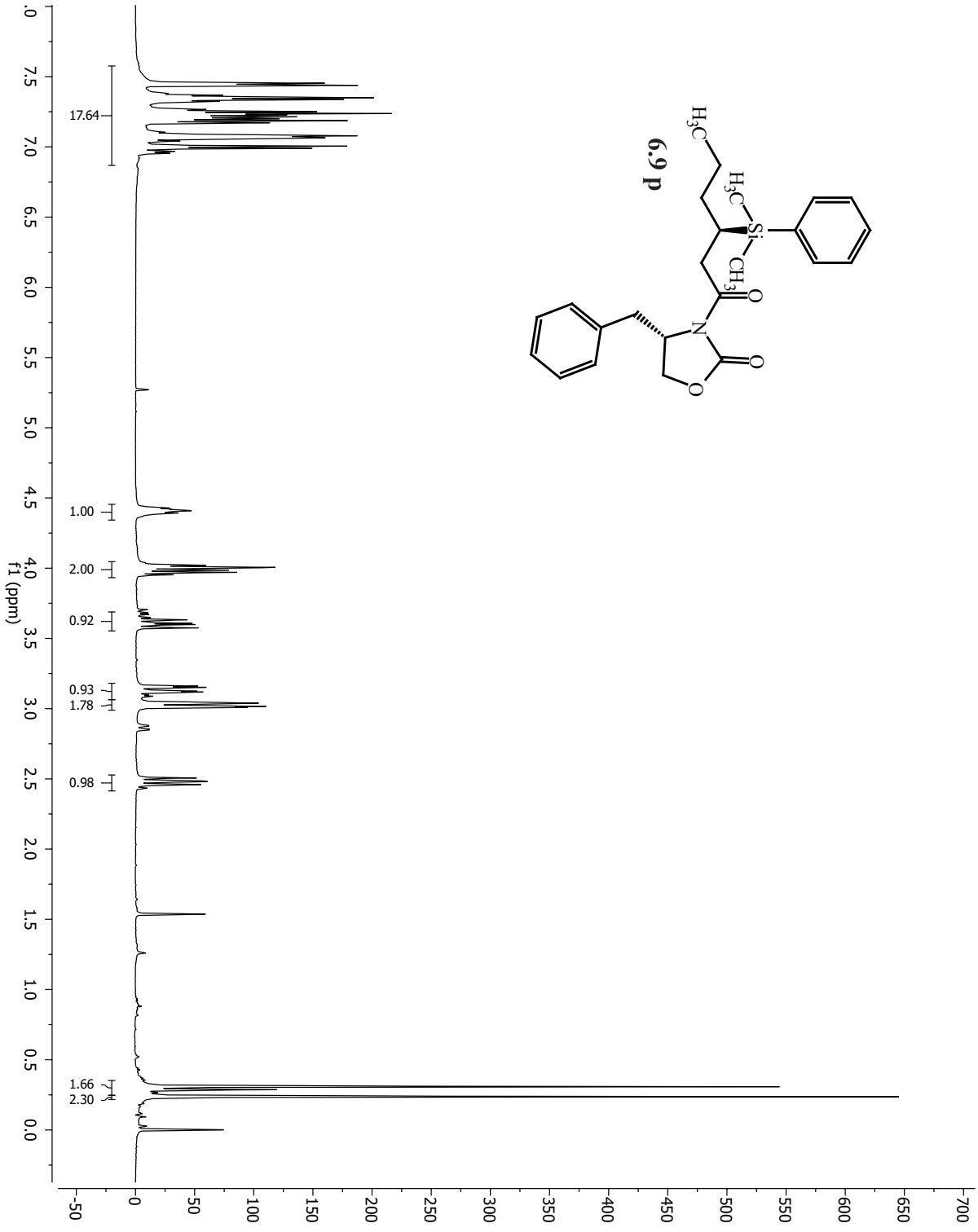

6.5 p
172.75
154.75
141.34
136.41
134.17
129.25
128.06
128.04
127.87
127.68
127.67
124.93
77.32
77.00
76.68
65.30
60.94
35.48
35.46
32.41
25.38
-4.22
-5.28
f1 (ppm)


6.9 p
2.22
3.49
1.12
1.03
1.00
2.11
1.19
1.00
3.18
9.66
2.76
6.96
f1 (ppm)

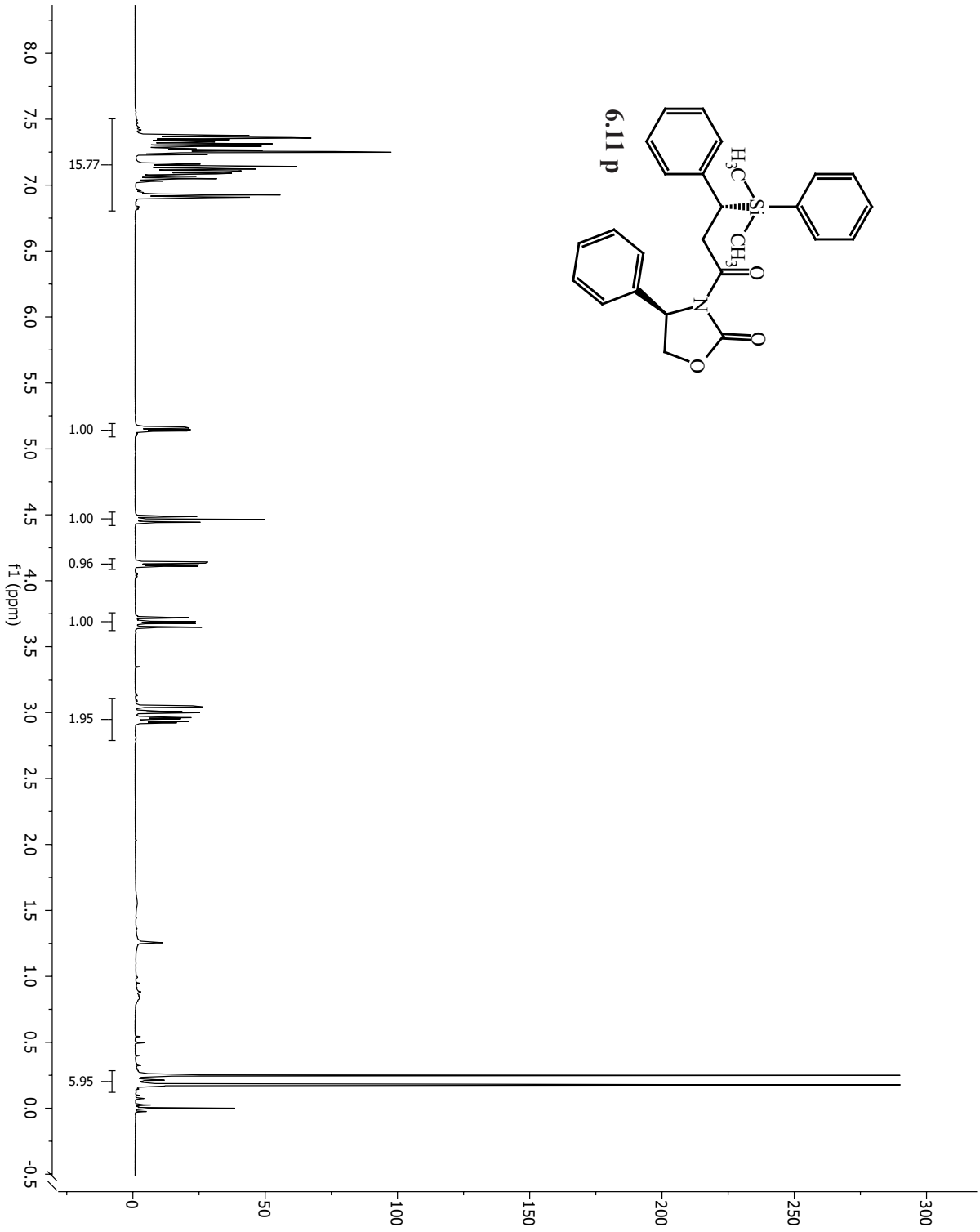

6.6 p
173.63
154.64
138.33
133.91
128.84
127.66
77.25
77.00
76.75
65.20
61.04
35.98
35.63
32.74
25.62
22.18
20.52
14.21
-3.86
-4.07
f1 (ppm)

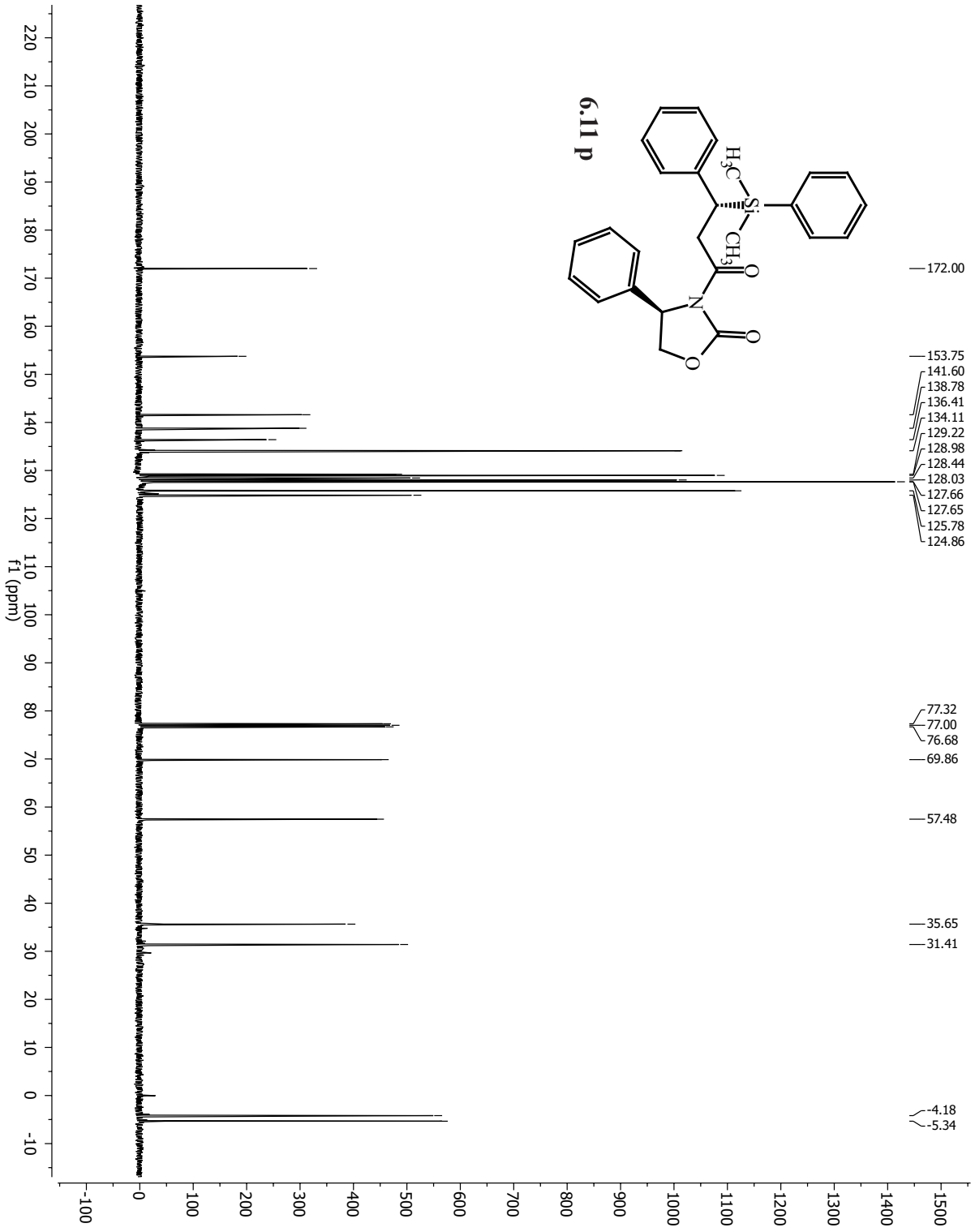

6.8 p
H3C
Si
CH3
O
N
O
O
16.42
0.98
1.83
1.00
0.88
1.73
0.97
2.22
2.46
f1 (ppm)

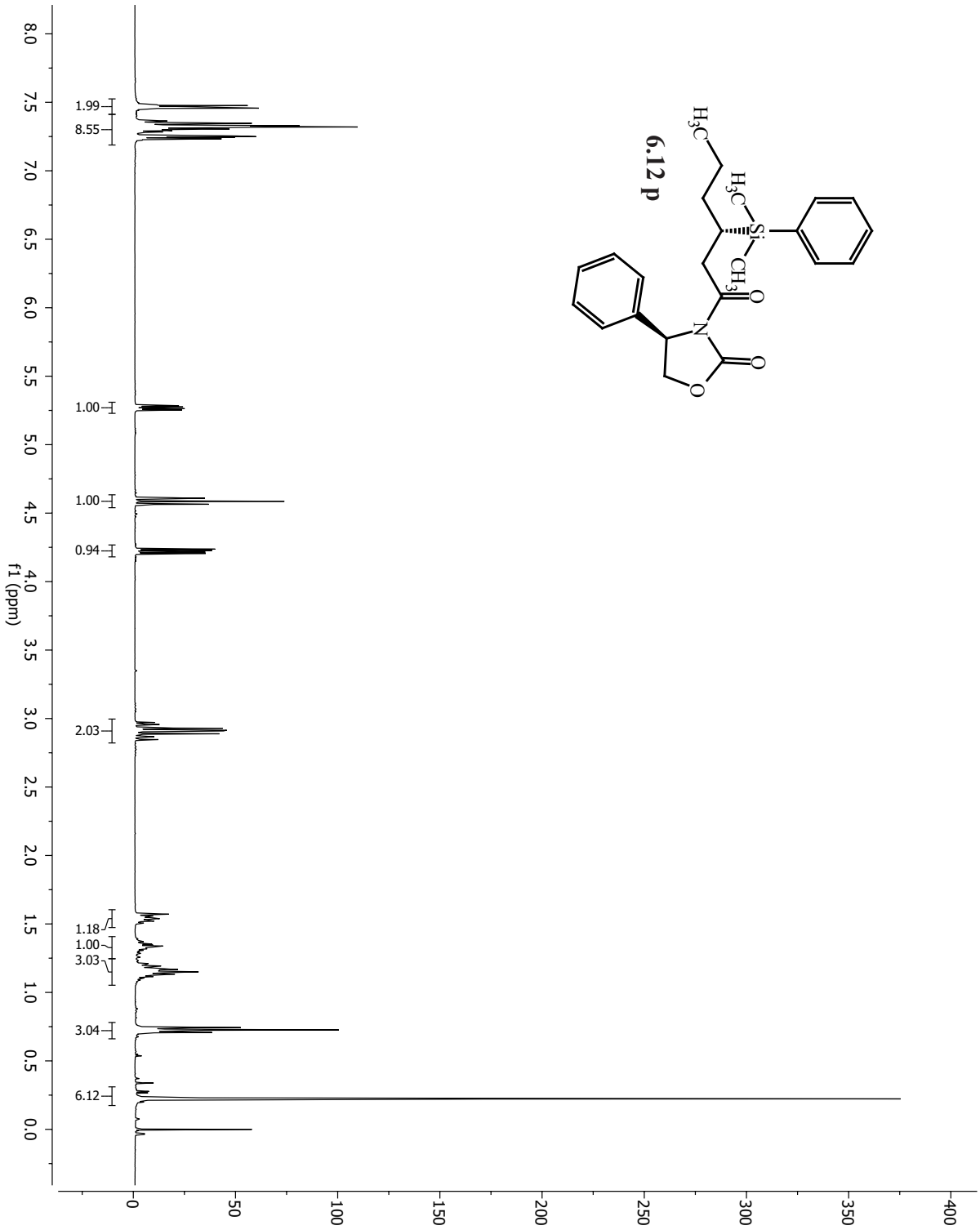

6.8 p
H3C
Si
CH3
O
N
O
O
172.51
153.46
141.77
136.57
135.34
134.18
129.26
128.82
128.10
127.75
127.74
127.17
124.98
77.25
77.00
76.75
66.13
55.07
37.67
35.81
31.66
-4.05
-5.39
f1 (ppm)

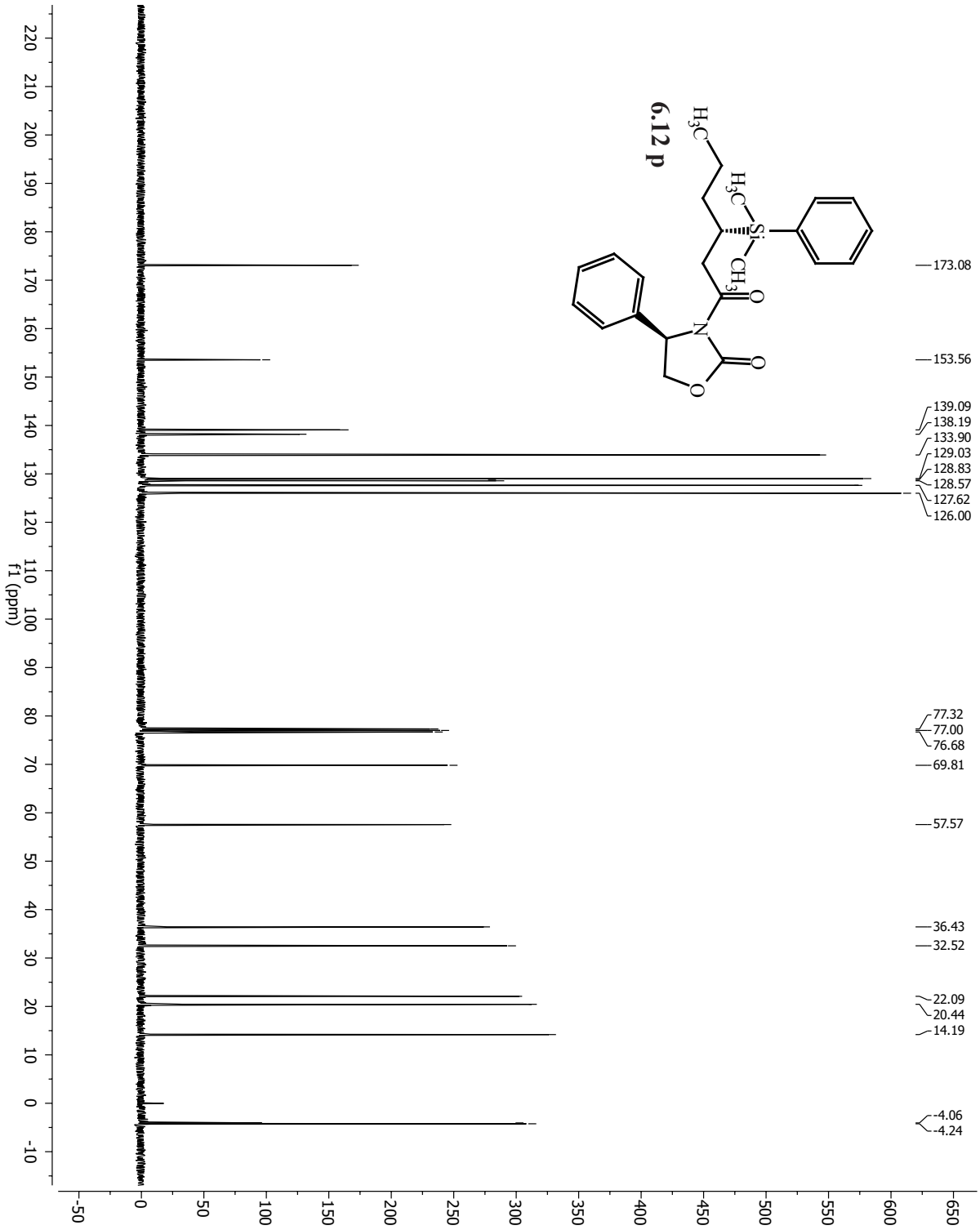

6.9 p
17.64
1.00
2.00
0.92
0.93
1.78
0.98
1.66
2.30
f1 (ppm)

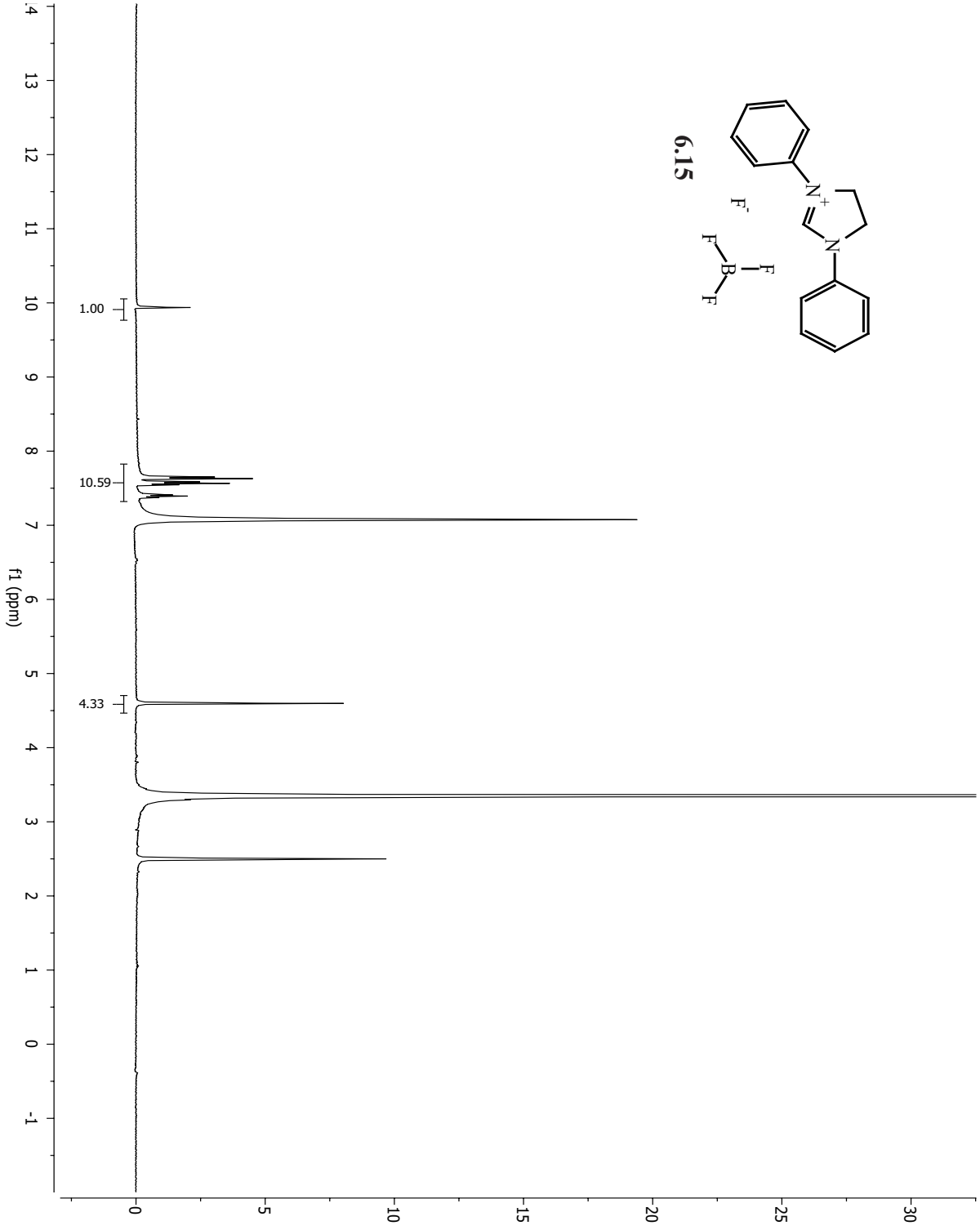

6.9 p
172.77
153.72
142.03
136.83
135.59
134.43
129.52
129.08
128.36
128.01
127.99
127.43
125.23
77.51
77.25
77.00
66.39
55.32
37.93
36.06
31.92
-3.79
-5.13
f1 (ppm)

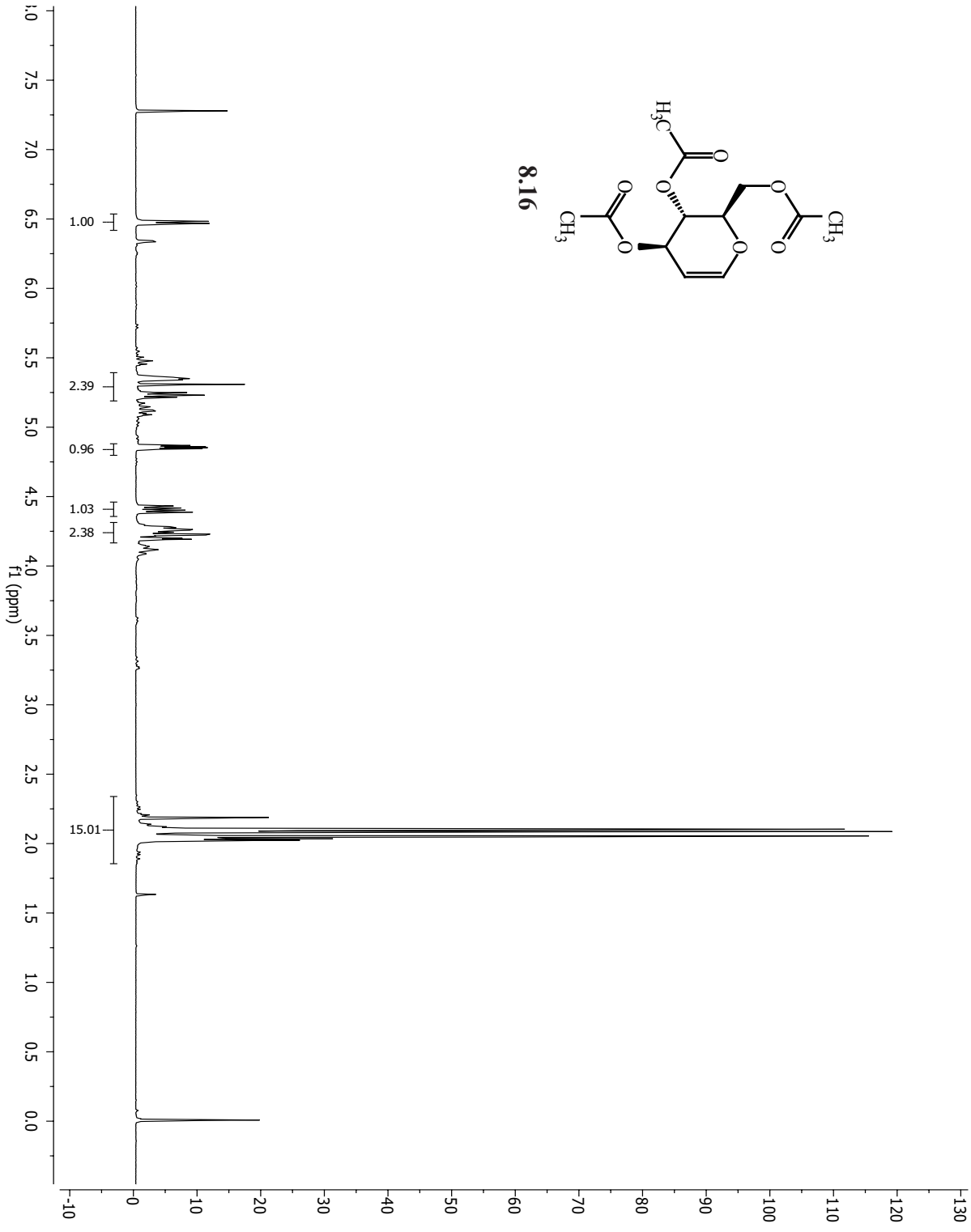

6.11 p
H3C
Si
CH3
O
N
O
O
15.77
1.00
1.00
0.96
1.00
1.95
5.95
f1 (ppm)


6.11 p
172.00
153.75
141.60
138.78
136.41
134.11
129.22
128.98
128.44
128.03
127.66
127.65
125.78
124.86
77.32
77.00
76.68
69.86
57.48
35.65
31.41
-4.18
-5.34
f1 (ppm)


6.12 p
f1 (ppm)
1.99
8.55
1.00
1.00
0.94
2.03
1.18
1.00
3.03
3.04
6.12


6.12 p
173.08
153.56
139.09
138.19
133.90
129.03
128.83
128.57
127.62
126.00
77.32
77.00
76.68
69.81
57.57
36.43
32.52
22.09
20.44
14.19
-4.06
-4.24
f1 (ppm)


6.15
1.00
10.59
4.33
f1 (ppm)


8.16
1.00
2.39
0.96
1.03
2.38
15.01
f1 (ppm)

REFERENCES

1. Asami, Y.; Kakeya, H.; Onose, R.; Yoshida, A.; Matsuzaki, H.; Osada, H. *Org. Lett.* **2002**, *4* (17), 2845-2848.

2. Asami, Y.; Kakeya, H.; Komi, Y.; Kojima, S.; Nishikawa, K.; Beebe, K.; Neckers, L.; Osada, H. *Cancer Sci.* **2008**, *99* (9), 1853.

3. Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97* (6), 2063-2192.

4. Pollock, P.; Dambacher, J.; Anness, R.; Bergdahl, M. *Tetrahedron Lett.* **2002**, *43* (20), 3693-3697.

5. Dambacher, J. and Bergdahl, M. *J. Org. Chem.* **2005**, *70* (2), 580-589.

6. Byrne, P. and Gilheany, D. *Chem. Soc. Rev.* **2013**, *42* (16), 6670-6696.

7. El-Batta, A.; Jiang, C.; Zhao, W.; Anness, R.; Cooksy, A.; Bergdahl, M. *J. Org. Chem.* **2007**, *72* (14), 5244-5259.

8. Kelly, M.; Fallot, L.; Gustafson, J.; Bergdahl, M. *J. Chem. Educ.* **2016**, *93* (9), 1631-1636.

9. Lipinski, C.; Lombardo, F.; Dominy, B.; Feeney, P. *Adv. Drug Delivery Rev.* **2001**, *46* (1), 3-26.

10. Li, L.; Chen, Z.; Zhang, X.; Jia, Y. *Chem. Rev.* **2018**, *118* (7), 3752-3832.

11. Bloch, P. and Tamm, C. *Helv. Chim. Acta*. **1976**, *59* (1), 133-137.

12. (a) Mohr, P. and Tamm, C. *Tetrahedron*. **1981**, *37* (1), 201-212. (b) Bloch, P. and Tamm, C. *Helv. Chim. Acta*. **1981**, *64* (1), 304-315. (c) Breitenstein, W.; Chexal, K.; Mohr, P.; Tamm, C. *Helv. Chim. Acta*. **1981**, *64* (2), 379-388.

13. (a) Dolder, M.; Shao, X.; Tamm, C. *Helv. Chim. Acta*. **1990**, *73* (1), 63-68. (b) Shao, X.; Dolder, M.; Tamm, C. *Helv. Chim. Acta*. **1990**, *73* (2), 483-491.

14. Shao, X. and Tamm, C. *Tetrahedron Lett.* **1991**, *32* (25), 2891-2892.

15. Wenke, J.; Anke, H.; Sterner, O. *Biosci. Biotech. Biochem.* **1993**, *57* (6), 961-964.

16. (a) Su, Z. and Tamm, C. *Helv. Chim. Acta.* **1995**, *78* (5), 1278-1290. (b) Su, Z. and Tamm, C. *Tetrahedron*. **1995**, *51* (41), 11177-11182.

17. Komagata, D.; Fujita, S.; Yamashita, N.; Saito, S.; Morino, T. *J. Antibiotics*. **1996**, *49* (9), 958-959.

18. Igarashi, Y.; Yabuta, Y.; Sekine, A.; Fujii, K.; Harada, K.; Oikawa, T.; Sato, M.; Furumai, T.; Oki, T. *J. Antibiotics.* **2004**, *57* (11), 748-754.

19. Ishikawa, M.; Ninomiya, T.; Akabane, H.; Kushida, N.; Tsujiuchi, G.; Ohyama, M.; Gomi, S.; Shito, K.; Murata, T. *Bioorg. Med. Chem. Lett.* **2009**, *19* (5), 1457-1460.

20. Mehedi, M.; Molla, A.; Khondkar, P.; Sultana, S.; Islam, M.; Rashid, M.; Chowdhury, R. *Asian J. Chem.* **2010**, *22* (4), 2611-2614.

21. Wang, F.; Li, D.; Zhu, T.; Zhang, M.; Gu, Q. *Can. J. Chem.* **2011**, *89* (1), 72-76.

22. Pinheiro, E.; Carvalho, J.; dos Santos, D.; Feitosa, A.; Marinho, P.; Guilhon, G.; de Souza, A.; da Silva, F.; Marinho, A. *Nat. Prod. Res.* **2013**, *27* (18), 1633-1638.

23. Yamada, T.; Ohshima, M.; Yuasa, K.; Kikuchi, T.; Tanaka, R. *Marine Drugs*. **2016**, *14* (4), 74.

24. Xu, L.; Cao, F.; Yang, Q.; Li, W.; Tian, S.; Zhu, H.; Zhao, Y.; Yang, X. *Tetrahedron*. **2016**, *72* (45), 7194-7199.

25. Aoki, S.; Ohi, T.; Shimizu, K.; Shiraki, R.; Takao, K.; Tadano, K. *Heterocycles*. **2002**, *58* (1), 57-61.

26. (a) Aoki, S.; Oi, T.; Shimizu, K.; Shiraki, R.; Takao, K.; Tadano, K. *Heterocycles*. **2004**, *62*, 161-166. (b) Aoki, S.; Oi, T.; Shimizu, K.; Shiraki, R.; Takao, K.; Tadano, K. *Bull. Chem. Soc. Jpn.* **2004**, *77* (9), 1703-1716.

27. Jones, J. and Thompson, J. *Can. J. Chem.* **1957**, *35* (9), 955-959.

28. Schmidt, O. *Methods in Carbohydrate Chemistry*, Whistler, R.; Wolfrom, M.; BeMiller, J., Editors. Academic Press, NY, **1963**, *2*, 318-325.

29. Brimacombe, J. and Ching, O. *Carbohydrate Research*. **1968**, *8* (1), 82-88.

30. Stamos, D. and Kishi, Y. *Tetrahedron Lett.* **1996**, *37* (48), 8643-8646.

31. Hine, J. and Brader, W. *J. Am. Chem. Soc.* **1954**, *77* (2), 361-364.

32. Hayashi, Y.; Shoji, M.; Yamaguchi, S.; Mukaiyama, T.; Yamaguchi, J.; Kakeya, H.; Osada, H. *Org. Lett.* **2003**, *5* (13), 2287-2290.

33. Hayashi, Y.; Shoji, M.; Yamaguchi, J.; Sato, K.; Yamaguchi, S.; Mukaiyama, T.; Sakai, K.; Asami, Y.; Kakeya, H.; Osada, H. *J. Am. Chem. Soc.* **2002**, *124* (41), 12078-12079.

34. Mitchell, J. and Finney, N. *Org. Biomol. Chem.* **2005**, *3* (23), 4274-4281.

35. Ando, O.; Satake, H.; Nakajima, M.; Sato, A.; Nakamura, T.; Kinoshita, T.; Furuya, K.; Haneishi, T. *J. Antibiotics*. **1991**, *44* (4), 382-389.

36. Igarashi, Y.; Yabuta, Y.; Furumai, T. *J. Antibiotics*. **2004**, *57* (8), 537-540.

37. Hayashi, Y.; Shoji, M.; Mukaiyama, T.; Gotoh, H.; Yamaguchi, S.; Nakata, M.; Kakeya, H.; Osada, H. *J. Org. Chem.* **2005**, *70* (14), 5643-5654.

38. Ishikawa, M. and Ninomiya, T. *J. Antibiotics*. **2008**, *61* (11), 692-695.

39. Mizoue, K.; Okazaki, T.; Hanada, K.; Amamoto, T.; Yamagashi, M.; Omura, S. *Eur. Pat. Appl.* EP 216607, J. P. Appl. 205278, **1987**; *Chem. Abstr*., **1987**, *107*, 132627x.

40. Orellana, A. and Rovis, T. *Chem. Commun.* **2008**, *6*, 730-732.

41. Hayashi, Y.; Sankar, K.; Ishikawa, H.; Nozawa, Y.; Mizoue, K.; Kakeya, H. *Bioorg. Med. Chem. Lett.* **2009**, *19* (14), 3863-3865.

42. Yamada, T.; Kitada, H.; Kajimoto, T.; Numata, A.; Tanaka, R. *J. Org. Chem.* **2010**, *75* (12), 4146-4153.

43. Chalupa, D.; Vojackova, P.; Partl, J.; Pavlovic, D.; Necas, M.; Svenda, J. *Org. Lett.* **2017**, *19* (4), 750-753.

44. Jiang, Y.; Chan, W.; Park, C. *J. Am. Chem. Soc.* **2012**, *134* (9), 4104-4107.

45. Yamada, T.; Imai, E.; Nakatuji, K.; Numata, A.; Tanaka, R. *Tetrahedron Lett.* **2007**, *48* (36), 6294-6296.

46. Lathrop, S. and Rovis, T. *Chem. Sci.* **2013**, *4* (4), 1668-1673.

47. Stierle, A.; Stierle, D.; Patacini, B. *J. Nat. Prod.* **2008**, *71* (5), 856-860.

48. Komori, K.; Taniguchi, T.; Mizutani, S.; Monde, K.; Kuramochi, K.; Tsubaki, K. *Org. Lett.* **2014**, *16* (5), 1386-1389.

49. Mizutani, S.; Komori, K.; Kai, C.; Kuramochi, K.; Tsubaki, K. *Tetrahedron*. **2016**, *72* (42), 6640-6645.

50. Jo, D. and Han, S. *Org. Chem. Frontiers*. **2017**, *4* (4), 506-509.

51. Kang, T.; Jo, D.; Han, S. *J. Org. Chem.* **2017**, *82* (18), 9335-9341.

52. Emoto, M.; Yano, K.; Choijamts, B.; Sakai, S.; Hirasawa, S.; Wakamori, S.; Aizawa, M.; Nabeshima, K.; Tachibana, K.; Kanomata, N. *Anticancer Research*. **2015**, *35* (5), 2739-2746.

53. Sugi, M.; Nagase, R.; Misaki, T.; Nakatsuji, H.; Tanabe, Y. *Eur. J. Org. Chem.* **2016**, *28*, 4834-4841.

54. (a) El-Batta, A.; Hage, T.; Plotkin, S.; Bergdahl, M. *Org. Lett.* **2004**, *6* (1), 107-110. (b) El-Batta, A. and Bergdahl, M. *Org. Synth.* **2007**, *84*, 192-198.

55. (a) Henrot, S.; Larcheveque, M.; Petit, Y. *Synthetic Commun.* **1986**, *16* (2), 183-190. (b) Axelsson, B.; O'Toole, K.; Spencer, P.; Young, D. *J. Chem. Soc. Perkin Trans. 1*. **1994**, *7*, 807-815.

56. (a) Kočalka, P.; Pohl, R.; Rejman, D.; Rosenberg, I. *Tetrahedron*. **2006**, *62* (24), 5763-5774. (b) Qiu, F.; Wei, L.; Lu, C. *Advanced Materials Research, Part 2: Adv in Chem. Eng*. **2012**, *vols. 396-398*, 1244-1247.

57. (a) de Figueiredo, R.; Voith, M.; Frohlich, R.; Christmann, M. *Synlett*. **2007**, *3*, 391-394. (b) Huang, P.; Zheng, X.; Wang, S.; Ye, J.; Jin, L.; Chen, Z. *Tetrahedron: Asymmetry*. **1999**, *10* (17), 3309-3317.

58. (a) Klaver, W.; Hiemstra, H.; Speckamp, W. *Tetrahedron Lett.* **1987**, *28* (14), 1581-1584. (b) Koot, W.; Hiemstra, H.; Speckamp, W. *J. Org. Chem.* **1992**, *57* (4), 1059-1061.

59. (a) Greene, T. and Wuts, P. *Protecting Groups in Organic Synthesis,* 3rd ed. John Wiley & Sons: NY. **1999**, 127-132. (b) Corey, E. and Venkateswarlu, A. *J. Am. Chem. Soc.* **1972**, *94* (17), 6190-6191.

60. Das, P.; Das, P.; Arunan, E. *J. Phys. Chem.* **2015**, *119* (16), 3710-3720.

61. Smith, A.; Rzepa, H.; White, A.; Billen, D.; Hii, K. *J. Org. Chem.* **2010**, *75* (9), 3085-3096.

62. (a) Murray, R. and Singh, M. *Org. Synth.* **1997**, *74*, 91; Coll. Vol. 9, 288. (b) Mikula, H.; Svatunek, D.; Lumpi, D.; Glocklhofer, F.; Hametner, C.; Frohlich, J. *Org. Proccess Res. Dev.* **2013**, *17* (2), 313-316.

63. Edmonds, D.; Muir, K.; Procter, D. *J. Org. Chem.* **2003**, *68* (8), 3190-3198.

64. Zimmer, R.; Homann, K.; Angermann, J.; Reissig, H. *Synthesis*. **1999**, *7*, 1223-1235.

65. (a) Barrett, A.; Head, J.; Smith, M.; Stock, N.; White, A.; Williams, D. *J. Org. Chem.* **1999**, *64* (16), 6005-6018. (b) Harris, M.; Geis, O.; Buchwald, S. *J. Org. Chem.* **1999**, *64* (16), 6019-6022.

66. (a) Sniady, A.; Morreal, M.; Dembinski, R. *Org. Synth.* **2007**, *84*, 199. (b) Eisenbraun, E. *Org. Synth.* **1965**, *45*, 28.

67. Sharma, V.; Kelly, G.; Watanabe, C. *Org. Lett.* **2008**, *10* (21), 4815-4818.

68. Mann, S.; Carillon, S.; Breyne, O.; Duhayon, C.; Hamon, L.; Marquet, A. *Eur. J. Org. Chem.* **2002**, *4*, 736-744.

69. Margaretha, P. *Tetrahedron Lett.* **1971**, *12* (51), 4891-4892.

70. Neises, B. and Steglich, W. *Angew. Chem. Int. Ed. Engl.* **1978**, *17* (7), 522-524.

71. (a) He, B.; Wu, T.; Yu, X.; Huang, P. *Tetrahedron: Asymmetry*. **2003**, *14* (14), 2101-2108. (b) Zhou, X. and Huang, P. *Synlett*. **2006**, *8*, 1235-1239. (c) Huang, P.; Wang, S.; Ruan, Y.; Gao, J. *Nat. Prod. Lett.* **1998**, *11* (2), 101-106. (d) Ohta, T.; Shiokawa, S.; Sakamoto, R.; Nozoe, S. *Tetrahedron Lett.* **1990**, *31* (50), 7329-7332. (e) Klaver, W.; Hiemstra, H.; Speckamp, W. *Tetrahedron Lett.* **1987**, *28* (14), 1581-1584.

72. (a) Kadam, A.; Nguyen, M.; Kopach, M.; Richardson, P.; Gallou, F.; Wan, Z.; Zhang, W. *Green Chem.* **2013**, *15* (7), 1880-1885. (b) Huang, P.; Chen, Q.; Chen, C.; Zhang, H. *Tetrahedron: Asymmetry*. **1999**, *10* (19), 3827-3832.

73. Chern, C.; Huang, Y.; Kan, W. *Tetrahedron Lett.* **2003**, *44* (5), 1039-1041.

74. Baker, R.; Cummings, W.; Hayes, J.; Kumar, A. *J. Chem. Soc. Chem. Commun.* **1986**, *16*, 1237-1239.

75. Fleming, I.; Barbero, A.; Walter, D. *Chem. Rev.* **1997**, *97* (6), 2063-2192.

76. Pollock, P.; Dambacher, J.; Anness, R.; Bergdahl, M. *Tetrahedron Lett.* **2002**, *43* (20), 3693-3697.

77. Palomo, C.; Aizpurua, J.; Iturburu, M.; Urchegui, R. *J. Org. Chem.* **1994**, *59* (1), 240-244.

78. Dambacher, J. and Bergdahl, M. *Chem. Commun.* **2003**, *1*, 144-145.

79. Dambacher, J.; Anness, R.; Pollock, P.; Bergdahl, M. *Tetrahedron*. **2004**, *60* (9), 2097-2110.

80. Dambacher, J. and Bergdahl, M. *J. Org. Chem.* **2005**, *70* (2), 580-589.

81. Oestreich, M. and Weiner, B. *Synlett*. **2004**, (12), 2139-2142.

82. Auer, G. and Oestreich, M. *Chem. Commun.* **2006**, *3*, 311-313.

83. Auer, G.; Weiner, B.; Oestreich, M. *Synthesis*. **2006**, *13*, 2113-2116.

84. Schmidtmann, E. and Oestreich, M. *Chem. Commun.* **2006**, *34*, 3643-3645.

85. Kanomata, N.; Maruyama, S.; Tomono, K.; Anada, S. *Tetrahedron Lett.* **2003**, *44* (18), 3599-3603.

86. Calderone, J. and Santos, W. *Org. Lett.* **2012**, *14* (8), 2090-2093.

87. Lee, K. and Hoveyda, A. *J. Org. Chem.* **2009**, *74* (12), 4455-4462.

88. Yoshida, M.; Ohmiya, H.; Sawamura, M. *J. Am. Chem. Soc.* **2012**, *134* (29), 11896-11899.

89. Wittig, G. and Schollkopf, U. *Chemische Berichte*. **1954**, *87* (9), 1318.

90. (a) Maryanoff, B. and Reitz, A. *Chem. Rev.* **1989**, *89* (4), 863-927. (b) Jasem, Y.; El-Esawi, R.; Thiemann, T. *J. Chem. Research*. **2014**, *38*, 453-463. (c) Lao, Z. and Toy, P. *Beilstein J. Org. Chem.* **2016**, *12*, 2577-2587.

91. Dambacher, J.; Zhao, W.; El-Batta, A.; Anness, R.; Jiang, C.; Bergdahl, M. *Tetrahedron Lett.* **2005**, *46* (26), 4473-4477.

92. Buchwald, S.; LaMaire, S.; Nielsen, R.; Watson, B.; King, S. *Org. Synth.* **1993**, *71*, 77.

93. (a) Enders, D.; Fey, P.; Kipphardt, H. *Org. Synth.* **1987**, *65*, 173. (b) Huang, P. *Synlett*. **2006**, *8*, 1133-1149.

94. Berliner, M. and Belecki, K. *Org. Synth.* **2007**, *84*, 102.

95. Corey, E. and Noe, M. *Org. Synth.* **2003**, *80*, 38.

96. Huang, P.; Chen, Q.; Chen, C.; Zhang, H. *Tetrahedron: Asymmetry*. **1999**, *10* (19), 3827-3832.

97. Wright, S.; Hageman, D.; Wright, A.; McClure, L. *Tetrahedron Lett.* **1997**, *38* (42), 7345-7348.

98. Krout, M.; Mohr, J.; Stoltz, B. *Org. Synth.* **2009**, *86*, 181.

99. Poterala, M. and Plenkiewicz, J. *Tetrahedron: Asymm.* **2011**, *22* (3), 294-299.

100. (a) Gage, J. and Evans, D. *Org. Synth.* **1990**, *68*, 77. (b) Nicolas, E.; Russell, K.; Hruby, V. *J. Org. Chem.* **1993**, *58* (3), 766-770.

101. Gage, J. and Evans, D. *Org. Synth.* **1990**, *68*, 83.

102. (a) Suginome, M.; Matsuda, T.; Ito, Y. *Organometallics*. **2000**, *19* (22), 4647-4649. (b) Fleming, I. *Organocopper Reagents*. Ed. Taylor, R. **1994**, Oxford University Press, Ch 12, 260.

103. Tucker, C.; Davidson, J.; Knochel, P. *J. Org. Chem.* **1992**, *57* (12), 3482-3485.

104. Shull, B.; Wu, Z.; Koreeda, M. *J. Carb. Chem.* **1996**, *15* (8), 955-964.

105. Hashimoto, Y.; Itoh, K.; Kakehi, A.; Shiro, M.; Suga, H. J. Org. Chem. 2013, 78 (12), 6182-6195.

106. Martinelli, M. J. Org. Chem. 1990, 55 (17), 5065-5073.

107. Soloshonok, V.; Ueki, H.; Tiwari, R. J. Org. Chem. 2004, 69 (15), 4984-4990.